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ORIGINAL ARTICLE

QSAR analysis for some β-carboline derivatives as anti-tumor

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Abstract β-Carboline moieties are important structural subunits which occur as components of many biologically interesting molecules for antitumor activity. Quantitative structure–activity relationship (QSAR) studies have been performed on β-carboline derivatives to explore the structural necessities for antitumor activity. 3D QSAR studies were done using V-Life Sciences MDS 3.0 drug designing module to explain the structural requirements for the anti-tumor activity. The 3D-QSAR was performed using the Step Wise K Nearest Neighbour Molecular Field Analysis [(SW) kNN MFA] technique with the partial least-square (PLS) method on a database. Obtained best 3D-QSAR model having high predictive ability with $q^2 = 0.743$, $r^2 = 0.721$, pred_$r^2 = 0.708$ and standard error = 0.346, explaining the majority of the variance in the data with partial least square (PLS) components. The results of the present study may be useful on the designing of more potent compounds as antitumor drugs.

1. Introduction

The β-carboline alkaloids are a class of synthetic and naturally occurring compounds that possess a large range of important pharmacological properties such as sedative, anxiolytic, hypnotic, anticonvulsant, antitumor, antiviral, antiparasitic, antimicrobial and anti-HIV activities (Caiping et al., 2010; Ishida et al., 2001). Other reports have revealed that β-carboline alkaloids can exert antitumor activities through multiple mechanisms, such as intercalating into DNA (Xiao et al., 2001), inhibiting topoisomerases I and II (Funayama et al., 1996), CDKs (cyclindependent kinases; Li et al., 2007), IκB kinases (Castro et al., 2003) and mitotic kinesin Eg5 (Sunder-Plassmann et al., 2005).

The β-carbolines bearing a flexible alkylamine side chain in position-3 showed potent DNA intercalating abilities resulting in noteworthy antitumor potencies (Xiao et al., 2001). The complex polycyclic ring system in position-1 of β-carboline nucleus of manzamine A can be replaced with simpler amino substituents to offer active compounds (Boursereau and Coldham, 2004). Structure–activity relationships (SARs) for in vitro and in vivo antitumor activities showed that (a) the antitumor

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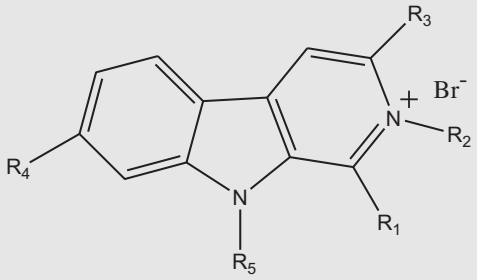
potential of β-carbolines correlated to both the planarity of the molecule and the presence of substituents in position-1, 3 and 9 of β-carboline nucleus; (b) the introduction of appropriate substituents into these positions of β-carboline scaffold played a crucial role in the modulation of their antitumor efficacies (Chunming et al., 2010). Most of these β-carboline derivatives are endowed with antitumor, and DNA intercalating properties and their high DNA binding affinity is thought to be partially responsible for their pharmacological action (Ikeda et al., 2011).

Quantitative structure–activity relationships (QSARs) are an effort to correlate the structural or property descriptors of compounds quantitatively with biological activities. The most important aspect of QSAR is to establish a correlation

Table 1 Structure of training and test sets of β-carboline derivatives and their experimental antitumor activity.



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Compound No.	Substituents					Actual activity Hela [IC50 (μM)]
	R_1	R_2	R_3	R_4	R_5	
1	3,4,5-trimethoxyphenyl	–	CO_2H	H	n-C_4H_9	166
2	H	–	$CONH(CH_2)_2NH_2$	H	n-C_4H_9	26.9
3	H	–	$CONH(CH_2)_6NH_2$	H	n-C_4H_9	53
4	CH_3	–	$CONH(CH_2)_2OH$	H	n-C_4H_9	80.4
5	CH_3	–	$CONH(CH_2)_2NH_2$	H	n-C_4H_9	13.3
6*	CH_3	–	$CONH(CH_2)_2NH_2$	H	$CH_2C_6H_5$	11
7	H	–	$CONH(CH_2)_2NH_2$	H	$CH_2C_6H_5$	42.8
8	H	–	$CONH(CH_2)_6NH_2$	H	$CH_2C_6H_5$	24.2
9	CH_3	–	CH_2OH	H	n-C_4H_9	100
10	CH_3	–	CHO	H	n-C_4H_9	169
11	CH_3	$CH_2C_6H_5$	H	H	H	69.2
12	CH_3	$(CH_2)_3C_6H_5$	H	H	H	49.8
13	CH_3	$CH_2C_6H_5$	$CO_2C_2H_5$	H	H	101
14*	CH_3	$CH_2C_6H_5$	H	OCH_3	H	77.6
15	H	n-C_4H_9	H	H	H	130
16	H	$CH_2C_6H_5$	H	H	H	85.4
17*	H	$(CH_2)_3C_6H_5$	H	H	H	44.3
18	CH_3	–	H	OH	C_2H_5	70.3
19	CH_3	–	H	OH	n-C_4H_9	89.8
20	CH_3	–	H	OH	i-C_4H_9	68.3
21*	CH_3	–	H	OH	$(CH_2)_3C_6H_5$	45.3
22	CH_3	–	H	OC_2H_5	C_2H_5	30.7
23	CH_3	–	H	$OCH_2C_6F_5$	C_2H_5	258
24	CH_3	–	H	OC_2H_5	n-C_4H_9	32.1
25	CH_3	–	H	$OCH(CH_3)_2$	n-C_4H_9	21.2
26	CH_3	–	H	OC_4H_9	n-C_4H_9	17.4
27	CH_3	–	H	$OC_{10}H_{21}$	n-C_4H_9	106
28	CH_3	–	H	OC_4H_9	i-C_4H_9	20.8
29	CH_3	–	H	$OCH_2C_6H_5$	i-C_4H_9	50.5
30*	CH_3	–	H	$OCH(CH_3)_2$	$(CH_2)_3C_6H_5$	48.6
31	CH_3	–	H	OC_8H_{17}	$(CH_2)_3C_6H_5$	69.6
32	CH_3	–	H	$OCH_2C_6H_5$	$(CH_2)_3C_6H_5$	72.6
33	CH_3	–	H	$OCH_2C_6F_5$	$(CH_2)_3C_6H_5$	73.5
34	CH_3	$CH_2C_6H_5$	H	OC_2H_5	C_2H_5	2.2
35	CH_3	$CH_2C_6H_5$	H	$OCH_2C_6F_5$	C_2H_5	0.93
36	CH_3	$CH_2C_6H_5$	H	OC_4H_9	i-C_4H_9	2.6
37	CH_3	$CH_2C_6H_5$	H	$OCH_2C_6H_5$	i-C_4H_9	12.4
38*	CH_3	$CH_2C_6H_5$	H	OC_8H_{17}	$(CH_2)_3C_6H_5$	2.2

* Asterisk showing test compounds.

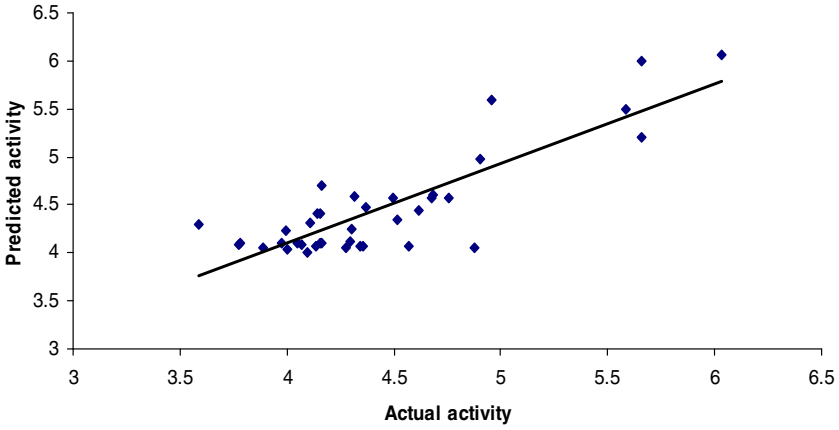

Figure 1 Comparison of actual activity versus predicted activity for regression analysis of 3D QSAR model.

Table 2 Uni-Column statistics for 3D QSAR model.

Data set	Average	Max.	Min.	Std. dev.	Sum
Training set	4.398	6.032	3.588	0.552	140.727
Test set	4.623	5.658	4.110	0.582	27.738

Max. = maximum, Min. = minimum, Std. dev. = Standard deviation.

between various molecular properties of a set of molecules with their experimentally known biological activity (Sahu et al., 2012). 3D QSAR is calculated initial from a geometrical or 3D representation of a molecule. These descriptors include molecular volume, molecular surface and other geometrical properties. There are different types of 3D descriptors for example electronic, steric, hydrogen bond donor, hydrogen bond acceptor and hydrophobic, etc. (Ravichandran et al., 2007).

In the search of newer β-carboline entities with improved antitumor activity present study deals with 3D QSAR approaches using V-Life Sciences Version 3.0 molecular design software to find out structure features required for biological activity.

2. Materials and methods

2.1. Data set

A dataset of thirty-eight β-carboline derivatives has been taken for the present QSAR studies (Cao et al., 2010) (Table 1). The activity data were given as IC_{50} values, where IC_{50} refers to the experimentally determined micromolar concentration of the β-carboline required to inhibit the cervical tumor cells by 50%.

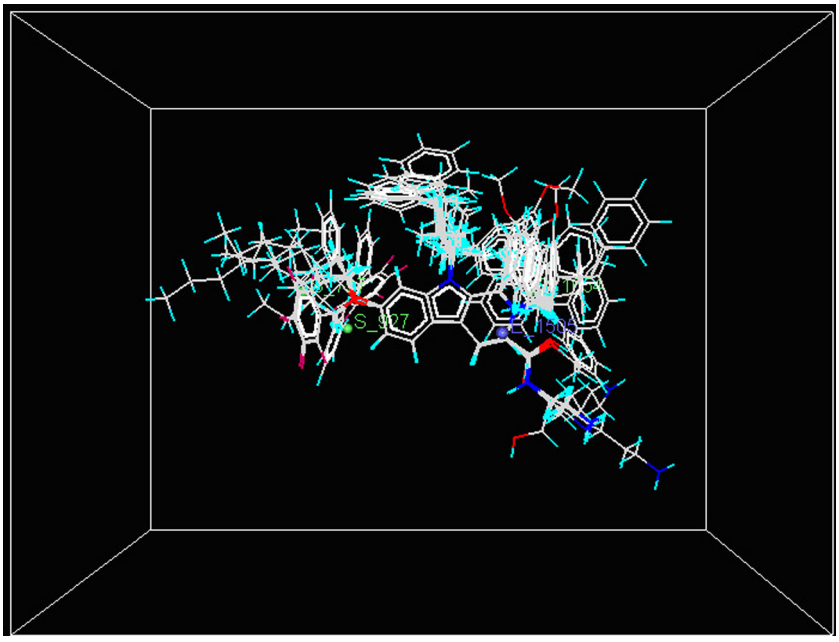

Figure 2 Stereoview of the molecular rectangular field grid around the superposed molecular units of β-carboline series of compounds using SW kNN MFA method (Alignment of the molecules).

The biological activity values [IC_{50} (μM)] reported in the literature were converted into their molar units and then further into negative logarithmic scale (pIC_{50}) and subsequently used as the dependent variable for the QSAR analysis. All thirty-eight compounds were drawn on the workspace of V-Life Science molecular modeling software version 3.0. Energy minimization is the essential step and was carried out using the standard Merck Molecular Force Field (MMFF) method with distance dependent-dielectric function with energy gradient of 0.001 kcal/mol and iteration limit of 10000 implemented in V-Life molecular milder database (Jain et al., 2008; Vaidya et al., 2011; Prasad et al., 2009). However, in 3D QSAR molecular alignment was carried out by template based alignment using compound having the highest pIC_{50} (compound No. 35) served as template, followed by generation of common rectangular grid of 2 around the aligned molecules.

2.2. Descriptors

For 3D QSAR steric and electrostatic fields were generated at the lattice points of grid using methyl probe of charge + 1. The fields were generated by kNN method with default energy of 30 kcal/mol and 10 kcal/mol, respectively. Partial atomic charges were calculated using the Gasteiger-Marsii method (Shen et al., 2003).

Negative range in electrostatic field descriptors (blue points in the dialog box) indicates that negative electronic potential is favorable for activity and more electronegative substituents group is favored in that position, positive electronic potential range indicates the vice versa of negative potential. Positive value of steric descriptors (green points in the dialog box) reveals that positive steric potential is constructive for an increase in activity and more bulky group is preferred in that region, negative steric potential range indicates the vice versa of negative potential.

2.3. Regression analysis

For 3D QSAR, regression analysis was performed via partial least-square (PLS) method and cross-validation was done using leave-one-out (LOO) method with 0.5 kcal/mol column filter. Models were generated with [(SW) kNN MFA] approach via stepwise forward–backward method set as variance cut-off 2.0 kcal/mol using auto scaling (Wold, 1995) (Fig. 1).

The final models were developed on the basis of statistical parameters including optimum number of components (N), correlation coefficient (r), square of correlation coefficient (r^2), cross-validated correlation coefficient (q^2), r^2 for external test set (pred_r^2), F-test (Fischer's value) for statistical significance and standard error of estimation (r^2 se) (Table 2).

From the statistical viewpoint, the ratio of the number of samples (N) to the number of variables used (M) should be $N/M \geqslant 5$.

2.4. Cross validation

The cross-validated correlation coefficient (q^2) of the generated model was calculated using the equation:

Table 3 Statistical results of 3D QSAR model generated by SW kNN MFA method for β-carboline derivatives.

Sr. No.	Statistical parameter	3D QSAR Results
1	r^2	0.721
2	r^2SE	0.306
3	q^2	0.743
4	q^2SE	0.346
5	Pred_r^2	0.708
6	Pred_r^2SE	0.395
7	F-test	24.185
8	N	32
9	Contributing descriptors	S_797 (17%) S_1654 (25%) E_1505 (41%) S_927 (−17%) Constant-4.113

Table 4 Predicted activity along with residual obtained from SW kNN MFA method of 3D-QSAR model.

Compound No.	Actual activity (pIC_{50})	3D QSAR model (pIC_{50})	
		Predicted activity	Residual
1	3.78	4.106	−0.326
2	4.57	4.065	0.505
3	4.276	4.048	0.228
4	4.095	4.003	0.092
5	4.876	4.274	0.602
6*	4.959	5.546	−0.587
7	4.368	4.472	−0.104
8	4.616	4.442	0.174
9	4	4.041	−0.041
10	3.772	4.079	−0.307
11	4.16	4.699	−0.539
12	4.303	4.247	0.056
13	3.996	4.239	−0.243
14*	4.11	4.308	−0.198
15	3.886	4.058	−0.172
16	4.068	4.078	−0.01
17*	4.353	4.066	0.287
18	4.153	4.094	0.059
19	4.047	4.095	−0.048
20	4.165	4.099	0.066
21*	4.344	4.069	0.275
22	4.513	4.348	0.165
23	3.589	4.299	−0.71
24	4.493	4.569	−0.076
25	4.674	4.577	0.097
26	4.759	4.569	0.19
27	3.975	4.099	−0.124
28	4.682	4.611	0.071
29	4.297	4.115	0.182
30*	4.313	4.58	−0.267
31	4.157	4.409	−0.252
32	4.139	4.407	−0.268
33	4.134	4.075	0.059
34	5.657	5.205	0.452
35	6.031	6.059	−0.028
36	5.585	5.49	0.095
37	4.906	4.976	−0.07
38*	5.657	6.005	−0.348

showing Residual, Residual = Actual − predicted activity.
* Asterisk showing test compounds.

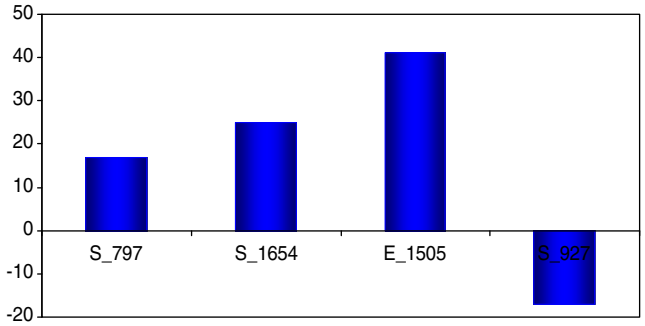

Figure 3 Contributions of descriptors for biological activity developed using SW-kNN-MFA equation for 3D QSAR.

$$q^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{\text{mean}})^2}$$

The predicted ability (pred_r^2) of statistical models indicates the predictive power of the current model for the external test and calculated using the equation:

$$\text{Pred}\_r^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{\text{mean}})^2}$$

Both summations are over all molecules in the test set.

Where y_i and $\hat{y}_i$ are the actual and predicted activities of the *i*th molecule in the test set, respectively, and y_{mean} is the average activity of all molecules in the training set. Both summations are over all molecules in the training set (Samee et al., 2008; www.Vlifesciences.com).

3. Results and discussion

In the present study the authors tried to develop the best 3D QSAR models using V-Life MDS to explain the correlation between the parameters and the antitumor activity of β-carboline derivatives.

3.1. 3D QSAR results

To derive 3D QSAR models via V-Life MDS, the kNN descriptors (steric and electrostatic) were used as independent variables and antitumor activity as a dependent variable. After alignment steric and electrostatic fields were generated to derive 3D QSAR models (Fig. 2). Various models have been developed by changing training and test set data. For the best selected model compound Nos. 06, 14, 17, 21, 30 and 38 serve as test set data, while remaining are training set compounds. The results of uni-column statistics are summarized in Table 2, which shows that the test is interpolative. Finally, the statistical results are listed in Table 3 and shows that the model having good internal and external predictive ability with minimum residual activity was selected (Table 4).

For the selected kNN MFA model, the cross-validated r^2 (q^2) value of the training set was 0.743 with principal component. The non-cross-validated r^2 value was 0.721 with standard error 0.346 and covariance ratio (F) of 24.185 (significant at 99.99% level). The predictive ability of model was also confirmed by external pred_r^2 having the value 0.708.

In kNN MFA model, the steric parameter contributes 59%, while electrostatic parameter accounts for 41%. Contributions of steric and electrostatic parameters are shown in Fig. 3. The contribution plot of steric and electrostatic field interactions indicates relative regions of the local fields (steric and electrostatic) around the aligned molecules, leading to activity distinction in the model. The green-colored balls specify the positions of the steric descriptors and the descriptor with positive or negative coefficients indicates a region where bulky substituent is favored or unfavored, respectively. Electrostatic field descriptors (blue-colored balls) with positive coefficients represent regions where less electronegative group is favorable, whereas

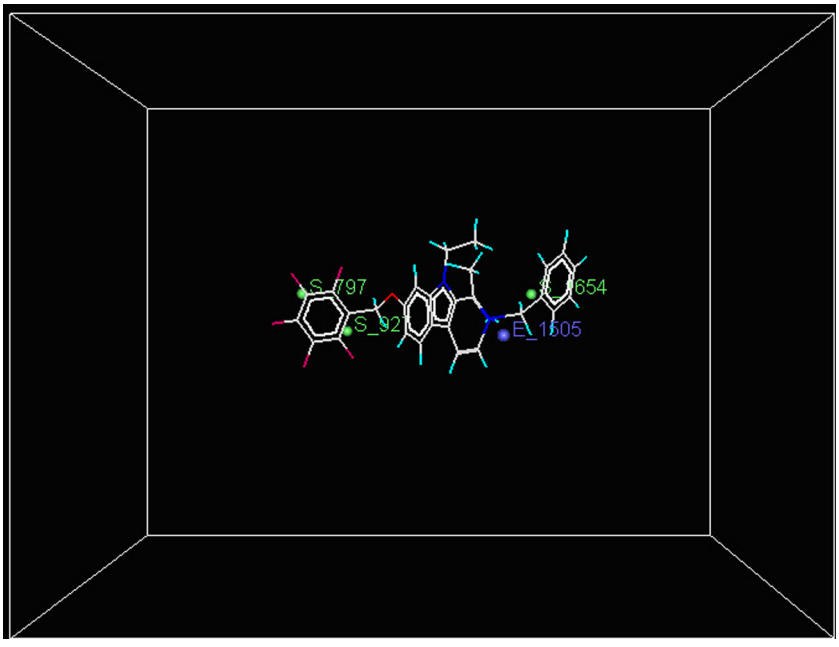

Figure 4 Common template used for alignment of β-carboline derivatives in the context of most potent compound.

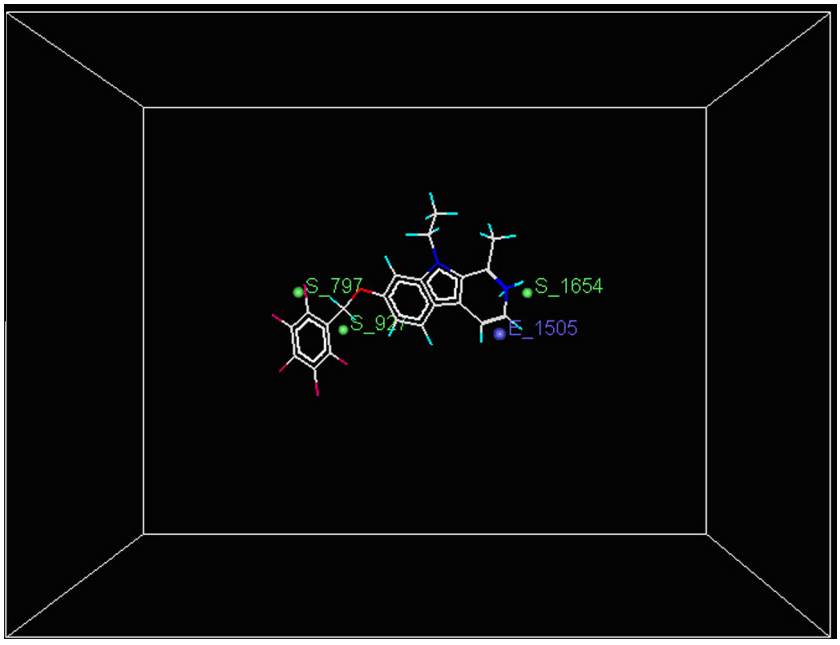

Figure 5 Common template used for alignment of β-carboline derivatives in the context of least active compound.

negative coefficient shows that more electronegative group is favorable in this region (Samee et al., 2008). It is observed that electrostatic descriptors like E_1505 (41%) with positive coefficient suggest favorability of less electronegative group in these regions for producing potent compounds. The compounds (like 23–33, 35) with higher activity having less electronegative substitution (benzyl or pentaflurobenzyl) at the R4 position of β-carboline ring. The presence of steric descriptors S_797 (17%), and S_1654 (25%) with positive coefficient suggests favorability of bulky groups in these regions for producing potent compounds. The compounds (like 2, 3, 4, 5, 6, 7) having higher activity with bulky DNA targeting substitution (-CONH (CH2)n NH2 or amino alkyl long side chain) at the R3 position of β-carboline ring. Most of the compounds (like 11–17, 34–38) with higher activity having bulky substitution (alkyl or aryl side chain) at the R2 position of β-carboline ring strongly support the above comment. It is observed that steric descriptor like S_927 (−17%) with negative coefficient is far from the β-carboline structure indicating that bulky groups are unfavorable on this site and the presence of less bulky groups is favorable for the activity.

The correlation between experimental and predicted activity for both training and test set of compounds is shown in Table 4 and represented graphically in Fig. 1 respectively. These results authenticate the good prediction ability of the generated 3D QSAR model. The model summary dialog box, showed the relative positions of the local fields around aligned molecules that were important for activity variation in the model (Figs. 4 and 5).

4. Conclusions

The present work reveals how a set of antitumor activity of various β-carboline may be treated statistically to find out the molecular characteristics which are essential for high activity. 3D-QSAR studies have been carried out on a series of β-carboline derivatives with antitumor activity. Additionally, we wish that the current study provides better insight into the designing of more potent β-carboline derivatives as antitumor in the future before their synthesis.

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References

Boursereau, Y., Coldham, I., 2004. Synthesis and biological studies of 1-amino β-carbolines. Bioorg. Med. Chem. Lett. 14, 5841–5844.

Caiping, T., Sensen, L., Shouhai, W., Sheng, H., Lingjun, Z., Yu, C., Minxu, W., Yiping, Z., Wu, L., Wenlie, P., Liangnian, J., Anlong, X., 2010. Nuclear permeable ruthenium(II) β-carboline complexes induce autophagy to antagonize mitochondrial-mediated apoptosis. J. Med. Chem. 53, 7613–7624.

Castro, A.C., Dang, L.C., Soucy, F., Grenier, L., Mazdiyasni, H., Hottelet, M., Parent, L., Pien, C., Palombella, V., Adams, J., 2003. Novel IKK inhibitors: β-carbolines. Bioorg. Med. Chem. Lett. 13, 2419–2422.

Cao, R., Guan, X., Shi, B., Chen, Z., Ren, Z., Peng, W., Song, H., 2010. Design, synthesis and 3D-QSAR of beta-carboline derivatives as potent antitumor agents. Eur. J. Med. Chem. 45, 2503–2515.

Chunming, M., Rihui, C., Buxi, S., Xiantai, Z., Qin, M., Jie, S., Liang, G., Wei, Y., Zhiyong, C., Huacan, S., 2010. Synthesis and cytotoxic evaluation of 1-carboxamide and 1-amino side chain substituted β-carbolines. Eur. J. Med. Chem. 45, 5513–5519.

Funayama, Y., Nishio, K., Wakabayashi, K., Nagao, M., Shimoi, K., Ohira, T., Hasegawa, S., Saijo, N., 1996. Effects of β and γ-carboline derivatives on DNA topoisomerase activities. Mutat. Res.: Fundam. Mol. Mech. Mutagen. 349, 183–191.

Ikeda, R., Kurosawa, M., Okabayashi, T., Takei, A., Yoshiwara, M., Kumakura, T., Sakai, N., Funatsu, O., Morita, A., Ikekita, M., Nakaike, Y., Konakahara, T., 2011. 3-(3-Phenoxybenzyl)amino-b-carboline: a novel antitumor drug targeting α-tubulin. Bioorg. Med. Chem. Lett. 21, 4784–4787.

Ishida, J., Wang, H.K., Oyama, M., Cosentino, M.L., Hu, C.Q., Lee, K.H., 2001. Anti-AIDS agents. 46. Anti-HIV activity of harman, an anti-HIV principle from *Symplocos setchuensis*, and its derivatives. J. Nat. Prod. 64, 958–962.

Jain, A.K., Ravichandran, V., Singh, R., Sharma, S., Mourya, V.K., Agrawal, R.K., 2008. Three-dimensional qsar study of 2,4-disubstituted-phenoxy acetic acid derivatives as a CRTh2 receptor antagonist: using the k-nearest neighbor method. Dig. J. Nanomater. Biostruct. 3, 63–73.

Li, Y., Liang, F.S., Jiang, W., Yu, F.S., Cao, R.H., Ma, Q.H., Da, X.Y., Jiang, J.D., Wang, Y.C., 2007. β-Carboline anti-cancer drug, inhibits the CDK activity of budding yeast. Cancer Biol. Ther. 6, 1193–1199.

Prasad, R.K., Narsinghani, T., Sharma, R., 2009. QSAR analysis of novel N-alkyl substituted isatins derivatives as anticancer agents. J. Chem. Pharm. Res. 1, 199–206.

Ravichandran, V., Mourya, V.K., Agrawal, R.K., 2007. QSAR study of novel 1,1,3-trioxo[1,2,4]-thiadiazine (TTDs) analogues as potent anti-HIV agents. Arkivoc 24, 204–212.

Sahu, N.K., Bari, S.B., Kohli, D.V., 2012. QSAR studies of some substituted 1,3-diaryl propenone derivatives as *Plasmodium falciparum* growth inhibitors. Lett. Drug Des. Discov. 9, 1–10.

Samee, W., Nunthanavanit, P., Ungwitayatorn, J., 2008. 3D-QSAR investigation of synthetic antioxidant chromone derivatives by molecular field analysis. Int. J. Mol. Sci. 9, 235–246.

Shen, M., Xiao, Y., Golbraikh, A., Gombar, V.K., Tropsha, A., 2003. Development and validation of k-nearest-neighbor QSPR models of metabolic stability of drug candidates. J. Med. Chem. 46, 3013–3020.

Sunder-Plassmann, N., Sarli, V., Gartner, M., Utz, M., Seiler, J., Huemmer, S., Mayer, T.U., Surrey, T., Giannis, A., 2005. Synthesis and biological evaluation of new tetrahydro-beta-carbolines as inhibitors of the mitotic kinesin Eg5. Bioorg. Med. Chem. 13, 6094–6111.

Vaidya, A., Jain, A.K., Kumar, P., Kashaw, S.K., Agrawal, R.K., 2011. Predicting anti-cancer activity of quinoline derivatives: CoMFA and CoMSIA approach. J. Enzyme Inhib. Med. Chem. 26, 854–861.

Wold, S., 1995. PLS for multivariate linear modeling. In: van de Waterbeemd, H. (Ed.), . In: QSAR: Chemometric Methods in Molecular Design, vol 2. Wiley-VCH, Weinheim, Germany, pp. 195–218.

V-Life Molecular Design Suite 3.0, VLife Sciences Technologies Pvt. Ltd., Baner Road, Pune, Maharashtra, India. (< http://www.Vlifesciences.com >).

Xiao, S.L., Lin, W., Wang, C., Yang, M., 2001. Synthesis and biological evaluation of DNA targeting flexible side-chain substituted betacarboline derivatives. Bioorg. Med. Chem. Lett. 11, 437–441.