Decomposition of the Wiener Topological Index. Application to Drug-Receptor Interactions

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The Wiener index W is the sum of topological distances between carbon atoms in a hydrocarbon molecule. It was shown that W is made up of terms related to different substructures of the molecule and terms related to the interactions between these substructures. The contributions of substituents and the interaction terms are the substituent indices. Linear regression equations were derived relating the pharmacological potencies of compounds and the sum of the substituent indices, and linear regression equations were derived between these potencies and the various substituent indices. These regression equations were compared. The comparison allowed a decision on whether variations in the experimental pharmacological potencies were due to global effects linked with the bulk of the molecules or due to substituent effects attributable to various sites of the interacting molecules.

Topological indices are used to characterize the molecular structure in quantitative terms.[1] The first topological index to be used in chemistry was defined by Wiener.[2] The Wiener index W of a hydrocarbon molecule is the sum of topological distances between the carbon atoms[2] [equation (1) where d_{ij}

$$W = \sum_{i<j}^{n} d_{ij} \qquad (1)$$

denotes the smallest number of bonds separating atoms i and j, double or triple bonds are treated as single bonds, and n denotes the number of atoms in the molecule; hydrogen atoms are neglected]. Boiling points and heats of vapourization of isomers of paraffin hydrocarbons were found to correlate well[2] with W. Since then W was used occasionally to explain thermodynamic properties of molecules.[3,4] It was used to derive rules for a topological characterization of condensed polycyclic hydrocarbons,[5] and to correlate the structure of molecules with their biological activity.[6] It was shown[7] that the Wiener index is related to the molecular branching index defined by Randic.[8] The branching index in turn served as a starting point for the development of the molecular connectivity index.[9]

Molecular connectivity is the topological index used most often in quantitative structure-activity studies,[10] but several other indices have also been proposed to investigate the correlation between the structure and the pharmacological potencies of the molecules. These are the MTD (minimal topological difference) index of Simon,[11] the Balaban index,[12] the electropy index,[13] the self-avoiding path approach,[14] the method of topological molecular transformations,[15] and the transport parameter approach.[16] The application of topological indices in pharmacology has been reviewed by Trinajstić *et al.*[17]

It is shown in this work that the Wiener number can be decomposed into contributions originating from the main part of the molecule and into those from the various substituents. The physical rationale of this decomposition is that various sites of the drug molecule may be non-equivalent during interactions with the receptor site. The topological indices of the substituents and the substituent-substituent interaction terms can be computed easily. This approach was also found to be useful for distinguishing global from substituent effects. The constant terms originating from the main (and constant) bulk of the molecule may be neglected, since this does not affect the results. Three independent series were considered. The calculated

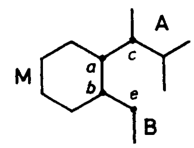


Figure. An example illustrating parent structure M, its substituents A and B, and the connecting atoms *a*, *b*, *c*, and *e*

indices were correlated with the pharmacological potencies of the molecules by using multiple linear regression analysis. The results were compared with regression equations derived for the pharmacological potencies and the sum of the individual contributions. The method allows more insight into the mechanism of drug-receptor interactions than by using the original (global) Wiener index W alone.

Theory

Let us assume that there is a series of derivatives with a common parent structure which is substituted at one or more sites. We shall not consider a series of derivatives with a single substitution site, because we are interested in comparing various sites of the molecule in terms of their role in drug-receptor interactions. We shall not consider series with more than two substitution sites, since our results for two sites can easily be generalized for these cases. Let us denote the substitution sites by a and b the respective substituents by A and B, and the parent structure by M (Figure). W [equation (1)] can be written as the sum of the contributions in equation (2). The topological

$$W = \sum_{\substack{i<j \\ i,j \in M}} d_{ij} + \sum_{\substack{i<j \\ i \in M, j \in A}} d_{ij} + \sum_{\substack{i<j \\ i,j \in A}} d_{ij} + \sum_{\substack{i<j \\ i \in M, j \in B}} d_{ij} + \sum_{\substack{i<j \\ i,j \in B}} d_{ij} + \sum_{\substack{i<j \\ i \in A, j \in B}} d_{ij} \qquad (2)$$

distance between atoms i and j, d_{ij}, can be calculated either by using the Warshall algorithm,[18] or by using the adjacency matrix approach.[9,19] The first term in equation (2) depends on M, only. This term is not affected by alteration of the substituents and can be neglected in regression analysis. The second term depends on M and A, the third term depends on A only, the fourth term depends on M and B, and the fifth term depends on

B only. The last term is due to the interaction between substituents A and B. The third and fifth terms in equation (2) are the Wiener indices of the substituents A and B; these will be denoted by W_A and W_B, respectively. Let us consider the second term in equation (2). This is the sum of distances between all atoms in A and all atoms in M. We can write equation (3) where

$$d_{ij} = n_A \sum_{j \in M} d_{aj} + n_A n_M + n_M \sum_{j \in A} d_{cj} \qquad (3)$$

n_A and n_M denote the number of atoms, and c and a denote the substitution sites in A and M, respectively (Figure). The term Σd_{aj} ($j \in$ M) was used by Seybold[20] to characterize the connectedness of a substitution site; it is denoted by s_a. Similarly Σd_{cj} ($j \in$ A) in equation (3) is denoted by s_c (Figure). The second term in equation (3) denotes the number of times we must pass the bond linking A and M. This analysis can be repeated for the fourth term in equation (2) replacing A with B, a with b and c with e (Figure). The last (interaction) term in equation (2) can be further decomposed giving equation (4) where $2n_An_B$ is the

$$\sum_{i \in A, j \in B} d_{ij} = n_B \sum_{j \in A} d_{cj} + n_A \sum_{j \in B} d_{ej} + 2n_An_B + n_An_Bd_{ab} \qquad (4)$$

number of times we must pass the bonds between A and M and between B and M, and we have to 'walk' along the path d_{ab} n_An_B times. Using equations (3) and (4), equation (2) can finally be written as (5). W_M denotes the Wiener number of the parent structure.

$$W = W_M + W_A + n_As_a + n_An_M + n_Ms_c + W_B + n_Bs_b + n_Bn_M + n_Ms_e + n_Bs_c + n_As_e + 2n_An_B + n_An_Bd_{ab} \qquad (5)$$

In this approach we have assumed that the 'length' of a bond connecting a carbon atom with a heteroatom or connecting two heteroatoms is 1 irrespective of the nature of this bond. This is certainly a crude simplification that has to be corrected in more advanced applications, but the application of this approximation yields quite acceptable results in pharmacology.[6] It has to be noted that an extension of the Wiener index for molecules with heteroatoms has been proposed[21] recently. A multiple linear regression equation used to describe the variation in the pharmacological potencies is considered here. The various terms of equation (5) are the parameters of this equation. The relation explaining the biological response R in terms of topological indices[22] is (6). Here c_i (i = 1, 2, . . . , 14) denotes

$$R = c_1W_M + c_2W_A + c_3n_As_a + c_4n_An_M + c_5n_Ms_c + c_6W_B + c_7n_Bs_b + c_8n_Bn_M + c_9n_Ms_e + c_{10}n_Bs_c + c_{11}n_As_e + c_{12}n_An_B + c_{13}n_An_Bd_{ab} + c_{14} \qquad (6)$$

the regression coefficients to be determined. A factor of 2 in the twelfth term of equation (5) is incorporated in c_{12}. We shall consider series with hydrocarbon substituents, with a parent structure containing carbon atoms and heteroatoms. In this case changes in bond 'lengths' involving heteroatoms (*e.g.* choosing d_{CO} = 1.5) do not affect the terms W_A, W_B, s_c, and s_e. The fourth term in equation (6), n_An_M, has to be modified if a is a heteroatom. The eighth term in equation (6) has to be changed if b is a heteroatom. The twelfth term n_An_B has to be changed if at least one of the atoms a and b is a heteroatom. W_A, s_a, s_b, and d_{ab} have to be changed if the uniform parameter set was replaced by a set taking heteroatoms into account. It must be noted however that despite these changes in the terms of equation (6), the resulting multiple correlation coefficient r is not affected. The reason for this fact is that substitution of W_M by W_M' in the regression equation, W_M' being computed by using various bond 'lengths', corresponds to a multiplication of W_M by a constant. The same argument applies for all terms that are affected by using the heteroatom approach. In addition W_M should be neglected in regression analysis, because in a series of closely related derivatives with a common parent structure, W_M is constant, irrespective of how topological distances might be defined.

There are 12 independent variables to be considered in multiple linear regression analysis between pharmacological activity and the topological indices,[22] even if the first term in equation (6) was neglected. In most cases this number of independent variables would be impractical, because only a series with more than 60 derivatives could be considered, in order to avoid chance correlations. We propose the following simplification. The second, third, fourth, and fifth terms in equation (6) depend on A and on M, only. These terms should be added and the resulting term should be treated like substituent constants in quantitative structure–activity relationship studies.[23] In order to distinguish it from a substituent constant, the term substituent index will be used to denote it. The substituent index related to substituent A is S_A [equation (7)]. A

$$S_A = W_A + n_As_a + n_An_M + n_Ms_c \qquad (7)$$

similar definition can be given for S_B, the substituent index related to B, by replacing A, a, and c with B, b, and e, respectively in equation (7). The interaction between substituents A and B is denoted by another substituent index S_{AB}. The differences

$$S_{AB} = n_Bs_c + n_As_e + n_An_B(2 + d_{ab}) \qquad (8)$$

between substituent constants and substituent indices are essential. Substitution indices depend on the site at which substitution takes place, whereas substituent constants do not depend on this fact. The topological approach provides an interaction term S_{AB} dependent on A and B, whereas substituent constant approaches assume the additivity of substituent effects. The interaction terms can only be simulated within the substituent constant approaches by adding indicator variables to the set of parameters in the multiple linear regression equation.[23,24]

The Wiener index is composed of the self-avoiding paths.[14] The bond between A and M for example, can be passed only once for a given pair of indices i ($i \in$ M) and j ($j \in$ A, Figure) in equation (1). Because of this it is easy to show that no new types of terms (*e.g.* three-substituent interaction terms S_{ABC}) appeared if the molecule was substituted on a third site C. However, the number of terms would increase in this case.

Calculations

Three series of molecules with known cytostatic[25] (Table 1), antihistaminic[26] (Table 2), and tumour inhibitory[27] (Table 3) activities were selected. The original antihistaminic activities of the 4-piperidinamine series (Table 2) were expressed in mg l^{-1} units.[26] These values were divided by the respective molecular weights.[1] Alkyl derivatives were considered in this study only, because the Wiener number was originally defined for hydrocarbons. The relation between the biological response R and the structure of the molecules was sought by replacing the parameters in equation (6) by S_A, S_B, and S_{AB}. The substituent indices were calculated for the respective series of molecules and multiple linear regression equations were developed between S_A, S_B, and S_{AB} and the pharmacological potencies. The results were compared with the regression equations derived between the pharmacological potencies and the sum of the substituent indices S_T ($S_T = S_A + S_B + S_{AB}$). The significance of the regression coefficients was tested by using the t-test and the significance of the regression equations was tested by using the

Table 1. 1*H*-Isoindolediones (**I**). Cytostatic activities[a] (*M*) and values of the substituent indices[b]

Compound	A	B	$-\log IC_{50}$	S_A	S_B	S_{AB}	S_T
(1)	NH_2	CH_3	5.481	58	49	7	114
(2)	NH_2	$CH(CH_3)_2$	6.000	58	175	23	256
(3)	NH_2	C_6H_5	5.509	58	429	51	538
(4)	$(CH_3)_2N$	CH_3	7.036	202	49	23	274
(5)	$(CH_3)_2N$	$CH(CH_3)_2$	6.721	202	175	75	452
(6)	$(CH_3)_2N$	C_6H_5	6.538	202	429	165	796
(7)	$(CH_3)_2N$	$C_6H_4CH_3$	6.638	202	541	200	943
(8)	C_2H_5NH	CH_3	6.468	214	49	24	287
(9)	C_2H_5NH	$CH(CH_3)_2$	6.149	214	175	78	467
(10)	C_2H_5NH	$C_6H_4CH_3$	6.167	214	541	207	962

[a] Ref. 25. [b] $d_{ab} = 5$, $s_a = 37$, $s_b = 46$, $n_M = 12$.

Table 2. 2-(Piperidin-4-ylamino)-1*H*-benzimidazoles (**II**). Antihistaminic activities[a] and values of the substituent indices[b]

Compound	A	B	$-\log A_{10}$	S_A	S_B	S_{AB}	S_T
(11)	CH_3	CH_3	3.946	94	63	8	165
(12)	$C_6H_5CH_2CH_2$	CH_3	4.921	1 168	63	86	1 317
(13)	i-C_3H_7	C_2H_5	3.855	318	143	55	516
(14)	$CH_2{=}CHCH_2$	C_2H_5	4.021	334	143	334	534
(15)	$C_6H_5CH{=}CHCH_2$	C_2H_5	4.116	1 420	143	213	1 776
(16)	$C_6H_5CH_2CH_2$	C_2H_5	4.743	1 168	143	180	1 492
(17)	CH_3	$C_6H_5CH_2$	5.216	94	723	71	888
(18)	n-C_4H_9	$C_6H_5CH_2$	4.857	482	723	326	1 531
(19)	$CH_2{=}CHCH_2$	$C_6H_5CH_2$	4.842	334	723	234	1 291
(20)	C_6H_5	$C_6H_5CH_2$	4.589	735	723	489	1 947
(21)	$C_6H_5CH_2$	$C_6H_5CH_2$	4.747	940	723	602	2 265
(22)	$(C_6H_5)_2CH$	$C_6H_5CH_2$	4.072	1 966	723	1 133	3 822
(23)	$C_6H_5CH(CH_3)$	$C_6H_5CH_2$	4.814	1 072	723	680	2 475
(24)	$C_6H_5CH_2CH_2CH_2$	$C_6H_5CH_2$	4.712	1 420	723	849	2 992
(25)	$C_6H_5CH{=}CHCH_2$	$C_6H_5CH_2$	4.313	1 420	723	849	2 992
(26)	$(C_6H_5)_2CHCH_2CH_2$	$C_6H_5CH_2$	4.098	2 686	723	1 464	4 873

[a] Ref. 26. [b] $d_{ab} = 6$, $s_a = 78$, $s_b = 47$, $n_M = 16$.

Table 3. 2-Phenylindoles (**III**). Estrogen binding affinities[a] and values of the substituent indices[b]

Compound	A	B	$\log R$	$\Sigma\pi$	S_A	S_B	S_{AB}	S_T	$10^{-5}\,S_T$
(27)	H	H	−2.00	0	0	0	0	0	0
(28)	H	CH_3	−1.22	0.56	0	67	0	67	0.044 89
(29)	H	C_2H_5	−0.89	1.02	0	152	0	152	0.231 04
(30)	CH_3	H	0.58	0.56	66	0	0	66	0.043 56
(31)	C_2H_5	H	1.20	1.02	150	0	0	150	0.225 00
(32)	C_3H_7	H	0.93	1.55	253	0	0	253	0.640 09
(33)	C_4H_9	H	0.63	2.13	376	0	0	376	1.413 76
(34)	CH_3	CH_3	1.00	1.12	66	67	4	137	0.187 69
(35)	C_2H_5	CH_3	1.52	1.58	150	67	9	226	0.510 76
(36)	C_3H_7	CH_3	1.11	2.11	253	67	15	335	1.122 25
(37)	i-C_3H_7	CH_3	1.11	2.09	236	67	14	317	1.004 89
(38)	CH_3	C_2H_5	0.77	1.58	66	152	9	227	0.515 29
(39)	C_2H_5	C_2H_5	1.32	2.04	150	152	20	322	1.036 84
(40)	C_3H_7	C_2H_5	1.28	2.57	253	152	33	438	1.918 44

[a] Ref. 27. [b] $d_{ab} = 2$, $s_a = 49$, $s_b = 50$, $n_M = 17$.

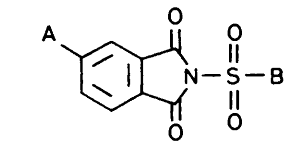
F-test.[28] The results were considered to be significant if the level of significance was $p < 0.01$.

Results and Discussion

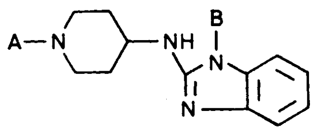
1H-*Isoindolediones* (**I**).—Table 1 contains the negative logarithms of the inhibitory potencies of 1*H*-isoindolediones,[25] and the calculated substituent indices. The regression equations (9)—(11) were derived for molecules (**1**)—(**10**). IC_{50} denotes

$$-\log IC_{50} = \underset{(2.0 \times 10^{-3})}{3.842 \times 10^{-4}} S_T + 6.074$$
$$N = 10, r = 0.226, F_{1,8} = 0.43 \quad (9)$$

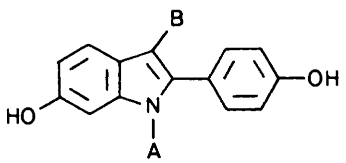
$$-\log IC_{50} = \underset{(7.5 \times 10^{-3})}{6.17 \times 10^{-3}} S_A - \underset{(4.80 \times 10^{-3})}{1.2 \times 10^{-4}} S_B - \underset{(1.46 \times 10^{-2})}{1.0 \times 10^{-3}} S_{AB} + 5.38312$$
$$N = 10, r = 0.810, F_{3,6} = 3.81 \quad (10)$$



(I)



(II)



(III)

$$-\log IC_{50} = 5.58 \times 10^{-3} S_A + 5.364$$
$$(3.52 \times 10^{-3})$$
$$N = 10, r = 0.791, F_{1.8} = 13.38 \quad (11)$$

the concentration (M) of ligands necessary to achieve 50% inhibition of the cell growth. N denotes the number of molecules considered. The numbers in parentheses are the 95% confidence intervals of the regression coefficients. F is the result of Fischer's test,[28] the subscripts denote the number of variables and the degrees of freedom, respectively. Equation (9) indicates that there is no correlation between the biological activity ($-\log IC_{50}$) and the sum of substituent indices S_T. S_T simulates W, because it differs from the Wiener number by a constant factor W_M ($W = S_T + W_M$). The correlation coefficient r would not be affected by replacing S_T with W in equation (9). Thus there is no correlation between $-\log IC_{50}$ and W, either. However, significant correlation coefficient ($p < 0.01$) could be demonstrated by replacing S_T by S_A, S_B, and S_{AB} in equation (10), although the moderate correlation again did not allow quantitative prediction of the activities. The regression coefficients of S_B and S_{AB} are not significant. By deleting these variables from equation (10), equation (11) was obtained, with practically the same correlation coefficient as equation (10). Equation (11) and hence the regression coefficient of S_A is significant.

Chan *et al.*[25] found that electron-donating substituents at position *a* increase activity, whereas electron-withdrawing groups at *a* decrease activity. The authors used substituent constant σ to model the electronic effects of substituents A. Using the same values of σ [-0.66 for NH_2, -0.83 for $(CH_3)_2N$, and -0.61 for C_2H_5NH], the regression coefficient obtained for equation (11) could be improved significantly. Equation (12)

$$-\log IC_{50} = 4.6 \times 10^{-3} S_A - 2.40\sigma + 3.82$$
$$(2.5 \times 10^{-3}) \quad (1.81)$$
$$N = 10, r = 0.917, F_{2.7} = 18.39 \quad (12)$$

explains more than 80% of the total sample variance. Chan *et al.*[25] used R_m indices obtained by chromatography to explain hydrophobic effects. We could not explain R_m in terms of our substituent indices. The correlation found between the reported values of R_m and S_T ($r = 0.448$) was not significant at the $p < 0.05$ level. The multiple correlation between R_m and S_A, S_B, and S_{AB} ($r = 0.838$) was significant, but in this case the regression coefficients were not significant.

Our results indicated that substitution sites *a* and *b* are not equivalent. The lack of correlation with S_T [equation (9)] indicates that global effects, perhaps partition between the cell membrane and the extracellular fluid, do not play an important role at this stage. However, in addition to the conclusions of Chan *et al.*[25] it may be expected that pharmacological activity will also increase if the Wiener index (and similarly the substituent index S_A) of the substituent A increases.

N-*Heterocyclic* 4-*Piperidinamines* (**II**).—Table 2 contains the negative logarithms of antihistaminic potencies[26] of 2-(piperidin-4-ylamino)-1*H*-benzimidazoles and the calculated substituent indices. Regression equations (13) and (14) were

$$-\log A_{10} = 2.33 \times 10^{-5} S_T + 4.536$$
$$(1.90 \times 10^{-4})$$
$$N = 16, r = 0.070, F_{1.14} = 0.07 \quad (13)$$

$$-\log A_{10} =$$
$$8.11 \times 10^{-4} S_A + 2.21 \times 10^{-3} S_B - 2.28 \times 10^{-3} S_{AB} + 3.640$$
$$(5.60 \times 10^{-4}) \quad (9.24 \times 10^{-4}) \quad (1.17 \times 10^{-3})$$
$$N = 16, r = 0.842, F_{3.12} = 9.74 \quad (14)$$

derived for molecules (**11**)—(**26**). A_{10} denotes the concentration (mmol l^{-1}) needed to evoke 10% of a standard pharmacological response.[26] S_T (and thus W) is again insufficient to account for the variation in the potencies of the drugs. Replacing S_T by S_A, S_B, and S_{AB} improved this correlation significantly [equation (14)] but the correlation is still insufficient for quantitative predictions, although all regression coefficients are significant. The regression coefficients for the two substitution sites are non-equivalent. Activity increases with increasing S_A and increasing S_B, but these effects are compensated by the negative interaction term between A and B. This indicates that the substituents are affected in a different way by the drug–receptor interaction, *i.e.* they are not equivalent as in bulk effects.

2-*Phenylindoles* (**III**).—Table 3 shows the logarithms of the relative estrogen receptor affinity (log R) of 2-phenylindoles,[27] and the calculated substituent indices. For molecules (**27**)—(**40**) regression equations (15)—(17) were derived. Equation (15) is

$$-\log R = 5.65 \times 10^{-3} S_T - 0.712$$
$$(3.88 \times 10^{-3})$$
$$N = 14, r = 0.677, F_{1.12} = 10.08 \quad (15)$$

$$-\log R = 1.78 \times 10^{-2} S_T - 2.80 \times 10^{-5} S_T^2 - 1.598$$
$$(1.23 \times 10^{-2}) \quad (2.7 \times 10^{-5})$$
$$N = 14, r = 0.794, F_{2.11} = 9.37 \quad (16)$$

$$-\log R =$$
$$5.13 \times 10^{-3} S_A + 1.35 \times 10^{-3} S_B + 2.65 \times 10^{-2} S_{AB} - 0.503$$
$$(6.19 \times 10^{-3}) \quad (1.39 \times 10^{-2}) \quad (9.18 \times 10^{-2})$$
$$N = 14, r = 0.696, F_{3.10} = 3.14 \quad (17)$$

significant. No improvement could be achieved by replacing S_T with its components S_A, S_B, and S_{AB} in equation (17). Global effects seem to account for the main part of the drug–receptor interaction. Addition of the squared term S_T^2 slightly improved the correlation [equation (16)], the regression coefficient of S_T^2

is negative, and is significant at the $p < 0.05$ level, only. Maxima might appear in regression curves derived between pharmacological potencies and the partition coefficients[23] of molecules. There is a highly significant relationship between the values[29] of $\Sigma\pi$ and S_T. Equation (18) indicates that S_T mimics the global

$$\Sigma\pi = 5.6 \times 10^{-3} S_T + 0.186$$
$$(5.0 \times 10^{-4})$$
$$N = 14, r = 0.990, F_{1,12} = 1\,142. \tag{18}$$

hydrophobic effects in this series. This result is contrary to the conclusion reached by Angerer *et al.*[27] who thought that the observed variation in the estrogen–receptor affinities is due to specific effects. Specificity in drug–receptor interactions is associated with the ability of the receptors to recognize and bind agents with special substructures. Correlation with global parameters does not support the specific interaction assumption.

In summary we may note that the present approach is somewhat similar to the method in which components of the partition coefficient of the molecules that are related to the individual substituents, are examined separately in quantitative structure–activity relationship studies.[24] It may be stated that our method allows us to determine whether the variation in the pharmacological potencies is due to bulk effects, or due to drug–receptor interactions involving definite portions of the molecule. The substituent indices can be calculated easily. In this form the method can be used for hydrocarbon substituents, only. However, the method could be extended for the connectivity indices, because the latter are partial sums of topological distances.[9] This extended procedure would also allow us to consider substituents with heteroatoms.

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References

1 D. H. Rouvray, *Sci. Am.*, 1986, **255**, 36.
2 H. Wiener, *J. Am. Chem. Soc.*, 1947, **69**, 17, 2636.
3 O. Mekenyan, D. Bonchev, and N. Trinajstić, *Int. J. Quantum Chem.*, 1980, **18**, 369.
4 P. G. Seybold, M. A. May, and M. L. Gargas, *Acta Pharm. Jugosl.*, 1986, **36**, 253.
5 D. Bonchev, O. Mekenyan, and N. Trinajstić, *Int. J. Quantum Chem.*, 1980, **17**, 845.
6 S. C. Basak, L. J. Monsrud, M. E. Rosen, C. M. Frane, and V. R. Magnuson, *Acta Pharm. Jugosl.*, 1986, **36**, 81.
7 D. Bonchev and N. Trinajstić, *J. Chem. Phys.*, 1977, **67**, 4517.
8 M. Randić, *J. Am. Chem. Soc.*, 1975, **97**, 6609.
9 L. B. Kier and L. H. Hall, (*a*) 'Molecular Connectivity in Chemistry and Drug Research,' Academic Press, New York, 1976; (*b*) *J. Pharm. Sci.*, 1983, **72**, 1170.
10 L. B. Kier and L. H. Hall, *Eur. J. Med. Chem.*, 1977, **12**, 307; A. Sabljić, N. Trinajstić, and D. Maysinger, *Acta Pharm. Jugosl.*, 1981, **31**, 71; A. K. Samanta, S. K. Ray, S. C. Basak, and S. K. Bose, *Arzneim. Forsch.-Drug Res.*, 1982, **32**, 15; A. Sabljić and M. Protić, *Chem.–Biol. Interactions*, 1982, **42**, 301; A. Sabljić and M. Protić-Sabljić, *Mol. Pharmacol.*, 1983, **23**, 213.
11 Z. Simon, I. Badilescu, and T. Racovitan, *J. Theor. Biol.*, 1977, **66**, 485; Z. Simon, *Studia Biophys.*, 1975, **51**, 49; 1977, **62**, 167; Z. Simon, S. Holban, and I. Motoc, *Rev. roum. Biochim.*, 1979, **16**, 141.
12 A. T. Balaban, I. Niculescu-Duvaz, and Z. Simon, *Acta Pharm. Jugosl.*, 1987, **37**, 7.
13 O. Mekenyan, D. Bonchev, A. Sabljić, and N. Trinajstić, *Acta Pharm. Jugosl.*, 1987, **37**, 75.
14 M. Randić, *Int. J. Quantum Chem.: Quantum Biol. Symp.*, 1984, **11**, 137; S. C. Grossman, B. Jerman-Blažić Džonova, and M. Randić, *ibid.*, 1986, **12**, 123; C. L. Wilkins and M. Randić, *Theor. Chim. Acta*, 1983, **58**, 45; M. Randić and C. L. Wilkins, *J. Phys. Chem.*, 1979, **83**, 1525.
15 Z. Gabányi, P. R. Surján, and G. Náray-Szabó, *Eur. J. Med. Chem.-Chim. Theor.*, 1982, **17**, 307.
16 M. Charton, in 'QSAR in Design of Bioactive Compounds,' ed. M. Kuchar, Prous, Barcelona, 1985.
17 N. Trinajstić, M. Randić, and D. J. Klein, *Acta Pharm. Jugosl.*, 1986, **36**, 267; A. Sabljić and N. Trinajstić, *ibid.*, 1981, **31**, 189.
18 S. Warshall, *J. Ass. Comput. Math.*, 1962, **9**, 11; see A. Graovac, I. Gutman, and N. Trinajstić, 'Lecture Notes in Chemistry,' Springer Verlag, Berlin–London–New York, No. 4, 1977, for further reading.
19 M. J. Clark and S. F. A. Kettle, *Inorg. Chim. Acta*, 1975, **14**, 201.
20 P. G. Seybold, *Int. J. Quantum Chem.: Quantum Biol. Symp.*, 1983, **10**, 103.
21 M. Barysz, G. Jashavi, R. S. Lall, V. K. Srivastava, and N. Trinajstić, in 'Chemical Applications of Topology and Graph Theory,' ed. R. B. King, Elsevier, New York, 1983.
22 E. A. Smolensky, *Zh. Fiz. Khim.*, 1964, **38**, 1288; M. Gordon and J. W. Kennedy, *J. Chem. Soc., Faraday Trans. 2*, 1973, **69**, 484.
23 Y. C. Martin, 'Quantitative Drug Design. A Critical Introduction,' Marcel Dekker, New York, 1978.
24 C. Hansch, *Acc. Chem. Res.*, 1969, **2**, 232.
25 C. L. Chan, E. J. Lien, and Z. A. Tokes, *J. Med. Chem.*, 1987, **30**, 509.
26 F. Janssens, J. Torremans, M. Janssen, R. A. Stokbroekx, M. Luyckx, and P. A. J. Janssen, *J. Med. Chem.*, 1985, **28**, 1925.
27 E. v. Angerer, J. Prekajac, and J. Strohmeier, *J. Med. Chem.*, 1984, **27**, 1439.
28 G. W. Snedecor and W. G. Cochran, 'Statistical Methods,' The Iowa State Univ. Press, Ames, 1972.
29 C. Hansch and A. Leo, 'Substituent Constants For Correlation Analysis in Chemistry and Biology,' Wiley, New York, 1979.

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