

**SATURATED NITROGEN AND N-ACYLATED HETEROCYCLES
POTENTIATING THE ACTIVITY OF AN ACTIVE ANTIBIOTIC AGAINST
MYCOBACTERIA**

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The present invention relates to a compound for use in the treatment of bacterial and mycobacterial infections, such as for example tuberculosis, leprosy and atypical mycobacterial infections.

10 The present invention also concerns new compounds that can be used as medicament, in particular as medicament in the treatment of bacterial and mycobacterial infections such as, for example, tuberculosis, leprosy and atypical mycobacterial infections.

15 The present invention also concerns pharmaceutical compositions comprising, as the active ingredient, at least one of the abovementioned compounds and optionally an antibiotic active against bacteria and/or mycobacteria, notably an antibiotic activatable via the EthA pathway, more particularly an antibiotic chosen from the family of thioamides, for example ethionamide or prothionamide.

20 The present invention also concerns products (kits) containing at least one of the aforementioned compounds and at least one antibiotic active against bacteria and/or mycobacteria, notably an antibiotic activatable via the EthA pathway, more particularly an antibiotic chosen from the family of thioamides, for example ethionamide or prothionamide, as combination products for use simultaneously, separately or spread out in time, in the therapy of tuberculosis, leprosy or general mycobacterial infections

25 Tuberculosis kills 2 million people every year in the world. The AIDS epidemics and the emergence of strains that are multi-resistant to antibiotics contribute to exacerbating the impact of this illness, considered by the World Health Organization as responsible for an increasingly dangerous worldwide epidemic and as a health emergency on a global scale.

30 An increasing number of *Mycobacterium tuberculosis* strains is characterized nowadays by multi-resistance to first-line antibiotics such as isoniazid (INH) and rifampicin (RIF). These antibiotics must then be replaced by second-line antibiotics such as ethionamide (ETH) to which the strains are not resistant but which have the disadvantage of having a low therapeutic index (the therapeutic index of an active ingredient is the ratio of therapeutic dose to toxic dose).

35 One strategy consisting in increasing the activity of ethionamide (ETH) by associating it to a specific compound has already been considered. In fact, ETH is a prodrug that is transformed *in vivo* into a therapeutically active form by the EthA enzyme

(see the article "Activation of the prodrug ethionamide is regulated in mycobacteria", A.R. Baulard *et al.*, Journal of Biological Chemistry, 2000, 275, 28326-28331). The observed resistances to ETH arise from the fact that the transcriptional repressor EthR of *M. tuberculosis* controls the expression of the EthA enzyme and restricts the transformation of ETH into a therapeutically active substance.

One aim of the present invention is to propose new compounds likely to potentiate notably the activity of antibiotics active against tuberculosis, in particular an antibiotic chosen from the thioamide family, such as ethionamide or prothionamide for example.

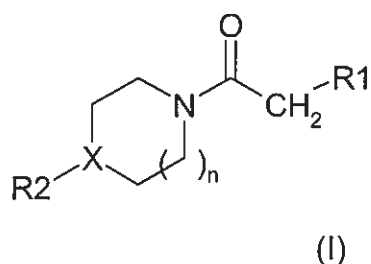
Another aim of the present invention is to propose compounds such as previously mentioned that, in combination with an antibiotic active against tuberculosis, chosen from the thioamide family, in particular ethionamide and/or prothionamide, and at identical antibiotics dosage, enable a greater efficiency to be achieved or that enable the aforementioned antibiotics dosage to be reduced to achieve a given efficiency.

Another aim of the present invention is to propose compounds such as previously mentioned that are simple and inexpensive to produce.

Another aim of the present invention is to propose compounds such as previously mentioned that are satisfactorily soluble in a biologic fluid.

Another aim of the present invention is to propose compounds such as previously mentioned that are likely to be active in particular orally and/or that cause fewer side effects.

To achieve at least one of the aforementioned aims, the present invention thus proposes compounds of the general formula (I):



in which:

n = 0 or 1;

R1 represents a group chosen from:

linear or branched and optionally substituted C1-C5 alkyl chains;

in particular substituted by at least one fluorine atom (F),

linear or branched C1-C3 alkyl chains substituted by at least one fluorine atom (F) or by a

C3-C6 saturated or unsaturated cyclic group; and

the groups CH₂CF₃, (CH₂)₂CF₃, CF₂CF₃ ;

X is chosen from N and CH;

R2 is chosen from the following groups: phenyl, benzyl, phenyl or benzyl groups substituted by at least one linear or branched C1-C4 alkyl chain, phenyl or benzyl groups substituted by at least one linear or branched and substituted C1-C4 alkyl chains, in particular substituted by at least one fluorine atom (F), phenyl groups substituted by at least one group chosen from Cl, F, CF₃, OCH₃, OCF₃, or OH, and the heterocycles having 6 vertices, saturated or unsaturated, comprising one, two or three nitrogen atoms.

Advantageously, $m = n = 1$. Such components in combination with ethionamide prove particularly active on mycobacteria, in particular on *M. tuberculosis*.

R1 can be chosen from the following groups: -CH₂-isopropyl; cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, and -CH₂-cyclopentyl.

Advantageously, R1 is a -CH₂CF₃ group. Such components exhibit a good potentiating activity of ethionamide, in particular on *M. tuberculosis*.

Advantageously, X = CH. Such components have proven more efficient in combination with ethionamide, in particular on the bacterium *M. tuberculosis*.

According to a first embodiment, R2 is a phenyl group.

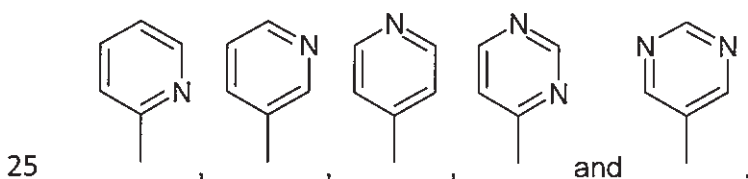
According to a second embodiment, R2 is a benzyl group.

According to a third embodiment, R2 is a phenyl group substituted by at least one F atom.

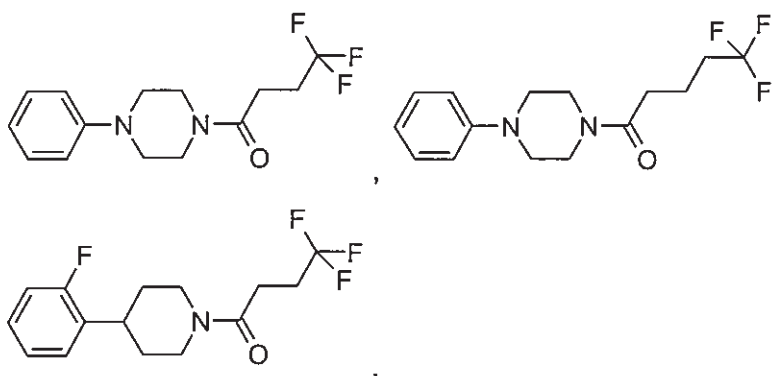
According to a fourth embodiment, R2 is a phenyl group substituted in meta position relative to the bonding to X, by Cl, F, CF₃ or CH₃.

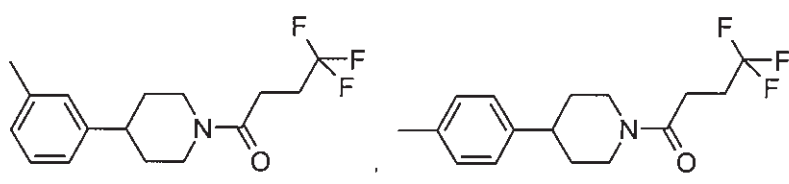
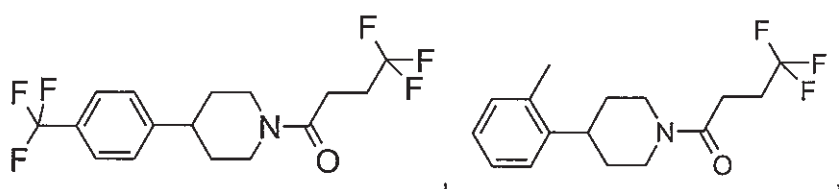
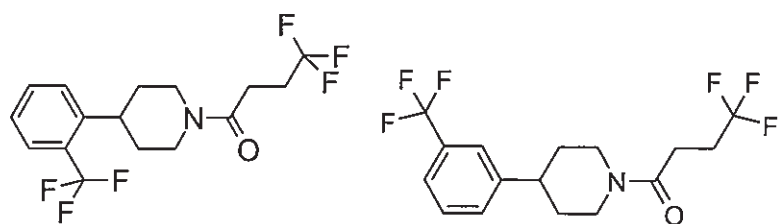
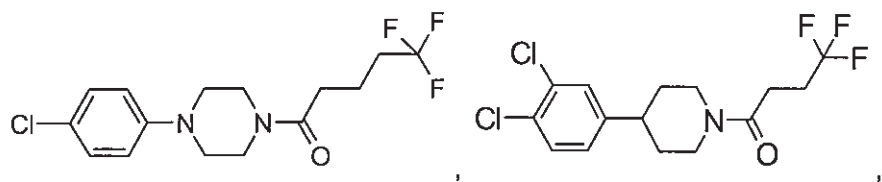
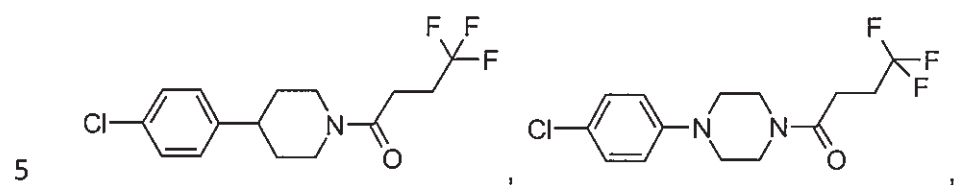
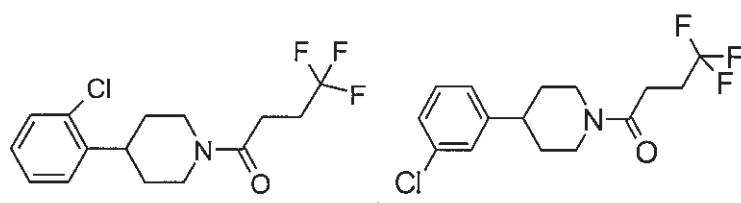
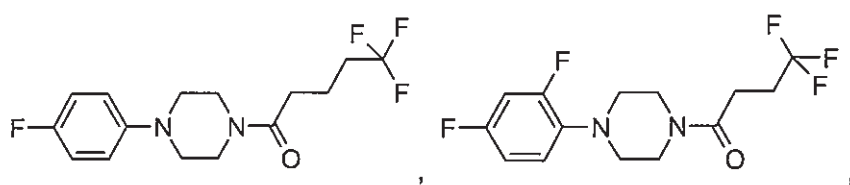
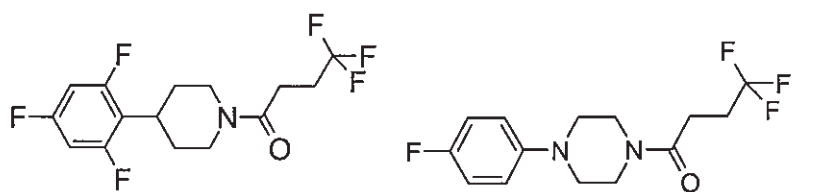
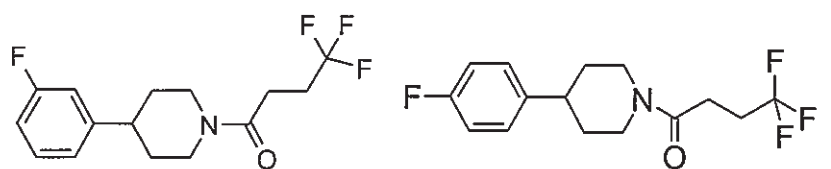
Advantageously, R2 is a phenyl group substituted in para position relative to its bonding to X by a fluorine atom F.

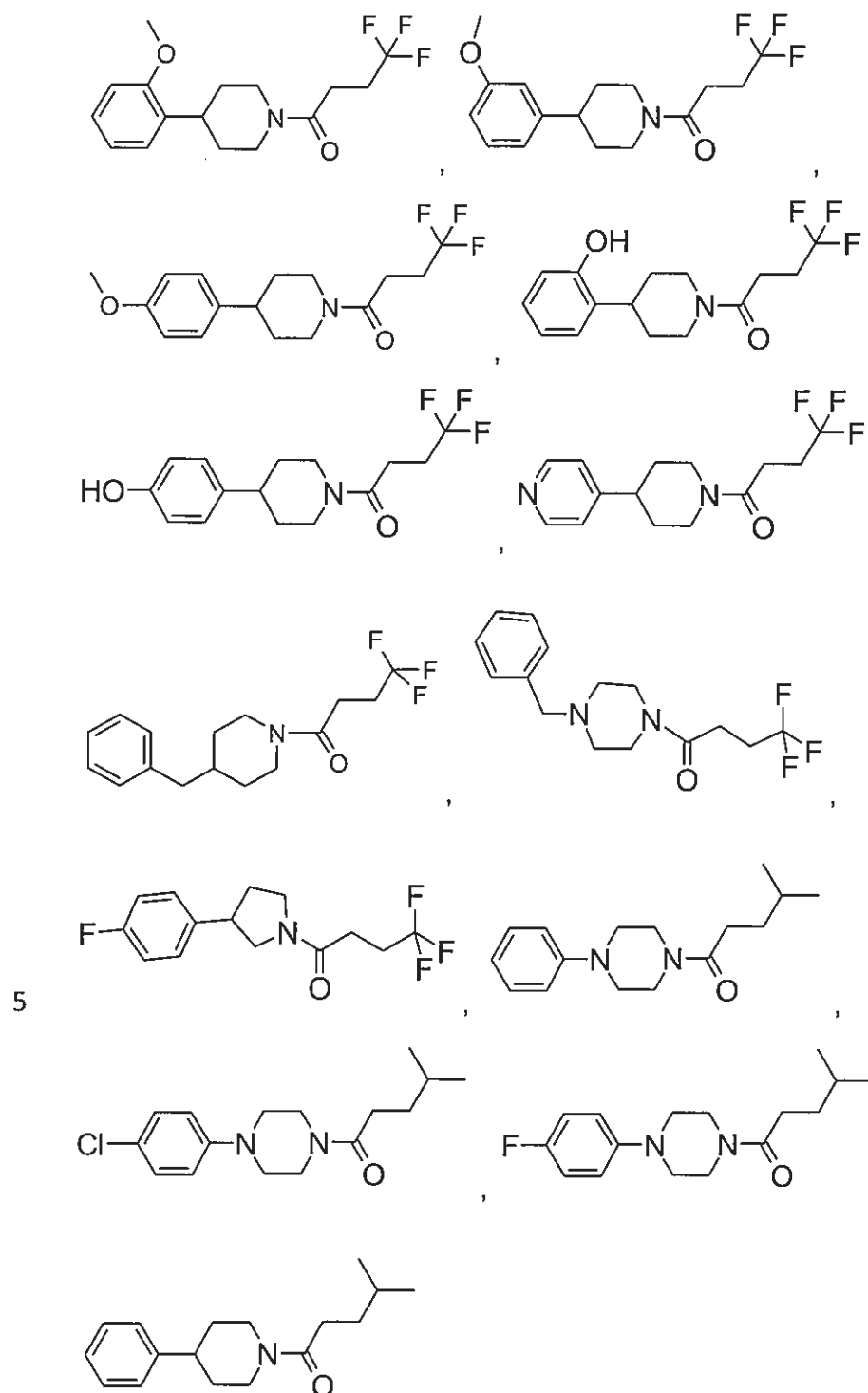
According to another embodiment, R2 is a group chosen from the following groups:



The inventive compound can be chosen from the following compounds:







The present invention also concerns the aforementioned compound for its use as
 10 medicament, in particular for its use in the treatment of bacterial and mycobacterial
 infections, notably in the treatment of tuberculosis, leprosy or atypical mycobacterial
 infections.

The present invention also concerns a pharmaceutical composition comprising, as the active ingredient, at least one compound of general formula (I) as previously mentioned and one pharmaceutically acceptable excipient.

Within the pharmaceutical compositions according to the invention, the compound
5 or compounds used as active ingredient(s) can be used in a quantity that enables unit doses comprised between 0.3mg and 1g approximately to be administered. Within the pharmaceutical compositions according to the invention, the antibiotic or antibiotics active against mycobacteria are, when present, advantageously used in a quantity enabling the administration of unit doses equal to or lower than the doses usually recommended by the
10 World Health Organization (WHO, Treatment of tuberculosis: Guidelines for National Programs. 2003; WHO/CDS/TB2003.313.), national or non-governmental health organizations or the competent pharmaceutical laboratories.

The one skilled in the art is able to choose one or several pharmaceutically acceptable excipients depending on the route of administration of the pharmaceutical
15 composition. The one skilled in the art will of course ensure in doing so that the excipient or excipients used are compatible with the intrinsic properties attached to the composition according to the present invention. Furthermore, the form of the medicament or pharmaceutical composition (for example a solution, a suspension, an emulsion, tablets, capsules, suppositories etc.) will depend on the chosen administration route.

Thus, in the sense of the present invention, the medicament or pharmaceutical
20 composition can be administered by any appropriate route, for example oral, anal, local (topical for example), systemic, intravenous, intramuscular or mucosal route, or else by using a patch, or else in encapsulated form in or immobilized on liposomes, microparticles, microcapsules, associated to nanoparticles and similar. By way of non-
25 limiting examples of excipients suitable for administration by the oral route, one can notably cite talcum, lactose, starch and its derivatives, cellulose and its derivatives, polyethylene glycols, acrylic acid polymers, gelatin, magnesium stearate, animal, vegetal or synthetic fats, paraffin derivatives, glycols, stabilizers, preservatives, anti-oxidants, wetting agents, anti-caking agents, dispersants, emulsifiers, taste modifying agents,
30 penetrating agents, solubilizing agents etc. The formulation and administration techniques for the medicaments and pharmaceutical compositions are well known in the art here under consideration, the one skilled in the art can notably refer to the work Remington's Pharmaceutical Sciences, latest edition.

The present invention also has the aim of using at least one compound according
35 to the invention for the manufacture of a medicament intended for the prevention and/or treatment of bacterial infections, preferably mycobacterial infections, and more particularly of tuberculosis, leprosy or atypical mycobacterial infections.

Advantageously, the pharmaceutical composition further comprises, as active ingredient, at least one antibiotic active against bacteria and/or mycobacteria, in particular an antibiotic activatable via the EthA pathway, more particularly an antibiotic chosen notably from the thioamide family, in particular from ethionamide and prothionamide.

5 However, the invention is not limited to these antibiotics.

The inventive compounds prove to be compounds potentiating antibiotics activatable via the EthA pathway ; however, the inventive compounds can also be used as potentiating agents of the antibiotic activity of antibiotics that can be bio-activated via another bio-activation pathway or pathways than the aforementioned one.

10 The present invention also concerns a kit or product containing at least one compound of formula (I) and at least one antibiotic active against bacteria and/or mycobacteria in particular, in particular an antibiotic activatable via the enzymatic EthA pathway, more particularly an antibiotic chosen from the thioamide family, in particular chosen from ethionamide and prothionamide as combination products for use,
15 simultaneously, separately or spread out in time, in the therapy of tuberculosis, leprosy or general mycobacterial infections.

DEFINITIONS

20 Within the whole of the present application, when it is not indicated that a group, whatever it is, is substituted, the latter is not substituted.

Within the meaning of the present invention, a substituted phenyl group is defined as a mono-, di- or tri-substituted phenyl group. The position of the substituent or substituents, when it is not indicated, is not limited according to the invention. When the
25 substituent or substituents are indicated, the phenyl group can also comprise one or several other substituents different from those mentioned.

Preferably, the phenyl groups substituted by Cl, CF₃, and CH₃ are mono-substituted and the substituent (Cl, CF₃ or CH₃) is preferably in meta position relative to the carbon of the benzene cycle bound to X. Preferably, X is CH.

30 In the case of a phenyl group substituted by a fluorine atom, all the groups mono-, di- or tri-substituted by fluorine atoms are included in the present invention. Advantageously, the phenyl groups substituted by one or several fluorine atoms are not substituted by another group or by another atom other than F. Thus, phenyl groups substituted by at least one fluorine atom include, within the meaning of the present
35 invention, phenyl groups mono-substituted by a fluorine atom, situated in ortho, meta or para position of the carbon of the benzene cycle bound to X, phenyl groups substituted by two fluorine atoms, in particular phenyl groups substituted by two fluorine atoms placed in

ortho and para position of the bond of the benzene cycle with X, phenyl groups having three carbon atoms substituted each by a fluorine atom, in particular a phenyl group tri-substituted by three fluorine atoms of which two fluorine atoms are in ortho position of the bond of the benzene cycle with X and one fluorine atom is in para position relative to this
5 bond.

Atypical mycobacterial infections are defined here as mycobacterial infections caused by at least one mycobacterium other than *M. Tuberculinum* and in particular mycobacterial infections involving *M. Kansasii*.

According to the present invention, the term "treatment" designates the curative
10 treatment and/or prophylactic treatment of the aforementioned infections. The term "treatment" includes all improvement of the patient's state, in particular any diminution of the number of bacteria present in at least one infection site of the patient.

Within the meaning of the present invention, an antibiotic active against bacteria and/or mycobacteria is defined as any agent capable of limiting or reducing at least *in vitro*
15 the proliferation of a bacterium and/or of a mycobacterium, in particular *M. tuberculosis*. An agent capable of destroying, at least *in vitro*, a mycobacterium, notably *M. tuberculosis*, is also an antibiotic active against mycobacteria within the meaning of the present invention. Among the antibiotics active against mycobacteria and activatable via the enzymatic EthA pathway, ethionamide, prothionamide, isoxyl, thiacetazone and the
20 mixtures of at least two of these antibiotics can be mentioned.

In the present invention, an antibiotic activatable via the EthA pathway is defined as any substance that at least *in vitro* reacts with the EthA enzyme to produce a substance having antibiotic properties. The one skilled in the art is able to determine if an antibiotic is activatable by the EthA pathway for example by applying the method described in the
25 following publication: "Activation of the prodrug ethionamide is regulated in mycobacteria" A.R. Baulard *et al.*, Journal of Biological Chemistry, 2000, 275, 28326-28331.

The antibiotic within the meaning of the present invention can also be an antibiotic activatable via another bio-activation pathway than the aforementioned one.

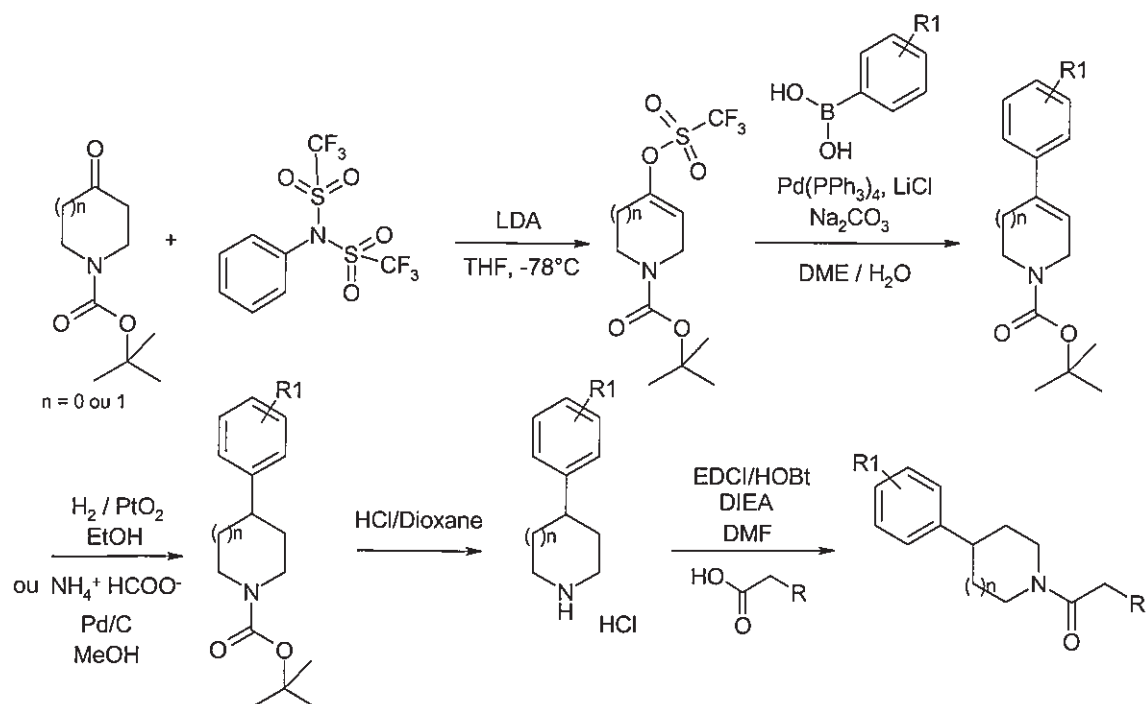
30 EXPERIMENTAL SECTION

SYNTHESIS PROCESS(ES)

Nuclear magnetic resonance spectra (NMR) ^1H and ^{13}C were performed at ambient temperature on a Bruker TM DPX 300 spectrometer at 300 MHz. The chemical shifts are
35 expressed in parts per million (ppm). The assignments have been performed using ^1H and ^{13}C one-dimensional (1D) or two-dimensional (2D) HSQC-COSY experiments. Mass

spectra were performed on an LCMS Waters Alliance Micromass ZQ 2000 system. The commercial reagents and solvents were used without ulterior purification.

General flow diagram of the synthetic process(es) for piperidino and pyrrolidino derivatives:

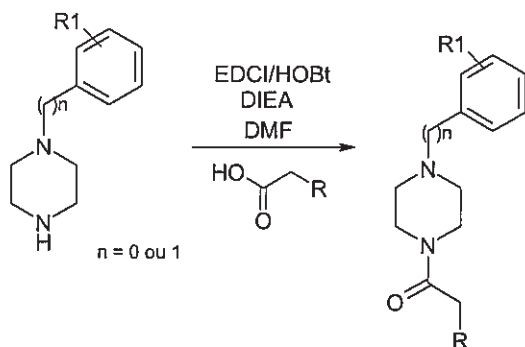


Protocol:

- The LDA (solution at 2M in THF/heptane/ethyl benzene, 3.3 mmole 1.1 eq) is added with 5mL anhydrous THF in a flask previously oven-dried and put under argon. The solution is cooled to -78°C. The N-Boc-4-piperidone (or N-Boc-3-pyrrolidinone) (3 mmol, 1 eq) dissolved in 5 mL THF is added drop-wise, then the reaction medium is agitated for 20 minutes at -78°C. The N-phenyl-trifluoromethane-sulphonimide (3.3 mmol, 1.1 eq) dissolved in 5 mL THF is added. The solution is agitated 2h at 0°C and then evaporated. The residue is dissolved in a mixture of cyclohexane/AcOEt 9:1 and then filtrated on alumina. The product (triflate) is used in the next step without purification.
- In a flask containing the triflate (1 eq) and put under argon, one adds the boronic acid (1.1 eq), LiCl (3 eq), the 2N solution of Na2CO3 (1.4 eq), the DME (0.34 M) and the tetrakis(triphenylphosphine)palladium (0.05 eq). The solution is heated between 1h and 16h under reflux and then evaporated. The residue is taken up in AcOEt and then washed once using water and once using a solution saturated with NaCl. The organic phase is dried and then evaporated. The residue is taken up in AcOEt and then filtrated on sintered glass. The solvent is evaporated, then the product is purified using chromatography on silica gel (cyclohexane/AcOEt).

- The unsaturated derivative (1 eq) is dissolved in ethanol (0.1M) with PtO_2 (0.1 eq) or Pd/C (0.1 eq). The reaction mixture is put under hydrogen and agitated at ambient temperature until the input product has disappeared. The solution is filtrated on celite, then evaporated.
- Or: the unsaturated derivative (1 eq) is dissolved in methanol (0.1M) with ammonium formate (5 eq) and Pd/C (10% by mass). The reaction mixture is heated under reflux until the input product has disappeared. The solution is filtrated on celite and then evaporated.
- The protected amine (1 eq.) is added in a flask with dioxane (1 M), then a solution of HCl 4N in dioxane (5 eq) is added. The solution is agitated 1 h at ambient temperature, then evaporated. The residue is taken over in light petroleum and then filtrated on sintered glass.
- The acid (1.3 eq) is activated using EDCI (1.3 eq) and HOBt (0.4 eq) in DMF (0.25 M) in the presence of DEIA (4 eq) and then the amine (1 eq) is added. The solution is agitated 3h at ambient temperature and then evaporated. The residue is dissolved in AcOEt and then washed twice using saturated NaHCO_3 , twice using HCl 1N and once using saturated NaCl . The organic phase is dried on MgSO_4 and then evaporated. The residue is purified using preparative HPLC.

General flow diagram of the synthetic process(es) for piperazines:

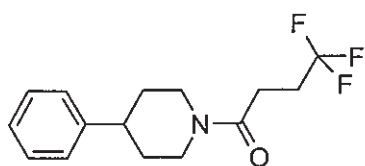


Protocol:

- The acid (1.3 eq) is activated using EDCI (1.3 eq) and HOBt (0.4 eq) in DMF (0.25 M) in the presence of DIEA (4 eq), then the commercially available piperazine (1 eq) is added. The solution is agitated 3h at ambient temperature, then evaporated. The residue is dissolved in AcOEt, then washed twice using saturated NaHCO₃, twice using HCl 1N and once using saturated NaCl. The organic phase is dried on MgSO₄ then evaporated. The residue is purified using preparative HPLC.

BDM_44647

- 4-phenylpiperidine is commercially available. Only the coupling has been performed.

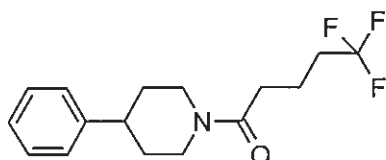


- ¹H NMR (CD₂Cl₂) δ 7.36-7.31 (m, 2H), 7.25-7.21 (m, 3H), 4.78-4.71 (m, 1H), 3.99-3.93 (m, 1H), 3.22-3.12 (m, 1H), 2.84-2.48 (m, 6H), 1.96-1.86 (m, 2H), 1.72-1.56 (m, 2H). MS [M + H]⁺ m/z 286.

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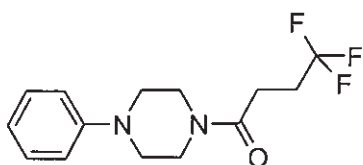
BDM_44648

4-phenylpiperidine is commercially available. Only the coupling has been performed.



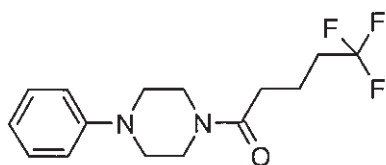
- ¹H NMR (CD₂Cl₂) δ 7.36-7.31 (m, 2H), 7.25-7.20 (m, 3H), 4.78-4.72 (m, 1H), 3.99-3.92 (m, 1H), 3.19-3.09 (m, 1H), 2.81-2.60 (m, 2H), 2.45 (t, J = 7.0 Hz, 2H), 2.29-2.16 (m, 2H), 1.97-1.87 (m, 4H), 1.70-1.54 (m, 2H). MS [M + H]⁺ m/z 300.

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BDM_44808

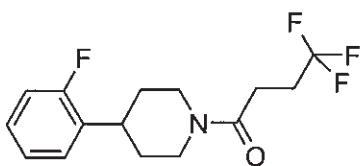
- ¹H NMR (CDCl₃) δ 7.34-7.28 (m, 2H), 6.97-6.94 (m, 3H), 3.83-3.80 (m, 2H), 3.67-3.64 (m, 2H), 3.24-3.17 (m, 4H), 2.68-2.49 (m, 4H). MS [M + H]⁺ m/z 287.

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BDM_44809

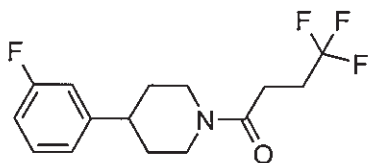
^1H NMR (CDCl_3) δ 7.34-7.28 (m, 2H), 6.97-6.94 (m, 3H), 3.82-3.79 (m, 2H), 3.65-3.62 (m, 2H), 3.22-3.16 (m, 4H), 2.48 (t, $J = 7.2$ Hz, 2H), 2.31-2.15 (m, 2H), 2.03-1.92 (m, 2H).

5 MS $[\text{M} + \text{H}]^+ m/z$ 301.

BDM_70666

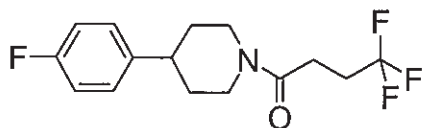
10 ^1H NMR (CD_2Cl_2) δ 7.27-7.20 (m, 2H), 7.16-7.03 (m, 2H), 4.79-4.73 (m, 1H), 3.98-3.93 (m, 1H), 3.24-3.08 (m, 2H), 2.74-2.48 (m, 5H), 1.95-1.86 (m, 2H), 1.74-1.63 (m, 2H).

MS $[\text{M} + \text{H}]^+ m/z$ 304.

BDM_70531

15 ^1H NMR (CD_2Cl_2) δ 7.27-7.20 (m, 2H), 7.16-7.02 (m, 2H), 4.79-4.74 (m, 1H), 3.99-3.94 (m, 1H), 3.24-3.09 (m, 2H), 2.75-2.49 (m, 5H), 1.95-1.86 (m, 2H), 1.75-1.59 (m, 2H).

MS $[\text{M} + \text{H}]^+ m/z$ 304.

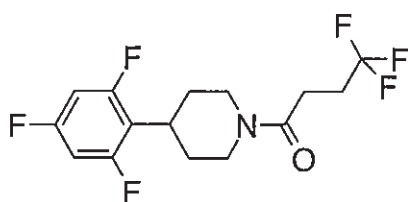
BDM_44751

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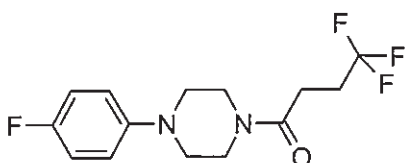
^1H NMR (CD_2Cl_2) δ 7.33-7.19 (m, 2H), 7.06-7.00 (m, 2H), 4.77-4.72 (m, 1H), 3.98-3.92 (m, 1H), 3.21-3.11 (m, 1H), 2.83-2.49 (m, 6H), 1.94-1.86 (m, 2H), 1.68-1.46 (m, 2H).

^{13}C NMR (CD_2Cl_2) δ 167.64, 161.45 (d, $J = 244$ Hz), 141.20, 127.42 (q, $J = 274$ Hz), 128.16 (d, $J = 8$ Hz), 115.11 (d, $J = 21$ Hz), 45.83, 42.40, 41.91, 33.81, 32.96, 29.53 (q, J

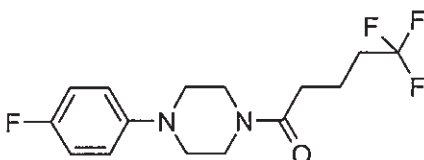
25 = 29 Hz), 25.79. MS $[\text{M} + \text{H}]^+ m/z$ 304.

BDM_71148

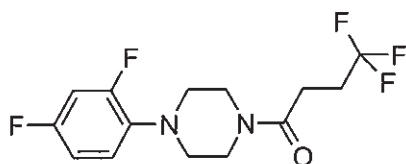
^1H NMR (CD_2Cl_2) δ 6.69 (t, $J = 8.7$ Hz, 2H), 4.78-4.72 (m, 1H), 3.98-3.92 (m, 1H), 3.27-3.10 (m, 2H), 2.68-2.48 (m, 5H), 2.07-1.90 (m, 2H), 1.82-1.74 (m, 2H). MS $[\text{M} + \text{H}]^+$ m/z 340.

BDM_44819

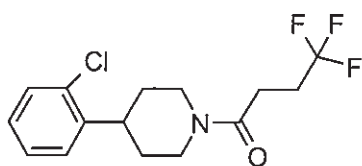
^1H NMR (CD_2Cl_2) δ 7.04-6.98 (m, 2H), 6.95-6.90 (m, 2H), 3.79-3.75 (m, 2H), 3.64-3.61 (m, 2H), 3.14-3.07 (m, 4H), 2.61-2.46 (m, 4H). MS $[\text{M} + \text{H}]^+$ m/z 305.

BDM_44820

^1H NMR (CD_2Cl_2) δ 7.04-6.98 (m, 2H), 6.94-6.89 (m, 2H), 3.77-3.74 (m, 2H), 3.62-3.59 (m, 2H), 3.12-3.06 (m, 4H), 2.45 (t, $J = 7.2$ Hz, 2H), 2.25-2.15 (m, 2H), 1.97-1.87 (m, 2H). MS $[\text{M} + \text{H}]^+$ m/z 319.

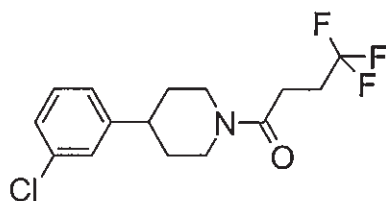
BDM_70669

^1H NMR (CD_2Cl_2) δ 6.99-6.82 (m, 3H), 3.79-3.76 (m, 2H), 3.64-3.61 (m, 2H), 3.05-2.99 (m, 4H), 2.67-2.48 (m, 4H). MS $[\text{M} + \text{H}]^+$ m/z 323.

BDM_70534

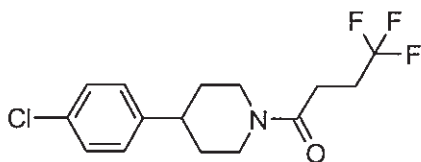
^1H NMR (CD_2Cl_2) δ 7.41-7.39 (m, 1H), 7.32-7.17 (m, 3H), 4.80-4.75 (m, 1H), 3.99-3.94 (m, 1H), 3.35-3.17 (m, 2H), 2.76-2.49 (m, 5H), 1.99-1.89 (m, 2H), 1.66-1.53 (m, 2H).

5 MS $[\text{M} + \text{H}]^+$ m/z 320.

BDM_70668

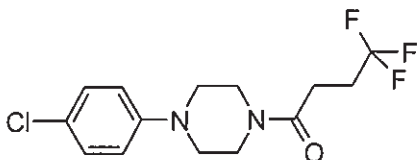
10 ^1H NMR (CD_2Cl_2) δ 7.32-7.21 (m, 3H), 7.15-7.13 (m, 1H), 4.78-4.72 (m, 1H), 3.98-3.93 (m, 1H), 3.21-3.11 (m, 1H), 2.83-2.48 (m, 6H), 1.95-1.87 (m, 2H), 1.69-1.52 (m, 2H).

MS $[\text{M} + \text{H}]^+$ m/z 320.

BDM_70535

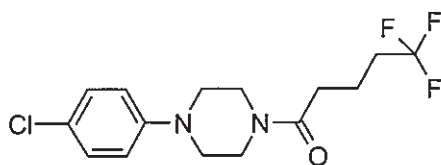
15 ^1H NMR (CD_2Cl_2) δ 7.33-7.30 (m, 2H), 7.20-7.17 (m, 2H), 4.78-4.71 (m, 1H), 3.99-3.92 (m, 1H), 3.21-3.11 (m, 1H), 2.82-2.48 (m, 6H), 1.94-1.86 (m, 2H), 1.67-1.51 (m, 2H).

MS $[\text{M} + \text{H}]^+$ m/z 320.

BDM_44811

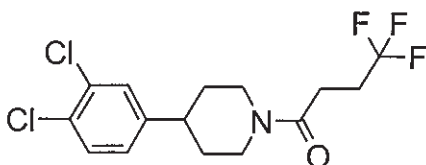
20

^1H NMR (CD_2Cl_2) δ 7.28-7.23 (m, 2H), 6.91-6.86 (m, 2H), 3.78-3.75 (m, 2H), 3.64-3.61 (m, 2H), 3.20-3.13 (m, 4H), 2.67-2.46 (m, 4H). MS $[\text{M} + \text{H}]^+$ m/z 321.

BDM_44812

^1H NMR (CD_2Cl_2) δ 7.27-7.22 (m, 2H), 6.91-6.86 (m, 2H), 3.77-3.74 (m, 2H), 3.62-3.59 (m, 2H), 3.18-3.12 (m, 4H), 2.45 (t, $J = 7.2$ Hz, 2H), 2.31-2.15 (m, 2H), 1.97-1.87 (m, 2H).

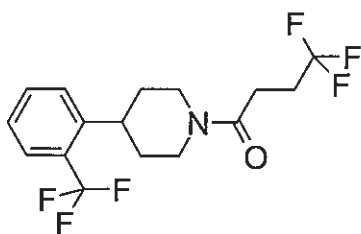
5 MS $[\text{M} + \text{H}]^+ m/z$ 335.

BDM_70716

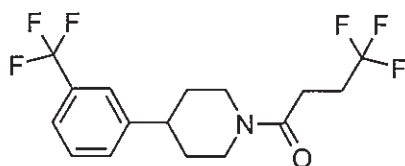
10 ^1H NMR (CDCl_3) δ 7.39 (d, $J = 8.3$ Hz, 1H), 7.29 (d, $J = 2.0$ Hz, 1H), 7.04 (dd, $J = 8.3$ Hz, $J = 2.0$ Hz, 1H), 4.82-4.77 (m, 1H), 4.00-3.94 (m, 1H), 3.21-3.12 (m, 1H), 2.79-2.48 (m, 6H), 1.96-1.88 (m, 2H), 1.67-1.51 (m, 2H).

^{13}C NMR (CDCl_3) δ 167.99, 145.10, 132.60, 130.58, 128.84, 127.11 (q, $J = 275$ Hz), 126.11, 45.74, 42.40, 41.90, 33.48, 32.53, 29.69 (q, $J = 29$ Hz), 25.95. MS $[\text{M} + \text{H}]^+ m/z$ 354.

15

BDM_70536

20 ^1H NMR (CD_2Cl_2) δ 7.68 (d, $J = 4.5$ Hz, 1H), 7.58 (t, $J = 4.5$ Hz, 1H), 7.46 (d, $J = 4.5$ Hz, 1H), 7.37 (t, $J = 4.5$ Hz, 1H), 4.81-4.77 (m, 1H), 4.00-3.97 (m, 1H), 3.23-3.17 (m, 2H), 2.73-2.52 (m, 5H), 1.92-1.85 (m, 2H), 1.75-1.68 (m, 2H). MS $[\text{M} + \text{H}]^+ m/z$ 354.

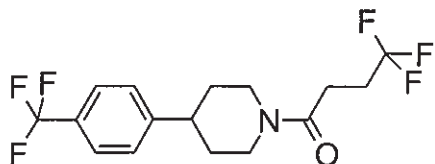
BDM_70546

^1H NMR (CD_2Cl_2) δ 7.51-7.46 (m, 4H), 4.80-4.75 (m, 1H), 4.01-3.95 (m, 1H), 3.23-3.14 (m, 1H), 2.93-2.82 (m, 1H), 2.74-2.50 (m, 5H), 1.99-1.90 (m, 2H), 1.74-1.57 (m, 2H).

^{13}C NMR (CD_2Cl_2) δ 167.72, 146.30, 130.56 (q, $J = 32$ Hz), 130.37, 129.09, 127.44 (q, $J = 275$ Hz), 124.35 (q, $J = 275$ Hz), 123.51 (q, $J = 4$ Hz), 123.25 (q, $J = 4$ Hz), 45.73, 42.48,

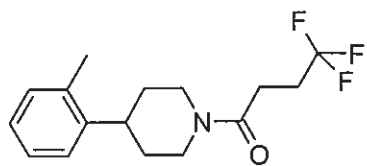
5 42.29, 33.46, 32.63, 29.52 (q, $J = 28$ Hz), 25.83. MS $[\text{M} + \text{H}]^+ m/z$ 354.

BDM_70667



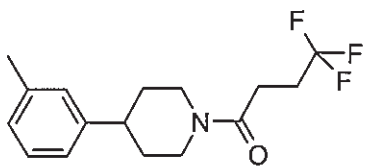
10 ^1H NMR (CD_2Cl_2) δ 7.61 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 4.80-4.74 (m, 1H), 4.01-3.95 (m, 1H), 3.23-3.13 (m, 1H), 2.92-2.82 (m, 1H), 2.73-2.48 (m, 5H), 1.98-1.89 (m, 2H), 1.73-1.61 (m, 2H). MS $[\text{M} + \text{H}]^+ m/z$ 354.

BDM_70665



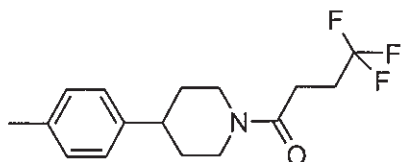
15 ^1H NMR (CD_2Cl_2) δ 7.19-7.09 (m, 4H), 4.80-4.74 (m, 1H), 4.00-3.94 (m, 1H), 3.23-3.14 (m, 1H), 3.06-2.95 (m, 1H), 2.74-2.47 (m, 5H), 2.38 (s, 3H), 1.88-1.80 (m, 2H), 1.71-1.54 (m, 2H). MS $[\text{M} + \text{H}]^+ m/z$ 300.

BDM_70664



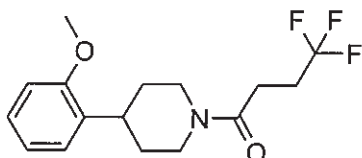
20 ^1H NMR (CD_2Cl_2) δ 7.23-7.20 (m, 1H), 7.06-7.01 (m, 3H), 4.77-4.71 (m, 1H), 3.98-3.92 (m, 1H), 3.20-3.11 (m, 1H), 2.79-2.46 (m, 6H), 2.33 (s, 3H), 1.94-1.85 (m, 2H), 1.71-1.53 (m, 2H). MS $[\text{M} + \text{H}]^+ m/z$ 300.

25 BDM_70663



^1H NMR (CD_2Cl_2) δ 7.16-7.10 (m, 4H), 4.77-4.70 (m, 1H), 3.97-3.91 (m, 1H), 3.20-3.10 (m, 1H), 3.06-2.95 (m, 1H), 2.77-2.47 (m, 5H), 2.33 (s, 3H), 1.93-1.85 (m, 2H), 1.69-1.51 (m, 2H). MS $[\text{M} + \text{H}]^+$ m/z 300.

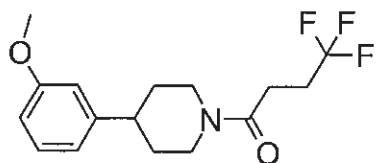
5 **BDM_70540**



^1H NMR (CD_2Cl_2) δ 7.25-7.15 (m, 2H), 6.98-6.91 (m, 2H), 4.78-4.72 (m, 1H), 3.97-3.92 (m, 1H), 3.86 (s, 3H), 3.28-3.14 (m, 2H), 2.75-2.47 (m, 5H), 1.94-1.84 (m, 2H), 1.69-1.54 (m, 2H).

10 ^{13}C NMR (CD_2Cl_2) δ 167.59, 156.89, 133.37, 127.49 (q, $J = 275$ Hz), 127.18, 126.35, 120.56, 110.44, 55.23, 46.16, 42.73, 35.54, 32.31, 31.48, 29.59 (q, $J = 29$ Hz), 25.81. MS $[\text{M} + \text{H}]^+$ m/z 316.

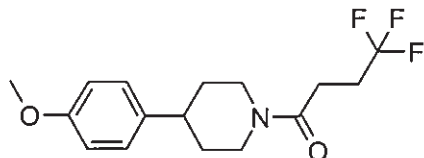
BDM_70538



15

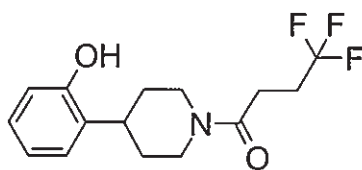
^1H NMR (CD_2Cl_2) δ 7.27-7.22 (m, 1H), 6.83-6.76 (m, 3H), 4.78-4.71 (m, 1H), 3.99-3.92 (m, 1H), 3.80 (s, 3H), 3.20-3.11 (m, 1H), 2.81-2.47 (m, 6H), 1.95-1.87 (m, 2H), 1.71-1.54 (m, 2H). MS $[\text{M} + \text{H}]^+$ m/z 316

20 **BDM_70537**

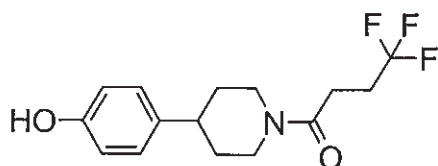


^1H NMR (CD_2Cl_2) δ 7.17-7.14 (m, 2H), 6.89-6.86 (m, 2H), 4.76-4.71 (m, 1H), 3.97-3.92 (m, 1H), 3.79 (s, 3H), 3.20-3.11 (m, 1H), 2.74-2.50 (m, 6H), 1.93-1.86 (m, 2H), 1.63-1.55 (m, 2H).

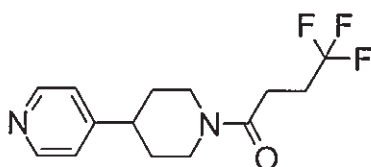
25 ^{13}C NMR (CD_2Cl_2) δ 168.38, 158.58, 138.06, 127.49 (q, $J = 275$ Hz), 127.56, 113.81, 55.16, 45.97, 42.53, 41.76, 34.06, 33.12, 29.56 (q, $J = 29$ Hz), 25.80. MS $[\text{M} + \text{H}]^+$ m/z 316.

BDM_70539

¹H NMR (MeOD) δ 7.08 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.00 (td, J = 7.6 Hz, J = 1.7 Hz, 1H), 6.80-6.74 (m, 2H), 4.71-4.64 (m, 1H), 4.09-4.02 (m, 1H), 3.27-3.15 (m, 2H), 2.80-2.70 (m, 3H), 2.58-2.47 (m, 2H), 1.96-1.83 (m, 2H), 1.74-1.53 (m, 2H). MS $[M + H]^+$ m/z 302.

BDM_45572

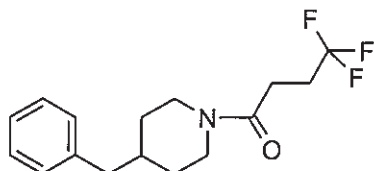
¹H NMR (MeOD) δ 7.04 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.67-4.61 (m, 1H), 4.04-3.98 (m, 1H), 3.21-3.12 (m, 1H), 2.75-2.66 (m, 4H), 2.58-2.46 (m, 2H), 1.89-1.79 (m, 2H), 1.67-1.44 (m, 2H). MS $[M + H]^+$ m/z 302.

BDM_70542

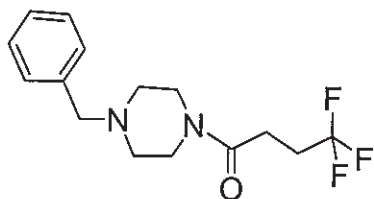
¹H NMR (CD₂Cl₂) δ 8.52 (d, J = 6.1 Hz, 2H), 7.16 (d, J = 6.1 Hz, 2H), 4.80-4.73 (m, 1H), 4.01-3.93 (m, 1H), 3.22-3.13 (m, 1H), 2.84-2.48 (m, 6H), 1.98-1.89 (m, 2H), 1.71-1.54 (m, 2H). MS $[M + H]^+$ m/z 287.

BDM_70670

4-benzylpiperidine is commercially available. Only the coupling has been performed.

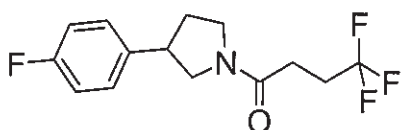


¹H NMR (CD₂Cl₂) δ 7.33-7.28 (m, 2H), 7.24-7.16 (m, 3H), 4.59-4.51 (m, 1H), 3.82-3.77 (m, 1H), 3.02-2.92 (m, 1H), 2.59-2.47 (m, 7H), 1.85-1.67 (m, 3H), 1.24-1.07 (m, 2H). MS $[M + H]^+$ m/z 300.

BDM_70719

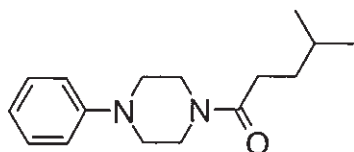
^1H NMR (CD_2Cl_2) δ 7.35-7.26 (m, 5H), 3.61 (t, J = 5.1 Hz, 2H), 3.54 (s, 2H), 3.45 (t, J = 5.1 Hz, 2H), 2.61-2.41 (m, 8H). MS $[\text{M} + \text{H}]^+$ m/z 301.

5

BDM_70717

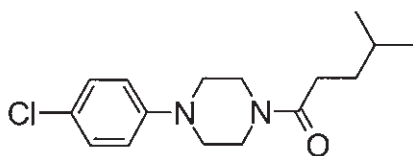
^1H NMR (CDCl_3) δ 7.24-7.18 (m, 2H), 7.07-7.00 (m, 2H), 4.09-3.99 (m, 0.5H), 3.91-3.81 (m, 1H), 3.72-3.64 (m, 0.5H), 3.60-3.31 (m, 3H), 2.61-2.50 (m, 4H), 2.46-2.27 (m, 1H), 2.16-1.95 (m, 1H). MS $[\text{M} + \text{H}]^+$ m/z 290.

10

BDM_44810

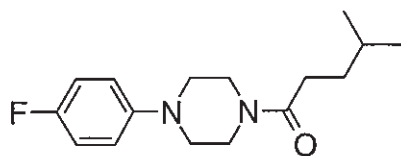
^1H NMR (CDCl_3) δ 7.34-7.28 (m, 2H), 6.97-6.90 (m, 3H), 3.80 (t, J = 5.1 Hz, 2H), 3.66 (t, J = 5.1 Hz, 2H), 3.22-3.15 (m, 4H), 2.42-2.37 (m, 2H), 1.70-1.53 (m, 3H), 0.95 (d, J = 6.3 Hz, 6H). MS $[\text{M} + \text{H}]^+$ m/z 261.

15

BDM_44813

^1H NMR (CDCl_3) δ 7.26-7.22 (m, 2H), 6.91-6.86 (m, 2H), 3.74 (t, J = 5.1 Hz, 2H), 3.63 (t, J = 5.1 Hz, 2H), 3.18-3.11 (m, 4H), 2.39-2.34 (m, 2H), 1.67-1.49 (m, 3H), 0.95 (d, J = 6.3 Hz, 6H). MS $[\text{M} + \text{H}]^+$ m/z 295.

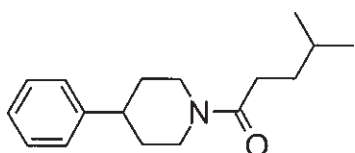
20

BDM_44821

¹H NMR (CDCl₃) δ 7.04-6.98 (m, 2H), 6.94-6.90 (m, 2H), 3.74 (t, J = 5.1 Hz, 2H), 3.63 (t, J = 5.1 Hz, 2H), 3.12-3.05 (m, 4H), 2.39-2.34 (m, 2H), 1.64-1.49 (m, 3H), 0.95 (d, J = 6.6 Hz, 6H). MS [M + H]⁺ m/z 279.

BDM_44649

4-phenylpiperidine is commercially available. Only the coupling has been performed.



¹H NMR (CD₂Cl₂) δ 7.36-7.31 (m, 2H), 7.25-7.20 (m, 3H), 4.77-4.73 (m, 1H), 4.02-3.98 (m, 1H), 3.18-3.09 (m, 1H), 2.81-2.71 (m, 1H), 2.66-2.57 (m, 1H), 2.39-2.34 (m, 2H), 1.94-1.85 (m, 2H), 1.69-1.51 (m, 5H), 0.95 (d, J = 6.4 Hz, 6H). MS [M + H]⁺ m/z 260.

Evaluation of the compounds' activity**Potentialiation of ethionamide cell test**

The test used makes it possible to ascertain that these compounds are capable of potentiating the bactericide activity of ethionamide on *M. tuberculosis* alone. This test is a "High Content Screening" (HCS) or dense content screening test. HCS tests are performed on cell cultures that enable certain phenotypic features of a microorganism (e.g. a bacterium) in a given environment to be studied. The phenotypic changes observed can range from the increase (or decrease) of the production of certain marked proteins to the modification of the morphology of the microorganism under consideration. The method is described in the following publication: "Ethionamide Boosters: Synthesis, Biological Activity, and Structure-Activity Relationships of a Series of 1,2,4-Oxadiazole EthR Inhibitors", M. Flipo *et al.*, Journal of Medicinal Chemistry, 2011, 54(8), 2994-3010.

This test aims to determine the ligand concentration necessary to potentiate ten times the activity of ethionamide (ETH).

To measure the ligand concentration necessary for potentiating ten times the activity of ETH, a constant concentration of ethionamide (0.1 µg/mL corresponding to 1/10th of its CMI₉₉) is chosen. By varying the ligand concentration, the concentration

necessary to inhibit 50% of the bacterial growth, i.e. the concentration necessary to potentiate ten times the activity of ethionamide, can be determined. This concentration will be denoted EC_{50} .

Measurement of the solubility

40 μ L of a solution at 10mM in DMSO of the sample are added to 1.96mL MeOH or PBS at pH 7.4. The samples are then agitated during 24h at RT, centrifuged during 5min and then filtrated on filters of 0.45 μ m size. 20 μ L of each solution are then added to 180 μ L MeOH and then analyzed by LC-MS. The solubility is determined as ratio of the surfaces of the mass signals PBS/MeOH.

MEASURED BIOLOGICAL ACTIVITIES

The tables I to III hereafter summarize the formulas of the inventive compounds tested as well as the values of the EC_{50} experimentally measured according to the aforementioned protocol.

Table I

ID_structure	R2	X	n	R1	EC_{50} (μ M)	Solubility (μ g/mL)
BDM_44647		CH	1	CH_2CF_3	0.0008	50.4
BDM_44648		CH	1	$(CH_2)_2CF_3$	<0.01	42.9
BDM_44751		CH	1	CH_2CF_3	0.001	51.9
BDM_70717		CH	0	CH_2CF_3	0.009	ND

With reference to the results of Table I, one observes that a CH_2CF_3 group affords a greater potentiating activity of ethionamide without negatively affecting the compound's solubility. The results show that for a same radical R1 and a same radical R2, the potentiating activity of the inventive compounds is improved when $n = 1$.

Table II

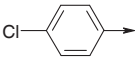
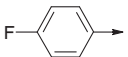
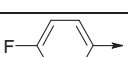
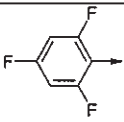
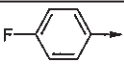
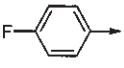
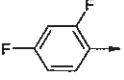
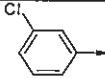
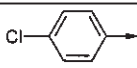
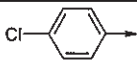
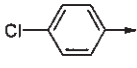
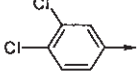
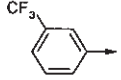
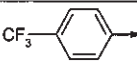
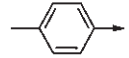
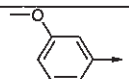
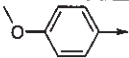
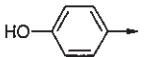
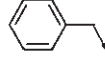
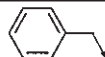
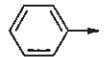
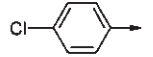
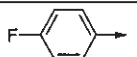
ID_structure	R2	X	n	R1	EC ₅₀ (μM)
BDM_44810		N	1	(CH ₂)isopropyl	0.06
BDM_44813		N	1	(CH ₂)isopropyl	0.1
BDM_44821		N	1	(CH ₂)isopropyl	0.1
BDM_44649		CH	1	(CH ₂)isopropyl	0.06

Table III hereafter summarizes the activities expressed in EC₅₀ for all the inventive compounds tested.

Table III

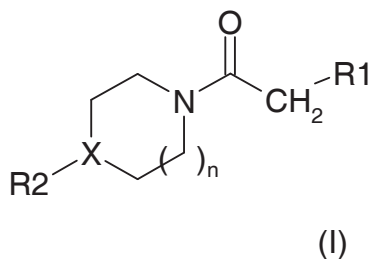
ID_structure	R2	X	n	R1	EC ₅₀ (μM)
BDM_44647		CH	1	CH ₂ CF ₃	0.0008
BDM_44648		CH	1	(CH ₂) ₂ CF ₃	<0.01
BDM_44649		CH	1	(CH ₂)isopropyl	0.06
BDM_44808		N	1	CH ₂ CF ₃	0.01
BDM_44809		N	1	(CH ₂) ₂ CF ₃	0.07
BDM_70666		CH	1	CH ₂ CF ₃	0.001
BDM_70531		CH	1	CH ₂ CF ₃	0.0008
BDM_44751		CH	1	CH ₂ CF ₃	0.001

BDM_71148		CH	1	CH ₂ CF ₃	0.001
BDM_44819		N	1	CH ₂ CF ₃	0.027
BDM_44820		N	1	(CH ₂) ₂ CF ₃	0.14
BDM_70669		N	1	CH ₂ CF ₃	0.021
BDM_70534		CH	1	CH ₂ CF ₃	0.11
BDM_70668		CH	1	CH ₂ CF ₃	0.0005
BDM_70535		CH	1	CH ₂ CF ₃	0.12
BDM_44811		N	1	CH ₂ CF ₃	0.010
BDM_44812		N	1	(CH ₂) ₂ CF ₃	<0.02
BDM_70716		CH	1	CH ₂ CF ₃	0.025
BDM_70536		CH	1	CH ₂ CF ₃	0.770
BDM_70546		CH	1	CH ₂ CF ₃	0.001
BDM_70667		CH	1	CH ₂ CF ₃	0.3
BDM_70665		CH	1	CH ₂ CF ₃	0.035

BDM_70664		CH	1	CH ₂ CF ₃	0.001
BDM_70663		CH	1	CH ₂ CF ₃	0.026
BDM_70540		CH	1	CH ₂ CF ₃	0.14
BDM_70538		CH	1	CH ₂ CF ₃	0.14
BDM_70537		CH	1	CH ₂ CF ₃	0.002
BDM_70539		CH	1	CH ₂ CF ₃	ND
BDM_45572		CH	1	CH ₂ CF ₃	0.28
BDM_70542		CH	1	CH ₂ CF ₃	0.33
BDM_70670		CH	1	CH ₂ CF ₃	0.054
BDM_70719		N	1	CH ₂ CF ₃	1.1
BDM_44810		N	1	(CH ₂)isopropyl	0.06
BDM_44813		N	1	(CH ₂)isopropyl	0.1
BDM_44821		N	1	(CH ₂)isopropyl	0.1
BDM_70717		CH	0	CH ₂ CF ₃	0.009

Claims:

1. A compound of formula (I) :



in which:

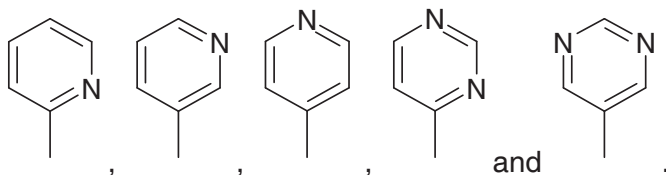
n is 0 or 1;

R1 is -CH₂CF₃;

X is N or CH;

R2 is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C1-C4 alkyl; phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

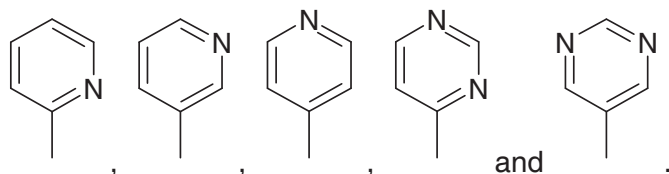
wherein said heterocycle is selected from the group consisting of:



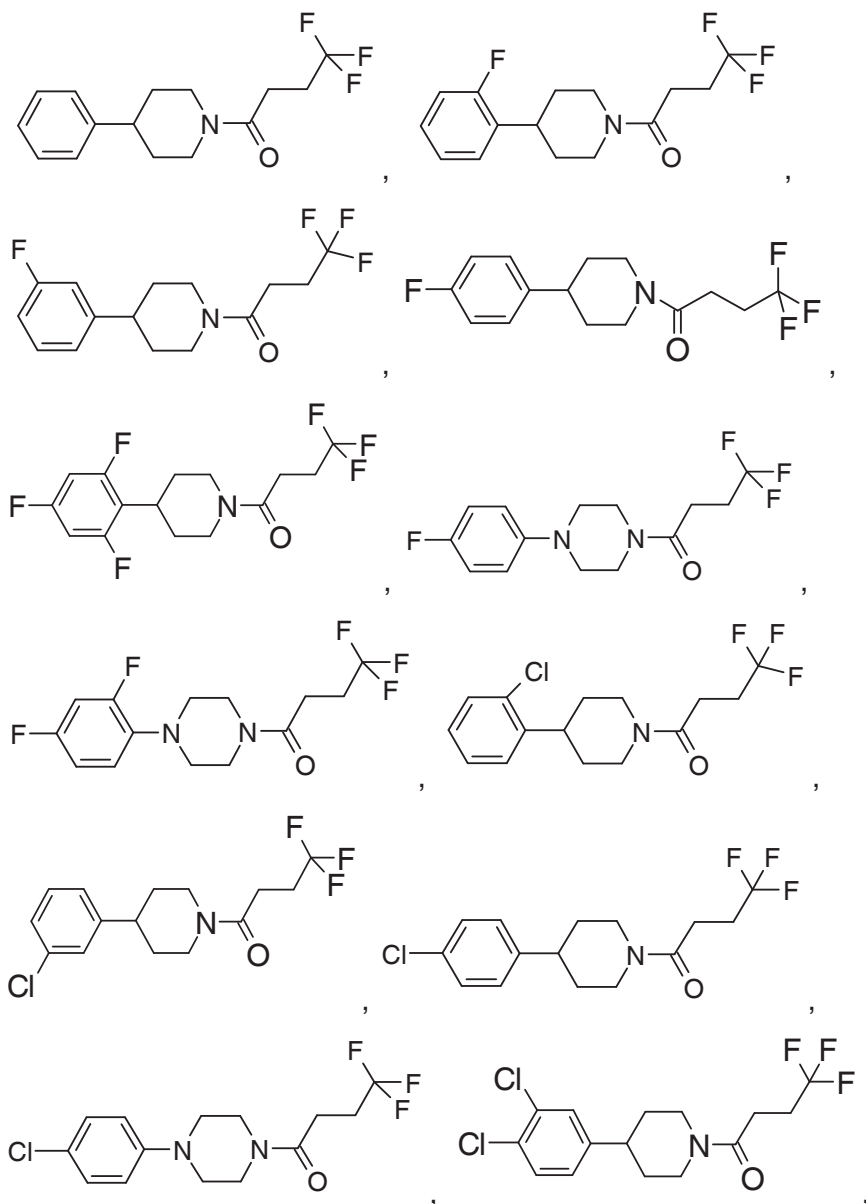
2. The compound according to claim 1, wherein n is 1.
- 3.. The compound according to claim 1 or 2, wherein X is CH.
4. The compound according to any one of claims 1 to 3, wherein R2 is phenyl.
5. The compound according to any one of claims 1 to 3, wherein R2 is phenyl substituted in meta position relative to the bond to X by a substituent selected from Cl, F, CF₃ and OCH₃.
6. The compound according to any one of claims 1 to 3, wherein R2 is phenyl substituted by fluorine.

7. The compound according to any one of claims 1 to 3, wherein R₂ is phenyl substituted by fluorine in para position relative to the bond to X.

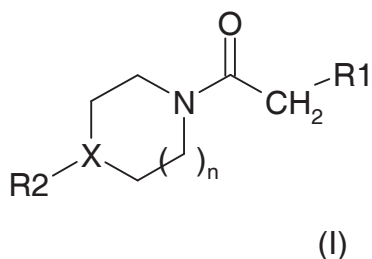
8. The compound according to any one of claims 1 to 3, wherein R² is selected from:



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



10. A compound according to any one of claims 1 to 9 for use as medicament.
11. A compound for use in the treatment of bacterial and mycobacterial infections, wherein said compound is a compound of formula (I) :



in which:

n is 0 or 1;

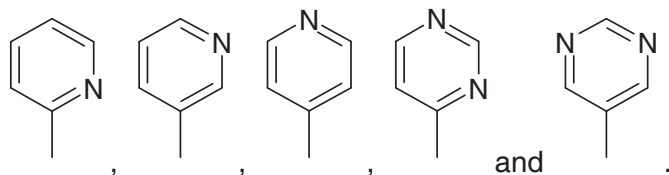
R1 is selected from the group consisting of: linear or branched C1-C5 alkyl optionally substituted by fluorine;

wherein said linear or branched C1-C5 alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

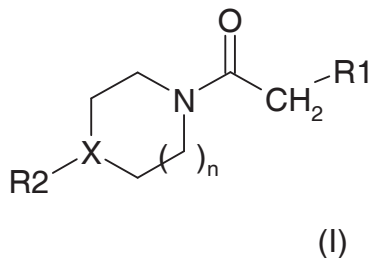
X is N or CH;

R2 is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C1-C4 alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:



12. A compound for use in the treatment of tuberculosis, leprosy and atypical mycobacterial infections, wherein said compound is a compound of formula (I) :



in which:

n is 0 or 1;

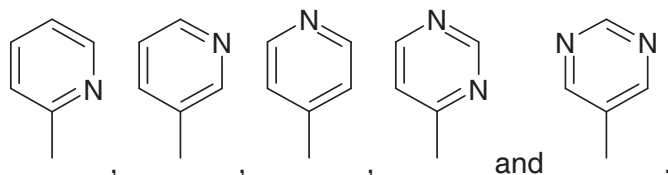
R1 is selected from the group consisting of: linear or branched C1-C5 alkyl optionally substituted by fluorine;

wherein said linear or branched C1-C5 alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

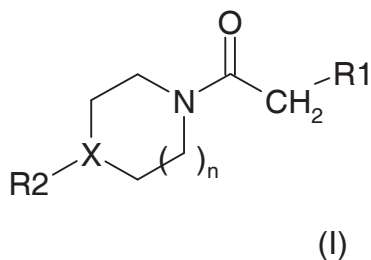
X is N or CH;

R₂ is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C₁-C₄ alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:



13. A pharmaceutical composition comprising as active ingredient a compound and a pharmaceutically acceptable excipient, wherein said compound is a compound of formula (I) :



in which:

n is 0 or 1;

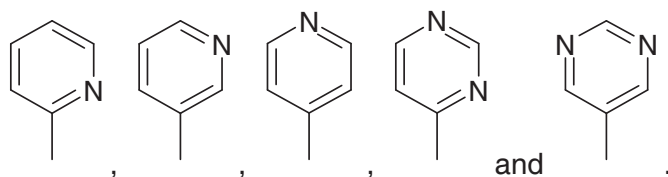
R₁ is selected from the group consisting of: linear or branched C₁-C₅ alkyl optionally substituted by fluorine;

wherein said linear or branched C₁-C₅ alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

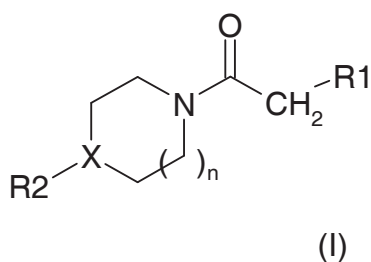
X is N or CH;

R₂ is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C₁-C₄ alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:



14. The pharmaceutical composition of claim 13 further comprising an antibiotic active against bacteria and/or mycobacteria.
15. The pharmaceutical composition of claim 13 further comprising an antibiotic activatable via the EthA pathway.
16. The pharmaceutical composition of claim 13 further comprising an antibiotic selected from the thioamide family.
17. The pharmaceutical composition of claim 13 further comprising ethionamide or prothionamide.
18. The use of a combination of a compound and of an antibiotic activatable via the EthA pathway in the manufacture of a medicament for the treatment of tuberculosis, leprosy and atypical mycobacterial infections, wherein said compound is a compound of formula (I) :



in which:

n is 0 or 1;

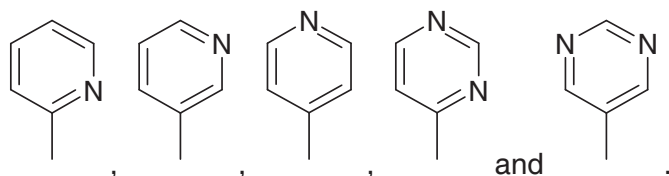
R1 is selected from the group consisting of: linear or branched C1-C5 alkyl optionally substituted by fluorine;

wherein said linear or branched C1-C5 alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

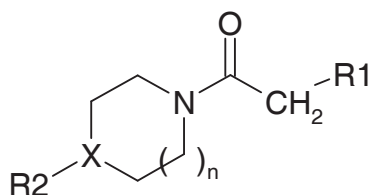
X is N or CH;

R2 is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C1-C4 alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:



19. The use of a compound of formula (I) :



(I)

in the manufacture of a medicament for the treatment of bacterial and mycobacterial infections in which:

n is 0 or 1;

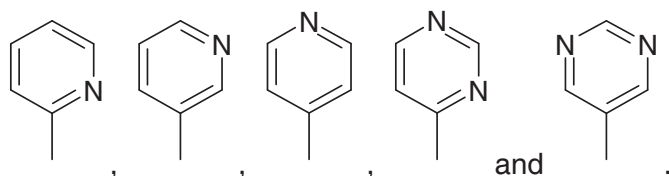
R1 is selected from the group consisting of: linear or branched C1-C5 alkyl optionally substituted by fluorine;

wherein said linear or branched C1-C5 alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

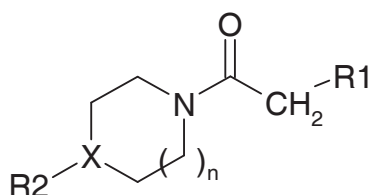
X is N or CH;

R2 is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C1-C4 alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:



20. The use of a compound of formula (I) :



(I)

in the manufacture of a medicament for the treatment of tuberculosis, leprosy and atypical mycobacterial infections in which:

n is 0 or 1;

R1 is selected from the group consisting of: linear or branched C1-C5 alkyl optionally substituted by fluorine;

wherein said linear or branched C1-C5 alkyl optionally substituted by fluorine is selected from the group consisting of -CH₂CF₃ and -CH₂-isopropyl;

X is N or CH;

R2 is selected from the group consisting of: phenyl; phenyl substituted by linear or branched C1-C4 alkyl phenyl substituted by one or more substituent selected from Cl, F, CF₃, OCH₃ and OH; and a six-membered heterocycle comprising one, two or three nitrogen atoms;

wherein said heterocycle is selected from the group consisting of:

