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Original article

Hypervalent iodine(III) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents

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ABSTRACT

A series of novel 2,5-disubstituted 1,3,4-oxadiazoles **4** have been conveniently synthesized by oxidative cyclization of pyrazolylaldehyde N-acylhydrazones **3** promoted by iodobenzene diacetate under mild conditions (11 examples, up to 92% isolated yields). All the eleven compounds were tested *in vitro* for their antibacterial activity against Gram-positive bacteria namely, *Staphylococcus aureus*, *Bacillus subtilis* and two Gram-negative bacteria namely, *Escherichia coli* and *Pseudomonas aeruginosa*. All the synthesized compounds were also tested for their inhibitory action against two strains of fungus.

1. Introduction

Among five-membered aromatic heterocycles, 1,3,4-oxadiazoles [1,2] are of particular interest, since some of the members belonging to this class display various biological activities including 5-HT-receptor antagonists [3], muscarinic receptor agonists [4,5], benzodiazepine receptor agonists [6], or tyrosinase inhibitors [7]. Oxadiazoles exhibit important biological activities such as anti-inflammatory [8], anticonvulsant [9,10], analgesic [11], antibacterial [12] and muscle relaxant properties [13]. Pyrazole nucleus has pronounced pharmacological applications as anti-anxiety [14], antidiabetic [15], antimicrobial [16–18], herbicidal [19,20], anti-inflammatory drugs [21] and antibacterial [22–24]. Besides the dehydration of diacylhydrazines, oxidative cyclization of aldehyde N-acylhydrazones is the most known method to prepare unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles, and several reagents have been reported to in the literature which include oxidation with ceric ammonium nitrate [25], chloramine T [26], lead tetraacetate [27,28], potassium permanganate under microwaves conditions [29], ferric chloride [30], bromine/sodium acetate [31], or yellow mercuric oxide/iodine [32]. In recent years, hypervalent iodine reagents have been successfully proven their usefulness as agents for oxidative cyclization of aldehyde N-acylhydrazones to synthesize 2,5-disubstituted 1,3,4-oxadiazoles [33–38]. In continuation of our ongoing interest in the development of hypervalent iodine mediated methodologies in heterocyclic synthesis coupled with the significant biological importance of oxadiazoles and pyrazole derivatives, prompted us to undertake the synthesis of hitherto unknown 2,5-disubstituted 1,3,4-oxadiazoles. We report herein synthesis of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles by the oxidation of pyrazolylaldehyde N-acylhydrazones using iodobenzene diacetate (IBD) in dichloromethane with an expectation to find new and more potent antibacterial and antifungal agents.

2. Chemistry

We have synthesized a series of pyrazolylaldehyde N-acylhydrazones in order to test the scope of their oxidative cyclization. These substrates are easily accessible in high yields and purity from N-benzoylhydrazine and formylpyrazoles. Accordingly, an ethanolic solution of N-benzoylhyrazine was refluxed with formylpyrazoles in the presence of two drops of acetic acid for about 1–2 h. Usual work-up of the reaction afforded the pure pyrazolylaldehyde N-benzoylhydrazones (**3a**–**3k**) in 88–96% yields (Scheme 1, Table 1) [39]. The structures of all the new compounds **3** were confirmed by their elemental analysis and also spectral

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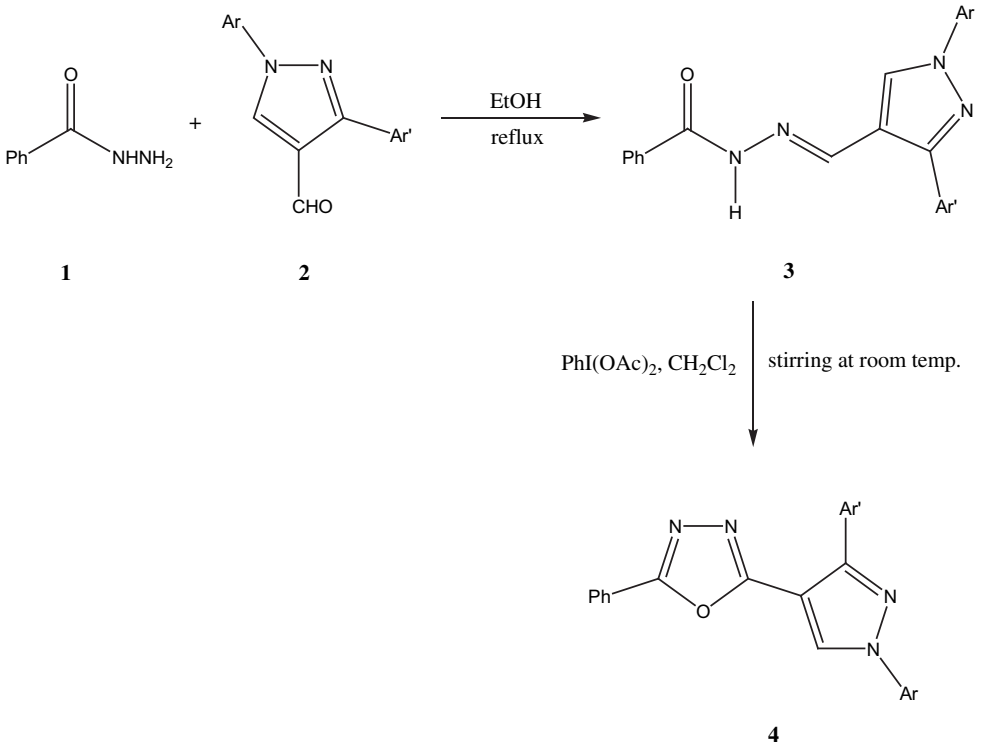

Scheme 1. Synthesis of 1,3,4-oxadiazoles **4** from N-benzoylhydrazones **3** using iodobenzene diacetate.

techniques (IR, ^{1}H NMR). The IR spectra of the compound **3a** exhibited characteristic absorption band at 1643 cm^{-1} and 3217 cm^{-1} due to for carbonyl and NH functional groups, respectively. The ^{1}H NMR spectra of the products **3a** showed two singlet due to C(5)-H of pyrazole ring and N=CH at δ 8.41 and δ 8.54, respectively and also a broad singlet due to NH at δ 9.69 which is disappears on addition of D_2O. Other protons appeared as multiplet in the aromatic regions.

Initially, the reaction of pyrazolylaldehyde N-acylhydrazone (**3a**) was carried out with 1.1 equivalents of IBD in dichloromethane by stirring at room temperature for 15–20 min. The usual work-up of the reaction afforded single product 2,5-disubstituted 1,3,4-oxadiazoles (**4a**) in 90% yield. To study the scope of reaction, we studied oxidation of a wide range of substituted pyrazolylaldehyde N-acylhydrazones (**3b**–**3k**) under similar conditions. It was observed that IBD mediated oxidative approach worked nicely to give the desired products **4b**–**4g** in all cases in 80–92% yields (Scheme 1, Table 1).

The structures of all new compounds **4** were confirmed by their spectral (IR, ^{1}H NMR) and elemental analytical data. The characterization of products **4** was based upon a careful comparison of their IR and ^{1}H NMR spectra with those of **3**. IR spectra of **4** were found to be transparent in the region of NH stretch and NH bends and also CO stretch, thus confirming the oxidation of **3** into **4**. An important characteristic feature in the ^{1}H NMR spectra of **4** was the disappearance of the singlet due to N=CH around δ 8.51–8.68, which present in the spectra of **3**.

The mechanism of this transformation is plausible which is analogous to earlier reports [37,38].

Table 1
Synthesis of bezoylhydrazones 3 and 1,3,4-oxadiazoles **4**.

Entry	Product 3	Product 4	Ar	Ar′
1	**3a**	**4a**	Ph	Ph
2	**3b**	**4b**	Ph	4-Cl–C_6H_4
3	**3c**	**4c**	Ph	4-F–C_6H_4
4	**3d**	**4d**	Ph	4-Br–C_6H_4
5	**3e**	**4e**	Ph	4-Me–C_6H_4
6	**3f**	**4f**	Ph	4-OMe–C_6H_4
7	**3g**	**4g**	Ph	4-NO_2–C_6H_4
8	**3h**	**4h**	4-NO_2–C_6H_4	Ph
9	**3i**	**4i**	4-NO_2–C_6H_4	4-OMe–C_6H_4
10	**3j**	**4j**	4-NO_2–C_6H_4	4-F–C_6H_4
11	**3k**	**4k**	4-NO_2–C_6H_4	4-NO_2–C_6H_4

3. Antibacterial activity

All the eleven compounds **4** were tested *in vitro* for their antibacterial activity against two Gram-positive bacteria namely, *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121), and two Gram-negative bacteria namely, *Escherichia coli* (MTCC 1652)

Table 2
Antibacterial activity of compounds **4** by using agar well diffusion assay method.

Compounds	Diameter of growth of inhibition zone (mm)[a]			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
4a	20.3	18.6	14.3	13.6
4b	21.6	19.6	15.6	13.6
4c	18.6	20.6	14.3	14.3
4d	20	18.3	16.6	14.6
4e	18.3	21.6	15.6	13.6
4f	22.6	20.3	16.3	14
4g	23.3	21.6	15.6	14.3
4h	20.6	24.3	18.6	15.3
4i	24.3	23.6	20.6	18.6
4j	21.3	24.3	20	16.6
4k	22.6	23.6	18.3	14.6
Ciprofloxacin	26.0	24.0	25.0	22.0

[a] Values, including diameter of the well (8 mm), are means of three replicates.

Table 3
Minimum inhibitory concentration (MIC) (in μg/ml) of compounds **4** by using macrodilution method.

Compounds	MIC (μg/ml)[a]			
	Staphylococcus aureus	*Bacillus Subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
4a	64	128	>128	>128
4b	32	64	>128	>128
4c	128	32	>128	>128
4d	64	128	128	>128
4e	128	16	>128	>128
4f	16	32	128	>128
4g	8	16	>128	>128
4h	64	8	128	>128
4i	8	8	64	64
4j	32	8	64	128
4k	16	8	128	>128
Ciprofloxacin	5	5	5	5

[a] Mean of three replicates.

and *Pseudomonas aeruginosa* (MTCC 741) (Tables 2 and 3). Minimum Inhibitory concentration (MIC) of those compounds was determined which are showing activity in primary screening. Standard antibiotics namely Ciprofloxacin was used for comparison with antibacterial activity shown by compounds **4a**–**4g**. All the compounds of the tested series possessed good antimicrobial activity. Two of these compounds **4i** and **4j** exhibited good antibacterial activity against both Gram-positive and Gram-negative bacteria. In case of Gram-positive bacteria compounds **4g** and **4i** were found to be most effective against *S. aureus* with zone of inhibition ranging between 23.3 and 24.3 and compounds **4h**, **4i**, **4j**, and **4k** were most effective against *B. subtilis*, with zone of inhibition ranging between 23.6 and 24.3. However, in case of Gram-negative bacteria, compound **4i** and **4j** were found to be most effective against *E. coli* and *P. aeruginosa* with zone of inhibition ranging between 16.6 and 20.6 (Table 2).

In the whole series, compounds **4g** and **4i** showed maximum antibacterial activity against *S. aureus* (MIC 8 μg/ml) and compounds **4h**, **4i**, **4j** and **4k** against *B. subtilis* (MIC 8 μg/ml) whereas in case of Gram-negative bacteria lowest MIC was found to be 64 μg/ml in case of *E. coli* by compounds **4i** and **4j** and 64 μg/ml in case of *P aeruginosa* by compound **4i** (Table 3).

4. Antifungal activity

All the eleven compounds were tested *in vitro* for their antifungal activity against two fungi, namely *Aspergillus niger* and *Aspergillus flavus*. Standard antibiotics namely Fluconazole was used for comparison with antifungal activity shown by compounds **4a**–**4k**. A careful analysis of percentage mycelial growth inhibition revealed that almost all of the newly synthesized compounds **4** showed comparable antifungal activity with commercial antibiotic Fluconazole as shown in Table 4. Compounds **4e** and **4h** showed maximum inhibition against both of the fungi, *A. niger* (66.6) and *A. flavus* (66.6). Compound **4c** was found more effective against *A. niger* (66.6). It also inhibited the growth of *A. flavus* (50). Compounds **4a**, **4f** and **4g** also showed maximum inhibition against *A. flavus* (66.6), but both inhibited the growth of *A. niger* (44.4). Compounds **4b**, **4d**, **4i**, **4j** and **4k** displayed almost same inhibition against both of the fungi.

Table 4
In vitro antifungal activity of compounds **4** using poisoned food method.

Compounds	Mycelial growth inhibition (%)[a]	
	Aspergillus niger	*Aspergillus flavus*
4a	44.4	61.1
4b	55.5	44.4
4c	66.6	50
4d	61.1	55.5
4e	66.6	61.1
4f	44.4	66.6
4g	50	61.1
4h	66.6	66.6
4i	55.5	50
4j	44.4	55.5
4k	55.5	44.4
Fluconazole	81.1	77.7

[a] Mean of three replicates.

5. Conclusion

We have described herein an efficient and convenient synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles *via* the oxidative cyclization of N-benzoyl-N′-pyrazolidene hydrazines, thereby emphasizing the increasing utility of hypervalent iodine (III) mediated methods and this method stands as a feasible alternative for convenient access to this class of heterocycles. The antibacterial and antifungal activities of compounds have proved them potent antibacterial and antifungal agents.

6. Experimental

Melting points were determined in open capillaries with electrical melting point apparatus and are uncorrected. The IR spectra were obtained with a Buck Scientific IR M-500 spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker (300 MHz) spectrometer using tetramethylsilane as an internal standard. All the new compounds gave satisfactory analytical results (within 0.4 of the theoretical values). The starting material formylpyrazoles were prepared by literature method [40].

6.1. N-Benzoyl-N′-pyrazolylidene hydrazines **3**

General procedure: To an ethanolic solution of phenyl hydrazide (**1**, 0.01 mol) was added formylpyrazoles (**2**, 0.011 mol) and the solution was refluxed in the presence of two drops of acetic acid for 1–2 h. The solvent was evaporated *in vacuo* to half its volume and cool to room temperature. The solid obtained was filtered and washed with ethanol.

6.1.1. N-Benzoyl-N′-(1,3-diphenyl-4-pyrazolylidene) hydrazine (**3a**)

Yield 96%, Mp 180–182 °C, IR (ν_{max}, in KBr): 3217 cm^{-1} (–NH str.), 1641 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.35 (m, 3H), 7.45–7.49 (m, 4H), 7.51–7.55 (m, 3H), 7.70–7.79 (m, 5H), 8.41 (s, 1H), 8.51 (s, 1H), 10.06 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{18}N_4O$: C 75.41, H 4.92, N 15.30; Found: C 75.11, H 4.76, N 15.38.

6.1.2. N-Benzoyl-N′-[1-phenyl-3-(4-chlorophenyl)-4-pyrazolylidene] hydrazine (**3b**)

Yield 92%, Mp 212–214 °C, IR (ν_{max}, in KBr): 3220 cm^{-1} (–NH str.), 1643 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.36 (m, 3H), 7.41–7.48 (m, 4H), 7.53–7.57 (m, 3H), 7.68–7.71 (m, 2H), 7.92–7.95 (m, 2H), 8.41 (s, 1H), 8.51 (s, 1H), 10.06 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{17}N_4OCl$: C 68.91, H 4.24, N 13.98; Found: C 68.71, H 4.22, N 14.07.

6.1.3. N-Benzoyl-N′-[1-phenyl-3-(4-fluorophenyl)-4-pyrazolylidene] hydrazine (**3c**)

Yield 88%, Mp 210–212 °C, IR (ν_{max}, in KBr): 3220 cm^{-1} (–NH str.), 1645 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17

(m, 2H), 7.33–7.38 (m, 1H), 7.45–7.57 (m, 5H), 7.65–7.69 (m, 2H), 7.80 (m, 2H), 7.89–7.91 (m, 2H), 8.42 (s, 1H), 8.68 (s, 1H), 9.64 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{17}N_4OF$: C 71.87, H 4.43, N 14.58; Found: C 71.92, H 4.34, N 14.69.

*6.1.4. N-Benzoyl-N′-[1-phenyl-3-(4-bromophenyl)-4-pyrazolylidene] hydrazine (**3d**)*

Yield 90%, Mp 220–222 °C, IR (ν_{max}, in KBr): 3226 cm^{-1} (–NH str.), 1639 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.36 (m, 3H), 7.41–7.48 (m, 4H), 7.53–7.57 (m, 3H), 7.68–7.71 (m, 2H), 7.92–7.95 (m, 2H), 8.41 (s, 1H), 8.51 (s, 1H), 10.06 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{17}N_4OBr$: C 62.03, H 3.82, N 12.59; Found: C 61.93, H 3.88, N 12.54.

*6.1.5. N-Benzoyl-N′-[1-phenyl-3-(4-methylphenyl)-4-pyrazolylidene] hydrazine (**3e**)*

Yield 96%, Mp 220–222 °C, IR (ν_{max}, in KBr): 3234 cm^{-1} (–NH str.), 1644 cm^{-1}(C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H, CH_3), 7.22–7.28 (m, 3H), 7.45–7.52 (m, 7H), 7.73–7.75 (m, 2H), 7.90–7.92 (m, 2H), 8.35 (s, 1H), 8.58 (s, 1H), 9.84 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{24}H_{20}N_4O$: C 75.79, H 5.26, N 14.74; Found: C 75.78, H 5.32, N 14.71.

*6.1.6. N-Benzoyl-N′-[1-phenyl-3-(4-methoxyphenyl)-4-pyrazolylidene] hydrazine (**3f**)*

Yield 95%, Mp 208–210 °C, IR (ν_{max}, in KBr): 3217 cm^{-1} (–NH str.), 1643 cm^{-1}(C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H, OCH_3), 7.00 (d, 2H, J = 8.7), 7.32–7.36 (m, 1H), 7.46–7.52 (m, 5H), 7.59 (d, 2H, J = 8.7 Hz), 7.78–7.81 (m, 2H), 7.87–7.89 (m, 2H), 8.29 (s, 1H), 8.67 (s, 1H), 9.35 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{24}H_{20}N_4O_2$: C 72.73, H 5.05, N 14.14; Found: C 72.61, H 4.98, N 14.19.

*6.1.7. N-Benzoyl-N′-[1-phenyl-3-(4-nitrophenyl)-4-pyrazolylidene] hydrazine (**3g**)*

Yield 95%, Mp 228–230 °C, IR (ν_{max}, in KBr): 3221 cm^{-1} (–NH str.), 1641 cm^{-1}(C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.42 (m, 1H), 7.49–7.57 (m, 5H), 7.78–7.81 (m, 2H), 7.89–7.92 (m, 4H), 8.31 (d, 2H, J = 7.8), 8.48 (s, 1H), 8.67 (s, 1H), 9.60 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{17}N_5O_3$: C 67.15, H 4.14, N 17.03; Found: C 67.16, H 4.12, N 17.05.

*6.1.8. N-Benzoyl-N′-[1-(4-nitrophenyl)-3-phenyl-4-pyrazolylidene] hydrazine (**3h**)*

Yield 94%, Mp 226–228 °C, IR (ν_{max}, in KBr): 3220 cm^{-1} (–NH str.), 1643 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.51–7.62 (m, 6H), 7.67–7.70 (m, 2H), 7.83–7.87 (m, 2H), 8.01–8.06 (m, 2H), 8.39–8.45 (m, 3H), 8.82 (s, 1H), 10.12 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{17}N_5O_3$: C 67.15, H 4.14, N 17.03; Found: C 67.09, H 4.06, N 17.02.

*6.1.9. N-Benzoyl-N′-[1-(4-nitrophenyl)-3-(4-methoxyphenyl)-4-pyrazolylidene] hydrazine (**3i**)*

Yield 95%, Mp 234–236 °C, IR (ν_{max}, in KBr): 3228 cm^{-1} (–NH str.), 1643 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H, OCH_3), 6.93 (d, 2H, J = 8.1 Hz), 7.37–7.49 (m, 3H), 7.58 (d, 2H, J = 8.1 Hz), 7.88–7.90 (m, 2H), 7.97 (d, 2H, J = 8.7 Hz), 8.27 (d, 2H, J = 8.7 Hz), 8.52 (s, 1H), 8.75 (s, 1H), 11.6 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{24}H_{19}N_5O_4$: C 65.31, H 4.31, N 15.87; Found: C 65.34, H 4.32, N 15.85.

*6.1.10. N-Benzoyl-N′-[1-(4-nitrophenyl)-3-(4-fluorophenyl)-4-pyrazolylidene] hydrazine (**3j**)*

Yield 96%, Mp 218–220 °C, IR (ν_{max}, in KBr): 3238 cm^{-1} (–NH str.), 1646 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, 2H, J = 8.1 Hz), 7.37–7.49 (m, 3H), 7.45 (d, 2H, J = 8.1 Hz), 7.88–7.90 (m, 2H), 7.97 (d, 2H, J = 8.7 Hz), 8.27 (d, 2H, J = 8.7 Hz), 8.52 (s, 1H), 8.75 (s, 1H), 11.6 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{16}N_5O_3$: C 64.33, H 3.73, N 16.32; Found: C 64.26, H 3.61, N 16.45.

*6.1.11. N-Benzoyl-N′-[1,3-di(4-nitrophenyl)-4-pyrazolylidene] hydrazine (**3k**)*

Yield 92%, Mp 230–232 °C, IR (ν_{max}, in KBr): 3224 cm^{-1} (–NH str.), 1641 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.49 (m, 3H), 7.87 (d, 2H, J = 8.1 Hz), 7.88–7.90 (m, 2H), 7.97 (d, 2H, J = 8.7 Hz), 8.27 (d, 2H, J = 8.7 Hz), 8.39 (d, 2H, J = 8.1 Hz), 8.52 (s, 1H), 8.75 (s, 1H), 11.6 (s, 1H, exchangeable with D_2O); Anal. Calculated for $C_{23}H_{16}N_6O_5$: C 60.53, H 3.51, N 18.42; Found: C 60.45, H 3.36, N 18.73.

*6.2. 2,5-Disubstituted 1,3,4-oxadiazoles **4***

General procedure: To a stirred solution of **3** (0.001 mol) in dichloromethane (25 mL) at room temperature was added IBD (0.011 mol) in four to five portions during 5 min and the mixture was stirred for 20–30 min. The solvent was evaporated on a steam bath and the residual mass containing product and iodobenzene triturated with petroleum ether to give solid product, which was recrystallised from methanol to yield pure 2,5-disubstituted 1,3,4-oxadiazoles **4** in 80–92% yields.

*6.2.1. 2-Phenyl-5-(1,3-diphenyl-4-pyrazolyl) 1,3,4-oxadiazole (**4a**)*

Yield 90%, mp 136–138 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.43 (m, 1H), 7.49–7.54 (m, 8H), 7.84–7.86 (m, 2H), 7.93–7.99 (m, 4H), 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.3, 119.2, 119.7, 123.8, 126.7, 126.9, 127.4, 127.8, 129.0, 129.4, 129.6, 130.1, 131.6, 139.1, 159.9, 163.8; Anal. Calculated for $C_{23}H_{16}N_4O$: C 75.82, H 4.39, N 15.38; Found: C 75.81, H 4.34, N 15.41.

*6.2.2. 2-Phenyl-5-[1-phenyl-3-(4-chlorophenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4b**)*

Yield 86%, mp 168–170 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.28 (m, 2H), 7.42–7.45 (m, 1H), 7.49 (d, 2H, J = 9.0 Hz), 7.53–7.61 (m, 3H), 7.84–7.87 (m, 2H), 7.97 (d, 2H, J = 9.0 Hz), 8.00–8.03 (m, 2H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.4, 119.4, 123.6, 126.8, 127.5, 128.5, 129.1, 129.5, 129.7, 130.2, 130.7, 131.7, 139.2, 150.6, 159.6, 163.9; Anal. Calculated for $C_{23}H_{15}N_4OCl$: C 69.26, H 3.76, N 14.05; Found: C 69.21, H 3.77, N 14.05.

*6.2.3. 2-Phenyl-5-[1-phenyl-3-(4-fluorophenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4c**)*

Yield 82%, mp 134–136 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.24–7.25 (t, 2H, J = 8.7 Hz), 7.41–7.43 (m, 1H), 7.55–7.58 (m, 5H), 7.84–7.87 (d, 2H, J = 9.0 Hz), 7.97–8.02 (m, 4H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.4, 119.5, 123.7, 126.8, 127.7, 127.9, 129.1, 129.4, 129.7, 130.9, 131.1, 131.7, 139.1, 150.9, 159.8, 163.9; Anal. Calculated for $C_{23}H_{15}N_4OF$: C 72.25, H 3.93, N 14.66; Found: C 72.03, H 3.83, N 14.78.

*6.2.4. 2-Phenyl-5-[1-phenyl-3-(4-bromophenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4d**)*

Yield 92%, mp 178–180 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.44 (m, 1H), 7.53–7.58 (m, 5H), 7.65 (d, 2H, J = 8.7 Hz), 7.83–7.87 (m, 2H), 7.90 (d, 2H, J = 8.7 Hz), 8.00–8.03 (m, 2H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.4, 119.4, 123.4, 123.7,

126.8, 127.8, 128.5, 129.1, 129.5, 129.7, 130.6, 131.7139.0, 150.7, 159.6, 163.9; Anal. Calculated for $C_{23}H_{15}N_4OBr$: C 62.32, H 3.39, N 12.64; Found: C 62.33, H 3.39, N 12.68.

*6.2.5. 2-Phenyl-5-[1-phenyl-3-(4-methylphenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4e**)*

Yield 86%, mp 106–108 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47 (s, 3H, CH_3), 7.33 (d, 2H, $J = 7.8$ Hz), 7.38–7.43 (m, 1H), 7.49–7.57 (m, 5H), 7.85–7.87 (m, 4H), 8.0 (d, 2H, $J = 7.8$ Hz), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 21.4, 106.3, 119.1, 119.6, 123.8, 126.8, 127.5, 127.8, 129.1, 129.5, 129.6, 130.1, 131.6, 139.2, 141.8, 159.9, 163.8; Anal. Calculated for $C_{24}H_{18}N_4O$: C 76.19, H 4.76, N 14.81; Found: C 76.04, H 4.68, N 14.86.

*6.2.6. 2-Phenyl-5-[1-phenyl-3-(4-methoxyphenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4f**)*

Yield 84%, mp 110–112 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.9 (s, 3H, OCH_3), 7.05 (d, 2H, $J = 8.7$ Hz), 7.38–7.42 (m, 1H), 7.51–7.57 (m, 5H), 7.83–7.87 (m, 2H), 7.93 (d, 2H, $J = 8.7$ Hz), 8.00–8.03 (m, 2H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 55.4, 106.2, 113.7, 119.4, 123.8, 124.2, 126.8, 127.5, 129.1, 129.4, 129.7, 130.4, 131.6, 139.2, 160.0, 160.3, 163.8; Anal. Calculated for $C_{24}H_{18}N_4O_2$: C 73.09, H 4.57, N 14.21; Found: C 73.13, H 4.52, N 14.28.

*6.2.7. 2-Phenyl-5-[1-phenyl-3-(4-nitrophenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4g**)*

Yield 82%, mp 220–222 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.47 (m, 1H), 7.54–7.61 (m, 5H), 7.84–7.89 (m, 2H), 8.03–8.06 (m, 2H), 8.32 (d, 2H, $J = 8.7$ Hz), 8.38 (d, 2H, $J = 8.7$ Hz), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.2, 119.1, 119.7, 122.5, 124.2, 126.8, 127.5, 129.1, 129.4, 129.7, 130.4, 131.6, 139.2, 148.1, 160.3, 163.8; Anal. Calculated for $C_{23}H_{15}N_5O_3$: C 67.48, H 3.67, N 17.11; Found: C 67.46, H 3.63, N 17.19.

*6.2.8. 2-Phenyl-5-[1-(4-nitrophenyl)-3-phenyl-4-pyrazolyl] 1,3,4-oxadiazole (**4h**)*

Yield 84%, mp 214–216 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, 2H, $J = 8.7$ Hz), 7.67–7.70 (m, 4H), 7.83–7.87 (m, 2H), 7.95 (d, 2H, $J = 8.7$ Hz), 8.01–8.06 (d, 2H), 8.39–8.45 (d, 2H, $J = 8.7$ Hz), 8.85 (s, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.2, 119.4, 123.3, 124.5, 126.8, 127.5, 129.1, 129.4, 129.7, 130.4, 130.8, 131.6, 144.5, 149.2, 159.3, 163.7; Anal. Calculated for $C_{23}H_{15}N_5O_3$: C 67.48, H 3.67, N 17.11; Found: C 67.53, H 3.59, N 17.16.

*6.2.9. 2-Phenyl-5-[1-(4-nitrophenyl)-3-(4-methoxyphenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4i**)*

Yield 88%, mp 222–224 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (s, 3H, OCH_3), 7.07 (d, 2H, $J = 8.1$ Hz), 7.50–7.59 (m, 3H), 7.93(d, 2H, $J = 8.1$ Hz), 8.01–8.07 (m, 4H), 8.43 (d, 2H, $J = 9.0$ Hz), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 56.2, 106.2, 113.7, 119.4, 121.3, 123.2, 126.8, 127.5, 129.1, 129.4, 129.7, 130.4, 131.6, 145.1, 149.2, 159.3, 163.7; Anal. Calculated for $C_{24}H_{17}N_5O_4$: C 65.60, H 3.87, N 15.95; Found: C 65.58, H 3.87, N 16.02.

*6.2.10. 2-Phenyl-5-[1-(4-nitrophenyl)-3-(4-fluorophenyl)-4pyrazolyl] 1,3,4-oxadiazole (**4j**)*

Yield 87%, mp 216–218 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.59 (m, 5H), 7.66 (d, 2H, $J = 8.1$ Hz), 7.89 (d, 2H, $J = 8.1$ Hz), 7.99 (d, 2H, $J = 9.0$ Hz), 8.43 (d, 2H, $J = 9.0$ Hz), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.2, 116.1, 119.4, 122.1, 123.5, 126.6, 127.5, 129.2, 129.4, 129.7, 131.1, 131.6, 144.9, 149.2, 162.1, 163.7; Anal. Calculated for $C_{23}H_{14}N_5O_3$: C 64.64, H 3.28, N 16.39; Found: C 64.62, H 3.31, N 16.45.

*6.2.11. 2-Phenyl-5-[1-(4-nitrophenyl)-3-(4-nitrophenyl)-4-pyrazolyl] 1,3,4-oxadiazole (**4k**)*

Yield 90%, mp 224–226 °C, IR (ν_{max}, in KBr): transparent in the region of –NH str. and C=O str.; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.49 (m, 3H), 7.88–7.90 (m, 2H), 7.91 (d, 2H, $J = 8.1$ Hz), 8.01 (d, 2H, $J = 8.7$ Hz), 8.31 (d, 2H, $J = 8.1$ Hz), 8.39 (d, 2H, $J = 8.7$ Hz), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 106.2, 119.1, 119.7, 122.1, 123.5, 126.6, 127.5, 129.2, 129.4, 129.7, 131.1, 131.6, 145.2, 145.6, 149.2, 163.7; Anal. Calculated for $C_{23}H_{14}N_6O_5$: C 60.79, H 3.08, N 18.50; Found: C 60.87, H 2.99, N 18.54.

7. Biological activity

Antibacterial [41–44] and antifungal activity [45–47] is carried out by the literature method.

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