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Original Research Paper

QSAR AND DOCKING STUDIES OF CHLORPROPAMIDE DERIVATES

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ABSTRACT

A study of 40 chlorpropamide derivatives, QSAR (Quantitative Structure Activity Relationship) and molecular docking approaches were applied to explore the structural requisites of chlorpropamide derivatives for CYTOCHROME P450 2C9 inhibitory activity. A set of forty chlorpropamide, was modeled, within the hypermolecule strategy; the predicted activity was LD_{50} and prediction was done on similarity clusters with the leaders chosen as the best docked ligands on the CYTOCHROME P450 2C9.

Keywords: Chlorpropamide, QSAR, log P, Similarity, Hypermolecule, Leave-one-out, AUTODOCK Vina, Docking, Receptor.

INTRODUCTION

Chlorpropamide is an oral hypoglycemic agent which lower blood glucose levels, which may result in coma, and may require hospitalization.[1] Chlorpropamide increase the secretion of insulin and also used in partial central diabetes insipidus.[2] Ability to control the drug opens new routes to discover a new compound.[3] QSAR approaches have successfully produced many classification and regression models that accurately predict a variety of LD_{50} properties for a diverse array of compounds.[4] The present work focuses on the molecular docking analysis of chlorpropamide and its analogues against protein.[5] This work was carried out by molecular docking studies to determine whether 40 molecules of chlorpropamide interact whit protein CYTOCHROME P450 2C9 and to find the orientation that enhances this interaction as well as minimizing the total energy of the interaction complex.[6,7] The compounds in the test set have a range of biological activity values similar to that of the training set. QSARs are based on Graph Theory, one of the most common techniques used in similarity cluster validation, using macromolecular descriptors, named topological indexes are calculated.[8,9]

In the present study, a molecular docking analysis has been performed on 40 chlorpropamide derivatives on the protein 1OG5, then we made a QSAR study to predicting LD_{50} of chlorpropamide derivatives. For targeting protein 1OG5 interactions, the critical binding motifs were replaced by chlorpropamide derivative ligands. The ligands will be ranked according to their binding affinity for the receptor.

In this article, we propose a new approach that develops clusters of similar structures aimed to be quasi-congeneric subsets in a better prediction of the toxicology activity, even the test set has been chosen the one with the lowest docking energies.

Structural Molecular Data

A set of 40 were taken from PubChem Database[10] (Table 1); 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 (calculated, Table 1) and LD_{50} (on mouse, oral route administrated, Table2).

Table 1: Chlorpropamide molecular structures and their log P (taken from PubChem)

Mol.	Canonical SMILES	log P	LD50
1	CCCNC(=O)NS(=O)(=O)C1=CC=C(C=C1)Cl	2.3	580
2	CCCCNC(=O)NS(=O)(=O)C1=CC=C(C=C1)C	2.3	490
3	CCCCNC(=O)NS(=O)(=O)C1=CC=C(C=C1)CO	1.1	490
4	CCCCNC(=O)NS(=O)(=O)C1=CC=C(C=C1)C(=O)O	1.7	490
5	COCCOC1=CN=C(N=C1)NS(=O)(=O)C2=CC=CC=C2	1.1	2800
6	C1=CC(=CC=C1N)S(=O)(=O)NC(=S)N	-0.7	3240
7	C1COCCN1S(=O)(=O)C2=CC=C(C=C2)N	0.1	2150
8	CC(=O)NCCC1=CC=C(C=C1)S(=O)(=O)Cl	1.6	200
9	CC1=CC=C(C=C1)S(=O)(=O)NC(=NCC2=CC=CC=C2)SC	3.8	300
10	CC(=O)NC1=CC=C(C=C1)S(=O)(=O)NC(=NCC2=CC=CC=C2)SC	2.6	300
11	CCOC(=O)NC1=CC=C(C=C1)S(=O)(=O)N2CCOCC2	0.6	2500
12	CC1=CC(=NC(=N1)NS(=O)(=O)C2=CC=C(C=C2)N)C	0.3	50000
13	COC1=CN=C(N=C1)NS(=O)(=O)C2=CC=C(C=C2)N	0.4	16000
14	C1=C(C(=CC(=C1Cl)Cl)Cl)NS(=O)(=O)C2=C(C(=CC(=C2Cl)Cl)Cl)Cl)O	6.4	179
15	CC1=C(ON=C1C)NS(=O)(=O)C2=CC=C(C=C2)N	1	6800
16	C1=CC(=CC(=C1)S(=O)(=O)N)N	-0.4	4500
17	C1=CC(=C(C=C1S(=O)(=O)N)Cl)N	0.8	2850
18	CNS(=O)(=O)C1=CC(=C(C=C1)N)Cl	1.2	3000
19	CC(=O)NC1=C(C=C(C=C1)S(=O)(=O)N)Cl	0.1	5000
20	C1=CC(=CC=C1S(=O)(=O)N)Br	1.4	1700
21	CCS(=O)(=O)C1=CC=C(C=C1)F	1.6	542
22	COS(=O)(=O)C1=CC=CC=C1	1.2	250
23	C1=CC(=CC=C1O)S(=O)(=O)O	0.2	6400
24	C1=CC(=CC=C1OS(=O)(=O)C2=CC=C(C=C2)Cl)Cl	4.3	1475
25	CC1=C(C=C(C=C1)S(=O)(=O)O)N(CCCl)CCCl	2.3	200
26	CS(=O)(=O)OC1=C(C=C(C=C1)Cl)Cl	2.8	1070
27	C1=CC(=C(C=C1S(=O)(=O)N)Cl)N	0.8	2950
28	CCS(=O)(=O)C1=CC=C(C=C1)N	0.2	1000
29	C(CS(=O)(=O)C1=C(C(=C(C(=C1Cl)Cl)C#N)Cl)Cl)CCl	4.3	300
30	CCCCNS(=O)(=O)C1=CC=CC=C1	2.1	2500
31	C1=CC=C(C=C1)NS(=O)(=O)C2=CC=C(C=C2)F	2.3	750
32	CC(=O)NC1=C(C=C(C=C1)S(=O)(=O)NC)Cl	0.5	3000
33	CNS(=O)(=O)C1=CC=C(C=C1)O	0.9	2500
34	C1=CC(=CC=C1N)S(=O)(=O)N	-0.6	3000
41	C1CCC(CC1)NC(=O)NS(=O)(=O)C2=CC=C(C=C2)Cl	3.4	1525
36	CC1=NC(=NC=C1)NS(=O)(=O)C2=CC=C(C=C2)N	0.1	25000
37	COC1=NC(=NC(=C1)NS(=O)(=O)C2=CC=C(C=C2)N)OC	1.6	3200
38	CC1=CC(=NC(=N1)NS(=O)(=O)C2=CC=C(C=C2)N)C(F)(F)F	0.8	4150
39	C1=CC(=CC(=C1)S(=O)(=O)NC2=NC=C(C=N2)Cl)N	1.1	700
40	COC1=NC=NC(=C1)NS(=O)(=O)C2=CC=C(C=C2)N	0.8	4680

A hypermolecule (Figure 1) was built up by superposing all the 40 molecules under study. The hypermolecule is considered to mimics the investigated statistical hyperspace.[11] According to the numbering of the hypermolecule positions, *binary vectors* were constructed, with 1 when in the current molecule exists a corresponding atom and zero, otherwise. In the above binary vectors, the values 1 are next replaced by local characteristics mass fragments or local

topological descriptors. We used here mass fragments in building the weighted vector for every molecule; the modeled property was LD_{50} (Table 4).

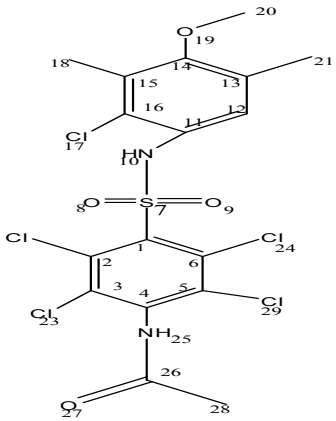

Figure 1: The hypermolecule comprising common features of the dataset

Protein

The protein (Figure 2) was downloaded from RCSB protein data bank, bearing the PDB code- 1OG5.[12]

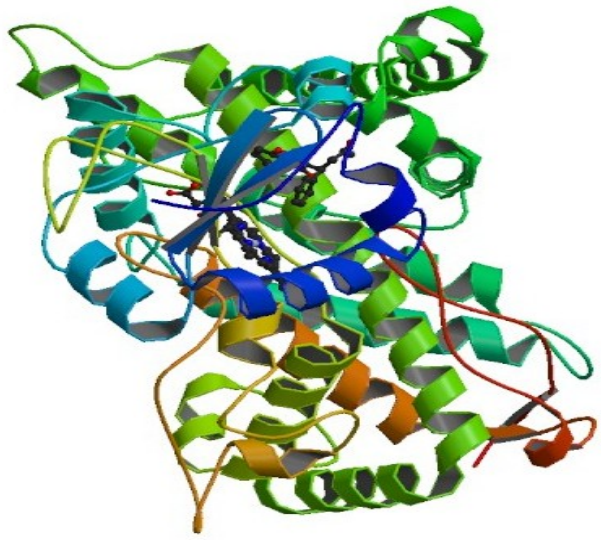

Figure 2: PDB Entry ID: CYTOCHROME P450 2C9 (from RCBS Protein data bank)

Docking Requirements

The software AutoDock Vina v.1.0.2 was used to perform molecular docking of chlorpropamide to CYTOCHROME P450 2C9 isoforms with the crystal structures from the Protein Data Bank. The docking parameters were set to the default values. The grid boxes were 90˚A×90˚A×90A˚, encompassing their active site cavities. The binding modes of chlorpropamide to CYTOCHROME P450 2C9 with lowest binding free energy were chosen for further optimum docking conformation, while probe substrates in the metabolism position closer to the heme sulfur were identified. The simulation results were presented by PyMOL.[13]

Table 2: List of ligands showing their molecular formula, molar mass, hydrogen bond acceptors, hydrogen bond donors, Log P and torsions

Ligand	Log P	Molecular Weight [g/mol]	Molecular Formula	H-Bond Donor	H-Bond Acceptor	Torsions
1	2.3	276.739	$C_{10}H_{13}ClN_2O_3S$	2	3	4
2	2.3	270.351	$C_{12}H_{18}N_2O_3S$	2	3	5
3	1.1	270.351	$C_{12}H_{18}N_2O_4S$	3	4	6
4	1.7	300.330	$C_{12}H_{16}N_2O_5S$	3	5	5
5	1.1	271.339	$C_{13}H_{15}N_3O_4S$	1	7	5
6	-0.7	231.299	$C_7H_9N_3O_2S_2$	3	4	1
7	0.1	242.298	$C_{10}H_{14}N_2O_3S$	1	5	3
8	1.6	261.728	$C_{10}H_{12}ClNO_3S$	1	4	5
9	3.8	334.462	$C_{16}H_{18}N_2O_2S_2$	1	4	6
10	2.6	377.487	$C_{17}H_{19}N_3O_3S_2$	2	5	7
11	0.6	314.360	$C_{13}H_{18}N_2O_5S_2$	1	7	5
12	0.3	278.334	$C_{12}H_{14}N_4O_2S$	2	6	4
13	0.4	280.307	$C_{11}H_{12}N_4O_3S$	2	7	5
14	6.4	455.959	$C_{12}H_5Cl_6NO_3S$	2	4	3
15	1	267.307	$C_{11}H_{13}N_3O_3S$	2	6	4
16	-0.4	172.204	$C_6H_8N_2O_2S$	2	4	3
17	0.8	206.652	$C_6H_7ClN_2O_2S$	2	4	4
18	1.2	220.679	$C_7H_9ClN_2O_2S$	2	4	4
19	0.1	248.689	$C_8H_9ClN_2O_3S$	2	4	4
20	1.4	236.088	$C_6H_6BrNO_2S$	1	3	2
21	1.6	188.219	$C_8H_9FO_2S$	0	3	2
22	1.2	172.201	$C_7H_8O_3S$	0	3	2
23	0.2	174.175	$C_6H_6O_4S$	2	4	3
24	4.3	303.164	$C_{12}H_8Cl_2O_3S$	0	3	4
25	3.4	316.807	$C_{13}H_{17}ClN_2O_3S$	2	3	3
26	2.8	241.093	$C_7H_6Cl_2O_3S$	0	3	2
27	0.8	206.652	$C_6H_7ClN_2O_2S$	2	4	3
28	0.2	185.246	$C_8H_{11}NO_2S$	1	3	3
29	4.3	381.493	$C_{10}H_6Cl_5NO_2S$	0	3	4
30	2.1	213.299	$C_{10}H_{15}NO_2S$	1	3	4
31	2.3	251.280	$C_{12}H_{10}FNO_2S$	1	4	3
32	0.5	262.715	$C_9H_{11}ClN_2O_3S$	2	4	3
33	0.9	187.218	$C_7H_9NO_3S$	2	4	3
34	-0.6	172.207	$C_6H_8N_2O_2S$	2	4	3
35	-0.7	231.299	$C_7H_9N_3O_2S_2$	3	4	5
36	0.1	264.308	$C_{11}H_{12}N_4O_2S$	2	6	4
37	1.6	310.332	$C_{12}H_{14}N_4O_4S$	2	8	6
38	0.8	332.305	$C_{12}H_{11}F_3N_4O_2S$	2	9	5
39	1.1	284.726	$C_{10}H_9ClN_4O_2S$	2	6	4
40	0.8	280.306	$C_{11}H_{12}N_4O_3S$	2	7	2

Computational Details

The structures have been optimized at PM3 and MM^{+}.[14] Topological indices have beed computed by TOPOCLUJ software[15]; some of them (Centric index of partial charges shells=Cen, Total adjacency = Adj, Detour = De, Distance = Di, D3D, SD), HOMO and LD_{50} are listed in Table 3.

Table 3: Topological indices computed for the in Table 1

Mol.	LD_{50}	SD	Homo	Ch	D3D	De	Di
1	580	64648.29	-10.04	0.15	650	730	570
2	490	64648.29	-9.74	0.03	770	870	690
3	490	64648.29	-9.61	0.10	890	1000	810
4	490	64648.29	-8.08	0.30	1000	1100	930
5	2800	64648.29	-10.15	0.05	770	870	690
6	3240	68090.50	-7.51	0.10	360	440	310
7	2150	67983.47	-9.19	-0.43	470	740	430
8	200	61608.92	-10.01	-0.08	510	630	470
9	300	66807.86	-8.81	0.18	1000	1600	1200
10	300	67260.78	-9.08	0.25	1400	2300	1700
11	2500	66234.93	-9.68	0.01	1100	1500	1000
12	50000	113734.93	-9.22	-0.35	730	1200	720
13	16000	79734.93	-9.25	-0.22	720	1100	760
15	6800	64938.32	-8.93	-0.20	650	970	610
16	4500	62046.72	-9.15	-0.23	180	250	150
17	2850	68851.22	-10.36	-0.22	230	310	190
18	3000	66666.35	-7.20	-0.28	290	370	240
19	5000	67706.79	-8.82	0.02	410	540	380
20	1700	67253.87	-10.64	-0.16	190	250	150
21	542	65069.00	-10.89	-0.02	240	300	200
22	250	65069.00	-8.13	-0.30	170	250	150
23	6400	67253.87	-8.10	-0.16	190	250	150
24	1475	64958.41	-8.24	-0.23	550	1000	640
25	200	63934.93	-10.07	0.07	990	1300	890
26	1070	65069.00	-9.15	0.15	270	390	250
27	2950	69835.92	-9.19	0.02	220	310	190
28	1000	67651.05	-9.22	-0.09	230	300	200
29	300	62247.53	-9.67	0.53	740	970	660
30	2500	65555.20	-9.99	0.03	290	380	260
31	750	65340.26	-9.34	0.09	560	870	540
32	3000	64537.21	-9.53	0.22	430	540	390
32	3000	64537.21	-9.53	0.22	430	540	390
33	2500	65069.00	-9.90	0.05	230	300	200
34	3000	69835.92	-9.31	-0.06	190	250	150
35	1525	68090.50	-9.10	-0.09	330	440	310
36	25000	78412.34	-9.01	-0.17	630	1000	640
37	3200	67211.11	-7.19	0.06	870	1500	940
39	700	70623.14	-9.11	0.24	600	1000	630
40	4680	66647.42	-9.67	0.25	630	1200	740

The models fit abilities were assessed by the cross-validation leave one out analysis[16] using a dedicated software.[17,18]

RESULTS AND DISCUSSION

Docking Results

Table 4: The final lamarckian genetic algorithm docked state – Binding energy of ligands With the active site of the protein during nine conformations

Ligand	1	2	3	4	5	6	7	8	9	Docked Energy (kcal/mol)
1	-7.0	-6.9	-6.7	-6.5	-6.5	-6.5	-6.4	-6.4	-6.2	-7.0
2	-5.8	-5.6	-5.4	-5.3	-5.3	-5.2	-5.2	-5.1	-5.1	-5.8
3	-6.2	-6.2	-6.1	-6.0	-6.0	-5.8	-5.8	-5.5	-5.5	-6.2
4	-6.0	-5.9	-5.9	-5.7	-5.6	-5.6	-5.5	-5.5	-5.5	-6.0
5	-5.6	-5.2	-5.0	-4.8	-4.7	-4.7	-4.6	-4.5	-4.5	-5.6
6	-7.1	-6.7	-6.2	-5.8	-5.8	-5.6	-5.3	-5.3	-5.2	-7.1
7	-6.6	-6.3	-6.1	-5.5	-5.4	-5.4	-5.3	-5.3	-5.2	-6.6
8	-5.7	-5.6	-5.0	-4.7	-4.6	-4.4	-4.2	-4.0	-4.0	-5.7
9	-5.0	-5.0	-4.9	-4.8	-4.1	-4.1	-3.9	-3.9	-3.9	-5.0
10	-5.3	-5.0	-5.0	-4.8	-4.7	-4.7	-4.5	-4.5	-4.3	-5.3
11	-5.2	-4.9	-4.8	-4.7	-4.4	-4.4	-4.3	-4.3	-4.2	-5.2
12	-7.6	-7.6	-7.4	-7.4	-7.2	-7.2	-7.1	-7.1	-6.7	-7.6
13	-6.9	-6.7	-6.0	-5.9	-5.6	-5.5	-5.4	-5.2	-5.2	-6.9
14	-5.7	-5.6	-5.5	-5.4	-5.4	-5.4	-5.3	-5.3	-5.3	-5.7
15	-5.4	-5.1	-5.1	-5.0	-4.9	-4.9	-4.9	-4.8	-4.8	-5.4
16	-5.7	-5.5	-5.5	-5.3	-4.9	-4.8	-4.7	-4.5	-4.4	-5.7
17	-5.7	-5.5	-5.3	-5.2	-5.1	-5.0	-4.7	-4.6	-4.6	-5.7
18	-4.6	-4.6	-4.6	-4.5	-4.4	-4.4	-4.4	-4.4	-4.3	-4.6
19	-5.6	-5.0	-4.9	-4.9	-4.8	-4.7	-4.6	-4.5	-4.4	-5.6
20	-4.7	-4.6	-4.5	-4.5	-4.4	-4.4	-4.3	-4.2	-4.2	-4.7
21	-5.7	-5.5	-5.3	-5.1	-5.0	-4.7	-4.3	-4.2	-4.2	-5.7
22	-6.0	-5.8	-5.6	-5.6	-5.3	-5.3	-5.2	-5.1	-5.1	-6.0
23	-5.6	-5.4	-5.4	-5.3	-5.0	-4.9	-4.8	-4.7	-4.5	-5.6
24	-6.5	-6.3	-6.1	-6.0	-5.7	-5.7	-5.5	-5.5	-5.5	-6.5
25	-6.0	-6.0	-5.9	-5.7	-5.7	-5.7	-5.7	-5.6	-5.6	-6.0
26	-5.7	-5.6	-5.6	-5.3	-5.2	-5.1	-5.0	-5.0	-4.9	-5.7
27	-5.8	-5.6	-5.2	-5.1	-5.0	-4.8	-4.6	-4.5	-4.5	-5.8
28	-4.8	-4.5	-4.4	-4.3	-4.3	-4.3	-4.3	-4.3	-4.2	-4.8
29	-6.7	-6.7	-6.5	-5.0	-4.9	-4.8	-4.8	-4.8	-4.7	-6.7
30	-5.6	-5.5	-5.5	-5.5	-5.2	-5.2	-5.2	-5.1	-5.0	-5.6
31	-7.3	-6.4	-5.3	-5.3	-5.1	-5.1	-5.1	-5.0	-5.0	-7.3
32	-6.1	-6.0	-6.0	-5.5	-5.0	-4.7	-4.5	-4.5	-4.4	-6.1
33	-4.4	-4.3	-4.2	-4.2	-4.2	-4.2	-4.1	-4.1	-4.1	-4.4
34	-5.4	-5.1	-4.9	-4.9	-4.7	-4.5	-4.5	-4.3	-4.3	-5.4
35	-4.9	-4.8	-4.8	-4.6	-4.6	-4.5	-4.5	-4.5	-4.4	-4.9
36	-6.4	-6.1	-6.0	-5.9	-5.9	-5.8	-5.8	-5.7	-5.7	-6.4
37	-7.3	-7.0	-5.6	-5.6	-5.5	-5.5	-5.4	-5.3	-5.3	-7.3
38	-6.2	-6.2	-6.1	-6.0	-6.0	-5.9	-5.8	-5.8	-5.8	-6.2
39	-8.9	-8.7	-8.2	-8.0	-8.0	-8.0	-7.8	-7.7	-7.5	-8.9
40	-6.3	-5.6	-5.6	-5.4	-5.4	-5.3	-5.3	-5.3	-5.2	-6.3

The compound 39, 12, 37 and 31 tested for docking study showed high affinity with low energy of -8 kcal/mol with employed protein. Binding between 1OG5 & compound indicates very good inhibition. Molecules 39, 12, 37, and 31 showed high affinity with low energy of -8.9 kcal/mol with employed protein (see in Table 3).[19]

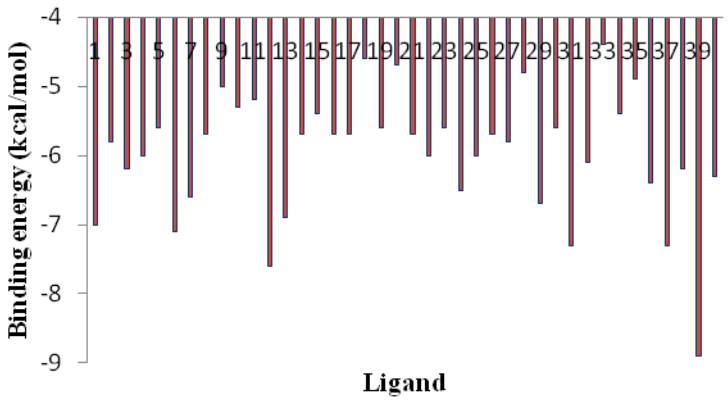

Figure 3: Graphical representation showing the binding energy (kcal/mol) values of ligands used in study

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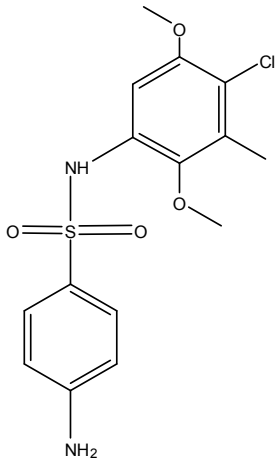

Figure 4 (a): Pharmacophore model

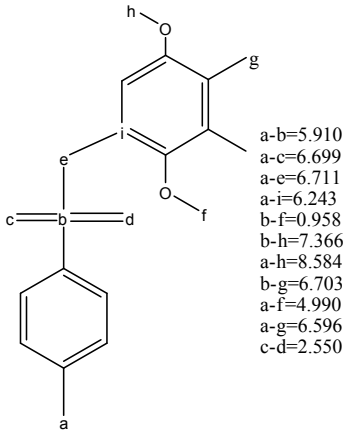

Figure 4 (b): Selected examples of active chlorpropamide found through a virtual screen using the four-point pharmacophore model

The second five- point pharmacophore, shown in Figure 4 (b), was built according to the lowest binding energy conformation of these molecules.

It contains five center pharmacophores:

- One aromatic ring

- The amino group and the nitrogen atom attached to –SO_2– group
- The methoxy and chlorine groups interacted with protein.

QSAR Study

Mass fragments description (LD_{50} based on the lowest energy docking)

Data reduction

Correlation weighting was performed on all the positions in the hypermolecule: the correlating coefficients of the statistically significant positions in the hypermolecule were used to multiply the local descriptors, actually the Mass fragments, thus resulting new weighted vectors CD_{ij}. Next, the local correlating descriptors are summed to give a global descriptor, $SD_i = \sum_j CD_{ij}$. This new descriptor is a linear combination of the local correlating descriptors for the significant positions in the hypermolecule (e.g. H5, H11, H12, H13, H14, H15, H16, H17, H18, H19, H21, H22, H25, H27, H29).

$LD_{50} = -63734.9 + 1 \times SD_{LD50}$

N=40; R^2=0.891; s=2943.93; F = 303.234

QSAR Models

The models were performed on the training set (25 structures in Table 4) and the best results (in decreasing order of R^2) are listed below and in Table 5.

(i) Monovariate regression

$LD_{50} = -61316.2 + 0.962 \times SD_{LD50}$

(ii) Bivariate regression

$LD_{50} = -59547.6 + 0.933 \times SD_{LD50} - 4486.9 \times Ch$

(iii)Three-variate regression

$LD_{50} = -62267.1 + 0.964 \times SD_{LD50} + 13.469 \times Di - 12.256 \times D3D$

Table 5: The best models in describing LD_{50} in the training set of chlorpropamide in Table 3

	Descriptors	R^2	Adjust. R^2	St. Error	F
1	SD_{LD50}	0.935	0.932	2586.587	316.085
2	Ch	0.193	0.157	9106.129	5.278
3	HOMO	0.008	-0.037	10099.838	0.174
4	CfDe	0.001	-0.044	10133.180	0.029
5	SD_{LD50}, Ch	0.940	0.934	2550.563	163.351
6	SD_{LD50}, Di	0.936	0.929	2634.734	152.421
7	SD_{LD50}, D3D	0.935	0.929	2646.640	150.958
8	SD_{LD50}, De	0.935	0.929	2641.130	151.633
9	SD_{LD50}, C	0.935	0.929	2647.456	150.859
10	SD_{LD50}, Di, D3D	0.944	0.936	2513.240	112.702
11	SD_{LD50}, De, Di	0.942	0.933	2567.502	107.710
12	SD_{LD50}, Di, Ch	0.940	0.931	2607.585	104.221
13	SD_{LD50}, De, D3D	0.939	0.930	2633.090	102.083
14	SD_{LD50}, De, IE[CfMax]	0.938	0.929	2645.840	101.037

Model Validation

(a) Leave-one-out

The performances in leave-one-out analysis related to the models listed as best in Table 5 are presented in Table 6.

Table 6: Leave-one-out analysis for best LD_{50} models

	Descriptors	Q^2	R^2-Q^2	St. $Error_{loo}$	F_{loo}
1	SD_{LD50}	0.129	0.806	9464.553	3.251
5	SD_{LD50}, Ch	0.177	0.763	9197.908	4.736
10	SD_{LD50}, Di, D3D	0.212	0.732	8999.516	5.928

(b) External validation

The values $LD_{50calc.}$ for each of the 15 molecules in the test set were chosen based on the lowest energy docking and computed with the same descriptors and the eq. 10, Table 5.[20]

Data are listed in Table 7 and the monovariate correlation: $LD50 = 0.580 \times LD50_{calc.} + 1329.4$; n=15; R^2=0.761; s=3510.249; F=41.371 plotted in Figure 5.

Table 7: Calculated values of LD_{50} for the molecules in the test set

Mol.	LD_{50}	$LD_{50calc.}$
1	580	1834.39
3	490	2125.71
4	490	2136.67
6	3240	4433.58
7	2150	4341.36
13	16000	14994.76
23	6400	3298.02
24	1475	-71.47
29	300	-371.10
31	750	1656.97
32	3000	970.02
36	25000	13978.00
37	3200	2734.06
39	700	6186.34
40	4680	1409.02

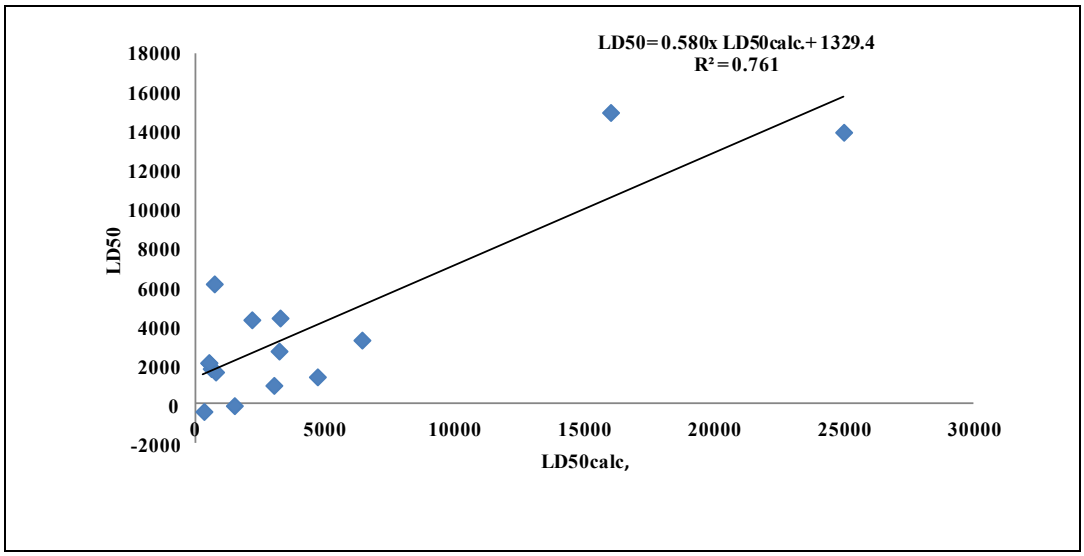

Figure 5: The plot LD_{50} vs. $LD_{50\ calc.}$ for the test set (external validation)

(c) Similarity cluster validation

Validation can also be performed by using clusters of similarity: each of the 15 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 25 structures of the learning set (each cluster comprising about 15-17 molecules).[21] The values LD_{50} calc. for each of the 15 molecules in the test set were chosen based on the lowest energy docking.

Data are listed in Table 8 and the monovariate correlation: $LD50 = 1.021 \times LD50_{calc.} + 400.86$; n=15; R^2=0.996 s=472.684; F=2985.482 plotted in Figure 6.

Table 8: Calculated values of LD_{50} by similarity clusters, for the moleculesin the test set

Mol.	LD_{50}	$LD_{50calc.}$
1	580	1188.26
3	490	1262.62
4	490	1503.12
6	3240	3583.96
7	2150	2301.96
13	16000	16093.27
23	6400	6138.98
24	1475	1745.26
29	300	968.68
31	750	958.16
32	3000	3050.12
36	25000	26613.14
37	3200	3378.21
39	700	1805.91
40	4680	5310.19

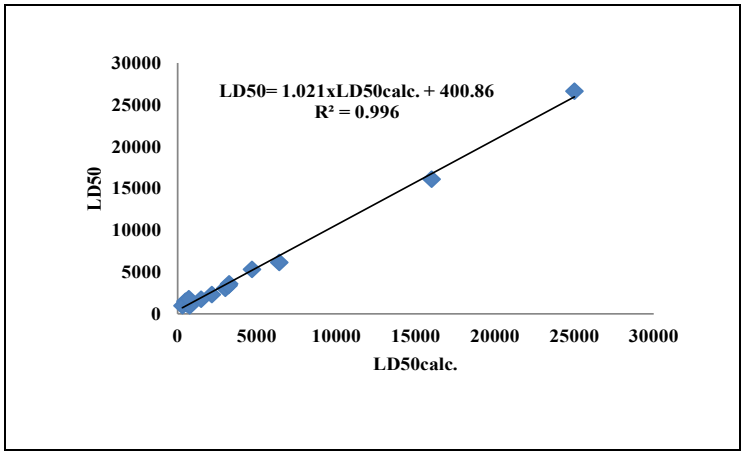

Figure 6: The plot LD50 vs. $LD_{50\ calc.}$ by similarity clusters

CONCLUSIONS

A set of 40 derivatives Chlorpropamide, downloaded from the PubChem database, was submitted to a QSAR study. The set was split into a learning set and a test set, the last one being used for the validation of the models, in the so-called external set validation. Also, the validation was made by a new version of prediction by using similarity clusters. CYTOCHROME P450 2C9 has been investigated for its potential binding affinity with selective chlorpropamide derivatives. The docking result of the study of 40 chlorpropamide molecules demonstrated that the binding energies were in the range of -8.9 kcal/mol to -4.4 kcal/mol, with the minimum binding energy of -8.9 kcal/mol.

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