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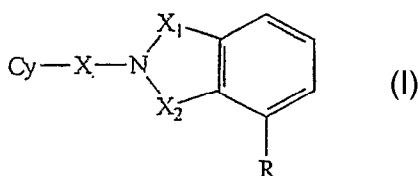
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(54) Title: ISOINDOLE DERIVATIVES AS ANTIMICROBIAL AGENTS



(57) Abstract: Provided herein are substituted aromatic compound of Formula (I), which are tRNA synthetase inhibitors, and hence can be used as antimicrobial agents. Compounds disclosed herein can be used for the treatment or prevention of a condition caused by or contributed to by gram positive, gram negative, anaerobic bacteria or fungal organisms, more particularly against bacterium, for example, *Staphylococci*, *Enterococci*, *Streptococci*, *Haemophilus*, *Moraxella*, *Escherichia*, *Chlamydia*, *Rickettsiae*, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Helicobacter*, *Clostridium*, *Bacteroides*, *Corynebacterium*, *Bacillus* or *Enterobacteriaceae*, and fungal organisms, for example, *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Hendersonula*, *Histoplasma*, *Microsporium*, *Paecilomyces*, *Paracoccidioides*, *Pneumocystis*, *Trichophyton*, or *Trichosporium*. Processes for the preparation of these compounds, pharmaceutical compositions thereof, and method of treating microbial infections are also provided.

ISOINDOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

Field of the Invention

Provided herein are substituted aromatic compounds, which are tRNA synthetase inhibitors, and hence can be used as antimicrobial agents. Compounds disclosed herein can be used for the treatment or prevention of a condition caused by or contributed to by gram positive, gram negative, anaerobic bacteria or fungal organisms, more particularly against bacterium, for example, *Staphylococci*, *Enterococci*, *Streptococci*, *Haemophilus*, *Moraxalla*, *Escherichia*, *Chlamydia*, *Rickettsiae*, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Helicobacter*, *Clostridium*, *Bacteroides*, *Corynebacterium*, *Bacillus* or *Enterobacteriaceae*, and fungal organisms, for example, *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Hendersonula*, *Histoplasma*, *Microsporum*, *Paecilomyces*, *Paracoccidioides*, *Pneumocystis*, *Trichophyton*, or *Trichosporium*. Processes for the preparation of these compounds, pharmaceutical compositions thereof, and method of treating microbial infections are also provided.

Background of the Invention

Antibiotics are of immense value for combating infectious diseases. In recent decades, the effectiveness of antibiotics has been threatened by an inexorable rise in the prevalence of microbial drug resistance. Some important pathogens have serious resistance problems. *Staphylococcus aureus* is perhaps the most significant of these pathogens. It causes community and hospital acquired infections and is associated with high morbidity and mortality rates. Vancomycin has been used as the antibiotic of last resort to treat methicillin-resistance *staphylococcus aureus* infections (MRSA) with multiple resistance. Strains with some level of resistance to vancomycin (Vancomycin-intermediates-resistant *S. aureus*, VISA) have been known since 1996, but the newly identified highly resistant strain (VRSA) heralds a new stage in the battle with this pathogen. Other serious treatment problems include multidrug resistance in tuberculosis, vancomycin resistant enterococci (VRE), resistance owing to extended spectrum β -lactamases (ESBLs) in Enterobacteriaceae and *Pseudomonas aeruginosa*, and penicillin resistance in *Streptococcus pneumoniae*.

A nation wide epidemic of multi drug resistant *Salmonell typhi* occurred in 1990 and has not yet fully subsided. Antimicrobial resistance among respiratory pathogens has

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become a common clinical problem, currently over 90% of *Morexella catarrhalis* and 25% of *Haemophilus influenzae* produce β lactamases, requiring treatment with a β lactamase stable cephalosporin or combination drugs. In the last several years, there has been a rapid increase in the number of strains resistant to penicillin, cephalosporins, macrolides and fluoroquinolones.

These circumstances have prompted efforts to develop new antibiotics that overcome the emerging antibiotic resistance bacteria. The amino acyl tRNA synthetases are essential enzymes found in all living organisms. These enzymes have emerged as an attractive target for the development of new antibiotics. Amino acyl tRNA synthetases charge tRNA molecules with their corresponding amino acid, an essential step in protein synthesis. There are 20 tRNA synthetases, most of which correspond to attractive broad-spectrum antibacterial targets. This is a validated target class in that pseudomonic acid A, also known as mupirocin, a natural product from *Pseudomonas fluorescens*, inhibits isoleucyl tRNA synthetase and is marketed as a topical antibiotic Bactropan. Other known natural products directed against amino acyl tRNA synthetases include borrelidin, furanomycin, granaticin, indolmycin, ochartoxin A, and cispentacin, none of them has been developed as antibiotic compounds.

U.S. Patent Application Nos. 2004/0224981 and 2003/0013724 disclose tRNA synthetase inhibitors. WO 00/18772 discloses condensed imidazolidinone as tRNA synthetase inhibitors. U.S. Patent Nos. 5,191,093 and 4,916,155 disclose crystalline pseudomonate, process for its production and its use in human and veterinary medicines. U.S. Patent No. 4,916,155 discloses crystalline calcium pseudomonate or the hydrate thereof, and their use in human and veterinary medicine.

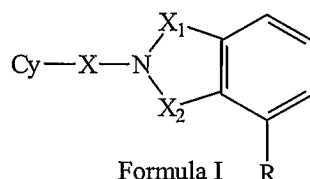
Novel synthetic compounds, which target tRNA synthetases, offer clear advantages as useful therapeutic agents to curb the threat of drug resistance.

Summary of the Invention

Herein are provided substituted aromatic compounds, which are tRNA synthetase inhibitors, and hence can be used for the treatment of microbial infections, and processes for the synthesis of these compounds. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites, polymorphs and N-oxides of these compounds having same type of activity are also provided. Pharmaceutical

compositions containing the disclosed compounds (Formula I) together with pharmaceutically acceptable carriers, excipients or diluents, which can be used for the treatment of microbial infections. Other aspects will be set forth in the accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In one aspect, there are provided compounds having the structure of Formula I,



pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites and N-oxide thereof, wherein:

Cy can be cycloalkyl or heterocyclyl; X can be alkylene; X_1 and X_2 can be independently CO, CS or CH_2 ; R can be hydrogen, hydroxy, nitro, halogen, OR_1 , $OCONHR_1$, $OCONHSO_2R_1$, SR_2 (wherein R_1 can be aryl or heteroaryl and R_2 can be hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroaryl or aryl) or NR_3R_4 {wherein R_3 and R_4 can be independently hydrogen, SO_2R_5 , COR_5 , CSR_5 , or $COOR_5$ [wherein R_5 can be alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, heterocycloalkyl, OR_6 , NHR_6 , $NHSO_2R_6$, $NHCOR_6$, $NHCSR_6$, or $NH_2C=NHSO_2R_6$ (wherein R_6 can be alkyl, aryl, heteroaryl or heterocyclyl)]}. Also, R_3 and R_4 can, together with the nitrogen to which they are attached, form a heterocyclic ring.

In another aspect, there is provided a method for treating or preventing a subject suffering from a condition caused by or contributed to by Gram-positive, Gram-negative, anaerobic bacteria or fungal organisms, comprising administering to the subject, a therapeutically effective amount of a compound or a pharmaceutical composition disclosed herein.

Bacterium, for example, *Staphylococci*, *Enterococci*, *Streptococci*, *Haemophilus*, *Moraxalla*, *Escherichia*, *Chlamydia*, *Rickettsiae*, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Helicobacter*, *Clostridium*, *Bacteroides*, *Corynebacterium*, *Bacillus* or *Enterobacteriaceae* may cause the bacterial infections.

Organisms, for example, *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Hendersonula*, *Histoplasma*, *Microsporum*, *Paecilomyces*, *Paracoccidioides*, *Pneumocystis*, *Trichophyton*, or *Trichosporium*, *Enterobacteriaceae* may cause the fungal infections.

The conditions may be, for example, community acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital acquired lung infections or bone and joint infections, and other bacterial infections, for example, mastitis, catheter infection, foreign body, prosthesis infections or peptic ulcer disease.

In a further aspect, there are provided processes for the preparation of compounds as disclosed herein.

The following definitions apply to terms as used herein:

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, a phenylene, sulphinyl, sulphonyl group or $-NR_{\alpha}$, wherein R_{α} can be hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_{\lambda}$, SO_mR_{ψ} or $-C(=O)NR_{\lambda}R_{\pi}$. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, $-CH=N-O(C_{1-6}alkyl)$, $-CH=N-NH(C_{1-6}alkyl)$, $-CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl$, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, $-NHC(=O)R_{\lambda}$, $-NR_{\lambda}R_{\pi}$, $-C(=O)NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-C(=O)heteroaryl$, $C(=O)heterocyclyl$, $-O-C(=O)NR_{\lambda}R_{\pi}$ {wherein R_{λ} and R_{π} are independently selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or carboxy}, nitro or $-SO_mR_{\psi}$ (wherein m is an integer from 0-2 and R_{ψ} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may

be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, -NR_λR_π, -C(=O)NR_λR_π, -OC(=O)NR_λR_π, -NHC(=O)NR_λR_π, hydroxy, alkoxy, halogen, CF₃, cyano, and -SO_mR_ψ; or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_α (wherein R_α, R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, -NR_λR_π, -C(=O)NR_λR_π, -O-C(=O)NR_λR_π, hydroxy, alkoxy, halogen, CF₃, cyano, and -SO_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkylene," as used herein, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms and one or more hydrogen can optionally be substituted with alkyl, hydroxy, halogen or oximes. This term can be exemplified by groups such as methylene, ethylene, propylene isomers (*e.g.*, -CH₂CH₂CH₂ and -CH(CH₃)CH₂) and the like. Alkylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, -COOR_ψ, -NHC(=O)R_λ, -NR_λR_π, -C(=O)NR_λR_π, -NHC(=O)NR_λR_π, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_λR_π, nitro, -S(O)_mR_λ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, alkenyl, alkynyl, carboxy, -COOR_ψ, -NR_λR_π, -C(=O)NR_λR_π, -OC(=O)NR_λR_π, -NHC(=O)NR_λR_π, hydroxy, alkoxy, halogen, CF₃, cyano, and -S(O)_mR_ψ (wherein R_λ, R_π, m and R_ψ are the same as defined earlier). Alkylene can also be optionally interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and -NR_α (wherein R_α is the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents selected from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, alkoxy, hydroxy, carboxy, -C(=O)OR_ψ, halogen, CF₃, cyano, -NR_λR_π, -S(O)_mR_ψ, -C(=O)NR_λR_π, -OC(=O)NR_λR_π, -CONH-, -C=O or -C=NOH (wherein R_λ, R_π, m and R_ψ are the same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or $SO_m R_\psi$ (wherein R_λ , R_π , m and R_ψ are the same as defined earlier).

Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $OC(=O)NR_\lambda R_\pi$, cyano or $-SO_m R_\psi$ (wherein R_λ , R_π , m and R_ψ are the same as defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

term "aryl," unless otherwise specified, refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (e.g., F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3 , cyano, nitro, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, $-SO_m R_\psi$, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, $CONHR_\pi$, $-OCOR_\pi$, $-COR_\pi$, $-NHSO_2 R_\pi$ or $-SO_2 NHR_\pi$ (wherein R_λ , R_π , m and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group,

wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms or a bicyclic or tricyclic aromatic group having from 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_{\lambda}R_{\pi}$, $CH=NOH$, $-(CH_2)_wC(=O)R_{\eta}$ {wherein *w* is an integer from 0-4 and R_{η} is hydrogen, hydroxy, OR_{λ} , $NR_{\lambda}R_{\pi}$, $-NHOR_{\omega}$ or $-NHOH$ }, $-C(=O)NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-SO_mR_{\psi}$, $-O-C(=O)NR_{\lambda}R_{\pi}$, $-O-C(=O)R_{\lambda}$, or $-O-C(=O)OR_{\lambda}$ (wherein *m*, R_{ψ} , R_{λ} and R_{π} are as defined earlier and R_{ω} is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinoxalinyl, carbazoyl phenothiazinyl, phenoxazinyl, benzothiazolyl or benzoxazolyl, and the like.

The The term "heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, $-O-C(=O)R_{\lambda}$, $-O-C(=O)OR_{\lambda}$, $-C(=O)NR_{\lambda}R_{\pi}$, SO_mR_{ψ} , $-O-C(=O)NR_{\lambda}R_{\pi}$, $-NHC(=O)NR_{\lambda}R_{\pi}$, $-NR_{\lambda}R_{\pi}$, mercapto, haloalkyl, thioalkyl, $-COOR_{\psi}$, $-COONHR_{\lambda}$, $-COR_{\lambda}$, $-NHSO_2R_{\lambda}$ or SO_2NHR_{λ} (wherein *m*, R_{ψ} , R_{λ} and R_{π} are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Such ring systems can be mono-, bi- or tricyclic. Carbonyl or sulfonyl group can replace carbon atom(s) of heterocyclyl. Unless otherwise constrained by the

definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl, 5 benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine or piperazinyl and the like.

10 The groups "aryl, heteroaryl and heterocyclyl" can optionally be substituted with substituent(s) selected from alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl, heterocycloalkyl, halogen, hydroxy, alkoxy, cyano, nitro, aryloxy, haloalkoxy, COR_b, CSR_b, COOR_b, S(O)_aR_b, OCOOR_b, NHSO₂R_b, NHCOR_b, NHCSR_b, (CH)₀₋₂C(=O)NR_cR_d or NR_cR_d (wherein R_b, R_c and R_d are independently selected from 15 hydrogen, alkyl, aryl, heteroaryl, heterocyclyl and a is an integer of from 0-2. Unless otherwise constrained, all substituents may optionally be further substituted by substituent(s) defined earlier.

 The term "pharmaceutically acceptable solvates" refers to solvates with either water (e.g., hydrates, hemihydrate or sesquihydrate), or pharmaceutically acceptable 20 solvents, for example solvates with common organic solvents as ethanol and the like. Such solvates are also encompassed within the scope of the disclosure.

 The present invention also includes within its scope prodrugs of these agents. In general, such prodrugs will be functional derivatives of these compounds, which are readily convertible *in vivo* into the required compound. Conventional procedure for the 25 selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H Bundgaard and, Elsevier, 1985. As used herein the term "prodrugs" refers to the compounds that are rapidly transformed *in vivo* to yield the parent compound of Formula I, for example by hydrolysis in blood.

 The disclosed compounds may get metabolized *in vivo* and these metabolites are 30 also encompassed within the scope of this invention.

The term "polymorphs" includes all crystalline form as well as amorphous forms for compounds described herein and as such are included in the present invention.

The phrase "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The term "pharmaceutically acceptable salts" refer to a salt prepared from pharmaceutically acceptable monovalent, divalent or trivalent non-toxic metal or organic base. Examples of such metal salts include, but are not limited to, lithium, sodium, potassium, calcium, magnesium, zinc, aluminum and the like. Examples of such organic bases include, but are not limited to, amino acid, ammonia, mono-alkyl ammonium, dialkyl ammonium, trialkyl ammonium and N-methyl glucamine and the like. The free acid forms of compounds of the present invention may be prepared from the salt forms, if desired, by contacting the salt with dilute aqueous solution of an acid, such as hydrochloric acid. The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point.

The term "pharmaceutically acceptable salts" can further refer to salts prepared from pharmaceutically acceptable non-toxic inorganic or organic acids. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitrous, nitric, carbonic, sulfuric, phosphoric acid, and the like. Appropriate organic acids include, but are not limited to aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, benzenesulfonic, panthenic, toluenesulfonic, 2-hydroxyethanesulfonic acid and the like.

The compounds of present invention include stereoisomers. The term "stereoisomer" refers to compounds, which have identical chemical composition, but differ with regard to arrangement of the atoms and the groups in space. These include enantiomers, diastereomers, geometrical isomers, atropisomer and conformational isomers

as defined by the IUPAC 1974 Recommendations for Section E. All these stereoisomers are included within the scope of this invention.

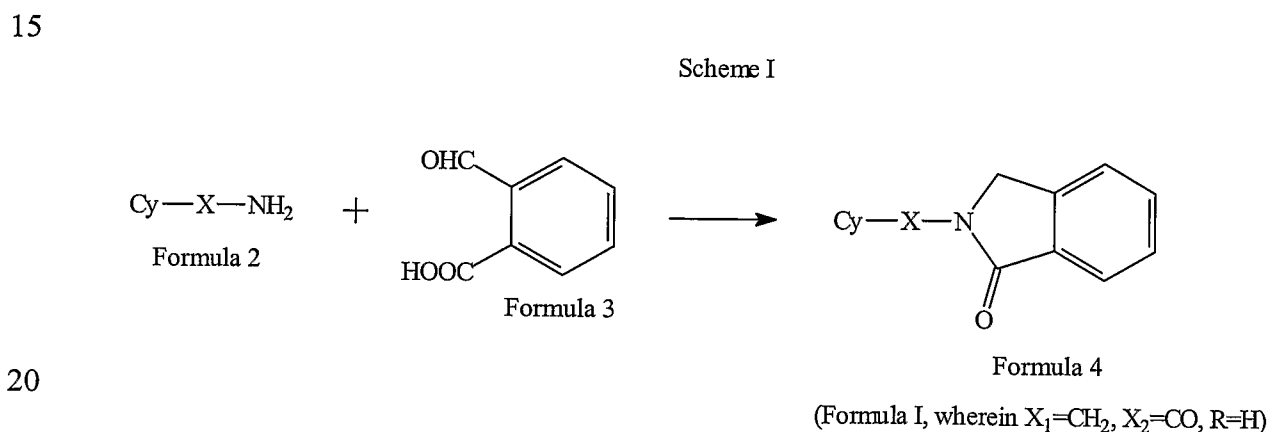
The term "subject" as used herein refers to human or lower mammal.

5 The term "treatment", as used herein, unless otherwise indicated, includes the treatment or prevention of a bacterial or fungal infection as provided in the method of the present invention.

The term "pharmaceutically acceptable" means approved by regulatory agency of the federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

10 Detailed Description of the Invention

The compounds disclosed herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds of the present invention may be prepared by the following reaction sequences as depicted in, for example, Schemes I and II.

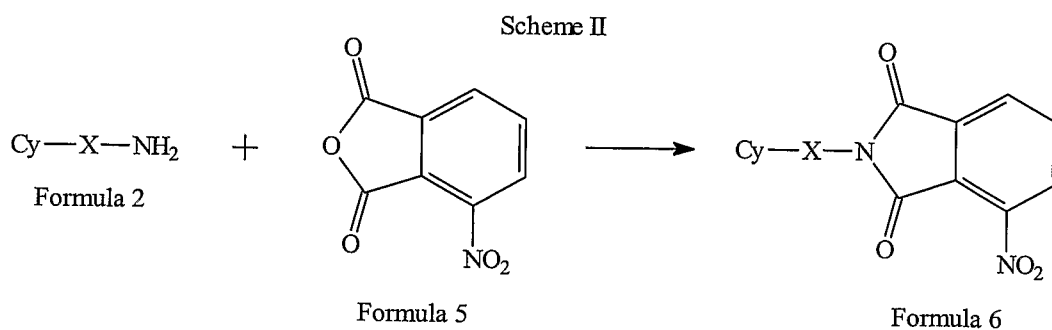


25 Compounds of Formula 4 can be prepared, for example, according to Scheme I. Thus, compounds of Formula 2 can be reacted with a compound of Formula 3 to form compounds of Formula 4 (wherein Cy can be cycloalkyl or heterocyclyl and X can be alkylene).

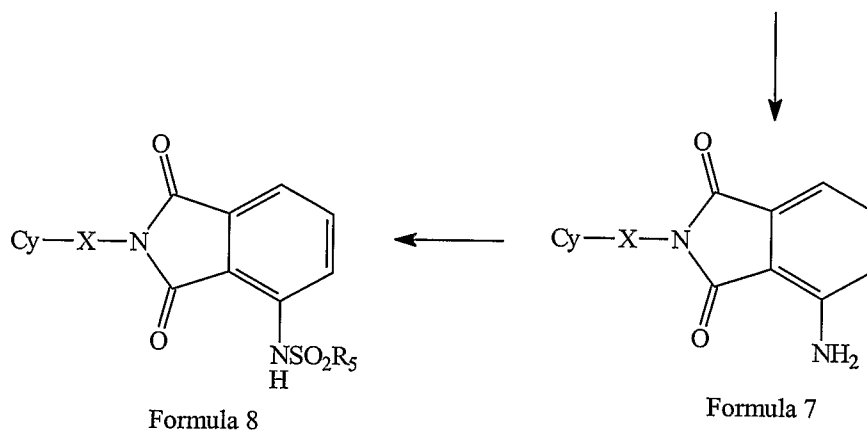
Compounds of Formula 2 can be reacted in one or more solvents, for example, chlorinated solvents (*e.g.*, chloroform, dichloromethane, carbon tetrachloride or dichloroethane), polar aprotic solvents (*e.g.*, dimethylsulfoxide, dimethylformamide, acetone, tetrahydrofuran or acetonitrile) or mixtures thereof.

Compounds of Formula 2 can also be reacted in one or more reducing agents, for example, sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, catalytic reducing agents, like hydrogen/Nickel, hydrogen/palladium, hydrogen/platinum or mixtures thereof.

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10



15

(Formula I, wherein, $\text{X}_1=\text{X}_2=\text{CO}$, $\text{R}=\text{NR}_3\text{R}_4$;
 $\text{R}_3=\text{H}$, $\text{R}_4=\text{SO}_2\text{R}_5$)

Compounds of Formula 8 can be prepared, for example, according to Scheme II. Thus, compound of Formula 2 can be reacted with a compound of Formula 5 to form compounds of Formula 6. Compounds of Formula 6 can be reduced to form compounds of Formula 7. Compounds of Formula 7 can be treated with compounds of Formula $\text{R}_5\text{SO}_2\text{Cl}$ (wherein R_5 can be alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, heterocycloalkyl, OR_6 , NHR_6 , NHSO_2R_6 , NHCOR_6 , NHCSR_6 , or $\text{NH}_2\text{C}=\text{NHSO}_2\text{R}_6$ (wherein R_6 can be alkyl, aryl, heteroaryl or heterocyclyl) to form compounds of Formula 8.

25

Compounds of Formula 2 can be reacted in one or more solvents, for example, chlorinated solvents (*e.g.*, chloroform, dichloromethane, carbon tetrachloride or dichloroethane). The reaction can also be carried out in one or more reagents, which can

act as dehydrating agents, for example, glacial acetic acid, sulfuric acid, perchloric acid or mixtures thereof.

Compounds of Formula 6 can be reduced in the presence of one or more reducing agents, for example, catalytic reducing agents (*e.g.* hydrogen/nickel, hydrogen/palladium or hydrogen/platinum), boron/tetrahydrofuran or mixtures thereof. The reduction can also be carried out in one or more solvents, for example, polar protic solvents (*e.g.* methanol, ethanol or isopropanol) in the presence of a base, for example, triethylamine, trimethylamine or ammonia.

Compounds of Formula 7 can be reacted in one or more solvents, for example, aprotic polar solvents (*e.g.* pyridine, dimethylformamide, dimethylacetamide, acetonitrile or dimethylsulfoxide) and in presence of one or more bases, for example, triethylamine, trimethylamine, tributylamine, 4-N-dimethylaminopyridine or mixtures thereof.

Particular illustrative compounds include those listed below:

2-[(1*S*)-2-cyclohexyl-1-methylethyl]isoindolin-1-one (Compound No. 1);

4-amino-2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 2);

2-[(1*S*)-2-cyclohexyl-1-methylethyl]-4-nitro-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 3);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 4);

2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 5);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 6);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 7);

N-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 8);

N-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-6-(1*H*-pyrrol-1-yl)pyridine-3-sulfonamide (Compound No. 9);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 10);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-3-fluoro-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 11);

5 *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (Compound No. 12);

10 *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 13);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 14);

15 *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 15); and

pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereo isomers, prodrugs, metabolites and N-oxides thereof.

20 Because of their antimicrobial activity, the compounds described herein may be administered to an animal for treatment orally, topically, rectally, internasally, or by a parenteral route. The pharmaceutical compositions of the present invention comprise a pharmaceutically effective amount of compounds described herein formulated together with one or more pharmaceutically acceptable carriers.

25 Solid form preparations for oral administration include capsules, tablets, pills, powders, granules, cachets and suppositories. For solid form preparations, the active compound can be mixed with at least one inert, pharmaceutically acceptable excipients or carrier, for example, sodium citrate, dicalcium phosphate and/or a filler or extenders, for example, starches, lactose, sucrose, glucose, mannitol and silicic acid; binders, for
30 example, carboxymethylcellulose, alginates, gelatins, polyvinylpyrrolidinone, sucrose, or acacia; disintegrating agents, for example, agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates and sodium carbonate; absorption accelerators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol, or glycerol mono stearate; adsorbants, for example, Kaolin; lubricants, for example, talc, calcium
35 stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulphate and mixture thereof. In the case of capsules, tablets, or pills, the dosage form may also comprise buffering agents.

The solid preparation of tablets, capsules, pills and granules can be prepared with coating and shells, for example, enteric coating and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. For liquid form preparations, the active compound can be mixed with water or other solvent, solubilizing agents and emulsifiers, for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1, 3-butylene glycol, dimethylformamide, oils, for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oil), glycerol, and fatty acid esters of sorbitan and mixture thereof. Besides inert diluents, the oral composition can also include adjuvants, for example, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents and perfuming agents.

Injectible preparations, for example, sterile injections, aqueous suspensions may be formulated according to the art using suitable dispersing or wetting and suspending agent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride.

Dosage forms for topical or transdermal administration of compounds provided herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active compound can be admixed under sterile condition with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations, eardrops, eye ointments, powder and solution are also contemplated as being within the scope of this invention.

The pharmaceutical preparation can be provided in a unit dosage form. In such forms, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be packaged preparation, the package containing discrete capsules, powders, in vials or ampoules, and ointments capsule, sachet, tablet, gel, cream itself or it can be the appropriate number of any of these packaged forms.

Examples set forth below demonstrate general synthetic procedures for the preparation of representative compounds. The examples are provided to illustrate

particular aspect of the disclosure and do not constrain the scope of the present invention as defined by the claims.

EXAMPLES

General Procedures

5 Example 1: Preparation of compounds of Formula 4

2-carboxy benzaldehyde (0.5 equiv.) of Formula 3 was added to a solution of compounds of Formula 2 (1 equiv.) in dichloroethane and the reaction mixture was stirred at room temperature for about 1 hour. Molecular sieves (1 gm) and sodium triacetoxo borohydride (1 equiv.) were added and the reaction mixture was stirred overnight at an ambient
10 temperature, filtered, and the mother liquor was washed with aqueous sodium bicarbonate solution. The organic layer was dried and evaporated under reduced pressure. The residue was purified by column chromatography to form compounds of Formula 4.

Example 2: Preparation of compounds of Formula 6

A solution of compounds of Formula 2 (1 equiv.) and 3-nitrophthalic anhydride (1
15 equiv.) of Formula 5 in acetic acid was stirred at about 100 °C for about 20 hours. Volatile matter was removed in *vacuo*, and the residue obtained was dissolved in dichloromethane. The solution was washed with sodium bicarbonate solution and with water. The dichloromethane layer was separated and the solvent was evaporated. The solid then obtained was purified over silica column using dichloromethane as eluent to form
20 compounds of Formula 6.

Example 3: Preparation of compounds of Formula 7

To a solution of compound of Formula 6 (1 equiv.) in methanol (50 mL) was added raney nickel (3 equiv.). To the stirred reaction mixture at room temperature hydrazine hydrate (3 equiv.) added slowly in about 1 hour and the reaction mixture was
25 allowed to stir at room temperature for about 3 hours. Filtered through a celite pad. The solid thus formed was purified by column chromatography to afford compounds of Formula 7.

Example 4: Preparation of compounds of Formula 8

N-acetamido phenyl sulfonyl chloride (1 equiv.) and triethylamine (5 equiv.) were added
30 to a solution of compound of Formula 7 (1.1 equiv.) in pyridine (5 mL). The reaction

mixture was stirred at room temperature for about 12 hours. Volatiles were removed in *vacuo* and the content was dissolved in dichloromethane. It was then washed with aqueous sodium bicarbonate solution. Dichloromethane layer collected was dried over anhydrous sodium sulfate. The solvent was removed and the solid obtained was purified over silica gel column, using dichloromethane as eluant to afford compounds of Formula 8.

The following compounds were prepared analogously, following the above general procedures:

Compound No. 1: 2-[(1*S*)-2-cyclohexyl-1-methylethyl]isoindolin-1-one

¹HNMR (CDCl₃): δ 7.86 (d; 1H), 7.53(d; 1H), 7.45 (t; 2H), 4.68 (m; 1H), 4.28 (dd, 2H), 1.95 (d, 1H), 1.58 (m, 5H), 1.42 (m, 1H). 1.25 (d, 3H), 1.17(m, 4H), 1.12 (m, 1H)
Mass (m/z): 258.2 (M+H);

Compound No. 2: 4-amino-2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione

¹HNMR (CDCl₃): δ 7.41 (t; 1H), 7.12 (d; 1H), 6.12 (d, 1H), 5.30 (bs, 2H), 4.44 (m; 1H), 2.04 (m, 1H), 1.8 (d, 2H), 1.62 (m, 4H), 1.51 (m, 1H). 1.42 (d, 3H). 1.12(m, 4H), 0.90 (m, 2H)
Mass (m/z): 287.2 (M+H);

Compound No. 3: 2-[(1*S*)-2-cyclohexyl-1-methylethyl]-4-nitro-1*H*-isoindole-1,3(2*H*)-dione

¹HNMR (CDCl₃): δ 8.10 (d; 2H), 7.90 (t; 1H), 4.53 (m; 1H), 2.02 (m, 1H), 1.8 (d, 2H), 1.58 (m, 5H), 1.42 (d, 3H). 1.17(m, 3H), 0.85 (m, 2H)
Mass (m/z): 317.1(M+H);

Compound No. 4: *N*-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl]amino)sulfonyl}phenyl}acetamide

¹HNMR (CDCl₃): δ 9.01 (bs, 1H), 7.89 (d, 2H), 7.82(d, 1H), 7.62 (t; 2H), 7.56 (t, 1H), 7.41 (d; 1H), 7.35 (bs, 1H), 4.39 (m; 1H), 2.19 (s, 3H), 1.96 (m, 1H), 1.80 (d, 2H), 1.60 (m, 5H), 1.40 (d, 3H). 1.12 (m, 4H), 0.90 (m, 2H)
Mass (m/z): 484.1 (M+H);

The following compounds can be prepared following the above general procedures

Compound No. 5: 2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione;

Compound No. 6: *N*-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl]amino)sulfonyl}phenyl}acetamide;

Compound No. 7: *N*-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl] amino)sulfonyl}phenyl}acetamide;

Compound No. 8: *N*-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide;

Compound No. 9: *N*-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-6-(1*H*-pyrrol-1-yl)pyridine-3-sulfonamide;

Compound No. 10: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide;

Compound No. 11: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-3-fluoro-4-(1*H*-pyrrol-1-yl)benzenesulfonamide;

Compound No. 12: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-1,2,4-triazol-1-yl)benzenesulfonamide;

Compound No. 13: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide;

Compound No. 14: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide;

Compound No. 15: *N*-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide;

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

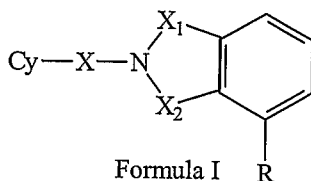
Microbiological activity

Microbroth minimum inhibitory concentration (MIC) is performed using NCCLS method in Cation adjusted Mueller Hinton broth for facultative cultures (*S.aureus*, Enterococcus) and Cation adjusted Mueller Hinton broth +2.5% lysed horse blood for *S.pneumoniae*. MIC against *H.influenzae* strains is performed by NCCLS broth dilution method using HTM broth. Overnight grown cultures are adjusted to 0.5 Mcfarland using normal saline and diluted 100 times. 1 mg/ml concentration of stock solution of drug in DMSO/ distilled water/ solvent given in NCCLS manual is prepared. NCCLS double dilutions are done to get the required concentration range of the drugs in the 96-well microtiter plates using the respective media. 100 µl of culture broth is added in wells already containing 100 µl of broth containing antibiotic to get approximately 3-7x10⁵ CFU/ml. The plates are incubated at 37°C for about 18- 24 hours. The concentration of drug at which there is complete disappearance of growth was considered as MIC.

Compounds 1-4 were tested for activity against *S.pneum* strains 3579, AB34, 49619 and 6303; against *H.influenza* strains 49427 and β -lac; against *S.pyo.* 19615; against *S.aureus* 25923; and against MRSA. The compounds gave MIC (μ g/ml) of between about 8 and about 32.

We claim:

1. A compound having the structure of Formula I,



pharmaceutically acceptable salts, pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites and N-oxide thereof, wherein:

Cy is cycloalkyl or heterocyclyl; X is alkylene; X₁ and X₂ are independently CO, CS or CH₂; and R is hydrogen, hydroxy, nitro, halogen, OR₁, OCONHR₁, OCONHSO₂R₁, SR₂ (wherein R₁ is aryl or heteroaryl and R₂ is hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroaryl or aryl) or NR₃R₄ {wherein R₃ and R₄ is independently hydrogen, SO₂R₅, COR₅, CSR₅, or COOR₅ [wherein R₅ is alkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, heterocycloalkyl, OR₆, NHR₆, NHSO₂R₆, NHCOR₆, NHCSR₆, or NH₂C=NHSO₂R₆ (wherein R₆ is alkyl, aryl, heteroaryl or heterocyclyl)]}, or R₃ and R₄, together with the nitrogen to which they are attached, form a heterocyclic ring.

2. A compound selected from the group consisting of:

2-[(1*S*)-2-cyclohexyl-1-methylethyl]isoindolin-1-one (Compound No. 1);

4-amino-2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 2);

2-[(1*S*)-2-cyclohexyl-1-methylethyl]-4-nitro-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 3);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 4);

2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 5);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 6);

N-{4-[(2-[(1*S*)-2-cyclohexyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl)amino)sulfonyl]phenyl}acetamide (Compound No. 7);

N-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 8);

N-{2-[(1*S*)-2-cyclohexyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-6-(1*H*-pyrrol-1-yl)pyridine-3-sulfonamide (Compound No. 9);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 10);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-3-fluoro-4-(1*H*-pyrrol-1-yl)benzenesulfonamide (Compound No. 11);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1*H*-1,2,4-triazol-1-yl)benzenesulfonamide (Compound No. 12);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 13);

N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 14);

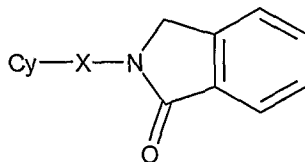
N-{2-[(1*S*)-2-cyclopentyl-1-methylethyl]-2,3-dihydro-1*H*-isoindol-4-yl}-4-(1,2,3-thiadiazol-4-yl)benzenesulfonamide (Compound No. 15);

3. A pharmaceutical composition comprising therapeutically effective amounts of one or more compounds of claim 1, together with pharmaceutically acceptable carrier, excipients, diluents or mixtures thereof.

4. A method for treating or preventing a subject suffering from a condition caused by or contributed to by bacterial infection or fungal infection, comprising administering to subject, a therapeutically effective amount of one or more compounds of claim 1.

5. A method according to claim 4 wherein bacterium is selected from *Staphylococci*, *Enterococci*, *Streptococci*, *Haemophilus*, *Moraxalla*, *Escherichia*, *Chlamydia*, *Rickettsiae*, *Mycoplasma*, *Legionella*, *Mycobacterium*, *Helicobacter*, *Clostridium*, *Bacteroides*, *Corynebacterium*, *Bacillus* or *Enterobacteriaceae*, and fungal organism, is selected from, *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Epidermophyton*, *Hendersonula*, *Histoplasma*, *Microsporium*, *Paecilomyces*, *Paracoccidioides*, *Pneumocystis*, *Trichophyton*, or *Trichosporium*.

6. A method for preparing the compounds of Formula 4,

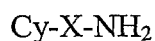


Formula 4

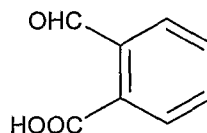
wherein Cy is cycloalkyl or heterocyclyl; **and** X is alkylene

the method comprising::

reacting a compound of Formula 2 with a compound of Formula 3



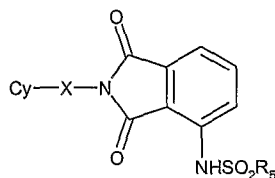
Formula 2



Formula 3

to form a compound of Formula 4.

7. A method of preparation of compounds of Formula 8,



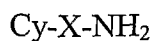
Formula 8

wherein Cy is cycloalkyl or heterocyclyl; X is alkylene; and R₅ is alkyl, aryl,

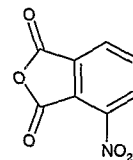
heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, heterocycloalkyl

the method comprising:

a) reacting a compound of Formula 2 with a compound of Formula 5



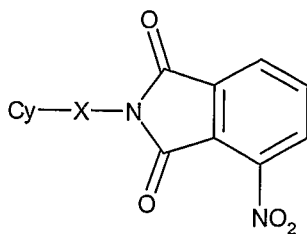
Formula 2



Formula 5

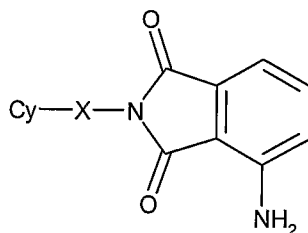
to give a compound of Formula 6;

- 22 -



Formula 6

- b) reducing the compound of Formula 6 to give a compound of Formula 7;
and



Formula 7

- c) reacting a compound of Formula 7 with a compound of R_5SO_2Cl to give a compound of Formula 8.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/002368

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/46 C07D209/48 C07D403/12 C07D401/12 C07D417/12
A61K31/4035 A61K31/4192 A61K31/4427 A61K31/433 A61P31/00

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)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/18772 A (CUBIST PHARM INC [US]) 6 April 2000 (2000-04-06) page 2 - page 6 claims 1-27	1-7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 10091186 XP002409495 abstract	1-3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 9408710 XP002409496 abstract	1,3,6,7
	----- -/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

28 November 2006

Date of mailing of the international search report

10/01/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Marzi, Elena

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/002368

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 3977741 XP002409497 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 171790 XP002409498 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 19390 XP002409499 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 14739 XP002409500 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 7645845 XP002409501 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 23320 XP002409502 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 198165 XP002409503 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 198169 XP002409504 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 197978 XP002409505 abstract	1,3,6,7
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/002368

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 8333220 XP002409506 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 8705946 XP002409507 abstract	1,3,6,7
X	----- DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHITI, W. ET AL: "Chemical structure and local anesthetic action. Tertiary alkylenamine derivatives of barbituric acid, urea, and phenylethylacetic acid" XP002409508 retrieved from STN Database accession no. 1959:105554 abstract & FARMACO, EDIZIONE SCIENTIFICA , 12, 551-75 CODEN: FRPSAX; ISSN: 0430-0920, 1957,	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 29121 XP002409509 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 253403 XP002409510 abstract	1,3,6,7
X	----- DATABASE BEILSTEIN CROSSFIRE Beilstein Institute of Organic Chemistry; BRN: 31066 XP002409511 abstract -----	1,3,6,7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002368

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 4-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/002368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0018772 A	06-04-2000	AU 6142199 A	17-04-2000