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2D-QSAR Studies on 1, 4-dihydropyridines as Ca^{++} Channel Blockers

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ABSTRACT

Calcium channel blockers are widely used for the treatment of various cardiac disorders. The existing calcium channel blockers have several short comings; hence there is a need to develop better drugs with better therapeutic profile. 2D-QSAR approach has been useful in such cases. A number of 1, 4- dihydropyridines like amlodipine are extensively used in therapy of cardio vascular disorders. Looking into importance of calcium channel blockers, a series of 1, 4-dihydropyridines was selected and different models based on Multiple linear regression (MLR), Principal component regression (PCR) and Partial Least Squares regression (PLR) analysis were generated to find out correlation between the physicochemical parameters and the biological activity. Multiple linear regression (MLR) coupled with stepwise variable selection led to a statistically significant model as compared to PLR and PCR with respect to r^2 (coefficient of determination 0.8986) and q^2 (cross- validation, > 0.5). Four descriptors are included in 2D- QSAR equation generated by using MLR.

Key words: - Ca^{++} channel blocker, QSAR, MLR, PCR, MLR.

INTRODUCTION

Cardiac disorders have been the main reason for death in developing countries. Different drugs like ACE-inhibitors, beta-adrenergic blockers, diuretics, potassium-channel openers and calcium-channel blockers are used to treat cardiac disorders [1-2].

The agents that cause dose dependent reduction of trans-membrane Ca^{++} influx into the cells of contractile systems are called calcium-channel blockers. These agents cause dilation of blood vessels [3].

Nifedipine is a prototype drug of class 1, 4-dihydropyridines, which is an important class of calcium-channel blockers. The major drawbacks associated with the calcium-channel blockers are poor bioavailability due to first pass metabolism, lesser selectivity and short half-life [4-5]. This problem was overcome by development of Amlodipine which is a highly activity calcium-channel blocker with longer half-life (35-50 h) and large volume of distribution, allowing its use as once a day in the treatment of hypertension and angina. Computational chemistry has developed into an important contributor to rational drug design. Quantitative structure activity relationship (QSAR) modeling results in a quantitative correlation between chemical structure and biological activity. The 2D-QSAR equations are generated by multiple linear regression (MLR), partial list square analysis (PLS) and principle component regression (PCR) and evaluated on the basis of various statistical terms like coefficient of determination (r^2), cross-validation (q^2) and Fischer test (F-test) [6-12]. The present work was undertaken to find a correlation between physicochemical parameters and the biological activity of various 1, 4-dihydropyridine analogues. These correlations will be helpful in the development of 1, 4-dihydropyridines with increased therapeutic efficacy.

Experimental Methods:

Biological data: A set of 30 molecules of Amlodipine analogues, substituted at 2-position with alkoxymethyl side chain were used for present study. Out of 30 molecules, 25 molecules were selected as training set and 5 molecules (26 to 30) were selected as test set. The biological data was expressed as IC_{50} negative logarithm of molar concentration required to block Ca^{++} channel at rat aorta[6] (Table I).

Calculation of Descriptors: The 2D-QSAR studies were performed on the Vlife MDS 3.5 software, which is fully automatic software running on Intel Core2duo processor on Windows XP. The software developed the model with a total of 239 physicochemical descriptors and more than 700 alignment independent descriptors. In all these, descriptors deselected the Dipole Moment, Electrostatic, Distance Based Topological Indices, Semi Empirical and Hydrophobicity base log P descriptors (as these are 3D descriptors). The software developes the equation according to 3 D structures of standard compounds and Log IC-50 values with best suitable descriptors. List of descriptors used are given in Table II

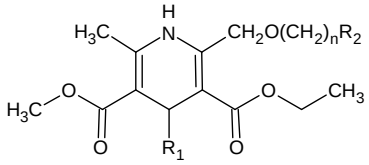

Table I: Compounds Used in 2D-QSAR Study

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S. No.	n	R_1	R_2	Log IC_{50}^*
1	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2$NPh4F	7.9
2	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH_2$Ph4Cl	8.0
3	2	1-naphthyl	c-$N(CH_3)_2$	7.1
4	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2$NH	6.8
5	2	2-ClC_6H_4	c-$N(CH_3)CH_2$Ph	7.4
6	2	2-ClC_6H_4	c-$NHCH_3$	8.5
7	3	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH_3$	8.4
8	3	2-ClC_6H_4	c-$N(CH_3)_2$	8.6
9	2	2-ClC_6H_4	c-$N(CH_3)_2$	8.1
10	2	2-ClC_6H_4	c-NNC_4H_8	7.9
11	2	2-ClC_6H_4	c-$N(CH_2CH_2)_2NCH(CH_3)_2$	8.2
12	2	2-$CF_3C_6H_4$	$N(CH_3)_2$	7.4
13	2	2-$CH_3C_6H_4$	$NHCH_3$	7.2
14	2	2-$OCH_3C_6H_4$	$NHCH_3$	7.2
15	2	Ph	NH_2	6.8
16	2	2-FC_6H_4	NH_2	7.8
17	2	2,3-$Cl_2C_6H_3$	NH_2	7.9
18	2	2-Cl-3-$CF_3C_6H_3$	NH_2	8.5
19	2	4-pyridyl	$N(CH_3)_2$	6.1
20	2	3-$NO_2C_6H_4$	$N(CH_3)_2$	8.0
21	2	2-Cl-6-FC_6H_3	$NHCH_3$	7.9
22	2	3-ClC_6H_4	NH_2	7.9
23	2	4-ClC_6H_4	NH_2	6.0
24	2	2-ClC_6H_4	NH_2	8.7
25	2	2-thienyl	$N(CH_3)_2$	6.9
26	2	2-FC_6H_4	c-$NHCH_3$	7.4
27	3	2-FC_6H_4	c-$N(CH_2CH_2)_2NCH_3$	8.1
28	2	2-Cl-3-$CF_3C_6H_3$	$NHCH_3$	8.0
29	2	4-FC_6H_4	NH_2	6.9
30	3	2-$CF_3C_6H_4$	$N(CH_3)_2$	7.6

Table II: Descriptors Used In the 2D-QSAR Study (Descriptors used three different models)

Descriptor	Type	Description
T_2_Cl_5	Alignment Independent (AI) Descriptor	This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from chlorine atom by 5 bonds in a molecule.
QM Dipole Y	Semi empirical	Induced dipole moment along Y-axis
XK Hydrophilic Area	Hydrophobicity X log pK	Vander walls surface descriptor showing hydrophilic surface area.(By Kellogg Method using X log p)
QM Dipole X	Semi empirical	Induced dipole moment along X-axis
SaaNE Index	E_{state} contributions	Electrotopological state indices for number of nitrogen atom connected with two aromatic bonds.
XZ Polarizability	Semi empirical	Induced polarizability along XZ axis

Generation of 2D-QSAR models:

Multiple linear regression (MLR), Principal component regression (PCR) and Partial Least Squares regression (PLR) were carried out to find out the factors responsible for the biological activity (Table III). Contribution chart, (% contributions of different descriptors in Model 1 / Equation 1) representing the contribution of descriptors in the 2D-QSAR model developed by MLR is shown in Fig 1.

Figure 1: Contribution chart of descriptors for MLR.

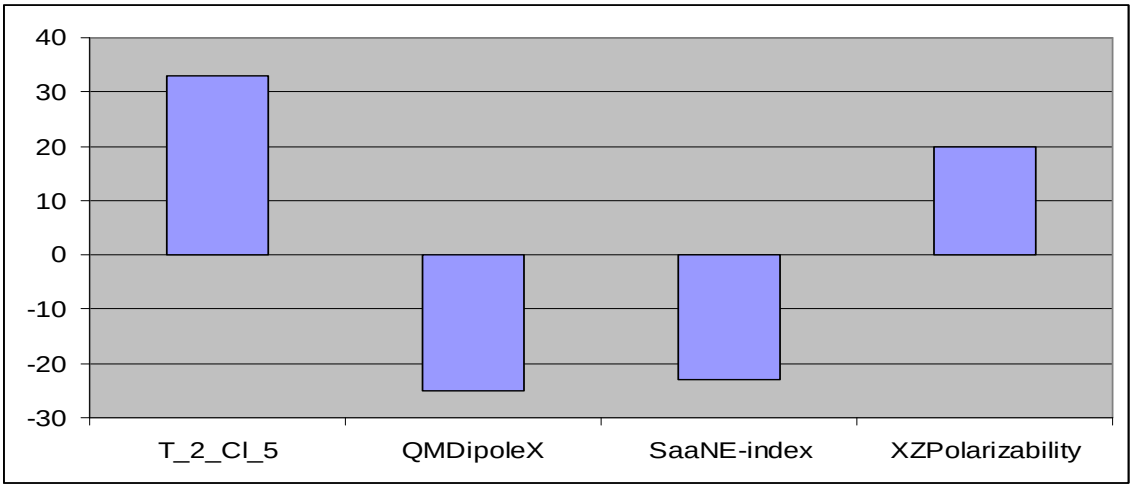


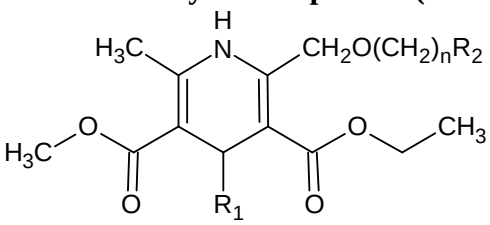
Table III: Developed 2D-QSAR Models. (For best three model developed by software).

S. No.	Equation	Statistical Method	N	r^2	q^2	F
1	IC_{50} = + 0.2025(± 0.0448) T_2_Cl_5 - 0.1307(± 0.0361) QMDipoleX - 0.3619(± 0.1152) SaaNE-index + 0.0188(± 0.0014) XZPolarizability + 6.8519	MLR	20	0.8986	0.5301	44.2872
2	IC_{50} = + 0.1562 T_2_Cl_5 - 0.3378 QMDipoleY - 0.0590 XKHydrophilicArea + 6.9547	PCR	21	0.8588	0.4669	42.5724
3	IC_{50} = + 0.2122 T_2_Cl_5 - 0.1602 QMDipoleX + 6.7053	PLR	23	0.7898	0.6117	86.3944

Prediction of activity:

The generated equation was used to predict the activity of test set as compare to actual activity (Table IV) with respect to various physicochemical parameters. The MLR model shows better results as compare to two other models (PCR and PLR). Therefore the activity predicted by MLR is only considered in this study (Table IV).

Table IV: Predicted Activity of Compounds (Test set) by MLR.



S.No.	R_1	R_2	Actual Log IC_{50}	Calculated Log IC_{50}	Residual
1	2-FC_6H_4	c-$NHCH_3$	7.4	6.92	0.48
2	2-FC_6H_4	c-$N(CH_2CH_2)_2NCH_3$	8.1	7.08	1.02
3	2-Cl-3-$CF_3C_6H_3$	$NHCH_3$	8.0	8.14	- 0.14
4	4-FC_6H_4	NH_2	6.9	6.81	0.09
5	2-$CF_3C_6H_4$	$N(CH_3)_2$	7.6	7.94	- 0.34

RESULT AND DISCUSSION

From the above studies it can be seen that Multiple linear regression (MLR) coupled with stepwise variable selection led to a statistically significant model as compared to PLR and PCR with respect to r^2 (coefficient of determination 0.8986) and q^2 (cross- validation, > 0.5). Four descriptors are included in 2D- QSAR equation generated by using MLR.

The developed MLR model reveals that the descriptor T_2_Cl_5 which is an Alignment Independent (AI) Descriptor that signifies the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from chlorine atom by 5 bonds in a molecule, positively contributes to the biological activity (~35%). The next descriptor is QMDipoleX, which is a semi empirical descriptor that signifies the induced dipole moment along X-axis is inversely proportional to the activity (~25%). The descriptor SaaNE-index i.e. Electrotopological state indices for number of nitrogen atom connected with two aromatic bonds. This is an Estate contributions type descriptor, also negatively contributing in the biological activity (~20%). The last descriptor XZPolarizability i.e. induced polarizability along XZ axis. This is also Semi empirical type descriptor, is positively contributing to the activity (~20%).

Five compounds were selected as test compounds to evaluate the validity of generated QSAR equation. As shown in table 5, the predicted activity using developed QSAR equation is in close agreement with the reported activity. Thus the present equation could be used to design 1, 4 dihydropyridines as potent calcium channel blockers.

CONCLUSION

In the present study a 2-D QSAR model has been developed for correlating activity of 1, 4-dihydropyridines as calcium channel blockers with physicochemical properties. The developed model is found to be good with regard to prediction of activity in test set and thus can be used for the development of 1, 4- dihydropyridines as calcium channel blockers.

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