

# Neural Network Approach to the Prediction of the Toxicity of Benzothiazolium Salts from Molecular Structure

Štefan Hatrík and Pavol Zahradník\*

Faculty of Natural Sciences, Comenius University, 842 15 Bratislava, Slovakia

Received February 12, 1996<sup>®</sup>

The prediction of the toxicity of benzothiazolium salts calculated by the neural network model is presented. The results are comparable with the previous calculations based on the Free–Wilson additivity model. The method of calculation of activity contributions of substituents is described.

## INTRODUCTION

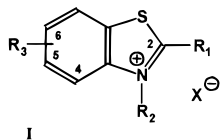
The computational methods available today allow the chemist to predict the structure of compounds with desired properties. Relationships between structure and biological activity are based mostly on linear regression analysis. Recently the interest in the application of the neural network technique in QSAR analysis to the investigation of biological activities increased considerably.<sup>1,2</sup> Computational neural networks were used to improve the accuracy of the linear predictions. They process entire patterns rather than individual items of data.<sup>3,4</sup>

In a previous paper<sup>5</sup> we have published the QSAR analysis of the biological activity of 91 benzothiazolium salts. The toxicity against microorganism *Euglena gracilis* has been measured, and quantitative activity contributions of substituents have been calculated by the Free–Wilson additivity method<sup>6</sup> in the Fujita–Ban modification.<sup>7</sup> The results obtained in the set of 91 compounds enable to predict biological activities of 1300 compounds.

In this paper we present neural network based calculations and predictions of biological activity of the same set of 91 benzothiazolium salts. To compare the Free–Wilson and neural networks models, a new method of calculation of substituent activity contributions by the neural networks method is presented.

## METHOD

A series of 91 benzothiazolium salts of general formula I was taken under consideration in this study.



The structures and observed biological activities taken from our previous paper<sup>5</sup> are listed in Tables 1 and 2. The  $\log(1000/ED_{50})$  values stand for the toxicity of investigated molecules.

The neural network (NN) which was trained by the back propagation of errors had the following architecture: the input layer consisted of 30 elements. Each of them represented a different substituent in the benzothiazolium salt structure (see formula I and Tables 1 and 2). If the given

substituent was present in the molecule then the input equaled one. In the opposite case the input was zero. The output layer consisted of one element, namely the antimicrobial activity. Input and output data were normalized between 0.1 and 0.9. The learning rate was initially set to 0.1 and was gradually decreased until the error function could no longer be minimized. In our experiments the best number of hidden elements was determined by training several different sized networks and picking the best. The hidden layer consisted of two elements. The neural network had a feedforward layered structure with connections allowed only between adjacent layers.

The program of the neural network was written in Turbo Pascal.

## RESULTS AND DISCUSSION

To attain a good generalization from training data to testing data and satisfactory training performance, the number of hidden elements should be as small as possible. For the determination of the number of hidden neurons the usefulness of parameter  $\rho$  was discussed.<sup>8</sup> This parameter is defined as a ratio of the number of data points and the number of connections in the network. According to Zupan and Gasteiger,<sup>9</sup>  $\rho$  should be equal to, or greater than, one. Lower  $\rho$  values can cause the neural network to “memorize” the data rather than learn a general rule.

The prediction ability of the neural network was tested in the following way. The experimental data were divided into a training set of 68 compounds which were used in the adaptation process and a testing set of 23 compounds. The parameter  $\rho$  of the network used in this calculation was 2.194. The adaptation of the neural network was accomplished by repeated cycling through the training data, presenting patterns at the input elements and indicating associations of all elements. The results of adaptation and testing processes were evaluated by the following characteristics: minimal error of calculated and experimental outputs ( $D_{\min}$ ), maximal error of calculated and experimental outputs ( $D_{\max}$ ), average error of calculated and experimental outputs ( $D_{\text{av}}$ ), sum-of-squares error of calculated and experimental outputs (SSO).

Data of training set of 68 compounds are listed in Table 1. For comparison the results obtained by the Free–Wilson (FW) method are also shown.<sup>5</sup> The adaptation process can be evaluated from the calculated errors for neural network model (in parentheses there are the same characteristics for FW data):  $D_{\min} = 0.000$  (0.000),  $D_{\max} = 0.042$  (0.562),  $D_{\text{av}}$

<sup>®</sup> Abstract published in *Advance ACS Abstracts*, June 15, 1996.

**Table 1.** Structure and Observed Toxicities<sup>5</sup> of a Training Set of 68 Benzothiazolium Salts and Differences between Calculated and Observed Data<sup>a</sup>

no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	tox <sub>obs</sub> <sup>5</sup>	diff <sub>NN</sub>	diff <sub>FW</sub>
1	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	H	I	2.811	-0.010	0.024
2	C <sub>3</sub> H <sub>7</sub>	C <sub>2</sub> H <sub>5</sub>	H	I	2.849	0.033	-0.243
3	C <sub>3</sub> H <sub>7</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	3.013	0.010	0.219
4	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	I	4.639	0.003	-0.376
5	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	I	3.658	-0.005	0.376
6	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	CH <sub>3</sub>	H	I	3.350	0.004	0.057
7	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	H	Br	3.102	-0.001	-0.057
8	SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	Br	4.415	0.007	-0.172
9	SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	4.572	0.002	0.172
10	CH <sub>3</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	H	Br	2.897	-0.042	-0.371
11	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	2.870	-0.014	-0.279
12	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	H	I	2.783	0.039	0.042
13	CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	H	I	2.801	0.040	-0.063
14	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub>	H	I	2.961	-0.007	0.019
15	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	I	3.197	0.025	0.435
16	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	2.840	-0.008	-0.007
17	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	H	Br	2.811	0.040	-0.043
18	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	H	I	2.924	-0.002	0.143
19	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	H	Br	2.855	-0.021	-0.192
20	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	H	Br	2.865	-0.010	-0.263
21	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COO- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	H	Br	2.551	0.025	-0.021
22	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	2.879	0.003	-0.201
23	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>4</sub> H <sub>9</sub>	H	I	3.326	0.007	-0.184
24	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	I	3.424	-0.002	0.369
25	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	2.898	0.023	0.097
26	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	H	Br	2.882	0.010	-0.058
27	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	H	I	3.289	0.04	-0.061
28	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	H	Br	2.891	0.022	-0.127
29	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COO- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	H	Br	2.888	-0.017	-0.196
30	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	2.929	-0.003	-0.089
31	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C≡CH	H	Br	5.541	0.006	-0.135
32	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOCH <sub>3</sub>	H	Br	3.892	0.016	0.336
33	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	H	Br	3.856	0.007	0.266
34	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COO- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	H	Br	3.773	0.011	0.217
35	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	4.855	0.000	-0.562
36	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	3.848	0.004	0.290
37	NH <sub>2</sub>	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	4-Cl	Br	3.135	-0.004	0.234
38	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	H	Br	3.618	-0.006	-0.077
39	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	6-CH <sub>3</sub>	Br	3.726	0.007	0.051
40	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	6-Cl	Br	3.721	0.000	0.026
41	NH <sub>2</sub>	C <sub>3</sub> H <sub>7</sub>	H	I	3.934	0.010	-0.361
42	NH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	4-Cl	Br	4.414	0.018	-0.120
43	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	6-Cl	Br	3.496	-0.002	0.049
44	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	4-CH <sub>3</sub>	Br	3.224	-0.002	0.366
45	NH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	6-CH <sub>3</sub>	Br	4.188	-0.007	0.081
46	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	H	I	2.833	-0.039	-0.173
47	CH <sub>3</sub>	CH <sub>2</sub> C≡CH	H	Br	3.214	0.005	0.490
48	H	C <sub>4</sub> H <sub>9</sub>	H	I	3.050	-0.002	0.131
49	H	CH <sub>2</sub> C≡CH	4-CH <sub>3</sub>	Br	4.498	-0.005	-0.101
50	H	CH <sub>2</sub> C≡CH	6-Cl	Br	4.363	0.001	-0.011
51	H	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	H	Br	3.065	0.007	-0.202
52	H	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	H	Br	3.047	0.014	-0.244
53	H	CH <sub>3</sub>	4-Cl	I	3.704	-0.002	-0.113
54	H	CH <sub>3</sub>	4-Cl	Br	3.487	0.004	0.000
55	H	CH <sub>2</sub> CH=CH <sub>2</sub>	6-Cl	Br	4.131	0.001	-0.197
56	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	6-Cl	I	3.287	0.007	0.054
57	H	CH <sub>3</sub>	4-CH <sub>3</sub>	Br	3.471	0.004	0.006
58	H	CH <sub>2</sub> CH=CH <sub>2</sub>	4-CH <sub>3</sub>	Br	4.249	0.007	-0.270
59	H	CH <sub>2</sub> CH=CH <sub>2</sub>	6-CH <sub>3</sub>	Br	4.301	-0.009	-0.338
60	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	6-CH <sub>3</sub>	I	3.303	0.020	0.070
61	H	CH <sub>3</sub>	H	I	2.844	0.010	0.487
62	H	C <sub>2</sub> H <sub>5</sub>	H	Br	2.738	0.016	0.260
63	H	CH <sub>2</sub> COOCH <sub>3</sub>	6-CH <sub>3</sub>	Br	3.089	0.003	0.115
64	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	H	Br	3.757	0.004	0.305
65	NH <sub>2</sub>	C <sub>2</sub> H <sub>5</sub>	H	I	3.884	0.010	-0.476
66	H	C <sub>3</sub> H <sub>7</sub>	H	I	3.030	-0.008	0.237
67	H	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	4.022	0.009	-0.294
68	H	CH <sub>2</sub> CH=CH <sub>2</sub>	H	I	4.095	-0.006	-0.263

<sup>a</sup> NN, neural network; FW, Free-Wilson method.

= 0.030 (0.019), SSO = 0.017 (3.779). Table 2 shows data for 23 compounds of testing set. Characteristics expressing

the prediction ability of the NN model are the following:  $D_{\min} = 0.007$  (0.006),  $D_{\max} = 0.562$  (0.750),  $D_{\text{av}} = 0.136$

**Table 2.** Structure and Observed Toxicities<sup>5</sup> of a Testing Set of 23 Benzothiazolium Salts and Differences between Calculated and Observed Data<sup>a</sup>

no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X	Tox <sub>obs</sub> <sup>5</sup>	Diff <sub>NN</sub>	Diff <sub>FW</sub>
1	H	CH <sub>3</sub>	H	Br	2.803	0.562	0.423
2	H	C <sub>2</sub> H <sub>5</sub>	H	I	2.841	0.302	0.261
3	H	C <sub>4</sub> H <sub>9</sub>	H	Br	2.981	0.177	0.096
4	H	CH <sub>2</sub> C≡CH	H	Br	4.308	-0.089	-0.162
5	CH <sub>3</sub>	CH <sub>3</sub>	H	I	2.755	0.179	0.133
6	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	3.044	-0.011	0.242
7	H	CH <sub>3</sub>	6-Cl	Br	3.414	0.095	0.018
8	H	CH <sub>3</sub>	6-CH <sub>3</sub>	I	3.501	0.081	0.065
9	H	CH <sub>3</sub>	6-CH <sub>3</sub>	Br	3.425	0.061	0.037
10	H	CH <sub>2</sub> C≡CH	6-CH <sub>3</sub>	Br	4.462	-0.054	-0.080
11	H	CH <sub>2</sub> COOCH <sub>3</sub>	H	Br	3.007	-0.080	-0.038
12	H	CH <sub>2</sub> COOCH <sub>3</sub>	6-Cl	Br	3.115	-0.156	0.059
13	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	3.040	0.070	-0.006
14	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	I	2.994	-0.013	0.136
15	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	I	2.908	-0.010	-0.006
16	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	I	3.043	0.150	0.249
17	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	I	5.340	-0.133	-0.750
18	CH=CHC <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	4.953	0.439	0.034
19	NH <sub>2</sub>	CH <sub>3</sub>	H	I	3.837	-0.031	-0.201
20	NH <sub>2</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	H	Br	4.106	0.207	-0.072
21	NH <sub>2</sub>	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	H	Br	2.984	0.007	0.185
22	NH <sub>2</sub>	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	H	Br	3.012	-0.036	0.096
23	NH <sub>2</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	Br	3.122	0.187	0.217

<sup>a</sup> NN, neural network; FW, Free-Wilson method.**Table 3.** Activity Contributions of Substituents Calculated by the Free-Wilson and Neural Networks Methods<sup>a</sup>

no.	substituent	FW	NN <sub>1</sub>	NN <sub>2</sub>	NN <sub>3</sub>	f
R <sub>1</sub>						
1	C <sub>3</sub> H <sub>7</sub>	-0.496	-0.332	0.023	-0.018	3
2	CH <sub>3</sub>	-0.443	-0.319	0.001	0.006	8
3	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-0.201	-0.291	0.049	0.074	11
4	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-0.039	-0.186	0.124	0.246	9
5	H	0.000	0.000	0.000	0.000	30
6	CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	0.076	-0.001	0.504	0.451	2
7	NH <sub>2</sub>	0.306	0.298	0.853	0.956	15
8	C <sub>6</sub> H <sub>5</sub>	0.932	0.947	0.848	1.694	2
9	SCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1.016	1.016	1.563	1.608	2
10	CH=CHC <sub>6</sub> H <sub>5</sub>	1.259	1.801	2.382	2.459	9
R <sub>2</sub>						
11	CH <sub>2</sub> COO- <i>i</i> -C <sub>3</sub> H <sub>7</sub>	-0.496	-0.327	0.315	0.303	3
12	CH <sub>2</sub> COOC <sub>3</sub> H <sub>7</sub>	-0.424	-0.324	0.197	0.239	6
13	CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub>	-0.363	-0.319	0.205	0.253	5
14	CH <sub>2</sub> COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-0.348	-0.321	-0.032	0.349	3
15	CH <sub>2</sub> COOCH <sub>3</sub>	-0.258	-0.312	0.207	0.113	7
16	C <sub>2</sub> H <sub>5</sub>	-0.228	-0.206	0.029	-0.021	7
17	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	-0.193	-0.179	-0.004	0.220	10
18	C <sub>4</sub> H <sub>9</sub>	-0.150	-0.158	0.136	0.159	5
19	C <sub>3</sub> H <sub>7</sub>	-0.063	-0.007	0.105	0.123	5
20	CH <sub>3</sub>	0.000	0.000	0.000	0.000	17
21	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> - <i>p</i> -NO <sub>2</sub>	0.009	-0.001	0.318	1.249	3
22	CH <sub>2</sub> CH=CH <sub>2</sub>	0.502	0.534	1.138	1.222	14
23	CH <sub>2</sub> C≡CH	0.920	0.979	1.405	1.508	6
R <sub>3</sub>						
24	H	0.000	0.000	0.000	0.000	68
25	6-Cl	0.206	0.180	0.509	0.647	7
26	6-CH <sub>3</sub>	0.235	0.155	0.583	0.584	8
27	4-CH <sub>3</sub>	0.250	0.211	0.647	0.606	4
28	4-Cl	0.260	0.206	0.787	0.710	4

Reference Compound: R<sub>1</sub> = R<sub>3</sub> = H; R<sub>2</sub> = CH<sub>3</sub>  
3.226 3.219 2.836 2.808<sup>a</sup> In NN<sub>x</sub> x is a number of hidden neurons; f is a frequency of a corresponding substituent.

(0.016), SSO = 0.850 (1.156). Higher values of SSO index for FW model can be explained by the additivity and linearity of calculated activities, while NN data include also nonlinear and cross product terms.

With the aim of comparing the two methods mentioned above we have defined and calculated the activity contributions of substituents by the neural networks. The calculation has been done in the following way. The training set included all 91 compounds. The NN activity of the reference compound (reference compound: R<sub>1</sub> = R<sub>3</sub> = H; R<sub>2</sub> = CH<sub>3</sub>; X = Br) was calculated. Then the structures with just one substituent were constructed, and their NN activities were calculated. The difference between NN activity of a substituted compound and the reference one represents the activity contribution of the corresponding substituent. When considering the structures with only one substituent we have excluded nonlinear and exactly noninterpretable effects which are typical for neural networks model, and the activity contribution of substituent has the clear physical meaning with the framework of additivity scheme.

We have also tested the appropriate neural network model with regard to the number of hidden neurons. The results are presented in Table 3. It can be seen that the agreement between NN values with one hidden neuron and FW contributions is very good.

## CONCLUSION

We showed that the neural network method based on simple encoding of the molecular structure of benzothiazolium salts is suitable for predicting of their biological activities. The calculated substituent activity contributions are similar both for NN and FW methods, and they can be used for the design of new structures with potential biological activity. Therefore the NN method can be used as a useful alternative of the linear Free-Wilson method for calculation of biological activities from known structures of molecules.

## REFERENCES AND NOTES

- (1) Aoyama, T.; Suzuki, Y.; Ichikawa, H. Neural Networks applied to Quantitative Structure-Activity Relationships Analysis. *J. Med. Chem.* **1990**, *33*, 2583.
- (2) Salt, D. W.; Yildiz, N. The use of artificial neural networks in QSAR. *Pesticide Sci.* **1992**, *36*, 161.

- (3) Rowe, R. C.; Mulley, V. J.; Hughes, J. C.; Nabney, J. T.; Debenham, R. M. Neural networks for chromatographic peak classification. *LG-GC* **1994**, *12*, 690–698.
- (4) Zupan, J.; Gasteiger, J. Neural networks: a new method for solving chemical problems or just a passing phase? *Anal. Chim. Acta* **1991**, *248*, 1–30.
- (5) Zahradník, P.; Foltínová, P.; Halgaš, J. QSAR Study of the Toxicity of Benzothiazolium Salts against *Euglena gracilis*: The Free–Wilson Approach. *SAR QSAR Envir. Res.* In press.
- (6) Free, S. M.; Wilson, J. W. A mathematical contribution to structure–activity studies. *J. Med. Chem.* **1964**, *7*, 395–399.
- (7) Fujita, T.; Ban, T. Structure–activity study of phenethylamines as substrates of biosynthetic enzymes of sympathetic transmitters. *J. Med. Chem.* **1971**, *14*, 148–152.
- (8) Cherqaoui, D.; Villemin, D. Use of a neural network to determine boiling point of alkanes. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 97–102.
- (9) Zupan, J.; Gasteiger, J. In *Neural Networks for Chemists*; VCH Publishers: New York, 1993; p 263.

CI960342H