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Synthesis and Antimicrobial Activity of 2,5-Disubstituted 1,3,4-Oxadiazole Derivatives

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A series of 2-(quinolin-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole [**3a-3j**] were synthesized. All the compounds were characterized by analytical and spectral analysis. The antibacterial and antifungal activities were screened for all the compounds. The antimicrobial activity revealed that the compounds **3c**, **3g** and **3h** showed significant antibacterial activity and **3d**, **3f** and **3i** exhibited better antifungal activity.

Key Words: Synthesis, Disubstituted oxadiazole derivatives, Antimicrobial activity.

INTRODUCTION

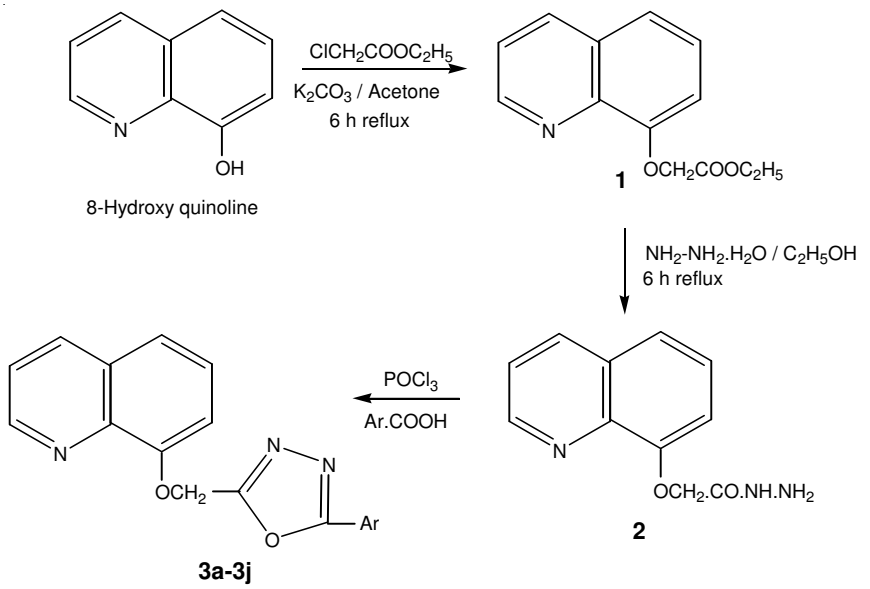
Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical and material interest which is documented by steadily increasing number of publication and patterns. It serves both as biomimetic and reactive pharmacophores and many are key elements with potential biological activities such as analgesic, antiinflammatory[1], muscle relexant[2], sedative and hypnotics[3], diuretic[4], anticonvulsant[5], antibacterial, antifungal[6]. Some material applications of 1,3,4-oxadiazole derivatives lie in the field of photosensitizers[7] and liquid crystals[8]. The common synthetic approaches of oxadiazoles[9] involved cyclization of diacyl hydrazine. A variety of reaction condition influences the cyclization reaction. Typically, the reaction is promoted by heat and anhydrous agents including thionyl chloride[10], phosphorus oxychloride[11], phosphorus pentoxide[12], triphenyl phosphine[13] and triflic anhydride[14].

By considering the above facts, it was thought to synthesize some 1,3,4-oxadiazole derivatives from 8-hydroxy quinoline moiety and screened for antibacterial and antifungal activities.

EXPERIMENTAL

Melting points of the newly synthesized compounds were determined by Veego digital melting point apparatus and uncorrected. Purity of the compound was checked by TLC using silica gel-GF254 plate, chloroform:acetone (9:1) as mobile phase and iodine vapours as detecting agent. IR spectra (KBr, cm^{-1}) were recorded on Perkin-Elmer FTIR spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance II 500 MHz instrument using TMS as internal standard and deuteriated

DMSO as solvent. Mass spectra were recorded using LC-MSD-Trap-SL. The synthesis of 2-(quinolin-8-yloxymethyl)-5-aryl-1,3,4-oxadiazole is given in the **Scheme-I**. The Physical data are given in Table-1.



Scheme-I

Synthesis of ethyl-2-(quinolin-8-yloxy) acetate (1): A mixture of 8-hydroxy quinoline (0.01 mol) ethyl chloro acetate (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in dry acetone were refluxed on a water bath for 6 h and poured into ice-cold water. Solid product obtained was filtered and recrystallized from ethanol. Yield 76 %.

Synthesis of 8-hydroxy quinoline acetyl hydrazide (2): A mixture of compound **1** (0.01 mol) hydrazine hydrate (99 % 0.07 mol) in methanol was refluxed for 5 h. From the resultant mixture excess of ethanol was removed by distillation. On cooling, white needle crystals separates out. It was recrystallized with ethanol. Yield 71 %.

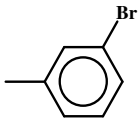
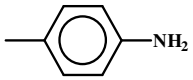
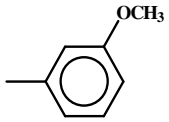
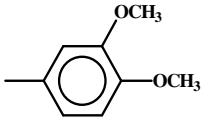
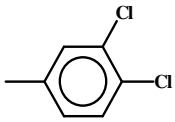
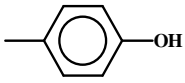
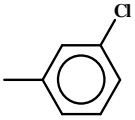
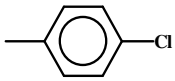
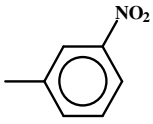
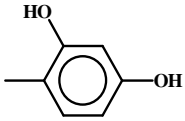
Synthesis of 2-(Quinolin-8yloxymethyl)-5-aryl-1,3,4-oxadiazole (3a-3j): A mixture of compound **2** (0.01 mol) and various aromatic acid (0.01 mol) in $POCl_3$ were refluxed for 6 h. The content was cooled and poured into ice cold water, then neutralized with $NaHCO_3$ solution, until a solid was obtained. The solid was separated by filtration and recrystallized with ethanol.

3a: IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H), 1578 (C=N), 1508 (C = C), 1206 (C-O-C), 574 (C-Br); ^{1}H NMR δ: 7.5-8.5 (m, 10H, ArH), 4.87 (s, 2H, OCH_2); MS: m/z 372.

3b: IR (KBr, ν_{max}, cm^{-1}): 3451 (N-H), 1594 (C=N), 1486 (C = C), 1092 (C-O-C); ^{1}H NMR δ: 7.5-8.5 (m, 10H, ArH), 5.8 (s, 2H, NH_2), 4.8 (s, 2H, OCH_2); MS : m/z 318.

3c: IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H), 1579 (C = N), 1508 (C = C), 1093 (C-O-C); ^{1}H NMR δ: 7-8 (m, 10H, ArH), 4.8 (s, 2H, OCH_2), 3.8 (s, 3H, OCH_3); MS: m/z (M^+) 335.

TABLE-1
PHYSICAL DATA OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

Compd.	Ar	Physical State	m.f (m.w)	m.p. (ºC)	Yield (%)
3a		Brown crystals	$C_{18}H_{13}N_3O_2Br$ (373)	139	67
3b		Yellow crystals	$C_{18}H_{15}N_4O_2$ (319)	191	62
3c		Brown crystals	$C_{19}H_{16}N_3O_3$ (334)	172	72
3d		Yellow crystals	$C_{20}H_{18}N_3O_4$ (364)	176	76
3e		Yellow crystals	$C_{18}H_{12}Cl_2N_3O_2$ (373)	157	63
3f		Brown crystals	$C_{18}H_{14}N_3O_3$ (320)	198	71
3g		Green crystals	$C_{18}H_{13}ClN_3O_2$ (338)	147	61
3h		Orange crystals	$C_{18}H_{13}ClN_3O_2$ (338)	156	61
3i		Orange crystals	$C_{18}H_{13}N_4O_4$ (349)	147	67
3j		Yellow crystals	$C_{18}H_{14}N_3O_4$ (336)	186	71

3d: IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H), 1624 (C = N), 1592 (C = C), 1165 (C-O-C); ^{1}H NMR δ: 7.4-8.5 (m, 9H, ArH), 5.6 (s, 2H, OCH_2), 3.8 (s, 6H, OCH_3); MS: m/z 364.

3e: IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H), 1578 (C = N), 1508 (C = C), 1223 (C-O-C), 710 (C-Cl); ^{1}H NMR δ: 7.1-8.2 (m, 9H, ArH), 5.05 (s, 2H, OCH_2); MS: m/z. 372.

3f: IR (KBr, ν_{max}, cm^{-1}): 3447 (OH), 2925 (CH), 1685 (C = N), 1452 (C = C), 1071 (C-O-C); ^{1}H NMR δ: 7.5-8.3 (m, 10H, ArH), 4.8 (s, 1H, OH), 4.6 (s, 2H, OC H_2); MS: m/z. 320.

3g: IR (KBr, ν_{max}, cm^{-1}): 2836 (CH), 1687 (C = N), 1583 (C = C), 1027 (C-O-C), 683 (C-Cl); ^{1}H NMR δ: 7.5-8.3 (m, 10H, ArH), 4.8 (s, 1H, OH), 4.6 (s, 2H, O CH_2); MS: m/z. 337.

3h: IR (KBr, ν_{max}, cm^{-1}): 3048 (CH), 1579 (C = N), 1508 (C = C), 1093 (C-O-C), 636 (C-Cl); ^{1}H NMR δ: 7.3-8.4 (m, 10H Ar H), 4.1 (s, 2H, OCH_2); MS: m/z: 338.

3i: IR (KBr, ν_{max}, cm^{-1}): 3048 (C-H), 1592 (C = N), 1579 (C = C), 1274 (N = O), 1165 (C-O-C); ^{1}H NMR δ: 7.2-8.5 (m, 10H, ArH), 4.8 (s, 2H, OCH_2); MS: m/z 349.

3j: IR (KBr, ν_{max}, cm^{-1}): 3414 (OH), 1579 (C = N), 1501 (C = C), 1107 (C-O-C); ^{1}H NMR δ: 7-8 (m, 9H, ArH), 5.6 (s, 2H, OCH_2), 5.2 (s, 2H, 2OH); MS: m/z 336.

Antimicrobial activity: Antibacterial activity of the synthesized compounds were screened against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia* using cup plate method. The compounds were tested at 50 μg/mL level. The results were compared with ciprofloxacin (10 μg/mL in DMSO). All the compounds showed moderate to good antibacterial activity (Table-2).

Antifungal activity of the synthesized compounds were screened against *Aspercillus niger* using cup plate method at 50 μg/mL level. Ketoconazole 10 μg/mL in DMSO was used as a standard for comparison. All the compounds showed moderate activity (Table-2).

TABLE-2
DATA OF ANIBACERIAL AND ANTIFUNGAL ACTIVITIES OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

Compd.	Diameter of zone inhibition (mm)				
	E. coli	*S. aureus*	*P. aeuroginosa*	*K. pneumonia*	*A. niger*
3a	14	12	13	13	10
3b	13	13	13	12	-
3c	14	18	14	13	11
3d	10	13	12	14	12
3e	12	11	10	11	-
3f	14	13	14	10	12
3g	13	15	16	17	11
3h	14	16	14	13	-
3i	11	13	13	14	13
3j	13	10	11	14	-
Ciprofloxacin	15	19	17	18	-
Ketoconazole	-	-	-	-	14

RESULTS AND DISCUSSION

Various 1,3,4-oxadiazole derivatives were synthesized from 8-hydroxy quinoline at position 2 and various aryl group at position 5 with the view of enhancing the biological activity. The structures of all the newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis.The compounds **3c**, **3g** and **3h** have exhibited significant antibacterial activity, where as compounds **3a**, **3f** and **3i** have shown moderate to good antibacterial activity when compared with the standard drug ciprofloxacin. The compounds **3a**, **3c**, **3d**, **3f**, **3g** and **3i** exhibited significant antifungal activity when compared with the standard drug ketoconazole.

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