Structure−Activity Correlation of Flavone Derivatives for Inhibition of cAMP Phosphodiesterase

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Quantitative structure−activity relationships (QSAR) were used to predict ability of 19 flavone derivatives to inhibit cyclic AMP (cAMP) phosphodiesterase. The approach uses the sets of orthogonalized and nonorthogonalized molecular descriptors. We obtained for the best model with three nonorthogonalized descriptors the following statistical parameters: $R = 0.9365$, $S = 6.99$, and $F = 35.70$. For the best model with three ordered orthogonalized descriptors, using procedure described recently (Lučić, B.; Nikolić, S.; Trinajstić, N.; Juretić, D. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 532−538.), we obtained the following statistical parameters: $R = 0.9841$, $S = 3.54$, and $F = 153.38$. The latter model is clearly superior to the former. This indicates that the QSAR model, based on the consideration of all possible orthogonalization orderings, can predict inhibition of cAMP phosphodiesterase with considerable accuracy.

INTRODUCTION

Flavonoids are broadly distributed throughout the plant kingdom. The term flavonoids embrace all those compounds whose structure is based on that of flavone (2-phenylchromone). They are divided into several structurally related groups.[1] Flavonoids are usually concentrated in leaves and flower parts where they act as pollinator-attracting pigments. Colorless flavonoids are important for plant pigmentation because they often interact with the colored flavonoids giving rise to the phenomenon called copigmentation.[2] Others provide plants with a defense against viral infections.[3] Many flavonoids exhibit pharmacological activity as well as activity on different enzymatic systems.[4] They act as antilipoperoxidant, vasoprotective, antiinflammatory, mutagenic, antiviral, antibacterial, antifungal, and antiradical substances and their antiproliferative activity on tumor cells has also been described.[5]

MOLECULAR DESCRIPTORS

Quantitative structure−activity relationships (QSAR) can be used to predict activity accurately without using costly, time-consuming, and hazardous experimental methods. The main purpose of QSAR is to relate a given biological activity to the structural features of a particular molecule. With increasing computer power it is useful to create a relatively large molecular descriptor pool that maximizes the amount of structural information, which can then be used to describe effectively activity through a suitable algebraic expression. Different models for predicting the inhibition of cyclic AMP (cAMP) by flavone derivatives can be achieved by considering various combinations of molecular descriptors. The structures of the flavone derivatives used in this study are shown in Figure 1.

A total of 34 descriptors were generated for each flavone derivative. The descriptor pool contained topological and electronic descriptors. The topological descriptors that were calculated include valence connectivity indexes[6] ${}^{0}\chi^{v}-{}^{5}\chi^{v}$, Wiener number W and path numbers[7] p_0-p_{10}, Balaban index[8] J, Harary indexes[9] H_1-H_6, and molecular topological index[10] MTI. The electronic descriptors include hardness indexes[11] (absolute hardness η, relative hardness η_r), energy of the highest occupied molecular orbital E(HOMO), and energy of the lowest unoccupied molecular orbital E(LUMO), topological resonance energy indices[12] (topological resonance energy TRE and topological resonance energy per electron TRE(PE)), and the sum of the charges of the atoms located in the chromone moiety $\sum_q^{chr}$ and in the phenyl moiety $\sum_q^{ph}$ of the flavone core.

COMPUTATIONAL PROCEDURE

The first step in a systematic search for optimum correlation is to find the regression of the activity (inhibition of enzyme) against all combinations of the adopted basis of nonorthogonalized descriptors. The second step is the use of orthogonalization procedure to construct an orthogonal basis of descriptors.[13] Multiple linear regression with orthogonalized descriptors is a more stable model, but not statistically better than the model with nonorthogonalized descriptors, since the values of the correlation coefficient (R), the standard error (S), and the F test remained the same for both models.[14] Our recently introduced approach,[15] based on the consideration of all possible orthogonalization order-

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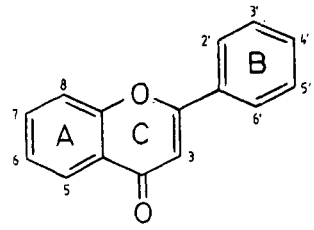

Flavone derivative	Substitution site 3	5	7	2′	3′	4′	5′
1	OH	OH	OH	H	OH	OH	H
2	OH	OH	OH	H	H	OH	H
3	NH_2	H	H	H	H	H	H
4	H	H	H	H	H	H	H
5	OH	OH	OCH_3	H	OH	OH	H
6	NH_2	H	OCH_3	H	OCH_3	OCH_3	H
7	OH	H	OH	H	-O-CH_2-O-		H
8	H	OH	OH	H	H	H	H
9	OH	OH	OH	OH	H	OH	H
10	OH	OH	OH	H	OH	OH	OH
11	OH	H	OH	H	OH	OH	OH
12	NH_2	H	OCH_3	H	H	OCH_3	H
13	Cl	$OCOCH_3$	$OCOCH_3$	H	H	H	H
14	OH	H	H	H	H	H	H
15	NHOH	H	H	H	OCH_3	OCH_3	H
16	OH	H	OH	H	OH	OH	H
17	NH_2	H	H	H	OCH_3	OCH_3	H
18	OH	OH	OH	H	Cl	Cl	H
19	OH	H	OH	H	Cl	Cl	H

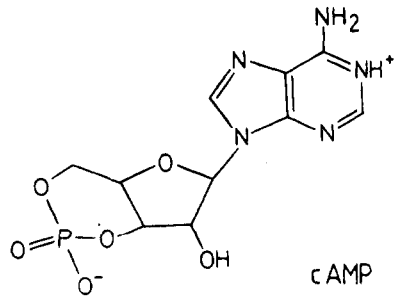

Figure 1. Structural formulas of studied flavone derivatives and cAMP.

ings and dominant descriptor analysis, improves the structure–property models.[16,17] The cornerstone in this procedure is computing the QSAR models for different orderings of orthogonalized descriptors. The procedure continues with selecting the dominant descriptors and removing insignificant descriptors from the model. Generally, the result is only a negligible diminution of the total R, but the value of S as well as the F test are significantly better, since the final model is the model with less descriptors. The procedure is fully described in our recent reports.[15,16]

RESULTS AND DISCUSSION

Descriptor selections for quantitative structure–activity relationships were performed using a multiple linear regression method. Descriptors that are redundant were eliminated as well as descriptors that are highly intercorrelated. On the basis, 18 descriptors were eliminated. From the remaining 16 descriptors, models were generated using multiple linear regression analysis. The best models generated are listed in Table 1 together with the descriptors used in each model.

Table 1. Best Possible Multiple Linear Regression Models (with I Descriptors) for Inhibition of cAMP with the Nonorthogonal Descriptors

$I = 1$
$R = 0.6417$ $S = 14.35$ $F = 11.90$
% INH = (167.913 ± 29.026) + (−7.935 ± 2.300)d3

$I = 2$
$R = 0.8895$ $S = 8.80$ $F = 30.33$
% INH = (230.011 ± 21.219) + (−14.319 ± 1.843)d3 + (5.588 ± 1.036)d8

$I = 3$
$R = 0.9365$ $S = 6.99$ $F = 35.70$
% INH = (−502.260 ± 227.049) + (−15.949 ± 1.545)d3 + (6.114 ± 0.837) d8 + (68.276 ± 21.112)d15

$I = 4$
$R = 0.9513$ $S = 6.36$ $F = 33.30$
% INH = (235.497 ± 33.159) + (−15.861 ± 4.003)d1 + (−7.856 ± 1.482)d5 + (10.243 ± 1.692)d8 + (0.606 ± 0.146)d9

$I = 5$
$R = 0.9677$ $S = 5.40$ $F = 38.26$
% INH = (178.828 ± 56.009) + (−31.722 ± 7.419)d2 + (−9.118 ± 1.449)d5 + (9.069 ± 1.555)d8 + (0.806 ± 0.181)d9 + (179.995 ± 69.195)d11

$I = 6$
$R = 0.9807$ $S = 4.35$ $F = 50.31$
% INH = (−89.354 ± 33.042) + (−13.718 ± 0.831)d5 + (9.369 ± 1.405)d^6 + (21.713 ± 2.647)d8 + (1.368 ± 0.224)d9 + (−0.117 ± 0.018)d10 + (829.627 ± 160.711)d12

$I = 7$
$R = 0.9875$ $S = 3.67$ $F = 61.62$
% INH = (2427.975 ± 274.795) + (−77.241 ± 5.545)d1 + (−20.687 ± 2.156)d4 + (20.592 ± 2.371)d7 + (20.625 ± 1.103)d8 + (744.724 ± 95.029)d13 + (−4206.060 ± 543.414)d14 + (−256.742 ± 39.024)d16

Descriptor		Explanation
d1	$^0\chi^v$	zero-order valence connectivity index
d2	$^1\chi^v$	first-order valence connectivity index
d3	$^2\chi^v$	second-order valence connectivity index
d4	$^3\chi^v$	third-order valence connectivity index
d5	$^4\chi^v$	fourth-order valence connectivity index
d6	p_2	number of the paths of length 2
d7	p_3	number of the paths of length 3
d8	p_{10}	number of the paths of length 10
d9	H2	Harary index with squares of reciprocal distances
d10	MTI	molecular topological index
d11	η	absolute hardness
d12	η_r	relative hardness
d13	E(LUMO)	energy of lowest unoccupied MO orbital
d14	TRE(PE)	topological resonance energy per electron
d15	$\sum_q^{chr}$	sum of the π charges in the chromone moiety
d16	$\sum_q^{ph}$	sum of the π charges in the phenyl moiety

The best model generated with seven nonorthogonalized descriptors includes the following molecular descriptors: $^0\chi^v$, $^3\chi^v$, p_3, p_{10}, E(LUMO), TRE(PE), and $\sum_q^{ph}$. Numerical values of favorable descriptors used in this study are listed in Table 2.

Many factors could affect the potency of flavone derivatives as cAMP phosphodiesterase inhibitors. It appears that the inhibition activity of flavones results from the competition with cAMP for the same nucleotide binding site. It is well-known that structural features and electronic properties of

Table 2. Calculated Values of Favorable Nonorthogonal Molecular Descriptors

compd	$^0\chi^v$	$^2\chi^v$	$^3\chi^v$	p_3	p_{10}	E(LUMO)	TRE(PE)	$\sum_q^{chr}$	$\sum_q^{ph}$
1	10.939 31	12.328 70	17.941 99	40	3	−0.480 38	0.0154	11.095	6.201
2	10.569 45	11.832 59	16.920 86	37	3	−0.480 34	0.0168	11.095	6.111
3	9.590 00	10.659 17	11.565 01	30	0	−0.434 47	0.0244	10.918	6.062
4	9.090 00	10.133 49	11.624 81	26	0	−0.393 54	0.0275	10.834	5.970
5	11.900 35	12.962 25	18.225 68	42	5	−0.480 36	0.0154	11.085	6.201
6	13.582 69	13.716 01	15.895 97	43	8	−0.473 72	0.0176	11.008	6.200
7	11.198 63	12.734 36	16.672 65	38	4	−0.446 31	0.0284	10.994	6.060
8	9.829 72	10.977 45	14.588 25	31	0	−0.417 82	0.0206	11.009	5.970
9	10.939 31	12.284 10	18.389 45	40	3	−0.497 64	0.0150	11.108	6.185
10	11.309 18	12.762 54	19.378 89	43	3	−0.480 44	0.0140	11.096	6.286
11	10.861 96	11.983 14	17.294 88	40	2	−0.465 14	0.0158	11.009	6.285
12	12.251 79	12.682 60	14.184 15	38	5	−0.473 69	0.0193	11.007	6.119
13	14.624 67	14.636 71	18.866 39	43	10	−0.424 85	0.0189	10.860	5.981
14	9.459 86	10.567 19	13.333 03	30	0	−0.425 48	0.0245	10.906	6.043
15	12.621 66	12.737 97	14.555 30	41	4	−0.456 96	0.0182	10.955	6.214
16	10.569 45	11.829 38	16.193 82	37	2	−0.465 11	0.0174	11.008	6.200
17	12.251 79	12.735 10	14.446 43	39	4	−0.452 78	0.0198	10.932	6.199
18	12.312 35	15.580 36	17.5337 74	40	3	−0.461 84	0.0159	11.082	6.067
19	11.942 49	15.081 03	15.785 55	37	2	−0.447 42	0.0180	10.995	6.067

molecules are among the most important factors responsible for biological activity. Thus, similarities between structural properties and electronic properties of the studied flavones with cAMP seem to be dominant factors affecting inhibition activity.

A reasonable explanation of why particular descriptors listed in Table 1 correlate fairly well with the inhibition activity of flavone derivatives could be as follows. Within structural descriptors it has been found that particular valence connectivity indices $^i\chi^v$ (i − 0, 1, 2, ...) correlate extremely well with the molecular shape for various classes of molecules and consequently correlate well with most molecular shape-dependent properties and processes.[18] Path lengths p_i (i = 0, 1, 2, ...) are the molecular descriptors that also reflect well the structure of the molecule. Among path numbers, the p_3•index (number of pairs of atoms separated with three bonds) is the descriptor that correlates with polarity and with the steric aspects of a molecule.[19]

The electronic properties of flavone derivatives and cAMP were studied by Ferrell and co-workers.[20] On the basis of quantum-chemical calculations, they found that there is a resemblance between the charge distribution of the pyranone ring of the inhibitor molecule and the pyrimidine ring of cAMP. Similarities in electrophilicity parameters were also found. Thus, the sum of π-electronic charges on atoms of a pyranone ring and the energy of the low-lying empty orbital E(LUMO) could be used as suitable QSAR indices. Recently, Rastelli *et al.*[21] proposed a similar net charge index for QSAR studies of anthocyanidins.

The size of the test sample (19 flavone derivatives) does not justify[22] the use of a nonorthogonal basis with seven descriptors. The use of three descriptors in this case would be statistically more sound. However, the statistical characteristics of the best model with three descriptors (model 3 from Table 1: R = 0.9365, S = 6.99, and F = 35.70) are not particularly good. Hence, we have to consider how to improve a regression that involves considered descriptors and how to reduce the number of descriptors while at the same time obtaining acceptable statistical characteristics. Our procedure described in our recent report in this journal,[15] based on the ordered orthogonalized basis and dominant component analysis, offers an acceptable solution.

The seven descriptors in the nonorthogonalized basis are used to develop an orthogonalized basis. Orthogonalization is carried out in all possible orderings, that is, in 7! orthogonalization orderings. This results in obtaining QSAR models with orthogonalized indices with better statistical parameters than the models based on the nonorthogonal basis. The best models with their statistical characteristics are listed in Table 3.

From examination the correlation coefficient (R), standard error (S), F-test, and a number of variables in the model, it appears that model 3 from Table 3 is statistically the best model. This model contains three orthogonalized descriptors and possesses the best values of the F test. Models that contain a larger set of descriptors do not significantly improve the R and S values. Table 4 presents numerical values of favorable orthogonalization ordering of seven descriptors from which the best model with three orthogonalized descriptors was generated.

The regression equation for best orthogonalized model with three descriptors (model 3 from Table 3) is as follows:

orthogonalization ordering:

$$\text{TRE(PE)}, p_3, {}^3\chi^v, {}^0\chi^v, \sum_{ph}^{ph}, E\,(\text{LUMO}), p_{10}$$

$$\%\ \text{INH} = (68.421 \pm 0.812) + (699.601 \pm 197.589)\text{TRE(PE)} + (10.182 \pm 1.202)^0\chi^v + (20.625 \pm 1.064)p_{10} \quad (1)$$

$$R = 0.9841 \qquad S = 3.54 \qquad F = 153.38$$

Table 5 provides a list of the experimental values of cAMP inhibition (%) as well as calculated values of inhibition (%) using eq 1.

The best model with six nonorthogonal descriptors is the model generated with the following descriptors: $^4\chi^v$, p_2, p_{10}, H_2, MTI, and η_r (R = 0.9807, S = 4.35, F = 50.31). For six descriptors there are 6! possibilities of different orthogonalization orderings. Models with two to six orthogonalized descriptors had statistical characteristics inferior to models generated with seven orthogonalized descriptors. However, it is interesting to note that a model with a single orthogonalized descriptor generated from six orthogonalized descriptors is superior to a corresponding model generated from seven orthogonalized descriptors. This result is obtained for the following orthogonalization ordering: p_2, p_3, H_2, MTI, η_r, and $^4\chi^v$ using orthogonalized descriptor $^4\chi^v$. The corre-

Table 3. Best Possible QSAR Models with *I*-Tuples of Orthogonalized Descriptors Obtained by Selecting the Optimum Orthogonalization Orderings of Descriptors[a]

$I = 1$; orthogonalization ordering: d16, d1, d13, d7, d14, d4, **d8**
$R = 0.8894$ $S = 8.55$ $F = 63.47$
% INH = (68.421 ± 1.962) + (20.625 ± 2.571)d8

$I = 2$; orthogonalization ordering: d8, d16, d13, **d1**, d7, d14, **d4**
$R = 0.9737$ $S = 4.40$ $F = 145.92$
% INH = (68.421 ± 1.009) + (29.140 ± 1.931)d1 + (−20.687 ± 2.584)d4

$I = 3$; orthogonalization ordering: **d14**, d7, d4, **d1**, d16, d13, **d8**
$R = 0.9841$ $S = 3.54$ $F = 153.38$
% INH = (68.421 ± 0.812) + (10.182 ± 1.202)d1 + (20.625 ± 1.064)d8 + (699.601 ± 197.589)d14

$I = 4$; orthogonalization ordering: **d14**, d7, **d4**, **d1**, d16, d13, **d8**
$R = 0.9864$ $S = 3.39$ $F = 125.90$
% INH = (68.421 ± 0.778) + (10.182 ± 1.152)d1 + (0.963 ± 0.629)d4 + (20.625 ± 1.019)d8 + (699.601 ± 189.308)d14

$I = 5$; orthogonalization ordering: **d8**, **d14**, d4, **d1**, d13, **d16**, **d7**
$R = 0.9874$ $S = 3.38$ $F = 101.41$
% INH = (68.421 ± 0.776) + (31.692 ± 1.630)d1 + (20.594 ± 2.187)d7 + (0.416 ± 0.305)d8 + (−866.171 ± 198.942)d14 + (−58.557 ± 13.201)d16

$I = 6$; orthogonalization ordering: **d8**, **d7**, d14, **d1**, **d4**, **d16**, **d13**
$R = 0.9875$ $S = 3.51$ $F = 78.41$
% INH = (68.421 ± 0.806) + (29.213 ± 1.655)d1 + (−5.431 ± 0.753)d4 + (1.393 ± 0.262)d7 + (0.417 ± 0.317)d8 + (744.713 ± 90.988)d13 + (100.455 ± 32.127)d16

[a] Boldface letters denote those descriptors (e.g., dominant descriptors)which, after the orthogonalization in the indicated order, take part in the construction the model.

Table 4. Set of Seven Orthogonalized Descriptors Presented in Favorable Orthogonalization Ordering

	orthogonalized descriptor						
	TRE(PE)	p_3	$^3\chi^v$	$^0\chi^v$	Σ_q^{ph}	E(LUMO)	p_{10}
1	−0.003 70	0.758 53	0.752 75	0.501 26	−0.010 42	−0.001 42	0.530 07
2	−0.002 30	2.575 36	0.802 35	0.107 73	−0.029 43	0.011 59	0.887 69
3	0.005 30	3.152 43	−1.427 75	0.444 80	−0.027 32	−0.002 45	0.356 57
4	0.008 40	4.532 55	0.238 25	−0.339 47	0.040 76	0.000 62	0.470 82
5	−0.003 70	−1.241 47	0.457 76	0.231 07	−0.005 35	−0.000 17	0.790 69
6	−0.001 50	−4.100 74	−1.842 78	−0.277 09	0.011 33	0.008 44	0.917 84
7	0.009 30	−8.228 07	1.944 26	0.901 33	−0.023 60	0.001 97	−0.576 26
8	0.001 50	5.363 89	0.755 97	−0.519 58	−0.035 77	−0.018 27	0.462 40
9	−0.004 10	1.096 58	1.142 30	0.351 07	−0.009 52	0.017 33	−0.211 26
10	−0.005 10	−1.058 29	1.118 93	0.786 49	0.021 14	−0.010 09	−0.135 81
11	−0.003 30	0.420 49	0.163 56	0.780 79	0.041 28	−0.010 40	−0.147 22
12	0.000 20	−0.537 45	−1.861 75	−0.269 19	−0.019 43	0.017 60	0.184 72
13	−0.000 20	−5.199 40	1.315 86	−1.983 34	0.018 15	−0.005 96	0.935 87
14	0.005 40	3.067 91	0.354 75	0.122 89	0.017 00	0.003 34	−0.258 71
15	−0.000 90	−2.607 81	−2.517 89	0.318 84	−0.021 35	−0.018 59	−0.121 00
16	−0.001 70	2.068 29	0.162 18	0.347 55	0.031 86	0.005 68	−0.077 41
17	0.000 70	−1.960 01	−1.816 42	0.086 92	0.027 25	−0.000 50	−0.532 75
18	−0.003 20	0.335 97	0.416 89	−0.723 40	−0.035 17	−0.003 57	−1.398 70
19	−0.001 10	1.561 21	−0.159 22	−0.868 69	0.008 60	0.004 86	−2.077 56

Table 5. Experimental and Computed Values of cAMP Inhibition[a]

flavone deriv	inhibition (%) exp[b]	calc	flavone deriv	inhibition (%) exp[b]	calc
1	90	82	11	70	71
2	85	86	12	70	70
3	85	84	13	70	67
4	80	81	14	65	68
5	80	84	15	65	69
6	80	83	16	65	69
7	75	72	17	60	59
8	75	74	18	30	30
9	70	65	19	15	16
10	70	70			

[a] The computed values are obtained from the best possible model with three ordered orthogonalized descriptors based on eq 1. [b] Experimental values are taken from ref 20.

sponding regression equation is as follows:

$$\% \text{ INH} = (68.421 \pm 1.554) + (13.718 \pm 1.292)^4\chi^v \quad (2)$$

$$R = 0.987 \qquad S = 6.77 \qquad F = 112.72$$

CONCLUDING REMARKS

We have demonstrated that a relatively simple model, based on the topological and electronic properties of flavone derivatives, can be used to predict successfully the percent inhibition of cAMP.

The best possible models that we obtained using ordered orthogonalized descriptors are much better than the corresponding best possible models that we derived using nonorthogonalized descriptors.

The differences between R, S, and F values for the QSAR models with ordered orthogonalized and QSAR models with nonorthogonalized descriptors are much larger in the case of inhibition of cAMP than in the cases that were studied in our recent reports.[15-17]

We point out that the structure–activity models based on the ordered orthogonalized basis set enable prediction of cAMP phosphodiesterase inhibition for yet untested flavone derivatives. Therefore, these models are expected to possess a considerable predictive power.

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REFERENCES AND NOTES

(1) Goodwin, T. W., Ed. *Chemistry and Biochemistry of Plant Pigments*. Academic Press: New York, 1976.
(2) Chen, L. H.; Hrazdina, G. Structural Aspects of Anthocyanin–Flavonoid Complex Formation and Its Role in Plant Color. *Phytochemistry* **1981**, *20*, 297–303.
(3) Harborne, J. B. Nature, Distribution and Function of Plant Flavonoids. In *Plant Flavonoids in Biology and Medicine*; Cody, B., Middleton, E., Jr., Harborne, J. B., Eds.; Alan Lyss: New York, 1986.
(4) Beretz, A.; Anton, R.; Cazenave, J. P. The Effects of Flavonoids on Cyclic Nucleotide Phosphodiesterases. In *Plant Flavonoids in Biology and Medicine*; Cody, B., Middleton, E., Jr., Harborne, J. B., Eds.; Alan Lyss: New York, 1986.
(5) Middleton, E., Jr.; Kandaswami, C. The Impact of Plant Flavonoids on Mammalian Biology: Implications for Immunity, Inflammation and Cancer. In *The Flavonoids–Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman and Hall: London, 1994.
(6) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Structure–Activity Analysis*; John Wiley and Sons, Inc.: New York, 1986.
(7) Wiener, H. Prediction of Isomeric Differences in Paraffin Properties. *J. Am. Chem. Soc.* **1947**, *69*, 17–20.
(8) Balaban, A. T. Highly Discriminating Distance-Based Topological Index. *Chem. Phys. Lett.* **1982**, *89*, 399–404.
(9) Plavšić, D.; Nikolić, D.; Trinajstić, N.; Mihalić, Z. On the Harary Index for the Characterization of Chemical Graphs. *J. Math. Chem.* **1993**, *12*, 235–250.
(10) Schultz, H. P. Topological Organic Chemistry. 1. Graph Theory and Topological Indices of Alkanes. *J. Chem. Inf. Comput. Sci.* **1989**, *29*, 227–228. Nikolić, S.; Trinajstić, N.; Mihalić, Z. Molecular Topological Index: An Extension to Heterosystems. *J. Math. Chem.* **1993**, *12*, 251–264.
(11) Zhou, Z.; Parr, G. R. New Measures of Aromaticity: Absolute Hardness and Relative Hardness. *J. Am. Chem. Soc.* **1989**, *111*, 7371–7379.
(12) Gutman, I.; Milun, M.; Trinajstić, N. Graph Theory and Molecular Orbitals. 19. Nonparametric Resonance Energies of Arbitrary Conjugated Systems. *J. Am. Chem. Soc.* **1977**, *99*, 1692–1704.
(13) Randić, M. Orthogonal Molecular Descriptors. *New J. Chem.* **1991**, *15*, 517–525.
(14) Randić, M.; Trinajstić, N. Viewpoint 4–Comparative Structure–Property Studies: the Connectivity Basis. *J. Mol. Struct. (THEOCHEM)* **1993**, *284*, 209–221.
(15) Lučić, B.; Nikolić, S.; Trinajstić, N.; Juretić, D. The Structure–Property Models Can Be Improved Using the Orthogonalization Descriptors. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 532–538.
(16) Lučić, B.; Nikolić, S.; Trinajstić, N.; Juretić, D.; Jurić, A. A Novel QSPR Approach to Physicochemical Properties of the α-Amino Acids. *Croat. Chem. Acta* **1995**, *68*, 417–434.
(17) Lučić, B.; Nikolić, S.; Trinajstić, N.; Jurić, A.; Mihalić, Z. A Structure–Property Study of the Solubility of Aliphatic Alcohols in Water. *Croat. Chem. Acta* **1995**, *68*, 435–450.
(18) Trinajstić, N. *Chemical Graph Theory*, 2nd ed.; CRC Press: Boca Raton, FL, 1992; Chapter 10.
(19) Platt, J. R. Prediction of Isomeric Differences in Paraffin Properties. *J. Phys. Chem.* **1952**, *56*, 328–336.
(20) Ferrell, J. E., Jr.; Chang Sing, P. D. G.; Loew, G.; King, R.; Mansour, J. M.; Mansour, T. E.; Structure/Activity Studies of Flavonoids as Inhibitors of Cyclic AMP Phosphodiesterase and Relationship to Quantum Chemical Indices. *Mol. Pharmacol.* **1979**, *16*, 556–568.
(21) Rastelli, G.; Costantino, L.; Albasini, A. Physico-Chemical Properties of Anthocyanidins. Part 1. Theoretical Evaluation of the Stability of the Neutral and Anionic Tautomeric Forms. *J. Mol. Struct. (THEOCHEM)* **1993**, *279*, 157–166.
(22) Andrea, T. A.; Kalayeh, H. Applications of Neural Networks in Quantitative Structure–Activity Relationships of Dihydrofolate Reductase Inhibitors. *J. Med. Chem.* **1991**, *34*, 2824–2836.

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