Journal of Computational Methods in Molecular Design, 2012, 2 (3):85-91

Scholars Research Library
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

2DQSAR of Novel 4-Substituted 1, 4 Dihydropyridines -3, 5-Dicarboxylate as Potential Antihypertensive Agent

Prasanna A. Datar* and Pratibha B. Auti

Department of Pharmaceutical Chemistry, STES's Sinhgad Institute of Pharmacy, Narhe, Pune, Maharshtra, India

---

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. A number of 1, 4- dihydropyridines like nifedipine or 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), was 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 with respect to r^2 (coefficient of determination 0.9101) and q^2 (cross- validation 0.640).

Key words: calcium channel blocker, QSAR, MLR, dihydropyridines

---

INTRODUCTION

Cardiovascular disease account for 12 million deaths, annually worldwide and known to be major group of 'killer disease'. Hypertension is one of the leading causes of disability, mortality and morbidity along the population [1, 2]. 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 [3, 4].

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.

The 2D-QSAR equations are generated by multiple linear regressions (MLR), and evaluated on the basis of various statistical terms like coefficient of determination (r^2), cross validation (q^2) and Fischer test (F-test) [5-9]. 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.

MATERIALS AND METHODS

Experimental Methods:

Biological data: A set of 29 molecules of 1, 4 dihydropyridine analogues, 29 compounds reported by Che-chien chang et al[10] were used for carrying out the present study on antagonism of 4-substituted 1,4-dihydropyridine-3,5-dicarboxylates toward voltage-dependent L- type Ca^{2+} channels $Ca_V1.3$ and $Ca_V1.2$. Molecules were optimized using MMFF force field keeping the Distance dependent dielectric function. Minimization was performed till the

convergence (rms gradient) of 0.01 is obtained. Descriptors were calculated using the categories such as physicochemical, element count, alignment independent parameters as provided by MDS 3.5[2].

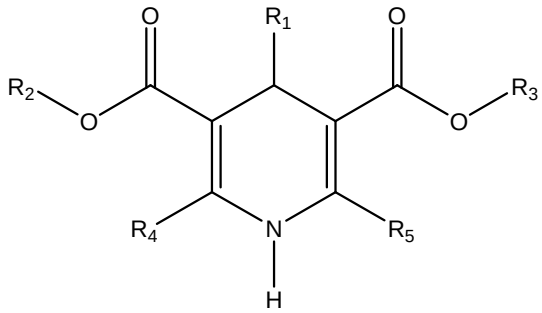
2D- QSAR was performed by Stepwise regression. After calculating descriptors, training and test sets were selected by manual data selection method, activity distribution was plotted. Various variable selection methods such as Stepwise Multiple linear regression were performed using forward, backward and forward options. Cross correlation limit of 0.5 and auto scaling was applied.

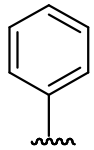
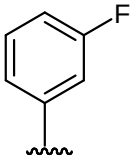
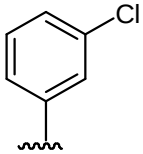
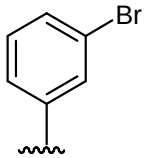
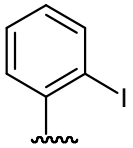
Training set of 19 molecules and Test set made of 10 molecules was selected manually by considering activity variation. Structure 1 shows R^1 varied as aromatic/non-aromatic rings while R^2, R^3, R^4, R^5 varied as methyl, ethyl groups. The negative logarithm of percentage antagonism was used as the biological activity for the 2D QSAR studies required to reduce hypertension (Table 1).

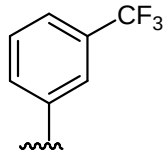
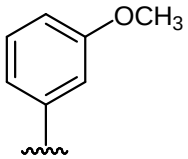
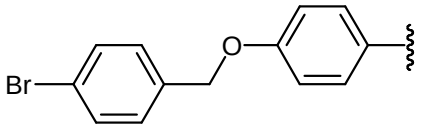
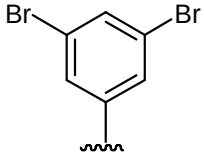
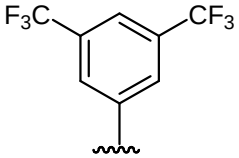
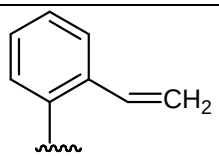
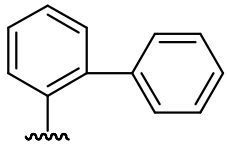
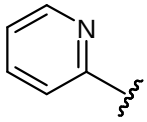
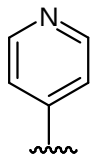
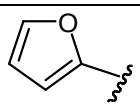
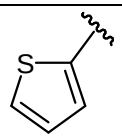
Calculation of Descriptors: The 2D-QSAR studies were performed on the Vlife MDS 3.5[2] Software, the software developed the model with a total of 239 physicochemical descriptors and more than 700 alignment independent descriptors. In all these, descriptors deselected the Dipole Moment, Electrostatic, Distance Based Topological Indices, Semi Empirical and Hydrophobicity base log P descriptors (as these are 3D descriptors).

Table 1: Compounds Used in 2D-QSAR Study

Structure No.1



No.	R_1	R_2	R_3	R_4	R_5	Log Activity
1.		C_2H_5	C_2H_5	CH_3	CH_3	1.6812
2.		C_2H_5	C_2H_5	CH_3	CH_3	1.8061
3.		C_2H_5	C_2H_5	CH_3	CH_3	1.7634
4.		C_2H_5	C_2H_5	CH_3	CH_3	1.9138
5.		C_2H_5	C_2H_5	CH_3	CH_3	1.9822

6.		C_2H_5	C_2H_5	CH_3	CH_3	1.9294
7.		C_2H_5	C_2H_5	CH_3	CH_3	1.8388
8.		C_2H_5	C_2H_5	CH_3	CH_3	1.5797
9.		C_2H_5	C_2H_5	CH_3	CH_3	1.8692
10.		C_2H_5	C_2H_5	CH_3	CH_3	1.5797
11.		C_2H_5	C_2H_5	CH_3	CH_3	1.4771
12.		C_2H_5	C_2H_5	CH_3	CH_3	1.8633
13.		C_2H_5	C_2H_5	CH_3	CH_3	1.3979
14.		C_2H_5	C_2H_5	CH_3	CH_3	1.4313
15.		C_2H_5	C_2H_5	CH_3	CH_3	1.8573
16.		C_2H_5	C_2H_5	CH_3	CH_3	1.7481
17.		C_2H_5	C_2H_5	CH_3	CH_3	1.8129

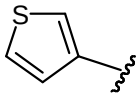
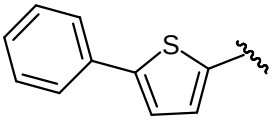
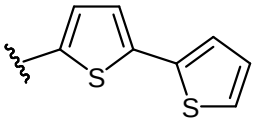
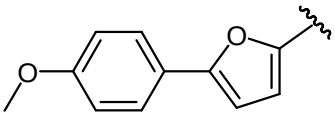
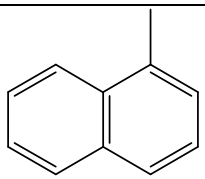
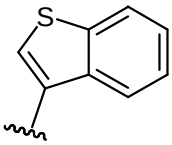
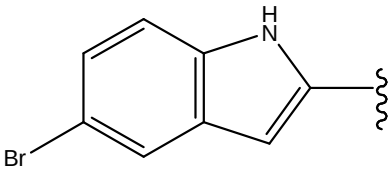
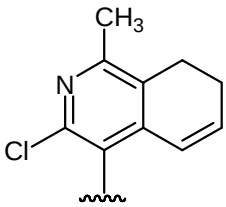
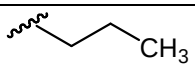
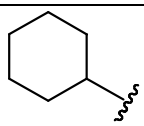
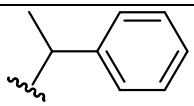
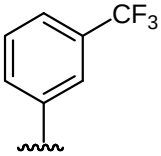
18.		C_2H_5	C_2H_5	CH_3	CH_3	1.7323
19.		C_2H_5	C_2H_5	CH_3	CH_3	1.6127
20.		C_2H_5	C_2H_5	CH_3	CH_3	1.544
21.		C_2H_5	C_2H_5	CH_3	CH_3	1.544
22.		C_2H_5	C_2H_5	CH_3	CH_3	1.2041
23.		C_2H_5	C_2H_5	CH_3	CH_3	1.2041
24.		C_2H_5	C_2H_5	CH_3	CH_3	1.6232
25.		C_2H_5	C_2H_5	CH_3	CH_3	1.903
26.		C_2H_5	C_2H_5	CH_3	CH_3	1.6232
27.		C_2H_5	C_2H_5	CH_3	CH_3	1.0791
28.		C_2H_5	C_2H_5	CH_3	CH_3	1.6232
29.		C_2H_5	C_2H_5	CH_3	CH_3	1.4149

Table 2. 2D QSAR Equation

Sr. No.	Statistical Method	Equation	r^2	q^2	F test	r^2 se	q^2 se
1	MLR	Activity = -0.1945 (± 0.0136) T_T_N_2 -0.2124(± 0.0836) SsssCHcount -0.3586 (± 0.0817) SdCH2count +0.0255 (± 0.0011) T_T_0_6 -0.0740 (± 0.0135) Rotatable Bond Count+3.1016	0.910	0.642	26.33	0.078	0.157

Generation of 2D-QSAR models:

Multiple linear regression (MLR) was carried out to find out the factors responsible for the biological activity (Table 2). Contribution chart, (% contributions of different descriptors in Equation representing the contribution of descriptors in the 2D-QSAR model developed by MLR is shown in Fig 1.'

Table 3. Unicolumn Statistics

	Antihypertensive Activity Training Set	Antihypertensive Activity Test Set
Average	1.6544	1.6610
Max	1.9822	1.9294
Min	1.0791	1.2041
StdDev	0.2237	0.2331
Sum	31.4345	16.6098

Figure 1: Contribution chart of descriptors for MLR

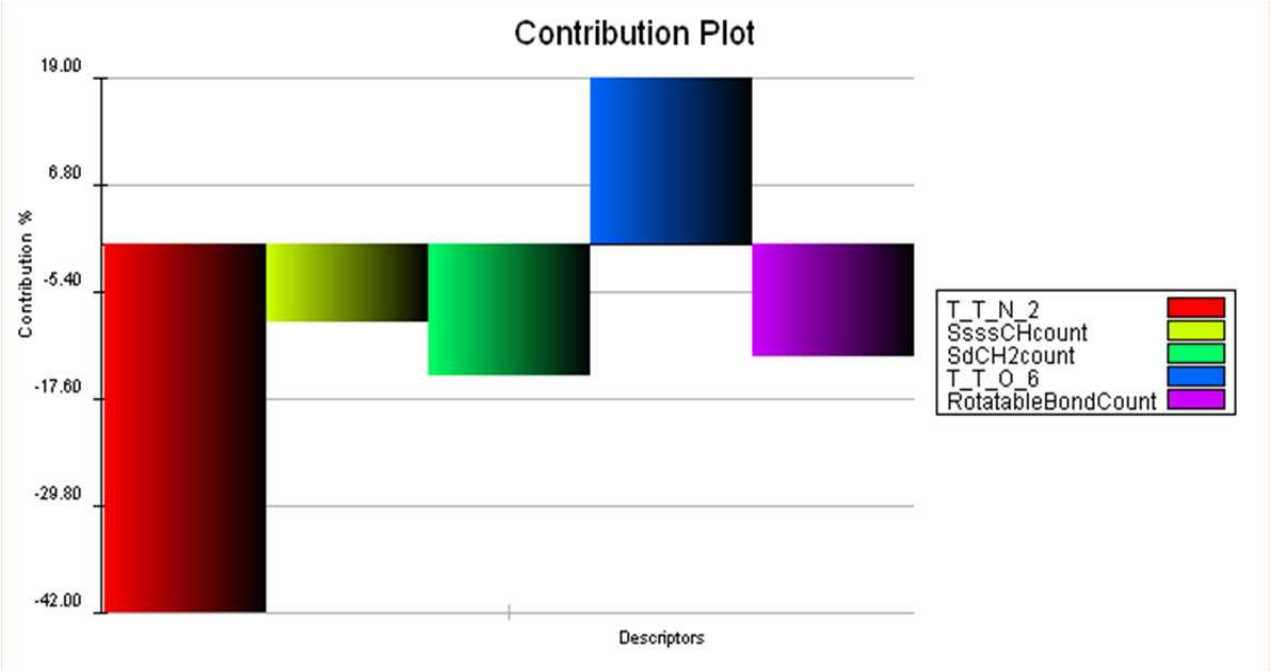


Table 4. Predicted Activity of Compounds (Test set) by MLR

Test Compound No.	Antihypertensive Activity	Predicted	Difference
02	1.8061	1.8075	-0.0014
06	1.9294	1.7335	0.1959
08	1.5797	1.6621	-0.0824
15	1.8573	1.8586	-0.0013
16	1.7481	1.9863	-0.2382
20	1.5440	1.7335	-0.1895
23	1.9030	1.9057	-0.0027
27	1.4149	1.5951	-0.1802

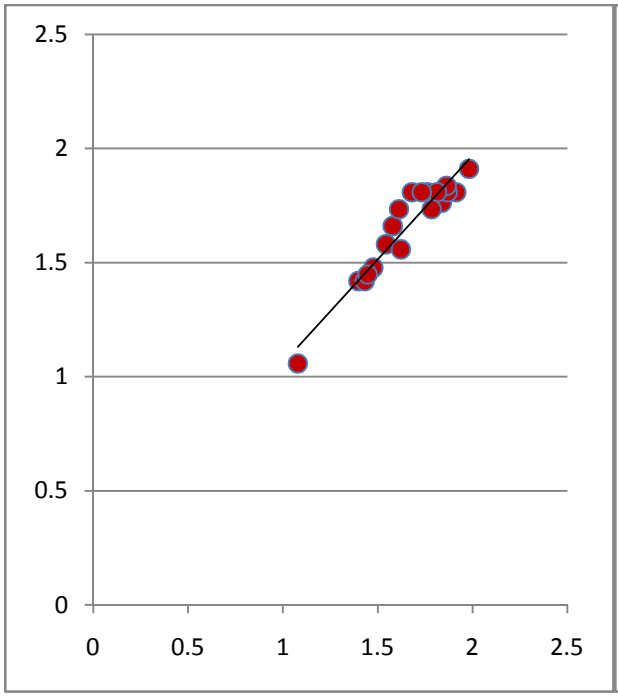


Figure 2: Fitness plot for Training set for Actual value V/s Predicted Value

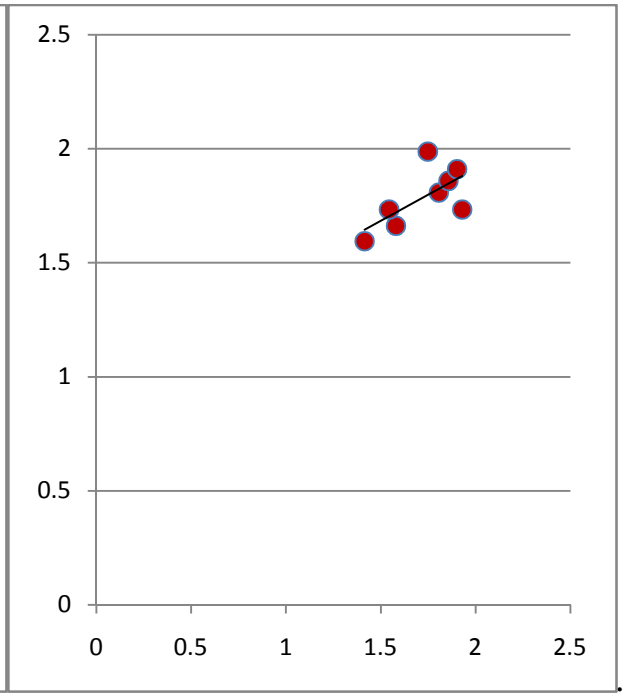


Figure 3: Fitness plot for Test set for Actual value V/s Predicted Value

RESULTS 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 equation with respect to r^2 (coefficient of determination 0.910) and q^2 (cross- validation 0.640).

The developed MLR model reveals that the descriptor T_T_N_2 which is an Alignment Independent (AI) Descriptor that signifies count of number of any atoms (single double or triple bonded) separated from Nitrogen atom (single double or triple bonded) by distance of 2 bonds in a molecule double negatively contributes to the biological activity (~42.86 %). The next descriptor is, SsssCHcount. This descriptor defines the total number of –CH group connected with three single bond is inversely proportional to the activity (~9.38 %). The descriptor SdCH2count It is the total number of –CH2 group with double bond, also negatively contributing in the biological activity (~15.83 %). T_T_O_6 It is the count of number of any atoms (single double or triple bonded) separated from any other Oxygen atom (single double or triple bonded) by distance of 6 bonds in a molecule, is positively contributing to the activity (~19.05%). The last descriptor RotableBondcount is negatively contributing to the activity (~13.65%).

Ten compounds were selected as test compounds to evaluate the validity of generated QSAR equation. As shown in table 4, the predicted activity using developed QSAR equation is in close agreement with the reported activity. A Z score value is calculated by the following formula.

$$z = (x - x\_mean)/s$$

The mean of standard scores is zero. When values are standardized, the units in which they are expressed are equal to the standard deviation, s. For the standardized scores, the standard deviation becomes 1. (Variance is also 1). The interpretation of the standard-score of a given value is in terms of the number of standard deviations the value is above or below the mean (of the distribution of standardized scores).

So, the standardization of a set of values involves two steps. First, the mean is subtracted from every value, which shifts the central location of the distribution to 0. Then the thus mean-shifted values are divided by the standard deviation, s. This now makes the standard deviation as 1. From test set, two outlier obtain in this study compound number 36 and 38 with Z score value 4.0529

Thus the present equation could be used to design 1, 4 dihydropyridines as potent antihypertensive activity.

CONCLUSION

T_T_O_6 are directly proportional to antihypertensive activity while T_T_N_2, SsssCHcount, SdCH2count and Rotatable Bond Count are inversely proportional to the antihypertensive activity. SsssCHcount resembles dihydropyridine (DHP) ring. The molecule should have least number of CH_2 groups connected with double bond .The DHP molecule should have least number of rotatable bonds. Descriptor values obtained helps us to understand the structural features require reducing the blood pressure. These descriptors are helpful in design of potential antihypertensive agent in the path of Drug Discovery and Development. QSAR studies may provide useful insights into the roles of various substitution patterns on the dihydropyridines skeleton. The developed equation 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 antihypertensive activity.

REFERENCES

[1] A Janis; D Triggle; *J. Med. Chem.* **1983**, 26, 775.
[2] B Materson; R Preston; *Arch. Intern. Med.* **1994**, 154, 513.
[3] RA Kloner; GW Vetrovec; BJ Materson; M Levenstein; *Am J Cardiol*.**1998**, 81,163.
[4] ED Frohlich; J *Am Cardiol.***1983**, 1, 225.
[5] D Juvale; V Kulkarni; *Indian Drugs* **2005,** 42, 8.
[6] Kharkar, P.S.; Desai, B.; Gaveria,H.; Varu, B.; Loriya, R.; Naliapara,Y.; Shah,A.; Kulkarni, V. M., *J. Med. Chem.* **2002**, *45*, 4858
[7] X Yao; H Liu; R Zhang; M Liu; Z Hue; JP Doucet; B Fan; *Molecular Pharmaceutics*. **2008**, 5, 348.
[8] ZA Si; T Wang; BT Fane; *Bioorganic & Medicinal Chemistry.* **2006**, 14, 4834
[9] RA Coburn; M Wierzba; MJ Suto; AJ Solo; A Janis; D Triggle; *J. Med. Chem.* **1988**,31, 2103.
[10] C Chang; S Cao; S Kang; L Kai; X Tian; P Pandey; SF Dunne; DJ Luan; RB Surmeier; *Bioorganic and Medicinal Chemistry*.**2010**, 18, 3147.
[11] VLife Sciences Technology Pvt. Ltd. Pune-411045, Web: www.vlifesciences.com