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(54) Title: OXAZOLIDINONE DERIVATIVES AS ANTIBACTERIAL AGENTS

(57) Abstract: A compound of the formula (I), or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof: formula (I) wherein C is selected from D and E, formula (D), formula (E) R<sub>2a</sub>, R<sub>6a</sub>, and R<sub>3a</sub> are independently selected from for example H, CF<sub>3</sub>, Me and Et; R<sub>2b</sub> and R<sub>6b</sub> are independently selected from for example H, F, CF<sub>3</sub>, Me and Et; R<sub>1b</sub> is for example acetamido; R<sub>4</sub> is for example an optionally substituted 5- or 6- membered heterocyclic ring system. Methods for making compounds of the formula (I), compositions containing them and their use as antibacterial agents are also described.



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## OXAZOLIDINONE DERIVATIVES AS ANTIBACTERIAL AGENTS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing substituted oxazolidinone rings. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

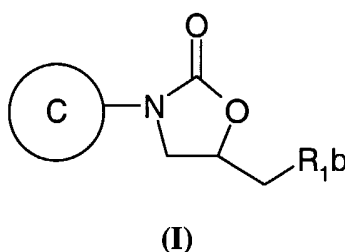
Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as  $\beta$ -lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including H.influenzae and M.catarrhalis.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and 1989, 32(8), 1673-81; Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Bacterial resistance to known antibacterial agents may develop, for example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective

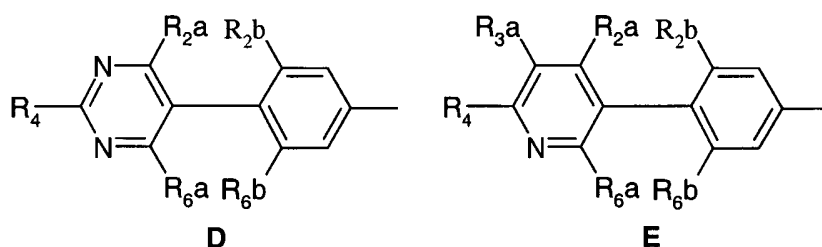
or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore, and/or (iii) the evolution of efflux pathways. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new, more potent, pharmacophores.

- 5 Accordingly the present invention provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,



10

wherein C is selected from D and E,



wherein in D and E the phenyl ring is attached to the oxazolidinone in (I);

- 15  $R_{1b}$  is  $-NR_{25}C(=W)R_{24}$  ;

wherein W is O or S;

$R_{24}$  is hydrogen, amino, (2-6C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, azido and cyano), methyl (substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, hydroxy, benzyloxy, ethynyl,

- 20 (1-4C)alkoxycarbonyl, azido and cyano), 5-halo-2-thienyl,  $-NHR_{26}$ ,  $-N(R_{26})(R_{27})$ ,  $-OR_{26}$  or  $-SR_{26}$ , (2-4C)alkenyl,  $-(1-8C)$ alkylaryl, per-halo(1-8C)alkyl,  $-(CH_2)_p(3-6C)$ cycloalkyl or  $-(CH_2)_p(3-6C)$ cycloalkenyl wherein p is 0, 1 or 2;

$R_{25}$  is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl,

- 25 fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl),  $-CO_2R_{28}$ ,  $-C(=O)R_{28}$ ,  $-C(=O)SR_{28}$ ,  $-C(=S)R_{29}$ ,  $P(O)(OR_{29})(OR_{30})$  and  $-SO_2R_{31}$ , wherein  $R_{28}$ ,  $R_{29}$ ,  $R_{30}$  and  $R_{31}$  are as defined hereinbelow;

- R<sub>28</sub> is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and -NR<sub>15</sub>R<sub>16</sub> (wherein R<sub>15</sub> and R<sub>16</sub> are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any N(R<sub>15</sub>)(R<sub>16</sub>) group, R<sub>15</sub> and R<sub>16</sub> may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring));
- R<sub>29</sub> and R<sub>30</sub> are independently selected from hydrogen and (1-4C)alkyl;
- 10 R<sub>31</sub> is (1-4C)alkyl or phenyl;
- R<sub>26</sub> and R<sub>27</sub> are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any N(R<sub>26</sub>)(R<sub>27</sub>) group, R<sub>26</sub> and R<sub>27</sub> may additionally be
- 15 taken together with the nitrogen atom to which they are attached to form an unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl ring, which ring may be optionally substituted by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl;
- 20 R<sub>2a</sub> and R<sub>6a</sub> are independently selected from H, CF<sub>3</sub>, OMe, SMe, Me and Et;
- R<sub>2b</sub> and R<sub>6b</sub> are independently selected from H, F, Cl, CF<sub>3</sub>, OMe, SMe, Me and Et;
- R<sub>3a</sub> is selected from H, (1-4C)alkyl, cyano, Br, F, Cl, OH, (1-4C)alkoxy, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 0, 1, or 2), amino, (1-4C)alkylcarbonylamino, nitro, -CHO, -CO(1-4C)alkyl, -CONH<sub>2</sub> and -CONH(1-4C)alkyl;
- 25 R<sub>4</sub> is selected from R<sub>4a</sub> and R<sub>4b</sub> wherein
- R<sub>4a</sub> is selected from azido, -NR<sub>7</sub>R<sub>8</sub>, OR<sub>10</sub>, (1-4C)alkyl, (1-4C)alkoxy, (3-6C)cycloalkyl, -(CH<sub>2</sub>)<sub>k</sub>-R<sub>9</sub>, AR1, AR2, (1-4C)alkanoyl, -CS(1-4C)alkyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl], -C(=O)<sub>l</sub>-R<sub>6</sub>, -COO(1-4C)alkyl, -C=OAR1, -C=OAR2, -COOAR1, S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -S(O)<sub>p</sub>AR1,
- 30 -S(O)<sub>p</sub>AR2 and -C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl chain may be optionally substituted by (1-4C)alkyl, cyano, hydroxy or halo; p = 0, 1 or 2;
- R<sub>4b</sub> is selected from HET-3;
- R<sub>6</sub> is selected from hydrogen, (1-4C)alkoxy, amino, (1-4C)alkylamino and

hydroxy(1-4C)alkylamino;

k is 1 or 2;

l is 1 or 2;

R<sub>7</sub> and R<sub>8</sub> are independently selected from H and (1-4C)alkyl, or wherein R<sub>7</sub> and R<sub>8</sub> taken

- 5 together with the nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> (wherein n = 1 or 2) in place of 1 carbon atom of the so formed ring; wherein the ring may be optionally substituted by one or two groups independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), AR<sub>1</sub>, AR<sub>2</sub>, ,  
 10 -C=OAR<sub>1</sub>, -C=OAR<sub>2</sub>, -COOAR<sub>1</sub>, -CS(1-4C)alkyl, -C(=S)O(1-4C)alkyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl], -S(O)<sub>p</sub>AR<sub>1</sub> and -S(O)<sub>p</sub>AR<sub>2</sub>; wherein any (1-4C)alkyl, (3-6C)cycloalkyl or (1-4C)alkanoyl group may be optionally substituted (except on a carbon atom adjacent to a heteroatom) by one or two substituents selected from (1-4C)alkyl, cyano, hydroxy, halo, amino, (1-4C)alkylamino and  
 15 di(1-4C)alkylamino; p = 0, 1 or 2;

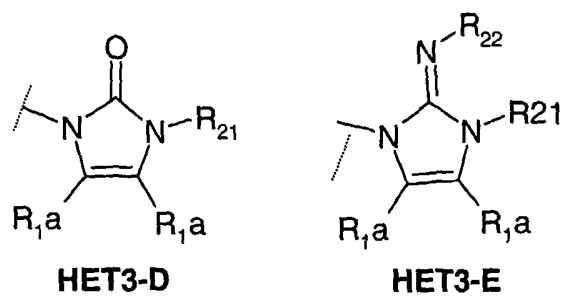
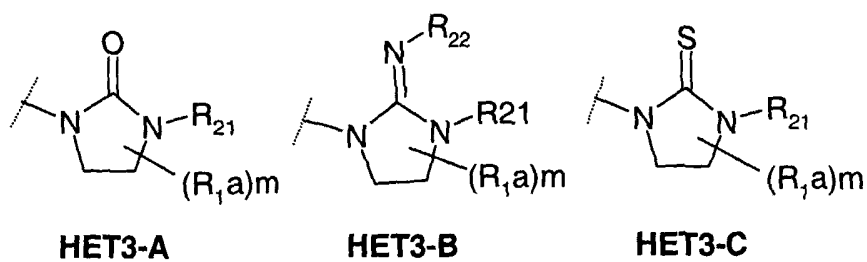
R<sub>9</sub> is independently selected from R<sub>9a</sub> to R<sub>9d</sub> below:

R<sub>9a</sub>: AR<sub>1</sub>, AR<sub>2</sub>, AR<sub>2a</sub>, AR<sub>2b</sub>, AR<sub>3</sub>, AR<sub>3a</sub>, AR<sub>3b</sub>, AR<sub>4</sub>, AR<sub>4a</sub>, CY<sub>1</sub>, CY<sub>2</sub>;

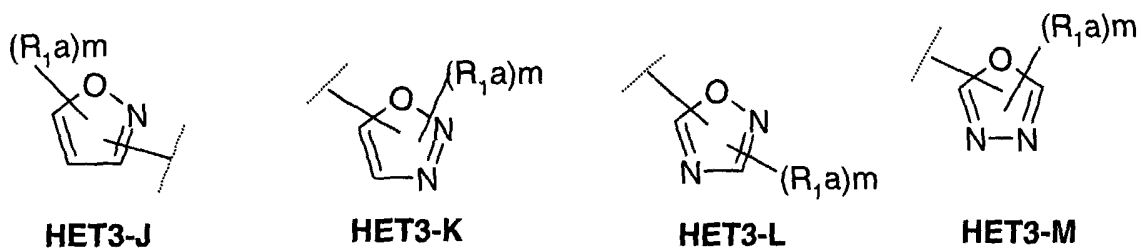
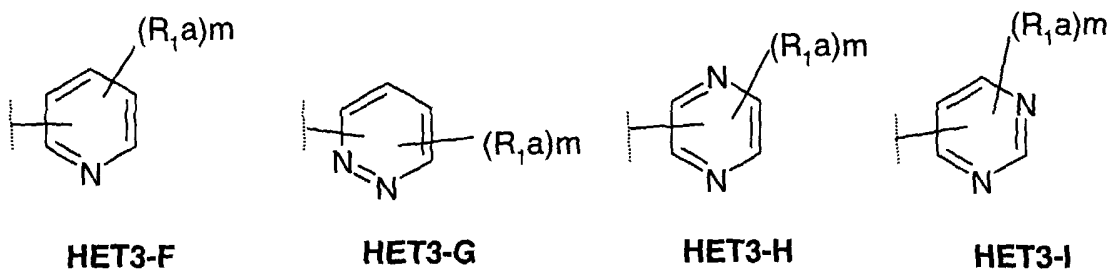
- R<sub>9b</sub>: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the  
 20 amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR<sub>1</sub>,  
 25 -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl; wherein any alkyl, alkanoyl or cycloalkyl may itself optionally be substituted by cyano, hydroxy or halo], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR<sub>1</sub>)ethenyl, 2-(AR<sub>2</sub>)ethenyl, 2-(AR<sub>2a</sub>)ethenyl;  
 30 R<sub>9c</sub>: (1-6C)alkyl  
 {optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)<sub>2</sub>,

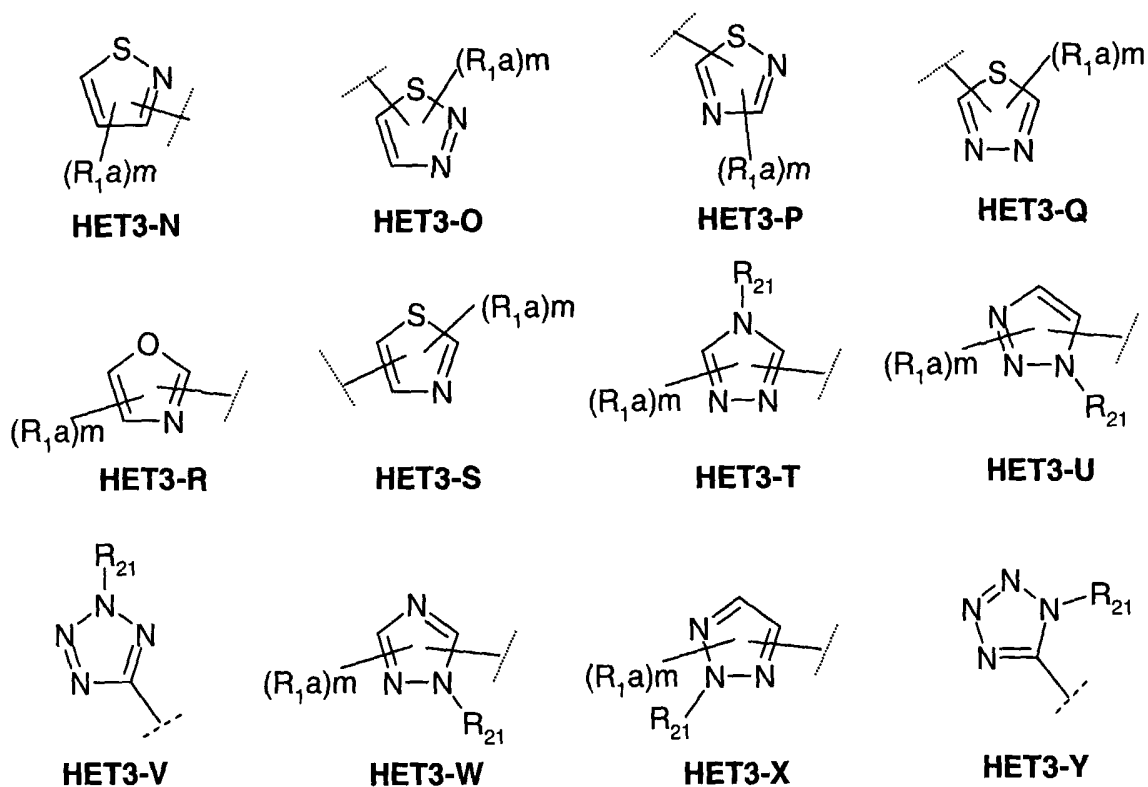
- and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are as hereinbefore defined], (=NOR<sub>v</sub>) wherein R<sub>v</sub> is as hereinbefore defined, (1-4C)alkylS(O)<sub>p</sub>NH, (1-4C)alkylS(O)<sub>p</sub>-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)<sub>p</sub>NH-, fluoro(1-4C)alkylS(O)<sub>p</sub>-((1-4C)alkyl)N-, (1-4C)alkylS(O)<sub>q</sub>-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)<sub>q</sub>-, AR2-S(O)<sub>q</sub>-, AR3-S(O)<sub>q</sub>-, AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups}; wherein any (1-4C)alkyl present in any substituent on R<sub>9c</sub> may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;
- R<sub>9d</sub>: R<sub>14</sub>C(O)O(1-6C)alkyl- wherein R<sub>14</sub> is AR1, AR2, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (R<sub>9c</sub>)};
- R<sub>10</sub> is selected from hydrogen, R<sub>9c</sub> (as hereinbefore defined), (1-4C)alkanoyl and (1-4C)alkylsulfonyl;
- HET-3 is selected from:
- a) a 5-membered heterocyclic ring containing at least one nitrogen and/or oxygen in which any carbon atom is a C=O, C=N, or C=S group, wherein said ring is of the formula HET3-A to HET3-E below:

- 6 -

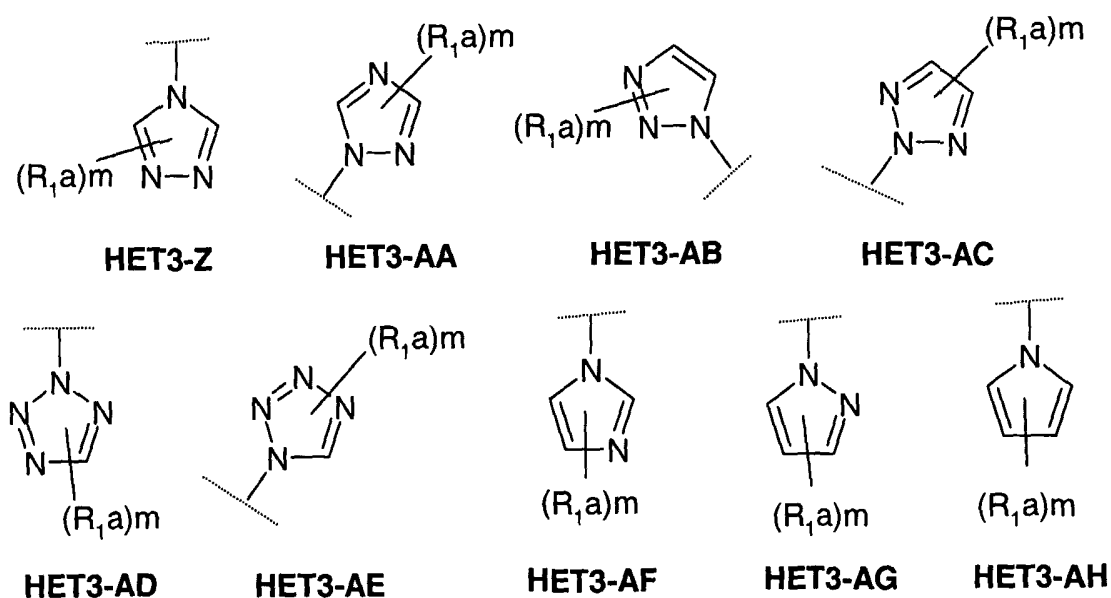


b) a carbon-linked 5- or 6-membered heteroaromatic ring containing 1, 2, 3, or 4 heteroatoms independently selected from N, O and S selected from HET3-F to HET3-Y below:





c) a nitrogen-linked 5- or 6-membered heteroaromatic ring containing 1, 2, 3, or 4 heteroatoms independently selected from N, O and S selected from HET3-Z to HET3-AH below:



5

wherein in HET-3,  $R_1a$  is a substituent on carbon;

$R_1a$  is independently selected from  $R_1a1$  to  $R_1a5$  below:

$R_1a1$ : AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;



- R<sub>1a2</sub>: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR<sub>1</sub>, -CS(1-4C)alkyl) and -C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)alkanoyl and (3-6C)cycloalkyl substituent may itself be substituted by cyano, hydroxy or halo, provided that, such a substituent is not on a carbon adjacent to a nitrogen atom of the piperazine ring], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR<sub>1</sub>)ethenyl, 2-(AR<sub>2</sub>)ethenyl, 2-(AR<sub>2a</sub>)ethenyl;
- R<sub>1a3</sub>: (1-10C)alkyl
- { optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR<sub>1</sub>, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl], (=NOR<sub>v</sub>) wherein R<sub>v</sub> is as hereinbefore defined, (1-4C)alkylS(O)<sub>p</sub>NH-, (1-4C)alkylS(O)<sub>p</sub>-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)<sub>p</sub>NH-,

fluoro(1-4C)alkylS(O)<sub>p</sub>((1-4C)alkyl)N-, (1-4C)alkylS(O)<sub>q</sub>-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)<sub>q</sub>-, AR2-S(O)<sub>q</sub>-, AR3-S(O)<sub>q</sub>-, AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups}; wherein any (1-4C)alkyl, (1-4C)alkanoyl and (3-

5 6C)cycloalkyl present in any substituent on R<sub>1a3</sub> may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

R<sub>1a4</sub>: R<sub>14</sub>C(O)O(1-6C)alkyl- wherein R<sub>14</sub> is AR1, AR2, AR2a, AR2b, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (R<sub>1a3</sub>)};

R<sub>1a5</sub>: F, Cl, hydroxy, mercapto, (1-4C)alkylS(O)<sub>p</sub>- (p = 0, 1 or 2), -NR<sub>7</sub>R<sub>8</sub> (wherein R<sub>7</sub> and R<sub>8</sub> are as hereinbefore defined) or -OR<sub>10</sub> (where R<sub>10</sub> is as hereinbefore defined);

m is 0, 1 or 2;

R<sub>21</sub> is selected from hydrogen, methyl [optionally substituted with cyano, trifluoromethyl, -C=WNR<sub>v</sub>R<sub>w</sub> (where W, R<sub>v</sub> and R<sub>w</sub> are as hereinbefore defined for R<sub>1a3</sub>), (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, CY1, CY2, AR1, AR2, AR2a, AR2b (not linked through nitrogen) or AR3], (2-10C)alkyl [optionally substituted other than on a carbon attached to the HET-3 ring nitrogen with one or two groups independently selected from the optional substituents defined for R<sub>1a3</sub>] and R<sub>14</sub>C(O)O(2-6C)alkyl-, wherein R<sub>14</sub> is as defined hereinbefore for R<sub>1a4</sub> and wherein R<sub>14</sub>C(O)O group is attached to a carbon other than the carbon attached to the HET-3 ring nitrogen;

R<sub>22</sub> is cyano, -COR<sub>12</sub>, -COOR<sub>12</sub>, -CONHR<sub>12</sub>, -CON(R<sub>12</sub>)(R<sub>13</sub>), -SO<sub>2</sub>R<sub>12</sub> (provided that R<sub>12</sub> is not hydrogen), -SO<sub>2</sub>NHR<sub>12</sub>, -SO<sub>2</sub>N(R<sub>12</sub>)(R<sub>13</sub>) or NO<sub>2</sub>, wherein R<sub>12</sub> and R<sub>13</sub> are as defined hereinbelow;

R<sub>12</sub> and R<sub>13</sub> are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any N(R<sub>12</sub>)(R<sub>13</sub>) group, R<sub>12</sub> and R<sub>13</sub> may be taken together with the nitrogen to which they are attached to form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein the ring may be optionally substituted by one or two groups independently selected from (1-4C)alkyl (optionally substituted on a carbon not adjacent to

- the nitrogen by cyano, hydroxy or halo), (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), AR1, AR2, , -C=OAR1, -C=OAR2, -COOAR1, -CS(1-4C)alkyl, -C(=S)O(1-4C)alkyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl ], -S(O)<sub>p</sub>AR1 and -S(O)<sub>p</sub>AR2; wherein any (1-4C)alkyl
- 5 chain may be optionally substituted by (1-4C)alkyl, cyano, hydroxy or halo; p = 0,1 or 2;
- AR1** is an optionally substituted phenyl or optionally substituted naphthyl;
- AR2** is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and
- 10 linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;
- AR2a** is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;
- AR2b** is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation),
- 15 linked via a ring carbon atom or linked via a ring nitrogen atom;
- AR3** is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;
- 20 **AR3a** is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;
- AR3b** is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation),
- 25 linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;
- AR4** is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and
- 30 linked via a ring carbon atom in any of the rings comprising the tricyclic system;
- AR4a** is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring;

wherein; optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a,

CY1 and CY2 are (on an available carbon atom) up to three substituents independently

- 5 selected from (1-4C)alkyl { optionally substituted by substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub>}, trifluoromethyl, hydroxy, halo, nitro, cyano, thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, 10 (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO<sub>2</sub>amino, (2-4C)alkenyl { optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and 15 (1-4C)alkoxy}, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; R<sub>w</sub> is hydrogen or (1-4C)alkyl];

and further optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from

- 20 trifluoromethoxy, benzoylamino, benzoyl, phenyl { optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, -SO<sub>2</sub>NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; R<sub>w</sub> is hydrogen or (1-4C)alkyl]; and

- 25 optional substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl { wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, 30 hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; R<sub>w</sub> is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are in-vivo hydrolysable esters of compounds of formula (1). Therefore in another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chosen from "0, 1 or 2" groups and "1 or 2" groups.

In this specification the term 'alkyl' includes straight chained and branched structures. For example, (1-4C)alkyl includes propyl and isopropyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chained version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. In this specification, the terms 'alkenyl' and 'cycloalkenyl' include all positional and geometrical isomers. In this specification, the term 'aryl' is an unsubstituted carbocyclic aromatic group, in particular phenyl, 1- and 2-naphthyl.

Within this specification composite terms are used to describe groups comprising more than one functionality such as (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkyl. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkyl includes methoxymethoxymethyl, ethoxymethoxypropyl and propoxyethoxymethyl.

It will be understood that where a group is defined such that is optionally substituted by more than one substituent, then substitution is such that chemically stable compounds are formed. For example, a trifluoromethyl group may be allowed but not a trihydroxymethyl group. This convention is applied wherever optional substituents are defined.

The term "a C5-C6 heteroaromatic ring" means a 5- or 6-membered aryl ring wherein (unless stated otherwise) 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulfur. Unless stated otherwise, such rings are fully aromatic. Particular examples of 5- or 6-membered heteroaryl ring systems are furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

- 5        Examples of **(1-4C)alkyl** and **(1-5C)alkyl** include methyl, ethyl, propyl, isopropyl and t-butyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl and hexyl; examples of **(1-10C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl and nonyl; examples of **(1-4C)alkanoylamino-(1-4C)alkyl** include formamidomethyl, acetamidomethyl and acetamidoethyl; examples of **hydroxy(1-4C)alkyl**  
 10 and **hydroxy(1-6C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxycarbonyl** include methoxymethoxycarbonyl, methoxyethoxycarbonyl and propoxymethoxycarbonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl** include  
 15 methoxymethoxymethoxycarbonyl, methoxyethoxymethoxycarbonyl and propoxyethoxymethoxycarbonyl; examples of **2-((1-4C)alkoxycarbonyl)ethenyl** include 2-(methoxycarbonyl)ethenyl and 2-(ethoxycarbonyl)ethenyl; examples of **2-cyano-2-((1-4C)alkyl)ethenyl** include 2-cyano-2-methylethenyl and 2-cyano-2-ethylethenyl; examples of **2-nitro-2-((1-4C)alkyl)ethenyl** include 2-nitro-2-methylethenyl and 2-nitro-2-ethylethenyl;  
 20 ethylethenyl; examples of **2-((1-4C)alkylaminocarbonyl)ethenyl** include 2-(methylaminocarbonyl)ethenyl and 2-(ethylaminocarbonyl)ethenyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkenyloxy** include allyloxy and vinyloxy; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(2-4C)alkynyloxy** include ethynyloxy and 2-propynyloxy; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkylcarbonyl** include acetyl and propionyl;  
 25 examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **(2-4C)alkenylamino** include vinylamino and allylamino; examples of **hydroxy(1-4C)alkylamino** include 2-hydroxyethylamino, 2-hydroxypropylamino and 3-hydroxypropylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and

bromo; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl and ethylsulfonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of **(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy** include 2-(methoxymethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy; 5 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of **(1-4C)alkylS(O)<sub>2</sub>amino** include methylsulfonylamino and ethylsulfonylamino; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkoxycarbonylamino** include methoxycarbonylamino and ethoxycarbonylamino; examples of **N-(1-4C)alkyl-N-(1-6C)alkanoylamino** include N-10 methylacetamido, N-ethylacetamido and N-methylpropionamido; examples of **(1-4C)alkylS(O)<sub>p</sub>NH-** wherein p is 1 or 2 include methylsulfinylamino, methylsulfonylamino, ethylsulfinylamino and ethylsulfonylamino; examples of **(1-4C)alkylS(O)<sub>p</sub>((1-4C)alkyl)N-** wherein p is 1 or 2 include methylsulfinylmethylamino, methylsulfonylmethylamino, 2-(ethylsulfinyl)ethylamino and 2-(ethylsulfonyl)ethylamino; 15 examples of **fluoro(1-4C)alkylS(O)<sub>p</sub>NH-** wherein p is 1 or 2 include trifluoromethylsulfinylamino and trifluoromethylsulfonylamino; examples of **fluoro(1-4C)alkylS(O)<sub>p</sub>((1-4C)alkyl)NH-** wherein p is 1 or 2 include trifluoromethylsulfinylmethylamino and trifluoromethylsulfonylmethylamino examples of **(1-4C)alkoxy(hydroxy)phosphoryl** include methoxy(hydroxy)phosphoryl and 20 ethoxy(hydroxy)phosphoryl; examples of **di-(1-4C)alkoxyphosphoryl** include di-methoxyphosphoryl, di-ethoxyphosphoryl and ethoxy(methoxy)phosphoryl; examples of **(1-4C)alkylS(O)<sub>q</sub>-** wherein q is 0, 1 or 2, and **-S(O)<sub>n</sub>(1-4C)alkyl** (wherein n = 1 or 2), include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **phenylS(O)<sub>q</sub>** and **naphthylS(O)<sub>q</sub>-** wherein q is 0, 1 or 2 are phenylthio, 25 phenylsulfinyl, phenylsulfonyl and naphthylthio, naphthylsulfinyl and naphthylsulfonyl respectively; examples of **benzyloxy-(1-4C)alkyl** include benzyloxymethyl and benzyloxyethyl; examples of a **(3-4C)alkylene** chain are trimethylene or tetramethylene; examples of **(1-6C)alkoxy-(1-6C)alkyl** include methoxymethyl, ethoxymethyl and 2-methoxyethyl; examples of **hydroxy-(2-6C)alkoxy** include 2-hydroxyethoxy and 3-30 hydroxypropoxy; examples of **(1-4C)alkylamino-(2-6C)alkoxy** include 2-methylaminoethoxy and 2-ethylaminoethoxy; examples of **di-(1-4C)alkylamino-(2-6C)alkoxy** include 2-dimethylaminoethoxy and 2-diethylaminoethoxy; examples of **phenyl(1-4C)alkyl** include benzyl and phenethyl; examples of **(1-4C)alkylcarbamoyl** include

methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **hydroxyimino(1-4C)alkyl** include hydroxyiminomethyl, 2-(hydroxyimino)ethyl and 1-(hydroxyimino)ethyl; examples of **(1-4C)alkoxyimino-(1-4C)alkyl** include methoxyiminomethyl, ethoxyiminomethyl,  
 5 1-(methoxyimino)ethyl and 2-(methoxyimino)ethyl; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **nitro(1-4C)alkyl** include nitromethyl, 1-nitroethyl, 2-nitroethyl and 3-nitropropyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl;  
 10 examples of **(1-4C)alkanesulfonamido** include methanesulfonamido and ethanesulfonamido; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl and ethylaminosulfonyl; examples of **di-(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of **(1-4C)alkanesulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy and  
 15 propylsulfonyloxy; examples of **(1-4C)alkanoyloxy** include acetoxyl and propionyl; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and diethylaminocarbonyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(3-6C)cycloalkenyl**  
 20 include cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl; examples of **(4-7C)cycloalkyl** include cyclobutyl, cyclopentyl and cyclohexyl; examples of **di(N-(1-4C)alkyl)aminomethylimino** include dimethylaminomethylimino and diethylaminomethylimino.

Particular values for AR2 include, for example, for those AR2 containing one  
 25 heteroatom, furan, pyrrole, thiophene; for those AR2 containing one to four N atoms, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- & 1,2,4-triazole and tetrazole; for those AR2 containing one N and one O atom, oxazole, isoxazole and oxazine; for those AR2 containing one N and one S atom, thiazole and isothiazole; for those AR2 containing two N atoms and one S atom, 1,2,4- and 1,3,4-thiadiazole.

30 Particular examples of AR2a include, for example, dihydropyrrole (especially 2,5-dihydropyrrol-4-yl) and tetrahydropyridine (especially 1,2,5,6-tetrahydropyrid-4-yl).

Particular examples of AR2b include, for example, tetrahydrofuran, pyrrolidine, morpholine (preferably morpholino), thiomorpholine (preferably thiomorpholino), piperazine



(preferably piperazino), imidazoline and piperidine, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Particular values for AR3 include, for example, bicyclic benzo-fused systems containing a 5- or 6-membered heteroaryl ring containing one nitrogen atom and optionally 5 1-3 further heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, indole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzisothiazole, benzoxazole, benzisoxazole, quinoline, quinoxaline, quinazoline, phthalazine and cinnoline.

Other particular examples of AR3 include 5/5-, 5/6 and 6/6 bicyclic ring systems 10 containing heteroatoms in both of the rings. Specific examples of such ring systems include, for example, purine and naphthyridine.

Further particular examples of AR3 include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 15 3H-pyrrolo[1,2-a]pyrrole, pyrrolo[2,1-b]thiazole, 1H-imidazo[1,2-a]pyrrole, 1H-imidazo[1,2-a]imidazole, 1H,3H-pyrrolo[1,2-c]oxazole, 1H-imidazo[1,5-a]pyrrole, pyrrolo[1,2-b]isoxazole, imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, indolizine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrazine, 20 pyrrolo[1,2-a]pyrimidine, pyrido[2,1-c]-s-triazole, s-triazole[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrazine, imidazo[1,5-a]pyrimidine, imidazo[1,2-b]-pyridazine, s-triazolo[4,3-a]pyrimidine, imidazo[5,1-b]oxazole and imidazo[2,1-b]oxazole. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazine, [3H]- 25 oxazolo[3,4-a]pyridine, [6H]-pyrrolo[2,1-c]oxazine and pyrido[2,1-c][1,4]oxazine. Other specific examples of 5/5- bicyclic ring systems are imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole or imidazo[2,1-b]oxazole.

Particular examples of AR3a and AR3b include, for example, indoline, 30 1,3,4,6,9,9a-hexahydropyrido[2,1c][1,4]oxazin-8-yl, 1,2,3,5,8,8a-hexahydroimidazo[1,5a]pyridin-7-yl, 1,5,8,8a-tetrahydrooxazolo[3,4a]pyridin-7-yl, 1,5,6,7,8,8a-hexahydrooxazolo[3,4a]pyridin-7-yl, (7aS)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, (7aS)[5H]-1,2,3,7a-tetrahydropyrrolo[1,2c]imidazol-6-yl,

(7aR)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, [3H,5H]-pyrrolo[1,2-c]oxazol-6-yl, [5H]-2,3-dihydropyrrolo[1,2-c]imidazol-6-yl, [3H,5H]-pyrrolo[1,2-c]thiazol-6-yl, [3H,5H]-1,7a-dihydropyrrolo[1,2-c]thiazol-6-yl, [5H]-pyrrolo[1,2-c]imidazol-6-yl, [1H]-3,4,8,8a-tetrahydropyrrolo[2,1-c]oxazin-7-yl, [3H]-1,5,8,8a-tetrahydrooxazolo[3,4-  
 5 a]pyrid-7-yl, [3H]-5,8-dihydroxazolo[3,4-a]pyrid-7-yl and 5,8-dihydroimidazo[1,5-a]pyrid-7-yl.

Particular values for AR4 include, for example, pyrrolo[a]quinoline, 2,3-pyrroloisoquinoline, pyrrolo[a]isoquinoline, 1H-pyrrolo[1,2-a]benzimidazole, 9H-imidazo[1,2-a]indole, 5H-imidazo[2,1-a]isoindole, 1H-imidazo[3,4-a]indole,  
 10 imidazo[1,2-a]quinoline, imidazo[2,1-a]isoquinoline, imidazo[1,5-a]quinoline and imidazo[5,1-a]isoquinoline.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen), W.L.Mosby (Interscience Publishers Inc., New York), 1961, Parts 1 and 2.

15 Where optional substituents are listed such substitution is preferably not geminal disubstitution unless stated otherwise. If not stated elsewhere, suitable optional substituents for a particular group are those as stated for similar groups herein.

Preferable optional substituents on Ar2b as 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl or 1,4-dioxan-2-yl are mono- or disubstitution by substituents independently  
 20 selected from (1-4C)alkyl (including geminal disubstitution), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, trifluoromethyl and phenyl].

Preferable optional substituents on CY1 & CY2 are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, and trifluoromethyl.

25 Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example  
 30 triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl D-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-

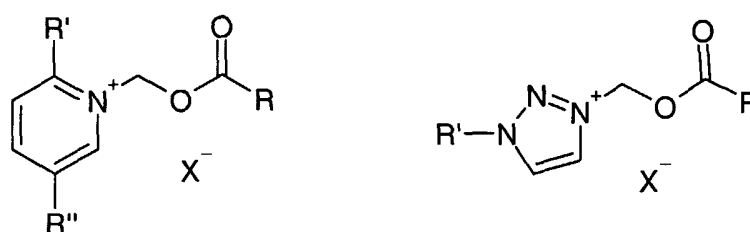
acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
  - b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
  - c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
  - d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
  - e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).
- Suitable pro-drugs for pyridine or triazole derivatives include acyloxymethyl pyridinium or triazolium salts eg halides; for example a pro-drug such as:



(Ref: T.Yamazaki *et al.* . 42<sup>nd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, 2002; Abstract F820).

- Suitable pro-drugs of hydroxyl groups are acyl esters of acetal-carbonate esters of formula  $\text{RCOOC}(\text{R}, \text{R}')\text{OCO}-$ , where R is (1-4C)alkyl and R' is (1-4C)alkyl or H. Further suitable prodrugs are carbonate and carbamate esters  $\text{RCOO}-$  and  $\text{RNHCOO}-$ .

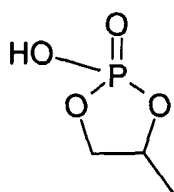
An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a carboxy or hydroxy group is, for example, a

pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent alcohol.

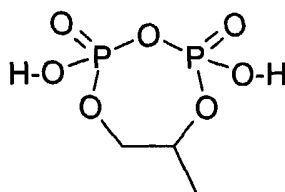
Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

- 10 An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and
- 15 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl, carboxy(2-5C)alkylcarbonyl and carboxyacetyl.
- 20 Examples of ring substituents on phenylacetyl and benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example,  $R^A C(O)O(1-6C)alkyl-CO-$  (wherein  $R^A$  is for example, optionally substituted
- 25 benzyloxy-(1-4C)alkyl, or optionally substituted phenyl; suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

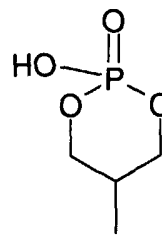
- Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a
- 30 pyrophosphate of formula (PD2), and a 1,3-diol may be cyclised to form a cyclic ester of the formula (PD3):



(PD1)



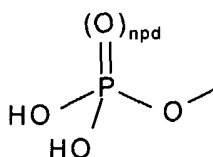
(PD2)



(PD3)

Esters of compounds of formula (I) wherein the HO- function/s in (PD1), (PD2) and (PD3) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of invention in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD4) :



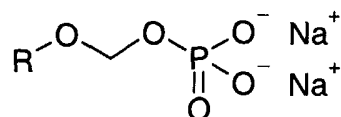
(PD4)

For the avoidance of doubt, phosphono is  $-P(O)(OH)_2$ ; (1-4C)alkoxy(hydroxy)-phosphoryl is a mono-(1-4C)alkoxy derivative of  $-O-P(O)(OH)_2$ ; and di-(1-4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of  $-O-P(O)(OH)_2$ .

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD4) in which either or both of the -OH groups in (PD1) is independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2), (PD3) and (PD4) may be prepared by reaction of a compound of invention containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

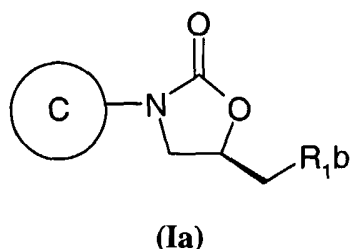
Other suitable prodrugs include phosphonoxymethyl ethers and their salts, for example a prodrug of R-OH such as:



When a compound of invention contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2), (PD3) and/or (PD4) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of invention contains two (PD4) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

The compounds of the present invention have a chiral centre at the C-5 positions of the oxazolidinone ring. The pharmaceutically active diastereomer is of the formula (Ia):



which is generally the (5R) configuration, depending on the nature of R<sub>1b</sub> and C.

Furthermore, some compounds of the invention may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereoisomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

The invention relates to all tautomeric forms of the compounds of the invention that

possess antibacterial activity.

It is also to be understood that certain compounds of the invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial  
5 activity.

It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial activity.

As stated before, we have discovered a range of compounds that have good activity  
10 against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics, together with activity against fastidious Gram negative pathogens such as *H.influenzae*, *M.catarrhalis*, *Mycoplasma* and *Chlamydia* strains. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

15 In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

20 In one aspect, an in-vivo hydrolysable ester of a compound of the formula (I) is a phosphoryl ester (as defined by formula (PD4) with npd as 1).

Compounds of the formula (I), or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein C is selected from group D or group E represent separate and independent aspects of the invention.

25 Particularly preferred compounds of the invention comprise a compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents R<sub>1a</sub>, R<sub>1b</sub>, R<sub>2a</sub>, R<sub>2b</sub>, R<sub>3a</sub>, R<sub>6a</sub> and R<sub>6b</sub> and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed  
30 hereinbefore or hereinafter):

In one embodiment are provided compounds of the formula (I) or pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof wherein group C is group D.

In another embodiment are provided compounds of the formula (I) or pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof wherein group C is group E.

In one aspect  $R_{2a}$  and  $R_{6a}$  are hydrogen.

- 5 In one aspect one  $R_{2b}$  and  $R_{6b}$  is fluoro and the other is hydrogen. In another aspect both one  $R_{2b}$  and  $R_{6b}$  are fluoro. In a further aspect  $R_{2b}$  is fluoro and  $R_{6b}$  is selected from Cl,  $CF_3$ , Me, Et, OMe and SMe.

In one aspect one of  $R_{2b}$  and  $R_{6b}$  is chloro and other hydrogen.

In another aspect one of  $R_{2b}$  and  $R_{6b}$  is  $CF_3$  and the other hydrogen.

- 10 In another aspect one of  $R_{2b}$  and  $R_{6b}$  is Me and the other hydrogen.

In another aspect one of  $R_{2b}$  and  $R_{6b}$  is Et and the other hydrogen.

In another aspect one of  $R_{2b}$  and  $R_{6b}$  is OMe and the other hydrogen.

In another aspect one of  $R_{2b}$  and  $R_{6b}$  is SMe and the other hydrogen.

- 15 In one aspect  $R_{3a}$  is selected from H, (1-4C)alkyl, cyano, Br, F, Cl, OH, (1-4C)alkoxy, -S(1-4C)alkyl, amino, nitro and -CHO. In a further aspect  $R_{3a}$  is selected from H, Cl, Br, F, Me, Et, OMe and SMe.

In one aspect  $R_{1b}$  is  $-NHC(=O)R_{24}$ . In another aspect  $R_{1b}$  is  $-NHC(=S)R_{24}$ .

In one aspect  $R_{24}$  is hydrogen, amino,  $-NHR_{26}$  or  $-N(R_{26})(R_{27})$  wherein  $R_{26}$  and  $R_{27}$  are as defined hereinbefore or hereinafter..

- 20 In another aspect  $R_{24}$  is (2-6C)alkyl optionally substituted with 1,2,3 or 4 halogen atoms.

In another aspect  $R_{24}$  is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, bromomethyl, azidomethyl and cyanomethyl.

- 25 In another aspect  $R_{24}$  is selected from hydroxymethyl, benzyloxymethyl, methylthiomethyl and methoxymethyl.

In another aspect  $R_{24}$  is selected from ethynylmethyl and (1-4C)alkoxycarbonylmethyl.

- In a further aspect,  $R_{24}$  is selected from -(1-8C)alkylaryl (for example -(1-8C)alkylphenyl, such as -(1-6C)alkylphenyl, such as -(1-4C)alkylphenyl, for example benzyl and per-halo(1-8C)alkyl (for example perfluoro(1-8C)alkyl (such as perfluoro(1-6C)alkyl or perfluoro(1-4C)alkyl, for example trifluoromethyl and pentafluoroethyl), or perchloro(1-8C)alkyl (such as perchloro(1-6C)alkyl or perchloro(1-4C)alkyl, for example trichloromethyl and pentachloroethyl).
- 30

In a further aspect  $R_{24}$  is -O  $R_{26}$  or -S  $R_{26}$ , preferably wherein  $R_{26}$  is optionally



substituted (1-4C)alkyl.

In a further aspect  $R_{24}$  is selected from (2-4C)alkenyl,  $-(CH_2)_p(3-6C)cycloalkyl$  and  $-(CH_2)_p(3-6C)cycloalkenyl$  wherein  $p$  is 0, 1 or 2, and preferably wherein  $p$  is 1 or 2. In this aspect  $R_{24}$  is for example selected from ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, methylcyclopropyl, methylcyclobutyl, methylcyclopentyl, methylcyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, methylcyclopropenyl, ethylcyclopropenyl, methylcyclobutenyl and methylcyclohexenyl.

In a further aspect  $R_{24}$  is 5-halo-2-thienyl.

Conveniently  $R_{24}$  is selected from cyclopropyl, dichloromethyl, methylthio and methoxy.

In one aspect  $R_{25}$  is selected from hydrogen, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl and benzyloxycarbonyl. Preferably  $R_{25}$  is hydrogen.

In another aspect,  $R_{25}$  is selected from (3-6C)cycloalkyl and (1-6C)alkyl (optionally substituted with cyano or (1-4C)alkoxycarbonyl).

In a further aspect  $R_{25}$  is selected from  $-CO_2R_{28}$ ,  $-C(=O)R_{28}$ ,  $-C(=O)SR_{28}$ ,  $-C(=S)R_{29}$ ,  $P(O)(OR_{29})(OR_{30})$  and  $-SO_2R_{31}$ , wherein  $R_{28}$ ,  $R_{29}$ ,  $R_{30}$  and  $R_{31}$  are as defined hereinbefore or hereinafter.

In one aspect,  $R_{28}$  is selected from (3-6C)cycloalkyl and (1-6C)alkyl (optionally substituted as hereinbefore described).

In another aspect  $R_{28}$  is selected from phenyl, benzyl and (1-5C)alkanoyl.

In a further aspect  $R_{28}$  is hydrogen.

In one aspect  $R_{26}$  is selected from hydrogen, phenyl (optionally substituted with one or two substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two or three halogen atoms) and (1-4C)alkyl (optionally substituted with one, two or three halogen atoms).

In one aspect  $R_{27}$  is selected from hydrogen, phenyl (optionally substituted with one or two substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two or three halogen atoms) and (1-4C)alkyl (optionally substituted with one, two or three halogen atoms).

In another aspect  $R_{26}$  and  $R_{27}$  taken together with the nitrogen atom to which they are attached to form an unsubstituted or substituted pyrrolidiny, piperidiny or morpholinyl ring, which ring may be optionally substituted by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl,  $-COO(1-4C)alkyl$ ,  $-S(O)_n(1-4C)alkyl$  (wherein  $n = 1$  or  $2$ ),

-COOAR1, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl. Conveniently, substituents on such a pyrrolidiny, piperidiny or morpholinyl ring are (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl and -COOAR1.

In one aspect R<sub>4</sub> is selected from R<sub>4a</sub>.

5 In another, preferred, aspect R<sub>4</sub> is selected from R<sub>4b</sub>.

In one aspect R<sub>4a</sub> is selected from (1-4C)alkyl, (3-6C)cycloalkyl, AR1, AR2, (1-4C)acyl, -CS(1-4C)alkyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl ], -COO(1-4C)alkyl, -C=OAR1, -C=OAR2, -COOAR1, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -S(O)<sub>p</sub>AR1, -S(O)<sub>p</sub>AR2 and -C(=S)O(1-4C)alkyl;

10 wherein any (1-4C)alkyl chain may be optionally substituted by (1-4C)alkyl, cyano, hydroxy or halo; p = 0,1 or 2).

In a further aspect R<sub>4a</sub> is selected from azido, -NR<sub>7</sub>R<sub>8</sub>, OR<sub>10</sub>(1-4C)alkoxy, -(CH<sub>2</sub>)<sub>m</sub>-R<sub>9</sub> and -(C=O)<sub>l</sub>-R<sub>6</sub>,

In one aspect HET-3 is selected from HET3-A, HET3-B, HET3-C, HET3-D and  
15 HET3-E.

In another aspect HET-3 is selected from HET3-F, HET3-G, HET3-H and HET3-I.

In another aspect HET-3 is selected from HET3-J, HET3-K, HET3-L, HET3-M, HET3-N, HET3-O, HET3-P, HET3-Q, HET3-R and HET3-S.

In a further aspect HET-3 is selected from HET3-J, HET3-L, HET3-M, HET3-N,  
20 HET3-P, HET3-Q, HET3-R and HET3-S.

In a further aspect HET-3 is selected from HET3-L and HET3-M.

In a further aspect HET-3 is selected from HET3-P and HET3-Q

In a further aspect HET-3 is selected from HET3-T, HET3-U, HET3-V, HET3-W, HET3-X and HET3-Y.

25 In a further aspect HET-3 is selected HET3-T, HET3-V, HET3-Y and HET3-W.

In a further aspect HET-3 is selected HET3-V, and HET3-Y.

In a further aspect HET-3 is selected HET3-U, and HET3-X.

In a further aspect HET-3 is selected HET3-T, and HET3-W.

In a further aspect HET-3 is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC,  
30 HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH.

In one embodiment, when Z is S, HET3 is triazolyl.

In another embodiment, when Z is S, HET3 is not tetrazolyl.

When m = 1, in one aspect R<sub>1a</sub> is selected from R<sub>1a1</sub>; in another aspect R<sub>1a</sub> is selected

from R<sub>1a2</sub>; in a further aspect R<sub>1a</sub> is selected from R<sub>1a3</sub>, in a further aspect R<sub>1a</sub> is selected from R<sub>1a4</sub> and in a further aspect R<sub>1a</sub> is selected from R<sub>1a5</sub>.

When m = 2, in one aspect both groups R<sub>1a</sub> are independently selected from the same group R<sub>1a1</sub> to R<sub>1a5</sub>. In a further aspect when m = 2, each R<sub>1a</sub> is independently selected from  
5 different groups R<sub>1a1</sub> to R<sub>1a5</sub>.

Conveniently m is 1 or 2. In one aspect, preferably m is 1. In another aspect, preferably m is 2.

Particular values for R<sub>1a</sub> when selected from R<sub>1a1</sub> are AR1 and AR2, more particularly AR2.

10 Particular values for R<sub>1a</sub> when selected from R<sub>1a2</sub> are cyano and -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the  
15 ring is substituted on the additional nitrogen by a group selected from (1-4C)alkyl (optionally substituted on a carbon not adjacent to the nitrogen), (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2;), -COOAR1, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)alkanoyl and (3-6C)cycloalkyl is optionally substituted by cyano, hydroxy or halo]. More particular values for R<sub>1a</sub> when  
20 selected from R<sub>1a2</sub> are cyano, formyl, -COO(1-4C)alkyl, -C(=O)NH<sub>2</sub>, -(C=O)morpholine and -(C=O)piperazine (substituted as hereinbefore described). Further particular values for R<sub>1a</sub> when selected from R<sub>1a2</sub> is -(C=O)piperazine (substituted as hereinbefore described).

Particular values for R<sub>1a</sub> when selected from R<sub>1a3</sub> are (1-10C)alkyl {optionally substituted by one or more groups (including geminal disubstitution) each independently  
25 selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-  
30 (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide nitrogen to which they

are attached can form a morpholine, pyrrolidine, piperidine or piperazine ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl and (1-4C)alkanoyl], (1-4C)alkylS(O)<sub>q</sub>-, (q is 0, 1 or 2), AR<sub>2</sub>, AR<sub>2</sub>-O-, AR<sub>2</sub>-NH-, and also AR<sub>2a</sub>, AR<sub>2b</sub> versions of AR<sub>2</sub> containing groups};

- 5 wherein any (1-4C)alkyl and (1-4C)alkanoyl present in any substituent on R<sub>1a3</sub> may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

More particular values for R<sub>1a</sub> when selected from R<sub>1a3</sub> are (1-10C)alkyl {optionally  
 10 substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)(OH)<sub>2</sub>], and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub>] and mono- and di-(1-4C)alkoxy derivatives thereof], carboxy, amino, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkylS(O)<sub>q</sub>  
 15 (preferably where q=2), AR<sub>2</sub> and AR<sub>2b</sub>. More particular values for R<sub>1a</sub> when selected from R<sub>1a3</sub> are (1-6C)alkyl substituted as hereinbefore described. Even more particular values for R<sub>1a</sub> when selected from R<sub>1a3</sub> are (1-4C)alkyl substituted as hereinbefore described.

Particular values for substituents on a (1-10C)alkyl, (1-6C)alkyl or (1-4C)alkyl group comprising R<sub>1a3</sub> are hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-  
 20 (1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)(OH)<sub>2</sub>], and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub>] and mono- and di-(1-4C)alkoxy derivatives thereof] and carboxy. Preferably R<sub>1a3</sub> is a (1-4C)alkyl group substituted with 1 or 2 hydroxy groups.

Particular values for R<sub>1a</sub> when selected from R<sub>1a4</sub> are R<sub>14</sub>C(O)O(1-6C)alkyl- wherein  
 25 R<sub>14</sub> is selected from AR<sub>1</sub>, AR<sub>2</sub>, AR<sub>2a</sub>, AR<sub>2b</sub> and (1-10C)alkyl (optionally substituted by one or more substituents independently selected from OH and di (1-4C)alkylamino. More particular values for R<sub>14</sub> are AR<sub>2a</sub>, AR<sub>2b</sub> and (1-6C)alkyl substituted with hydroxy. More particular values for R<sub>14</sub> are AR<sub>2a</sub>, AR<sub>2b</sub> and (1-4C)alkyl substituted with hydroxy.

Particular values for R<sub>1a</sub> when selected from R<sub>1a5</sub> are fluoro, chloro and hydroxy.

30 Particular values for other substituents (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter) are :-

- a) in one aspect R<sub>7</sub> and R<sub>8</sub> are independently H or (1-4C)alkyl
- b) in a further aspect R<sub>7</sub> and R<sub>8</sub> taken together with the nitrogen to which they are

attached form a 5-7 membered ring, optionally substituted as defined hereinbefore or hereinafter

- c) preferably  $R_7$  and  $R_8$  taken together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring, more preferably a pyrrolidinyl or  
5 piperidinyl ring.
- d) preferable optional substituents on  $R_7$  and  $R_8$  as a pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl ring are (1-4C)alkyl and (1-4C)alkanoyl, wherein the (1-4C)alkyl or (1-4C)alkanoyl group itself may be optionally substituted with one or two substituents selected from hydroxy, amino, (1-4C)alkylamino and di(1-4C)alkylamino
- 10 e) In one aspect  $R_9$  is selected from  $R_{9a}$ , preferably selected from AR2, AR2a and AR2b
- f) In another aspect  $R_9$  is selected from  $R_{9b}$ , preferably selected from  $-C(=W)NR_vR_w$ , wherein wherein W is O,  $R_v$  and  $R_w$  are independently H, or (1-4C)alkyl and wherein  $R_v$  and  $R_w$  taken together with the amide nitrogen to which they are attached can form a morpholine, pyrrolidine, piperidine or piperazine ring; wherein when said ring is a piperazine ring, the ring  
15 may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl and (1-4C)alkanoyl, and wherein any (1-4C)alkyl and (1-4C)alkanoyl may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present
- 20 g) In a further aspect  $R_9$  is selected from  $R_{9c}$ , wherein  $R_{9c}$  is (1-6C)alkyl {optionally substituted by one, two or three groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl  $[-O-P(O)(OH)_2]$ , and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl  $[-O-P(OH)_2]$  and mono- and di-(1-4C)alkoxy  
25 derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-,  $-C(=W)NR_vR_w$  [wherein W is O,  $R_v$  and  $R_w$  are independently H,  
30 or (1-4C)alkyl and wherein  $R_v$  and  $R_w$  taken together with the amide nitrogen to which they are attached can form a morpholine, pyrrolidine, piperidine or piperazine ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl and (1-4C)alkanoyl], (1-4C)alkylS(O) $_q$ - ( $q$  is 0, 1 or 2),

- AR2, AR2-O-, AR2-NH-, and also AR2a, AR2b versions of AR2 containing groups}; wherein any (1-4C)alkyl and (1-4C)alkanoyl present in any substituent on R<sub>9c</sub> may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present.
- h) In a further aspect R<sub>9</sub> is selected from R<sub>9c</sub>, wherein R<sub>9c</sub> is (1-6C)alkyl {optionally substituted by one, two or three groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)(OH)<sub>2</sub>], and mono- and di-(1-4C)alkoxy derivatives thereof}, phosphiryl [-O-P(OH)<sub>2</sub>] and mono- and di-(1-4C)alkoxy derivatives thereof}, carboxy, amino, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkylS(O)<sub>q</sub> (preferably where q=2), AR2 and AR2b. More particular values for R<sub>9c</sub> is (1-4C)alkyl, optionally substituted as hereinbefore described.
- i) In a further aspect R<sub>9</sub> is selected from R<sub>9d</sub> wherein R<sub>9d</sub> is R<sub>14</sub>C(O)O(1-6C)alkyl- and R<sub>14</sub> is selected from AR1, AR2, AR2a, AR2b and (1-10C)alkyl (optionally substituted by one or two substituents independently selected from OH and di(1-4C)alkylamino). Particular values for R<sub>14</sub> are AR2a, AR2b and (1-6C)alkyl substituted with hydroxy. More particular values for R<sub>14</sub> are AR2a, AR2b and (1-4C)alkyl substituted with hydroxy.
- j) Particular values for R<sub>21</sub> is R<sub>14</sub>C(O)O(2-6C)alkyl-, wherein R<sub>14</sub> is preferably selected from AR1, AR2, AR2a, AR2b and (1-10C)alkyl (optionally substituted by one or two substituents independently selected from OH and di(1-4C)alkylamino).
- k) Further particular values for R<sub>21</sub> are (2-10C)alkyl, optionally substituted other than on a carbon attached to the HET-3 ring nitrogen with one or two groups independently selected from the optional substituents defined hereinbefore or hereinafter for R<sub>1a3</sub>; further particular values for R<sub>21</sub> are optionally substituted (2-6C)alkyl, more particularly optionally substituted (2-4C)alkyl.
- l) Particular substituents for a (2-6C)alkyl or (2-4C)alkyl group comprising R<sub>21</sub> are 1 or 2 substituents independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)(OH)<sub>2</sub>], and mono- and di-(1-4C)alkoxy derivatives thereof}, phosphiryl [-O-P(OH)<sub>2</sub>] and mono- and di-(1-4C)alkoxy derivatives thereof}, carboxy, amino, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkylS(O)<sub>q</sub> (preferably where q=2), AR2 and AR2b
- m) Further particular values for substituents on a (2-6C)alkyl or (2-4C)alkyl group

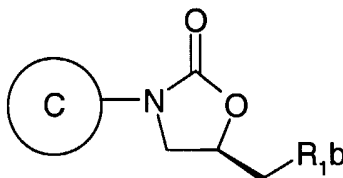
comprising  $R_{21}$  are 1 or 2 substituents independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)(OH)<sub>2</sub>], and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinoyl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof] and carboxy. Preferably substituents on a (2-6C)alkyl or (2-4C)alkyl group comprising  $R_{21}$  are 1 or 2 hydroxy groups.

n) Preferably  $R_{22}$  is cyano.

o) Particularly preferred values for AR<sub>2</sub>, AR<sub>2a</sub> and AR<sub>2b</sub> groups are those containing a basic nitrogen, for example pyridine, pyrrolidine, piperazine and piperidine, optionally substituted as hereinbefore defined.

10

In one embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof,



15

(Ia)

wherein group C is group D;  $R_{2a}$  and  $R_{6a}$  are both hydrogen;  $R_{2b}$  and  $R_{6b}$  are independently hydrogen or fluorine; and  $R_4$  is selected from HET-3.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D;  $R_{2a}$  and  $R_{6a}$  are both hydrogen;  $R_{2b}$  and  $R_{6b}$  are independently hydrogen or fluorine; and  $R_4$  is selected from HET3-T, HET3-U, HET3-V, HET3-W, HET3-X and HET3-Y.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D;  $R_{2a}$  and  $R_{6a}$  are both hydrogen;  $R_{2b}$  and  $R_{6b}$  are independently hydrogen or fluorine; and  $R_4$  is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D;  $R_{2a}$  and  $R_{6a}$  are both hydrogen;  $R_{2b}$  and  $R_{6b}$  are independently hydrogen or

30

fluorine; R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH; m=1 and R<sub>1a</sub> is selected from R<sub>1a3</sub>.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is  
5 group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine; and R<sub>4</sub> is selected from HET3-T, HET3-U, HET3-V, HET3-W, HET3-X and HET3-Y.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine;  
10 and R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine;  
15 R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH; m=1 and R<sub>1a</sub> is selected from R<sub>1a3</sub>.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or  
20 fluorine; R<sub>4</sub> is selected from HET3-T, HET3-U, HET3-V, HET3-W, HET3-X and HET3-Y, and R<sub>1b</sub> is -NHC(O)R<sub>24</sub>.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or  
25 fluorine; and R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH, and R<sub>1b</sub> is -NHC(O)R<sub>24</sub>.

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or  
30 fluorine; R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH; m=1, R<sub>1a</sub> is selected from R<sub>1a3</sub>, and R<sub>1b</sub> is -NHC(O)R<sub>24</sub>.

In another embodiment is provided a compound of the formula (Ia) or a



pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine; and R<sub>4</sub> is selected from HET3-T, HET3-U, HET3-V, HET3-W, HET3-X and HET3-Y, and R<sub>1b</sub> is -NHC(O)R<sub>24</sub>.

5 In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine; and R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH, and R<sub>1b</sub> is -NHC(O)R<sub>24</sub>.

10 In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine; R<sub>4</sub> is selected from HET3-Z, HET3-AA, HET3-AB, HET3-AC, HET3-AD, HET3-AE, HET3-AF, HET3-AG and HET3-AH; m=1, R<sub>1a</sub> is selected from R<sub>1a3</sub>, and R<sub>1b</sub> is

15 -NHC(O)R<sub>24</sub>

In another embodiment is provided a compound of the formula (Ia) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E; R<sub>2a</sub> and R<sub>6a</sub> are both hydrogen; R<sub>2b</sub> and R<sub>6b</sub> are independently hydrogen or fluorine; R<sub>4</sub> is HET3-V, R<sub>1b</sub> is -NHC(O)R<sub>24</sub>, R<sub>24</sub> is cyclopropyl, methoxy or methylthio.

20 In all of the above definitions the preferred compounds are as shown in formula (Ia).

Particular compounds of the present invention include each individual compound described in the Examples, each of which provides a separate aspect of the invention.

#### Process section:

25 In a further aspect the present invention provides a process for preparing a compound of invention or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and

30 later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in

the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it  
5 may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection  
10 conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid  
15 as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by  
20 treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl  
25 group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group,  
30 for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic

acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon. Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

5           A compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the  
10 following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of  
15 an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the certain Patent Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference; for example WO 94-13649; WO 98-54161; WO 99-64416; WO 99-64417; WO 00-21960; WO 01-40222.

20           In particular we refer to our PCT patent applications WO 99/64417 and WO 00/21960 wherein detailed guidance is given on convenient methods for preparing oxazolidinone compounds.

          The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the  
25 Examples herein, to obtain necessary starting materials, and products. For example, the skilled chemist will be able to apply the teaching herein for compounds of formula (I) in which two central phenyl groups are present (that is when group C is group D) to prepare compounds in which group C is any of groups E to L as hereinbefore defined. Similarly, in the processes illustrated below the skilled chemist will be able to apply the teaching as  
30 necessary to prepare compounds in which both rings A and B are isoxazoline and those compounds in which one of rings A and B is isoxazoline and the other oxazolidinone.

          Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and in-vivo hydrolysable esters thereof, can be prepared by

a process (a) to (f); and thereafter if necessary:

- i) removing any protecting groups;
- ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or
- iii) forming a pharmaceutically-acceptable salt;

5 wherein said processes (a) to (f) are as follows (wherein the variables are as defined above unless otherwise stated):

- a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees or Advanced  
10 Organic Chemistry (Wiley-Interscience), Jerry March or Houben-Weyl, Methoden der Organischen Chemie); for example:

an acylamino group may be converted into a thioacylamino group either directly or through the intermediacy of the corresponding amino group;

- an acylamino group or thioacylamino group may be converted into another acylamino or  
15 thioacylamino; heterocyclyl for instance tetrazolyl or thiazolyl, or heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom) either directly or through the intermediacy of the corresponding amino group;

an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy

20 group);

an alkyl halide such as alkylbromide or alkyliodide may be converted into an alkyl fluoride or nitrile;

an alkyl sulfonate such as alkyl methanesulfonate may be converted into an alkyl fluoride or nitrile;

- 25 an alkylthio group such as methylthio may be converted into a methanesulfinyl or methanesulfonyl group;

an arylthio group such as phenylthio may be converted into a benzenesulfinyl or benzenesulfonyl group;

- an amidino or guanidino group may be converted into a range of 2-substituted 1,3-diazoles  
30 and 1,3-diazines;

an amino group may be converted for instance into acylamino or thioacylamino for instance an acetamide (optionally substituted), alkyl- or dialkyl-amino and thence into a further range

of N-alkyl-amine derivatives, sulfonylamino, sulfinylamino, amidino, guanidino, arylamino, heteroarylamino;

an aryl- or heteroaryl-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling

5 into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino substituted aryl or heteroaryl groups;

an aryl- or heteroaryl-sulfonate group such as an aryl- or hetero-aryl trifluoromethanesulfonate may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino

10 substituted aryl or heteroaryl groups;

an aryl- or heteroaryl-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of trialkyltin, dialkylboronate, trialkoxysilyl, substituted aryl or heteroaryl groups useful as intermediates for the synthesis of compounds of the invention;

15 an azido group may be converted for instance into a 1,2,3-triazolyl or amine and thence by methods that are well known in the art into any of the range common amine derivatives. such as acylamino for instance acetamido group;

a carboxylic acid group may be converted into trifluoromethyl, hydroxymethyl, alkoxycarbonyl, aminocarbonyl optionally substituted on nitrogen, formyl, or acyl groups;

20 a cyano group may be converted into a tetrazole, or an imidate, an amidine, an amidrazone, an N-hydroxyamidrazone, an amide, a thioamide, an ester, or an acid and thence by methods that are well known in the art into any of the range of heterocycles derived from such nitrile derivatives;

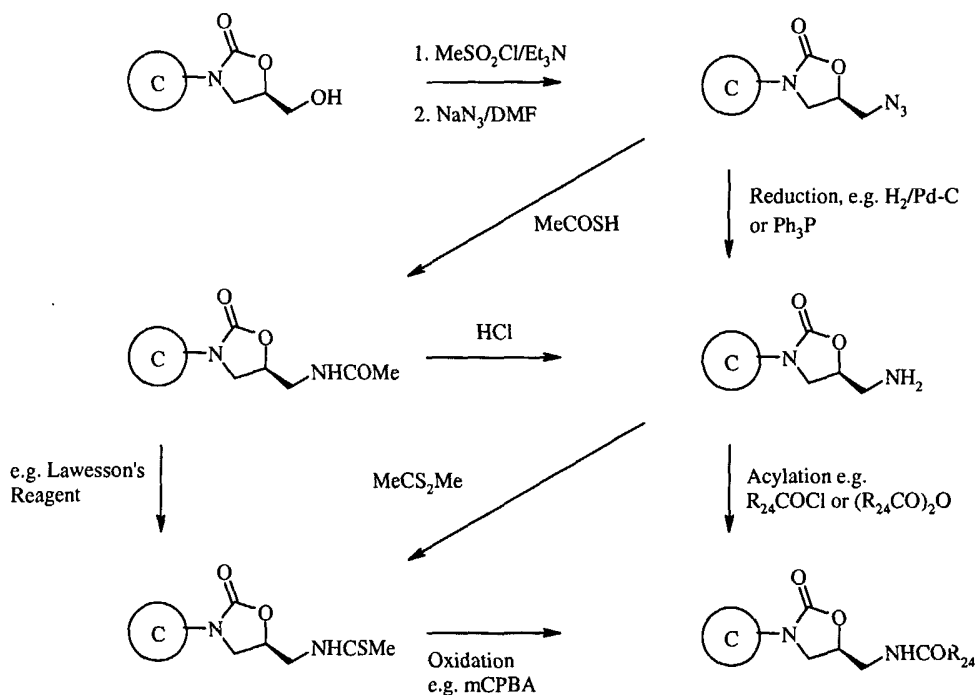
a hydroxy group may be converted for instance into an alkoxy, cyano, azido, alkylthio, keto

25 and oximino, fluoro, bromo, chloro, iodo, alkyl- or aryl-sulfonyloxy for instance trifluoromethanesulfonate, methanesulfonate, or tosylsulfonate, silyloxy ; acylamino or thioacylamino , for instance an acetamide (optionally substituted or protected on the amido-nitrogen atom); acyloxy, for instance an acetoxy; phosphono-oxy group; such conversions of the hydroxy group taking place directly (for instance by acylation or Mitsunobu reaction) or  
30 through the intermediacy of one or more derivatives (for instance a mesylate or an azide);

a silyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);

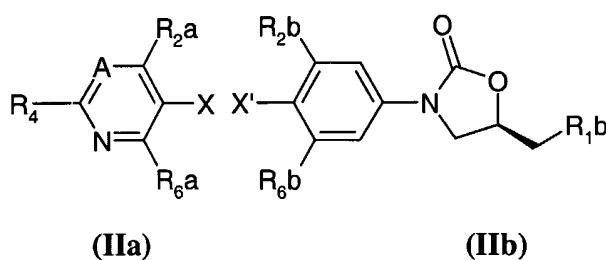
a keto group may be converted into a hydroxy, thiocarbonyl, oximino, or difluoro group;  
 a nitro-group may be converted into an amino group and thence by methods that are well known in the art into any of the range common amine derivatives such as acylamino for instance acetamido group;

- 5 a 2-, 4-, or 6-pyridyl or 2-, 4-, or 6-pyrimidyl halide such as chloride or sulfonate such as mesylate substituent may be converted into alkoxy, alkythio, amino, alkylamino, dialkylamino, or N-linked heterocyclic substituents;  
 moreover, an optionally substituted heteroaromatic ring D or E may be converted into another heteroaromatic ring D or E by introduction of a new substituent ( $R_{2a}$ ,  $R_{3a}$ , or  $R_{6a}$ ) or by  
 10 refunctionalisation of an existing substituent ( $R_{2a}$ ,  $R_{3a}$ , or  $R_{6a}$ );  
 a heterocyclyl group linked through nitrogen may be converted into another heterocyclyl group linked through nitrogen by introduction of a new ring substituent or by refunctionalisation of an existing ring substituent;  
 for instance, examples drawn from the methods for conversion of an amino group into an  
 15 amido- or thioamido-group are illustrated by the scheme:



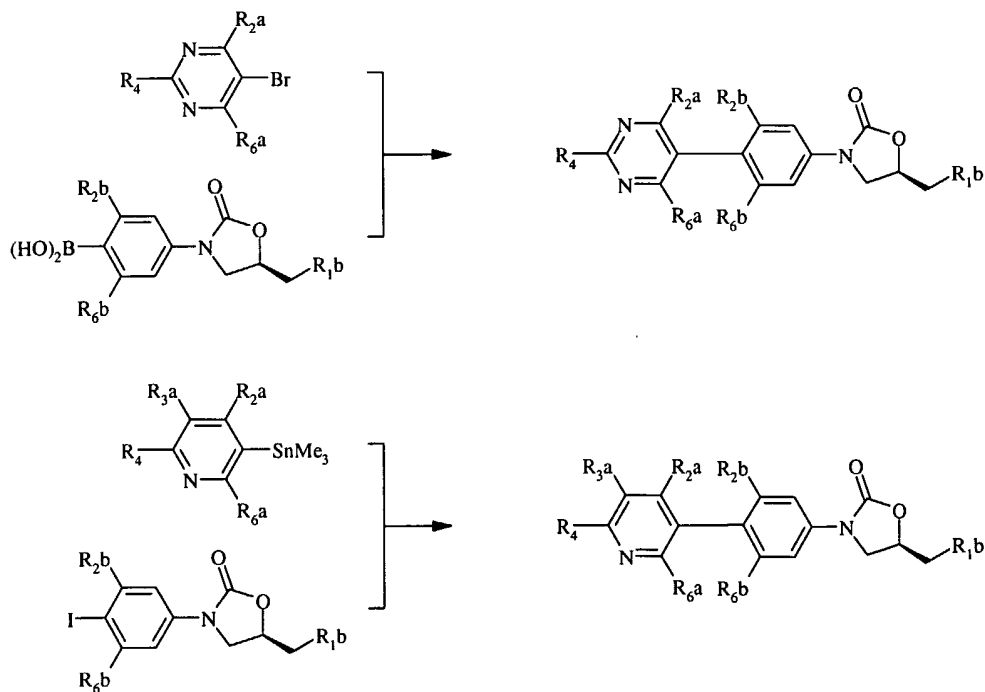
- b) by reaction of a molecule of a compound of formula (IIa) [wherein X is a leaving group useful in palladium coupling (for example chloride, bromide, iodide,  
 20 trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue) and in this instance A is either N or C- $R_{3a}$ ] with a molecule of a compound of formula (IIb) (wherein

X' is a leaving group useful in palladium coupling, for example chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue) wherein X and X' are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds. Such methods are now well known, see for instance J.K. Stille, *Angew Chem. Int. Ed. Eng.*, **1986**, 25, 509-524; N. Miyaura and A Suzuki, *Chem. Rev.*, **1995**, 95, 2457-2483, D. Baranano, G. Mann, and J.F. Hartwig, *Current Org. Chem.*, **1997**, 1, 287-305, S.P. Stanforth, *Tetrahedron*, 54 **1998**, 263-303, and P.R. Parry, C. Wang, A.S. Batsanov, M.R. Bryce, and B. Tarbit, *J. Org. Chem.*, **2002**, 67, 7541-7543;



the leaving groups X and X' are chosen to be different and to lead to the desired cross-coupling products of formula (I);

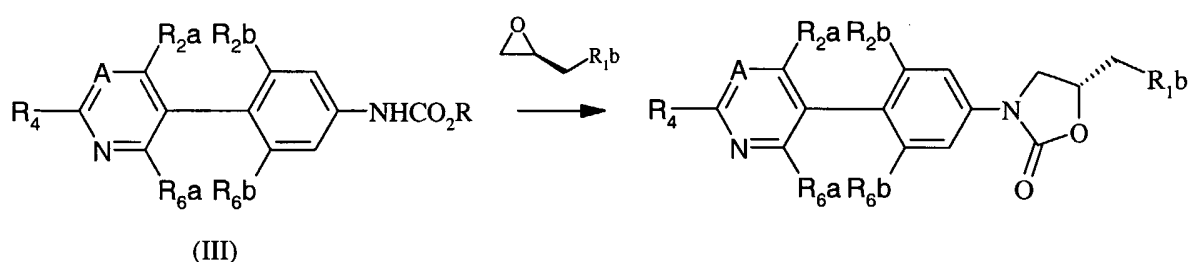
for example



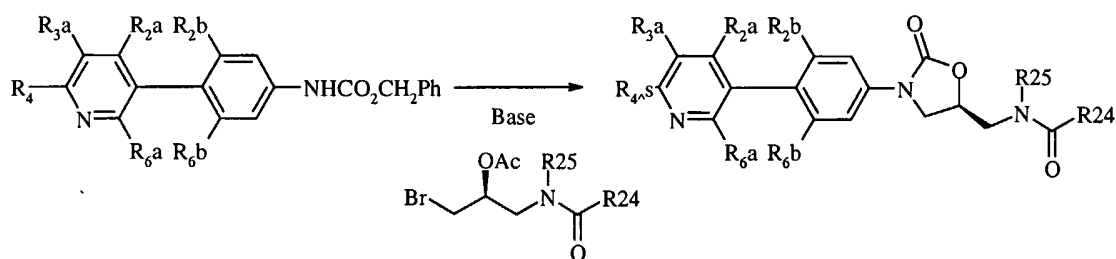
the pyridines, pyrimidines, and aryl oxazolidinones required as reagents for process b) or as intermediates for the preparation of reagents for process b) may be prepared by standard

organic methods, for instance by methods analogous to those set out in process sections c) to f), methods for the introduction and interconversion of Groups X and X' are well known in the art;

- 5 c) by reaction of a heterobiaryl derivative (III) carbamate [where in this instance A is either N or C-R<sub>3a</sub>] with an appropriately substituted oxirane to form an oxazolidinone ring;

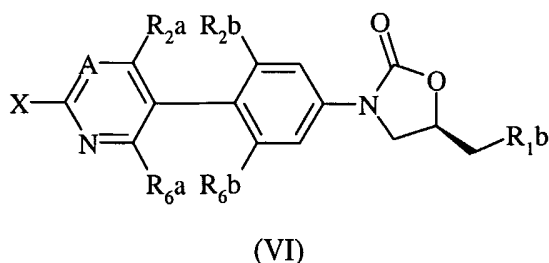


- 10 variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-CH<sub>2</sub>CH(O-optionally protected)CH<sub>2</sub>R<sub>1b</sub> where X is a displaceable group are also well known in the art; for example,



15

- (d) by reaction of a compound of formula (VI) :



- 20 where X is a replaceable substituent - such as chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue and A is either N or CR<sub>3a</sub> with a compound of the formula (VII):



- 40 -

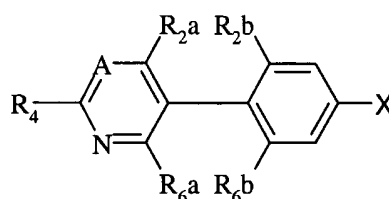
T-X'

(VII)

wherein T-X' is HET3 as herein above defined and X' is a replaceable C-linked substituent - such as chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl,

5 or a boronic acid residue; wherein the substituents X and X' are chosen to be complementary pairs of substituents known in the art to be suitable as complementary substrates for coupling reactions catalysed by transition metals such as palladium(0); or

(d(i)) by reaction catalysed by transition metals such as palladium(0) of a compound of formula (VIII):

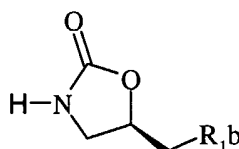


10

(VIII)

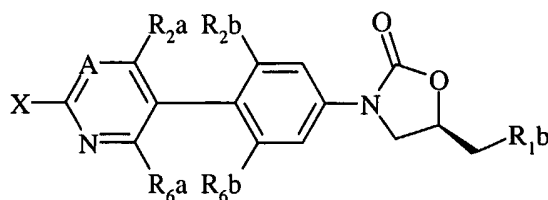
wherein X is a replaceable substituent - such as chloride, bromide, iodide, trifluoromethylsulfonyloxy, trimethylstannyl, trialkoxysilyl, or a boronic acid residue and wherein in this instance A is either N or C-R3a with a compound of the formula (IX)

15 (*Tetrahedron Letts.*, **2001**, 42(22), 3681-3684):



(IX)

(d(ii)) by reaction of a compound of formula (X):



20

(X)

wherein X is a replaceable substituent - such as chloride, bromide, iodide, trifluoromethylsulfonyloxy - and wherein in this instance A is either N or C-R3a with a compound of the formula (XI):

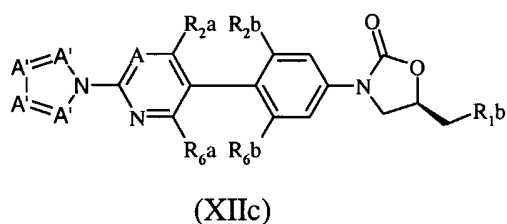
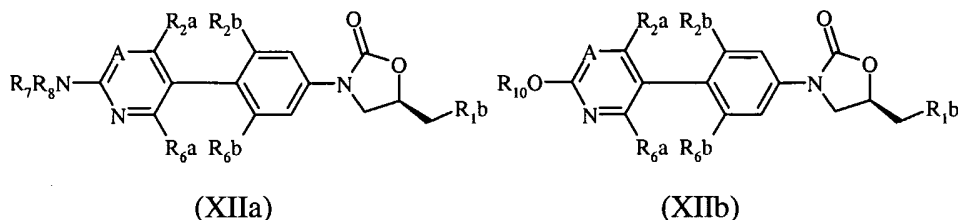
25

T-H

(XI)

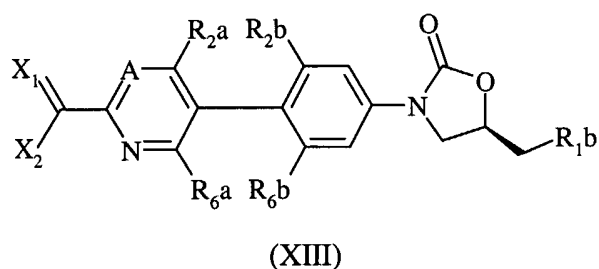
wherein T-H is an amine  $R_7R_8NH$ , an alcohol  $R_{10}OH$ , or an azole with an available ring-NH group to give compounds (XIIa), (XIIb), or (XIIc) wherein in this instance A is nitrogen or C-

5  $R_{3a}$  and A' is nitrogen or carbon optionally substituted with one or more groups  $R_{1a}$ .



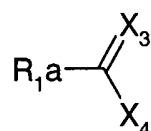
10

(e) by reaction of a compound of formula (XIII):



wherein  $X_1$  and  $X_2$  here are independently optionally substituted heteroatoms drawn in

15 combination from O, N, and S such that  $C(X_1)X_2$  constitutes a substituent that is a carboxylic acid derivative substituent and wherein in this instance A is either N or C- $R_{3a}$  with a compound of the formula (XIV) and  $X_3$  and  $X_4$  are independently optionally substituted heteroatoms drawn in combination from O, N, and S:



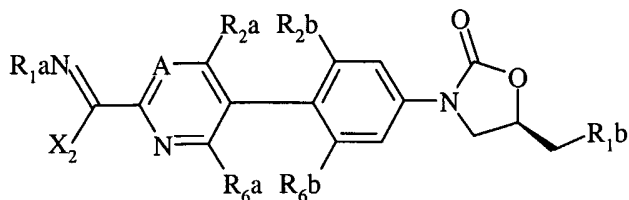
(XIV)

20

and wherein one of  $C(X_1)X_2$  and  $C(X_3)X_4$  constitutes an optionally substituted hydrazide, thiohydrazide, or amidrazone, hydroximate, or hydroxamidine and the other one of  $C(X_1)X_2$  and  $C(X_3)X_4$  constitutes an optionally substituted acylating, thioacylating, or imidoylating agent such that  $C(X_1)X_2$  and  $C(X_3)X_4$  may be condensed together to form a 1,2,4-heteroatom

5-membered heterocycle containing 3 heteroatoms drawn in combination from O, N, and S, for instance thiadiazole, by methods well-known in the art; or

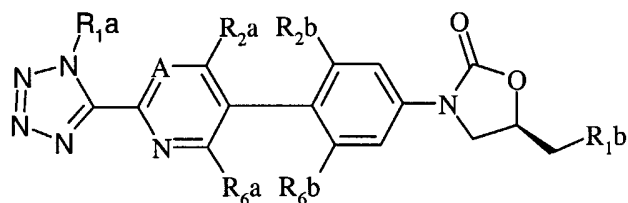
(e (i)) by reaction of a compound of formula (XV):



5

(XV)

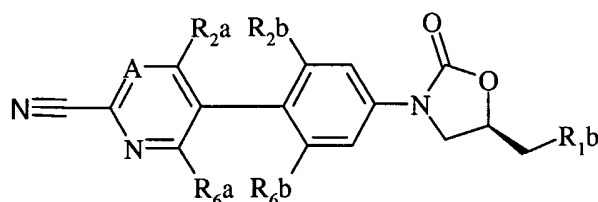
wherein  $X_2$  is a displaceable group such as ethoxy or diphenylphosphonyloxy and wherein in this instance A is either N or C- $R_3a$  with a source of azide anion such as sodium azide to give a tetrazole (XVI);



10

(XVI)

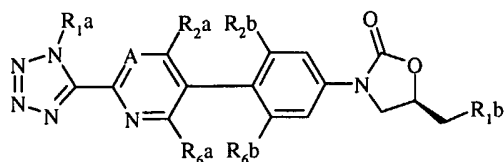
alternatively nitriles of formula (XVII)



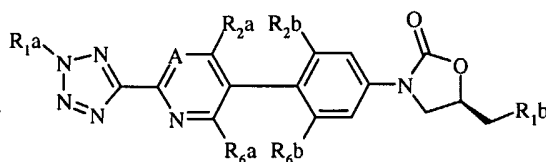
(XVII)

[wherein in this instance A is either N or C- $R_3a$ ] may be reacted directly with azides such as

15 ammonium azide or trialkylstannylazides to give tetrazoles (XVI,  $R_1a = H$ ) that are subsequently alkylated with groups  $R_1a \neq H$  to give tetrazoles (XVIIIa) and (XVIIIb) or;

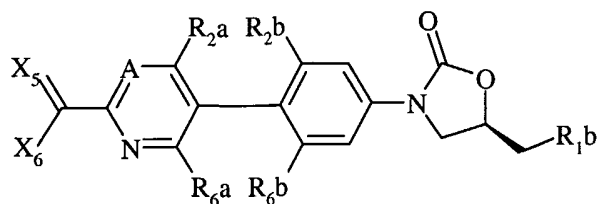


(XVIIIa)



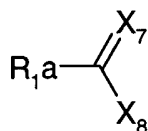
(XVIIIb)

(f) by reaction of a compound of formula (XIX):



(XIX)

[wherein in this instance A is either N or C-R<sub>3a</sub>] with a compound of the formula (XX):



(XX)

5

wherein one of C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> constitutes an optionally substituted alpha-(leaving-group-substituted)ketone, wherein the leaving group is for example a halo-group or an (alkyl or aryl)-sulfonyloxy-group, and the other one of C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> constitutes an optionally substituted amide, thioamide, or amidine, such that C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> are groups that may be condensed together to form a 1,3-heteroatom 5-membered heterocycle containing 2 heteroatoms drawn in combination from O, N, and S, for instance thiazole, by methods well-known in the art.

The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an *in vivo* hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on these steps, for example the preparation of *in-vivo* hydrolysable ester prodrugs has been provided, for example, in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the

invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such  
5 treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of  
10 a compound of the invention of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an  
15 in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical  
20 composition which comprises a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible  
25 powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration as eye-drops, for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous,  
30 subcutaneous, sub-lingual, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain (ie through co-formulation) or be co-administered

(simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example,  $\beta$ -lactams, macrolides, quinolones or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to  
5 broaden the therapeutic effectiveness. Compounds of this invention may also be co-formulated or co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents. . Compounds of this invention may also be co-formulated or co-administered with a vitamin, for example Vitamin B, such as Vitamin B2,  
10 Vitamin B6, Vitamin B12 and folic acid. Compounds of the invention may also be formulated or co-administered with cyclooxygenase (COX) inhibitors, particularly COX-2 inhibitors.

In one aspect of the invention, a compound of the invention is co-formulated with an antibacterial agent which is active against gram-positive bacteria.

15 In another aspect of the invention, a compound of the invention is co-formulated with an antibacterial agent which is active against gram-negative bacteria.

In another aspect of the invention, a compound of the invention is co-administered with an antibacterial agent which is active against gram-positive bacteria.

In another aspect of the invention, a compound of the invention is co-administered  
20 with an antibacterial agent which is active against gram-negative bacteria.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. A pharmaceutical composition to be dosed intravenously may contain  
25 advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding  
30 agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the

gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol. Solubility enhancing agents, for example cyclodextrins may be used.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 50 mg to 5 g of active



agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 200 mg to about 2 g of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in  
5 Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a  
10 compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this  
15 invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of  $0.5 \text{ mg kg}^{-1}$  to  $20 \text{ mg kg}^{-1}$  of a compound of this invention, the composition being administered 1 to 4 times per day. In another embodiment a daily dose of  $5 \text{ mg kg}^{-1}$  to  $20 \text{ mg kg}^{-1}$  of a compound of this invention is administered. The intravenous,  
20 subcutaneous and intramuscular dose may be given by means of a bolus injection.

Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

25 In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

#### Antibacterial Activity :

30 The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity

against enterococci, pneumococci and methicillin resistant strains of *S. aureus* and coagulase negative staphylococci, together with haemophilus and moraxella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of  $10^4$  CFU/spot. Typically, compounds are active in the range 0.01 to 256  $\mu\text{g/ml}$ .

Staphylococci were tested on agar, using an inoculum of  $10^4$  CFU/spot and an incubation temperature of  $37^\circ\text{C}$  for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of  $10^4$  CFU/spot and an incubation temperature of  $37^\circ\text{C}$  in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms. Fastidious Gram negative organisms were tested in Mueller-Hinton broth, supplemented with hemin and NAD, grown aerobically for 24 hours at  $37^\circ\text{C}$ , and with an inoculum of  $5 \times 10^4$  CFU/well.

For example, the following results were obtained for the compound of Example 2:

<u>Organism</u>		<u>MIC (<math>\mu\text{g/ml}</math>)</u>
Staphylococcus aureus:	MSQS	2
	MRQR	2
Streptococcus pneumoniae		0.5
Haemophilus influenzae		>64
Moraxella catarrhalis		0.5
Enterococcus faecium		1
Linezolid Resistant Streptococcus pneumoniae		4

MSQS = methicillin sensitive and quinolone sensitive

MRQR = methicillin resistant and quinolone resistant

Certain intermediates and/or Reference Examples described hereinafter are within the scope of the invention and may also possess useful activity, and are provided as a further feature of the invention.

The invention is now illustrated but not limited by the following Examples in which  
5 unless otherwise stated :-

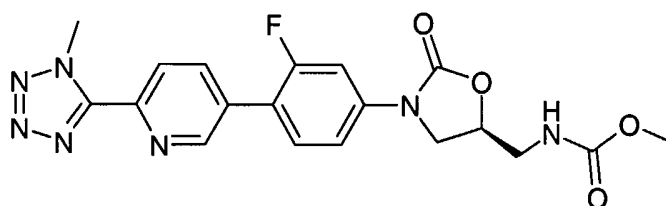
- (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;
- (ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and without exclusion of air unless otherwise stated, or unless the skilled person  
10 would otherwise work under an inert atmosphere;
- (iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structure of the end-products of the invention were generally confirmed by NMR  
15 and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-d<sub>6</sub> unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard ( $\delta$  scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB  
20 or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]; optical rotations were determined at 589nm at 20°C for 0.1M solutions in methanol using a Perkin  
25 Elmer Polarimeter 341;
- (vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;
- (vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; CDCl<sub>3</sub> is deuterated chloroform; MS is

mass spectroscopy; ESP is electrospray; EI is electron impact; CI is chemical ionisation; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is (HO)<sub>2</sub>-P(O)-O-; phosphiryl is (HO)<sub>2</sub>-P-O-; Bleach is "Clorox" 6.15% sodium hypochlorite;

5 (viii) temperatures are quoted as °C.

**Example 1: [((5*S*)-3-{3-Fluoro-4-[6-(1-methyl-1*H*-tetrazol-5-yl)pyrid-3-yl]phenyl}-1,3-oxazolidin-2-on-5-yl)methyl]carbamic acid methyl ester**



10

A stirred mixture ((5*S*)-3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolidin-2-on-5-yl)methyl]carbamic acid methyl ester (219 mg, 0.55mmol), 5-bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine (147 mg, 0.61 mmol) and sodium carbonate (235 mg, 2.2 mmol) in *N,N*-dimethylformamide:water (10:1; 5 mL) was degassed and maintained under

15 an atmosphere of nitrogen. The mixture was treated with

*tetrakis*(triphenylphosphine)palladium(0) (64 mg, 10 mol %) and then heated at 70 °C for 2 hours. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The involatile residue was fractionated by chromatography on silica gel [elution with dichloromethane:*N,N*-dimethylformamide (30:1)] to give the crude product as a solution

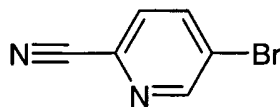
20 in eluent. The solution in eluent was concentrated to a small volume (ca. 2 mL) and then

treated with dichloromethane (5 mL) and hexanes (20 mL) to give a precipitate. The precipitate was isolated by filtration to give the title compound as a colorless solid (149 mg, 63 %).

**MS (ESP):** 428.20 (MH<sup>+</sup>) for C<sub>19</sub>H<sub>18</sub>FN<sub>7</sub>O<sub>4</sub>

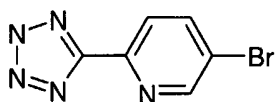
25 **<sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>)** δ: 3.37 (m, 2H); 3.53 (s, 2H); 3.84 (dd, 1H); 4.19 (dd, 1H); 4.44 (s, 3H); 4.76 (m, 1H); 7.49 (m, 1H); 7.55 (dd, 1H); 7.67 (m, 1H); 7.77 (m, 1H); 8.25-8.34 (m, 2H); 9.00 (s, 1H).

The intermediates for Example 1 were prepared as follows:

3-Bromo-6-cyano-pyridine

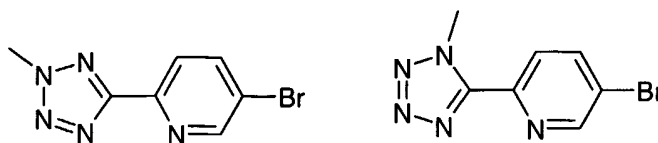
A stirred solution of 2,5-dibromopyridine (39.465 g, 0.17 mol) in anhydrous NMP (100 mL) was treated with CuCN (14.42 g, 0.17 mol) for 20 hours at 110°C under nitrogen. The reaction mixture was cooled to 40°C and treated with aqueous sodium hydroxide (2M; 200 mL) and then with ethyl acetate (200 mL). The mixture was stirred for 1 hour and then filtered through Celite to remove the resulting precipitate. The retained solid was washed with aqueous sodium hydroxide (2M; 600 mL) and then with ethyl acetate (600 mL). The organic layers were combined and washed with aqueous ammonium hydroxide (5M; 800 mL), dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The involatile residue was purified by chromatography on silica gel [elution gradient 1% to 7% of ethyl acetate in hexanes] to give the title compound (8.538 g, 28%), as a colorless amorphous solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) (300 MHz) δ 8.05 (d, 1H); 8.40 (dd, 1H); 8.95 (d, 1H).

5-Bromo-2-tetrazol-5-ylpyridine

A mixture of 3-bromo-6-cyano-pyridine (2 g, 10.9 mmol), sodium azide (0.85 g, 13 mmol), and ammonium chloride (0.59 g, 11 mmol) in *N,N*-dimethylformamide (20 mL) was heated for 1 h at 120 °C. The reaction mixture was diluted with ethyl acetate (~100 mL) and the product was isolated by filtration and then washed with ethyl acetate to give the title compound, an off-white amorphous solid which was used in the next step without further purification.

5-Bromo-2-(2-methyl-2H-tetrazol-5-yl)pyridine and 5-bromo-2-(1-methyl-1H-tetrazol-5-yl)pyridine



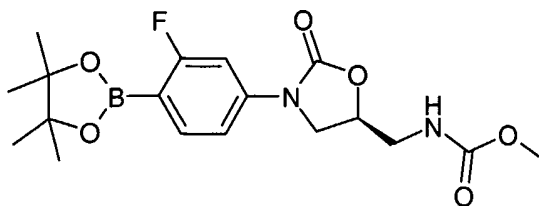
5-Bromo-2-(2-methyl-2*H*-tetrazol-5-yl)pyridine and 5-bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine were prepared according to the procedure described by Dong A Pharmaceuticals (WO 01/94342).

5 A mixture of 6.5 g unpurified 5-bromo-2-tetrazol-5-ylpyridine [Dong A Pharmaceuticals (WO 01/94342)] (~28 mmol) and sodium hydroxide (9 g, 125 mmol) in dry DMF was evaporated to dryness under reduced pressure. A stirred solution of the involatile residue in dry DMF (50 mL) was treated dropwise at ice-bath temperature with iodomethane (3.0 mL, 48 mmol). The stirred reaction mixture was allowed to warm and then maintained at room temperature for 2  
10 hours. The reaction mixture was partitioned between iced water and ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate, and then evaporated under reduced pressure to give a residue that was purified by chromatography on silica gel [elution with dichloromethane:ethyl acetate (60:1)] to give:

1. 5-bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine (1.397 g), a colorless solid, (TLC: silica-gel, hexanes:ethyl acetate (4:1), R<sub>f</sub> : 0.3), <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) (300 MHz) δ: 4.38 (s, 3H); 8.17 (d, 1H); 8.35 (dd, 1H); 8.96 (d, 1H).
  2. 5-bromo-2-(2-methyl-2*H*-tetrazol-5-yl)pyridine (1.07 g), a colorless solid, (TLC: silica-gel, hexanes:ethyl acetate (4:1), R<sub>f</sub>: 0.1). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) (300 MHz) δ 4.46 (s, 3H); 8.09 (d, 1H); 8.28 (dd, 1H); 8.88 (d, 1H).
- 20 Structure assignment based on nmr HMBC experiments, in which long range coupling of the protons of CH<sub>3</sub> to the C5 of the tetrazole ring is observed in the 1-methyl-1*H*-isomer of R<sub>f</sub> 0.3, but not in the 2-methyl-2*H*-isomer of R<sub>f</sub> 0.1). The compound referred to as 5-bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine is thus the isomer of R<sub>f</sub> 0.3 and the compound referred to as 5-bromo-2-(2-methyl-2*H*-tetrazol-5-yl)pyridine is thus the isomer of R<sub>f</sub> 0.1

25

((1*S*)-3-[3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-oxazolidin-2-on-5-yl)methyl carbamic acid methyl ester

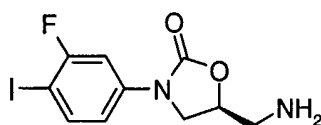


A stirred solution of (5*S*)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-on-5-ylmethylcarbamic acid methyl ester (285 mg, 0.72 mmol), *bis*(pinacolato)diboron (459 mg, 1.8 mmol) and potassium acetate (248 mg, 2.5 mmol) in dimethylsulfoxide (7 mL) was degassed and maintained under an atmosphere of nitrogen. The mixture was treated with dichloro[1,1']*bis*(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (40 mg, 0.05 mmol) and then heated to 80°C for 4 hours. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (2 x) and the combined organic layers were washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The involatile residue was purified by chromatography on silica gel [elution with hexanes:ethyl acetate (1:1) and then hexanes:acetone (2:1)] to give the title compound (221 mg, 78%).

MS (ESP): 395.14 (MH<sup>+</sup>) for C<sub>18</sub>H<sub>24</sub>BFN<sub>2</sub>O<sub>6</sub>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.28 (s, 12H); 3.34 (m, 2H); 3.52 (s, 3H); 3.77 (dd, 1H); 4.12 (dd, 1H); 4.72 (m, 1H); 7.32 (m, 1H); 7.42 (m, 1H); 7.53 (dd, 1H); 7.63 (m, 1H).

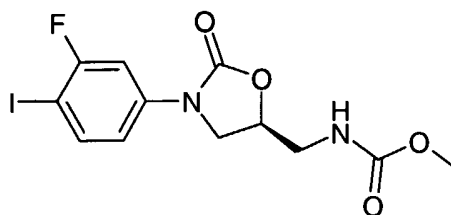
(5*S*)-5-(Aminomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one



A suspension of *N*-{[(5*S*)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-on-5-yl]methyl}acetamide (15.00 g, 40.00 mmol) in methanol (475 ml) and hydrochloric acid (6*N*, 475 ml) was heated at 65 °C for *ca.* 5 days and then cooled to 0 °C. The product crystallized and was collected by filtration to give the title compound (6.14 g).

MS (ESP): 337 (M + 1) for C<sub>10</sub>H<sub>10</sub>FIN<sub>2</sub>O<sub>2</sub>

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ: 3.17-3.29 (m, 2H); 3.89 (dd, 1H); 4.19 (t, 1H); 4.99 (m, 1H); 7.17 (dd, 1H); 7.55 (dd, 1H); 7.85 (t, 1H); 8.46 (br s, 2H).

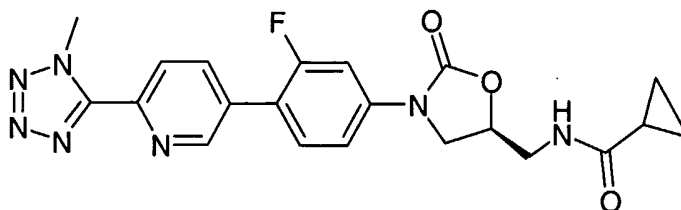
[[*(5S)*-3-(3-Fluoro-4-iodophenyl)oxazolidin-2-on-5-yl]methyl] carbamic acid methyl ester

A stirred suspension of (*5S*)-5-(aminomethyl)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (2.00 g, 5.95 mmol) in dichloromethane (20 ml) and pyridine (1.00 ml, 12.36 mmol) was treated dropwise at 0 °C with methyl chloroformate (0.60 ml, 7.76 mmol). The reaction mixture was stirred at 0 °C for 1 hour, then warmed to room temperature and stirred for a further *ca.* 16 hours. The reaction mixture was partitioned between water and ethyl acetate and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed sequentially with brine and saturated aqueous ammonium chloride solution, dried over MgSO<sub>4</sub>, and concentrated under vacuum to give the title compound (1.3 g) sufficiently pure for use in the subsequent step.

MS (ESP): 395 (M + 1) for C<sub>12</sub>H<sub>12</sub>FIN<sub>2</sub>O<sub>4</sub>

<sup>1</sup>H-NMR (300 MHz, DMSO-d<sub>6</sub>) δ: 3.37 (m, 2H overlapping with water); 3.53 (s, 3H); 3.77 (dd, 1H); 4.11 (t, 1H); 4.74 (m, 1H); 7.19 (dd, 1H); 7.55 (dd, 1H); 7.83 (dd, 1H).

**Example 2: *N*-[[*(5R)*-3-[3-Fluoro-4-[6-(1-methyl-1*H*-1,2,3,4-tetrazol-5-yl)-3-pyridinyl]phenyl]oxazolidin-2-on-5-yl]methyl] cyclopropanecarboxamide**



A stirred solution of [[*(5R)*-3-(3-fluoro-4-iodophenyl)-oxazolidin-2-on-5-yl]methyl] cyclopropanecarboxamide (290 mg, 0.72 mmol), *bis*(pinacolato)diboron (456 mg, 1.8 mmol) and potassium acetate (247 mg, 2.52 mmol) in methylsulfoxide (5 mL) was degassed and maintained under an atmosphere of nitrogen. The mixture was treated with dichloro[1,1']bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (40 mg, 0.05 mmol) and then heated to 75°C for 1 hours. The reaction mixture was cooled to



room temperature, diluted with ethyl acetate, filtered through Celite, washed sequentially with water and brine, and then dried over sodium sulfate. Solvent was evaporated under reduced pressure and the involatile residue was purified by chromatography on silica gel [elution with hexanes:ethyl acetate (1:1)] to give the pinacolatoboronate corresponding to the iodo-starting material (280 mg), which was used without further characterization in the next step.

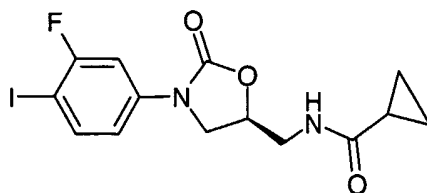
A stirred mixture of the pinacolatoboronate obtained above, 5-bromo-[2-(1-methyl-1H-1,2,3,4-tetrazol-5-yl)]pyridine (175 mg, 0.73 mmol), and potassium carbonate (479 mg, 3.47 mmol) in *N,N*-dimethylformamide:water (8 mL, 7:1) was degassed and then maintained under an atmosphere of nitrogen. The mixture was treated with *Tetrakis*(triphenylphosphine)palladium (0) (84 mg, 10 mol %) and then heated at 75 °C for 1.5 hours. The reaction mixture was cooled to room temperature, filtered through Celite, and then the filtrate was reduced under vacuum to a solution of crude product in a small volume of DMF (~1.5 mL). The solution of crude product was diluted with dichloromethane (3 mL) and purified by chromatography on silica gel [elution with dichloromethane:*N,N*-dimethylformamide (20:1) to give the title compound (135 mg, 43 % from the iodide) as a colourless amorphous solid.

MS (ESP): 438.29 (MH<sup>+</sup>) for C<sub>21</sub>H<sub>20</sub>FN<sub>7</sub>O<sub>3</sub>

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.62 (m, 4H); 1.59 (m, 1H); 3.47 (dd, 2H); 3.81 (dd, 1H); 4.19 (dd, 1H); 4.45 (s, 3H); 4.78 (m, 1H); 7.50 (m, 1H); 7.68 (dd, 1H); 7.78 (m, 1H); 8.25-8.35 (m, 2H); 8.49 (dd, 1H); 9.01 (s, 1H).

The intermediate for Example 2 was prepared as follows:

[[[(5*R*)-3-(3-Fluoro-4-iodophenyl)oxazolidin-2-on-5-yl]methyl] cyclopropanecarboxamide



25

A stirred mixture of [[[(5*R*)-3-(3-fluoro-4-iodophenyl)oxazolidin-2-on-5-yl]methyl] amine (306 mg, 0.91 mmol), cyclopropanecarboxylic acid chloride (286 mg, 2.73 mmol), and triethylamine (0.7 mL, 5 mmol) in dichloromethane (10 mL) was maintained at room temperature for 30 minutes, quenched with water, washed with brine, and dried over

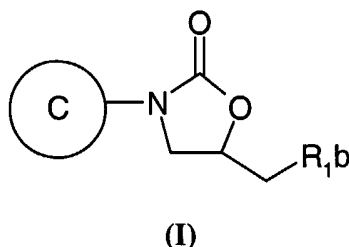
magnesium sulfate. Solvent was removed under reduced pressure and the residual in volatile product was purified by precipitation from dichloromethane by addition of hexanes to give the title compound (290 mg) sufficiently pure for use in the next step.

MS (ESP): 405.02 (MH<sup>+</sup>) for C<sub>14</sub>H<sub>14</sub>FIN<sub>2</sub>O<sub>3</sub>

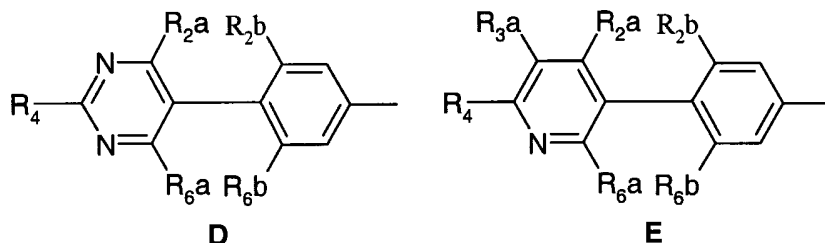
**Claims**

1. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

5



wherein C is selected from D and E,



10

wherein in D and E the phenyl ring is attached to the oxazolidinone in (I);

$R_{1b}$  is  $-NR_{25}C(=W)R_{24}$  ;

wherein W is O or S;

- 15  $R_{24}$  is hydrogen, amino, (2-6C)alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, azido and cyano), methyl (substituted by 1, 2 or 3 substituents independently selected from methyl, chloro, bromo, fluoro, methoxy, methylthio, hydroxy, benzyloxy, ethynyl, (1-4C)alkoxycarbonyl, azido and cyano), 5-halo-2-thienyl,  $-NHR_{26}$ ,  $-N(R_{26})(R_{27})$ ,  $-OR_{26}$  or
- 20  $-SR_{26}$ , (2-4C)alkenyl,  $-(1-8C)alkylaryl$ , per-halo(1-8C)alkyl,  $-(CH_2)_p(3-6C)cycloalkyl$  or  $-(CH_2)_p(3-6C)cycloalkenyl$  wherein p is 0, 1 or 2;
- $R_{25}$  is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl),  $-CO_2R_{28}$ ,  $-C(=O)R_{28}$ ,  $-C(=O)SR_{28}$ ,  $-C(=S)R_{29}$ ,  $P(O)(OR_{29})(OR_{30})$  and
- 25  $-SO_2R_{31}$ , wherein  $R_{28}$ ,  $R_{29}$ ,  $R_{30}$  and  $R_{31}$  are as defined hereinbelow;
- $R_{28}$  is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy,

- cyano, up to 3 halogen atoms and  $-NR_{15}R_{16}$  (wherein  $R_{15}$  and  $R_{16}$  are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for
- 5 any  $N(R_{15})(R_{16})$  group,  $R_{15}$  and  $R_{16}$  may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring));
- $R_{29}$  and  $R_{30}$  are independently selected from hydrogen and (1-4C)alkyl;
- $R_{31}$  is (1-4C)alkyl or phenyl;
- $R_{26}$  and  $R_{27}$  are independently selected from hydrogen, phenyl (optionally substituted with one
- 10 or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any  $N(R_{26})(R_{27})$  group,  $R_{26}$  and  $R_{27}$  may additionally be taken together with the nitrogen atom to which they are attached to form an unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl ring, which ring may be optionally
- 15 substituted by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl,  $-COO(1-4C)alkyl$ ,  $-S(O)_n(1-4C)alkyl$  (wherein  $n = 1$  or  $2$ ),  $-COOAR1$ ,  $-CS(1-4C)alkyl$  and  $-C(=S)O(1-4C)alkyl$ ;
- $R_{2a}$  and  $R_{6a}$  are independently selected from H,  $CF_3$ , OMe, SMe, Me and Et;
- $R_{2b}$  and  $R_{6b}$  are independently selected from H, F, Cl,  $CF_3$ , OMe, SMe, Me and Et;
- 20  $R_{3a}$  is selected from H, (1-4C)alkyl, cyano, Br, F, Cl, OH, (1-4C)alkoxy,  $-S(O)_n(1-4C)alkyl$  (wherein  $n = 0, 1, \text{ or } 2$ ), amino, (1-4C)alkylcarbonylamino, nitro,  $-CHO$ ,  $-CO(1-4C)alkyl$ ,  $-CONH_2$  and  $-CONH(1-4C)alkyl$ ;
- $R_4$  is selected from  $R_{4a}$  and  $R_{4b}$  wherein
- $R_{4a}$  is selected from azido,  $-NR_7R_8$ ,  $OR_{10}$ , (1-4C)alkyl, (1-4C)alkoxy, (3-6C)cycloalkyl,
- 25  $-(CH_2)_k-R_9$ ,  $AR1$ ,  $AR2$ , (1-4C)alkanoyl,  $-CS(1-4C)alkyl$ ,  $-C(=W)NR_vR_w$  [wherein W is O or S,  $R_v$  and  $R_w$  are independently H, or (1-4C)alkyl ],  $-(C=O)_l-R_6$ ,  $-COO(1-4C)alkyl$ ,  $-C=OAR1$ ,  $-C=OAR2$ ,  $-COOAR1$ ,  $S(O)_n(1-4C)alkyl$  (wherein  $n = 1$  or  $2$ ),  $-S(O)_pAR1$ ,  $-S(O)_pAR2$  and  $-C(=S)O(1-4C)alkyl$ ; wherein any (1-4C)alkyl chain may be optionally substituted by (1-4C)alkyl, cyano, hydroxy or halo;  $p = 0, 1$  or  $2$ ;
- 30  $R_{4b}$  is selected from HET-3;
- $R_6$  is selected from hydrogen, (1-4C)alkoxy, amino, (1-4C)alkylamino and hydroxy(1-4C)alkylamino;
- k is 1 or 2;

l is 1 or 2;

R<sub>7</sub> and R<sub>8</sub> are independently selected from H and (1-4C)alkyl, or wherein R<sub>7</sub> and R<sub>8</sub> taken together with the nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> (wherein n = 1 or 2) in place of 1 carbon atom of the so formed ring; wherein the ring may be optionally substituted by one or two groups independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), AR1, AR2, , -C=OAR1, -C=OAR2, -COOAR1, -CS(1-4C)alkyl, -C(=S)O(1-4C)alkyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl], -S(O)<sub>p</sub>AR1 and -S(O)<sub>p</sub>AR2; wherein any (1-4C)alkyl, (3-6C)cycloalkyl or (1-4C)alkanoyl group may be optionally substituted (except on a carbon atom adjacent to a heteroatom) by one or two substituents selected from (1-4C)alkyl, cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino; p = 0, 1 or 2;

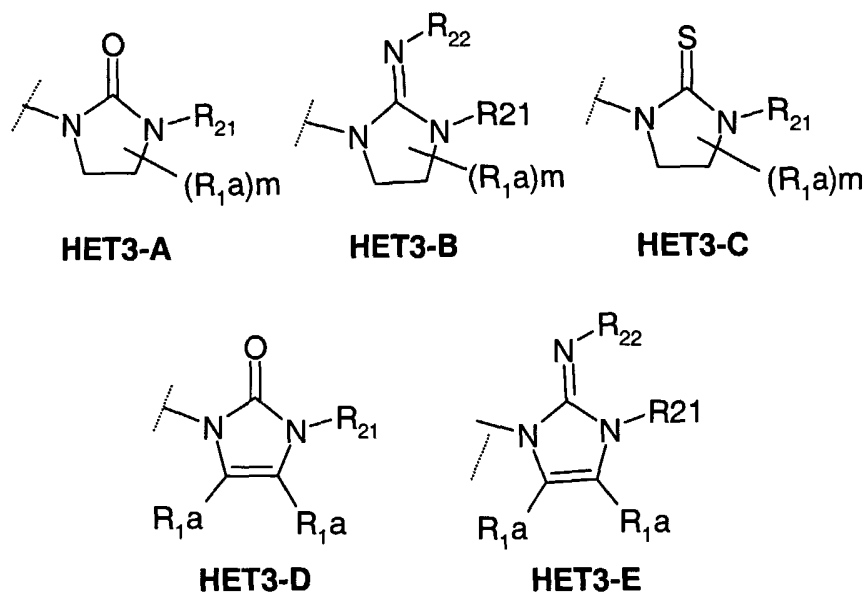
R<sub>9</sub> is independently selected from R<sub>9a</sub> to R<sub>9d</sub> below:

15 R<sub>9a</sub>: AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

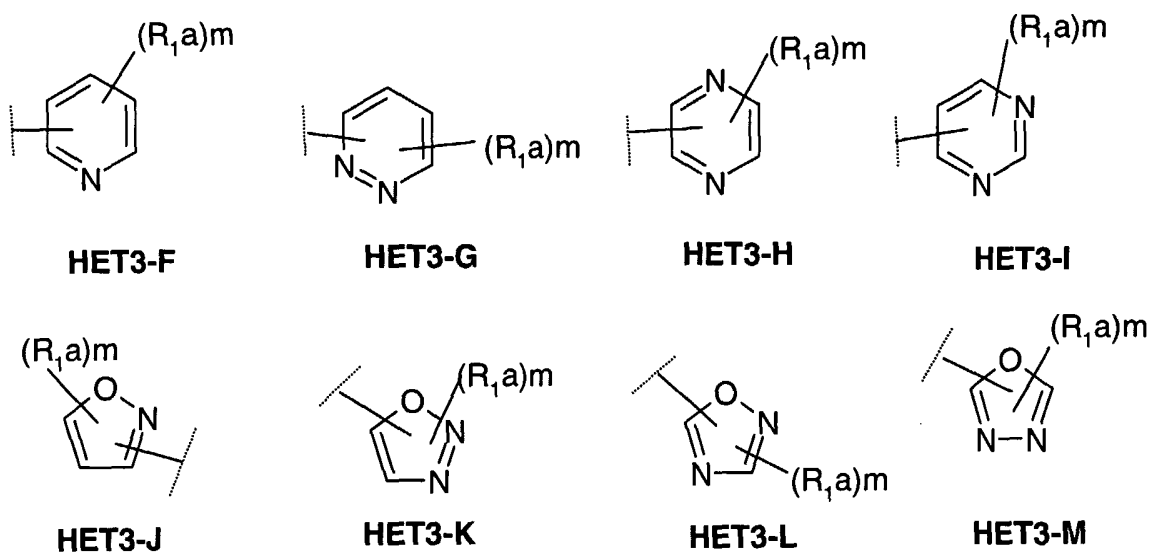
R<sub>9b</sub>: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl; wherein any alkyl, alkanoyl or cycloalkyl may itself optionally be substituted by cyano, hydroxy or halo]], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

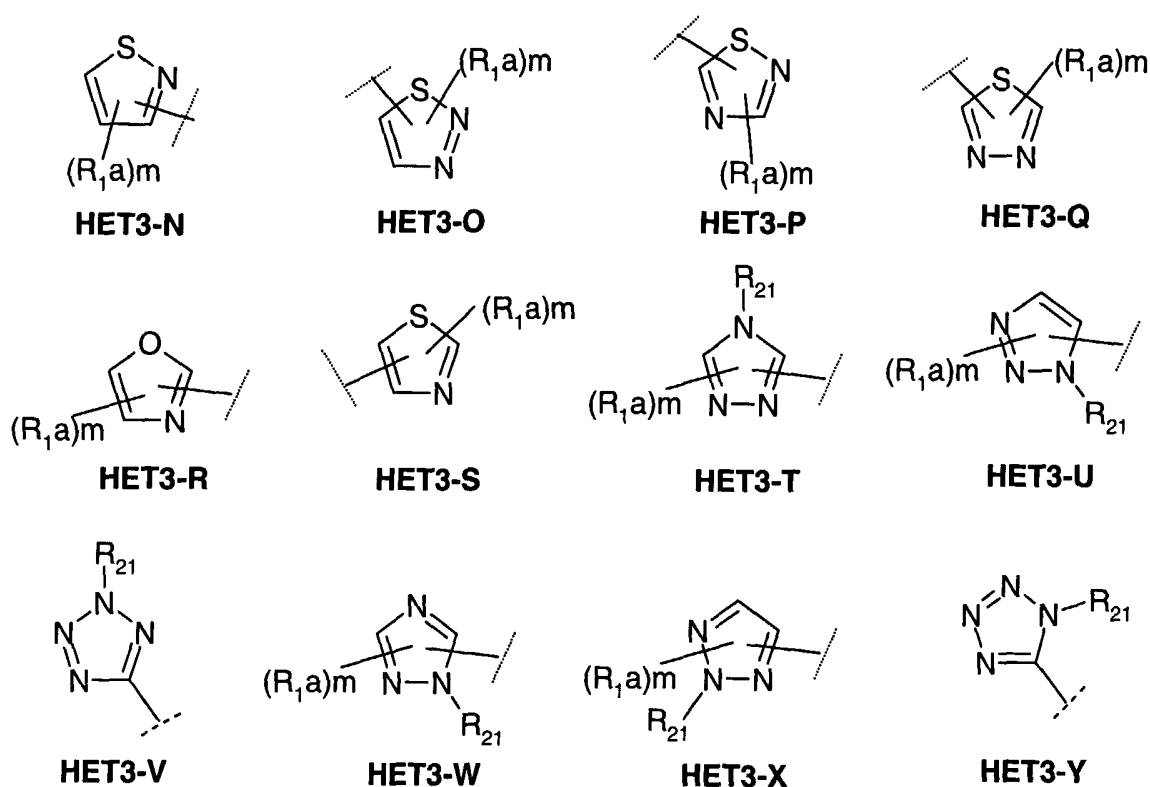
25 R<sub>9c</sub>: (1-6C)alkyl  
{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group

- selected from carboxy, phosphonate [phosphono,  $-P(O)(OH)_2$ , and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [ $-P(OH)_2$  and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-,  $-C(=W)NR_vR_w$  [wherein W is O or S,  $R_v$  and  $R_w$  are as hereinbefore defined],  $(=NOR_v)$  wherein  $R_v$  is as hereinbefore defined, (1-4C)alkylS(O) $_p$ NH, (1-4C)alkylS(O) $_p$ -((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O) $_p$ NH-, fluoro(1-4C)alkylS(O) $_p$ -((1-4C)alkyl)N-, (1-4C)alkylS(O) $_q$ -, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-  
 10 , AR1-S(O) $_q$ -, AR2-S(O) $_q$ -, AR3-S(O) $_q$ -, AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups}; wherein any (1-4C)alkyl present in any substituent on  $R_{9c}$  may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon  
 15 adjacent to a heteroatom atom if present;
- $R_{9d}$ :  $R_{14}C(O)O(1-6C)alkyl$ - wherein  $R_{14}$  is AR1, AR2, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for ( $R_{9c}$ )};
- $R_{10}$  is selected from hydrogen,  $R_{9c}$  (as hereinbefore defined), (1-4C)alkanoyl and (1-4C)alkylsulfonyl;
- 20 HET-3 is selected from:
- a) a 5-membered heterocyclic ring containing at least one nitrogen and/or oxygen in which any carbon atom is a C=O, C=N, or C=S group, wherein said ring is of the formula HET3-A to HET3-E below:

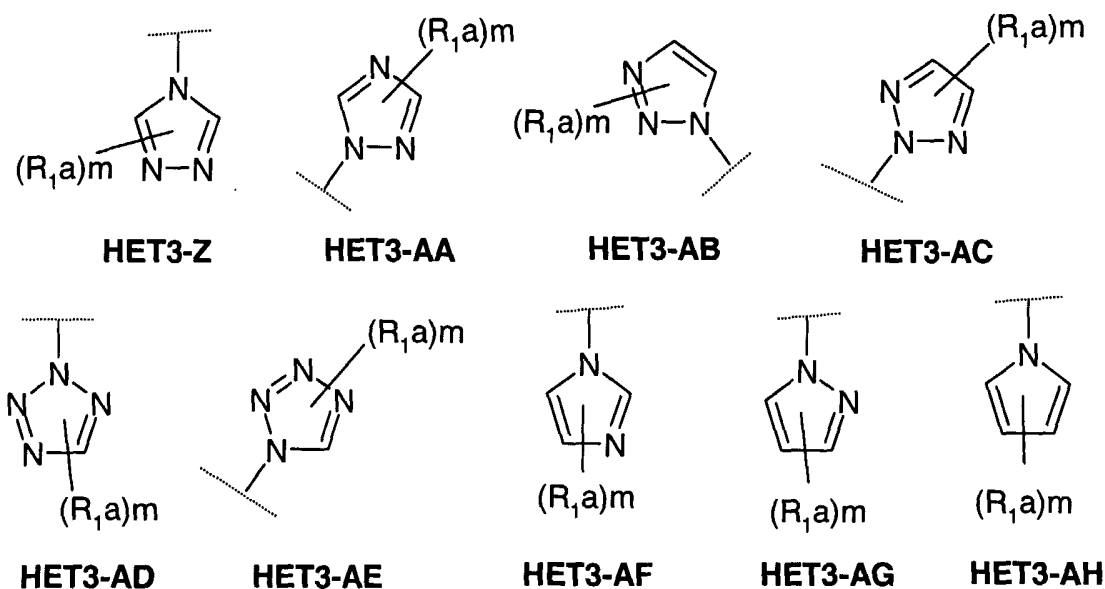


b) a carbon-linked 5- or 6-membered heteroaromatic ring containing 1, 2, 3, or 4 heteroatoms independently selected from N, O and S selected from HET3-F to HET3-Y below:





c) a nitrogen-linked 5- or 6-membered heteroaromatic ring containing 1, 2, 3, or 4 heteroatoms independently selected from N, O and S selected from HET3-Z to HET3-AH below:



5

wherein in HET-3,  $R_1a$  is a substituent on carbon;

$R_1a$  is independently selected from  $R_1a1$  to  $R_1a5$  below:

$R_1a1$ : AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;



- R<sub>1a2</sub>: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR<sub>1</sub>, -CS(1-4C)alkyl) and -C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)alkanoyl and (3-6C)cycloalkyl substituent may itself be substituted by cyano, hydroxy or halo, provided that, such a substituent is not on a carbon adjacent to a nitrogen atom of the piperazine ring], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR<sub>1</sub>)ethenyl, 2-(AR<sub>2</sub>)ethenyl, 2-(AR<sub>2a</sub>)ethenyl;
- R<sub>1a3</sub>: (1-10C)alkyl
- { optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)(OH)<sub>2</sub>, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)<sub>2</sub> and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NR<sub>v</sub>R<sub>w</sub> [wherein W is O or S, R<sub>v</sub> and R<sub>w</sub> are independently H, or (1-4C)alkyl and wherein R<sub>v</sub> and R<sub>w</sub> taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, -S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), -COOAR<sub>1</sub>, -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl], (=NOR<sub>v</sub>) wherein R<sub>v</sub> is as hereinbefore defined, (1-4C)alkylS(O)<sub>p</sub>NH-, (1-4C)alkylS(O)<sub>p</sub>-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)<sub>p</sub>NH-,

fluoro(1-4C)alkylS(O)<sub>p</sub>((1-4C)alkyl)N-, (1-4C)alkylS(O)<sub>q</sub>-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)<sub>q</sub>-, AR2-S(O)<sub>q</sub>-, AR3-S(O)<sub>q</sub>-, AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups}; wherein any (1-4C)alkyl, (1-4C)alkanoyl and (3-

5 6C)cycloalkyl present in any substituent on R<sub>1a3</sub> may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

R<sub>1a4</sub>: R<sub>14</sub>C(O)O(1-6C)alkyl- wherein R<sub>14</sub> is AR1, AR2, AR2a, AR2b, (1-4C)alkylamino, 10 benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (R<sub>1a3</sub>)};

R<sub>1a5</sub>: F, Cl, hydroxy, mercapto, (1-4C)alkylS(O)<sub>p</sub>- (p = 0, 1 or 2), -NR<sub>7</sub>R<sub>8</sub> (wherein R<sub>7</sub> and R<sub>8</sub> are as hereinbefore defined) or -OR<sub>10</sub> (where R<sub>10</sub> is as hereinbefore defined);

m is 0, 1 or 2;

R<sub>21</sub> is selected from hydrogen, methyl [optionally substituted with cyano, trifluoromethyl, 15 -C=WNR<sub>v</sub>R<sub>w</sub> (where W, R<sub>v</sub> and R<sub>w</sub> are as hereinbefore defined for R<sub>1a3</sub>), (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, CY1, CY2, AR1, AR2, AR2a, AR2b (not linked through nitrogen) or AR3], (2-10C)alkyl [optionally substituted other than on a carbon attached to the HET-3 ring nitrogen with one or two groups independently selected from the optional substituents defined 20 for R<sub>1a3</sub>] and R<sub>14</sub>C(O)O(2-6C)alkyl-, wherein R<sub>14</sub> is as defined hereinbefore for R<sub>1a4</sub> and wherein R<sub>14</sub>C(O)O group is attached to a carbon other than the carbon attached to the HET-3 ring nitrogen;

R<sub>22</sub> is cyano, -COR<sub>12</sub>, -COOR<sub>12</sub>, -CONHR<sub>12</sub>, -CON(R<sub>12</sub>)(R<sub>13</sub>), -SO<sub>2</sub>R<sub>12</sub> (provided that R<sub>12</sub> is not hydrogen), -SO<sub>2</sub>NHR<sub>12</sub>, -SO<sub>2</sub>N(R<sub>12</sub>)(R<sub>13</sub>) or NO<sub>2</sub>, wherein R<sub>12</sub> and R<sub>13</sub> are as defined 25 hereinbelow;

R<sub>12</sub> and R<sub>13</sub> are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any N(R<sub>12</sub>)(R<sub>13</sub>) group, R<sub>12</sub> and R<sub>13</sub> may be taken 30 together with the nitrogen to which they are attached to form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)<sub>n</sub> in place of 1 carbon atom of the so formed ring; wherein the ring may be optionally substituted by one or two groups independently selected from (1-4C)alkyl (optionally substituted on a carbon not adjacent to

the nitrogen by cyano, hydroxy or halo), (3-6C)cycloalkyl, (1-4C)alkanoyl, -COO(1-4C)alkyl, S(O)<sub>n</sub>(1-4C)alkyl (wherein n = 1 or 2), AR1, AR2, , -C=OAR1, -C=OAR2, -COOAR1, -CS(1-4C)alkyl, -C(=S)O(1-4C)alkyl, -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl ], -S(O)<sub>p</sub>AR1 and -S(O)<sub>p</sub>AR2; wherein any (1-4C)alkyl

5 chain may be optionally substituted by (1-4C)alkyl, cyano, hydroxy or halo; p = 0,1 or 2;

**AR1** is an optionally substituted phenyl or optionally substituted naphthyl;

**AR2** is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms

independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and

10 linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

**AR2a** is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

**AR2b** is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation),

15 linked via a ring carbon atom or linked via a ring nitrogen atom;

**AR3** is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

20 **AR3a** is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

**AR3b** is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation),

25 linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

**AR4** is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and

30 linked via a ring carbon atom in any of the rings comprising the tricyclic system;

**AR4a** is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring;

wherein; optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a,

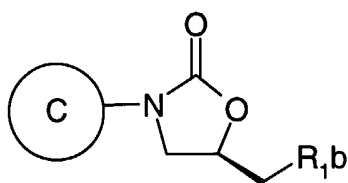
CY1 and CY2 are (on an available carbon atom) up to three substituents independently

- 5 selected from (1-4C)alkyl {optionally substituted by substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub>}, trifluoromethyl, hydroxy, halo, nitro, cyano, thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, 10 (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO<sub>2</sub>amino, (2-4C)alkenyl {optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and 15 (1-4C)alkoxy}, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; R<sub>w</sub> is hydrogen or (1-4C)alkyl];

and further optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from

- 20 trifluoromethoxy, benzoylamino, benzoyl, phenyl {optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, -SO<sub>2</sub>NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; 25 R<sub>w</sub> is hydrogen or (1-4C)alkyl]; and optional substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl {wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, 30 hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)<sub>q</sub>- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONR<sub>v</sub>R<sub>w</sub> or -NR<sub>v</sub>R<sub>w</sub> [wherein R<sub>v</sub> is hydrogen or (1-4C)alkyl; R<sub>w</sub> is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

2. A compound of the formula (I) as claimed in claim 1, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein  $R_{1b}$  is  $-NHC(W)R_{24}$ .
3. A compound of the formula (I) as claimed in claim 1 or claim 2, or a  
5 pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein  $R_4$  is  $R_{4b}$ .
4. A compound of the formula (I) as claimed in any preceding claim or a pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein HET-3 is selected from HET3-T, HET3-V, HET3-Y and HET-3-W.  
10
5. A compound of the formula (I) as claimed in any preceding claim, or a pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein HET-3 is selected from HET3-V and HET3-Y.
- 15 6. A compound of the formula (I) as claimed in any preceding claim, or a pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein  $R_{1a}$  is  $R_{1a3}$ .
7. A compound of the formula (I) as claimed in any preceding claim, or a  
20 pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein group C is group D.
8. A compound of the formula (I) as claimed in claims 1 to 6, or a pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein group C is group E.  
25
9. A compound of the formula (I) as claimed in claims 1 to 6, or a pharmaceutically-acceptable salt, or an in-vivo hydrolysable ester thereof, wherein W is O.
10. A compound of the formula (Ia), or a pharmaceutically-acceptable salt, or an in-vivo  
30 hydrolysable ester thereof, wherein groups C and  $R_{1b}$  have meanings as stated in any one of the preceding claims.



(Ia)

5 11. A pro-drug of a compound as claimed in any one of the previous claims.

12 A method for producing an antibacterial effect in a warm blooded animal which  
comprises administering to said animal an effective amount of a compound of the invention as  
claimed in any one of claims 1 to 10, or a pharmaceutically-acceptable salt, or in-vivo  
10 hydrolysable ester thereof.

13. A compound of the invention as claimed in any one of claims 1 to 10, or a  
pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a  
medicament.

15

14. The use of a compound of the invention as claimed in any one of claims 1 to 10, or a  
pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of  
a medicament for use in the production of an antibacterial effect in a warm blooded animal.

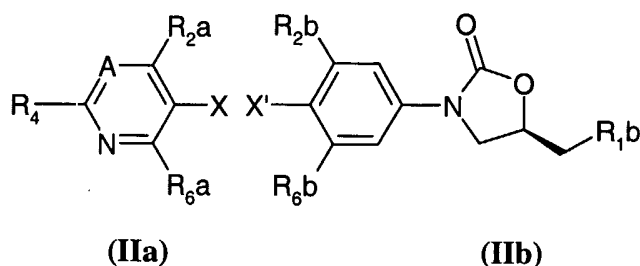
20 15. A pharmaceutical composition which comprises a compound of the invention as  
claimed in any one of claims 1 to 10, or a pharmaceutically-acceptable salt or an in-vivo  
hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

16. A process for the preparation of a compound of formula (I) as claimed in claim 1 or  
25 pharmaceutically acceptable salts or in-vivo hydrolysable esters thereof, which process  
comprises one of processes (a) to (f); and thereafter if necessary:

- i) removing any protecting groups;
- ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or
- iii) forming a pharmaceutically-acceptable salt;

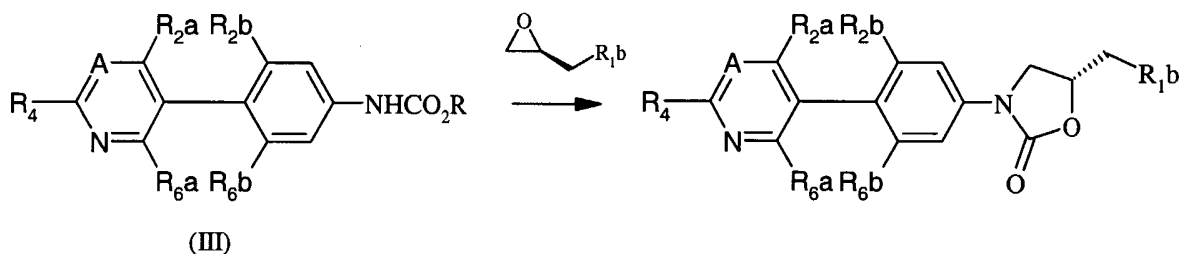
30 wherein said processes (a) to (f) are:

- a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry;
- b) by reaction of a molecule of a compound of formula (IIa) [wherein X is a leaving group useful in palladium coupling and in this instance A is either N or C-R<sub>3a</sub>] with a
- 5 molecule of a compound of formula (IIb) (wherein X' is a leaving group useful in palladium coupling,) wherein X and X' are such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds;



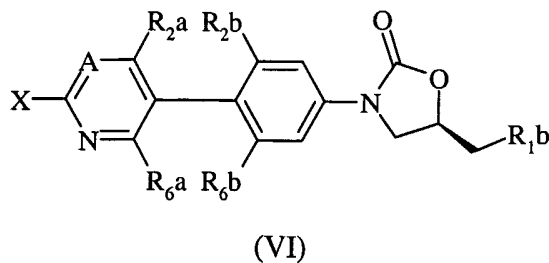
- 10 and X and X' are chosen to be different lead to the desired cross-coupling products of formula (I);

- c) by reaction of a heterobiaryl derivative (III) carbamate [where A is either N or C-R<sub>3a</sub>] with an appropriately substituted oxirane to form an oxazolidinone ring;



15

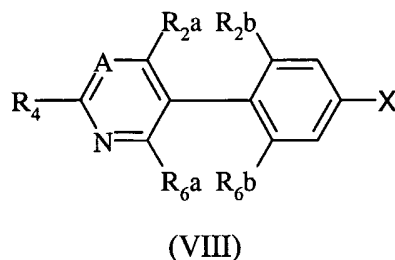
- (d) by reaction of a compound of formula (VI) :



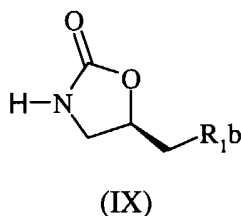
- 20 where X is a replaceable substituent and A is either N or CR<sub>3a</sub> with a compound of the formula (VII):



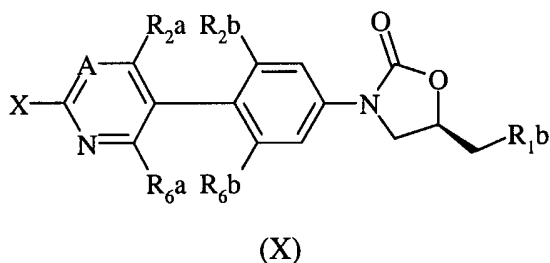
wherein T-X' is HET3 as herein above defined and X' is a replaceable C-linked substituent -  
 wherein the substituents X and X' are chosen to be complementary pairs of substituents  
 known in the art to be suitable for coupling reactions catalysed by transition metals; or  
 (d(i)) by reaction catalysed by transition metals such as palladium(0) of a compound of  
 5 formula (VIII):



wherein X is a replaceable substituent and wherein in this instance A is either N or C-R<sub>3a</sub> with  
 a compound of the formula (IX):



(d(ii)) by reaction of a compound of formula (X):

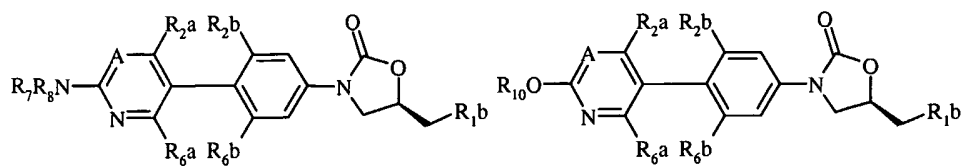


wherein X is a replaceable substituent and wherein in this instance A is either N or C-R<sub>3a</sub>  
 with a compound of the formula (XI):



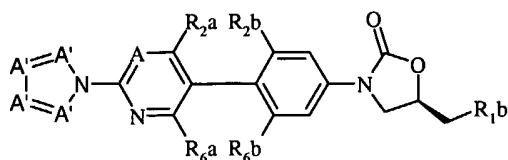
20 wherein T-H is an amine R<sub>7</sub>R<sub>8</sub>NH, an alcohol R<sub>10</sub>OH, or an azole with an available ring-NH  
 group to give compounds (XIIa), (XIIb), or (XIIc) wherein in this instance A is nitrogen or C-  
 R<sub>3a</sub> and A' is nitrogen or carbon optionally substituted with one or more groups R<sub>1a</sub>.





(XIIa)

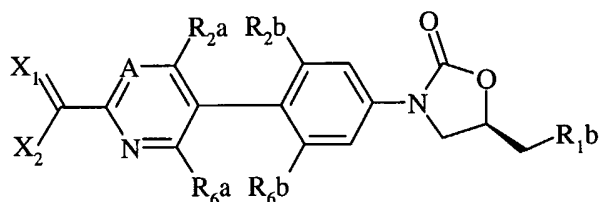
(XIIb)



(XIIc)

5

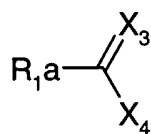
(e) by reaction of a compound of formula (XIII):



(XIII)

wherein  $X_1$  and  $X_2$  here are independently optionally substituted heteroatoms drawn in

10 combination from O, N, and S such that  $C(X_1)X_2$  constitutes a substituent that is a carboxylic acid derivative substituent and wherein in this instance A is either N or C- $R_{3a}$  with a compound of the formula (XIV) and  $X_3$  and  $X_4$  are independently optionally substituted heteroatoms drawn in combination from O, N, and S:



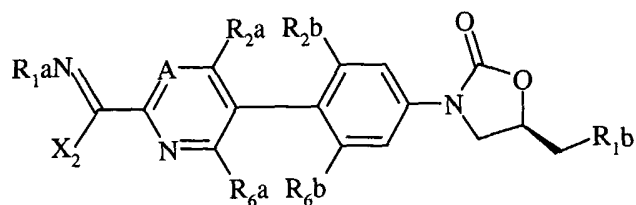
(XIV)

15

and wherein one of  $C(X_1)X_2$  and  $C(X_3)X_4$  constitutes an optionally substituted hydrazide, thiohydrazide, or amidrazone, hydroximidate, or hydroxamidine and the other one of  $C(X_1)X_2$  and  $C(X_3)X_4$  constitutes an optionally substituted acylating, thioacylating, or imidoylating agent such that  $C(X_1)X_2$  and  $C(X_3)X_4$  may be condensed together to form a 1,2,4-heteroatom

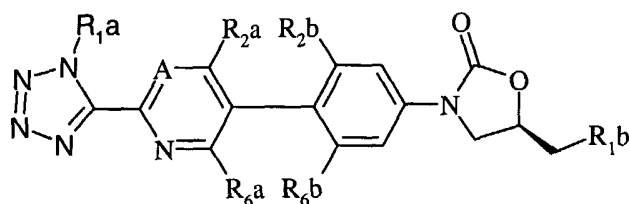
20 5-membered heterocycle containing 3 heteroatoms drawn in combination from O, N, and S, for instance thiadiazole; or

(e (i)) by reaction of a compound of formula (XV):



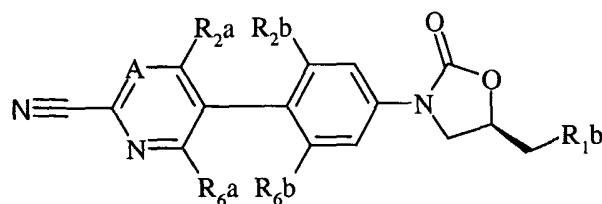
(XV)

wherein  $X_2$  is a displaceable group and wherein in this instance A is either N or C- $R_{3a}$  with a source of azide anion to give a tetrazole (XVI)



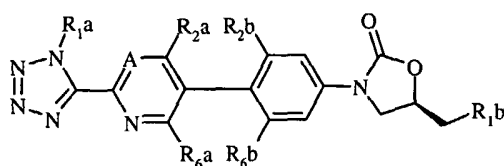
(XVI)

or where nitriles of formula (XVII)

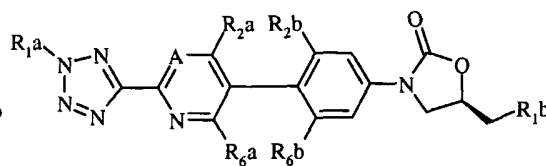


(XVII)

- 10 [wherein in this instance A is either N or C- $R_{3a}$ ] may be reacted directly with azides such as ammonium azide or trialkylstannylazides to give tetrazoles (XVI,  $R_{1a} = H$ ) that are subsequently alkylated with groups  $R_{1a} \neq H$  to give tetrazoles (XVIIIa) and (XVIIIb) or;



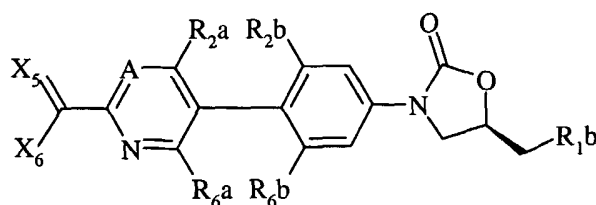
(XVIIIa)



(XVIIIb)

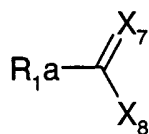
15

- (f) by reaction of a compound of formula (XIX):



(XIX)

[wherein in this instance A is either N or C-R<sub>3a</sub>] with a compound of the formula (XX):



(XX)

wherein one of C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> constitutes an optionally substituted alpha-(leaving-  
 5 group-substituted)ketone, wherein the leaving group is for example a halo-group or an (alkyl  
 or aryl)-sulfonyloxy-group, and the other one of C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> constitutes an  
 optionally substituted amide, thioamide, or amidine, such that C(X<sub>5</sub>)X<sub>6</sub> and C(X<sub>7</sub>)X<sub>8</sub> are  
 groups that may be condensed together to form a 1,3-heteroatom 5-membered heterocycle  
 containing 2 heteroatoms drawn in combination from O, N, and S.

# INTERNATIONAL SEARCH REPORT

PCT/GB 03/05498

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07D413/14 C07D413/10 A61K31/44 //(C07D413/14,263:00, 257:00,213:00)		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, EMBASE, BIOSIS, PAJ, WPI Data, CHEM ABS Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03 022824 A (SWAIN MICHAEL LINGARD ;ASTRAZENECA UK LTD (GB); MILLS STUART DENNE) 20 March 2003 (2003-03-20) example 60 ---	1, 2, 8-11, 13-15
Y	WO 01 94342 A (DONG A PHARM CO LTD ;CHO JONG HWAN (KR); CHOI SUNG HAK (KR); LEE J) 13 December 2001 (2001-12-13) the whole document ---	1-11, 13-16
Y	WO 00 29396 A (RADDATZ SIEGFRIED ;BARTEL STEPHAN (DE); BAYER AG (DE); HAERTER MIC) 25 May 2000 (2000-05-25) the whole document --- -/--	1-11, 13-16
<div style="display: flex; justify-content: space-between;"> <span><input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.</span> <span><input checked="" type="checkbox"/> Patent family members are listed in annex.</span> </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>*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</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*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.</p> <p>*&amp;* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">25 March 2004</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">05/04/2004</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Frelon, D</div>

## INTERNATIONAL SEARCH REPORT

PCT/GB 03/05498

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 33839 A (CHEIL JEDANG CORP ;KANG JIN AH (KR); LEE KOUN HO (KR); LEE YOUN HA) 8 July 1999 (1999-07-08) the whole document ---	1-11, 13-16
Y	WO 98 54161 A (HESTER JACKSON B JR ;NIDY ELDON GEORGE (US); PERRICONE SALVATORE C) 3 December 1998 (1998-12-03) cited in the application the whole document ---	1-11, 13-16
Y	WO 93 09103 A (UPJOHN CO) 13 May 1993 (1993-05-13) examples 1,8,11,18,21,24,27,30 ---	1-11, 13-16
Y	EP 0 352 781 A (DU PONT) 31 January 1990 (1990-01-31) examples 38,105,107,135 ---	1-11, 13-16
Y	US 5 565 571 A (BARBACHYN MICHAEL R ET AL) 15 October 1996 (1996-10-15) abstract; claims ---	1-11, 13-16
A	WO 99 03846 A (RADDATZ SIEGFRIED ;RIEDL BERND (DE); BARTEL STEPHAN (DE); BAYER AG) 28 January 1999 (1999-01-28) abstract; claims ---	1-11, 13-16
A	WO 97 21708 A (UPJOHN CO ;TUCKER JOHN A (US); BRICKNER STEVEN JOSEPH (US); ULANOW) 19 June 1997 (1997-06-19) abstract; claims ---	1-11, 13-16
A	CHUNG-HO PARK ET AL: "ANTIBACTERIALS. SYNTHESIS AND STRUCTURE-ACTIVITY STUDIES OF 3-ARYL-2-OXOOXAZOLIDINES. 4 MULTIPLY-SUBSTITUTED ARYL DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 6, 20 March 1992 (1992-03-20), pages 1156-1165, XP000567006 ISSN: 0022-2623 page 1159, summary --- -/--	1-11, 13-16

## INTERNATIONAL SEARCH REPORT

PCT/GB 03/05498

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PAE A N ET AL: "Synthesis and in vitro activity of new oxazolidinone antibacterial agents having substituted isoxazoles" BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 18, 20 September 1999 (1999-09-20), pages 2679-2684, XP004179951 ISSN: 0960-894X the whole document -----</p>	1-11, 13-16

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Expressions "in vivo hydrolysable ester", "prodrug" do not bring more specification to the claimed domain and appear, rather, to claim desirable properties or results to be obtained which are not achieved yet at the filing time. They encompass a great, non-limitative variety of compounds which differ from the claimed active compounds, either in the side chain(s) or in the core structure.

Present claims 1-11, 13 to 16 relate to an extremely large number of possible compounds and processes. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and processes claimed (in fact, two examples). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds including the definitions specified in claims 4 and 8, as they appear to be illustrated, and analogous thereof (it is noted the wording of claim 4 -contrarily to the one of claim 8- is not limiting as such since the given specifications for HET-3 do not exclude other definitions of R4 like does the specification of group C to be E which excludes group D).

Apparently the definition of R24 has been drafted to exclude the value CH<sub>3</sub> without using the formulation of a proviso. This results in unclear redundances of the definition of R24.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

PCT/GB 03/05498

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
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:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ 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 claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

PCT/GB 03/05498

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