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TOPS–MODE and DRAGON Descriptors in QSAR. 1. Skin Permeation [#]

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Abstract

Motivation. The TOPological Sub–Structural MOlecular DEsign (TOPS–MODE) approach has been applied to the study of the permeability coefficient of various compounds through human skin. A model with good statistical parameters was developed (R^2 = 0.938, S = 0.24, F = 151.06) with the use of the mentioned approach for the 37 organic compounds used in the training set. In contrast, none of nine different approaches, including the use of constitutional (R^2 = 0.84, S = 0.38), topological (R^2 = 0.85, S = 0.37), BCUT (R^2 = 0.84, S = 0.38), 2D autocorrelations (R^2 = 0.79, S = 0.44), geometrical (R^2 = 0.87, S = 0.34), RDF (R^2 = 0.81, S = 0.41), 3D Morse (R^2 = 0.90, S = 0.29), GETAWAY (R^2 = 0.87, S = 0.35) and WHIM (R^2 = 0.70, S = 0.53) descriptors was able to obtain a correlation coefficient superior to 0.9 in the mentioned property with the same number of descriptors. On the other hand, the TOPS–MODE approach obtains the higher cross validation correlation coefficient of the all models (q^2 = 0.907). In addition the TOPS MODE allows a simple interpretation of the model in comparison with others methodologies.

Method. Briefly, this method codifies the molecular structure by means of the edge adjacency matrix **E**. The **E** matrix is a square table of order m. The elements of such a matrix (e_{ij}) are equal to 1 if the bonds i and j are adjacent or 0 otherwise. To codify information related to heteroatoms, the TOPS–MODE approach use **B**(w_{ij}) weighted matrices instead of **E**. The weights (w_{ij}) are chemically meaningful numbers such as bond distances, bond dipole, bond polarizabilities, or even mathematical expressions involving atomic weights such as hydrophobicity.

Results. We have shown that the TOPS–MODE approach is able to describe the permeability of different compounds through human skin.

Conclusions. We have developed a model for predicting the permeability coefficient which is both statistically and chemically sound. This model explains more than 93% of the variance in the experimental permeability coefficients and shows good predictive ability in cross–validation. These features are significantly better than those obtained for other nine different methodologies used to predict this property.

Keywords. Molecular descriptors; permeability coefficients; QSPR; TOPS–MODE.

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1 INTRODUCTION

The barrier function of human skin is important both to the transdermal administration of drugs and to the uptake of toxic chemicals following dermal exposure. As a result, several models to predict molecular transport through human skin have been developed [1–3]. Various synthetic membranes have been employed in drug release studies. The most commonly used artificial membranes are polydimethylsiloxane (PDMS) and cellulose acetate [4–10]. PDMS (for example, Silastic) is an isotropic polymer widely employed as an alternative model barrier for *in vitro* percutaneous penetration. It behaves according to Fick's first law of diffusion and possesses lipid–like properties, making it a good model for the stratum corneum [11]. Cellulose acetate membranes have similarly found use in such experiments and also in the characterization of ionophoretic delivery [12–16]. However, these membranes have often been shown to overestimate significantly the flux across skin and their use is significantly limited. Further, Cronin *et al*. [17], in a mechanistic study of penetration across a PDMS membrane, indicated that penetration is related primarily to the ability of the penetrants to form hydrogen bonds and not to their lipophilicity, as suggested by similar studies on skin *ex vivo*.

Early quantitative structure–activity relationship (QSAR) studies to predict skin permeation of chemicals revealed that hydrophobicity was correlated linearly with increasing permeability [18,19]. Patel *et al*. [20] demonstrated in an excellent paper as the hydrophobicity, molecular size and the hydrogen bonding capability of a molecule affect its ability to permeate skin. In the context of *in silico* methods for modeling physicochemical and biological properties of chemicals the topological sub–structural molecular design (TOPS–MODE) approach has been introduced [21–25]. The successful applications of this theoretical approach for the modeling of physical and physical–chemical properties [26,27] have inspired us to perform a more exhaustive study in order to test and/or to validate the TOPS MODE applicability in this area. Therefore, the aim of this study was to investigate the role that TOPS–MODE and other molecular descriptors calculated from the molecular structure plays on the explanation of such property using a data set of 37 organic compounds.

2 MATERIALS AND METHODS

2.1 The TOPS–MODE Approach

TOPS–MODE is based on the computation of the spectral moments of the bond matrix, the mathematical basis of which has been described previously [21–24]. The TOPS–MODE approach has been recently reviewed in the literature [28], and both the methodology and its software implementation have been described [29]. According to the authors, the application of the TOPS–MODE approach to the study of quantitative structure–permeability relationships (QSPR) can be

summarized in the following steps:

(1) Draw the hydrogen–depleted molecular graphs for each molecule of the data set.

(2) Use appropriate bond weights in order to differentiate the molecular bonds, *e.g.*, bond distance, bond dipoles, bond polarizabilities.

(3) Compute the spectral moments of the bond matrix with the appropriate weights for each molecule in the data set, generating a table in which rows correspond to the compounds and columns correspond to the spectral moments of the bond matrix. Spectral moments are defined as the trace of the different powers of the bond matrix [30].

(4) Find QSPR by using a suitable linear or non–linear multivariate statistical technique, such as multi–linear regression analysis (MRA), etc. to obtain an equation of the form:

$$P = a_0\mu_0 + a_1\mu_1 + a_2\mu_2 + a_3\mu_3 \ldots\ldots\ldots a_k\mu_k + b \quad (1)$$

where P is the property measurement, μ_k is the *k*th spectral moment, and a_k's are the coefficients obtained by the MRA.

(5) Test the predictive capability of the QSPR model by using cross–validation techniques.

2.2 Data Sets and Computational Strategies

A data set of 37 compounds for which the permeability coefficients are reported in the literature was selected [31]. The parameter studied is $\log(p_{er})$ where p_{er} is the permeability coefficient through human epidermis. The names of the compounds, as well as the calculated and experimental values of $\log(p_{er})$ are shown in Table 1.

TOPS–MODE [29] and DRAGON [32] computer software were employed to calculate the molecular descriptors. In the case of TOPS–MODE software, the polar surface, dipole moment, Gasteiger–Marsilli charges and hydrophobicity were used to weigh the bond adjacency matrix. The selection of only these four types of descriptors from the whole pool of ten types included in TOPS–MODE methodology was carried out by the sake of simplicity and on the belief that steric and polarity parameters influence the permeability of compounds through skin layers [11,14]. The total number of descriptors used for obtaining this model was 64 spectral moments.

On the other hand, nine other models were developed using the kind of descriptors in the computer software Dragon [32]. In this sense, we carry out geometry optimization calculations for each compound of this study using the semi–empirical method AM1 [33] included in MOPAC 6.0 [34] and calculating the Constitutional, Topological, BCUT, 2D autocorrelations, Geometrical, RDF, 3D–MORSE, GETAWAY and WHIM descriptors [35]. The statistical processing to obtain the QSAR models was carried out by using the forward stepwise regression methods.

Table 1. Observed, predicted, and residual values of logarithm of the permeability coefficients (cm^2/s) through human skin for the 37 compounds used to derive the QSPR [31].

Number	Compounds	Observed	Predicted	Residuals	Deleted Residuals
1	water	–6.130	–5.871	–0.259	–0.356
2	methanol	–6.680	–7.165	0.485	0.603
3	methanoic acid	–7.080	–7.402	0.322	0.405
4	ethanol	–6.660	–6.635	–0.025	–0.029
5	ethanoic acid	–7.010	–6.946	–0.064	–0.073
6	*n*–propanol	–6.410	–6.362	–0.048	–0.052
7	*n*–propanoic acid	–7.010	–6.633	–0.377	–0.442
8	butane–2–one	–5.900	–5.590	–0.310	–0.402
9	benzene	–4.510	–4.336	–0.174	–0.200
10	diethyl ether	–5.350	–5.003	–0.347	–0.381
11	*n*–butanol	–6.160	–6.090	–0.070	–0.075
12	*n*–butanoic acid	–6.360	–6.340	–0.020	–0.024
13	phenol	–5.640	–5.518	–0.122	–0.128
14	toluene	–3.560	–3.918	0.358	0.451
15	styrene	–3.750	–3.860	0.110	0.130
16	*n*–pentanol	–5.780	–5.817	0.037	0.040
17	phenylmethanol	–5.780	–5.776	–0.004	–0.005
18	*n*–pentanoic acid	–6.010	–6.064	0.054	0.063
19	2–chlorophenol	–5.040	–4.719	–0.321	–0.338
20	4–chlorophenol	–5.000	–4.954	–0.046	–0.049
21	*m*–cresol	–5.380	–5.245	–0.135	–0.141
22	*o*–cresol	–5.360	–5.068	–0.292	–0.304
23	*p*–cresol	–5.290	–5.271	–0.019	–0.020
24	4–bromophenol	–5.000	–4.823	–0.177	–0.190
25	4–nitrophenol	–5.810	–5.728	–0.082	–0.098
26	3–nitrophenol	–5.810	–5.624	–0.186	–0.228
27	2–nitrophenol	–4.560	–4.796	0.236	0.580
28	ethylbenzene	–3.480	–3.886	0.406	0.481
29	*n*–hexanol	–5.450	–5.545	0.095	0.101
30	*n*–hexanoic acid	–5.440	–5.791	0.351	0.413
31	β–naphthol	–3.700	–3.714	0.014	0.017
32	*n*–heptanol	–5.050	–5.273	0.223	0.239
33	*n*–heptanoic acid	–5.280	–5.518	0.238	0.286
34	*n*–octanol	–4.840	–5.000	0.160	0.176
35	*n*–octanoic acid	–5.210	–5.246	0.036	0.045
36	*n*–nonanol	–4.770	–4.728	–0.042	–0.048
37	*n*–decanol	–4.660	–4.456	–0.204	–0.242

The statistical significance of the models was determined by examining the regression coefficient, the standard deviation, the number of variables, the cross validation leave–one–out statistics and the proportion between the cases and variables in the equation.

3 RESULTS AND DISCUSSION

3.1 Quantitative Structure Permeation Relations

The best QSPR model obtained with the TOPS–MODE descriptors is given below together with the statistical parameters of the regression.

$$\log(p_{er}) = -5.87 - 1.12\cdot10^{-9}\cdot\mu_{15}{}^{D} + 1.11\cdot10^{-7}\cdot\mu_{15}{}^{GM} + 0.76\cdot\mu_{1}{}^{H} - 0.02\cdot\mu_{1}{}^{PS}$$
$$N = 37 \quad S = 0.24 \quad R^2 = 0.938 \quad F = 151.06 \quad p < 0.001 \quad q^2 = 0.907 \quad S_{cv} = 0.351 \qquad (2)$$

where N is the number of compounds included in the model, R^2 is the correlation coefficient, S the standard deviation of the regression, F the Fisher ratio, q^2 the correlation coefficient of the cross–validation, p is the significance of the variables in the model and S_{cv} is the standard deviation of the cross–validation.

The variables included in the model are designated as follows: the sub–index represents the order of the spectral moment and the super–index the type of bond weight used, *i.e.*, D for dipole moment, PS for polar surface and H for hydrophobicity.

Consideration of the outliers removed from a QSAR is essential. An outlier to a QSAR is identified normally by having a large standard residual and can indicate the limits of applicability of a QSAR models. In the current work, any compounds posses a large residual. For this reason, here any compound was considered as outlier. From the statistical point of view this model is a robust one as can be seen from the statistical parameters of the cross–validation.

As we previously mentioned, one of the objectives of the current work deal with to compare the reliability of the TOPS–MODE approach to describe the property under study and to as compare them other with different descriptors and methods. Consequently, nine other models were developed using the same data set and the same number of variables that was included in the TOPS–MODE QSPR model. The results obtained with the use of Constitutional, Topological, BCUT, 2D autocorrelations, Geometrical, RDF, 3D Morse, GETAWAY and WHIM descriptors are given in Table 2.

Table 2. Statistics of regressions models obtained for the ten types of descriptors (see [35] for variable definition)

Descriptors	Variables	S	R^2	F	p	q^2
Spectral moments	μ_{15}^{D}, μ_{15}^{GM}, μ_{1}^{H}, μ_{1}^{PS}	0.240	0.938	151.06	< 0.001	0.907
Constitutional	nC, nN, nO, nX	0.378	0.843	43.22	< 0.001	0.741
Topological	SPI, Jhete, PW4, SEigv	0.370	0.851	45.75	< 0.001	0.801
BCUT	BELe3, BELe4, BELp6, BELp5	0.381	0.841	42.415	< 0.001	0.791
2D autocorrelations	ATS1e, ATS4e, ATS4p, GATS1p	0.440	0.789	29.908	< 0.001	0.701
Geometrical	MAXDP, G2, SPAM, G(N..O)	0.340	0.873	55.291	< 0.001	0.824
RDF	RDF010u, RDF020e, RDF010p, RDF020p	0.415	0.812	34.577	< 0.001	0.742
3D–MORSE	Mor28v, Mor26u, Mor32m, Mor31u	0.293	0.906	77.628	< 0.001	0.861
GETAWAY	H2u, H1e, R1e, R1p	0.349	0.867	52.147	< 0.001	0.817
WHIM	G2p, Ts, Au, Ap	0.527	0.702	18.873	< 0.001	0.632
Mixed Model	Mor32m, Mor28v, R1e, G2, nO	0.274	0.911	89.546	< 0.001	0.852
Potts and Guy	MV, Hd, Ha, $\log(D_o/\delta)$	–	0.940	165.00	–	–

3.2 Comparison with Other Approaches

Although, the number of compounds is small to reach a definite conclusion can be seen there are remarkable differences concerning the explanation of the experimental variance given by these models compared to the TOPS–MODE one. While the TOPS–MODE QSPR model explains more than 93% of the experimental permeability the rest of the models are unable to explain beyond 90% of such variance: constitutional (R^2 = 0.84, S = 0.38), topological (R^2 = 0.85, S = 0.37), BCUT (R^2 =

0.84, $S = 0.38$), 2D autocorrelations ($R^2 = 0.79$, $S = 0.44$), geometrical ($R^2 = 0.87$, $S = 0.34$), RDF ($R^2 = 0.81$, $S = 0.41$), 3D Morse ($R^2 = 0.90$, $S = 0.29$), GETAWAY ($R^2 = 0.87$, $S = 0.35$) and WHIM ($R^2 = 0.70$, $S = 0.53$).

The TOPS–MODE model is superior to the other nine models not only in the statistical parameters of the regression but also, and more importantly, in its stability upon inclusion/exclusion of compounds as measured by the correlation coefficient and standard deviation of the cross–validation. Because of the structural variability of the compounds in the data set these statistics of the leave–one–out cross validation might be considered as a good measurement of the predictive ability of the models. As can be seen in Table 2, the value of the determination coefficient of leave–one–out cross–validation for the model obtained with the spectral moments ($q^2 = 0.907$) was the highest of all. In addition, a leave–10%–out and leave–20%–out as cross–validation method was carried out for demonstrate the stability of the find model. The correlation coefficient obtained for these procedures were $q^2 = 0.872$ and $q^2 = 0.863$, demonstrating the stability of the model using the spectral moments.

However, in all previous studies we only consider models with a specified family of molecular descriptors. Thence, in order to complete the demonstration of the potentialities of TOPS–MODE over the remnant ones mixed model considering all the molecular descriptors at the same time must be developed. The result of this model appears in Table 2. This result has shown that the TOPS–MODE approach not only explains the experimental data, but seems to be the best one in doing so.

On the other hand, the model reported by Potts and Guy [31] present a correlation coefficient of 0.94, when we compare this model with the obtained with the spectral moments, represented by Eq. (2), it is possible to observe that both show similar R^2 (0.940 *vs*. 0.938). However, the model presented by Potts and Guy included four physical–chemical properties as variables in their equation. These variables were obtained from the literature for the authors [36–37]. As Randić [38] states there are some parameters which QSAR models must fulfill, one of them is not to include measures of experimental properties such as molecular volume (MV), log P, boiling points, among others, because for the determination of these properties it is necessary the synthesis of molecules that are under study. So if we include chemical–physical variables in our model what do we wear away in making experimental approximations to predict a property of a molecule that has not been synthesized with the aim of reducing costs for? On the other hand, if we value this physico–chemical property with any of the software available, for using this property subsequently which has already been valued with a series of approximations in a new approximation we would be deserving in a greater error which would eliminate the possibilities of a prediction of the nearest possible to the reality of the studied property.

3.3 Interpretation of the QSPR Model

One of the most important advantages that TOPS–MODE brings to the study of QSPR and QSAR is concerned with the structural interpretability of the models. This interpretability comes from the fact that the spectral moments can be expressed as linear combinations of structural fragments.

According to the Eq. (2), the permeation coefficient decreases as the polar surface increases in the molecule and an increase of the hydrophobicity increase the permeability. The polarity of the atoms produces a higher interaction of the permeant with the polymer and therefore an increase of the hydrophobicity leads to a higher flux across the human skin. This behavior was reported by Moss *et al*. in an excellent review [39] where the main role of hydrophobicity in accounting for this property was explained. However, the contributions of the heteroatom are also dependent on its volume [39]. The atomic volume of sulfur is larger than that of nitrogen, but the polarity of the latter atom is higher than that of the former and thence the result of this effect is a delay in the permeation process [40].

Finally, this decrease of the permeability when increase the polarity of the molecule also should be due to the oxygen and nitrogen present the possibility to form a hydrogen bond with the polar compounds in the human skin. Potts and Guy [31] and Patel *et al*. [20] pointed out that the hydrogen bonding capability of a molecule affects its ability to permeate the skin. Similar results were obtained by Lipinski *et al*. [41] where the hydrogen bond acceptors sites could potentially hamper skin permeation. This study demonstrated that the diffusion chemicals throughout a human skin in this set of compounds are controlled by the hydrophobicity and the polarity. In addition we demonstrated that the TOPS MODE is an excellent tools for the prediction of the skin permeability.

4 CONCLUSIONS

We have shown that the TOPS–MODE approach is able to describe the permeability of different compounds through human skin. In fact, we have developed a model for predicting the permeability coefficient of a data set of 37 permeants, which is both statistically and chemically sound. This model explains more than 93% of the variance in the experimental permeability coefficients and shows good predictive ability in cross–validation. These features are significantly better than those obtained for other nine different methodologies used to predict this property. Therefore, the spectral moments show a better performance than other kind of descriptors, which suggests that they can be used in new QSPR applications.

Finally, the present results were compared to others obtained in previous works and evidence was obtained on the similarity of the properties that explain the phenomenon.

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5 REFERENCES

[1] G. B. Kasting, R. L. Smith, and E. R. Cooper. Effect of lipid solubility and molecular size on percutaneous absorption. In Skin Pharmacokinetics, B. Shroot and H. Schaefer (eds.), Karger, Basel **1987**, *32*, 138–153.

[2] B. D. Anderson, W. I. Higuchi, and P. V. Raykar. Heterogeneity effects on permeability–partition coefficient relationships in human stratum corneum. *Pharm. Res*. **1988**, *5,* 566–573.

[3] B. D. Anderson, W. I. Higuchi, and P. V. Raykar. Solute structure–permeability relationships in human stratum corneum. *J. Invest. Dermatol*. **1989**, *93*, 280–286.

[4] A. D. Woolfson and D. F. McCafferty. Percutaneous local anaesthesia: drug release characteristics of the amethocaine phase–change system. *Int. J. Pharm*. **1993**, *94*, 75–80.

[5] Y. Kurosaki, N. Nagahara, W. A. Taniza, H. Nishimura, T. Nakayama, and T. Kimura. Use of lipid disperse systems in transdermal drug delivery – comparative study of flufenamic acid permeation among rat abdominal skin, silicon rubber membrane and stratum corneum sheet isolated from hamster cheek pouch. *Int. J. Pharm*. **1991**, *67*, 1–9.

[6] N. A. Megrab, A. C. Williams, and B. W. Barry, Estradiol permeation through human skin and Silastic membrane – effects of propylene glycol and supersaturation. *J. Control. Release* **1995**, *36*, 277–294.

[7] N. A. Megrab, A. C. Williams, and B. W. Barry. Estradiol permeation through human skin, Silastic and snake skin membranes the effects of ethanol–water co–solvent systems. *Int. J. Pharm*. **1995**, *116*, 101–112.

[8] P. W. Stott, A. C. Williams, and B. W. Barry. Characterisation of complex coacervates of some tricyclic antidepressants and evaluation of their potential for enhancing transdermal flux. *J. Control. Release* **1996**, *41*, 215–227.

[9] D. van Hal, A. van Rensen, T. Vringer, H. Junginger, and J. Bouwstra. Diffusion of estradiol from non–ionic surfactant vesicles through human stratum corneum *in vitro*. *STP Pharma Sciences* **1996**, *6*, 72–78.

[10] P. Minghetti, A. Casiraghi, F. Cilurzo, L. Montanari, M. Marazzi, L. Falcone, and V. Donati. Comparison of different membranes with cultures of keratinocytes from man for percutaneous absorption of nitroglycerine. *J. Pharm. Pharmacol.* **1999**, *51*, 673–678.

[11] M. T. D. Cronin, J. C. Dearden, G. P. Moss, and G. Murray–Dickson. Investigation of the mechanism of flux across human skin *in vitro* by quantitative structure–permeability relationships. *Eur. J. Pharm. Sci*. **1999**, *7*, 325–330.

[12] R. Cichon and S. Janicki. Effect of polyoxyethylene glycols (PEG) on properties of the matrix model of transdermal therapeutic system (TTS) with testosterone. *Pharmazie* **1991**, *46*, 719–723.

[13] S. H. Yuk, S. J. Lee, T. Okano, B. Berner, and S. W. Kim. One–way membrane for transdermal drug delivery systems 1. Membrane preparation and characterization. *Int. J. Pharm*. **1991**, *77*, 221–229.

[14] D. Foley, J. Corish, and O. I. Corrigan. Iontophoretic delivery of drugs through membranes including human stratum corneum. *Solid State Ionics* **1992**, *53*, 184–196.

[15] A. M. R. Bayon, J. Corish, and O.I. Corrigan. *In vitro* passive and iontophoretically assisted transport of salbutamol sulfate across synthetic membranes. *Drug Development Industrial Pharmacy* **1993**, *19*, 1169–1181.

[16] J. Ramis, L. Conte, X. Segado, J. Forn, J. Lauroba, A. Calpena, E. Escribano, and J. Domenech. Influence of formulation on the *in vitro* transdermal penetration of flutrimazole. *Arzneimittel–Forschung/ Drug Research* **1997**, *47*, 1139–1144.

[17] M. T. D. Cronin, J. C. Dearden, R. Gupta, and G. P. Moss. An investigation of the mechanism of flux across polydimethylsiloxane membranes by use of quantitative structure–permeability relationships. Journal of Pharmacy

and Pharmacology **1998**, *50*, 143–152.
[18] R. J. Scheuplein, and I. H. Blank. Permeability of the skin. Physiological Reviews **1971**, *51*, 702–747.
[19] M. S. Roberts, R. A. Anderson, and J. Swarbrick. Permeability of human epidermis to phenolic compounds. *J. Pharma. Pharmacol*. **1977**, *29*, 677–683.
[20] H. Patel, W. ten Berge, and M. T. D. Cronin. Quantitative structure–activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. *Chemosphere*. **2002**, *48*, 603–613.
[21] E. Estrada. Spectral moments of the edge adjacency matrix in molecular graphs. 1. Definition and applications to the prediction of physical properties of alkanes. *J. Chem*. *Inf. Comput*. *Sci*. **1996**, *36*, 844–849.
[22] E. Estrada. Spectral moments of the edge adjacency matrix in molecular graphs. 2. Molecules containing heteroatoms and QSAR applications. *J. Chem*. *Inf. Comput*. *Sci*. **1997**, *37*, 320–328.
[23] E. Estrada. Spectral moments of the edge adjacency matrix in molecular graphs. 3. Molecules containing cycles. *J. Chem*. *Inf. Comput*. *Sci*. **1998**, *38*, 23–27.
[24] E. Estrada. Modeling the diamagnetic susceptibilities of organic compounds by a substructural graph theoretical approach. *J. Chem*. *Soc*. *Faraday Trans*. **1998**, *94*, 1407–1411.
[25] E. Estrada. Generalized Spectral Moments of the interacted line graph sequence. A novel approach to QSPR studies. *J. Chem*. *Inf. Comput*. *Sci*. **1998**, *39*, 90–95.
[26] E. Estrada and Y. Gutiérrez. Modeling chromatographic parameters by a novel graph theoretical sub–structural approach. *J. Chromatogr*. *A* **1999**, *858*, 187–199.
[27] E. Estrada, Y. Gutiérrez, and H. González. Modeling diamagnetic and magnetooptic properties of organic compounds with the TOSS–MODE approach. *J. Chem*. *Inf. Comput*. *Sci*. **2000**, *40*, 1386–1399.
[28] Y. Gutierrez and E. Estrada. TOSS–MODE (1997) (Topological Sub–Structural Molecular Design) for Windows Version 4.0, Universidad de Santiago de Compostela, Spain.
[29] Y. Gutierrez and E. Estrada, Modes Lab ®, **2002**, version 1.0 b.
[30] E. Estrada, Edge Adjacency relationship and a novel topological index related to molecular volume, *Inf. Comput*. *Sci*. **1995**, *35*, 31–33.
[31] R. O. Potts and R. H. Guy. A predictive algorithm for skin permeability: The effects of molecular size and hydrogen bond activity. Pharmaceutical Research. **1995**, *12*, 1628–1633.
[32] R. Todeschini, V. Consonni, and M. Pavan, 2002 Dragon. Software version 2.1.
[33] J. S. Michael, E. Dewar, G. Zoebisch, F. Eamonn, and J. P. Stewart. *J. Am. Chem. Soc*. **1985**, *107*, 3902.
[34] J. J. P. Stewar, **1990** MOPAC manual, 6th ed., p 189, Frank J. Seiler Research Laboratory, U. S. Air Force academy, Colorado Springs, CO.
[35] R. Todeschini and V. Consonni, *Handbook of molecular descriptors*. Wiley–VCH, Weinheim, Germany, **2000**.
[36] M. H. Abraham, H. S Chadha, and R. C. Mitchell. Hydrogen bonding part 33; The factors that influence the distribution of solutes between blood and brain. *J. Pharm. Sci*. **1994**, *83*, 1257–1268.
[37] A. Bondi. Van der Waals volumes and radii. *J. Phys. Chem*. **1964**, *68*, 441–451.
[38] M. Randić. Generalized molecular descriptors. *J. Math*. *Chem*. **1997**, *7*, 155–168.
[39] G. P. Moss, J. C. Dearden, H. Patel, and M. T. D. Cronin Quantitative structure–permeability relationships (QSPRs) for percutaneous absorption. *Toxicol. in Vitro* **2002**, *16*, 299–317.
[40] M. P. Gonzalez and A. H. Morales. TOPS–MODE versus DRAGON descriptors to predict permeability coefficients through Low–density polyethylene. *J. Comp. Aided Mol. Design* **2003**, *17*, 665–672.
[41] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev*. **1997**, *23*, 3–25.
[42] R B. Kowalski and S. Wold. Pattern recognition in chemistry, In: Handbook of statistics. Eds: Krishnaiah, P. R. and Kanal, L. N. North Holland Publishing Company, Amsterdam. 1982, 673–697.