



QSAR^a Study of 2-(1-Alkylpiperidine-4-yl)-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl] Acetamide Derivatives as Novel Antihypertensive Agents

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Abstract: We have studied antihypertensive activities of certain derivatives of 2-(1-Alkylpiperidine-4-yl)-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl] acetamide with respect to certain topological parameters viz. ZM, MSD, GGI1, SpMax2m, Ssssch along with Hydrophilic factor (Hy) and Keir and Hall connectivity index (X0). Our analysis revealed that bi-parametric multiple regression parameters Hy and Ssssch collectively gave the best results with a variance of 0.9538.

a-Quantitative Structure-Activity Relationship

Sasumi Watanaki et al.^[1] reported that Structure-activity relationship studies had revealed that the position of amide structure was important for the potent inhibitory activity toward T-type Ca²⁺ channels. In addition, the introduction of an appropriate substituent on the pendant benzene ring played a crucial role for the selectivity towards T-type Ca²⁺ channels over L-type Ca²⁺ channels and the potent bradycardic activity of these derivatives. Oral administration of N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]-2-(1-{2-[2-(2-methoxyethoxy)phenyl]ethyl}piperidin-4-yl)acetamide (Comp 6, Table 1), which had superior selectivity for T-type Ca²⁺ channels over L-type Ca²⁺ channels, lowered blood pressure in spontaneously hypertensive rats without inducing reflex tachycardia, which is often caused by traditional L-type Ca²⁺ channel blockers. They have further reported that extra cellular calcium enter into cells through Voltage Operated Calcium (VOC) channels^[2]. VOC channels are found in the nervous, endocrine, cardiovascular and skeletal systems and are classified into six main categories: L(Long lasting), T (Transient), N (Neuronal), P (Purkinje cells), Q (After P) and R (remaining or resistant). L-type and T-type channels, in particular, are proposed to be associated with several cardiovascular diseases. L-type Ca²⁺ channel is responsible for inward movement of Ca²⁺ which initiates contraction in cardiac and smooth muscle cells. Therefore, L-type Ca²⁺ channel blockers are currently recommended for first-line treatment for hypertension and angina. In contrast, T-type Ca²⁺ channels are thought to contribute to the regulation of cardiovascular activities including heart rate (HR), and arterial and venous smooth muscle intervention and tone.

They have elaborated that nearly all therapeutic Ca²⁺ channel blockers currently in the market have selective effect on L-type over T-type Ca²⁺ channels. However, mibefradil (Fig-1) was reported to show 10 to 30 fold higher selectivity for T-type Ca²⁺ channels. Mibefradil demonstrated superior out come over traditional L-type Ca²⁺ channel blockers for treating hypertension and angina. Notably the adverse effects often associated with L-type Ca²⁺ channel blockers such as reflex tachycardia, negative inotropy, vaso-constrictive hormone disease and peripheral edemawere not reported.

Susumu Watanuki et al synthesized and tested several compounds starting from compounds shown in FIG-2 and FIG-3.

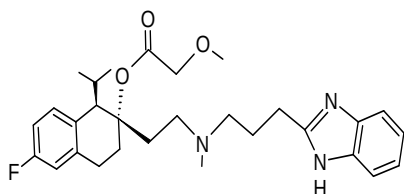


FIG-1

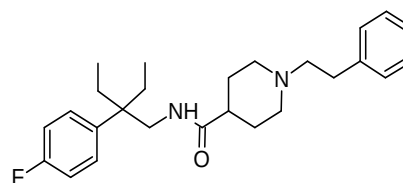


FIG-2

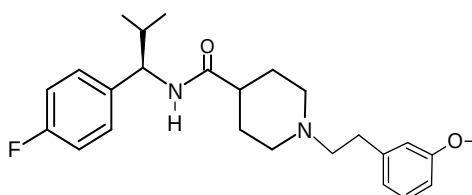


FIG-3

We have taken their compounds for our study, which are listed in Table 1 with their respective antihypertensive activities.

Comp No.	Structure	T-type IC ₅₀ (μM)*
1		0.062
2		0.16
3		0.20
4		0.24
5		0.30
6		0.19
7		0.42
8		0.31
9		0.31
10		0.26

* Inhibition of Ca²⁺ ion influx through T-type Ca²⁺ channel

TABLE 1

The data set in Table 1 consists of structurally diverse compounds reported for antihypertensive activity viz Ca^{2+} channel blocking activity through T-type Ca^{2+} channel. The selected series comprises of ten 2-(1-Alkylpiperidine-4-yl)-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl] acetamide derivatives. The antihypertensive activity of the data set is reported as IC_{50} value, which refers to experimentally determined concentration required to inhibit or block the calcium channel activity by 50%.

Now we used Dragon (Software for Molecular Descriptor Calculation)^[3] to calculate certain molecular descriptors which were giving significantly impressive indications of their involvement in the antihypertensive activity of above mentioned compounds. After several trials we found Hydrophilic factor (Hy)^[4], Keir and Hall connectivity index (X_0)^[5], and topological parameters like ZM_1 ^[6], MSD ^[7], GGI_1 ^[8], SpMax2m ^[9] and Atom type E-state index SsssCH ^[10] important in the present study. The values of these descriptors for different compounds are given in Table 2. Table-3 here gives details of descriptors which have been used.

Comp.	IC_{50}	ZM_1	MSD	X_0	GGI_1	SpMax2m	SsssCH	Hy
1	0.062	144	7.992	20.64	6	3.848	0.627	-0.439
2	0.16	154	8.361	22.217	6.5	3.867	0.573	-0.425
3	0.2	154	8.497	22.217	7	3.865	0.582	-0.425
4	0.24	154	8.642	22.217	7	3.864	0.588	-0.425
5	0.3	164	8.965	23.794	7.5	3.878	0.542	-0.412
6	0.19	166	9.162	24.338	6.5	3.869	0.541	-0.421
7	0.42	172	9.235	25.209	7	3.884	0.418	-0.401
8	0.31	172	9.291	25.209	7.5	3.882	0.436	-0.401
9	0.31	172	9.246	25.209	7.5	3.882	0.418	-0.401
10	0.26	172	9.194	25.209	7	3.884	0.394	-0.401

TABLE 2: CALCULATED VALUE OF DESCRIPTORS

Sn.	Descriptors	Descriptors Detailed name
1	Spmax2m	Largest eigenvalue n. 2 of Burden matrix weighted by mass
2	Hy	Hydrophilic factor
3	ZM_1	First Zagreb index
4	MSD	Mean Square Distance index (Balaban)
5	X_0	Connectivity index of order 0
6	GGI_1	Topological charge index of order 1
7	SsssCH	Sum of sssCH E-states

TABLE-3: DETAILED NAME OF DESCRIPTORS

We know that QSAR analysis is one of the most effective approaches for optimizing lead compounds and designing new drugs. Excellent QSAR model can aid in understanding the mechanism of the action of drugs and may save the cost and time in the course of developing a new drug when compared with empirical procedures.^{[11],[12],[13]}

Hence, after calculating various descriptors we applied QSAR techniques to visualize any relationship among the descriptors and the activity. We have used NCSS 2007^[14] for statistical analysis of the data in hand. The relatedness among the descriptors used and their correlation with antihypertensive activity (IC_{50}) is demonstrated in Table-4. This shows that almost all variables have statistically significant correlation with antihypertensive activity. Results of regression analysis are given in the Table-5. The result of cross validation analysis is given in the Table-6, Finally Table-7 shows the predicted and observed antihypertensive activity with residuals.

	IC_{50}	ZM_1	MSD	X_0	GGI_1	SpMax2m	SsssCH	Hy
IC_{50}	1.0000							
ZM_1	0.8225	1.0000						
MSD	0.8167	0.9793	1.0000					
X_0	0.8105	0.9994	0.9803	1.0000				
GGI_1	0.7805	0.6843	0.6993	0.6645	1.0000			
SpMax2m	0.8824	0.9553	0.9117	0.9458	0.7815	1.0000		
SsssCH	-0.7690	-0.9333	-0.8604	-0.9319	-0.5970	-0.9117	1.0000	
Hy	0.8744	0.9621	0.9118	0.9548	0.7704	0.9799	0.9620	1.0000

TABLE-4: CORRELATION MATRIX OF DESCRIPTORS

Model No.	Parameters Used	A_i (1-7)	Intercept	MSE	R^2	AR^2	F-Ratio	$\text{Q} = \text{R}/\text{MSe}$
1	Spmax2m	7.4203±1.3987	-28.4883	0.0024	0.7787	0.7510	28.144	367.6832
2	Hy	6.2861±1.2333	2.8546	0.0026	0.7646	0.7351	25.981	336.3131
3	ZM_1	0.0080±0.0020	-1.0519	0.0036	0.6765	0.6361	16.730	228.4711
4	MSD	0.1772±0.0443	-1.3249	0.0036	0.6670	0.6254	16.024	226.8612
5	X_0	0.0477±0.0122	-0.8820	0.0038	0.6569	0.6141	15.320	213.2878
6	GGI_1	0.1553±0.0440	-0.8343	0.0043	0.6092	0.5604	12.472	181.5145
7	SsssCH	0.8837±0.2597	0.6976	0.0045	0.5919	0.5404	11.583	170.9667
8	SsssCH	1.1145±0.6476	0.5687	0.0021	0.8346	0.7873	17.657	435.0306

	Hy	12.9944±4.0516						
9	ZM1	0.1126±0.0501	-3.0521	0.0025	0.8009	0.7441	14.083	357.9720
	X0	0.6374±0.3034						
10	GGI1	0.0465±0.0539	-22.8678	0.0025	0.7999	0.7427	13.991	357.7485
	SpMax2m	5.8854±2.2788						
11	GGI1	0.0523±0.0537	1.8864	0.0026	0.7927	0.7334	13.382	342.4373
	Hy	4.8298±1.9406						
AFTER DELETING COMPOUND NO. 7								
12	SsssCH	1.3426±0.2929	5.0787	0.0004	0.9538	0.9384	61.919	2441.567
	Hy	13.339±1.8145						

TABLE-5: RESULTS OF REGRESSION ANALYSIS

Model No.	PRESS	SSY	PRESS/SSY	R ² CV	SPRESS
1	0.0296	0.0881	0.3359	0.6640	0.0608
2	0.0339	0.0881	0.3847	0.6152	0.0651
8	0.0279	0.0881	0.3165	0.6834	0.0630
12	0.0052	0.0542	0.0959	0.9040	0.0273

TABLE-6: RESULTS OF CROSS VALIDATION

PRESS → Predicted Residual Sum of Squares, SSY → Sum of Squares of Y, R²CV → Cross Validative Coefficient of determination, SPRESS → Uncertainty of prediction

Comps.	Observed IC ₅₀	From Regression No. 8		From Regression No.12	
		Predicted IC ₅₀	Residual	Predicted IC ₅₀	Residual
1	0.062	0.063	-0.001	0.069	-0.007
2	0.16	0.185	-0.025	0.183	-0.023
3	0.2	0.195	0.005	0.195	0.005
4	0.24	0.201	0.039	0.203	0.037
5	0.3	0.319	-0.019	0.314	-0.014
6	0.19	0.201	-0.011	0.193	-0.003
7	0.42	0.324	0.096	-	-
8	0.31	0.344	-0.034	0.319	-0.009
9	0.31	0.324	-0.014	0.295	0.015
10	0.26	0.297	-0.037	0.262	-0.002

TABLE-7: OBSERVED AND PREDICTED VALUES OF IC₅₀

In the first step of the present study activity of deferent substituted 2-(1-Alkylpiperidine-4-yl)-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl] acetamide is correlated with deferent descriptors. In this study, QSAR has been carried out using the model proposed by Hanch *et al*^[15]. Using the data Table 2 a correlation matrix was calculated as well as the co-linearity between the descriptors. A high inter relationship was observed between X0 and ZM1 (r= 0.9994) and the low inter relationship between ZM1 and GGI1 (r=0.6840). Correlation matrix also represents the relationship between the dependent variable structural descriptors. It is also clear from Table-4 that all descriptors are strongly correlated with antihypertensive activity.

Validity of QSAR model is justified by statistical parameters such as R², MeanSqaure Error, F-Ratio, PRESS/SSY and R²CV. In this study many significant mono parametric regressions models are obtained. Some significant models are given here:

1-IC₅₀= -28.4883+7.4203 (±1.3987) SpMax2m, n=10, MSE=0.0024, R² =0.7787, AR² = 0.7510, F-ratio = 24.144 Q=367.6832.

2-IC₅₀ = 2.8546+6.2861±1.2333 Hy, n=10, MSE=0.0026, R² =0.7646, AR² = 0.7351, F-ratio = 25.981 Q=336.3131.

3-IC₅₀ = 0.6976+0.8837±0.2597 SsssCH, n=10, MSE=0.0045 R² =0.5919, AR² = 0.5404, F-ratio = 11.583 Q=170.9667.

From above equations, it is clear that these all descriptors are strongly correlated with antihypertensive activity. Among these SpMax2m gives best results with a variance of above 75% (0.7787) and Descriptor SsssCH is poorly correlated with antihypertensive activity (59%)

Consequent to above analysis, to improve the statistics we have adopted multiple regression analysis. According to rule of thumb only bi-parametric regressions are allowed here. Out of the several bi-parametric regressions attempted the one containing SsssCH and Hy gave the best result:-

4-IC₅₀ =0.5687+1.1145 (±0.6476)SsssCH+12.9914±4.0516 Hy, n=10, MSE= 0.0021. R² = 0.8346, AR² = 0.7831, F-ratio = 17.657 Q= 435.0366

There was a dramatic change it the statistics when we omitted compound no. 7 as an outlier due to abnormally high value of IC₅₀. Value of variance was changed from 0.8346 to 0.9538 and MSE was changed from 0.0021 to 0.0004.

5-IC₅₀ = 5.0787+1.3426±0.6476 SsssCH+13.3301±1.8145 Hy, n=9, MSE= 0.0004. R² = 0.9538, AR² = 0.9384, F-ratio = 61.919 Q= 2441.567.

In all the models mentioned above we have discussed about the value of Q, called the Pogliani Quality factor^{[16],[17]}. This is defined as the ratio of correlation coefficient (R) to the mean square error of estimation (MSE) i.e. $Q = R/MSE$. In many cases this Q factor is used to account for the predictive potential of the model. Here value of Q for equation 4 is 435.0366 and for equation 5 is 2441.567, hence equation 5 is better than eqn. 4. So regression model no.12 is the best model due to higher value of variance (0.9538), very high value of F-test (61.919) and smaller value of MSE (0.0004). PRESS is also an important cross-validation parameter to predict the validity of model. To be a significant model the ratio PRESS/SSY should be smaller than 0.4 and the value of this ratio smaller than 0.1 indicates an excellent model. In this study results of cross validation as in Table No. 6 indicates that model no 12 is excellent due to the smaller value of PRESS/SSY as 0.0959. It also proves that model no 12 is the best model of this QSAR study.

Graphs in Fig-4 and 5 are very clearly depicting the findings of our discussion, hence conclusion.

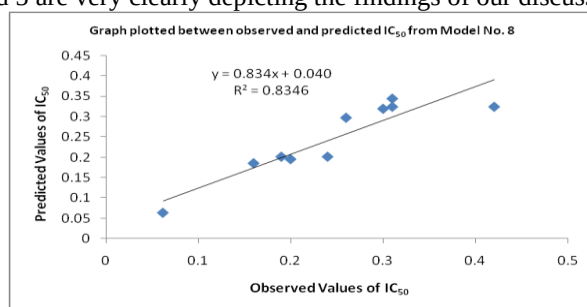


Fig-4

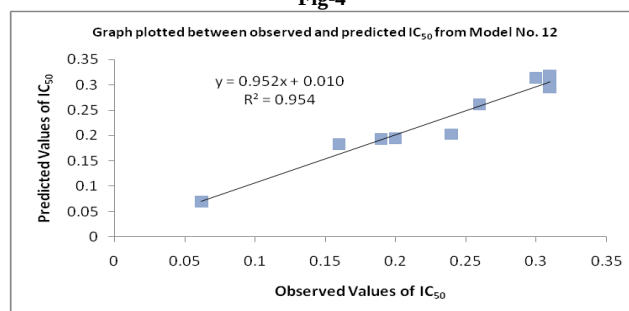


Fig-5

Conclusion:

- (I) - In this study hydrophilic factor and sum of sssCh E-states play a major role.
- (II) - Hydrophilic factor gives a positive influence while value of Atom type E-state gives a negative influence on activity.

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