Pharmacological Classification of Drugs by Principal Component Analysis Applying Molecular Modeling Descriptors and HPLC Retention Data

Leszek Bober[1], Marcin Koba[2], Urszula Judycka-Proma[1], and **Tomasz Baczek[3,*]**

[1]POLPHARMA SA Pharmaceutical Works, Starogard Gdański, Poland; [2]Department of Medicinal Chemistry, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University of Gdańsk, Gdański, Poland

Abstract

Pharmacological classification of drugs by principal component analysis (PCA) based on molecular modeling and high-performance liquid chromatography (HPLC) retention data is proposed. First, a group of 20 drugs of recognized pharmacological classification are chromatographed in eight diversified HPLC systems, applying columns with octadecylsilanes, phosphatidylcholine, as well as α_1-glycoprotein and albumin. Additionally, molecular modeling studies, based on the structural formula of the drugs considered, are performed. Sixteen structural descriptors are derived. A matrix of 20×24 HPLC data together with molecular parameters are subjected to principal component analysis, and this revealed five main factors with eigenvalues higher than 1. The first principal component (factor 1) accounted for 47.8% of the variance in the data, and the second principal component (factor 2) explained 21.0% of data variance. The total data variance was 82.6% and is explained by the first three factors. The clustering of drugs is in accordance with their pharmacological classification, which proved that the PCA of the HPLC retention data, together with their structural descriptors, allowed the drugs to be segregated accurately to their pharmacological properties. This may be of help in reducing the number of biological assays needed in the development of a new drug.

Introduction

Molecular modeling is the term used to refer to theoretical methods and computational techniques which enable modeling or mimic the behavior of molecules. These techniques are used in the areas of computational chemistry, computational biology, and materials science for studying molecular systems, in both small chemical systems as well as large biological molecules. The main feature of recognized molecular modeling techniques is the atomistic level description for the molecular systems. It means that the most basic level of information is based on individual atoms or small groups of atoms. However, this is in contrast to already existing and applied techniques in the practice of quantum chemistry, where electronic structure calculations are considered explicitly.

Computational chemistry belongs to a branch of chemistry that applies computer sciences to assist in solving chemical problems using the results of theoretical chemistry to calculate the physicochemical properties of molecules. Additionally, several major areas may be distinguished within computational chemistry; for example, identifying correlations between chemical structures and activities (quantitative structure-activity relationships, QSAR) to help during the efficient synthesis of compounds, or to design molecules that interact in specific ways with other molecules (1).

The software programs used in computational chemistry allow for the generation of a large number of molecular descriptors. They are usually based on the empirical, semi-empirical, or *ab initio* methods employed to cover static and dynamic situations of the individual molecule. The methods known as empirical or semi-empirical employ additional experimentally obtained results to facilitate and improve the calculations. Methods that do not include any empirical parameters are directly derived from theoretical principles and are called *ab initio* methods (2).

Molecular descriptors are powerful tools in QSAR studies, and, according to definition, are the final results of the logical and mathematical procedure transforming chemical information encoded within a symbolic representation of a molecule into useful numbers used in some standardized experiments. Molecular descriptors play an increasing role in scientific calculations. Due to their large number within diversified sources of chemical information, they are useful in understanding relationships between molecular structure and experimental evidence. Knowledge of statistics, chemometrics, and QSAR approaches can, therefore, be considered as necessary, especially in combination with multiple linear regression (MLR), partial least squares regression (PLSR), classification methods, principal component analysis (PCA), factor analysis (FA), or artificial neural networks (ANN) (3).

Principal component analysis (PCA) is a data processing method designed to extract and visualize systematic patterns or trends in large data matrices. By PCA or FA, one can reduce the number of variables in a data set using findings of linear combinations of variables explaining most of the variability. It is commonly known that the independent variables in multiple linear

regression analysis can often be mutually inter-correlated and, therefore, are not directly suitable for this kind of analysis. On the other hand, such variables can be subjected to multivariate analysis such as PCA or FA. Using those techniques, all original parameters can be combined in a linear manner to the limited number of orthogonal principal components (factors) (4).

On the other hand, high-performance liquid chromatography (HPLC), which is the most widely used chromatographic technique in medicinal chemistry, can be used to determine some physicochemical measures, such as lipophilicity parameters for pharmacologically active compounds. It often combins the unique properties of HPLC retention parameters with a view to model the pharmacokinetic activities of drugs and is based on two general facts. The first one is associated with the fundamental processes of drug actions. Biological processes of absorption, distribution, excretion, and receptor binding are dynamic in nature, as is the analyte distribution process in chromatography. The same, or at least similar, basic intermolecular interactions determine the behavior of chemical compounds, both in biological and chromatographic environments. The second fact is that HPLC is a unique method producing large amounts of precise and reproducible data. More importantly, in contrast to biological systems, all experimental conditions in chromatography can be kept constant, and, finally, the analyte structure becomes the single independent variable in the analyzed system (5,6).

Pharmacological classification of a large set of drugs can be predicted on the basis of HPLC retention data using the chemometric method of analysis as the principal component analysis (PCA) (7–10). Therefore, structural descriptors derived by calculation chemistry, or based solely on the structural formula of a given compound in combination with HPLC retention data, can be found as a value of a wide application in QSAR analysis for predicting the pharmacological classification of drugs with the use of PCA (11–13).

The aim of the study was to test the influence of molecular modeling descriptors, obtained with the use of both semi-empirical and ab intio methods along with HPLC retention data, on the prediction of pharmacological classification of the selected drugs applying principal component analysis method. The following 20 pharmacologically closely related drugs were selected for the studies: acyclovir from a group of antiviral drugs (14); pyrantel from a group of antihelmintic drugs (15); metronidazole, ronidazole, and tinidazole from a group of antiprotozoal nitroimidazole antibiotics (16); ciprofloxacin, ofloxacin, and gatifloxcin from a group of antibacterial fluoroquinolones (17); sulphanilamide, sulphacetamide, sulphacarbamide, sulphaguanidine, sulphathiazole, sulphamethoxazole, sulphamoxol, sulphadiazine, sulphamerazine, sulphamethazine, sulphadimethoxine, and sulphaquinoxaline from a group of antibacterial sulphonamides (16).

Materials and Methods

Drugs

In all experiments, the following drugs were investigated. Acyclovir (1), pyrantel (2), metronidazole (3), tinidazole (5), sulphanilamide (9), sulphacetamide (10), sulphacarbamide (11),

sulphaguanidine (12), sulphadimethoxine (15), sulphaquinoxaline (16), and sulphathiazole (19) were from Polpharma S.A. (Starogard Gdanski, Poland). Sulphamerazine (13), sulphadiazine (14), sulphamoxol (17), sulphamethoxazole (18), and sulphamethazine (20) were from Sigma-Aldrich (Deisenhofen, Germany). Ronidazole (4) was from Menadiona S.A. (Barcelona, Spain). Ciprofloxacin (6) was from Madex Pharmaceuticals Ltd. (Logano, Switzerland). Ofloxacin (7) was from Ranbaxy Laboratories Ltd. (New Delhi, India), and gatifloxcin (8) was form Alfa Chem (Kings Points, NY).

Molecular descriptors

The structures of the tested compounds were preceded by molecular modeling with the use of HyperChem 7.5 software (HyperCube Inc., Gainesville, FL). First, the structures of the compounds were geometrically pre-optimized, applying a molecular mechanics force field procedure (with MM+ method). It allowed for the preparation of the drugs' structures for further optimization steps. The resulting structures were optimized then by means of the semi-empirical AM1 method and the Polak-Ribiere algorithm, and a gradient limit of 0.01 kcal/Å was used. Moreover, structures of compounds were geometrically optimized with the use of the *ab initio* 6-31G method along with the Polak-Ribiere algorithm, with a gradient limit of 0.01 kcal/Å.

The following molecular descriptors obtained with both semi-empirical and *ab initio* methods were taken under the following considerations: total energy (TE), highest occupied molecular orbital energy (E_HOMO), lowest unoccupied molecular orbital energy (E_LUMO), the values of the highest positive (MAX_POS), and negative (MAX_NEG) atom charges that constitute a molecule, total dipole moment (TDM), surface area of the molecule available for solvent (SA), and molecule volume (V).

Chromatographic analysis

Chromatographic analysis was performed with the use of a Waters SM 2690 Alliance HPLC system equipped with a PDA 996 diode detector (Waters Corporation, Milford, MA) and Compaq Deskpro computer (Compaq Computer Corporation, Houston, TX) with the Millennium 3.2 program for data collection and the process control. The following HPLC columns were employed: (*i*) XTerra RP$_{18}$ column, 50×3.0 mm i.d. (Waters Corporation, Milford, MA) packed with a hybrid stationary phase on the basis silica gel and silicaorganic compounds, with chemically bounded octadecylsilane, with particles size 5 µm; (*ii*) XTerra RP$_8$ column, 150×3.9 mm i.d. (Waters Corporation) packed with hybrid stationary phase on the basis silica gel and silicaorganic compounds, with chemically bounded octadecylsilane, with particles size 5 µm; (*iii*) IAM PC C$_{10}$/C$_3$ column, 150×4.6 mm i.d. (Regis Chemical Company, Morton Grove, IL) packed with silica propylamine with the unreacted propylamine moieties endcapped with methyl glycolate, and chemically bounded phosphatidylcholine, with particles size 12 µm; (*iv*) AGP column, 100×4.6 mm i.d. (ChromTech, Norsborg, Sweden) packed with silica gel with chemically bounded α_1-glycoprotein (AGP), with particles size 5 µm; and (*v*) Hypersil HSA column, 50×4.6 mm i.d. (Thermo-Hypersil-Keystone, Cheshire, UK), packed with silica gel and bounded human blood serum albumin, with particles size 5 µm.

The compounds studied were chromatographed in isocratic conditions on the columns mentioned previously at ambient temperature. The mobile phase was 100% 0.025 M phosphate buffer of pH 2.5 and 7.0. However, in the case of the AGP and Hypersil columns, the experiments were performed with propanol–0.025 M phosphate buffer of pH 7.0 with the proportion 5:95 (% v/v) (the higher ionic strength and the concentration of the organic modifier could cause denaturation of the protein as α1-glycoprotein or albumine bounded to silica gel stationary phase). The mobile phases used in HPLC were filtered through a GF–F glass microfiber filter (Whatman, Maidstone, UK) and degassed by ultrasonication immediately before use. The detection wavelength was 220 nm. The compounds studied were dissolved in methanol.

The logarithm of the HPLC retention factors (log k) for individually chromatographed compounds in the given chromatographic system were calculated, and their mean value obtained from 3 independent experiments were subjected to further principal component analysis.

Statistical analysis

The chemometric analysis was performed with the use of Statistica 8.0 software (StatSoft, Tulsa, OK) with the application of principal component analysis (PCA). The ordinal PCA method was used with earlier data normalization. Moreover, the criterions, such as the Kaiser criterion for the selection of statistically important factors, as well as the comprehensibility criterion for the selection factors important for scores for pharmacological interpretation, were used. Additionally, according to the rule that the highest PC (factor) loadings among the variables over 0.7 are statistically important, the parameters (descriptors) which have the most influence (significance) on the factors were selected. On the other hand, any direct clustering algorithms were not applied, and eventual clustering was done by individual marks done on two-dimensional scatter plot of the scores of some properties (pharmacologically and chemically related properties of the compound studied) connected clusters and/or subclusters.

Results and Discussion

The chemical structures of the considered 20 compounds are presented in Figure 1. The values of all parameters both from 8 HPLC retention parameters (XTerra RP18 2.5-Hypersil 7.0) as well as 16 structural descriptors (TE-V*) for considered compounds are presented in Table IA–IB. The results of the principal component analysis (factor 1 to factor 6) as eigenvalue, the percentage of the variance explained and the total variance explained, obtained with the use of all 24 parameters, are presented in Table II. The results of the principal component analysis obtained with the use of all 24 parameters are presented in Figure 2. Principal component analysis led to the extraction of five main factors with eigenvalue higher than 1 from the analyzed groups of parameters,
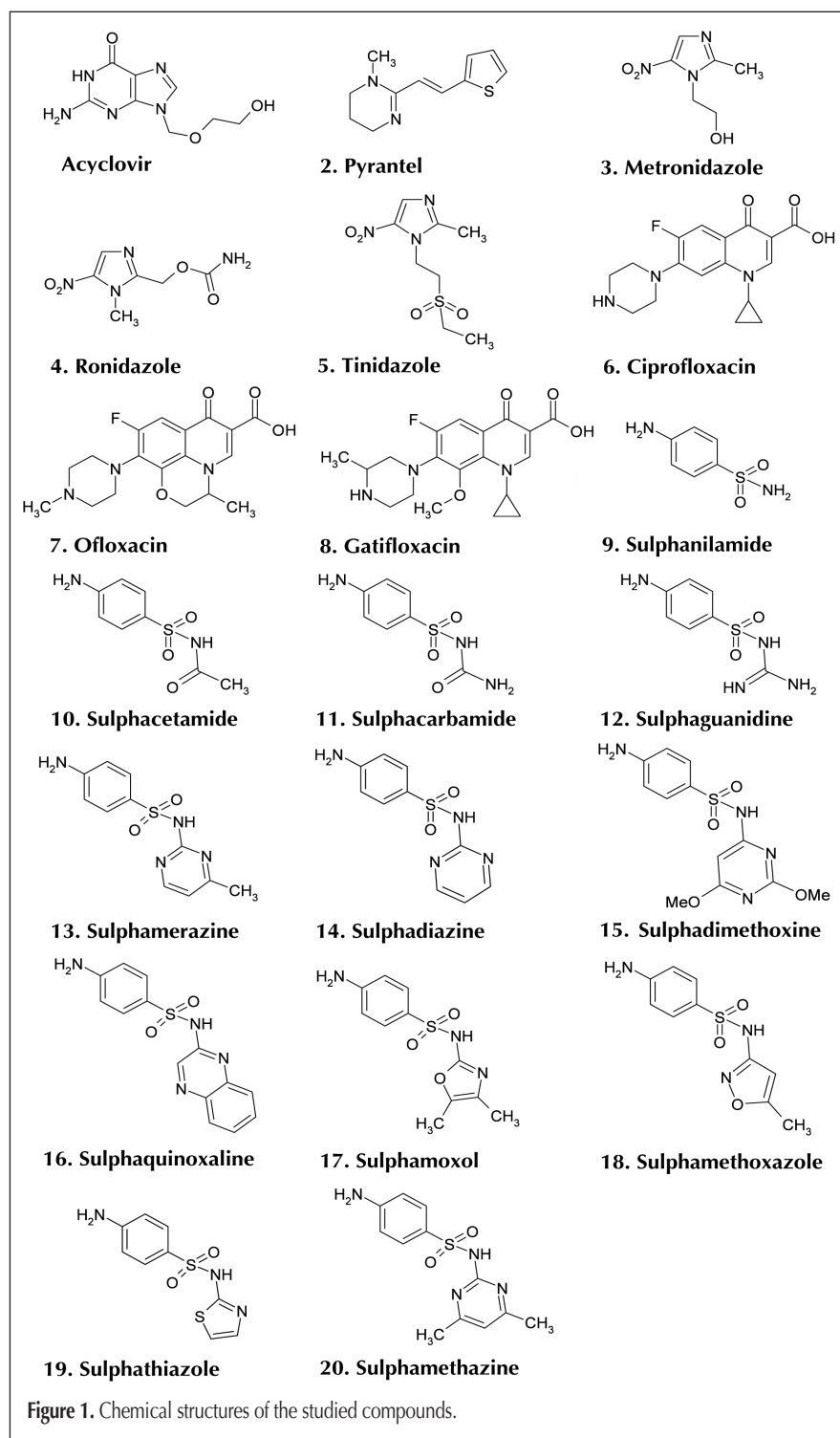

Figure 1. Chemical structures of the studied compounds.

Table IA. Values of HPLC Retention Data and Molecular Descriptors Used in the Principal Component Analysis*

	HPLC retention data							
Compound	XTerra RP18 2.5	XTerra RP18 7.0	XTerra RP8 2.5	XTerra RP8 7.0	IAM PC 2.5	IAM PC 7.0	AGP 7.0	Hypersil 7.0
1	0.43	0.56	0.34	0.45	0.10	0.16	–0.27	0.09
2	1.19	1.35	0.95	1.02	0.46	1.95	0.42	0.43
3	0.55	0.80	0.48	0.71	0.19	0.32	-0.28	0.11
4	0.79	0.82	0.73	0.75	0.34	0.30	–0.24	0.11
5	1.03	1.13	0.88	0.97	0.46	0.43	–0.29	0.11
6	2.22	1.70	1.28	1.19	1.30	1.84	0.18	0.51
7	2.03	2.24	1.20	1.26	1.00	1.66	0.20	0.57
8	2.53	1.95	1.37	1.37	1.48	1.93	0.08	0.47
9	0.36	0.44	0.40	0.49	0.26	0.32	–0.15	0.11
10	0.86	0.12	0.90	0.11	0.59	–0.12	–0.51	0.08
11	0.69	0.02	0.74	0.02	0.54	–0.12	–0.40	0.06
12	0.31	0.40	0.35	0.45	0.23	0.34	-0.10	0.16
13	1.13	1.16	1.12	1.13	0.94	0.92	0.11	0.55
14	0.93	0.58	0.93	0.56	0.65	0.24	–0.25	0.26
15	2.49	1.73	1.66	1.58	1.91	1.04	–0.08	1.85
16	2.65	1.94	1.73	1.83	2.26	1.23	0.24	1.90
17	1.39	1.46	1.26	1.31	0.92	0.91	0.01	0.45
18	1.67	0.85	1.62	0.77	1.35	0.35	–0.25	0.35
19	1.09	1.04	1.02	0.99	0.70	0.56	–0.11	0.34
20	1.27	1.46	1.12	1.30	0.75	0.84	0.02	0.33

* See the "Materials and methods" section for HPLC columns characteristics and definitions of molecular parameters.

with the first factor accounting for approximately 48% of the variance and the second for approximately 21%. These data indicated that the majority of the information (approximately 69%) contained in the original data matrix can be explained by two principal components, and it can be interpreted that the two principal components contain the significant part of information held previously in original HPLC retention and molecular properties variables. Moreover, the factor 1 depended mostly on log k values obtained generally on all used columns (factor loadings over 0.7) in the set of HPLC retention parameters, however, with less influence of such columns as AGP and Hypersil HSA with chemically bounded proteins. Additionally, factor 1 depended mostly on total energy (TE and TE*), surface area of the molecule available for solvent (SA and SA*), and the molecule volume (V and V*) in the set of molecular parameters obtained using both the semi-empirical and the *ab initio* methods. It is evident that these parameters reflect the size (bulkiness) of the compounds studied, and condenses mainly the information of their approximate molecular size. Chromatographically, the bulkiness of the dissolved compounds mostly reflects their

Table IB. Values of HPLC Retention Data and Molecular Descriptors Used in the Principal Component Analysis*

	Molecular descriptors															
	Semi-empirical AM1 method								*Ab initio* method							
Comp.	TE	E_HOMO	E_LUMO	MAX_POS	MAX_NEG	TDM	SA	V	TE*	E_HOMO*	E_LUMO*	MAX_POS*	MAX_NEG*	TDM*	SA*	V*
1	–3170	–8.7	–0.19	0.26	–0.33	4.0	424	657	–21928	–8.4	3.49	1.03	–1.04	6.6	407	638
2	–2208	–8.5	–0.26	0.77	–0.52	2.8	406	648	–25328	–7.7	2.35	0.71	–0.92	2.9	408	648
3	–2470	–10.0	–1.07	0.62	–0.39	3.7	332	508	–16869	–10.0	0.78	0.63	–0.95	3.5	329	502
4	–2984	–10.1	–1.07	0.62	–0.42	6.5	365	555	–20371	–10.3	0.79	1.02	–0.93	7.4	360	548
5	–3295	–10.1	–1.24	2.81	–0.94	2.1	415	666	–31840	–10.4	0.36	1.46	–0.96	2.4	440	679
6	–4490	–8.8	–0.66	0.37	–0.41	7.6	533	901	–31051	–8.2	2.24	0.79	–1.07	8.7	521	884
7	–4967	–9.0	–0.83	0.37	–0.41	7.3	553	948	–34150	–8.5	2.15	0.79	–1.07	8.4	550	944
8	–5121	–8.8	–0.74	0.37	–0.41	6.3	575	1000	–35210	–8.4	2.20	0.79	–1.07	7.7	567	990
9	–2127	–9.2	–0.33	2.88	–0.95	6.2	327	491	–24152	–8.8	2.92	1.71	–1.01	7.7	337	503
10	–2732	–9.4	–0.72	2.87	–0.94	4.2	381	595	–28280	–9.2	2.48	1.82	–1.11	9.1	385	605
11	–2797	–9.4	–0.75	2.88	–0.95	7.4	377	581	–28716	–9.1	2.42	1.80	–1.11	8.9	381	586
12	–2696	–9.4	–0.63	2.88	–0.95	7.8	387	598	–28175	–8.8	3.02	1.83	–1.09	10.8	395	611
13	–2925	–9.0	–0.65	2.89	–0.92	7.8	427	669	–39554	–9.0	2.52	1.79	–1.09	9.1	421	674
14	–3079	–9.2	–0.38	2.88	–0.92	5.1	436	684	–31265	–8.9	2.67	1.84	–1.14	7.6	444	693
15	–4031	–9.4	–0.65	2.87	–0.93	7.6	526	843	–37461	–9.2	2.48	1.80	–1.15	11.6	529	848
16	–3619	–9.1	–0.59	2.89	–0.92	6.6	507	816	–35417	–8.6	1.88	1.83	–1.18	8.6	510	822
17	–3362	–8.7	–0.59	2.88	–0.92	5.8	476	752	–32897	–8.6	2.87	1.82	–1.17	7.3	479	762
18	–3205	–9.3	–0.58	2.88	–0.93	8.8	449	700	–31834	–9.1	2.73	1.82	–1.16	12.7	454	710
19	–3236	–9.2	–0.49	2.89	–0.92	4.8	470	741	–32327	–8.9	2.86	1.84	–1.14	6.7	472	747
20	–3391	–9.2	–0.30	2.88	–0.92	4.6	493	792	–33389	8.8	3.00	1.84	–1.18	6.8	500	799

* See the "Materials and methods" section for HPLC columns characteristics and definitions of molecular parameters.

capacity to participate in non-specific interactions with the components of HPLC system. Moreover, negative values of factor 1 of HPLC retention parameters (loadings) proves that attractive dispersion interactions between the compound molecule and the moieties of the stationary phases are weaker than the corresponding dispersive interactions of the compound molecule and

Table II. Summation of the Results of the Principal Component Analysis

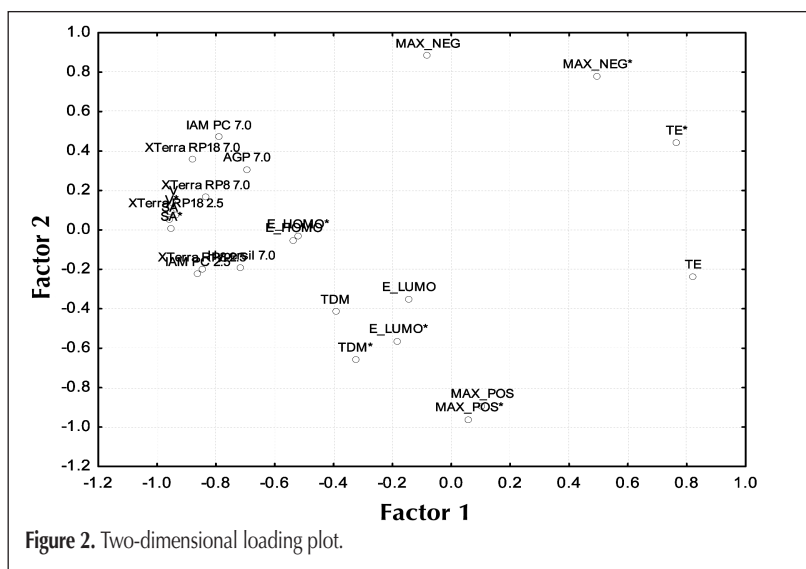| No. of factor	Eigenvalue	Variance explained (%)	Total variance explained (%)
1	11.47	47.81	47.81
2	5.04	20.98	68.79
3	3.30	13.75	82.54
4	1.62	6.76	89.31
5	1.13	4.69	94.00
6	0.57	2.36	96.36

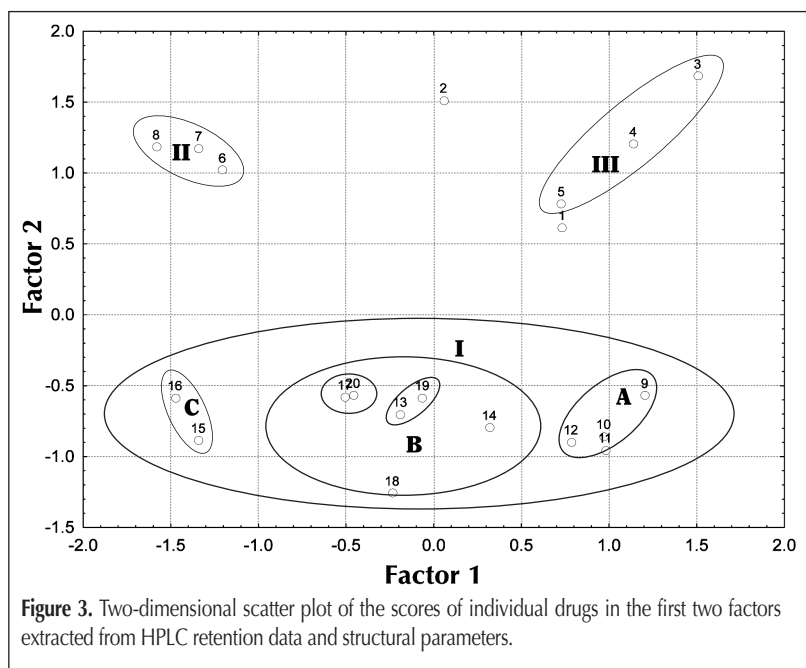**Figure 2.** Two-dimensional loading plot.

Figure 3. Two-dimensional scatter plot of the scores of individual drugs in the first two factors extracted from HPLC retention data and structural parameters.

the molecules of the eluent. On the other hand, the factor 2 depended mostly only on the values of the highest positive (MAX_POS and MAX_POS*) and negative (MAX_NEG and MAX_POS*) charge of the atoms that constitutes a molecule in the set of molecular parameters, also obtained from both the semi-empirical and the *ab initio* methods. In this case, factor 2 presented properties related to electronic properties rather than their bulkiness.

As it is indicated herein, a significant part of information (total data variance approximately 69%) can be explained by the first two principal components. Therefore, a comparison of particular compounds can be done on the basis of two principal component scores (objects) plots. The obtained principal component scores and positions of particular compounds on the plane determined by factors 1 and 2 obtained for all 24 considered parameters are presented in Figure 3. On the scatter diagram, the three main clusters (I–III) have shown differentiation in pharmacological features as well as in the chemical structure. The first main and the largest cluster I included compounds from a group of antibacterial sulphonamides (compounds 9–20), with the range of values of factor 1 from –1.5 to 1.2 and factor 2 from –0.3 to –0.5. Additionally, compounds from this main cluster I form three small clusters (see clusters IA–IC in Figure 3), and show generally the similarities and dissimilarities in the chemical structures of the antibacterial sulphonamides studied. It is also important to note that antibacterial sulphonamides are active against *chlamydia* and both Gram-positive and Gram-negative bacteria, and inhibit folic acid biosynthesis in prokaryotes by blocking the synthesis of dihydrofolic acid by inhibition of the dihydropteroate synthase (16). The positions of compounds such as sulphacetamide (10), sulphacarbamide (11), and sulphaguanidine (12) with sulphanilamide (9), a little further away form cluster (see cluster IA in Figure 3), comprising un-substituted sulphonamides and N1-substituted by non-heterocyclic groups such as acetylcarbonyl–, aminocarbonyl–, and aminoiminometyl–. The points on the diagram of compounds such as sulphamerazine (13), sulphadiazine (14), sulphamoxol (17), sulphamethoxazole (18), sulphathiazole (19), and sulphamethazine (20) form the next cluster (see cluster IB in Figure 3), comprising sulphonamides N1-substituted by five- or six-atoms heterocyclic groups (thiazole or a pyrimidine ring) being un-substituted or methyl-substituted (isoxazole and oxazole, or a pyrimidine ring), compared to the cluster (see cluster IC in Figure 3) including other chemically structural sulphonamides such as sulphadimetxoxine (15) with two methoxyl- group linked to an N1-substituted by six-atoms heterocyclic pyrimidine ring, and sulpaquinoxaline (16) with N1-substituted by two six-atoms heterocyclic quinoxaline group. Moreover, compounds such as sulphamoxol (17) and sulphamethazine (20), and compounds such as sulphamerazine (13) and sulphathiazole (19) form two

small clusters in cluster IB. The first cluster contains two methyl-substituted sulphonamides, and the second one contains sulphonamides with one methyl-substituted of N1-heterocyclic group, respectively.

On the scatter diagram (cluster II, Figure 3), the second main cluster, however small, was also observed and formed by the antibacterial fluoroquinolones ciprofloxacin (6), ofloxacin (7), and gatifloxacin (8) with the range of values of factor 1 from –1.6 to –1.2 and factor 2 from 1.0 to 1.2, and characterized a broad-spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria by inhibiting bacterial enzymes, DNA gyrase and topoisomerase IV (17). Additionally, the compounds ciprofloxacin (6) and gatifloxacin (7) are closer together and show their chemical structure-related similarities connected with the presence of the same cyclopropyl- group attached to a quinoline ring.

Moreover, on the scatter diagram (cluster III, Figure 3) the third main, but small and scattered cluster is located and formed by compounds from the group of antiprotozoal nitroimidazole antibiotics such as metronidazole (3), ronidazole (4), and tinidazole (5), with the range of values of factor 1 from 0.7 to 1.5 and factor 2 from 0.7 to 1.7. Some distances between compounds located in this cluster are probably connected with their dissimilarities in chemical structures as well as in some of their additional pharmacological properties. Metronidazole (2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethanol) and tinidazole (1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole) are mainly used in the treatment of infections caused by amoebae, anaerobic bacteria and protozoa as well as in the treatment of vaginal *Trichomona* and *Helicobacter pylori*, whereas ronidazole (1-methyl-2-(carbamoyloxymethyl)-5-nitroimidazole) is characterized by *in vivo* antiparasitic and antimycoplasmal activity, and also by some *in vivo* antibacterial activity (16).

Finally, on the scatter diagram, Figure 3, there are two drugs acyclovir (1) and pyrantel (2) not classified in any of the proposed and pharmacologically related three main clusters. The latter compound belongs to antihelmintic agents used in the treatment of helminthes, hookworms, and roundworms (15). On the other hand, aciclovir is a guanosine analogue antiviral drug used for the treatment of herpes simplex virus infections, as well as in the treatment of varicella zoster virus (14), and its location on the scatter diagram (Figure 3) near tinidazole (5), located in a cluster of antiprotozoal nitroimidazole antibiotics seems to be rather unexpected.

Conclusions

Concluding the observations presented herein, the distribution of individual drugs on the plane determined by two factors obtained on the basis of molecular modeling structural parameters with the use of both the semi-empirical and the *ab initio* methods, and log k values as theHPLC retention data produced patterns in good agreement with pharmacological properties as well as the chemical structures of the drugs in question.

From among all the 24 parameters, the most influence on the value of factor 1 possessed all chromatographic parameters and selected structural parameters reflecting the size (bulkiness) of the compounds studied, in contrast to the lower influence related to the electronic properties of the drugs the value of the factor 2.

References

1. C.J. Cramer. *Essentials of Computational Chemistry*, John Wiley & Sons, 2002.
2. K.I. Ramachandran, G. Deepa, and P.K. Krishnan Namboori. *Computational Chemistry and Molecular Modeling Principles and Applications*, Springer-Verlag GmbH, Berlin Heidelberg, 2008.
3. R. Todeschini, V. Consonni, R. Mannhold, H. Kubinyi, and H. Timmerman. *Handbook of Molecular Descriptors*, Wiley-VCH, Weinheim 2000.
4. S. Wold, C. Albano, W.J. Dunn III, U. Edlund, K. Esbensen, P. Gelodi, S. Hellberg, E. Johansson, W. Lindberg, and M. Sjostomin: B.R. Kowalski (Ed.). *Chemometrics*, Reidel, Dordrech 1984.
5. R. Kaliszan. *Structure and Retention in Chromatography. A Chemometric Approach*, Harwood Academic, Amsterdam 1997.
6. M.H. Abraham, H.S. Chadha, R.A.E. Leitao, R.C. Mitchell, W.J. Lambert, R. Kaliszan, A. Nasal, and P. Haber. Determination of solute lipophilicity, as log P(octanol) and log P(alkane) using poly(styrene-divinylbenzene) and immobilised artificial membrane stationary phases in reversed-phase high-performance liquid chromatography. *J. Chromatogr. A* **766:** 35–47 (1997).
7. R. Gami-Yilinkou, A. Nasal, and R. Kaliszan. Application of chemometrically processed chromatographic data for pharmacologically relevant classification of antihistamine drugs. *J. Chromatogr.* **633:** 57–63 (1993).
8. J. Petrusewicz, R. Gami-Yilinkou, R. Kaliszan, B. Pilarski, and H. Foks. Pyrazine CH- and NH-acids. Antithrombotic activity and chromatographic behaviour. *Gen. Pharmacol.* **24:** 17–22 (1993).
9. A. Nasal, A. Bucinski, L. Bober, and R. Kaliszan. Prediction of pharmacological classification by means of chromatographic parameters processed by principal component analysis. *Int. J. Pharm.* **159:** 43–55 (1997).
10. A. Nasal, A. Wojdełko, T. Baczek, R. Kaliszan, M. Cybulski, and Z. Chilmonczyk. Relationship between chromatographic behavior and affinity to 5–HT1A serotonin receptors of new buspirone analogues. *J. Sep. Sci.* **25:** 273–279 (2002).
11. M. Koba, J. Stasiak, L. Bober, and T. Baczek. Evaluation of molecular descriptors and HPLC retention data of analgesic and anti-inflamatory drugs by factor analysis in relation to their pharmacological activity. *J. Mol. Model.* **16:** 1319–1331 (2010).
12. J. Stasiak, M. Koba, L. Bober and T. Baczek. Principal Component Analysis of HPLC Retention Data and Molecular Modeling Structural Parameters of Cardiovascular System Drugs in View of Their Pharmacological Activity. *Int. J. Mol. Sci.* **11:** 2681–2698 (2010).
13. M. Koba, L. Bober, U. Judycka-Proma, and T. Baczek. Influence of HPLC retention data and molecular modeling descriptors on prediction of pharmacological classification of drugs using principal component analysis method. *Comb. Chem. High Throughput Screen.* **13:** 765–776 (2010).
14. J.J. O'Brien and D.M. Campoli-Richards. Aciclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* **37:** 233–309 (1989).
15. R.J. Martin. Modes of action of anthelmintic drugs. *Vet. J.* **154:** 11–34 (1997).
16. S. Rossi. *Australian Medicines Handbook*, Australian Medicines Handbook Pty Ltd., Adelaide, 5th ed. 2004.
17. C.M. Oliphant and G.M. Green. Quinolones: a comprehensive review. *Am. Fam. Physician* **65:** 455–464 (2002).