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Declarations under Rule 4.17:

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(54) Title: ANTIBACTERIAL AGENTS

(57) Abstract: Naphthalene, quinoline, quinoxaline and naphthyridine derivatives useful in the treatment of bacterial infections in mammals, particularly humans, are disclosed herein.

WO 2006/010040 A2

TITLE

ANTIBACTERIAL AGENTS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

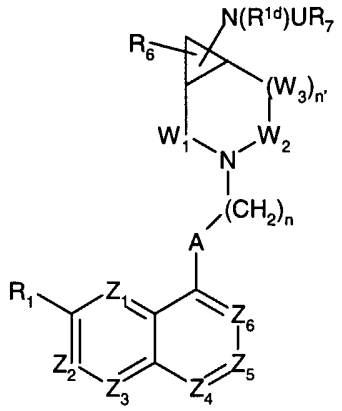
The emergence of pathogens resistant to known antibiotic therapy is becoming a serious global healthcare problem (Chu, et al., (1996) *J. Med. Chem.*, 39: 3853-3874). Thus, there is a need to discover new broad spectrum antibiotics useful in combating multidrug-resistant organisms. Importantly, it has now been discovered that certain compounds have antibacterial activity, and, therefore, may be useful for the treatment of bacterial infections in mammals, particularly in humans.

SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I), as described hereinafter, which are useful in the treatment of bacterial infections. This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier. This invention is also processes for the preparation of compounds of formula (I), as well as processes for the preparation of intermediates useful in the synthesis of compounds of formula (I). This invention is also a method of treating bacterial infections in mammals, particularly in humans.

DETAILED DESCRIPTION OF THE INVENTION

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



(I)

wherein:

Z_1, Z_3, and Z_4 are independently N or CR^{1a};

Z_2, Z_5, and Z_6 are each CR^{1a};

R_1 and R^{1a} are independently at each occurrence hydrogen; cyano; halogen; hydroxy; (C_{1-6})alkoxy unsubstituted or substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or R_1 and R^{1a} of Z_2 together form ethylenedioxy;

A is $NR^{1b}(C=O)$ or CR_2R_3;

W_1, W_2, and W_3 are each CR_4R_5;

R^{1b} and R^{1d} are independently at each occurrence hydrogen, trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; aryl; aralkyl; (C_{3-8})cycloalkyl; heterocyclyl; or heterocyclylalkyl;

R_2, R_3, R_4, R_5, and R_6 are independently hydrogen; thiol; (C_{1-6})alkylthio; halogen; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{2-6})alkenyloxycarbonyl; aralkyl; aryl; heterocyclyl; heterocyclylalkyl; hydroxy; amino; $NR^{1c}R^{1c'}$; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally and independently substituted by hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl or aralkyl;

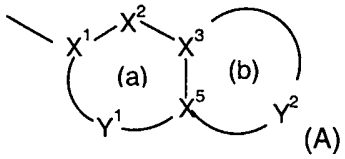
R^{1c} and $R^{1c'}$ are independently at each occurrence hydrogen; (C_{1-6})alkyl; aralkyl; aryl; heterocyclyl; heterocyclylalkyl; or together with the nitrogen that they are attached forn an aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring (wherein said aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring are optionally substiuted with from 1 to 3 substituents selected from halogen, hydroxy; cyano; nitro; (C_{1-6})alkyl; and aryl);

n' is 0 or 1;

n and n" are independently and at each occurrence 0, 1, or 2;

U is CH_2; C(=O); or SO_2;

R_7 is a substituted or unsubstituted 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_8 when part of a non aromatic ring;

X^2 is N, NR_9, O, $S(O)_{n"}$, CO or CR_8 when part of an aromatic or non-aromatic ring or may in addition be $CR_{10}R_{11}$ when part of a non aromatic ring;

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

Y' is a 0 to 4 atom linker group each atom of which is independently selected from N, NR_9, O, $S(O)_{n'}$, CO and CR_8 when part of an aromatic or non-aromatic ring or may additionally be $CR_{10}R_{11}$ 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_9, O, $S(O)_{n'}$, CO and CR_8 when part of an aromatic or non-aromatic ring or may additionally be $CR_{10}R_{11}$ when part of a non aromatic ring;

R_8, R_{10} and R_{11} are at each occurrence independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; trifluoromethoxy; nitro; cyano; carboxy; amino or aminocarbonyl unsubstituted or substituted by (C_{1-4})alkyl;

R_9 is at each occurrence independently hydrogen; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxy, carboxy, (C_{1-4})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; or aminocarbonyl wherein the amino group is optionally substituted with (C_{1-4})alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, this invention describes a compound according to formula (I) wherein Z_1 and Z_4 are N; and Z_3 is CR^{1a}.

In certain embodiments, this invention describes a compound according to formula (I) wherein Z_1 and Z_3 are CR^{1a}; and Z_4 is N.

In some embodiments, this invention describes a compound according to formula (I) wherein R_1 is OCH_3.

In certain embodiments, this invention describes a compound according to formula (I) wherein R^{1a} is at each occurrence independently hydrogen; halogen; or cyano.

In some embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_4 are N; Z_3 is CR^{1a}; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; and R_1 is OCH_3.

In certain aspects, this invention desacribes a compound of formula (I) wherein A is CH_2; and n of $(CH_2)_n$ is 1.

In some embodiments, this invention describes a compound of formula (I) wherein n' is 0.

In certain embodiments, this invention describes a compound of formula (I) wherein n' is 1.

In some embodiments, this invention describes a compound of formula (I) wherein R^{1d} is hydrogen and U is CH_2.

In certain aspects, this invention describes a compound of formula (I) wherein R^{1d} is hydrogen and U is C(=O).

In some embodiments, this invention describes a compound of formula (I) wherein R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-benzo[1,4]dioxin-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; 4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl; 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl; 2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl; 2,3-Dihydro-benzofuran-7-carbonitrile-5-yl; 7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl; 3-Oxa-1-thia-5-aza-indan-5-yl; 5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl; 6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl; 2,3-Dihydro-benzofuran-5-yl; 7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 4H-Benzo[1,4]thiazin-3-oxo-6-yl; or 8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

In certain embodiments, this invention describes a compound of formula (I) wherein R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

In some embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; and n' is 0.

In certain embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; n' is 0; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; and U is CH_2 or (C=O).

In certain embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; n' is 0; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; U is CH_2 or (C=O); and R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-benzo[1,4]dioxin-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; 4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl; 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl; 2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl; 2,3-Dihydro-benzofuran-7-carbonitrile-5-yl; 7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl; 3-Oxa-1-thia-5-aza-indan-5-yl; 5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl; 6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl; 2,3-Dihydro-benzofuran-5-yl; 7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 4H-Benzo[1,4]thiazin-3-oxo-6-yl; or 8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

In certain embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; n' is 0; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; U is CH_2 or

(C=O); and R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

In some embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; and n' is 1.

In certain embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; and n' is 1; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; and U is CH_2 or (C=O).

In some embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; and n' is 1; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; U is CH_2 or (C=O); and R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-benzo[1,4]dioxin-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; 4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl; 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl; 2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl; 2,3-Dihydro-benzofuran-7-carbonitrile-5-yl; 7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl; 3-Oxa-1-thia-5-aza-indan-5-yl; 5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl; 6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl; 2,3-Dihydro-benzofuran-5-yl; 7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl; 4H-Benzo[1,4]thiazin-3-oxo-6-yl; or 8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

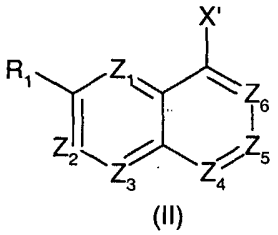
In some embodiments, this invention describes a compound of formula (I) wherein Z_1 and Z_3 are CR^{1a}; Z_4 is N; R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen; R^{1a} of Z_6 is fluorine or cyano; R_1 is OCH_3; A is CH_2; n of $(CH_2)_n$ is 1; and n' is 1; R_4, R_5 and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy; R^{1d} is hydrogen; U is CH_2 or (C=O); and R_7 is 4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl; 4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or 7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

In certain embodiments, this invention describes a compound of formula (I) wherein the compound is 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; 6-{[((3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one; 7-chloro-6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one; *N*-(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)-3-

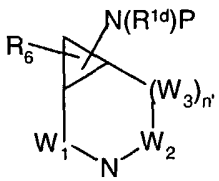
oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; or 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; or a pharmaceutically acceptable salt or solvate thereof.

In certain aspects, this invention describes a process for the preparation of intermediates of formula (IV) useful in the preparation of compounds of formula (I), which process comprises:

(a) reacting a compound of formula (II) with a compound of formula (III) to give a useful intermediate having formula (IV):



(II)



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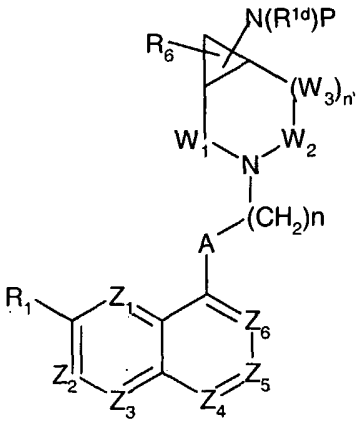


(IV)

wherein:

Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, n, n', W_1, W_2, W_3, R_1, R_2, R_3, R_6, and R^{1d} are as defined in claim 1; and

X' is $CH{=}CH_2$ or A-$(CH_2)_n$-L;

A is CR_2R_3;

L is a leaving group; and

P is hydrogen or an amine protecting group.

In some embodiments, this invention describes a process for the preparation of a compound of claim 1, which process comprises:

(a) reacting a compound of formula (II) with a compound of formula (III) to give a compound of formula (IV);

(b) reacting the compound of formula (IV) with a compound of formula (V);

(c) removing P (where P is not hydrogen) to give a compound of formula (I);

(d) optionally converting to a pharmaceutically acceptable salt or solvate, thereof;

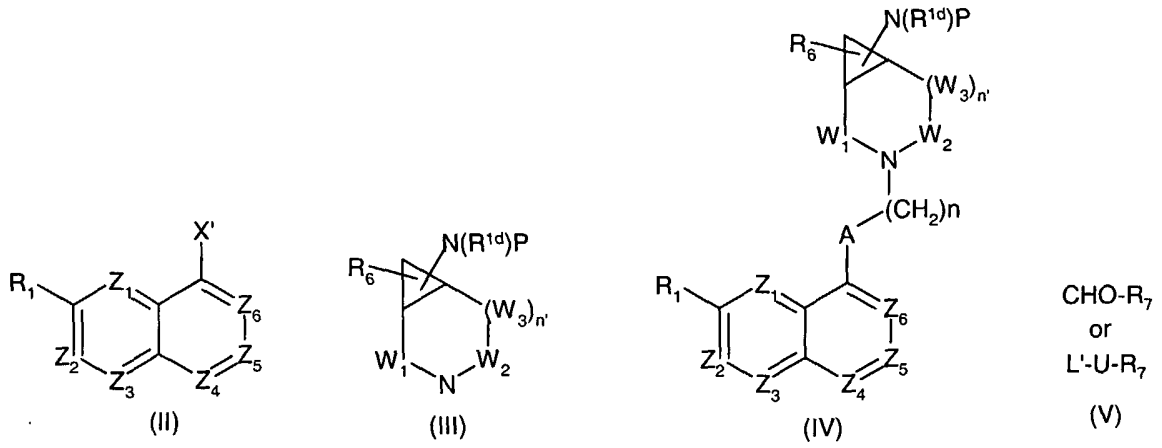
or

(a) reacting a compound of formula (II) with a compound of formula (III) to give a compound of formula (IV);

(b) removing P (where P is not hydrogen); and

(c) reacting the product of step (b) with a compound of formula (V) to give a compound of formula (I);

(d) optionally converting to a pharmaceutically acceptable salt or solvate, thereof;



wherein:

Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, n, n', W_1, W_2, W_3, R_1, R_2, R_3, R_6, R_7, U and R^{1d} are as defined in claim 1;

X' is $CH=CH_2$ or $A-(CH_2)_n-L$;

A is CR_2R_3;

L and L' are leaving groups; and

P is hydrogen or an amine protecting group.

In certain embodiments, this invention describes a pharmaceutical composition comprising a compound of formula I or any one of the embodiments described herein, and a pharmaceutically acceptable carrier.

In some embodiments, this invention describes a method of treating bacterial infections which comprises administering to a mammal in need thereof an effective amount of a compound of formula I or any of its embodiments described herein.

In some embodiments, this invention describes compounds of formula I wherein the (a) and (b) rings of R_{11} are both aromatic as demonstrated by the following non-limiting examples: 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.

In yet other embodiments, R_{11} is defined by a non-aromatic (a) ring and aromatic (b) ring as illustrated by the following non-limiting examples: (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, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 1-oxo-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl.

In still other embodiments, R_{11} is defined by an aromatic (a) ring and a non aromatic (b) ring as illustrated by the following non-limiting examples: 1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-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-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, 3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl.

Unless otherwise defined, the term "alkyl" when used alone or when forming part of other groups (such as the 'alkoxy' group) includes substituted or unsubstituted, straight or branched chain alkyl groups containing the specified range of carbon atoms. For example, the term "(C_{1-6})alkyl" include methyl, ethyl, propyl, butyl, iso-propyl, sec-butyl, tert-butyl, iso-pentyl, and the like.

The term "alkenyl" means a substituted or unsubstituted alkyl group of the specified range of carbon atoms, wherein one carbon-carbon single bond is replaced by a carbon-carbon double bond. For example, the term "(C_{2-6})alkenyl" include ethylene, 1-propene, 2-propene, 1-butene, 2-butene, and isobutene, and the like. Both cis and trans isomers are included.

The term "cycloalkyl" refers to subsituted or unsubstituted carbocyclic system of the specifed range of carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. For example, the term "(C_{3-7})cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, and cycloheptyl.

The term "alkoxy" refers to an O-alkyl radical where the alkyl group contains the specified range of carbon atoms and is as defined herein.

The term "acyl" refers to a C(=O)alkyl or a C(=O)aryl radical. In some embodiments, the alkyl group contains 13 or less carbons; in some embodiments 10 or less carbon atoms; in some embodiments 6 or less carbon atoms; and is as otherwise defined. Aryl is as defined herein.

The term "alkylcarbonyl" refers to a (C_{1-6})alkyl(C=O)(C_{1-6})alkyl group wherein alkyl is as otherwise defined herein.

The term "alkylsulphonyl" refers to a SO_2alkyl radical wherein the alkyl group contains the specified range of carbon atoms and is as defined herein.

The term "alkylthio" refers to a Salkyl wherein the alkyl group contains the specified range of carbon atoms and is as defined herein.

The term "aminosulphonyl" refers to a SO_2N radical wherein the nitrogen is substituted as specified.

The term "aminocarbonyl" refers to a carboxamide radical wherein the nitrogen of the amide is substituted as defined.

The term "heterocyclylthio" refers to a S-heterocyclyl radical wherein the heterocyclyl moiety is as defined herein.

The term "heterocyclyloxy" refers to an O-heterocyclyl radical wherein heterocyclyl is as defined herein.

The term "arylthio" refers to an S-aryl radical wherein aryl is as defined herein.

The term "aryloxy" refers to an O-aryl radical wherein aryl is as defined herein.

The term "acylthio" refers to a S-acyl radical wherein acyl is as defined herein.

The term "acyloxy" refers to an O-acyl radical wherein acyl is as defined herein.

The term "alkoxycarbonyl" refers to a CO_2alkyl radical wherein the alkyl group contains the specified range of carbon atoms and is as defined herein.

The term "alkenyloxycarbonyl" refers to a CO_2alkyl radical wherein the alkenyl group contains the specified range of carbon atoms and is as defined herein.

The term "alkylsulphonyloxy" refers to an O-SO_2alkyl radical wherein the alkyl group contains the specified range of carbon atoms and is as defined herein.

The term "arylsulphonyl" refers to a SO_2aryl radical wherein aryl is as herein defined.

The term "arylsulphoxide" refers to a SOaryl radical wherein aryl is as defined herein.

Unless otherwise defined, suitable substituents for any alkyl, alkoxy, alkenyl, and cycloalkyl groups includes up to three substituents selected from the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, amidino, sulphonamido, unsubstituted (C_{1-3})alkoxy, trifluromethyl, and acyloxy.

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

The term "haloalkyl" refers to an alkyl radical containing the specified range of carbon atoms and is as otherwise defined herein, which is further substituted with 1-3 halogen atoms.

The term "haloalkoxy" refers to an alkoxy radical of the specified range and as defined herein, which is further substituted with 1-3 halogen atoms.

The term "hydroxyalkyl" refers to an alkyl group as defined herein, further substituted with a hydroxy group.

Unless otherwise defined, the term "heterocyclic" or "heterocyclyl" as used herein includes optionally substituted aromatic and non-aromatic, single and fused, mono- or bicyclic 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; (C_{1-4})haloalkoxy; (C_{1-4})haloalkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy, (C_{1-4})alkyl; (C_{1-4})thioalkyl; (C_{1-}

$_4$)alkoxy; nitro; cyano, carboxy; (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.

Each heterocyclic ring suitably has from 3 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 hydrogen; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-4})alkoxy, (C_{1-4})alkylthio, halo or trifluoromethyl; and (C_{2-4})alkenyl.

The term "heterocyclylalkyl" refers to a (C_{1-6})alkyl radical which bears as a substituent a heterocyclyl group, wherein heterocyclyl and alkyl are as herein defined. The heterocyclyl group maybe joined to a primary, secondary or tertiary carbon of the (C_{1-6})alkyl chain.

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

Aryl groups may be optionally substituted with up to five, preferably up to three, groups selected from (C_{1-4})alkylthio; halo; (C_{1-4})haloalkoxy; (C_{1-4})haloalkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; (C_{1-4})hydroxyalkyl; (C_{1-4})alkylthio; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted by (C_{1-4})alkyl; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl.

The term "aralkyl" refers to a (C_{1-6})alkyl radical which bears as a substituent an aryl group, wherein aryl and alkyl are as herein defined. The aryl group maybe joined to a primary, secondary or tertiary carbon of the (C_{1-6})alkyl chain.

This invention also contemplates that some of its structural embodiments maybe present as a solvate. Solvates maybe produced from crystallization from a given solvent or mixture of solvents, inorganic or organic. Solvates may also produced upon contact or exposure to solvent vapors, such as water. This invention includes within its scope stoichiometric and non-stoichiometric solvates including hydrates.

Furthermore, it will be understood that phrases such as "a compound of Formula I or a pharmaceutically acceptable salt, solvate or derivative thereof" are intended to encompass the compound of Formula I, a derivative of formula (I), a pharmaceutically

acceptable salt of the compound of formula (I), a solvate of formula (I), or any pharmaceutically acceptable combination of these. Thus by way of non-limiting example used here for illustrative purpose, "a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof" may include a pharmaceutically acceptable salt of a compound of formula (I) that is further present as a solvate.

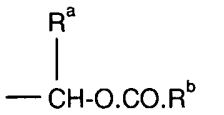
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are 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 salts 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. One of skill in the art will recognize that where compounds of the invention contain multiple basic sites, a compound of the invention maybe present as a salt complexed with more than one equivalent of a corresponding acid or mixture of acids.

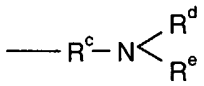
Pharmaceutically acceptable derivatives refers to compounds of formula (I) that have been covalently modifed with a group that undergoes at least some in vivo cleavage to a compound of formula (I).

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)



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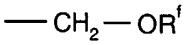
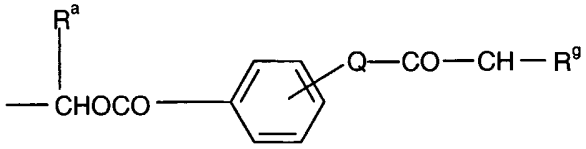
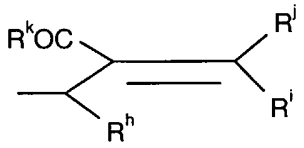


(iii)



(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

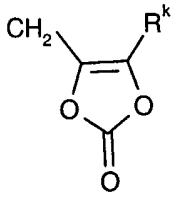
1-$(C_{1-6}$ alkyl)amino(C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6})alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (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, acetoxyethyl, pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as

ethoxycarbonyloxymethyl, 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.

Compounds of formula (I) may also be prepared as the corresponding N-oxides.

Certain of the 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 form, including pure isomeric forms. 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.

One of skill in the readily appreciates that optimization for a given reaction may require some routine variation in reaction parmeters such as reaction time, temperature, energy source, pressure, light, pressure, solvent or solvents used, co-reagents, catalysts, and the like.

Protective groups wherever found herein maybe designated by their specific formula or alternatively, maybe referred to generically by P or P_n (wherein n is an integer). It is to be appreciated that where generic descriptors are used, that such descriptors are at each occurrence independent from each other. Thus, a compound with more than one of the same generic descriptors (e.g. P) does not indicate that each P is the same protective group, they maybe the same or different, so long as the group is suitable to the chemistry being employed. Where protection or deprotection is generically referred to, one of ordinary skill in the art will understand this to mean that suitable conditions are employed that will allow for the removal of the protecting group to be removed while minimizing reaction at other positions of the molecule, unless otherwise indicated. Many

protective groups and protective group strategies are known to those of skill in the art in maybe found in numerous references including, Greene, et al. "Protective Groups in Organic Synthesis" (Published by Wiley-Interscience), which is herein incorporated by reference in its entirety.

Leaving groups wherever found herein maybe designated by a specific chemical formula, or alternatively, maybe generically referred to as L or Ln (wherein n is an integer). It is to be appreciated that where a generic descriptor is used, that such descriptors are at each occurrence independent from each other. Leaving groups can be single atoms such as Cl, Br, or I, or maybe a group such as OSO_2CH_3, $OC(=O)CH_3$, $O(C=O)CF_3$, OSO_2CF_3, and the like. Leaving groups may be formed during the course of a reaction and thus a compound containing a leaving group may not always be an isolated material but rather as a reactive intermediate. By way of non-limiting example, a carboxylic acid maybe reacted with a coupling reagent such as DCC, CDI, EDCI, isobutyl chloroformate, etc, and the corresponding reative intermediate thus formed is further reacted with the nucleophilic coupling partner. In such cases, one of skill in the art appreciates that the activation step maybe performed before the introduction of the nucleophilic coupling partner, or in some cases, even in the presence of the nucleophilic coupling partner (depending upon the identity of the particular activating agent, carboxylic acid and nuclephilic coupling partner used). One skilled in the art readily ascertains that leaving groups generally refer to atoms or groups which can be eliminated, substituted or otherwise dissociate during the course of the reaction.

The antibacterial 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 antibacterials.

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 composition may be formulated for administration by any route. 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 polyvinylpyrrolidone; 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 derivative 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 antibacterials. If the other antibacterial is a β-lactam then a β-lactamase inhibitor may also be employed.

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

The compounds of this invention may also be used in the manufacture of medicaments useful in treating bacterial infections in humans or other mammals.

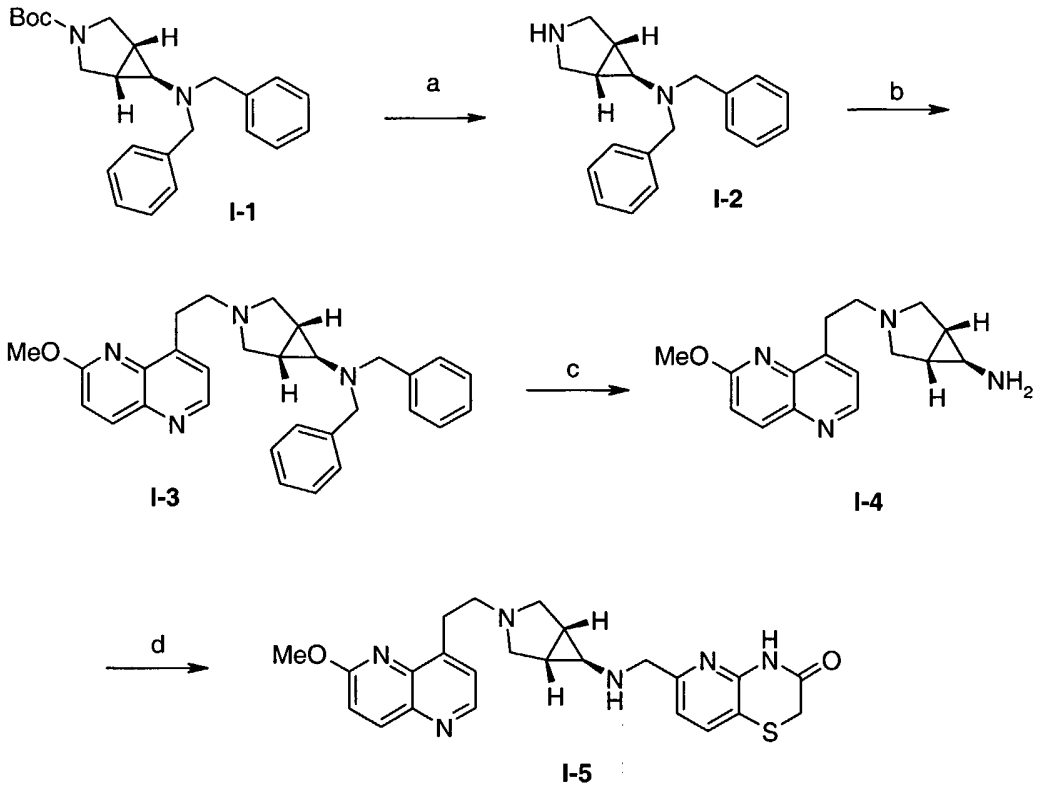
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference (whether specifically stated to be so or not) as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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.

The stereochemistry where shown for specific examples is relative only.

The compounds of the present invention were prepared by the methods illustrated in Schemes I, II and III. One of skill in the art readily appreciates that although the following schemes describe specific examples, they maybe more generally applied to produce additional embodiments of this invention. Furthermore, the examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

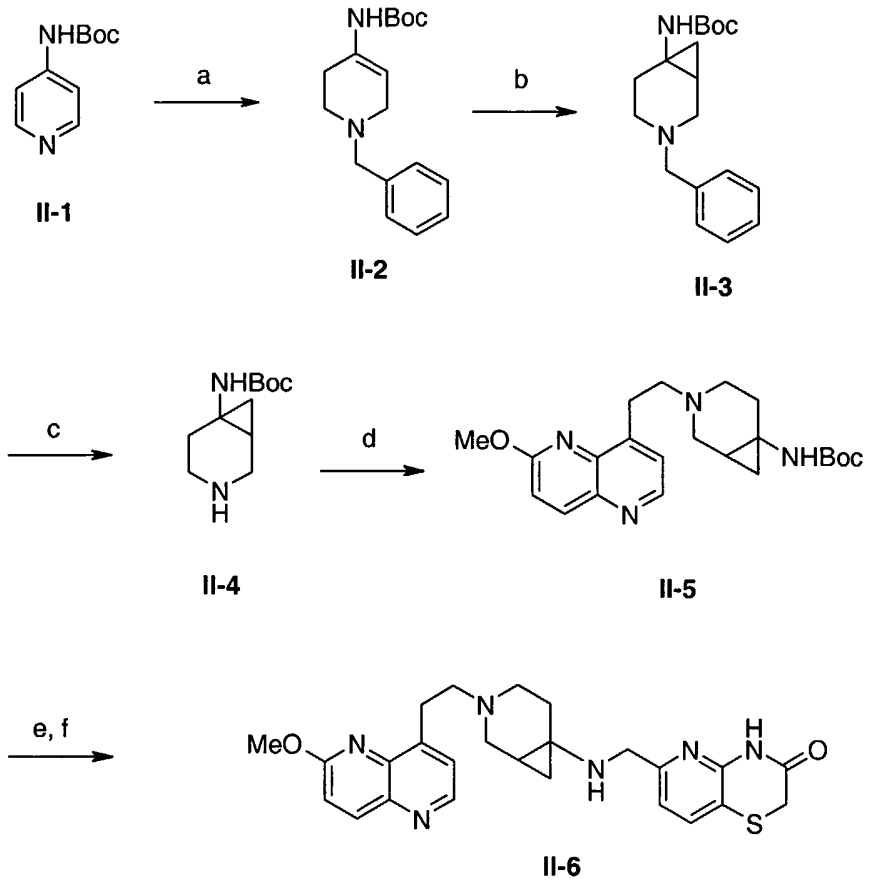
Scheme I



Reagents and conditions: (a) TFA, CH_2Cl_2, RT; (b) 8-ethenyl-2-(methyloxy)-1,5-naphthyridine, DMF, 100 °C; (c) $Pd(OH)_2$, H_2 (1atm), EtOH, RT; (d) 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde, CH_2Cl_2, EtOH; then $NaBH_4$, EtOH.

Removal of the Boc group from **I-1** [*Chem. Eur. J.* **2002**, 8 , No. 16] was achieved with TFA in methylene chloride to afford amine **I-2**. Amine **I-2** was then heated with 8-ethenyl-2-(methyloxy)-1,5-naphthyridine in DMF generating the product **I-3**. Deprotection of the benzyl functionality was performed under hydrogenolysis conditions to give amine **I-4**. The primary amine derivative **I-4** was then converted to a secondary amine **I-5** by reaction with 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde and subsequent reduction. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-}Pr)_2NEt$), or K_2CO_3, may be used. Many additional methods for reductive aminations are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), herein incorporated by reference in its entirety.

Scheme II

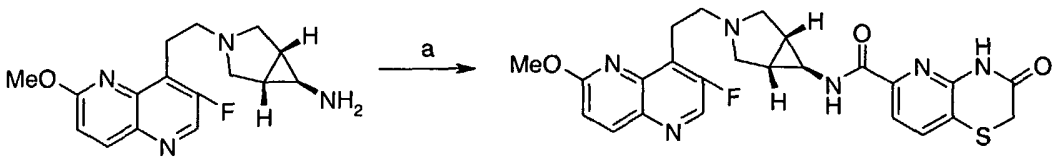


Reagents and conditions: (a) BnCl, Et_2O, the $NaBH_4$, EtOH; (b) CH_2ICl, Zn/Cu, Et_2O; (c) Pd/C, H_2, EtOH; (d) 8-ethenyl-2-(methyloxy)-1,5-naphthyridine, DMF, 100 °C; (e) TFA, DCM, RT; (f) 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde, CH_2Cl_2, EtOH; then $NaBH_4$, EtOH.

Quaternization and reduction of the pyridine species **II-1** was accomplished in one pot with the use of $NaBH_4$. For further description of this method, see "Borane Reagents" in the Best Synthetic Methods series by Pelter, Smith and Brown which is herein incorporated by reference in its entirety. Cyclopropanation of the alkene moiety was accomplished with CH_2ICl and Zn/Cu to afford cyclopropyl derivative **II-3**. Cycloproponation reactions are well known to those skilled in the art of organic synthesis and can be achieved using several classical organometallic reagents, see, for example, the text "Principles and Applications of Organotransition Metal Chemistry" by Collman, Hegedus, Norton and Finke; University Science Books, which is herein incorporated by reference in its entirety. Hydrogenolysis of the benzyl group afforded amine **II-4** which was

subsequently heated with 8-ethenyl-2-(methyloxy)-1,5-naphthyridine in DMF to afford **II-5**. Removal of the Boc group was achieved with TFA in methylene chloride to afford the free amine which was then reacted with 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde which was subsequently reduced to form an imine which was subsequently reduced to yield **II-6**.

Scheme III



III-1 **III-2**

Reagents and conditions: (a) EDC-HCl, HOBt, (*i*-Pr)$_2$NEt, DMF, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid.

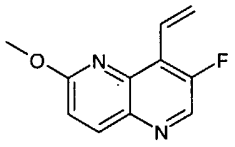
Amine **III-1** (prepared as described in the General section, *infra*), was coupled to 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid using EDC-HCl and HOBT. Many additional methods for converting a carboxylic acid to an amide are known to those of skill in the art, and can be found in, for example, standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag), which are herein incorporated by reference, in their entirety.

General

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES)

ionization techniques. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical HPLC was performed on Beckman chromatography systems. Preparative HPLC was performed using Gilson chromatography systems. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Preparation 1



Preparation of 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine

a) (2-[(6-Methoxypyridin-3-ylamino)methylene]malonic acid diethyl ester

A solution of 5-amino-2-methoxypyridine (Aldrich, 100g, 0.806 mole) and diethyl ethoxymethylenemalonate (Aldrich, 163 mL, 0.806 mole) in EtOH (1 L) was heated at reflux for 4 hours, then was cooled to RT. Concentration to dryness gave the title compound (238 g, quantitative).

b) 6-Methoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid ethyl ester

Dowtherm A (Fluka, 500 mL) was brought to boiling (250 °C) in a 2 L 3-neck flask fitted with a still-head and a reflux condenser. 2-[(6-Methoxypyridin-3-ylamino)methylene]malonic acid diethyl ester (100 g, 0.34 mole) was added portionwise over 5 min. The solution was heated at reflux for an additional 15 min, allowing some solvent to distil over. The resulting solution was cooled to RT and diluted with hexanes (750 mL). The mixture was cooled in ice for 1 hr, then the brown solid was filtered off,

washed with hexanes, and dried under vacuum to afford the title compound (61.72g, 73%).

c) 4-Bromo-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester

A suspension of 6-methoxy-4-oxo-1,4-dihydro-[1,5]naphthyridine-3-carboxylic acid ethyl ester (74.57 g, 300 mmole) in dry DMF (260 mL) under argon was stirred efficiently* in a water bath (to maintain approximately RT - may need slight ice-cooling on a large scale). Phosphorus tribromide (30.0 mL, 316 mmole) was added dropwise over 15 min and stirring was continued for an additional 30 min. Water (1 L) was added, followed by saturated sodium carbonate solution to pH 7. The solid was collected by suction filtration, washed with water and dried under vacuum over phosphorus pentoxide to give the title compound (83.56 g, 90%).

d) 4-Bromo-6-methoxy-[1,5]naphthyridine-3-carboxylic acid

2 N NaOH (300 mL, 600 mmole) was added dropwise over 30 min to a stirred solution of 4-bromo-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester (83.56 g, 268 mmole) in THF (835 mL). Stirring was continued overnight, at which time LC/MS showed that the saponification was complete. 2 N HCl was added to pH 6 and the THF was removed *in vacuo*. 2 N HCl was added to pH 2, then water (250 mL) was added, and the mixture was cooled thoroughly in ice. The solid was collected by suction filtration, washed with water and dried (first using a rotary evaporator at 50 °C and then under high vacuum at 50 °C overnight) to give the title compound (76.7 g, slightly over quantitative). This material was used without further purification.

e) 4-Bromo-6-methoxy-[1,5]naphthyridin-3-ylamine

A suspension of 4-bromo-6-methoxy-[1,5]naphthyridine-3-carboxylic acid (50 g, 177 mmole) in dry DMF (600 mL) was treated with triethylamine (222.5 mL, 1.60 mole), *tert*-butanol (265 mL, 2.77 mole), and diphenylphosphoryl azide (41.75 mL, 194 mmole). The reaction was stirred under argon at 100 °C for 1 hr, then was cooled to RT and concentrated to low volume. Ethyl acetate and excess aqueous sodium bicarbonate solution were added, the mixture was shaken, and some insoluble solid was filtered off. The layers were separated and the organic phase was washed with water (2x) and dried ($MgSO_4$). Concentration to dryness gave a crude mixture of 4-bromo-6-methoxy-[1,5]naphthyridin-3-ylamine (minor product) and (4-bromo-6-methoxy-[1,5]naphthyridin-3-ylamine)carbamic acid *tert*-butyl ester (major product) along with impurities.

Without further purification, this mixture was dissolved in CH_2Cl_2 (150 mL) and treated with trifluoroacetic acid (100 mL). The reaction was stirred for 3 hr then was concentrated to dryness. The residue was partitioned between $CHCl_3$ and saturated sodium bicarbonate solution and the layers were separated. The aqueous phase was extracted with $CHCl_3$, and the combined organics were dried ($MgSO_4$) and concentrated to low volume. The solid was collected by suction filtration, washed with a small volume of $CHCl_3$ and dried under vacuum to afford a first crop of the title compound (31.14 g). The filtrate was purified by flash chromatography on silica gel (30% EtOAc/$CHCl_3$) to afford further material (2.93 g, total = 34.07 g, 76%). Alternatively, the filtrate was left at RT overnight and then filtered to give a second crop of the title compound (2.5 g).

f) 4-Bromo-6-methoxy-[1,5]naphthyridine-3-diazonium tetrafluoroborate

A solution of 4-bromo-6-methoxy-[1,5]naphthyridin-3-ylamine (25.2 g, 99.2 mmole) in dry THF (400 mL) was maintained at -5 °C while nitrosonium tetrafluoroborate (12.9 g, 110 mmole) was added portionwise over 30 min (approximately 2 g portions). The reaction was continued for an additional 1 hr at -5 °C, at which time TLC and LC/MS indicated that the reaction was complete. The orange solid was collected by suction filtration, washed with ice-cold THF and dried under vacuum to provide the title compound (31.42 g, 90%).

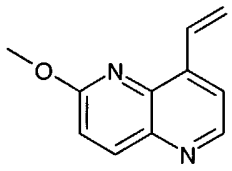
g) 4-Bromo-3-fluoro-6-methoxy-[1,5]naphthyridine

A suspension of 4-bromo-6-methoxy-[1,5]naphthyridine-3-diazonium tetrafluoroborate (31.42 g, 89.0 mmole) in decalin (mixed isomers, 500 mL) in a 2 L flask* was heated to 180 °C and held at this temperature for 5 min. The mixture was cooled and diluted with $CHCl_3$ (500 mL, to keep the product in solution), and the resulting mixture was stirred vigorously for 30 min to break up a black solid byproduct. The mixture was then poured onto a column of silica gel and the column was eluted with $CHCl_3$ to remove decalin and then with 3% EtOAc/$CHCl_3$ to afford the title compound (9.16 g, 40%).

h) 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine

To a solution of 8-bromo-7-fluoro-2-(methyloxy)-1,5-naphthyridine (2.0 g, 7.81 mmol), potassium carbonate (1.08 g, 7.81 mmole), tetrakis-triphenylphosphine (90 mg, 0.08 mmole) in DME (60 mL) and H_2O (20 mL) was added 2,4,6-trivinylcycloborane-pyridine complex (0.94 g, 3.91 mmole). After stirring for 10 hours at 85°C the reaction contents were concentrated and the product purified by chromatography on silica gel (hexanes/EtOAc, 4:1) to give a low melting solid (1.43 g, 90%).

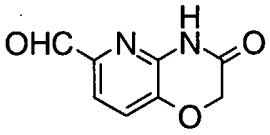
Preparation 2



Preparation of 8-ethenyl-2-(methyloxy)-1,5-naphthyridine

According to Preparation 1, except substituting 6-(methyloxy)-1,5-naphthyridin-4-yl trifluoromethanesulfonate (5.0 g, 16.23 mmole) for 8-bromo-7-fluoro-2-(methyloxy)-1,5-naphthyridine, the title compound was prepared (2.11 g, 70%) to give a yellow oil : LC-MS (m/z) (ES) 187 $(M+H)^+$.

Preparation 3



Preparation of 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde

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

3-Hydroxy-2-nitropyridine (20 g, 0.143 mole) was dissolved in methanol (400 mL) and a solution of 25% sodium methoxide in methanol (33 mL, 0.13 mole) 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 mole) was added slowly. The reaction was 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

2-Bromo-5-hydroxy-6-nitropyridine (30 g, 0.14 mole) was suspended in acetone (200 ml), and potassium carbonate (39 g, 0.28 mole) was added, followed by ethyl bromoacetate (15.7 ml, 0.14 mmole). The reaction was heated at reflux for 10 hr, 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 (6-bromo-2-nitro-pyridin-3-yloxy)acetate (38 g, 0.125 mole) was dissolved in glacial AcOH (150 mL), and iron powder (20 g, 0.36 mole) was added. The mixture was mechanically stirred and heated at 90 °C for 5 hr, 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 $(M + H)^+$.

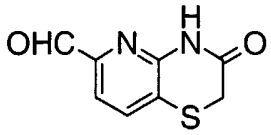
d) 6-((*E*)-Styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

6-Bromo-4*H*-pyrido[3,2-b][1,4]oxazin-3-one (6.0 g, 26.3 mmole) and *trans*-2-phenylvinylboronic acid (3.9 g, 26.3 mmole) were dissolved in 1,4-dioxane (150 mL) and the solution was degassed with argon. $(Ph_3P)_4Pd$ (230 mg, 0.2 mmole) was added, followed by a solution of potassium carbonate (6.9 g, 50 mmole) 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

6-((*E*)-Styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (1.2 g, 4.8 mmole) was dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to -78 °C. Ozone was bubbled through the solution with stirring until a pale blue color appeared, then the excess ozone was removed by bubbling oxygen through the solution for 15 min. Dimethylsulfide (1.76 mL, 24 mmole) was added to the solution, and the reaction was stirred at -78 °C for 3 hr, 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 $(M + H)^+$.

Preparation 4



Preparation of 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde

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 give the ester (0.95g); 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 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (788 mg) in dioxan (120 ml)/water (30 mL) was treated dropwise over 2 hours with 0.5M NaOH solution (8 mL) and stirred overnight. After evaporation to approx. 3 ml, water (5 mL) was added and 2M HCl to pH4. The precipitated solid was filtered off, washed with a small volume of water and dried under vacuum to give a solid (636 mg); MS (APCI$^-$) *m/z* 209 ([M-H]$^-$, 5%), 165([M-COOH]$^-$, 100%).

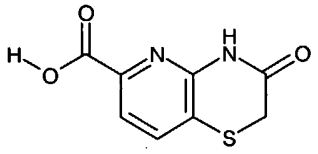
c) 6-Hydroxymethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine

A solution of 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (500mg) in THF (24 mL) with triethylamine (0.396 mL) was cooled to -10°C and isobutyl chloroformate (0.339ml) added. After 20 minutes the suspension was filtered through kieselguhr into an ice-cooled solution of sodium borohydride (272 mg) in water (8 mL), the mixture stirred 30 minutes 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 a white solid (346mg); 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 6-Hydroxymethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine (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 hour (730 mg) and 16 hours (300 mg). After a total of 20 hours the mixture was filtered through kieselguhr and the filtrate evaporated. The product was triturated with EtOAc/hexane (1:1) and collected to give a solid (180mg); MS (APCI$^-$) *m/z* 195 ([M-H]$^-$, 95%), 165 (100%).

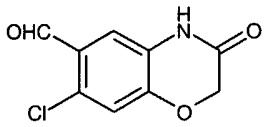
Preparation 5



Preparation of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

This acid was prepared from 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde (890 mg) by oxidation with Oxone (potassium peroxymonosulphate) (3.1g) in a DMF solution (50 mL). After 1.5 hours at room temperature, dilution with water (50 mL) filtration and drying in vacuo afforded the acid as a white solid (750 mg, 77%).

Preparation 6



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

3-Hydroxy-2-nitropyridine (20 g, 0.143 mole) was dissolved in methanol (400 mL) and a solution of 25% sodium methoxide in methanol (33 mL, 0.13 mole) 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 mole) was added slowly. The reaction was 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

The hydroxypyridine (30 g, 0.14 mole) was suspended in acetone (200 ml), and potassium carbonate (39 g, 0.28 mole) was added, followed by ethyl bromoacetate (15.7 ml, 0.14 mmole). The reaction was heated at reflux for 10 hr, 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

The nitropyridine (38 g, 0.125 mole) was dissolved in glacial AcOH (150 mL), and iron powder (20 g, 0.36 mole) was added. The mixture was mechanically stirred and heated at 90 °C for 5 hr, 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

The bromopyridine (10c) (6.0 g, 26.3 mmole) and *trans*-2-phenylvinylboronic acid (3.9 g, 26.3 mmole) were dissolved in 1,4-dioxane (150 mL) and the solution was degassed with argon. $(Ph_3P)_4Pd$ (230 mg, 0.2 mmole) was added, followed by a solution of potassium carbonate (6.9 g, 50 mmole) 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

The pyridine (10d) (1.2 g, 4.8 mmole) was dissolved in CH_2Cl_2 (200 mL) and the solution was cooled to -78 °C. Ozone was bubbled through the solution with stirring until a pale blue color appeared, then the excess ozone was removed by bubbling oxygen

through the solution for 15 min. Dimethylsulfide (1.76 mL, 24 mmole) was added to the solution, and the reaction was stirred at -78 °C for 3 hr, 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 $(M + H)^+$.

f) 6-Bromo-7-chloro-4H-pyrido[3,2-b][1,4]oxazin-3-one

6-Bromo-4H-pyrido[3,2-b][1,4]oxazin-3-one (20g, 87.7 mmole) was dissolved in DMF (175 mL) and cooled in an ice bath. Chlorine gas was then slowly bubbled in for 45 minutes, and then the saturated solution was stirred in the ice bath for 2 hours. The mixture was purged with nitrogen and slowly added with stirring to 1L of ice water which contained 100g of Na_2SO_3, making sure to keep the temperature <15 °C. After stirring 30 minutes the product was filtered, washed thoroughly with water and dried to afford (22.5g, 98%) of a white solid.

^1H NMR (400 MHz, DMSO-*d6*): 4.76 (2H, s,), 7.78 (1H, s),11.71 (1H, s).

g) 7-Chloro-6-((*E*)-styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

6-Bromo-7-chloro-4*H*-pyrido[3,2-b][1,4]oxazin-3-one (22 g, 83.7 mmole) and *trans*-2-phenylvinylboronic acid (17.33 g, 117 mmole) were dissolved in 1,4-dioxane (300 mL) and the solution was degassed with argon. $(Ph_3P)_4Pd$ (1.9 g, 2 mole %) was added, followed by a solution of potassium hydrogen carbonate (21 g, 210 mmole) in H_2O (100 mL). The reaction was heated at reflux under argon overnight, then was cooled to room temperature and diluted with ethyl acetate (1 L). The solution was washed sequentially with H_2O and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was slurried with chloroform (120 mL), then diluted with diethyl ether (100 mL). The precipitated product was collected by filtration and washed with ether to provide the product (16.4 g, 68%) as an off-white solid.

^1H NMR (400 MHz, DMSO-*d6*): 4.71 (2H, s), 7.32-7.46 (3H, m), 7.54-7.74 (4H, m), 11.6 (1H, s).

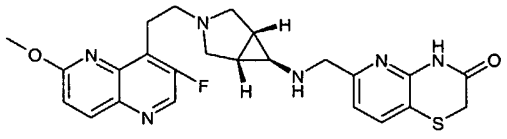
h) 7-Chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde

7-Chloro-6-((*E*)-styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (8.0 g, 27.9 mmole) was dissolved in a mixture of DMF (400 mL) and methanol (40 mL), and the solution was cooled to -78 °C. Ozone was bubbled through the solution with stirring for 45 minutes, then the excess ozone was removed by bubbling oxygen through the solution for 30 min.

Dimethylsulfide (21 mL, 279 mmole) was added to the solution, and the reaction was stirred at -78 °C for 3 hr, then at room temperature overnight. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O (150 mL). The collected solid was washed with additional Et_2O and dried to afford a white solid (4 g, 68%).

^1H NMR (400 MHz, DMSO-*d6*): 4.86 (2H, m), 7.73 (1H, s); 10.05 (1H, s), 11.84 (1H, s).

Example 1



Preparation of 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

a) *N,N*-bis(phenylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine

To a stirred solution of 1,1-dimethylethyl 6-[bis(phenylmethyl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate [*Chem. Eur. J.* **2002**, 8 , No. 16] (7.0 g, 18.5 mmole), in dry CH_2Cl_2 (200 mL) at RT was added trifluoroacetic acid (75 mL). After 2h at RT, the reaction contents were concentrated under vacuum. The residue was dissolved in $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The organic phase was separated and dried over Na_2SO_4 and concentrated in vacuo to give the title compound (5.1 g, 99%) as colorless oil: LC-MS (ES) m/e 279 $(M+H)^+$.

b) 3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N,N*-bis(phenylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine

To a stirred solution of *N,N*-bis(phenylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine (1.02 g, 3.67 mmole), in DMF (5 mL) was added 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (0.75 g, 3.67 mmole). After 24h at 100 °C, the reaction contents were concentrated under vacuum and purified on silica ($CHCl_3$/MeOH, 9:1 containing 5% NH_4OH) to give the title compound (1.38 g, 78%) as light yellow oil: LC-MS (ES) m/e 483 $(M + H)^+$.

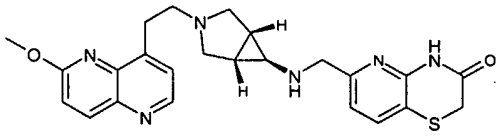
c) 3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hexan-6-amine

To a stirred solution of 3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*,*N*-bis(phenylmethyl)-3-azabicyclo[3.1.0]hexan-6-amine (1.38 g, 2.86 mmole) in MeOH (100 mL) was added Pearlman's catalyst (200 mg). After 48h at RT under 1 atmosphere of H_2 with stirring, the reaction contents were filtered through celite (MeOH) and concentrated under vacuum to give the title compound (0.86 g, 93%) as light yellow oil: LC-MS (ES) m/e 303 $(M + H)^+$.

(d) 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

To a stirred solution of 3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hexan-6-amine (0.14 g, 0.46 mmole) in dry CH_2Cl_2 (25 mL) and dry EtOH (20 mL) at RT was added 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.15 g, 0.77 mmole). After 24h, at RT was added $NaBH_4$ (19 mg, 0.51 mmole). After 6h more, silica gel (5 g) was added to the reaction solution and the suspension was concentrated under vacuum to a dry solid. Purification on silica ($CHCl_3$/MeOH, 9:1 containing 5% NH_4OH) afforded the title compound (0.25 g, 70%) as white foam: ^1H NMR (400 MHz, CD_3OD) δ 8.78 (br s, 1H), 8.58 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.09 (s, 3H), 3.80 (s, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.18 (d, *J* = 8.7 Hz, 2H), 2.80 (m, 2H), 2.55 (d, *J* = 8.7 Hz, 2H), 2.37 (s, 1H), 1.50 (br s, 2H). LC-MS (ES) m/e 481 $(M + H)^+$.

Example 2

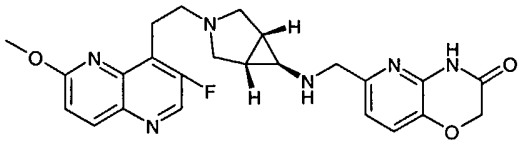


Preparation of 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

According to the procedure of Example 1, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (1.0 g, 5.39 mmole) for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine, the title compound was produced as a off-white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 5.6 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 5.6 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 4.09 (s, 3H),

3.80 (s, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.18 (d, J = 8.7 Hz, 2H), 2.80 (m, 2H), 2.55 (d, J = 8.7 Hz, 2H), 2.37 (s, 1H), 1.50 (br s, 2H). LC-MS (ES) m/e 463 $(M + H)^+$.

Example 3

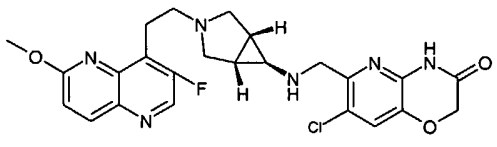


Preparation of 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one

According to the procedure of Example 1, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]oxazine-6-carboxaldehyde (0.23 g, 1.32 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde, the title compound was produced as a off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 4.55 (s, 2H), 4.04 (s, 3H), 3.73 (s, 2H), 3.28 (m, 4H), 2.84 (m, 2H), 2.53 (m, 2H), 2.27 (br s, 1H), 1.55 (br s, 2H). LC-MS (ES) m/e 465 $(M + H)^+$.

Example 4

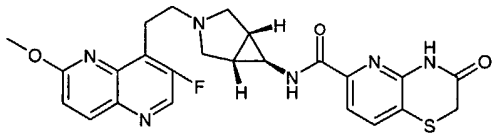
Preparation of 7-chloro-6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one



According to the procedure of Example 1, except substituting 7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carbaldehyde (0.28 g, 1.32 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde, the title compound was produced as a off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 9.0 Hz, 1H), 4.49 (s, 2H), 4.04 (s, 3H), 3.80 (s, 2H), 3.41 (d, J = 4.8

Hz, 2H), 3.39 (m, 2H), 2.95 (m, 2H), 2.61 (m, 2H), 2.12 (br s, 1H), 1.62 (br s, 2H). LC-MS (ES) m/e 499 $(M + H)^+$.

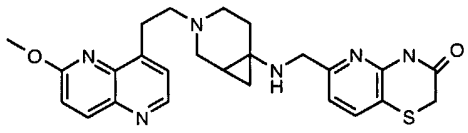
Example 5



Preparation of *N*-(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

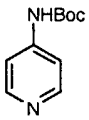
To a stirred solution of (1*R*,5*S*)-3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hexan-6-amine (1.5 g, 4.49 mmole) in dry in DMF (25 mL) at RT was added diisopropylethylamine (0.69 mL, 3.96 mmole), 3-oxo-3,4-dihydro-2*H*-pyrido[3,2*b*][1,4]thiazine-6-carboxylic acid (0.30 g, 1.45 mmole), hydroxybenzotriazole hydrate (0.20 g, 1.45 mmole) and EDC (0.28 g, 1.45 mmole). After 18h, the reaction contents were concentrated under high vacuum. Purification on silica ($CHCl_3$/MeOH, 9:1 containing 5% NH_4OH) afforded the title compound (0.37 g, 57%) as a light yellow solid: ^1H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.21 (d, *J* = 9.0 Hz, 1H), 7.90 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 4.15 (s, 3H), 3.61 (m, 2H), 3.41 (m, 2H), 3.13 (m, 2H), 3.05 (m, 2H), 2.89 (m, 2H), 2.62 (d, *J* = 8.9 Hz, 2H), 1.75 (br s, 1H). LC-MS (ES) m/e 495 $(M + H)^+$.

Example 6



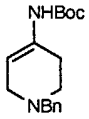
Preparation of 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

a) 1,1-dimethylethyl 4-pyridinylcarbamate



To 4-pyridinamine (3.0 g, 31.87 mmol) in MeCN (159 mL) at 25°C was added bis(1,1-dimethylethyl) dicarbonate (9 mL, 38.2 mmol). The solution stirred for 0.5 h, was concentrated and used without further purification: MS (ES) m/e 195 $(M + H)^+$.

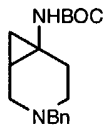
b) 1,1-dimethylethyl [1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]carbamate



To 1,1-dimethylethyl 4-pyridinylcarbamate (4, 4g, 21.2 mmol) in MeCN (10 mL) was added benzyl chloride (4.8 mL, 41.4 mmol). The solution stirred for 12h at reflux, then cooled and concentrated. The resulting residue was washed with Et_2O and used without further purification: MS (ES) m/e 229 $(M + H)^+$.

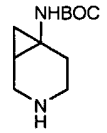
The above salt (1g, 3.13 mmol) in EtOH (15 mL) was added dropwise to a solution of $NaBH_4$ (470 mg, 12.5 mmol) in EtOH (15 mL) at 0°C. The resulting solution warmed to 25°C over 2h, was concentrated and purified via column chromatography (silica, 0-1% MeOH in DCM with 1% NH_4OH) affording the title compound (731 mg, 81%) as an orange oil: MS (ES) m/e 289 $(M + H)^+$.

c) 1,1-dimethylethyl [3-(phenylmethyl)-3-azabicyclo[4.1.0]hept-6-yl]carbamate



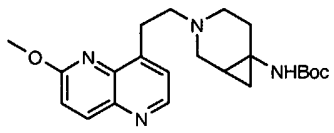
Zn/Cu (1.1 g, 1.1 wt.%) [prepared according to the procedure of Shank and Shechter *J. Chem. Soc.* **1959**, 24, 1825.] and chloroiodomethane (506 µL, 6.94 mmol) in dry Et_2O (7.0 mL) were heated to reflux over 2h. Upon cooling of the solution to 0°C, 1,1-dimethylethyl [1-(phenylmethyl)-1,2,3,6-tetrahydro-4-pyridinyl]carbamate (1.0 g, 3.47 mol) in dry THF (2.0 mL) was added dropwise. The solution slowly warmed to 25°C over 1h and was heated to 40°C for an additional 1h. The solution was cooled and quenched with NH_4OH and partitioned between H_2O/CH_2Cl_2. The aqueous phase was back extracted several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated, and purified by column chromatography (silica, 1% MeOH in CH_2Cl_2) affording the title compound (780 mg, 74%) as clear oil: MS (ES) m/e 303 $(M + H)^+$.

d) 1,1-dimethylethyl 3-azabicyclo[4.1.0]hept-6-ylcarbamate



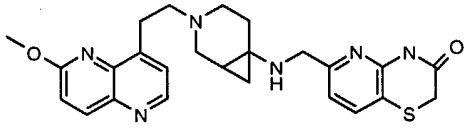
To 1,1-dimethylethyl [3-(phenylmethyl)-3-azabicyclo[4.1.0]hept-6-yl]carbamate (780 mg, 2.58 mmol) in EtOH (20 mL) was added 5% Pd/C (230 mg, 30 wt%) and the solution was hydrogenated under 50psi using a Parr Shaker for 12h. The resulting solution was filtered through Celite, concentrated and purified via column chromatography (silica, 4% MeOH in DCM with 1% NH_4OH) affording the title compound (400 mg, 73%) as a clear oil: MS (ES) m/e 213 $(M + H)^+$.

e) 1,1-dimethylethyl (3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)carbamate



1,1-dimethylethyl 3-azabicyclo[4.1.0]hept-6-ylcarbamate (200 mg, 0.95 mmol) and 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (177 mg, 0.95 mmol) in dry DMF (1.0 mL) were stirred at 90°C for 12h. The solution was concentrated and the residue was purified via column chromatography (silica, 3% MeOH in DCM with 1% NH_4OH) affording the title compound (300 mg, 80%) as an orange oil: MS (ES) m/e 399 $(M + H)^+$.

f) 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one



To 1,1-dimethylethyl (3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)carbamate (300 mg, 0.754 mmol) in DCM (8.0 mL) at 0°C was added dropwise an excess of 4M HCl in dioxane (1.1 mL, 4.52 mmol). The solution warmed to 25°C over 12h, was concentrated and used without further purification: MS (ES) m/e 299 $(M + H)^+$.

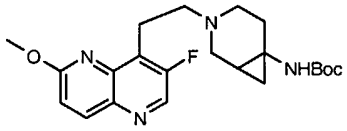
To the above salt in a solution of DCM-EtOH (1:1, 4.0 mL) and DIPEA (1.3 mL, 7.54 mmol) at 25°C were added Na_2SO_4 (128 mg, 0.905 mmol) and 3-oxo-3,4-dihydro-2*H*-

pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (147 mg, 0.754 mmol). After 12h, $NaBH_4$ (34 mg, 0.905 mmol) was added and the solution stirred an additional 2h, then was concentrated and purified via column chromatography (silica, 1% MeOH in DCM with 1% NH_4OH) affording the title compound (94 mg, 31%) as a yellow solid: MS (ES) m/e 477 $(M + H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.48 (d, J = 4.6 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.42 (J + 4.8 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.68 (AB quartet, 2H), 3.20-3.25 (m, 4H), 2.83-2.88 (m, 1H), 2.60-2.62 (m, 2H), 2.56-2.58 (m, 1H), 2.30-2.41 (m, 1H), 2.00-2.19 (m, 1H), 1.90-1.98 (m, 2H), 1.02-1.08 (m, 1H), 0.63-0.67 (m, 1H), 0.37-0.40 (m, 1H).

Example 7

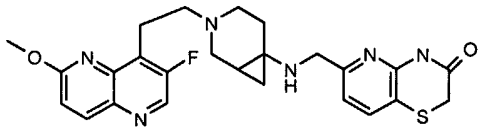
Preparation of 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

a) 1,1-dimethylethyl (3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)carbamate



According to procedure of Example 6, except substituting 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (194 mg, 0.948 mmol) for 8-ethenyl-2-(methyloxy)-1,5-naphthyridine, the title compound (129 mg, 33%) was obtained as an orange oil following purification by column chromatography (silica, 0.5% MeOH in DCM with 1% NH_4OH): MS (ES) m/e 417 $(M + H)^+$.

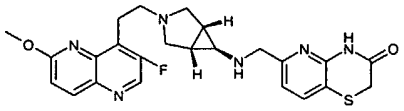
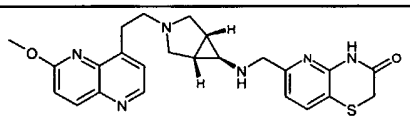
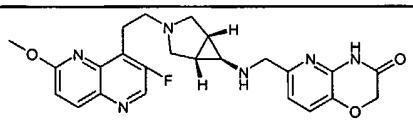
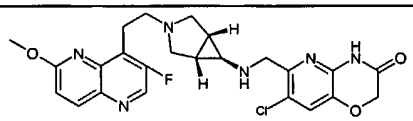
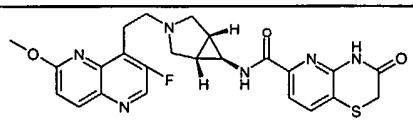
b) 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one

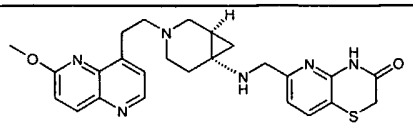
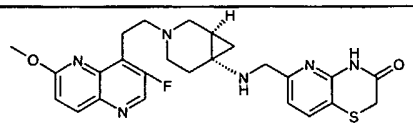


According to procedure 3, the title compound (40 mg, 26%) was obtained as a light yellow solid following purification by column chromatography (silica, 0.5% MeOH in DCM

with 0.5% NH_4OH): MS (ES) m/e 495 $(M + H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.51 (s, 1H), 8.07 (d, J = 9.1Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 3.99 (s, 3H), 3.69 (AB quartet, 2H), 3.29-3.30 (m, 1H), 3.07-3.23 (m, 3H), 2.83 (dd, J = 6.3, 11.4 Hz, 1H), 2.56-2.62 (m, 3H), 2.35-2.40 (m, 1H), 2.17-2.22 (m, 1H), 1.88- 1.98 (m, 2H), 1.05-1.10 (m, 1H), 0.63 (dd, J = 4.7, 9.7 Hz, 1H), 0.32-0.39 (m, 1H).

Examples

Example	Structure	Formula
1		6-{[(-3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one
2		6-{[((3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one
3		6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
4		7-chloro-6-{[(-3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
5		N-(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxamide

6		6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one
7		6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one

Example 8

Antimicrobial Activity Assay:

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A6, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compounds were tested in serial two-fold dilutions ranging from 0.016 to 16 mcg/mL.

Compounds were evaluated against a panel of Gram-positive organisms, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis* and *Enterococcus faecium*.

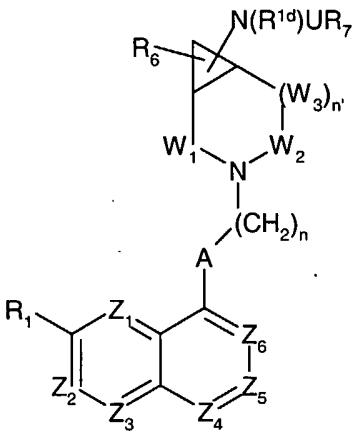
In addition, compounds were evaluated against a panel of Gram-negative strains including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Chlamydophila pneumoniae*, *Legionella pneumonaphila*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*.

The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

One skilled in the art would consider any compound with a MIC of less than 20 mg/mL to be a potential lead compound. For instance, each of the listed Examples (1 to 7), as identified in the present application, had a MIC $\leq$20 mg/ml against at least one of the organisms listed above.

What is claimed is:

1. A compound of formula (I)



(I)

wherein:

Z_1, Z_3, and Z_4 are independently N or CR^{1a};

Z_2, Z_5, and Z_6 are each CR^{1a};

R_1 and R^{1a} are independently at each occurrence hydrogen; cyano; halogen; hydroxy; (C_{1-6})alkoxy unsubstituted or substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or R_1 and R^{1a} of Z_2 together form ethylenedioxy;

A is $NR^{1b}(C=O)$ or CR_2R_3;

W_1, W_2, and W_3 are each CR_4R_5;

R^{1b} and R^{1d} are independently at each occurrence hydrogen, trifluoromethyl; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenyloxycarbonyl; aryl; aralkyl; (C_{3-8})cycloalkyl; heterocyclyl; or heterocyclylalkyl;

R_2, R_3, R_4, R_5, and R_6 are independently hydrogen; thiol; (C_{1-6})alkylthio; halogen; trifluoromethyl; azido; (C_{1-6})alkyl; (C_{2-6})alkenyl; (C_{1-6})alkoxycarbonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{2-6})alkenyloxycarbonyl; aralkyl; aryl; heterocyclyl; heterocyclylalkyl; hydroxy; amino; $NR^{1c}R^{1c'}$; (C_{1-6})alkylsulphonyl; (C_{2-6})alkenylsulphonyl; or (C_{1-6})aminosulphonyl wherein the amino group is optionally and independently substituted by hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl or aralkyl;

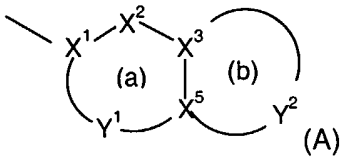
R^{1c} and $R^{1c'}$ are independently at each occurrence hydrogen; (C_{1-6})alkyl; aralkyl; aryl; heterocyclyl; heterocyclylalkyl; or together with the nitrogen that they are attached forn an aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring (wherein said aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring are optionally substiuted with from 1 to 3 substituents selected from halogen, hydroxy; cyano; nitro; (C_{1-6})alkyl; and aryl);

n' is 0 or 1;

n and n" are independently and at each occurrence 0, 1, or 2;

U is CH_2; C(=O); or SO_2;

R_7 is a substituted or unsubstituted 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_8 when part of a non aromatic ring;

X^2 is N, NR_9, O, $S(O)_{n''}$, CO or CR_8 when part of an aromatic or non-aromatic ring or may in addition be $CR_{10}R_{11}$ 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_9, O, $S(O)_{n''}$, CO and CR_8 when part of an aromatic or non-aromatic ring or may additionally be $CR_{10}R_{11}$ 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_9, O, $S(O)_{n''}$, CO and CR_{14} when part of an aromatic or non-aromatic ring or may additionally be $CR_{10}R_{11}$ when part of a non aromatic ring;

R_8, R_{10} and R_{11} are at each occurrence independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; trifluoromethoxy; nitro; cyano; carboxy; amino or aminocarbonyl unsubstituted or substituted by (C_{1-4})alkyl;

R_9 is at each occurrence independently hydrogen; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxy, carboxy, (C_{1-4})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; or aminocarbonyl wherein the amino group is optionally substituted with (C_{1-4})alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein

Z_1 and Z_4 are N; and

Z_3 is CR^{1a}.

3. A compound according to claim 1, wherein:

Z_1 and Z_3 are CR^{1a}; and

Z_4 is N.

4. A compound according to claim 1, wherein:

R_1 is OCH_3.

5. A compound according to claim 1, wherein R^{1a} is at each occurrence independently hydrogen; halogen; or cyano.

6. A compound according to claim 2, wherein:

R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen;

R^{1a} of Z_6 is fluorine or cyano; and

R_1 is OCH_3.

7. A compound according to claim 1, wherein:
A is CH_2; and
n of $(CH_2)_n$ is 1.

8. A compound according to claim 1, wherein:
n' is 0.

9. A compound according to claim 1, wherein:
n' is 1.

10. A compound accoring to claim 1, wherein:
R^{1d} is hydrogen; and
U is CH_2.

11. A compound according to claim 1, wherein:
R^{1d} is hydrogen; and
U is C(=O).

12. A compound acording to claim 1, wherein R_7 is:
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-benzo[1,4]dioxin-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl;
4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl;
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl;
2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl;
2,3-Dihydro-benzofuran-7-carbonitrile-5-yl;
7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl;
3-Oxa-1-thia-5-aza-indan-5-yl;
5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl;
6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl;
2,3-Dihydro-benzofuran-5-yl;
7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
4H-Benzo[1,4]thiazin-3-oxo-6-yl; or

8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

13. A compound according to claim 1, wherein R_7 is:
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

14. A compound according to claim 2, wherein:
R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen;
R^{1a} of Z_6 is fluorine or cyano;
R_1 is OCH_3;
A is CH_2;
n of $(CH_2)_n$ is 1; and
n' is 0.

15. A compound according to claim 14, wherein:
R_4, R_5, and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy;
R^{1d} is hydrogen; and
U is CH_2 or (C=O).

16. A compound according to claim 15, wherein R_7 is:
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-benzo[1,4]dioxin-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl;
4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl;
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl;
2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl;
2,3-Dihydro-benzofuran-7-carbonitrile-5-yl;
7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl;
3-Oxa-1-thia-5-aza-indan-5-yl;
5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl;
6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl;
2,3-Dihydro-benzofuran-5-yl;
7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
4H-Benzo[1,4]thiazin-3-oxo-6-yl; or

8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

17. A compound according to claim 16, wherein R_7 is:
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

18. A compound according to claim 2, wherein:
R^{1a} of Z_2, Z_3, and Z_5 are each hydrogen;
R^{1a} of Z_6 is fluorine or cyano;
R_1 is OCH_3;
A is CH_2;
n of $(CH_2)_n$ is 1; and
n' is 1.

19. A compound according to claim 18, wherein:
R_4, R_5, and R_6 are independently hydrogen; halogen; (C_{1-6})alkyl; or hydroxy;
R^{1d} is hydrogen; and
U is CH_2 or (C=O).

20. A compound according to claim 19, wherein R_7 is:
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-benzo[1,4]dioxin-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl;
4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
2,3-Dihydro-furo[2,3-*c*]pyridin-5-yl;
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl;
2,3-Dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl;
2,3-Dihydro-benzofuran-7-carbonitrile-5-yl;
7-Methyl-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl;
3-Oxa-1-thia-5-aza-indan-5-yl;
5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl;
6-Fluoro-2,3-dihydro[1,4]dioxin-7-yl;
2,3-Dihydro-benzofuran-5-yl;
7-Fluoro-4*H*-benzo[1,4]thiazin-3-oxo-6-yl;
4H-Benzo[1,4]thiazin-3-oxo-6-yl; or

8-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl.

21. A compound according to claim 20, wherein R_7 is :
4H-Pyrido[3,2-b][1,4]thiazin-3-oxo-6-yl;
4*H*-Pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl; or
7-Chloro-4*H*-pyrido[3,2-*b*]oxazin-3-oxo-6-yl.

22. A compound according to claim 1, wherein the compound is:

a) 6-{[(3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one;

b) 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one;

c) 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one;

d) 7-chloro-6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one;

e) *N*-(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[3.1.0]hex-6-yl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

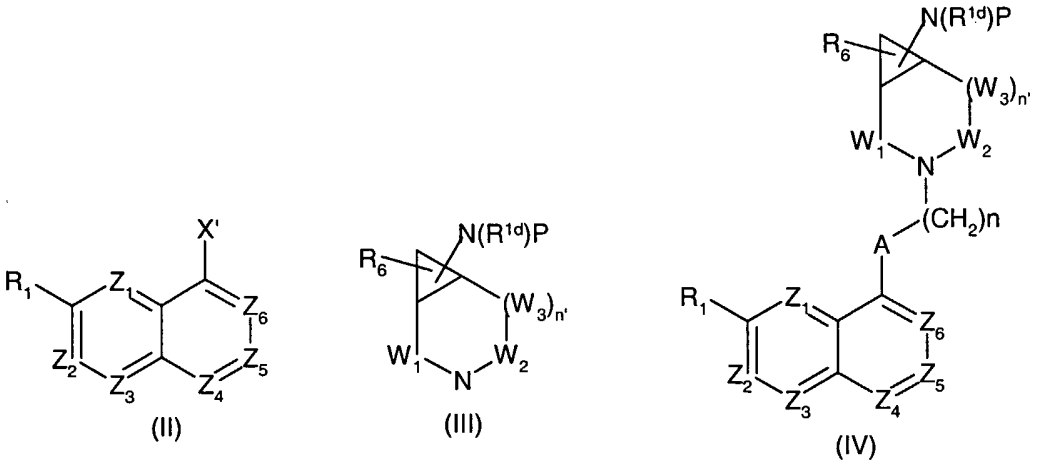
f) 6-{[((1*R*,6*R*)-3-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; or

g) 6-{[(3-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-azabicyclo[4.1.0]hept-6-yl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one; or

a pharmaceutically acceptable salt or solvate thereof.

23. A process for the preparation of intermediates of formula (IV) useful in the preparation of compounds of formula (I), which process comprises:

(a) reacting a compound of formula (II) with a compound of formula (III) to give a useful intermediate having formula (IV):



wherein:

Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, n, n', W_1, W_2, W_3, R_1, R_2, R_3, R_6, and R^{1d} are as defined in claim 1; and

X' is $CH{=}CH_2$ or $A\text{-}(CH_2)_n\text{-}L$;

A is CR_2R_3;

L is a leaving group; and

P is hydrogen or an amine protecting group.

24. A process for the preparation of a compound of claim 1, which process comprises:

(a) reacting a compound of formula (II) with a compound of formula (III) to give a compound of formula (IV);

(b) reacting the compound of formula (IV) with a compound of formula (V);

(c) removing P (where P is not hydrogen) to give a compound of formula (I);

(d) optionally converting to a pharmaceutically acceptable salt or solvate, thereof;

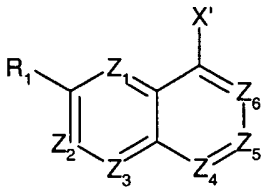
or

(a) reacting a compound of formula (II) with a compound of formula (III) to give a compound of formula (IV);

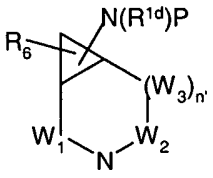
(b) removing P (where P is not hydrogen); and

(c) reacting the product of step (b) with a compound of formula (V) to give a compound of formula (I);

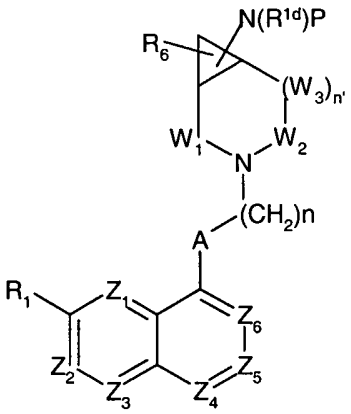
(d) optionally converting to a pharmaceutically acceptable salt or solvate, thereof;



(II)



(III)



(IV)

CHO-R_7
or
L'-U-R_7

(V)

wherein:

Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, n, n', W_1, W_2, W_3, R_1, R_2, R_3, R_6, R_7, U and R^{1d} are as defined in claim 1;

X' is $CH=CH_2$ or A-$(CH_2)_n$-L;

A is CR_2R_3;

L and L' are leaving groups; and

P is hydrogen or an amine protecting group.

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

26. A method of treating bacterial infections in mammals which comprises administering to a mammal in need thereof an effective amount of a compound according to claim 1.