IJASRM

International Journal of Advanced Scientific Research and Management, Special Issue 5, April 2019

www.ijasrm.com

ISSN 2455-6378

QSAR studies of β-Carboline derivatives as potentantiviral agents

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Abstract

Three dimensionalQuantitative structure–activity relationship (3D QSAR) studies have been performed on β-carboline derivatives to explore the structural necessities for antiviral activity. 3D QSAR studies were done using V-Life Sciences MDS 3.0 drug designing module to explain the structural requirements for the anti-viral activity. The 3D-QSAR was performed using the Step Wise K Nearest Neighbor Molecular Field Analysis technique with the partial least-square (PLS) method on a database. The results are discussed on the basis of statistical data. High agreements between experimental and predicted antiviral activity inhibitory values are obtained thus simplifying design of new biological active molecule.

Keywords: *QSAR, MLR, Antiviral Activity*

1. Introduction

The β-carboline nucleus is common to many natural and synthetic products associated with a broad spectrum of biochemical effects and pharmaceutical properties. These compounds have been shown to intercalate into DNA [1-3] , to inhibit CDK [4,5] topisomerase [1,3,6] and monoamine oxidase [7- 9] , and to interact with benzodiazepine receptors (BZ) [10-12] , 5-hydroxy serotonin receptors (5-HT) [13,14] , dopamine (DA) [15] and imidazoline receptors [16,17] . In addition, individual β -carboline derivative might selectively interact with specific targets so as to lead to a variety of pharmacological actions in vitro and in vivo. So far, β -carboline derivatives has been found to have various pharmaceutical functions including sedative, anxiolytic, hypnotic, anti-convulsant [18-20],antimicrobial [21,22] , antiviral [23,24] parasiticidal [25,26] as well as antithrombotic activities [27,28] Previous investigations focused on the effects of β -carbolineon the central nervous system (CNS). However, interests in these alkaloids were stimulated by their promising antiviral activities in the last decades. Preliminary structure activity relationships (SARs) analysis suggested that the introduction of appropriate substituents into position-2,-3and-9played a vital role in determining their antitumor effects [34,35,36]. Despite these recent undoubted advances, β -carboline derivatives still present some limitations arising from the relative weak anti-viral activities in animal models and the poorly understood action of mechanism [38] .Obviously, to acquire more information about the structural requirements for the possible improvement of the cyto- toxic potential and to elucidate SARs between substituents properties in β -carboline and antiviral activities, design and synthesis of more novel β -carboline derivatives with various substituents at different position of the β -carboline nucleus are needed.

The purpose of this study is to elucidate the antiviral structureactivity relationships (SARs) of β -carbolinein finer detail, with the ultimateaim of developing a reliable 3D-QSAR model to probe the structural requirement at the 3D levels for highly potent antiviral activity.

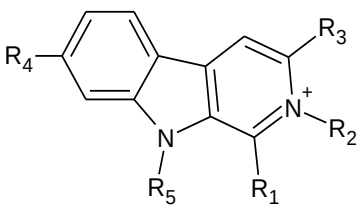

Figure 1.1: General structure of compound; 9*H*-[2, 3-b] indol-1 ium

2. Materials and Methods

Data set

A data set of 40 molecules have been taken from the reputed published results [20]. Antiviral activity was expressed as pIC_{50} values [Table-1]. It is essential to assess the predictive power of the models by using a test set of compounds. This was achieved by arbitrarily setting aside some compounds as a test set. The structures and anticancer activity data of compounds are listed in Table 1.

Molecular structure generation

All the molecular modeling and statistical analysis were performed using Vlife MDS software [27-29]. The structures of the compounds were built using molecular sketching facilities provided in the modeling environment of Vlife. Energy minimization and batch optimization was carried out using Merck Molecular force field. All the molecules were initially optimized and then used for the calculation of descriptors and further QSAR study.

QSAR study

All the 2D descriptors (thermodynamic, spatial, electronic and topological parameters) were calculated for QSAR analysis using Vlife MDS software. Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and receptor [30]. Random Selection method and Sphere Exclusion Method were used for the selection of the training and test set. For variable selection Stepwise forward-backward method was used. A suitable statistical method coupled with a variable selection method allows analyses of this data in order to establish a QSAR model with the subset of descriptors that are most statistically significant in determining the biological activity [31-33]. The QSAR models were generated by Multiple Regression Analysis method.

3. Results and Discussion

Regression Analysis

For QSAR analysis regression was performed using pIC_{50} values as dependent variables and calculated parameters as independent variables. In any thorough investigation of the effects of molecular properties, it is essential to prove that the results are both statistically valid and make chemical sense. It would be appropriate to obtain insight into the physical meaning of the correlation obtained as an output of the regression analysis. The magnitude of a descriptor could be used as a guideline to improve the antiviral activity of molecules.The biological activities of these compounds in terms of log 1/IC50 are reported in Table 2. Table 2 also contains calculated parameters viz- Balaban and Balaban type indices and zero to three order valence-connectivity indices. The correlation matrix among all the topological indices and biological activity is reported in Table 3. A close look at this table clearly indicates that for modeling log1/IC50 activity connectivity indices play a dominant role. However, it is interesting to observe that higher order valence-connectivity indices show a decreasing trend. The 1st and 2nd order connectivity-indices show good correlation. The data was subjected to regression analysis and the best obtained correlations are summarized in Table 4. With reference to Table 3 the selected descriptors are used for mono parametric (Model no.01) development which shows the importance of Wap which is directly proportional with the antiviral activity as positively correlated. The mono parametric (Model no.01) is given below,

pIC_{50}=4.1205+ 1.0647E-05*Wap **(1)**

Low statistical results indicate needs for the development of multiparamteric and more QSAR models follow rule of thumb. The Model no.02 has significant importance in which Wap and X_2A has positive contribution with the antiviral activity while the GMTIV show inverse contribution with antiviral activity. The statistical descriptors are given in Table no.4 (Model no.3).

pIC_{50}= -5.9475-5.7217E-05*GMTIV + 7.01209E-05*Wap + 37.8101X_2A **(2)**

The QSAR (Model no.03) show their significant statistical importance with six parametric model in which SMTIV and MSD are directly proportional with the antiviral activity while rest are inversely proportional with the antiviral activity (Model no.06).

pIC_{50}=2.0733+ 0.8698MSD -4.9927E-03*SMTI + 5.3929E-03*SMTIV 1.4831E-03*GMTIV+ 1.49163E-04*Wap -1.2431*PHI **(3)**

The above described all models are not statistically excellent indicates the deletion of outliers

compound whose activity are not uniform and After deleting Compound no.02, 21, 30 and 33 resulting the development of high statistically significant (Model no.07) indicates that the topological descriptors play a major role in the antiviral activity.

pIC_{50}= 0.7020+ 1.1216*MSD -5.7399E-03*SMTI + 6.14758E03*

SMTIV1.6827E-03*GMTIV+1.5873E-04*Wap-1.2165*PHI **(4)**

These models were generated in stepwise manner by forward-backward selection method starting with best single variable and adding further significant variable according to their contribution to the model. Various models of the data set were obtained which showed individual correlation of all calculated parameters with IC50 of antiviral activity.

Among the generated QSAR models; three models were selected on the basis of various statistical parameters such as squared correlation co-efficient which is relative measure of quality of fit. Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity. When observed activity values are plotted against estimated values, we obtained a graph which is reported in Fig. 1. The predictive power of the model comes out to be 0.8282.

Further confirmation is obtained by calculating cross-validated parameters and values are given in Table 4. Also cross-validation R^2 value for model 7 comes to be 0.8283 which is the highest among all the discussed models. All the parameters show the value within the permissible limit. Therefore the model is free from any kind of defect. Ridge trace(Fig.2) suggests that there is no co- linearity in the model.

IJASRM

International Journal of Advanced Scientific Research and Management, Special Issue 5, April 2019

www.ijasrm.com

ISSN 2455-6378

Table 1: General structure of the compounds with their substituents

Comp.	R_1	R_2	R_3	R_4	R_5	pIC_{50}
1	3,4,5 trimethoxyphenyl	H	$CO_2C_2H_5$	H	H	3.78
2	3,4,5 trimethoxyphenyl	H	COOH	H	n-C_4H_9	3.68
3	H	H	$CONH(CH_2)_2OH$	H	n-C_4H_9	4.06
4	H	H	$CONH(CH_2)_2NH_2$	H	n-C_4H_9	4.08
5	CH_3	H	$CONH(CH_2)_6NH_2$	H	n-C_4H_9	4.02
6	CH_3	H	$CONH(CH_2)_2OH$	H	n-C_4H_9	3.85
7	CH_3	H	$CONH(CH_2)_2NH_2$	H	n-C_4H_9	4.66
8	H	H	$CONH(CH_2)_2NH_2$	H	$CH_2C_6H_5$	4.46
9	H	H	$CONH(CH_2)_2NH_2$	H	$CH_2C_6H_5$	3.98
10	H	H	$CONH(CH_2)_6NH_2$	H	$CH_2C_6H_5$	4.23
11	H	H	CH_2OH	H	n-C_4H_9	3.89
12	H	H	CHO	H	n-C_4H_9	3.84
13	CH_3	$CH_2C_6H_5$	H	H	H	4.16
14	CH_3	$(CH_2)_3C_6H_5$	H	H	H	4.48
15	CH_3	$CH_2C_6H_5$	$COOC_2H_5$	H	H	4.28
16	H	$CH_2C_6H_5$	H	$0CH_3$	H	4.26
17	H	n-C_4H_9	H	H	H	4.03
18	H	$CH_2C_6H_5$	H	H	H	4.11
19	CH_3	$(CH_2)_3C_6H_5$	H	H	H	4.35
20	CH3	H	H	OH	C_2H_5	4.87
21	CH_3	H	H	OH	n-C_4H_9	4.09
22	CH_3	H	H	OH	i-C_4H_9	3.94
23	CH_3	H	H	OH	$(CH_2)_3C_6H_5$	4.55
24	CH_3	H	H	OC_2H_5	C_2H_5	4.16
25	CH_3	H	H	$OCH_2C_6F_5$	C_2H_5	3.63
26	CH_3	H	H	OC_2H_5	n-C_4H_9	4.36
27	CH_3	H	H	$OCH(CH_2)_2$	n-C_4H_9	4.52
28	CH_3	H	H	OC_4H_9	n-C_4H_9	4.81
29	CH_3	H	H	$OC_{10}H_{21}$	n-C_4H_9	3.9
30	CH_3	H	H	OC_4H_9	n-C_4H_9	4.92
31	CH_3	H	H	$OCH_2C_6H_5$	i-C_4H_9	4.65
32	CH_3	H	H	$OCH(CH_2)_2$	$(CH_2)_3C_6H_5$	4.84
33	CH_3	H	H	OC_8H_{17}	$(CH_2)_3C_6H_5$	3.98
34	CH_3	H	H	$OCH_2C_6H_5$	$(CH_2)_3C_6H_5$	4.8
35	CH_3	H	H	$OCH_2C_6F_5$	$(CH_2)_3C_6H_5$	3.83
36	CH_3	$CH_2C_6H_5$	H	OC_2H_5	C_2H_5	4.84
37	CH_3	$CH_2C_6H_5$	H	$OCH_2C_6F_5$	C_2H_5	5.8
38	CH_3	$CH_2C_6H_5$	H	OC_4H_9	i-C_4H_9	5.74
39	CH_3	$CH_2C_6H_5$	H	$OCH_2C_6H_5$	i-C_4H_9	5.72
40	CH_3	$CH_2C_6H_5$	H	OC_8H_{17}	$(CH_2)_3C_6H_5$	5.41

IJASRM

International Journal of Advanced Scientific Research and Management, Special Issue 5, April 2019

www.ijasrm.com

ISSN 2455-6378

Table 2: Calculated topological descriptors used in QSAR/QSPR modeling

Comp.	pIC_{50}	ZM1Per	MSD	SMTI	SMTIV	GMTIV	XU	Wap	PHI	X_2A	X_3A
1	3.78	828.08	5.822	9659	20031	41734	9839	31142	4.757	0.268	0.168
2	3.68	885.39	5.846	10992	23130	48554	11093	37841	5.078	0.269	0.164
3	4.06	966.93	6.345	14132	30022	63499	14202	45156	6.092	0.27	0.167
4	4.08	577.22	5.438	5073	10301	20363	5027	11023	3.508	0.278	0.171
5	4.02	669.38	7.044	8785	17697	35231	8783	16803	4.894	0.286	0.177
6	3.85	623.49	5.394	5482	11442	23159	5404	12050	3.657	0.277	0.168
7	4.66	610.7	5.394	5482	11264	22458	5404	12050	3.602	0.277	0.168
8	4.46	687.5	5.858	7823	15379	30758	8090	23338	3.642	0.276	0.17
9	3.98	654.02	5.909	7321	14230	28255	7613	21685	3.541	0.276	0.173
10	4.23	746.18	7.457	11881	23126	46147	12313	31217	4.816	0.283	0.178
11	3.89	494.63	4.378	3206	6402	12302	3160	7718	2.554	0.27	0.164
12	3.84	494.63	4.378	3206	6402	12302	3160	7718	2.554	0.27	0.164
13	4.16	487.08	5.083	4269	7584	14070	4596	13578	2.279	0.271	0.173
14	4.48	533.16	6.03	5931	10592	19926	6402	16742	2.816	0.275	0.177
15	4.28	664.58	5.386	6867	13270	26224	7171	20234	3.469	0.273	0.171
16	4.26	571.1	5.564	5463	10309	20118	5794	17488	2.738	0.271	0.174
17	4.03	410.28	4.451	2633	4909	8938	2646	6152	2.153	0.272	0.172
18	4.11	510.12	5.553	5053	9001	16826	5449	15116	2.542	0.273	0.176
19	4.35	499.16	6.102	5502	9654	17957	5989	15455	2.713	0.279	0.179
20	4.87	459.53	3.822	2331	4693	9003	2292	6014	1.858	0.27	0.16
21	4.09	505.61	4.301	3163	6389	12379	3110	7738	2.379	0.276	0.162
22	3.94	505.93	4.176	3091	6251	12099	3030	7652	2.264	0.283	0.159
23	4.55	628.49	5.674	6620	12632	24839	6974	19528	3.04	0.278	0.169
24	4.16	509.17	4.424	3214	6469	12475	3162	7941	2.458	0.271	0.161
25	3.63	941.9	6.648	10789	23838	53336	11151	35686	4.317	0.268	0.171
26	4.36	555.25	4.8	4182	8453	16427	4108	9969	3.038	0.276	0.163
27	4.52	574.57	5.127	4827	9850	19439	4749	11255	3.255	0.279	0.166
28	4.81	601.33	5.49	5568	11221	21915	5490	12656	3.665	0.281	0.167
29	3.9	739.57	8.06	12254	24437	48299	12260	23533	5.778	0.291	0.176
30	4.92	601.65	5.396	5480	11051	21571	5394	12546	3.498	0.286	0.164
31	4.65	678.45	6.097	8154	15586	30543	8520	25011	3.558	0.283	0.167
32	4.84	697.45	6.279	9037	17539	34851	9405	26045	3.914	0.28	0.171
33	3.98	816.37	8.016	15477	29968	59335	15990	40420	5.653	0.288	0.177
34	4.8	801.01	7.167	13789	25647	50643	14872	50699	4.361	0.28	0.174
35	3.83	1110.86	7.853	19805	41961	92468	20949	79644	5.574	0.274	0.175
36	4.84	655.17	5.837	7229	13933	27450	7537	23042	3.405	0.269	0.168
37	5.8	1065.02	7.471	16729	35601	78789	17721	77543	4.974	0.266	0.172
38	5.74	748.45	6.457	10451	20333	40170	10749	32141	4.131	0.283	0.166
39	5.72	825.25	7.129	14378	26908	53222	15407	57606	4.214	0.281	0.168
40	5.41	962.37	8.716	24103	45889	91210	25373	79515	6.625	0.284	0.18

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International Journal of Advanced Scientific Research and Management, Special Issue 5, April 2019

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ISSN 2455-6378

Table 3: Correlation matrix between calculated topological descriptors and antiviral activity

	pIC_{50}	ZMIPer	MSD	SMTI	SMTIV	GMTIV	XU	Wap	PHI	X_2A	X_3A
pIC_{50}	1.0000										
ZMIPer	0.1899	1.0000									
MSD	0.2592	0.7892	1.0000								
SMTI	0.3023	0.9144	0.9124	1.0000							
SMTIV	0.2640	0.9446	0.8944	0.9947	1.0000						
GMTIV	0.2402	0.9608	0.8726	0.9837	0.9966	1.0000					
XU	0.2799	0.9389	0.9292	0.9705	0.9695	0.93	1.0000				
Wap	0.3788	0.9155	0.8063	0.9549	0.9578	0.9613	0.9100	1.0000			
PHI	0.1030	0.8821	0.8706	0.9030	0.9142	0.9035	0.9357	0.7770	1.0000		
X_2A	0.1987	0.0018	0.4269	0.2228	0.1751	0.1224	0.2442	0.0198	0.3071	1.0000	
X_3A	0.0012	0.3077	0.7234	0.5103	0.4725	0.4467	0.5057	0.4114	0.4410	0.2710	1.0000

Table 4: Validated statistical and cross validated statistical descriptors

Model No.	QSAR/QSPR Models	N	R^2	R^2a	MS	PRESS	R	CV	F-
1.	pIC_{50}=4.1205+ 1.0647E-05*Wap	40	0.1	0.12	0.27	12.5857	0.	0.11	6.63
2.	pIC_{50}= 4.4031-4.2386E-05*GMTIV+ 5.4879E-05*Wap	40	0.3	0.31	0.21	9.7767	0.	0.10	9.80
3.	pIC_{50}= -5.9475-5.72105* GMTIV+ 7.01209E-05* Wap+ 37.8101X_2A	40	0.4	0.45	0.17	8.1882	0.	0.09	11.8

4.	pIC_{50}=13.5428+0.7425MSD-8.1764E-05*GMTIV+6.8955E-05*Wap-74.1305*X3A	40	0.5	0.52	0.14	7.3925	0.	0.08	11.8
5.	pIC_{50}= 15.7482+ 0.7359* MSD6.4021E05*GMTIV + 6.6492E-05*Wap-82.6035X_3A -1.8608E-03*ZM1per	40	0.5	0.53	0.14	7.9946	0.	0.08	9.95
6.	pIC_{50}= 2.0733+ 0.8698MSD -4.9927E-03*SMTI+ 5.3929E-03*SMTIV-1.4831E 03*GMTIV+ 1.49163E-04*Wap-1.2431*PHI	40	0.6	0.63	0.11	6.6560	0.	0.77	12.2
After deleting the outlier no.02,21,30, and 33									
7.	pIC_{50}= 0.7020+ 1.1216*MSD-5.7399E-03*SMTI + 6.14758E-03*SMTIV-1.6827E-03*GMTIV+ 1.5873E-04*Wap -1.2165*PHI	3	**0.8**	0.79	0.00	3.40	0.692	0.05	23.3

Table 5: Results of regression analysis

Model No.	Parameters Used	Ai (1,…..3)	Intercept	MSE	R^2	AR^2
1.	Wap	1.0647E-05	4.1205	0.2765	0.1435	0.1210
2.	GMTIV Wap	-4.2386E-05 5.4879E-05	4.4031	0.2167	0.3464	0.3111
3.	GMTIV Wap X_2A	-5.7217E-05 7.01209E-05 37.8101	-5.9475	0.1712	0.4977	0.4558
4.	MSD GMTIV Wap X_2A	0.7425 -8.1764E-05 6.8955E-05 -74.1305	13.5428	0.1488	0.5755	0.5270
5.	MSD GMTIV Wap X_3A ZM1per	0.7359 -6.4021E-05 6.6492E-05 -82.6035 -1.8608E-03	15.7482	0.1464	0.5942	0.5345
6.	MSD	0.8698				

	SMTI SMTIV GMTIV Wap PHI	-4.9927E-03 5.3929E-03 -1.4831E-03 1.49163E-04 -1.2431	2.0733	0.1145	0.6895	0.6330
7.	MSD SMTI SMTIV GMTIV Wap PHI	1.1216 -5.7399E-03 6.14758E-03 -1.6827E-03 1.5873E-04 -1.2165	0.7020	3.0065	0.8283	0.7928

ISSN 2455-6378

Table 6: Actual and predicted antiviral activity

Comp.	Actual pIC_{50}	Predicted pIC_{50}	Residual pIC_{50}
1	3.78	3.86	-0.08
2	4.06	4.16	-0.10
3	4.08	4.22	-0.14
4	4.02	4.40	-0.38
5	3.85	4.11	-0.26
6	4.66	4.27	0.39
7	4.46	4.42	0.04
8	3.98	4.37	-0.39
9	4.23	4.48	-0.25
10	3.89	3.98	-0.09
11	3.84	3.98	-0.14
12	4.16	4.22	-0.06
13	4.48	4.23	0.25
14	4.28	3.76	0.52
15	4.26	4.55	-0.29
16	4.03	4.07	-0.04
17	4.11	4.25	-0.14
18	4.35	4.25	0.10
19	4.09	4.151	-0.06

ISSN 2455-6378

20	3.94	4.17	-0.23
21	4.55	4.32	0.23
22	4.16	4.26	-0.10
23	3.63	3.43	0.20
24	4.36	4.29	0.07
25	4.52	4.41	0.11
26	4.81	4.55	0.26
27	4.92	4.674	0.25
28	4.65	4.79	-0.14
29	4.84	4.42	0.42
30	4.80	4.78	0.02
31	3.83	4.05	-0.22
32	4.84	4.733	0.11
33	5.80	5.593	0.21
34	5.74	5.43	0.31
35	5.72	6.04	-0.32
36	5.41	5.31	0.10

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International Journal of Advanced Scientific Research and Management, Special Issue 5, April 2019

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ISSN 2455-6378

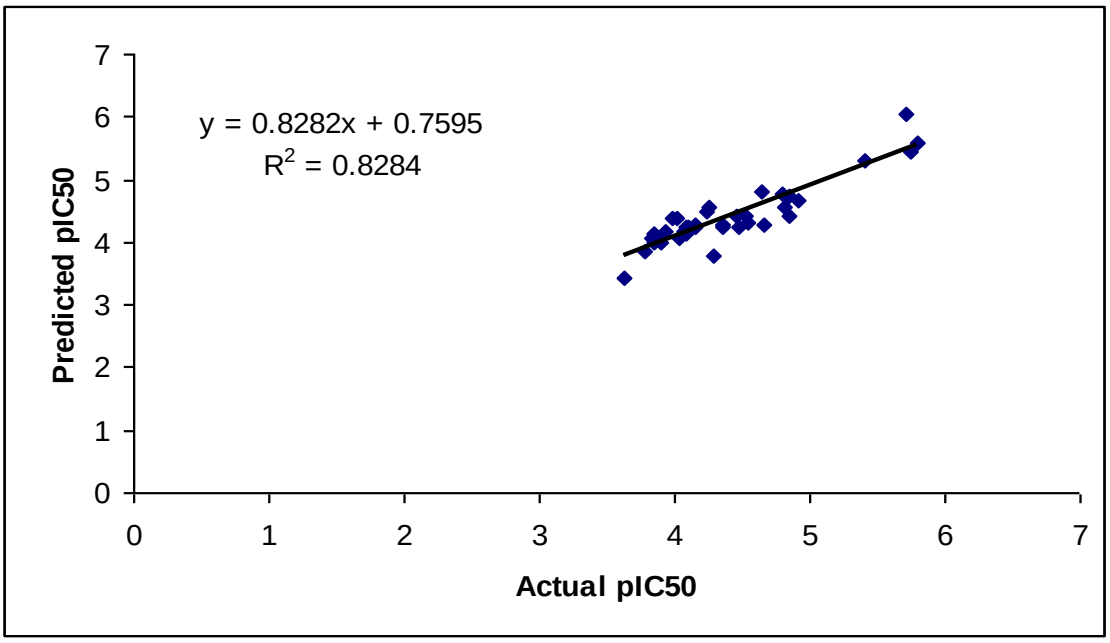

Figure 1: Graph plotted between predicted pIC_{50} and actual pIC_{50} of β-Carboline derivative

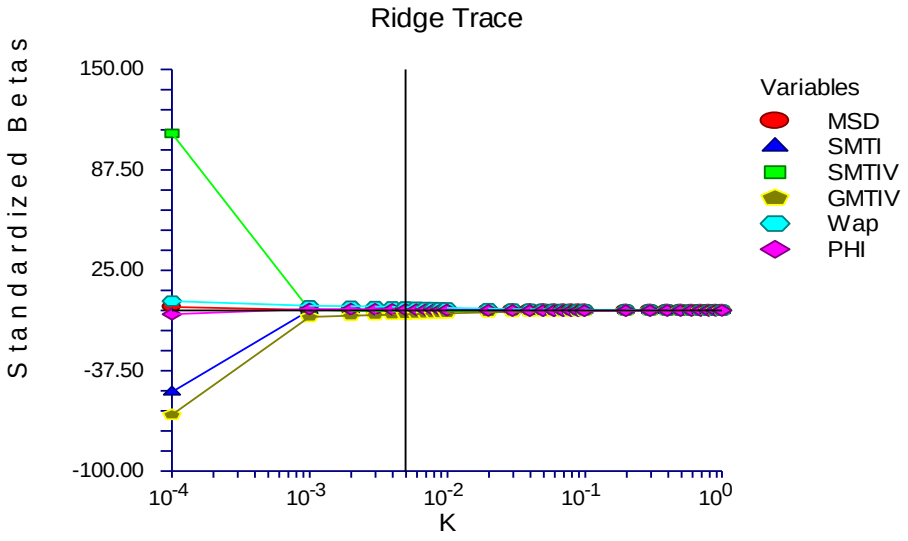

Figure 2: Graph plotted between K and standardized beats of used descriptors in QSAR modeling

5. Conclusion

From the derived QSAR model it can be concluded that antiviral activity by the β-Carbolineis strongly influenced by the topological descriptors interactions and electro-topological nature of substituents. Pattern of substitution can be extracted from the developed model. The descriptors showed by QSAR study can be used further for study and designing of new compounds. Consequently this study may prove to be helpful in development and optimization of existing antiviral activity of this class of compounds.

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