Indian Journal of Heterocyclic Chemistry
Vol. 25,July-Sept., 2015, pp. 37-44

SYNTHESIS, ANTIBACTERIAL AND ANTITUBERCULAR ACTIVITIES OF NOVEL N^1-[2-(SUBSTITUTED PHENYLAMINO) ACETYL]-4-(1*H*-PYRROL-1-YL)-BENZOHYDRAZIDE DERIVATIVES

M.R. Pradeep Kumar[1,2], Shrinivas D. Joshi*[2], Sheshagiri R. Dixit[2] and V.H. Kulkarni[2]

[1]Centre for Research and Development, PRIST University, Thanjavur-613 403

[2]Novel Drug Design and Discovery Laboratory, Department of Pharmaceutical Chemistry, SET's College of Pharmacy, Dharwad-580002

E-mail : shrinivasdj@rediffmail.com

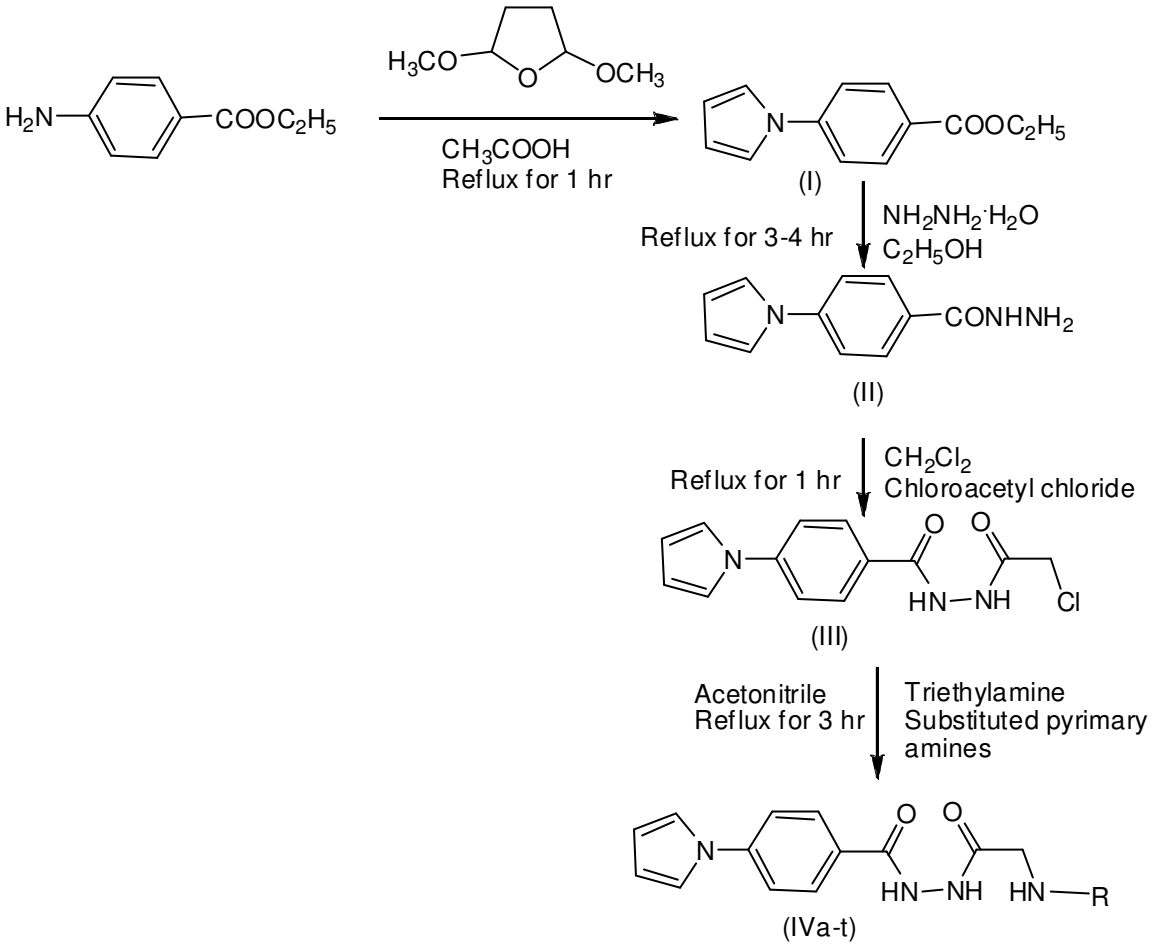
Received 17 March 2015; Accepted 14 May 2015

With an objective of synthesizing potent antitubercular agents, here we have synthesized some novel pyrrole derivatives. In this ethyl-4-pyrrol-1-yl-benzoate (**I**) was synthesized by the reaction of benzocaine with 2,5-dimethoxytetrahydrofuran in the presence of glacial acetic acid. Compound (**I**) on treatment with hydrazine hydrate yielded-4-pyrrol-1-yl benzoic acid hydrazide (**II**). Compound (**II**) on treatment with chloroacetyl chloride yielded N^1-(2-chloroacetyl)-4-(1*H*-pyrrol-1-yl) benzohydrazide (**III**), compound (**III**) on reaction with different aromatic amines and triethylamine yielded N^1-[2-(substituted phenylamino) acetyl] 4-(1*H*-pyrrol-1-yl))-benzohydrazide derivatives (**IV**a-t). Structures of the newly synthesized compounds were confirmed on the basis of physico-chemical and spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass). All the synthesized compounds were screened for their antibacterial and antitubercular activities using broth dilution method and Microplate Alamar Blue Assay (MABA) method respectively. For antibacterial and antitubercular activities ciprofloxacin, norfloxacin and isoniazid were used as standard drugs respectively. Among the synthesized compounds **IV**b, **IV**d, **IV**f, **IV**g, **IV**k, **IV**o and **IV**r showed good antibacterial activity and compounds **IV**a, **IV**d, **IV**g, **IV**h, **IV**j, **IV**l, **IV**n, **IV**q, **IV**r and **IV**t showed good antitubercular activity.

Tuberculosis (TB) is an infectious disease. Over the last decade nearly 30 million people have died due to infection of TB and nearly one third of the world population is infected with latent or persistent *Mycobacterium tuberculosis* infection. Every year nearly 8 million people develop active TB. If it is not controlled there will be a total of 36 million disease related deaths by the year 2020[1-3]. Due to the development of XDR-TB and MDR-TB, the situation has become still more serious. Due to the development of resistance by the micro organisms against the infectious disease, there is a need to develop some novel, potent antitubercular and antibacterial agents to fight against the infection caused by these microorganisms.

Pyrrole is one of the most important heterocyclic rings that are found in a broad range of natural products and drugs that are of growing relevance in material science. Pyrrole structures are characteristic of haemoglobin, which is a unique oxygen carrier on which living organisms breath[4]. Pyrroles have been successfully employed as starting materials for the production of biologically active compounds. Due to the versatile pharmacological activities shown by the pyrrole moiety, substituted pyrroles with various substitutents at different position have been synthesized and reported.

With an objective of synthesizing some potent and novel antibacterial and antitubercular agents here we have synthesized N^1-[2-(substituted phenylamino) acetyl]-4-(1*H*-pyrrol-1-yl)-benzohydrazide derivatives. The pharmacophore present in these compounds is pyrrole which shows versatile biological activities like anticonvulsant[5], analgesic[6], antiandrogenic[7], antitumor[8], hypoglycemic[9], antihypertensive[10], antiviral[11] and antitubercular[12] etc.



Where,

IVa R=C_6H_5

IVb R=4-Cl-C_6H_4

IVc R= 4-Br-C_6H_4

IVd R= 4-OCH_3-C_6H_4

IVe R=4-NO_2-C_6H_4

IVf R=3-Cl-C_6H_4

IVg R= 2-Cl-C_6H_4

IVh R=2-Br-C_6H_4

IVi R=2-OCH_3-C_6H_4

IVj R=3-Br-C_6H_4

IVk R=2-NO_2-C_6H_4

IVl R=4-OH-C_6H_4

IVm R= 2-OH-C_6H_4

IVn R=3-OH-C_6H_4

IVo R=3-OCH_3-C_6H_4

IVp R=2,5-Cl_2-C_6H_3

IVq R=2,4-Cl_2-C_6H_3

IVr R=2,3-Cl_2-C_6H_3

IVs R-C_5H_4N

IVt R=4-Br-2,5-Cl_2-C_6H_2

SCHEME-1

Table-1
Antibacterial activity screening results of newly synthesized compounds **IV**(a-t)

Compd	MIC values (μg ml^{-1})					
	Gram-positive bacteria[a]			Gram-negative bacteria[b]		
	Sa	Sf	Bs	Kp	Ec	Pa
IVa	25	>100	50	100	100	>100
IVb	50	25	50	12.5	50	>100
IVc	100	>100	6.25	>100	50	>100
IVd	100	50	12.5	6.25	100	50
IVe	25	25	100	>100	25	>100
IVf	100	6.25	6.25	100	50	100
IVg	12.5	50	25	50	12.5	100
IVh	50	12.5	100	25	>100	>100
IVi	100	25	>100	50	100	100
IVj	50	12.5	>100	50	50	>100
IVk	12.5	100	50	6.25	50	100
IVl	50	>100	>100	100	>100	25
IVm	>100	6.25	50	>100	>100	50
IVn	50	12.5	>100	50	>100	>100
IVo	100	12.5	25	12.5	25	50
IVp	50	25	>100	100	>100	50
IVq	6.25	100	25	>100	6.25	100
IVr	100	12.5	50	12.5	25	50
IVs	12.5	50	>100	>100	6.25	25
IVt	100	12.5	100	12.5	25	100
Ciprofloxacin	<5	<5	≤1	≤1	≤1	<5
Norfloxacin	<5	<5	≤1	≤1	≤1	<5

[a]Gram-positive bacteria : *Staphylococcus aureus* ATCC 11632 (Sa), *Streptococcus faecalis* ATCC 14506 (Sf), *Bacillus subtilis* ATCC 60511 (Bs).
[a]Gram-negative bacteria : *Klebsiella pneumoniae* ATCC 10031 (Kp), *Escherichia coli* ATCC 10536 (Ec), *Pseudomonas aeruginosa* ATCC 10145 (Pa).

Therefore as a result of above facts and in continuation of our research work on novel antibacterial and antitubercular agents[13-18], we herein report the synthesis of some novel N^1-[2-(substituted phenylamino) acetyl]-4-(1*H*-pyrrol-1-yl)-benzohydrazide derivatives.

In this work N^1-(2-chloroacetyl)-4-(1*H*-pyrrol-1-yl)-benzohydrazide (**III**), was synthesized by refluxing the solution of hydrazide in dry methylene chloride

Table-2
Antitubercular activity screening results of newly synthesized comounds **IV**(a-t)

Compd	MIC values (μg ml^{-1}) *M. tuberculosis* $H_{37}Rv$
IVa	25
IVb	50
IVc	>100
IVd	12.5
IVe	100
IVf	50
IVg	25
IVh	6.25
IVi	50
IVj	25
IVk	100
IVl	25
IVm	100
IVn	6.25
IVo	50
IVp	50
IVq	12.5
IVr	25
IVs	>100
IVt	12.5
Isoniazid	0.25

with chloroacetyl chloride. The IR spectrum of **(III)** showed characteristic peaks at around 3249 cm^{-1} for NH, 1685, 1645 for C=O and 1612 for C=N. The ^1H NMR showed characteristic singlet peaks at around 10 and 11 δ ppm for –NH's and singlet at around of 4 for $–CH_2$.

Further the mixture of compound (**III**) with appropriate amine and triethylamine in dry acetonitrile was refluxed to obtain N^1-[2-(substituted phenylamino) acetyl]-4-(1*H*-pyrrol-1-yl)-benzohydrazide derivatives **IV**a-t. The IR spectra of these compounds **IV**a-t showed characteristic peaks at around 3350 for NH's 1680 and 1650 for C=O and 1610 for C=N. The ^1H NMR showed characteristic singlet peaks at around 10, 10.5 and 11 for –NH's and singlet at around 4 for $–CH_2$.

Antibacterial activity

The MIC determination of the tested compounds was carried out simultaneously in comparison with ciprofloxacin, norfloxacin against Gram-positive (*Staphylococcus aureus, Streptococcus faecalis, Bacillus subtilis*) and Gram-negative bacteria (*Klebsiella pneumoniae Escherichia coli, Pseudomonas aeruginosa*) by broth microdilution method[19-20]. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton broth. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 ml). Further progressive dilutions were done to obtain final concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50 and 100 μg ml^{-1}. The tubes were inoculated with 10^5 cfu mL^{-1} (colony forming unit/ml) and incubated at 37^0 for 18 hr. The MIC was the lowest concentration of the tested compound that yields no visible growth on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and DMSO had no effect on the microorganisms in the concentrations studied. The MIC values are given in μg/ml. The preliminary results of antibacterial activities are shown in Table-1. Compounds showed antibacterial activity between MIC of > 100-6.25 μg/ml.

Compounds **IV**b, **IV**d, **IV**f, **IV**g, **IV**k, **IV**o and **IV**r showed significant antibacterial activity. All these compounds can be considered as potential candidates for antimicrobial activity against both Gram-positive and Gram-negative organisms after structural modification.

Antitubercular activity

MIC values were determined for the newly synthesized compounds against *M. tuberculosis* strain $H_{37}Rv$ using the Microplate Alamar Blue Assay (MABA)[21], using isoniazid as the standard drug. The 96 wells plate received 100 μl of Middlebrook 7H9 broth and serial dilution of compounds were made directly on the plate with drug concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50 and 100 μg/

ml. Plates were covered and sealed with parafilm and incubated at 37^0 for 5 days. Then, 25 µl of freshly prepared 1:1 mixture of almar blue reagent and 10% Tween 80 was added to the plate and incubated for 24 hr. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC was defined as the lowest drug concentration, which prevented color change from blue to pink. Compounds showed antitubercular activity between MIC of >100-6.25 µg/ml.

Compounds **IV**a, **IV**d, **IV**g, **IV**h, **IV**j, **IV**l, **IV**n, **IV**q, **IV**r and **IV**t showed significant antitubercular activity. Table-2 reveals antitubercular activity (MIC) data for all the synthesized compounds.

Experimental

Melting points of synthesized compounds were determined by open capillary method and are uncorrected. FTIR spectra were recorded on Bruker Alpha-T by using KBr pellets. The ^{1}H NMR spectra were recorded on Bruker Avance II NMR 400 MHz instrument using $CDCl_3$/DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). Purity of the compounds was confirmed by TLC plates using silica gel G as stationary phase and suitable solvent system as mobile phase and iodine vapors as visualizing agent.

Synthesis of N^1-(2-chloroacetyl)-4-(1*H*-pyrrol-1-yl)-benzohydrazide (III)

To a solution of hydrazide (**II**) (6.2 mmol) in dry methylene chloride (25 ml), chloroacetyl chloride (6.8 mmol) was added and the mixture was refluxed for 1 hr. After cooling the reaction mixture, it was filtered, dried and the solid obtained was recrystallized from ethanol, m.p. 200-202^0, yield 88%. IR (KBr) cm^{-1}: 3249 (NH), 1685, 1645 (C=O), 1612 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.54 (s, 1H, -CONH), 10.39 (s, 1H, -NHCO), 7.95 (d, 2H, phenyl C_2 and C_6-H), 7.76 (d, 2H, phenyl C_3 and C_5-H), 7.47 (d, 2H, pyrrole C_2 and C_5-H), 6.29 (d, 2H, pyrrole C_3 and C_4-H), 4.18 (s, 2H, CH_2).

Synthesis of N^1-(2-(substituted phenylamino) acetyl)-4-(1*H*-pyrrol-1-yl)-benzohydrazide derivatives (IVa-t)

A mixture of compound (**III**) (4.2 mmol), the appropriate amine (4.2 mmol) and triethylamine (8.4 mmol) in dry acetonitrile was refluxed for 3 hr. The mixture was cooled, poured on crushed ice and filtered. The residue was washed with cold water and dried. The crude product was recrystallized from ethanol to get the titled compounds.

IVa: M.P. 214-216^0, yield 68%. IR (KBr): 3468 (NH's), 1699, 1625 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.34 (s, 1H, -CONH), 10.06 (s, 1H, -NHCO), 7.93-7.02 (m, 4H, of bridging phenyl, 5H of phenyl and NH), 6.58 (d, 2H, pyrrole C_2 and C_5-H), 6.24 (d, 2H, pyrrole C_3 and C_4-H), 3.77 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 45.34, 111.22, 112.45, 119.01, 128.83, 129.15, 142.24, 148.33, 164.57, 169.91. Mass : m/z molecular ion peak at 335.

IVb: M.P. 224-216^0, yield 61%. IR (KBr): 3363 (NH's), 1706, 1641 (C=O), 1606 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): 10.45 (s, 1H, -CONH), 10.10 (s, 1H, -NHCO), 7.97-6.60 (m, 4H of bridging phenyl, 4H, of 4-Cl phenyl and NH), 7.42 (d, 2H, pyrrole C_2 and C_5-H), 6.34 (d, 2H, pyrrole C_3 and C_4-H), 3.81 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 45.22, 111.27, 113.86, 119.71, 127.52, 128.54, 128.64, 129.20, 142.30, 147.33, 164.67, 169.66. Mass : m/z molecular ion peak at 368.

IVc: M.P. 290-292^0, yield 70%. IR (KBr): 3365 (NH's), 1705, 1641 (C=O), 1607 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.57 (s, 1H, -CONH), 10.18 (s, 1H, -NHCO), 7.97-6.60 (m, 4H, of bridging phenyl, 4H of 4-Br phenyl and NH), 7.47 (d, 2H, pyrrole C_2 and C_5-H), 6.31 (d, 2H, pyrrole C_3 and C_4-H), 3.79 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 53.56, 111.27, 114.43, 118.60, 119.03, 127.52, 128.66, 129.19, 131.35, 142.29, 147.69, 161.21, 169.59 .Mass : m/z : Molecular ion peak at 413.

IVd: M.P. 244-246^0, yield 74%. IR (KBr): 3319 (NH's), 1864, 1648 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.30 (s, 1H, -CONH), 10.18 (s, 1H, -NHCO), 7.8-6.60 (m, 4H of bridging phenyl, 4H of 4-OCH_3 phenyl and NH), 7.31 (d, 2H, pyrrole C_2 and C_5-H), 6.39 (d, 2H, pyrrole C_3 and C_4-H), 4.11 (s, 2H, CH_2), 1.31 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6), 46.32, 55.38, 111.26, 113.58, 114.56, 119.02, 127.52, 129.19, 142.53, 151.27, 170.17. Mass : m/z : Molecular ion peak at 364.

IVe: M.P. 230-232^0, yield 68%. IR (KBr): 3361 (NH's), 1777, 1632 (C=O), 1602 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.12 (s, 1H, -CONH), 10.00 (s, 1H, -NHCO), 8.14-6.62 (m, 9H, 4H of bridging phenyl, 4H of 4-NO_2 phenyl and NH), 7.32 (d, 2H, pyrrole C_2 and

C_5-H), 6.30 (d, 2H, pyrrole C_3 and C_4-H), 4.74 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 45.63, 110.24, 112.52, 119.65, 126.63, 128.18, 142.72, 148.44, 165.87, 169.32. Mass : m/z : Molecular ion peak at 378.

IVf: M.P. 236-238^0, yield 72%. IR (KBr): 3351 (NH's), 1708, 1645 (C=O), 1607 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.32 (s, 1H, -CONH), 10.01 (s, 1H, -NHCO), 8.09-6.59 (, 4H of bridging phenyl, 4H of 3-Cl phenyl and NH), 7.34 (d, 2H, pyrrole C_2 and C_5-H), 6.30 (d, 2H, pyrrole C_3 and C_4-H), 3.88 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 44.89, 111.28, 115.79, 118.48, 127.53, 129.21, 142.31, 149.93, 164.67, 169.55. Mass : m/z : Molecular ion peak at 368.

IVg : M.P. 256-258^0, yield 63%. IR (KBr): 3245 (NH's), 1705, 1649 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 11.02 (s, 1H, -CONH), 10.68 (s, 1H, -NHCH), 8.17-6.63 (m, 4H of bridging phenyl, 4H of 2-Cl phenyl and NH), 7.35 (d, 2H, pyrrole C_2 and C_5-H), 6.30 (d, 2H, pyrrole C_3 and C_4-H), 4.05 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 46.24, 64.68, 1118.18, 111.29, 118.50, 119.4, 126.37, 127.53, 128.96, 129.21, 142.32, 161.53. Mass : m/z Molecular ion peak at 367.

IVh: M.P. 270-272^0, yield 69%. IR (KBr): 3249 (NH's), 1650, 1608 (C=O), 1583 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.40 (s, 1H, -CONH), 10.16 (s, 1H, -NHCO), 8.15-6.62 (m, 4H of bridging phenyl, 4H of 2-Br phenyl and NH), 7.32 (d, 2H, pyrrole C_2 and C_5-H), 6.29 (d, 2H, pyrrole C_3 and C_4-H), 3.99 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 53.79, 64.70, 111.20, 118.38, 119.05, 126.38, 127.56, 128.26, 129.24, 132.17, 141.35, 142.34, 146.86, 161.23. Mass : m/z :Molecular ion peak at 411.

IVi: M.P. 252-254^0, yield 60%. IR (KBr): 3233 (NH's), 1656, 1607 (C=O), 1513 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.30 (s, 1H, -CONH), 10.18 (s, 1H, -NHCO), 8.13-7.50 (m, 4H of bridging phenyl, 4H of 2-OCH_3 phenyl and NH), 7.33 (d, 2H, pyrrole C_2 and C_5-H), 6.30 (d, 2H, pyrrole C_3 and C_4-H), 4.04 (s, 2H, CH_2), 1.26 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 45.20, 55.42, 64.69, 111.21, 116.54, 118.50, 119.05, 121.09, 127.55, 128.65, 129.22, 141.36, 146.60, 164.69, 169.77. Mass : m/z :Molecular ion peak at 364.

IVj: M.P. 266-268^0, yield 65%. IR (KBr): 3349 (NH's), 1704, 1645 (C=O), 1607 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 11.10 (s, 1H, -CONH), 10.16 (s, 1H, -NHCO), 8.13-6.59 (m, 4H of bridging phenyl, 4H of 3-Br phenyl and NH), 7.30 (d, 2H, pyrrole C_2 and C_5-H), 6.74 (d, 2H, pyrrole C_3 and C_4-H), 4.73 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 44.84, 64.65, 111.13, 112.71, 118.99, 127.47, 129.16, 142.24, 146.77, 164.58, 169.43. Mass : m/z : Molecular ion peak at 412.

IVk : M.P. 208-210^0, yield 69%. IR (KBr): 3338 (NH's), 1702, 1651 (C=O), 1606 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.32 (s, 1H, -CONH), 10.10 (s, 1H, -NHCO), 8.34-6.58 (m, 4H of bridging phenyl, 4H of 2-NO_2 phenyl and NH), 7.31 (d, 2H, pyrrole C_2 and C_5-H), 6.34 (d, 2H, pyrrole C_3 and C_4-H), 4.23 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 45.80, 64.64, 111.12, 115.47, 118.42, 125.37, 126.33, 127.46, 129.14, 146.76, 161.15. Mass : m/z : Molecular ion peak at 379.

IVl: M.P. 204-206^0, yield 64%. IR (KBr): 3380 (NH's), 1694, 1649 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 11.10 (s, 1H, -CONH), 10.68 (s, 1H, -NHCO), 8.22-6.49 (m, 4H of bridging phenyl, 4H of 4-OH phenyl and NH), 7.36 (d, 2H, pyrrole C_2 and C_5-H), 6.28 (d, 2H, pyrrole C_3 and C_4-H), 5.26 (s, 1H, OH), 4.75 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 46.64, 63.45, 111.22, 113.83, 115.59, 118.42, 127.47, 128.66, 142.23, 148.90, 164.54, 170.26. Mass : m/z : Molecular ion peak at 350.

IVm: M.P. 274-276^0, yield 76%. IR (KBr): 3303 (NH's), 1705, 1649 (C=O), 1609 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 53.96, 63.45, 111.12, 118.44, 119.00, 127.46, 129.15, 142.28, 146.53, 161.16. Mass: m/z : Molecular ion peak at 349.

IVn: M.P. 240-242^0, yield 80%. IR (KBr): 3361 (NH's), 1705, 1649 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.98 (s, 2H, -CONH), 10.38 (s, 2,4, -NHCO), 5.05-6.13 (m, 4H of bridging phenyl, 4H of 3-OH phenyl and NH), 7.26 (d, 2H, pyrrole C_2 and C_5-H), 6.28 (d, 2H, pyrrole C_3 and C_4-H), 5.52 (s, 1H, OH), 4.72 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): 45.48, 64.66, 99.62, 103.89, 111.15, 118.43, 126.35, 127.49, 129.49, 142.24, 146.79, 161.19, 169.95. Mass : m/z : Molecular ion peak at 350.

IVo: M.P. 278-280^0, yield 66%. IR (KBr): 3329 (NH's), 1815 1644 (C=O), 1603 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): 10.61 (s, 1H, NH), 10.26 (s, 1H, NH), 8.16-6.60 (m, 4H of bridging phenyl, 4H of 3-OCH_3 phenyl and NH), 7.32 (d, 2H, pyrrole C_2 and C_5-

H), 6.60 (d, 2H, pyrrole C_3 and C_4-H), 3.84 (s, 2H, CH_2), 1.24 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 47.30, 54.52, 98.14, 106.82, 111.08, 118.45, 128.57, 129.54, 140.04, 149.70, 160.30, 169.88. Mass : m/z : Molecular ion peak at 363.

IVp : M.P. 298-300^0, yield 75%.IR (KBr): 3367 (NH's), 1699, 1652 (C=O), 1609 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 45.18, 111.06, 116.89, 118.13, 119.00, 128.04, 129.17, 130.59, 141.18, 142.29, 167.06. Mass : m/z : Molecular ion peak at 402.

IVq: M.P. 286-288^0, yield 69%. IR (KBr): 3254 (NH's), 1681, 1639 (C=O), 1608 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 53.50, 64.66, 99.62, 111.08, 116.26, 117.37, 118.45, 126.35, 127.49, 129.18, 141.31, 146.78, 161.19. Mass : m/z : Molecular ion peak at 402.

IVr: M.P. 220-224^0, yield 62%. IR (KBr): 3408 (NH's), 1700, 1642 (C=O), 1608 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 53.69, 64.65, 111.13, 113.62, 118.45, 127.47, 128.03, 141.30, 146.77, 161.17. Mass : m/z : Molecular ion peak at 401.

IVs : M.P. 294-296^0, yield 78%. IR (KBr): 3236 (NH's), 1704, 1640 (C=O), 1609 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 53.98, 64.63, 111.04, 118.43, 126.33, 127.45, 128.54, 141.28, 161.14. Mass : m/z : Molecular ion peak at 335.

IVt: M.P. 248-250^0, yield 66%. IR (KBr): 3301 (NH's), 1703, 1639 (C=O), 1609 (C=N). ^{13}C NMR (100 MHz, DMSO-d_6): 64.66, 105.16, 111.09, 118.68, 127.44, 130.02, 140.92, 141.27, 161.193. Mass : m/z : Molecular ion peak at 478.

Acknowledgement

The authors gratefully acknowledge the financial support from the Council of Scientific and Industrial Research, New Delhi, India (Letter No. 02(0139)/13/EMR-II dated 12.04.2013). We thank Shri H.V. Dambal, President and Dr. T.M. Aminabhavi, Research Director, S.E.T.'s College of Pharmacy for providing the necessary facilities to carry out this research work. We thank Dr. K.G. Bhat of Mahatha Mandal's Dental College, Hospital and Research Centre, Belgaum, for providing antibacterial and antitubercular activities data. We also thank The Director, SAIF, Punjab University, Chandigarh, Punjab, India for providing spectral data.

References

1. V. Estervez, M. Villacampa and J.C. Menendez, *Chem. Soc. Rev.*, **39** (2010), 4402.
2. D.G. Russell, C.E. Barry and J.L. Flynn, *Science,* **328** (2010), 852.
3. C. Dye and B.G. Williams, *Science,* **328** (2010), 856.
4. C. Dye, K.J. Lonnroth, E. Aramillo and M. Raviglione, *Bull. World Health Organ.,* **87** (2009), 683.
5. A. Idhayadhulla, R. S. Kumar, A. J. A. Nasser, S. Kavimani and S. Indumathy, *Med. Chem. Res.,* **21** (2012), 3699.
6. D. Nikolai, B. Atanas, Y. Diana, V. Stanislava and N. Irina, *Arch Pharm. Chem. Life Sci.,* **339** (2006), 670.
7. G. A. Ael, N.A. A. Lalif and M.M. Abdalla, *Bioorg. Med. Chem.,* **14** (2006), 373.
8. S. Wageeh, E.l. Hamouly, M.A. Kamelia, A. Samy, El. Assaly, A. Eman and El. M. Abd, *Der Pharma Chemica*, **3** (2011), 293.
9. B.L. Braj and L. Vidya, *Pure Appl. Chem.*, **77** (2005), 179.
10. D. Seref, C.K. Ahmet and B. Rana, *Eur. J. Med. Chem.,* **39** (2004), 1089.
11. P. Weiping, C.P. Daniel, J.L. Martha, D.K. Paul, D.L. Scott, R.N. Richard and J.M. David, *J. Infect Disc.,* **199** (2009), 950.
12. S.D. Joshi, H.M. Vagdevi, P.V. Vaidya and G.S. Gadaginamath, *Eur. J. Med. Chem.,* **43** (2008), 1989.
13. S.D. Joshi, Y. More, H.M. Vagdevi, V.P. Vaidya, G.S. Gadaginamath and V.H. Kulkarni, *Med. Chem. Res.,* **22** (2013), 1073.
14. U.A. More, S.D. Joshi, T.M. Aminabhavi, A.K. Gadad, M.N. Nadagouda M.N. Kulkarni and V.H. Kulkarni, *Eur. J. Med. Chem.,* **71** (2014), 199.
15. S.D. Joshi, U.A. More, T.M. Aminabhavi and A.M. Badiger, *Med. Chem. Res.,* **23** (2014), 107.
16. S.D. Joshi, S.R. Dixit, U.A. More, S. Rai and V.H. Kulkarni, *Indo Am. J. Pharm Res.,* **4** (2014), 2323.

17. S.D. Joshi, U.A. More, S.R. Dixit, H.H. Korat, T.M. Aminabhavi and A.M. Badiger, *Med. Chem. Res.*, **23** (2014), 1123.

18. S.D. Joshi, S.R. Dixit, U.A. More and V.H. Kulkarni, *Indian J. Heterocyclic Chem.,* **24** (2014), 137.

19. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 3rd ed. Approved standard. NCCLS document M100-S12, Wayne, PA, USA (2002).

20. Clinical and Laboratory Standards Institute. Susceptibility testing of mycobacteria, nocardiae and other aerobic actinomycetes; Approved standard NCCLS document M24 A, Wayne (2003).

21. Clinical and Laboratory Standards Institute (CL-SI) (formerly NCCLS): Antimycobacterial susceptibility testing for *M. tuberculosis* tentative standard NCCLS document M24-T, Villanova, PA (2002).

3328/2015