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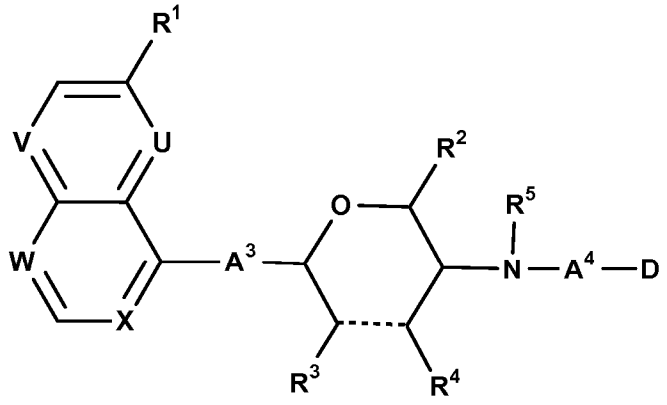
(54) Title: ANTIBIOTIC COMPOUNDS



(A1)

(57) Abstract: The invention relates to selected antibiotics of formula (Al) wherein R_1 represents alkyl, alkoxy, haloalkoxy, halogen or cyano; one or two of U, V, W and X represent(s) N, the remaining represent CH, or, in case of U, V and/or W, may also represent CR^a and, in the case of X, may also represent CR^b, R^a representing halogen and R^b representing halogen or alkoxy; A^3 represents NHCO, CH_2CH_2, CH=CH, $COCH_2$, $CH(OH)CH_2$, CH2CH(OH), CH(OH)CH(OH) or OCH_2; A^4 represents CH_2, CO, CH_2CH=CH, COCH=CH or CH_2CONH; R^2 represents hydrogen, alkyl, hydroxyalkyl, alkylcarbonyloxyalkyl, carbamoyloxyalkyl, carboxyalkyl or carbamoylalkyl; R^3 and R^4 each independently represent hydrogen, hydroxy or alkylcarbonyloxy; or R^3 and R^4 together represent a bridged dimethylmethylenedioxy chain attached to the carbons bearing R^3 and R^4; R^5 represents hydrogen, alkyl or hydroxyalkyl; and the dotted line represents a single bond or, when R^3 and R^4 represent hydrogen, also a double bond; and D represents alkyl, aryl or heteroaryl. An example of such an antibiotic is (E)-2-{(2R,3R,6R)-3-[3-(2,5-difluoro-phenyl)- allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol.

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ANTIBIOTIC COMPOUNDS

The present invention concerns novel antibiotics, pharmaceutical antibacterial compositions containing them and the use thereof 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 micro-organisms 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-lactam and quinolone antibiotics and now even to vancomycin;
- *S. pneumoniae* is becoming resistant to penicillin and 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.

Further new emerging organisms like *Acinetobacter spp.* or *C. difficile*, which have been selected during therapy with the currently used antibiotics, are becoming a real problem in hospital settings.

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.

A new type of quinoline or naphthyridine derivatives having antibacterial activity and therefore useful for treating infections in mammals, particularly in humans, has been reported in the last few years.

WO 99/37635, WO 00/21948, WO 00/21952, WO 00/43383, WO 03/101138, WO 01/025227, WO 02/040474 and WO 2004/011454 disclose quinoline, naphthyridine and quinazoline derivatives containing a 4-methylpiperidinyl spacer.

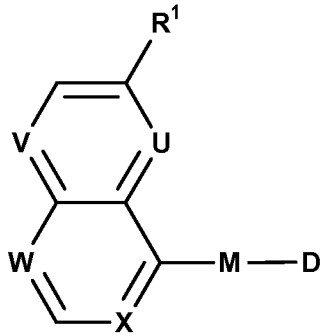
WO 00/78748, WO 02/50040 and WO 02/050061 disclose quinoline and naphthyridine derivatives containing a piperazinyl spacer.

WO 01/07432, WO 01/07433, WO 02/08224, WO 02/056882, WO 03/064421, WO 03/064431, WO 2004/02490 and WO 2004/058144 disclose quinoline, quinoxaline and naphthyridine derivatives containing a 4-aminopiperidinyl spacer.

WO 04/035569 and WO 2006/014580 disclose quinoline and naphthyridine derivatives containing a 3-aminomethylpiperidinyl spacer.

WO 2004/002992, WO 03/087098, WO 2004/014361 and WO 2004/035569 disclose quinoline, quinoxaline and naphthyridine derivatives containing a 4-aminocyclohexyl spacer.

In addition, PCT application No. PCT/EP2005/010154 (published as WO 2006/032466) describes certain bicyclic derivatives as useful antimicrobial agents that are effective against a variety of multi-drug resistant bacteria. Said bicyclic derivatives have the formula (A1)



(A1)

wherein R^1 represents alkyl, alkoxy, haloalkoxy, halogen or cyano;

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

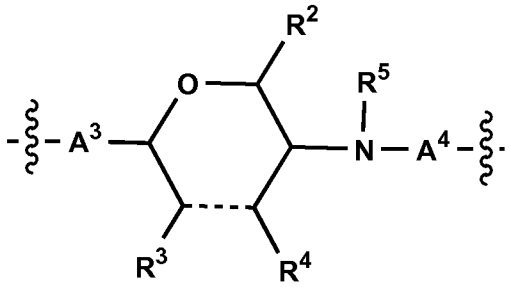
R^a represents halogen;

R^b represents halogen or alkoxy;

D represents alkyl, aryl or heteroaryl;

M is notably the group M^2:

M^2 =



wherein

A^3 represents NHCO, CH_2CH_2, CH=CH, $COCH_2$, $CH(OH)CH_2$, $CH_2CH(OH)$, CH(OH)CH(OH) or OCH_2;

A^4 represents CH_2, CO, CH_2CH=CH, COCH=CH or CH_2CONH;

R^2 represents hydrogen, alkyl, hydroxyalkyl, alkylcarbonyloxyalkyl, carbamoyloxyalkyl, carboxyalkyl or carbamoylalkyl;

R^3 and R^4 each independently represent hydrogen, hydroxy or alkylcarbonyloxy; or R^3 and R^4 together represent a bridged dimethylmethylenedioxy chain attached to the carbons bearing R^3 and R^4;

R^5 represents hydrogen, alkyl or hydroxyalkyl; and

the dotted line represents a single bond or, when R^3 and R^4 represent hydrogen, also a double bond.

This invention relates to selected compounds of formula (A1) as described above and salts thereof.

Thus, the compounds of this invention are selected from the following:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;

- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,*5*R,*6*R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2R,3R,6S*)-2-(2-hydroxy-ethyl)-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- [(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-2-yl]-acetic acid;

and salts thereof.

The invention relates in particular to compounds selected from the following:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;

- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

and to salts thereof.

The following invention compounds are preferred:

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

as well as their salts.

According to a first embodiment, the compounds of this invention will be selected from the following:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

or will be salts of these compounds.

According to said first embodiment, the compounds of this invention will in particular be selected from the following:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

or will be salts of these compounds.

According to said first embodiment, the compounds of this invention can also be selected from the following:

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

or be salts of these compounds.

According to one variant of this first embodiment, the compounds of this invention will be selected from the following:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;
- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;
- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;
- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

or will be salts of these compounds.

According to said variant of this first embodiment, the compounds of this invention will in particular be selected from the following:

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

or will be salts of these compounds.

According to another variant of this first embodiment, the compounds of this invention will be selected from the following:

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;
- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;
- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

or will be salts of these compounds.

According to a second embodiment, the compounds of this invention will be selected from the following:

- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

or will be salts of these compounds.

The compounds of this invention 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*.

The compounds according to this 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.*

The compounds according to this 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.

As well as in humans, bacterial infections can also be treated in other species like pigs, ruminants, horses, dogs, cats and poultry.

The present invention also relates to pharmacologically acceptable salts, or solvates and hydrates, respectively, and to compositions and formulations of the compounds mentioned above.

Examples of pharmacologically acceptable salts of sufficiently basic compounds of this invention are selected from the group consisting of salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound of this invention may form alkali or earth alkaline metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts. The compounds of this invention may be solvated, especially hydrated. The hydratation can occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds of this invention.

The pharmaceutical composition according to the present invention contains at least one compound of one of the above compound lists (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.

As mentioned above, therapeutically useful agents that contain compounds according to this invention, their solvates, salts or formulations are also comprised in the scope of the present invention. In general, the compounds according to this invention will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragee, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystal or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containing the active ingredient, topical or intranasal. The substance of the present invention can also be used to impregnate or coated devices that are foreseen for implantation like catheters or artificial joints. The pharmaceutically useful agents may also contain additives for conservation, stabilisation, e.g. UV stabilizers, emulsifiers, sweetener, aromatisers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

Another aspect of the invention concerns a method for the treatment of disease comprising the administration to the patient of a pharmaceutically active amount of a compound according to this invention (or a pharmaceutically acceptable salt thereof).

Moreover, the compounds according to this invention 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 according to this invention could be contained in a solution or in a spray formulation.

PREPARATION OF THE COMPOUNDS OF THIS INVENTION

Abbreviations:

The following abbreviations are used:

AcOH	acetic acid
AD-mix α	1,4-*bis*(dihydroquinine)phthalazine, $K_3Fe(CN)_6$, K_2CO_3 and $K_2OsO_4.2H_2O$
AD-mix β	1,4-*bis*(dihydroquinidine)phthalazine, $K_3Fe(CN)_6$, K_2CO_3 and $K_2OsO_4.2H_2O$
AIBN	2,2'-azoisobutyronitrile
aq.	aqueous
BINAP	2,2'-*bis*-(diphenylphosphino)-1,1'-binaphthyl
Boc_2O	di-*tert*-butyl dicarbonate
dba	dibenzylideneacetone
DCC	dicyclohexyl carbodiimide
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
$(DHQ)_2PHAL$	1,4-*bis*(dihydroquinine)phthalazine
$(DHQD)_2PHAL$	1,4-*bis*(dihydroquinidine)phthalazine
DIAD	diisopropyl azodicarboxylate
DIBAH	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
1,2-DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone

EA	ethyl acetate
ESI	electron spray ionisation
ether or Et_2O	diethyl ether
EtOH	ethanol
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
Hept	heptane
Hex	hexane
HV	high vacuum conditions
KHMDS	potassium hexamethyldisilazide
MeOH	methanol
min	minute(s)
MCPBA	*meta*-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimide
n-BuLi	*n*-butyl lithium
org.	organic
Pd/C	palladium on carbon
PPh_3	triphenylphosphine
PTSA	*para*-toluene sulfonic acid
quant.	quantitative
rac	racemic
Rf	retention factor
sat.	saturated
SiO_2	silica gel

rt	room temperature
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TsCl	*para*-toluene sulfonyl chloride
wt%	weight percent

Preparation methods:

The compounds of this invention can be prepared according to the procedures described in the examples hereafter which illustrate the preparation of the pharmacologically active compounds of the invention but do not limit the scope thereof.

Whenever the invention compounds 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 chromatography on a chiral stationary phase). Whenever the invention compounds are obtained in the form of mixtures of diasteromers they may be separated by an appropriate combination of silica gel chromatography, high performance liquid chromatography (HPLC) and crystallization techniques.

EXAMPLES

All temperatures are stated in °C. All analytical and preparative HPLC investigations on non-chiral phases are performed using RP-C18 based columns. Analytical HPLC investigations are performed on two different instruments with cycle-times of ~2.5 min and ~3.5 min respectively.

Preparation A: 3-methoxy-quinoline-5-carbaldehyde:

A.i. *3,5-dibromoquinoline*:

To concentrated H_2SO_4 (130 ml) was added dropwise at 0°C, over 80 min, 3-bromoquinoline (50 g) at a rate allowing the internal temperature to be maintained between 0° and 10°C. After

the addition was complete, NBS (48 g) was added portionwise and the reaction mixture was stirred at rt overnight. The reaction mixture was poured onto ice (2 l) and the resulting solid was dissolved in DCM (600 ml). The aq. layer was further extracted with DCM (600 ml) and the combined extracts were washed with 1*M* NaOH (300 mL) and concentrated *in vacuo*. The residue was dispersed in SiO_2 and the resulting dispersal was loaded on the top of a column and eluted with a DCM-Hex (1-1, 3 l) then DCM (3 l) and finally DCM-ether (1-1, 2 l). The title compound was recovered from the last fraction after evaporation to yield 40 g of a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.94 (d, J = 2.2 Hz, 1H); 8.73 (d, J = 2.2 Hz, 1H); 8.08 (d, J = 8.5 Hz, 1H); 7.88 (d, J = 7.5 Hz, 1H); 7.62 (dd, J = 7.5, 8.5 Hz, 1H).

A.ii. *5-bromo-3-methoxyquinoline*:

To a mixture of sodium methoxide (14.5 g) in DMPU (350 ml) heated at 125°C, was added in one portion intermediate A.i (34.5 g). The reaction was then heated at the same temperature for 1 h. The reaction mixture was then cooled to rt and poured onto ice (300 g). After the ice melt, the solid was filtered off and dried under vacuum. The filtrate was extracted with ether (4 x 150 ml). The combined extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was evaporated and the residue was purified over SiO_2 (Hex-EA 4-1) to afford a material that was pooled with the solid. The material was dissolved in DCM and dried over Na_2SO_4. After filtration and evaporation, the solid was further dried under HV to afford the title compound (24.5 g) as a beige solid.

^{1}H NMR ($CDCl_3$) δ: 8.68 (d, J =2.8 Hz, 1H); 8.03 (d, J = 8.3 Hz, 1H); 7.80 (d, J = 7.5 Hz, 1H); 7.72 (d, J = 2.8 Hz, 1H); 7.42 (dd, J = 7.5, 8.3 Hz, 1H); 4.02 (s, 3H).

MS (ESI, m/z): 239.7 [$M+H^+$].

A.iii. *3-methoxy-quinoline-5-carbaldehyde*:

To a solution of intermediate A.ii (10 g) in THF (250 ml) cooled to –78°C, was added *n*-BuLi (22 ml). After 15 min, a solution of DMF (10 ml) in ether (20 ml) was quickly added. The solution was stirred 15 min and EtOH (5 ml), followed by 1*M* $NaHSO_4$ (40 ml), was added. After warming to rt, the organic layer was diluted with EA (100 ml). The two layers were separated and the aq. layer was extracted once with EA (100 ml). The combined org. layers were washed with brine and concentrated to dryness. The residue was chromatographed over SiO_2 (EA-Hex 1-2 then 1-1) to afford the title compound (4.75 g) as a yellowish solid.

^{1}H NMR ($CDCl_3$) δ: 10.32 (s, 1H); 9.02 (d, J = 2.9 Hz, 1H); 8.75 (d, J = 2.9 Hz, 1H); 8.31 (d, J = 8.3 Hz, 1H); 8.02 (d, J = 7.1 Hz, 1H); 7.72 (dd, J = 7.1, 8.3 Hz, 1H); 4.02 (s, 3H).
MS (ESI, m/z): 187.9 [$M+H^+$].

Preparation B: 6-methoxy-[1,5]naphthyridine-4-carbaldehyde:

B.i. *2-methoxy-8-styryl-[1,5]naphthyridine*:

Trifluoromethanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (1.5 g, 4.86 mmol), *trans*-phenylvinyl boronic acid (0.8 g, 5.35 mmol) and K_2CO_3 (0.9 g, 6.32 mmol) were introduced in a two-neck flask. The atmosphere was flushed with nitrogen. Dioxane (20 ml) and water (5 ml) were added. The mixture was stirred at rt for 5 min and $(P(Ph)_3)_4Pd$ (0.28 g, 0.24 mmol) was added. The mixture was heated at reflux for 5 h. After cooling, the reaction mixture was diluted with EA (10 ml) and water (50 ml). The aqueous layer was extracted with EA (2 x 100 ml). The combined extracts were concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 1-1) to afford the title alkene (1.26 g, 4.8 mmol) as an oil that crystallized on standing.

^{1}H NMR (d6-DMSO) δ: 8.77 (d, J = 4.7 Hz, 1H); 8.28 (d, J = 9.0 Hz, 1H); 8.19 (d, J = 16.7 Hz, 1H); 8.01 (d, J = 4.7 Hz, 1H); 7.91 (d, J = 16.7 Hz, 1H); 7.74 (m, 2H); 7.40-7.34 (m, 3H); 7.30 (d, J = 9.0 Hz, 1H); 4.12 (s, 3H).

B.ii. *1-(6-methoxy-[1,5]naphthyridin-4-yl)-2-phenyl-ethane-1,2-diol*:

To a mixture of intermediate B.i (1.26 g, 4.8 mmol) in 2-methyl-2-propanol (24 ml) and water (24 ml) were added methanesulfonamide (0.52 g) and AD mix β® (7 g). The mixture was stirred at rt for 12 h. Sodium bisulfite (7.5 g) was added carefully and stirring was continued 20 min. The two layers were decanted and the aqueous layer was extracted with EA (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was triturated in Hex-EA (1-3, 30 ml) and the resulting solid was filtered off and dried *in vacuo* to afford the title diol (1.3 g) as a white solid.
MS (ESI, m/z): 297.1 [$M+H^+$].

B.iii. *6-methoxy-[1,5]naphthyridine-4-carbaldehyde*:

To a solution of intermediate B.ii (1.3 g, 4.4 mmol) in acetone (15 ml) was added a solution of $NaIO_4$ (2.35 g, 10.96 mmol) in water (5 ml). The reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with THF (100 ml) and the solids were filtered off.

The filtrate was concentrated to dryness and the residue was resuspended in water (100 ml), ether (10 ml) and Hex (100 ml). The slurry was stirred at rt for 15 min and filtered. The solids were washed with water and Hex. After drying, the title aldehyde (0.42 g) was recovered as a white solid.

^{1}H NMR (d_6-DMSO) δ: 11.25 (s, 1H); 9.02 (d, J = 4.4 Hz, 1H); 8.42 (d, J = 9.1 Hz, 1H); 7.92 (d, J = 4.4 Hz, 1H); 7.40 (d, J = 9.1 Hz, 1H); 4.11 (s, 3H).

Preparation C: *(E)*-3-(2,5-difluoro-phenyl)-propenal:

C.i. *(E)-3-(2,5-difluoro-phenyl)-acrylic acid ethyl ester*:

To an iced chilled suspension of NaH (1.13 g, 60% in oil dispersion, 28.2 mmol) in THF (32 ml) was added triethylphosphonoacetate (5.6 ml, 28.2 mmol). The reaction mixture was stirred at rt for 20 min. 2,5-difluoro-benzaldehyde (3.34 g, 23.5 mol) was added dropwise. After 30 min, 10% aq. $NaHSO_4$ (100 ml) was added and the mixture was diluted with EA (150 ml). The two phases were separated and the aq. layer was extracted twice (2 x 100 ml). The combined org. layers were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 19-1) to afford the title unsaturated ester (5.0 g, 100%) as colourless oil.

^{1}H NMR ($CDCl_3$): 7.76 (dd, J = 1, 16.1 Hz, 1H); 7.26-7.21 (m, 1H); 7.13-7.03 (m, 2H); 6.52 (d, J = 16.1Hz, 1H); 4.29 (q, J = 7.1 Hz, 2H); 1.36 (t, J = 7.1 Hz, 3H).

C.ii. *(E)-3-(2,5-difluoro-phenyl)-prop-2-en-1-ol*:

To a solution of intermediate C.i (5.0 g, 23.5 mmol) in ether (100 ml), cooled to 0°C, was added a DIBAH (1*M* in Hex, 60 ml, 60 mmol). The mixture was stirred at the same temperature for 40 min. Water (6 ml) was added and the mixture was stirred 30 min. The solid was filtered off and thoroughly washed with ether. The filtrate was concentrated to dryness to afford the title alcohol (4.0 g, 98% yield) as colorless oil.

^{1}H NMR ($CDCl_3$): 7.15 (ddd, J = 3.1, 5.9, 9.0 Hz, 1H); 7.00 (td, J = 4.6, 9.0 Hz, 1H); 6.95-6.87 (m, 1H); 6.75 (dd J= 1.3, 16.1 Hz, 1H); 6.45 (td, J = 5.3, 16.1 Hz, 1H); 4.38 (br d, J = 5.3 Hz, 2H); 1.63 (s, 1H).

C.iii. *(E)-3-(2,5-difluoro-phenyl)-propenal*:

To a solution of intermediate C.ii (1.70 g, 10 mmol) in DCM (20 ml) was added at rt, a solution of Dess-Martin periodinane (15 wt% in DCM, 20 ml). The mixture was stirred at rt

for 3 h. After concentration to dryness, the residue was chromatographed over SiO_2 (Hex-EA 9-1) to afford the title aldehyde (1.06 g, 63% yield) as a white solid.

^{1}H NMR (d6-DMSO): 9.74 (d, J = 7.6Hz, 1H); 7.88-7.81 (m, 1H); 7.79 (overlapped dd, J = 1.4, 16.0 Hz, 1H); 7.46-7.37 (m, 2H); 6.67 (dd, J = 7.6, 16.0 Hz, 1H).

Preparation D: 3-methoxy-quinoxaline-5-carbaldehyde:

D.i. *2-cyano-N-(2-methyl-6-nitro-phenyl)-acetamide*:

To a solution of 2-methyl-6-nitroaniline (25 g, 164.3 mmol) in benzene (200 ml) were added cyanoacetic acid (14.5 g, 170.46 mmol) and PCl_5 (35 g, 168 mmol). The reaction mixture was heated at 60°C for 7 h. After cooling to rt, the reaction mixture was filtered and the solid was washed with benzene and water. The solid was dried under reduced pressure to afford the title acetamide (24 g, 109 mmol) as a yellow solid.

^{1}H NMR (d6-DMSO) δ: 10.2 (s, 1H); 7.78 (d, J = 8.3 Hz, 1H); 7.65 (d, J = 8.3 Hz, 1H); 7.43 (t, J= 8.3 Hz, 1H); 3.95 (s, 2H); 2.30 (s, 3H).

D.ii. *3-hydroxy-5-methyl-1-oxy-quinoxaline-2-carbonitrile*:

To a solution mixture of intermediate D.i (24 g, 109.5 mmol) in 1*M* aq. NaOH (100 ml) was added pyridine (100 ml). The reaction mixture was stirred at rt for 4 h. The pH was adjusted to 6 by addition of 1*M* aq. HCl. The solid was filtered off and washed with water. The solid was triturated with EtOH. After drying under HV, the title nitrile (17.7 g, 87.9 mmol) was obtained as a yellow solid.

MS (ESI, m/z): 202.1 $[M+H]^+$.

D.iii. *8-methyl-quinoxalin-2-ol*:

To a solution of intermediate D.ii (17.7 g, 87.9 mmol) in water (300 ml) and EtOH (24 ml) was added sodium dithionite (35.4 g, 203.9 mmol). The reaction mixture was heated at 60°C for 1 h. The reaction mixture was filtered till warm, and the pH of the filtrate was adjusted to 2 by adding 1*M* aq. HCl. The pH of the solution was subsequently made basic by adding solid NaOH (10 g). EA (150 ml) was added. The aq. layer was extracted twice more with EA (2 x 150 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was dried under HV to afford the title intermediate (11.1 g, 69 mmol) as a yellow solid.

^{1}H NMR (d6-DMSO) δ: 11.75 (br s, 1H); 8.17 (s, 1H); 7.62 (d, J = 8.4 Hz, 1H); 7.40 (d, J = 8.4 Hz, 1H); 7.21 (t, J = 8.4 Hz, 1H); 2.42 (s, 3H).
MS (ESI, m/z): 161.1 $[M+H]^+$.

D.iv. *2-chloro-8-methyl-quinoxaline*:

A solution of intermediate D.iii (11.1 g, 69.5 mmol) in phosphorus oxychloride (80 ml) was heated at 110°C during 2 h. After cooling to rt, the reaction mixture was poured onto ice (200 g). The aqueous layer was extracted with EA (2 x 200 ml). The combined extracts were washed with brine (100 ml), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over silica gel (Hex-EA 1-1) to afford the title intermediate (12.5 g, 69.5 mmol) as a red solid.
^{1}H NMR (d6-DMSO) δ: 8.99 (s, 1H); 7.97 (m, 1H); 7.80 (m, 2H); 2.68 (s, 3H).
MS (ESI, m/z): 179.2 $[M+H]^+$.

D.v. *2-methoxy-8-methyl-quinoxaline*:

To a solution of intermediate D.iv (12.5 g, 69.5 mmol) in DMF (80 ml) was added sodium methoxide (9 g, 166 mmol). The reaction mixture was heated at 45°C for 4 h. After cooling to rt, the reaction mixture was partitioned between water (10 ml) and EA (200 ml). The organic layer was washed once with water (100 ml), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over silica gel (Hex-EA 1-4) to afford the title intermediate (10.2 g, 58.55 mmol) as a yellow solid.
^{1}H NMR ($CDCl_3$) δ: 8.48 (s, 1H); 7.88 (d, J = 7.9 Hz, 1H); 7.55 (d, J = 7.9 Hz, 1H); 7.47 (t, J = 7.9 Hz, 1H); 4.12 (s, 3H); 2.69 (s, 3H).
MS (ESI, m/z): 175.4 $[M+H]^+$.

D.vi. *8-dibromomethyl-2-methoxy-quinoxaline*:

To a solution of intermediate D.v (10.2 g) in CCl_4 (560 ml) were added AIBN (0.96 g) and NBS (25.9 g, 145.5 mmol). The reaction mixture was heated at 80°C for 3 h. After cooling to rt, the reaction mixture was washed with water (200 ml) and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was triturated with MeOH to give, after drying under HV, the title dibromide (14.4 g, 43.3 mmol) as a slightly beige solid.
^{1}H NMR (d6-DMSO) δ: 8.69 (s, 1H); 8.25 (dd, J = 1.3, 7.5 Hz, 1H); 8.07 (dd, J = 1.3, 8.3 Hz, 1H); 8.02 (s, 1H); 7.74 (dd, J = 7.5, 8.3 Hz, 1H); 4.14 (s, 3H).
MS (ESI, m/z): 332.8 $[M+H]^+$.

D.vii. *3-methoxy-quinoxaline-5-carbaldehyde*:

To a solution of intermediate D.vi (10.7 g, 32.2 mmol) in EtOH (330 ml) was added, at rt, a solution of silver nitrate (15 g) in water (70 ml). The reaction was stirred at rt for 1 h. The reaction mixture was diluted with MeCN (200 ml) and the solids were filtered off and the filtrate was concentrated *in vacuo*. The residue was filtered over a silica gel pad (eluent: EA) to afford the title aldehyde (6.2 g, 32.2 mmol) as a slightly yellow solid.

^{1}H NMR (d6-DMSO) δ: 11.15 (s, 1H); 8.74 (s, 1H); 8.36 (dd, J = 1.3, 8.1 Hz, 1H); 8.21 (dd, J = 1.3, 7.9 Hz, 1H); 7.80 (dd, J = 7.9, 8.1 Hz, 1H); 4.14 (s, 3H).

MS (ESI, m/z): 189.2 $[M+H]^+$.

Preparation E: 3-fluoro-6-methoxy-[1,5]naphthyridine-4-carbaldehyde:

E.i. *trans*-7-fluoro-2-methoxy-8-styryl-[1,5]naphthyridine:

8-bromo-7-fluoro-2-methoxy-[1,5]naphthyridine (prepared as in WO 2004/058144; 7 g, 27.2 mmol), *trans*-phenylvinyl boronic acid (4.23 g, 1.05 eq) and K_2CO_3 (4.9 g) were introduced in a two-necked flask. The atmosphere was flushed with nitrogen and dioxane (40 ml) and water (10 ml) were added. The mixture was stirred at rt for 5 min and $Pd(PPh_3)_4$ (1.56 g, 5 mol%) was added. The mixture was heated at reflux overnight. After cooling, the solvent was evaporated *in vacuo* and the residue was extracted with EA (2 x 150 ml). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed (Hept-EA 2-1) to afford the title compound (7.2 g, 94% yield) as a white solid.

MS (ESI, m/z): 281.0 $[M+H]^+$.

E.ii. *1-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-2-phenyl-ethane-1,2-diol*:

The title diol (7.6 g, 94% yield) was obtained as a white foam, starting from intermediate E.i (7.2 g, 8.9 mmol) and using the procedure of Example 2, step 2.iv. The compound was purified by chromatography using EA as an eluent.

^{1}H NMR ($CDCl_3$) δ: 8.42 (d, J = 0.7 Hz, 1H); 8.28 (d, J = 9.1 Hz, 1H); 7.24-7.15 (m, 4H); 7.08 (m, 2H); 6.70 (br s, 1H); 5.28 (br s, 1H); 5.10 (d, J = 7.9 Hz, 1H); 4.11 (s, 3H); 3.85 (br s, 1H).

E.iii. *3-fluoro-6-methoxy-[1,5]naphthyridine-4-carbaldehyde*:

To a solution of intermediate E.ii (7.6 g, 23.95 mmol) in acetone (150 ml) was added a solution of $NaIO_4$ (12.8 g) in water (30 ml). The mixture was stirred at rt for 1 h. The solvent was removed in vacuo and the residue was diluted with water (500 ml). The resulting solid was filtered off, thoroughly washed with water, collected and dried under HV to afford the title aldehyde (4.0 g) as a light beige solid.

^{1}H NMR (d6-DMSO) δ: 11.08 (s, 1H); 9.01 (d, J = 1.3 Hz, 1H); 8.41 (d, J = 9.1 Hz, 1H); 7.37 (d, J= 9.1 Hz, 1H); 4.09 (s, 3H).

MS (ESI, m/z): 206.9 $[M+H]^+$.

Preparation F: 3-fluoro-6-methoxy-quinoline-5-carbaldehyde:

F.i. *5-bromo-3-fluoro-6-methoxy-quinoline*:

To a solution of 3-fluoro-6-methoxy-quinoline (0.89 g) in MeCN (9 ml), cooled to 0°C, was added NBS (1 g). The mixture was stirred 2 h at this temperature. The reaction mixture was allowed to warm up to rt and proceeded overnight. 10% aq. $NaHSO_3$ (20 ml) was added. The mixture was further diluted with water (100 ml) and the resulting solid was filtered off, washed with water and dried *in vacuo* to afford the title compound (1.03 g, 80% yield) as a white solid.

^{1}H NMR (d_6-DMSO) δ: 8.85 (d, J = 2.7 Hz, 1H); 8.18 (dd, J = 2.7, 10.2 Hz, 1H); 8.14 (d, J = 9.0 Hz, 1H); 7.77 (d, J = 9.0 Hz, 1H); 4.04 (s, 3H).

MS (ESI, m/z): 255.7 $[M-H^+]$.

F.ii. *3-fluoro-6-methoxy-quinoline-5-carbaldehyde*:

This aldehyde (0.68 g, 3.31 mmol) was obtained as a white solid, starting from intermediate F.i (1.0 g, 3.9 mmol) and using the procedures described in Preparation E, steps E.i, E.ii and E.iii.

^{1}H NMR (d_6-DMSO) δ: 10.69 (s, 1H); 9.16 (dd, J = 2.9, 11.7 Hz, 1H); 8.88 (d, J = 2.9 Hz, 1H); 8.38 (d, J = 9.0 Hz, 1H); 7.83 (d, J = 9.0 Hz, 1H); 4.12 (s, 3H).

Preparation G: (3*R*,6*S*)-[6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester:

G.i. *toluene-4-sulfonic acid (2S,5R)-5-tert-butoxycarbonylamino-tetrahydro-pyran-2-ylmethyl ester*:

To an ice-chilled solution of (3*R*,6*S*)-(6-hydroxymethyl-tetrahydro-pyran-3-yl)-carbamic acid *tert*-butyl ester (obtained as described in *Eur. J. Org. Chem.* (2003); 25 g, 108 mmol) in DCM (650 ml) were added TEA (30 ml), DMAP (1.8 g) and TsCl (22.6 g). The reaction was stirred at rt for 4 h. Saturated $NaHCO_3$ (100 ml) was added. The volatiles were removed under reduced pressure and the residue was taken up in EA (400 ml). The org. layer was washed with saturated $CuSO_4$ (2 x 150 ml), water (3 x 150 ml) and brine (100 ml). The org. layer was dried over Na_2SO_4, filtered and concentrated to dryness to afford after drying a white solid (41.8 g) that was carried on without further purification.

G.ii. *(3R,6S)-(6-iodomethyl-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester*:

To a solution of intermediate G.i (18 g, 46.7 mmol) in acetone (200 ml) was added NaI (20 g). The reaction mixture was heated at reflux 24 h. After cooling to rt, water (200 ml) was added and the volatiles were removed *in vacuo*. The residue was filtered, thoroughly washed with water and Hex and dried under HV to afford the iodide (12.2 g, 76% yield) as a beige solid.
MS (ESI, m/z): 342.2 [$M+H^+$].

G.iii. *(3R,6S)-[6-(1-phenyl-1H-tetrazol-5-ylsulfanylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of 1-phenyl-1*H*-tetrazole-5-thiol (7 g, 39 mmol) in EtOH (100 ml) was added KOH (3.0 g). The reaction mixture was refluxed for 1 h and intermediate G.ii (11.6 g, 34 mmol) was added. The mixture was refluxed overnight. Water (150 ml) was added and the volatiles were removed under reduced pressure. The solid was filtered off, thoroughly washed with water and dried under HV to afford the sulphide (13.3 g, quant.) as a white solid.
MS (ESI, m/z): 392.5 [$M+H^+$].

G.iv. *(3R,6S)-[6-(1-phenyl-1H-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate G.iii (13.3 g, 34 mmol) in EtOH (150 ml) and THF (150 ml) were added ammonium molybdate tetrahydrate (11 g, 8.9 mmol) and then 30% H_2O_2 (50 ml). The mixture was heated at 60°C overnight. The reaction mixture was cooled to rt, diluted with water (200 ml) and the volatiles were removed under reduced pressure. The residue was partitioned between EA (300 ml) and water (100 ml) and the aq. layer was extracted with EA (2 x 300 ml). The combined extracts were concentrated to dryness. The residue was resuspended in ether. The solids were filtered off, washed with water and Hex to afford the title sulfone (11.8 g, 81% yield) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.69-7.60 (m, 5H); 4.23 (m, 1H); 3.95-3.80 (m, 2H); 3.68-3.52 (m, 2H); 2.86 (t, J = 10.7 Hz, 1H); 2.11 (m, 1H); 1.79 (m, 1H); 1.60-45 (m, 2H); 1.43 (s, 9H); 1.37 (m, 1H).

MS (ESI, m/z): 424.5 [$M+H^+$].

Preparation H: 6-fluoro-quinoline-4-carbaldehyde:

Starting from 4-bromo-6-fluoro-quinoline (see WO 2004/014361 for a preparation; 6 g, 26.5 mmol), the title aldehyde (4.3 g, 24.5 mmol) was prepared as a beige solid using the procedures described in Preparation E, steps E.i, E.ii and E.iii.

^{1}H NMR (d6-DMSO) δ: 10.50 (s, 1H); 9.23 (d, J = 4.2 Hz, 1H); 8.68 (dd, J = 2.9, 10.8 Hz, 1H); 8.25 (dd, J = 5.8, 9.3 Hz, 1H); 8.11 (d, J = 4.2 Hz, 1H); 7.83 (ddd, J = 2.9, 9.3, 10.8 Hz, 1H).

Preparation I: (3*S*,6*R*)-[6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester:

I.i. *(S)-(1-hydroxymethyl-pent-4-enyl)-carbamic acid tert-butyl ester*:

To a suspension of $LiBH_4$ (1.15 g, 53 mmol) in THF (300 ml) at rt was added a solution of (*S*)-2-*tert*-butoxycarbonylamino-hex-5-enoic acid methyl ester (12.9 g, 53 mmol, prepared according to *J. Org. Chem.* (1995), 60, 2210) in THF (100 ml). The mixture was stirred at rt for 4 h, poured into water and extracted with EA. The organic layer was washed with brine,

dried over $MgSO_4$ and concentrated to give the title alcohol (11.4 g, 99% yield) as a colourless oil.

^1H NMR ($CDCl_3$) δ: 5.75-5.65 (m, 1H), 5.00-4.90 (m, 2H), 4.5 (br, 1H, OH), 3.70-3.45 (m, 3H), 2.10-2.00 (m, 2H), 1.60-1.35 (m, 2H), 1.38 (s, 9H).

I.ii. *(1S,3RS,4RS)-(1-hydroxymethyl-3-oxiranyl-propyl)-carbamic acid tert-butyl ester*:

Intermediate I.i (11.4 g, 53 mmol) was dissolved in 1,2-DCE (300 ml) and water (250 ml) and 1*M* phosphate buffer pH 8 (150 ml) was added. MCPBA (14.3 g, 1.1 eq, 70%) was added and the mixture vigorously stirred overnight. The two phases were separated and the aqueous phase was extracted once more with DCM. The combined organic layers were washed with a sat. $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by chromatography over SiO_2 (Hex:EA 1:1 then EA) to give the title epoxide (7.74 g, 63% yield, mixture of diastereomers) as a colourless oil.

^1H NMR ($CDCl_3$) δ: 4.90-4.85 (m, 1H), 3.75-3.50 (m, 3H), 3.00-2.90 (m, 1H), 2.80-2.51 (m, 1H), 2.6 (br, 1H, OH), 2.55-2.50 (m, 1H), 1.80-1.40 (m, 4H), 1.42 (s, 9H).

I.iii. *(3S,6R)-(6-hydroxymethyl-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester*:

A solution of intermediate I.ii (2.3 g, 10 mmol) in DCM (50 ml) was treated with *D,L*-10-camphor sulfonic acid (0.1 eq). The reaction was slightly exothermic. The mixture was stirred at rt for 3 h, concentrated and purified by chromatography over SiO_2 (EA) to give the title tetrahydropyran derivative (0.874 g, 37% yield) as a colourless solid.

^1H NMR ($CDCl_3$) δ: 4.28 (br, 1H), 4.20-10 (m, 1H), 3.70-3.30 (m, 5H), 3.04 (t, 1H, J =10.6 Hz), 2.20-2.00 (m, 2H, 1.75-1.20 (m, 11H).

I.iv. *(3R,6S)-[6-(1-phenyl-1H-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

This sulfone (5.9 g, 13.9 mmol) was obtained as a white solid starting from intermediate I.iii (8.2 g, 35.4 mmol) and using the procedures described in Preparation G.

Example 1: (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol:

1.i. *[(2R,3R,6S)-6-(tert-butyl-dimethyl-silanyloxymethyl)-2-((2RS)-2,3-dihydroxy-propyl)-3,6-dihydro-2H-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a mixture of (2*R*,3*R*,6*S*)-[2-allyl-6-(*tert*-butyl-dimethyl-silanyloxymethyl)-3,6-dihydro-2*H*-pyran-3-yl]-carbamic acid *tert*-butyl ester (obtained as described in *Eur. J. Org. Chem.* (2003), 2418-2427; 60.7 g, 158.2 mmol) in 2-methyl-2-propanol (750 ml) and water (750 ml) were added potassium ferricyanide (182.4 g, 553.8 mmol), potassium carbonate (65.8 g, 476.0 mmol), $(DHQ)_2PHAL$ (1.12 g, 1.4 mmol) and potassium osmate dihydrate (0.118 g). The reaction mixture was mechanically stirred at rt for 24 h. Sodium bisulfite (316 g) was added slowly. The two layers were decanted and the aq. layer was extracted once more with EA (500 ml). The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was filtered through a pad of SiO_2 (Hex-EA 1-4) to afford the title diol as a yellow oil (61.0 g, 146.0 mmol). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 418.0 $[M+H^+]$.

1.ii. *[(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-hydroxymethyl-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a mixture of intermediate 1.i (61 g, 146.0 mmol) in THF (710 ml) were added PTSA (1.38 g, 7.3 mmol) and 2,2-dimethoxypropane (54.0 ml, 439.1 mmol). The reaction mixture was stirred at rt for 90 min. TBAF (1*M* in THF, 230 ml) was added. The reaction proceeded for 90 min. The reaction mixture was concentrated to dryness and the residue was chromatographed over SiO_2 (Hex-EA 1-4) to afford the title compound as a thick oil (44.7 g, 130.1 mmol). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 344.2 $[M+H^+]$.

1.iii. *[(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-hydroxymethyl-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 1.ii (19.7 g, 57.3 mmol) in EA (230 ml) was added platinum oxide (0.7 g). The resulting suspension was stirred under hydrogen for 5 h. The catalyst was removed by filtration through celite and the filtrate evaporated under reduced pressure. The

residue was purified by column chromatography over SiO_2 (EA-Hex 4-1 to 1-0) to afford the title compound as a white solid (19.43 g). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 346.1 [$M+H^+$].

1.iv. *[(2R, 3R, 6S)-2-((4R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(1-phenyl-1H-tetrazol-5-ylsulfanylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To an ice-chilled solution of intermediate 1.iii (19.4 g, 56.1 mmol) in THF (500 ml) were added PPh_3 (29 g), phenyltetrazole thiol (14 g) and DIAD (16.7 ml) dropwise. The resulting solution was stirred at rt overnight. The reaction mixture was concentrated to dryness and the residue purified by column chromatography over SiO_2 (EA-Hex 1-3 to 1-0) to afford the title sulfide as a colorless solid (28.85g, 99% yield). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 506.0 [$M+H^+$]

1.v. *[(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(1-phenyl-1H-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 1.iv (28.4 g) in EtOH (240 ml) and THF (240 ml) were added ammonium molybdate heptahydrate (17.73 g) and 50% aq. H_2O_2 (82.5 ml). The mixture was heated at 60°C overnight. After cooling to rt, the reaction mixture was diluted with water (250 ml) and the volatiles were removed under reduced pressure. EA (150 ml) was added to the aq. residue and the phases were separated. The aq. layer was extracted three times with EA. The combined org. layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 to 9-1) to afford first the desired sulfone as a colourless thick oil (4.9 g), then [(2*R*,3*R*,6*S*)-2-((2*RS*)-2,3-dihydroxy-propyl)-6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid *tert*-butyl ester as a white foam (9.4 g). The latter was taken up in THF (90 ml), and was treated with PTSA (0.187 g) and 2,2-dimethoxypropane (6.95 ml). The reaction mixture was stirred at rt for 2.5 h. Water (8 ml) and aq. $NaHCO_3$ were added before concentration to dryness. The residue was partitioned between water and EA and the phases were separated. The org. layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was further dried under HV to afford more of the title sulfone (9.94 g).

MS (ESI, m/z): 538.0 [$M+H^+$].

1.vi. *{(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-trans-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of 6-methoxy-[1,5]naphthyridine-4-carbaldehyde (see preparation B; 1.7 g, 9.03 mmol) and intermediate 1.v (4 g, 7.45 mmol) in 1,2-DME (40 ml) cooled to -78°C, was added dropwise, over 10 min, KHMDS (0.5*M* in toluene, 24 ml). The mixture was stirred 30 min at this temperature. The reaction was then allowed to warm up to rt over 30 min, whereupon water (50 ml) was added. The two layers were decanted, the aq. layer was extracted twice with EA (2 x 150 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 1-1 then 1-4) to afford the title alkene (2.8 g, 62% yield) as a colourless foam.

MS (ESI, m/z): 500.4 [$M+H^+$]

1.vii.a. *{(2R,3R,6S)-2-(2-hydroxy-ethyl)-6-trans-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

and

1.vii.b. *{(2R,3R,6R)-2-(2-hydroxy-ethyl)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

A solution of intermediate 1.vi (2.8 g, 5.6 mmol) in a THF-AcOH-water mixture (1-3-1, 50 ml) was heated at 60°C for 6 h. The reaction mixture was concentrated to dryness, and the residue was partitioned between EA and saturated $NaHCO_3$. The pH was adjusted to 7 by adding solid $NaHCO_3$. The aq. layer was extracted once with EA and the combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was taken up in acetone (100 ml) and a warm solution of $NaIO_4$ (3 g) in water (10 ml) was added. The mixture was stirred 1 h. The reaction mixture was filtered through a pad of celite and the solvent was removed *in vacuo*. The residue was extracted twice with EA. The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was taken up in MeOH (30 ml) and $NaBH_4$ (0.7 g) was added. The reaction proceeded for 15 min. 10% aq. $NaHSO_4$ (100 ml) was added. The volatiles were removed *in vacuo* and the aq. residue was extracted three times with EA (3 x 100 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (DCM-MeOH 19-1) to afford a colourless foam (1.76 g) which was characterized as a mixture of the two title compounds.

MS (ESI, m/z): 430.1 [M+H$^+$].

1.viii.a. *{(2R,3R,6R)-2-(2-hydroxy-ethyl)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

and

1.viii.b. *[(2R,3R,6S)-6-[(1R,2R)-1,2-dihydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-2-(2-hydroxy-ethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 1.vii (1.76 g, mixture of compounds), was added potassium ferricyanide (4.04 g), K_2CO_3 (1.7 g) methanesulfonamide (0.47 g), $(DHDQ)_2PHAL$ (0.035 g) and potassium osmate dihydrate (0.005 g). The mixture was stirred 40 h at rt. Sodium bisulfite (6 g) was added. The two layers were decanted and the aq. layer was extracted twice with EA (2 x 150 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (DCM-MeOH 19-1) to afford first the title alkane 1.viii.a (1.34 g, 3.1 mmol) as a colourless foam.
MS (ESI, m/z): 432.0 [M+H$^+$].
Elution was pursued with DCM-MeOH 6-1 to give the title diol 1.viii.b (0.4 g, 0.86 mmol) as a colourless foam.
MS (ESI, m/z): 464.3 [M+H$^+$].

1.ix. *(2R,3R,6R)-2-{3-amino-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol*:

A solution of intermediate 1.viii.a (1.34 g, 3.1 mmol) in TFA (10 ml) was stirred at rt for 15 min. After evaporation to dryness, the residue was dissolved in water (50 ml), washed once with EA (50 ml). The pH of the aq. layer was adjusted to 12 adding 3*M* aq. NaOH and the aq. layer was extracted four times with DCM-MeOH 9-1 mixture (4 x 100 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. After further drying under HV, the residue was purified by chromatography over SiO_2 (DCM-MeOH 6-1 containing 1% aq. NH_4OH) to give the title amine (0.65 g, 63% yield) as a colourless foam .
MS (ESI, m/z): 332.3 [M+H$^+$].

1.x. *(E)-2-{(2R,3R,6R)-3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol*:

To a solution of intermediate 1.ix (0.1 g, 0.3 mmol) in 1,2-DCE (4.5 ml) and MeOH (1.5 ml) were added (*E*)-3-(2,5-difluoro-phenyl)-propenal (see Preparation C, 0.055 g, 1.1 eq.) and 3Å molecular sieves (1 g). The mixture was heated at 50°C overnight. After cooling to rt, $NaBH_4$ (0.1 g) was added. The reaction proceeded for 2 h before filtration through a pad of hydromatrix® (treated with saturated aq. $NaHCO_3$). The filtrate was concentrated to dryness. The residue was chromatographed over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH) (0.09 g, 61% yield) was obtained as a colourless oil.

MS (ESI, m/z): 484.1 $[M+H^+]$.

Example 2: {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid:

2.i. *{(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[(E)-2-(3-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

A Julia coupling was performed as described in Example 1, step 1.vi, starting from intermediate 1.v (1.99 g, 3.7 mmol) and 3-methoxy-quinoline-5-carbaldehyde (see Preparation A; 0.67 g) to afford the title compound as a white foam (1.07 g, 2.14 mmol). The compound was purified by column chromatography over SiO_2 (EA-Hex 1-1). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 499.2 $[M+H^+]$.

2.ii. *{(2R,3R,6R)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 2.i (1.07 g, 2.14 mmol) in EA (35 ml) was added 10% Pd/C (0.23 g). The resulting suspension was stirred under hydrogen for 1 h. The catalyst was removed by filtration. The filtrate was evaporated under reduced pressure and further dried under HV to afford the title compound as a white foam (1.03 g, 2.05 mmol). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 501.1 $[M+H^+]$.

2.iii. *3-(2RS)-{(2R,3R,6R)-3-amino-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

A solution of intermediate 2.ii (1.03 g) in TFA (21 ml) was stirred for 10 min. Water (7 ml) was added. The resulting mixture was stirred for 1 h and concentrated to dryness. The residue was basified with 1*M* aq. NaOH. DCM-MeOH 9-1 was added and the phases were separated. The aq. layer was extracted six times with DCM-MeOH 9-1 and the combined extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The title compound (0.69 g, 1.91 mmol) was obtained as a white foam. This was obtained as a 2-1 mixture of epimers.

^1H NMR ($CDCl_3$) main signals δ: 8.65 (d, J = 2.8 Hz, 1H); 7.89 (d, J = 8.4 Hz, 1H); 7.56 (m, 1H); 7.45 (m, 1H); 7.31 (m, 1H); 4.03 (m, 1H); 3.94 (s, 3H); 3.79 (m, 1H); 3.63 (m, 2H); 3.47 (m, 1H); 3.14 (m, 2H); 2.95 (m, 1H); 2.25-2.05 (m, 5H); 2.03-1.87 (m, 3H); 1.85-1.67 (m, 3H); 1.59 (m, 1H); 1.23 (m, 1H).

MS (ESI, m/z): 361.1 [$M+H^+$].

2.iv. *(E)-3-(2,5-difluoro-phenyl)-N-{(2R,3R,6R)-2-((2RS)-2,3-dihydroxy-propyl)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-3-yl}-acrylamide*:

To a solution of intermediate 2.iii (0.360 g, 1 mmol) and 3-(2,5-difluoro-phenyl)-acrylic acid (0.203 g, 1.1 mmol) in DMF (15 ml) were added DIPEA (0.514 ml, 3 mmol) and HATU (0.456 g, 1.2 mmol). The reaction mixture was stirred at rt for 90 min and concentrated to dryness. The residue was dissolved in DCM-MeOH 9-1 (50 ml) and washed with saturated $NaHCO_3$ (20 ml). The aq. layer was extracted twice with DCM-MeOH 9-1 (2 x 20 ml) and the combined org. layers were dried over $MgSO_4$, 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 to DCM-MeOH 9-1 containing 1% aq. NH_4OH) to afford the title amide (0.331 g, 62% yield) as orange solid.

^1H NMR (d_6-DMSO) main signals δ: 8.69 (d, J = 2.7 Hz, 1H); 8.30 (d, J = 8.6 Hz, 1H); 7.87-7.79 (m, 2H); 7.56-7.50 (m, 4H); 7.40-7.27 (m, 2H); 7.02 (dd, J = 5.1, 15.9 Hz, 1H); 4.58 (m, 2H); 4.23 (m, 1H); 4.06 (overlapped m, 2H); 4.02 (overlapped s, 3H); 3.86-3.76 (m, 2H); 3.45-3.24 (overlapped m, 2H); 3.09-2.99 (m, 1H); 2.16 (m, 1H); 2.00 (m, 3H); 1.67 (m, 2H); 1.37 (m, 1H); 1.21 (m, 1H).

MS (ESI, m/z): 527.0 [$M+H^+$].

2.v. *(E)-3-(2,5-difluoro-phenyl)-1-{(2RS,5R)-2-hydroxy-5-[2-(3-methoxy-quinolin-5-yl)-ethyl]-hexahydro-pyrano[3,2-b]pyrrol-1-yl}-propenone*:

To a solution of intermediate 2.iv (0.153 g) in acetone (1.7 ml) was added at rt a solution of $NaIO_4$ (0.156 g) in water (0.5 ml). The reaction mixture was stirred for 30 min and concentrated to dryness. The residue was purified over SiO_2 (EA-Hex 2-1) to afford a colourless gum (0.118 g, 82% yield).

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

2.vi. *{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid*:

To a solution of intermediate 2.v (0.114 g, 0.23 mmol) in 2-methyl-2-propanol (5 ml) and 2-methyl-2-butene (1.2 ml) was added dropwise a solution of sodium chlorite (0.193 g) and sodium dihydrogen phosphate (0.193 g) in water (2 ml). The resulting solution was stirred at rt overnight and the volatiles were removed under HV. The residue was diluted with water and Hex. The phases were separated and the org. layer was extracted once with Hex. The aq. layer was acidified to pH 3 and extracted three times with EA. The combined extracts were washed with cold water and evaporated under reduced pressure. The colourless gum thus obtained was triturated in ether, filtered and dried under reduced pressure to give the title compound as a white solid (0.069 g, 58% yield).

^1H NMR (d_6-DMSO) δ: 12.32 (br. s, 1H); 8.82 (m, 1H); 8.58 (m, 1H); 8.05 (m, 2H); 7.51 (m, 4H); 7.37 (m, 2H); 7.03 (m, 1H); 4.36 (m, 1H); 4.02 (overlapped s, 3H); 4.01 (overlapped m, 1H); 3.86 (m, 1H); 3.39 (m, 1H); 3.10 (m, 1H); 2.44 (overlapped m, 2H); 2.25 (m, 1H); 1.92 (m, 2H); 1.65 (m, 2H); 1.37 (m, 1H).

MS (ESI, m/z): 511.0 $[M+H^+]$.

Example 3: {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid:

3.i. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid {(2R,3R,6R)-2-((2RS)-2,3-dihydroxy-propyl)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-3-yl}-amide*:

Starting from intermediate 2.iii (0.270 g, 0.75 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (0.174 g, 1.1 eq), the title compound

(0.187 g, 0.32 mmol) was obtained as a pale brown-orange foam using the procedure of Example 2, step 2.iv. The compound was obtained as a 2-1 mixture of epimers.

^{1}H NMR (d_6-DMSO) main signals δ: 11.29 (s, 1H); 8.69 (dd, J = 1.7, 2.7 Hz, 1H); 8.36 (d, J = 9.3Hz, 1H); 8.01 (d, J = 7.9 Hz, 1H); 7.88-7.79 (m, 2H); 7.66 (dd, J = 1.3, 7.9 Hz, 1H); 7.51 (m, 1H); 4.64 (d, J = 5.2 Hz, 2H); 4.58 (m, 1H); 4.25 (m, 1H); 4.08 (overlapped m, 1H); 4.03 (overlapped s, 3H); 3.95 (m, 1H); 3.77 (m, 1H); 3.69 (d, J = 5.1 Hz, 2H); 3.39-3.25 (overlapped m, 4H); 3.07 (m, 1H); 2.28 (m, 1H); 1.98 (m, 2H); 1.83-1.58 (m, 3H); 1.27 (m, 1H); 1.20 (m, 1H).

3.ii. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid [(2R,3R,6R)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-2-(2-oxo-ethyl)-tetrahydro-pyran-3-yl]-amide*:

Starting from intermediate 3.i (0.148 g, 0.27 mmol), and using the procedure of Example 2, step 2.v, the title aldehyde (0.078 g, 56% yield) was obtained as a colourless foam.
MS (ESI, m/z): 521.1 [M+H$^+$].

3.iii. *{(2R,3R,6R)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 3.ii (0.073 g, 0.14 mmol), the title acid (0.032 g, 42% yield) was obtained as an off-white solid using the procedure described in Example 2, step 2.vi. The compound was purified by trituration in ether.

^{1}H NMR (d_6-DMSO) δ: 11.29 (s, 1H); 8.76 (m, 1H); 8.55 (m, 1H); 8.12-7.87 (m, 3H); 7.67-7.47 (m, 3H); 4.45 (m, 1H); 4.14 (overlapped m, 1H); 4.04 (overlapped s, 3H); 3.96 (overlapped m, 1H); 3.76 (m, 1H); 3.46-3.25 (m, 2H); 3.04 (m, 1H); 2.53-2.20 (m, 4H); 2.01 (m, 2H); 1.69 (m, 2H); 1.30 (m, 1H).
MS (ESI, m/z): 537.0 [M+H$^+$].

Example 4: {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid trihydrochloride:

4.i. *(2RS)-3-{(2R,3R,6R)-3-amino-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

The title compound (1.30 g, 94% yield) was obtained as a white solid starting from intermediate 1.vi (1.98 g, 3.98 mmol) using the procedures of Example 2, steps 2.ii and 2.iii.
MS (ESI, m/z): 362.1 [$M+H^+$].

4.ii. *6-({(2R,3R,6R)-2-((2RS)-2,3-dihydroxy-propyl)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4H-pyrido[3,2-b][1,4]thiazin-3-one*:

Starting from intermediate 4.i (0.644 g, 1.78 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (0.380 g, 1.1 eq.), the title compound (0.583 g, 60% yield) was obtained as a white foam using the procedure of Example 1, step 1.x.
^{1}H NMR (d_6-DMSO) δ: 10.93 (s, 1H); 8.69 (dd, J = 1.1, 4.4 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.78 (dd, J = 1.3, 7.9 Hz, 1H); 7.56 (t, J = 4.4 Hz, 1H); 7.28 (d, J = 9.0 Hz, 1H); 7.12 (d, J = 7.9 Hz, 1H); 4.65-4.46 (m, 2H); 4.20-4.05 (overlapped m, 1H); 4.05 (overlapped s, 3H); 3.70 (overlapped s, 2H); 3.70-3.56 (overlapped m, 2H); 3.56 (overlapped s, 2H); 3.41-3.19 (overlapped m, 3H); 3.17-3.07 (m, 1H); 2.74 (m, 1H); 2.09 (m, 1H); 1.92-1.70 (m, 5H); 1.51 (m, 1H); 1.37 (m, 1H); 1.25 (m, 1H).
MS (ESI, m/z): 540.0 [$M+H^+$].

4.iii. *{(2R,3R,6R)-2-((2RS)-2,3-dihydroxy-propyl)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-carbamic acid tert-butyl ester*:

To a solution of intermediate 4.ii (0.5 g, 0.92 mmol) in dioxane (4.5 ml) and water (0.6 ml) was added 1*M* aq. NaOH (1 ml). The solution was cooled to 0°C and Boc_2O (0.303 g) was added. After stirring overnight, 1*M* aq. NaOH (0.5 ml) and Boc_2O (0.3 g) were added. After 4 h, 1*M* aq. NaOH (1 ml) and Boc_2O (0.3 g) were added again and the reaction mixture was stirred for 16 h. EA was added and the phases were separated. The aq. layer was extracted twice with EA and the combined org. layers were washed with brine, dried over $MgSO_4$, 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 compound as a pale yellow foam (0.449 g, 76% yield).

^1H NMR ($CDCl_3$) main signals δ: 9.27 (br. s, 1H); 8.64 (dd, J = 1.3, 4.5 Hz, 1H); 8.19 (dd, J = 1.2, 9.0 Hz, 1H); 7.56 (m, 1H); 7.36 (m, 1H); 7.10 (dd, J = 1.8, 9.0 Hz, 1H); 6.84 (br. d, J = 5.4 Hz, 1H); 4.66-4.53 (m, 2H); 4.39-4.09 (m, 2H); 4.04 (overlapped s, 3H); 4.00 (overlapped m, 1H); 3.73-3.51 (m, 3H); 3.47 (d, J = 5.4 Hz, 2H); 3.23-3.09 (m, 2H); 2.12-1.13 (m, 19H).

MS (ESI, m/z): 640.0 [$M+H^+$].

4.iv. *[(2R,3R,6R)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-2-(2-oxo-ethyl)-tetrahydro-pyran-3-yl]-(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-carbamic acid tert-butyl ester*:

Starting from intermediate 4.iii (0.444 g, 0.69 mmol), and using the procedure of Example 2, step 2.v, the title aldehyde (0.372 g, 88% yield) was obtained as a colourless thick oil. The compound was purified by column chromatography over SiO_2 using DCM-MeOH 19-1 as an eluent.

^1H NMR ($CDCl_3$) δ: 9.77 (br. s, 1H); 8.65 (d, J = 4.5 Hz, 1H); 8.37 (br. s, 1H); 8.19 (d, J = 9.0 Hz, 1H); 7.57 (d, J = 8.0 Hz, 1H); 7.36 (d, J = 4.5 Hz, 1H); 7.10 (d, J = 9.0 Hz, 1H); 6.84 (d, J = 7.7 Hz, 1H); 4.83 (m, 1H); 4.20-4.13 (m, 2H); 4.06 (s, 3H); 3.60 (m, 1H); 3.48 (d, J = 2.3 Hz, 2H); 3.23 (m, 1H); 3.07 (m, 1H); 2.90 (m, 1H); 2.59 (m, 1H); 1.90 (m, 2H); 1.75 (m, 3H); 1.34 (m, 11H).

MS (ESI, m/z): 608.0 [$M+H^+$].

4.v. *{(2R,3R,6R)-3-[tert-butoxycarbonyl-(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 4.iv (0.365 g, 0.6 mmol), the title acid (0.258 g, 69% yield) was obtained as a yellow solid using the procedure of Example 2, step 2.vi. The compound was purified by trituration in ether.

^1H NMR (d_6-DMSO) δ: 12.28 (s, 1H); 10.92 (s, 1H); 8.68 (d, J = 4.4 Hz, 1H); 8.26 (d, J = 9.0 Hz, 1H); 7.76 (d, J = 8.0 Hz, 1H); 7.56 (d, J = 4.4 Hz, 1H); 7.27 (d, J = 9.0 Hz, 1H); 6.82 (d, J = 8.0 Hz, 1H); 4.50 (m, 2H); 4.19 (m, 2H); 4.05 (s, 3H); 3.64 (m, 1H); 3.56 (d,

J = 3.4 Hz, 2H); 3.22 (m, 1H); 3.07 (m, 1H); 2.79 (m, 1H); 2.37 (m, 1H); 1.93 (m, 1H); 1.87-1.73 (m, 4H); 1.46-1.37 (m, 6H); 1.26 (m, 4H).

MS (ESI, m/z): 624.0 [$M+H^+$].

4.vi. *{(2R, 3R, 6R)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid trihydrochloride*:

To a suspension of intermediate 4.v (0.256 g, 0.41 mmol) in dioxane (1 ml) was added anhydrous HCl in dioxane (5*N*, 0.86 ml). The resulting solution was stirred at rt for 3 h. The mixture was concentrated to dryness. The residual solid was diluted with ether and evaporated under reduced pressure. The solid thus obtained was triturated in ether and filtered. After drying under HV, the trihydrochloride salt was collected as a white solid (0.260 g).

^{1}H NMR (d_6-DMSO) δ: 11.16 (s, 1H); 9.53 (br. s, 1H); 9.18 (br. s, 1H); 8.95 (d, J = 5.1 Hz, 1H); 8.56 (d, J = 9.0 Hz, 1H); 7.92 (m, 2H); 7.53 (d, J = 9.2 Hz, 1H); 7.30 (d, J = 7.9 Hz, 1H); 4.65 (m, 1H); 4.28 (br. s, 2H); 4.11 (s, 3H); 3.82 (m, 1H); 3.64 (overlapped s, 2H); 3.60 (overlapped m, 1H); 3.26 (m, 2H); 2.86-2.66 (m, 2H); 2.09 (m, 1H); 1.96 (m, 4H); 1.34 (m, 1H).

MS (ESI, m/z): 524.7 [$M+H^+$].

Example 5: {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride:

5.i. *(2RS)-3-{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 4.i (0.470 g, 1.3 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.240 g; 1.1 eq.), the title compound (0.450 g, 67% yield) was obtained as a white foam according to the procedure of Example 1, step 1.x.

^{1}H NMR (d_6-DMSO) δ: 8.69 (dd, J = 1.1, 4.4 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.58-7.48 (m, 2H); 7.31-7.22 (m, 2H); 7.18-7.10 (m, 1H); 6.62 (t, J = 16.1 Hz, 1H); 6.52 (m, 1H); 4.73 (br. s, 1H); 4.55-4.44 (m, 2H); 4.17 (m, 1H); 4.05 (s, 3H); 3.69-3.58 (m, 2H); 3.38 (overlapped m, 2H); 3.28 (overlapped m, 2H); 3.12 (m, 1H); 2.77 (m, 1H); 1.99-1.72 (m, 6H); 1.54-1.23 (m, 3H).

MS (ESI, m/z): 514.0 [$M+H^+$].

5.ii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(2R,3R,6R)-2-((2RS)-2,3-dihydroxy-propyl)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 5.i (0.73 g, 1.42 mmol), the title compound (0.65 g, 74% yield) was obtained as a white foam using the procedure of Example 4, step 4.iii. The compound was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 then 9-1). This was obtained as a 2-1 mixture of epimers.

^{1}H NMR ($CDCl_3$) main signals δ: 8.66 (d, J = 3.7 Hz, 1H); 8.30 (dd, J = 6.3, 9.0 Hz, 1H); 7.42 (m, 1H); 7.14 (overlapped d, J = 9.1 Hz, 1H); 7.09 (overlapped m, 1H); 7.01-6.93 (m, 1H); 6.90-6.84 (m, 1H); 6.52 (d, J = 16.0 Hz, 1H); 6.24 (m, 1H); 4.35-4.20 (m, 3H); 4.06 (s, 3H); 3.96-3.89 (m, 1H); 3.83 (dd, J = 5.2, 16.9 Hz, 1H); 3.66 (m, 2H); 3.50 (m, 1H); 3.26-3.14 (m, 3H); 2.27-2.20 (br. m, 2H); 2.10-1.84 (m, 6H); 1.47 (overlapped s, 9H); 1.46 (overlapped m, 1H).

MS (ESI, m/z): 614.1 [$M+H^+$].

5.iii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-[(2R,3R,6R)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-2-(2-oxo-ethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

Starting from intermediate 5.ii (0.645 g, 1.05 mmol), the title aldehyde (0.557 g, 91% yield) was obtained as a white foam, using the procedure of Example 2, step 2.v. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 97-3 to 19-1).

^{1}H NMR ($CDCl_3$) δ: 9.75 (m, 1H); 8.65 (d, J = 4.6 Hz, 1H); 8.29 (d, J = 9.1 Hz, 1H); 7.43 (d, J = 4.6 Hz, 1H); 7.14 (overlapped d, J = 9.1 Hz, 1H); 7.08 (overlapped m, 1H); 7.02-6.95 (m, 1H); 6.92-6.85 (m, 1H); 6.52 (d, J = 16.1 Hz, 1H); 6.22 (td, J = 5.2, 15.8 Hz, 1H); 4.79 (m, 1H); 4.24 (m, 1H); 4.08 (s, 3H); 3.76 (dd, J= 4.5, 16.8Hz, 1H); 3.66-3.58 (m, 1H); 3.31-3.21 (m, 1H); 3.14-3.04 (m, 1H); 2.89-2.80 (m, 1H); 2.54 (dd, J = 4.7, 15.3 Hz, 1H); 1.93-1.89 (m, 4H); 1.86-1.79 (m, 1H); 1.48 (overlapped s, 9H); 1.47 (overlapped m, 2H).

MS (ESI, m/z): 582.0 [$M+H^+$]

5.iv. *{(2R,3R,6R)-3-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 5.iii (0.557 g, 0.96 mmol), the title acid (0.58 g, 99% yield) was obtained as a colourless foam using the procedure of Example 2, step 2.vi. The compound was purified by trituration in ether.

^{1}H NMR ($CDCl_3$) δ: 8.52 (d, J = 4.6 Hz, 1H); 8.36 (d, J = 9.1 Hz, 1H); 7.27 (overlapped m, 1H); 7.12-6.86 (m, 4H); 6.53 (d, J = 15.8 Hz, 1H); 6.27 (m, 1H); 4.60 (m, 1H); 4.30-4.07 (m, 2H); 3.99 (s, 3H); 3.85-3.70 (m, 2H); 3.02 (m, 2H); 2.79 (m, 1H); 2.49 (dd, J = 3.7 , 14.2 Hz, 1H); 1.94-1.90 (m, 3H); 1.84-1.77 (m, 3H); 1.52-1.40 (overlapped m, 3H); 1.27 (s, 9H).

MS (ESI, m/z): 598.1 [M+H$^+$].

5.v. *{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride*:

Starting from intermediate 5.iv (0.100 g, 0.167 mml), the title compound (0.074 g, 78% yield) was obtained as a white solid, using the procedure of Example 4, step 4.vi.

^{1}H NMR (D_2O) δ: 8.80 (d, J = 9.2 Hz, 1H); 8.36 (d, J = 9.2 Hz, 1H); 8.03 (d, J = 6.0 Hz, 1H); 7.51 (d, J = 9.3 Hz, 1H); 7.31 (m, 1H); 7.15 (m, 2H); 6.97 (d, J = 16.3 Hz, 1H); 6.35 (m, 1H); 4.79 (overlapped s, 1H); 4.61 (m, 1H); 4.14 (s, 3H); 4.06-3.84 (m, 3H); 3.58 (m, 1H); 3.45 (m, 2H); 2.90-2.79 (m, 1H); 2.59 (dd, J = 3.6, 15.0 Hz, 1H); 2.25-2.00 (m, 3H); 1.96-1.79 (m, 3H); 1.54-1.40 (m, 1H).

MS (ESI, m/z): 498.0 [M+H$^+$].

Example 6: {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride:

6.i. *[(2R,3R,6S)-6-[(1R,2R)-1,2-dihydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a suspension of intermediate 1.vi (1.274 g, 2.55 mmol) and methane sulfonamide (0.291 g, 3.06 mmol) in 2-methyl-2-propanol (13 ml), water (13 ml) and EA (4 ml) was added AD-mix β (4.5 g). The reaction mixture was stirred at rt for 24 h. Sodium metabisulfite (10 g) and EA (50 ml) were added. The two layers were decanted and the aq. layer was extracted twice with EA. The combined org. layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (DCM-MeOH 9-1) to afford the desired diol as a white foam (1.2 g). The compound was obtained as a 2-1 mixture of epimers.
MS (ESI, m/z): 534.0 [M+H$^+$].

6.ii. *{(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[(4R,5R)-5-(6-methoxy-[1,5]naphthyridin-4-yl)-2-oxo-[1,3]dioxolan-4-yl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To an ice-chilled solution of intermediate 6.i (1.22 g, 2.30 mmol) in DCM (12 ml) were added pyridine (1.12 ml, 13.80 mmol) and triphosgene (0.341 g, 1.15 mmol). The reaction was stirred 30 min at 0°C and then 1 h at rt. The reaction mixture was diluted with saturated $NaHCO_3$ and the two layers were decanted. The org. layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was chromatographed over SiO_2 (DCM-MeOH 19-1) to afford the title cyclic carbonate (1.18 g, 92% yield) as a a white foam. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 560.0 [$M+H^+$].

6.iii. *{(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 6.ii (1.178 g, 2.11 mmol) in EA (80 ml) was added 20% $Pd(OH)_2$ on carbon (moisturized, 0.443 g) and the suspension was stirred under hydrogen atmosphere for 2 h. The catalyst was filtered off and the filtrate concentrated to dryness. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 9-1) to afford the title compound (0.973 g, 89% yield) as a white foam.

MS (ESI, m/z): 518.0 [$M+H^+$].

6.iv. *(2RS)-3-{(2R,3R,6S)-3-amino-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 6.iii (0.97 g, 1.87 mmol), and using the procedure of Example 2, step 2.iii, the title amine (0.57 g, 80% yield) was obtained as a brown foam. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d*6*-DMSO) main signals δ: 8.69 (d, J = 4.4 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.59 (d, J = 4.5 Hz, 1H); 7.27 (d, J = 9.0 Hz, 1H); 4.57-4.42 (m, 2H); 4.06 (overlapped s, 3H); 4.05-3.89 (overlapped m, 2H); 3.68 (m, 1H); 3.59-3.45 (m, 2H); 3.28 (m, 3H); 2.93-2.82 (m, 2H); 1.87-1.69 (m, 1H); 1.62-1.57 (m, 3H); 1.54-1.27 (m, 4H).

MS (ESI, m/z): 378.2 [$M+H^+$].

6.v. *(2RS)-3-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 6.iv (0.570g, 1.51mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.279 g, 1.1 eq), the title compound (0.420g. 52% yield) was obtained as a white solid according to the procedure described in Example 1, step 1.x.

^{1}H NMR (d_6-DMSO) main signals δ: 8.69 (d, J = 4.4 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.59 (d, J = 4.5 Hz, 1H); 7.52 (m, 2H); 7.32-7.23 (m, 2H); 7.22-7.10 (m, 1H); 6.62 (overlapped t, J = 16.3 Hz, 1H); 6.53 (overlapped m, 1H); 4.58 (m, 1H); 4.48 (d, J = 6.5 Hz, 1H); 4.26-4.09 (m, 1H); 4.04 (s, 3H); 3.91 (m, 1H); 3.72 (m, 1H); 3.53 (m, 2H); 3.40-3.29 (m, 4H); 2.92 (m, 1H); 2.76 (m, 1H); 1.96 (m, 1H); 1.82-1.68 (m, 4H); 1.62-1.37 (m, 3H).

Rf = 0.38 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 529.8.

6.vi. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(2R,3R,6S)-2-((2RS)-2,3-dihydroxy-propyl)-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 6.v (0.363 g, 0.69 mmol), and using the procedure of Example 4, step 4.iii, the title *N*-protected amine (0.279 g, 64% yield) was obtained as a white foam. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 629.9 [$M+H^+$].

6.vii. *{(2R,3R,6S)-3-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 6.vi (0.275 g, 0.43 mmol), the title acid (0.257 g, 99% yield) was obtained as a colourless foam using the procedure described in Example 2, steps 2.v and vi.

MS (ESI, m/z): 614.0 [M^+].

6.viii. *{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride*:

Starting from intermediate 6.vii (0.252 g, 0.41 mmol), the title acid (0.24 g, 99% yield) was obtained as a yellowish solid, using the procedure described in Example 4, step 4.vi. The compound was triturated in ether.

^{1}H NMR (d_6-DMSO) δ: 8.69 (d, J = 4.4 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.59 (d, J = 4.5 Hz, 1H); 7.52 (m, 2H); 7.32-7.23 (m, 2H); 7.22-7.10 (m, 1H); 6.62 (overlapped t, J = 16.3 Hz, 1H); 6.53 (overlapped m, 1H); 4.58 (m, 1H); 4.48 (d, J = 6.5 Hz, 1H); 4.26-4.09 (m, 1H); 4.04 (s, 3H); 3.91 (m, 1H); 3.72 (m, 1H); 3.53 (m, 2H); 3.40-3.29 (m, 4H); 2.92 (m, 1H); 2.76 (m, 1H); 1.96 (m, 1H); 1.82-1.68 (m, 4H); 1.62-1.37 (m, 3H).

MS (ESI, m/z): 514.0 [$M+H^+$].

Example 7: (1*RS*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol:

7.i. *(2R,3S,6R)-6-allyl-2-(tert-butyl-diphenyl-silanyloxymethyl)-3,6-dihydro-2H-pyran-3-ol*:

To an ice-chilled solution of (2*R*,3*S*,6*R*)-6-allyl-2-hydroxymethyl-3,6-dihydro-2*H*-pyran-3-ol (obtained as described in *Eur. J. Org. Chem.* (2003), 2418-2427; 31.55 g, 185.4 mmol) in DCM (650 ml) was added imidazole (24.96 g, 2 eq.). A solution of *tert*-butylchlorodiphenylsilane (50.45 g, 210.7 mmol) in DCM (130 ml) was added dropwise over 90 min. After 2 h, aq. sat. $NaHCO_3$ (250 ml) was added. The two layers were separated and the org. layer was washed twice with brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 5-1) to afford the title compound as a yellow oil (51.52 g, 68% yield).

^{1}H NMR ($CDCl_3$) δ: 7.74-7.68 (m, 4H); 7.47-7.38 (6H); 5.87-5.76 (m, 3H); 5.10-5.04 (m, 2H); 4.19-4.15 (m, 2H); 3.89 (dd, J = 5.3, 10.0 Hz, 1H); 3.79 (dd, J = 7.3, 10.0 Hz, 1H); 3.68 (m, 1H); 2.70 (br s, 1H); 2.38 (m, 1H); 2.28 (m, 1H); 1.09 (s, 9H).

7.ii. *(2RS)-3-[(2R,5S,6R)-6-(tert-butyl-diphenyl-silanyloxymethyl)-5-hydroxy-5,6-dihydro-2H-pyran-2-yl]-propane-1,2-diol*:

To a solution of intermediate 7.i (51.52 g, 126.1 mmol) in 2-methyl-2-propanol (560 ml), EA (15 ml) and water (560 ml), were added potassium ferricyanide (189.48 g, 3 eq.), K_2CO_3

(67.10 g, 3 eq.), $(DHQD)_2PHAL$ (1.5121 g, 0.015 eq.) and potassium osmate dihydrate (0.1907 g, 0.004 eq.). The reaction mixture was stirred two days and sodium bisulfite (150.92 g) was added. The two layers were decanted and the aq. layer was extracted twice with EA (2 x 350 ml). The combined org. layers were washed with brine (500 ml), dried over $MgSO_4$, filtered and concentrated to dryness. The residue was filtered over SiO_2 (Hex-EA 1-1, then EA) to afford the title product as a yellow oil (36.33 g, 65% yield). The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d_6-DMSO) δ: 7.71-7.65 (m, 4H); 7.47-7.40 (m, 6H); 5.80-5.65 (m, 2H); 4.95 (m, 1H); 4.50-4.35 (m, 3H); 3.92- 3.28 (m, 7H); 1.80-1.65 (m, 1.33H); 1.17 (m, 0.67H); 0.99 (s, 9H).

7.iii. *(2R,3S,6R)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3,6-dihydro-2H-pyran-3-ol*:

To a solution of intermediate 7.ii (34.83 g, 78.7 mmol) in DCM (575 ml) were added at rt PTSA (0.90 g, 4.7 mmol) and 2,2-dimethoxypropane (24 ml, 195.2 mmol). After 2h., water (100 mL) and saturated $NaHCO_3$ (200 ml) were added and the two phases were separated. The aq. layer was extracted with DCM (260 ml). The combined org. layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 1-1) to afford the title compound as a yellow oil (36.19 g, 74.9 mmol). The compound was obtained as a 2-1 mixture of epimers.

^1H NMR ($CDCl_3$) δ: 7.72-7.67 (m, 4H); 7.50-7.39 (m, 6H); 5.85-5.77 (m, 2H); 4.23-3.41 (m, 8H); 2.80 (br s, 1H); 2.06 (m, 0.33H); 1.80-1.65 (1.67H); 1.40 (s, 3H); 1.33 (s, 3H); 1.09 (s, 9H).

7.iv. *(2R,3S,6R)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydro-pyran-3-ol*:

To a solution of intermediate 7.iii (36.16 g, 74.9 mmol) in EA (600 ml) was added platinum oxide hydrate (1.1 g, 4.8 mmol). The reaction mixture was stirred under hydrogen for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness to yield the title alcohol (36.18 g, 99% yield) as a thick oil. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 485.2 $[M+H^+]$.

7.v. *(2R,6S)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-dihydro-pyran-3-one*:

To a solution of intermediate 7.iv (12 g, 24.75 mmol) in DCM (100 ml) was added a solution of Dess-Martin periodinane (15 wt% in DCM, 50 ml). The mixture was stirred at rt for 4 h. The reaction mixture was diluted with DCM (30 ml) and washed with sat. $NaHCO_3$ (30 ml). The org. layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed (Hex-EA 3-1) to afford the title compound (10.9 g, 91% yield) as a colourless oil. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR ($CDCl_3$) δ: 7.72-7.61 (m, 4H); 7.46-7.38 (m, 6H); 4.55 (m, 1H); 4.32 (m, 1H); 4.13-3.90 (m, 7H); 3.59 (m, 1H); 2.65-2.59 (m, 2H); 2.2-2.05 (m, 1.33H); 1.91-1.71 (m, 2.66H); 1.42 (s, 3H); 1.38 (s, 2H); 1.36 (s, 1H); 1.05 (s, 9H).

7.vi. *(2S,3RS,6S)-benzyl-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydro-pyran-3-yl]-amine*:

To a solution of intermediate 7.v (10.9 g, 22.58 mmol) in 1,2-DCE (60 ml) were added benzylamine (2.5 ml, 1 eq.) and sodium triacetoxyborohydride (6.7 g, 1.4 eq.). The mixture was stirred overnight at rt. Saturated $NaHCO_3$ (200 ml) was added. The two layers were decanted and the org. layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 3-1) to afford the title compound (9.7 g, 74% yield) as a yellowish oil. The compound was obtained as a mixture of four isomers.

MS (ESI, m/z): 574.8 [$M+H^+$].

7.vii. *(2S,3RS,6S)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydro-pyran-3-ylamine*:

To a solution of intermediate 7.vi (9.7 g, 16.9 mmol) in EtOH (190 ml) was added AcOH (1.1 ml) and 10% Pd/C (4 g). The reaction mixture was then stirred under hydrogen atmosphere for 8 h. The reaction mixture was filtered and the catalyst was washed with EtOH and water. After concentration, the residue was diluted with sat. $NaHCO_3$ (100 ml) and then extracted with EA (2 x 250 mL). The combined org. extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (DCM-MeOH 97-3 containing 1% aq. NH_4OH) to afford the title amine (5.5 g, 67% yield) as a colourless oil.

MS (ESI, m/z): 484.1 [$M+H^+$].

7.viii. *(2S,3R,6S)-[2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 7.vii (5.5 g, 11.37 mmol) in DCM (65 ml) were added Boc_2O (3.0 g, 1.2 eq.) and TEA (3.2 mL, 2.0 eq.). The reaction mixture was stirred overnight at rt. After concentration to dryness, the residue was chromatographed over SiO_2 (Hex-Toluene-DCM-EA 13-3-1-3) to afford first the (2*S*,3*S*,6*S*)-isomer (1.98 g, 29% yield) as a 2-1 mixture of epimers, and then the desired isomer (4.0 g, 60% yield) as a 2-1 mixture of epimers.
^{1}H NMR ($CDCl_3$) δ: 7.71-7.67 (m, 4H); 7.48-7.38 (m, 6H); 5.39 (d, J = 7.5 Hz, 1H); 4.18-3.43 (m, 8H); 2.12 (m, 0.33H); 1.89-1.49 (m, 5.67H); 1.43 (s, 9H); 1.37 (s, 3H); 1.31 (s, 1H); 1.28 (s, 2H); 1.07 (s, 9H).

7.ix. *[(2S,3R,6S)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-((2RS)-2,3-dihydroxy-propyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

A solution of intermediate 7.viii (4.0 g, 6.85 mmol) in AcOH (30 ml), water (10 ml) and THF (10 ml) was heated at 50°C for 3 h. The reaction mixture was concentrated to dryness and the residue was partitioned between sat. $NaHCO_3$ (40 ml) and EA (100 ml). The org. layer was dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 1-3) to afford the title diol (3.38 g, 90% yield) as a colourless oil.
MS (ESI, m/z): 544.2 [$M+H^+$].

7.x. *[(2S,3R,6S)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-(2-oxo-ethyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 7.ix (1.5 g, 2.75 mmol) in acetone (30 ml) was added at rt a solution of $NaIO_4$ (1.5 g, 2.5 eq.) in water (10 ml). The reaction was stirred 40 min, the solids were filtered off and the filtrate was concentrated *in vacuo*. The residue was partitioned between water (50 ml) and EA (100 ml). The aq. layer was extracted once with EA (100 ml) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 2-1) to afford the title aldehyde (1.3 g) as a colourless foam.
^{1}H NMR ($CDCl_3$) δ: 9.74 (t, J = 1.9 Hz, 1H); 7.69-7.66 (m, 4H); 7.49-7.39 (m, 6H); 5.45 (d, J = 6.75 Hz, 1H); 4.26 (m, 1H); 3.96-3.61 (m, 4H); 2.68 (m, 1H); 2.44 (ddd, J = 1.8, 5.4, 16.3 Hz, 1H); 1.92-1.78 (m, 3H); 1.44 (s, 9H); 1.43 (m, 1H); 1.07 (s, 9H).

7.xi. *{(2S,3R,6S)-2-(tert-butyl-diphenyl-silanyloxymethyl)-6-[(2RS)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of DIPA (0.9 ml, 2.5 eq.) in THF (17 ml) was added at -78°C, *n*-BuLi (2.5*N* in hexanes, 2.5 ml). The mixture was stirred 5 min at this temperature before warming to 0°C. After 15 min, the solution was cooled to -78°C and a solution of 3-fluoro-6-methoxy-quinoline (prepared as described in WO 2005/049575; 1.12 g, 2.5 eq.) in THF (5 ml) was added. The reaction proceeded for 4 h. A solution of intermediate 7.x (1.3 g, 2.54 mmol) in THF (5 ml) was added dropwise and the reaction proceeded for 10 min before quick warming to rt. The reaction was further stirred for 20 min and was quenched with 10% aq. $NaHSO_4$ (30 ml). The org. layer was diluted with EA (100 ml). The two layers were decanted and the aq. layer was extracted twice with EA. The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 2- then 1-1) to afford the title compound (0.98 g, 56% yield) as a colourless foam. The compound was obtained as a 1-1 mixture of epimers.
MS (ESI, m/z): 689.0 [$M+H^+$].

7.xii. *{(2S,3R,6S)-6-[(2RS)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 7.xi (0.98 g, 1.42 mmol) in THF (5 ml) was added TBAF (1*M* in THF, 2.2 ml). The reaction proceeded at rt for 1 h. After concentration to dryness, the residue was chromatographed on SiO_2 (EA-Hex 3-1) to afford the title compound (0.57 g, 89% yield) as a colourless foam. The compound was obtained as a 1-1 mixture of isomers.
MS (ESI, m/z): 451.0 [$M+H^+$].

7.xiii. *(1RS)-2-((2S,5R,6S)-5-amino-6-hydroxymethyl-tetrahydro-pyran-2-yl)-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol*:

To a solution of intermediate 7.xii (0.57 g, 1.26 mmol) in dioxane (3 ml) was added HCl in dioxane (5*N*, 3 ml). The mixture was stirred at rt for 3 h. The solvent was removed *in vacuo* and the residue was dissolved in water (5 ml). The pH was adjusted to 7 adding K_2CO_3. Water was evaporated and the residue chromatographed on SiO_2 (DCM-MeOH 6-1 1% aq. NH_4OH) to afford the title amine (0.4 g, 90% yield) as a colourless foam. The compound was obtained as a 1-1 mixture of isomers.
MS (ESI, m/z): 351.0 [$M+H^+$].

7.xiv. *(1RS)-2-{(2S,5R,6S)-5-[trans-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol*:

Starting from intermediate 7.xiii (0.1 g, 0.285 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.053 g, 1.1 eq), the title compound (0.135 g, 94% yield) was obtained as a colourless foam using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 (DCM-MeOH 93-7 containing 1% aq. NH_4OH). The compound was obtained as a 1-1 mixture of isomers.

MS (ESI, m/z): 503.2 [$M+H^+$].

Example 8: 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide dihydrochloride:

8.i. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(2R,3R,6R)-2-hydroxycarbamoylmethyl-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester* and *{(2R,3R,6R)-2-carbamoylmethyl-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-[(E)-3-(2,5-difluoro-phenyl)-allyl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 5.v (0.11 g, 0.19 mmol) in DMF (2.3 ml) were added DIPEA (0.16 ml, 0.93 mmol) and HATU (0.11 g, 0.28 mmol). The resulting solution was stirred at rt for 30 min. Hydroxylamine hydrochloride (0.019 g, 0.28 mmol) was added. After stirring at rt overnight, hydroxylamine hydrochloride (0.019 g, 0.28 mmol) was added and the reaction was further stirred at rt for 24 h. The reaction mixture was concentrated to dryness. The residue was partitioned between water and DCM-MeOH 9-1 and the phases were separated. The aq. layer was extracted five times with DCM-MeOH. The combined org. layers were 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 9-1 containing 1% aq. NH_4OH) to afford the title amide as a yellow oil (0.032 g, 29% yield) and then the title hydroxamic acid (0.045 g, 40% yield).

Amide : MS (ESI, m/z): 597.0 [$M+H^+$].

Hydroxamic acid: MS (ESI, m/z): 613.0 [$M+H^+$].

8.ii. *2-{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide dihydrochloride*:

Starting from {(2*R*,3*R*,6*R*)-2-carbamoylmethyl-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-[(*E*)-3-(2,5-difluoro-phenyl)-allyl]-carbamic acid *tert*-butyl ester (0.030 g, 0.049 mmol), the title compound (0.017 g, 60% yield) was obtained as a yellow solid using the procedure of Example 4, step 4.vi. The compound was purified by trituration in ether.

MS (ESI, m/z): 497.0 [$M+H^+$].

Example 9: 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide:

9.i. *{(2R, 3R, 6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[2-(3-methoxy-quinoxalin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

The Julia coupling was performed as in Example 1, step 1.vi, starting from intermediate 1.v (9.67 g, 18 mmol) and 3-methoxy-quinoxaline-5-carbaldehyde (see Preparation D; 3.38 g), affording the title compound as a yellowish foam (3.72 g, 41% yield). The compound was purified by column chromatography over SiO_2 (EA-Hex 1-1). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 500.1 [$M+H^+$].

9.ii. *{(2R,3R,6S)-2-((2RS)-2,3-dihydroxy-propyl)-6-[(E)-2-(3-methoxy-quinoxalin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

A solution of intermediate 9.i (3.72 g) in AcOH (60 ml), water (20 ml) and THF (20 ml) was heated at 60°C for 5 h. The reaction mixture was concentrated to dryness and the residue partitioned between EA (200 ml) and saturated $NaHCO_3$ (200 ml). The pH of the aq. layer was adjusted to 8 by adding 1*M* aq. NaOH. The precipitate was then extracted twice with EA (2 x 150 ml). The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed over SiO_2 (EA-Hept 4-1) to afford the title compound (2.45 g) as a colourless foam. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 460.1.1 [$M+H^+$].

9.iii. *{(2R,3R,6S)-3-tert-butoxycarbonylamino-6-[(E)-2-(3-methoxy-quinoxalin-5-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 9.ii (2.45 g, 5.3 mmol), the title acid (0.65 g, 1.46 mmol) was obtained as a colourless foam using the procedure of Example 2, steps 2.v and 2.vi. The compound was purified by chromatography over SiO_2 using EA-Hex 1-2 as an eluent.
MS (ESI, m/z): 443.8 [$M+H^+$].

9.iv. *{(2R,3R,6S)-2-carbamoylmethyl-6-[(E)-2-(3-methoxy-quinoxalin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 9.iii (0.65 g, 1.46 mmol) in THF (10 ml) were added at 0°C, TEA (0.265 ml) and *i*-butylchloroformate (0.24 g). The reaction was stirred 1 h at this temperature then aq. NH_4OH (3 ml) was added. The reaction was vigorously stirred for 30 min. EA (50 ml) was added. The two layers were decanted and the aq. layer was extracted once with EA (50 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was triturated (Hex) to afford the title amide (0.47 g) as a light beige solid of 75% purity.
MS (ESI, m/z): 442.8 [$M+H^+$].

9.v. *{2R,3R,6S)-2-carbamoylmethyl-6-[(1R,2R)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

The asymmetric dihydroxylation of intermediate 9.iv (0.47 g, 1.05 mmol) was performed using the procedure of Example 6, step 6.i to give the title diol (0.19 g, 38% yield) as a colourless foam. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 as an eluent.
^1H NMR (d_6-DMSO) δ: 8.60 (s, 1H); 7.91-7.87 (m, 2H); 7.63 (dd, J = 7.3, 8.2 Hz, 1H); 7.39 (br s, 1H); 6.89 (br s, 1H); 6.82 (d, J = 8.8 Hz, 1H); 5.62 (d, J = 7.2 Hz, 1H); 5.11 (d, J = 7.2 Hz, 1H); 4.35 (d, J = 3.7 Hz, 1H); 4.06 (m, 1H); 4.03 (overlapped s, 3H); 4.02-3.92 (m, 2H); 3.57 (m, 1H); 2.39 (dd, J = 10.4, 15.9 Hz, 1H); 2.10-2.04 (m, 2H); 1.85 (m, 1H); 1.68-1.57 (m, 2H); 1.40 (s, 9H).
MS (ESI, m/z): 477.0 [$M+H^+$].

9.vi. *2-{2R,3R,6S)-3-amino-6-[(1R,2R)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]tetrahydro-pyran-2-yl}-acetamide*:

The title amine (0.071 g, 47% yield) was obtained as a colourless foam starting from intermediate 9.v (0.19 g, 0.4 mmol) and using the procedure of Example 1, step 1.ix.

MS (ESI, m/z): 377.2 [$M+H^+$].

9.vii. *2-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1R,2R)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide*:

Starting from intermediate 9.vi (0.071 g, 0.285 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.031 g, 1.1 eq), the title compound (0.020 g, 20% yield and 75% purity) was obtained as as a colorless foam according to the procedure described in Example 1, step 1.x. The compound was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 528.7 [$M+H^+$].

Example 10: {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride:

10.i. *{(2R,3R,6R)-3-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 1.v (5.68 g, 10.57 mmol) and 6-methoxy-quinoline-4-carbaldehyde (1.8 g, 9.6 mmol), the title compound (1.48 g, 2.41 mmol) was obtained as a colourless foam using successively the procedures of Example 1, step 1.vi (Julia coupling, 46% yield), Example 2, steps 2.ii (hydrogenation, 96% yield) and 2.iii (acetonide and Boc deprotection, 99% yield), Example 1, step 1.x (reductive amination, 78% yield), Example 4, step 4.iii (Boc formation, 68% yield), and Example 2, steps 2.v (periodic cleavage, 95% yield) and 2.vi (acid formation, 99% yield).

MS (ESI, m/z): 581.1 [$M+H^+$].

10.ii. *{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid dihydrochloride*:

Starting from intermediate 10.i (0.283 g, 0.475 mmol), the title acid (0.267 g, 96% yield) was obtained as a beige solid using the procedure of Example 4, step 4.vi. The compound was purified by trituration in ether.

MS (ESI, m/z): 497.0 [M+H$^+$].

Example 11: 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide dihydrochloride:

11.i. *{(2R,3R,6R)-2-carbamoylmethyl-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-[(E)-3-(2,5-difluoro-phenyl)-allyl]-carbamic acid tert-butyl ester*:

Starting from intermediate 10.i (1.15 g, 1.93 mmol), the title acetamide (0.506 g, 44% yield) was obtained as an off-white foam using the procedure of Example 9, step 9.iv. The compound was purified by chromatography over SiO_2, using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.

MS (ESI, m/z): 596.0 [M+H$^+$].

11.ii. *2-{(2R,3R,6R)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide*:

Starting from intermediate 11.i (0.045 g, 0.076 mmol), the title compound (0.034 g, 80% yield) was obtained as a yellowish solid, using the procedure of Example 4, step 4.vi. The compound was purified by trituration in ether.

MS (ESI, m/z): 496.0 [M+H$^+$].

Example 12: 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide:

12.i. *{(2R,3R,6S)-2-carbamoylmethyl-6-[(S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-[(E)-3-(2,5-difluoro-phenyl)-allyl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 6.vii (0.724 g) in THF (8 ml) were added at 0°C, TEA (0.427 ml) and *i*-butylchloroformate (0.367 ml). The reaction was stirred 1 h at this

temperature then aq. ammonia (2.5 ml) was added. The reaction was vigorously stirred for 45 min. EA (20 ml) was added. The two layers were decanted and the aq. layer was extracted once with EA (10 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH then 9-1 containing 1% aq. NH_4OH) to give the title amide as an off-white foam (0.485 g).

MS (ESI, m/z): 613.0 [$M+H^+$].

12.ii. *2-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(S)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide*:

5*N* HCl in dioxane (0.346 ml) was added to a solution of intermediate 12.i (0.1 g) in dioxane (0.311 ml). After evaporation to dryness, the residue was finally purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH, then 9-1 containing 1% aq. NH_4OH) to afford the title compound as a off-white foam (0.032 g).

Rf = 0.33 in DCM-MeOH 9-1 containing 1% aq. NH_4OH.

MS (ESI, m/z): 513.0 [$M+H^+$].

Example 13: 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*RS*)2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide:

Starting from intermediate 7.xiii (0.100 g, 0.29 mmol) and *(E)*-3-(2,5-difluoro-phenyl)-acrylic acid (0.058 g, 0.31 mmol), and using the procedure of Example 2, step 2.iv, the title amide (0.123 g, 83% yield) was obtained as a yellow foam. The compound was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH) and obtained as a 1-1 mixture of epimers.

Rf = 0.41 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

MS (ESI, m/z): 517.2 [$M+H^+$].

Example 14: 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*RS*)2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide:

Starting from intermediate 7.xiii (0.100 g, 0.29 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (0.06 g, 1 eq.) and using the procedure of

Example 2, step 2.iv, the title amide (0.072 g, 46% yield) was obtained as a beige solid. The compound was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH) and obtained as a 1-1 mixture of epimers.

Rf = 0.41 (DCM-MeOH 9-1 containing 1% aq. NH_4OH).

^1H NMR (d_6-DMSO) δ: 11.24 (s, 0.5H); 11.16 (s, 0.5H); 8.69 (d, J = 1.8 Hz, 0.5H); 8.68 (d, J = 1.8 Hz, 0.5H); 8.32 (d, J = 8.9 Hz, 0.5H); 8.27 (d, J = 8.9 Hz, 0.5H); 7.98-7.90 (m, 3H); 7.62 (d, J = 4.4 Hz, 0.5H); 7.59 (d, J = 4.4 Hz, 0.5H); 7.40 (d, J = 2.2 Hz, 0.5H); 7.37 (d, J = 2.2 Hz, 0.5H); 5.79 (m, 1H); 5.62-5.50 (two overlapped m, 2 x 0.5H); 4.66 (t, J = 5.0 Hz, 0.5H); 4.61 (t, J = 5.5 Hz, 0.5H); 4.27 (m, 0.5H); 4.12-4.02 (m, 1H); 3.91 (s, 3H); 3.91 (overlapped m, 0.5H); 3.80 (m, 0.5H); 3.70-3.60 (m, 2.5H); 3.45-3.34 (m, 2H); 2.61 (m, 0.5H); 2.27 (m, 0.5H); 2.11 (m, 1H); 2.15-2.06 (m, 0.5H); 1.99-1.64 (m, 2.5H); 1.45-1.33 (m, 1H).

MS (ESI, m/z): 542.8 [M^+].

Example 15: 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2RS*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide:

15.i. *2-(tert-butyl-diphenyl-silanyloxymethyl)-6-[(2RS)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of 5-bromo-3-methoxyquinoline (3.12 g) in THF (70 ml), cooled to -78°C, was added *n*-BuLi (2.5*N*, 5.2 ml). The mixture was stirred at the same temperature for 15 min and a solution of intermediate 7.x (1.6 g, 3.12 mmol) in THF (5 ml) was quickly added. The reaction proceeded for 5 min before warming to rt. After 15 min, 10% aq. $NaHSO_4$ (100 ml) was added. The two layers were decanted and the aq. layer was extracted with EA (100 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed on SiO_2 (Hept-EA 3-1 then 1-1) to afford the title compound (0.46 g) as a colourless foam. The compound was obtained as a 2-1 mixture of isomers.

MS (ESI, m/z): 671.0 [$M+H^+$].

15.ii. *{(2S,3R,6S)-6-[(2RS)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

This alcohol (0.26 g, 86% yield) was obtained as a colourless foam, starting from intermediate 15.i (0.46 g, 0.68 mmol) and using the procedure of Example 7, step 7.xii. The compound was purified by chromatography over SiO_2 using EA as eluent. The compound was obtained as a 2-1 mixture of isomers.

MS (ESI, m/z): 432.9 [M^+].

15.iii. *(2RS)-2-[(2S,5R,6S)-5-amino-6-hydroxymethyl-tetrahydro-pyran-2-yl]-1-(3-methoxy-quinolin-5-yl)-ethanol*:

This amine (0.15 g, 84% yield) was obtained as a colourless foam, starting from intermediate 15.ii (0.23 g, 0.53 mmol) and using the procedure of Example 1, step 1.ix.

MS (ESI, m/z): 333.1 [$M+H^+$].

15.iv. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid {(2S,3R,6S)-6-[(2RS)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide*:

Starting from intermediate 15.iii (0.05 g, 0.15 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (0.032 g, 1 eq.) and using the procedure of Example 2, step 2.iv, the title amide (0.030 g, 38% yield) was obtained as an off-white solid. The compound was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH) and obtained as a 2-1 mixture of epimers.

^1H NMR (d_6-DMSO) δ: 11.24 (s, 0.34H); 11.18 (s, 0.66H); 8.66 (m, 1H); 8.34 (d, J = 9.0 Hz, 0.34H); 8.26 (d, J = 9.0 Hz, 0.66H); 7.99-7.94 (m, 1.66H); 7.74-7.69 (m, 1.34H); 7.71 (m, 1H); 7.63-7.55 (m, 2H); 5.48-5.35 (m, 2H); 4.75 (t, J = 5.5 Hz, 0.34H); 4.67 (t, J = 5.1 Hz, 0.66H); 4.33 (m, 0.34H); 4.09 (m, 0.66H); 3.97 (s, 3 x 0.34H); 3.95 (s, 3 x 0.66H); 3.96 (overlapped m, 1H); 3.80 (m, 0.66H); 3.66-3.60 (m, 2H); 3.52 (m, 0.34H); 3.41 (t, J = 5.6Hz, 1H); 2.43-2.27 (two overlapped m, 1H); 2.03-1.83 (m, 3H); 1.69-1.59 (m, 2H); 1.51-1.41 (m, 1H).

MS (ESI, m/z): 525.6 [$M+H^+$].

Example 16: 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2RS*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide:

Starting from intermediate 15.iii (0.1 g, 0.3 mmol) and *(E)*-3-(2,5-difluoro-phenyl)-acrylic acid (0.055 g, 1 eq.) and using the procedure of Example 2, step 2.iv, the title amide (0.095 g, 63% yield) was obtained as a colourless oil. The compound was purified by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH) and obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 498.9 [$M+H^+$].

Example 17: 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide:

17.i. *{(2R,3R,6S)-2-((4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-[(E)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from 3-fluoro-6-methoxy-[1,5]naphthyridine-4-carbaldehyde (see Preparation E; 3.17 g, 15.37 mmol) and intermediate 1.v (8.98 g, 16.71 mmol), the title alkene (4.02 g, 50% yield) was obtained as a pale yellow foam using the procedure of Example 1, step 1.vi. The compound was purified by chromatography over SiO_2 using Hept-EA 1-2 as an eluent. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 500.4 [$M+H^+$].

17.ii. *{2-carbamoylmethyl-6-[2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 17.i (3.85 g, 7.44 mmol), this amide (0.759 g, 1.65 mmol) was obtained as an off-white solid, using the procedures of Example 9, steps 9.ii (deprotection, 80% yield), 9.iii (aldehyde formation then oxidation, respectively 93% and 62% yield) and 9.iv (amide formation, 51% yield).

^1H NMR (d_6-DMSO) δ: 8.81 (d, J = 3.8 Hz, 1H); 8.29 (d, J = 9.0 Hz, 1H); 7.35 (br s, 1H); 7.28-7.20 (m, 3H); 6.88 (br d, J = 8.4 Hz, 1H); 6.82 (br s, 1H); 4.52 (m, 1H); 4.33 (m, 1H);

4.05 (s, 3H); 3.66 (m, 1H); 2.58 (dd, J = 10.3, 14.8 Hz, 1H); 2.13-1.98 (m, 2H); 1.72-1.53 (m, 3H); 1.40 (s, 9H).
MS (ESI, m/z): 460.7 [$M+H^+$].

17.iii. *2-{(2R,3R,6S)-3-amino-6-[2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide*:

This amine (0.132 g, 65% yield) was obtained as a beige solid, starting from intermediate 17.ii (0.258 g, 0.56 mmol) and using the procedure of Example 1, step 1.ix.
MS (ESI, m/z): 361.0 [$M+H^+$].

17.iv. *2-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide*:

Starting from intermediate 17.iii (0.126 g, 0.35 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.065 g, 1.1 eq.), the title compound (0.060 g, 33% yield) was obtained as a white solid using the procedure of Example 1, step 1.x.
^{1}H NMR (d_6-DMSO) δ: 8.82 (d, J = 2.1 Hz, 1H); 8.28 (d, J = 9.0 Hz, 1H); 7.49 (m, 1H); 7.35 (br s, 1H); 7.31-7.20 (m, 4H); 7.13 (m, 1H); 6.81 (br s, 1H); 6.62 (d, J = 16.0 Hz, 1H); 6.51 (td, J = 5.3, 16.0 Hz, 1H); 4.51-4.41 (m, 2H); 4.05 (s, 3H); 3.42-3.34 (m, 2H); 2.80 (m, 1H); 2.62 (dd, J = 9.7, 14.4 Hz, 1H); 2.35 (dd, J = 3.8, 14.4 Hz, 1H); 1.95-1.74 (m, 3H); 1.61-1.43 (m, 2H).
MS (ESI, m/z): 512.9 [$M+H^+$].

Example 18: (2*S*,5*R*,6*R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide:

18.i. *(2S,5R,6R)-5-tert-butoxycarbonylamino-6-[(4RS)2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-tetrahydro-pyran-2-carboxylic acid*:

To an ice-chilled solution of intermediate 1.ii (5 g, 14.48 mmol) in DCM (32 ml), MeCN (32 ml) and water (46 ml) was added $NaIO_4$ (14.6 g, 68.17 mmol) and $RuCl_3$ (0.030 g, 0.15 mmol). The reaction mixture was stirred at the same temperature for 5 h. The reaction mixture was diluted with EA (150 ml) and the solids were removed by filtration. MeOH (30 ml) was added and the resulting suspension was filtered. The filtrate was treated with aqueous 10% $NaHSO_3$ (60 ml). The phases were separated and the aq. layer was extracted three times with EA. The combined org. layers were washed with brine, dried over Na_2SO_4,

filtered and evaporated under reduced pressure to give a brown foam (quant.). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 360.1 [$M+H^+$].

18.ii. *{(2S,5R,6R)-6-carbamoyl-2-[(4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 18.i (5.27 g, 14.6 mmol), the title amide (3.16 g, 60% yield) was obtained as a colourless foam using the procedure of Example 12, step 12.i. The compound was purified by chromatography over SiO_2 using EA-cyclohexane 4-1 as an eluent. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 359.1 [$M+H^+$].

18.iii. *{(2S,5R,6R)-2-[(4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a mixture of intermediate 18.ii (2.3 g, 6.42 mmol), *rac*-BINAP (0.288 g, 0.46 mmol), $(dba)_3Pd_2.CHCl_3$ (0.120 g, 0.12 mmol) and cesium carbonate (2.56 g, 7.86 mmol) was added dioxane (82 ml). The mixture was sonicated for 10 min, whereupon trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (prepared as described in WO 03/064431; 2.10 g, 6.81 mmol) was added in one portion. The resulting mixture was heated at 100°C for 4 h. The reaction mixture was filtrated through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified over SiO_2 (DCM-MeOH 19-1) to afford the title amide (3.27 g, 6.32 mmol) as a reddish foam.. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 477.0 [$M+H^+$].

18.iv. *(2S,5R,6S)-5-amino-6-[(2RS)-2,3-dihydroxy-propyl]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

Starting from intermediate 18.iii (2.72 g, 2.06 mmol), the title amine (1.27 g, 64% yield) was obtained as a reddish solid using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 using DCM-MeOH 6-1 containing 1% aq. NH_4OH as an eluent. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d_6-DMSO) δ: 10.59 (s, 0.66H); 10.51 (s, 0.34H); 8.70 (d, J = 5.0 Hz, 1H); 8.45 (d, J = 5.0 Hz, 0.34H); 8.39 (d, J = 5.0Hz, 0.66H); 8.28 (d, J = 9.0 Hz, 1H); 7.33 (d, J = 9.0 Hz, 1H); 4.50 (br s, 1H); 4.47 (dd, J = 4.3, 7.0 Hz, 0.34H); 4.31 (dd, J = 3.5, 9.0 Hz, 0.66H);

4.11 (m, 0.66H); 4.09 (s, 3 x 0.34H); 4.08 (s, 3 x 0.66H); 3.96 (m, 0.34H); 3.63 (m, 1H); 3.37-3.21 (m, 5H), 2.97 (m, 0.66H); 2.91 (m, 0.34H); 2.08 (m, 1H); 1.96 (m, 0.66H); 1.82-1.42 (m, 4.34H).

MS (ESI, m/z): 377.0 [$M+H^+$].

18.v. *(2S,5R,6R)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(2RS)-2,3-dihydroxy-propyl]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

Starting from intermediate 18.iv (0.58 g, 1.55 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.286 g, 1.1 eq.), the title compound (0.393 g, 48% yield) was obtained as a white solid using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d_6-DMSO) δ: 10.64 (s, 0.66H); 10.56 (s, 0.34H); 8.69 (d. J = 5.0 Hz, 1H); 8.42 (d, J = 5.0 Hz, 0.34H); 8.37 (d, J = 5.0 Hz, 0.66H); 8.28 (d, J = 9.0 Hz, 1H); 7.49 (m, 1H); 7.32 (d, J = 9.0 Hz, 1H); 7.27 (m, 1H); 7.12 (m, 1H); 6.63 (d, J = 16.2 Hz, 1H); 6.49 (m, 1H); 4.52-4.42 (m, 3H); 4.26 (m, 1H); 4.06 (s, 3 x 0.34H); 4.04 (s, 3 x 0.66H); 3.65 (m, 1H); 3.44-3.24 (m, 4H); 2.81 (m, 1H); 2.12-1.41 (m, 7H).

MS (ESI, m/z): 529.0 [$M+H^+$].

18.vi. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(2R,3R,6S)-2-[(2RS)-2,3-dihydroxy-propyl]-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from the intermediate 18.v (0.351 g, 0.66 mmol), this diol (0.307 g, 73% yield) was obtained as a colourless foam, using the procedure of Example 4, step 4.iii. The compound was purified by chromatography over SiO_2 using DCM containing 7.5% MeOH, and was recovered as a 2-1 mixture of epimers.

MS (ESI, m/z): 629.0 [$M+H^+$].

18.vii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-[(2R,3R,6S)-2-(2-hydroxy-ethyl)-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 18.vi (0.294 g, 0.47 mmol) in acetone (4 ml) was added a solution of $NaIO_4$ (0.25 g, 1.17 mmol) in water (0.9 ml). The reaction proceeded 1 h. The solids were filtered off and the filtrate concentrated to dryness. The white residual foam was taken up in MeOH (3 ml) and $NaBH_4$ (0.042 g, 1.12 mmol) was added portionwise. The

reaction was stirred for 1 h at rt. Water was added and the volatiles were evaporated under reduced pressure. DCM-MeOH was added and the phases were separated. The aq. layer was extracted twice with DCM-MeOH 9-1 and the combined org. layers were dried over Na_2SO_4 and evaporated under reduced pressure. After drying under HV, the title compound (0.272 g, 97% yield) was obtained as yellow foam.

Rf = 0.30 in DCM-MeOH 19-1.

MS (ESI, m/z): 599.1 [$M+H^+$].

18.viii. *(2S,5R,6R)-(5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl)-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

The title compound (0.271 g, 96% yield) was obtained as a off-white foam, starting from intermediate 18.vii. (0.268 g, 0.45 mmol) and using the procedure of Example 2, step 2.iii.

^1H NMR (d_6-DMSO) δ: 10.56 (s, 1H); 8.70 (d, J = 5.0 Hz, 1H); 8.39 (d, J = 5.0 Hz, 1H); 8.28 (d, J = 9.0 Hz, 1H); 7.48 (m, 1H); 7.32 (d, J = 9.0 Hz, 1H); 7.24 (m, 1H); 7.13 (m 1H); 6.65 (d, J = 16.1 Hz, 1H); 6.51 (td, J = 5.6, 16.1 Hz, 1H); 4.40 (br s, 1H); 4.36 (m, 1H); 4.26 (m, 1H); 4.04 (s, 3H); 3.65-3.54 (m, 2H); 3.51-3.35 (m, 2H); 2.85 (m, 1H); 2.14 (m, 1H); 1.97 (m, 1H); 1.80-1.70 (m, 2H); 1.68-1.54 (m, 3H).

Example 19: (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide:

19.i. *(3R,6S)-(6-carbamoyl-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester*:

To a solution of (2*S*,5*R*)-5-*tert*-butoxycarbonylamino-tetrahydro-pyran-2-carboxylic acid (obtained as described in *Eur. J. Org. Chem.* (2003), 2418-2427; 3 g) in EA (50 ml) was added NHS (1.5 g) and DCC (2.7 g). The reaction was stirred overnight at rt. The solids were removed by filtration. The filtrate was concentrated *in vacuo* and the residue was taken up in THF (180 ml). NH_3 was bubbled through the solution for 10 min, and the resulting turbid mixture was stirred at rt for 1 h. SiO_2 (20 g) was added in the mixture, and the volatiles were removed by rotatory evaporation. The material was chromatographed over SiO_2 (DCM-MeOH 19-1) to afford the title compound (1.3 g) as a white solid.

MS (ESI, m/z) : 245.3 [$M+H^+$].

19.ii. *[(3R,6S)-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a mixture of intermediate 19.i (0.8 g), cesium carbonate (1.3g), *rac*-BINAP (0.145 g) and $(dba)_3Pd_2.CHCl_3$ (0.057 g) was added dioxane (41 ml). The mixture was sonicated 15 min and trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (1.0 g) was added. The mixture was heated at 100°C overnight. After filtration, the filtrate was concentrated to dryness and the residue was purified over SiO_2 (DCM-MeOH 19-1) to afford the title amide (1.3 g) as a foam.

^1H NMR ($CDCl_3$) δ: 10.57 (s, 1H); 8.70 (d, J = 5.2 Hz, 1H); 8.51 (d, J = 5.2 Hz, 1H); 8.22 (d, J = 9.0 Hz, 1H); 7.16 (d, J = 9.0 Hz, 1H); 4.32 (m, 2H); 4.12 (s, 3H); 4.01 (dd, J = 2.5, 11.4 Hz, 1H); 3.72 (m, 1H); 3.23 (t, J = 10.6 Hz, 1H); 2.39 (qd, J = 2.8, 10.2 Hz, 1H); 2.22 (m. 1H); 1.76 (m, 1H); 1.47 (overlapped m, 1H); 1.47 (s, 9H).

MS (ESI, m/z) : 403.6 $[M+H^+]$.

19.iii. *(2S,5R)-5-amino-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

The title amine (0.5 g) was obtained as a white solid, starting from intermediate 19.ii (1.3 g) and using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% concentrated aq. NH_4OH).

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

19.iv. *(2S,5R)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

Starting from intermediate 19.iii (0.254 g, 0.84 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.141 g, 1.0 eq.), the title compound (0.12 g, 31% yield) was obtained as a white solid using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 97-3 containing 0.5% aq. NH_4OH as an eluent.

^1H NMR (d_6-DMSO) δ: 10.52 (s, 1H); 8.71 (d, J = 5.0 Hz, 1H); 8.38 (d, J = 5.0 Hz, 1H); 8.27 (d, J = 9.0 Hz, 1H); 7.48 (m, 1H); 7.32 (d, J = 9.0 Hz, 1H); 7.25 (m, 1H); 7.11 (m, 1H); 6.63 (d, J = 16.2 Hz, 1H); 6.50 (td, J = 5.3, 16.2 Hz, 1H); 4.21 (dd, J = 3.2, 10.7 Hz, 1H); 4.08 (dd, J = 2.1, 10.7 Hz, 1H); 4.02 (s, 3H); 3.48-3.35 (m, 2H); 3.25 (t, J = 10.5 Hz, 1H); 2.69 (m, 1H); 2.18-2.14 (m, 2H); 1.99 (br s, 1H); 1.55 (m, 1H); 1.35 (m, 1H).

MS (ESI, m/z): 454.9 [M+H$^+$].

Example 20: (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-Fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol:

20.i. *{(3R,6S)-6-[2-(3-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from (3*R*,6*S*)-[6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid *tert*-butyl ester (see Preparation G; 15 g, 35.4 mmol) and 3-methoxy-quinoline-5-carbaldehyde (see Preparation F; 6.3 g, 33.7 mmol), the title alkene (9.9 g, 76% yield) was obtained as a colourless solid, using the procedure of Example 1, step 1. vi. The compound was purified by trituraton in a Hex-ether mixture.

^{1}H NMR ($CDCl_3$) δ: 8.72 (d, J = 4.5 Hz, 1H); 8.02 (d, J = 9.2 Hz, 1H); 7.36-7.25 (m, 3H); 7.26 (d, J = 15.8 Hz, 1H); 6.42 (dd, J = 5.2, 15.8 Hz, 1H); 4.27 (m, 1H); 4.08 (m, 1H); 3.98 (s, 3H); 3.74 (br s, 1H); 3.18 (t, J = 10.6 Hz, 1H); 2.22 (m, 1H); 1.98 (m, 1H); 1.75-1.60 (m, 2H); 1.48 (s, 9H), 1.47 (overlapped m, 1H).

MS (ESI, m/z): 385.3 [M+H$^+$].

20.ii. *{(3R,6S)-6-[(1S,2S)-1,2-dihydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 20.i (9.9 g, 25.7 mmol), the title diol (10.5 g, 97% yield) was obtained as a colourless foam using the procedure of Example 6, step 6.i. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 as eluent.

^{1}H NMR (d_6-DMSO) δ: 8.71 (d, J = 4.5 Hz, 1H); 7.93 (d, J = 9.0 Hz, 1H); 7.54 (d, J = 4.5 Hz, 1H); 7.44-7.38 (m, 2H); 6.851 (br s, 1H); 6.65 (d, J = 8.2 Hz, 1H); 5.43 (d, J = 5.4 Hz, 1H); 5.36 (m, 1H); 4.83 (d, J = 6.3 Hz, 1H); 3.89 (s, 3H); 3.79 (m, 1H); 3.56 (m, 1H); 3.37 (br s, 1H); 2.72 (t, J = 10.6 Hz, 1H); 1.85 (m, 1H); 1.71-1.65 (m, 2H); 1.36 (s, 9H); 1.21 (m, 1H).

20.iii. *(3R,6S)-{6-[(4R,5R)-5-(6-methoxy-quinolin-4-yl)-2-oxo-[1,3]dioxolan-4-yl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To an ice-chilled solution of intermediate 20.ii (10.2 g) in DCM (130 ml) were added pyridine (12 ml) and triphosgene (3.62 g). The reaction was stirred 30 min at this temperature and then 90 min at rt. The reaction mixture was diluted with aq. $NaHCO_3$ and the two layers were decanted. The org. layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The

residue was chromatographed over SiO_2 (DCM-MeOH 19-1) to afford the title cyclic carbonate (10.5 g) as a a colourless foam.

^{1}H NMR ($CDCl_3$) δ: 8.82 (d, J = 4.5 Hz, 1H); 8.10 (d, J = 9.3 Hz, 1H); 7.49-7.43(m, 2H); 7.21 (br. s, 1H); 6.27 (d, J = 4.2 Hz, 1H); 4.61 (m, 1H); 4.28 (ddd, J = 2.0, 4.7, 10.6 Hz, 2H); 3.95 (s, 3H); 3.70 (m, 2H); 3.18 (t, J = 10.7 Hz, 1H); 2.27 (m, 1H); 1.84 (m, 2H); 1.46 (s, 9H); 1.45 (m overlapped, 1H).

MS (ESI, m/z): 445.0 [$M+H^+$].

20.iv. *(3R,6S)-{6-[(1S)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 20.iii (2.75 g) in EA (250 ml) under argon was added Pd/C (1.32 g). The resulting suspension was stirred under hydrogen atmosphere. After 2.5 h, more Pd/C (0.66 g) was added and the reaction was stirred overnight under hydrogen atmosphere. The catalyst was filtered off and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography over SiO_2 (DCM-MeOH 19-1 containing 1% aq. NH_4OH) to afford the title compound as a white foam (1.23 g).

^{1}H NMR (d_6-DMSO) δ: 8.62 (d, J = 4.4 Hz, 1H); 7.92 (d, J = 9.0 Hz, 1H); 7.42 (d, J = 2.5 Hz, 1H); 7.40 (dd, J = 2.7, 9.0 Hz, 1H); 7.33 (d, J = 4.4 Hz, 1H); 6.76 (br d, J = 8.0 Hz, 1H); 4.83 (d, J = 6.4 Hz, 1H); 3.91 (s, 3H); 3.90 (overlapped m, 1H); 3.74 (m, 1H); 3.38 (br. s, 1H); 3.29 (overlapped dd, visible J = 3.8 Hz, 1H); 3.12 (d, J = 10.4 Hz, 1H); 2.98 (t, J = 10.3 Hz, 1H); 2.97 (m overlapped, 1H); 1.90 (d, J = 9.2 Hz, 1H); 1.60 (m, 2H); 1.39 (s, 9H); 1.38 (m overlapped, 1H).

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

20.v. *(1S)-1-((2S,5R)-(5-amino-tetrahydro-pyran-2-yl)-2-(6-methoxy-quinolin-4-yl)-ethanol*:

A solution of intermediate 20.iv (1.23 g) in TFA (15 ml) was stirred for 10 min. The solution was concentrated to dryness, basified with a 2*M* aq. NaOH solution, diluted with DCM-MeOH 9-1 and the phases separated. The aq. layer was extracted 6 times with DCM-MeOH 9-1. The combined org. layers were dried over Na_2SO_4, filtered and concentrated to dryness to afford a white solid (0.768 g).

^{1}H NMR (DMSO) δ: 8.62 (d, J = 4.4 Hz, 1H); 7.92 (d, J = 9.1 Hz, 1H); 7.44 (d, J = 2.7 Hz, 1H); 7.39 (dd, J = 2.8, 9.1 Hz, 1H); 7.32 (d, J = 4.4 Hz, 1H); 4.79 (d, J = 6.3 Hz, 1H); 3.91 (s, 3H); 3.88 (ddd, J = 1.8, 4.4, 10.5 Hz, 1H); 3.73 (m, 1H); 3.31 (dd, J = 4.0, 13.6 Hz, 1H);

3.10 (dt, J = 3.4, 10.4 Hz, 1H); 2.93 (m overlapped, 1H); 2.87 (t overlapped, J = 10.5 Hz, 1H); 2.61 (m, 1H); 1.92 (m, 1H); 1.56 (m, 2H); 1.39 (br s, 2H)1.13 (m, 1H).
MS (ESI, m/z): 303.2 [$M+H^+$].

20.vi. *(1S)-1-{(2S,5R)-5-[(E)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol*:

Starting from intermediate 20.v (0.1 g, 0.33 mmol) and and (*E*)-3-(3-fluoro-phenyl)-propenal (0.050 g, 1.0 eq.), the title compound (0.063 g, 43% yield) was obtained as a white solid using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 97-3 containing 0.5% aq. NH_4OH as an eluent.
MS (ESI, m/z): 437.0 [$M+H^+$].

Example 21: 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one:

Starting from intermediate 20.v (0.051 g, 0.17 mmol) and 7-fluoro-3-oxo-3,4-dihydro-2*H*-benzo[1,4]thiazine-6-carbaldehyde (obtained as described in WO 02/056882, 0.036 g, 1.0 eq.), the title compound (0.020 g, 23% yield) was obtained as a white solid using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.
^1H NMR (d_6-DMSO) δ: 10.55 (s, 1H); 8.62 (d, J = 4.4 Hz, 1H); 7.91 (d, J = 9.0 Hz, 1H); 7.42-7.40 (m, 2H); 7.32 (d, J = 4.4 Hz, 1H); 7.20 (d, J = 9.0 Hz, 1H); 7.09 (d, J = 6.8 Hz, 1H); 4.79 (d, J = 6.3 Hz, 1H); 4.04 (m, 1H); 3.90 (s, 3H); 3.77-3.71 (m, 3H); 3.46 (s, 2H); 3.30 (dd, J = 3.8, 13.1 Hz, 1H); 3.15 (m, 1H); 3.00-2.90 (m, 2H); 2.50 (overlapped m, 1H); 2.09-1.99 (m, 2H); 1.66-1.51 (m, 2H); 1.18 (m, 1H).
MS (ESI, m/z): 498.1 [$M+H^+$].

Example 22: 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide:

Starting from intermediate 20.v (0.1 g, 0.33 mmol) and (*E*)- 3-(2-fluoro-phenyl)-acrylic acid (0.055 g, 1.0 eq.), the title compound (0.085 g, 57% yield) was obtained as a white solid using the procedure of Example 2, step 2.iv. The compound was purified by chromatography over SiO_2 using DCM-MeOH 97-3 containing 0.5% aq. NH_4OH as an eluent.

^{1}H NMR (d_6-DMSO) δ: 8.63 (d, J = 4.2 Hz, 1H); 8.13 (d, J = 7.2 Hz, 1H); 7.95 (d, J = 9.0 Hz, 1H); 7.64 (t, J = 7.2 Hz, 1H); 7.62-7.19 (m, 7H); 6.70 (d, J = 15.8 Hz, 1H); 4.87 (d, J = 6.4 Hz, 1H); 4.02 (m, 1H); 3.92 (s, 3H); 3.92-3.78 (m, 2H); 3.35 (m, 1H); 3.21 (m, 1H); 3.08-2.93 (m, 2H); 1.98 (m, 1H); 1.80-1.60 (m, 2H); 1.43 (m, 1H).

Example 23: 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide:

Starting from intermediate 20.v (0.1 g, 0.33 mmol) and (*E*)- 3-(3-fluoro-phenyl)-acrylic acid (0.055 g, 1.0 eq.), the title compound (0.030 g, 20% yield) was obtained as a white solid using the procedure of Example 2, step 2.iv. The compound was purified by chromatography over SiO_2 using DCM-MeOH 97-3 containing 0.5% aq. NH_4OH as an eluent.

^{1}H NMR (d_6-DMSO) δ: 8.63 (d, J = 4.2 Hz, 1H); 8.05 (d, J = 7.8 Hz, 1H); 7.92 (d, J = 9.0 Hz, 1H); 7.56-7.25 (m, 7H); 7.19 (m, 1H); 6.62 (d, J = 15.8 Hz, 1H); 4.87 (d, J = 6.5 Hz, 1H); 4.02 (m, 1H); 3.92 (s, 3H); 3.92-3.78 (m, 2H); 3.35 (m, 1H); 3.21 (m, 1H); 3.08-2.93 (m, 2H); 2.01 (m, 1H); 1.80-1.60 (m, 2H); 1.43 (m, 1H).

Example 24: 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile:

24.i. *(3R,6S)-(6-formyl-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester*:

To a solution of oxalyl chloride (3.5 ml) in DCM (25 ml) cooled to -78°C, was added dropwise a solution of DMSO (3.5 ml) in DCM (25 ml). After 15 min stirring, a solution of (3*R*,6*S*)-(6-hydroxymethyl-tetrahydro-pyran-3-yl)-carbamic acid *tert*-butyl ester (prepared as described in *Eur. J. Org. Chem.* (2003), 2418-2427) in DCM (25 ml) was added dropwise. The reaction mixture was stirred 1 h and a solution of TEA (15 ml) in DCM (15 ml) was added dropwise. The reaction proceeded for 1 h, with warming to 0°C. Saturated $NaHCO_3$ (50 ml) was added. The org. layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Hex-EA 1-2) to afford the title aldehyde (2.5 g) as a colourless solid.

24.ii. *(3R,6S)-(6-ethynyl-tetrahydro-pyran-3-yl)-carbamic acid tert-butyl ester*:

To a solution of *p*-toluenesulfonyl azide (3.08 g) in MeCN (200 ml) were added K_2CO_3 (5.38 g) and dimethyl-2-oxophosphonate (2.13 ml). The mixture was stirred 2 h at rt and a

solution of intermediate 24.i (2.5 g) in MeOH (30 ml) was added. The mixture was stirred overnight at rt. After concentration to dryness, the residue was partitioned between water (50 ml) and EA (100 ml). The aq. layer was extracted with EA (2 x 100 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was filtered through SiO_2 (EA-Hex 1-3) to afford the title alkyne (1.9 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 4.78 (m, 1H); 4.39 (m, 1H); 4.14 (dd, J = 3.0, 11.4 Hz, 1H); 3.71 (m, 1H); 3.34 (m, 1H); 2.50 (d, J = 2.2 Hz, 1H); 2.11-1.99 (m, 2H); 1.73 (m, 1H); 1.60 (m, 1H); 1.46 (s, 9H).

MS (ESI, m/z): 226.2 [$M+H^+$].

24.iii. *cis,trans-[(3R,6S)-6-(2-tributylstannanyl-vinyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a solution of intermediate 24.ii (1.95 g, 8.65 mmol) in THF (26 ml) was added bis(triphenylphosphine) palladium dichloride (0.12 g, 0.17 mmol) and then tributyltin hydride (2.75 ml, 10.38 mmol). The mixture was stirred at rt for 20 min. The reaction mixture was concentrated to dryness and the residue was chromatographed over SiO_2 (Hex then Hex-EA 9-1) to afford the title stannane (3.4 g) as an equimolar mixture of *cis* and *trans* isomers.

24.iv. *trans-{(3R,6S)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 24.iii (5 g) in dioxane (freshly distilled, 50 ml) were added trifluoromethanesulfonic acid 2-cyano-quinolin-8-yl ester (2.0 g, 6.6 mmol), LiCl (0.936 g), 2,6-di-*tert*-butyl-4-methylphenol (few seeds), $(PPh_3)_4Pd$ (0.153 g). The mixture was heated at 100°C overnight. After cooling, the solids were filtered off and the filtrate was concentrated to dryness. The residue was chromatographed over SiO_2 (Hex-EA 1-1) to afford the title alkene (1.80 g, 71% yield) as a white solid.

^{1}H NMR (d_6-DMSO) δ: 8.72 (d, J = 4.7 Hz, 1H); 8.25 (d, J = 9.0 Hz, 1H); 7.84 (d, J = 4.7 Hz, 1H); 7.55 (d, J = 16.5 Hz, 1H); 7.28 (d, J = 9.0 Hz, 1H); 6.93 (dd, J = 5.3 Hz, 16.5 Hz, 1H); 6.85 (d, J = 7.7 Hz, 1H); 4.04 (s, 3H); 4.01 (partially overlapped m, 1H); 3.90 (m, 1H); 3.39 (br s, 1H); 3.10 (t, J = 10.6 Hz, 1H); 1.89 (m, 2H); 1.50 (m, 2H); 1.39 (s, 9H).

MS (ESI, m/z): 386.1 [$M+H^+$].

24.v. *(3R,6S)-{6-[(1R,2R)-2-(cyano-quinolin-8-yl)-1,2-dihydroxy-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

The title diol (1.60 g, 81% yield) was obtained as a white solid starting from intermediate 24.iv (1.80 g, 4.74 mmol) and using the procedure of Example 6, step 6.i.

MS (ESI, m/z): 419.2 [$M+H^+$].

24.vi. *8-[(1R,2R)-2-((2S,5R)-5-amino-tetrahydro-pyran-2-yl)-1,2-dihydroxy-ethyl]-quinoline-2-carbonitrile*:

The title amine (0.62 g, 74% yield) was obtained as a colourless solid starting from intermediate 24.v (1.1 g, 2.61 mmol) and using the procedure of Example 1, step 1.ix.

MS (ESI, m/z): 314.2 [$M+H^+$].

24.vii. *8-((1R,2R)-2-{(2S,5R)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile*:

Starting from intermediate 24.vi (0.158 g, 0.5 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.084 g, 1.0 eq.), the title compound (0.04 g, 17% yield) was obtained as a white solid according to the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.

^1H NMR (d_6-DMSO) δ: 8.65 (d, J = 8.5 Hz, 1H); 8.07-7.99 (m, 3H); 7.80 (dd, J = 7.2, 8.3 Hz, 1H); 7.49 (m, 1H); 7.25 (m, 1H); 7.13 (m, 1H); 6.61 (d, J = 16.4 Hz, 1H); 6.48 (td, J = 5.4, 16.4 Hz, 1H); 5.77 (dd, J = 2.9, 6.3 Hz, 1H); 5.16 (d, J = 7.6 Hz, 1H); 4.35 (d, J = 6.3 Hz, 1H); 3.91 (m, 1H); 3.60 (m, 1H); 3.42-3.32 (m, 2H), 3.24 (m, 1H); 2.81 (t, J = 10.3 Hz, 1H); 2.56 (overlapped m, 1H); 2.11 (m, 1H); 1.90 (m, 1H); 1.76 (br s, 1H); 1.56 (m, 1H); 1.24 (m, 1H).

MS (ESI, m/z): 465.6 [$M+H^+$].

Example 25: [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine:

25.i. *{(3R,6S)-6-[(E)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from (*3R,6S*)-[6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid *tert*-butyl ester (described in Preparation G; 1.43 g, 3.4 mmol) and 3-fluoro-

6-methoxy-quinoline-5-carbaldehyde (0.462 g, 2.25 mmol), the title alkene (0.85 g, 62% yield) was obtained as a white solid, using the procedure of Example 1, step 1. vi. The compound was purified by chromatography over SiO_2 using EA-Hex 1-1as eluent.

^{1}H NMR (d_6-DMSO) δ: 8.90 (d, J = 2.7 Hz, 1H); 8.32 (dd, J = 3.0, 11.4 Hz, 1H); 8.12 (d, J = 9.3 Hz, 1H); 7.78 (d, J = 9.3 Hz, 1H); 7.99 (d, J = 16.2 Hz, 1H); 6.93 (d, J = 8.1 Hz, 1H); 6.35 (dd, J = 5.7, 16.2 Hz, 1H); 4.12-3.99 (m, 2H); 4.10 (s, 3H); 3.50 (br s, 1H); 3.21 (t, J = 10.5 Hz, 1H); 2.03-2.00 (m, 2H); 1.62 (m, 1H); 1.49 (m, 1H); 1.49 (s, 9H).

25.ii. *6-[(3R,6S)-(E)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-ylamine*:

The title amine (0.16 g, 71% yield) was obtained as a white solid starting from intermediate 25.i (0.3 g, 0.745 mmol) and using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as eluent.

MS (ESI, m/z): 465.6 [$M+H^+$].

25.iii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{3R,6S)-6-[(E)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine*:

Starting from intermediate 25.ii (0.1 g, 0.33 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.055 g, 1.0 eq.), the title compound (0.034 g, 22% yield) was obtained as a colourless oil using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.

MS (ESI, m/z): 455.0 [$M+H^+$].

Example 26: [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine:

26.i. *{(3R,6S)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 25.i (0.55 g, 1.36 mmol) in EA (6 ml) and MeOH (20 ml) was added 10% Pd/C (0.25 g). The reaction was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to dryness to afford the title compound (0.55 g) as a white solid.

MS (ESI, m/z): 405.0 [$M+H^+$].

26.ii. *(3R,6S)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamine*:

The title amine (0.3 g, 72% yield) was obtained as a colourless oil, starting from intermediate 26.i (0.55 g, 1.36 mmol) and using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as eluent.

MS (ESI, m/z): 305.1 [$M+H^+$].

26.iii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(3R,6S)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine*:

Starting from intermediate 26.ii (0.15 g, 0.49 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.082 g, 1.0 eq.), the title compound (0.17 g, 75% yield) was obtained as a colourless oil using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.

^1H NMR (d*6*-DMSO) δ : 8.77 (d, J = 2.7 Hz, 1H); 8.12 (dd, J = 3.2, 11.2 Hz, 1H); 7.97 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H); 7.48 (m, 1H); 7.24 (m, 1H); 7.11 (m, 1H) 6.59 (d, J = 16.1 Hz, 1H); 6.48 (td, J = 5.2, 16.2 Hz, 1H); 4.02 (m 1H); 3.95 (s, 3H); 3.37 (m, 2H), 3.13-2.92 (m, 3H); 2.88 (t, J = 10.5 Hz, 1H); 2.55 (m, 1H); 1.96 (m, 1H); 1.75 (br s, 1H); 1.66-1.55 (m, 3H); 1.26-1.10 (m, 2H).

MS (ESI, m/z): 456.9 [$M+H^+$].

Example 27: 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one:

Starting from intermediate 26.ii (0.15 g, 0.49 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (0.095 g, 1.0 eq.), the title compound (0.035 g, 17% yield) was obtained as an off-white solid using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.

MS (ESI, m/z): 482.8 [$M+H^+$].

Example 28: (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol:

28.i. *{(3S,6R)-6-[(E)-2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from (3*S*,6*R*)-[6-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-tetrahydro-pyran-3-yl]-carbamic acid *tert*-butyl ester (see preparation I, 1.69 g, 4 mmol) and 3-methoxy-quinoline-5-carbaldehyde (see preparation D, 0.7 g, 4 mmol), the title alkene (1.03 g, 69% yield) was obtained as a white solid, using the procedure of Example 1, step 1. vi. The compound was purified by chromatography over SiO_2 using Hept-EA 1-1 then 1-4 as eluent.
MS (ESI, m/z): 373.1 [$M+H^+$].

28.ii. *{(3S,6R)-6-[(1R,2R)-2-(6-fluoro-quinolin-4-yl)-1,2-dihydroxy-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 28.i (0.497 g, 1.33 mmol), the title diol (0.54 g, 99% yield) was obtained as a white solid using the procedure of Example 6, step 6.i.The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 as eluent.
MS (ESI, m/z): 407.0 [$M+H^+$].

28.iii. *(1R,2R)-1-[(2R,5S)-5-amino-tetrahydro-pyran-2-yl]-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol*:

The title amine (0.21 g, 51% yield) was obtained as a colourless foam, starting from intermediate 28.ii (0.54 g, 1.32mmol) and using the procedure of Example 1, step 1.ix.
MS (ESI, m/z): 307.1 [$M+H^+$].

28.iv. *(1R,2R)-1-{(2R,5S)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol*:

Starting from intermediate 28.iii (0.21 g, 0.68 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.115 g, 1.0 eq.), the title compound (0.095 g, 31% yield) was obtained as a white foam using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.
MS (ESI, m/z): 458.9 [$M+H^+$].

Example 29: [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine:

29.i. *(3S,6R)-6-[(E)-2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-ylamine*:

The title amine (0.135 g, 82% yield) was obtained as a colourless foam, starting from intermediate 28.i (0.226 g, 0.6 mmol) and using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.

MS (ESI, m/z): 273.2 [$M+H^+$].

29.ii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(3S,6R)-(E)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine*:

Starting from intermediate 29.i (0.131 g, 0.48 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.089 g, 1.1 eq.), the title compound (0.112 g, 54% yield) was obtained as a colourless oil according to the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 97-3 containing 0.3% aq. NH_4OH as an eluent.

^1H NMR (d_6-DMSO) δ : 8.82 (d, J = 4.6 Hz, 1H); 8.09 (dd, J = 5.7, 9.2 Hz, 1H); 7.97 (dd, J = 2.7, 10.6 Hz, 1H); 7.72-7.65 (M, 2H); 7.48 (m, 1H); 7.31 (d, J = 15.8 Hz, 1H); 7.24 (m, 1H); 7.11 (m, 1H); 6.63 (d, J = 15.8 Hz, 1H); 6.62 (d, J = 15.8 Hz, 1H); 6.51 (td, J = 5.5, 15.8 Hz, 1H); 4.11-4.03 (m, 2H); 3.48-3.35 (m, 2H); 3.10 (t, J = 10.5 Hz, 1H); 2.60 (m, 1H); 2.10 (m, 1H); 1.90-1.88 (m, 2H); 1.54-1.23 (m, 2H).

MS (ESI, m/z): 425.0 [$M+H^+$].

Example 30: [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine:

30.i. *{(3S,6R)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

This alkane (0.267 g, 95% yield) was obtained as a colourless foam starting from intermediate 28.i (0.277 g, 0.74 mmol) and using the procedure of Example 2, step 2.ii. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.

MS (ESI, m/z): 375.1 [$M+H^+$].

30.ii. *(3S,6R)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamine*:

The title amine (0.155 g, 81% yield) was obtained as a yellowish oil, starting from intermediate 30.i (0.261 g, 0.7 mmol) and using the procedure of Example 1, step 1.ix. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.

MS (ESI, m/z): 275.1 [$M+H^+$].

30.iii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(3S,6R)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine*:

Starting from intermediate 30.ii (0.08 g, 0.29 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.054 g, 1.1 eq.), the title compound (0.106 g, 85% yield) was obtained as a colourless oil according to the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 19-1 containing 0.5% aq. NH_4OH as an eluent.

MS (ESI, m/z): 426.7 [$M+H^+$].

Example 31: 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one:

Starting from intermediate 30.ii (0.064 g, 0.24 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbaldehyde (0.050 g, 1.0 eq.), the title compound (0.063 g, 60% yield) was obtained as a white foam using the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 using DCM-MeOH 9-1 containing 1% aq. NH_4OH as an eluent.

^1H NMR (d_6-DMSO) δ : 10.87 (s, 1H); 8.77 (d, J = 4.4 Hz, 1H); 8.08 (dd, J = 5.7, 9.2 Hz, 1H); 7.85 (dd, J = 2.8, 10.7 Hz, 1H); 7.73 (d, J = 7.8 Hz, 1H); 7.66 (m, 1H); 7.39 (d, J = 4.4 Hz, 1H); 7.09 (d, J = 7.8 Hz, 1H); 4.00 (m, 1H); 3.78-3.68 (m, 2H); 3.53 (s, 2H); 3.17 (m, 1H); 3.10-3.00 (m, 2H); 2.94 (t, J = 10.5 Hz, 1H); 2.50 (m, 1H); 2.11 (m, 1H); 1.99 (m, 1H); 1.79-1.65 (m, 3H); 1.32-1.11 (m, 2H).

MS (ESI, m/z): 452.8 [$M+H^+$].

Example 32: 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2R,3R,6S*)-2-(2-hydroxy-ethyl)-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide:

32.i. *3-{3-amino-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 1.vi (2.19 g, 4.39 mmol), the title compound (1.35 g, 85% yield) was obtained as an off-white solid using the procedure of Example 2, step 2.iii. The compound was obtained as a 2-1 mixture of epimers.
MS (ESI, m/z): 360.3 [$M+H^+$].

32.ii. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid {(2R,3R,6S)-2-((2R)-2,3-dihydroxy-propyl)-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid {(2R,3R,6S)-2-((2S)-2,3-dihydroxy-propyl)-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide*:

Starting from intermediate 32.i (0.2 g, 0.55 mmol) and 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid (0.116 g, 1.1 eq.) and using the procedure described in Example 1, step 1.x., the title compounds were obtained as white solids. The isomers were partially separated by chromatography over SiO_2 (DCM-MeOH 93-7 containing 0.7% aq.NH_4OH) to afford a first eluting isomer (0.019 g, 6% yield), a fraction containing both isomers (0.12 g, 39% yield) and the second eluting isomer (0.055 g, 18% yield).
MS (ESI, m/z): 551.9 [$M+H^+$] (mixture of isomers).

32.iii. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid [6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-2-(2-oxo-ethyl)-tetrahydro-pyran-3-yl]-amide*:

Starting from intermediate 32.ii (0.12 g, 0.21 mmol), the title aldehyde (0.09 g, 72% yield) was obtained as a white solid using the procedure of Example 2, step 2.v.
^1H NMR (d_6-DMSO) δ: 11.24 (s, 1H); 9.72 (s, 1H); 8.77 (d, J = 4.5 Hz, 1H); 8.34 (d, J = 9.0 Hz, 1H); 8.28 (d, J = 9.0 Hz, 1H); 8.02-7.94 (m, 2H); 7.68-7.57 (m, 2H); 7.30 (d, J = 9.0 Hz, 1H); 7.11 (dd, J = 4.0, 16.8 Hz, 1H); 4.76 (m, 1H); 4.65 (m, 1H); 4.05 (m, 1H); 4.03 (s, 3H); 3.72 (s, 2H); 2.57 (m, 2H); 2.18-1.90 (m, 2H); 1.94-1.89 (m, 2H).
MS (ESI, m/z): 520.1 [$M+H^+$].

32.iv. *3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxylic acid {(2R,3R,6S)-2-(2-hydroxy-ethyl)-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide*:

To a solution of intermediate 32.iii. (0.07 g, 0.13 mmol) in MeOH (3 ml) and THF (1 ml) was added, at 0°C, $NaBH_4$ (0.02 g). The reaction was stirred 1 h at this temperature. Water (2 ml) was added. The volatiles were removed *in vacuo* and the residue was chromatographed (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH) to afford a solid that was further triturated in ether, filtered and dried under HV. The title alcohol (0.025 g, 35% yield) was obtained as a white solid.

MS (ESI, m/z): 521.8 $[M+H^+]$.

Example 33: 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide:

33.i. *{(2R,3R,6S)-2-carbamoylmethyl-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 1.vi (5.5 g, 11 mmol), the title amide (0.602 g, 1.36 mmol) was obtained as a yellowish solid, using the procedures described respectively in Example 9, step 9.ii. (deprotection, 89% yield), Example 2, steps 2.v (aldehyde formation, 99% yield) and 2.vi (acid formation, 76% yield) and Example 9, step 9.iv (30% yield).

MS (ESI, m/z): 521.8 $[M+H^+]$.

33.ii. *2-{3-amino-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide*:

Starting from intermediate 33.i (0.6 g, 1.36 mmol), the title amine (0.33 g, 71% yield) was obtained as a brown solid using the procedure of Example 1, step 1.ix.

MS (ESI, m/z): 343.0 $[M+H^+]$.

33.iii. *2-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide*:

Starting from intermediate 33.ii (0.110 g, 0.32 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.059 g, 1.1 eq), the title compound (0.054 g, 34% yield) was obtained as as a white solid according to the procedure of Example 1, step 1.x. The compound was purified by chromatography over SiO_2 (DCM-MeOH 19-1 containing 0.5% aq. NH_4OH).

MS (ESI, m/z): 495.0 [M+H$^+$].

Example 34: (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid:

34.i. *3-fluoro-6-methoxy-quinoline-4-carbaldehyde*:

To a solution of DIPA (3.5 ml) in THF (100 ml), cooled to -78°C, was added *n*-BuLi (2.5*N* in hexanes, 10 ml). The reaction mixture was stirred 5 min at this temperature before warming to 0°C. The reaction mixture was stirred 15 min before cooling to -78°C. 3-fluoro-6-methoxy-quinoline (4.38 g, 24.7 mmol) in THF (20 ml + 5 ml rinse) was added and the mixture was stirred 3 h at -78°C. DMF (3 ml) was added dropwise. After 15 min, the reaction mixture was warmed up to rt. 10% aq. $NaHSO_4$ (10 ml) was added. The volatiles were removed *in vacuo* and the residue was made basic with sat. sodium bicarbonate. The aq. layer was extracted twice with EA (2 x 200 ml). The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed (Hex-EA 1-1) to afford the title aldehyde (3.05 g, 60% yield) as a yellowish solid. The compound was contaminated by 20% of the remaining starting material.

^{1}H NMR ($CDCl_3$) δ : 10.86 (s, 1H); 8.81 (d, J = 1.8 Hz, 1H); 8.50 (d, J = 2.8 Hz, 1H); 8.03 (d, J = 9.2 Hz, 1H); 7.40 (dd, J = 2.8, 9.2 Hz, 1H); 4.01 (s, 3H).

34.ii. *{(2R,3R,6S)-2-[(4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-6-[(E)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 34.i (3.05 g, 11.9 mmol) and intermediate 1.v (6.95 g, 12.9 mmol), the title alkene (5.38 g, 80% yield) was obtained as a pale yellow foam using the procedure of Example 1, step 1.vi. The compound was purified by chromatography using Hept-EA 1-2 as an eluent. The compound was obtained as a 2-1 mixture of epimers and a 3-1 *E*-Z mixture.
MS (ESI, m/z): 517.1 [M+H$^+$].

34.iii. *(2RS)-3-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 34.ii (2.63 g, 5.1 mmol), the title compound (1.62 g) was obtained as a yellowish foam, using the procedures described in Example 2, step 2.iii (deprotection, 67% yield) and in Example 1, step 1.x (reductive amination, 91% yield). After each step, the crude reaction mixture was purified by chromatography over SiO_2 using respectively

DCM-MeOH 6-1 containing 1% aq. NH_4OH and DCM-MeOH 9-1 containing 1% aq. NH_4OH as eluents. The compound was obtained as a 2-1 mixture of epimers and a 3-1 *E*-Z mixture.

MS (ESI, m/z): 567.7 [$M+H^+$].

34.iv. *(2R,3R,6S)-{3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 34.iii (1.58 g, 3 mmol), the title compound (0.037 g) was obtained as an off-white solid using the procedures described in Example 4, step 4.iii (Boc formation, 74% yield), Example 2, steps 2.v (aldehyde formation, 82% yield) and 2.vi (acid formation, 98% yield), and Example 4, step 4.vi (52% yield). The compound was purified by chromatography over SiO_2 using DCM-MeOH 6-1 containing 1% aq. NH_4OH) after the last step. The compound was obtained as a 2-1 E-Z mixture.

MS (ESI, m/z): 513.0 [$M+H^+$].

Example 35: {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid:

35.i. *(2RS)-3-{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-propane-1,2-diol*:

Starting from intermediate 32.i (1.43 g, 4 mmol) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.672 g, 1.0 eq), the title compound (1.34 g, 65% yield) was obtained as as a colourless foam using the procedure of Example 1, step 1.x. After purification by chromatography over SiO_2 (DCM-MeOH 9-1 containing 1% aq. NH_4OH), the compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d6-DMSO) δ: 8.71 (d, J = 4.6 Hz, 1H); 8.24 (d, J = 9.0 Hz, 1H); 7.84 (d, J = 4.5 Hz, 0.33H); 7.82 (d, J = 4.5 Hz, 0.67H); 7.58-7.45 (m, 2H); 7.27 (d, J = 9.0 Hz, 1H); 7.25 (m, 1H); 7.12 (m, 1H); 7.01-6.92 (m, 1H), 6.63 (d, J = 16.1 Hz, 1H); 6.51 (td, J = 5.1, 16.1 Hz, 1H); 4.68 (br s, 0.67H); 4.51-4.35 (m, 2.33H); 4.21 (m, 0.67H); 4.11 (m, 0.33H); 4.04 (s, 3 x 0.33H); 4.02 (s, 3 x 0.67H); 3.62 (m, 1H); 3.39-3.25 (m, 4H); 2.75 (m, 1H); 2.05-1.37 (m, 7H).

MS (ESI, m/z): 512.0 [$M+H^+$].

35.ii. *[(E)-3-(2,5-difluoro-phenyl)-allyl]-{(2R,3R,6S)-2-[(2RS)-2,3-dihydroxy-propyl]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

To a solution of intermediate 35.i (1.34 g, 2.62 mmol) in DCM (13 ml) was added di-*tert*-butyl dicarbonate (0.9 g) and TEA (0.75 ml). The mixture was stirred at rt for 24 h. Di-*tert*-butyl dicarbonate (0.5 g) was added and the reaction proceeded further 24 h. The reaction mixture was concentrated to dryness and the residue was chromatographed over SiO_2 (DCM-MeOH 19-1 then 9-1) to afford the title compound (0.77 g, 48% yield) as a colourless foam.

^{1}H NMR ($CDCl_3$) δ: 8.71 (d, J = 4.7 Hz, 1H); 8.23 (d, J = 9.0 Hz, 0.67H); 8.22 (d, J = 9.0 Hz, 0.33H); 7.68-7.61 (m, 2H); 7.14 (d, J = 9.0 Hz, 1H); 7.13 (m, 1H); 7.01 (m, 1H); 6.94 (m, 1H); 6.77 (dd, J = 5.6, 16.5 Hz, 1H), 6.57 (d, J = 16.1 Hz, 1H); 6.29 (td, J = 5.1, 16.1 Hz, 1H); 4.64 (m, 0.33H); 4.48-4.24 (m, 3.67H); 4.12 (s, 3 x 0.33H); 4.11 (s, 3 x 0.67H); 4.10-3.92 (m, 2H); 3.71 (app td, J = 3.4, 11.0 Hz, 1H); 3.58 (m, 1H); 2.31-1.71 (m, 8H); 1.50 (s, 9H).

35.iii. *{(2R,3R,6S)-3-{tert-butoxycarbonyl-[(E)-3-(2,5-difluoro-phenyl)-allyl]-amino}-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid*:

Starting from intermediate 35.ii (0.77 g, 1.25mmol), the title acid (0.48 g) was prepared as a colourless foam using the procedures described in Example 2, steps 2.v (aldehyde formation, 82% yield) and 2.vi (acid formation, 98% yield). The compound was purified by chromatography over SiO_2 using DCM-MeOH 93-7) after the last step.

^{1}H NMR (d6-DMSO) δ: 12.19 (br s, 1H); 8.72 (d, J = 4.8 Hz, 1H); 8.25 (d, J = 9.0 Hz, 1H); 7.85 (d, J = 4.8 Hz, 1H); 7.57-7.47 (m, 2H); 7.27 (d, J = 9.0 Hz, 1H); 7,24 (m, 1H); 7.13 (m, 1H); 6.91 (dd, J = 16.1, 5.3 Hz, 1 H); 6.52 (d, J = 16.1 Hz, 1H); 6.43 (td, J = 5.0, 16.1 Hz, 1H); 4.55-4.45 (m, 2 H); 4.27-4.04 (m, 2H); 4.04 (s, 3H); 3.85 (dd, J = 4.8, 16.9 Hz, 1H); 2.88 (dd, J = 9.8, 14.7 Hz, 1H); 2.38 (dd, J = 4.6, 14.7 Hz, 1H); 2.17 (m, 1 H); 2.02-1.85 (m, 2H); 1.61 (m, 1 H); 1.40 (s, 9 H).

35.iv. *{(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(E)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid*:

A solution of intermediate 35.iii. (0.1 g, 0.17 mmol) in TFA (2 ml) was stirred at rt for 15 min. The solvent was removed *in vacuo* and the residue was taken up in water (10 ml) and DCM-MeOH (9-1, 30 ml). The pH of the aq. layer was adjusted to 7 and the org. layer was

separated. The aq. layer was extracted once more with DCM-MeOH (9-1, 30 ml) and the combined org. layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was triturated in ether and the solid was filtered off, dried under HV to afford the title compound (0.045 g, 54% yield) as a colourless solid.

MS (ESI, m/z): 496.4 [$M+H^+$].

Example 36: [(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-2-yl]-acetic acid:

36.i. *(2S,5R,6R)-5-tert-butoxycarbonylamino-6-[(4RS)2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-tetrahydro-pyran-2-carboxylic acid*:

To an ice-chilled solution of intermediate 1.ii (5 g, 14.48 mmol) in DCM (32 ml), MeCN (32 ml) and water (46 ml) was added $NaIO_4$ (14.6 g, 68.17 mmol) and $RuCl_3$ (0.030 g, 0.15 mmol). The reaction mixture was stirred at the same temperature for 5 h. The reaction mixture was diluted with EA (150 ml) and the solids were removed by filtration. MeOH (30 ml) was added and the resulting suspension was filtered. The filtrate was treated with aq. 10% $NaHSO_3$ (60 ml). The phases were separated and the aq. layer was extracted three times with EA. The combined org. layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a brown foam (quant.). The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 360.1 [$M+H^+$].

36.ii. *{(2S,5R,6R)-6-carbamoyl-2-[(4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl]-tetrahydro-pyran-3-yl}-carbamic acid tert-butyl ester*:

Starting from intermediate 36.i (5.27 g, 14.6 mmol), the title amide (3.16 g, 60% yield) was obtained as a colourless foam using the procedure of Example 10, step 10.ii. The compound was purified by chromatography using EA-cyclohexane 4-1 as an eluent. The compound was obtained as a 2-1 mixture of epimers.

MS (ESI, m/z): 359.1 [$M+H^+$].

36.iii. *{(2S,5R,6R)-2-[(4RS)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-3-yl]-carbamic acid tert-butyl ester*:

To a mixture of intermediate 36.ii (2.3 g, 6.42 mmol), *rac*-BINAP (0.288 g, 0.46 mmol), $(dba)_3Pd_2.CHCl_3$ (0.120 g, 0.12 mmol) and cesium carbonate (2.56 g, 7.86 mmol) was added

dioxane (82 ml). The mixture was sonicated for 10 min, whereupon trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (prepared as described in WO 03/064431, 2.10 g, 6.81 mmol) was added in one portion. The resulting mixture was heated at 100°C for 4 h. The reaction mixture was filtrated through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was purified over SiO_2 (DCM-MeOH 19-1) to afford the title amide (reddish foam; 3.27 g, 6.32 mmol) as a 2-1 mixture of epimers.

MS (ESI, m/z): 477.0 [$M+H^+$].

36.iv. *(2S,5R,6S)-5-amino-6-[(2RS)-2,3-dihydroxy-propyl]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

Starting from intermediate 36.iii (2.72 g, 2.06 mmol), the title amine (1.27 g, 64% yield) was obtained as a reddish solid using the procedure of Example 1, step 1.viii. The compound was purified by chromatography using DCM-MeOH 6-1 containing 1% aq. NH_4OH as an eluent. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d6-DMSO) δ: 10.59 (s, 0.66H); 10.51 (s, 0.34H); 8.70 (d, J = 5.0 Hz, 1H); 8.45 (d, J = 5.0 Hz, 0.34H); 8.39 (d, J = 5.0 Hz, 0.66H); 8.28 (d, J = 9.0 Hz, 1H); 7.33 (d, J = 9.0 Hz, 1H); 4.50 (br s, 1H); 4.47 (dd, J = 4.3, 7.0 Hz, 0.34H); 4.31 (dd, J = 3.5, 9.0 Hz, 0.66H); 4.11 (m, 0.66H); 4.09 (s, 3 x 0.34H); 4.08 (s, 3 x 0.66H); 3.96 (m, 0.34H); 3.63 (m, 1H); 3.37-3.21 (m, 5H), 2.97 (m, 0.66H); 2.91 (m, 0.34H); 2.08 (m, 1H); 1.96 (m, 0.66H); 1.82-1.42 (m, 4.34H).

MS (ESI, m/z): 377.0 [$M+H^+$].

36.v. *(2S,5R,6R)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(2RS)-2,3-dihydroxy-propyl]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide*:

To a solution of intermediate 36.iv (1.0 g, 2.65 mmol) in 1,2-DCE (30 ml) and MeOH (10 ml) were added 3Å molecular sieves (10 g) and (*E*)-3-(2,5-difluoro-phenyl)-propenal (0.49 g, 1.1 eq). The mixture was heated at 50°C for 18 h. After cooling to 0°C, $NaBH_4$ (1 g) was added, and the reaction proceeded for 45 min. The reaction mixture was filtered and the solids were washed with DCM-MeOH (9-1, 200 ml). The filtrate was washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was chromatographed (DCM-MeOH 93-7 containing 0.7% aq. NH_4OH) to afford the title diol (1.1 g, 78% yield) as a colourless foam. The compound was obtained as a 2-1 mixture of epimers.

^1H NMR (d6-DMSO) δ: 10.64 (s, 0.66H); 10.56 (s, 0.34H); 8.69 (d. J = 5.0 Hz, 1H); 8.42 (d, J = 5.0 Hz, 0.34H); 8.37 (d, J = 5.0 Hz, 0.66H); 8.28 (d, J = 9.0 Hz, 1H); 7.49 (m, 1H);

7.32 (d, J = 9.0 Hz, 1H); 7.27 (m, 1H); 7.12 (m, 1H); 6.63 (d, J = 16.2 Hz, 1H); 6.49 (m, 1H); 4.52-4.42 (m, 3H); 4.26 (m, 1H); 4.06 (s, 3 x 0.34H); 4.04 (s, 3 x 0.66H); 3.65 (m, 1H); 3.44-3.24 (m, 4H); 2.81 (m, 1H); 2.12-1.41 (m, 7H).

MS (ESI, m/z): 529.0 [$M+H^+$].

36.vi. *[(2R,3R,6S)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-2-yl]-acetic acid*:

Starting from intermediate 36.v (1.1 g, 2.1 mmol), the title compound (0.080 g) was obtained as a white solid using the procedures described in Example 4, step 4.iii (Boc formation, 68% yield), Example 2, steps 2.v (aldehyde formation) and 2.vi (acid formation, 30% yield, two steps), and Example 35, step 35.vi (deprotection, 54% yield). The compound was purified by chromatography over SiO_2 using DCM-MeOH 6-1 containing 1% aq. NH_4OH after the last step.

MS (ESI, m/z): 513.4 [$M+H^+$].

Pharmacological properties of the invention compounds

In vitro assay

Experimental method:

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 Examples 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.	***S. aureus* A798**	***S. Pneumoniae* 49619**	***M. catarrhalis* A894**
1	<=.031	<=.031	<=.031
9	<=.031	<=.031	<=.031
16	0.063	1	0.25
21	0.125	0.5	<=.031

CLAIMS

1. A compound selected from the group consisting of:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S*,5*R*,6*R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;
- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine; and
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2R,3R,6S*)-2-(2-hydroxy-ethyl)-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amide;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- [(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(6-methoxy-[1,5]naphthyridin-4-ylcarbamoyl)-tetrahydro-pyran-2-yl]-acetic acid;

or a salt of one of these compounds.

2. A compound according to claim 1, which is selected from the group consisting of:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;

- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;

- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;

- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;

- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;

- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;

- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine; and
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

or a salt of one of these compounds.

3. A compound according to claim 1, which is selected from the group consisting of:

- (*E*)-2-{(2*R*,3*R*,6*R*)-(3-[3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-ethanol;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-acryloylamino]-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- (1*R*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- (1*S*)-2-{(2*S*,5*R*,6*S*)-5-[*trans*-3-(2,5-difluoro-phenyl)-allylamino]-6-hydroxymethyl-tetrahydro-pyran-2-yl}-1-(3-fluoro-6-methoxy-quinolin-4-yl)-ethanol;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- 2-{(2*R*,3*R*,6*S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(1*R*,2*R*)-1,2-dihydroxy-2-(3-methoxy-quinoxalin-5-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;
- {(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetic acid;
- 2-{(2*R*,3*R*,6*R*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 2-{(2*R*,3*R*,6*S*)-3-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*S*)-1-hydroxy-2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-tetrahydro-pyran-2-yl}-acetamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(2,5-difluoro-phenyl)-*N*-{(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;

- (2*S,5R,6R*)-(5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-(2-hydroxy-ethyl))-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-carboxylic acid (6-methoxy-[1,5]naphthyridin-4-yl)-amide;

- (1S)-1-{(2*S*,5*R*)-5-[(*E*)-3-(3-fluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-methoxy-quinolin-4-yl)-ethanol;

- 3-(2-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 3-(3-fluoro-phenyl)-*N*-{(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-(*E*)-acrylamide;

- 8-((1*R*,2*R*)-2-{(2*S*,5*R*)-5-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-1,2-dihydroxy-ethyl)-quinoline-2-carbonitrile;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;

- (1*R*,2*R*)-1-{(2*R*,5*S*)-5-[(E)-3-(2,5-difluoro-phenyl)-allylamino]-tetrahydro-pyran-2-yl}-2-(6-fluoro-quinolin-4-yl)-ethane-1,2-diol;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;

- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-yl}-amine;
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

or a salt of one of these compounds.

4. A compound according to claim 3, which is selected from the group consisting of:

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{3*R*,6*S*)-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-5-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- [(*E*)-3-(2,5-difluoro-phenyl)-allyl]-{(3*S*,6*R*)-(*E*)-6-[2-(6-fluoro-quinolin-4-yl)-vinyl]-tetrahydro-pyran-3-yl}-amine;
- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;
- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

or a salt of one of these compounds.

5. A compound according to claim 4, which is selected from the group consisting of:

- 2-{(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetamide;
- (*2R,3R,6S*)-{3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

- {(*2R,3R,6S*)-3-[(*E*)-3-(2,5-difluoro-phenyl)-allylamino]-6-[(*E*)-2-(6-methoxy-[1,5]naphthyridin-4-yl)-vinyl]-tetrahydro-pyran-2-yl}-acetic acid;

or a salt of one of these compounds.

6. A compound according to claim 1, which is selected from the group consisting of:

- {(2*R*,3*R*,6*R*)-6-[2-(3-methoxy-quinolin-5-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carbonyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- {(2*R*,3*R*,6*R*)-6-[2-(6-methoxy-[1,5]naphthyridin-4-yl)-ethyl]-3-[(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-ylmethyl)-amino]-tetrahydro-pyran-2-yl}-acetic acid;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*R*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(2*S*,3*R*,6*S*)-6-[(2*S*)-2-(3-fluoro-6-methoxy-quinolin-4-yl)-2-hydroxy-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2R*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxylic acid {(*2S,3R,6S*)-6-[(*2S*)-2-hydroxy-2-(3-methoxy-quinolin-5-yl)-ethyl]-2-hydroxymethyl-tetrahydro-pyran-3-yl}-amide;
- 7-fluoro-6-({(3*R*,6*S*)-6-[(1*S*)-1-hydroxy-2-(6-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-benzo[1,4]thiazin-3-one;
- 6-({(3*R*,6*S*)-6-[2-(6-fluoro-3-methoxy-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;
- 6-({3*S*,6*R*)-6-[2-(6-fluoro-quinolin-4-yl)-ethyl]-tetrahydro-pyran-3-ylamino}-methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

or a salt of one of these compounds.

7. As a medicament, a compound as defined in one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition containing, as active principle, a compound as defined in one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

9. Use of a compound according to one of claims 1 to 6, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the prevention or treatment of infection(s).