QSAR Analysis of Hypoglycemic Agents Using the Topological Indices

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The molecular topology model and discriminant analysis have been applied to the prediction of some pharmacological properties of hypoglycemic drugs using multiple regression equations with their statistical parameters. Regression analysis showed that the molecular topology model predicts these properties. The corresponding stability (cross-validation) studies performed on the selected prediction models confirmed the goodness of the fits. The method used for hypoglycemic activity selection was a linear discriminant analysis (LDA). We make use of the pharmacological distribution diagrams (PDDs) as a visualizing technique for the identification and selection of new hypoglycemic agents, and we tested on rats the predictive ability of the model.

INTRODUCTION

Ever since the influence of chemical structure on the pharmacological action of molecules was first observed, scientists have been developing methods to make it possible to relate these two factors. Quantitative structure−activity relationships (QSAR)[1] allow us to explain the relationships between a determined property and the chemical structure of a series of molecules and obtain, by inverting the process, new structures that possess the studied activity or property.

For this reason we have approached the question of how to the depict the chemical structure from several angles. One of these is topology, by which the structure of the molecule is represented by a series of numbers, called indices, that contain information on the number and type of connections between the atoms that form the molecule.

A large number of quantitative structure−activity relationship (QSAR) studies has been reported in recent literature that use theoretical molecular descriptors in predicting the physicochemical, pharmacological, and toxicological properties of molecules.[2−10] The important common feature of all those descriptors is the independence of their numerical values on renumbering atoms in a chemical structure. To perform quantitative "structure−activity" and "structure−property" (QSAR/QSPR) studies correctly, chemists have had to design a variety of molecular graph invariants.[11−14]

The aim of the work was to discriminate between hypoglycemic drugs (drugs that decrease the glucose concentration in plasma) and nonactive compounds by topological methods and to select new hypoglycemic agents from among new structures. Finally, pharmacological tests were carried out to determine the hypoglycemic activity of the molecules selected in experimental animals.

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Table 1. Experimental Values of Several Pharmacological Properties of a Group of Hypoglycemic Drugs Used in the Connectivity Functions

compound	*P* (log *P*)	LD-50m i.p. (g/kg)	PPB (%)
acetohexamide	0.3522		90
carbutamide	0.1761	2.10	
chlorpropamide	0.699	0.76	91.8
glibenclamide	2.243	5.90	97
glibornuride	1.6021	5.00	95
glybuzole	0.699		
gliclazide	1.1761		93
glymidine	0.6021		
glypizide		3.00	95.4
gliquidone	1.7782		96
glipentide			95
metahexamide	1		
tolazamide	0.699	2.20	94
tolbutamide	0	1.27	96.7
tolciclamide	0.301		

MATERIALS AND METHODS

a. Data. Because of their usefulness in designing molecules, a thorough review of the literature on the different pharmacological properties of a group of 15 hypoglycemic agents was carried out as a starting point to obtain the QSARs.

The following pharmacological properties were investigated: potency relative to tolbutamide (*P*), percentage of protein plasmatic binding (PPB), and lethal dose 50 i.p. in mouse (LD-50m) ($g \cdot kg^{-1}$). The three QSAR selected here try to cover the main features of this therapeutic group.

The experimental values for these properties were obtained from different bibliographic sources[15−19] (Table 1).

b. Connectivity Indices. In the connectivity method, molecular structure is expressed topologically by the hydrogen-suppressed graph. It should be noted that information concerning the contributions of the hydrogen atoms is implicit in this graphical formulation.

In this work we have used Kier and Hall's connectivity indices ($^m\chi_t$)[20] using computer software developed in our

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department.[21] These indices are evaluated as a sum of terms over all the distinct connected subgraphs and are defined by the general equation

$$^{m}\chi_t = \sum_{j=1}^{n_m} {}^{m}S_j \quad (1)$$

where m = order of a subgraph, i.e., number of edges of a subgraph; n_m = number of type t subgraphs of order m; and $^{m}S_j$ = quantity calculated for each subgraph and defined by

$$^{m}S_j = [\prod_{i=1}^{m+1}(\delta_i)]^{-1/2} \quad (2)$$

where j denotes the particular set of edges that constitute the subgraph.

We used connectivity indices up to the fourth order: path (p), cluster (c), path-cluster (pc), valence (v), and nonvalence indices.[2,22] The vertex valences, δ^{v}, of the unsaturated carbon atoms and the heteroatoms (N, S, O) can be calculated using

$$\delta^{v} = Z^{v} - H \quad (3)$$

where Z^{v} is the number of valence electrons of the atom and H is the number of hydrogen atoms attached to it. The empirically derived values for the halogens were also used.[2]

c. Statistical Methods. A multiple regression analysis was used to find the relationship between the pharmacological properties and the topological indices

$$C(\chi) = P = A_0 + \sum_{i=1}^{n} A_i \cdot \chi_i \quad (4)$$

here P is a property and A_o and A_i represent the regression coefficients of the obtained equation.

The QSAR (eq 4) was obtained by multilinear regression with the BMDP 9R program of the Biomedical Computer Programs biostatistic package.[23] To test the quality of the regression equations, the following statistical parameters were used: multiple correlation coefficient (r), standard deviation (SD), F-Snedecor function values (F), Mallow's CP, and Student's t-test (statistical significance) as well as the corresponding cross-validation of the selected functions (potency relative to tolbutamide (P), percentage of protein plasmatic binding (PPB), and lethal dose 50 i.p. in mouse (LD-50m)).

Cross-validation for the selected functions was carried out using the jackknife method.[24] With this method, n observations are eliminated by means of a random process, and a regression program is applied. The process was repeated as many times as necessary until all the observations have been eliminated at least once and at most four times. Finally, the coefficients of the independent variables calculated, the correlation coefficients, standard deviations, and the residuals are compared with those obtained in the selected equation.

The linear discriminant analysis (LDA) was carried out by means of the BMDP statistical package, using the connectivity indices as independent variables.[2] LDA was used to select the parameters (pharmacological and/or structural) that identify the active or inactive character of the molecules. The analysis is carried out on two large groups of molecules, one with demonstrated hypoglycemic activity and the other inactive. The criteria for the selection of the best LDA equation were as follows: comparison of the tabulated F and Wilk's U statistical values; determination of the percentage of molecules correctly classified; and prediction of the classification of molecules not included in the training process (cross-validation).

Once we have obtained the optimal discrimination conditions for classifying the hypoglycemic activity of a particular compound, the next step is to get new active compounds. For this purpose the final LDA equation was used to select new hypoglycemic agents from a database of 1500 structures without known therapeutic activity. The topological indices were calculated, and the molecules were classified as active or inactive by applying to them the discriminant function.

d. Pharmacological Distribution Diagram (PDD). The discriminant functions are capable of describing pharmacological activity patterns and also nonactivity patterns. In other words, this function points out not only the active drugs according to their distribution but also the inactive compounds. When applied to the discrimination of concrete pharmacological actions, we call them pharmacological distribution diagram (PDD).[25]

A PDD is a frequency distribution diagram of a dependent variable in which the ordinate represents the expectancies of this variable for every interval. The expectancies of this variable are defined as the probability that a compound will be active or inactive for a value of the discriminant function and are obtained by means of the expressions indicated in the text, in which 100 appears in the denominator to avoid dividing by zero:

Activity Expectancy:

Ea = percentage of actives/(percentage of inactives + 100)

Inactivity Expectancy:

Ei = percentage of inactives/(percentage of actives + 100)

The main advantage of these diagrams is that they make it possible to determine visually the intervals of property in which there is a maximum probability of finding new active compounds and a minimum of encountering inactive ones.

The active molecules had its pharmacological properties calculated by means of the QSAR obtained.

The hypoglycemic assay compared the validity of these results and of the followed discrimination and selection method. The animals used in these tests were male Wistar rats whose blood glucose levels were monitored for 6 h after producing an overcharge of glucose at 2 h.[26] The study was approved by the Committee of Ethics of Animal Use.

RESULTS AND DISCUSSION

Table 2 shows the molecular connectivity indices for the 15 hypoglycemic agents examined in the present study.

The QSAR obtained by multilinear regression and the statistical parameters for several pharmacological properties are shown in Table 3.

Cross-validation for the equations was carried out by varying the number of eliminations and the number of runs

Table 2. Connectivity Indices Values of a Group of Hypoglucemic Agents Used in the Correlation Equations

compound	$^0\chi$	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$^2\chi^v$	$^3\chi_c^v$	$^4\chi_c$	$^4\chi_c^v$	$^4\chi_p^v$
acetohexamide	14.751	12.745	8.814	7.744	5.982	0.742	0.177	0.031	2.767
carbutamide	12.552	10.423	7.193	6.034	4.272	0.508	0.177	0.031	1.501
chlorpropamide	11.845	10.342	6.693	5.847	4.280	0.613	0.177	0.031	1.465
glibenclamide	21.811	19.504	13.320	11.654	8.873	1.057	0.177	0.031	4.194
glibornuride	17.577	15.279	10.227	8.965	8.611	2.316	0.177	0.277	4.817
glybuzole	12.956	11.793	7.236	6.722	6.283	1.836	0.427	0.281	2.253
gliclazide	14.698	12.862	9.177	8.007	6.703	1.024	0.177	0.031	3.643
glymidine	13.732	11.673	8.250	6.551	4.490	0.479	0.177	0.031	1.736
glypizide	20.181	17.709	12.342	10.742	8.095	0.919	0.177	0.031	3.654
gliquidone	24.389	21.655	14.805	12.916	10.594	1.807	0.302	0.156	5.240
glipentide	20.181	17.670	12.409	10.641	7.898	0.857	0.177	0.031	3.804
metahexamide	14.466	12.337	8.627	7.495	5.920	0.784	0.177	0.031	2.691
tolazamide	14.251	12.414	8.710	7.541	5.749	0.691	0.177	0.031	2.499
tolbutamide	12.552	10.845	7.193	6.246	4.516	0.579	0.177	0.031	1.572
tolciclamide	13.544	11.837	8.210	7.290	5.715	0.723	0.177	0.031	2.615

Table 3. Connectivity Function Relationship Obtained by Multilinear Regression for Several Pharmacological Properties[a]

property	equation	*n*	*r*	SD	*F*	CP	*p*
lethal dose 50 i.p. in mouse (g/kg)	LD-50m = $(1.24 \pm 0.25)^4\chi_p^v - (0.59 \pm 0.78)$	7	0.91112	0.860308	24.44		<0.010
potency (log *P*) relative to tolbutamide	$\log(P) = -(5.57 \pm 4.21)^4\chi_c^v + (1.20 \pm 0.79)^3\chi_c^v + (0.09 \pm 0.05) - {}^0\chi^v(1.15 \pm 0.41)$	13	0.89411	0.345169	11.96	4.00	<0.010
protein plasmatic binding (%)	PPB = $-(11.43 \pm 10.92)^1\chi^v + (6.53 \pm 8.60)^1\chi + (2.71 \pm 2.12)^0\chi^v + (88.92 \pm 2.75)$	10	0.67960	1.999360	1.72	4.00	<0.5

[a] *n* = number of values, *r* = coefficient correlation, SD = standard deviation, *F* = Snedecor function, CP = Mallow's CP, *p* = significance.

Table 4. Cross-Validation (Jackknife Method) for the Regression Model Corresponding to the Lethal Dose-50 (i.p. in Mouse) Values of Hypoglycemic Drugs

	original model (no deletions)		two deletions per run (seven runs)	
	regression value	SD	regression value	SD
correlation coefficient	0.911		0.955	
SD	0.860		0.023	
coefficient of $^4\chi_p^v$	1.238	0.250	1.417	0.143
constant	−0.593	0.776	−1.331	0.178
average residual	-1.43×10^{-5}	0.727	2×10^{-5}	0.569
residuals < 1 SD (%)	57.14		73.33	
residuals between 1 and 2 SD (%)	42.86		26.67	
residuals > 2 SD (%)	0.00		0.00	

Table 5. Cross-Validation (Jackknife Method) for the Regression Model Corresponding to the Potency (log *P*) Relative to Tolbutamide Values of Hypoglycemic Drugs

	original model (no deletions)		two deletions per run (13 runs)	
	regression value	SD	regression value	SD
correlation coefficient	0.894		0.900	
SD	0.345		0.014	
coefficient of $^4\chi_c^v$	−5.570	4.211	−4.704	0.652
coefficient of $^3\chi_c^v$	1.205	0.788	1.100	0.179
coefficient of $^0\chi^v$	0.093	0.053	0.084	0.035
constant	−1.149	0.412	−1.033	0.348
average residual	-7.69×10^{-6}	0.287	-6.06×10^{-6}	0.270
residuals < 1 SD (%)	53.85		57.58	
residuals between 1 and 2 SD (%)	46.15		42.42	
residuals > 2 SD (%)	0.00		0.00	

for each specific property. We found that raising the number of eliminations made the model more unstable, which, on the other hand, was to be expected because the degrees of freedom were considerably diminished. In all the equations, the stability corresponding to two eliminations was chosen,

Table 6. Cross-Validation (Jackknife Method) for the Regression Model Corresponding to the Plasma Protein Binding Values of Hypoglycemic Drugs

	original model (no deletions)		two deletions per run (10 runs)	
	regression value	SD	regression value	SD
correlation coefficient	0.680		0.764	
SD	1.999		0.088	
coefficient of $^1\chi^v$	−11.426	10.923	−17.125	0.088
coefficient of $^1\chi$	6.534	8.604	10.975	4.812
coefficient of $^0\chi^v$	2.708	2.118	3.055	1.241
constant	88.921	2.753	89.110	1.764
average residual	0.000	1.549	0.000	1.359
residuals < 1 SD (%)	70.00		66.67	
residuals between 1 and 2 SD (%)	30.00		29.17	
residuals > 2 SD (%)	0.00		4.16	

Table 7. Best Obtained Equation by Linear Discriminant Analysis (LDA) Applied to Hypoglycemic Activity[a]

parameter	coefficient	*F* to remove	*U* statistical
$^0\chi$	−0.67058	25.1564	0.6712
$^2\chi^v$	2.68237	28.7209	0.7677
$^3\chi_c^v$	−7.78414	17.0495	0.8930
$^4\chi_c$	17.33495	3.8120	0.9790
constant	−0.56684		

[a] Discriminant function $\Delta P = -0.67058\,{}^0\chi + 2.68237\,{}^2\chi^v - 7.78414\,{}^3\chi_c^v + 17.33495\,{}^4\chi_c - 0.56684$.

and the process was repeated a total of 7, 13, and 10 runs for the lethal dose 50 (i.p.) in mouse, potency (log *P*), and plasma protein binding equations, respectively. This means that in all cases, approximately 10% of the observations were eliminated, and this value coincides with the one recommended by some authors[4] (Tables 4−6). Comparison between the values obtained with the selected model and the model of two eliminations, depending on the specific case,

Table 8. Results Obtained by Linear Discriminant Analysis, Carried out with 84 Different Compounds with Hypoglycemic Activity and 88 Different Inactive Compounds[a]

Part a[b]

compound	active group classif	ΔP	probability (%)
1-butyl-3-metanilylurea	+	1.590	83
phenylalanine deriv [a] comp 10	+	0.461	61
phenylalanine deriv [a] comp 13	U	0.170	54
phenylalanine deriv [a] comp 14	+	1.645	84
phenylalanine deriv [a] comp 19	U	−0.136	47
diarylsulfonylurea deriv [b] comp 2	+	0.851	70
diarylsulfonylurea deriv [b] comp 10	+	0.775	69
diarylsulfonylurea deriv [b] comp 17	+	0.902	71
diarylsulfonylurea deriv [b] comp 39	+	0.575	64
diarylsulfonylurea deriv [b] comp 57	+	1.673	84
diarylsulfonylurea deriv [b] comp 59	+	1.150	76
diarylsulfonylurea deriv [b] comp 63	+	0.746	68
diarylsulfonylurea deriv [b] comp 65	+	1.346	79
diarylsulfonylurea deriv [b] comp 67	+	1.023	74
diarylsulfonylurea deriv [b] comp 69	+	0.700	67
diarylsulfonylurea deriv [b] comp 87	+	1.303	79
benzyloxazolidine-2,4-dione deriv [c] comp 15	+	0.281	57
benzyloxazolidine-2,4-dione deriv [c] comp 17	+	4.804	99
benzyloxazolidine-2,4-dione deriv [c] comp 19	+	0.746	68
benzyloxazolidine-2,4-dione deriv [c] comp 29	+	0.251	56
benzyloxazolidine-2,4-dione deriv [c] comp 31	−	−0.324	42
benzyloxazolidine-2,4-dione deriv [c] comp 33	+	1.922	87
midaglizole	+	1.608	83
pyracine deriv [d] comp 4	+	0.846	70
pyracine deriv [d] comp 16k	+	0.442	61
linogliride	+	1.384	80
N-(aminoalkilidene)carboximidamide deriv [e] comp 6b	+	0.591	64
N-(aminoalkilidene)carboximidamide deriv [e] comp 6d	−	−0.262	44
N-(aminoalkilidene)carboximidamide deriv [e] comp 6f	−	−0.999	27
N-(aminoalkilidene)carboximidamide deriv [e] comp 6h	+	1.749	85
N-(aminoalkilidene)carboximidamide deriv [e] comp 6j	−	−0.498	38
N-(aminoalkilidene)carboximidamide deriv [e] comp 6l	+	0.591	64
N-(aminoalkilidene)carboximidamide deriv [e] comp 6n	+	0.731	68
N-(aminoalkilidene)carboximidamide deriv [e] comp 6p	+	1.073	75
N-(aminoalkilidene)carboximidamide deriv [e] comp 6r	−	−0.875	29
N-(aminoalkilidene)carboximidamide deriv [e] comp 6t	−	−1.564	17
N-(aminoalkilidene)carboximidamide deriv [e] comp 6v	+	1.264	78
N-(aminoalkilidene)carboximidamide deriv [e] comp 6y	+	0.860	70
N-(aminoalkilidene)carboximidamide deriv [e] comp 6aa	−	−0.551	37
N-(aminoalkilidene)carboximidamide deriv [e] comp 6 cm^3	+	0.483	62
N-(aminoalkilidene)carboximidamide deriv [e] comp 6ee	+	0.350	59
N-(aminoalkilidene)carboximidamide deriv [e] comp 6hh	U	0.119	53
N-(aminoalkilidene)carboximidamide deriv [e] comp 6kk	−	−0.955	28
hydroxyurea deriv [f] comp 3	U	−0.118	47
hydroxyurea deriv [f] comp 7	−	−1.254	22
hydroxyurea deriv [f] comp 9	U	0.000	50
hydroxyurea deriv [f] comp 11	−	−0.524	37
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 42	+	0.540	63
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 44	+	0.745	68
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 47	+	0.721	67
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 49	+	0.996	73
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 51	+	0.972	73
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 54	+	0.972	73
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 56	+	0.563	64
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 61	+	0.769	68
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 63	+	0.656	66
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 66	+	1.036	74
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 68	+	3.443	97
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 74	U	0.122	53
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 78	+	0.696	67
acidic azole deriv [h] comp 11	−	−0.252	44
acidic azole deriv [h] comp 31	+	0.418	60
azirine deriv [i] comp 5	+	2.398	92
azirine deriv [i] comp 6	−	−1.010	27
thiazolidine-2,4-dione deriv [j] comp 18	U	0.177	54
thiazolidine-2,4-dione deriv [j] comp 22	+	0.371	59
thiazolidine-2,4-dione deriv [j] comp 38	U	0.044	51
thiazolidine-2,4-dione deriv [j] comp 48	+	5.469	100
ciglitazone	+	1.799	86
troglitazone	+	0.433	61

Table 8 (Continued)

compound	active group classif	Δ*P*	probability (%)
pioglitazone	+	1.042	74
isoxazolidine-3,5-dione deriv [k] comp 2	+	0.237	56
carbutamide	+	1.581	83
chlorpropamide	+	1.264	78
glibornuride	U	0.053	51
gliclazide	+	2.651	93
glipizide	+	3.522	97
gliquidone	+	2.660	94
glybuthiazole	U	0.025	51
glymidine	+	1.603	83
karanjin	U	0.115	53
methahexemide	+	2.572	93
tolazamide	+	2.984	95
tolbutamide	+	1.687	84

Part b[c]

compound	inactive group classif	Δ*P*	probability (%)	compound	inactive group classif	Δ*P*	probability (%)
acebutolol	−	−1.732	85	nitrazepam	−	−0.624	65
aciclovir	−	−1.766	85	norfloxacine	−	−0.732	68
acifran	−	−0.809	69	oxametacine	−	−1.596	83
alclofenac	−	−1.333	79	oxprenolol	−	−1.178	77
allobarbital	−	−1.514	82	pefloxacine	−	−1.572	83
atenolol	−	−1.855	87	phenyltoloxamine	U	−0.112	53
beclofibrate	U	−0.160	54	practolol	−	−1.951	88
binifibrate	−	−0.535	63	sparfloxacine	−	−4.936	99
bupranolol	−	−1.066	74	sulindac	−	−1.558	83
ciprofibrate	−	−6.486	100	temazepam	−	−0.673	66
clofibrate	−	−1.068	74	plafibride	−	−0.433	61
diflunisal	−	−2.115	89	nicotinic acid	−	−1.173	76
etofibrate	−	−0.596	65	etiroxate	−	−0.288	57
fenoprofen	−	−0.550	63	eritaden	−	−2.617	93
gemfibrozil	−	−2.236	90	amoxiciline	−	−3.759	98
gentisic acid	−	−2.173	90	cefazoline	+	0.990	27
idoxuridine	−	−1.483	82	ceftriaxone	−	−0.251	56
indometacine	−	−1.441	81	dicloxacilline	−	−3.779	98
mefenamic acid	−	−1.306	79	gentamicine	−	−1.022	74
niceritrol	−	−0.719	67	imipenem	−	−0.338	58
nicofibrate	−	−0.322	58	minocycline	−	−3.261	96
oxiniacic acid	−	−1.800	86	netilmicine	−	−0.534	63
pentaeritritol	−	−4.152	99	pivampicilline	−	−4.793	99
phenacetine	−	−1.250	78	tobramycine	−	−3.381	97
phenobarbital	−	−0.960	72	acetophenazine	+	2.403	8
pravastatine	−	−1.451	81	epanolol	U	−0.130	53
ronifibrate	U	−0.114	53	nadoxolol	−	−0.845	70
simvastatine	−	−1.145	76	promazine	+	1.475	19
xenbucin	U	0.179	46	thiothixene	+	2.417	8
aceclofenac	−	−1.237	78	codeine	+	0.509	38
acetanilide	−	−0.744	68	meperidine	U	−0.172	54
antipyrine	−	−0.810	69	cycloserine	−	−1.521	82
benzydamine	+	0.401	40	isoniazide	−	−1.253	78
carbamazepine	+	0.269	43	metronidazole	−	−2.414	92
carbinoxamine	−	−0.761	68	artesunate	+	1.693	16
cinnarizine	+	3.107	4	hexoprenaline	+	0.346	41
ciprofloxacine	−	−2.526	93	primaquine	U	−0.087	52
doxylamine	U	−0.180	55	quinine	+	0.963	28
enfenamic acid	+	0.409	40	terbutaline	−	−1.427	81
enoxacin	−	−0.924	72	propanolol	−	−0.461	61
flumequine	−	−1.123	76	bopindolol	+	0.488	38
ibufenac	−	−1.769	85	etersalate	−	−1.424	81
ketorolac	+	0.282	43	fenethazine	+	0.633	35
labetalol	−	−0.589	64	tenoxicam	+	1.243	22

[a] [a] *J. Med. Chem.* **1989**, *32* (7), 1436−1441; [b] *J. Med. Chem.* **1990**, *33* (9), 2393−2407; [c] *J. Med. Chem.* **1991**, *34* (5), 1538−1544; [d] *J. Med. Chem.* **1992**, *35* (21), 3845−3857; [e] *J. Med. Chem.* **1993**, *36* (11), 1597−1603; [f] *J. Med. Chem.* **1993**, *36* (15), 2238−2240; [g] *J. Med. Chem.* **1993**, *36* (17), 2485−2493; [h] *J. Med. Chem.* **1995**, *38* (4), 617−628; [i] *J. Med. Chem.* **1995**, *38* (16), 3034−3042; [j] *J. Med. Chem.* **1998**, *41* (7), 1084−1091; [k] *J. Med. Chem.* **1998**, *41* (11), 1927−1933. [b] Undetermined (U) = 13.10%, false inactivity = 14.29%, overall accuracy = 72.62%, adjusted accuracy (excluded undetermined) = 83.56%. [c] Undetermined (U) = 9.09%, false activity = 18.18%, overall accuracy = 72.73%, adjusted accuracy (excluded undetermined) = 80.00%.

shows the predictability of the selected equations. This is made patent by the equality of the obtained terms as well as by the low standard deviations in each of them. Analysis of the obtained residuals with the selected model as well as for

Table 9. Results Obtained by Applying the Final Discriminant Function to a Group of 82 Active Compounds and a Group of 84 Inactive Compounds Not Included in the LDA (Cross-Validation)[a]

Part a[b]

compound	active group classif	ΔP	probability (%)
phenylalanine deriv [a] comp 11	+	1.099	75
phenylalanine deriv [a] comp 15	−	−0.469	39
phenylalanine deriv [a] comp 16	+	2.120	89
phenylalanine deriv [a] comp 20	−	−0.934	28
diarylsulfonylurea deriv [b] comp 1	+	3.673	98
diarylsulfonylurea deriv [b] comp 3	+	2.315	91
diarylsulfonylurea deriv [b] comp 16	+	1.098	75
diarylsulfonylurea deriv [b] comp 18	+	0.695	67
diarylsulfonylurea deriv [b] comp 56	+	4.248	99
diarylsulfonylurea deriv [b] comp 58	+	1.477	81
diarylsulfonylurea deriv [b] comp 62	+	0.953	72
diarylsulfonylurea deriv [b] comp 64	+	0.626	65
diarylsulfonylurea deriv [b] comp 66	+	3.598	97
diarylsulfonylurea deriv [b] comp 68	+	0.827	70
diarylsulfonylurea deriv [b] comp 76	+	0.911	71
bencyloxazolidine-2,4-dione deriv [c] comp 16	−	−0.370	41
bencyloxazolidine-2,4-dione deriv [c] comp 18	−	−0.272	43
bencyloxazolidine-2,4-dione deriv [c] comp 20	+	1.952	88
bencyloxazolidine-2,4-dione deriv [c] comp 30	−	−0.315	42
bencyloxazolidine-2,4-dione deriv [c] comp 32	+	0.716	67
pyracine deriv [d] comp 2	+	2.580	93
pyracine deriv [d] comp 16f	+	0.467	62
pyracine deriv [d] comp 25m	+	0.467	62
oxazole-2,4-thiazolidinedione deriv [l] comp 7	+	1.163	76
N-(aminoalkilidene)carboximidamide deriv [e] comp 6a	−	−0.411	40
N-(aminoalkilidene)carboximidamide deriv [e] comp 6c	−	−0.613	35
N-(aminoalkilidene)carboximidamide deriv [e] comp 6e	+	2.321	91
N-(aminoalkilidene)carboximidamide deriv [e] comp 6g	U	−0.007	50
N-(aminoalkilidene)carboximidamide deriv [e] comp 6i	+	0.836	70
N-(aminoalkilidene)carboximidamide deriv [e] comp 6k	+	0.759	68
N-(aminoalkilidene)carboximidamide deriv [e] comp 6m	−	−0.384	41
N-(aminoalkilidene)carboximidamide deriv [e] comp 6o	+	2.080	89
N-(aminoalkilidene)carboximidamide deriv [e] comp 6q	−	−1.861	14
N-(aminoalkilidene)carboximidamide deriv [e] comp 6s	+	1.118	75
N-(aminoalkilidene)carboximidamide deriv [e] comp 6u	+	0.415	60
N-(aminoalkilidene)carboximidamide deriv [e] comp 6x	U	−0.188	45
N-(aminoalkilidene)carboximidamide deriv [e] comp 6z	+	0.819	69
N-(aminoalkilidene)carboximidamide deriv [e] comp 6bb	U	−0.106	47
N-(aminoalkilidene)carboximidamide deriv [e] comp 6dd	−	−1.115	25
N-(aminoalkilidene)carboximidamide deriv [e] comp 6ff	+	0.271	57
N-(aminoalkilidene)carboximidamide deriv [e] comp 6ii	−	−0.454	39
hydroxyurea deriv [f] comp 8	−	−1.115	25
hydroxyurea deriv [f] comp 10	U	−0.136	47
hydroxyurea deriv [f] comp 12	−	−1.092	25
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 43	+	0.844	70
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 45	+	0.721	67
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 48	+	1.132	76
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 50	+	0.981	73
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 52	+	0.789	69
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 55	+	0.625	65
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 59	+	0.466	61
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 62	+	0.679	66
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 65	+	1.136	76
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 67	+	3.467	97
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 70	+	0.830	70
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 77	+	0.333	58
naphthalenyl 3H-1,2,3,5-oxathiadiazole 2-oxide deriv [g] comp 79	+	0.566	64
acidic azole deriv [h] comp 13	U	−0.135	47
acidic azole deriv [h] comp 38	+	2.816	94
azirine deriv [i] comp 4	+	0.251	56
azirine deriv [i] comp 8	−	−2.097	11
thiazolidine-2,4-dione deriv [j] comp 17	−	−0.309	42
thiazolidine-2,4-dione deriv [j] comp 20	+	0.422	60
thiazolidine-2,4-dione deriv [j] comp 24	U	−0.101	48
thiazolidine-2,4-dione deriv [j] comp 41	−	−0.516	37
thiazolidine-2,4-dione deriv [j] comp 56	U	−0.031	49
thiazolidine-2,4-dione deriv [m] comp 3g	+	1.614	83
englitazone	+	2.157	90
isoxazolidine-3,5-dione deriv [k] comp 10	−	−0.594	36

Table 9 (Continued)

compound	active group classif	Δ*P*	probability (%)
cryptolepine	+	0.937	72
acetohexamide	+	2.877	95
cicloheptamide	+	3.589	97
glibenclamide	+	3.443	97
glimepiride	+	2.120	89
glisentide	+	3.483	97
glisoxepide	+	3.189	96
glybuzole	+	0.706	67
glyhexamide	+	4.728	99
glypinamide	+	3.036	95
phenbutamide	+	2.262	91
tolciclamide	+	3.115	96
benfluorex	+	2.968	95

Part b[c]

compound	inactive group classif	Δ*P*	probability (%)	compound	inactive group classif	Δ*P*	probability (%)
alprenolol	−	−0.894	71	phemiramine	U	0.144	46
aminopyrine	−	−1.760	85	pindolol	−	−0.831	70
azacosterol	+	1.002	27	pipemidic acid	−	−0.530	63
barbital	+	33.764	0	salicylamide	−	−1.413	80
bezafibrate	−	−0.433	61	temafloxacin	−	−1.800	86
bufuralol	−	−0.274	57	tolmetin	−	−1.489	82
clofibric acid	−	−1.272	78	triazolam	U	−0.031	51
cytaradine	−	−2.365	91	triprolidine	+	1.858	14
etedolac	−	−0.421	60	clofibride	−	−1.280	78
fenofibrate	−	−1.118	75	doxazosine	U	−0.197	55
flufenamic acid	+	2.083	11	clomestrone	U	−0.193	55
ibuprofen	−	−2.303	91	thyrotropic acid	−	−0.368	59
ketoprofen	−	−0.631	65	phenylbutazone	−	−0.482	62
lovastatine	+	0.602	35	amikacine	−	−4.256	99
naproxen	−	−1.208	77	carbenicilline	−	−3.391	97
nicoclonate	−	−1.211	77	cefadroxile	−	−0.879	71
pantethine	U	−0.176	54	ceftazidine	U	0.100	48
pirifibrate	−	−0.799	69	cephaloridine	+	1.933	13
probucol	−	−11.374	100	chlorampicilline	−	−3.225	96
simfibrate	−	−0.227	56	doxycycline	−	−3.297	96
theofibrate	−	−1.723	85	metampicilline	−	−2.802	94
triparanol	+	0.747	32	rifampicine	−	−3.909	98
vidaravine	−	−2.364	91	tetracycline	−	−2.035	88
zomepirac	−	−1.885	87	butaclamol	+	2.029	12
acetaminphen	−	−1.458	81	nadolol	−	−0.424	60
acetylsalycilsalycilic acid	−	−1.610	83	sulpiride	+	2.633	7
benoxaprofen	−	−0.979	73	fentanyl	+	2.328	9
bromfenac	−	−1.118	75	anisomycine	−	−0.955	72
chlorpheniramine	−	−0.380	59	ethambutol	−	−0.719	67
clemastine	+	1.837	14	streptomicine	−	−4.526	99
clinafloxacine	−	−3.531	97	nifurtimox	+	1.285	22
diclofenac	−	−0.793	69	chloroquine	U	0.121	47
enrofloxacine	−	−2.979	95	ephedrine	−	−0.858	70
esmolol	−	−1.452	81	protokylol	−	−1.091	75
glafenin	−	−0.827	70	quinidine	+	0.963	28
indoprofen	−	−0.456	61	nipradilol	−	−2.122	89
lorazepam	−	−0.730	68	benorylate	−	−1.597	83
mepindolol	−	−1.300	79	clindanac	+	2.151	10
nalidixic acid	−	−1.772	86	kanamycine a	−	−4.082	98
niflumic acid	+	1.817	14	loxoprofen	U	0.186	45
nordiazepam	+	0.243	44	sisomicine	−	−1.069	74
oxolinic acid	−	−1.428	81	timolol	+	0.600	35

[a] [a] *J. Med. Chem.* **1989**, *32* (7), 1436−1441; [b] *J. Med. Chem.* **1990**, *33* (9), 2393−2407; [c] *J. Med. Chem.* **1991**, *34* (5), 1538−1544; [d] *J. Med. Chem.* **1992**, *35* (21), 3845−3857; [e] *J. Med. Chem.* **1993**, *36* (11), 1597−1603; [f] *J. Med. Chem.* **1993**, *36* (15), 2238−2240; [g] *J. Med. Chem.* **1993**, *36* (17), 2485−2493; [h] *J. Med. Chem.* **1995**, *38* (4), 617−628; [i] *J. Med. Chem.* **1995**, *38* (16), 3034−3042; [j] *J. Med. Chem.* **1998**, *41* (7), 1084−1091; [k] *J. Med. Chem.* **1998**, *41* (11), 1927−1933; [l] *J. Med. Chem.* **1992**, *35* (24), 4613−4627; [m] *J. Med. Chem.* **1998**, *41* (10), 1619−1630. [b] Undetermined (U) = 8.54%, false inactivity = 20.73%, overall accuracy = 70.73%, adjusted accuracy (excluded undetermined) = 77.33%. [c] Undetermined (U) = 9.52%, false inactivity = 20.24%, overall accuracy = 70.24%, adjusted accuracy (excluded undetermined) = 77.63%.

two-elimination model reveals minimum discrepancies in the measurements and in their standard deviation, and this aspect of the study strengthens the predictive quality of the model.

A comparison between the experimental and calculated values for the selected properties is shown in Figures 1−3, respectively.

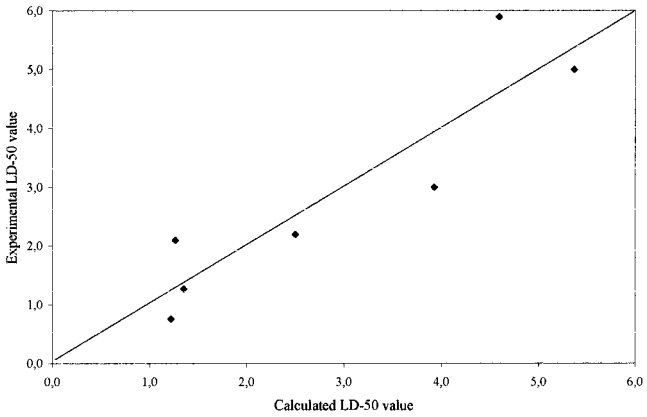


Figure 1. Correlation between experimental and calculated LD-50m (i.p.) values of hypoglycemic drugs (equation in Table 3).

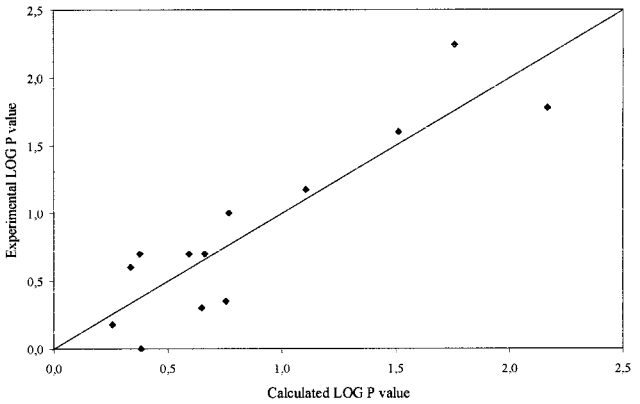


Figure 2. Correlation between experimental and calculated log *P* values of hypoglycemic drugs (equation in Table 3).

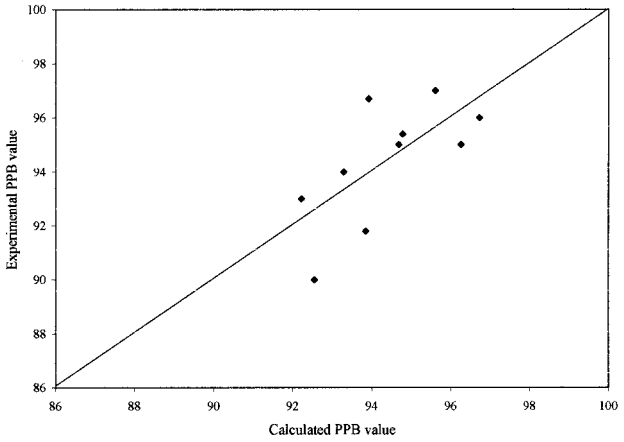


Figure 3. Correlation between experimental and calculated PPB percentage values of hypoglycemic drugs (equation in Table 3).

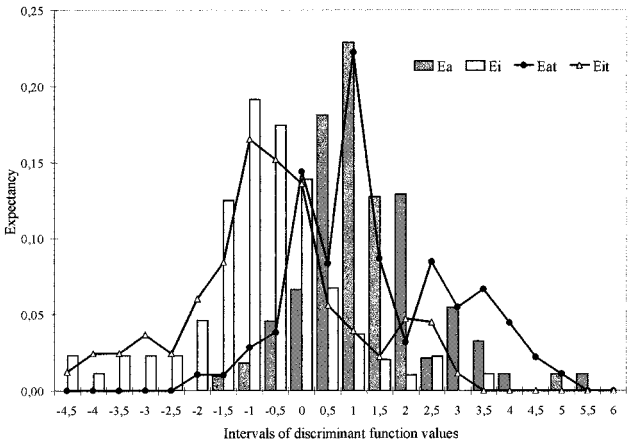


Figure 4. Pharmacological distribution diagram (PDD) for the discriminant function of hypoglycemic activity (Ea and Eat, activity expectancy of reference and test groups, respectively; Ei and Eit, inactivity expectancy of reference and test groups, respectively).

In the linear discriminant analysis, the connectivity indices are used as independent variables of each molecule. The best discrimination function was obtained with the variables ${}^0\chi$, ${}^2\chi^v$, ${}^3\chi_c{}^v$, and ${}^4\chi_c$. Table 7 shows the discriminant function (ΔP), obtained as the difference between the variables defining the groups of active and inactive molecules, together with the values for F-Snedecor and Wilk's U statistical parameters used with each variable. Molecules with discriminant function values higher than zero ($\Delta P > 0$) were classified as active, while $\Delta P < 0$ corresponds to inactive molecules.

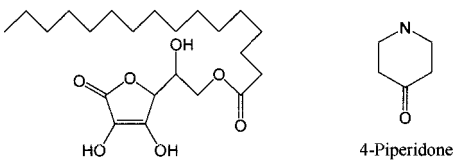
Table 8a,b shows the results obtained using 84 molecules with demonstrated hypoglycemic activity and 88 inactive molecules in the linear discriminant analysis. Compounds were classified as indeterminate if the probability of activity or inactivity was between 50% and 55% ($0 < \Delta P < 0.2$), i.e., this margin was too tight for a decision to be made as to whether they were active or inactive. Misclassified compounds are those whose results were incorrectly predicted by the final LDA equation.

Overall accuracy was 72.62% in the active group and 72.73% in the inactive group. These percentages increase to 83.56% and 80.00%, respectively, if the undetermined molecules are eliminated. The cross-validation test was applied to the ΔP function with a group of 82 hypoglycemic agents and 84 theoretical inactives not used in the discriminant function. Table 9a,b shows the results obtained. The fact that both the overall accuracy (%) and the adjusted accuracy (%) are similar to those of the group used in the LDA demonstrates the quality of the selected discriminant function that is able to classify correctly about 80% of the molecules belonging to each group.

Figure 4 shows the classification function obtained through stepwise linear discriminant analysis and the corresponding PDD. In this plot, the maximum of the Ei and the Ea values are distributed in both sides of $\Delta P = 0$. We obtain positive values for active compounds (with a maximum value around $\Delta P = 1$) and negative values for inactive compounds (with a maximum value of $\Delta P = -1$, approximately), in both groups of discrimination and the test groups. The values calculated for the discriminant function and the corresponding classification appear in Tables 8a,b and 9a,b.

The obtained equation allowed the selection of two new hypoglycemic candidates among the structures without known therapeutic activity of a database. The topological indices were determined, and the molecules were classified as active or inactive by applying to them the discriminant function. Their structures are presented in Figure 5.

We calculated the predicted values of LD-50m i.p., potency, and PPB for these molecules by means of the QSARs obtained. As these values (see Table 10) are similar to the corresponding values of the antidiabetic drugs used



L-Ascorbic Acid 6-Palmitate

Figure 5. Selected chemical structures of two new hypoglycemic agents.

Table 10. Calculated Values of Several Pharmacological Properties of Two New Hypoglycemic Agents Selected by the Discriminant Function

selected compounds	potency	LD-50m i.p. (g/kg)	PPB (%)
L-ascorbic acid 6-palmitate	9.30	3.56	94.58
4-piperidone monohydrate hydrochloride	0.28	0.43	93.24

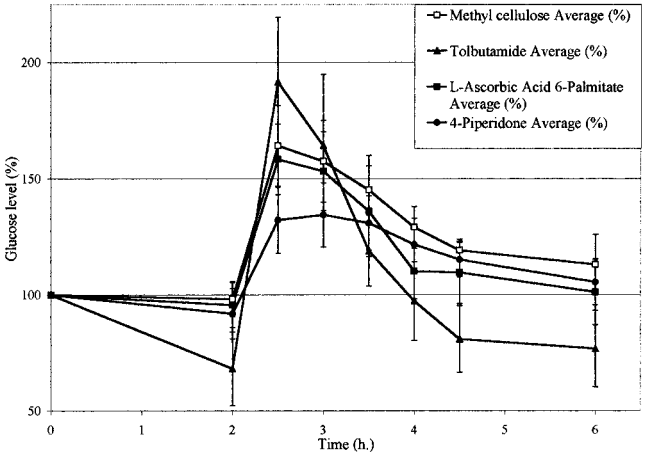


Figure 6. Glucose levels after the administration of 4-piperidone and L-ascorbic acid 6-palmitate followed by an oral glucose overcharge with respect to the vehicle (methyl cellulose 0.5%) and reference drug (tolbutamide).

Table 11. Area under the Curve Values from 0 to 6 Hours (AUC) for 4-Piperidone, L-Ascorbic Acid 6-Palmitate, Vehicle, and Tolbutamide

compound	AUC
vehicle	724 ± 38
tolbutamide	610 ± 54
L-ascorbic acid 6-palmitate	684 ± 44
4-piperidone	669 ± 46

in the prediction, activity tests were performed for both compounds.

Figure 6 shows the mean blood glucose concentrations versus time obtained in the activity tests, with a control of the vehicle used (methyl cellulose 0.5%), a reference drug (tolbutamide), and the products.

Table 11 lists the values of area under the curve from 0 to 6 h (AUC). As can be seen, the administration of these new drugs candidates produces a significant reduction in AUC with respect to the vehicle, pointing out its hypoglycemic activity. Moreover, they do not affect normal glycaemia blood levels, which represents an advantage over classical sulfonylurea derivatives.

CONCLUSIONS

Molecular connectivity indices are simple and useful descriptors for discriminating and selecting new structures with possible hypoglycemic activity. The discriminant function obtained allows the classification of the compounds in actives and inactives with a high percentage of accuracy (around 80%). The PDD constitutes a valuable tool in discriminating and consequently in searching for new lead drugs.

The selected compounds by means of the discriminant function, L-ascorbic acid 6-palmitate and 4-piperidone, are good hypoglycemic candidates, worthy of further study.

These results verify the method proposed and suggest that it constitutes a simple tool for finding chemical structures which can become new hypoglycemic drugs.

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