Synthesis and the biological activity of 6-acetamido-2-alkylthiobenzothiazoles

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6-Acetamido-2-alkylthiobenzothiazoles were obtained by acetylation of 2-alkylthio-6-aminobenzothiazoles; their antimycobacterial activity is comparable with that of isonicotinic acid hydrazide.

Посредством ацетилирования 2-алкилтио-6-аминобензотиазолов ацетангидридом были синтезированы 6-ацетамидо-2-алкилтиобензотиазолы; их антимикобактериальная активность сравнима с активностью изоникотингидразида.

This paper is aimed to investigate the effect of acetylation of the amino group in 2-alkylthio-6-aminobenzothiazoles [1] on antimycobacterial activity. In this series only methyl [2] and allyl derivatives [3] were prepared.

According to the nature of the starting thiobenzothiazole either an equivalent amount or a 10-fold excess of acetic anhydride were used at room or at reflux temperatures. As found, the amount of acetic anhydride used did virtually not influence the yields. It was, however advantageous to employ an excess of acetic anhydride as a solvent for derivatives with a higher alkyl, since isolation of the product was easier.

6-Acetamido-2-alkylthiobenzothiazoles, like the starting 2-alkylthio-6-aminobenzothiazoles, revealed a good antimycobacterial effect against tuberculous mycobacteria (Table 1); nevertheless, 6-amino-2-benzylthiobenzothiazole, the most active derivative in this series, completely lost its activity upon acetylation to position 6. The enhanced antimycobacterial activity of derivatives with a branched alkyl at sulfur attached to position 2 is more pronounced than with the starting 2-alkylthio-6-aminobenzothiazoles and is comparable with that of known antituberculotica [4]. They reveal a considerable effect against atypical tuberculous mycobacteria. The *dosis tolerata maxima* (DTM) of compounds *II*, *IV*, *IX*, and *X*

Table 1

Antimycobacterial activity (MIC/(μg cm^3)) of 2-alkylthio-6-acetamidobenzothiazoles, isonicotinic acid hydrazide, and 2-mercaptobenzothiazole

Compound	*Mycobacterium*			
	tbc. $H_{37}R_v$	*kansasii*	*avium*	*fortuitum*
I	100	200	>200	>200
II	25 (10)	25	150	>200
III	50	50	>200	>200
IV	1	25	200	150
V	10 (5)	25	150 (100)	200 (150)
VI	5 (1)	25 (10)	150	>200
VII	10 (5)	25	50	150 (100)
VIII	5 (1)	25 (10)	100	150
IX	5	10	25	150
X	10	25	>200	>200
XI	10 (5)	10 (5)	>200	200
XII	100	50	>200	>200
XIII	100	50	>200	>200
XIV	>200	>200	>200	>200
INH	1	10	100	100
2-MBT	10	25	100	50

MIC = minimum inhibitory concentration. The partial inhibitory concentration is given in parentheses. INH = isonicotinic acid hydrazide, 2-MBT = 2-mercaptobenzothiazole.

was found to be 500 mg/kg, whilst that of isonicotinic hydrazide (INH) was 125 mg/kg, which means that the acute toxicity of 6-acetamido-2-alkylthiobenzothiazoles is by four times lower than that of INH.

Experimental

The starting products were prepared according to [1]. Physical constants, analytical data, and yields of 6-acetamido-2-alkylthiobenzothiazoles are listed in Table 2. The melting points were determined on a Kofler micro hot-stage.

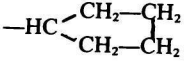
The antimycobacterial activity was determined in liquid Šula substrate by a dilution test [5], dimethyl sulfoxide being the solvent. The final mass concentration of compounds in the substrate was: ϱ/(μg cm^{-3}): 0.5, 1, 5, 10, 25, 50, 100, 150, and 200. *Mycobacterium tuberculosis* $H_{37}R_v$ and *M. avium* No. 999 (Collection of the Research Institute of Preventive Medicine, Centre for Epidemiology and Microbiology, Bratislava), *M. kansasii PKG 8* (Collection of Dr. Runyon, Salt Lake City), and *M. fortuitum* (Collection of the Institut d'hygiène et épidémiologie, Lausanne) were the microorganisms tested. The effect of products was compared with that of INH (Isoniazid, Jenapharm, GDR) and 2-mercaptobenzothiazole [6] applied under the same conditions.

Table 2

6-Acetamido-2-alkylthiobenzothiazoles

Compound	Alkyl	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		Ref.
I	$-CH_3$	$C_{10}H_{10}N_2OS_2$	238.3	50.40	4.23	11.75	26.91	79.9	167.0—168.5
				50.64	4.23	11.62	27.12	92.4*	145—147 [2]
II	$-C_2H_5$	$C_{11}H_{12}N_2OS_2$	252.4	52.35	4.79	11.10	25.41	93.8	130.0—131.5
				52.09	4.78	10.91	25.48	95.2*	
III	$-(CH_2)_2CH_3$	$C_{12}H_{14}N_2OS_2$	266.4	54.11	5.30	10.52	24.07	99.4	117.5—119.0
				54.19	5.48	10.30	24.04		
IV	$-CH(CH_3)_2$	$C_{12}H_{14}N_2OS_2$	266.4	54.11	5.30	10.52	24.07	94.0	125.0—126.5
				54.04	5.42	10.41	24.31	95.9*	
V	$-CH_2CH=CH_2$	$C_{12}H_{12}N_2OS_2$	264.4					97.7	124.5—125.5
								94.7	122.0—123.0 [3]
VI	$-(CH_2)_3CH_3$	$C_{13}H_{16}N_2OS_2$	280.4	55.58	5.75	9.99	22.87	97.6*	101.0—102.5
				55.76	5.70	9.75	22.89		
VII	$-CH_2CH(CH_3)_2$	$C_{13}H_{16}N_2OS_2$	280.4	55.68	5.75	9.99	22.87	51.8	93.5—95.5
				55.96	5.75	9.91	22.98		

Table 2 (Continued)

Compound	Alkyl	Formula	M_r	w_i(calc.)/% w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		Ref.
VIII	$-CH(CH_3)C_2H_5$	$C_{13}H_{16}N_2OS_2$	280.4	55.68	5.75	9.99	22.87	76.8	88—91
				55.40	5.77	10.02	22.89		
IX		$C_{14}H_{16}N_2OS_2$	292.4	57.50	5.52	9.58	21.93	99.3	115—117
				57.33	5.52	9.36	21.93		
X	$-(CH_2)_5CH_3$	$C_{15}H_{20}N_2OS_2$	308.5	58.41	6.54	9.08	20.79	97.4	102.0—103.5
				58.11	6.63	8.86	20.92		
XI	$-(CH_2)_6CH_3$	$C_{16}H_{22}N_2OS_2$	322.5	59.59	6.88	8.69	19.89	91.5	91—93
				59.34	6.88	8.52	19.96		
XII	$-(CH_2)_7CH_3$	$C_{17}H_{24}N_2OS_2$	336.5	60.68	7.19	8.32	19.06	98.1	100.0—101.5
				60.91	7.20	8.19	19.06		
XIII	$-(CH_2)_8CH_3$	$C_{18}H_{26}N_2OS_2$	350.5	61.67	7.48	7.99	18.29	94.3	90.5—92.0
				61.62	7.56	7.83	18.36		
XIV	$-CH_2-C_6H_5$	$C_{16}H_{14}N_2OS_2$	314.4	61.12	4.49	8.91	20.39	98.0	171.5—172.5
				61.03	4.47	8.62	20.49		

Yields marked by an asterisk are given for the 1:1 mole ratio of acetic anhydride to 2-alkylthio-6-aminobenzothiazole; the nonmarked refer to a 10:1 ratio.

Dosis tolerata maxima was estimated with white mice according to [7]. A 95 % mortality of mice after administration of the compound by an oesophageal probe was contrasted with a group to which only solvent without any substance and a group to which INH were administered.

6-Acetylamino-2-alkylthiobenzothiazoles I—XIV

2-Alkylthio-6-aminobenzothiazole (3 mmol) dissolved in an equivalent amount or in an excess of acetic anhydride was left to stand at room temperature for 10 min to 24 h (the mixture was heated to boiling temperature when preparing compounds *XI* and *XIII*). The mixture turned clear and in some experiments the product immediately separated. A 5-fold volume of water heated to 60 °C was added either after separation of the product, or after 24 h, the mixture was cooled to 5 °C, after 30 min the crystals were filtered off and recrystallized from ethanol—water in the volume ratio = 1 : 1 to 4 : 1, charcoal being added.

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