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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new 4-(2,5-dimethylpyrrol-1-yl)/4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: a novel class of potential antibacterial, antifungal and antitubercular agents

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Abstract A series of 4-(2,5-dimethylpyrrol-1-yl)/4-pyrrol-1-yl benzoic acid hydrazide analogs, some derived 1,3,4-oxadiazoles, 5-substituted-4-amino-1,2,4-triazolin-3-thione and 2,5-dimethyl pyrroles have been synthesized in good yields and structures of these compounds were established by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral and elemental analysis. These compounds were evaluated for their preliminary in vitro antibacterial, antifungal and antitubercular activities against *Mycobacterium tuberculosis* H_{37}Rv strain by broth dilution assay method. Twelve of these compounds displayed good antimicrobial activity, with a minimum inhibitory concentration (MIC) values 1–4 μg mL^{-1}. Several compounds **4**, **8d**, **9**, **12c–d** and **12f–h** exhibited good in vitro antitubercular activity with MIC values 1–2 μg mL^{-1}. Further, some title compounds were also assessed for their cytotoxic activity (IC_{50}) against mammalian Vero cell lines and A_{549} (lung adenocarcinoma) cell lines using MTT assay method. The results reveal that these compounds exhibit antitubercular activity at non-cytotoxic concentrations.

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Introduction

Tuberculosis (TB) is one of the dreadful infectious diseases world-wide with diverse manifestations caused by *Mycobacterium tuberculosis*, which has been a scourge of humanity for thousands of years and still remains one of the prevalent health tribulations in the world (Dutt and Stead, 1999). Today, TB is among the top five causes of global mortality. The history of TB highlights man's struggle for existence against a disease that dates from antiquity and is the story of failures and successes of disaster and hope (Das, 2000). It has been estimated that one-third of the world's population is currently infected with the Bacillus and about 30 million people would be infected within next 20 years if proper control is not further strengthened. In developing countries, where rates of both infection and active disease have always been high, the number of cases skyrocketed, so dramatically which led the World Health Organization (WHO) to declare TB as a global health emergency in 1993 and for the first time an infectious disease achieved such a dubious distinction (Martien *et al*., 2002; Rouhi, 1999). Approximately, 80 % of TB cases are found in 23 countries; the highest rates of incidence being found in Southeast Asia and Africa (Dye, 2002).

In addition, HIV-1 and HIV-2 infections, which impairs the immune system and allows large number of people already infected with the TB to progress to active disease. The pathogenic synergy of tuberculosis with HIV enhances

the overall incidence of TB in HIV-positive patients by 50 times relative to the rate for HIV-negative individuals (Maher *et al*., 2002).

Antitubercular drugs available at present for the treatment were discovered in the period of 1945–1965. No new drugs were synthesized during the last few decades (Desai *et al*., 2001). Moreover, the recent outbreaks of multidrug-resistant-tuberculosis (MDR-TB) and extensive drug-resistant-tuberculosis (XDR-TB) have made the disease hard to be treated (Sriram *et al*., 2005). This obstacle in the treatment of tuberculosis and also the statistical facts about its prevalence stress the strong need for searching and synthesizing more potent and less resistant new therapeutics with least side effects. The development of new potential drugs would be one of the possible solutions to treat various infectious diseases with multi-drug treatment over a prolonged period of time.

Pyrrole is one of the most ubiquitous heterocycles in the plant and animal kingdom because of its participation as a subunit of chlorophyll in plant cells and hemin and vitamin B12 in animal cells. 2,5-Dimethylpyrrole compounds are promising starting materials in drug research in view of their various biological activities such as antibacterial (Demirayak *et al*., 1999), antihypertensive (Demirayak *et al*., 2004) and antitubercular (Biava *et al*., 1999). Several macromolecular antibiotics having pyrrole structure were isolated from biological sources and their activities were defined (Jones and Bean, 1997; Jones, 1992).

Careful literature survey for functional groups which could be considered as pharmacophores for the antitubercular activities revealed that the hydrazone moiety is common among most of the antitubercular agents such as saliniazid and verazide (Sriram *et al*., 2006). Several Schiff bases, hydrazones and hydrazides of isoniazid have shown good activity against tubercular, fungal and bacterial infections (Desai *et al*., 1984; Shah *et al*., 1985; Vigorita *et al*., 1999).

Lipophilicity is a key property that influences the ability of a drug to reach the target by transmembrane diffusion and to have a major effect on the biological activity. The azole antituberculars are regarded as emerging class and oxadiazoles known as lipophilic analogs similar to imidazoles are expected to increase log *P*. 1,3,4-Oxadiazoles are utilized as pharmacophores because of their favourable metabolic profile and ability to engage in hydrogen bonding. Biological activities of oxadiazole and 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoline ring systems are well documented (Suresh Kumar *et al*., 2010; Khalil *et al*., 1993).

Therefore, in view of the above facts and in continuation of our search for biologically active pyrroles (Joshi *et al*., 2008a, b, 2010), it was contemplated to synthesize some novel hydrazones and 1,3,4-oxadiazole derivatives containing pyrrole/2,5-dimethylpyrrole moieties and study their antimicrobial, antitubercular activities followed by cytotoxic activity.

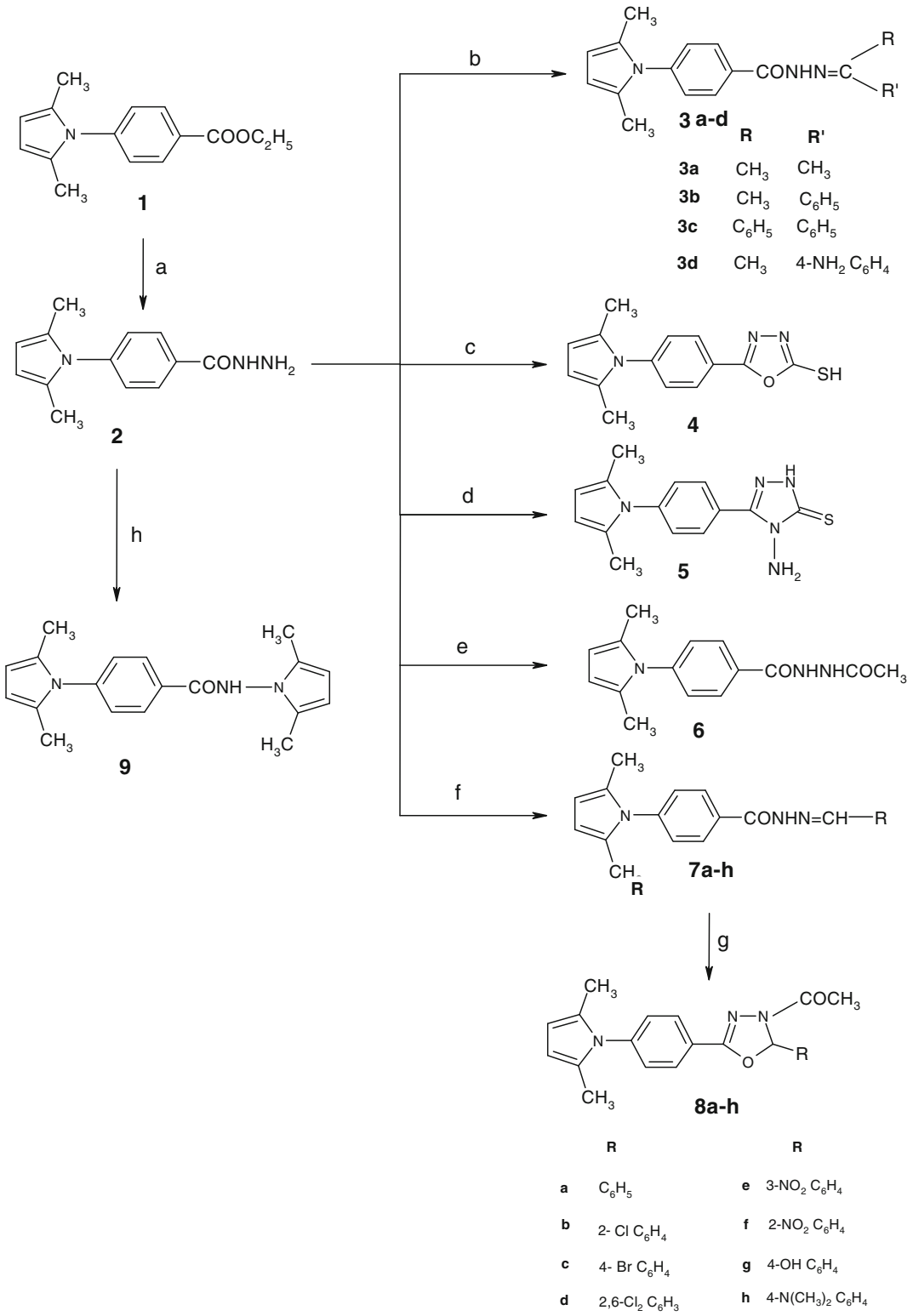
Methods and materials

Chemistry

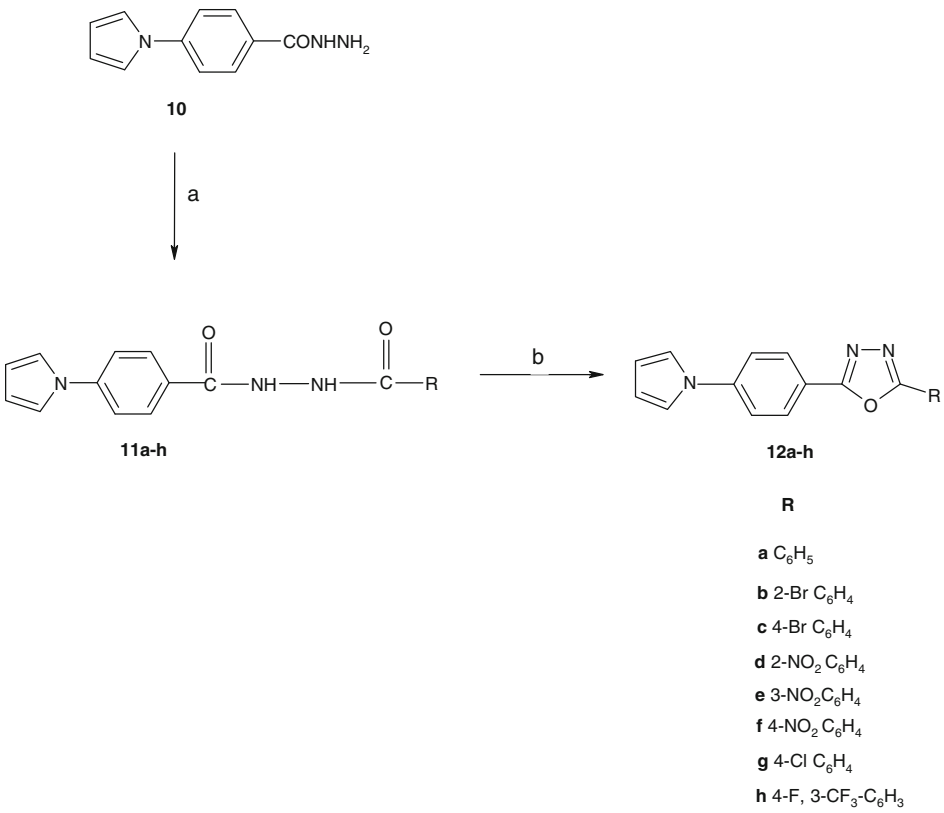
The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2. The compound 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**) was chosen as starting compound to design several hydrazones and oxadiazoles. Ethyl 4-aminobenzoate was prepared by the reaction of 4-amino benzoic acid and absolute ethanol in presence of HCl gas. Paal–Knorr condensation reaction between ethyl 4-aminobenzoate and acetonyl acetone in glacial acetic acid furnished ethyl 4-(2,5-dimethylpyrrol-1-yl)benzoate (**1**). Nucleophilic reaction of hydrazine hydrate with the ester **1** in ethanolic medium produced 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**). Reacting the starting compound **2** with acetone resulted in the formation of the corresponding 4-(2,5-dimethyl-pyrrol-1-yl)-benzoic acid isopropylidene-hydrazide (**3a**). Condensation of **2** with acetophenone, benzophenone and 4-aminoacetophenone yielded corresponding hydrazone derivatives **3b**, **3c** and **3d**. The preparation of the 5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-1,3,4-oxadiazole-2-thiol (**4**) was achieved by adopting a simple one-pot procedure that involves reacting compound **2** with carbon disulphide under strong basic conditions followed by acidification with dil. HCl. Hydrazide **2** was converted into the corresponding potassium dithiocarbazinate, which on cyclisation with hydrazine hydrate afforded 4-amino-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2,4-dihydro-1,2,4-triazole-3-thione (**5**). Warming **2** with acetic anhydride afforded *N*-acetyl-4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**6**). The reaction of compound **2** with different aldehydes in alcohol gave Schiff bases **7a**–**h**. Cyclisation of **7a**–**h** with acetic anhydride afforded the desired 1,3,4-oxadiazole derivatives **8a**–**h.** Further, **2** reacted with acetonyl acetone to afford *N*-(2,5-dimethyl-pyrrol-1-yl)-4-(2,5-dimethylpyrrol-1-yl) benzamide (**9**).

As shown in Scheme 2, treatment of hydrazide **10** with appropriate acyl chlorides in DMF produced the intermediates **11a**–**h** through *N*-acylation which on cyclodehydration with P_2O_5 in dry DMF gave 5-substituted-1,3,4-oxadiazoles **12a**–**h**.

The structures of newly synthesized compounds were assigned on the basis of their spectral and analytical data. The physical data, FTIR, NMR and mass spectral data for all the synthesized compounds are reported in experimental protocols.



Scheme 1 Synthetic route of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide-derived hydrazones and oxadiazoles **3a–d**, **4**, **5**, **6**, **7a–h**, **8a–h** and **9**. *a* Hydrazine hydrate, ethanol, reflux, 2 h, *b* ketone, ethanol, reflux, 5 h, *c* potassium hydroxide, carbon disulphide, ethanol reflux, 10 h, *d* potassium hydroxide, carbon disulphide, ethanol, stir, 18 h, hydrazine hydrate, reflux, 7 h, *e* acetic anhydride, warm, 2 h, *f* aromatic aldehyde, ethanol, reflux, 6 h, *g* acetic anhydride, reflux, 4 h, *h* acetonyl acetone, ethanol, reflux, 5 h



Scheme 2 Synthetic route of a novel series of 4-(pyrrol-1-yl)benzoic acid hydrazide-derived 1,3,4-oxadiazoles **11a–h** and **12a–h**. *a* Acyl chloride, DMF, reflux, 8 h, *b* phosphorus pentoxide, DMF, reflux, 4 h

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2. IR, ^{1}H NMR, ^{13}C NMR and mass spectral data are in agreement with the proposed structures of all newly synthesized compounds.

Experimental

Chemicals used in the synthesis of the titled compounds were purchased from Sigma-Aldrich, S. D. Fine-Chem Limited and Spectrochem Pvt. Ltd. The melting points of synthesized compounds were determined on Shital scientific industries melting point apparatus and are uncorrected; infra-red spectra were recorded on a Bruker spectrophotometer by using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz and Bruker AVANCE III 500 MHz instruments using dimethylsulphoxide-d_6 (DMSO-d_6) as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). Mass spectra (MS) were taken in JEOL GCMATE II GC-Mass spectrometer and Schimadzu QP 20105 GC-Mass spectrometer. Microanalyses of compounds were also performed on Leco Tru Spec CHNS Analyser for the determination of percentage of C, H and N. All the new compounds exhibited spectral data consistent with the proposed structures and values of microanalysis are within $\pm$0.4 % of the theoretical values. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany), visualizing by long- and short-wavelength ultraviolet (UV) lamps.

Synthesis of ethyl 4-(2,5-dimethylpyrrol-1-yl)benzoate (**1**)

A mixture of acetonyl acetone (13.69 g, 0.12 mol) and ethyl 4-aminobenzoate (16.5 g, 0.1 mol) in glacial acetic acid (100 mL) was refluxed for 1 h. The solvent was removed under reduced pressure, residue thus obtained was collected by filtration, washed with water, dried and recrystallized from ethanol (yield 65 %). mp 87–88 °C.

Synthesis of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**)

Compound **2** was synthesized by refluxing a mixture of ethyl 4-(2,5-dimethylpyrrol-1-yl)benzoate (**1**) (3.64 g, 15 mmol) with hydrazine hydrate (10 mL) in absolute ethanol (10 mL) for 3 h (monitored by TLC). The cooled mixture was poured gradually onto crushed ice cubes with stirring. The mixture was allowed to stand and solid was separated. It was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol (yield 80 %). mp 170–172 °C; IR (KBr) 3,285, 3,195 (NH/NH_2), 1,655 (amide C=O) cm^{-1}; ^{1}H NMR

(300 MHz, DMSO-d_6) δ ppm: 1.95 (s, 6H, pyrrole methyls), 4.51 (s, 2H, NH_2, disappeared on D_2O exchange), 5.80 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.33 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 7.94 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*), 10.00 (s, 1H, *NH*, disappeared on D_2O exchange); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 165.18 (amide C=O), 140.60 (bridging phenyl-C_4), 132.35 (bridging phenyl-C_1), 128.54 (bridging phenyl-C_2 and C_6), 127.79 (bridging phenyl-C_3 and C_5), 127.50 (pyrrole-C_2 and C_5), 106.33 (pyrrole-C_3 and C_4), 12.85 ($2CH_3$); MS *m/z*: found 229 [M^+], 230 [M+1], 213, 209, 171, 94; calcd. 229.28 Anal $C_{13}H_{15}N_3O$.

Synthesis of *N*′-(propan-2-ylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**3a**)

A solution of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**) (1.14 g, 5 mmol) in acetone (70 mL) was refluxed for 1 h. Evaporation of solvent furnished a solid which was recrystallized from ethanol (yield 78 %). mp 196–198 °C; IR (KBr) 3,214 (NH), 1,647 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.95 (s, 6H, $2CH_3$), 1.97 (s, 6H, $2CH_3$), 5.81 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.37 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 7.93 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*), 10.57 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 162.61 (amide C=O), 160.52 (C=N–NH), 140.76 (bridging phenyl-C_4), 133.19 (bridging phenyl-C_1), 128.70 (bridging phenyl-C_2 and C_6), 127.74 (bridging phenyl-C_3 and C_5), 127.53 (pyrrole-C_2 and C_5), 106.39 (pyrrole-C_3 and C_4), 25.10 (CH_3), 18.08 (CH_3) 12.91 (pyrrole-$2CH_3$); FAB MS *m/z*: found 270 [M^++H], 271 [M^++H+1], 242, 226, 198, 171, 165, 154, 136, 94; calcd. 269.34. Anal $C_{16}H_{19}N_3O$.

General procedure for the synthesis of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid(arylidene)hydrazides (**3b**–**3d**)

A mixture of **2** (3 mmol) and appropriate ketones (3 mmol) in ethanol (20 mL) was refluxed for 5 h in the presence of few drops of glacial acetic acid. The solvent was evaporated and the product was poured onto cold water, filtered and dried. The crude solid was recrystallized from aqueous DMF to give the products **3b**–**d**.

N′*-(1-Methylbenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl) benzohydrazide (**3b**)*

(Yield 65 %). mp 202–204 °C; IR (KBr) 3,224 (NH), 1,669 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.99 (s, 6H, pyrrole-$2CH_3$), 2.38 (s, 3H, CH_3), 5.82 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.36–8.00 (m, 9 H, *Ar–H*), 10.91 (s, 1H, *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.62 (amide C=O), 156.20 (C=N–NH), 140.10 (bridging phenyl-C_4), 132.20 (bridging phenyl-C_1), 131.14 (phenyl-C_1), 130.60 (phenyl-C_4), 129.02 (phenyl-C_2 and C_6), 128.60 (phenyl-C_3 and C_5), 128.40 (bridging phenyl-C_2 and C_6), 128.12 (pyrrole-C_2 and C_5), 127.90 (bridging phenyl-C_3 and C_5), 107.02 (pyrrole-C_3 and C_4), 17.63 (CH_3), 10.10 (pyrrole-$2CH_3$); MS *m/z*: found 331 [M^+], 332 [M+1], 286, 270, 214, 171, 154, 136, 94; calcd. 331.41 Anal $C_{21}H_{21}N_3O$.

*N'-(Benzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl) benzohydrazide (**3c**)*

(Yield 55 %). mp 252–254 °C; IR (KBr) 3,252 (NH), 1,646 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.10 (s, 6H, pyrrole-$2CH_3$), 5.72 (s, 2H, pyrrole-C_3 and C_4—*H*), 7.42–8.56 (m, 14 H, *Ar–H*), 10.21 (s, 1H, *NH*, disappeared on D_2O exchange); MS *m/z*: found 393 [M^+], 394 [M+1]; calcd. 393.48 Anal $C_{26}H_{23}N_3O$.

*4-(2,5-Dimethylpyrrol-1-yl)benzoic acid[1-(4-aminophenyl)ethylidene]hydrazide (**3d**)*

(Yield 56 %). mp 248–250 °C; IR (KBr) 3,268 (NH), 1,652 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.40 (s, 3H, CH_3), 2.02 (s, 6H, pyrrole-$2CH_3$), 4.4 (s, 2H, NH_2), 5.68 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.22–8.68 (m, 14 H, *Ar–H*), 10.56 (s, 1H, *NH*, disappeared on D_2O exchange); MS *m/z*: found 346 [M^+], 347 [M+1], 331, 252, 238, 224, 171, 154, 136, 94; calcd. 346.43 Anal $C_{21}H_{22}N_4O$.

Synthesis of 5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-1,3,4-oxadiazole-2-thiol (**4**)

Acid hydrazide **2** (0.687 g, 3 mmol) was dissolved in a solution of potassium hydroxide (0.336 g, 6 mmol) in water (2 mL) and ethanol (20 mL). Carbon disulphide (2 mL) was then added while stirring and the reaction mixture was refluxed for 10 h. The solvents were removed under reduced pressure; the residue was treated with water and then filtered. The filtrate was cooled, neutralized to pH 6 using dil. HCl and the separated product was filtered, washed with water, dried and recrystallized from ethyl acetate.

(Yield 75 %). mp 255–257 °C; IR (KBr) 2,770 (SH), 1,615 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.92 (s, 6H, pyrrole methyls), 3.43 (*SH* merged in HOD peak of DMSO-d_6), 5.84 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.36 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 7.94 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*); ^{13}C NMR

(300 MHz, DMSO-d_6) δ ppm: 175.24 (oxadiazole-C_2), 158.48 (oxadiazole-C_5), 141.64 (bridging phenyl-C_4), 131.42 (bridging phenyl-C_1), 128.24 (bridging phenyl-C_2 and C_6), 127.55 (bridging phenyl-C_3 and C_5), 127.21 (pyrrole-C_2 and C_5), 107.98 (pyrrole-C_3 and C_4), 12.51 ($2CH_3$); MS *m/z*: found 272 [M^++H], 273 [M^++H+1], 239, 171, 94; calcd. 271.34 Anal $C_{14}H_{13}N_3OS$.

Synthesis of 4-amino-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2,4-dihydro-1,2,4-triazole-3-thione (**5**)

To a solution of potassium hydroxide (0.37 g, 6.7 mmol) in absolute ethanol (30 mL) acid hydrazide **2** (0.687 g, 3 mmol), carbon disulphide (0.45 mL, 6 mmol) were added and the reaction mixture was agitated for 18 h. To the resulting solution anhydrous ether was added and the precipitated potassium dithiocarbazinate was collected by filtration, washed with ether and dried under vacuum. The potassium salt was obtained in quantitative yield and was used in the next step without further purification.

A suspension of the potassium salt, hydrazine hydrate (1.5 mL) and water (1.0 mL) was refluxed for 7 h. Hydrogen sulphide evolved and homogenous solution resulted which was diluted with 50 mL water and subsequent acidification with dilute acetic acid gave a white precipitate which was filtered, washed with water and recrystallized from aqueous DMF.

(Yield 75 %). mp 279–281 °C; IR (KBr) 3,292 (NH_2), 3,122 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.89 (s, 6H, pyrrole methyls), 5.50 (s, 2H, *NH_2*, disappeared on D_2O exchange), 5.82 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.44 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 8.22 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*), 12.42 (s, 1H, *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 166.22 (triazole-C=S), 148.26 (triazole-C_5), 143.52 (bridging phenyl-C_4), 130.78 (bridging phenyl-C_1), 128.88 (bridging phenyl-C_2 and C_6), 127.66 (bridging phenyl-C_3 and C_5), 127.11 (pyrrole-C_2 and C_5), 106.22 (pyrrole-C_3 and C_4), 13.87 ($2CH_3$); MS *m/z*: found 286 [M^++H], 287 [M^++H+1], 270, 171, 94; calcd. 285.37. Anal $C_{14}H_{15}N_5S$.

Synthesis of *N*-acetyl-4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**6**)

Acid hydrazide **2** (0.687 g, 3 mmol) was warmed with acetic anhydride (5 mL) for 2 h and the reaction mixture was left to stand at room temperature. The deposited pale yellow solid was filtered, washed and recrystallized from ethanol.

(Yield 65 %). mp 244–246 °C; IR (KBr) 3,384, 3,315 (NH), 1,685 (acetyl C=O), 1,655 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.92 (s, 6H, pyrrole methyls), 1.96 (s, 3H, *CH_3*), 5.90 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.84 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 8.54 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*), 9.54 (s, 1H, amide *NH*, disappeared on D_2O exchange), 11.42 (s, 1H, *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.26 (acetyl-C=O), 164.24 (amide-C=O), 145.46 (bridging phenyl-C_4), 130.85 (bridging phenyl-C_1), 128.56 (bridging phenyl-C_2 and C_6), 127.23 (bridging phenyl-C_3 and C_5), 127.05 (pyrrole-C_2 and C_5), 107.25 (pyrrole-C_3 and C_4), 22.52 (CH_3), 12.54 ($2CH_3$); MS *m/z*: found 272 [M^++H], 273 [M^++H+1], 228, 171, 94; calcd. 271.31. Anal $C_{15}H_{17}N_3O_2$.

General procedure for the synthesis of *N*'-(arylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7a**–**h**)

Equimolar quantity of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**) and different aromatic aldehydes was refluxed in ethanol for 4–6 h in the presence of few drops of glacial acetic acid. The solvent was evaporated and the product was poured onto cold water, filtered and dried. The crude solid was recrystallized from aqueous DMF to give the products.

*N'-(Benzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7a**)*

(Yield 60 %). mp 240–242 °C; IR (KBr) 3,230 (NH), 1,666 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.02 (s, 6H, pyrrole-2*CH_3*), 5.74 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.45–8.42 (m, 9H, *Ar–H*), 8.56 (s, 1H, *–N=CH–Ar*), 11.50 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 168.20 (amide C=O), 152.38 (CH=N), 142.22 (bridging phenyl-C_4), 133.34 (bridging phenyl-C_2 and C_6), 132.61 (phenyl-C_4), 131.04 (phenyl-C_1), 130.54 (phenyl-C_2 and C_6), 129.73 (C_1), 128.88 (pyrrole-C_2 and C_5), 127.66 (phenyl-C_3 and C_5), 125.36 (C_3 and C_5), 108.26 (pyrrole-C_3 and C_4), 11.22 (pyrrole-2CH_3); MS *m/z*: found 317 [M^+], 318 [M+1], 241, 171, 94; calcd. 317.38. Anal $C_{20}H_{19}N_3O$.

*N'-(2-Chlorobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7b**)*

(Yield 58 %). mp 236–238 °C; IR (KBr) 3,244 (NH), 1,658 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.16 (s, 6H, pyrrole-2*CH_3*), 5.74 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.42–8.76 (m, 9H, *Ar–H* and *–N=CH–Ar*), 12.20 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.99 (amide C=O), 154.76 (CH=N), 141.54 (bridging phenyl-C_4), 134.64 (phenyl-C_6), 133.32 (phenyl-C_1), 132.77 (phenyl-C_4), 131.26 (bridging phenyl-C_2 and C_6), 130.54 (phenyl-C_2),

129.53 (bridging phenyl-C_1), 128.63 (pyrrole-C_2 and C_5), 127.43 (phenyl-C_3 and C_5), 126.86 (bridging phenyl-C_3 and C_5), 107.32 (pyrrole-C_3 and C_4), 10.32 (pyrrole-2CH_3); MS *m/z*: found 352 [M^+], 353 [M+1], 317, 229, 171, 94; calcd. 351.83. Anal $C_{20}H_{18}ClN_3O$.

*N′-(4-Bromobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7c**)*

(Yield 55 %). mp 245–247 °C; IR (KBr) 3,260 (NH), 1,645 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.14 (s, 6H, pyrrole-2*CH*$_3$), 5.72 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.48–8.66 (m, 9H, *Ar–H* and *–N=CH–Ar*), 10.62 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.24 (amide C=O), 154.34 (CH=N), 143.33 (bridging phenyl-C_4), 133.44 (phenyl-C_3 and C_5), 132.56 (bridging phenyl-C_2 and C_6), 131.74 (phenyl-C_2 and C_6), 130.42 (phenyl-C_1), 130.22 (bridging phenyl-C_1), 129.64 (pyrrole-C_2 and C_5), 129.56 (bridging phenyl-C_3 and C_5), 125.60 (phenyl-C_4), 110.87 (pyrrole-C_3 and C_4), 10.44 (pyrrole-2CH_3); FAB MS *m/z*: found 397 [M^++H], 398 [M^++H+1], 317, 229, 171, 94; calcd. 396.28. Anal $C_{20}H_{18}BrN_3O$.

*N′-(2,6-Dichlorobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7d**)*

(Yield 55 %). mp 234–236 °C; IR (KBr) 3,255 (NH), 1,638 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.10 (s, 6H, pyrrole-2*CH*$_3$), 5.70 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.24–8.72 (m, 8H, *Ar–H* and *–N=CH–Ar*), 11.90 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 171.56 (amide C=O), 153.44 (CH=N), 140.65 (bridging phenyl-C_4), 135.64 (phenyl-C_2 and C_6), 133.80 (phenyl-C_4), 132.54 (phenyl-C_1), 131.44 (bridging phenyl-C_2 and C_6), 129.84 (pyrrole-C_2 and C_5), 129.54 (bridging phenyl-C_1), 127.64 (phenyl-C_3 and C_5), 126.66 (bridging phenyl-C_3 and C_5), 108.42 (pyrrole-C_3 and C_4), 10.67 (pyrrole-2CH_3); FAB MS *m/z*: found 387 [M^++H], 388 [M^++H+1], 317, 229, 171, 94; calcd. 386.27. Anal $C_{20}H_{17}Cl_2N_3O$.

*N'-(3-Nitrobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7e**)*

(Yield 62 %). mp 225–227 °C; IR (KBr) 3,223 (NH), 1,659 (amide C=O), 1,532 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.97 (s, 6H, pyrrole-2*CH*$_3$), 5.84 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.42–8.55 (m, 8H, *Ar–H* and *–N=CH–Ar*), 12.25 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 162.83 (amide C=O), 148.25 (CH=N), 145.50 (3-nitro-phenyl-C_5), 141.38 (bridging phenyl-C_4), 136.17 (3-nitro-phenyl-C_1), 133.46 (3-nitro-phenyl-C_2), 132.17 (bridging phenyl-C_2 and C_6), 130.51 (3-nitro-phenyl-C_3), 128.83 (bridging phenyl-C_1), 128.03 (3-nitro-phenyl-C_6), 127.58 (3-nitro-phenyl-C_4), 124.34 (bridging phenyl-C_3 and C_5), 120.98 (pyrrole-C_2 and C_5), 106.56 (pyrrole-C_3 and C_4), 12.95 (pyrrole-2CH_3); MS *m/z*: found 362 [M^+], 363 [M+1], 317, 229, 171, 94; calcd. 362.38. Anal $C_{20}H_{18}N_4O_3$.

*N'-(2-Nitrobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7f**)*

(Yield 62 %). mp 229–231 °C; IR (KBr) 3,227 (NH), 1,630 (amide C=O), 1,535 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.95 (s, 6H, pyrrole-2*CH*$_3$), 5.78 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.50–8.86 (m, 8H, *Ar–H* and *–N=CH–Ar*), 12.30 (s, 1H, amide *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 164.52 (amide C=O), 147.44 (CH=N), 144.26 (2-nitro-phenyl-C_5), 142.87 (bridging phenyl-C_4), 135.26 (2-nitro-phenyl-C_1), 133.89 (2-nitro-phenyl-C_2), 131.23 (bridging phenyl-C_2 and C_6), 130.22 (2-nitro-phenyl-C_3), 128.92 (bridging phenyl-C_1), 128.10 (2-nitro-phenyl-C_6), 127.44 (2-nitro-phenyl-C_4), 124.78 (bridging phenyl-C_3 and C_5), 121.57 (pyrrole-C_2 and C_5), 107.44 (pyrrole-C_3 and C_4), 13.84 (pyrrole-2CH_3); MS *m/z*: found 362 [M^+], 363 [M+1], 317, 229, 171, 94; calcd. 362.38. Anal $C_{20}H_{18}N_4O_3$.

*N′-(4-Hydroxybenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7g**)*

(Yield 58 %). mp 256–258 °C; IR (KBr) 3,457 (OH), 3,268 (NH), 1,648 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.93 (s, 6H, pyrrole-2*CH*$_3$), 5.82 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.66–8.90 (m, 8H, *Ar–H* and *–N=CH–Ar*), 11.38 (s, 1H, amide *NH*, disappeared on D_2O exchange), 12.22 (s, 1H, *OH,* disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 165.62 (amide C=O), 148.63 (CH=N), 143.82 (bridging phenyl-C_4), 143.56 (4-hydroxy-phenyl-C_5), 136.54 (4-hydroxy-phenyl-C_1), 132.54 (4-hydroxy-phenyl-C_2), 131.54 (bridging phenyl-C_2 and C_6), 130.29 (4-hydroxy-phenyl-C_3), 128.84 (bridging phenyl-C_1), 128.16 (4-hydroxy-phenyl-C_6), 127.22 (4-hydroxy-phenyl-C_4), 123.84 (bridging phenyl-C_3 and C_5), 121.26 (pyrrole-C_2 and C_5), 107.54 (pyrrole-C_3 and C_4), 13.84 (pyrrole-2CH_3); MS *m/z*: found 334 [M^+], 335 [M+1], 317, 229, 171, 94; calcd. 333.38. Anal $C_{20}H_{19}N_3O_2$.

*N′-(4-N,N-Dimethylaminobenzylidene)-4-(1H-2,5-dimethylpyrrol-1-yl)benzohydrazide (**7h**)*

(Yield 65 %). mp 230–232 °C; IR (KBr) 3,274 (NH), 1,664 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6)

δ ppm: 1.95 (s, 6H, pyrrole-2CH_3), 2.96 (s, 6H, 2CH_3), 5.81 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.52–8.46 (m, 8H, *Ar–H* and *–N=CH–Ar*), 12.12 (s, 1H, amide *NH*, disappeared on D_2O exchange); MS *m/z*: found 361 [M^+], 362 [M+1], 317, 229, 171, 94; calcd. 360.45. Anal $C_{22}H_{24}N_4O$.

General procedure for the synthesis of 3-acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-substituted-2,3-dihydro-1,3,4-oxadiazoles (**8a**–**8h**)

A mixture of **7** (3 mmol) and acetic anhydride (10 mL) was refluxed for 4 h. After the reaction mixture attained room temperature, excess acetic anhydride was decomposed by water and the mixture was stirred for further 30 min. The separated product was filtered, washed with water, dried and recrystallized from ethanol to give the products.

*3-Acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-phenyl-2,3-dihydro-1,3,4- oxadiazole (**8a**)*

(Yield 62 %). mp 225–227 °C; IR (KBr) 1,650 (acetyl C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.95 (s, 6H, pyrrole-2CH_3), 2.18 (s, 3H, acetyl-CH_3), 5.81 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.09 (s, 1H, oxadiazole-C_2–*H*), 7.52–7.82 (m, 9H, *Ar–H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 171.24 (acetyl C=O), 155.45 (oxadiazole-C_5), 142.88 (phenyl-C_4 at C_5 of oxadiazole), 141.34 (bridging phenyl-C_4), 132.70 (phenyl-C_1 at C_5 of oxadiazole), 131.22 (bridging phenyl-C_1), 129.68 (bridging phenyl-C_2 and C_6), 129.36 (pyrrole-C_2 and C_5), 127.33 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 126.34 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 122.44 (bridging phenyl-C_3 and C_5), 111.22 (pyrrole-C_3 and C_4), 94.32 (oxadiazole-C_2), 26.12 (CH_3), 12.08 (pyrrole-2CH_3); FAB MS *m/z*: found 360 [M^++H], 361 [M^++H+1], 317, 241, 171, 94; calcd. 359.42. Anal $C_{22}H_{21}N_3O_2$.

*3-Acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-(2-chloro phenyl)-2,3-dihydro-1,3,4-oxadiazole (**8b**)*

(Yield 58 %). mp 210–212 °C; IR (KBr) 1,656 (acetyl C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.02 (s, 6H, pyrrole-2CH_3), 2.16 (s, 3H, acetyl-CH_3), 5.74 (s, 2H, pyrrole-C_3 and C_4–*H*), 6.82 (s, 1H, oxadiazole-C_2–*H*), 7.20–8.46 (m, 8H, *Ar–H*),; ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.32 (acetyl C=O), 154.25 (oxadiazole-C_5), 141.44 (phenyl-C_4 at C_5 of oxadiazole), 140.12 (bridging phenyl-C_4), 132.90 (phenyl-C_1 at C_5 of oxadiazole), 130.56 (bridging phenyl-C_1), 129.67 (bridging phenyl-C_2 and C_6), 127.63 (pyrrole-C_2 and C_5), 127.38 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 126.78 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 124.22 (bridging phenyl-C_3 and C_5), 110.42 (pyrrole-C_3 and C_4), 93.12 (oxadiazole-C_2), 27.54 (CH_3), 11.88 (pyrrole-2CH_3); FAB MS *m/z*: found 395 [M^++H], 396 [M^++H+1], 352, 317, 241, 171, 94; calcd. 393.87 Anal $C_{22}H_{20}ClN_3O_2$.

*3-Acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-(2-bromo phenyl)-2,3-dihydro-1,3,4-oxadiazole (**8c**)*

(Yield 55 %). mp 229–231 °C; IR (KBr) 1,666 (acetyl C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.06 (s, 6H, pyrrole-2CH_3), 2.18 (s, 3H, acetyl-CH_3), 5.70 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.02 (s, 1H, oxadiazole-C_2–*H*), 7.32–8.68 (m, 8H, *Ar–H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 171.42 (acetyl C=O), 154.88 (oxadiazole-C_5), 141.78 (phenyl-C_4 at C_5 of oxadiazole), 140.26 (bridging phenyl-C_4), 132.52 (phenyl-C_1 at C_5 of oxadiazole), 131.44 (bridging phenyl-C_1), 129.25 (bridging phenyl-C_2 and C_6), 127.48 (pyrrole-C_2 and C_5), 127.12 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 126.26 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 124.48 (bridging phenyl-C_3 and C_5), 110.88 (pyrrole-C_3 and C_4), 94.56 (oxadiazole-C_2), 26.48 (CH_3), 10.56 (pyrrole-2CH_3); FAB MS *m/z*: found 439 [M^++H], 440 [M^++H+1], 396, 317, 241, 171, 94; calcd. 438.32. Anal $C_{22}H_{20}BrN_3O_2$.

*3-Acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-(2,6-dichloro phenyl)-2,3-dihydro-1,3,4-oxadiazole (**8d**)*

(Yield 51 %). mp 195–198 °C; IR (KBr) 1,606 (acetyl C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.91 (s, 6H, pyrrole-2CH_3), 2.12 (s, 3H, acetyl-CH_3), 5.82 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.12 (s, 1H, oxadiazole-C_2–*H*), 7.51–7.96 (m, 7H, *Ar–H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.25 (acetyl C=O), 155.42 (oxadiazole-C_5), 141.52 (bridging phenyl-C_4), 141.26 (phenyl-C_4 at C_5 of oxadiazole), 132.88 (phenyl-C_1 at C_5 of oxadiazole), 131.56 (bridging phenyl-C_1), 129.82 (bridging phenyl-C_2 and C_6), 128.28 (pyrrole-C_2 and C_5), 127.56 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 126.84 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 125.36 (bridging phenyl-C_3 and C_5), 110.54 (pyrrole-C_3 and C_4), 93.86 (oxadiazole-C_2), 27.24 (CH_3), 12.46 (pyrrole-2CH_3); FAB MS *m/z*: found 429 [M^++H], 430 [M^++H+1], 386, 317, 241, 171, 94; calcd. 428.31. Anal $C_{22}H_{19}Cl_2N_3O_2$.

*3-Acetyl-5-[4-(2,5-dimethylpyrrol-1-yl)phenyl]-2-(3-nitro phenyl)-2,3-dihydro-1,3,4-oxadiazole (**8e**)*

(Yield 53 %). mp 218–220 °C; IR (KBr) 1,648 (acetyl C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.98 (s, 6H, pyrrole-2CH_3), 2.14 (s, 3H, acetyl-CH_3), 5.82 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.02 (s, 1H, oxadiazole-C_2–*H*), 7.80–8.00 (m, 8H, *Ar–H*); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.32 (acetyl C=O), 156.44 (oxadiazole-C_5), 145.12

(phenyl-C_4 at C_5 of oxadiazole), 139.42 (bridging phenyl-C_4), 131.56 (phenyl-C_1 at C_5 of oxadiazole), 130.24 (bridging phenyl-C_1), 129.52 (bridging phenyl-C_2 and C_6), 127.24 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 121.24 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 120.46 (bridging phenyl-C_3 and C_5), 116.48 (pyrrole-C_2 and C_5), 111.24 (pyrrole-C_3 and C_4), 95.24 (oxadiazole-C_2), 27.44 (CH_3), 12.02 (pyrrole-2CH_3); MS *m/z*: found 404 [M^+], 405 [M+1], 362, 311, 239, 235, 171, 94; calcd. 404.42. Anal $C_{22}H_{20}N_4O_4$.

Synthesis of *N*-(2,5-dimethyl-pyrrol-1-yl)-4-(2,5-dimethylpyrrol-1-yl)benzamide (**9**)

To a suspension of 4-(2,5-dimethylpyrrol-1-yl)benzoic acid hydrazide (**2**) (0.687 g, 3 mmol) in ethanol (10 mL) were added acetonyl acetone (0.684 g, 6 mmol) and glacial acetic acid (1 mL) and the reaction mixture was heated on a boiling water bath for 5 h. The reaction mixture was concentrated to half of original volume and poured into crushed ice (50 g). The separated solid was filtered, washed with water, dried and recrystallized from ethanol.

(Yield 74 %). mp 236–238 °C; IR (KBr) 3,266 (NH), 1,672 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.88 (s, 6H, pyrrole methyls), 2.10 (s, 6H, pyrrole methyls), 5.68 (s, 2H, dimethyl pyrrole-C_3 and C_4–*H*), 5.84 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.78 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_3 and C_5–*H*), 8.20 (d, $J = 8.5$ Hz, 2H, bridging phenyl-C_2 and C_6–*H*), 12.16 (s, 1H, *NH*, disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 164.64 (amide C=O), 144.64 (bridging phenyl-C_4), 131.56 (bridging phenyl-C_1), 128.26 (bridging phenyl-C_2 and C_6), 127.84 (bridging phenyl-C_3 and C_5), 127.55 (dimethyl pyrrole-C_2 and C_5), 127.15 (pyrrole-C_2 and C_5), 107.87 (pyrrole-C_3 and C_4), 105.54 (dimethyl pyrrole-C_3 and C_4), 12.08 (2CH_3), 11.44 (2CH_3); MS *m/z*: found 308 [M^+], 309 [M+1], 214, 171, 94; calcd. 307.39. Anal $C_{19}H_{21}N_3O$.

Synthesis of 4-pyrrol-1-yl benzoic acid hydrazide (**10**)

(Joshi *et al*., 2008a) Ethyl 4-pyrrol-1-yl benzoate (**3**) (3.22 g, 15 mmol) was refluxed with hydrazine hydrate (10 mL) in absolute ethanol (10 mL) for 3 h. The reaction mixture was cooled and the crystalline mass obtained was recrystallized from ethanol (yield 74 %) mp 180–182 °C.

General procedure for the synthesis of *N′*-(arylcarbonyl)-4-(1H-pyrrol-1-yl)benzohydrazide derivatives (**11a**–**h**)

A mixture of **10** (1 mmol) and substituted acyl chlorides (1.5 mmol) in 10 mL of dry DMF was refluxed for 7–8 h (monitored by TLC). The reaction mixture was cooled and slowly quenched onto crushed ice with stirring and neutralized with saturated sodium bicarbonate solution. The solid which separated was filtered, washed with cold ethanol, dried and recrystallized from aqueous DMF to give the products.

*N-(4-Pyrrol-1-yl)benzoyl)benzoic acid hydrazide (**11a**)*

(Yield 91 %). mp 291–294 °C; IR (KBr) 3,241 (NH), 3,135 (NH), 1,683 (amide C=O), 1,645 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 6.36 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.56–8.14 (m, 11H, pyrrole-C_2 and C_5–*H*, Ar–*H*), 9.40 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.61 (s, 1H, *NHCO,* disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 167.20 (C=O), 144.21 (bridging phenyl-C_4), 133.12 (phenyl-C_1), 129.12 (phenyl-C_4), 128.16 (bridging phenyl-C_2 and C_6), 127.30 (phenyl-C_2 and C_6), 124.02 (bridging phenyl-C_1), 121.26 (phenyl-C_3 and C_5), 119.32 (bridging phenyl-C_3 and C_5), 118.90 (pyrrole-C_2 and C_5), 111.20 (pyrrole-C_3 and C_4); MS *m/z*: found 307 [M^++H], 229, 153, 143, 66; calcd. 305.33 Anal $C_{18}H_{15}N_3O_2$.

*N-(4-Pyrrol-1-yl)-2-bromo benzoyl)benzoic acid hydrazide (**11b**)*

(Yield 86 %). mp 268–270 °C; IR (KBr) 3,199 (NH), 1,605 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 6.34 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.44–8.09 (m, 10H, pyrrole-C_2 and C_5–*H*, Ar–*H*), 9.35 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.54 (s, 1H, *NHCO,* disappeared on D_2O exchange); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 167.52 (C=O), 143.80 (bridging phenyl-C_4), 132.80 (2-bromo phenyl-C_1), 129.20 (2-bromo phenyl-C_4), 128.20 (bridging phenyl-C_2 and C_6), 127.52 (2-bromo phenyl-C_2 and C_6), 124.22 (bridging phenyl-C_1), 122.40 (2-bromo phenyl-C_3 and C_5), 119.12 (bridging phenyl-C_3 and C_5), 118.80 (pyrrole-C_2 and C_5), 111.40 (pyrrole-C_3 and C_4); MS *m/z*: found 385 [M^++1] 229, 153, 143, 66; calcd. 384.23 Anal $C_{18}H_{14}BrN_3O_2$.

*N-(4-Pyrrol-1-yl)-4-bromo benzoyl)benzoic acid hydrazide (**11c**)*

(Yield 80 %). mp 262–264 °C. IR (KBr) 3,138 (NH), 1,608 (amide C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 6.30 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.42–8.26 (m, 10H, pyrrole-C_2 and C_5–*H*, Ar–*H*), 9.50 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.62 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 385 [M^++1] 229, 153, 143, 66; calcd. 384.23 Anal $C_{18}H_{14}BrN_3O_2$.

N-(4-Pyrrol-1-yl)-2-nitro benzoyl)benzoic acid hydrazide ***(11d)***

(Yield 76 %). mp 274–276 °C. IR (KBr) 3,181 (NH), 1,606 (amide C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.32 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.52-8.46 (m, 10H, pyrrole-C_2 and C_5–*H*, Ar–*H*), 9.48 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.40 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 351 [M^++1] 229, 153, 143, 66; calcd. 350.33 Anal $C_{18}H_{14}N_4O_4$.

N-(4-Pyrrol-1-yl)-3-nitro benzoyl)benzoic acid hydrazide ***(11e)***

(Yield 80 %). mp 280–284 °C. IR (KBr) 3,181 (NH), 1,606 (amide C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.32 ppm (s, 2H, pyrrole-C_3 and C_4–*H*), 7.62–8.24 (m, 10H, pyrrole-C_2 and C_5–*H*, Ar–*H*), 9.44 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.64 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 351 [M^++1] 229, 153, 143, 66; calcd. 350.33 Anal $C_{18}H_{14}N_4O_4$.

N-(4-Pyrrol-1-yl)-4-nitro benzoyl)benzoic acid hydrazide ***(11f)***

(Yield 58 %). mp 278–280 °C. IR (KBr) 3,195 (NH), 1,693 (amide C=O), 1,607 (amide C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.34 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.52 (s, 2H, pyrrole-C_2 and C_5–*H*), 7.78–8.42 (m, 8H, Ar–*H*), 9.46 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.80 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 351 [M^++1] 229, 153, 143, 66; calcd. 350.33 Anal $C_{18}H_{14}N_4O_4$.

N-(4-Pyrrol-1-yl)-4-chloro benzoyl)benzoic acid hydrazide ***(11g)***

(Yield 90 %). mp 262–264 °C; IR (KBr) 3,191 (NH), 1,605 (amide C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.30 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.42 (s, 2H, pyrrole-C_2 and C_5–*H*), 7.82–8.46 (m, 8H, Ar–*H*), 9.44 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.56 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 341 [M^++1] 229, 153, 143, 66; calcd. 339.78 Anal $C_{18}H_{14}ClN_3O_2$.

N-(4-Pyrrol-1-yl)-4-fluoro-3-trifluoromethyl benzoyl)benzoic acid hydrazide ***(11h)***

(Yield 57 %). mp 272–274 °C; IR (KBr) 3,195 (NH), 1,610 (amide C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.34 (s, 2H, pyrrole-C_3 and C_4–*H*), 7.46 (s, 2H, pyrrole-C_2 and C_5–*H*), 7.78–8.56 (m, 7H, Ar–*H*), 9.56 (s, 1H, *CONH,* disappeared on D_2O exchange), 10.82 (s, 1H, *NHCO,* disappeared on D_2O exchange); MS *m/z*: found 392 [M^+ + 1] 229, 153, 143, 66; calcd. 391.32 Anal $C_{19}H_{13}F_4N_3O_2$.

General procedure for the synthesis of 2-aryl-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole derivatives (**12a**–**h**)

To a suspension of **11** (1 mmol) in dry DMF (50 mL), phosphorus pentoxide (2.0 g) was added portion wise with stirring at room temperature and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled and then filtered. The resulting solid that separated was washed with water, dried and recrystallized from aqueous DMF to give the products.

2-Phenyl-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole ***(12a)***

(Yield 85 %). mp 284–286 °C; IR (KBr) 1,637 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.34 (dd, 2H, pyrrole-C_3 and C_5–*H*), 7.55 (dd, 2H, pyrrole-C_2 and C_4–*H*), 7.65 (d, 2H, C_3–*H* and C_5–*H*), 7.88 (d, 2H, C_2–*H* and C_6–*H* of phenyl ring at oxadiazole), 8.15–8.20 (m, 5H, C_2–*H* and C_6–*H*, C_3, C_4 and C_5–H of phenyl ring at oxadiazole); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 164.40 (oxadiazole-C_5), 164.10 (oxadiazole-C_2), 142.78 (bridging phenyl-C_4), 132.50 (phenyl-C_1 at C_5 of oxadiazole), 129.89 (phenyl-C_4 at C_5 of oxadiazole), 128.75 (bridging phenyl-C_2 and C_6), 127.11 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 123.86 (bridging phenyl-C_1), 120.21 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 119.91 (bridging phenyl-C_3 and C_5), 119.51 (pyrrole-C_2 and C_5), 111.9 (pyrrole-C_3 and C_4); FAB MS *m/z*: found 288 [M^+], 211, 170, 153, 143, 66; calcd. 287.32 Anal $C_{18}H_{13}N_3O$.

2-(2-Bromophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole ***(12b)***

(Yield 88 %). mp 264–266 °C; IR (KBr) 1,618 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.32 (dd, 2H, pyrrole-C_3 and C_5–*H*), 7.51 (dd, 2H, pyrrole-C_2 and C_4–*H*), 7.72 (d, 2H, C_3–H and C_5–*H*), 7.78–8.06 (m, 6H, C_2–*H* and C_6–*H*, C_3, C_4, C_5, and C_6–*H* of phenyl ring at oxadiazole); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 163.70 (oxadiazole-C_5), 154.88 (oxadiazole-C_2), 142.79 (bridging phenyl-C_4), 133.37 (bridging phenyl-C_1), 130.02 (phenyl-C_1 at C_5 of oxadiazole), 129.05 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 128.79 (bridging phenyl-C_2 and C_6), 127.96 (phenyl-C_4 at C_5 of oxadiazole), 119.96 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 119.48 (bridging phenyl-C_3 and C_5), 118.77 (pyrrole-C_2 and C_5), 111.90 (pyrrole-C_3

and C_4); MS *m/z*: found 367 [M^++1], 287, 211, 170, 153, 143, 66; calcd. 366.21 Anal $C_{18}H_{12}BrN_3O$.

*2-(4-Bromophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12c**)*

(Yield 76 %). mp 258–260 °C; IR (KBr) 1,605 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ ppm: 6.33 (d, 2H, pyrrole-C_2 and C_5–*H*), 7.54 (d, 2H, pyrrole-C_3 and C_4–*H*), 7.83 (d, 2H, C_3–*H* and C_5–*H*), 7.87 (d, 2H, C_2–*H* and C_6–*H* of phenyl ring at oxadiazole), 8.09 (d, 2H, C_2–*H* and C_6–*H*), 8.19 (d, 2H, C_3–*H* and C_5–*H* of phenyl ring at oxadiazole); MS *m/z*: found 367 [M^+], 287, 211, 170, 153, 143, 66, calcd. 366.21. Anal $C_{18}H_{12}BrN_3O$.

*2-(2-Nitrophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12d**)*

(Yield 70 %). mp 270–272 °C. IR (KBr) 1,605 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.30 (dd, 2H, pyrrole-C_3 and C_4–*H*), 7.48 (dd, 2H, pyrrole-C_2 and C_5–*H*), 7.72 (d, 2H, C_6–*H* and C_2–*H*), 7.78 (s, 2H, C_3–*H* and C_5–*H*), 8.06–8.09 (m, 4H, C_3, C_4, C_5, and C_6–*H* of phenyl ring at oxadiazole); MS *m/z*: found 332 [M^+], 211, 170, 153, 143, 66, calcd. 332.31. Anal $C_{18}H_{12}N_4O_3$.

*2-(3-Nitrophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12e**)*

(Yield 85 %). mp 274–276 °C; IR (KBr) 1,604 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.32 (dd, 2H, pyrrole-C_3 and C_4–*H*), 7.51 (dd, 2H, pyrrole-C_2 and C_5–*H*), 7.71 (d, 2H, C_3–*H* and C_5–*H*), 7.87 (t, 1H, C_5–*H* of phenyl ring at oxadiazole), 8.03 (d, 2H, C_2–*H* and C_6–*H*), 8.37 (dd, 1H, C_6–*H* of phenyl ring at oxadiazole), 8.46 (dd, 1H, C_4–*H* of phenyl ring at oxadiazole), 8.75 (t, 1H, C_2–*H* of phenyl ring at oxadiazole); MS *m/z*: found 332 [M^+], 287, 211, 170, 153, 143, 66, calcd. 332.31. Anal $C_{18}H_{12}N_4O_3$.

*2-(4-Nitrophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12f**)*

(Yield 64 %). mp 268–270 °C; IR (KBr) 1,619 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.32 (dd, 2H, pyrrole-C_3 and C_4–*H*), 7.51 (dd, 2H, pyrrole-C_2 and C_5–*H*), 7.71 (d, 2H, C_3–*H* and C_5–*H*), 8.02 (d, 2H, C_2–*H* and C_6–*H*), 8.16 (dd, 2H, C_2–*H* and C_6–*H* of phenyl ring at oxadiazole), 8.38 (dd, 2H, C_3–*H* and C_5–*H* of phenyl ring at oxadiazole); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 165.41 (oxadiazole-C_5), 164.86 (oxadiazole-C_2), 149.92 (bridging phenyl-C_4), 142.88 (bridging phenyl-C_1), 138.61 (phenyl-C_4 at C_5 of oxadiazole), 129.66 (bridging phenyl-C_2 and C_6), 129.47 (phenyl-C_1 at C_5 of oxadiazole), 129.01 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 124.26 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 119.49 (bridging phenyl-C_3 and C_5), 119.02 (pyrrole-C_2 and C_5), 111.75 (pyrrole-C_3 and C_4); MS *m/z*: found 332 [M^+], 287, 211, 170, 153, 143, 66, calcd. 332.31. Anal $C_{18}H_{12}N_4O_3$.

*2-(4-Chlorophenyl)-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12g**)*

(Yield 86 %). mp 254–256 °C; IR (KBr) 1,601 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.35 (dd, 2H, pyrrole-C_3 and C_4–*H*), 7.50 (s, 2H, pyrrole-C_2 and C_5–*H*), 7.54 (d, 1H, bridging phenyl-C_6–*H*), 7.74 (d, 1H, bridging phenyl-C_2–*H*), 7.87 (d, 1H, C_5–*H* of phenyl ring at oxadiazole), 7.95 (d, 1H, C_3–*H* of phenyl ring at oxadiazole), 8.00 (d, 1H, C_6–*H* of phenyl ring at oxadiazole), 8.11 (d, 1H, C_2–*H* of phenyl ring at oxadiazole), 8.19 (d, 2H, C_3–*H* and C_5–*H*); MS *m/z*: found 323 [M+1], 170, 153, 143, 139, 112, 66, calcd. 321.76. Anal $C_{18}H_{12}ClN_3O$.

*2-[4-Fluoro-3-(trifluoromethyl)phenyl]-5-[4-(1H-pyrrol-1-yl)phenyl]-1,3,4-oxadiazole (**12h**)*

(Yield 56 %) mp 266–268 °C; IR (KBr) 1,614 (C=N) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 6.33 (dd, 2H, pyrrole-C_3 and C_5–*H*), 7.52 (dd, 2H, pyrrole-C_2 and C_4–*H*), 7.69–8.33 (m, 7H, C_2, C_3, C_5, C_6–*H* and C_2, C_5, C_6–*H* of phenyl ring at oxadiazole); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 165.39 (trifluoromethyl-C), 164.00 (oxadiazole-C_5), 163.70 (oxadiazole-C_2), 142.86 (bridging phenyl-C_4), 120.10 (bridging phenyl-C_1), 135.32 (phenyl-C_1 at C_5 of oxadiazole), 129.08 (bridging phenyl-C_2 and C_6), 128.79 (phenyl-C_2 and C_6 at C_5 of oxadiazole), 127.96 (phenyl-C_4 at C_5 of oxadiazole), 119.95 (phenyl-C_3 and C_5 at C_5 of oxadiazole), 119.48 (bridging phenyl-C_3 and C_5), 119.03 (pyrrole-C_2 and C_5), 111.90 (pyrrole-C_3 and C_4); MS *m/z*: found 373 [M^+], 211, 170, 164, 143, 66, calcd. 373.30. Anal $C_{19}H_{11}F_4N_3O$.

Biological activities

In vitro evaluation of antimicrobial activity

The minimum inhibitory concentration (MIC) determination of the tested compounds (**2**, **3a–d**, **4**, **5**, **6**, **7a–h**, **8a–h**, **9**, **11a–h**, **12a–h**) 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 (Goto *et al*., 1981). The antifungal activity was assayed against yeasts (*Candida tropicalis*, *Saccharomyces cerevisiae*) and moulds (*Aspergillus niger*). Serial dilutions of the test compounds and reference drugs were prepared in Mueller–Hinton broth for bacteria and Sabouraud Liquid Medium for fungi. Drugs (10 mg) were dissolved in DMSO (1 mL). Further progressive dilutions were done to obtain final concentrations of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 μg mL^{-1}. The tubes were inoculated with 10^5 cfu mL^{-1} (colony forming unit mL^{-1}) and incubated at 37 °C for 18 h. 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.

In vitro anti-*M. tuberculosis* assay

The preliminary antitubercular screening for test compounds (**2**, **3a–d**, **4**, **5**, **6**, **7a–h**, **8a–h**, **9**, **11a–h**, **12a–h**) was carried for *M. tuberculosis* $H_{37}Rv$, the MIC of each drug was determined by broth dilution assay method (Suling *et al*., 2000; Yajko *et al*., 1995) and is defined as the lowest concentration of drug, which inhibits ≥99 % of bacterial population present at the beginning of the assay. A frozen culture in Middlebrook 7H9 broth supplemented with 10 % albumin–dextrose–catalase and 0.2 % glycerol was thawed and diluted in broth to 10^5 cfu mL^{-1} for *M. tuberculosis* and used as the inoculum. In the assay, U-tubes were used to accommodate compounds in 1–500 μg mL^{-1} dilutions. Each test compound was dissolved in DMSO and then diluted in broth at twice the desired concentration. The final concentration of DMSO in the assay medium was 1.3 %. Each U-tube was then inoculated with 0.05 mL of standardized culture and then incubated at 37 °C for 21 days. The growth in the U-tubes was compared with visibility against positive control (without drug), negative control (without drug and inoculum) and with a standard drug isoniazid. The tests were carried out in triplicate.

Cytotoxic activity

The cellular conversion of MTT [3-(4,5-dimethylthiazo-2-yl)-2,5-diphenyl-tetrazolium bromide] into a formazan product (Mosmann, 1983) was used to evaluate cytotoxic activity (IC_{50}) of some synthesized compounds (**4**, **5**, **6**, **11a–h** and **12a–h**) against mammalian Vero cell lines and A_{549} (lung adenocarcinoma) cell lines up to concentrations of 62.5 μg mL^{-1} using the Promega Cell Titer 96 non-radioactive cell proliferation assay (Gundersen *et al*., 2002). The IC_{50} values are mean ± SEM of three independent experiments and are presented in Table 2.

Results and discussion

Synthetic and spectral studies

In the IR spectrum of **2**, broad stretching bands around 3,285 and 3,195 cm^{-1} were due to amine/amide NH while strong stretching band at 1,655 cm^{-1} was assigned to amide carbonyl. The ^1H NMR spectrum of **2** showed a singlet at δ 1.95 which was accounted for two methyl groups on pyrrole ring. A singlet at δ 4.51 was assigned to NH_2 group which disappeared on D_2O exchange. The C_3 and C_4 protons of pyrrole ring appeared as singlet at δ 5.80. Four protons of phenyl moiety resonated as two doublets at δ 7.94 and 7.33. A broad singlet appeared at δ 10.0 was accounted for NH which vanished on D_2O exchange. The mass spectrum of **2** displayed a molecular ion peak at *m/z* 229 which confirmed its molecular weight.

Disappearance of NH_2 stretching band in the IR spectrum of **3a** confirmed the formation of hydrazone. A stretching band at 3,214 cm^{-1} was due to amide NH, while strong stretching band at 1,647 cm^{-1} was related to amide carbonyl. The ^1H NMR spectrum of **3a** showed two singlets at δ 1.95 and 1.97 which were accounted for four methyl groups. The C_3 and C_4 protons of pyrrole ring appeared as singlet at δ 5.81. The four protons of phenyl moiety resonated as two doublets at δ 7.93 and 7.37. A singlet appeared at δ 10.57 was accounted for NH which vanished on D_2O exchange. The ^{13}C NMR data of **3a** also supported the structure which displayed a peak at δ 12.91 due to two methyl carbons of pyrrole. Peaks at δ 18.08 and 25.10 were due to two methyl groups. The C=N resonance appeared at δ 160.52. The FAB mass spectrum of **3a** showed a molecular ion peak (M^++H) at *m/z* 270 which confirmed its molecular weight.

Lack of ^1H NMR resonances observed with NH and NH_2 functions in the ^1H NMR spectrum of **4** proved that ring closure starting from **2** resulted in the formation of 1,3,4-oxadiazole ring. This was further substantiated by the ^{13}C NMR data of **4** which showed a peak at δ 175.24 and 158.48 due to C_2 and C_5 carbons of oxadiazole. Mass spectrum of **4** displayed a molecular ion base peak at *m/z* 272 which confirmed its molecular weight.

The IR spectrum of **5** exhibited stretching bands at 3,292 and 3,122 cm^{-1} due to NH/NH_2. The ^1H NMR spectrum of this compound showed a singlet at δ 12.42 and 5.50 which were accounted for NH and NH_2, respectively. ^{13}C NMR spectrum of **5** showed signals at δ 166.22 and 148.26 due to C=S of triazole and C_5 carbon of triazole, respectively. The

mass spectrum of **5** displayed a molecular ion peak at *m/z* 286 which confirmed its molecular weight.

The three singlets at δ 1.96, 9.54 and 11.42 in the ^{1}H NMR spectrum of **6** were assigned to CH_3, amide NH and NH protons, respectively. The structure of **6** was further confirmed by the ^{13}C NMR data which displayed signals at δ 22.52, 164.24 and 170.26 due to CH_3, benzamide and acetyl carbonyl carbons, respectively. The mass spectrum exhibited the molecular ion peak at *m/z* 272 which confirmed its molecular weight.

Hydrazones **7a–h** obtained from hydrazide **2** showed carbonyl amide stretching bands in 1,600–1,660 cm^{-1} region and N–H bands in 3,250–3,460 cm^{-1} region. ^{1}H NMR and ^{13}C NMR data were also in agreement with the formation of hydrazones. ^{1}H NMR spectra of **7a** showed two singlets at δ 8.56 and 11.50 which were attributed to the N=CH and NH protons, respectively.

IR spectra of **8a–h** had different characteristics as they showed no NH stretching bands and only C=O bands at around 1,650 cm^{-1} which were attributed to the C=O stretching of acetyl group. Two singlets at around δ 7.00 and 2.16 in the ^{1}H NMR spectra of **8a–h** were attributed to the O–CHR–N resonance of the oxadiazolines ring and acetyl CH_3, respectively. The formation of the oxadiazolines was further supported by the ^{13}C NMR data of compounds **8a–h**. While the N=CH carbon of compounds in hydrazone structures were observed at around δ 148–154 in their ^{13}C NMR spectra, the same carbon atoms (OCHR–N) were observed at around δ 93–95 after cyclisation of oxadiazoline ring. In the ^{13}C NMR spectrum of **8a**, this signal was observed at δ 94.32 due to the sp^3 hybridization.

The ^{1}H NMR spectrum of **9** showed singlet at δ 2.10 due to methyl protons of pyrrole, while singlet at δ 5.68 was due to two protons of pyrrole. The mass spectrum of **9** showed a molecular ion peak at *m/z* 308 which confirmed its molecular weight.

Evidence for the structure **11a** was obtained by the IR spectrum which showed the presence of absorption bands at 3,241, 3,135 cm^{-1} and 1,683 cm^{-1}, 1,645 cm^{-1} which were due to amide –NH and carbonyl stretching frequencies. The ^{1}H NMR spectrum of **11a** showed a singlet at δ 6.36 which was accounted for C_3 and C_4 protons of pyrrole. The multiplets between δ 7.56 and 8.14 were assigned for two protons of C_2 and C_5 protons of pyrrole and nine protons of aromatic rings, respectively. Two broad peaks at δ 9.40 and 10.61 were attributed to –NHCO and –CONH protons, respectively. The FAB mass spectrum of **11a** showed a molecular ion peak (M^++H) at *m/z* 307 which confirmed its molecular weight. Disappearance of –NH stretching bands in the IR spectrum of **12a** confirmed the formation of oxadiazole ring. The C=N stretching band appeared at 1,637 cm^{-1}. The ^{1}H NMR spectrum of **12a** showed two doublet of doublet at δ 6.34 and 7.55 which were accounted for four protons of pyrrole ring. Two doublets were observed at δ 7.65 and 7.88 which were assigned to two protons of C_3 and C_5 of phenyl ring and two protons of C_2 and C_6 of phenyl ring at oxadiazole, respectively. Multiplets between δ 8.15 and 8.20 were assigned to two protons of C_2 and C_6 of phenyl ring and three protons of C_3, C_4 and C_5 of phenyl ring at oxadiazole, respectively. Formation of oxadiazoles was further confirmed by their ^{13}C NMR and mass spectra. In ^{13}C NMR spectrum of **12a**, we have observed most characteristic signals appeared at δ 164.10 and 164.40 for C_2 and C_5 carbons of oxadiazole, respectively. The signals appeared at around δ 119.51 and 111.91 C_3, C_4, C_2 and C_5 carbons of pyrrole ring and carbons of Ph groups at δ 120.21–142.78 ppm. The mass spectrum of **12a** showed a molecular ion peak at *m/z* 288 which corresponds to its molecular weight.

Antimicrobial activity

The results of antimicrobial activities of the synthesized compounds against selected three Gram-positive, three Gram-negative bacteria, yeasts, moulds and *M. tuberculosis* H_{37}Rv are illustrated in Tables 1 and 2, respectively. The antimicrobial and antifungal activity results are expressed in MIC values along with the activity of ciprofloxacin, norfloxacin and fluconazole for comparison.

The antimicrobial screening data revealed that all the compounds showed moderate to significant microbial inhibition. Compounds **2**, **3a–d**, **4**, **5**, **6**, **7a–h**, **8a–h** and **9** (Scheme 1) showed antimicrobial activity at MIC values of 2–500 μg mL^{-1}. Compounds showed enhanced activity against Gram-positive bacteria than the Gram-negative bacteria. Compounds **4**, **8d** and **9** were found to be more active than the others at an MIC value of 2 μg mL^{-1} against *Staphylococcus aureus.* The synthesized compounds showed antimicrobial activity with MIC values between 4 and 62.5 μg mL^{-1} against *B. subtilis.* Compounds exhibited lower potencies against *Streptococcus faecalis.* All the compounds exhibited moderate activity against *K. pneumoniae.* Compounds showed lower activity against *E. coli* and *P. aeruginosa.* Compounds **8a–h** which have 2,3-dihydro-1,3,4-oxadiazole ring were more active than the starting Schiff bases **7a–h** against some of the test microorganisms.

Compounds **11a–h** and **12a–h** (Scheme 2) showed antimicrobial activity at MIC values of 1–500 μg mL^{-1}. Compound **12h** was found to be more active than the others at an MIC value of 1 μg mL^{-1} against *B. subtilis*. The synthesized compounds showed antimicrobial activity with MIC values between 8 and 62.5 μg mL^{-1} against *Streptococcus faecalis.* Compounds exhibited lower potencies against *K. pneumoniae. C*ompounds showed good activity

Table 1 In vitro antimicrobial activity

Compounds	MIC values (μg mL^{-1})								
	Gram-positive organisms			Gram-negative organisms			Yeasts		
	Sa	*Sf*	*Bs*	*Kp*	*Ec*	*Pa*	*Sc*	*Ct*	*An*
2	62.5	62.5	62.5	62.5	500	500	62.5	62.5	62.5
3a	31.25	31.25	16	500	500	500	62.5	31.25	62.5
3b	62.5	31.25	16	500	500	500	62.5	62.5	62.5
3c	62.5	31.25	31.25	500	500	500	62.5	62.5	62.5
3d	31.25	62.5	62.5	500	500	500	62.5	62.5	62.5
4	2	4	4	62.5	62.5	62.5	8	2	8
5	16	16	31.25	500	500	500	4	2	4
6	31.25	31.25	16	500	500	500	62.5	62.5	62.5
7a	31.25	62.5	31.25	62.5	62.5	62.5	62.5	31.25	31.25
7b	16	31.25	8	62.5	500	500	31.25	8	16
7c	16	31.25	16	500	500	>500	31.25	8	16
7d	16	16	16	500	500	500	31.25	4	4
7e	31.25	31.25	31.25	500	500	500	31.25	16	16
7f	62.5	31.25	31.25	>500	>500	>500	31.25	16	16
7g	16	16	31.25	62.5	500	500	16	16	16
7h	31.25	31.25	31.25	62.5	500	500	31.25	31.25	31.25
8a	62.5	62.5	16	62.5	500	500	62.5	16	31.25
8b	16	31.25	8	31.25	500	500	31.25	8	16
8c	16	31.25	8	31.25	500	500	31.25	8	16
8d	2	2	4	62.5	16	8	16	4	4
8e	31.25	31.25	16	62.5	62.5	62.5	31.25	8	8
8f	31.25	31.25	16	500	500	500	31.25	8	8
8g	31.25	31.25	16	31.25	62.5	62.5	31.25	8	8
8h	31.25	31.25	16	31.25	500	500	31.25	31.25	31.25
9	2	16	16	62.5	500	500	16	4	16
11a	62.5	62.5	16	>500	31.25	62.5	31.25	31.25	31.25
11b	62.5	62.5	16	>500	16	16	31.25	8	16
11c	62.5	31.25	16	>500	16	16	31.25	8	16
11d	62.5	31.25	16	>500	31.25	16	31.25	31.25	31.25
11e	62.5	62.5	16	>500	16	16	31.25	31.25	31.25
11f	62.5	31.25	16	>500	16	16	31.25	31.25	31.25
11g	62.5	31.25	16	>500	16	16	31.25	8	31.25
11h	62.5	31.25	16	>500	8	8	16	4	8
12a	31.25	31.25	8	>500	8	8	31.25	31.25	31.25
12b	31.25	31.25	8	>500	8	8	31.25	4	16
12c	31.25	16	4	>500	4	8	31.25	4	8
12d	31.25	16	4	>500	4	4	31.25	31.25	31.25
12e	31.25	31.25	8	>500	8	8	31.25	31.25	31.25
12f	31.25	16	4	>500	4	4	31.25	31.25	31.25
12g	31.25	16	4	>500	4	4	8	4	16
12h	31.25	8	1	>500	2	2	4	2	4
Ciprofloxacin	<5	<5	≤1	≤1	≤1	>5	–	–	–
Norfloxacin	<5	<5	≤1	≤1	≤1	>5	–	–	–

Table 1 continued

Compounds	MIC values (μg mL^{-1})								
	Gram-positive organisms			Gram-negative organisms			Yeasts		
	Sa	*Sf*	*Bs*	*Kp*	*Ec*	*Pa*	*Sc*	*Ct*	*An*
Fluconazole	–	–	–	–	–	–	≤1	≤1	≤1

MIC is expressed in μg mL^{-1}; Gram-positive bacteria: *Sa Staphylococcus aureus* ATCC 11632, *Sf Streptococcus faecalis* ATCC 14506, *Bs Bacillus subtilis* ATCC 60511; Gram-negative bacteria: *Kp K. pneumoniae* ATCC 10031, *Ec E. coli* ATCC 10536, *Pa P. aeruginosa* ATCC 10145; Yeasts: *Sc Saccharomyces cerevisiae* (ATCC 9763) and *Ct C. tropicalis* (ATCC 1369), mould: *An A. niger* (ATCC 6275)

against *E. coli* and *P. aeruginosa.* Compounds **12a–h** which have oxadiazole ring were more active than the starting compounds **11a–h**. Compounds **12c**, **12d**, **12f**, **12g** and **12h** which have electron-withdrawing substituents on phenyl ring were found to be the most active compounds against the tested bacteria. The majority of compounds exhibited good inhibitory activity against Gram-positive bacteria, moulds and yeasts than Gram-negative bacteria.

Antitubercular activity

The tested compounds (Scheme 1) showed activities against mycobacteria with MIC values ranging from 2 to 62.5 μg mL^{-1} (Table 2). Preliminary examination of the antimycobacterial activity revealed that compounds **8a–h**, containing the 1,3,4-oxadiazoline ring and acetyl group, showed better activity against *M. tuberculosis* $H_{37}Rv$ and compounds **4**, **8d** and **9** exhibited highest activity (MIC 2 μg mL^{-1}). The compounds **11a–h** and **12a–h** (Scheme 2) showed activities against mycobacteria with MIC values ranging from 1 to 8 μg mL^{-1} (Table 2). Compounds **12c**, **12d**, **12f** and **12g** showed antitubercular activity at MIC value of 2 μg mL^{-1}. Compound **12h** showed the highest activity at MIC value of 1 μg mL^{-1} when compared with first-line drug isoniazid (MIC = 0.25 μg mL^{-1}).

It is a well-known fact that the biological activity associated with the hydrazone compounds is attributed due to the presence of the active pharmacophore (–CONH–N=C–). Hence many hydrazone compounds **7** containing the active moiety (–CONH–N=C–) showed good antibacterial/antitubercular activities. The interesting observation is that the conversion of the (–CONH–N=C–) moiety in active compounds **7a–h**, into 1,3,4-oxadiazoles **8a–h**, strengthened their activities. The presence of electron-withdrawing groups on the aromatic ring increases the antibacterial and antitubercular activities as evidenced by compounds **8b–d**. Compounds **8b–d** and **8e–f** have the electron-withdrawing groups but compounds **8b–d** are more active than the compounds **8e–f** which indicates the fact that the electron-withdrawing halo group is more effective in improving the antibacterial and antitubercular activities than electron-withdrawing nitro group. The significant activity of compound **8d** may be attributed due to the presence of an additional electron-withdrawing group in it. Furthermore, the derivatives having 1,3,4-oxadiazoles **12a–h** have more pronounced antimycobacterial potency compared to its precursor compounds **11a–h** having (–CONH–NHCO–) moiety. The high bioactivity of compounds **12a–h** makes them suitable hits for additional in vitro and in vivo evaluations, to develop new antimycobacterial drugs with potential use in the treatment of tuberculosis.

Cytotoxic activity

Some compounds **4**, **5**, **6**, **11a–h** and **12a–h** were further examined for toxicity (IC_{50}) in mammalian Vero cell lines and A_{549} (lung adenocarcinoma) cell lines up to 62.5 μg mL^{-1} concentrations. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay and results are summarized in Table 2. Among the 13 derivatives tested, showed IC_{50} values ranging from 175.4 to 268.2 μM against mammalian Vero cell lines. All the compounds did not show significant activity against mammalian Vero cell line at concentrations <100 μM. Among the test compounds, 1,3,4-oxadiazole derivatives **12a–h** showed inferior toxicity with IC_{50} values of >250 μM against both mammalian Vero cell lines and A_{549} (lung adenocarcinoma) cell lines. A comparison of the substitution pattern on pyrrole nucleus demonstrated that 2,5-dimethyl substituted analogs were more cytotoxic than the 2,5-unsubstituted pyrrole analogs. These results are important as these compounds with their increased cytoliability are much attractive in the development of new chemical entities for the treatment of TB. This is primarily due to the fact that the disease is chronic by its nature, the therapy needs to be continued for at least about 1–2 years in most of the cases and the need for an agent with a high margin of safety becomes a primary concern. The IC_{50} for the compound **12h** was found to be 268.2 μM against the mammalian Vero cell lines tested.

Table 2 Cytotoxicity and antimycobacterial activities of pyrrole derivatives

Compounds	MIC values (μg mL^{-1}) *M. tuberculosis* $H_{37}Rv$	IC_{50} (μM)	
		MV cell lines[c]	A^{d}_{549}
2	62.5	NT	NT
3a	31.25	NT	NT
3b	31.25	NT	NT
3c	31.25	NT	NT
3d	31.25	NT	NT
4	2	261.2 ± 0.9	254 ± 0.9
5	4	160.1 ± 1.1	170 ± 0.7
6	4	172.5 ± 1.3	180 ± 0.5
7a	31.25	NT	NT
7b	16	NT	NT
7c	16	NT	NT
7d	16	NT	NT
7e	62.5	NT	NT
7f	62.5	NT	NT
7g	31.25	NT	NT
7h	31.25	NT	NT
8a	16	190.2 ± 1.2	198 ± 0.4
8b	8	200.6 ± 0.8	206 ± 1.3
8c	8	195.1 ± 0.7	195 ± 1.6
8d	2	220.5 ± ± 0.8	224 ± 0.7
8e	31.25	188.4 ± 1.2	197 ± 0.4
8f	31.25	175.4 ± 2.3	182 ± 2.1
8g	16	187.2 ± 1.7	190 ± 1.9
8h	16	175.4 ± 1.5	186 ± 0.9
9	2	230.1 ± 0.6	225 ± 1.3
11a	8	200.4 ± 0.7	215 ± 0.8
11b	8	198.2 ± 1.5	201 ± 0.7
11c	8	185.6 ± 1.2	201 ± 0.9
11d	8	182.3 ± 1.4	205 ± 1.3
11e	8	194.7 ± 1.3	203 ± 2.3
11f	8	190.1 ± 0.9	198 ± 2.2
11g	8	179.3 ± 0.9	185 ± 0.9
11h	8	196.2 ± 0.5	200 ± 0.7
12a	8	250.2 ± 0.7	256 ± 1.6
12b	8	258.2 ± 1.5	252 ± 1.3
12c	2	260.1 ± 1.6	264 ± 0.9
12d	2	266.2 ± 1.8	267 ± 0.4
12e	8	251.4 ± 1.6	256 ± 0.8
12f	2	257.6 ± 1.2	258 ± 0.4
12g	2	253.1 ± 1.9	256 ± 1.3
12h	1	268.2 ± 0.6	270 ± 1.6
Isoniazid	0.25	>450	>450

MIC is expressed in μg mL^{-1}; cytotoxicity is expressed as IC_{50}, is the concentration of compound, which is reduced by 50 % of the optical density of treated cells with respect to untreated cells using the MTT assay; A_{549} (lung adenocarcinoma) cell lines

MV Mammalian Vero, *NT* not tested

Conclusion

The synthesis of novel pyrrole derivatives were described, which were also evaluated for their preliminary in vitro antibacterial, antifungal and antitubercular activities against *M. tuberculosis* $H_{37}Rv$ strain by broth dilution assay method. Further, some title compounds were also assessed for their cytotoxic activity (IC_{50}) against mammalian Vero cell lines and A_{549} (lung adenocarcinoma) cell lines using MTT assay method. The results indicated that these compounds exhibit antitubercular activity at non-cytotoxic concentrations. Due to the better activity against tested microorganisms and mycobacteria, compounds **4**, **8d**, **9** and **12h** have been selected for further development and studies to acquire more information about structure–activity relationships are in progress in our laboratories. In summary, we have identified a novel series of substituted pyrrole derivatives which may be developed into potential class of antitubercular and antimicrobial agents.

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