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(54) Title: AMINOCYCLOHEXENE QUINOLINES AND THEIR AZAISOSTERIC ANALOGUES WITH ANTIBACTERIAL ACTIVITY

(57) Abstract: Cyclohexene derivatives and pharmaceutically acceptable derivatives thereof useful in methods of treatment of bacterial infections in mammals, particularly man.

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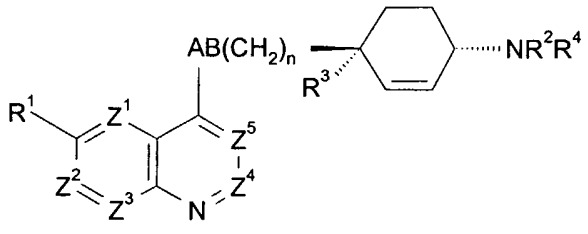
AMINOCYCLOHEXENE QUINOLINES AND THEIR AZAISOSTERIC ANALOGUES WITH ANTIBACTERIAL ACTIVITY

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

WO099/37635, WO00/21948, WO00/21952, WO00/43383, WO00/78748, WO01/07433, WO01/07432, WO02/08224, WO02/24684, WO02/50040, WO02/50061, WO01/25227 and WO02/040474 disclose quinoline and naphthyridine derivatives having antibacterial activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH, or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, CONH2, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, or when Z^1 is CR^{1a}, R^1 and R^{1a} may together represent (C_{1-2})alkylenedioxy, or when Z^5 is CR^{1a}, R^{1a} may instead be, cyano, hydroxymethyl or carboxy,
provided that when Z^1, Z^2, Z^3, Z^4 and Z^5 are CR^{1a} or CH, then R^1 is not hydrogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:
amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

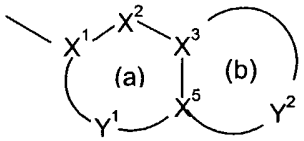
R^3 ishydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl;

R^{10} is selected from (C_{1-4})alkyl and (C_{2-4})alkenyl either of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl;

R^4 is a group $-CH_2-R^5{}_1$ in which $R^5{}_1$ is selected from:
(C_{4-8})alkyl; hydroxy(C_{4-8})alkyl; (C_{1-4})alkoxy(C_{4-8})alkyl; (C_{1-4})alkanoyloxy(C_{4-8})alkyl; (C_{3-8})cycloalkyl(C_{4-8})alkyl; hydroxy-, (C_{1-6})alkoxy- or (C_{1-6})alkanoyloxy-(C_{3-8})cycloalkyl(C_{4-8})alkyl; cyano(C_{4-8})alkyl; (C_{4-8})alkenyl; (C_{4-8})alkynyl; tetrahydrofuryl; mono- or di-($C_{1-6})$alkylamino(C_{4-8})alkyl; acylamino$(C_{4-}$

8)alkyl; (C_{1-6})alkyl- or acyl-aminocarbonyl(C_{4-8})alkyl; mono- or di- (C_{1-6})alkylamino(hydroxy) (C_{4-8})alkyl; or

R^4 is a group –U-$R^5{}_2$ where $R^5{}_2$ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_X$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_X$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_X$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; arylcarbonyl; heteroarylcarbonyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-}

4)alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

each x is independently 0, 1 or 2;

U is CO, SO_2 or CH_2; or

R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$ in which:

X^{1a} is CH_2, CO or SO_2;

X^{2a} is $CR^{14a}R^{15a}$;

X^{3a} is NR^{13a}, O, S, SO_2 or $CR^{14a}R^{15a}$; wherein:

each of R^{14a} and R^{15a} is independently selected from the groups listed above for R^{14} and R^{15}, provided that R^{14a} and R^{15a} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14a} and R^{15a} together represent oxo;

R^{13a} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14a} groups or an R^{13a} and an R^{14a} group on adjacent atoms together represent a bond and the remaining R^{13a}, R^{14a} and R^{15a} groups are as above defined; or

two R^{14a} groups and two R^{15a} groups on adjacent atoms together represent bonds such that X^{2a} and X^{3a} is triple bonded;

X^{4a} is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and: optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and

optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-}

4)alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1 and AB is $NR^{11}CO$, $CONR^{11}$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $O\text{-}CR^8R^9$, $CR^6R^7\text{-}O$, $NHR^{11}\text{-}CR^8R^9$, $CR^6R^7\text{-}NHR^{11}$, $NR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$, provided that n=0, B is not NR^{11}, O or SO_2,
and provided that R^6 and R^7, and R^8 and R^9 are not both optionally substituted hydroxy or amino;
and wherein:
each of R^6, R^7, R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

in optionally substituted amino the amino group is optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

in optionally substituted aminocarbonyl the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^6, R^7, R^8 or R^9 contains a carboxy group they may together with R^3 form a cyclic ester linkage.

The invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition, in particular for use in the treatment of bacterial infections in mammals, comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment of an effective amount of a a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

Preferably Z^5 is CH, Z^3 is CH or CF, Z^1 is CH or C-OCH_3 and Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH

Compounds of formula (I) in which the enantiomeric configuration of the substituted cyclohexene group corresponds to that of enantiomer E2 described in the Examples are preferred.

When R^1 or R^{1a} is substituted alkoxy it is preferably (C_{2-6})alkoxy substitituted by optionally N-substituted amino, guanidino or amidino, or (C_{1-6})alkoxy substituted by piperidyl. Suitable examples of R^1 alkoxy include methoxy, trifluoromethoxy, n-propyloxy, i-butyloxy, aminoethyloxy, aminopropyloxy, aminobutyloxy, aminopentyloxy, guanidinopropyloxy, piperidin-4-ylmethyloxy or 2-aminocarbonylprop-2-oxy. Preferably R^1 is methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro.

Preferably R^1 and R^{1a} are independently methoxy, amino(C_{3-5})alkyloxy, guanidino(C_{3-5})alkyloxy, piperidyl(C_{3-5})alkyloxy, nitro or fluoro; more preferably methoxy, fluoro, amino(C_{3-5})alkyloxy or guanidino(C_{3-5})alkyloxy. Preferably R^{1a} is H, methoxy or F. Most preferably R^1 is methoxy or fluoro and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

When Z^5 is CR^{1a}, R^{1a} is preferably hydrogen, cyano, hydroxymethyl or carboxy, most preferably hydrogen.

R^2 is preferably hydrogen; (C_{1-4})alkyl substituted with carboxy, optionally substituted hydroxy, optionally substituted aminocarbonyl, optionally substituted amino or (C_{1-4})alkoxycarbonyl; or (C_{2-4})alkenyl substituted with (C_{1-4})alkoxycarbonyl or carboxy. More preferred groups for R^2 are hydrogen, carboxymethyl, hydroxyethyl,

aminocarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonylallyl and carboxyallyl, most preferably hydrogen.

R^3 is preferably hydroxy or (C_{1-6}) alkoxy, most preferably hydroxy.

When R^3 and R^6, R^7, R^8 or R^9 together form a cyclic ester linkage, it is preferred that the resulting ring is 5-7 membered. It is further preferred that the group A or B which does not form the ester or amide linkage is CH_2.

When A is CH(OH) the R-stereochemistry is preferred.

Preferably A is NH, NCH_3, CH_2, CHOH, $CH(NH_2)$, C(Me)(OH) or CH(Me).

Preferably B is CH_2 or CO.

Preferably n=0.

Most preferably:

n is 0 and either A is CHOH, CH_2 and B is CH_2 or A is NH and B is CO.

Preferably R^{11} is hydrogen or (C_{1-4})alkyl e.g. methyl, more preferably hydrogen.

When R^4 is $CH_2R^5{}_1$, preferably $R^5{}_1$ is (C_{6-8})alkyl.

When R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$:

X^{1a} is preferably CH_2.

X^{2a} is preferably CH_2 or together with X^{3a} forms a CH=CH or C≡C group.

X^{3a} is preferably CH_2, O, S or NH, or together with X^{2a} forms a CH=CH or C≡C group.

Preferred linker groups $-X^{1a}-X^{2a}-X^{3a}-$ include $-(CH_2)_2$-O-, $-CH_2$-CH=CH-, $-(CH_2)_3$-, $-(CH_2)_2$-NH- or $-CH_2$CONH-.

Monocyclic aromatic heterocyclic groups for X^{4a} include pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thienyl, isoimidazolyl, thiazolyl, furanyl and imidazolyl, 2H-pyridazone, 1H-pyrid-2-one. Preferred aromatic heterocyclic groups include pyrid-2-yl, pyrid-3-yl, thiazole-2-yl, pyrimidin-2-yl, pyrimidin-5-yl and fur-2-yl.

Preferred substituents on heterocyclic X^{4a} include halo especially fluoro, trifluoromethyl and nitro.

Preferred substituents on phenyl X^{4a} include halo, especially fluoro, nitro, cyano, trifluoromethyl, methyl, methoxycarbonyl and methylcarbonylamino.

Preferably X^{4a} is 2-pyridyl, 3-fluorophenyl, 3,5-difluorophenyl or thiazol-2-yl.

Preferably R^4 is $-U-R^5{}_2$.

The group –U– is preferably $-CH_2-$.

Preferably $R^5{}_2$ is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13}.

Alternatively and preferably the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic and Y^2

has 3-5 atoms including NR^{13}, O or S bonded to X^5 and NHCO bonded via N to X^3, or O bonded to X^3. Examples of rings (A) include optionally substituted:

(a) and (b) aromatic

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, indan-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2yl, benzimidazol-2-yl, benzothiophen-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzooxazol-2-thione-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-2-yl, 3H-quinazolin-4-one-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyridazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimdin-4-one-2-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, thiazolo[5,4-b]pyridin-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl, 1-oxo-1,2-dihydro-isoquinolin-3-yl, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, 2H-isoquinolin-1-one-3-yl

(a) is non aromatic

(2S)-2,3-dihydro-1H-indol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 3-(S)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 3-substituted-3H-quinazolin-4-one-2-yl,

(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro-1 λ^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl, benzo[1,3]dioxol-5-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-

dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triaza-naphthalen-3-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3-substituted-3H-benzooxazol-2-one-6-yl, 3-substituted-3H-benzooxazole-2-thione-6-yl, 3-substituted-3H-benzothiazol-2-one-6-yl, 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinoxalin-2-one-7-yl, 6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one-2-yl, 5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl, 2-oxo-3,4-dihydro-1*H*-[1,8]naphthyridin-6-yl.

R^{13} is preferably H if in ring (a) or in addition (C_{1-4})alkyl such as methyl or isopropyl when in ring (b). More preferably, in ring (b) R^{13} is H when NR^{13} is bonded to X^3 and (C_{1-4})alkyl when NR^{13} is bonded to X^5.

R^{14} and R^{15} are preferably independently selected from hydrogen, halo, hydroxy, (C_{1-4}) alkyl, (C_{1-4})alkoxy, trifluoromethoxy, nitro, cyano, aryl(C_{1-4})alkoxy and (C_{1-4})alkylsulphonyl.

More preferably R^{15} is hydrogen.

More preferably each R^{14} is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, trifluoromethoxy, benzyloxy, nitro, cyano and methylsulphonyl. Most preferably R^{14} is selected from hydrogen, hydroxy, fluorine or nitro. Preferably 0-3 groups R^{14} are substituents other than hydrogen.

Most preferred groups $R^5{}_2$ include:

[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
1H-pyrrolo[2,3-b]pyridin-2-yl
2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl
2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
2,3-dihydro-benzo[1,4]dioxin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
4H-benzo[1,4] thiazin-3-one-6-yl

4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl
6-nitro-benzo[1,3]dioxol-5-yl
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
8-hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl
8-hydroxyquinolin-2-yl
benzo[1,2,3]thiadiazol-5-yl
benzo[1,2,5]thiadiazol-5-yl
benzothiazol-5-yl
thiazolo-[5,4-b]pyridin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl

especially
benzo[1,2,5]thiadiazol-5-yl
4H-benzo[1,4] thiazin-3-one-6-yl
2,3-dihydro-benzo[1,4]dioxin-6-yl
benzo[1,2,3]thiadiazol-5-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl

most especially
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl .
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl.

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term 'heterocyclic' as used herein includes aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; optionally substituted aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl..

When used herein the term 'aryl', includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from(C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano, carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; phenyl, phenyl(C_{1-4})alkyl or phenyl(C_{1-4})alkoxy.

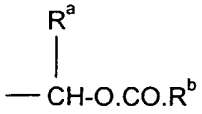
The term 'acyl' includes (C_{1-6})alkoxycarbonyl, formyl or (C_{1-6}) alkylcarbonyl groups.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

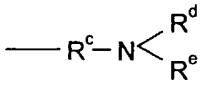
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

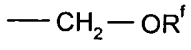
Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



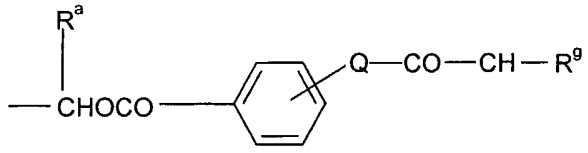
(i)



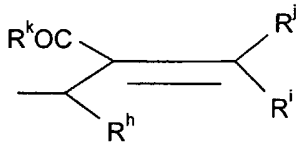
(ii)



(iii)



(iv)



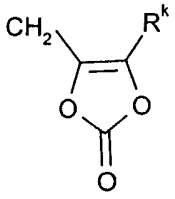
(v)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-$(C_{1-6}$ alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as ethoxycarbonyloxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as

dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C_{1-6})alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:

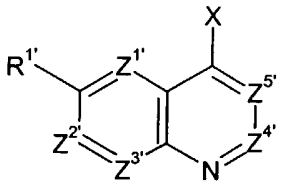


wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

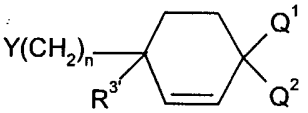
R is preferably hydrogen.

Certain of the above-mentioned compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For examples the invention includes compound in which an A-B group CH(OH)-CH_2 is in either isomeric configuration the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses..

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



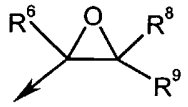
(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1 and R^3 as defined in formula (I) or groups convertible thereto;
Q^1 is $NR^{2'}R^{4'}$ or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;
and X and Y may be the following combinations:

(i) one of X and Y is CO_2R^Y and the other is $CH_2CO_2R^X$;

(ii) X is CHR^6R^7 and Y is $C(=O)R^9$;
(iii) X is $CR^7=PR^z_3$ and Y is $C(=O)R^9$;
(iv) X is $C(=O)R^7$ and Y is $CR^9=PR^z_3$;
(v) one of Y and X is COW and the other is $NHR^{11'}$;
(vi) X is $NHR^{11'}$ and Y is $C(=O)R^8$ or X is $C(=O)R^6$ and Y is $NHR^{11'}$;
(vii) X is $NHR^{11'}$ and Y is CR^8R^9W;
(viii) X is W or OH and Y is CH_2OH;
(ix) X is $NHR^{11'}$ and Y is SO_2W;
(x) one of X and Y is $(CH_2)_p$-W and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1;
(xi) one of X and Y is OH and the other is $-CH=N_2$;
(xii) Xis W and Y is $CONHR^{11}$;
(xiii) X is W and Y is -C≡CH followed by selective reduction of the intermediate –C≡C- group;

in which W is a leaving group, e.g. halo or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);
and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^2, R^3, R^4 and NR^{11}; converting A-B to other A-B, interconverting R^v, R^w, R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

Process variant (i) initially produces compounds of formula (I) wherein A-B is $CO-CH_2$ or CH_2-CO.

Process variant (ii) initially produces compounds of formula (I) wherein A-B is $CR^6R^7-CR^9OH$.

Process variant (iii) and (iv) initially produce compounds of formula (I) wherein A-B is $CR^7=CR^9$.

Process variant (v) initially produces compounds of formula (I) where A-B is $CO-NR^{11}$ or $NR^{11}-CO$.

Process variant (vi) initially produces compounds of formula (I) wherein A-B is $NR^{11}-CHR^8$. or CHR^6-NHR^{11}.

Process variant (vii) initially produces compounds of formula (I) wherein A-B is $NR^{11'}$-CR^8R^9.

Process variant (viii) initially produces compounds of formula (I) wherein A-B is O-CH_2.

Process variant (ix) initially produces compounds where AB is $NR^{11}SO_2$.

Process variant (x) initially produces compounds of formula (I) wherein one of A and B is CH_2 and the other is NHR^{11}, O or S.

Process variant (xi) initially produces compounds of formula (I) wherein A-B is OCH_2 or CH_2O, providing that if A is CH_2, n = 1.

Process variant (xii) produces compounds where AB is $NR^{11}CO$.

Process variant (xiii) produces compounds where AB is $-CH_2CH_2-$ or –CH=CH-.

In process variant (v) the reaction is a standard amide formation reaction involving e.g.:

1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester, O-acyl-isourea or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Acid Derivatives, Pt. 1* (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in *The Chemistry of Functional Groups (Ed. Patai, S.) Suppl. B: The Chemistry of Amides (Ed. Zabricky, J.)* (John Wiley and Sons, 1970), p 73 ff. The acid and amine are preferably reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT) or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU); or
2. The specific methods of:

a. *in situ* conversion of an acid into the amine component by a modified Curtius reaction procedure (Shioiri, T., Murata, M., Hamada, Y., *Chem. Pharm. Bull.* 1987, 35, 2698)

b. *in situ* conversion of the acid component into the acid chloride under neutral conditions (Villeneuve, G. B.; Chan, T. H., *Tetrahedron. Lett.* 1997, 38, 6489).

A' may be, for example. protected hydroxymethylene.

In process variant (i) the process is two step: firstly a condensation using a base, preferably sodium hydride or alkoxide, sodamide, alkyl lithium or lithium dialkylamide, preferably in an aprotic solvent e.g. ether, THF or benzene; secondly, hydrolysis using an inorganic acid, preferably HCl in aqueous organic solvent at 0-100°C. Analogous routes are described in DE330945, EP31753, EP53964 and H. Sargent, J. Am. Chem. Soc. **68**, 2688-2692 (1946). Similar Claisen methodology is described in Soszko et. al., Pr.Kom.Mat. Przyr.Poznan.Tow.Przyj.Nauk., (1962), 10, 15.

In process variant (ii) the reaction is carried out in the presence of a base, preferably organometallic or metal hydride e.g. NaH, lithium diisopropylamide or NaOEt,

preferably in an aprotic solvent, preferably THF, ether or benzene at -78 to 25°C (analogous process in Gutswiller et al. (1978) J. Am. Chem. Soc. 100, 576).

In process variants (iii) and (iv) if a base is used it is preferably NaH, KH, an alkyl lithium e.g. BuLi, a metal alkoxide e.g. NaOEt, sodamide or lithium dialkylamide e.g.di-isopropylamide. An analogous method is described in US 3989691 and M.Gates et. al. (1970) J. Amer.Chem.Soc., 92, 205, as well as Taylor et al. (1972) JACS 94, 6218.

In process variant (vi) the reaction is a standard reductive alkylation using, e.g., sodium borohydride or sodium triacetoxyborohydride (Gribble, G. W. in *Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)* (John Wiley and Sons, 1995), p 4649).

The process variant (vii) is a standard alkylation reaction well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; *Advanced Organic Chemistry, Edition 3* (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide

In process variant (viii) where X is W such as halogen, methanesulphonyloxy or trifluoromethanesulphonyloxy, the hydroxy group in Y is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium. Where X is OH, the hydroxy group in Y is activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623). Alternatively the X=O and Y=CH_2OH groups can be reacted directly by activation with dichlorocarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377).

In process variant (ix) the reaction is conducted in the presence of an organic base such as triethylamine or pyridine such as described by Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945. The X=$NR^{11}SO_2W$ or Y=SO_2W intermediates can be formed from the requisite amine e.g. by reaction with SO_2Cl_2 analogously to the procedure described by the same authors Fuhrman et.al., J. Amer. Chem. Soc.; **67**, 1245, 1945.

In process variant (x) where one of X and Y contains NHR^{11} the leaving group W is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in *Comprehensive Organic Chemistry,* Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in *Comprehensive Organic Chemistry,* Vol. 6, p 946-947 (reaction index); Smith, D. M. in *Comprehensive Organic Chemistry*, Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (x) where one of X and Y contains OH or SH, this is preferably converted to an OM or SM group where M is an alkali metal by treatment of an alcohol, thiol or thioacetate with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, for SH, metal alkoxide such as sodium methoxide. The X/Y group containing the thioacetate $SCOR^x$ is prepared by treatment of an alcohol or alkyl halide with thioacetic acid or a salt thereof under Mitsunobu conditions. The leaving group V is a halogen. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956),1563, Gilligan et. al., J. Med. Chem., (1992), **35**, 4344, Aloup et. al., J. Med. Chem. (1987), **30**, 24, Gilman et al., J.A.C.S. (1949), **71**, 3667 and Clinton et al., J.A.C.S. (1948), **70**, 491, Barluenga et al., J. Org. Chem. (1987) **52**, 5190. Alternatively where X is OH and Y is CH_2V, V is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

In process variant (xi) the reaction is as described in den Hertzog et. al., recl.Trav. Chim. Pays-Bas, (1950),**69**, 700.

In process variant (xii) the leaving group W is preferably chloro, bromo or trifluoromethylsulphonyl and the reaction is the palladium catalysed process known as the "Buchwald" reaction (J. Yin and S. L. Buchwald, Org.Lett., 2000, 2, 1101).

In process variant (xiii) coupling of the acetylene compound (V) with the compound (IV) is accomplished using standard Pd-mediated chemistry, for example using $Pd(Ph_3P)_2Cl_2$ as the catalyst along with the addition of CuI in a mixture of triethylamine and dimethylformamide. . Selective reduction of the intermediate –C≡C- group is carried out either partially to –CH=CH- over a suitable catalyst eg Linlar catalyst, or fully to $-CH_2-CH_2-$ by other means.

Reduction of a carbonyl group A or B to CHOH can be readily accomplished using reducing agents well known to those skilled in the art, e.g. sodium borohydride in aqueous ethanol or lithium aluminium hydride in ethereal solution. This is analogous to methods described in EP53964, US384556 and J. Gutzwiller *et al, J. Amer. Chem. Soc.*, 1978, 100, 576.

The carbonyl group A or B may be reduced to CH_2 by treatment with a reducing agent such as hydrazine in ethylene glycol, at e.g. 130-160°C, in the presence of potassium hydroxide.

Reaction of a carbonyl group A or B with an organometallic reagent yields a group where R^6 or R^8 is OH and R^7 or R^9 is alkyl.

A hydroxy group on A or B may be oxidised to a carbonyl group by oxidants well known to those skilled in the art, for example, manganese dioxide, pyridinium chlorochromate or pyridinium dichromate.

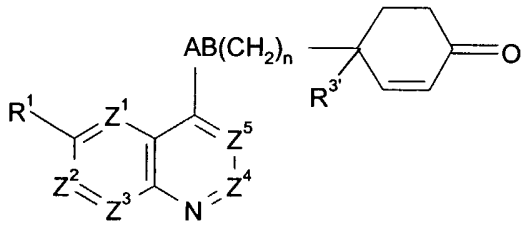
A hydroxyalkyl A-B group CHR^7CR^9OH or $CR^7(OH)CHR^9$ may be dehydrated to give the group $CR^7=CR^9$ by treatment with an acid anhydride such as acetic anhydride.

An amide carbonyl group may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

A hydroxy group in A or B may be converted to azido by activation and displacement e.g. under Mitsunobu conditions using hydrazoic acid or by treatment with diphenylphosphorylazide and base, and the azido group in turn may be reduced to amino by hydrogenation.

An example of a group Q^1 convertible to $NR^2\ R^4$ is $NR^{2'}R^{4'}$ or halogen. Halogen may be displaced by an amine $HNR^{2'}R^{4'}$ by a conventional alkylation.

When Q^1 Q^2 together form a protected oxo group this may be an acetal such as ethylenedioxy which can subsequently be removed by acid treatment to give a compound of formula (VI):



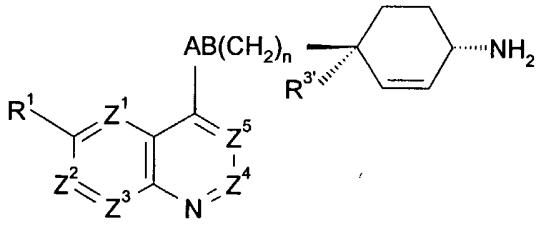
(VI)

wherein the variables are as described for formula (I)

Intermediates of formula (VI) are novel and as such form part of the invention.

The ketone of formula (VI) is reacted with an amine $HNR^{2'}R^{4'}$ by conventional reductive alkylation as described above for process variant (x).

Other novel intermediates of the invention are compounds of formula (VII):



wherein the variables are as described for formula (I).

Examples of groups $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, are $CR^{1a'}$ where $R^{1a'}$ is a group convertible to R^{1a}. $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$ and $Z^{5'}$ are preferably Z^1, Z^2, Z^3, Z^4 and Z^5.

$R^{1a'}$, $R^{1'}$ and $R^{2'}$ are preferably R^{1a}, R^1 and R^2. $R^{1'}$ is preferably methoxy. $R^{2'}$ is preferably hydrogen. $R^{3'}$ is R^3 or more preferably hydrogen, vinyl, alkoxycarbonyl or carboxy. $R^{4'}$ is R^4 or more preferably H or an N-protecting group such as t-butoxycarbonyl, benzyloxycarbonyl or 9-fluorenylmethyloxycarbonyl.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ and interconversions of R^{1a}, R^1, R^2, R^3 and R^4 are conventional. In compounds which contain an optionally substituted

hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N protecting groups are removed by conventional methods.

For example $R^{1'}$ methoxy is convertible to $R^{1'}$ hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et. al. (1973) J.Amer.Chem.Soc.,7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide and a protected amino, piperidyl, amidino or guanidino group or group convertible thereto, yields, after conversion/deprotection, R^1 alkoxy substituted by optionally N-substituted amino, piperidyl, guanidino or amidino.

R^3 hydroxy may be derivatised by conventional esterification or etherification.

The cyclohexenylamine NH_2 is converted to NR^2R^4 by conventional means such as amide or sulphonamide formation with an acyl derivative for compounds where U or X^{1a} is CO or SO_2 or, where R^4 is $-CH_2R^5{}_1$ or U or X^{1a} is CH_2, by alkylation with an alkyl halide or other alkyl derivative R_4-W in the presence of base, acylation/reduction or reductive alkylation with an aldehyde.

Where one of R^6, R^7, R^8 or R^9 contains a carboxy group and they may together with R^3 form a cyclic ester linkage. This linkage may form spontaneously during coupling of the compounds of formulae (IV) and (V) or in the presence of standard peptide coupling agents.

It will be appreciated that under certain circumstances interconvertions may interfere, for example, hydroxy groups in A or B and R^3 OH and the cyclohexenylamine will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for nitrogen, during conversion of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ or $R^{4'}$, or during the coupling of the compounds of formulae (IV) and (V).

Compounds of formulae (IV) and (V) are known compounds, (see for example Smith *et al, J. Amer. Chem. Soc.*, 1946, 68, 1301) or prepared analogously, see for example the references cited above.

The 4-amino derivatives are commercially available or may be prepared by conventional procedures from a corresponding 4-chloro derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

4-Alkenyl compounds of formula (IV) may be prepared by conventional procedures from a corresponding 4-halogeno-derivative by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345.

4-Halogeno derivatives of compounds of formula (IV) are commercially available, or may be prepared by methods known to those skilled in the art. A 4-chloroquinoline is

prepared from the corresponding quinolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A-4-bromo-substituent may be prepared from the quinolin- or naphthyridin-4-one by reaction with phosphorus tribromide (PBr3) in DMF. A 4-chloroquinazoline is prepared from the corresponding quinazolin-4-one by reaction with phosphorus oxychloride ($POCl_3$) or phosphorus pentachloride, PCl_5. A quinazolinone and quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield. Where the required compound of formula (IV) is a 4-halo-5,6-disubstituted quinoline (Z^1=CR^{1a}), the corresponding 5,6-disubstituted quinolin-4-one may be prepared from a 6-bromo-3,4-disubstituted aniline, by condensation with 2,2-dimethyl-[1,3]dioxane-4,6-dione and triethylorthoformate followed by heating of the resulting 2,2-dimethyl-5-[(arylamino)methylidene]-1,3-dioxane-4,6-dione intermediate in refluxing Dowtherm A, to produce the corresponding 8-bromo-5,6-disubstituted quinolin-4-one. Hydrogenolytic removal of the bromine atom using hydrogen under palladium catalysis then generates the required 5,6-disubstituted quinolin-4-one.

Activated carboxy derivatives X=A'COW of formula (IV) may be prepared from X=A'CO_2H derivatives in turn prepared from CO_2H derivatives by conventional methods such as homologation.

4-Carboxy derivatives of compounds of formula (IV) are commercially available or may be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art. For example, quinazolines may be prepared by standard routes as described by T.A. Williamson in *Heterocyclic Compounds*, 6, 324 (1957) Ed. R.C. Elderfield. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to hydroxymethyl derivatives with for example lithium aluminium hydride. Reaction with mesyl chloride and triethylamine would give the mesylate derivative. A diazo compound (X is –CH=N_2) may be prepared from the 4-carboxaldehyde via the tosyl hydrazone. The 4-carboxaldehyde may be obtained from from the acid by standard procedures well known to those skilled in the art.

A 4-oxirane derivative of compounds of formula (IV) is conveniently prepared from the 4-carboxylic acid by first conversion to the acid chloride with oxalyl chloride and then reaction with trimethylsilyldiazomethane to give the diazoketone derivative. Subsequent reaction with 5M hydrochloric acid gives the chloromethylketone. Reduction with sodium borohydride in aqueous methanol gives the chlorohydrin which undergoes ring closure to afford the epoxide on treatment with base, e.g. potassium hydroxide in ethanol-tetrahydrofuran.

Alternatively and preferably, 4-oxirane derivatives can be prepared from bromomethyl ketones which can be obtained from 4-hydroxy compounds by other routes well known to those skilled in the art. For example, hydroxy compounds can be converted to the corresponding 4-trifluoromethanesulphonates by reaction with trifluoromethanesulphonic anhydride under standard conditions (see K. Ritter, Synthesis, 1993, 735). Conversion into the corresponding butyloxyvinyl ethers can be achieved by a Heck reaction with butyl vinyl ether under palladium catalysis according to the procedure of W. Cabri *et al,* J. Org. Chem, 1992, **57** (5), 1481. (Alternatively, the same intermediates can be attained by Stille coupling of the trifluoromethanesulphonates or the analaogous chloro derivatives with (1-ethoxyvinyl)tributyl tin, T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.) The alkyloxyvinyl ethers are then converted into the corresponding bromomethylketones by treatment with N-bromosuccinimide in aqueous tetrahydrofuran in a similar manner to the procedures of J. F. W. Keana, J. Org. Chem., 1983, **48**, 3621 and T. R. Kelly, J. Org. Chem., 1996, **61**, 4623.

The 4-hydroxyderivatives can be prepared from an aminoaromatic by reaction with methylpropiolate and subsequent cyclisation, analogous to the method described in N. E. Heindel et al, J. Het. Chem., 1969, **6**, 77. For example, 5-amino-2-methoxy pyridine can be converted to 4-hydroxy-6-methoxy-[1,5]naphthyridine using this method.

If a chiral reducing agent such as (+) or (-)-B-chlorodiisopinocamphenylborane ['DIP-chloride'] is substituted for sodium borohydride, the prochiral chloromethylketone is converted into the chiral chlorohydrin with ee values generally 85-95% [see C. Bolm *et al, Chem. Ber.* 125, 1169-1190, (1992)]. Recrystallisation of the chiral epoxide gives material in the mother liquor with enhanced optical purity (typically ee 95%).

The *(R)*-epoxide, when reacted with an amine derivative gives ethanolamine compounds as single diastereomers with *(R)*-stereochemistry at the benzylic position.

Alternatively, the epoxide may be prepared from the 4-carboxaldehyde by a Wittig approach using trimethylsulfonium iodide [see G.A. Epling and K-Y Lin, *J. Het. Chem.*, 1987, 24, 853-857], or by epoxidation of a 4-vinyl derivative.

Pyridazines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 3, Ed A.J. Boulton and A. McKillop and napthyridines may be prepared by routes analogous to those described in Comprehensive Heterocyclic Chemistry, Volume 2, Ed A.J. Boulton and A. McKillop.

4-Hydroxy-1,5-naphthyridines can be prepared from 3-aminopyridine derivatives by reaction with diethyl ethoxymethylene malonate to produce the 4-hydroxy-3-carboxylic acid ester derivative with subsequent hydrolysis to the acid, followed by thermal decarboxylation in quinoline (as for example described for 4-Hydroxy-[1,5]naphthyridine-3-carboxylic acid, J. T. Adams *et al., J.Amer.Chem.Soc.,* 1946, **68**,

1317). A 4-hydroxy-[1,5]naphthyridine can be converted to the 4-chloro derivative by heating in phosphorus oxychloride, or to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base. A 4-amino 1,5-naphthyridine can be obtained from the 4-chloro, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with n-propylamine in pyridine.

Similarly, 6-methoxy-1,5-naphthyridine derivatives can be prepared from 3-amino-6-methoxypyridine.

1,5-Naphthyridines may be prepared by other methods well known to those skilled in the art (for examples see P.A. Lowe in "Comprehensive Heterocyclic Chemistry" Volume 2, p581-627, Ed A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984).

The 4-hydroxy and 4-amino-cinnolines may be prepared following methods well known to those skilled in the art [see A.R. Osborn and K. Schofield, *J. Chem. Soc.* 2100 (1955)]. For example, a 2-aminoacetopheneone is diazotised with sodium nitrite and acid to produce the 4-hydroxycinnoline with conversion to chloro and amino derivatives as described for 1,5-naphthyridines.

The compounds of formula (V) are either commercially available or may be prepared by conventional methods.

For compounds of formula (V), where Y is $NHR^{11'}$ suitable amines may be prepared from the corresponding 4-substituted cyclohexenyl acid or alcohol. In a first instance, an N-protected cyclohexenyl amine containing an acid bearing substituent, can undergo a Curtius rearrangement and the intermediate isocyanate can be converted to a carbamate by reaction with an alcohol. Conversion to the amine may be achieved by standard methods well known to those skilled in the art used for amine protecting group removal. For example, an acid substituted N-protected cyclohexenyl amine can undergo a Curtius rearrangement e.g. on treatment with diphenylphosphoryl azide and heating, and the intermediate isocyanate reacts in the presence of 2-trimethylsilylethanol to give the trimethylsilylethylcarbamate (T.L. Capson & C.D. Poulter, *Tetrahedron Lett.*, 1984, 25, 3515). This undergoes cleavage on treatment with tetrabutylammonium fluoride to give the 4-amine substituted N-protected compound of formula (V). Alternatively, an acid group $(CH_2)_{n-1}CO_2H$ may be converted to $(CH_2)_nNHR^{11}$ by reaction with an activating agent such as isobutyl chloroformate followed by an amine $R^{11'}NH_2$ and the resulting amide reduced with a reducing agent such as $LiAlH_4$.

In a second instance, an N-protected cyclohexenyl amine containing an alcohol bearing substituent undergoes a Mitsunobu reaction (for example as reviewed in Mitsunobu, *Synthesis*, (1981), 1), for example with phthalimide in the presence of diethyl azodicarboxylate and triphenylphosphine to give the phthalimidoethyl cyclohexenyl

amine. Removal of the phthaloyl group, for example by treatment with methylhydrazine, gives the amine of formula (V).

Compounds of formula (V) where n=1 may be prepared from the compound where n=0 by homologation eg starting from a compound of formula (V) where Y=CO_2H.

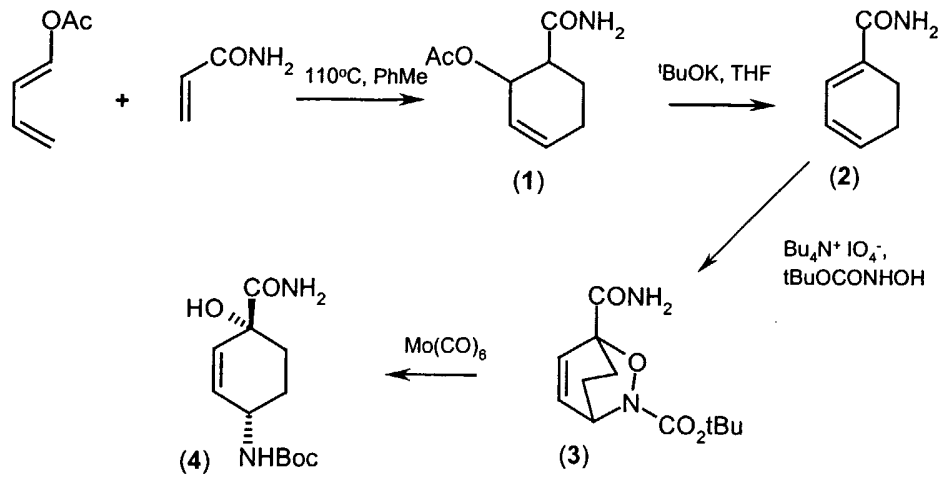
Compounds of formula (V) with a –C≡CH group may be prepared from the ketone treated with trimethylsilylacetylene and n-butyl lithium in dimethylformamide at low temperature followed by removal of the trimethylsilyl group with potassium carbonate in methanol or a fluoride source such as KF or tetrabutylammonium fluoride.

Compounds of formula (V) with a –CONHR^{11} group may be prepared from the corresponding nitrile by partial hydrolysis under basic conditions.

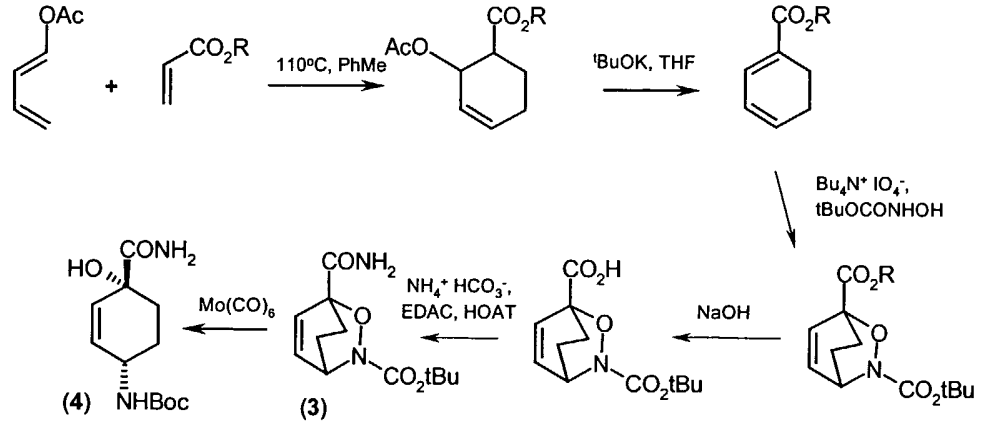
Compounds of formula (V) substituted by R^3 = OH may be prepared from a 1-keto derivative via a cyanohydrin reaction with sodium cyanide/hydrochloric acid in an ether/water two phase system (J. Marco *et al* Tetrahedron, 1999, **55**, (24), 7625), or using trimethylsilylcyanide and zinc iodide catalysis in dichloromethane (A. Abad et al, J. Chem. Soc., Perkin 1, 1996, **17**, 2193), followed by hydrolysis to give the α-hydroxy acid (Compound(V), Y=CO_2H, n=0, $R^{3'}$ =OH and Q^1 is $NR^{2'}R^{4'}$) or partial hydrolysis to the carboxamide –$CONH_2$ as described above. In examples where there is trimethylsilyl protection of the alcohol, this is removed under the hydrolysis conditions. It will be appreciated that the amine protecting group eg N-carboxylic acid *tert*-butyl ester may be concommitantly removed during the hydrolysis step, necessitating a standard reprotection with di-*tert*-butyl dicarbonate, giving key intermediates (V) such as (4-carbamoyl-4-hydroxy-cyclohexyl)-carbamic acid *tert*-butyl ester. It is noteworthy that during the cyanohydrin formation there is little or no stereoselectivity with regard to relative stereochemistry, and the (4-carbamoyl-4-hydroxy-cyclohexyl)-carbamic acid *tert*-butyl ester produced in this process is a mixture of *cis* and *trans* stereoisomers.

A Reformatsky reaction with the keto-derivative and an α-bromocarboxylic acid ester and zinc, followed by acid hydrolysis would afford the β-hydroxycarboxylic acid directly (Compound (V) Y=CO_2H, n=1, $R^{3'}$ =OH)..

Compounds of formula (V) substituted by R^3 = OH and n=0 may preferably be prepared with control of relative stereochemistry by cycloaddition chemistry. A Diels Alder reaction between acrylamide and acetoxy butadiene gives (1). Elimination of acetic acid and hetero Diels Alder reaction with an *in-situ* generated acyl nitroso compound gives the tricyclic hydroxylamine product (3). The NO bond is cleaved, for example by molybdenum hexacarbonyl or by other methods known in the literature.



Alternatively an ester of acrylic acid can be used which can subsequently be deprotected and converted to the amide by standard procedures:



The Boc group in the acyl nitroso component may be replaced by another protecting group which may be subsequently removed during the synthesis and replaced by Boc. The nitroso acyl group and/or the acylate ester moiety may be homochiral allowing the synthesis of individual enantiomers.

R^4-halides and R^4-W derivatives, acyl derivatives or aldehydes are commercially available or are prepared conventionally. The aldehydes may be prepared by partial reduction of the corresponding ester with lithium aluminium hydride or di-isobutylaluminium hydride or more preferably by reduction to the alcohol, with lithium aluminium hydride or sodium borohydride (see *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., Wiley, N.Y., 1997; *JOC*, 3197, 1984; *Org. Synth. Coll.*, 102, 1990; 136, 1998; *JOC*, 4260, 1990; *TL*, 995, 1988; *JOC*, 1721, 1999; *Liebigs Ann./Recl.*, 2385, 1997; *JOC*, 5486, 1987) , followed by oxidation to the aldehyde with manganese (II) dioxide. The aldehydes may also be prepared from carboxylic acids in two stages by conversion to a mixed anhydride for example by reaction with isobutyl chloroformate followed by reduction with sodium borohydride (R. J. Alabaster et al., Synthesis, 598, 1989) to give the hydroxymethyl substituted heteroaromatic or aromatic

and then oxidation with a standard oxidising agent such as pyridinium dichromate or manganese (II) dioxide. Acyl derivatives may be prepared by activation of the corresponding ester. R^4-halides such as bromides may be prepared from the alcohol R^4OH by reaction with phosphorus tribromide in dichloromethane/triethylamine. Where X^{2a} is CO and X^{3a} is NR^{13a} the R^4-halide may be prepared by coupling an X^{4a}-NH_2 amine and bromoacetyl bromide. R^4-W derivatives such as methanesulphonyl derivatives may be prepared from the alcohol R^4OH by reaction with methane sulphonyl chloride. The leaving group W may be converted to another leaving group W, e.g. a halogen group, by conventional methods. Alternatively the aldehyde $R^5{}_2CHO$ and sulphonic acid derivative $R^5{}_2SO_2W$ may be generated by treatment of the $R^5{}_2H$ heterocycle with suitable reagents. For example benzoxazinones, or more preferably their N-methylated derivatives can be formylated with hexamine in either trifluoroacetic acid or methanesulfonic acid, in a modified Duff procedure [O. I. Petrov et al. *Collect. Czech. Chem. Commun.* **62**, 494-497 (1997)]. 4-Methyl-4H-benzo[1,4]oxazin-3-one may also be formylated using dichloromethyl methyl ether and aluminium chloride giving exclusively the 6-formyl derivative.

Reaction of a $R^5{}_2H$ heterocycle with chlorosulphonic acid gives the sulphonic acid derivative (by methods analogous to Techer *et. al., C.R.Hebd. Seances Acad. Sci. Ser.C*; **270**, 1601, 1970).

The aldehyde $R^5{}_2CHO$ may be generated by conversion of an $R^5{}_2$halogen or $R^5{}_2$trifluoromethane sulphonyloxy derivative into an olefin with subsequent oxidative cleavage by standard methods. For example, reaction of a bromo derivative under palladium catalysis with trans-2-phenylboronic acid under palladium catalysis affords a styrene derivative which upon ozonolysis affords the required $R^5{}_2CHO$ (Stephenson, G. R., Adv. Asymmetric Synth. (1996), 275-298. Publisher: Chapman & Hall, London).

Where $R^5{}_2$ is an optionally substituted benzoimidazol-2-yl group, the compound of formula (V) where $R^{4'}$ is R^4 may be obtained by converting a $R^{4'}$ cyanomethyl group with partial hydrolysis to give the 2-ethoxycarbonimidoylethyl group which can then be condensed with an appropriately substituted 1,2-diaminobenzene to give the required benzoimidazol-2-yl group.

$R^5{}_2H$ heterocycles are commercially available or may be prepared by conventional methods. For example where a benzoxazinone is required, a nitrophenol may be alkylated with for example ethyl bromoacetate and the resulting nitro ester reduced with Fe in acetic acid (alternatively Zn/AcOH/HCl or H_2 Pd/C or H_2 Raney Ni). The resulting amine will undergo spontaneous cyclisation to the required benzoxazinone. Alternatively a nitrophenol may be reduced to the aminophenol, which is reacted with chloroacetyl chloride [method of X. Huang and C. Chan, *Synthesis* 851 (1994)] or ethyl

bromoacetate in DMSO [method of Z. Moussavi et al. *Eur. J. Med. Chim. Ther.* **24**, 55-60 (1989)]. The same general routes can be applied to prepare benzothiazinones [See for example F. Eiden and F. Meinel, Arch. Pharm. 312, 302-312 (1979), H. Fenner and R Grauert *Liebigs. Ann. Chem.* 193-313 (1978)]]. A variety of routes are available to prepare aza analogues of benzothiazinones via the key corresponding aldehydes. For instance, 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-b][1,4]thiazine-7-carbaldehyde may be accessed from 5-fluoro-2-picoline (E. J. Blanz, F. A. French, J. R. DoAmaral and D. A. French, J. Med. Chem. **1970**, *13*, 1124-1130) by constructing the thiazinone ring onto the pyridyl ring then functionalising the methyl substituent, as described in the Examples. The dioxin analogue of this aza substitution patern, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde is accessible from Kojic acid by aminolysis from pyrone to pyridone then annelating the dioxin ring, again as described in the subsequent experimental data. Other aza substitution patterns with pyridothiazin-3-one, pyridooxazin-3-one, and pyridodioxin ring systems are also accessible, again as descibed in the Examples. Ortho-aminothiophenols may be conveniently prepared and reacted as their zinc complexes [see for example V. Taneja et al *Chem. Ind.* 187 (1984)]. Benzoxazolones may be prepared from the corresponding aminophenol by reaction with carbonyl diimidazole, phosgene or triphosgene. Reaction of benzoxazolones with diphosporus pentasulfide affords the corresponding 2-thione. Thiazines and oxazines can be prepared by reduction of the corresponding thiazinone or oxazinone with a reducing agent such as lithium aluminium hydride.

The amines $R^{2'}R^{4'}NH$ are available commercially or prepared conventionally. For example amines may be prepared from a bromo derivative by reaction with sodium azide in dimethylformamide (DMF), followed by hydrogenation of the azidomethyl derivative over palladium-carbon. An alternative method is to use potassium phthalimide/DMF to give the phthalimidomethyl derivative, followed by reaction with hydrazine in DCM to liberate the primary amine.

Amines where X^{2a} is CO and X^{3a} is NR^{13a} may be prepared by reacting an N-protected glycine derivative $HO_2C\text{-}X^{1a}\text{-}NH_2$ with $X^{4a}\text{-}NH_2$ by conventional coupling using eg EDC.

Conversions of $R^{1a'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ may be carried out on the intermediates of formulae (IV) and (V) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In

preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

EXAMPLES

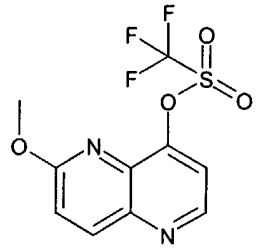
General Procedure for Reductive Alkylation

The amine (0.32 mmol) under argon in MeOH (10 mL) and DMF (10 mL) was treated with aldehyde (0.32 mmol), and 3A molecular sieves (250 mg), followed by AcOH (1 mL). (Polystyrylmethyl)trimethylammonium cyanoborohydride (0.64 mmol) was added after 2 h. Once the reaction had gone to completion the resin was removed by filtration,

and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 0-12% of 2M NH_3/MeOH in dichloromethane) to give the title compound.

Intermediate 1

1,1,1-Trifluoromethanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (I1)



Method A

(a) 4-Hydroxy-6-methoxy-[1,5]-naphthyridine

5-Amino-2-methoxypyridine (55 g, 0.44 mol) in methanol (1000 mL) with methyl propiolate (40 mL, 0.44 mol) was stirred for 48 hours, then evaporated and the product purified by chromatography on silica gel (dichloromethane) followed by recrystallisation from dichloromethane-hexane (44.6 g, 48%).

The unsaturated ester (10.5g, 0.05 mol) in warm Dowtherm A (50 mL) was added over 3 minutes to refluxing Dowtherm A, and after a further 20 minutes at reflux the mixture was cooled and poured into diethyl ether. The precipitate was filtered to give a solid (6.26 g, 70%).

(b) 1,1,1-Trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester

4-Hydroxy-6-methoxy-[1,5]-naphthyridine (1a Method A) (10 g, 0.057 mol) in dichloromethane (200 mL) containing 2,6-lutidine (9.94 mL, 0.086 mol) and 4-dimethylaminopyridine (0.07 g, 0.0057 mol) was cooled in ice and treated with trifluoromethanesulfonic anhydride (10.5 mL, 0.063 mol). After stirring for 2.5 h the mixture was washed with saturated ammonium chloride solution, dried, evaporated and purified on silica gel (dichloromethane) to give a solid (13.2 g).

Method B

(a) 2,2-Dimethyl-5-({[6-(methoxy)-3-pyridinyl]amino}methylidene)-1,3-dioxane-4,6-dione

A mixture of 6-(methoxy)-3-pyridinamine (50g, 403 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (68g, 472 mmol) and triethylorthoformate (66g, 446 mmol) in ethanol (300 ml) was heated to reflux for 3 hours, then left for 2 days at room temperature. Filtration and drying afforded a white solid (102g, 91%).

MS (APCI$^+$) *m/z* 279 (MH$^+$).

(b) 6-(Methoxy)-1,5-naphthyridin-4(1*H*)-one

Meldrum's adduct (1a Method B) (51g, 183 mmol) was added portionwise over 5 minutes to refluxing Dowtherm A (300ml) (NB Dowtherm A is a commercially available eutectic mixture comprising 26.5% biphenyl and 73.5% biphenyl ether). After the addition was complete, heating was continued for a further 5 minutes then allowed to cool to room temperature. The solution was added to ether (600 ml) and the resulting suspension filtered affording a pale brown solid (24g, 74%).

MS (APCI$^+$) *m/z* 177 (MH$^+$).

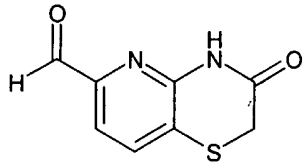
(c) 1,1,1-Trifluoromethanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester

A suspension of naphthyridone (1b Method B) (25 g, 0.142 mol) in dichloromethane (300 mL) at 0°C was treated, after 30 minutes, with 2,6-lutidine (25 mL, 0.21 mol) and 4-dimethylaminopyridine (1.5g, 12.3 mmol). After a further 15 minutes, a solution of triflic anhydride (26.5 mL, 0.158 mol) in dichloromethane was added dropwise over 30 minutes. The reaction mixture was stirred at 0°C for 45 minutes and at room temperature for a further 30 minutes. The mixture was then washed with saturated ammonium chloride, dried over magnesium sulfate and evaporated in vacuo. The solid residue was purified by flash chromatography on silica gel (eluent dichloromethane) to afford a white solid (24.8 g, 57%).

MS (APCI$^+$) *m/z* 309 (MH$^+$).

Intermediate 2

3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde (I2)



(a) Methyl 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate

A solution of ethyl 2-mercaptoacetate (1.473 mL) in DMF (48 mL) was ice-cooled and treated with sodium hydride (540 mg of a 60% dispersion in oil). After 1 hour methyl 6-amino-5-bromopyridine-2-carboxylate (3 g) (T.R. Kelly and F. Lang, *J. Org. Chem. 61*, **1996**, 4623-4633) was added and the mixture stirred for 16 hours at room temperature. The solution was diluted with EtOAc (1 litre), washed with water (3 x 300 mL), dried and evaporated to about 10 mL. The white solid was filtered off and washed with a little EtOAc to afford the title compound (0.95 g).

MS (APCI$^-$) *m/z* 223 ([M-H]$^-$, 100%)

(b) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

A solution of methyl ester (2a) (788 mg) in dioxan (120 mL)/water (30 mL) was treated dropwise over 2 h with 0.5M NaOH solution (8 mL) and stirred overnight. After evaporation to approx. 3 mL, water (5 mL) was added and 2N HCl to pH4. The precipitated solid was filtered off, washed with a small volume of water and dried under vacuum to give the title compound as a solid (636 mg).

MS (APCI$^-$) *m/z* 209 ([M-H]$^-$, 5%), 165([M-COOH]$^-$, 100%)

(c) 6-Hydroxymethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine

A solution of carboxylic acid (2b) (500 mg) in THF (24 mL) with triethylamine (0.396 mL) was cooled to -10°C and isobutyl chloroformate (0.339 mL) added. After 20 min the suspension was filtered through kieselguhr into an ice-cooled solution of sodium borohydride (272 mg) in water (8 mL), the mixture stirred 30 min and the pH reduced to 7 with dilute HCl. The solvent was evaporated and the residue triturated under water. The product was filtered and dried under vacuum to give the title compound as a white solid (346 mg).

MS (APCI$^-$) *m/z* 195 ([M-H]$^-$, 50%), 165(100%)

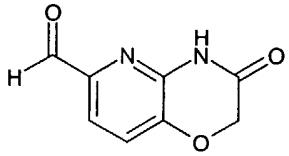
(d) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde

A solution of alcohol (2c) (330 mg) in dichloromethane (30 mL)/THF (30 mL) was treated with manganese dioxide (730 mg) and stirred at room temperature. Further manganese dioxide was added after 1 h (730 mg) and 16 h (300 mg). After a total of 20 h the mixture was filtered through kieselguhr and the filtrate evaporated. The product was triturated with EtOAc/hexane (1:1) and collected to give the title compound as a solid (180 mg).

MS (APCI$^-$) *m/z* 195 ([M-H]$^-$, 95%), 165 (100%)

Intermediate 3

3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (I3)



(a) 2-Bromo-5-hydroxy-6-nitropyridine

3-Hydroxy-2-nitropyridine (20 g, 0.143 mol) was dissolved in methanol (400 mL) and a solution of 25% sodium methoxide in methanol (33 mL, 0.13 mol) was added at room temperature. The mixture was stirred for 30 min, then was cooled to 0 °C, and

bromine (7.2 mL, 0.14 mol) was added slowly. The reaction was then stirred at 0 °C for 30 min, then was quenched with glacial AcOH (2.5 mL). The solvent was removed *in vacuo* to afford material (30 g, 96%), which was used without further purification.
MS (ES) *m/z* 219.0 $(M + H)^+$.

(b) Ethyl (6-bromo-2-nitro-pyridin-3-yloxy)acetate

Nitropyridine (3a) (30 g, 0.14 mol) was suspended in acetone (200 mL), and potassium carbonate (39 g, 0.28 mol) was added, followed by ethyl bromoacetate (15.7 ml, 0.14 mol). The reaction was heated at reflux for 10 h, then was cooled to room temperature and diluted with Et_2O. The precipitate was removed by suction filtration, and the filtrate was concentrated *in vacuo* to afford material (38 g, 89%), which was used without further purification.
MS (ES) *m/z* 305.0 $(M + H)^+$.

(c) 6-Bromo-4*H*-pyrido[3,2-b][1,4]oxazin-3-one

Ethyl ester (3b) (38 g, 0.125 mol) was dissolved in glacial AcOH (150 mL), and iron powder (20 g, 0.36 mol) was added. The mixture was mechanically stirred and heated at 90 °C for 5 h, then was cooled to room temperature and diluted with EtOAc (300 mL). The mixture was filtered through a pad of silica gel and the filtrate was concentrated *in vacuo* and the residue recrystallized from MeOH (15 g, 52%).
MS (ES) *m/z* 229.0 $(M + H)^+$.

(d) 6-((*E*)-Styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

Pyridooxazinone (3c) (6.0 g, 26.3 mmol) and *trans*-2-phenylvinylboronic acid (3.9 g, 26.3 mmol) were dissolved in 1,4-dioxane (150 mL) and the solution was degassed with argon. $(Ph_3P)_4Pd$ (230 mg, 0.2 mmol) was added, followed by a solution of potassium carbonate (6.9 g, 50 mmol) in H_2O (20 mL). The reaction was heated at reflux under argon overnight, then was cooled to room temperature and diluted with EtOAc (200 mL). The solution was washed sequentially with H_2O and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The solid residue was purified by flash chromatography on silica gel (5-10% EtOAc/$CHCl_3$) to afford a solid (2.5 g, 38%). MS (ES) *m/z* 253.0 $(M + H)^+$.

(e) 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde

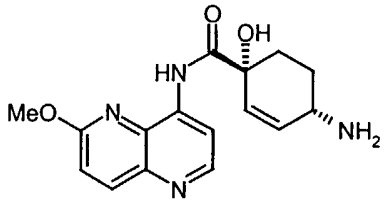
Pyridooxazinone (3d) (1.2 g, 4.8 mmol) was dissolved in DCM (200 mL) and the solution was cooled to -78 °C. Ozone was bubbled through the solution with stirring until a pale blue colour appeared, then the excess ozone was removed by bubbling oxygen through the solution for 15 min. Dimethylsulfide (1.76 mL, 24 mmol) was added to the

solution, and the reaction was stirred at -78 °C for 3 h, then at room temperature overnight. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O (50 mL). The collected solid was washed with additional Et_2O and dried to afford a solid (700 mg, 82%).

MS (ES) *m/z* 179.0 $(M + H)^+$.

Intermediate 4

(1*R*,4*S*)-4-Amino-1-hydroxy-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide and (1*S*,4*R*)-4-Amino-1-hydroxy-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (I4)



(a) Acetic acid 6-carbamoyl-cyclohex-2-enyl ester

1-Acetoxy-1,3-butadiene (20.79 g, 185 mmol) was dissolved in toluene (21 mL). To this was added acrylamide (11.98 g, 168 mmol) and hydroquinone (111 mg). The colourless solution was heated at 110°C for 116 h under argon. More 1-acetoxy-1,3-butadiene (5.67 g, 51 mmol) was then added, and heating continued for a further 24 h. The solution was cooled then DCM added. This solution was purified by Biotage 75 chromatography twice on silica gel (2 x 400 g) (DCM:MeOH 0-3%) to give the title compound as a viscous oil (21.76 g, 119 mmol, 70%), which solidified on standing; δH ($CDCl_3$) 1.83-2.33 (7H, m), 2.51-2.66 (1H, m), 5.54-6.05 (5H, m).

(b) Cyclohexa-1,3-dienecarboxylic acid amide

To acetic acid ester (4a) (4.00 g, 21.8 mmol) in dry THF (75 mL) was added, over 20 min, potassium *tert*-butoxide in THF (1 M, 24 mL, 24 mmol). After stirring for 2.8 h, EtOAc (300 mL) was added and the solution washed with water (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound as a brown oil (>100%). This was used immediately without further purification.

(c) 1-Carbamoyl-2-oxa-3-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic acid *tert*-butyl ester

To the crude amide (4b) (max 21.8 mmol) in DCM (160 mL) was added *N*-hydroxy carbamic acid *tert*-butyl ester (3.05 g, 22.9 mmol). This solution was cooled in an ice bath then a solution of tetrabutylammonium periodate (9.93 g, 22.9 mmol) in DCM (30 mL) was added dropwise. After stirring for a further 17 h the mixture was reduced to

a small volume *in vacuo* then diluted with EtOAc. The mixture was then washed with water, aqueous sodium bisulphite (x2), and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel, Pet 40-60:EtOAc 2-60%), to give the title compound as a white solid (1.77 g, 6.96 mmol, 32%).

δH ($CDCl_3$) 1.47 (9H s), 1.52-1.62(1H, m), 1.74-1.84 (1H, m), 2.12-2.20 (1H, m), 4.73-4.78 (1H, m), 5.48 (1H, br s), 6.57-6.62 (3H, m).

m/z (ES+) 277 (MNa^+, 100%).

(d) (4-Carbamoyl-4-hydroxy-cyclohex-2-enyl)-carbamic acid *tert*-butyl ester

To *tert*-butyl ester (4c) (998 mg, 3.93 mmol) in MeCN:H_2O (15:1) (70 mL) was added molybdenum hexacarbonyl (2.07 g, 7.85 mmol) and the mixture heated to reflux. After 14 h the reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, DCM:MeOH 0-10%), to give the title compound as a white solid (454 mg, 1.77 mmol, 45%).

δH (CD_3OD) 1.44 (9H s), 1.60-1.71 (1H, m), 1.77-1.82 (1H, m), 1.91-1.98 (1H, m), 2.05-2.12 (1H, m), 4.03-4.07 (1H, m), 5.62-5.65 (1H, m), 5.81-5.84 (1H, m).

m/z (ES+) 279 (MNa^+, 100%).

Enantiomeric resolution of intermediate 4d by chiral HPLC.

Intermediate 4d (0.5g) was dissolved in ethanol (10mL) and applied to a column of ChiralPak AS (100 x 200 mm, 20u) . Elution with 80:20 hexane: isopropyl alcohol was carried out with a flow rate of 450 mL/min, and UV detection at 220 nm. A total of 2g was separated in 4 runs of 0.5 g each, yielding the separate enantiomers:

E1 (0.856 g) alpha D +111° (c= 0.7 CH_3OH) with retention time 5.3 mins on analytical chiral HPLC (Chiralpak AS 4.6x 150 mm, 10u, 1.0 mL/min, 80:20 hexane:isopropyl alcohol).

E2 (0.792g) alpha D -113° (c= 0.7 CH_3OH) with retention time 7.6 mins on analytical chiral HPLC (Chiralpak AS 4.6x 150 mm, 10u, 1.0 mL/min, 80:20 hexane:isopropyl alcohol).

(e) [4-Hydroxy-4-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-cyclohex-2-enyl]-carbamic acid *tert*-butyl ester

A mixture of ester (4d) (427 mg, 1.67 mmol), cesium carbonate (689 mg, 2.11 mmol), tris(dibenzylideneacetone)dipalladium(0) (30.5 mg, 0.033 mmol), and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (62 mg, 0.1 mmol) in dry 1,4-dioxane (22 mL) under argon, was sonicated for 20 minutes then 1,1,1-trifluoromethanesulfonic acid 6-

methoxy-[1,5]naphthyridin-4-yl ester Intermediate 1 (514 mg, 1.67 mmol) added, and the mixture stirred and heated under argon at 60°C. After 15 h the mixture was cooled, filtered, and the filtrate concentrated *in vacuo* to give a residue which was purified by flash column chromatography (silica gel, DCM:MeOH 0-5%), to give the title compound as a white solid (364 mg, 0.877 mmol, 53%).

δH (CD_3OD) 1.46 (9H s), 1.71-1.81 (1H, m), 1.91-1.97 (1H, m), 2.02-2.07 (1H, m), 2.22-2.29 (1H, m), 4.10-4.16 (1H, m), 4.14 (3H, s), 5.75-5.79 (1H, m), 5.94-5.96 (1H, m), 7.28 (1H, d), 8.21 (1H, d), 8.51 (1H, d), 8.64 (1H, d).

m/z (ES+) 415 (MH^+, 100%).

(f) 4-Amino-1-hydroxy-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide

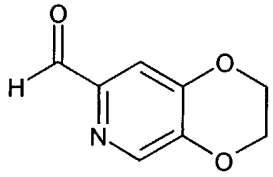
[*tert*-butyl ester (4e) (362 mg, 0.873 mmol) in dry DCM (30 mL) was treated with trifluoroacetic acid (10 mL). After 30 min the solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica gel, DCM:MeOH/NH_3 (2M) 0-10%) to give the title compound as a white solid (242 mg, 0.771 mmol, 88%).

δ_H (CD_3OD) 1.61-1.70 (1H, m), 1.91-1.98 (1H, m), 2.02-2.08 (1H, m), 2.19-2.27 (1H, m), 3.41-3.45 (1H, m), 4.14 (3H, s), 5.72-5.76 (1H, m), 5,97-6.01 (1H, m), 7.28 (1H, d), 8.20 (1H, d), 8.51 (1H, d), 8.64 (1H, d).

m/z (ES+) 315 (MH^+, 100%).

Intermediate 5

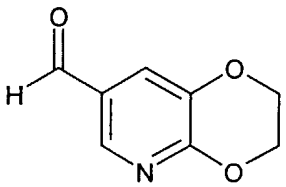
2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carbaldehyde (I5)



The title compound was prepared as described in Example 24c of WO02056882.

Intermediate 6

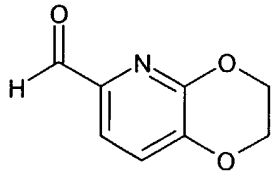
2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine-7-carbaldehyde (I6)



The title compound was prepared as described in Example 40e of WO02056882.

Intermediate 7

2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine-6-carbaldehyde (I7)



(a) 6-Methyl-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine-N-oxide

6-Methyl-2,3-dihydro-[1,4]dioxino[2,3-b]pyridine (Example 19b of WO02056882.) (190mg, 1.26mmol) was dissolved in dichloromethane (10mL) and cooled to 0°C. To this solution was added *meta*-chloroperbenzoic acid (388mg, 1.26mmol) and stirring was continued for 5 hours at room temperature. The volatiles were removed under reduced pressure and the residue purified on silica gel using a dichloromethane and methanol gradient. This provided the desired compound as a white solid (146mg, 69%).

MS (APCI+) m/z 168 (MH+).

(b) Acetic acid 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-ylmethyl ester

N-oxide (7a) (146mg, 0.874mmol) was dissolved in acetic anhydride (5mL). The solution was heated to reflux for 10 hours after which time the volatiles were removed. This afforded the desired product which was used without further purification.

(c) (2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl)-methanol

Ester (7b) (182mg, 0.87mmol) was dissolved in a mixture of tetrahydrofuran and water (1:1, 4mL) and treated with sodium hydroxide (70mg, 1.74mmol). The resulting solution was stirred at room temperature for 12 hours after which time the solvent was removed under reduced pressure. The product obtained in this fashion was used without further purification.

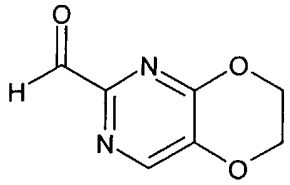
(d) 2,3-Dihydro-[1,4]dioxino[2,3-b]pyridine-6-carbaldehyde

Alcohol (7c) (145mg, 0.87mmol) was dissolved in dichloromethane (5mL) and treated with manganese dioxide (151mg, 1.74mmol). The resulting slurry was stirred at room temperature and after 5 hours a further batch of manganese dioxide (151mg, 1.74mmol) was added. The slurry was stirred for a further 10 hours and then filtered through Celite and the volatiles removed *in vacuo*. The residue was purified on silica gel to afford the desired product (95mg, 66%).

MS (APCI+) m/z 166 (MH+).

Intermediate 8

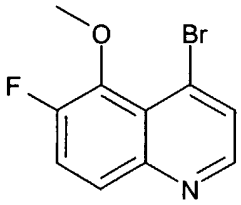
6,7-dihydro[1,4]dioxino[2,3-*d*]pyrimidine-2-carbaldehyde (I8)



The carboxaldehyde was prepared from 5-benzyloxy-2-hydroxymethyl-3H-pyrimidin-4-one (A. Harris, Aust. J. Chem., 1976, 29, 1335) by hydrogenolysis of the benzyl protecting group and cyclisation with dibromoethane to give (6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl)-methanol followed by oxidation with manganese(II)oxide to afford the product.

Intermediate 9

4-bromo-6-fluoro-5-(methyloxy)quinoline (I9)



(a) 4-bromo-2-fluorophenyl ethyl carbonate

A solution of 4-bromo-2-fluorophenol (25 g, 130 mmol) and triethylamine (21.6 mL, 155 mmol) in dichloromethane (120 mL) at 0°C was treated with a solution of ethylcloroformate (14.8 mL, 155 mL) in dichloromaethane (40 mL) added dropwise. The reaction micture was stirred at 0°C for 1 hour and allowed to reach room temperature. The reaction mixture was then washed twice with water. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford the product as a colorless oil (32 g, 93%).

MS (+ve ion electrospray) m/z 263 (MH^+).

(b) 4-bromo-2-fluoro-5-nitrophenyl ethyl carbonate

To a solution of (9a) (32 g, 130 mmol) in concentrated sulfuric acid (55mL) at 10°C, fuming nitric acid (8.49 mL, 195 mmol) was added dropwise. After 2 hours, the reaction mixture was poured onto ice/water and extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo* to afford the product as a yellow oil (35 g, 93%).

MS (+ve ion electrospray) m/z 309 (MH^+).

(c) 4-bromo-2-fluoro-5-nitrophenol

A solution of (9b) (35 g, 113 mmol) in methanol (200 mL) was treated with sodium bicarbonate (19 g, 227 mmol). The reaction mixture was stirred at 60°C for 4 hours. Methanol was evaporated under vacuum. Water (55 mL) was added to the residue and the aqueous layer was acidified to pH5 by addition of a solution of hydrogen chloride 5N. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo* to afford the product as a yellow solid (25 g, 93%).
MS (+ve ion electrospray) m/z 237 (MH^+).

(d) 4-bromo-2-fluoro-5-nitrophenyl methyl ether

A solution of phenol (9c) (25 g, 106 mmol) in DMF (200 mL) was treated with potassium carbonate (28.9 g, 212 mmol) and methyl iodide (12.8 mL, 212 mmol). The reaction mixture was stirred at 60°C for 5 hours and evaporated in vacuo. The mixture was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated in vacuo to afford the product as a yellow solid (25.6 g, 97%).
MS (+ve ion electrospray) m/z 251 (MH^+).

(e) 2-bromo-4-fluoro-5-(methyloxy)aniline

A mixture of (9d) (25.5 g, 102 mmol), acetic acid (250 mL), ethanol (250 mL) and iron powder (22.7 g, 408 mmol) was heated at 100°C for 4 hours. The reaction mixture was cooled down to room temperature, diluted with water, neutralised by addition of potassium carbonate and filtered through celite. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo* to afford the product as a white solid (15 g, 67%).
MS (+ve ion electrospray) m/z 220 (MH^+).

(f) 5-({[2-bromo-4-fluoro-5-(methyloxy)phenyl]amino}methylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

A mixture of (9e) (15 g, 68 mmol), 2,2-dimethyl-[1,3]dioxane-4,6-dione (11.8 g, 82 mmol) and trimethylorthoformate (13.6 ml) in ethanol (70 ml) was refluxed for 3hours. After cooling the solid was filtered off, washed with ethanol and air dried. The product was obtained as an off-white solid (23.3 g, 92%).
MS (+ve ion electrospray) m/z 374 (MH+).

(g) 8-bromo-6-fluoro-5-(methyloxy)-4(1*H*)-quinolinone

Intermediate (9f) (13 g, 34.8 mmol) was slowly added over five minutes to refluxing Dowtherm A (40 ml). After an additional five minutes at reflux, the mixture was allowed to cool to room temperature then ether was added. The product was filtered off, thoroughly washed with ether then dried *in vacuo* to afford the product as a gold coloured solid (5.4 g, 57%).
MS (+ve ion electrospray) m/z 273 (MH+).

(h) 6-fluoro-5-(methyloxy)-4(1*H*)-quinolinone

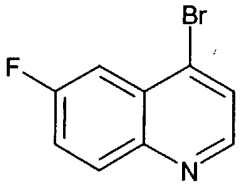
A suspension of bromoquinolone (9g) (3.5 g, 12.8 mmol) in dioxan/water 300mL/100mL was treated with a solution of sodium hydroxide 1N (12.8 mL, 12.8 mmol). The solution was hydrogenated with palladium on charcoal. The reaction mixture was filtered through kieselguhr, acidified by addition of a solution of hydrogen bromide and evaporated to dryness. The residue was treated with water (30 mL), filtered and dried in vacuo to afford the product as a white solid (3.0 g, 60%).
MS (+ve ion electrospray) m/z 194 (MH+).

(i) 4-bromo-5-fluoro-6-(methyloxy)quinoline

To a solution of (9h) (2 g, 10 mmol) in DMF (13 ml) was added dropwise phosphorus tribromide (1.2 ml, 12.4 mmol) over five minutes (slightly exothermic). The reaction was allowed to cool to room temperature and was then diluted with ice water and stirred 1 hour then diluted with additional water. The product was filtered off, washed with water and dried *in vacuo* to afford the product as a white solid (1.8 g, 71%).
MS (+ve ion electrospray) m/z 257 (MH+).

Intermediate 10

4-bromo-6-fluoroquinoline (I10)



(a) 5-{[(4-fluorophenyl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione

A mixture of 4-fluoroaniline (21.3 mL, 225 mmol), 2,2-dimethyl-[1,3]dioxane-4,6-dione (38.9 g, 270 mmol) and trimethylorthoformate (44.9 ml) in ethanol (130 ml) was refluxed for 3hours. After cooling the solid was filtered off, washed with ethanol and air dried. The product was obtained as an off-white solid (55.3 g, 93%).
MS (+ve ion electrospray) m/z 265 (MH+).

(b) 6-fluoro-4(1*H*)-quinolinone

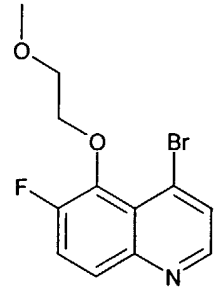
Intermediate (10a) (10.9 g, 41 mmol) was slowly added over five minutes to refluxing Dowtherm A (50 ml). After an additional five minutes at reflux, the mixture was allow to cool to room temperature then ether (50 ml) was added. The product was filtered off, thoroughly washed with ether then dried *in vacuo* to afford the product as a gold coloured solid (16.2 g, 94%).
MS (+ve ion electrospray) m/z 164 (MH+).

(c) 4-bromo-6-fluoroquinoline

To a solution of (10b) (11.3 g, 69.3 mmol) in DMF (350 ml) was added dropwise phosphorous tribromide (7.1 ml, 76.3 mmol) over five minutes (slightly exothermic). The reaction was allowed to cool to room temperature and was then diluted with ice water and stirred 1 hour then diluted with additional water. The product was filtered off, washed with water and dried *in vacuo* to afford the product as a white solid (12.0 g, 76%).
MS (+ve ion electrospray) m/z 226 (MH+).

Intermediate 11

4-bromo-6-fluoro-5-{[2-(methyloxy)ethyl]oxy}quinoline (I11)



(a) 1-bromo-5-fluoro-4-{[2-(methyloxy)ethyl]oxy}-2-nitrobenzene

A solution of 4-bromo-2-fluoro-5-nitrophenol (15 g, 59.5 mmol) in DMF (130 mL) was treated with potassium carbonate (16.4 g, 119 mmol) then bromoethyl methyl ether (7 mL, 74.4 mmol). The reaction mixture was stirred at 40°C for 7 hours. DMF was evaporated in vacuo.Partition with water and ethyl acetate. Aqueous layer was extracted several times with ethyl acetate. Combined organic layers were dried over magnesium sulfate and evaporated in vacuo to afford the product as a yellow oil (13 g, 74%).
MS (+ve ion electrospray) m/z 295 (MH+).

(b) 2-bromo-4-fluoro-5-{[2-(methyloxy)ethyl]oxy}aniline

A mixture of (11a) (11.8 g, 40.2 mmol), acetic acid (120 mL), ethanol (120 mL) and iron powder (9 g, 161 mmol) was heated at 100°C for 4 hours. The reaction mixture was cooled down to room temperature, diluted with water, neutralised by addition of

potassium carbonate and filtered through celite. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo* to afford the product as a white solid (10.2 g, 96%).
MS (+ve ion electrospray) m/z 265 (MH^+).

(c) 5-{[(2-bromo-4-fluoro-5-{[2-(methyloxy)ethyl]oxy}phenyl)amino]methylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione

A mixture of (11b) (10.2 g, 38.6 mmol), 2,2-dimethyl-[1,3]dioxane-4,6-dione (6.7 g, 46.3 mmol) and trimethylorthoformate (7.7 ml) in ethanol (45 ml) was refluxed for 3hours. After cooling the solid was filtered off, washed with ethanol and air dried. The product was obtained as an off-white solid (12.9 g, 80%).
MS (+ve ion electrospray) m/z 419 (MH+).

(d) 8-bromo-6-fluoro-5-{[2-(methyloxy)ethyl]oxy}-4(1*H*)-quinolinone

Intermediate (11c) (12.9 g, 31 mmol) was slowly added over five minutes to refluxing Dowtherm A (50 ml). After an additional five minutes at reflux, the mixture was allow to cool to room temperature then ether was added. The product was filtered off, thoroughly washed with ether then dried *in vacuo* to afford the product as a gold coloured solid (7.9 g, 81%).
MS (+ve ion electrospray) m/z 317 (MH+).

(e) 6-fluoro-5-{[2-(methyloxy)ethyl]oxy}-4(1*H*)-quinolinone

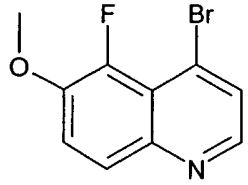
A suspension of bromoquinolone (11d) (8.2 g, 26 mmol) in dioxan/water 200mL/100mL was treated with a solution of sodium hydroxide 2N (26 mL, 52 mmol). The solution was hydrogenated with palladium on charcoal. The reaction mixture was filtered trough celite, acidified by addition of a solution of hydrogen bromide and evaporated to dryness. The residue was treated with water (30 mL), filtered and dried in vacuo to afford the product as a white solid (7.9 g, 100%).
MS (+ve ion electrospray) m/z 238 (MH+).

(f) 4-bromo-6-fluoro-5-{[2-(methyloxy)ethyl]oxy}quinoline

To a solution of (11e) (3.99 g, 13 mmol) in DMF (35 ml) was added dropwise phosphorus tribromide (1.4 ml, 15.6 mmol) over five minutes (slightly exothermic). The reaction was allowed to cool to room temperature and was then diluted with ice water and stirred 1 hour then diluted with additional water. The product was filtered off, washed with water and dried *in vacuo* to afford the product as a white solid (1.3 g, 33%).
MS (+ve ion electrospray) m/z 301 (MH+).

Intermediate 12

4-bromo-5-fluoro-6-(methyloxy)quinoline (I12)



(a) 2-bromo-5-fluoro-4-(methyloxy)aniline

A solution of bromine (3.15 mL, 61.3 mol) in dichloromethane (100mL) was added dropwise to a suspension of 3-fluoro-4-methoxyaniline (8.65 g, 61.3 mmol) and potassium carbonate (8.9 g, 64.4 mmol) in dichloromethane (200 mL) at –15°C. At the end of the addition, the reaction mixture was stirred for 30 minutes at –15°C. The reaction mixture was then treated with water (250 mL). The organic layer was separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were washed with a solution of sodium metabisulfite and dried over magnesium sulfate. Evaporation and flash silica chromatography eluting with petroleum ether/ethyl acetate 9/1 afforded the product as a pale yellow solid (10.2 g, 76%).

MS (+ve ion electrospray) m/z 220 (MH+).

(b) 5-({[2-bromo-5-fluoro-4-(methyloxy)phenyl]amino}methylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

A mixture of (12a) (10.2 g, 46.5 mmol), 2,2-dimethyl-[1,3]dioxane-4,6-dione (8.0 g, 55.9 mmol) and trimethyl orthoformate (9.3 ml) in ethanol (60 ml) was refluxed for 3hours. After cooling the solid was filtered off, washed with ethanol and air dried. The product was obtained as an off-white solid (15.6 g, 90%).

MS (+ve ion electrospray) m/z 374 (MH+).

(c) 8-bromo-5-fluoro-6-(methyloxy)-4(1*H*)-quinolinone

Intermediate (12b) (15.6 g, 41.8 mmol) was slowly added over five minutes to refluxing Dowtherm A (50 ml). After an additional five minutes at reflux, the mixture was allow to cool to room temperature then ether (50 ml) was added. The product was filtered off, thoroughly washed with ethyl acetate (20 mL) and ether (3 x 20 mL) then dried *in vacuo* to afford the product as a gold coloured solid (16.2 g, 94%).

MS (+ve ion electrospray) m/z 273 (MH+).

(d) 5-fluoro-6-(methyloxy)-4(1*H*)-quinolinone

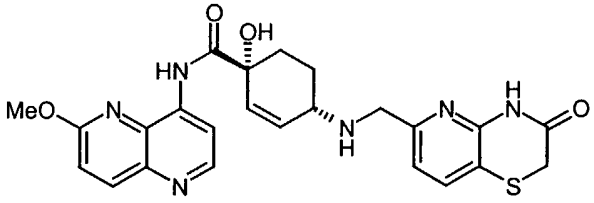
A suspension of bromoquinolone (12c) (3.3 g, 12.3 mmol) in dioxan/water 300mL/100mL was treated with a solution of sodium hydroxide 2N (12.6 mL, 24.6 mmol). The solution was hydrogenated with palladium on charcoal. The reaction mixture was filtered through celite, acidified by addition of a solution of hydrogen bromide and evaporated to dryness. The residue was treated with water (30 mL), filtered and dried in vacuo to afford the product as a white solid (5.2 g, 100%).
MS (+ve ion electrospray) m/z 194 (MH+).

(e) 4-bromo-5-fluoro-6-(methyloxy)quinoline

To a solution of (12d) (5.2 g, 26.9 mmol) in DMF (150 ml) was added dropwise phosphorus tribromide (2.8 ml, 29.6 mmol) over five minutes (slightly exothermic). The reaction was allowed to cool to room temperature and was then diluted with ice water and stirred 1 hour then diluted with additional water. The product was filtered off, washed with water and dried *in vacuo* to afford the product as a white solid (4.7 g, 69%).
MS (+ve ion electrospray) m/z 256 (MH+).

Example 1

(1*R*,4*S*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide dihydrochloride and (1*S*,4*R*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide dihydrochloride

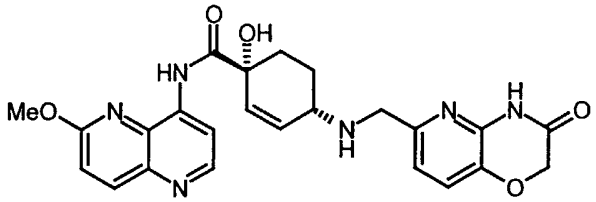


Prepared by the General Procedure for Reductive Alkylation from Intermediate 2 and racemic Intermediate 4f to give the free base of the title compound in 77% yield; δ_H ($CDCl_3/CD_3OD$) 1.68-1.79 (1H, m), 1.95-2.02 (1H, m), 2.07-2.13 (1H, m), 2.19-2.26 (1H, m), 3.32-3.38 (1H, m), 3.51 (2H, s), 3.91 (2H, s), 4.14 (3H, s), 5.80-5.83 (1H, m), 6.09-6.11 (1H, m), 7.04 (1H, d), 7.25 (1H, d), 7.67 (1H, d), 8.18 (1H, d), 8.50 (1H, d), 8.62 (1H, d); *m/z* (ES+) 493 (MH^+, 100%).

This material as a solution in DCM/MeOH 1:1 was treated with 4M HCl in 1,4-dioxane (0.5 mL), evaporated to dryness, then dried under vacuum to provide the title compound as a white solid.

Example 2

(1*R*,4*S*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide dihydrochloride and (1*S*,4*R*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide dihydrochloride



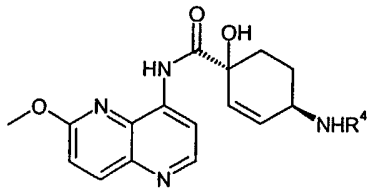
Prepared by the General Procedure for Reductive Alkylation from Intermediate 3 and Intermediate 4f on a 0.305 mmol scale to give the free base of the title compound in 72% yield; δ_H ($CDCl_3/CD_3OD$) 1.67-1.77 (1H, m), 1.98-2.02 (1H, m), 2.08-2.13 (1H, m), 2.21-2.28 (1H, m), 3.34-3.38 (1H, m), 3.88 (2H, s), 4.15 (3H, s), 4.62 (2H, s), 5.81-5.85 (1H, m), 6.07-6.09 (1H, m), 6.96 (1H, d), 7.23 (1H, d), 7.26 (1H, d), 8.19 (1H, d), 8.52 (1H, d), 8.63 (1H, d); *m/z* (ES+) 477 (MH^+, 100%).

This material as a solution in DCM/MeOH 1:1 was treated with 4M HCl in 1,4-dioxane (0.5 mL), evaporated to dryness, then dried under vacuum to provide the title compound as a white solid.

General synthetic route

The coupling of the corresponding aryl derivative and either the racemic cyclohexenyl amide (I4d) or the optically active form (E1 or E2), was carried out as described in the preparation of (4e). After deprotection of the t-butoxycarbonyl group as described in the preparation of compound I4f, the reductive alkylation with the appropriate aldehyde was carried out as described in the General Procedure, with yields as given in the following tables. The compounds were converted to the corresponding dihydrochlorides as described in Example 1.

Table 1 Methoxynaphthyridines



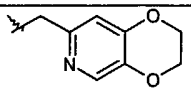
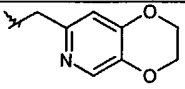
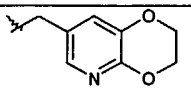
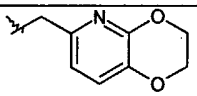
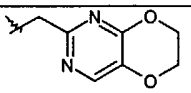
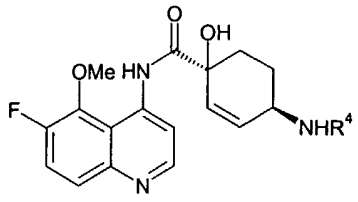
Example	R^4	amide	Aryl derivative	Aldehyde	Yield of final product	MS of final product
3		E1	I1	I5	74%	ESI 464 (MH^+, 100%)
4		E2	I1	I5	43%	ESI 464 (MH^+, 100%)
5		E2	I1	I6	43%	ESI 464 (MH^+, 100%)
6		E2	I1	I7	7%	ESI 464 (MH^+, 100%)
7		E2	I1	I8	25%	ESI 465 (MH^+, 100%)

Table 2 6-Fluoro-5-methoxy Quinolines



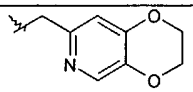
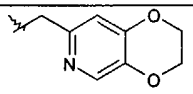
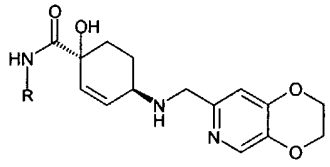
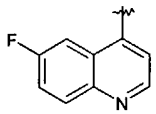
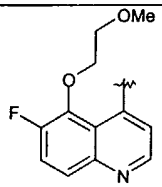
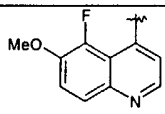
Example	R^4	Amide	Aryl derivative	Aldehyde	Yield of final product	M+ of final product
8		E1	I9	I5	56%	ES^+ 481 (MH^+,100%)
9		E2	I9	I5	62%	ES^+ 481 (MH^+, 100%)

Table 3 Dioxinopyridines



Example	R	Amide	Aryl derivative	Aldehyde	Yield of final product	M+ of final product
10		E2	I10	I5	12%	ES^+ 525 (MH^+, 100%)
11		E2	I11	I5	34%	ES^+ 525 (MH^+, 100%)
12		E2	I12	I5	40%	ES^+ 481 (MH^+, 100%)

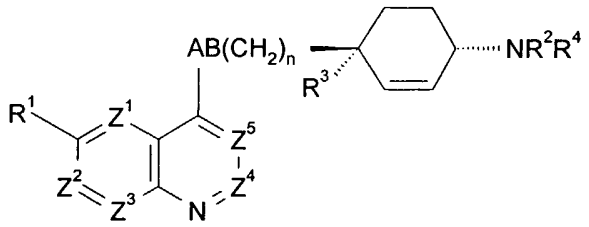
Biological Activity

The MIC (μg/ml) of test compounds against various organisms was determined including: **S. epidermidis CL7, S. aureus WCUH29, S. pneumoniae 1629, S. pyogenes CN10, H. influenzae ATCC 49247, E.faecalis 2, M. catarrhalis Ravasio, E. coli 7623.**

Examples 1, 2, 3, 4, 5 and 9 have an MIC $\leq$2 μg/ml versus all these organisms.
Examples 8, 10 have an MIC $\leq$16 μg/ml versus all these organisms.
Examples 6, 7, 11, 12 have an MIC $\leq$1 μg/ml versus some of these organisms.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

one of Z^1, Z^2, Z^3, Z^4 and Z^5 is N, one is CR^{1a} and the remainder are CH, or one of Z^1, Z^2, Z^3, Z^4 and Z^5 is CR^{1a} and the remainder are CH;

R^1 and R^{1a} are independently selected from hydrogen; hydroxy; (C_{1-6}) alkoxy optionally substituted by (C_{1-6})alkoxy, amino, piperidyl, guanidino or amidino any of which is optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, CONH2, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted (C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluromethyl; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide or an amino, piperidyl, guanidino or amidino group optionally N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups, or when Z^1 is CR^{1a}, R^1 and R^{1a} may together represent (C_{1-2})alkylenedioxy, or when Z^5 is CR^{1a}, R^{1a} may instead be, cyano, hydroxymethyl or carboxy,
provided that when Z^1, Z^2, Z^3, Z^4 and Z^5 are CR^{1a} or CH, then R^1 is not hydrogen;

R^2 is hydrogen, or (C_{1-4})alkyl or (C_{2-4})alkenyl optionally substituted with 1 to 3 groups selected from:
amino optionally substituted by one or two (C_{1-4})alkyl groups; carboxy; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, aminocarbonyl(C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-4})alkenylsulphonyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl or (C_{2-4})alkenylcarbonyl; cyano; tetrazolyl; 2-oxo-oxazolidinyl optionally substituted by R^{10}; 3-

hydroxy-3-cyclobutene-1,2-dione-4-yl; 2,4-thiazolidinedione-5-yl; tetrazol-5-ylaminocarbonyl; 1,2,4-triazol-5-yl optionally substituted by R^{10}; 5-oxo-1,2,4-oxadiazol-3-yl; halogen; (C_{1-4})alkylthio; trifluoromethyl; hydroxy optionally substituted by (C_{1-4})alkyl, (C_{2-4})alkenyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl; oxo; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or (C_{1-4})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

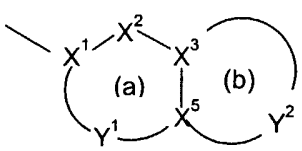
R^3 ishydroxy optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylcarbonyl or (C_{2-6})alkenylcarbonyl;

R^{10} is selected from (C_{1-4})alkyl and (C_{2-4})alkenyl either of which may be optionally substituted by a group R^{12} as defined above; carboxy; aminocarbonyl wherein the amino group is optionally substituted by hydroxy, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, trifluoromethylsulphonyl, (C_{2-6})alkenylsulphonyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; (C_{1-6})alkylsulphonyl; trifluoromethylsulphonyl; (C_{2-6})alkenylsulphonyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; and (C_{2-6})alkenylcarbonyl;

R^4 is a group $-CH_2-R^5{}_1$ in which $R^5{}_1$ is selected from:

(C_{4-8})alkyl; hydroxy(C_{4-8})alkyl; (C_{1-4})alkoxy(C_{4-8})alkyl; (C_{1-4})alkanoyloxy(C_{4-8})alkyl; (C_{3-8})cycloalkyl(C_{4-8})alkyl; hydroxy-, (C_{1-6})alkoxy- or (C_{1-6})alkanoyloxy-(C_{3-8})cycloalkyl(C_{4-8})alkyl; cyano(C_{4-8})alkyl; (C_{4-8})alkenyl; (C_{4-8})alkynyl; tetrahydrofuryl; mono- or di-(C_{1-6})alkylamino(C_{4-8})alkyl; acylamino(C_{4-8})alkyl; (C_{1-6})alkyl- or acyl-aminocarbonyl(C_{4-8})alkyl; mono- or di- (C_{1-6})alkylamino(hydroxy) (C_{4-8})alkyl; or

R^4 is a group $-U-R^5{}_2$ where $R^5{}_2$ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; aryl(C_{1-4})alkoxy;

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, carboxy, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl (C_{1-4})alkyl; arylcarbonyl; heteroarylcarbonyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

each x is independently 0, 1 or 2;

U is CO, SO_2 or CH_2; or

R^4 is a group $-X^{1a}-X^{2a}-X^{3a}-X^{4a}$ in which:

X^{1a} is CH_2, CO or SO_2;

X^{2a} is $CR^{14a}R^{15a}$;

X^{3a} is NR^{13a}, O, S, SO_2 or $CR^{14a}R^{15a}$; wherein:

each of R^{14a} and R^{15a} is independently selected from the groups listed above for R^{14} and R^{15}, provided that R^{14a} and R^{15a} on the same carbon atom are not both selected from optionally substituted hydroxy and optionally substituted amino; or

R^{14a} and R^{15a} together represent oxo;

R^{13a} is hydrogen; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl; or

two R^{14a} groups or an R^{13a} and an R^{14a} group on adjacent atoms together represent a bond and the remaining R^{13a}, R^{14a} and R^{15a} groups are as above defined; or

two R^{14a} groups and two R^{15a} groups on adjacent atoms together represent bonds such that X^{2a} and X^{3a} is triple bonded;

X^{4a} is phenyl or C or N linked monocyclic aromatic 5- or 6-membered heterocycle containing up to four heteroatoms selected from O, S and N and: optionally C-substituted by up to three groups selected from (C_{1-4})alkylthio; halo; carboxy(C_{1-4})alkyl; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; (C_{1-4})alkoxycarbonyl; formyl; (C_{1-4})alkylcarbonyl; (C_{2-4})alkenyloxycarbonyl; (C_{2-4})alkenylcarbonyl; (C_{1-4})alkylcarbonyloxy; (C_{1-4})alkoxycarbonyl(C_{1-4})alkyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl; aryl, aryl(C_{1-4})alkyl or aryl(C_{1-4})alkoxy; and

optionally N substituted by trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-6})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; aryl; aryl(C_{1-4})alkyl; (C_{1-4})alkoxycarbonyl; (C_{1-4})alkylcarbonyl; formyl; (C_{1-6})alkylsulphonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylcarbonyl, (C_{2-4})alkenyloxycarbonyl, (C_{2-4})alkenylcarbonyl, (C_{1-4})alkyl or (C_{2-4})alkenyl and optionally further substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl;

n is 0 or 1 and AB is $NR^{11}CO$, $CONR^{11}$, $CO\text{-}CR^8R^9$, $CR^6R^7\text{-}CO$, $O\text{-}CR^8R^9$, $CR^6R^7\text{-}O$, $NHR^{11}\text{-}CR^8R^9$, $CR^6R^7\text{-}NHR^{11}$, $NR^{11}SO_2$, $CR^6R^7\text{-}SO_2$ or $CR^6R^7\text{-}CR^8R^9$,

provided that n=0, B is not NR^{11}, O or SO_2,

and provided that R^6 and R^7, and R^8 and R^9 are not both optionally substituted hydroxy or amino;

and wherein:

each of R^6, R^7 , R^8 and R^9 is independently selected from: H; (C_{1-6})alkoxy; (C_{1-6})alkylthio; halo; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; (C_{2-6})alkenylcarbonyl; hydroxy, amino or aminocarbonyl optionally substituted as for corresponding substituents in R^3; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;
or R^6 and R^8 together represent a bond and R^7 and R^9 are as above defined;

in optionally substituted amino the amino group is optionally mono- or disubstituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkylsulphonyl, (C_{2-6})alkenylsulphonyl or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

in optionally substituted aminocarbonyl the amino group is optionally substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl or (C_{2-6})alkenylcarbonyl and optionally further substituted by (C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, aminocarbonyl(C_{1-6})alkyl or (C_{2-6})alkenyl;

and each R^{11} is independently H; trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkoxycarbonyl, (C_{1-6})alkylcarbonyl, (C_{2-6})alkenyloxycarbonyl, (C_{2-6})alkenylcarbonyl, (C_{1-6})alkyl or (C_{2-6})alkenyl and optionally further substituted by (C_{1-6})alkyl or (C_{2-6})alkenyl;

or where one of R^6, R^7, R^8 or R^9 contains a carboxy group they may together with R^3 form a cyclic ester linkage.

2. A compound according to claim 1 wherein Z^5 is CH, Z^3 is CH or CF, Z^1 is CH or C-OCH_3 and Z^2 and Z^4 are each CH, or Z^1 is N, Z^3 is CH or CF and Z^2, Z^4 and Z^5 are each CH

3. A compound according to any preceding claim wherein R^1 is methoxy or fluoro and R^{1a} is H or when Z^3 is CR^{1a} it may be C-F.

4. A compound according to any preceding claim wherein R^2 is hydrogen.

5. A compound according to any preceding claim wherein R^3 is hydroxy.

6. A compound according to any preceding claim wherein n is 0 and either A is CHOH or CH_2 and B is CH_2 or A is NH and B is CO, and $AB(CH_2)_n$ and NR^2R^4 are trans.

7. A compound according to any preceding claim wherein R^4 is $-U-R^5{}_2$, the group –U– is $-CH_2-$, and $R^5{}_2$ is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} or the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic and Y^2 has 3-5 atoms including NR^{13}, O or S bonded to X^5 and NHCO bonded via N to X^3, or O bonded to X^3.

8. A compound according to any of claims 1 to 6 wherein $R^5{}_2$ is selected from:benzo[1,2,5]thiadiazol-5-yl
4H-benzo[1,4] thiazin-3-one-6-yl
2,3-dihydro-benzo[1,4]dioxin-6-yl
benzo[1,2,3]thiadiazol-5-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl.

9. A compound selected from:
(1*R*,4*S*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide and
(1*S*,4*R*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide
(1*R*,4*S*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide and
(1*S*,4*R*)-1-Hydroxy-4-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-ylmethyl)-amino]-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide 1-

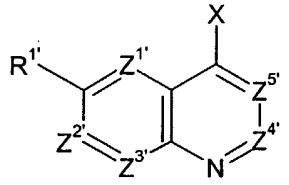
Hydroxy-*t*-4-[(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-ylmethyl)-amino]-*r*-cyclohex-2-enecarboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide (E2 isomer) or a pharmaceutically acceptable derivative thereof.

10. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.

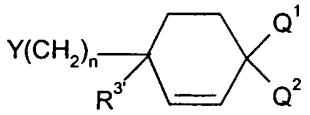
11. The use of a compound according to claim 1, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

12. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier.

13. A process for preparing a compound according to claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

wherein n is as defined in formula (I); $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$ and $R^{3'}$ are Z^1, Z^2, Z^3, Z^4, Z^5, R^1 and R^3 as defined in formula (I) or groups convertible thereto;
Q^1 is $NR^{2'}R^{4'}$ or a group convertible thereto wherein $R^{2'}$ and $R^{4'}$ are R^2 and R^4 as defined in formula (I) or groups convertible thereto and Q^2 is H or $R^{3'}$ or Q^1 and Q^2 together form an optionally protected oxo group;
and X and Y may be the following combinations:

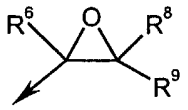
(i) one of X and Y is CO_2R^y and the other is $CH_2CO_2R^x$;
(ii) X is CHR^6R^7 and Y is $C(=O)R^9$;
(iii) X is $CR^7=PR^z_3$ and Y is $C(=O)R^9$;
(iv) X is $C(=O)R^7$ and Y is $CR^9=PR^z_3$;
(v) one of Y and X is COW and the other is $NHR^{11'}$;
(vi) X is $NHR^{11'}$ and Y is $C(=O)R^8$ or X is $C(=O)R^6$ and Y is $NHR^{11'}$;
(vii) X is $NHR^{11'}$ and Y is CR^8R^9W;
(viii) X is W or OH and Y is CH_2OH;
(ix) X is $NHR^{11'}$ and Y is SO_2W;
(x) one of X and Y is $(CH_2)_p$-W and the other is $(CH_2)_qNHR^{11'}$, $(CH_2)_qOH$, $(CH_2)_qSH$ or $(CH_2)_qSCOR^x$ where p+q=1;

(xi) one of X and Y is OH and the other is -CH=N_2;

(xii) Xis W and Y is $CONHR^{11}$;

(xiii) X is W and Y is -C≡CH followed by selective reduction of the intermediate –C≡C- group;

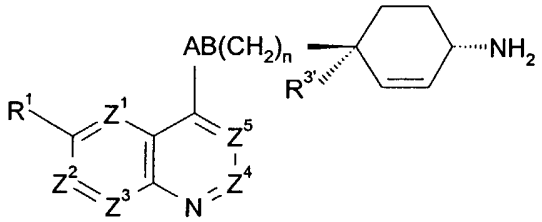
in which W is a leaving group, e.g. halo or imidazolyl; R^x and R^y are (C_{1-6})alkyl; R^z is aryl or (C_{1-6})alkyl; A' and $NR^{11'}$ are A and NR^{11} as defined in formula (I), or groups convertible thereto; and oxirane is:



wherein R^6, R^8 and R^9 are as defined in formula (I);

and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting A', $Z^{1'}$, $Z^{2'}$, $Z^{3'}$, $Z^{4'}$, $Z^{5'}$, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $NR^{11'}$ to A, Z^1, Z^2, Z^3, Z^4, Z^5, R^1, R^2, R^3, R^4 and $NR^{11'}$; converting A-B to other A-B, interconverting R^v, R^w, R^1, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable derivative thereof.

14. A compound of formula (VII):



wherein the variables are as described for formula (I) in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08153

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/33 C07D519/00 A61P31/04 //(C07D519/00,513:00, 471:00),(C07D519/00,498:00,471:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 08224 A (DAVIES DAVID THOMAS ;MARKWELL ROGER EDWARD (GB); JONES GRAHAM ELGI) 31 January 2002 (2002-01-31) cited in the application	1-14
Y	page 66, line 11 - line 23; examples 1-625	1
X	WO 01 07432 A (DAVIES DAVID THOMAS ;MARKWELL ROGER EDWARD (GB); LIGHTFOOT ANDREW) 1 February 2001 (2001-02-01) cited in the application page 31; claim 1	1
Y	WO 00 78748 A (DAVIES DAVID THOMAS ;MARKWELL ROGER EDWARD (GB); PEARSON NEIL DAVI) 28 December 2000 (2000-12-28) page 37; claims 1-7	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2003	19/12/2003

Name and mailing address of the ISA	Authorized officer
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	Goss, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08153

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Y	page 81; examples 1-204	1
A	WO 01 07433 A (MARKWELL ROGER EDWARD ;PEARSON NEIL DAVID (GB); SMITHKLINE BEECHAM) 1 February 2001 (2001-02-01) the whole document	1

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Information on patent family members

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			WO	0107433 A2	01-02-2001
			EP	1202987 A2	08-05-2002
			JP	2003505456 T	12-02-2003