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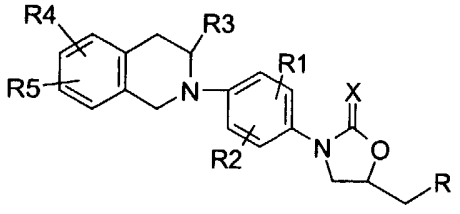
(54) Title: 1H-ISOQUINOLINE-OXAZOLIDINONE DERIVATIES AND THEIR USE AS ANTIBACTERIAL AGENTS



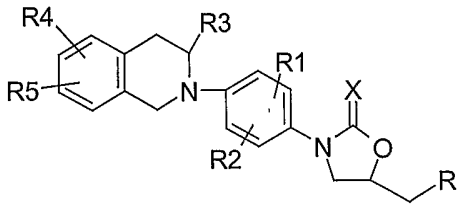
(I)

(57) Abstract: The present invention provides novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel oxazolidinone derivatives of the general formula (I)

NOVEL COMPOUNDS AND THEIR USE AS ANTIBACTERIAL AGENTS

FIELD OF THE INVENTION

The present invention provides novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel oxazolidinone derivatives of the general formula (I)



(I)

The present invention also provides a process for the preparation of the above said novel oxazolidinone derivatives of the formula (I) their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel oxazolidinone derivatives of the present invention may be useful as antibacterial agents. The novel oxazolidinone derivatives of the present invention are useful in the treatment of conditions such as nosocomial pneumoniae, community acquired pneumoniae, vancomycin resistance enterococci (VRE) caused by methicillin resistance staphylococcus aureus (MRSA) and penicillin resistance streptococcus pneumoniae. The compounds of the present invention are effective against a number of human or animal pathogens, clinical isolates, including Vancomycin resistant organisms, methicillin resistant organisms.

BACKGROUND OF THE INVENTION

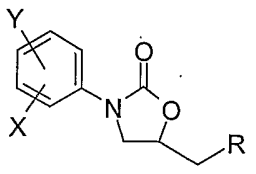
The oxazolidinone class of compounds represent totally synthetic antibacterials endowed with a mechanism different from the mode of action of known antibacterial compounds. The oxazolidinone interact with 50S ribosomal subunit to form an initiation complex and thus prevent the bacterial translation necessary for the replication of the bacteria. These compounds had shown antibacterial activity against gram + ve organisms and a host of opportunistic pathogens such as methicillin resistant Staphylococcus aureus (MRSA), penicillin resistant Streptococcus pneumoniae (PRSE), vancomycin resistant Enterococci (VRE). The best represented compounds are linezolid and eperezolid, linezolid being approved by US FDA for treatment of severe bacterial infections. Since then a lot of work had been done and there is still a need for research to extend the activity of oxazolidinone to act against gram negative pathogens. Some literature and patents are available where efforts have been made to modify the oxazolidinone moiety to impart the gram negative activity.

WO publication No. 00/73301 discloses bicyclic oxazolidinones useful as antibacterials.

WO publication No. 01/42242 discloses a series of bicyclic heterocyclic substituted phenyl oxazolidinones useful as antibacterial agents.

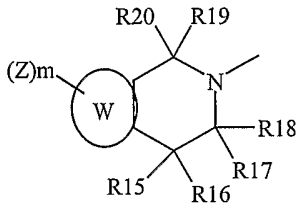
WO publication No. 98/54161 discloses amides, thioamides useful as antibacterial agents.

WO publication No. 02/64574 discloses oxazolidinone derivatives of formula (II)



(II)

wherein R is selected from the group consisting of OH, N_3, -OR^1, O-aryl, O-heteroaryl, OSO_2R^2, -NR^3R^4, etc, wherein (i) R^1, is benzyl or C_{2-6} acyl; (ii) ^{R2} is selected from the group consisting of phenyl, tolyl, and C_{1-6} alkyl; and (iii) R^3 and R^4 are independently selected from the group consisting of hydrogen, C_{3-6} cycloalkyl, phenyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, -CO_2-R^5, -CO-R^5, -CO-SR^5, -CS-R^5, P(O)(OR^6)(OR^7), $S0_2$-R^8 and C_{1-6} alkyl optionally substituted with 1 to 3 members independently selected from the group consisting of C_{1-5} alkoxycarbonyl, OH, cyano, and halogen, etc, wherein R^5 is selected from the group consisting of hydrogen, C_{3-6} cycloalkyl, trifluoromethyl, phenyl, benzyl, etc, R^6 and R^7 are independently hydrogen or C_{1-4} alkyl; R^8 is phenyl or C_1-$_4$ alkyl; X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-C_{1-6}, C_{1-8} alkoxy, etc, Y is a radical of formula



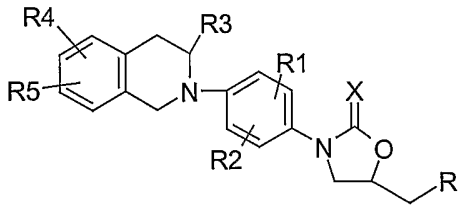
wherein R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are each independently selected from the group consisting of hydrogen, CN, nitro, C_{1-6} alkyl, halo-C_1-$_6$ alkyl, formyl, carboxy, or R^{15} and R^{16} and/or R^{17} and R^{18} and/or R^{19} and R^{20} together form an oxo group; the moiety W represents any five- to ten-membered aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 4 members selected from the group consisting of S, O, and N; Z is selected from the group consisting of hydrogen, halogen, amino, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, CN, CHO, alkyl-CO-, alkoxy, etc.

OBJECTIVE OF THE INVENTION

We have focused our research to identify novel oxazolidinone derivatives, which are effective against resistant organisms. Our sustained efforts have resulted in novel oxazolidinone derivatives of the formula (I). The novel oxazolidinone derivatives of the present invention may be useful as antibacterial agents and hence are useful in the treatment of conditions such as nosocomial pneumoniae, community acquired pneumoniae, vancomycin resistance enterococci (VRE) caused by methicillin resistance staphylococcus aureus (MRSA) and penicillin resistance streptococcus pneumoniae. The compounds of the present invention are effective against a number of human or animal pathogens, clinical isolates, including Vancomycin resistant organisms, methicillin resistant organisms.

SUMMARY OF THE INVENTION

The present invention provides compounds of the general formulas I



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R represents $NHC(=Y)R^6$, SR^7, $N(R^{8a}R^{8b})$, where R^{8a} and R^{8b} may be same or different and independently represent substituted or unsubstituted groups selected from heteroaryl, heterocyclyl, heteroaralkyl or an aminoacid residue which is attached through acid moiety; or wherein Y represents O or S; R^6 represents substituted or unsubstituted groups selected from amino, alkenyl, alkoxyalkyl,

alkylthio, alkylamino, alkenylamino, arylamino, heteroarylamino, heteroaryl, heterocyclyl; R^7 represents substituted or unsubstituted group selected from alkyl, alkenyl, alkoxyalkyl, acyl, aryl, heteroaryl, heterocyclyl; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring.

Suitable groups represented by R^1 and R^2 are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine or iodine; hydroxyl, (C_1-C_6)alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; (C_1-C_6)alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like.

Suitable groups represented by R^3, R^4 and R^5 are selected from hydrogen, cyano, nitro, amino, hydroxyl, (C_1-C_6)alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; (C_1-C_6)alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; (C_1-C_6)alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like; (C_3-C_6)cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like or together represent methylenedioxy group; aromatic group such as phenylene; heterocyclic group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl; carboxylic acid or its esters.

Suitable groups represented by R^6 are selected from amino, (C_2-C_6)alkenyl, alkoxyalkyl such as methoxymethyl, methoxyethyl, ethoxymethyl,

ethoxyethyl and the like; (C_1-C_6)alkylthio; $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$; arylamino group such as phenylamino or naphthylamino, which may be substituted; (C_2-C_6)alkenylamino, heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thiazolin, oxazolin, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, heterocyclyl group such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like; heteroarylamino wherein the heteroaryl group is as defined above.

Suitable groups represented by R^7 are selected from (C_1-C_6)alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; (C_2-C_6)alkenyl, alkoxyalkyl such as methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, benzoyl, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$ and the like; aryl group such as phenyl, naphthyl and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thiazolin, oxazolin, imidazolyl, isooxazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like; heterocyclyl group such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like.

Suitable groups represented by R^{8a} and R^{8b} may be selected from heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isooxazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyranyl, benzofuranyl, benzimidazolyl,

benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like; heterocyclyl group such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like; heteroaralkyl group wherein the heteroaryl moiety is as defined above; an aminoacid residue group selected from glycine, alanine, lysine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, iso-leucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine or valine.

The substituents on any of the groups represented by R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b} are selected from halogen, hydroxy, formyl, nitro, cyano, azido, amino, alkyl, aryl, alkylamino, alkylaminocarbonyl, haloalkyl, alkylthio, acylamino, alkoxy, acyl, carboxylic acid or its derivatives such as esters or amides and these substituents are as defined above.

Pharmaceutically acceptable salts of the present invention include salts of the alkali metal like Li, Na, and K, alkaline earth metal like Ca and Mg, salts of organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Representative compounds according to the present invention include:

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]acrylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]methacrylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]crotonylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl](5-chlorothiophen-2-yl)carbonyl amine ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy thioacetamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]acetyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]allyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,2,4-triazol-3-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-4-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]phenyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazolin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyrimidin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,3-benzothiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](5-methyl-1,3,4-thiadiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-methylthiourea ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-phenylthiourea ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-allylthiourea ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]acrylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]methacrylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]crotonylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl](5-chlorothiophen-2-yl)carbonyl amine ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy thioacetamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]acetyl thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]allyl thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-2-yl)thiomethanol ;

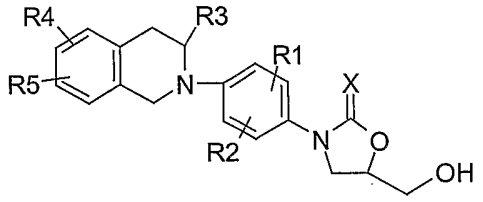
N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,2,4-triazol-3-yl)thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-4-yl)thiomethanol and

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]phenyl thiomethanol.

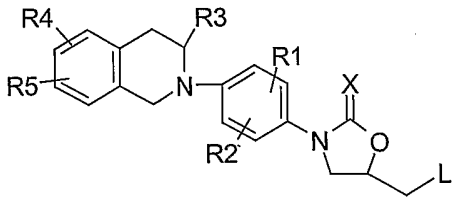
According to another embodiment of the present invention, there is provided a process for the preparation of novel oxazolidinone derivatives of the formula (I) where R represents $NHC(=Y)R^6$; where Y is O or S, R^6 and all other symbols are as defined above, which comprises :

i) converting the compound of formula (IIa)



(IIa)

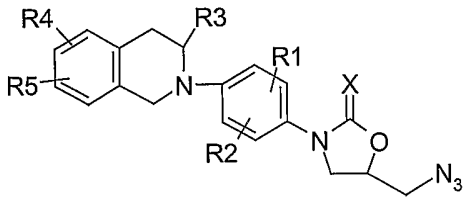
wherein all symbols are as defined earlier, to produce a compound of formula (IIb)



(IIb)

where L represents a leaving group such as mesylate, tosylate or triflate and all other symbols are as defined earlier,

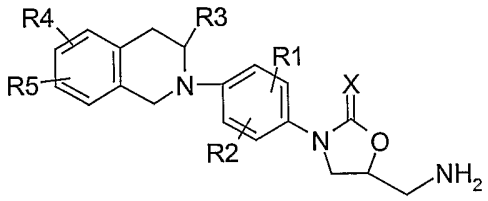
ii) converting the compound of formula (IIb) to produce compound of formula (IIc)



(IIc)

wherein all symbols are as defined earlier,

iii) reducing the compound of formula (IIc) to produce a compound of formula (IId),



(IId)

where all symbols are as defined earlier and

iv) acylating the compound of formula (IId) to produce a compound of formula (I), wherein R represents $NHC(=Y)R^6$ and all other symbols are as defined earlier.

The conversion of compound of formula (IIa) may be carried out using sulfonyl chlorides in the presence of appropriate solvents like tetrahydrofuran, chloroform, dichloromethane, dichloroethane, ethylacetate, o-dichlorobenzene or a mixture thereof. The reaction may be carried out in the presence of base

selected from dimethylamino pyridine, triethylamine, pyridine and the like. The reaction may be carried out at a temperature in the range of 0 °C to room temperature. The duration of the reaction may range from 1 to 4 hrs.

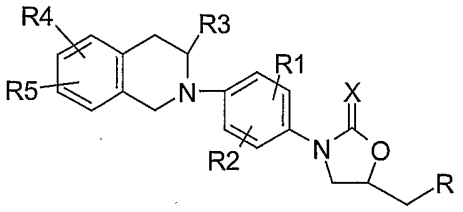
The conversion of compound of formula (IIb) may be carried out in the presence of one or more equivalents of metal azide such as LiN_3, NaN_3 or trialkyl silylazide. The reaction may be carried out in the presence of solvent such as THF, acetone, DMF, DMSO and the like or mixtures thereof. The reaction may be carried out in inert atmosphere, which may be maintained using N_2 or Ar. The reaction may be carried out at a temperature in the range of ambient temperature to reflux temperature of the solvent, preferably at a temperature in the range of 80 °C to 100 °C. The reaction time may range from 0.5 to 18 h.

The reduction of compound of formula (IIc) may be carried out in the presence of gaseous hydrogen and a catalyst such as Ru, Pd, Rh, Pt, Ni on solid beads such as charcoal, alumina, asbestos and the like. The reduction may be conducted in the presence of a solvent such as dioxane, acetic acid, ethyl acetate, THF, alcohol such as methanol, ethanol, isopropanol and the like or mixtures thereof. A pressure between atmospheric pressure to 60 psi may be used. The reaction may be carried out at a temperature in the range of 25 to 60 °C, preferably at room temperature. The reaction time ranges from 2 to 48 h. The reduction may also be carried out by employing metal in mineral acids such as Sn/HCl, Fe/HCl, Zn/HCl, Zn/CH_3CO_2H and the like.

Acylation of compound of formula (IId) may be carried out using acylating agents such as anhydrides like acetic anhydride, propionic anhydride, acid chlorides like acetyl chloride, propionyl chloride, thioacids such as thioacetic acid. The reaction may be carried out in the presence of appropriate solvents like tetrahydrofuran, chloroform, dichloromethane, dichloroethane, ethylacetate, o-dichlorobenzene or a mixture thereof. The reaction may be carried out at a

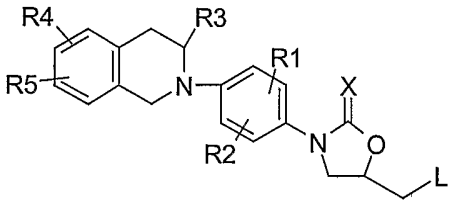
temperature in the range of 0 °C to room temperature. The duration of the reaction may range from 6 to 12 hrs.

In yet another embodiment of the present invention, there is provided a process for the preparation of compounds of formula (I)



(I)

where R represents SR^7, wherein R^7 is as defined earlier which comprises reacting the compound of formula (IIb)

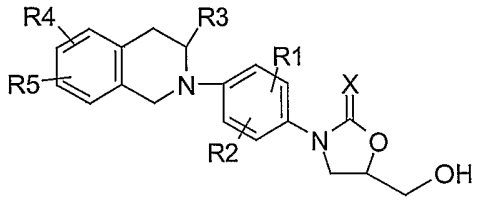


(IIb)

with R^7SH where R^7 is as defined earlier.

The conversion of compounds of formula (IIb) to a compound of formula (I) may be carried out by heating in the presence of base selected from NaH, KH, t-BuOK and the like and solvents such as DMF, THF, DCM, DMA and the like. The reaction temperature may range from 0 °C to room temperature. The duration of the reaction may range from 2 to 6 hrs.

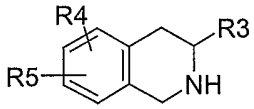
According to another embodiment of the present invention, there is provided a process for the preparation of compound of formula (IIIa)



(IIa)

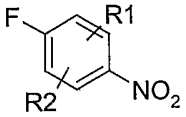
where all symbols are as defined earlier, which comprises :

i) reacting the compound of formula (IIe)



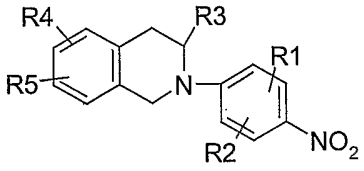
(IIe)

with compound of formula (IIf)



(IIf)

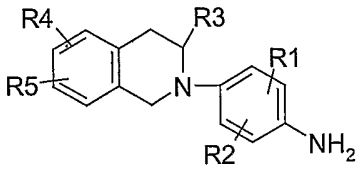
to produce compound of formula (IIg)



(IIg)

where all symbols are as defined earlier,

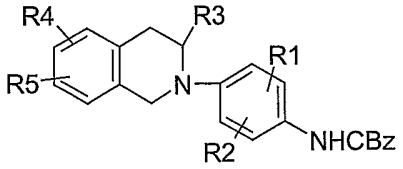
ii) reducing the compound of formula (IIg) using conventional methods to produce a compound formula (IIh)



(IIh)

where all symbols are as defined earlier,

iii) converting the compound of formula (IIh) to produce a compound of formula (IIi)



(IIi)

where all symbols are as defined earlier and

iv) cyclizing the compound of formula (IIe) with R-(-)-glycidyl butyrate to produce a compound of formula (IIIa) where all symbols are as defined earlier.

The reaction of a compound of the general formula (IIe) with a compound of formula (IIf) may be carried out in the presence of a solvent selected from acetonitrile, DMF, dimethyl acetamide and the like or mixtures thereof. The reaction may be carried out in the presence of base such as diethylamine, triethylamine, DIEA and the like. The reaction temperature may range from 40 °C to reflux temperature. The duration of the reaction may range from 6 to 10 h.

The reduction of compound of formula (IIg) may be carried out in the presence of gaseous hydrogen and a catalyst such as Ru, Pd, Rh, Pt, Ni on solid beads such as charcoal, alumina, asbestos and the like. The reduction may be conducted in the presence of a solvent such as dioxane, acetic acid, ethyl acetate, THF, alcohol such as methanol, ethanol, isopropanol and the like or mixtures thereof. A pressure between atmospheric pressure to 60 psi may be used. The reaction may be carried out at a temperature in the range of 25 to 60 °C, preferably at room temperature. The reaction time ranges from 2 to 48 h. The reduction may also be carried out by employing metal in mineral acids such as Sn/HCl, Fe/HCl, Zn/HCl, Zn/CH_3CO_2H and the like.

The conversion of compound of formula (IIh) to compound of formula (IIi) may be carried out using benzyloxycarbonyl chloride and sodium bicarbonate, in the presence of solvents such as acetone, DMF, water, THF and

the like or mixtures thereof. The reaction temperature may range from –20 °C to room temperature. The duration of the reaction may range from 3 to 6 hrs.

The cyclization of compound of formula (IIi) may be carried out in the presence of base such as n-butyl lithium, LDA, potassium bis(trimethylsilyl)amide, lithium-bis(trimethylsilyl)amide and the like. The reaction may be carried out in the presence of solvent such as THF, DMF and the like. The reaction is carried out using chiral ester such as R-(-)-glycidyl butyrate. The reaction is carried out at a temperature in the range from –78 °C to –50 °C. The duration of the reaction may range from 2 to 12 hrs.

In another embodiment of the present invention, there is provided a process for the conversion of compounds of formula (I) where R represents the formula –NHC(=Y)R^6; where Y is O, R^6 and all other symbols are as defined above to compounds of formula (I) where R represents the formula –NHC(=Y)R^6; where Y is S, R^6 and all other symbols are as defined earlier. The conversion may be carried out using Lawesson's reagent in the presence of base such as triethyl amine, pyridine and the like and solvents such as toluene, DCC, tetrahydrofuran, chloroform, dichloromethane, dichloroethane, ethylacetate, o-dichlorobenzene or a mixture thereof. The reaction may be carried out at a temperature in the range of 0 °C to room temperature. The duration of the reaction may range from 1 to 2 hrs.

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above-mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Amino acid such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc may be used for the preparation of amino acid salts. Alternatively, acid addition salts wherever applicable are prepared by the treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, dibenzoyl tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used

methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Pharmaceutically acceptable solvates of the compounds of formula (I) forming part of this invention may be prepared by conventional methods such as dissolving the compounds of formula (I) in solvents such as water, methanol, ethanol, mixture of solvents such as acetone:water, dioxane:water, N,N-dimethylformamide:water and the like, preferably water and recrystallizing by using different crystallization techniques.

The present invention provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable hydrates and solvates in combination with the usual

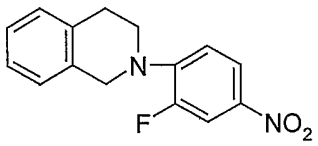
pharmaceutically employed carriers, diluents and the like, useful antibacterial agents and hence are useful in the treatment of conditions such as nosocomial pneumoniae, community acquired pneumoniae, vancomycin resistance enterococci (VRE) caused by methicillin resistance staphylococcus aureus (MRSA) and penicillin resistance streptococcus pneumoniae. The compounds of the present invention are effective against a number of human or animal pathogens, clinical isolates, including Vancomycin resistant organisms, methicillin resistant organisms.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavoring agents, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The present invention is provided by the examples below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

Preparation 1

3-Fluoro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)nitrobenzene



To a solution of 3,4-difluoro nitrobenzene (13.9 ml, 125.7 mmol) in acetonitrile (300 ml), 1,2,3,4-tetrahydroisoquinoline (35.17 ml, 276.6 mmol) was added and the resulting mixture was warmed for 1.5 hrs and then heated to reflux for 4 hrs.

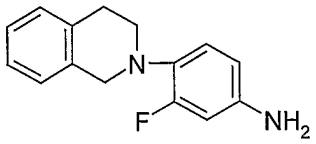
The reaction mixture was brought to room temperature and excess acetonitrile was removed by evaporation to afford a nearly dry mass, which was taken up with water (200 ml) and extracted with ethylacetate (3x300 ml) and the organic phase was separated. The organic layer was combined and washed with brine solution, water and dried over Na_2SO_4. The solvent was evaporated and dried under vacuum to afford the title compound as yellow solid which was purified through silica gel column (34 gm, yield 99%),

H^1 NMR ($CDCl_3$) δ : 3.01-3.04 (t, 2H), 3.68-3.71 (t, 2H), 4.53 (s, 2H), 6.93-6.97 (t, 1H), 7.15-8.0 (7 aromatic protons).

Mass (M^++1) : 273.

Preparation 2

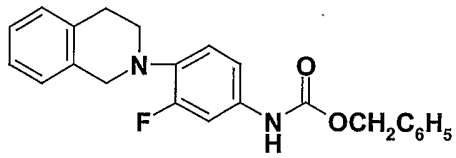
3-Fluoro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)aniline



3-Fluoro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)nitrobenzene (prepared according to the procedure described in preparation 1) (15.2 gm, 55.88 mmol) was dissolved in dry ethyl acetate (250 ml) and degassed by passing through a slow stream of nitrogen for 10 min. To this 10% Pd/C (1.52 gm) was added in portions with stirring and the reduction was carried out under H_2 balloon at ambient temperature. After completion of the reduction the residue was filtered, washed 2-3 times with ethyl acetate and concentrated to afford the title compound, which was used as such for the next step without purification.

Preparation 3

Benzyl 3-fluoro-4-(1,2,3,4-tetrahydroisoquinoline-2-yl)phenyl carbamate



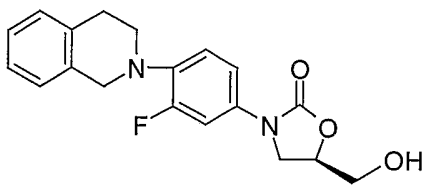
To a solution of 3-fluoro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)aniline (prepared according to the procedure described in preparation 2) (13 gm, 53.7 mmol), in dry tetrahydrofuran (480 ml), dimethylaniline (13.6 ml, 107.4 mmol) was added followed by benzyl chloroformate (18.7 ml, 128.9 mmol) over a period of 10-15 minutes while the reaction mixture was stirred at 4 °C. After complete addition, the reaction mixture was brought to ambient temperature and allowed to run at the same temperature until completion. Then the reaction mixture was quenched with water (200 ml) and the carbamate was extracted with ethyl acetate (3x200 ml). The ethyl acetate layer was combined, washed with saturated NaCl solution and water. The excess solvent was evaporated under vacuum to obtain the crude title compound which was purified by silica gel column using 20% ethyl acetate in hexane as eluent (19 gm, yield 95%), mp : > 250 °C.

H^1 NMR ($CDCl_3$) δ : 2.98 (t, 2H), 3.93 (t, 2H), 4.25 (s, 1H), 6.9-7.4, (12 H, aromatic protons).

Mass (M^++1) : 377.

Preparation 4

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methanol



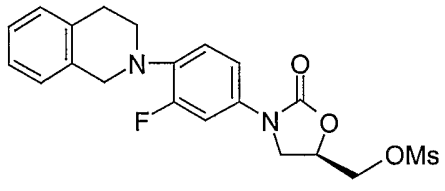
A solution of benzyl 3-fluoro-4-(1,2,3,4-tetrahydroisoquinoline-2-yl)phenyl carbamate (prepared according to the procedure described in preparation 3) (16.9 gm, 45.2 mmol) in dry tetrahydrofuran (500 ml) was cooled to –78 °C and to this n-BuLi (15% solution in hexane, 109 ml, 255 mmol), was added over a period of 20-30 min. under argon atmosphere and maintaining the temperature at around –70 °C. After complete addition, the reaction was allowed to incubate at the same temperature for 30-45 min. Then R-(-)-glycidyl butyrate (12.5 ml, 88.2 mmol) was added slowly at –78 °C over 10 min. avoiding moisture. The reaction mixture was left overnight while stirring at ambient temperature. Saturated solution of NH_4Cl (30 ml) was added to the reaction mixture containing a heavy precipitate to quench the reaction followed by addition of ethyl acetate (300 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (2x100 ml). The combined organic layer, after drying over Na_2SO_4 was filtered and solvent was evaporated and purified by chromatography to obtain the title compound (9 gm, yield 49%) as a pale yellow solid.

H^1 NMR ($CDCl_3$) δ : 2.9-3.0 (t, 2H), 3.4 (t, 2H), 3.7-3.8 (m, 1H), 3.9-4.0 (m, 3H), 4.28 (s, 2H), 4.71-4.76 (m, 1H), 6.9-7.5 (7 aromatic protons).

Mass (M^++1) : 343.

Preparation 5

N-(S)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate

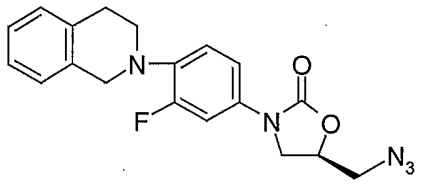


To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methanol (prepared according to the procedure described in preparation 4) (4.12 gm, 12.05 mmol) in dry dichloromethane (75 ml), triethyl amine (2.52 ml, 18 mmol) and methane sulphonyl chloride (1.17 ml, 15.09 mmol) was added at 4 °C. After complete addition, the reaction mixture was brought to room temperature and allowed to react at ambient temperature until completion. The excess solvent was removed under vacuum, water (100 ml) was poured to the reaction mixture and extracted with ethyl acetate (3x100 ml). The organic layers were combined, dried over Na_2SO_4 and evaporated to dryness to afford the title compound as a white solid (4.2 gm, yield 83%), which was used for further reaction without purification.

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.11 (s, 3H), 3.42-3.45 (t, 2H), 3.93 (t, 1H), 4.10-4.14 (t, 1H), δ 4.29 (s, 2H), δ 4.43 (dd, 1H), 4.48 (dd, 1H), 4.9-4.99 (m, 1H), 7.01-7.46 (7 aromatic protons).

Preparation 6

N-(S)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylazide



To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (prepared according to the procedure described in preparation 5) (4.2 gm, 10.04 mmol), in DMF (75 ml), sodium azide (2.6 gm, 40.2 mmol) was added. The reaction mixture was heated upon stirring under N_2 for 4-6 hrs. The reaction mixture was cooled and poured

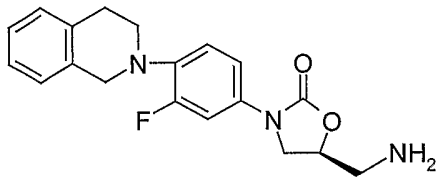
into water (100 ml) and the azide was extracted with ethyl acetate (2x100 ml). The product was filtered, dried over Na_2SO_4, and evaporated under reduced pressure and purified over silica gel column using 60 % ethyl acetate in hexane as the eluent to afford the title compound (3.2 gm, yield 85%).

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.42-3.45 (t, 2H), 3.57-3.61(dd, 1H), 3.69-3.72 (dd, 1H), 3.8-3.84 (t, 1H), 4.03-4.07 (t, 1H), 4.28 (s, 2H), 4.76-4.8 (m, 1H), 6.96-7.46 (7 aromatic protons).

Mass (M^++1) : 368.

Preparation 7

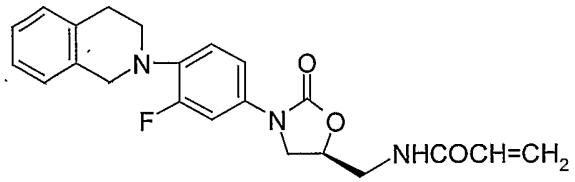
N-(S)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine



To a solution of N-(S)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylazide (prepared according to the procedure described in preparation 6) (150 mg, 0.41 mmoles) in dry ethyl acetate (15 ml) 10% Pd/C (15 mg) was added. The reduction was carried out under H_2 balloon condition at RT to produce the title compound, which was used without purification.

Example 1

Preparation of N-(S)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]acrylamide



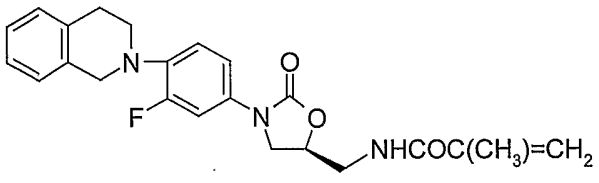
To N-(S)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine, (prepared according to the procedure described in preparation 7) pyridine (80.8 mg, 1.02 mmoles) and acryloyl chloride (46.24 mg, 0.51 mmoles) were added at room temperature with constant stirring. The reaction mixture was pressed through a celite bed followed by washing with ethyl acetate (3 x 50 ml) and filtered. The filtrate was pooled and evaporated to dryness to afford the title compound (60 mg, yield 37%) after passing through a silica gel column eluting with ethyl acetate in hexane, mp : 182.3 °C.

H^1 NMR ($CDCl_3$) δ : 3.04 (t, 2H), 3.49 (t, 2H), 3.7-3.82 (m, 3H), 4.01-4.07 (t, 1H), 4.35 (s, 2H), 4.82 (m, 1H), 5.70-5.73 (dd, 1H), 6.10-6.17 (t, 1H), 6.35 (d, 1H), 7.1-7.56 (7 aromatic protons).

Mass (M^++1) : 396.

Example 2

Preparation of N-(S)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]methacrylamide



To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (prepared according to the procedure described in preparation 7) (103 mg, 0.30 mmoles) in dry dichloromethane (15

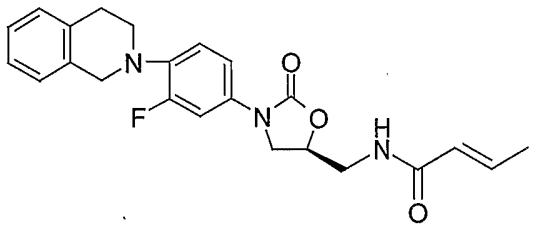
ml), pyridine (49 µl, 0.60 mmoles) was added and the reaction mixture was stirred at 0-4 °C in an ice bath. Then methacryloyl chloride (37.5 µl, 0.39 mmoles) dissolved in DCM (2 ml) was added under N_2. The ice bath was removed and the reaction was left overnight upon stirring at ambient temperature. The product was extracted with EtOAc, dried over Na_2SO_4, filtered and solvent was evaporated under vacuum. The title compound was obtained by passing through a silica gel column using 60 % ethyl acetate in hexane as eluent (76 mg, yield 61%), mp : 173.1 °C.

H^1 NMR ($CDCl_3$) δ : 1.96 (s, 3H), 3.08 (t, 2H), 3.52 (t, 2H), 3.7 (m, 1H), 3.71-3.8 (t, 2H), 4.06 (t, 1H), 4.38 (s, 2H), 4.81 (m, 1H), 5.4 (s, 1H), 5.73 (s, 1H), 7.06-7.56 (7 aromatic protons).

Mass (M^++1) : 410.

Example 3

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]crotonylamide



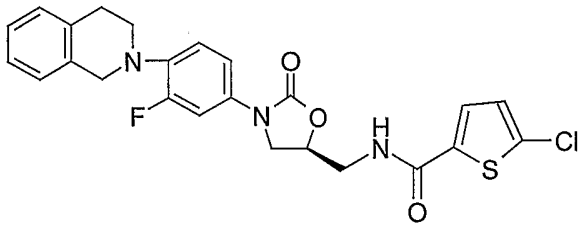
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (100 mg, 0.29 mmoles) (obtained in preparation 7) and (0.34 mmoles) crotonyl chloride by following the procedure described in example 2 (81 mg, yield 68%), mp : 197.9 °C.

H^1 NMR ($CDCl_3$) δ : 1.86 (dd, 3H), 2.97 (t, 2H), 3.42 (t, 2H), 3.72-3.78 (m, 3H), 4.01 (t, 1H), 4.27 (s, 2H), 4.79 (m, 1H), 5.81 (dd, 1H), 6.85 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 401.

Example 4

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl](5-chlorothiophen-2-yl)carbonylamine



To a solution of 5-chlorothiophene-2-carboxylic acid (61.8 mg, 0.38 mmoles) dissolved in dioxane (2 ml), N-hydroxy succinimide (48.9 mg, 0.42 mmoles) was added followed by dicyclohexyl carbodimide (85 mg, 0.41 mmoles) and the activation of the acid was allowed to proceed under nitrogen for 6 hrs. The precipitate of dicyclohexyl urea formed in the reaction was removed by filtration and the activated ester was collected as filtrate and used as such. To this activated ester, N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (126 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 7) was added and the reaction was allowed to stir at ambient temperature overnight. The reaction mixture was poured in to water and the product was extracted with ethyl acetate. The organic layer was separated and dried over Na_2SO_4 and solvent evaporated off under reduced

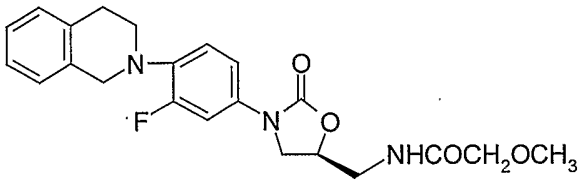
pressure. The product was purified onto a silica gel column using ethylacetate (60 %) in hexane to afford the title compound (137 mg, yield 77%), mp : > 250 °C.

H^1 NMR ($CDCl_3$) δ : 3.03 (t, 2H), 3.47 (t, 2H), 3.75 (m, 1H), 3.85 (t, 2H), 4.07 (t, 1H), 4.32 (s, 2H), 4.88 (m, 1H), 6.88-7.46 (7 aromatic protons).

Mass (M^++1) : 486.

Example 5

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide



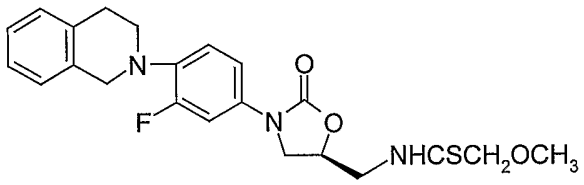
To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (154.4 mg, 0.45 mmoles) (prepared according to the procedure described in preparation 7) in dichloromethane (15 ml), pyridine (92 µl, 1.14 mmoles) and methoxy acetyl chloride (48 µl, 1.92 mmoles) were added at 0 °C and the reaction mixture brought to ambient temperature after 10 min. After the reaction was over, the reaction content was poured in to water and product was extracted with ethyl acetate. The organic layer was evaporated off and purified over silica gel chromatography using 70 % ethyl acetate in hexane as the eluent to afford the title compound (114 mg, yield 61%), mp : 127.4 °C.

H^1 NMR ($CDCl_3$) δ : 2.97 (t, 2H), 3.4 (s, 3H), 3.44 (t, 2H), 3.6 (m, 1H), 3.75 (m, 2H), 3.9 (d, 2H), 4.04 (t, 1H), 4.29 (s, 2H), 4.77 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 414

Example 6

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy thioacetamide



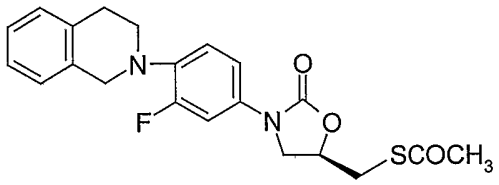
A solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide (70.4 mg, 0.17 mmol) (obtained in Example 5) in toluene (15 ml) was treated with Lawesson's reagent (96 mg, 0.26 mmoles). The reaction mixture was heated to reflux for 4 hrs. The reaction mixture was cooled to room temperature and poured in to water and extracted with ethyl acetate. The organic layer dried over Na_2SO_4, and the solvent was removed under reduced pressure and purified onto a silica gel column using 50 % EtOAc in hexane to afford the title compound (24 mg, yield 33%), mp : 160.8 °C.

H^1 NMR ($CDCl_3$) δ : 2.97 (t, 2H), 3.42 (m, 5H), 3.81 (t, 1H), 4.09 (t, 1H), 4.32 (m, 2H), 4.9 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 430

Example 7

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]acetyl thiomethanol



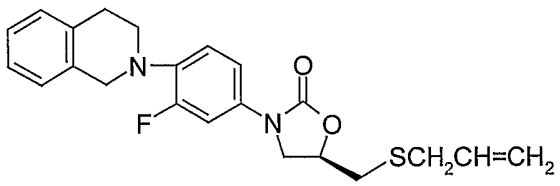
To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (100 mg, 0.24 mmoles) (prepared according to the procedure described in preparation 5) in DMF (6 ml) potassium thioacetate (41 mg, 0.36 mmoles) was added and the mixture was heated at 100 °C in an oil bath for 4 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in to water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and was purified onto a silica gel column using 30 % ethyl acetate in hexane as eluent to give the title compound (95 mg, yield 99%), mp : 195.3 °C

H^1 NMR ($CDCl_3$) δ : 2.98 (t, 2H), 3.3 (t, 2H), 3.42 (t, 2H), 3.66 (t, 1H), 4.06 (t, 1H), 4.27 (s, 2H), 4.78 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 401

Example 8

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]allyl thiomethanol



To a suspension of NaH (18 mg, 0.75 mmoles, 60 % in oil) in DMF (10 ml) allyl mercaptan (31.8 mg, 0.43 mmoles) dissolved in DMF (1 ml) was added at 0 °C. After 15 min. the temperature was brought to room temperature and the reaction

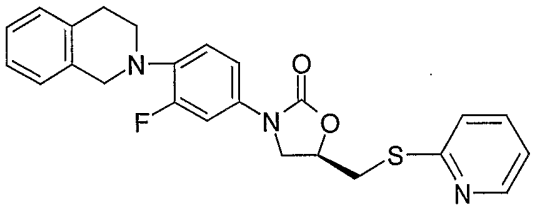
was allowed to run for 30 min. To this N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (159.3 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 5) dissolved in DMF (1 ml) was added through rubber septum. The resulting mixture was heated under N_2 until completion of the reaction. After completion, the reaction mixture was taken with ethyl acetate and water and the ethyl acetate layer was washed well with water. The organic layer was dried over Na_2SO_4 and solvent was evaporated off under vacuum and purified onto a silica gel column using 60 % EtOAc in hexane to give the title compound (22.5 mg), mp : 151.6 °C.

H^1 NMR ($CDCl_3$) δ : 2.75-2.81 (dd, 1H), 2.88-2.93 (dd, 1H), 3.22-3.24 (d, 2H), 3.41-3.44 (t, 2H), 3.79-3.83 (dd, 1H), 4.06-4-10 (t, 1H), 4.28 (s, 2H), 4.77 (m, 1H), 5.16 (s, 1H), 5.19 (d, 1H), 5.75-5.82 (m, 1H), 6.98-7.46 (aromatic protons).

Mass (M^++1) : 399

Example 9

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-2-yl)thiomethanol



The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (100 mg (0.24 mmoles) (prepared according to the procedure

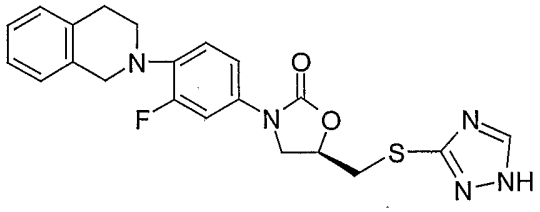
described in preparation 5) and 2-mercapto pyridine (32 mg, 0.29 mmoles) by following the procedure described in example 8 (97 mg, yield 93%).

H^1 NMR ($CDCl_3$) δ : 2.06 (s, 3H), 2.97 (t, 2H), 3.42 (t, 2H), 3.79 (t, 1H), 4.06 (t, 1H), 4.27 (s, 2H), 4.33 (m, 2H), 4.83 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 436.

Example 10

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,2,4-triazol-3-yl)thiomethanol



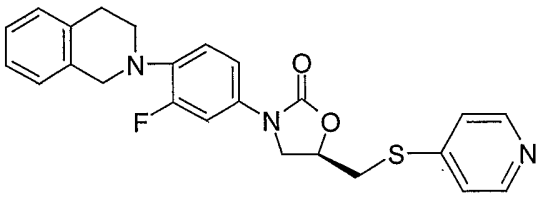
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (100 mg, 0.24 mmoles) (prepared according to the procedure described in preparation 5) and 3-mercapto-1,2,4-triazole (29 mg, 0.29 mmoles) by following the procedure described in example 8 (66 mg, yield 65%), mp : 120 °C.

H^1 NMR ($CDCl_3$) δ : 2.97 (t, 2H), 3.42 (t, 2H), 3.66 (dd, 1H), 3.91 (t, 1H), 4.12 (t, 1H), 4.27 (s, 2H), 4.99 (m, 1H), (m, 1H), 7.0-7.46 (7 aromatic protons).

Mass (M^++1) : 426

Example 11

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-4-yl)thiomethanol



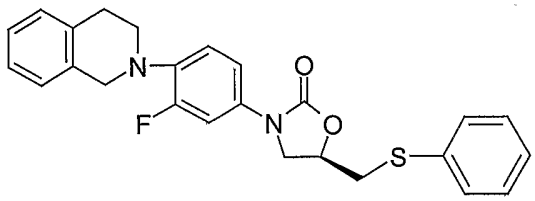
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (150.6 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 5) and 4-mercapto pyridine (47.8 mg, 0.43 mmoles) by following the procedure described in example 8 (57 mg, yield 36%), mp : 135.9 °C.

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.22-3.27 (dd, 1H), 3.41-3.44 (t, 2H), 3.51-3.56 (dd, 1H), 3.81-3.85 (dd, 1H), 4.11-4-15 (t, 1H), 4.28-4.38 (s, 2H), 4.80-4.86 (m, 1H), 6.95-7.46 (7 aromatic protons).

Mass (M^++1) : 436

Example 12

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]phenyl thiomethanol



The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (105.4 mg, 0.25 mmoles) (prepared according to the

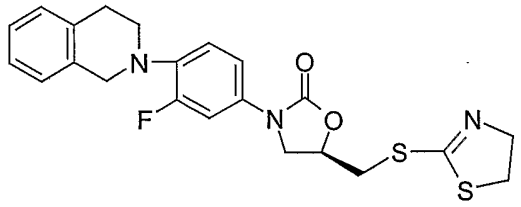
procedure described in preparation 5) and thiophenol (70 mg, 0.64 mmoles) by following the procedure described in example 8 (35 mg, yield 33%), mp : 249 °C.

H^1 NMR ($CDCl_3$) δ : 2.9 (t, 2H), 3.0 (dd, 1H), 3.46 (m, 3H), 3.82 (dd, 1H), 4.06 (t, 1H), 4.27 (s, 2H), 4.7 (m, 1H), 7.00-7.46 (7 aromatic protons).

Mass (M^++1) : 435

Example 13

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazolin-2-yl)thiomethanol



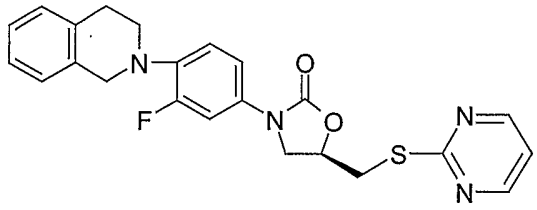
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (152.2 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 5) and 2-mercapto thiazoline (106.7 mg, 0.89 mmoles) by following the procedure described in example 8 (70 mg, yield 44 % yield), mp : > 250 °C.

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.36-3.47 (m, 5H), 3.6-3.65 (dd, 1H), 3.81-3.85 (dd, 1H), 4.08-4.11 (t, 1H), 4.17-4-21 (t, 2H), 4.28 (s, 2H), 4.92-4.99 (m, 1H), 6.97-7.46 (7 aromatic protons).

Mass (M^++1) : 444

Example 14

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyrimidin-2-yl)thiomethanol



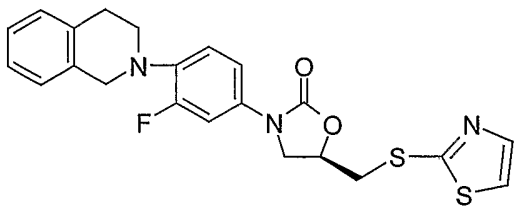
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (125 mg, 0.30 mmoles) (prepared according to the procedure described in preparation 5) and 2-mercapto pyrimidine (40 mg, 0.36 mmoles) by following the procedure described in example 8 (97 mg, yield 75%).

H^1 NMR ($CDCl_3$) δ : 2.06 (t, 3H), 2.97 (t, 2H), 3.42 (m, 2H), 3.77 (m, 2H), 4.11 (t, 1H), 4.27 (s, 2H), 4.97 (m, 1H), (m, 1H), 6.99-7.46 (7 aromatic protons).

Mass (M^++1) : 385

Example 15

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazol-2-yl)thiomethanol



The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (150 mg, 0.36 mmoles) (prepared according to the procedure

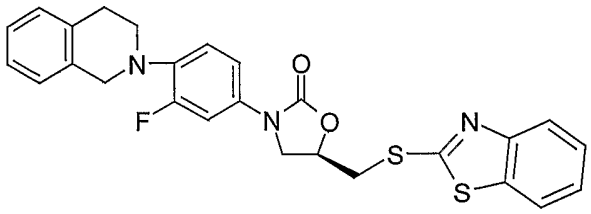
described in preparation 5) and 2-mercapto thiazole (48 mg, 0.41 mmoles) by following the procedure described in example 8 (21 mg, yield 13%), mp : 106.1 °C.

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.38-3.40 (t, 2H), 3.5 (dd, 1H), 3.74-3.78 (dd, 1H), 3.9 (dd, 1H), 4.10-4.15 (t, 1H), 4.27 (s, 1H), 4.9-5.04 (m, 1H), 6.97 - 7.10 (9 aromatic protons).

Mass (M^++1) : 442

Example 16

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,3-benzothiazol-2-yl)thiomethanol



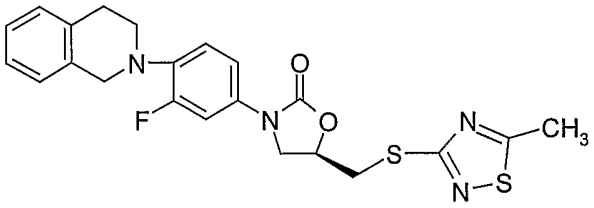
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (151 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 5) and 2-mercapto-1,3-benzothiazole (72.3 mg, 0.42 mmoles) by following the procedure described in example 8 (20 mg, yield 12%), mp : > 250 °C.

H^1 NMR ($CDCl_3$) δ : 2.97-3.0 (t, 2H), 3.4-3.43 (t, 2H), 3.6-3.71 (dd, 1H), 3.9-3.98 (m, 2H), 4.13-4.17 (t, 1H), 4.27 (s, 2H), 5.1-5.14 (m, 1H), 6.95-7.86 (10 aromatic protons).

Mass (M^++1) : 492

Example 17

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](5-methyl-1,3,4-thiadiazol-2-yl)thiomethanol



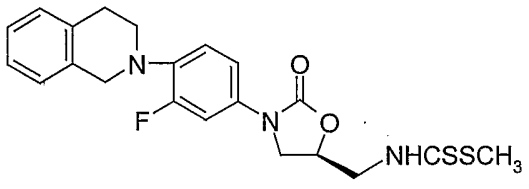
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methyl methanesulphonate (150.6 mg, 0.36 mmoles) (prepared according to the procedure described in preparation 5) and 5-methyl-2-mercapto-1,3,4-thiadiazole (88 mg, 0.67 mmoles) by following the procedure described in example 8 (40 mg, yield 25%), mp : 186.8 °C.

H^1 NMR ($CDCl_3$) δ : 2.74 (s, 3H), 2.97-3.1 (t, 2H), 3.4-3.43 (t, 2H), 3.68-3.8 (m, 2H), 3.88-3.90 (t, 1H), 4.13-4.18 (t, 1H), 4.28 (s, 2H), 5.0-5.12 (m, 1H), 6.97-7.46 (7 aromatic protons).

Mass (M^++1) : 457

Example 18

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]dithiocarbamate



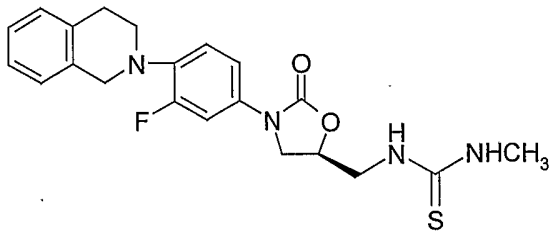
To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (104.4 mg, 0.30 mmoles), (prepared according to the procedure described in preparation 7) dissolved in ethyl acetate (5 ml), Et_3N (96 µl, 0.7 mmoles) and carbon disulphide (24 µl, 0.40 mmoles) and few drops of water were added. The reaction mixture was allowed to stir at room temperature for 6 hrs. Then CH_3I (20 µl, 0.34 mmoles) was added to the resulting solution and allowed to stir at ambient temperature until completion. The reaction mixture was filtered and excess solvent was removed under vacuum. The nearly dried material was extracted with water and ethyl acetate and the organic layer was dried over Na_2SO_4, and the solvent was evaporated. The product was purified onto a silica gel column using 20 % EtOAc in hexane as the eluent to give the title compound (29 mg, yield 22%), mp : 148.1 °C.

H^1 NMR ($CDCl_3$) δ : 2.65 (s, 3H), 2.97-2.99 (t, 2H), 3.41-3.44 (t, 2H), 3.7-3.82 (t, 1H), 4.05-4.13 (m, 2H), 4.28 (s, 2H), 4.32-4.36 (d, 1H), 4.94-4.96 (m, 1H), 7.0 -7.46 (7 aromatic protons).

Mass (M^++1) : 432.

Example 19

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-methylthiourea



To a solution of N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (102.61 mg, 0.30 mmoles) (prepared

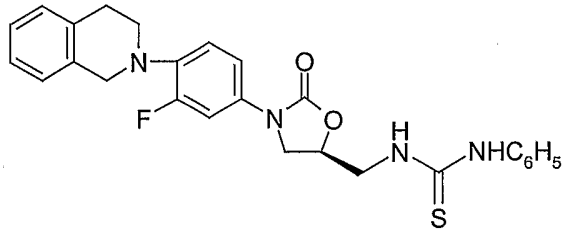
according to the procedure described in preparation 7) in DCM (15 ml) Et_3N (165 µl, 1.18 mmoles) and methyl isothiocyanate (51 µl, 0.75 mmoles) were added at 0-4 °C. After complete addition, the ice bath was removed and the reaction mixture was brought to room temperature. The reaction was allowed to run at the ambient temperature for 4-6 hrs for completion. After completion, the product was extracted with water and ethyl acetate. The ethyl acetate layer was evaporated to dryness and purified onto a silica gel column using 1:1 EtOAc in hexane to give the title compound (61 mg, yield 49 %), mp : > 250 °C.

H^1 NMR ($CDCl_3$) δ : 2.85 (s, 2H), 2.90 (t, 2H), 3.79 (s, 3H), 4.11 (t, 1H), 4.20 (s, 2H), 4.85 (s, 1H), 7.11-7.52 (7 aromatic protons).

Mass (M^++1) : 415

Example 20

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-phenylthiourea



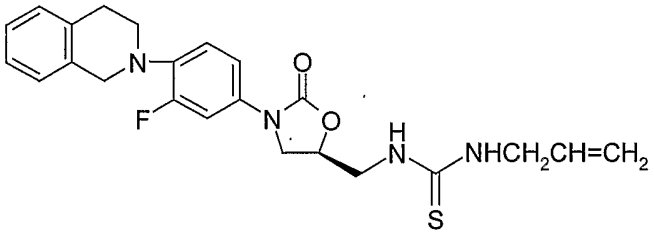
The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (108.4 mg, 0.32 mmoles) (prepared according to the procedure described in preparation 7) and phenyl isothiocyanate (76 µl, 0.64 mmoles) by following the procedure described in example 19 (120 mg, yield 79%), mp : > 250 °C.

Mass (M^++1) : 477

H^1 NMR ($CDCl_3$) δ : 2.98-3.0 (t, 2H), 3.41-3.44 (t, 2H), 3.93-3.97 (t, 1H), 4.05-4.13 (m, 3H), 4.29 (s, 2H), 4.91-4.95 (m, 1H), 7.03-7.51 (12 aromatic protons).

Example 21

Preparation of N-(*S*)-[3-[4-(3,4-dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-allylthiourea



The title compound was prepared from N-(*S*)-[3-[4-(3,4-dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]methylamine (115.4 mg 0.33 mmoles) (prepared according to the procedure described in preparation 7) and allyl isothiocyanate 80 µl (0.82 mmoles) by following the procedure described in example 19 (107 mg, yield 72%), mp : 162 °C.

H^1 NMR ($CDCl_3$) δ : 2.90-2.98 (t, 2H), 3.40-3.43 (t, 2H), 4.0-4.06 (m, 5H), 4.27 (s, 2H), 4.33 (s, 1H), 4.89-4.93 (t, 1H), 5.13-5.23 (m, 2H), 5.78-5.85 (m, 1H), 6.97-7.42 (7 aromatic protons).

Mass (M^++1) : 441.

Antimicrobial Testing

The compounds of invention showed *in vitro* antibacterial activity when tested by the Agar Dilution Method as specified in documents published by the National Committee for Clinical Laboratory Standards (NCCLS), USA.

Briefly, the compounds of invention were weighed, dissolved in Dimethyl Sulfoxide, serially diluted in the same solvent and then incorporated into molten

Mueller Hinton Agar in a petridish before solidification, with each petridish containing a different concentration of a compound.

The Bacterial Inoculum was prepared by touching the tops of 3 to 5 well isolated bacterial colonies with the same morphological appearance from an 18 hour old culture with an inoculating loop, transferring the growth to a tube containing 5ml of normal saline and adjusting the turbidity of the saline suspension to 0.5 Macfarland Turbidity Standard equivalent to a bacterial population of 1.5×10^8 colony forming units (CFU) per milliliter of suspension.

The bacterial inoculum prepared in the above manner was inoculated onto petri dishes containing Mueller Hinton Agar which had earlier been incorporated with different dilutions of the compounds of invention by a Multipoint Inoculator with each inoculum spot containing approximately 1×10^4 colony forming units (CFU) of bacteria.

The inoculated petridishes were incubated at 35°Celsius in an ambient atmosphere for 20 hours. Petridishes containing different concentrations of Vancomycin and Oxacillin and inoculated with *Staphylococcus aureus*, Coagulase Negative *Staphylococci* and *Enterococci* were incubated for 24 hours.

The petridishes after incubation, were placed on a dark non reflecting surface and the Minimum Inhibitory Concentration (MIC) recorded as the concentration which showed no growth of the inoculated culture.

The following minimum inhibitory concentrations (μg/ml) were obtained for representative compounds of the invention which are given in the following table :

Antimicrobial Screening (MIC) (µg/ml)

Organism	Example No.		
	1	18	19
S. aureus MRO 00013	>16	8	8
S. aureus MRO 00055	>16	16	8
S. aureus MRO 002046	8	4	4
S. aureus MRO 002053	>16	16	4
S. aureus MRO 0001	16	4	4
S. aureus MRO 00048	>16	4	8
S. aureus MRO 00059	16	2	2
S. aureus MRO 02002	16	2	2
S. aureus MRO 02045	16	8	4
S. aureus MRO 02095	16	8	4
S. aureus MRO 02064	8	2	2
S. aureus MRO 04045	16	4	8
S. aureus MRO 04036	>16	16	8
E. faecalis (ATCC 51299)	16	>16	8
E. faecalis (ATCC 29212)	16	>16	8
S.aureus (ATCC 29213)	8	2	4
S.aureus (ATCC 43300)	8	16	4

1) S.aureus - *Staphylococus aureus*

2) Ent. Faecalis - *Enterococcus faecalis*

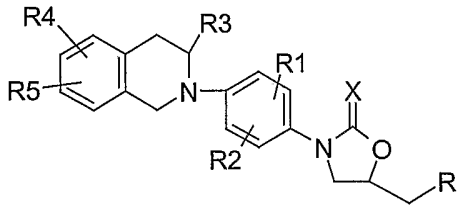
3).E. faecium - *Enterococcus* faecium

ATCC – American Type Culture Collection

MRO - Microbial Resource Orchid

Claims :

1. A compound of the formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R represents $NHC(=Y)R^6$, SR^7, $N(R^{8a}R^{8b})$, where R^{8a} and R^{8b} may be same or different and independently represent substituted or unsubstituted groups selected from heteroaryl, heterocyclyl, heteroaralkyl or an aminoacid residue which is attached through acid moiety; or wherein Y represents O or S; R^6 represents substituted or unsubstituted groups selected from amino, alkenyl, alkoxyalkyl, alkylthio, alkylamino, alkenylamino, arylamino, heteroarylamino, heteroaryl, heterocyclyl; R^7 represents substituted or unsubstituted group selected from alkyl, alkenyl, alkoxyalkyl, acyl, aryl, heteroaryl, heterocyclyl; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyl, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring.

2. A compound of formula (I) as claimed in claim 1, which is selected from :

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]acrylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]methacrylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]crotonylamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl](5-chlorothiophen-2-yl)carbonyl amine ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy thioacetamide ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]acetyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]allyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,2,4-triazol-3-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-4-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]phenyl thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazolin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyrimidin-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](thiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,3-benzothiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](5-methyl-1,3,4-thiadiazol-2-yl)thiomethanol ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-methylthiourea ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-phenylthiourea ;

N-(*S*)-[3-[4-(3,4-Dihydro-1H-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-N^1-allylthiourea ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]acrylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]methacrylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]crotonylamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl](5-chlorothiophen-2-yl)carbonyl amine ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy acetamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-ylmethyl]-α-methoxy thioacetamide ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]acetyl thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]allyl thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-2-yl)thiomethanol ;

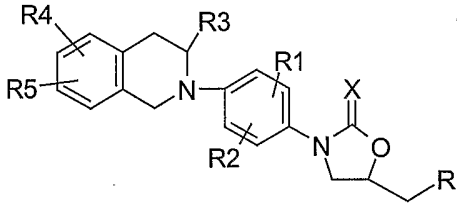
N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](1,2,4-triazol-3-yl)thiomethanol ;

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl](pyridin-4-yl)thiomethanol and

N-(*R*)-[3-[4-(3,4-Dihydro-(1H)-isoquinolin-2-yl)-3-fluorophenyl]-2-oxo-oxazolidin-5-yl]phenyl thiomethanol.

3. The compound as claimed in claim 3, wherein the salt is selected from hydrochloride or hydrobromide.

4. A process for the preparation of compound of the formula (I)

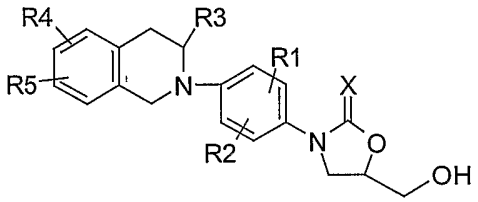


(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R represents $NHC(=Y)R^6$; where Y is O or S, R^6 represents substituted or unsubstituted groups selected from amino, alkenyl, alkoxyalkyl, alkylthio, alkylamino, alkenylamino, arylamino, heteroarylamino, heteroaryl, heterocyclyl; R^1 and R^2 may be same or different and independently represent hydrogen,

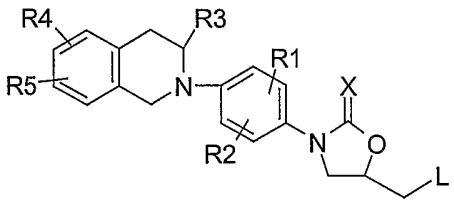
halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring , which comprises :

i) converting the compound formula (IIa)



(IIa)

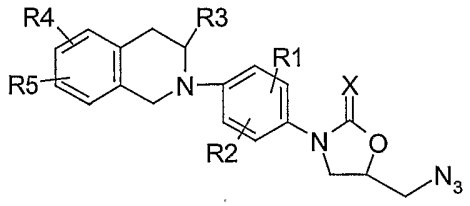
wherein all symbols are as defined above, to produce a compound of formula (IIb)



(IIb)

where L represents a leaving group and all other symbols are as defined above,

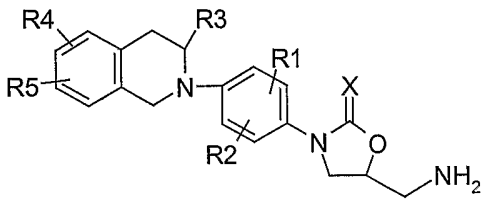
ii) converting the compound of formula (IIb) to produce compound of formula (IIc)



(IIc)

wherein all symbols are as defined above,

iii) reducing the compound of formula (IIc) to produce a compound of formula (IId),

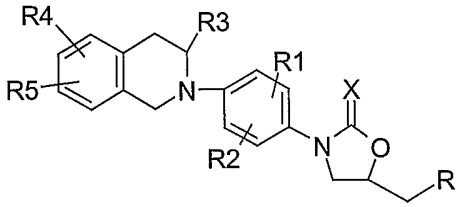


(IId)

where all symbols are as defined above and

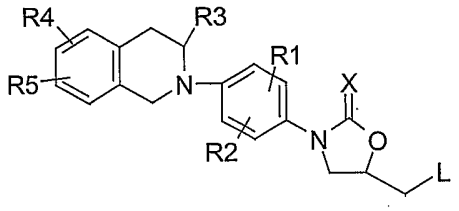
iv) acylating the compound of formula (IId) to produce a compound of formula (I), wherein R represents $NHC(=Y)R^6$ and all other symbols are as defined above.

5. A process for the preparation of compound of the formula (I)



(I)

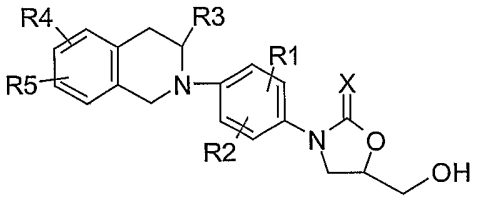
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R represents SR^7, R^7 represents substituted or unsubstituted group selected from alkyl, alkenyl, alkoxyalkyl, acyl, aryl, heteroaryl, heterocyclyl; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyl, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring, which comprises reacting the compound of formula (IIb)



(IIb)

with R^7SH where R^7 is as defined above.

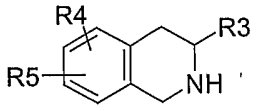
6. A process for the preparation of compound of the formula (IIIa)



(IIa)

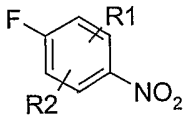
their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, acyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring, which comprises :

i) reacting the compound of formula (IIe)



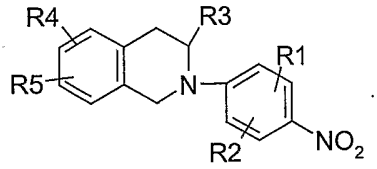
(IIe)

with compound of formula (IIf)



(IIf)

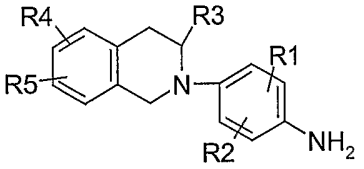
to produce compound of formula (IIg)



(IIg)

where all symbols are as defined above,

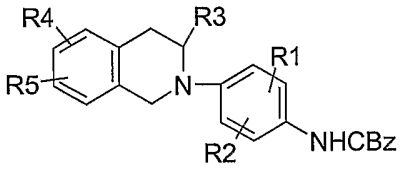
ii) reducing the compound of formula (IIg) using conventional methods to produce a compound formula (IIh)



(IIh)

where all symbols are as defined above,

iii) converting the compound of formula (IIh) to produce a compound of formula (IIi)

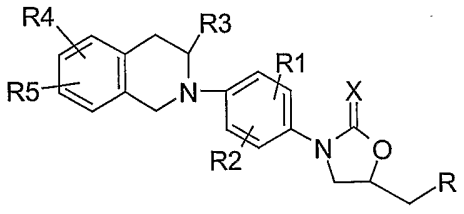


(IIi)

where all symbols are as defined above and

iv) cyclizing the compound of formula (IIe) with R-(-)-glycidyl butyrate to produce a compound of formula (IIIa) where all symbols are as defined above.

7. A process for the conversion of compound of the formula (I)

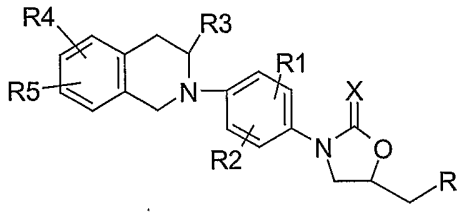


(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their

pharmaceutically acceptable compositions wherein X represents oxygen or sulfur; R represents $NHC(=Y)R^6$, where Y is O, R^6 represents substituted or unsubstituted groups selected from amino, alkenyl, alkoxyalkyl, alkylthio, alkylamino, alkenylamino, arylamino, heteroarylamino, heteroaryl, heterocyclyl; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxy, alkyl, alkoxy; R^3, R^4 and R^5 may be same or different and independently represent hydrogen, cyano, nitro, amino, hydroxyl, substituted or unsubstituted groups selected from $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, acyl, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkyl, carboxylic acid or its esters; or R^4 and R^5 when present on adjacent carbon atoms may also form methylenedioxy group, aromatic ring, 5 or 6 membered heterocyclic ring to a compound of formula (I) R represents the formula $-NHC(=Y)R^6$; where Y is S, and all other symbols are as defined above using Lawesson's reagent in the presence of base.

8. A pharmaceutical composition, which comprises a compound of formula (I)



(I)

as defined in claim 1 and a pharmaceutically acceptable carrier, diluents, excipient or solvate.

9. A pharmaceutical composition as claimed in claim 8, in the form of a tablet, capsule, powder, syrup, solution, aerosol or suspension.

10. Use of compound of formula (I) claimed in claim 1, for treating or preventing an infectious disorder in a human or animal.

11. Use of compound as claimed in claim 10, wherein the infectious disorder is caused by bacteria.

12. Use of compound claimed in claim 2, for treating or preventing an infectious disorder in a human or animal.

13. Use of compound as claimed in claim 12, wherein the infectious disorder is caused by bacteria.

14. Use of pharmaceutical composition as claimed in claim 8, for treating or preventing an infectious disorder in a human or animal.

INTERNATIONAL SEARCH REPORT

Inter I Application No
PCT/IB 03/02602

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/10 C07D413/14 C07D417/14 //(C07D413/10,263:00, 217:00),(C07D413/14,333:00,263:00,217:00),(C07D413/14,263:00, 217:00,213:00),(C07D413/14,263:00,249:00,217:00),(C07D417/14,

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 02 064574 A (ORTHO MCNEIL PHARM INC) 22 August 2002 (2002-08-22) cited in the application Compounds 2 and 3	1
A	WO 01 42242 A (ORTHO MCNEIL PHARM INC) 14 June 2001 (2001-06-14) Examples 1-4 and data according to table 1	1
A	WO 96 23788 A (UPJOHN CO ;HUTCHINSON DOUGLAS K (US)) 8 August 1996 (1996-08-08) the whole document	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2003	26/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goss, I

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INTERNATIONAL SEARCH REPORT

Inter l Application No
PCT/IB 03/02602

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 277:00,263:00,217:00),(C07D413/14,263:00,239:00,217:00)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goss, I

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INTERNATIONAL SEARCH REPORT

Interi Application No
PCT/IB 03/02602

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