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Synthesis and Analgesic Activity of Some 2-[{4-(Alkyl thio-ureido)phenyl}sulphonamido]-6-substituted benzothiazoles

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Series of sulphonamide derivatives (**5a–i**) were prepared by condensation of 2-(4-aminophenyl sulphonamido)-6-substituted benzothiazoles with alkyl isothiocyanates. The compound **5g** with methoxy substitution showed maximum analgesic activity in the series. Highly significant results were also observed with compound **5b, 5f** and **5h** whereas other compounds of the series showed a decrease in analgesic activity.

Key Words: Benzothiazole, Alkylisothiocyanate, Analgesic.

INTRODUCTION

Benzothiazoles and aminobenzothiazoles represent the most active class of heterocyclic compounds possessing wide spectrum of pharmacological activities. Their chemistry and biological potencies have been widely investigated and extensively reviewed in past years. The literature survey reveals the various substituted benzothiazoles possessing wide range of therapeutic activities[1–5]. With a view to develop potent analgesics it was therefore thought worthwhile to synthesize new derivatives of benzothiazole sulphonamides and screen them for their analgesic activity.

EXPERIMENTAL

All solvents were purified by standard methods before use. Melting points were determined in open capillary and uncorrected. Purity of compounds were checked by TLC on silica gel-G layers. IR spectra were recorded in KBr on JASCO FT-IR 410 spectrophotometer. ^{1}H NMR spectra on Bruker Model DRX-300 NMR spectrometer in $CDCl_3$/DMSO-d_6 using TMS as reference.

Synthesis of the Compounds

2-Amino-6-fluoro benzothiazole (1a): A mixture of *p*-fluoroaniline (1.11 g, 0.01 mol) and potassium thiocyanate (7.76 g, 0.08 mol) in glacial acetic acid (30 mL) was cooled and stirred. To this solution, bromine (1.6 mL) was added dropwise at such a rate to keep the temperature below 10°C throughout the addition. Stirring was continued for additional 3 h and the separated hydrochloride salt was filtered, washed with acetic acid and dried. The product was dissolved

in hot water and neutralized with 25% aqueous ammonia solution. The solid compound **(1a)** obtained was filtered and recrystallized from benzene.

2-(4-Acetamidophenyl sulphonamido)-6-flouro benzothiazole (3a): The compound **1a** (1.7 g, 0.01 mol) was taken in a mixture of pyridine (4 mL) and acetic anhydride (20 mL). To this mixture, *p*-acetamidobenzene sulphonyl chloride **(2)** (2.5 g, 0.01 mol) was added and the mixture was heated for 2 h on a water bath. The reaction mixture was poured on to 30 mL of water; the solid product obtained was filtered and crystallized from ethanol (80%) so as to obtain compound **(3a).**

2-(4-Aminophenyl sulphonamido)-6-flouro benzothiazole (4a): The compound **3a** (2.9 gm, 0.008 mol) was hydrolyzed by boiling it in 50 mL of 80% acetic acid for 6 h to obtain the product **(4a)**

2[4-{(Methyl thioureido)phenyl}sulphonamido]-6-fluoro benzothiazole (5a): The compound **4a** (1.9 g, 0.006 mol) was refluxed in ethanol (25 mL) with methyl isothiocyanate for 2 h. The solid product **(5a)** was filtered and recrystallized from chloroform and DMSO.

Yield 65%, m.p. 224°C IR (KBr) cm^{-1}: 3220–2990 (—NH), 1300 (SO_2NH_2), 1200 (C=S), ^1H NMR (DMSO-d_6) δ ppm: 2.87 (s, $C\underline{H}_3$), 7.08–7.64 (Ar—7H), 12.00 (s, 3NH). Similarly other compounds of the series **(5b–i)** were also synthesized and their physical constants are given in Table-1.

TABLE-1
PHYSICAL PARAMETERS OF 2-[4-{(ALKYL THIOUREIDO)PHENYL} SULPHONAMIDO]-6-SUBSTITUTED BENZOTHIAZOLES **(5a–i)**

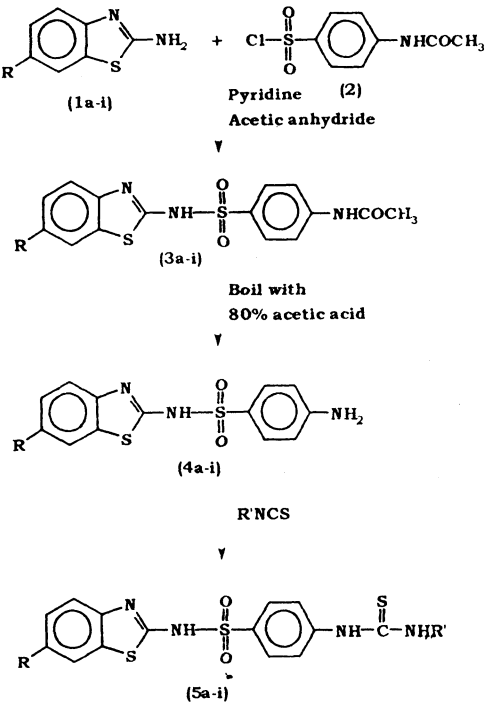
Compd. No.	R	R′	m.p. (°C)	Yield (%)	R_f values	m.f.
5a	F	CH_3	224	65	0.91	$C_{15}H_{13}N_4FO_2S_3$
5b	F	C_2H_5	221	70	0.85	$C_{16}H_{15}N_4FO_2S_3$
5c	Cl	CH_3	232	58	0.86	$C_{15}H_{13}N_4ClO_2S_3$
5d	Cl	C_2H_5	230	54	0.90	$C_{16}H_{15}N_4ClO_2S_3$
5e	Br	CH_3	222	68	0.87	$C_{15}H_{13}N_4BrO_2S_3$
5f	Br	C_2H_5	220	65	0.92	$C_{16}H_{15}N_4BrO_2S_3$
5g	OCH_3	CH_3	235	55	0.79	$C_{16}H_{16}N_4O_3S_3$
5h	OCH_3	C_2H_5	234	60	0.83	$C_{17}H_{18}N_4O_3S_3$
5i	CH_3	C_2H_5	215	52	0.94	$C_{17}H_{18}N_4O_2S_3$

R_f values were determined in (TEF 5 : 4 : 1).

RESULTS AND DISCUSSION

The condensation of 2-amino-6-substituted benzothiazoles **(1a–i)** with *p*-acetamido benzesulphonyl chloride in pyridine and acetic anhydride mixture resulted in compounds **(3a–i)**, which on hydrolysis with acetic acid and reacting with alkyl isothiocyanate yielded compounds **(5a–i)**. The condensation takes place by elimination of HCl. Pyridine being a weak base when used as solvent was not sufficiently strong to remove proton as HCl. Therefore a mixture of

pyridine and acetic anhydride was used as a solvent to form N-acetylpyridinium complex which facilitated the condensation.



R = CH_3, OCH_3, Cl, Br, F
R' = CH_3, C_2H_5

The structure of the compound **5a** corresponding to molecular formula $C_{15}H_{13}N_4O_2S_3F$ was confirmed on the basis of their spectral data. The IR spectra of the compound **5a** showed absorption band at 3220–2930 cm^{-1} due to the presence of NH group. An absorption band at 1300 cm^{-1} showed the presence of SO_2NH_2 group whereas another absorption band at 1200 cm^{-1} confirms the (C=S) group.

^1H NMR spectra of compound **5a** showed a singlet at δ 2.87 for the presence of methyl protons. A multiplet at δ 7.08–7.64 showed the presence of aromatic protons. The presence of NH group was confirmed due to the appearance of a singlet at δ 12.00. The other related compounds **(5b–i)** also showed IR and NMR data in the similar range.

Analgesic activity was performed by tail compression method[6] on albino mice of either sex. The compounds **5b, 5d, 5f, 5g** and **5h** showed potent analgesic activity ($p < 0.001$) and were found to be equipotent to the standard drug aspirin (20 mg/kg p.o). Highest percentage analgesia was observed with compound **5g,** with a methoxy substitution at 6-position of benzothiazole ring [R = OCH_3] and a methyl substitution at thiorueido group (R′ = CH_3]. Replacement of methyl

group with an ethyl group, compound **5h** [R = OCH_3, R′ = C_2H_5], showed a slight decrease in activity whereas significant value ($p < 0.001$) remained unchanged. Replacement of ethyl group with a methyl group in compound **5a** (R = F, R′ = CH_3] and compound **5e** [R = Br, R′ = CH_3] showed complete loss in activity. When 6-bromo was replaced by 6-chloro group the compound **5c** [R = Cl, R′ = CH_3] was found to have significant analgesic activity. Highly significant result ($p < 0.01$) was also observed with compound **5i** [R = CH_3, R′ = C_2H_5]. The results have been summarized in Table-2.

TABLE-2
ANALGESIC ACTIVITY OF 2-[4-{(ALKYL THIOUREIDO) PHENYL} SULPHONAMIDO]-6-SUBSTITUTED BENZOTHIAZOLES (**5a–i**)

Compd. No.	Dose/kg (p.o.)	Mean BRT ± SEM	Mean RT after drug administration ± SEM	Percentage increased in BRT
5a	100 mg	2.0 ± 0.28	11.0 ± 2.33	13.7
5b	100 mg	1.6 ± 0.35	10.2 ± 186	96.22‡
5c	100 mg	1.8 ± 0.80	3.80 ± 2.51	35.8*
5d	100 mg	2.0 ± 0.28	10.0 ± 2.77	94.3‡
5e	100 mg	1.2 ± 0.17	1.40 ± 0.21	13.2
5f	100 mg	1.6 ± 0.21	10.4 ± 2.22	98.1‡
5g	100 mg	1.2 ± 0.17	13.6 ± 0.45	128.3‡
5h	100 mg	1.6 ± 0.21	13.2 ± 0.65	124.5‡
5i	100 mg	2.4 ± 0.35	9.20 ± 3.00	86.7†
Aspirin	20 mg	1.2 ± 0.17	10.6 ± 2.34	100.0‡
Control	10 mL	1.4 ± 0.21	1.20 ± 0.17	1.13

n = 5; *P < 0.05, †P < 0.01, ‡P < 0.001

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