2-Alkylthio-6-(3-nitrobenzoylamino)benzothiazoles and their antimycobacterial activity

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Dedicated to Professor RNDr. V. Sutoris, CSc., in honour of his 60th birthday

2-Alkylthio-6-(3-nitrobenzoylamino)benzothiazoles obtained from 6-(3-nitrobenzoylamino)-2-benzothiazolinethione were found to exhibit a less pronounced antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R_v$ and *M. kansasii* than 2-alkylthio-6-benzoylaminobenzothiazoles.

2-Алкилтио-6-(3-нитробензоиламино)бензотиазолы, полученные из 6-(3-нитробензоиламино)-2-бензотиазолинтиона, обладают менее выраженной антимикобактериальной активностью по отношению к *Mycobacterium tuberculosis* $H_{37}R_v$ и *M. kansasii*, чем 2-алкилтио-6-бензоиламинобензотиазолы.

Some 2-alkylthio-6-benzoylaminobenzothiazoles reveal antimycobacterial activity against typical and atypical tubercular mycobacteria [1] and therefore, the effect of nitro group in position 3 at the benzoyl substituent on the antimycobacterial activity was investigated.

Starting material for the synthesis of this series of compounds was 6-amino-2-benzothiazolinethione [2]. Acylation of the latter with 3-nitrobenzoyl chloride in pyridine afforded 6-(3-nitrobenzoylamino)-2-benzothiazolinethione (*I*) similarly as with acylation of the not nitrated analogue [1]. Dissolution of *I* in potassium hydroxide furnished the potassium salt of 6-(3-nitrobenzoylamino)-2-mercaptobenzothiazole analogously as reported with 6-benzoylamino-2-benzothiazolinethione and 6-(bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-2-benzothiazolinethione [3]. The potassium salt was alkylated with alkyl halogenides to give 2-alkylthio-6-(3-nitrobenzoylamino)benzothiazoles *II*—*XVII* (Scheme 1, Table 1). The structure of 2-methylthio-6-(3-nitrobenzoylamino)benzothiazole was verified by preparation of this compound by an independent procedure from 6-amino-2-methylthiobenzothiazole [4] and 3-nitrobenzoyl chloride.

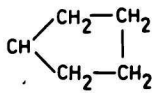
2-Alkylthio-6-(3-nitrobenzoylamino)benzothiazoles were tested for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}R_v$ and *M. kansasii*

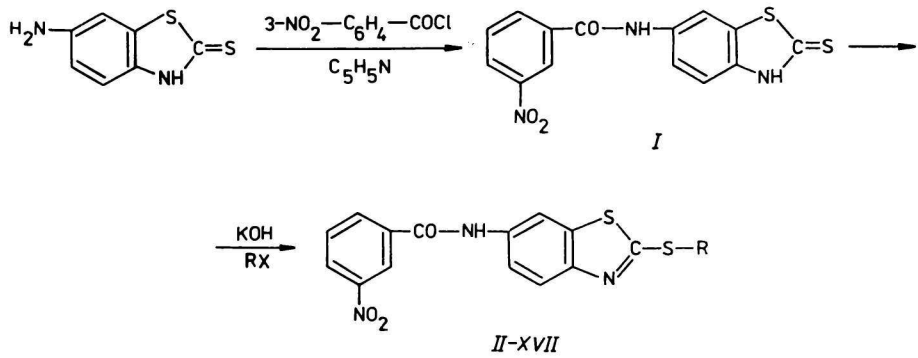
Table 1

2-Alkylthio-6-(3-nitrobenzoylamino)benzothiazoles

Compound	Alkyl	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		
II	CH_3	$C_{15}H_{11}N_3O_3S_2$	345.4	52.16	3.21	12.17	18.57	53.6	179—180
				51.99	2.95	12.24	18.47		
III	C_2H_5	$C_{16}H_{13}N_3O_3S_2$	359.4	53.47	3.65	11.69	17.84	56.9	155—157
				53.17	3.37	11.68	17.69		
IV	$(CH_2)_2CH_3$	$C_{17}H_{15}N_3O_3S_2$	373.5	54.67	4.05	11.25	17.17	59.0	142—144
				54.44	3.78	11.14	16.90		
V	$CH_2(CH_3)_2$	$C_{17}H_{15}N_3O_3S_2$	373.5	54.67	4.05	11.25	17.17	63.0	154—156
				54.65	4.01	11.39	17.22		
VI	$(CH_2)_3CH_3$	$C_{18}H_{17}N_3O_3S_2$	387.5	55.80	4.42	10.84	16.55	69.7	138–140
				55.68	4.34	10.94	16.66		
VII	$CH_2CH(CH_3)_2$	$C_{18}H_{17}N_3O_3S_2$	387.5	55.80	4.42	10.84	16.55	72.3	131—133
				55.53	4.32	10.88	16.61		
VIII	$CH(CH_3)C_2H_5$	$C_{18}H_{17}N_3O_3S_2$	387.5	55.80	4.42	10.84	16.55	64.5	151—153
				55.84	4.31	10.75	16.44		
IX	$(CH_2)_4CH_3$	$C_{19}H_{19}N_3O_3S_2$	401.5	56.84	4.77	10.47	15.97	67.1	125—126
				56.55	4.74	10.44	15.96		

Table 1 (Continued)

Compound	Alkyl	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		
X	$(CH_2)_2CH(CH_3)_2$	$C_{19}H_{19}N_3O_3S_2$	401.5	56.84 56.58	4.77 4.73	10.47 10.54	15.97 15.80	72.5	149—151
XI		$C_{19}H_{17}N_3O_3S_2$	399.5	57.12 56.83	4.29 4.15	10.52 10.50	16.05 15.89	77.5	149—151
XII	$(CH_2)_5CH_3$	$C_{20}H_{21}N_3O_3S_2$	415.5	57.81 57.56	5.09 5.10	10.11 10.11	15.43 15.59	60.2	118—121
XIII	$(CH_2)_6CH_3$	$C_{21}H_{23}N_3O_3S_2$	429.6	58.72 58.64	5.40 5.39	9.78 9.97	14.93 14.99	73.3	126—127
XIV	$(CH_2)_7CH_3$	$C_{22}H_{25}N_3O_3S_2$	443.6	59.57 59.47	5.68 5.74	9.47 9.52	14.46 14.49	83.3	107—109
XV	$(CH_2)_8CH_3$	$C_{23}H_{27}N_3O_3S_2$	457.6	60.37 60.10	5.95 5.95	9.18 9.16	14.01 13.71	87.4	108—110
XVI	$CH_2C_6H_5$	$C_{21}H_{15}N_3O_3S_2$	421.5	59.84 59.79	3.59 3.60	9.97 10.05	15.21 15.22	94.9	200—201
XVII	CH_2CH_2OH	$C_{16}H_{13}N_3O_4S_2$	375.4	51.19 51.27	3.49 3.44	11.19 11.24	17.08 17.06	50.6	182—183



Scheme 1

PKG 8 and their effect was contrasted with those of isonicotinoyl hydrazide (INH) and analogous 2-alkylthio-6-benzoylaminobenzothiazoles [1]. A more significant effect against the above-mentioned strains of mycobacteria was shown by derivatives of 2-alkylthio-6-benzoylaminobenzothiazoles with alkyls possessing 2 to 5 carbons, whilst in the synthesized series a higher effect was observed with *sec*-butyl, n-pentyl, cyclopentyl, 2-hydroxyethyl, and n-hexyl derivatives (Table 2). The total effect of the latter derivatives is weaker, in other words substitution of the benzoyl group of 2-alkylthio-6-benzoylaminobenzothiazoles by a nitro group in position 3 was without positive effect on the antimycobacterial activity.

Experimental

The antimycobacterial activity was determined on a liquid semisynthetic Šula substrate by a dilution test [5]. The solvent used was dimethyl sulfoxide. The final concentration of compounds was 5 μg cm^{-3}, 10 μg cm^{-3}, 25 μg cm^{-3}, 50 μg cm^{-3}, and 100 μg cm^{-3}. *Mycobacterium tuberculosis* $H_{37}R_v$ and *M. kansasii PKG 8* were microorganisms from the collection of the Research Institute of Preventive Medicine. The results were evaluated after a 14-day incubation at 37 °C and contrasted with isonicotinoyl hydrazide (INH, Isoniazid, Jenapharm, GDR) (Table 2).

6-(3-Nitrobenzoylamino)-2-benzothiazolinethione (I)

Pyridine (50 cm^3) was added to 6-amino-2-benzothiazolinethione (18.2 g; 0.1 mol) and 3-nitrobenzoyl chloride (18.6 g; 0.1 mol) at room temperature. The exothermal reaction was completed by a 3 h reflux, the mixture was moderately cooled and filled with cold water up to 800 cm^3. The title product separated from the stirred solution in form of fine yellowish

Table 2

Antimycobacterial activity (MIC/(μg cm^{-3})) of 2-alkylthio-6-(3--nitrobenzoylamino)benzothiazoles (3-NO_2), analogous 2-alkylthio-6--benzoylaminobenzothiazoles (3-H), and isonicotinoyl hydrazide (INH)

Compound	*M. tuberculosis* $H_{37}R_v$		*M. kansasii PKG 8*	
	3-NO_2	3-H	3-NO_2	3-H
II	>100	>200	>100	>200
III	>100	103.6	>100	>103.6
IV	>100	108.2	>100	108.2
V	>100	12.1	>100	12.1
VI	>100	>112.9	>100	>112.9
VII	>100	12.6	>100	12.6
VIII	25 (10)	1.3	10	4.1
IX	10	117.8	25	>117.8
X	>100	>117.8	>100	>117.8
XI	10	>116.8	25	13.0
XII	50	>122.1	100	>122.1
XIII	100	>127.1	100	>127.1
XIV	100	>131.6	>100	>131.6
XV	>100	>136.2	>100	>136.2
XVI	>100	>124.0	>100	>124.0
XVII	50	3.9	>100	3.9
INH	1	0.5	25	1.6

MIC — minimum inhibitory concentration; the partial inhibitory concentration is given in parentheses.

granules, which were first washed with hot water, then with dilute hydrochloric acid, and finally with hot water. Yield = 32.3 g (97.4 %), m.p. = 275—277 °C.

For $C_{14}H_9N_3O_3S_2$ (M_r = 331.4) w_i(calc.): 50.74 % C, 2.74 % H, 12.68 % N, 19.35 % S; w_i(found): 50.82 % C, 2.79 % H, 12.56 % N, 19.14 % S.

2-Alkylthio-6-(3-nitrobenzoylamino)benzothiazoles (II—XVII)

Potassium hydroxide (0.7 g; 0.11 mol) dissolved in water (8 cm^3) and the respective alkyl halogenide (11 mmol) were added to a solution of *I* (3.3 g; 10 mmol) in ethanol (50 cm^3). The mixture was refluxed for 10 min, decoloured with charcoal and cooled. The separated crystalline product was washed with 50 % ethanol and crystallized from acetone to which charcoal was added. (Derivatives with higher alkyls were dissolved by addition of ethanol to acetone.)

2-Methylthio-6-(3-nitrobenzoylamino)benzothiazole (II)

Pyridine (15 cm^3) was added to a mixture consisting of 6-amino-2-methylthiobenzothiazole [4] (5.9 g; 30 mmol) and 3-nitrobenzoyl chloride (5.6 g; 30 mmol) at an ambient

temperature. The mixture was then refluxed for 3 min, moderately cooled, poured on crushed ice and filled with cold water up to 600 cm^3. The separated crystals were washed with dilute hydrochloric acid, warm water and crystallized from acetone using charcoal. Yield = 5.8 g (56 %), m.p. = 179—180 °C. The mixed melting point with 2-methylthio-6-(3-nitrobenzoylamino)benzothiazole prepared from 6-(3-nitrobenzoylamino)-2--benzothiazolinethione did not show any depression.

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