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Synthesis and evaluation of novel 4-nitropyrrole-based 1,3,4-oxadiazole derivatives as antimicrobial and anti-tubercular agents

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ABSTRACT

We report synthesis and antimicrobial evaluation of 42 novel 4-nitropyrrole-based 1,3,4-oxadiazoles. The synthesized molecules were evaluated for anti-bacterial, anti-fungal and anti-tubercular activities. Promisingly, most of the compounds showed equal or more potency than standard ciprofloxacin against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. Compound **5e** exhibited highest anti-tubercular activity (0.46 μg/mL) close to that of standard Isoniazid (0.40 μg/mL). Equal antifungal activity (1.56 μg/mL) compared to standard Amphotericin-B was shown by most of the compounds. All the N-methylated compounds showed more potent to equal activity against MSSA (MIC 0.39–1.56 μg/mL) and MRSA (MIC 0.78–1.56 μg/mL). All compounds were tested for mammalian cell toxicity using VERO cell line and were found to be non-toxic.

1. Introduction

1,3,4-Oxadiazole is an important class of heterocyclic bioactive compounds [1]. The widespread use of them as a scaffold in medicinal chemistry establishes this moiety as a member of the privileged structures. Differently substituted 1,3,4-oxadiazoles have been found to exhibit anti-inflammatory [2], hypoglycemic [3], anti-anxiety [4], antidepressant [5], anti-proliferative [6], anti-fungal [7,8], antibacterial [9] and anti-tubercular activities [10,11]. Moreover, 1,3,4-oxadiazole heterocycles are very good bioisosteres of amides and esters, which contribute substantially to increasing pharmacological activity by participating in hydrogen bonding interactions with the receptors.

Natural nitropyrroles are the metabolites of bacterium *Actinosporangium vitaminophilium*, [12] and *Streptomyces* sp. [13]. Recently nitropyrrole-based natural products and their derivatives are reported for having potential antimicrobial activities [13–16]. For instance, N-substituted pyrrolomycin, a compound with 4-nitropyrrole moiety have shown antifungal activity better than clotrimazole [17], while anti-tubercular activity was reported for pyrrolonitrins [18]. Anti-malarial and antimicrobial properties were reported for 4-nitropyrrol-2-carboxaldehyde derivatives by Colwell et al. [19]. Krajewska and Midura-Nowaczek [20] synthesized and tested 4-nitropyrrole based-chloramphenicol derivative for their antibacterial properties, where MIC of 0.8 μg/mL was reported against *Staphylococcus aureus* (ATCC 12600). Etoposide analogs of 4-nitropyrrole are reported to have potent anti-tumor activity inhibiting DNA Topoisomerase II [21]. The antifungal and antibacterial properties of 1,2,4-triazoles substituted with 4-nitropyrrole scaffold was reported by Pourmorad and Shafiee [22] (Fig. 1). Based on the observations, an attempt to design a series of novel antimicrobial molecules by coupling 1,3,4-oxadiazole with 4-nitropyrrole moiety using molecular hybridization approach has been put forward. We synthesized 4-nitropyrrole based 1,3,4-oxadiazoles containing diverse set of aromatic and hetero-aromatic substitutions and evaluated them for their anti-bacterial, antifungal and anti-tubercular activities. Further we also evaluated effect of N-methylation on antimicrobial and anti-tubercular activity (Fig. 2).

2. Results and discussions

2.1. Chemistry

In the present work, the proposed molecules were synthesized as shown in Scheme 1. Acetylation of pyrrole was done using calculated amounts of trichloroacetyl chloride in diethyl ether as

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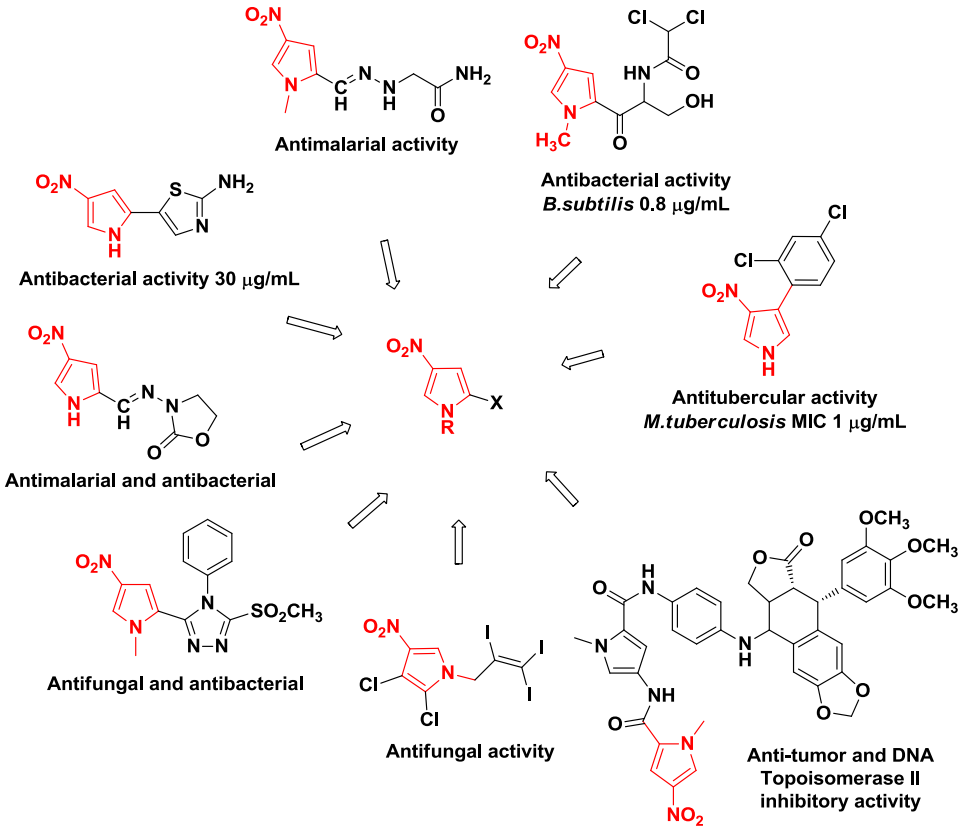


Fig. 1. Literature reports on nitropyrrole containing molecules [12–22].

solvent. Addition of pyrrole to trichloroacetyl chloride was done slowly over a period of 1–2 h using a dropping funnel. After the complete addition of pyrrole, the solvent was evaporated using rotary evaporator and the product was dried [11,23,24]. The formed acetylated pyrrole was nitrated using fuming nitric acid in acetic anhydride at ice-cold temperatures to give good yield of 4-nitro-2-trichloroacetyl-1*H*-pyrrole [25–27]. The nitrated product was converted to its hydrazide by treating with excess hydrazine hydrate in absolute alcohol and stirred for an hour to give 4-nitro-1*H*-pyrrole-2-carbohydrazide [11,24]. The obtained carbohydrazide when reacted with aromatic or heteroaromatic acids, in the presence of phosphorous oxychloride under reflux conditions, gave the final required compound 2-(4-nitro-1*H*-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole [11]. Using N-methylpyrrole the same reaction procedure was carried out to give 2-(4-nitro-1-methyl-pyrrole-2-yl)-5-aryl-1,3,4-oxadizoles.

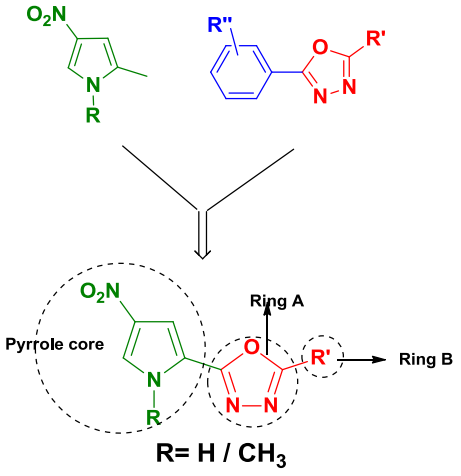
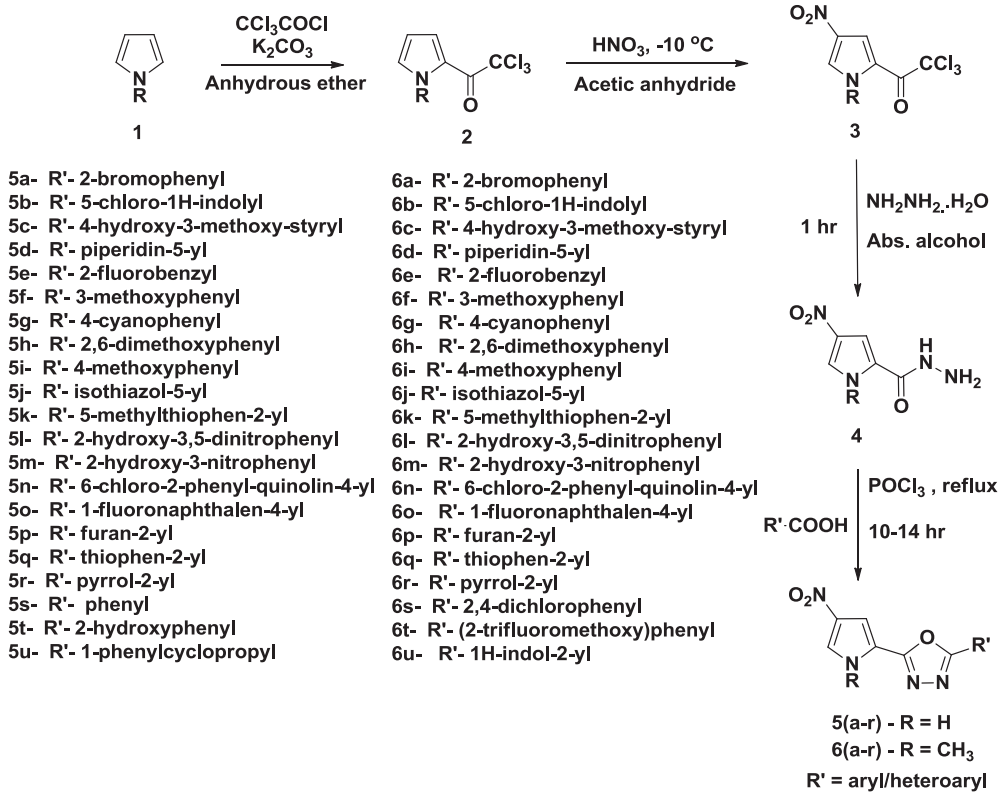


Fig. 2. Design of 4-nitropyrrole-based 1,3,4-oxadiazoles using molecular hybridization approach.

The synthesized compounds were characterized by ^{1}H NMR, MS, ^{13}C NMR and IR whose results confirmed the proposed structures of the synthesized molecules. The (M + H)+ molecular ion peak of all the compounds confirmed the respective molecular weights. In ^{1}H NMR spectra, the NH proton of pyrrole showed peak in the range of δ 13.6–13.3 ppm, while the N–CH_3 protons resonated between δ 4.2–4.0 ppm. The aryl protons of the ring B resonated between δ 9-6 ppm. IR spectroscopy showed a peak ranging between 3130 and 3142 cm^{-1} confirming the NH stretch and nitro group gave two sharp peaks at around 1498–1541 cm^{-1} and 1393–1414 cm^{-1}. The C=N stretch of oxadiazole ring was observed between 1620 and 1635 cm^{-1}.

2.2. Biological activity result

The synthesized molecules exhibited promising and encouraging antibacterial, antifungal and anti-tubercular activities (Table 1). Most of the compounds showed a broad spectrum of activity against both gram-positive and gram-negative bacterial strains. All the tested molecules showed moderate to high potency compared to standard ciprofloxacin against gram-positive bacterium *S. aureus* except **5c** and **5s**. Compounds **5p**, **5r** and **5u** exhibited two-fold activity (0.78 μg/mL) more than the standard ciprofloxacin. This indicated that presence of substituted phenyl ring and heterocyclic ring at ring B position is favorable and increasing the distance between ring A and ring B is unfavorable for activity against *S. aureus*. All the N-methylated compounds showed two to three fold potent



Scheme 1. Synthesis of 2-(4-nitro-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole derivatives.

activity (MIC range 0.78 μg/mL–0.39 μg/mL) against *S. aureus* than standard ciprofloxacin (MIC-1.56 μg/mL) indicating presence of N-methyl group on pyrrole enhances the activity compared to their NH free analogs. Three-fold superior activity was observed for compounds **6b**, **6n**, **6r** and **6s** (MIC 0.39 μg/mL) against *S. aureus* revealing that presence of halogen atoms like chlorine and presence of heterocyclic ring plays important role for activity against *S. aureus*. Heterocyclic substitution containing halogen like chlorine at ring B position is favorable for the activity against *S. aureus* (**6b**, **6n**, **6r** and **6s**). Compounds **6a**, **6c**–**m**, **6o**–**q**, **6t** and **6u** (0.78 μg/mL) exhibited two-fold superior activity than standard ciprofloxacin (MIC 1.56 μg/mL). The NH free analogs **5a**, **5b**, **5d**–**o**, **5q** and **5t** (MIC 1.56 μg/mL) showed equal potency as that of standard ciprofloxacin (MIC 1.56 μg/mL).

All the N-methylpyrrole containing analogs have shown potent or equal (MIC range 0.78 μg/mL–1.56 μg/mL) against *B. subtilis* compared to standard ciprofloxacin (MIC 1.56 μg/mL). However their NH free analogs showed two fold less potency than standard ciprofloxacin except compounds **5a**, **5e**, **5p**, **5q** and **5r** (MIC 1.56 μg/mL). Compounds **6a**, **6e**, **6r** and **6s** (MIC 0.78 μg/mL) were found to be two time more potent than standard indicating that the presence of halogen atoms like bromine, chlorine and fluorine on ring B is beneficial for activity against *Bacillus subtilis*. Compound **6e** showed two-fold activity against *B. subtilis* compared to standard ciprofloxacin indicating that presence of methyl linker between ring A and ring B is favorable for activity. Compounds **5a**, **5e** and **5r** (MIC 1.56 μg/mL) exhibited equal anti- *B. subtilis* activity compared to standard ciprofloxacin. But when compared with their N-methylated analogs, the activity was found to be lesser indicating that protection of nitrogen in pyrrole core with methyl group is favorable for activity against *B. subtilis*.

For activity against gram-negative bacterium *E. coli*, highest activity was shown by compounds **6l** and **6n** (MIC values 0.39 μg/mL) with three fold potency than standard ciprofloxacin (MIC 1.56 μg/mL) followed by compounds **5n** and **5r** (0.78 μg/mL) which exhibited two fold superior potency. This indicated that presence of heterocyclic rings or hydroxyl and nitro containing phenyl ring at ring B position lead to improvement of activity against gram-negative bacterium *Escherichia coli*. Compounds **5a**, **5b**, **5e**, **5q**, **5t**, **5u**, **6a**, **6b**, **6e**, **6r** and **6s** showed equivalent activity (MIC 1.56 μg/mL) as that of standard ciprofloxacin against *E. coli*. Presence of halogens like fluorine and chlorine at phenyl ring are proved to be important for antibacterial activity against *E. coli*. Here analogous to above observation, the protection of pyrrole nitrogen by methyl group was found to have profound effect on the anti-bacterial activity. Two-fold less activity against *E. coli* were shown by compounds **5c**, **5d**, **5f**, **5g**, **5h**, **5l**, **5o**, **5p**, **6c**, **6d**, **6f**, **6m**, **6p** and **6t** (MIC 3.125 μg/mL) compared to standard ciprofloxacin. The decrease in activity of compounds **5c** and **6c** against *E. coli* compared to standard ciprofloxacin indicates the presence of linker between ring A and ring B is unfavorable for the activity. All compounds tested against *Klebsiella pneumoniae* were found to be less active than standard ciprofloxacin (MIC 1.56 μg/mL) with MIC values ranging between 12.5 μg/mL – 100 μg/mL. Compounds **6a**–**o** and **6r**–**u** (MIC 12.5 μg/mL), except **6c, 6p** and **6q** (MIC 50 μg/mL) showed better activity than their NH free pyrrole core indicating N-methylation of pyrrole core played an important role in enhancing the antimicrobial activity against *K. pneumoniae*.

The synthesized compounds when tested against *Methicillin Susceptible S. aureus* (MSSA) showed good activity when compared with Ciprofloxacin. All the N-methylated compounds **6a**–**d**, **6f**–**j**, **6m**–**o** and **6r**–**u** showed two fold potent activity (MIC 0.39 μg/mL) than the standard Ciprofloxacin (MIC = 1.56 μg/mL). Equivalent activity (MIC 1.56 μg/mL) as standard was observed in all the NH-free pyrrole compounds, except **5q** (MIC 3.125 μg/mL) and N-methylated compounds **6e**, **6k**, **6l**, **6p** and **6q** (MIC 1.56 μg/mL). The

Table 1
Antimicrobial results (MIC in μg/mL) of synthesized 4-nitropyrrole-based 1,3,4-oxadiazoles.

Compound	*S. aureus*[a]	*B. subtilis*[a]	*E. coli*[a]	*K. pneumoniae*[a]	MSSA	MRSA	*C. albicans*[b]	Antitubercular activity[c]	IC_{50} (μM)[d]
5a	1.56	1.56	1.56	25	1.56	3.125	3.125	0.81	190.4
5b	1.56	3.125	1.56	25	1.56	3.125	3.125	3.4	329.1
5c	3.125	3.125	3.125	100	1.56	3.125	25	23.7	220.5
5d	1.56	3.125	3.125	25	1.56	3.125	3.125	12.5	317.8
5e	1.56	1.56	1.56	25	1.56	3.125	3.125	0.46	620.1
5f	1.56	3.125	3.125	25	1.56	3.125	3.125	13.5	429.2
5g	1.56	3.125	3.125	25	1.56	3.125	3.125	26.8	198.6
5h	1.56	3.125	3.125	25	1.56	3.125	3.125	5.4	170.0
5i	1.56	3.125	6.25	25	1.56	3.125	3.125	34.0	409.2
5j	1.56	3.125	6.25	25	1.56	3.125	3.125	62.7	532.4
5k	1.56	3.125	6.25	25	1.56	3.125	3.125	–	328.9
5l	1.56	3.125	3.125	25	1.56	3.125	3.125	0.72	279.1
5m	1.56	3.125	6.25	25	1.56	3.125	3.125	1.8	498.5
5n	1.56	3.125	0.78	25	1.56	3.125	1.56	97.2	281.2
5o	1.56	3.125	3.125	25	1.56	3.125	3.125	64.8	229.3
5p	0.78	1.56	3.125	25	1.56	3.125	3.125	42.8	369.5
5q	1.56	1.56	1.56	25	3.125	3.125	6.25	87.1	418.2
5r	0.78	1.56	0.78	12.5	1.56	1.56	1.56	15.7	226.5
5s	3.125	3.125	6.25	25	1.56	3.125	12.5	56.3	423.3
5t	1.56	3.125	1.56	25	1.56	3.125	3.125	2.1	374.7
5u	0.78	3.125	1.56	25	1.56	3.125	25	56.8	380.3
6a	0.78	0.78	1.56	12.5	0.39	1.56	1.56	12.8	302.8
6b	0.39	1.56	1.56	12.5	0.39	1.56	1.56	24.0	743.0
6c	0.78	1.56	3.125	50	0.39	1.56	12.5	51.8	202.5
6d	0.78	1.56	3.125	12.5	0.39	1.56	1.56	35.6	611.2
6e	0.78	0.78	1.56	12.5	1.56	1.56	1.56	8.6	244.6
6f	0.78	1.56	3.125	12.5	0.39	1.56	1.56	37.4	298.9
6g	0.78	1.56	6.25	12.5	0.39	1.56	1.56	84.6	314.6
6h	0.78	1.56	6.25	12.5	0.39	1.56	1.56	32.0	177.4
6i	0.78	1.56	6.25	12.5	0.39	1.56	1.56	–	281.1
6j	0.78	1.56	6.25	12.5	0.39	1.56	1.56	–	319.5
6k	0.78	1.56	6.25	12.5	1.56	1.56	1.56	–	98.3
6l	0.78	1.56	0.39	12.5	1.56	1.56	1.56	2.6	169.6
6m	0.78	1.56	3.125	12.5	0.39	1.56	1.56	–	269.0
6n	0.39	1.56	0.39	12.5	0.39	1.56	0.78	–	327.5
6o	0.78	1.56	6.25	12.5	0.39	1.56	1.56	–	119.2
6p	0.78	1.56	3.125	50	1.56	1.56	1.56	60.2	190.5
6q	0.78	1.56	6.25	50	1.56	1.56	1.56	–	520.8
6r	0.39	0.78	1.56	12.5	0.39	0.78	0.78	29.3	208.3
6s	0.39	0.78	1.56	12.5	0.39	0.78	1.56	18.4	387.1
6t	0.78	1.56	3.125	12.5	0.39	1.56	1.56	3.8	308.0
6u	0.78	1.56	6.25	12.5	0.39	1.56	1.56	–	109.4
Standard[e]	1.56	1.56	1.56	1.56	1.56	3.125	3.125	0.40	NT

[a] MIC values are determined by broth dilution method (two fold dilution).
[b] MIC values are determined by agar dilution method (two fold dilution).
[c] MIC values are determined by Resazurin micro titer assay (REMA).
[d] Cytotoxic concentration of drugs in VERO cells; NT, not tested.
[e] Standard – Ciprofloxacin for antibacterial, Ampotericin-B for antifungal and Isoniazid for anti-tubercular activities were used respectively.

synthesized compounds showed potent to equal activity when tested against *Methicillin Resistant Staphylococcus aureus* (MRSA) strain with MIC ranging from 0.78 μg/mL to 3.125 μg/mL. Compounds **6r** and **6s** (MIC 0.78 μg/mL) were found to be most potent with 2-fold activity than the standard Ciprofloxacin (MIC 3.125 μg/mL). This strengthens the fact that N-methylation is favorable towards activity against *Staphylococcus aureus*.

In the anti-fungal study, all the N-methylated compounds, other than compound **6c** (MIC 12.5 μg/mL), showed two to three-fold more potent activity (MIC range 0.78–1.56 μg/mL) against *C. ablicans* than standard drug Amphotericin-B (MIC 3.125 μg/mL). Compounds **6n** and **6r** exhibited three-fold superior activity (MIC 0.78 μg/mL) than standard Amphortericin-B. This strengthens the fact that the heterocyclic substitutions at ring B position proved to be important for the activity. All the N-methyl pyrrole compounds **6a**, **6b**, **6d**–**m**, **6o**–**q**, **6s**–**u** and NH-free pyrrole compounds **5n** and **5r** showed (MIC - 1.56 μg/mL) two-fold better activity than standard Amphotericin-B (MIC 3.125 μg/mL). Compounds **5a**, **5b**, **5d**–**m**, **5o**, **5p** and **5t** showed antifungal activity equivalent to standard Amphotericin-B (MIC 3.125 μg/mL). This indicated that N-methylation of pyrrole core is favorable for activity against *Candida albicans*. Overall strong antibacterial and antifungal spectrum shown by compounds **6n** and **6r** indicated that the presence of heterocyclic moieties at ring B position and N-methylation of pyrrole core is important for the antimicrobial activity.

Most of the compounds showed moderate to good activity against *Mycobacterium tuberculosis* (MIC range 0.46 μg/mL–97.2 μg/mL) compared to the standard Isoniazid (MIC 0.40 μg/mL). Compound **5e** (MIC 0.46 μg/mL) showed highest anti-tubercular activity close to standard Isoniazid (MIC 0.40 μg/mL). The presence of halogen atom, fluorine, and a methyl linker between ring A and ring B is strongly favored for anti-tubercular activity. Whereas the N-methyl analog **6e**, containing same substitution, showed comparatively less activity (MIC 8.6 μg/mL) indicating that the methylation of nitrogen on pyrrole core is not favored for anti-tubercular activity. Compound **5l** (MIC 0.72 μg/mL) showed promising tubercular activity which can be attributed to the presence of two nitro substitution on phenyl ring. Compound **5a** also

exhibited promising anti-tubercular activity (MIC 0.81 μg/mL) strengthening the fact that presence of halogen at second position of phenyl ring is favored for the activity. Among the halogen substitutions, fluorine substituted compound showed better anti-tubercular activity compared to that substituted with bromine. Corresponding N-methylated analogs exhibited less anti-tubercular potency than their N–H free analogs. This gives an insight that the N-methylation of pyrrole core is not favored for anti-tubercular activity. Good anti-tubercular activity with MIC less than 3.0 μg/mL were shown by compounds **5m** (MIC 1.8 μg/mL), **5t** (MIC 2.1 μg/mL) and **6l** (MIC 2.6 μg/mL). Overall this study gave us a glimpse that the presence of heterocyclic moieties like quinoline or pyrrole and N-methylation of pyrrole core is favorable for anti-bacterial and antifungal studies whereas presence of methyl linkers between ring A and ring B and N–H free pyrrole core is strongly favorable for the anti-tubercular activity.

All the compounds were further examined for toxicity (IC_{50}) in a mammalian VERO cell line at a concentration of 62.5 μg/mL. After 72 h 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 [33]. The compounds were non-toxic as represented in Table 1 and their mammalian cell cytotoxicity was found to be much higher than their respective MICs.

The structure activity relational studies gives us a glimpse that the N-alkylation of pyrrole core has shown better activity in terms of antibacterial and antifungal activity and also against MSSA and MRSA strains. But NH-free pyrrole has shown better activity when tested against *M. tuberculosis*. The presence of substitutions like halogens and heterocyclic substitutions helps to improved anti-microbial activity profiles.

3. Conclusion

The synthesized nitropyrrole containing 1,3,4-oxadiazoles were tested for their antimicrobial and anti-tubercular activity. These compounds showed promising antibacterial activity against *S. aureus, B. subtilis*, *E. coli, MRSA* and *MSSA*. Highest anti-tubercular activity was showed by compound **5e** (0.46 μg/mL). Anti-tubercular MIC values as low as 0.46 μg/mL, 0.72 μg/mL 0.81 μg/mL and 1.8 μg/mL for compounds **5e**, **5l**, **5a** and **5m** respectively indicated that these can act as novel leads for development of newer anti-tubercular drugs. Equal antifungal activity compared to standard Amphotericin-B was shown by compounds **5n**, **5r**, **6a**, **6b**, **6d–m**, **6o–q** and **6s–u** (1.56 μg/mL). The promising antibacterial, antifungal and anti-tubercular results of the synthesized nitropyrrole-based oxadiazoles including their non-toxicity for mammalian cell have indicated their potential for further exploration and modifications to get newer antimicrobial drug with better spectrum and potency.

4. Experimental protocol

4.1. General

All reactions were carried out under an inert nitrogen atmosphere under anhydrous conditions and by using Molecular sieve (4 Å 1/16″ pellets), Ethanol, methanol, n-hexane, ethylacetate and ACN were freshly distilled from $CaCl_2$. All chromatographic solvents were distilled before use. Silica gel of 60–120 mesh and 200–400 mesh were obtained for column and flash chromatography. Some of the starting materials were obtained from S.D. Fine Pvt. Ltd., SRL, Spectrochem/Aldrich and some of them were prepared in laboratory and used without further purification. All Melting Points (MP) were recorded on Thermomik Compbell electronics, having oil-heating system and were uncorrected. Analytical Thin Layer Chromatography (TLC) was carried out on precoated plates SiO_2 (silica gel 60, F 254, Merck). FTIR spectra were recorded on Perkin Elmer RX I spectrometer using KBr pellets. All the NMR spectra were recorded on JEOL AL-300 FT-NMR spectrometer with DMSO-d_6 as solvent using Tetramethyl Silane (TMS) as internal reference. Mass spectra were obtained on THERMO FINNINGAN LCQ advantage max (LCMS).

4.2. General procedure for synthesis of 2-pyrrolyl trichloromethyl ketone *2a* & *2b*

The desired compound was synthesized as given in the literature procedure [11,23,24].

4.3. General procedure for synthesis of 2,2,2-trichloro-1-(4-nitro-1H-pyrrol-2-yl)ethanone *3a* & 2,2,2-trichloro-1-(1-methyl-4-nitro-pyrrol-2-yl)ethanone *3b*: [25–27]

The reaction was carried out using the by dissolving appropriate amounts (1 equiv) of **2a** or **2b** in acetic anhydride. The solution was cooled to −10 °C using ice-salt mixture. Calculated amount of fuming nitric acid (1.2 equiv) was added to the reaction mixture dropwise, slowly over a period of 1 h. The reaction was then stirred for another 2 h in icebath, later removed and stirred for an hour at room temperature. The completion of reaction was monitored through TLC. The reaction mixture was poured over crushed ice and allowed to precipitate. The precipitate was filter through vacuum and the product was recrystallized using absolute alcohol or methanol.

2,2,2-Trichloro-1-(4-nitro-1H-pyrrol-2-yl) ethanone **3a**: M.P 177–178 °C.

2,2,2-Trichloro-1-(1-methyl-4-nitro-pyrrol-2-yl) ethanone **3b**: M.P.136–138 °C.

4.4. General procedure for synthesis of 4-nitro-1H-pyrrole-2-carbohydrazide *4a* and 4-nitro-1-methyl-pyrrole-2-carbohydrazide *4b*: [11,24]

In a round bottom flask, equipped with sealed mechanical stirrer, 1 mol of trichloroethanone **3a** or **3b** derivative was added in 30 mL of ethanol and stirred until the entire solution becomes homogeneous. To above mixture 2.5 equivalents (3–4 mL) Hydrazine hydrate (99 %v/v) was added and stirred at room temperature till precipitate starts to appear. The whole reaction mixture was poured over crushed ice. The obtained solid precipitate was filtered by vacuum and dried. The precipitate was washed with hexane and recrystallized from absolute alcohol.

4-Nitro-1H-pyrrole-2-carbohydrazide **4a**: Yield: 67–69%; M.P.: 275.5–277 °C.

1-methyl-4-nitro-pyrrole-2-carbohydrazide **4b**: Yield: 61–63%; M.P.: 220–221 °C.

4.5. General procedure for synthesis of 2-(4-nitro-1H-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole *5(a–r)* & 2-(1-methyl-4-nitro-pyrrol-2-yl)-5-aryl-1,3,4-oxadiazole *6(a–r)* analogs: [11]

The target compounds were synthesized using the procedure given in literature by refluxing aryl/heteroaryl acids with carbohydrazide **4a** or **4b** in phosphorous oxychloride. The reaction was monitored with the help of TLC to check its completion. After completion of reaction, the mixture was poured over crushed ice and allowed to precipitate. The precipitate was vacuum filtered, dried and recrystallized from methanol. Column chromatography was done on using n-hexane: ethylacetate mixture (7:3). Solvent

was evaporated invacuo using rotary evaporator to obtain pure product.

*4.5.1. 2-(2-Bromophenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5a**)*

Yield: 87%; M.P: 319–321 °C; IR (KBr) V_{max} cm^{-1}: 3135.65 (N–H), 1632.97 (C=N), 1540.85 & 1396.29 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.6 (s, 1H, Pyrrole NH), 7.92 (s, 1H, Pyrrole H_5), 7.88–7.65 (m, 4H, Aryl), 7.42 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.57, 162.29, 136.11, 134.43, 131.81, 129.55, 129.08, 127.97, 123.88, 121.11, 111.85; Exact mass: 333.9702; MS *m*/*z*: 334.1273 (M + H)+, 304.1711 (M + H − NO), 288.1157 (M + H − NO_2).

*4.5.2. 2-(5-Chloro-1H-indol-2-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5b**)*

Yield: 63%; M.P.: 289–290 °C; IR (KBr) V_{max} cm^{-1}: 3130.21 (N–H), 1629.98 (C=N), 1541.11 & 1397.58 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.52 (s, 1H, Pyrrole NH), 9.15 (s, 1H, Indole NH), 8.15 (s, 1H, Pyrrole H_5), 7.77–7.21 (m, 4H, indolyl), 7.43 (s, 1H, Pyrrole H_3), 6.97 (s, 1H, indol); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 135.5, 135.1, 130.6, 129.6, 125.2, 124.1, 122.9, 121.6, 114.3, 112.3, 104.6, 100.2; Exact mass: 329.2952; MS *m*/*z*: 330.3032 (M + H)+, 300.2971 (M + H − NO), 284.2977 (M + H − NO_2).

*4.5.3. 2-(4-Hydroxy-3-methoxy-styryl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5c**)*

Yield: 47%; M.P.: 280–282 °C; IR (KBr) V_{max} cm^{-1}: 3135.12 (N–H), 1629.06 (C=N), 1539.67 & 1399.63 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.40 (s, 1H, Pyrrole NH), 7.93 (s, 1H, Pyrrole H_5), 7.69–7.54 (m, 3H, Aryl), 7.39 (s, 1H, Pyrrole H_3), 6.65–6.83 (d, 2H, CH=CH), 6.21 (s, 1H, OH)3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 160.9, 149.3, 147,7, 135.4, 133.9, 130.8, 130.2, 124.6, 122.3, 112.4, 116.4, 109.6, 104.2, 56.1; Exact mass: 328.0808; MS *m*/*z*: 329.1792 (M + H)+, 299.7234 (M + H − NO), 283.7240 (M + H − NO_2).

*4.5.4. 2-(Piperidin-5-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5d**)*

Yield: 28%; M.P.: 275–277 °C; IR (KBr) V_{max} cm^{-1}: 3134.88 (N–H), 1628.23 (C=N), 1540.49 & 1399.45 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.38 (s, 1H, Pyrrole NH), 7.98 (s, 1H, Pyrrole H_5), 7.42 (s, 1H, Pyrrole H_3), 3.15–2.42 (m, 4H, piperidinyl), 1.68–1.41 (m, 4H, piperidinyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 164.7, 135.4, 130.6, 112.3, 104.9, 52.6, 48.2, 36.5, 30.8, 25.3; Exact mass: 263.1092; MS *m*/*z*: 264.8651 (M + H)+, 234.7096 (M + H − NO), 218.1108 (M + H − NO_2).

*4.5.5. 2-(2-fluorobenzyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5e**)*

Yield: 56%; M.P.: 194–196 °C; IR (KBr) V_{max} cm^{-1}: 3136.10 (N–H), 1630.01 (C=N), 1540.97 & 1399.43 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.45 (s, 1H, Pyrrole NH), 8.10 (s, 1H, Pyrrole H_5), 7.78–7.62 (m, 4H, Ar–H), 7.38 (s, 1H, Pyrrole H_3), 2.54 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 164.8, 161.3, 135.9, 130.9, 130.3, 127.5, 124.3, 124, 115.3, 112.6, 104.9, 24.2; Exact mass: 287.2055; MS *m*/*z*: 288.0692 (M + H)+, 258.9013 (M + H − NO), 242.9665 (M + H − NO_2).

*4.5.6. 2-(3-Methoxyphenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5f**)*

Yield: 65%; M.P.: 273–275 °C; IR (KBr) V_{max} cm^{-1}: 3136.90 (N–H), 1628.73 (C=N), 1537.78 & 1393.45 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.52 (s, 1H, Pyrrole NH), 7.92 (s, 1H, Pyrrole H_5), 7.92–7.74 (dd, 4H, Ar–H), 7.45 (s, 1H, Pyrrole H_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 161.2, 135.6, 130.9, 130, 127.3, 119.4, 114.9, 112.4, 111.4, 104.5, 55.3; Exact mass: 286.0707; MS *m*/*z*: 287.4092 (M + H)+, 257.4458 (M + H − NO), 241.4905 (M + H − NO_2).

*4.5.7. 2-(4-Cyanophenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5g**)*

Yield: 59%; M.P.: 262–264 °C; IR (KBr) V_{max} cm^{-1}: 3136.74 (N–H), 1630.04 (C=N), 1537.07 & 1391.61 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.42 (s, 1H, Pyrrole NH), 8.12 (s, 1H, Pyrrole H_5), 7.82–7.54 (m, 4H, Aryl), 7.42 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 135.6, 132.9, 130.8, 130.1, 128.4, 118.2, 112.4, 112.1, 104.7; Exact mass: 281.0599; MS *m*/*z*: 282.8103 (M + H)+, 252.7114 (M + H − NO), 236.1332 (M + H − NO_2).

*4.5.8. 2-(2,6-Dimethoxyphenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5h**)*

Yield: 81%; M.P.: 284–286 °C; IR (KBr) V_{max} cm^{-1}: 3136.41 (N–H), 1623.43 (C=N), 1510.78 & 1395.12 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.50 (s, 1H, Pyrrole NH), 8.20 (s, 1H, Pyrrole H_5), 7.71–7.62 (d, 3H, Ar–H), 7.35 (s, 1H, Pyrrole H_3), 3.84–3.77 (2s, 6H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 158.9, 135.6, 130.2, 130, 112.5, 108.1, 107.6, 104.1, 56.3; Exact mass: 316.0808; MS *m*/*z*: 317.1086 (M + H)+, 287.5910 (M + H − NO), 271.3305 (M + H − NO_2).

*4.5.9. 2-(4-Methoxyphenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5i**)*

Yield: 77%; M.P.: 340–342 °C; IR (KBr) V_{max} cm^{-1}: 3134.66 (N–H), 1626.30 (C=N), 1498.35 & 1396.65 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.45 (s, 1H, Pyrrole NH), 8.15 (s, 1H, Pyrrole H_5), 7.87–7.71 (dd, 4H, Ar–H), 7.36 (s, 1H, Pyrrole H_3), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.2, 135.2, 130.9, 129.2, 115.4, 114.6, 112.3, 104.5, 55.2; Exact mass: 286.0277; MS *m*/*z*: 287.3058 (M + H)+, 257.4401 (M + H − NO), 241.5083 (M + H − NO_2).

*4.5.10. 2-(Isothiazol-5-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5j**)*

Yield: 61%; M.P.: 190–192 °C; IR (KBr) V_{max} cm^{-1}: 3134.06 (N–H), 1628.40 (C=N), 1503.06 & 1396.07 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.51 (s, 1H, Pyrrole NH), 8.05 (s, 1H, Pyrrole H_5), 6.89–6.75 (d, 2H, Thiazole), 7.43 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 161.2, 157.9, 147.2, 135.6, 130.2, 120.9, 104.6, 112.5; Exact mass: 263.0133; MS *m*/*z*: 264.1088 (M + H)+, 234.9213 (M + H − NO), 218.0801 (M + H − NO_2).

*4.5.11. 2-(5-Methylthiophen-2-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5k**)*

Yield: 55%; M.P.: 320–322 °C; IR (KBr) V_{max} cm^{-1}: 3136.44 (N–H), 1630.98 (C=N), 1515.90 & 1395.98 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.35 (s, 1H, Pyrrole NH), 7.98 (s, 1H, Pyrrole H_5), 7.45 (s, 1H, Pyrrole H_3), 6.73 (d, 2H, Thiophen), 2.85 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 161.2, 135.6, 134.7, 130.5, 129.2, 127.8, 127.1, 112.3, 104.5, 15.3; Exact mass: 276.7031; MS *m*/*z*: 277.4982 (M + H)+, 247.4095 (M + H − NO), 231.6960 (M + H − NO_2).

*4.5.12. 2-(2-Hydroxy-3,5-dinitrophenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5l**)*

Yield: 70%; M.P.: 250–252 °C; IR (KBr) V_{max} cm^{-1}: 3132.58 (N–H), 1620.14 (C=N), 1528.29 & 1398.16 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.58 (s, 1H, Pyrrole NH), 8.8–8.6 (d, 2H, Ar–H), 8.16 (s, 1H, Pyrrole H_5), 7.38 (s, 1H, Pyrrole H_3), 6.28 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 164.5, 157.3, 141.6, 138.2, 135.1, 130.6, 130.1, 122.6, 113.6, 112.3, 112.7; Exact mass: 362.0244; MS *m*/*z*:

363.9177 (M + H)+, 333.8011 (M + H − NO), 317.5119 (M + H − NO_2).

*4.5.13. 2-(2-Hydroxy-3-nitrophenyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5m**)*

Yield: 34%; M.P.: 268–270 °C; IR (KBr) V_{max} cm^{-1}: 3137.22 (N–H), 1628.62 (C=N), 1525.60 & 1398.93 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.40 (s, 1H, Pyrrole NH), 8.16 (s, 1H, Pyrrole H_5), 8.0–7.9 (d, 2H, Ar–H), 7.41 (s, 1H, Pyrrole H_3), 6.82 (s, 1H, Ar–H), 6.25 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 164.6, 150.8, 144.2, 137.2, 135.1, 130.9, 128.6, 122.6, 113.1, 112.6, 104.1; Exact mass: 317.3069; MS *m*/*z*: 318.2144 (M + H)+, 288.5109 (M + H − NO), 272.7124 (M + H − NO_2).

*4.5.14. 2-(6-Chloro-2-phenyl-quinolin-4-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5n**)*

Yield: 49%; M.P.: 306–308 °C; IR (KBr) V_{max} cm^{-1}: 3142.42 (N–H), 1624.97 (C=N), 1530.17 & 1383.92 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.5 (s, 1H, Pyrrole NH), 9.23 (s, 1H, quinoline H_8), 8.21 (s, 1H, Pyrrole H_5), 8.28–7.75 (m, 4H, Quinolin), 7.67–7.51 (m, 5H, Phenyl), 7.39 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 156.3, 143.2, 143, 139.2, 135.6, 135.1, 130.9, 130.4, 129.6, 127.9, 127.2, 127, 120.6, 112.3, 104.5, 104; Exact mass: 417.0699; MS *m*/*z*: 418.6911 (M + H)+, 388.4053 (M + H − NO), 372.8401 (M + H − NO_2).

*4.5.15. 2-((1-Fluoronaphthalen-4-yl)methyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5o**)*

Yield: 45%; M.P.: 228–230 °C; IR (KBr) V_{max} cm^{-1}: 3137.01 (N–H), 1633.63 (C=N), 1506.24 & 1399.01 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.39 (s, 1H, Pyrrole NH), 8.15 (s, 1H, Pyrrole H_5), 8.14–7.49 (m, 6H, napthalene), 7.34 (s, 1H, Pyrrole H_3), 4.12 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 156.5, 143.8, 143.5, 139.1, 135.6, 131.6, 130.5, 129.1, 127.8, 127.5, 127.1, 123.6, 120.4, 112.1, 104.5, 104; Exact mass: 338.9001; MS *m*/*z*: 339.9081 (M + H)+, 308.9020 (M + H -NO), 292.9026 (M + H - NO_2).

*4.5.16. 2-(Furan-2-yl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5p**)*

Yield: 68%; M.P.: 242–244 °C; IR (KBr) V_{max} cm^{-1}: 3142.51 (N–H), 1630.99 (C=N), 1510.72 & 1395.18 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.48 (s, 1H, Pyrrole NH), 7.95 (s, 1H, Pyrrole H_5), 7.79–7.03 (m, 3H, furan), 7.31 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 157.2, 147.8, 138.3, 135.1, 130.2, 112.7, 104.8; Exact mass: 246.0389; MS *m*/*z*: 247.1189 (M + H)+, 217.9126 (M + H − NO), 201.8041 (M + H − NO_2).

*4.5.17. 2-(4-Nitro-1H-pyrrol-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (**5q**)*

Yield: 51%; M.P.: 276–278 °C; IR (KBr) V_{max} cm^{-1}: 3138.25 (N–H), 1621.14 (C=N), 1508.66 & 1399.07 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.41 (s, 1H, Pyrrole NH), 8.05 (s, 1H, Pyrrole H_5), 7.70–7.53 (m, 3H, thiophene), 7.28 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 161.7, 135.6, 132.9, 131.8, 128.6, 128.0, 112.9, 104.2; Exact mass: 262.0161; MS *m*/*z*: 263.2446 (M + H)+, 233.8071 (M + H − NO), 215.9106 (M + H − NO_2).

*4.5.18. 2-(4-Nitro-1H-pyrrol-2-yl)-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5r**)*

Yield: 70%; M.P.: 264–266 °C; IR (KBr) V_{max} cm^{-1}: 3131.69 (N–H), 1626.87 (C=N), 1516.52 & 1406.48 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.52 (s, 1H, NO_2-Pyrrole NH), 13.21 (s, 1H, pyrrole NH), 8.09 (s, 1H, Pyrrole H_5), 6.89–6.52 (m, 3H, pyrrole), 7.36 (s, 1H, Pyrrole H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9, 135.2, 130.5, 128.8, 120.2, 112.4, 106.8, 104.9; Exact mass: 245.0549; MS *m*/*z*: 246.0816 (M + H)+, 216.7135 (M + H − NO), 200.9103 (M + H − NO_2).

*4.5.19. 2-Phenyl-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5s**)*

Yield: 78%; M.P.: 309–310 °C; IR (KBr) V_{max} cm^{-1}: 3134.72 (N–H), 1628.33 (C=N), 1541.58 & 1398.98 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.5 (s, 1H, Pyrrole NH), 8.1 (s, 1H, Pyrrole H_5), 7.75–7.55 (m, 5H, Aryl), 7.4 (s, 1H, Pyrrole H_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 135.4, 133.7, 130.2, 129.2, 128.5, 127.4, 112.3, 104.7; Exact mass: 256.2217; MS *m*/*z*: 257.2296 (M + H)+, 227.2235 (M + H − NO), 211.2241 (M + H − NO_2).

*4.5.20. 2-(2-Hydroxyphenyl)-5-(4nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5t**)*

Yield: 73%; M.P.: 231–234 °C; IR (KBr) V_{max} cm^{-1}: 3136.26 (N–H), 1630.31 (C=N), 1539.21 & 1399.48 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.45 (s, 1H, Pyrrole NH), 8.12 (s, 1H, Pyrrole H_5), 7.98–7.73 (m, 4H, Aryl), 7.38 (s, 1H, Pyrrole H_3), 6.25 (s, OH, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 164.9, 157.4, 135.9, 130.6, 130, 126.4, 121.4, 117.9, 112.3, 108.9, 104.7; Exact mass: 272.0559; MS *m*/*z*: 273.2189 (M + H)+, 243.2128 (M + H − NO), 227.2134 (M + H − NO_2).

*4.5.21. 2-(1-Phenylcyclopropyl)-5-(4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**5u**)*

Yield: 51%; M.P.: 240–242 °C; IR (KBr) V_{max} cm^{-1}: 3136.89 (N–H), 1634.31 (C=N), 1512.01 & 1398.93 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 13.42 (s, 1H, Pyrrole NH), 8.20 (s, 1H, Pyrrole H_5), 7.41 (s, 1H, Pyrrole H_3), 7.45–7.15 (m, 5H, Ar–H), 1.10–0.95 (m, 4H, Cyclopropyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 163.3, 146.5, 135.6, 130.1, 128.1, 125.7, 125, 112.3, 104.7, 25.6, 16.8; Exact mass: 296.0909; MS *m*/*z*: 297.1962 (M + H)+, 267.1901 (M + H − NO), 251.1907 (M + H − NO_2).

*4.5.22. 2-(2-Bromophenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6a**)*

Yield: 68%; M.P.: 204–206 °C; IR (KBr) V_{max} cm^{-1}: 1620.39 (C=N), 1528.52 & 1398.39 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H, Pyrrole H_5), 7.72–7.35 (m, Ar–H, 4H), 7.34 (s, 1H, Pyrrole H_3), 4.13 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 139.6, 136.2, 133.1, 132.5, 130.4, 129.4, 128.4, 124.3, 120.5, 104.2, 27.4; Exact mass: 347.9820; MS *m*/*z*: 348.99 (M + H)+, 318.9839 (M + H − NO), 302.9845 (M + H − NO_2).

*4.5.23. 2-(5-Chloro-1H-indol-2-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6b**)*

Yield: 63%; M.P.: 184–186 °C; IR (KBr) V_{max} cm^{-1}: 1606.20 (C=N), 1526.04 & 1407.10 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H, Indol NH), 8.15 (s, 1H, Pyrrole H_5), 7.75–7.05 (m, 4H, indol), 7.41 (s, 1H, Pyrrole H_3), 4.20 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.1, 136.5, 135.1, 133.6, 129.5, 125.6, 124.1, 122.9, 121.8, 114.6, 104.3, 100.3, 27.6; Exact mass: 343.0472; MS *m*/*z*: 344.6137 (M + H)+, 314.6076 (M + H − NO), 298.6082 (M + H − NO_2).

*4.5.24. 2-(4-Hydroxy-3-methoxy-styryl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6c**)*

Yield: 43%; M.P.: 234–236 °C; IR (KBr) V_{max} cm^{-1}: 1627.45 (C=N), 1525.33 & 1399.38 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.18 (s, 1H, Pyrrole H_5), 7.45–7.10 (m, 3H, Ar–H), 7.35 (s, Pyrrole H_3, 1H), 6.85–6.74 (d, 2H, CH=CH), 6.23 (s, 1H, OH), 4.15 (s, 3H, Pyrrole N–CH_3), 3.89 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.2, 149.3, 147.1, 136.6, 133.5, 133.1, 130.5, 124.8, 124.6, 122.6, 116.6, 109.3, 104.2, 56.3, 27.1; Exact mass: 342.0964; MS *m*/*z*: 343.2108 (M + H)+, 313.2047 (M + H − NO), 297.2053 (M + H − NO_2).

*4.5.25. 2-(Piperidin-5-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6d**)*

Yield: 27%; M.P.: 298–300 °C; IR (KBr) V_{max} cm^{-1}: 1621.25 (C=N), 1520.93 & 1398.11 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.14 (s, 1H, Pyrrole H_5), 7.40 (s, 1H, Pyrrole H_3), 4.12 (s, 3H, Pyrrole N–CH_3), 3.10–2.35 (m, 4H, piperidinyl), 1.85–1.43 (m, 4H, piperidinyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.2, 164.5, 136.3, 133.6, 124.1, 104.6, 52.1, 48.2, 36.3, 30.2, 27.6, 25.4; Exact mass: 277.1175; MS *m/z*: 278.2813 (M + H)+, 248.2752 (M + H − NO), 232.2758 (M + H − NO_2).

*4.5.26. 2-(2-Fluorobenzyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6e**)*

Yield: 48%; M.P.: 278–280 °C; IR (KBr) V_{max} cm^{-1}: 1629.67 (C=N), 1521.01 & 1397.56 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.11 (s, 1H, Pyrrole H_5), 7.85–7.54 (m, 4H, Aryl), 7.38 (s, 1H, Pyrrole H_3), 4.15 (s, 3H, Pyrrole N–CH_3), 2.48 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 164.2, 161.3, 136.3, 133.8, 130.6, 127.9, 124.8, 124.5, 123.9, 115.6, 104.3, 27.6, 24.1; Exact mass: 302.0815; MS *m/z*: 303.0918 (M + H)+, 273.0857(M + H − NO), 257.0863 (M + H − NO_2).

*4.5.27. 2-(3-Methoxyphenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6f**)*

Yield: 75%; M.P.: 220–222 °C; IR (KBr) V_{max} cm^{-1}: 1629.10 (C=N), 1528.92 & 1403.77 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.21 (s, 1H, Pyrrole H_5), 7.83–7.24 (s, 4H, Aryl), 7.45 (s, 1H, Pyrrole H_3), 4.11 (s, 3H, Pyrrole N–CH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 161.2, 136.5, 133.5, 130.5, 127.5, 124.6, 119.9, 114.6, 111.3, 104.6, 55.6, 27.6; Exact mass: 300.0859; MS *m/z*: 301.1043 (M + H)+, 271.0982 (M + H − NO), 255.0988 (M + H − NO_2).

*4.5.28. 2-(4-Cyanophenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6g**)*

Yield: 69%; M.P.: 300–302 °C; IR (KBr) V_{max} cm^{-1}: 1625.92 (C=N), 1524.76 & 1399.24 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H, Pyrrole H_5), 7.67–6.89 (m, 4H, Aryl), 7.32 (s, 1H, Pyrrole H_3), 4.08 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 136.5, 133.6, 132.5, 130.5, 128.6, 124.6, 118.5, 112.6, 104.6, 27.7; Exact mass: 295.0705; MS *m/z*: 296.0715 (M + H)+, 266.0654 (M + H − NO), 250.0660 (M + H − NO_2).

*4.5.29. 2-(2,6-Dimethoxyphenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6h**)*

Yield: 81%; M.P.: 200–202 °C; IR (KBr) V_{max} cm^{-1}: 1629.26 (C=N), 1510.12 & 1410.25 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H, Pyrrole H_5), 7.42–7.04 (m, 3H, Aryl), 7.43 (s, 1H, Pyrrole H_3), 4.10 (s, 3H, Pyrrole N–CH_3), 3.85–3.68 (2s, 6H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 156.8, 136.9, 133.6130.5, 124.6, 108.6, 107.5, 104.5,56.2, 27.6; Exact mass: 330.0964; MS *m/z*: 331.1107 (M + H)+, 300.0966 (M + H − NO), 284.0972 (M + H − NO_2).

*4.5.30. 2-(4-Methoxyphenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6i**)*

Yield: 87%; M.P.: 256–258 °C; IR (KBr) V_{max} cm^{-1}: 1622.08 (C=N), 1510.53 & 1401.97 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.18 (s, 1H, Pyrrole H_5), 7.78–7.21 (m, 4H, Aryl), 7.39 (s, 1H, Pyrrole H_3), 4.14 (s, 3H, Pyrrole N–CH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 160.2, 136.6, 133.4, 129.5, 124.6, 115.6, 114.3, 104.6, 55.8, 27.9; Exact mass: 300.0859; MS *m/z*: 301.1043 (M + H)+, 271.0982 (M + H − NO), 255.0988 (M + H − NO_2).

*4.5.31. 2-(Isothiazol-5-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6j**)*

Yield: 45%; M.P.: 178–180 °C; IR (KBr) V_{max} cm^{-1}: 1625.04 (C=N), 1526.62 & 1414.61 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.16 (s, 1H, Pyrrole H_5), 7.31 (s, 1H, Pyrrole H_3), 6.73–6.61 (d, 2H, Thiazole), 4.15 (s, 1H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 161.3, 157.6, 147.6, 136.5, 133.6, 124.9, 120.6, 104.4, 27.8; Exact mass: 277.0270; MS *m/z*: 278.1095 (M + H)+, 248.1034 (M + H − NO), 232.1040 (M + H − NO_2).

*4.5.32. 2-(5-Methylthiophen-2-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6k**)*

Yield: 60%; M.P.: 238–240 °C; IR (KBr) V_{max} cm^{-1}: 1620.42 (C=N), 1514.04 & 1401.04 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.13 (s, 1H, Pyrrole H_5), 7.44 (s, 1H, Pyrrole H_3), 6.65 (d, 2H, thiophene), 4.08 (s, 3H, Pyrrole N–CH_3), 2.81 (s, 3H, thiophen-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3, 161.5, 136.9, 134.8, 133.5, 129.4, 127.9, 127.2, 124.1, 104.6, 27.6, 15.3; Exact mass: 290.0474; MS *m/z*: 291.0385 (M + H)+, 261.0324 (M + H − NO), 245.0330 (M + H − NO_2).

*4.5.33. 2-(2-Hydroxy-3,5-dinitrophenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6l**)*

Yield: 71%; M.P.: 188–190 °C; IR (KBr) V_{max} cm^{-1}: 1627.09 (C=N), 1527.30 & 1399.17 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.69–8.62 (d, 2H, Aryl), 8.21 (s, 1H, Pyrrole H_5), 7.42 (s,1H, Pyrrole H_3), 6.22 (s, 1H, OH), 4.13 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.9, 164.5, 157.6, 141.6, 138.2, 136.5, 133.2, 130.6, 124.1, 122.2, 113.6, 104.1, 27.5; Exact mass: 376.0404; MS *m/z*: 377.2108 (M + H)+, 347.2074 (M + H − NO), 331.2053 (M + H − NO_2).

*4.5.34. 2-(2-Hydroxy-3-nitrophenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6m**)*

Yield: 44%; M.P.: 268–270 °C; IR (KBr) V_{max} cm^{-1}: 1625.72 (C=N), 1522.26 & 1400.61 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.22 (s, 1H, Pyrrole H_5), 8.02 (s, 1H, Aryl), 7.38 (s, 1H, Pyrrole H_3), 6.79–6.61 (d, 2H, Aryl), 6.20 (s, 1H, OH), 4.02 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.5, 164.2, 150.6, 144.3, 137.6, 136.6, 133.2, 122.5, 128.6, 124.3, 113.2, 104.2, 27.8; Exact mass: 331.0553; MS *m/z*: 332.0571 (M + H)+, 302.0510 (M + H − NO), 286.0516 (M + H − NO_2).

*4.5.35. 2-(6-Chloro-2-phenyl-quinolin-4-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6n**)*

Yield: 39%; M.P.: 280–282 °C; IR (KBr) V_{max} cm^{-1}: 1623.58 (C=N), 1529.66 & 1413.04 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 9.21 (s, 1H, quinoline H_8), 8.16 (s, 1H, Pyrrole H_5), 8.28–7.51 (m, 8H, Aryl), 7.45 (s, 1H, Pyrrole H_3), 4.07 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.4, 156.6, 143.9, 143.2, 139.2, 136.4, 133.2, 131.6, 130.2, 129.5127.9, 127.6, 127.2, 124.3, 123.6, 120.3, 104.2, 104, 27.3; Exact mass: 431.0785; MS *m/z*: 432.9150 (M + H)+, 402.9089 (M + H − NO), 386.9095 (M + H − NO_2).

*4.5.36. 2-((1-Fluoronaphthalen-4-yl)methyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6o**)*

Yield: 53%; M.P.: 158–160 °C; IR (KBr) V_{max} cm^{-1}: 1626.25 (C=N), 1505.99 & 1403.87 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.24 (s, 1H, Pyrrole H_5), 7.81–6.89 (m, 6H, Naphthalene), 7.43 (s, 1H, Pyrrole H_3), 4.42 (s, 2H, CH_2), 4.12 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.2, 164.3, 154.5, 136.9, 134.5, 133.9, 130.2, 128.6, 126.3, 125.2, 124.1, 123.9, 123.4, 121.6, 112.2, 104.2, 29.1, 27.5; Exact mass: 352.0972; MS *m/z*: 353.3921 (M + H)+, 323.3860 (M + H − NO), 307.3866 (M + H − NO_2).

*4.5.37. 2-(Furan-2-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6p**)*

Yield: 68%; M.P.: 192–194 °C; IR (KBr) V_{max} cm^{-1}: 1631.56 (C=N), 1512.81 & 1406.93 (NO_2); ^1H NMR (300 MHz, DMSO-d_6): δ 8.17

(s, 1H, Pyrrole H_5), 7.86–6.69 (m, 3H, furan), 7.38 (s, 1H, Pyrrole H_3), 4.08 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.9, 157.1, 147.9, 138.7, 136.5, 133.2, 124.7, 115.0, 112.1, 104.8, 26.9; Exact mass: 260.0546; MS *m/z*: 261.8015 (M + H)+, 231.5905 (M + H − NO), 215.0901 (M + H − NO_2).

*4.5.38. 2-(1-Methyl-4-nitro-1H-pyrrol-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (**6q**)*

Yield: 51%; M.P.: 224–226 °C; IR (KBr) V_{max} cm^{-1}: 1634.22 (C=N), 1501.88 & 1402.44 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H, Pyrrole H_5), 7.78–7.43 (m, 3H, thiophene), 7.32 (s, 1H, Pyrrole H_3), 4.01 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.1, 161.9, 136.6, 133.8, 132.2, 131.0, 128.7, 128.1, 124.4, 104.1, 27.1; Exact mass: 276.0317; MS *m/z*: 277.9104 (M + H)+, 247.8802 (M + H − NO), 231.1096 (M + H − NO_2).

*4.5.39. 2-(1-Methyl-4-nitro-1H-pyrrol-2-yl)-5-(1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6r**)*

Yield: 70%; M.P.: 180–182 °C; IR (KBr) V_{max} cm^{-1}: 1625.71 (C=N), 1516.39 & 1409.11 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16 (s, 1H, Pyrrole H_5), 7.78–7.43 (m, 3H, pyrrole), 7.32 (s, 1H, Pyrrole H_3), 4.01 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 136.9, 133.2, 128.5, 124.7, 120.8, 112.5, 106.1, 104.4, 27.3; Exact mass: 259.0705; MS *m/z*: 260.0816 (M + H)+, 230.7135 (M + H − NO), 214.9103 (M + H − NO_2).

*4.5.40. 2-(2,4-Dichlorophenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6s**)*

Yield: 57%; M.P.: 232–234 °C; IR (KBr) V_{max} cm^{-1}: 1621.20 (C=N), 1527.94 & 1401.15 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (s, 1H, Pyrrole H_5), 7.92–7.59 (m, 3H, Ar–H), 7.44 (s, 1H, Pyrrole H_3), 4.10 (s, 1H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 136.6, 135.9, 135.6, 133.4, 133, 130.8, 130.1, 127.6, 124.5, 104.6, 27.6; Exact mass: 337.9973; MS *m/z*: 338.9671 (M + H)+, 308.9610 (M + H − NO), 292.9616 (M + H − NO_2).

*4.5.41. 2-((2-Trifluoromethoxy)phenyl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-oxadiazole (**6t**)*

Yield: 76%; M.P.: 168–170 °C; IR (KBr) V_{max} cm^{-1}: 1620.36 (C=N), 1528.34 & 1401.34 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16 (s, 1H, Pyrrole H_5), 7.31 (s, 1H, Pyrrole H_3), 7.55–7.05 (m, 4H, Aryl), 4.03 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 164.5, 157.3, 136.3, 133.8, 130.2, 130, 129.2, 124.6, 116.3, 112.5, 104.8, 27.9; Exact mass: 354.0576; MS *m/z*: 355.6302 (M + H)+, 325.6241 (M + H − NO), 309.6247 (M + H − NO_2).

*4.5.42. 2-(1H-Indol-2-yl)-5-(1-methyl-4-nitro-1H-pyrrol-2-yl)-1,3,4-Oxadiazole (**6u**)*

Yield: 52%; M.P.: 310–312 °C; IR (KBr) V_{max} cm^{-1}: 1605.42 (C=N), 1505.25 & 1401.14 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.18 (s, 1H, indol NH), 8.22 (s, 1H, Pyrrole H_5), 7.64–6.81 (m, 5H, Indolyl), 7.40 (s, 1H, Pyrrole H_3), 4.11 (s, 3H, Pyrrole N–CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6, 137.4, 136.2, 133.6, 128.5, 124.9, 124.1, 121.6, 120.6, 119.1, 111.6, 104.6, 100.3, 27.6; Exact mass: 309.0862; MS *m/z*: 310.3015 (M + H)+, 280.2954 (M + H − NO), 264.2960 (M + H − NO_2).

4.6. Antimicrobial activity

The synthesized compounds were tested for their antibacterial activity against *Staphylococcus aureus* (ATCC- 25923), *B. subtilis* (ATCC 6633), *E. coli* (ATCC 25922), *K. pneumoniae* (recultured) bacterial strains, *Methicillin resistant Staphylococcus aureus* (MRSA; ATCC 43866) and *Methicillin susceptible staphylococcus aureus* (MSSA; ATCC 35556). Minimum inhibitory concentrations (MICs) were determined by broth dilution technique [28,29]. Ciprofloxacin was used as a standard drug for antibacterial study. The lowest concentration or the highest dilution required to arrest the growth of bacteria was considered as minimum inhibitory concentration. The MIC values are given in Table 1. The anti-fungal activity testing of the synthesized nitropyrrole oxadiazoles was done on *C. albicans* by agar dilution method using DMSO [30,31]. The nutrient broth, which contained logarithmic serially two-fold diluted amount of test compound and controls inoculated with approximately 1.6×10^4–6×10^4 CFU/mL, was used. The cultures were incubated for 48 h at 35 °C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentration (MIC). The fungal activity of each compound was compared with Amphotericin-B as standard drug. The minimum inhibitory concentration values for antifungal activity are given in Table 1.

The anti-tubercular activity of the compounds, against *M. tuberculosis* $H37R_V$, was performed using Resazurin Microtiter assay (REMA) [32]. Isoniazid was used as reference drug in the study. Homogenous mycobacterial (H37Rv) culture suspension was seeded in microtitre plates at density of 10^5 cells per well in 100 μL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI, USA) and the test compounds were serially diluted directly on the plate. The control received equivalent amount of DMSO. The plates were incubated at 37 °C for 7 days. Freshly prepared resazurin dye (0.02%) was added and plates were again incubated for 48 h. MIC is the lowest concentration at which complete inhibition was observed and was determined by visual inspection (color change from blue to pink).

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References

[1] F.A. Omar, N.M. Mehfouz, M.A. Rahman, Eur. J. Med. Chem. 31 (1996) 819.
[2] E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu, G. Altinok, Farmaco 57 (2002) 101.
[3] T. Ramalingum, P.B. Sattur, Eur. J. Med. Chem. 25 (1990) 541.
[4] M. Harfenist, D.J. Heuser, C.T. Joyner, J.F. Batchelor, H.L. White, J. Med. Chem. 39 (1996) 1857.
[5] Y. Ergun, F.O. Orhan, U.G. Ozer, G. Gisi, Eur. J. Pharmacol. 630 (2010) 74.
[6] L. Jin, J. Chen, B. Song, Z. Chen, S. Yang, Q. Li, D. Hu, R. Xu, Bioorg. Med. Chem. Lett. 16 (2006) 5036.
[7] F. Liu, X.Q. Luo, B.A. Song, P.S. Bhadury, S. Yang, L.H. Jin, W. Xue, D.Y. Hu, Bioorg. Med. Chem. Lett. 16 (2008) 3632.
[8] C.J. Chen, B.A. Song, S. Yang, G.F. Xu, P.S. Bhadury, L.H. Jin, D.Y. Hu, Q.Z. Li, F. Liu, W. Xue, P. Lu, Z. Chen, Bioorg. Med. Chem. Lett. 15 (2007) 3981.
[9] W.M. Xu, F.F. Han, M. He, D.Y. Hu, J. He, S. Yang, B.A. Song, J. Agric. Food Chem. 60 (2012) 1036.
[10] M.J. Ahsan, J.G. Samy, H. Khalilullah, M.S. Nomani, P. Saraswat, R. Gaur, A. Singh, Bioorg. Med. Chem. Lett. 21 (2011) 7246.
[11] R.A. Rane, S.G. Gutte, N.U. Sahu, Bioorg. Med. Chem. Lett. 22 (2012) 6429.
[12] N. Ezaki, M. Koyama, T. Shomura, T. Tsuruoka, S. Inouye, J. Antibiot. 36 (1963) 1263.
[13] Ritesh Raju, M.P. Andrew, Leticia X. Barrientos Diaz, K. Zeinab, J.C. Robert, Org. Lett. 12 (2010) 5158.
[14] C.K. Hak, D.M. Ana Paula, P. Jin-Soo, Alejandra Prieto-Davo, R. Mickea, R.J. Paul, F. William, J. Nat. Prod. 73 (2010) 2047.
[15] Y.W. Ching, W.C. Chung, M. Keiji, D.M. Preston, T.B. George, Antimicrob. Agents Chemother. 8 (1975) 216.
[16] D.S. Roberto, C. Roberta, A. Marino, M. Silvio, L. Giorgio, D. Delia, P. Raffaello, Bioorg. Med. Chem. Lett. 8 (1998) 2931.
[17] (a) M. Koyama, N. Ohtani, F. Kai, I. Moriguchi, S. Inouye, J. Med. Chem. 30 (1987) 552.
[18] (a) A.K. Garkushenko, G.P. Sagitullina, Chem. Heterocycl. Compd. 47 (2012) 1189;
(b) L. Ballell, R.A. Field, K. Duncan, R.J. Young, Antimicrob. Agents Chemother. 49 (2005) 2153.
[19] W.T. Colwell, J.H. Lange, D.W. Henry, J. Med. Chem. 11 (1968) 282.
[20] D. Krajewska, K. Midura-Nowaczek, Acta Pol. Pharm-Drug Res. 66 (2009) 69.

[21] Z. Ji, H.-K. Wang, K.F. Bastow, X.-K. Zhu, S.J. Cho, Y.-C. Cheng, K.-H. Lee, Bioorg. Med. Chem. Lett. 7 (1997) 607.
[22] F. Pourmorad, A. Shafiee, J. Sci. Islamic Repub. Iran 9 (1998) 30.
[23] (a) M.B. Denis, E.J. Robert, F.A. Noel, Org. Synth. 6 (1988) 618, 51 (1971) 100; (b) M.B. Denis, R.E. Johnson, J.U. Salvador, J. Med. Chem. 16 (1973) 1298.
[24] R.A. Rane, V.N. Telvekar, Bioorg. Med. Chem. Lett. 20 (2010) 5681.
[25] E.E. Baird, P.B. Dervan, J. Am. Chem. Soc. 118 (1996) 6141.
[26] K.J. Morgan, D.P. Morrey, Tetrahedron 27 (1970) 245.
[27] R.E. Bremer, J.W. Szewczyk, E.E. Baird, P.B. Dervan, Bioorg. Med. Chem. 8 (2000) 1947.
[28] D. Schillaci, S. Petruso, V. Sciortino, Int. J. Antimicrob. Agents 25 (2005) 338.
[29] NCCLS Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria, fifth ed., NCCLS, Villanova, PA, 2000.
[30] Z.K. Khan, In vitro and vivo screening techniques for bioactivity screening and evaluation, in: Proceedings of the International Workshop UNIDO-CDRI, 1997, p. 210.
[31] R.S. Varma, Antifungal Agents: Past, Present and Future Prospects, National Academy of Chemistry & Biology, Lucknow, India, 1998.
[32] J.C. Palomino, A. Martin, M. Camacho, H. Guerra, J. Swings, F. Portaels, Antimicrob. Agents Chemother. 46 (2002) 2720.
[33] L.L. Gundersen, J. Nissen-Meyer, B. Spilsberg, J. Med. Chem. 45 (2002) 1383.