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Prediction of properties of chiral compounds by molecular topology

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A common assumption in chemistry is that chiral behavior is associated with 3-D geometry. However, chiral information is related to symmetry, which allows the topological handling of chiral atoms by weighted graphs and the calculation of new descriptors that give a weight to the corresponding entry in the main diagonal of the topological matrix. In this study, it is demonstrated that, operating in this way, chiral topological indices are obtained that can differentiate the pharmacological activity between pairs of enantiomers. The 50% inhibitory concentration (IC_{50}) values of the D_2 dopamine receptor and the σ receptor for a group of 3-hydroxy phenyl piperidines are specifically predicted. Moreover, the sedative character of a group of chiral barbiturates can be identified. © *1998 by Elsevier Science Inc.*

Keywords: connectivity indices, topological charge indices, chirality, dopamine receptors, sigma receptors, 3-phenylpiperidines, barbiturates

INTRODUCTION

Chirality is not a geometric feature. The description of a chiral molecule through geometric parameters such as bond lengths and bond angles is necessarily partial. On the other hand, describing the molecule by means of an orthogonal three-dimensional coordinate system is possible only if a criterion for the algebraic sense of the axes has been previously defined. In addition, the concept of chirality is not restricted to 3-D space.[1] Therefore, to characterize the static molecular structure completely, chiral information must be supplied in addition to geometric data. With this in mind, it is conceivable that a pregeometric molecular paradigm such as a topological model could incorporate chiral information.[2,3]

In graph theory, molecular structures are represented as hydrogen-depleted graphs, in which vertices and axes represent atoms and covalent bonds, respectively. Each vertex can be associated with a number called the local vertex invariant, LOVI,[4] which characterizes the kind of atom. This allows chiral information to be introduced,[3] and in this way chiral topological indices can be obtained that provide proper consideration of the asymmetric carbon isomerism.

In one of our previous papers,[5] we demonstrated that molecular connectivity can be used to predict chromatographic parameters in chiral separations. However, relationships between connectivity indices and separation factors were established only for enantiomeric pairs of hydantoins, aromatic amino acids, and arylamides, and no attempt was made to characterize or quantify the chirality.

Dopamine receptors have been classified as D_1 and D_2. The D_2 receptor is presynaptic, inhibiting the subsequent release of norepinephrine and inducing vasodilation. σ receptors mediate effects induced by various opioids. However, some dopamine antagonists bind to σ receptors, and this is a potential cause of severe side effects. Racemic mixtures of the barbiturates are used as both hypnotics and general anesthesics and therefore the characterization of the affinity of the dopamine receptor ligands is of great interest.[6] However, it is known that chirality can condition the more or less sedative character for a given enantiomer, or even its stimulant character.[7]

In this study, it is demonstrated that it is possible to differentiate pharmacological activity between pairs of enantiomers. The log IC_{50} (50% inhibitory concentration) values of the D_2 dopamine receptor and the σ receptor for a group of N-alkylated 3-(3-hydroxyphenyl) piperidines[6] are predicted. Furthermore, we identify the enantiomers in a group of chiral barbiturates that have sedative character.

DESCRIPTORS AND METHOD

Connectivity indices are numerical values associated with chemical graphs for the purpose of correlating chemical structures with several properties. All of them can be computationally calculated from the adjacency matrix in whose main diagonal information relative to the type of atoms, such as different kinds of weights, is placed. This connectivity matrix, with the main diagonal weighted, holds all the information about adja-

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Received 1 December 1997; revised 8 May 1998; accepted 11 May 1998.

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1093-3263/98/$19.00
PII S1093-3263(98)00013-8

Table 1. Results of prediction of the log IC_{50} for the D_2 dopamine receptor and for the σ receptor in a group of N-alkylated 3-(3-hydroxyphenyl) piperidines

Compound	log IC_{50}			log IC_{50}		
	From Ref. 6[a]	From Eq. (1)[b]	Residual	From Ref. 6[c]	Eq. (2)[d]	Residual
(*R*)-3-HPP	0.36	0.10	0.26	−0.66	−0.77	0.11
(*R*)-3-HP-*N*-methyl-P	−0.61	−0.62	0.01	0.43	0.11	0.32
(*R*)-3-HP-*N*-ethyl-P	−0.54	−0.56	0.02	0.95	0.77	0.18
(*R*)-3-HP-*N*-*n*-propyl-P	−0.23	−0.48	0.25	1.52	1.53	−0.01
(*R*)-3-HP-*N*-*iso*-propyl-P	−1.08	−1.03	−0.05	0.61	1.12	−0.51
(*R*)-3-HP-*N*-*n*-butyl-P	−0.43	−0.58	0.15	2.05	2.07	−0.02
(*R*)-3-HP-*N*-2-phenylethyl-P	−0.09	0.14	−0.23	2.10	2.02	0.08
(*S*)-3-HPP	−0.24	0.10	−0.34	−1.19	−0.77	−0.42
(*S*)-3-HP-*N*-methyl-P	−0.29	−0.22	−0.07	−0.28	−0.63	0.35
(*S*)-3-HP-*N*-ethyl-P	−0.12	0.35	−0.47	−0.01	0.21	−0.22
(*S*)-3-HP-*N*-*n*-propyl-P	0.38	0.43	−0.05	0.81	0.96	−0.15
(*S*)-3-HP-*N*-*iso*-propyl-P	0.45	0.46	−0.01	0.68	0.73	−0.05
(*S*)-3-HP-*N*-*n*-butyl-P	0.56	0.33	0.23	1.51	1.51	0.00
(*S*)-3-HP-*N*-2-phenylethyl-P	1.36	1.06	0.30	1.80	1.46	0.34

[a] Values of the log IC_{50} for the D_2 dopamine receptor taken from Ref. 6.
[b] Values calculated from Eq. (1).
[c] Values of the log IC_{50} for the σ receptor taken from Ref. 6.
[d] Values calculated from Eq. (2).
Abbreviations: HP, 3-Hydroxyphenyl; P, piperidine.

cency and LOVIs. Examples of simple LOVIs are the vertex degrees, and they are calculated by summing the entries a_{ij} over rows or columns in the connectivity matrix.

Most of the descriptors used in this study have been defined in previous papers: Kier–Hall indices to the fourth order,[8,9] and others that include the topological charge indices.[10]

Topological charge indices G_k and J_k are defined as

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

where N is the number of vertices (atoms different from hydrogen), d_{ij} represents the elements of the topological distance matrix, δ is the Kronecker's delta, and $c_{ij} = m_{ij} - m_{ji}$; and

$$\mathbf{M} = \mathbf{A} \cdot \mathbf{Q}$$

where **A** is the connectivity matrix and **Q** is the Coulombic matrix, for $i \neq j$, $q_{ij} = 1/d_{ij}^2$ and $q_{ii} = 0$.

We represent a matrix as an uppercase boldface letter, and its elements with the same letter in lowercase with subindices. The product of two symmetric matrices, such as **A** and **Q** does not necessarily result in a symmetric matrix, as occurs in **M**. The matrix **C** has nonzero terms.

Thus, G_k represents the sum of all the c_{ij} terms for every pair of vertices i and j at topological distance k. In this article, $k < 6$.

Valence topological charge indices G_k^V and J_k^V are calculated by following the former procedure with a modified $\mathbf{A}'$ matrix, in whose main diagonal values that describe the electronegativity of the heteroatoms are placed.[10]

For descriptors derived from Kier–Hall indices,[10,11] we use the following notation:

$$^mD_t = {}^m\chi_t - {}^m\chi_t^v$$

where $^m\chi_t$ are the indices of type t and order m and $^m\chi_t^v$ the corresponding valence indices.

Other indices used in this paper are as follows:

N: Number of vertices
R: Number of ramifications (vertices linked to three axes in the graph)
PR1: Number of pairs of adjacent ramifications
PR2: Number of pairs of ramifications at topological distance 2
PR3: Number of pairs of ramifications at topological distance 3
E: Shape factor[12,13]

Moreover, a set of modified connectivity indices called chiral topological indices are now introduced. The modification affects the main diagonal of the connectivity matrix and consists of introducing a weight of +1 for an (*R*) carbon or −1 for an (*S*) carbon into the corresponding entries. For these indices we use the following notation: $^m\chi_t^*$, G_k^*, J_k^*, $^mD_t^*$. The indices *N*, *R*, PR, and E have no chiral counterpart.

To evaluate the effectiveness of these modified indices, we have tested their ability to predict pharmacological properties in groups with a known stereochemical influence. The pharmacological property log IC_{50} for the D_2 dopamine receptor and the σ receptor is correlated with chiral topological indices and topological geometric indices.

In a second numerical experiment, stepwise linear discriminant analysis is applied to the classification of a structurally heterogeneous set of sedative and stimulant compounds, using achiral unmodified indices. The same equation is then tested

Table 2. Classification according to the discriminant function *F* of two sets of compounds: Sedative and stimulant

Sedative compounds			CNS stimulants		
Compound	Probability	Classification	Compound	Probability	Classification
Acecarbromal	1.000	Sedative	Amphetamine	0.940	Stimulant
Apronalide	0.988	Sedative	Bemegride	0.825	Stimulant
Brotizolam	1.000	Sedative	Brucine	1.000	Stimulant
Butoctamide	0.993	Sedative	Caffeine	0.728	Stimulant
Carbocloral	0.957	Sedative	Chlorphentermine	0.996	Stimulant
Chlorhexadol	0.999	Sedative	Diethadione	1.000	Stimulant
Doxefazepam	1.000	Sedative	Diethylpropion	0.992	Stimulant
Doxylamine	0.996	Sedative	Ethamivan	0.999	Stimulant
Etaqualone	0.876	Sedative	Fenozolone	0.999	Stimulant
Ethinamate	0.845	Sedative	Homocamfin	0.999	Stimulant
Etomidate	0.998	Sedative	Mazindol	0.891	Stimulant
Fenadiazole	0.705	Sedative	Mefexamide	0.990	Stimulant
Mecloqualone	1.000	Sedative	Nikethamide	0.999	Stimulant
Mecloxamine	0.488	Stimulant	Pemoline	0.987	Stimulant
Meparfynol	0.994	Sedative	Phendimetrazine	1.000	Stimulant
Novonal	1.000	Sedative	Pipradrol	0.554	Stimulant
Piperidione	0.850	Sedative	Prolintane	0.996	Stimulant
Thalidomide	0.966	Sedative			
Triclofos	1.000	Sedative			
Trimetozine	1.000	Sedative			

for a group of chiral barbiturates, introducing the chiral modification.

RESULTS AND DISCUSSION

Equation (1) obtained for the correlation of log IC_{50} for D_2 dopamine receptor is

$$\log IC_{50}(D_2) = 17.19J_3^v* - 9.68{}^3D_C^* + 0.91PR3 - 2.15 \quad (1)$$

$$r = 0.925 \quad SE = 0.265 \quad F = 19.75 \quad p < 0.0001.$$

The presence of the index PR3, which takes identical values for every enantiomer in every pair, can be seen. It reveals structural facts that are common to the two enantiomers having relevance in the inhibitory action. Chiral character is taken into account by J_3^V* and ${}^3D_C^*$.

If we work only with normal achiral indices, the best equation obtained contains just J_3^V, ${}^3D_C$, and PR3, with $r = 0.536$ and SE = 0.588. It can be concluded that in the prediction of this property, descriptors that contain chiral information play an essential role.

Equation (2) obtained for the σ receptor is

$$\log IC_{50}(\sigma) = 5.30{}^3D_C^* - 0.56PR2 - 1.75E + 4.08 \quad (2)$$

$$r = 0.965 \quad SE = 0.301 \quad F = 45.70 \quad p < 0.0001.$$

The presence of PR2 and E, contributing negatively to the property, takes into account the common influence of the two enantiomers. It is known that the shape factor E gives information about the more spherical or elliptical molecular shape.[13]

The equation obtained with ${}^3D_C$, PR2, and E shows $r = 0.934$, SE = 0.412, and $F = 22.89$, but the variable ${}^3D_c^*$ has no statistical significance. A better function is obtained just with PR2 and E, with the same r value, SE = 0.393, and $F = 37.77$. The addition of the chiral variable ${}^3D_c^*$ improves the correlation and lowers the SE by 25%.

The index ${}^3D_C^*$ has proved to be important in both correlations in spite of the fact that the property for D_2 receptors follows Pfeiffer-type behavior, while the property for the σ receptor is more complex.[6] Both equations are statistically significant.

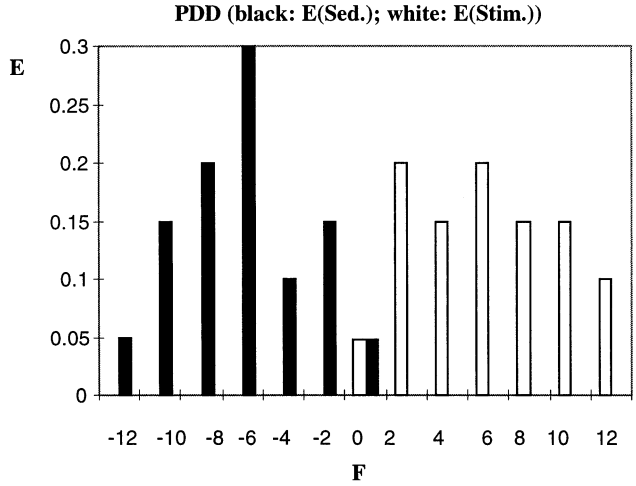

Figure 1. Pharmacological distribution diagram representing sedative (black bars) and stimulant (white bars) activities obtained through Equation 3.

Table 3. Classification according to the discriminant function *F of a set of chiral barbiturates, including (*S*)- and (*R*)-enantiomers**

(*S*)-Barbiturates			(*R*)-Barbiturates		
Compound	*F**	Activity	Compound	*F**	Activity
(*S*)-Butabarbital	−4.50	Sedative	(*R*)-Butabarbital	−11.78	Sedative
(*S*)-Butallyonal	−9.69	Sedative	(*R*)-Butallyonal	−16.26	Sedative
(*S*)-Hexobarbital	0.71	Stimulant	(*R*)-Hexobarbital	−5.97	Sedative
(*S*)-Mephobarbital	5.24	Stimulant	(*R*)-Mephobarbital	−5.98	Sedative
(*S*)-Narcobarbital	−2.73	Sedative	(*R*)-Narcobarbital	−16.83	Sedative
(*S*)-Proxibarbital	−3.77	Sedative	(*R*)-Proxibarbital	−10.75	Sedative
(*S*)-Talbutal	−1.49	Sedative	(*R*)-Talbutal	−8.17	Sedative
(*S*)-Tetrabarbital	6.78	Stimulant	(*R*)-Tetrabarbital	−11.04	Sedative
(*S*)-Vinylbital	3.18	Stimulant	(*R*)-Vinylbital	−6.47	Sedative

Table 1 shows the results of prediction of log IC_{50} values for both receptors.

A set of 80 structurally heterogeneous compounds with sedative or stimulant activity has been analyzed by stepwise linear discriminant analysis, using achiral indices. Descriptor selection was performed using the *F*-Snedecor parameter. The classification criterion used was the minimum value of Mahalanobis. The quality of the discriminant function is evaluated through the Wilk's *U*-statistical parameter. The classification function chosen was

$$F = -2.98^{3}\chi_p - 323.77G_5 + 30.36^{1}D - 55.11^{3}D_p - 23.03^{3}D_c + 36.13^{4}D_{pc} + 3.67N - 4.09R + 3.91\mathrm{PR1} - 15.65 \quad (3)$$

$$N = 80 \quad F = 9.56 \quad U\text{-statistical} = 0.23$$

The function *F* (sedative–stimulant discrimination), is able to classify correctly 95% of the sedative compounds, and 100% of the stimulant compounds, when dealing with achiral compounds. A sample of the training group can be seen in Table 2. Figure 1 displays graphically the data in Table 2. It shows a pharmacological distribution diagram (PDD) representing the expectancy for every classification group in each interval of *F*.

Mecloxamine is misclassified with a calculated probability of 0.488, which could be considered as doubtful, if another criterion were chosen. There seems that no structural trivial facts influence the probability obtained.

In general, the expectancy[14] for a group *A* along each interval *x* is defined as

$$E = \text{Percentage of } A \text{ in } x/(\text{percentage of non-}A \text{ in } x + 100)$$

Figure 1 shows a small overlapping region, which is indicative of the discriminant power of *F*.

Using the same function *F* in Eq. (3), the first six indices can be modified to include chiral weights. The resulting function, named *F**, was applied to a group of chiral barbiturates. Table 3 shows the results obtained.

As can be seen, *F** classifies the sedative character of the barbiturates studied, although none of these compounds was included in the training set of *F*. All the (*R*)-enantiomers are correctly classified as sedative. The (*S*)-enantiomers have an *F** value greater than those of the (*R*)-enantiomers. Four are correctly classified as stimulants by Eq. (3). There exists experimental evidence that among some barbiturates the (*R*)-isomer is the most active in a racemic mixture, whereas the (*S*)-enantiomer is a weak stimulant (see Ref. 7, and Refs. 2 and 5 cited therein). To confirm this fact in other examples, further studies are needed.

This is simple, preliminary attempt to consider chirality in the framework of molecular connectivity. Its only justification is that it can operate successfully, depending on the weights chosen. It must be noted that the criterion used to assign the different weights into the connectivity matrix is the Cahn–Ingold–Prelog rule, which is, in principle, a wholly conventional notation, showing no correlation with chiral properties such as optical activity. It would be possible to use another criterion (for example, the Wipke assignation for chiral centers,[2]) or another based on different assignments.

CONCLUSION

This work demonstrates that through chiral topological indices it is possible to consider the chirality within a topological model.

ACKNOWLEDGMENTS

This study has been fully funded by CICYT, SAF96-0158-C02-02 (Ministry of Education), and GV-3300/95 (Generalitat Valenciana).

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