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Note

Synthesis of some ethyl 2-arylamino-5-phenylthiothiazole-4-carboxylates and their sulphones as potential analgesic, antiinflammatory and antimicrobial agents†

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Ethyl 2-arylamino-5-phenylthiothiazole-4-carboxylates **2a-f** have been synthesised by nucleophilic displacement reaction of ethyl 2-arylamino-5-bromothiazole-4-carboxylates **1a-f** and thiophenoxide anion in boiling ethanol. Their corresponding sulphones **3a-f** have been obtained by the oxidation of **2** with hydrogen peroxide in glacial acetic acid. Compounds **3a-f** are found to possess good analgesic, antiinflammatory and fungicidal activities.

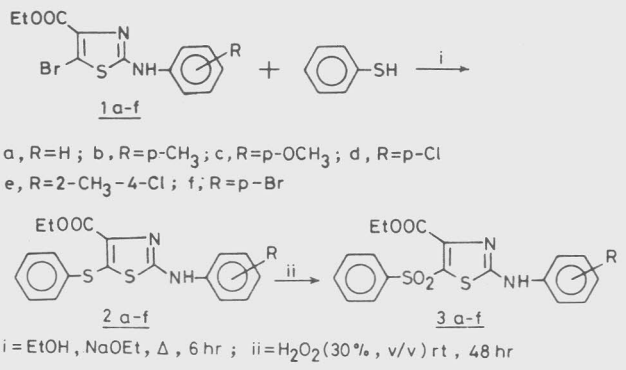
In continuation of our work[1] on ethyl 2-amino/-acetamido-5-arylthiothiazole-4-carboxylates and their sulphones, we report herein the synthesis and biological activities of twelve new ethyl 2-aryl-amino-5-phenylthiothiazole-4-carboxylates **2a-f** and their sulphones **3a-f**.

The target compounds **2** were synthesised by nucleophilic displacement reaction of ethyl 2-arylamino-5-bromothiazole-4-carboxylates **1a-f** and thiophenoxide anion in boiling ethanol. Their purification was done by recrystallisation from ethanol and column chromatography on neutral alumina. Compounds **2** were further converted into their sulphones **3** by oxidation with hydrogen peroxide in glacial acetic acid at room temperature (Scheme I). Complete conversion into **3** was ensured by observing strong IR absorption due to νSO_2 in the region of 1165-1135 cm^{-1}. Structures of **2** and **3** were established by elemental analysis and spectral (IR, ^{1}HNMR and mass) data.

Analgesic and antiinflammatory activity

The LD_{50} values of test compounds **2** and **3** were determined by the method of Miller and Tainter[2].

†Taken in part from the Ph.D. thesis of M M Baddi



Scheme I

Approximately 1/10th of LD_{50} values of the test compounds and 150 mg/kg b.w. dose of the reference compounds were used. *Albino* rats of either sex weighing 150 to 200 g were used. The analgesic activity was carried out by the Rat caudal immersion method[3]. The sulphides **2** showed poor analgesic activity while the sulphones **3** showed activity comparable to that of paracetomol. Introduction of chloro/methyl/methoxy group at *p*-position of 2-arylamino group of **3a** enhanced the analgesic potency of **3b-f** (cf-Table I).

Method of Winter *et al.*[4] was adopted for testing the antiinflammatory activity of **2** and **3**. Compound **2** showed 20 to 50% inhibition while **3** showed pronounced inhibition comparable to that of phenylbutazone (cf.Table I). Improved activity of **3b-f** (80 to 100% inhibition) indicated the influence of *p*-substitution of 2-arylamino group of **3a**.

Antimicrobial activity

Compounds **2** and **3** were screened for their fungicidal activity against *C. albicans* and *A. niger*, and bactericidal activity against *E. coli* and *S. aureus* by cup-plate method[5] at 100 μg concentration in DMF. Gressofulvin and norfloxacin were used at reference drugs. Zone of inhibition of reference drugs was measured as diameter and is shown by (++++). Rating of activity of the test compounds was made on this basis (see Table II).

Table I— Characterisation data and antimicrobial activities of compounds **2a-f** and **3a-f**

Compd[a]	R	Yield (%)	m.p. °C	Mol. formula[b]	Fungicidal activity		Bactericidal activity	
					A. niger	*C.albicans*	*E. coil*	*S. aureus*
2a	H	76	165-66	$C_{18}H_{16}N_2O_2S_2$	++	+	+	+
2b	*p*-CH_3	62	185-86	$C_{19}H_{18}N_2O_2S_2$	++	+	+	+
2c	*p*-OCH_3	70	148-49	$C_{19}H_{18}N_2O_3S_2$	+++	++	+	+
2d	*p*-Cl	72	220-21	$C_{18}H_{15}ClN_2O_2S_2$	+++	++	+	++
2e	2-CH_3-4-Cl	76	175-76	$C_{19}H_{17}ClN_2O_2S_2$	+++	+	+	++
2f	*p*-Br	64	178-79	$C_{18}H_{15}BrN_2O_2S_2$	++	++	+	+
3a	H	70	125-26	$C_{18}H_{16}N_2O_4S_2$	+++	++	+	++
3b	*p*-CH_3	60	95-96	$C_{19}H_{18}N_2O_4S_2$	++++	++	++	++
3c	*p*- OCH_3	65	127-28	$C_{19}H_{18}N_2O_5S_2$	+++	++	+	++
3d	*p*-Cl	66	98-99	$C_{18}H_{15}ClN_2O_4S_2$	++++	++	++	++
3e	2-CH_3-4-Cl	70	140-41	$C_{19}H_{17}ClN_2O_4S_2$	++++	+++	++	++
3f	*p*-Br	62	114-15	$C_{18}H_{15}BrN_2O_4S_2$	++++	++	++	++
Gressofulvin					++++	++++		
Norfloxacin							++++	++++

(a) all the compounds were obtained as colourless needles
(b) all the compounds gave satisfactory C, H and N analyses

Table II – Analgesic and antiinflammatory activities of compounds **2a-f** and **3a-f**

Compd	Analgesic activity				Compd	Antiinflammatory activity				Increase in paw vol. after 3 hr	% inhibition of oedema after 3 hr
	dose (mg/Kg b.w)	Mean time (seconds)				dose (mg/Kg b.w)	Mean paw volume (ml)				
		0 hr	1 hr	3 hr			0 hr	1 hr	3 hr		
Control	-	2.12	2.12	2.30	Control	-	0.52	0.67	1.00	0.48	—
2a	25	2.20	2.25	2.40	**2a**	25	0.56	0.68	0.93	0.37	22
2b	25	2.20	2.30	2.48	**2b**	25	0.58	0.65	0.88	0.30	37.5
2c	25	2.18	2.40	2.50	**2c**	25	0.55	0.67	0.84	0.29	40
2d	25	2.25	2.90	3.10	**2d**	25	0.60	0.70	0.87	0.27	45
2e	25	2.25	2.80	3.00	**2e**	25	0.54	0.68	0.80	0.26	46
2f	25	2.30	3.00	3.20	**2f**	25	0.60	0.72	0.84	0.24	48
3a	200	2.50	3.50	4.80	**3a**	200	0.78	0.88	0.92	0.14	71
3b	200	2.50	3.50	6.40	**3b**	200	0.80	0.95	0.90	0.10	79.5
3c	200	2.60	3.25	5.95	**3c**	200	0.80	0.94	0.89	0.09	81
3d	200	2.80	3.20	6.40	**3d**	200	0.78	0.86	0.78	0.00	100
3e	200	2.45	3.60	6.30	**3e**	200	0.82	0.90	0.84	0.02	96
3f	200	2.55	3.60	6.40	**3f**	200	0.80	0.91	0.83	0.03	94
Paracetomol	150	2.50	3.80	6.40	Phenyl-butazone	150	0.82	0.94	0.82	0.00	100

Compounds **2** showed moderate activity against *A. niger* and poor activity against *C. albicans, E. coli* and *S. aureus*. On the other hand, **3** showed very good activity against *A. niger*. Particularly, **3d, 3e** and **3f** competed well with gressofulvin, but failed to show similar activity at lower concentration. Compounds **3** showed inferior activity against *C. albicans, E. coli* and *S. aureus* (cf. Table II).

Experimental

Starting compounds **1a-f** were prepared by the method reported by us earlier[6].

Ethyl 2-arylamino-5-phenylthiothiazole-4-carboxylates (2a-f) Compound **2a** was prepared according to the procedure[1] reported by us by heating a mixture of **1a** (100 mmoles) and thiophenol (100 mmoles) in the ethanol containing sodium ethoxide (100 mmoles) for 6 hr. **2a**: colourless shining needles (ethanol), yield 76%, m.p. 165-66° (Found: C, 60.48; H, 4.31; N, 7.69 $C_{18}H_{16}N_2O_2S_2$ requires C, 60.67; H, 4.49; N, 7.86%); IR 3280 (NH), 1720 (C=O), 1530 (C=N), 750 and 695 (C_6H_5); ^{1}HNMR ($CDCl_3$): 7.82 (br, s, 1H, NH disappeared in D_2O), 7.58-7.05 (m, 10H, ArH), 4.35 (q, 2H, CH_2), 1.24 (t, 3H, CH_3); MS: m/z 356 (M^+). Compounds **2b-f** were prepared similarly. The characterisation data of **2a-f** are given in Table II.

Ethyl 2-arylamino-5-benezenesulphonylthiazole-4-carboxylates (3a-f). Compound **3a** was prepared by the oxidation of **2a** (10 mmoles) with hydrogen peroxide (30%, v/v) in glacial acetic acid according to the procedure [1] reported by us.

3a: colourless shining needles (ethanol), yield 70%, m.p. 125-26° (Found: C, 55.58; H, 4.32; N, 7.38. $C_{18}H_{16}N_2O_4S_2$ requires C, 55.67; H, 4.12; N, 7.21%); IR: 3290 (NH), 1730 (C=O), 1530 (C=N), 1155 (SO_2), 750 and 700 (C_6H_5); ^{1}HNMR ($CDCl_3$): 8.10-7.10 (m, 11H, ArH and NH), 4.38 (q, 2H, CH_2), 1.26 (t, 3H, CH_3); MS: m/z 388 (M^+). Compounds **3b-f** were prepared similarly. The characterisation data of **3b-f** are given in Table II.

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