Preparation and biological activity of 1-(2-R-thio-6-benzothiazolylaminomethyl)-5-(R^1-phenyl)-1,2,3,4-tetrazoles

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By Mannich reaction of 6-amino-2-R-thiobenzothiazoles with formaldehyde and 5-(R^1-phenyl)-1,2,3,4-tetrazoles, 1-(2-alkyl-, -aryl-, and -benzylthio--6-benzothiazolylaminomethyl) derivatives of substituted tetrazoles have been prepared. The highest biological activity has been found with 2-ethyl derivatives of the prepared compounds.

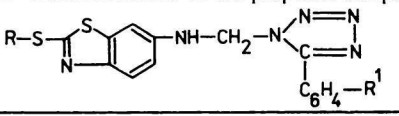
Реакцией Манниха 6-амино-2-R-тиобензтиазолов с формальдегидом и 5-(R^1)-фенил-1,2,3,4-тетразолами были приготовлены 1-(2-алкил, 2-арил и 2-бензилтио-6-бензтиазолиламинометил) – производные замещенных тетразолов. Самой высокой биологической активностью обладают 2-этилпроизводные приготовленных соединений.

When studying the Mannich reactions of 2-mercaptobenzothiazole, 6-nitro-2-mercaptobenzothiazole, and 2-hydroxybenzothiazole as H-active components it was found that, depending on the used amine, the products were mono or bis derivatives [1—4]. As amino components differently substituted aliphatic, alicyclic, aromatic, and heterocyclic amines were used. In the present paper we have used as the amino components 6-amino-2-R-thiobenzothiazoles with high pK_B values [2] which should react, according to conclusions of [1], with the prepared tetrazoles (as H-active components) and formaldehyde under the formation of mono derivatives of Mannich bases.

The aim of our work was to find out if the change in the structure of the H-active component affects the Mannich products or the formation of mono or bis derivatives depends on the basicity of amines only. Previous experience with this type of compounds prompted us to test some of the prepared derivatives for activity against mycobacteria and viruses.

It was found that the reaction of the used amino compounds of known pK_B values [2] with 5-substituted 1,2,3,4-tetrazoles as H-active components and

Table 1. Characterization of the prepared compounds



Compound	R	R^1	Formula	*M*	Calculated/found				Yield %	M.p. °C
					% C	% H	% N	% S		
I	CH_3	H	$C_{16}H_{14}N_6S_2$	354.46	54.21	3.98	23.70	18.09	57	141—143
					54.14	3.89	23.38	18.47		
II	CH_3CH_2	H	$C_{17}H_{16}N_6S_2$	368.48	55.41	4.37	22.80	17.40	85	150—152
					55.47	4.37	22.91	17.39		
III	$CH_3(CH_2)_2$	H	$C_{18}H_{18}N_6S_2$	382.53	56.51	4.74	21.96	16.76	78	134—136
					56.89	4.88	21.94	16.56		
IV	$CH_3(CH_2)_3$	H	$C_{19}H_{20}N_6S_2$	396.54	57.55	5.08	21.19	16.17	56	105—108
					57.48	5.12	21.31	16.26		
V	$iCH_3(CH_2)_3$	H	$C_{19}H_{20}N_6S_2$	396.54	57.55	5.08	21.19	16.17	70	137—139
					57.90	5.14	21.38	16.22		
VI	$CH_3(CH_2)_4$	H	$C_{20}H_{22}N_6S_2$	410.56	58.50	5.39	20.46	15.62	62	95—97
					58.32	5.30	20.19	15.36		
VII	$CH_3(CH_2)_7$	H	$C_{23}H_{28}N_6S_2$	452.62	61.02	6.23	18.56	14.16	77	97—100
					61.11	6.31	18.49	14.16		
VIII	$CH_3(CH_2)_8$	H	$C_{24}H_{30}N_6S_2$	466.67	61.76	6.47	18.00	13.74	70	109—111
					62.05	6.57	18.19	13.66		
IX	$CH_2{=}CH{-}CH_2$	H	$C_{18}H_{16}N_6S_2$	380.49	56.82	4.23	22.08	16.85	73	130—132
					56.48	4.25	21.85	16.87		
X	$C_6H_5{-}CH_2$	H	$C_{22}H_{18}N_6S_2$	430.55	61.37	4.21	19.51	14.89	93	145—147
					61.35	4.29	19.03	14.92		
XI	CH_3CH_2	4-NO_2	$C_{17}H_{15}N_7S_2O_2$	413.49	49.38	3.65	23.71	15.50	72	168—169
					49.09	3.59	23.71	15.64		
*XII**	CH_3CH_2	3,4-diCl	$C_{17}H_{14}N_6S_2Cl_2$	437.38	46.68	3.22	19.21	14.66	81	140—142
					46.76	3.19	19.22	14.80		

* % Cl calculated 16.21, found 16.24.

formaldehyde resulted in new, so far not described mono derivatives of Mannich bases (Table 1). Thus, it seems that formation of mono or bis derivatives depends only on basicity [1, 2, 4] and nucleophility [3], respectively, of amines used in these reactions so far and is independent of the composition and structure of the H-active component.

Some of the prepared compounds showed noticeable activity in tests against different strains of mycobacteria (Table 2) and viruses (Table 3). 1-(2--Ethylthio-6-benzothiazolylaminomethyl)-5-phenyl-1,2,3,4-tetrazole (*II*) was shown to be equally active against resistant strains of mycobacteria as the chemotherapeutical standard Izoniazid (isonicotinohydrazide). This compound was observed to be less active against *Mycobacterium tuberculosis* $H_{37}R_v$ and its activity against other strains of mycobacteria was low as well.

In tests for antiviral activity against *Vakcinia,* NDV, and WEE viruses the compound *II* was found to show the lowest activity when compared with that of the standard 6-azauridine. 1-(2-Ethylthio-6-benzothiazolylaminomethyl)-5-(4′-nitrophenyl)-1,2,3,4-tetrazole (*XI*) was almost equally active. The highest activity against *Vakcinia* viruses (when compared with that of the compounds *II* and *XI* as well as the standard) was shown by 1-(2-ethylthio-6-benzothiazolylaminomethyl)-5-(3′,4′-dichlorophenyl)-1,2,3,4-tetrazole (*XII*). This compound was, however, totally inactive against the WEE virus when compared to the compounds *II* and *XI.* All compounds tested were inactive against NDV viruses.

Experimental

6-Amino-2-R-thiobenzothiazoles were prepared by the reaction of potassium salt of 6-amino-2-mercaptobenzothiazole with the appropriate R-halides according to [5, 6]. 5-(R^1-Phenyl)-1,2,3,4-tetrazoles were prepared by the reaction of unsubstituted and substituted phenyl cyanides with sodium azide and ammonium chloride in dimethylformamide after [7]. Sodium salt of 5-(4′-nitrophenyl)-1,2,3,4-tetrazole was prepared from the appropriate tetrazole and sodium methoxide solution by evaporation to dryness. Analytical data of the prepared Mannich bases are presented in Table 1. Antimycobacterial activity was determined by the classical method modified for mycobacteria according to [8]. Antiviral activity was investigated using the screening test according to [9].

1-(2-Alkyl-, -aryl-, and -benzylthio-6-benzothiazolylaminomethyl)-5--phenyl-1,2,3,4-tetrazoles (I—X)

2-Alkyl-, aryl-, and -benzylthio-6-aminobenzothiazole (0.01 mol), respectively, was mixed with 5-phenyl-1,2,3,4-tetrazole (0.01 mol) and 96% ethanol (20—40 ml) at room temperature. The mixture was heated to 35°C under stirring while a light-yellow solution was formed. Into this solution 34% formaldehyde (0.02 mol) was added dropwise and the

Table 2

Antimycobacterial activity (minimal inhibition concentration in mg/ml)

Compound	*M. tuberculosis* $H_{37}R_v$	*M. tuberculosis* INH-R "67"	*M. avium*	*M. kansasii*	*M. fortuitum*
II	25	25	200	200	200
Izoniazid	1	25	50	100	100

INH-R — strain of mycobacteria resistant to Izoniazid.
II dissolved in dimethylformamide.

Table 3

Antiviral activity

Compound	Concentration mg/ml Solvent DMFA	Toxicity zone (diameter, mm)	Inhibition zone (diameter, mm)		
			Vakcinia	NDV	WEE
II	100	8	25	0	14
XI	100	0—12	28	0	18
XII	50	25	48	0	0
6-Azauridine			62		

DMFA — dimethylformamide; WEE — Western equine encephalomyelitis; NDV — Newcastle disease virus.

mixture was heated to 40°C. After 5 to 30 min at this temperature the solution became turbid and later the product crystallized. After 30 min the mixture was cooled to room temperature, the crystalline compound was sucked and washed with ethanol on the filter. If the product did not crystallize, acetone (3—5 ml) was poured into the mixture, then it was cooled to −5°C and water was added dropwise under stirring till the first turbidity appeared. The mixture was allowed to stay at −22°C for 12 h. The crystals of the base were purified by washing with ethanol.

1-(2-Ethyl-6-benzothiazolylaminomethyl)-5-(3′,4′-dichlorophenyl)-1,2,3,4-tetrazole (*XII*) was prepared by the same procedure.

1-(2-Ethylthio-5-benzothiazolylaminomethyl)-5-(4′-nitrophenyl)-1,2,3,4-tetrazole (XI)

Sodium salt of 5-(4′-nitrophenyl)-1,2,3,4-tetrazole (0.01 mol) was mixed with 2-ethylthio-6-aminobenzothiazole (0.01 mol) and 96% ethanol (40 ml). The mixture was heated to 40°C under stirring and 34% formaldehyde (0.02 mol) was added dropwise. After 10 min 36% hydrochloric acid (1 ml) was added while the reaction product started to crystallize. After 10 min the mixture was cooled to room temperature and the yellow crystalline compound was sucked and washed with water and ethanol (added dropwise) on the filter.

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