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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW SERIES OF 2-PHENYL-3-[2-(5-SUBSTITUTED-1,3,4-OXADIAZOL-2-YL) ETHYL]-1*H*-INDOLES

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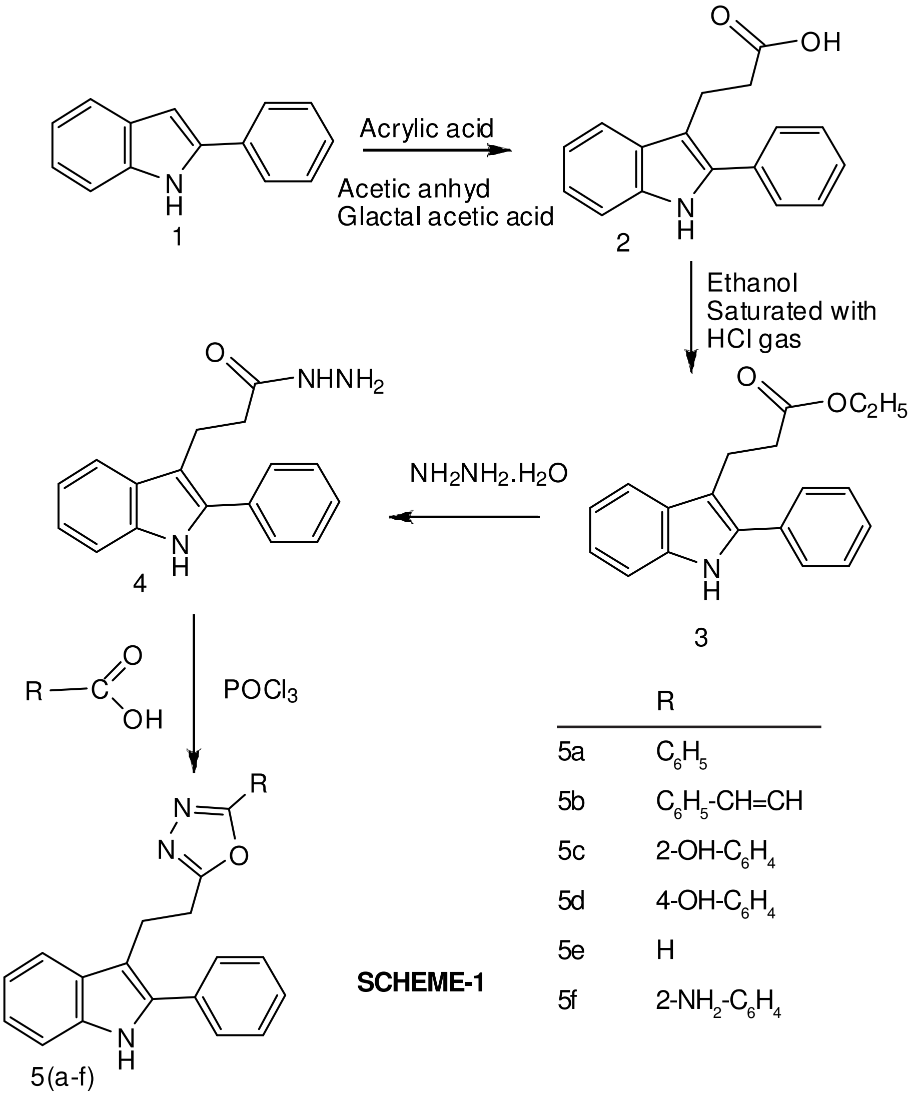
This research article presents the synthesis and antimicrobial activity of a new series of 2-phenyl-3-[2-(5-substituted-1,3,4-oxadiazol-2-yl) ethyl]-1*H*-indoles **5**(a-f). The structures of the compounds were confirmed by FT-IR, ^{1}H NMR and Mass spectral data. All the derivatives have shown moderate to excellent antimicrobial activities. **5**a has shown remarkable Minimum Inhibitory Concentration especially against *Bacillus subtilis, Klebsiella pneumoniae, Candida albicans, Aspergillus niger* when compared with the standard drugs.

Indoles are one of the most important nitrogen containing heterocyclic molecules, found extensively in biological system which play vital role in biochemical process. Indole derivatives have been found to possesses wide range of biological activities such as antibacterial[1], antifungal[1], analgesic[2], antiinflammatory[2], antioxidant[3], antidiabetic[4], antitubercular[5], anticonvulsant[6], antiviral[7], antihistaminic[8], antidepressant[9], cardiovascular[9] and anthelmintic[9]. The presence of oxygen and nitrogen in heterocyclic system has attracted the attention of medicinal chemists because of the diverse biological activities and profound efficacy[10]. The role of nitrogen and oxygen containing hetero compounds which are endowed with unique structure and potent antibacterial activity need to be over emphasized. In the recent past, it has been observed and reported, that considerable antibacterial and antifungal activity has been exhibited by 1,3,4-oxadiazole derivatives, suitably substituted at 2nd and 5th positions[11]. 1,3,4-Oxadiazole with different heterocyclic compounds are known to have a wide range of biological activities such as antiinflammatory[12], analgesic[12,13], antiulcerogenic[14], anthelmintic[16], muscle relaxant[17], antiviral[18], antitubercular[19], anticancer[20], anticonvulsant[21] and antifungal[22] activities.

Antimicrobial activity

In vitro antimicrobial activity was tested by disc diffusion method[23] and broth micro dilution method[24], using pathogenic strains of *Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli*. The fungi used *were Candida albicans, Aspergillus niger* and *Aspergillus flavus*. Known antibiotics Ciprofloxacin and Norfloxacin were used as standard drugs for antibacterial activity and Fluconazole and Griseofulvin were used as standard drug for antifungal activity & results are depicted in Table-2 & 3. The experimental results of antibacterial and antifungal activity indicated a variable degree of efficacy of the compounds against different strains. Among the synthesized compounds, compound **5**a which is having aromatic substituent at C-5 of the oxadiazole ring is found active against Gram positive bacterium *Bacillus subtilis* at concentration of (0.044 μM/ml) and against Gram negative bacterium *Klebsiella pneumoniae* at concentration of (0.022 μM/ml). The compound **5**b which is having (CH=CH) at C-6 of aromatic ring is found active against Gram positive bacterium *Bacillus subtilis* at concentration of (0.041 μM/ml). The compound **5**d which is having hydroxyl substitution at para position of aromatic ring is found



	R
5a	C_6H_5
5b	C_6H_5-CH=CH
5c	2-OH-C_6H_4
5d	4-OH-C_6H_4
5e	H
5f	2-NH_2-C_6H_4

SCHEME-1

active against Gram positive bacterium *Staphylococcus aureus* at concentration of (0.021 μM/ml). Among the synthesized compounds, compound **5**a which is having aromatic substituent at C-5 of the oxadiazole ring is found active against *Candida albicans* and *Aspergillus niger* at concentration of (0.0055μM/ml). The compound **5**e which is having no substituent in at C-5 of the oxadiazole ring is found active against *Candida albicans* at concentration of (0.0067 μM/ml).

Experimental

Melting points of synthesized compounds were determined on a SHITAL-Digital programmable melting point apparatus and are uncorrected; FT-IR spectra were recorded on a Bruker spectrophotometer by using KBr pellets. The ^{1}H NMR were recorded on a Bruker Avance III NMR 300 MHz instruments using DMSO as solvent and TMS as internal standard (chemical shifts in δ) and the homogeneity of the compounds was determined by TLC on silica gel G plates and

Table-1
Physical data of synthesized compounds **5**(a-f)

Compd	R	M.P. (^{0}C)	Yield (%)
5a	C_6H_5	150-52	66
5b	C_6H_5-CH=CH	172-74	72
5c	2-OH-C_6H_4	178-80	38
5d	4-OH-C_6H_4	114-16	36
5e	H	100-02	35
5f	2-NH_2-C_6H_4	194-96	67

spots were visualized in iodine vapour. The physical properties of the synthesized final compounds are depicted in Table-1. The structure of the compounds **5**(a-f) were established by their spectral data (IR, ^{1}H NMR and Mass).

Synthesis of 2-phenyl indole (1): General procedure

A mixture of acetophenone (10g, 0.83 mol), phenyl hydrazine (9g, 083 mol) and alcohol 30 ml containing two three drops of gl acetic acid is warmed (100^0) for 15 min. The separated phenyl hydrazone is filtered washed with dil. HCl (5 ml), ethanol (5 ml) & crystallized from ethanol. The yield is 11g and M.P. is 106^0.

The above acetophenone phenyl hydrazone (7g) is heated with polyphosphoric acid (40g) on boiling water bath in a conical flask. The mixture is heated at 100-120^0 for 10 min. Water (100 ml) is added & the separated product is filtered & washed with water. It is crystallised from ethanol. The yield is 5g (79%), M.P. 187^0.

Synthesis of 5,7-substituted 2-arylindole propionic acid (2) : General procedure

Compound **1** (36 mmol), acrylic acid (71 mmol) and acetic anhyd (71 mmol) in 35 ml acetic acid was heated at 90^0 for 24 hr. Volatile material is removed under high vacuum pressure at 90^0. The remaining residue is dissolved in 1N NaOH and subsequently acidified to pH 1 with conc. HCl. The aq solution is extracted with 5 time of ethyl acetate. Organic extract is combined and dried over anhyd magnesium sulphate. Filtered and concentrated to yield the product.

Synthesis of indole propionic ester (3) : General procedure

Placed 80 ml of absolute ethanol in a 250 ml two necked flask equipped with a double surface reflux condenser and a gas inlet tube. Dry hydrogen chloride gas was passed through the alcohol until saturated-the increase in weight is about 20g, gas inlet tube was removed, 12g (0.088 mol) of (**2**) was introduced and heated the mixture under reflux for 2 hr. Upon cooling the reaction mixture sets as solid mass of the hydrochloride of (**2**). It is better, however to pour the hot solution into 300 ml of water (no hydrochloride separates) and solid sodium carbonate was added carefully to the clear solution until it is neutral to litmus. Filtered off the precipitated ester at the pump and dried in the air. Recrystallized from ethanol.

Synthesis of 3-(2-phenyl-1*H*-indole-3-yl) propane hydrazide[25] (4) : General procedure

A mixture of (**3**) (106g, 0.5mol) and hydrazine hydrate (99%, 25 g, 0.5 mol) in ethanol (100 ml) was refluxed for 8 hr. The solution on cooling gave a solid mass of hydrazide which was collected by filtration and recrystallized from ethanol.

Synthesis of 1,3,4-oxadiazole substituted 2-phenyl indoles[26] 5(a-f) : General procedure

A mixture of 0.01 mol of (**4**) and 0.01 mol of different substituted carboxylic acid was dissolved in phosphorus oxychloride and refluxed for 18-22 hr. The reaction mixture was slowly poured over crushed ice and kept overnight. The solid mass thus separated out was then neutralized filtered, dried and purified by recrystallization from ethanol.

Table-2
MIC (µM/ml) of the synthesized compounds **5**(a-f)

Compd	*Staphylococcus aureus*	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Escherichia coli*
5a	0.171	0.044	0.022	0.086
5b	0.320	0.041	0.159	0.640
5c	0.656	0.082	0.082	0.656
5d	0.021	0.082	0.082	0.164
5e	1.730	0.108	0.865	0.216
5f	0.822	0.165	0.329	1.316
Ciprofloxacin	0.0052	0.0052	0.0026	0.0026
Norfloxacin	0.0094	0.0031	0.0031	0.0313

2-Phenyl-5-(2-(2-phenyl-1*H*-indol-3-yl-ethyl)-1,3,4-oxadiazole) (5a)

IR spectra (KBr cm^{-1}): 1690 (C=N str), 2819 (aromatic –CH str), 3058 (-NH str), 2849 (aliphatic-CH str), 1528 (aromatic C-C str), 1028 (C-O-C str); ^{1}H NMR: δ (ppm) 11.34 (s, 1H, NH), 7.98-8.00 (d, 2H, aromatic protons), 7.41-7.57 (m, 10H, aromatic protons), 7.10 (d, 2H, aromatic protons), 3.37 (d, 2H, CH_2), 2.50-2.51 (d, 2H, CH_2); m/z 365 (M+1).

2-(2-(2-Phenyl-1*H*-indole-3-yl-ethyl)-5-styryl-1,3,4-oxadiazole (5b)

IR spectra (KBr): 1605 (C=N str), 2918 (aromatic –CH str), 3083 (-NH str), 2850 (aliphatic-CH str), 1507 (aromatic C-C str), 1060 (C-O-C str), ^{1}H NMR : 11.28 (s, 1H, NH), 7.0 (t, 2H, aromatic protons), 7.52-7.55 (m, 5H, aromatic protons), 7.38-7.49 (m, 7H, aromatic protons), 6.93-6.95 (m, 2H, CH), 3.67-3.68 (t, 2H, CH2), 2.6 (d, 2H, CH_2): m/z 392 (M+1).

2-5-(2-(2-Phenyl-1*H*-indole-3-yl-ethyl)-1,3,4-oxadiazole-2) phenol (5c)

IR spectra (KBr): 1609 (C=N str), 2920 (aromatic –CH str), 3111 (-NH str), 2851 (aliphatic –CH str), 3219 (-OH str), 1534 (aromatic C-C str), 1066 (C-O-C str); m/z 381 (M^+).

4-(5-(2-(2-Phenyl-1*H*-indole-3-yl)-ethyl)-1,3,4-oxadiazole-2-yl) phenol (5d)

IR spectra (KBr): 1605 (C=N str), 2922 (aromatic –CH str), 3119 (-NH str), 2851 (aliphatic –CH str), 3343 (-OH str); m/z 381 (M^+).

2-(2-(2-Phenyl-1*H*-indol-3-yl)-ethyl)-1,3,4-oxadiazole (5e)

IR spectra (KBr): 1906 (C=N str), 2950 (aromatic –CH str), 3111 (-NH str), 2920 (aliphatic –CH str), 3343 (-OH str.), 1534 (aromatic C-C str.), 1066 (C-O-C str); m/z289 (M+1).

2-(5-(2-(2-Phenyl-1*H*-indole-3-yl)-ethyl)-1,3,4-oxadiazole-2-yl) aniline (5f)

IR spectra (KBr): 1599 (C=N str), 3113 (aromatic –CH str), 3254, 3435 (-NH, NH_2 str), 2923 (aliphatic –CH str), 1517 (aromatic C-C str), 1070 (C-O-C str). ^{1}H NMR : 11.27 (s, 1H, NH), 7.42-7.47 (m, 8H, aromatic protons), 7.14-7.15 (m, 3H, aromatic protons), 6.64-6.66 (t, 2H, aromatic protons), 6.65-6.67 (t, 2H, NH_2), 3.3 (d, 2H, CH_2), 2.5 (d, 2H, CH_2): m/z 382 (M+2).

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Table-3
MIC (μM/ml) of the synthesized compounds **5**(a-f)

Compd	*Candida albicans*	*Aspergillus niger*	*Aspergillus flavus*
5a	0.0055	0.0055	0.0219
5b	0.0409	0.0799	0.0409
5c	0.0419	0.0419	0.0209
5d	0.0105	0.1640	0.0419
5e	0.0067	0.2163	0.0554
5f	0.0822	0.2105	0.0105
Fluconazole	0.0523	0.0261	0.0261
Griseofulvin	1.6325	0.3265	0.3265

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