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RESEARCH PAPER

STUDIES OF ANTI-HYPERTENSIVE ACTIVITY OF 1, 4-DIHYDROPYRIDINE DERIVATIVES: COMBINATIONS OF DFT-QSAR AND DOCKING APPROACHES

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1,4-Dihydropyridine (1,4-DHP) derivatives have been recognized as calcium channel blocker (CCB) agent. In this research, a series of 1,4-dihydropyridine (1,4-DHP) derivatives were theoretically examined for inhibitory activity against hypertension using density functional theory (DFT), quantitative structure activity relationship (QSAR) and docking approaches. The calculated molecular descriptors from DFT were used to develop QSAR model that related the descriptors to the bioactivity (IC_{50}). The QSAR analysis indicated that the energy of highest occupied molecular orbital (HOMO), dipole moment, solvation energy and average of electronic charges on heteroatoms are crucial parameters for the observed biological activity. The QSAR model predicted bioactivity (IC_{50}) agreed well with the experimental IC_{50}. All these compounds were docked against hypertensive cell receptors (PBD: 1IMT) and the binding free energy of ligand-receptor interactions agreed with the observed bioactivity (IC_{50}) of the 1, 4-DHPs with the receptor.

Key words: 1, 4-Dihydropyridine derivative, Calcium channel blocker, DFT, QSAR, Docking.

INTRODUCTION

Calcium channel blockers (CCBs) are drugs with heterogeneous set of compounds, categorized according to chemical structure such as dihydropyridines and diphenylalkylamines. CCBs also known as calcium antagonists help in the treatment of hypertension. CCBs act through voltage-dependent Ca^{2+} channel by preventing the entrance of calcium ions into cardiac and vascular smooth muscle cells (Lip and Beevers, 2001).

Hypertension, a diastolic blood pressure with BP greater than 90 mmHg and systolic blood pressure with BP greater than 140 mmHg, is the only risk factor that develops stroke, congestive heart failure, chronic kidney disease, and coronary artery disease and eventually leads to deaths (Ogah and Rayner, 2013). Hypertension is easily identified and can be managed if the patients undergo effective treatment but yet to be effectively controlled especially with people that as advanced in age (Havas *et al* 1993; Whitworth, 2003).

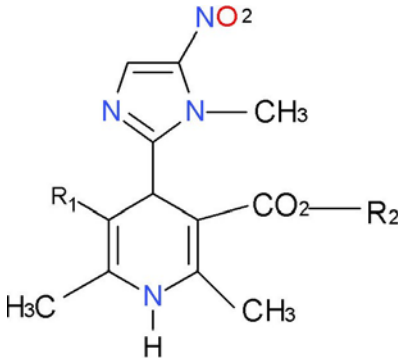
Chemotherapy is one of effective ways of managing hypertension and among CCBs, 1, 4-dihydropyridines (DHPs) are well known for their effectiveness. DHP is a pyridine based molecule and the parent to a set of molecules which are semi-saturated with two substituents that replace one double bond. They are well recognized in pharmacology as L-type calcium channel blockers, as well as in the treatment of hypertension. Therefore, the structural features of 1, 4-DHPs are well recognized as essential descriptors for their bioactivity as drugs that treat hypertension. Several DHPs class L-type

calcium channel blockers which have been commercialized include felodipine, nifedipine, nicardipine (Oyebamiji and Semire, 2016; ALJumali, 2015).

Quantitative structural activity relationship (QSAR) models are regression simulations useful in the chemical and biological sciences analysis. In QSAR modeling, the molecular descriptors which are the predictors recapitulate the link between biological activity (IC_{50}) and the generated descriptors in a series of molecules in order to predict the activities of newly sets of molecule (Nantasenamat *et al* 2009; Tropsha, 2010). However to develop a good and functional QSAR model, higher quality data, the choice of descriptors and statistical methods used for modeling are of paramount importance in QSAR modeling (Wold and Eriksson, 1995).

Molecular docking as a growing essential device for drug discovery is a main tool in structural molecular biology and computer-based drug design (Sharma *et al* 2011; Balasubramanian and Vijaya Gopal, 2012; Sharma and Kumar, 2014). It can be used to execute virtual screening on huge set of compounds, scoring and expose how the ligands prevent the target binding site, which is important in optimization (Morris and Lim-Wilby, 2008). Two popular methods in molecular docking are (i) matching technique which describes the protein and the chemical compound (ligand) as complementary surfaces and (iii) the second method mimics the real docking process that calculate the ligand-protein interaction energies which was used for the present work (Meng *et al* 1992; Goldman and Wipke, 2000).

Seven compounds, previously studied for their bioactivity as calcium antagonists (Miri *et al* 2008), were optimized using DFT method for the calculations of molecular descriptors in the present study. These compounds are 3-isopropyl-5- nitro-2,6- dimethyl- 4- (1-methyl-5-nitro-1*H*-imidazol-2-yl)- 1,4-dihydropyridine-3-carboxylate (B_1), 3-ethyl-5-cyano-2,6-dimethyl-4- (1- methyl- 5-nitro- 1*H*-imidazol- 2-yl)- 1,4-dihydropyridine-3-carboxylate (B_2), 3-(2-cyano ethyl)- 5-cyano- 2,6- dimethyl- 4- (1-methyl-5-nitro-1*H*-imidazol-2-yl)- 1,4- dihydropyridine-3-carboxylate (B_3), 3-isopropyl-5-Cyano-2,-6-dimethyl- 4- (1-methyl- 5-nitro- 1*H*-imidazole-2-yl)-1,4-dihydropyridine-3-carboxylate (B_4), 3-propyl- 5- cyano- 2,6- dimethyl- 4-(1-methyl-5-nitro- 1*H*-imidazol-2-yl)- 1,4-dihydropyridine-3-carboxylate (B_5), 3-butyl-5-cyano-2,6-dimethyl-4- (1- methyl- 5-nitro- 1*H*-imidazol- 2-yl)-1,4- di-hydro pyridine-3-carboxylate (B_6) and 3-methyl-5-cyano- 2,6- dimethyl- 4-(1-methyl- 5-nitro-1*H*- imidazol- 2-yl)-1,4- dihydropyridine- 3-carboxylate (B_7) (**Figure 1**). The major objectives of the present study are (i) to use quantum chemical method *via* DFT to calculate molecular descriptors, (ii) to use calculated descriptors to develop QSAR model that relates the descriptors to the observed bioactivity and (iii) to find suitable conformation as well as calculations of binding affinity of these compounds through molecular docking to the targeted receptor (PDB: 1IMT).



	R_1	R_2
B_1	NO_2	$CH(CH_3)_2$
B_2	CN	CH_2CH_3
B_3	CN	CH_2CH_2CN
B_4	CN	$CH(CH_3)_2$
B_5	CN	$CH_2CH_2CH_3$
B_6	CN	$CH_2CH_2CH_2CH_3$
B_7	CN	CH_3

Fig. 1. The schematic structures of the studied molecules

Computational details

Quantum chemical method

Conformational search was performed on the 1, 4-DPHs derivatives considered in this research work employing semi-empirical AM1 method with Monte Carlo search algorithm and the lowest-energy conformer of this conformational search was taken for further DFT calculations. The equilibrium geometries for all the lowest-energy conformers were optimized at Density Functional Theory (DFT) with the standard 6-31G (d,p) basis set.

The DFT method used consist of the three-parameter density functional, that includes

Becke's gradient exchange correction (Becke, 1993) and the Lee, Yang, Parr correlation functional (*i.e.* B3LYP) (Lee *et al* 1988). The choice of the selected functional and basis sets was attributed to the accuracy of DFT calculations and the selected basis set, 6-31G (d,p) has been proved to be sufficient for calculation of the excited properties of ligands. The studied molecules were optimized to generate molecular descriptors that described the bioactivity (IC_{50}) of the compounds. Also, the optimized structures were used for molecular docking.

Some of the molecular parameters calculated are the LUMO, the HOMO, dipole moment and global molecular descriptors such as chemical hardness, softness and chemical potential. Solvation energy using SM5.4 model, a semi-empirical method (AM1) as implemented on quantum chemical software, Spartan 10 and molecular descriptors, calculated using quantum mechanical methods have been used in many QSAR studies (Todeschini and Consonni, 2000; Eroğlu *et al* 2007).

Furthermore, the selected descriptors were used to develop quantitative structure-activity relationship (QSAR) model that relates cytotoxicity to the molecular descriptors of the compounds (Goodarzi *et al* 2012). Multiple linear regression (MLR) analysis, a frequent statistical and mathematical method was used to develop the QSAR model. The QSAR studies have been tools of predicting endpoints of interest in organic molecules acting as drugs (Karelson, 2000).

The calculated molecular descriptors used in QSAR studies using DFT method have better correlation to the experimental data than those calculated form semi-empirical methods (Stewart, 1989; Dewar *et al* 1985; Zhang *et al* 2004; Singh *et al* 2004).

Finally, molecular docking was performed on the compounds to find suitable conformation as well as calculations of binding affinities. The X-ray crystal of the 1IMT protein complex (PDB ID: 1IMT) was obtained from protein data bank (Liu *et al* 1996). Discovery studio was used to treat the receptor by removing the ligands, water molecules, and cofactors that were present (Biovia, 2005). Autodock tool was used to convert the protein and the ligands to pdbqt format and the docking analysis was performed using AutoDockVina, which Darwinian evolution theory motivated to be iterative optimization method (Rani *et al* 2014).

RESULTS AND DISCUSSION

Molecular descriptors

The most stable conformation of each 1,4-DHPs was considered for geometry optimization at B3LYP/6-31G** level of theory for the calculation of essential molecular descriptors that could be used to describe the cytotoxicity of the compounds. The molecular descriptors that were calculated include the HOMO and LOMO energies, solvation energy, polar surface area (PSA), dipole moment (DM), weight, hydrophobicity (log P), volume (V), area, ovality and heteroatoms (average of electronic charges on all heteroatom in the compound). The calculated frontial molecular orbital (HOMO, LUMO, band gap) energies were -5.79,-1.69 and 4.17eV for B_1; -5.26,-1.55 and 3.71eV for B_2; -5.56 eV, -1.67eV and 3.89eV for B_3; -5.68eV, -1.36eV and 4.32eV for B_4; -5.20eV, 0.67eV and 4.53eV for B_5; -5.26, -1.62eV, and 4.00eV for B_6; and -5.58eV, -1.28eV and 4.30eV for B_7 for HOMO, LUMO and band gap respectively (**Table 1**). Since, HOMO energy relates to the ability of a molecule to donate electrons to the surrounding receptor and likewise lower LUMO enhances the ability of a molecule to accept electrons form the receptor.

Also, lower the band gap energy leads to easy excitation of electrons and facilitates better ability of a molecule to donate the electron to the surrounding molecule. Therefore, it is expected that HOMO and LUMO energies as well as band gap energy should play crucial roles in binding of the ligand to the receptor, thus enhances non-bonding interactions such as hydrogen bonding and hydrophilic interactions. However, know clear relationship was found between the cytotoxicity of these compounds and the LUMO or band gap energies, only HOMO energies showed a fair correlation as shown in **Figure 1**. Similarly, the values of other parameters calculated such as log P, dipole moment (DM), ovality and solvation energy show no clear relationship with the observed anti-hypertensive activities of these compounds.

Generation of QSAR model using multiple linear regressions

Pearson's matrix expresses the liaison among bioactivities of molecular descriptors against CCB. The positive correlation between the IC_{50} and HOMO is 0.813 and the negative correlation between the IC_{50} is -0.503.

These correlation are fair since R^2 is greater than the 0.5. Other descriptors are fair in their

relationship to each other, for example, HOMO is correlated to LUMO by 0.622, Dipole moment is correlated to solvation energy by 0.695, dipole moment is correlated to heteroatom by 0.803 and solvation energy is correlated heteroatom by 0.803. Also, the followings are negatively correlated to each other; HOMO is correlated with solvation energy by -0.664, dipole moment is correlated to LUMO by -0.778, solvation energy is correlated to LUMO by -0.902 and heteroatom is correlated to LUMO by -0.7777 (**Table 2**).

Table 1. Selected molecular parameters obtained by B3LYP/6-31G** for anti-hypertensive

Mol	HOMO (eV)	LUMO (eV)	SE kJ/mol	BG	DM (Debye)	ɲ	μ
B_1	-5.79	-1.69	-19.12	4.10	3.88	2.05	-3.74
B_2	-5.26	-1.55	-60.30	3.71	6.31	1.86	-3.41
B_3	-5.56	-1.67	-82.80	3.89	4.26	1.95	-3.62
B_4	-5.68	-1.36	-48.59	4.32	2.73	2.16	-3.52
B_5	-5.20	-0.67	-49.37	4.53	1.03	2.27	-2.94
B_6	-5.62	-1.62	-56.61	4.00	6.26	2.00	-3.62
B_7	-5.58	-1.28	-76.65	4.30	3.48	2.15	-3.43

Table 1. *Contd.*

Mol	ω	H	MW (amu)	log P	Ovality	V (A^3)	A (A^2)	PSA (A^2)
B_1	0.29	-0.93	462.37	0.68	1.63	370.52	407.14	82.55
B_2	0.32	-0.94	333.35	-0.69	1.54	326.12	353.11	102.03
B_3	0.30	-0.97	358.36	-0.66	1.59	346.16	378.02	115.40
B_4	0.35	-0.98	347.38	-0.38	1.58	344.56	374.66	99.33
B_5	0.53	-1.01	351.41	-1.20	1.60	354.43	386.76	108.05
B_6	0.31	-0.94	361.40	0.21	1.60	363.00	393.64	101.86
B_7	0.37	-0.94	319.32	-1.03	1.51	307.68	333.26	102.85

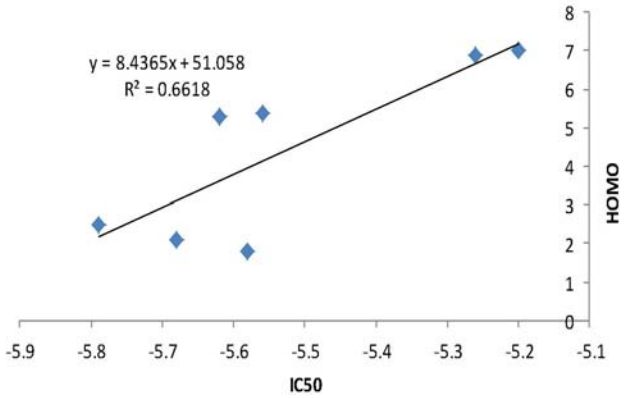


Fig. 1. Correlation between IC_{50} and the HOMO energies (eV)

Moreover, the fitting value is not sufficient to authenticate the enactment of QSAR, therefore, the statistical analysis are carried out as described methodology to calculate the predicted R^2 (0.999) which shows the promising reproductive power of this QSAR model as displayed in equation 1. Calculated regression parameters for 1, 4-DHPs used in the validation of QSAR model for anti-hypertensive activity includes R^2, CV.R^2, R^2_a as shown in **Table 3**. The calculated R^2 (0.996) revealed a good fitness. The calculated CV.R^2 (0.996) revealed the reliability of the model, since it is greater than 0.5 (Ponce *et al* 2004). R^2_a was calculated to be 0.976. This make the QSAR model to be predictive since it is greater than 0.6.The calculated bioactivity (IC_{50}) is fitted (R_2 =0.996) into the experimental values as shown in the **Figure 2**.

Docking and scoring

CCBs are several medications that disturb the drive of calcium (Ca^{2+}) through calcium channels. Calcium channel blockers are used as antihypertensive drug *i.e.* as medications to decrease blood pressure in patients with hypertension. Ligands used as antihypertensive are particularly effective against large vessel stiffness which is one of the common causes of elevated systolic blood pressure in elderly patients (Olson, 2011).

Table 2. Pearson's correlation matrix for descriptors

	IC_{50}	HOMO	DM	SE	HETEROATOM	LUMO
IC_{50}	1.000					
HOMO	0.813	1.000				
DM	0.191	-0.130	1.000			
SE	-0.503	-0.664	0.695	1.000		
HETEROATOM	-0.312	-0.453	0.803	0.803	1.000	
LUMO	0.247	0.622	-0.778	-0.902	-0.777	1.000

Table 3. Evaluation of the QSAR model for CCB

Equation	N	R^2	CV.R^2	R_a^2
-10.534 + 5.601(HOMO) + 0.837 (DM) – 0.241 (SE) – 36.908 (H) – 4.597(LUMO)----1	7	0.996	0.996	0.976

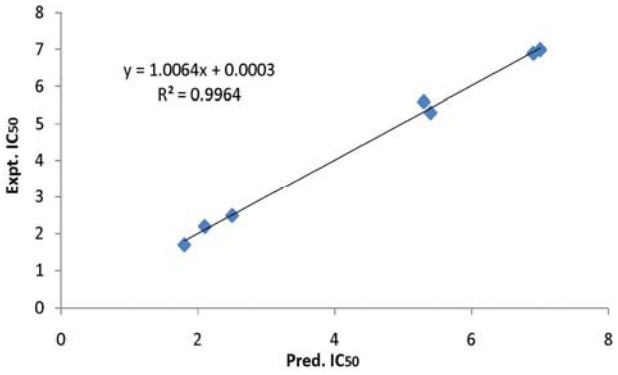


Fig. 2. Correlation between experimental and predicted IC_{50}

Therefore, molecular docking simulations were performed on the optimized structures of these compounds obtained at DFT level against 1IMT and the conformation in each ligand-receptor complex with highest free energy of interactions was taken. The conformation with utmost binding energy in each docking is presumed to be the best conformation. Therefore, the free energy of the interactions (docking scores) for these compounds were -4.10 kCal/mol for B_1, -3.90 kCal/mol for B_2, -4.30 kCal/mol for B_3, -3.00 kCal/mol for B_4, -4.10 kCal/mol for B_5, -3.60 kCal/mol for B_6 and -4.10 kCal/mol for B_7 as presented in **Table 4**. It was observed the compounds formed a number of hydrogen bonds (HIs) with 1IMT in the active site; B_2, B_5, B_6, and B_7 formed four HIs each with 1IMT receptor, B_3 and B_4 formed three and five HIs with 1IMT respectively (**Table 5**). No HIs between B_1 and the receptor was observed, however B_1 would be stabilized in the active site of 1IMT by other non-bonding interactions (**Figure 3a**).

Table 4. Docking scores for studied 1,4-dihydro pyridine derivatives

Compound	Affinity (kcal/mol)
B_1	-4.10
B_2	-3.90
B_3	-4.30
B_4	-3.00
B_5	-4.10
B_6	-3.60
B_7	-4.10

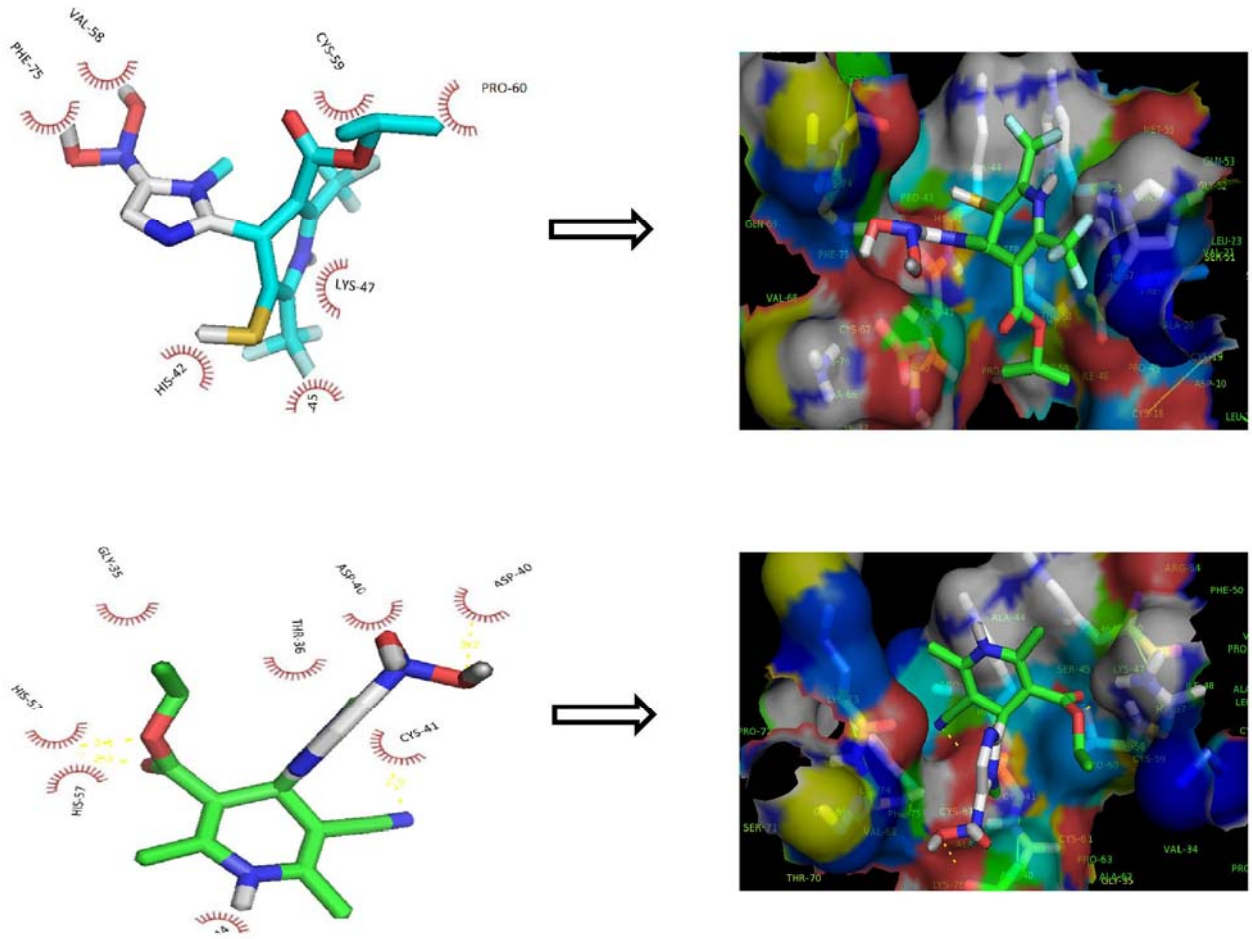
Table 5. Interactions among amino acid residues of 1IMT and ligands

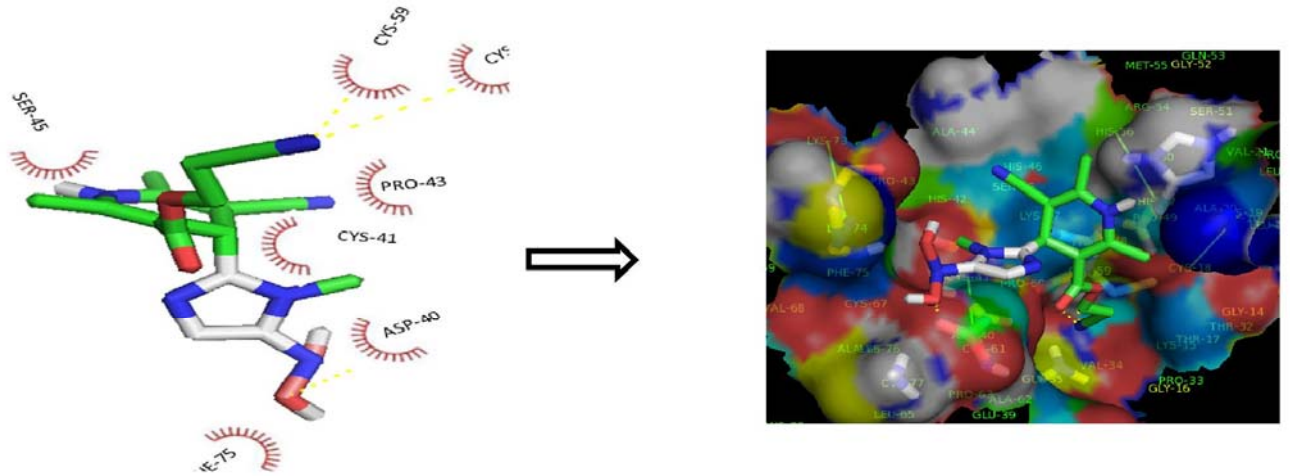
S. No.	H-Bond between amino acid residues and ligand	Distance	No of H-bonds
B_1	Nil	Nil	Nil
B_2	(i) CYS-41 LIG:N (ii) ASP-40 LIG:O (iii) HIS-57 LIG:O (iv) HIS-57 LIG:O	2.9, 3.2, 2.1, 2.3	4
B_3	(i) ASP-40 LIG:O (ii) CYS-59 LIG:N (iii) CYS-59 LIG:N	3.0, 3.5, 2.4	3
B_4	(i) ASP-40 LIG:O (ii) CYS-41 LIG:O (iii) PHE-75 LIG: O (iv) LYS-73 LIG:O (v) CYS-41 LIG:O	2.9, 3.3, 2.3, 2.8, 2.9	5
B_5	(i) ASP-40 LIG:O (ii) HIS-57 LIG:O (iii) HIS-57 LIG:O (iv) CYS-41 LIG:H	3.0, 2.4, 1.9, 2.1	4

B_6	(i) CYS-41 LIG:N (ii) ASP-40 LIG:O (iii) HIS-57 LIG:O (iv) HIS-57 LIG:O	2.9, 2.9, 2.4, 2.1	4
B_7	(i) CYS-41 LIG:N (ii) HIS-57 LIG:O (iii) THR-58 LIG:O (iv) ASP-40 LIG:O	3.1,2.3, 2.1, 3.2	4

The binding modes of all the seven compounds in the active site of 1IMT are shown in **Figure 3**. The analysis of binding mode of B2 showed that it has HIs with three residues: CYS-41/LIG: N (cyano-group of pyridine ring) with HI distance of 2.9 Å, ASP-40 LIG:O (carboxylic group of pyridine ring) with HI distance 3.2 Å, HIS-57 LIG:O (nitro-group of imidazole ring) with HI of 2.1Å and HIS-57 LIG:O(carboxylic group of pyridine ring) with HI distance 2.3 Å (**Figure 3b**). Also, ASP-40 LIG:O (nitro-group of imidazole ring) withHI distance 3.0 Å, CYS-59 LIG:N (cyano-group of pyridine ring) withHI distance 3.5 Å and CYS-59 LIG:N(cyano-group of pyridine ring) with HI distance 2.4 Å for B_3 (**Figure 3c**); Likewise, ASP-40 LIG:O(nitro-group of imidazole ring) with HI distance 2.9 Å, CYS-41 LIG:O (nitro-group of imidazole ring) withHI distance 3.3 Å, PHE-75 LIG:O (nitro-group of imidazole ring) with HI distance 2.3 Å, LYS-73 LIG:O(nitro-group of imidazole ring) with HI distance 2.8Å and CYS-41 LIG:O (nitro-group of imidazole ring) with HI distance 2.9 Å for B_4 (**Figure 3d**). Furthermore, ASP-40 LIG:O (nitro-group of imidazole ring) with HI distance 3.0 Å, HIS-57 LIG:O (carboxylic-group of pyridine ring) with HI distance 2.4 Å, HIS-57 LIG:O (carboxylic-group of pyridine ring) with HI distance 1.9 Å and CYS-41 (amino group) LIG:H (Hydrogen) for B_5 (**Figure 3e**).

In addition, CYS-41 LIG:N (cyano-group of pyridine ring) with HI distance 2.9 Å, ASP-40 LIG:O (nitro-group of imidazole ring) with HI distance 2.9 Å, HIS-57 LIG:O (carboxylic-group of pyridine ring) with HI distance 2.4 Å, and HIS-57 LIG:O (carboxylic-group of pyridine ring) with HI distance 2.1 Å for B_6 (**Figure 3f**). Finally, CYS-41 LIG:N (cyano-group of pyridine ring) with HI distance 3.1 Å, HIS-57 LIG:O (carboxylic-group of pyridine ring) with HI distance 2.3 Å, THR-58 LIG:O (carboxylic-group of pyridine ring) with HI distance 2.1 Å and ASP-40 LIG:O (nitro-group of imidazole ring) with HI distance 3.2 Å for B_7 (**Figure 3g**).

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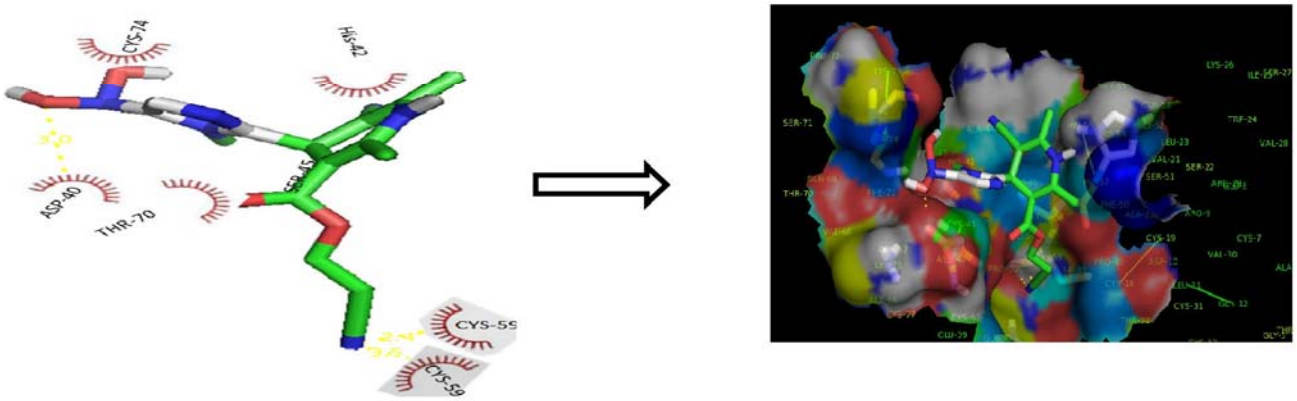
SER-45
PRO-43
CYS-41
ASP-40
ILE-75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ASP-40
THR-70
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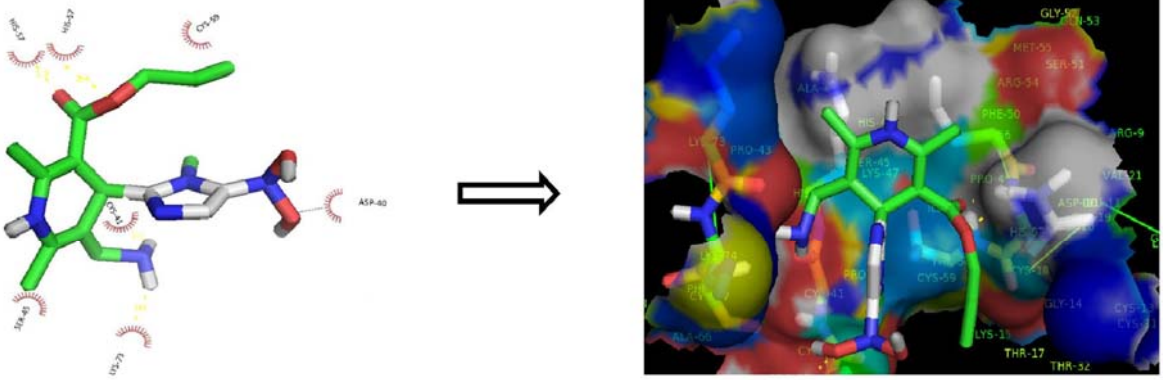
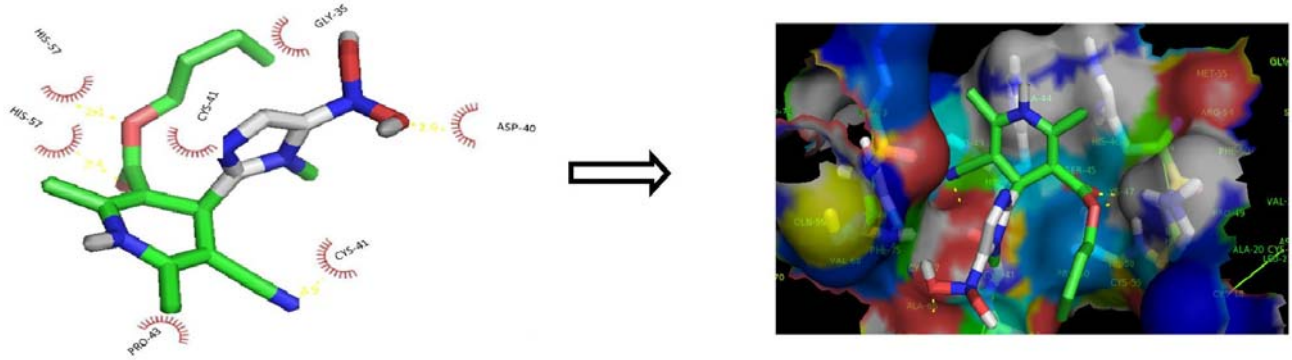

ASP-40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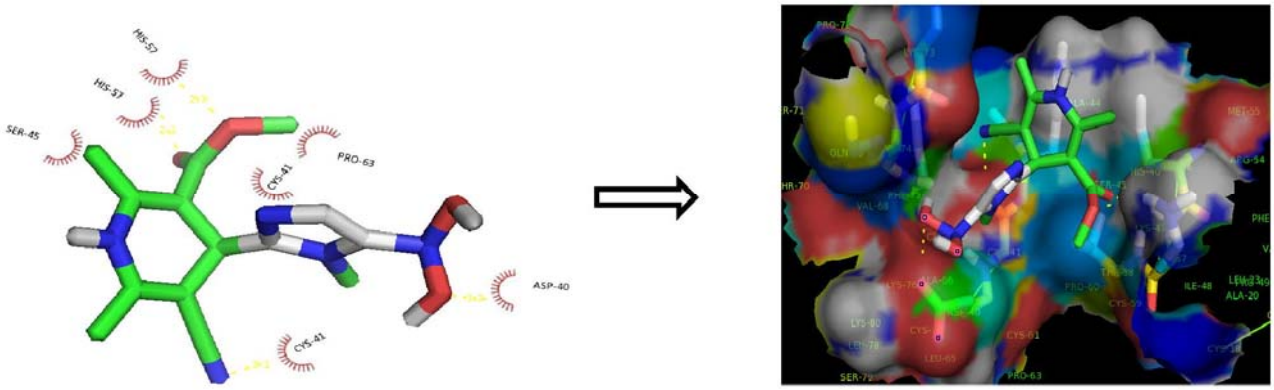

Fig. 3a-g. Binding interaction of B_1- B_7 with 1IMT

Conclusion

The study presented quantum chemical calculations of molecular descriptors for the development of a QSAR model that relates the molecular parameters of the studied compounds to their cytotoxicity. In present work, seven compounds which were previously studied for their bioactivity as calcium antagonists, were optimized using DFT method for the calculations of molecular descriptors. The QSAR model developed for calcium channel blocker activity was based on four molecular descriptors (the HOMO, dipole moment, solvation energy and average electronic charges on all heteroatoms) in order to avoid multi-collinearity. The selected molecular descriptors were used to model the effectiveness of the compounds as potential CCB and the IC_{50} calculated from the developed QSAR model agreed with the experimental data. Pharmacophore studies revealed that hydrogen bonds with the amino acid residues in the binding site as well as conformation of the ligand are essential significant features for ligand-receptor binding.

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