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Use of molecular topology for the prediction of physico-chemical, pharmacokinetic and toxicological properties of a group of antihistaminic drugs

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Abstract

We used molecular connectivity to search mathematical models for predicting physico-chemical (e.g. the partition coefficient, P), pharmacokinetic (e.g. the time of maximum plasma level, and toxicological properties (lethal dose, LD) for a group of antihistaminic drugs. The results obtained clearly reveal the high efficiency of molecular topology for the prediction of these properties. Randomization and cross-validation by use of leave-one-out tests were also performed in order to assess the stability and the prediction ability of the connectivity functions selected.

Keywords: Antihistaminic drugs; Pharmacokinetic; Molecular topology

1. Introduction

A large number of synthetic antihistaminic drugs for oral use have been developed over the last thirty years. Also, synthetic compounds and natural products have been investigated for antihistaminic activity in both pharmacological and clinical terms.

Nowadays, the antihistaminic drugs, particularly antagonists of the H1-receptors (Hardman et al., 1996), are used to avoid the health problems related to widespread allergic affections, a high incidence pathology on the population: Indeed, allergic rhinitis affects between 15 and 25% of the US general population (Meltzer and Grant, 1999). These drugs exhibit their highest activity in allergies of the respiratory tract, (specifically in

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seasonal rhinitis and conjunctivitis), but are also used in catarrhal rhinitis and gripals. They are also employed in dermatology to treat allergic dermatosis (particularly in relation to acute urticaria).

One important field of research in contemporary chemistry is the modelling and prediction of physico-chemical and biological properties of molecules. This kind of study is based on the paradigm that physico-chemical and biological properties are dependent on molecular structure. As a consequence, one of the most important points in such research is the selection of suitable descriptors containing the information stored in molecular structures.

Various types of formalisms including molecular mechanics (Siebel and Kollman, 1990), quantum chemical descriptors (Weinstein et al., 1979), similarity/dissimilarity approaches (Johnson and Maggiora, 1990), topological descriptors (Hall and Kier, 1991; Basak et al., 1997; Gálvez et al., 1995a; Estrada et al., 1998) and 3D-QSAR (Medvedev et al., 1999) have so far been used in this context. Some of these methods are extremely efficient, whether the main goal is the accurate prediction of a given physical, chemical or biological property for a compound exhibiting a well-defined pharmacological activity.

The graph-theoretical approaches to structure and quantitative structure-activity relationships (SAR and QSAR, respectively) (Devillers, 2000; Oblak et al., 2000) rely on a well-defined mathematical representation of molecular structure. The molecular descriptors derived from them are commonly known as 'topological indices'. Such indices are usually numbers containing relevant information about molecular structure.

Topological indices have proved useful in the prediction of diverse physical, chemical and biological properties (Kier and Hall, 1986), particularly for purposes such as designing new antiviral (Julian-Ortiz et al., 1999), analgesic (García-Domenech et al., 1996), bronchodilator (Rios-Santamarina et al., 1998), antihistaminic (Duart et al., 2001) and antimicrobial drugs (Gozalbes et al., 2000).

In this work, we use molecular topology on a set of antihistaminics to look for mathematical models able to predict a physico-chemical property playing a key role on pharmacokinetics: The octanol/water partition constant (P). We also search predictive models for T_{max}, i.e. time as necessary to reach the maximum level of drug into the bloodstream, what is also a critical pharmacokinetic parameter, as well as a toxicological property: Lethal Dose-50 (LD_{50}). The predictions of P (specifically log P) and T_{max}, are particularly interesting for those compounds administrated by oral pathway since the degree of absorption and the time necessary to achieve therapeutic effects, are closely related to those properties. On the other side, LD_{50} is a good measure of the acute toxicity to be expected for a drug.

2. Material and methods

2.1. Calculation of topological descriptors

The descriptors used were the 20 single Topological Charge Indices (TCI), G_i and J_i, up to the fifth order (Gálvez et al., 1994, 1995b), Topological Geometrical Indices (TGI) (Gálvez et al., 1995a), and subgraph Randic–Kier–Hall Molecular Connectivity Indices (Kier et al., 1976; Kier and Hall, 1983) up to the fourth order. Other indices such as the differences and quotients between valence and non-valence connectivity indices were also determined.

The TCI G_k and J_k of order k for a given graph, are defined as:

$$G_k = \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} |c_{ij}| \delta(k, d_{ij}) \quad and \quad J_k = \frac{G_k}{(N-1)}$$

where N is the number of vertices in the chemical graph representing the molecular structure, i.e. the number of atoms other than hydrogen in the molecule; and c_{ij} is the charge term between the vertices i and j, which is defined as $c_{ij} = m_{ij} - m_{ji}$ (m_{ij} and m_{ji} being elements of the $N \times N$ matrix M obtained as the product of two matrices, $M = A \times Q$).

Consequently:

$$m_{ij} = \sum_{h=1}^{N} a_{ih} q_{hj}$$

Matrix A is called *connectivity or adjacency matrix*. Its elements, a_{ih}, represent the bonds between the atoms corresponding to vertices i and h in the graph. Element a_{ih} is 0 if either $i = h$ or i is not linked to h; 1 if i is bonded to h via a single bond; 1.5 if the bond is aromatic; 2 if it is a double bond; and 3 if it is a triple one. Matrix Q is known as the *Coulombian matrix*. Its elements, q_{hj}, are 0 if $h = j$; otherwise, $q_{hj} = 1/d_{hj}{}^2$, where d_{hj} is the topological distance between vertices h and j.

δ represents the Kronecker delta symbol ($\delta(\alpha,\beta) = 1$ if $\alpha = \beta$; $\delta(\alpha,\beta) = 0$ if $\alpha \neq \beta$)and d_{ij} is the topological distance between vertices i and j, which is the minimum number of bonds, of any order, that separates atoms i from j.

Thus, G_k represents the overall sum of the c_{ij} charge terms for every pair of vertices i and j, at a topological distance k. Valence TCI, $G_k{}^{v}$ and $J_k{}^{v}$, are defined in a similar way, by substituting the matrix A by A^{v}. The elements of both matrices are identical except for the main diagonal of A^{v}, which is obtained by replacing the zeroes in the main diagonal by the corresponding Pauling electronegativity EN, weighed for EN(Cl) = 2.

The other indices used in this work were as follows: V3, number of graph vertices with topological valence 3; V4, number of graph vertices with topological valence 4; L, length of the graph (number of connections linking the two most distant vertices via the shortest path).

The Wiener (Wiener, 1947) index (W) was also used. Therefore, each compound was characterized by a set of 62 indices.

2.2. Search of quantitative structure-activity relationship

Regression equations were obtained by correlating the experimental values of three properties: a toxicological property (LD_{50}), a pharmacokinetic property,(T_{max}), and a physico-chemical property (log P), with the calculated topological indices, using multilinear regression analysis, (MLRA), which yielded an equation of general form:

$$P_i = A_0 + \sum A_i X_i$$

where P_i is a property, X_i are the topological indices, and A_0 and A_i are the regression coefficients of the equation obtained. The equations were obtained by multilinear regression, using the biostatistics BMDP package (Dixon, 1982). The program searched subsets with 1, 2, 3, etc independent variables and selected the equation exhibiting the smallest Mallows Cp parameter, defined as

$$C\mathrm{p} = \mathrm{RSS}/(s^2 - (N - 2p))$$

were RSS is the residual sum of squares for a model with p independent variables, s^2 residual mean square based on the regression using all independent variables and N the number of cases. Each selected function is given together with the

Table 1
Connectivity functions selected through MLRA

Descriptor	Coeff. (B)	SE (B)	P-level
LD_{50} (i.p. in mouse, g/Kg)			
Constant	−0.307	0.102	0.012
G_3	0.387	0.035	0.000
$J_3{}^{V}$	−6.709	0.829	0.000
$J_5{}^{V}$	17.973	2.981	0.000
V_4	−0.153	0.025	0.000
$N = 16$	SEE = 0.059	$P < 0.000$	
$F = 54.41$	$r^2 = 0.952$	$r^2(\mathrm{cv}) = 0.915$	
T_{max} (h)			
Constant	5.351	0.550	0.000
${}^{0}\chi$	−2.280	0.234	0.000
${}^{2}\chi$	4.030	0.452	0.000
${}^{4}\chi_{PC}$	−2.003	0.334	0.000
$G_4{}^{V}$	0.831	0.197	0.000
$C^{4}\chi_c$	1.403	0.291	0.005
V_3	0.228	0.046	0.000
$N = 24$	SEE = 0.511	$P < 0.000$	
$F = 18.27$	$r^2 = 0.866$	$r^2(\mathrm{cv}) = 0.702$	
Log P (octanol/water)			
Constant	−30.517	6.338	0.000
${}^{3}\chi_p$	0.479	0.134	0.001
$G_1{}^{V}$	−0.146	0.027	0.000
$G_2{}^{V}$	−0.439	0.062	0.000
G_4	1.029	0.305	0.002
J_2	8.238	1.683	0.000
$\Delta^{1}\chi$	−5.693	1.004	0.000
$C^{2}\chi$	26.700	5.644	0.000
L	0.431	0.065	0.000
V_3	0.190	0.060	0.003
$N = 51$	SEE = 0.488	$P < 0.000$	
$F = 22.84$	$r^2 = 0.834$	$r^2(\mathrm{cv}) = 0.718$	

Table 2
Results obtained from MLRA on LD_{50}

Compound	LD_{50}exp.[a]	LD_{50}calc.[b]	LD_{50}calc.(cv)[c]
Azatadine	0.360	0.358	0.357
Azelastine	0.130	0.133	0.135
Brompheniramine	0.340	0.311	0.305
Carbinoxamine	0.260	0.335	0.349
Chlorcyclizine	0.460	0.446	0.443
Chlorothen	0.350	0.371	0.374
Chlorpheniramine	0.380	0.322	0.307
Cyproheptadine	0.170	0.220	0.287
Diphenhydramine	0.220	0.212	0.205
Isothipendil	0.190	0.295	0.316
Ketotifen	0.290	0.252	0.234
Mequitazine	0.170	0.135	0.119
Methaphenilene	0.450	0.469	0.476
Promethazine	0.500	0.399	0.384
Terfenadine	1.080	1.084	1.122
Tripelennamine	0.160	0.158	0.157

[a] From reference Peggs and Shimp (1995), Woodward (1998).
[b] From the mathematical model (Table 1).
[c] From cross-validation analysis.

following statistical parameters: N, r^2, cross-validation r^2_{cv}, standard error of estimation, (SEE), F-Statistical, (F) and the level of statistical significance, (p).

The narrow range spanned by the values of the studied properties ($0.1 < LD_{50} < 1.08$; $0 < T_{max} < 6.5$; $1 < \log P < 6$) may result in fortuitous good correlations. In order to avoid it, we subjected each equation to cross-validation using the leave-one-out and randomness approaches.

In addition, test groups were randomly selected for the properties T_{max} and $\log P$ ($\approx 15\%$ for T_{max} and 25% for $\log P$). These percentages were used to ensure a reasonably good level of statistical significance.

2.3. Randomization and predictive ability tests

The predictive ability of the selected mathematical models was evaluated through cross-validation, using the leave-one-out (Allen, 1974) method. To do this, one compound in the set was removed and the model was recalculated using the remaining $N-1$ compounds as training set. The property was then predicted for the removed element. This process was repeated for all the compounds in the set to obtain a prediction for each. A plot of the residual vs. cross-validation residual (cv) allowed the detection of outliers.

In order to identify potential fortuitous correlations, the randomization test was used. The values of the property of each compound were randomly permuted and linearly correlated with the above mentioned descriptors. This process was repeated as many times as compounds were in the set. The usual form of representing the results of a randomization test is by plotting correlation coefficients versus prediction ones (r^2 and r^2_{cv}, respectively).

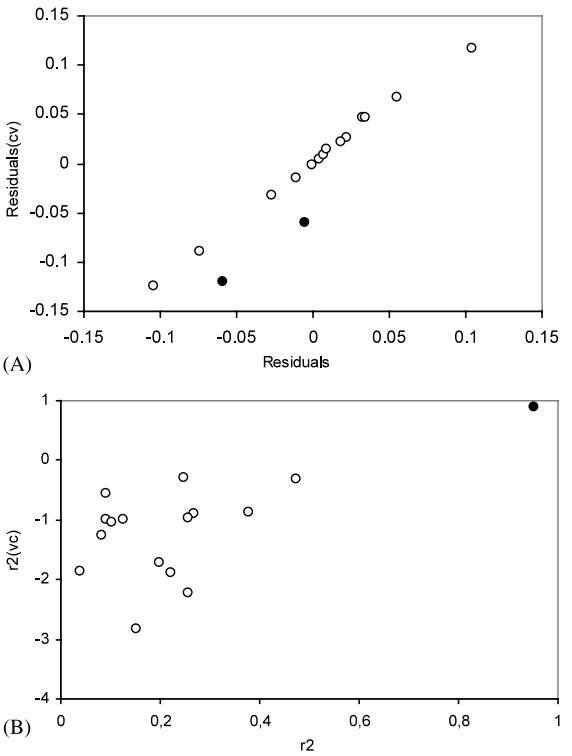

Fig. 1. Validation of the mathematical model obtained for the property LD_{50}. (A) Residuals obtained from the best regression versus Residuals obtained by cross-validation (black points = outliers). (B) Correlation coefficient, r^2_{cv}, versus prediction coefficient, r^2, obtained by randomization study.

Table 3
Results obtained for T_{max} from MLRA

Compound	T_{max} exp.[a]	T_{max} calc.[b]	T_{max} calc.(cv)[c]
Acrivastine	1.40	1.16	1.08
Almitrine	1.80	1.39	1.14
Astemizol	2.50	2.32	2.29
Azatadine	4.00	4.13	4.17
Azelastine	4.50	3.83	3.66
Flunarizine	3.00	2.55	2.45
ChlorPheniramine	2.50	2.43	2.42
Cinnarizine	3.30	3.72	3.98
Clemastine	4.00	3.08	2.49
Dimethindene	2.00	2.16	2.18
Diphenhydramine	2.70	2.71	2.72
Doxylamine	4.00	4.03	4.06
Ebastine	3.30	3.87	4.23
Hydroxyzine	2.50	2.48	2.48
Ketotifen	3.00	3.32	3.40
Levocabastine	1.50	1.50	1.51
Loratadine	1.50	2.02	2.29
Mequitazine	6.20	5.86	5.41
Oxatomide	4.00	3.63	3.54
Picumast	1.20	1.01	0.87
Promethazine	2.50	2.24	2.12
Terfenadine	1.50	2.35	2.85
Tripelennamine	3.00	3.33	3.38
Triprolidine	2.00	2.76	2.86
Test group			
Pheniramine	2.50	2.99	
Temelastine	0.60	−0.25	
Brompheniramine	3.10	2.44	
Cetiririzine	1.50	2.65	

[a] From references Estelle and Simons (1999), Paton and Webster (1985).
[b] From the mathematical model (Table 1).
[c] From cross-validation analysis.

3. Results and discussion

Table 1 shows the functions that predict each property. For each equation, the indexes for each function, the value of their coefficients (B), the standard error (SE(B)), the level of statistical significance (p) of each term, and the global statistical parameters of each function (N, r^2, r^2_{cv}, SEE, F and p) are shown.

Several general suggestions can be drawn from the mathematical-statistical aspects, namely:

(1)If we observe the column p-level (Table 1), all the present indices are statistically significant at above 99% (most even above 99.9%). This indicates that all contain, at a significant level, topological and structural information enough to quantify the different properties.

(2)The descriptors in the selected equations are mainly TCI, which take account of intra-molecular charge transfers, and also χ_i indices, which encode topological information on molecular assembling. All the equations include Vn descriptors ($n=3$ or $n=4$), which account for the presence of ramifications, tertiary amines and carbons, and quaternary carbons, respectively.

(3)The three connectivity functions exhibit r^2 values above 0.80 (0.952, 0.866 and 0.834 for LD_{50}, T_{max} and log P, respectively), what explains over 80% of the variance. It should be noted, however, that a high r^2 coefficient does not necessarily imply a good predictive model: The mere addition of a new variable to the regression

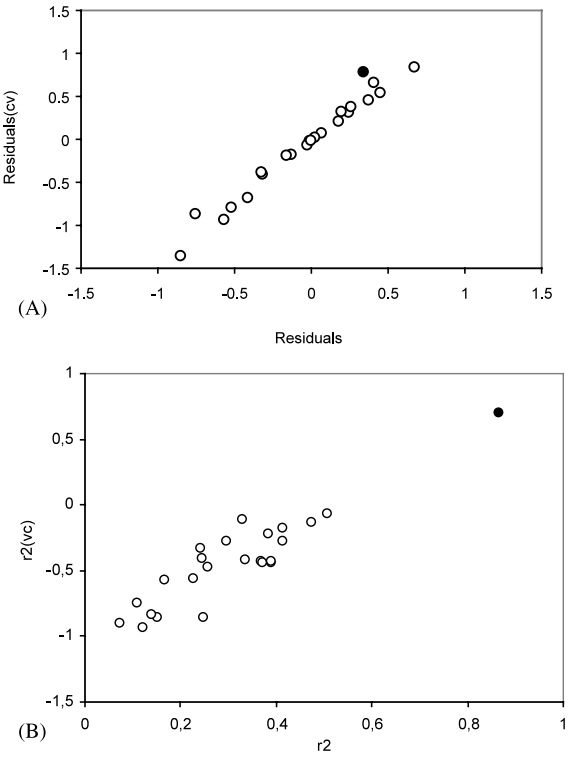

Fig. 2. Validation of the mathematical model obtained with the property T_{max}. (A) Residuals obtained with the best regression versus Residuals obtained by cross-validation (black points = outliers). (B) Correlation coefficient, r^2_{cv}, versus prediction coefficient, r^2, obtained by randomization study.

equation increases the value of this parameter, even if the added descriptor does not contribute to the predictiveness of the model. In order to evaluate the predictive ability of the model, other measurements must be used.

From the cross-validation analysis using the leave-one-out formalism we can determine r^2_{cv}. For the three studied properties r^2_{cv} was greater than 0.70 (0.915, 0.702 and 0.718 for LD_{50}, T_{max} and log P, respectively). These models account for more than 70% of the variance. A value of $r^2_{cv} > 0.5$ is commonly accepted as satisfactory (Carbó Dorca et al., 2000).

Several interesting features can be drawn regarding the quality of each proposed model for each individual property: Table 2 shows the results obtained for LD_{50}. Eighty percent of the compounds have residuals smaller than ± 1 SEE; also,

Table 4
Results obtained by MLRA for log P

Compound	Log P[a]	Log P[b]	Log P[c]	Compound	Log P[a]	Log P[b]	Log P[c]
Control Group							
Antazoline	4.25	3.36	3.10	Ketotifen	3.56	3.89	4.03
Astemizol	5.92	5.83	5.77	Loratadine	5.07	3.94	3.55
Azatadine	3.60	3.73	3.75	Mebhydroline	4.43	4.41	4.41
Azelastine	3.88	4.21	4.26	Mequitazine	5.12	5.68	5.90
Bamipine	4.10	4.25	4.26	Mianserine	4.26	4.07	4.05
Bromodiphenhydramine	3.80	3.49	3.44	Oxatomide	5.42	5.63	5.77
Brompheniramine	2.88	2.82	2.79	Phenindamine	3.74	4.16	4.25
Carbinoxamine	2.17	2.56	2.59	Pheniramine	2.02	2.40	2.46
Cetiririzine	2.19	3.15	3.34	Phenyltoloxamine	3.90	4.27	4.44
Clemizol	4.71	4.45	4.42	Picumast	5.50	5.33	5.23
Closiram	3.58	4.67	4.85	Promethazine	4.65	4.67	4.67
Cycliramine	3.71	3.66	3.66	Propiomazine	5.00	4.61	4.55
Cyclizine	3.79	3.82	3.82	Prothipendyl	3.56	3.82	3.85
Cyproheptadine	4.92	4.97	4.99	Pyrathiazine	5.17	5.21	5.22
Chlorcyclizine	4.68	4.00	3.96	Pyrilamine	2.77	2.64	2.62
Chloropyramine	3.56	3.02	2.95	Pyroxamine	4.30	4.18	4.16
Chlorpheniramine	2.73	3.01	3.03	Rocastin	1.12	1.65	1.96
Deptropine	4.35	4.36	4.37	Rotoxamine	2.60	2.56	2.56
Dexchlorpheniramine	2.73	3.01	3.03	Temelastine	3.55	4.13	4.77
Dimethindene	3.42	3.35	3.34	Thenaldine	3.75	3.58	3.54
Diphenhydramine	3.36	3.28	3.26	Thenyldiamine	2.50	2.44	2.42
Diphenylpyraline	3.35	4.23	4.34	Trimeprazine	4.59	4.61	4.62
Dorastin	4.61	4.31	4.28	Trimethobenzamide	1.67	1.46	0.74
Fenpiprane	5.17	4.47	4.26	Triprolidine	3.47	2.94	2.86
Histapyrrodine	4.68	4.20	4.15	Zolamine	2.54	2.50	2.48
Test group							
Azanator	3.69	4.43		Methapyrilene	2.50	1.83	
Chlorothen	3.25	0.56		Methdilazine	4.77	5.01	
Diethazine	5.32	6.22		Moxastin	3.76	3.53	
Doxylamine	2.28	2.61		Orphenadrine	3.86	3.01	
Embramin	4.62	3.88		Promazine	4.28	4.70	
Fenethazine	4.42	4.39		Thonzylamine	1.97	1.96	
Levocabastine	2.02	6.53		Tolpropamine	3.99	3.44	
Medrylamine	3.28	2.83		Tripelennamine	2.85	2.94	
Methaphenilene	3.46	2.80		Tritoqualine	3.15	7.08	

[a] From reference Sammes (1990).
[b] From the mathematical model (Table 1).
[c] From cross-validation study.

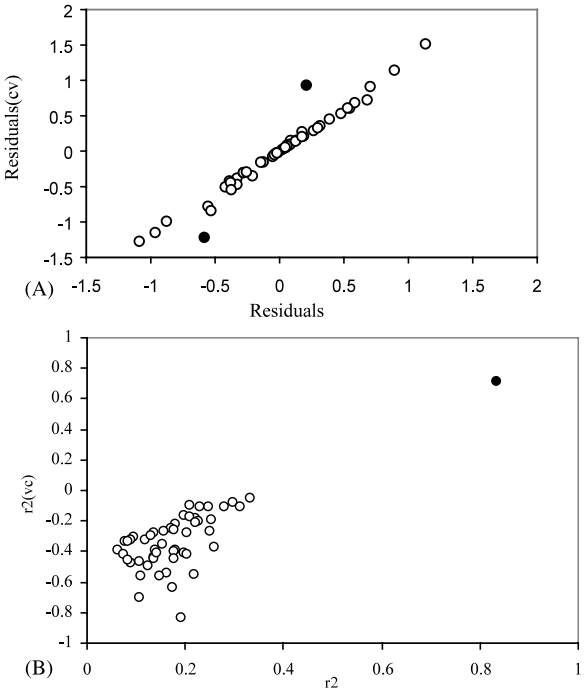

Fig. 3. Validation of the mathematical model obtained for the property log P. (A) Residuals obtained with the best regression versus Residuals obtained by cross-validation (black points = outliers). (B) Correlation coefficient, r^2_{cv}, versus prediction coefficient, r^2, obtained by randomization.

none has a residual exceeding ± 2 SEE. This reflects the high predictive capability achieved. Also, the results of the cross-validation and randomness tests (Fig. 1), suggest a high predictive ability and stability. The presence of only two outliers (terfenadine (-0.004, -0.042) and cyproheptadine (-0.050, -0.117), see black point in Fig. 1B) indicates that the equation accurately predicts 90% of the compounds. By the way, a compound is considered as an *outlier*, what means it is not predicted accurately enough by the model, if its value of residual is more than twice of the mean residual for the whole set.

Table 3 and Fig. 2 show the stability and predictive ability results for T_{max}. There is one outlier (mequitazine (0.338, 0.786)), so we can consider that the equation has a high predictive ability. As can be seen from Fig. 2B, the regressions are rather poor except for the selected equation. Consequently, we used in this case a small test group for validation. The overall accuracy was acceptable for every compound.

The index ${}^4C_c = {}^4\chi_c/{}^4\chi_c{}^v$ at the equation for T_{max} is zero for every compound except when the molecular structure exhibits quaternary branching. However, if the index is removed from the correlation, SEE increases up to 0.764 (by $\sim$ 50%). This descriptor must therefore encodes important information regarding the prediction of this property for the selected set of molecules. Thus, the predicted values for the molecules containing quaternary ramifications (e.g. clemastine, doxylamine, ebastine, levocabastine and terfenadine) are very close to the experimental ones; if the index is removed, however, the predicted values become 2.2, 2.5, 3.04, 1.91 and 2.55, respectively, which are rather different from the real ones.

The log P results are shown in Table 4 and Fig. 3. No residual in the training set is greater than ± 2 SEE; also, for 90% of them, it is less than ± 1 SEE. Only three compounds in the test group, (chloroten, levocabastine and tritoqualine) possess a residual greater than ± 2 SEE.

The results of the randomness tests (Fig. 3B) suggests a high stability of the model; also, the cross-validation test (Fig. 3A) exhibits 2 outliers for trimethobenzamide (0.207, 0.933) and temelastine (-0.584, -1.217), respectively. Therefore, the predictions were accurate for 94% of the studied compounds. The results of prediction of log P for the test set showed predictive errors below 20% for 80% of the cases.

4. Conclusions

In this work, various models to predict the properties of structurally heterogeneous compounds exhibiting antihistaminic activity were developed. The models are based on topological patterns that skip over the parent skeleton concept (the basis for the congeneric series notion). The topological descriptors used for this purpose (Randic–Kier–Hall connectivity indices, TCI and TGI) are easily calculated and contain the topological and structural information required to search for mathematical models predicting accu-

rately the selected properties. Statistical studies of predictive capability (cross-validation) and randomness, confirmed that the predictive models are effective in profiling major properties of antihistaminic drugs.

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