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Research Article

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2DQSAR of novel 1,4-dihydropyridine derivative blocking n-type - calcium channels

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ABSTRACT

Cilnidipine is a 1,4-dihydropyridine derived L/N-type calcium channel dual blocker possessing neuroprotective and analgesic effects which are related to its N-type calcium channel inhibitory activity. 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 cardiovascular 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 0.9176) and q2 (cross- validation > 0.6673). Three descriptors are included in 2D- QSAR equation generated by using MLR.

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

INTRODUCTION

Voltage-dependent calcium channels (VDCCs), which have been divided into five subtypes (L, CaV1; P/Q, CaV2.1; N, CaV2.2; R, CaV2.3; T, CaV3) based on their pharmacological and biophysical properties, mediate a range of cytoplasmic responses, including muscle contraction, release of neurotransmitters, calcium-dependent gene transcription, and the regulation of neuronal excitability [1]. Among them, N-type calcium channels are extensively distributed on the sympathetic nerve endings and related to the neuroprotection and neuropathic pain [2]. Several reports have suggested that a blockade or lack of N-type calcium channels can suppress the pathological processes of ischemic brain injury and pain in animal models [3]. Cilnidipine is a 1, 4-dihydropyridine derived long acting calcium channel blocker which inhibits both L-type and N-type calcium channels [4] and is currently used for the treatment of essential hypertension in Japan [5]. Its inhibitory effect for N-type calcium channel can be clinically observed in the reduction of white coat effect, cold pressor stress-induced platelet aggregation, urinary catecholamine excretion, and cardiac sympathetic overactivity in hypertensive patients [6]. Moreover, N-type calcium channel-blocking profile of cilnidipine may contribute to its neuroprotective action in the animal focal brain ischemia model and its intrathecal analgesic effect in rat formalin-induced pain model [7,8].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 regressions (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 (q2) and Fischer test (F-test) [9-22]. 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 SECTION

Biological data: A set of 22 molecules of 1, 4 dihydropyridine analogues, 22 compounds reported by Takashi Yamamoto [23] were used for carrying out the present study. 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].

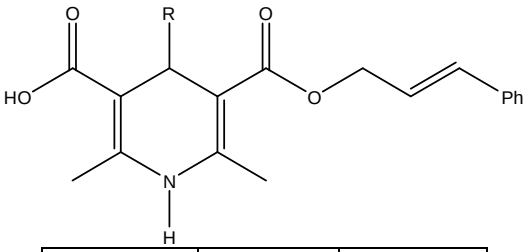
2D- QSAR was performed by Stepwise regression. After calculating descriptors, training and test sets were selected by manual data selection method, activity distribution was plotted. Various variable selection methods such as Stepwise Multiple linear regression were performed using forward, backward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

Training set of 15 molecules and Test set made of 07 molecules was selected manually by considering activity variation. The biological data was expressed in IC50 value (Table 1).

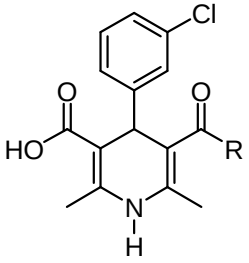
Calculation of Descriptors: The 2D-QSAR studies were performed on the Vlife MDS 3.5[2] Software, the software developed the model with a total of 239 physicochemical descriptors and more than 700 alignment independent descriptors. In all these, descriptors deselected the Dipole

Moment, Electrostatic, Distance Based Topological Indices, Semi Empirical and Hydrophobicity base log P descriptors (as these are 3D descriptors). The software developes the equation according to 3 D structures of standard compounds and Log values with best suitable descriptors. List of descriptors used are given in Table 2

Table 1: Compounds Used in 2D-QSAR Study



Compound no.	R	1/log Activity
1	Ph	-0.3010
2	3-CO_2Me-Ph	-0.6627
3	3-CO_2H-Ph	-1.5682
4	3-Me-Ph	-0.2552
5	3-F-Ph	-0.1139
6	3-Cl-Ph	0.1023
7	3-Br-Ph	0.0000
8	3-I-Ph	-0.2304
9	3-pyridyl	-1.3802
10	3-thienyl	-0.4623
11	3-furyl	-1.0413



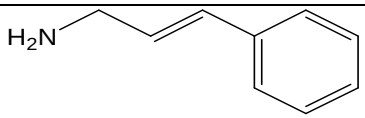
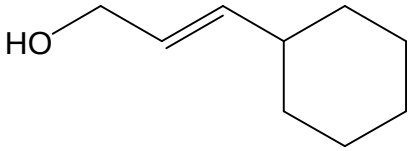
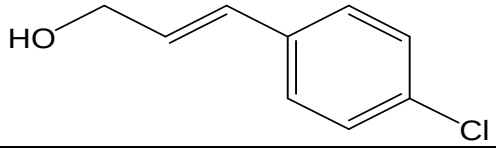
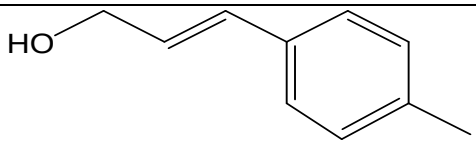
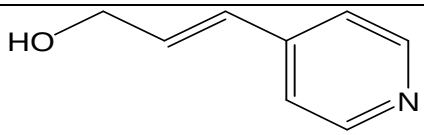
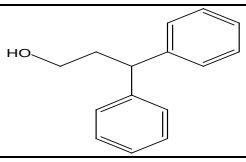
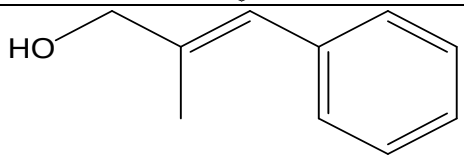
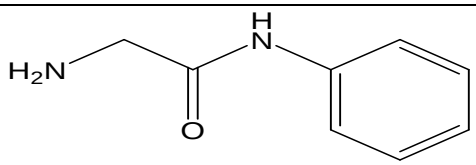
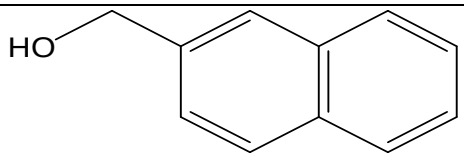
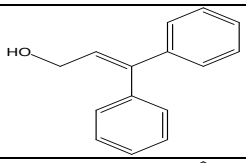
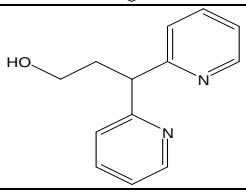
12		**0.6532**
13		**0.0809**
14		**-0.1760**
15		**0.0506**
16		**-0.7923**
17		**0..1674**
18		**-1.44710.0000**
19		**0.0000**
20		**-0.5910**
21		**-0.0413**
22		**-1.0000**

Table 2. 2D QSAR Equation

S. No.	Statistical Method	Equation	r^2	q^2	F test	r^2 se	q^2 se
1	MLR	**1/log Activity** = -0.0402 (±0.009) PolarSurfaceArea -0.4527 (±0.1109) T_O_O_6 -0.7437 (±0.2218) T_N_N_6 +4.7112	0.9176	0.6673	40.84	0.0213	0.4298
2	PLS	**1/log Activity** = -0.0402 PolarSurfaceArea -0.9071 T_O_O_6 -0.7421 T_N_N_6 +6.5281	0.9155	0.6670	66.83	0.2047	0.4114
3	PCR	**1/log Activity** = -0.0294 PolarSurfaceArea -0.1486 T_O_O_6 -0.9207 T_N_N_6 +4.9330	0.9001	0.6677	81.72	0.1866	0.3398

Table 3: Descriptors Used In the 2D-QSAR Study (Descriptors used different Models)

Descriptor	Type	Description
Polar Surface Area	Polar Surface Area	1.PolarSurfaceArea Excluding PandS: This descriptor signifies total polar surface area excluding phosphorous and sulphur. 2.PolarSurfaceAreaIncludingPandS: This descriptor signifies total polar surface area including phosphorous and sulphur.
T_O_O_5	Physicochemical descriptors(Sub class :Estate Numbers)	T_O_O_5: This is the count of number of Oxygen atoms (single double or triple bonded) separated from any other Oxygen atom (single double or triple bonded) by 6 bonds in a molecule.
T_N_N_6	Physicochemical descriptors (Sub class :Estate Numbers)	T_N_N_6: This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any other Nitrogen atom (single double or triple bonded) by 6 bonds in a molecule.

Table 4: Unicolumn Statistics

	Antihypertensive Activity Training Set	Antihypertensive Activity Test Set
Average	-0.4468	-0.3295
Max	0.6532	0.0809
Min	-1.5682	-1.0413
StdDev	0.6604	0.4166
Sum	-6.7020	-2.3065

Table 5: Comparative observed and predicted activities of QSAR model

Test Compound No.	Antihypertensive Activity	Predicted	Difference
1	**-0.3010**	-0.3008	-0.0002
2	**-0.6627**	-0.6625	-0.0002
3	**-1.5682**	-1.5672	-0.0010
4	**-0.2552**	-0.2548	-0.0004
5	**-0.1139**	-0.1125	-0.014
6	**0.1023**	0.1019	0.0004
7	**0.0000**	0.0039	-0.0039
8	**-0.2304**	-0.2304	-0.0000
9	**-1.3802**	-1.3791	-0.0011
10	**-0.4623**	-0.46107	0.0016
11	**-1.0413**	-1.0367	0.0046
12	**0.6532**	0.6522	0.0010
13	**0.0809**	0.0794	0.0015
14	**-0.1760**	-0.1749	0.0011
15	**0.0506**	0.0490	0.0016
16	**-0.7923**	-0.7900	-0.0023
17	**0.1674**	0.1599	0.0075
18	**-1.4471**	-1.4430	0.0041
19	**0.0000**	0.0017	-0.0017
20	**-0.5910**	-0.5900	0.0010
21	**-0.0413**	-0.0389	-0.0023
22	**-1.0000**	-1.0017	0.0017

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.

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 model with respect to r^2 (coefficient of determination 0.9176) and q^2 (cross-validation, > 0.6673). Three descriptors are included in 2D- QSAR equation generated by using MLR. The developed MLR model reveals that the descriptor Polar Surface Area is PolarSurfaceAreaExcludingPandS: This descriptor signifies total polar surface area excluding phosphorous and sulphur. Second descriptor is PolarSurfaceAreaIncludingPandS: This descriptor signifies total polarsurfaceareaincludingPhosphorousandsulphur are negatively contributes to the biological activity. The next descriptor is T_O_O_5 it shows the count of number of Oxygen atoms (single double or triple bonded) separated from any other Oxygen atom (single double or triple bonded) by 6 bonds in a molecule, is inversely proportional to the activity. The descriptor T_N_N_6: This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any other Nitrogen atom (single double or triple bonded) by 6 bonds in a molecule. It is also negatively contributing in the biological activity .

Eight compounds were selected as test compounds to evaluate the validity of generated QSAR equation. 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 derivative as blocking N-type calcium channels.

CONCLUSION

PolarSurfaceAreaExcludingPandS are inversely proportional to the antihypertensive activity. T_O_O_5 descriptor, T_N_N_6 descriptor are inversely proportional to activity these descriptors are helpful in design of potential antihypertensive agent in the path of Drug Discovery and Development. 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 blocking N-type calcium channels.

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