SYNTHESES AND BIOLOGICAL ACTIVITY OF 2-(4'-DIETHYLSULFONAMIDE PHENYL)-4-SUBSTITUTED AMINOMETHYL- 1,3,4-OXADIAZOLIN-5-THIONES

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Abstract : 4-(Chlorosulfonyl) benzoic acid was condensed with diethyl amine to afford 4-(diethylsulfamoyl) benzoic acid 1 which was esterified to obtain methyl ester 2. The condensation of compound 2 with hydrazine hydrate gave hydrazino derivative 3. This intermediate undergoes cyclization with carbon disulphide and potassium hydroxide to yield substituted 1,3,4-oxadiazolin-5-thione 4. Aminomethylation of 4 using different amines furnished 4-substituted aminomethyl-2-(4'-diethylsulphonamide phenyl)-1,3,4-oxadiazolin-5-thiones 5a-e. The structure of the newly synthesized compounds have been established by analytical and spectral data. These compounds have also been screened for their biological activity.

Keywords : 1,3,4-oxadiazolin-5-thiones, antibacterial, antifungal

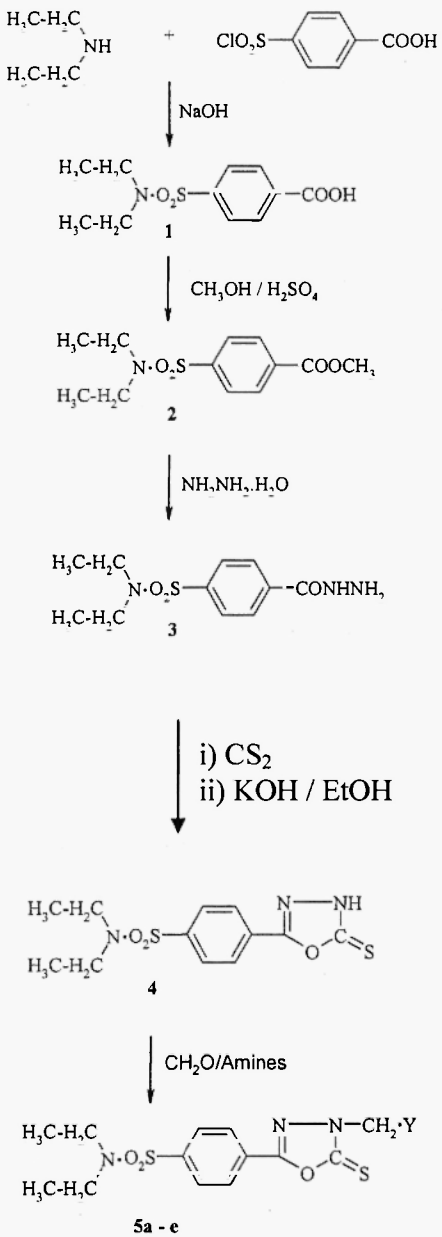
Introduction

Oxadiazolin-thiones exhibit analgesic[1], antibacterial[2], antifungal[3], anti-inflammatory[4], antileishmanial[5] and antitubercular[6] activity. These properties encouraged us to study the activity of some new 1,3,4- oxadiaolin-5-thione derivatives. A series of these compound have been synthesized and screened for their antibacterial and antifungal activity.

4-(Chlorosulfonyl) benzoic acid was condensed with diethyl amine to afford 4-(diethylsulfamoyl) benzoic acid **1.** This was esterified using methanol to obtain the methyl ester **2** which was condensed with hydrazine hydrate to yield hydrazide derivative **3.** The hydrazide **3** on condensation with carbon disulphide and potassium hydroxide afforded the substituted 1,3,4-oxadiazolin-5-thione **4.** Aminomethylation of **4** using various amines gave 2-(4'-diethylsulfonamide phenyl)-4-substituted aminomethyl-1,3,4-oxadiazolin-5-thiones **5a-e** [Scheme-1]. The melting points, yields and analytical data are given in Table-1.

Table-1 : Characterization data of 2-(4'-diethylsulfonamide phenyl)-4-substituted aminomethyl-1,3,4-oxadiazolin-5-thiones 5a-e

Compound	Y	M.P. °C	Yield %	Molecular Formula (mol.wt.)	Analysis % N	
					Calcd	Found
5a	Morpholino	197	72	$C_{17}H_{24}N_4O_4S_2$ (412)	13.58	13.49
5b	Piperidino	185	65	$C_{18}H_{26}N_4O_3S_2$ (410)	13.65	13.69
5c	Anilino	213	59	$C_{19}H_{22}N_4O_3S_2$ (418)	13.38	13.45
5d	p-Chloroanilino	210	54	$C_{19}H_{21}ClN_4O_3S_2$ (452.5)	13.39	13.28
5e	p-Anisidino	203	68	$C_{20}H_{24}N_4O_3S_2$ (448)	12.49	12.53



Scheme-1

Screening for Biological Activity : All the compounds **5a-e** were screened in **vitro** for their antibacterial activity against **Staphylococcus aureus, Escherichia coli, Bacillus subtilis and Salmonella typhosa** by the ditch-plate technique[7]. The compounds synthesized were also tested for antifungal activity against **Aspergillus niger, Candida albicans, Cryptococcus neoformans and Thielaviopsis paradoxa** by paper-disc diffusion method[8] using concentrations of 2 and 5 mg/ml. Nutrient agar was employed as culture media and DMF was used as solvent control for both antibacterial and antifungal activity. The result of such studies are given in **Table-2.**

Table-2 : Biological activity data of compounds 5a-e

Antibacterial activity *Antifungal activity*

Compd	S.aureus		E coli		B.subtilis		S.typhosa		A niger		C.albicans		C.neoformans		T.paradoxa	
	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml	2mg/ml	5mg/ml
5a	+	+	+	+	-	+	-	+	+	+	+	++	-	-	-	+
5b	-	-	-	+	+	++	+	++	-	+	-	+	+	+	-	-
5c	+	+	+	++	-	+	-	-	-	+	+	+	-	-	+	+
5d	+	++	-	-	+	+	-	+	-	-	-	+	-	+	+	+
5e	-	+	+	+	-	+	+	+	+	+	-	+	+	++	-	-

Inhibition zone diameter in mm: -

(-) < 11mm [inactive]

(+) 11-14 mm [weakly active]

(++) 15-18 mm [moderately active]

Experimental

The melting points were taken in open capillaries on a Veego melting point apparatus and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on SHIMADZU 8201 PC FTIR Spectrophotometer. ^1H NMR spectra were recorded on a VARIAN VXR-300SH (300 MHz) NMR Spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm) and mass spectra on a Hitachi RMU GL mass spectrometer at 70 eV. The purity of the compounds was monitored by thin layer chromatography.

4-(Diethylsulfamoyl) benzoic acid **1**

To a suspension of diethylamine (4.23 g, 0.05 mol) and 10 per cent NaOH (80 cm^3), 4-(chlorosulfonyl) benzoic acid (11.02 g, 0.05 mol) was added portion wise over a period of half an hour and stirred at 30°C for 3 hours. The reaction mixture was then acidified with dilute HCl. The compound obtained was filtered, washed with water and crystallised from ethanol to give **1** (10.29 g, 80%), m.p. 183 °C (Found: C, 51.42; H, 5.79; N, 5.41. $C_{11}H_{15}NO_4S$ requires: C, 51.33; H, 5.88; N, 5.44 %); IR (KBr) 2904 (-OH str.), 1702 (C=O str.), 1326,1294 (-SO_2 asym. str.), 1154 (-SO_2 sym. str.), 1110 (C-N str.),

Methyl-4-(diethylsulfamoyl) benzoate **2**

The mixture of compound **1** (12.86 g, 0.05 mol) in methanol (100 cm^3) was refluxed with catalytic amount of concentrated sulfuric acid (1 cm^3). The reaction mixture was quenched into ice water, the compound obtained was filtered, washed with water and crystallized from ethanol to afford **2** (11.26 g, 83%), m.p. 206 °C (Found: C, 53.16; H, 6.36; N, 5.05. $C_{12}H_{17}NO_4S$ requires: C, 53.11; H, 6.32; N, 5.16 %); IR (KBr) 1728 (C=O str.), 1326,1294 (-SO_2 asym. str.), 1215, 1105 (C-O str.), 1154 (-SO_2 sym. str.).

4-(Diethylsulfamoyl) benzoyl hydrazine **3**

A mixture of **2** (13.57 g, 0.05 mol), hydrazine hydrate (20 cm^3) in ethanol (150 cm^3) was refluxed for 8 hours. The excess solvent was removed under vacuum and the reaction mixture was then allowed to cool to room temperature. The solid obtained was filtered, washed with water and recrystallized from ethanol to give 3 (10.17 g, 75%), m.p. 126 °C (Found: C, 48.64; H, 6.35; N, 15.45. $C_{11}H_{17}N_3O_3S$ requires: C, 48.68; H, 6.32; N, 15.48 %); IR (KBr) 3296 (N-H str.), 1610 (C=O str.), 1322,1294 (-SO_2 asym. str.), 1154 (-SO_2 sym. str.).

2-(4'-Diethylsulfonamide phenyl)-1,3,4-oxadiazolin-5-thione 4

To a mixture of **3** (13.57 g, 0.05 mol) in ethanol (100 cm^3) was added a solution of potassium hydroxide (4.2 g, 0.075 mol) in ethanol (100 cm^3) followed by carbon disulphide (20 cm^3). The reaction mixture was refluxed for 8 hours. It was then concentrated, acidified with dilute hydrochloric acid and the resulting solid was collected, washed with water and recrystallized from ethanol to yield 4 (10.59 g, 68%), m.p. 242 °C (Found: C, 46.32; H, 4.80; N, 13.52. $C_{12}H_{15}N_3O_3S_2$ requires: C, 46.28; H, 4.86; N, 13.50 %); IR (KBr) 3089 (C-H aromatic), 2702 (C-H str.), 1675 (C=N str.), 1326,1294 (-SO_2 asym. str.), 1254 (C-O-C str.), 1154 (-SO_2 sym. str.), 1010 (C=S str.).

2-(4'-Diethylsulfonamide phenyl)-4-substituted aminomethyl-1, 3,4-oxadiazolin-5-thiones **5a-e**

The compound **4** (15.57 g, 0.05 mol) was dissolved in dimethyl formamide (20 cm^3), followed by slow addition of formaldehyde (10 cm^3) and appropriate amine (0.05 mol). The reaction mixture was stirred for 1 hour and left overnight at room temperature. The solid thus separated was filtered, washed with water and recrystallized from chloroform and petroleum ether to afford **5**. Other oxadiazolin-5-thiones were obtained in a similar manner. **5a**: IR (KBr) 2850 (C-H str.), 1610 (C=N str.), 1467 (CH_2 bending), 1326,1294 (-SO_2 asym. str.), 1150 (-SO_2 sym. str.), 1147(C-O-C str.) 1071 (C=S str.); NMR (DMSO-d_6) δ 1.02-1.07 (t, 3H, -CH_3), 2.88 (t, 4H, -CH_2-N-CH_2), 3.16-3.24 (q, 2H, -CH_2) 3.7 (t, 4H, -CH_2-O-CH_2), 5.11 (s, 2H, -N-CH_2-N), 7.96 (m, 4H, ArH), Mass m/z 412 (M+), 313, 298, 241, 177 (B), 133, 104, 90, 76

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