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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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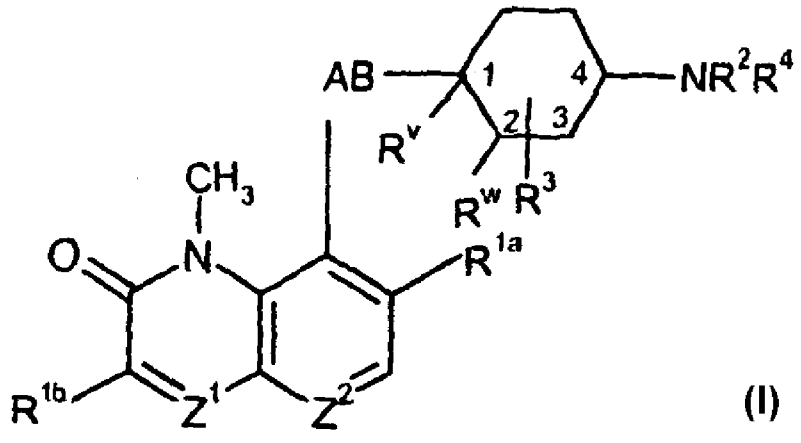
[Continued on next page]

(54) Title: SUBSTITUTED (AZA) -1-METHYL-1H-QUIN0LIN-2-0NES AS ANTIBACTERIALS



(I)

(57) Abstract: Bicyclic nitrogen containing compounds and their use as antibacterials (Formula I).

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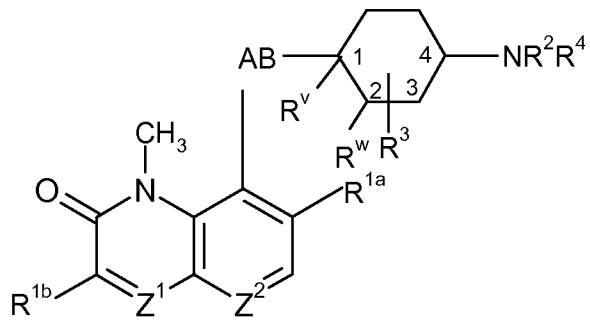
SUBSTITUTED (AZA)-1-METHYL-1H-QUINOLIN-2-ONES AS ANTIBACTERIALS

This invention relates to novel compounds, compositions containing them and their use as antibacterials including use in the treatment of tuberculosis.

WO02/08224, WO02/50061, WO02/56882, WO02/96907, WO2003087098, WO2003010138, WO2003064421, WO2003064431, WO2004002992, WO2004002490, WO2004014361, WO2004041210,WO2004096982, WO2002050036, WO2004058144, WO2004087145, WO2006002047, WO2006014580, WO2006010040, WO2006017326, WO2006012396, WO2006017468, WO2006020561, WO2006081179, WO2006081264, WO2006081289, WO2006081178, WO2006081182, WO2004024712, WO2004024713, WO2004035569, WO2004087647, WO2005016916, WO2005097781, WO2006010831, WO2006021448, WO2006032466, WO2006038172, WO2006046552, WO06099884, WO06126171, WO06137485, WO06105289, WO06125974, WO06134378, WO07016610, WO07081597, WO07071936, WO07115947, WO07118130, WO07122258, WO08006648, WO08003690, WO08009700, WO01/25227, WO02/40474, WO02/07572, WO2004035569 and WO2004089947 disclose quinoline, naphthyridine, morpholine, cyclohexane, piperidine and piperazine derivatives having antibacterial activity.

This invention provides a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof:



(I)

wherein:

Z^1 and Z^2 are independently selected from N and CH;

AB is OCH_2, CH_2O, $NR^{11}CH_2$ or CH_2NR^{11};

R^{11} is selected from $C_{(1-2)}$alkyl; formyl; (C_{1-2})alkylcarbonyl; and (C_{1-2})alkylsulphonyl;

R^{1a} is selected from hydrogen; halogen; cyano; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; carboxy ; hydroxy optionally substituted with (C_{1-6})alkyl or (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl;

hydroxy (C_{1-6})alkyl; an amino group optionally N-substituted by one or two (C_{1-6})alkyl, formyl, (C_{1-6})alkylcarbonyl or (C_{1-6})alkylsulphonyl groups; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl;
R^{1b} is H or F;
R^2 is hydrogen;

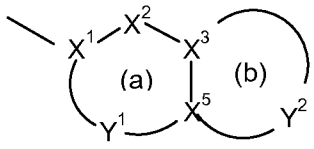
R^V and R^W are hydrogen, R^V is absent and R^3 is in the 1-position and R^W is hydrogen or R^V and R^W together are a bond;

R^3 is hydrogen; or
when R^V and R^W are a bond, R^3 is in the 2-, 3- or 4- position and when R^W is hydrogen, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:
hydroxy optionally substituted by (C_{1-6})alkyl; amino optionally mono- or disubstituted independently by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl; fluoro; carboxy; cyano; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl, or
(C_{1-4})alkyl optionally substituted with any of the groups listed above for R^3;
provided that when R^3 is in the 4- position it is not optionally substituted hydroxyl or amino;
provided that when R^3 is in the 1-position and AB is CH_2NR^{11} or R^3 is in the 4-position, it is not optionally substituted hydroxyl or amino;
and provided that when R^3 is in the 1-position and AB is CH_2O, it is not optionally substituted amino;

R^4 is UR^5;

U is selected from CO and CH_2 and

R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (B):



(A)

containing up to four heteroatoms in each ring in which

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

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

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

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

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

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

each of R^{14} and R^{15} is independently selected from: H; (C_{1-2})alkylthio; halo; carboxy(C_{1-2})alkyl; (C_{1-2})alkyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkoxy (C_{1-2})alkyl; hydroxy; hydroxy(C_{1-24})alkyl; (C_{1-2})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally mono- or di-substituted by (C_{1-2})alkyl; or

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

each R^{13} is independently H; trifluoromethyl; (C_{1-2})alkyl optionally substituted by hydroxy, (C_{1-2})alkoxy, (C_{1-2})alkylthio, halo or trifluoromethyl; (C_2)alkenyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkylsulphonyl; aminocarbonyl wherein the amino group is optionally mono or disubstituted by (C_{1-2})alkyl;

each x is independently 0, 1 or 2.

This invention also provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, and a pharmaceutically acceptable carrier.

In one aspect, the invention provides a compound of formula (IA), or a pharmaceutically acceptable salt and/or N-oxide thereof, which is a compound of formula (I) wherein Z^1 is CH; Z^2 is N; AB is OCH_2, CH_2O, $NHCH_2$ or CH_2NH; and R^3 is hydrogen; or

when R^V and R^W are a bond, R^3 is in the 2-, 3- or 4- position and when R^W is hydrogen, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:

hydroxy optionally substituted by (C_{1-6})alkyl; amino optionally mono- or disubstituted by (C_{1-6})alkyl; fluoro; carboxy; cyano; or
(C_{1-4})alkyl optionally substituted with any of the groups just listed for R^3.

In another aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, which is other than a compound of formula (IA).

In particular embodiments:
(1) Z^1 is CH and Z^2 is N;
(2) Z^1 and Z^2 are both CH;
(3) Z^1 is N and Z^2 is CH
(4) Z^1 and Z^2 are both N.

In a particular aspect R^{1a} is hydrogen, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkyl, cyano, carboxy, hydroxymethyl or halogen; more particularly hydrogen, cyano, or halogen.

In some embodiments only one group R^{1a} or R^{1b} is other than hydrogen. In a particular embodiment R^{1a} is halo such as chloro or fluoro or cyano and R^{1b} is hydrogen.

In other embodiments both R^{1a} and R^{1b} are hydrogen.

In a particular aspect R^2 is hydrogen.

Particular examples of R^3 include hydrogen; optionally substituted hydroxy; optionally substituted amino; fluoro; (C_{1-4}) alkyl; 1-hydroxy-(C_{1-4}) alkyl. More particular R^3 groups are hydrogen; 1-hydroxyalkyl e.g. CH_2OH; optionally substituted hydroxy e.g. methoxy; optionally substituted amino; and fluoro. Most particularly R^3 is hydrogen or hydroxy, and if hydroxy, most preferably substituted in the 1- or 3-position.

In particular embodiments AB is OCH_2, $NHCH_2$ or CH_2NH.

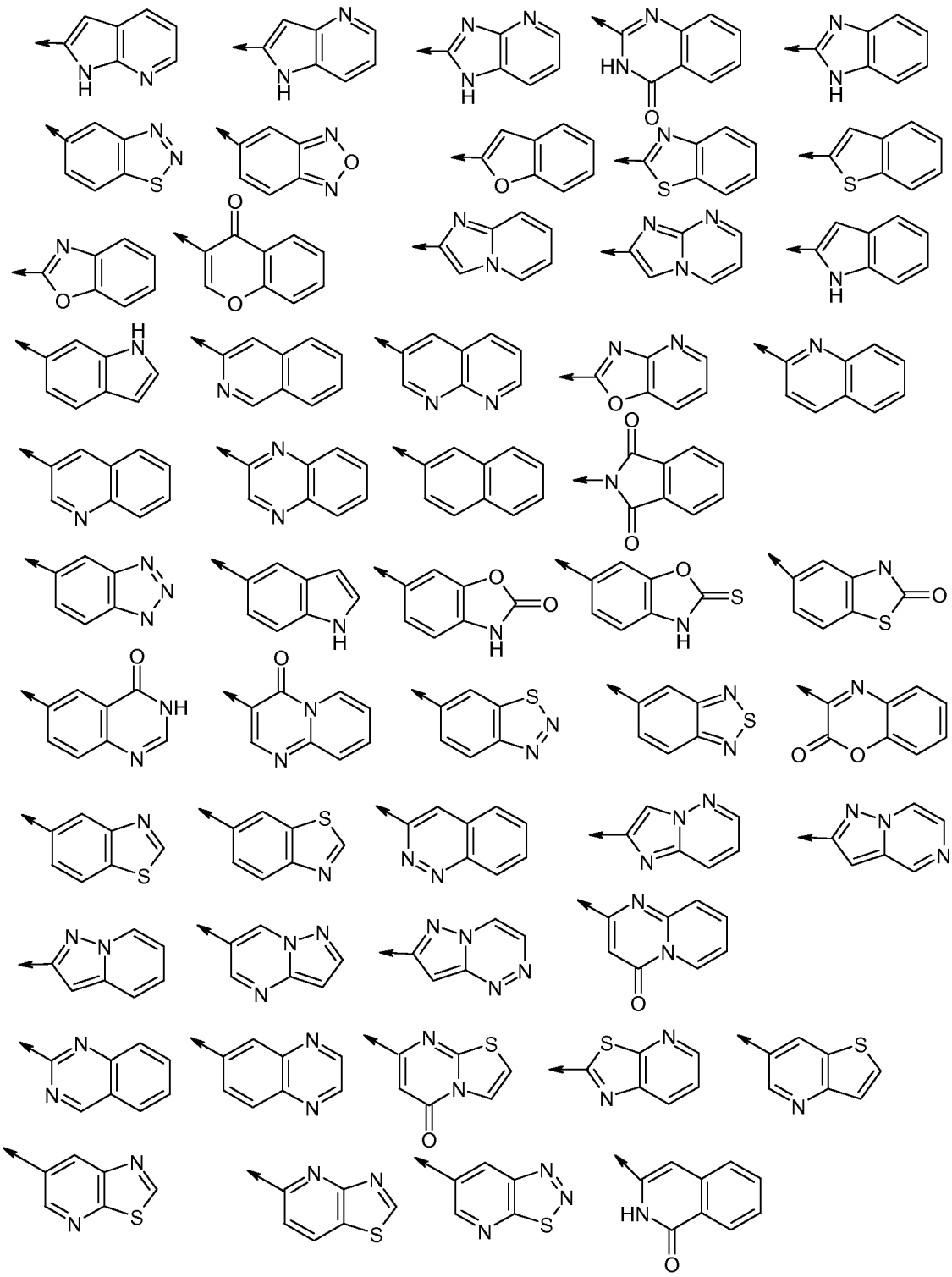
In certain embodiments U is CH_2.

In certain embodiments R^5 is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} in which, in particular embodiments, Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3.

In alternative embodiments the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo, pyrido, pyridazino and pyrimidino and ring (b) non aromatic and Y^2 has 3-4 atoms including at least one heteroatom, with O, S, CH_2 or NR^{13} bonded to X^5, where R^{13} is other than hydrogen, and either NHCO bonded via N to X^3, or O, S, CH_2, or NH bonded to X^3. In a particular aspect the ring (a) contains aromatic nitrogen, and more particularly ring (a) is pyridine. Examples of rings (A) include optionally substituted:

(a) and (b) aromatic

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2yl, 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-6-yl, pyrido[1,2-a]pyrimidin-4-one-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, 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, 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, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, 2H-isoquinolin-1-one-3-yl



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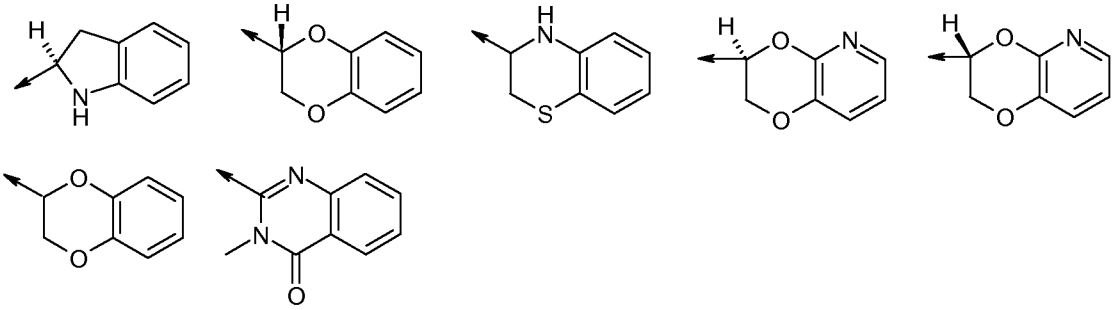
(a) is non aromatic

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

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



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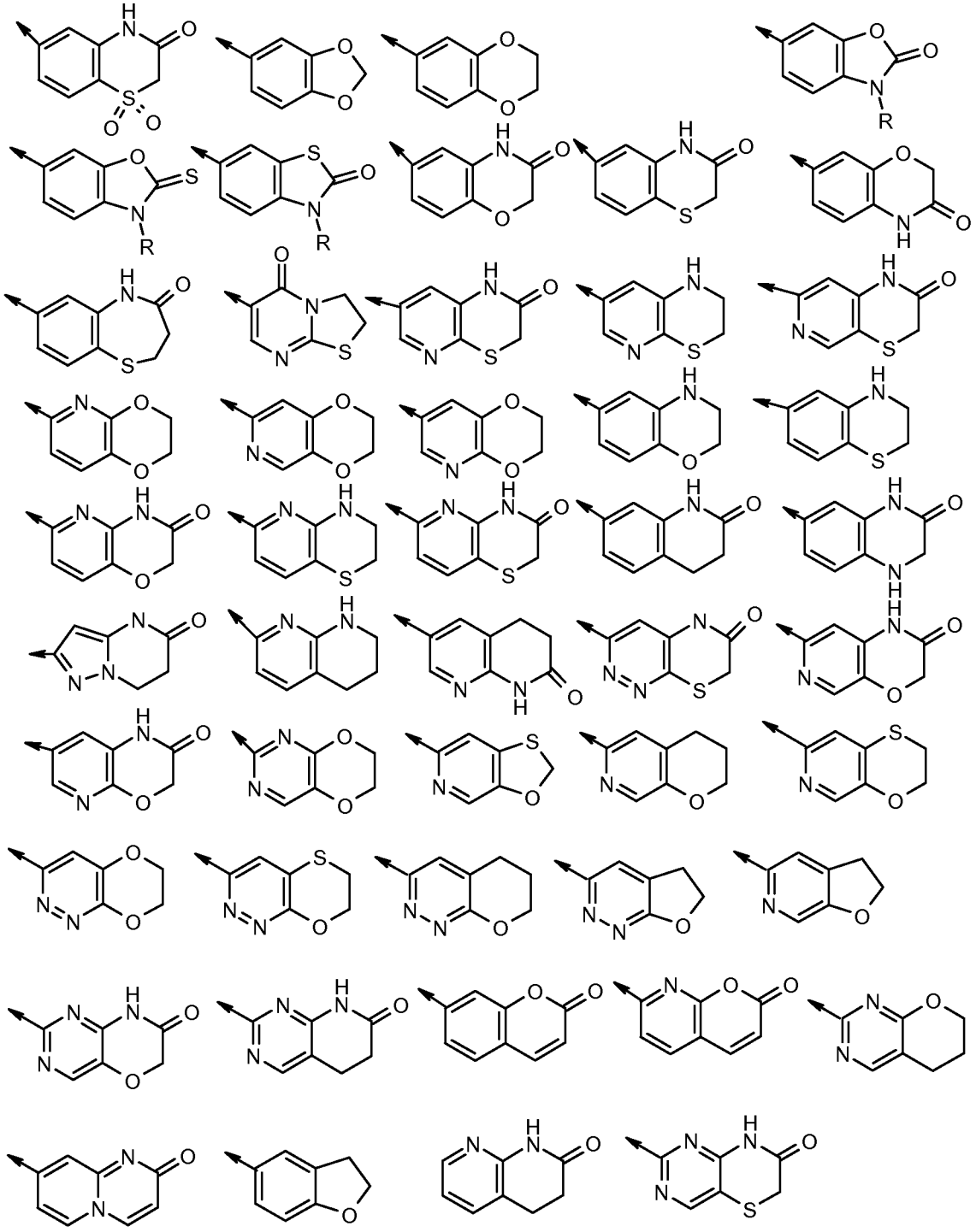
(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro1 l^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-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, 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, 1H-pyrido[2,3-b][1,4]thiazin-2-one-7-yl (2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl), 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b]thiazin-7-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, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][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, 1,2,3,4-tetrahydro-[1,8]naphthyridin-7-yl, 2-oxo-3,4-dihydro-1*H*-[1,8]naphthyridin-6-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triaza-naphthalen-3-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, 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, [1,3]oxathiolo[5,4-*c*]pyridin-6-yl, 3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-yl, 2,3-dihydro[1,4]oxathiino[2,3-*c*]pyridine-7-yl, 6,7-dihydro[1,4]dioxino[2,3-*c*]pyridazin-3-yl, 6,7-dihydro[1,4]oxathiino[2,3-*c*]pyridazin-3-yl, 6,7-dihydro-5H-pyrano[2,3-c]pyridazin-3-yl, 5,6-dihydrofuro[2,3-*c*]pyridazin-3-yl, 2,3-dihydrofuro[2,3-c]pyridin-5-yl, 2-substituted 1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one, 2-substituted 5,6-dihydropyrido[2,3-*d*]pyrimidin-7(1*H*)-one, 7- substituted 2H-chromen-2-one, 7-substituted 2*H*-pyrano[2,3-*b*]pyridin-2-one, 2-substituted 6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidine, 8-substitited 2*H*-pyrido[1,2-*a*]pyrimidin-2-one, 2,3-

dihydro-1-benzofuran-5-yl, 7-substituted 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one, 2-substituted 1*H*-pyrimido[5,4-*b*][1,4]thiazin-7(6*H*)-one.



→ is the point of attachment

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

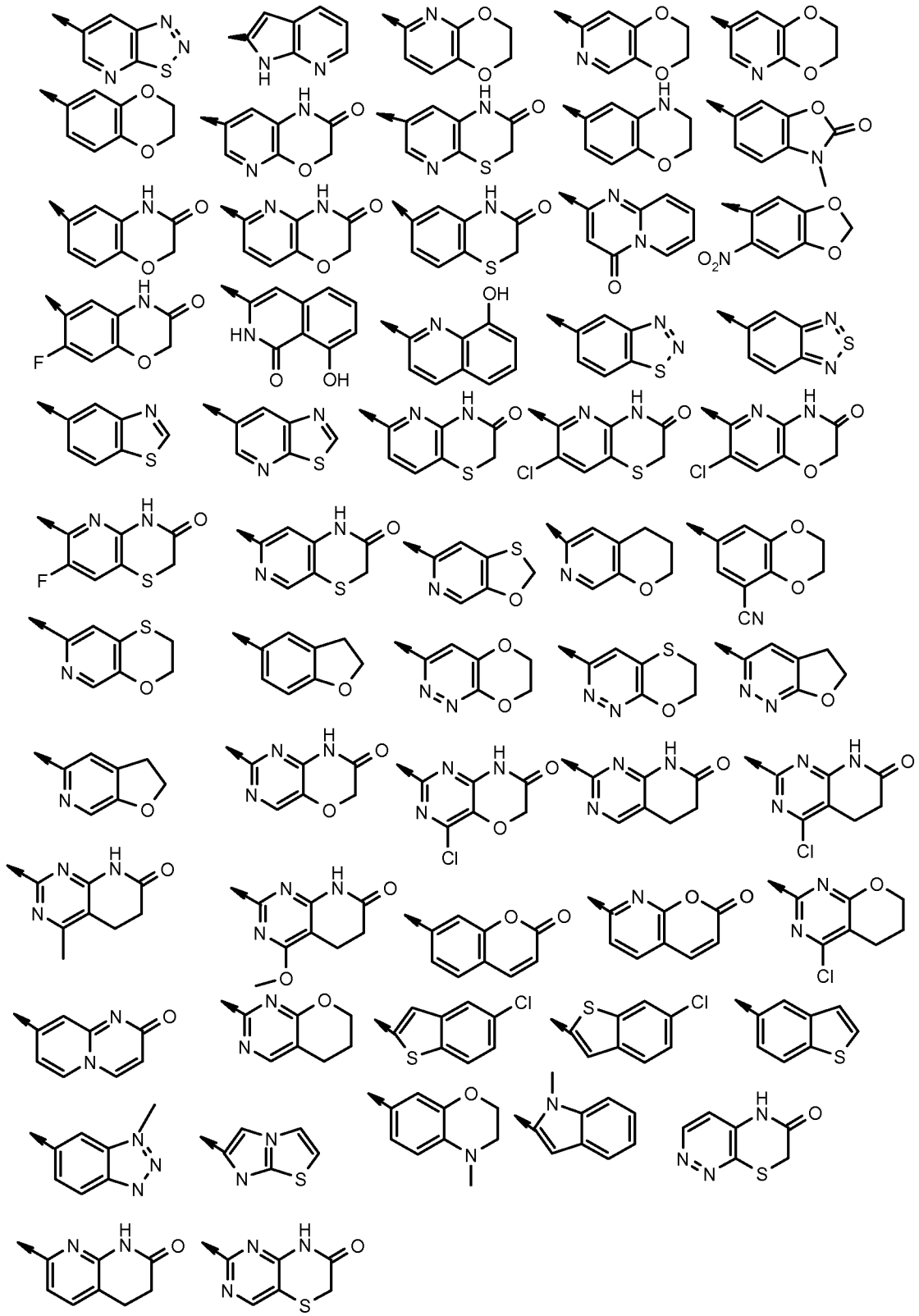
In futher embodiments R^{14} and R^{15} are independently selected from hydrogen, halo, hydroxy, (C_{1-4}) alkyl, (C_{1-4})alkoxy, nitro and cyano. More particularly R^{15} is hydrogen.

More particularly each R^{14} is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, nitro and cyano. Still more particularly R^{14} is selected from hydrogen, fluorine or nitro.

Most particularly R^{14} and R^{15} are each H.

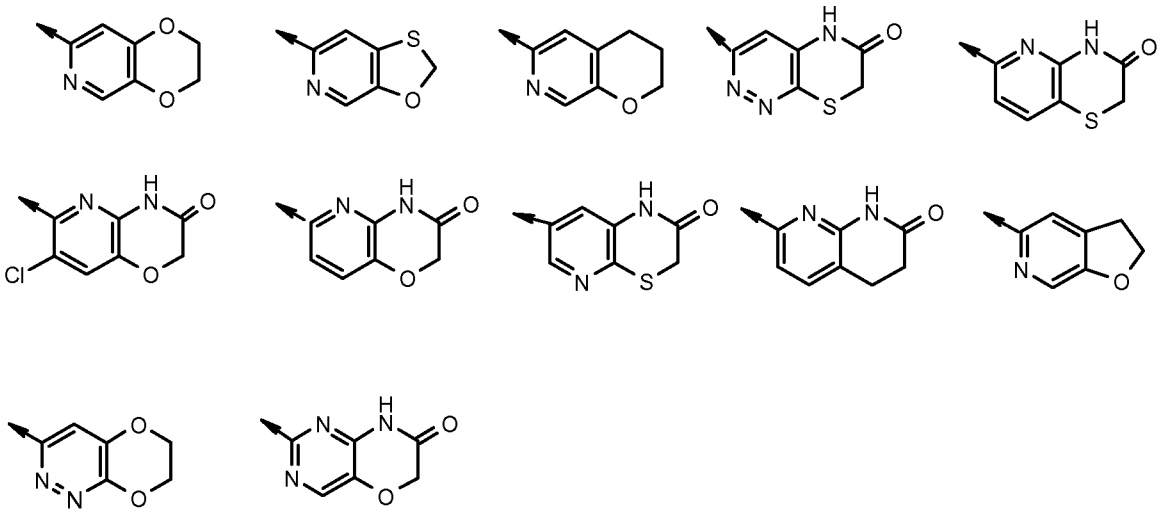
Particular groups R^5 include:
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
1H-pyrrolo[2,3-b]pyridin-2-yl
2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl
2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
2,3-dihydro-benzo[1,4]dioxin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl (6-substituted 2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one)
3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl (4H-benzo[1,4] thiazin-3-one-6-yl)
4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl
6-nitro-benzo[1,3]dioxol-5-yl
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
8-hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl
8-hydroxyquinolin-2-yl
benzo[1,2,3]thiadiazol-5-yl
benzo[1,2,5]thiadiazol-5-yl
benzothiazol-5-yl
thiazolo-[5,4-b]pyridin-6-yl
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl (6-substituted 2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one)
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl (6-substituted 7-chloro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one)
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl

2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl
[1,3]oxathiolo[5,4-*c*]pyridin-6-yl
3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-yl
2,3-dihydro-5-carbonitro-1,4-benzodioxin-7-yl (7-substituted 2,3-dihydro-1,4-benzodioxin-5-carbonitrile)
2,3-dihydro[1,4]oxathiino[2,3-*c*]pyridine-7-yl
2,3-dihydro-1-benzofuran-5-yl
6,7-dihydro[1,4]dioxino[2,3-*c*]pyridazin-3-yl
6,7-dihydro[1,4]oxathiino[2,3-*c*]pyridazin-3-yl
6,7-dihydro-5H-pyrano[2,3-c]pyridazin-3-yl
5,6-dihydrofuro[2,3-c]pyridazin-3-yl
2-substituted 1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one
2-substituted 4-chloro-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one
2-substituted 5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-chloro-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-methyl-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-methyloxy-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
7-substituted 2H-chromen-2-one
7-substituted 2*H*-pyrano[2,3-*b*]pyridin-2-one
4-chloro-6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl
8-substituted 2*H*-pyrido[1,2-*a*]pyrimidin-2-one
6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidin-2-yl)
5-chloro-1-benzothiophen-2-yl
6-chloro-1-benzothiophen-2-yl
1-benzothiophen-5-yl
1-methyl-1H-1,2,3-benzotriazol-6-yl
imidazo[2,1-b][1,3]thiazol-6-yl
4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl
1-methyl-1H-indol-2-yl
3-substituted 5*H*-pyridazino[3,4-*b*][1,4]thiazin-6(7*H*)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one
2-substituted 1*H*-pyrimido[5,4-*b*][1,4]thiazin-7(6*H*)-one



→ is the point of attachment

especially
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
[1,3]oxathiolo[5,4-*c*]pyridin-6-yl
3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-yl
3-substituted *5-H*-pyridazino[3,4-b][1,4]-thiazin-6-(7H)-one
6-substituted 2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one
6-substituted 7-chloro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one
6-substituted 2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one
7-substituted 1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one
5-substituted 2,3-dihydrofuro[3,2-*b*]pyridine
3-substituted 6,7-dihydro[1,4]dioxino[2,3-*c*]pyridazine
2-substituted 1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one



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

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

Haloalkyl moieties include 1-3 halogen atoms.

Compounds within the invention contain a heterocyclyl group and may occur in two or more tautomeric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including

hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Furthermore, it will be understood that phrases such as "a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof" are intended to encompass the compound of formula (I), an N-oxide 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.

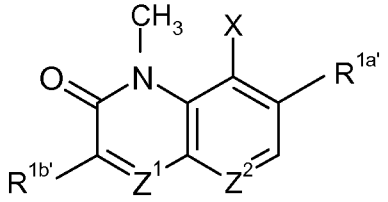
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that in particular embodiments they are provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and particularly at least 85%, especially at 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 more particularly from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable salt and/or N-oxide thereof.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable N-oxides, salts and solvates.

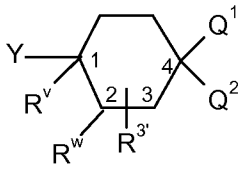
Pharmaceutically acceptable salts of the above-mentioned compounds of formula (I) include the acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic,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

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 forms, in particular the pure isomeric forms. For example, the invention includes compounds in which the configuration of the 1,4-substituted cyclohexyl moiety is *cis* or *trans*, in particular *trans*. 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. Certain compounds of formula (I) may also exist in polymorphic forms and the invention includes such polymorphic forms.

In a further aspect of the invention there is provided a process for preparing compounds of formula (I), and pharmaceutically acceptable salts and/or N-oxides thereof, which process comprises reacting a compound of formula (II) with a compound of formula (III):



(II)



(III)

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

(i) Y is COW and X is NHR^{11};

(ii) X is NHR^{11} and Y is CH(=O) or X is CH(=O) and Y is NHR^{11};

(iii) X is OH and Y is CH_2OH;

(iv) one of X and Y is $(CH_2)_p$-W and the other is $(CH_2)_qNHR^{11}$ or $(CH_2)_qOH$, where p+q=1;

(v) X is OH and Y is $-CH=N_2$;

(vi) X is W and Y is $CONH_2$:

(vii) X is OH and Y and $R^{3'}$ together form an epoxide group;

in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl;
and thereafter optionally or as necessary converting Q^1 and Q^2 to $NR^{2'}R^{4'}$; converting $R^{1a'}$, $R^{1b'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ to R^{1a}, R^{1b}, R^2, R^3 and R^4; converting intermediate linker A'-B' formed by the reaction of X and Y to A-B, converting A-B to other A-B, interconverting R^V, R^W, R^{1a}, R^{1b}, R^2, R^3 and/or R^4, and/or forming a pharmaceutically acceptable salt and/or N-oxide thereof.

Process variant (i) initially produces compounds of formula (I) where A-B is NH-CO which may be converted to A-B $NH-CH_2$.

Process variant (ii) produces compounds of formula (I) wherein A-B is $NH-CH_2$. or CH_2-NH.

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

Process variant (iv) produces compounds of formula (I) wherein one of A and B is CH_2 and the other is NH or O.

Process variant (v) produces compounds of formula (I) wherein A-B is OCH_2.

Process variant (vi) initially produces compounds of formula (I) where A-B is NHCO which may be converted to A-B NH-CH_2.

Process variant (vii) produces compounds of formula (I) wherein A-B is OCH_2 and R^3 is OH in the 1-position.

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

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

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

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

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

In process variant (iii) the X=OH and Y=CH_2OH groups can be reacted directly by activation with 1,3-dicyclohexylcarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997 or Angewante Chemie 1963 75, 377), or the X=OH compound is reacted with a base, for example sodium hydride, followed by reaction with a methylcyclohexane-derived alkylating agent, such as a cyclohexylmethyl methanesulphonate. The latter may be prepared from a hydroxymethyl cyclohexane (prepared from the corresponding acid by reduction with eg. borane-dimethylsulphide complex) by treatment with methanesulphonyl chloride and triethylamine.

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

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

In process variant (iv) where one of X and Y contains OH, this is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, metal alkoxide such as sodium methoxide. The leaving group W is a halogen, methanesulphonyloxy, ethanesulphonyloxy or trifluoromethanesulphonyloxy. The reaction may be carried out as described in Chapman et.al., J. Chem Soc., (1956),1563, Gilligan et. al., J. Med. Chem., (1992), **35**, 4344, Aloup et. al., J. Med. Chem. (1987), **30**, 24, Gilman et al., J.A.C.S. (1949), **71**, 3667 and Clinton et al., J.A.C.S. (1948), **70**, 491, Barluenga et al., J. Org. Chem. (1987) **52**, 5190. Alternatively where X is OH and Y is CH_2W, W is a hydroxy group activated under Mitsunobu conditions (Fletcher et.al. J Chem Soc. (1995), 623).

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

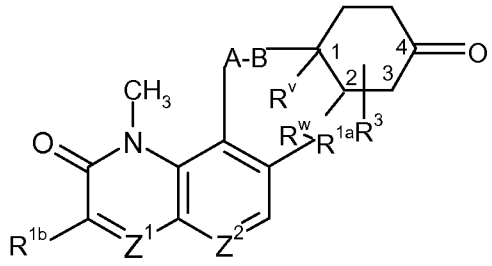
In process variant (vi) the leaving group W is preferably chloro, bromo or trifluoromethylsulphonyl and the reaction is the palladium catalysed process known as the "Buchwald" reaction (J. Yin and S. L. Buchwald, Org.Lett., 2000, 2, 1101).This utilizes a suitable palladium catalyst/ligand combination, for example tris(dibenzylideneacetone)dipalladium(0) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos), and a base, for example caesium carbonate.

In process variant (vii) the process is the standard epoxide opening of the epoxide (III) with the anion OM where M is an alkali metal, formed by treatment of the alcohol (II) where X=OH with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, metal alkoxide such as sodium methoxide. The epoxide (III) is obtainable from the corresponding ketone (Y and $R^{3'}$ together form an oxo group) using the reaction described in Corey et al. Org. Synth. Coll. 5, 755 (1973).

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

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

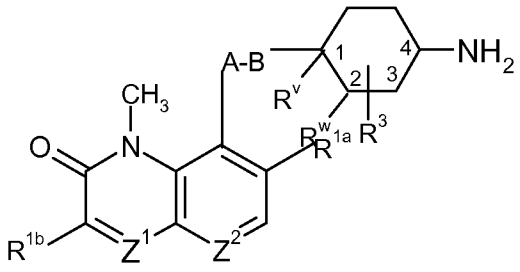
When Q^1 Q^2 together form a protected oxo group this may be an acetal such as ethylenedioxy which can subsequently be removed by acid treatment to give a compound of formula (X):



(X)

wherein the variables are as described for formula (I). The ketone of formula (X) is reacted with an amine $HNR^{2'}R^{4'}$ by conventional reductive alkylation as described above for process variant (iv).

Other intermediates are of formula (XI):



(XI)

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

Conveniently one of $R^{2'}$ and $R^{4'}$ is an N-protecting group, such as such as t-butoxycarbonyl, benzyloxycarbonyl, 9-fluorenylmethyloxycarbonyl or trifluoroacetyl. This may be removed by several methods well known to those skilled in the art (for examples see "*Protective Groups in Organic Synthesis*, T.W. Greene and P.G.M. Wuts, Wiley-Interscience, 1999), for example conventional acid hydrolysis (e.g.trifluoroacetic acid/dichloromethane, hydrochloric acid/dichloromethane/methanol), or potassium carbonate/methanol, liberation of the aminocyclohexane free base (conveniently using a polymer-bound carbonate base), and the free amine converted to NR^2UR^5 by conventional means such as amide formation with an acyl derivative R^5COW, for compounds where U is CO or, where U is CH_2, by alkylation with an alkyl halide R^5CH_2-halide in the presence of base, acylation/reduction with an acyl derivative R^5COW or reductive alkylation with an aldehyde R^5CHO under conventional conditions

(see for examples Smith, M.B.; March, J.M. *Advanced Organic Chemistry*, Wiley-Interscience). Suitable conditions include a borohydride reducing agent such as sodium cyanoborohydride (in methanol/chloroform/acetic acid). If the amine (III) is a hydrochloride salt then sodium acetate may be added to buffer the reaction. Sodium triacetoxyborohydride is an alternative reducing agent.

The appropriate reagents containing the required R^5 group are known compounds or may be prepared analogously to known compounds, see for example WO02/08224, WO02/50061, WO02/56882, WO02/96907, WO2003087098, WO2003010138, WO2003064421, WO2003064431, WO2004002992, WO2004002490, WO2004014361, WO2004041210,WO2004096982, WO2002050036, WO2004058144, WO2004087145, WO06002047, WO06014580, WO06010040, WO06017326, WO06012396, WO06017468, WO06020561, WO2004/035569, WO2004/089947, WO2003082835, WO06002047, WO06014580, WO06010040, WO06017326, WO06012396, WO06017468, WO06020561, WO06132739, WO06134378, WO06137485, WO06081179, WO06081264, WO06081289, WO06081178, WO06081182, WO07016610, WO07081597, WO07071936, WO07115947, WO07118130, WO07122258, WO08006648, WO08003690, WO08009700, WO2007067511 and EP0559285.

Interconversions of A-B, R^v, R^w, R^{1a}, R^{1b}, R^2, R^3 and/or R^4, are conventional. For example R^{1a} halo may be introduced by conventional halogenation reactions eg chlorination with chlorosuccinimide in acetic acid to introduce a chloro group at R^{1a}. In compounds which contain an optionally protected hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N-protecting groups are removed by conventional methods.

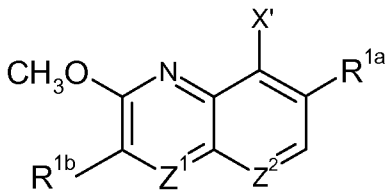
R^{1a} methoxy is convertible to R^{1a} hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland *et al*, *J. Amer. Chem. Soc.*, 1973, 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide, yields R^{1a} substituted alkoxy. R^{1a} halogen is convertible to other R^{1a} by conventional means, for example to hydroxy, alkylthiol (via thiol) and amino using metal catalysed coupling reactions, for example using copper as reviewed in Synlett (2003), 15, 2428-2439 and Angewandte Chemie, International Edition, 2003, 42(44), 5400-5449.

$R^{1a'}$ and $R^{1b'}$ are preferably R^{1a} and R^{1b}.

$R^{3'}$ is R^3 or more preferably hydrogen or hydroxy. Conversions of $R^{3'}$ to R^3 and interconversions of R^3 are carried out conventionally, for example as described in WO2004002992 or WO03087098.

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

Compounds of formula (II) are known compounds or may be prepared analogously to known compounds. For example compounds of formula (II) in which X is OH, Br or CHO, Z^1 is CH and Z^2 is N may be prepared from compounds of formula (IV):

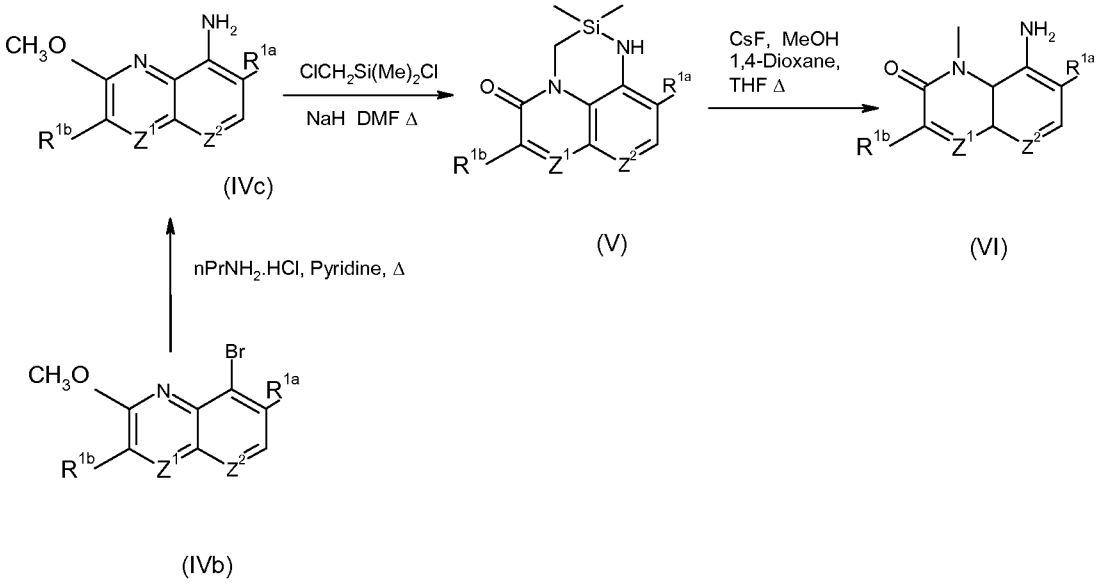


(IV)

,

where Z^1 is CH, Z^2 is N, X' is OH (IVa), see for example WO2008006648.

Compounds of formula (II) where X is NH_2 (VI) may be prepared by the following Scheme 1, from a compound of formula (IV) where X' is NH_2 (IVc) (itself prepared from the 4-bromo analogue (IVb) by heating with n-propylamine hydrochloride in pyridine):

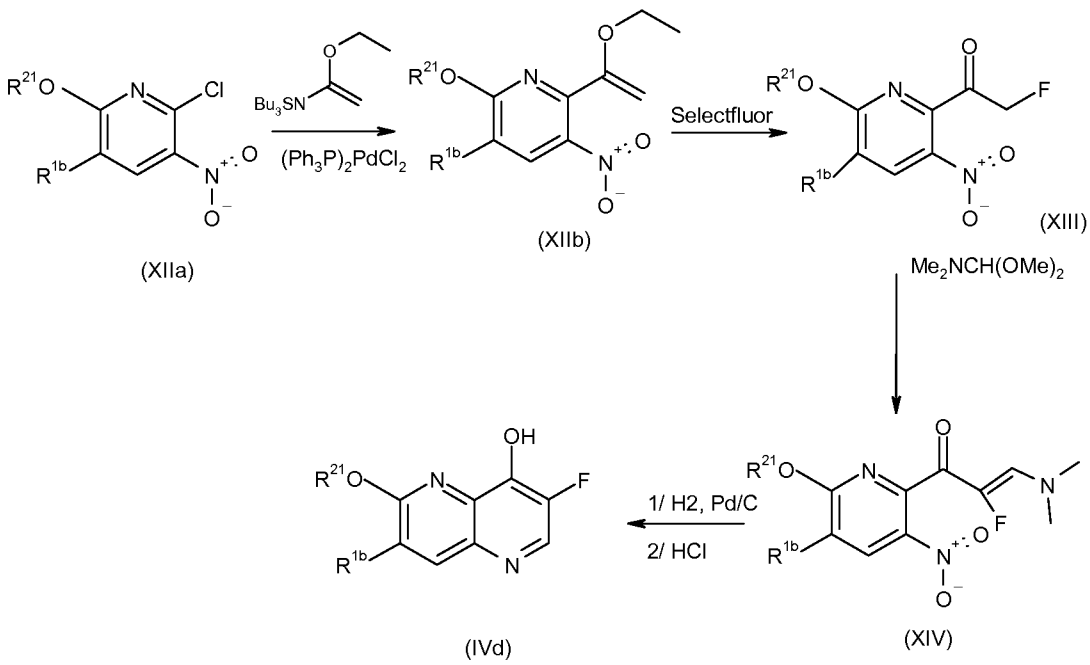


(IVc) (V) (VI)

(IVb)

Scheme 1

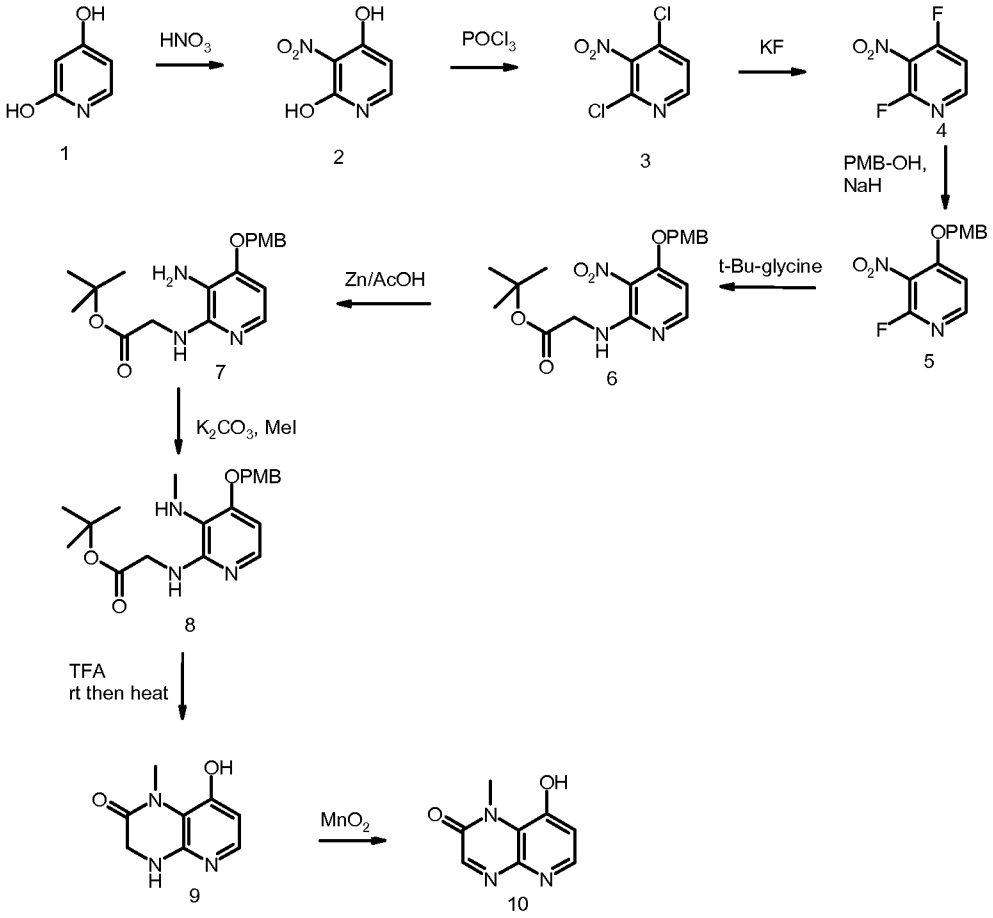
A preparation of compounds of formula (IV) where Z^1 is CH, Z^2 is N ,X is OH and R^{1a} is fluoro (IVd) is shown below in Scheme 2.



Scheme 2

2-Chloro-6-alkoxy-4-nitropyridine (XIIa) is ethoxyvinylated using 1-(ethoxyvinyl)tributylstannane in the presence of dichlorobis(diphenylphosphine) palladium(2). The resulting vinyl ether (XIIb) is fluorinated with a fluorinating agent such as 1-chloromethyl-4-fluoro-1,4-diazoniumbicyclo[2.2.2]octane bis (tetrafluoroborate) Selectfluor® and the resulting fluoroketone (XIII) is treated with dimethylformamide diethylacetal to give dimethylaminovinyl ketone (XIV). This is then hydrogenated to reduce the nitro group and cyclised by treatment with hydrochloric acid to give the 3-fluoro-4-hydroxynaphthyridine (IVd).

Compounds of formula (II) in which Z^1 and Z^2 are N and X=OH may be prepared by the following Scheme 3:



Scheme 3

PMB = para-methoxy benzyl

2,4-pyridinediol **1** is mono-nitrated with, for example nitric acid and converted to the corresponding 2,4-dichloro-3-nitropyridine **3** using standard conditions with a chlorinating agent such as phosphorus oxychloride. Di-substitution by a nucleophilic fluoride source such as potassium fluoride followed by mono-substitution by an alkoxide anion delivers the ether **5**. A protected glycine is introduced under thermal conditions followed by selective reduction of the nitro group with a suitable reducing agent such as zinc in acetic acid,to give the amine **7**. Standard N-methylation with eg methyl iodide followed by acid-mediated cyclisation/deprotection delivers 8-hydroxy-1-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one **9**. The final step is oxidation using a mild oxidant such as activated manganese dioxide to deliver 8-hydroxy-1-methylpyrido[2,3-b]pyrazin-2(1H)-one **10**.

Other compounds of formula (II) may be prepared conventionally. For example a 4-hydroxy-derivative of formula (II) can be converted to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base.

The 4-amino derivatives of formula (II) may be prepared as described in Scheme 1, or by conventional procedures from a corresponding 4-halo, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

The compound of formula (II) where X is –CHO may be prepared from a corresponding 4-vinyl derivative-CH_2=CH_2 by ozonolysis followed by decomposition of the ozonide by conventional means, eg dimethylsulfide (Me_2S).

4-Vinyl derivatives may be prepared by conventional procedures from a corresponding 4-halogeno derivative of formula (II) by e.g. a Heck synthesis as described in e.g. *Organic Reactions*, 1982, 27, 345. Alternatively 4-vinyl derivatives may be prepared from the 4-bromo derivative of formula (II) by conventional procedures such as a Suzuki reaction via trivinylcyclotriboroxane (J.Org. Chem. 2002, 67, 4968-4971), see also WO2008006648.

4-Vinyl derivatives may be converted to 4-hydroxymethyl compounds of formula (II) by ozonolysis with sodium borohydride to decompose the ozonide.

4-Carboxaldehyde and 4-hydroxymethyl derivatives of compounds of formula (II) may be prepared by reduction of 4-carboxy derivatives which may themselves be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art, for example by carbonylation of the corresponding 4-bromo or 4-trifluoromethanesulphonyloxy derivative using a palladium catalyst. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to the 4-carboxaldehyde and 4-hydroxymethyl derivatives with for example lithium aluminium hydride or sodium borohydride. Reaction of the 4-hydroxymethyl derivative with mesyl chloride and triethylamine would give the mesylate derivative, while halogenation with phosphorus oxychloride or triphenylphosphine/carbon tetrachloride would give the halomethyl derivative. The 4-carboxaldehyde may be obtained from from the acid or 4-alkenyl derivative by standard procedures well known to those skilled in the art.

4-Aminomethyl derivatives of formula (II) may be prepared from a 4-CH_2W derivative by displacement with sodium azide to give 4-CH_2N_3 followed by conventional reduction of the azide, or by displacement of the leaving group W with sodium or potassium succinimide followed by cleavage with eg hydrazine or methylhydrazine to give the amine (Gabriel synthesis).

4-Bromo derivatives may be reacted with sodium malonate in DMF to give the malonate which is decarboxylated with eg lithium chloride in wet DMSO, to give the mono-ester (4-carboxymethyl ester).

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

Compounds of formula (II), (III) and (IV) are known compounds or may be prepared analogously to known compounds, see for example WO2008006648 for compounds of formula (II), WO2003087098 and WO2004002992 for compounds of formula (III) and WO2004058144, WO0021948, WO2002096907, WO2003087098, WO2003010138 and WO2008006648 for compounds of formula (IV).

Further details for the preparation of compounds of formula (I) are found in the examples.

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 may be formulated for administration by any route and 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 compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, 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 50-1000 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 about 1.5 to about 50 mg/kg per day. Suitably the dosage is from 5 to 30 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) may be used in the treatment of bacterial infections caused by a wide range of organisms including both Gram-negative and Gram-positive organisms, such as upper and/or lower respiratory tract infections, skin and soft tissue infections and/or urinary tract infections. Compounds of formula (I) may be also used in the treatment of tuberculosis caused by *Mycobacterium tuberculosis*. Some compounds of formula (I) may be active against more than one organism. This may be determined by the methods described herein.

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 including *Mycobacterium tuberculosis*.

Examples and Experimental

General

Abbreviations in the examples:

MS = mass spectrum

ES = Electrospray mass spectroscopy

HPLC = High Performance Liquid Chromatography

MDAP or Mass directed autoprep = mass directed preparative HPLC

Psi = pounds per square inch. 1psi = 0.069bar or 6.9kPa

rt = room temperature

Certain reagents are also abbreviated herein. DMF refers to dimethylformamide, TFA refers to trifluoroacetic acid, THF refers to tetrahydrofuran, Pd/C refers to palladium on carbon catalyst, DCM refers to dichloromethane, MeOH refers to methanol, Et2O refers to diethyl ether, EtOAc refers to ethyl acetate. DIAD refers to diisopropyl azodicarboxylate.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 or 250 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. All temperatures are reported in degrees Celsius.

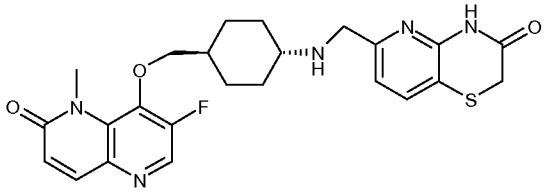
MP-carbonate refers to macroporous triethylammonium methylpolystyrene carbonate (Argonaut Technologies).

The SCX (Strong Cation eXchange) column has benzene sulphonic acid covalently attached to a silica support and as such strongly retains high pKa (ie basic) organic molecules such as amines, which can be subsequently liberated with excess ammonia in an appropriate solvent.

As will be understood by the skilled chemist, references to preparations carried out in a similar manner to, or by the general method of, other preparations, may encompass variations in routine parameters such as time, temperature, workup conditions, minor changes in reagent amounts etc.

Reactions involving metal hydrides including lithium hydride, lithium aluminium hydride, di-isobutylaluminium hydride, sodium hydride, sodium borohydride and sodium triacetoxyborohydride are carried out under argon or other inert gas.

Example 1 6-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one hydrochloride



(a) 2-[1-(Ethyloxy)ethenyl]-6-(methyloxy)-3-nitropyridine

2-Chloro-6-methoxy-3-nitropyridine (600g, 3.18mol) and dichlorobis(triphenylphosphine)palladium (II) (33.5g, 477mmol) were dissolved in acetonitrile (4200ml). The yellow coloured suspension was heated to 65°C and (1-ethoxyvinyl)-tributyl-stannane (1182ml, 1264g.) was added dropwise over 2 hours, maintaining the temperature at ~65°C by the rate of addition. The resulting brown coloured suspension was left to stir at 65°C for 4 hours then left to cool to room temperature, with stirring, overnight.

The reaction mixture was quenched with 10% potassium fluoride aq. solution (3600ml) with vigorous stirring and left to stir for 1 hour. The resulting solid was removed by vacuum filtration and washed with acetonitrile (2 x 3000ml). The layers were separated and the organic layer was evaporated to 3000ml. This was filtered, ethyl acetate (3600ml) was added and the volume reduced by rotary evaporation to 1800ml. Cyclohexane (3600ml) was added and the volume reduced by rotary evaporation to 3000ml. Cyclohexane (2400ml) and silica gel (600g) were added and allowed to stir at r.t. for 1.5 h. The solid was removed by vacuum filtration and washed with ethyl acetate:cyclohexane, 1:8 (4200ml). The filtrate was reduced to 1800 ml. The last four steps were repeated, and finally the solvents were evaporated. Acetonitrile (2000ml) was added and evaporated to give an orange coloured oil (730.3g, 102.4%).

^{1}H NMR confirmed correct structure with ~8% MeCN.

(b) 2-Fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]ethanone

1-Chloromethyl-4-fluoro-1,4-diazoniumbicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor®) (1300g, 3.67mol) was dissolved in acetonitrile (2060ml) and water (820ml). A solution of 2-[1-(ethyloxy)ethenyl]-6-(methyloxy)-3-nitropyridine (730g, 3.18mol) in acetonitrile (1425ml) was added dropwise to the white suspension over 1.5h, maintaining the temperature below 15°C using an ice/water bath. The resulting yellow coloured solution was left to stir at r.t. overnight. The reaction mixture was quenched with sat. aq. sodium bicarbonate (2140ml) and left to stir for 30 minutes. The volume was reduced by rotary evaporation to 3250ml. To the resulting yellow suspension was

added ethyl acetate (4400ml) and water (720 ml) and this was stirred for 15 min. The layers were separated and the aqueous extracted with ethyl acetate (2 x 1000ml). The organic layers were combined and washed with water (1000ml) and sat. brine (1000ml). The organic layer was dried over $MgSO_4$ (269g), filtered and evaporated. Acetonitrile (1000ml) was added and evaporated to give an orange oil (715.4g, 105.0%)

(c) 3-(Dimethylamino)-2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]-2-propen-1-one

To a solution of 2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]ethanone (715.4g, 3.18moles maximum) in toluene (2700 ml) was added *N,N*-dimethylformamide dimethylacetal (1550ml). The solution turned dark brown in colour. The reaction mixture was heated to 50°C and left to stir for 3 hours, under N_2. Product precipitated out after ~1 h. The reaction was stirred for a further 45 min at 50°C. Cyclohexane (2000ml) was added and the reaction mixture left to cool slowly over 1 h, then to 10°C using an ice/water bath. The solid was collected by vacuum filtration and washed with ethyl acetate:cyclohexane, 1:1 (3 x 1000ml), then dried in the oven, under vacuum at 40°C overnight to give a yellow solid (591.5g, 69.0 %).

(d) 3-Fluoro-6-(methyloxy)-1,5-naphthyridin-4-ol

3-(Dimethylamino)-2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]-2-propen-1-one (591g, 2.20mol) was dissolved in DMF (6100ml) by warming to 40°C and hydrogenated over 5 % Pd/C (140g water wet, 59g actual) at 15 psi and 40°C for 2.5h. The reaction mixture was warmed to 60°C and filtered hot to remove the catalyst. Further DMF was added to bring the total volume to 11800ml and the dark yellow solution was cooled to 5°C using an ice/water bath. 6N hydrochloric acid (368ml, 2.20mol) was added dropwise to the reaction mixture over 30 minutes, with temperature maintained below 10°C. The reaction was allowed to warm to room temperature and left to stir overnight. The volume was reduced to ~4000ml by rotary evaporation at 50°C. The yellow suspension was cooled to 10°C using an ice/water bath. Water (5900ml) was added slowly over 30 minutes, temperature maintained below 15°C. The reaction mixture was stirred vigorously for 30 minutes at 7°C. The solid was collected by vacuum filtration and washed with water (2950ml) then ethyl acetate:cyclohexane, 1:1 (3 x 2000ml), then dried in the oven, under vacuum at 50°C for 4 days to give a pale brown solid (339.8g, 79.7 %).

MS: *m/z* 195.0 [MH^+], 216.9 [MNa^+].

(e) 10-Fluoro-2,2-dimethyl-2,3-dihydro-5*H*-[1,4,2]oxazasilino[6,5,4-*de*]-1,5-naphthyridin-5-one

To a solution of 3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-ol (15g, 77.25mmol) in dry dimethyl formamide (500ml) was added sodium hydride (60% in oil, 6.18g, 154.5mmol) in portions. The mixture was stirred for 1.5h, then chloro(chloromethyl)dimethylsilane (19.5ml, 136.35mmol) was added dropwise by syringe. The mixture was stirred for 1h at room temperature, then heated at 100°C overnight. Solvent was evaporated, toluene was added and evaporated, and the residue was dissolved in dichloromethane/methanol and evaporated onto silica gel. Chromatography on silica, eluting with 5-20% methanol/dichloromethane, gave the title compound (16.0g, 83%).
MS (+ve ion electrospray): *m/z* 251 [MH^+].

(f) 7-Fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1*H*)-one

10-Fluoro-2,2-dimethyl-2,3-dihydro-5*H*-[1,4,2]oxazasilino[6,5,4-*de*]-1,5-naphthyridin-5-one (16.03g, 64.1mmol) and caesium fluoride (29.0g, 192mmol) were stirred at 85°C (external temp.) in 1,4-dioxine (700ml) and methanol (350ml) for 4 days. Solvent was evaporated and the residue was dissolved in a minimal volume of water and methanol. The resulting solution was acidified to pH4 with dil. HCl and the solid product was filtered off, washed with a little water and methanol and dried under vacuum at 60°C to give the title compound (12.97g, 100%).
MS (+ve ion electrospray): *m/z* 195 [MH^+].

(g) 1,1-Dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate

trans-4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (commercially available or for a preparation see Example 18A(a)) (19.1g) in THF (300ml) was treated dropwise with borane-dimethyl sulphide (2M in THF, 43.2ml, diluted with 200ml THF). The mixture was stirred briefly then left overnight before evaporation. The residue was dissolved in methanol and evaporated again. This was repeated twice before chromatography on silica, eluting with 50-100% ether/hexane, to give the alcohol (12.3g, 68%).

(h) [*trans*-4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl methanesulfonate

A solution of 1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (6.1g, 26.6mmol) and triethylamine (3.66ml) in dichloromethane (240ml) was cooled in ice and methanesulfonyl chloride (2.07ml) was added by syringe. The mixture was stirred for 1h while warming to room temperature, then left overnight. The mixture was washed with aq. sodium bicarbonate, the aqueous phase was extracted twice with

dichloromethane and the organic fractions were dried and evaporated to give the methanesulfonate (8.2g).
MS (+ve ion electrospray): *m/z* 330 [MNa^+], 252 [(MH^+)-C_4H_8].

(i) 1,1-Dimethylethyl (trans-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate

A suspension of 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1*H*)-one (0.30 g) in dry DMF (25 ml) was treated portionwise with sodium hydride (60% suspension in oil: 78 mg) and the mixture was heated at 50°C (with occasional sonication) for 30 minutes. [*trans*-4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl methanesulfonate (0.474 g) was added and the mixture was heated at 110°C for 48 hours, cooled, evaporated, quenched with water, extracted with chloroform and dried (sodium sulphate). The product was chromatographed on silica (methanol-DCM) to afford an oil (0.30 g).
LC/MS (+ve ion electrospray): *m/z* 406 [MH^+] , 428 [MNa^+].

Alternative synthesis of intermediate of Example 1(i)
(1) [trans-4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl ethanesulfonate

A partial solution of (1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (for a preparation see Example 1(g)) (3.3905 g, 14.79 mmol) in dry dichloromethane (100ml) was stirred and cooled in ice and treated with triethylamine (2.081 ml, 14.93 mmol) followed by ethanesulphonyl chloride (1.415 ml, 14.93 mmol) added dropwise. The resulting cloudy solution was stirred thus for 0.5hrs then allowed to warm to 21°C and stirred thus for 4 hrs then stood overnight. The reaction was washed with sat aq $NaHCO_3$ solution and the aqueous phase extracted with DCM (x2). The combined organic fractions were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give a white solid (4.88g, 103%). This was used in subsequent reactions without further purification.
MS (ES+) m/z 322 [MH^+].

(2) 1,1-Dimethylethyl (trans-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate

A suspension of 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 1(f)) (100 mg, 0.515 mmol) in dry N,N-dimethylformamide (15 mL) was stirred at 21°C and treated with potassium carbonate (78 mg, 0.567 mmol). The resulting slight suspension was heated at 60°C (bath temp) for 30 mins then ([trans-4-

({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl ethanesulfonate (166 mg, 0.515 mmol) added. The resulting mixture was then heated at 120 °C overnight. The reaction was then allowed to cool, evaporated in vacuo, quenched with water and extracted with $CHCl_3$, then 10%MeOH/$CHCl_3$ (x2). The combined organic fractions were washed with brine, dried (Na_2SO_4) and evaporated in vacuo to give a brown gum (210mg) which was purified on a silica column using DCM/MeOH (100/0-90/10) as a gradient eluent which gave a pale yellow oil which crystallised (149mg, 71%).
MS (ES+) m/z 406 [MH^+].

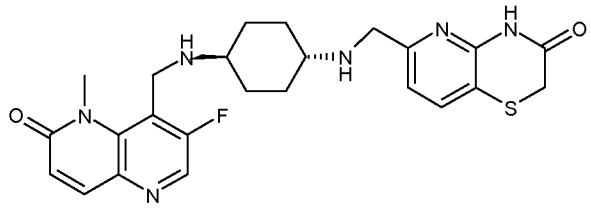
(j) 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride

1,1-Dimethylethyl (trans-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate (0.40g) in dry methanol (10ml) and dry DCM (20ml) was treated with 4M HCl in 1,4-dioxane (20ml), stirred at room temperature for 2 hours and evaporated to give a solid.
LC/MS (+ve ion electrospray): *m/z* 306 [MH^+].

(k) Title compound

8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (60mg) was dissolved in dry methanol (2ml), chloroform (2ml) and acetic acid (6 drops). Anhydrous sodium acetate (115mg) was added followed by 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde (for a synthesis see WO2004058144, Example 7(d)) (45.4mg) and excess 3A molecular sieves. The mixture was stirred at room temperature for 2.5 hours then sodium cyanoborohydride (50mg) was added and the mixture was stirred at room temperature for 3.5 hours. Aqueous sodium carbonate was added and the mixture extracted with dichloromethane, dried (sodium sulphate), evaporated and chromatographed on silica gel (0-15% methanol-DCM) to afford the free base. It was treated with 4M hydrogen chloride in 1,4-dioxane and the solution was evaporated to give the title compound (37mg), after trituration with ether.
^{1}H NMR (CD_3OD) δ 1.35 (2H, q), 1.55 (2H, q), 2.00 (1H, br.s) 2.13 (2H, d), 2.31 (2H, d), 3.22 (1H, m), 3.58 (2H, s), 3.94 (3H, s), 4.16 (2H, m), 4.33 (2H, s), 6.86 (1H, d), 7.12 (1H, s), 7.82 (1H, d), 7.90 (1H, d), and 8.48 (1H, s).
LC/MS (+ve ion electrospray): *m/z* 484 [MH^+].

Example 2 6-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)methyl]amino}cyclohexyl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one dihydrochloride



(a) 8-Bromo-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

A suspension 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 1(f)) (12.97g, 66.9mmol) in dimethylformamide (500ml) was cooled in ice and phosphorus tribromide (9.98ml, 105mmol) was added dropwise over 5min. The resulting mixture was stirred for 3.75h at room temperature, then evaporated. Toluene was added and evaporated off, then the residue was cooled in ice, treated cautiously with aq. sodium bicarbonate until basic, then extracted four times with dichloromethane. The extracts were dried and evaporated to give the title compound (14.75g, 86%).

MS (+ve ion electrospray): *m/z* 257& 259 [MH^+].

(b) 8-Ethenyl-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

A solution of 8-bromo-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (2.0g, 7.81mmol) in 1,2-dimethoxyethane (80ml) was flushed with argon, then tetrakis(triphenylphosphine)palladium (0) (0.53g, 0.44mmol), potassium carbonate (1.31g), triethenylboroxin pyridine complex (1.69g, 7.11mmol) and water (20ml) were added. The mixture was heated under reflux for 6h, then water and diethyl ether were added and the phases were separated. The aqueous phase was extracted with ether three times, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-100% ethyl acetate/ hexane, gave the title compound (1.62g, 100%).

MS (+ve ion electrospray): *m/z* 205 [MH^+].

(c) 3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-4-carbaldehyde

A solution of 8-ethenyl-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (0.47g, 2.3mmol) in dichloromethane (100ml) was cooled to -78°C and ozone in oxygen was passed through the solution for1h. The mixture was flushed with oxygen and argon, then methyl sulfide (12ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with dichloromethane and washed with brine/sodium bicarbonate. The aqueous phase was extracted thoroughly with dichloromethane, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-10% methanol/dichloromethane, gave the title compound (90mg, 19%).

MS (+ve ion electrospray): *m/z* 207 [MH^+].

(d) 1,1-Dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)methyl]amino}cyclohexyl)carbamate

3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-4-carbaldehyde (90mg, 0.44mmol) and 1,1-dimethylethyl (*trans*-4-aminocyclohexyl)carbamate hydrochloride (165mg, 0.66mmol) were stirred overnight in dry chloroform/methanol (1:1, 6ml) with sodium acetate (270mg), acetic acid (10 drops) and 3A molecular sieves. Sodium cyanoborohydride (82mg) was added and the mixture was stirred for 6h, then basified with aq. sodium bicarbonate and extracted well with dichloromethane. The extracts were dried and evaporated. Chromatography on silica, eluting with 0-2% methanol/dichloromethane, gave the title compound as a solid (120mg, 67%).
MS (+ve ion electrospray): *m/z* 405 [MH^+], 349 [(MH^+)-C_4H_8]

(e) 8-{[(*trans*-4-Aminocyclohexyl)amino]methyl}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

A solution of 1,1-dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)methyl]amino}cyclohexyl)carbamate (120mg, 0.3mmol) in dichloromethane (2ml) was treated dropwise with trifluoroacetic acid (2ml). After standing at room temperature for 1.75h, the mixture was evaporated. The residue was triturated twice with ether, then dissolved in dichloromethane/methanol (30-40ml) and stirred with MP-carbonate resin (1.2mmol) until the mixture was basic to damp pH indicator paper. The resin was filtered off, washed several times alternately with 10% dichloromethane/methanol and methanol and the liquors evaporated to give the title compound (114mg, approx. 80% pure).
MS (+ve ion electrospray): *m/z* 305 [MH^+], 288 [(MH^+)- NH_3].

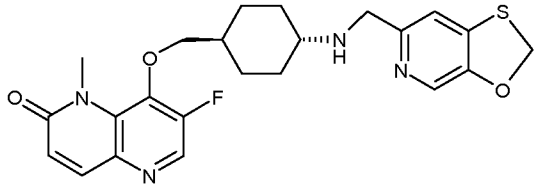
(f) Title compound

8-{[(*trans*-4-Aminocyclohexyl)amino]methyl}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (0.15mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde (for a synthesis see WO 2004058144 Example 7(d)) (29mg, 0.15mmol) were stirred for 1.75h in dry chloroform/methanol (1:1, 4ml) with acetic acid (6 drops) and 3A molecular sieves. Sodium cyanoborohydride (34mg) was added and the mixture was stirred for 4.5h, then basified with aq. sodium bicarbonate and extracted well with dichloromethane/methanol. The extracts were dried and evaporated. Chromatography on silica, eluting with 0-20% methanol/dichloromethane, gave the free base of the title compound (31mg, 43%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.39(1H, s), 7.84(1H, d), 7.58(1H, d), 6.97(1H, d), 6.86(1H, d), 4.08(3H, s), 4.04(2H d), 3.86(2H, s), 3.49(2H, s), 2.61(1H m), 2.51(1H m), 2.05(4H, m), 1.23(4H, m).
MS (+ve ion electrospray): *m/z* 483 [MH^+].

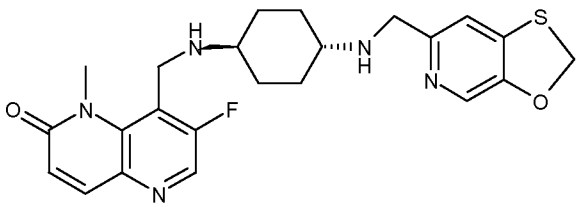
The free base was treated with 2 mole equivalents of 0.4M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (34mg).

Example 3 7-Fluoro-1-methyl-8-[({*trans*-4-[([1,3]oxathiolo[5,4-*c*]pyridin-6-ylmethyl)amino]cyclohexyl}methyl)oxy]-1,5-naphthyridin-2(1*H*)-one hydrochloride



The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (60mg) and [1,3]oxathiolo[5,4-*c*]pyridine-6-carbaldehyde (39mg) (for a synthesis see WO2004058144, Example 61) by the general method of Example 1(k). The crude product, after work-up, was chromatographed on a reverse-phase HPLC system with mass-directed collection (eluent acetonitrile/water/formic acid, monitoring for *m/z* 457) followed by treatment with 4M hydrogen chloride in 1,4-dioxane. The solution was evaporated to give the title compound (31 mg), after trituration with ether.
^{1}H NMR (CD_3OD) δ 1.35 (2H, q), 1.55 (2H, q), 2.00 (1H, br.s) 2.13 (2H, d), 2.30 (2H, d), 3.22 (1H, m), 3.58 (2H, s), 3.94 (3H, s), 4.20 (2H, m), 4.32 (2H, s), 5.90 (2H, s), 6.90 (1H, d), 7.48 (1H, s), 7.90 (1H, d), 8.10 (1H, d), and 8.54 (1H, s).
LC/MS (+ve ion electrospray): *m/z* 457 [MH^+].

Example 4 7-Fluoro-1-methyl-8-[({*trans*-4-[([1,3]oxathiolo[5,4-*c*]pyridin-6-ylmethyl)amino]cyclohexyl}amino)methyl]-1,5-naphthyridin-2(1*H*)-one dihydrochloride



8-{[(*trans*-4-Aminocyclohexyl)amino]methyl}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 2(e)) (0.15mmol) and [1,3]oxathiolo[5,4-*c*]pyridine-6-carbaldehyde (for a synthesis see WO2004058144,

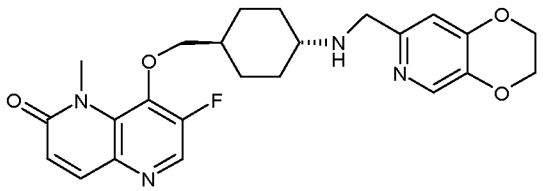
Example 61) (25mg, 0.15mmol) were stirred overnight in dry chloroform/methanol (1:1, 4ml) with acetic acid (6 drops) and 3A molecular sieves. Sodium cyanoborohydride (34mg) was added and the mixture was stirred for 6h, then diluted with dichloromethane and basified with aq. sodium bicarbonate. The aqueous phase was extracted a few times with dichloromethane/methanol, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-20% methanol/dichloromethane, gave the free base of the title compound (26mg, 38%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38(1H, s), 8.01(1H, s), 7.84(1H, d), 7.19(1H, s), 6.86(1H, d), 5.74(2H, d), 4.08(3H, s), 4.04(2H d), 3.85(2H, s), 2.58(2H m), 2.05(4H, m), 1.23(4H, m).

MS (+ve ion electrospray): *m/z* 456 [MH^+].

The free base was treated with 2 mole equivalents of 0.4M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (30mg).

Example 5 8-[({*trans*-4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]cyclohexyl}methyl)oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride

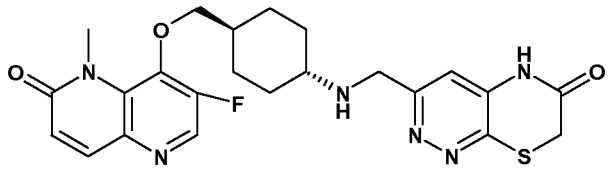


The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (60mg) and 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(c) or WO2003087098 Example 19(d)) (38.5mg), by the general method of Example 1(k). The crude product, after work-up, was chromatographed on a reverse-phase HPLC system with mass-directed collection (MDAP) (eluent acetonitrile/water/formic acid, monitoring for *m/z* 455) followed by treatment with 4M hydrogen chloride in 1,4-dioxane. The solution was evaporated to give the title compound (41 mg), after trituration with ether.

^{1}H NMR δ(CD_3OD) 1.35 (2H, q), 1.55 (2H, q), 2.05 (1H, br.s) 2.13 (2H, d), 2.35 (2H, d), 3.32 (1H, m), 3.96 (3H, s), 4.29 (2H, m), 4.51 (4H, s), 4.64 (2H, m), 6.95 (1H, d), 7.64 (1H, s), 7.91 (1H, d), 8.54 (1H, s), and 8.62 (1H, d).

LC/MS (+ve ion electrospray): *m/z* 455 [MH^+].

Example 6 3-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-5*H*-pyridazino[3,4-*b*][1,4]thiazin-6(7*H*)-one hydrochloride

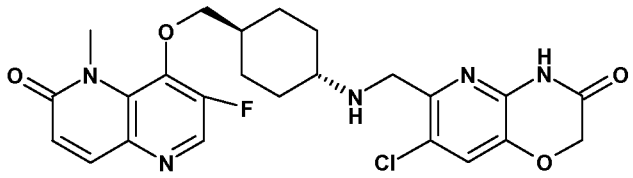


The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (80 mg) and 6-oxo-6,7-dihydro-5H-pyridazino[3,4-b][1,4]thiazine-3-carbaldehyde (for a synthesis see WO2004058144, Example 58) (50% pure; 91 mg) by the general method of Example 1(k) (elution with 0-20% methanol-DCM in the silica gel chromatography) to give a yellow solid (31 mg), after conversion to a hydrochloride salt.

^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.15 (4H, q), 1.87 (1H, br.s) 1.93 (2H, d), 2.10 (2H, d), 2.55 (1H, m), 3.65 (2H, s), 3.92 (3H, s), 4.05 (2H, m), 4.11 (2H, s), 6.87 (1H, d), 7.08 (1H, s), 7.81 (1H, d), and 8.38 (1H, s).

LC/MS (+ve ion electrospray): *m/z* 485 [MH^+].

Example 7 7-Chloro-6-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one hydrochloride

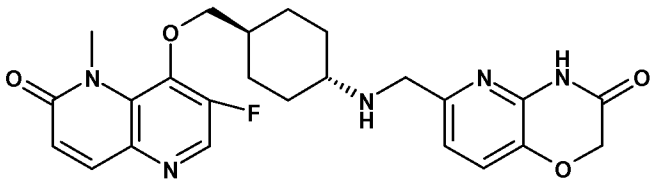


The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (35 mg) (for a synthesis see WO2003064421, Example 15(c)) by the general method of Example 1(k) to give a yellow solid (29 mg), after conversion to the hydrochloride salt.

^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.15 – 1.35 (4H, m), 1.87 (1H, br.s) 1.93 (2H, d), 2.12 (2H, d), 2.53 (1H, m), 3.92 (3H, s), 3.98 (2H, s), 4.04 (2H, m), 4.65 (2H, s), 6.85 (1H, d), 7.26 (1H, s) (underneath $CHCl_3$ signal), 7.82 (1H, d), and 8.37 (1H, s).

LC/MS (+ve ion electrospray): *m/z* 502/4 [MH^+].

Example 8 6-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one hydrochloride

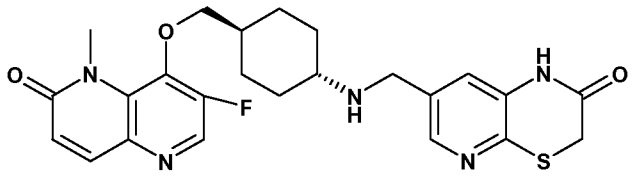


The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (29 mg) (for asynthesis see WO2004058144, Example 1(l)) by the general method of Example 1(k) to give a yellow solid (56 mg), after conversion to the hydrochloride salt.

^{1}H NMR (400 MHz) (HCl salt) (MeOD) δ 1.32 (2H,q),1.56 (2H, q), 2.00 (1H, br.s) 2.12 (2H, d), 2.32 (2H, d), 3.22 (1H, m), 3.65 (2H, s), 3.95 (3H, s), 4.25 (2H, m), 4.28 (2H, s), 4.70 (2H, s), 6.92 (1H, d), 7.11 (2H, d), 7.45 (2H, d), 7.90 (1H, d), and 8.59 (1H, s).

LC/MS (+ve ion electrospray): *m/z* 468 [MH^+].

Example 9 7-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one hydrochloride

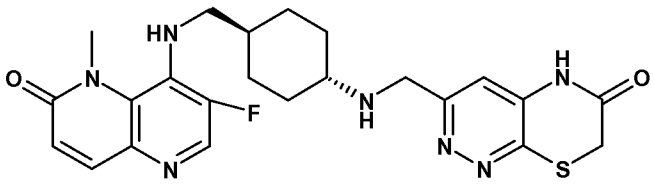


The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (80 mg) and 2-oxo-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]thiazine-7-carboxaldehyde (for a synthesis see WO2004058144, Example 48(e)) by the general method of Example 1(k) to give a yellow solid (46 mg) after conversion to the HCl salt.

^{1}H NMR (400 MHz) (free base; CDCl3) δ 1.16 (4H, q), 1.88 (1H, br.s) 1.93 (2H, d), 2.08 (2H, d), 2.50 (1H, m), 3.57 (2H, s), 3.83 (2H, s), 3.92 (3H, s), 4.03 (2H, m), 6.85 (1H, d), 7.20 (1H, s), 7.80 (1H, d), 8.15 (1H, s), and 8.38 (1H, s).

LC/MS (+ve ion electrospray): *m/z* 484 [MH^+].

Example 10 3-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)amino]methyl}cyclohexyl)amino]methyl}-5*H*-pyridazino[3,4-*b*][1,4]thiazin-6(7*H*)-one dihydrochloride



(a) 3-Fluoro-6-(methyloxy)-1,5-naphthyridin-4-amine

A mixture of 8-bromo-7-fluoro-2-(methoxy)-1,5-naphthyridine (for a preparation see WO200458144 Ex 53(g)) (25 g), n-propylamine hydrochloride (55 g) in dry pyridine (800 ml) was heated at 115 °C for 4 days, cooled, evaporated and azeotroped (x2) with toluene. Sodium bicarbonate was added and the mixture was extracted with DCM, dried (sodium sulphate), evaporated and chromatographed on silica gel (methanol-DCM) to give the amine (11.0 g) (ca. 75% pure).
LC/MS (+ve ion electrospray): *m/z* 194 [MH^+].

(b) 10-Fluoro-2,2-dimethyl-2,3-dihydro-1*H*,5*H*-[1,4,2]diazasilino[6,5,4-*de*]-1,5-naphthyridin-5-one

The title compound was prepared from 3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-amine (1.8 g), sodium hydride (0.58 g), chloro(chloromethyl)dimethylsilane (2.4 ml) in DMF (40 ml) by the general method of Example (1e) to give a solid.
LC/MS (+ve ion electrospray): *m/z* 250 [MH^+].

(c) 8-Amino-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

The title compound was prepared from crude 10-fluoro-2,2-dimethyl-2,3-dihydro-1*H*,5*H*-[1,4,2]diazasilino[6,5,4-*de*]-1,5-naphthyridin-5-one and caesium fluoride (7.0 g) by the general method of Example 1(f) (heated at 110°C for 24 hours). The crude product was chromatographed on silica gel (methanol-DCM) to give a solid (0.78 g).
LC/MS (+ve ion electrospray): *m/z* 194 [MH^+].

(d) 1,1-Dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)amino]methyl}cyclohexyl)carbamate

The title compound was prepared from 8-amino-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (0.78 g) and [*trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl methanesulfonate (for a preparation see Example 1(h)) (1.365 g) by the general method of Example 1(i) (heated at

110 – 115°C for 48 hours) to give an oil (0.75 g) (after chromatography, and azeotroping with toluene to remove DMF) [contains 20% of mesylate impurity].
LC/MS (+ve ion electrospray): *m/z* 405 [MH^+].

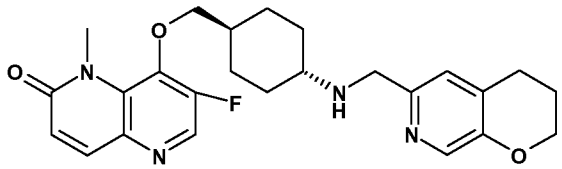
(e) 8-{[(*trans*-4-Aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

The title compound was prepared from 1,1-dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)amino]methyl}cyclohexyl)carbamate (0.8 g) with HCl-1,4-dioxane by the general method of Example 1(j), followed by treatment with MP-carbonate resin (2.8-3.5 mmol/g) (3.0 g) in DCM-methanol (1:1) (50 ml) for 5 hours at room temperature, to give the oily free base. It was chromatographed on silica gel [DCM-methanol-0.88 ammonia (90:9:1)] to give a brown solid (0.34 g).
LC/MS (+ve ion electrospray): *m/z* 305 [MH^+].

(f) Title compound

The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (62 mg; 95% purity) and 6-oxo-6,7-dihydro-5H-pyridazino[3,4-b][1,4]thiazine-3-carboxaldehyde (for a synthesis see WO2004058144, Example 58)) (50% pure; 76 mg) by the general method of Example 1(k) to give a yellow solid (26 mg) after conversion to the dihydrochloride salt.
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 0.99 (2H, q), 1.10 (2H, q), 1.48 (1H, br. s), 1.82 (2H, d), 2.02 (2H, d), 2.47 (1H, m), 2.95 (2H, m), 3.63 (2H, s), 3.88 (3H, s), 4.05 (2H, m), 4.09 (2H, s), 6.83 (1H, d), 7.10 (1H, s), 7.80 (1H, d), and 8.30 (1H, s).
LC/MS (+ve ion electrospray): *m/z* 484 [MH^+].

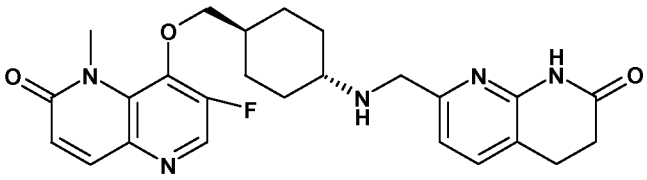
Example 11 8-[({*trans*-4-[(3,4-Dihydro-2*H*-pyrano[2,3-*c*]pyridin-6-ylmethyl)amino]cyclohexyl}methyl)oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride



The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-carbaldehyde (for a synthesis see WO2004058144, Example 126(e)), by the general method of Example 1(k). The chromatographed product was

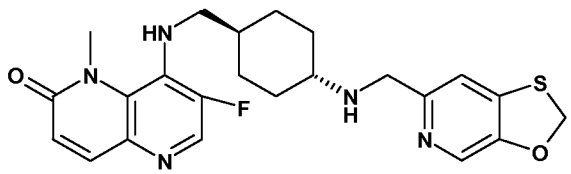
further purified by chromatography on a reverse-phase HPLC system with mass-directed collection (eluent acetonitrile/water/formic acid, monitoring for M 452), to give a white solid (20 mg) after conversion to the title hydrochloride salt..
LC/MS (+ve ion electrospray): *m/z* 453 [MH^+].

Example 12 7-Fluoro-1-methyl-8-{[(trans-4-{[(7-oxo-1,5,6,7-tetrahydro-1,8-naphthyridin-2-yl)methyl]amino}cyclohexyl)methyl]oxy}-1,5-naphthyridin-2(1H)-one hydrochloride



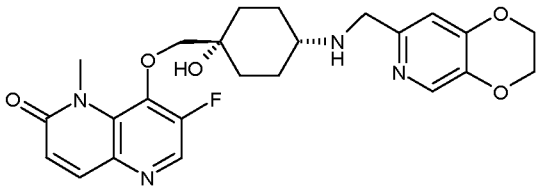
The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (80 mg) and 7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridine-2-carboxaldehyde (42 mg) (for a synthesis see WO2003087098, Example 307(f)) by the general method of Example 1(k). The product was chromatographed on silica gel (0-15% methanol-DCM) and the second eluted product was converted to the title hydrochloride salt (16 mg).
LC/MS (+ve ion electrospray): *m/z* 466 [MH^+].

Example 13 7-Fluoro-1-methyl-8-[({*trans*-4-[([1,3]oxathiolo[5,4-*c*]pyridin-6-ylmethyl)amino]cyclohexyl}methyl)amino]-1,5-naphthyridin-2(1*H*)-one dihydrochloride



The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 10(e)) (65 mg; 90% purity) and [1,3]oxathiolo[5,4-*c*]pyridine-6-carbaldehyde (for a synthesis see WO2004058144, Example 61) (32.5 mg) by the general method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (71 mg) after conversion to the title dihydrochloride salt).
LC/MS (+ve ion electrospray): *m/z* 456 [MH^+].

Example 14 8-[({*cis*-4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]-1-hydroxycyclohexyl}methyl)oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one dihydrochloride



(a) 1,1-Dimethylethyl (3*s*,6*s*)-1-oxaspiro[2.5]oct-6-ylcarbamate

A solution of trimethylsulphoxonium iodide (7.74g, 35.2 mmol) in dry dimethylsulphoxide (150ml) was treated portionwise with sodium hydride (60% in oil, 1.40g, 35.1 mmol) at 0°C. The mixture was stirred for 30 min. at 0-10°C, then 1,1-dimethylethyl (4-oxocyclohexyl)carbamate (5.0g, 23.5 mmol) was added in portions. The mixture was stirred for 1h at 10-16°C, then refrigerated overnight. After warming to room temperature, water (400ml) was added and the mixture was extracted three times with ether. The extracts were dried and evaporated, and the crude product was recrystallised twice from ethyl acetate/petroleum ether to give a solid (1.93g, 36%). NMR analysis showed <5% other isomer present.

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.47(1H, br.), 3.57(1H, br.m), 2.66(2H, s), 1.94(4H, br.m), 1.52(2H, dd), 1.45(9H, s), 1.35(2H, m).

(b) 1,1-Dimethylethyl (*cis*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}-4-hydroxycyclohexyl)carbamate

To a suspension of sodium hydride (60% in oil, 0.022g, 0.56 mmol) in dry dimethylformamide (6ml) was added 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 1(f)) (0.10g, 0.51 mmol). After stirring at room temperature for 45 min., 1,1-dimethylethyl (3*s*,6*s*)-1-oxaspiro[2.5]oct-6-ylcarbamate (0.12g, 0.51 mmol) was added and the mixture was heated at 110°C overnight. Another portion of the epoxide (0.12g) was added and heating continued for 3 days. The mixture was evaporated and the residue was dissolved in dichloromethane/water. The aqueous phase was extracted several times with dichloromethane and the extracts were dried and evaporated. Chromatography on silica gel, eluting with 0-20% methanol/dichloromethane gave the title compound (39mg, 18%).

MS (+ve ion electrospray): *m/z* 444 [MNa^+], 366 [(MH^+)-C_4H_8], 322 [(MH^+)-$C_5H_8O_2$].

(c) 8-{[(*cis*-4-Amino-1-hydroxycyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one dihydrochloride

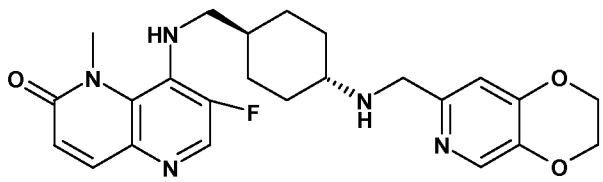
A solution of 1,1-dimethylethyl (*cis*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}-4-hydroxycyclohexyl)carbamate (39mg, 0.093 mmol) in dichloromethane (1ml), methanol (0.5ml) and 4M hydrogen chloride/1,4-dioxane (1.5ml) was stirred for 1.5h, then evaporated to dryness to give a solid (36mg, 98%).
MS (+ve ion electrospray): *m/z* 322 [MH^+].

(d) Title compound

This was prepared from 8-{[(*cis*-4-amino-1-hydroxycyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one dihydrochloride (36mg) and 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(c) or WO2003087098 Example 19(d)) (15mg), by the general method of Example 1(k) (initial stirring time 1h, then 5h after addition of borohydride). The crude product was chromatographed on silica gel, eluting with 0-20% methanol/dichloromethane to give the free base of the title compound (23mg, 54%).
^{1}H NMR (250MHz,$CDCl_3$) δ1.58 (4H, m), 1.85 (m obscured by water signal), 2.60 (1H, m), 3.86 (2H, s), 3.94 (3H, s), 4.01 (2H, d), 4.28 (2H, m), 4.34 (2H, m), 6.84 (1H, s), 6.86 (1H, d), 7.80 (1H, d), 8.10 (1H, s), and 8.39 (1H, d).
LC/MS (+ve ion electrospray): *m/z* 471 [MH^+].

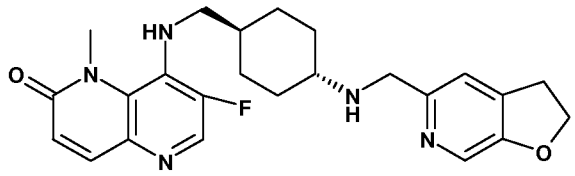
The free base was treated with 2 mole equivalents of 0.4M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (26mg).

Example 15 8-[({*trans*-4-[(2,3-Dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amino]cyclohexyl}methyl)amino]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one dihydrochloride



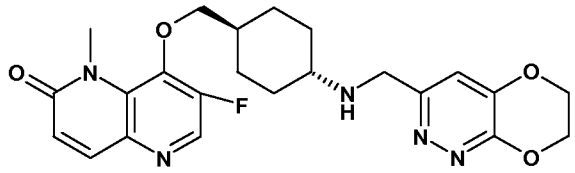
The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 10(e)) (65 mg; 90% purity) and 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(c) or WO2003087098 Example 19(d)) (32 mg) by the general method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (29 mg) after conversion to the title dihydrochloride salt.
LC/MS (+ve ion electrospray): *m/z* 454 [MH^+].

Example 16 8-[({*trans*-4-[(2,3-Dihydrofuro[2,3-*c*]pyridin-5-ylmethyl)amino]cyclohexyl}methyl)amino]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one dihydrochloride



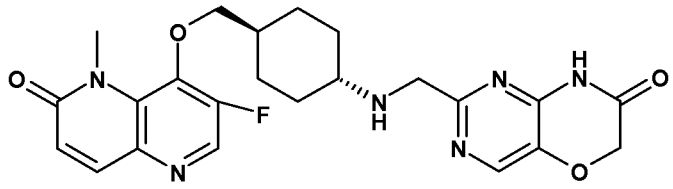
This was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (for a preparation see Example 10(e)) (62 mg; 95% purity) and 2,3-dihydrofuro[2,3-c]pyridine-5-carbaldehyde (for synthesis see WO2008009700 Example 38(f)) (29 mg) by the general method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (56 mg) after conversion to the title dihydrochloride salt.
LC/MS (+ve ion electrospray): *m/z* 438 [MH^+].

Example 17 8-[({*trans*-4-[(6,7-Dihydro[1,4]dioxino[2,3-*c*]pyridazin-3-ylmethyl)amino]cyclohexyl}methyl)oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride



The title compound was prepared from 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one hydrochloride (for a preparation see Example 1(j)) (75 mg; assume 50 mg of pure free base) and 6,7-dihydro[1,4]dioxino[2,3-c]pyridazine-3-carbaldehyde (for a synthesis see WO2007081597 Example 10A(e)) (28 mg) by the general method of Example 1(k) to give a solid (22 mg) after conversion to the hydrochloride salt.
MS (+ve ion electrospray) m/z 456 (MH+).

Example 18A 2-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one hydrochloride



(a) *trans*-4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid

To a stirred solution of trans-4-aminocyclohexanecarboxylic acid (1 g, 6.98 mmol) in tert-BuOH (10 mL) and NaOH (0.307 g, 7.68 mmol) in H_2O (10 mL) was added di-tert-butyldicarbonate (1.7 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. To the reaction mixture hexane (50 mL) was added and the pH was adjusted to pH ~6 with 6N HCl. The mixture was extracted with ethyl acetate (3×50 mL) and washed with brine solution (1×25 mL). Evaporation of the solvent under reduced pressure afforded a white powder (1.4 g, 82.8%).
MS (ES-) m/z 242 [MH^-].

(b) 1,1-Dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate

A solution of *trans*-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexanecarboxylic acid (1.45 g, 5.96 mmol) in THF (40 mL) was added to BH_3-DMS (5.2 mL, 17.28 mmol) in THF (40 mL) at 0 °C. The contents were allowed to stir at room temperature for 3 hrs. To the reaction mixture MeOH (10 mL) was added and evaporated to dryness under reduced pressure. The residue was co distilled with MeOH 3 times. The resulting residue was dissolved in DCM and washed with brine solution. Evaporation of the solvent under reduced pressure afforded a white solid (1.3 g, 94%). This crude product was carried over to the next step without further purification.

(c) 1,1-Dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate

To a stirred solution of 7-fluoro-1-methyl-1,5-dihydro-1,5-naphthyridine-2,8-dione (7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1*H*)-one, for a preparation see Example 1(f)) (670 mg, 3.48 mmol) in THF (10 mL) was added 1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (for a preparation see Example 1(g) or 18A(b)) 1 g, 4.36 mmol), PPh_3 (1.42 g, 5.45 mmol) and stirred for 10 minutes. To the mixture DIAD (1.07 mL, 5.45 mmol) in THF (10 mL) was added dropwise. The contents were stirred at 70 °C for 16 hrs. The solvent was removed under reduced pressure and 10% diethyl ether in hexane (10 mL) was added at 0 °C and the reaction mixture was stirred for 30 minutes. The white residue (PPh_3O) thus obtained were filtered and discarded; concentration of the filtrate under reduced pressure afforded the crude compound. The crude compound was purified by silica gel (100-200 mesh) column chromatography using 20%-50% ethyl acetate in petroleum ether. The mixture was then eluted on a preparative HPLC column with 80-20-80% 0.01M ammonium acetate/acetonitrile and the major fraction concentrated to afford a white solid (250 mg, 14.2%).
MS (ES+) m/z 406 [MH^+].

(d) 8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one

To a solution of CF_3COOH and DCM (1: 1) (8 mL) was added 1,1-dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl} cyclohexyl)carbamate (200 mg, 0.493 mmol) and stirred for 2 hours at room temperature. The reaction mixture was evaporated to dryness, added water (5 mL) and adjusted the pH~ 10 using 1N NaOH solution. Extracted with ethyl acetate (20 mL) and evaporation of the solvent afforded a yellow solid (100 mg, 67%).

MS (ES+) m/z 306 [MH^+]

The isolated yield of 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one can be improved by and using unpurified 1,1-dimethylethyl (*trans*-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate material in the deprotection step.

(e) 2-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one

To a stirred solution of 8-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1*H*)-one (55 mg, 0.180 mmol) and 7-oxo-6,7-dihydro-1*H*-pyrimido[5,4-*b*][1,4]oxazine-2-carbaldehyde (for a synthesis see WO2008009700 Preparation F) (32 mg,0.180 mmol) in DCM (3 mL) and MeOH (0.25 mL) was added sodiumtriacetoxyborohydride (76 mg, 0.360 mmol) and the contents were allowed to stir for 16 hrs at room temperature. The reaction mixture was filtered and washed with DCM (3 mL) leaving a white inorganic salt. The filtrate was concentrated to obtain the crude compound. The crude compound was washed thoroughly with diethyl ether to obtain the free base of the title compound as a pale yellow solid (30 mg, 36%).

MS (ES+) m/z 469 [MH^+].

^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.14-1.32 (5H, m), 1.97 (2H, d), 2.10 (2H, d), 2.49-2.56 (1H, m), 3.93 (3H, s), 3.99 (2H, s), 4.05 (2H, dd), 4.73 (2H, s), 6.86 (1H, d), 7.81 (1H, d), 8.26 (1H, s), and 8.38 (1H, d).

(f) Title compound

To a solution of 2-{[(trans-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (42 mg, 0.090 mmol) in methanol (3 mL) at rt was added hydrochloric acid (1 M in diethyl ether) (0.090 mL, 0.090 mmol). The solvent was removed and the solid was dried under high vacuum to deliver the title compound (45 mg).

MS (ES+) m/z 469 [MH^+].

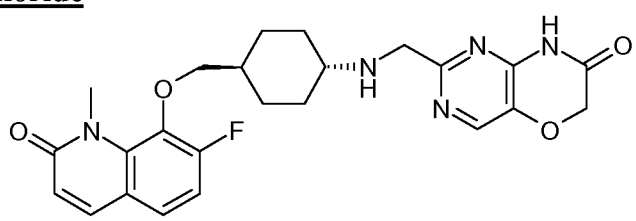
Example 18B 2-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one dihydrochloride

2-{[(*trans*-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one (free base) (for a preparation see Example 18A) (380 mg, 0.81 mmol) was dissolved in DCM (6 mL) and MeOH (0.6 mL) and added 3M HCl in diethyl ether (5 mL) at 0 °C. The resulting solution was allowed to stir at 0 °C for 30 minutes. The solvents were evaporated to dryness under reduced pressure. The crude compound was triturated with DCM (20 mL) and filtered. The residue was dried in vacuum to afford the title compound (360 mg) (dihydrochloride salt).

^{1}H (DMSO-d6 , 400MHz) δ1.2 (2H, m), δ 1.52-1.6 (2H, m), δ 1.8 (1H, m) δ 1.9-2.0 (2H, d), δ 2.2 (2H, d), δ 3.2 (1H, s), δ 3.8 (3H, s), δ 4.1 (2H, d), δ 4.3 (2H, s) δ 4.8 (2H, s) , δ 6.83 (1H, d),δ 7.83 (1H, d), δ 8.4 (1H, s) , δ 8.6 (1H,s) , δ 9.2 (1H, s) , δ 11.9 (1H,s).

MS (ES+) m/z 469 [MH^+].

Example 19 2-{[(*trans*-4-{[(7-Fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl}cyclohexyl)amino]methyl}-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one hydrochloride



(a) 7-Fluoro-8-hydroxy-1-methyl-2(1H)-quinolinone

8-Bromo-7-fluoro-1-methyl-2(1H)-quinolinone (2.06 g, 8.04 mmol) (for a synthesis see WO2008006648 Example 31(h)) was dissolved in THF (200 mL) and cooled to -70°C under nitrogen atmosphere with stirring. 2.5M n-Butyllithium (4 mL, 10 mmol) was added and the mixture stirred at -70°C for 1h. Trimethyl borate (1.35 mL, 12.07 mmol) was then added and the mixture allowed to warm to rt over 1h. Acetic acid (1.38 mL, 24.13 mmol) and hydrogen peroxide (4.23 mL, 24.13 mmol) were then added and the mixture stirred at rt for 48h. Water was added and then the mixture was extracted with EtOAc (x 2). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. This crude residue was combined with another batch arising from a duplicate reaction on the same scale. The combined residues were purified by silica chromatography, eluting with methanol/DCM (5-10%) to deliver an impure product.

This was re-purified by silica chromatography, eluting with methanol/DCM (2-12%) to deliver an orange solid which was triturated with Et_2O (30 ml), filtered, washed with more Et_2O (2 x 20 ml) then dried to give the title compound (0.41 g).
MS (ES+) m/z 194 [MH+].

(b) 1,1-Dimethylethyl (*trans*-4-{[(7-fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl}cyclohexyl)carbamate

To a mixture of 7-fluoro-8-hydroxy-1-methyl-2(1H)-quinolinone (0.25 g, 1.17 mmol), 1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (0.27 g, 1.17 mmol, for a preparation see Example 1(g)) and triphenylphosphine (0.40 g, 1.51 mmol) in THF (10 mL) was added DIAD (0.294 mL, 1.514 mmol) and the mixture stirred at rt for 1.5h.. The mixture was combined with that from a duplicate reaction on trial scale (0.419 mmol of starting material) and evaporated. The residue was purified by silica chromatography, eluting with 0-100% (4%methanol/ethyl acetate) in cyclohexane to deliver the title compound (0.7 g) containing residual triphenylphosphine oxide. This product was carried forward to next step without further purification.
MS (ES+) m/z 405 [MH+].

(c) 8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinolinone

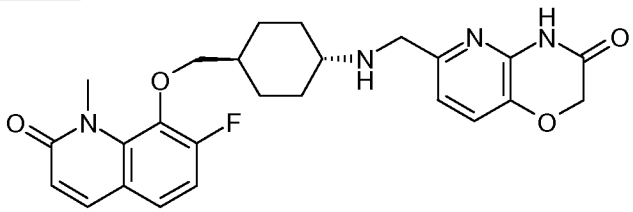
Trifluoroacetic acid (5 mL, 64.9 mmol) was added to a solution of 1,1-dimethylethyl (*trans*-4-{[(7-fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl}cyclohexyl)carbamate (0.7g) in DCM (10 mL) and the mixture stirred at rt for 1h. The mixture was evaporated and the residue partitioned between water (20 mL) and DCM (20 mL). The aqueous was then washed with more DCM (30 mL), then $CHCl_3$ (30 ml) to remove Ph_3PO from previous reaction. The aqueous was then basified with K_2CO_3 and then extracted with 10% methanol/DCM (3 x 30 ml), dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 0-12% NH_3/MeOH/DCM to give the title compound (0.12 g).
MS (ES+) m/z 305 [MH+].

(d) Title compound

To 8-{[(trans-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinolinone (0.04 g, 0.131 mmol) and 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (0.023 g, 0.118 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) in chloroform (5 mL) and methanol (0.5 mL) was added sodium

triacetoxyborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18h.. Saturated $NaHCO_3$ solution (15 ml) was added and the mixture extracted with 10% methanol/DCM (3 x 15 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (26 mg, 42%). The free base was dissolved in methanol (3 ml) and 1 eq. of 4.0M hydrogen chloride in 1,4-dioxane (0.015 ml) was added. The solvent was evaporated to deliver the title hydrochloride salt (28 mg).
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.14-1.38 (5H, m), 1.85-1.89 (1H, m), 2.00 (2H, d), 2.11 (2H, d), 2.56-2.63 (1H, m), 3.58 (2H, br s), 3.78 (2H, d), 3.94(3H, s), 4.03 (2H, s), 4.70 (2H, s), 6.64(1H, d), 6.99 (1H, dd), 7.22 (1H, dd), and 7.56 (1H, d).
MS (ES+) m/z 468 [MH+].

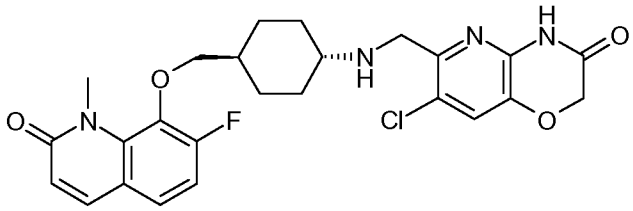
Example 20 6-{[(*trans*-4-{[(7-Fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl}cyclohexyl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one hydrochloride



(a) Title compound

To 8-{[(trans-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinolinone (0.04g, 0.131 mmol) (for a preparation see Example 19(c)) and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (0.021 g, 0.118 mmol, for a synthesis see WO2004058144, Example 1(l)) in chloroform (5 mL) and methanol (0.5 mL) was added sodium triacetoxyborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18 h. Saturated $NaHCO_3$ solution (15 ml) was added and the mixture extracted with 10% methanol/DCM (3 x 15 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (37 mg, 61%). The free base was dissolved in methanol (3 ml) and 1 eq. of 4.0 M hydrogen chloride in 1,4-dioxane (0.021 ml) was added. The solvent was evaporated to deliver the title hydrochloride salt (40 mg).
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.13-1.34 (5H, m), 1.85-1.89 (1H, m), 1.99 (2H, d), 2.09 (2H, d), 2.50-2.57 (1H, m), 3.79 (2H, d), 3.88 (2H, s), 3.95(3H, s), 4.64 (2H, s), 6.64(1H, d), 6.94-7.02 (2H, m), 7.20-7.24 (2H, m), and 7.56 (1H, d).
MS (ES+) m/z 467 [MH+].

Example 21 7-Chloro-6-{[(*trans*-4-{[(7-fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl}cyclohexyl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one hydrochloride

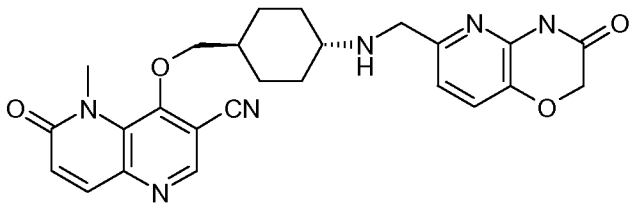


To 8-{[(trans-4-aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinolinone (0.04g, 0.131 mmol) (for a synthesis see Example 19 (c)) and 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (0.025 g, 0.118 mmol, for a synthesis see WO2003064421, Example 15(c)) in chloroform (5 mL) and methanol (0.5 mL) was added sodium triacetoxyborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18h. Saturated $NaHCO_3$ solution (15 ml) was added and the mixture extracted with 10% methanol/DCM (3 x 15 ml), dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (43 mg, 66%). The free base was dissolved in methanol (3 ml) and 1 eq. of 4.0 M hydrogen chloride in 1,4-dioxane (0.021 ml) was added. The solvent was evaporated to deliver the title hydrochloride salt (46 mg).

^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.17-1.40 (5H, m), 1.88-1.92 (1H, m), 2.03 (2H, d), 2.15 (2H, d), 2.55-2.62 (1H, m), 3.82 (2H, d), 3.97 (3H, s), 4.02 (2H, s), 4.65 (2H, s), 6.66(1H, d), 7.02 (1H, dd), 7.2-7.29 (2H, m), and 7.58 (1H, d).

MS (ES+) m/z 501 [MH+].

Example 22 5-Methyl-6-oxo-4-{[(*trans*-4-{[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}cyclohexyl)methyl]oxy}-5,6-dihydro-1,5-naphthyridine-3-carbonitrile



(a) Methyl 5-methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate

To a suspension of methyl 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate (5 g, 21.35 mmol) (for a synthesis see WO2008006648 Example 23(b)) in DMF (200 mL) at rt was added small portions of 60% sodium hydride

(60% in oil) (0.940 g, 39.2 mmol). The green reaction mixture was then heated at 60 °C for 45mins then p-methoxybenzyl chloride (3.18 mL, 23.48 mmol) added dropwise. The solution was then heated at 120°C for 2.5h then allowed to cool and stood at rt overnight. The reaction was then evaporated, quenched with water and extracted with $CHCl_3$ (x 3). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated a solid which was purified by silica chromatography, eluting with MeOH/DCM (0-15%) to give the title compound (3.61g, 48%).
MS (ES+) m/z 355 [MH+].

(b) 5-Methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylic acid

A suspension of methyl 5-methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate (3.59 g, 10.12 mmol) in THF) (40 mL and water (40.0 mL) was stirred at rt and 2 M sodium hydroxide (20.23 mL, 40.5 mmol) was added slowly. The resulting mixture was stirred for 1.5 h and then acidified to pH 2 with 2 M HCl. The reaction was evaporated then filtered, washed with water and dried to give the title compound (2.95 g, 86%).
MS (ES+) m/z 341 [MH+].

(c) 5-Methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxamide

A suspension of 5-methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylic acid (2.95 g, 8.68 mmol) in DMF (80 ml) was stirred at rt and treated with HATU (*O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (3.63 g, 9.55 mmol) followed by DIPEA (di-*iso*-propylethylamine) (1.68ml, 9.55mmol). The brown solution was at rt for 10 min then treated with ammonium chloride (9.29 g, 174 mmol) and more DIPEA (30.29 ml, 53.49 mmol). The orange reaction mixture was stirred at rt for 2 h then evaporated and the residue dissolved in 10% MeOH/$CHCl_3$ and washed with water (x 2). The combined aqueous phases were extracted with $CHCl_3$ and the combined organics washed with brine, dried (Na_2SO_4) and evaporated to give a solid which was treated with DMF and heated, then left to stand at 0 °C overnight, then filtered, washed with Et_2O and dried to give the title compound (2.73 g, 93%).
MS (ES+) m/z 340 [MH+].

(d) 5-Methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile

A mixture of 5-methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxamide (2.73 g, 8.04 mmol)), p-toluenesulphonyl chloride (2.45 g, 12.86 mmol) and pyridine (30 mL) was stirred and heated to 85° C for 2 h. The reaction was allowed to cool, treated with DCM (25 ml) and water (25 ml) then stirred for 10 min. The aqueous phase was separated and extracted with more DCM (x 2) and 10%MeOH/DCM. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give the title compound (2.56g, 99%).
MS (ES+) m/z 322 [MH+].

(e) 4-Hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile

A suspension of 5-methyl-4-({[4-(methyloxy)phenyl]methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (2.56 g, 5.88 mmol) in DCM (10 mL) was stirred and treated dropwise with TFA (10 ml, 130 mmol). The resulting orange solution was heated at reflux overnight. The reaction was heated for a further 24 h, then evaporated and the residue azeotroped with toluene then $CHCl_3$ (x 3) to give a beige solid (2.43 g). Ca. 1 g of this solid was partitioned between saturated aqueous $NaHCO_3$ solution and $CHCl_3$ and the aqueous phase was separated and acidified with 2M HCl solution and extracted with 10% MeOH/$CHCl_3$ (x 3). The combined organics were evaporated to give the title compound (0.65 g, 55%).
MS (ES+) m/z 202 [MH+].

(f) 1,1-Dimethylethyl (*trans*-4-{[(3-cyano-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate
Method 1

A suspension of 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (100 mg, 0.50 mmol) in THF (10 mL) was stirred at rt and treated with (1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (114 mg, 0.50 mmol), triphenyl phosphine (261 mg, 0.99 mmol) and DIAD (0.20 mL, 0.99 mmol) added dropwise. The resulting pale yellow suspension was stirred at rt for 20 min then heated at 80 °C overnight. The reaction was then heated at 60 °C over the weekend. The reaction was then evaporated to give a yellow gum which was purified by silica chromatography, eluting with MeOH/DCM (0-10%) to give the title compound (0.51 g), containing residual triphenylphosphine oxide. This may be used in the next step without further purification.
MS (ES+) m/z 413 [MH+].
Method 2

A suspension of 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (0.33g, 1.640 mmol) in DMF (25 mL) was stirred at rt and treated with 60%

sodium hydride in oil (82mg, ~1.91mmol, 1.25eq) added in small portions. The resulting mixture was heated at 60°C for 40 min then trans-4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclohexyl]methyl ethanesulfonate (0.492 g, 1.53 mmol) (for a synthesis see alternative synthesis of Example 1(i)(a)) added in small portions and the resulting brown slight suspension heated at 120°C overnight . The reaction was then heated for a further 24 hours, allowed to cool, evaporated , quenched with water and extracted with 10% MeOH/$CHCl_3$ (x4). The combined organic layers were dried (Na_2SO_4) and evaporated to give a residue which was purified by silica chromatography (x 3), eluting with 0-10% MeOH/DCM to give an impure product which may be used in the next step without further purification.

(g) 4-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile

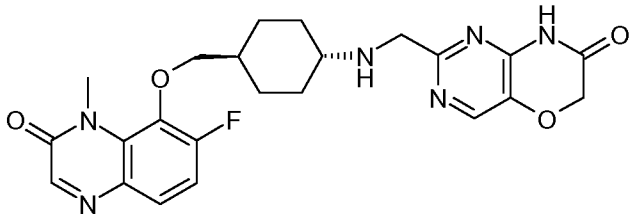
A solution of 1,1-dimethylethyl (*trans*-4-{[(3-cyano-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate (0.50 g) (containing triphenylphosphine oxide) in DCM (8 mL) was stirred at rt and treated slowly with trifluoroacetic acid (4 mL, 53.8 mmol). The resulting yellow solution was stirred at rt for 2 h. The reaction was then evaporated and the residue partitioned between DCM and water. The aqueous phase was separated and basified to pH~12 with 1 M NaOH solution n and extracted with 10% MeOH/DCM (x 3). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give a cream solid which was combined with a second batch of crude material (16 mg). The combined residues were purified by silica chromatography, eluting with MeOH/DCM (0-75%) to give the title compound (59 mg).
MS (ES+) m/z 313 [MH+].

(h) Title compound.

A solution of 4-{[(*trans*-4-aminocyclohexyl)methyl]oxy}-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (58 mg, 0.19 mmol) in DCM (5 ml) and methanol (1 ml) was stirred at rt and treated with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (33 mg, 0.19 mmol) (for a synthesis see WO2004058144, Example 1(l)). The resulting orange solution was stirred at rt overnight then sodium triacetoxyborohydride (79 mg, 0.37 mmol) was then added in small portions and the resulting reaction stirred for 3 h. The reaction was then evaporated to give an orange gum which was purified by silica chromatography, eluting with 2M NH_3 in MeOH/DCM (0-15%) to give a pale pink foam which was re-purified by silica chromatography, eluting

with 2M NH_3 in MeOH/DCM (0-10%) to give the title compound as a mixture containing approximately 50 mol% of an unidentified impurity (21 mg, 24%).
^{1}H NMR (600 MHz) ($CDCl_3$) δ 1.15-2.02 (9H, m), 2.43-4.47 (1H, m), 3.81 (2H, s), 3.90 (3H, s), 4.20 (2H, d), 4.64 (2H, s), 6.92 (1H, d), 7.02 (1H, d), 7.20 (1H, dd), 7.87 (1H, d), and 8.59 (1H, s).
MS (ES+) m/z 475 [MH+].

Example 23 2-{[(*trans*-4-{[(6-Fluoro-4-methyl-3-oxo-3,4-dihydro-5-quinoxalinyl)oxy]methyl}cyclohexyl)amino]methyl}-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one hydrochloride



(a) (2-Bromo-3-fluoro-6-nitrophenyl)amine

A solution of 2-bromo-1,3-difluoro-4-nitrobenzene (32.14 g, 135.4 mmol) (for a synthesis see EP184384 Example 1 (a)), triethylamine (56.5 ml, 405 mmol) and ammonium carbonate (12.83 g, 135.4 mmol) in DMF (220 mL) were stirred at rt for 24 h then evaporated then the residue was dissolved in DCM/water. The aqueous phase was extracted with DCM (x 2), the organic layers were then dried and evaporated. The crude residue was recrystallised from diethyl ether: petroleum ether (40-60) and the so-obtained product (20.67 g) was combined with the recrystallised mother liquor (3.62 g) (recrystallised from diethyl ether: petroleum ether (40-60) then ethanol) to deliver the title compound (24.29 g, 76%).
^{1}H NMR (250 MHz) ($CDCl_3$) δ 6.52-6.60 (1H, m), 6.82 (2H, br s),and 8.19-8.25 (1H, m).

(b) N-(2-Bromo-3-fluoro-6-nitrophenyl)-2-cyanoacetamide

To a mixture of (2-bromo-3-fluoro-6-nitrophenyl)amine 24.29 g (103.4 mmol) and cyanoacetic acid (17.75 g, 206.3 mmol) in toluene (740 ml) at rt was added PCl_5 (45.15 g, 206.3 mmol) portionwise. The mixture was then heated at 125-130 °C for 2.25 h while passing a slow stream of air over the mixture. Additional cyanoacetic acid (1.8 g, 20.6 mmol) and PCl_5 (5.5 g, 20.6 mmol) were then added and the mixture was heated at 125-130 °C for a further 1.25 h. The mixture was then cooled, evaporated and the residue was dissolved in EtOAc and washed with brine, $NaHCO_3$, brine then the organics were dried and evaporated. The material as then resuspended in toluene (700 ml) then additional cyanoacetic acid (8.9 g, 105 mmol) and PCl_5 (22.5 g, 105 mmol) were then

added and the mixture was heated at 90 °C for a further 3 h. The mixture was then cooled, evaporated and the residue was dissolved in EtOAc and washed with brine, $NaHCO_3$, brine then the organics were dried and evaporated to deliver the title compound containing unidentified impurities (32.84 g).
MS (ES-) m/z 301[M-H].

(c) 5-Bromo-6-fluoro-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide

To a solution of N-(2-bromo-3-fluoro-6-nitrophenyl)-2-cyanoacetamide (32.84 g) in pyridine (120 ml) was added 1 M NaOH (105 ml, 105 mmol) and the mixture was stirred at rt for two nights then water was added and the mixture filtered, washing the precipitate with water. The filtrate was acidified to pH5 through addition of concentrated HCl and the mixture was filtered, washing the precipitate with water. The precipitate was dried then triturated with diethyl ether (x 2) and dried to deliver the title compound (23.59 g, 81% over 2 steps).
MS (ES-) m/z 282[M-H].

(d) 8-Bromo-7-fluoro-2(1H)-quinoxalinone

A mixture of 5-bromo-6-fluoro-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide (5.0 g, 17.5 mmol) and sodium sulfate (9 g, 43.9 mmol) in ethanol (50 ml) and water (100 ml) was heated under reflux for 2.5 h then cooled and acidified to pH 1 with 5 M HCl. The reaction was stirred at rt for 30 min then taken to pH 8 with 2 M NaOH and the ethanol was evaporated. The pH of the mixture was then taken to pH13-14 with 8 M NaOH and the mixture was allowed to stand for 4 h. Concentrated HCl was then added to the mixture to acidify to pH 2 and the resulting suspension was filtered and the filtrate was evaporated. The residue was suspended in water (500 ml) and re-acidified with dilute HCl and extracted several times with 10% MeOH/DCM. The combined organic extracts were dried and evaporated to deliver the title compound (2.37 g, 56%).
MS (ES+) m/z 245 [MH+].

(e) 8-Bromo-7-fluoro-2-(methyloxy)quinoxaline

A solution of 8-bromo-7-fluoro-2(1H)-quinoxalinone (0.1 g, 0.41 mmol) in DMF (4 ml) was added to a flask containing sodium hydride (60% dispersion in oil) (25 mg, 0.62 mmol) and stirred for 10 min then methyl iodide (0.051 ml, 0.82 mmol) was added and the reaction mixture was stirred for 1.5 h then poured into a mixture of water (5 ml), brine (5 ml) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organics were washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO4 and evaporated. The crude

residue was purified by silica chromatography, eluting with EtOAc/hexanes (0-70%) to give the title compound (41 mg, 39%).
MS (ES+) m/z 258 [MH+].

(f) 6-Fluoro-3-(methyloxy)-5-quinoxalinol

8-bromo-7-fluoro-2-(methyloxy)quinoxaline (200mg, 0.778 mmol), $Pd_2(dba)_3$ tris(dibenzylideneacetone)dipalladium(0) (3.56 mg, 3.89 μmol), *bis*(1,1-dimethylethyl)[3,4,5,6-tetramethyl-2',4',6'-tris(1-methylethyl)-2-biphenylyl]phosphane (7.48 mg, 0.016 mmol), KOH (131 mg, 2.334 mmol) were dissolved in degassed 1,4-dioxane (1 ml) and degassed water (1 ml). The reaction was then stirred at 100°C for 1.5 h (the purple solution turned orange after a few minutes). The reaction was allowed to cool to room temperature and acidified using 1M HCl. The resulting mixture was then extracted with ethyl acetate (3 x 5ml). The organics were combined, dried and evaporated to give the crude product. This was dissolved in DCM (5 ml) and filtered. The filtrate was evaporated to give the title compound (130 mg, 68%).
MS (ES+) m/z 195 [MH+].

(g) 10-Fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[4,5,6-de]quinoxalin-5-one

6-Fluoro-3-(methyloxy)-5-quinoxalinol (130 mg, 0.670 mmol) was suspended in DMF (5 mL) and treated with NaH (48.2 mg, 1.205 mmol). chloro(chloromethyl)dimethylsilane (0.176 mL, 1.339 mmol) was then added and the reaction stirred at rt for 1h. The reaction was then heated to 100 °C overnight. The solvent was evaporated and the crude purified using silica chromatography 0-5% MeOH/DCM to deliver the title compound (155 mg, 92%).
MS (ES+) m/z 251 [MH+].

(h) 7-Fluoro-8-hydroxy-1-methyl-2(1H)-quinoxalinone

A solution of 10-fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[4,5,6-de]quinoxalin-5-one (155 mg, 0.619 mmol) in 1,4-dioxane (10 mL) and methanol (5.00 mL) was treated with cesium fluoride (282 mg, 1.858 mmol) and stirred at 85 °C overnight. Solvents were evaporated and the residue was dissolved in MeOH/water (1:1, 3mL) and acidified to pH 3 with 5 N HCl. The aqueous was extracted with 20% MeOH/DCM (3 x 50mL). The organic layers were dried ($MgSO_4$), filtered and evaporated to afford the title compund (150 mg) which was used in the next step without further purification.
MS (ES+) m/z 195 [MH+].

(i) 1,1-Dimethylethyl (*trans*-4-{[(6-fluoro-4-methyl-3-oxo-3,4-dihydro-5-quinoxalinyl)oxy]methyl}cyclohexyl)carbamate

To a mixture of 7-fluoro-8-hydroxy-1-methyl-2(1H)-quinoxalinone (150 mg), 1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (142 mg, 0.618 mmol, for a preparation see Example 1(g)) and triphenylphosphine (195 mg, 0.742 mmol) in THF (10 mL) was added DIAD (0.144 mL, 0.742 mmol) and the mixture was stirred at rt for 1 h then triphenylphosphine (195 mg, 0.742 mmol) and DIAD (0.144 mL, 0.742 mmol) were added and the reaction was stirred at rt overnight. The solvent was evaporated and the residue was purified using silica chromatography (0-20%CH_3CN/DCM) to afford the title compound (272 mg) which was used in the next step without further purification.
MS (ES+) m/z 423 [MNH_4+].

(j) 8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinoxalinone

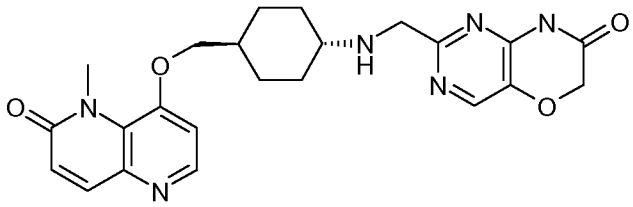
1,1-Dimethylethyl (*trans*-4-{[(6-fluoro-4-methyl-3-oxo-3,4-dihydro-5-quinoxalinyl)oxy]methyl}cyclohexyl)carbamate (272 mg) was dissolved in chloroform (5 mL) and treated with HCl (5 mL, 20.00 mmol) (4M in 1,4-dioxane). The reaction was stirred at rt for 45min then additional HCl (5 mL, 20.00 mmol) (4M in 1,4-dioxane) was added and the reaction mixture was stirred at rt for 30 min then evaporated. The crude was purified on an SCX cartridge eluting with metanol, then 2 M NH_3 in methanol, to deliver the title compound (36 mg, 15% over 3 steps (h,i,j).
MS (ES+) m/z 306 [MH+].

(k) Title compound

8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-2(1H)-quinoxalinone (36 mg, 0.094 mmol) was dissolved in chloroform (5 mL) and methanol (0.5 mL) and then 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (18.59 mg, 0.094 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM)was added. The mixture was stirred at rt for 0.5h and then sodium triacetoxyborohydride (60.0 mg, 0.283 mmol) was added. After 1.5h additional sodium triacetoxyborohydride (30.0 mg, 0.141 mmol) were added. Sat. aq. $NaHCO_3$ (15mL) was added and the aqueous was extracted with 20%MeOH/DCM (3 x 25mL). The organic layers were dried ($MgSO_4$), filtered and evaporated then the residue was purified by silica chromatography eluting with 0-20%MeOH/DCM to afford the free base of the title compound (25 mg, 51%). The free base was dissolved in DCM-MeOH and treated with

one equivalent of 1M HCl in Et_2O. The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (25 mg).
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.15-1.39 (4H, m), 1.89-2.14 (5H, m), 2.58-2.63 (1H, m), 3.83-3.84 (2H, m), 3.94 (3H, s), 4.02-4.04 (2H, m), 4.71-4.76 (3H, m), 7.08-7.13 (1H, m), 7.57-7.61 (1H, m), and 8.21-8.24 (2H, m).
MS (ES+) m/z 469 [MH+].

Example 24 2-{[(trans-4-{[(5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one hydrochloride



(a) 1,1-Dimethylethyl (*trans*-4-{[(5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate

A suspension of 8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (70 mg, 0.397 mmol) (for a synthesis see WO2008006648 Example 19(b)) in THF (7 mL) was stirred at rt and treated with 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (91 mg, 0.397 mmol, for a preparation see Example 1(g)), triphenylphosphine (135 mg, 0.517 mmol) and DIAD (0.102 mL, 0.517 mmol). The suspension was placed in a sonic bath for 5 min at rt then removed and heated at 80°C overnight. Additional DIAD (0.117 mL, 0.596 mmol), additional triphenylphosphine (156 mg, 0.596 mmol), additional 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (137 mg, 0.596 mmol) were added and the suspension was heated at 80°C for a further 5 h. The reaction was evaporated to dryness. The residue was purified by silica chromatography eluting with 0-50% DCM/MeOH to give the title compound (88 mg, 57%)
MS (ES+) m/z 388 [MH+].

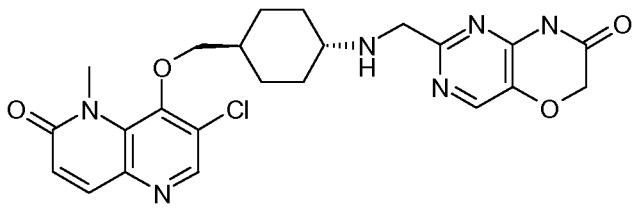
(b) 8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-1-methyl-1,5-naphthyridin-2(1H)-one

A solution of 1,1-dimethylethyl (trans-4-{[(5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate (88 mg, 0.227 mmol) in DCM (2 mL) was stirred at rt and treated with TFA (1.2 mL, 15.58 mmol). The solution was stirred for 2 h then evaporated. This residue was purified on an SCX cartridge eluting with 0-100% 2 M ammonia in MeOH/MeOH to give the title compound (40 mg, 58%).
MS (ES+) m/z 288 [MH+].

(c) Title compound

8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-1-methyl-1,5-naphthyridin-2(1H)-one (40 mg, 0.139 mmol) was dissolved in chloroform (5 mL) and methanol (0.500 mL) at rt and then 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (27.4 mg, 0.139 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) was added. The mixture was stirred at rt for 0.5h and then sodium triacetoxyborohydride (89 mg, 0.418 mmol) was added and stirred overnight at rt. Saturated aq. $NaHCO_3$ (15 mL) was added and the aqueous was extracted with 20%MeOH/DCM (3 x 25mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica chromatography (0-20%MeOH/DCM) to deliver the free base of the title compound (12 mg, 19%). The free base was dissolved in DCM-MeOH and treated with one equivalent of 1M HCl in Et_2O. The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (14 mg).
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.21-1.35 (4H, m), 1.91-2.01 (3H, m), 2.12 (2H, d), 2.55-2.60 (1H, m), 3.13 (2H, br s), 3.95-3.97 (5H, m), 4.02 (2H, s), 4.72 (2H, s), 6.90 (2H, m), 7.86 (1H, d), 8.24 (1H, s) and 8.38 (1H, d).
MS (ES+) m/z 451 [MH+].

Example 25 2-{[(*trans*-4-{[(3-Chloro-5-methyl-6-methylidene-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)amino]methyl}-6H-pyrimido[5,4-b][1,4]oxazin-7(8H)-one hydrochloride



(a) 1,1-Dimethylethyl (*trans*-4-{[(3-chloro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate

A suspension of 7-chloro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (1 g, 4.75 mmol) (for a synthesis see WO2008006648 Example 1(c)) in THF (24 ml) was stirred at rt and treated with 1,1-dimethylethyl [*trans*-4-(hydroxymethyl)cyclohexyl]carbamate (1.089 g, 4.75 mmol, for a preparation see Example 1(g)), triphenylphosphine (1.619 g, 6.17 mmol) and DIAD (1.215 ml, 6.17

mmol). The resulting yellow suspension was stirred for 30 min then heated at 80°C for 3.5 hours. Additional triphenylphosphine (0.8 g, 3.05 mmol) and DIAD (0.6 ml, 3.05 mmol) were added and the suspension (now orange) was heated to 80°C for 2 hours. The suspension was cooled and stirred at rt overnight. The solvent was evaporated under vacuum and to deliver an orange gum. Chromatography on silica, eluting with 0-50% DCM/CH_3CN gave a white solid that contained residual triphenylphosphine oxide. Diethylether (50 mL) was added and the resulting suspension was stirred for 30 minutes, filtered under vacuum. The precipitate was dissolved in DCM, filtered and the filtrate was evaporated to give the title compound (1.16 g, 42%).
MS (ES+) m/z 422 [MH+].

(b) 8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-chloro-1-methyl-1,5-naphthyridin-2(1H)-one

1,1-Dimethylethyl (*trans*-4-{[(3-chloro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl)carbamate (307 mg, 0.524 mmol) was dissolved in chloroform (10 mL) and treated with HCl in 1,4-dioxane (10 mL, 40.0 mmol). The reaction was stirred at rt for 45 min then further HCl in 1,4-dioxane (10 mL, 40.0 mmol) was added. After 1.5h at rt the reaction was evaporated and the crude was dissolved in MeOH (5 mL) and purified on an SCX cartridge to deliver a yellow gum. This was then further purified by chromatography on silica eluting with 2 M NH_3 in methanol/DCM, 0-100%to give the title compound (121 mg, 68%).
MS (ES+) m/z 322 [MH+].

(c) Title compound

8-{[(*trans*-4-Aminocyclohexyl)methyl]oxy}-7-chloro-1-methyl-1,5-naphthyridin-2(1H)-one (121 mg, 0.376 mmol) was dissolved in chloroform (10 mL) and methanol (1 mL) and then 2-(dihydroxymethyl)-6H-pyrimido[5,4-b][1,4]oxazin-7(8H)-one (78 mg, 0.396 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) was added. The reaction mixture was stirred at rt for 0.5 h and then sodium triacetoxyborohydride (239 mg, 1.128 mmol) was added. The suspension was stirred at rt for 3 h then additional sodium triacetoxyborohydride (239 mg, 1.128 mmol) was added and the suspension was stirred at rt overnight. Additional sodium triacetoxyborohydride (398 mg, 1.880 mmol) was added and the suspension was stirred at rt for a further 1.5 h. Saturated aq. $NaHCO_3$ (50mL) was added to the reaction and the aqueous layer was extracted with 20%MeOH/DCM (3 x 50mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica chromatography (0-50%MeOH/DCM) to

deliver the free base of the title compound (50 mg, 27%). The free base was dissolved in DCM-MeOH (2mL) and treated with one equivalent of 1M HCl in Et_2O (0.103mL). The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (46 mg).
^{1}H NMR (400 MHz) (free base) ($CDCl_3$) δ 1.15-1.25 (2H, m), 1.29-1.38 (2H, m) 1.92-2.03 (3H, m), 2.12 (2H, d), 2.56-2.63 (1H, m), 3.78 (2H, d), 3.90 (3H, s), 4.04 (2H, s), 4.69 (2H, s), 5.57 (2H, br s), 6.89 (1H, d), 7.84 (1H, d), 8.22 (1H, s) and 8.46 (1H, s).
MS (ES+) m/z 485 [MH+].

Preparation A 7-Oxo-6,7-dihydro-1H-pyrimido[5,4-b][1,4]thiazine-2-carbaldehyde

(a) Ethyl [(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)thio]acetate

A solution of 5-bromo-2,4(1H,3H)-pyrimidinedione (15 g, 79 mmol) and ethyl mercaptoacetate (8.58 ml, 79 mmol) in DMF (200mL) was treated with tetrabutylammonium hydrogen sulfate (6.67 g, 19.64 mmol) and potassium carbonate (23.88 g, 173 mmol) and stirred at ambient temperature overnight. The solution was filtered and concentrated under reduced pressure to yield crude title compound as a yellow oil which foams up under reduced pressure.
MS (ES+) m/z 231.1 (MH^+).

(b) Ethyl [(2,4-dichloro-5-pyrimidinyl)thio]acetate

A suspension of ethyl [(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)thio]acetate (crude material) (18.19 g, 79 mmol) in phosphorus oxychloride (100 ml, 1073 mmol) was treated with dimethyl aniline (2.500 ml, 19.72 mmol), and the reaction was heated to reflux and stirred for 2 hours. The solution was allowed to cool to room temperature and poured slowly onto ice to quench the excess phosphorus oxychloride. Once quenched, the aqueous layer was extracted with CH_2Cl_2 (3X). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was chromatographed using a gradient of 0-50% EtOAc/Hexanes. The product was isolated as a dark yellow oil.
1H NMR (400 MHz, chloroform-*d*) ppm 1.22 (t, *J*=7.07 Hz, 3 H) 3.71 (s, 2 H) 4.15 (d, *J*=7.33 Hz, 1 H) 8.53 (s, 1 H)

(c) Ethyl [(4-amino-2-chloro-5-pyrimidinyl)thio]acetate

A solution of ethyl [(2,4-dichloro-5-pyrimidinyl)thio]acetate (2.0 g, 7.49 mmol) in DMF (75ml) was treated with ammonia in isopropanol (7.49 ml, 14.97 mmol) in a pressure tube. The tube was capped, and the reaction was stirred at ambient temperature. Upon completion, the solution was concentrated under reduced pressure and pumped on

to remove any residual DMF. The crude material was chromatographed using a gradient of 0-10% acetone/chloroform. The product contained a small amount of cyclized material (which is the product of the next step). The product was isolated as a light yellow solid.
MS (ES+) m/z 248.0 (MH^+).

(d) 2-Chloro-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one

A suspension of ethyl [(4-amino-2-chloro-5-pyrimidinyl)thio]acetate (0.786 g, 3.17 mmol) in ethanol (50 ml) was heated to 70°C. Cesium carbonate (1.034 g, 3.17 mmol) was added and the solution was heated for a further 5 minutes. A white solid precipitated out of solution almost immediately. The solution was concentrated under reduced pressure. The residue was dissolved in water and brought to pH = 5 with 1N HCl. The aqueous layer was extracted with CH_2Cl_2 (2X). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a light yellow solid.
MS (ES+) m/z 202.0 (MH^+).

(e) 2-Ethenyl-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one

2-Chloro-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one (0.639 g, 3.17 mmol) was treated with tributylvinyl tin (1.388 ml, 4.76 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.293 g, 0.254 mmol) in 1,4-dioxane (4 ml) and toluene (4 mL) in a microwave vial. The reaction was heated in the microwave at 140°C for 20 minutes. The solution was diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (2X). The organic solution were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was chromatographed using a gradient of 0-60% CH_2Cl_2/(CH_2Cl_2/MeOH/NH_4OH) (90:10:1). The product was isolated as a mixture of the desired product and triphenylphosphine. Pure material was obtained by triturating and washing with diethyl ether. The product was isolated as an orange solid.
MS (ES+) m/z 194.0 (MH^+).

(f) Title compound

A solution of 2-ethenyl-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one (0.262 g, 1.356 mmol) in methanol/DCM was cooled to -78°C and treated with ozone until the solution turned blue. The solution was stirred at -78°C for an additional 5 minutes. Dimethyl sulfide (5.0 ml, 67.6 mmol) was added and the solution was allowed to warm to room temperature and stir overnight. The solution was concentrated onto silical gel and the crude material was chromatographed using a gradient of 0-100%

$CH_2Cl_2/(CH_2Cl_2/MeOH/NH_4OH)$ (90:10:1). The product was isolated as a light yellow solid.
MS (ES+) m/z 195.9 (MH^+).

Biological Activity

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-A7, "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.

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.

Compounds were evaluated against Gram-positive organisms, selected from *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis* and *Enterococcus faecium*.

In addition, compounds were evaluated against Gram-negative organisms selected from *Haemophilus influenzae*, *Moraxella catarrhalis*, *Acinetobacter baumanii, Escherichia coli*, *Pseudomonas aeruginosa, Proteus mirabilis, Legionella pneumophila, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*.

The *L. pneumophila* isolates were tested using a modified CLSI procedure for broth microdilution. For this assay, compounds were tested in serial doubling dilutions over a concentration range of 0.03 to 32 mcg/mL. An inoculum of each test isolate was prepared in buffered yeast broth and adjusted to a density equivalent to a 0.5 McFarland standard. After inoculation, the microtitre plates were incubated at 37°C for 72 hours.

Each of the listed Examples, as identified in the present application, was tested in at least one exemplified salt or free base form. The tested Examples had a MIC <2μg/ml against a strain of at least one of the organisms listed above. For at least one strain of every organism listed above, at least one Example had a MIC ≤2μg/ml.

Mycobacterium tuberculosis H37Rv Inhibition Assay

The measurement of the minimum inhibitory concentration (MIC) for each tested compound was performed in 96 wells flat-bottom, polystyrene microtiter plates. Ten two-fold drug dilutions in neat DMSO starting at 400μM were performed. Five μl of these drug solutions were added to 95 μl of Middlebrook 7H9 medium. (Lines A-H, rows 1-10

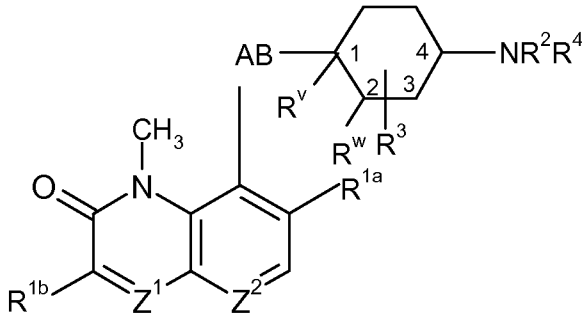
of the plate layout). Isoniazid was used as a positive control, 8 two-fold dilution of Isoniazid starting at 160 μgml^{-1} was prepared and 5 µl of this control curve was added to 95µl of Middlebrook 7H9 (Difco catalogue Ref. 271310) + ADC medium (Becton Dickinson Catalogue Ref. 211887). (Row 11, lines A-H). Five µl of neat DMSO were added to row 12 (growth and Blank controls).

The inoculum was standardised to approximately $1x10^7$ cfu/ml and diluted 1 in 100 in Middlebrook 7H9+ADC medium and 0.025% Tween 80 (Sigma P4780), to produce the final inoculum of H37Rv strain (ATCC25618). One hundred µl of this inoculum was added to the entire plate but G-12 and H-12 wells (Blank controls). All plates were placed in a sealed box to prevent drying out of the peripheral wells and they were incubated at 37^oC without shaking for six days. A resazurin solution was prepared by dissolving one tablet of resazurin (Resazurin Tablets for Milk Testing; Ref 330884Y VWR International Ltd) in 30 ml sterile PBS (phosphate buffered saline). 25 µl of this solution was added to each well. Fluorescence was measured (Spectramax M5 Molecular Devices, Excitation 530nm, Emission 590nm) after 48 hours to determine the MIC value.

Examples 1, 5, 7-9, 14, 15, 18A and 18B were tested in the *Mycobacterium tuberculosis* H37Rv inhibition assay. Example 9 showed an MIC value of 1.1 µg/ml or lower. Examples 1, 7, 8, 18A and 18B showed an MIC value of 0.2 µg/ml or lower. Examples 5, 14 and 15 gave MIC values higher than 2.5 µg/ml.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof:



(I)

wherein:

Z^1 and Z^2 are independently selected from N and CH;

AB is OCH_2, CH_2O, $NR^{11}CH_2$ or CH_2NR^{11};

R^{11} is selected from $C_{(1-2)}$alkyl; formyl; (C_{1-2})alkylcarbonyl; and (C_{1-2})alkylsulphonyl;

R^{1a} is selected from hydrogen; halogen; cyano; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; carboxy ; hydroxy optionally substituted with (C_{1-6})alkyl or (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; hydroxy (C_{1-6})alkyl; an amino group optionally N-substituted by one or two (C_{1-6})alkyl, formyl, (C_{1-6})alkylcarbonyl or (C_{1-6})alkylsulphonyl groups; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl;

R^{1b} is H or F;

R^2 is hydrogen;

R^V and R^W are hydrogen, R^V is absent and R^3 is in the 1-position and R^W is hydrogen or R^V and R^W together are a bond;

R^3 is hydrogen; or

when R^V and R^W are a bond, R^3 is in the 2-, 3- or 4- position and when R^W is hydrogen, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:

hydroxy optionally substituted by (C_{1-6})alkyl; amino optionally mono- or disubstituted independently by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl; fluoro; carboxy; cyano; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl, or

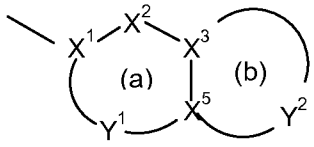
(C_{1-4})alkyl optionally substituted with any of the groups listed above for R^3;

provided that when R^3 is in the 4- position it is not optionally substituted hydroxyl or amino;
provided that when R^3 is in the 1-position and AB is CH_2NR^{11} or R^3 is in the 4-position, it is not optionally substituted hydroxyl or amino;
and provided that when R^3 is in the 1-position and AB is CH_2O, it is not optionally substituted amino;

R^4 is UR^5;

U is selected from CO and CH_2 and

R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (B):



(A)

containing up to four heteroatoms in each ring in which

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

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

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

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

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

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

each of R^{14} and R^{15} is independently selected from: H; (C_{1-2})alkylthio; halo; carboxy(C_{1-2})alkyl; (C_{1-2})alkyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkoxy (C_{1-2})alkyl; hydroxy; hydroxy(C_{1-24})alkyl; (C_{1-2})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally mono- or di-substituted by (C_{1-2})alkyl; or

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

each R^{13} is independently H; trifluoromethyl; (C_{1-2})alkyl optionally substituted by hydroxy, (C_{1-2})alkoxy, (C_{1-2})alkylthio, halo or trifluoromethyl; (C_2)alkenyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkylsulphonyl; aminocarbonyl wherein the amino group is optionally mono or disubstituted by (C_{1-2})alkyl;

each x is independently 0, 1 or 2.

2. A compound according to claim 1 wherein:
(1) Z^1 is CH and Z^2 is N;
(2) Z^1 and Z^2 are both CH;
(3) Z^1 is N and Z^2 is CH
(4) Z^1 and Z^2 are both N.

3. A compound according to claim 1 or 2 wherein R^{1a} is halo or cyano and R^{1b} is hydrogen or both R^{1a} and R^{1b} are hydrogen.

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

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

6. A compound according to any preceding claim wherein AB is OCH_2, $NHCH_2$ or CH_2NH.

7. A compound according to any preceding claim wherein U is CH_2.

8. A compound according to any preceding claim wherein R^5 is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} in which Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3, or the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo, pyrido, pyridazino and pyrimidino and ring (b) non aromatic and Y^2 has 3-4 atoms including at least one heteroatom, with O, S, CH_2 or NR^{13} bonded to X^5, where R^{13} is other than hydrogen, and either NHCO bonded via N to X^3, or O, S, CH_2, or NH bonded to X^3.

9. A compound according to any of claims 1 to 7 wherein R^5 is selected from:
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
[1,3]oxathiolo[5,4-*c*]pyridin-6-yl
3,4-dihydro-2*H*-pyrano[2,3-*c*]pyridine-6-yl
3-substituted *5-H*-pyridazino[3,4-b][1,4]-thiazin-6-(7H)-one
6-substituted 2*H*-pyrido[3,2-*b*][1,4]thiazin-3(4*H*)-one
6-substituted 7-chloro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one
6-substituted 2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-one

7-substituted 1*H*-pyrido[2,3-*b*][1,4]thiazin-2(3*H*)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1*H*)-one
5-substituted 2,3-dihydrofuro[3,2-*b*]pyridine
3-substituted 6,7-dihydro[1,4]dioxino[2,3-*c*]pyridazine
2-substituted 1*H*-pyrimido[5,4-*b*][1,4]oxazin-7(6*H*)-one

10. A compound according to claim 1 which is the free base of the compound of any one of Examples 1 to 25 or a pharmaceutically acceptable salt thereof.

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

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/065505

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D491/048 C07D491/052 C07D491/056 C07D497/04
C07D498/04 C07D513/04 A61K31/4704 A61P31/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/002992 A (GLAXO GROUP LTD [GB]; AXTEN JEFFREY MICHAEL [US]; DAINES ROBERT A [US]) 8 January 2004 (2004-01-08) cited in the application claims 1,10-12	1-13
Y	WO 2008/006648 A (GLAXO GROUP LTD [GB]; DAVIES DAVID THOMAS [GB]; JONES GRAHAM ELGIN [GB) 17 January 2008 (2008-01-17) cited in the application claims 1,9-11 examples 4,10-13	1-13

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2009	15/05/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gutke, Hans-Jürgen

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/065505

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/035569 A (MORPHOCHEM AG KOMB CHEMIE [DE]; SURIVET JEAN-PHILIPPE [FR]; ZUMBRUNN C) 29 April 2004 (2004-04-29) cited in the application claims 1,12,13 examples 48,50	1-13
Y	WO 03/087098 A (SMITHKLINE BEECHAM PLC [GB]; BROOKS GERALD [GB]; DAVIES DAVID THOMAS [) 23 October 2003 (2003-10-23) cited in the application claims 1,10-12	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/065505

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