Benzothiazole compounds

XIX. Synthesis of 3-benzylbenzothiazolium salts, their growth regulation effects, and antimicrobial activities

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By treatment of substituted benzothiazole with substituted benzyl bromides the corresponding 3-benzylbenzothiazolium salts have been prepared. The ^{1}H-n.m.r. shifts of signals were correlated with σ constants of the substituents on the benzyl part. The whole group of the synthesized compounds showed lower stimulation effect on plant growth than the used standards (IAA; 2,4-D) and mean or even low antibacterial and antifungal activities. The activity against *Staphylococcus aureus* was quantitatively evaluated by the Free—Wilson analysis. The substituents on the benzyl part brought about a decrease in biological activity when compared to the unsubstituted derivatives.

Действием замещенных бензилбромидов на замещенный бензотиазол были получены соответствующие 3-бензилбензотиазолиевые соли. Проведена корреляция ^{1}H-ЯМР сдвигов с σ-константами заместителей в бензильной части. Вся группа полученных соединений проявляла меньший стимулирующий эффект на рост растений, чем использованные стандарты (IAA; 2,4-D), а также обладала средней или низкой антибактериальной и антигрибковой активностью. Активность по отношению к *Staphylococcus aureus* была количественно оценена с помощью анализа Фри—Вильсона. Заместители в бензильной части приводят к понижению биологической активности по сравнению с незамещенными соединениями.

On the basis of the stimulation effect of 3-benzylbenzothiazolium bromide on plant growth (+6.7 mm at 1×10^{-7} mol dm^{-3}) found in [1], derivatives with different substituents R on the benzyl part and R^1 on benzothiazole in the positions 4 and 6, respectively, were synthesized with the aim to enlighten the relationship between the structure and biological activity. The substituents were chosen so that they represented the widest spectrum from the viewpoint of electron effects, lipophility, and steric requirements. The starting 4- and 6-substituted benzothiazoles were prepared by deamination of the appropriate 2-aminobenzothiazoles with pentyl nitrite in anhydrous tetrahydrofuran analogously as in the case of some aromatic and heteroaromatic amines [2]. The yields obtained were: 4-methylbenzothiazole 69%, 4-chlorobenzothiazole 72%, 6-methylbenzothiazole 78%, and 6-chlorobenzothiazole 66%. In comparison with 2-aminothiazole (yield of deamination 16% [2]), the benzene ring in 2-aminobenzothiazoles probably increases the stability of the appropriate diazonium cation as well as that of the radical. Of the examined solvents (acetone, acetonitrile, dimethylformamide, nitromethane), the mixture of dimethylformamide and acetone (2:1) was proved to be the best medium for the final quaternization reaction. Majority of derivatives were prepared by the general method described in [1]. Quaternization of 4-substituted benzothiazole derivatives was by far more difficult than that of the 6-substituted ones. We assume that in this reaction steric factors play the determining role similarly as in quaternization of 8-substituted quinolines [3]. 4-Substituted benzothiazolium salts were prepared by heating in a sealed tube at 95—100 °C for 30 h but the yields were low, *e.g.* of 3-(2-chlorobenzyl)-4-methylbenzothiazolium bromide only 26%. Moreover, quaternary salts were often accompanied by impurities of 4-methylbenzothiazolium bromide which could not be removed from the product. Only five derivatives *LXI—LXV* were prepared in a sufficiently pure state. Quaternary salts of 4-chlorobenzothiazole were not prepared in pure state (Table 1).

In the ^{1}H-n.m.r. spectra of 3-benzylbenzothiazolium salts shifts of signals were observed in dependence on the substituents on the ring of the benzyl group. The signals belonging to protons of CH_2 group and proton of the benzothiazole system in the position 2 were measured (Table 2). Fig. 1 illustrates the δ (CH_2) and δ (H-2) values for *m*- and *p*-substituted benzyl derivatives *I—XIX* (R^1 = H) in dependence on the Hammett σ constants of the substituents [6]. 3-Bromo derivative departed mostly from the regression line. For the other 14 *m*- and *p*-substituted derivatives the following statistical parameters of correlations were obtained by the least-square method

Correlation	n	r	ϱ	s_ϱ	q	s_q	s
$\delta(CH_2) - \sigma$	14	0.960	0.249	0.021	6.173	0.021	0.025
δ(H-2) $- \sigma$	14	0.854	0.130	0.023	10.911	0.023	0.027

Table 1

Characterization of the synthesized 3-benzylbenzothiazolium salts

Compound	R	R^1	X^-	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
I	H	H	I	$C_{14}H_{12}INS$	353.23	47.61	3.42	3.97	9.08	82	170—172
						47.69	3.43	3.74	9.05		
II	2-CH_3	H	Br	$C_{15}H_{14}BrNS$	320.25	56.26	4.41	4.37	10.01	65	199—201
						56.09	4.35	4.40	9.90		
III	3-CH_3	H	Br	$C_{15}H_{14}BrNS$	320.25	56.26	4.41	4.37	10.01	69	180—181
						56.02	4.38	4.48	9.87		
IV	4-CH_3	H	Br	$C_{15}H_{14}BrNS$	320.25	56.26	4.41	4.37	10.01	72	180—182
						56.11	4.40	4.50	9.86		
V	2-Cl	H	Br	$C_{14}H_{11}BrClNS$	340.67	49.36	3.25	4.11	9.41	63	212—215
						49.18	3.20	4.14	9.36		
VI	3-Cl	H	Br	$C_{14}H_{11}BrClNS$	340.67	49.36	3.25	4.11	9.41	76	184—185
						49.37	3.27	4.05	9.50		
VII	4-Cl	H	Br	$C_{14}H_{11}BrClNS$	340.67	49.36	3.25	4.11	9.41	70	176—178
						49.15	3.28	4.00	9.33		
VIII	2-NO_2	H	Br	$C_{14}H_{11}BrN_2O_2S$	351.22	47.88	3.16	7.97	9.13	66	193—194
						47.84	3.08	7.78	9.13		
IX	3-NO_2	H	Br	$C_{14}H_{11}BrN_2O_2S$	351.22	47.88	3.16	7.97	9.13	76	198—199
						47.65	3.23	7.87	9.02		
X	3-Br	H	Br	$C_{14}H_{11}Br_2NS$	385.12	43.66	2.88	3.64	8.33	61	175—177
						43.70	2.63	3.46	8.15		
XI	4-Br	H	Br	$C_{14}H_{11}Br_2NS$	385.12	43.66	2.88	3.64	8.33	64	118—121
						43.83	3.01	3.76	8.21		
XII	3-F	H	Br	$C_{14}H_{11}BrFNS$	324.21	51.87	3.42	4.32	9.89	67	195—198
						51.88	3.48	4.20	9.83		
XIII	4-F	H	Br	$C_{14}H_{11}BrFNS$	324.21	51.87	3.42	4.32	9.89	59	174—176
						52.05	3.40	4.21	9.85		

Table 1 (Continued)

Compound	R	R^1	X^-	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
XIV	4-OCH_3	H	Br	$C_{15}H_{14}BrNOS$	336.25	53.58	4.20	4.17	9.54	65	166—167
						53.43	4.11	4.08	9.52		
XV	4-CN	H	Br	$C_{15}H_{11}BrN_2S$	331.23	54.39	3.35	8.46	9.68	67	205—206
						54.21	3.36	8.31	9.47		
XVI	2,3-$(CH)_4$	H	Br	$C_{18}H_{14}BrNS$	356.28	60.63	3.96	3.93	9.00	62	219—220
						60.55	3.91	3.89	9.01		
XVII	3,4-$(CH)_4$	H	Br	$C_{18}H_{14}BrNS$	356.28	60.63	3.96	3.93	9.00	71	192—193
						60.49	3.98	4.04	8.89		
XVIII	4-SO_2NH_2	H	Br	$C_{14}H_{13}BrN_2O_2S_2$	385.31	43.64	3.40	7.27	16.64	56	209—211
						43.41	3.22	7.09	16.44		
XIX	4-OSO_2CH_3	H	Br	$C_{15}H_{14}BrNO_3S$	400.31	45.01	3.53	3.50	16.02	48	153—155
						44.83	3.38	3.39	15.84		
XX	H	CH_3	Br	$C_{15}H_{14}BrNS$	320.25	56.26	4.41	4.37	10.01	79	211—212
						56.05	4.27	4.48	9.80		
XXI	H	CH_3	I	$C_{15}H_{14}INS$	367.27	49.06	3.84	3.81	8.73	76	192—194
						49.21	3.77	3.65	8.60		
XXII	2-CH_3	CH_3	Br	$C_{16}H_{16}BrNS$	334.29	57.49	4.82	4.19	9.59	63	205—207
						57.26	4.76	4.03	9.51		
XXIII	3-CH_3	CH_3	Br	$C_{16}H_{16}BrNS$	334.29	57.49	4.82	4.19	9.59	69	215—218
						57.26	4.80	4.02	9.58		
XXIV	4-CH_3	CH_3	Br	$C_{16}H_{16}BrNS$	334.29	57.49	4.82	4.19	9.59	76	201—203
						57.24	4.70	4.07	9.44		
XXV	2-Cl	CH_3	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	68	203—205
						50.59	3.62	3.83	8.98		
XXVI	3-Cl	CH_3	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	79	234—237
						50.72	3.71	3.77	9.08		
XXVII	4-Cl	CH_3	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	63	117—120
						50.43	3.81	3.79	8.86		

Table 1 (Continued)

Compound	R	R^1	X^-	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
XXVIII	2-NO_2	CH_3	Br	$C_{15}H_{13}BrN_2O_2S$	365.26	49.33	3.59	7.67	8.78	66	210—212
						49.09	3.52	7.51	8.79		
XXIX	3-NO_2	CH_3	Br	$C_{15}H_{13}BrN_2O_2S$	365.26	49.33	3.59	7.67	8.78	71	189—191
						49.40	3.58	7.57	8.78		
XXX	4-NO_2	CH_3	Br	$C_{15}H_{13}BrN_2O_2S$	365.26	49.33	3.59	7.67	8.78	74	218—220
						49.11	3.61	7.54	8.57		
XXXI	3-Br	CH_3	Br	$C_{15}H_{13}Br_2NS$	399.16	45.14	3.28	3.51	8.03	65	213—215
						45.02	3.09	3.36	7.93		
XXXII	4-Br	CH_3	Br	$C_{15}H_{13}Br_2NS$	399.16	45.14	3.28	3.51	8.03	70	158—160
						45.10	3.36	3.84	7.88		
XXXIII	3-F	CH_3	Br	$C_{15}H_{13}BrFNS$	338.25	53.26	3.87	4.14	9.48	75	234—237
						53.11	3.80	4.08	9.70		
XXXIV	4-F	CH_3	Br	$C_{15}H_{13}BrFNS$	338.25	53.26	3.87	4.14	9.48	67	196—198
						52.98	3.63	3.95	9.32		
XXXV	4-OCH_3	CH_3	Br	$C_{16}H_{16}BrNOS$	350.29	54.86	4.60	4.00	9.15	62	181—183
						54.69	4.57	3.86	8.96		
XXXVI	4-CN	CH_3	Br	$C_{16}H_{13}BrN_2S$	345.27	55.65	3.80	8.11	9.29	59	221—223
						55.64	3.82	8.12	9.11		
XXXVII	2,3-$(CH)_4$	CH_3	Br	$C_{19}H_{16}BrNS$	370.32	61.63	4.35	3.78	8.66	64	194—196
						61.47	4.24	3.55	8.72		
XXXVIII	3,4-$(CH)_4$	CH_3	Br	$C_{19}H_{16}BrNS$	370.32	61.63	4.35	3.78	8.66	67	180—182
						61.35	4.30	3.59	8.42		
XXXIX	4-SO_2NH_2	CH_3	Br	$C_{15}H_{15}BrN_2O_2S_2$	399.34	45.12	3.79	7.01	16.06	57	230—233
						44.81	3.75	6.90	15.87		
XL	4-OSO_2CH_3	CH_3	Br	$C_{16}H_{16}BrNO_3S_2$	414.35	46.38	3.89	3.38	15.48	52	162—164
						46.06	3.85	3.16	15.77		
XLI	H	Cl	Br	$C_{14}H_{11}BrClNS$	340.67	49.36	3.24	4.11	9.41	77	210—211
						49.12	3.17	4.02	9.23		

Table 1 (Continued)

Compound	R	R¹	X⁻	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
XLII	H	Cl	I	$C_{14}H_{11}ClINS$	387.68	43.37	2.86	3.61	8.27	82	192—193
						43.23	2.79	3.52	8.13		
XLIII	2-CH_3	Cl	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	69	195—198
						50.46	3.70	3.91	8.98		
XLIV	3-CH_3	Cl	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	73	167—169
						50.45	3.81	3.91	8.68		
XLV	4-CH_3	Cl	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	78	220—223
						50.63	3.72	3.92	8.95		
XLVI	2-Cl	Cl	Br	$C_{14}H_{10}BrCl_2NS$	375.12	44.83	2.69	3.73	8.55	60	223—226
						44.70	2.70	3.56	8.62		
XLVII	3-Cl	Cl	Br	$C_{14}H_{10}BrCl_2NS$	375.12	44.83	2.69	3.73	8.55	69	220—222
						44.57	2.97	3.93	8.36		
XLVIII	4-Cl	Cl	Br	$C_{14}H_{10}BrCl_2NS$	375.12	44.83	2.69	3.73	8.55	63	175—177
						44.41	2.82	3.92	8.38		
XLIX	2-NO_2	Cl	Br	$C_{14}H_{10}BrClN_2O_2S$	385.67	43.60	2.61	7.25	8.31	67	193—195
						43.71	2.52	7.22	8.28		
L	3-NO_2	Cl	Br	$C_{14}H_{10}BrClN_2O_2S$	385.67	43.60	2.61	7.25	8.31	71	201—203
						43.46	2.58	7.13	8.25		
LI	4-NO_2	Cl	Br	$C_{14}H_{10}BrClN_2O_2S$	385.67	43.60	2.61	7.25	8.31	74	208—210
						43.70	2.54	7.12	8.27		
LII	3-Br	Cl	Br	$C_{14}H_{10}Br_2ClNS$	419.57	40.08	2.40	3.34	7.64	66	190—191
						40.25	2.31	3.16	7.41		
LIII	4-Br	Cl	Br	$C_{14}H_{10}Br_2ClNS$	419.57	40.08	2.40	3.34	7.64	63	206—207
						40.19	2.23	3.29	7.63		
LIV	3-F	Cl	Br	$C_{14}H_{10}BrClFNS$	358.66	46.88	2.81	3.91	8.94	67	212—213
						46.57	3.08	4.10	8.75		

Table 1 (Continued)

Compound	R	R¹	X⁻	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
LV	4-F	Cl	Br	$C_{14}H_{10}BrClFNS$	358.66	46.88	2.81	3.91	8.94	73	180—183
						47.05	2.85	3.77	8.99		
LVI	4-OCH_3	Cl	Br	$C_{15}H_{13}BrClNOS$	370.70	48.60	3.53	3.78	8.65	65	147—150
						48.32	3.43	3.61	8.61		
LVII	4-CN	Cl	Br	$C_{15}H_{10}BrClN_2S$	365.68	49.27	2.76	7.66	8.77	72	217—219
						49.08	2.80	7.50	8.83		
LVIII	2,3-$(CH)_4$	Cl	Br	$C_{18}H_{13}BrClNS$	390.73	55.33	3.35	3.58	8.21	60	218—221
						55.12	3.32	3.63	8.22		
LIX	3,4-$(CH)_4$	Cl	Br	$C_{18}H_{13}BrClNS$	390.73	55.33	3.35	3.58	8.21	56	173—174
						55.08	3.58	3.79	8.05		
LX	4-SO_2NH_2	Cl	Br	$C_{14}H_{12}BrClN_2O_2S_2$	419.75	40.06	2.88	6.67	15.28	61	231—234
						39.82	2.80	6.78	15.31		
LXI	H	4-CH_3	Br	$C_{15}H_{14}BrNS$	320.25	56.26	4.41	4.37	10.01	34	211—213
						56.02	4.44	4.14	10.10		
LXII	H	4-CH_3	I	$C_{15}H_{14}INS$	367.27	49.06	3.48	3.81	8.73	45	160—162
						49.19	3.65	3.61	8.46		
LXIII	2-Cl	4-CH_3	Br	$C_{15}H_{13}BrClNS$	354.71	50.79	3.69	3.95	9.04	26	225—227
						50.46	3.57	3.88	9.16		
LXIV	4-F	4-CH_3	Br	$C_{15}H_{13}BrFNS$	338.25	53.26	3.87	4.14	9.48	28	217—219
						53.41	3.85	4.17	9.56		
LXV	4-NO_2	4-CH_3	Br	$C_{15}H_{13}BrN_2O_2S$	365.26	49.33	3.59	7.67	8.78	31	203—205
						49.20	3.61	7.61	8.72		

Table 2

^{1}H-NMR data of the synthesized compounds

Compound	$R^1 = H$		Compound	$R^1 = 6\text{-}CH_3$		Compound	$R^1 = 6\text{-}Cl$		Compound	$R^1 = 4\text{-}CH_3$	
	—CH_2—	H-2		—CH_2—	H-2		—CH_2—	H-2		—CH_2—	H-2
Ia	6.160	10.875	*XX*	6.131	10.773	*XLI*	6.195	10.901	*LXI*	6.338	10.493
II	6.148	10.491	*XXII*	6.124	10.436	*XLII*	6.151	10.493	*LXIII*	6.329	10.478
III	6.171	10.940	*XXIII*	6.109	10.826	*XLIV*	6.144	10.879	*LXV*	6.519	10.654
IV	6.143	10.895	*XXIV*	6.120	10.816	*XLV*	6.081	10.778	*LXIV*	6.315	10.380
V	6.256	10.719	*XXV*	6.179	10.546	*XLVI*	6.216	10.664			
VI	6.239	10.974	*XXVI*	6.100	10.718	*XLVII*	6.219	10.938			
VII	6.250	10.974	*XXVII*	6.184	10.855	*XLVIII*	6.174	10.866			
VIII	6.465	10.646	*XXVIII*	6.461	10.615	*XLIX*	6.509	10.774			
IX	6.379	11.011	*XXIX*	6.361	10.944	*L*	6.304	10.913			
IXa	6.379	10.984	*XXX*	6.384	10.940	*LI*	6.414	11.029			
X	6.101	10.913	*XXXI*	6.135	10.791	*LII*	6.193	10.908			
XI	6.196	10.923	*XXXII*	6.064	10.659	*LIII*	6.184	10.899			
XII	6.239	10.965	*XXXIII*	6.148	10.780	*LIV*	6.185	10.880			
XIII	6.224	10.934	*XXXIV*	6.168	10.825	*LV*	6.183	10.875			
XIV	6.108	10.856	*XXXV*	6.078	10.774	*LVI*	6.093	10.806			
XV	6.361	11.023	*XXXVI*	6.248	10.806	*LVII*	6.306	10.944			
XVI	6.386	11.005	*XXXVIII*	6.346	10.918						
XVIII	6.298	10.979	*XL*	6.194	10.836						
XIX	6.226	10.920									

Ia: 3-Benzylbenzothiazolium bromide [4]; *IXa*: 3-(4-nitrobenzyl)benzothiazolium bromide [5].

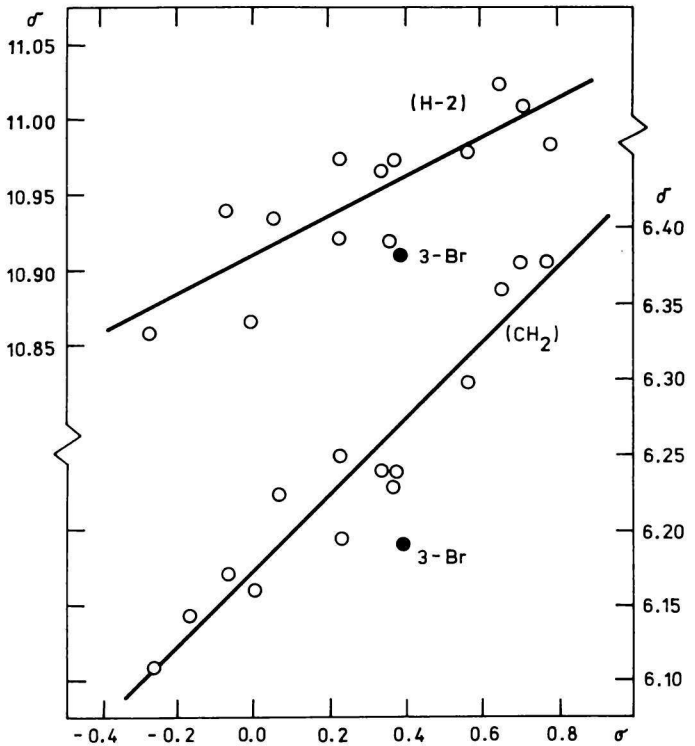


Fig. 1. Dependence of chemical shifts δ on σ constants of the substituents of 3-benzylbenzothiazolium salts.

n — number of dots; r — correlation coefficient; ϱ — slope; s_ϱ — standard deviation of ϱ; q — intercept on the y axis; s_q — standard deviation of q; s — standard deviation of correlation.

The $\delta(CH_2)$ values well correlate with the σ constants of the substituents. Essentially less significant correlation was found with the δ(H-2) values of the same derivatives. The slope ϱ(H-2), expressing the sensitivity of the proton in the position 2 to the substituent effects, was approximately half of the slope $\varrho(CH_2)$. This decreased sensitivity reflects the transfer of effects through the quaternary nitrogen. Analogous correlations of further groups of 3-benzylbenzothiazolium salts ($R^1 = 6\text{-}CH_3$, 6-Cl) were statistically less significant.

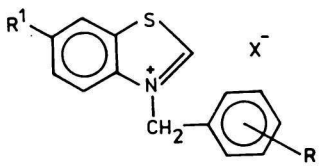
Table 3 presents the antimicrobial activity of some 3-benzylbenzothiazolium salts. The activity with other derivatives was even lower, approximately on the level with *LVI*. Only the compounds with unsubstituted benzyl group showed higher activity. The results were proved also by the Free—Wilson analysis [7] excluding

Table 3

Antimicrobial activity of some 3-benzylbenzothiazolium salts

Compound	Minimum inhibitory concentration μg/disc				Fungicidal/-statical concentration μg/ml		*1*	
	1	*2*	*3*	*4*	*5*	*6*	ED_{100}	ED_{50}
Ia	12.5	12.5	200	200	200/50	50/12.5	18.2	7.5
I	12.5	12.5	200	200	200/50	50/12.5	18.0	7.5
II	50	12.5	200	200	200/50	50/12.5	18.4	8.6
III	50	12.5	200	200	200/50	50/12.5	18.5	8.6
IV	50	12.5	200	200	200/50	50/12.5	18.5	8.6
V	50	50	200	200	200/50	50/12.5	26.0	12.0
VI	50	50	200	200	200/50	200/50	26.0	14.0
XX	12.5	12.5	200	200	200/50	200/50	14.4	6.8
XLI	12.5	12.5	200	200	200/50	50/12.5	12.5	5.5
LVI	50	50	200	200	200/200	200/50	28.0	13.0

the compounds *XVI, XVII, XXXVII, XXXVIII, LVIII,* and *LIX.* The analyzed group was composed of 56 compounds (including *Ia* and *IXa*) of the general formula



R^1 represents three substituents, R four substituents in the position 2, six substituents in the position 3, and ten in the position 4, X^- represents two anions. With 25 substituents in five positions the system has 35 degrees of freedom. The measured antibacterial activity on *Staphylococcus aureus* was expressed in the ED_{50} and ED_{100} values in linear scale (μg/ml) and logarithmic scale (molar concentrations). The results of the Free—Wilson analysis are presented in Table 4. The correlation coefficients *r* differed each from the other only little and indicated a good statistical significance for all four correlations. The *F* values corresponded to 99.5% probability level. The z_{jk} values proved the increase of activity in dependence on the substituent in the position 6 (R^1) in the order $H < CH_3 < Cl$. However, the changes were not significant. The highest contribution to the activity observed in the group of R substituents was unambiguously that of hydrogen. The substituents in *p* position on the benzyl group could be ranged according to the

Table 4

Results of the Free—Wilson analysis

Position	Substituent	Number of substituents	ED_{50}		$-\log c$ (ED_{50})		ED_{100}		$-\log c$ (ED_{100})	
			z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}
	H	19	0.854		−0.051		3.040		−0.069	
R[1]	CH_3	19	0.259	2.034	−0.016	0.122	0.177	6.451	−0.012	0.155
	Cl	18	−1.180		0.071		−3.411		0.086	
	H	47	−0.695		0.029		−1.376		0.025	
2-R	CH_3	3	2.571	5.000	−0.129	0.204	3.724	11.633	−0.083	0.195
	Cl	3	4.305		−0.175		7.624		−0.138	
	NO_2	3	4.038		−0.150		10.257		−0.170	
	H	41	−1.414		0.056		−2.875		0.049	
	CH_3	3	1.986		−0.108		2.391		−0.062	
3-R	F	3	4.420	6.900	−0.197	0.253	9.758	15.300	−0.192	0.241
	Cl	3	3.986		−0.161		6.025		−0.112	
	Br	3	5.486		−0.162		12.425		−0.162	
	NO_2	3	3.486		−0.131		8.791		−0.146	
	H	30	−2.765		0.103		−5.923		0.097	
	CH_3	3	0.635		−0.061		−0.590		−0.016	
	F	3	3.168		−0.152		6.577		−0.142	
	Cl	3	2.202		−0.100		2.710		−0.060	
4-R	Br	3	4.102	7.867	−0.113	0.304	9.410	16.633	−0.115	0.289
	NO_2	3	1.868		−0.073		5.210		−0.090	
	OCH_3	3	5.102		−0.201		10.710		−0.192	
	CN	3	4.068		−0.171		9.377		−0.166	

Table 4 (Continued)

Position	Substituent	Number of substituents	ED_{50}		$-\log c$ (ED_{50})		ED_{100}		$-\log c$ (ED_{100})	
			z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}	z_{jk}	Δz_{jk}
	SO_2NH_2	3	3.468		−0.094		9.210		−0.116	
	OSO_2CH_3	2	4.556		−0.106		9.920		−0.100	
X	Br	53	0.029	0.534	−0.006	0.108	0.046	0.866	−0.005	0.092
	I	3	−0.505		0.102		−0.820		0.087	
Constant μ			11.468		4.509		25.226		4.169	
Multiple correlation coefficient r			0.937		0.939		0.924		0.934	
F value			12.639		13.108		10.225		11.961	

z_{jk} — Contribution of the substituent; Δz_{jk} — maximal range of contributions of substituents in the given position; c — molar concentration corresponding to ED_{50} and ED_{100} value.

decreasing contributions z_{jk} (logarithmic expression of molar concentrations) into the series:

For ED_{50} $H > CH_3 > NO_2 > SO_2NH_2 > Cl > OSO_2CH_3 > Br > F > CN > OCH_3$.

For ED_{100} $H > CH_3 > Cl > NO_2 > OSO_2CH_3 > Br > SO_2NH_2 > F > CN > OCH_3$.

The difference in contributions by bromide and iodide ions was small, the contribution by iodide being somewhat higher. The calculated values of biological activities were in good agreement with the measured ones. The results in Table 4 permit calculations of biological activities totally for $3 \times 4 \times 6 \times 10 \times 2$ compounds. However, it is clear that none of the final products with new combinations of substituents would be more active than the basic derivatives with unsubstituted benzyl groups in the position 3 of benzothiazole already tested.

The synthesized compounds were tested also for stimulation and inhibitory effects on growth of vetch. The most active derivatives are presented in Table 5. With the other compounds the maxima of stimulation activities were, in the average, below +2 mm at different concentrations. For completeness also those concentrations are given at which the compounds became inhibitors. From the practical point of view the compounds *XV*, *XXI*, *XXVIII*, and *XXXII* were of interest.

Table 5

Stimulation and inhibitory effects of 3-benzylbenzothiazolium salts on growth of vetch

Compound	Stimulation		Inhibition	
	+ mm	mol dm^{-3}	− mm	mol dm^{-3}
IV	2.20	10^{-5}	3.75	10^{-3}
V	2.10	10^{-7}	3.65	10^{-3}
VIII	2.70	10^{-11}	1.45	10^{-3}
XII	2.25	10^{-5}	7.40	10^{-3}
XV	4.50	10^{-9}	4.15	10^{-3}
XVI	2.05	10^{-9}	11.20	10^{-3}
XVII	5.25	10^{-5}	2.10	10^{-3}
XXI	6.50	10^{-9}	2.50	10^{-3}
XXVIII	4.40	10^{-9}	—	
XXIX	3.35	10^{-9}	—	
XXX	4.15	10^{-7}	2.90	10^{-3}
XXXII	6.30	10^{-3}	—	
XXXVI	3.95	10^{-5}	—	
XXXIX	2.45	10^{-9}	2.05	10^{-3}
IAA	3.10	10^{-12}	18.55	10^{-6}
2,4-D	4.95	10^{-9}	23.30	10^{-5}

IAA: β-Indolylacetic acid; 2,4-D: 2,4-dichlorophenoxyacetic acid.

Experimental

Melting points, determined on a Kofler block, and analytical data of the synthesized compounds are presented in Table 1. ^{1}H-N.m.r. spectra were measured on a Tesla BS 487 A apparatus at 80 MHz; 10% or saturated solutions in deuterated dimethyl sulfoxide with hexamethyldisiloxane as internal standard were used.

Antimicrobial activity was followed on *Staphylococcus aureus (1), Bacillus subtilis (2), Escherichia coli (3), Pseudomonas aeruginosa (4), Microsporum gypseum (5),* and *Trichophyton rubrum (6).* The activities of benzothiazolium salts against gram-positive (*1, 2*) and gram-negative (*3, 4*) bacterial strains were tested by the plate-diffusion method [8] at concentrations 200, 50, 12.5, and 3.1 μg/disc. The test-tube dilution method [9] was used with the pathogenic moulds (*5, 6*) at the same concentrations (μg/ml). The activity against the bacterial strain (*1*) was examined also on a Spekol-ZV spectrophotometer and was expressed in ED_{100} and ED_{50} values (μg/ml). The Free—Wilson analysis was accomplished according to [10] on a Siemens 4004/15 computer and the results are presented in Table 4. Growth stimulation of roots was established by the modified method [11]. The general method for the preparation of 3-benzylbenzothiazolium salts was described in [1, 11].

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