Synthesis of New (Pyrazol-3-yl)-1,3,4-oxadiazole Derivatives by Unexpected Aromatization During Oxidative Cyclization of 4,5-Dihydro-1*H*-pyrazole-3-carbohydrazones and Their Biological Activities

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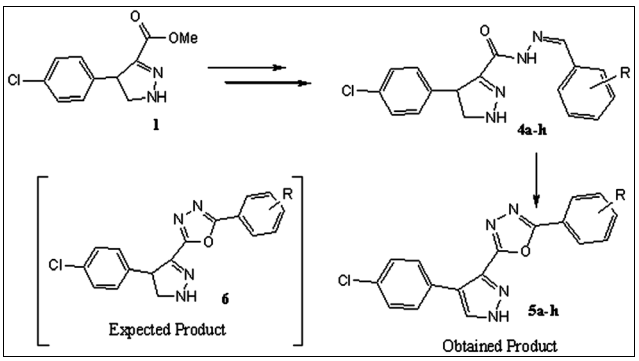

A series of novel 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(Aryl)-1,3,4-oxadiazoles were synthesized by unexpected aromatization during oxidative cyclization of 4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazones using chloramine-T as an oxidant. The hydrazones were derived from 4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide and various substituted aldehydes. The structure of the synthesized compounds was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The synthesized compounds were evaluated for their antitubercular and antioxidant activities. All the compounds **4a–h** and **5a–h** showed good antitubercular activity against *Mycobacterium tuberculosis* (minimum inhibitory concentration = 25 μg/mL for **4f** and **4g**, 50–100 μg/mL for the rest). However, all the compounds exhibited poor antioxidant activity against 1,1-diphenyl-2-picryl-hydrazil free radical.

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INTRODUCTION

The development of drug resistance to clinically used agents has increased the demand for discovery of new chemical scaffolds with antimicrobial activity. Tuberculosis is a common and often deadly infectious disease caused by *Mycobacterium tuberculosis* in humans, and it is estimated that one-third of the world's population is currently infected with TB bacillus and, annually, 2.0 million deaths were found [1]. The incidence of TB infection has steadily risen in the last decade. The reemergence of TB infection has been linked to coinfection with the human immunodeficiency virus [2], and the treatment of tuberculosis has become a major problem because of the emergence of multidrug-resistant strains and extensively drug-resistant strains of *M. tuberculosis* [3]. In this context, there is an urgent need for new chemical entities to fight against this disease with a novel mechanism of action.

Five-membered heterocycles are privileged structures with utility in medicinal chemistry. Among them, the 1,3,4-oxadiazole motif has been extensively used for many years as a bioisosteric replacement of acid, ester, and amide functionalities in medicinal chemistry, and its derivatives have a wide range of pharmaceutical and biological activities including antimicrobial [4], anticancer [5], insecticidal [6], anti-inflammatory [7], and antimycobacterial [8] activities. Biologically relevant entities containing the 1,3,4-oxadiazole motif include the human immunodeficiency virus integrase inhibitor **I** and the angiogenesis inhibitor **II** (Fig. 1) [9,10]. The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocycles. These molecules are also utilized as pharmacophores because of their favorable metabolic profile and ability to engage in hydrogen bonding with the receptors.

Many pyrazole derivatives are acknowledged to possess a wide range of bioactivities. The pyrazole motif makes up the core structure of numerous biologically active compounds. 1*H*-Pyrazole and 4,5-dihydro-1*H*-pyrazole derivatives have been found to possess diverse applications in medicine, viz. antimicrobial [11–13], antiviral [14], antidiabetic [15], anti-inflammatory [16], anticancer [17], insecticidal [18], and antitubercular [19] activities.

In view of this, we made an effort to synthesize some new 4,5-dihydro-1*H*-pyrazol-3-yl)-1,3,4-oxadiazoles **6** by treating 4,5-dihydro-1*H*-pyrazole-3-carbohydrazones **4** with chloramine-T. Interestingly, we ended up with (pyrazol-3-yl)-1,3,4-oxadiazoles **5** by unexpected aromatization during

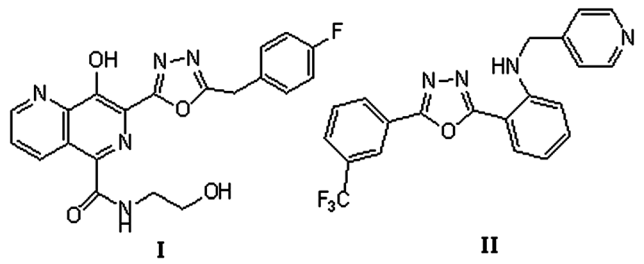


Figure 1. Biologically active compounds with the 1,3,5-oxadiazole motif.

oxidative cyclization of 4,5-dihydro-1*H*-pyrazole-3-carbohydrazones **4**. The newly synthesized compounds were tested for their antitubercular and antioxidant activities.

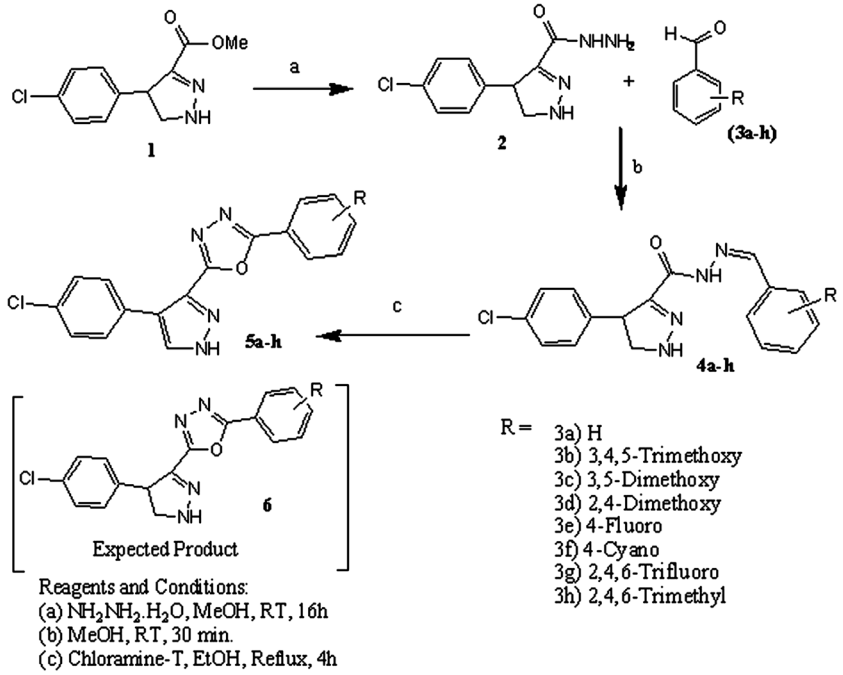
RESULTS AND DISCUSSION

Chemistry. The synthetic route for the preparation of pyrazoline-3-carbohydrazone derivatives **4a–h** and pyrazolo-oxadiazole derivatives **5a–h** is summarized in Scheme 1. The starting compound methyl 4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate **1** was treated with hydrazine hydrate in methanol to obtain corresponding carbohydrazide **2**. The structure of **2** was confirmed by spectral analysis. The ^{1}H NMR spectrum of **2** in DMSO-d_6 revealed three multiplets at δ 3.31, 3.68, and 4.35 that represent three nonequivalent protons of pyrazoline ring, broad singlet at 4.21 represents -NH_2 protons, two doublets at δ 7.18 and 7.36 with $J = 8.4$ correspond to 4-chlorophenyl ring, and two singlets at 7.73 and 9.18 belong to CONH and pyrazoline NH, respectively. Its LC-MS showed M + 1 peak (239.1), and the FTIR also showed carbonyl and NH stretching frequencies.

Pyrazoline-3-carbohydrazide **2** was condensed with different aldehydes **3a–h** in methanol to obtain corresponding hydrazones **4a–h** in high yields (Scheme 1). All these hydrazones have not been reported hitherto. The structure of the hydrazones was confirmed by ^{1}H NMR, MS, and FTIR spectral data. In each case, their ^{1}H NMR spectra in DMSO-d_6 revealed two characteristic signals in the region δ 8.11–8.15 and 8.26–8.44 that represents -N=CH-proton and -CONH proton, respectively. Their FTIR spectra showed the N-H stretch of the hydrazone as a broad band in the region 3449–3221 cm^{-1}. Further, their MS spectra showed [M + 1] peak in ES positive mode.

The oxidation of hydrazones **4a–h** with chloramine-T [20] to generate nitrilimines followed by intramolecular cyclization with adjacent carbonyl group yielded 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(aryl)-1,3,4-oxadiazoles **5a–h** instead of expected 2-(4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)-

Scheme 1. Reaction sequence for the synthesis of 4,5-dihydro-1*H*-pyrazole-3-carbohydrazones **4a–h** and (pyrazol-3-yl)-1,3,4-oxadiazole derivatives **5a–h**.



5-(aryl)-1,3,4-oxadiazoles **6**. This is due to the unexpected aromatization of 4,5-dihydropyrazoline ring to pyrazole by second mole of chloramine-T under reflux conditions. Reaction mechanism for the formation of **5a–h** is given in Scheme 2.

Two moles of chloramine-T reagent were needed for the completion of the reaction with one mole of the substrate. One mole reagent was utilized for oxidation of hydrazone and another mole was consumed for the oxidation of 4,5-dihydropyrazoline ring. All the synthesized 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(aryl)-1,3,4-oxadiazoles **5a–h** were characterized by FTIR, ^{1}H NMR, and mass spectral analysis. IR spectrum of oxadiazoles **5a–h** showed the absence of amide carbonyl frequency in the region 1730–1660 cm^{-1} and showed a new peak at 1626–1590 cm^{-1} because of C═N frequency. ^{1}H NMR showed peaks due to aromatic protons and other substituents in the expected region. Further ^{13}C NMR, DEPT-135, and mass spectra confirm the structures of **5a–h**. The physical data of the compounds **2**, **4a–h**, and **5a–h** were given in Table 1.

Biological activity

Antitubercular activity. The antimycobacterial activity of the compounds **4a–h** and **5a–h** was assessed against *M. tuberculosis* H_{37}Rv (ATCC 27294) using microplate Alamar Blue assay [21]. This methodology is nontoxic, uses a thermally stable reagent, and shows good correlation with proportional and BACTEC radiometric methods [22,23], and the activity is expressed as the minimum inhibitory concentration (MIC) in μg/mL. The MIC is defined as the lowest drug concentration required to complete inhibition of bacterial growth. Pyrazinamide was used as standard. All the tested compounds **4a–h** and **5a–h** showed better *in vitro* activity (MIC 25–50 μg/mL) than pyrazinamide (MIC of 100 μg/mL). The MICs of the compounds were depicted in Table 2.

Antioxidant activity. All the newly synthesized compounds **4a–h** and **5a–h** were screened for their free radical scavenging activity. The free radical scavenging activity of the synthesized compounds was determined by the 1,1-diphenyl-2-picryl-hydrazil (DPPH) method [24]. The samples were prepared at different concentrations in methanol (10, 20, 50, 75, and 100 μg/mL). Butylated hydroxy toluene (BHT), which is a good antioxidant, is taken as a standard in this study. However, all the compounds showed poor antioxidant activity (<30%) when compared with standard BHT (97%). This low activity is most probably due to the inability of all the compounds to catch free radicals. The percentage of free radical scavenging activity is shown in Table 3.

CONCLUSION

In conclusion, some new pyrazolo-oxadiazole derivatives were obtained by cyclization and unexpected aromatization of 4,5-dihydropyrazoline-3-carbohydrazones by chloramine-T trihydrate. Antitubercular activity study revealed that compounds **4f**, **4g** showed potent activity (25 μg/mL); **4a**, **4b**, **4c**, **4d**, **4e**, **4h**, **5a**, **5c**, **5d**, **5e**, **5f**, **5g** (50 μg/mL) displayed good activity than pyrazinamide by Alamar Blue assay method. The structure and biological activity relationship of title compounds showed that the presence of pyrazoline nucleus with carbohydrazone moiety (-CONHN═C-) and 1,3,4-oxadiazole nucleus with 4-chlorophenyl pyrazole moiety as well as biologically active fluoro, cyano, and methoxy groups attached to the phenyl ring are responsible for good antitubercular activity. All the compounds **4a–h** and **5a–h** displayed poor antioxidant activity when compared with standard BHT. This is most probably due to the inability of all the compounds to catch free radicals.

Scheme 2. Reaction mechanism for the formation of 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(aryl)-1,3,4-oxadiazoles **5a–h** from **4a–h**.

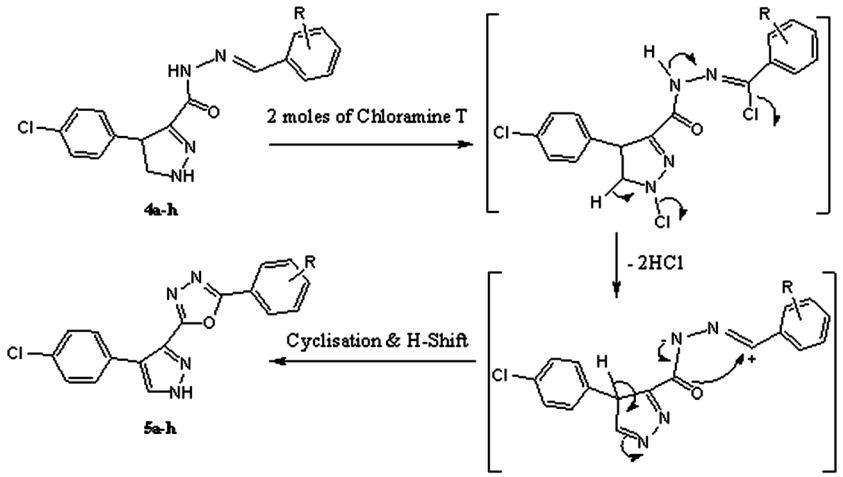


Table 1

Physical data of the compounds **2**, **4a–h**, and **5a–h**.

Compound	R	Yield (%)	mp (°C)	*m/z*
2		84.2	173–175	238
4a	H	89.6	187–188	326
4b	3,4,5-Trimethoxy	84.7	196–197	416
4c	3,5-Dimethoxy	88.2	191–193	386
4d	2,4-Dimethoxy	85.1	185–187	386
4e	4-Fluoro	88.6	191–192	344
4f	4-Cyano	83.4	214–215	351
4g	2,4,6-Trifluoro	90.2	187–189	380
4h	2,4,6-Trimethyl	91.7	163–165	386
5a	H	61.4	219–220	333
5b	3,4,5-Trimethoxy	62.6	242–244	412
5c	3,5-Dimethoxy	64.7	214–216	382
5d	2,4-Dimethoxy	58.7	146–148	382
5e	4-Fluoro	62.7	246–247	340
5f	4-Cyano	60.2	255–257	347
5g	2,4,6-Trifluoro	58.3	215–216	376
5h	2,4,6-Trimethyl	59.6	224–226	382

EXPERIMENTAL

General. Analytical grade solvents and commercially available reagents were used without further purification. The column chromatography was carried out over silica gel (60–120 mesh), purchased from Sisco Research Laboratories Pvt Ltd. Melting points were determined in open capillaries in electrical melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 400-MHz and 500-MHz Bruker spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. Chemical shifts are given in δ relative to TMS; the coupling constants are given in Hz. IR spectra in KBr disk were recorded from 4000 to 400 cm^{-1} on Avatar 330 FTIR spectrometer equipped with DTGS detector (Thermo Scientific, India). Mass spectra were recorded using Agilent 1100 MSD spectrometer (Agilent Technologies) in electro spray mode. Compounds were checked for their purity by TLC on silica gel G plates, and spots were located by exposing to UV light and iodine vapors.

Procedure for the synthesis of 4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (2). To a turbid solution of methyl 4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate **1** (5.0 g, 21 mmol) in methanol (25 mL) in an Round Bottom flask was added hydrazine hydrate (98%, 63 mmol,

Table 2

Antitubercular activity of **4a–h** and **5a–h** against *Mycobacterium tuberculosis* H_{37}Rv strain (ATCC 27294) by MABA method.[a]

Compound	MIC (μg/mL)[b] *M. tuberculosis* H_{37}Rv
4a	50
4b	50
4c	50
4d	50
4e	50
4f	25
4g	25
4h	50
5a	50
5b	100
5c	50
5d	50
5e	50
5f	50
5g	50
5h	100
Pyrazinamide	100

MIC, minimum inhibitory concentration.
[a]Microplate Alamar Blue assay.
[b]Sample concentrations tested from 0.2 to 100 μg/mL.

Table 3

Antioxidant activity of **4a–h** and **5a–h** against DPPH free radical.

	% inhibition at different concentrations (μg/mL)				
Compound	10	20	50	75	100
4a	7	9	15	18	19
4b	8	11	16	18	20
4c	6	9	14	17	18
4d	7	10	14	18	19
4e	8	11	16	17	18
4f	8	10	14	16	17
4g	9	13	19	25	26
4h	8	12	17	19	20
5a	3	6	8	9	9
5b	3	5	8	10	11
5c	2	5	9	9	10
5d	3	6	8	10	11
5e	4	7	9	9	10
5f	2	6	8	8	9
5g	4	7	9	10	12
5h	4	6	8	10	11
BHT	43	59	82	95	97

DPPH, 1,1-diphenyl-2-picryl-hydrazil; BHT, butylated hydroxy toluene.

3.05 mL), and the resulting clear reaction mixture (slight exothermic) was stirred for 16 h at room temperature. After the reaction was completed by TLC, excess methanol was evaporated from the reaction mixture under reduced pressure, and the resultant white precipitate was washed twice with little amount of water and was air-dried to obtain the pure compound **2** as a white solid.

Yield 4.21 g (84.2%). mp 173–175°C; IR υ (KBr) 3549, 3353, 3045, 2941, 1668 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.31 (m, 1H, C_5Ha of pyrazoline), 3.68 (m, 1H, C_5Hb of pyrazoline), 4.21 (brs, 2H, NH_2), 4.35 (m, 1H, C_4H of pyrazoline), 7.18 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.36 (d, J = 8.4 Hz, 2H, C_3 and C_5H of 4-Cl-Phenyl), 7.73 (s, 1H, -CONH-), 9.18 (s, 1H, pyrazoline-NH); LC-MS: 239.1 (M + 1).

General procedure for the synthesis of *N*′-(substituted benzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide derivatives (4a–h). To a stirred suspension of **2** (2.1 mmol, 0.5 g) in methanol (8 mL) was added the appropriate aldehyde **3** (2.1 mmol) and stirred at room temperature for 30 min. The completion of the reaction was confirmed by TLC, and the precipitate formed was diluted with chilled water, filtered off, washed with water, and air-dried to give the corresponding hydrazide-hydrazone derivatives **4**. The physical and spectral data of **4a–h** are as follows.

***N*′-Benzylidene-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4a)**. Off white solid (yield 0.59 g, 86.2%). mp 187–188°C; IR υ (KBr) 3441, 3247, 3129, 2943, 1674 cm^{-1}; ^1H NMR (300 MHz) (DMSO-d_6): δ 3.48 (m, 1H, C_5Ha of pyrazoline), 3.90 (m, 1H, C_5Hb of pyrazoline), 4.44 (m, 1H, C_4H of pyrazoline), 7.21 (d, J = 8.1 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.36–7.42 (m, 5H, C_3,C_5H of 4-Cl-Phenyl and C_3,C_4,C_5H of Phenyl), 7.60 (m, 2H, C_2,C_6H Phenyl), 8.15 (s, 1H, -CH═N-), 8.38 (s, 1H, -CONH-), 11.60 (s, 1H, pyrazoline-NH); LC-MS: 327.0 (M + 1).

***N*′-(3,4,5-Trimethoxybenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4b)**. Pale yellow solid (yield 0.74 g, 84.7%). mp 196–197°C; IR υ (KBr) 3435, 3221, 3108, 2928, 1656 cm^{-1}; ^1H NMR (300 MHz) (DMSO-d_6): δ 3.46 (m, 1H, C_5Ha of pyrazoline), 3.68 (s, 3H, 4-Methoxy), 3.79 (s, 6H, 3,5-Dimethoxy), 3.89 (m, 1H, C_5Hb of pyrazoline), 4.43 (m, 1H, C_4H of pyrazoline), 6.89 (s, 2H, C_2,C_6H of 3,4,5-Trimethoxyphenyl), 7.21 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.37 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.14 (s, 1H, -CH═N-), 8.28 (s, 1H, -CONH-), 11.60 (s, 1H, pyrazoline-NH); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 48.25, 56.68, 57.27, 60.98, 104.80, 129.29, 129.82, 130.90, 132.15, 139.78, 141.45, 146.50, 147.47, 153.94, 158.80; LC-MS: 417.0 (M + 1).

***N*′-(3,5-Dimethoxybenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4c)**. Pale yellow solid (yield 0.71 g, 88.2%). mp 191–193°C; IR υ (KBr) 3432, 3124, 2927, 1642 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.47 (m, 1H, C_5Ha of pyrazoline), 3.75 (s, 6H, 3,5-Dimethoxy), 3.89 (m, 1H, C_5Hb of pyrazoline), 4.43 (m, 1H, C_4H of pyrazoline), 6.52 (s, 1H, C_4H of 3.5-Dimethoxyphenyl), 6.74 (s, 2H, C_2,C_6H of 3,5-Drimethoxyphenyl), 7.21 (d, J = 8 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.37 (d, J = 7.6 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.15 (s, 1H, -CH═N-), 8.29 (s, 1H, -CONH-), 11.59 (s, 1H, pyrazoline-NH); LC-MS: 387.1 (M + 1).

***N*′-(2,4-Dimethoxybenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4d)**. Pale yellow solid (yield 0.69 g, 85.1%). mp 185–187°C; IR υ (KBr) 3439, 3143, 2936, 1668 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.45 (m, 1H, C_5Ha of pyrazoline), 3.81 (s, 3H, 4-Methoxy), 3.84 (s, 3H, 2-Methoxy), 3.90 (m, 1H, C_5Hb of pyrazoline), 4.43 (m, 1H, C_4H of pyrazoline), 6.69 (d, J = 8.4 Hz, 1H, C_5H of 2,4-Dimethoxyphenyl), 6.74 (s, 1H, C_3H of 2,4-Dimethoxyphenyl), 7.44 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.61 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.73 (d, J = 8 Hz, 1H, C_6H of 2,4-Dimethoxyphenyl), 8.13 (s, 1H, -CH═N-), 8.26 (s, 1H, -CONH-), 11.58 (s, 1H, pyrazoline-NH); MS: 387.0 (M + 1).

***N*′-(4-Fluorobenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4e)**. White solid (yield 0.64 g, 88.6%). mp 191–192°C; IR υ (KBr) 3431, 3327, 3117, 2925, 2854, 1695, 1636 cm^{-1}; ^1H NMR (300 MHz) (DMSO-d_6): δ 3.47 (m, 1H, C_5Ha of pyrazoline), 3.88 (m, 1H, C_5Hb of pyrazoline), 4.43 (m, 1H, C_4H of pyrazoline), 7.21 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.27 (d, J = 8.7 Hz, 2H, C_2 and C_6H of 4-F-Phenyl), 7.37 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.65 (t, J = 14.1 Hz, 2H, C_3,C_5H of 4-F-Phenyl), 8.15 (s, 1H, -CH═N-), 8.37 (s, 1H, -CONH-), 11.60 (s, 1H, pyrazoline-NH); MS: 345.1 (M + 1), 367.1 (M + Na).

***N*′-(4-Cyanobenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4f)**. Off white solid (yield 0.64 g, 86.8%). mp 214–215°C; IR υ (KBr) 3471, 3325, 3096, 2923, 2227, 1670 cm^{-1}; ^1H NMR (300 MHz) (DMSO-d_6): δ 3.49 (m, 1H, C_5Ha of pyrazoline), 3.92 (m, 1H, C_5Hb of pyrazoline), 4.45 (m, 1H, C_4H of pyrazoline), 7.21 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.37 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.77 (d, J = 8.4 Hz, 2H, C_2,C_6H of 4-CN-Phenyl), 7.87 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-CN-Phenyl), 8.27 (s, 1H, -CH═N-), 8.43 (s, 1H, -CONH-), 11.85 (s, 1H, pyrazoline-NH); MS: 352.1 (M + 1), 350.1 (M − 1).

***N*′-(2,4,6-Trifluorobenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4g)**. Off white solid (yield 0.72 g 90.2%). mp 187–189°C; IR υ (KBr) 3448, 3134, 2931, 1673 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.48 (m, 1H, C_5H_a of pyrazoline), 3.91 (m, 1H, C_5H_b of pyrazoline), 4.44 (m, 1H, C_4H of pyrazoline), 7.20 (d, J = 8 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.27 (t, J = 16.8 Hz, 2H, C_3,C_5H of 2,4,6-trifluorophenyl), 7.37 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.21 (s, 1H, -CH═N-), 8.44 (s, 1H, -CONH-), 11.79 (s, 1H, pyrazoline-NH); LC-MS: 381.1 (M + 1).

***N*′-(2,4,6-Trimethylbenzylidene)-4-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carbohydrazide (4h)**. White solid (yield 0.68 g, 87.9%). mp 163–165°C; IR υ (KBr) 3448, 3297, 3109, 2934, 1697 cm^{-1}; ^1H NMR (300 MHz) (DMSO-d_6): δ 2.11 (s, 3H, 4-Me), 2.22 (s, 6H, 2,6-Dimethyl), 3.46 (m, 1H, C_5H_a of pyrazoline), 3.88 (m, 1H, C_5H_b of pyrazoline), 4.41 (m, 1H, C_4H of pyrazoline), 6.87 (s, 2H, C_3,C_5H of 2,4,6-trimethylphenyl), 7.22 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.37 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.11 (s, 1H, -CH═N-), 8.71 (s, 1H, -CONH-), 11.45 (s, 1H, pyrazoline-NH); MS: 369.1 (M + 1), 391.1 (M + Na).

General procedure for the synthesis of 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(aryl)-1,3,4-oxadiazole derivatives (5a–h). A mixture of **4** (1.55 mmol) and chloramine-T trihydrate (3.72 mmol) in ethanol (10 mL) was refluxed under stirring for 4 h. The reaction mixture was then concentrated under reduced pressure, and the residue was extracted with ethyl acetate (25 mL). The extract was washed with 10% $NaHCO_3$ (10 mL), water (10 mL), and then dried over Na_2SO_4. The solvent was evaporated, and the resulted crude product was subjected to the column chromatography using ethyl acetate–pet ether (12:88) as eluent to obtain 2-(4-(4-chlorophenyl)-1*H*-pyrazol-3-yl)-5-(aryl)-1,3,4-oxadiazole derivatives **5**. The physical and spectral data of **5a–h** are as follows.

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-phenyl-1,3,4-oxadiazole (5a). White solid (yield 0.32 g, 64.9%). mp 219–220°C; IR υ (KBr) 3438, 3135, 1597 cm^{-1}; ^1H NMR (500 MHz) (DMSO-d_6): δ 7.49 (d, J = 8.5 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.61–7.71 (m, 5H, C_3,C_5H of 4-Cl-Phenyl and C_3,C_4,C_5H of Phenyl), 7.99 (d, 2H, J = 8 Hz, C_2,C_6H Phenyl), 8.30 (s, 1H, Pyrazole-H), 13.91 (brs, 1H, Pyrazole-NH); MS: APCI$^+$ 323.0 (M + 1). *Anal*. Calcd For $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36; Found: C, 63.39; H, 3.37; N, 17.29.

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (5b). Off white solid (yield 0.31 g, 62.6%). mp 242–244°C; IR υ (KBr) 3435, 3149, 2924, 1590 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.74 (s, 3H, 4-Methoxy), 3.86 (s, 6H, 3,5-Dimethoxy), 7.16 (s, 2H, C_2,C_6H of 3,4,5-Trimethoxyphenyl), 7.51 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.65 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.29 (s, 1H, Pyrazole-H), 13.89 (s, 1H, pyrazole-NH); ^{13}C NMR (75 MHz) (DMSO-d_6): δ 56.52, 60.70, 104.22, 118.81, 121.86, 128.65, 130.68, 130.93, 131.16, 132.43, 133.60, 141.04, 153.91, 160.49, 163.79; MS: ES$^+$ 413.22 (M + 1). *Anal.* Calcd For $C_{20}H_{17}ClN_4O_4$: C, 58.19; H, 4.15; N, 13.57; Found: C, 58.12; H, 4.12; N, 13.39.

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(3,5-dimethoxyphenyl)-1,3,4-oxadiazole (5c). Light brown solid (yield 0.32 g, 64.7%). mp 214–216°C; IR υ (KBr) 3447, 3148, 2921, 1602 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.83 (s, 6H, 3,5-Dimethoxy), 6.76 (s, 1H, C_4H of 3.5-Dimethoxyphenyl), 7.04 (s, 2H, C_2,C_6H of 3,5-Drimethoxyphenyl), 7.49 (d, J = 8 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.67 (d, J = 6.8 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.27 (s, 1H, Pyrazole-H), 13.89 (s, 1H, pyrazole-NH); LC-MS: 383.0 (M + 1). *Anal.* Calcd For $C_{19}H_{15}ClN_4O_3$: C, 59.61; H, 3.95; N, 14.64; Found: C, 59.53; H, 3.91; N, 14.48.

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (5d). Off white solid (yield 0.29 g, 58.7%). mp 146–148°C; IR υ (KBr) 3467, 3086, 2925, 1617 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 3.84 (s, 3H, 4-Methoxy), 3.87 (s, 3H, 2-Methoxy), 6.72 (d, J = 8.4 Hz, 1H, C_5H of 2,4-Dimethoxyphenyl), 6.77(s, 1H, C_3H of 2,4-Dimethoxyphenyl), 7.48 (d, J = 7.6 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.66 (d, J = 7.2 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.78 (d, J = 8 Hz, 1H, C_6H of 2,4-Dimethoxyphenyl), 8.29 (s, 1H, Pyrazole-H), 13.84 (brs, 1H, pyrazole-NH); MS: 383.1 (M + 1).

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (5e). White solid (yield 0.31 g, 62.7%). mp 246–247°C; IR υ (KBr) 3446, 3142, 1604 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 7.46–7.50 (m, 4H, C_2,C_6H of 4-Cl-Phenyl, and C_2,C_6H of 4-F-Phenyl), 7.70 (d, J = 7.2 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.05 (t, J = 13.2 Hz, 2H, C_3,C_5H of 4-F-Phenyl), 8.29 (s, 1H, Pyrazole-H), 13.91 (s, 1H, pyrazole-NH); ^{13}C NMR (125 MHz) (DMSO-d_6): δ 117.23 (d, J = 22.5 Hz), 120.43, 121.76, 128.66, 129.72 (d, J = 10 Hz), 130.69, 130.81, 130.96, 132.34, 133.45, 160.61, 163.28, 164.60 (d, J = 248.75 Hz). DEPT-135: δ 117.22 (d, J = 22 Hz), 128.66, 129.71 (d, J = 8.75 Hz), 130.70, 130.96. MS: 341.0 (M + 1).

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(4-cyanophenyl)-1,3,4-oxadiazole (5f). White solid (yield 0.31 g, 62.7%). mp 255–257°C; IR υ (KBr) 3438, 3135, 2231, 1602 cm^{-1}; ^1H NMR (400 MHz) (DMSO-d_6): δ 7.47 (d, J = 7.6 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.68 (d, J = 7.6 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 8.08 (d, J = 7.6 Hz, 2H, C_2,C_6H of 4-CN-Phenyl), 8.14 (d, J = 7.6 Hz, 2H, C_3,C_5H of 4-CN-Phenyl), 8.30 (s, 1H, pyrazole-H), 13.94 (s, 1H, pyrazole-NH). *Anal*. Calcd For $C_{18}H_{10}ClN_5O$: C, 62.17; H, 2.90; N, 20.14; Found: C, 62.03; H, 2.87; N, 19.97.

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(2,4,6-trifluorophenyl)-1,3,4-oxadiazole (5g). Off white solid (yield 0.29 g, 58.3%). mp 215-216°C; IR υ (KBr) 3436, 3146, 1603 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$): 6.88 (t, J = 16.4 Hz, 2H, C_3,C_5H of 2,4,6-trifluorophenyl), 7.41 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.57 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.95 (s, 1H, pyrazole-H), 11.96 (br, 1H, pyrazole-NH); LC-MS: 377.1 (M + 1).

2-(4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-5-(2,4,6-trifluorophenyl)-1,3,4-oxadiazole (5h). White solid (yield 0.33 g, 66.8%). mp 224-226°C; IR υ (KBr) 3431, 3149, 2929, 1626 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$): δ 2.23 (s, 6H, 2,6-Dimethyl), 2.32 (s, 3H, 4-Me), 6.95 (s, 2H, C_3,C_5H of 2,4,6-trimethylphenyl), 7.38 (d, J = 8.4 Hz, 2H, C_2 and C_6H of 4-Cl-Phenyl), 7.51 (d, J = 8.4 Hz, 2H, C_3,C_5H of 4-Cl-Phenyl), 7.83 (s, 1H, pyrazole-H), 12.78 (br, 1H, pyrazole-NH); LC-MS: 365.1 (M + 1). *Anal.* Calcd For $C_{20}H_{17}ClN_4O$: C, 65.84; H, 4.70; N, 15.36; Found: C, 65.69; H, 4.65; N, 15.17.

Antitubercular activity. Briefly, 200 μL of sterile deionized water was added to all outer perimeter wells of sterile 96-well plate to minimized evaporation of medium in the test wells during incubation. The 96-well plate received 100 μL of the Middlebrook 7H9 broth, and a serial dilution of compounds was made directly on plate. The final drug concentrations tested were 0.2 to 100 μg/mL. Plates were covered and sealed with parafilm and incubated at 37°C for 5 days. After this time, 25 μL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC was defined as lowest drug concentration that prevented the color change from blue to pink.

Antioxidant activity. Briefly, 1 mL of 0.1 mM methanolic solution of DPPH was added to 3 mL of the synthesized samples at different concentrations in methanol (10, 20, 50, 75, 100 μg/mL). The samples were kept in the dark for 30 min; after which, the absorbance was measured at 517 nm in UV spectrophotometer (Systronics 2202). In its radical form, DPPH absorbs at 517 nm, but upon reduction by an antioxidant or a radical species, its absorption decreases. Lower absorbance of the reaction mixture indicates higher free radical scavenging activity. BHT, which is a good antioxidant, is taken as a standard in this study.

The capability to scavenge the DPPH radical was calculated using the following equation:DPPH. Scavenging effect (%) = $[(A_c - A_s)/A_o)\ 100]$ where A_c is the absorbance of the control reaction and A_s is the absorbance in the presence of sample.

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