invent new strategies to control infection with drug resistant mycobacteria. One such strategy could be methods or compounds that enhance the host immune system.

SUMMARY OF THE INVENTION

[0005] In one example, there is disclosed the use of at least one compound in the manufacture of a medicament for preventing, treating or inhibiting mycobacterial infections, wherein the at least one compound is selected from the group consisting of: N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*]cycloocta[*jkl*]cyclopenta*[e]*-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR).

In another example, there is disclosed the use of at least one compound in the manufacture of a medicament for increasing the acidity of bacterial phagosomes to inhibit mycobacterial growth in a cell, wherein the use comprises contacting the cell with at least one of the compounds selected from the group consisting of:

N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*]cycloocta[*jkl*]cyclopenta[*e*]-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR). In yet another example, there is disclosed the use of at least one compound in the manufacture of a medicament for increasing mitrochondrial reactive oxygen species (mROS) generation to inhibit mycobacterial growth in a cell, wherein the use comprises contacting the cell with at least one of the compounds selected from the group consisting of: N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*] cycloocta[*jkl*]cyclopenta[*e*]-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR).

In the fourth aspect, the present invention refers to a pharmaceutical composition comprising: at least one of the compounds selected from the group consisting of: N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*]cycloocta[*jkl*]cyclopenta[*e*]-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR); and anti-tuberculosis drug. In aspect further example, there is disclosed the use of at least one compound in the manufacture of a medicament for eliciting an immune response to an intracellular mycobacteria, wherein the at least one compound is selected from the group consisting of:

N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*] cycloocta[*jkl*]cyclopenta[*e*]-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-

dicarboxylate (Nitrendipine); (RS)-2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl]-(methyl)amino}-2-prop-2-ylpentanenitrile (Verapamil); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR), in the manufacture of a medicament to inhibit bacterial growth in a cell.

[0012] In another example, there is provided a method for eliciting an immune response to intracellular bacteria. The method comprises administering at least one compound selected from the group consisting of: N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate (Bay K8644); 2,5-Dimethyl-4-[2-(phenylmethyl)benzoyl]-1H-pyrrole-3-carboxylic acid methyl ester (FPL 64176); 2',5'-Dideoxyadenosine; 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]- N,N-dimethyl-2,2-diphenylbutanamide hydrochloride (Loperamide); (5R,6S,8S)-Hexyl 6-hydroxy-5-methyl-13-oxo-6,7,8,13,14,15-hexahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[*b,h*]cycloocta[*jkl*]cyclopenta[*e*]-as-indacene-6-carboxylate (KT 5720); N-(dicyclopropylmethyl)-4,5-dihydro-1,3-oxazol-2-amine (Rilmenidine); 3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nimodipine); (RS)-ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Nitrendipine); (RS)-2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl]-(methyl)amino}-2-prop-2-ylpentanenitrile (Verapamil); (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine (Amiodarone); and [(2R,3S,4R,5R)-5-(4-Carbamoyl-5-aminoimidazol-1-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate (AICAR). In one aspect, the present invention refers to use of at least one compound in the manufacture of a medicament for preventing, treating or inhibiting mycobacterial infections, wherein the at least one compound is selected from the group consisting of N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); wherein the medicament further comprises an anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof. In another aspect, the present invention refers to use of at least one

compound in the manufacture of a medicament for inhibiting mycobacterial growth, wherein the medicament comprises at least one of the compounds selected from the group consisting of N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); wherein the medicament further comprises an anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof.

In yet another aspect, the present invention refers to a pharmaceutical composition comprising at least one of the compounds selected from the group consisting of: N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and 3,5,4'-trihydroxy-trans-stilbene (Resveratrol); and anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0014] **Figure 1** shows bar graphs of inhibition of intracellular mycobacterial growth by experimental compounds. THP1 cells were infected with *Mycobacterium bovis* BCG with a multiplicity of infection (MOI) of 5 for 3 hrs. Infected cells were washed to remove

Claims

1. Use of at least one compound in the manufacture of a medicament for preventing, treating or inhibiting mycobacterial infections, wherein the at least one compound is selected from the group consisting of:
N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and
3,5,4'-trihydroxy-trans-stilbene (Resveratrol);
wherein the medicament further comprises an anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof.

2. The use of claim 1, wherein the mycobacterial infection is an intracellular bacterial infection.

3. The use of claim 1, wherein the mycobacteria is selected from the group consisting of *M. tuberculosis, M. bovis, M. bovis BCG, M. africanum, M. canetti, M. caprae, M. microti, M. leprae, M. avium, M. paratuberculosis* and *M. pinnipedii*.

4. The use of claim 3, wherein the mycobacteria are *M. tuberculosis*.

5. The use of claim 3, wherein the mycobacteria are drug resistant *M. tuberculosis*.

6. The use of any one of the preceding claims, wherein the anti-tuberculosis drug is to be administered together with or separately from any one of the at least one compounds.

7. The use of any one of the preceding claims, wherein the at least one compound is selected from the group consisting of N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin) and 3,5,4'-trihydroxy-trans-stilbene (Resveratrol).

8. The use of any one of the preceding claims, wherein the concentration of the compound is about 250 mg/kg or about 500 mg/kg of body weight of the patient.

9. The use of any one of the preceding claims, wherein the route of administration is selected from the group consisting of systemic administration, oral administration, intravenous administration and parenteral administration.

10. Use of at least one compound in the manufacture of a medicament for inhibiting mycobacterial growth, wherein the medicament comprises at least one of the compounds selected from the group consisting of:
N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and
3,5,4'-trihydroxy-trans-stilbene (Resveratrol);
; wherein the medicament further comprises an anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof.

11. The use of claim 10, wherein the mycobacteria are drug resistant *M. tuberculosis*.

12. A pharmaceutical composition comprising:
at least one of the compounds selected from the group consisting of:
N,N-dimethyl imidodicarbonimidic diamide hydrochloride (Metformin); and 3,5,4'-trihydroxy-trans-stilbene (Resveratrol);
and anti-tuberculosis drug; wherein the anti-tuberculosis drug is selected from the group consisting of isoniazid, pyrazinamide, rifampicin, ethionamide, rifabutin, amikacin, ethambutol, PA824, bedaquiline, streptomycin, kanamycin, fluoroquinolone antibiotic and combinations thereof.

13. The use of claim 1, the use of claim 10, and the pharmaceutical composition of claim 12, wherein the compound comprises metformin, pyrazinamide and isoniazid.