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Artificial neural networks analysis used to evaluate the molecular interactions between selected drugs and human α_1-acid glycoprotein

Adam Buciński[a,*], Małgorzata Wnuk[a], Krzysztof Goryński[a], Anna Giza[a], Joanna Kochańczyk[a], Alicja Nowaczyk[b], Tomasz Bączek[c,d], Antoni Nasal[c]

[a] Department of Biopharmacy, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland
[b] Department of Organic Chemistry, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland
[c] Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gen. J. Hallera 107, 80-416 Gdańsk, Poland
[d] Department of Medicinal Chemistry, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland

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ABSTRACT

Quantitative structure-retention relationships (QSRR) were proposed for α_1-acid glycoprotein (AGP) column using physicochemical molecular descriptors of the selected drugs and interacting with that column. The set of 52 structurally diverse drug compounds, with experimentally derived logarithms of retention factors ($\log k$) values was considered. Thirty-six physicochemical property descriptors were calculated by standard molecular modeling and used to establish QSRR and predict the retention data by artificial neural network (ANN). The QSRR indicated that heat of formation (HF), Moriguchi *n*-octanol–water partition coefficient (M $\log P$) and the energy of the highest occupied molecular orbital (HOMO) are the most important for interactions between drugs and AGP. The proposed ANN model based on selected molecular descriptors showed a high degree of correlation between $\log k$ observed and computed. The final model possessed a 36-5-1 architecture and correlation coefficients for learning, validating and testing sets equaled 0.975, 0.950 and 0.972, respectively.

1. Introduction

Affinity chromatography (AC) is a liquid chromatography technique based on reversible interactions between the binding site of a macromolecule and an analyte molecule. Affinity chromatographic systems are obtained by immobilization of one of the pair of interacting molecules on a solid support and packing it into a column [1]. The stationary phase in AC is the main factor controlling the separation of compounds. Protein stationary phases were introduced first in the early 1980s [2–4]. For enantiospecific separations on AC supports containing ovomucoid [5], flavoprotein [6], avidin [7] and pepsin [8] were developed. Macromolecules currently used to form AC stationary phases are: human serum albumin [9], α_1-acid glycoprotein (AGP) [10], keratin [11], collagen [12], melanin [13], amylose tris(3,5-dimethylphenylcarbamate) [14] and the basic fatty acid-binding protein from chicken liver [15].

Affinity chromatography, followed by quantitative structure-retention relationships (QSRR) analysis, provides information on both the analytes and the macromolecules forming the stationary phases. QSRR equations derived for test series of analytes (often drugs) are interpreted in terms of structural requirements of the specific binding sites on macromolecules. Chromatographically demonstrated differences in analyte/macromolecule interactions may be relevant in view of molecular pharmacology and rational drug design. Moreover, specific high-performance affinity-chromatographic separations can be optimized by rational selection of chiral columns, the characteristics of which are provided by QSRR.

Barbato et al. [16] derived the relationships between the retention on AGP column and the lipophilic parameters of 23 amines. It was concluded that only the (*S*)-forms of neutral congeners get into mainly lipophilicity-driven interactions with AGP. On the other hand, the (*R*)-forms interact by a more complex mechanism, not exactly explained by $\log P$ or chromatographically determined lipophilicity parameter obtained on the so-called immobilized artificial membrane (IAM) column ($\log k_{wIAM}$).

An AGP column was employed in the experiments performed by Kaliszan et al. [17]. The aim of that study was to characterize structurally the binding site for organic-base drugs on the protein stationary phase. For a short series of β-adrenolytic drugs, for which the AGP-binding data determined by a standard biochemical procedure were available, a good correlation was found between the percent binding and $\log k$ from AC. The same authors [18] examined the retention mechanism on an AGP column of 16 antihistamine drugs. It appeared that the $\log k_{AGP}$ values from AC correlated significantly with the chromatographic hydrophobicity

* Corresponding author. Tel.: +48 52 585 39 09.
E-mail address: kizbiofarmacji@cm.umk.pl (A. Buciński).

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parameter determined on IAM column ($\log k_{IAM}$). In a detailed QSRR analysis of $\log k_{AGP}$ data, the structural parameters reflecting the molecular size of the analyte (S_T), and the electron excess charge on the aliphatic nitrogen (N_{ch}), also appeared statistically significant.

A further investigation on an AGP column included a wider group of analytes [18]. Retention data ($\log k_{AGP}$), were determined for 52 basic drugs of diverse chemical structures and pharmacological activities. Among them, one could find: antagonists of histamine H1 and H2 receptors, antagonists of β-adrenoceptors, and drugs acting on α-adrenergic receptors.

Accurate predictions of retention could be achieved theoretically, if the nature of intermolecular interactions determining molecular recognition of the analytes by the counterparts forming the chromatographic systems were properly quantified. But that situation is rather unrealistic. Therefore, in chemical practice approximate, predictions however useful, can be realized which are valid in statistical terms rather than in strict thermodynamic categories [19]. QSRR are statistically derived relationships between dependent variable (a chromatographic parameter) and independent variables (the descriptors characterizing the molecular structure of analytes). QSRR have been applied not only for evaluate properties of HPLC stationary phases (e.g., to predict relative differences in binding activity of drugs to AGP immobilized on the silica surface), but also to: (i) predict retention for a new analyte, (ii) get insight into the molecular mechanism of separation operating in a given chromatographic system, (iii) identify the most informative structural descriptors of analytes and (iv) evaluate complex physicochemical properties of analytes [20].

In the chemical-property-prediction studies a few standard calculation procedures are employed. QSRR are most commonly derived by multiple regression analysis (MRA) [20]. The fundamental problem with multiple regression is that considering simultaneously a number of structural parameters (independent variables) cannot be mutually related, i.e., they should be as much orthogonal as possible. At the same time, the properties within the series of analytes requested to derive statistically significant and physically meaningful QSRR should be evenly distributed and cover a wide range of individual structural descriptor values. In addition, the series of model analytes must be large enough to exclude chance correlations but not too big to save time and effort necessary for chromatographic and structural analysis [20]. It may appear that for individual series of analytes it is impossible to observe all those requirements. The question arises then if other data processing methods are able to provide acceptable retention prediction. Specially promising from that point of view appear currently the artificial neural networks (ANN).

The artificial neural network analysis is a method of data analysis, which is to emulate the human brain's way of working. Neural nets exhibit the way in which arrays of neurons probably function in biological learning and memory. ANN differs from classical computer programs in that they "learn" from a set of examples rather than are programmed to get the right answer. The information is encoded in the strength of the network's "synaptic" connections [21]. In chemistry and related fields of research a consequently increasing interest in neural-network computing has been noted since 1986. Very recently several attempts were reported to use ANN to model chromatographic retention [22]. ANNs found also application to compound classification, modeling of structure–activity relationships [23], identification of potential drug targets and the localization of structural and functional features of biopolymers [24].

The aim of the current study was to design and test the appropriate ANN, which could allow to predict chromatographic retention on the basis of structural descriptors describing the structure of the selected basic drugs.

2. Materials and methods

2.1. Structural parameters from molecular modeling

Descriptors of the structure of drugs were calculated by standard molecular modeling. HyperChem program for personal computers with the extension ChemPlus (Hypercube, Waterloo, Canada) was used. The software performed geometry optimization by the molecular mechanics MM+ force field method which was followed by quantum chemical calculations according to the semi-empirical AM1 method. Moreover, the set of structural descriptors was supplemented with Dragon software (Milan Chemometris and QSAR Research Group, Milan, Italy). The list of descriptors is presented in Table 1.

2.2. RP HPLC retention data of drugs

A Merck-Hitachi (Vienna, Austria) HPLC system was employed for chromatographic measurements of binding of the compounds

Table 1
List of structural parameters of drugs employed in ANN analysis.

Number	Name	Descriptor
Electronic parameters		
1.	Dipole moment	μ
2.	HOMO energy	HOMO
3.	LUMO energy	LUMO
4.	Energy difference between molecular orbitals (LUMO and HOMO)	DLH
5.	Dielectric energy	DE
Parameters reflecting the size (bulkiness) of the agents		
6.	Atom count	AC
7.	Molecular weight	MW
8.	Molar refractivity	MR
9.	Molar refractivity-GC	MR-GC
10.	Molecular connectivity index of zero order	X-0
11.	Molecular connectivity index of first order	X-1
12.	Molecular connectivity index of second order	X-2
13.	Valence connectivity index of zero order	X0vC
14.	Valence connectivity index of first order	X1vC
15.	Valence connectivity index of second order	X2vC
16.	Molecular shape index of first order	κ-1
17.	Molecular shape index of second order	κ-2
18.	Molecular shape index of third order	κ-3
19.	Conformation minimum energy	CME
20.	Steric energy	SE
21.	Sum of atomic Van der Waals volumes (scaled on a carbon atom)	Sv
22.	V total size index/unweighted	Vu
23.	V total size index/weighted by atomic masse	Vm
24.	V total size index/weighted by atomic van der Waals volumes	Vv
25.	V total size index/weighted by atomic Sanderson electronegatives	Ve
26.	V total size index/weighted by atomic polarizabilities	Vp
27.	V total size index/weighted by atomic electrotopological states	Vs
28.	Sum of Kier–Hall electrotopological states	Ss
29.	Fragment-based polar surface area	PSA
30.	Solvent accessibility surface area	SASA
31.	Polarizability	*P*
32.	Sum of atomic Sanderson electronegatives (scaled on a carbon atom)	Se
33.	Sum of atomic polarizabilities (scaled on a carbon atom)	Sp
34.	Total energy	TE
35.	Heat of formation	HF
Lipophilicity parameters		
36.	Moriguchi *n*-octanol–water partition coefficient	M log *P*
Logarithm of HPLC retention factor (AGP column) – experimental		log *k* (AGP)

Table 2
List of drugs studied, log k (AGP) values and structural parameters.

Name	Group*	AC	MW	TE	HF	HOMO	LUMO	DLH	MR	MR-GC	P	μ	M log P	X-0	X-1	X-2	X0vC	X1vC
Acebutolol	C	52	336.43	−187.306	−165.968	−9.037	−0.211	8.826	93.087	93.664	37.526	4.314	1.548	18.113	11.329	10.13	14.887	8.321
Alprenolol	C	41	249.352	−133.923	−59.285	−9.179	0.093	9.272	74.662	74.931	29.576	1.973	2.37	13.38	8.63	7.247	11.225	6.362
Antazoline	A	39	265.357	−134.364	66.911	−8.622	0.099	8.721	84.668	74.189	33.279	1.272	2.629	13.623	9.916	8.284	11.496	7.028
Atenolol	C	41	266.339	−148.362	−116.559	−9.127	0.194	9.321	73.504	73.773	29.638	3.042	0.925	14.251	8.969	8.17	11.426	6.386
Betaxolol	C	51	307.432	−167.855	−97.87	−9.078	0.228	9.306	88.638	88.907	35.838	1.691	2.383	15.786	10.631	9.268	13.755	8.341
Bisoprolol	C	54	325.447	−181.557	−163.648	−9.166	0.209	9.375	92.151	92.42	36.814	1.573	1.595	17.079	10.969	9.572	14.749	8.296
Bopindolol	C	56	380.486	−202.842	−69.011	−8.182	−0.199	7.983	109.514	110.841	44.75	1.027	3.214	20.148	13.315	12.845	16.912	9.539
Bromonidine	D	27	292.138	−121.805	86.149	−8.802	−0.942	7.86	68.79	62.458	28.645	2.921	1.542	11.665	8.343	7.291	10.529	6.083
Bupranolol	C	40	271.786	−140.372	−92.761	−9.171	−0.142	9.029	74.858	75.127	30.03	2.7	2.729	13.759	8.277	8.437	12.213	6.476
Celiprolol	C	60	379.498	−210.94	−169.87	−9.18	−0.32	8.86	106.463	107.04	42.603	5.035	1.654	20.613	12.568	11.918	17.257	9.338
Chlorpheniramine	A	38	274.793	−132.847	37.297	−9.047	−0.164	8.883	80.953	86.08	32.598	1.83	3.101	13.665	9.165	8.053	12.139	6.855
Chloropyramine	A	40	289.807	−142.182	43.964	−8.599	−0.084	8.515	86.08	80.953	34.14	1.985	3.53	14.372	9.648	8.491	12.716	7.079
Cimetidine	B	33	252.337	−127.872	77.351	−8.951	−0.374	8.577	72.458	59.833	26.147	2.391	0.821	12.51	8.274	6.369	10.765	6.38
Cinnarizine	A	56	368.521	−182.634	94.535	−8.792	−0.069	8.723	119.865	111.144	47.551	0.663	4.809	19.02	13.899	11.589	16.322	10.179
Cirazoline	D	38	244.336	−128.178	13.362	−8.968	0.24	9.208	74.561	64.351	29.778	1.778	2.384	12.535	8.754	7.816	11.123	6.756
Cicloprolol	C	52	323.431	−180.026	−125.138	−8.822	0.164	8.986	89.823	90.361	36.519	2.052	1.863	16.493	11.131	9.622	14.163	8.481
Diphenhydramine	A	40	255.359	−131.075	9.22	−9.145	0.143	9.288	79.927	79.927	31.687	1.068	3.262	13.502	9.271	7.785	11.621	6.634
Dimethindene	A	46	292.423	−146.541	52.182	−8.725	−0.12	8.605	94.428	93.554	37.558	2.292	3.88	15.527	10.648	9.585	13.712	8.018
Doxazosin	D	58	451.481	−250.591	−97.431	−8.415	−0.745	7.67	121.638	113.988	49.863	3.816	0.876	22.949	16.067	14.352	18.484	10.686
Esmolol	C	46	295.378	−165.461	−166.498	−9.172	0.135	9.307	81.052	81.321	32.658	2.076	1.836	15.665	10.007	8.631	12.964	7.209
Famotidine	B	37	352.447	−177.328	−9.359	−8.695	−0.793	7.902	90.809	58.62	28.416	7.618	−0.509	15.88	9.76	9.683	13.34	9.036
Pheniramine	A	38	240.347	−121.08	44.151	−9.002	−0.062	8.94	76.148	76.148	30.518	1.642	3.019	12.795	8.771	7.431	11.082	6.377
Phentolamine	D	40	281.357	−146.63	19.338	−8.566	−0.039	8.527	85.745	76.089	34.118	2.153	2.357	14.656	10.22	9.102	12.082	7.127
Isothipendyl	A	39	285.406	−138.266	61.452	−7.942	−0.434	7.508	86.661	77.025	32.469	1.274	2.733	14.113	9.665	8.773	12.892	7.641
Carteolol	C	45	292.377	−161.261	−125.494	−9.057	−0.247	8.81	81.359	80.369	33.142	2.852	1.306	15.458	9.849	9.815	12.902	7.326
Ketotifen	A	41	309.425	−149.988	28.183	−9.081	−0.992	8.089	93.476	88.532	35.141	4.073	3.717	15.104	10.737	9.777	13.58	8.717
Clonidine	D	23	230.096	−107.462	32.09	−8.975	−0.19	8.785	59.384	52.308	23.618	1.982	2.616	9.966	6.771	5.936	8.861	5.021
Labetalol	C	48	328.41	−177.45	−97.076	−9.326	−0.069	9.257	93.93	93.93	37.677	3.76	2.124	17.527	11.469	10.199	13.775	8.052
Mepyramine	A	44	285.388	−149.788	13.123	−8.555	0.168	8.723	87.738	88.007	34.703	2.413	2.293	15.079	10.186	8.66	12.99	7.124
Metiamide	B	31	244.372	−115.057	51.612	−8.537	−0.553	7.984	72.993	73.824	22.895	4.226	0.137	11.096	7.236	5.82	10.595	6.322
Metoprolol	C	44	267.367	−147.95	−119.421	−9.048	0.233	9.281	76.696	76.965	30.597	1.566	1.653	14.088	9.113	7.683	12.056	6.736
Moxonidine	D	28	241.68	−126.553	2.702	−9.07	−0.557	8.513	64.18	55.142	24.996	2.616	0.009	11.544	7.703	6.772	9.798	5.217
Nadolol	C	49	309.405	−173.022	−169.887	−9.055	0.33	9.385	85.524	85.793	34.378	2.089	1.358	16.328	10.26	10.323	13.542	7.788
Naphazoline	D	30	210.278	−105.38	52.557	−8.91	−0.596	8.314	67.3	56.821	26.737	2.318	2.879	10.795	7.933	6.786	9.11	5.672
Nifenalol	C	32	224.259	−126.748	−44.848	−9.8	−1.08	8.72	61.759	61.759	23.948	6.468	1.8	12.129	7.503	6.867	9.382	5.162
Nizatidine	B	42	331.45	−168.148	42.176	−9.081	−0.645	8.436	93.6	85.746	30.536	6.291	0.296	15.665	10.007	8.716	14.091	8.471
Oxprenolol	C	40	263.336	−144.659	−82.439	−8.993	0.289	9.282	73.372	71.391	29.794	1.856	1.439	13.828	9.113	8.057	11.374	6.579
Pindolol	C	38	248.324	−134.836	−50.923	−8.309	0.071	8.38	71.492	71.73	28.917	2.576	1.182	12.958	8.665	7.7	10.811	6.269
Pizotifen	A	42	295.442	−139.675	54.993	−8.862	−0.334	8.528	92.843	87.445	34.836	1.049	4.221	14.234	10.326	9.238	13.379	8.763
Practolol	C	41	266.339	−148.331	−116.835	−8.781	0.08	8.861	73.456	73.725	29.823	2.354	1.193	14.251	8.969	8.17	11.642	6.39
Prazosin	D	49	383.406	−212.97	−57.567	−8.376	−0.701	7.675	102.974	96.374	42.281	2.439	0.797	19.673	13.601	12.019	15.714	8.874
Promathazine	A	40	284.418	−136.11	54.705	−7.893	−0.203	7.69	88.504	80.671	32.955	2.234	3.942	14.113	9.665	8.773	13.022	7.781
Propranolol	C	40	259.347	−137.945	−53.353	−8.672	−0.467	8.205	76.825	77.093	31.043	1.323	2.492	13.665	9.165	8.053	11.466	6.686
Ranitidine	B	43	314.402	−168.974	−0.493	−9.098	−0.769	8.329	87.591	87.607	31.303	6.487	0.613	15.665	10.007	8.716	13.404	7.734
Roxatidine	B	48	306.404	−168.347	−117.475	−9.049	0.258	9.307	87.166	84.537	34.878	2.777	1.281	15.623	10.775	8.79	13.091	8.094
Sotalol	C	38	272.362	−145.305	−109.033	−9.112	−0.51	8.602	71.489	68.989	26.906	2.845	0.709	13.759	8.277	8.494	11.66	7.661
Tiamenidine	D	27	219.732	−102.984	9.008	−9.201	0.011	9.212	60.251	52.434	20.971	2.894	1.555	9.259	6.271	5.582	9.159	6.062
Timolol	C	45	316.418	−171.129	−108.999	−8.942	−0.925	8.017	85.956	71.131	31.391	2.404	−0.479	15.295	9.955	9.535	13.65	7.897
Tramazoline	D	33	215.297	−111.185	27.293	−8.837	0.233	9.07	67.257	60.925	26.711	2.097	3.069	10.795	7.933	6.786	9.422	6.095
Tripelennamine	A	40	255.362	−130.406	52.225	−8.675	0.099	8.774	81.275	81.275	32.04	1.794	2.589	13.502	9.254	7.869	11.659	6.601
Triprolidine	A	43	278.396	−139.341	53.418	−8.98	−0.41	8.57	89.349	83.67	35.809	0.558	3.489	14.493	10.326	8.81	12.626	7.737
Tymazoline	A	37	232.325	−122.563	−20.594	−9.195	0.179	9.374	71.322	61.112	28.108	1.699	2.128	12.251	8.165	7.314	10.786	6.171

Table 2 (*Continued*)

Name	X2vC	SASA	DE	κ-1	κ-2	κ-3	CME	SE	Sv	Se	Sp	Ss	Vu	Vm	Vv	Ve	Vp	Vs	PSA	log *k* AGP
Acebutolol	6.093	393.152	−0.769	22.042	11.584	8.792	−166.007	−7.62	29	52	31	59	208	128	158	204	167	120	87.66	0.676
Alprenolol	4.628	304.02	−0.27	16.056	8.992	6.667	−59.352	1.134	23	40	25	39	56	32	41	55	44	30	41.49	1.49
Antazoline	4.932	297.785	−0.366	14.917	7.852	4.496	66.901	20.897	24	38	26	38	118	60	82	113	88	54	3.24	1.154
Atenolol	4.815	319.037	−0.667	17.053	9.031	8	−119.668	−17.566	23	41	24	47	98	58	68	96	73	58	84.58	0.499
Betaxolol	6.44	381.206	−0.385	18.34	9.988	7.422	−97.908	271.846	28	50	30	45	141	75	98	137	106	68	50.72	0.838
Bisoprolol	6.144	403.435	−0.456	21.043	12.375	11.224	−163.671	7.935	30	53	32	49	178	88	125	171	136	73	59.95	0.694
Bopindolol	8.005	410.008	−0.591	22.68	10.347	7.039	−69.06	−0.075	34	55	36	60	151	88	117	145	124	80	63.35	1.94
Bromonidine	4.426	255.525	−0.525	12.055	5.325	2.56	86.137	−0.285	18	27	19	36	42	38	33	41	36	25	62.2	0.831
Bupranolol	5.937	305.048	−0.293	16.056	6.963	6.667	−92.831	−0.508	23	39	25	40	81	38	56	78	59	38	41.49	0.981
Celiprolol	7.465	426.107	−0.797	25.037	11.87	9.36	−169.894	−27.577	33	59	36	65	160	85	111	155	120	82	90.9	0.7
Chlorpheniramine	5.387	305.616	−0.303	15.39	7.695	4.795	37.269	−3.748	25	39	26	40	98	79	79	97	86	63	19.37	1.202
Chloropyramine	5.476	307.81	−0.252	16.372	8.444	5.732	43.941	4.558	24	37	25	38	85	67	67	85	72	55	16.13	1.431
Cimetidine	4.369	280.955	−1.331	15.059	9	5.928	77.299	1.19	20	33	21	39	98	58	74	97	74	69	89.8	0.482
Cinnarizine	7.374	402.415	−0.308	21.24	11.408	6.25	94.514	12.551	35	54	37	51	248	158	197	242	207	152	6.48	2.148
Cirazoline	5.237	282.65	−0.343	13.005	5.551	2.659	13.292	274.117	22	37	24	34	74	34	50	71	54	29	9.23	1.082
Cicloprolol	6.366	395.078	−0.433	19.326	10.78	8.081	−125.212	273.885	29	51	31	48	163	86	114	157	123	78	59.95	0.735
Diphenhydramine	4.875	305.829	−0.257	15.39	8.323	5.12	9.169	−7.388	24	39	26	37	94	52	70	91	74	48	12.47	1.14
Dimethindene	6.429	338.86	−0.346	16.844	7.713	4.11	52.183	0.828	28	44	30	41	99	56	70	97	74	51	16.13	1.382
Doxazosin	7.81	443.459	−0.926	24.684	10.948	5.259	−97.45	−8.225	36	59	37	74	203	127	145	199	154	132	112.27	1.798
Esmolol	5.248	353.803	−0.508	19.048	10.68	8.889	−166.517	−3.313	26	46	27	50	114	67	79	113	84	66	67.79	0.649
Famotidine	6.783	355.674	−1.932	19.048	9.209	9.586	−9.378	−87.166	22	38	24	59	128	88	91	128	93	99	199.04	0.731
Pheniramine	4.81	286.936	−0.301	14.41	7.556	4.566	44.129	−3.867	23	37	24	34	63	35	46	62	49	32	16.13	0.926
Phentolamine	5.197	304.751	−0.481	15.879	7.513	4.26	19.34	36.687	25	39	26	44	140	75	92	138	100	71	23.47	1.264
Isothipendyl	6.402	294.021	−0.297	14.917	6.406	3.122	61.428	24.035	24	38	26	38	78	44	58	75	62	40	44.67	1.58
Carteolol	6.426	325.035	−0.566	17.355	7.513	5.606	−125.519	−13.806	26	44	27	48	101	60	72	99	77	59	70.59	0.706
Ketotifen	7.118	305.334	−0.412	15.523	6.481	2.922	28.174	31.528	27	39	29	47	84	61	65	83	70	58	48.55	1.459
Clonidine	3.693	227.207	−0.426	10.516	4.68	2.534	32.092	2.77	15	23	16	31	34	25	26	34	28	20	24.06	0.847
Labetalol	5.99	371.717	−0.773	20.314	10.222	6.682	−97.081	−30.123	29	47	30	59	127	88	93	128	98	97	95.58	1.106
Mepyramine	5.261	329.541	−0.367	17.355	9.209	5.95	13.072	−1.781	26	43	28	42	143	80	102	140	110	72	28.6	1.113
Metiamide	4.546	283.154	−1.679	13.067	7.302	5.04	51.584	5.988	18	30	20	31	62	34	45	61	46	34	110.13	0.517
Metoprolol	4.915	332.184	−0.368	17.053	9.834	8	−120.966	1.938	24	43	26	41	101	54	69	98	74	50	50.72	0.564
Moxonidine	3.586	255.952	−0.549	12.457	5.558	3.03	2.698	0.43	17	28	18	36	53	23	34	50	37	22	21.26	0.528
Nadolol	7.032	340.953	−0.595	18.34	7.713	5.551	−173.837	11.769	27	48	29	52	149	92	110	146	117	91	81.95	0.606
Naphazoline	4.07	242.44	−0.34	11.111	5.104	2.488	52.555	−6.188	19	29	20	30	38	19	25	37	27	16	0	1.092
Nifenalol	3.927	258.981	−0.702	14.063	6.667	4.817	−44.855	−5.49	18	32	19	44	60	44	42	61	44	49	66.4	0.639
Nizatidine	6.576	349.508	−1.35	19.048	10.68	8.889	42.1	12.382	24	42	27	50	163	110	122	163	126	111	114.98	0.46
Oxprenolol	4.978	296.955	−0.269	15.39	7.136	3.986	−82.479	1.503	23	39	24	42	52	31	38	51	41	31	50.72	1.21
Pindolol	4.723	294.008	−0.555	14.41	6.963	4.267	−50.956	4.433	22	37	23	39	96	58	72	93	76	57	57.28	0.87
Pizotifen	7.197	300.739	−0.219	14.583	6.246	2.813	54.988	13.793	27	41	29	36	100	63	71	98	78	52	31.48	1.898
Practolol	4.733	320.611	−0.629	17.053	9.031	8	−116.843	−12.971	23	41	24	46	101	61	72	99	77	61	70.59	0.509
Prazosin	6.39	386.753	−0.889	21.24	9.428	4.542	−57.582	19.214	30	49	31	64	264	150	182	256	196	146	106.95	1.39
Promethazine	6.545	295.423	−0.261	14.917	6.406	3.122	54.673	28.341	25	39	27	37	73	43	55	71	58	40	31.78	1.833
Propranolol	5.005	306.437	−0.313	15.39	7.695	4.795	−53.454	−10.441	23	39	25	40	80	49	60	78	64	48	41.49	1.612
Ranitidine	5.768	354.18	−1.485	19.048	10.68	8.889	−0.65	11.332	24	43	26	51	140	81	101	138	102	88	99.88	0.6
Roxatidine	5.694	357.061	−0.634	18.34	10.714	7.422	−117.509	−1.455	27	47	29	49	177	109	132	174	140	104	61.8	0.773
Sotalol	6.323	301.704	−1.07	16.056	6.963	6.667	−109.084	−0.002	21	38	23	47	72	48	49	73	52	52	86.81	0.516
Tiamenidine	5.393	231.305	−0.488	9.551	4.022	2.083	8.983	−2.775	16	27	18	26	34	28	27	34	30	21	61.72	0.808
Timolol	6.617	338.6	−0.568	17.355	8.022	5.95	−109.065	37.764	25	45	27	46	124	99	104	122	114	85	82.2	0.696
Tramazoline	4.432	249.14	−0.463	11.111	5.104	2.488	27.258	2.934	20	32	21	29	47	23	32	46	34	20	36.42	1.315
Tripelennamine	4.898	299.988	−0.297	15.39	8.323	5.479	52.216	−3.485	24	39	25	36	110	57	79	106	86	52	19.37	1.066
Triprolidine	5.707	323.083	−0.317	15.879	8.022	4.488	53.418	2.901	26	42	28	39	127	69	90	124	96	61	16.13	1.185
Tymazoline	4.74	272.102	−0.324	13.432	6.25	3.729	−20.598	3.76	21	36	23	33	46	22	30	44	33	18	9.23	1.306

[*] The agents studied belong to the following pharmacological groups: antagonists of histamine H1 receptors (A), antagonists of histamine H2 receptors (B), β-adrenolytics (C) and drugs acting on α-adrenoreceptors (D).

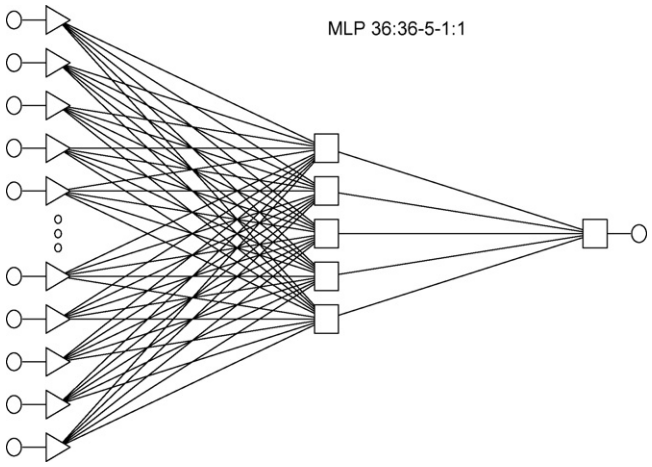

Fig. 1. Architecture of artificial neural network predicting chromatographic retention on the basis of selected structural descriptors. ANN model type: MLP 36:36-5-1:1.

studied to AGP [18]. The retention factors of the compounds studied were determined isocratically on Chiral AGP column 100 mm × 4 mm I.D. (ChromTech, Norsborg, Sweden) packed with α_1-acid glycoprotein chemically bound to silica particles of 5 μm diameter. The mobile phase was isopropanol – 0.01 M Sørensen phosphate buffer pH 6.5 (5:95, v/v). The mobile phase flow-rate was 0.5 ml/min. The detection wavelength was 215 nm. Logarithms of retention factors, $\log k_{ACP}$, were calculated taking the sodium nitrate peak as a measure of dead volume. A 1 mg amount of a drug solute was dissolved in 4 ml of methanol. The solution was diluted 10-fold with methanol and 20 μl of the final solution was injected onto the column. The logarithms of retention factors of a series of drugs determined on AGP column taken from literature [18] were collected in Table 2 .

2.3. Artificial neural network (ANN) analysis

HPLC retention data on AGP column – $\log k$ (AGP), for all the analytes from Table 1 were divided randomly into three groups. Variables for the analyzed drugs were divided into learning set with 26 compounds, validation set with 16 compounds and testing set with 10 compounds. Fig. 1 presents the architecture of the ANN model used for predictions of molecular interactions between AGP and selected drugs. An artificial neural network based on a multilayer perceptron consisting of 36 artificial neurons in the input layer, five in the hidden layer and one neuron in the output layer was used. A two-stage procedure with back-propagation and conjugate gradient descent methods were used to train the network. In the case of the network applied, learning was completed in 100 epochs by back-propagation method and 37 epochs by conjugate gradient descent method. First, ANN analysis was performed with the training and validation sets of data by means of iterative minimalization procedure allowing to optimize parameters of the network. Data from the learning set were presented in a randomized manner during the learning process. The third data set (test set) was served as checking of the generalization ability of the learned ANN.

3. Results and discussion

The list of numerical values of the structural parameters of the drugs studied derived from calculation chemistry, reflecting their electronic properties, size (bulkiness) and lipophilicity are summarized in Table 1. The final model possessed a 36-5-1 architecture and correlation coefficients for learning, validating and testing sets equaled 0.975, 0.950 and 0.972, respectively (Table 3).

Table 3
Statistics of ANN processing used during the study.

Statistics	Learning set	Validating set	Testing set
Mean	0.951	1.111	1.108
Data S.D.[a]	0.379	0.414	0.540
Error Mean[b]	−0.006	0.024	0.037
Error S.D.[c]	0.084	0.130	0.173
Abs. E. Mean[d]	0.067	0.107	0.144
Correlation[e]	0.975	0.950	0.972

[a] Standard deviation of the target output variable.
[b] Average error of the output variable.
[c] Standard deviation of errors for the output variable.
[d] Average absolute error (difference between target and actual output values) of the output variable.
[e] The standard Pearson-*R* correlation coefficient between the target and actual output values.

An ANN model was used to correlate chromatographic behavior of the set of structurally diverse drugs with their structural descriptors and to create a model useful to prediction of retention values. A correlation between experimental and predicted $\log k$ (AGP) values in learning, validating and testing set is given in Fig. 2.

Table 1 contains the list of the structural parameters of the drugs studied derived from calculation chemistry, reflecting their electronic properties, size (bulkiness) and lipophilicity. The numerical values of descriptors along with $\log k$ (AGP) of the agents are summarized in Table 2. In Table 4 the results of sensitivity analysis of inputs are presented, which one was used to identify significance of individual molecular descriptors and to select descriptors that were considered the most important.

Using the proposed method, i.e., artificial neural network, it was possible to predict what physicochemical property descriptors influence on interactions between AGP and selected drugs (the sensitivity above one). Molecular descriptors with sensitivities lower than one were seemed to be detrimental to the model ANN.

It is rather expected that highly significant structural parameters for ANN processing of retention data are lipophilicity of drugs (CM $\log P$) and their electronic descriptors (highest occupied molecular orbital (HOMO) and DLH). They correspond to second, fourth and eleventh sensitivity ranks, respectively. The results obtained confirmed also that the bulkiness of the molecules of basic drugs is also very important for their binding to AGP. This physicochemical property is reflected mainly by the following parameters: heat of formation (HF), AC, MR, as well as by connectivity indices: X-1, κ-3, X1vC. The first order connectivity index, X-1 encodes single bond properties and κ present information concern-

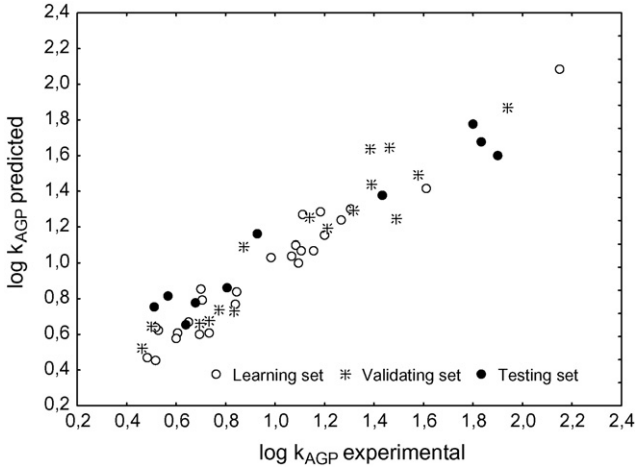

Fig. 2. Correlations between the calculated and the experimental retention data determined on an α_1-acid glycoprotein column.

Table 4
Sensitivity analysis results for the structural parameters of drugs considered in ANN analysis.

Descriptor	Error	Rank
HF	1.620	1
M log *P*	1.478	2
X-1	1.241	3
HOMO	1.185	4
AC	1.166	5
MR	1.162	6
κ-3	1.160	7
X1vC	1.134	8
P	1.127	9
Sp	1.104	10
DLH	1.104	11
CME	1.103	12
Se	1.067	13
PSA	1.059	14
κ-2	1.059	15
X2vC	1.058	16
Ss	1.048	17
Vu	1.031	18
SASA	1.031	19
Ve	1.030	20
Sv	1.022	21
X-2	1.014	22
X-0	1.013	23
TE	1.010	24
Vs	1.006	25
μ	0.998	26
Vm	0.996	27
LUMO	0.994	28
X0vC	0.990	29
κ-1	0.990	30
MW	0.981	31
Vv	0.969	32
DE	0.968	33
Vp	0.964	34
MR-GC	0.961	35
SE	0.955	36

ing the shape, size, branching pattern and similarity of molecular graphs.

In fact, it was rather surprising that heat of formation occurred the most significant descriptor affecting the retention of the agents on AGP column. Heat of formation reflect basically the differences in bulkiness among the analytes [20], hence that descriptor can be treated as describing significantly a geometry of the molecular structure. The other significance values for sensitivity ranks were polarizability parameters (*P* and Sp), conformation minimum energy (CME), polar surface area (PSA) and further connectivity and topological shape indices (connectivity indices X-1 and κ-3) (Table 4). PSA can provide information about surface diffusion, absorption, contact surface and information about size of the molecules. In turn the contact surface area can be used an accurate predictor of water solubility and can be viewed as advice of the extent to which the solute is exposed to intermolecular interaction with the solvent. PSA can also be useful tool to indicates the possibility of a compound to form hydrogen bonds which are an essential component of intermolecular interaction, e.g., protein–drug.

4. Conclusions

In the present study, a set of thirty-six descriptors, including both stationary phase and analytes properties, is adopted to build a QSRR model able to describe the retention behaviour of 52 basic drugs of diverse chemical structures as follows antagonists of histamine H1 and H2 receptors, β-adrenolytics, and drugs acting on α-adrenoreceptors. A artificial neural network provides an accurate QSRR model. In addition, ANNs model is able to detect relationships between depend ($\log k$) and independent (descriptors) variables. Finally, AGP columns can serve as instrument with ability to demonstrate types of interactions between acid glycoprotein and drugs. Useful information can be derived from the chemical structure of a drug to calculate descriptors describing various properties of that drug.

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