Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Graphics and Modelling 25 (2006) 30–36
Journal of Molecular Graphics and Modelling
www.elsevier.com/locate/JMGM

Combined electronic-topological and neural networks study of some hydroxysemicarbazides as potential antitumor agents

F. Kandemirli [a,*], N. Shvets [b], V. Kovalishyn [c], A. Dimoglo [b]

[a] Department of Chemistry, Kocaeli University, 41000 Izmit, Turkey
[b] Gebze Institute of Technology, PK-141, 41400 Gebze/Kocaeli, Turkey
[c] Biomedical Department, Institute of Bioorganic Chemistry & Petrochemistry, Murmanskaya1, Kyiv 02094, Ukraine

Received 1 August 2005; received in revised form 17 October 2005; accepted 25 October 2005
Available online 28 November 2005

Abstract

Structure–activity relationships study was performed for a series of Schiff bases hydroxysemicarbazide as potential antitumor agents by using the electronic-topological method combined with neural networks (ETM-NN). Data for the approach were obtained from conformational and quantum–chemical calculations and arranged first as matrices called electronic-topological matrices of contiguity, by one for each compound. Then specific molecular fragments were found for active compounds ('activity features') from the ETM application. After this, a system of prognosis was developed as the result of training the Kohonen self-organizing maps (SOM) by the most significant fragments.

Keywords: Electronic-topological method; Neural networks; Hydroxysemicarbazides

1. Introduction

The great majority of new potentially effective drugs is created by one of the three approaches listed: (1) chemical modification of molecules representing well known drugs; (2) biological activity screening for enormous quantities of natural preparations and their modifications; (3) directed synthesis based on the rational design that takes into account the whole complex of mechanisms of biological action, as well as the chemical structure and physical–chemical properties of the compounds under investigation. The last approach is the most effective and perspective one. It is based on the QSAR (quantitative structure–activity relationship) researches. Their realization requires the use of the most modern theories and methods taken from chemistry, physics, mathematics, biology, and practically in all stages of technological process of drug design computer technologies are widely used.

Recent years have been characterized by extreme progress in 3D QSAR (three-dimensional QSAR) methods. The electronic-topological method (ETM) [1–4] can be considered as one of them. It is aimed in searching rules for the different activities prediction, based on the pharmacophores (features of activity) found previously by specific ETM calculations. The method uses data obtained from quantum–chemical calculations and arranged in the form of electron-topological matrices of conjunction (ETMC), which combine geometric and electronic features in a natural way. Molecular mechanics programs and quantum–chemical approaches are usually used to determine structural and electronic parameters for each compound in the series under study. Logical–structural analysis and pattern recognition is applied to data being the descriptions of molecules. They result in the features of activity, or pharmacophores, determination.

Artificial neural networks (ANNs) is a group of methods that are increasingly being used in drug design to study QSAR [5–7]. This approach is able to elucidate structure–activity relationships by taking into account non-linear character of these relationships. Thus, this method can be of significant interest for the 3D QSAR researches.

In this study, the structure–activity relationships (SAR) have been investigated for Schiff bases of hydroxysemicarbazide as potential antitumor agents in the frameworks of combined electronic-topological and neural networks approach (ETM-NN). ribonucleotide reductase (RNR) plays an important role in

* Corresponding author at: Department of Chemistry, Kocaeli University, 41380 Umuttepe Kocaeli, Turkey. Tel.: +90 262 528 57 61/303 20 31; fax: +90 262 303 20 03.
E-mail address: fkandemirli@yahoo.com (F. Kandemirli).

1093-3263/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.jmgm.2005.10.011

the critical early cases involved in tumor promotion [8]. Therefore, RNR is a promising target for the design and development of anticancer drugs. RNR is the enzyme that catalyses the reduction of ribonucleotides into deoxyribonucleotides. Taking in account that DNA replication and repair are essential mechanisms for cell integrity and are dependent on the availability of deoxyribonucleotides, many researchers are giving special attention to this enzyme, since it is an attractive target to treat several diseases of our time, especially cancer [9]. Structure, function, and mechanism of RNR were studied in [10].

Several different classes of compounds such as hydroxyguanidine, thiosemicarbazone, and substituted benzohydroxamic acid and their derivatives have been shown to be RNR inhibitors [11–13]. Thirty Schiff bases of hydroxysemicarbazide (Ar–CH=NNHCONHOH) have been synthesized and tested against L1210 murine leukemia cells [14]. The inhibitory concentrations (IC_{50}) values were found to be in a range from 2.7×10^{-6} to 9.4×10^{-4} M. Some of the active compounds have shown in vivo anticancer activities and clinical potential. 3D QSAR studies using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) methods were performed on a series of Schiff bases of hydroxysemicarbazide analogues possessing antitumor activities against L1210 cells [15].

To solve the problem posed, the ETM was applied to elucidate fragments that present either activity features or the features that break the activity in view, and ANNs were applied to the fragments with the aim to find out the most significant features causing the substances activities. To validate the features obtained, the sliding examination is being carried out usually.

2. Materials and methods

2.1. Data sets

Compounds under study (30 in total, [14,15]) are shown in Table 1. Their common structural skeletons are given in Fig. 1 along with all possible substituents. Activities of the compounds are measured against the L1210 murine leukemia cells quantitatively but used qualitatively (i.e. as active/inactive, in which case there are two classes of compounds to be studied). Ideally, to carry out properly the ETM calculations, the series must be representative enough, and about a half of its compounds should be inactive. The molecules with $\log(1/IC_{50}) < 4.04$ were classified as active (17 molecules) and molecules with $\log(1/IC_{50}) \geq 4.04$ were considered to be inactive (13 compounds).

In our case, the ETMCs include charges for atoms as diagonal elements and bond multiplicity values as off-diagonal ones. When there is no bond, the distance between corresponding two atoms is used instead. The ETM has been applied to each of the two classes mentioned (active/inactive compounds) separately to identify activity features (pharmacophores) and inactivity features (anti-pharmacophores).

2.2. Combined ETM and neural network method (ETM-NN)

The ETM in detail can be found in literatures [16–21]. Molecular mechanics (MMX) [22] and quantum–chemistry calculations (AM1) [23] were carried out for the selected series of Schiff bases of hydroxysemicarbazide as the first step of the study. The data on the compounds electronic structures and space arrangement, which had been extracted from the results of these calculations, were used to form ETMC (by one ETMC for each molecule in the series under study). Then every ETMC from the series was compared with the ETMC of an active compound (the template) to found their common substructures (S_i, $i \in I$). Only those from these structural fragments were selected that were in correspondence with the predefined value of probability of their co-occurrence in active structures. A probabilistic criterion for the probability estimation is taken as

$$P_\alpha = (n_1 + 1)/(n_1 + n_2 + 2),$$

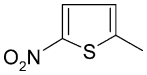
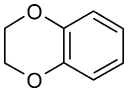
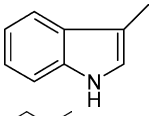
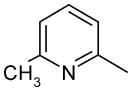
where n_1 is the number of molecules possessing the activity feature in view in the class of active compounds and n_2 has same meaning relative to the class of inactive compounds.

As far as the order of an ETMC depends on the number of atoms of the corresponding molecule, ETMCs cannot be used in a straightforward manner as the input for ANNs. Consequently, the information contained in ETMCs should be rearranged somehow in order to serve as input vectors of equal dimensionality for an ANN. To overcome this problem, a special algorithm being a combination of feed forward neural networks (FFNNs) and the Kohonen's self-organizing map (SOM) [24,25] has been proposed. The supervised learning was performed using a variant of FFNN known as the associative neural network (ASNN) [26].

The self-organizing map is a neural network using the algorithm based on the unsupervised learning. The size of our Kohonen's map was 1641 nodes ($x = 41$, $y = 40$). The training procedure for the SOM consisted of two phases [27]. The first phase, of 100,000 iterations, was used to roughly order the weight vectors of the map neurons. During the second phase, of 50,000 iterations, the values of the weight vectors were fine-tuned. The initial learning rate (α) and neighborhood radius of the SOM (σ) were selected to be $\alpha_1 = 0.6$, $\sigma_1 = 2/5(xy)^{0.5}$ for the first phase and $\alpha_2 = 0.15$, $\sigma_2 = 2/5\sigma_1$ the second one, where x and y correspond to the size of the SOM map. These parameters were selected being based on the guidelines and examples of the SOM_PAK manual [28].

The supervised learning was performed using a variant of feed forward neural networks (FFNNs) trained with the back propagation algorithm known as the associative neural network (ASNN) [29,30]. The architecture of the ASNN consisted of three-layers with five neurons in one hidden layer. Two output nodes were used to code class activities of Schiff bases of hydroxysemicarbazide. The bias neuron was present in the input and hidden layers. At least $M = 100$ independent ASNN were trained to analyse each set of variables. The details of this algorithm are described in [31].

Table 1
A list of compounds studied

Compound no.	Skeleton type	R	Log(1/IC_{50}) (M)	Activity	
				Observed	Predicted
1	II	3,4-OH	5.56	+	+
2	V	CH_3	5.36	+	+
3	II	3,5-I	5.33	+	+
4	V	Cl	5.27	+	+
5[a]	II	3,5-Cl	5.19	+	+
6	II	3,5-Br	5.14	+	+
7	II	5-Br	5.00	+	+
8	III		4.98	+	+
9	IV	5,7-Cl	4.55	+	+
10[a]	I	2,5-OCH_3	4.52	+	–
11	IV	7-($CH(CH_3)_2$)	4.49	+	–
12	II	3-(OCH_3),5-Br	4.42	+	+
13	I	3-(CF_3)	4.40	+	+
14	I	4-Ph	4.37	+	+
15[a]	I	4-OCH_2-Ph	4.32	+	+
16	II	4-OCH_3	4.22	+	+
17	I	3-I	4.10	+	–
18	II	4,6-OCH_3	4.04	–	–
19	II	4-OH	3.88	–	–
20[a]	III		3.75	–	+
21	I	4-CN	3.68	–	–
22	I	4-OCH_3	3.50	–	–
23	I	3-OCH_3	3.43	–	–
24	I	3-NO_2	3.40	–	–
25[a]	I	4-$N(CH_3)_2$	3.35	–	–
26	III		3.32	–	–
27	III		3.22	–	–
28	II	3,4-NO_2	3.09	–	–
29	III		3.05	–	–
30[a]	I	4-$NHOCCH_3$	3.02	–	–

[a] Compounds of test set.

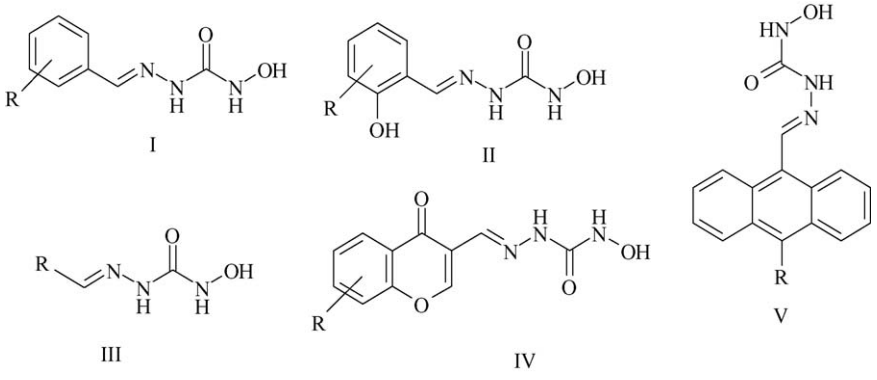


Fig. 1. Common molecular skeletons of the studied compounds.

It has been shown that pruning algorithms [32,33] may be used to optimize the number of input parameters for the FFNN learning algorithms and select the most significant of them. These algorithms operate in a manner similar to step-wise multiple regression analysis and exclude on each step by one input parameter that has been estimated as a non-significant one. The pruning algorithms were used in the current study to determine significant submatrices of the ETMCs (or ETSC, for short).

The algorithm that analyses data resulting from the ETM calculations (ETM-data) is developed on the base of volume learning algorithm. This method is implemented as a recurrent iterative application of the Kohonen SOMs and ASNNs. The general block-schema of the ETM-NN's data analysis is presented in Fig. 2.

The principal idea of this new approach is to determine initially for each molecule the number of clusters that contain elements of its ETMC, and, afterwards, to use the averaged values of each cluster for the ASNNs training. The algorithm proposed for supervised training makes it possible to evaluate the weights of fragments represented by the ETSCs that have been obtained from the ETM calculations. To do this, their projections on the Kohonen's maps corresponding to each ETMC are calculated. In this way, the degree of each fragment's presence in a molecule can be determined. This approach by several orders decreases the number of input parameters required for neural network training, preserves the spatial structural information of molecules and calculates neural network models with high generalization ability.

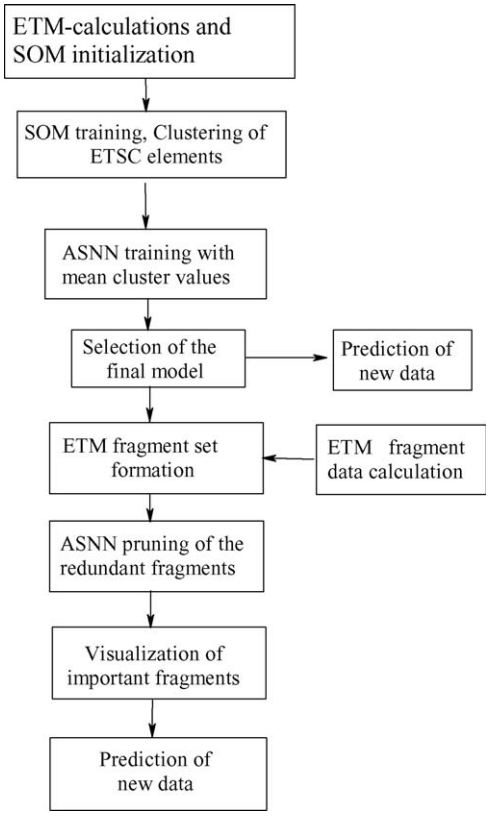


Fig. 2. Block-scheme of data analysis by means of ETM-NN approach.

3. Results and discussion

Effective charges on atoms (Q_i) were chosen as diagonal elements (local atomic characteristics, in ē); for the off-diagonal elements either bond characteristics (Wiberg's indices, in ē) or optimised distances (in Å) were used. To have more stable activity features, every active compound was used as a template for comparison with the rest of ETMCs. As a result of this comparison, some pharmacophores and anti-pharmacophores were found.

As an example, three pharmacophores (Ph1–Ph3) are given in Fig. 3, and two anti-pharmacophores (APh1, APh2) are given in Fig. 4. The probability P_α of the Ph1 pharmacophore's realization in the active class was estimated as 0.86, approximately. The ETMC of the template compound 1 and characteristics of Ph1 are given in Fig. 3a. The Ph1 is formed of five atoms that enter mainly into the hydroxysemicarbazide group. These atoms are N1, O4, N5, C6 and C9. The pharmacophore Ph1 (see Fig. 3a) is found in 11 of 17 active compounds.

The pharmacophore Ph2 (see Fig. 3b, template compound 2) is found in nine active compounds and one inactive compound. The probability of the Ph2 realization is estimated as 0.83. Atoms presenting the pharmacophore are the O4 atom from the hydroxysemicarbazide group and C8, C10, C11, C25 atoms of the antracene ring.

The Ph3 pharmacophore (see Fig. 3c) is found relative to the template compound 3, and its submatrix (ETSC) is of the order 7. Charges of these atoms are −0.15ē, −0.24ē, −0.04ē, −0.02ē, −0.24ē, 0.21ē and 0.25ē, respectively. The H16 and H17 atoms have positive charges. The probability of the Ph3 occurrence in active compounds is 0.79. The Ph3 is found in 10 active and 2 inactive compounds.

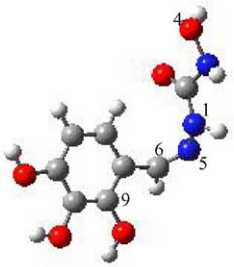
The search for anti-pharmacophores has been carried out in the class of inactive molecules in the same way. In Fig. 4, as an example, two of anti-pharmacophores found for the class of inactive compounds (APh1, APh2) are given. APh1 consists of seven atoms. Atoms of the groups that break the compounds activity have positive charges, as seen from Fig. 3. When $–CF_3$ or –I are attached to the position 3 of phenyl ring as substituents, the compounds obtained are active. If $–NO_2$ and $–OCH_3$ groups are attached to phenyl ring as replacing $–CF_3$ and –I substituents, the compounds are inactive.

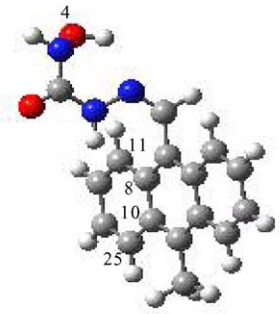
Pharmacophores that have been found as the result of the ETM-NN approach, were used as the basis for a system formation, which is capable of the antitumor activities prediction against L1210 cells. The forecasting ability of the system mentioned is clearly demonstrated in Fig. 5. The frequencies of the Ph1–Ph3, APh1 and APh2 appearance in the compounds of the teaching set are given in dependence on the level of antitumor activity of the compounds.

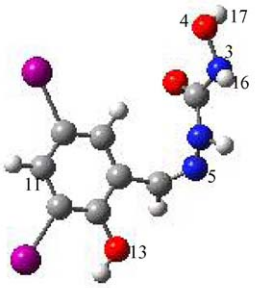
As seen from Fig. 5, the system of prognostication divides the teaching set into classes of active and inactive compounds clearly enough. As seen from the graph in the figure, in the class of active compounds there is a group of high-active compounds and another group of inactive compounds. As seen from Fig. 5, the pharmacophores appear with high values of frequencies in

N1	O4	N5	C6	C9
-0.30	3.58	1.00	2.30	4.80
	-0.24	4.80	5.20	7.40
P_α=0.86		-0.05	1.80	3.70
n1/n2=11/1			-0.10	2.50
				0.05

(a)







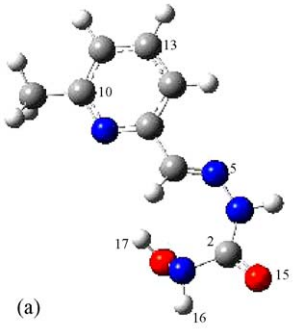
O4	**C8**	**C10**	**C11**	**C25**
-0.24	7.12	8.31	6.90	0.93
	-0.01	1.24	1.15	7.56
		-0.04	2.47	8.66
P_α=0.83			-0.13	7.48
n1/n2=9/1				0.24

(b)

N3	**O4**	**N5**	**C11**	**O13**	**H16**	**H17**
-0.15	1.02	3.74	8.66	6.68	0.92	1.86
	-0.24	4.77	9.48	7.09	1.90	0.93
		-0.04	5.08	4.24	3.95	4.98
P_α=0.79			-0.02	3.64	9.00	9.45
n1/n2=10/2				-0.24	7.31	6.83
					0.21	2.69
						0.25

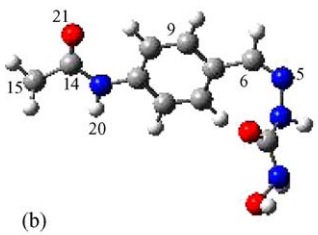
(c)

Fig. 3. Ph1–Ph3 pharmacophores (a_{ii} are atomic charges, a_{ij} are either Wiberg's indices for bonds or distances, otherwise; Δ_1, Δ_2 are the present corresponding limits for the diagonal and off-diagonal elements comparison).



(a)

C2	N5	C10	C13	O15	H16	H17
0.29	2.48	6.57	6.64	1.73	2.07	2.52
	-0.05	4.74	4.27	2.93	3.95	4.96
		-0.01	2.42	6.12	8.48	8.53
$P_{i\alpha}$=0.80			-0.01	6.65	8.21	8.99
n2/n1=7/1				-0.36	3.14	2.44
					0.20	2.69
						0.25



(b)

N5	C6	C9	C14	C15	H20	O21
-0.06	1.81	3.67	7.60	8.94	6.81	7.67
	-0.09	2.46	6.66	8.08	6.17	6.59
$P_{i\alpha}$=0.80		-0.08	4.42	5.91	4.47	4.18
n2/n1=7/1			0.31	0.94	2.05	1.78
				-0.25	2.55	2.40
					0.20	3.18
						-0.34

Fig. 4. Submatrices of the corresponding template compounds for the APh1 (a) and APh2 (b) anti-pharmacophores.

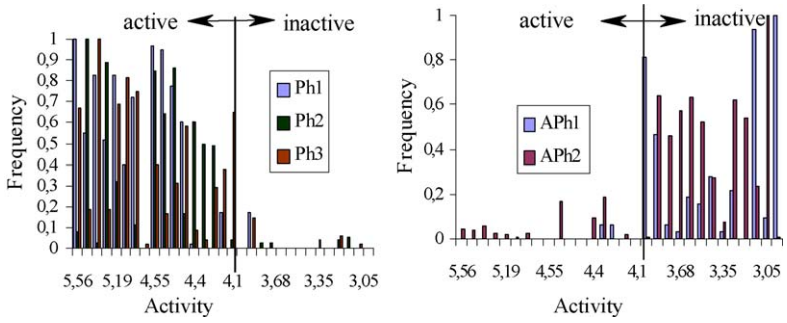


Fig. 5. Frequencies of the pharmacophores (Ph1–Ph3) and anti-pharmacophores (APh1, APh2) occurrence in the compounds from the series under study.

the class of active compounds. However, they are practically absent in the class of inactive compounds. In a similar way, maximal values are observed for the frequencies of the APh1 and APh2 anti-pharmacophores appearance in the class of inactive compounds, while for the Ph1–Ph3 pharmacophores their frequencies are close to zero.

A data set containing 30 examples was used in ETM-NN investigations. While 24 of the compounds were used for the model development, 6 randomly selected compounds were used for the model validation.

The first stage of the data analysis was in finding a model using weights of fragments as descriptors. The weights of 210 fragments (pharmacophore or anti-pharmacophore) were calculated, as descriptors for each compound, from their projection errors, relative to the same nodes of the Kohonen's map as in the template ETMC. Using this number of descriptors, the ASNNs recognized correctly 83.4%, or 20 from 24 compounds, while for the test set the result was lower, i.e. 50%, or 3 compounds from 6.

At the second stage, only five the most significant ETMC fragments were selected by the pruning methods. By this, ASNN classified correctly 91.7%, or 22 compounds from 24, for the training set and 66.7%, or 4 compounds from 6, for the test set. The results of prediction can be summarized as shown in Table 2.

4. Summary

A series of new Schiff bases of hydroxysemicarbazide, which are potential antitumor agents, is studied by means of the ETM-NN approach, because the ETM calculations take into account both structural and electronic characteristics of molecules. A system for the activity prognostication is developed from the following application of ANNs. The system is based on the pharmacophores and anti-pharmacophores that have been found previously by the ETM-software as submatrices of template compounds, containing the most important spatial and quantum–chemistry characteristics.

Table 2
Statistic parameters of active and inactive compounds for studied series

Predicted	Active	Inactive	Total
Pharmacophores	$a = 14$	$b = 3$	$a + b = 17$
Anti-pharmacophores	$c = 1$	$d = 12$	$c + d = 13$
Total	$a + c = 15$	$b + d = 15$	$n = 30$

Sensitivity = $a/(a + c)$% of correctly = 14/15 = 94% predicted actives; specificity = $d/(b + d)$% of correctly = predicted inactives = 12/15 = 80%; active predictive value = $a/(a + b)$% = 14/17 = 82% − %predicted actives that are actually inactive; inactive predictive value = $d/(c + d)$% = 12/13 = 92% − %predicted inactives that are actually active; concordance = $(a + d)/n$% = 26/30 = 87%.

Acknowledgement

This study was financially supported by Research Center of Kocaeli University.

References

[1] A.S. Dimoglo, Compositional approach to electronic structure description of chemical compounds, oriented on computer analysis of structure–activity relationships, Chim. Pharm. Zh (Russ.) 19 (1985) 438–444.
[2] N.M. Shvets, Applied program system for the prognosis of biological activity of chemical compounds: development and use, Comp. Sci. J. Moldova (Kishinev) 1 (1993) 101–110.
[3] N.M. Shvets, The study of data and control flows and the user interface organization in an applied system used in chemistry and medicine for the biological activities prediction, Comp. Sci. J. Moldova (Kishinev) 5 (1997) 301–311.
[4] I.B. Bersuker, A.S. Dimoglo, in: K. Lipkowitz, D. Boyd (Eds.), The Electron-Topological Approach to the QSAR Problem in Book: Reviews in Computational Chemistry, vol. 2, VCH, New York, 1991, pp. 423–460.
[5] J. Zupan, J. Gasteiger, Neural Networks for Chemistry and Drug Design: An Introduction, 2nd ed., VCH, Weinheim, 1999.
[6] D.T. Manallack, D. Livingstone, Neural networks in drug discovery: have they lived up to their promise, J. Eur. J. Med. Chem. 34 (1999) 195–208.
[7] I. Kovesdi, M.F. Dominguez-Rodrigue, L. Orfi, G. Naray-Szabo, A. Varro, J.G. Papp, P. Matyus, Med. Res. Rev. 19 (1999) 249–269.
[8] G. Nocentini, Ribonucleotide reductase inhibitors: new strategies for cancer chemotherapy, Crit. Rev. Oncol. Hematol. 22 (1996) 89–126.
[9] Cerqueira, M.F.S.A. Nuno, S. Pereira, P.A. Fernandes, M.J. Ramos, Overview of ribonucleotide reductase inhibitors: an appealing target in anti-tumour therapy, Curr. Med. Chem. 12 (11) (2005) 1283–1294.
[10] M. Kolberg, K.R. Strand, P.K. Graff, K.K. Andersson, Biochim. Biophys. Acta 1699 (2004) 1–34.
[11] E.J. Lien, Ribonucleotide reductase inhibitors as anticancer and antiviral agents, Prog. Drug Res. 31 (1987) 1–26.
[12] E.J. Lien, SAR Side Effects and Drug Design, Marcel Dekker, New York, 1987, pp. 163–182.
[13] A. Das, M.D. Trousdale, S.J. Ren, E.J. Lien, Inhibition of herpes simplex virus Type 1 and adenovirus Type 5 by heterocyclic Schiff bases of aminohydroxyguanidine tosylate, Antiviral Res. 44 (1999) 201–208.
[14] S. Ren, R. Wang, K. Komatsu, P. Bonaz-Krause, Y. Zyrianov, C.E. McKenna, C. Csipke, Z.A. Tokes, J. Lien, Synthesis, biological evalua-

tion, and quantitative structure–activity relationship analysis of new Schiff bases of hydroxysemicarbazide as potential antitumor agents, J. Med. Chem. 45 (2002) 4419–4427.
[15] A.V. Raichurkar, V.M. Kulkarni, Understanding the antitumor activity of novel hydroxysemicarbazide derivatives as ribonucleotide reductase inhibitors using CoMFA and CoMSIA, J. Med. Chem. 46 (2003) 4419–4427.
[16] N.M. Shvets, A.S. Dimoglo, Structure–odor relationships: results of an applied electronic-topological approach, Nahrung 42 (1998) 364–370.
[17] A.S. Dimoglo, A.A. Beda, N.M. Shvets, M.Yu. Gorbachov, L.A. Kheifits, I.S. Aulchenko, Investigation of the relationship between sandalwood odor and chemical structure: electronic-topologial approach, N. J. Chem. 19 (1995) 149–154.
[18] A.S. Dimoglo, P.F. Vlad, N.M. Shvets, M.N. Coltsa, Structure–ambergris odour relationships investigation in a mixed series of decalin and non-decalin compounds: the electronic-topological approach, N. J. Chem. 25 (2001) 283–288.
[19] A.S. Dimoglo, N.M. Shvets, I.V. Tetko, D.J. Livingstone, Electronic-topological investigation of the structure–acetylcholinesterase inhibitor activity relationship in the series of *N*-benzylpiperidine derivatives, QSAR (2001) 20–31.
[20] F. Kandemirli, N. Tokay, N.M. Shvets, A.S. Dimoglo, Electronic-topological study of the structure–activity relationships in a series of steroids with mineralocorticoid binding affinity, Arzneimettel-Forschung/Drug Res. 53 (2) (2003) 133–138.
[21] A.S. Dimoglo, E.P. Sim, N.M. Shvets, V. Ahsen, Electronic-topological study of structurally diverse cyclooxygenase-2 inhibitors, Mini Rev. Med. Chem. 2 (3) (2003) 293–306.
[22] K. Gilbert, J.A. Gaevski, MMPi Molecular Mechanics Program, Indiana University, Indiana, 1985.
[23] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, The development and use of quantum–mechanical molecular-models. 76. AM1—a new general-purpose quantum–mechanical molecular-model, J. Am. Chem. Soc. 107 (13) (1985) 3902–3909.
[24] I.V. Tetko, A.E.P. Villa, D. Livingstone, Neural network studies. 2. Variable selection, J. Chem. Inf. Comput. Sci. 36 (1996) 794–803.
[25] V.V. Kovalishyn, I.V. Tetko, A.I. Luik, V.V. Kholodovych, A.E.P. Villa, D.J. Livingstone, Neural network studies. 3. Variable selection in the cascade-correlation learning architecture, J. Chem. Inf. Comput. Sci. 38 (1998) 651–659.
[26] I.V. Tetko, D.J. Livingstone, A.I. Luik, Neural network studies. 1. Comparison of overfitting and overtraining, J. Chem. Inf. Comput. Sci. 35 (1995) 826–833.
[27] T. Kohonen, Self-organisation Maps, Springer-Verlag, Berlin, 1995.
[28] Kohonen, T., Hinninen, J., Kangas, J., Laaksonen, J. SOM_PAK The Self-organizing Map Program Package is Obtainable Via Anonymous Ftp from The Internet Address "cochlea.hut.fi" (130.233.168.48).
[29] I.V. Tetko, Neural network studies. 4. Introduction to associative neural networks, J. Chem. Inf. Comput. Sci. 42 (2002) 717–728.
[30] Virtual Computational Chemistry Laboratory (http://www.vcclab.org).
[31] A. Dimoglo, V. Kovalishyn, N. Shvets, V. Ahsen, The Structure-inhibitory activity relationships study in a series of cyclooxygenase-2 inhibitors: a combined electronic-topological and neural networks, Mini-Rev. Med. Chem. 5 (10) (2005) 879–892.
[32] I.V. Tetko, A.E.P. Villa, D.J. Livingstone, Neural network studies. 2. Variable selection, J. Chem. Inf. Comput. Sci. 36 (1996) 794–803.
[33] V.V. Kovalishyn, I.V. Tetko, A.I. Luik, V.V. Kholodovych, A.E.P. Villa, D.J.J. Livingstone, Neural network studies. 3. Variable selection in the cascade-correlation learning architecture, J. Chem. Inf. Comput. Sci. 38 (1998) 651–659.