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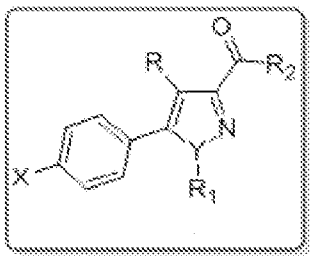
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(54) Title: PYRAZOLE CARBOXYLIC ACID ANALOGUES AS ANTI-MYCOBACTERIAL DRUG CANDIDATES



(1)

(57) Abstract: The present invention relates to the pyrazole carboxylic acid analogues of Formula (1) or stereoisomers, or esters or pharmaceutically acceptable salts thereof, as potent anti- mycobacterial agents. Formula Further it discloses the pharmaceutical composition comprising compounds of Formula-I for the treatment of mycobacterial infections.

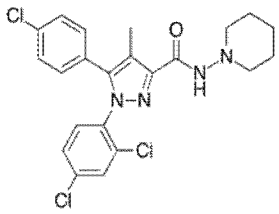
PYRAZOLE CARBOXYLIC ACID ANALOGUES AS ANTI-MYCOBACTERIAL DRUG CANDIDATES

The following specification particularly describes the invention and the manner in which it is to be performed:

FIELD OF INVENTION: The invention relates to pyrazole carboxylic acid analogues of formula-I as potent anti-mycobacterial drug candidates. Particularly the invention provides novel pyrazole carboxylic acid analogues of formula-I, and pharmaceutically acceptable salts thereof for treatment of mycobacterial infections. **BACKGROUND AND PRIOR ART:** Tuberculosis (TB) is one of the deadliest diseases afflicting mankind. One third of the world's population is infected with TB. In 2011, nearly 9 million people around the world suffered from TB. There were around 1.4 million TB-related deaths worldwide. TB is a leading killer of people who are HIV infected.

Anti-tuberculosis drug resistance is a major public health problem that threatens progress made in TB care and control worldwide. Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients. This improper use is a result of a number of actions including, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. A patient who develops active disease with a drug-resistant TB strain can transmit this form of TB to other individuals. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis are generally thought to have high mortality rates. Multidrug-resistant is the combination of at least four drugs to which the *Mycobacterium tuberculosis* isolate is likely to be susceptible. Among the first group (the oral first-line drugs) high-dose isoniazid, pyrazinamide, and ethambutol are thought of as an adjunct for the treatment of MDR and XDR tuberculosis. The MDR TB patients with HIV/AIDS lack the immunity to fight the TB infection and are at great risk of developing drug resistance. Therefore research and funding is needed in the diagnosis, prevention and treatment of TB and MDR TB. To combat continuous rise in multi-drug resistant TB, scientific efforts are concentrated on inventing new agents for treatment of TB. New drug discovery is a long and tedious process consuming several years and the regulatory approval process following drug discovery involves several tests and trials. At the current stage it would be highly beneficial and attractive to identify a candidate effective for treatment of TB, such that the candidate has been approved as a drug by regulatory authorities. This would enable a quick introduction of the drug into the market for TB treatment. While Rimonabant, a pyrazole carboxylic acid derivative was withdrawn from market, the reason for the withdrawal was that its benefits did not outweigh the risks. But the fact that it was marketed establishes that it is safe for administration in humans.

Rimonabant or 5-(4-Chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide **(1)**

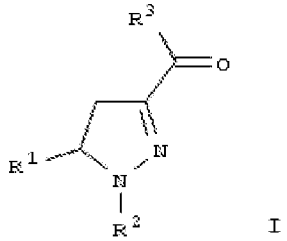


(1)

Rimonabant, a pyrazole carboxylic acid derivative was discovered by Sanofi-Synthelabo in 1994 as the first potent, orally active, selective CB1 cannabinoid receptor antagonist and sold under several trade names as an anorectic antiobesity drug, but withdrawn from the market due to its side effects. It is an inverse agonist for the cannabinoid receptor CB1. Its main effect is reduction in appetite. Rimonabant was the first selective CB1 receptor blocker to be approved for use anywhere in the world. In Europe, it was indicated for use in conjunction with diet and exercise for patients with a body mass index (BMI) greater than 30 kg/m², or patients with a BMI greater than 27 kg/m² with associated risk factors, such as type 2 diabetes or dyslipidaemia. In the UK, it was available beginning in July 2006, but the drug was officially withdrawn by the EMEA (European Medicines Agency) on 16 January 2009.

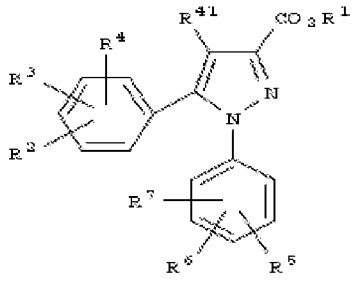
As like Rimonabant, substituted pyrazole and its analogs have been used as precursors for synthesis of various biologically active molecules. Pyrazole derivatives are the subject of many research studies due to their widespread potential biological activities such as antimicrobial, antiviral, antitumor, antihistaminic, antidepressant, insecticides and fungicides.

WO 2007017125 describes pyrazolinecarboxamides of formula-I as CB1 antagonists or inverse antagonists as therapeutical agents for the treatment of inflammation involving gene expression.



I

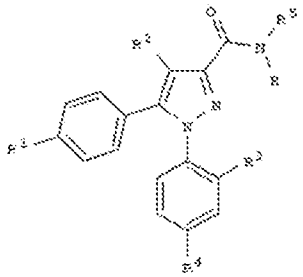
WO'125 also describes preparation of N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide. WO 2007009701 describes use of substituted pyrazole compounds of formula-I for the treatment of cardiovascular risk factors caused by metabolic syndrome in humans and animals



I

EP1743637 discloses use of substituted pyrazole compounds and combinations thereof for the treatment of metabolic syndrome. Mohamed Jawed Ahsana et al. in European Journal of Medicinal Chemistry, vol 46, (11), Nov 2011, Pg. 5694–5697 discloses synthesis of a series of 3a,4-dihydro-3H-indeno [1,2-c] pyrazole-2-carboxamide analogues and evaluation of antitubercular activity thereof. Sudalaiandi Kumaresan et al. in IJAPR Feb. 2013 vol. 4 (2) 1402-1412 discloses antimycobacterial activity of the N,1-Diphenyl-1,4-Dihydrothiochromeno[4,3-c] Pyrazole-3-Carboxamide analogues" compounds with minimum inhibitory concentrations of 7.5-6.25 M. Further, antitubercular activity of cyclic azole substituted diphenyl ether derivatives is disclosed by Suvarna G. Kini, in European Journal of Medicinal Chemistry 44, (2), February 2009, Pages 492–500

Further in Journal of Medicinal Chemistry (2003), 46(4), 642-645 by Reeti Katoch-Rouse et al. discloses synthesized a series of less lipophilic analogues of compound of Formula-I to serve as potential radioligands. Binding affinities of the series and a functional electrophysiological assay of three of our compounds have been presented.



I

Pyrazole derivatives as cannabinoid receptor agonists are also reported in US 5624941, EP 576357, US 8030323.

In the light of the above, it is clear that there are several important anti-TB drug candidates such as PA-824 and BM212, which are structurally reminiscent to Rimonabant.

Rimonabant is an approved drug, with established safety. Rimonabant and its analogues are also shown to have promising activities and also are proved safe to human. Since Rimonabant was recently withdrawn from the market following postmarketing surveillance studies, which confirmed a risk of depressive disorders amongst users, there is need for modification or elimination of the carboxamide side chain, which is responsible for crossing the blood-brain barrier, might reduce these side effects.

Therefore, the present inventors have modified the core structure of rimonabant i.e. pyrazole carboxylic acid to obtain a safe, alternative drug candidate for treatment of mycobacterial infections.

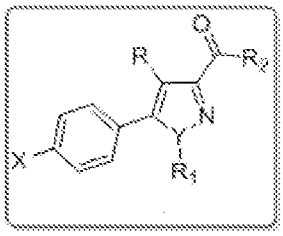
OBJECT OF THE INVENTION: The main object of invention is to provide Pyrazole carboxylic acid analogues for the treatment of Mycobacterium Tuberculosis.

Still another object of the present invention is to introduce rimonabant and its analogues as potential drug candidates for treatment of mycobacterial infection.

Yet another object of the present invention is to provide a pharmaceutical composition for the treatment of mycobacterial infections in human.

SUMMARY OF INVENTION:

Accordingly the present invention provides the pyrazole carboxylic acid analogues of Formula 1, or stereoisomers, or esters or pharmaceutically acceptable salts thereof, for use as a medicament for treating mycobacterial infections,



Formula 1

wherein, Y represents heteroatom N, S or O;

X represents hydrogen, or halogen;

R_1 represents (un)substituted aryl, hydrogen, where substituents are mono, di or tri halogen;

R_2 represents OH, (C1-C6) alkyl, (C1-C6) alkoxy, piperidine, 1-amino piperidine, morpholine, pyridine-4-carbohydrazide, 1-methylpiperazine, 1-methylpiperazine, thiomorpholine, hydrazine, amino acids, Schiff bases, heterocycles;

and R represents (C1-C4) linear or branched alkyl, hydrogen.In an embodiment of the present invention, the pyrazole carboxylic acid analogues of Formula 1, encompasses the following compounds;

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1)**

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**

Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(5)**

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**

5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**

1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**

N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**

5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**

1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**

5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**

5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(14)**

1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**

(5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**

5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**

1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(19).**

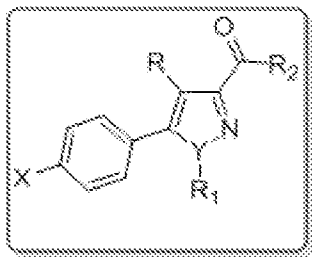
In still another embodiment of the present invention, the minimum inhibitory concentration (MIC) of the pyrazole carboxylic acid analogues of Formula 1, against *Mycobacterium tuberculosis* (strain H37Rv) is in the range of 3 to 30 μg/ml and for *Mycobacterium smegmantis* the MIC is in the range of 1-35 μg/ml.

In yet another embodiment of the present invention, a pharmaceutical composition comprising pyrazole carboxylic acid analogues of the Formula I, together with pharmaceutically acceptable excipient(s) and/or vehicle(s), for the treatment of mycobacterial infections in human.

In still another embodiment of the present invention, the pharmaceutical composition comprising pyrazole carboxylic acid analogues of general formula I, optionally with an additional antitubercular agent together with pharmaceutically acceptable excipient(s) and/or vehicle(s).

In yet another embodiment of the present invention, the *Mycobacterium* species is selected from the group consisting of *Mycobacterium tuberculosis* (strain H37Rv) and *Mycobacterium smegmatis* (strain MC2 155).

In still another embodiment of the present invention, a method of treating or inhibiting or controlling growth of *Mycobacterium* species in human, comprising administrating pyrazole carboxylic acid analogues of general formula-I, together with pharmaceutically acceptable excipient(s) and/or vehicle(s).



Formula 1

wherein, Y represents heteroatom N, S or O;

X represents hydrogen, or halogen;

R_1 represents (un)substituted aryl, hydrogen, where substituents are mono, di or tri halogen;

R_2 represents OH, (C1-C6) alkyl, (C1-C6) alkoxy, piperidine, 1-amino piperidine, morpholine, pyridine-4-carbohydrazide, 1-methylpiperazine, 1-methylpiperazine, thiomorpholine, hydrazine, amino acids, Schiff bases, heterocycles;

and R represents (C1-C4) linear or branched alkyl, hydrogen.

In yet another embodiment of the present invention, the method of treating or inhibiting or controlling growth of *Mycobacterium* species in human, comprising administrating pyrazole carboxylic acid analogues of general formula- I, wherein the compounds are selected from the group consisting of ;

i. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1)**

ii. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**

iii. Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

iv. N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**

v. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(5)**

vi. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**

vii. 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

viii. 1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**

ix. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**

x. N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**

xi. 5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**

xii. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**

xiii. 5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**

xiv. 5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(14)**

xv. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**

xvi. (5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**

xvii. 5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**

xviii. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**

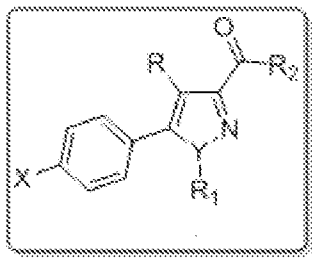
xix. 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(19).**

In still another embodiment of the present invention the *Mycobacterium* species is selected from the group consisting of *Mycobacterium tuberculosis* (strain H37Rv) *and Mycobacterium smegmatis* (strain MC2 155).

Further the invention furnishes evaluation of anti-mycobacterial activity of synthesized compounds of Formula-I.

DETAILED DESCRIPTION OF INVENTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated. In a preferred embodiment, the invention provides the pyrazole carboxylic acid analogues of Formula 1 or stereoisomers, or esters or pharmaceutically acceptable salts thereof, for use as a medicament for mycobacterial infections,



Formula 1

wherein, Y represents heteroatom N, S or O;

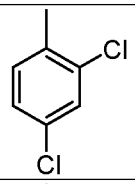
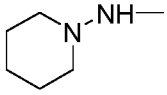
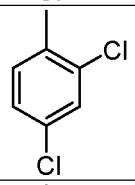
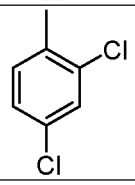
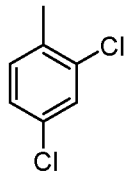
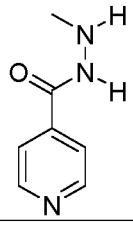
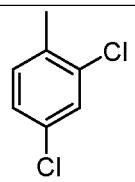
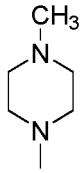
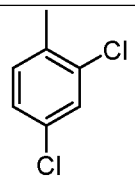
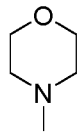
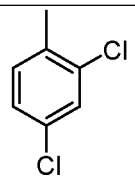
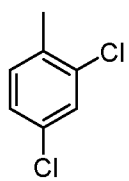
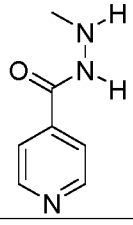
X represents hydrogen, halogen

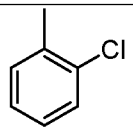
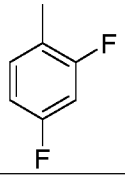
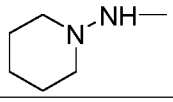
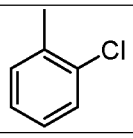
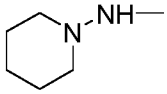
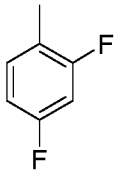
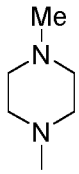
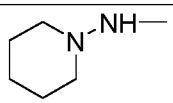
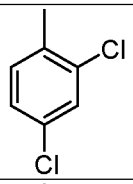
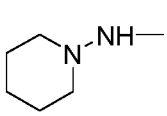
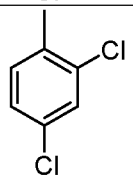
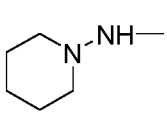
R_1 represents (un)substituted aryl, hydrogen, where substituents are mono, di or tri halogen; R_2 represents OH,(C1-C6)alkyl, (C1-C6) alkoxy, piperidine, 1-amino piperidine, morpholine, pyridine-4-carbohydrazide, 1-methylpiperazine, 1-methylpiperazine,

and R represents (C1-C4) linear or branched alkyl, hydrogen.

According to the above preferred embodiment, the pyrazole carboxylic acid analogues of Formula 1, having anti-mycobacterial activity encompass the compounds as listed in table 1.

Table 1:

Compound	X	Y	R	R_1	R_2	% inhibition M. smegmatis	MIC in MTB[b]
1.	Cl	N	CH_3			99.33 MIC 13.56 µg/ml	25
2.	Cl	N	CH_3		OH	22.84	12.5
3.	Cl	N	CH_3		OCH_2CH_3	14.07	25
4.	Cl	N	CH_3			19.21	12.5
5.	Cl	N	CH_3			14.50	25
6.	Cl	N	CH_3			NT[a]	>25
7.	Cl	N	CH_3	C_6H_5	OH	17.70	12.5
8.	Cl	N	CH_3	C_6H_5	CH_2CH_3	22.70	25
9.	H	N	CH_3		OH	15.73	6.25
10.	H	N	CH_3			1.362	25
11.	Cl	N	CH_3	H	OH	NT[a]	12.5

12.	Cl	N	CH_3		OH	NT[a]	25
13.	Cl	N	CH_3		OH	NT[a]	6.25
14.	Cl	N	CH_3	C6H5		99.70	3.13
15.	Cl	N	CH_3			NT[a]	12.5
16.	Cl	N	CH_3			NT[a]	12.5
17.	Cl	O	CH_3			NT[a]	12.5
18.	H	N	CH_3			32.37	12.5
19.	Cl	N	H			NT[a]	25
20.	Rifampicin	-	-	-	-	-	0.2
21.	Ethambutol	-	-	-	-	-	3.25
22.	Pyrazinamide	-	-	-	-	-	50.0

[a]NT: Not tested [b]Mycobacterium tuberculosis $H_{37}Rv$

In accordance with Table 1, the anti-mycobacterial pyrazole carboxylic acid analogues of Formula-1 are selected from the group consisting of;

i. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1)**

ii. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**

iii. Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

iv. N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**

v. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methyl piperazin-1-yl) methanone **(5)**

vi. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**

vii. 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

viii. 1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**

ix. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**

x. N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**

xi. 5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**

xii. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**

xiii. 5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**

xiv. 5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(14)**

xv. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**

xvi. (5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**

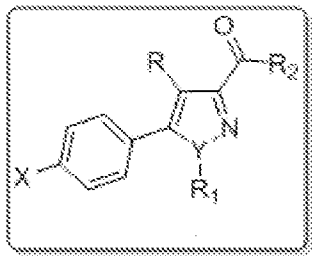
xvii. 5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**

xviii. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**

xix. 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(19)**

With regards to the antibacterial activity of the compounds of the Formula-I, the initial studies involved screening of Rimonabant **(1)** against *Mycobacterium smegmatis*, which showed a MIC value 13.56 μg/ml. Therefore, its 18-analogues were synthesized and few of them were screened against *Mycobacterium smegmatis*. They showed moderate to excellent activity (**Table 1**). Similarly Rimonabant and all the synthesized analogues were then screened for anti-bacterial activity against *Mycobacterium tuberculosis* (virulent strain H37Rv) *in vitro*. The precursor of Rimonabant, acid **2** showed improved MTB activity and ester **3** retains the activity as compared to Rimonabant. Similarly analogues **2, 4, 7, 11 & 15-18** showed enhanced activity and the analogues **3, 5, 6, 8, 10, 12 & 19** retains the activity. Most importantly the analogues **9** and **13** showed drastic increase in MTB activity. The analogue **14** came out to be a promising lead with highest activity. Compared with one of the first line anti-TB drug Ethambutol (MIC 3.25 μg/ml), the analogue **14** was found to be equally active. When compared to Pyrazinamide (MIC 50.0 μg/ml) all the 18 analogues were found to be more potent. The analogue **13** was a simplified lead molecule. Based on the analogue **9**, a simple replacement of chlorine by hydrogen might provide a more active analogue of **13**. The anti-

mycobacterial activity of compounds of Formula-I against mycobacterial species is measured in the range of 1 to 50 μg/ml, particularly anti-mycobacterial activity against *Mycobacterium tuberculosis* (strain H37Rv) is evaluated in the range of 3 to 30 μg/ml and for *Mycobacterium smegmantis* the MIC is calculated in the range of 1-35 μg/ml, In another preferred embodiment, the invention provides, novel pyrazole carboxylic acid analogues of Formula 1 having anti-mycobacterial activity as disclosed in above Table 1,



Formula 1

wherein, Y represents heteroatom N or O;

X represents hydrogen, Cl

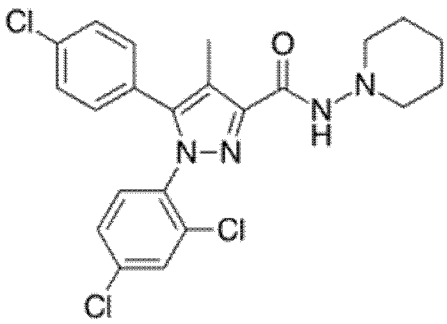
R_1 represents phenyl, 2-4 dichlorophenyl, 2-4 difluorophenyl;

R_2 represents OH, ethyl, piperidine, 1-aminopiperidine, pyridine-4-carbohydrazide, 1-methylpiperazine; and R represents methyl, hydrogen.

According to the above embodiment, the novel anti-mycobacterial agents of formula-I are selected from the group consisting of;

1. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(5)**
2. 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**
3. 1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**
4. N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**
5. (5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**
6. 5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**

In another optional embodiment, the pyrazole carboxylic acid analogues of Formula 1 is Rimonabant or 5-(4-Chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide, wherein the minimum inhibitory concentration of Rimonabant against *Mycobacterium smegmatis* is 13.56 μg/ml and against *Mycobacterium tuberculosis 25* μg/ml.



Rimonabant

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula 1, or its stereoisomers, esters or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier(s), diluent(s) vehicle(s), and/or excipient(s).

The compound of formula 1 disclosed herein is present in the composition in an amount which is effective to treat the disease or the condition caused by the bacterial strains mentioned above.

The pharmaceutical compositions of the invention can be prepared by combining compounds of Formula-I with appropriate pharmaceutically acceptable carriers, diluents or excipients, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, injections, gels and microspheres.

In another embodiment, the present invention relates to administering 'an effective amount' of the 'composition of invention' to the subject suffering from said disease. Accordingly, compound of Formula 1 and pharmaceutical compositions containing them may be administered using any amount, any form of pharmaceutical composition via any route of administration effective for treating the disease. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal.

Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient may take the form of one or more dosage units. The dosage forms can also be prepared as sustained, controlled, modified and immediate dosage forms.

The excipients or carriers are selected from the group such as diluents, disintegrants, crosslinked polymers, binders, lubricants, coatings layer.

Further the synergistic effect of instant pharmaceutical composition can be achieved in combination with additional known anti-tubercular drugs such as Rifampcin, Ethambutol, Pyrazinamide.

In another embodiment, the invention provides a method of treating or inhibiting growth of a bacteria preferably *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* in a subject (i.e. human or animal) comprising administrating anti-mycobacterial compounds of Formula-I, optionally with at

least one additional active compound or anti-tubercular agent together with pharmaceutically acceptable excipients and/or vehicles.

In another embodiment, the invention provides pyrazole carboxylic acid compounds of Formula-I for use in treating or inhibiting growth of a bacteria preferably *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* in a subject. The subject according to the invention is an animal or human.

In yet another embodiment, the invention furnishes pyrazole carboxylic acid compounds of Formula-I for the preparation of medicament useful for treating or inhibiting the growth of *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* in human.

EXAMPLES

The following examples are given by way of illustrating the present invention and should not be construed to limit the scope of the present invention

1. Anti- mycobacterial activity assay *(Mycobacterium smegmatis* MC^2155 strain)**:**

Anti-mycobacterial activity of the compounds was performed with *Mycobacterium smegmatis* MC^2155 strain by performing a growth inhibition assay by agar dilution followed turbidometry method. The assay was semi-throughput and conducted in a 96 well plate (sterile). Isolated single colonies of *M. smegmatis MC² 155* (ATCC 14468) grown on 7H10 agar plate were grown overnight in Middlebrook 7H9 medium (0.47% Middlebrook 7H9 broth base, 10% ADS, 0.2% glycerol, and 0.1% Tween-80) to mid exponential phase inoculated in 5 ml Middlebrook 7H9 medium. The secondary culture was incubated overnight and allowed to grow at 37^0C to early log phase ($OD_{600} \approx$ 0.3). For the anti-mycobacterial assay, 98 µl of 1:1000-folds dilution of secondary culture was dispensed into 96-well microtiter plate per well along with 2µl of test compound in triplicate. 240 µl of sterile water were added to each well of the peripheral rows of 96-well plate to minimize media evaporation during assay incubation. The final concentration of the test compound (Rimonabant) in each well was 30µM. Bacterial growth was assessed after 32 hours of incubation by measuring turbidity at 600nm OD_{600} values using TECAN **Infinite 200 PRO™** (Tecan Instruments, Switzerland). Depending upon the percentage of growth, the percentage of inhibition was calculated at the standard concentration of 30µM. Isoniazid and Rifampicin were included in every assay plate as positive controls of growth inhibition using stock solutions of INH (10 mg/mL, HiMedia) and Rifampicin (10 mg/mL, HiMedia) to achieve the final concentration of 16 g/mL for INH and 2 g/mL for Rifampicin. Additional controls DMSO (solvent without compound) and medium without inoculums were included in all the assay plates avoiding intra assay variability. The results were analyzed as the percentage of growth inhibition.

2. MIC Assay:

After the compounds were screened for percentage inhibition, those compounds which were found to be promising were further screened to obtain their MIC values. MIC / Minimum Inhibitory

Concentration is that concentration of compound which inhibits the 90 % growth of bacteria under optimum conditions. The growth inhibition assays were carried out in the same analogy as explained above various concentrations of the test compounds prepared by serial dilutions 100 μM, 50 μM, 25 μM, 12.5 μM and 6.25 μM (DMSO as solvent) to obtain the final concentrations of 46.37μg/ml, 23.18 μg/ml, 11.59 μg/ml, 5.79 μg/ml, 2.89 μg/ml respectively. From the rate of inhibition bacterial growth, the ascertained MIC of the compound was calculated.

The MIC value of the test compound JMG 005 i.e. Rimonabant is 13.56 μg/ml (29.24 μM ± 1.47).

3. Anti- Mycobacterial Activity for *M.tuberculosis* (General Procedure)

Ten fold serial dilutions of each test compound were prepared and incorporated into Middle brook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M.tuberculosis* H37Rv ATCC 27294 (MTB) was prepared from fresh Middle brook 7H11 agar slants with OADC growth supplement adjusted to 1mg/ml (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration approximately 10^{7} cfu/ml. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of compounds per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to completely inhibit the bacterial growth. Rifampicin, Ethambutol and Pyrazinamide were used as reference compounds. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards[11] for the determination of minimum inhibitory concentration (MIC) in triplicate.

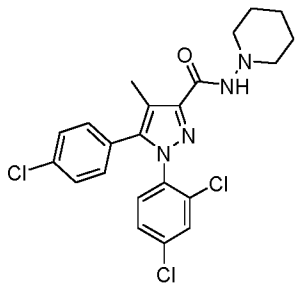
Examples:

General Information:

All reagents and solvents were used as received from commercial sources unless and otherwise noted. All experiments were carried out under an atmosphere of Argon in round bottom flask. Pre-coated plates (silica gel 60 PF254, 0.25 mm or 0.5 mm) were utilized for Thin Layer Chromatography (TLC). Column chromatographic purifications were carried out on flash silica-gel (100-200 mesh) using either petroleum ether and ethyl acetate or dichloromethane and methanol as eluents. Melting points are uncorrected. The IR spectra were recorded on an FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on 200/400/500 MHz and 50/100/125 MHz NMR spectrometer respectively in $CDCl_3$/DMSO-d_6. Mass spectra were taken on LC-MS (ESI) mass spectrometer. HRMS were scanned at NCL, Pune.

Example 1:

Synthesis of 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1):**



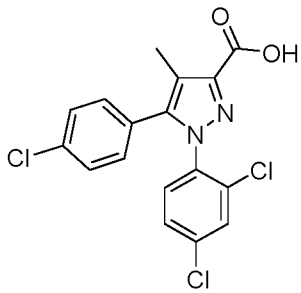
Modified Procedure:

To a stirred solution of compound 2 (382 mg; 1.0 mmol) in toluene (10 ml) one drop of dimethyl formamide was added. The reaction mixture was cooled to 0°C and added thionyl chloride (140 mg: 1.2mmol) in 2ml toluene drop-wise for the period of 2 minutes at the same temperature. The reaction mixture was allowed to attain room temperature and heated at 100°C for 4 h. Excess of thionyl chloride and toluene was distilled off under reduced pressure. In another flask under nitrogen atmosphere was introduced 1- amino piperidine (100 mg; 1.0 mmol) and triethyl amine (101 mg; 1.0 mmol) in 5.0 ml dichloromethane. The flask was cooled to 0°C. To this was added a cooled solution of acid chloride drop-wise at the same temperature. The resulting reaction mixture was allowed to attain room temperature and then it was stirred for 12h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (10 ml) and organic layer was separated, washed with water (2×5 ml) and brine solution(5ml), dried over Na_2SO_4(anhydrous) and concentrated in vacuo. The residue was purified by column chromatography over silica gel (ethyl acetate/petroleum ether 1:9(v/v)) afforded pure product.

R_f: 0.4 (3:7 EtOAc : Pet Ether); Solid; 292 mg, 63%; m.p. 182-183 °C ;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s,1H), 7.41-7.36 (m, 1H), 7.30-7.26 (m, 3H), 7.04 (d, J=8.28 Hz, 2H), 2.93-2.78 (m, 4H), 2.35 (s, 3H), 1.78-1.70 (m, 4H), 1.48-1.37 (m, 2H);
^{13}C NMR (CDCl3, 100 MHz): δ 159.9, 144.4, 142.9, 136.0, 135.9, 134.9, 132.9, 130.8, 130.6, 130.3, 128.9, 127.9, 127.2, 118.2, 57.0, 25.4, 23.3, 9.3;
HRMS-ESI (m/z) Calcd $C_{22}H_{22}ON_3Cl_3 + H)^+$: 463.0854 found:463.0853.

Example 2:

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**



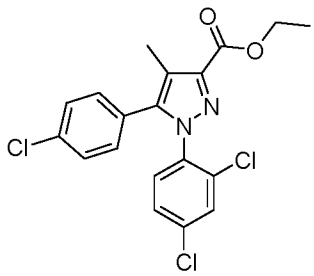
Synthesis of 2 was accomplished by the reported procedure.

R_f: 0.6 (5:95 MeOH : Dichloromethane); Solid; 979 mg, 65% ; m.p. 208-209 °C;

^{1}H NMR (CDCl3, 400 MHz): δ 7.44-7.41 (m, 1H), 7.35 (d, J=1.89 Hz, 1H), 7.33-7.28 (m, 3H), 7.09 (d, J=8.47 Hz, 2H), 2.36 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 143.3, 136.2, 135.6, 135.1, 133.5, 130.8, 130.5, 129.8, 128.9, 127.8, 127.7, 126.7, 119.6, 9.6;
HRMS-ESI (m/z) Calcd $C_{17}H_{11}O_2N_2Cl_3Na$: 402.9778 found: 402.978.1.

Example 3:

Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

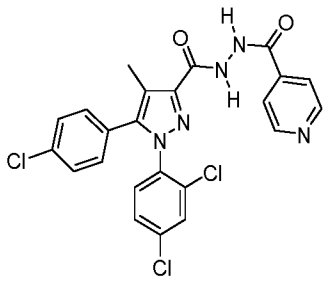


Compound 3 was prepared by the reported procedure.

R_f: 0.6 (1:9 EtOAc : Pet ether); Solid; 697 mg, 45% ; m.p. 128-129 °C;
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.39 (d, J=2.02 Hz, 1H), 7.34 (d, J=1.37 Hz, 1H), 7.33-7.28 (m, 3H), 7.08 (d, J=8.59 Hz, 2H), 4.51-4.41 (q, J= 7.08 Hz, 2H), 2.34 (s, 3H), 1.43 (t, J =7.08 Hz, 3H);
^{13}C NMR (CDCl3, 100 MHz): δ 162.7, 142.9, 136.0, 135.9, 135.0, 133.0, 130.9, 130.7, 130.1, 128.9, 127.7, 127.0, 119.1, 60.9, 14.4, 9.6;
HRMS-ESI (m/z) Calcd $C_{19}H_{15}O_2N_2Cl_3$ + H)+: 409.0272 found: 409.0265.

Example 4:

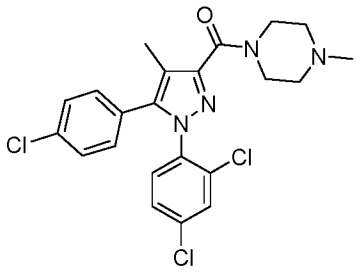
N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**



Compound 4 was synthesized from 2 according to the procedure applied to 1.

R_f : 0.6 (1:9 MeOH : Dichloromethane); Solid; 499 mg, 59% ; m.p. 237-239 °C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.33 (s, 1H), 9.44 (s, 1H), 8.71 (s, 1H), 7.74 (s, 2H), 7.41 (s, 1H), 7.30-7.32 (m, 5H), 7.05 (d, J=8.53 Hz, 2H), 2.17 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 161.2, 150.2, 143.3, 142.4, 136.2, 135.6, 135.2, 132.7, 130.7, 130.5, 130.3, 128.9, 128.8, 127.9, 126.7, 118.4, 30.9, 9.2;
HRMS-ESI (m/z) Calcd $C_{23}H_{16}O_2N_5C_{l3}$ + H)+ : 500.0442 found: 500.0443.

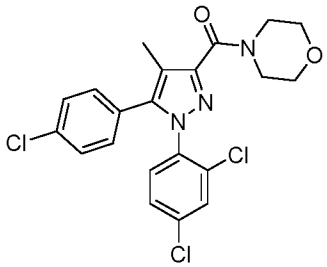
Example 5: (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(5)**



Compound 5 was synthesized from 2 according to the procedure applied to 1.

R_f : 0.68 (5:95 MeOH : Dichloromethane); Solid; 306 mg, 50% ; m.p. 111-113 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (s, 1H), 7.31-7.34 (m, 3H), 7.20 (d, J=8.54 Hz, 1H), 7.10 (d, J=8.28 Hz, 2H), 3.99-3.80 (m, 4H), 2.61-2.45 (m, 4H), 2.37 (s, 3H), 2.24 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.2, 146.4, 141.9, 135.9, 135.7, 134.8, 133.0, 130.6, 128.9, 127.8, 127.3, 116.8, 55.5, 54.7, 47.1, 45.9, 41.9, 9.0;
HRMS-ESI (m/z) Calcd $C_{22}H_{21}ON_4Cl_3$ + H)+: 463.0854 found: 463.0862.

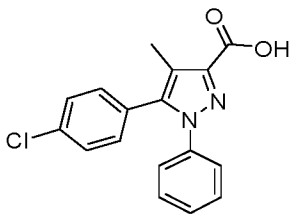
Example 6: (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**



Compound 6 was synthesized from 2 according to the procedure applied to **1**.

R_f : 0.68 (5:95 MeOH : Dichloromethane); Solid; 590 mg, 63% ; m.p. 170-172 °C;
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, J=2Hz, 1H), 7.33 (d, J=8.54 Hz, 2H), 7.27-7.30 (m, 1H), 7.19 (d, J=8.55 Hz, 1H), 7.09 (d, J=8.54 Hz, 2H), 3.85-3.92 (m, 4H), 3.75-3.83 (m, 4H), 2.25 (s, 3H);
^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.2, 146.0, 142.1, 135.9, 135.8, 134.9, 133.0, 130.6, 130.5, 130.3, 128.9, 127.8, 127.3, 117.2, 67.3, 66.9, 47.8, 42.6, 9.1;
HRMS-ESI (m/z) Calcd $C_{21}H_{18}O_2N_3Cl_3Na$:472.0357 found: 472.0355.

Example 7: 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

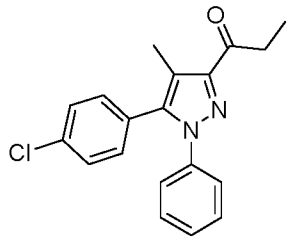


Compound 7 was synthesized by the procedure applied to **2.**

R_f : 0.5 (5:95 MeOH:Dichloromethane); Solid; 719 mg, 58% ; m.p. 203-204 °C;
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.46 (s, 1H), 7.32-7.38 (m, 5H), 7.30-7.20 (m, 2H), 7.13 (d, J= 6.36 Hz, 2H), 2.35 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9, 141.3, 140.9, 139.0, 134.9, 131.3, 129.0, 128.2, 127.6, 125.4, 125.1, 120.5, 9.6;
HRMS-ESI (m/z) Calcd $C_{17}H_{13}O_2N_2ClNa$: 335.0571 found: 335.0566.

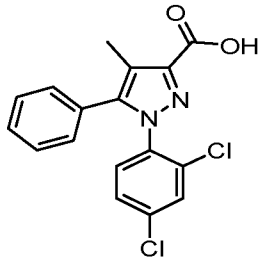
Example 8: 1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**



Synthesis of compound 8 was done by the reported procedure.

R_f: 0.8 (1:9 EtOAc : Pet ether); Solid; 595 mg, 48% ; m.p. 121-123 °C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.36 (m, 5H), 7.24-7.27 (m, 2H), 7.10 (d, J=8.6 Hz, 2H), 4.48 (q, J=14.14 Hz, 2H), 2.33 (s, 3H), 1.46 (t, J=7.07 Hz, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 142.3, 140.9, 139.3, 134.7, 131.3, 128.9, 128.0, 127.9, 127.0, 125.4, 120.0, 60.8, 14.4, 9.7;
HRMS-ESI (m/z) Calcd $C_{19}H_{17}O_2N_2ClNa$: 363.0871 found: 363.0868

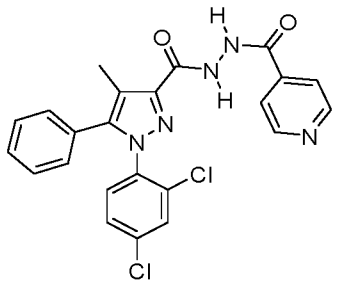
Example 9: 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**



Compound **9** was synthesized by the procedure applied to **2**.

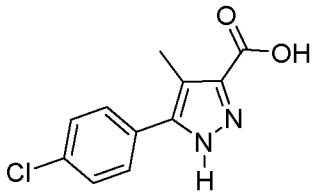
R_f: 0.5 (5:95 MeOH : Dichloromethane); Solid; 865 mg, 59%; m.p. 188-189 °C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (s, 1H), 7.16-7.27 (m, 5H), 7.08 (s, 2H), 6.02 (s, 1H), 2.17 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 145.6, 136.0, 135.1, 132.2, 131.2, 130.8, 129.6, 129.1, 128.5, 128.3, 128.2, 127.8, 118.0, 9.7;
HRMS-ESI (m/z) Calcd $C_{17}H_{12}O_2N_2Cl_2Na$: 369.0168 found: 369.0164.

Example 10: N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**



Compound **10** was synthesized from **9** according to the procedure applied to 1.
R_f : 0.7 (5:95 MeOH : Dichloromethane); Solid; 273 mg, 68%; m.p. 167-168°C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.28 (bs, 1H), 9.43 (s, 1H), 8.71 (bs, 1H), 7.75 (s, 1H), 7.41 (d, J=1.47, 2H), 7.28-7.34 (m, 5H), 7.14 (d, J=4.40, 2H), 7.01-7.04(m, 1H) 2.33 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.4, 161.2, 150.3, 144.4, 142.3, 138.8, 135.9, 135.8, 132.8, 130.5, 130.2, 129.5, 128.9, 128.6, 128.2, 127.8, 121.2, 118.3, 9.3;
HRMS-ESI (m/z) Calcd $C_{23}H_{17}O_2N_5Cl_2$ + H)+: 466.0832 found: 463.0830.

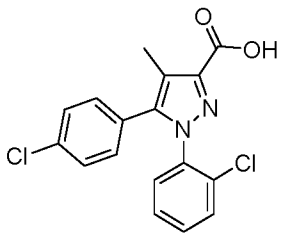
Example 11: 5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**



Compound **11** was synthesized by the procedure applied to **2**.

R_f : 0.5 (2:8 MeOH : Dichloromethane); Solid; 387 mg, 45%; m.p. 288-290 °C ;
^{1}H NMR (DMSO-d_6, 500 MHz): δ 13.54 (s, 1H), 7.89, (d, J=8.24 Hz, 2H), 7.77 (d, J=8.24 Hz, 2H), 2.61 (s, 3H);
^{13}C NMR (DMSO-d_6, 125 MHz): δ 162.4, 132.7, 130.9, 129.4, 128.9, 128.5, 117.0, 60.5, 9.9;
HRMS-ESI (m/z) Calcd $C_{11}H_9O_2N_2ClNa$: 259.0245 found: 259.0243.

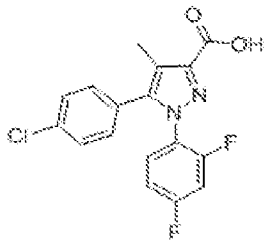
Example 12: 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**



Compound **12** was synthesized by the procedure applied to **2**.

Rf: 0.7 (5:95 MeOH : Dichloromethane); Solid; 656 mg, 52%; m.p. 204- 206 °C;
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33-7.42 (m, 4H), 7.26 (d, J=6.41 Hz, 2H), 7.04 (d, J=7.79 Hz, 2 H), 2.32 (s, 3H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 143.3, 141.7, 136.9, 134.9, 131.9, 130.9, 130.3, 130.0, 129.8, 128.8 127.5, 126.9, 119.4, 9.6;
HRMS-ESI (m/z) Calcd $C_{17}H_{12}O_2N_2Cl_2Na$: 369.0168 found: 369.0168.

Example 13: 5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**



Compound **13** was synthesized by the procedure applied to **2**

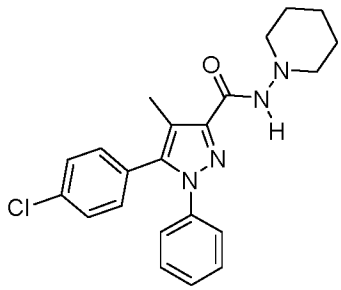
Rf: 0.5 (5:95 MeOH : Dichloromethane); Solid; 781 mg, 62%; m.p. 196-198°C;

^{1}H NMR (CDCl3, 500 MHz): δ 9.31 (bs, 1H), 7.44 (s, 1H), 7.27 (d, J=8.46 Hz, 2H), 7.03 (d, J=8.46 Hz, 2H), 6.87 (s, 1H), 6.72 (s, 1H), 2.25 (s, 3H);

^{13}C NMR (CDCl3, 125 MHz): δ 161.7, 157.5, 155.5, 143.1, 135.0, 130.7, 130.0, 128.9, 127.0, 123.7, 119.5, 112.1, 111.9, 104.8, 9.6;

HRMS-ESI (m/z) Calcd $C_{17}H_{11}O_2N_2ClF_2Na$: 371.0369 found: 371.0369.

Example 14: 5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(14)**



Compound 14 was synthesized from **7** according to the procedure applied to **1**.

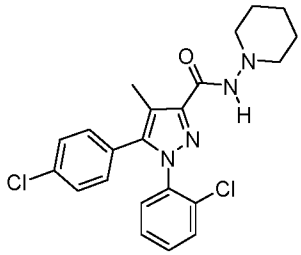
R_f : 0.3 (1:9 MeOH : Dichloromethane); Solid; 580 mg, 65%; m.p. 201-202°C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (bs, 1H), 7.33 (d, J=7.27 Hz, 5H), 7.21 (d, J=7.78 Hz, 2H), 7.08 (d, J=8.28 Hz, 2H), 2.98-2.79 (m, 4H), 2.35 (s, 3H), 1.85-1.68 (m, 4H), 1.52-1.38 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 143.5, 140.9, 139.3, 134.6, 131.2, 129.0, 128.9, 128.0, 127.9, 125.0, 119.1, 57.1, 25.4, 23.3, 9.3.

HRMS-ESI (m/z) Calcd $C_{22}H_{23}ON_4Cl$ + H)+: 395.1633 found: 395.1631.

Example 15: 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**

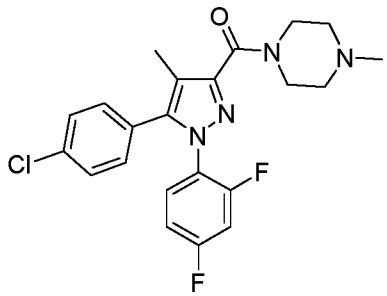


Com pound 15 was synthesized from **12** according to the procedure applied to **1**.

R_f: 0.5 (1:1 EtOAc : Pet ether); Solid; 207 mg, 42% ; m.p. 248-250 °C;

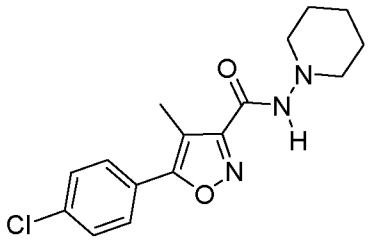
^{1}H NMR (CDCl3, 200MHz): δ 7.69 (bs, 1H), 7.37-7.30 (m, 1H),7.29-7.24 (m, 2H), 7.23-7.15 (m, 3H), 6.98 (d, J=8.71 Hz, 2H), 2.95-2.72 (m, 4H), 2.30 (s,3H), 1.78-1.61 (m, 4H), 1.45-1.29 (m, 2H);
^{13}C NMR (CDCl3, 100 MHz): δ 160.3, 143.4, 141.1, 136.5, 135.0, 131.5, 130.9, 130.8, 130.3, 129.8, 128.8, 127.7, 126.6, 118.3, 55.7, 23.8, 21.1, 9.2;
HRMS-ESI (m/z) Calcd $C_{22}H_{22}ON_4Cl_2$ + H)+: 429.1243 found: 429.1246

Example 16: (5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**



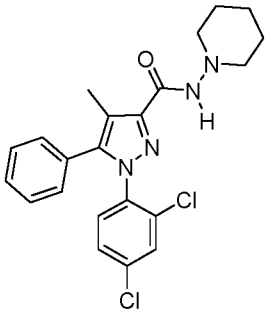
Compound 16 was synthesized from **13** according to the procedure applied to **1**.
R_f : 0.6 (5:95 MeOH : Dichloromethane); Solid; 518 mg, 84%; m.p. 174-176 °C;
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.24 (m, 1H), 7.24-7.20 (m, 2H), 7.06-6.96 (m, 2H), 6.91-6.69 (m, 2H), 3.91-3.63 (m, 4H), 2.56-2.34 (m, 4H), 2.29 (s, 3H), 2.12 (s, 3H);
^{13}C NMR ($CDCl_3$, 50 MHz): δ 163.2, 146.6, 141.9, 134.8, 130.5, 129.7, 128.8, 127.4, 124.1, 116.8, 112.1, 111.6, 105.0, 104.5, 55.5, 54.7, 47.0, 45.9, 41.8, 8.9;
HRMS-ESI (m/z) Calcd $C_{22}H_{21}ON_4ClF_2$ + H)+: 431.1445 found: 431.1447.

Example 17: 5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**



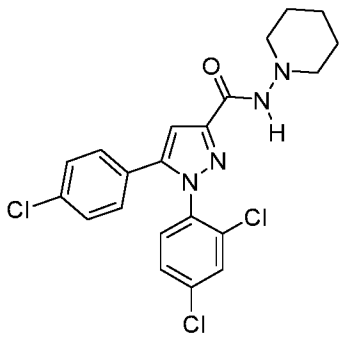
Compound 17 was synthesized from the corresponding acid according to the procedure applied to 1.
R_f : 0.6 (2:8 EtOAc:Pet ether); Solid; 240 mg, 45% ; m.p. 103-104 °C;
^{1}H NMR ($CDCl_3$, 500MHz): δ 7.63-7.64 (d, J=8.24 Hz, 1H), 7.57-7.58 (d, J=8.24 Hz, 1H), 7.47-7.49 (d, J=8.24 Hz, 2H), 2.99-2.81 (m, 4H), 2.45 (s, 3H), 1.85-1.71 (m, 4H), 1.53-1.41 (m, 2H);
^{13}C NMR ($CDCl_3$, 125MHz): δ 165.8, 163.0, 157.3, 156.4, 136.1, 129.2, 126.0, 111.7, 56.9, 25.2, 23.1, 8.3;
HRMS-ESI (m/z) Calcd $C_{16}H_{18}O_2N_3Cl$ + H)+: 320.1160 found: 320.1161.

Example 18: Synthesis of 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**



Compound 18 was synthesized from **9** according to the procedure applied to **1**.
R_f : 0.6 (5:95 MeOH:Dichloromethane); Solid; 288 mg, 61%; m.p. 172-173 °C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (s, 1H), 7.41 (s, 1H), 7.27-7.32 (m, 5H), 7.11 (s, 2H), 3.05-2.75 (m, 4H), 2.38 (s, 3H), 1.91-1.65 (m, 4H), 1.54-1.34 (m, 2H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 144.2, 144.0, 136.1, 135.7, 133.0, 130.6, 130.2, 129.5, 128.6, 128.6, 128.4, 127.7, 117.9, 57.0, 25.3, 23.2, 9.3;
HRMS-ESI (m/z) Calcd $C_{22}H_{22}ON_4Cl_2$ + H)+: 429.1243 found: 429.1244.

Example 19: 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(19)**



Compound **19** was synthesized from the corresponding acid according to the procedure applied to **1.**
R_f : 0.7 (5:95 MeOH : Dichloromethane); Solid; 199 mg, 53%; m.p. 139-140 °C;
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J =2.29 Hz, 1H), 7.57 (s, 1H), 7.55 (d, J=2.29 Hz, 1H), 7.53 (d, J = 1.83 Hz, 1H), 7.42 (d, J = 9.15 Hz, 2H), 7.26 (d, 2H), 7.23 (s, 1H), 3.35-3.19 (m, 4H), 2.01-1.95 (m, 4H), 1.70-1.59 (m, 2H);
^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.8, 146.8, 145.6, 136.3, 135.7, 135.1, 132.8, 130.5, 130.4, 129.1, 129.0, 128.2, 127.3, 107.5, 56.8, 24.9, 22.7;
HRMS-ESI (m/z) Calcd $C_{21}H_{19}ON_4Cl_3$ + H)+: 449.0697 found: 449.0701.

Example 20: Rimonabant (1)

Composition:

Rimonabant	10.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Then the active ingredient **(Rimonabant**, Compound **1)** and Magnesium stearate was mixed and filled in a sample vial.

Mode of administration: Disperse the powder in water/juice.

Example 21: Rimonabant (1) Composition:

Rimonabant	20.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Then the active ingredient **(Rimonabant**, Compound **1)** and Magnesium stearate was mixed and filled in a sample vial.

Mode of administration: Disperse the powder in water/juice.

Example 22: Composition:

Compound **JMG-14**	10.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Mix active ingredient **(JMG-14)** and Magnesium stearate and may be filled in a capsule of suitable size.

Mode of administration: The capsule may be had with water of juice

Example 23: Composition:

Compound **JMG-14**	20.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Mix active ingredient **(JMG-14)** and Magnesium stearate and may be filled in a capsule of suitable size.

Mode of administration: The capsule may be had with water of juice

Example 24: Composition:

Compound **11**	10.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Mix active ingredient **(Compound-11)** and Magnesium stearate and may be filled in a capsule of suitable size.

Mode of administration;

Mode of administration: The tablet may be had with water of juice

Example 25: Composition:

Compound **16**	5.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Mix active ingredient **(Compound 16)** and Magnesium stearate and may be compressed as tablet.

Mode of administration: The tablet may be had with water of juice

Example 26: Composition:

Compound **17**	10.0% w/w
Colour Iron oxide red	0.3% w/w
Strawberry Flavour	0.7% w/w
Magnesium stearate	2.0% w/w
Mannitol	q.s. to 100.0%w/w

Procedure: Dissolve mannitol in 2.0 ml of water. Then iron oxide red was added followed by strawberry flavour.

Water was evaporated on rotary vapour to adsorb colour and flavour on mannitol.

Mix active ingredient **(Compound -17)** and Magnesium stearate and fill in pouch or bottle.

Mode of administration:

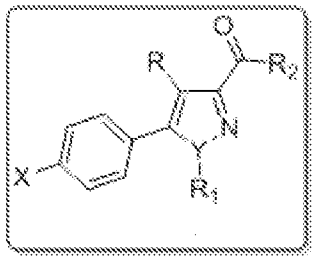
Disperse the powder in water/juice.

ADVANTAGES OF THE INVENTION:

- Novel candidates with anti-mycobacterial activity

The claims:

1. Pyrazole carboxylic acid analogues of Formula 1, or stereoisomers, or esters or pharmaceutically acceptable salts thereof, for use as a medicament for treating



Formula 1

mycobacterial infections,

wherein, Y represents heteroatom N, S or O;

X represents hydrogen, or halogen;

R_1 represents (un)substituted aryl, hydrogen, where substituents are mono, di or tri halogen;

R_2 represents OH, (C1-C6) alkyl, (C1-C6)alkoxy, piperidine, 1-amino piperidine, morpholine, pyridine-4-carbohydrazide, 1-methylpiperazine, 1-methylpiperazine, thiomorpholine, hydrazine, amino acids, Schiff bases, heterocycles;

and R represents (C1-C4) linear or branched alkyl, hydrogen.

2. The pyrazole carboxylic acid analogues of Formula 1, according to claim 1, encompasses the following compounds;

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1)**

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**

Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methyl piperazin-1-yl) methanone **(5)**

(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**

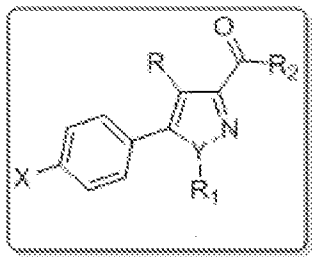
5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**

1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**
N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**
5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**
1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**
5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**
5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(14)**
1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**
(5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**
5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**
1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**
5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(19).**

3. The pyrazole carboxylic acid analogues of Formula 1, as claimed in claim 1, wherein Minimum inhibitory concentration(MIC) against *Mycobacterium tuberculosis* (strain H37Rv) is in the range of 3 to 30 µg/ml and for *Mycobacterium smegmantis* the MIC is in the range of 1-35 µg/ml,
4. A pharmaceutical composition comprising pyrazole carboxylic acid analogues of the Formula I, according to claim 1, together with pharmaceutically acceptable excipient(s) and/or vehicle(s), for the treatment of mycobacterial infections in human.
5. The pharmaceutical composition comprising pyrazole carboxylic acid analogues of general formula I, according to claim 3, optionally with an additional anti tubercular agent together with pharmaceutically acceptable excipient(s) and/or vehicle(s).
6. The pyrazole carboxylic acid analogues of Formula 1, according to any of the preceding claim, wherein *Mycobacterium* species is selected from the group consisting of *Mycobacterium tuberculosis* (strain H37Rv) and *Mycobacterium smegmatis* (strain MC2 155).

7. A method of treating or inhibiting or controlling growth of *Mycobacterium* species in human, comprising administrating pyrazole carboxylic acid analogues of general formula- I, together with pharmaceutically acceptable excipient(s) and/or vehicle(s).



Formula 1

wherein, Y represents heteroatom N, S or O;

X represents hydrogen, or halogen;

R_1 represents (un)substituted aryl, hydrogen, where substituents are mono, di or tri halogen; R_2 represents OH, (C1-C6) alkyl, (C1-C6) alkoxy, piperidine, 1-amino piperidine, morpholine, pyridine-4-carbohydrazide, 1-methylpiperazine, 1-methylpiperazine, thiomorpholine, hydrazine, amino acids, Schiff bases, heterocycles; and R represents (C1-C4) linear or branched alkyl, hydrogen.

8. The method of treating or inhibiting or controlling growth of *Mycobacterium* species in human, comprising administrating pyrazole carboxylic acid analogues of general formula- I, according to claim 7. , wherein the compounds are selected from the group consisting of ;

i. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1-H-pyrazole-3-carboxamide **(1)**

ii. 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(2)**

iii. Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate **(3)**

iv. N'-(5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(4)**

v. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methyl piperazin-1-yl) methanone **(5)**

vi. (5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazol-3-yl) (morpholino) methanone **(6)**

vii. 5-(4-Chlorophenyl)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid **(7)**

viii. 1-(5-(4-chlorophenyl)-4-methyl-1-phenyl-1H-pyrazol-3-yl)propan-1-one **(8)**

ix. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid **(9)**

x. N'-(1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carbonyl) isonicotinohydrazide **(10)**

xi. 5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(11)**

xii. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(12)**

xiii. 5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid **(13)**

xiv. 5-(4-chlorophenyl)-4-methyl-1-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(14)**

xv. 1-(2-chlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(15)**

xvi. (5-(4-chlorophenyl)-1-(2,4-difluorophenyl)-4-methyl-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl) methanone **(16)**

xvii. 5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)isoxazole-3-carboxamide **(17)**

xviii. 1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide **(18)**

xix. 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(piperidin-1-yl)-1H-pyrazole-3-carbox amide **(19).**

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060936

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/12 C07D231/14 C07D401/12 A61K31/415 A61K31/4155
A61P31/06 A61P31/04
ADD.
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

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/011850 A2 (ABBOTT LAB [US]; BREINLINGER ERIC C [US]; CUSACK KEVIN P [US]; HOBSON) 22 January 2009 (2009-01-22) pages 8,20; claims	1-8
Y	WO 2007/075896 A2 (KEMIA INC [US]; BOMAN ERIK [US]; MONTALBAN ANTONIO GARRIDO [US]; PEI Y) 5 July 2007 (2007-07-05) claims 10,65	1-8
Y	EP 1 188 754 A1 (TEIKOKU HORMONE MFG CO LTD [JP]) 20 March 2002 (2002-03-20) paragraph [0005]; claims	1-8

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[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent 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	Date of mailing of the international search report
24 July 2014	20/08/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frelon, Didier

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060936

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	METAFERIA, BELHU B. ET AL: "Synthesis of Natural Product-Inspired Inhibitors of Mycobacterium tuberculosis Mycothiol-Associated Enzymes: The First Inhibitors of GlcNAc-Ins Deacetylase", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, 2007, pages 6326-6336, XP002727670, DOI: 10.1021/JM070669H scheme 7, compound 45	1-8
Y	PIERONI, MARCO ET AL: "NOC chemistry for tuberculosis-further investigations on the structure-activity relationships of antitubercular isoxazole-3-carboxylic acid ester derivatives", CHEMMEDCHEM, vol. 5, no. 10, 2010, pages 1667-1672, XP002727671, DOI: 10.1002/CMDC.201000169 example 4; table 2	1-8
Y	BERESFORD, NICOLA J. ET AL: "Inhibition of MptpB phosphatase from Mycobacterium tuberculosis impairs mycobacterial survival in macrophages", JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 63, 2009, pages 928-936, XP002727672, DOI: 10.1093/JAC/DKP031 examples 6,11; table 1	1-8
Y	TAN, LAY PHENG ET AL: "High-Throughput Discovery of Mycobacterium tuberculosis Protein Tyrosine Phosphatase B (MptpB) Inhibitors Using Click Chemistry", ORGANIC LETTERS, vol. 11, no. 22, 2009, pages 5102-5105, XP002727673, DOI: 10.1021/OL9023419 figure 1; example W7	1-8
Y	MORASKI, GARRETT C. ET AL: "Generation and exploration of new classes of antitubercular agents: The optimization of oxazolines, oxazoles, thiazolines, thiazoles to imidazo[1,2-a]pyridines and isomeric 5,6-fused scaffolds", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 20, no. 7, 2012, pages 2214-2220, XP002727674, DOI: 10.1016/J.BMC.2012.02.025 examples 6,7; table 1	1-8

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060936

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LILIENKAMPF, ANNAMARIA ET AL: "Rational Design of 5-Phenyl-3-isoxazolecarboxylic Acid Ethyl Esters as Growth Inhibitors of Mycobacterium tuberculosis: A Potent and Selective Series for Further Drug Development", JOURNAL OF MEDICINAL CHEMISTRY, vol. 53, 2010, pages 678-688, XP002727675, DOI: 10.1021/JM901273N tables 1,2	1-8
Y	PATHAK, RAVINDRA B. ET AL: "Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 22, no. 15, 2012, pages 5129-5133, XP002727676, DOI: 10.1016/J.BMCL.2012.05.063 examples 5,6	1-8
Y	SUDALAIANDI KUMARESAN ET AL: "Syntheses, Characterization, Antimicrobial-, Antituberculosis-, and Antitumor Activity of N,1-Diphenyl-1,4-dihydrothiochromeno[4,3-c]pyrazole-3-carboxamide Analogues", IJAPR INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACEUTICAL RESEARCH, vol. 4, no. 2, February 2013 (2013-02), pages 1402-1412, XP055128032, India ISSN: 2230-7583 examples 6i,6j	1-8
A	KATOCH-ROUSE, REETI ET AL: "Synthesis, Structure-Activity Relationship, and Evaluation of SR141716 Analogues: Development of Central Cannabinoid Receptor Ligands with Lower Lipophilicity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 4, 2003, pages 642-645, XP002727677, DOI: 10.1021/JM020157X scheme 1, compound 7; abstract	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/060936

Box No. 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:

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 No. 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:

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

compounds of Formula 1

1.1. claims: 1-8(partially)

compounds of Formula 1 wherein R2 represents OH or C1-6 alkoxy and wherein X is hydrogen

1.2. claims: 1-8(partially)

compounds of Formula 1 wherein R2 represents OH or C1-6 alkoxy and wherein X is halogen

1.3. claims: 1-8(partially)

compounds of Formula 1 wherein R2 represents C1-6 alkyl

1.4. claims: 1-8(partially)

compounds of Formula 1 wherein R2 represents heterocycles

1.5. claims: 1-8(partially)

compounds of Formula 1 wherein R2 is a group linked through a segment NH-N< represented by piperidin-1-yl amino.

1.6. claims: 1-8(partially)

compounds of Formula 1 wherein R2 is a group linked through a segment NH-N< represented by hydrazine or isonicotino-hydrazide.

1.7. claims: 1, 3-7(all partially)

compounds of Formula 1 wherein R2 represents an amino acid

1.8. claims: 1, 3-7(all partially)

compounds of Formula 1 wherein R2 represents a Schiff base

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/060936

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009011850 A2	22-01-2009	TW 200911232 A	16-03-2009
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WO 2007075896 A2	05-07-2007	NONE	
EP 1188754 A1	20-03-2002	AT 296820 T	15-06-2005
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		US 2004087628 A1	06-05-2004
		WO 0075131 A1	14-12-2000