DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention provides novel phenicol derivatives, their use for the treatment of infections in mammals, pharmaceutical compositions containing these novel compounds, and methods for the preparation of these compounds.

BACKGROUND OF THE INVENTION

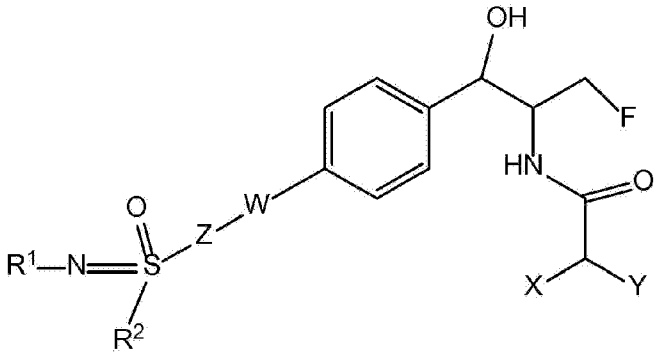
[0002] There is a growing need for new antibiotic agents for the treatment of bacterial infections in animals, and in particular there is a need for new agents which overcome increasing bacterial resistance to existing antibiotics.

[0003] Florfenicol is a broad spectrum phenicol antibiotic used exclusively in veterinary medicine. Phenicol antibiotics as a class are potent inhibitors of bacterial protein biosynthesis. Florfenicol has a broad spectrum of activity against many gram-negative and gram-positive bacteria, and is useful in the prevention and treatment of bacterial infections due to susceptible pathogens in birds, reptiles, fish, shellfish and mammals. An important use of florfenicol is in the treatment of respiratory infections in cattle, such as those caused by, for example, *Mannheimia haemolytica, Pasteurella multocida* and *Haemophilus somnus*. Effective treatment of bovine respiratory disease (BRD) plays a significant role in reducing what is otherwise one of the leading causes of economic loss to both the dairy and beef industries worldwide.

[0004] WO2003/077828 describes certain aryl and heteroaryl sulfone and cyano analogs of phenicol as antibacterial agents. WO2012/125832 describes certain aryl and heteroaryl amines, nitrates, and sulfone analogs of phenicol as antibacterial agents. EP0014437A2 describes certain aryl-acylamido-propanols as broad spectrum antibiotics. Reports in recent years indicate that bacterial resistance to florfenicol is developing and has been observed across multiple bacterial genera and species, such as *Salmonella* (Bolton, L. F., et al., Clin. Microbiol., 1999, 37, 1348), *E. coli* (Keyes, K., et al., Antimicrob. Agents Chemother., 2000, 44, 421), *Klebsiella pneumoniae* (Cloeckaert, A., et al., Antimicrob. Agents Chemother., 2001, 45, 2381), and in the aquacultural pathogen, *Photobacterium damselae* subsp. *piscicida* (formerly *Pasteurella piscicida*) (Kim, E., et al., Microbiol. Immunol., 1996, 40, 665). In light of the increasing threat of florfenicol resistance and the apparent mobility of the resistance genes across bacterial species and animal hosts (Cloeckaert, A., et al., Antimicrob. Agents Chemother., 2000, 44, 2858), there is an important need for new antibiotics that maintain or surpass the activity of florfenicol, while also overcoming the challenges of florfenicol resistance. The compounds of the present invention represent such an improvement.

SUMMARY OF THE INVENTION

[0005] The present invention provides for compounds of formula I



I

wherein R^1 is

1. a) -H,
2. b) -C(O)-R^3,
3. c) -C_1-C_6 alkyl, or
4. d) -CN;

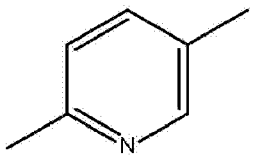
R^2 is

1. a) -C_1-C_6 alkyl optionally substituted with one to three halo, or
2. b) cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

R^3 is -C_1-C_6 alkyl;

W is

1. a)



or

2. b) absent;

X and Y are each independently halo;

Z is

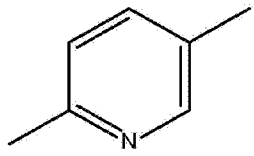
1. a) -C_1-C_2 alkyl-,
2. b) cylopropyl or cyclobutyl, or

3. c) absent;

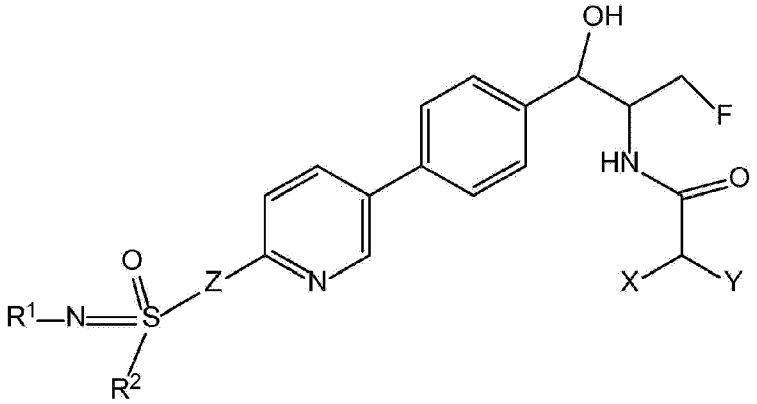
or a pharmaceutical acceptable salt thereof.

[0006] More particularly, the present invention provides for compounds of formula I wherein X and Y are each chloro, or X and Y are each fluoro.

[0007] The present invention also provides for compounds of formula I wherein W is



[0008] Thus, the present invention provides for compounds of formula II

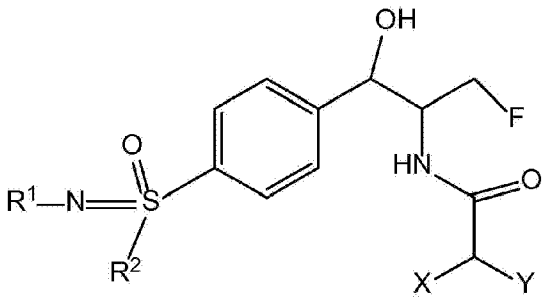


II

[0009] More particularly, the present invention provides for compounds of formula II wherein R^1 is -H or -CN, R^2 is $-CH_3$, and Z is $-CH_2-$ or absent.

[0010] Also, the present invention provides for compounds of formula I wherein W is absent and Z is absent.

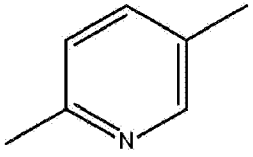
[0011] Thus, the present invention provides for compounds of formula III



III

[0012] More particularly, the present invention provides for compounds of formula III wherein R^1 is -H or -CN and R^2 is $-CH_3$ or $-CH_2$-F.

[0013] Also, the present invention provides for compounds of formula I wherein W is



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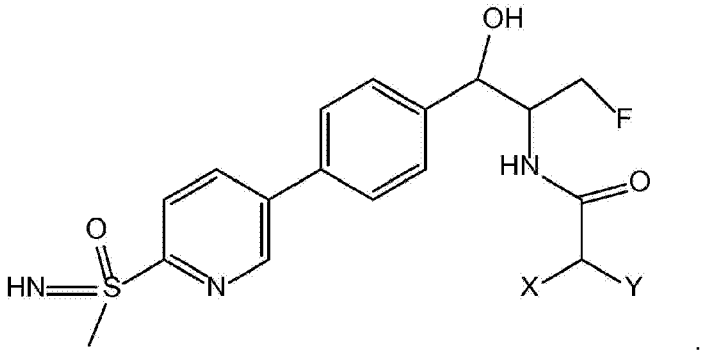
Z is absent, R^1 is -H, and R^2 is $-CH_3$.

[0014] Thus, the present invention provides for compounds of formula IV



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IV

[0015] More particularly, the present invention provides for compounds of formula IV wherein X and Y are each chloro or X and Y are each fluoro.

[0016] In another aspect, the present invention also provides for:

pharmaceutical compositions which comprise a pharmaceutically acceptable carrier and a compound of formula I (including compounds of formula II, III and IV);

compounds or pharmaceutical compositions as provided herein for use as a medicament. The use as a medicament comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula I (including compounds of formula II, III and IV) or a pharmaceutically acceptable salt thereof;

compounds or pharmaceutical compositions as provided herein for use in controlling or treating bovine respiratory disease infections in livestock. The use comprises administering to an animal in need thereof a therapeutically effective amount of a compound of formula I (including compounds of formula II, III and IV) or a pharmaceutically acceptable salt thereof.

[0017] Also disclosed herein are methods for the preparation of compounds of the present invention.

DETAILED DESCRIPTION

[0018] With respect to the above compound, and throughout the application and claims, the following terms have the meanings defined below.

[0019] The term "halo" refers to chloro, bromo, fluoro, and iodo.

[0020] The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-4} alkyl refers to alkyl of one to four carbon atoms, inclusive; C_{1-6} alkyl refers to alkyl of one to six carbon atoms, inclusive; and C_{1-8} alkyl refers to alkyl of one to eight carbon atoms, inclusive.

[0021] The term alkyl refers to straight or branched monovalent hydrocarbon groups, and reference to an individual radical such as "propyl" embraces the straight chain radical or a branched chain isomer such as "isopropyl".

[0022] The term "cycloalkyl" refers to a mono ring such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0023] The term "mammal" refers to human or animals including livestock and companion animals. The phrase "companion animal" or "companion animals" refers to animals kept as pets. Examples of companion animals include cats, dogs, and horses. The term "livestock" refers to animals reared or raised in an agricultural setting to make products such as food or fiber, or for its labor. In some embodiments, livestock are suitable for consumption by mammals, for example humans. Examples of livestock animals include mammals, such as cattle, goats, horses, pigs, sheep, including lambs, and rabbits, as well as birds, such as chickens, ducks and turkeys. Specifically, livestock animals of the present invention refer to cattle and pigs. The compounds of the present invention may also be useful in aquaculture, such as fish.

[0024] The term "controlling", "treating" or "treatment" of a disease includes: (1) preventing the disease, i.e. causing the clinical symptoms or signs of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms/signs of the disease; (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms/signs; or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms/signs.

[0025] The term "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0026] The term "pharmaceutically acceptable" means suitable for use in mammals, companion animals or livestock animals.

[0027] Included within the scope of the compounds described herein are *cis*-, trans-isomers, enantiomers, and diastereomers both alone and as any mixtures. All of these forms, including enantiomers, diastereomers, cis, trans, syn, anti, solvates (including hydrates), tautomers, and mixtures thereof, are included in the described compounds.

[0028] A specific value for X is halo.

[0029] A specific value for Y is halo.

[0030] A specific value for X and Y is chloride.

[0031] A specific value for X and Y is fluoride.

[0032] Examples of compounds of the present invention include the following: 2,2-difluoro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamide and 2,2-dichloro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamide.

[0033] The reaction schemes below illustrate the general synthetic procedures of the compounds of the present invention. All starting materials are prepared by procedures described in these schemes or by procedures known to one of ordinary skill in the art.

Pharmaceutical Salts

[0034] The compound of formula I may be used in its native form or as a salt. In cases where forming a stable nontoxic acid or base salt is desired, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Pharmaceutically acceptable salts of the compounds of formula I include the acetate, ascorbate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, etoglutarate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, glycerophosphate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Composition/Formulation

[0035] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

[0036] Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compound into preparations, which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remington's Pharmaceutical Sciences", Mack Pub. Co., New Jersey (1991).

[0037] The formulations of the invention can be designed to be short-acting, fast-releasing, long-acting, extended-releasing, or controlled-releasing. Specifically, the formulation of the invention can be an extended release form. Thus, the pharmaceutical formulations can also be formulated for controlled release or for slow release.

Dosage

[0038] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.,* control or the treatment of infections. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms/signs of infections or prolong the survival of the subject being treated.

[0039] The quantity of active component, which is the compound of this invention, in the pharmaceutical composition and unit dosage form thereof, may be varied or adjusted widely depending upon the manner of administration, the potency of the particular compound and the desired concentration. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, the quantity of active component will range between 0.01% to 99% by weight of the composition.

[0040] Generally, a therapeutically effective amount of dosage of active component will be in the range of about 0.1 mg to about 100 mg/kg of body weight/day; for example, about 0.1 to about 50 mg/kg of body weight/day; and for example, about 5 to about 50 mg/kg of body weight/day; and, for example, about 20 to about 50 mg/kg of body weight/day. It is to be

understood that the dosages may vary depending upon the requirements of each subject and the severity of the infections.

[0041] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired plasma concentration. On the other hand, the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

Medical and Veterinary Uses

[0042] Compounds of the present invention provides novel phenicol antibacterial agents for the treatment of bovine respiratory disease infections in cattle caused by Gram-negative respiratory pathogens, such as *M. haemolytica, P. multocida, H. somnus, and M. bovis.*

Antibacterial Assays

[0043] Compounds of the present invention are tested against an assortment of Gram-negative and Gram-positive organisms using the industrial standard techniques described in M31-A3. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Clinical and Laboratory Standards Institute, Approved Standard-Third Edition. The compounds of the present invention demonstrate very good antibacterial activity against BRD pathogens, for example, *M. haemolytica, P. multo., H. somnus and M. bovis.*

Examples

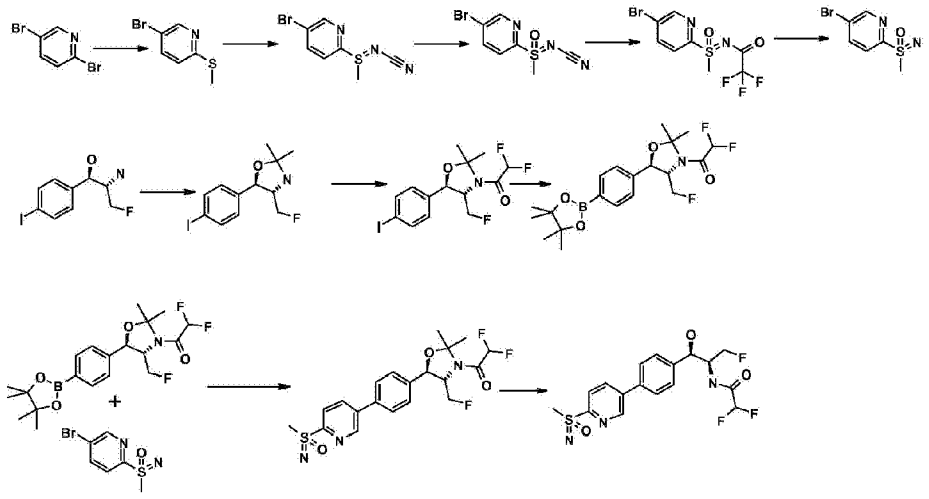
[0044] The synthesis of compounds of the present invention is further illustrated by the following examples. The starting materials and various intermediates utilized in the examples may be obtained from commercial sources, or are readily prepared from commercially available organic compounds, using well-known methods to one skilled in the art. Additional compounds of the present invention can be prepared by using procedures described in the following references: N-acylation: Synthesis, (7), 879-887, 2002; Synlett, (3), 361-364, 2011; Advanced Synthesis & Catalysis, 355(8), 1490-1494, 2013; and N-alkylation: Journal of Organic Chemistry, 58(7), 1922-1923, 1993; Synthesis, (7), 879-887; 2002.

Example 1 Preparation of 2, 2-difluoro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(6-(S-

methylsulfonimidoyl)pyridin-3-yl)phenyl)propan-2-yl)acetamide

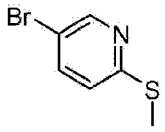
[0045]

Scheme 1



Step-1 Preparation of 5-Bromo-2-methylsulfanyl-pyridine

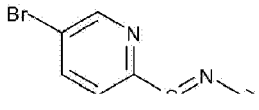
[0046]



[0047] To a solution of 2,5-Dibromo-pyridine (6g, 25.327 mmol) in DMF (60 mL) is added sodium thiomethoxide (1.95g, 27.86mmol) at 0°C. Reaction mixture is allowed to come to room temperature and resulting reaction mixture is stirred at room temperature for 12h. Reaction mixture is quenched with water and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by column chromatography using silica (100-200) mesh size and using 4% ethyl acetate in hexane as an eluent to get (4.5g) of yellow solid title compound. ^{1}H-NMR (400 MHz, DMSO) δ: 2.49 (s, 3H), 7.29 (d, 1H, *J*=8.76 Hz), 7.85-7.88 (dd, 1H, *J1*=2.44Hz, *J2*=8.48Hz), 8.55 (d, 1H, *J*=2.4 Hz). LC-MS (*m/z*): M+H = 206.1.

Step-2 Preparation of 5-bromo-2-N-(cyano) methyl pyridine sulfilimine

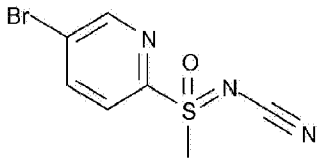
[0048]



[0049] To a solution of 5-Bromo-2-methylsulfanyl-pyridine (4.5g, 22.059mmol) in methanol (50 mL) is added t-BuOK (2.965g, 26.471mmol), NH_2CN (50% aqueous solution) (2.638g, 28.676mmol) and NBS (5.89g, 33.088mmol) at 0°C. The resulting reaction mixture is stirred at 0°C for 1h. Solvent is evaporated *in vacuo,* reaction mixture is quenched with aqueous sodium metabisulphate solution and extracted with DCM. Organic layer is dried over sodium sulphate, concentrated and purified by silica gel column chromatography (100-200 mesh size) using 3% methanol in DCM as an eluent to give the title compound (4.7g) as a yellow solid. LC-MS (*m/z*): M+H = 243.8.

Step-3 Preparation of 5-bromo-2-N-(cyano) methyl pyridine sulfoximine

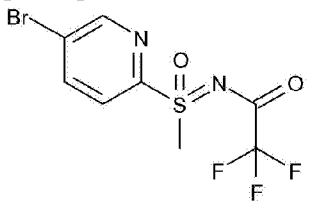
[0050]



[0051] To a solution of 5-bromo-2-N-(cyano) methyl pyridine sulfilimine (4.7g, 19.262mmol) in ethanol (50mL) is added K_2CO_3 (7.975gm, 57.787mmol) followed by mCPBA (6.645gm,38.525mmol) at 0°C. The resulting reaction mixture is stirred at 0°C for 10h. Solvent is evaporated *in vacuo,* reaction mixture is quenched with water and extracted with DCM. Organic layer is dried over sodium sulphate, concentrated and purified by silica gel column chromatography (100-200 mesh size) using 50% ethyl acetate in n-Hexane as an eluent to give the title compound (2.1g) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO) δ: 3.75 (s, 3H), 8.18 (d, 1H, *J*=8.44Hz), 8.55-8.58 (dd, 1H, *J1*=2.2 Hz, *J2*=8.48Hz), 9.09 (d, 1H, *J*=2.24Hz), LC-MS (*m/z*): M+H = 259.7.

Step-4 Preparation of 5-bromo-2-N-(trifluoroacetyl) methyl pyridine sulfoximine

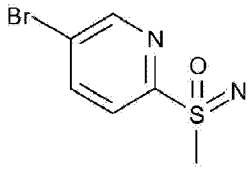
[0052]



[0053] To a solution of 5-bromo-2-N-(cyano) methyl pyridine sulfoximine (1g, 3.846mmol) in DCM (10 mL) is added Trifluoroacetic anhydride (1.615mL, 11.538mmol) at 0°C. Reaction mixture is allowed to stir at room temperature for 8h. Excess of Trifluoroacetic acid and DCM is evaporated in *vacuo*. Reaction crude is taken in water and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by silica gel column chromatography (100-200 mesh size) using 20% ethyl acetate in n-Hexane as an eluent to give (560mg) the title compound as a yellow solid. ^{1}H-NMR (400 MHz, DMSO) δ: 3.75 (s, 3H), 8.19 (d, 1H, *J*= 8.44 Hz), 8.53-8.56 (dd, 1H, *J1*= 2.32Hz, *J2*= 8.4Hz), 9.03 (d, 1H, *J*= 2.16 Hz). LC-MS (*m/z*): M+H = 333.0.

Step-5 Preparation of 5-bromo-2-NH-methyl pyridine sulfoximine

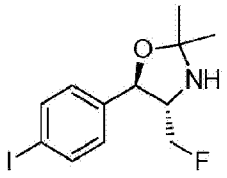
[0054]



[0055] To a solution of 5-bromo-2-N-(Trifluoroacetyl) methyl pyridine sulfoximine (560mg, 1.692mmol) in Methanol (8 mL) is added K_2CO_3 (1167mg, 8.459mmol) at 0°C. Reaction mixture is allowed to stir at room temperature for 2h. Solvent is evaporated in *vacuo* to give the title compound as a yellow solid (340mg). ^{1}H-NMR (400 MHz, DMSO) δ: 3.15 (s, 3H), 4.55 (bs, 1H), 8.0 (d, 1H, *J*=8.32Hz), 8.35-8.38 (dd, 1H, *J1*= 2.36Hz, *J2*= 8.44 Hz), 8.87 (d, 1H, *J*= 2.08Hz). LC-MS (*m/z*): M+H = 237.0.

Step-6 Preparation of (4S,5R)-4-(fluoromethyl)-5-(4-iodophenyl)-2,2-dimethyloxazolidine

[0056]

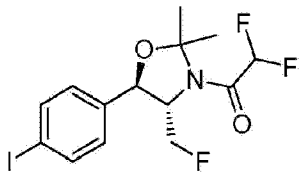


[0057] Acetone (150mL) is added to commercially available (1R,2S)-2-amino-3-fluoro-1-(4-iodophenyl)propan-1-ol (15.0 g, 50.8 mmol). After stirring overnight at room temperature the solvent is removed under reduced pressure to give the title compound (17.6 g): *m/z* (CI) M+H 335.

Step-7 Preparation of 2,2-difluoro-1-((4S,5R)-4-(fluoromethyl)-5-(4-iodophenyl)-2,2-

dimethyloxazolidin-3-yl)ethanone

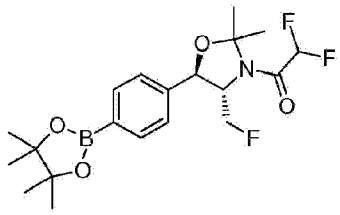
[0058]



[0059] To a stirring solution of the product of Step 6 (3.0 g, 8.9 mmol) in CH_2Cl_2 (50 mL) at 0°C is added triethylamine (6.2 mL, 44.8 mmol) followed by dropwise addition of difluoroacetyl chloride (2.2 mL, 27.0 mmol). The reaction mixture is slowly allowed to warm to room temperature. After 1 hour the reaction mixture is diluted with water (75 mL) and extracted with CH_2Cl_2 (2 x 75 mL). The combined organic phase is dried over $MgSO_4$ and concentrated under vacuum. The crude material is chromatographed (80 g Redi-Sep column) eluting from 100% hexanes to 25:75 EtOAc:hexanes to afford the title compound (3.54 g): *m/z* (CI) M+H 413.0.

Step-8 Preparation of 2,2-difluoro-1-((4S,5R)-4-(fluoromethyl)-2,2-dimethyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-3-yl)ethanone

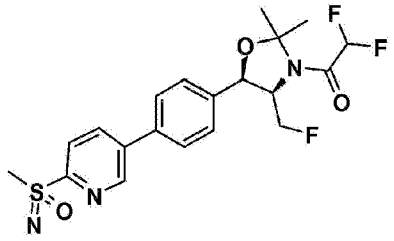
[0060]



[0061] To a solution of the product of Step 7 (3.5 g, 8.4 mmol) in dioxane (100 mL) is added bis(pinacolato)diboron (2.4 g, 9.3 mmol), potassium acetate (2.5 g, 25.4 mmol), and $Pd(PPh_3)_2Cl_2$ (300 mg, 0.4 mmol). The reaction is heated to 90°C under nitrogen for 22 hours. Reaction mixture is cooled to room temperature and concentrated under vacuum to remove dioxane to a volume of ~50 mL. The residue is diluted with water (150 mL) and extracted with CH_2Cl_2 (2 x 125 mL). The combined organic phases are dried over Na_2SO_4 and concentrated under vacuum. The crude material is purified by chromatography (120g Redi-Sep column) eluting from 100% hexanes to 25:75 EtOAc:hexanes to the title compound (2.06 g): *m/z* (CI) M+H 413.2.

Step-9 Preparation of 2,2-difluoro-1-((4R,5R)-4-(fluoromethyl)-2,2-dimethyl-5-(4-(6-(methylsulfonimidoyl)pyridin-3-yl)phenyl)oxazolidin-3-yl)ethanone

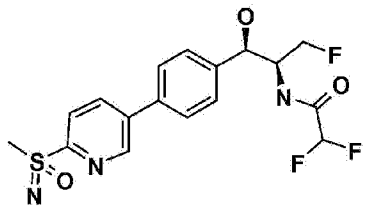
[0062]



[0063] To a stirred solution of 2,2-Difluoro-1-{(4R,5R)-4-fluoromethyl-2,2-dimethyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-oxazolidin-3-yl}-ethanone (250mg, 0.605mmol) and 5-bromo-2-NH-methyl pyridine sulfoximine (170.70mg, 0.726 mmol) in 1,4-Dioxane:water (5mL:5mL) is added K_2CO_3 (250.60mg, 1.816mmol) at room temperature. The resulting reaction mixture is degassed with nitrogen for 15minutes then $Pd(dppf)_2 \cdot Cl_2$ (44.24mg, 0.061mmol) is added and heated to 80°C for 8h. Solvent is evaporated *in vacuo* and the crude material is diluted using water and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by silica gel column chromatography (100-200 mesh size) using 2% methanol in DCM as an eluent to afford the title compound (250mg) as yellow solid. LC-MS (*m/z*): M+H = 442.1.

Step-10 Preparation of 2,2-difluoro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)pyridin-3-yl)phenyl)propan-2-yl)acetamide

[0064]



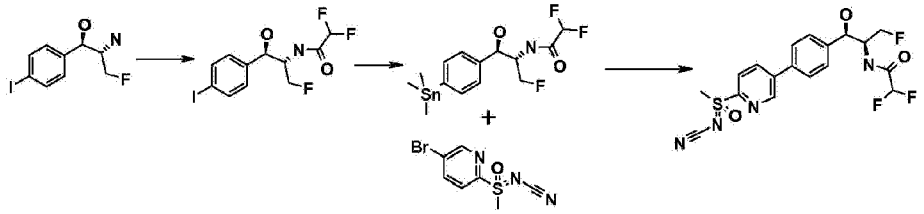
[0065] To a stirred solution of 2,2-difluoro-1-((4R,5R)-4-(fluoromethyl)-2,2-dimethyl-5-(4-(6-(methylsulfonimidoyl)pyridin-3-yl)phenyl)oxazolidin-3-yl)ethanone (250mg, 0.567mmol) in DCM (8mL) is added TFA (1mL) at 0°C. The reaction mixture is allowed to stir at room temperature for 4h. Volatiles are removed under reduced pressure and crude is diluted using aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by silica gel column chromatography (100-200 mesh size) using 8% methanol in DCM as an eluent to afford the title compound (170mg) as a brown solid. ^{1}NMR (400 MHz, DMSO) δ: 3.19 (d, 3H, *J*= 0.76Hz), 4.32-4.37 (m, 1.5H), 4.42-4.46 (m, 0.5H), 4.48 (bs, 1H), 4.53-4.56 (m, 0.5H), 4.66-4.69 (m, 0.5H), 4.91 (t, 1H), 5.97 (d, 1H, *J*=4.48Hz),

6.20 (t, 1H, *J*=53.72Hz), 7.51 (d, 2H, *J*=8.24Hz), 7.79 (d, 2H, *J*=8.28Hz), 8.12 (d, 1H, *J*=8.24Hz), 8.36-8.39 (dd, 1H, *J1*=2.32Hz, *J2*=8.24Hz), 8.87 (d, 1H, *J*=8.64Hz), 9.03 (d, 1H, *J*=1.76Hz). LC-MS (*m/z*): M+H = 402.1.

Example 2 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6-N-(cyano) methyl pyridine sulfoximine-3-yl)-phenyl]-ethyl}-acetamide

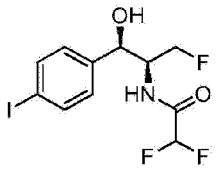
[0066]

Scheme 2



Step-1 Preparation of 2,2-difluoro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-iodophenyl)propan-2-yl)acetamide

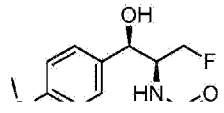
[0067]



[0068] To the solution of (1R,2S)-2-amino-3-fluoro-1-(4-iodophenyl)propan-1-ol (20.0 g, 67.8 mmol) in methanol (250 mL) is added triethylamine (15 g, 148.5 mmol) and ethyldifluoro acetate (18 g, 148.4 mmol) and reaction mixture is stirred at room temperature for 16 hours. The solvent is evaporated *in vacuo* and the crude material purified by column chromatography on silica gel using MeOH/DCM afford the title compound (18.3g): 1H NMR (400 MHz, $CDCl_3$) 7.72 (2H, d), 7.13 (2H, d), 6.78 (1H, d), 5.85 (1H, t), 5.06 (1H, s), 4.67-4.28 (3H, m), 2.58 (1H, s).

Step-2 Preparation of 2,2-difluoro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(trimethylstannyl)phenyl)propan-2-yl)acetamide

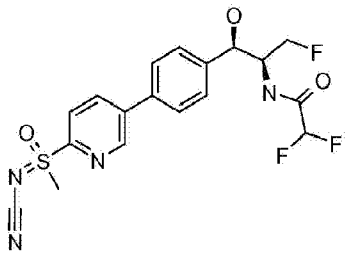
[0069]



[0070] Hexamethylditin (9.9g, 29.9mmol) is added to a deoxygenated solution of the product of Example 17 - Step 2 (10.6g, 28.5mmol), dichlorobis(triphenylphosphine)palladium (490mg, 0.68mmol) in dioxane (143mL) and the mixture heated to 80C for 1 hour. After cooling to r.t. the mixture is purified using column chromatography eluting from neat heptanes to neat EtOAc to give the title compound (9.3g): 1H NMR (400 MHz, $CDCl_3$) 7.27 (2H, d), 7.09 (2H, d), 6.59 (1H, d), 5.62 (1H, t), 4.81-4.79 (1H, t), 4.44-4.08 (3H, m), 2.20 (1H, d), 0.14-0.00 (9H, m).

Step-3 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6-N-(cyano) methyl pyridine sulfoximine-3-yl)-phenyl]-ethyl}-acetamide

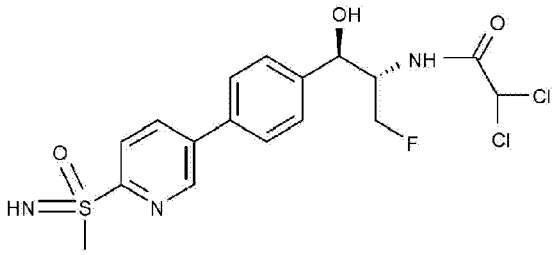
[0071]



[0072] To a solution of 2,2-Difluoro-N-[(1S,2R)-1-fluoromethyl-2-hydroxy-2-(4-trimethylstannanyl-phenyl)-ethyl]-acetamide (500mg,1.22mmol) in 1,4 Dioxane (10 mL) is added 5-bromo-2-N-(cyano) methyl pyridine sulfoximine (380mg,1.463mmol) at room temperature. Reaction mixture is degassed with nitrogen for 10minutes followed by addition of Pd(pph3)2.Cl2 (85mg,0.122mmol) and resulting reaction mixture is heated at 50°C for 8h. After completion of reaction diluted with water and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, evaporated in *vacuo* and purified by silica gel column chromatography (100-200 mesh size) using 3% methanol in DCM as an eluent to give (300mg) as a yellow liquid compound which is repurified by preparative HPLC to afford the title compound (135mg) as off white solid. ^{1}H-NMR (400 MHz, DMSO) δ: 3.77 (s, 3H), 4.32-4.35 (m, 1.5H), 4.42-4.47 (m, 0.5H), 4.56-4.57 (m, 0.5H), 4.67-4.70 (m, 0.5H), 4.93 (bs, 1H), 6.00 (bs, 1H), 6.20 (t, 1H, J = 53.72 Hz), 7.54 (d, 2H, J = 8.32 Hz), 7.88 (d, 2H, J = 8.32 Hz), 8.28 (d, 1H, J = 8.28 Hz), 8.56-8.58 (dd, 1H, J1= 2.24Hz, J2= 8.32Hz), 8.89 (d, 1H, J = 8.56 Hz), 9.24(d, 1H, J = 1.84 Hz). LC-MS (*m/z*): M+H = 427.1. HPLC = 97.19%.

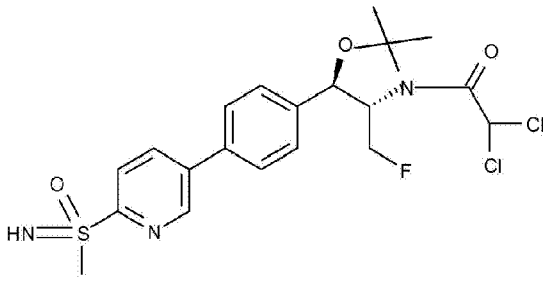
Example 3 Preparation of 2,2-dichloro-N-((1R,2S)-3-fluoro-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)pyridin-3-yl)phenyl)propan-2-yl)acetamide

[0073]



Step-1 Preparation of 5-{4-[(4S,5R)-3-(dichloroacetyl)-4-(fluoromethyl)-2,2-dimethyl-1,3-oxazolidin-5-yl]phenyl}-2-(S-methylsulfonimidoyl)pyridine

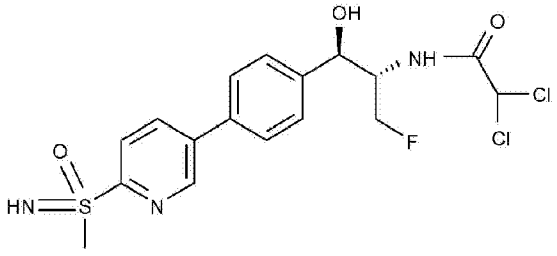
[0074]



[0075] Following the general procedure of Example 1 (Steps 1-6) and making non-critical variations but using 5-bromo-2-(S-methylsulfonimidoyl)pyridine 145 mg), the title compound is obtained (118 mg, 50%) as a tan solid, MS (ESI+) *m/z* 474 [M+H].

Step-2 Preparation of 2,2-dichloro-N-[(1S,2R)-1-(fluoromethyl)-2-hydroxy-2-{4-[6-(S-methylsulfonimidoyl)pyridin-3-yl]phenyl}ethyl]acetamide

[0076]



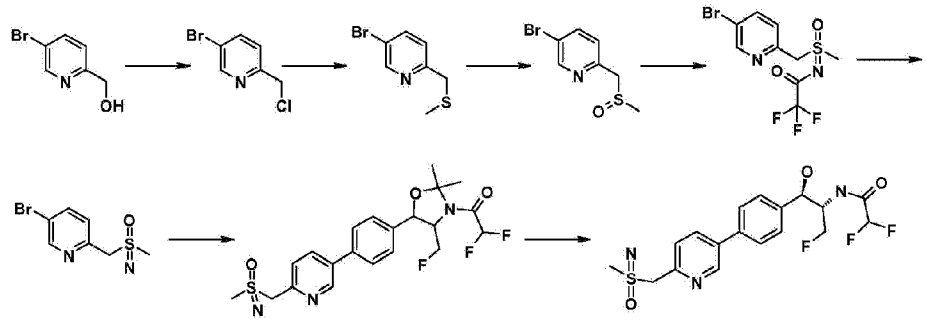
[0077] Following the general procedure of Example 1 (Step 7) and making non-critical variations but using 5-{4-[(4S,5R)-3-(dichloroacetyl)-4-(fluoromethyl)-2,2-dimethyl-1,3-oxazolidin-5-yl]phenyl}-2-(S-methylsulfonimidoyl)pyridine (Step 1, 115 mg) and purification by silica gel chromatography (40 g, 1-4% methanol/methylene chloride eluent), the title compound

is obtained (83 mg, 79%) as a glass, ^{1}H NMR (400 MHz, DMSO) d 3.20 (s, 3H), 4.25 (m, 1.5H), 4.45 (m, 0.5H), 4.48 (m, 1H), 4.59 (m, 0.5H), 4.71 (m, 0.5H), 4.94 (m, 1H), 6.05 (d, 1H), 6.53 (s, 1H), 7.52 (d, 2H), 7.79 (d, 2H), 8.12 (d, 1H), 8.37 (dd, 1H), 8.66 (bd, 1H), 9.03 (s, 1H). MS (ESI+) *m/z* 434 [M+H].

Example 4 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6(S-methylsulfonimidoylmethyl) pyridine-3-yl)-phenyl]-ethyl}-acetamide

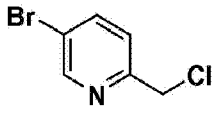
[0078]

Scheme 3



Step-1 Preparation of 5-Bromo-2-chloromethyl-pyridine

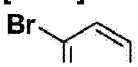
[0079]

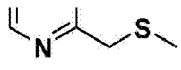


[0080] To the stirred solution of (5-Bromo-pyridin-2-yl)-Methanol (5gm, 26.59mmol, 1eq) in DCM (50mL) at 0°C is added Thionyl chloride (3mL) drop wise at RT then stirred at RT for 4h. After completion, the reaction mixture quenched with saturated sodium bicarbonate solution and extracted with DCM (3X100mL). The combined organic layer dried over sodium sulphate and evaporated under reduced pressure. The crude is purified by column chromatography using silica 100-200 mesh using 10% EtOAc: Hexane as eluent to afford title compound (4g) as brown colored liquid. 1NMR (400 MHz, DMSO) δ: 4.77 (s, 2H), 7.54 (d, *J* = 8.64Hz, 1H), 8.09-8.12 (dd, *J1* = 2.4Hz, *J2* = 8.32Hz, 1H), 8.70 (d, *J* = 5.96Hz, 1H).

Step-2 Preparation of 5-Bromo-2-methylsulfanylmethyl-pyridine

[0081]

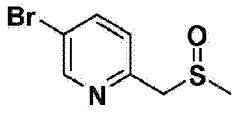




[0082] To the stirred solution of 5-Bromo-2-chloromethyl-pyridine (3.5gm, 16.99mmol) in DMF (25mL) at 0°C is added Sodium thiomethoxide (1.31gm, 18.68mmol) resulting reaction mixture is stirred at 0°C for 2h. After completion quenched with water and extracted with ethyl acetate (3X100mL). The Combined organic layer is washed with brine and organic layer dried over sodium sulphate, evaporate under reduced pressure. The crude is purified by column chromatography using silica 100-200mesh using 10% EtOAc: Hexane as eluent to afford title compound (3g) as brown colored liquid. 1NMR (400 MHz, DMSO) δ: 2.00 (s, 3H), 3.75 (s, 2H), 7.39 (d, *J*= 8.32 Hz, 1H), 7.99-8.02 (dd, *J1* = 2.44Hz, *J2* = 8.32Hz, 1H), 8.60 (d, *J* = 2.28Hz, 1H). LC-MS (*m/z*): M+H = 220.1.

Step-3 Preparation of 5-Bromo-2-methanesulfinylmethyl-pyridine

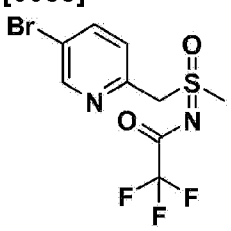
[0083]



[0084] To the stirred solution of 5-Bromo-2-methylsulfanylmethyl-pyridine (1.1gm, 5.04mmol) in MeOH: water (10:2mL) at 0°C is added sodium periodate (1.08gm, 5.046mmol) resulting reaction mixture is stirred RT for 5h. After completion, solvent is evaporated under reduced pressure then residue is diluted with water and extract with EtOAc (3X50mL). The combine organic layer is dried over sodium sulphate and evaporated under reduced pressure to get crude which is purified by combi flash using 8% MeOH:DCM as eluent to afford title compound (900mg) as off white solid. 1NMR (400 MHz, DMSO) δ: 2.56 (s, 3H), 4.11 (d, *J* =12.6 Hz, 1H), 4.26 (d, *J* = 12.64Hz, 1H), 7.36 (d, *J* = 8.28Hz, 1H), 8.05-8.08 (dd, *J1* = 2.44Hz, *J2* = 8.28Hz, 1H), 8.71 (d, *J* = 2.32Hz, 1H). LC-MS (*m/z*): M+H = 235.9.

Step-4 Preparation of 5-bromo-2-N-[(Trifluoroacetyl)methyl]-methyl pyridine sulfoximine

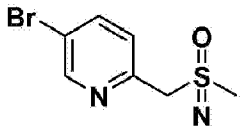
[0085]



[0086] To the stirred of 5-Bromo-2-methanesulfinylmethyl-pyridine (500mg, 2.13mmol) in DCM (10mL) at 0°C is added Triflouro acetamide (482mg, 4.2mmol), MgO (344mg, 8.55mmol) and Rh2 (OAC) 4 (28mg, 0.64mmol) at RT then resulting reaction mixture is stirred RT for 16h. After completion, reaction is quenched with water and extract with EtOAc (3X25mL). The combine organic layer is dried over sodium sulphate and evaporated under reduced pressure. The crude is purified by combi flash using 30% EtOAc: Hexane as eluent to afford title compound (300mg) as yellow colored solid. 1NMR (400 MHz, DMSO) δ: 3.56 (s, 3H), 5.22-5.31 (m, 2H), 7.50 (d, *J* = 8.32Hz, 1H), 8.17-8.20 (dd, *J1* = 2.4 Hz, *J2* = 8.28Hz, 1H), 8.77 (d, J = 2.28, 1H). LC-MS (*m/z*): M+H = 245.0.

Step-5 Preparation of 5-bromo-2-(S-methylsulfonimidoylmethyl) pyridine

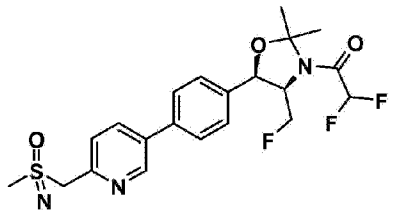
[0087]



[0088] To the stirred solution of 5-bromo-2-N-[(Trifluoroacetyl) methyl]-methyl pyridine sulfoximine (300mg, 0.87mmol) in MeOH (2mL) at 0°C is added K2CO3 (600mg, 4.38mmol) resulting reaction mixture stirred RT for 30min. After completion, solvent is evaporated under reduced pressure then water is added to the residue and extract with Ethyl acetate (3X25mL). The combine organic layer is dried over sodium sulphate and evaporated under reduced pressure to afford title compound (110mg) as yellow colored solid. 1NMR (400 MHz, DMSO) δ: 2.87 (s, 3H), 3.80 (bs, 1H), 4.46-4.56 (m, 2H), 7.47 (d, *J* = 8.36Hz, 1H), 8.08-8.811 (dd, *J1* = 2.4Hz, *J2* = 8.28Hz, 1H), 8.70 (d, J = 2.28Hz, 1H). LC-MS (*m/z*): M+H = 250.9.

Step-6 Preparation of 2, 2-Difluoro-1-{(4R, 5R)-4-fluoromethyl-5-[4-(6-(S-methylsulfonimidoylmethyl)-pyridin-3-yl)-phenyl]-2, 2-dimethyl-oxazolidin-3-yl}-ethanone

[0089]

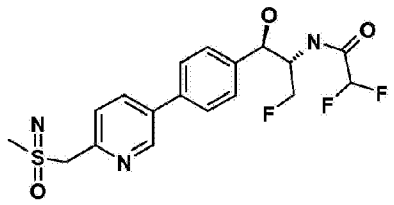


[0090] To the degassed (30min with nitrogen) solution of 2,2-Difluoro-1-{(4R,5R)-4-fluoromethyl-2,2-dimethyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-

oxazolidin-3-yl}-ethanone (100mg, 0.242mmol, 1eq), 5-bromo-2-(S-methylsulfonimidoylmethyl) pyridine (60mg, 0.242mmol,1eq) and K2CO3 (100mg, 0.726mmol, 3eq) in Dioxane:water (1mL:0.2mL) is addition of PdCl2(dppf)2 (17mg, 0.024mmol, 0.1eq) at RT. The resulting reaction is stirred at 80°C for 16h. After completion, reaction quenched with water and extracted with ethyl acetate (3X25mL). The combine organic layer is dried over sodium sulphate and evaporated under reduced pressure to get crude which is purified by combi flash using 5% MeOH:DCM as eluent to afford title compound (100mg) as sticky brown colored liquid. 1NMR (400 MHz, DMSO) δ: 1.53 (s, 3H), 1.60 (s, 3H), 2.91 (s, 3H), 3.81 (s, 1H), 3.94 (s, 1H), 4.52-4.61 (m, 2H), 4.69-4.70 (m, 1H), 4.82-4.84 (m , 0.5H), 4.91-4.95 (m, 0.5H), 5.27 (d, *J* = 3.4 Hz, 1H), 6.64 (t, *J* = 52.76Hz, 1H), 7.57-7.62 (m, 3H), 7.82 (d, *J* = 8.16Hz, 2H), 8.14-8.16 (m, 1H), 8.91 (s, 1H). LC-MS (*m/z*): M+H = 456.0

Step-7 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6(S-methylsulfonimidoylmethyl) pyridine-3-yl)-phenyl]-ethyl}-acetamide

[0091]

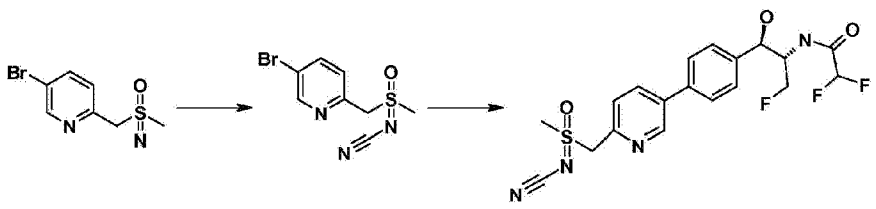


[0092] To the stirred solution of 2, 2-Difluoro-1-{(4R, 5R)-4-fluoromethyl-5-[4-(6-(S-methylsulfonimidoylmethyl)-pyridin-3-yl)-phenyl]-2,2-dimethyl-oxazolidin-3-yl}-ethanone (100mg, 0.22mmol, 1eq) in DCM (2mL) at 0°C is added TFA (1mL) drop wise resulting reaction mixture is stirred at room temperature for 8h. After completion, reaction solvent is evaporated under reduced pressure and residue is quenched with saturated bicarbonate solution then extracted with 10% MeOH in DCM (3X25mL). The combined organic layer is dried over sodium sulphate and evaporated under reduced pressure. The crude is purified by combiflash using 11% MeOH in DCM as eluent to afford to title compound (23mg) as faint brown colored solid. 1NMR (400 MHz, DMSO) δ: 2.90 (s ,3H), 3.80 (bs, 1H), 4.30-4.33 (m, 1.5H), 4.40-4.44 (m, 1H), 4.51-4.60 (m, 2H), 4.66-4.68 (m, 0.5), 4.89 (bs, 1H), 5.92 (d, *J* = 3.96Hz, 1H), 6.20 (t, *J* = 53.76 Hz, 1H), 7.47 (d, *J* = 8.24Hz, 2H), 7.56 (d, *J* = 8.2Hz, 1H), 7.73 (d, *J* = 8.32Hz, 2H), 8.11-8.14 (dd, *J1* = 2.4Hz, *J2* = 8.04Hz, 1H), 8.85-8.89 (m, 2H). LC-MS (*m/z*): M+H = 416.0.

Example 5 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6-N-[(cyano) methyl]-methyl pyridine sulfoximine-3-yl)-phenyl]-ethyl}-acetamide

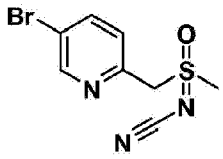
[0093]

Scheme 4



Step-1 Preparation of 5-bromo-2-N-[(cyano) methyl]-methyl pyridine sulfoximine

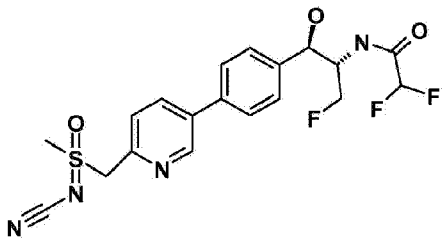
[0094]



[0095] To the stirred solution of 5-bromo-2-(S-methylsulfonimidoylmethyl) pyridine (150mg, 0.602mmol, 1eq) in DCM (2mL) at 0°C is added DMAP (0.081mg, 0.663mmol, 1.1eq) and cynogen bromide (127mg, 1.20mmol, 2eq) at RT then stirred for 16h at same temperature. After completion, reaction quenched with water then aqueous extracted with DCM (3X25mL). The combined organic layer is dried over sodium sulphate and evaporated under reduced pressure. The crude is purified by column chromatography using 35% EtOAc:Hexane as eluent to afford title compound (90mg) as yellow colored solid. 1NMR (400 MHz, $CDCl_3$) δ: 3.23 (s, 3H), 4.68-4.77 (m, 2H), 7.46 (d, *J* = 8.24Hz, 1H), 7.94-7.97 (dd, *J1* = 2.24Hz, *J2* = 8.24 Hz, 1H), 8.69 (d, *J* = 2.08Hz, 1H). LC-MS (*m/z*): M+H = 274.9.

Step-2 Preparation of 2, 2-Difluoro-N-{(1S, 2R)-1-fluoromethyl-2-hydroxy-2-[4-(6-N-[(cyano) methyl]-methyl pyridine sulfoximine-3-yl)-phenyl]-ethyl}-acetamide

[0096]



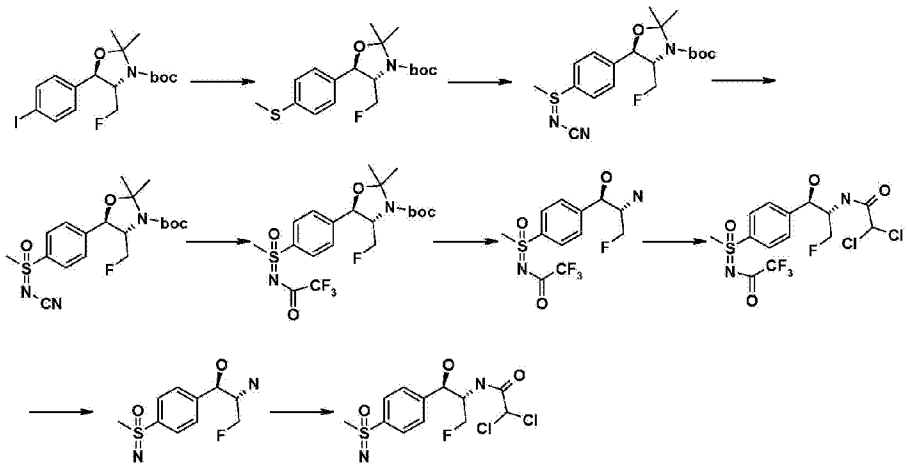
[0097] To the degassed (30min by nitrogen) solution of 2,2-Difluoro-N-[(1S,2R)-1-fluoromethyl-2-hydroxy-2-(4-trimethylstannanyl-phenyl)-ethyl]-acetamide (130 mg, 0.317mmol, 1eq), 5-bromo-2-N-[(cyano) methyl]-methyl pyridine sulfoximine (86mg, 0.317mmol, 1eq) in NMP (3mL) is added of Pd2(dba)3 (29mg, 0.032mmol, 0.1eq), Tri-2-furylphosphine (14mg,

0.063mmol, 0.2eq) at RT. The resulting reaction is stirred at 60°C for 16h. After completion, reaction is quenched with water and extract with ethyl acetate (3X25mL). The combined organic layer washed with brine solution, dried over sodium sulphate and evaporated under reduced pressure. The crude is purified by combi flash using 7% MeOH:DCM as eluent to afford (32mg) as colorless gummy compound which is repurified by prepTLC using 5%MeOH:DCM to afford the title compound (15mg) as off-white solid. 1NMR (400 MHz, DMSO) δ: 3.52 (s, 3H), 4.30 (m, 1.5H), 4.41-4.43 (m, 0.5H), 4.55 (m, 0.5H), 4.67 (m, 0.5H), 4.90 (s, 1H), 5.24 (s, 2H), 5.94 (s, 1H), 6.20 (t, *J* = 53.92Hz, 1H), 7.48 (d, *J* = 7.84Hz, 2H), 7.67 (d, *J* = 7.8Hz, 1H), 7.76 (d, *J* = 7.8Hz, 2H), 8.22 (d, *J* = 8.16Hz, 1H), 8.85 (d, *J* = 8.04Hz, 1H), 8.97 (s, 1H). LC-MS (*m/z*): M-H = 439.2.

Example 6 Preparation of 2, 2-dichloro-N-((1R, 2S)-3-fluoro-1-hydroxy-1-(4-(S-methylsulfonimidoyl) phenyl) propan-2-yl) acetamide

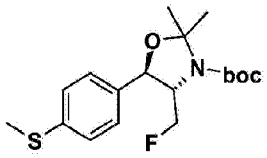
[0098]

Scheme 5



Step-1 Preparation of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(methyl thio) phenyl) oxazolidine-3-carboxylate

[0099]

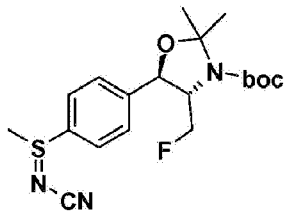


[0100] To a solution of (4S,5R)-4-Fluoromethyl-5-(4-iodo-phenyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (4.6g, 10.575 mmol) in DMSO (50mL) is added Sodium thiomethoxide (0.88g, 12.69mmol), CuI (0.201g, 1.057mmol) and L-proline sodium salt (0.29g,

2.115mmol) and heated the mixture at 90°C for 48h. Reaction mixture is quenched with water and extracted with ethyl acetate. Organic layer is washed with brine and dried over sodium sulphate, concentrated and purified by column chromatography using silica (100-200) mesh size using 3% ethyl acetate in hexane as an eluent to afford title compound (1.7g) as faint yellow oil. ^{1}H-NMR (400 MHz, DMSO): δ 1.42 (s, 9H), 1.47 (s, 3H), 1.59 (s, 3H), 2.47 (s, 3H), 3.73-3.79 (m, 1H), 4.37-4.92 (m, 1H), 4.71-4.94 (m, 1H), 5.01 (d, *J* = 7.44 Hz, 1H), 7.27 (d, *J*=8.28 Hz, 2H), 7.39 (d, *J*= 8.36 Hz, 2H). LC-MS (*m/z*): M+H = 356.2.

Step-2 Preparation of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfinimidoyl) phenyl) oxazolidine-3-carboxylate

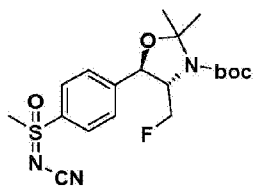
[0101]



[0102] To a solution of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(methyl thio) phenyl) oxazolidine-3-carboxylate (1.6g, 4.507mmol) in methanol (75 mL) is added NH2CN (50% aqueous solution) (0.27g, 5.859mmol) and t-BuOK (0.606g, 5.408mmol) at 0°C followed by addition of NBS (1.203g, 6.761 mmol) is added and resulting reaction mixture is stirred at RT for 1h. Solvent is evaporated in *vacuo*; reaction mixture is quenched with aqueous sodium metabisulphate solution and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by combi-flash chromatography using 10% methanol in DCM as an eluent to afford title compound (1.7g) as colorless oil. ^{1}H-NMR (400 MHz, DMSO): δ 1.42 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 3.16 (s, 3H), 3.88-3.94 (m, 1H), 4.51-4.61 (m, 1H), 4.80 (m, 1H), 5.19 (d, *J* = 7.08 Hz, 1H), 7.77 (d, *J*=8.36 Hz, 2H), 7.92 (d, *J*= 8.24 Hz, 2H). LC-MS (*m/z*): M+H = 394.2.

Step-3 Preparation of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfoximine) phenyl) oxazolidine-3-carboxylate

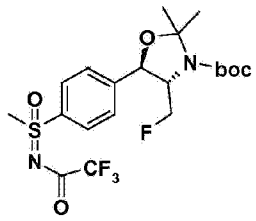
[0103]



[0104] To a solution of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfinimidoyl) phenyl) oxazolidine-3-carboxylate (1.6g, 4.051mmol) in ethanol (580mL) is added K_2CO_3 (1.677g, 12.152mmol) at 0°C followed by addition of m-CPBA (1.014g, 6.076mmol) at 0°C. The resulting reaction mixture is stirred at 0°C for 10h. Solvent is evaporated in vacuo, reaction mixture is quenched with water and extracted with DCM. Organic layer is dried over sodium sulphate, concentrated and purified by combi-flash chromatography using 30% ethyl acetate in n-Hexane as an eluent to afford title compound (1g) yellow oil. LC-MS (*m/z*): M+H = 412.0.

Step-4 Preparation of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2,2-dimethyl-5-(4-(S-methyl-N-(2,2,2-trifluoroacetyl)sulfonimidoyl)phenyl)oxazolidine-3-carboxylate

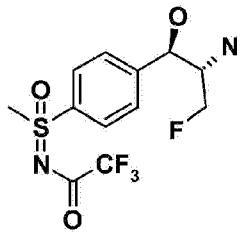
[0105]



[0106] To a solution of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfoximine) phenyl) oxazolidine-3-carboxylate (930mg, 2.263mmol) in DCM (20 mL) is added Trifluoroacetic anhydride (1.42mL). Reaction mixture is allowed to stir at room temperature for 16h. Excess of Trifluoroacetic acid and DCM is evaporated in *vacuo,* stripped with toluene followed by washing with n-pentane and diethyl ether to afford title compound (500mg, crude) as faint yellow sticky mass which is used as such for next step.

Step-5 Preparation of (1R, 2S)-2-Amino-3-fluoro-1-(4-(methyl-N-(2,2,2-trifluoroacetyl)sulfonimidoyl)phenyl)-propan-1-ol

[0107]

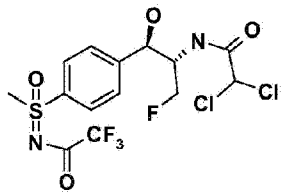


[0108] To a solution of (4S,5R)-tert-butyl 4-(fluoromethyl)-2,2-dimethyl-5-(4-(methyl-N-(2,2,2-trifluoroacetyl)sulfonimidoyl)phenyl)oxazolidine-3-carboxylate (500mg, 1.168mmol) in DCM (20 mL) is added Trifluoroacetic acid (2.0mL). Reaction mixture is allowed to stir at room

temperature for 2h. Excess of Trifluoroacetic acid and DCM is evaporated in *vacuo,* stripped with toluene followed by washing with n-pentane and diethyl ether to afford crude title compound (426mg, TFA salt) as faint yellow sticky mass which is used as such for next step.

Step-6 Preparation of 2, 2-Dichloro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(methyl-N-(2, 2, 2-trifluoroacetyl) sulfonimidoyl) phenyl)-ethyl]-acetamide

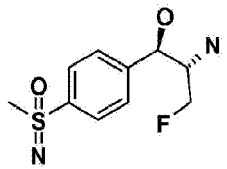
[0109]



[0110] To a solution of (1R, 2S)-2-Amino-3-fluoro-1-(4-(methyl-N-(2,2,2-trifluoroacetyl)sulfonimidoyl)phenyl)-propan-1-ol TFA salt (426mg, 1.479mmol) in Methanol (5 mL) is added TEA (0.299mL, 2.95mmol) followed by addition of ethyldichloroacetate (0.279mL, 1.775mmol) The resulting reaction mixture is stirred at room temperature for 16h. Solvent is evaporated in *vacuo* to get crude which is purified by combi-flash chromatography using 10.3% MeOH in DCM as an eluent to afford title compound (212mg) as yellow oil. ^{1}H-NMR (400 MHz, DMSO) δ: 3.02 (s, 3H), 4.19-4.13 (m, 1H), 4.15 (bs, 1H), 4.36-4.41 (m, 1.5H), 4.44-4.56 (m, 1H), 4.66-4.69 (m, 0.5H), 4.93 (t, *J* = 4.56 Hz, 1H), 6.0 (d, *J* = 4.64 Hz, 1H), 7.54 (d, *J* = 8.28 Hz, 2H), 7.87 (d, *J*= 8.36 Hz, 2H), 9.49 (d, *J* = 8.36 Hz, 1H). LC-MS (*m/z*): M+H = 343.1 (fragment).

Step-7 Preparation of (1R, 2S)-2-amino-3-fluoro-1-(4-(S-methylsulfonimidoyl) phenyl) propan-1-ol

[0111]

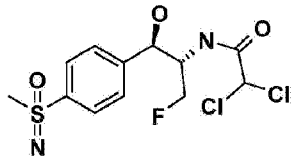


[0112] To a solution of 2, 2-Dichloro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(methyl-N-(2, 2, 2-trifluoroacetyl) sulfonimidoyl) phenyl)-ethyl]-acetamide (212mg, 0.468mmol) in Methanol (20 mL) is added K2CO3 (322.9mg, 2.34mmol) the resulting reaction mixture is stirred at room temperature for 16h. Solvent is evaporated in *vacuo* to get crude which is purified by combi-flash chromatography using 15% MeOH in DCM as an eluent and washed with n-pentane and

diethyl ether to afford title compound (80mg). ^{1}H-NMR (400 MHz, DMSO) δ: 1.60 (bs, 2H), 3.04 (s, 3H), 4.13-4.15 (m, 1.5H), 4.21-4.42 (m, 0.5H), 4.42-4.31 (m, 0.5H), 4.39-4.43 (m, 0.5H), 4.66 (bs,1H), 7.55 (d, *J*= 8.28 Hz, 2H), 7.87 (d, *J*= 8.32 Hz, 2H). LC-MS (*m/z*): M+H = 247.2.

Step-8 Preparation of 2, 2-dichloro-N-((1R, 2S)-3-fluoro-1-hydroxy-1-(4-(S-methylsulfonimidoyl)phenyl)propan-2-yl)acetamide

[0113]

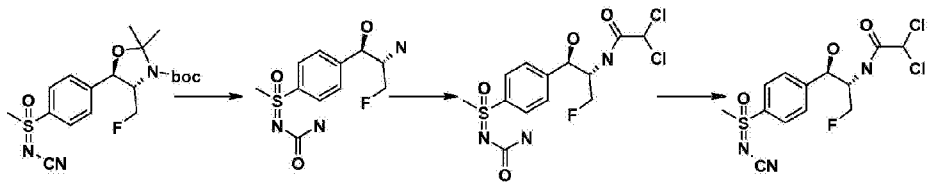


[0114] To a solution of (1R, 2S)-2-amino-3-fluoro-1-(4-(S-methylsulfonimidoyl)phenyl)propan-1-ol (76mg, 0.308mmol) Methanol (5 mL) is added TEA (0.047mL, 0.462mmol) followed by addition of ethyldichloroacetate (0.048mL, 0.308mmol) The resulting reaction mixture is stirred at room temperature for 16h. Solvent is evaporated in *vacuo* to get crude which is purified by combi-flash chromatography using 0.6% MeOH in DCM as an eluent to get 40mg of the compound which is re-purified by prep HPLC to afford title compound (25mg) white solid. ^{1}H-NMR (400 MHz, DMSO) δ: 3.0 (s, 3H), 4.19-4.25 (m, 2H), 4.28-4.32 (m, 0.5H), 4.40-4.44 (m, 0.5H), 4.56-4.59 (m, 0.5H), 4.67-4.71 (m, 0.5H), 4.96 (bs,1H), 6.12 (d, 1H, *J* = 3.6 Hz), 6.47 (d, 1H, *J* = 1.88 Hz), 7.56 (d, 2H, *J* = 8.28 Hz), 7.54 (d, 2H, *J*= 8.28 Hz), 8.82 (d, 1H, *J* = 8.28 Hz). LC-MS (*m/z*): M+H = 357.0.

Example 7 Preparation of 2, 2-Dichloro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(cyano)-methyl-phenyl sulfoximine)-ethyl]-acetamide

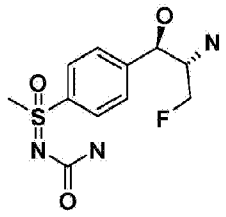
[0115]

Scheme 6



Step-1 Preparation of (1R, 2S)-2-Amino-3-fluoro-1-(4-(N-carbamoyl-S-methylsulfonimidoyl) phenyl)-propan-1-ol

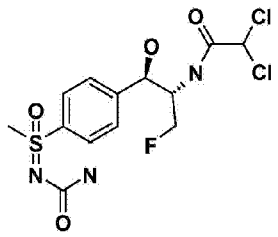
[0116]



[0117] To a solution of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfoximine) phenyl) oxazolidine-3-carboxylate (290mg, 0.706mmol) in DCM (5mL) is added Trifluoroacetic anhydride (1.16mL) at 0°C and stirred at 0°C for 6h. After completion of reaction, excess of Triflouroacetic acid and DCM is evaporated in *vacuo,* stripped with toluene followed by washing with n-pentane and diethyl ether to afford title compound (250mg, TFA salt) as off white solid. LC-MS (*m/z*): M+H = 290.2.

Step-2 Preparation of N-((1R, 2S)-1-(4-(N-carbamoyl-S-methylsulfonimidoyl) phenyl)-3-fluoro-1-hydroxypropan-2-yl)-2,2-dichloroacetamide

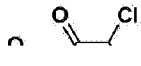
[0118]

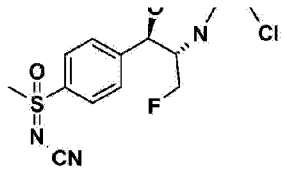


[0119] To a solution of (1R, 2S)-2-Amino-3-fluoro-1-(4-(N-carbamoyl-S-methylsulfonimidoyl) phenyl)-propan-1-ol TFA salt (250mg, 0.865mmol) in Methanol (5mL) is added TEA (0.175mL, 1.73mmol) followed by addition of ethyldichloroacetate (128.72mL, 1.038mmol) at room temperature. The resulting reaction mixture is stirred at room temperature for 16h. Solvent is evaporated in *vacuo* and obtained crude is purified by combi-flash chromatography using 6% MeOH in DCM as an eluent to give 200mg of title compound as off white solid. ^{1}H-NMR (400 MHz, DMSO): δ 2.99 (s, 3H), 4.25-4.32 (m, 1.5H), 4.40-4.44 (m, 0.5H), 4.56-4.59 (m, 0.5H), 4.67-4.71 (m, 0.5H), 4.97 (bs, 1H), 6.05 (bs, 1H), 6.18 (m, 1H), 6.46-6.48 (m, 1H), 7.61 (d, *J* = 7.52 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 8.63-8.67 (m, 2H). LC-MS (*m/z*): M+H = 399.8.

Step-3 Preparation of 2, 2-Dichloro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(cyano)-methyl-phenyl sulfoximine)-ethyl]-acetamide

[0120]

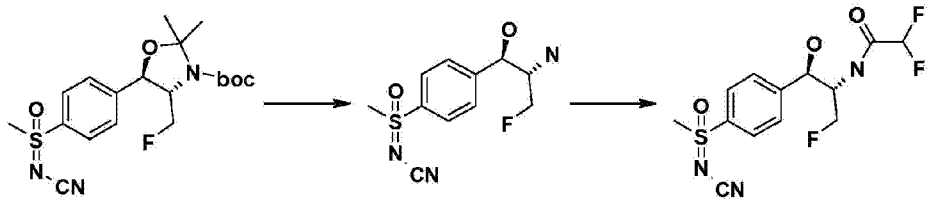




[0121] To a solution of N-((1R, 2S)-1-(4-(N-carbamoyl-S-methylsulfonimidoyl) phenyl)-3-fluoro-1-hydroxypropan-2-yl)-2, 2-dichloroacetamide (200mg, 0.501mmol) in THF (2mL) is added Triflouroacetic anhydride (0.084mL, 0.602mmol) at 0°C. After 5minutes stirring TEA (101mg, 1.003 mmol) is added. The resulting reaction mixture is stirred at room temperature for 24h then at 50°C for 16h. Solvent is evaporated in *vacuo* and obtained crude is purified by prep HPLC to give 5mg of title compound and 25mg of the compound. Analytical data for 43732-315082: ^{1}H-NMR (400 MHz, DMSO): δ 3.31 (s, 3H), 4.34-4.37 (m, 1H), 4.48-4.51 (m, 0.5H), 4.56-4.62 (m, 1H), 4.63-4.69 (m, 0.5H), 5.23 (bs, 1H), 5.81 (d, 1H, *J* = 3.04Hz), 7.01 (d, *J* = 6.24 Hz, 1H), 7.69 (d, *J* = 8.32 Hz, 2H), 7.94 (d, *J* = 7.84Hz, 2H). LC-MS (*m/z*): M+H = 382.0.

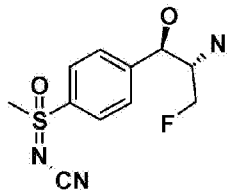
Example 8 Preparation of 2, 2-Difluoro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(cyano)-methyl-phenyl sulfoximine)-ethyl]-acetamide

[0122]
Scheme 7



Step-1 Preparation of (1R, 2S)-2-Amino-3-fluoro-1-(4-(cyano)-methyl sulfoximine-phenyl)-propan-1-ol

[0123]

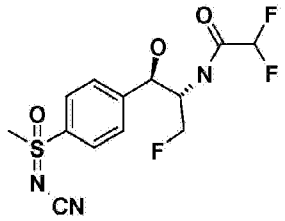


[0124] To a solution of (4S, 5R)-tert-butyl 4-(fluoromethyl)-2, 2-dimethyl-5-(4-(S-(cyano) methyl sulfoximine) phenyl) oxazolidine-3-carboxylate (200mg, 0.487mmol) in DCM (10 mL) is

added Trifluoroacetic acid (0.8mL). Reaction mixture is allowed to stir at room temperature for 2h. Excess of Trifluoroacetic acid and DCM is evaporated in *vacuo,* stripped with toluene followed by washing with n-pentane and diethyl ether to afford title compound (121mg, TFA salt) as faint yellow sticky mass. LC-MS (*m/z*): M+H = 272.0.

Step-2 Preparation of 2, 2-Difluoro-N-[(1S, 2R)-1-fluoromethyl-2-hydroxy-2-(4-(cyano)-methyl-phenyl sulfoximine)-ethyl]-acetamide

[0125]

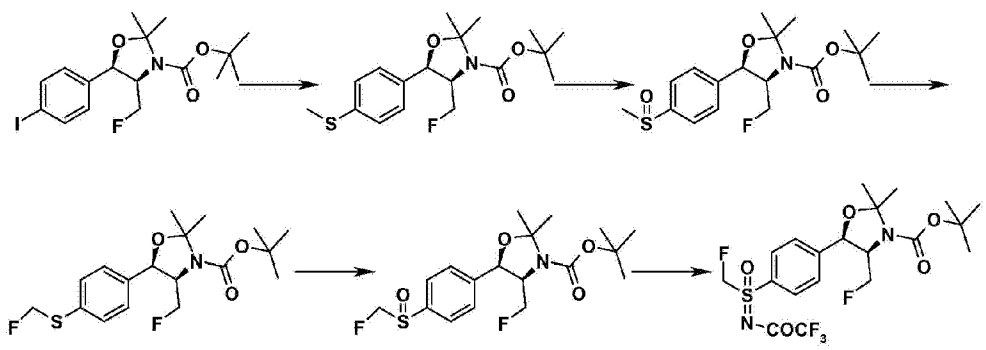


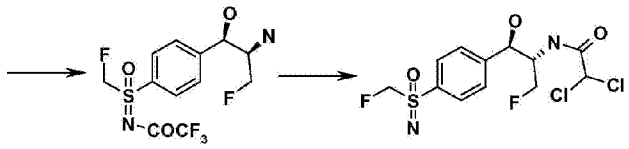
[0126] To a solution of (1R, 2S)-2-Amino-3-fluoro-1-(4-(cyano)-methyl sulfoximine-phenyl)-propan-1-ol TFA salt (121mg, 0.294mmol) in Methanol (5 mL) is added TEA (1167mg, 0.05mL, 0.589mmol) followed by addition of ethyldifluoroacetate (0.044mL, 0.353mmol) The resulting reaction mixture is stirred at room temperature for 16h. Solvent is evaporated in *vacuo* to get crude which is purified by combi-flash chromatography using 6% MeOH in DCM as an eluent to afford 40mg of the compound which is repurified by prep HPLC to afford title compound (13mg) as white sticky mass. ^{1}H-NMR (400 MHz, DMSO) δ: 3.70 (s, 3H), 4.31-4.38 (m, 1.5H), 4.43-4.47 (m, 0.5H), 4.57-4.58 (m, 0.5H), 4.67-4.69 (m, 0.5H), 5.00 (d, *J* = 2.92 Hz, 1H), 6.16 (t, *J* = 53.72 Hz, 1H), 6.21 (bs, 1H), 7.74 (d, *J* = 7.72 Hz, 2H), 8.0 (d, J= 8.4 Hz. 2H,), 8.91 (d, *J* = 7.12 Hz, 1H). LC-MS (*m/z*): M+H = 348.2.

Example 9 Preparation of 2, 2-dichloro-N-((1R, 2S)-3-fluoro-1-(4-(S-(fluoromethyl) sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl)acetamide

[0127]

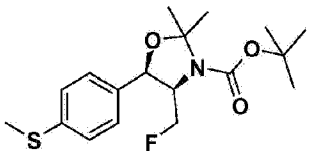
Scheme 8





Step-1 Preparation of (4R, 5R)-4-Fluoromethyl-2, 2-dimethyl-5-(4-methylsulfanyl-phenyl)-oxazolidine-3-carboxylic acid tert-butyl ester

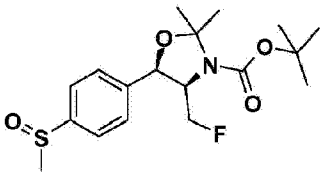
[0128]



[0129] To a solution of (4R,5R)-4-Fluoromethyl-5-(4-iodo-phenyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (2.4 g, 5.51mmol) in DMSO (40 mL) is added Sodium thiomethoxide (0.463g, 6.621mmol), CuI (0.105g, 0.552mmol) and L-proline sodium salt (0.151g, 1.103mmol) and heated the mixture at 90°C for 24h. Reaction mixture is quenched with water and extracted with ethyl acetate. Organic layer is washed with brine and dried over sodium sulphate, concentrated and purified by CombiFlash using 120g column with 9.26% ethyl acetate in hexane as an eluent to afford title compound (1.7g) as faint yellow solid. ^{1}H-NMR (400 MHz, DMSO): δ 1.42 (s, 9H), 1.47 (s, 3H), 1.59 (s, 3H), 2.47 (s, 3H), 3.73-3.79 (m, 1H), 4.37-4.92 (m, 1H), 4.71-4.94 (m, 1H), 5.01 (d, *J* = 7.44 Hz, 1H), 7.27 (d, *J*=8.28 Hz, 2H), 7.39 (d, *J*= 8.36 Hz, 2H). LC-MS (*m/z*): M+H = 356.2.

Step-2 Preparation of (4R, 5R)-4-Fluoromethyl-5-(4-methanesulfinyl-phenyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

[0130]

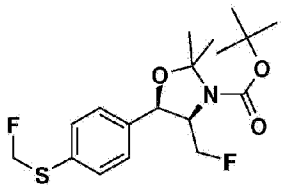


[0131] To a solution of (4R,5R)-4-Fluoromethyl-2,2-dimethyl-5-(4-methylsulfanyl-phenyl)-oxazolidine-3-carboxylic acid tert-butyl ester (6g, 16.91mmol) in ethanol (300 mL) is cooled to 0°C followed by addition of K2CO3 (4.665g, 33.80mmol) and m-CPBA (2.90, 16.90mmol) at 0°C and resulting reaction mixture is stirred at 0°C for 10h. After completion, reaction mixture

is quenched with water and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by CombiFlash using 120g column with 100% ethyl acetate in hexane as an eluent to afford title compound (4g) as colorless oil. ^{1}H-NMR (400 MHz, DMSO): δ 1.43 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.74 (s, 3H), 3.82-3.89 (m, 1H), 4.46-4.57 (m, 1H), 4.81 (m, 1H), 5.15 (d, *J* = 7.28 Hz, 1H), 7.65-7.72 (m, 4H). LC-MS (*m/z*): M+H = 372.3.

Step-3 Preparation of (4R, 5R)-4-Fluoromethyl-5-(4-fluoromethylsulfanyl-phenyl)-2, 2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

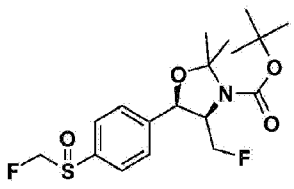
[0132]



[0133] To a solution of (4R, 5R)-4-Fluoromethyl-5-(4-methanesulfinyl-phenyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (1.0g, 2.69mmol) in DCM (50mL) is cooled to 0°C followed by addition of SbCl3 (0.018g, 0.081mmol) and DAST (0.6mL, 4.582mmol). The resulting reaction mixture is stirred at RT for 16h. After completion reaction mixture is quenched with aqueous bicarbonate solution and extracted with ethyl acetate. Organic layer is dried over sodium sulphate, concentrated and purified by combi-flash chromatography (12g column) using 8% ethyl acetate in n-Hexane as an eluent to afford title compound (564mg) as colorless oil. ^{1}H-NMR (400 MHz, DMSO): δ 1.41 (s, 9H), 1.48 (s, 3H), 1.61 (s, 3H), 377-.382 (m, 1H), 4.42-4.53 (m, 1H), 4.76-4.92 (m, 1H), 5.06 (d, *J* = 7.36 Hz, 1H), 5.99 (d, *J* = 52.32 Hz, 2H), 7.46-7.51 (m, 4H). LC-MS (*m/z*): M+H = 374.1.

Step-4 Preparation of (4R, 5R)-5-(4-Fluoromethanesulfinyl-phenyl)-4-fluoromethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

[0134]

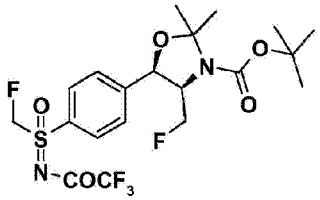


[0135] To a solution of (4R, 5R)-4-Fluoromethyl-5-(4-fluoromethylsulfanyl-phenyl)-2, 2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (2.67g, 7.158mmol) in DCM (250 mL) is

cooled to -78°C followed by addition of solution of m-CPBA (1.59g, 7.158mmol) in DCM (25mL). Reaction mixture is allowed to stir -78°C for 20 minutes. After completion of the reaction mixture is quenched with aqueous bicarbonate solution and extracted with DCM. Organic layer is dried over sodium sulphate, concentrated and purified by combi-flash chromatography (40g column) using 78% ethyl acetate in hexane as an eluent to afford title compound (1.88g) as colorless oil. ^{1}H-NMR (400 MHz, DMSO): δ 1.42 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 383-.388 (m, 1H), 4.46-4.58 (m, 1.5H), 4.75-4.84 (m, 1.5H), 5.17 (d, J = 7.2 Hz, 1H), 5.25-5.27 (dd, J = 1.12 Hz, J = 8.8 Hz, 0.5H), 5.37-5.39 (m, 0.5H), 5.51-5.54 (dd, J = 2.44 Hz, J = 8.84 Hz, 0.5H), 5.63-5.64 (m, 0.5H), 7.70-7.77 (m, 4H). LC-MS (*m/z*): M+H = 390.4.

Step-5 Preparation of (4R, 5R)-5-(N-[(Trifluoroacetyl) methyl phenyl sulfoximine)-4-fluoromethyl-2, 2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

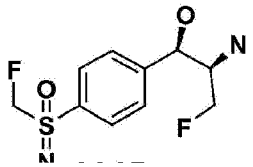
[0136]



[0137] To the stirred of (4R, 5R)-5-(4-Fluoromethanesulfinyl-phenyl)-4-fluoromethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (1.88g, 4.833mmol) in DCM (140mL) is added Trifluoro acetamide (1.092g, 9.66mmol), PhI(OAc)2(2.33g, 7.249mmol) and MgO (0.779g, 19.332mmol) and resulting reaction mixture is degassed with nitrogen for 15 minutes followed by addition of Rh2(OAC)4 (0.534g, 1.208mmol) resulting reaction mixture is stirred RT for 16h. After completion reaction mixture is quenched with water and extract with DCM combine organic layer is dried over sodium sulphate and evaporated under reduced pressure to get crude which is purified by combi flash (40g column) and compound is eluted with 55% EtOAc:Hexane to afford title compound (1.46g) as colorless oil. 1NMR (400 MHz, DMSO)δ: 1.42 (s, 9H), 1.51 (s, 3H), 1.63(s, 3H), 3.91-3.97 (m, 1H), 4.55-4.67 (m, 1.5H), 4.77-4.90 (m, 1.5H), 5.28 (d, J = 6.92 Hz, 1H), 6.22-6.40 (m, 2H), 7.91 (d, J = 8.52 Hz, 2H), 8.05 (d, J = 8.52 Hz, 2H). LC-MS (*m/z*): M+H = 499.1.

Step-6 Preparation of (1R, 2S)-2-Amino-3-fluoro-1-(N-[(Trifluoroacetyl) methyl phenyl sulfoximine)-propan-1-ol

[0138]

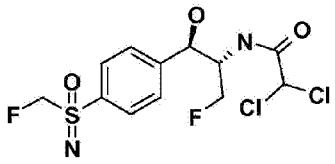


^{N}~$COCF_3$

[0139] To a solution of (4R, 5R)-5-(N-[(Trifluoroacetyl) methyl phenyl sulfoximine)-4-fluoromethyl-2, 2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (1.46g, 5.489mmol) in DCM (30 mL) is added Trifluoroacetic acid (3mL). Reaction mixture is allowed to stir at room temperature for 4h. Excess of Trifluoroacetic acid and DCM is evaporated in *vacuo,* stripped with DCM followed by washing with n-pentane and diethyl ether to afford title compound (700mg, crude TFA salt) as sticky white solid which is used as such for next step. ^{1}H-NMR (400 MHz, DMSO): δ 4.19-4.24 (m, 0.5H), 4.27-4.36 (m, 0.5H), 4.48-4.54 (m, 0.5H), 4.60-4.66 (m, 0.5H), 4.90 (t, J = 3.64 Hz, 1H), 6.24-6.43 (m, 2H), 6.73 (bs, 1H), 7.84 (d, J = 8.44 Hz, 2H), 8.08 (d, J = 8.48 Hz, 2H), 8.31 (bs, 3H). LC-MS (*m/z*): M+H = 361.0.

Step-7 Preparation of 2, 2-dichloro-N-((1R, 2S)-3-fluoro-1-(4-(S-(fluoromethyl) sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl) acetamide

[0140]

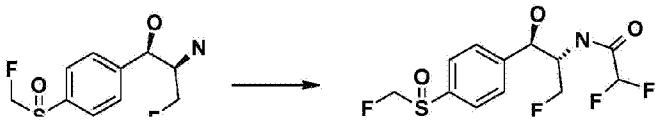


[0141] To a solution of (1R, 2S)-2-Amino-3-fluoro-1-((N-[(Trifluoroacetyl) methyl phenyl sulfoximine)-propan-1-ol TFA salt (70mg, 0.194mmol) in Methanol (10 mL) is added TEA (0.056mL, 0.389mmol) followed by addition of ethyldichloroacetate (0.061mL, 0.389mmol). The resulting reaction mixture is stirred at room temperature for 16h. After completion of the reaction, solvent is evaporated in *vacuo* to get crude which is purified by combi-flash (4g column) chromatography using 5.7% MeOH in DCM as an eluent to afford title compound (24mg) as sticky colorless mass. ^{1}H-NMR (400 MHz, DMSO) δ: 4.12-4.14 (m, 0.5H), 4.27-4.31 (m, 1H), 4.43 (m, 0.5H), 4.57-4.58 (m, 0.5H), 4.69-4.70 (m, 0.5H), 4.81-4.84 (m, 1H), 4.97-4.99 (m, 1H), 5.20-5.37 (m, 2H), 6.6 (d, J = 4.36 Hz, 1H), 6.46 (d, J = 1.96 Hz, 1H), 7.61 (d, J = 8.28 Hz, 2H), 7.85 (d, J= 8.36 Hz, 2H), 8.63 (d, J= 8.16 Hz, 1H). LC-MS (*m/z*): M-H = 373.1.

Example 10 Preparation of 2, 2 -dichloro-N-((1R, 2S)-3-fluoro-1-(4-(S-(fluoromethyl) sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl) acetamide

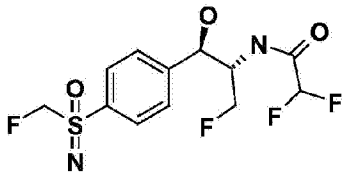
[0142]

Scheme 9



Preparation of 2,2-difluoro-N-((1R, S)-3-fluoro-1-(4-(S-(fluoromethyl) sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl) acetamide

[0143]



[0144] To a solution of (1R, 2S)-2-Amino-3-fluoro-1-((N-[(Trifluoroacetyl) methyl phenyl sulfoximine)-propan-1-ol TFA salt (350 0.972mmoll) in Methanol (15 mL) is added TEA (0.281mL, 1.944mmol) followed by addition of ethyldifluoroacetate (0.241mL, 1.944mmol). The resulting reaction mixture is stirred at room temperature for 16h. After completion of the reaction, solvent is evaporated in *vacuo* to get crude which is purified by combi-flash chromatography using 58% ethyl acetate in hexane as an eluent to afford title compound (53mg) as white solid. ^{1}H-NMR (400 MHz, DMSO) δ: 4.35-4.37(m, 1.5H), 4.41-4.45 (m, 0.5H), 4.53-4.58 (m, 0.5H), 4.65-4.69 (m, 0.5H), 4.84-4.85 (m, 1H), 4.95 (t, J = 3.56 Hz, 1H), 5.21-5.42 (m, 2H), 6.08 (d, J = 4.44 Hz, 1H), 6.17 (t, J = 53.64 Hz, 1H), 7.60 (d, J = 8.36 Hz, 2H), 7.87 (d, J= 8.32 Hz, 2H), 8.85 (d, J= 8.52Hz, 1H), LC-MS (*m/z*): M+H = 343.1.

REFERENCES CITED IN THE DESCRIPTION

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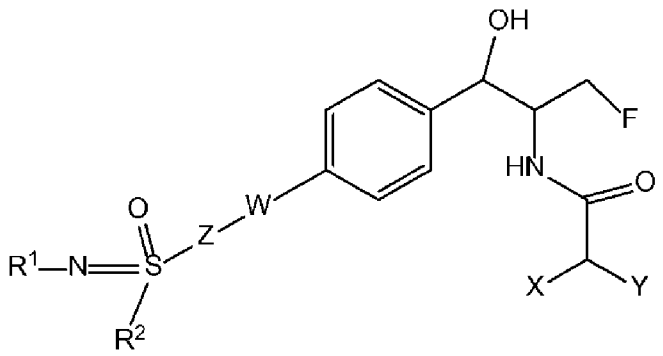
- Journal of Organic Chemistry, 1993, vol. 58, 71922-1923 [0044]

Patentkrav

1. Forbindelse med formel I



I

hvori R^1 er

a) -H,

b) -C(O)-R^3,

c) -C_1-C_6-alkyl eller

d) -CN;

R^2 er

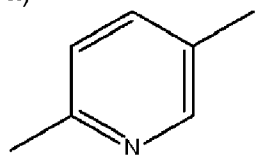
a) -C_1-C_6-alkyl, eventuelt substitueret med en til tre halogen, eller

b) cyclopropyl, cyclobutyl, cyclopentyl eller cyclohexyl;

R^3 er -C_1-C_6-alkyl;

W er

a)



eller

b) fraværende;

X og Y hver uafhængigt er halogen;

Z er

a) -C_1-C_2-alkyl-,

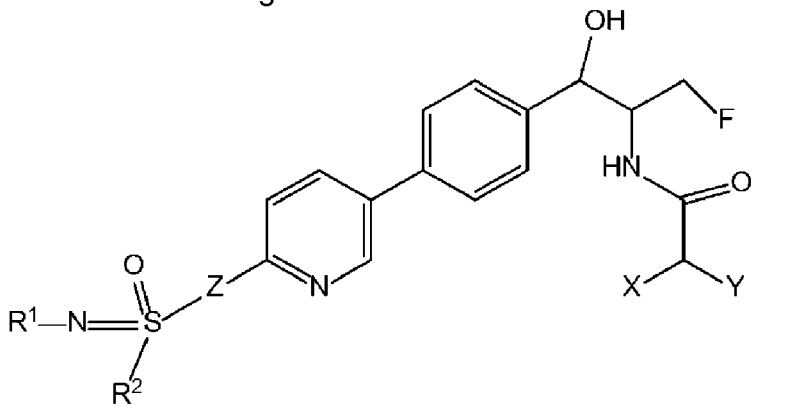
b) cyclopropyl eller cyclobutyl eller

c) fraværende;

eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelse ifølge krav 1, hvor X og Y hver er chlor, eller X og Y hver er fluor.

3. Forbindelse ifølge krav 1 med formel II

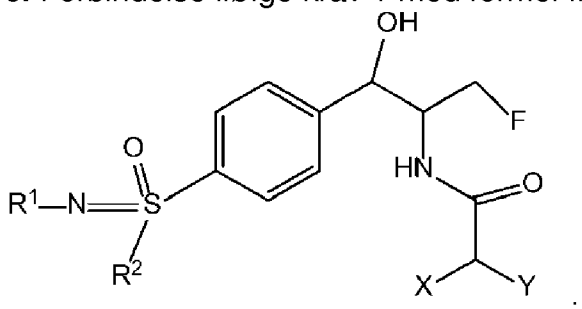


II

4. Forbindelse ifølge krav 3, hvor R^1 er -H eller -CN, R^2 er $-CH_3$, og Z er $-CH_2-$ eller fraværende.

5. Forbindelse ifølge krav 4, udvalgt fra gruppen bestående af:
2,2-difluor-N-((1R,2S)-3-fluor-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamid;
2,2-difluor-N-{(1S,2R)-1-fluormethyl-2-hydroxy-2-[4-(6-N-(cyano)methylpyridinsulfoximin-3-yl)-phenyl]-ethyl}-acetamid;
2,2-dichlor-N-((1R,2S)-3-fluor-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamid;
2,2-difluor-N-{(1S, 2R)-1-fluormethyl-2-hydroxy-2-[4-(6(S-methylsulfon-imidoylmethyl) pyridin-3-yl)-phenyl]-ethyl}-acetamid; og
2,2-difluor-N-{(1S, 2R)-1-fluormethyl-2-hydroxy-2-[4-(6-N-[(cyano) methyl]-methylpyridinsulfoximin-3-yl)-phenyl]-ethyl}-acetamid.

6. Forbindelse ifølge krav 1 med formel III

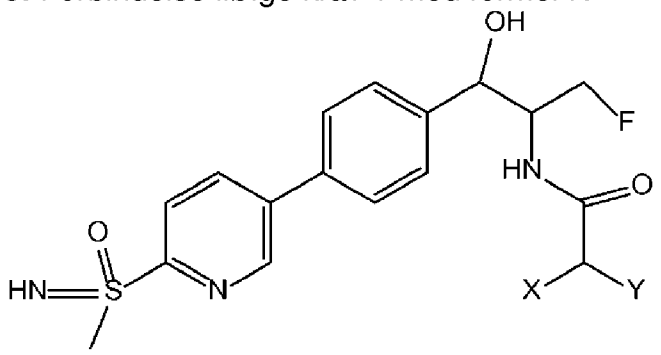


III

7. Forbindelse ifølge krav 6, hvor R^1 er -H eller -CN, og R^2 er $-CH_3$ eller $-CH_2$-F.

8. Forbindelse ifølge krav 7 udvalgt fra gruppen bestående af
2,2-dichlor-N-((1R, 2S)-3-fluor-1-hydroxy-1-(4-(S-methylsulfonimidoyl) phenyl)propan-2-yl)acetamid;
2,2-dichlor-N-[(1S, 2R)-1-fluormethyl-2-hydroxy-2-(4-(cyano)-methyl-phenylsulfoximin)-ethyl]-acetamid;
2,2-difluor-N-[(1S, 2R)-1-fluormethyl-2-hydroxy-2-(4-(cyano)-methyl-phenylsulfoximin)-ethyl]-acetamid;
2,2-dichlor-N-((1R, 2S)-3-fluor-1-(4-(S-(fluormethyl)sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl)acetamid; og
2,2-di-fluor-N-((1R,2S)-3-fluor-1-(4-(S-(fluormethyl)sulfonimidoyl) phenyl)-1-hydroxypropan-2-yl)acetamid.

9. Forbindelse ifølge krav 1 med formel IV



IV

10. Forbindelse ifølge krav 9, hvor X og Y hver er chlor, eller X og Y hver er fluor.

11. Forbindelse ifølge krav 10 udvalgt fra gruppen bestående af:
2,2-difluor-N-((1R,2S)-3-fluor-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamid;
2,2-di-chlor-N-((1R,2S)-3-fluor-1-hydroxy-1-(4-(6-(S-methylsulfonimidoyl)-pyridin-3-yl)phenyl)propan-2-yl)acetamid; og
2,2-difluor-N-{(1S, 2R)-1-fluormethyl-2-hydroxy-2-[4-(6(S-methylsulfon-imidoylmethyl) pyridin-3-yl)-phenyl]-ethyl}-acetamid.

12. Farmaceutisk sammensætning omfattende en forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller et farmaceutisk acceptabelt salt deraf og en farmaceutisk acceptabel bærer.

13. Forbindelse eller sammensætning ifølge et hvilket som helst af kravene 1 til 12 til anvendelse som et medikament.

14. Forbindelse eller sammensætning ifølge et hvilket som helst af kravene 1 til 12 til anvendelse til bekæmpelse eller behandling af infektion med bovin luftvejssygdom hos kvæg.