Design and synthesis of new 1,4-dihydropyridines containing 4(5)-chloro-5(4)-imidazolyl substituent as a novel calcium channel blocker

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Docking and QSAR studies of new 1,4-dihydropyridines containing 4(5)-chloro-2-methyl-5(4)-imidazolyl substituent

Asghar Davood · Maryam Iman · Alireza Nematollahi · Abbas Shafiee

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Abstract 1,4-Dihydropyridine (1,4-DHP) derivatives have been recognized as calcium channel blocker (CCB) agent. In this research, a newly synthesized dihydropyridine, containing 4-[4(5)-chloro-2-methyl-5(4)-imidazolyl] moiety, as subjected to docking study and QSAR analysis. DHPs were built by HYPERCHEM program, and conformational studies were performed through semi-empirical method followed by PM3 method. QSAR descriptors were obtained from the EDRAGON and HYPERCHEM. QSAR equations were derived from multilinear regression method. This simple equation can be used to estimate the CCB's activity for new derivatives of this series of compounds. The sums of the HATS2v, Mor09p, Mor06p, and CIC5 were identified as the most significant descriptors. Docking study was performed using AutoDock4 program on all of the compounds. The results show that experimental pIC50 values agree with docking results for potent compounds. These computational studies can offer useful references for understanding the action mechanism and molecular design or modification of this series of the CCB agents.

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Keywords 1,4-Dihydropyridine · CCBs · Molecular modeling · Docking · QSAR · Imidazole

Introduction

Quantitative structure activity relationships (QSARs) are widely used in the drug design process wherever detailed structural information on the ligand–receptor interactions are not experimentally available (Gaudio *et al*., 1994; Hansch and Fujita, 1964; Hansch, 1969). QSAR models are mathematical equations relating the chemical structure to their biological activity (Hansch and Leo, 1995; Kubinyi, 1997a, b). The first component in the definition of a QSAR model is the computation of the structural descriptors from the three-dimensional structure of the molecule; various geometrical, quantum, or molecular field descriptors were proposed in the recent years to replace the Hansch substituent constants (Gaudio *et al*., 1994; Hansch and Fujita, 1964; Hansch, 1969). The second component of a QSAR model is an explicit mathematical structure activity equation establishing a statistical relationship between a dependent variable (biological activity) and a set of independent variables (descriptors) (Gaudio *et al*., 1994; Hansch and Fujita, 1964; Hansch, 1969). The mathematical QSAR equations can be produced using a large number of statistical models, such as multilinear regression and partial least squares (PLS) (Gramatica and Papa, 2003; Hansch *et al*., 2001; Cramer *et al*., 1988; Clark *et al*., 1990).

Calcium channel blocker (CCB) has been established as one of the drugs for treatment of hypertension because of its promising depressor effect and relatively good tolerability (Ana *et al*., 2006). Among the various classes of CCBs, dihydropyridines (DHPs) have been the largest and

the most widely studied class. Not only are DHPs important as cardiovascular drugs, but they also have been extensively used to study the structure and function of the voltage-activated calcium channels (Belleman 1986). The development of 4-aryl-1,4-dihydropyridines (DHPs), related to the first generation CCB, nifedipine, as a therapeutic agent for the treatment of cardiovascular disorders (Ramesh *et al*., 1987; Fleckenstein, 1977), has stimulated many structure–activity relationship studies (Janis and Triggle 1983). Changes in the substitution pattern at the C-3, C-4, and C-5 positions of nifedipine alter potency (Coburn *et al*. 1988); tissue selectivity (Ramesh *et al*., 1987; Fleckenstein, 1977); and the conformation of the DHP ring (Rovnyak *et al*., 1988). One of the structural requirements is that the substituted aromatic ring occupies an axial position perpendicularly bisecting the boat-like DHP ring with the substituent in a syn-periplanar orientation. A syn-cis-carbonyl ester orientation with respect to the olefinic double bond is also needed for high activity (Ochoa *et al*., 1998; Arrowsmith *et al*., 1986). It is possible to replace phenyl ring on the C-4 position with some heterocyclic rings (Navidpour *et al*., 2004; Davood *et al*., 2006; Hemmateenejad *et al*., 2007).

In previous studies, the authors have synthesized some compounds, in which a C-4 imidazolyl substituent was isosteric with a nitrophenyl substituent, and they were potent CCBs (Pourmorad *et al*., 1997; Shafiee *et al*., 1997). In this article, docking, molecular modeling, and QSAR analysis of the DHPs, containing a 4-[4(5)-chloro-2-methyl-5(4)-imidazolyl] moiety, are reported. For selection of this moiety, the following points were taken into account:

(a) Substitution of chlorine instead of NO_2 in the 4-aryl ring produces active compounds (Arrowsmith *et al*., 1986).
(b) A bulky substituent in the 2- and 5-positions of imidazole was tolerated by the receptor (Pourmorad *et al*., 1997; Shafiee *et al*., 1997; Shafiee *et al*., 1996; Goldmann and Stoltefuss, 1991).
(c) Considering the tautomeric forms of the 2-methyl-4(5)-chloro-5(4)-imidazolyl moiety, both the nitrogen atoms can probably interact with the receptor through hydrogen binding (donor–acceptor) and so both of tautomeric forms should be pharmacologically active. Our molecular modeling studies indicate that the 4-chloro tautomer is the main form and is more stable than the 5-chloro tautomer, in which 4-H is syn-perpendicular and has good compatibility with the reference drug, nifedipine. In addition, it has been shown that 4-aryl in DHPs have a lipophilic pocket in the DHP receptor (Davood *et al*., 2001). In order to adjust the lipophilic property of the imidazole ring, methyl and chloro groups were inserted in the 2- and 4(5) positions of the imidazole ring, respectively.

To rationalize these findings, we docked the compounds into the active site of L-type calcium channel (Fig. 1a). Furthermore, to obtain a quantitative understanding of the SAR of these antagonists, a QSAR analysis was performed. Our QSAR models will be based on the CCB activity, pIC50, from a set of 23 dihydropyridine derivatives, which were synthesized in a previous experiment by the authors (Davood *et al*., 2001).

Materials and methods

Molecular modeling and docking, software, and method

Software

The chemical structure of all the 23 desired compounds (Tables 1, 2) was built using HYPERCHEM software (version 7, Hypercube Inc.). Conformational analysis of the designed compounds was performed through semi-empirical molecular orbital calculations (PM3) method using the HYPERCHEM software. Total energy gradient calculated as a root mean square (RMS) value. The molecular structures were optimized using the Polak–Ribiere (conjugate

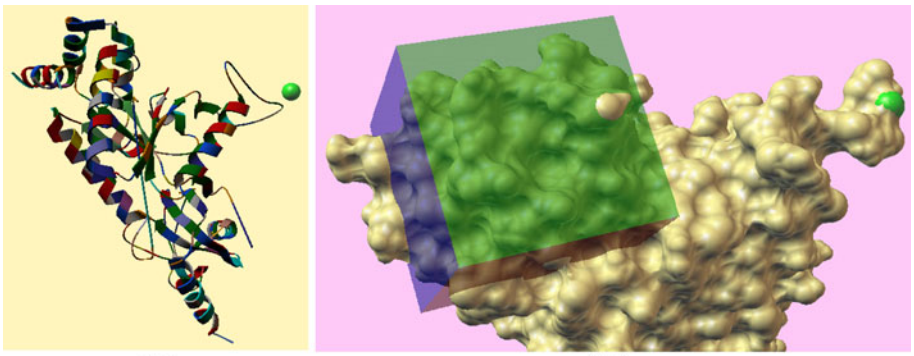
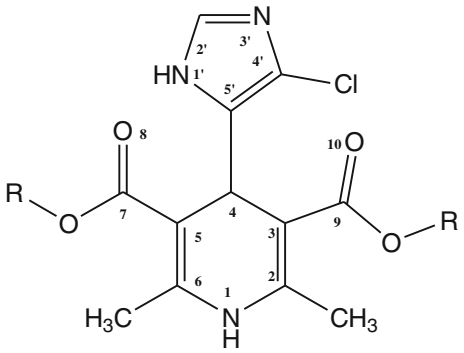


Fig. 1 **a** L-type calcium channel (PDB entry: 1T0J), **b** L-type calcium channel grid box

Table 1 Calcium channel blocker activity of symmetric (5a–5l) esters



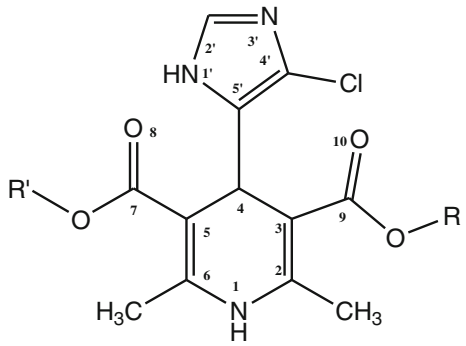
DHP	R′	pIC50 Exp.[a]	pIC50 Calc.[b]	REP%[c]
5a	CH_3	5.92	6.32	0.063
5b	CH_2CH_3	6.36	6.19	0.027
5c	$CH_3CH_2CH_3$	7.20	7.10	0.014
5d	$CH(CH_3)_2$	7.42	6.82	0.087
5e	$CH_2CH(CH_3)CH_3$	7.02	7.01	0.001
5f	$C(CH_3)_3$	5.39	5.49	0.018
5g	Cyclopentyl	7.01	6.96	0.007
5h	Cyclohexyl	6.02	6.47	0.069
5i	Cyclohexylmethyl	6.20	6.16	0.006
5j	Benzyl	7.38	7.33	0.006
5k	Phenethyl	9.74	9.95	0.021
5l	Phenpropyl	8.76	8.62	0.016

[a] The pIC50 in guinea pig ileal smooth muscle by KCl (80 mM) was determined graphically from the dose–response curve. The number of experiments was six for all compounds

[b] The calculated pIC50 by using multilinear regression equation 1

[c] The relative error prediction

Table 2 Calcium channel blocker activity of asymmetric esters



DHP	R	R′	pIC50 Exp.[a]	pIC50 Calc.[b]	REP%[c]
7a	CH_3	CH_2CH_3	6.18	6.41	0.035
7b	CH_3	$CH_2CH_2CH_3$	6.36	6.32	0.006
7c	CH_3	$C(CH_3)_3$	5.73	5.79	0.010
7d	CH_3	Cyclohexylmethyl	6.45	6.41	0.006
7e	CH_3	Benzyl	7.03	7.17	0.019
7f	CH_3	Phenethyl	7.10	7.05	0.007
7g	CH_2CH_3	$CH_2CH_2CH_3$	6.39	6.23	0.025
7h	CH_2CH_3	$C(CH_3)_3$	5.78	5.74	0.006
7i	CH_2CH_3	Cyclohexylmethyl	6.29	6.35	0.009
7j	CH_2CH_3	Benzyl	7.04	7.05	0.001
7k	CH_2CH_3	Phenethyl	7.15	6.97	0.025

[a] The pIC50 in guinea pig ileal smooth muscle by KCl (80 mM) was determined graphically from the dose–response curve. The number of experiments was six for all compounds

[b] The calculated pIC50 by using multilinear regression equation 2

[c] The relative error prediction

gradient) algorithm until the RMS gradient was 0.01 kcal mol^{-1}. The gradient (G) is the rate of change (first derivative) of total energy (E) with respect to displacement of each atom in the x, y, and z directions for atoms from 1 to n. HyperChem package reports this value for geometry optimization and single point calculations. An RMS gradient of zero means that the structure is at a local minimum or saddle point in the potential energy surface, not necessarily at the structure and state of the lowest energy (global minimum). Among all the energy minima conformers, the global minimum of compounds were used in docking calculations, and the resulted geometry was transferred into Autodock (version 4) program package, which was developed by Arthur J. Olson Chemometrics Group (Morris *et al*., 2009), and docking calculations were performed using AutoDockTools (ADT). In the L-type channel (Fig. 1a) which was downloaded from PDB bank server (PDB entry 1T0J), some amino acids side chain atoms are missing. A reconstruction of the whole side chain as attempted using swiss-pdb viewer 4.0.1.

Method

Docking studies were carried out using the program AUTODOCK 4. This program starts with a ligand molecule in an arbitrary conformation, orientation, and position and finds favorable docking in a protein-binding site using both simulating annealing and genetic algorithms. The program ADT, which has been released as an extension suite to the Python Molecular Viewer, was used to prepare the protein and the ligand. For the macromolecule, crystal structure of L-type calcium channel (Fig. 1a), polar hydrogens were added, and then Kollman United Atom charges and atomic solvation parameters were assigned. The grid maps of docking studies were computed using the AutoGrid4 included in the Autodock4 distribution. Grid center that was centered on the active site (Fig. 1b) was obtained by trial and error and based on the previous study by Cosconati

(Cosconati *et al*., 2007; Davood *et al*., 2009), and 60 × 60 × 60 points with grid spacing of 0.375 were calculated. The GA–LS method was adopted to perform the molecular docking. The parameters for GA were defined as follows: a maximum number of 250,000 energy evaluations; a maximum number of generations of 27,000; mutation and crossover rates of 0.02 and 0.8, respectively. Pseudo-Solis & Wets parameters were used for local search, and 300 iterations of Solis & Wets local search were imposed. The number of docking runs was set to 50. Both Autogrid and Autodock computations were performed on Cygwin. After docking, all the structures generated were assigned to clusters based on a tolerance of 1 Å all-atom RMSD from the lowest-energy structure. Hydrogen bonding and hydrophobic interactions between docked potent agents and macromolecule were analyzed using ADT (Version 1.50). The best docking result can be considered to be the conformation with the lowest (docked) energy.

Computation of structural descriptors and QSAR equations

Software

The resulted geometry of optimized DHPs was transferred into Dragon program package, which was developed by Milano Chemometrics and QSAR Group (Todeschini, 2008). SPSS software (version15) was used for the MLR method.

Data set and descriptor generation

The biological data used in this study are CCB activity, pIC50, from a set of 23 dihydropyridine derivatives, which were synthesized in a pervious experiment (Davood *et al*., 2001), and the structural features of these compounds are listed in Tables 1, 2, and 3 and then used for subsequent QSAR analysis as dependent variables. A large number of molecular descriptors were calculated using Hyperchem, and Dragon package. Some chemical parameters including molecular volume (V), molecular surface area (SA), hydrophobicity (LogP), hydration energy (HE), refractivity (Rf), partial charge (PC), molecular polarizability (MP), and different quantum chemical descriptors including, dipole moment (DM), local charges, HOMO, and LOMO energies were calculated using Hyperchem Software. Dragon software calculated different functional groups: topological, geometrical, and constitutional descriptors for each molecule.

Data screening and model building

The calculated descriptors were collected in a data matrix whose number of rows and columns were the number of molecules and descriptors, respectively. MLR with factor analysis (FA) as the data pre-processing step for variable selection (FA-MLR), and principal component regression analysis (PCRA) methods were used to derive the QSAR equations. The chemical structure, experimental pIC50, and calculated pIC50 values of DHPs are presented in Tables 1, 2, 3.

Results and discussion

Molecular modeling and docking

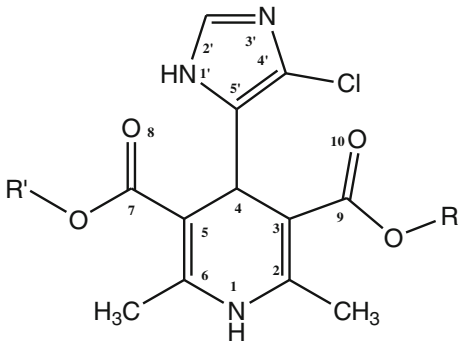
Conformational search and docking studies were performed using Hyperchem (PM3) and Autodock. It suggests that electronic interaction play an important role in ligand–channel interaction and antagonist activity of these compounds. Based on in vivo results of symmetric ester series, increasing the length of the chain in C3- and C5-ester substituents increased the activity. The most potent compound was found to be bis-phenylethyl ester derivative (5k). It is more active than the reference drug, nifedipine. Bis-phenpropyl ester (5l) and bis-benzyl ester (5j) derivatives have comparable activity with nifedipine. In asymmetrical diester series, when R is methyl or ethyl, increasing lipophilic properties of R′ substituent, increases the activity. The most potent and active compounds are methyl/phenethyl (7f) and ethyl/phenethyl (7k) ester derivatives. Their activities are comparable with those of nifedipine. In general, increasing the volume and surface area in each group has positive effect on CCB's potency.

Flexible docking of all data sets, used for the computational study, was carried out on the active site of L-type calcium channel. The predicted binding energies of these inhibitors are listed in Table 4. The predicted binding energy is the sum of the intermolecular energy and the torsional free-energy penalty which is a constant times the number of rotatable bonds in the ligand, which both can affect the mode of interaction of DHPs with the channel. The semi-empirical free energy force field, which was used by Autodock to evaluate conformation during docking simulation, includes six pair-wise evaluations (V) and an estimate of the conformational entropy lost upon binding (ΔS_{conf}):

$$\Delta G = \left(V^{\text{L-L}}_{\text{bound}} - V^{\text{L-L}}_{\text{bound}}\right) + \left(V^{\text{P-P}}_{\text{bound}} - V^{\text{P-P}}_{\text{bound}}\right) + \left(V^{\text{P-L}}_{\text{bound}} - V^{\text{P-L}}_{\text{unbound}} + \Delta S_{\text{conf}}\right)$$

where L refers to the "ligand" and P refers to the "protein" in a ligand–protein docking calculation. Each of the pair-wise energetic terms includes evaluations for dispersion/repulsion, hydrogen bonding, electrostatics, and desolvation that all of them can be affected by changing the substituents in the DHPs 5a–5l and 7a–7k.

Table 3 Calcium channel blocker activity of symmetric (5a–5l) and asymmetric (7a–7k) esters



DHP	R	R′	pIC50 Exp.[a]	pIC50 Cacl.[b]	REP%[c]
5a	CH_3	CH_3	5.92	6.11	0.031
5b	CH_2CH3	CH_2CH_3	6.36	6.32	0.006
5c	$CH_3CH_2CH_3$	$CH_3CH_2CH_3$	7.20	7.02	0.025
5d	$CH(CH_3)_2$	$CH(CH_3)_2$	7.42	7.18	0.033
5e	$CH_2CH(CH_3)CH_3$	$CH_2CH(CH_3)CH_3$	7.02	7.00	0.002
5f	$C(CH_3)_3$	$C(CH_3)_3$	5.39	5.70	0.054
5g	Cyclopentyl	Cyclopentyl	7.01	6.90	0.015
5h	Cyclohexyl	Cyclohexyl	6.02	6.23	0.033
5i	Cyclohexylmethyl	Cyclohexylmethyl	6.20	6.29	0.014
5j	Benzyl	Benzyl	7.38	7.35	0.004
5k	Phenethyl	Phenethyl	9.74	9.92	0.018
5l	Phenpropyl	Phenpropyl	8.76	8.43	0.039
7a	CH_3	CH_2CH_3	6.18	6.11	0.011
7b	CH_3	$CH_2CH_2CH_3$	6.36	6.67	0.046
7c	CH_3	$C(CH_3)_3$	5.73	5.88	0.025
7d	CH_3	Cyclohexylmethyl	6.45	6.00	0.075
7e	CH_3	Benzyl	7.03	6.83	0.029
7f	CH_3	Phenethyl	7.10	7.12	0.002
7g	CH_2CH_3	$CH_2CH_2CH_3$	6.39	6.79	0.058
7h	CH_2CH_3	$C(CH_3)_3$	5.78	5.55	0.041
7i	CH_2CH_3	Cyclohexylmethyl	6.29	6.16	0.021
7j	CH_2CH_3	Benzyl	7.04	7.09	0.007
7k	CH_2CH_3	Phenethyl	7.15	7.31	0.021

[a] The pIC50 in guinea pig ileal smooth muscle by KCl (80 mM) was determined graphically from the dose–response curve. The number of experiments was six for all the compounds

[b] The calculated pIC50 by using multilinear regression equation 3

[c] The relative error prediction

We have docked all of DHPs, 5a–5l and 7a–7k in the active site of L-type calcium channel, and the orientation of the two most potent CCBs, compounds 5k and 7k, are shown in Fig. 2. This study indicates that in the compound 5k, the oxygen of ester (O10) and the N3′ of imidazole ring form a hydrogen bond with the NH of HIS 363(distance = 2.01) and OH of ILE353 (distance = 1.94) (Fig. 2a, b). In the compound 7k the oxygen of ester (O10) and the N3′ of imidazole ring form a hydrogen bond with the NH of HIS 363 (distance = 2.05) and OH GLN367 (distance = 2.094) (Fig. 2c).

These observations and experimental results provide a good explanation for the potent and the selective inhibitory activity of these compounds.

Table 4 Docking results using AutoDock 4 software

DHP	Binding energy[a]	DHP	Binding energy[a]
5a	−4.58	7a	−4.70
5b	−5.39	7b	−4.80
5c	−4.42	7c	−5.03
5d	−4.42	7d	−4.47
5e	−4.40	7e	−5.36
5f	−4.74	7f	−5.66
5g	−5.85	7g	−4.67
5h	−5.47	7h	−4.99
5i	−5.63	7i	−4.14
5j	−5.75	7j	−5.11
5k	−6.45	7k	−5.74
5l	−5.87	Nif	−5.95

[a] The predicted binding energy (kcal/mol)

Quantitative structure activity relationship (QSAR) equations

Based on the procedure explained in the "Materials and methods" section, by using a stepwise MLR method, the following two-parametric equation 1 and one-parametric equation 2 were derived for symmetric and asymmetric diesters, respectively.

The following two-parametric equation was used for symmetric compounds:

$$\begin{aligned} \text{pIC50} &= -2.115\,\text{Mor09p} - 0.944\,\text{Mor06p} + 5.303 \\ n &= 12, F = 84.5, R^2 = 0.95, S = 0.30, P < 0.0001 \end{aligned} \quad (1)$$

Equation 1 could explain 95% of the variance in the pIC50 data. This equation describes the effect of two of the 3D-MoRSE (Mor09p, Mor06p) indices on CCB activity.

The 3D-MoRSE (Mor09p, Mor06p) descriptors appearing in the model are important because they are related to bonds and distances (bond orders, saturation, and ratio of multiple bonds to single bonds, Mor09 (06) p = 3D-MoRSE − signal 09(06)/weighted by atomic polarizabilities). The MoRSE descriptors, 3D-Molecule Representation of Structure based on Electron diffraction, provide 3D information in the same 3D co-ordinates and use the same transformation as electron diffraction. Also, 3D-MoRSE descriptors implicitly take into account the 3D structure and atomic properties, such as partial atomic charges.

The following one-parametric equation was used for asymmetric compounds:

$$\begin{aligned} \text{pIC50} &= -29.271\,\text{X0Av} + 24.704 \\ n &= 11, F = 154.1, R^2 = 0.95, S = 0.13, P < 0.0001 \end{aligned} \quad (2)$$

Equation 2 could explain 95% of the variance in the pIC50 data. This equation describes the effect of X0Av indices on CCB activity, where X0Av encodes information about size, branching, cyclization, unsaturation, and heteroatom

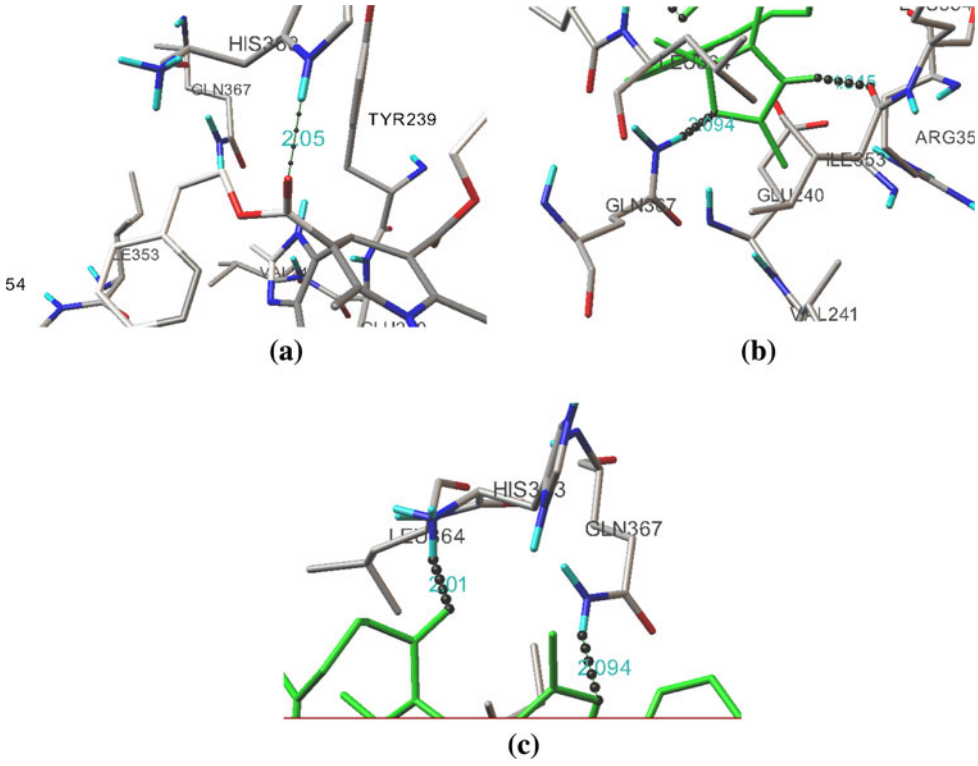


Fig. 2 **a** and **b** docked structures of 5k in the model of LCC, **c** docked structure of 7k in the model of LCC. DHPs are displayed as *sticks*, and Hydrogen bonds are represented with *dashed lines*. (Docking study by using ADT program and LCC model obtained from PDB server)

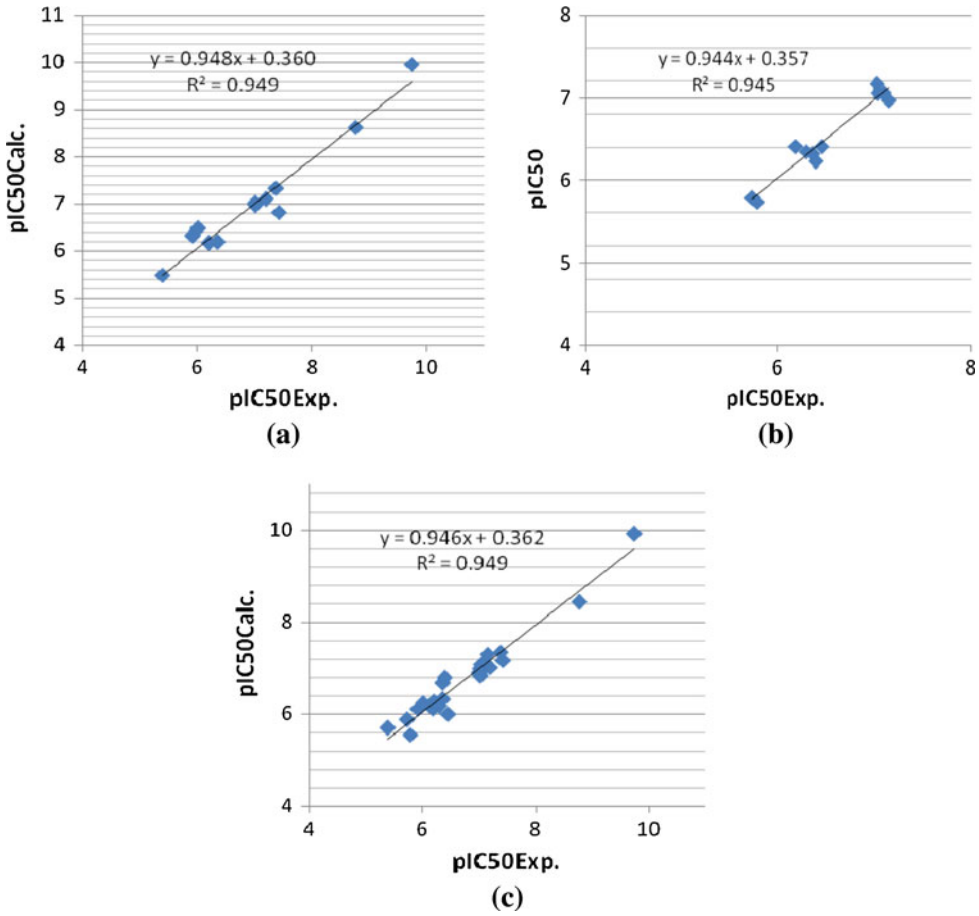


Fig. 3 Plots of cross-validated calculated activity obtained by Eqs. 1, 2, and 3 **a** symmetric DHPs; **b** asymmetric DHPs; **c** both symmetric and asymmetric DHPs

content in the molecule. It emphasizes the importance of the branching of the molecules for the improved activity (http://www.vcclab.org).

When both the symmetric and asymmetric were considered, four-parametric equation 3 was derived for them in which HATS2v is the main descriptor.

$$\begin{aligned} \mathrm{pIC50} &= 52.519\,\mathrm{HATS2v} - 1.173\,\mathrm{Moro6p} + 0.818\,\mathrm{CIC5} \\ &\quad - 0.984\,\mathrm{Moro9p} + 0.604 \\ n = 23, F &= 83.325, R^2 = 0.949, S = 0.24, P < 0.0001 \end{aligned} \tag{3}$$

This equation could explain 95% of the variance in the pIC50 data and describe the effect of GETAWAY (HATS2v), two of the 3D-MoRSE (Mor09p, Mor06p), and topological (CIC5) indices on calcium channel antagonist activity. The HATS2v, leverage-weighted autocorrelation of lag2/weighted by atomic van der Waals volumes, is a 3D-autocorrelation descriptor obtained from MIM (molecular influence matrix), and the CIC5 is among the topological class, and it corresponds to complementary information contents having neighborhood symmetry of the fifth order.

The large amount of F, small S, very small P-value, as well as R^2 value close to one were employed to judge the validity of the regression equation. In general, the regression model is significant at P-value <0.001 using the F statistics, and so our QSAR models are significant.

Finally, plots of cross-validated calculated activity and the experimental values for Eqs. 1, 2, and 3 are shown in Fig. 3a, b, and c, respectively.

Conclusions

Based on the above mentioned results, increases in the volume and size of the molecule lead to the increased lipophilicity and activity of molecules. Using docking study, we have shown that the symmetrical shape is not important, and in both of the symmetric and asymmetric derivatives, oxygen of ester (O10) and the N3′ of imidazole ring have a main role in drug receptor interaction and form a hydrogen bond with the receptor. The results obtained from QSAR equations emphasize that electro-topological properties are very important in DHP potency. Therefore, for future study, it is recommended that we keep the main structure, but in order to achieve better potency, we can change imidazole ring with other heterocyclic ring with an

added lipophilic group. The results from this study are presently being used for the design of newer compounds with better CCB activity.

Acknowledgments We thank Professor Arthur J. Olson for his kindness in offering us the AutoDock 4 program. The technical assistance by the medicinal chemistry department of AZAD University in performing the computational studies is gratefully acknowledged.

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