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The Application of CoMFA Approach for the Design of 1,4-Dihydropyridines as Calcium Channel Blockers

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Abstract: TCalcium channel blockers are important molecular entities involved in the treatment ofmany cardiovascular disorders especially hypertension. 1,4-Dihydropyridineis a well-established class of calcium channel blockers approved for treatment of hypertension and angina. Comparative Molecular Field Analysis (CoMFA) was applied to a set of 1,4-dihydropyridines to build a3D-QSAR model which have been utilized for the design and prediction of novel 1,4-dihydropyridines. The significant modelwas developed with R^2> 0.9 and lower value of standard error (SE). The predictive efficacy of the model was established by the activity prediction of a test set and was observed to be of reasonable accuracy. New molecules were designed by analysis of the contours, obtained from the model. Subsequent prediction of activities and docking at the 1,4-dihydropyridine receptor model active site of the designed molecules gave good results.

Keywords: 1,4-Dihydropyridines; Calcium channel blockers; 3D-QSAR; CoMFA, Molecular docking

Introduction

Calcium channel blockers are imperative drugs for the treatment of many cardiovascular disorders including hypertension and angina pectoris[1-3].1,4-Dihyropyridines (DHPs) are one of calcium channel blockers that modulate the calcium entry through binding to a high-affinity binding site in L-type voltage-gated calcium channels[4-7]. Inhibition of calcium entry into the cells results in relaxation of vascular smooth muscle and reduction of the elevated blood pressure [8, 9].DHPs have a negative inotropic effect on the cardiac muscle [10, 11].DHPs are not restricted to the treatment of cardiovascular disorders but also implemented in the anticancer drugs [9, 12-16], anti-inflammatory [17-20]and antiepileptic drugs[21-23].

Quantitative structure–activity relationship (QSAR) is a powerful drug design tool that is widely usedtoconstruct a predictive relationship between physicochemical properties of chemical substances and their biological activities. Comparative Molecular Field Analysis (CoMFA) is a mainstream 3D-QSAR which inspects the three-dimensional properties of the ligands by considering various factors, including molecular conformation and alignment, field descriptors and grid spacing to predict their biological activities using robust chemometric techniques [24]. It has served as a valuable predictive tool in the design and optimization of pharmaceutical lead compounds. QSAR certainly decreases the number of compounds to be synthesized by facilitating the selection of the most promising candidates. Several success stories of QSAR have attracted the medicinal chemists to investigate the relationships of structural properties with biological activity [25-27].

This paper reports the development of 3D QSAR model using CoMFA with the help of the reported experimental calcium antagonist activityfora series of 4-methylsulfonylimidazolyl-1,4-dihydropyridines.Analysis of the steric and electrostatic contours of the model was used to design the new molecules. Moreover, the activities of the designed molecules have been predicted and their docking studies were carried out in the 3D structure of 1,4-DHP receptor model.

Materials and methods

CoMFA 3D QSAR Modeling

A set oftwenty-fivecompounds and nifedipinewith their calcium antagonist activities in terms of $pIC_{50}$was selected from the literature[28] c.f., Table 1. The structures of these compounds were drawn and geometry optimized using Marvin Sketch V5.1.3 [29]. The optimized structures were exported to Sybyl-X 1.1 in Mol2 file format. Energy minimization by Powell method after assigning Gasteiger-Marsili charges [30]was performed to all structures. The optimized structures were aligned to 2,6-dimethyl-1,4-dihydropyridine-3,5-dicrboxylic acid as a template structure. The set of nineteen molecules (Table 1) were used as a training set for model building and a test set of 6 molecules were used for model validation. CoMFA was performed using the QSAR option of SYBYL. A sp3 carbon atom with a radius of 1.53 Å and a charge of +1.0 was used as a probe to calculate the steric and electrostatic energies among the probe and the molecules using the Tripos force field[31]. The truncation for both the steric and the electrostatic energies was set to 30 kcal/mol.

Docking studies

Docking process was performed using the 3D coordinates of the active siteof the DHP receptor model developed by Shaldam et al.[32]. The most promising designed molecules along with nifedipine were drawn into Marvin Sketch V5.1.3 [29]. The most energetically favored conformer was saved as (*.mol2) file format for docking. The optimal geometry of the ligands was determined during the docking process. Docking was performed in a multistep procedure using Molegro Virtual Docker V6.0 program. Firstly, nifedipine was placed in the proposed active site defined by SAR [32]. The NH-group of DHP is considered as the most crucial part of the ligand that forms H-bond with the receptor. Consequently, docking template was generated in attempts to align all ligands to the orientation of nifedipine. This is a demanding to bias the formation of H-bond with Tyr^{1149} -an important DHP sensing residue while takes the orientation described by SAR [32]. Docking template consisted of one hydrogen bond donor, two rings, three hydrogen bond acceptors and five steric moieties. The iterative simplex algorithm was chosen to perform docking process with 10 runs per ligand, 200 population size, 1000 max

iteration and 8 poses for each ligand. Secondly, MolDock docking engine [33],using docking template and the optimized ligands, was executed. Finally, the top returned poses were manually modified to maximize binding to DHP sensing residues.

Results and Discussion

CoMFA 3D QSAR Modeling

The major objective of the analysis was to build good predictive models that can be effectively used for designing novel 1,4-DHP as calcium channel blockers. The dataset molecules have been chosen to cover a broad range of activity. The training set and test set molecules align well with the template (Figure 1). A good predictive model was obtained as indicated by higher correlation coefficient (R^2), higher Fischer's statistical value (Fvalue) and lowstandard error of estimate (SEE). Cross validated correlation coefficient (R^2_{CV})of 0.542 is good enough to at least rank the activity of proposed new compounds.In the CoMFA model steric and electrostatic fields contribute to the QSAR equations by 74 and26, respectively. The molecular structure of compound 6 wasdisplayed inside the contour maps and the reference compoundnifedipine (Figure2). ThisCoMFA modelwas used to predict the respective pIC_{50} values of the training set and test set molecules (Table 1). The statistical outcomes (Table 2) and the scatter plot (Figure3) for the model illustrate the corresponding predictive abilities of the model. The pIC_{50} of the test set moleculeswerepredicted with reasonable accuracy (Table 1).

Table 2.PLS Statistics of CoMFA Models

Parameters	Values
No.ofmoleculesinthetrainingset	19
No.ofmoleculesinthetestset	6
R^2	0.922
R^2_{CV}	0.542
No.ofcomponents	4
SEE	0.936
Fvalue	41.09
Stericfieldcontributions	0.74
Electrostaticfieldcontributions	0.26

The CoMFA contours of the steric maps are shown in green and yellow colors and those for theelectrostatic fieldare shown in red colors. Greater values of "bioactive measurement" arecollected, with more bulk near the green-colored contours and less bulk near the yellow-coloredcontours; more positive charge near the blue-colored contours and more negative charge near the red-colored contours. The steric fields contribution was about 74% andelectrostatic fieldscontribution was about 26% of the model (Table 2).The steric effect has the higher contribution in the model. This suggested that calcium antagonist activity can be predominantly determined by steric properties. The contour maps of the 1,4-DHP model includestwogreen steric regions at the 3 and 4 positions and ayellow steric region at 5-position. The electrostatic mapshoweda negatively charged region onone side chain and a side of the aromatic ring at the 4-position requiredfor chelating calcium ion in the channel's selectivity filter. A positively charged region at 4-position encouraged electron withdrawal substituent on the aromatic ring (Figure2). The molecular structure of compound 6and nifedipinehave been displayed inside the fields as the reference structure.

Designing of new molecules

Studying the steric and electrostatic contour mapsin the model beneficial for the activities and the optimum features were determined for designing the newchemical entities depending on the observation of the favorable and unfavorable overlaps of these contours.The

Figure1 Structural alignment of the molecules in the training set and test set (left side) and structural alignment of the designed molecules (right side).

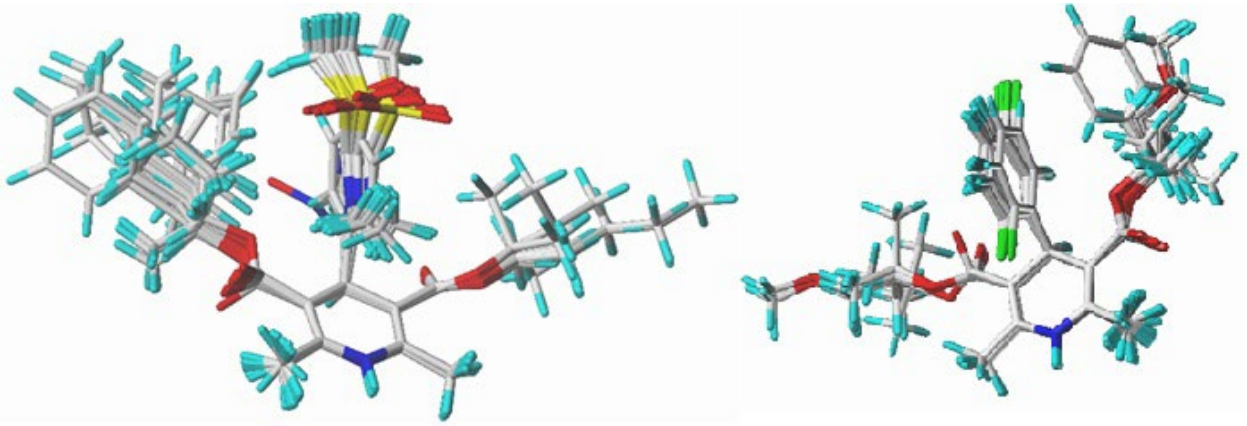


Figure 2 The 3D structure of compound 6, test compounds and nifedipine inside the contour map of the CoMFA model; steric contour map (left side), electrostatic contour map (middle) and overlay of contour maps (right side).

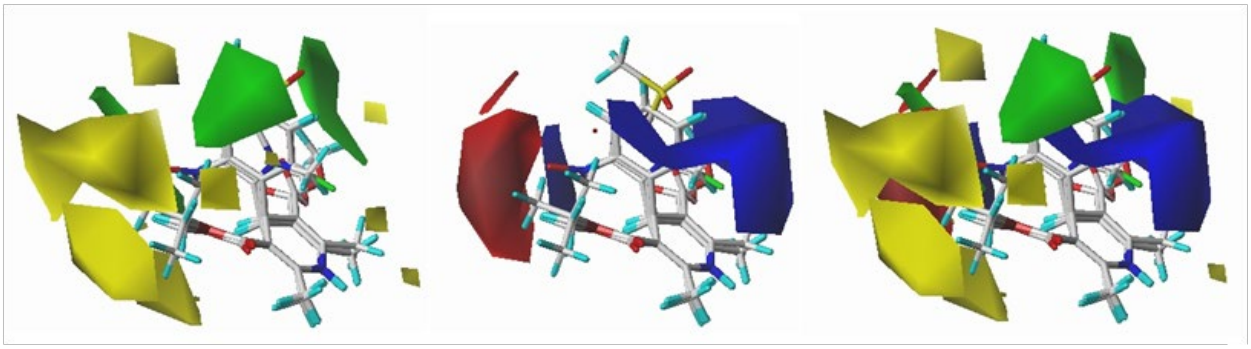
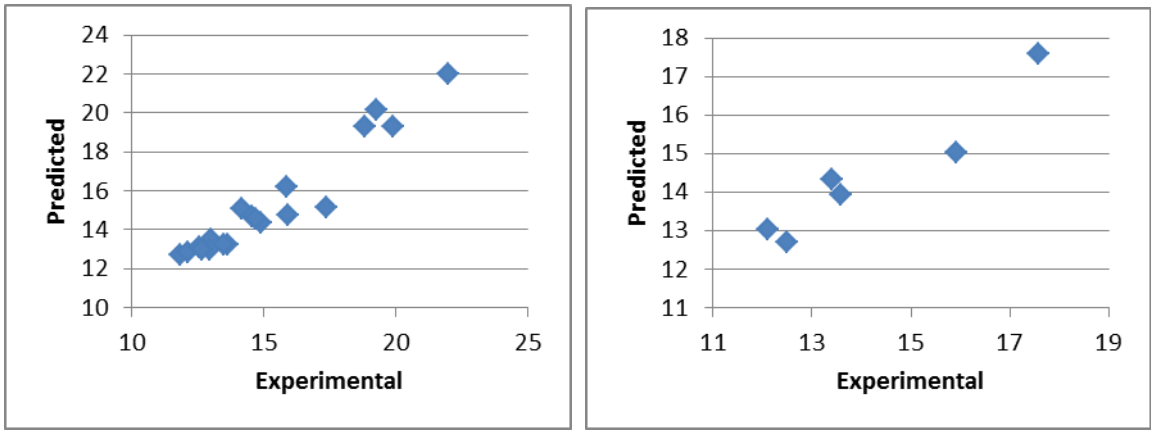
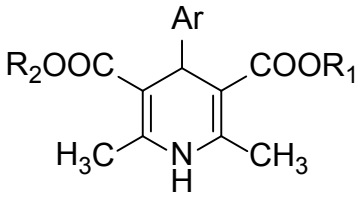


Figure 3 The scatter plot of the predicted pIC_{50} values against experimental values for both training set (left side) and test set (right side)



following rational structural modifications on the templatewere made to design some new compounds with acceptable predicted calcium antagonist activity (Table 3). Structural variations have been carried out on the 4-postion of the template and the side chain at 3- and 5-positions.2- and 3-bromophenyl ring wereemployed for satisfying the electronic requirementsof the models for the improvement of the activities. The dimethoxy ethyl ester groups at 3- and 5-positions satisfy both the steric and electrostatic properties making compounds 30, 38 and 43the most promising compounds with predicted pIC50 19.13 and 19.39 respectively (pIC50 for nifedipine is 22.02).

Table 3. The predicted Ca^{+2}antagonist pIC_{50}values for the designed DHP compounds used theCoMFA model.



Antagonist	R_1	R_2	Ar	Predicted ($-Log\ IC_{50}$)
25	$-CH_2CH_2OCH_3$	$-C_2H_5$	2-bromobenzaldehyde	18.89
26	$-CH_2CH_2OCH_3$	$-CH_3$	2-bromobenzaldehyde	17.54
27	$-CH(CH_3)_2$	$-CH_3$	2-bromobenzaldehyde	16.10
28	$-C(CH_3)_3$	$-CH_3$	2-bromobenzaldehyde	15.44
29	$-C(CH_3)_3$	$-C(CH_3)_3$	2-bromobenzaldehyde	17.16
30	$-CH_2CH_2OCH_3$	$-CH_2CH_2OCH_3$	2-bromobenzaldehyde	19.13
31	-CH3	$-C_2H_5$	2-bromobenzaldehyde	17.93
32	$-CH(CH_3)_2$	$-C_2H_5$	2-bromobenzaldehyde	16.55
33	$-CH_2CH(CH_3)_2$	$-C_2H_5$	2-bromobenzaldehyde	16.48
34	$-C(CH_3)_3$	$-C_2H_5$	2-bromobenzaldehyde	15.68
35	C_6H_5	C_2H_5	3-bromobenzaldehyde	17.60
36	$-CH_2C_6H_5$	$-CH_3$	2-bromobenzaldehyde	17.51
37	$-CH(CH_3)_2$	$-CH(CH_3)_2$	3-bromobenzaldehyde	16.41
38	$-CH_2CH_2OCH_3$	$-C_2H_5$	3-bromobenzaldehyde	19.15
39	$-CH_2CH_2OCH_3$	$-CH_3$	3-bromobenzaldehyde	18.88
40	$-CH(CH_3)_2$	-CH3	3-bromobenzaldehyde	16.31
41	$-CH_2C_6H_5$	$-CH_3$	3-bromobenzaldehyde	18.46
42	$-C(CH_3)_3$	$-C(CH_3)_3$	3-bromobenzaldehyde	16.90
43	$-CH_2CH_2OCH_3$	$-CH_2CH_2OCH_3$	3-bromobenzaldehyde	19.39
44	$-CH_3$	$-C_2H_5$	3-bromobenzaldehyde	18.55
45	$-CH(CH_3)_2$	$-C_2H_5$	3-bromobenzaldehyde	16.58
46	$-CH_2CH(CH_3)_2$	$-C_2H_5$	3-bromobenzaldehyde	18.57
47	$-C(CH_3)_3$	$-C_2H_5$	3-bromobenzaldehyde	15.73

Docking studies of designed molecules

The docking study of the most promising compounds (30, 38 and 43) into the active site of 1,4-DHP model was performed to get aninsightof understanding the structural basis fortheir calcium antagonist activity. All compounds make the interaction of 1,4-DHP nucleus as it is kept without modification in the newly designed compounds including the H-Bond of the NH with Tyr ^{1149}and the hydrophobic interaction of the bromophenyl ring at the 4-position with Tyr ^{1460} aromatic ring.Figure 4gives the lowest energetic pose of compound30and 43into the active site. The oxygen atom of themethoxy ethyl side chain makes this group suitable for the hydrophilic nature of the selectivity filter. This group is more suitable for projection in the water lake of the channel compared with small ethyl group in the same position. In spite of the bromophenyl group lacks the ability to share in the chelation of calcium ion in the selectivity filter that nifedipine nitro group does, the oxygen atom in the proximal methoxy group can do this. The methoxy ethyl group can effectively stabilize the hydrophobic bracelet (Leu^{397},Leu^{745}, Met^{1158} and Ile^{1468}) more than ethyl group. This is obvious from comparing the docking score of 30 and 38 with 43 as shown in Table 4. Figure 4 gives the lowest energetic pose of compound30 and 43 into the active site. The lowest energy pose of compound 38 was shown in Figure5.

Table 4. The docking scores for the most promising designed compounds and the reference compound nifedipine

Compound	Docking score
30	-136.65
43	-68.61
38	-47.88
Nifedipine	-32.59

Figure 4 Molecular docking of compounds 30 and 43 showing the lowest energy pose for each structure.

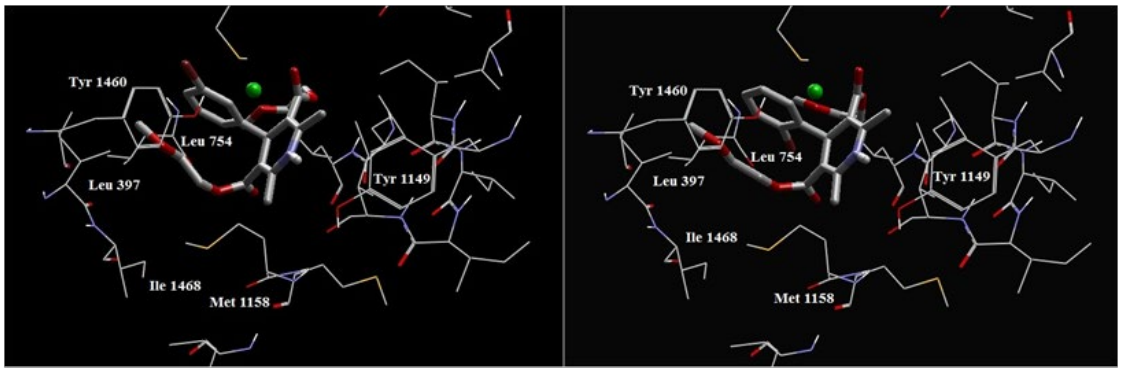
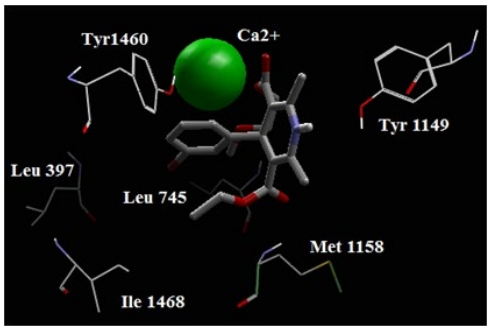


Figure 5 Molecular docking of compound 38 showing the lowest pose for each structure.



Conclusions

Although there are many 2D QSAR models for 1,4-DHP calcium antagonists, we first report 3D QSAR CoMFA model with statistical significance and good predictive abilities.The proposed model gave important indications for structural variations for designing new compoundsas calciumantagonistic activity. The contours of the models thus obtained were explored to designnovel calciumantagonists and the newly designed molecules were predicted with the developed model.Docking studies were carried out at the activesite of 1,4DHP model. Finally, the most promisingmolecules were selected as reasonably good calcium antagonist by comparing the predicted activities and docking scores with respect to the standard molecules. This new compounds (**25-47**) will be synthesized and tested in our laboratory for more investigations. The new 3D QSAR CoMFA model will guide medicinal chemists to design new compounds and provide further insightsto support thestructure-baseddesign of calcium antagonist.

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