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Abstract: Factor analysis (FA) was performed for some analgesic, anti-inflammatory and antipyretic drugs to model relationships between molecular descriptors and HPLC retention parameters. Factor analysis obtained with the use of various sets of parameters as structural parameters (including 26 parameters), HPLC retention data (including 26 parameters), and altogether considered parameters (including all 52 parameters) led to extract two main factors. The first principal component (factor 1) accounted for by 65-73% of the variance in the data. The second principal component (factor 2) explained 27-35% of data variance. Moreover, among 52 parameters the high highest influence on the value of the factors have had chromatographic parameters and selected structural parameters (i.e. to energy quantum-chemical parameters and electron affinity specifying parameters). Additionally, distribution of individual drugs on the plane determined by two principal components (factors 1 and 2) enabled to obtain pattern in good agreement with their pharmacological (analgesic, anti-inflammatory and antipyretic) features, what was discussed finally in view of structure-activity relationships.

Response to Reviewers: Responses to Referee Comments

1) "The English language and certain terms must undergo major revision. For instance,"
"a. On page 3, line 2: "also know as a pain killers", would be better replaced by "also know as pain killers""

The present version of the manuscript has been corrected according to kind suggestions of the Reviewer.

"b. On page 3, last line: "phenoles", would be better replaced by "phenols""
Corrected.

"c. On page 4, lines 16 and 17: the AM1 method, although relevant, should not be considered "sophisticated" as the authors say. Currently, there are far more advanced methods in computational chemistry"

Yes, we agree with the Reviewer that AM1 method cannot be considered directly as "sophisticated". The current of the manuscript has been corrected taking into account that fact.

"d. On page 5, line 19: although it is not wrong, the term "polycratically" has a very limited use in technical texts"

It is true, in fact. Instead of "polycratically" just the term "isocratic conditions", which is of common use, was applied in the present version of the text.

"e. On page 7, line 19: the term "binding energy" appears for the first time without being previously defined"

Corrected. Now, the term "binding energy" was defined also on page 4, line 19 along with all other descriptors used in the study.

"2) In some parts of the text there are inaccuracies or the meaning is not clear. For instance,"

"a. On page 7, lines 25 and 26: The authors conclude "Namely, factor 1 presented mainly properties connected with molecular bulkiness, whereas factor 2 presented properties related to molecular polarity. I think that the terms "binding energy (BE), atom interaction energy (IAE), electron energy (EE), electronegativity (EN) and electron orbital density HOMO (ED_HOMO)" on lines 19 and 20 of the same page are not correlated with bulkiness"

We agree that the "binding energy (BE), atom interaction energy (IAE), electron energy (EE), electronegativity (EN) and electron orbital density HOMO (ED_HOMO) cannot be related evidently to the molecular bulkiness. That mistake was corrected in the current version of the text.

"b. On page 8, line 4: "more influence have depended on pH polar properties of molecules""

The sentence was corrected. The final version should be as following "more influence have depended on polar properties of molecules".

"c. On page 8, line 13: "almost the where information (total data variance) can be explained by the first two principal components""

The sentence was corrected. The final version should be as following "almost the whole information (total data variance) can be explained by the first two principal components".

"d. On page 8, line 27: with respect to the piroxicam the authors refer "moderate anti-inflammatory and analgesic activity". On the other hand, Attia et al. (Int J Pharm. 2004 May 19;276(1-2):11-28) refer piroxicam as a strong anti-inflammatory and analgesic agent. Whereas the classification of drugs is not precise (strong, moderate or low activity/effect) I am afraid that other disagreements as mentioned above can be found for other drugs of this work."

Information on classification of drugs according to their anti-inflammatory and analgesic activity can be found in the literature. However, there is a common difficulty to find the whole classification just in one source comprising all available anti-inflammatory drugs. Moreover, it is true that depending on the source, that classification cannot be equivocal and precise enough. Disagreements related to strong, moderate or low activity of the individual anti-inflammatory drugs can be really found and they result probably often because of the scientific approach applied in the literature source. It is quite reasonable that scientific papers discuss different anti-inflammatory drugs proposing in variable manner their activity strength taking into account the selected drugs. Nevertheless, some agreements can be found and provided, and the final classification can be done according to the internationally recognized literature. In the current version of the manuscript we proposed the compiled classification of the drugs of interest. It allowed the more precise discussion of the results obtained. What is even more important, the conclusions drawn are similar to the previous one and are justified additionally by the literature data. Modified version of manuscript was supplemented with that information and discussed in the text.

Evaluation of the molecular and HPLC retention data of analgesic and *anti-inflammatory* drugs by factor analysis in view of their pharmacological activity

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Abstract

Factor analysis (FA) was performed for some analgesic, *anti-inflammatory* and antipyretic drugs to model relationships between molecular descriptors and HPLC retention parameters. Factor analysis obtained with the use of various sets of parameters as structural parameters (including 26 parameters), HPLC retention data (including 26 parameters), and altogether considered parameters (including all 52 parameters) led to extract two main factors. The first principal component (factor 1) accounted for by 65-73% of the variance in the data. The second principal component (factor 2) explained 27-35% of data variance. Moreover, among 52 parameters the high hest influence on the value of the factors have had chromatographic parameters and selected structural parameters (*i.e.* to energy quantum-chemical parameters and electron affinity specifying parameters). Additionally, distribution of individual drugs on the plane determined by two principal components (factors 1 and 2) enabled to obtain pattern in good agreement with their pharmacological (analgesic, *anti-inflammatory* and antipyretic) features, what was discussed finally in view of structure-activity relationships.

Keywords Analgesic and *anti-inflammatory* drugs · Factor analysis (FA) · Molecular modeling · High-performance liquid chromatography (HPLC)

Introduction

Analgesics (also known as pain killers) are members of a diverse group of drugs used to relieve pain. The word *analgesic* was derived from Greek with *an-* ("without") and *algos-* ("pain"). Analgesic drugs act in various ways on the peripheral and central nervous systems and include non-steroidal *anti-inflammatory* drugs (NSAIDs) as acetaminophen [1-2], aminophenazone [2], acetylsalicylic acid (ASA) [2-3], diclofenac [4-5], etodolac [4-7], ketorolac [6, 8], nimesulide [9-10], noramidopyrine [11-12], piroxicam [5], salicylamide [11-12], sulindac [13], or synthetic drugs with narcotic properties such as tramadol [14], and many others. Analgesics usually are drugs with antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with *anti-inflammatory* effects. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other disorders, such as cancer and cardiovascular disease. Analgesics are generally indicated for the symptomatic relief of the following disorders: rheumatoid arthritis, osteoarthritis, inflammatory arthropathies (*e.g.*, ankylosing spondylitis, psoriatic arthritis, and Reiter's syndrome), acute gout, dysmenorrhoea (menstrual pain), metastatic bone pain, headache and migraine or postoperative pain. They have also been found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer.

Factor analysis (FA) is a chemometric technique based on principle component analysis (PCA), which belongs to data-processing method intending to extract and visualize systematic patterns or trends in large data sets. By FA, one reduces the number of variables in a data set by finding linear combinations of those variables that explains most of the variability. Unfortunately, the independent variables applied were often mutually *inter-correlated*. For this reason, *inter-correlated* chemical, spectroscopic, chromatographic and other data are often unsuitable for direct multiple regression analysis and can be subjected to multivariate analysis as factor analysis. In other words, by FA all those original parameters which are interrelated by simple or multiple correlations are linearly combined to two orthogonal principal components (factors). So far FA (or PCA) was applied for classification of a number of compounds (drugs) with HPLC retention data [15-19], TLC data [20-23] or others [24].

The subject of the presented work was to determine the relationships between HPLC retention parameters of a series of drugs differing in chemical structure and characterized by similar pharmacological (analgesic, *anti-inflammatory* and antipyretic) activity and their structural

parameters obtained by molecular modeling calculations applying factor analysis method. The following 12 compounds: acetaminophen, aminophenazone, acetylsalicylic acid, diclofenac, etodolac, ketorolac, nimesulide, noramidopyrine, piroxicam, salicylamide, sulindac and tramadol, were selected to the proposed studies. These drugs belong to weak carboxylic acids (ASA, diclofenac, etodolac, ketorolac, sulindac), free bases (aminophenazone and tramadol), sulfonic acids (noramidopyrine), sulfonamides (nimesulide), amides (salicylamide), phenols (acetaminophen) or enoloacids (piroxicam). The aim of the work was to evaluate the relationships between structural molecular descriptors along with chromatographic data obtained for the studied analgesics in view of their pharmacological activity by means of factor analysis.

Materials and methods

Drugs

In all experiments the following drugs were investigated: (1) acetylsalicylic acid (ASA), (2) salicylamide, (3) diclofenac (as sodium salt), (4) noramidopyrine (as sodium salt), all from Polpharma S.A., Starogard Gdański, Poland; (5) acetaminophen from Rhône-Poulenc, Köln, Germany; (6) aminophenazone from Polfa, Pabianice, Poland; (7) etodolac from Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel; (8) ketorolac from Ranbaxy, New Delhi, India; (9) nimesulide from Chemex GmbH, Wien, Austria; (10) piroxicam from Jelfa, Jelenia Góra, Poland; (11) sulindac from Dipharma, Basiliano, Italy and (12) tramadol (as hydrochloride) from Grünenthal GmbH, Aachen, Stoltenberg, Germany.

Structural parameters

The structures of the tested compounds were investigated by molecular modeling with the use of HyperChem 7.5 software (HyperCube Inc., Gainesville, FL, USA). First, the structures of the compounds were pre-optimized geometrically with the molecular mechanics force field procedure (with MM+ method). It allowed to prepare structures for further optimization steps. The resulting structures were optimized then by means of the quantum-based method, namely semi-empirical AM1 method and applying the Polak-Ribiere algorithm with gradient limit of $0.01 \text{ kcal } \text{Å}^{-1}$.

The following molecular descriptors were considered: total energy (TE), binding energy (BE), atom interaction energy (IAE), electronic energy (EE), heat of formation (HF), highest occupied molecular orbital energy (EHOMO), lowest unoccupied molecular orbital energy (ELUMO), ionization energy (potential) (IE_IP) and electron affinity (EA). That last descriptor was calculated as the differences between the heat of molecular positive ion formation and neutral molecules (ionization potential) or between molecular negative ion and neutral molecules (electron affinity), expressed in electronvolts. Electronegativity (EN) was calculated as an arithmetic mean of ionization potential and electron affinity according to Mulliken [25-26]. The “hardness” of molecules (HARD) was calculated according to Parr and Pearson [27] as well as Robles and Bartolotti [28] and presented as half of the difference between the ionization potential and the electron affinity. Additionally, the following values were used: the highest (ED_MAX) and the lowest (ED_MIN) free electron density, electron orbital density HOMO (ED_HOMO) and LUMO (ED_LUMO), the values of the highest positive (MAX_POS) and negative (MAX_NEG) charge of atoms that constitute a molecule, the difference between the highest positive and negative charges of atoms constituting a molecule (DELTA_Q), total dipole moment (TDM), energy equivalent to the length of the longest electron transition for which the energy value of an oscillator was different than zero (E_L), and the value of the most intensive one for which the energy value of an oscillator took the maximum value of electron transition (E_MAX) (the value of wave numbers calculated into eV), as well as the maximum energy value of the oscillator (OS_EMAX).

Moreover, other structural parameters were considered: partial values of molar volume in water (V_MOL) and the interaction energy with water (E_INT) calculated by the ChromSword 1.0 program (Merck, Darmstadt, Germany). The logarithms of the *n*-octanol-water partition coefficient (LG_P), which reflect the hydrophobicity of the drugs studied, were calculated according to Nys and Rekker [29]. Molecular refractivity (MR) was calculated as the sum of the bond refractivities for all pairs of connected atoms.

Chromatographic analysis

Chromatographic analysis was performed with a Waters SM 2690 Alliance HPLC system equipped with a PDA 996 diode detector (Waters Corporation, Milford, MA, USA) and Compaq Deskpro computer (Compaq Computer Corporation, Houston, TX, USA) with the Millennium 3.2 program for data collection and the process control. The following HPLC columns were employed: (a) Nucleosil C18 AB column, 50 x 3.0 mm i.d. (Macherey-Nagel,

Düren, Germany), packed with octadecylsilica with particles size 5 μm ; (b) Nucleogel 100-5 RP column, 150 x 4.6 mm i.d. (Macherey-Nagel, Düren, Germany), packed with polystyrene copolymer cross-linked by divinylbenzene with particles size 5 μm ; (c) Aluspher RP select B column, 125 x 4.0 mm i.d. (Merck, Darmstadt, Germany), packed with aluminum oxide with chemically bounded polybutadiene, with particles size 5 μm .

The compounds studied were chromatographed applying isocratic conditions on the mentioned above columns at ambient temperature. The mobile phases were acetonitrile:0.01 M phosphate buffer of pH 2.5, 7.0 or 11.0, methanol:0.01 M phosphate buffer of pH 2.5, 7.0 or 11.0, tetrahydrofuran:0.01 M phosphate buffer of pH 2.5, 7.0 or 11.0 with the following proportions 70:30, 60:40, 50:50, 40:60 and 30:70 (% v/v). However, in the case of Nucleosil C18 AB column, experiments were performed only at pH 2.5 and 7.0, because stationary phases on the basis of silica gel are sensitive to media with pH > 8 and hydrolysis of the chemically bounded phase with silica and silica dissolution were observed. The detection wavelength was 254 nm. Additionally, all 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 compounds studied were dissolved in methanol.

The logarithms of the HPLC retention factors ($\log k$) for particular chromatographed compounds in the given chromatographic system were regressed against the volume fraction of organic modifier in the eluent. The linear part of relationship was extrapolated to a hypothetical retention factor corresponding to 0% of organic modifier in the mobile phase. The resulting retention parameters were normalized to pure buffer using linear or quadratic extrapolation and defined as $\log k_{w(L)}$ or $\log k_{w(SQ)}$, respectively. Those HPLC retention parameters were subjected further to factor analysis. Their symbols are presented below and were derived from buffer pH, column's name, type of organic modifier in the mobile phase used in chromatographic system, and type of data extrapolation:

LGKW2NAL – Nucleosil C18 AB, acetonitrile:buffer pH 2.5, linear extrapolation

LGKW2NAS – Nucleosil C18 AB, acetonitrile:buffer pH 2.5, quadratic extrapolation

LGKW7NAL – Nucleosil C18 AB, acetonitrile:buffer pH 7.0, linear extrapolation

LGKW7NAS – Nucleosil C18 AB, acetonitrile:buffer pH 7.0, quadratic extrapolation

LGKW2NML – Nucleosil C18 AB, methanol:buffer pH 2.5, linear extrapolation

LGKW2NMS – Nucleosil C18 AB, methanol:buffer pH 2.5, quadratic extrapolation

LGKW7NML – Nucleosil C18 AB, methanol:buffer pH 7.0, linear extrapolation
LGKW7NMS – Nucleosil C18 AB, methanol:buffer pH 7.0, quadratic extrapolation
LGKW2NTL – Nucleosil C18 AB, tetrahydrofuran:buffer pH 2.5, linear extrapolation
LGKW2NTS – Nucleosil C18 AB, tetrahydrofuran:buffer pH 2.5, quadratic extrapolation
LGKW7NTL – Nucleosil C18 AB, tetrahydrofuran:buffer pH 7.0, linear extrapolation
LGKW7NTS – Nucleosil C18 AB, tetrahydrofuran:buffer pH 7.0, quadratic extrapolation
LGKW2GL – Nucleogel 100-5 RP, acetonitrile:buffer pH 2.5, linear extrapolation
LGKW2GSQ – Nucleogel 100-5 RP, acetonitrile:buffer pH 2.5,quadratic extrapolation
LGKW7GL – Nucleogel 100-5 RP, acetonitrile:buffer pH 7.0, linear extrapolation
LGKW7GSQ – Nucleogel 100-5 RP, acetonitrile:buffer pH 7.0, quadratic extrapolation
LGKW7GHL – Nucleogel 100-5 RP, acetonitrile:buffer pH 7.0, linear extrapolation
LGKW7GHS – Nucleogel 100-5 RP, acetonitrile:buffer pH 7.0, quadratic extrapolation
LGKW11GL – Nucleogel 100-5 RP, acetonitrile:buffer pH 11.0, linear extrapolation
LGKW11GS – Nucleogel 100-5 RP, acetonitrile:buffer pH 11.0, quadratic extrapolation
LGKW2AL – Aluspher RP select B, acetonitrile:buffer pH 2.5, linear extrapolation
LGKW2ASQ – Aluspher RP select B, acetonitrile:buffer pH 2.5, quadratic extrapolation
LGKW7AL – Aluspher RP select B, acetonitrile:buffer pH 7.0, linear extrapolation
LGKW7ASQ – Aluspher RP select B, acetonitrile:buffer pH 7.0,quadratic extrapolation
LGKW11AL – Aluspher RP select B, acetonitrile:buffer pH 11.0, linear extrapolation
LGKW11AS – Aluspher RP select B, acetonitrile:buffer pH 11.0,quadratic extrapolation.

Statistical analysis

The chemometric analysis allowing the discussion on quantitative structure-activity relationships (QSAR) was performed with the use of Statistica 5.1 software (StatSoft, Tulsa, OK, USA) with the application of factor analysis (FA) with optimized Varimax method for factors rotation.

Results and discussion

The chemical structures of the considered compounds are presented in Fig. 1. The values of all 52 structural parameters used for 12 selected compounds are presented in Table 1. The results of factor analysis which represent the first two loadings (factor 1 and 2) of each variables and their two-dimensional scatter plots obtained with the use of various sets of parameters as structural parameters, HPLC retention data, all parameters (comprising all 52 parameters from structural parameters and HPLC retention data) were collected in Table 2 and Fig. 2A, Table 3 and Fig. 2B, Table 4 and Fig. 2C, respectively. The highest factor loadings among the variables over 0.7 were presented in bold type. Factor analysis led to extract two main factors from all analyzed groups of parameters. In the set of structural parameters (Fig. 2A) the first factor accounted for by 67% of the data variance and the second one for by 33%. On the other hand, in the set of HPLC retention data (Fig. 2B) and all 52 parameters (Fig. 2C) the first factor accounted for by 73.2% and 64.6% of the data variance, respectively, and second one for by 26.8% and 35.4%, respectively. The obtained data indicated that the majority of the information contained in the original data matrix can be explained by two principal components. It can be interpreted that two principal components contain almost the whole information held previously in original variables. Moreover, in the set of structural parameters (Fig. 2A) the factor 1 depended mostly on molar volume (V_MOL), molar refractivity (MR), total energy (TE), binding energy (BE), atom interaction energy (IAE), electron energy (EE), electronegativity (EN) and electron orbital density HOMO (ED_HOMO), whereas factor 2 depended mostly on electron affinity (EA), hardness (HARD), LUMO energy (ELUMO), the values of the highest positive (MAX_POS) and negative (MAX_NEG) charge of atoms that constitutes a molecule and the difference between the highest positive and negative charges of atoms constituting a molecule (DELTA_Q). The results were in accordance with previous observations [30] for similar considerations on structural parameters. Namely, factor 1 presented mainly properties connected with molecular bulkiness (like V_MOL, MR or TE), whereas factor 2 presented properties related to electronic properties (like ELUMO, MAX_POS, MAX_NEG or DELTA_Q).

In the case of the set of HPLC retention data (Fig. 2B) factor 1 depended mostly on chromatographically data linked hydrophobicity parameters ($\log k_w$) achieved mainly at pH 2.5 on all tested columns, buffers, type of organic modifier in mobile phase and type of data extrapolation, as well as $\log k_w$ values obtained only on Nucleosil C18 AB column at pH 7.0.

On the other hand, factor 2 depended mainly on $\log k_w$ parameters obtained at pH 7.0 but only on columns packed with stationary phases other than octadecylsilica, *i.e.*, Nucleogel 100-5 RP and Aluspher RP select B columns, packed with polystyrene copolymer cross-linked by divinylbenzene and aluminium oxide with chemically bounded polybutadiene, respectively. These observations indicated that in the case of retention data obtained on stationary phases on the basis of polystyrene copolymer cross-linked by divinylbenzene or aluminium oxide with chemically bounded polybutadiene, more influence have depended on polar properties of molecules of studied compounds, than their bulkiness or masses.

In the set of all parameters considered (Fig. 2C) factor 1 depended only on the majority of chromatographic parameters (except of data obtained on Aluspher RP select B column at pH 7.0 and 11.0). However, factor 2 depended mainly on the compound's interaction energy with water (E_{INT}), total energy (TE), electron affinity (EA) and electronegativity (EN), LUMO energy (ELUMO) and the values of the highest positive (MAX_POS) and negative (MAX_NEG) charge of atoms that constitute a molecule, the difference between the highest positive negative charges of atoms constituting a molecule (ΔQ) and the value of the most intensive electron transition for which the energy value of an oscillator took the maximum value (E_{MAX}).

As it was indicate above, almost the whole information (total data variance) can be explained by the first two principal components. Therefore, comparison of particular compounds can be done on the basis of two principal component scores (objects) plots. Principal component scores calculated for all studied compounds and their individual positions on the plane determined by the two factor axes and performed only for structural parameters, only for HPLC retention data, and for all considered above parameters are presented in Table 5 and Fig. 3A-C. The comparison of activities of the selected compounds was quite difficult because of the needs to compare the results of pharmacological research made in the same conditions. Moreover, most of the studied compounds possess various pharmacological properties (analgesic, *anti-inflammatory*, antipyretic and also *anti-rheumatic*), and it would be necessary to estimate their activity in the mentioned aspects. The classification of *anti-inflammatory* drugs according to their analgesic, *anti-inflammatory* and antipyretic activity based on literature data is presented in Table 6. Moreover, it is important to note, that in some previous works [15-17] it was established that compounds characterized by identical mechanism of action in the charts of factor analysis form clusters, *e.g.*, classifications of compounds of α - and β -adrenergic action, antagonists of histamine receptors H_1 and H_2 and psychotropic drugs.

The positions of particular compounds on the plane determined by factors 1 and 2 obtained for structural parameters was presented in Fig. 3A and characterized by an arrangement in to three clusters. In the case of the first cluster, the most closely were noramidopyrine, piroxicam and sulindac, with further lied nimesulide. All these compounds are characterized by strong (piroxicam and sulindac) or mild (noramidopyrine and nimesulide) analgesic and diverse (low to strong) *anti*-inflammatory activity, with additional mild antipyretic activity of noramidopyrine and sulindac (Table 6) [31-36]. Moreover, all presented compounds possess in their structure sulfur atom. On scatter diagram (Fig. 3A) a clusters was made by acetylsalicylic acid (ASA), salicylamide (derivative of salicylic acid) with further oriented acetaminophen (derivative of *p*-aminophenole). Acetaminophen as well as derivatives of salicylic acid are characterized by strong antipyretic and analgesic activity with mild *anti*-inflammatory properties (Table 6). Additionally, other drugs such as tramadol, aminophenazone, diclofenac and ketorolac as compounds with unsubstituted or chlorine or methoxy- substituted phenyl group with linked some aromatic systems (as pyrazole, *o*-aminophenylacetic acid residue, pyrrolepyrrolidine or cycloheksanol) form the last cluster characterized by variable analgesic, *anti*-inflammatory and antipyretic activity (Table 6). Aminophenazone analgesic and *anti*-inflammatory activity can be lower and higher, respectively, compared to analgesic and *anti*-inflammatory activity of salicylic acid derivatives whereas diclofenac is characterized by similar or lower *anti*-inflammatory and antipyretic activity compared to salicylates. On the other hand, ketorolac is characterized by mild and tramadol by strong analgesic activity with their low *anti*-inflammatory and without antipyretic properties [37-39].

The positions of particular compounds on the plane determined by factors 1 and 2 obtained by HPLC retention data is presented in Fig. 3B. On the scatter diagram the small cluster containing diclofenac, etodolac and nimesulide was observed, which is rather related to their strong *anti*-inflammatory and *anti*-rheumatic activity. Moreover, on that diagram one can also identify two other clusters comprising 1) piroxicam, ketorolac and sulindac, and 2) acetaminophen, noramidopyrine and ASA, what can be connected with mild or strong analgesic activity in the case of compounds from cluster 1), and mild or strong antipyretic activity in the case of compounds from cluster 2) presented above (Table 6).

Fig. 3C presents the positions of particular compounds on the plane determined by factors 1 and 2 obtained for all 52 parameters. In this case, particular compounds were generally more scattered compared to above mentioned diagrams (Fig. 3A-B). This time three clusters comprising only 1) etodolac and diclofenac, 2) salicylamide and aminophenazone and 3)

acetaminophen and ASA can be distinguished, what can be connected with strong *anti-inflammatory* activity in the case of compounds from cluster 1), moderate and very strong analgesic and *anti-inflammatory* activity, respectively, for aminophenazone, compared to ASA in the case of compounds from cluster 2), and the same antipyretic, *anti-inflammatory* and analgesic activity in the case of compounds from cluster 3).

Conclusions

Concluding observations presented above, distribution of individual drugs on the plane determined by two principal components (factors 1 and 2) obtained on the basis of structural parameters and $\log k_w$ values was able to produce patterns in good agreement with their physicochemical characteristic as well as with their pharmacological features.

On the basis of the results discussed above the following more detailed conclusions may be also put forward.

Factor analysis showed that from among the whole group 52 parameters two factors can be extracted. However, according to the character and number of the parameters used, the first principle component (factor 1) accounted for 65-73% of variance in the data, and second principal component (factor 2) explained 27-35% of data variance.

From among all the 52 parameters the most influence on the value of the factors possessed chromatographic parameters and selected structural parameters (relevant to energy quantum-chemical parameters and electron affinity specifying parameters).

The approach proposed after optimization of datasets, could be used to preliminary classification of analgesic and *anti-inflammatory* drugs, and also be incorporated into the QSAR analysis during the new drug design strategies.

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Tables

Table 1 Values of HPLC retention data and molecular descriptors used in factor analysis

Compound		HPLC retention data																			
No.	Name	LGK W2NAL	LGK W2NAS	LGK W7NAL	LGK W7NAS	LGK W2NML	LGK W2NMS	LGK W7NML	LGK W7NMS	LGK W2NTL	LGK W2NTS	LGK W7NTL	LGK W7NTS	LGK W2GL	LGK W2GSQ	LGK W7GL	LGK W7GSQ	LGK W7GHL	LGK W7GHS	LGK W11GL	LGK W11GS
1	acetaminophen	0.02	0.05	0.06	0.11	0.08	0.12	0.07	0.12	-0.01	0.17	-0.02	0.17	-0.16	0.31	-0.04	0.74	0.01	0.52	0.06	0.35
2	aminophenazone	-0.19	0.37	0.44	1.0	-0.01	0.09	1.4	2.5	-0.11	0.06	0.14	0.48	-0.23	0.99	0.70	2.7	1.1	1.8	1.4	2.2
3	ASA	0.71	1.1	-0.07	0.09	1.5	2.5	0.06	0.09	0.71	1.1	-0.12	0.12	0.82	1.5	0.13	2.1	-0.04	0.20	0.10	0.25
4	diclofenac	3.0	5.0	1.1	2.7	4.8	6.0	3.5	5.1	2.7	5.0	0.82	2.4	2.7	4.4	1.2	2.7	1.8	3.2	2.3	3.9
5	etodolac	2.7	4.5	0.93	2.5	4.7	6.8	3.5	4.5	2.6	4.7	0.88	2.4	2.2	3.7	1.1	2.8	1.7	3.3	2.0	3.5
6	ketorolac	1.5	2.9	0.10	-0.22	3.0	4.9	1.8	3.3	1.4	2.6	-0.01	0.08	1.8	3.1	1.3	2.4	0.60	1.7	0.87	1.8
7	nimesulide	2.6	4.1	1.7	3.2	3.3	4.8	2.5	4.5	2.4	4.2	1.4	2.9	2.7	4.1	2.6	4.3	2.1	3.2	1.4	3.1
8	noramidopyrine	-0.05	0.15	0.01	0.01	0.10	0.07	0.10	0.11	-0.11	0.01	-0.04	-0.22	-0.43	0.58	-0.06	0.71	-0.22	0.62	0.23	0.44
9	piroxicam	1.3	2.1	0.09	-0.01	2.4	3.5	1.7	3.6	1.0	1.8	0.04	0.08	1.9	2.9	0.73	2.3	0.88	1.9	1.1	2.1
10	salicylamide	0.50	0.86	0.46	0.78	1.1	1.8	0.8	1.6	0.74	1.3	0.67	1.3	0.68	1.3	0.89	2.3	0.78	1.3	0.06	0.16
11	sulindac	1.6	3.5	0.02	0.18	4.0	6.5	27	5.1	0.78	1.7	0.01	0.14	1.9	3.7	0.37	2.7	0.35	2.1	1.2	2.9
12	tramadol	0.08	0.22	0.42	0.78	0.70	2.1	1.4	1.9	-0.07	0.08	0.29	0.33	-0.02	0.92	1.4	2.9	1.3	2.1	1.8	2.5
Compound		HPLC retention data										Molecular descriptors									
No.	Name	LGK W2AL	LGK W2ASQ	LGK W7AL	LGK W7ASQ	LGK W11AL	LGK W11AS	V_ MOL	E_I NT	LG_ P	MR	TE	BE	IAE	EE	HF	IE_IP	EA	EN	HARD	E HOMO
1	acetaminophen	-0.28	-0.23	-0.30	-0.03	-0.56	-0.33	126	-111	-0.56	41	-46026	-2125	-43901	-211886	-57	8.0	-0.41	3.8	4.2	-8.6
2	aminophenazone	-0.72	-1.4	-0.63	0.89	0.10	1.2	201	-102	-0.76	68	-65415	-3435	-61980	-427308	71	7.0	-0.99	3.0	4.0	-8.5
3	ASA	0.40	0.31	-1.5	-1.2	-0.84	-0.16	136	-123	0.29	43	-58671	-2335	-56336	-285517	-142	8.9	-1.2	3.9	5.1	-9.8
4	diclofenac	2.5	3.6	-0.12	0.67	-0.04	1.1	223	-124	3.7	75	-81620	-3310	-78310	-487947	-54	7.8	-0.80	3.5	4.3	-8.6
5	etodolac	1.9	2.8	0.63	2.0	-0.11	0.90	239	-149	2.5	80	-83818	-4399	-79420	-612908	-108	7.5	-0.52	3.5	4.0	-8.2
6	ketorolac	1.4	1.6	-0.66	-0.02	-0.69	0.45	184	-157	1.4	69	-75323	-3578	-71745	-462515	-45	8.2	-1.1	3.6	4.6	-9.0
7	nimesulide	1.6	2.6	0.30	0.52	-0.33	-0.10	220	-146	-0.99	81	-93050	-3472	-89578	-594540	-35	8.8	-2.2	3.3	5.5	-9.8
8	noramidopyrine	0.59	0.71	-1.7	-0.12	-1.4	0.08	227	-161	-5.3	83	-92060	-3790	-88271	-630482	-39	7.2	-1.9	2.6	4.6	-8.7
9	piroxicam	0.85	0.99	-0.61	0.44	-0.57	-0.60	231	-227	-4.5	89	-96718	-3927	-92792	-683306	-42	7.8	-1.9	2.9	4.8	-8.8
10	salicylamide	0.26	0.85	0.30	0.84	-0.71	0.23	117	-97	0.10	36	-42435	-1845	-40590	-185297	-52	8.9	-0.83	4.0	4.9	-9.5
11	sulindac	1.5	3.0	-0.34	0.71	-0.72	0.24	289	-168	3.7	99	-102256	-4653	-97603	-698329	-86	8.3	-2.1	3.1	5.2	-9.0
12	tramadol	-1.1	1.3	1.7	2.9	1.1	0.61	245	-147	2.8	77	-74742	-4347	-70395	-551781	-78	7.9	-0.22	3.8	4.1	-8.9

Table 1. Continued.

Compound		Molecular descriptors											
No.	Name	E_LUMO	ED_MAX	ED_MIN	ED_HOMO	ED_LUMO	MAX_POS	MAX_NEG	DELTA_Q	TDM	E_L	E_MAX	OS_MAX
1	acetaminophen	0.04	1.9	0.76	1.5	1.0	0.31	-0.36	0.67	3.2	3.6	5.6	0.89
2	aminophenazone	-0.10	1.9	0.76	1.2	0.94	0.31	-0.32	0.62	3.4	3.9	5.9	0.81
3	ASA	-0.56	1.9	0.72	1.9	1.12	0.36	-0.37	0.73	2.2	4.0	5.8	1.1
4	diclofenac	-0.22	2.0	0.75	1.2	1.0	0.31	-0.38	0.69	0.94	3.9	5.3	0.48
5	etodolac	0.14	1.9	0.72	0.93	1.9	0.32	-0.39	0.71	0.97	3.7	5.2	1.1
6	ketorolac	-0.44	1.9	0.72	1.1	1.5	0.34	-0.35	0.69	1.6	4.3	4.3	0.57
7	nimesulide	-1.3	1.9	0.71	1.0	0.92	2.8	-0.95	3.8	4.0	4.3	4.3	0.44
8	noramidopyrine	-0.95	1.9	0.72	1.2	0.97	2.8	-0.93	3.7	3.2	3.7	5.2	0.52
9	piroxicam	-0.93	1.9	0.70	0.78	0.81	2.9	-0.93	3.8	3.6	3.2	4.8	0.62
10	salicylamide	-0.32	1.9	0.75	1.3	1.1	0.35	-0.44	0.79	2.4	3.8	6.3	0.97
11	sulindac	-1.2	2.0	0.76	0.95	1.2	1.4	-0.78	2.2	6.6	3.3	4.8	0.71
12	tramadol	0.41	1.9	0.80	1.2	0.98	0.15	-0.33	0.48	1.2	3.9	6.0	0.97

Table 2 The factor analysis loadings by structural parameters

Structural parameters	Factor 1	Factor 2
V_MOL	-0.9212	-0.0890
E_INT	0.6809	0.4346
LG_P	0.0131	0.5190
MR	-0.9382	-0.2515
TE	0.8582	0.4384
BE	0.9304	-0.0397
IAE	0.8481	0.4581
EE	0.9264	0.2866
HF	-0.1721	-0.0100
IE_IP	0.6564	-0.4188
EA	0.3089	0.9237
EN	0.7273	0.4415
HARD	0.1953	-0.8996
EHOMO	-0.5885	0.6132
ELUMO	0.1710	0.9564
ED_MAX	-0.2401	-0.4751
ED_MIN	0.1370	0.6487
ED_HOMO	0.8145	0.1777
ED_LUMO	-0.1232	0.4303
MAX_POS	-0.4095	-0.8434
MAX_NEG	0.4151	0.8597
DELTA_Q	-0.4118	-0.8489
TDM	-0.1793	-0.6236
E_L	0.3857	0.0562
E_MAX	0.5037	0.5456
OS_EMAX	0.3726	0.6040

Table 3 The factor analysis loadings by HPLC retention data

HPLC retention data	Factor 1	Factor 2
LGKW2NAL	0.9675	0.2206
LGKW2NAS	0.9728	0.2083
LGKW7NAL	0.5120	0.6852
LGKW7NAS	0.5497	0.6715
LGKW2NML	0.9548	0.1577
LGKW2NMS	0.9079	0.1773
LGKW7NML	0.7875	0.5240
LGKW7NMS	0.7942	0.4226
LGKW2NTL	0.9232	0.2533
LGKW2NTS	0.9301	0.2724
LGKW7NTL	0.5285	0.6354
LGKW7NTS	0.6328	0.5739
LGKW2GL	0.9635	0.1358
LGKW2GSQ	0.9622	0.1918
LGKW7GL	0.4540	0.6861
LGKW7GSQ	0.5061	0.6558
LGKW7GHL	0.4951	0.8312
LGKW7GHS	0.6813	0.7067
LGKW11GL	0.4604	0.7520
LGKW11GS	0.6386	0.6445
LGKW2AL	0.9707	-0.1297
LGKW2ASQ	0.8457	0.2297
LGKW7AL	0.0053	0.8557
LGKW7ASQ	-0.0770	0.8629
LGKW11AL	-0.1594	0.8978
LGKW11AS	0.0614	0.6292

Table 4 The factor analysis loadings by all data

All data	Factor 1	Factor 2
LGKW2NAL	0.8953	-0.1981
LGKW2NAS	0.9017	-0.2324
LGKW7NAL	0.7705	0.0983
LGKW7NAS	0.8032	0.1532
LGKW2NML	0.8704	-0.2177
LGKW2NMS	0.8538	-0.2048
LGKW7NML	0.9641	-0.0874
LGKW7NMS	0.8987	-0.2519
LGKW2NTL	0.8676	-0.0860
LGKW2NTS	0.8906	-0.0835
LGKW7NTL	0.7484	0.1188
LGKW7NTS	0.8020	0.1625
LGKW2GL	0.8343	-0.3023
LGKW2GSQ	0.8804	-0.3345
LGKW7GL	0.7427	0.0533
LGKW7GSQ	0.7700	-0.0021
LGKW7GHL	0.8717	0.1874
LGKW7GHS	0.9719	-0.0193
LGKW11GL	0.8564	0.1108
LGKW11GS	0.9240	-0.0713
LGKW2AL	0.7042	-0.3951
LGKW2ASQ	0.8278	-0.2304
LGKW7AL	0.5301	0.5006
LGKW7ASQ	0.4976	0.3790
LGKW11AL	0.4383	0.5782
LGKW11AS	0.4689	0.5064
V_MOL	0.5522	-0.4813
E_INT	-0.1621	0.7490
LG_P	0.5678	0.5210
MR	0.5091	-0.6421
TE	-0.4931	0.7681
BE	-0.5039	0.3968
IAE	-0.4888	0.7802
EE	-0.4819	0.6702
HF	-0.0989	-0.0566
IE_IP	0.0219	0.0343
EA	-0.0138	0.9352
EN	0.0048	0.7805
HARD	0.0232	-0.6253
EHOMO	0.1347	0.1525
ELUMO	0.0075	0.9049
ED_MAX	0.3851	-0.5215
ED_MIN	-0.1077	0.6473
ED_HOMO	-0.5602	0.4967
ED_LUMO	0.3834	0.2722
MAX_POS	-0.0148	-0.9064
MAX_NEG	-0.0220	0.9230
DELTA_Q	-0.0078	-0.9121
TDM	-0.2011	-0.6460
E_L	0.2171	0.3522
E_MAX	-0.4328	0.7029
OS_EMAX	-0.2246	0.6675

Table 5 The factor analysis scores of the studied compounds

Compound		^(a) Structural parameters		^(b) HPLC retention data		^(c) All data	
No.	Name	Factor 1	Factor 2	Factor 1	Factor 2	Factor 1	Factor 2
1	acetaminophen	1.0456	0.6015	-1.0472	-0.6845	-1.2696	0.7849
2	aminophenazone	-0.1986	0.8386	-1.2331	0.8583	-0.4690	0.6542
3	ASA	1.6881	-0.3670	-0.2405	-1.3482	-1.0567	0.3373
4	diclofenac	-0.2681	0.5157	1.4641	0.5574	1.4967	0.4407
5	etodolac	-1.0309	1.3545	1.0776	0.8893	1.5020	0.6681
6	ketorolac	0.0284	0.1713	0.5466	-0.7141	0.1345	-0.0117
7	nimesulide	0.1347	-1.8468	1.0970	0.9176	1.1997	-0.9607
8	noramidopyrine	-0.7647	-0.8255	-0.7357	-1.2018	-1.2640	-1.3614
9	piroxicam	-1.0063	-1.0683	0.2569	-0.5618	-0.1940	-1.5448
10	salicylamide	1.7548	-0.0226	-0.5205	0.0276	-0.5578	0.9627
11	sulindac	-1.0315	-0.7307	0.7671	-0.5882	0.3754	-1.2319
12	tramadol	-0.3513	1.3793	-1.4323	1.8484	0.1027	1.2626

^(a)factor analysis performed only for structural parameters, ^(b)factor analysis performed only for HPLC retention data, ^(c)factor analysis performed for structural parameters along with HPLC retention data.

Table 6 The classification of *anti*-inflammatory drugs according to their analgesic, *anti*-inflammatory and antipyretic activity

No.	Compound	Analgesic activity	Anti-inflammatory activity	Antipyretic activity
1	acetaminophen	(+++) ^a (++) ^b	(++) ^a	(+++) ^a
2	aminophenazone	(++) ^b	(++++) ^b	(-)
3	ASA	(+++) ^a (+) ^b	(++) ^a	(+++) ^a
4	diclofenac	(+) ^a (+++) ^c	(+++) ^a (++) ^c	(+) ^a (+) ^c
5	etodolac	(+) ^d	(+++) ^d	(-)
6	ketorolac	(++) ^a (+) ^c	(+) ^a	(+) ^a
7	nimesulide	(++) ^e (++) ^f	(++) ^e (++) ^f	(-)
8	noramidopyrine	(++) ^g	(+) ^g	(++) ^g
9	piroxicam	(+++) ^d (+++) ^h	(+++) ^d (+++) ^h	(-)
10	salicylamide	(+++) ^a	(++) ^a	(+++) ^a
11	sulindac	(+++) ⁱ	(++) ^h	(++) ^h
12	tramadol	(+++) ^j	(-)	(-)

Analgesic, *anti*-inflammatory and antipyretic activity were presented as very strong (++++), strong (+++), mild (++), low (+), lack of activity data (-).

^(a)data were taken from [37]; ^(b)data were taken from [2]; ^(c)data were taken from [38]; ^(d)data were taken from [31]; ^(e)data were taken from [32]; ^(f)data were taken from [33]; ^(g)data were taken from [34]; ^(h)data were taken from [35]; ⁽ⁱ⁾data were taken from [36]; ^(j)data were taken from [39].

Figure captions

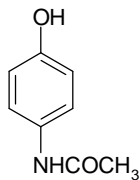
Fig. 1 Chemical structures of the studied compounds

Fig. 2 Two-dimensional scatter plots of the loadings of the first two factors: **A)** by structural parameters, **B)** by HPLC retention data, **C)** by structural parameters along with HPLC retention data

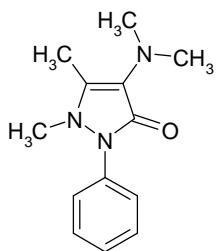
Fig. 3 Two-dimensional scatter plots of the scores of individual drugs in the first two factors extracted: **A)** from structural parameters, **B)** from HPLC retention data, **C)** from structural parameters along with HPLC retention data

Figure 1

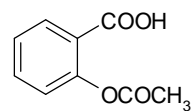
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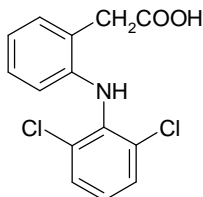
acetaminophen



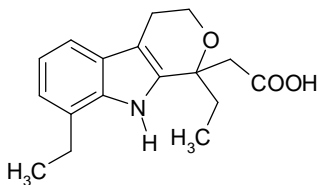
aminophenazone



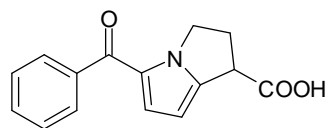
acetylsalicylic acid (ASA)



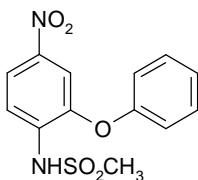
diclofenac (free acid)



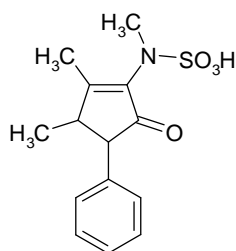
etodolac



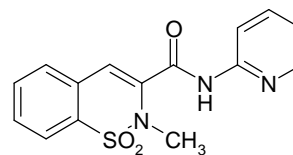
ketorolac



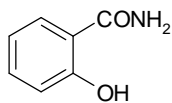
nimesulide



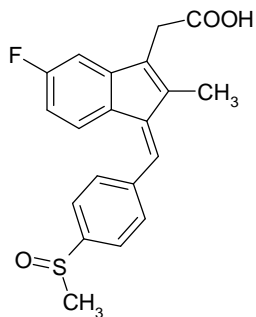
noramidopyrine (free acid)



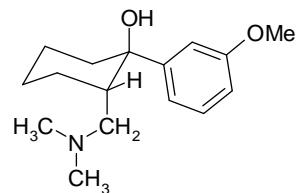
piroxicam



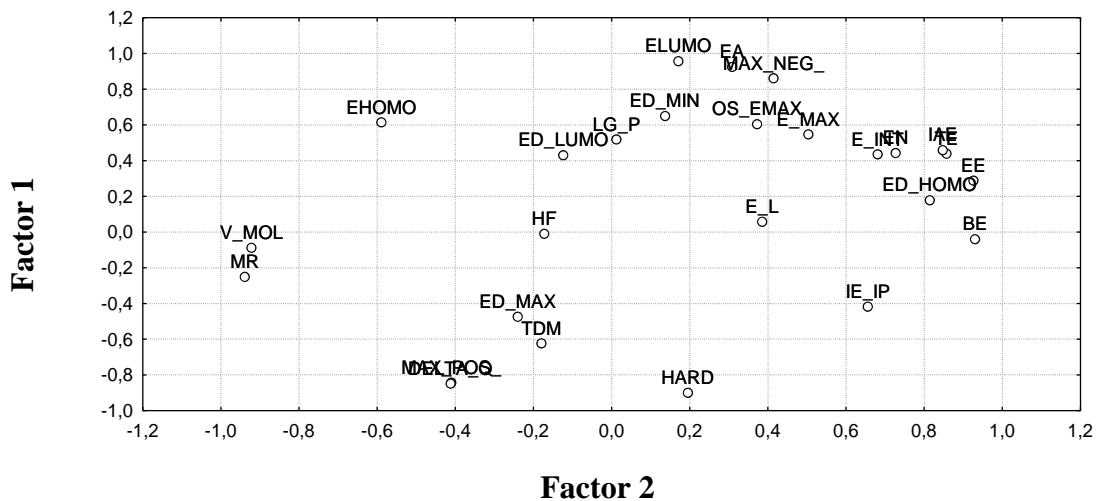
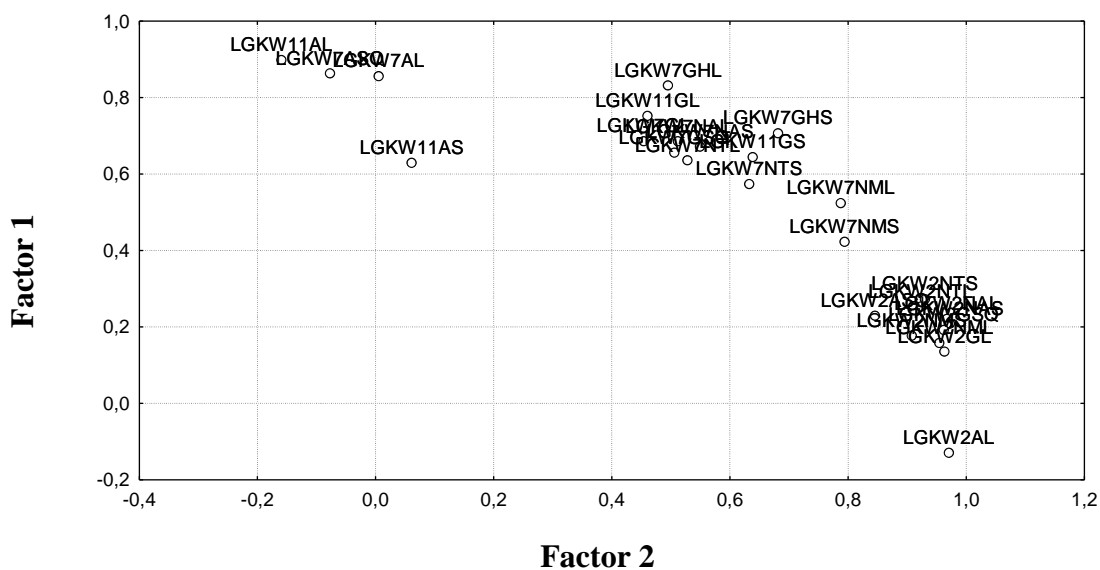
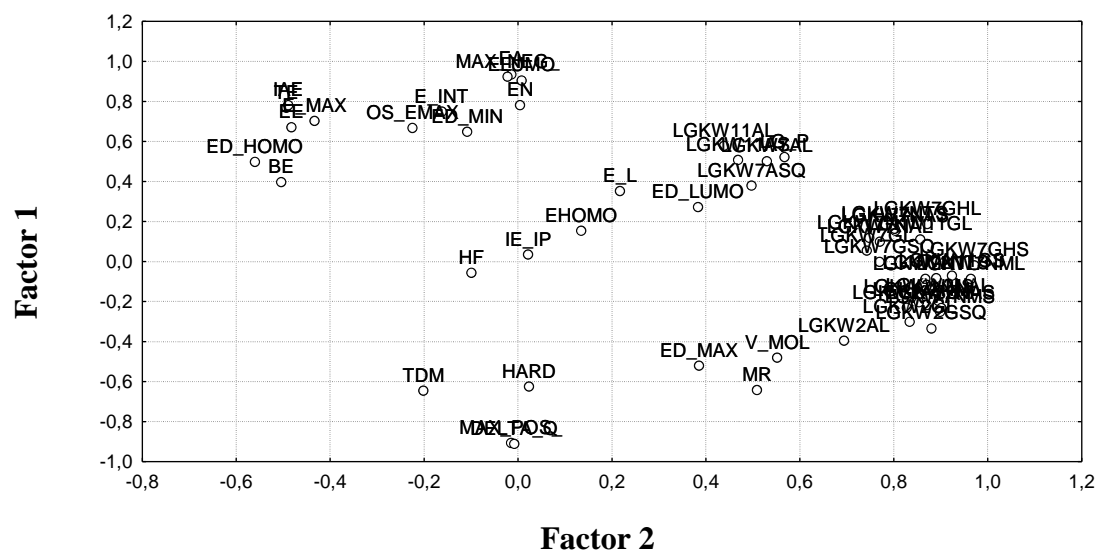
salicylamide



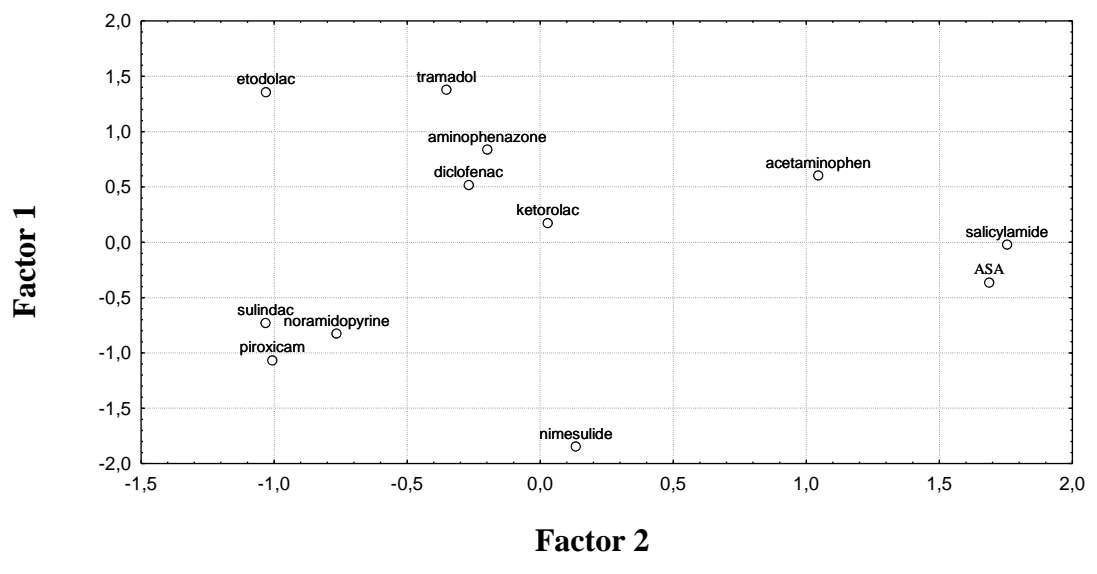
sulindac



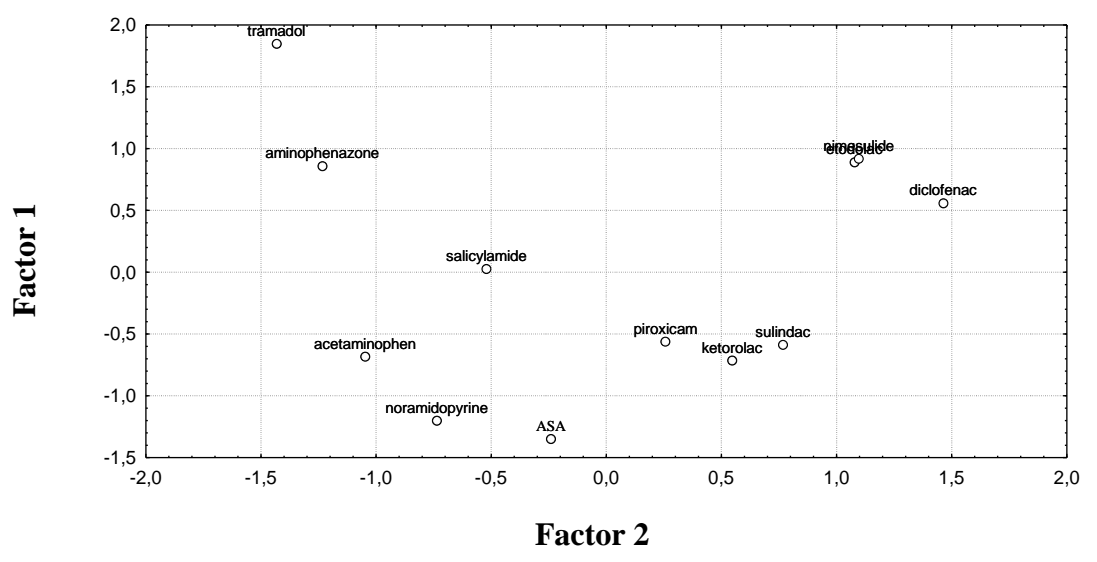
tramadol

A)**B)****C)**

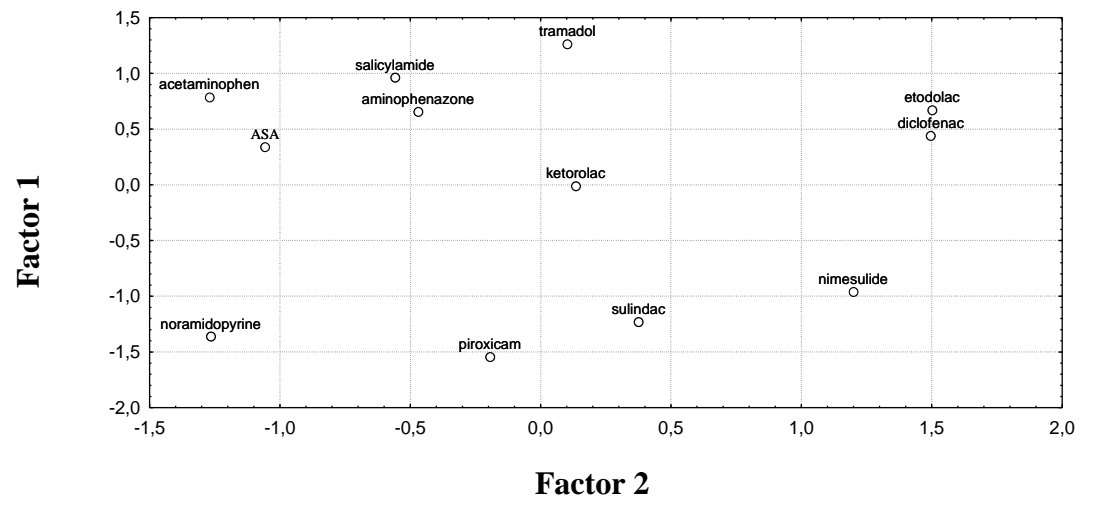
A)



B)



C)



L