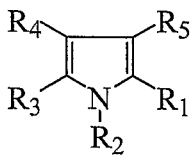
PYRROLE DERIVATIVES AS ANTIMYCOBACTERIAL COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel 3-and /or 4-(4-substituted- piperazinyl)alkyl pyrroles of Formula (I),



(I)

and their pharmaceutically acceptable acid addition salts thereof, possessing excellent antimycobacterial activity against clinically sensitive as well as resistant strains of *Mycobacterium tuberculosis*. The antimycobacterial activity of the compounds of the present invention are found to be superior to those of previously known compounds. The present invention also relates to use of the novel compounds for treatment of latent tuberculosis including Multi Drug Resistant Tuberculosis (MDR TB). The invention further relates to methods for preparation of the novel compounds and pharmaceutical compositions containing the said novel compounds.

BACKGROUND OF THE INVENTION

Tuberculosis (TB) is a contagious disease, which usually runs a protracted course, ending in death in majority of the cases, with relapse being a common feature of the disease. It is one of the most important causes of prolonged disability and chronic ill health. It is caused by the tubercle bacillus *Mycobacterium tuberculosis*, which is comparatively difficult to control. Drugs such as isoniazid, rifampicin, pyrazinamide, ethambutol streptomycin, para-aminosalisylic acid, ethionamide, cycloserine, capreomycin, kanamycin, thioacetazone etc. have been and are being currently used to treat TB. Amongst these, isoniazid, rifampicin, ethambutol and pyrazinamide are the first-line drugs of choice, which are administrated either as a single drug formulation or as a fixed-dose combination of two or more of the aforesaid drugs.

Even though, each of the abovementioned first-line drug regimen is highly effective for treatment of TB, however, they are associated with shortcomings, such as unpleasant side-effects and relatively long course of treatment. The later one results in non-compliance of the patient to the treatment leading often to failure of the treatment and most importantly, development of drug resistance. The development of drug resistance has long constituted a principal difficulty in treating human tuberculosis. The second-line drugs, on the other hand are less effective, more expensive and more toxic.

It is estimated that in the next twenty years over one billion people would be newly infected with TB, with 35 million people succumbing to the disease (WHO Fact Sheet No. 104, Global Alliance for TB Drug Development- Executive Summary of the Scientific Blueprint for TB Development : http://www.who.int/inf-fs/en/fact104.html). With the emergence of HIV related TB, the disease is assuming alarming proportions as one of the killer diseases in the world today.

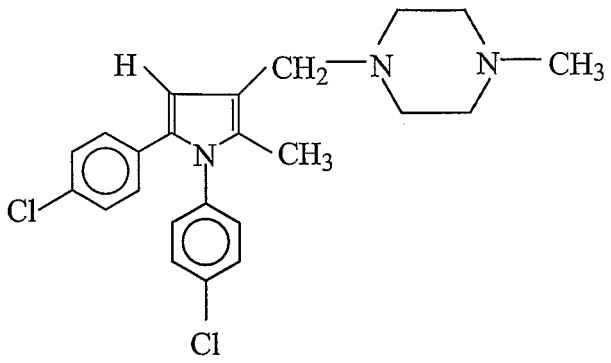
A major thrust in research on antimycobacterials in the last decade has witnessed the development of new compounds for treatment of the disease,

a) differing widely in structures,
b) having different mode/mechanism of action,
c) possessing favourable pharmacokinetic properties,
d) which are safe and having low incidence of side-effects, and
e) which provide a cost-effective dosage regimen.

Several new class of compounds have been synthesized and tested for activity against *Mycobacterium tuberculosis,* the details of chemistry and biology of which could be found in a recent review by B. N. Roy et. al. in *J. Ind. Chem. Soc.*, **April 2002**, 79, 320-335 and the references cited therein.

Substituted pyrrole derivatives constitute another class of compounds, which hold promise as antimycobacterial agents. The pyrrole derivatives which have been synthesized and tested for antitubercular as well as non-tubercular activity has been disclosed by :

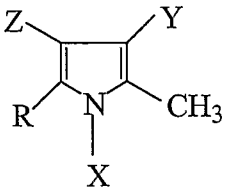
a) D. Deidda et. al. in *Antimicrob. Agents and Chemother.*, **Nov 1998**, 3035-3037. This article describes the inhibitory activity shown by one pyrrole compound, viz. BM 212 having the structure shown below, against both *Mycobacterium tuberculosis* including drug-resistant *mycobacteria* and some non-tuberculosis *mycobacteria*.



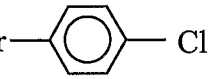
BM 212

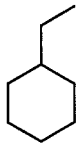
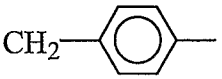
The MIC value (μg/ml) against the *M. tuberculosis* strain 103471 exhibited by BM 212 was 0.70 as against 0.25 found for isoniazid.

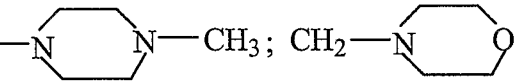
b) M. Biava et. al. in *J. Med. Chem. Res.*, **1999**, 19-34 have reported the synthesis of several analogues of BM 212, having the general formula (The compounds disclosed by M. Biava et. al. in *J. Med. Chem. Res.*, **1999**, 19-34.) shown hereunder



wherein,

R is CH_3 or 

X is H,  ;  ; CH_2-$(CH_2)_4$-CH_3

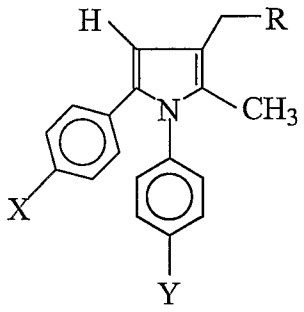
Y IS 

Z is H ; Y

and the *in vitro* antimicrobial activity of the compounds against *Candida albicans*, *Candida sp*, *Cryptococcus neoformans*, Gram- positive or Gram-negative bacteria, isolates of pathogenic plant fungi, Herpes simplex virus, both HSV1 and HSV2, *M. tuberculosis*, *M. smegmatis*, *M. marinum* and *M. avium*.

However, the MIC values (μg/ml) of these compounds against the *M. tuberculosis* strain 103471 are found to be inferior to BM 212 and are in the range of 4-16.

c) M. Biava et. al. in *Bioorg. & Med. Chem. Lett.*, **1999**, 9, 2983-2988. This article describes the synthesis of pyrrole compounds of formula (: The compounds disclosed by M. Biava et. al. in *Bioorg. & Med. Chem. Lett.*, **1999**, 9, 2983-2988) shown hereunder



wherein,

X is H or Cl
Y is H or Cl
R is N-methyl piperazinyl or thiomorphinyl

and their respective *in vitro* activity against *M. tuberculosis* and non-tuberculosis species of *mycobacteria*.

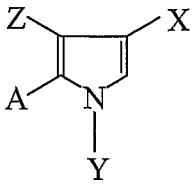
However, the MIC values (μg/ml) of these compounds against the *M. tuberculosis* strain 103471 are found to be inferior to BM 212 and are in the range of 2-4.

d) F. Cerreto et. al. in *Eur. J. Med. Chem.*, **1992**, 27, 701-708 have reported the synthesis of certain 3-amino-1,5-diary-2-methyl pyrrole derivatives and their *in vitro* anti-fungal activity against *Candida albicans* and *Candida sp*. However, there is no report on the activity of such compounds against *M. tuberculosis*.

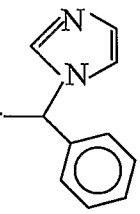
e) C. Gillet et. al. in *Eur. J. Med. Chem.-Chimica Therapeutica*, **March-April 1976**, 11(2), 173-181 report the synthesis of several pyrrole derivatives useful as anti-inflammatory agents and as anti-allergants.

f) R. Ragno et. al., *Bioorg. & Med. Chem.*, **2000**, 8, 1423-1432. This article reports the synthesis and biological activity of several pyrrole derivatives as well as describes a structure activity relationship between the said pyrrole compounds and antimycobacterial activity. The compounds (The compounds disclosed by R. Rango et.

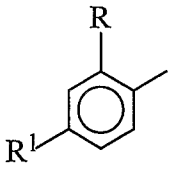
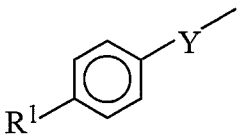
al., *Bioorg. & Med. Chem.*, **2000**, 8, 1423-1432)synthesized and tested by the authors is summarized hereunder



wherein,

X is COOH, COOEt, $CONHNH_2$, CH_2OH, $CH(OH)C_6H_5$, NO_2 or 

Y is H, CH_3, OCH_3, CH_2, SO_2, or a group of formula

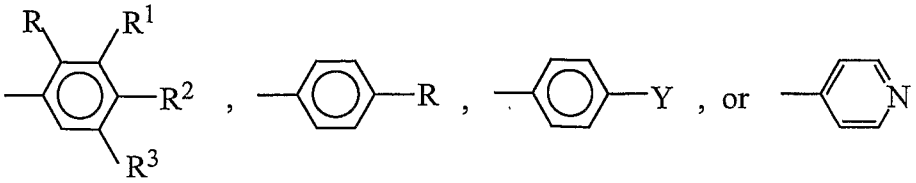
 , or 

wherein,

R is H, Cl, C_2H_5, or OCH_3 and R^1 is H, Cl, F, CH_3, or NO_2,

A is H or R

Z is a group of formula,



R^2 is H, Cl, OH, or OCH_3 and R^3 is H or Cl

None of the abovementioned disclosures report or suggest the *in vivo* efficacy including toxicity of any of the compounds described therein against experimental tuberculosis in animal model. Moreover, the higher MIC values of the compounds reported suggest that they may not be very effective in inhibition of *Mycobacterium tuberculosis*.

OBJECTS OF THE INVENTION :

It is thus the basic object of the present invention to meet the urgent demand, that exists for new antimycobacterial compounds by providing novel pyrrole derivatives which,

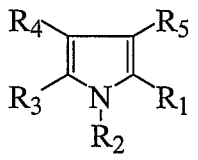
a) exhibit significantly greater antimycobacterial activity, than existing drugs,

b) provide safe and specific treatment of Multi Drug Resistant tuberculosis (MDR TB), and

c) are useful in treatment of patients who harbour quiescent/latent tuberculosis.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a compound of formula (I) its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof



(I)

wherein,

R_1 is

a) C_1-C_4 alkyl, or

b) C_1-C_4 alkoxy, or

c) C_1-C_4 thioalkoxy, or

d) trifluoroalkyl, or

e) trifluoroalkoxy, or

f) hydroxyalkyl

R_2 is selected from a group consisting of

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

v) unsubstituted or substituted pyridine, or

vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

R_3 is

a) phenyl or substituted phenyl, or

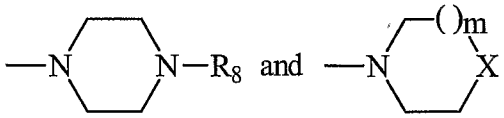
b) aryl, or

c) unsubstituted or substituted heteroaryl.

R_4 and R_5 are each independently

i) hydrogen, or

ii) a group of formula $-(CH_2)_n-R_7$ wherein n = 1-3 and R_7 is selected from the groups



wherein,

R_8 is

a) phenyl which is unsubstituted or substituted with 1or 2 substitutents each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, amino, haloalkyl, haloalkoxy or

b) unsubstituted or substituted benzyl; unsubstituted or substituted heteroaryl; unsubstituted or substituted heteroaroyl; unsubstituted or substituted diphenylmethyl , and

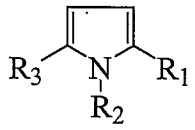
and m = 0-2, and

X = -NCH_3, CH_2, S, SO, or SO_2.

The above disclosed compound of formula (I), and its various forms including its pharmaceutically acceptable salts are safe and exhibit significantly low toxicity.

Another aspect of the present invention provides methods for synthesis of compound of formula (I) its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof comprising :

reacting a compound of formula (V)



(V)

wherein R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

R_2 is selected from a group consisting of

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

v) unsubstituted or substituted pyridine, or

vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

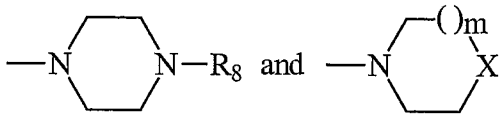
R_3 is

a) phenyl or substituted phenyl, or

b) aryl, or

c) unsubstituted or substituted heteroaryl.

with an amine of formula R_7H, wherein R_7 is selected from the groups



wherein R_8 is phenyl which is unsubstituted or substituted with 1-2 substitutents each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, amino, haloalkyl, haloalkoxy etc.; unsubstituted or substituted benzyl; unsubstituted or substituted heteroaryl; unsubstituted or substituted heteroaroyl; unsubstituted or substituted diphenylmethyl ,

m = 0-2 and

X = -NCH_3, CH_2, S, SO, or SO_2

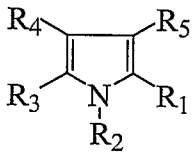
It yet another further aspect the present inventions provides pharmaceutical compositions useful in the treatment of mycobacterial conditions such as tuberculosis including Multi Drug Resistant Tuberculosis (MDR TB)comprising a) atleast one of compound of formula (I), its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof and b) pharmaceutically acceptable additives.

In yet another aspect, the present invention provides a method of inhibiting/treating the microbial cell/conditions with a compound selected from compound of formula (I), its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs, its pharmaceutically acceptable salts with or without pharmaceutically acceptable carriers .The microbial cell/condition can be of *Mycobacterium tuberculosis*, drug resistant *Mycobacterium*

tuberculosis, *Mycobacterium avium-intracellulare complex*, *Mycobacterium fortuitum* or *Mycobacterium kansasi*.

DETAILED DESCRIPTION OF THE INVENTION

In the pharmaceutically active compound of formula (I) of this invention,



(I)

the definition of the groups R_1, R_2, R_3, R_4, and R_5 are as follows :

R_1 is

a) C_1-C_4 alkyl, both straight and branched, or

b) C_1-C_4 alkoxy, or

c) C_1-C_4 thioalkoxy, or

d) trifluoroalkyl, or

e) trifluoroalkoxy, or

f) hydroxyalkyl

Suitable alkyl groups are methyl, ethyl, n-propyl, n-butyl, iso-propyl, iso-butyl, or tert-butyl. Methyl is preferred.

Suitable alkoxy groups are methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-propopxy, iso-butoxy, and tert-butoxy.

Suitable thioalkyl groups are thiomethyl, thioethyl, 1-propanethio, 2-propanethio, 1-butanethio, 1-methyl-1-propanethio, and 1-methyl-2-propanethio.

Suitable trifluoroalkyl groups are trifluoromethyl, and trifluoroethyl.

Suitable trifluoroalkoxy groups are trifluoromethoxy, and trifluoroethoxy.

Suitable hydroxyalkyl groups are selected from trifluoromethoxy and trifluoroethoxy,

R_2 is selected from a group consisting of :

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

v) unsubstituted or substituted pyridine, or

vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

The substituted phenyl groups are selected from but not limited to chlorobenzene, bromobenzene, fluorobenzene, 1,2-dichlorobenzene, 1,2-dibromobenzene, 1,2-difluorobenzene, 1,3-dichlorobenzene, 1,3-dibromobenzene, 1-3,difluorobenzene, 1,4-difluorobenzene, 1-4-dibromobenzene, 1,4-difluorobenzene, methylbenzene, ethylbenzene, o-xylene, m-xylene, p-xylene, 2-ethyl toluene, 3-ethyl toluene, 4-ethyl toluene, propyl benzene, cumene, butyl benzene, sec-butyl benzene, iso-butyl benzene, tert-butyl benzene, , o-cymene, m-cymene, p-cymene, 1,2-diethyl benzene, 1,3-diethyl benzene, 1,4-diethylbenzene, 1,3-di-tert-butyl benzene, 1,4-di-tert-butyl benzene, 4-tert butyl toluene, anisole, 2-methyl anisole, 3-methyl anisole, 4-methyl anisole, 1,2-benzenedimethanol, 1,3-benzenedimethanol, 1,4-benzenedimethanol, 1,2-dimethoxybenzene, 2-ethoxyanisole, 3,5-diethoxytoluene, benzylmercaptan, phenethylmercaptan, 1,2-benzenedimethanethiol, 1,3-benzenedimethanethiol, 1,4-benzenedimethanethiol, nitrobenzene, 1,2-dinitrobenzene, 1,3-dinitrobenzene, 1,4-dinitrobenzene, benzyl chloride, benzyl bromide, trifluoromethoxy, trifluoroethoxy etc.

In group R_6, the term heteroaryl refers to any aryl ring containing one or more of heteroatoms selected from N, O, and S, whereas the term heterocycle refers to any heterocyclic ring systems.

R_3 is,

a) Phenyl or substituted phenyl. Suitable substituted phenyl groups are selected from but not limited to chlorobenzene, bromobenzene, fluorobenzene, 1,2-dichlorobenzene, 1,2-dibromobenzene, 1,2-difluorobenzene, 1,3-dichlorobenzene, 1,3-dibromobenzene, 1-3,difluorobenzene, 1,4-difluorobenzene, 1-4-dibromobenzene, 1,4-difluorobenzene, methylbenzene, ethylbenzene, o-xylene, m-xylene, p-xylene, 2-ethyl toluene, 3-ethyl toluene, 4-ethyl toluene, propyl benzene, cumene, butyl benzene, sec-butyl benzene, iso-butyl benzene, tert-butyl benzene, , o-cymene, m-cymene, p-cymene, 1,2-diethyl benzene, 1,3-diethyl benzene, 1,4-diethylbenzene, 1,3-di-tert-butyl benzene, 1,4-di-tert-butyl benzene, 4-tert butyl toluene, anisole, 2-methyl anisole, 3-methyl anisole, 4-methyl anisole, 1,2-benzenedimethanol, 1,3-benzenedimethanol, 1,4-benzenedimethanol, 1,2-dimethoxybenzene, 2-ethoxyanisole, 3,5-diethoxytoluene, benzylmercaptan, phenethylmercaptan, 1,2-benzenedimethanethiol, 1,3-benzenedimethanethiol, 1,4-benzenedimethanethiol, nitrobenzene, 1,2-dinitrobenzene, 1,3-dinitrobenzene, 1,4-dinitrobenzene, benzyl chloride, benzyl bromide,trifluoromethoxy, trifluoroethoxy etc., or

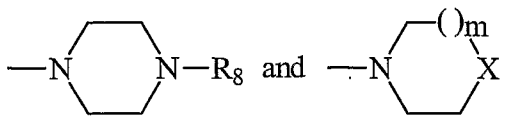
b) an aryl group, or

c) an unsubstituted or substituted heteroaryl, as defined hereinearlier.

R_4 and R_5 are each independently

i) hydrogen, or

ii) a group of formula $-(CH_2)_n-R_7$ wherein n = 1-3 and R_7 is selected from the groups



wherein,

R_8 is

a) phenyl which is unsubstituted or substituted with 1or 2 substitutents each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4

thioalkoxy, nitro, amino, haloalkyl, haloalkoxy, wherein the substituents are as defined hereinearlier, or

b) unsubstituted or substituted benzyl; unsubstituted or substituted heteroaryl; unsubstituted or substituted heteroaroyl; unsubstituted or substituted diphenylmethyl , wherein

m = 0-2, and

X = -NCH_3, CH_2, S, SO, or SO_2.

Furthermore, the compound of formula (I) of this invention includes its pharmaceutically acceptable, non-toxic, acid addition salts formed with inorganic or organic acids by methods well known in the art. These salts may be used in place of the free bases. Examples of suitable acids for formation of such acid addition salts are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene, salicylic, methanesulphonic ethanedisulphonic, acetic, propionic, tartaric, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfamic, phosphoric, hydrobromic, sulfuric, hydrochloric, and nitric acids, and the like.

The present invention also includes the possible tautomers, enantiomers, diastereomers, N-oxides, prodrugs, polymorphs and metabolites of compound of formula (I), having the same activity.

The present invention also includes within its scope prodrugs of the compounds of Formula (I). In general, such prodrugs will be functional derivatives of these compounds which are readily converted *in vivo* into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

The present invention also provides pharmaceutical compositions containing compound of formula (I), for the treatment of *M. tuberculosis* . These compositions comprise an effective amount of compound of formula (I), or its prodrugs, metabolites, tautomers, enantiomers, diastereomers, N-oxides, pharmaceutically acceptable salts or polymorphic forms thereof, in combination with a pharmaceutically acceptable carrier and optionally in the presence of excipients.

Some preferred specific novel compounds No. 1-91 of formula (I) (named according to IUPAC or CAS nomenclature) that form part of this invention are named hereunder:

1. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl) piperazine
2. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxy- phenyl) piperazine
3. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoro-methylphenyl)piperazine
4. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)- piperazine
5. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyrimidyl)-piperazine
6. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(diphenyl- methyl) piperazine
7. 4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl-2-furyl-ketone
8. 5-[(4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl)- methyl]-2H-benzo[d]1,3-dioxolene
9. 4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyloxolan-2-yl-ketone
10. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methyl-5-cholrophenyl) piperazine
11. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide
12. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenyl-pyrrolyl)-4-pyridylcarboxamide
13. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide
14. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide
15. N-(2-methyl-5-phenyl-3-{[4-benzylpiperazinyl]methyl}pyrrolyl)-4-pyridyl-carboxamide

16. N-{2-methyl-3-[(4-methylpiperazinyl]methyl}-5-phenylpyrrolyl)-4-pyridyl-carboxamide
17. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide
18. N-(2-methyl-5-phenyl-3-(piperidylmethyl)pyrrolyl]-4-pyridylcarboxamide
19. N-(2-methyl-5-phenyl-3-(pyrrolidinylmethyl)pyrrolyl]-4-pyridylcarboxamide
20. N-[2-methyl-3-(morpholin-4-ylmethyl)-5-phenylpyrrolyl]-4-pyridyl- carboxamide
21. N-(2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]-4-pyridyl carboxamide
22. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide
23. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenyl-pyrrolyl)-4-pyridylcarboxamide
24. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-5-methyl -2-phenylpyrrolyl)-4-pyridylcarboxamide
25. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)- pyrazin-2-ylcarboxamide
26. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-pyrazin-2-ylcarboxamide
27. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenyl-pyrrolyl) pyrazin-2-ylcarboxamide
28. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
29. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
30. N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-pyrazin-2-ylcarboxamide
31. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)- pyrazin-2-ylcarboxamide
32. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-pyrazin-2-ylcarboxamide

33. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenyl-pyrrolyl)pyrazin-2-ylcarboxamide
34. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide
35. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide
36. N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-pyrazin-2-ylcarboxamide
37. N-(5-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
38. N-(5-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
39. N-(5-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
40. N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide
41. N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)pyrazin-2-ylcarboxamide
42. N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide
43. N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide
44. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine
45. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine
46. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine
47. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)piperazine
48. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-diphenylmethyl)piperazine

49. 1-{[1-(2,4-difluorophenyl)-2-(4-chlorophenyl)-5-methylpyrrol-3-yl]methyl}-4-(diphenylmethyl)piperazine
50. 5-[(4-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]-methyl}-piperazinyl)methyl]-2H-benzo[d]1,3-dioxolene
51. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine
52. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine
53. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine
54. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine
55. 1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl) piperazine
56. 1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl) piperazine
57. 1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine
58. 1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine
59. 1-{[5-(4-chlorophenyl)-2-methylnaphthylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine
60. 1-{[5-(4-chlorophenyl)-2-methylnaphthylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine
61. 1-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine
62. 5-[(4-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-piperazinyl)-methyl]2H-benzo[d]1,3-dioxolene
63. 1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl) piperazine
64. 1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine

65. 1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine
66. N-(5-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-pyrrolyl)-4-pyridylcarboxamide
67. N-(5-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl pyrrolyl)-4-pyridylcarboxamide
68. N-(5-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methylpyrrolyl)-4-pyridylcarboxamide
69. N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl- pyrrolyl)-4-pyridylcarboxamide
70. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}-5-(4-chloro-phenyl)-2-methylpyrrolyl)-4-pyridylcarboxamide
71. N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)-4-pyridylcarboxamide
72. N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)-4-pyridylcarboxamide
73. N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)-4-pyridylcarboxamide
74. N-(2-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methyl pyrrolyl)-4-pyridylcarboxamide
75. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}-2-(4-chlorophenyl)-5-methylpyrrolyl)-4-pyridylcarboxamide
76. 4-(4-fluorophenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine
77. 4-(2-methoxyphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine
78. 4-(3-trifluoromethylphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)-methyl]piperazine
79. 1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)piperazine
80. [(2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]piperazinyl}methyl)-2H-benzo[d]1,3-dioxolene

81. 4-(4-fluorophenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine
82. 4-(2-methoxyphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine
83. 4-(3-trifluoromethylphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)- methyl] piperazine
84. 1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)piperazine
85. 5-({4-[(5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]piperazinyl}-methyl) - 2H-benzo[d]1,3-dioxolane
86. 1-{[1,5bis(4-cholorophenyl)-2ethylpyrrol-3-yl]methyl}-4-(3-trifluoromethyl-phenyl) piperazine
87. 4-{2-methyl-1,5-diphenylpyrrol-3-yl)methyl]1,4-thiazaperhydroin-1-one
88. 4-[(2-methyl-1,5-diphenylpyrrol3-yl)methyl](1,4-thiazaperhydroin-1,1-dione
89. N-[5-(4-chlorophenyl)-2-methyl–3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]4-pyridylcarboxamide
90. 2-[3-(hydroxymethyl)-5-methyl-2-phenyl-4-(1,4-thiazaperhydroin-4-ylmethyl)-pyrrolyl]butan-1-ol
91. 2-[2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]butan-1-ol

The above compounds of Formula I their pharmaceutically acceptable acid salts, thereof and the various possible tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites and polymorphs thereof are all found to be pharmaceutically active especially in treatment of mycobacterial conditions such as mycobacterium tuberculosis, drug resistant, mycobacterium tuberculosis, mycobacterium avium-intracellulare complex, mycobacterium fortuitum or mycobacterium kansasi.

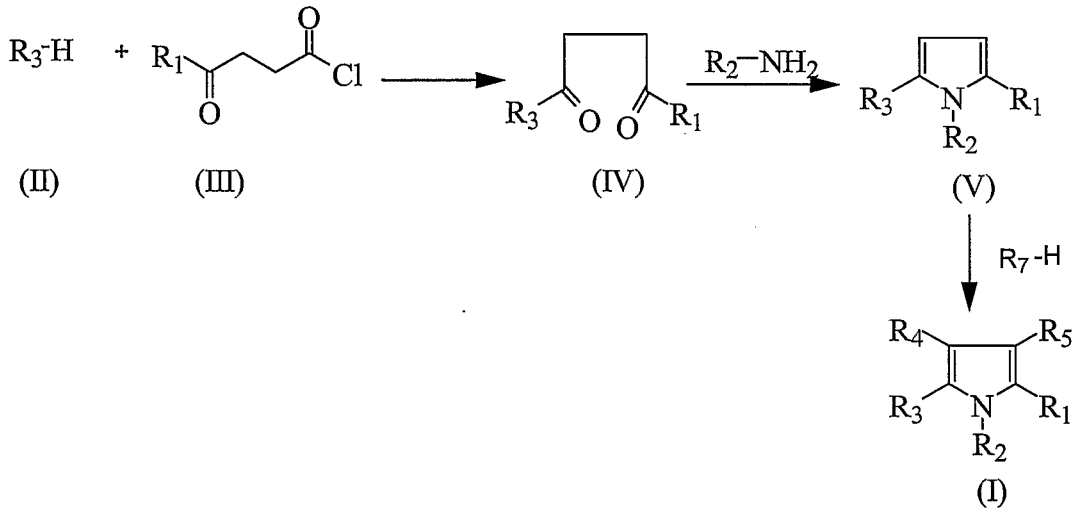
The pharmaceutically active compounds of formula (I) of this invention can be prepared by any one of the methods given below :

Method-I :

Scheme-I shows the synthesis of compounds of the Formula (I) in which R_1 is CH_3 , R_3 designates substituted or unsubstituted phenyl groups and R_2,R_4 and R_5 are as defined earlier.

The method comprises condensation compound, R_3H of the formula (II) with acid chloride of formula (II), in the presence of $AlCl_3$ at a temperature ranging from 20-30° C for a period varying between 1-2 hours to produce diketones of formula (IV), which on condensation with appropriate amines (R_2-NH_2) followed by cyclisation in the presence of an organic solvent at a temperature ranging between 80-120° C for a period varying between 2-3 hours gives the corresponding pyrroles of the formula (V), as described by M. Biava et. al. in *Bioorg. & Med. Chem. Lett.*, **1999**, 9, 2983-2988 . The compounds of the formula (V) on reaction with various heterocyclic amines (R_7H) in presence of an organic solvent at a temperature ranging from 20-30° C for a period varying between 2-4 hours afford compounds of formula (I), wherein R_1, R_2, R_3, R_4, and R_5 have the same meanings as defined hereinabove.

The starting acid chlorides of the formula (III) are known in the art and may be synthesized by the procedure described by Bui-Hoi, N. P. in *J. Org. Chem.*,**1960**, 25, 390



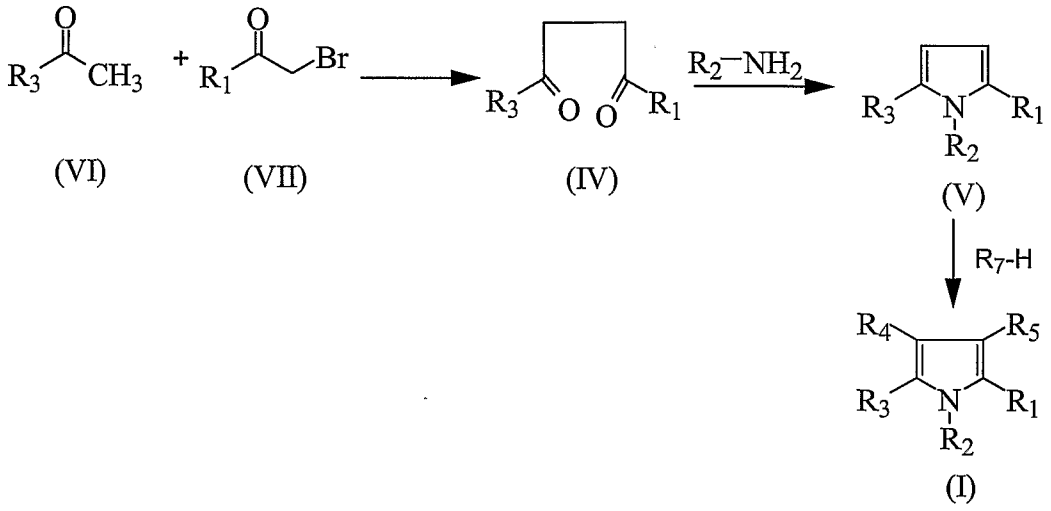
(II) (III) (IV) (V) (I)

Scheme- I : Synthesis of compound of formula (I)

Method-II :

In this method, summarized in Scheme-II, methyl ketones of formula (VI) are condensed with α -Bromomethyl ketones of formula (VII), in the presence of a base and an organic solvent at a temperature ranging from 20-30°C for a period varying between 2-6 days to produce diketones

of formula (IV), which on condensation with appropriate amines (R_2-NH_2) followed by cyclisation in the presence of an organic solvent at a temperature ranging between 80-120°C for a period varying between 2-3 hours give corresponding pyrroles of the formula (V) . Reaction of compounds of the formula (V) with various amines (R_7H) in presence of an organic solvent at a temperature ranging from 20-30°C for period varying between 2-4 hours afford compounds of formula (I), wherein R_1, R_2, R_3, R_4, and R_5 have the same meanings as defined hereinabove.



(VI) (VII) (IV) (V) (I)

Scheme- II : Synthesis of compound of formula (I)

In the above Schemes, where specific bases, acids , solvents etc., are mentioned , it is to be understood that other acids, bases solvents etc., known to those skilled in the art may also be used . Similarly, the reaction temperature and duration of the reactions may be adjusted according to the desired needs.

While the invention has been described by reference to specific embodiments, this is for purposes of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are deemed to be within the scope of the invention.

The following examples demonstrate the general as well as the specific preparation of compounds embodied in formula (I), which, however, should not be construed as to limiting the scope of the invention.

EXAMPLE-1

Preparation of 1-{[1,5-bis(4-chlorophenyl)-2-methylpyrrol-3yl]methyl}-4-(3-trifluoro- methyl phenyl)piperazine (Compound No.3 of Formula I) as per Method-I

Step1: *1-(4-chlorophenyl)pentane-1,4-dione*

To a well stirred suspension of anhydrous aluminium chloride (29.66gm,0.223mol) in 154.7 ml. of chlorobenzene was added 4-oxopentanoylchloride (25.0gm, 0.187mol) drop-wise, over a period of 30-35 minutes at room temperature (25-30°C). The reaction mixture was stirred at the same temperature for 1hour. After decomposition of the reaction mixture by the addition of solid ice and hydrochloric acid (10ml). the precipitated solid was filtered and filtrate was concentrated in a rotary evaporation to remove all the solvents. The residue was dissolved in ethyl acetate (400ml.), washed with water (2x100ml.), brine (100ml.). The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product so obtained was chromatographed over silica gel (100-200 mesh) using chloroform-hexane (90:10) as eluent to give 5.3gm (13.60 %) of the title compound.

Step-2 : *1,2-bis (4-chlorophenyl)-5-methylpyrrole*

A mixture of 1- (chlorophenyl)pentane–1,4-dione (5.0gm., 0.024 mol, as obtained in Step-1) and 4- chloroaniline (3.33gm, 0.026 mol) in benzene (5.0 ml.) was refluxed either over molecular sieves or using a Dean Stark apparatus. After three hours, benzene was removed under reduced pressure and the residue dissolved in ethyl acetate, washed with water (2x100 ml.) and brine (1x50 ml.).The ethyl acetate layer was dried over anhydrous sodium sulfate, and the solvent evaporated off. The solid so obtained was washed with hexane to give 2.83 gm (39.45%) of the title compound.

Step-3 : *1-{[1,5-bis(4-chlorophenyl)-2-methylpyrrol-3yl]methyl}-4-(3-trifluoromethyl-phenyl) piperazine*

To a stirred solution of 1,2-bis (4-chlorophenyl)-5-methylpyrrole (1.76gm, 0.006mol, as obtained in Step-2) in acetonitrile (18 ml.) was added a mixture of 1-(3-trifluoromethylphenyl) piperazine hydrochloride (1.55gm, 0.006 mol), 40% formaldehyde (0.45ml, 0.006 mol) and acetic acid (5.23 ml.) drop-wise. After the completion of addition, the reaction mixture was stirred at room temperature for 3-4 hours. The reaction mixture was neutralized with NaOH (20% aq. soln.) and extracted with ethyl acetate (2x100 ml.). The combined ethyl acetate extract was washed with water (2x50 ml.), brine (1x30 ml.), dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product so obtained was purified by column chromatography over silica gel using ethyl acetate hexane (80:10) as eluent to give 2.1gm (66.24 %) of the title compound.

m.p. 165-167° C, MS: m/z 544 (M+1)

^{1}HNMR ($CDCl_3$, δ) : 2.05 (s, 3H, $C\underline{H}_3$), 2.77 (bs, 4H, 2xN-$C\underline{H}_2$), 3.31 ((bs, 4H, 2xN-$C\underline{H}_2$), 3.59 (s,2H,N-$C\underline{H}_2$) , 6.34 (s,1H,H-4), 6.85-7.31 (m,12H,Ar-H).

EXAMPLE-2

Preparation of N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide (Compound No. 23of ***Formula I)***

and

Preparation of N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide (Compound No. 12 of Formula I) as per Method-I

Step 1: *1-(4-chlorophenyl)pentane-1,4-dione*

To a well stirred suspension of anhydrous aluminium chloride (27.0gm, 205.9mmol) in 126ml.of chlorobenzene was added oxopentanoylchloride (23.0gm, 171.6mmol)drop-wise, over a period of 30-35 minutes at room temperature (25-30°C). The reaction mixture was stirred at the same temperature for 1 hour. After decomposition of the reaction mixture by the addition of

solid ice and hydrochloric acid (10ml) the precipitated solid was filtered and the filtrate evaporated on a rotary evaporator to remove all the solvents. The residue was dissolved in ethyl acetate (400ml.), washed with water (2x100ml.), brine (100ml.) and dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product so obtained was chromatographed over silica gel (100-200 mesh) using chloroform as eluent to give 8.6gm (24.07%) of the title compound.

Step-2 : *N-(5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide*

A mixture of 1- (chlorophenyl)pentane-1,4-dione (6.0g,28.50mmol, as obtained in Step-1) and isonicotinic hydrazide (4.30gm, 31.35mmol) in benzene (6.0 ml.) was refluxed by over molecular sieves. After two hours, benzene was removed under reduced pressure and the residue dissolved in ethyl acetate, washed with water (2x100 ml.) and brine (1x50 ml.). The ethyl acetate layer was dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product so obtained was purified by column chromatography over silica gel (100-200 mesh) using 0.2% methanol in chloroform as eluent to give 3.50gm (39.42 %) of the title compound.

Step-3 : *N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenyl pyrrolyl)-4-pyridylcarboxamide (compound No. 23 of Formula I)*
and
N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide (compound No. 12 of Formula I)

To a stirred solution of N-(5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide (0.300gm, 1.083mmol, as obtained in Step-2) in acetonitrile (5.0 ml.) was added a mixture of 1-(3-trifluoromethylphenyl)piperazine hydrochloride (0.288gm, 1.083mmol), 40% formaldehyde (0.032gm ,1.083mmol) and acetic acid (0.09 ml), drop-wise. After the completion of addition, the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was neutralized with sodium hydroxide (20% aq. Soln.) and extracted with ethyl acetate (2x50 ml.). The combined ethyl acetate extract was washed with water (2x25 ml.), brine (1x20 ml.), and dried over anhydrous sodium sulfate and the solvent evaporated off. TLC of the crude product

indicated two spots, which were separated by column chromatography over silica gel (100-200mesh).

The less polar compound eluted out using 60% ethyl acetate- hexane mixture was obtained in 11.25 % (0.060 gm) yield and was identified as N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-4-pyridyl- carboxamide (Compound 23).

m.p. 105-107° C, MS: m/z 520 (M+1)

^{1}H NMR ($CDCl_3$, δ): 2.14 (s,3H,C<u>H</u>$_3$), 2.49 (bs,4H,2xN-C<u>H</u>$_2$), 3.12 (4H,bs,2xN-C<u>H</u>$_2$), 3.34 (s,2H,N-C<u>H</u>$_2$), 6.03 (s,1H,H-3), 6.96-6.99 (m, 4h,Ar<u>H</u>), 7.09-7.27 (m,5H,Ar<u>H</u>), 7.40 (d,2H,J=6Hz,pyridyl ring), 8.60 (d,2H,J=6Hz,pyridyl ring).

The more polar compound eluted out using 80% ethyl acetate- hexane mixture was obtained in 24.34 % (0.130 gm) and was identified as N-(3-{[4-(3-trifluoromethylphenyl) piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide (Compound 12)

m.p.80-82° C, MS: m/z 520 (M+1)

^{1}H NMR($CDCl_3$, δ) : 2.13 (s,3H,C<u>H</u>$_3$), 2.60 (bs,4H,2xN-C<u>H</u>$_2$), 3.18 (bs,4H,2xN-C<u>H</u>$_2$),3.41 (s,2H,N-C<u>H</u>$_2$), 6.24 (s,1H,H-4), 6.97-7.03 (4H,m,Ar<u>H</u>), 7.22-7.29 (m, 5H,ArH), 7.53 (d,2H,J=6Hz,pyridyl ring), 8.50 (bs,1H,NH D_2O exchangeable), 8.70 (d,2H,J=6Hz,pyridyl ring).

EXAMPLE-3

Preparation of 1-{[1,5- bis (4-chlorophenyl)-2-ethylpyrrol-3yl]methyl}-4-(3-trifluoro-methylphenyl)piperazine (Compound No. 86 of Formula I) as per Method-II

Step 1 : *1-(4-chlorophenyl)hexane-1,4-dione*

Anhydrous zinc chloride (3.71gm, 27.2mmol) was placed into a round bottom flask and dried by melting under vacuum at 250-350°C for 15 minutes. After cooling under vacuum to room temperature , benzene (15 ml.), triethylamine (2.7 ml.,19.42mmol) and tert-butanol (1.83ml., 19.42mmol) were successively added. The mixture was stirred until zinc chloride was fully dissolved (approx. 2 hour) and 1-(4-chlorophenyl)ethan-1-one (3.0gm, 19.42mmol) and 1-bromobutan-2-one (2.05gm,13.6mmol) were successively added. The mixture was stirred for 1 hour and allowed to stand for 4 days at room temperature, and thereafter quenched with 5% aq. Sulfuric acid. The organic layer was separated, washed with water (2x50ml.) , brine (1x25ml.), dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product was purified by column chromatography over silica gel (100-200mesh) using chloroform as eluent to give 2.30 gm (75.63%) of the title compound.

Step-2 : *1,2-bis(4-chlorophenyl)-5-ethylpyrrole*

A mixture of 1- (4- chlorophenyl)hexane-1,4-dione (2.10gm, 9.35mmol, as obtained in Step-1), 4- chloro aniline (1.31gm, 10.29mmol), and p-toluene sulfonic acid (0.321gm, 1.80mmol) in toluene (5.0 ml.) was refluxed over molecular sieves or using a Dean Stark apparatus. The progress of the reaction was monitored by TLC and after three hours, toluene was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 ml), washed with aqueous sodium bicarbonate solution (2 x 75 ml), followed by washing with water (2 x 50 ml.) and brine (1 x 25 ml). The ethyl acetate layer was dried over anhydrous sodium sulfate and the solvent evaporated off. The solid so obtained was washed with hexane to give 2.39gm (81%) of the title compound.

Step-3 : *1-{[1,5-bis(4-chlorophenyl)-2-ethylpyrrol-3yl]methyl}-4-(3-trifluoromethyl- phenyl) piperazine*

To a stirred solution of 1,2-bis (4-chlorophenyl)-5-ethylpyrrol (1.20gm,3.80mmol, as obtained in Step-2) in acetonitrile (15 ml.) was added a mixture of 1-(3-trifluoromethylphenyl)piperazine hydrochloride (1.01gm, 3.80 m mol), 40% formaldehyde (0.114gm,3.80mmol) and acetic acid (3.6 ml.), drop-wise. After the completion of addition, the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was neutralized with sodium hydroxide (20% aq.

solnution) and extracted with ethyl acetate (2x100 ml.). The combined ethyl acetate extract was washed with water (2x50 ml.), brine (1x30 ml.), dried over anhydrous sodium sulfate and the solvent evaporated off. The crude product so obtained was chromatographed over silica gel using ethyl acetate-hexane (80:10) as eluent to give 1.05 gm (47.22 %) of 1-{[1,5- bis (4-chlorophenyl)-2-ethylpyrrol-3yl]methyl}-4-(3-trifluoro- methylphenyl)piperazine (Compound No. 86 of **Formula I**).

MS: m/z 365 (M+1)

^{1}HNMR ($CDCl_3$, δ) : 1.05 (t, 3H, $C\underline{H}_3$), 2.66(q,2H,J=8Hz,CH2CH3) 2.98-3.10 (bs, 4H, 2xN-$C\underline{H}_2$), 3.50-3.55 (bs, 4H, 2xN-$C\underline{H}_2$), 3.94 (s,2H,N-$C\underline{H}_2$) , 6.50 (s,1H,H-4), 7.20-7.38 (m,12H,Ar-H).

EXAMPLE-4

Preparation of hydrochloride salt of Compound No. 3 of Formula I

The compound No. 3 (1.1gm) as obtained in Step –3 of Example-1 was dissolved in dichloromethane (3ml) under stirring .To this mixture 6.43 M HCl-Ethanol (295.22 mg, 8.08 mmoles,1.3 ml, 4 equivalent) was added drop-wise under stirring at 10°C. The reaction mixture was stirred for additional 2 minutes and was diluted with diethyl ether (10 ml.). Stirring was continued for another 15 minutes at the same temperature .The solvents were evaporated at reduced pressure and solid was dried in vaccum desiccator for 1 hour to give 1.22 gm of the title hydrochloride salt.

m.p. 140-142°C

^{1}H NMR(DMSO d_6, δ) : 2.03 (s,3H,$C\underline{H}_3$), 3.10 (bs,4H,2xN-$C\underline{H}_2$), 3.91 (bs,4H,2xN-$C\underline{H}_2$) 4.17 (s, 2H N-$C\underline{H}_2$), 6.57 (s,1H,H-4), 6.91-7.48 (m, 12H,ArH).

EXAMPLE-5

Preparation of hydrochloride salt of Compound No. 12 of Formula I

The Compound No. 12 (0.405gm), obtained by Step-3 of Example-2 was dissolved in a mixture of diethyl ether(0.5ml.) and dichloromethane (0.5ml) under stirring.To this mixture 1.20M HCl-Ethereal (142.35mg., 3.90 mmoles,3.25 ml,5 equivalent) was added drop-wise under stirring at 10°C. The reaction mixture was stirred for additional 2 minutes and was diluted with diethyl ether (10 ml.). Stirring was continued for another 15 minutes at the same temperature .The solvents were evaporated at reduced pressure and solid was dried in vaccum desiccator for 1 hour to give 0.428 gm of the title hydrochloride salt.

m.p. 174-176°C)

^{1}H NMR (DMSO d_6, δ) : 2.10 (s,3H,CH_3), 3.15 (bs,4H,2xN-CH_2), 3.84 (bs,4H,2xN-CH_2), 4.13 (s,2H,N-CH_2), 6.47 (s,1H,H-4), 7.00-7.38 (m,8H,ArH), 7.85 (d,2H,J=6Hz,pyridyl ring), 8.76 (d,2H,J=6Hz,pyridyl ring).

An illustrative list of the compounds of the invention which were synthesized by one or more of the above described methods is now given below.

EXAMPLE-6

By utilization of the prodecure described in Examples 1-3, Compound Nos. 1-2, 4-11, 13-22, 24-85, and 87-91 of Formula I were prepared having characteristics detailed hereunder :

1. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)-piperazine m.p. 193-195° C, MS: m/z 494 (M+1)
2. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxy phenyl) piperazine m.p. 140-142° C, MS: m/z 506 (M+1)

4. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)- piperazine m.p. 152-154° C, MS: m/z 477 (M+1)
5. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyrimidyl)- piperazine m.p. 184-186° C, MS: m/z 478 (M+1)
6. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(diphenylmethyl)-piperazine m.p. 188 -190° C, MS: m/z 566 (M+1)
7. 4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl2-furyl- ketone m.p. 84-86° C, MS: m/z 494 (M+1)
8. 5-[(4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl)- methyl]-2H-benzo[d]1,3-dioxolene m.p. 135-137° C, MS: m/z 534 (M+1)
9. 4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyloxolan-2-yl-ketone m.p. 150-152° C, MS: m/z 498 (M+1)
10. 1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methyl-5-cholro-phenyl)piperazine m.p. 156-158° C, MS: m/z 524 (M+1)
11. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide m.p.98-100° C, MS: m/z 470 (M+1)

13. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide mp.125-128° C, MS: m/z 482 (M+1)
14. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridyl-carboxamide m.p. 93-95° C, MS: m/z 453 (M+1)
15. N-(2-methyl-5-phenyl-3-{[4-benzylpiperazinyl]methyl}pyrrolyl)-4-pyridyl-carboxamide m.p. 87-89° C, MS: m/z 466 (M+1)
16. N-{2-methyl-3-[(4-methylpiperazinyl]methyl}-5-phenylpyrrolyl)-4-pyridyl-carboxamide MS: m/z 390 (M+1)
17. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide m.p. 95-97° C, MS: m/z 510 (M+1)
18. N-(2-methyl-5-phenyl-3-(piperidylmethyl)pyrrolyl]-4-pyridylcarboxamide m.p. 98-100° C, MS: m/z 376 (M+1)
19. N-(2-methyl-5-phenyl-3-(pyrrolidinylmethyl)pyrrolyl]-4-pyridylcarboxamide m.p. 72-73° C, MS: m/z 361 (M+1)

20. N-[2-methyl-3-(morpholin-4-ylmethyl)-5-phenylpyrrolyl]-4-pyridylcarboxamide m.p. 160-162° C, MS: m/z 377 (M+1)
21. N-(2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]-4-pyridyl-carboxamide m.p. 87-89° C, MS: m/z 393 (M+1)
22. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide m.p.98-99 °C, MS: m/z 470 (M+1)

24. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}}-5-methyl -2-phenylpyrrolyl)-4-pyridylcarboxamide m.p. 96-98° C, MS: m/z 510 (M+1)
25. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p. 80-82° C, MS: m/z 471 (M+1)
26. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p76-78° C, MS: m/z 483 (M+1)
27. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenyl-pyrrolyl) pyrazin-2-ylcarboxamide m.p. 83-85° C, MS: m/z 521 (M+1)
28. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p.119-121° C, MS: m/z 454 (M+1)
29. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p.186-188° C, MS: m/z 511 (M+1)
30. N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p. 91-93° C, MS: m/z 543 (M+1)
31. N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p. 200-202° C, MS: m/z 471 (M+1)
32. N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p. 74-76° C, MS: m/z 483 (M+1)
33. N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenyl-pyrrolyl)pyrazin-2-ylcarboxamide m.p. 231-233° C, MS: m/z 521 (M+1)
34. N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)pyrazin-2-yl carboxamide m.p. 208-210° C, MS: m/z 454 (M+1)
35. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 81-83° C, MS: m/z 511 (M+1)

36. N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)- pyrazin-2-ylcarboxamide m.p. 95-97° C, MS: m/z 543 (M+1)
37. N-(5-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 110-112° C, MS: m/z 505 (M+1)
38. N-(5-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 100-102° C, MS: m/z 517 (M+1)
39. N-(5-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 96-98° C, MS: m/z 555 (M+1)
40. N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenyl-pyrrolyl)pyrazin-2-ylcarboxamide m.p. 104-106° C, MS: m/z 488 (M+1)
41. N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)pyrazin-2-ylcarboxamide m.p. 202-204° C, MS: m/z 505 (M+1)
42. N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)pyrazin-2-ylcarboxamide m.p. 96-98° C, MS: m/z 517 (M+1)
43. N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 226-228° C, MS: m/z 555 (M+1)
44. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine m.p. 132-134° C, MS: m/z 496 (M+1)
45. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine m.p. 65-67° C, MS: m/z 508 (M+1)
46. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine m.p. 112-114° C, MS: m/z 546 (M+1)
47. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)piperazine m.p. 124-126° C, MS: m/z 479 (M+1)
48. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-diphenylmethyl)piperazine m.p.70-72° C, MS: m/z 568 (M+1)
49. 1-{[1-(2,4-difluorophenyl)-2-(4-chlorophenyl)-5-methylpyrrol-3-yl]methyl}-4-(diphenylmethyl)piperazine m.p. 76-78° C, MS: m/z 568 (M+1)
50. 5-[(4-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-piperazinyl)methyl]-2H-benzo[d]1,3-dioxolene MS: m/z 536 (M+1)

51. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine m.p. 140-142° C, MS: m/z 462 (M+1)
52. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine m.p. 64-66° C, MS: m/z 474 (M+1)
53. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine m.p. 122-124° C, MS: m/z 512 (M+1)
54. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine m.p. 144-146° C, MS: m/z 445 (M+1)
55. N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 104-106° C, MS: m/z 488 (M+1)
56. N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 202-204° C, MS: m/z 505 (M+1)
57. N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 96-98° C, MS: m/z 517 (M+1)
58. N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide m.p. 226-228° C, MS: m/z 555 (M+1)
59. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine m.p. 132-134° C, MS: m/z 496 (M+1)
60. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine m.p. 65-67° C, MS: m/z 508 (M+1)
61. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine m.p. 112-114° C, MS: m/z 546 (M+1)
62. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)piperazine m.p. 124-126° C, MS: m/z 479 (M+1)
63. 1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-diphenylmethyl)piperazine m.p.70-72° C, MS: m/z 568 (M+1)
64. 1-{[1-(2,4-difluorophenyl)-2-(4-chlorophenyl)-5-methylpyrrol-3-yl]methyl}-4-(diphenylmethyl)piperazine m.p. 76-78° C, MS: m/z 568 (M+1)
65. 5-[(4-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-piperazinyl)methyl]-2H-benzo[d]1,3-dioxolene MS: m/z 536 (M+1)

66. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine m.p. 140-142° C, MS: m/z 462 (M+1)
67. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine m.p. 64-66° C, MS: m/z 474 (M+1)
68. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine m.p. 122-124° C, MS: m/z 512 (M+1)
69. 1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine m.p. 144-146° C, MS: m/z 445 (M+1)
70. N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}-5-(4-chlorophenyl)-2-methylpyrrolyl)-4-pyridylcarboxamide m.p. 69-71° C, MS: m/z 544 (M+1)
71. N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl- pyrrolyl)-4-pyridylcarboxamide m.p. 70-72° C, MS: m/z 504 (M+1)
72. N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methylpyrrolyl)-4-pyridylcarboxamide m.p. 92-94° C, MS: m/z 516 (M+1)
73. N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)-4-pyridylcarboxamide m.p. 144-146° C, MS: m/z 554 (M+1)
74. N-(2-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methylpyrrolyl)-4-pyridylcarboxamide MS: m/z 487 (M+1)
75. N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}-2-(4-chlorophenyl)-5-methylpyrrolyl)-4-pyridylcarboxamide m.p. 65-67° C, MS: m/z 544 (M+1)
76. 4-(4-fluorophenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]- piperazine m.p. 126-128° C, MS: m/z 427 (M+1)
77. 4-(2-methoxyphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine m.p. 92-94° C, MS: m/z 439 (M+1)
78. 4-(3-trifluoromethylphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)-methyl]piperazine m.p. 106-108° C, MS: m/z 477 (M+1)
79. 1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)piperazine m.p. 128-130° C, MS: m/z 410 (M+1)
80. [(2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]piperazinyl}methyl)-2H-benzo[d]1,3-dioxolene MS: m/z 467 (M+1)

81. 4-(4-fluorophenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]- piperazine MS: m/z 427 (M+1)
82. 4-(2-methoxyphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine m.p. 120-122° C, MS: m/z 439 (M+1)
83. 4-(3-trifluoromethylphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)- methyl] piperazine MS: m/z 477 (M+1)
84. 1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)piperazine, MS: m/z 410 (M+1)
85. 5-({4-[(5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]piperazinyl}methyl)-2H-benzo[d]1,3-dioxolane MS: m/z 467 (M+1)

87. 4-{2-methyl-1,5-diphenylpyrrol-3-yl)methyl]-1,4-thiazaperhydroin-1-one m.p. 135-137° C, MS: m/z 439 (M+1)
88. 4-{2-methyl-1,5-diphenylpyrrol-3-yl)methyl]-1,4-thiazaperhydroin-1,1dione m.p. 140-142° C, MS: m/z 381 (M+1)
89. N-[5-(4-chlorophenyl)-2-methyl–3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl] 4-pyridylcarboxamide m.p.220-222° C, MS: m/z 439 (M+1)
90. 2-[3-(hydroxymethyl)-5-methyl-2-phenyl-4-(1,4-thiazaperhydroin-4-ylmethyl)-pyrrolyl]butan-1-ol m.p. 102-104° C, MS: m/z 375 (M+1)
91. 2-[2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]butan-1-ol m.p. 90-92° C, MS: m/z 345 (M+1)

Microbiology :

Pharmacological Testing

The ability of the compounds of the invention to display antimycobacterial activity can be assessed by growth inhibition assays BACTEC 460 TB System and *in vitro* agar dilution method as shown in the examples given below.

In vitro growth inhibition and agar dilution assay to determine the minimum inhibitory concentration (MIC) described below indicated that compound of formula (I) of present invention posseses significantly lower MIC values against strains of *M. tuberculosis*, *M.avium*,

M. fortiutum, and *M.kansasii*. The compound (I) of the present invention also inhibits the growth of drug resistant strains of *M. tuberculosis*. Further, the examples given below describe a method to treat experimental tuberculosis in mice. The compounds of the present invention induced better protection at lower doses in comparison to known drugs such as Isoniazid. The compounds can be orally administered in pharmaceutical compositions.

***in vitro* Growth Inhibition assay :**

The ability of the compounds of present invention to inhibit the growth of *Mycobacterium* species was determined by the BACTEC 460 TB system. The reference strain *M. tuberculosis* $H_{37}Rv$ ATCC 27294 was grown in Middlebrook 7H9 broth containing 10% ADC supplement at 37°C on a rotary shaker at 150 rpm for 7days. The turbidity of the culture was adjusted to 1.0 Mc farland. The Middlebrook 7H12B medium vials were seeded with 0.1ml of the 1.0 Mc farland adjusted *M. tuberculosis* culture. In the control vials 0.1ml of the culture was added after 100fold dilution of the initial inoculum. Stock solution of 1mg/ml of each compound was prepared in DMSO in separate sterile tubes. The compounds were further diluted to concentration of 25 g/100 l. 0.1ml was than added to the 7H12B vial containing mycobacterial culture so that final concentration of the compound is 6.25 g/ml. The cap in all the vials were cleaned with isopropanyl alcohol and kept in racks. The vials were then incubated at 37°C without shaking. Test vials was read daily on the BACTEC system till the GI of the control vial reached > 30.Once the GI in the control reached 30 GI(GI = $GI_{(n)} - GI_{(n-1)}$)was determined for all test and control vials. If GI of test vial is less than that of the control vial the culture was sensitive to the test compound.

Table-I gives the *in vitro* activity observed for the compound of formula (I) against sensitive and resistant strains of *M. tuberculosis*.

Table-I

Sr No.	Compound No.	Growth inhibition of *M.tuberculosis 27294*	MIC (µg/ml) against		
			M.tuberculosis 27294	Clinical isolates	
				Sensitive	Resistant
01	1	+	0.5	0.5-2.0	2.0-4.0
02	89	+	1.0	2.0-8.0	4.0-8.0
03	6	-	ND		
04	2	+	0.25	0.125-0.25	0.25-1.0
05	4	+	0.5	0.25-1.0	0.5-4.0
06	7	+	4.0	1.0-4.0	2.0-4.0
07	8	+	1.0	0.5-1.0	1.0-4.0
08	10	+	1.0	1.0-2.0	1.0-4.0
09	3	+	0.125	0.125-0.25	0.25-0.5
10	9	-	ND		
11	5	+	0.25	0.5-1.0	0.5-2.0
12	21	+	0.5	0.5-1.0	1.0-4.0
13	87	+	8.0	8.0-16.0	8.0->16.0
14	88	+	0.5	1.0-4.0	2.0-8.0
15	14	+	4.0	4.0-8.0	4.0-8.0
16	90	-	>16.0	>16.0	>16.0
17	91	+	4.0	4.0-8.0	8.0->16.0
18	13	+	0.5	0.5-2.0	1.0-2.0
19	22	+	2.0	2.0-4.0	2.0-4..0
20	11	+	1.0	0.5-1.0	0.5-2.0
21	23	+	0.25	0.25-1.0	0.25-1.0
22	12	+	0.25	0.25-0.5	0.5-1.0
23	46	+	2.0	2.0-4.0	4.0-16.0
24	48	+	>16.0	>16.0	>16.0
25	47	+	0.25	0.25-1.0	1.0-4.0
26	44	+	1.0	1.0-2.0	2.0-4.0
27	45	+	0.5	0.5-2.0	4.0->16.0
28	50	+	2.0	2.0-4.0	4.0-16.0
29	24	+	8.0	4.0->16.0	4.0->16.0
30	17	+	2.0	2.0-4.0	4.0-8.0
31	18	-	ND		
32	19	-	16.0	8.0->16.0	>16.0
33	20	+	2.0	1.0-4.0	4.0-8.0
34	16	+	2.0	2.0-4.0	4.0-16.0
35	15	+	0.5	0.5-1.0	4.0-8.0
36	60	+	4.0	2.0-8.0	4.0-16.0
37	62	+	>16.0	>16.0	>16.0
38	25	+	2.0	2.0-4.0	4.0
39	32	-	>16.0	>16.0	>16.0
40	26	+	1.0	2.0	4.0-16.0
41	33	+	2.0	2.0-8.0	4.0-8.0
42	27	+	2.0	1.0-4.0	8.0
43	36	+	0.5	0.5-1.0	1.0-4.0
44	30	+	2.0	2.0-4.0	4.0-16.0

Table-I (Contd.....)

45	34	+	16.0	16.0-16.0	>16.0
46	28	-	2.0	1.0-4.0	4.0-16.0
47	35	+	>16.0	>16.0	>16.0
48	29	+	>16.0	>16.0	>16.0
49	41	-	>16.0	>16.0	>16.0
50	37	-	16.0	8-16.0	16->16.0
51	43	-	>16.0	>16.0	>16.0
52	39	+	4.0	4.0-8.0	8.0->16.0
53	42	+	8.0	8.0	8.0->16.0
54	38	-	>16.0	>16.0	>16.0
55	55	-	>16.0	>16.0	>16.0
56	51	-	>16.0	>16.0	>16.0
57	56	+	8.0	8.0	8.0-16.0
58	52	+	8.0	8.0	8.0-16.0
59	57	+	>16.0	>16.0	>16.0
60	53	-	>16.0	>16.0	>16.0
61	58	+	8.0	8.0	8.0-16.0
62	54	+	2.0	4.0	4.0
63	64	-	>16.0	>16.0	>16.0
64	61	+	4.0	4.0-8.0	4.0-8.0
65	59	-	>16.0	>16.0	>16.0
66	63	+	8.0	4.0-8.0	4.0-16.0
67	**Isoniazid**	+	0.25	0.125-0.25	8.0->16.0
68	**Rifampin**	+	0.25	0.25	4.0-16.0

Table-II gives the MIC values of compound of formula (I) against different species of *Mycobacteria*.

Table-II

Sr. No	**Compound No.**	**MIC (µg/ml)**				
		M.tuberculosis		***M.avium-intracellulare complex*** (n=13)	***M. fortuitum*** (n=8)	***M.kansasii*** (n=2)
		Sensitive (n=17)	**Resistant** (n=26)			
1	2	0.125-0.25	0.25-1.0	4.0-8.0	8.0-16.0	8.0
2	3	0.125-0.25	0.25-0.5	4.0-8.0	4.0-8.0	4.0
3	5	0.5-1.0	1.0-2.0	4.0-8.0	8.0-16.0	8.0
4	**Isoniazid**	0.25	8.0->16.0	8.0->16.0	>16.0	>16.0

n: - Number of strains tested

***in vitro* Agar Dilution assay :**

MIC of compounds against strains of Mycobacterium were determined by a reference agar dilution method as per the NCCLS- M24-T2 recommendations. The compounds were dissolved in DMSO and diluted twofold to obtain ten serial dilutions of each compound. Appropriate volume of compounds were incorporated into duplicate plates of Middlebrook7H10 agar medium supplemented with 10% Middlebrook supplement oleic acid-albumin-dextrose catalase (OADC) enrichment at concentration of 0.03 g/ml to 16 g/ml. Test organisms (Mycobacterium strains) were grown in Middle brook 7H9 broth containing 0.05% Tween-80 and 10% ADC supplement. After 7 days of incubation at 37°C the broths were adjusted to the turbidity of 1.0 McFarland standard; the organism were further diluted 10 fold in sterile saline containing 0.10% Tween-80. The resulting mycobacterial suspensions were spotted (3-5 l/spot) onto drug supplemented 7H10 media plates. The plates were sealed and incubated at 37°Cfor 3-4 weeks in upright position. The MIC was recorded as the highest dilution of the drug that completely inhibited the growth of test organisms. Test isolates included 10 clinical isolates that were generally susceptible to common tubercular agents and 10 strains that were resistant to one or more standard anti tubercular drugs. Appropriate reference strains and control drug was included in each batch of test.

***in vivo* studies :**

The efficacy of the compounds of present invention was also evaluated in murine model of pulmonary tuberculosis. *Mycobacterium tuberculosis* $H_{37}Rv$ cultures grown in Middle brook 7H9 broth containing 0.05% Tween-80 and 10% ADC supplement at 37°C for 7 days on a rotary shaker at 150 rpm. For, animal inoculation liquid cultures were declumped by brief sonication and were diluted appropriately in 7H9 broth to obtain a concentration of $1x10^7$CFU's/ 0.2ml. Four-week-old male outbred Swiss albino mice housed in a pathogen free, biosafety level 3 environments within microisolator cages were used throughout the study. Infections were produced by intravenous inoculation of 0.2ml of declumped *M. tuberculosis* suspension into caudal tail vein. Following infection mice were randomly distributed in different groups of six each.

Treatment for initial study started 1 day after infection. For the treatment, the compound No 3 was dissolved and diluted in 50% polyethylene glycol 400(PEG-400), Isoniazid was dissolved

in sterile water. The drugs were prepared each morning prior to administration. Therapy was given 5 days a week for four weeks. All the agents were administered by gavage and were dosed at 50,25,12.5mg / kg of body weight. Control group of infected but untreated mice were killed at the initiation of therapy (early control) or at the end of the treatment period (late control). Mice were sacrificed by cervical dislocation 3-5 days after the administration of the last dose of drug. Target organs i.e. spleen and right lung were removed aseptically and homogenized in tissue homogenizer. At least 4 serial tenfold dilution of the homogenate was made in 7H9 broth and plated onto selective Middlebrook 7H11 agar plates in duplicate. The colony counts were recorded after incubation at 37°C for 4 weeks. The viable cell counts were converted to Log_{10} values. A compound showing 2 log_{10} reduction in viable counts compared to the early controls was considered significant.

The *in vivo* activity of compound No. 3 of formula (I) against *M. tuberculosis ATCC 27294*[a] infection in Swiss albino mice is summarized in **Table-III**

Table-III

Sr. No.	Drug& Dose [b] (mg/kgday^{-1}) or group	Mean Log_{10} No. of CFU		Mean Log_{10} no. of reduction [c]	
		Lung	Spleen	Lung	Spleen
1	**Compound No. 3**				
	50mg/kg	1.97	1.94	2.51	2.64
	25mg/kg	2.13	2.07	2.35	2.29
	12.5mg/kg	2.63	2.6	1.85	2.03
2	**Isoniazid**				
	50mg/kg	1.95	2.12	2.53	2.51
	25mg/kg	2.16	2.21	2.36	2.27
	12.5mg/kg	2.93	2.91	1.55	1.72
3	Infected early control	4.48	4.63		
4	Infected late control	6.68	6.67		

a- inoculation of log_{10}:- 7.00 Mycobacteria

b- mice were dosed 5 day/week for 4 week. From day 1 -28

c- difference in mean log_{10} number CFU from that of early controls

The *in vivo* efficacy of Compound No. 3 of Formula I against *M. tuberculosis $H_{37}Rv$ infection* in mice model treated 14 days post-infection and its comparison with isoniazid is summarized in **Table-IV**.

Table-IV

Sr. No.	Drug& Dose [b] ($mg/kgday^{-1}$) or group	Mean Log_{10} No. of CFU		Mean Log_{10} no. of reduction [c]	
		Lung	Spleen	Lung	Spleen
1	Compound No. 3				
	50mg/kg	2.74+0.36	2.78+0.32	2.85	3.17
	25mg/kg	2.87+0.15	2.83+0.29	2.72	3.12
	12.5mg/kg	4.18+0.38	4.41+0.26	1.41	1.54
2	**Isoniazid**				
	50mg/kg	2.97+0.46	2.89+0.27	2.62	3.06
	25mg/kg	3.19+0.6	3.08+0.44	2.4	2.87
	12.5mg/kg	4.56+0.24	4.93+0.42	1.03	1.02
3	Infected early control	5.59+0.29	5.95+0.42		
4	Infected late control	7.3+0.2	7.27+0.42		

a- inoculation of log_{10}:- 7.00 Mycobacteria

b- mice were dosed 5 day/week for 4 week. From day 1 -28

c- difference in mean log_{10} number CFU from that of early controls

The *in vivo* efficacy of Compound No. 3 **of** Formula I against *M. tuberculosis (Resistant strain)* treated 01 day post-infection in mice model and its comparison with isoniazid is summarized in **Table-V**.

Table-V

Sr. No.	Drug& Dose [b] (mg/kgday^{-1}) or group	Mean Log_{10} No. of CFU		Mean Log_{10} No. of reduction [c]	
		Lung	Spleen	Lung	Spleen
1	**Compound No. 3**				
	50mg/kg	1.99+0.3	1.97+0.4	2.48	2.66
	25mg/kg	2.3+0.17	2.2+0.31	2.17	2.43
	12.5mg/kg	2.98+0.5	2.91+0.4	1.49	1.72
2	**Isoniazid**				
	50mg/kg	4.43+0.5	4.7+0.31	0.04	-0.07
	25mg/kg	5.12+0.6	5.43+0.5	-0.65	-0.8
	12.5mg/kg	5.8+0.4	5.79+0.4	-1.33	-1.16
3	Infected early control	4.47+0.31	4.63+0.21		
4	Infected late control	6.39+0.5	6.23+0.21		

a- inoculation of log_{10}:- 7.00 Mycobacteria

b- mice were dosed 5 day/week for 4 week. From day 1 -28

c- difference in mean log_{10} number CFU from that of early controls

The *in vivo* efficacy of Compound No. 12 of Formula I against *M. tuberculosis* H_{37} *Rv* treated 01 day post-infection in mice model and its comparison with isoniazid is summarized in **Table-VI.**

Table-VI

Sr. No.	Drug& Dose [b] ($mg/kgday^{-1}$) or group	Mean Log_{10} No. of CFU		Mean Log_{10} No. of reduction [c]	
		Lung	Spleen	Lung	Spleen
1	**Compound No. 12**				
	50mg/kg	1.89+0.24	1.94+0.23	2.68	2.75
	25mg/kg	2.1 +0.24	2.13+0.28	2.47	2.56
	12.5mg/kg	2.34+0.18	2.26+0.21	2.23	2.43
2	**Isoniazid**				
	50mg/kg	2.02+0.31	2.07+0.33	2.55	2.62
	25mg/kg	2.23+0.33	2.21+0.44	2.34	2.48
	12.5mg/kg	2.89+0.27	2.91+0.42	1.68	1.78
3	Infected early control	4.57+0.2	4.69+0.21	-	
4	Infected late control	6.39+0.5	6.2+0.32	-	

a- inoculation of log_{10}:- 7.00 Mycobacteria

b- mice were dosed 5 day/week for 4 week. From day 1 -28

c- difference in mean log_{10} number CFU from that of early controls

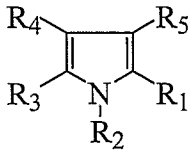
While, the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Acute toxicity study in mice

Compound No.3 of Formula I was administered, as a single oral dose, in Swiss albino mice. Two dose levels of 500 and 2000 mg./kg were employed. The mice were observed for 14 days. No clinical symptom or mortality was observed. The mice were sacrificed on day 15 but no pathological changes were seen in any organ. Therefore LD_0 was >2000mg./kg by oral route in mice. Reported LD_{50} of INH (Isoniazid) is 139 mg./kg in mice by oral route. Similarily in compound No.12 of Formula I, LD_0 was >500mg./kg.by oral route in mice.

CLAIMS

1. A compound of formula (I), its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof



(I)

wherein,

R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

R_2 is selected from a group consisting of

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

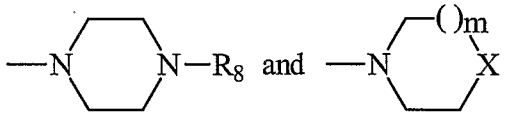
v) unsubstituted or substituted pyridine, or

vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

R_3 is phenyl or substituted phenyl, aryl, unsubstituted or substituted heteroaryl,

R_4 and R_5 are each independently H, $-(CH_2)_n-R_7$ wherein n = 1-3 and R_7 is selected from the groups



wherein R_8 is phenyl which is unsubstituted or substituted with 1-2 substitutents each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, amino, haloalkyl, haloalkoxy etc.; unsubstituted or substituted benzyl; unsubstituted or substituted heteroaryl; unsubstituted or substituted heteroaroyl; unsubstituted or substituted diphenylmethyl ,

m = 0-2 and

X = $-NCH_3$, CH_2, S, SO, or SO_2

2. A compound its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof as claimed in claim 1 wherein the compound of Formula I is selected from the group of

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluoro-phenyl)piperazine,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxy phenyl)piperazine,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoro-methylphenyl)piperazine,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2pyridyl) piperazine,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyrimidyl) piperazine,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(diphenyl-methyl)piperazine,

4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl2-furyl ketone,

5-[(4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl} piperazinyl) methyl]-2H-benzo[d]1,3- dioxolene,

4-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyloxolan-2-yl-ketone,

1-{[1,5-bis(4-cholorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methyl-5-cholrophenyl)piperazine,

N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(3trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenyl-pyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenyl- pyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(2-methyl-5-phenyl-3-{[4-benzylpiperazinyl]methyl}pyrrolyl)-4-pyridylcarboxamide,

N-{2-methyl-3-[(4-methylpiperazinyl]methyl}-5-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(2-methyl-5-phenyl-3-(piperidylmethyl)pyrrolyl]-4-pyridylcarboxamide,

N-(2-methyl-5-phenyl-3-(pyrrolidinylmethyl)pyrrolyl]-4-pyridylcarboxamide,

N-[2-methyl-3-(morpholin-4-ylmethyl)-5-phenylpyrrolyl]-4-pyridyl- carboxamide,

N-(2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]-4-pyridylcarboxamide,

N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenyl-pyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-5-methyl-2-phenylpyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenyl- pyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenyl pyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-2-methyl-5-phenyl pyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-2-phenyl pyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methyl-2-phenyl pyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}}-5-methyl-2-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(3-{[4-(diphenylmethyl)piperazinyl]methyl}-5-methyl-2-phenyl pyrrolyl)pyrazin-2-ylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-5-phenylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methylpyrrolyl)pyrazin-2-ylcarboxamide,

1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(2-pyridyl)piperazine,

1-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}-4-(4-diphenylmethyl)piperazine,

1-{[1-(2,4-difluorophenyl)-2-(4-chlorophenyl)-5-methylpyrrol-3-yl]methyl}-4-(diphenylmethyl)piperazine,

5-[(4-{[1-(2,4-difluorophenyl)-5-(4-chlorophenyl)-2-methylpyrrol-3-yl]methyl}piperazinyl)methyl]-2H-benzo[d]1,3-dioxolene,

1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl)piperazine ,

1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-2-methyl-5-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl) piperazine,

1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(4-fluorophenyl) piperazine,

1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl) piperazine,

1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(3-trifluoro methylphenyl)piperazine,

1-{[1-(2,4-difluorophenyl)-5-methyl-2-phenylpyrrol-3-yl]methyl}-4-(2-pyridyl) piperazine,

1-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(4-fluorophenyl) piperazine,

1-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl) piperazine,

1-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(3-trifluoro-methylphenyl)piperazine,

1-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-pyridyl)-piperazine,

5-[(4-{[5-(4-chlorophenyl)-2-methyl-1-naphthylpyrrol-3-yl]methyl}- piperazinyl) methyl]2H-benzo[d]1,3-dioxolene,

1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-methoxyphenyl) piperazine,

1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(3-trifluoromethylphenyl)piperazine ,

1-{[2-(4-chlorophenyl)-5-methyl-1-naphthylpyrrol-3-yl]methyl}-4-(2-pyridyl)piperazine,

N-(5-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-2-methylpyrrolyl)-4-pyridylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-2-methylpyrrolyl)-4-pyridylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-2-methyl pyrrolyl)-4-pyridylcarboxamide,

N-(5-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-2-methyl-pyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2H-benzo[d]1,3-dioxolen-5-ylmethyl)piperazinyl]methyl}-5-(4-chlorophenyl) -2-methylpyrrolyl)-4-pyridylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(4-fluorophenyl)piperazinyl]methyl}-5-methyl-pyrrolyl)-4-pyridylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(2-methoxyphenyl)piperazinyl]methyl}-5-methylpyrrolyl)-4-pyridylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(3-trifluoromethylphenyl)piperazinyl]methyl}-5-methyl pyrrolyl)-4-pyridylcarboxamide,

N-(2-(4-chlorophenyl)-3-{[4-(2-pyridyl)piperazinyl]methyl}-5-methyl- pyrrolyl)-4-pyridylcarboxamide,

N-(3-{[4-(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)piperazinyl]methyl}-2-(4-chloro phenyl)-5-methylpyrrolyl)-4-pyridylcarboxamide,

4-(4-fluorophenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine,

4-(2-methoxyphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine,

4-(3-trifluoromethylphenyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl] piperazine,

4-(2-pyridyl)-1-[2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]- piperazine,

1-[(2-methyl-5-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)- piperazine,

4-(4-fluorophenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine,

4-(2-methoxyphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-piperazine,

4-(3-trifluoromethylphenyl)-1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)-methyl]piperazine,

1-[5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]-4-(2-pyridyl)- piperazine,

5-({4-[(5-methyl-2-phenyl-1-(2-pyridyl)pyrrol-3-yl)methyl]piperazinyl}- methyl)-2H-benzo[d]1,3-dioxolane,

1-{[1,5bis(4-cholorophenyl)-2ethylpyrrol-3-yl]methyl}-4-(3-trifluoromethyl-phenyl) piperazine,

4-[(2-methyl-1,5-diphenylpyrrol-3-yl)methyl]-1,4-thiazaperhydroin-1-one,

4-{(2-methyl-1,5-diphenylpyrrol-3-yl)methyl]-1,4-thiazaperhydroin-1,1-dione,

N-[5-(4-chlorophenyl)-2-methyl–3-(1,4-thiazaperhydroin-4-ylmethyl)- pyrrolyl]-4-pyridyl carboxamide,

2-[3-(hydroxymethyl)-5-methyl-2-phenyl-4-(1,4-thiazaperhydroin-4-ylmethyl)-pyrrolyl]butan-1-ol, and

2-[2-methyl-5-phenyl-3-(1,4-thiazaperhydroin-4-ylmethyl)pyrrolyl]butan-1-ol.

3. A pharmaceutically composition comprising a) atleast one of any compound of anyone of claims 1 or 2, its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts and b) a pharmaceutically acceptable carrier thereof.

4. A pharmaceutically composition as claimed in claim 3 comprising a solid or liquid preparation.

5. A pharmaceutical composition as claimed in claim 3 for oral or parenteral administration.

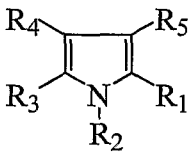
6. A method of inhibiting the growth of microbial cell with atleast one of a compound of formula (I), its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof with or without pharmaceutical carriers thereof.

7. A method as claimed in claim 5 wherein the micobacterial cell is *Mycobacterium tuberculosis,* drug resistant *M. tuberculosis, M. avium- intracellulare complex, M. fortuitum, and M. kansasii.*

8. A method of treating micobacterial conditions in mammals comprising administration of an antimycobacterial effective amount of atleast one of a compound of formula I, its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof.with or without pharmaceutically acceptable carriers thereof.

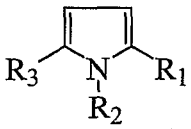
9. A method as claimed in claim 7 for treating tuberculosis in a mammal which comprises administration of an antimycobacterially effective amount of atleast one of compound of formula (I) its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof with or without pharmaceutically acceptable carriers thereof.

10. A process for preparing a compound of formula (I) comprising



(I)

reacting a compound of formula (V)



(V)

wherein

R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

R_2 is selected from a group consisting of

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

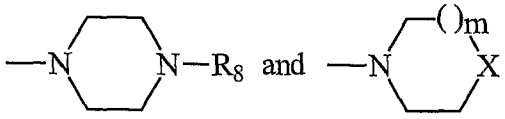
v) unsubstituted or substituted pyridine, or

vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

R_3 is phenyl or substituted phenyl, aryl, unsubstituted or substituted heteroaryl,

with an amine of formula R_7H, wherein R_7 is selected from the groups

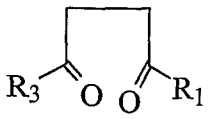


wherein R_8 is phenyl which is unsubstituted or substituted with 1-2 substitutents each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, amino, haloalkyl, haloalkoxy etc.; unsubstituted or substituted benzyl; unsubstituted or substituted heteroaryl; unsubstituted or substituted heteroaroyl; unsubstituted or substituted diphenylmethyl ,

m = 0-2 and

X = -NCH_3, CH_2, S, SO, or SO_2

11. A process according to Claim 10, wherein the compound of formula (V) is prepared by reacting compound of formula (IV)



(IV)

wherein R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

R_3 is phenyl or substituted phenyl, aryl, unsubstituted or substituted heteroaryl,

with an amine of formula R_2 NH_2, wherein R_2 is selected from a group consisting of

i) phenyl which is unsubstituted or substituted with 1 or 2 substituents, each independently selected from the group consisting of halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, nitro, haloalkyl, haloalkoxy, unsubstituted or substituted piperazine, morpholine, thiomorpholine, pyrrolidine, and piperidine, or

ii) hydroxyalkyl, or

iii) unsubstituted or substituted thiazole, or

iv) unsubstituted or substituted thiadiazole, or

v) unsubstituted or substituted pyridine, or

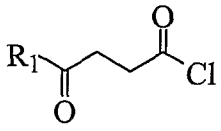
vi) unsubstituted or substituted naphthalene, or

vii) $NHCOR_6$ wherein R_6 is aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl.

12. A process according to Claim 11, wherein the compound of formula (IV) is prepared by reacting compound of formula (II)

R_3-H (II)

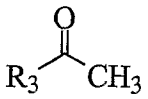
wherein R_3 is phenyl or substituted phenyl, aryl, unsubstituted or substituted heteroaryl, with a compound of formula (III)



(III)

wherein R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

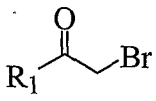
13. A process according to Claim 12, wherein the compound of formula (IV) is prepared by reacting compound of formula (VI)



(VI)

wherein R_3 is phenyl or substituted phenyl, aryl, unsubstituted or substituted heteroaryl,

with a compound of formula (VII)



(VII)

wherein R_1 is C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 thioalkoxy, trifluoroalkyl, trifluoroalkoxy or, hydroxyalkyl,

14. A compound of formula I ,its tautomers, enantiomers, diastereomers, N-oxides, prodrugs, metabolites, polymorphs and pharmaceutically acceptable salts thereof and pharmaceutical compositions obtained thereof substantially as herein defined and illustrated .