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QSAR Analysis on β-carboline as Antitumor Agent

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ABSTRACT

A quantitative structure activity relationship (QSAR) study on β-Carboline derivatives as an anti-tumor agent was performed with 30 compounds of β-Carboline derivatives on different cancer cell lines from reported work. Molecular modeling studies were performed using ChemBioDraw Ultra 11.0. The sketched structures were subjected to energy minimization and the lowest energy structure was used to calculate the physiochemical properties. The regression analysis was carried out using a computer program called Valstat. The best models were selected from the various statistically significant equations. From the derived QSAR model, it can be concluded that the cytotoxic activity of β-carboline derivatives is strongly influenced by the thermodynamic and electronic nature of the substituents.

Key words: Anti-tumor agent, β-carboline, QSAR

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INTRODUCTION

Research on antitumor alkaloids isolated from plants have been actively explored in the last 30 years, in which the anti-tumor effects of the naturally occurring β**-c**arboline derivative have been noticed recently after an intensive concentration on their high affinity to 5-HT[1] and benzodiazepines receptors[2,3] that cause CNS effect. As far the antitumor activity, harmine is a β-Carboline derivative shown to have strong cytotoxic activity to tumor cell lines *in vitro*.[4] It was recently discovered that β-carboline derivatives may function their antitumor activity through multiple mechanisms such as inhibiting topoisomerase - I and II,[5-9] β-kinase complex,[10,11] and intercalating DNA.[12] There are several reports on other biological activity of β-carboline derivatives[13,14] as well. QSAR is a useful tool for a retinal search of bioactive compounds. It provides a deeper insight into the mechanism of drug receptor interaction. Hence, in the present paper we report a QSAR study on a set of β-carboline derivatives for their *in vitro* antitumor activity against 6 different cell lines. In short, this study may provide a framework for designing a novel anti-tumor agent.

MATERIALS AND METHODS

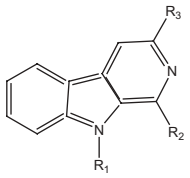
Data set

Data sets of 30 molecules have been taken from the published results.[12] The cytotoxic activity expressed as IC_{50} values have been converted into –log molar concentration ($p\ IC_{50}$) to reduce the stewness of the data set. The structure and cytotoxic activity data ($p\ IC_{50}$) are given in Table 1.

Molecular structure generation

The structure of the β-carboline derivatives were sketched using ChemBioDraw Ultra 11.0[15] and it has been saved as a template structure. The molecular mechanics ($MM_{2)}$ method was applied to search for lower energy conformations for

Table 1: Cytotoxicity of β-carboline derivatives to tumor cell lines and its p IC50



Sl.No	R_1	R_2	R_3	p IC_{50}					
				BEL 7402	Hela	C^6	Lovo	PLA 801	BCGA23
1	H	CH_3	-	0.612	0.471	0.835	0.271	0.430	0.602
2	H	CH_3	$-COOCH_3$	0.632	0.705	0.943	1.070	0.795	0.930
3	H	CH_3	$-COOC_3H_7$	0.477	0.460	0.298	0.804	0.477	0.419
4	H	CH_3	$-COOC_4H_9$	0.943	1.114	1.075	1.562	1.058	1.197
5	H	CH_3	$-CONHNH_2$	0.304	0.279	0.392	0.628	0.139	0.069
6	H	CH_3	$-CONH(CH_2)_2NH_2$	0.292	0.392	0.155	0.431	0.123	0.501
7	H	CH_3	$-CONH(CH_2)_2OH$	0.226	0.614	0.606	0.421	0.447	0.465
8	H	CH_3	$-CONH(CH_2)_6NH_2$	0.340	0.774	0.515	0.465	0.575	0.671
9	H	H	$-CONH(CH_2)_2OH$	0.250	0.625	0.274	20.025	0.087	0.863
10	H	H	$-CONH(CH_2)_6NH_2$	0.600	0.850	0.841	0.158	0.133	0.005
11	CH_3	CH_3	$-COOC_4H_9$	0.514	0.476	0.281	1.216	0.583	0.067
12	C_2H_5	CH_3	$-COOC_4H_9$	0.444	0.571	0.358	0.647	0.359	0.759
13	$CH_2C_6H_5$	CH_3	$-COOC_4H_9$	1.000	0.261	0.982	0.649	0.581	0.239
14	C_2H_5	CH_3	$-CONH(CH_2)_2NH_2$	1.795	1.801	1.690	1.321	0226	1.378
15	n-C_4H_9	CH_3	$-CONH(CH_2)_2NH_2$	1.520	2.167	1.943	1.511	1.365	1.657
16	$CH_2C_6H_5$	CH_3	$-CONH(CH_2)_2NH_2$	2.251	0.931	2.214	1.943	1.224	1.395
17	CH_3	H	$-CONH(CH_2)_2NH_2$	1.860	1.469	1.364	1.173	1.084	1.303
18	C_2H_5	H	$-CONH(CH_2)_2NH_2$	1.533	1.497	1.673	1.896	1.415	1.787
19	$CH_2C_6H_5$	H	$-CONH(CH_2)_2NH_2$	2.146	1.798	1.560	1.690	1.460	1.504
20	CH_3	CH_3	$-CONH(CH_2)_2OH$	1.474	0.721	1.640	2.157	1.636	1.688
21	C_2H_5	CH_3	$-CONH(CH_2)_2OH$	0.910	0.623	0.892	0.118	1.542	1.332
22	n-C_4H_9	CH_3	$-CONH(CH_2)_2OH$	0.759	0.705	0.903	1.148	0.835	0.829
23	CH_3	H	$-CONH(CH_2)_2OH$	0.966	1.000	1.434	0.943	1.244	1.195
24	C_2H_5	H	$-CONH(CH_2)_2OH$	1.484	1.501	1.645	0.716	0.835	1.118
25	n-C_4H_9	H	$-CONH(CH_2)_2OH$	0.917	0.441	1.030	1.026	0.056	1.151
26	$CH_2C_6H_5$	H	$-CONH(CH_2)_2OH$	1.571	1.812	1.173	2.085	1.621	1.250
27	$CH_2C_6H_5$	CH_3	$-CONH(CH_2)_6NH_2$	0.378	0.478	0.416	0.370	0.288	0.423
28	CH_3	H	$-CONH(CH_2)_6NH_2$	0.374	0.151	0.825	0.920	0.882	0.954
29	C_2H_5	H	$-CONH(CH_2)_6NH_2$	0.628	1.180	1.375	1.063	1.025	0.793
30	$CH_2C_6H_5$	H	$-CONH(CH_2)_6NH_2$	1.718	2.020	2.188	1.790	1.459	1.576

each molecule. The energy minimized molecules were subjected to re-optimization via the Austin model - 1 method until the root mean square gradient attained a value smaller than 0.001k cal/mol using molecular orbital property accompany name (MOPAC). The geometry optimization of the lowest energy structure was carried out using the Eigen vector following (EF) routine.

The thermodynamic, spatial, electronic, and topological parameters shown in Table 2 were calculated for QSAR analysis. Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters were quantified for steric features of drug molecules required for its complimentary fit with the receptor. Electronic parameters describe weak non–covalent bonding between drug molecules and the receptor.

Statistical analysis

In order to select the predominant descriptors affecting the cytotoxic activity, the correlation analysis was performed using the statistical software Valstat.[16] Multiple regression analysis was used to generate QSAR analysis. The statistical measures used were: n=number of samples in the regression, r=correlation coefficient, and s=standard deviation. The robustness and applicability of the QSAR equation obtained on the structural analogs were further performed using various validation methods, bootstrapping squared correlation coefficients (r^2bs), and randomized biological data test (chance).

RESULTS AND DISCUSSION

Among the several models, one of the best models was selected from each cell line and the results are summarized in Table 3. The best QSAR model has characters of large F, small r and s, low p-value, r^2 and q^2 values close to 1, as well as $P<0.001$. So the tabulated QSAR shows significant statistical quality. The equation was further validated using

Table 2: Descriptors used in present QSAR study

S. No.	Descriptors	Type	Descriptors (units)
1	BP	Thermodynamic	Boiling point (Kelvin)
2	CP	Thermodynamic	Critical pressure (Kelvin)
3	CT	Thermodynamic	Critical temperature (bar)
4	TORERG	Thermodynamic	Torsion energy (kcal/mol)
5	LogP	Thermodynamic	Logarithmic partition coefficient
6	MP	Thermodynamic	Melting point (Kelvin)
7	MR	Thermodynamic	Molar refractivity (cm^3/mol)
8	VWD	Thermodynamic	Van der Waals force (kcal/mol)
9	STERG	Thermodynamic	Stretch energy (kcal/mol)
10	SBE	Thermodynamic	Strech bend energy (kcal/mol)
11	SE	Thermodynamic	Stretch energy (kcal / mol)
12	CAA	Steric	Connolly accessible surface area (Å)
13	CMA	Steric	Connolly molecular surface area (Å)
14	CSEV	Steric	Connolly solvent-excluded volume (Å)
15	EM	Steric	Exact mass (g/mol)
16	MW	Steric	Molecular weight
17	PMI	Steric	Principle moment of inertia
17	E_{HOMO}	Electronic	Highest occupied molecular orbital energy
18	DIPOLE M	Electronic	Dipole moment (Debye)
19	E_{LUMO}	Electronic	Lowest occupied molecular orbital energy

the Loo cross validation method to confirm the internal consistency given in Table 4 and it suggests a good correlation between the physiochemical parameters and the antitumor activity. The bootstrapping r^2bs value showed that the model is quite robust.

For the cell line BGC823, the thermodynamic parameters, log P, CMA, and EM play a significant role. The negative coefficient of log p indicates that the length of the carbon chain should be optimized and the hydrophobicity should be reduced. The negative contribution of EM indicates that the bulkiness should be reduced. The electronic parameter LUMO contributes negative coefficients for the cell lines Lovo, Hela, and C[6].The energy LUMO is directly related to the electron affinity and characterize the susceptibility of the molecule towards attack of nucleophile. The energy of LUMO can be decreased by an electron releasing substituent and the lowering of LUMO energy will increase the magnitude of inhibitory activity. When a molecule acts as a lewis base in bond formation, the electrons are supplied from the molecules. A positive contribution of HOMO in the cell line C6 indicates that they are more susceptible to electrophilic attack. The thermodynamic parameters SE and SBE showed positive contribution to the cell lines LOVO and Hela. The geometric descriptor principal moment of inertia (PMI) helps to characterize the shape of the molecules and shows a positive effect on all the cell lines expect BGC823. The descriptor VDW energy is non bonded Van der Waals energy between the molecule and the receptor shows a negative contribution to Be17402 cell line.

CONCLUSION

In summary, from the derived QSAR model, it may be concluded that selective cytotoxic activity by the β-carboline derivative is strongly influenced by the thermodynamic and electronic nature of the substituents. Patterns of substitution can be extracted from the developed model, which may be helpful in the development and optimization of cytotoxic inhibitors of this class of compounds.

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Table 3: Summary of equation and multiple regressions analysis

Line	Equation	n	r^2	Q^2	Std	F	r^2bs	Press	Variance	Chance
PLA 801	BA = -11.42 – CMA X 0.0277+ CSEV X 3.49 + PMI X 16.16	30	0.757	0.64	0.581	16.2	0.87	0.561	0.051	<0.001
BGC823	BA = -4.49 – Log P X 0.07 + CMA X 0.01 – EM X 0.148	30	0.88	0.82	0.253	19.8	0.81	0.510	0.062	<0.001
Bel7402	BA = 0.203 + PMI X 0.008 – VDW X 0.02 – SE X 0.02	30	0.85	0.97	0.430	18.4	0.87	0.377	0.028	<0.0005
Lovo	BA = 0.63 + PMI X 0.066 + SBE X 0.112 – LUMO X 4.27	30	0.82	0.78	0.192	20.4	0.92	0.284	0.041	<0.0005
Hela	BA = 0.186 + PMI X 0.011 – SE X 0.017 – LUMO x 6.01	30	0.63	0.72	0.640	23.6	0.69	0.631	0.019	<0.001
C[6]	BA = 1.013 + PMI X 0.018 + HOMO X 1.78 – LUMO X 3.36	30	0.79	0.84	0.320	33.4	0.78	0.420	0.064	<0.001

Table 4: Predicated activity from best equation obtained

S. No	BEL 7402			Hela			C6		
	Calculated	Predicted	Deviation	Calculated	Predicted	Residual	Calculated	Predicted	Residual
1	0.612	0.631	0.019	0.471	0.441	0.030	0.835	0.840	0.005
2	0.632	0.628	0.004	0.705	0.724	0.019	0.943	0.901	0.042
3	0.477	0.466	0.011	0.460	0.450	0.010	0.298	0.306	0.008
4	0.943	0.971	0.028	1.114	1.128	0.014	1.075	1.120	0.045
5	0.304	0.318	0.014	0.279	0.250	0.029	0.392	0.410	0.018
6	0.292	0.301	0.009	0.392	0.401	0.009	0.155	0.151	0.004
7	0.226	0.243	0.017	0.614	0.635	0.021	0.606	0.621	0.015
8	0.340	0.412	0.072	0.774	0.784	0.010	0.515	0.523	0.008
9	0.250	0.291	0.041	0.625	0.617	0.008	0.274	0.301	0.027
10	0.600	0.618	0.080	0.850	0.830	0.020	0.841	0.848	0.007
11	0.514	0.498	0.016	0.476	0.494	0.018	0.281	0.342	0.061
12	0.444	0.424	0.020	0.571	0.598	0.027	0.358	0.320	0.038
13	1.000	0.984	0.016	0.261	0.251	0.010	0.982	0.952	0.030
14	1.795	1.841	0.046	1.801	1.792	0.009	1.690	1.531	0.159
15	1.52	1.74	0.22	2.167	2.152	0.015	1.943	2.014	0.071
16	2.251	2.151	0.1	0.931	0.921	0.01	2.214	2.428	0.214
17	1.860	1.902	0.042	1.469	1.472	0.003	1.364	1.461	0.097
18	1.533	1.740	0.207	1.497	1.504	0.007	1.673	1.642	0.031
19	2.146	2.011	0.135	1.798	1.807	0.009	1.560	1.580	0.020
20	1.474	1.399	0.075	0.721	0.726	0.005	1.640	1.720	0.080
21	0.910	0.942	0.032	0.623	0.624	0.001	0.892	0.901	0.009
22	0.759	0.771	0.012	0.705	0.708	0.003	0.903	0.899	0.040
23	0.966	0.951	0.015	1.00	1.047	0.047	1.434	1.461	0.0027
24	1.484	1.431	0.053	1.501	1.490	0.011	1.645	1.675	0.030
25	0.917	0.924	0.007	0.441	0.404	0.037	1.030	1.021	0.009
26	1.571	1.502	0.069	1.812	1.890	0.007	1.173	1.119	0.054
27	0.378	0.304	0.074	0.478	0.439	0.039	0.416	0.420	0.004
28	0.374	0.397	0.023	0.151	0.174	0.023	0.825	0.836	0.011
29	0.628	0.684	0.056	1.180	1.163	0.017	1.375	1.407	0.032
30	1.718	1.694	0.024	2.020	2.201	0.181	2.188	2.162	0.026

Table 4: continued..

	Lovo			PLA 801			BCGA23		
	Calculated	Predicted	Residual	Calculated	Predicted	Residual	Calculated	Predicted	Residual
1	0.271	0.341	0.070	0.430	0.381	0.049	0.602	0.584	0.018
2	1.070	1.124	0.054	0.795	0.840	0.045	0.930	0.972	0.042
3	0.804	0.841	0.037	0.477	0.481	0.004	0.419	0.402	0.017
4	1.562	1.584	0.022	1.058	1.103	0.045	1.197	1.204	0.007
5	0.628	0.742	0.114	0.139	0.120	0.019	0.069	0.081	0.012
6	0.431	0.531	0.100	0.123	0.109	0.014	0.501	0.587	0.086
7	0.421	0.348	0.073	0.447	0.487	0.040	0.465	0.442	0.023
8	0.465	0.434	0.031	0.575	0.564	0.011	0.671	0.628	0.043
9	2.025	2.620	0.595	0.087	0.094	0.007	0.863	0.904	0.041
10	0.158	0.113	0.045	0.133	0.164	0.031	0.005	0.012	0.007
11	1.216	1.198	0.018	0.583	0.524	0.059	0.067	0.074	0.007
12	0.647	0.604	0.043	0.359	0387	0.028	0.759	0.775	0.016
13	0.649	0.621	0.028	0.581	0.642	0.061	0.239	0.241	0.002
14	1.321	1.306	0.015	0226	0.394	0.168	1.378	1.305	0.073
15	1.511	1.490	0.021	1.365	1.682	0.317	1.657	1.675	0.018
16	1.943	2.061	0.118	1.224	1.204	0.020	1.395	1.424	0.029
17	1.173	1.421	0.248	1.084	1.101	0.017	1.303	1.312	0.009
18	1.896	1.903	0.007	1.415	1.381	0.034	1.787	1.891	0.102
19	1.690	1.654	0.036	1.460	1.420	0.040	1.504	1.581	0.077
20	2.157	2.113	0.044	1.636	1.690	0.054	1.688	1.708	0.020
21	0.118	0.199	0.080	1.542	1.520	0.022	1.332	1.294	0.038
22	1.148	1.214	0.066	0.835	0.804	0.031	0.829	0.903	0.074
23	0.943	1.401	0.458	1.244	1.284	0.040	1.195	1.241	0.046
24	0.716	0.694	0.022	0.835	0.843	0.008	1.118	1.211	0.093
25	1.026	1.009	0.017	0.056	0.087	0.011	1.151	1.203	0.052
26	2.085	2.163	0.078	1.621	1.648	0.027	1.250	1.270	0.020
27	0.370	0.297	0.073	0.288	0.398	0.110	0.423	0.400	0.023
28	0.920	0.908	0.012	0.882	0.879	0.003	0.954	0.963	0.009
29	1.063	1.142	0.921	1.025	1.020	0.005	0.793	0.807	0.014
30	1.790	1.890	0.100	1.459	1.421	0.038	1.576	1.526	0.050

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