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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; GLAXO WELLCOME HOUSE, Berkeley Avenue, Greenford, Middlesex, UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DAINES, Robert, A.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **PRICE, Alan, T.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(74) Agents: **SAUERMELCH, Loretta, J.** et al.; GLAXOSMITHKLINE, CORPORATE INTELLECTUAL PROPERTY, UW2220, 709 Swedeland Road, P.O. Box 1539, King Of Prussia, PA 19406-0939 (US).

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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.

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

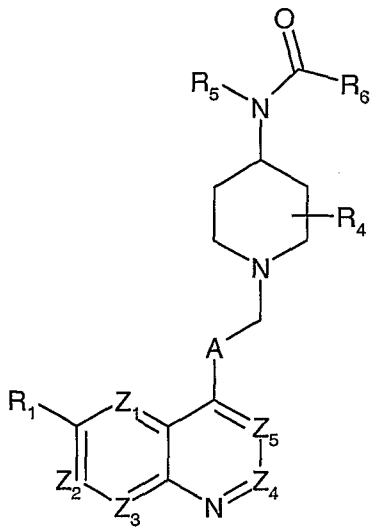
The emergence of pathogens resistant to known antibiotic therapy is becoming a serious global healthcare problem (Chu, et al., (1996) *J. Med. Chem.*, 39: 3853-3874). Thus, there is a need to discover new broad spectrum antibiotics useful in combating multidrug-resistant organisms. Importantly, it has 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. WO0125227, WO0240474, WO0207572, WO04024712, WO04024713, WO9937635, WO0021948, WO0021952, WO0043383, WO0078748, WO0107433, WO0107432, WO0208224, WO0224684, WO0250061, WO0250040, WO0256882, WO0296907, WO03087098, WO03010138, WO03064431, WO03064421, WO04002992, and WO0400249 disclose quinoline and/or naphthyridine derivatives having antibacterial activity.

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

In one aspect, this invention provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof:



(I)

wherein:

Z_1 is N or CR^{1a}; and

two of Z_2, Z_3, Z_4, and Z_5 are CR^{1a} and the rest are CH;

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, hydroxyl, 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, $CONH_2$, hydroxyl, (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 CR_2R_3;

R_2 is hydrogen; halogen; hydroxyl; (C_{1-6})alkyl; (C_{1-6})alkoxy; $NR^{1b}R^{1b'}$or acyloxy;

R_3 is hydrogen or (C_{1-6})alkyl;

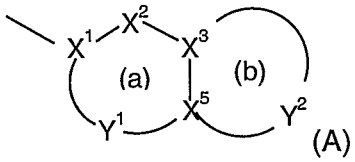
R^{1b} and $R^{1b'}$ are each independently hydrogen; (C_{1-6})alkyl; aryl; heteroaryl; or together with the nitrogen they are attached form an aziridine, azetidine, pyrrolidine,

piperidine or hexamethyleneimine ring (wherein said aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring is optionally substituted with 1 to 3 substitutents selected from halogen, (C_{1-6})alkyl, hydroxyl or aryl);

R_4 is hydrogen; hydroxyl; C_{1-6} alkyl; halogen; or $NR^{1b}R^{1b'}$;

R_5 is (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, acyloxy, carboxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is unsubstituted or N-substituted by one or two aryl, heteroaryl, halogen, unsubstituted (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxyl, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{3-7})cycloalkyl; (C_{1-6})alkylcarbonyl; or (C_{2-6})alkenylcarbonyl;

R_6 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_7 when part of a non aromatic ring;

X^2 is N, NR_8, O, $S(O)_x$, CO or CR_7 when part of an aromatic or non-aromatic ring or may in addition be CR_9R_{10} 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_8, O, $S(O)_x$, CO and CR_7 when part of an aromatic or non-aromatic ring or may additionally be CR_9R_{10} 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_8, O, $S(O)_x$, CO and CR_7 when part of an aromatic or non-aromatic ring or may additionally be CR_9R_{10} when part of a non aromatic ring;

R_7, R_9 and R_{10} are at each occurrence independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxyl; 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_8 is at each occurrence independently hydrogen; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxyl, 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;

each x is independently 0, 1 or 2;

or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, this invention describes a compound of formula (I) wherein Z_1 is N.

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

In some embodiments, this invention describes a compound of formula (I) wherein R^{1a} is hydrogen; fluorine; chlorine; or cyano.

In some embodiments, this invention describes a compound of formula (I) wherein R_2 is hydrogen or hydroxyl.

In some embodiments, this invention describes a compound of formula (I) wherein R_3 is hydrogen.

In some embodiments, this invention describes a compound of formula (I) wherein R_4 is hydrogen; hydroxyl; or fluorine.

In some embodiments, this invention describes a compound of formula (I) wherein R_5 is CH_3.

In some embodiments, this invention describes a compound of formula (I) wherein R_6 is 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide; 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide; 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide; 7-Bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; 4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]thiazepine-7-carboxamide; 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxamide; or 7-Cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide.

In some embodiments, this invention describes a compound of formula (I), wherein the compound is: *N*-((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-((3*R*,4*R*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide; *N*-[2-(methyloxy)ethyl]-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-[2-(dimethylamino)ethyl]-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide; *N*-ethyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-(2-methylpropyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-cyclopropyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-((3*R*,4*R*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide; *N*-(1-{2-[3-cyano-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-(1-{2-[3-cyano-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide; *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-

b][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; 7-bromo-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]thiazepine-7-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide; *N*-((3*R*,4*S*)-3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; *N*-(1-{(2*R*)-2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]-2-hydroxyethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-((3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-hydroxy-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxamide; *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; or 7-cyano-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; or a pharmaceutically acceptable salt or solvate thereof.

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.

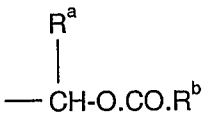
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are 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.

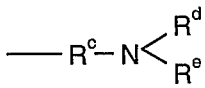
Pharmaceutically acceptable derivatives refers to compounds of formula (I) that have been covalently modified with a group that undergoes at least some in vivo cleavage to a compound of formula (I).

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.

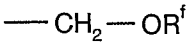
Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



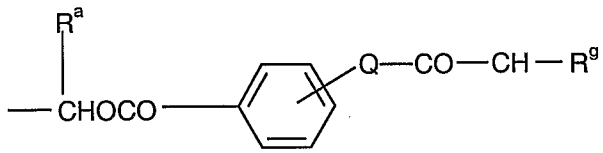
(i)



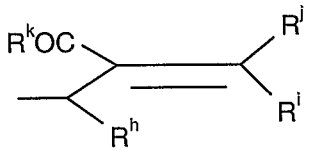
(ii)



(iii)



(iv)



(v)

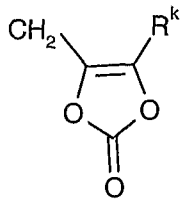
wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6})alkoxy, phenyl, benzyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyloxy, (C_{1-6})alkyl(C_{3-7}) cycloalkyl, 1-amino(C_{1-6})alkyl, or

1-(C_{1-6} alkyl)amino(C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6})alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or

(C_{1-6}) alkyl; R^l 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^k 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 reactive 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.

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.

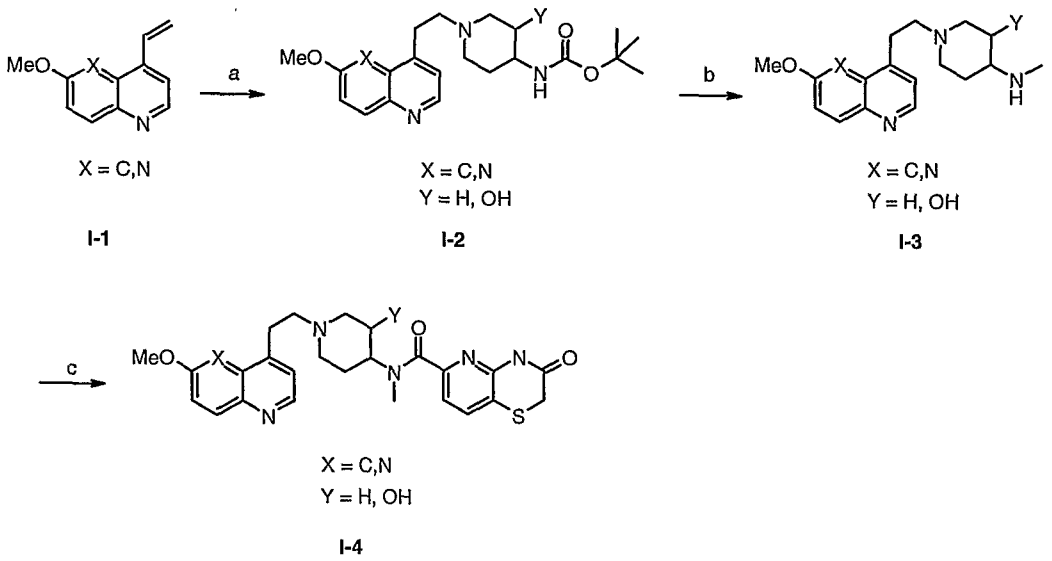
The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms. Although specific examples are described in the schemes, one of skill in the art appreciates that the methods are more generally applicable.

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.

The compounds of the present invention were prepared by the methods illustrated in Schemes I-III.

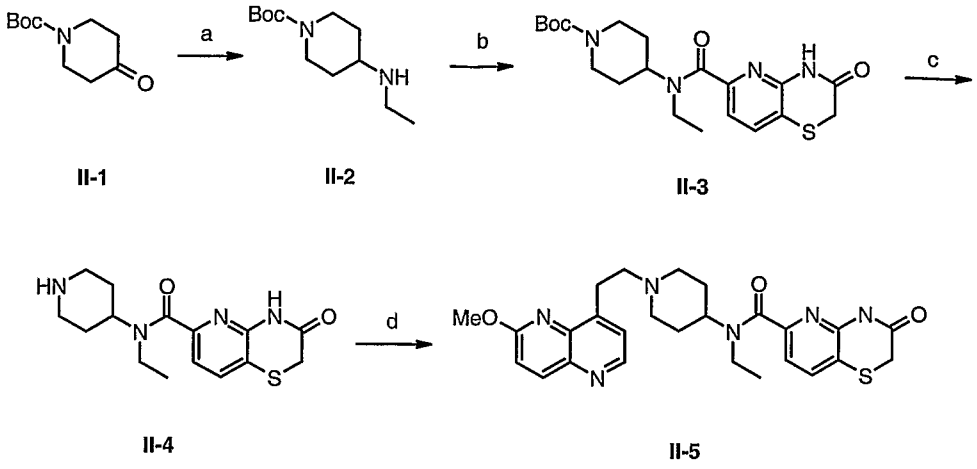
Scheme I



Reagents and conditions: (a) BOC 4-aminopiperidine, DMF, 90 °C; (b) LAH, THF; (c) CDI, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid.

Vinyl napthyridine or quinoline, **I-1**, undergoes Michael addition with the aminopiperidine derivative to provide the adduct (**I-2**). The reaction proceeds most readily under high solvent concentration using protic or aprotic solvents, either EtOH or DMF. The Boc group can be reduced with LAH to the secondary amine (**I-3**), which is subsequently coupled with the appropriate carboxylic acid, in this example 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid, in the presence of an activating agent such as carbonyldiimmidazole (CDI) or diphenyphosphoryl azid (DPPA) to provide the amide **I-4**.

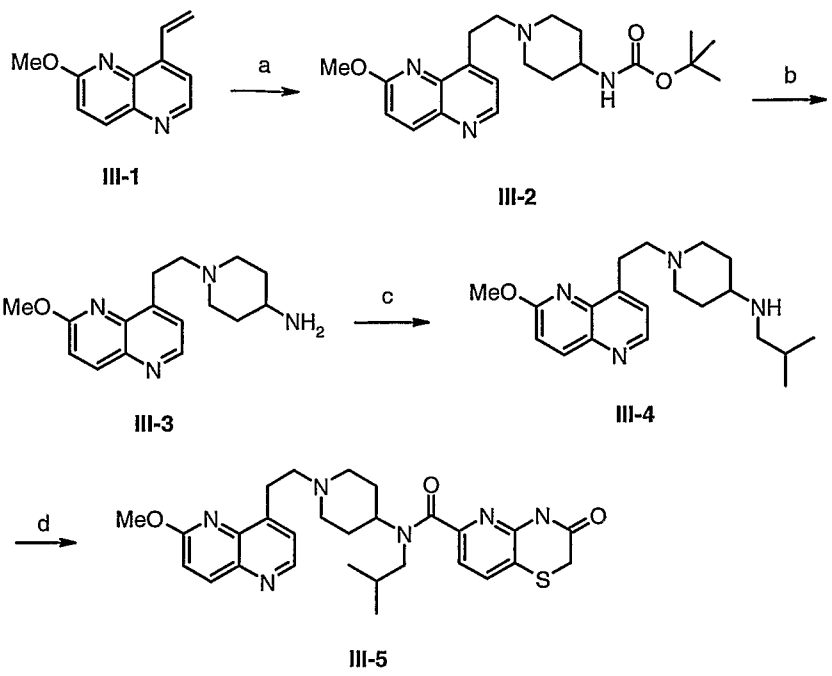
Scheme II



Reagents and conditions: (a) $EtNH_2$, $NaCNBH_4$, 3Å molecular sieves; (b) CDI, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid; (c) TFA; (d) 8-ethenyl-2-(methyloxy)-1,5-naphthyridine, DMF, 90 °C.

The piperidinone **II-1** is reacted with ethylamine and the resulting imine reduced with sodium cyanoborohydrate to provide N-ethylaminomethylpiperidine **II-2**. The amine **II-2** is reacted with an appropriate carboxylic acid, in this example 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid, in the presence of an activating agent such as carbonyldiimmidazole (CDI) or diphenylphosphoryl azide (DPPA) to provide the amide **II-3**. The BOC protecting group is removed via standard treatment with acid, in this example TFA in dioxane, to generate the piperidine **II-4** as an HCl salt. The secondary amine **II-4** is heated together with a vinyl electrophile such as 8-ethenyl-2-(methyloxy)-1,5-naphthyridine either under neat conditions or in an appropriate solvent such as DMF, dioxane or DME to give the product **II-5**. If the amine exists as a salt, the free base is generated by the addition of a suitable base such as Et_3N, diisopropylethylamine or $NaHCO_3$.

Scheme III



Reagents and conditions: (a) BOC 4-aminopiperidine, DMF, 90 °C; (b) TFA; (c) isovaleraldehyde, $NaCNBH_4$, 3Å molecular sieves; (c) CDI, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid.

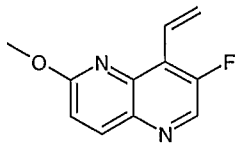
The Micheal addition of the vinyl napthyridine with the priperidine derivative is completed with the same method as described in Scheme I. The Boc group is removed with TFA. The free amine (**III-3**) is reacted with isovaleraladehyde under the standard reductive amination condition. The resulting secondary amine (**III-4**) is subsequently coupled with the carbonic acid, using diphenylphosphoryl azid (DPPA) or carbonyldiimmidazole (CDI) as the coupling regeant, to provide the final amide (**III-5**).

General

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 400 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal solvent standard $CHCl_3$ or MeOH. 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 and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. 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, 100 g, 0.806 mole) and diethyl ethoxymethylenemalonate (Aldrich, 163 mL, 0.806 mole) in EtOH (1 L) was heated at reflux for 4 h, then was cooled to room temperature. Concentration to dryness gave the title compound (238 g, quantitative) as a light brown solid which was used without further purification: LC/MS (ES) *m/z* 295 $[M+H]^+$.

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 room temperature and diluted with hexane (750 mL). The mixture was cooled in ice for 1 h, then the brown solid was

filtered off, washed with hexane, and dried under vacuum to afford the title compound (61.7g, 73%) as a grey solid which was used without further purification: LC/MS (ES) *m/z* 249 $[M+H]^+$.

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 mmol) in dry DMF (260 mL) under argon was stirred efficiently* in a water bath (to maintain approximately room temperature - may need slight ice-cooling on a large scale). Phosphorus tribromide (30.0 mL, 316 mmol) 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 (83.6 g, 90%) as an off-white solid which was used without further purification: LC/MS (ES) *m/z* 312 $[M+H]^+$.

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

A solution of NaOH (300 mL, 600 mmol, 2M in H_2O) 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 mmol) 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 neutralize the solution till 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) as a brown solid, which was used without further purification: LC/MS (ES) *m/z* 284 $[M+H]^+$.

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 mmol) 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 mmol). The reaction was stirred under argon at 100 °C for 1 h, then was cooled to room temperature 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 h 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 organic fractions 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 in $CHCl_3$) to afford further material (2.93 g, total = 34.07 g, 76%). Alternatively, the filtrate was left at room temperature overnight and then filtered to give a second crop of the title compound (2.5 g): LC/MS (ES) *m/z* 255 $[M+H]^+$.

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 mmol) in dry THF (400 mL) was maintained at -5°C while nitrosonium tetrafluoroborate (12.9 g, 110 mmol) was added portionwise over 30 min (approximately 2 g portions). The reaction was continued for an additional 1 h 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%): LC/MS (ES) *m/z* 353 $[M+H]^+$.

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

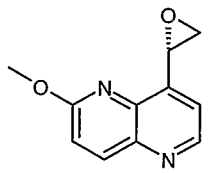
A suspension of 4-bromo-6-methoxy-[1,5]naphthyridine-3-diazonium tetrafluoroborate (31.42 g, 89.0 mmol) in decalin (mixed isomers, 500 mL) in a 2 L flask* was heated to 180 °C and held at this temperature for 5 min. The mixture was cooled and diluted with $CHCl_3$ (500 mL, to keep the product in solution), 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%): LC/MS (ES) *m/z* 258 $[M+H]^+$.

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 mmol), tetrakis-triphenylphosphine (90 mg, 0.08 mmol) in DME (60 mL) and H_2O (20 mL) was added 2,4,6-trivinylcycloborane-pyridine complex (0.94 g, 3.91 mmol). After stirring for 10 h at 85 °C the reaction contents were concentrated and the product purified by chromatography (silica, 25% EtOAc in hexane) to give a low melting solid (1.43 g, 90%): LC/MS (ES) *m/z* 205 $[M+H]^+$.

Preparation 2



Preparation of (*S*)-2-(6-Methoxy-[1,5]-naphthyridin-4-yl)oxirane

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

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

The unsaturated ester (10.5g, 0.05mol) in warm Dowtherm A (50ml) was added over 3 minutes to refluxing Dowtherm A, and after a further 20 minutes at reflux the mixture was cooled and poured into ether. The precipate was filtered to give the title compound (6.26g, 70%): LC/MS (ES) *m/z* 177 $[M+H]^+$.

b) bromomethyl-(6-methoxy-[1,5]-naphthyridin-4-yl)-ketone

4-Hydroxy-6-methoxy-[1,5]-naphthyridine (10g, 0.057mol) in DCM (200ml) containing 2,6-lutidine (9.94ml, 0.086mol) and 4-dimethylaminopyridine (0.07g, 0.0057mol) was cooled in ice and treated with trifluoromethanesulfonic anhydride (10.5ml, 0.063mol). After stirring for 2.5 hr the mixture was washed with saturated ammonium

chloride solution, dried, evaporated and purified on silica (DCM). The triflate (13.2g, 0.044mol) in DMF (200ml) with TEA (12ml, 0.086mol), butyl vinyl ether (22ml, 0.17mol), 1,3-bis(diphenylphosphino)propane (1.77g, 0.0044mol) and palladium (II) acetate (0.97g, 0.0044mol) was heated at 60°C for 3 hr then evaporated and chromatographed on silica gel (DCM) to give a yellow solid (10.7g, 95%). This was dissolved in THF (250ml), water (40ml) and treated with N-bromosuccinimide (7.4g.0.042 mol) for 1 h, then evaporated and chromatographed on silica gel (DCM) to give the title product (10.42g, 98%): LC/MS (ES) *m/z* 287 $[M+H]^+$.

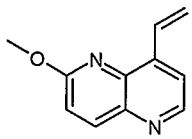
(c) (*R*)-2-bromo-1-(6-methoxy-[1,5]-naphthyridin-4-yl)ethanol

Bromomethyl-(6-methoxy-[1,5]-naphthyridin-4-yl)-ketone (6.6g, 0.023mol) in toluene was treated with (+)-B-chlorodiisopinocamphenylborane ((+)-DIP-chloride) (12g, 0.037mol) and stirred overnight, then diethanolamine (15g, 0.14mol) was added and the mixture was stirred for 3 h, filtered and evaporated. Purification with columne chromatography (silica, ethyl acetate-hexane)gave the title compound as a white solid (4.73g, 73%): LC/MS (ES) *m/z* 283 $[M+H]^+$.

(d) (*R*)-2-(6-methoxy-[1,5]-naphthyridin-4-yl)oxirane

(*R*)-2-Bromo-1-(6-methoxy-[1,5]-naphthyridin-4-yl)ethanol (4.8g, 0.017mol) in MeOH (20ml) was stirred with potassium carbonate (2.6g, 0.019 mol) for 1 h, then evaporated and chromatographed on silica gel (ethyl acetate-hexane-dichloromethane) to give a solid (3.14g, 92%), (91% ee by chiral HPLC): LC/MS (+ve ion electrospray) m/z 203 (M+H+).

Preparation 3

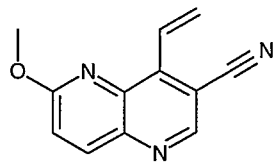


Preparation of 8-ethenyl-2-(methyloxy)-1,5-naphthyridine

To a solution of 6-(methyloxy)-1,5-naphthyridin-4-yl trifluoromethanesulfonate (from Prep. 2b) (5.0 g, 16.23 mmol) in DME (80 mL) and H_2O (40 mL) was added trivinyl boronate (1.96 g, 8.1 mmol), K_2CO_3 (2.23 g, 16.23 mmol) and $Pd(PPh_3)_4$ (0.19 g, 0.16

mmol). After 3 h at 90 °C under N_2, the reaction solution was concentrated under vacuum and purified on silica (hexane/EtOAc, 4:1) to give the title compound as a yellow oil (2.44 g, 81%): LC/MS (m/z) (ES) 187 $(M+H)^+$.

Preparation 4



Preparation of 4-ethenyl-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile

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

A solution of NaOH (300 mL, 600 mmole, 2 M in H_2O) 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 till 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), which was used without further purification.

e) 4-chloro-6-(methyloxy)-1,5-naphthyridine-3-carboxamide

To a solution of 4-Bromo-6-methoxy-[1,5]naphthyridine-3-carboxylic acid ethyl ester (840 mg, 3.0 mmol) in toluene (10 mL) was added thionyl chloride (3 mL) as one portion under N2 protection. After refluxing at 100 °C for 2h, the mixture was concentrated and azotropically dried with toluene to afford a yellow solid, which was dissolved in anhydrous DCM (3 mL). The resulting solution was cooled down to 0 °C and treated with NH_3 solution (5 mL, 50% in water). After stirring at 0 °C for 30 min, the reaction mixture was warmed up to 25 °C and stirred for 12h. DCM was removed, and the solid was collected by suction filtration, washed with water and dried under vacuum over phosphorus pentoxide to give the title compound (648 mg, 91%).

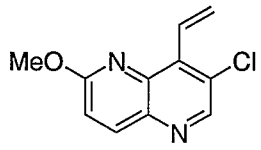
f) 4-chloro-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile

To a solution of 4-chloro-6-(methyloxy)-1,5-naphthyridine-3-carboxamide (647 mg, 2.7 mmol) in anhydrous DCM (2 mL) with triethyamine (2 mL) at 0 °C was added trifluororacetic anhydride (1 mL) slowly. The resulting solution was warmed up to 25 °C and stirred for 1h. The mixture was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted several times with $CHCl_3$. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-25% ethyl acetate/hexane) affording the title compound as an off-white solid (540 mg, 91%): LC/MS (ES) m/e 220 $(M+H)^+$.

g) 4-ethenyl-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile

To a solution of 4-chloro-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile (280 mg, 1.28 mmol), potassium carbonate (885 mg, 6.4 mmole), tetrakis-triphenylphosphine (30 mg, 0.026 mmole) in DME/H_2O (20 mL, 3:1) was added 2,4,6-trivinylcycloborane-pyridine complex (154 mg, 0.64 mmole). After stirring for 1h at 90 °C, another batch of tetrakis-triphenylphosphine (30 mg, 0.026 mmol) was added. After refluxing for another 1.5 h, the mixture contents were cooled down to room temperature and extrated with diethyl ether. The ether fractions were combined, concentrated and purified by column chromatography (silica, 0-10% ehtyl acetate in hexane) to give the title compound as a light yellow solid (176 mg, 65%): LC/MS (ES) m/e 212 $(M+H)^+$.

Preparation 5



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

a) 3-chloro-6-methoxy-quinolin-4-ol

6-Methoxy-quinolin-4-ol (18.5 g) in acetic acid (750 mL) was treated with N-chlorosuccinimide (15.52 g) and the mixture was heated at 60°C for 4.5 hr, cooled, and evaporated. Excess sodium bicarbonate solution was added and the solid collected and washed with water and dried *in vacuo* at 40°C overnight, to give a yellow solid (21.3 g). MS (ES) *m/z* 210/212 $(M + H)^+$.

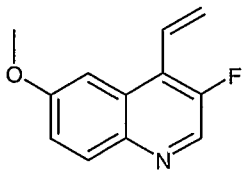
(b) 4-bromo-3-chloro-6-methoxy-quinoline

3-Chloro-6-methoxy-quinolin-4-ol from above in dry DMF (80 mL) was cooled in ice and phosphorus tribromide (15.6 mL) added drop-wise, and the mixture was stirred, with ice-cooling for 30 minutes then allowed to warm to room temperature and stirred for a further 3.5 hours. It was cooled in ice and sodium carbonate solution was added and the solid was collected, washed well with water, and dried *in vacuo*, to afford a pale yellow solid (13.2 g). MS (ES) *m/z* 272/274/276 $(M + H)^+$.

c) 7-chloro-2-methoxy-8-vinyl-quinoline

4-Bromo-3-chloro-6-methoxy-quinoline (0.5 g) in DME (14 mL) under argon, was treated with tetrakis(triphenylphosphine)palladium(0) (0.104 g) and the mixture stirred at room temperature for 20 minutes. Anhydrous potassium carbonate (0.25 g), water (4 mL), and vinylborane:pyridine complex was added and the mixture was heated at 100°C for 1 hr. It was cooled, diluted with water and extracted with ether, dried (sodium sulfate) and evaporated to dryness. As starting material (4b) was still present the crude reaction product was reacted again, as above, and heated for a further 6 hours. After work-up the product was chromatographed on silica gel, eluting with DCM to afford a white solid (0.35 g): MS (ES) *m/z* 220/222 $(M + H)^+$.

Preparation 6



Preparation of 4-ethenyl-3-fluoro-6-(methyloxy)quinoline

a) 4-Hydroxy-6-methoxy-quinoline-3-carboxylic acid ethyl ester

A solution of 4-methoxyaniline (40g, 0.32 mole) and diethyl ethoxymethylenemalonate (65 mL, 0.32 mole) in Dowtherm A (500 mL) was heated at reflux in a flask fitted with side-arm and condenser, and heating was continued until all the ethanol had distilled off (ca. 0.5 hr). The solution was cooled and pentane was added to give a sticky precipitate. The solvents were decanted off and the residue was treated with more pentane and allowed to stand overnight. The solid was filtered off and washed well with pentane to give the title compound (62.4 g; 78%, contains traces of Dowtherm A).

b) 4-bromo-6-methoxy-quinoline-3-carboxylic acid ethyl ester

PBr_3 (64.5 g, 22.5 mL, 0.239 mole) was added dropwise to a stirred, ice cold suspension of 4-hydroxy-6-methoxy-quinoline-3-carboxylic acid ethyl ester (59 g, 0.239 mole) in DMF (750 mL); the temperature rose to 15-20 °C for 30 min and then dropped to ca. 5 °C (the starting material dissolved fairly quickly and a new solid precipitated out). After 3 hr the solid was collected, washed sequentially with cold DMF, hexane, and water,

then was dried at 40 °C in vacuo overnight to give the title compound (41 g, 78%): LC/MS (ES) *m/e* 310/312 $(M + H)^+$.

c) 4-bromo-6-methoxyquinoline-3-carboxylic acid

4-Bromo-6-methoxy-quinoline-3-carboxylic acid ethyl ester (41 g, 0.132 mole), partially dissolved in THF (600 mL), was treated dropwise with aqueous 2 M sodium hydroxide (198.4 mL, 0.396 mole). After 24 hr, the reaction was complete by TLC (2% MeOH/CH_2Cl_2). The mixture was neutralized with 5 M HCl then the THF was removed in vacuo. The residue was dissolved in water and acidified with 5 M HCl. The solid product was collected under suction, washed well with water, and dried in vacuo to give the title compound (34 g, 91%) as a white solid: MS (ES) *m/e* 282/284 $(M + H)^+$.

d) (4-bromo-6-methoxy-quinolin-3-yl)-carbamic acid *tert*-butyl ester

To a solution of 4-Bromo-6-methoxyquinoline-3-carboxylic acid (34 g, 0.121 mole), triethylamine (141 mL) and *tert*-butanol (181 mL) in dry DMF (400 mL) was added diphenylphosphoryl azide (36.6 g, 28.6 mL, 0.133 mole). The mixture was heated at 100 °C for 1h (see Note), then cooled and concentrated. The residue was dissolved in CH_2Cl_2 and washed with water (some insoluble material was removed by filtration). The aqueous phase was extracted with dichloromethane and the combined organics were dried (Na_2SO_4) and concentrated. Chromatography on silica gel (1 kg, 1:1 ether/light petroleum ether) gave the carbamate (22.7 g, 53 %): MS (ES) *m/e* 309/311 $(M + H)^+$, 354/6.

Further elution with ether gave several mixed fractions then pure 3-amino-4-bromo-6-methoxyquinoline (2.0 g, 6.5%): MS (ES) *m/e* 309/311 $(M + H)^+$, 254/6.

e) 3-amino-4-bromo-6-methoxyquinoline

(4-Bromo-6-methoxy-quinolin-3-yl)-carbamic acid *tert*-butyl ester (22.7 g, 0.0643 mole) was dissolved in CH_2Cl_2 (200 mL) and treated with trifluoroacetic acid (100 mL). After 3.5 hr at RT, the mixture was concentrated and the residue was dissolved in water. The solution was made basic with aqueous sodium carbonate. The precipitate was filtered off, washed with water, and dried at 40 °C in vacuo overnight, to give the title compound (16.46 g, 101%) as a white solid: LC/MS (ES) *m/e* 254/256 $(M+H)^+$.

f) 4-bromo-3-methoxyquinolin-3-yl-diazonium tetrafluoroborate

3-Amino-4-bromo-6-methoxyquinoline (18.4 g, 0.0727 mole) was dissolved in dry THF (250 mL) and the solution was cooled to –8 °C (EtOH-ice bath). Nitrosonium tetrafluoroborate (9.34 g, 0.08 mole) was added in portions over 10 min, keeping the temperature less than –2 °C. The mixture was stirred at –5 to 0 °C for 30 min, then the yellow precipitate was filtered off and washed sequentially with cold THF and hexane. Drying in vacuo gave the title compound (19.4 g, 76%) an insoluble orange-yellow solid.

g) 4-bromo-3-fluoro-6-methoxyquinoline

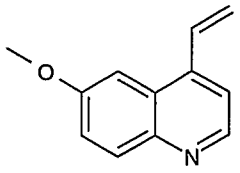
A well stirred solution of decahydronaphthalene (mixed isomers, 120 mL) was heated to ca. 167-170 °C (internal temperature) and the diazonium tetrafluoroborate salt (6.0 g) was added portionwise over 30 sec, when the solid turned black. The reaction mixture was immediately cooled and the decahydronaphthalene was filtered off. The filtrate was saved for further processing. The residue was extracted with dichloromethane (3x). Some insoluble material remained. The solution was concentrated and the residue was chromatographed on silica gel (CH_2Cl_2 then $CHCl_3$) to give the title compound (1.1 g) as a white solid: MS (ES) *m/e* 256/258 $(M + H)^+$, Rt = 2.65 min. About 4% of a dibromo impurity was present: MS (ES) *m/e* 316/318/320 $(M + H)^+$ Rt = 2.94 min.

The decahydronaphthalene solution was treated with excess ethereal HCl and the solid hydrochloride salt was collected and washed with hexane. This was converted to the free base by reaction with aqueous sodium carbonate followed by extraction with CH_2Cl_2. This gave additional title compound (0.87 g; total yield = 1.97 g, 45%).

h) 4-ethenyl-3-fluoro-6-(methyloxy)quinoline

4-Bromo-3-fluoro-6-(methoxy)quinoline (2.3 mmol) in DME (26 mL) under argon, was treated with tetrakis(triphenylphosphine)palladium(0) (0.13 g, 0.115 mmol) and the mixture stirred at room temperature for 20 minutes. Anhydrous potassium carbonate (0.32 g, 2.3 mmol), water (7 mL), and vinylborane:pyridine complex (see F. Kerins and D O'Shea J. Org. Chem. **2002**, *67*, 4968-4971) (0.22 g, 0.92 mmol) were added and the mixture was heated at 100°C for 2 hr. It was cooled, diluted with water and extracted with ether, dried over magnesium sulfate and evaporated to dryness. After work-up the product was chromatographed on silica gel, eluting with 10 %methanol in DCM to afford a white solid (0.44g, 90%): MS (+ve ion electrospray) *m/z* 203 (MH+).

Preparation 7



Preparation of 4-ethenyl-3-fluoro-6-(methyloxy)quinoline

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

To a solution of *p*-anisidine (20 g, 162 mmol) in ethyl alcohole (162 mL) were added 2, 2-dimethyl-1,3-dioxane-4,6-dione (28 g, 194 mmol) followed with triethyl orthoformate (29.7 mL, 178 mmol). After refluxing for 2 h, the mixture was cooled down to room temperature. A white percipitate was crashed out. The percipitate was filtered, washed with icy EtOH and dried to afford the title compound (39.2 g, 87%): LC/MS (ES) m/e 278 $(M+H)^+$.

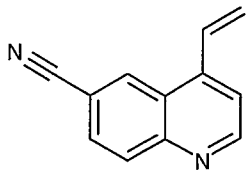
b) 6-(methyloxy)-4-quinolinol

To a flask with Dowthern (250 mL) at 255°C was added 2,2-dimethyl-5-({[4-(methyloxy)phenyl]amino}methylidene)-1,3-dioxane-4,6-dione (39.1 g, 141 mmol) in portions. The resulting solution was heated for 5 min., cooled down to room temperature and diluted with diethyl ether. A percipitate was filtered, washed with diethy ether and dried in the vaccume line to generate the title compound as a whitel solid (23,7 g, 96%): LC/MS (ES) m/e 176 $(M+H)^+$.

c) 4-bromo-6-(methyloxy)quinoline

To a solution of 6-(methyloxy)-4-quinolinol (23.6 g, 135 mmol) in DNF (100 mL) was added PBr_3 (16 mL, 169 mmol) in portions. The flask was filled with a bubbler. When bubbling ceased, the suspension was dumped into icy water with stirring. The resulting mixture was diluted with a large volume of water (~600 mL). The percipitate was filtered, washed with water and dried under vaccume line to afford the title compound as an off-white solid (31.4 g, 97%): LC/MS (ES) m/e 239 $(M+H)^+$.

Preparation 8



Preparation of 4-ethenyl-6-quinolinecarbonitrile

a) 4-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzonitrile

A mixture of 4-aminobenzonitrile (12.5 g, 0.106 mole), Meldrum's acid (18.3 g, 0.127 mole) and triethylorthoformate (16 mL) in ethanol (100 mL) was refluxed 3 hr. After cooling to room temperature the percipitate was filtered, washed with cold ethanol and air dried to afford the title compound as an off-white solid (27.9 g, 97%): LC/MS (ES) *m/e* 273 $(M + H)^+$.

b) 4-oxo-1,4-dihydro-quinoline-6-carbonitrile

4-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzonitrile (27.5 g, 0.10 mol) was added portionwise over 5 minutes to refluxing Dowtherm A (200 mL). After refluxing an additional 5 minutes, the mixture was allowed to cool to room temperature and diluted with ether (200 mL) with stirring. The percipitate was filtered off, washed thoroughly with ether and air dried to provide the title compound as a gold solid (16.2 g, 94%): LC/MS (ES) *m/e* 171 $(M + H)^+$.

(c) 4-bromo-quinoline-6-carbonitrile

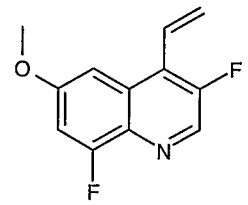
4-Oxo-1,4-dihydro-quinoline-6-carbonitrile (12.0 g, 70.5 mmol) in DMF (60 mL) was treated dropwise with phosphorous tribromide (8.0 mL, 84.6 mmole) over 10 minutes (exothermic). After allowing to stir and cool to room temperature, ice water (100 mL) was added and the mixture was stirred 30 minutes, then neutralized to pH=8 by dropwise addition of 50% NaOH with cooling. The percipitate was filterd off, washed with water and air dried to afford the title compound as a tan solid (14.3 g, 87%): LC/MS (ES) *m/e* 234 $(M+H)^+$.

d) 4-ethenyl-6-quinolinecarbonitrile

A solution of 4-Bromo-quinoline-6-carbonitrile (1.0 g, 4.3 mmole), tributylvinyltin (1.5 mL, 5.17 mmole), and tetrakistriphenylphosphine palladium (0) (245 mg, 5 mole %) in toulene (20 mL) was refluxed under nitrogen atmosphere for 2 hr. The mixture was concentrated and purified with column chromatography (silica, 30% ethyl acetate in hexane) to afford the title compound as a pale yellow solid (500 mg, 64%): MS (ES) *m/e* 181 $(M+H)^+$.

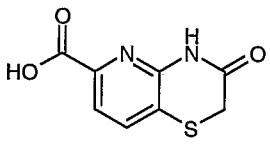
Preparation 9

Preparation of 8-ethenyl-4,7-difluoro-2-(methyloxy)-1,5-naphthyridine



(see WO20044058144)

Preparation 10



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

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 hr 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 hr at room temperature. The solution was diluted with EtOAc (1 L), washed with water (3 x 300 mL), dried and evaporated to about 10 mL. A white percipitate was crashed out, which was filtered off and washed with a little ethyl acetate 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 hr with 0.5M NaOH solution (8 mL) and stirred overnight. After evaporation to approx. 3 ml, water (5 mL) was added and 2M HCl till pH4. The precipitated solid was filtered off, washed with a small volume of water and dried under vacuum to give a solid (636 mg): LC/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): LC/MS ($APCI^-$) *m/z* 195 ($[M-H]^-$, 50%), 165(100%).

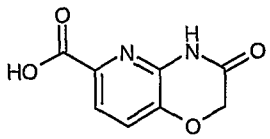
d) 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde

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 hr (730 mg) and 16 hr (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): LC/MS ($APCI^-$) *m/z* 195 ($[M-H]^-$, 95%), 165 (100%).

e) 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%): LC/MS ($APCI^-$) *m/z* 209 ($[M-H]^-$, 95%).

Preparation 11



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

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, and 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, cooled to room temperature and diluted with ethyl ether. The precipitate was removed by 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 water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The solid residue was purified by flash chromatography (silica, 5-10% ethyl acetate in chloroform) to afford the title compound as an off-white solid (2.5 g, 38%): LCMS (ES) *m/z* 253.0 $(M + H)^+$.

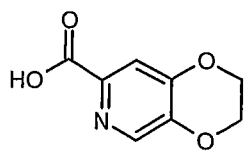
e) 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde

6-((*E*)-Styryl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one (1.2 g, 4.8 mmole) was dissolved in DCM (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) 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid

This acid was prepared from 3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (900 mg) by oxidation with Oxone (potassium peroxymonosulphate) (3.7g) in a DMF solution (50 mL). After 1.5 hr at room temperature, dilution with water (50 mL) filtration and drying in vacuo afforded the acid as an off-white solid (687 mg, 70%): LCMS (ES) m/e 195 $(M+H)^+$.

Preparation 12



Preparation of 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid

a) 5-benzyloxy-2-hydroxymethyl-1 *H*-pyridin-4-one

A mixture of 5-benzyloxy-2-hydroxymethyl-4-pyrone (prepared from Kojic acid by the method of D. Erol, J. Med. Chem., 1994, **29**, 893) (9.7 g, 40 mmol), concentrated aqueous (880) ammonia (100 mL), and ethanol (20 mL) was heated to reflux overnight. The mixture was allowed to cool to room temperature then filtered. The resultant solid was washed with ether and dried in vacuo (5.9 g): MS ($APCI^+$) m/z 232 ($M+H^+$).

b) (2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)-methanol

A solution of 5-Benzyloxy-2-hydroxymethyl-1 *H*-pyridin-4-one (2 g, 8.7 mmol) in water (220 mL) containing sodium hydroxide (17 mmol) was hydrogenated over 10% palladium on charcoal (1 g) for 4 hours. The mixture was filtered and evaporated to give a white solid. This solid was dissolved in N,N-dimethylformamide (8 mL) then treated with potassium carbonate (2.9 g) and 1,2-dibromoethane (0.6 mL, 7 mmol). The mixture was heated at 85°C overnight. The cooled mixture was evaporated onto silica and chromatographed eluting with 10-30% methanol in ethyl acetate affording a white solid (250 mg, 21 %): MS (APCI+) m/z 168 ($M+H^+$).

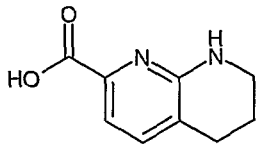
c) 2,3-dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde

A solution of (2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl)-methanol (250 mg, 1.5 mmol) in dichloromethane (5 mL) was treated with manganese dioxide (650 mg, 7.5 mmol). After 3 days the mixture was filtered and evaporated affording a white solid (150 mg, 61%): LC/MS ($APCI^+$) m/z 166 ($M+H^+$).

d)2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid

To a solution of 2,3-Dihydro-[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (780 mg, 4.74 mmol) in acetone-H_2O (1:4, 47 mL) at 25°C were added $NaClO_2$ (575 mg, 6.36 mmol) followed by H_2NSO_3H (599 mg, 6.17 mmol). After 2h, the solution was concentrated and the residue purified through a plug of silica (10% MeOH in DCM (1% NH_4OH)) affording the title compound as an off-white solid (600 mg, 70%): LC/MS (ES) m/e 182 $(M+H)^+$.

Preparation 13



Preparation of 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid

a) 2-(trichloromethyl)-1,8-naphthyridine

To a solution of 2-methyl-1,8-naphthyridine (3.0 g, 20.7 mmol) in CH_2Cl_2 (300 ml) was added *N*-chlorosuccimide (11.1 g, 81.6 mmol) and AIBN (15 mg). The reaction was refluxed for 4h with additional AIBN (7mg) added each hour, followed by reflux for 30h. The cooled reaction solution was washed well with aqueous Na_2CO_3, brine, dried over $MgSO_4$, and concentrated to give the desired product (5.12g, 100%) as a tan solid: LC/MS (ES) *m/z* 247.2 $[M+H]^+$.

b) methyl 1,8-naphthyridine-2-carboxylate

2-(trichloromethyl)-1,8-naphthyridine (3.0 g, 12.2 mmol) was added in portions to 85% phosphoric acid (20 mL). After heating at 140° for 3h, the solution was cooled down and diluted slowly with methanol (45ml). The resulting mixture was refluxed for 12h. The reaction was concentrated under reduced pressure and the residue was carefully treated with the saturated aqueous Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2. The organic layers were combined, washed with aqueous NaCl, dried over $MgSO_4$ and concentrated to give the title compound as a beige solid (1.13g, 49%): LC/MS (ES) *m/z* 189.2 $[M+H]^+$.

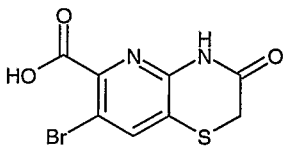
c) methyl 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylate

To a solution of methyl 1,8-naphthyridine-2-carboxylate (1.01 g, 5.37 mmol) in methanol (52 ml) was added 10% palladium on carbon (306 mg, 50% by weight with water). The mixture was hydrogenated at atmospheric pressure for 16h, filtered through a pad of Celite®, and concentrated. Purification by flash column chromatography (silica, 0-80% ethyl acetate in hexane) yielded the title compound as a yellow oil (628 mg, 61%): LC/MS (ES) *m/z* 193.2 $[M+H]^+$.

d) 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid

To a solution of methyl 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylate (300 mg, 1.55 mmol) in dioxane (2 mL) was added the solution of NaOH (3 mL, 0.15 mmol, 0.5 N in H_2O). After refluxing for 18 hr, the mixture was concetrated to 1 mL and acidified with HCl solution (3N in H_2O) to pH 4. A white percipitate was crashed out. The percipitate was filetered, washed with hexane and dried to afford the tilte compound as a white solid (237 mg, 85%): LC/MS (ES) *m/z* 179 $[M+H]^+$.

Preparation 14



Preparation of 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

a) methyl 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate

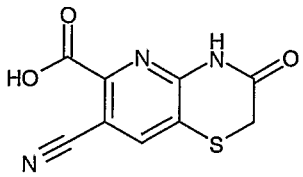
To a solution of ethyl-2-mercaptoacetate (2.97 mL, 3.26 g, 27.1 mmol) in DMF (100 mL) at 0°C was added NaH (1.08 g, 27.1 mmol, 60% in mineral oil). Afer stirrring for 1h, methyl-6-amino-3,5-dibromopyridine-2-carboxylate (8.0 g, 25.8 mmol) was added. The mixture was warmed up to room temperature and stirred for 18 hr. It was then treated with addition of another batch of the mixture of NaH (0.124 g, 5.16 mmol) and ethyl-2-mercaptoacetate (0.57 mL, 5.16 mmol) which was prepared as indicated above. The resulting solution was diluted with ethyl acetate and water. The organic layer was separated and concentrated at high temperature to afford a residue. The residue was dissolved in acetic acid (100 mL) and heated at 100°C for 18 hr. The mixture was cooled down to room temperature affording a precipitate. The percipitate was triturated with ethyl acetate, filtered and dried to provide the title compound as an off-white solid (5.0 g, 64%): LC/MS (ES) m/e 304 $(M+H)^+$.

b) 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

A solution of methyl 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (400 mg, 1.3 mmol) in dioxane/H_2O (50 mL, 4:1) was mixed with an aqueous solution of NaOH (6 mL, 3 mmol, 0.5 M) and stirred for 12 hr. The solution was extracted with DCM. The organic fractions were combined and concentrated to afford the title

compound as an off-white solid which was used without further purification: LC/MS (ES) m/e 290 $(M+H)^+$.

Preparation 15



Preparation of 7-cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

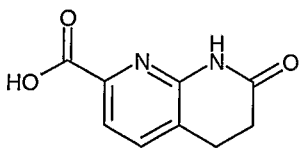
a) methyl 7-cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate

Methyl 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (100 mg, 0.32 mmol, prepared from Preparation 14a) and CuCN (57 mg, 0.64 mmol) was mixed in DMf (3 mL) and refluxed for 2 hr. The mixture was filtered and concentrated to afford the title compound which was used without further purification (48 mg, 60%): LC/MS (ES) m/e 250 $(M+H)^+$.

b) 7-cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid

To a solution of methyl 7-cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (48 mg, 0.19 mmol) in THF/MeOH (5 mL, 1:1) was added the solution of NaOH (0.77 mL, 0.77 mmol, 1M in water). After stirring for 1 hr, the mixtyre was concentrated to affod a residur which was diluted with water. The resulting solution was acidified with HCl and a white percipitate was crashed out. The percipitate was filtered and dried to afford the title compound as a white solid (36 mg, 80%): LC/MS (ES) m/e 236 $(M+H)^+$.

Preparation 16



Preparation of 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid

a) methyl 6-amino-5-[3-(ethyloxy)-3-oxopropyl]-2-pyridinecarboxylate

To a solution of methyl 6-amino-5-[(1*E*)-3-(ethyloxy)-3-oxopropyl]-2-pyridinecarboxylate (3.15g, 12.6 mmol) in ethanol/ethyl acetate/DMF (200 mL, 1:1:0.1) was added palladium on carbon (629 mg, 50% by weight with water). The mixture was hydrogenated at atmospheric pressure for 24 hr. The suspension was filtered through a pad of Celite®. The filtrate was concentrated to yield the title compound as a light brown oil (3.51g, 100%) which was used without further purification: LC/MS (ES) *m/z* 253.2 $[M+H]^+$.

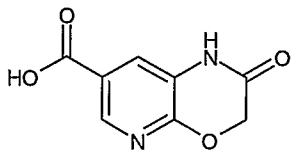
b) methyl 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylate

A solution of methyl 6-amino-5-[3-(ethyloxy)-3-oxopropyl]-2-pyridinecarboxylate (3.51g, 13.0mmol) in glacial acetic acid (200 mL) was heated at 100° for 70 min. Removal of the acetic acid under reduced pressure, followed by drying under vacuum for 48 hr gave the title compound as a light brown solid (2.98g, 85%) which was used without further purification: LC/MS (ES) *m/z* 207.0 $[M+H]^+$.

c) 7-Oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid

To a solution of methyl 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylate (2.0g, 9.71 mmol) in methanol/HF (35 mL, 1:7) was added the solution of NaOH (5 mL, 12.5 mmol, 2.5 M in H_2O). After stirring at ambient temperature for 6 hr, the solvents were removed under reduced pressure. The residue was suspended in a small volume of water and the pH was adjusted to 4 with the aqueous 6M HCl solution. The mixture was chilled and stirred at 0° until precipitation was complete. The solid was collected, washed well with water, and dried under vacuum to provid the title compound as a white solid (1.84g, 99%), which was used without further purification: LC/MS (ES) *m/z* 193.0 $[M+H]^+$.

Preparation 17



Preparation of 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxylic acid

a) methyl 6-{[2-(methyloxy)-2-oxoethyl]oxy}-5-nitro-3-pyridinecarboxylate

To a solution of methyl 6-chloro-5-nitro-3-pyridinecarboxylate (2 g, 9.3 mmol) in dioxane (40 mL) were added NaH (0.4 g, 10.2 mmol, 60% in mineral oil) and methyl

hydroxyacetate (0.78 g, 9.3 mmol). After stirring at 25°C for 24 hr, the solution was partitioned between ethyl acetate and water. The aqueous solution was extracted several times with ethyl acetate. The organic fractions were combined, concentrated and purified with column chromatography (silica, 5 –30% ehtyl acetate in hexane) to provide the title compound as a white solid (1.3 g, 56%): LC/MS (ES) m/e 271 $(M+H)^+$.

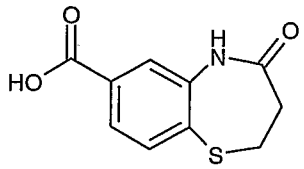
b) methyl 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxylate

A solution of methyl 6-{[2-(methyloxy)-2-oxoethyl]oxy}-5-nitro-3-pyridinecarboxylate (1.31 g, 4.8 mmol) in acetic acid ((10 mL) was treated with iron (4 g, 71.5 mmol) and heated at 60°C for 3 hr. The solvent was removed to afford a residue which was triturated with ethyl acetate. The orgnic fractions were combined, concentrated and washed through a silica pad with 10% MeOH in chloroform, affording the title compound as an off-white solid (600 mg, 60%): LC/MS (ES) m/e 209 $(M+H)^+$.

c) 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxylic acid

To a solution of methyl 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxylate (200 mg, 0.96 mmol) in THF/MeOH/H_2O (12 mL, 5:5:2) was added a solution of NaOH (2 mL, 2 mmol, 2.0 M in H_2O). After stirring at room temperature for 12 hr, the solution was concetrated and extracted with DCM. The organic fractions were combined, washed with brine and concentrated to afford the title compound as an off-white solid (160 mg, 85%) which was used without further purification: LC/MS (ES) m/e 195 $(M+H)^+$.

Preparation 18



Preparation of 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-7-carboxylic acid

a) methyl 4-{[3-(methoxy)-3-oxopropyl]thio}-3-nitrobenzoate

To a solution of methyl 4-chloro-3-nitrobenzoate (4.53 g, 0.021 mol) and methyl 3-mercaptopropionate (2.78 g, 0.023 mol) in DMF (15 mL) was added anhydrous potassium carbonate (0.023 mol, 3.17g). After stirring at ambient temperature for 16 h, the reaction was quenched with ice water. The precipitated product was filtered, washed well with water and dried under vacuum to give the title compound as a bright yellow solid (6.11 g, 97%) which was used without further purification: LC/MS (ES) *m/z* 300 $(M+H)^+$.

b) methyl 3-amino-4-{[3-(methoxy)-3-oxopropyl]thio}benzoate

To a solution of methyl 4-{[3-(methoxy)-3-oxopropyl]thio}-3-nitrobenzoate (7.58 g, 0.025 mol) in glacial acetic acid (186 mL) was added iron powder (14.0 g, 0.250 mmol). After heating at 75º for 6 h, the warm mixture was filtered and the filtrate concentrated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous sodium chloride. The organic layer was dried over $MgSO_4$ and concentrated to provide the title compound as an off-white solid (7.03g, quantit.), which was used without further purification: LC/MS (ES) *m/z* 270 $(M+H)^+$.

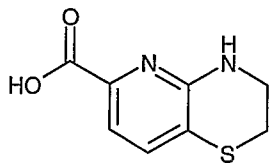
c) methyl 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-7-carboxylate

A suspension of methyl 3-amino-4-{[3-(methoxy)-3-oxopropyl]thio}benzoate (3.00g, 0.011 mol) in Decalin™ (120 ml) was heated at 160º for 40 h. The reaction was allowed to cool down to room temperature and the precipitate was collected by filtration. The solid was dissolved in 1:1 acetone: methanol and treated with decolorizing carbon. Removal of solvent and vacuum drying afforded the title compound as a light tan solid (1.67g, 73%): LC/MS (ES) *m/z* 238 $(M+H)^+$.

d) 4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]thiazepine-7-carboxylic acid

To a solution of methyl 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-7-carboxylate (500 mg, 2.11 mmol) in DMF (5 mL) were added lithium iodide (1.19g, 8.90 mmol) and anhydrous sodium acetate (145 mg, 1.77 mmol). After heating at 150° for 4h, the reaction mixture was diluted with ice water. The solution was acidified with 6N HCl, followed by extraction with DCM. The organic layers were combined, washed with aqueous sodium chloride and dried over $MgSO_4$. Trituration with acetonitrile gave the title compound as a tan solid (317mg, 68%): LC/MS (ES) *m/z* 224.2 $(M+H)^+$.

Preparation 19



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

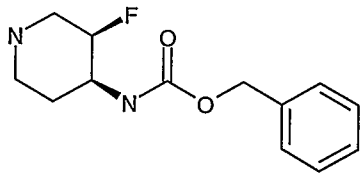
a) methyl 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate

Methyl 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (160 mg, 0.71 mmol, prepared as described in Preparation 10a) was mixed with $POCl_3$ (3 mL) and heared at 70°C for 3 hr. The mixture was concentrated to generate a brown reside which was dissolved in DME (16 mL). The solution was cooled down to 0°C and was added $NaBH_4$ (54 mg, 1.4 mmol). The mixture was gradually warmed up to 25°C and stirrred for 12 hr. The solution was then diluted with 1N HCl in water. The aqueous solution was extracted several times with DCM. The organic fractions were pooled, concentrated and purified with chromatography separation (silica, 0-20% ethyl acetate in hexane) affordingthe title compond as an off-white solid (110 mg, 69%): LC/MS (ES) m/e 211 $(M+H)^+$.

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

To a solution of methyl 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylate (110 mg, 0.52 mmol) in dioxane/water (12 mL, 5:1) was added the solution of NaOH (1 mL, 0.5 mmol, 0.5 M in H_2O). After stirring at room temperature for 12 hr, the solution was acidified to PH 4-5 with 2N HCl. A white percipitate was crashed out. The precipitate was filtered and dried to provide the title compound as a white solid (94 mg, 92%) which was used without further purification: LC/MS (ES) m/e 197 $(M+H)^+$.

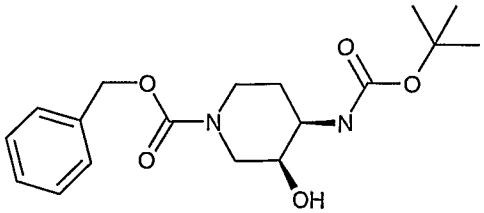
Preparation 20



Preparation of phenylmethyl-cis (3-fluoro-4-piperidinyl)carbamate

Phenylmethyl-cis (3-fluoro-4-piperidinyl)carbamate was prepared and separated according to the methods described in WO03064421. The enantiomer chosen for use in the preparation of Example 32 was the E1 isomer giving a positive optical rotation.

Preparation 21



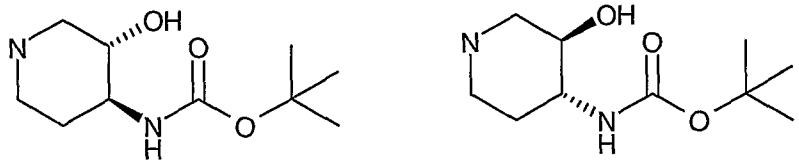
Preparation of Racemic cis-4-tert-Butoxycarbonylamino-3-hydroxy-piperidine-1-carboxylic acid benzyl ester

Racemic cis-4-tert-Butoxycarbonylamino-3-hydroxy-piperidine-1-carboxylic acid benzyl ester was prepared according to the procedure outlined by Kim et al. [Syn. Comm. 2001, 31, 1081-1089]. The racemic mixture was separated into its two enantiomers according to the methods described in WO2004002490.

Preparation 22

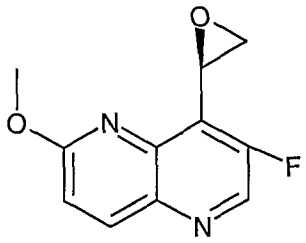
Preparation of 1,1-dimethylethyl [(3S,4S)-3-hydroxy-4-piperidinyl]carbamate (two enantiomers)

See WO2004058144



Preparation 23

Preparation of 7-fluoro-2-(methyloxy)-8-[(2R)-2-oxiranyl]-1,5-naphthyridine



(a) 1-[3-fluoro-6-(methoxy)-1,5-naphthyridin-4-yl]-1,2-ethanediol

To a solution of AD-mixβ (50 g) in tert-butanol/water (200 mL/200 mL), cooled in an ice-bath for 30 minutes, vinyl-naphthyridine (53h) (8 g, 39.2 mmol) was added and the reaction mixture was stirred at room temperature for 48 hours. Sodium sulfite (75 g) was added and the mixture was stirred for a further 30 minutes. It was extracted with diethyl ether then several times with 10% methanol in chloroform. The organic extract was

evaporated under vacuum to afford the desired product as an oil (8.93 g, 96%). MS (+ve ion electrospray) *m/z* 239 (MH+).

enantiomeric excess = 44%, as determined by chiral analytical hplc

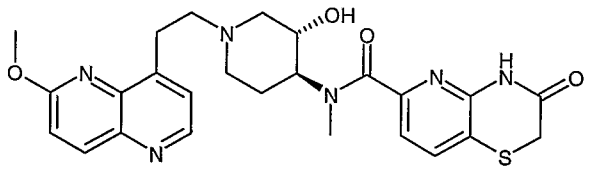
(b) 2-[3-fluoro-6-(methoxy)-1,5-naphthyridin-4-yl]-2-hydroxyethyl 4-methylbenzenesulfonate

To a solution of diol (a) (16.5g) in dichloromethane (200 mL), triethylamine (10 mL) and dibutyltin oxide (350 mg) was added tosyl chloride (13.2g). After 3 hours, the mixture was diluted with water/sodium bicarbonate and extracted several times with chloroform. The combined organic extracts were dried over magnesium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with 20-30% ethyl acetate in chloroform to afford the desired product (20.3 g, 75%). MS (+ve ion electrospray) *m/z* 393 (MH+).

(c) 7-fluoro-2-(methoxy)-8-(2-oxiranyl)-1,5-naphthyridine

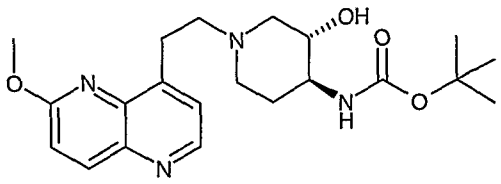
To a suspension of tosylate (b) (10.5 g, 26.7 mmol) in anhydrous methanol (160 mL), cooled in an ice-bath, potassium carbonate (7.03 g, 50.9 mmol) was added. After 15 minutes with cooling, the mixture was stirred at room temperature for a further 1.75 hours. It was then diluted with water, extracted several times with dichloromethane, dried over magnesium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with dichloromethane, chloroform then 20% ethyl acetate in chloroform to afford the product as an oil (5.55 g, 94%). MS (+ve ion electrospray) *m/z* 221 (MH+).

Example 1



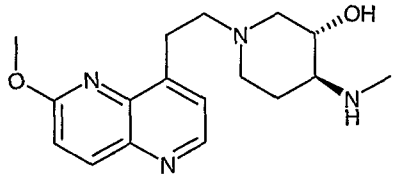
Preparation of *N*-((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide (E1 isomer

(a) 1,1-dimethylethyl ((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate



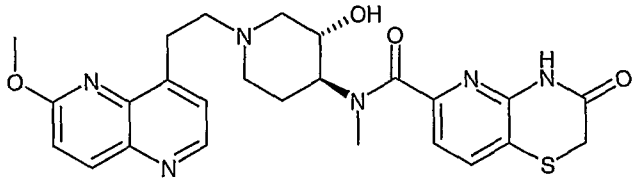
1,1-dimethylethyl [(3*S*,4*S*)-3-hydroxy-4-piperidinyl]carbamate (469 mg, 2.5 mmol, E1 isomer) (See WO2004058144) and 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (490 mg, 2.5 mmol) were combined in DMF (0.4 mL) and stirred at 90°C over 12h. The solution was then concentrated and the residue purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound (770 mg, 76%) as an orange oil: LC/MS (ES) m/e 403 $(M + H)^+$.

(b) (3*S*,4*S*)-4-(methylamino)-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-piperidinol



To a solution of 1,1-dimethylethyl ((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate (171 mg, 0.43 mmol) in THF (10 mL) was added dropwise a solution of LAH (0.85 mL, 0.85 mmol, 1M in THF). The reaction mixture heated at 70°C for 4h and was subsequently quenched by dropwise addition of a saturated solution of potassium sodium tartrate. The aqueous phase was extracted several times with ethyl acetate and the combined organic fractions were dried over Na_2SO_4, concentrated and purified with chromatography separation (silica, 0-8% MeOH in chloroform (1% NH_4OH)) yielding the title compound as a yellow oil (45 mg, 33%): LC/MS (ES) m/e 317 $(M+H)^+$.

(c) *N*-((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

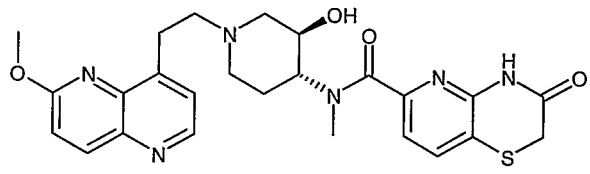


To a solution of (3*S*,4*S*)-4-(methylamino)-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-piperidinol (68 mg, 0.22 mmol) in DMF(3 ml) was added carbonyldiimmidazole

(38 mg, 0.24 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (68 mg, 0.22 mmol). After 18h at 25°C, the reaction was concentrated under reduced pressure and purified via trituration with MeOH affording the title compound as a off-white solid (13 mg, 12%): LC/MS (ES) m/e 509 (M+H)+; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.49-8.52 (m, 1H), 8.05-8.10 (m, 1H), 7.72-7.78 (m, 1H), 7.45-7.49 (m, 1H), 7.08-7.14 (m, 2H), 4.02 (s, 3H), 3.98 (s, 1H), 3.51-3.54 (m, 2H), 3.27-3.45 (m, 3H), 3.21 (s, 2H), 2.92 (s, 3H), 3.7-3.78 (m, 1H), 1.77-2.04 (m, 5H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 2

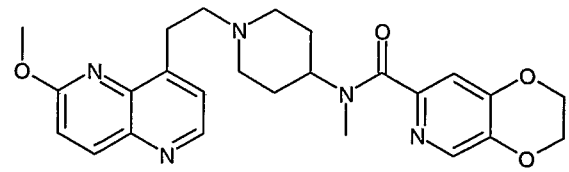


Preparation of *N*-((3*R*,4*R*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide (E2 isomer,)

The title compound (47 mg, 19%) was prepared as an off-white solid according to Example 1, except substituting E2 isomer of 1,1-dimethylethyl [(3*R*,4*R*)-3-hydroxy-4-piperidinyl]carbamate (1 g, 5.3 mmol) (See WO2004058144) for the E1 isomer: LC/MS (ES) m/e 509 (M+H)+; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.49-8.52 (m, 1H), 8.05-8.10 (m, 1H), 7.72-7.78 (m, 1H), 7.45-7.49 (m, 1H), 7.08-7.14 (m, 2H), 4.02 (s, 3H), 3.98 (s, 1H), 3.51-3.54 (m, 2H), 3.27-3.45 (m, 3H), 3.21 (s, 2H), 2.92 (s, 3H), 3.7-3.78 (m, 1H), 1.77-2.04 (m, 5H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 3

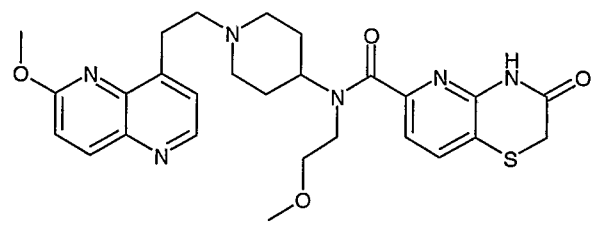


Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide

The title compound (28 mg, 16%) was prepared as an off-white solid according to Example 1, except substituting 1,1-dimethylethyl 4-piperidinylcarbamate for the E1 isomer of 1,1-dimethylethyl [(3*S*,4*S*)-3-hydroxy-4-piperidinyl]carbamate and 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid (110 mg, 0.37 mmol) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid: LC/MS (ES) m/e 464 (M+H)+; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.59-8.62 (m, 1H), 8.15-8.19 (m, 1H), 8.07 (s, 1H), 7.52-7.59 (m, 1H), 7.18-7.21 (m, 1H), 7.08 (s, 1H), 4.36-4.42 (m, 4H), 4.06-4.09 (m, 3H), 3.32-3.48 (m, 3H), 2.28-2.32 (m, 1H), 2.16-2.18 (m, 1H), 3.0 (s, 2H), 2.8-2.89 (m, 3H), 2.32-2.41 (m, 1H), 1.98-2.01 (m, 3H), 1.82-1.89 (m, 2H).

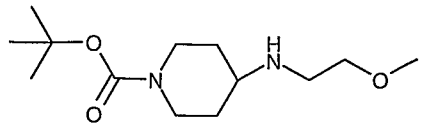
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 4



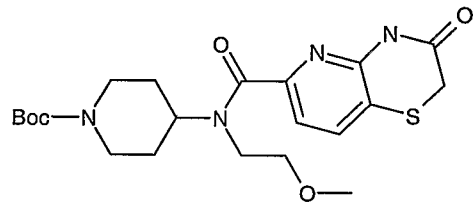
Preparation of *N*-[2-(methyloxy)ethyl]-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

(a) 1,1-dimethylethyl 4-{[2-(methyloxy)ethyl]amino}-1-piperidinecarboxylate



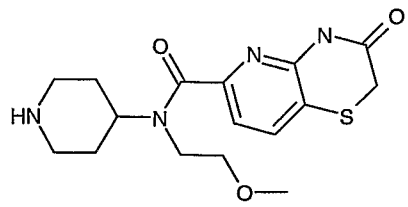
To a solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (1 g, 5.0 mmol), acetic acid (0.3 mL, 5.0 mmol) and [2-(methyloxy)ethyl]amine (0.44 mL, 5.0 mmol) in MeOH (20 mL) were added $NaCNBH_4$ (346 mg, 5.5 mmol). After 12 h at 25 °C, the solution was diluted with the aqueous solution of Na_2CO_3. The aqueous solution was extracted several times with ethyl acetate. The organic fractions were combined, concentrated and purified with chromatography separation (silica, 0-10% MeOH in DCM) yielding the title compound (1.2 g, 93%) as a yellow oil: LC/MS (ES) m/e 259 $(M+H)^+$.

(b) 1,1-dimethylethyl 4-{[2-(methyloxy)ethyl][(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate



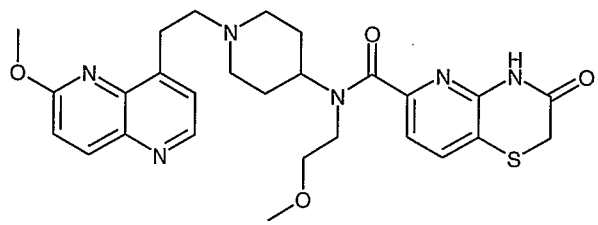
To a suspension mixture of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (60 mg, 0.28 mmol) in DCM (3 mL) were added oxayl chloride (0.13 mL, 1.4 mmol) and the catalytic amount of DMF. After 2.5 h at 25 °C, the mixture was concentrated to provide a brown residue which was re-dissolved in anhydrous DCM (1 mL). The solution was treated with a solution of 1,1-dimethylethyl 4-{[2-(methyloxy)ethyl]amino}-1-piperidinecarboxylate (80 mg, 0.25 mmol) with triethylamine (0.08 mL, 0.25 mmol). After stirred at 25 °C for 12 hr, the mixture was partitioned between DCM and the aqueous solution of Na_2CO_3. The aqueous phase was extracted several times with DCM. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in DCM) to generate the title compound as an off-white solid (100 mg, 71%): LC/MS (ES) m/e 451 $(M+H)^+$.

(c) *N*-[2-(methyloxy)ethyl]-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



To a solution of 1,1-dimethylethyl 4-{[2-(methyloxy)ethyl][(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate (420 mg, 0.93 mmol) in DCM (10 mL) at 25 °C was added dropwise an HCl solution (2.3 mL, 9.3 mmol, 4M HCl in dioxane). After 2 h, the solution was concentrated and washed with diethyl ether to afford the HCl salt of the title compound (370 mg, 94%) as a yellow foam, which was used without further purification: LC/MS (ES) m/e 351 $(M+H)^+$.

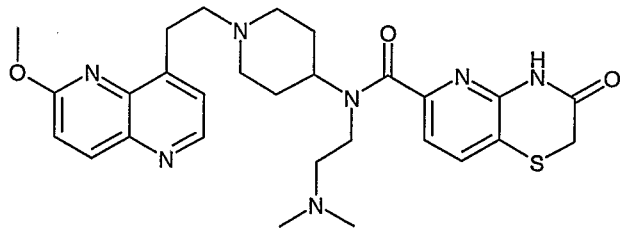
(d) *N*-[2-(methyloxy)ethyl]-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



A solution of HCl salt of *N*-[2-(methyloxy)ethyl]-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide (80 mg, 0.19 mmol) was treated with MP-carbonate resin (0.8 mmol) for 2 hr. The resin was filtered and the filtrate was concentrated to generate the free base (56 mg, 0.16 mmol) as a brown oil. The amine was mixed with 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (30 mg, 0.51 mmol) and heated at 90°C for 1 h. The solution was then concentrated and the residue was purified via column chromatography (silica, 0-10% MeOH in chloroform (1% NH_4OH)) yielding the title compound (55 mg, 64%) as a white foam; LC/MS (ES) m/e 537 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.57-8.61 (m, 1H), 8.2-8.24 (m, 1H), 7.77-7.8 (m, 1H), 7.53-7.62 (m, 1H), 7.12-7.21 (m, 2H), 4.06 (s, 3H), 3.78-3.82 (m, 1H), 3.69-3.72 (m, 1H), 3.48-3.62 (m, 6H), 3.11-3.3 (m, 8H), 2.97-3.07 (m, 1H), 2.54-2.71 (m, 1H), 2.04-2.22 (m, 4H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

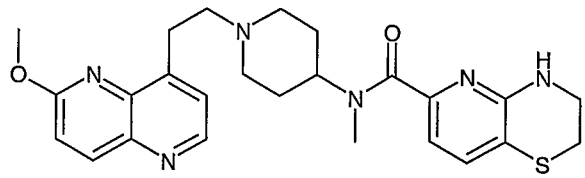
Example 5



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

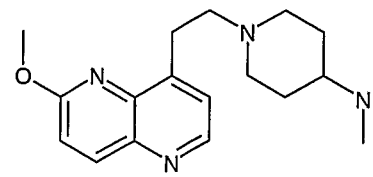
The title compound (120 mg, 57%) was prepared as an off-white solid according to Example 4, except substituting *N,N*-dimethyl-1,2-ethanediamine (440 mg, 5.0 mmol) for 2-(methyloxy)ethyl amine: LC/MS (ES) m/e 550 (M+H)+; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.4-8.41 (m, 1H), 7.95 (d, *J* = 2 Hz, 1H), 7.64 (d, *J* = 2 Hz, 1H), 7.35-7.37 (m, 1H), 6.97-7.05 (m, 2H), 3.93 (s, 3H), 3.1-3.36 (m, 6H), 2.9 (d, *J* = 1.5 Hz, 1H), 2.64-2.7 (m, 1H), 2.57-2.61 (m, 1H), 2.41-2.45 (m, 1H), 2.32-2.39 (m, 1H), 2.12-2.2 (m, 4H), 1.68-1.89 (m, 4H).

Example 6



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

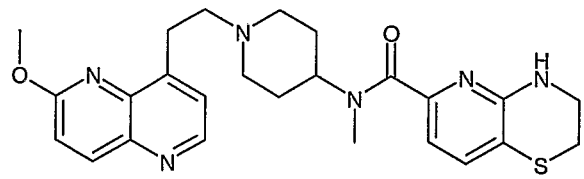
(a) *N*-methyl-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinamine



The title compound (77 mg, 43%) was prepared as a brown oil according to Example 1b, except substituting 1,1-dimethylethyl 4-piperidinylcarbamate for the E1

isomer of 1,1-dimethylethyl [(3*S*,4*S*)-3-hydroxy-4-piperidinyl]carbamate: LC/MS (ES) m/e 301 $(M+H)^+$.

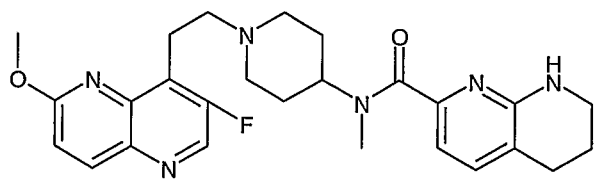
(b) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



To a solution of *N*-methyl-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinamine (77 mg, 0.26 mmol) in DMF (2 mL) were added 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (50 mg, 0.26 mmol), triethylamine (0.15 mL, 1.07 mmol) and diphenylphosphoryl azide (0.06 mL, 0.28 mmol). After stirring at 25°C for 48 hr, the mixture was diluted with the solution of $NaHCO_3$ in water. The aqueous phase was extracted several times with DCM. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in chloroform (1% NH_4OH)) affording the title compound as an off-white solid: (40 mg, 32%): LC/MS (ES) m/e 479 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.62-8.65 (m, 1H), 8.18-8.22 (m, 1H), 7.62-7.68 (m, 1H), 7.39 (d, J = 5.6 Hz, 1H), 7.22-7.28 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 4.13 (s, 3H), 3.75 (s, 3H), 3.41-3.5 (m, 2H), 3.32 (d, J = 1.3 Hz, 1H), 3.2 (d, J = 1.3 Hz, 1H), 2.82-3.01 (m, 6H), 2.34-2.39 (m, 1H), 1.82-2.18 (m, 6H).

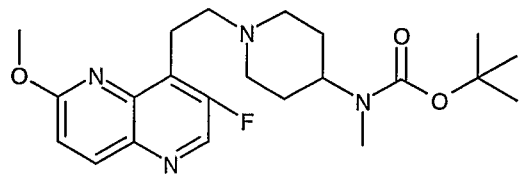
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 7



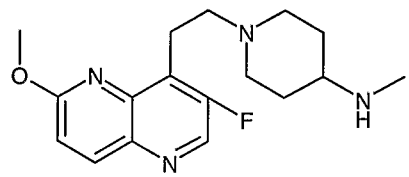
Preparation of *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide

(a) 1,1-dimethylethyl (1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)methylcarbamate



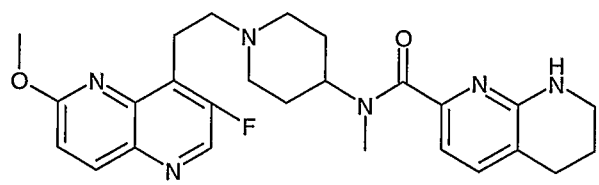
1,1-Dimethylethyl methyl(4-piperidinyl)carbamate (419 mg, 1.96 mmol) and 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (400 mg, 1.96 mmol) were combined in DMF (0.2 mL) and stirred at 90°C over 12 hr. The solution was then concentrated and the residue purified via column chromatography (silica, 0-5% MeOH in DCM) yielding the title compound (540 mg, 66%) as an orange oil: LC/MS (ES) m/e 419 $(M+H)^+$.

(b) 1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*-methyl-4-piperidinamine



To a solution of 1,1-dimethylethyl (1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)methylcarbamate (540 mg, 1.29 mmol) in DCM (10 mL) at 25°C was added dropwise an HCl solution (2.2 mL, 8.8 mmol, 4M HCl in dioxane). After 2.5 h, the solution was concentrated and washed with diethyl ether to afford the HCl salt of the title compound (377 mg, 92%) as a yellow foam, which was used without further purification: LC/MS (ES) m/e 319 $(M+H)^+$.

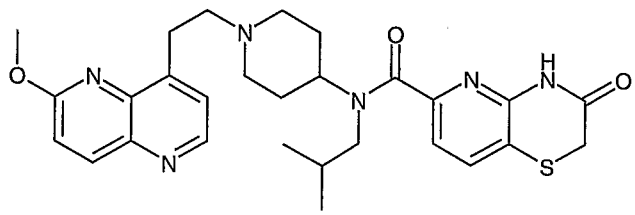
(c) *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide



To a solution of 1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*-methyl-4-piperidinamine (177 mg, 0.56 mmol) in DMF (2 mL) at 0°C were added 1,5,6,7-

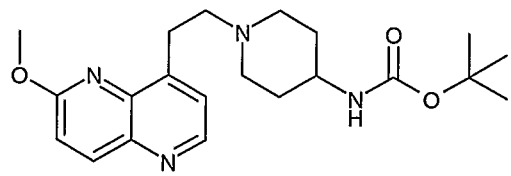
tetrahydro-1,8-naphthyridine-2-carboxylic acid (100 mg, 0.56 mmol), triethylamine (0.3 mL, 2.14 mmol) and diphenylphosphoryl azide (0.12 mL, 0.56 mmol). After stirring at 25°C for 48 hr, the mixture was diluted with the solution of $NaHCO_3$ in water. The aqueous phase was extracted several times with DCM. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in chloroform (1% NH_4OH)) followed by Gilson purification (0-50% CH_3CN in H_2O (1% TFA)) affording the trifluoracetic acid salt of the title compound as an off-white solid: (89 mg, 27%): LC/MS (ES) m/e 479 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.62 (s, 1H), 8.15 (d, *J* = 9.1 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 9.1 Hz, 1H), 6.81 (d, *J* = 6.7 Hz, 1H), 4.04 (s, 3H), 3.81-3.9 (m, 2H), 3.6-3.66 (m, 2H), 3.42-3.5 (m, 4H), 3.23-3.25 (m, 1H), 2.92 (s, 3H), 2.79-2.81 (m, 2H), 1.89-2.24 (m, 8H).

Example 8



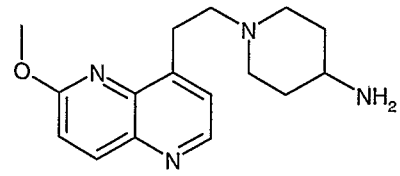
Preparation of *N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-(2-methylpropyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

(a) 1,1-dimethylethyl (1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate



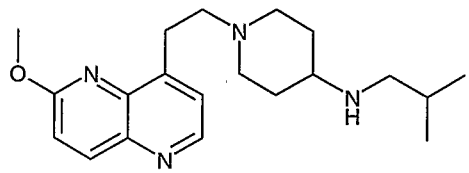
4-Boc-aminopiperidine (5.8 g, 32 mmol) and 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (6.1 g, 32 mmol) were combined in DMF (6 mL) and stirred at 90°C for 20h. The solution was then concentrated and the residue purified via column chromatography (silica, 0-10% MeOH in DCM) yielding the title compound (5.8 g, 46%) as an off-white solid: LC/MS (ES) m/e 443 $(M+H)^+$.

(b) 1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinamine



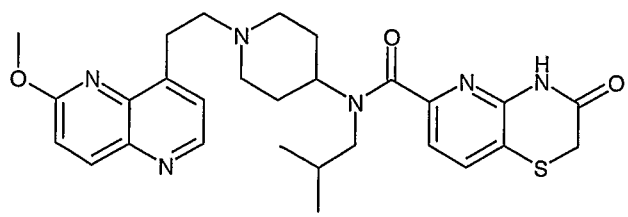
To a solution of 1,1-dimethylethyl (1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate (369 mg, 0.83 mmol) in DCM (3 mL) at 25°C was added dropwise an HCl solution (2.1 mL, 2.1 mmol, 1M HCl in dioxane). After 2 h, the solution was concentrated and washed with diethyl ether to afford the HCl salt of the title compound (285 mg, quantit.) as a yellow foam, which was used without further purification: LC/MS (ES) m/e 343 $(M+H)^+$.

(c) 1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*-(2-methylpropyl)-4-piperidinamine



To a solution of the HCl salt of 1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinamine (40 mg, 0.1 mmol) in MeOH:DCM (6 mL, 1:1) were added $NaHCO_3$ (42 mg, 0.5 mmol) followed by 2-methylpropanal (72 mg, 0.1 mmol). After 20 h at 25°C, $NaBH_4$ (3.7 mg, 0.1 mmol) was added. After 2h, the reaction was concentrated and the residue was partitioned between DCM-H_2O. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried over $MgSO_4$, concentrated and purified via column chromatography (silica, 0-10% MeOH in DCM (1% NH_4OH)) yielding the title compound (25 mg, 72%) as a colorless oil: LC/MS (ES) m/e 343 $(M+H)^+$.

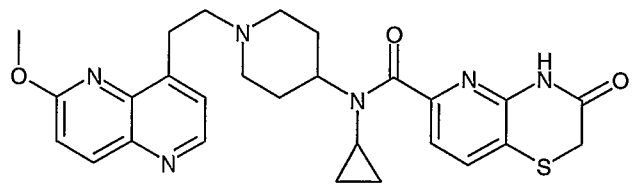
(d) *N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-(2-methylpropyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



To a solution of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (49 mg, 0.23 mmol) in anhydrous DMF (0.5 mL) was added carbonyldiimmidazole (37 mg, 0.23 mmol). After 3.5 h at 25°C, 1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*-(2-methylpropyl)-4-piperidinamine (80 mg, 0.23 mmol) was added and the resulting misture was heated at 50°C for 72 hr. The solution was concentrated and purified with column chromatography (silica, 0-5% MeOH in DCM (1% NH_4OH)) affording the title compound (13 mg, 11%) as an off-white solid: LC/MS (ES) m/e 535 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.48-8.51 (m, 1H), 7.79-7.80 (m, 1H), 7.7-7.78 (m, 1H), 7.43-7.48 (m, 1H), 7.03-7.10 (m, 2H), 3.97-4.01 (m, 1H), 3.95 (s, 3H), 3.48 (s, 3H), 3.19-3.35 (m, 9H), 3.0-3.03 (m, 1H), 2.76-2.89 (m, 1H), 2.7-2.74 (m, 1H), 2.09-2.18 (m, 3H), 1.9-1.99 (m, 1H), 1.78-1.87 (m, 4H).

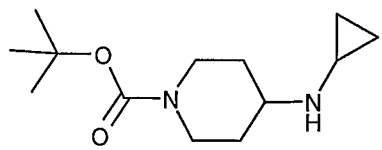
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 9



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

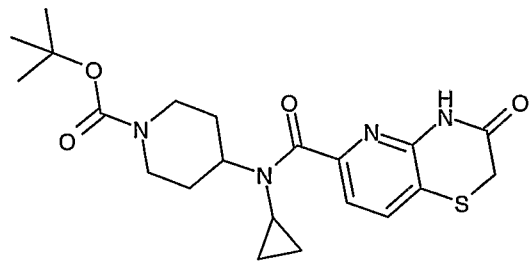
(a) 1,1-dimethylethyl 4-(cyclopropylamino)-1-piperidinecarboxylate



To a solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (5.25 g, 0.026 mol) in MeOH (50 mL) at 0°C were added cyclopropylamine (1.9 mL, 0.026 mmol), activated molecular sieve and $NaCNBH_4$ (1.63 g, 0.026 mmol). The mixture was warmed up to 25°C gradually. After stirring for 14 hr, the mixture was filtered and diluted with water. MeOH was removed to generate a brown residue which was re-dissolved in 1N HCl solution. The resulting solution was extracted several times with DCM. The organic fractions were combined, washed with brine and concentrated to provide the desired

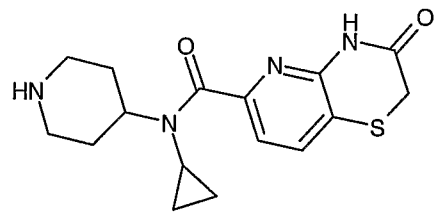
product as a colorless oil (4.8 g, 77%) which was used without further purification: LC/MS (ES) m/e 241 $(M+H)^+$.

(b) 1,1-dimethylethyl 4-{cyclopropyl[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate



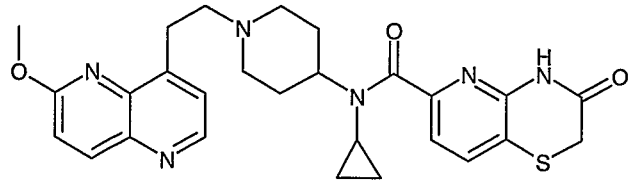
3-Oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (307 mg, 1.46 mmol) was dissolved in oxalyl chloride (2 mL) and refluxed for 1.5 hr. The solution was concentrated and azotropically dried three times with anhydrous toluene to provide a brown oil, which was cooled down to 0°C, dissolved in anhydrous DCM (2 mL) and treated with 1,1-dimethylethyl 4-(cyclopropylamino)-1-piperidinecarboxylate (350 mg, 1.46 mmol) and triethylamine (0.5 mL). The mixture was subsequently warmed up to 25°C. After stirring for 14 hr, it was concentrated and purified with column chromatography (silica, 0-5% MeOH in DCM (1% NH_4OH)) affording the title compound as an off-white solid (410 mg, 65%): LC/MS (ES) m/e 434 $(M+H)^+$.

(c) *N*-cyclopropyl-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



To a solution of 1,1-dimethylethyl 4-{cyclopropyl[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate (400 mg, 0.92 mmol) in DCM (5 mL) at 25°C was added dropwise an HCl solution (2.3 mL, 2.3 mmol, 1M HCl in dioxane). After 3 h, the solution was concentrated and washed through a silica gel pad (0-10 % MeOH in DCM (2% NH_4OH)) affording the title compound as a brown oil (244 mg, 80%): LC/MS (ES) m/e 333 $(M+H)^+$.

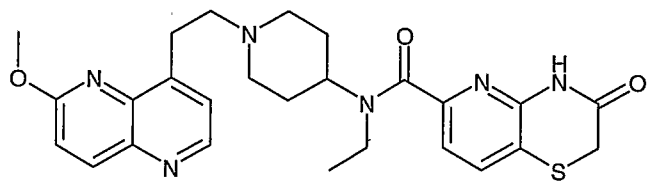
(d) *N*-cyclopropyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



N-cyclopropyl-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide (244 mg, 0.73 mmol) and 8-ethenyl-2-(methyloxy)-1,5-naphthyridine (137 mg, 0.73 mmol) was mixed and heated at 80°C for 18 h. The resulting mixture was purified with column chromatography (silica, 0-8% MeOH in DCM (1% NH_4OH)) affording the title compound as a yellow solid (127 mg, 27%): LC/MS (ES) m/e 519 $(M+H)^+$; $)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.6-8.64 (m, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.59-7.62 (m, 1H), 7.21-7.27 (m, 2H), 4.15 (s, 3H), 3.6 (s, 2H), 3.46-3.5 (m, 2H), 3.26-3.3 (m, 2H), 2.87-2.93 (m, 4H), 2.26-2.63 (m, 4H), 1.97-2.04 (m, 2H), 0.5-0.67 (m, 4H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 10

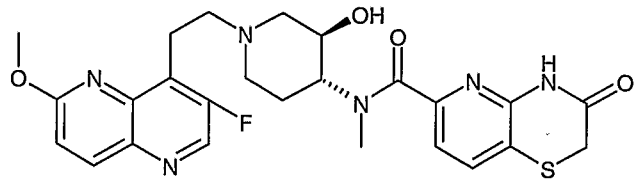


Preparation of *N*-ethyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (61 mg, 46%) was prepared as an off-white solid according to Example 9, except substituting ethylamine for cyclopropylamine: LC/MS (ES) m/e 507 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.48-8.51 (m, 1H), 7.79-7.80 (m, 1H), 7.7-7.78 (m, 1H), 7.43-7.48 (m, 1H), 7.03-7.10 (m, 2H), 3.91-4.08 (m, 4H), 3.47-3.52 (m, 3H), 3.19-3.35 (m, 9H), 3.0-3.03 (m, 1H), 2.76-2.89 (m, 1H), 2.7-2.74 (m, 1H), 1.81-2.22 (m, 4H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 11

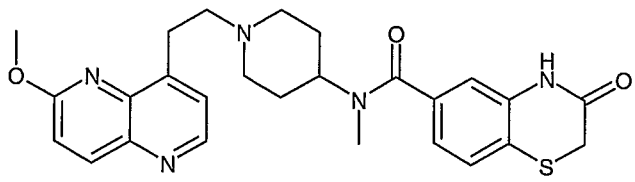


Preparation of *N*-((3*R*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-hydroxy-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (29 mg, 92%) was prepared as a yellow solid according to Example 1, except substituting 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (408 mg, 2.0 mmol) for 8-ethenyl-2-(methyloxy)-1,5-naphthyridine and the combination of diphenylphosphoryl azide (16.5 mg, 0.06 mmol) and triethylamine (0.5 mL) for carbonyldiimmidazole as the coupling reagent: LC/MS (ES) m/e 527 (M+H)+; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.52-8.56(m, 1H), 8.07-8.13 (m, 1H), 7.71-7.28 (m, 1H), 7.05-7.15 (m, 2H), 3.98-4.05 (m, 4H), 3.46-3.52 (m, 2H), 3.32-3.35 (m, 1H), 3.38-3.42 (m, 1H), 2.95-3.07 (m, 3H), 2.68-2.82 (m, 3H), 1.93-2.25 (m, 4H), 1.76-1.82 (m, 2H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 12

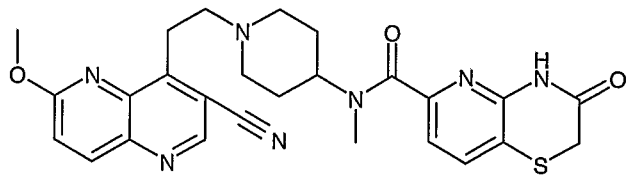


Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide

The title compound (96 mg, 65%) was prepared as an off-white solid according to Example 1, except substituting 1,1-dimethylethyl 4-piperidinylcarbamate for the E1 isomer of 1,1-dimethylethyl [(3*S*,4*S*)-3-hydroxy-4-piperidinyl]carbamate, 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxylic acid (62 mg, 0.3 mmol) for 3-oxo-3,4-dihydro-2*H*-

pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid and diphenylphosphoryl azide (82.5 mg, 0.3 mmol) with triethyl amine (0.2 mL) for carbonyldiimmidazole: LC/MS (ES) m/e 492 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.54-8.58 (m, 1H), 8.08 (d, J = 10.7 Hz, 1H), 7.5-7.56 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 6.9-7.02 (m, 2H), 4.01-4.07 (M, 3H), 3.34-343 (s, 5H), 3.03-3.11 (m, 1H), 2.72-2.94 (m, 5H), 2.25-2.31 (m, 1H), 1.68-1.97 (m, 5H).

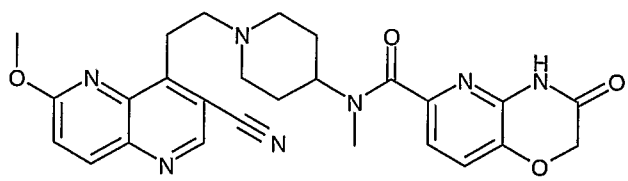
Example 13



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

The title compound (51 mg, 41%) was prepared as a yellow solid according to Example 7, except substituting 4-ethenyl-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (53 mg, 0.25 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 502 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.84-8.89 (m, 1H), 8.24-8.29 (m, 1H), 7.8-7.84 (m, 1H), 7.32-7.35 (m, 1H), 7.17-7.23 (m, 1H), 7.5 (s, 2H), 4.03-4.09 (m, 3H), 3.56-3.75 (m, 7H), 3.03-3.15 (m, 2H), 2.33-2.4 (m, 1H), 2.07-2.14 (m, 1H), 1.72-1.98 (m, 5H).

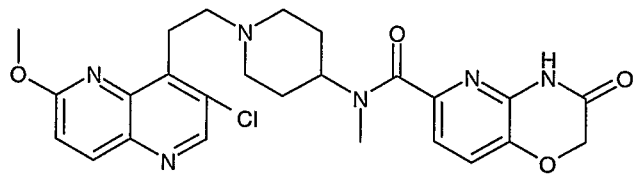
Example 14



Preparation of *N*-(1-{2-[3-cyano-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

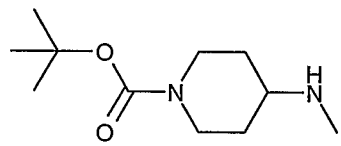
The title compound (48 mg, 38%) was prepared as a yellow solid according to Example 7, except substituting 4-ethenyl-6-(methyloxy)-1,5-naphthyridine-3-carbonitrile for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (49 mg, 0.25 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 518 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.90-8.93 (m, 1H), 8.31-8.8.33 (m, 1H), 7.38-7.44 (m, 2H), 7.29-7.31 (m, 1H), 4.8-4.81 (m, 2H), 4.18-4.21 (m, 3H), 3.67-3.78 (m, 3H), 3.31-3.37 (m, 1H), 3.2-3.26 (m, 1H), 1.9-2.04 (m, 4H), 2.38-2.42 (m, 1H), 2.21-2.27 (m, 1H), 1.87-2.09 (m, 5H).

Example 15



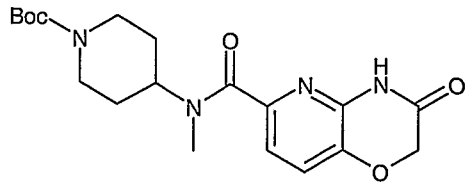
Preparation of *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

(a) 1,1-dimethylethyl 4-(methylamino)-1-piperidinecarboxylate



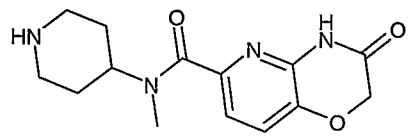
To a solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (5.25 g, 0.026 mol) in MeOH (50 mL) at 0°C were added methylamine (0.81 g, 0.026 mol), activated molecular sieve and $NaCNBH_4$ (1.63 g, 0.026 mmol). The mixture was warmed up to 25°C gradually. After stirring for 14 hr, the mixture was filtered and diluted with water. MeOH was removed to generate a brown residue which was re-dissolved in $NaHCO_3$ solution. The aqueous solution was extracted several times with DCM. The organic fractions were combined, concentrated and purified with column chromatppgraphy (0-10% MeOH in DCM (1% NH_4OH)) to provide the desired product as a colorless oil (4.5 g, 80%): LC/MS (ES) m/e 215 $(M+H)^+$.

(b) 1,1-dimethylethyl 4-{methyl[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate



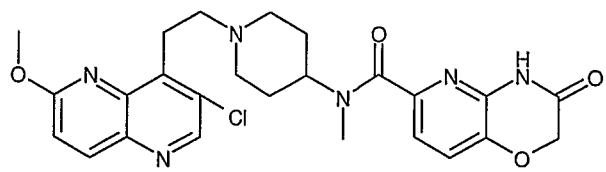
To a solution of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (485 mg, 2.5 mmol) in DMF (5 mL) was added carbonyldiimidizole (405 mg, 2.5 mmol). After stirring ar room temperature for 2 hr, the mixture was treated with a solution of 1,1-dimethylethyl 4-(methylamino)-1-piperidinecarboxylate (640 mg, 3.0 mmol) in DMF (1 mL) and heated at 50°C for 12 hr. The solution was comcentrated and purified with column chromatography (silica, 0- 10% MeOH in DCM) affording the title compound as an off-white solid (650 mg, 66%): LC/MS(ES) *m/z* 391 $[M+H]^+$.

(c) *N*-methyl-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide



To a solution of 1,1-dimethylethyl 4-{cyclopropyl[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl)carbonyl]amino}-1-piperidinecarboxylate (630 mg, 1.6 mmol) in DCM (10 mL) at 25°C was added dropwise an HCl solution (2 mL, 8.0 mmol, 2M HCl in dioxane). After 4 h, the solution was concentrated and washed through a silica gel pad (0-10 % MeOH in DCM (2% NH_4OH)) affording the title compound as a brown oil (210 mg, 50%): LC/MS (ES) m/e 291 $(M+H)^+$.

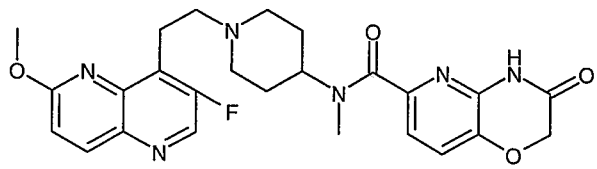
(d) *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide



7-Chloro-8-ethenyl-2-(methoxy)-1,5-naphthrydine (113 mg, 0.515 mmol) and *N*-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2,b][1,4]oxazine-6-carboxamide (150 mg, 0.515

mmol) were mixed in DMF (250 ul) and heated at 60° for 20 h. Purification by HPLC reverse phase chromatography (YMC Pack ODS-A, 50mm x 20 mm I.D., 0% to 100% water in acetonitrile with 0.1% trifluoroacetic acid, UV detection at 214nm) yielded the desired compound an off-white amorphous powder (70.2 mg, 18 %): LC/MS(ES) *m/z* 511.4 $[M+H]^+$; ^1H NMR (DMSO, 400 MHz) δ 11.44 (bd, *J* = 27.6 Hz, 1H), 9.92 (bs, 1H), 8.87 (s, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 4.77 (d, *J* = 7.5 Hz, 2H), 4.13 (bd, *J* = 17.3 Hz, 3H), 3.92-3.84 (m, 1H), 3.67-3.82 (m, 4H), 3.17-3.97 (m,2H), 2.05-3.17 (m, 2H), 2.89 (s, 3H), 2.05-2.18 (m, 4H).

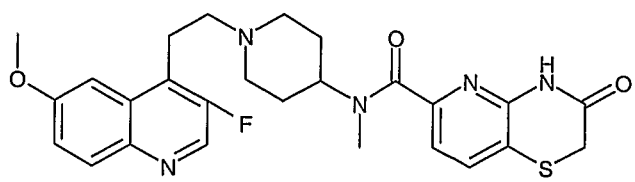
Example 16



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

The title compound (90 mg, 38%) was prepared as a pale yellow solid according to Example 7, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (93 mg, 0.48 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 495 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H), 8.39 (bd, *J* =50.3 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.18-7.42 (m, 4H), 4.73 (d, *J* = 6.3 Hz, 2H), 3.96 (d, *J* = 5.3 Hz, 3H), 3.62-3.76 (m, 1H), 3.15-3.32, (m, 3H), 3.09-3.13 (m, 1H), 2.96 (d, *J* = 34.9 Hz, 3H), 2.67 (dt, *J* = 37.1 Hz, 8.1Hz, 2H), 2.33, (bt, *J* = 10.3 Hz, 2H), 1.73-1.98, (m, 4H).

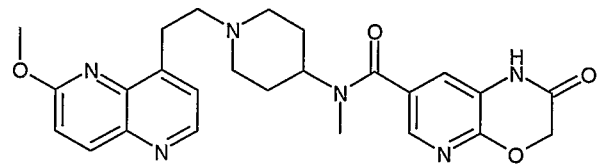
Example 17



Preparation of *N*-(1-{2-[3-fluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (128 mg, 52%) was prepared as a pale yellow solid according to Example 7, except 4-ethenyl-3-fluoro-6-(methyloxy)quinoline was substituted for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 3-oxo-3,4-dihydro-2H-pyrido{3,2-b][1,4]thiazine -6-carboxylic acid (101 mg, 0.48 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 511 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, *J* =6.2 Hz, 1H), 8.20 (bd, *J* = 40.0 Hz, 1H), 7.94 (dd, *J* = 9.1 Hz, 2.0 Hz, 1H), 7.62-7.64 (m, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 7.10-7.18 (m, 2H) 3.89 (d, *J* = 5.8 Hz, 3H) 3.52-3.60 (m, 1H) 3.47 (d, *J* = 8.9 Hz, 2H), 3.16-3.41 (m, 3H), 3.11-3.14 (m, 1H), 2.89 (d, *J* = 42.4 Hz, 3H), 2.60 (dt, *J* = 37.1Hz, 8.1 Hz, 2H), 2.26 (bt, *J* = 10.3 Hz, 2H), 1.76-1.96 (m, 4H).

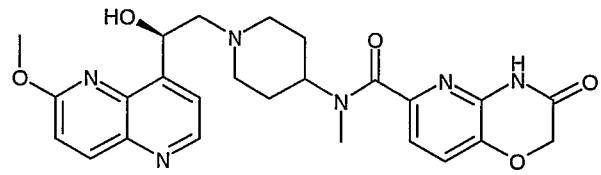
Example 18



Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxamide

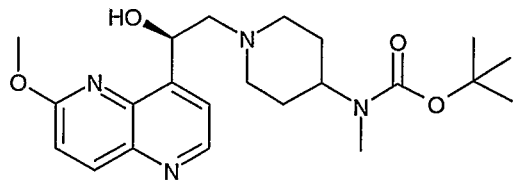
The title compound (30 mg, 17%) was prepared as a yellow solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxylic acid (74 mg, 0.38 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyrdine-2-carboxylic acid: LC/MS (ES) m/e 477 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.66 (d, *J* = 4.2 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 7.93-8.0 (br, 1H), 7.49 (s, 1H), 7.42 (s, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 4.88 (s, 2H), 4.53-4.62 (m, 1H), 4.11 (s, 3H), 3.65-3.74 (m, 1H), 3.33-3.47 (m, 2H), 3.2-3.29 (m, 2H), 3.02-3.07 (m, 3H), 2.81-2.93 (m, 2H), 2.43-2.5 (m, 1H)< 1.78-2.22 (m, 4H).

Example 19



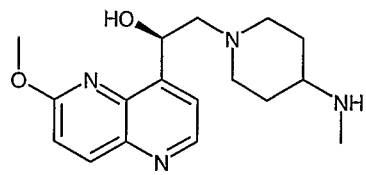
Preparation of *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

(a) 1,1-dimethylethyl (1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)methylcarbamate



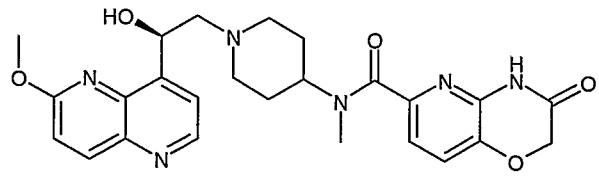
A solution of 2-(methyloxy)-8-(2-oxiranyl)-1,5-naphthyridine (712 mg, 3.51 mmol) and 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (751 mg, 3.51 mmol) in DMF (1 mL) were heated to 90°C. After 12h, the resulting solution was concentrated and purified via column chromatography (silica, 2% MeOH in DCM (1% NH_4OH) yielding the title compound as an orange oil (1.33 g, 91%): LC/MS (ES) m/e 417 $(M+H)^+$.

(b) (1*R*)-2-[4-(methylamino)-1-piperidinyl]-1-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethanol



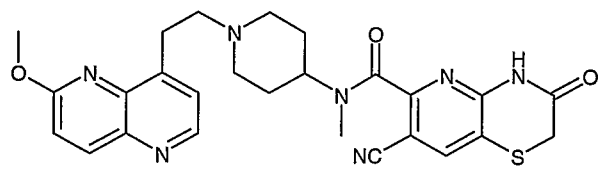
To a solution of 1,1-dimethylethyl (1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)methylcarbamate (1.0 g, 2.13 mmol) in DCM (5 mL) at 25°C was added dropwise an HCl solution (5.0 mL, 5.0 mmol, 1M HCl in dioxane). After 4 h, the solution was concentrated and washed through a silica gel pad (0-10 % MeOH in DCM (2% NH_4OH)) affording the title compound as a brown oil (540 mg, 80%): LC/MS (ES) m/e 317 $(M+H)^+$.

(c) *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide



To a solution of (1*R*)-2-[4-(methylamino)-1-piperidinyl]-1-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethanol (101 mg, 0.320 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (63 mg, 0.323 mmol) in DMF (5 mL) at 0°C were added a solution of diphenylphosphoryl azide (0.090 mL, 0.416 mmol) in DMF (1 mL) followed immediately with a solution of triethylamine (0.070 mL, 0.502 mmol) in DMF (0.5 mL). The mixture was warmed up to room temperature. After stirring for 12 h, it was concentrated under reduced pressure at low heat (<40°C). The resulting residue was disolved in $CHCl_3$ (100 mL). The solution was subsequently washed with 5% citric acid (2x20 mL), Na_2CO_3 (20 mL) and brine (20 mL). The organic layer was concentrated and purified with column chromatography (silica, 0- 10% MeOH in $CHCl_3$ (1% NH4OH)) giving the title compound as a tan solid (208 mg, 59%): LC/MS (+ve ion electrospray) m/z 493 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.62-8.67 (m, 1H), 8.08-8.14 (m, 1H), 7.75-7.80 (m, 1H), 7.26-7.31 (m, 1H), 7.06-7.13 (m, 1H), 5.82-5.88 (m, 1H), 1.50-5.11 (m, 18H), 1.18-1.23 (m, 1H).

Example 20

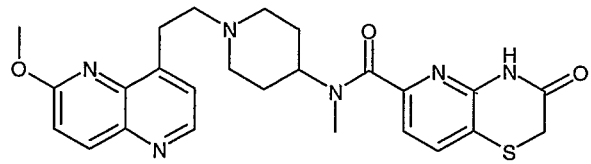


Preparation of 7-cyano-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (32 mg, 40%) was prepared as a yellow solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 7-cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (36 mg, 0.153 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 518 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the hydrochloride salt of the title product.

Example 21

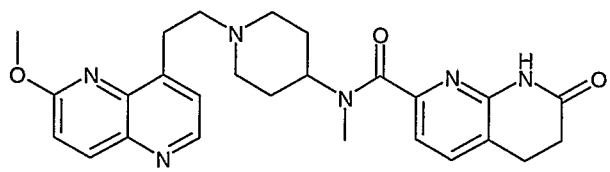


Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (55 mg, 44%) was prepared as a white solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (52 mg, 0.25 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid and 1,1'-carbonyldiinidizole (40 mg, 0.25 mmol) for diphenylphosphoryl azide as the coupling agent in the amide formation: LC/MS (ES) m/e 493 $(M+H)^+$; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 11.2-11.25 (m, 2H), 8.92-9.0 (m, 1H), 8.52-8.55 (m, 1H), 7.99-8.08 (m, 2H), 7.53-7.57 (m, 1H), 7.32-7.34 (m, 1H), 4.24-4.26 (m, 3H), 3.5-3.88 (m, 8H), 3.3-3.39 (m, 1H), 3.05-3.17 (m, 1H), 3.02 (s, 3H), 2.5-2.59 (m, 2H), 2.18-2.22 (m, 1H), 1.98-2.0 (m, 1H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 22



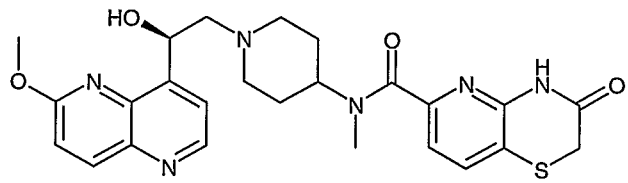
Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide

The title compound (41 mg, 31%) was prepared as a pale white solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine, 7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-

carboxylic acid (50 mg, 0.28 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid and 1,1'-carbonyldiinidizole (50 mg, 0.28 mmol) for diphenylphosphoryl azide as the couplig agent in the amid formation: LC/MS (ES) m/e 475 $(M+H)^+$; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 10.65-10.69 (m, 1H), 9.1 (s, 3H), 8.97-8.99 (m, 1H), 8.5-8.56 (m, 1H), 7.94-8.02 (m, 2H), 7.48-7.54 (m, 1H), 7.18-7.26 (m, 1H), 4.2-4.26 (m, 4H), 3.71-3.82 (m, 3H), 3.22-3.63 (m, 5H), 2.9-3.11 (m, 4H), 2.42-2.51 (m, 2H), 2.1-2.17 (m, 1H), 1.89-1.91 (m, 1H).

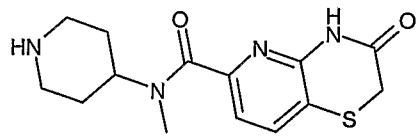
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 23



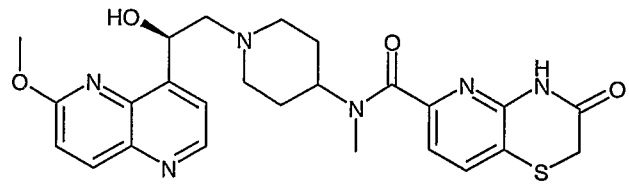
Preparation of *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

(a) *N*-methyl-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



The title compound was prepared as a pale white solid according to Example 15c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid: LC/MS (ES) m/e 307 $(M+H)^+$.

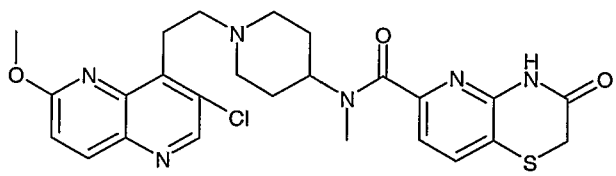
(b) *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide



Potassium carbonate (36 mg, 0.31 mmol), 2-(methyloxy)-8-[(2*R*)-2-oxiranyl]-1,5-naphthyridine (53 mg, 0.26 mmol), lithium perchlorate (28 mg, 0.26 mmol) and *N*-methyl-3-oxo-*N*-4-piperidinyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide (80 mg, 0.26 mmol) were mixed in DMF and heated at 90°C for 12 hr. The solution was diluted with water and extracted several times with ethyl acetate. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in chloroform (1% NH_4OH)) affording the title compound as a tan solid (12 mg, 9.1%): LC/MS (ES) m/e 509 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.70-8.74 (m, 1H), 8.17-8.22 (m, 1H), 7.83-7.88 (m, 2H), 7.16-7.24 (m, 2H), 5.89-5.99 (m, 1H), 4.09-4.12 (m, 3H), 3.57-3.6 (m, 2H), 3.46-3.49 (m, 1H), 3.35-3.42 (m, 1H), 3.10 (s, 2H), 2.94 (s, 2H), 2.79-2.83 (m, 1H), 2.39-2.66 (m, 3H), 1.82-2.15 (m, 5H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

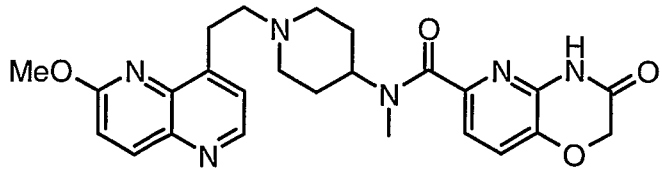
Example 24



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

The title compound (32 mg, 30%) was prepared as a white solid according to Example 23, except substituting 7-chloro-8-ethenyl-2-(methyloxy)-1,5-naphthyridine (44 mg, 0.2 mmol) for 2-(methyloxy)-8-[(2*R*)-2-oxiranyl]-1,5-naphthyridine: LC/MS (ES) m/e 527 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.68-8.71 (m, 1H), 8.14-8.21 (m, 1H), 7.88-7.9 (m, 1H), 7.19-7.27 (m, 2H), 4.09 (s, 3H), 3.66-3.69 (m, 6H), 3.2-3.26 (m, 1H), 2.98-3.04 (m, 4H), 2.84-2.88 (m, 1H), 2.71-2.76 (m, 1H), 1.88-2.1 (m, 5H).

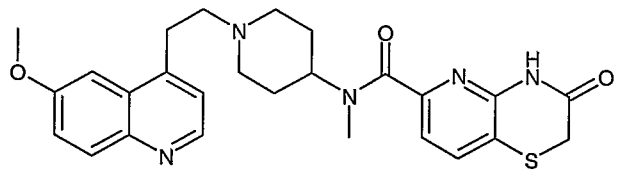
Example 25



Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

The title compound (85 mg, 36%) was prepared as a white solid according to Example 9, except substituting methylamine for cyclopropylamine and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid. Purification of the final compound was carried out with silica column (0-10% MeOH in DCM) followed by Agile reverse phase HPLC column (C18 column, 0-65% CH_3CN in H_2O (1% $CF_3C(O)OH$) to provide the trifluoroacetic acid salt of the title compound: LC/MS (ES) m/e 477 $(M+H)^+$; ^1H NMR ($(CD_3)_2SO$, 400 MHz) δ 11.34-10.48 (m, 2H), 9.05 (s, 1H), 8.57-8.6 (m, 1H), 7.98-8.02 (m, 1H), 7.5-7.58 (m, 2H), 7.21-7.3 (m, 1H), 4.17-4.28 (m, 3H), 3.8-3.89 (m, 3H), 3.45-3.7 (m, 4H), 2.9-3.39 (m, 8H), 2.11-2.18 (m, 2H), 1.9-1.96 (m, 1H).

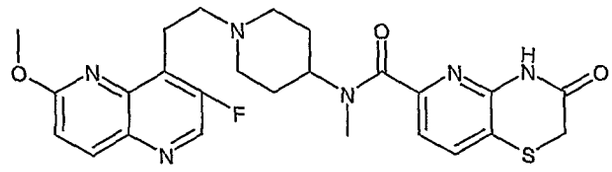
Example 26



Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (85 mg, 36%) was prepared as a white solid according to Example 9, except substituting methylamine for cyclopropylamine and 4-ethenyl-6-(methyloxy)quinoline for 8-ethenyl-2-(methyloxy)-1,5-naphthyridine: LC/MS (ES) m/e 492 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67-8.68 (m, 1H), 8.19 (dd, 1H), 7.95 (d, 1H), 7.68-7.75 (m, 2H), 7.40 (dd, 1H), 7.12 (m, 1H), 4.05-4.10 (m, 3H), 3.52-3.56 (m, 2H), 3.10-3.22 (m, 2H), 3.24-3.27 (m, 1H), 3.16-3.18 (m, 1H), 2.92 (s, 2H), 2.81-2.86 (m, 1H), 2.74-2.85 (m, 4H), 2.28-2.38 (m, 1H), 1.76-2.05 (m, 5H).

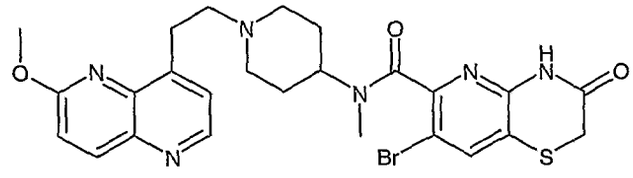
Example 27



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

The title compound (38 mg, 37%) was prepared as a white solid according to Example 7, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (42 mg, 0.2 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 511 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62-8.63 (m, 1H), 8.17-8.20 (m, 1H), 7.96-8.03 (m, 1H), 7.70-7.73 (m, 1H), 7.06-7.1 (m, 1H), 4.07-4.09 (m, 3H), 3.55-3.6 (m, 2H), 3.38-3.5 (m, 2H), 3.22-3.27 (m, 1H), 3.16-3.18 (m, 1H), 3.04 (s, 2H), 2.92 (s, 2H), 2.81-2.86 (m, 1H), 2.72-2.76 (m, 1H), 2.33-2.4 (m, 1H), 1.81-2.09 (m, 5H).

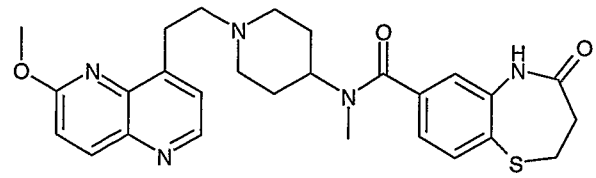
Example 28



Preparation of 7-bromo-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (30 mg, 20%) was prepared as a grey solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 7-bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (75 mg, 0.26 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 572 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.61-8.67 (m, 1H), 8.15-8.19 (m, 1H), 8.06-8.08 (m, 1H), 7.58-7.62 (m, 1H), 7.17-7.2 (m, 1H), 4.05-4.11 (m, 3H), 3.59-3.62 (m, 2H), 3.33-3.48 (m, 3H), 3.12-3.16 (m, 1H), 3.0 (s, 2H), 2.89-2.94 (m, 2H), 2.78 (s, 2H), 2.3-2.37 (m, 1H), 1.79-2.08 (m, 5H).

Example 29

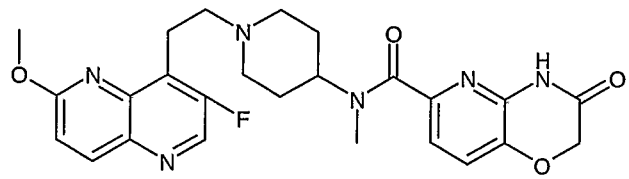


Preparation of *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-7-carboxamide

The title compound (30 mg, 17%) was prepared as a solid according to Example 7, except substituting 8-ethenyl-2-(methyloxy)-1,5-naphthyridine for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-7-carboxylic acid (75 mg, 0.34 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 506 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65-8.68 (m, 1H), 8.17-8.21 (m, 1H), 7.89-7.98 (m, 1H), 7.67-7.74 (m, 2H), 7.38-7.42 (m, 1H), 4.05-4.09 (m, 4H), 3.52-3.56 (m, 2H), 3.9 (s, 2H), 3.32-3.42 (m, 2H), 3.1-3.23 (m, 2H), 3.0 (s, 1H), 2.91 (s, 1H), 2.74-2.87 (m, 2H), 2.29-2.36 (m, 1H), 1.81-2.01 (m, 7H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 30

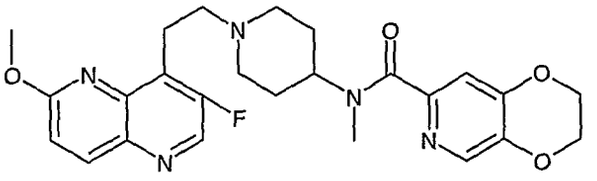


Preparation of *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

The title compound (94 mg, 38%) was prepared as a white solid according to Example 7, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (116 mg, 0.6 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 495 $(M+H)^+$; ^1H NMR (CD_3OD 400 MHz) δ 8.63-8.66 (m, 1H), 8.2-8.23 (m, 1H), 8.0 (s, 1H), 7.38-7.4 (m, 1H), 7.15-7.25 (m, 2H), 4.72-4.75 (m, 3H), 3.29-3.54 (m, 6H), 3.12-3.22 (m, 2H), 2.74-2.88 (m, 2H), 2.32-2.38 (m, 1H), 2.05-2.13 (m, 2H), 1.92-1.99 (m, 3H), 1.75-1.82 (m, 1H).

This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 31

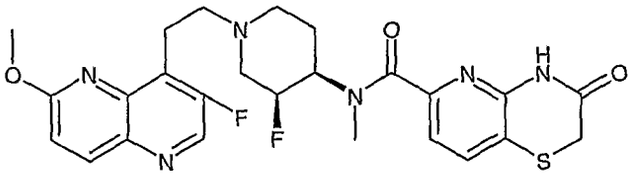


Preparation of *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide

The title compound (150 mg, 63%) was prepared as an orange solid according to Example 7, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxylic acid (136 mg, 0.75 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 482 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.89-8.92 (m, 1H), 8.3-8.42 (m, 2H), 7.31-7.43 (m, 2H), 4.49-4.6 (m, 4H), 3.85-3.92 (m, 1H), 3.7-3.78 (m, 2H), 3.5 (s, 3H), 3.28-03.41 (m, 3H), 2.98-3.03 (m, 2H), 3.54-3.62 (m, 4H), 1.99-2.16 (m, 4H).

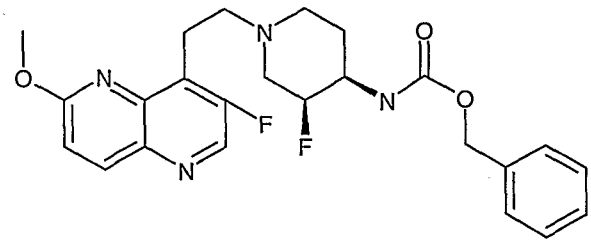
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 32



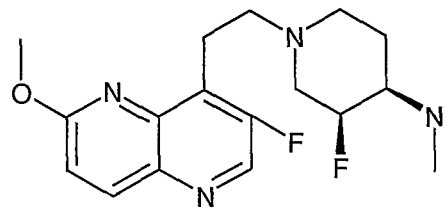
Preparation of Cis (E1)-N-3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-N-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxamide

(a) Phenylmethyl *cis* (E1) 3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate



8-Ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (0.04 g, 0.2 mmol) and *cis* (+) phenylmethyl 3-fluoro-4-piperidinyl]carbamate from preparation 20 (0.06 g, 0.24 mmol) were combined, neat and stirred at 90°C for 14h. The solution was then diluted in 2 mL DCM and purified via column chromatography (silica, 0-10% MeOH in DCM) yielding the title compound (0.08 g, 85%) as an off-white solid: LC/MS (ES) m/e 457 $(M+H)^+$.

(b) *cis* (E1)-3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-*N*-methyl-4-piperidinamine



To phenylmethyl *cis* (E1) 3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)carbamate (0.70 g, 0.15 mmol) THF (2 mL) at rt was added 0.45 mL of a 1N LAH/THF solution (0.45 mmol). The reaction was heated to 50 °C and allowed to stir for 1h. The reaction was cooled to rt and quenched with 1 mL of MeOH. The reaction was diluted with 10 mL of EtOAc and stirred with 0.50 g of anhydrous, granular sodium sulfate. The solution was filtered, the filtrate was concentrated under reduced pressure and the yellow residue (0.04 g, 80%) was used in the next reaction without further purification: LC/MS (ES) m/e 337 $(M+H)^+$.

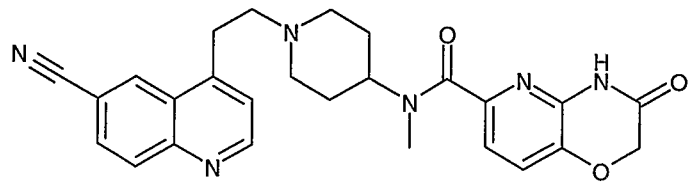
(c) Cis (+)-N-3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-N-methyl-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxamide

The title compound (7 mg, 13%) was prepared as an orange solid according to Example 1, The enantiomer used from prep 20 was the enantiomer which results in Example 32 (having a positive rotation): LC/MS (ES) m/e 529 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.66-8.68 (m, 1H), 8.17-8.21 (m, 1H), 7.96-8.03 (m, 1H), 7.70-7.73 (m, 1H), 7.06-7.1 (m, 1H), 4.07-4.09 (m, 3H), 3.55-3.6 (m, 2H), 3.38-3.5 (m, 2H), 3.22-3.27 (m,

1H), 3.16-3.18 (m, 1H), 3.04 (s, 3H), 2.92 (s, 2H), 2.80-2.85 (m, 1H), 2.72-2.76 (m, 1H), 2.36-2.4 (m, 1H), 1.81-2.09 (m, 4H).

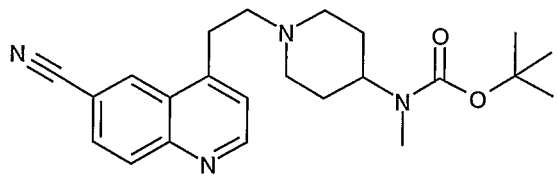
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 33



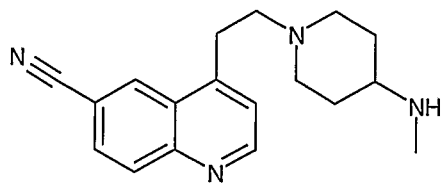
Preparation of *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

(a) 1,1-dimethylethyl {1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}methylcarbamate



4-Ethenyl-6-quinolinecarbonitrile (90 mg, 0.5 mmol) and 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (107 mg, 0.5 mmol) were melted together at 90°C and allowed to react for 4 h. The mixture was cooled down to room temperature and purified with column chromatography (silica, 0-90% MeOH in DCM) to afford the title compound as an off-white solid (183 mg, 90%): LC/MS (ES) m/e 395 $(M+H)^+$.

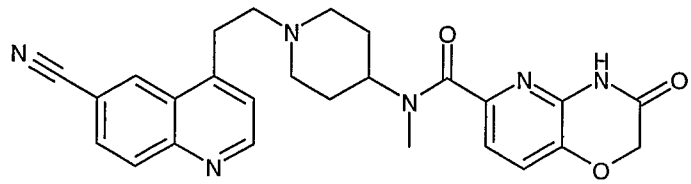
(b) 4-{2-[4-(methylamino)-1-piperidinyl]ethyl}-6-quinolinecarbonitrile



To a solution of 1,1-dimethylethyl {1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}methylcarbamate (175 mg, 0.44 mmol) in DCM (10 mL) at 25°C was added

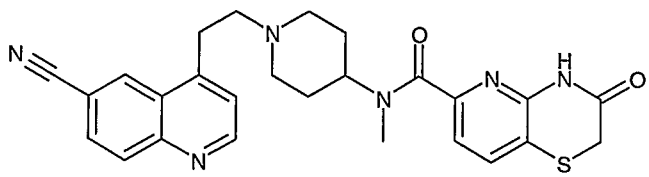
dropwise an HCl solution (0.5 mL, 2.0 mmol, 4M HCl in dioxane). After 4 h, the solution was concentrated under reduced pressure to provide the desired compound as the HCl salt (160 mg, quantit.) which was used without further purification: LC/MS (ES) m/e 295 $(M+H)^+$.

(c) *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide



A solution of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid (60 mg, 0.31 mmol) in DCM (3 mL) were added oxalyl chloride (60 mg, 0.46 mmol) and a catalytic amount of DMF. After stirring for 2 h, the mixture was concentrated to generate a brown residue which was treated with a solution of 4-{2-[4-(methylamino)-1-piperidinyl]ethyl}-6-quinolinecarbonitrile (90 mg, 0.31 mmol) in DCM (3 mL) and triethylamine (85 mL, 0.6 mmol). After stirring at 25°C for 12 h, the mixture was diluted with water and subsequently extracted several times with DCM. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0- 10% MeOH in DCM (1% NH_4OH)) affording the title compound as a white solid (20 mg, 14%): : LC/MS (ES) m/e 471 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.94-8.96 (m, 1H), 8.45-8.54 (m, 1H), 8.21-8.24 (m, 1H), 7.86-7.9 (m, 2H), 7.39-7.43 (m, 1H), 7.24-7.27 (m, 1H), 4.75 (s, 3H), 3.22-3.33 (m, 3H), 3.02-3.15 (m, 6H), 2.67-2.8 (m, 3H), 2.29-2.34 (m, 1H), 1.8-2.03 (m, 6H).

Example 34

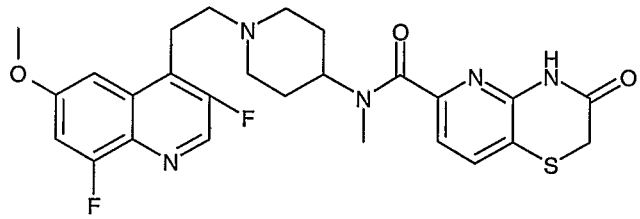


Preparation of *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (120 mg, 82%) was prepared as a white solid according to Example 33, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-

carboxylic acid (650 mg, 0.31 mmol) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxylic acid: LC/MS (ES) m/e 487 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.97-8.99 (m, 1H), 8.46-8.52 (m, 1H), 8.21-8.23 (m, 1H), 7.89-7.9 (m, 1H), 7.72-7.77 (m, 1H), 7.38-7.42 (m, 1H), 7.24-7.3 (m, 1H), 4.55-4.63 (m, 1H), 7.31-7.36 (m, 2H), 7.22-7.31 (m, 2H), 3.05-3.17 (m, 3H), 2.9 (s, 1H), 2.7-2.81 (m, 2H), 2.29-2.38 (m, 1H), 1.8-2.07 (m, 6H).

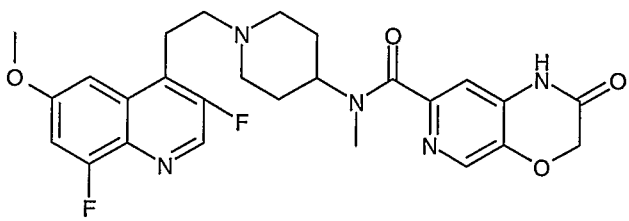
Example 35



Preparation of *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (85 mg, 50%) was prepared as a white solid according to Example 7, except substituting 4-ethenyl-3,8-difluoro-6-(methyloxy)quinoline (see WO20044058144) for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (83 mg, 0.4 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 528 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65-8.67 (m, 1H), 7.98-8.07 (m, 1H), 8.7-8.74 (m, 1H), 6.95-7.06 (m, 2H), 3.96 (s, 3H), 3.53-3.58 (m, 3H), 3.5 (s, 3H), 3.1-3.17 (m, 4H), 3.68-3.72 (m, 1H), 2.59-2.64 (m, 1H), 2.28-2.35 (m, 1H), 1.82-2.03 (m, 5H).

Example 36

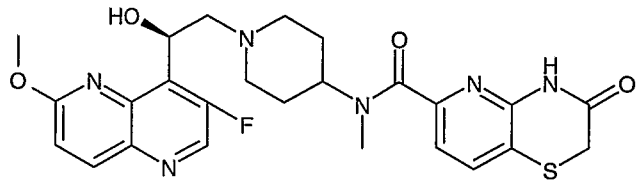


Preparation of *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide

The title compound (39 mg, 76%) was prepared as a tan solid according to Example 7, except substituting 4-ethenyl-3,8-difluoro-6-(methyloxy)quinoline (see

WO20044058144) for 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine and 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-7-carboxylic acid (20 mg, 0.1 mmol) for 1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxylic acid: LC/MS (ES) m/e 512 $(M+H)^+$; ^1H NMR (DMSO, 400 MHz) δ 11.1 (s, 1H), 5.57-8.59 (m, 1H), 8.0 (s, 1H), 7.14-7.19 (M, 1H), 7.0-7.08 (M, 1H), 6.89 (s, 1H), 4.6 (s, 2H), 3.78-3.82 (m, 3H), 3.01-3.11 (m, 4H), 2.9-2.93 (M, 1H), 2.81-2.83 (m, 1H), 2.71-2.79 (m, 3H), 1.41-1.77 (m, 7H).

Example 37

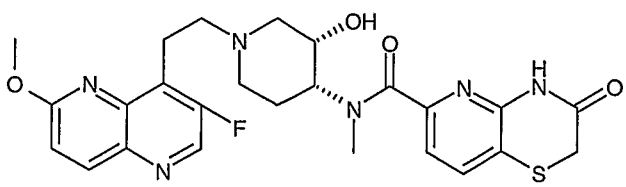


Preparation of *N*-(1-{(2*R*)-2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]-2-hydroxyethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

The title compound (12 mg, 7%) was prepared as a tan solid according to Example 23, except substituting 7-fluoro-2-(methyloxy)-8-[(2*R*)-2-oxiranyl]-1,5-naphthyridine (75 mg, 0.35 mmol) for 2-(methyloxy)-8-[(2*R*)-2-oxiranyl]-1,5-naphthyridine: LC/MS (ES) m/e 527 $(M+H)^+$; ^1H NMR (CDCl3, 400 MHz) δ 8.58-8.62 (m, 1H), 8.18-8.20 (m, 1H), 8.02-8.10 (m, 1H), 7.61-7.63 (m, 1H), 7.01-7.03 (m, 1H), 5.89-5.99 (m, 1H), 5.41-5.64 (m, 1H), 3.97-4.08 (m, 3H), 3.57-3.6 (m, 3H), 3.35-3.42 (m, 1H), 3.05-3.12 (m, 1H), 2.98 (s, 2H), 2.84 (s, 2H), 2.61-2.73 (m, 1H), 2.19-2.31 (m, 1H), 1.70-1.98 (m, 5H).

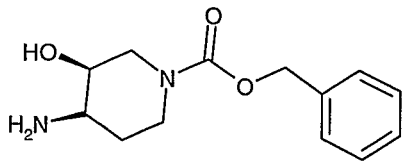
This material, as a solution in MeOH, was treated with an excess of 4M HCl in dioxane and evaporated to dryness to provide the dihydrochloride salt of the title product.

Example 38



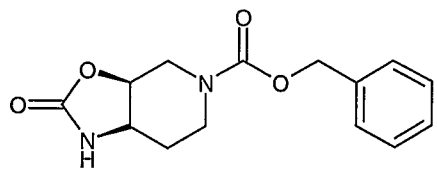
Preparation of *N*-((3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-hydroxy-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

(a) phenylmethyl (3*S*,4*R*)-4-amino-3-hydroxy-1-piperidinecarboxylate



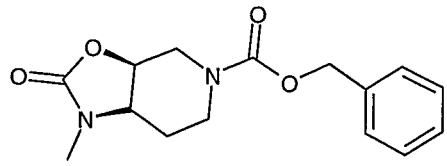
To a solution of phenylmethyl (3*S*,4*R*)-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-3-hydroxy-1-piperidinecarboxylate (350 mg, 1.0 mmol) (Preparation 21) in DCM (10 mL) was added a solution of HCl (1 mL, 4.0 mmol, 4.0M in dioxane). After stirring at 25°C for 14 h, the mixture was concentraed to afford an off-white solid as the HCl salt of the title compound (285 mg, quantit.) which was used without further purification: LC/MS (ES) m/e 251 $(M+H)^+$.

(b) phenylmethyl (3a*S*,7a*R*)-2-oxohexahydro[1,3]oxazolo[5,4-*c*]pyridine-5(2*H*)-carboxylate



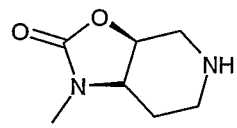
A suspension solution of HCl salt of phenylmethyl (3*S*,4*R*)-4-amino-3-hydroxy-1-piperidinecarboxylate (285 mg, 1.0 mmol) in THF (10 mL) was cooled down to 0°C and treated with carbonyldiimmidazole (162 mg, 1.0 mmol). The mixture was gradually warmed up to 25°C and stirred for 14 h. THF was removed under reduced pressure to provide a brown residue which was subsequently partitioned between DCM and brine. The aqueous layer was extracted several times with DCM. The organic fractions were pooled, concentrated and purified with column chromatography (silica, 0-10% MeOH/DCM) affording the title compound as an off-white solid (200 mg, 73%): LC/MS (ES) m/e 277 $(M+H)^+$.

(c) phenylmethyl (3a*S*,7a*R*)-1-methyl-2-oxohexahydro[1,3]oxazolo[5,4-*c*]pyridine-5(2*H*)-carboxylate



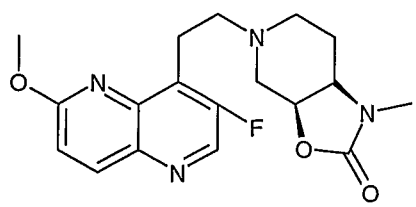
To a solution of phenylmethyl (3a*S*,7a*R*)-2-oxohexahydro[1,3]oxazolo[5,4-*c*]pyridine-5(2*H*)-carboxylate (200 mg, 0.72 mmol) in THF (5 mL) at 0°C was added KHMDS (0.75 mL, 0.75 mmol, 1.0M in toluene). After 1 h at 0°C, the solution was warmed up to 25°C and treated with methyl iodide (0.05 mL, 0.8 mmol). The mixture was stirred at 25°C for 14 h and subsequently partitioned between ethyl acetate and aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate. The organic fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in DCM) providing the title compound as an off-white solid (150 mg, 75%): LC/MS (ES) m/e 291 $(M+H)^+$.

(d) (3a*S*,7a*R*)-1-methylhexahydro[1,3]oxazolo[5,4-*c*]pyridin-2(1*H*)-one



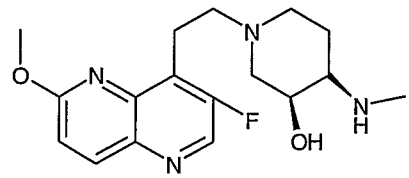
A solution of phenylmethyl (3a*S*,7a*R*)-1-methyl-2-oxohexahydro[1,3]oxazolo[5,4-*c*]pyridine-5(2*H*)-carboxylate (150 mg, 0.54 mmol) in EtOH (5 mL) was treated with Pearlman's catalyst (20 mg). A ballon of H_2 was placed on the reaction. After stirring at 25°C for 12 h, the suspension mixture was filtered through a celite pad. The filtrate was concentrated to give the title compound as a brown oil (85 mg, quantit.) which was used without further purification: LC/MS (ES) m/e 157 $(M+H)^+$.

(e) (3a*S*,7a*R*)-5-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-1-methylhexahydro[1,3]oxazolo[5,4-*c*]pyridin-2(1*H*)-one



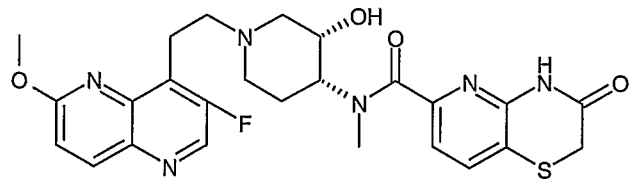
(3a*S*,7a*R*)-1-methylhexahydro[1,3]oxazolo[5,4-*c*]pyridin-2(1*H*)-one (80 mg, 0.5 mmol), 8-ethenyl-7-fluoro-2-(methyloxy)-1,5-naphthyridine (100 mg, 0.5 mmol) and 1,1,3,3-tetramethylguanidine (1 drop) were mixed in DMF (0.25 mL) and heated at 90°C for 14 h. The mixture was concentrated and purified with column chromatography (silica, 0-10% MeOH in DCM) affording the title compound as an off-white solid (135 mg, 75%): LC/MS (ES) m/e 361 $(M+H)^+$.

(f) (3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-(methylamino)-3-piperidinol



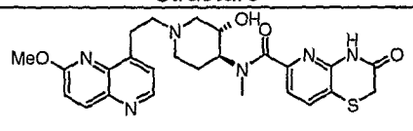
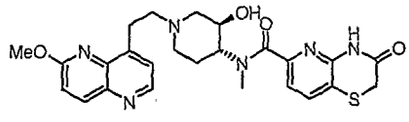
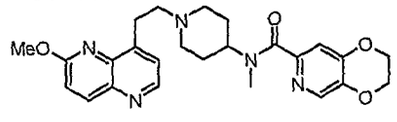
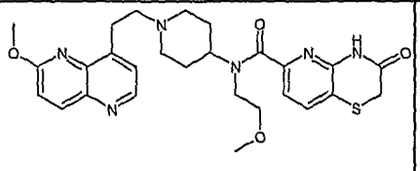
To a solution of (3a*S*,7a*R*)-5-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-1-methylhexahydro[1,3]oxazolo[5,4-*c*]pyridin-2(1*H*)-one (100 mg, 0.277 mmol) in THF (1 mL) was added a solution of $Ba(OH)_2$ (1 mL, 1.0 mmol, 1.0 M in H_2O). After stirring at 50°C for 14 h, the solution was cooled down to room temperature and neutralized with the aqueous solution of NH_4Cl. The aqueous solution was extracted with ethyl acetate. The organic fractions were pooled, concentrated and purified with column chromatography (silica, 0-10% MeOH in DCm (5% NH_4OH)) affording the title compound as an off-white solid (50 mg, 54%): LC/MS (ES) m/e 335 $(M+H)^+$.

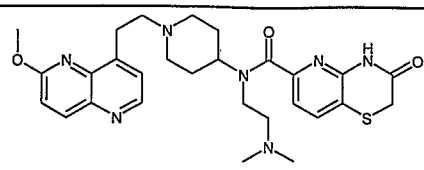
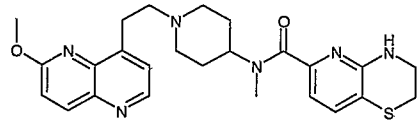
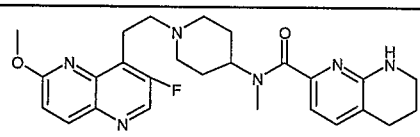
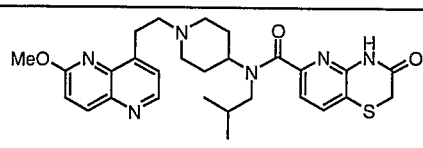
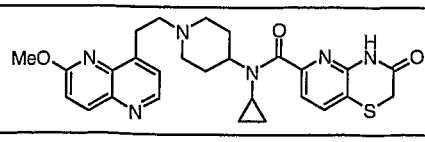
(g) *N*-((3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-hydroxy-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide

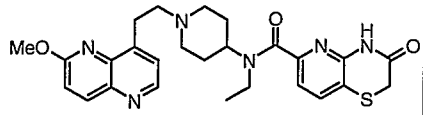
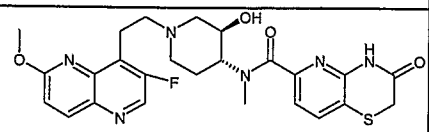
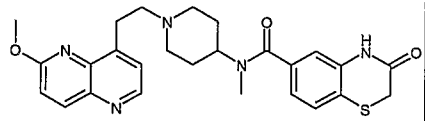
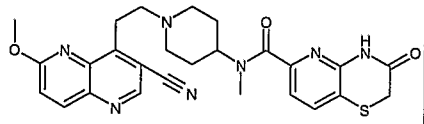


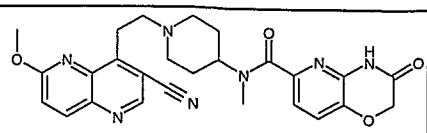
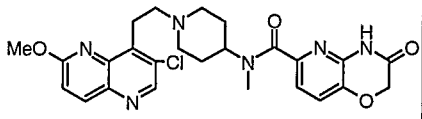
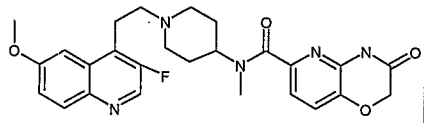
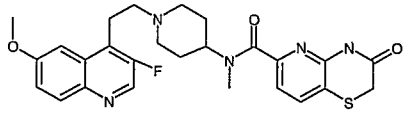
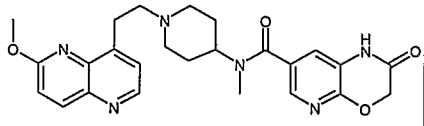
To a solution of (3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-(methylamino)-3-piperidinol (50 mg, 0.15 mmol) in DMF (0.5 mL) at 0°C were added 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (31 mg, 0.15 mmol), triethylamine (0.1 mL, 0.71 mmol) and diphenylphosphoryl azide (0.05 mL, 0.18 mmol). After stirring at 25°C for 14 hr, the mixture was diluted with the aqueous solution of $NaHCO_3$. The aqueous phase was extracted several times with DCM. The organic

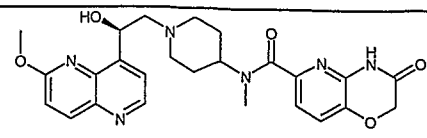
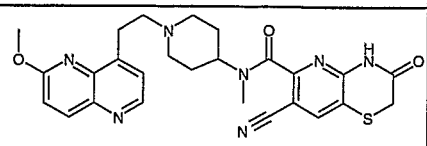
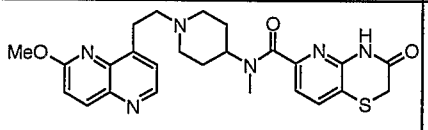
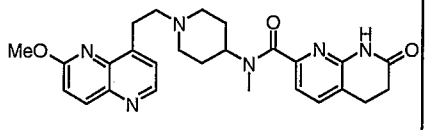
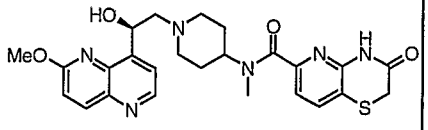
fractions were combined, concentrated and purified with column chromatography (silica, 0-10% MeOH in chloroform (5% NH_4OH)) followed by another column chromatography (0-10% ethyl MeOH in ethyl acetate (5% NH_4OH)) affording the the title compound as a yellow solid: (25 mg, 32%): LC/MS (ES) m/e 527 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 8.56-8.51 (m, 1H), 8.08-8.12 (m, 1H), 7.73-7.76 (m, 1H), 7.05-7.11 (m, 2H), 5.38 (s, 2H), 3.96-4.06 (m, 5H), 3.47-3.62 (m, 2H), 3.25-3.4 (m, 2H), 3.27-3.3 (m, 2H), 2.98-3.17 (m, 5H), 2.25-3.33 (m, 1H), 1.47-1.55 (m, 1H).

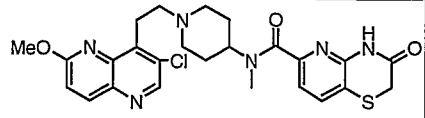
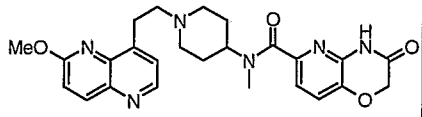
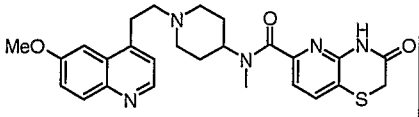
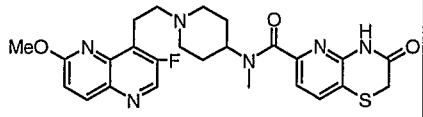
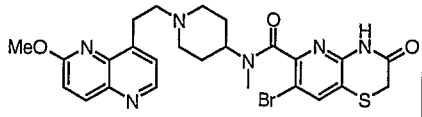
Cmp. No.	Structure	MIC (ug/mL)
Example 1		0.125-0.5 (S. aureus, n=7) 0.125-0.25 (S. epiderm., n=2) 2 (E. faecalis, n=1) 8 (E. faecium, n=1) 0.125-0.5 (S. pneum., n=3) 0.5-1 (S. pyogenes, n=3) 8 (H. influenzae, n=30) 0.25 (M. cat., n=2) 0.03-2 (E. coli, n=1)
Example 2		0.5-1 (S. aureus, n=7) 0.5 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 0.25-0.5 (S. pneum., n=3) 0.5-2 (S. pyogenes, n=3) 16 (H. influenzae, n=30) 2 (M. cat., n=2) 0.125-8 (E. coli, n=2)
Example 3		2-4 (S. aureus, n=7) 4 (S. epiderm., n=2) 4 (E. faecalis, n=1) 16 (E. faecium, n=1) 4-8 (S. pneum., n=5) 8-16 (S. pyogenes, n=3) >16 (H. inf., n=30) 2-4 (M. cat., n=2) 0.125-16 (E. coli, n=2)
Example 4		2-16 (S. aureus, n=7) 16 (S. epiderm., n=2) >16 (E. faecalis, n=1) >16 (E. faecium, n=1) >16 (S. pneum., n=5)

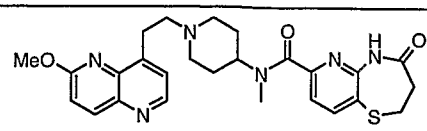
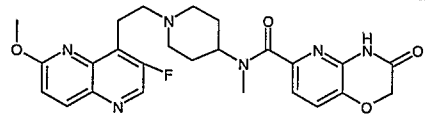
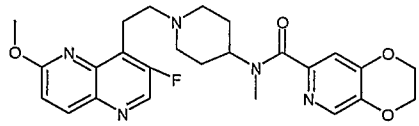
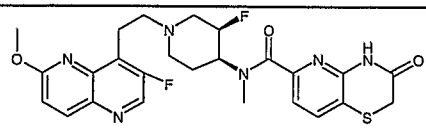
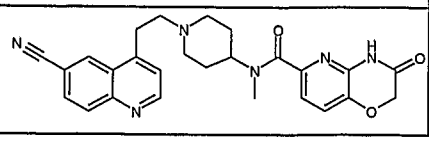
		16 (S. pyogenes, n=3) >16 (H. inf., n=30) 4 (M. cat., n=1) 0.5-4 (E. coli, n=2)
Example 5		>16 (S. aureus, n=7) >16 (S. epiderm., n=2) >16 (E. faecalis, n=1) >16 (E. faecium, n=1) >16 (S. pneum., n=5) 16 (S. pyogenes, n=3) >16 (H. inf., n=30) >16 (M. cat., n=1) 8-16 (E. coli, n=2)
Example 6		0.25-2 (S. aureus, n=7) 8 (S. epiderm., n=2) 16 (E. faecalis, n=1) 8 (E. faecium, n=1) 1-8 (S. pneum., n=5) >16 (S. pyogenes, n=3) >16 (H. inf., n=30) 0.5-1 (M. cat., n=2) 0.25-16 (E. coli, n=2)
Example 7		0.25-1 (S. aureus, n=7) 2-4 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 1-4 (S. pneum., n=5) 8 (S. pyogenes, n=3) >16 (H. inf., n=30) 2 (M. cat., n=2) 0.25->16 (E. coli, n=2)
Example 8		0.5-2 (S. aureus, n=7) 1 (S. epiderm., n=2) 8 (E. faecalis, n=1) 8 (E. faecium, n=1) 2-4 (S. pneum., n=5) 8-16 (S. pyogenes, n=3) >16 (H. inf., n=30) 1 (M. cat., n=2) 0.25-8 (E. coli, n=2)
Example 9		1-8 (S. aureus, n=7) 16 (S. epiderm., n=2) >16 (E. faecium, n=1)

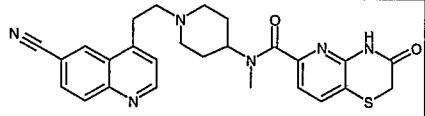
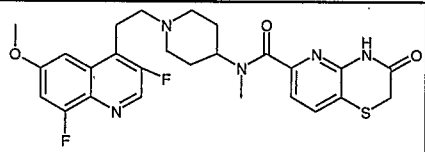
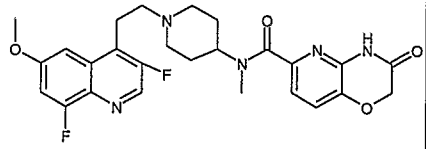
		>16 (S. pneum., n=5) >16 (S. pyogenes, n=3) >16 (H. inf., n=30) 2 (M. cat., n=2) 0.5-16 (E. coli, n=2)
Example 10		0.5-4 (S. aureus, n=7) 8 (S. epiderm., n=2) 16 (E. faecalis, n=1) >16 (E. faecium, n=1) 8-16(S. pneum., n=5) >16 (S. pyogenes, n=3) >16 (H. inf., n=30) 1-2 (M. cat., n=2) 0.125-16 (E. coli, n=2)
Example 11		0.03-0.25 (S. aureus, n=7) 0.125 (S. epiderm., n=2) 2 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.25-1 (S. pneum., n=5) 0.5 (S. pyogenes, n=3) 16 (H. inf., n=30) 0.125-0.25 (M. cat., n=2) 0.03-2 (E. coli, n=2)
Example 12		0.125-1 (S. aureus, n=7) 1 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 0.5-8 (S. pneum., n=5) 8(S. pyogenes, n=3) 16 (H. inf., n=30) 0.125-0.25 (M. cat., n=2) 0.016-2 (E. coli, n=2)
Example 13		0.016-0.125 (S. aureus, n=7) 0.125 (S. epiderm., n=2) 1 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.03-2 (S. pneum., n=5) 2 (S. pyogenes, n=3) 16 (H. inf., n=30) 0.06 (M. cat., n=2) 0.06-2 (E. coli, n=2)
Example 14		0.03-0.25 (S. aureus, n=7) 0.25 (S. epiderm., n=2)

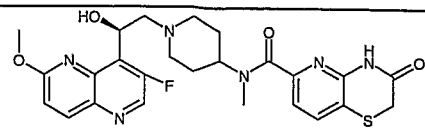
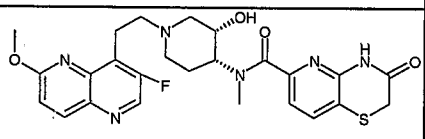
		2 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.5-2 (S. pneum., n=5) 1-2 (S. pyogenes, n=3) >16 (H. inf., n=30) 0.25 (M. cat., n=2) 0.03-2 (E. coli, n=2)
Example 15		0.03-0.25 (S. aureus, n=7) 0.25 (S. epiderm., n=2) 2 (E. faecalis, n=1) 4 (E. faecium, n=1) 1-4 (S. pneum., n=5) 2 (S. pyogenes, n=3) 16 (H. inf., n=30) 0.06-0.125 (M. cat., n=2) 0.06-2 (E. coli, n=2)
Example 16		0.016-0.25 (S. aureus, n=7) 0.06-0.125 (S. epiderm., n=2) 0.5 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.06-0.25 (S. pneum., n=5) 1 (S. pyogenes, n=3) 4 (H. inf., n=30) 0.06 (M. cat., n=2) 0.016-1 (E. coli, n=2)
Example 17		0.016-0.125 (S. aureus, n=7) 0.03-0.06 (S. epiderm., n=2) 0.5 (E. faecalis, n=1) 1 (E. faecium, n=1) 0.06-0.125 (S. pneum., n=5) 0.125-0.25 (S. pyogenes, n=3) 2 (H. inf., n=30) 0.016 (M. cat., n=2) 0.016-0.5 (E. coli, n=2)
Example 18		>16 (S. aureus, n=7) >16 (S. epiderm., n=3) >16 (E. faecalis, n=1) >16 (E. faecium, n=1) >16 (S. pneum., n=5) >16 (S. pyogenes, n=3) >16 (H. inf., n=30) 4-8 (M. cat., n=2) 0.25-16 (E. coli, n=2)

Example 19		0.25-1 (S. aureus, n=7) 0.5-1 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 1-4 (S. pneum., n=5) 2-8 (S. pyogenes, n=3) 16 (H. inf., n=30) 0.5 (M. cat., n=2) 0.5-4 (E. coli, n=2)
Example 20		0.06-0.25 (S. aureus, n=7) 0.06-0.5 (S. epiderm., n=2) 2 (E. faecalis, n=1) 4 (E. faecium, n=1) 0.5-4 (S. pneum., n=5) 2-4 (S. pyogenes, n=3) 8 (H. inf., n=30) 0.125 (M. cat., n=2) 0.016-1 (E. coli, n=2)
Example 21		0.06-0.25 (S. aureus, n=7) 0.25-0.5 (S. epiderm., n=2) 2 (E. faecalis, n=1) 4 (E. faecium, n=1) 0.25-2 (S. pneum., n=5) 2 (S. pyogenes, n=3) 8 (H. inf., n=30) 0.06-0.125 (M. cat., n=2) 0.016-1 (E. coli, n=2)
Example 22		4-16 (S. aureus, n=7) >16 (S. epiderm., n=2) 1 (E. faecalis, n=1) >16 (E. faecium, n=1) 8-16 (S. pneum., n=5) 16 (S. pyogenes, n=3) >16 (H. inf., n=30) 8 (M. cat., n=2) 0.25-16 (E. coli, n=2)
Example 23		0.125-0.5 (S. aureus, n=7) 0.5 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 0.5-4 (S. pneum., n=5) 2-4 (S. pyogenes, n=3) 16 (H. inf., n=30)

		0.25 (M. cat., n=2) 0.03-2 (E. coli, n=2)
Example 24		0.06-0.125 (S. aureus, n=7) 0.06-0.125 (S. epiderm., n=2) 1 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.125-1 (S. pneum., n=5) 0.5 (S. pyogenes, n=3) 8 (H. inf., n=30) 0.016-0.03 (M. cat., n=2) 0.016-1 (E. coli, n=2)
Example 25		0.125-1 (S. aureus, n=7) 1-2 (S. epiderm., n=2) 4 (E. faecalis, n=1) 16 (E. faecium, n=1) 0.5-8 (S. pneum., n=5) 16 (S. pyogenes, n=3) >16 (H. inf., n=30) 0.5 (M. cat., n=1) 0.03-2 (E. coli, n=2)
Example 26		0.06-0.25 (S. aureus, n=7) 0.5 (S. epiderm., n=2) 2 (E. faecalis, n=1) 4 (E. faecium, n=1) 0.125-2 (S. pneum., n=5) 2 (S. pyogenes, n=3) 16 (H. inf., n=30) 0.125 (M. cat., n=1) 0.016-1 (E. coli, n=2)
Example 27		0.016-0.125 (S. aureus, n=7) 0.06-0.125 (S. epiderm., n=2) 1 (E. faecalis, n=1) 1 (E. faecium, n=1) 0.03-1 (S. pneum., n=5) 0.5 (S. pyogenes, n=3) 4 (H. inf., n=30) 0.03 (M. cat., n=2) 0.016-0.5 (E. coli, n=2)
Example 28		0.25-4 (S. aureus, n=7) 4-8 (S. epiderm., n=2) 8 (E. faecalis, n=1) 16 (E. faecium, n=1) >16 (S. pneum., n=5)

		>16 (S. pyogenes, n=3) >16 (H. inf., n=30) 1-2 (M. cat., n=2) 0.25-16 (E. coli, n=2)
Example 29		8-16 (S. aureus, n=7) >16 (S. epiderm., n=2) >16 (E. faecalis, n=1) >16 (E. faecium, n=1) >16 (S. pneum., n=5) >16 (S. pyogenes, n=3) >16 (H. inf., n=30) 4-8 (M. cat., n=2) 0.25-16 (E. coli, n=2)
Example 30		0.03-0.125 (S. aureus, n=7) 0.25 (S. epiderm., n=2) 2 (E. faecalis, n=1) 2 (E. faecium, n=1) 0.5-2 (S. pneum., n=5) 0.5-2 (S. pyogenes, n=3) 8 (H. inf., n=30) 0.06 (M. cat., n=2) 0.016-1 (E. coli, n=2)
Example 31		0.5-2 (S. aureus, n=7) 1-2 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 2-4 (S. pneum., n=5) 2-4 (S. pyogenes, n=3) >16 (H. inf., n=30) 1 (M. cat., n=2) 0.125-16 (E. coli, n=2)
Example 32		0.03-0.25 (S. aureus, n=7) 0.25-0.5 (S. epiderm., n=2) 4 (E. faecalis, n=1) 8 (E. faecium, n=1) 2 (S. pneum., n=5) 2-4 (S. pyogenes, n=2) >16 (H. inf., n=30) 0.25-0.5 (M. cat., n=2) 0.125-16 (E. coli, n=2)
Example 33		0.5-4 (S. aureus, n=7) 4 (S. epiderm., n=2) 8 (E. faecalis, n=1)

		>16 (E. faecium, n=1) 2-4 (S. pneum., n=5) 4-8 (S. pyogenes, n=3) >16 (H. inf., n=30) 2 (M. cat., n=2) 0.125-8 (E. coli, n=2)
Example 34		0.125-2 (S. aureus, n=7) 2-4 (S. epiderm., n=2) 4 (E. faecalis, n=1) 16 (E. faecium, n=1) 0.5-2 (S. pneum., n=5) 2 (S. pyogenes, n=3) >16 (H. inf., n=30) 0.5-1 (M. cat., n=1) 0.06-4 (E. coli, n=2)
Example 35		0.016-0.03 (S. aureus, n=7) 0.016-0.25 (S. epiderm., n=2) 0.5 (E. faecalis, n=1) 1 (E. faecium, n=1) 0.06-0.5 (S. pneum., n=5) 0.25 (S. pyogenes, n=3) 4 (H. inf., n=30) 0.016-0.3 (M. cat., n=2) 0.016-0.5 (E. coli, n=2) 1 (S. paerug., n=1) >16 (E. cloac., n=1) 16 (E. aerog., n=1) 8-16 (K. pneum., n=2) 4 (S. maltop., n=1) 0.016 (S. aureus., n=1) >0.016 (S. saprophy., n=1)
Example 36		0.25-1 (S. aureus, n=7) 8 (E. faecalis, n=1) 16 (E. faecium, n=1) 2-8 (S. pneum., n=5) 0.25 (S. pyogenes, n=3) >16 (H. inf., n=30) 0.5-1 (M. cat., n=2) 0.06-4 (E. coli, n=2) >16 (S. paerug., n=1) >16 (E. cloac., n=1) >16 (E. aerog., n=1) >16 (K. pneum., n=2)

		4 (S. maltop., n=1) 0.5 (S. aureus., n=1) 0.25 (S. saprophy., n=1)
Example 37		0.25-1 (S. aureus, n=7) 8 (E. faecalis, n=1) 16 (E. faecium, n=1) 2-8 (S. pneum., n=5) 4-8 (S. pyogenes, n=2) >16 (H. inf., n=30) 1 (M. cat., n=1) 0.06-8 (E. coli, n=2) 1 (S. paerug., n=1) >16 (E. cloac., n=1) >16 (E. aerog., n=1) >16 (K. pneum., n=2) >16 (S. maltop., n=1)
Example 38		0.016-0.06 (S. aureus, n=7) 1 (E. faecalis, n=1) 0.5 (E. faecium, n=1) 0.125-0.5 (S. pneum., n=5) 0.25 (S. pyogenes, n=2) 4 (H. inf., n=30) 0.03 (M. cat., n=1) >0.016-0.5 (E. coli, n=2) 1 (S. paerug., n=1) >16 (E. cloac., n=1) >16 (E. aerog., n=1) 4-16 (K. pneum., n=2) 4 (S. maltop., n=1) 16 (C. pneum., n=2)

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*, and *Enterococcus faecalis*.

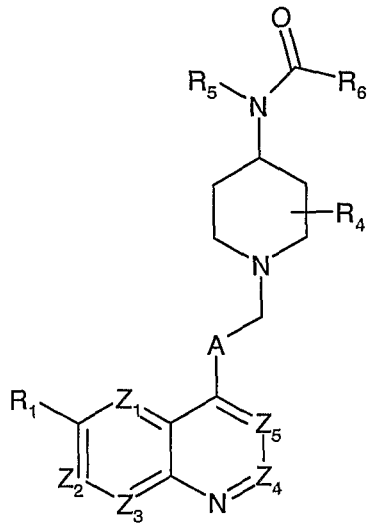
In addition, compounds were evaluated against a panel of Gram-negative strains including *Haemophilus influenzae*, *Escherichia coli*, and *Moraxella catarrhalis* Ravisio. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. 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. Compound examples 1, 2, 11, 12, 13, 15, 19-21, 23, 24, 26, and 30 have MIC $\leq$20 mg/ml versus all of the organisms named above. Examples 16, 17, 27, 35, and 38 had MIC's $\leq$4 mg/ml versus all of the organisms named above. All other examples had MIC's $\leq$20 mg/ml for at least one of the organisms named above.

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

What is claimed is:

1. A compound of formula (I)



(I)

wherein:

Z_1 is N or CR^{1a}; and

two of Z_2, Z_3, Z_4, and Z_5 are CR^{1a} and the rest are CH;

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, hydroxyl, 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, $CONH_2$, hydroxyl, (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 CR_2R_3;

R_2 is hydrogen; halogen; hydroxyl; (C_{1-6})alkyl; (C_{1-6})alkoxy; $NR^{1b}R^{1b'}$or acyloxy;

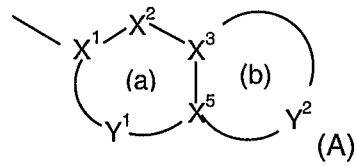
R_3 is hydrogen or (C_{1-6})alkyl;

R^{1b} and $R^{1b'}$ are each independently hydrogen; (C_{1-6})alkyl; aryl; heteroaryl; or together with the nitrogen they are attached form an aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring (wherein said aziridine, azetidine, pyrrolidine, piperidine or hexamethyleneimine ring is optionally substituted with 1 to 3 substitutents selected from halogen, (C_{1-6})alkyl, hydroxyl or aryl);

R_4 is hydrogen; hydroxyl; C_{1-6} alkyl; halogen; or $NR^{1b}R^{1b'}$;

R_5 is (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, acyloxy, carboxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is unsubstituted or N-substituted by one or two aryl, heteroaryl, halogen, unsubstituted (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxyl, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{3-7})cycloalkyl; (C_{1-6})alkylcarbonyl; or (C_{2-6})alkenylcarbonyl;

R_6 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_7 when part of a non aromatic ring;

X^2 is N, NR_8, O, $S(O)_x$, CO or CR_7 when part of an aromatic or non-aromatic ring or may in addition be CR_9R_{10} 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_8, O, $S(O)_x$, CO and CR_7 when part of an aromatic or non-aromatic ring or may additionally be CR_9R_{10} 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_8, O, $S(O)_x$, CO and CR_7 when part of an aromatic or non-aromatic ring or may additionally be CR_9R_{10} when part of a non aromatic ring;

R_7, R_9 and R_{10} are at each occurrence independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxyl; 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_8 is at each occurrence independently hydrogen; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxyl, 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;

each x is independently 0, 1 or 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according o claim 1, wherein:
Z_1 is N.

3. A compound according to claim 1, wherein:
R_1 is OCH_3.

4. A compound according to claim 1, wherein:
R^{1a} is hydrogen; fluorine; chlorine; or cyano.

5. A compound according to claim 1, wherein:
R_2 is hydrogen or hydroxyl.

6. A compound according to claim 1, wherein:
R_3 is hydrogen.

7. A compound according to claim 1, wherein:
R_4 is hydrogen; hydroxyl; or fluorine.

8. A compound according to claim 1, wherein:
R_5 is CH_3.

9. A compound according to claim 1, wherein:

R_6 is 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl;

2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-yl;

3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl;

1,5,6,7-tetrahydro-1,8-naphthyridine-2-yl;

3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl;

7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-yl;

7-Bromo-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl;

4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]thiazepine-7-yl;

2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-yl; or

7-Cyano-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl.

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

a) *N*-((3*S*,4*S*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

b) *N*-((3*R*,4*R*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

c) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide;

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

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

f) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

g) *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide;

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

i) *N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-(2-methylpropyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

j) *N*-cyclopropyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

k) *N*-((3*R*,4*R*)-3-hydroxy-1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

l) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-6-carboxamide;

m) *N*-(1-{2-[3-cyano-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

n) *N*-(1-{2-[3-cyano-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

o) *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

p) *N*-(1-{2-[3-fluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

q) *N*-(1-{2-[3-fluoro-6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

r) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

s) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridine-2-carboxamide;

t) *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

u) *N*-(1-{2-[3-chloro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

v) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

w) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-4-quinolinyl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

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

y) 7-bromo-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

z) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]thiazepine-7-carboxamide;

aa) *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

ab) *N*-(1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxamide;

ac) *N*-((3*R*,4*S*)-3-fluoro-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

ad) *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

ae) *N*-{1-[2-(6-cyano-4-quinolinyl)ethyl]-4-piperidinyl}-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

af) *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

ag) *N*-(1-{2-[3,8-difluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide;

ah) *N*-(1-{(2*R*)-2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]-2-hydroxyethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

ai) *N*-((3*S*,4*R*)-1-{2-[3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-3-hydroxy-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide;

aj) *N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazine-7-carboxamide;

ak) *N*-(1-{(2*R*)-2-hydroxy-2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-*N*-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxamide; or

al) 7-cyano-*N*-methyl-*N*-(1-{2-[6-(methyloxy)-1,5-naphthyridin-4-yl]ethyl}-4-piperidinyl)-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxamide; or a pharmaceutically acceptable salt or solvate thereof.

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

12. A method of treating bacterial infections which comprises administering to a mammal in need thereof an effective amount of a compound according to claim1.