The Interrelation of Physicochemical Parameters and Topological Descriptors for a Series of β-Blocking Agents

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The intercorrelation between a series of physicochemical parameters and topological indices for a set of β-blockers is investigated. Partition coefficients are calculated using the ClogP program, and the results are compared with previous data, both experimental and theoretical. These data are complemented by hydrophilicity and solubility calculations, together with the determination of molecular area and volume. Connectivity indices, of order 1 and 2, including simple, valence, and differential terms, are evaluated. The derivation of a recently proposed topological descriptor, the eccentric adjacency index, from the adjacency and distance matrices, is presented. The corresponding valence term, a novel descriptor, is developed, and other indices related to the distance matrix, the Wiener and Hyper-Wiener terms, are included. A high degree of linear correlation between the connectivity indices is noted. The correlations for first-order terms are slightly superior to the corresponding second-order values. This is particularly true when considering the valence terms compared with the nonvalence terms. The relationship between these terms and reported pharmacological properties are investigated. A decrease in the eccentric adjacency index resulted in an increase in the pharmacological property.

INTRODUCTION

Lipophilicity is a major determinant of several aspects of the disposition and biological action of drugs.[1−3] Calculative procedures have been developed to allow a proper quantification of drug lipophilicity.[1,2,4−6] In the present study, the ClogP values of a series of β-adrenoceptor antagonists (Figure 1) are calculated, and the results are compared with previous data.[1] A feature of this range of compounds is their extensive lipophilicity range.[7−9] The range (extending over four log units) in partitioning behavior of the series is a consequence of the differences in aromatic substitution. The compounds may be classified as very lipophilic (e.g. propranolol and bevantolol), lipophilic (e.g. metoprolol, oxprenolol, and timolol), and hydrophilic (e.g. nadolol). It has been suggested that CNS-related side effects may be due to the lipophilicity of these agents.[10−13] The values are also compared with available experimental data.[1,7,14]

Quantitative structure/property relationships (QSPR) and quantitative structure/activity relationships (QSAR), based on topological indices, are widely used in pharmaceutical research.[15] The connectivity index, developed by Kier and co-workers,[16−18] has been employed in many structure/activity studies.[19−24] A differential molecular connectivity index and a shape index have also been developed.[25,26] The Wiener Index,[27,28] derived from the Distance Matrix,[28] is also a useful topological descriptor in carrying out such studies. A comparative study of several such descriptors for vertex- and edge-weighted molecular graphs was successful in a QSAR study involving 47 nitrobenzenes.[29] The Hyper-Wiener Index,[30] a distance-related descriptor, is also calculated for the series of molecules under study. The Eccentric Adjacency Index has been recently developed, and its descriminating power has been investigated.[31] An integrated approach, reviewing both graph-theoretical indices and quantum chemical data, has been applied to structure activity correlations.[32]

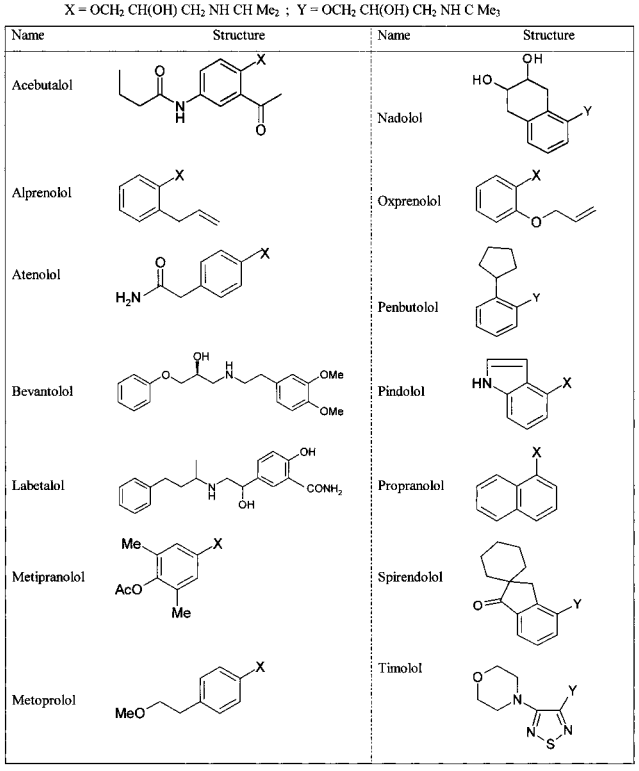

Figure 1. The structures of the β-blockers under study.

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A series of topological descriptors are calculated for the set of compounds under study, and their interrelationships are examined. The applicability of such indices in both QSAR and QSPR studies and their suitability as topological descriptors may be assessed.[33,34] This work will focus on the interdependence of lipophilic and topological properties for a series of β-blockers, extending earlier such studies[1,21] to incorporate the differential molecular connectivity index, eccentric adjacency indices,[31] and molecular area and volume properties.

CALCULATIONS

Partition Coefficients and Solubilities. The log of the octanol/water partition coefficient (log K_{OW}) was determined using fragment constants after the Hansch/Leo method.[35] An alternative substructure approach involves the application of the ClogP algorithm (www.biobyte.com) in the calculation of the partition coefficient. The version of the ClogP program used is MacLogP 4.0 (BioByte Corp., 1999). The values from both methods are compared and also with those calculated using an earlier version of the ClogP algorithm. Fragmental methods apply correction factors coupled with molecular connectivity. Fragments larger than a single atom can be defined, so that significant electronic interactions are comprised within one fragment. This is the basis for the *constructionist* approach for the calculation. A SMILES (**S**implified **M**olecular **L**ine **E**ntry **S**ystem) string is computed for each compound and provides the input for the program. This system is widely used as a general-purpose chemical nomenclature and data exchange format.

A Molecular Modeling program (Molecular Modeling Pro, ChemSW) is used to estimate the percentage hydrophilic surface area, while the method devised by Yalkowsky and co-workers[36,37] is employed in the water solubility calculations. The general solubility equation is

$$\log S_W = 0.5 - 0.01\,(MP - 25) - \log K_{OW} \qquad (1)$$

where K_{OW} is the octanol/water partition coefficient and MP is the melting point (°C).

The Connectivity and Shape Index. Graphs may be associated with several topological matrices.[38] The adjacency matrix **A** of a graph G is defined as

$$a_{ij} = 1 \text{ if } i \neq j \text{ and the vertices are connected}$$
$$= 0 \text{ otherwise} \qquad (2)$$

A nonzero entry appears in **A** only if an edge connects vertices i and j.

The connectivity indices may be derived from the adjacency matrix and are defined as

$$^{m}\chi_t = \sum_{j=1}^{N_m} {}^{m}S_j \qquad (3)$$

where m is the subgraph order (i.e. the number of edges or bonds in the subgraph) and N_m is the number of subgraphs of type t and order m. For $m \leq 2$, all subgraphs are of the *path* type (i.e. all subgraph valencies are no greater than 2), and the subscript t in the above equation is superfluous. The subscript j denotes the particular set of edges that constitute the subgraph. $^{m}S_j$, a factor associated with each subgraph, is defined as

$$^{m}S_j = \left[\prod_{i=1}^{m+1} (\delta_i)_j\right]^{-1/2} \qquad (4)$$

where j denotes the particular set of edges (bonds) that constitutes the subgraph and δ_i is the valence of each vertex within the subgraph. The vertex valences (incorporating the superscript v to allow for calculations involving multiple bonding and heteroatoms) are defined as follows

$$\delta_i^v = Z^v - h_i \qquad (5)$$

where Z^v is the number of valence electrons of the vertex (atom) and h_i is the number of hydrogen atoms attached to it. Combining eqs 3 and 4, the first-order ($m = 1$) and second-order ($m = 2$) connectivity indices may be defined, respectively, by

$$^{1}\chi^v = \sum_{s=1}^{N_m} (\delta_i^v\, \delta_j^v)_s^{-1/2} \qquad (6)$$

and

$$^{2}\chi^v = \sum_{s=1}^{N_m} (\delta_i^v\, \delta_j^v\, \delta_k^v)_s^{-1/2} \qquad (7)$$

where each subgraph is denoted by s. The values of Z^v for carbon, nitrogen, and oxygen atoms are, respectively, 4, 5, and 6. The value assigned to sulfur (in timolol) is 0.67.

A differential molecular connectivity index[25] has been defined by

$$\Delta^m\chi = {}^{m}\chi - {}^{m}\chi^v \qquad (8)$$

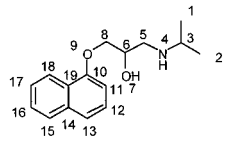
where m is the order of the index. The information contained in this index is largely electronic, and it encodes information about a non sp^3 atom and its environment within m atom fragments.

The shape index ($^{2}\kappa$), defined by Kier,[26] is defined by

$$^{2}\kappa = \frac{2(^{2}P_{max})(^{2}P_{min})}{(^{2}P_i)^2} \qquad (9)$$

where the term ^{2}P indicates the count of the number of two-bond fragments in a graph. The term $^{2}P_{min}$ indicates the count of the minimum number of two-bond fragments, equated to A-2, where A is the number of vertices in the graph. The associated structure is a linear graph. The term $^{2}P_{max}$ represents the corresponding maximum number and is given by (A-1)(A-2)/2. The graph structure in this case is a star structure. For a given molecule, i, the number of two-bond fragments is given by $^{2}P_i$.

The Eccentric Adjacency Index. This topological index is based both on adjacency and distance matrices.[31] The method of calculation is outlined in Figure 2, taking propranolol as an example. The matrices drawn up are all 19×19. For example, $a_{13} = 1$ and $a_{41} = 0$. The adjacency matrix (**A**), as defined above, is constructed. This is a symmetric matrix, i.e. $\mathbf{A}^T = \mathbf{A}$. It is noteworthy that the



The Adjacency (**A**) and Additive Adjacency ($\mathbf{A}^{\alpha}$) matrices

	i				a_{ij}					a^{α}_{ij}								
j	1	3	4	7	9	10	14	18	19	1	3	4	7	9	10	14	18	19
1	0	1	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0
3	1	0	1	0	0	0	0	0	0	1	0	2	0	0	0	0	0	0
4	0	1	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	1	0	0	0	0	0	0	0	0	3	0	0	0
10	0	0	0	0	1	0	0	0	1	0	0	0	0	2	0	0	0	3
14	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	3
18	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	3
19	0	0	0	0	0	1	1	1	0	0	0	0	0	0	3	3	2	0

The Additive Valence Adjacency ($\mathbf{A}^{\alpha v}$) and Distance (**D**) matrices

	i				$a^{\alpha v}{}_{ij}$					d_{ij}								
j	1	3	4	7	9	10	14	18	19	1	3	4	7	9	10	14	18	19
1	0	3	0	0	0	0	0	0	0	0	1	2	5	6	7	9	9	8
3	1	0	4	0	0	0	0	0	0	1	0	1	4	5	6	8	8	7
4	0	3	0	0	0	0	0	0	0	2	1	0	3	4	5	7	7	6
7	0	0	0	0	0	0	0	0	0	5	4	3	0	3	4	6	6	5
9	0	0	0	0	0	4	0	0	0	6	5	4	3	0	1	3	3	2
10	0	0	0	0	6	0	0	0	0	7	6	5	4	1	0	2	2	1
14	0	0	0	0	0	0	0	0	4	9	8	7	6	3	2	0	2	1
18	0	0	0	0	0	0	0	0	4	9	8	7	6	3	2	2	0	1
19	0	0	0	0	0	4	4	3	0	8	7	6	5	2	1	1	1	0

Figure 2. Selected matrix elements for the adjacency matrices (**A**), the additive adjacency matrices ($\mathbf{A}^{\alpha}$, $\mathbf{A}^{\alpha V}$), and distance matrices (**D**), exemplified by the calculations for propranolol using the numbering scheme shown.

valence value of a particular vertex is obtained by summing the matrix elements across the appropriate row (or column) in the matrix, i.e.

$$\delta_i = \sum_{j=1}^{N} a_{ij} \tag{10}$$

The additive adjacency matrix ($\mathbf{A}^{\alpha}$) may be constructed by considering the valency of each vertex in the graph. The matrix $\mathbf{A}^{\alpha}$ is defined as

$$a_{ij}^{\alpha} = \delta_j \quad \text{if } i \neq j \text{ and the vertices are connected}$$

$$= 0 \quad \text{otherwise} \tag{11}$$

The nonzero entries in any column are therefore equal to the valence of the relevant vertex. For example, $a_{34}^{\alpha} = 2$ and $a_{14}^{\alpha} = 0$. This matrix is nonsymmetric. The sum of the vertex valences adjacent to any given vertex i, denoted by σ_i, is given by

$$\sigma_i = \sum_{j=1}^{N} a_{ij}^{\alpha} \tag{12}$$

The distance matrix of the graph G, **D**(G), is the real symmetric N × N matrix, which contains elements d_{ij} (G), representing the length of the shortest path between the ith and jth vertices of G. The matrix **D** is thus defined as

$$d_{ij} = l_{ij} \quad \text{if } i \neq j$$

$$= 0 \quad \text{otherwise} \tag{13}$$

where l_{ij} is the length of the shortest path between i and j in G. The distance matric is clearly symmetric, i.e. $\mathbf{D}^T = \mathbf{D}$.

The eccentricity of vertex i (E_i) in a graph G is defined as the distance from vertex i to the vertex j that is farthest from it, i.e., E_i = max (d_{ij}) for all values of j in the graph G. In the case of the propranolol example (Figure 2), $E_{1j} = 11$ (the distance between vertices 1 and 16 is 11 edges) and $E_{8j} = 6$ (the distance between vertices 8 and 16 is 6 edges). The eccentricity adjacency index (ξ) is given by

$$\xi = \sum_{i=1}^{N} \frac{\sigma_i}{E_i} \tag{14}$$

A novel, valence eccentricity adjacency index may be calculated if the vertex valence is used rather than the simple connectivity value, i.e. if δ^v were used in eq 11, rather than δ. The valence additive adjacency matrix ($\mathbf{A}^{\alpha v}$) will be somewhat different from the additive adjacency matrix. In the propranolol example, the entry for i = 10 and j = 9 is 6 (rather than 2). The value of σ_i will be similarly modified. The corresponding valence index is given by

$$\xi^v = \sum_{i=1}^{N} \frac{\sigma_i^v}{E_i} \tag{15}$$

In an analogous manner to the definition of a differential molecular connectivity index (eq 8), a differential eccentric adjacency index may be expressed by

$$\Delta\xi = \xi - \xi^v \tag{16}$$

The Wiener and Hyper-Wiener Indices. The Wiener index W = W(G) of a molecular graph G is defined as the half-sum of the off-diagonal elements of the molecular distance matrix **D** = **D**(G)

$$W = \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} d_{ij} \tag{17}$$

Other related topological indices have been developed,[27−30,39−41] among them being the Hyper-Wiener number,[42] defined by

$$WW = \frac{1}{4} \sum_{i=1}^{N} \sum_{j=1}^{N} [d_{ij} + d_{ij}^2] \tag{18}$$

Molecular Area and Volume. The SPARTAN program (www.wavefun.com) was used in the estimation of molecular areas and volumes. These calculations involved geometry optimization using semiempirical methods with minimum neglect of differential overlap (MNDO).

RESULTS AND DISCUSSION

The calculated logP data are presented in Table 1 and compared with experimental values available. Calculative procedures may be categorized as those based on fragmental methods, those based on atomic contributions, and those based on molecular properties.[2,4] The ClogP values are compared with previous data, to those computed by other means (using Molecular Modeling Pro and LOGKOW[14]) and experimentally determined data.[7,8,11,43,44] The ClogP value from this work is 0.35 units higher for bevantolol than that obtained using an earlier version of the CLOGP program. This is due to an assignment of −0.35 to a normal interaction in ring 1, rather than the earlier value of −0.55 and an extra proximity factor, accounting for a value of 0.15, for a phenyl-NH fragment pair. The difference observed for oxprenolol

Table 1. Calculated and Experimental log P Values for the Series of β-Blockers Studied

	ClogP							
	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]
acebutalol	1.70	1.61	0.98	1.19	1.71		1.90	−0.17
alprenolol	2.65	2.74	2.62	2.81	3.13		2.60	0.52
atenolol	−0.11	−0.11	−0.15	−0.03	0.78	0.16[j]	0.23	−1.82
bevantolol	3.00		2.27	2.68[i]		3.00	1.20	
labetolol	2.50		1.51	2.41				1.06
metipranolol	2.55	3.13	2.46	2.11[i]	2.66			
metoprolol	1.35	1.35	1.42	1.69	1.98	1.88	2.15	−0.01
nadolol	0.38		0.21	1.17		0.93	0.70	−1.18
oxprenolol	2.09	1.62	1.70	1.83	2.29	2.37	2.18	
penbutolol	4.04	4.19	4.60	4.20[i]	3.92	4.15		
pindolol	1.67	1.65	1.07	1.48	1.97		1.75	−0.09
propranolol	2.75	2.75	2.43	2.60	3.17	3.21	3.65	1.31
spirendolol	3.84		3.54	4.22[i]				
timolol	1.53		−0.07	1.75		1.91	2.10	

[a] ClogP, this work (MacLogP version 4.0). [b] ClogP, ref 1. [c] Calculated values, Molecular Modeling Pro. [d] Reference 14; LOGKOW program. [e] Experimental values, ref 1. [f] References 7 and 8. [g] Reference 11. [h] Reference 44. [i] This work. [j] Reference 43.

Table 2. Correlation Matrix for the Correlation of logP Values[a]

	ClogP(1)	log P (3)	log P (4)	log P (5)	log P (6)	log P (7)	log P (8)
ClogP(1)	1.000						
log P (3)	0.923	1.000					
log P (4)	0.952	0.911	1.000				
log P (5)	0.974	0.970	0.985	1.000			
log P (6)	0.992	0.916	0.976	0.996	1.000		
log P (7)	0.710	0.654	0.707	0.935	0.772	1.000	
log P (8)	0.969	0.892	0.921	0.944	0.998	0.993	1.000

[a] The number in parentheses corresponds to the appropriate column in Table 1.

may be accounted for the former interaction, with an extra proximity correction for the oxygen-allyl interaction (0.20). The values calculated for acebutalol and pindolol using the LOGKOW program are rather low and high, respectively. With the exception of labetolol, all contain the same aryloxypropan-2-ol amino unit. Amino substitution is either isopropyl or tertiary butyl. A marked correlation between potency and lipophilicity has been shown for these compounds.[9] There are also clinical implications in respect of side effects.[10,12−13] The correlation matrix for the correlation of the various sets of data is shown in Table 2. All data, both calculated and experimental, are quite self-consistent and highly linearly related. The somewhat lower values for column 7[11] may be due to a rather high reported value for propranolol. The ClogP/logKow data are plotted in Figure 3.

The percentage hydrophilic surface area and solubilities, estimated using eq 1, are presented in Table 3. There is a reasonable correlation between these parameters and ClogP ($r = -0.706$; ClogP/% hydrophilic area and $r = 0.822$; logSw/% hydrophilic area). In Table 4 we list the connectivity indices (eqs 6 and 7), together with the corresponding differential descriptors (eq 8) and the shape index (eq 9). The differential molecular connectivity indices may be interpreted as a quantification of the electronic structure, encoding information about the presence of π and lone pair electrons in a molecule and has been shown to correlate with the ionization potential.[25] The second-order term is, on average, 0.8 units larger than the corresponding first-order term.

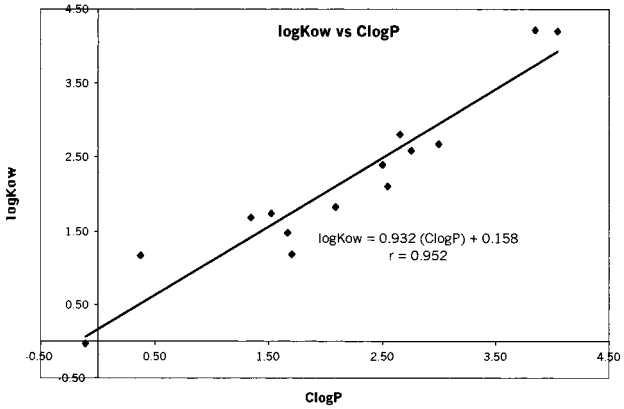


Figure 3. The plot of log K_{ow} against ClogP for the set of β-blockers.

Table 3. Percent Hydrophilic Surface Area and Estimated Solubility (log S_W) for the Series of β-Blockers[a]

compound	% hydrophilic surface area	log S_W/M
acebutalol	43.571	
alprenolol	34.031	−2.973 (hydrochloride)
atenolol	51.449	−0.632
bevantolol	44.147	
labetolol	48.811	
metipranolol	43.768	−2.792
metoprolol	38.640	−1.896 (tartrate)
nadolol	46.061	
oxprenolol	39.658	−2.033 (hydrochloride)
penbutolol	27.142	
pindolol	39.911	−2.035
propranolol	36.381	−3.329 (hydrochloride)
spirendolol	29.855	
timolol	55.240	−1.174 (maleate)

[a] The salts used in the solubility calculation are noted.

Table 4. Molecular Connectivity Indices (Simple, Valence, and Differential) and Shape Index for the Series of β-Blockers

compound	$^1\chi^v$	$^2\chi^v$	$^1\chi$	$^2\chi$	$^1\Delta$	$^2\Delta$	$^2\kappa$
acebutalol	8.32	6.09	11.33	10.13	3.01	4.04	11.59
alprenolol	6.36	4.63	8.63	7.25	2.27	2.62	8.99
atenolol	6.39	4.82	8.97	8.17	2.58	3.36	9.03
bevantolol	8.00	5.42	11.72	9.49	3.72	4.07	11.58
labetolol	8.05	5.99	11.47	10.20	3.42	4.21	10.22
metipranolol	7.13	5.51	9.79	9.24	2.66	3.73	9.21
metoprolol	6.74	4.92	9.11	7.68	2.38	2.77	9.83
nadolol	7.79	7.03	10.26	10.32	2.47	3.29	7.71
oxprenolol	6.50	4.57	9.13	7.60	2.63	3.03	9.83
penbutolol	8.58	7.56	10.44	9.97	1.86	2.42	8.74
pindolol	6.27	4.72	8.67	7.70	2.40	2.98	6.96
propranolol	6.69	5.01	9.17	8.05	2.48	3.05	7.70
spirendolol	9.53	8.73	11.81	11.72	2.27	2.99	7.94
timolol	7.75	6.51	9.96	9.54	2.21	3.03	8.02

The calculation of the eccentric adjacency index is outlined in the previous section. The additive adjacency matrix ($\mathbf{A}^\alpha$) is defined (eq 11), and, hence, the sum of degrees of vertices adjacent to a particular vertex (σ_i) is obtained (eq 12). The eccentricity (E_i) is derived from the distance matrix (**D**), and the descriptor is calculated using eq 14. A novel descriptor, the valence eccentric adjacency index, may be evaluated in an analogous manner to the molecular connectivity indices (eq 15), and the corresponding differential term may be determined (eq 16). The details are presented in Figure 2 and outlined in the previous section. These data, together with the Wiener and Hyper-Wiener indices (eqs 17 and 18)

Table 5. Eccentricity Adjacency Index, Differential Eccentricity Adjacency Index, and Wiener (W) and Hyper-Wiener (WW) Indices for the Set of β-Blockers

compound	ξ^{A}	ξ^{AV}	$-\Delta\xi$	W	WW
acebutalol	10.650	15.839	5.189	1570.5	6799.5
alprenolol	9.708	13.964	4.256	711.0	2544.0
atenolol	9.103	13.477	4.374	890.0	3650.0
bevantolol	9.299	14.043	4.744	1744.5	8535.5
labetolol	10.872	15.265	4.393	1607.0	7191.0
metipranolol	10.375	15.242	4.867	1090.0	4396.0
metoprolol	8.541	12.741	4.200	907.5	3794.0
nadolol	11.823	16.317	4.494	1167.5	4538.0
oxprenolol	9.720	14.649	4.929	834.0	3116.0
penbutolol	12.122	16.090	3.968	1038.0	3924.0
pindolol	11.282	16.369	5.087	687.0	2409.0
propranolol	11.048	16.147	5.099	792.0	2849.0
spirendolol	13.854	18.323	4.469	1598.0	6525.0
timolol	11.454	16.942	5.488	1063.0	4138.0

Table 6. Molecular Areas and Volumes for the Series of Compounds under Study

compound	area/Å^2	volume/Å^3
acebutalol	463.28	419.75
alprenolol	360.15	325.78
atenolol	368.06	331.79
bevantolol	440.35	403.70
labetolol	420.00	398.61
metipranolol	407.07	368.97
metoprolol	384.82	344.44
nadolol	382.10	357.38
oxprenolol	352.23	316.84
penbutolol	405.83	379.50
pindolol	334.21	306.35
propranolol	336.01	312.96
spirendolol	477.36	452.29
timolol	397.07	366.50

are presented in Table 5. The values of $-\Delta\xi$ lie in the range 3.97−5.49. The range of values of ξ^{A} is broader than those of the connectivity indices. Molecular areas and volumes are presented in Table 6.

The correlation matrices for the correlation of ClogP with the structural descriptors are shown in Tables 7 and 8. These data indicate a high degree of linear correlation between the connectivity indices. This is particularly true when considering the valence terms compared with the nonvalence terms. The ξ^{A}/ξ^{AV} and W/WW correlation coefficients are also quite high. Table 7 reveals that the quality of correlations is high when comparing an index with its corresponding valence value, i.e., $^{1}\chi$, $^{1}\chi^{V}$ ($r = 0.906$); $^{2}\chi$, $^{2}\chi^{V}$ ($r = 0.909$); ξ^{A}/ξ^{AV} ($r = 0.956$) and, as is evident from the definition of both the Wiener and Hyper-Wiener indices (eqs 17 and 18), r (W/WW) is quite high and has a value of 0.988. As these indices are derived from the distance matrix, it is reasonable to expect that they reflect the connectivity relationships within a molecule, without having specific recourse to the individual valence values. The distance matrix has been used for the characterization of molecular branching.[45] It is unsurprising that r($^{m}\chi$,W) and r($^{m}\chi^{V}$,W) are rather similar for $m = 1$ and 2, while the latter are somewhat lower than the former. The correlations for $m = 1$ are slightly superior to those for $m = 2$. The eccentric adjacency index correlates reasonably well with the second-order connectivity indices. This is not unexpected as the index is based on both adjacency and distance properties. It is noted that the elements in the correlation matrix presented in Table 8 are rather low, with the notable exception of the area/volume coefficient. It is expected that the correlation between the area and volume would be high, as is observed ($r = 0.987$). There is a surprisingly poor correlation between the shape index ($^{2}\kappa$) and the area ($r = 0.502$) and the volume ($r = 0.408$), respectively. Further studies are required to ascertain whether these relationships are generally true, and a degree of circumspection is necessary in this regard. However, the choice of parameters employed in structure/activity studies may be aided by the results presented.

Quantitative structure−property relationships (QSPR) involve the relevant description of molecular structures, informative data on properties, and meaningful correlations.[46−47] The descriminating power of the eccentric adjacency index was found to be rather encouraging.[31]

The relationship between the physicochemical parameters and topological descriptors described in this paper and pharmacological properties[21,22] of the compounds studied are investigated. The equation for the angor treatment dose, ATD (mg day^{-1}),[22] is

$$\mathrm{ATD} = (193.70 \pm 63.74)\ ^{1}\chi - (85.38 \pm 58.9)\ \xi^{A} - (798.55 \pm 702.4) \quad (19)$$

The statistical parameters for this equation were as follows: $n = 9$; $r = 0.781$; $s = 174.6$; ν (DF) $= 6$; $F = 4.68$. For $^{1}\chi$, $t = 3.04$ ($P = 0.023$) and for ξ^{A}, $t = 1.45$ ($P = 0.197$).

The equation for the LD_{50} (mg kg^{-1})[22] is

$$\mathrm{LD_{50}} = (7.742 \pm 1.721)\ ^{1}\chi^{v} - (2.266 \pm 1.605)\ \xi^{A} - (49.876 \pm 12.21) \quad (20)$$

The statistical parameters for this equation were as follows: $n = 7$; $r = 0.781$; $s = 2.517$; ν (DF) $= 4$; $F = 31.8$. For $^{1}\chi^{v}$, $t = 4.5$ ($P = 0.011$) and for ξ^{A}, $t = 1.41$ ($P = 0.231$).

Table 7. Correlation Matrix for the Correlation of ClogP Values with a Selection of Structural Descriptors

	ClogP	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	$^{2}\kappa$	ξ^{A}	ξ^{Av}	W	WW
ClogP	1.000									
$^{1}\chi$	0.415	1.000								
$^{1}\chi^{v}$	0.501	0.906	1.000							
$^{2}\chi$	0.314	0.885	0.951	1.000						
$^{2}\chi^{v}$	0.399	0.688	0.916	0.909	1.000					
$^{2}\kappa$	0.072	0.452	0.170	0.075	−0.195	1.000				
ξ^{A}	0.431	0.433	0.683	0.714	0.842	−0.539	1.000			
ξ^{Av}	0.351	0.394	0.602	0.651	0.731	−0.523	0.956	1.000		
W	0.291	0.975	0.807	0.807	0.548	0.566	0.264	0.245	1.000	
W W	0.255	0.938	0.723	0.715	0.430	0.643	0.128	0.116	0.988	1.000

Table 8. Correlation Matrix for the Correlation of ClogP Values with a Selection of Structural Descriptors

	ClogP	$^2\kappa$	$^1\Delta$	$^2\Delta$	$-\Delta\xi$	area (Å^2)	vol (Å^3)
ClogP	1.000						
$^2\kappa$	0.072	1.000					
$^1\Delta$	−0.043	0.719	1.000				
$^2\Delta$	−0.145	0.618	0.903	1.000			
$-\Delta\xi$	−0.175	−0.068	0.174	0.295	1.000		
area (Å^2)	0.372	0.502	0.345	0.469	−0.080	1.000	
vol (Å^3)	0.421	0.408	0.318	0.445	−0.102	0.987	1.000

The equation for $\log(LD_{50})$ (mg kg^{-1})[21] is

$$\text{Log}\,(LD_{50}) = (0.158 \pm 0.075)\,{}^1\chi^v - (0.268 \pm 0.060)\,\xi^A - (3.324 \pm 0.650) \quad (21)$$

The statistical parameters for this equation were as follows: $n = 6$; $r = 0.933$; $s = 0.134$; ν (DF) $= 3$; $F = 10.1$. For $^1\chi^v$, $t = 2.11$ ($P = 0.126$) and for ξ^A, $t = 4.46$ ($P = 0.021$).

The contribution of the eccentric adjacency index (ξ^A) to the value of each property above is negative. A decrease in this parameter will result in an increase in the pharmacological property. However, the numerical values of the coefficients in each case are rather low.

The topological descriptors related to the distance matrix (ξ^A, W, and WW) have been examined, and their intercorrelations have been studied. These were supplemented by the calculation of the connectivity indices, along with partition data, the shape index, and molecular areas and volumes. The corresponding valence indices were evaluated, and the appropriate differential indices were calculated.

This study has examined a range of physicochemical parameters and 3D properties (ClogP, Log K_{OW}, area, and volume), together with graph theoretical and topological indices. The evaluation of these indices from both the adjacency and distance matrices has been outlined for a series of β-blockers and their interrelationships explored. The first-order connectivity indices correlated well with those derived from the distance matrix, i.e., W and WW and these were found to be somewhat favored over the second-order indices.

Particular attention was devoted to the evaluation of the eccentric adjacency index (ξ^A). One of the principal objectives of this work is the exploration of the graph-theoretical basis of this topological index, with the presentation of selected matrix elements (Figure 2). A novel valence associated index (ξ^{Av}) has been derived, the evaluation of which is systematically outlined. A further index ($\Delta\xi$) is presented and is derived in a manner analogous to the differential molecular connectivity index ($\Delta^m\chi$). This allows the quantification of the electronic components. It is envisaged that this index will be useful in encoding further information which may be employed in structure/activity studies.

Through an adequate choice of topological descriptor, it is possible to predict the pharmacological properties of the series of β-blockers under study. The advantage of incorporating the eccentric adjacency index is that it may facilitate structural interpretations in respect of drug-receptor interactions.

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