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Research Paper

QSAR and docking studies of 1,4-dihydropyridine calcium antagonists with methylsulfonylimidazolyl substituent based on genetic function approximation

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Abstract: Genetic function approximation (GFA), a statistical modeling algorithm was used to develop a quantitative model for prediction of activity, as a potential screening mechanism for 1,4-dihydropyridine (DHP) calcium channel blockers. A nonlinear, four-descriptor model based on GFA algorithm with R^2 (adjusted correlation coefficient) = 0.948 and R^2 (cross validated correlation coefficient) = 0.922 was estimated. Nifedipine was used as a reference calcium antagonist. Experimental calcium antagonist potency expressed as – log IC_{50} was compared with the calculated (predicted) values. Docking studies of ligands and DHP receptor model were done to explain the difference of potencies of nifedipine analogs with methylsulfonylimidazolyl substituent.

Introduction

1,4-Dihydropyridine (DHP) calcium channel blockers are important class of drugs which induce relaxation of vascular smooth muscle, preferentially in arteries, and display a negative inotropic effect on isolated cardiac muscle [1]. They exert these effects by binding to a high affinity binding site in L-type voltage-dependent Ca^{2+} channels [2]. So, this class of drugs is effective in the treatment of hypertension, angina pectoris and other cardiovascular disorders [3]. DHPs may lead to other beneficial effects such as regression of left ventricular pressure and vascular hypertrophy, renal protection, weak anti-platelet, anti-ischemic and anti-atherogenic activity [4–6].

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In general, IC_{50} (the molar concentration of the drug required to inhibit 50% of the contraction of guinea pig ileum induced by high K^+ concentration) is used to evaluate the efficiency of a drug [7, 8]. However, the optimal interaction and therapeutic efficacy of the compound depend on its chemical structure. Therefore, quantitative structure–property/activity relationship (QSPR/QSAR) was proposed for predicting the IC_{50} of DHP [9-13].

The advances in QSAR studies have widened the scope of rationalizing drug design and the search for the mechanisms of drug actions [14–16]. In addition, they are useful in areas such as design of virtual compound libraries, computational-chemical optimization of compounds and design of combinatorial libraries with appropriate ADME (absorption,

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distribution, metabolism and excretion) properties. Method of building the QSAR model plays a key role for the quality of the models.

In this paper, QSAR and docking processes were proposed for implementation of DHPs activities as calcium channel blocker. QSAR study involves mathematical correlation between molecular structure and its activity. For quantitative modeling, different methods are available to develop QSPR/QSAR models. Genetic function approximation (GFA) is a statistical modeling algorithm which builds functional models of experimental data. GFA, a genetic algorithm with a term to penalize models that are over fitting, uses Friedman's lack-of fit (LOF) error measure to control the number of terms in the model whilst minimizing the least squares error [17]. The docking process involves the prediction of ligand conformation and orientation (or posing) within a targeted binding site. In general, there are two aims of docking studies: accurate structural modeling and correct prediction of activity [18]. In this work, docking study will be used to assess activity of the compounds in terms of binding affinities to the DHP receptor model.

Briefly, experimental calcium antagonist activity was compared to predicted values obtained from GFA and the docking study assessed and explained the potency differences of the calcium antagonist.

Materials and Methods

QSAR

The structures and experimental -log IC_{50} values of 1,4-dihydro-2,6-dimethyl-4-(1-methyl-2-methylsulfonyl-5-imidazolyl)-3,5-pyridine dicarboxylic acid diesters (**1-24**) and nifedipine (**25)** were obtained from literature [19] and are listed in **Table 1**. Compounds **1-18** are asymmetric esters (chiral compounds) and **19-25** are symmetric esters (achiral compounds). All molecules were drawn using Marvin Sketch. A more precise molecular geometry optimization was done using Accelrys Material Studio Program. This was performed with a semi-empirical molecular orbital package (VAMP geometry optimization, using AM1* at restricted Hartree-Fock level and optimization ends when gradient norm below 0.10).

For analysis purposes – log IC_{50} values were used as the dependant variables and are given in **Table 1**. The training set was used to build the model and the test set was used to evaluate its prediction ability. The optimized structures were used to calculate class of descriptors: fast descriptors, atomistic descriptors, VAMP electrostatics, spatial descriptors and forcite energetics. A genetic function approximation (GFA) algorithm was used to build the model. The GFA algorithm is a genetic algorithm (GA) derived from the previously-reported G/SPLINE S algorithm [20-22], and has been successfully applied to the generation of QSAR models [23, 24]. The GFA parameters used included: population of 700, maximum generations of 5000, constant equation length of 5, scoring function Friedman LOF, scaled LOF smoothness parameter of 0.5, mutation probability of 0.1 and using both linear and quadratic splines.

Docking

Docking process requires a three-dimensional (3D) structure of both protein and ligand (usually derived from X-ray/NMR experiments or homology modeling (HM)). Coordinates of the dihydropyridine receptor model with ligands were obtained from Boris S. Zhorov and et al [25]. All ligands were drawn into Marvin Sketch. The optimal geometry of the ligands was determined

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during the docking process. Docking was performed in a multistep procedure using Molegro Virtual Docker Program.

First, docking template was generated using coordinates available from Boris S. Zhorov [25]. As shown in **Figure 1**, docking template consisted of one hydrogen bond donor, two rings, three hydrogen bond acceptors and five steric moieties.

Secondly, MolDock docking engine using docking template and the optimized ligands was executed and finally, the top returned poses were manually modified to maximize binding to DHP sensing residues [25].

Results and Discussion

QSAR

Eighty two descriptors were calculated for DHP calcium antagonists, hundred and ten models were generated with genetic function approximation algorithm in Accelrys Material Studio Program. Top model was returned based on four molecular descriptors. The involved molecular descriptors and their physicochemical meaning are given in **Table 2**. The adjusted correlation coefficient R^2 was 0.948 and cross validated correlation coefficient R^2 was 0.922.

$$
\begin{aligned}
&-\text{Log IC}_{50} \\
&= 4.037437468 \times \text{CIC}^2 \\
&- 0.000373929 \times \text{VE}^2 \\
&- 166.577196926 \\
&\times \text{ramp}(\text{SAFZXP} - 0.590177359) \\
&+ 858.784288098 \\
&\times \left(\text{ramp}(\text{SAFZXP} - 0.565478166)\right)^2 \\
&- 0.000000227 \\
&\times \left(\text{ramp}(8361.693271136 - \text{PMIZ})\right)^2 \\
&+ 29.198590169
\end{aligned}
$$

The generated model was based on four descriptors: (1) **CIC** (Complementary Information Content), which measures the deviation of information content from its maximum possible value corresponding to the partition into classes containing one element each [26-29]. (2) **VE** (Valence Energy), the energy of valence interactions is generally accounted for by diagonal terms: bond stretching (bond), valence angle bending (angle), dihedral angle torsion (torsion) and inversion, also called out-of-plane interactions (OOP) terms, which are part of nearly all force fields for covalent systems. Urey-Bradley (UB) term may be used to account for interactions between atom pairs involved in 1-3 configurations (i.e., atoms bound to a common atom) [30]:

$$
\begin{aligned}
E_{\text{valence}} = E_{\text{bond}} + E_{\text{angle}} + E_{\text{torsion}} \\
+ E_{\text{OOP}} + E_{\text{UB}}
\end{aligned}
$$

(3) **SAFZXP** (Shadow Area Fraction ZX Plane) and (4) **PMIZ** (Principal Moment of Inertia Z) are geometric descriptors encodes the structural characteristics related to connectivity and the shape of the molecules providing that the hydrophobic and steric interaction are very important for the binding between the antagonist and the receptor. Molecular shadow indices are calculated by projecting the molecular surface on three mutually perpendicular planes, XY, YZ, and XZ. These descriptors depend not only on conformation, but also on the orientation of the molecule. To calculate them, the molecules are first rotated to align the principal moments of inertia with the X, Y and Z axes. Shadow area fraction ZX plane is the fraction of area for molecular shadow in the XZ plane over area of enclosing rectangle (Sxz, f) [31].

Figure 2 shows the plot of predicted - log IC_{50} versus experimental values for training and test sets. The correlation

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coefficient (R^2) of both training set and test set were 0.963 and 0.927 respectively.

Docking

Coordinates of the DHP receptor model with nifedipine were used to build the docking templates, c.f., **Figure 1**. Since the NH-group is considered as the most important part of the DHP pharmacophore that forms H-bonds with the receptor, docking templates aim to align all ligands to the orientation of nifedipine, trying to bias the formation of H-bond with Tyr^{3310} - an important DHP sensing residue-while takes the orientation described by Boris S. Zhorov et al [25], elaborating differences in interaction with the receptor between agonist and antagonist. Nifedipine NH group make H-bond with Tyr^{3310}, hydrophobic interaction between aromatic ring and Tyr^{3411}, Ca^{2+} chelating NO_2 group and oxygen of the carbonyl group, the down ester methyl group make hydrophobic interaction with Met^{3319} Leu^{1319} and Ile^{4319} and the two methyl groups of DHP ring make hydrophobic interaction with Ile^{3311} and Ile^{3314}. The Affinity of nifedipine as a reference compound to DHP receptor has been explained with interaction with seven residues, c.f., **Figure 3**.

From the experimental – log IC_{50} values (**Table 1**), all the compounds in the series have lower activity than the reference compound nifedipine which suggests that they have lower interaction with the receptor or unfavorable interaction and hence a lower affinity to the receptor. From fitting to the docking template they all match H-bond donor NH group at the stern important for formation of H-bond with Tyr^{3310} which explain loss of activity upon oxidation of DHP ring to pyridine. Fitting to the docking template was not hundred percent due to difference in the aromatic ring which results in Ca^{2+} chelating imidazole ring and sulfonyl group making no interaction with Tyr^{4311} and hence lower affinity than the reference drug. [25]

Compounds **10**, **22** and **24** have comparable activities to nifedipine. Regarding compound **10**, c.f., **Figure 3**, benzyl group makes more favorable hydrophobic interaction with pore facing hydrophobic bracelet (Met^{3319}, Leu^{2319}, Leu^{1319} and Ile^{4319}) that border the water lake cavity and responsible for stabilization of closed channel conformation [19]. Compounds **11** and **12** have similar structures to compound **10** having the same conformation; the binding energy for compound **12** is higher and compound **11** is the highest compared to each other which suggests unfavorable interaction. This is because of the presence of the nonpolar ethyl group in water lack cavity in both **11** and **12** near Ca^{2+}. Compound **12** has extra methyl which projects the benzyl inside the hydrophobic bracelet this produce more favorable interaction than compound **11**.

Compound **19** is similar to nifedipine that both have the smallest ester side chain. Attempts to increase the side chain in homologues series activity, decreases activity from **19** to **20** due to increase unfavorable interaction (presence of the nonpolar group in the water lack cavity and increase again for compound **21** reaching the length of five carbons side chain ester).

Compound **22**, has a comparable activity to nifedipine as mentioned before. This can be explained by two favorable interactions; firstly, the downside ester chain stabilizes the hydrophobic bracelet and so closed conformation (but still less efficient than benzyl group, compound **10**). Secondly, the upside ester chain makes hydrophobic interaction with Met^{2256}, c.f., **Figure 4**.

Comparing compounds **22**, **23** and **24,** which have the same number of carbon

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atoms, **22** is more active than **24** than **23**. Both **23** and **24** cannot reach to the site of interaction with Met^{2256}. So, both compounds have lower activity than **22**. Compound **24** is more active than **23** as it has a higher stabilization of the hydrophobic bracelet, lower projection in the water lack cavity and a lower surface area, c.f., **Figure 5**.

Conclusion

Based on genetic function approximation (GFA) algorithm, a statistically significant QSAR model with good prediction ability (adjusted correlation coefficient 0.948 and cross validated correlation coefficient 0.922), was obtained for nifedipine analogs with methylsulfonylimidazolyl substituent. Experimental IC_{50} was compared to calculated ones. Besides, a docking study of the ligand and DHP receptor, was performed to explain the activity differences among the studied compounds.

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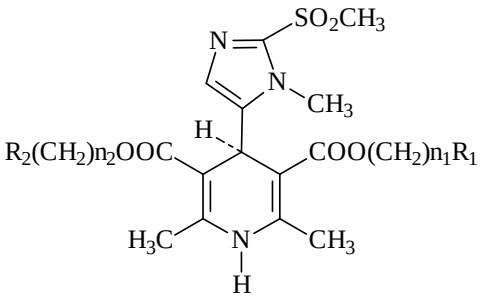
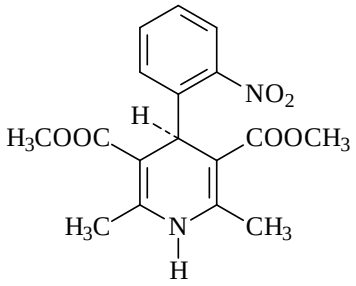


1-24



Nifedipine **(25)**

Table 1: Experimental and predicted calcium antagonist activity (- log IC_{50}) of **1-25**.

Compound	R_1	R_2	n_1	n_2	Calcium channel antagonist activity - log IC_{50} (M)	
					Experimental	Predicted (GFA)
1	CH_3	C_2H_5	2	0	11.83	12.08
2	$CH(CH_3)_2$	CH_3	0	0	12.12	11.94
3[a]	$CH(CH_3)_2$	C_2H_5	0	0	12.49	12.61
4	CH_3	CH_3	3	0	13.00	12.14
5	CH_3	C_2H_5	3	0	13.64	14.36
6[a]	$C(CH_3)_3$	CH3	0	0	12.11	12.39
7	$C(CH_3)_3$	C_2H_5	0	0	12.56	12.10
8	$CH(CH_3)_2$	CH_3	1	0	14.16	13.16
9	$CH(CH_3)_2$	C_2H_5	1	0	15.91	15.95
10	C_6H_5	CH_3	1	0	19.93	19.32

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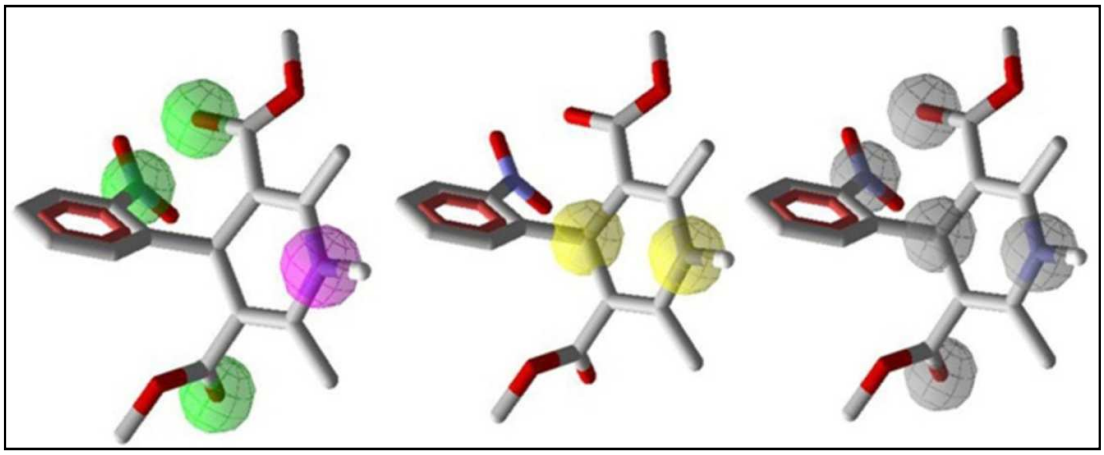
11	C_6H_5	C_2H_5	1	0	15.89	16.60
12[a]	C_6H_5	C_2H_5	2	0	17.59	19.46
13	c-C_6H_{11}	CH3	0	0	13.46	14.03
14	c-C_6H_{11}	C_2H_5	0	0	12.94	13.90
15	c-C_6H_{11}	CH_3	1	0	14.57	14.48
16	c-C_6H_{11}	C_2H_5	1	0	14.89	14.66
17[a]	c-C_5H_9	CH_3	3	0	13.41	14.96
18[a]	c-C_5H_9	C_2H_5	3	0	13.59	13.24
19	CH_3	CH_3	1	1	17.38	17.42
20	CH_3	CH_3	2	2	12.66	13.41
21	CH_3	CH_3	3	3	14.69	14.43
22	CH_3	CH_3	4	4	19.27	18.63
23[a]	$CH(CH_3)_2$	$CH(CH_3)_2$	1	1	15.92	16.22
24	$C(CH_3)_3$	$C(CH_3)_3$	0	0	18.86	19.07
25 (Nifedipine)					22.01	22.07

[a]Test set.

Figure 1: Docking template of 1,4-dihydropyridines (DHPs).



Hydrogen bond donor (magenta), rings (yellow), hydrogen bond acceptors (green) and steric moieties (grey).

Table 2: Correlation matrix of the used descriptors.

Descriptors	**CIC**	**PMIZ**	**SAFZXP**	**VE**
CIC	1.00	0.30	-0.26	0.02
PMIZ		1.00	-0.41	0.59
SAFZXP			1.00	-0.16
VE				1.00

CIC: (Complementary Information Content), VE: (Valence Energy (diagonal terms)), SAFZXP: (Shadow Area Fraction ZX Plane) and PMIZ: (Principal Moment of Inertia Z).

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Figure 2: (A) Plot of predicted (calculated) – log IC_{50} versus experimental (observed) values for training and test sets; (B) Fitting curve of training set and (C) Fitting curve of test set.

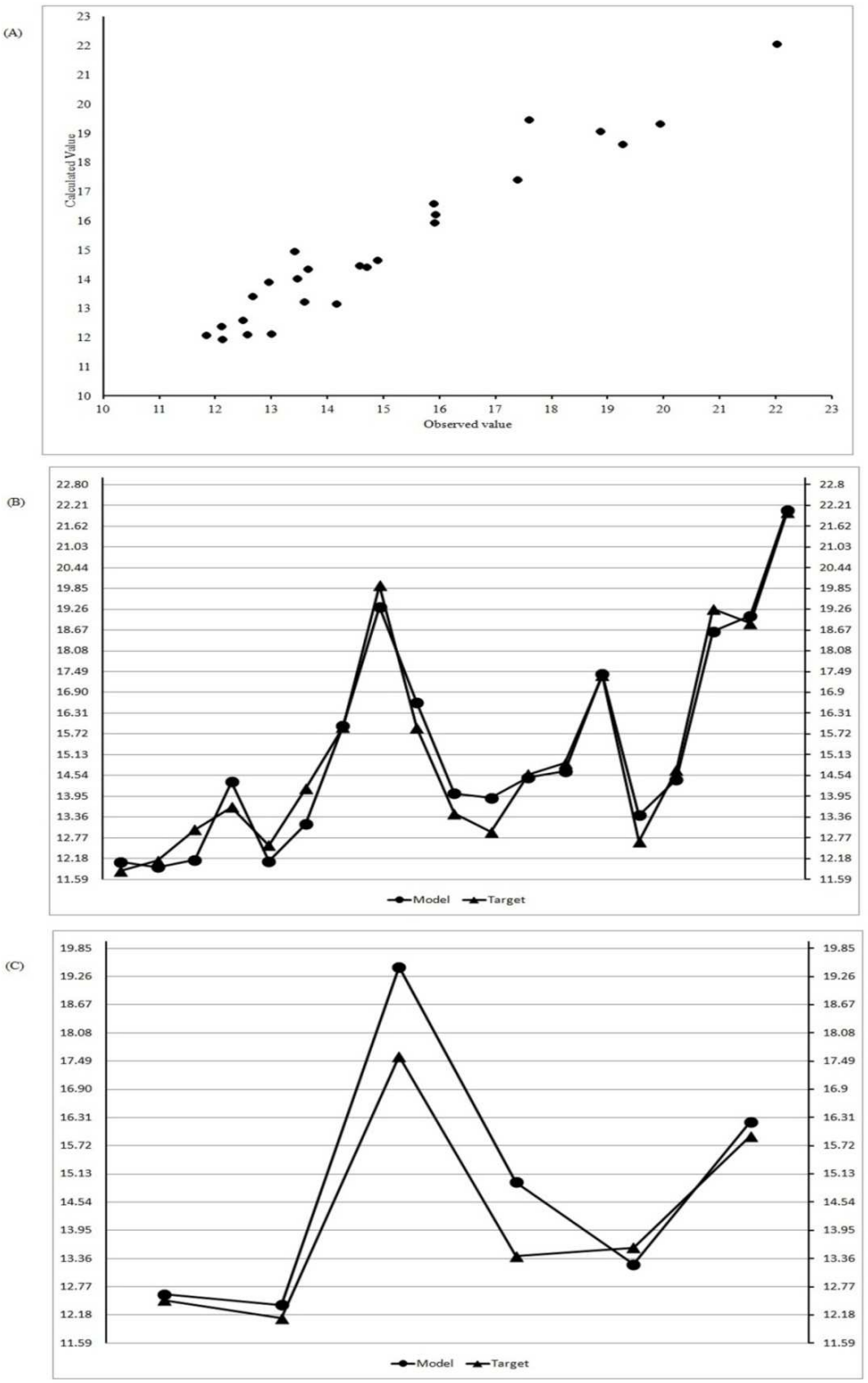

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Figure 3: (A) Shows interaction between nifedipine and DHP receptor; (B) Compound **10** benzyl group hydrophobic interaction with pore facing hydrophobic bracelet (Met^{3319}, Leu^{2319}, Leu^{1319} and Ile^{4319}) is shown. Ligands are shown in thick stick, receptor residues in thin stick and both colored by element.

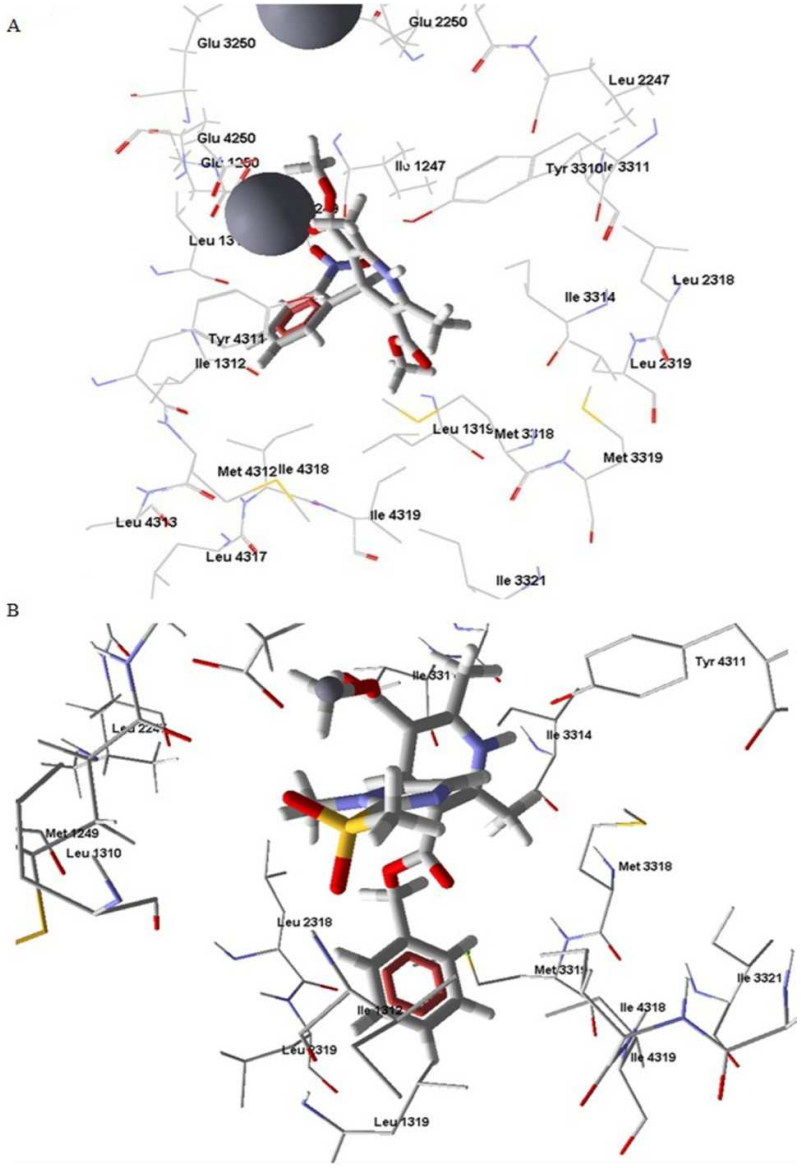

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Figure 4: (A) Comparison between compounds **10**, **11** and **12** shows difference in phenyl group position in downside ester chain and difference between methyl and ethyl in upside ester chain. (B) Compounds **19**, **20**, **21** and **22** show different side-chain length interaction with hydrophobic bracelet in downside-chain and Met^{2256} in upside-chain.

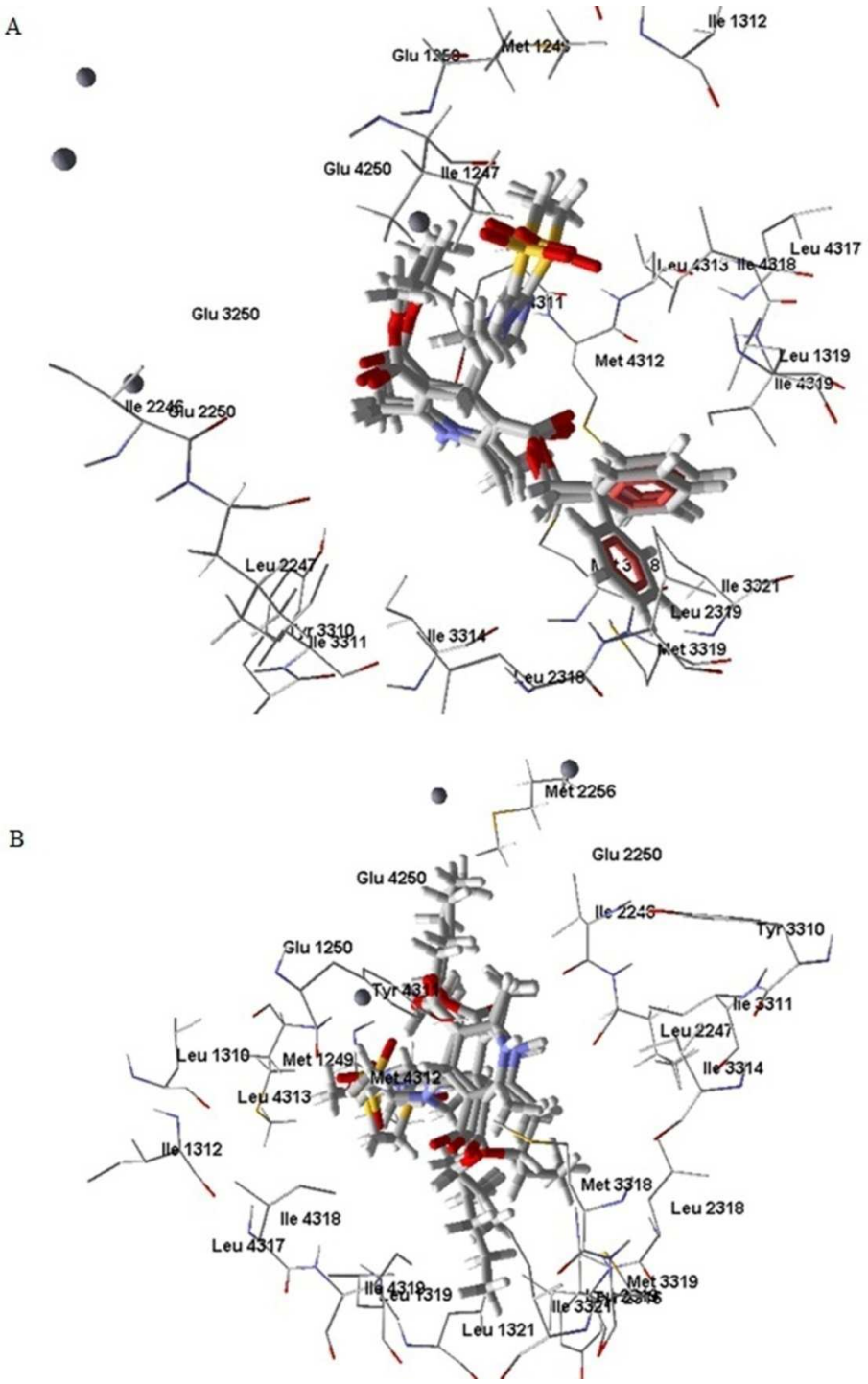

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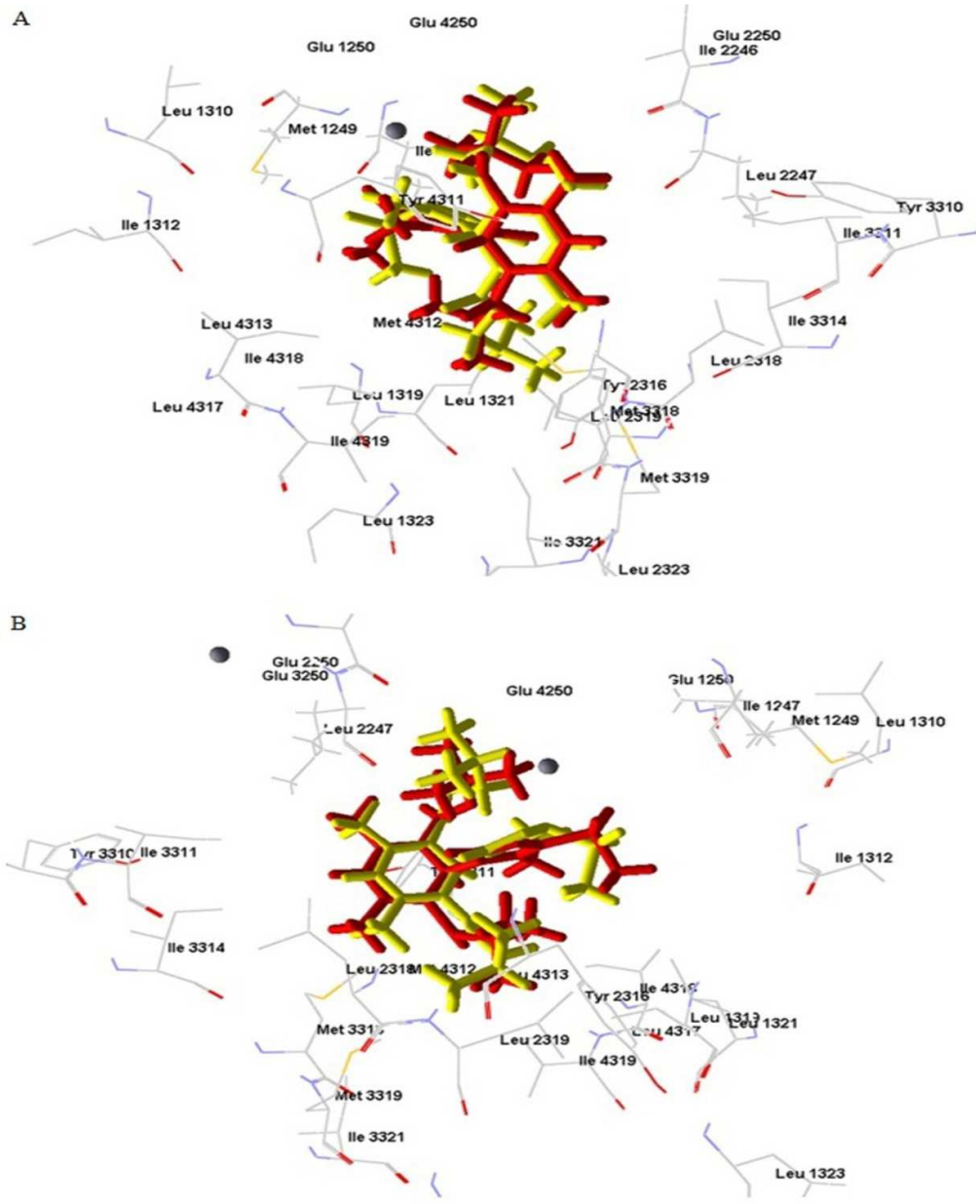
Figure 5: Front and back view of compounds **23** and **24** (A, B). Difference in surface area between the two compounds and projection in both water lake cavity and hydrophobic bracelet are shown.



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