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Prediction of Antihypertensive Activity of 1-Alkyl-N-[(1R)-1-(fluorophenyl)-2-methylpropyl]Piperidine-4-Carboxamide Derivatives

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Abstract: We have studied a series of 1-Alkyl-N-[(1R)-1-(4-fluorophenyl)-**2-methylpropyl] piperidine-4-carboxamide** Derivatives as Novel Antihypertensive Agents by incorporating QSAR methodology. We found that parameters EtaBetaS (Extended Topochemical Atom Index sigma VEM count), EtaLA (Eta average local composite index) , PVSAp1 (P van der Waals surface area-like index on Polarizability) SMTI (Schultz Molecular Topological Index) are very closely related with antihypertensive activity of these derivatives.
Keywords: Antihypertensive Activity, 1-Alkyl-N-[(1R)-1-(fluorophenyl)-2-methylpropyl]Piperidine-4-Carboxamide, Derivatives.

Introduction:

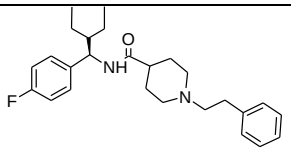
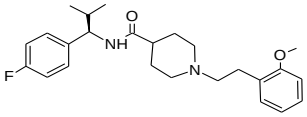
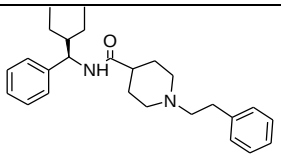
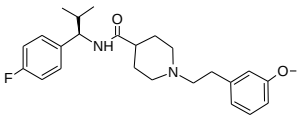
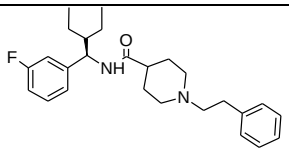
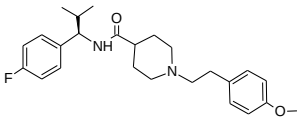
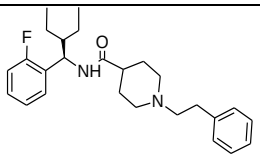
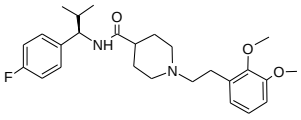
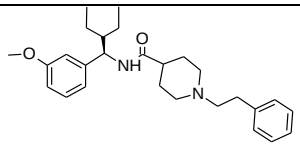
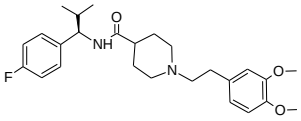
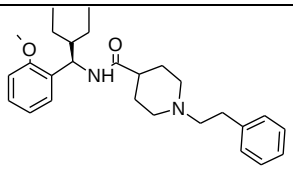
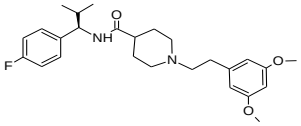
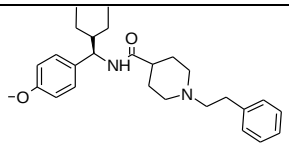
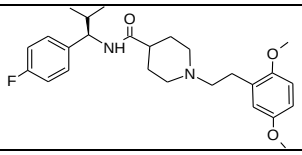
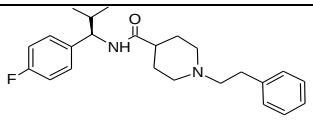
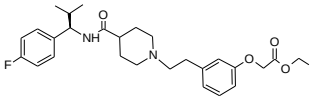
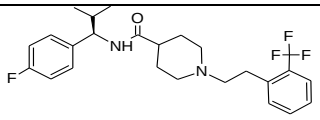
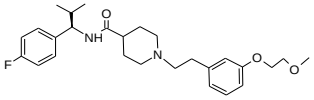
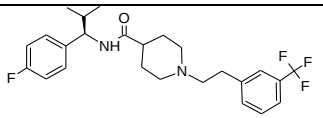
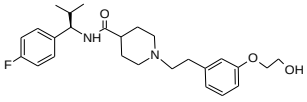
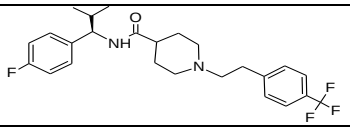
Studies and experiments have shown that Calciumions are essential for life and the most common signal transduction element in cells, transmitting signals by entering cells through ion channels on the plasma membrane in response to membrane depolarization.[1] Investigation intothe different subtypes of voltage-dependent Ca^{2+} channels has resulted in definition of two main classes: one respondingto strong depolarization known as a high-voltage-activated (HVA) Ca^{2+} channel, and another responding to weak depolarization, known as low-voltage-activated (LVA) Ca^{2+} channel. Based on results of several functional and pharmacological studies, HVA Ca^{2+} channels may be further subdividedinto L-, N-, P/Q-, and R-types, with LVA Ca^{2+}channel otherwise known as T-type channels.[2],[3] Among these sub-divisions, T-type Ca^{2+} channels are believed to play an importantrole in initial depolarization of the sinus and atrio-ventricular(AV) nodes[4] and are therefore regarded as important therapeutic targets for treating various cardiovascular disease such as **hypertension, angina, heart failure, and arrhythmia.**

Recently Susumu WATANUKI et al[5]have synthesized and studied a series of **1-Alkyl-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide** Derivatives as Novel Antihypertensive Agents. We have taken queue from them in studying and predicting antihypertensive activity of these compounds based on certain structural parameters suitably chosen by us.

Materials and Method:

We have taken 1-Alkyl-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Derivatives compounds synthesized by Susumu Watanuki et al along with their IC_{50}values which refer to experimentally determined concentration required to inhibit or block Ca^{2+}T-type Calcium channel activity by 50%. These are listed in Table 1.

Table 1: Compounds with Their Respective Activities (IC_{50})

Comps	Structure	IC_{50} (μM)	Comps	Structure	IC_{50} (μM)
1		**0.13**	**12**		**0.11**
2		**0.55**	**13**		**0.076**
3		**0.53**	**14**		**0.13**
4		**0.39**	**15**		**0.13**
5		**0.26**	**16**		**0.12**
6		**0.33**	**17**		**0.13**
7		**0.26**	**18**		**0.21**
8		**0.15**	**19**		**0.13**
9		**0.21**	**20**		**0.15**
10		**0.16**	**21**		**0.42**
11		**0.26**			

We have used Dragon6 (Software for Molecular Descriptor Calculation)[6] to calculate certain molecular descriptors which were giving significantly impressive indications of their involvement it the antihypertensive activity of above mentioned compound. After several trials we foundTopological indices ZM1[7], MSD[8],SMTI[9], PW2[10], MAXDN, MAXDP[11] and LogP and Eta core counts PVSALogP1, PVSAp1[12], Eta_alpha, EtaBetaS, EtaLA, EtaFLA, Etashp[13]and Indicator parameter IR1are important in the

present study. The values of these descriptors for different compounds are given in Table 3A and 3B while Table 2 gives details of descriptors which have been used.

Table 2: Detailed Name of Descriptors

Descriptors	Description of Parameters
ZM1	First Zagreb index, Topological indices, Vertex degree-based indices
MSD	Mean Square Distance index (Balaban), Topological indices, Distance-based ind
SMTI	Schultz Molecular Topological Index (MTI), Topological indices, MTI indices
PW2	Path/Walk 2 - Randic shape index, Topological indices, Path/walk indices
MAXDN	Maximal Electrotopological Negative variation, Topological indices,E-state indi
MAXDP	Maximal electrotopological Positive variation, Topological indices,E-state indic
PVSALogP1	P_VSA-like on LogP, bin 1, P_VSA-like descriptors, LogP
PVSAp1	P_VSA-like on Polarizability, bin 1, P_VSA-like descriptors, Polarizability,
Eta_alpha	Eta core count, ETA indices ,Basic descriptors
EtaBetaS	Eta sigma VEM count, ETA indices, Basic descriptors
EtaLA	Eta average local composite index, ETA indices, Basic descriptors
EtaFLA	Eta average local functionality index, ETA indices, Basic descriptors
Etashp	Eta p shape index, ETA indices, Basic descriptors
IR1	Presence of Methoxy group on Phenyl Side Chain attached to Piperidine

Table 3a- Calculated Value of Descriptors Along with Antihypertensive Activity Ic_{50}:

Compound	IC50	ZM1	MSD	SMTI	PW2	MAXDN	MAXDP
1	0.13	148	7.638	12037	0.565	1.906	6.067
2	0.55	142	7.459	11019	0.558	1.423	6.075
3	0.53	148	7.57	11941	0.564	1.913	6.066
4	0.39	148	7.508	11846	0.563	1.898	6.483
5	0.26	152	7.725	12985	0.559	1.456	6.198
6	0.33	152	7.605	12794	0.558	1.467	6.233
7	0.26	152	7.856	13177	0.56	1.449	6.173
8	0.15	140	7.512	10311	0.575	1.916	5.836
9	0.21	164	8.17	14474	0.591	5.598	5.866
10	0.16	164	8.412	14841	0.593	5.58	5.86
11	0.26	164	8.668	15209	0.594	5.563	5.857
12	0.11	150	7.873	12322	0.575	1.923	5.903
13	0.076	150	8.014	12505	0.576	1.922	5.892
14	0.13	150	8.165	12689	0.577	1.922	5.884
15	0.13	160	8.235	14573	0.574	1.929	5.959
16	0.12	160	8.48	14940	0.575	1.928	5.941
17	0.13	160	8.357	14771	0.575	1.928	5.949
18	0.21	160	8.245	14604	0.575	1.929	5.959
19	0.13	172	9.506	19845	0.571	2.04	5.977
20	0.15	162	8.975	16730	0.567	1.926	5.958
21	0.42	158	8.632	15191	0.569	1.931	5.928

Table 3b- Calculated Value of Descriptors Along with Antihypertensive Activity IC_{50}:

Compound	PVSA LogP1	PVSA p1	EtaAlpha	EtaBetaS	EtaLA	EtaFLA	Etashp
1	17.65	415.178	14.419	17.75	0.298	0.189	0.112
2	17.65	411.989	14.133	17	0.302	0.188	0.094
3	17.65	415.178	14.419	17.75	0.298	0.189	0.112
4	17.65	415.178	14.419	17.75	0.298	0.189	0.112

5	28.533	435.531	14.967	18.5	0.297	0.192	0.122
6	28.533	435.531	14.967	18.5	0.297	0.192	0.122
7	28.533	435.531	14.967	18.5	0.297	0.192	0.122
8	17.65	368.093	13.419	16.75	0.281	0.202	0.121
9	17.65	401.202	14.776	19.5	0.275	0.199	0.168
10	17.65	401.202	14.776	19.5	0.275	0.198	0.168
11	17.65	401.202	14.776	19.5	0.275	0.198	0.168
12	28.533	391.635	14.252	18.25	0.277	0.205	0.149
13	28.533	391.635	14.252	18.25	0.277	0.205	0.149
14	28.533	391.635	14.252	18.25	0.277	0.205	0.149
15	39.417	415.178	15.086	19.75	0.274	0.208	0.174
16	39.417	415.178	15.086	19.75	0.274	0.208	0.174
17	39.417	415.178	15.086	19.75	0.274	0.207	0.174
18	39.417	415.178	15.086	19.75	0.274	0.208	0.174
19	26.476	438.72	16.419	21.5	0.278	0.203	0.149
20	28.533	438.72	15.586	20.25	0.282	0.201	0.136
21	17.65	403.406	15.086	19.5	0.283	0.2	0.129

Table-4a: Corelation Matrix of Descriptors

	IC50	**ZM1**	**MSD**	**SMTI**	**PW2**	**MAXDN**	**MAXDP**	**PVSA LogP1**
IC50	1							
ZM1	-0.3976	1						
MSD	-0.4510	0.8773	1					
SMTI	-0.3606	0.9381	0.9549	1				
PW2	-0.4944	0.5066	0.4110	0.2881	1			
MAXDN	-0.1402	0.4985	0.2839	0.2529	0.8598	1		
MAXDP	0.5185	-0.3222	-0.4603	-0.2663	-0.7226	-0.4316	1	
PVSA LogP1	-0.5470	0.2548	0.2189	0.2635	-0.1129	-0.4200	-0.0672	1
PVSAp1	0.1894	0.3731	0.2598	0.4775	-0.5422	-0.2941	0.5574	0.3120
Etaalpha	-0.1870	0.8336	0.7840	0.9197	-0.0475	0.0091	0.0566	0.3767
EtaBetaS	-0.4388	0.9674	0.9134	0.9721	0.3449	0.2728	-0.2866	0.4094
EtaLA	0.7797	-0.5879	-0.6180	-0.4826	-0.8050	-0.4380	0.7966	-0.3768
EtaFLA	-0.8101	0.4161	0.5261	0.3979	0.4951	0.0264	-0.6821	0.6460
Etashp	-0.7123	0.7082	0.5671	0.5267	0.7606	0.4884	-0.5979	0.5308
IR1	-0.5704	-0.0327	0.0484	-0.0638	0.1777	-0.2203	-0.3241	0.6218

Table-4b: Corelation Matrix of Descriptors

	PVSAp1	**EtaAlpha**	**EtaBetaS**	**EtaLA**	**EtaFLA**	**Etashp**	**IR1**
IC50							
ZM1							
MSD							
SMTI							
PW2							
MAXDN							
MAXDP							
PVSALogP1							
PVSAp1	1						
Etaalpha	0.7660	1					
EtaBetaS	0.4587	0.9065	1				
EtaLA	0.4094	-0.1884	-0.5715	1			
EtaFLA	-0.3106	0.1956	0.5002	-0.9072	1		

Etashp	-0.1542	0.3359	0.6678	-0.9076	0.7998	1	
IR1	-0.3012	-0.1319	0.0507	-0.5009	0.6677	0.4817	1

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. [14], [15], [16]Hence, after calculating various descriptors we applied QSAR techniques to visualize any relationship among the descriptors and the activity. We have used NCSS 2007[17] 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 4A and 4B. 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.

Table-5 : Results of Regression Analysis

Model No.	Parameters Used	Ai (1-4)	Intercept	MSE	R2	AR2	F-Ratio	Q= R/MSe
1	EtaFLA	-16.4353±2.8037	3.5133	0.0071	0.6563	0.6372	34.364	114.1019
2	EtaLA	10.5410±1.9949	-2.7504	0.0082	0.6080	0.5862	27.919	95.0907
3	EtabetaS	-0.0532±0.0257	1.2409	0.0168	0.1925	0.1477	4.292	26.1160
4	PVSAp1	0.0014±0.0017	-0.3463	0.0200	0.0359	0.0000	0.670	9.4737
5	SMTI	0.0000±0.0000	0.5603	0.0181	0.1300	0.0817	2.690	19.9202
6	EtaLA PVSAlogP1	9.0379±1.9937 -0.0050±0.0025	-2.1942	0.0070	0.6827	0.6454	18.292	118.0367
7	EtaFLA MAXDN	16.3715±2.8260 -0.0120±0.0141	3.5292	0.0073	0.6704	0.6316	17.287	112.1616
8	EtaFLA PW2	-15.1930±3.2643 -1.5939±2.0739	4.1780	0.0073	0.6678	0.6287	17.087	111.9439
9	EtaFLA Etashp	-13.537±14.7252 -0.9887±1.2893	3.0770	0.0073	0.6677	0.6287	17.083	111.9355
10	EtaFLA EtaLA	-11.7727±6.7430 3.4246±4.4930	1.6134	0.0073	0.6676	0.6285	17.072	111.9271
11	EtaBetaS EtaLA PVSAp1	0.1437±0.0472 26.0242±5.1316 -0.0085±0.0026	-6.3445	0.0055	0.7645	0.7203	17.310	158.9740
12	EtaLA PVSAp1 ZM1	20.7355±3.8272 -0.0054±0.0018 0.0133±0.0048	-5.4652	0.0059	0.7497	0.7028	15.976	146.7546
13	EtaAlpha EtaBetaS EtaLA	-0.6481±0.2201 0.4116±0.1406 29.5130±6.7428	-6.3229	0.0060	0.7459	0.6982	15.652	143.9425
14	EtaBetaS EtaLA PVSAp1 SMTI	0.3400±0.1133 33.1523 ±6.0920 -0.0115 ±0.0029 -0.0001 ±0.0000	-9.7907	0.0048	0.8094	0.7585	15.922	187.4305
15	EtaAlpha EtaBetaS PVSAp1 EtaLA	-0.4133±0.2246 0.3649±0.1280 33.6917±6.3462 -0.0061±0.0028	-7.5844	0.0048	0.8078	0.7566	15.766	187.2452
16	EtaBetaS EtaLA Etashp PVSAp1	0.1681±0.0464 36.9287±7.7873 3.3991±1.9078 -0.0110±0.0028	-9.3748	0.0049	0.8056	0.7538	15.540	183.1739

Table-6: Results of Cross Validation

Model No.	PRESS	SSY	PRESS/SSY	R^2CV	SPRESS
11	0.1596	0.3750	0.4256	0.5744	0.09989
12	0.1507	0.3750	0.4019	0.5981	0.09705
14	0.1382	0.3750	0.3685	0.6315	0.09599
15	0.1456	0.3750	0.3883	0.6117	0.09852
16	0.1486	0.3750	0.3963	0.6037	0.09953

PRESS → Predicted Residual Sum of Squares, SSY → Sum of Squares of Y, R^2CV → Cross Validative Coefficient of determination, SPRESS→ Uncertainty of prediction

Table 7- Predicted and Observed Antihypertensive Activity with Residuals for Model 14 of Table 5

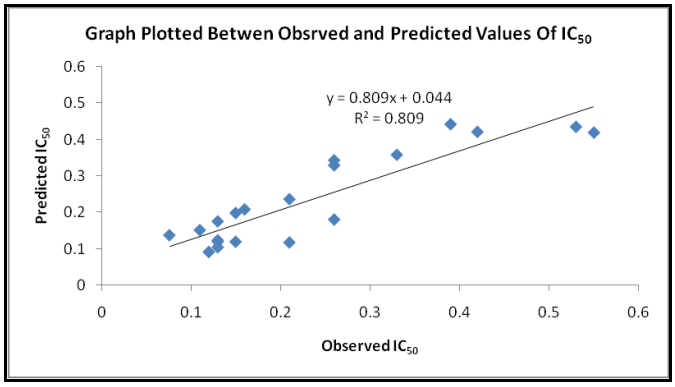
Compound No.	log IC_{50}	Predicted log IC_{50}	Residual
1	0.55	0.419	0.038
2	0.53	0.435	0.03
3	0.39	0.442	0.031
4	0.26	0.343	0.031
5	0.33	0.358	0.033
6	0.26	0.329	0.031
7	0.15	0.198	0.048
8	0.21	0.236	0.032
9	0.16	0.208	0.025
10	0.26	0.18	0.025
11	0.11	0.151	0.026
12	0.076	0.137	0.027
13	0.13	0.123	0.029
14	0.13	0.119	0.031
15	0.12	0.091	0.026
16	0.13	0.104	0.028
17	0.21	0.117	0.03
18	0.13	0.175	0.057
19	0.15	0.119	0.04
20	0.42	0.421	0.051

Results and Discussion:

In the first step of the present study,activity of deferent substituted ***1-Alkyl-N-[(1R)-1-(fluorophenyl)-2-methylpropyl]Piperidine-4-Carboxamide Derivetives*** is correlated with deferent descriptors. In this study, QSAR has been carried out using the model proposed by Hanschetal[18]. Using the data in Table 3, a correlation matrix was calculated along with the co-linearity between the descriptors (Table 4). The best correlation is observed between the antihypertensive activity and EtaFLA but being negative it could not be part of our best model in multiple regression while other better correlated parameter like EtaLA was part of our best models in multiple regressions. We know that validity of QSAR model is justified by statistical parameters such as R^2, Mean Square Error, F-Ratio, $PRESS/SS_Y$ and R^2_{CV}. In mono-parametric regressions EtaFLA stood first with an R^2 value of 0.6563 but it could not do well when combined with other parameters while on the other hand parameters EtaBetaS, PVSAp1 and SMTI which were poor performers in mono-parametric regressions became significant in multi-parametric models. In bi-parametric models Model 6 of Table 5 was better with parameters EtaLA and PVSAlogP1, and similarly Model 11 was the best in tri-parametric models with parameters EtaBetaS, EtaLA and PVSAp1 and value of R^2 = 0.7645. We have studied upto four parametric multiple regressions as our sample size was 20 and we found three models of significance out of which Model 14 was the best with an R^2 value of 0.8094. All these three, four parametric models have parameters EtaBetaS, EtaLA and PVSAp1 in common. Presence of SMTI, EtaAlpha and Etashp respectively in three models (14, 15 & 16) as fourth parameter improves the result in decreasing order. We had also taken an indicator parameter IR1 but it did not influence the results significantly.

In all the models mentioned above we have discussed about the value of Q, called the Pogliani Qaulity factor[19],[20]. 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 3 is 187.2452 followed by equation 4 which is 187.2452, hence equation 3 is the best.

PRESS is also an important cross-validation parameter to predict the validity of model. To be a significant model the ratio $PRESS/SS_Y$ should be smaller than 0.4 and in our study models 14, 15 and 16 have this value less than 0.4. Thus, from cross validation it is also realized that models are better among suggested models of this study model 14 is the best because of having the smallest value of $PRESS/SS_Y$. SPRESS, uncertainty in prediction is also least in for model 14 (0.09599), showing that it is the best model of our present study.



Conclusion:

Parameters EtaBetaS(Extended Topochemical AtomIndices sigma VEM count), EtaLA(Eta average local composite index),PVSAp1 (P van der Waals surface area -like on Polarizability) SMTI (Schultz Molecular Topological Index) are very closely related with antihypertensive activity of compounds discussed above.

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