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Pharmacological distribution diagrams: A tool for *de novo* drug design

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Discriminant analysis applied to SAR studies using topological descriptors allows us to plot frequency distribution diagrams: a function of the number of drugs within an interval of values of discriminant function vs. these values. We make use of these representations, pharmacological distribution diagrams (PDDs), in structurally heterogeneous groups where generally they adopt skewed Gaussian shapes or present several maxima. The maxima afford intervals of discriminant function in which exists a good expectancy to find new active drugs. A set of β-blockers with contrasted activity has been selected to test the ability of PDDs as a visualizing technique, for the identification of new β-blocker active compounds. © 1996 by Elsevier Science Inc.

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INTRODUCTION

Stepwise linear discriminant analysis is a statistical tool with the capacity to classify a set of numerically describable objects by finding the linear combination of variables that best predicts the category to which an object belongs. This combination of variables constitutes a classification function. A histogram of classification function intervals will show an object distribution for each category, with a greater or lesser degree of overlap between them. Sometimes, properties used in quantitative structure–activity relationship (QSAR) studies can be used as discriminant properties. For example, within a homologous group of potentially active compounds one can define a range of logP within which active compounds are gathered. Most frequently, correlations of an activity with discriminant molecular parameters are obtained through multivariate analysis. Usually the activity correlated is a pharmacological property.[1] In our research we have found that it is possible to obtain correlations between connectivity indices and pharmacokinetic properties that can act as discriminant functions. We designate as *limiting properties* any properties that can be used as classification functions. The identification of limiting properties is performed with the aid of modified frequency histograms. When applied to the discrimination of concrete pharmacological actions, we call them *pharmacological distribution diagrams* (PDDs). This concept is closely related to the notion of the topological pharmacological distribution function, first introduced by Galvez.[2]

METHOD

A set of β-blocker compounds with contrasting activity was selected to test the ability of PDDs to identify new active compounds. All the descriptors used to characterize the β-blocker compounds were connectivity indices, obtained from the adjacent matrix, and they have all been defined in previous papers.[3]

An initial classification function was obtained through stepwise linear discriminant analysis. The group of inactives consisted of compounds with non-β-blocker pharmacological activity. For the purpose of finding limiting properties that add other classification functions, two properties were correlated: the oral LD_{50} (50% lethal dose) in mice and the distribution half-life. Given an interval of values for a continuous variable, the expectancies of this variable E are defined as:

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Activity expectancy:

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

Inactivity expectancy:

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

A PDD is a frequency distribution diagram of a dependent variable in which the ordinate represents the expectancies of this variable for every interval.

RESULTS

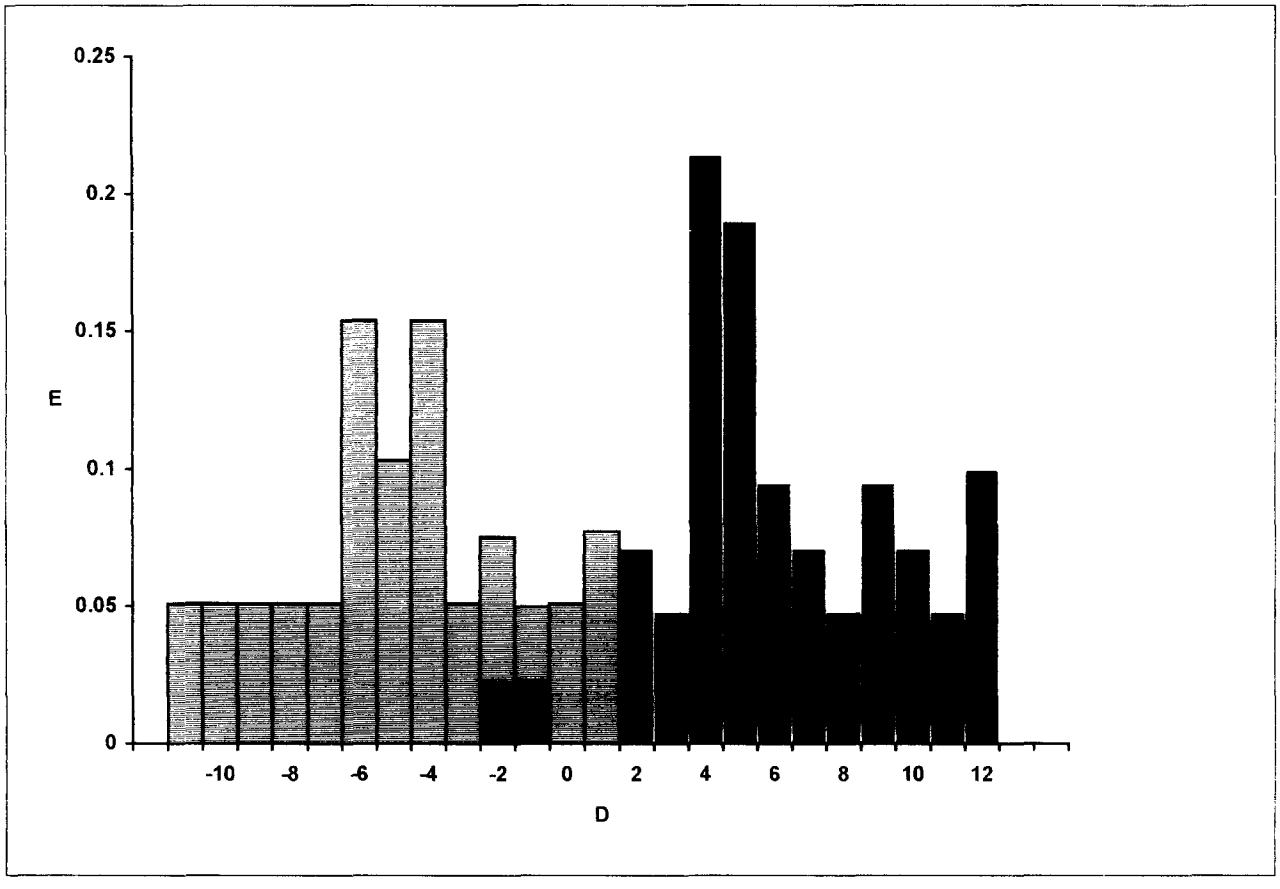
Figure 1 shows the classification function obtained through stepwise linear discriminant analysis, and the corresponding PDD. In this plot, as in the others in this article, the overlapping of E_i can be seen in the E_a region. The less the overlap, the more purposeful the PDD. As may be seen, this function establishes the distinction between β-blocker and non-β-blocker active compounds. Calculated values for the discriminant function and corresponding classification appear in Table 1.

This function has been applied to an extensive group of compounds, some with therapeutic use in humans. Among the compounds that show positive values of the discriminant function, D, probucol (hypolipidemic, D = 11.8), filipin III (antifungal, D = 10.7), clidanac (analgesic, D = 1.4), and β-carotene (provitamin A, D = 5.1) standout.

The distribution half-life ($t_{1/2}$) equation and plot can be seen in Figure 2. Although the equation was obtained with only 17 β-blocker compounds, it generalizes well: The PDD was obtained applying the equation to 50 active and 50 inactive compounds.

Figure 3 shows the PDD of the LD_{50} and its corresponding equation. The PDD was obtained by applying the equation to 50 active and 198 inactive compounds. The group of inactive compounds was randomly chosen.

As can be appreciated, the overlapping of E_a and E_i in the case of the LD_{50} (Figure 3) is greater than in the case of $t_{1/2}$ (Figure 2). Consequently, $t_{1/2}$ is a better limitant property



$D = -22.96 - 2.26\ {}^{1}\chi^{v} + 6.48\ {}^{2}\chi - 5.74\ {}^{4}\chi_{pc} - 4.01\ G_4{}^{v} + 147.67\ J_4 - 1.06\ {}^{4}\chi_{c}/{}^{4}\chi_{c}{}^{v} + 0.0005\ W - 0.404\ PR2$

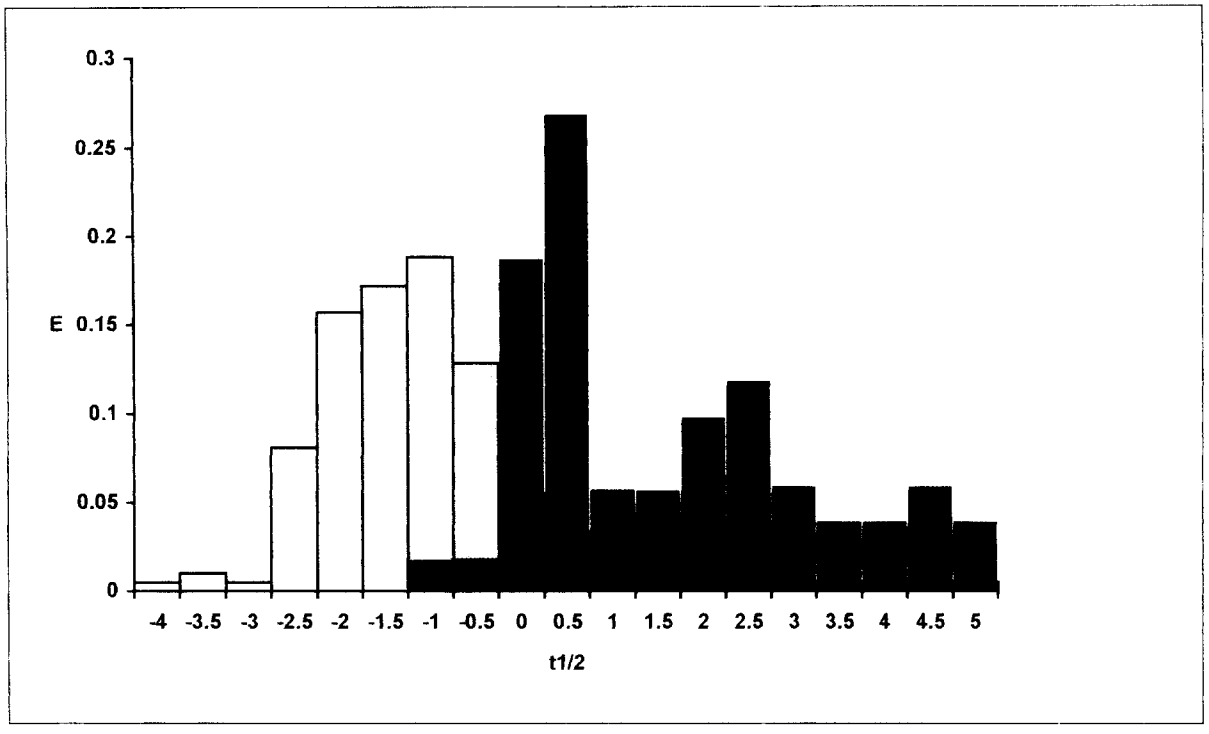
N = 81 F = 23.4 U-statistics (Wilks'λ) = 0.28

Figure 1. PDD and equation for the classification function of β*-blocker activity. Black bars, E_a; light gray bars, E_i; dark gray bars, overlap.*

Table 1. Results obtained applying the stepwise linear discriminate analysis to β-blocker activity

Active group			Inactive group		
Compound	D	Class[a]	Compound	D	Class[a]
			Training group		
Acebutolol	4.60	+	Acipimox	−3.75	−
Arotinolol	3.95	+	Aminopyrine	−11.50	−
Atenolol	4.14	+	Antrafenine	−9.39	−
Befunolol	8.09	+	Azacitidine	−5.54	−
Betaxolol	9.18	+	Beclobrate	−6.34	−
Bevantolol	4.95	+	Bezafibrate	−4.91	−
Bisoprolol	10.30	+	Bromosalicylchloranilide	1.12	+
Bopindolol	7.80	+	Buclosamide	−1.47	−
Bucumolol	8.23	+	Candicidin	−7.21	−
Bufetolol	9.72	+	Carboquone	−1.18	−
Bufuralol	3.74	+	Carmustine	−10.13	−
Bunitrolol	3.45	+	Chlorambucil	0.64	+
Bupranolol	5.61	+	Chlordantoin	−2.22	−
Butidrine	−3.25	−	Chlormidazole	−7.59	−
Butofilolol	8.15	+	Diamthazole	−2.60	−
Carazolol	4.52	+	Diflunisal	0.47	+
Carteolol	6.44	+	Doxorubicin	−4.61	−
Carvedilol	7.19	+	Econazole	−0.57	−
Celiprolol	9.66	+	Enilconazole	−3.17	−
Cetamolol	5.57	+	Etofibrate	−4.58	−
Cloranolol	6.13	+	Fenofibrate	−6.17	−
Dilevalol	4.92	+	Gemfibrozil	−6.75	−
Epanolol	3.30	+	Glafenine	−0.34	−
Esmolol	3.16	+	Idoxuridine	−6.17	−
Indenolol	2.79	+	Improsulfan	0.58	+
Labetalol	2.39	+	Indomethacin	−5.67	−
Levobunolol	4.77	+	Metampicillin	−11.85	−
Metipranolol	4.53	+	Minocycline	−9.15	−
Metoprolol	5.63	+	Oxytetracycline	−5.92	−
Moprolol	1.84	+	Pirifibrate	−4.57	−
Nadolol	10.28	+	Ramifenazone	−8.32	−
Nifenalol	3.93	+	Ribavirin	−4.88	−
Oxprenolol	1.94	+	Rolitetracycline	−6.65	−
Pindolol	4.26	+	Ronifibrate	−5.15	−
Practolol	3.59	+	Salsalate	−6.70	−
Pronethalol	−1.25	−	Sancycline	−10.27	−
Propanolol	1.76	+	Tetracycline	−8.31	−
Sotalol	5.17	+	Vidarabine	−2.58	−
Sulfinalol	6.25	+	Zidovudine	−4.34	−
Talinolol	8.96	+			
Timolol	3.42	+			
Xibenolol	3.44	+			
			Test group		
Alprenolol	0.15	+	Acedapsone	−4.01	−
Amosulalol	1.84	+	Ancitarabine	−4.46	−
Mepindolol	6.31	+	Bufexamac	−4.24	−
Nadoxolol	0.42	+	Butoconazole	−1.80	−
Nipradilol	11.26	+	Cefotiam	−0.81	−
Penbutolol	5.91	+	Cytarabine	−5.16	−
Tertatolol	4.95	+	Dermostatin	13.99	+
Toliprolol	1.07	+	Fenoprofen	−9.29	−
			Lomustine	−7.93	−
			Naproxen	−5.21	−
			Nimustine	−5.91	−

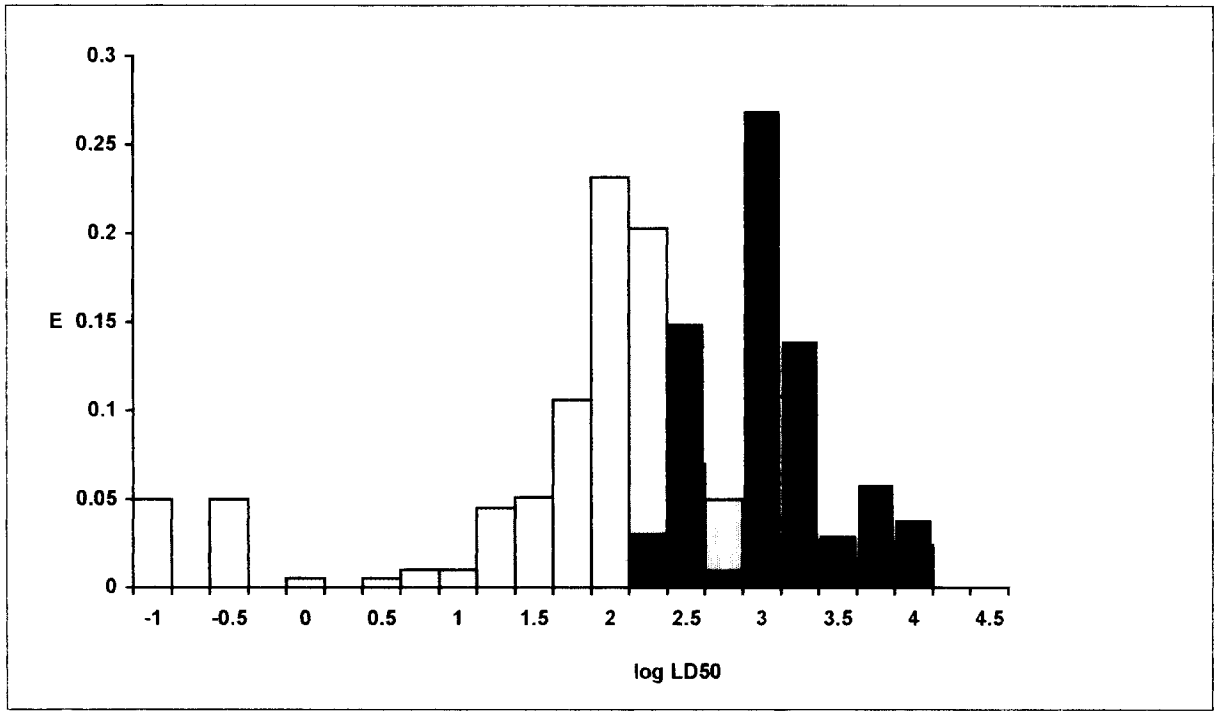
[a]A compound is classified as active (+) if $D > 0$ and as inactive (−) if $D < 0$.



$t_{1/2} = 2.187\ {}^{2}\chi^{v} - 0.477\ {}^{0}\chi^{v} + 2.01\ {}^{4}\chi_{p} - 3.533\ {}^{4}\chi_{p}^{v} - 0.051\ G_{2}^{V} - 0.174\ PR0 - 3.323$

N = 17 r = 0.99051 SE = 0.186 F = 60.6

Figure 2. PDD and equation of distribution half-life. Black bars, E_a; light gray bars, E_i; dark gray bars, overlap.



$\log LD50or = 1.56 + 1.79\ {}^{1}\chi - 1.81\ {}^{1}\chi^{v} + 0.36\ {}^{2}\chi + 2.37\ {}^{4}\chi_{p}^{v} - 2.76\ {}^{4}\chi_{p}$

N = 17 r = 0.9052 SE = 0.208 F = 10.1 p = 0.0008

Figure 3. PDD and equation of logarithm of oral semilethal dose in mice. Black bars, E_a; light gray bars, E_i; dark gray bars, overlap.

than the LD_{50}. This limitant property was calculated for all compounds selected by the classification function D. It was found that β-carotene ($t_{1/2}$ = 1.82 h) had the highest expectancy to be active (E_a = 0.098, E_i = 0.014). The effectiveness of β-carotene in preventing the development of coronary heart disease, especially myocardial infarction, has been demonstrated. This study has revealed that supplemental administration of 50 mg of β-carotene led to a 50% reduction of incidence in a group of sick volunteers.[4]

CONCLUSION

This work demonstrates that through use of the PDD it is possible to discriminate β-blocker activity within a structurally heterogeneous set of compounds; it constitutes a valuable tool in the validation of limiting properties and consequently in the search for new lead drugs. We have applied this procedure to other therapeutic groups of compounds.

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