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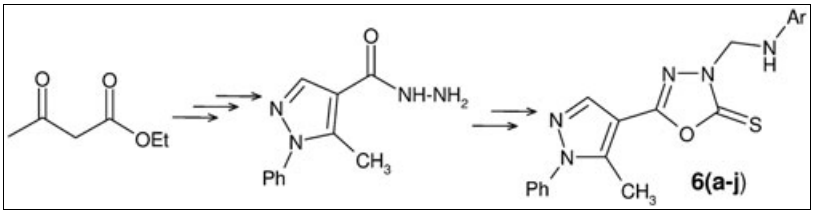

A new series of 3-(arylaminomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones **6a–j** has been synthesized by the reaction of 5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-1,3,4-oxadiazol-2-ylhydrosulfide **5** with formaldehyde and corresponding anilines. The chemical structures of newly synthesized compounds were elucidated by IR, ^{1}H, ^{13}C-NMR, MS, and elemental analyses. The compounds **6a–j** were evaluated for their antibacterial activity against three representative Gram positive bacteria *viz*. *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11) and *Staphylococcus aureus* (MTCC 96), and three Gram negative bacteria *viz*. *Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39) and *Chromobacterium violaceum*. Among the screened **6b**, **6d**, **6i**, and **6j** in which oxadiazole moiety bearing 4-fluoroanilinomethyl, 4-chloroanilinomethyl, 2-trifluoromethylanilinomethyl, and 2,5-difluoroanilinomethyl groups, respectively, showed high activity against all the microorganisms used. In addition these compounds were also screened for their antifungal activity against four fungal organisms *viz*. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996). Most of these new compounds showed appreciable activity against test fungi, and emerged as potential molecules for further development.

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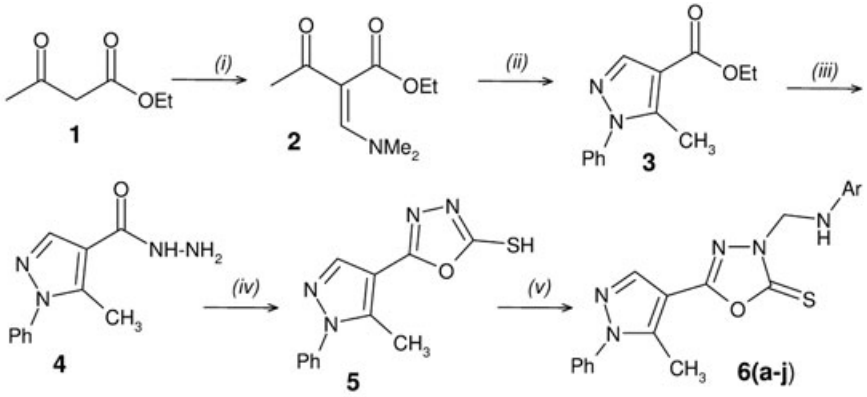
INTRODUCTION

Pyrazole and their derivatives could be considered as possible antimicrobial agents [2]. The other activities include antidepressant [3], inhibitors of protein kinases [4], antiaggregating [5], antiarthritic [6], and cerebro-protectors [7]. Some aryl pyrazoles [8] were reported to have non-nucleoside human immunodeficiency virus-1 reverse transcriptase inhibitory [9], COX-2 inhibitory [10], activator of the nitric oxide receptor and soluble guanylate cyclase activity [11]. In addition, 1,3,4-oxadiazole derivative were reported to possess significant antibacterial [12] and anti-inflammatory [13], tyrosinase inhibitory [14], antiviral [15], antihypertensive [16], cortical muscarinic receptor agonists [17], herbicidal [18], Ca^{2+} channel blocker [19], antitumour [20], anticonvulsant [21], antielmintic [22], and antioxidant activities [23]. In view of these reports and in continuation of our ongoing research on the synthesis of new heterocyclic compounds [24,25], it was thought of interest to accommodate pyrazole, oxadiazole moieties in a single molecular frame work and to obtain a new class of heterocyclic compounds with potential biological activity. In this article, we wish to report the synthesis of a new class of 3-(arylaminomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones **6a–j** in good yields from 5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-1,3,4-oxadiazol-2-ylhydrosulfide **5** (Scheme 1) and their evaluated *in vitro* antibacterial and antifungal activity.

RESULTS AND DISCUSSION

The starting material, (*E*)-2-acetyl-3-(dimethylamino)-2-propenoate **2**, required for the synthesis of title compounds was prepared by the condensation of ethylacetaoacetate **1** with *N*,*N*-dimethyldimethoxymethanamine [26], which on cyclo-condensation with phenyl hydrazine gave the ethyl-5-methyl-1-phenyl-1*H*-4-pyrazole-carboxylate **3**. The 5-methyl-1-phenyl-1*H*-4-pyrazole-carbohydrazide **4** was obtained in 72% yield *via* hydrazinolysis of compound **3** with hydrazine hydrate. The hydrazide **4** on reaction with carbon disulfide and potassium hydroxide, in ethanol, followed by acidification resulted the 5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-1,3,4-oxadiazol-2-ylhydrosulfide **5** in 70% yield. The *N*-Mannich derivatives, 3-(arylaminomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones **6a–j**, were prepared in excellent

Scheme 1. Reagents and conditions: (i) $Me_2NCH(OMe)_2$/EtOH, reflux; (ii) Ph NH NH_2, reflux, 80%; (iii) NH_2 $NH_2 \cdot H_2O$/EtOH, reflux, 72%; (iv) CS_2, KOH/EtOH, reflux, 70%; and (v) Ar-NH_2, CH_2O/EtOH, stirring, 66–74%.



6: Ar = **a**) C_6H_5; **b**) 4-F-C_6H_4; **c**) 2-Cl-C_6H_4; **d**) 4-Cl-C_6H_4; **e**) 4-Br-C_6H_4; **f**) 3-NO_2-C_6H_4; **g**) 4-NO_2-C_6H_4; **h**) 4-MeO-C_6H_4; **i**) 2-CF_3-C_6H_4; **j**) 2,5-$(F)_2$-C_6H_3

yields *via* the reaction of **5** with formaldehyde solution and the corresponding aromatic primary amine in ethanol at room temperature (Scheme 1).

The structures of the newly synthesized compounds were confirmed by their IR, ^1H, ^{13}C-NMR MS and elemental analyses. In the IR spectra of compounds **6a–j**, the absorption band corresponding to the NH stretching of arylamino group was observed at 3326 cm^{-1} and the absorption band corresponding to the C N of the oxadiazole ring was observed at about 1604 cm^{-1}. All other aromatic and aliphatic C H stretching frequencies were observed at the expected regions.

In the ^1H-NMR spectra of compounds **6a–j**, recorded in DMSO-d_6, the signal due to methylene bridge protons of arylaminomethyl group, appeared at 5.47 ppm as a doublet, the NH proton of arylamino group at 5.10 ppm as a triplet, the signal corresponding to the CH_3 group of pyrazole appeared at 2.57 ppm as a singlet. The protons of phenyl group on pyrazole ring and aryl group of arylamino moiety were appeared at 7.00–7.10 and 7.25–7.30 ppm as multiplet, respectively. The aromatic proton of the pyrazole ring at 4-position appeared at 8.10 ppm as a singlet. These signals demonstrate the structure of compounds **6a–j**.

In the ^{13}C-NMR spectrum of compounds **6a–j**, recorded in DMSO-d_6, the prominent signals corresponding to the carbons of pyrazole ring in all compounds observed nearly at 122.9, 138.7, and 143.2 ppm, similarly the signals of oxadiazole ring observed nearly at 155.0 and 171.4 ppm, are proof of further evidence of their structures. Mass spectra of all the synthesized compounds showed M^+/M^{+1} peaks, in agreement with their molecular formulae. In summary, all the synthesized compounds exhibited satisfactory spectral data consistent with their structures.

Antibacterial assay. All the newly prepared compounds **6a–j** were screened for their antibacterial activity against three representative Gram positive bacteria *viz. Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11) and *Staphylococcus aureus* (MTCC 96), and three Gram negative bacteria *viz. Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39), and *Chromobacterium violaceum* (MTCC 2656) by disc diffusion/tube dilution methods [27,28]. In addition, the minimum inhibitory concentration (MIC, μg/mL) of all the compounds were determined by the broth dilution method [29]. For the antibacterial assay standard inoculums (1–2 × 10^7 c.f.u/mL0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculum. The discs measuring 6.26 mm in diameter were prepared from Whatman No. 1 filter paper and sterilized by dry heat at 140°C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37°C. The inhibition zones were measured and compared with the standards (Table 1). For the determination of MIC bacteria were grown over night in Luria Bertani broth at 37°C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in DMSO. Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 50–0.8 μg/mL. Ten microliters of the broth containing about 10^5 c.f.u/mL of test bacteria were added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37°C, and the growth was monitored visually and spectrometrically. The lowest concentration required to arrest the growth of bacteria

Table 1

Antibacterial activity of compounds **6a–j**.

Compound	Diameter of growth inhibition zone (mm at 100 μg/mL) and minimum inhibitory concentration					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
6a	14 (12.5)[a]	14 (25.0)[a]	18 (12.5)[a]	16 (12.5)[a]	14 (12.5)[a]	10 (25.0)[a]
6b	23 (6.25)	30 (3.12)	35 (3.12)	25 (3.12)	25 (6.25)	20 (6.25)
6c	14 (25.0)	14 (12.5)	20 (12.5)	10 (25.0)	18 (12.5)	10 (25.0)
6d	27 (6.25)	25 (6.25)	38 (6.25)	25 (1.56)	25 (3.12)	25 (3.12)
6e	16 (12.5)	13 (12.5)	19 (6.25)	11 (25.0)	10 (25.0)	11 (25.0)
6f	18 (12.5)	15 (12.5)	21 (12.5)	12 (25.0)	11 (25.0)	12 (25.0)
6g	19 (12.5)	10 (25.0)	21 (6.25)	14 (12.5)	13 (12.5)	10 (25.0)
6h	20 (12.5)	11 (25.0)	20 (6.25)	16 (12.5)	15 (12.5)	14 (25.0)
6i	25 (3.12)	30 (3.12)	38 (3.12)	26 (1.56)	25 (1.56)	22 (3.12)
6j	24 (3.12)	30 (6.25)	40 (3.12)	20 (1.56)	25 (3.12)	25 (6.25)
Streptomycin	30 (6.25)	30 (6.25)	41 (6.25)	15 (6.25)	25 (1.56)	20 (3.12)
Penicillin	25 (1.56)	28 (3.12)	40 (1.56)	25 (1.56)	30 (6.25)	25 (12.5)

[a]Values in the parentheses indicate the minimum inhibitory concentration (MIC, μg/mL).

was regarded as MIC (μg/mL), and were determined. The antibacterial activity of each compound was compared with the standard drugs streptomycin and penicillin. The inhibition zone data and the MIC values of the compounds screened are presented in Table 1.

The antibacterial screening data showed that almost all the compounds **6a–j** are active and showing moderate to good antibacterial activity, among the screened **6b**, **6d**, **6i**, and **6j** in which oxadiazole moiety bearing 4-fluoro-anilinomethyl, 4-chloroanilinomethyl, 2-trifluoromethyl-anilinomethyl, and 2,5-difluoroanilinomethyl groups, respectively showed high activity against all the microorganisms used. The activities of these compounds are almost equal to the standards. The remaining compounds showed moderate to good antibacterial activity.

Antifungal assay. The newly prepared compounds **6a–j** were also screened for their antifungal activity against four fungal organisms *viz*. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996) in DMSO by agar diffusion method [30]. In addition, the MIC values are also determined by broth dilution method [29]. For the antifungal assay Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty millilitres of agar media was poured into each petri-dish, excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h. Using an agar punch wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37°C for 3–4 days. The *C. albicans* was grown for 48 h at 28°C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* were plated in potato dextrose agar (Difco) and incubated at 28°C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculums size of 10^5 spores/mL. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range 100–0.8 μg/mL. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/mL of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for about 48–72 h at 28°C. The antifungal activity of each compound was compared with the standard drug amphotericin B. The zone of fungal inhibition and MIC values of the compounds screened are presented in Table 2.

The antifungal screening data showed moderate activity of the test compounds, among the screened, the compounds **6b**, **6d**, and **6j** in which oxadiazole ring bearing 4-fluoroanilinomethyl, 4-chloroanilinomethyl, and 2,5-difluoroanilinomethyl moiety, respectively, showed highest activity against all the microorganisms used. The activity of these compounds is almost equal to the standard. Compounds **6c** and **6i** in which the oxadiazole ring containing 2-chloroanilinomethyl and 2-trifluoro-anilinomethyl moiety showed good inhibition towards *C. albicans* at the concentration of 3.12 μg/mL, which is less than amphotericin B standard. Further, comparison of the antifungal activity (diameter of growth inhibition zone) of the selected compounds **6** and standard drug against different fungi is presented in Figure 1.

Table 2

Antifungal activity of compounds **6a–j**.

Compound	Diameter of growth inhibition zone (mm at 100 μg/mL) and minimum inhibitory concentration			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagrophytes*
6a	15 (12.5)[a]	9 (25.0)[a]	15 (12.5)[a]	9 (25.0)[a]
6b	26 (6.25)	21 (3.12)	20 (6.25)	20 (3.12)
6c	22 (3.12)	10 (25.0)	12 (25.0)	9 (50.0)
6d	25 (6.25)	20 (3.12)	20 (3.12)	20 (3.12)
6e	12 (12.5)	16 (12.5)	10 (25.0)	10 (50.0)
6f	10 (25.0)	12 (12.5)	9 (50.0)	9 (50.0)
6g	12 (25.0)	10 (25.0)	18 (6.25)	12 (12.5)
6h	16 (25.0)	6 (50.0)	12 (12.5)	14 (12.5)
6i	25 (3.12)	10 (12.5)	11 (12.5)	12 (25.0)
6j	26 (6.25)	20 (6.25)	22 (3.12)	19 (6.25)
Amphotericin B	25 (6.25)	20 (3.12)	20 (3.12)	18 (3.12)

[a]Values in the parentheses indicated the minimum inhibitory concentration (MIC, μg/mL).

In conclusion, a new series of 3-(arylaminomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones **6a–j** has been synthesized and evaluated for their antibacterial and antifungal activity. Among the synthesized compounds **6b**, **6d**, **6i**, and **6j** showed good activity against test microorganisms and emerged as potential molecules for further development.

EXPERIMENTAL

Research chemicals were either purchased from Aldrich or Fluka and used without further purification in the reactions or were prepared according to procedures described in the literature. Column chromatography was performed on silica gel 60 (0.043–0.060 mm), Merck. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FTIR 5000 spectrometer, using KBr pellet. ^{1}H, ^{13}C-NMR spectra were recorded on a Varian Gemini spectrometer, operating at 300, 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million downfield from tetramethyl silane. Mass spectra were obtained on a VG micro mass 7070H spectrometer. Elemental analyses were performed on a Perkin–Elmer 240 CHN elemental analyzer.

Ethyl 5-methyl-1-phenyl-1*H*-4-pyrazolecarboxylate (3). A mixture of compound **2** (0.01 mol) and phenyl hydrazine hydrochloride (0.01 mol) in ethanol (20 mL) was heated under reflux for 3 h on a water bath. After completion of the reaction, ethanol was evaporated. The residue was poured in ice-cold water, neutralized with sodium bicarbonate and extracted with ether. The solvent was evaporated under reduced pressure to get the compound **3** as yellow-brown liquid; Yield 80%; bp 260–262°C; IR (KBr): v 3010, 1698, 1630, 1610, 1247 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.10 (t, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.05 (q, 2H, CH_2), 7.15–7.25 (m, 5H, ArH), 7.80 (s, 1H, ArH); ^{13}C-NMR ($CDCl_3$): δ 14.5, 15.4, 62.0, 111.5, 124.9, 127.5, 128.3, 139.1, 139.9, 141.2, 162.8; MS: *m/z* 230 (M^+). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.76; H, 6.08; N, 12.15.

5-Methyl-1-phenyl-1*H*-4-pyrazolecarbohydrazide (4). A mixture of compound **3** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (25 mL) was refluxed for 4 h. The reaction mixture was cooled to room temperature and the solid thus separeated, was filtered, washed with water and recrystallized from ethanol to afford pure intermediate **4** as white solid; Yield 72%, mp 162–64°C; IR (KBr): v 3269, 3062, 2933, 1660, 1612, 1501 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.61 (s, 3H, CH_3), 5.49 (s, 2H, NH_2), 7.15–7.25 (m, 5H, ArH), 8.26 (s, 1H, ArH), 8.96 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ 15.6, 110.7, 124.9, 127.7, 128.3, 138.5, 139.6, 141.0, 165.1; MS: *m/z* 217 (M^++1). Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.06; H, 5.65; N, 25.95.

5-(5-Methyl-1-phenyl-1*H*-4-pyrazolyl)-1,3,4-oxadiazol-2-yl hydrosulfide (5). A mixture of compound **4** (0.01 mol), potassium hydroxide (0.01 mol) and carbon disulfide (0.015 mol), in ethanol (100 mL) was heated under reflux with stirring for 12 h and the solvent was distilled *in vacuo*. The residual mass was poured over crushed ice, neutralized the alkaline solution with 10% hydrochloric acid. The precipitated crude product was filtered, washed with water, dried, and crystallized from ethanol to give compound **5** as white solid; Yield 70%, mp 136–38°C; IR (KBr): v 3162, 2914, 2845, 1612, 1604, 1504, 1343, 1266 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.52 (s, 3H, CH_3), 7.15–7.28 (m, 5H, ArH), 8.21 (s, 1H, ArH). 11.61 (s, 1H, NH/SH); ^{13}C-NMR (DMSO-d_6): δ 13.7, 124.0, 125.1, 127.5, 128.7, 136.7,

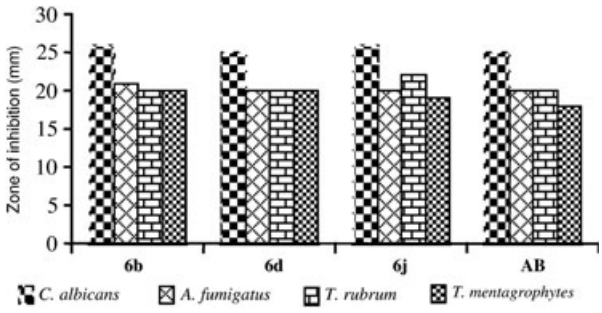


Figure 1. Comparison of antifungal activity of selected compounds with amphotericin B (AB).

138.5, 139.7, 157.8, 170.0; MS: *m/z* 258 (M^+). Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.86; H, 3.82; N, 21.64.

3-(Arylaminomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6a–j). To a solution of compound **5** (0.01 mol) in ethanol (25 mL), appropriate primary aromatic amine (0.01 mol) and 40% formaldehyde solution (20 mL) were added and the mixture was stirred at room temperature for 4 h and allowed to stand overnight. The precipitate separated was filtered, washed with cold ethanol, dried and crystallized from ethanol to afford pure compounds.

3-(Anilinomethyl)-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6a). This compound was obtained as yellow solid; Yield 70%; mp 127–29°C; IR (KBr): v 3336, 3034, 2909, 2849, 1604, 1457, 1370, 1258 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 5.10 (t, 1H, NH), 5.47 (d, 2H, CH_2), 7.00–7.10 (m, 5H, ArH), 7.25–7.30 (m, 5H, ArH), 8.12 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.7, 56.4, 120.7, 121.0, 122.9, 126.3, 127.9, 128.0, 129.5, 136.1, 138.7, 139.8, 143.2, 155.0, 171.2; MS: *m/z* 363 (M^+). Anal. Calcd. for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.27. Found: C, 62.73; H, 4.71; N, 19.23.

3-[(4-Fluoroanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6b). This compound was obtained as yellow solid; Yield 67%; mp 122–24°C; IR (KBr): v 3351, 3039, 1609, 1370, 1254 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 5.10 (t, 1H, NH), 5.46 (d, 2H, CH_2), 6.72 (d, *J* = 8.8 Hz, 2H, ArH), 7.25–7.30 (m, 7H, ArH), 8.12 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.4, 54.5, 119.2, 120.5, 122.9, 126.0, 128.2, 129.0, 135.2, 138.7, 139.8, 140.1, 141.6, 155.0, 171.0; MS: *m/z* 381 (M^+). Anal. Calcd. for $C_{19}H_{16}FN_5OS$: C, 59.83; H, 4.23; N, 18.36. Found: C, 59.80; H, 4.20; N, 18.29.

3-[(2-Chloroanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6c). This compound was obtained as yellow solid; Yield 71%; mp 136–38°C; IR (KBr): v 3342, 3042, 1610, 1370, 685 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 5.15 (t, 1H, NH), 5.90 (d, 2H, CH_2), 6.60–6.70 (m, 2H, ArH), 7.25–7.30 (m, 7H, ArH), 8.12 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.3, 54.5, 115.4, 119.6, 122.0, 122.8, 126.1, 127.6, 128.1, 128.7, 129.3, 135.1, 138.6, 138.9, 139.8, 155.0, 171.0; MS: *m/z* 398 (M^+). Anal. Calcd. for $C_{19}H_{16}ClN_5OS$: C, 57.36; H, 4.05; N, 17.60. Found: C, 57.31; H, 4.06; N, 17.55.

3-[(4-Chloroanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3, 4-oxadiazole-2-thione (6d). This compound was obtained as white solid; Yield 66%; mp 141–43°C; IR (KBr): v 3337, 3041, 2927, 1605, 686 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 5.10 (t, 1H, NH), 5.46 (d, 2H, CH_2), 6.70 (d, *J* = 8.6 Hz, 2H, ArH), 7.20–7.30 (m, 7H, ArH), 8.14 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.7, 54.5, 120.8, 122.8, 123.4, 126.2, 128.0, 128.7, 129.4, 135.2, 138.7, 139.7, 143.7, 155.0, 170.2; MS: *m/z* 398 (M^+). Anal. Calcd. for $C_{19}H_{16}ClN_5OS$: C, 57.36; H, 4.05; N, 17.60. Found: C, 57.35; H, 4.01; N, 17.56.

3-[(4-Bromoanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6e). This compound was obtained as brown solid; Yield 70%; mp 154–56°C; IR (KBr): v 3347, 3032, 2931, 1606, 582 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 5.11 (t, 1H, NH), 5.48 (d, 2H, CH_2), 6.71 (d, *J* = 8.4 Hz, 2H, ArH), 7.20–7.30 (m, 7H, ArH), 8.11 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.6, 55.4, 109.2119.0, 122.7, 126.4, 128.2, 130.0, 130.8, 136.2, 138.6, 139.7, 143.6, 155.1, 171.5; MS: *m/z* 442 (M^+). Anal. Calcd. for $C_{19}H_{16}BrN_5OS$: C, 51.59; H, 3.65; N, 15.83. Found: C, 51.55; H, 3.66; N, 15.78.

5-(5-Methyl-1-phenyl-1*H*-4-pyrazolyl)-3-[(3-nitroanilino) methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione (6f). This compound was obtained as brown solid; Yield 74%; mp 166–68°C; IR (KBr): v 3345, 3031, 2930, 1607, 1520, 1370 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 5.10 (t, 1H, NH), 5.46 (d, 2H, CH_2), 7.05 (s, 1H, ArH), 7.20–7.30 (m, 7H, ArH), 7.65 (d, *J* = 8.3 Hz, 1H, ArH), 8.21 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.6, 55.3, 112.2, 116.5, 117.1, 122.8, 126.1, 128.1, 128.9, 130.1, 135.1, 138.7, 139.8, 146.0, 146.5, 155.2, 170.4; MS: *m/z* 408 (M^+). Anal. Calcd. for $C_{19}H_{16}N_6O_3S$: C, 55.87; H, 3.95; N, 20.58. Found: C, 55.84; H, 3.90; N, 20.60.

5-(5-Methyl-1-phenyl-1*H*-4-pyrazolyl)-3-[(4-nitroanilino) methyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione (6g). This compound was obtained as brown solid; Yield 68%; mp 160–62°C; IR (KBr): v 3334, 3032, 1609, 1540, 1367, 1252 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 5.12 (t, 1H, NH), 5.45 (d, 2H, CH_2), 7.05 (d, *J* = 8.7 Hz, 2H, ArH), 7.25–7.30 (m, 5H, ArH), 8.10 (s, 1H, ArH), 8.20 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.4, 56.3, 120.5, 122.8, 124.8, 126.0, 128.2, 130.2, 135.2, 138.0, 138.6, 139.8, 145.1, 155.2, 170.1; MS: *m/z* 408 (M^+). Anal. Calcd. for $C_{19}H_{16}N_6O_3S$: C, 55.87; H, 3.95; N, 20.58. Found: C, 55.84; H, 3.91; N, 20.54.

3-[(4-Methoxyanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6h). This compound was obtained as yellow solid; Yield 66%; mp 140–42°C; IR (KBr): v 3320, 3026, 1609, 1370, 1072 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.55 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.10 (t, 1H, NH), 5.44 (d, 2H, CH_2), 6.60–6.70 (m, 4H, ArH), 7.25–7.30 (m, 5H, ArH), 8.15 (s, 1H, ArH), 8.10 (s, 1H, ArH), 8.20 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.5, 54.7, 56.0, 115.4, 121.8, 122.8, 126.4, 128.1, 129.4, 136.2, 138.0, 138.7, 139.7, 153.1, 155.0, 170.7; MS: *m/z* 393 (M^+). Anal. Calcd. for $C_{20}H_{19}N_5O_2S$: C, 61.05; H, 4.87; N, 17.80. Found: C, 61.01; H, 4.83; N, 17.76.

5-(5-Methyl-1-phenyl-1*H*-4-pyrazolyl)-3-[2-(trifluoromethyl) anilino]methyl-2,3-dihydro-1,3,4-oxadiazole-2-thione (6i). This compound was obtained as brown solid; Yield 67%; mp 152–54°C; IR (KBr): v 3325, 3025, 2910, 1604, 1367 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 5.11 (t, 1H, NH), 5.42 (d, 2H, CH_2), 6.60 (m, 1H, ArH), 7.20–7.30 (m, 8H, ArH), 8.12 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.6, 55.7, 116.9, 120.1, 120.9, 122.8, 124.9, 126.3, 128.1, 129.4, 129.8, 132.4, 136.2, 138.7, 139.6, 143.3, 155.1, 170.1; MS: *m/z* 432 (M^+). Anal. Calcd. for $C_{20}H_{16}F_3N_5OS$: C, 55.68; H, 3.74; N, 16.23. Found: C, 55.66; H, 3.72; N, 16.21.

3-[(2,5-Difluoroanilino)methyl]-5-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (6j). This compound was obtained as yellow solid; Yield 70%; mp 141–43°C; IR (KBr): v 3328, 3021, 2930, 1611, 1362 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 5.10 (t, 1H, NH), 5.44 (d, 2H, CH_2), 6.27 (s, 1H, ArH), 6.90–7.00 (m, 2H, ArH), 7.25–7.30 (m, 5H, ArH), 8.14 (s, 1H, ArH); ^{13}C-NMR (DMSO-d_6): δ 12.6, 55.8, 104.6, 111.6, 117.8, 122.8, 126.3, 127.6, 128.1, 129.5, 136.2, 138.7, 139.5, 155.0, 168.2, 169.2; MS: *m/z* 339 (M^+). Anal. Calcd. for $C_{19}H_{15}F_2N_5OS$: C, 57.14; H, 3.79; N, 17.53. Found: C, 57.10; H, 3.73; N, 17.50.

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