Journal of Computer-Aided Molecular Design, **15:** 561–572, 2001.
KLUWER/ESCOM

Optimization of a mathematical topological pattern for the prediction of antihistaminic activity

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Received 20 September 2000; accepted 18 April 2001

Key words: antihistaminic drugs, linear discriminant analysis, molecular topology

Summary

Molecular topology was used to develop a mathematical model capable of classifying compounds according to antihistaminic activity. The equations used for this purpose were derived using multilinear regression and linear discriminant analysis. The topological pattern of activity obtained allows the reliable prediction of antihistaminic activity in drugs frequently used for other therapeutic purposes. Based on the results, the proposed pattern is seemingly only valid for drugs that interact with histamine through competitive inhibition with H1 receptors.

Introduction

The search for drugs with appropriate biological properties for therapeutic use, has promoted interesting research in Medicinal Chemistry.

Notwithstanding the advances in this field in recent years, a number of pathologies including parasitism (malaria, Chagas) and infectious (e.g., resistance to antibiotics, infections by *Mycobacterium avium*, tuberculosis) fungal (e.g., infections by *Candida albicans*) and viral diseases (e.g., AIDS), among others, still lack an effective therapy.

However, one can exploit the vast amount of chemical information available for synthetic and naturally occurring compounds (their number it is estimated to be over 15 million), as well as those included in virtual libraries or even the countless ones that could be derived by combinatorial chemistry to find appropriate treatments for such diseases. It therefore seems to be reasonable to obtain such information by using methodologies capable of expeditiously selecting the potential candidates with the most suitable properties for further development. Because the trial-and-error procedure is slow and expensive, it has naturally been superseded by computer assisted methods for drug selection and design; a number of them are currently available, both commercially and in academia environments. All these methods are based on the relationship between the chemical structure and experimental properties (whether physical, physico-chemical or biological) of molecules. Various types of formalisms including molecular mechanics [1], quantum chemical descriptors [2], similarity/dissimilarity approaches [3], topological descriptors [4–7] and 3D-QSAR [8, 9] have been used in this contest. Some of these methods are extremely efficient in accurately predicting a given property of a compound with a well-known pharmacological activity. One can also obtain excellent results by refining a scaffold looking for improved pharmacological profiles. On the other hand, the search for new lead drugs can be a much more difficult task because of their unknown specific mechanism of action. As a consequence, computational drug design formalisms should go behind the biochemical advances allowing the information required about such mechanisms of action to be obtain. This constraint can be overcome, however. Thus, our group has shown that new lead drugs can be designed and/or selected even if their mechanism of action is completely unknown, by using algorithms [6, 13] based on molecular topology [10–12].

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The mathematical background for such algorithms is Graph Theory. This is a mathematical formalism in which a molecule is assimilated to a graph where each vertex represents one atom and each axis one bond. From the connections among vertices one can build an adjacency topological matrix whose ij elements take a value of either one or zero depending on whether vertex i is connected to vertex j or not, respectively. Appropriate processing of this matrix provides a set of topological indices or descriptors that characterize each graph and can be used to implement QSPR [14–16] and QSAR [17–19]. This has allowed new leads to be designed and/or selected in widely different pharmacological fields [20–23]. The results single these algorithms out from other methods traditionally used for drug design, which can be ascribed to the direct relationship between TIs and molecular structure, as a direct algebraic representation of such structure. This also explains why the inverse problem (i.e., designing new compounds directly from pre-established properties) can be solved as well. This subject has been dealt with by several authors [24, 25].

In this work, we focussed on antihistamines, (particularly on the antagonists of H1-receptors [26]) on account of the major health problems posed by widespread allergic affections. These drugs are especially effective against respiratory tract allergies, particularly seasonal rhinitis and conjunctivitis (hay fever, pollinosis); they are also used to treat catarrhal rhinitis and gripals, as well as in allergic dermatosies (especially acute urticaria).

The principal aims of this work were as follows:

– To conduct QSAR topological studies with a view to determining the time, t_{iw}, needed for histamine-induced weal and flare to be significantly suppressed.

– To find patterns of topological similarity of antihistaminic activity by using multilinear regression and linear discriminant analysis techniques.

– To use the models thus developed to identify and select drugs with significant activity currently being used in other therapeutical profiles.

– To elucidate the mechanism of interaction of the selected drugs with histamine.

Material and methods

Compound selection

An overall 78 compounds belonging to the therapeutic category of antihistaminic drugs in the Merck Index were studied. Information on a large group of structurally heterogeneous drugs classified as non-antihistamines, under Therap. Cat. in the Merck Index [27] was used as the database for the linear discriminant analysis. Tables 2–5 give the names of all the drugs studied. As noted earlier, tiw value were also used as property for correlation. Table 2 shows the value for each selected drug.

Topological indices

Table 1 shows all calculate indices and the references describing their calculation in detail. All descriptors were computed from the adjacency topological matrix obtained from the hydrogen depleted graph.

QSAR study

Multilinear regression analysis was used to obtain the connectivity function relating tiw to the selected TIs. The Furnival–Wilson algorithm [34] was used to select descriptor subsets; the equations selected were those with the lowest value in Mallows' Cp parameter [35]. A cross-validation test was carried out to validate each equation. The test was performed using the leave-one-out method and applying regression analysis to the N-1 remaining cases, the t_{iw} value for the case left out being predicted at a later stage. The procedure was repeated as many times as cases were considered. The residuals were used to determine the standard error of estimate, $SE_{(CV)}$.

Linear discriminant analysis

The aim of linear discriminant analysis, (LDA), an *heuristic* algorithm capable of distinguishing among two or more categories of objects, is to find a linear function allowing one to discriminate between active and inactive compounds. Two large sets comprising substances with proven pharmacological activity (antihistamines) and inactive compounds, respectively, were considered. Discriminant ability was assessed in terms of the proportion of correct classifications in each set. LDA was done using the BMDP 7M package [36]. Descriptors were selected on the basis of Snedecor's value, and the classification criteri on used was the shortest Mahalanobis distance (distance of each case to the mean of all cases used in the regression equation). 7M chooses the variables used in computing the linear classification functions in a stepwise manner: in each step, the variable adding the most to separation of the groups is entered into

Table 1. Symbols and definitions of topological indices

Index symbol	Definition	References
${}^{m}\chi_{p}$	Path connectivity index of order $m = 0$–4	28
${}^{m}\chi_{p}^{v}$	Path valence connectivity index or order $m = 0$–4	28
${}^{m}\chi_{c}$	Cluster connectivity index of order $m = 0$–4	28
${}^{m}\chi_{c}^{v}$	Cluster valence connectivity index or order $m = 0$–4	28
${}^{m}\chi_{pc}$	Path-cluster connectivity index of order $m = 0$–4	28
${}^{m}\chi_{pc}^{v}$	Path-cluster valence connectivity index or order $m = 0$–4	28
G_m	Charge index or order $m = 0$–5	12
J_m	Bound charge index of order $m = 0$–5	12
G_m^v	Valence charge index or order $m = 0$–5	12
J_m^v	Valence bound charge index of order $m = 0$–5	12
κ	Kappa index	29
Si	Sum-electrotopological indexes	30
Sum-I	Sum-intrinsic state values	30
Sum-ΔI	Sum-Delta intrinsic state values.	30
PR_i	Number of pairs of ramifications separated by i edges	31
W	Wiener index	32
L	Graph length	31
I_{Shannon}	Shannon index based in the information theory	33

(or the variable adding the least is removed from) the discriminant function. The quality of the discriminant function is evaluated by the Wilk's lambda parameter or U-statistic, which is obtained by a multivariate analysis of variance statistic that tests the equality of group means for the variable(s) in the discriminant function.

Pharmacological activity distribution diagrams

In recent work [37], we found that connectivity functions can be used not only to predict properties or classify compounds according to activity classification, but also to predict the activity of a given compound in a specific pharmacological context. This is accomplished by using pharmacological distribution diagrams (PDDs), which allow one to estimate the probability of a given molecule being active. These diagrams have proved useful with various types of drugs (e.g., bronchodilators, antibacterials and antimalarials [38–40]). They involve applying the connectivity function with property 'P' to the group of active compounds and to a representative group of inactive molecules. Structures are grouped within the interval of predicted values for the property, and its frequency occurrence along each interval of P is determined; in this way, the expectancy 'E' of finding a molecule with a desired value of P can be obtained. For each arbitrary interval of whatever function, activity expectancy can be expressed as: $Ea = a\backslash(i+1)$, where 'a' is the ratio of the number of active compounds in the interval to the total number of active compounds, similarly, 'i' is the ratio of inactive compounds, one can also express an expectancy of inactivity as $Ei = i\backslash(a+1)$. In our case, Ea denotes expectancy of antihistaminic activity and Ei expectancy of non-antihistaminic activity. When Ea acquires the form of a distribution and Ei tends to 0 over the curve for a connectivity function, overlap is minimal, so the function can be expected to be efficient for selection and molecular design. This permits one to determine the intervals of the function where the probability of finding out new active compounds will be maximal relative to that of obtaining a false active.

Results and discussion

In recent work [41] on the same subject, we carried out a QSAR study on two pharmacological properties, Cmax (the maximum plasmatic concentration) and sedative effect, which allowed us to develop straightforward mathematical models for predicting these properties. In this work we examined one other interesting pharmacological property, t_{iw} [42, 43], which helped us assess the degree of antihistaminic

Table 2. Results of prediction in the QSAR study of t_{iw}

Compound	I_{Shannon}	Sum-I	Sum-ΔI	t_{iw} (exp.)[a]	t_{iw} (cal.)[b]	t_{iw} (CV)[c]
Acrivastine	1.32	57.50	11.65	1.75	2.48	2.70
Azelastine	1.39	56.44	13.94	4.00	5.10	5.35
Cetirizine	1.30	61.11	14.03	4.00	4.83	5.04
Chlorpheniramine	1.18	38.44	5.74	11.00	10.52	10.01
Clemastine	1.28	46.69	8.61	6.80	6.39	6.33
Dimethindene	1.32	41.17	4.64	2.00	2.31	2.52
Epinastine	1.28	37.67	6.36	9.00	9.02	9.03
Hydroxyzine	1.28	53.95	10.53	5.00	4.64	4.56
Levocabastine	1.48	77.00	24.88	8.00	7.94	7.81
Loratadine	1.39	57.44	14.30	5.00	5.00	5.00
Temelastine	1.45	60.58	14.35	2.00	0.83	−0.11
Terfenadine	1.31	70.33	17.10	3.50	2.99	2.54

[a]Obtained from [43, 44].
[b]Obtained from Eqation 1.
[c]Obtained from Cross-validation.

efficiency. Table 2 shows the drugs studied and the experimental values of t_{iw}.
The equation selected through linear regression was

$$t_{iw} = 67.19(\pm 5.81) - 32.94(\pm 4.34) I_{\text{Shannon}} - 0.72(\pm 0.07)\text{Sum-}I + 1.73(\pm 0.16)\text{Sum}-\Delta I \quad (1)$$

with $N = 12$, $r = 0.975$, $SE = 0.77$, $SE_{(\text{CV})} = 0.99$, $F = 52$ and $p < 0.00001$. The connectivity indices arising in Equation 1 were to be expected as they encompass the topological and electronic global contributions of each compound (Sum-I and Sum -ΔI [30], as well as indices based on the theory of information such as I_{Shannon}). I_{Shannon} descriptor evaluates the chemical nature of vertices, as well as their bonding pattern, on the basis of an equivalence relation where two atoms of the same graph are considered equivalent if they possess an identical first-order topological neighborhood [33].

In order to avoid colineality, intercorrelation between variables was examined. A linear relationship between Sum-I and Sum-ΔI ($r > 0.9$) was thus identified. However, suppressing either variable significantly raised SEE by more than 200%; thus, eliminating Sum-I increased SEE to 2.724 whilst deleting Sum-ΔI raised it to 2.879, based on these results, both variables are significant, so they may be included in the regression equation.

Table 2 shows the t_{iw} values calculated from this equation for each drug. As can be seen, predictions are quite acceptable: no residual was greater than ± 2SE and only three were greater than ±1 SE.

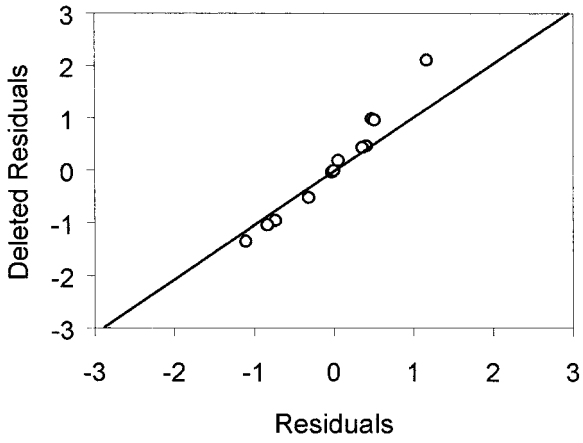

Figure 1. Graphic representation of the residuals obtained in the cross-validation versus the residuals obtained with the Equation 1.

Validation of the selected regression equation using the cross-validation method revealed that the predicted values of t_{iw} (t_{iw} column (CV)) were worse than those obtained with the entire group (SE increased by about 20%, as shown in Table 2); however, the mathematical pattern represented by Equation 1 accurately predicts this property as all the compounds except temelastine exhibited a cross-validation residual of the same order of magnitude as the one obtained from Equation 1 (see Figure 1).

Application of Equation 1 to the two large sets of drugs (one comprising compounds exhibiting antihistaminic activity and the other those not possessing it) reveals that most of the antihistaminics gathered within $t_{iw} < 10$, while the non-antihistamines gen-

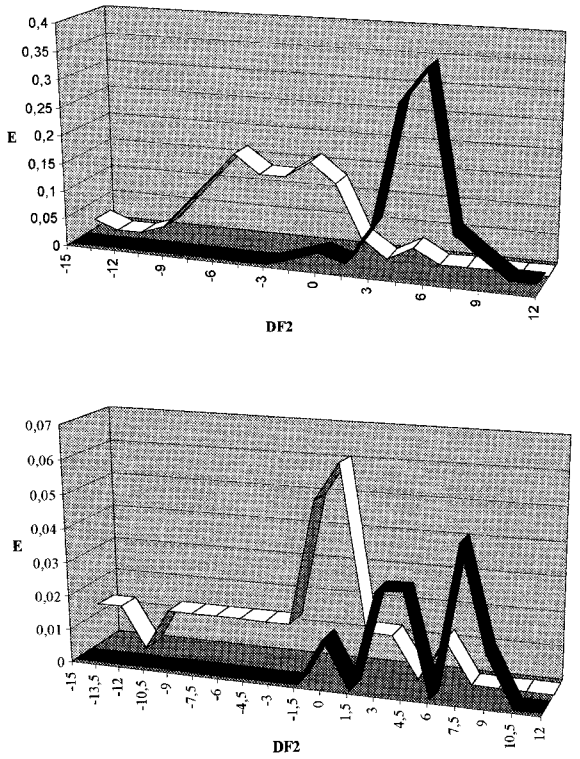

Figure 2. Pharmacological distribution diagram for antihistaminic activity from the discriminant function DF2. Upper : training group. Lower: testing group. White line: non-antihistaminic drugs. Black line: antihistaminic drugs.

erally fall outside this interval (see Tables 3–5). This suggests that the t_{iw} values obtained from Equation 1 are related to topological indices that are somehow measures of antihistaminic activity, so the equation can be used as a discriminant function for this type of activity.

Figure 4 shows the pharmacological activity distribution diagram obtained from t_{iw}. As can be seen, the antihistaminic drugs gathered mainly within the tiw interval 0–10 few non-antihistamines (only 12 out of 72) fell in it.

One other way of classifying the drugs according to activity is by LDA. A set of 146 structurally heterogeneous compounds with either antihistaminic or non-antihistaminic activity were analysed for this purpose. Each group was split into two, namely: a training set including active and inactive compounds and allowed the discriminant function to be derived; and a test set also including active and inactive structures (randomly chosen from the training group), which allowed the quality of the selected discriminant function to be assessed.

The discriminant functions chosen were

$$\mathrm{DF1} = 7.20^{3}\chi_{cv} + 0.25^{1}G_{v} - 47.96J_{1} - 22.98J_{3}^{v} - 4.89D^{4}\chi_{\mathrm{pc}} - 0.36L + 12.65 \quad (2)$$

with $N = 146$, $F = 34.5$, and U-statistics (Wilks' λ) = 0.347, and

$$\mathrm{DF2} = 2.13\mathrm{SdssC} + 1.37\mathrm{SaaCH} - 0.68\mathrm{SdsN} + 0.90\mathrm{SsssN} - 0.10\mathrm{SsOH} - 0.18\mathrm{SdO} - 2.77 \quad (3)$$

with $N = 146$, $F = 44.1$, and U-statistics (Wilks' λ) = 0.298.

Equation 2 it contains connectivity indices that evaluate both fundamental topological aspects of each compound (χ_i, L) and the distributions of intramolecular charge (*Gi* and *Ji*). The accuracy of this equation is about 92% and hence very close to that for inactive group (about 92.6%). The descriptors in Equation 3 are all atomic sum-electrotopological indices, Si, that encompass both electronic and topological properties. The accuracy of this equation is 94% for the active set and 91.3% for the inactive one.

Tables 3–5 summarize the classification of the results obtained with the DF discriminant functions for each group. A compound will be selected as antihistaminic if DFi > 0 and as non-antihistaminic if DFi < 0. As can be inferred from the tables, the training and test groups exhibit an average overall accuracy higher than 90%. Also the probability of success is higher than 80% in all casses (see Prob. in Tables 3–5). The intercorrelation study based on Equation 2 and 3 provided a value of $r < 0.5$ in all cases, which can be considered acceptable.

The PDDs obtained by using Equations 2 and 3 are shown in Figures 2 and 3. The maximum expectancy zone for new antihistaminics is that spanning the range 0–9 for DF1 and 1.5–10.5 for DF2, respectively, in both the training and the test set.

In the light of the previous results, a pattern of topological similarity of antihistaminic activity can be formulated through Equations 2 and 3. When the two functions are used, the proportion of correctly classified inactive compounds is 98.8%; that of accurately classified active compounds is 86.6%. The accuracy for active compounds is thus decreased whereas that for inactive ones is increased so the probability of a falsely active compound being selected is decreased. As can be seen from Figure 4, the property tiw can be used as a discriminant by itself; thus a given compound can be selected as a potential antihistaminic provided it fulfills the following requirements:

Table 3. Results obtained in the LDA study and classification of the compounds from the pattern of antihistaminic activity proposed. Training active group

Compound	DF1	Prob.[a]	DF2	Prob.[a]	t_{iw}	Class[b]
Acrivastine	2.26	0.90	1.93	0.87	2.49	+
Ahistan	3.65	0.97	4.14	0.98	14.31	–
Alloclamide	0.30	0.57	6.81	1.00	13.32	–
Astemizole	−0.70	0.33	5.30	0.99	−4.44	–
Azatadine	3.08	0.97	7.00	1.00	4.16	+
Azelastine	1.28	0.78	0.22	0.56	5.10	–
Bamipine	4.24	0.99	5.51	1.00	7.44	+
Bromodiphenhydramine	6.39	1.00	3.89	0.98	10.77	–
Brompheniramine	5.36	0.99	4.15	0.98	9.58	+
Carbinoxamine	4.64	0.99	2.82	0.94	10.99	–
Cetirizine	4.77	0.99	3.33	0.96	4.84	+
Cetoxime	−1.08	0.25	−0.81	0.31	10.75	–
Chlorcyclizine	5.58	1.00	6.45	1.00	9.58	+
Chloropyramine	3.66	0.97	5.38	0.99	7.81	+
Chlorothen	5.01	0.99	5.51	1.00	7.95	+
Chlorpheniramine	3.74	1.00	3.55	0.97	10.52	–
Clemastine	4.15	0.98	3.64	0.97	6.39	+
Clemizole	2.11	0.89	4.22	0.99	5.65	+
Deptropine	2.41	0.92	7.38	1.00	10.45	–
Diphenhydramine	5.62	1.00	2.45	0.92	18.05	–
Doxylamine	4.29	0.99	1.96	0.88	9.94	+
Isothipendil	4.46	0.99	8.05	1.00	5.26	+
Fenethazine	5.94	1.00	8.78	1.00	11.12	–
Hydroxyethylpromethazine	7.18	1.00	5.60	1.00	7.46	+
Hydroxyzine	7.28	1.00	5.51	1.00	6.87	+
Isopromethazine	5.54	1.00	8.82	1.00	9.64	+
Levocabastine	0.77	0.68	4.43	0.99	7.95	+
Loratadine	−0.56	0.36	4.47	0.99	5.00	–
Medrylamine	3.39	0.97	3.49	0.97	9.70	+
Mequitazine	7.10	1.00	9.64	1.00	6.90	+
Methafurylene	3.00	0.95	3.85	0.98	9.76	+
Methapyrilene	4.48	0.99	4.63	0.99	8.08	+
Orphenadrine	4.66	0.99	4.27	0.99	8.24	+
Phenindamine	3.48	0.97	5.50	1.00	5.87	+
Pheniramine	4.63	0.99	2.67	0.93	10.59	–
Phenyltoloxamine	2.58	0.93	4.02	0.98	9.12	+
Picumast	0.73	0.67	5.64	1.00	0.37	–
Pyrilamine	2.41	0.92	5.58	1.00	5.91	+
Terfenadine	7.00	1.00	3.01	0.95	2.99	+
Thenaldine	4.62	0.99	5.62	1.00	7.89	+
Thenyldiamine	3.24	0.96	4.60	0.99	8.17	+
Thiazinamium Methyl Sulfate	8.29	1.00	6.84	1.00	9.59	+
Thonzylamine	2.20	0.90	5.04	0.99	8.91	+
Tolpropamine	3.07	0.96	4.96	0.99	9.65	+
Triprolidine	4.67	0.99	4.43	0.99	6.36	+
Tritoqualine	1.15	0.76	4.70	0.99	10.25	–

[a]Activity probability.
[b]Classification from proposed pattern.

$$10 > t_{iw} > 0,$$

$$9 > \mathrm{DF1} > 0,$$

$$10.5 > \mathrm{DF2} > 1.5.$$

The LDA study revealed that 100% of the non-antihistaminic compounds were classified correctly with this model, and so were about 65% of the antihistaminic drugs are also correctly classified. The pattern is quite restrictive when the goal is to identify a compound as antihistaminic so that many potential drugs can be discarded; when a specific compound is selected, however, the probability of success is very high. It is obviously possible to arrange the discrimi-

Table 4. Results obtained in the LDA study and classification of the compounds from the proposed pattern of antihistaminic activity . Training inactive group

Compound	DF1	Prob.[a]	DF2	Prob.[a]	t_{iw}	Class[b]
Acebutol	−4.96	0.99	−6.06	1.00	14.40	–
Acyclovir	−2.29	0.91	−9.56	1.00	20.34	–
Alfentanil	−1.29	0.78	−4.87	0.99	7.65	–
Allopurinol	−1.78	0.85	−3.75	0.98	26.24	–
Althiazide	−7.64	1.00	−4.22	0.99	28.24	–
Aminorex	−3.21	0.96	−3.90	0.98	24.87	–
Amphetamine	−0.56	0.64	−0.96	0.72	27.99	–
Aspidin	−8.40	1.00	−15.32	1.00	25.47	–
Atovaquone	−0.40	0.60	−6.52	1.00	14.25	–
Baclofen	−4.57	0.99	−3.37	0.97	23.47	–
Benfluorex	−5.01	0.99	−4.24	0.99	16.37	–
Benorylate	−6.15	1.00	−7.17	1.00	13.67	–
Benoxinate	−1.57	0.83	−0.77	0.68	13.10	–
Benzestrol	−1.10	0.75	−0.32	0.58	11.11	–
Bisacodyl	−2.11	0.89	−1.35	0.79	12.87	–
Bumetanide	−4.62	0.99	−9.81	1.00	19.11	–
Cadralazine	−5.45	1.00	−2.51	0.92	12.72	–
Cefepime	2.09	0.11	−11.08	1.00	14.01	–
Chloroxine	−2.83	0.94	−2.80	0.94	22.00	–
Clometacillin	−2.20	0.90	−2.42	0.92	11.28	–
Clonitazene	−1.12	0.75	0.13	0.47	4.77	–
Dapsone	−5.17	0.99	−5.01	0.99	35.56	–
Diethofencarb	−0.54	0.63	−2.23	0.90	16.22	–
Mazindol	−0.71	0.67	−0.55	0.63	15.42	–
Propanol	0.13	0.47	−2.64	0.93	12.60	–
Rabeprazole	−1.49	0.82	−1.03	0.74	8.60	–
Roquinimex	−2.74	0.94	−3.50	0.97	13.45	–
Sorbitol	−8.64	1.00	−8.11	1.00	14.16	–
Tolazamide	−6.26	1.00	−6.08	1.00	24.43	–
Naftopidil	1.50	0.18	4.28	0.01	−0.29	–
Ondansetron	−1.75	0.85	−1.01	0.73	7.84	–
Penfluridol	−3.02	0.95	−1.72	0.85	20.95	–
Phenobarbital	−8.02	1.00	−8.13	1.00	28.31	–
Piperidine	−10.83	1.00	−6.82	1.00	31.81	–
Diflunisal	−5.50	1.00	−9.62	1.00	21.74	–
Edatrexate	−6.95	1.00	−7.77	1.00	8.22	–
Famotidine	−9.17	1.00	−9.41	1.00	16.21	–
Flecaine	−7.57	1.00	−6.39	1.00	24.53	–
Fluvoxamine	−4.15	0.98	−5.56	1.00	18.74	–
Glyburide	−4.91	0.99	−8.72	1.00	15.25	–
Indapamide	−4.15	0.98	−4.76	0.99	16.22	–
Isoxicam	−11.12	1.00	−8.88	1.00	23.26	–
Lidocaine	−5.08	0.99	1.37	0.20	19.55	–
Losartan	−0.19	0.55	−3.42	0.97	−2.90	–

[a]Activity probability.
[b]Classification from proposed pattern.

Table 5. Results obtained in the LDA study and classification of the compounds from the proposed pattern of antihistaminic activity. Test group

Compound	DF1	Prob.[a]	DF2	Prob.[a]	t_{iw}	Class[b]
	Test active group					
Antazoline	2.59	0.93	−0.20	0.45	8.30	−
Cinnarizine	5.62	1.00	7.43	1.00	−0.92	−
Dimethindene	2.88	0.95	4.84	0.99	2.32	+
Ebastine	7.94	1.00	3.42	0.97	−0.17	−
Etymemazine	3.96	0.98	10.99	1.00	−0.28	−
Histapyrrodine	5.36	0.99	5.44	1.00	4.64	+
Methaphenilene	4.90	0.99	5.16	0.99	8.81	+
Metron	−0.28	0.43	−2.77	0.06	24.43	−
Promethazine	5.07	0.99	8.81	1.00	9.55	+
Talastine	1.58	0.83	−0.87	0.30	7.34	−
Tripelennamine	4.37	0.99	4.52	0.99	7.85	+
Zolamine	1.71	0.85	5.72	1.00	8.14	+
Cyproheptadine	5.08	0.99	6.90	1.00	7.67	+
Diphenylpyraline	3.59	0.97	2.77	0.94	16.71	−
Embramine	5.84	1.00	3.84	0.94	9.59	+
Pyrrobutamine	3.98	0.98	4.21	0.98	6.66	+
Mebhydroline	1.27	0.78	7.42	1.00	3.34	+
Epinastine	−0.94	0.28	3.40	0.97	9.02	−
Moxastine	4.86	0.99	2.41	0.92	16.46	−
Azelastine	1.28	0.78	0.22	0.56	5.10	−
Isothipendil	4.46	0.99	8.05	1.00	5.26	+
Phenindamine	3.48	0.97	5.50	1.00	5.87	+
Hydroxyzine	7.28	1.00	5.51	1.00	6.87	+
Isopromethazine	5.54	1.00	8.82	1.00	9.64	+
Levocabastine	0.77	0.68	4.43	0.99	7.95	+
Cetirizine	4.77	0.99	3.33	0.96	4.84	+
Setastine	4.97	0.99	3.73	0.98	6.87	+
	Test inactive group					
Buformin	−8.38	1.00	−2.77	0.94	23.64	−
Cafaminol	−10.10	1.00	−5.63	1.00	17.50	−
Citiolone	−8.71	1.00	−6.53	1.00	29.43	−
Clopirac	−7.68	1.00	−1.43	0.81	14.14	−
Diazepam	−1.02	0.74	−1.85	0.86	12.21	−
Fluvastatin	−0.78	0.69	−2.12	0.89	7.17	−
Isradipine	−3.92	0.98	−6.41	1.00	13.15	−
Methotrexate	−6.27	1.00	−6.55	1.00	7.41	−
Modafinil	2.19	0.10	−4.35	0.99	27.70	−
Nefazodone	−0.02	0.50	3.06	0.04	−2.07	−
Primaquine	−1.20	0.77	−0.23	0.56	9.93	−
Probenecid	−8.67	1.00	−8.32	1.00	28.58	−
Simvastatin	0.45	0.39	−8.11	1.00	14.16	−
Sumatriptan	−6.31	1.00	−2.16	0.90	15.83	−
Tetrabenazine	−1.77	0.85	2.83	0.05	11.64	−
Vetrabutine	−0.07	0.52	5.09	0.00	3.83	−
Warfarin	−2.85	0.94	−5.92	1.00	16.18	−
Benomyl	−5.42	1.00	−6.89	1.00	13.57	−
Alprazolam	−1.37	0.80	−4.62	0.99	6.24	−
Apazone	−6.98	1.00	−2.80	0.94	14.97	−
Benserazide	−10.07	1.00	−10.21	1.00	20.54	−
Benzocaine	−4.31	0.99	−3.11	0.96	26.79	−
Dicumarol	−6.56	1.00	−7.57	1.00	26.70	−
Gossypol	−1.18	0.77	−16.38	1.00	28.69	−
Mefenamic acid	−3.14	0.96	−0.00	0.50	11.48	−
Meperidine	0.39	0.40	−1.41	0.80	20.05	−
Clebopride	−0.89	0.71	1.19	0.23	8.54	−
Salazosulfapyridine	−7.52	1.00	−14.75	1.00	16.24	−

[a]Activity probability.
[b]Classification from proposed pattern.

Table 6. Results of prediction of antihistaminic activity obtained when applying the mathematical model proposed to a wide group of drugs showing other pharmacological activities

Compound	Therapeutic Group	DF1	DF2	t_{iw}	Class[a]	Class[b]
Cloperastine	Antitussive	5.25	3.74	8.62	+	Active (45)
Fentanyl	Analgesic	0.51	2.49	6.06	+	n.f.
Picoperine	Antitussive	5.50	5.08	4.70	+	n.f.
Trihexyphenidyl	Antiparkinsonian	1.01	1.67	12.64	+/−	n.f.
Olanzapine	Antipsychotic	1.63	6.26	5.28	+	Active (46)
Bencyclane	Vasodilat	3.34	1.20	11.4	+/−	Active (47)
Chlorprotixene	Antipsychotic	6.79	7.43	3.38	+	Active (48)
Clothiapine	Antipsychotic	5.28	5.48	4.42	+	Active (49)
Amorolfine	Antifungal	4.3	3.56	7.14	+	n.f.
Benzpiperilone	Analgesic.anti-inflammat.	0.58	1.75	6.22	+	n.f.
Clomacran	Antipsychotic	2.8	7.39	5.61	+	n.f.
Benzydamine	Aine	2.29	2.54	3.83	+	Active (41)
Miconazole	Antifungal	5.88	4.45	5.24	+	n.f.
Clozapine	Antipsychotic	2.53	4.76	5.13	+	Active (48.49.50.51)
Levomepromazine	Analgesic	4.23	9.80	0.92	+	Active (52)
Bifemelane	Nootropic	1.91	2.16	7.15	+	n.f.
Methopromazine	Antipsychotic	4.37	9.78	1.90	+	n.f.
Mecloxamine	Anticol.sed	2.71	3.25	9.55	+	Active (47)
Loxapine	Ansiolytic	1.87	3.72	7.07	+	Active (53)
Trimeprazine	Antipruritic	4.19	8.91	7.86	+	Active (54.55)
Homochlorcyclizine	Serotonin antagonist	5.56	6.53	6.13	+	Active (56)
Pizotifen	Antimigraine	2.83	7.84	4.31	+	Active (57)
Thioridazine	Antipsychotic	5.36	5.50	9.19	+	Active (58)
Femoxetine	Antidepressant	1.97	3.79	6.64	+	n.f.
Calcifediol	Calcium regulator	5.95	4.19	3.59	+	n.f.
Prenoxdiazine	Antitussive	1.18	5.13	6.01	+	n.f.
Promazine	Antipsychotic	5.62	8.89	9.26	+	Active (59)
Pergolide	Antiparkinsonian	3.33	4.07	4.08	+	n.f.
Mirtazapine	Antidepressant	2.08	9.15	6.5	+	Active (60)
Niaprazine	Sedative-hypnotic	0.72	1.33	8.03	+/−	Active (61)
Phenazocine	Analgesic	2.63	5.05	5.30	+	n.f.
Quinupramine	Antidepressant-tricyclics	3.8	10.22	8.85	+	Active (62.63)
Protriptyline	Antidepressant-tricyclics	4.34	4.98	10.78	+/−	Active (62.63)
Opipramol	Antidepressant-tricyclics	5.72	10.06	1.34	+	Active (62.63)
Noxiptilin	Antidepressant-tricyclics	3.52	3.04	10.00	+	Active (62.63)
Nortriptyline	Antidepressant-tricyclics	3.26	5.14	10.5	+/−	Active (62.63)
Melitracen	Antidepressant-tricyclics	8.06	7.01	7.49	+	Active (62.63)
Iprindole	Antidepressant-tricyclics	2.23	5.74	3.28	+	Active (62.63)
Doxepin	Antidepressant-tricyclics	4.22	5.70	4.39	+	Active (62.63.64)
Dimetacrine	Antidepressant-tricyclics	6.63	9.19	7.84	+	Active (60.61)
Dibenzepin	Antidepressant-tricyclics	2.23	5.52	5.86	+	Active (60.61)
Butriptyline	Antidepressant-tricyclics	3.37	7.81	8.68	+	Active (60.61)
Amoxapine	Antidepressant-tricyclics	1.92	1.58	9.24	+	Active (60.61)
Imipramine	Antidepressant-tricyclics	2.20	9.39	9.11	+	Active (60.61)
Amitriptyline	Antidepressant-tricyclics	3.96	3.20	8.77	+	Active (60.61)
Dothiepin	Antidepressant-tricyclics	6.33	6.95	1.79	+	Active (60.61)
Trimipramine	Antidepressant-tricyclics	1.91	9.41	7.77	+	Active (60.61)

[a]Classification from mathematical model proposed.
[b]Classification cited from bibliographic references.
n.f. not found

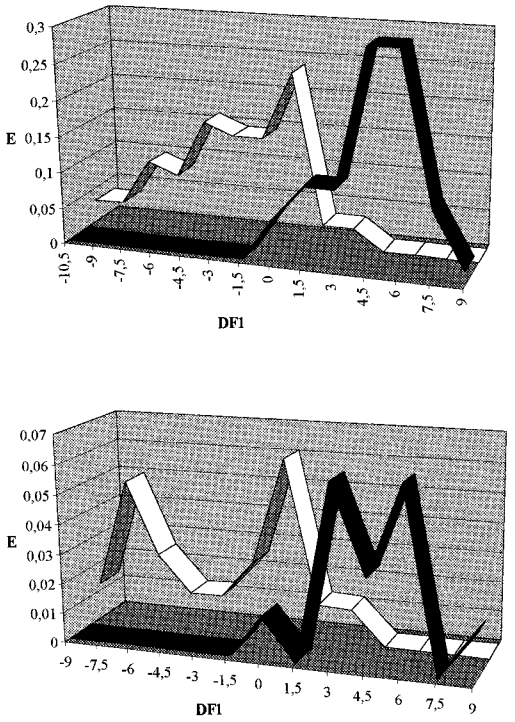

Figure 3. Pharmacological distribution diagrams for antihistaminic activity from the discriminant function DF1. Upper: training group. Lower: testing group. White lines: non-antihistaminic drugs. Black lines: antihistaminic drugs.

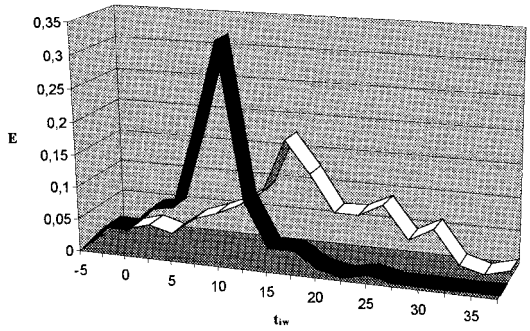

Figure 4. Pharmacological distribution diagrams for antihistaminic activity from the connectivity function t_{iw}. White lines: Non-antihistaminic drugs. Black lines: antihistaminic drugs.

nant functions so that both sets are more compensated; because our aim here was to find new leads, we used the functions as such, however.

As state above, we aimed to find new antihistaminics among drugs exhibiting other pharmacological actions. This was accomplished by scanning databases containing more than 20000 compounds and including the Merck Index and the Sigma and Aldrich databases, among others. After a first screening a group of 70 compounds was selected as candidates to experimental tests. Twenty-three of them were chemical reagents and the other 47 drugs exhibiting other pharmacological activity.

Table 6 summarizes the results. The first two columns identify each drug and its main therapeutic category. The following columns show the numeric values of DF1, DF2, t_{iw}, and the classification obtained using to the proposed model. A literature scan was subsequently conducted for each selected drug, which revealed that 70% of them had previously been reported to posses antihistaminic properties (see column Class(b)). Some drugs used as analgesics (methotrimeprazine), antifungals (miconazole), antipsychotics (chlorprothixene, clothiapine), ansiolytics (loxapine), tricyclic antidepressants (dimethacrine, amoxapine,. . .), antitussives (cloperastine), etc., also exhibit antihistaminic activity. This searching procedure can be of great use with a view to fighting different pathologies with the same drug.

The proposed mathematical model, was developed by including compounds acting through a competitive inhibition mechanism at the H1 receptor level. However, the detrimental effects of histamine can be neutralized by other mechanism of actions. [44] such the following:

(1) Physiological antagonists: drugs that act on receptors other than those of the histamine and hence have opposing effects. Such is the case with adrenaline, which responds to histamine-induced broncho-spasms by acting on beta-adrenergic receptors (which are bronco-spasmolitic) and producing bronchial relaxation.

(2) Antagonists of histamine release (e.g. chromoglicate, nedocromile).

(3) Antagonists of H1-histamine receptors, which antagonize histamine H1 receptors by competitive inhibition.

(4) H2 receptor antagonists, which are drugs that competitively antagonize the action of histamine on such receptors.

We checked whether our mathematical model was capable of distinguishing between H1 antagonists and the other drugs exhibiting different mechanisms of action. Table 7 classifies the compounds according to mechanism of interaction with histamine. None of the selected compounds except the H1 antagonists was recognized as antihistaminic. This suggests that the drugs selected as antihistaminics using the proposed topological approach are significantly likely

Table 7. Results of prediction of the antihistaminic activity obtained when applying the mathematical model proposed to a group of drugs that interact in different form with histamine

Compound	Action	DF1	DF2	t_{iw}	Class
Histamine	–	−2.12	−3.16	2.39	–
Adrenaline	Physiological antagonist	−5.73	−4.68	0.05	–
Nedocromile	Antagonits of the histamine liberation	−5.76	−5.10	−2.27	–
Cromoglicate disodium	Antagonits of the histamine liberation	−6.45	−9.04	−1.91	–
Betahistina	Agonist H1	2.79	−1.19	2.09	–
2-methylhistamine	Agonist H1	−9.26	−4.49	2.02	–
2-piridilethylamine	Agonist H1	1.65	−1.76	2.18	–
2-tyazolilethylamine	Agonist H1	−1.94	−2.61	2.38	–
Impromidine	Agonist H2	−2.25	−0.41	0.94	–
Dimaprit	Agonist H2	−3.30	−1.20	2.27	–
4(5)-methylhistamine	Agonist H2	−6.65	−4.24	1.45	–
Betazol	Agonist H2	−2.97	−3.14	2.44	–
Cimetidine	Antagonist H2	−3.56	−1.78	−0.49	–
Nizatidine	Antagonist H2	−1.41	−0.70	1.47	–
Ranitidine	Antagonist H2	−3.04	−2.46	1.43	–
Famotidine	Antagonist H2	−9.17	−7.60	10.39	–

to possess antihistaminic activity through competitive antagonism at the H1 receptor level.

Conclusions

Molecular topology has demonstrated to be a useful methodology for identifying new compounds with antihistaminic activity. In addition, the proposed model seems to be efficient in elucidating their mechanisms of action.

By using multilinear regression and LDA, a pattern of topological similarity of antihistaminic activity was developed that was successfully applied to the search for drugs exhibiting significant antihistaminic activity in addition to other pharmacological properties.

One additional advantage is that it affords screening of large databases in a short time. The proposed model also allows one to elucidate the mechanism of action involved. The results suggest that the selected compounds interact with histamine only through competitive inhibition of H1 receptors.

Acknowledgements

This study was supported by GV99-91-1-12 and GV00-016-2 from Generalitat Valenciana (Spain). The authors also wish to express their gratitude to Professor Rama K. Mishra for his helpful suggestions.

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