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(RECOMMENDED CITATION)

QSAR STUDIES ON DERIVATIVES OF RESVERATROL

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ABSTRACT. A set of 40 resveratrol derivatives, downloaded from the PubChem database, was submitted to a QSAR study, following Diudea's algorithm, involving the hypermolecule concept, in a procedure similar to that of the „alignment" of drug molecules to the biological receptors. The best models describing log P of this set of resveratrols were validated by the leave-one-out procedure, in the external test set and in a new version of prediction by using clusters of similar molecules. The structures have been optimized at HF 6-31G(d,p) level of theory. Topological indices have been computed by TOPOCLUJ software.

Keywords: *resveratrol, QSAR, hypermolecules, log P.*

INTRODUCTION

Resveratrol is a plant polyphenolic derivative, highly abundant in grapes, peanuts, and other plants [1,2]. Numerous studies have reported interesting properties of trans-resveratrol as a preventive agent of several important pathologies: vascular diseases, cancers, viral infection, neurodegenerative processes such as Alzheimer's [3-6].

The octanol–water partition coefficient (log P) is a key parameter in the passive transport of drug molecules to the biological receptors [7].

Quantitative structure-activity relationships (QSAR) are widely used to relate biological activity with chemical structure, by means of topological indices [8]. Among thousands of topological indices [9], the Cluj indices (proposed by Diudea [10, 11]) are used for molecular graph description.

In testing the predictive ability of QSAR models, among many other tests, the leave one out LOO is a simple and useful method. [12].

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STRUCTURAL MOLECULAR DATA

A set of 40 resveratrol derivatives, taken from PubChem Database [13] (Table 1), were divided into a training set (25 molecules) and a test set (15 molecules), taken randomly; the modelled property was log P (Table 1).

Table 1. Resveratrol derivatives molecular structures (in SMILES code) and their log P (taken from PubChem).

Mol.	Canonical SMILES	log P	CID
1	C1=CC(=CC=C1CCC2=CC(=CC(=C2)O)O)O	3.1	185914
2	CC(=CC1=CC=C(C=C1)O)C2=CC(=CC(=C2)O)O	3.7	75071272
3	C1=CC(=CC(=C1)O)CCC2=CC(=CC(=C2)O)O	3.1	21574990
4	C1=CC=C(C=C1)CCC2=CC(=CC(=C2)O)O	3.4	442700
5	CC(CC1=CC(=CC(=C1)O)O)C2=CC=C(C=C2)O	3.4	58892268
6	COC1=C(C=CC(=C1)C=CC2=CC(=CC(=C2)O)O)O	3.2	5318650
7	COC1=C(C=C(C=C1)CC(C2=CC(=C(C(=C2)OC)OC)OC)O)O	2.6	335929
8	C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O	3.1	445154
9	C1=CC(=CC(=C1)O)CCC2=CC=C(C=C2)O	3.5	181511
10	C1=CC=C(C=C1)COC2=CC=C(C=C2)O	3.4	7638
11	C1=CC=C(C=C1)C2C(O2)C3=CC=CC=C3	2.9	5742860
12	CCC(C1=CC=C(C=C1)O)C(CC)C2=CC=C(C=C2)O	5.2	3606
13	O(C1=CC(=CC(=C1)OC)\C(=C(\C2=CC=C(OC)C=C2)[H])[H])C	4.1	5388063
14	COC1=CC=C(C=C1)C=CC2=CC(=C(C(=C2)OC)OC)OC	4.1	125922
15	COC1=C(C=C(C=C1)C(C(C2=CC(=C(C(=C2)OC)OC)OC)O)O)O	1.4	10247286
16	COC1=CC(=CC(=C1O)OC)C(CC2=CC(=C(C=C2)O)OC)OC	2.8	75149948
17	COC1=CC(=CC(=C1O)O)C(CC2=CC=C(C=C2)O)OC	2.5	74429419
18	CCOC(CC1=CC=C(C=C1)O)C2=CC(=C(C(=C2)OC)O)O	2.8	74429420
19	CC(C(=CC1=CC(=C(C=C1)OC)O)C2=CC(=C(C(=C2)OC)OC)OC)O	3.5	54586166
20	COC1=CC=C(C=C1)CC(C2=C(C(=C(C=C2)OC)OC)O)O	3.1	44429048
21	COC1=CC=C(C=C1)C(C(C2=CC(=C(C(=C2)OC)OC)OC)O)O	1.8	10592816
22	COC1=C(C=C(C=C1)CC(C2=CC(=CC(=C2)OC)OC)O)OC	2.5	66673695
23	COC1=CC=C(C=C1)CC(C2=CC(=C(C(=C2)OC)OC)OC)O	2.9	57423765
24	COC1=C(C(=C(C=C1)C(C(C2=CC(=C(C(=C2)OC)OC)OC)O)O)O)O	1.6	54129628
25	COC1=C(C=C(C=C1)C=C(CO)C2=CC(=C(C(=C2)OC)OC)OC)O	3.1	11078510
26	COC1=C(C=C(C=C1)C(CC2=CC(=C(C(=C2)OC)OC)OC)O)OC	2.9	356755
27	COC1=CC(=CC(=C1OC)OC)C(CC2=CC=CC=C2)O	2.9	353079
28	CC(=CC1=CC(=CC(=C1)OC)OC)C2=CC=C(C=C2)OC	4.7	75071221
29	COC1=CC=CC(=C1)C=CC2=CC(=CC(=C2)OC)OC	4.1	69452320
30	COC1=CC(=O)OC(C1)C=CC2=CC=CC=C2	2.5	5369129
31	COC1=CC(=CC(=C1)C=CC2=CC=CC=C2)OC	4.1	13556468
32	CC(=CC1=CC(=CC(=C1)OC)OC)C2=CC=CC=C2	4.8	68796507
33	O(C1=CC(=CC(=C1)OC)C=CC2=CC(=CC(=C2)OC)OC)C	4.1	67145168

Mol.	Canonical SMILES	log P	CID
34	COC1=CC(=CC(=C1)C=CC2=CC=C(C=C2)C=C)OC	4.9	70184295
35	CCOC1=CC=C(C=C1)C=CC2=CC(=CC(=C2)OC)OC	4.5	69899106
36	CC1=CC=C(C=C1)C=CC2=CC(=CC(=C2)OC)OC	4.5	58240360
37	CCOC1=CC=C(C=C1)C=CC2=CC(=CC(=C2)OCC)OCC	5.2	67435273
38	O(C2=C(C=CC1=CC(=CC(=C1)OC)OC)C=CC(=C2)OC)C	4.1	5491
39	COC1=CC(=CC(=C1)CC(=C)C2=CC=CC=C2)OC	4.8	69940018
40	CC(C)OC1=CC=C(C=C1)C=CC2=CC(=CC(=C2)OC)OC	4.9	66674282

On the set of 40 resveratrols, a Hypermolecule [14] was built up, as a reunion of their substructures (Figure 1).

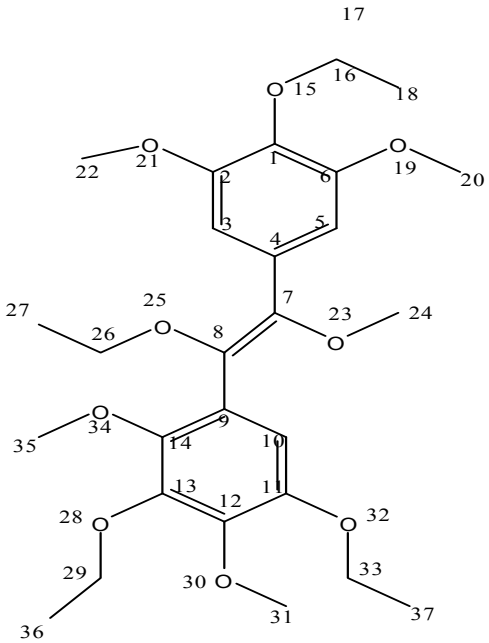

Figure 1. The hypermolecule built on 40 resveratrols of the dataset

COMPUTATIONAL DETAILS

The structures have been optimized at Hartree-Fock HF (3-21g(,p)) level of theory, in gas phase, by Gaussian 09 [15]. Topological indices have beed computed by TOPOCLUJ software [16]; some of them (Conectivity =C, Total adjacency = Adj, Charges=Ch, Detour = De, Distance = Di, D3D, SD), HOMO (in au) and log P are listed in Table 2.

RESULTS AND DISCUSSION

Two cases are discussed in the Hypermolecule description: (1) mass fragments and (2) partial charges (HF level of theory).

1. Mass fragments description (case 1)

1.1.Data reduction

The local correlation-weighted descriptors are summed to give SD1 global descriptor, over the following significant positions in the hypermolecule: H1, H5, H6, H7, H8, H13, H15, H17, H22, H23, H25, H26, H28. SD_1 correlation with log P: $\log P = 116.302 + 1.00001 \times SD_1$, R^2=0.934, n=40, s=0.253, F=536.085, and the best results are listed below and in Table 3.

1.2. QSAR models

The models were performed on the training set (25 structures in Table 1) and the best results are listed below and in Table 3. The number of descriptors was limited to four, to fulfil the considerations of Topliss and Costello [17].

Table 2. Log P, correlating descriptors SD_k, and topological indices for the set of 40 Resveratrols in Table 1.

Mol.	log P	SD_1	SD_2	HOMO	Ch	C	Di	D3D	De
1	3.1	-113.037	-1.181	-8.971	0.12	24	582	564.13	956
2	3.7	-112.731	-0.690	-8.764	0.074	26	650	629.21	1052
3	3.1	-113.538	-1.513	-8.981	0.22	24	572	550.25	966
4	3.4	-113.053	-0.872	-9.005	0.11	23	485	472.69	831
5	3.4	-112.656	-0.583	-8.990	0.089	25	651	625.47	1053
6	3.2	-112.661	-0.992	-8.813	0.25	27	780	718.72	1258
7	2.6	-113.882	-2.115	-9.092	0.37	31	1417	1269.69	2095
8	3.1	-112.689	-1.089	-8.558	0.11	25	582	622.57	956
9	3.5	-113.037	-1.144	-8.989	0.051	23	499	488.45	829
10	3.4	-112.944	-0.960	-8.712	0.015	22	420	462.68	708
11	2.9	-112.914	-1.742	-9.733	0.11	23	387	438.72	738
12	5.2	-111.713	0.345	-8.919	-0.054	27	814	815.42	1222
13	4.1	-112.126	-0.135	-8.712	0.15	28	926	877.77	1422
14	4.1	-112.093	-0.212	-8.669	0.2	30	1175	1090.57	1751
15	1.4	-114.860	-3.114	-9.105	0.46	32	1530	1344.92	2242

Mol.	log P	SD_1	SD_2	HOMO	Ch	C	Di	D3D	De
16	2.8	-113.547	-1.801	-8.991	0.41	31	1372	1234.4	2072
17	2.5	-113.564	-1.649	-8.929	0.3	28	960	930.04	1474
18	2.8	-113.587	-1.640	-8.926	0.27	29	1081	1055.79	1625
19	3.5	-112.301	-0.938	-8.965	0.31	34	1681	1603.94	2427
20	3.1	-113.345	-1.043	-9.033	0.34	29	1132	1063.14	1704
21	1.8	-114.322	-2.474	-8.975	0.38	31	1384	1274.14	2024
22	2.5	-113.830	-1.470	-9.004	0.35	30	1276	1138.86	1936
23	2.9	-113.345	-1.519	-8.981	0.29	30	1276	1177.67	1884
24	1.6	-114.921	-2.893	-8.951	0.54	33	1665	1533.68	2481
25	3.1	-113.486	-1.527	-8.528	0.26	32	1417	1325.27	2095
26	2.9	-113.410	-1.784	-9.019	0.36	32	1584	1425.58	2332
27	2.9	-113.394	-1.519	-9.229	0.27	28	956	918.89	1500
28	4.7	-111.745	0.041	-8.940	0.12	28	1016	1005.11	1544
29	4.1	-112.100	-0.164	-8.983	0.19	28	902	825.24	1446
30	2.5	-113.801	-1.871	-9.406	0.25	24	574	579.89	962
31	4.1	-112.176	-0.109	-8.920	0.14	26	669	645.06	1101
32	4.8	-111.795	0.486	-8.988	0.1	27	746	724.84	1210
33	4.1	-112.241	-0.553	-8.908	0.29	30	1155	1086.77	1819
34	4.9	-111.601	0.193	-8.769	0.051	29	926	880.89	1422
35	4.5	-111.435	0.352	-8.700	0.12	29	1084	1027.89	1612
36	4.5	-111.601	-0.438	-8.755	0.14	27	788	750.88	1252
37	5.2	-111.435	0.336	-8.669	0.041	31	1396	1331.03	2026
38	4.1	-112.142	-0.177	-8.821	0.37	30	1155	1058.79	1819
39	4.8	-111.757	0.266	-8.961	0.1	27	746	747.63	1210
40	4.9	-111.435	0.568	-8.668	0.082	30	1244	1173.82	1804

(i) Monovariate regression

$$\log P = 111.136 + 0.954 \times SD_1$$

(ii) Bivariate regression

$$\log P = 108.915 + 0.933 \times SD_1 - 0.0002 \times D3D$$

(iii) Three-variate regression

$$\log P = 109.175 + 0.939 \times SD_1 - 0.003 \times Di + 0.002 \times De$$

(iv) Four-variate regression

$$\log P = 111.411 + 0.927 \times SD_1 + 0.433 \times HOMO + 0.004 \times De - 0.005 \times CjDi$$

Table 3. Best models in describing log P in the training set of resveratrol derivates in Table 1.

	Descriptors	R^2	Adjust. R^2	St. Error	F
1	**SD1**	0.951	0.949	0.205	448.907
2	**HOMO**	0.150	0.113	0.857	4.072
3	**Di**	0.149	0.112	0.858	4.029
4	**De**	0.149	0.112	0.858	4.036
5	**SD1, D3D**	0.956	0.952	0.200	237.196
6	**SD1, Di**	0.955	0.951	0.201	235.945
7	**SD1, CjDe**	0.955	0.951	0.202	233.911
8	**SD1, De**	0.955	0.951	0.202	232.918
9	**SD1, HOMO**	0.952	0.948	0.209	217.899
10	**SD1, Di, De**	0.961	0.955	0.193	171.693
11	**SD1, De, CjDi**	0.960	0.954	0.196	165.871
12	**SD1, HOMO, D3D**	0.958	0.952	0.199	160.408
13	**SD1, HOMO, Di**	0.958	0.952	0.200	159.512
14	**SD1, D3D, De**	0.958	0.952	0.199	159.893
15	**SD1, HOMO, Ch**	0.957	0.951	0.201	156.987
16	**SD1, D3D, Di**	0.956	0.950	0.204	152.179
17	**SD1, HOMO, De, CjDi**	0.964	0.957	0.189	133.954
18	**SD1, HOMO, D3D, De**	0.961	0.953	0.198	122.206
19	**SD1, De, D3D, Di**	0.961	0.953	0.197	122.716
20	**SD1, C, Di, D3D**	0.958	0.950	0.204	115.137

1.3. Model Validation

(a) Leave-one-out

The performances in leave-one-out analysis related to the models listed as the best in Table 3 are presented in Table 4 [18,19].

Table 4. Leave-one-out analysis for best log P models (Table 3).

	Descriptors	Q^2	R^2-Q^2	St. Error$_{loo}$	F_{loo}
1	**SD_1**	**0.941**	0.1	0.225	368.511
5	**SD_1, D3D**	**0.938**	0.018	0.231	349.079
11	**SD_1, Di, De**	**0.944**	0.017	0.219	389.566
19	**SD_1, HOMO, De, CjDi**	**0.944**	0.02	0.219	389.113

(b) External Validation

The values log P for the test set of resveratrols (Table 1) were calculated by using the best equation (with three variables) in Table 3, entry 10. Data are listed in Table 5 and the monovariate correlation: $\log P = 0.763 \times \log P_{calc.} + 0.876$; n=15; R^2=0.859; s=0.411; F=79.105 is plotted in Figure 2.

Table 5. Calculated values of log P for the molecules in the test set (Table 1)

Mol.	log P	log $P_{calc.}$
5	3.4	3.67
6	3.2	3.72
7	2.6	2.40
8	3.1	3.65
9	3.5	3.30
10	3.4	3.36
11	2.9	3.58
12	5.2	4.40
13	4.1	4.11
14	4.1	4.08
15	1.4	1.45
37	5.2	4.60
38	4.1	4.28
39	4.8	4.57
40	4.9	4.59

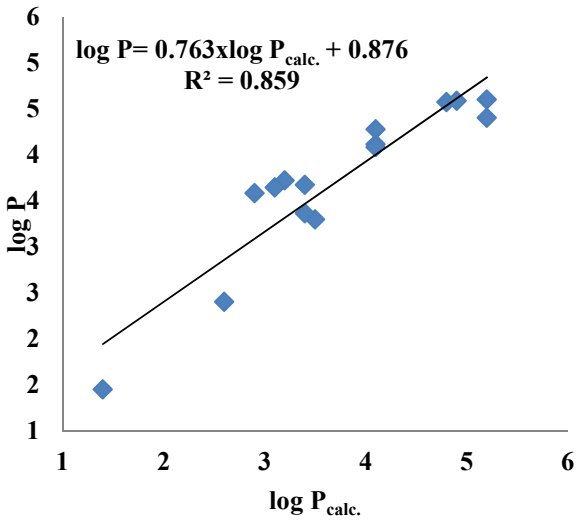

Figure 2. The plot log P vs. log $P_{calc.}$ for the test set (external validation)

(c) Similarity Cluster Validation

Validation can be performed by calculating log P for the molecules in the test set with equations learned on clusters of similarity: each of the 15 molecules is the leader in its own cluster, selected by (2D) similarity among the 25 structures of the initial learning set. The values log $P_{calc.}$ for each of the 15 molecules in the test set were computed by 15 new equations (the leader being left out) with the same descriptors as in eq. 10, Table 3. Data are listed in Table 6 and the monovariate correlation: $\log P = 0.923 \times \log P_{calc.} + 0.288$; n=15; R^2=0.979; s=0.157; F=622.623 is plotted in Figure 3 [20].

Table 6. Calculated values of log P by similarity clusters, for the molecules in the test set (Table1)

Mol.	log P	log $P_{calc.}$
5	3.4	3.31
6	3.2	3.31
7	2.6	2.57
8	3.1	3.28
9	3.5	3.32
10	3.4	3.39
11	2.9	3.15
12	5.2	4.88
13	4.1	4.12
14	4.1	4.08
15	1.4	1.52
37	5.2	5.08
38	4.1	4.27
39	4.8	4.60
40	4.9	5.03

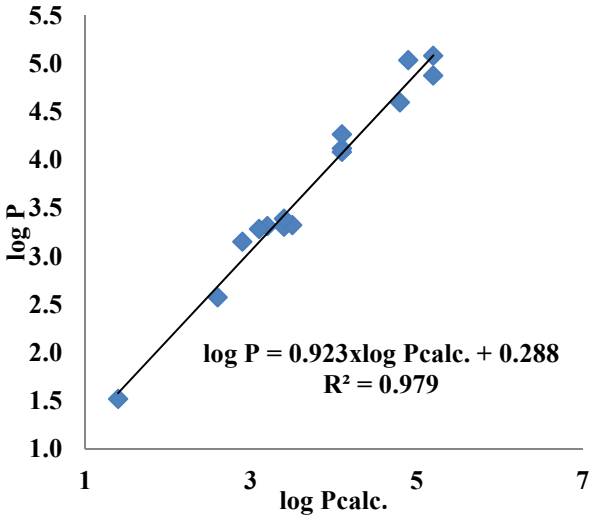

Figure 3. The plot log P vs. log $P_{calc.}$ for the test set (similarity clusters)

2. Partial charges description (case 2)

2.1. Data reduction (for log P)

This new descriptor SD_2, that is a linear combination of the local correlating descriptors for the significant positions in the hypermolecule H1, H3, H4, H7, H8, H9, H13, H14, H16, H17, H18, H20, H23, H29, H30, H31, eq., $\log P = 4.428 + 0.999 \times SD_2$ R^2=0.940, s=0.240, F=600.419.

2.2. QSAR models (for log P)

QSAR models using different combinations of descriptors were tried, but the models which provided best correlation coefficient for training set are described below and in Table 7 [21].

(i) Monovariate regression

$$\log P = 4.458 + 1.025 \times SD_2$$

(ii) Bivariate regression

$$\log P = 7.993 + 0.994 \times SD_2 + 0.399 \times HOMO$$

(iii) Three-variate regression

$$\log P = 3.377 + 0.872 \times SD_2 - 1.706 \times Ch. + 0.046 \times C$$

(iv) Four-variate regression

$$\log P = 3.878 + 1.039 \times SD_2 - 0.004 \times Di + 0.003 \times D3D. + 0001 \times De$$

Table 7. Best models in describing log P in the training set of resveratrol derivatives in Table1.

	Descriptors	R^2	Adjust. R^2	St. Error	F
1	**SD_2**	0.949	0.947	0.243	430.049
2	**HOMO**	0.232	0.199	0.945	6.967
3	**De**	0.158	0.121	0.990	4.309
4	**Di**	0.146	0.108	0.997	3.918
5	**SD_2, HOMO**	0.953	0.949	0.239	222.847
6	**SD_2, C**	0.952	0.947	0.243	216.235
7	**SD_2, D3D**	0.952	0.947	0.242	216.767
8	**SD_2, Di**	0.951	0.947	0.244	214.565
9	**SD_2, CjDe**	0.951	0.947	0.244	214.150
10	**SD_2, De**	0.951	0.947	0.244	214.662
11	**SD_2, Ch, C**	**0.961**	0.956	0.223	172.920
12	**SD_2, Di, Ch**	0.960	0.954	0.226	168.094
13	**SD_2, D3D, Di**	0.954	0.947	0.243	144.189
14	**SD_2, HOMO, D3D**	0.953	0.947	0.244	142.881
15	**SD_2, HOMO, Di**	0.953	0.946	0.245	142.271
16	**SD_2, Di, C**	0.952	0.945	0.248	138.131
17	**SD_2, CjDi, CjDe**	0.952	0.945	0.247	139.068
18	**SD_2, D3D, De**	0.952	0.945	0.247	139.724
19	**SD_2, Di, D3D, De**	0.955	0.946	0.246	105.304
20	**SD_2, HOMO, D3D, De**	0.954	0.945	0.249	103.317
21	**SD_2, C, D3D, Di**	0.954	0.945	0.248	104.166

2.3. Model Validation (for log P)

(a) Leave-one-out

The performances in leave-one-out analysis related to the models listed as the best in Table 7 are presented in Table 8 [22].

Table 8. Leave-one-out analysis for best log P models in Table 7.

	Descriptors	Q^2	R^2-Q^2	St. Error$_{loo}$	F_{loo}
1	**SD_1**	**0.941**	0.008	0.262	367.752
5	**SD_1, HOMO**	**0.943**	0.01	0.258	377.825
11	**SD_1, Ch, C**	**0.949**	0.012	0.244	426.74
19	**SD_1, Di, D3D, De**	**0.933**	0.022	0.279	321.249

(b) External Validation

The values log P for the test set of resveratrols (Table 1),were calculated by using the best equation in Table 7, entry 11. Data are listed in Table 9 and the monovariate correlation: $\log P = 1.031 \times \log P_{calc.} - 0.051$; n=15; R^2=0.938; s=0.213; F=195.279 is plotted in Figure 4 [23].

Table 9. Calculated values of log P for the molecules in the test set (Table 1)

Mol.	log P	log $P_{calc.}$
1	3.1	3.26
2	3.7	3.86
3	3.1	2.80
4	3.4	3.50
5	3.4	3.88
6	3.2	3.34
7	2.6	2.34
8	3.1	3.40
9	3.5	3.36
10	3.4	3.54
11	2.9	2.74
12	5.2	5.03
13	4.1	4.31
14	4.1	4.25
15	1.4	1.37

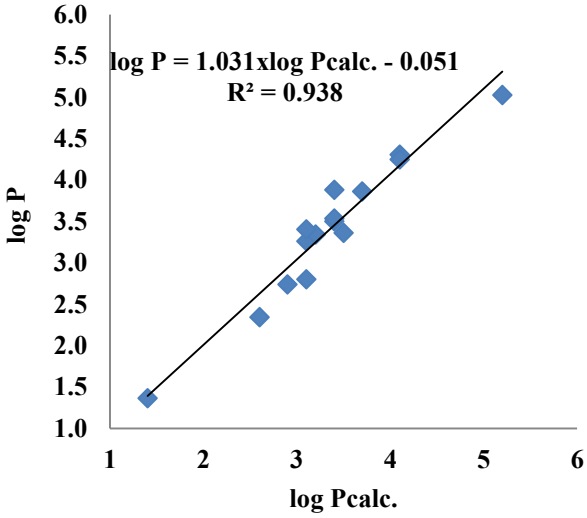

Figure 4. The plot log P vs. log $P_{calc.}$ for the test set (external validation)

(c) Similarity Cluster Validation

The values log P calc. for each of the 15 molecules in the test set were computed with the same descriptors as in eq. 11, Table 7. Data are listed in Table 10 and the monovariate correlation: $\log P = 1.020 \times \log P_{calc.} + 0.002$; n=15; R^2=0.981; s=0.119; F=659.369 plotted in Figure 5 [22].

Table 10. Calculated values of log P by similarity clusters, for the molecules in the test set (Table 1)

Mol.	log P	log $P_{calc.}$
1	3.1	3.29
2	3.7	3.84
3	3.1	2.90
4	3.4	3.53
5	3.4	3.58
6	3.2	3.34
7	2.6	2.69
8	3.1	3.13
9	3.5	3.42
10	3.4	3.55
11	2.9	2.97
12	5.2	5.14
13	4.1	4.31
14	4.1	4.23
15	1.4	1.34

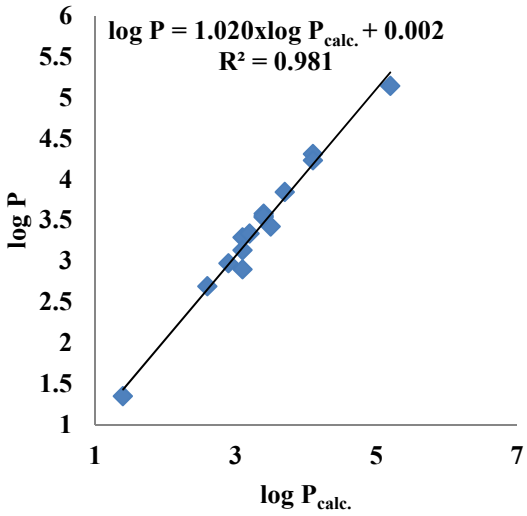

Figure 5. The plot log P vs. log P calc. for the test set (similarity clusters)

CONCLUSIONS

A set of 40 resveratrol derivatives, downloaded from the PubChem database, was submitted to a QSAR study. The best models have been validated in the external test set and in a new version of validation/prediction by using clusters of similarity, that favorise apparition of „quasi-congeneric" state, mandatory for a best correlation.

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