BABEŞ-BOLYAI UNIVERSITY
FACULTY OF CHEMISTRY AND CHEMICAL
ENGINEERING

QSAR STUDY OF COMPOUNDS OF OXYGEN

Abatract

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Content







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Keywords: QSAR, flavonoids and resveratrol, anthraquinones, testosterone, similarity, topological indices, molecular docking, leave-one-out, hipermolecula, log P, LD50.

INTRODUCTION

In the thesis presents theoretical and own contributions on the QSAR study of organic compounds with oxygen groups, involving the concept of hipermoleculă a similar procedure to align biologic drugs receiver.

This thesis is part of an important area of research in chemistry, bringing contributions to the development of theoretical concepts on relations structure-biological properties of molecules with applications in the pharmaceutical industry in the discovery of new drugs based on similarities molecular thus reducing cost production.

QSAR and molecular docking study was performed on the following classes of compounds: flavonoids, testosterone, anthraquinones and resveratrol due to the outstanding biological properties of these classes of compounds have been downloaded from the database PubCHEM. For CCD topological indices were calculated using the program TOPO Cluj and optimizing structures was performed with Gaussian program.

These methods QSAR / QSPR is based on statistical analysis of the correlation between the known properties and topological descriptors for which there is no known functional relationships. Such biological activity or toxicity, reactivity of molecules can be determined depending on various properties after the law simpler (linear regression) or complex (multiple regression). This may involve a multiline dependence of reactivity, biological activity, toxicity of some chemical physical, biological measured or calculated. You can establish such

statistics about which properties have statistically significant influence on the biological activities (toxicity) and what properties can be excluded as irrelevant removed.

QSAR modeling by applying the algorithm proposed by Diudea and property are subject to modeling: log P and LD50. Modeling was performed on training set, and the best models that describe the biological activity and toxicity of this set of molecules is validated by the procedure leave-one-out in the set External test and by a new version of prediction using clusters Molecular Similarity .

The molecules that are structurally similar properties have similar concept is used in drug discovery after comparing molecules.

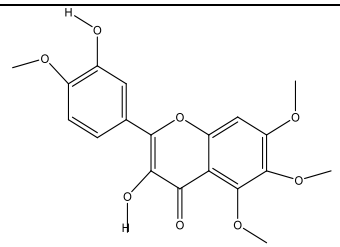
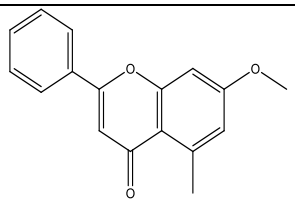
In the study of molecular modeling, docking (docking) is a method to predict the binding mode of the ligand protein to form a stable complex. The program used is AutoDock VINA docking and binding energy based pharmacophore was built.

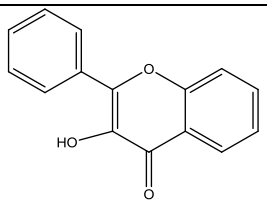
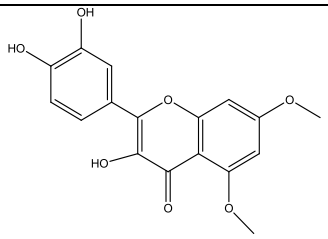
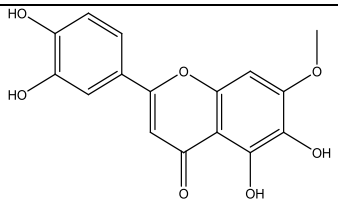
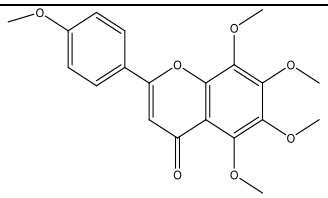
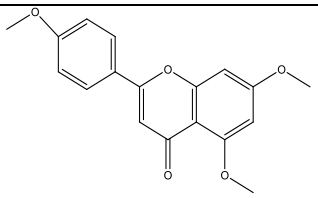
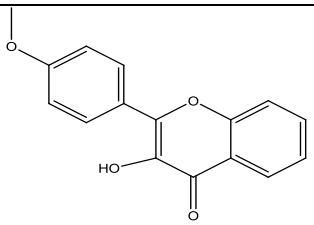
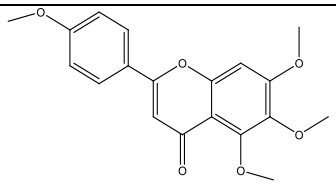
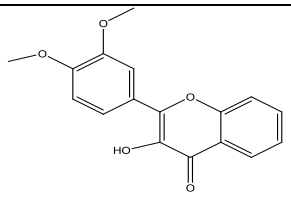
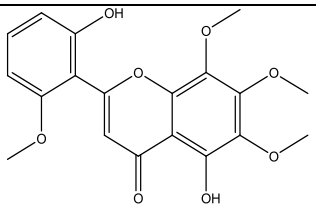
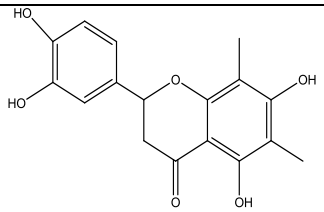
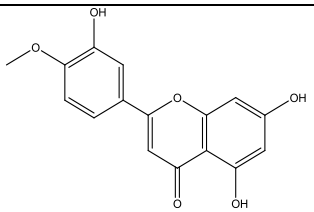
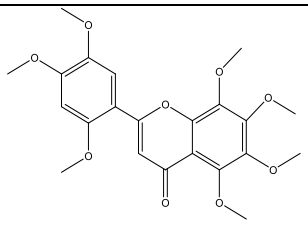
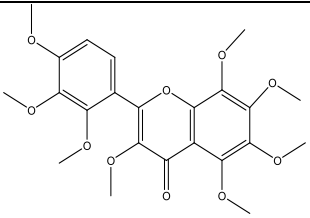
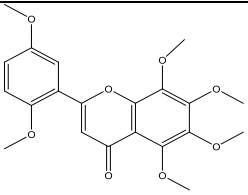
II. PERSONAL CONTRIBUTIONS

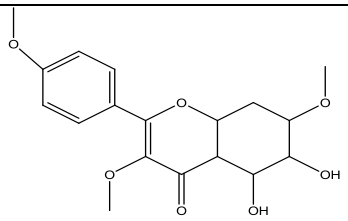
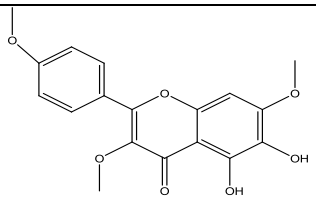
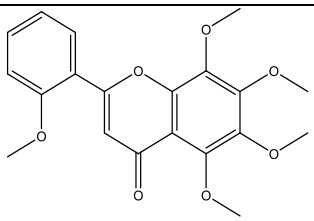
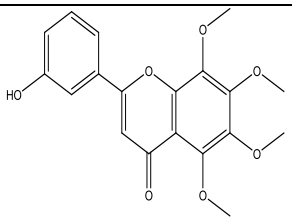
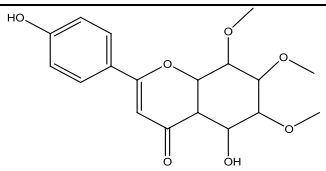
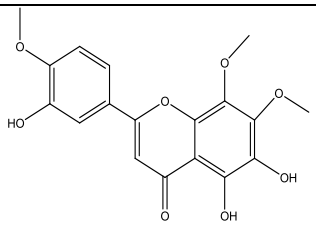
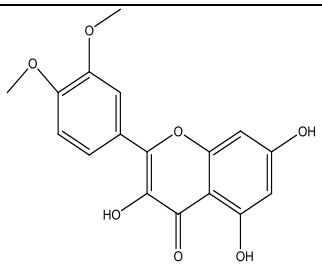
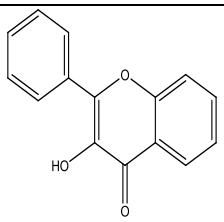
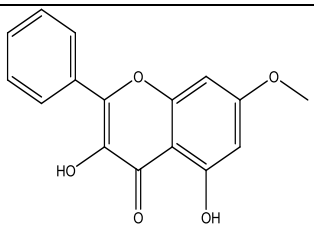
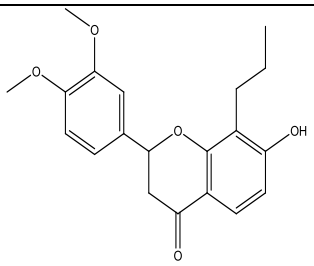
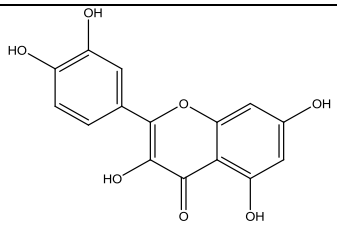
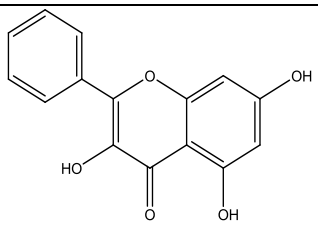
1. QSAR and Molecular Docking Study of flavonoid derivatives based on clusters similarity

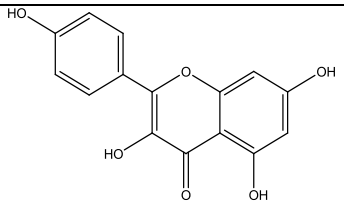
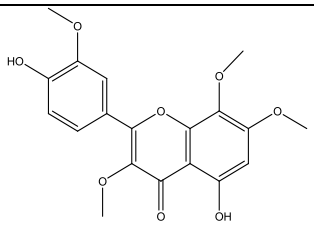
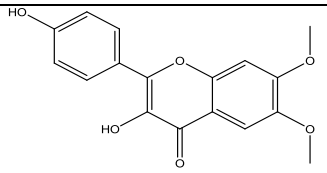
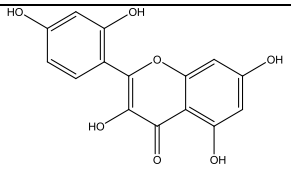
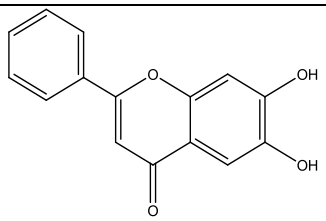
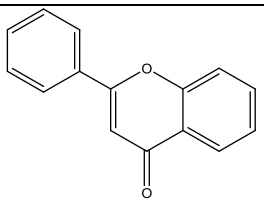
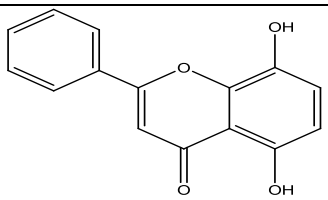
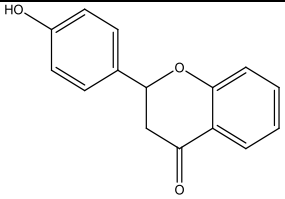
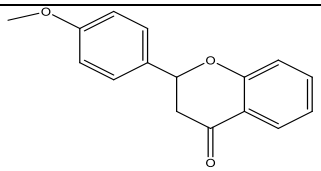
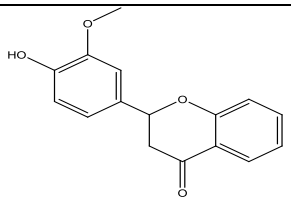
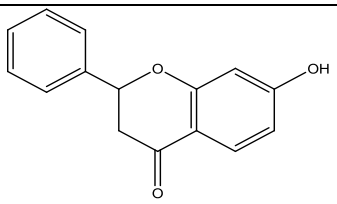
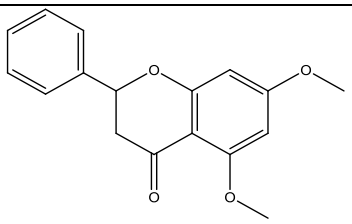
A set of 40 flavonoids were taken from PubChem Database [93](Table 1) and were divided into a training set (30 molecules) and a test set (ten molecules), taken randomly. The property chosen for modeling was log P (see Table 1), the (calculated) partition coefficient between n-octanoland water, a measure of hydrophobicity, involved in the passive transport of a drug molecule through cell membrane and LD50 (mouse, oral)[94].

Table 1. Flavonoid molecular structures and their log P (taken from PubChem)

	Structure	log P		Structure	log P
1		2.8	2		3.5

3		3.4	4		1.6
5		2.3	6		3
7		2.2	8		3.4
9		3.1	10		3.3
11		2.9	12		2.8
13		1.7	14		3
15		3.2	16		3

17		2.9	18		3.1
19		3	20		2.7
21		3.1	22		2.6
23		2.2	24		2.6
25		2.6	26		3.8
27		1.5	28		2.3

29		1.8	30		3.1
31		2.6	32		1.5
33		1.7	34		3.2
35		2.1	36		2.8
37		3.1	38		2.5
39		2.7	40		2.8

(b) External Validation

The values log P for the test set of flavonoids were calculated by using equation cf. entry 19, Table 4. Data are listed in Table 6 and the monovariate correlation:

log P = 0.804×log Pcalc. + 0.983; n=15; R^2=0.883; s=0.219; F=98.164 is plotted in Figure 9. The number of descriptors was limited to four, to fulfill the considerations of Topliss and Costello [110].

Table 7. Calculated values of log P for the molecules in the test set (see Table 1)

Molecules	log P	log $P_{calc.}$
2	3.5	3.935
4	1.6	2.357
5	2.3	2.578
11	2.9	3.386
13	1.7	2.375
16	3	3.309
20	2.7	3.238
21	2.8	2.948
22	2.6	2.908
24	2.6	3.334
27	1.5	2.217
29	1.8	2.131
32	1.5	2.407
35	2.1	2.560
38	2.5	3.125

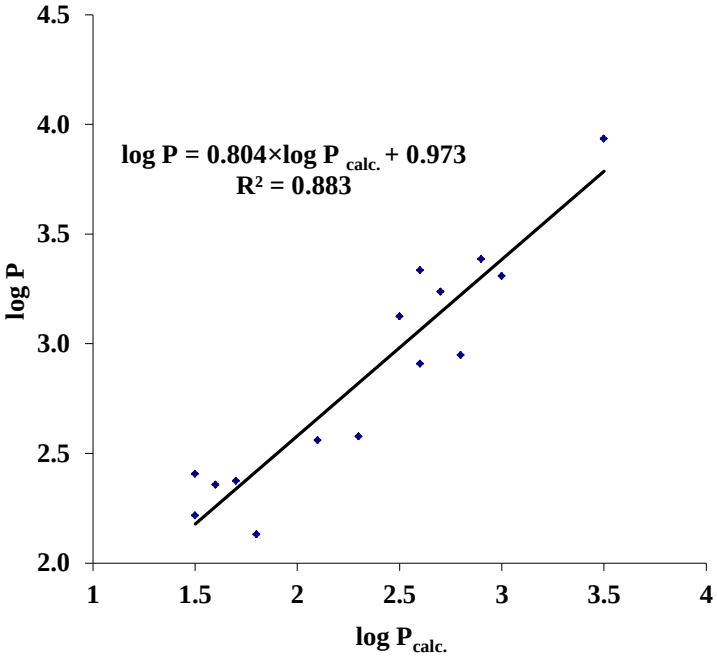


Figure 6. The plot log P vs. log $P_{calc.}$ for the test set (external validation)

(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. 11, Table 4. Data are listed in Table 7 and the monovariate correlation: log P = 0.740×log $P_{calc.}$ + 1.037; n=15; R^2=0.907; s=0.195; F=126.972 is plotted in Figure 10.

Also, the validation can be performed by calculating log P for the molecules in the test set by using clusters of similarity and the same descriptors as in eq. 19, Table 4. Data are listed in Table 8 and the monovariate correlation: log P = 0.7898×log Pcalc. + 0.715; n=15; R^2=0.932; s=0.167; F=176.737 is plotted in Figure 11.

Even the number of descriptors per sample is higher than in the case of external validation, the loose in generality is compensated by a better prediction: compare R^2=0.883 (external validation) and R^2=0.932 (similarity cluster validation), at the same number of descriptors. In case of data in Table 7 the prescribtions of Topliss and Costello [27] are fulfilled for three variables and again the prediction (R^2=0.907) is better than in case of classical external validation of the model. A similarity measure, that quantifies the degree of structural resemblance between the target structure and each of the database structure, is based on maximum superposed molecular substructures, at topological level (2D). The volume of each of the 15 clusters is of 12 molecules.

Table 6. Calculated values of log P by similarity clusters, for the molecules in the test set as in eq. 11

Molecules	log P	log $P_{calc.}$
2	3.5	3.77
4	1.6	2.33
5	2.3	2.58
11	2.9	3.17
13	1.7	2.35
16	3	3.18
20	2.7	3.01
21	2.8	2.91
22	2.6	2.83
24	2.6	3.18
27	1.5	2.13
29	1.8	2.20
32	1.5	2.27
35	2.1	2.56
38	2.5	3.13

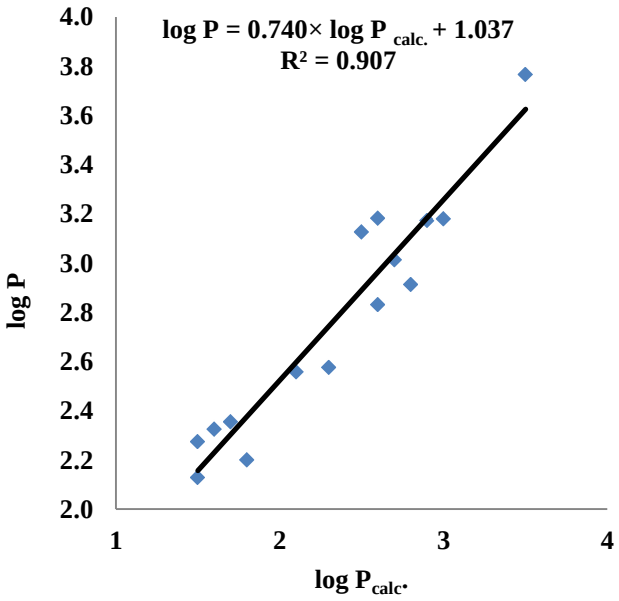


Figure 10. The plot log P vs. log $P_{calc.}$ by similarity clusters

Table 8. Calculated values of log P by similarity clusters, for the molecules in the test set as in eq. 19

Molecules	log P	log $P_{calc.}$
2	3.5	3.469
4	1.6	2.036
5	2.3	2.353
11	2.9	2.898
13	1.7	1.974
16	3	3.214
20	2.7	3.005
21	2.8	2.885
22	2.6	2.861
24	2.6	2.739
27	1.5	1.748
29	1.8	2.057
32	1.5	2.124
35	2.1	2.554
38	2.5	2.530

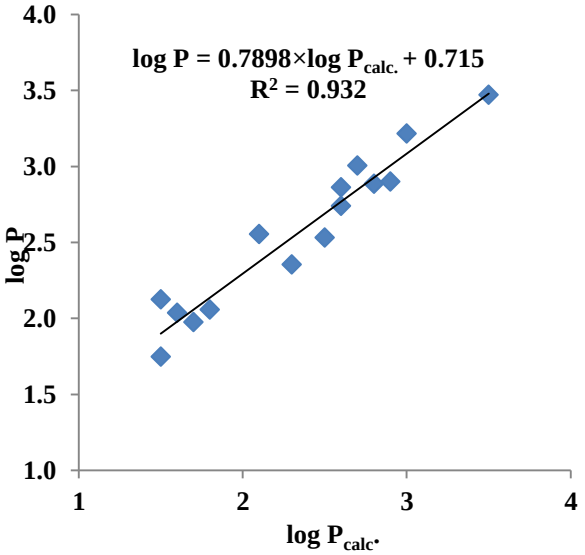


Figure 11. The plot log P vs. log $P_{calc.}$ by similarity clusters

- **Case LD50**

(b) Validarea externă

The values LD50 for the test set of flavonoids were calculated by using equation cf. entry 19, Table 10. Data are listed in Table 12 and the monovariate correlation: LD50 = 1.036×$LD50_{calc.}$ + 293.19; n=10; R^2=0.637 s=183.325; F=14.057 is plotted in Figure 12.

Table 12. Calculated values of LD50 for the molecules in the test set (Table 1)

Mol.	LD50	$LD50_{calc.}$
1	10	41.948
2	300	540.105
3	56	758.130
8	300	634.108
9	300	374.332
11	200	514.784
19	1000	1289.931
27	18	195.801
29	300	970.905
30	115	305.196

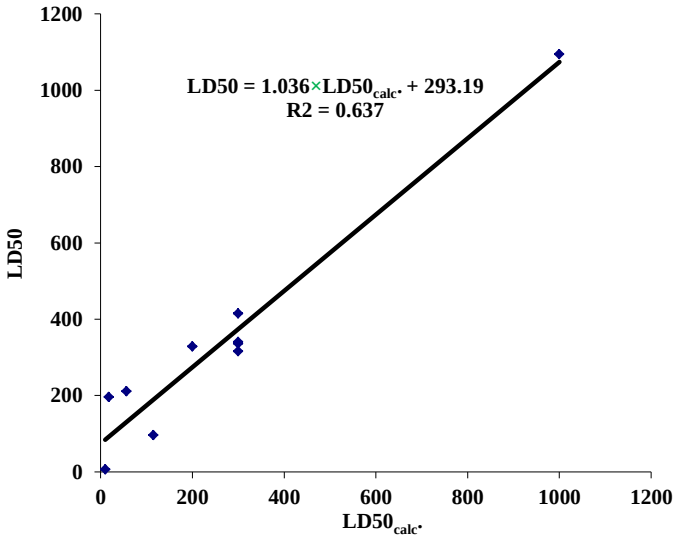


Figure 12. The plot LD50 vs. $LD50_{calc.}$ for the test set

(external validation)

(c) Similarity Cluster Validation

Validation can be performed by calculating LD50 for the molecules in the test set by using clusters of similarity, as in Section (b); the values LD50calc. were computed with the same descriptors as in eq. 11, Table 10. Data are listed in Table 13 and the monovariate correlation: LD50 = 1.013×LD50calc. + 63.337; n=10; R2=0.922; s=85.228; F=94.053 is plotted in Figure 13.

Table 13. Calculated values of LD50 by similarity clusters, for the molecules in the test set as in eq. 11.

Molecules	LD50	$LD50_{calc.}$
1	10	22.10
2	300	332.54
3	56	299.08
8	300	367.49
9	300	349.53
11	200	247.45
19	1000	1058.68
27	18	-26.88
29	300	484.81
30	115	131.96

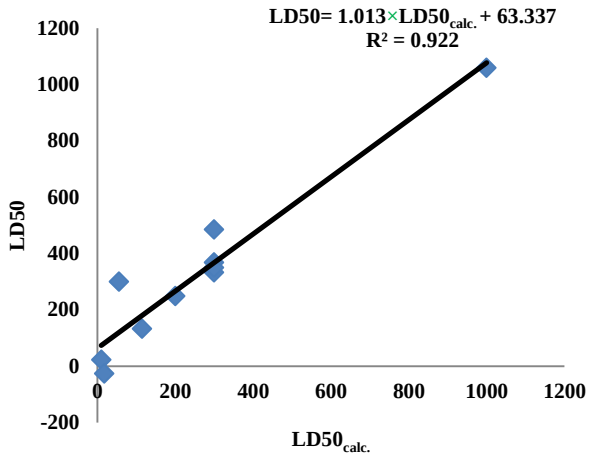


Figure 13. The plot LD50 vs. $LD50_{calc.}$ by similarity clusters

Also, the validation can be performed by calculating LD50 for the molecules in the test set with the same descriptors as in eq. 19, Table 10. Data are listed in Table 14 and the monovariate correlation: LD50 = 0.9998×LD50calc. + 74.227; n=10; R2=0.945; s=71.347; F=137.629 is plotted in Figure 14.

Table 14. Calculated values of LD50 by similarity clusters, for the molecules in the test set as in eq. 11.

Molecules	LD50	$LD50_{calc.}$
1	10	6.178
2	300	340.495
3	56	211.207
8	300	315.652
9	300	335.965
11	200	329.016
19	1000	1095.035
27	18	195.801
29	300	414.866
30	115	96.605

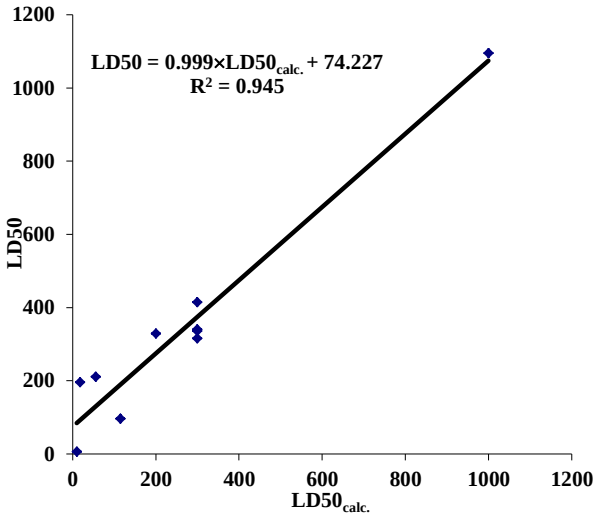


Figure 14. The plot LD50 vs. $LD50_{calc.}$ by similarity clusters

As in the case above, the prediction of LD50 is much better done by using the clusters of similarity that by the classical external validation of the model. Our interest was not providing a general model but the best prediction for a study case.

1.2. Molecular Docking Studies of Flavonoids Derivatives

A set of 30 Flavonoid derivatives were taken from PubChem Database (in Smiles code, Table 15).

Table 1. Flavonoid derivatives molecular structure, in SMILES code (taken from PubChem).

Mol.	Canonical SMILES :
1	COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(C(=C(C=C3O2)OC)OC)O)O)O
2	COC1=CC2=C(C=C1)C(=O)C=C(O2)C3=CC=CC=C3
3	C1=CC=C(C=C1)C2=C(C(=O)C3=CC=CC=C3O2)O
4	COC1=CC(=C2C(=C1)OC(=C(C2=O)O)C3=CC(=C(C=C3)O)O)OC
5	COC1=C(C(=C2C(=C1)OC(=CC2=O)C3=CC(=C(C=C3)O)O)O)O
6	COC1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C(=C3OC)OC)OC)OC
7	COC1=CC=C(C=C1)C2=CC(=O)C3=C(C=C(C=C3O2)OC)OC
8	COC1=CC=C(C=C1)C2=C(C(=O)C3=CC=CC=C3O2)O
9	COC1=CC=C(C=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC)OC)OC
10	COC1=CC=CC(=C1C2=CC(=O)C3=C(O2)C(=C(C(=C3O)OC)OC)OC)O
11	CC1=C(C2=C(C(=C1O)C)OC(CC2=O)C3=CC(=C(C=C3)O)O)O
12	COC1=C(C=C(C=C1)C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
13	COC1=CC=C(C=C1)C2=C(C(=O)C3=C(C(=C(C=C3O2)OC)O)O)OC
14	COC1=CC=CC=C1C2=CC(=O)C3=C(O2)C(=C(C(=C3OC)OC)OC)OC
15	COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)OC

16	C1=CC=CC(=C1)C3=C(C(C2=CC=CC=C2C3)=O)O
17	COC1=CC(=C2C(=C1)OC(=C(C2=O)O)C3=CC=CC=C3)O
18	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O
19	C1=CC=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
20	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
21	COC1=C(C=CC(=C1)C2=C(C(=O)C3=C(O2)C(=C(C=C3O)OC)OC)OC)O
22	COC1=C(C=C2C(=C1)C(=O)C(=C(O2)C3=CC=C(C=C3)O)O)OC
23	C1=CC(=C(C=C1O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
24	C1=CC=C(C=C1)C2=CC(=O)C3=CC(=C(C=C3O2)O)O
25	C1C(OC2=CC=CC=C2C1=O)C3=CC=CC=C3
26	C1=CC=C(C=C1)C2=CC(=O)C3=C(C=CC(=C3O2)O)O
27	C1C(OC2=CC=CC=C2C1=O)C3=CC=C(C=C3)O
28	COC1=CC=C(C=C1)C2CC(=O)C3=CC=CC=C3O2
29	COC1=C(C=CC(=C1)C2CC(=O)C3=CC=CC=C3O2)O
30	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=CC=C3

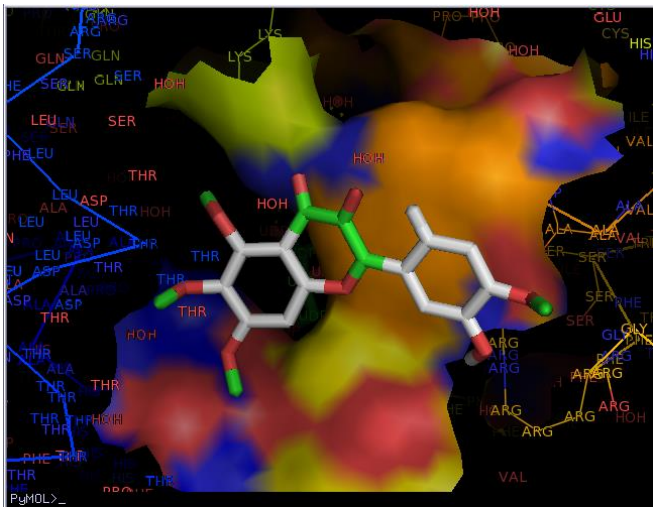


Figure 16 : The interaction of flavonoids with Flavonoid 3-O-glucosyltransferase

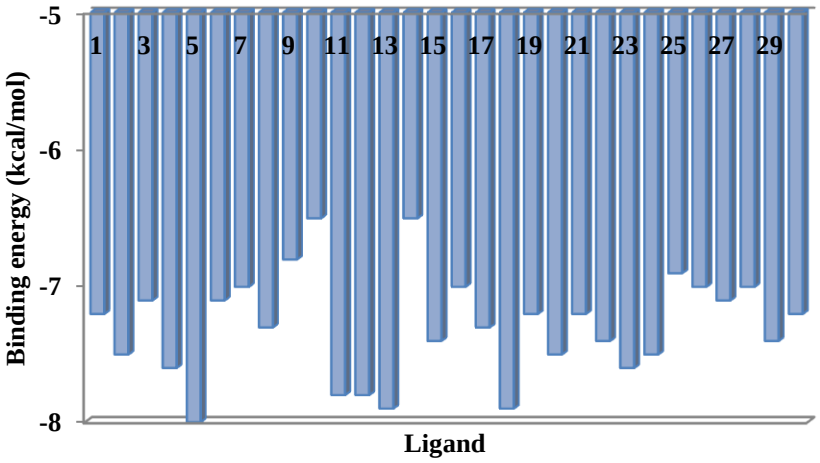


Figure 17: The free energy of binding elicited at the vicinity of active

site by the ligands.

To obtain the pharmacophore model for the Flavonoid 3-O-glucosyltransferase receptor, the best scored (from docking) conformers were chosen: the ligands # 5, 27, 18 and 2 (with the binding energy between -8 and -7.5). The resulting pharmacophore is shown in Figure 18.

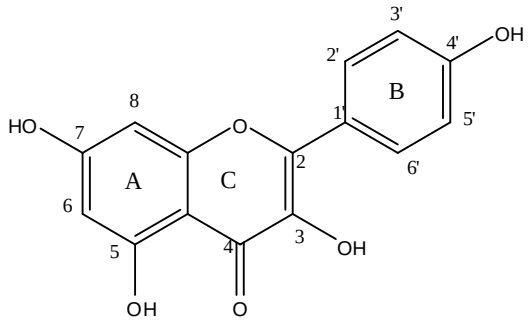


Figure 18: Pharmacophore model for the receptor Flavonoid 3-O-glucosyltransferase

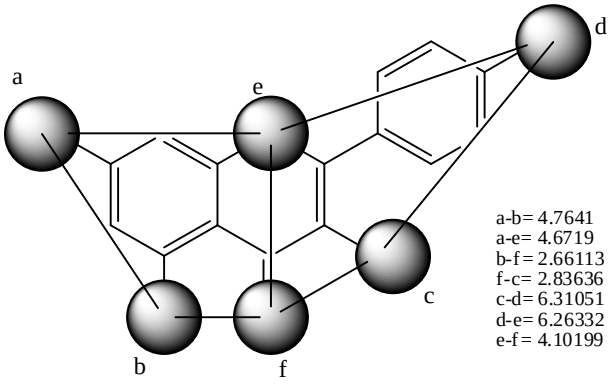


Figure 18(b): Distances within pharmacophore features (Å).

1.2.3.2. QSAR study based on energy docking

(b) External Validation

The values LD50 for the test set of flavonoids were calculated by using eq 15 in Table 20. Data are listed in Table 22 and the monovariate correlation: $LD50 = 0.787 \times LD50_{calc.} + 351.25$; n =10; R^2=0.787; s=354.005; F=19.292 is plotted in Figure 20 [27].

Table 22. Calculated values of LD50 for the molecules in the test set (see Table 1)

Mol.	LD50	$LD50_{calc.}$
2	300	408.58
4	1410	1040.06
5	2000	2254.1
11	800	1170.1
12	300	318.26
13	1000	1124.03
18	18	756.95
20	300	1023.86
23	555	528.23
24	300	383.83

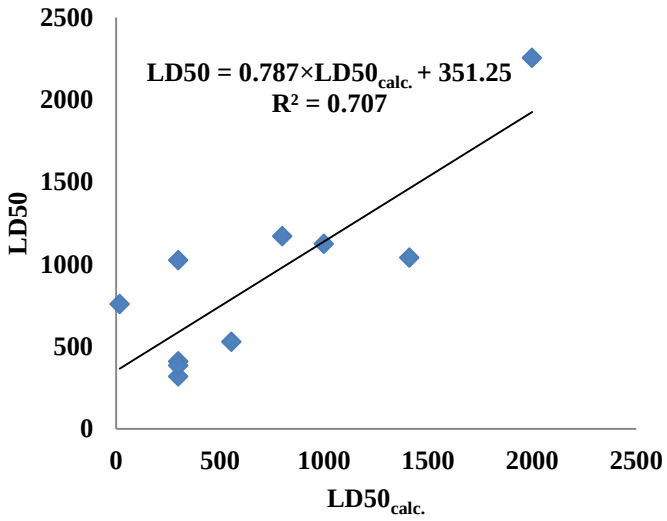


Figure 20. The plot LD50 vs. $LD50_{calc.}$ for the test set (external validation)

From Table 22 and Figure 20, **o**ne can see that our models are not particularly good in prediction but this is not a backtracking, since the models are asked to give info on the best descriptors not on the best models.

(c) Similarity Cluster Validation

Validation can also be performed by using clusters of similarity: each of the 10 molecules in the test set (chosen as the best scored in the docking set) is the leader of its own cluster, selected by 2D similarity among the 20 structures of the learning set (each cluster comprising about 15-17 molecules). The values $LD50_{calc}$ were predicted by 10 new equations (the leader being left out) with the same descriptors as in

Eq 15, Table 18. Data are listed in Table 23 and the monovariate correlation: $LD50 = 0.996 \times LD50_{calc.} + 58.008$; n =10; R^2=0.928; s=175.605; F=102.912 is plotted in Figure 21 [26].

Table 23. Calculated values of LD50 by similarity clusters, for the molecules in the test set

Mol.	LD50	$LD50_{calc}$
2	300	333.02
4	1410	1265.67
5	2000	2281.45
11	800	595.18
12	300	342.23
13	1000	1130.75
18	18	363.89
20	300	408.81
23	555	542.53
24	300	272.08

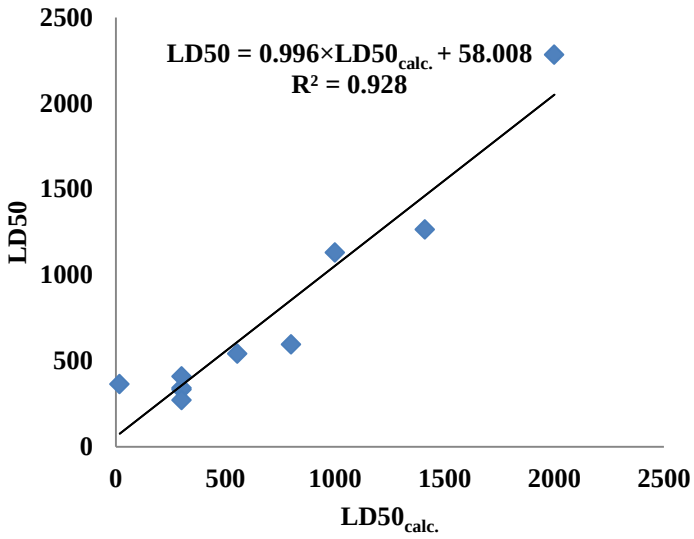


Figure 21. The plot LD50 vs. $LD50_{calc.}$ by similarity clusters

Prediction of LD50 is much better done by using the clusters of similarity (R^2= 0.928) that by the classical external validation of the model (R^2= 0.707).

Lowest binding energy it correlates with $LD50_{calc.}$ for test set (R^2= 0.317), the lowest docking energies is use just for chosen the test set.

2. QSAR STUDY ON TESTOSTERON DERIVATIVES

A set of 40 testosterones were taken from PubChem Database (Table 22) and were divided into a training set (25 molecules) and a test set (15 molecules), taken randomly. The property chosen for modeling was log P (calculated) partition coefficient between n-octanol and water (see Table 24) and LD50 (on mouse, oral route administered)[119].

Table 24. . Testosterone molecular structures (in SMILES code) and their log P and LD50 (taken from PubChem)

Nr. Crt	**Canonical SMILES**	Log P	LD50
1	CC12CCC3C(C1CCC2O)CCC4=CC(=O)CCC34C	3.3	5000
2	CCC(=O)OC1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C	4.4	1000
3	CC12CCC(=O)C=C1CCC3C2CCC4(C3CCC4(C)O)C	3.4	2500
4	CC12CCC(CC1CCC3C2CCC4(C3CCC4=O)C)O	3.7	980
5	CCCCCCC(=O)OC1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C	6.3	1000
6	CC12CCC3C(C1CCC2OC(=O)CCC4=CC=CC=C4)CCC5=CC(=O)CCC35	5.1	595
7	CCCCC(=O)OC1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C	5.3	980
8	CC(=O)OC1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C	3.9	980
9	CC12CCC3C(C1CCC2(C#C)O)CCC4=CC(=O)CCC34	3	2000
10	CC12CCC3C(C1CCC2=O)CC(=C)C4=CC(=O)C=CC34C	3.1	980

11	CC(=O)OC1(CCC2C1(CCC3C2CCC4=CC(=O)CCC34)C)C#C	3.5	980
12	CC1CC2C(CCC3(C2CCC3(C(=O)C)OC(=O)C)C)C4(C1=CC(=O)CC4)C	4.1	6400
13	CC(=O)OC1CCC2C1(CCC3C2CCC4=C(C(=O)CCC34C)Cl)C	4.7	980
14	CCC12CCC3C(C1CCC2(C#C)O)CCC4=CC(=O)CCC34	3.3	5010
15	CC12CCC3C(C1CCC2OC(=O)C4=CC=CC=C4)CCC5=CC(=O)CCC35C	5.6	980
16	CC12CCC(=O)C=C1CCC3C2CCC4(C3CCC4(C#C)O)C	3.5	980
17	CCC12CC(=C)C3C(C1CCC2(C#C)O)CCC4=CC(=O)CCC34	3.3	980
18	CC12CCC3C(C1CCC2O)CCC4=CC(=O)C=CC34C	3.5	980
19	CC1CC2C3CCC(C3(CC(C2C4(C1=CC(=O)CC4)C)O)C)C(=O)C	2.7	980
20	CC12CC(C3C(C1CCC2(C(=O)CO)O)CCC4=CC(=O)C=CC34C)O	1.6	250
21	CC12CCC(=O)C=C1CCC3C2C(CC4(C3CCC4(C(=O)CO)O)C)O	1.6	5000
22	CCC(=O)C1(C(CC2C1(CC(C3C2CCC4=CC(=O)C=CC34C)O)C)C)C	3.5	980
23	CC1CC2C3CCC(C3(CC(C2C4(C1=CC(=O)C=C4)C)O)C)(C(=O)CO)O	1.9	4000
24	CC1CC2C3CCC(C3(CC(C2C4(C1=CC(=O)C=C4)C)O)C)(C(=O)COC(=O)C)O	2.7	10000
25	CC12CCC(=O)C=C1CCC3C2CCC4(C3CCC4(C#C)O)C	3.5	980
26	CC12CCC3C(C1CCC2(C)O)CCC4C3(COC(=O)C4)C	3.7	10000
27	CC12C=CC3=C4CCC(=O)C=C4CCC3C1CCC2(CC=C)O	2.8	980
28	CC12CCC3C(C1CCC2OC(=O)C4=CC=CC=C4)CCC5=CC(=O)CCC35C	5.6	980
29	CC12CCC(=O)C=C1CCC3C2C(CC4(C3CCC4(C(=O)O)O)C)O	1.6	980
30	CC12CCC3C(C1CCC2(C)O)CCC4=CC(=O)C=CC34C	3.6	1000
31	CC1CC(=O)CC2C1(C3CCC4(C(C3CC2)CCC4O)C)C	4.1	980
32	CC1=CC2C(CCC3(C2CCC3(C(=O)C)OC(=O)C)C)C4(C1=CC(=O)CC4)C	3.1	980
33	CC12CCC3C(C1CCC2C(=O)COC(=O)C(C)(C)C)CCC4=CC(=O)CCC34C	4.5	980
34	CCCCCC(=O)OC1(CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C)C(=O)C	5.7	980
35	CC1CC2(C(CCC3C2CCC4(C3CCC4O)C)CC1=O)C	4.2	980
36	CC12CCC(=O)C=C1CCC3C2CCC4(C3CCC4(C#C)O)C	3.5	2000
37	CC12CCC3C(C1CCC2(C#C)O)CCC4=C3CCC(=O)C4	2.1	980
38	CCC(=O)OC1CCC2C1(CCC3C2CCC4C3(CC(C(=O)C4)C)C)C	5.3	980
39	CC1=CC(=O)CC2C1(C3CCC4(C(C3CC2)CCC4OC(=O)C)C)C	4.4	4000
40	CC12CCC(=O)C(=C1CCC3C2CCC4(C3CCC4(C)O)C)O	3.2	980

Mass fragments description (case 1)

(b) External Validation

The values log P for the test set of testosterone (the last 15 structures in Table 1), were calculated by using the best trivariate equation in Table 27, entry 9. Data are listed in Table 29 and the monovariate correlation: $\log P = 0.845 \times \log P_{calc.} + 2.306$;n=15; R^2=0.722; s=0.652;

F= 33.8 is plotted in Figure 23.

Table 29. Calculated values log P for the molecules in the test set (Table 1)

Mol.	logP	log $P_{calc.}$
26	3.7	3.70
27	2.8	5.86
28	5.6	7.39
29	1.6	3.53
30	3.6	5.08
31	4.1	5.68
32	3.1	4.90
33	4.5	6.68
34	5.7	7.33
35	4.2	5.68
36	3.5	4.77
37	2.1	4.44
38	5.3	6.75
39	4.4	6.06
40	3.2	5.27

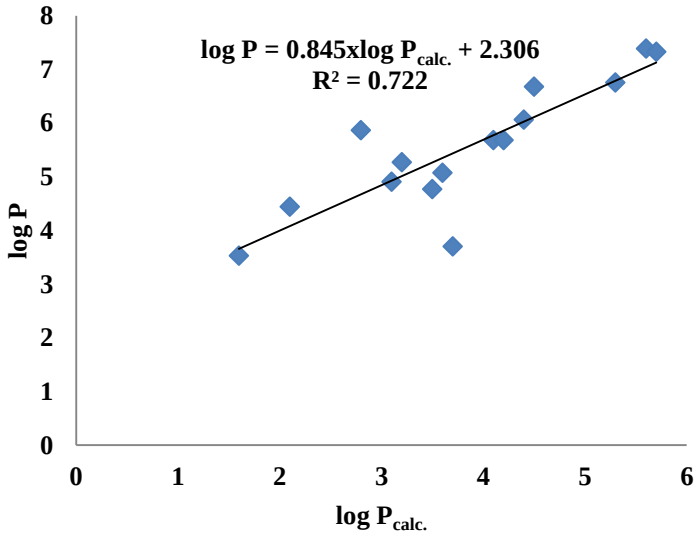


Figure 23. The plot log P vs. log $P_{calc.}$ for the test set (external validation)

(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. 9, Table 27. Data are listed in Table 30 and the monovariate correlation: : $\log P = 0.943 \times \log P_{calc.} + 0.376$; n=15; R^2=0.951; s=0.273; F=254.62 is plotted in Figure 24.

Table 30. Calculated values of log P for the molecules in the test set (Table 1)

Mol.	logP	$logP_{calc.}$
26	3.7	3.70
27	2.8	2.96
28	5.6	5.43
29	1.6	1.60
30	3.6	3.52
31	4.1	4.34
32	3.1	3.72
33	4.5	4.97
34	5.7	5.86
35	4.2	4.42
36	3.5	3.28
37	2.1	2.45
38	5.3	5.14
39	4.4	4.62
40	3.2	3.75

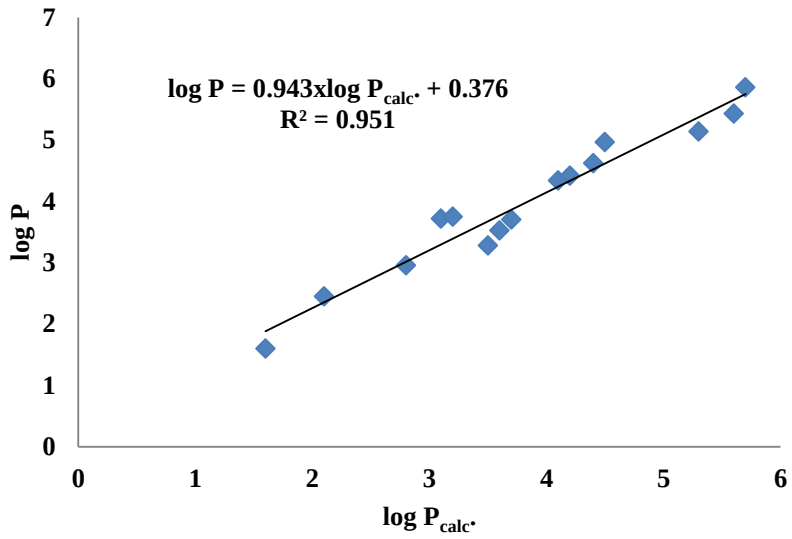


Figure 24 The plot log P vs. log P calc. for the test set (external validation)

(b) External Validation

The values LD50 for the test set of testosterone (last 15 structures) were calculated by using the best equation in Table 31, entry 14. Data are listed in Table 33 and the monovariate correlation: $LD50 = 883.48 + 0.655 \times LD50_{calc.}$;n=15; R^2=0.658; s=1618.663; F= 24.96 is plotted in Figure 25.

Table 33 . Calculated values of LD50 for the molecules in the test set

Mol.	LD50	$LD50_{calc.}$
1	5000	1497.73
6	595	1660.89
8	980	1240.10
15	980	1240.63
16	980	1694.42
17	980	1009.40
18	980	1544.38
19	980	2120.44
20	250	1940.07
21	5000	1829.83
22	980	1483.04
23	4000	5876.90
24	10000	8954.71
25	980	1694.42
30	1000	1536.21

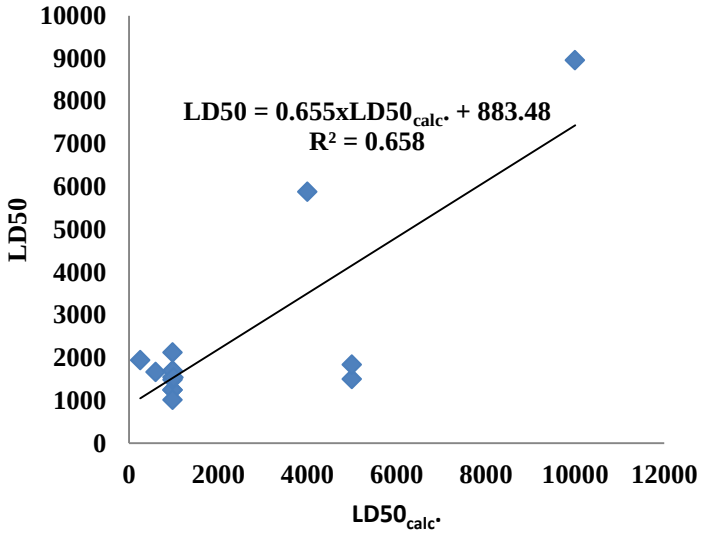


Figure 25. The plot LD50 vs. $LD50_{calc.}$ for the test set (external validation)

(c) Similarity Cluster Validation

Validation was performed by calculating LD50 for the molecules in the test set. The values $LD50_{calc.}$ were computed with the same descriptors as in eq. 14, Table 31. Data are listed in Table 34 and the monovariate correlation: $LD50 = 0.877 \times LD50_{calc.} + 142.53$; n=15; R^2=0.935; s=706.157; F=186.44 is plotted in Figure 26.

Table 34. Calculated values of LD50 by similarity clusters, for the molecules in the test set

Mol.	LD50	$LD50_{calc.}$
1	5000	2507.05
6	595	881.54
8	980	1194.66
15	980	1082.21
16	980	954.23
17	980	985.43
18	980	922.69
19	980	922.69
20	250	612.35
21	5000	4839.34
22	980	944.58
23	4000	4498.85
24	10000	9413.14
25	980	954.23
30	1000	952.63

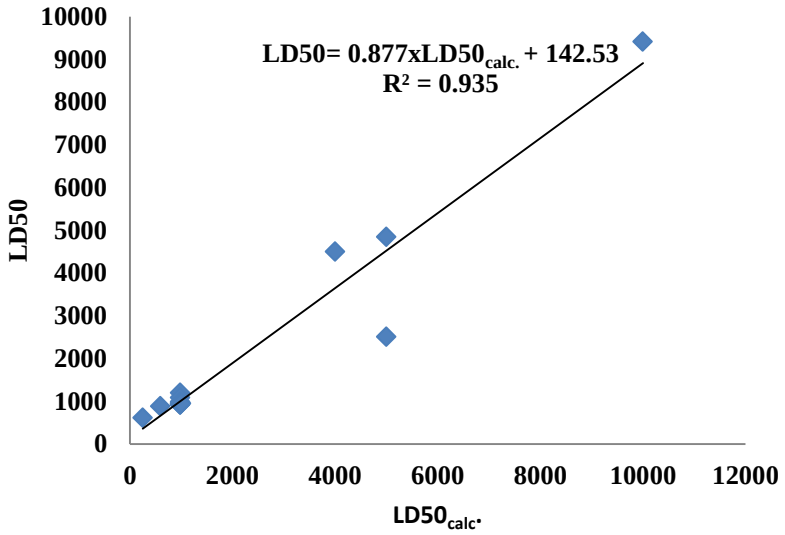


Figure 26. The plot LD50 vs. $LD50_{calc.}$ by similarity clusters

Partial charges description (case 2)

(b) External Validation (log P)

The values log P for the test set of testosterone (Table 24),were calculated by using the best equation in Table 35, entry 10. Data are listed in Table 37 and the monovariate correlation: $\log P = 0.809 \times \log P_{calc.} + 0.722$; n=15; R^2=0.938; s=0.347; F=195.43 is plotted in Figure 27.

Table 37. Calculated values of log P for the molecules in the test set (Table 1)

Mol.	log P	log $P_{calc.}$
1	3.3	3.83
2	4.4	4.55
3	3.4	3.58
4	3.7	3.40
5	6.3	5.94
18	3.5	3.44
19	2.7	2.51
20	1.6	1.78
21	1.6	2.26
22	3.5	3.20
23	1.9	2.54
37	2.1	2.71
38	5.3	5.15
39	4.4	4.06
40	3.2	3.07

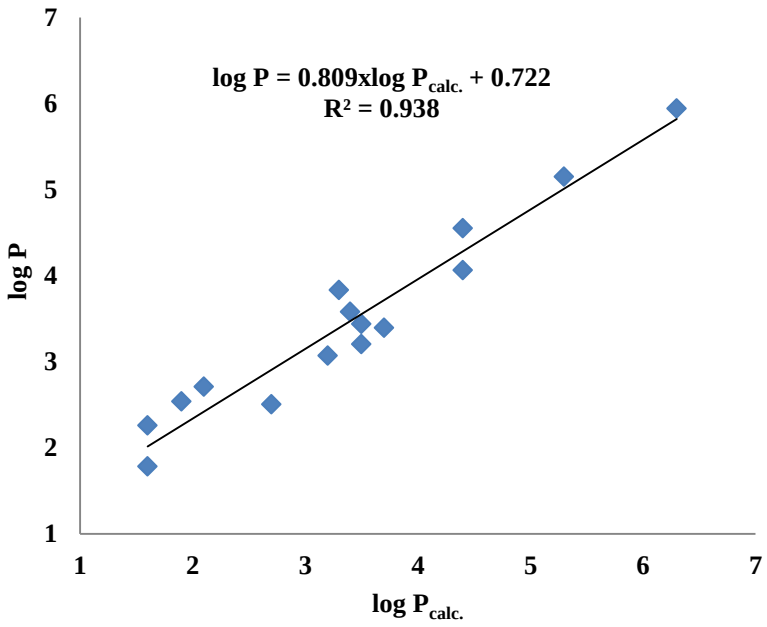


Figure 27. The plot log P vs. log P calc. for the test set (external validation)

(c) Similarity Cluster Validation

Validation was performed by calculating log P for the molecules in the test set. The values log $P_{calc.}$ were computed with the same descriptors as in eq. 10, Table 35. Data are listed in Table 38 and the monovariate correlation: $\log P = 0.900 \times \log P_{calc.} + 0.443$; n=15; R^2=0.97; s=0.240; F=420.87 is plotted in Figure 28.

Table 38. Calculated values of log P by similarity clusters, for the molecules in the test set

Mol.	log P	log $P_{calc.}$
1	3.3	3.65
2	4.4	4.42
3	3.4	3.62
4	3.7	3.71
5	6.3	6.13
18	3.5	3.48
19	2.7	2.52
20	1.6	1.59
21	1.6	2.12
22	3.5	3.31
23	1.9	2.41
37	2.1	2.56
38	5.3	5.45
39	4.4	4.27
40	3.2	3.23

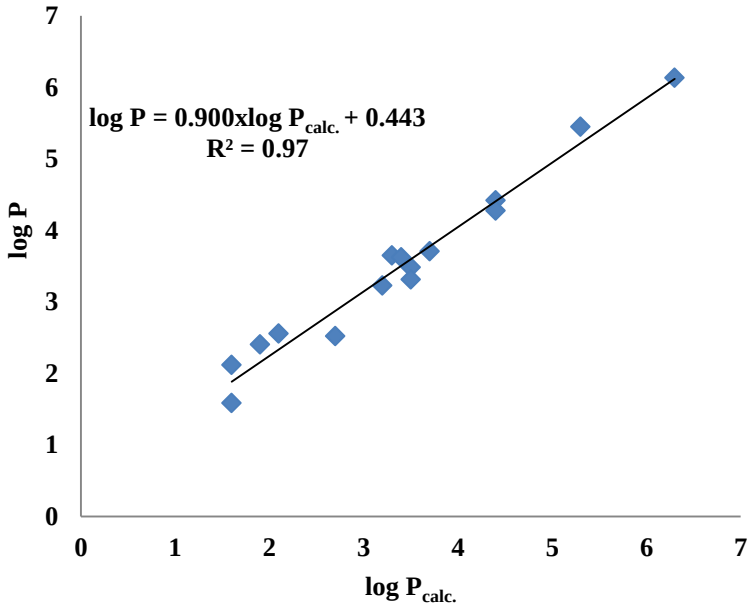


Figure 28. The plot Log P vs. log $P_{calc.}$ by similarity clusters

(a) External Validation The values LD50 for the test set of testosterone,were calculated by using the best equation in Table 39, entry 10. Data are listed in Table 41 and the monovariate correlation: $LD50 = 0.830 \times LD50_{calc.} + 839.36$; n=15; R^2=0.840; s=1039.906; F=68.31 is plotted in Figure 29.

Table 41. Calculated values of LD50 for the molecules in the test set

Mol.	LD50	$LD50_{calc.}$
1	5000	2967.99
2	1000	1745.51
3	2500	3699.88
4	980	530.19
5	1000	1834.74
6	595	1619.14
7	980	1563.68
8	980	1751.13
9	2000	2467.30
22	980	3051.90
23	4000	2819.61
24	10000	10376.48
25	980	1666.63
37	980	1973.52
38	980	1886.35

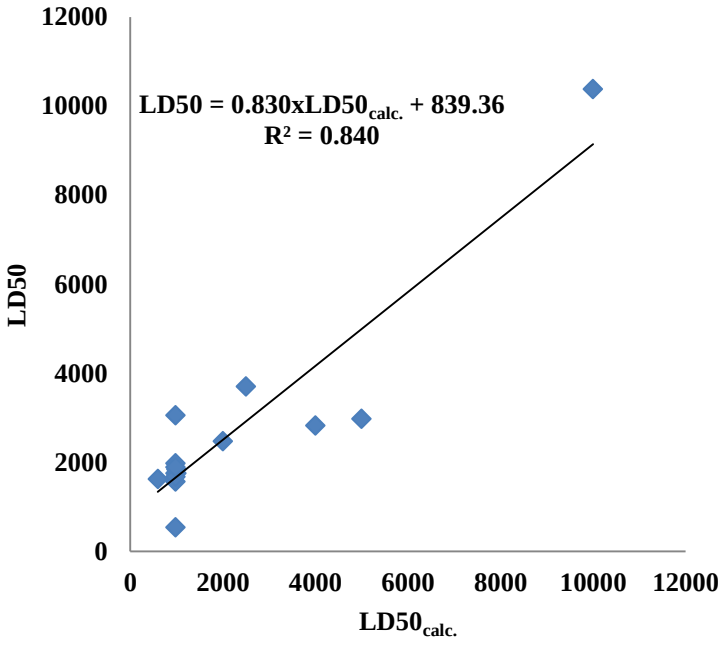


Figure 29. The plot LD50 vs. $LD50_{calc.}$ (external validation)

(b)Similarity Cluster Validation

Validation was performed by calculating LD50 for the molecules in the test set. The values $LD50_{calc}$. were computed with the same descriptors as in eq. 10, Table 39. Data are listed in Table 42 and the monovariate correlation: $LD50 = 464.29 + 0.832 \times LD50_{calc.}$;n=15; R^2=0.943; s=622.801; F= 213.68 is plotted in Figure 30.

Table 42. Calculated values of LD50 by similarity clusters for the molecules in the test set

Mol.	LD50	$LD50_{calc.}$
1	5000	3632.01
2	1000	1382.42
3	2500	3207.06
4	980	1225.48
5	1000	860.77
6	595	350.34
7	980	1372.07
8	980	1282.10
9	2000	2463.65
22	980	1554.78
23	4000	2913.17
24	10000	9339.85
25	980	1722.29
37	980	1303.88
38	980	1758.71

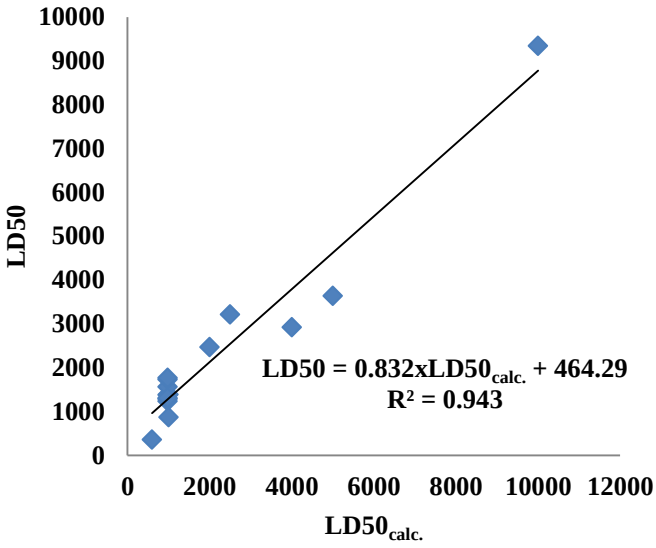


Figure 30. The plot LD50 vs. $LD50_{calc.}$ for the test set by similarity clusters

3. QSAR and docking studies of anthraquinone derivatives

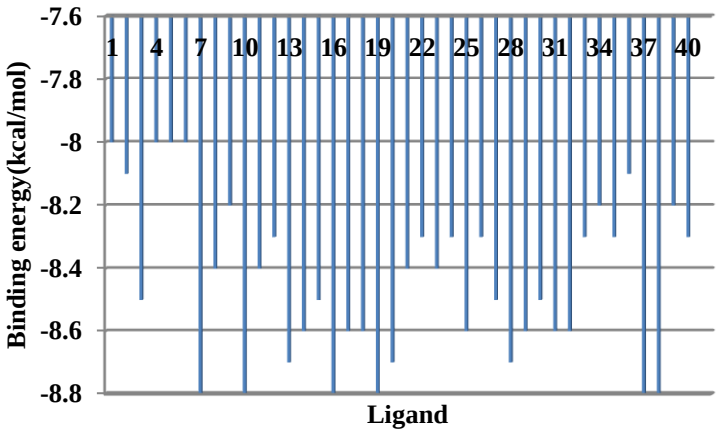
A set of 40 anthraquinones were taken from PubChem Database [122] (Table 43); the set was divided into a training set (25 molecules) and a test set (15 molecules), taken randomly. The property chosen for modeling was log P and LD50 (on rat, oral route administrated, Table 44).

Table 1. Anthraquinone molecular structures and their log P (taken from PubChem)

Nr. Crt.	Canonical SMILES	CID	log P
1	C1=CC=C2C(=C1)C(=O)C3=CC=CC=C3C2=O	6780	3.4
2	C1=CC=C2C(=C1)C(=O)C3=C(C2=O)C=C(C=C3)O	11796	3
3	CC1=CC(=C2C(=C1)C(=O)C3=C(C2=O)C(=CC=C3)O)O	10208	3.5
4	C1C2=C(C(=CC=C2)O)C(=O)C3=C1C=CC=C3O	2202	3.2
5	C1=CC2=CC3=C(C(=CC=C3)O)C(=C2C(=C1)O)O	10187	3.9
6	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=CC=C3O	2950	3.2
7	CC1=C(C2=C(C=C1)C(=O)C3=C(C2=O)C=CC(=C3O)O)O	442756	3.3
8	CC1=C(C=C2C(=C1)C(=O)C3=CC=CC=C3C2=O)O	10889963	2.9
9	C1=C(C=C2C(=C1O)C(=O)C3=C(C=C(C=C3C2=O)O)O)O	3016789	2
10	CC1=CC(=C2C(=C1)C(=O)C3=CC(=C(C(=C3C2=O)O)O)O)O	12548	2.4
11	CC1=CC(=C2C(=C1)CC3=CC(=CC(=C3C2=O)O)O)O	122635	3.2
12	CC1=CC2=C(C=C1)C(=O)C3=C(C2=O)C(=CC=C3)O	155237	3.9
13	CC1=C(C2=C(C=C1)C(=O)C3=C(C2=O)C=CC(=C3)O)O	124063	3.1
14	CC1=C(C2=C(C=C1)C(=O)C3=CC(=C(C=C3C2=O)O)O)O	25202820	2.7
15	CC1=C(C(=C2C(=C1)C(=O)C3=C(C2=O)C=CC=C3O)O)O	12322346	3.3
16	CC1=CC2=C(C=C1)C(=O)C3=C(C2=O)C=CC(=C3O)O	5319503	3.1
17	CC1=CC=CC2=C1C(=O)C3=C(C2=O)C(=C(C=C3)O)O	57536669	3.1
18	CC1=C(C(=C2C(=C1)C(=O)C3=CC=CC=C3C2=O)O)O	429241	3.1
19	CC1=CC(=C2C(=C1)C(=O)C3=C(C2=O)C(=C(C=C3)O)O)O	12313148	2.7
20	CC1=C(C(=C2C(=C1)C(=O)C3=C(C2=O)C(=CC=C3)O)O)O	442759	2.7
21	C1=CC2=C(C(=C1)O)C(=O)C3=CC(=C(C=C3C2=O)O)O	11196140	2.8
22	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C(=C(C=C3)O)O	436367	3.4
23	C1=CC2=C(C=C1O)C(=O)C3=C(C2=O)C(=C(C=C3)O)O	65739	2.4
24	C1=CC=C2C(=C1)C(=O)C3=C(C2=O)C(=C(C=C3)O)O	6293	3.2
25	C1=CC2=C(C=C1O)C(=O)C3=C(C2=O)C=CC(=C3O)O	1320	2.4
26	CC1=C2C(=CC(=C1O)O)C(=O)C3=CC=CC=C3C2=O	11391150	2.5
27	C1=CC(=C(C2=C1C(=O)C3=C(C2=O)C=CC(=C3O)O)O)O	69440	2.5
28	CC1=C(C=C2C(=C1)C(=O)C3=C(C2=O)C(=CC=C3)O)O	71368906	3.1
29	C1=CC(=C(C2=C1C(=O)C3=C(C2=O)C(=C(C=C3)O)O)O)O	22643725	2
30	CC1=C(C=C2C(=C1C)C(=O)C3=C(C2=O)C=CC=C3O)O	57745748	3.4
31	CC1=C(C2=C(C=C1)C(=O)C3=CC(=C(C(=C3C2=O)O)O)O)O	25203424	2.4
32	CC1=C(C(=C2C(=C1)C(=O)C3=CC(=CC(=C3C2=O)O)O)O)O	11818503	2.4
33	CC1=C2C(=CC(=C1)O)C(=O)C3=C(C2=O)C(=CC=C3)O	3085033	3.1
34	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=CC(=C3)O	14886011	3.2
35	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3)O	12628831	3.2
36	C1=CC=C2C(=C1)C(=O)C3=CC(=C(C=C3C2=O)O)O	11031986	2.7
37	CC1=C(C=C2C(=C1)C(=O)C3=C(C2=O)C=C(C=C3)O)O	10060853	2.5
38	CC1=CC(=C(C2=C1C(=O)C3=C(C=C(C=C3C2=O)O)O)O)O	9817337	2.9
39	C1=CC(=C(C2=C1C(=O)C3=C(C=CC(=C3C2=O)O)O)O)O	5004	2.5
40	C1=C2C(=CC(=C1O)O)C(=O)C3=CC(=C(C=C3C2=O)O)O	44300874	1.4

Figure 33 shows the binding energies of the ligand docking.

Figure 33: Binding energy (kcal/mol) for the docked ligands



To obtain the pharmacophore for the interaction of anthraquinones with the 3Q3B protein, which could be inferred in their toxicity, the conformers with the highest affinity, as resulted from the docking procedure, have been selected; these are ligands 7, 10, 16, 19, 37 and 38 (binding energy -8.8 kcal/mol). The resulting pharmacophore is shown in Figure 34 (a and b).

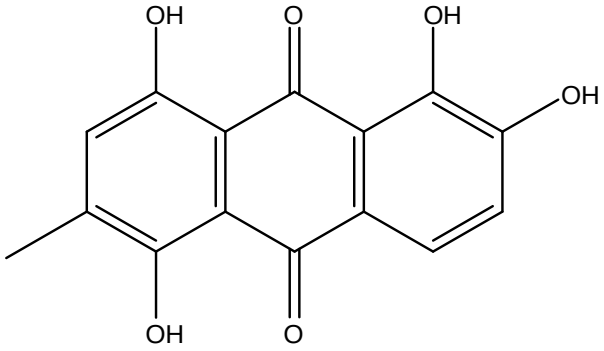


Figure 34(a): Pharmacophore model for the receptor Glycogen synthase kinase-3 beta

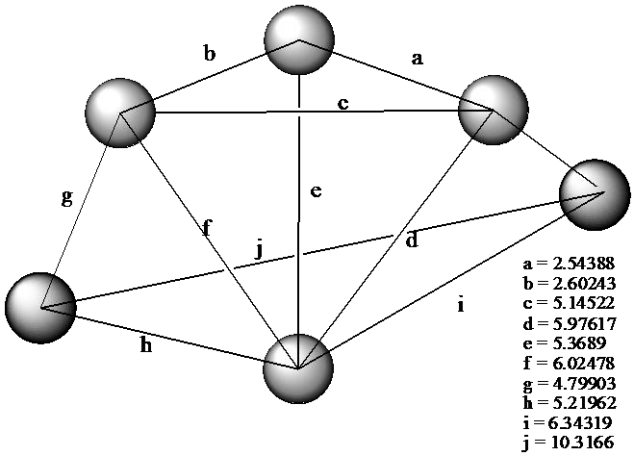


Figure 34(b): Selected data on the pharmacophore model of anthraquinone/3Q3B protein interaction.

(b) External Validation

The values log P for the test set of anthraquinones were calculated by using equation 11 in Table 49. Data are listed in Table 51 and the monovariate correlation: $\log P = 0.934 \times \log P_{calc.} + 0.298$; n=15; R^2=0.754; s=0.201; F=39.749 is plotted in Figure 35.

Table 51. Calculated values of log P for the molecules in the test set (mass fragments) Table 1

Molecules	log P	log $P_{calc.}$
1	3.4	3.69
2	3	2.92
4	3.2	3.64
5	3.9	3.64
8	2.9	3.12
11	3.2	3.39
12	3.9	4.06
13	3.1	3.32
14	2.7	2.77
16	3.1	3.23
17	3.1	3.13
18	3.1	3.23
24	3.2	3.01
26	2.5	2.80
36	2.7	2.45

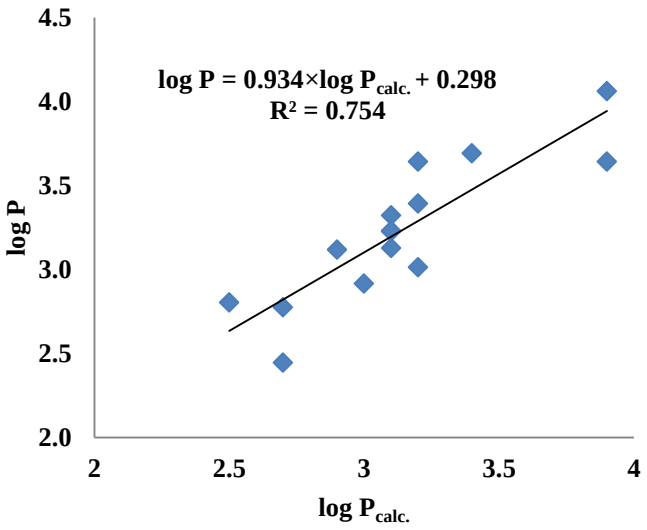


Figure 35. The plot log P vs. log $P_{calc.}$ for the test set (mass fragments, external validation)

(c) Similarity Cluster Validation

Clusters of similarity were performed by using as leaders the 15 molecules in the external set; each leader will have its own cluster, selected by 2D similarity among the 25 structures of the initial learning set. The values log $P_{calc.}$ were computed by 15 new equations (the leader being left out) with the same descriptors as in eq. 11, Table 49. Data are listed in Table 52 and the monovariate correlation: $\log P = 1.039 \times \log P_{calc.} - 0.042$; n=15; R^2=0.961; s=0.080; F=317.747 is plotted in Figure 36.

Table 52. Calculated values of log P by similarity clusters, for the molecules in the test set (mass fragments), Table 1

Molecules	log P	log $P_{calc.}$
1	3.4	3.47
2	3	2.91
4	3.2	3.35
5	3.9	4.06
8	2.9	3.04
11	3.2	3.32
12	3.9	4.00
13	3.1	3.29
14	2.7	2.75
16	3.1	3.19
17	3.1	3.13
18	3.1	3.20
24	3.2	3.13
26	2.5	2.65
36	2.7	2.69

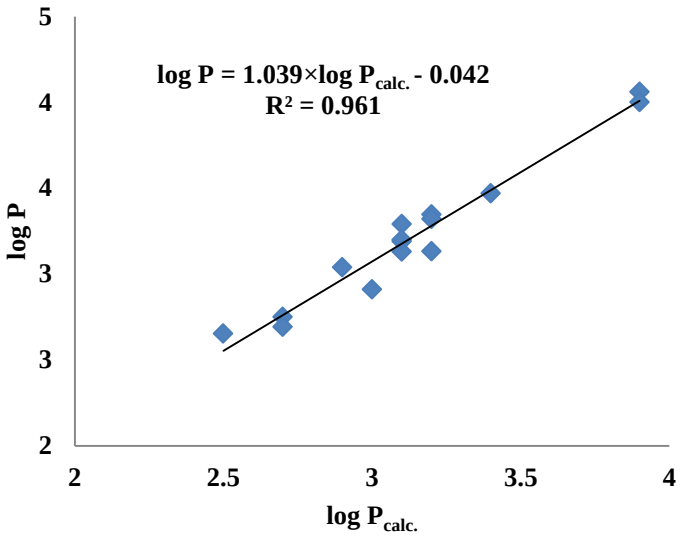


Figure 36. The plot log P vs. log $P_{calc.}$ by similarity clusters (mass fragments)

Partial charges description; LD50.

(b) External Validation

The values $LD50_{calc.}$ for each of the 12 molecules in the test set were chosen based on the lowest energy docking and computed with the same descriptors and the eq. 10, Table 57. Data are listed in Table 59 and the monovariate correlation: $LD50 = 0.866 \times LD50_{calc.} + 545.6$; n=12; R^2=0.904; s=477.245; F=95.201 plotted in Figure 39.

Table 59. Calculated values of LD50 for the molecules in the test set, (partial charges)

Mol.	LD50	$LD50_{calc.}$
3	2500	2586.67
7	1230	1850.72
13	4000	3709.78
14	2000	2484.99
16	2795	1980.80
18	5000	4816.41
19	35	688.14
20	308	366.56
25	1870	2448.36
28	2795	3423.44
32	3950	4365.44
38	2795	3185.28

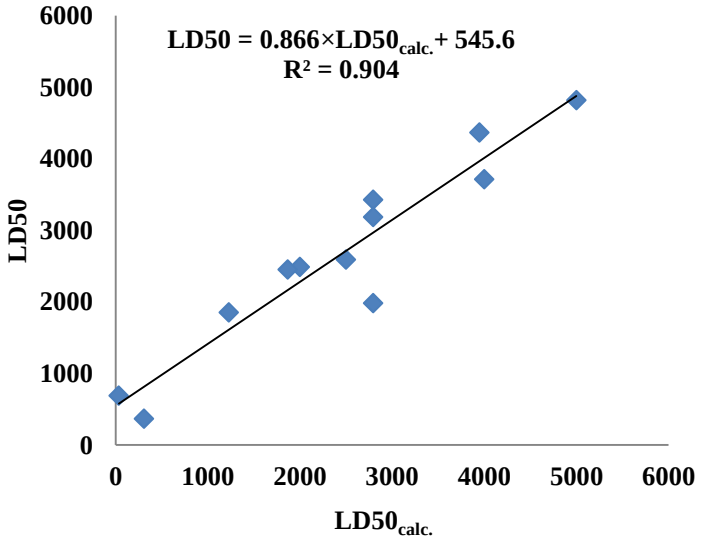


Figure 39. The plot LD50 vs. LD50 $_{calc.}$ for the test set (partial charges, external validation)

(c) Similarity Cluster Validation

The clusters of similarity in this section were performed by using as leaders the 12 molecules best scored in the docking step.

The predicted values LD50 are listed in Table 60 and the monovariate correlation: $LD50 = 0.861 \times LD50_{calc.} + 506.19$; n=12; R^2=0.959 s=314.696; F=231.948 plotted in Figure 40.

Table 60. Calculated values of LD50 by similarity clusters, for the molecules in the test set (partial charges)

Mol.	LD50	$LD50_{calc.}$
3	2500	2528.503
7	1230	1622.526
13	4000	3463.02
14	2000	2377.399
16	2795	2796.373
18	5000	4810.405
19	35	594.5576
20	308	366.6446
25	1870	2432.604
28	2795	3328.103
32	3950	4081.971
38	2795	2872.895

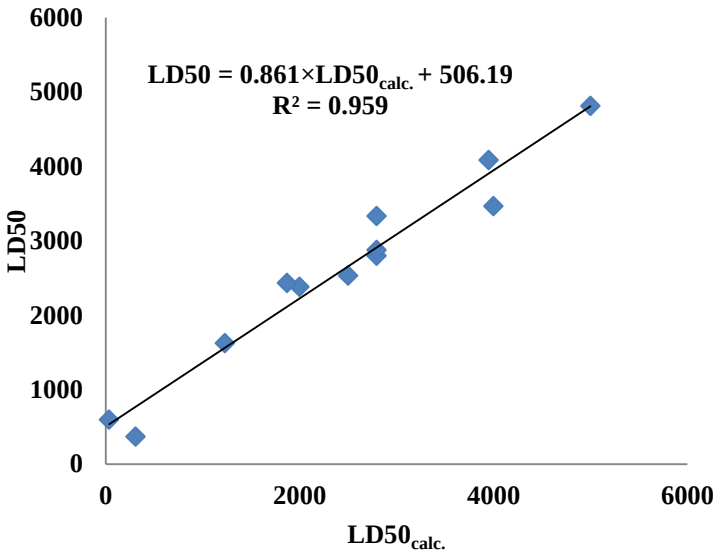


Figure 40. The plot LD50 vs. LD50 $_{calc.}$ by similarity clusters (partial charges)

4. QSAR and docking studies of resveratrol derivatives

4.1. QSAR studies of resveratrol derivatives

A set of 40 resveratrol derivatives, taken from PubChem Database [129] (Table 61), were divided into a training set (25 molecules) and a test set (15 molecules), taken randomly; the modelled property was log P .

Table 61. 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
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

(b) External Validation

The values log P for the test set of resveratrols (Table 61) were calculated by using the best equation (with three variables) in Table 63, entry 10. Data are listed in Table 65 and the monovariate correlation: $\log P = 0.763 \times \log P_{calc.} + 0.876$; n=15; R2=0.859; s=0.411; F=79.105 is plotted in Figure 42.

Table 65. Calculated values of log P for the molecules in the test set

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

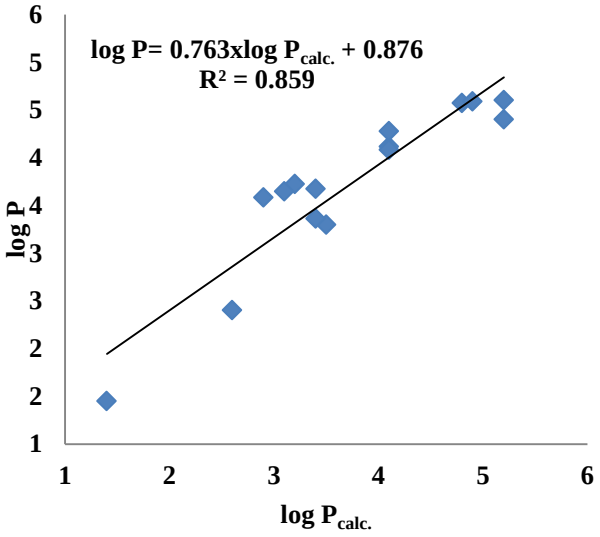


Figure 42. The plot log P vs. log Pcalc. for the test set (external validation)

(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 67. Data are listed in Table 67 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 44.

Table 66. Calculated values of log P by similarity clusters, for the molecules in the test set

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

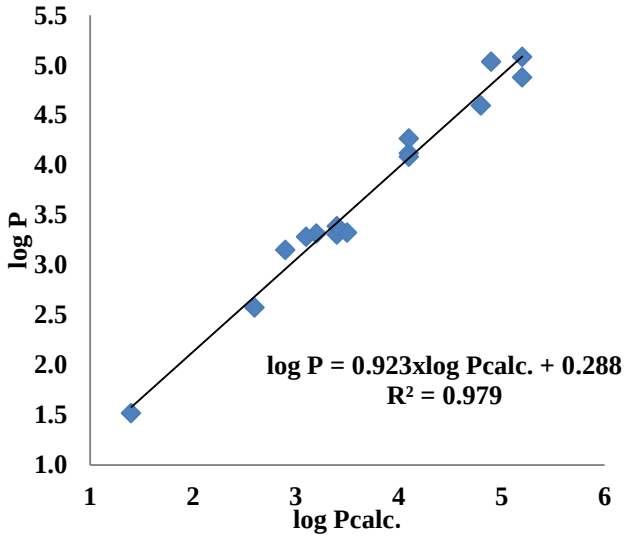


Figure 43. The plot log P vs. log P calc. for the test set (similarity clusters)

Partial charges description (case 2)

Model Validation (for log P)

(b) External Validation

The values log P for the test set of resveratrols (Table 61),were calculated by using the best equation in Table 67, entry 11. Data are listed in Table 69 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 44.

Table 69. Calculated values of log P for the molecules in the test set (Table 61)

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

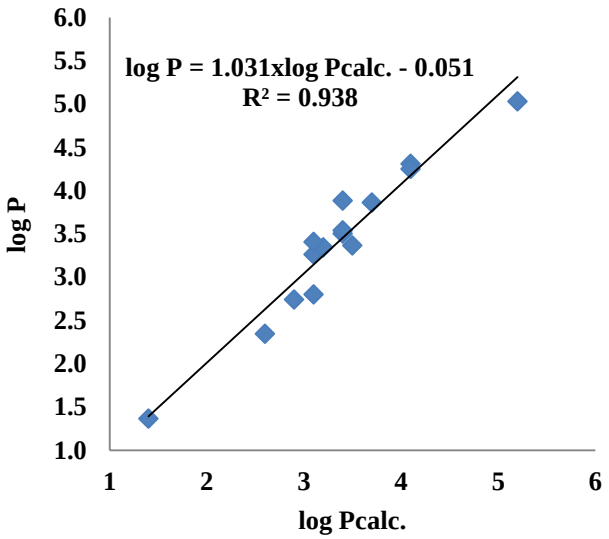


Figure 44. The plot log P vs. log Pcalc. for the test set (external validation)

(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 67. Data are listed in Table 70 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 45.

Table 70. Calculated values of log P by similarity clusters, for the molecules in the test set

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

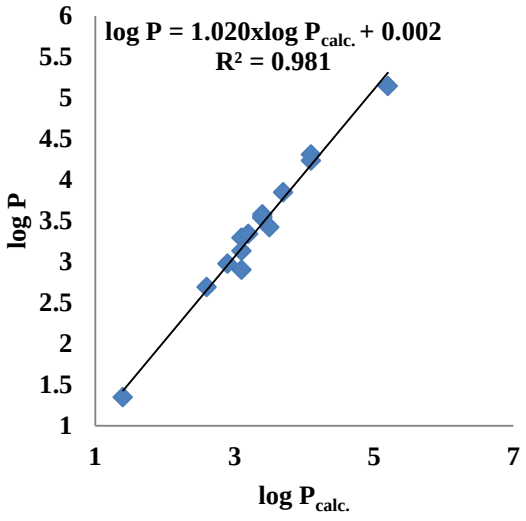


Figure 45. The plot log P vs. log P calc. for the test set (similarity clusters)

4.2. DOCKING STUDY

The molecular docking study was carried out to explore the binding mode of resveratrol derivatives (Table 1) within the stilbene synthase and to understand their structure activity relationship using AutoDock Vina as docking software [131, 132].

To study the interaction between resveratrol derivatives and 1Z1F protein (see Figure 47), AutoDock Vina,a molecular modeling program was run, to simulate the binding between resveratrol derivatives and 1Z1F (Table 68).

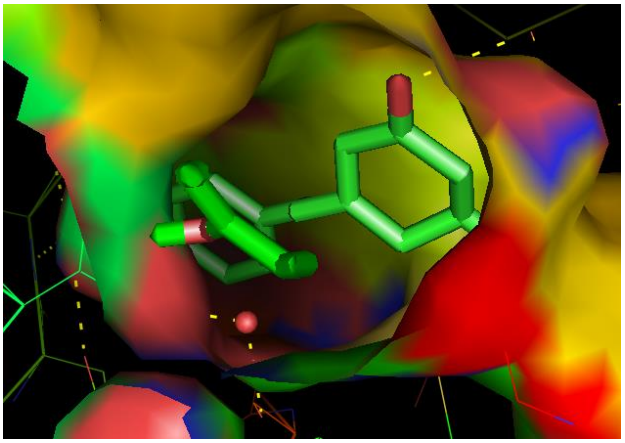


Figure 68: The interaction of resveratrol whit Stilbene synthase

To obtain a pharmacophore model for receptor resveratrol Stilbene synthase was chosen conformers with the most favorable interactions with the receptor resulting from docking. Ligands 8, 3, 32, 5, 31 have the lowest binding energy between -7.3 and -7.0, based on this compound we constructed the pharmacophore. The resulting pharmacophore is shown in Figure 68.

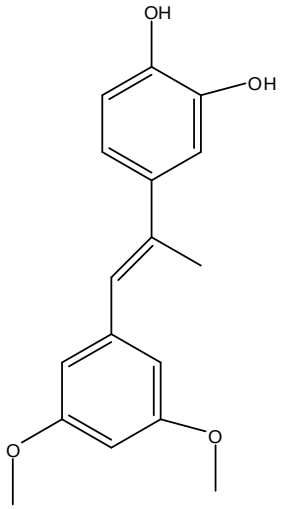


Figure 68: Pharmacophore model for the receptor resveratrol Stilbene synthase

CONCLUSIONS

The present study aimed to treat and obtaining of theoretical methods of obtaining new compounds with biological properties particular to be able to be used in industry, production of new drugs without being required testing them on animals so as to reduce the cost of production.

Molecular docking permit assessment of the binding mode of ligand molecules to the biologically active site of the receptor protein such that the binding energy is minimized. Molecular Docking require information about biological receptor and using QSAR method allows the correlation of biological activity shown by the following classes of compounds: flavonoids, testosterone, anthraquinones and resveratrol.

A new QSAR approach based on correlation weight or partial loads hipermoleculei was done on several classes of compounds: flavonoids, testosterone, anthraquinones that resveratrol or downloaded from the database PubCHEM. A new procedure similar to "alignment" of drug molecules from biological receptor.

The dataset was divided into a school set and test set, the last is used to validate the model, the so-called "external validation set". Validation also is achieved by a new version of prediction using clusters of similarity. Clusters of similarity enables a set of structures "quasi-congener", demonstrating a better prediction than in the classical case of external validation.

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