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Molecular Modeling and QSAR Analysis of Some 4,5-Dichloroimidazolyl-1,4-DHP-Based Calcium Channel Blockers

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The effects of the structural features of some 4,5-dichloroimidazolyl-1,4-dihydropyridine on their calcium channel antagonist activity have been studied using molecular modeling and quantitative structure activity-relationship analysis. Both symmetrical and asymmetrical dihydropyridine derivatives were used. AM1 semi-empirical quantum chemical calculation was used to find the optimum 3-D geometry of the molecules. Four different sets of descriptors, including chemical, topological, quantum chemical and substituent constant, were then calculated for each molecule. For each set of descriptors, the best multilinear QSAR equations were obtained by the stepwise variable selection method using leave-one-out cross-validation as selection criterion. Separate QSAR models were first obtained for symmetrical and asymmetrical derivatives, after which a general model was proposed for the entire set of molecules. This model has root mean square error of 0.45 and reproduces more than 82% of the variances in the calcium channel antagonist activity data. The sum of the negative charges, the energy of the highest occupied molecular orbital, molecular volume and the least negative charge were identified as the most significant descriptors.

Keywords: QSAR, Molecular modeling, Dihydropyridine, Calcium channel antagonist

INTRODUCTION

The influx of extracellular calcium through potential dependent calcium channels is responsible for the regulation of many physiological functions, including smooth and cardiac muscle contraction [1-3]. Therefore, calcium channel blockers (CCBs) have found widespread use in the treatment of cardiovascular disease. Among the various classes of CCBs, the dihydropyridines (DHPs) have been the largest and most widely studied [4]. DHPs are not only important as cardiovascular drugs but also have been extensively used to study the structure and function of voltage-activated calcium channels [5].

These types of compounds (Fig. 1), the prototype of which is nifedipine, have been the aim of many SAR [6-10] and QSAR studies [11-19]. QSAR models are mathematical equations relating chemical structure to their biological activity. They give information useful for drug design and medicinal chemistry [20-22]. Cobrun *et al*. [11] have applied the Hansch analysis method to a series of 4-phenyl substituted DHPs (Fig. 1A). They concluded that the biological activity of DHPs is dependent on the lipophilic as well as the electronic and steric properties of the substituents on 4-phenyl DHP analogues of nifedipine. Mahmoudian and Richard [12,13] have conducted a Hansch analysis on a small number of the same DHPs and found that the bulky and lipophilic groups at

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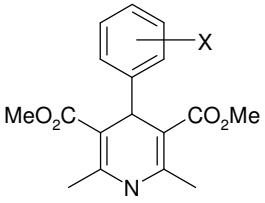
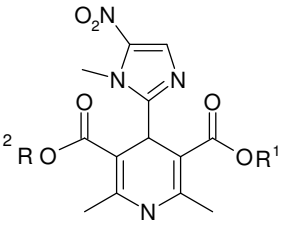
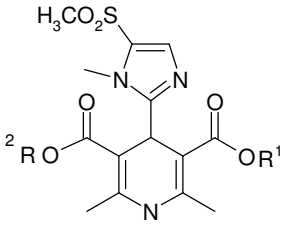


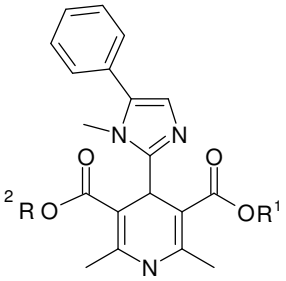
(A) 4-phenyl derivatives



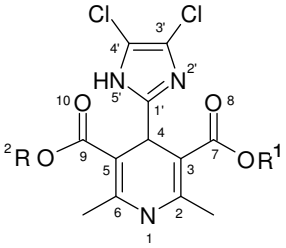
(B) 4-nitroimydazolyl derivatives



(C) 4-methylsulfonylimidazolyl derivatives



(D) 4-phenylimidazolyl derivatives



(E) 4,5-dichloroimidazolyl derivatives

Fig. 1. Chemical structures of DHP derivatives used in different QSAR studies.

the *ortho* position and bulky groups with high Hammett constants at the *meta* position of the 4-phenyl ring increase DHP activity. Recently, Guadio *et al*. [17] have reported a QSAR study on a large number of 4-phenyl substituted nifedipine analogs using a combination of substituent constants and molecular descriptors. They found that the activity of a *meta*-substituted compound is affected by both the steric and electronic parameters, while hydrophobic and electronic parameters of the *para*-substituted DHPs affect the drug activity. We also studied the effects of different electronic features of these types of DHPs utilizing *ab intio* quantum chemical calculations [23].

In our research group we synthesized a large number of DHP derivatives with nitroimidazolyl (Fig. 1B), methylsulfonylimidazolyl (Fig. 1C) and phenylimidazolyl (Fig. 1D) at the C-4 position and different substitutions at the C-3 and C-5 positions of the DHP ring, and determined their calcium channel blocking activity in guinea-pig ileum [24-28]. In previous QSAR studies of this type of DHP derivative, we first applied the classical Hansch analysis method and found that both electronic and hydrophobic interactions occur between the nifedipine analogues and the receptor [29]. Then, partial least squares (PLS) [30] and principal component-artificial neural network (PC-ANN) [31] were employed using

theoretically derived descriptors. A genetic algorithm (GA) was used for the selection of the best set of descriptors in PLS regression and for selection of the best set of principal components in PC-ANN model [31]. The significance of topological indices and autocorrelation descriptors were indicated in these studies. In addition, the quantum chemical-QSAR study of these compounds indicated the importance of the electronic features of the DHP derivatives for receptor binding [23]. Conformational analysis of the 4-nitroimidazolyl derivatives has also been performed to obtain the conformational patterns of the active DHP derivatives [32].

In continuation of our studies on the effect of structural parameters on the calcium channel antagonist activity of different DHP derivatives, we will discuss the results of our molecular modeling and QSAR analyses of some newly synthesized 1,4-dihydropyridine derivatives containing 4-dichloroimidazolyl substituents (Fig. 1F). We aimed to analyze the effect of different electronic, topological, constitutional and chemical parameters on their biological activity. AM1 semiempirical calculations were used to optimize the 3-D geometry of the molecules and multiple linear regression (MLR) analysis was employed for construction of multilinear QSAR models.

EXPERIMENTAL

Data Set

The biological data used in this study are the calcium channel antagonist activity in guinea-pig ileum (IC_{50}) of a series of C-3 and C-5 substituted 4-(4,5-dichloroimidazolyl)-1,4-dihydropyridine derivatives. Some compounds are symmetric and have the same substituent at C-3 and C-5 and the others are asymmetric. The synthesis and determination of the activity of these compounds have already been reported by Amini *et al*. Their study indicated that the 4-(4,5-dichloroimidazolyl) moiety is a bioisoester of the nitrophenyl and 2,3-dichlorophenyl moieties [33]. Tables 1 and 2 list the structural features and calcium channel antagonist activity of the respective symmetrical and asymmetrical compounds under study. The biological data were converted to logarithmic scale (pIC_{50}) and then used for subsequent QSAR analysis as dependent variables.

Molecular Modeling

The chemical structures of the molecules were constructed using Hyperchem software (Version 7, Hypercube Inc.). The Z-matrices of the structures were constructed by the software and transferred to the Gaussian 98 program [34]. Complete geometry optimization was performed taking the most extended conformations as starting geometries. Semi-empirical molecular orbital calculations (AM1) of the structures were performed using the Gaussian 98 program. For superimposition of the optimized molecular structures [35], nifedipine was used as the reference compound. The molecules were superimposed onto nifedipine using a fitting procedure in the HyperChem program that minimized the RMS deviation of their respective position using the C-3, C-4 and C-5 atoms of the DHP ring.

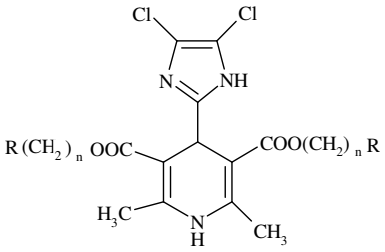
Descriptor Generation

A large number of molecular descriptors were calculated using HyperChem, Gaussian 98 and Dragon [36] software. The Gaussian 98 program was employed for the calculation of different quantum chemical descriptors including heat of formation, dipole moment, local charges, and HOMO and LUMO energies. The Dragon program was used to calculate different topological and constitutional descriptors for each molecule. Chemical parameters including molar volume (V), molecular surface area (SA), hydrophobicity (logP), hydration energy (HE) and molecular polarizability (MP) were calculated using Hyperchem software. Classical substituent constants including the Hansch hydrophobic constant (π), Hammett electronic constants (σ) and Taft field effect (FI) and resonance (R) substituent constants were also used as descriptors in this study.

Model Development

The calculated descriptors were gathered in a data matrix, **D**. First, the descriptors were checked for constant or near constant values and those detected were discarded from the original data matrix. Then, the descriptors were correlated with each other and with the activity data. Among the colinear descriptors detected, the one most highly correlated with activity was retained and the rest were omitted. Finally, MLR with stepwise selection and elimination of variables was

Table 1. Structural Features, Experimental Activity and Corresponding Predicted Activity[a] of Symmetrical DHP Derivatives



No.	R	n	$(pIC_{50})_{EXP}$	$(pIC_{50})_{CALC}$ [b]	REP (%)[c]
6a	CH_3	0	6.58	6.23	-5.32
6b	CH_3	1	7.61	7.76	1.97
6c	CH_3	2	8.69	8.73	0.46
6d	CH_3	3	8.29	8.31	0.24
6e	CH_3	4	8.08	7.73	-4.33
6f	$CH(CH_3)_2$	0	7.41	7.70	3.91
6g	$CH(CH_3)_2$	1	7.91	7.94	0.38
6h	$CH(CH_3)_2$	2	7.18	7.21	0.42
6i	$C(CH_3)_3$	0	4.75	4.39	-7.58
6j	C_5H_9	0	8.62	8.43	-2.20
6k	C_6H_{11}	0	8.52	8.78	3.05
6l	C_6H_{11}	1	7.39	7.88	6.63
6m	C_6H_{11}	2	5.65	5.86	3.72
6n	C_6H_5	1	8.65	8.33	-3.70
6o	4-Me-C_6H_4	1	8.01	7.95	-0.75
6p	C_6H_5	2	9.79	9.09	-7.15
6q	C_6H_5	3	8.40	8.30	-1.19
6r	C_6H_5	4	8.85	9.52	7.57

[a]By MLR Eq. A5. [b]Cross-validation values calculated using Eq. A5. [c]Percent of the relative error of prediction.

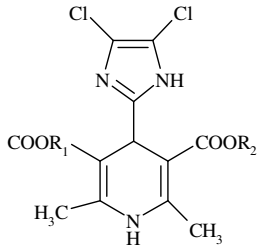
applied to the development of QSAR models using SPSS software (SPSS Inc., version 11). The resulting models were validated by leave-one-out cross-validation procedures to check their predictivity and roubustness. All calculations were run on a Pentium IV personal computer (2.6 MB CPU) with the Windows XP operating system.

RESULTS AND DISCUSSION

Conformational Analysis

As an important tool for studying the calcium channel structure and function, the conformational features of DHP analogues have been the subject of a great deal of investigation, from both the theoretical and experimental perspectives [37-40]. Despite many studies on the structure-activity relationship of DHP derivatives, debates still remain regarding the exact stereochemical/conformational activity requirements [41]. The X-ray crystal structure of some DHPs reveal that the 1,4-DHP ring adopts a boat conformation [42-43]. It was proposed that calcium channel modulation (agonist *vs*. antagonist activity) is dependent on the absolute configuration at C-4 [45]. In addition, other studies have

Table 2. Structural Features, Experimental Activity and the Corresponding Predicted Activity[a] of Asymmetrical DHP Derivatives



No.	R_1	R_2	$(pIC_{50})_{EXP}$	$(pIC_{50})_{CALC}$[b]	REP(%)[c]
8a	CH_3	CH_2CH_3	7.23	7.38	2.07
8b	CH_3	$CH(CH_3)_2$	7.83	7.81	-0.26
8c	CH_3	$CH(CH_2)_2CH_3$	8.47	8.29	-2.13
8d	CH_3	$C(CH_3)_3$	6.63	6.91	4.22
8e	CH_3	$C_6H_{11\ (cyclohexyl)}$	8.79	8.80	0.11
8f	CH_3	$CH_2C_6H_5$	9.04	9.21	1.88
8g	CH_3	$CH_2CH_2C_6H_5$	8.41	8.27	-1.66
8h	CH_2CH_3	$CH(CH_3)_2$	8.73	8.73	0.01
8i	CH_2CH_3	$CH(CH_2)_2CH_3$	8.19	8.46	3.30
8j	CH_2CH_3	$C(CH_3)_3$	7.43	7.40	-0.40
8k	CH_2CH_3	$C_6H_{11\ (cyclohexyl)}$	9.31	8.97	-3.65
8l	CH_2CH_3	$CH_2C_6H_5$	8.89	9.13	2.70
8m	CH_2CH_3	$CH_2CH_2C_6H_5$	8.39	8.81	5.00
8n	$CH(CH_3)_2$	$CH(CH_2)_2CH_3$	8.21	8.50	3.55
8o	$CH(CH_3)_2$	$C(CH_3)_3$	7.72	7.61	-1.43
8p	$CH(CH_3)_2$	$C_6H_{11\ (cyclohexyl)}$	7.38	7.05	-4.47
8q	$CH(CH_3)_2$	$CH_2C_6H_5$	9.14	9.31	1.86
8r	$CH(CH_3)_2$	$CH_2CH_2C_6H_5$	8.81	8.35	-5.22

[a]By MLR Eq. A5. [b]Cross-validation values calculated using Eq. A5. [c]Percent of the relative error of prediction.

confirmed the flexibility of both the ester and C-4 aryl groups of DHPs [43,45]. Some previous conformational analyses of 4-phenyl DHP confirmed these findings [42-45].

There are several conformational features considered in this study, the most important of which include the orientation of the carbonyl groups, orientation of the methyl of the nitroimidazolyl ring, relative position of the nitroimidazolyl ring, and deviation from the planarity of the DHP ring. The *cis* or *trans* orientation of carbonyl groups bonded at C3 and C5 are reflected by the C2-C3-C7-O8 (α_1) and C5-C6-C9-O10 (α_2) dihedral angles. If these angles were between -90° and +90°, the orientation would be considered *cis*, and the *trans* orientation would be assumed if the dihedral angels were between (+90°)-(+180°) or (-90°)-(-180°). The molecules were assigned as *cis-cis*, *cis-trans*, and *trans-trans* based on orientation of the individual carbonyl groups. If the orientation of the methyl of the nitroimidazolyl ring with respect to the hydrogen atom bonded at C4 was in the same direction as that of the hydrogen (i.e. out of the plane of the DHP ring), the conformation would be assigned *syn-periplanar (sp)*;

otherwise the conformation would be named *anti-periplanar (ap)*. The relative position of the nitroimidazolyl ring with respect to the DHP ring is measured by the N1-C4-C3-C2 (α_3) dihedral angle. The deviation from planarity of DHP ring is measured by the C2-C3-C5-C6 (α_4) dihedral angle.

Here, semi-empirical quantum chemical calculation using AM1 Hamiltonian was used to find the optimum 3-D geometry of the molecules. The Polak-Ribier algorithm with a root mean squares gradient of 0.1 kcal mol^{-1} was selected for optimization. In order to prevent the structures from locating at the local minima, geometry optimization was run many times with different starting points for each molecule. The calculated dihedral angles of the molecules are shown in Table 3.

The results indicate that almost all of the molecules have the semi-boat conformation of the DHP ring. The respective dihedral angle (2-3-5-6) is varied between 0-0.5 degrees. The numbering of the atoms is represented in Fig. 1. The resulting 1'-4-3-2 dihedral angle also indicates that the dichloroimidazolyl ring bisects the DHP ring and stands in the pseudoaxial conformation. The 6-5-9-10 and 2-3-7-8 dihedral angles reveal that, except for the **6o** derivative, the carbonyl groups of all of the studied chloroimidazolyl DHP derivatives adopted a *cis-cis* conformation. The overlaid three-dimensional stereo plot of the most active chloroimidazolyl derivatives with nifedipine, 4-nitroimidazolyl, 4-sulfonyl-imidazolyl, and 4-phenylimidazolyl derivatives, is shown in Fig. 2. We can clearly see that the different 1,4-DHP derivatives represent the same three-dimensional geometry. The major differences are the orientation of the carbonyl group attached to the C-5 of the DHP ring.

QSAR Analysis

To obtain the effects of the structural parameters of the investigated DHP derivatives on their calcium channel blocker activity, QSAR analysis was performed with various molecular descriptors. For this purpose, the symmetrical and asymmetrical derivatives were analyzed separately. The octanol-water partition coefficient (logP), the hydration energy and hydrophobic factor have been considered as descriptors for the hydrophobic effect. The steric effect has been described by means of the surface area, molecular volume, and topological and geometrical indices. The electronic descriptors

Table 3. Some Important Dihedral Angles of the Most Stable Conformers of the DHP Derivatives Used in this Study

No.	2-3-5-6	1'-4-3-2	6-5-9-10	2-3-9-10
6a	0.31	99.03	4.26	-0.34
6b	0.40	84.13	4.28	0.79
6c	0.34	83.81	0.50	4.35
6d	0.35	83.95	0.62	4.27
6e	0.59	84.13	-3.66	11.18
6f	0.39	84.28	1.25	4.62
6g	0.42	82.76	1.02	4.44
6h	0.37	84.13	0.65	4.25
6i	0.28	81.63	0.02	4.53
6j	0.31	81.28	-1.58	4.33
6k	0.54	83.22	2.17	6.00
6l	0.54	84.10	1.78	7.12
6m	0.35	84.13	0.76	4.29
6n	0.48	86.43	0.57	3.32
6o	0.12	81.13	-170.24	-163.3
6p	0.32	83.62	0.47	4.17
6q	0.41	85.41	1.44	4.66
6r	0.32	83.63	0.52	4.19
8a	0.36	84.35	0.74	4.25
8b	0.39	84.42	1.08	4.14
8c	0.35	84.12	0.60	4.25
8e	0.34	82.54	0.09	4.08
8f	0.24	80.90	2.47	3.87
8g	0.30	84.04	0.08	4.07
8h	0.40	84.31	0.68	4.31
8i	0.29	81.09	-0.98	4.24
8j	0.35	83.89	0.57	4.27
8k	0.31	82.27	0.06	4.09
8l	0.32	81.89	-0.42	2.29
8m	0.40	86.64	0.53	4.69
8n	0.32	84.09	0.64	4.38
8o	0.33	83.79	0.69	4.29
8p	0.32	82.41	0.22	4.54
8q	0.32	81.63	-0.41	4.26
8r	0.44	86.64	0.65	5.36
8s	0.32	99.03	4.26	-0.34

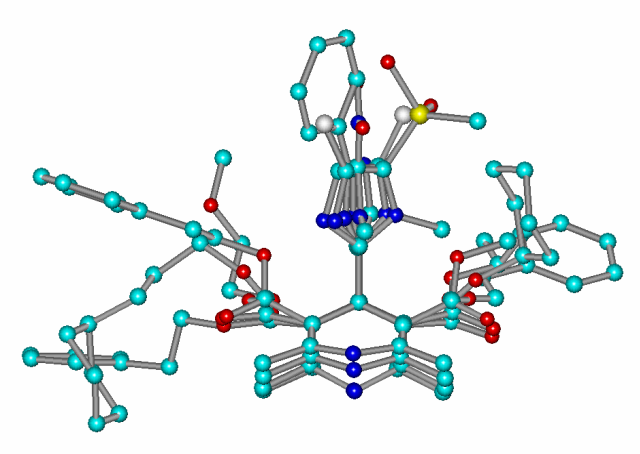


Fig. 2. Pverlaid three-dimentional stereo plot of Nifedipine with the most active derivative of 4-chloroimidazolyl, 4-nitroimidazolyl, 4-sulfonylimidazolyl, 4-phenylimidazolyl classes.

(E_{HOMO}, E_{LUMO}, and local charges) have been derived using AM1 calculation. Indices of electronegativity, electrophilicity, hardness and softness were calculated from the E_{HOMO} and E_{LUMO}. Constitutional descriptors were used to describe the effect of different fragments of the molecules. Finally, substituent constant such as σ, π, and *FI* parameters were used as molecular descriptors for the classical Hansch analysis method.

For each set of descriptors, the best multilinear regression equations were obtained by the stepwise selection methods of MLR subroutine of SPSS software. The correlation coefficient (R^2), standard error of regression (*SE*), correlation coefficient for cross-validation significance (Q^2), root mean square error (RMS), and significance level (*P*) were employed to judge the validity of regression equation. The resulting regression equations are summarized in Tables 4 and 5 for the asymmetrical and symmetrical derivatives, respectively.

Asymmetrical derivatives. Table 4 represents the QSAR models for asymmetrical derivatives by using different sets of molecular descriptors. The equation, found by using chemical descriptors (A1), explains the effect of lipophilicity and steric hindrance (i.e. logP and molecular volume, respectively) on the calcium channel antagonist activity of the DHP derivatives. In this equation, which has good statistical quality, logP has a positive effect and MV has a negative effect. This indicates that there is a challenge between the logP and size of the molecule to transport across the cell membrane and reach to the receptor [29,30]. Increasing in lipophilicity facilitates both the transport of molecule from the hydrophobic membrane and hydrophobic interaction with receptor. Otherwise, increasing the volume and size of molecule results in an increase in lipophilicity and so the activity of molecules. On the other hand, a further increase in the volume hinders the ligand from passing through the cell membrane and thus decreasing the activity. Therefore, we can deduce that lipophilcity and geometrical parameters should be optimized.

As seen from equation A2, a valuable QSAR model has been obtained for the calcium channel antagonist activity of the studied asymmetrical DHP derivatives from topological descriptors (X3A and IDDE). This equation describes the structure-activity relationships better than those obtained from the chemical descriptors. The two-parameter equation has correlation coefficient and standard error equal to 0.903 and 0.375, respectively. The predictivity of this model is confirmed by high cross-validation statistic (Q^2 = 0.901). Indeed, a very low difference between R^2 and Q^2 indicates the model is not overfitted.

Equation A3 indicates the strong dependency of the calcium channel antagonist activity on the electronic features of the DHPs [23]. Sum of negative charge (SNC) is the most important parameter appeared in this equation and reveals the presence of coulombic interactions between the ligands and receptors. The negative sign of the coefficient of SNC demonstrates that the ligands with the least SNC could interact with receptor more efficiently. This indicates that there is probably a positive region in receptor which produces a coloumbic interaction with the ligand. The highest-occupied molecular orbital (HOMO) energy has also negative effect and dipole moment on the x-direction (DMx) has positive effect on calcium channel blocker activity. These contributions suggest that electronic interaction play important role in antagonist activity of these compounds.

Another QSAR model was obtained by using descriptors of substituents on molecules (i.e. substituent constant) instead of using descriptors from whole molecular structure. In this case, no information about the three-dimensional structure of the molecules is necessary and therefore the computation time is decreased dramatically. Equation A4, which derived from a pool of substitution constants, shows the dependency of the

Table 4. MLR Analysis with Different Types of Descriptors for Asymmetrical Derivatives

Eq.	MLR Equation	Descriptor type
A1	pIC_{50} = 6.407 (±1.683) logP - 0.020 (±0.08) Volume + 3.566 (±0.766) N = 15, R^2 = 0.795, SE = 0.3797,Q^2 = 0.725, F = 23.224, RMS = 0.411, P = 0.001	Chemical
A2	pIC_{50} = 3.306 (±0.720) IDDE + 105.129 (±33.814) X_3A - 24.145 (±5.348) N = 15, R^2 = 0.903, SE = 0.375, Q^2 = 0.901, F = 26.480, RMS = 0.244, P = 0.000	Topological
A3	pIC_{50} = -8.159 (±1.602) SNC - 690.417 (±195.190) HOMO + 1.465 (±0.597) DMx - 1074.930 (±300.242) N =15, R^2 = 0.855, SE = 0.367, Q^2 = 0.741, F = 27.918, RMS = 0.451, P = 0.000	Quantum
A4	pIC_{50} = -195.532 (±21.303) $\sigma_{R2}{}^2$ - 34.46 (±4.220) $\sum\sigma$ - 23.418 (±5.922) $\sum R^2$ + 5.023 (±0.771) N = 18, R^2 = 0.895, SE = 0.316, Q^2 = 0.831, F = 39.696, RMS = 0.367 P = 0.000	Substitutional
A5	pIC_{50} = 3.755 (±0.488) IDDE + 6.529 (±1.285) PJI3 - 15.009 (±4.097) F_{R1} - 12.777 (±1.828) N = 17, R^2 = 0.926, SE = 0.237, Q^2 = 0.861, F = 50.419, RMS = 0.315, P = 0.003	All

Table 5. MLR Analysis with Different Types of Descriptors for Symmetrical Derivatives

Eq.	MLR Equation	Type of descriptor
S1	pIC_{50} = 1.449 (±0.193) LogP - 0.057 (±0.012) MR + 10.646 (±0.948) N =15, R^2 = 0.930, SE = 0.298, Q^2 = 0.902,F = 80.331, RMS = 0.328, P = 0.001	Chemical
S2	pIC_{50} = -5.363 (±0.763) IC_2 + 3.474 (±0.628) IC_4 -0.001 (±0.001) VRA_1 + 13.644 (±2.053) N =15, R^2 = 0.894, SE = 0.425,Q^2 = 0.801,F = 30.835, RMS = 0.543, P = 0.001	Topological
S3	pIC_{50} = -686.684 (±238.696) LUMO + 6.355 (±2.514) LNC - 1051.582 (±368.508) N =15, R^2 = 0.805, SE = 0.537, Q^2 = 0.701, F = 24.813, RMS = 1.783, P = 0.0001	Quantum
S4	pIC_{50} = -177.729 (±28.008) σ^2 - 225.084 (±52.648) FI^2 + 12.026 (±0.725) N =15, R^2 = 0.822, SE = 0.580, Q^2 = 0.782, F27.737, RMS = 0.593, P = 0.000	Substitutional
S5	pIC_{50} = 0.844 (±0.066) LogP + 6.815 (±0.948) LNC - 0.241 (±0.089) DMx - 0.025 (±0.004) MR + 8.882 (±0.414) N =18, R^2 = 0.966, SE = 0.255, Q^2 = 0.905, F = 91.224, RMS = 0.418, P = 0.0001	All

calcium channel antagonist activity of the studied DHPs on the electronic properties (σ_{R1} and σ_{R2}) of the substituents on the C-3 and C-5 carbon atoms. The sign of this parameter, which is positive for electron withdrawing groups and negative for electron donating substituents, indicates that substituents with low σ values (electron donating substituents) block calcium channels. Another parameter ($\sum R$) is the sum of resonance substituent constants for R1 and R2 groups.

The above QSAR models (Eqs. A1-A4) indicate the effects of the different types of descriptors on the calcium channel antagonist activity of the studied DHP derivatives. A unified QSAR model (Eq. A5) with high statistical quality (R^2 = 0.926, SE = 0.237, Q^2 = 0.861) was obtained from the pool of all type of descriptors. This equation contains two topological descriptors (IDDE; mean information content on distance degree equality and PJI3, 3D Petijean shape index) and one substituent constant (F_{R1}). The calculated values of the pIC50 using Eq. A5 among with the corresponding percent of the relative errors of prediction (REP) are listed in Table 1.

The REP values are distributed between ±0.4 and ±7.5, which indicate the good predictive ability of the resulting model. The plots of cross-validated calculated activity and the corresponding residuals against the experimental values are represented in Figs. 3A and 3B, respectively. The data shown in Fig. 3B are scattered around a straight line with the respective slope and intercept equal to 0.99 and 0.09, which are very close to the ideal values; one and zero, respectively. The residual plot shows the relatively uniform distribution of data around the zero line. Two compounds (i.e. **6r** and **6p**) represent higher deviation in relative to the others; however, the REP for these compounds is around ±7%.

Symmetrical derivatives. Comparing the reported calcium channel antagonist activity of the dichloroimidazolyl-DHP derivatives (Tables 1 and 2) reveals that the symmetrical derivatives represent more diverse activity, i.e. the pIC50 of the asymmetrical derivatives varies between 6.91 and 9.31, whereas that of symmetrical derivatives lies between 4.39 and 9.52. Meanwhile, the symmetrical derivatives represent lower activity. Table 5 lists the resulting QSAR equations for symmetrical DHP derivatives. The equation, obtained by chemical descriptors (S1), shows approximately the same results as those obtained for asymmetrical derivatives. The positive effect of logP on the calcium channel antagonist activity is revealed by this equation.

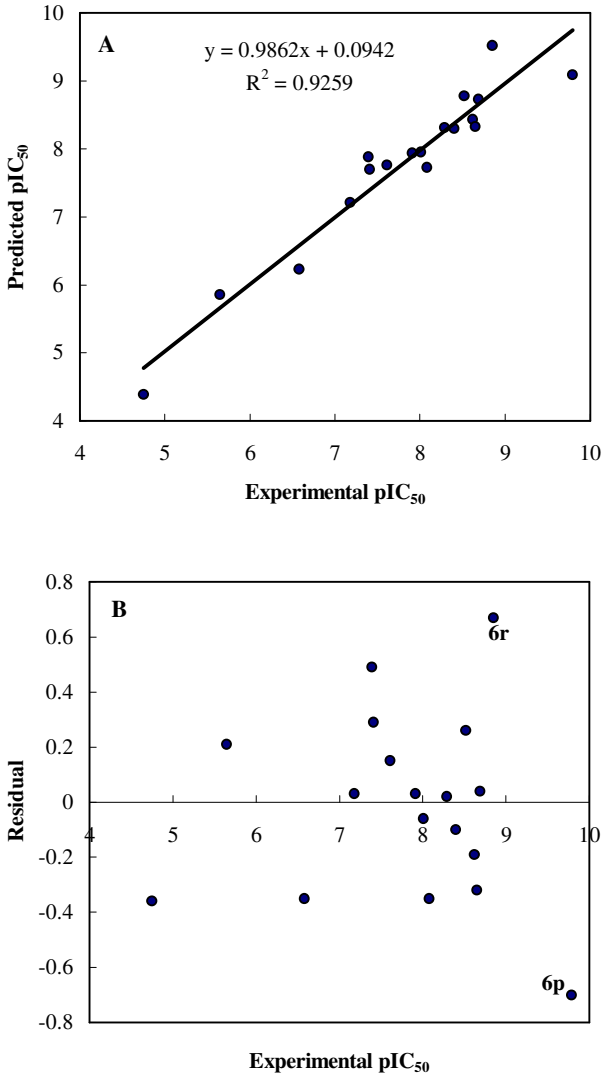


Fig. 3. Plot of (A) cross-validated calculated activity obtained by Eq. A5 and (B) residuals against the experimental activity for asymmetrical DHP derivatives.

Equation S2 demonstrates the effect of two information content indices (neighborhood symmetry of 2-order, IC_2; neighborhood symmetry of 4-order, IC4) and a Randic-type eigenvector-based index from distance matrix (VRA1) on the activity of symmetrical derivatives. The respective correlation coefficient and standard error of regression of the equation is 0.894 and 0.425. Equation S3 shows that, among the quantum

chemical descriptors, the effect of LNC and LUMO on the activity of symmetrical derivatives is similar to that obtained for asymmetrical DHPs. These observations confirm the presence of coloumbic and transient interactions, respectively.

This equation also has good statistical quality. The equation obtained from the substituent constant parameters (S5) shows approximately the same results as asymmetrical derivatives. The two-parameter QSAR models, containing Hammett (σ) and Taft FI parameters, confirm the significance of the electronic interaction between these types of DHP derivatives and their receptor on the calcium channel.

The last equation (S5) was obtained from the pool of all types of descriptors. Stepwise selection and elimination of variables produced a five-parameter QSAR equation. This equation, which has high statistical quality (R^2 = 0.966, SE = 0.255, Q^2 = 0.905), demonstrates that quantum (DM_x, LNC) and chemical (MR, logP) parameters are two major factors controlling the binding of the symmetrical derivatives to the receptor. It should be noted that substitutional parameters did not appear in the final QSAR model. The cross-validated calculated values of pIC50 of the symmetrical DHP derivatives using Eq. S5 and the corresponding relative error of prediction are listed in Table 2. The graphical representation of the data is shown in Figs. 4A and 4B, respectively. Similar to asymmetrical DHP, the data of the plot of the calculated activity against the experimental values show a linear behavior distributed around a straight line, the slope and intercept of which represent a slight deviation from the ideal values. Although the statistical quality of the data shown in Fig. 4A is moderately lower than those of Fig. 3A, the residual plot of the former (as shown in Fig. 4B) represents more uniform distribution without any significant outliers.

General model for entire set of molecules. Finally, attempts were made to find a general model combining both symmetrical and asymmetrical chloroimidazolyl DHP derivatives. To do so, a descriptor data matrix composed of all molecules and all calculated descriptors was used. The following 5-parameter multilinear QSAR model was the result of a stepwise selection of variables:

pIC_{50} = -1.245 (±0.588) $I_{ter\text{-}butyl}$ + 0.558 (±0.060) LogP + 11.756 (±1.865) ∑R - 0.226 (±0.053) $N_{Rotable\ bond}$ + 19.757 (±0.863) X2AV + 6.733 (±1.153)

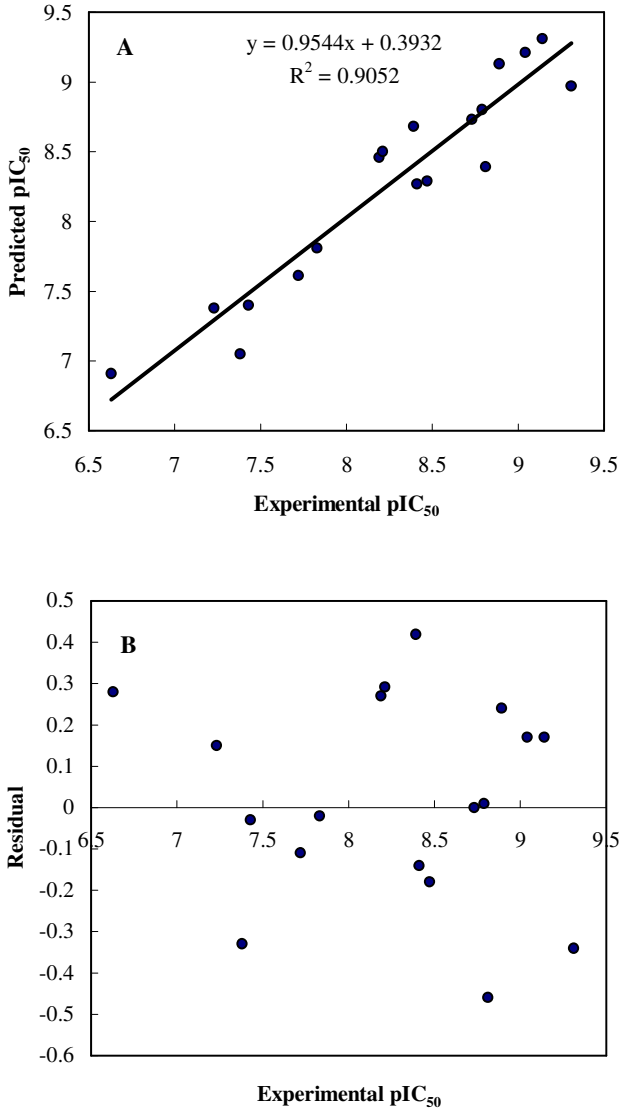


Fig. 4. Plot of (A) cross-validated calculated activity obtained using Eq. S5 and (B) residuals against the experimental activity for asymmetrical DHP derivatives.

where N = 36, R^2 = 0.880, SE = 0.396, Q^2 = 0.821, F = 39.493, RMS = 0.456, P = 0.003

In this equation, $I_{ter\text{-}butyl}$ is an indicator variable describing the presence or absence of tertio-butyl group on the molecule. The positive sign of the coefficient of this variable suggests

that the presence of this group is directed toward calcium channel antagonist activity. In the same manner as previous equations, a lipophilicity parameter, an electronic property and a topological index appear in the equation found for the entire set of molecules. Interestingly, the number of rotatable bonds has been selected as an important parameter, which has a negative effect on the calcium channel antagonist activity. This implies that higher molecular rigidity corresponds with higher calcium blocker activity. As expected, the statistical quality of the model is lower than those found for each separate type of molecule. However, this model possesses a good cross-validated correlation coefficient (Q^2 = 0.821) and can reproduce more than 82% of the variances in the calcium blocker activity of the studied chloroimidazolyl DHP derivatives.

It should be noted that we considered only the MLR method for constructing the QSAR models. Although the use of nonlinear models may present more predictability for the suggested QSAR, for such a relatively low number of molecules, the descriptive models are preferred over predictive ones. Nonlinear modeling methods such as artificial neural networks (ANN) produce predictive models whose chemical interpretations are difficult. Meanwhile, nonlinear modeling with ANN is more complex than MLR analysis and requires higher computer skills. Meanwhile, the predictivity of the proposed QSAR models by MLR analysis was not low. Models with a Q^2 larger than 0.75 can be considered predictive models [46]. Therefore, in this work we did not try to obtain extra predictive models by nonlinear methods such as ANN.

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