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Synthesis and Biological Activity of Some 2,5-Disubstituted 1,3,4-Oxadiazoles

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Some new 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazoles (**IIIa–h**) were synthesized by reacting hydrazide **II** of 3-carbethoxycoumarin (**I**) with various aromatic acids in presence of phosphorus oxychloride. Their elemental, IR and ^{1}H NMR data characterized these oxadiazoles. All the compounds were tested for their analgesic and antimicrobial activity against *S. aureus*, *E. coli* and *C. albicans*. Compounds **IIIb, IIIc** and **IIIf** exhibited interesting results.

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

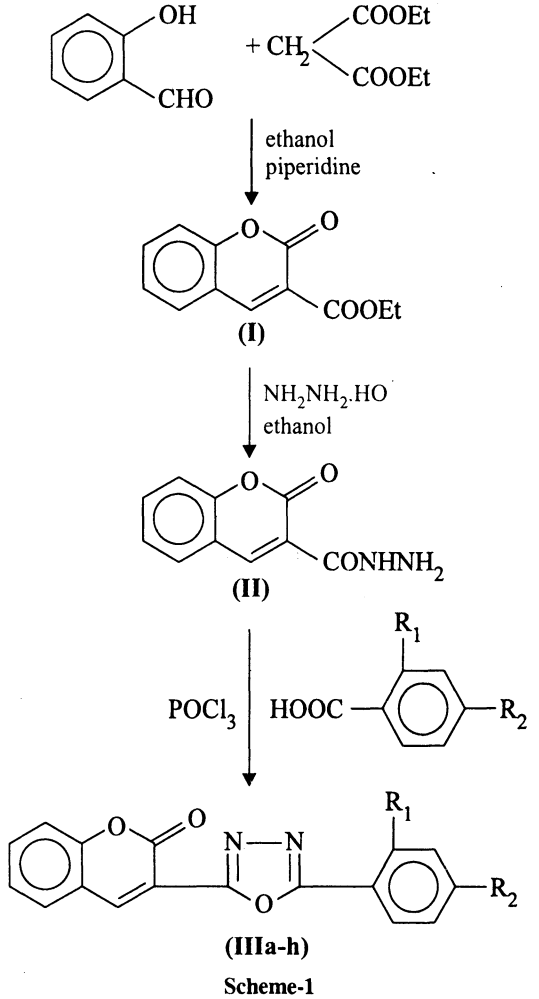
INTRODUCTION

1,3,4-oxadiazole derivatives are reported to show a broad spectrum of biological activities[1–4]. The drugs containing coumarin nucleus are used in therapeutics for a wide variety of conditions as oral anticoagulants[5, 6], antibiotics[7, 8] and skin pigmenting agents[9, 10]. Other activities that are reported in coumarin containing drugs include antiinflammatory[11, 12], analgesic, hypnotic, sedative, antifungal, antitubercular, antiatherosclerotic, antispasmodic and anticarcinogenic[13]. In view of these observations it was thought of interest to study some pharmacological activities of compounds incorporating both the moieties and hence 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazole derivatives were synthesized from 3-carbethoxycoumarin[14] **(I)**. Hydrazide of 3-carbethoxycoumarin was synthesized by reacting it with hydrazine hydrate. This hydrazide on condensation with substituted aromatic acids in presence of $POCl_3$ afforded the title compounds, 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazoles **(IIIa–h) (Scheme-1).** The structures of all these compounds were established on the basis of their IR, ^{1}H NMR and elemental data.

RESULTS AND DISCUSSION

The antimicrobial activity of oxadiazole derivatives against *S. aureus* revealed that compound **IIIc** exhibited highest activity while compounds **IIId** and **IIIh** showed moderate activity. All other compounds exhibited mild activity against this bacterium. Compound **IIIb** showed highest activity while rest of the

compounds exhibited mild to moderate antimicrobial activity against *E. coli.* In case of *C. albicans,* **IIIb** exhibited highest activity and all other compounds showed mild to moderate antifungal activity. The analgesic activity of these oxadiazole derivatives revealed that compound **IIIf** exhibited promising analgesic activity followed by **IIIh.** All other compounds showed mild to moderate analgesic activity.



Scheme-1

To sum up the findings most of the compounds exhibited mild to moderate antimicrobial and analgesic activity compared with their respective standards. Interestingly, compound **IIIb** having 2-Cl group on the phenyl ring showed highest activity against *E. coli* and *C. albicans* but to a lesser extent compared with respective standards. Compound **IIIf** with 2,4-dichloro group on the phenyl ring also showed highest analgesic activity but to a lesser extent compared to standard (diclofenac).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Purity of compounds was checked by TLC on silica gel plates and spots were visualized by exposure to the iodine vapours. IR (KBr) spectra were recorded on a Perkin-Elmer 783 spectrophotometer. ^1H NMR ($CDCl_3$, DMSO-d_6) spectra were recorded on Bruker model DRX-300 NMR spectrophotometer using TMS as internal reference (δ in ppm). Elemental analysis was performed on Carlo-Erba 1108 analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of the theoretical value. Physical data of the compounds and the percentage yield of various reactions are given in Table-1.

TABLE-1
PHYSICAL DATA OF 2-(COUMARIN-3-YL)-5-ARYL-1,3,4-OXADIAZOLES

Compd.	R_1	R_2	m.f.	m.w.	Recrystallization solvent	m.p. (°C)	% yield	R_f value*
IIIa	H	NH_2	$C_{17}H_{11}N_3O_3$	305	Benzene : acetone	197–199	55	0.70
IIIb	Cl	H	$C_{17}H_9N_2O_3Cl$	324	Pet. ether : Benzene	179–181	45	0.63
IIIc	H	OH	$C_{17}H_{10}N_2O_4$	306	Aqueous ethanol	>300	50	0.68
IIId	H	H	$C_{17}H_{10}N_2O_3$	290	Benzene : acetone	188–190	55	0.59
IIIe	NH_2	H	$C_{17}H_{11}N_3O_3$	305	Benzene : acetone	225–227	45	0.55
IIIf	Cl	Cl	$C_{17}H_8N_2O_3Cl_2$	359	Benzene	220–222	50	0.65
IIIg	NO_2	H	$C_{17}H_9N_3O_5$	335	Aqueous ethanol	170–172	40	0.62
IIIh	NO_2	NO_2	$C_{17}H_8N_4O_7$	380	Aqueous ethanol	201–203	40	0.71

* R_f value were determined in toluene : ethylacetate : formic acid (5 : 4 : 1).

Synthesis of hydrazide derivative of 3-carbethoxycoumarin (II): 3-Carbethoxycoumarin[13] (0.01 mol) and hydrazine hydrate (0.02 mol) were dissolved in sufficient quantity of ethanol to give a clear solution and refluxed for 3 h. The contents were concentrated to small volume. On cooling, the crystals of hydrazide separated out which were filtered and recrystallized from ethanol to give TLC pure colourless needles: m.p. 135–137°C; yield 70%; IR (KBr, cm^{-1}): 3310 ν(—NH—), 1710 ν(C=O, coumarin), 1660 ν(C=O), 1608, 1534 (aromatic), 970, 750; ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 6.90 (m, 2H, H—6, H—8), 7.45 (m, 1H, H—7), 7.55 (m, 1H, H—5), 8.17 (s, 1H, H—4), 8.43 (s, 1H, CONH), 8.64 (d, J = 12 Hz, 2H, NH_2); Anal. ($C_{10}H_8N_2O_3$) Found: C, 58.78%; H, 3.88%; N, 13.66%; Calculated: C, 58.82%; H, 3.94%; N, 13.71%.

Synthesis of 2-(coumarin-3-yl)-5-aryl-1,3,4-oxadiazoles (IIIa–h): In a 100 mL round-bottom flask was taken a solution of compound **II** (0.01 mol) in phosphorus oxychloride (5 mL) and different substituted aromatic acids (0.01 mol) were added. The reaction mixture was refluxed for 5–8 h, cooled to room temperature and poured into crushed ice. On neutralization with 20% $NaHCO_3$ solution, a solid mass separated out which was filtered, washed with water and recrystallized from appropriate solvent system to give the title compounds.

2-(Coumarin-3-yl)-5-(4-aminophenyl)-1,3,4-oxadiazole (IIIa): IR (KBr, cm^{-1}): 3459 ν(—NH—), 1717 ν(C=O), 1630 ν(C=C), 1565 ν(C=N), 1495, 1455, 1376, 1247, 1021 (oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.43 (m, 4H, Ar—H), 7.75 (m, 3H, Ar—H), 7.92 (d, J = 12 Hz, 2H, Ar—H), 10.78 (s, 2H, NH_2): Anal. ($C_{17}H_{11}N_3O_3$) Found: C, 66.74%; H, 3.58%; N, 13.66%; Calculated: C, 66.88%; H, 3.63%; N, 13.76%.

2-(Coumarin-3-yl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (IIIb): IR (KBr, cm^{-1}): 1722 ν(C=O), 1630 ν(C=C), 1565 ν(C=N), 1527, 1487, 1368, 1273, 1091 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.08 (s, 2H, Ar—H), 7.51 (d, J = 12 Hz, 2H, Ar—H), 7.64 (d, J = 12 Hz, 2H, Ar—H), 7.81 (m, 3H, Ar—H); Anal. ($C_{17}H_9N_2O_3Cl$) Found: C, 62.79%; H, 2.70%; N, 8.55%; Calculated: C, 62.88%; H, 2.79%; N, 8.62%.

2-(Coumarin-3-yl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazole (IIIc): IR (KBr, cm^{-1}): 3304 ν(—OH—), 1702 ν(C=O), 1640 ν(C=C), 1560 ν(C= N), 1453, 1375, 1207, 1003 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.30 (m, 1H, Ar—H), 7.46 (m, 1H, Ar—H), 7.75 (m, 2H, Ar—H), 7.78 (m, 1H, Ar—H), 8.03 (d, J = 12 Hz, 1H, Ar—H), 8.70 (s, 2H, Ar—H), 8.89 (d, J = 12 Hz, 1H, Ar—H), 10.52 (s, 1H, OH); Anal. ($C_{17}H_{10}N_2O_4$) Found: C, 66.55%; H, 3.22%; N, 9.09%; Calculated: C, 66.66%; H, 3.29%; N, 9.14%.

2-(Coumarin-3-yl)-5-phenyl-1,3,4-oxadiazole (IIId): IR (KBr, cm^{-1}): 1719 ν(C=O), 1635 ν(C=C), 1555 ν(C=N), 1494, 1368, 1276, 1206, 1051 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.26 (d, J = 12 Hz, 2H, Ar—H), 7.57 (t, J = 8 Hz, 2H, Ar—H), 7.61 (t, J = 8 Hz, 2H, Ar—H), 8.03 (d, J = 12 Hz, 2H, Ar—H), 8.67 (s, 2H, Ar—H); Anal. ($C_{17}H_{10}N_2O_3$) Found: C, 70.29%; H, 3.42%; N, 9.58%; Calculated: C, 70.34%; H, 3.47%; N, 9.65%.

2-(Coumarin-3-yl)-5-(2-aminophenyl)-1,3,4-oxadiazole (IIIe): IR (KBr, cm^{-1}): 3379 ν(—NH—), 1717 ν(C=O), 1650 ν(C=C), 1560 ν(C=N), 1490, 1376, 1247, 1021 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.47 (m, 2H, Ar—H), 7.73 (m, 2H, Ar—H), 8.04 (m, 1H, Ar—H), 8.58 (s, 2H, Ar—H), 8.82 (s, 2H, Ar—H), 10.78 (s, 2H, NH_2); Anal. ($C_{17}H_{11}N_3O_3$) Found: C, 66.77%; H, 3.61%; N, 13.64%; Calculated: C, 66.88%; H, 3.63%; N, 13.76%.

2-(Coumarin-3-yl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole (IIIf): IR (KBr, cm^{-1}): 1739 ν(C=O), 1650 ν(C=C), 1565 ν(C=N), 1490, 1425, 1320, 1091 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.44 (t, J = 8 Hz, 1H, Ar—H), 7.73 (m, 6H, Ar—H), 7.92 (t, J = 8 Hz, 1H, Ar—H): Anal. ($C_{17}H_8N_2O_3Cl_2$) Found: C, 56.79%; H, 2.18%; N, 7.73%; Calculated: C, 56.85%; H, 2.24%; N, 7.79%.

2-(Coumarin-3-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole (IIIg): IR (KBr, cm^{-1}): 1710 ν(C=O), 1630 ν(C=C), 1545 ν(C=N), 1485, 1360, 1220, 1035 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.02 (m, 4H, Ar—H), 7.42 (m, 2H, Ar—H), 7.73 (d, J = 12 Hz, 2H, Ar—H), 7.89 (s, 1H, Ar—H); Anal. ($C_{17}H_9N_3O_5$) Found: C, 60.86%; H, 2.66%; N, 12.45%; Calculated: C, 60.90%; H, 2.70%; N, 12.53%.

2-(Coumarin-3-yl)-5-(2,4-dinitrophenyl)-1,3,4-oxadiazole (IIIh): IR (KBr, cm^{-1}): 1725 ν(C=O), 1655 ν(C=C), 1545 ν(C=N), 1470, 1415, 1325, 1026 ν(oxadiazole nucleus); ^1H NMR ($CDCl_3$, DMSO-d_6, δ ppm): 7.25 (m, 2H,

Ar—H), 7.62 (m, 4H, Ar—H), 7.85 (t, J = 8 Hz, 2H, Ar—H); Anal. ($C_{17}H_8N_4O_7$) Found: C, 53.57%; H, 2.07%; N, 14.71%; Calculated: C, 53.69%; H, 2.12%; N, 14.73%.

Antimicrobial activity: The *in vitro* antimicrobial activity was carried out against 24 h old culture of two bacteria and one fungus. The bacteria used were *S. aureus* and *E.coli* and fungus used was *Candida albicans*. These activities were performed by cup-plate method[15]. The compounds were tested at a concentration of 100 μg/mL in dimethylformamide solution using Amikacin (100 μg/mL) for antibacterial and fluconazole (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 fungus. Each experiment was repeated thrice and average of three independent determinations was recorded.

Analgesic activity: Test for analgesic activity was performed by tail flick technique[16] using Wistar albino mice (25–35 g) of either sex selected by random sampling technique. Diclofenac (25 mg/kg) was used as standard drug for comparison. The test compounds were administered at dose of 25 mg/kg. The reaction time was recorded after 1 h of the administration of standard/test compounds. The per cent analgesic activity (PAA) was calculated by the following formula:

$$PAA = (T_2/T_1) \times 100$$

where T_1 is the reaction time(s) before treatment and T_2 is the reaction time(s) after treatment. The results of antimicrobial and analgesic activity are summarized in Table-2.

TABLE-2
BIOLOGICAL ACTIVITY OF 2-(COUMARIN-3-YL)-5-ARYL-1,3,4-OXADIAZOLES

Compd.	% Antimicrobial activity*			% Analgesic activity	
	S. aureus	*E. coli*	*Candida albicans*	Mean RT ± SEM	% activity
IIIa	65.83	71.61	55.55	6.05 ± 0.86	59.84
IIIb	64.46	80.29	78.98	5.51 ± 0.50	54.49
IIIc	79.45	47.74	37.47	6.33 ± 1.45	62.60
IIId	70.37	62.93	67.28	7.03 ± 0.80	69.42
IIIe	55.38	70.30	46.47	5.43 ± 0.78	53.70
IIIf	63.56	54.25	67.66	8.30 ± 0.81	82.08
IIIg	59.92	62.49	48.67	5.80 ± 1.32	57.36
IIIh	72.64	60.76	58.45	7.34 ± 1.40	72.59
Amikacin	100	100	—	—	—
Fluconazole	—	—	100	—	—
Control	—	—	—	2.5 ± 0.50	—
Diclofenac	—	—	—	10.11 ± 0.70	100

Zone of inhibition of amikacin = 24 mm (*S. aureus*), 26 mm (*E. coli*), zone of inhibition of Fluconazole = 28 mm (*C. albicans*), zone of inhibition of N,N-dimethylformamide = 0 mm, *Average of three independent determinations.

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