(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 March 2009 (19.03.2009)

PCT

(10) International Publication Number
WO 2009/034546 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/IB2008/053688

(22) International Filing Date:
12 September 2008 (12.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB2007/053698
13 September 2007 (13.09.2007) IB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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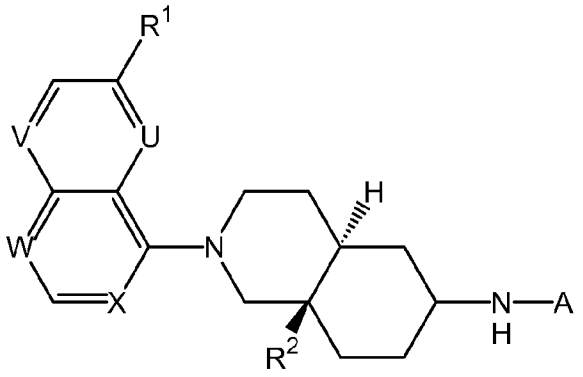
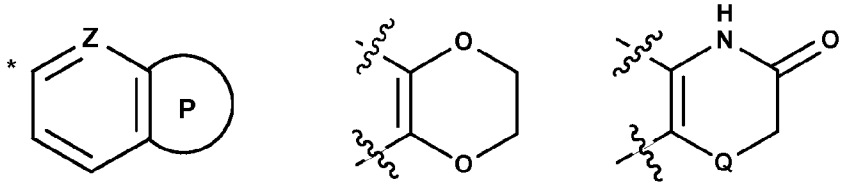
(54) Title: TRANS-DECAHYDROISOQUINOLINE DERIVATIVES



(I)



(57) Abstract: The invention relates to antibacterial compounds of formula (I) wherein R^1 is alkoxy, one or two of U, V, W, X represent(s) N, the remaining represents CH, whereby V may also represent CR^a, W may also represent CR^b and X may also represent CR^C, R^a is hydroxyalkyl; R^b is alkoxycarbonyl, carboxy or hydroxyalkyl; R^c is halogen, R^2 is alkoxycarbonyl, carboxy, hydroxyalkyl or aminoalkyl, A is CH_2B, C(=O)B or $CH_2CH=CHD$, B is the group (II) wherein Z is N or CH and the ring P is selected from the formula (III) in which Q is O or S, and D is aryl (e.g. 1,4-difluoro-2 -phenyl).

WO 2009/034546 A2

Published:

— *without international search report and to be republished upon receipt of that report*

TRANS-DECAHYDROISOQUINOLINE DERIVATIVES

The present invention concerns novel *trans*-decahydroisoquinoline derivatives, a pharmaceutical antibacterial composition containing them and the use of these compounds in the manufacture of a medicament for the treatment of infections (e.g. bacterial infections). These compounds are useful antimicrobial agents effective against a variety of human and veterinary pathogens including among others Gram-positive and Gram-negative aerobic and anaerobic bacteria and mycobacteria.

The intensive use of antibiotics has exerted a selective evolutionary pressure on microorganisms to produce genetically based resistance mechanisms. Modern medicine and socio-economic behaviour exacerbates the problem of resistance development by creating slow growth situations for pathogenic microbes, e.g. in artificial joints, and by supporting long-term host reservoirs, e.g. in immuno-compromised patients.

In hospital settings, an increasing number of strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus spp.*, and *Pseudomonas aeruginosa*, major sources of infections, are becoming multi-drug resistant and therefore difficult if not impossible to treat:

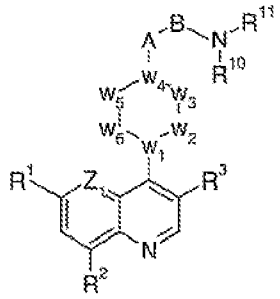
- *S. aureus* is resistant to ß-lactams, quinolones and now even to vancomycin;
- *S. pneumoniae* is becoming resistant to penicillin or quinolone antibiotics and even to new macrolides;
- *Enteroccocci* are quinolone and vancomycin resistant and ß-lactam antibiotics are inefficacious against these strains;
- *Enterobacteriacea* are cephalosporin and quinolone resistant;
- *P. aeruginosa* are ß-lactam and quinolone resistant.

Furthermore, the incidence of multi-drug-resistant Gram-negative strains such as *Enterobacteriacea* and *Pseudomonas aeruginosa,* is steadily increasing and new emerging organisms like *Acinetobacter spp.*, which have been selected during therapy with the currently used antibiotics, are becoming a real problem in hospital settings. Therefore, there is a high medical need for new antibacterial agents which overcome multidrug-

resistant Gram-negative bacilli such as *A. baumannii*, ESBL-producing *E. coli* and *Klebsiella* species and *Pseudomonas aeruginosa* (*Clinical Infectious Diseases* (2006), 42657-68).

In addition, microorganisms that are causing persistent infections are increasingly being recognized as causative agents or cofactors of severe chronic diseases like peptic ulcers or heart diseases.

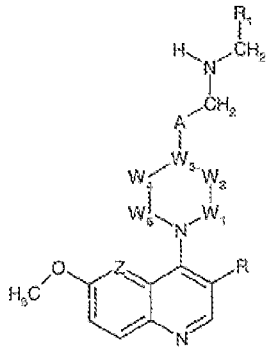
WO 2004/087145 describes antibacterial compounds of the formula (A1)



(A1)

wherein Z_1 can notably be N or CH, R^1 can notably be alkoxy, R^2 can be hydrogen or also, when Z_1 is not N, halogen, W_1 can notably be N, W_4 can notably be CH, W_2, W_3, W_5 and W_6 can notably each be a substituted methylene group, A-B can notably be a substituted ethylene group, R^{10} can notably be hydrogen and R^{11} can notably be a group $-U-R^{12}$ wherein U can notably be CH_2 or CO and R^{12} is a substituted or unsubstituted bicyclic carbocyclic or heterocyclic ring system wherein at least one of the rings is aromatic. However, the possibility of having B and W_3 or W_5 forming an additional ring is not mentioned.

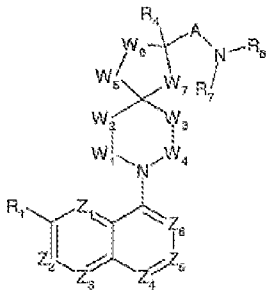
WO 2006/081289 describes antibacterial compounds of the formula (A2)



(A2)

wherein Z is CH or N, R is H or F, W_3 is CH, C(OH) or N, W_1, W_2, W_4 and W_5 are CH_2 or one W_1, W_2, W_4 and W_5 is C=O and the others are CH_2, A is CH_2 or CH(OH) and R_1 is 4*H*-pyrido[3,2-*b*][1,4]thiazin-3-oxo-6-yl, 4*H*-pyrido[3,2-*b*][1,4]oxazin-3-oxo-6-yl or 2,3-dihydro-[1,4]dioxino[2,3-*c*]-pyridin-6-yl.

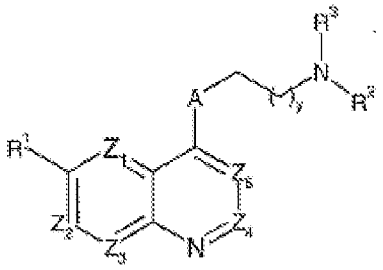
WO 2006/081182 describes spiro annelated antibacterial compounds of the formula (A3)



(A3)

wherein Z_1 can notably be CH or N, R_1 can notably be alkoxy, Z_2 and Z_5 can each notably be CH, Z_3 and Z_4 can each independently be N or CR^{1a}, R^{1a} can notably be hydrogen, halogen, hydroxy, alkyl, alkoxy, acyl or acyloxy, W_1, W_2, W_3, W_4, W_5, W_6 and W_7 are each CR_2R_3 whereby R_2 and R_3 can notably each independently be hydrogen, hydroxy, alkyl, alkoxycarbonyl, amino, alkylamino or dialkylamino, A can notably be a bond, R_7 can notably be hydrogen and R_8 is U-R_9 wherein U can notably be CH_2 or CO and R_9 is a substituted or unsubstituted bicyclic carbocyclic or heterocyclic ring system wherein at least one of the rings is aromatic.

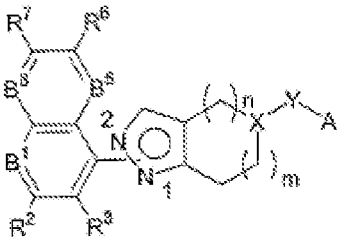
WO 2004/096982 describes antibacterial compounds of the formula (A4)



(A4)

wherein R^1 can notably be alkoxy, one of Z_1, Z_2, Z_3, Z_4 and Z_5 is N, one is or CR^{1a} and the remainder are CH, R^{1a} can notably be hydrogen, halogen, hydroxy, alkyl, alkoxy, acyl or acyloxy, A can notably represent a possibly substituted 5 membered aromatic heterocyclic ring, y is 1 or 2, R^2 can notably be hydrogen and R^3 can notably be a group –U-R^4 wherein U can notably be CH_2 or CO and R^4 is a substituted or unsubstituted bicyclic carbocyclic or heterocyclic ring system wherein at least one of the rings is aromatic.

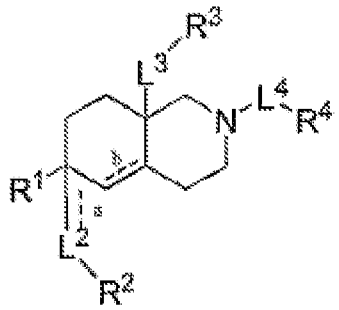
WO 2006/105289 describes antibacterial compounds of the formula (A5)



(A5)

wherein one or two of B^1, B^5 and B^8 can be N and the other(s) is (are) CR^a, R^a, R^2, R^3, R^6 and R^7 can each notably be independently hydrogen, halogen, hydroxyalkyl, carboxy or alkoxycarbonyl, m is 0 or 1 and n is 1 or 2, m + n being 2 or 3, X can notably be CH, Y can notably be -NH-CH_2-, -NH-CO- or -NH-CH_2CH=CH- and A can notably be an optionally substituted phenyl ring or also a phenyl or pyridine ring fused with a -O-$(CH_2)_{1-4}$-O-, -NH-C(O)-$(CH_2)_{1-2}$-O- or -NH-C(O)-$(CH_2)_{1-2}$-S- disubstituent at two adjacent carbons.

Besides, WO 2005/070893 describes glucocorticoid receptor inhibitors of the formula (A6)



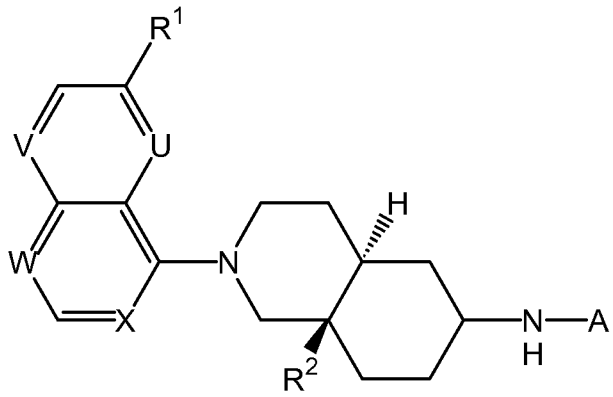
(A6)

wherein the dashed lines a and b are optionally a bond, R^1 can notably be hydrogen, L^2 can notably be a heteroalkylene chain (which could *inter alia* represent –NH-CH_2-, -NH-C(=O)- or -NH-CH_2-CH=CH-), R^2 can notably be unsubstituted or substituted aryl or heteroaryl, L^4 can notably be a bond and R^4 can notably be unsubstituted or substituted aryl or heteroaryl. Although general formula (A6) generically covers the compounds of the instant invention, there is no concrete example of any compound comprising either a heteroaromatic bicyclic ring directly attached to the nitrogen of the decahydroisoquinoline motif or a side chain attached through a nitrogen atom at the position 6 of the decahydroisoquinoline motif.

It has now surprisingly been found that certain *trans*-decahydroisoquinoline derivatives corresponding to formula I as described hereafter are useful antibacterial compounds.

Various embodiments of the invention are presented hereafter:

i) The invention firstly relates to compounds of formula I



I

wherein

R^1 is alkoxy;

one or two of U, V, W, X represent(s) N, the remaining represents CH, whereby V may also represent CR^a, W may also represent CR^b and X may also represent CR^c;

R^a is hydroxyalkyl;

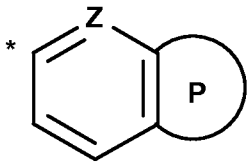
R^b is alkoxycarbonyl, carboxy or hydroxyalkyl;

R^c is halogen;

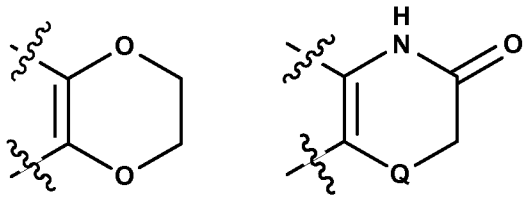
R^2 is alkoxycarbonyl, carboxy, hydroxyalkyl or aminoalkyl;

A is CH_2B, C(=O)B or $CH_2CH=CHD$;

B is the group:



wherein Z is N or CH and the ring P is selected from the following:



in which Q is O or S;

D is aryl (especially 1,4-difluoro-2-phenyl);

and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I.

The compounds of formula I may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms. Substituents at a double bond may be present in the *Z*- or *E*-configuration unless indicated otherwise. The compounds of Formula I may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the

specification and claims, unless an otherwise expressly set out definition provides a broader or narrower definition:

- The term "alkyl", used alone or in combination, refers to a straight or branched chain alkyl group, containing from one to four carbon atoms. Representative examples of alkyl groups include methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl. The term "(C_1-C_x)alkyl" (x being an integer) refers to a straight or branched chain alkyl group containing 1 to x carbon atoms.

- The term "alkoxy", used alone or in combination, refers to a straight or branched chain alkoxy group, containing from one to four carbon atoms. Representative examples of alkoxy groups include methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. The term "(C_1-C_x)alkoxy" refers to a straight or branched chain alkoxy group containing 1 to x carbon atoms.

- The term "halogen" refers to fluorine, chlorine, bromine or iodine, preferably to fluorine or chlorine.

- The term "hydroxyalkyl" refers to a straight or branched chain alkyl group substituted once by hydroxy and containing from one to four carbon atoms. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl and 2-hydroxyethyl. The term "(C_1-C_x)hydroxyalkyl" (x being an integer) refers to a straight or branched chain hydroxyalkyl group containing 1 to x carbon atoms.

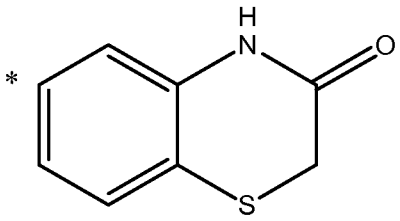
- The term "aminoalkyl" refers to a straight or branched chain alkyl group substituted once by amino and containing from one to four carbon atoms. Representative examples of aminoalkyl include, but are not limited to, aminomethyl and 2-aminoethyl. The term "(C_1-C_x)aminoalkyl" (x being an integer) refers to a straight or branched chain aminoalkyl group containing 1 to x carbon atoms.

- The term "alkoxycarbonyl" refers to an ester group wherein the alkoxy group is a straight or branched chain alkoxy group containing from one to four carbon atoms. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl and ethoxycarbonyl.

- The term "aryl" refers to a phenyl group, which may be substituted one to three times by substituents each independently selected from the group consisting of halogen,

alkyl, alkoxy and nitro. Representative examples of aryl include, but are not limited to, phenyl, 3-fluoro-phenyl and 1,4-difluoro-2-phenyl.

Moreover, the sign "*" placed near an atom will be used to designate the point of attachment of a radical to the rest of a molecule. For example:

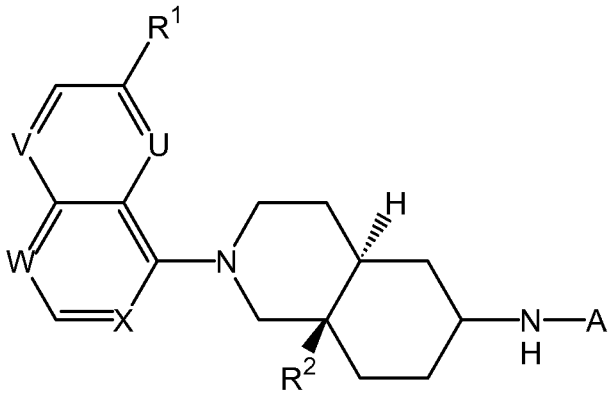


designates the 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-yl radical.

Besides, the term "room temperature" as used herein refers to a temperature of 25°C.

Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C.

ii) In particular, the invention relates to compounds of formula I that are also compounds of formula I_{CE}



I_{CE}

wherein

R^1 is alkoxy;

U and W each represent N, V represents CH or CR^a, R^a being hydroxyalkyl, and X represents CH,

or U and W each represent N, V represents CH and X represents CR^c, R^c being halogen (especially fluorine),

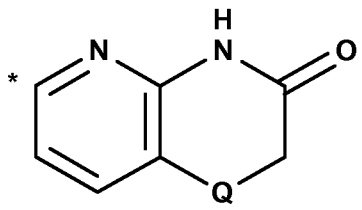
or W and X each represent N and U and V each represent CH,

or U represents N, V and X each represent CH and W represents CR^b, R^b being alkoxycarbonyl;

R^2 is alkoxycarbonyl, carboxy, hydroxyalkyl or aminoalkyl;

A is CH_2B, C(=O)B or $CH_2CH=CHD$;

B is the group:



in which Q is O or S;

D is phenyl substituted by two halogen atoms (especially 1,4-difluoro-2-phenyl);

and to salts (in particular pharmaceutically acceptable salts) of compounds of formula I_{CE}.

iii) According to a preferred embodiment of this invention, the compounds of formula I as defined in embodiment i) or ii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that R^1 is $(C_1\text{-}C_3)$alkoxy (notably methoxy or ethoxy and in particular methoxy).

iv) Another preferred embodiment of this invention relates to the compounds of formula I as defined in embodiment i), ii) or iii) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein U and W each represent N, V represents CH or CR^a, R^a being hydroxyalkyl, and X represents CH, or U and W each represent N, V represents CH and X represents CR^c, R^c being halogen (especially fluorine), or W and X each represent N and U and V each represent CH, U represents N, V and X each represent CH and W represents CR^b, R^b being alkoxycarbonyl.

v) According to one variant of the preferred embodiment iv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that U and W each represent N and V and X each represent CH or CR^c, R^c being halogen (especially fluorine).

vi) According to one subvariant of embodiment variant v) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that U and W each represent N and V and X each represent CH.

vii) According to another subvariant of embodiment variant v) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that U and W each represent N, V represents CH and X represents CR^c, R^c being halogen (especially fluorine).

viii) According to another variant of the preferred embodiment iv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that U and W each represent N, X represents CH and V represents CR^a, R^a being hydroxyalkyl (preferably (C_1-C_3)hydroxyalkyl and notably hydroxymethyl).

ix) According to a further variant of the preferred embodiment iv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that W and X each represent N and U and V each represent CH.

x) According to yet another variant of the preferred embodiment iv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that U represents N, V and X each represent CH and W represents CR^b, R^b being alkoxycarbonyl.

xi) Yet another preferred embodiment of this invention relates to the compounds of formula I as defined in one of embodiments i) to ix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein R^2 is carboxy, hydroxyalkyl or aminoalkyl (and notably carboxy, hydroxymethyl or aminomethyl).

xii) According to one variant of the preferred embodiment xi) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that R^2 is carboxy.

xiii) According to another variant of the preferred embodiment xi) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that R^2 is hydroxyalkyl (notably $(C_1$-$C_2)$hydroxyalkyl and in particular hydroxymethyl).

xiv) According to yet another variant of the preferred embodiment xi) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that R^2 is aminoalkyl (notably $(C_1$-$C_2)$aminoalkyl and in particular aminomethyl).

xv) Yet another preferred embodiment of this invention relates to the compounds of formula I as defined in one of embodiments i) to xiv) above or their salts (among which the pharmaceutically acceptable salts will be preferred) wherein A is CH_2B, C(=O)B or CH_2CH=CHD, B being selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl, and D being phenyl substituted by two halogen atoms.

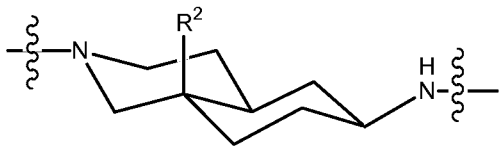
xvi) According to one variant of the preferred embodiment xv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is CH_2CH=CHD, D being phenyl substituted by two halogen atoms (especially 1,4-difluoro-2-phenyl).

xvii) According to another variant of the preferred embodiment xv) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is CH_2B or C(=O)B, B being selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl (B being in particular 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl).

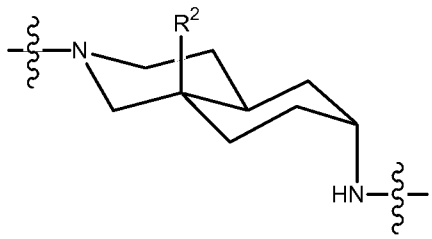
xviii) According to a subvariant of said variant xvii) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is CH_2B, B being selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl (B being in particular 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl).

xix) According to another subvariant of said variant xvii) above, the compounds of formula I or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that A is C(=O)B, B being selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl (B being in particular 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl).

xx) Preferably, the compounds of formula I as defined in one of embodiments i) to xix) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that their decahydroisoquinoline ring has one of the configurations DH_C or DH_T:



DH_C



DH_T

xxi) More preferably, the compounds of formula I as defined in embodiment xx) above or their salts (among which the pharmaceutically acceptable salts will be preferred) will be such that their decahydroisoquinoline ring has the configuration DH_C.

xxii) Particularly preferred are the following compounds of formula I as defined in embodiment i) or ii):

- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- 2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- 2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid;
- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid;

- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;
- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- [6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid [8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-amide;
- [8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[(*E*)-3-(2,5-difluoro-phenyl)-allyl]-amine;
- 2-(8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol;
- 6-({2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;
- 8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester;
- 6-{[2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

and the salts (in particular pharmaceutically acceptable salts) thereof.

xxiii) Furthermore, the following compounds of formula I as defined in embodiment i) or ii) are particularly preferred:

- (*4aS,6R,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- (*4aR,6S,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- (*4aS,6S,8aR*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester;

- (*4aR,6R,8aS*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester;

- (*4aS,6S,8aR*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid;

- (*4aR,6R,8aS*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid;

- (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid;

- (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid;

- [(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;

- [(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;

- (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;

- (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;

- [(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;

- [(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid *(4aS,6S,8aR)*-[8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-amide;

- (*4aS,6S,8aR*)-[8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[(*E*)-3-(2,5-difluoro-phenyl)-allyl]-amine;

- 2-((*4aS,6S,8aR*)-8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol;

- 2-((*4aR,6R,8aS*)-8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol;
- 6-({(*4aS,6S,8aR*)-2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;
- 6-({(*4aR,6R,8aS*)-2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;
- 8-{(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester;
- 8-{(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester;
- 6-{[*(4aS,6S,8aR)*-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 6-{[*(4aR,6R,8aS)*-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

and salts (in particular pharmaceutically acceptable salts) thereof.

xxiv) Besides, in a general manner, the radical B, when present in the compounds of formula I according to embodiment i) or any preferred embodiment, variant or subvariant according to embodiment i), will preferably be selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-yl, 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-yl, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl (B being notably 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl or 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl and in particular 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl).

Compounds of formula I are suitable for the use as chemotherapeutic active compounds in human and veterinary medicine and as substances for preserving inorganic and organic materials in particular all types of organic materials for example polymers, lubricants, paints, fibres, leather, paper and wood.

These compounds according to the invention are particularly active against bacteria and bacteria-like organisms. They are therefore particularly suitable in human and veterinary

medicine for the prophylaxis and chemotherapy of local and systemic infections caused by these pathogens as well as disorders related to bacterial infections comprising pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. faecium*, *E. casseliflavus*, *S. epidermidis*, *S. haemolyticus*, or *Peptostreptococcus spp.*; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Corynebacterium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; blood and tissue infections, including endocarditis and osteomyelitis, caused by *S. aureus*, *S. haemolyticus*, *E. faecalis*, *E. faecium*, *E. durans*, including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides; uncomplicated skin and soft tissue infections and abscesses, and puerperal fever related to infection by *Staphylococcus aureus,* coagulase-negative staphylococci (i.e., *S. epidermidis*, *S. haemolyticus*, etc.), *Streptococcus pyogenes*, *Streptococcus agalactiae*, Streptococcal groups C-F (minute colony streptococci), viridans streptococci, *Corynebacterium minutissimum*, *Clostridium spp.*, or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus aureus*, coagulase-negative staphylococcal species, or *Enterococcus spp.*; urethritis and cervicitis; sexually transmitted diseases related to infection by *Chlamydia trachomatis*, *Haemophilus ducreyi*, *Treponema pallidum*, *Ureaplasma urealyticum*, or *Neiserria gonorrheae*; toxin diseases related to infection by *S. aureus* (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; infections caused by *Mycobacterium tuberculosis*, *M. leprae*, *M. paratuberculosis*, *M. kansasii*, or *M. chelonei*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans

streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*.

Compounds of formula I according to the present invention are further useful for the preparation of a medicament for the treatment of infections that are mediated by bacteria such as *E. coli, Klebsiella pneumoniae* and other Enterobacteriaceae, *Acinetobacter spp.*, *Stenothrophomonas maltophilia*, *Neisseria meningitidis*, *Bacillus cereus*, *Bacillus anthracis*, *Corynebacterium spp.*, *Propionibacterium acnes* and bacteroide *spp.*

Compounds of formula I according to the present invention are further useful to treat protozoal infections caused by *Plasmodium malaria*, *Plasmodium falciparum*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Trypanosoma brucei* and *Leishmania spp.*

The present list of pathogens is to be interpreted merely as examples and in no way as limiting.

One aspect of this invention therefore relates to the use of a compound of fomula I according to this invention, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a bacterial infection.

As well as in humans, bacterial infections can also be treated using compounds of formula I (or pharmaceutically acceptable salts thereof) in other species like pigs, ruminants, horses, dogs, cats and poultry.

The present invention also relates to pharmacologically acceptable salts and to compositions and formulations of compounds of formula I.

Any reference to a compound of formula I is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts. Reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

A pharmaceutical composition according to the present invention contains at least one compound of formula I (or a pharmaceutically acceptable salt thereof) as the active agent and optionally carriers and/or diluents and/or adjuvants, and may also contain additional known antibiotics.

The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parenteral administration.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula I or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Another aspect of the invention concerns a method for the prevention or the treatment of a bacterial infection in a patient comprising the administration to said patient of a pharmaceutically active amount of a derivative according to formula I or a pharmaceutically acceptable salt thereof.

Besides, any preferences indicated for the compounds of formula I (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to compounds of formula I_{CE}.

Moreover, the compounds of formula I may also be used for cleaning purposes, e.g. to remove pathogenic microbes and bacteria from surgical instruments or to make a room or an area aseptic. For such purposes, the compounds of formula I could be contained in a solution or in a spray formulation.

The compounds of formula I can be manufactured in accordance with the present invention using the procedures described hereafter.

PREPARATION OF COMPOUNDS OF FORMULA I

Abbreviations:

The following abbreviations are used throughout the specification and the examples:

Ac	acetyl
AcOH	acetic acid
Alloc	allyloxycarbonyl
app.	apparent
aq.	aqueous
br.	broad
Boc	*tert*-butoxycarbonyl
n-BuLi	*n*-butyllithium
t-Bu	*tert*-butyl
Cbz	benzyloxycarbonyl
DCC	*N,N'*-dicyclohexylcarbodiimide
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EA	ethyl acetate
ESI	Electron Spray Ionisation
eq.	equivalent
ether	diethyl ether
Et	ethyl
EtOH	ethanol
Fmoc	9-fluorenylmethoxycarbonyl

HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
Hex	hexane
Hept	heptane
HOBT	1-hydroxybenzotriazole hydrate
HV	high vacuum conditions
LC	Liquid Chromatography
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MS	Mass Spectroscopy
Ms	methanesulfonyl (mesyl)
NBS	*N*-bromosuccinimide
NMO	*N*-methyl-morpholine *N*-oxide
org.	organic
OTf	trifluoromethylsulfonyloxy or triflyloxy
Pd/C	palladium on carbon
$Pd(OH)_2/C$	palladium dihydroxide on carbon
Ph	phenyl
i-Pr	*iso*-propyl
Pyr	pyridine
quant.	quantitative
rac.	racemic
rt	room temperature
sat.	saturated
SiO_2	silica gel
TBAF	tetrabutyl ammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl

TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
$TMSCHN_2$	trimethylsilyldiazomethane
Ts	*para*-toluenesulfonyl

General reaction techniques:

Part 1: reductive amination:

The reaction between the amine and the aldehyde or ketone is performed in a solvent system allowing the removal of the formed water through physical or chemical means (e.g. distillation of the solvent-water azeotrope or presence of drying agents such as molecular sieves, $MgSO_4$ or Na_2SO_4). Such solvent is typically toluene, Hex, THF, DCM or 1,2-DCE or mixture of solvents such as 1,2-DCE/MeOH. The reaction can be catalyzed by traces of acid (usually AcOH). The intermediate imine is reduced with a suitable reducing agent (e.g. $NaBH_4$, $NaBHCN_3$, or $NaBH(OAc)_3$ or through hydrogenation over a noble catalyst such as Pd/C. The reaction is carried out between -10°C and 110°C, preferably between 0°C and 60°C. The reaction can also be carried out in one pot. It can also be performed in protic solvents such as MeOH or water in presence of a picoline-borane complex (*Tetrahedron* (2004), **60**, 7899-7906).

Part 2: amide formation:

The carboxylic acid is reacted with the amine in presence of an activating agent such as DCC, EDC, HOBT, n-propylphosphonic cyclic anhydride, HATU or di-(*N*-succinimidyl)-carbonate, in a dry aprotic solvent such as DCM, MeCN or DMF between –20°C and +60°C (see G. Benz in *Comprehensive Organic Synthesis*, B.M. Trost, I. Fleming, Eds; Pergamon Press: New York (1991), vol. **6**, p. 381). Alternatively, the carboxylic acid can be activated by conversion into its corresponding acid chloride by reaction with oxalyl chloride or thionyl chloride neat or in a solvent like DCM between -20° and +60°C.

Further activating agents can be found in *Comprehensive Organic Transformations. A guide to Functional Group Preparations;* 2nd Edition, R. C. Larock, Wiley-VC; New York, Chichester, Weinheim, Brisbane, Singapore, Toronto, 1999. Section nitriles, carboxylic acids and derivatives p.1941-1949.

Part 3: reduction of an ester into an alcohol:

The ester dissolved in a dry solvent such as ether, THF is treated between –20°C and 70°C with either an aluminium hydride reagent such as $LiAlH_4$ or $NaAlH_2(OCH_2CH_2OMe)_2$ or a borohydride reagent such as $NaBH_4$.

Part 4: hydrolysis of an ester into an acid:

When the ester side chain is a linear alkyl, the hydrolysis is usually performed by treatment with an alkali hydroxide such as LiOH, KOH or NaOH in a water-dioxane or water –THF mixture between 0°C and 80°C. When the ester side chain is *tert*-butyl, the hydrolysis can also be performed in neat TFA or diluted TFA or HCl in an organic solvent such as ether or THF. When the ester side chain is the allyl group, the reaction is performed in presence of tetrakis(triphenylphosphine)palladium(0) in presence of an allyl cation scavenger such as morpholine, dimedone or tributyltin hydride between 0°C and 50°C in a solvent such as THF. When the ester side chain is benzyl, the reaction is performed under hydrogen in presence of a noble metal catalyst such as Pd/C in a solvent such as MeOH, THF or EA. Further strategies to introduce other acid protecting groups and general methods to remove them have been described in Protecting Groups in Organic Synthesis 3rd Ed; 1999, 369-441; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

Part 5: conversion of an alcohol into an amine:

The alcohol is reacted with MsCl, TfCl or TsCl in presence of a base such as TEA in a dry aprotic solvent such as Pyr, THF or DCM between -30°C and 50°C. In the case of the triflate or mesylate, Tf_2O or Ms_2O can also be used. The resulting sulfonate is reacted with sodium azide in a solvent such as THF or DMF between 20°C and 100°C. The resulting azide is converted into the corresponding amine after either hydrogenolysis over a noble metal catalyst such as Pd/C or platinum in a solvent such as THF, methanol or ethyl acetate, or by reaction with PPh_3 followed by the addition of water.

Part 6: substitution reaction:

The sulfonate or the halogenide is reacted with the corresponding amine in presence of an organic base such as DIPEA in a solvent such as DMF between 50°C and 110°C.

Part 7: amine protection:

Amines are usually protected as carbamates such as Alloc, Cbz, Fmoc or Boc. They are obtained by reacting the amine with allyl, fluorenylmethyl or benzyl chloroformate or with di tert-butyl dicarbonate in presence of a base such as NaOH, TEA, DMAP or imidazole. Further strategies to introduce other amine protecting groups have been described in Protecting Groups in Organic Synthesis, 3rd Ed (1999), 494-653; T.W. Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

Part 8: amine deprotection:

The benzyl carbamates are deprotected by hydrogenolysis over a noble catalyst (e.g. Pd/C or $Pd(OH)_2/C$). The Boc group is removed under acidic conditions such as HCl in an organic solvent such as MeOH or dioxane, or TFA neat or diluted in a solvent such DCM. Further general methods to remove amine protecting groups have been described in *Protecting Groups in Organic Synthesis*, 3rd Ed (1999), 494-653; T.W. Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

Part 9: silyl ether formation:

The alcohol derivative is treated with the desired silylchloride (e.g. TMSCl, TBDMSCl) in a solvent such as THF or DCM between –20°C and 50°C in presence of an organic base such as TEA and traces of DMAP or imidazole.

Part 10: silyl ether removal:

The silyl ether groups are removed either using fluoride anion sources such as TBAF in THF between 0°C and 40°C or HF in MeCN between 0°C and 40°C or using acidic conditions such as AcOH in THF/MeOH or HCl in MeOH. Further methods to remove the TBDMS, TMS and TBDPS groups are given in *Protecting Groups in Organic Synthesis* 3rd Ed; 1999, 133-139 and 142-143 respectively; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.). Further general methods to remove alcohol protecting groups are described in Protecting Groups in Organic Synthesis 3rd Ed; 1999,

23-147; T.W.Greene, P.G.M. Wuts; (Publisher: John Wiley and Sons, Inc., New York, N.Y.).

Part 11: triflate formation:

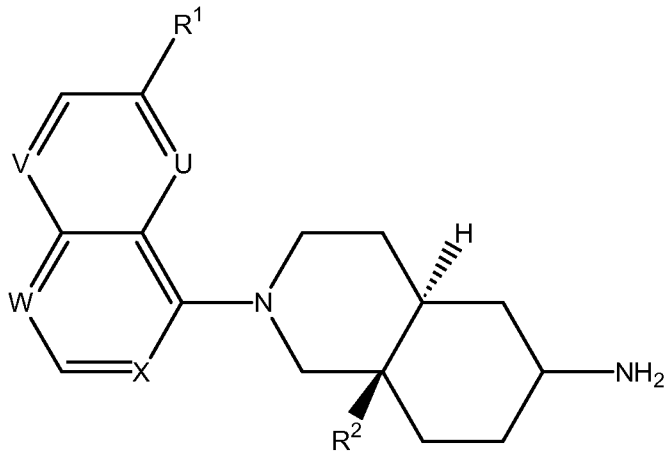
The alcohol or phenol is treated in a solvent such as THF, DCM or DMF between -20°C and 60°C with *N*-phenyl-bis(trifluoromethanesulfonimide), trifluoromethylsulfonyl anhydride or trifluoromethylsulfonyl chloride in presence of an organic base such as TEA or DIPEA.

General preparation methods:

Preparation of compounds of formula I:

The compounds of formula I can be manufactured in accordance with the present invention by

a) reaction of a compound of formula II



II

wherein R^1, R^2, U, V, W, X are as in formula I

with an aldehyde of formula III

B-CHO

III

wherein B is as in formula I, as described in part 1 of the section "General reaction techniques"; or

b) reaction of a compound of formula II as defined in a) above with a carboxylic acid of formula IV

B-COOH

IV

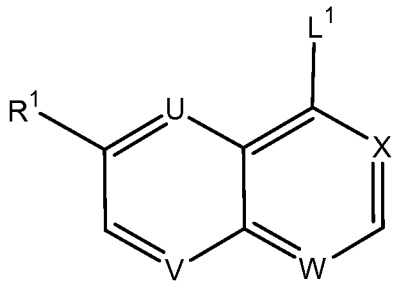
wherein B is as in formula I, as described in part 2 of the section "General reaction techniques"; or

c) reduction of a compound of formula I wherein R^2 is alkoxycarbonyl into a compound of formula I wherein R^2 is hydroxyalkyl as described in part 3 of the section "General reaction techniques"; or

d) hydrolysis of a compound of formula I wherein R^2 is alkoxycarbonyl into a compound of formula I wherein R^2 is carboxy as described in part 4 of the section "General reaction techniques"; or

e) transformation of a compound of formula I wherein R^2 is hydroxyalkyl into a compound of formula I wherein R^2 is aminoalkyl as described in part 5 of the section "General reaction techniques"; or

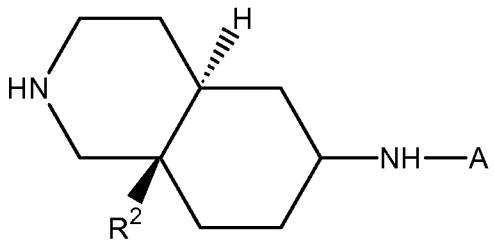
f) reaction of a compound of formula V



V

wherein R^1, U, V, W, X are as in formula I and L^1 represents halogen or OTf

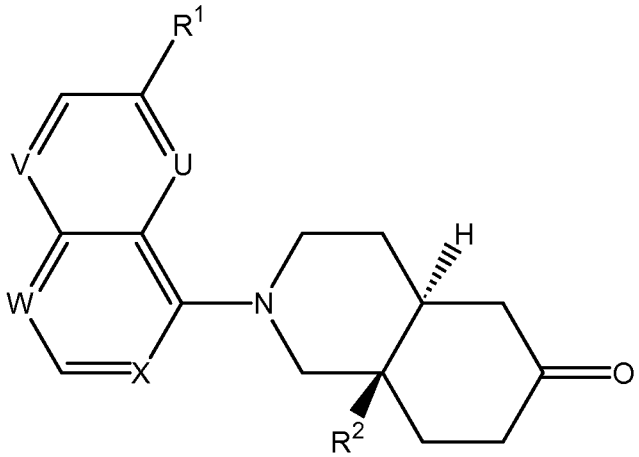
with a compound of formula VI



VI

wherein R^2 and A are as in formula I as described in part 6 of the section "General reaction techniques"; or

g) reaction of a compound of formula VII



VII

wherein R^1, U, V, W, X are as in formula I and R^2 represents alkoxycarbonyl or hydroxyalkyl with an amine of formula VIII

$$A\text{-}NH_2$$

VIII

as described in part 1 of the section "General reaction techniques".

The compounds of formula I thus obtained may, if desired, be converted into their salts, and notably into their pharmaceutically acceptable salts.

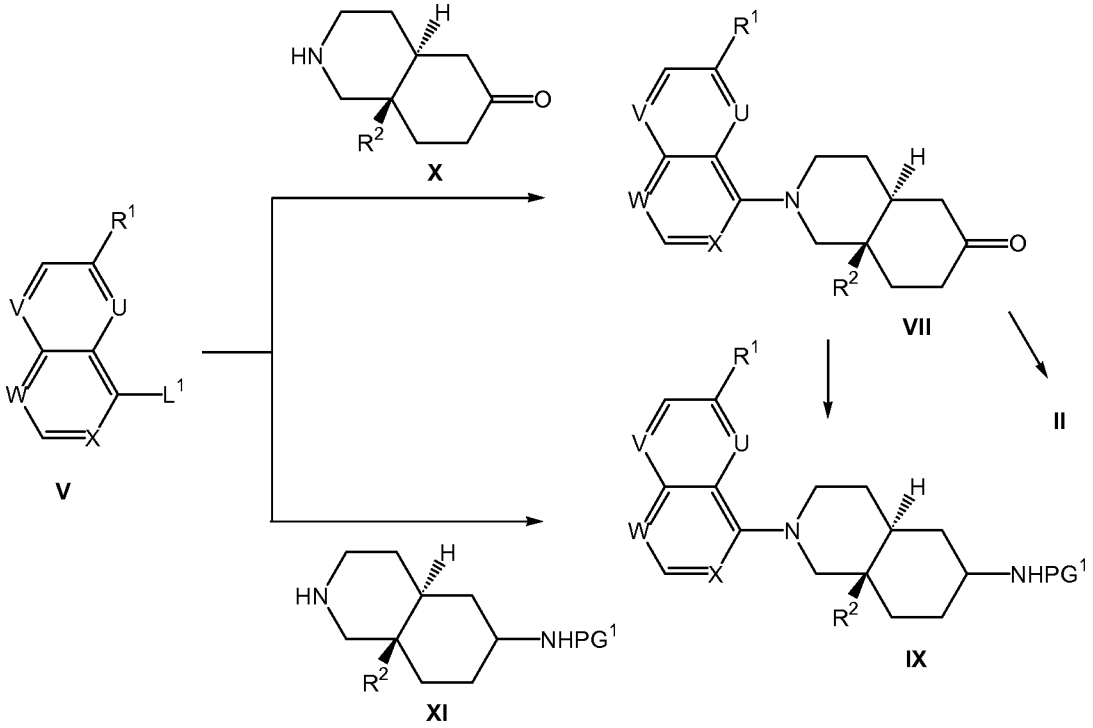
Compounds of formula I with controlled stereochemistry at the chiral carbons on the decahydroisoquinoline group can be obtained either by separation of the diastereomeric

mixtures obtained from the chiral starting material of formula XII (described later) on non chiral columns, or by separation of the racemates obtained starting from the racemic intermediates of formula VI, X, XI or XII (the intermediates of formula X, XI or XII being described later) on a chiral column.

Whenever the compounds of formula I are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such as a Regis Whelk-O1(R,R) (10 mm) column, a Daicel ChiralCel OD-H (5-10 mm) column, or a Daicel ChiralPak IA (10 mm) or AD-H (5 mm) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (EtOH, in presence or absence of an amine such as triethylamine, diethylamine) and eluent B (hexane), at a flow rate of 0.8 to 150 mL/min.

Preparation of the compounds of formula II:

The compounds of formula II can be obtained by deprotection of compounds of formula IX as described in part 7 of the section "General reaction techniques". The compounds of formula II can also be obtained as summarised in Scheme 1 hereafter.

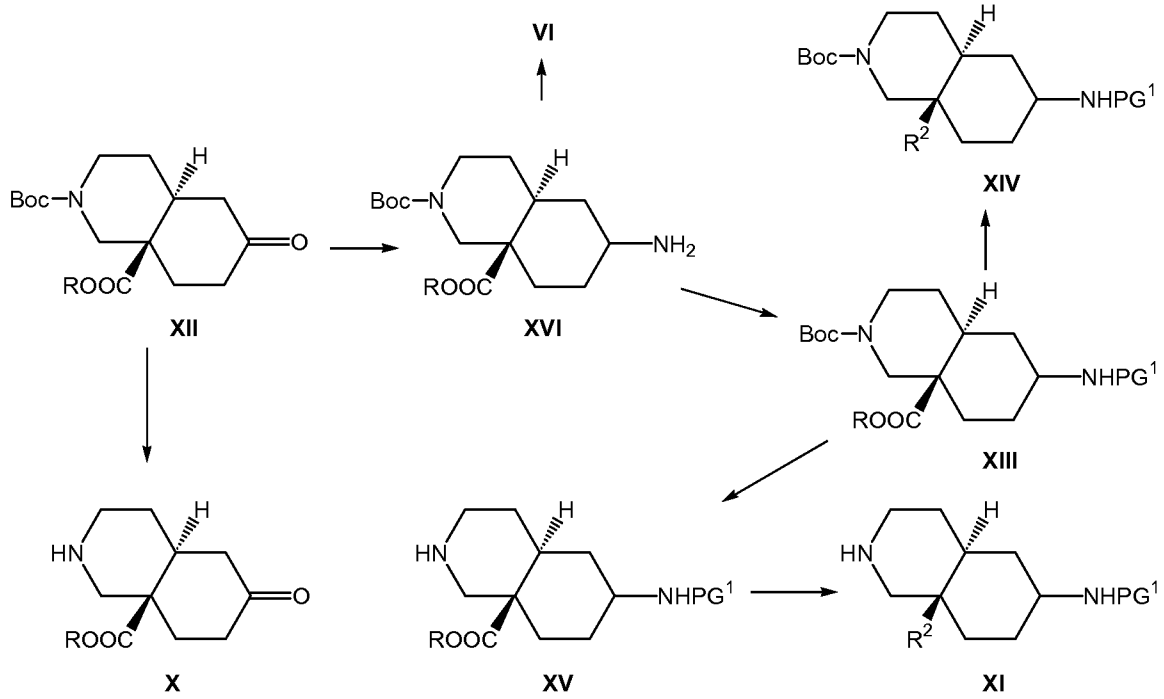


Scheme 1

In Scheme 1 R^1, R^2, U, V, W, X are as in formula I, L^1 represents halogen or OTf and PG^1 represents an amine protecting group such as Boc, Fmoc or Cbz.

The compounds of formula II can thus be obtained (Scheme 1) from the intermediate of formula V after reaction with the amine of formula X, as described in part 6 of the section "General reaction techniques" followed by sequential reductive amination of the ketone of formula VII with benzylamine as described in part 1 of the section "General reaction techniques" followed by hydrogenolysis over a noble metal catalyst such as Pd/C or platinum oxide. The compounds of formula IX can be obtained by reaction of the intermediate of formula V with the amine of formula XI as described in part 6 of the section "General reaction techniques".

The amines of formula XI can be prepared as summarised in Scheme 2 hereafter.



Scheme 2

In Scheme 2, R represents alkyl and PG^1 represents an amine protecting group such as Cbz or Fmoc.

The amines of formula XI (PG = Cbz, Fmoc) can be obtained (Scheme 2) from the known ketones of formula XII (obtained according to *Org. Lett.* (2004), **6**, 1171-1173) by reductive amination with benzylamine as described in part 1 of the section "General

reaction techniques" followed by hydrogenolysis over a noble metal catalyst such as Pd/C or platinum oxide affording the amines of formula XVI. The compounds of formula XVI can be transformed into the compounds of formula VI after reductive amination with the aldehydes of formula III followed by removal of the Boc protecting group as described in part 7 of the section "General reaction techniques". The amines of formula XVI can also be protected as Cbz or Fmoc derivatives of formula XIII as described in part 8 of the section "General reaction techniques". The Boc group of these *bis*-protected amines can then be removed as described in part 7 of the section "General reaction techniques" to afford the compounds of formula XV, which can be further elaborated into the compounds of formula XI wherein R^2 is hydroxymethyl or aminomethyl following procedures described in parts 3 and 5 of the section "General reaction techniques". The compounds of formula XIII can be further elaborated into the compounds of formula XIV wherein R^2 is hydroxymethyl or aminomethyl as described in part 3 and 5 of the section "General reaction techniques".

Preparation of the compounds of formula III and IV:

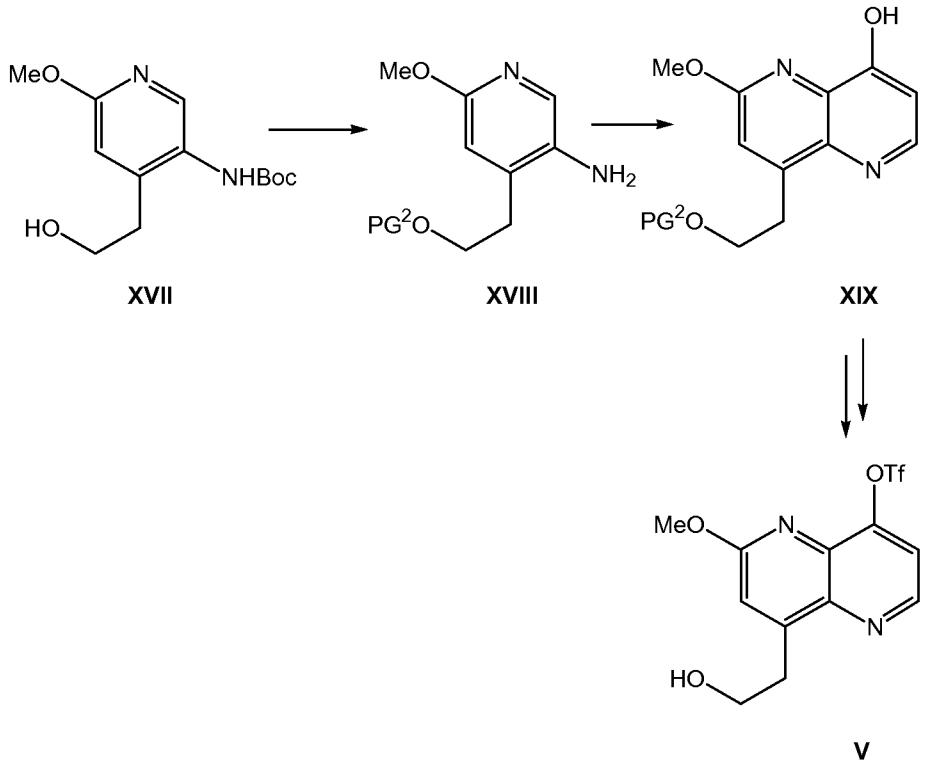
The compounds of formula III and IV are commercially available or can be prepared by methods known to one skilled in the art, e.g. methods derived from those described in WO 2007/042325 (compounds of formula III wherein Q = S and Z = N) or WO 2006/032466 (compounds of formula III or IV wherein D = 1,4-difluorophen-2-yl).

Preparation of the compounds of formula V:

The compounds of formula V wherein U = W = N, V = CH, X = CH or CF, R^1 = OMe and L^1 = Br are commercially available. The compounds of formula V wherein W = N, U = V = CH, X = CH, R^1 = OMe and L^1 = Br and the compounds wherein W = X = N, U = V = CH, R^1 = OMe and L^1 = Br are also commercially available. The compound of formula V wherein W = N, U = V = CH, X = CF, R^1 = OMe and L^1 = Br can be prepared according to WO 2006/002047.

The compounds of formula V wherein L^1 is OTf can be prepared according to literature procedures (WO 02/08224 when R^1 = OMe, U = W = N and V = X= CH; WO 00/40554 when R^1 = OMe, U = V= X = CH and W = N) and as described in part 11 of the section "General reaction techniques".

The compounds of formula V wherein U = N, W = X = CH, R^1 = OMe, L^1 = OTf and V = CCH_2CH_2OH can be prepared as shown in Scheme 3 hereafter.

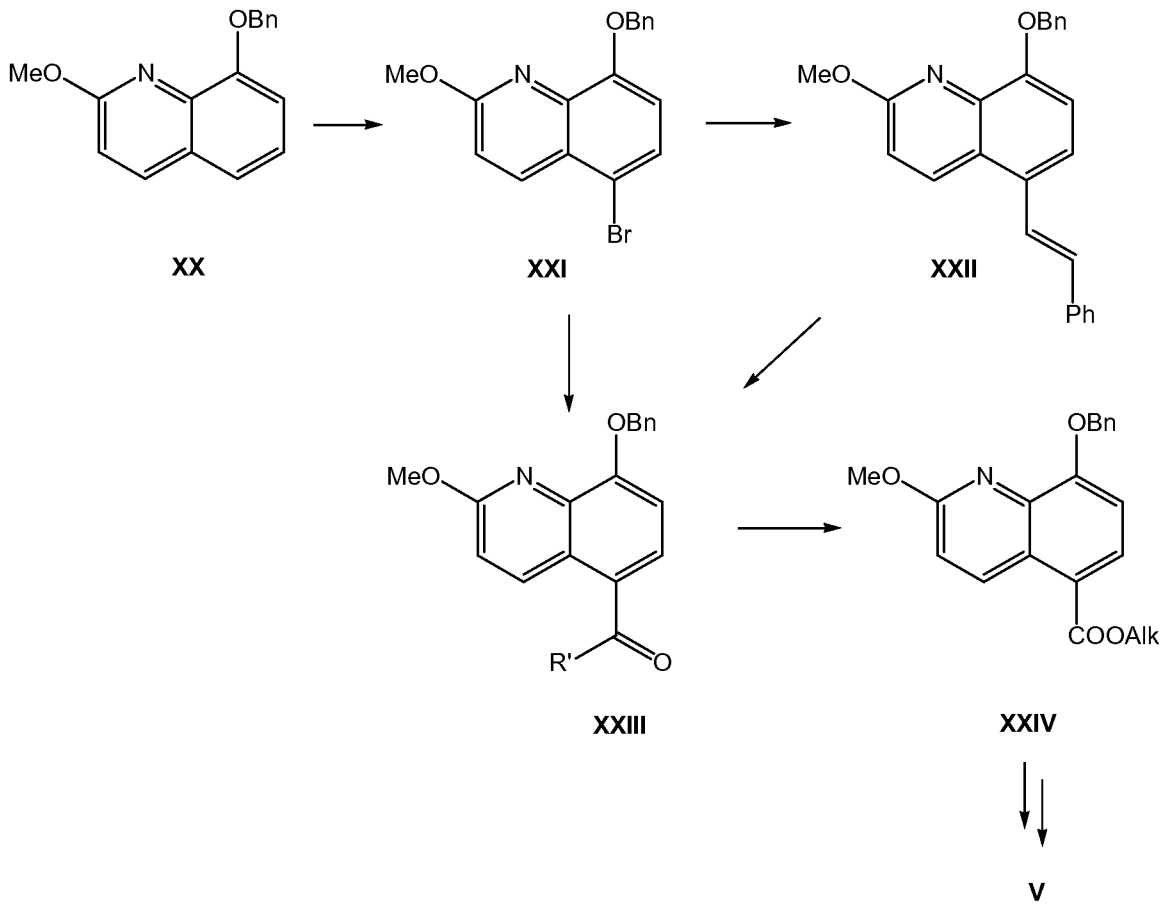


Scheme 3

In Scheme 3, PG^2 represents TMS or TBDMS.

The compounds of formula V wherein U = N, W = X= CH, R^1 = OMe, L^1 = OTf and V = CCH_2CH_2OH can be prepared (Scheme 3) starting from the know pyridine derivative of formula XVII (EP 152 135). Protection of the alcohol function as a silyl ether as described in part 9 of the section "General reaction techniques" followed by the removal of the Boc protective group as described in part 7 of the section "General reaction techniques" leads to the formation of the amine of formula XVIII, which can be reacted with triethylorthoformate and Meldrum's acid. The compound of formula V can then be obtained by converting the resulting naphthyridinol derivative of formula XIX into the corresponding triflate (see part 11 of the section "General reaction techniques") and removing the silyl protecting group PG^2 (see part 10 of the section "General reaction techniques").

The compounds of formula V wherein U = N, V = X = CH and W is alkoxycarbonyl can be prepared as summarised in Scheme 4 hereafter.



Scheme 4

In Scheme 4, R' is H, OH or OMe and Alk is alkyl.

The compounds of formula V wherein U = N, V = X = CH, W is CR^b, R^b being alkoxycarbonyl, and L^1 = OTf can be prepared (Scheme 4) by reacting the known quinolines of formula XX (see WO 2004/002992) with NBS. The resulting bromo derivatives of formula XXI can be subjected to a Heck reaction with vinyl boronic acids such as *trans*-2-phenylvinyl boronic acid in presence of a palladium catalyst such as $Pd[P(Ph)_3]_4$ followed by the oxidation of the double bond into the corresponding aldehydes of formula XXIII (R' = H) either by ozonolysis or by a tandem *cis*-dihydroxylation with potassium osmiate/oxidation with NMO. The aldehydes can be further oxidised into the corresponding acids of formula XXIII (R' = OH) with sodium chlorite and protected as its methyl ester after reaction with a diazomethane derivative such as $TMSCHN_2$.

Alternatively, the methyl ester of formula XXIII (R' = OMe) can also be obtained by reaction of the bromo quinoline of formula XXI with a strong base such as *n*-BuLi and methyl chloroformate. The benzyl ether protecting group of the compounds of formula XXIV can then be removed upon hydrogenolysis over a noble metal catalyst such as Pd/C and the intermediate obtained further transformed into the corresponding triflate of formula V as described in part 11 of the section "General reaction techniques".

Preparation of the compounds of formula VI:

The preparation of the compounds of formula VI has already been dealt with previously (see "preparation of compounds of formula II", Scheme 2).

Preparation of the compounds of formula VII:

The preparation of the compounds of formula VII has already been dealt with previously (see "preparation of compounds of formula II", Scheme 1).

Preparation of the compounds of formula VIII:

The compounds of formula VIII are obtained from the corresponding aldehydes of formula III after reduction into the corresponding alcohol and transformation into the corresponding amine as described in part 5 of the section "General reaction techniques".

Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

EXAMPLES

All analytical and preparative HPLC investigations on non-chiral phases were performed using RP-C18 based columns.

Example 1: (*4aS,6R,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (*4aR,6S,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester:

1.i. *Rac-(4aS,6RS,8aR)-6-benzylamino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of *rac*-(4aS,8aR)-6-oxo-2-*tert*-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester (prepared as described in *Org. Lett.* (2004), **6**, 1171; 1.73 g, 5.54 mmol) in 1,2-DCE (70 mL) were added benzylamine (0.667 mL, 1.1 eq.) and sodium triacetoxy borohydride (1.70 g, 1.45 eq.). The reaction mixture was stirred at rt for 3 h. Sat. aq. $NaHCO_3$ was added and the phases were separated. The aq. layer was extracted once with DCM-MeOH (9-1, 50 mL) . The combined org. layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified over SiO_2 (DCM-MeOH 97-3 containing 0.3% aq. NH_4OH) to afford the title compound as a yellow oil (1.99 g, 89% yield). The compound was obtained as a 1-1 mixture of epimers. MS (ESI, m/z): 403.0 $[M+H^+]$.

1.ii. *Rac-(4aS,6RS,8aR)-6-amino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of intermediate 1.i (1.93 g, 4.8 mmol) in MeOH (35 mL) containing AcOH (0.303 mL) was added 10% Pd/C (0.45 g). The resulting suspension was stirred under hydrogen atmosphere for 4 h. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. The residue was partitioned between sat. aq. $NaHCO_3$ and DCM-MeOH (9-1, 100 mL). The phases were separated and the aq. layer was extracted 4 times (4 x 50mL). The combined org. layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column

chromatography over SiO_2 (from DCM-MeOH 9-1 containing 1% aq.NH_4OH to DCM-MeOH 4-1 containing 1% aq. NH_4OH) to afford the title amine as a yellow oil (1.33 g, 88% yield).

MS(ESI, m/z): 313.1 [$M+H^+$].

1.iii. *Rac-(4aS,6RS,8aR)-6-benzyloxycarbonylamino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of intermediate 1.ii (1.33 g, 4.25 mmol) in acetone (17 mL) and water (17 mL) were added $NaHCO_3$ (1.43 g) and benzylchloroformate (0.657 mL, 1 eq.) at rt under vigorous stirring. The reaction was stirred 1 h. The solvent was removed under reduced pressure and the residue was extracted with EA (2 x 150 mL). The combined org. layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the title compound as a pale yellow oil (1.89 g).

MS (ESI, m/z): 447.0 [$M+H^+$].

1.iv. *Rac-(4aS,6RS,8aR)-6-benzyloxycarbonylamino octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

A solution of intermediate 1.iii (1.4 g, 3.1 mmol) in TFA (10 mL) was stirred at RT for 20 min and the reaction mixture was concentrated to dryness. The residue was diluted with DCM-MeOH (9-1, 100 mL) and 1*M* NaOH was added until pH 10 was reached. The phases were separated and the aq. layer was extracted three times with DCM-MeOH (9-1, 3 x 50 mL). The combined org. layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH then DCM-MeOH 9-1 containing 1% aq. NH_4OH) to afford the title amine as pale yellow foam (0.804 g, 74% yield). The compound was obtained as a 1.8-1 mixture of isomers.

^1H NMR ($CDCl_3$) δ: 7.35 (m, 5H); 5.10 (br. d, J = 4.8 Hz, 2H); 5.1 (br. d, 0.36H); 4.64 (br. d, 0.64H); 3.98 (m, 0.64H); 3.73 (s, 3 × 0.36H); 3.72 (s, 3 × 0.64H); 3.66 (m, 0.36H); 3.28 (m, 1H); 3.12 (m, 1H); 2.69 (m, 1H); 2.38 (d, J = 12.2 Hz, 0.64H); 2.35 (d, J = 12.2 Hz, 0.36H); 2.20 (m, 0.64H); 2.20-1.09 (m, 9.36 H).

MS (ESI, m/z): 347.0 [$M+H^+$].

1.v. *Rac-(4aS,6RS,8aR)-6-benzyloxycarbonylamino-2-(6-methoxy-[1,5]naphthyridin-4-yl)- octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of intermediate 1.iv (0.802 g, 2.31 mmol) in DMF (16 mL) were added DIPEA (0.793 mL) and trifluoromethanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (0.785 g, 1.1 eq.). The resulting mixture was heated at 100°C for 3 h. The reaction mixture was concentrated to dryness and purified by column chromatography over SiO_2 (DCM-MeOH 97-3 containing 1% aq. NH_4OH then DCM-MeOH 19-1 containing 1% aq. NH_4OH) to afford the title compound as a red-brown oil (0.89 g, 76% yield).
MS (ESI, m/z): 505.9 [$M+H^+$].

1.vi. *Rac-(4aS,6RS,8aR)-6-amino-2-(6-methoxy-[1,5]naphthyridin-4-yl)- octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of intermediate 1.v (0.88 g) in EA (25 mL) was added 10% Pd/C (0.742 g). The reaction was stirred under hydrogen atmosphere for 4 h. More 10% Pd/C (0.380 g) was added and the reaction mixture stirred for 1 h. The reaction mixture was filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH) to afford the title compound as an off-white foam (0.336 g, 52% yield). The compound was obtained as a 1.8-1 mixture of isomers.
^1H NMR (d6-DMSO) δ: 8.42 (d, 5.2 Hz, 1H); 8.14 (d, J = 9.0 Hz, 1H); 7.18 (d, J = 9.0 Hz, 1H); 6.94 (d, J = 5.3 Hz, 0.64H); 6.93 (d, J = 5.3 Hz, 0.36H); 4.98 (dd, J = 1.7, 12.5 Hz, 0.36H); 4.88 (dd, J = 1.7, 12.5 Hz, 0.64H); 4.54 (m, 1H); 4.00 (s, 3H); 3.21-2.96 (m, 2H), 3.21 (s, 3 × 0.64H); 3.20 (s, 3 × 0.36H); 2.65-2.20 (m, 0.36H); 2.40 (m, 0.64H); 2.16-2.02 (m, 2H); 1.92-1.27 (m, 8H).
MS (ESI, m/z): 371.2 [$M+H^+$].

1.vii. *(4aS,6R,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (4aR,6S,8aS)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a solution of intermediate 1.vi (0.165 g, 0.45 mmol) in MeOH (1.8 mL) and 1,2-DCE (6.2 mL) were added 3Å molecular sieves (2.6 g) and 3-(2,5-difluoro-phenyl)-propenal

(0.082 g, 1.1 eq.). The mixture was stirred at 50°C overnight. $NaBH_4$ (0.165 g) was added and the reaction mixture was stirred for 2 h. The reaction mixture was filtered over hydromatrix® (treated with sat. $NaHCO_3$) and the filtrate was evaporated under reduced pressure. The residue was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH) to afford as a white foam (0.078 g, 33% yield) a mixture of (*4aS,6R,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (*4aR,6S,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester.

^1H NMR (d6-DMSO) δ: 8.42 (d, J = 5.3 Hz, 1H); 8.14 (d, J = 9.0 Hz, 1H); 7.51 (ddd, J = 3.1, 6.0, 9.3 Hz, 1H); 7.27 (m, 1H); 7.18 (d, J = 9.0 Hz, 2H); 7.13 (m, 1H); 6.93 (d, J = 5.3 Hz, 1H); 6.64 (d, J = 16.4 Hz, 1H); 6.54 (dt, J = 5.16, 16.4 Hz, 1H); 4.89 (br. d, J = 12.7 Hz, 1H); 4.55 (br. d, J = 12.5 Hz, 1H); 3.99 (s, 3H); 3.36 (d, J = 2.6 Hz, 2H); 3.11 (s, 3H); 3.09-2.94 (m, 3H); 2.37 (qd, J = 3.7, 6.2 Hz, 1H); 2.17-1.99 (m, 2H); 1.98 (br. s, 1H); 1.90-1.82 (m, 2H); 1.81-1.53 (m, 2H); 1.35 (dd, J = 10.6, 33.50 Hz); 1.23 (m, 1H).

MS (ESI, m/z): 523.0 [$M+H^+$].

R_f (DCM-MeOH 19-1 containing 1% aq. NH_4OH) = 0.31.

The elution was continued to afford a mixture of the isomers (0.055 g) and then the second isomer was obtained as an off-white foam (see Example 2; 0.013 g, 5% yield).

MS (ESI, m/z): 523.0 [$M+H^+$].

R_f (DCM-MeOH 19-1 containing 1% aq. NH_4OH) = 0.21.

Example 2: (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester:

2.i. *Rac-(4aS,6S,8aR)-6-benzylamino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

To a mixture of *rac*-(*4aS,8aR*)-6-oxo-2-*tert*-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester (prepared as described in *Org. Lett.* (2004), **6**, 1171; 25.31 g, 81.3 mmol) in 1,2-DCE (400 mL) were added successively benzyl amine

(10.0 mL, 91.4 mmol) and sodium triacetoxy borohydride (25.48 g, 120.2 mmol). The reaction mixture was stirred at rt overnight and aq. sat. $NaHCO_3$ (500 mL) was added and the two phases were separated. The aq. layer was extracted once more with a DCM-MeOH mixture (9-1, 200 mL). The combined org. layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was chromatographed over SiO_2 (DCM-MeOH 97-3 containing 0.3% aq. NH_4OH to DCM-MeOH 9-1 containing 1% aq. NH_4OH) to afford the first isomer as a dark oil (15 g, 46% yield) and then the title isomer as a dark oil (15 g, 46% yield).

MS (ESI, m/z): 403.0 [$M+H^+$].

2.ii. *Rac-(4aS,6S,8aR)-6-benzylamino-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

A solution of intermediate 2.i (0.275 g, 0.68 mmol) in TFA (3 mL) was stirred at rt for 20 min and the reaction mixture was concentrated to dryness. The residue was partitioned between sat. $NaHCO_3$ (30 mL) and DCM-MeOH 9-1 (50 mL). The pH was adjusted to 9-10 by addition of 1*M* NaOH. The two layers were separated and the aq. layer was extracted 6 times with DCM-MeOH 9-1 (6 x 50 mL). The combined org. layers were dried over $MgSO_4$, filtered, evaporated under reduced pressure and further dried under HV to give the title amine as a yellow oil (0.19 g, 92% yield).

MS (ESI, m/z): 303.2 [$M+H^+$].

2.iii. *Rac-(4aS,6S,8aR)-6-benzylamino-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 2.ii (0.19 g, 0.63 mmol), the title compound was obtained as a brownish oil (0.257 g, 89% yield) using the procedure of Example 1, step 1.v. The crude material was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).

MS (ESI, m/z): 460.8 [$M+H^+$]

2.iv. *Rac-(4aS,6S,8aR)-6-amino-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 2.iii (0.257 g, 0.56 mmol), the title amine was obtained as a yellowish foam (0.163 g, 79% yield) using the procedure of Example 1, step 1.ii. The

crude material was purified by chromatography over SiO_2 (DCM-MeOH 6-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 371.0 $[M+H^+]$

2.v. *(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (4aR,6R,8aS)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 2.iv (0.148 g, 0.4 mmol), the title compound was obtained as a white foam (0.135 g, 65% yield) using the procedure of Example 1, step 1.vii. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).

MS (ESI, m/z): 523.0 $[M+H^+]$.

Example 3 : (*4aS,6S,8aR*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (*4aR,6R,8aS*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester:

To a solution of intermediate 1.vi (0.156 g, 0.42 mmol) in MeOH (1.7 mL) and 1,2-DCE (5.8 mL) were added 3Å molecular sieves (1.56 g) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (0.090 g, 1.1 eq.). The mixture was stirred at 50°C overnight. $NaBH_4$ (0.156 g) was added and the reaction mixture was stirred for 2 h. The reaction mixture was filtered over hydromatrix® (treated with sat. $NaHCO_3$) and the filtrate was evaporated under reduced pressure. The residue was purified over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH) to afford first *rac-(4aS,6R,8aR)*-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester as a yellowish foam (0.117 g, 51% yield).

MS (ESI, m/z): 549.0 $[M+H^+]$.

R_f (DCM-MeOH 19-1 containing 1% aq. NH_4OH) = 0.21.

The elution was continued to afford the title compounds as a white foam (0.063 g, 28% yield).

MS (ESI, m/z): 549.1 [M+H$^+$].

R_f (DCM-MeOH 19-1 containing 1% aq. NH_4OH) = 0.17.

Example 4 : (*4aS,6S,8aR*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid and (*4aR,6R,8aS*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid:

A solution of the compound mixture of Example 3 (0.055 mg, 0.105 mmol) was refluxed in 6*N* HCl (2 mL) overnight. The reaction mixture was concentrated to dryness, diluted with water (10 mL) and the pH was adjusted to 7 by addition of 50% aq. KOH. The mixture was extracted twice with DCM-MeOH 9-1 (2 x 50mL). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 93-7 containing 1% aq. NH_4OH) to afford the title compounds as a pale yellow solid (0.006 g, 19% yield).

MS (ESI, m/z): 535.1 [M+H$^+$].

Example 5 : (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid and (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid:

Starting from a mixture of the compound mixtures of Example 2 and Example 1 (5:1, 0.055 g, 0.105 mmol), the title compounds were obtained as a white solid (0.024 g, 45% yield) using the procedure of Example 4. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 93-7 containing 1% aq. NH_4OH), followed by trituration in ether.

MS (ESI, m/z): 509.0 [M+H$^+$].

Example 6: [(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol and [(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol:

6.i. *Rac-(4aS,6S,8aR)-6-amino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 2.i (14.14 g, 35.14 mmol), the title amine was obtained as a yellowish solid (10.01 g, 91% yield) using the procedure of Example 1, step 1.ii. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 313.1 [$M+H^+$].

6.ii. *Rac-(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-hexahydro-isoquinoline-2,8a-dicarboxylic acid 2-tert-butyl ester 8a-methyl ester*:

Starting from intermediate 6.i (4 g, 12.8 mmol); the title compound was obtained as a yellowish oil (4.65 g, 78% yield) using the procedure of Example 1, step 1.vii. The crude material was purified by chromatography over SiO_2 (DCM-MeOH 97-3 containing 0.3% aq. NH_4OH).

MS (ESI, m/z): 465.0 [$M+H^+$].

6.iii. *Rac-(4aS,6S,8aR)-6-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-hexahydro-isoquinoline-2,8a-dicarboxylic acid 2-tert-butyl ester 8a-methyl ester*:

To a solution of intermediate 6.ii (4.65 g, 10.01 mmol) in dioxane (50 mL) and water (7 mL) was added 1*M* NaOH (11 mL). The solution was cooled to 0°C and di-*tert*-butyl dicarbonate (3.38 g, 15.01 mmol) was added. After stirring 3 days, 1*M* NaOH (10 mL) and di-*tert*-butyl dicarbonate (97%, 1.5 g) were added. The reaction mixture was then stirred for 3 more days. EA (60 mL) was added and the phases were separated. The aq. layer was extracted with EA (2 x 50 mL) and the combined org. layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (EA-Hept 1-2 then 1-1) to afford the title compound as a white foam (5.55 g).

MS (ESI, m/z): 565.1[M+H$^+$].

6.iv. *Rac-(4aS,6S,8aR)-6-{tert-butoxycarbonyl-[3-(2,5-difluoro-phenyl)-allyl]-amino}-8a-hydroxymethyl-octahydro-isoquinoline-2-carboxylic acid tert-butyl ester*:

To a solution of intermediate 6.iii (0.233 g, 0.41 mmol) in Et_2O (3.5 mL) at -10°C was added $LiAlH_4$ (0.047 g, 1.24 mmol). The reaction mixture was stirred at 0°C for 2 h then at rt for 3 h. The reaction mixture was diluted with Et_2O (5 mL) and saturated Na_2SO_4 (1 mL) was added. The suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (EA-Hept 1-2) to afford the title alcohol as a white foam (0.129 g, 58% yield).

MS (ESI, m/z): 537.0 [M+H$^+$].

6.v. *Rac-(4aS,6S,8aR)-{6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-octahydro-isoquinolin-8a-yl}-methanol*:

Starting from intermediate 6.iv (0.112 g, 0.21 mmol), the title compound was obtained as a yellow gum (0.03 g, 42% yield) using the procedure of Example 2, step 2.ii. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 6-1 containing 1% aq. NH_4OH then DCM-MeOH 4-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 337.1 [M+H$^+$].

6.vi. *[(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol and [(4aR,6R,8aS)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol*:

Starting from intermediate 6.v (0.029 g, 0.085 mmol), the title compounds were obtained as a yellowish solid (0.018 g, 44% yield) using the procedure of Example 1, step 1.v. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).

MS (ESI, m/z): 495.1 [M+H$^+$].

Example 7: (*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester:

7.i. *Rac-(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 6.iii (0.510 g, 0.9 mmol), the title compound was obtained as a yellowish oil (0.330 g, 100% yield) using the procedure of Example 2, step 2.ii.
MS (ESI, m/z): 365.2 [$M+H^+$].

7.ii. *(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester and (4aR,6R,8aS)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 7.i (0.330 g, 0.090 mmol) and 4-chloro-6-methoxy-quinazoline (0.228 g, 1.3 eq.), the title compound was obtained as a yellowish solid (0.435 g, 92% yield) using the procedure of Example 1, step 1.v. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).
^1H NMR (DMSO) δ: 8.57 (d, J = 18.9 Hz, 1H); 7.79 (t, J = 9.0 Hz, 1H); 7.54-7.41 (m, 2H); 7.26 (overlapped dd, J = 2.9, 42.8 Hz, 1H); 7.27-7.06 (overlapped m, 2H); 6.58 (overlapped t, J = 15.8 Hz, 1H); 6.57-6.44 (overlapped m, 1H); 4.54 (d, J = 12.0 Hz, 1H); 4.22 (br. d, J = 13.5 Hz, 1H); 3.90 (s, 3H); 3.37 (d, J = 4.8 Hz, 2H); 3.34 (s, 3H); 3.08 (m, 1H); 2.90 (d, J = 12.6 Hz, 1H); 2.57-2.52 (overlapped m, 1H); 2.32 (m, 1H); 1.99-1.26 (m, 8H); 0.96-0.83 (m, 1H).
MS (ESI, m/z): 523.3 [$M+H^+$].

Example 8 : [(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol and [(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol:

Starting from the mixture of compounds of Example 7 (0.095 g, 0.18 mmol), the title compounds were obtained as a yellowish foam (0.014 g, 16% yield) using the procedure of Example 6, step 6.iv. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 97-3 containing 0.3% aq. NH_4OH then DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).

MS (ESI, m/z): 495.4 [$M+H^+$].

Example 9: [(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol:

9.i. *(4aS,6S,8aR)-6-benzylamino-2-tert-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from (*4aS,8aR*)-6-oxo-2-*tert*-butyloxy carbonyl octahydro-isoquinoline-8a-carboxylic acid methyl ester (prepared as described in *Org. Lett.* (2004), **6**, 1171; 7.5 g, 24.08 mmol), the title compound was obtained as a yellowish oil (4.29 g, 44% yield) using the procedure of Example 2, step 2.i.

MS (ESI, m/z): 403.2 [$M+H^+$].

9.ii. *(4aS,6S,8aR)-6-benzyloxycarbonylamino octahydro-isoquinoline-8a-carboxylic acid methyl ester*:

Starting from intermediate 9.i (4.26 g, 10.58 mmol), the title compound was obtained as a pale yellow oil (5.25 g), using sequentially the procedures of Example 1, steps 1.ii and 1.iii.

MS (ESI, m/z): 447.3 [$M+H^+$].

9.iii. *(4aS,6S,8aR)-6-benzyloxycarbonylamino-8a-hydroxymethyl-octahydro-isoquinoline-2-carboxylic acid tert-butyl ester*:

Starting from intermediate 9.ii (4.51 g), the title compound was obtained as a colourless oil (4.22 g) using the procedure of Example 6, step 6.iv. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 93-7 containing 0.7% aq. NH_4OH).
MS (ESI, m/z): 419.4 $[M+H^+]$.

9.iv. *(4aS,6S,8aR)-(8a-hydroxymethyl-decahydro-isoquinolin-6-yl)-carbamic acid benzyl ester*:

Starting from intermediate 9.iii (4.22 g, 10.1 mmol), the title compound was obtained as a yellowish foam (1.67 g, 52% yield) using the procedure of Example 1, step 1.iv. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).
MS (ESI, m/z): 319.3 $[M+H^+]$.

9.v. *(4aS,6S,8aR)-[8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-carbamic acid benzyl ester*:

Starting from intermediate 9.iv (0.57 g, 1.8 mmol), the title compound was obtained as a yellowish foam (0.437 g, 51% yield) using the procedure of Example 1, step 1.v. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).
MS (ESI, m/z): 477.1 $[M+H^+]$.

9.vi. *(4aS,6S,8aR)-[6-amino-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol*:

Starting from intermediate 9.v (0.431 g, 0.9 mmol), the title compound was obtained as a yellowish foam (0.138 g, 45% yield) using the procedure of Example 1, step 1.vi. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 4-1 containing 1% aq. NH_4OH).
MS (ESI, m/z): 343.4 $[M+H^+]$.

9.vii. *[(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol*:

Starting from intermediate 9.vi (0.080 g, 0.234 mmol) the title compound was obtained as an off-white foam (0.083 g, 72% yield) using the procedure of Example 1, step 1.vii. The crude product was purified by column chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

^1H NMR (DMSO) δ: 8.41 (d, J = 5.4 Hz, 1H); 8.12 (d, J = 9.0 Hz, 1H); 7.47 (ddd, J = 3.0, 6.0, 9.6 Hz, 1H); 7.28-7.06 (overlapped m, 2H); 7.17 (overlapped d, J = 9.0 Hz, 1H); 6.96 (d, J = 5.1 Hz, 1H); 6.60 (overlapped t, J = 16.8 Hz, 1H); 6.59-6.48 (overlapped m, 1H); 4.88 (d, J = 11.1 Hz, 1H); 4.21 (t, J = 4.5 Hz, 1H); 3.98 (overlapped s, 3H); 3.94 (overlapped d, 1H); 3.76 (dd, J = 5.3, 10.4 Hz, 1H); 3.54 (m, 1H); 3.41 (d, J = 5.1 Hz, 2H); 2.81 (t, J = 11.4 Hz, 1H); 2.58 (overlapped m, 1H); 2.42 (d, J = 11.7 Hz, 1H); 1.86-1.09 (m, 9H), 0.93-0.83 (m, 1H).

MS (ESI, m/z): 495.1 $[M+H^+]$.

Example 10 : 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid *(4aS,6S,8aR)*- [8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-amide:

To a solution of intermediate 9.vi (0.059 g, 0.17 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (0.040 g, 0.19 mmol) in DMF (2.5 mL) were added DIPEA (0.088 mL, 0.52 mmol) and HATU (0.078 g, 0.21 mmol). The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The residue was dissolved in DCM-MeOH 9-1 (20 mL) and the solution was washed once with sat. $NaHCO_3$ (20 mL). The combined org. layers were evaporated under reduced pressure. The residue was filtered through SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH then DCM-MeOH 9-1 containing 1% aq. NH_4OH) affording a yellow foam that was further triturated in ether, filtered and dried under HV to obtain a yellow solid (0.055 g).

MS (ESI, m/z): 535.5 $[M+H^+]$.

Example 11: (*4aS,6S,8aR*)-[8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[(*E*)-3-(2,5-difluoro-phenyl)-allyl]-amine:

11.i. *[(E)-3-(2,5-difluoro-phenyl)-allyl]- (4aS,6S,8aR)-[8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-carbamic acid tert-butyl ester*:

To a solution of the compound of Example 9 (0.44 g, 0.89 mmol) in DCM (5 mL) were added TEA (0.248 mL, 1.78 mmol) and Boc_2O (97%, 0.22 g, 0.98 mmol). The reaction proceeded overnight. Sat. $NaHCO_3$ (10 mL) was added and the phases were separated. The aq. layer was extracted once with DCM-MeOH 9-1 (10 mL). The combined org. layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dried under HV to give the title compound as a yellowish solid (0.468 g, 88% yield).

MS (ESI, m/z): 595.5 [$M+H^+$].

11.ii. *Toluene-4-sulfonic acid (4aS,6S,8aR)- 6-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-ylmethyl ester*:

To a solution of intermediate 11.i. (0.461 g, 0.77 mmol) in DCM (3.5 mL) cooled at 0°C was added DMAP (0.172 g, 1.39 mmol) and TsCl (0.164 g, 0.85 mmol). The reaction was stirred for 30 min at this temperature then allowed to warm slowly to rt over 4 h 45. A sat. $CuSO_4$ solution (10 mL) was added and the phases were separated. The org. layer was washed once with sat. $CuSO_4$ (10 mL), once with brine (10 mL) and concentrated to dryness. The dark residue was purified by column chromatography over SiO_2 (DCM-MeOH 97-3 then 19-1), affording a yellow foam (0.472 g, 81% yield).

MS (ESI, m/z): 749.1 [$M+H^+$].

11.iii. *(4aS,6S,8aR)-[8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[3-(2,5-difluoro-phenyl)-allyl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 11.ii (0.456 g, 0.61 mmol) in DMF (2.5 mL) were added sodium azide (0.200 g, 1.52 mmol) and tetrabutylammonium iodide (98%, 0.002 g, 0.006 mmol) and the mixture was stirred at 80°C over 3 days. The reaction mixture was diluted with water (5mL). The resulting beige precipitate was filtered and dried under HV.

The crude azide (0.344 g) was taken up in THF (5 mL) and PPh_3 (99%, 0.423 g, 1.22 mmol) and water (1 mL) were added. The mixture was heated at 60°C for 2 h then concentrated to dryness. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH to DCM-MeOH 4-1 containing 1% aq. NH_4OH) to give the title amine as a yellow gum (0.181 g, 50% yield).
MS (ESI, m/z): 594.4 [$M+H^+$].

11.iv. *(4aS,6S,8aR)-[8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amine*:

Starting form intermediate 11.iii (0.177 g, 0.30 mmol), the title compound was obtained as a yellow foam (0.060 g, 41% yield) using the procedure of Example 1, step 1.iv. The crude product was purified by column chromatography over SiO_2 (DCM-MeOH 6-1 containing 1% aq. NH_4OH).
MS (ESI, m/z): 494.3 [$M+H^+$].

Example 12: 2-((*4aS,6S,8aR*)-8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol and 2-((*4aR,6R,8aS*)-8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol:

12.i. *{4-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxy-pyridin-3-yl}-carbamic acid tert-butyl ester*:

To an ice-chilled solution of [4-(2-hydroxy-ethyl)-6-methoxy-pyridin-3-yl]-carbamic acid *tert*-butyl ester (prepared as described in EP 1 526 135; 18.66 g, 69.55 mmol) in DCM (185 mL) were added TEA (19.8 mL, 2 eq.), TBDPS-Cl (20.2 mL, 1.1 eq.) and DMAP (1.72 g, 0.2 eq.). The resulting mixture was stirred at RT for 2 h and quenched with sat. $NaHCO_3$ (200 mL). The two layers were separated and the org. layer was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by filtration through a pad of SiO_2 (EA-Hept 1:4) to afford the title compound as a pale yellow oil (31.32 g, 89% yield).
^1H NMR ($CDCl_3$) δ: 7.51-7.29 (m, 12H); 6.48 (s, 1H); 3.93 (s, 3H); 3.79 (t, J = 5.6 Hz, 2H); 2.80 (t, J = 5.6 Hz, 2H); 1.48 (s, 9H); 1.03 (s, 9H).

MS (ESI, m/z): 507.3 [M+H$^+$].

12.ii. *4-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxy-pyridin-3-ylamine*:

A solution of intermediate 12.i (31.32 g, 61.81 mmol) in TFA (50 mL) was stirred at rt for 15 min. The volatiles were removed *in vacuo* and the residue was partitioned between a mixture of sat. $NaHCO_3$ (500 mL) and NaOH 1*M* (300 mL) and DCM-MeOH (9:1, 500 mL). The two layers were separated and the aq. layer was extracted once more with DCM-MeOH (9-1, 200 mL). The combined org. layers were dried over $MgSO_4$, filtered and concentrated to dryness to afford the title amine as a yellow oil (27.1 g).

^{1}H NMR ($CDCl_3$) δ: 7.74-7.32 (m, 11H); 6.51 (s, 1H); 4.47 (br. s, 2H); 3.91 (t, J = 6.2 Hz, 2H); 3.90 (s, 3H); 2.80 (t, J = 6.2 Hz, 2H); 1.02 (s, 9H).

MS (ESI, m/z): 407.5 [M+H$^+$].

12.iii. *8-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxy-[1,5]naphthyridin-4-ol*:

To a solution of intermediate 12.ii (27.1 g, 66.65 mmol) in EtOH (135 mL) were added triethylorthoformate (14.7 mL, 1.3 eq.) and Meldrum's acid (11.17 g, 1.2 eq.). The reaction mixture was refluxed overnight and then cooled to rt. The mixture was concentrated to dryness and dried under HV to afford a solid (35.82 g). To refluxing Dowtherm A (300 mL) the latter solid was added portionwise. The mixture was heated 3 min and cooled to rt. The resulting solution was filtered through SiO_2 (Hept then EA-MeOH 9:1) to afford the title compound as a beige solid (12.81 g, 42% yield).

^{1}H NMR ($CDCl_3$) δ: 7.54-7.25 (m, 12H); 7.02 (br. s, 1H); 6.94 (br. s, 1H); 4.08 (t, J = 6.2 Hz, 2H); 4.05 (s, 3H); 3.37 (m, 2H); 1.00 (s, 9H).

MS (ESI, m/z): 459.2 [M+H$^+$].

12.iv. *Trifluoro-methanesulfonic acid 8-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxy-[1,5]naphthyridin-4-yl ester*:

To a solution of intermediate 12.iii (12.81 g, 27.93 mmol) in DMF (120 mL) were added TEA (5.8 mL, 1.5 eq.) and *N*-phenyl-bis(trifluoromethanesulfonimide) (11.97 g, 33.51 mmol). The reaction mixture was heated to 50°C overnight. After cooling, the solvent was removed *in vacuo* and the residue was partitioned between sat. $NaHCO_3$ (500 mL) and DCM (400 mL). The two layers were separated and the aq. layer was extracted once more with DCM (300 mL). The combined org. layers were dried over

$MgSO_4$, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (EA-Hept 1-9) to afford the title triflate as a yellowish solid (16.03 g, 97% yield).

^1H NMR ($CDCl_3$) δ: 8.68 (d, J = 5.0 Hz, 1H); 7.54-7.25 (m, 11H); 7.12 (s, 1H); 4.12 (s, 3H); 4.07 (t, J = 6.4 Hz, 2H); 3.41 (t, J = 6.4 Hz, 2H); 0.98 (s, 9H).

MS (ESI, m/z): 591.3 [$M+H^+$].

12.v. *Rac-(4aS,6S,8aR)- (8a-hydroxymethyl-decahydro-isoquinolin-6-yl)-carbamic acid benzyl ester*:

Starting from intermediate 2.i (14.14 g, 35.1 mmol), the title compound was obtained as a yellowish foam (2.16 g) using sequentially the procedures of Example 9, steps 9.ii. to 9.iv.

MS (ESI, m/z): 319.3 [$M+H^+$].

12.vi. *Rac-(2-((4aS,6S,8aR)-{8-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-6-methoxy-[1,5]naphthyridin-4-yl}-8a-hydroxymethyl-decahydro-isoquinolin-6-yl)-carbamic acid benzyl ester*:

Starting from intermediate 12.v (1.36 g, 4.27 mmol) and intermediate 12.iv. (2.77 g, 4.7 mmol), the title compound was obtained as a white foam (0.89 g, 27% yield) using the procedure of Example 1, step 1.v. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 97-3 containing 0.3% aq. NH_4OH).

MS (ESI, m/z): 760.4 [$M+H^+$].

12.vii. *Rac-(4aS,6S,8aR)-{2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-yl}-carbamic acid benzyl ester*:

To a solution of intermediate 12.vi (0.888 g, 1.17 mmol) in THF (6.5 mL) was added TBAF (1*M* in THF; 1.8 mL). The reaction mixture was stirred for 6 h. More TBAF (1*M* in THF, 0.585 mL) was added. The reaction mixture was stirred for 1 h and concentrated to dryness. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 93-7 containing 0.7% aq. NH_4OH) to afford a yellowish gum (0.692 g), slightly contaminated with remaining TBAF.

MS (ESI, m/z): 521.1 [$M+H^+$].

12.viii. *Rac-2-[(4aS,6S,8aR)-8-(6-amino-8a-hydroxymethyl-octahydro-isoquinolin-2-yl)-2-methoxy-[1,5]naphthyridin-4-yl]-ethanol*:

Starting from intermediate 12.vii (0.609 g, 1.17 mmol), the title compound was prepared as a yellowish foam (0.307 g, 68% yield) using the procedure of Example 1, step 1.vi. The crude material was purified by chromatography over SiO_2 (DCM-MeOH 4-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 387.3 [$M+H^+$].

12.ix. *2-((4aS,6S,8aR)-8-{6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol and 2-((4aR,6R,8aS)-8-{6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol*:

Starting from intermediate 12.viii (0.091 g, 0.235 mmol) the title compound (0.100 g, 80% yield) was obtained as yellowish foam using the procedure of Example 1, step 1.vii. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

^1H NMR (DMSO) δ: 8.40 (d, J = 5.1 Hz, 1H); 7.46 (ddd, J = 3.6, 6.3, 9.6 Hz, 1H); 7.27-7.19 (m, 1H); 7.13-7.06 (m, 1H); 7.04 (s, 1H); 6.96 (d, J = 5.1 Hz, 1H); 6.59 (overlapped t, J = 16.2 Hz, 1H); 6.59-6.47 (overlapped m, 1H); 4.85 (d, J = 12.0 Hz, 1H); 4.75 (m, 1H); 4.19 (t, J = 4.2 Hz, 1H); 3.95 (s, 3H); 3.89 (d, J = 11.4 Hz, 1H); 3.80-3.69 (m, 3H); 3.53 (dd, J = 4.5, 10.8 Hz, 1H); 3.54 (m, 1H); 3.40 (d, J = 5.4 Hz, 2H); 3.23 (t, J = 6.9 Hz, 2H); 2.78 (t, J = 11.7 Hz, 1H); 2.41 (d, J = 12.0 Hz, 1H); 1.79-1.13 (m, 9H); 0.94-0.85 (m, 1H).

MS (ESI, m/z): 539.3 [$M+H^+$].

Example 13 : 6-({(*4aS,6S,8aR*)-2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one and 6-({(*4aR,6R,8aS*)-2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one:

Starting from intermediate 12.viii (0.094 g, 0.244 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carbaldehyde (0.048 g, 1.1 eq.), the title compound was

obtained as on off-white foam (0.065 g, 49% yield) using the procedure of Example 1, step 1.vii. The crude material was purified by column chromatography over SiO_2 (DCM-MeOH 9-1 containing 1%aq. NH_4OH).

MS (ESI, m/z): 549.4 $[M+H^+]$.

Example 14: 8-{(*4aS,6S,8aR*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester and 8-{(*4aR,6R,8aS*)-6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester:

14.i. *8-benzyloxy-5-bromo-2-methoxy-quinoline*:

To an ice-chilled solution of 8-benzyloxy-2-methoxy-quinoline (prepared as described in WO 2004/002992; 71.09 g, 268 mmol) in DCM (1.6 L) was added NBS (53.0 g, 1.11 eq.). The mixture was stirred for 5 h allowing the temperature to gradually reach rt. The solution was washed with sat. $NaHCO_3$ (6 x 500 mL), brine (4 x 500 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was dried under HV to give the title bromide as a light brown solid (89.37 g, 97% yield).

^1H NMR ($CDCl_3$) δ: 8.34 (d, J = 9.0 Hz, 1H); 7.57-7.53 (m, 2H); 7.50 (d, J = 8.2 Hz, 1H); 7.42-7.29 (m, 3H); 7.02 (d, J = 9.0 Hz, 1H); 6.98 (d, J = 8.2 Hz, 1H); 5.34 (s, 2H); 4.13 (s, 3H).

14.ii. *8-benzyloxy-2-methoxy-5-(E)-styryl-quinoline*:

To a solution of the intermediate 14.i. (59.76 g, 173.6 mmol), *trans*-2-phenylvinyl boronic acid (25.69 g, 1 eq.) in dioxane (320 mL) and water (80 mL) were added K_2CO_3 (31.2 g, 225.7 mmol) and $Pd[P(Ph)_3]_4$ (5 g, 2.5 mol%). The resulting mixture was heated to 100°C overnight. After cooling to rt, EA (800 mL), water (500 mL) and 10% $NaHSO_4$ (300 mL) were added. The two layers were decanted and the aq. layer was extracted twice with DCM (2 x 300 mL). The combined org. layers were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was triturated in ether, filtered and dried under HV to afford the title compound as a white solid (62 g, 97% yield).

^{1}H NMR ($CDCl_3$) δ: 8.39 (d, J = 9.0 Hz, 1H); 7.66 (d, J = 16.1 Hz, 1H); 7.60-7.53 (m, 5H); 7.43-7.27 (m, 6H); 7.14 (d, J = 8.2 Hz, 1H); 7.05 (d, J = 16.1 Hz, 1H); 6.99 (d, J = 9.0 Hz, 1H); 5.39 (s, 2H); 4.14 (s, 3H).

14.iii. *8-benzyloxy-2-methoxy-quinoline-5-carbaldehyde*:

To a solution of intermediate 9.ii (24.1 g, 65.6 mmol) in DCM (300 mL) and water (50 mL) were added NMO (15.84 g, 2 eq.) and potassium osmate dihydrate (0.725 g, 3 mol%). The resulting mixture was stirred at rt overnight. After treatment with 10% $NaHSO_3$ (2 x 250 mL) and 10% $NaHSO_4$ (250 mL), the org. layer was dried over $MgSO_4$, filtered and concentrated to dryness to afford the title diol as a brown foam (25.7 g). The latter was taken up in acetone (400 mL), warmed with a water bath at around 40°C, and treated with a solution of $NaIO_4$ (34.23 g, 160.0 mmol) in water (50 mL). The mixture was stirred at the same temperature for 30 min. Water (700 mL) was added and the volatiles were removed *in vacuo*. The aq. layer was extracted with DCM (500 mL). The org. layer was dried over $MgSO_4$, filtered and concentrated to dryness. The resulting residue was poured into water, filtered, rinsed several times with water and dried under HV to afford the title aldehyde as a dark solid (18.93 g, 64.5 mmol).

^{1}H NMR ($CDCl_3$) δ: 10.1 (s, 1H); 9.48 (d, J = 9.08 Hz, 1H); 7.75 (d, J = 8.2 Hz, 1H); 7.60-7.55 (m, 2H); 7.44-7.31 (m, 3H); 7.16 (d, J = 8.2 Hz, 1H); 7.11 (d, J = 9.08 Hz, 1H); 5.42 (s, 2H); 4.12 (s, 3H).

14.iv. *8-benzyloxy-2-methoxy-quinoline-5-carboxylic acid*:

To a solution of intermediate 9.iii (20 g, 68.2 mmol) in 2-methyl-2-propanol (500 mL) and DCM (100 mL) were added 2-methyl-2-butene (200 mL) and a solution of sodium chlorite (77 g, 10 eq., 80% purity) and sodium dihydrogen phosphate (75.27 g, 8 eq.) in water (300 mL). The reaction was stirred overnight at RT. The reaction mixture was diluted with water (200 mL) and EA (200 mL). The two layers were decanted and the aq. layer was extracted once with EA (200 mL). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to afford the title acid as a white solid (16.0 g, 75% yield).

^{1}H NMR ($CDCl_3$) δ: 9.37 (d, J = 9.4 Hz, 1H); 8.27 (d, J = 8.50 Hz, 1H); 7.60-7.56 (m, 2H); 7.44-7.30 (m, 3H); 7.10 (d, J = 8.5 Hz, 1H); 7.08 (d, J = 9.4 Hz, 1H); 5.42 (s, 2H); 4.14 (s, 3H).

Alternative method:

To a solution of intermediate 14.i (70 g, 203.3 mmol) in THF (500 mL) was added, dropwise at -78°C, *n*-BuLi (2.3*N* in hexanes, 100 mL, 230 mmol). After stirring 20 min at the same temperature, ethyl chloroformate (30 mL, 313.7 mmol) in solution in THF (70 mL) was added at once. After 15 min, 10% aq. $NaHSO_4$ (100 mL) was added and the mixture was quickly warmed to RT. The aq. layer was diluted with sat. $NaHCO_3$ and extracted with EA (2 x 500 mL). The org. layer was dried over Na_2SO_4, filtered and concentrated to dryness. The latter was taken up in THF (500 mL) and 2*M* NaOH (200 mL) was added. The solution was stirred at 70°C during 2 days and the solvent was removed in vacuo. The pH of the aq. layer was adjusted to 4 using 2*M* HCl. The solid was extracted with DCM-MeOH (9-1, 1 L). The org. layer was dried over Na_2SO_4, filtered and concentrated to dryness to afford the title acid as a white solid (43.68 g, 141.21 mmol).

^{1}H NMR ($CDCl_3$) δ: 9.37 (d, J = 9.4 Hz, 1H); 8.27 (d, J = 8.50 Hz, 1H); 7.60-7.56 (m, 2H); 7.44-7.30 (m, 3H); 7.10 (d, J = 8.5 Hz, 1H); 7.08 (d, J = 9.4 Hz, 1H); 5.42 (s, 2H); 4.14 (s, 3H).

14.v. *8-benzyloxy-2-methoxy-quinoline-5-carboxylic acid methyl ester*:

To a solution of intermediate 14.iv (15.8 g, 51.1 mmol) in benzene (450 mL) and MeOH (80 mL) was added a solution of $TMSCHN_2$ (2*M* in ether, 30 mL, 60 mmol) dropwise. The reaction was stirred 45 min at rt and AcOH (enough to destroy the excess of reagent) was added. The reaction mixture was diluted with sat. $NaHCO_3$ (300 mL). The aq. layer was separated and extracted twice with EA (2 x 200 mL). The combined org. layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound as a white solid (15.8 g, 95% yield).

^{1}H NMR (d6-DMSO) δ: 9.15 (d, J = 9.4 Hz, 1H); 8.06 (d, J = 8.5 Hz, 1H); 7.59-7.53 (m, 2H); 7.44-7.36 (m, 2H); 7.35-7.29 (m, 2H); 7.18 (d, J = 9.4 Hz, 1H); 5.40 (s, 2H); 4.01 (s, 3H); 3.87 (s, 3H).

MS (ESI, m/z): 324.2 [$M+H^+$].

14.vi. *8-hydroxy-2-methoxy-quinoline-5-carboxylic acid methyl ester*:

To a solution of intermediate 14.v (15.8 g, 48.9 mmol) in EA (380 mL) was added 10% Pd/C (3.03 g). The reaction was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The catalyst

was removed by filtration and the filtrate evaporated under reduced pressure. After drying under HV, the title compound was obtained as a white solid (10.84 g, 95% yield).

^{1}H NMR (d6-DMSO) δ: 9.96 (br. s, 1H); 9.18 (d, J = 9.4 Hz, 1H); 8.03 (d, J = 8.5 Hz, 1H); 7.16 (d, J = 9.4 Hz, 1H); 7.10 (d, J = 8.5 Hz, 1H); 4.06 (s, 3H); 3.85 (s, 3H).

MS (ESI, m/z): 234.3 [M+H$^+$].

14.vii. *2-methoxy-8-trifluoromethanesulfonyloxy-quinoline-5-carboxylic acid methyl ester*:

Starting from intermediate 14.vi (10.84 g, 46.5 mmol), the title compound was obtained as an off-white solid (21.9 g) using the procedure of Example 12, step 12.iv. The crude material was filtered through SiO_2 (DCM).

MS (ESI, m/z): 366.1 [M+H$^+$].

14.viii. *8-{(4aS,6S,8aR)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester and 8-{(4aR,6R,8aS)-6-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester*:

Starting from intermediate 12.v (0.441 g, 1.38 mmol) and intermediate 14.vii (0.557 g, 1.1 eq.), the title compound was obtained as a yellowish oil (0.07 g) using sequentially the procedures of Example 12, steps 12.vi, 12.viii and 12.ix. The crude product was purified by chromatography over SiO_2 (DCM-MeOH 93-7 containing 0.7% aq. NH_4OH).

^{1}H NMR (DMSO) δ: 9.23 (d, J = 9.0 Hz, 1H); 8.01 (d, J = 6.0 Hz, 1H); 7.47 (ddd, J = 3.0, 6.0, 9.0 Hz, 1H); 7.27-7.19 (m, 1H); 7.16-7.06 (m, 3H); 6.60 (overlapped t, J = 15.0 Hz, 1H); 6.59-6.48 (overlapped m, 1H); 4.61 (d, J = 12.0 Hz, 1H); 4.23 (m, 1H); 4.0 (s, 3H); 3.99-3.91 (overlapped m, 1H); 3.86 (s, 3H); 3.68 (d, J = 9.0 Hz, 1H); 3.57-3.52 (m, 1H); 3.40 (d, J = 6.0 Hz, 2H); 2.73-2.51 (overlapped m, 2H); 2.45 (d, J = 12.0 Hz, 1H); 1.94-1.12 (m, 9H); 0.95-0.83 (m, 1H).

MS (ESI, m/z): 552.3 [M+H$^+$].

Example 15 : 6-{[(*4aS,6S,8aR*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one and 6-{[(*4aR,6R,8aS*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one:

Starting from intermediate 12.v (1.14 g, 3.57 mmol) and 8-bromo-7-fluoro-2-methoxy-[1,5]naphthyridine (1.01 g, 1.1 eq.), the title compound was obtained as a beige solid (0.086 g) using sequentially the procedures of Example 12, steps 12.vi and 12.viii and of Example 3. After the reductive amination step, the crude material was purified by chromatography (DCM-MeOH 93-7 containing 0.7% aq. NH_4OH). If necessary, the crude mixture was purified over SiO_2 using a suitable eluent.

^{1}H NMR (DMSO) δ: 10.82 (s, 1H); 8.52 (d, J = 4.5 Hz, 1H); 8.15 (d, J = 8.7 Hz, 1H); 7.73 (d, J = 8.1 Hz, 1H); 7.16 (d, J = 9.0 Hz, 1H); 7.11 (d, J = 8.1 Hz, 1H); 4.22 (d, J = 12.0 Hz, 1H); 4.06 (m, 1H); 3.98 (s, 3H); 3.81 (overlapped m, 2H); 3.76 (overlapped s, 2H); 3.54 (overlapped s, 2H); 3.50 (overlapped m, 1H); 3.07 (m, 1H); 2.84 (d, J = 12.0 Hz, 1H); 2.19 (m, 1H); 1.93-1.15 (m, 9H); 0.86-0.78 (m, 1H).

MS (ESI, m/z): 552.3 [$M+H^+$].

Pharmacological properties of the invention compounds

In vitro assays

Experimental methods:

These assays have been performed following the description given in "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 4th ed.; Approved standard: NCCLS Document M7-A4; National Committee for Clinical Laboratory Standards: Villanova, PA, USA, 1997". Minimal inhibitory concentrations (MICs; mg/l) were determined in cation-adjusted Mueller–Hinton Broth (BBL) by a microdilution method following NCCLS guidelines (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility). The pH of the test medium was 7.2–7.3.

Results:

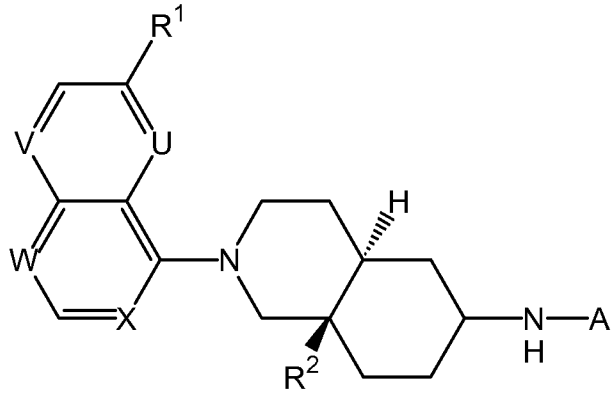
All Example compounds were tested against several Gram-positive and Gram-negative bacteria.

Typical antibacterial test results are given in the table hereafter (MIC in mg/l).

Example No.	***M. catarrhalis* A894**
1	2
2	0.125
3	≤ 0.031
4	≤ 0.031
5	≤ 0.031
6	≤ 0.031
7	0.125
8	≤ 0.031
9	≤ 0.031
10	0.25
11	0.125
12	≤ 0.031
13	0.125
14	0.125
15	≤ 0.031

Claims

1. A compound of formula I



I

wherein

R^1 is alkoxy;

one or two of U, V, W, X represent(s) N, the remaining represents CH, whereby V may also represent CR^a, W may also represent CR^b and X may also represent CR^c;

R^a is hydroxyalkyl;

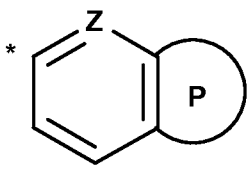
R^b is alkoxycarbonyl, carboxy or hydroxyalkyl;

R^c is halogen;

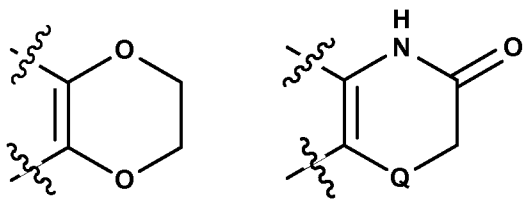
R^2 is alkoxycarbonyl, carboxy, hydroxyalkyl or aminoalkyl;

A is CH_2B, C(=O)B or $CH_2CH=CHD$;

B is the group:



wherein Z is N or CH and the ring P is selected from the following:

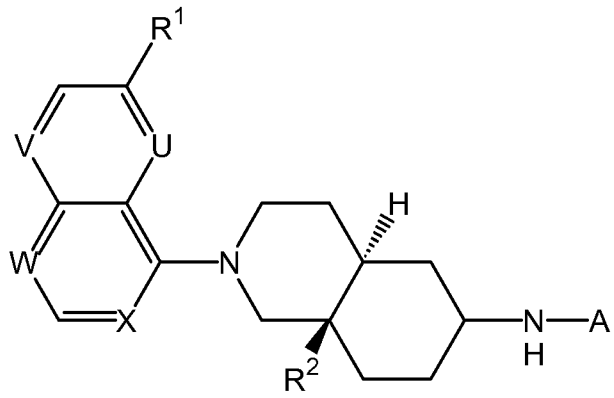


in which Q is O or S;

D is aryl;

or a salt thereof.

2. A compound of formula I according to claim 1, which is also a compound of formula I_{CE}



I_{CE}

wherein

R^1 is alkoxy;

U and W each represent N, V represents CH or CR^a, R^a being hydroxyalkyl, and X represents CH,

or U and W each represent N, V represents CH and X represents CR^c, R^c being halogen (especially fluorine),

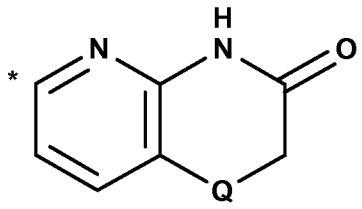
or W and X each represent N and U and V each represent CH,

or U represents N, W and X each represent CH and W represents CR^b, R^b being alkoxycarbonyl;

R^2 is alkoxycarbonyl, carboxy, hydroxyalkyl or aminoalkyl;

A is CH_2B, C(=O)B or $CH_2CH=CHD$;

B is the group:



in which Q is O or S;

D is phenyl substituted by two halogen atoms;

or a salt of a compound of formula I_{CE}.

3. A compound of formula I according to claim 1 or 2, wherein R^1 is methoxy;

or a salt of such a compound.

4. A compound of formula I according to claim 1 or 2, wherein U and W each represent N, V represents CH or CR^a, R^a being hydroxyalkyl, and X represents CH, or U and W each represent N, V represents CH and X represents CR^c, R^c being halogen (especially fluorine), or W and X each represent N and U and V each represent CH, U represents N, W and X each represent CH and W represents CR^b, R^b being alkoxycarbonyl;

or a salt of such a compound.

5. A compound of formula I according to claim 1 or 2, wherein R^2 is carboxy, hydroxymethyl or aminomethyl;

or a salt of such a compound.

6. A compound of formula I according to claim 1 or 2, wherein A is $CH_2CH=CHD$, D being phenyl substituted by two halogen atoms;

or a salt of such a compound.

7. A compound of formula I according to claim 1 or 2, wherein A is C(=O)B or CH_2B, B being selected from the group consisting of 3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazine-6-yl, 3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-yl, 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-yl and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-yl;

or a salt of such a compound.

8. A compound of formula I according to claim 1 or 2, which is selected from the following:

- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- 2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid methyl ester;

- 2-(6-methoxy-[1,5]naphthyridin-4-yl)-6-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-octahydro-isoquinoline-8a-carboxylic acid;
- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid;
- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-[1,5]naphthyridin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;
- 6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinoline-8a-carboxylic acid methyl ester;
- [6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-2-(6-methoxy-quinazolin-4-yl)-octahydro-isoquinolin-8a-yl]-methanol;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid [8a-hydroxymethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-amide;
- [8a-aminomethyl-2-(6-methoxy-[1,5]naphthyridin-4-yl)-decahydro-isoquinolin-6-yl]-[(*E*)-3-(2,5-difluoro-phenyl)-allyl]-amine;
- 2-(8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-[1,5]naphthyridin-4-yl)-ethanol;
- 6-({2-[8-(2-hydroxy-ethyl)-6-methoxy-[1,5]naphthyridin-4-yl]-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;
- 8-{6-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-8a-hydroxymethyl-octahydro-isoquinolin-2-yl}-2-methoxy-quinoline-5-carboxylic acid methyl ester;
- 6-{[2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-8a-hydroxymethyl-decahydro-isoquinolin-6-ylamino]-methyl}-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

or a salt of such a compound.

9. As a medicament, a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition containing, as active principle, a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

11. Use of a compound of formula I as defined in claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of a bacterial infection.

12. A compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of a bacterial infection.