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Synthesis, antimicrobial testing and QSAR study of new 2-phenylethenylbenzothiazolium salts substituted by cyclic amines

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A series of new 2-phenylethenylbenzothiazolium salts substituted by cyclic amines has been prepared by the condensation of 2-methyl benzothiazolium bromide with substituted benzaldehydes. The nucleophilic substitution of 4-fluorobenzaldehyde with appropriate cyclic amines has been used to obtain the starting benzaldehydes. The compounds with saturated cycloamino substituents have shown enhanced activity against *Euglena* and some derivatives with piperazine substituent were active against Gram positive bacteria.

1. Introduction

Benzothiazolium salts are reported to be active as anthelmintic [1], antineoplastic [2] and antimicrobial [3, 4] agents. Recently we have designed and synthesized benzothiazolium derivatives with enhanced activity against the model microorganism *Euglena gracilis* [5, 6]. The structural features connected with the biological activity of studied benzothiazolium compounds have been suggested as follows: the phenyl ring bearing an electron-donating substituent (sec amino group in para position is preferred) bridged to the carbon C-2 of the benzothiazole; the bridge that makes possible the conjugated connection between benzothiazolium and phenyl ring; the allyl, propargyl or methyl group bonded to the heterocyclic nitrogen.

The next step in the modification of the structure under study is the modulation of the secondary amino group. In this paper we would like to present the synthesis and the study of new antimicrobial benzothiazole derivatives with a cycloamino substituent in the para position of the phenyl ring.

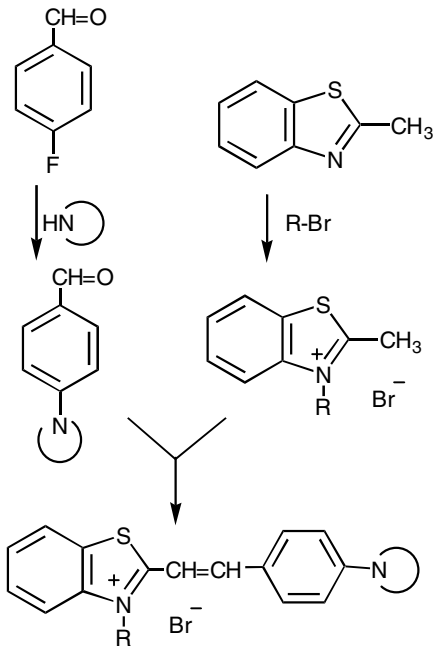
29 new compounds with a saturated or heteroaromatic secondary cycloamino group were prepared, biologically tested and examined by QSAR methods.

2. Investigations and results

2.1. Synthesis of the compounds

Substituted 2-phenylethenylbenzothiazolium salts were prepared according to the procedures shown in the Scheme. The starting substituted benzaldehydes were obtained by nucleophilic substitution of 4-fluorobenzaldehyde with appropriate cyclic amines or azoles in DMSO and in the presence of potassium carbonate as a base [7 to 9]. 3-Allyl and 3-propargyl-2-methyl benzothiazolium bromides were prepared by alkylation of 2-methylbenzothiazole. The decisive factor for good yields of quarternary salt is the temperature. While the yield of 3-allyl-2-methylbenzothiazolium bromide did not exceed 25% when reactants were heated to 70 °C (b.p. of allylbromide) in various solvents (acetonitrile, nitromethane, DMF), heating of 2-methylbenzothiazole with an excess of allylbromide to 120 °C in an autoclave afforded the raw product in 95% yield. Refluxing of 2-methylbenzothiazole in the neat propargylbromide gave the desired salt in sufficient yield. Using of an autoclave in this case can be dangerous because of the explosiveness of the neat propargylbromide. Condensation of 2-methylbenzothiazolium salts with p-substituted benzaldehydes (Scheme) proceeded in refluxing methanol in good yields. The reaction time was set to 3 h as a result of monitoring the absorbances of both reactants and product for the preparation of compound **6**. Yields of the salts prepared were determined by their solubility in methanol, the second crop could be obtained when methanol solution was concentrated, but their purity was much worse. All the compounds were characterized by physical constants, elemental analysis (Tables 1, 2), ^{1}H NMR (Tables 3, 5) and ^{13}C NMR (Tables 4, 6) spectral data. The chemical shifts were assigned using model spectra calculated by ACD program and for some salts were also done HETCOR experiments.

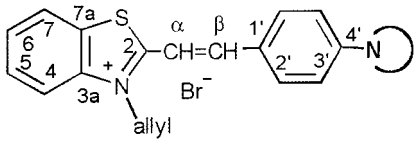
Scheme



R = -CH_2-CH=CH_2 **1 - 17**

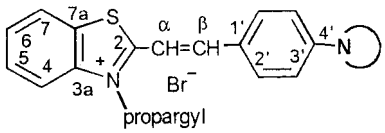
R = -CH_2-C≡CH **18 - 29**

Table 1: Physico-chemical data of 3-allyl-2-styrylbenzotiazole bromides 1–17



Compd.	–N	Yield (%)	M.p. (°C)	Formula	Relative molecular mass
1	-N	97	243–245	$C_{22}H_{23}BrN_2S$	427.4
2	-N	65	221–224	$C_{23}H_{25}BrN_2S$	441.4
3	-N	75	203–208	$C_{24}H_{27}BrN_2S$	455.5
4	-N O	33	235 dec.	$C_{22}H_{23}BrN_2OS$	443.4
5	-N N-CH_3	82	214–220	$C_{23}H_{26}BrN_3S$	456.5
6	-N N-C_7H_{15}	42	198–201	$C_{29}H_{38}BrN_3S$	540.6
7	-N N-C_8H_{17}	69	207–209	$C_{30}H_{40}BrN_3S$	554.6
8	-N N-CH(CH_3)(n-C_6H_{13})	18	191–195	$C_{30}H_{40}BrN_3S$	554.6
9	-N N-CH_2-CH_2-N(C_2H_5)$_2$	26	229–232	$C_{28}H_{37}BrN_4S$	541.6
10	-N N-$COOC_2H_5$	54	199–202	$C_{25}H_{28}BrN_3O_2S$	514.4
11	-N NH	52	260–266	$C_{32}H_{40}BrN_3S$	578.7
12	-N	48	242–243	$C_{22}H_{19}BrN_2S$	423.4
13	-N N	82	215–217	$C_{21}H_{18}BrN_3S$	424.4
14	-N N N	49	253–257	$C_{20}H_{17}BrN_4S$	425.4
15	-N N	79	206–209	$C_{25}H_{20}BrN_3S$	474.4
16	-N N N	56	236–238	$C_{24}H_{19}BrN_4S$	475.4
17	-N N N	95	309–311	$C_{24}H_{19}BrN_4S$	475.4

Table 2: Physico-chemical data of 3-propargyl-2-styrylbenzotiazole bromides 18–29



Compd.	–N	Yield (%)	M.p. (°C)	Formula	Relative molecular mass
18	-N	94	241–248	$C_{22}H_{21}BrN_2S$	425.4
19	-N	68	195 dec.	$C_{23}H_{23}BrN_2S$	439.4
20	-N	81	223–231	$C_{24}H_{25}BrN_2S$	453.5
21	-N O	94	231–233	$C_{22}H_{21}BrN_2OS$	441.4
22	-N N-CH_3	91	240 dec.	$C_{23}H_{24}BrN_3S$	454.4
23	-N N-$COOC_2H_5$	42	210–213	$C_{25}H_{26}BrN_3O_2S$	512.5
24	-N	43	238–240	$C_{22}H_{17}BrN_2S$	421.4
25	-N N	90	231 dec.	$C_{21}H_{16}BrN_3S$	422.4
26	-N N N	95	240–243	$C_{20}H_{15}BrN_4S$	423.3
27	-N N	58	204–208	$C_{25}H_{18}BrN_3S$	472.4
28	-N N N	48	249–252	$C_{24}H_{17}BrN_4S$	473.4
29	-N N N	68	315–318	$C_{24}H_{17}BrN_4S$	473.4

2.2. Biological studies

The compounds prepared were tested on the autotrophic form of unicellular flagellate *Euglena gracilis* on growth and on the plastid system. This effect was monitored in a liquid Cramer-Myers medium containing appropriate concentrations (2.0–300 μg/ml) of the test substances. Fresh solutions of substances were prepared by dissolving in DMSO. The inoculum *Euglena gracilis* was taken from the exponential growth phase and cultivation was performed 96 h under permanent illumination at 26 ± 2 °C. The following data were ascertained: toxicity and bleaching activity (induction of the chloroplast-free mutants). The ED_{50} toxicity values (in 10^{-3} mol $\cdot$ l^{-1}) were interpolated from nonlinear cubic functions. The log ($1000/ED_{50}$) values were used in QSAR studies and they are presented in Table 7.

All compounds reported herein were tested *in vitro* for their antimicrobial activity against Gram-positive (*Staphylococcus aureus* Mau 29/58, *Staphylococcus aureus* CCM 2394, *Bacillus subtilis* CCM 18/64) and Gram-negative bacteria (*Escherichia coli* 326/71) as well as a yeast (*Candida albicans* Pn-10) and a mould (*Microsporum gypseum*). Antimicrobial activities were tested by the standard plate diffusion method using Mueller-Hinton and Sabouraud agar, or by the standard dilution method in Sabouraud medium [10]. Minimum inhibitory concentrations (MIC in μg/ml) are given in Table 7.

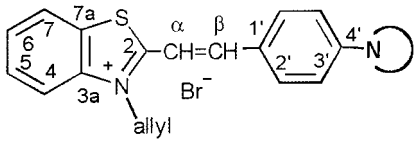
2.3. QSAR investigation

The compounds **1**–**29** have been investigated by the Hansch regression analysis [11]. Three categories of structural descriptors were used, theoretical indices obtained from semiempirical quantum chemical calculations, the experimental ^{13}C NMR shifts and one topological index. The following parameters were chosen:

–log P – theoretically calculated [12] value of log P of bonded cycloamines;

$-\Delta E$ – a descriptor that characterizes the basicity of bonded cycloamines. It is defined as the difference between the theoretically (AM1) calculated heat of formation of a protonized and unprotonized cycloamine (in kcal/mol): $\Delta E = HF_{\overset{+}{N}H_2} - HF_{NH}$

Table 3: ^{1}H NMR data of compounds 1–17 (δ ppm, J = Hz)



Compd.	H-4		H-5	H-6		H-7	H-α		H-β	H-2′		H-3′	CH_2N^+	–CH=	$=CH_2$ *cis*	$=CH_2$ *trans*	R
	$J_{4,5}$			$J_{6,7}$			$J_{\alpha,\beta}$			$J_{2',3'}$							
1	8.31	8.5	7.66	7.75	8.0	8.04	8.09	15.4	7.55	7.91	8.8	6.70	5.49	6.07	5.33	5.25	3.42 2.00
2	8.34	8.2	7.69	7.78	8.0	8.08	8.11	15.4	7.62	7.90	9.1	7.05	5.52	6.07	5.33	5.25	3.52 1.63 (sb, 6 H)
3	8.31	8.2	7.67	7.76	8.0	8.05	8.09	15.3	7.54	7.89	9.1	6.89	5.49	6.06	5.32	5.25	3.64 1.76 1.49
4	8.39	8.1	7.75	7.80	7.5	8.13	8.15	15.4	7.72	7.96	8.9	7.08	5.58	6.08	5.33	5.27	3.42 3.75
5	8.36	7.5	7.71	7.79	8.0	8.11	8.12	15.4	7.70	7.93	8.2	7.21	5.55	6.07	5.33	5.27	3.81 1.5–2.0 (m, 20 H, CH_2) 1.26 (sb, 1 H, NH)
6	8.39	8.1	7.72	7.80	8.1	8.13	8.16	15.3	7.73	7.97	9.0	7.12	5.58	6.08	5.33	5.27	3.61 2.88 2.54
7	8.36	8.0	7.72	7.80	7.7	8.11	8.15	15.2	7.69	7.94	8.8	7.08	5.54	6.08	5.33	5.26	3.52 (sb, 8 H), 4.08 (q, 2 H, CH_2) 1.21 (t, 3 H, CH_3)
8	8.37	8.0	7.73	7.80	7.4	8.12	8.15	15.2	7.71	7.94	8.8	7.10	5.56	6.08	5.33	5.26	3.47 2.6 (sb, 6 H, CH_2N), 1.51 (sb, 2 H, $NCH_2\underline{CH_2}C$), 1.29 (m, 8 H, $CH_3(\underline{CH_2})_4$) 0.87 (t, 3 H, CH_3)
9	8.37	7.0	7.72	7.80	8.0	8.12	8.15	15.0	7.70	7.94	8.8	7.10	5.56	6.08	5.33	5.26	3.53 2.73 (sb, 6 H, CH_2N), 1.54 (sb, 2 H, $NCH_2\underline{CH_2}C$), 1.28 (m, 10 H, $CH_3(\underline{CH_2})_5$) 0.87 (t, 3 H, CH_3)
10	8.40	7.4	7.75	7.84	7.7	8.15	8.19	15.2	7.74	7.99	8.8	7.16	5.59	6.08	5.33	5.27	3.5 2.5 1.48 (sb, 2 H, $NCH\underline{CH_2}C$) 1.29 (m, 11 H, CH_3 $(\underline{CH_2})_4$,$\underline{CH_3}CH$) 0.87 (t, 3 H, $\underline{CH_3}CH_2$)
11	8.36	8.2	7.71	7.79	7.4	8.11	8.13	15.4	7.68	7.94	8.9	7.10	5.55	6.08	5.33	5.26	3.48 3.08 (sb, 6 H, CH_2N), 2.61 (m, 6 H, CH_2N) 1.18 (t, 6 H, CH_3)
12	8.50	8.4	7.82	7.89	7.8	8.26	8.33	15.9	8.04	8.19	8.7	7.86	5.69	6.17	5.37	5.33	7.62 (H-2″,5″) 6.37 (H-3″,4″)
13	8.51	8.1	7.83	7.90	8.0	8.27	8.35	15.8	8.10	8.25	8.5	7.94	5.71	6.17	5.37	5.34	8.6 (H-2″) 8.00 (H-4″) 7.24 (H-5″)
14	8.52	8.8	7.84	7.91	8.0	8.28	8.36	15.9	8.12	8.29	8.8	8.11	5.71	6.16	5.37	5.34	9.51 (H-3″) 8.35 (H-5″)
15	8.52	8.0	7.85	7.91	8.0	8.29	8.42	15.8	8.16	8.35	8.8	7.96	5.71	6.17	5.38	5.34	8.75 (H-2″) 7.78 (H-4″) 7.37 (H-5″) 7.42 (H-6″) 7.81 (H-7″)
16	8.52	9.3	7.84	7.91	8.2	8.29	8.45	16.2	8.19	8.39	8.8	8.17	5.73	6.18	5.38	5.34	8.10 (H-4″) 7.75 (H-5″) 7.59 (H-6″) 8.26 (H-7″)
17	8.52	8.2	7.84	7.91	7.9	8.29	8.41	15.9	8.18	8.52	8.8	8.36	5.73	6.18	5.38	5.33	8.08 (H-4″,7″) 7.58 (H-5″,6″)

$-Q_N$ – the calculated (AM1) value of charge density at the cycloamine nitrogen (the values are multiplied by 1000) ;

$-e_{HOMO}$ – the theoretical energy of the highest occupied orbital of cycloamine (in eV);

$-C_\alpha$, C_β, $C_{1'}$ – the experimental ^{13}C-NMR shifts of corresponding carbons (in ppm);

–I – the topological index "indicator variable", that differentiates compounds substituted by saturated amines (I = 0) from those substituted by heteroaromatic amines (I = 1).

The theoretical values of log P were gained by the additive Crippen's method implemented in the Molecular Editor program [12].

The quantum chemical calculations were performed at a semiempirical level using the AM1 Hamiltonian with full optimization of all bond lengths, angles and torsion angles involved in the AMPAC system of programs [13]. As the studied compounds differ by the cycloamine substituent, three quantum chemical descriptors which describe the basicity of cycloamines, namely ΔE, Q_N and e_{HOMO} were received from the calculation of the corresponding cycloamine. The values of the theoretical descriptors are presented in the Table 8.

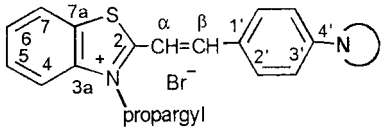
3. Discussion

As it can be seen from the Table 7 the activity against *Euglena* is very high in the case of saturated cycloamino substituents (compounds **1**–**3**, **18**–**21**), much higher than for the related *p*-dimethylamino compound (5.344 for the allyl derivative). This could be caused by the stronger electrondonating effect of the cycloamino substituent compared with $N(CH_3)_2$. The presence of the next polar atom in the substituent ring causes a decrease in activity. The long straight- or branched alkyl chain bonded to pipera-

Table 4: ^{13}C NMR shifts of compounds 1–17 (δ ppm)*

Compd.	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-α	C-β	C-1′	C-2′	C-3′	C-4′	CH_2N^+	-CH=	$=CH_2$	R
1	171.12	140.89	115.61	128.76	126.75	123.78	127.18	104.89	151.15	121.21	133.24	112.32	151.01	49.63	130.53	118.71	47.55, 24.70
2	171.50	140.94	115.84	128.90	126.95	123.91	127.43	106.15	153.62	122.08	133.05	113.33	150.42	49.76	130.55	118.71	47.76, 24.99, 23.80
3	171.27	140.99	115.73	128.87	126.83	123.91	127.30	105.15	152.67	121.23	133.50	111.69	150.79	49.68	130.61	118.73	49.34, 26.49, 25.96
4	172.39	141.00	116.14	129.07	127.27	124.11	127.70	107.56	153.85	123.42	132.62	113.51	150.30	50.05	130.65	118.87	46.43, 65.74
5	171.93	140.98	116.15	129.07	127.29	124.09	127.73	107.83	153.06	123.60	132.56	114.00	150.15	50.05	130.61	118.85	53.01, 44.90, 43.74
6	171.74	141.09	116.07	129.10	127.19	124.11	127.66	107.41	153.21	122.56	133.22	112.77	150.23	50.02	130.73	118.22	59.92, 51.22, 32.92, 25.02, 21.40
7	171.85	141.02	116.17	129.10	127.29	124.16	127.70	107.45	153.37	123.22	132.79	113.71	150.32	50.09	130.73	118.90	45.92, 42.76, 154.66, 60.95, 14.60
8	171.86	141.01	116.10	129.05	127.23	124.08	127.68	107.38	153.45	123.18	132.68	113.74	150.29	50.01	130.63	118.85	51.96, 45.76, 57.20, 26.65, 28.45, 31.09, 31.14, 21.98, 13.87,
9	171.86	141.03	116.10	129.08	127.23	124.08	127.70	107.29	153.60	123.14	132.73	113.70	150.36	50.00	130.65	118.87	52.17, 45.97, 57.44, 26.78, 28.60, 28.82, 30.63, 31.20, 22.03, 13.91
10	172.04	140.99	116.27	129.14	127.40	124.16	127.83	108.46	152.52	123.38	132.45	114.25	150.00	50.19	130.61	118.89	47.04, 43.80, 61.10, 30.92, 25.34, 28.34, 30.05, 21.90, 13.83, 13.23
11	171.89	141.10	116.16	129.13	127.28	124.16	127.74	107.29	153.72	123.16	132.83	113.75	150.35	50.07	130.74	118.88	52.26, 46.93, 48.62, 47.86, 46.21, 8.90,
12	172.57	141.31	116.98	129.68	128.30	124.66	128.58	112.67	148.83	130.68	131.56	119.22	142.73	50.77	130.86	119.39	119.09 (C-2″), 111.71 (C-3″)
13	172.17	141.06	116.87	129.54	128.24	124.44	128.48	113.74	147.86	132.53	131.48	120.48	138.97	50.83	130.51	119.29	135.47 (C-2″), 128.72 (-4″), 118.08 (C-5″)
14	172.19	141.10	116.93	129.59	128.33	124.51	128.55	114.03	147.79	133.08	131.40	119.50	138.95	50.87	130.57	119.32	152.75 (C-3″), 142.80 (C-5″)
15	172.23	141.16	116.98	129.65	128.34	124.58	128.60	111.10	147.96	132.45	131.62	123.94	143.66	50.91	130.66	119.33	143.16 C-2″, 138.80 C-3a″, 119.99 C-4″, 123.94 C-5″, 123.02 C-6″, 114.14 C-7″, 132.95 C-7a″
16	172.18	141.13	116.96	129.65	128.42	124.52	128.63	111.23	147.71	129.06	131.46	122.70	138.87	50.90	130.56	119.35	145.96 C-3a″, 119.87 C-4″, 125.02 C-5″, C-6″, 114.56 C-7″, 133.90 C-7a″
17	172.37	141.34	117.15	129.86	128.65	124.72	128.85	114.86	147.74	131.36	131.55	120.87	141.67	50.96	130.77	119.53	144.97C-3a″ 128.46 C-4″ 118.42 C-5″

Table 5: ^{1}H NMR data of compounds 18–29 (δ ppm, J = Hz)



Compd.	H-4		H-5	H-6		H-7	H-α		H-β	H-2′		H-3′	CH_2N^+	–C≡H	
		$J_{4,5}$			$J_{6,7}$			Jα,β			$J_{2',3'}$				R
18	8.29	8.4	7.67	7.79	7.5	8.09	8.09	14.6	7.66	7.92	8.6	6.67	5.79	3.74	3.40 1.99
19	8.32	8.4	7.70	7.82	7.5	8.14	8.15	14.9	7.72	7.93	9.0	7.09	5.79	3.73	3.55 1.64 (sb, 6 H)
20	8.31	7.5	7.68	7.80	7.4	8.12	8.13	15.1	7.67	7.92	9.1	6.92	5.77	3.72	3.66 1.77 1.49
21	8.36	8.5	7.74	7.84	7.7	8.21	8.20	15.6	7.82	7.97	8.9	7.12	5.83	3.75	3.46 3.76
22	8.41	9.1	7.76	7.87	7.7	8.23	8.23	15.7	7.90	8.03	9.1	7.19	5.89	3.77	3.39 (sb, 8 H) 2.84
23	8.37	8.5	7.74	7.85	7.7	8.21	8.20	15.4	7.81	7.98	9.1	7.10	5.84	3.75	3.54 3.35 4.09 (q, 2 H, CH_2) 1.22 (t, 3 H, CH_3)
24	8.49	9.1	7.83	7.93	8.0	8.32	8.36	16.2	8.15	8.19	8.8	7.87	5.97	3.81	7.62 (H-2″, 5″) 6.37 (H-3″, 4″)
25	8.52	8.4	7.85	7.95	8.0	8.35	8.39	15.8	8.21	8.26	8.8	7.95	5.99	3.82	8.55 (H-2″) 7.99 (H-4″) 7.21 (H-5″)
26	8.53	8.4	7.87	7.97	8.2	8.37	8.42	15.9	8.24	8.31	8.8	8.14	6.00	3.83	9.52 (H-3″) 8.39 (H-5″)
27	8.53	8.0	7.86	7.97	8.0	8.36	8.47	15.8	8.27	8.36	8.5	7.99	6.01	3.83	8.76 (H-2″) 7.80 (H-4″) 7.38 (H-5″) 7.42 (H-6″) 7.83 (H-7″)
28	8.53	8.1	7.87	7.97	7.2	8.38	8.44	16.0	8.31	8.41	8.5	8.20	6.02	3.84	8.12 (H-4″) 7.60 (H-5″) 7.76 (H-6″) 8.26 (H-7″)
29	8.54	8.5	7.87	7.97	8.0	8.35	8.45	15.9	8.30	8.54	8.8	8.38	6.04	3.85	8.08 (H-4″, 7″) 7.58 (H-5″, 6″)

zine nitrogen enhanced the activity. The reason in this case is rather the lipophility than the electronic effect. The derivatives with the aromatic cycloamines as a substituent are much less active as those with saturated cycloamines owing to lowered electron-donating effect of nitrogen.

The Hansch regression analysis has been carried out separately for the allyl and propargyl benzothiazolium salts. The results obtained for the allyl derivatives are not significant. Some improvement has been observed introducing the topological "indicator variable" I, that allowed to differentiate compounds with saturated and aromatic cycloamine substituents. The value of the indicator variable I equals 1 in the case of aromatic cyloamines and I = 0 for the saturated cycloamines. The values of the multiple correlation coefficient of two parameters regression equations (the second parameter is I) of the series of allyl derivatives **1–17** are presented in parenthesis:

log P (0,625), C_α (0,565), C_β (0,589), $C_{1'}$ (0,661), ΔE (0,532), Q_N (0,504), e_{HOMO} (0,516).

Better results were obtained for the propargyl series (compounds **18–29**). For the three best descriptors the complete regression equations are presented, the other descriptors are represented by the correlation coefficients:

$BA = -0{,}78\ C_{1'} + 5{,}25\ I + 101{,}02;\ n = 12,\ r = 0{,}909,\ s = 0{,}651,\ F = 21{,}287$

$BA = 0{,}54\ C_\alpha + 1{,}84\ I + 62{,}41;\ n = 12,\ r = 0{,}853,\ s = 0{,}813,\ F = 12{,}059$

$BA = 1{,}00\ \log P - 2{,}50\ I + 5{,}32;\ n = 12,\ r = 0{,}833,\ s = 0{,}862,\ F = 10{,}226$

ΔE (0,744), C_β (0,724), Q_N (0,707), e_{HOMO} (0,704).

The regression has not been improved even after introducing more parameters into the equation.

The antimicrobial activity depends on the type of microorganism. The compounds are inactive against Gram negative *E. coli*, but active against Gram positive organisms. Probably lipophility is the reason of an enhanced activity of compounds with long alkyl chain against *Microsporum gypseum*.

4. Experimental

4.1. Material and methods

Melting points were determined on a Kofler block and are uncorrected. IR spectra were taken on Specord 75 spectrophotometer in nujol. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 2000, 300 MHz instrument in $CDCl_3$ and [D_6] DMSO using TMS as an internal standard. Elemental analyses for C,H,N were determined on Carlo Erba 1016 instrument and were within ± 0.4% of the theoretical values. CC was performed in a flash arrangement using silica gel (mesh 40/100). TLC was performed on silica precoated plates Silufol UV-254 (Kavalier, Czech Republic).

4.2. 3-Allyl-2-methylbenzothiazolium bromide

A solution of 2-methylbenzothiazole (9.0 g, 0.06 mol) in allylbromide (25 ml, 0.29 mol) and boron trifluoride etherate (3 drops) were placed into a steel autoclave and heated at 120 °C for 10 h. A crude gray crystalline product (15.4 g) was filtered off, washed with acetone, dried and recrystallised from chloroform/acetonitrile (1 : 1) to give white crystals (13.5 g, 83%): m.p. 215–217 °C. ^{1}H NMR (300 MHz, [D_6] DMSO, TMS, ppm): 3,24 (s, 3 H, CH_3), 5,35 (d, J = 17 Hz, 1 H, $=CH_2$*trans*), 5,37 (d, J = 10,2 Hz, 1 H, $=CH_2$*cis*), 5,48 (d, J = 5,1 Hz, 2 H, CH_2N^+), 6,09 (m, 1 H, –CH=), 7,81 (m, 1 H, H-6), 7,89 (m, 1 H, H-5), 8,31 (d, J = 8,3 Hz, 1 H, H-4), 8,52 (d, J = 7,5 Hz, 1 H, H-7) ^{13}C NMR (75 MHz, [D_6]DMSO, TMS, ppm): 17,03 (CH_3), 51,13 (CH_2N^+), 116,91 (C-4), 119,91 (CH_2=), 124,76 (C-7), 128,09 (C-6), 129,11 (C-7a), 129,36 (C-5), 129,50 (–CH=), 140,72 (C-3a), 177,76 (C-2).

4.3. 3-Propargyl-2-methylbenzothiazolium bromide

A mixture of 2-methylbenzothiazole (7.5 g, 0.05 mol), propargylbromide (20 ml, 0.26 mol) and boron trifluoride etherate (2 drops) was refluxed for 16 h. The crude product (10.3 g) was filtered off, washed with acetone, dried and recrystallised from chloroform/methanol (10 : 7) to give white crystals (7.0 g, 52%): m.p. 237–239 °C. ^{1}H NMR (300 MHz, [D_6]DMSO, TMS, ppm): 3,31 (s, 3 H, CH_3), 3,86 (t, J = 2,5 Hz, 1 H, HC≡), 5,81 (d, J = 2,5 Hz, 2 H, CH_2N^+), 7,84 (m, 1 H, H-6), 7,95 (m, 1 H, H-5), 8,40 (d, J = 8,4 Hz, 1 H, H-4), 8,54 (d, J = 8,3 Hz, 1 H, H-7) ^{13}C NMR (75 MHz, [D_6]DMSO, TMS, ppm): 17,28 (CH_3), 38,83 (CH_2N^+), 74,59 (HC≡), 78,97 (–C≡), 116,59 (C-4), 124,82 (C-7), 128,15 (C-6), 128,86 (C-7a), 129,41 (C-5), 129,50 (–CH=), 140,08 (C-3a), 178,28 (C-2).

4.4. General procedure for the synthesis of 3-allyl-2-styryl- and 3-propargyl-2-styryl benzothiazolium bromides 1–30

A mixture of 3-allyl-2-styryl benzothiazolium bromide (0.54 g, 2 mmol) or 3-propargyl-2-styryl benzothiazolium bromide (0.54 g, 2 mmol) and 4-substituted benzaldehyde (2 mmol) in methanol (5 ml) was refluxed for 3 h. The mixture was then allowed to cool to room temperature (eventually to –20 °C until crystals appeared), the crystalline product separated by filtration, washed with cold methanol and dried in vacuo. Physical properties and spectral data of compounds **1–29** are given in Tables 1–4.

Table 6: ^{13}C NMR shifts of compounds 18–29 (δ ppm)*

Compd.	C-2	C-3a	C-4	C-5	C-6	C-7	C-7a	C-α	C-β	C-1′	C-2′	C-3′	C-4′	CH_2N^+	–CH=	=CH2	R
18	171.07	140.36	115.41	128.92	126.50	123.97	127.34	104.49	151.78	121.35	133.63	112.59	151.47	37.43	78.02	76.03	47.71, 24.77
19	171.44	140.36	115.61	129.02	126.68	124.06	127.52	105.72	153.83	122.11	133.45	113.34	151.18	37.65	78.11	75.92	47.49, 25.09, 23.82
20	171.13	140.36	115.46	128.95	126.52	124.02	127.37	104.74	152.96	121.34	133.85	111.83	151.48	37.52	78.03	76.02	49.41, 26.48, 25.95
21	171.93	140.39	115.87	129.18	126.96	124.20	127.80	107.09	154.04	123.34	132.91	113.50	151.08	37.87	78.27	75.86	46.39, 65.72
22	172.14	140.41	116.04	129.27	127.13	124.31	127.96	108.05	152.78	124.07	132.76	114.30	150.80	38.10	78.38	75.84	52.12, 43.93, 42.40
23	171.75	140.36	115.88	129.17	126.97	124.25	127.75	106.95	153.47	123.08	133.10	113.57	151.04	38.03	78.37	76.00	45.80, 42.70, 154.65 (C=O), 60.96 (OCH_2), 14.61 (CH_3)
24	172.52	140.46	116.56	129.60	127.86	124.56	128.49	112.25	149.32	130.42	131.85	119.01	142.65	38.69	78.74	75.57	118.93 C-2″, 111.53 C-3″
25	172.55	140.57	116.76	129.79	128.06	124.70	128.73	113.57	148.68	132.44	131.71	120.35	139.35	37.91	78.90	75.61	135.61 C-2″, 129.21 C-4″, 117.97 C-5″
26	172.51	140.53	116.73	129.76	128.10	124.66	128.71	113.80	148.53	133.04	131.50	119.56	139.11	38.79	78.87	75.49	152.76 C-3″, 142.82 C-5″
27	172.50	140.55	116.73	129.77	128.11	124.68	128.72	111.08	148.66	132.41	131.66	123.63	143.64	38.78	78.86	75.53	143.08 C-2″, 138.96 C-3a″, 119.94 C-4″, 122.98 C-5″, 123.88 C-6″, 113.87 C-7″, 132.88 C-7a″
28	171.97	139.99	116.16	129.24	128.22	124.49	128.52	113.72	147.87	130.82	131.01	122.13	138.43	38.21	78.22	74.85	145.36 C-3a″, 119.27 C-4″, 124.10 C-5″, 127.59 C-6″, 110.67 C-7″, 133.27 C-7a″
29	172.36	140.54	116.78	129.82	128.27	124.71	128.79	114.42	148.19	131.15	131.47	119.96	141.51	37.43	78.95	75.54	144.72 C-3a″, 128.01 C-4″, 118.15 C-5″

Table 7: Biological activities of the compounds 1–29 (*Euglena gracilis*: log (1000/ED_{50}) in µmol/l, other microorganisms: MIC in µg/ml)

Compd.	*Euglena gracilis*	*Staphyl. aur.* Mau 29/58	*Staphyl. aur* CCM 2394	*Bacill.subtil.* 18/64	*E. coli* 326/71	*Cand.. albi.* Pn-10	*Microsp. gypseum*
1	6.46	10	50	250	> 250	50	100/50
2	6.48	2	10	50	250	50	200/100
3	6.66	2	10	10	250	50	200/100
4	3.50	250	250	> 250	> 250	> 250	> 400/400
5	3.52	20	> 250	> 250	> 250	> 250	> 400/400
6	5.54	2	2	50	250	50	40/10
7	5.51	2	2	10	250	50	40/10
8	6.42	10	10	50	250	50	10/2
9	3.87	10	10	50	> 250	250	40/20
10	5.18	10	50	50	250	250	50/10
11	6.01	50	50	250	250	250	50/10
12	4.93	50	50	250	> 250	250	50/10
13	3.23	250	250	> 250	> 250	> 250	250/50
14	3.17	> 250	> 250	> 250	> 250	> 250	> 300/300
15	3.32	250	250	> 250	> 250	> 250	250/50
16	3.32	50	250	50	> 250	250	250/50
17	4.74	50	50	250	> 250	250	50/10
18	6.45	10	50	50	250	250	200/100
19	6.55	10	10	50	> 250	250	200/100
20	6.76	10	10	50	250	250	200/100
21	3.59	> 250	> 250	> 250	> 250	> 250	> 400/400
22	3.74	250	> 250	> 250	> 250	> 250	> 400/200
23	3.74	10	50	50	250	250	50/10
24	3.99	50	50	250	> 250	250	250/50
25	3.23	50	50	50	250	250	250/250
26	3.18	> 250	> 250	> 250	> 250	> 250	> 300/300
27	3.28	50	50	250	250	50	250/250
28	3.99	50	50	50	> 250	250	250/250
29	3.32	> 250	> 250	> 250	> 250	> 250	300/150

Table 8: Theoretical descriptors used in QSAR studies

Compd.	log P	ΔE (kcal/mol)	$Q_N \times 10^3$	eHOMO (eV)	I
1, 18	0.12	150.34	−273	9.511	0
2, 19	0.52	150.18	−275	9.421	0
3, 20	0.91	146.26	−315	9.139	0
4, 21	−0.55	155.803	−270	9.467	0
5, 22	−0.4	155.039	−296	9.041	0
6	1.99	148.928	−298	9.037	0
7	2.39	149.977	−299	9.032	0
8	2.41	150.343	−298	8.967	0
9	0.26	152.009	−297	8.984	0
10, 23	−0.13	153.981	−300	9.531	0
11	1.88	147.548	−287	9.077	0
12, 24	1.05	172.762	−181	8.657	1
13, 25	−0.25	182.985	−208	9.159	1
14, 26	−0.26	192.258	−197	10.27	1
15, 27	0.92	170.428	−249	8.996	1
16, 28	1.09	134.842	−240	9.426	1
17, 29	1.5	169.214	−88	9.121	1

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