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Synthesis and Antimicrobial Screening of 2-Methyl-3-[5-substituted phenyl-1,3,4-oxadiazol-2-yl]-1*H*-indoles

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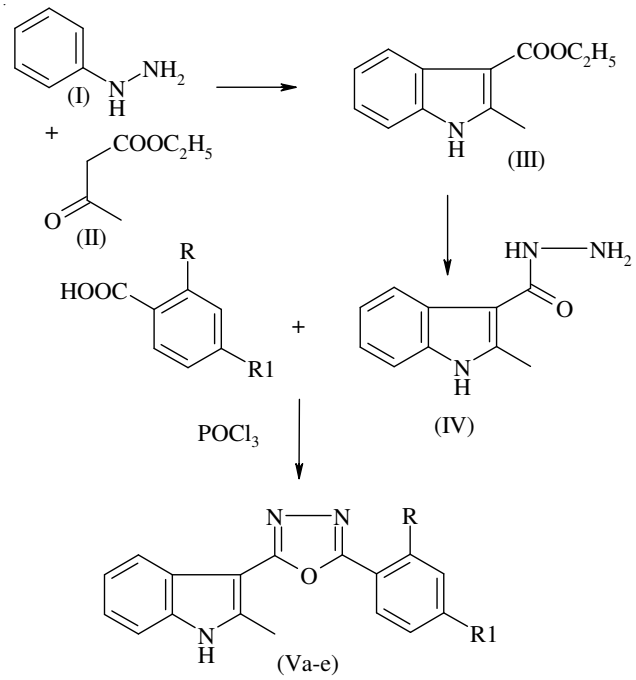
Some 2-methyl-3-[5-substituted phenyl-1,3,4-oxadiazol-2-yl]-1*H*-indoles (**Va-e**) were synthesized by reacting oxoacetohydrazide (**IV**) with various aromatic acid in presence of phosphorus oxychloride. The structures of the compounds have been established on their analytical and spectral data. All the compounds have been screened for their antimicrobial activity against *Bacillus subtillis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Aspergillus niger* and *Candida albicans*. Compounds **Ve** and **Vb** exhibited interesting results.

Key Words: 1,3,4-Oxadiazoles, Indoles, Antimicrobial activity.

INTRODUCTION

1,3,4-Oxadiazoles constitute a unique class of nitrogen and oxygen containing five member heterocycles. During the past years considerable evidence has also accumulated to demonstrate the efficacy of 1,3,4-oxadiazoles including antifungal[1], anticancer[2,7], anticounvulsant[3-5], insecticidal[6], antibacterial[7,8], antiinflammatory[9] and other biological activities. We report herein, the synthesis of several 2-methyl-3-[5-substituted phenyl-1,3,4-oxadiazol-2-yl]-1*H*-indoles (**Va-e**) and result of their antimicrobial activity. 2-(2-Methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (**IV**) by treatment with aromatic acid in presence of phosphorus oxychloride affords 2-methyl-3-[5-substituted phenyl-1,3,4-oxadiazol-2-yl]-1*H*-indoles (**Va-e**) (**Scheme-I**). The compound 2-(2-methyl-1*H*-indol-3-yl)-2 oxoacetohydrazide (**IV**) required for the preparation of the target compounds was obtained by refluxing ethyl (2-methyl-1*H*-indol-3-yl)-2-oxoacetate (**III**) and hydrazine hydrate. Compound **III** was obtained by refluxing phenyl hydrazine (**I**) and ethyl acetoacetate (**II**). The structures of the synthesized compounds have been established based on their analytical and spectral data. All the compounds have been screened for their antimicrobial activity.



Scheme-I

EXPERIMENTAL

Melting points of the compounds were determined in open capillaries and are uncorrected. Purity of the compounds was checked by micro TLC using silica gel G coated glass plates using benzene-methanol (9:1, v/v) as irritant and iodine vapour as detecting agent. The IR (KBr) spectra were recorded on a Perkin-Elmer Infrared-283 spectrophotometer. ^{1}H NMR ($CDCl_3$, DMSO-d_6) spectra were recorded on a Bruker DPX-200 MHz NMR spectrophotometer; chemical shifts (δ) are reported in ppm, with TMS as internal standard. GC Mass spectra were recorded on a Shimadzu QP 50000. Elemental analyses for C, H and N were performed on a Perkin Elmer 240 C elemental analyzer and were with in ± 0.4 % of the theoretical value. Physical data of the compounds and the percentage yield of various reactions are given in Table-1.

Synthesis of ethyl-(2-methyl-1*H*-indol-3-yl)-2-oxoacetate (III): In a 500 mL three-necked flask fitted with a dropping funnel a sealed stirrer unit and reflux condenser. Heat under reflux a mixture of ethyl acetoacetate (**II**) (0.1mol) and acetic acid with stirring and add phenyl hydrazine (**I**) (0.1 mol) during 1 h. Continue the stirring for another 1 h. Pour the reaction mixture into water stir vigorously while it solidifies. Cool to 5°C, filter at vacuum pump and recrystallized from ethanol. Yield 70 %.

TABLE-1
PHYSICAL DATA OF 2-METHYL-3-[5-(SUBSTITUTED PHENYL)-1,3,4-OXADIAZOLE-2-YL]-1*H*-INDOLES

Compd.	R	R_1	m.f.	m.w.	Recryst-allization solvent	m.p. (ºC)	Yield (%)	R_f values*
Va	H	H	$C_{17}H_{13}N_3O$	275	DMF	152	64	0.53
Vb	OH	H	$C_{17}H_{13}N_3O_2$	291	DMF	162	66	0.65
Vc	NH_2	H	$C_{17}H_{14}N_4O$	290	GAA	144	69	0.66
Vd	H	NH_2	$C_{17}H_{14}N_4O$	290	DMF	136	67	0.60
Ve	Cl	H	$C_{17}H_{12}N_3OCl$	309	DMF	146	62	0.58

*R_f value was determined in benzene:methanol (9:1). DMF-Dimethyl formamide, GAA-Glacial acetic acid

Synthesis of 2-(2-methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (IV): A mixture of ethyl-(2-methyl-1*H*-indol-3-yl)-2-oxoacetate (**III**), hydrazine hydrate in equimolar portion and 15 mL ethanol were taken in a round bottom flask and refluxed for 6 h. Excess solvent was removed by distillation. The crude product on recrystallization from ethanol to obtain silky white crystals (**IV**). Yield 65 %.

Synthesis of 2-methyl-3-[5-substitutedphenyl-1,3,4-oxadiazol-2-yl]-1*H*-indoles (Va-e): 2-(2-Methyl-1*H*-indol-3-yl)-2-oxoacetohydrazide (**IV**) (1.9 g, 0.01 mol) and different aromatic acid (0.01 mol) in phosphorus oxychloride (5-10 mL) were refluxed for 6 h. cooled to room temperature and poured into crushed ice. On neutralization with 10 % sodium bicarbonate solution, a solid mass separated out which was filtered, washed with water and recrystallized from appropriate solvent system to give the title compounds.

2-Methyl-3-[5-phenyl-1,3,4-oxadiazol-2-yl]-1*H*-indole (Va): IR (KBr, ν_{max}, cm^{-1}) 3413 (-NH-), 2922 (-C-H) and 1596 (-C=N) 1275 (-C-O). ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.7-7.4 (m, 10H, Ar-H & NH) and 2.2 (s, 3H, CH_3); m/z: 275 (M^+); Anal. ($C_{17}H_{13}N_3O$) Found (%) C, 74.32: H, 4.85: N, 15.62. Calcd. (%): C, 74.17; H, 4.76; N, 15.26.

2-Methyl-3-[5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-1*H*-indole (Vb): IR (KBr, ν_{max}, cm^{-1}) 3575 (-OH), 3365 (NH), 1604 (-C=N) and 1204 (-C-O). ^1H NMR ($CDCl_3$, DMSO-d_6, *d* ppm): 7.6-7.2 (m, 9H, Ar-H & NH), 5.4 (s, 1H, OH) and 2.4 (s, 3H, CH_3); m/z: 291 (M^+); Anal. ($C_{17}H_{13}N_3O_2$) Found (%) C, 69.85; H, 4.29; N, 14.72. Calcd. (%): C, 70.09; H, 4.50; N, 14.42.

2-Methyl-3-[5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl]-1*H*-indole (Vc): IR (KBr, ν_{max}, cm^{-1}) 3452 (NH_2), 3311 (NH), 1696 (-C=N-) and 1261 (-C-O). ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 8.2 (s, 2H, NH_2) and 7.6-7.2 (m, 9H, Ar-H & NH), 2.3 (s, 3H, CH_3); m/z: 290 (M^+); Anal.

($C_{17}H_{14}N_4O$) Found (%) C, 70.07; H, 4.43; N, 19.62; Calcd. (%) C, 70.33; H, 4.86; N, 19.30.

2-Methyl-3-[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]-1*H*-indole (Vd): IR (KBr, ν_{max}, cm^{-1}) 3453 (NH_2), 3323 (NH, 1595 (-C=N-) and 1177 (-C-O). ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 9.2 (s, 2H, NH_2) and 7.6-7.2 (m, 9H, Ar-H & NH), 2.2(s, 3H, CH_3); m/z: 290 (M^+); Anal. ($C_{17}H_{14}N_4O$) Found (%) C, 69.82; H, 5.22; N, 19.65; Calcd. (%) C, 70.33; H, 4.86; N, 19.30.

2-Methyl-3-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1*H*-indole (Ve): IR (KBr, ν_{max}, cm^{-1}) 3446 (NH), 2923 (-C-H-), 1594 (-C=N-) and 762 (-C-O). ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.8-7.4 (m, 9H, Ar-H & NH) 2.2 (s, 3H, CH_3); m/z: 309 (M^+); Anal. ($C_{17}H_{12}ClN_3O$) Found (%) C, 66.22; H, 4.10; N, 13.26; Calcd. (%) C, 65.92; H, 3.90; N, 11.45.

Antimicrobial activity: The *in vitro* antimicrobial activity was carried out against 24 h old culture of four bacteria and two fungi. The bacteria used were *Bacillus subtillis, Staphylococcus aures, Pseudomonas aeruginosa* and *Escherichia coli* and fungi used were *Candida albicans* and *Aspergillus niger* (Table-2). These activities were performed by cup plate method[10]. The compounds were tested at a concentration of 100 μg/mL in dimethyl formamide solution using ciprofloxacin (100 μg/mL) for antibacterial and clotrimoxazole (100 μg/mL) for antifungal activity as the standard for comparison of antibacterial and antifungal activity, respectively. Inhibition was recorded by measuring the diameter of the inhibition zone at the end of 24 h for bacteria and 48 h for fungi. Each experiment was repeated thrice and average of three independent determinations was recorded.

RESULTS AND DISCUSSION

All the compounds have been screened for their antimicrobial activity against bacteria *Bacillus subtillis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*, against fungi *Aspergillus niger* and *Candida albicans*. The antimicrobial activity of oxadiazole derivatives against microorganisms revealed that compound **Ve** and **Vb** exhibited highest activity against *Aspergillus niger*.

Result conclude that most of the compounds exhibited mild to moderate antibacterial and antifungal activity compared with their respective standards. Interestingly, compound **Ve** having chloro group on the phenyl ring showed highest activity against *Aspergillus niger* and *Staphylococcus aureus*.

TABLE-2
ANTIMICROBIAL ACTIVITY OF 2-METHYL-3-[5-(SUBSTITUTED PHENYL)-1,3,4-OXADIAZOLE-2-YL]-1*H*-INDOLES

Compd.	Antibacterial activity* (%)				Antifungal activity* (%)	
	BS	SA	PA	EC	CA	AN
Va	56	68	63	56	37	56
Vb	40	63	45	60	56	81
Vc	72	78	77	60	43	50
Vd	36	42	54	65	37	43
Ve	64	73	68	56	68	93
Ciprofloxacin	100	100	100	100	-	-
Clotrimoxazole	-	-	-	-	100	100

Zone of inhibition of ciprofloxacin = 25 mm (BS = *Bacillus subtillis*), 19 mm (SA = *Staphylococcus aureus*), 22 mm (PA = *Pseudomonas aeruginosa*), 23 mm (EC = *Escherichia coli*). Zone of inhibition of clotrimoxazole = 16 mm (CA = *Candida albicans*), 16 mm (AN = *Aspergillus niger*). Zone of inhibition of N,N-dimethylformamide = 0 mm.
*Average of three independent determinations.

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REFERENCES

1. Y. Li, J. Liu, H. Zhang, X. Yang and Z. Liu, *Bioorg. Med. Chem. Lett.*, **16**, 2278 (2006).
2. A.S. Aboraia, H.M. Abdel-Rahman, N.M. Mahfouz and M.A. EL-Gendy, *Bioorg. Med. Chem. Lett.*, **14**, 1236 (2006).
3. A. Zarghi, M. Faizi, B. Shafaghi, A. Ahadian, H.R. Khojastehpoor, V. Zanganeh, S.A. Tabatabai and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **15**, 3126 (2005).
4. A. Zarghi, S.A. Tabatabai, M. Faizi, A. Ahadian, P. Navabi, V. Zanganeh and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **15**, 1863 (2005).
5. A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, A. Dalvandi and A. Shafiee, *Bioorg. Med. Chem. Lett.*, **14**, 6057 (2004).
6. T.P. Mohan, B. Vishalakshi, K.S. Bhat, K.S. Rao and G.N. Kendappa, *Indian J. Chem.*, **43B**, 1798 (2004).
7. K.S. Bhat, M.S. Karthikeyan, B.S. Holla and N.S. Shetty, *Indian J. Chem.*, **43B**, 1765 (2004).
8. M.G. Bhovi, G.S. Gadaginamath and V.B. Megadi, *Indian J. Chem.*, **38B**, 572 (1999).
9. M. Amir and S. Kumar, *Indian J. Heterocycl. Chem.*, **14**, 51 (2004).
10. A.L. Barry, The Antimicrobial Susceptibility Test: Principle and Practice Lea & Febiger, Philadelphia, pp. 180-193 (1976).

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