9th International Electronic Conference on Synthetic Organic Chemistry. ECSOC-9
1-30 November 2005. http://www.usc.es/congresos/ecsoc/9/ECSOC9.HTM & http://www.mdpi.net/ecsoc/

[G005]

Prediction the human skin permeation through a Topological Substructural approach.

Maykel Pérez González[1, 2, *] and Aliuska Morales Helguera[2].

[1] Unit of Services, Experimental Sugar Cane Station "Villa Clara-Cienfuegos", Ranchuelo, Cuba.

[2] Department of Drug Design, Chemical Bioactive Center, Central University of Las Villas, Santa Clara, Villa Clara. Cuba.

ABSTRACT

A *TO*Pological *S*ubstructural *MO*lecular *DE*sign (TOPS-MODE) was used to predict the flux across human skin permeability coefficient for heterogeneous set of compounds. The obtained model explained more than 84 % of data variance and shown the importance of the hydrogen bonding and the hydrophobicity to describe the property under study. Finally, the TOPS-MODE was used to calculate the contribution of different fragments to the human skin coefficient for studied compounds. The present approximation proved to be a good method to studying the permeability skin human coefficient for the heterogeneous compounds, which could be extended to other series of compounds.

Keywords: **Human skin, Permeability coefficients, QSPR, TOPS-MODE.**

***Corresponding Author: mpgonzalez76@yahoo.es**
Tel: 53-42-281473; Fax: 53-42-281130

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 iontophoretic 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 to 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 validate the TOPS MODE applicability in this area.

Therefore, the aim of this study was to investigate the role that TOPS-MODE play on the explanation of such property using a data set of 114 organic compounds and we will show here how TOPS – MODE is able to produce good QSPR models that permit easy structural interpretation of the results in terms of group contributions to skin permeability.

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. To draw the hydrogen-depleted molecular graphs for each molecule of the data set,
2. To use appropriate bond weights in order to differentiate the molecular bonds, e.g., hydrophobicity, bond dipoles, bond polarizability, etc.,
3. To 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. To 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:

   $P = a_0\mu_0 + a_1\mu_1 + a_2\mu_2 + a_3\mu_3 \ldots\ldots\ldots a_k\mu_k + b$ (Eq. 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. To test the predictive capability of the QSPR model by using cross-validation techniques.
6. To compute the contributions of different groups of interest in order to determine their quantitative contribution to the permeability activity of molecules under study.

The computation of fragment contributions to the activity under study is probably the most important advance of the TOPS-MODE approach to the study of permeability variables compared to the traditional QSAR and QSPR methods. The procedure consists of calculating the spectral moment for all the fragments contained in a given substructure, and by difference of these moments we obtain the contribution of the substructure. The general algorithm for this computational approach is as follows:

First, we select the substructure whose contribution to the moments we would like to determine. Then, we generate all the fragments, which are contained in the corresponding substructure, and calculate the spectral moments for both, the substructure and all their fragments. The contribution of the substructure to the spectral moments is finally obtained as the difference between the spectral moments of the substructure and all those from their fragments. Once, the contributions of the different structural fragments are obtained, we only need to substitute these contributions into the quantitative model developed to describe the property studied.

Data Sets and Computational Strategies

A data set of 114 compounds for which the permeability coefficients were reported in the literature was selected [31]. Briefly, these data are a compilation from both literature and regulatory sources [32-33]. As these data come from a variety of sources it may be assumed that there is variability in the exact methodology.

The parameter studied is log(p) where p is the permeability coefficient through human skin. The names of the compounds, as well as the calculated and experimental values of log(p) in units of cm\h as despite equation 4 are shown in Table 1.

Table 1. Observed, predicted, and residual values of permeability coefficients (cm/h) through human skin for the 110 compounds used to derive the QSPR (Eq. 3).

Number	Compounds	Observed	Predicted	Deleted Residuals
1	1,2-dichloropropene	-2.00	-1.55	-0.46
2	17-hydroxyprogesterone	-3.22	-3.72	0.61
3	2,3-butanediol	-4.39	-3.47	-0.94
4	2,4,6-trichlorophenol	-1.23	-1.75	0.55
5	2,4-Dichlorophenol	-1.22	-1.91	0.72
6	2-butanone	-2.95	-2.43	-0.52
7	2-butoxyethanol	-2.85	-3.01	0.17
8	2-chlorophenol	-1.48	-2.07	0.61
9	2-cresol	-2.00	-2.02	0.02
10	2-heptanone	-2.00	-2.06	0.06
11	2-hexanone	-2.35	-2.21	-0.14
12	2-pentanone	-2.6	-2.34	-0.27
13	2-toluidine	-1.44	-2.21	0.79
14	3-cresol	-2.00	-2.02	0.03
15	3-xylene	-1.10	-1.12	0.02
16	4-bromophenol	-1.44	-2.01	0.59
17	4-chloro-3,5-xylenol	-1.28	-1.61	0.35
18	4-chlorophenol	-1.44	-2.07	0.65
19	4-ethyl phenol	-1.46	-1.77	0.32
20	4-methyl-2-pentanol	-2.33	-2.00	-0.35
21	Acetaldehyde	-3.15	-2.66	-0.50
22	Acetic acid	-3.21	-2.85	-0.37
23	Acetone	-3.29	-2.62	-0.68
24	Acetonitrile	-3.21	-2.56	-0.67
25	Acrolein	-3.07	-2.60	-0.49
26	Acrylic acid	-3.05	-2.62	-0.44
27	Acrylonitrile	-2.87	-2.35	-0.54
28	Aldosterone	-5.52	-5.38	-0.20
29	Allyl alcohol	-2.95	-2.97	0.02

30	Amobarbital	-2.64	-3.24	0.69
31	Aniline	-2.65	-2.40	-0.25
32	Atropine	-5.07	-3.56	-0.58
33	Benzyl alcohol	-2.22	-2.75	0.54
34	Butobarbital	-3.71	-4.08	0.41
35	Butyl acrylate	-2.00	-2.22	0.23
36	Butyric acid	-3.00	-2.64	-0.37
37	Catechol	-2.77	-2.89	0.12
38	Cortexolone	-4.13	-3.72	-0.49
39	Corticosterone	-4.22	-4.61	0.49
40	Cortisone	-5.00	-5.21	0.27
41	Cresol	-2.00	-2.02	0.02
42	Cumene	-0.85	-0.61	-0.26
43	Cyclohexanone	-2.74	-3.19	0.47
44	Diethanolamine	-4.38	-4.59	0.22
45	Diethyl ether	-1.80	-1.75	-0.05
46	Diethylamine	-2.75	-1.64	-1.14
47	Digitoxin[a]	-4.89	-	-
48	Dimethyl acetamide	-2.80	-3.39	0.60
49	Dioxane	-3.45	-3.31	-0.14
50	Epichlorohydrin	-3.43	-3.04	-0.40
51	Estriol	-4.40	-4.01	-0.56
52	Estrone	-2.44	-2.55	0.11
53	Ethanol	-3.10	-2.83	-0.27
54	Ethanolamine	-4.02	-4.19	0.19
55	Ethyl acrylate	-2.39	-2.45	0.06
56	Ethyl benzene	-1.15	-1.10	-0.05
57	Ethyl formate	-3.01	-2.98	-0.03
58	Ethylamine	-3.09	-2.85	-0.24
59	Ethylene dichloride	-2.00	-1.94	-0.06
60	Ethylene glycol	-4.07	-4.18	0.12

61	Ethylhexyl phthalate	-1.52	-1.31	-0.32
62	Etorphine	-2.44	-2.47	0.05
63	Fentanyl[a]	-2.25	-	-
64	Formaldehyde	-2.65	-2.69	0.04
65	Heptanol[a]	-1.50	-	-
66	Hexachlorobutadiene	-0.92	-1.04	0.13
67	Hexachloroethane	-1.40	-1.63	0.24
68	Hexanoic acid	-1.85	-2.41	0.57
69	Hydrocortisone	-5.52	-4.70	-1.05
70	Hydromorphone	-4.82	-4.30	-0.56
71	Isoamyl alcohol	-2.00	-2.46	0.48
72	Isobutanol	-2.65	-2.50	-0.16
73	Isopropyl alcohol	-3.05	-2.46	-0.60
74	Isopropylamine	-2.90	-2.49	-0.42
75	Isoquinoline	-1.78	-1.87	0.10
76	Meperidine	-2.43	-1.71	-0.78
77	Methanol	-3.46	-3.41	-0.06
78	Methyl acrylate	-2.68	-3.13	0.46
79	Methyl acrylic acid	-2.58	-2.64	0.06
80	Methyl cellosolve	-3.73	-3.94	0.22
81	Monomethylhydrazine	-3.75	-4.11	0.43
82	Morphine	-5.03	-4.13	-0.96
83	Morpholine	-3.86	-3.39	-0.48
84	n,n-dimethyl aniline	-1.70	-2.03	0.33
85	Naproxen	-3.40	-1.94	-0.64
86	n-butanol	-1.55	-2.69	0.02
87	n-decanol	-1.10	-1.49	0.48
88	n-heptanoic acid	-1.70	-2.24	0.56
89	n-hexanol	-1.89	-2.41	0.55
90	Nicotine	-1.71	-2.79	0.32
91	n-nitrosodiethanolamine	-5.22	-5.50	0.33

92	n-octanoic acid	-1.60	-2.04	0.47
93	n-octanol	-1.28	-2.01	0.79
94	n-pentanol	-2.22	-2.57	0.36
95	n-propanol	-2.91	-2.77	-0.14
96	Pentanoic acid	-2.70	-2.54	-0.17
97	Phenobarbital	-3.34	-3.64	0.34
98	Phenol	-2.00	-2.07	0.07
99	Phenylglycinyl ether	-2.84	-2.04	-0.82
100	Progesterone	-2.82	-3.24	0.52
101	Propionic acid	-2.94	-2.71	-0.24
102	Propylene dichloride	2.00	-1.61	-0.41
103	Propylene oxide	-3.05	-2.79	-0.26
104	Pyridine	-2.74	-2.35	-0.40
105	Resorcinol	-2.82	-2.89	0.07
106	Salicylic acid	-2.20	-2.90	0.73
107	Scopolamine	-4.30	-4.75	0.50
108	Styrene	-0.19	-1.16	1.02
109	Sucrose[a]	-5.28	-	-
110	Testosterone	-3.40	-3.57	0.20
111	Thymol	-1.28	-0.93	-0.37
112	Toluene	-1.30	-1.36	0.07
113	Triethylamine	-2.31	-0.64	-0.16
114	Vinyl acetate	-2.73	-2.82	0.09

[a] Compounds indicates an outlier removed from Eq. (2)

TOPS-MODE [29] computer software was employed to calculate the molecular descriptors. Here, the hidrophobicity was used to weigh the bond adjacency matrix. The selection of only this type of descriptor from the whole pool of ten types included in TOPS-MODE methodology was carried out for the sake of simplicity and on the belief that steric and hydrophobicity parameters influence the permeability of compounds through skin layers. We also used multiplications of spectral moments as independent

variables to describe permeability characteristics. In this case we only multiplied μ_0 and μ_1 for the fifteen first spectral moments obtaining thirty new variables. The total number of descriptors used in this model was 45 (15 spectral moments + 30 multiplications of moments). On the other hand, another structural variable employed in this study was an indicator of hydrogen bond capability of groups in the molecule. The total numbers of lone pairs capable of accepting and donating hydrogen bonds was taken according to Charton and Charton [34]. In this scheme oxygen, having two lone pairs is assumed to be capable of accepting two hydrogen bonds [35].

The statistical processing to obtain the QSAR model was carried out by using the forward stepwise regression methods. The statistical significance of the model 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. The identification of outliers following analysis of the residuals from the predicted fits was performed using least-squares regression analysis [36].

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.

$$\log(p) = -2.88 - 0.21 \cdot HA_{LP} + 0.43 \cdot \mu_1^H - 8.55 \cdot 10^{-12} \cdot \mu_1 \mu_{15}{}^H - 5.93 \cdot 10^{-2} \cdot \mu_3{}^H + 0.02 \cdot \mu_2{}^H + 6.89 \cdot 10^{-13} \cdot \mu_0 \mu_{15}{}^H \quad \textbf{(Eq. 2)}$$

N = 114 S = 0.573 R^2 = 0.760 F = 56.452 p < 0.0001 q^2 = 0.723 S_{cv} = 0.653

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., H for hydrophobicity and HA_{LP} is the total number of lone pairs that can accept hydrogen bonds on the molecule.

Analysis of the residuals for equation 2 identified four potential outliers. These outliers have removed from the complete data set. It is not appropriate to remove compounds from a data set simply to improve a correlation, and indeed much important information may be gleaned from the analysis of outliers omitted from QSPR.

The most significant of these were digitoxin and sucrose is atypical of this data set as they are able to form many more hydrogen bonds than the other compounds. These outliers have been reported by Cronin et al. [11]. On the other hand, these very large number of hydrogen bond acceptors could potentially impede skin permeation.

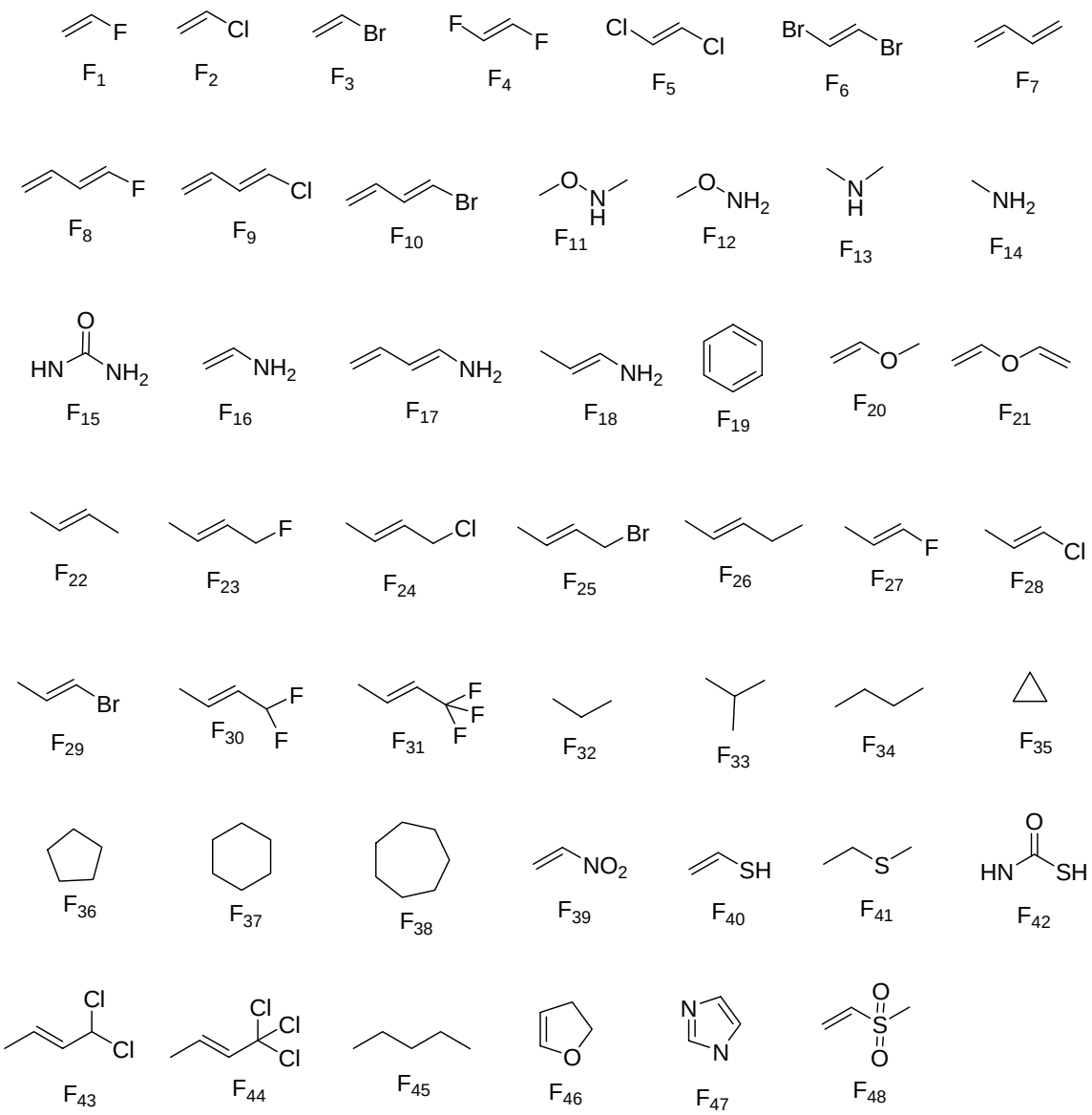
Based on this evidence it was felt that it would be necessary, and justified, to omit these outliers in this study in order to better model the data. Removal of these compounds and subsequent re-analysis of the data set produced the following QSPR:

$$\log(p) = -2.49 - 0.24 \cdot HA_{LP} + 0.36 \cdot \mu_1^{H} - 2.00 \cdot 10^{-10} \cdot \mu_1 \mu_{15}^{H} - 2.50 \cdot 10^{-5} \cdot \mu_7^{H} + 1.71 \cdot 10^{-8} \cdot \mu_0 \mu_8^{H} + 9.15 \cdot 10^{-10} \cdot \mu_1 \mu_{14}^{H} \quad \textbf{(Eq. 3)}$$

N = 110 S = 0.439 R^2 = 0.844 F = 93.347 p < 0.0001 q^2 = 0.817 S_{cv} = 0.518

An improved correlation coefficients is observed for equation 3 in which the outliers have been removed when compared with equation 2. Due to the statistical quality of this relationship the removal of more outliers is not justified. From the statistical point of view this model is a robust one as can be seen from the statistical parameters of the cross-validation. The figure 1 shows a linear regression between the predicted and observed values for log (p).

Figure 1. The linear relation between observed and predicted permeability for the compounds of the training set.



To complete our permeability study of this set of is absolutely necessary to know which are the possible contributions at the skin permeability of some chemical groups that appear in the training set.

FRAGMENTS CONTRIBUTIONS

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. In such a way, we can determine the fragments with a positive or negative contribution to the property under study, which can be interpreted in terms of the physicochemical or biological processes influencing its.

The figure 2 and in the table 2 showing that the increase of the aliphatic rings size of the fragment series F_{35} to F_{38} leads to increase too the contribution to the property. In agreement with the equation 2, higher hydrophobicity of the fragment increases its contribution to the permeability in human skin. This behavior has been established by Cronin et al. [11] and Pots and Guy [40]. This authors show how the percutaneous absorption across excised human skin in vitro is governed by hydrophobicity property.

Table 2.Contribution of some selected fragments to the permeation across human skin property.

Fragment	Contribution	Fragment	Contribution	Fragment	Contribution
F_1	0.68	F_{17}	-0.42	F_{33}	1.27
F_2	0.86	F_{18}	-0.24	F_{34}	1.49
F_3	0.92	F_{19}	-0.38	F_{35}	1.43
F_4	0.52	F_{20}	1.10	F_{36}	0.21
F_5	0.88	F_{21}	0.57	F_{37}	0.45
F_6	1.01	F_{22}	1.04	F_{38}	0.58
F_7	1.01	F_{23}	0.98	F_{39}	0.88
F_8	0.86	F_{24}	0.72	F_{40}	0.46
F_9	1.04	F_{25}	0.82	F_{41}	1.04
F_{10}	1.10	F_{26}	0.94	F_{42}	1.47
F_{11}	-0.33	F_{27}	1.28	F_{43}	-0.06
F_{12}	-1.36	F_{28}	0.74	F_{44}	0.97
F_{13}	-0.52	F_{29}	0.93	F_{45}	1.16
F_{14}	-1.01	F_{30}	0.99	F_{46}	1.61
F_{15}	-1.56	F_{31}	0.76	F_{47}	0.31
F_{16}	0.68	F_{32}	0.84	F_{48}	-0.46

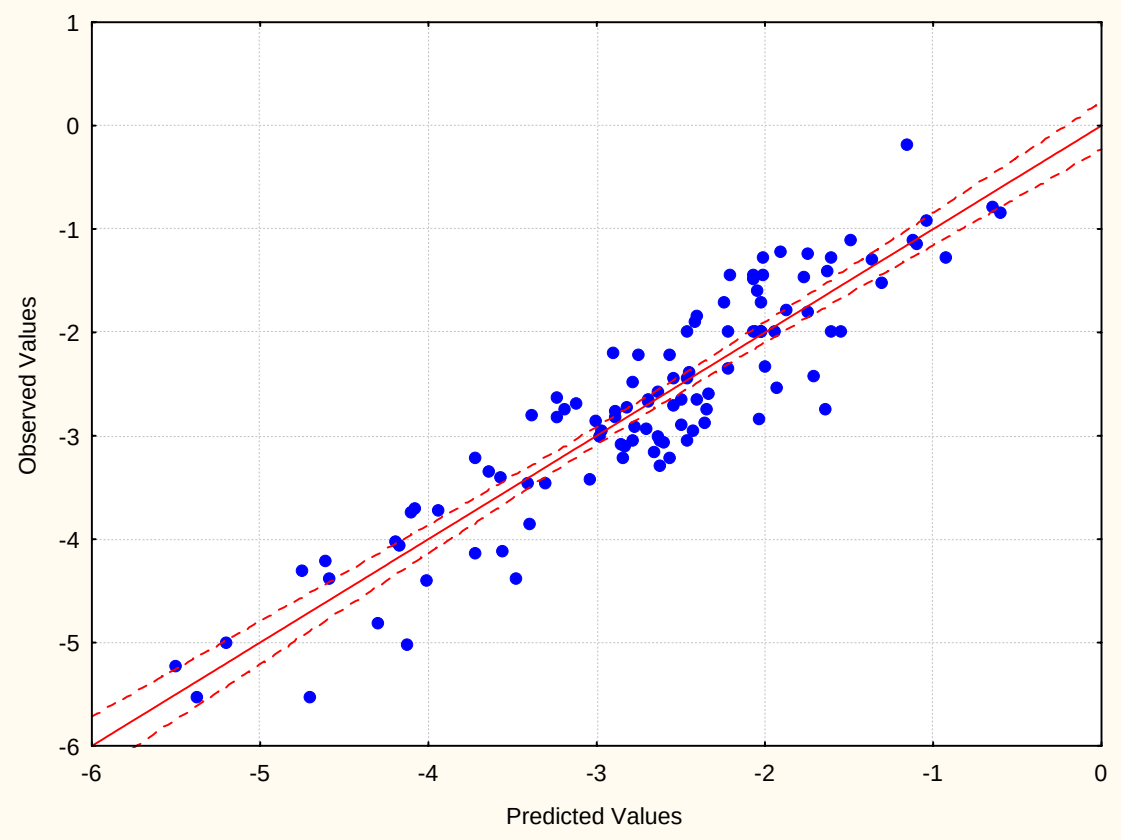


Figure 2. Structures of selected fragments for which their contribution to the human skin permeability appears in table 2.

The increase of the aliphatic contribution to the fragments F_{32}, F_{34} an F_{45} by longer aliphatic chains straight forward leads to increase the permeability of human skin. Without further considerations Cronin et al. [11] and Pots and Guy [40] proposed that a molecular size of substituent have played a central role in the increase of the permeation human skin coefficient. Hence they emphasize the strong dependence of permeation in

human skin on the compounds size. According their regression coefficient an increase in molecular size leads to an increase in absorption.

As it is seen from the fragments F_{33} and F_{34}, these fragments have a slightly higher absorption; it does not satisfy Cronin et al. [11] and Pots and Guy [40] conclusion. Even though certain shift of the ramification of the fragments F_{33} and F_{34}, do not provide steady changes in their hydrophobicity. On the basis of the above results we supported that the hydrophobicity determines the absorption, but no the molecular size.

In fragments F_{19} when we compared with F_{37}, there are a smaller contribution of benzene ring to the hydrophobicity, but this fragment showed a higher sorption due to their interaction with the positive fraction of proteins and others receptors in human skin.

Other example of predominance of the electronic interactions of compounds this series where observed by the fragments F_{13}, F_{14}, F_{16} where could be appreciated an arrangement of the contribution $F_{16} > F_{13} > F_{14}$. This behavior obeys to ability of these amines to form hydrogen bonding. The fragment F_{16} corresponds to amine, which has a conjugated double bond, hence it stimulates and strong this kind of interaction. Thus it is clearly the negative contribution of F_{14} to the absorption. We can conclude that the ability to the formation of hydrogen bonds between compounds and proteins prevents their absorption across the human skin.

Finally, when the number of halogen is increased in a fragment of these families (F_{23}, F_{30}, F_{31}); (F_{24}, F_{43}, F_{44}) a remarkable increase of the absorption coefficient is observed. This is the special interest for some time due to the toxicological properties of these compounds. Müller recently demonstrated how, in general sense an increasing of the halogen atoms in a chemical structure increase the agonist effect of the adenosine receptors [41]. Therefore, this involve that possess a big absorption coefficient in human skin and for that reason is possible that this compounds present a higher trouble for their toxicology effect in the body, property not desirable for new potential drugs.

For this reason combine models are necessary in the future for resolve this type of problems.

CONCLUDING REMARKS

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 114 permeants, which is both statistically and chemically sound. This model explains more than 84% of the variance in the experimental permeability coefficients and shows good predictive ability in cross-validation. Therefore, the spectral moments show a performance, which suggests that they can be used in new QSPR applications.

On the other hand, the main advantage of using a TOPS-MODE approach in QSPR/QSAR has been confirmed again in this work. This approach is able to derive group contributions and simultaneously provides the means of interpreting them thus contributing to our understanding of the physicochemical or biological processes involved. 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.

Acknowledgments

Maykel Pérez thanks at the owners of the software Modeslab 1.0 for the donation of this valuable tool to the completion of this work.

REFERENCES

1. Kasting, G. B.; Smith, R. L.; Cooper, E. R. Effect of lipid solubility and molecular size on percutaneous absorption. In Skin Pharmacokinetics, B. Shroot and H. Schaefer (eds.), Karger, Basel, **1987,** 138-153.
2. Anderson, B.D.; Higuchi, W. I.; Raykar, P. V. Heterogeneity effects on permeability-partition coefficient relationships in human stratum corneum. *Pharm. Res*. **1988**, 5 566-573.
3. Anderson, B.D.; Higuchi, W. I.; Raykar, P. V. Solute structure-permeability relationships in human stratum corneum. *J. Invest. Dermatol*. **1989,** 93, 280-286.

4. Woolfson, A.D.; McCafferty, D.F. Percutaneous local anaesthesia: drug release characteristics of the amethocaine phase-change system. *Int. J. Pharm.* **1993,** 94, 75–80.
5. Kurosaki, Y.; Nagahara, N.; Taniza, W.A.; Nishimura, H.; Nakayama, T.; Kimura T. 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. Megrab, N.A.; Williams, A.C.; Barry, B.W. Estradiol permeation through human skin and Silastic membrane — effects of propylene glycol and supersaturation. *Journal of Controlled Release* **1995,** 36, 277–294.
7. Megrab, N.A.; Williams, A.C.; Barry, B.W. 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. Stott, P.W.; Williams, A.C.; Barry, B.W. Characterisation of complex coacervates of some tricyclic antidepressants and evaluation of their potential for enhancing transdermal flux. *Journal of Controlled Release* **1996**, 41, 215–227.
9. van Hal, D.; van Rensen, A.; Vringer, T.; Junginger, H.; Bouwstra, J. Diffusion of estradiol from non-ionic surfactant vesicles through human stratum corneum in vitro. *STP Pharma Sciences* **1996,** 6, 72–78.
10. Minghetti, P.; Casiraghi, A.; Cilurzo, F.; Montanari, L.; Marazzi, M.; Falcone, L.; Donati, V. Comparison of different membranes with cultures of keratinocytes from man for percutaneous absorption of nitroglycerine. *Journal of Pharmacy and Pharmacology*. **1999,** 51, 673–678.
11. Cronin, M.T.D.; Dearden, J.C.; Moss, G.P.; Murray-Dickson, G. Investigation of the mechanism of flux across human skin in vitro by quantitative structure-permeability relationships. *European Journal of Pharmaceutical Sciences* **1999,** 7, 325–330.
12. Cichon, R.; Janicki, S. Effect of polyoxyethylene glycols (PEG) on properties of the matrix model of transdermal therapeutic system (TTS) with testosterone. *Pharmazie* **1991,** 46, 719–723.

13. Yuk, S.H.; Lee, S.J.; Okano, T.; Berner, B.; Kim, S.W. One-way membrane for transdermal drug delivery systems 1. Membrane preparation and characterization. *International Journal of Pharmaceutics* **1991,** 77, 221–229.
14. Foley, D.; Corish, J.; Corrigan, O.I. Iontophoretic delivery of drugs through membranes including human stratum corneum. *Solid State Ionics* **1992,** 53, 184–196.
15. Bayon, A.M.R.; Corish, J.; Corrigan, O.I. In vitro passive and iontophoretically assisted transport of salbutamol sulfate across synthetic membranes. *Drug Development and Industrial Pharmacy* **1993,** 19, 1169–1181.
16. Ramis, J.; Conte, L.; Segado, X.; Forn, J.; Lauroba, J.; Calpena, A.; Escribano, E.; Domenech, J. Influence of formulation on the in vitro transdermal penetration of flutrimazole. *Arzneimittel-Forschung/ Drug Research* **1997**, 47, 1139–1144.
17. Cronin, M.T.D.; Dearden, J.C.; Gupta, R.; Moss, G.P. 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. Scheuplein, R.J.; Blank, I.H. Permeability of the skin. *Physiological Reviews* **1971,** 51, 702–747.
19. Roberts, M.S.; Anderson, R.A.; Swarbrick, J. Permeability of human epidermis to phenolic compounds. *Journal of Pharmacy and Pharmacology* **1977,** 29, 677–683.
20. Patel, H.; ten Berge, W.; Cronin, M.T.D. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. *Chemosphere*. **2002,** 48, 603-613.
21. Estrada, E. 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. Estrada, E. 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. Estrada, E. Spectral moments of the edge adjacency matrix in molecular graphs. 3. Molecules containing cycles. *J. Chem. Inf. Comput. Sci*., **1998**. 38, 23-27.
24. Estrada, E. Modeling the diamagnetic susceptibilities of organic compounds by a substructural graph theoretical approach. *J. Chem. Soc. Faraday Trans*., **1998.** 94, 1407-1411.
25. Estrada, E. 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. Estrada, E.; Gutiérrez, Y. Modeling chromatographic parameters by a novel graph theoretical sub-structural approach. *J. Chromatogr*. *A*, **1999,** 858, 187-199.
27. Estrada, E.; Gutiérrez, Y.; González, H. Modeling diamagnetic and magnetooptic properties of organic compounds with the TOSS-MODE approach. *J. Chem. Inf. Comput. Sci*., **2000**, 40, 1386-1399.
28. Gutierrez, Y.; Estrada, E.; TOSS-MODE (1997) (Topological Sub-Structural Molecular Design) for Windows Version 4.0, Universidad de Santiago de Compostela, Spain.
29. Gutierrez, Y. and Estrada, E.. Modes Lab ®, **2002**, version 1.0 b.
30. Estrada, E. Edge Adjacency relationship and a novel topological index related to molecular volume, *Inf. Comput. Sci*., **1995**, 35, 31-33.
31. Kirchner, L.A., Moody, R.P., Doyle, E., Bose, B., Jeffry, J., Chu, I.,. The prediction of skin permeability by using physicochemical data. *ATLA* **1997**, 25, 359–370.
32. Flynn, G.L. Physicochemical determinants of skin absorption. In: Gerrity, T.R., Henry, C.J. (Eds.), Principle of Route-to-Route Extrapolation for Risk Assessment. Elsevier, New York, **1990**, pp. 93–127.
33. Wittiker, C.; Walker, J.D.; Gay, D.A.; Neal, M.W. OSHA chemical referred to the ISCA Interagency Testing Committee for percutaneous absorption testing and prioritization and analysis of OSHA skin notation criteria. *Toxicologist.* **1993**, 13, 101.
34. Charton, M.; Charton, B.I. The structural dependence of amino acid hydrophobicity parameters. *J. Theoret. Biol.* **1982**, 99, 619–624.

35. Estrada, E.; Molina, E.; Uriarte, E. Quantitative structure-toxicity relationships using TOPS-MODE. 2. Neurotoxicity of a non-congeneric series of solvents. *SAR and QSAR Environm. Res.* **2001**, 12, 445-459.
36. Kowalski, R B.; Wold, S. Pattern recognition in chemistry, In: Handbook of statistics. Eds: Krishnaiah, P. R. and Kanal, L. N. North Holland Publishing Company, Amsterdam. **1982,** 673-697.
37. Moss, G.P.; Dearden, J.C.; Patel, H.; Cronin, M.T.D. Quantitative structure–permeability relationships (QSPRs) for percutaneous absorption. *Toxicology in Vitro*. **2002**, 16, 299-317.
38. Gonzalez, M. P.; and Helguera, A. M. TOPS-MODE versus DRAGON descriptors to predict permeability coefficients through Low-density polyethylene. J. Comp. Aided Mol. Design. (*in press*)
39. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev*. **1997,** 23, 3–25.
40. Potts, R.O.; Guy, R.H. Predicting skin permeability. *Pharm. Res.* **1992**, 9, 663-669.
41. Müller C. E. Adenosine Receptor Ligands-Recent Developments Part I. Agonists. *Current Medicinal Chemistry*, **2000**, 12, 1269-1288.