Synthesis and biological activity of 2-alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles

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2-Alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles, prepared from 2-alkylthio-6-aminobenzothiazoles and 4-nitrobenzaldehyde, have been tested for antimycobacterial and anthelmintic activities.

2-Алкилтио-6-(4-нитробензилиденамино)бензотиазолы, полученные из 2-алкилтио-6-аминобензотиазолов и 4-нитробензальдегида были проверены на антимикобактериальную и антигельминтную активности.

2-Alkylthio-6-aminobenzothiazoles were found to exhibit good antimycobacterial activity [1]. The aim of the present work was to prepare further new potential antimycotics and anthelmintics by substitution of hydrogens of the amino group with 4-nitrobenzylidene group.

The compounds *I*—*XV* were prepared from the respective 2-alkylthio-6-aminobenzothiazoles [1] in the reaction with 4-nitrobenzaldehyde at boiling (Table 1). Their antimycobacterial activities were shown to be lower than those of the starting 2-alkylthio-6-aminobenzothiazoles *Ia*—*XVa* (Table 2), though the activities of some derivatives against atypical tuberculous mycobacteria were comparable to those of the preparations generally used (Isoniazid and Etionamid). The disadvantage of these compounds is their low solubility in common solvents. Anthelmintic activity was observed only with the compounds *XI* and *XII* against *Nematospiroides dubius* and with the compound *III* against *Heterakis spumosa* (Table 3). However, the results were not reproducible perhaps due to administration of the compounds in the form of suspensions.

Experimental

The starting compounds were prepared according to [1]. Physical constants, analytical data, melting points, determined on a Kofler block, and the yields of 2-alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles are presented in Table 1.

Table 1

2-Alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles

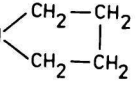
Compound	Alkyl	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		
I	$-CH_3$	$C_{15}H_{11}N_3O_2S_2$	329.4	54.69	3.37	12.76	19.47	69.0	198—200
				54.38	3.14	12.52	19.27		
II	$-C_2H_5$	$C_{16}H_{13}N_3O_2S_2$	343.4	55.96	3.82	12.24	18.67	90.2	139—141
				55.81	3.82	12.23	18.61		
III	$-(CH_2)_2CH_3$	$C_{17}H_{15}N_3O_2S_2$	357.5	57.12	4.23	11.76	17.94	78.3	107—109
				56.80	4.11	11.48	18.20		
IV	$-CH(CH_3)_2$	$C_{17}H_{15}N_3O_2S_2$	357.5	57.12	4.23	11.76	17.94	90.2	119.5—121
				56.91	4.22	11.68	17.94		
V	$-CH_2-CH=CH_2$	$C_{17}H_{13}N_3O_2S_2$	355.4	57.45	3.69	11.82	18.04	89.3	139.5—141
				57.77	3.66	11.99	18.09		
VI	$-(CH_2)_3CH_3$	$C_{18}H_{17}N_3O_2S_2$	371.5	58.20	4.61	11.31	17.26	89.5	90.5—91.5
				58.05	4.63	11.28	17.52		
VII	$-CH_2CH(CH_3)_2$	$C_{18}H_{17}N_3O_2S_2$	371.5	58.20	4.61	11.31	17.26	94.2	99—99.5
				58.29	4.67	11.24	17.51		
VIII	$-CH(CH_3)C_2H_5$	$C_{18}H_{17}N_3O_2S_2$	371.5	58.20	4.61	11.31	17.26	91.9	68—69.5
				58.42	4.64	11.24	17.29		
IX		$C_{19}H_{17}N_3O_2S_2$	383.5	59.51	4.47	10.96	16.72	91.4	125.5—126.5
				59.67	4.56	10.82	16.81		
X	$-(CH_2)_5CH_3$	$C_{20}H_{21}N_3O_2S_2$	399.5	60.12	5.30	10.52	16.05	56.3	84—86
				59.91	5.35	10.33	15.82		
XI	$-(CH_2)_6CH_3$	$C_{21}H_{23}N_3O_2S_2$	413.6	60.99	5.61	10.16	15.51	62.9	93.5—94.5
				60.70	5.54	10.08	15.56		

Table 1 (Continued)

Compound	Alkyl	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield/%	M.p./°C
				C	H	N	S		
XII	$-(CH_2)_7CH_3$	$C_{22}H_{25}N_3O_2S_2$	427.6	61.80	5.89	9.83	15.00	71.4	89—90
				61.54	5.89	9.91	15.13		
XIII	$-(CH_2)_8CH_3$	$C_{23}H_{27}N_3O_2S_2$	441.6	62.55	6.16	9.52	14.52	70.9	82.5—84
				62.70	6.32	9.50	14.32		
XIV	$-CH_2-C_6H_5$	$C_{21}H_{15}N_3O_2S_2$	405.5	62.20	3.73	10.36	15.81	79.0	189—191
				62.45	3.80	10.38	15.78		
XV	$-CH_2CH_2OH$	$C_{16}H_{13}N_3O_3S_2$	359.4	53.47	3.65	11.69	17.84	72.3	157—159
				53.43	3.65	11.69	17.76		

Table 2

Antimycobacterial activity (MIC/(μg cm^{-3})) of 2-alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles *I—XV* and of the starting 2-alkylthio-6-aminobenzothiazoles *Ia—XVa*

Compound	*Mycobacterium*			
	tbc. $H_{37}R_v$	*kansasii PKG 8*	*avium 1618*	*fortuitum*
I	50	200	50	>200
Ia	100(50)	>100	100	>100
II	50	200	50	>200
IIa	50(25)	>100	100	100
III	25	50	25	50
IIIa	50(25)	50	50	50
IV	25	50	50	50
IVa	50(25)	50	50	50
V	200	>200	50	200
Va	25(10)	50	50	50
VI	10(5)	50	50	50
VIa	25	50(25)	25	25
VII	50	50	50(25)	100
VIIa	50(25)	50	50	50
VIII	25	25	50(25)	50
VIIIa	50(25)	50	25	50
IX	25	>200	25	100
IXa	25(10)	25	25	25
X	10	50	50	b
Xa	5	5	50	25
XI	25	50	>200	50
XIa	25	25	>100	100
XII	25	25	25	100
XIIa	50(25)	50(25)	25	50(25)
XIII	25	25	>200	>200
XIIIa	10	10	25	50
XIV	100	100	50	100
XIVa	25(10)	25	25	25
XV	50	100	>200	>200
XVa	>100	>100	>100	>100
Isoniazid	1	25	25	50
Etionamid	10	25	100	50

b = not tested.
Partial inhibition concentration is given in parentheses.

Table 3

Activity/% in primary anthelmintic screening (*in vivo*)

Helminths	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*	*XIII*	*XIV*	*XV*
Trichinella spiralis	0	0	0	0	10	0	0	0	0	0	0	0	0	0	0
Aspiculuris tetraptera	0	0	0	0	0	0	40	0	20	0	0	0	0	0	0
Nematospiroides dubius	0	0	0	10	0	0	0	20	0	0	80 40	80 25	15	15	15
Heterakis spumosa	30 0	0	70 30	0	0	0	0	15	10	0	20	20	10	25	15

Antimycobacterial activity was determined in the liquid Šula medium by the dilution test [2] using dimethyl sulfoxide as solvent. The resulting numerical values of mass concentrations $\varrho/(\mu g\ cm^3)$ of the compounds in the medium were 0.5, 1, 5, 10, 25, 50, 100, and 200. *Mycobacterium (M.) tuberculosis* $H_{37}R_v$ and *M. avium 1618* (Collection of the Research Institute of Preventive Medicine, Centre for Epidemiology and Microbiology), *M. kansasii PKG 8* (Collection of Dr. Runyon, Salt Lake City), and *M. fortuitum* (Collection of Institut d'hygiène et épidémiologie, Lausanne) were used for tests. The activities of compounds were compared to those of isonicotinohydrazide (INH, Isoniazid, Jenapharm, GDR) and 2-ethylthioisonicotineamide (Etionamid, Trécator, Teraplix, Paris).

Anthelmintic activity was tested *in vivo* on white mice (VELAZ, Prague) as hosts. The invasion stages of the individual helminths were obtained according to the procedures published in [3—5] and modified at the Institute of Helminthology, Slovak Academy of Sciences [6]. The mice were invaded *per os*. The compounds tested were applied as follows: in the case of enteronematodes immediately after the prepatent period, in the case of *T. spiralis* on the fourth day after invasion. The compounds dispersed in the Dorfmann solution were applied by an oesophageal sound thrice in mass fraction 150 ppm during three days. The activity of compounds was tested by the method of critical controlled test [5]; with enteronematodes on the eighth day after the first application of the compound, in the case of *T. spiralis* on the fortieth day after invasion.

2-Alkylthio-6-(4-nitrobenzylideneamino)benzothiazoles I—XV

To the warm solution of 2-alkylthio-6-aminobenzothiazole (0.02 mol) in ethanol (40 cm^3) 4-nitrobenzaldehyde (3.0 g; 0.02 mol) was added and the reaction mixture was refluxed for 10 min. The precipitated yellow crystals were purified by crystallization from ethanol using charcoal.

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