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QSAR analysis for antimicrobial activity of veratric acid derivatives using artificial neural network

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ABSTRACT

This paper uses artificial neural network in Quantitative Structure-Activity Relationships (QSAR) model of the antimicrobial activity of veratric acid derivatives. The application of ANN as a QSAR has been provided with respect to the prediction of antimicrobial activity of veratric acid derivatives based on their topological parameters generated by chemistry calculation. The simulation results of ANN QSAR model are very promising.

Keywords: Veratric acid; Antibacterial activity; Antifungal activity; QSAR; Artificial neural network

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INTRODUCTION

Microbial infections are associated with rates of attributable morbidity and mortality [2]. The resistance of common pathogens to standard antibiotic therapies is rapidly becoming a major public health problem throughout the world. The incidence of multi-drug resistant Gram-positive and Gram-negative bacteria is increasing and infections caused by them are becoming problematic now-a-days [3]. Quantitative structure activity relationship (QSAR), one of the most important areas in chemistry, gives information that is useful for drug design and medicinal chemistry. The derived relationship between molecular descriptors and activity is used to estimate the property of other molecules and/or to find the parameters affecting the biological activity [4].Nowadays many researchers work on QSAR. Frid et al use QSAR for early detection of drug- induced cardiac toxicities. They use QSAR for prediction of drug related cardiac adverse effects [5]. Sharma et al use multiple linear regression coupled with simulated annealing as QSAR for studying of Tetrazole [6]. Bhatiya et al. use QSAR for analyzing of furanone derivatives [7].

Darnag et al use neural network as QSAR for prediction of HIV protease inhibitors [8]. Yangali-Quintanilla et al use QSAR for predicting rejection of emerging contaminants[9].Veratric acid obtained from the stem bark of Tabebuia impetiginosa [10] have been reported to have antibacterial [11], antifungal [4], antioxidant [12], anti-inflammatory [13] and antispasmodic activities [14].

The objective of this work was to determine the quantitative relationships between structural parameters and antimicrobial activity of veratric acid derivatives applying artificial neural networks (ANNs). Section 2 gives an

overview on artificial neural network. Section 3 gives methodology. The simulation results of ANN as QSAR are presented in section 4 and finally section 5 includes conclusions and discussions.

2. An overview on artificial neural networks

As you read these words you are using a complex biological neural network. You have a highly interconnection set of approximately100,000,000,000 neurons to facilitate your reading, breathing, motions and thinking. Some of your neural structures were with you at the time of your birth. Other parts have been developed by experience. Scientists have just begun to understand how biological neural networks operate. It is generally understood that all biological neural function, including memory, are in the interconnections between neurons. Learning is viewed as the establishment of new connections between neurons or modification of existing connections [16-18]. The neurons that we consider here are not biological; they are extremely simple abstraction of biological neurons, realized as elements in program or elements in a VLSI circuit. In chemistry and related fields of research an increasing use of neural network computing has been noted since 1986. ANN has also been applied in cancer cell identification and other research fields in life science [18-21]. ANNs found application in compound classification modeling of structure-activity relationships, identification of potential drug targets and localization of specific structural and functional sites of biopolymers. ANNs have also been reported among the methods of QSAR analysis. The ANNs found application in modeling of structure-activity relationships, compound classification, and identification of potential drug candidates and localization of specific structural and functional features of biocompounds.

The most important issues that you can perform with ANN are:
Compute and approximate an unknown function, pattern recognition, and signal processing [18].

A single layer network of S neurons is shown below. Note that each of the R inputs is connected to each neuron and that the weight matrix has S rows.

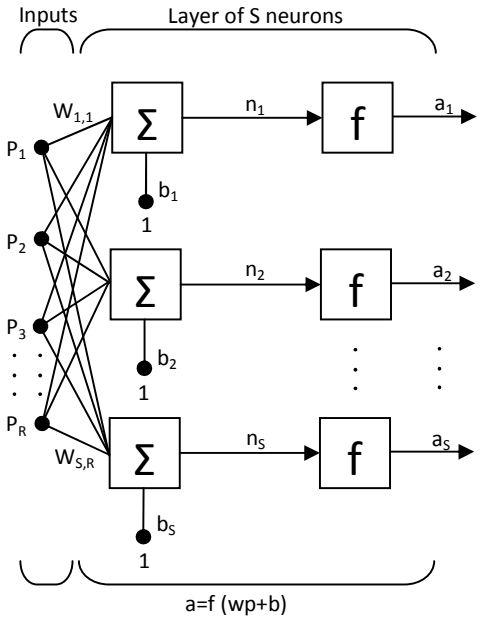

Fig 1: Typical structure single layer of S neurons

Now consider a network with several layers. Each layer has its own weight matrix *W*, its own bias *b*, a net input vector *n* and an output vector *a*. Tuning of parameter in ANN called learning. We use Levenberg-Marquadrt method for learning.

Next section gives methodology of data gathering and experiments.

3. Methodology

3.1. Data set

In vitro antibacterial activity of the veratic acid derivatives were evaluated against Gram-positive Bacillus subtilis MTCC 2423,Gram negative Escherichia coli MTCC 739 using ciprofloxacin as reference compound by standard serial dilution method. Also antifungal activity of the derivatives were tested against Candida albicans MTCC 227 and Aspergillus niger MTCC 2425 using fluconazole as reference compound by standard serial dilution method. [1] The data set used in this study was obtained from the work of Balasubramanian Narasimhan[1]. The results of antimicrobial study are presented in Tables 1 and 2.

Table 1 Antimicrobial activity of veratric acid derivatives (mg/ml)

Compound	MIC (mg/ml)				
	S. aureus	B. subtilis	E. coli	C. albicans	A. niger
1	18.00	9.00	16.00	11.00	14.00
2	18.00	12.00	18.00	12.00	14.00
3	22.00	16.00	20.00	12.00	12.00
4	24.00	14.00	12.50	18.00	14.00
5	22.00	14.00	14.00	10.00	12.50
6	22.00	12.50	18.00	18.00	14.00
7	19.00	15.00	19.00	15.00	17.00
8	20.00	14.00	16.00	13.50	12.50
9	19.00	16.00	19.00	11.00	16.00
10	20.00	15.00	20.00	10.00	12.00
11	20.00	12.50	20.00	20.00	20.00
12	20.00	12.50	16.00	16.00	12.50
13	16.50	12.50	16.00	13.00	14.00
14	16.00	12.50	14.00	16.00	12.00
15	18.00	14.00	16.00	12.50	11.50
16	21.50	12.50	18.00	13.50	14.00
17	11.00	9.00	8.50	13.50	14.00
18	23.00	15.00	20.00	10.00	11.00
19	22.00	13.00	17.00	13.00	12.50
20	17.00	13.00	15.00	10.00	10.00
21	23.50	13.00	20.00	10.00	11.50
22	19.00	13.00	19.00	12.50	12.00
23	21.00	15.00	19.00	11.50	11.50
24	16.50	12.50	16.50	12.50	12.00
25	19.00	13.00	19.00	13.00	12.00
26	21.00	13.00	17.00	11.00	12.00
27	17.50	12.00	20.00	14.00	13.00
28	23.00	14.00	23.00	14.00	15.00
29	23.00	14.00	23.00	16.00	13.00
30	15.00	12.00	17.00	13.50	13.50
31	20.00	12.00	17.00	15.00	14.00
32	19.00	15.00	17.00	13.50	14.50
33	17.00	15.00	18.50	13.00	11.00
34	17.00	13.00	17.00	10.00	12.50
35	18.50	13.00	17.00	13.00	12.50
36	17.00	13.00	17.00	15.00	14.00
37	18.00	12.00	19.00	12.50	11.50
38	18.00	10.50	13.00	16.00	13.00
39	17.00	11.50	21.00	14.00	13.00
40	19.00	13.00	19.00	15.00	12.50
41	17.00	15.00	19.00	12.00	12.00

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3.2 Quantitative structure activity relationship

Studies

Linear free energy relationship model (LFGR) by Hansch and Fujita was used to establish a QSAR between the in vitro antimicrobial activity of 41 veratic acid derivatives and descriptors coding for lipophilic , electronic, steric and topological properties of the molecules. This QSAR can be used for understanding the experimental antimicrobial data on theoretical basis.

Antimicrobial activities of the vatic acid devivities were calculated as MIC values and transformed in to pMIC values. Then pMIC values on molar basis are listed in Table 2.

Table 2 Antimicrobial activity of veratric acid derivatives (pMIC in mM/ml)

Compound	pMICsa	pMICbs	pMICec	pMICca	pMICan
1	1.01	1.31	1.06	1.22	1.11
2	1.04	1.20	1.04	1.20	1.15
3	0.98	1.12	1.02	1.23	1.23
4	0.98	1.20	1.25	1.10	1.20
5	1.01	1.20	1.20	1.35	1.25
6	1.00	1.25	1.10	1.10	1.20
7	1.10	1.20	1.10	1.20	1.15
8	1.08	1.23	1.17	1.25	1.28
9	1.10	1.17	1.10	1.34	1.17
10	1.08	1.20	1.08	1.38	1.30
11	1.10	1.31	1.10	1.10	1.10
12	1.10	1.31	1.20	1.20	1.30
13	1.20	1.33	1.22	1.30	1.28
14	1.25	1.35	1.30	1.25	1.37
15	1.15	1.27	1.21	1.30	1.34
16	1.10	1.34	1.18	1.30	1.29
17	1.45	1.53	1.56	1.35	1.34
18	0.90	1.09	0.95	1.25	1.20
19	0.95	1.18	1.05	1.28	1.18
20	1.08	1.21	1.15	1.31	1.31
21	0.95	1.21	1.01	1.31	1.26
22	1.08	1.23	1.08	1.25	1.28
23	1.04	1.18	1.08	1.29	1.29
24	1.21	1.31	1.21	1.31	1.36
25	1.15	1.32	1.15	1.32	1.36
26	1.08	1.28	1.17	1.37	1.33
27	1.15	1.33	1.10	1.25	1.28
28	0.93	1.15	0.93	1.15	1.12
29	1.05	1.25	1.04	1.20	1.29
30	1.28	1.39	1.23	1.34	1.34
31	1.17	1.39	1.23	1.29	1.32
32	1.19	1.28	1.39	1.34	1.30
33	1.20	1.26	1.16	1.31	1.40
34	1.20	1.31	1.20	1.42	1.35
35	1.15	1.31	1.20	1.32	1.35
36	1.23	1.34	1.23	1.29	1.32
37	1.20	1.38	1.18	1.36	1.40
38	1.22	1.46	1.36	1.27	1.36
39	1.25	1.41	1.16	1.32	1.35
40	1.25	1.40	1.25	1.34	1.44
41	1.20	1.26	1.16	1.36	1.36
SD[a]	0.11	0.09	0.12	0.08	0.08
Standard	3.33[b]	3.33[b]	3.33[b]	2.64[c]	2.64[c]

a Standard deviation.
b Ciprofloxacin.
c Fluconazole.

The values of the molecular descriptors are listed in table 3. These data including logarithm of octanolewater partition coefficient (log P), molar refractivity (MR), Kier's molecular connectivity (χ , χ^v , χ , χ^v , χ , χ^v), Wiener topological index (W), total energy (Te).

4. Simulation Results of Artificial Neural Network as QSAR

Artificial neural network analysis was performed with the use of Matlab version 7.6 software. The network has three interconnected layers: input layer, hidden layer, and output layer. The molecular descriptors (Table 3) are sent to the input layer where they are subsequently passed on to the nodes of the hidden layer for further processing. The signals are then relayed onto the output layer. The connections between the nodes of each layer are assigned by randomized weight value. The number of artificial neurons in the hidden layer was adjusted experimentally. The hidden layer consisted of 30 artificial neurons of Tansig activation function. The data subjected to ANN analysis

were divided into four sets: half learning set, quarter validation set, quarter testing set. The learning set of data is used in ANNs to recognize the relationships between input and output data. Levenberg-Merquardt method is used as learning method [21]. Testing set with was provided to be an independent evaluation of the ANN model.

Table 3 Values of selected descriptors of veratric acid derivatives used in LR analysis

Compound	Log P	MR	0χ	1χ	1χv	2χ	2χv	W	Te
1	1.24	45.74	9.84	6.19	3.64	5.15	2.37	246.00	-2571.42
2	1.27	50.51	10.55	6.72	4.03	5.30	2.56	307.00	-2726.66
3	1.61	55.26	11.26	7.22	4.62	5.68	2.79	382.00	-2882.45
4	2.08	59.78	11.97	7.72	5.12	6.03	3.21	472.00	-3038.28
5	2.03	59.68	12.13	7.58	5.01	6.52	3.52	459.00	-3038.16
6	2.01	59.67	11.97	7.72	4.73	6.03	2.96	472.00	-3009.57
7	2.48	64.39	12.67	8.22	5.62	6.38	3.56	578.00	-3194.11
8	2.49	64.26	12.84	8.08	5.47	6.86	4.06	564.00	-3193.97
9	2.50	64.20	12.84	8.12	5.55	6.64	3.69	552.00	-3193.96
10	2.11	64.32	13.05	7.87	5.33	7.65	4.57	538.00	-3193.73
11	2.88	68.99	13.38	8.72	6.12	6.74	3.91	701.00	-3349.95
12	2.81	68.93	13.54	8.58	5.97	7.21	4.39	686.00	-3349.84
13	3.27	73.59	14.09	9.22	6.62	7.09	4.27	842.00	-3505.78
14	3.67	78.19	14.79	9.72	7.12	7.44	4.62	1002.00	-3661.62
15	2.95	70.29	13.66	9.24	5.74	7.63	3.77	756.00	-3393.29
16	3.05	75.12	14.37	9.74	6.17	7.97	4.13	910.00	-3549.38
17	3.04	84.21	16.23	11.22	7.01	9.52	4.79	1238.00	-3997.55
18	0.37	47.57	9.84	6.19	3.71	5.15	2.43	246.00	-2471.44
19	0.62	52.46	10.55	6.72	4.17	5.30	2.65	307.00	-2626.77
20	0.87	57.36	11.42	7.10	4.53	6.01	3.27	370.00	-2782.05
21	0.96	57.21	11.26	7.22	4.73	5.68	2.93	382.00	-2782.59
22	1.43	61.73	11.97	7.72	5.23	6.03	3.33	472.00	-2938.41
23	0.18	58.75	11.97	7.72	4.84	6.03	3.05	472.00	-3103.24
24	- 0.02	69.94	14.25	9.17	5.91	7.11	3.81	734.00	-3734.94
25	2.40	77.07	14.37	9.74	6.28	7.97	4.24	910.00	-3449.60
2 6	0.53	66.43	12.96	8.76	5.85	7.17	3.97	621.00	-3386.32
27	1.59	69.50	12.96	8.76	6.27	7.17	4.42	621.00	-3221.97
28	0.36	52.05	10.55	6.72	3.96	5.30	2.54	307.00	-2691.27
29	2.30	72.24	13.66	9.24	5.83	7.63	3.89	756.00	-3293.88
30	2.82	77.04	14.54	9.65	6.34	8.14	4.44	858.00	-3654.00
31	2.82	77.04	14.54	9.63	6.34	8.26	4.51	871.00	-3653.97
32	2.82	77.04	14.54	9.63	6.34	8.25	4.50	884.00	-3654.00
33	2.77	77.28	14.54	9.65	6.24	8.14	4.34	858.00	-3449.73
34	2.77	77.28	14.54	9.63	6.24	8.26	4.39	871.00	-3449.75
35	2.77	77.28	14.54	9.63	6.24	8.25	4.39	884.00	-3449.75
36	2.05	78.70	15.24	10.19	6.36	8.34	4.22	980.00	-3769.74
37	2.05	78.70	15.24	10.17	6.35	8.42	4.25	1032.00	-3769.72
38	2.26	79.56	16.11	10.56	6.33	9.08	4.30	1104.00	-4124.81
39	2.26	79.56	16.11	10.55	6.33	9.15	4.33	1182.00	-4124.81
40	3.09	79.86	14.54	9.63	6.74	8.25	4.97	884.00	-3633.51
41	2.02	73.93	14.54	9.63	5.96	8.26	4.07	871.00	-3614.51

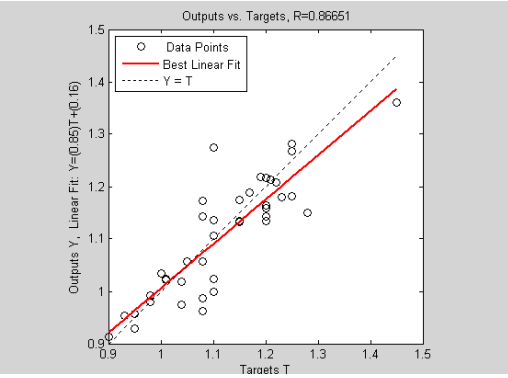

Figure 1: Predicted pMIC $_{sa}$ Using QSAR and Experimental pMIC$_{sa}$

The learning was continued with the use of validation set until mean square error reached the smallest value with regards to the validation set of data. Learning program was set as automatic one.

RESULTS AND DISCUSSION

The results of regression analysis obtained by ANN analysis are depicted in Figs. (1-5).The mean square error is illustrated in Fig. 6. It can be seen that the ANN model designed reflects properly the relationship between the theoretically calculated antimicrobial activity of veratric acid derivativrs on the basis of molecular descriptors and the experimentally determined antimicrobial activity for the set of considered learning, validation and testing subsets. The predictive power of the derived ANN models appears to be reasonably high.

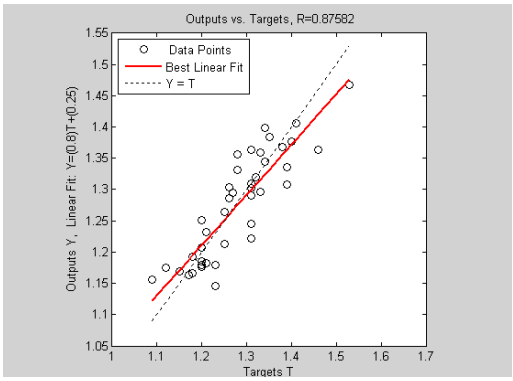

Figure2: Predicted $pMIC_{bs}$ Using QSAR and Experimental $pMIC_{bs}$

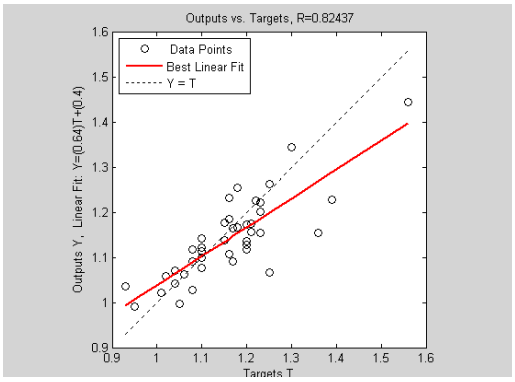

Figure 3: Predicted $pMIC_{ec}$ Using QSAR and Experimental $pMIC_{ec}$

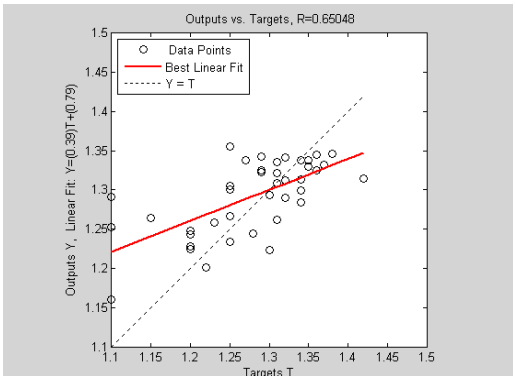

Figure 4: Predicted $pMIC_{ca}$ Using QSAR and Experimental $pMIC_{ca}$

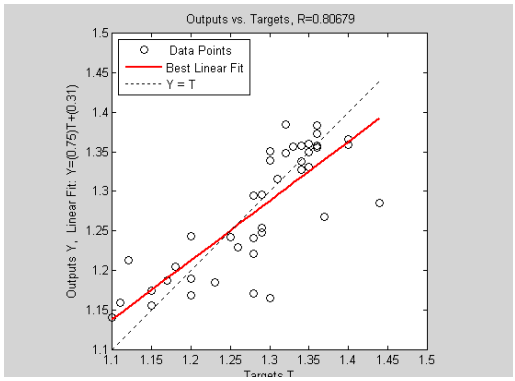

Figure 5: Predicted $pMIC_{an}$ Using QSAR and Experimental $pMIC_{an}$

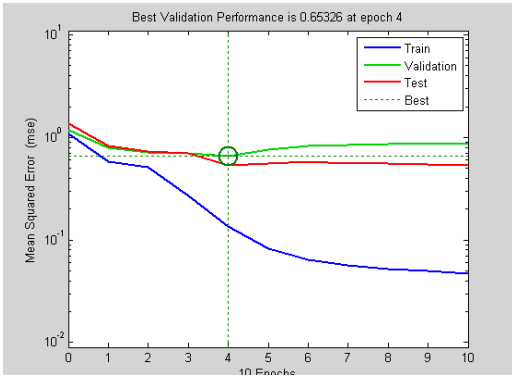

Figure 6: Mean square error of learning process

CONCLUSION

We have demonstrated the application of artificial neural network for predicting the antimicrobial activity of veratric acid derivatives as QSAR. This study has explored the use of QSAR as efficient methodologies for classifying and

predicting the antimicrobial activity of veratric acid. ANN analysis could be considered thus as helpful supporting tool for designing synthesis and further biological experiments in rational search for veratric acid derivatives most promising as a potential antimicrobial agents. Comparison of experiment results and QSAR results are very promising.

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