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QSAR® Study of Spiro-Piperidine Azetidedines and Azetidinones as Calcium Channel Blocker Antihypertensive Agents

Shailja Sachan¹, Amitabh Tripathi², Pradeep Chandra Shukla³

¹Department of Chemistry, Govt. MSG College, Rewa, M.P. India, ² Department Of Chemistry, Awadhesh Pratap Singh University, Rewa, M.P. India, ³Department of Chemistry, Y.P.S. College, Sirmour, Rewa, M.P., India

Abstract: Spiro-PiperidineAzetidedines and Azetidinones were found to be potent T-type Calcium Channel Blockers. We have made QSAR study of a series of derivatives of aforesaid compounds. We took 12 different descriptors to study their effects on the antihypertensive activity of these compounds and found that presence of pyridyl group and ketonic group at some specific locations did not favour the T-type calcium channel blocking activity of these compounds. However, hydrophilic factor and connectivity indices were better indicators of the said activity.

@ Quantitative Structure Activity Relationship

I. INTRODUCTION:

We found that Elizabeth M. Smith et al^[1] have already reported that a family of integral membrane proteins, collectively referred to as voltage-gated calcium channels, represent major pathways for calcium influx in diverse tissues throughout the body. Based on biophysical properties, pharmacology, and molecular sequences, the family of voltage-gated calcium channels is divided into the following subtypes: L- (Ca_v1.1–Ca_v1.4), P/Q- (Ca_v2.1), N- (Ca_v2.2), R- (Ca_v2.3), and T-type (Ca_v3.1–Ca_v3.3).^[2] Control of calcium influx across the plasma membrane is a critical component for spatial and temporal regulation of intracellular calcium levels and also for determining trans-membrane potential. Cellular functions regulated by intracellular calcium include muscle contraction, neurotransmitter release, gene expression, and chemotaxis.^{[3],[4]} T-type calcium channels serve two primary roles in excitable tissues; providing current for rhythmic pace making and generation of low level depolarization from which neuronal burst firing can occur.^[3] Ca_v3.x channels are widely distributed in excitable tissue but in an isoform-dependent manner.^{[5],[6]}

Among the therapeutic indications proposed for T-type calcium channels are: hypertension, heart failure, insomnia, metabolic syndrome, epilepsy, and neuropathic pain.^{[6],[7],[8]} T-type channels are present in DRG and in regions of the CNS involved in pain processing.^{[5],[6]} Sasumi Watanaki et al^[9] have reported that Ca²⁺ channel blockers are effective antihypertensive agents, hence we have used findings of Elizabeth M. Smith et al as starting point for our QSAR study of antihypertensive effect of calcium channel blocking activity of compounds synthesized by them. They^[1] have also reported that from an in-house screening effort, the spiro-piperidineazetidedines Fig 1 to 3, were identified as blockers of Ca_v3.2 channel. These hits, as mixtures of stereoisomers, exhibited good activity in IonWorks HT and manual patch clamp assays.^[10] Their^[1] initial goal was to separate the mixtures and determine if the T-type calcium channel blocker activity resided solely in one of the stereo-isomers, and then to evaluate the DMPK profiles of those hits. They studied T-type channel blocking activities of several compounds based on the structures shown in Figures 1 to 3. Thus they synthesized and studied more than 70 derivatives of these compounds including stereo-isomers of a few. We found from the data given by them that out of two such isomers *a* and *b*, *a* was showing better activity against T-type calcium channel hence we have left all *b* isomers from our present study. All such compounds are listed in Table-1 and Table-2 along based on basic structures shown in Fig-4 and Fig-5 along with respective IC₅₀ of Antihypertensive activity as a T-type Calcium Channel blocker.

II. MEHOD AND MATERIAL:

The data set in Table 1 and Table 2 consists of structurally diverse compounds reported for Ca_v3.2 T-type Calcium channel blocking activity which we have already mentioned is an antihypertensive activity. The selected series lists thirty seven derivatives of Spiro-piperidine Azetidedines and Azetidinones. The antihypertensive activity of the data set is reported as IC₅₀ value which refers to experimentally determined concentration required to inhibit or block hCa_v3.2 T-type Calcium channel activity by 50%.

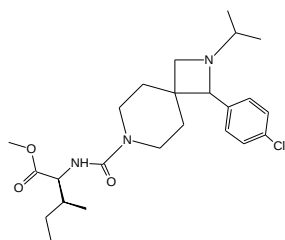


FIG 1

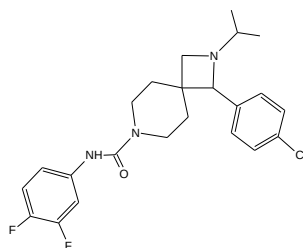


FIG 2

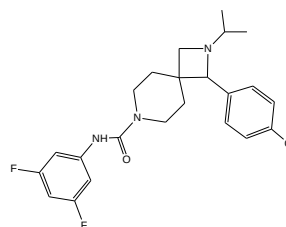


FIG 3

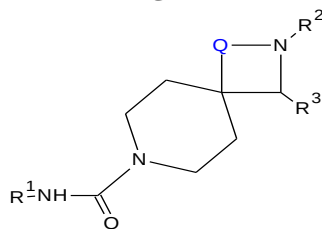


FIG 4

Comp. No	R¹N(H)-	R²	R³	Q	IC ₅₀ (nM)
1	Ile-OMe	Me	4-Cl-C ₆ H ₄ -	CH ₂	410
2	3,5-F ₂ -C ₆ H ₃ -N(H)-	Me	4-Cl-C ₆ H ₄ -	CH ₂	214
3	Ile-OMe	Me	4-Cl-C ₆ H ₄ -	C=O	800
4	3,5-F ₂ -C ₆ H ₃ -N(H)-	Me	4-Cl-C ₆ H ₄ -	C=O	920
5	3,5-F ₂ -C ₆ H ₃ -N(H)-	i-Bu	4-Cl-C ₆ H ₄ -	CH ₂	177
6	Ile-OMe	i-Pr	4-F-C ₆ H ₄ -	CH ₂	256
7	3,5-F ₂ -C ₆ H ₃ -N(H)-	i-Pr	4-F-C ₆ H ₄ -	CH ₂	172
8	3,5-F ₂ -C ₆ H ₃ -N(H)-	Me	4-F-C ₆ H ₄ -	CH ₂	410
9	Ile-OMe	Cyclopropyl	4-Cl-C ₆ H ₄ -	CH ₂	325
10	3,5-F ₂ -C ₆ H ₃ -N(H)-	Cyclopropyl	4-Cl-C ₆ H ₄ -	CH ₂	398
11	3,5-F ₂ -C ₆ H ₃ -N(H)-	Cyclopropyl	4-Cl-C ₆ H ₄ -	C=O	2258
12	Ile-OMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	CH ₂	146
13	Ile-OMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	45
14	Ile-nitrile	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	35
15	Ile-OPr-i	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	45
16	Ile-NHMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	182
17	Ser(t-Bu)-OMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	251
18	Ala-OMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	827
19	Ser-OMe	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	3333
20		3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	139
21		3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	351
22		3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	82
23		3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	224
24		3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	1251
25	3-CNC ₆ H ₄ -N(H)-	3-F-C ₆ H ₄ -	4-Cl-C ₆ H ₄ -	C=O	183
26	3,5-F ₂ -C ₆ H ₃ -N(H)-	3-Cl,4-F-C ₆ H ₃ -	2-Pyridyl	CH ₂	60
27	3,5-F ₂ -C ₆ H ₃ -N(H)-	3-Cl,4-F-C ₆ H ₃ -	2-Pyridyl	CH ₂	4
28	3,5-F ₂ -C ₆ H ₃ -N(H)-	3-Cl,4-F-C ₆ H ₃ -	2-Pyridyl	C=O	41
29	3-F ₃ CC ₆ H ₃ -N(H)-	3,4-F ₂ -C ₆ H ₃ -	2-Pyridyl	C=O	17
30	3,4-F ₂ -C ₆ H ₃ -N(H)-	3-Cl-C ₆ H ₄ -	2-Pyridyl	C=O	116

31	3-NCC ₆ H ₄ -N(H)-	3-Cl-C ₆ H ₄ -	2-Pyridyl	C=O	57
32	3,5-F ₂ -C ₆ H ₃ -N(H)-	3-Cl-C ₆ H ₄ -	2-Pyridyl	C=O	18
33	3,5-F ₂ -C ₆ H ₃ -N(H)-	3-NC-C ₆ H ₄ -	2-Pyridyl	C=O	247
34	3,5-F ₂ -C ₆ H ₃ -N(H)-	5-Cl-Pyrid-3-yl	2-Pyridyl	C=O	519

TABLE 1: COMPOUNDS WITH THEIR RESPECTIVE ACTIVITIES (IC₅₀)

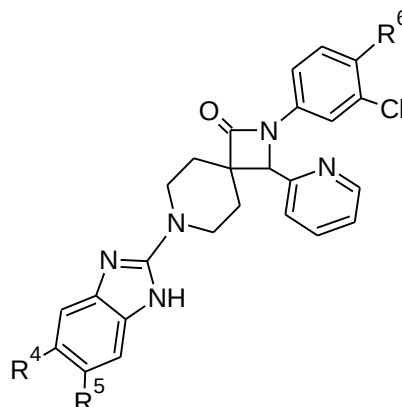


FIG 5

Comp. No	R ⁴	R ⁵	R ⁶	IC ₅₀ (nM)
35	F	CF ₃	H	44
35	H	Cl	F	78
37	F	CF ₃	F	29

Table 2

III. RESULTS AND DISCUSSION:

We have used Dragon (Software for Molecular Descriptor Calculation)^[11] to calculate certain molecular descriptors which were giving significantly impressive indications of their involvement in the antihypertensive activity of above mentioned compound. After several trials we found Hydrophilic factor(Hy)^[12], Keir and Hall connectivity index (X0)^[13], X1^[14] and topological parameters like GATS1m^[15], SpMax1Bhm^[16], PVSAMR1^[17], PVSAv1^[18], Eta_Alpha^[19], IR¹, IR², IR³, IR⁴ important in the present study. The values of these descriptors for different compounds are given in Table 3 and Table 4 gives details of descriptors which have been used.

Com p.	Log IC ₅₀	GATS1 m	SpMax1 Bhm	PVSAM R1	PVSAv1	Eta Alp ha	Hy	IR ₁	IR ₂	IR ₃	IR ₄	X ₀	X ₁
1	2.612783857	0.75	4.044	306.049	364.904	0.48	-0.336	1	0	0	0	21.181	13.808
2	2.330413773	0.61	4.045	230.029	247.193	0.476	-0.323	0	0	0	0	19.889	13.36
3	2.903089987	0.711	4.054	282.506	341.362	0.475	-0.316	1	0	0	1	22.052	14.245
4	2.963787827	0.58	4.055	206.487	223.651	0.471	-0.302	0	0	0	1	20.759	13.797
5	2.247973266	0.664	4.052	241.8	317.82	0.478	-0.361	0	0	0	0	22.173	14.808
6	2.408239965	0.903	4.003	297.467	411.989	0.467	-0.361	1	0	0	0	22.759	14.718
7	2.235528447	0.732	4.006	221.447	294.278	0.463	-0.349	0	0	0	0	21.466	14.27
8	2.612783857	0.69	3.997	244.989	247.193	0.46	-0.323	0	0	0	0	19.889	13.36
9	2.511883361	0.749	4.06	282.506	388.446	0.481	-0.361	1	1	0	0	22.173	14.88
10	2.599883072	0.615	4.061	206.487	270.735	0.477	-0.349	1	1	0	0	20.88	14.432
11	3.353723938	0.585	4.073	182.945	247.193	0.473	-0.329	1	1	0	1	21.75	14.87
12	2.164352856	0.699	4.063	332.78	376.675	0.477	-0.373	1	0	0	0	25.165	16.774
13	1.653212514	0.668	4.074	309.238	353.133	0.473	-0.355	0	0	0	1	26.035	17.212
14	1.544068044	0.643	4.074	273.924	317.82	0.475	-0.355	0	0	0	1	26.035	17.212
15	1.653212514	0.697	4.075	285.695	400.217	0.475	-0.374	0	0	0	1	27.612	18.067
16	2.260071388	0.678	4.074	309.238	353.133	0.477	-0.373	1	0	0	1	25.328	16.674
17	2.399673721	0.674	4.074	238.611	376.675	0.47	-0.348	1	0	0	1	27.665	17.947
18	2.91750551	0.621	4.073	215.069	282.506	0.471	-0.322	1	0	0	1	23.75	15.763
19	3.522835314	0.628	4.074	238.611	270.735	0.467	0.235	0	0	0	1	24.457	16.301
20	2.1430148	0.638	4.075	238.611	306.049	0.482	-0.401	0	0	0	1	24.579	16.887
21	2.545307116	0.638	4.075	238.611	306.049	0.482	-0.401	0	0	0	1	24.579	16.887
22	1.913813852	0.612	4.075	241.8	294.278	0.476	-0.383	0	0	0	1	25.449	17.281
23	2.350248018	0.654	4.075	273.924	329.591	0.482	-0.41	0	0	0	1	25.286	17.425
24	3.09725731	0.661	4.073	215.069	306.049	0.48	-0.361	0	0	0	1	22.173	14.852
25	2.26245109	0.588	4.075	215.069	247.193	0.479	-0.373	0	0	0	1	24.579	16.908

26	1.77815125	0.572	4.071	244.989	247.193	0.471	-0.334	0	0	1	1	23.872	16.343
27	0.602059991	0.548	4.082	221.447	223.651	0.467	-0.316	0	0	1	0	24.742	16.781
28	1.612783857	0.548	4.082	221.447	223.651	0.467	-0.316	0	0	1	1	24.742	16.797
29	1.230448921	0.587	4.045	218.258	235.422	0.451	-0.311	0	0	1	1	26.372	17.598
30	2.064457989	0.569	4.071	218.258	235.422	0.472	-0.334	0	0	1	1	23.872	16.387
31	1.755874856	0.601	4.071	200.109	247.193	0.482	-0.363	0	0	1	1	23.709	16.514
32	1.255272505	0.569	4.071	218.258	235.422	0.472	-0.334	0	0	1	1	23.872	16.37
33	2.392696953	0.638	4.042	218.258	235.422	0.464	-0.345	0	0	1	1	24.579	16.908
34	2.715167358	0.558	4.066	206.487	223.651	0.469	-0.304	0	0	1	1	23.872	16.37
35	1.643452676	0.532	4.121	191.527	223.651	0.465	-0.311	0	0	0	1	25.949	17.67
36	1.892094603	0.521	4.142	191.527	223.651	0.487	-0.334	0	0	0	1	23.449	16.459
37	1.462397998	0.517	4.123	194.716	211.88	0.46	-0.296	0	0	0	1	26.819	18.081

TABLE 3: CALCULATED VALUE OF DESCRIPTORS

	Description of variables
GATS1m →	Geary autocorrelation of lag 1 weighted by mass, 2D autocorrelations, Geary autocorrelations
SpMax1_Bh(m) →	largest eigenvalue n. 1 of Burden matrix weighted by mass, Burden eigenvalues Largest eigenvalues
P_VSA_MR_1 →	P_VSA-like on Molar Refractivity, bin 1, P_VSA-like descriptors, Molar Refractivity
P_VSA_v_1 →	P_VSA-like on van der Waals volume, bin 1, P_VSA-like descriptors, Van der Waals volume
Eta_alpha_A →	eta average core count, ETA indices, Basic descriptors
Hy →	hydrophilic factor, Molecular properties, Basic descriptors
IR¹,IR²,IR³,IR⁴	Indicator Parameters representing the Presence of Methoxy Group, Flourine, Pyridyl group & Ketonic Group respectively with value 1.
X₀ →	connectivity index of order 0, Connectivity indices, Kier-Hall molecular connectivity indices
X₁ →	connectivity index of order 1 (Randic connectivity index), Connectivity indices, Kier-Hall molecular connectivity indices

TABLE 4: 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.^{[20], [21], [22]} Hence, after calculating various descriptors we applied QSAR techniques to visualize any relationship among the descriptors and the activity. We have use NCSS 2007^[23] for statistical analysis of the data in hand.

The relatedness among the descriptors used and their correlation with logarithm of antihypertensive activity(IC₅₀) is demonstrated in Table 5. This shows thatalmost all variable have statistically significant correlation with antihypertensive activity. Results of regression analysis are given in the Table 6. The result of cross validation analysis is given in the Table 7, Finally Table 8 shows the predicted and observed antihypertensive activity with residuals.

	log IC ₅₀	GATS1m	SpMaxBhm	PVSAMR1	PVSAv1	Eta_AlphaA	Hy	IR1	IR2	IR3	IR4	X0	X1
log IC₅₀	1												
GATS1m	0.32583	1											
SpMaxBhm	-0.29138	-0.681	1										
PVSAMR1	0.00968	0.720974	-0.31907	1									
PVSAv1	0.19069	0.848896	-0.29322	0.83839	1								
Eta_AlphaA	0.21484	0.11093	0.29445	0.22829	0.34946	1							
Hy	0.31952	-0.13291	0.05994	-0.13378	-0.21253	-0.30116	1						
IR1	0.40570	0.517302	-0.19217	0.40739	0.55652	0.16186	-0.10533	1					
IR2	0.29947	0.062126	-0.02125	-0.12361	0.07339	0.16638	-0.05	0.48809	1				
IR3	-0.45815	-0.42457	0.00264	-0.31574	-0.51573	-0.33941	0.00708	-0.34503	-0.16841	1			
IR4	-0.02675	-0.49734	0.55680	-0.2978	-0.27629	0.01715	0.09543	-0.31482	-0.26514	0.20318	1		
X0	-0.51537	-0.22035	0.51960	0.13080	0.13148	-0.14896	-0.01479	-0.18362	-0.33553	0.14757	0.55743	1	
X1	-0.54879	-0.37701	0.60942	-0.02073	-0.03543	-0.08821	-0.04043	-0.297	-0.29281	0.24461	0.60356	0.9691	1

TABLE-5: CORRELATION MATRIX OF DESCRIPTORS

Model No.	Parameters Used	Ai (1-7)	Intercept	MSE	R2	AR2	F-Ratio	Q= R/MSe
1	IR4	0.6591±0.2201	7.7189	0.2247	0.4470	0.4145	13.742	2.975437
	X1	-0.3727±0.0712						
2	IR3	-0.5564±0.1889	5.6536	0.2378	0.4149	0.3804	12.053	2.708694
	X0	-0.1387±0.0402						
3	IR3	-0.5338±0.1665	7.3014	0.1765	0.5784	0.5400	15.089	4.30893
	IR4	0.7041±0.1956						
	X1	-0.3407±0.0639						
4	IR1	0.4795±0.1702	7.0952	0.1867	0.5542	0.5137	13.674	3.987392
	IR4	0.7613±0.2.39						
	X1	-0.3461±0.0655						
5	PVSAv1	0.0058±0.0012	7.3466	0.1375	0.6815	0.6417	17.120	6.003856
	Hy	2.2780±0.6352						
	IR4	0.8329±0.1828						
	X0	-0.2790±0.0390						
6	IR1	0.4471±0.1609	6.7648	0.1547	0.6417	0.5969	14.329	5.178163
	IR3	-0.5010±0.1616						
	IR4	0.7429±0.1821						
	X0	-0.2136±0.0387						
7	Hy	1.8732±0.5866	7.1928	0.1201	0.7304	0.6869	16.797	7.116024
	IR1	0.4869±0.1424						
	IR3	-0.4849±0.1425						
	IR4	0.6901±0.1613						
	X0	-0.2046±0.0342						
8	PVSAMR1	-0.0061±0.0029	7.7049	0.1238	0.7223	0.6775	16.127	6.864962
	PVSAv1	0.0089±0.0018						
	Hy	2.3971±0.6052						
	IR4	0.7590±0.1768						
	X0	-0.2668±0.0374						
9	SpMax1Bhm	-6.1307±2.4376	31.4169	0.1025	0.7774	0.7328	17.457	8.601979
	Hy	1.9113±0.5421						
	IR1	0.4644±0.1318						
	IR3	-0.5417±0.1336						
	IR4	0.8397±0.1605						
10	X0	-0.1783±0.0333	6.0116	0.1079	0.7657	0.7188	16.338	8.109758
	GATS1m	2.0364±0.9583						
	Hy	1.9659±0.5576						
	IR1	0.3755±0.1448						
	IR3	-0.3952±0.1415						
11	IR4	0.8273±0.1660	7.2119	0.1109	0.7592	0.7110	15.762	7.856815
	X0	-0.2118±0.0326						
	PVSAv1	0.0027±0.0014						
	Hy	2.0911±0.5752						
	IR1	0.3441±0.1562						
12	IR3	-0.3426±0.1562	34.8242	0.1365	0.7134	0.6442	10.313	6.187766
	IR4	0.7980±0.1651						
	X0	-0.2384±0.0374						
	SpMax1Bhm	-9.1194±3.5733						
	Eta_AlphaA	17.7339±10.6709						
13	Hy	2.2107±0.6871	32.0964	0.0967	0.7970	0.7479	16.260	9.232146
	IR3	-0.6006±0.1860						
	IR4	0.7232±0.1830						
	X0	-0.1548±0.1577						
	X1	0.0078±0.2549						
14	SpMax1Bhm	-8.1286±2.6517	53.3259	0.1002	0.7898	0.7390	15.562	8.869331
	Eta_AlphaA	14.9062±8.9090						
	Hy	2.2896±0.5730						
	IR1	0.4443±0.1286						
	IR3	-0.4753±0.1362						
14	IR4	0.8210±0.1563						
	X0	-0.1563±0.0349						
	PVSAMR1	-16.4856±2.5515						
14	Eta_AlphaA	-0.0071±0.0016	53.3259	0.1002	0.7898	0.7390	15.562	8.869331
	Hy	38.2916±8.6133						
	IR1	2.8168±0.5685						
14	IR3	0.5671±0.1354						
	IR3	-0.5401±0.1487						

	IR4	0.5701±0.1487						
15	SpMax1Bhm	-8.3302±2.9426	39.5412	0.0872	0.8231	0.7726	16.289	10.40423
	PVSAv1	0.0023±0.0016						
	Hy	2.4635±0.5429						
	IR1	0.5068±0.1477						
	IR3	-0.5686±0.1583						
	IR4	0.8785±0.1504						
	X0	-0.5647±0.1482						
	X1	0.5928±0.2316						

TABLE-6 : RESULTS OF REGRESSION ANALYSIS

Model No.	PRESS	SSY	PRESS/SSY	R ² CV	SPRESS
1	11.1496	13.8185	0.8069	0.1931	0.3279
3	7.3683	13.8185	0.5332	0.4668	0.2233
5	7.0148	13.8185	0.5076	0.4924	0.2192
15	6.2552	13.8185	0.4527	0.5473	0.2234

TABLE-7: 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

Compound No.	log IC ₅₀	Predicted log IC ₅₀	Residual
1	2.613	2.6	0.013
2	2.33	2.309	0.021
3	2.903	3.157	-0.254
4	2.964	2.87	0.094
5	2.248	1.889	0.359
6	2.408	2.637	-0.229
7	2.236	2.328	-0.092
8	2.613	2.709	-0.096
9	2.512	2.535	-0.023
10	2.6	2.749	-0.149
11	3.354	3.291	0.063
12	2.164	1.886	0.278
13	1.653	1.925	-0.272
14	1.544	1.843	-0.299
15	1.653	1.595	0.058
16	2.26	2.468	-0.208
17	2.4	2.018	0.381
18	2.918	2.79	0.128
19	3.523	3.539	-0.016
20	2.143	2.324	-0.181
21	2.545	2.324	0.221
22	1.914	2.084	-0.17
23	2.35	2.276	0.074
24	3.097	2.592	0.506
25	2.262	2.27	-0.007
26	1.778	1.895	-0.117
27	0.602	0.683	-0.081
28	1.613	1.571	0.042
29	1.23	1.473	-0.243
30	2.064	1.894	0.171
31	1.756	2.017	-0.261
32	1.255	1.884	-0.628
33	2.393	2.018	0.375
34	2.715	1.972	0.743
35	1.643	1.663	-0.02
36	1.892	2.125	-0.233
37	1.462	1.409	0.054

TABLE 8- PREDICTED AND OBSERVED ANTIHYPERTENSIVE ACTIVITY WITH RESIDUALS FOR MODEL 15 OF TABLE 6

In the first step of the present study, activity of deferent substituted Spiro-PiperidineAzetidedines and Azetidinones is correlated with deferent descriptors. In this study, QSAR has been carried out using the model proposed by Hanchetal^[24]. Using the data in Table 3, a correlation matrix was calculated along with the co-linearity

between the descriptors. A high inter relationship was observed between X0 and X1 ($r=0.9691$) and next highest is between PVSAv1 and GATS1m (0.8489). Correlation matrix also represents the relationship between the dependent variable and structural descriptors. It is also clear from Table-4 that all descriptors are strongly correlated with antihypertensive activity but X1 is most collinearly related ($r=0.5488$) and PVSAMR1 is least ($r=0.0097$) this is why PVSAMR1 is not part of our best model.

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 this study no significant mono parametric regression model was obtained hence we have followed the path of multiple regression and we started obtaining significant regression models from bi-parametric regression. We carried out multiple regressions up to eight parameters as total number of samples was 37. Some significant models of different multiple regressions are given here

$$1-\log IC_{50} = 7.7189 + 0.6591 \pm 0.2201 IR_3 - 0.3727 \pm 0.0712 X1$$

$n=37$, MSE= 0.2247, $R^2 = 0.4470$, $AR^2 0.4145$, F-ratio = 13.742, Q= 2.975437

$$2-\log IC_{50} = 7.3014 - 0.5338 \pm 0.1665 IR_3 + 0.7041 \pm 0.1956 IR_4 - 0.3407 \pm 0.0639 X1$$

$n=37$, MSE= 0.1765, $R^2 = 0.5784$, $AR^2 0.5400$, F-ratio = 15.089, Q= 4.30893

$$3-\log IC_{50} = 7.3466 + 0.0058 \pm 0.0012 PVSAv1 + 2.2780 \pm 0.6352 Hy + 0.8329 \pm 0.1828 IR_4 - 0.2790 \pm 0.0390 X0$$

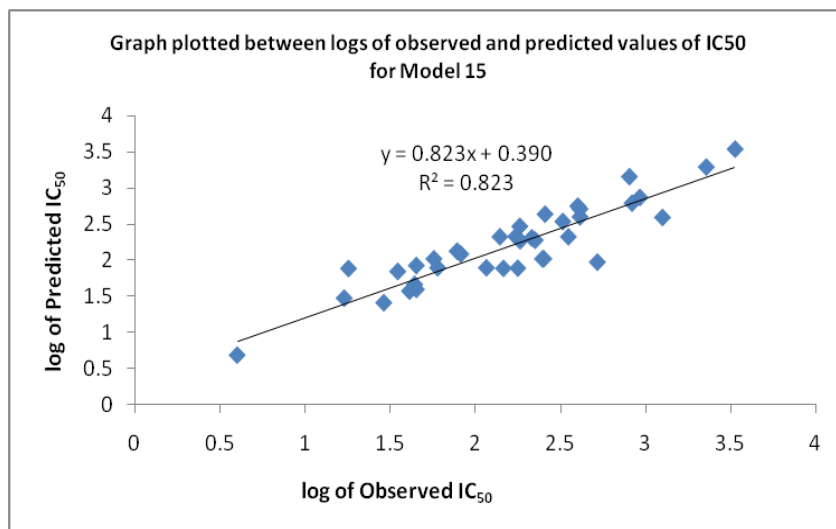
$n=37$, MSE= 0.1375, $R^2 = 0.6815$, $AR^2 0.6417$, F-ratio = 17.120, Q= 6.003856

$$4-\log IC_{50} = 39.5412 - 8.3302 \pm 2.9426 SpMax1Bhm + 0.0023 \pm 0.0016 PVSAv1 + 2.4635 \pm 0.5429 Hy + 0.5068 \pm 0.1477 IR_1 - 0.5686 \pm 0.1583 IR_3 + 0.8785 \pm 0.1504 IR_4 - 0.5647 \pm 0.1482 X0 + 0.5928 \pm 0.2316 X1$$

$n=37$, MSE= 0.0872, $R^2 = 0.8231$, $AR^2 = 0.7726$, F-ratio = 16.289, Q= 10.40423

In all the models mentioned above we have discussed about the value of Q, called the Pogliani Quality factor^{[25],[26]}. 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 10.40423, hence equation 4 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 the value of this ratio smaller than 0.1 indicates an excellent model. But here the value of PRESS/SS_Y is not less than 0.4 in any model. Only model No. 4 represents this value nearer to 0.4. So from cross validation it is also realized that model No. 4 is best among suggested models of this study.



IV. CONCLUSION:

- (i) Presence of pyridyl group in place of R₃ and presence of Ketonic group in place of R₄ do not favor the T-type calcium channel blocking activity of these Spiro-Piperidine Azetidines and Azetidines Derivatives
- (ii) Hydrophilic factor and connectivity indices are also useful for the study of these compounds.

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