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Quantum Chemical Descriptor Based QSAR Study on β-Carbolines Binding to Benzodiazepine Receptor

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QSAR study of derivatives of β-carboline has been made with the help of quantum chemical descriptors. For QSAR study, the molecular modeling and geometry optimization for all the derivatives were carried out with CAChe Pro software using PM3 methods. QSAR model, "RE23 = -0.0141829*ΔH_f^0 + 0.0428252* M_W + 0.150185* E_T -1.42607*εLUMO + 5.56043" can be useful for predicting the activity of new β-carbolines prior to their synthesis. ΔH_f^0, M_W, E_T and εLUMO are reliable descriptor for predicting activity. QSAR model indicates that these descriptors have significant relationships with observed bioactivity.

Key Words: β-Carboline, Quantum chemical descriptors, PM3, BzR.

INTRODUCTION

Benzodiazepines (BDZs) are the drugs of choice in the pharmacotherapy of anxiety and related emotional disorders, sleep disorders, status epilepticus and other convulsive states. They are used as centrally acting muscles relaxants, for premedication and as inducing agents in anesthesiology. They act *via* the benzodiazepine receptor site (BzR) on the γ-aminobutyric acid receptor ($GABA_A$) family and have been subjected to extensive quantitative structure-activity relationship (QSAR) studies[1-4]. There are relatively several structural classes of non-benzodiazepine (non-BDZ) compounds that have reasonable affinity for the BzR and shows pharmacologic activity *in vivo*. But, in this study we have propose to make QSAR study of a series of β-carboline derivatives as non-BDZ molecules. β-Carbolines posssess a broad spectrum of pharmacological actions (as muscle relaxants) mediated *via* occupation of benzodiazepine receptor (BzR) in the central nervous system. There is always a search for better medicines, which have better pharmacological action and fewer side effects. Non-BDZ compounds, which have better results in respect of their action against the disease, have regularly been searched. β-Carboline (Fig. 1) is one such a compound, which binds to the same receptor site at which benzodiazepine bind.

Survey of the literature shows that biological activity of several β-carboline derivatives have been measured and discussed in detail[5-11]. The survey of the literatures also indicates that no QSAR study of β-carboline derivatives has been made with the quantum chemical parameters: (1) Heat of formation

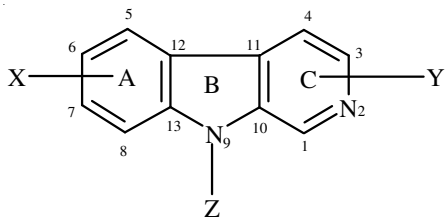
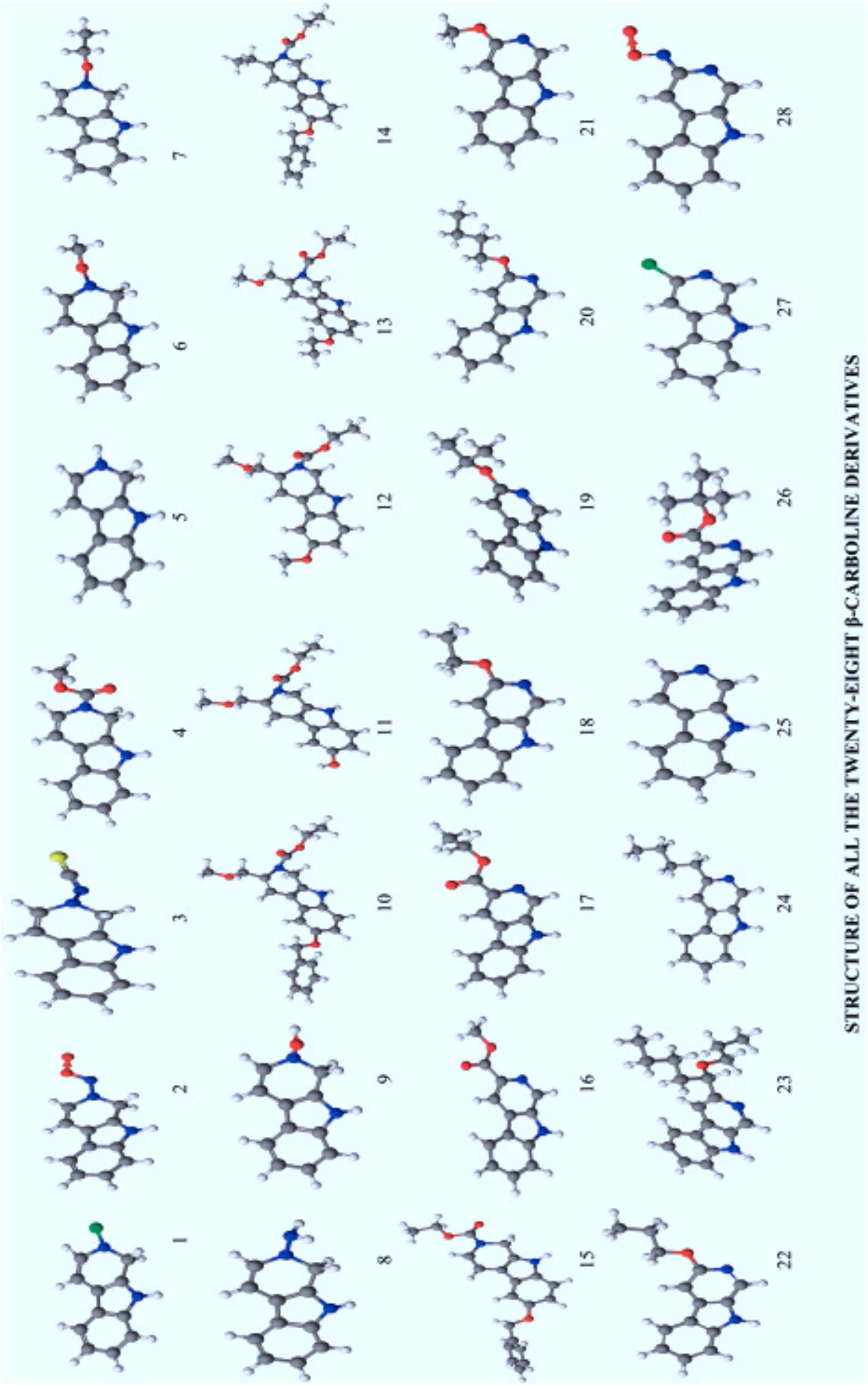


Fig. 1

(ΔH_f^0), (2) molecular weight (m.w.), (3) Total energy (E_T), (4) HOMO energy (εHOMO), (5) LUMO energy (εLUMO), (6) absolute hardness (η) and (7) electronegativity (χ).

EXPERIMENTAL

The study materials of this work are 28 β-carboline derivatives with their observed biological activity in terms of IC_{50} inhibition of [^{3}H]diazepam binding to the benzodiazepine receptor (compound No. **1-15**) and IC_{50} antagonistic activity on benzodiazepine receptor (compound No. **16-28**). For QSAR study, the 3D modeling and geometry optimization of all the twenty eight compounds have been carried out on CAChe software by applying semiemperical PM3 method[12,13]. Multilinear regression analysis has been made by Project Leader software associated with CAChe[14], using the above descriptors in different combinations. All the values required for the determi-nation of the value of heat of formation, molecular weight, total energy, energy of HOMO, energy of LUMO, absolute hardness and electronegativity have been evaluated from this software by solving the equations[15].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STRUCTURE OF ALL THE TWENTY-EIGHT β-CARBOLINE DERIVATIVES

RESULTS AND DISCUSSION

QSAR study on benzodiazepine has been extensively made but on β-carboline derivatives such studies are remotely reported. We in this research work report QSAR studies on 28 derivatives of β-carboline with the help of quantum chemical descriptor namely heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity. There is great importance of QSAR studies because such a study reduces the cost and time of research. QSAR study provides information about the quality of drug before its synthesis. The center of gravity of approach of medicinal chemistry has shifted from how to make a drug to what drug to make. In this work, we have developed equation through which the pharmacological activity of β-carboline derivatives can be reliably predicted. The best prediction has been reported by combination of descriptors: heat of formation, molecular weight, total energy and LUMO energy. The quality of prediction has been obtained by multilinear regression analysis. For QSAR prediction of β-carbolines we have performed the MLR analysis by using the above descriptors. Various QSAR models using descriptors in different combinations have been developed and the models having reliable predicting power are selected and described below:

RE1=-0.00562694*ΔH_f^0 +0.00792708* M_W +5.55104
rCV^2=0.24402
r^2=0.521491
RE2=-0.00593047*ΔH_f^0 -0.0259334* E_T +5.90225
rCV^2=0.320431
r^2=0.498792
RE3=-0.0143793*ΔH_f^0 -1.60023*εLUMO +6.72171
rCV^2=0.420885
r^2=0.638828
RE4=-0.0142793*ΔH_f^0 -3.56068*χ+21.4422
rCV^2=0.486675
r^2=0.543353
RE5=-0.0125827*ΔH_f^0 -1.46302*η+1.09
rCV^2=0.44115
r^2=0.577544
RE6=-0.0458143* E_T -0.944693*εHOMO -3.26741
rCV^2=0.265954
r^2=0.504544
RE7=-0.00833631*ΔH_f^0 +0.0455858* M_W +0.145872* E_T +5.33247
rCV^2=0.241162
r^2=0.574813
RE8=-0.0058516*ΔH_f^0 +0.00801492* M_W -0.967399*εHOMO -2.52135
rCV^2=0.331691
r^2=0.586691
RE9=-0.0113268*ΔH_f^0 +0.00409791* M_W -1.40959*εLUMO +5.78274
rCV^2=0.45826
r^2=0.658685
RE10=-0.0105733*ΔH_f^0 +0.00428381* M_W -2.59555*χ+16.5935
rCV^2=0.33931
r^2=0.560337
RE11=-0.00839595*ΔH_f^0 +0.00622669* M_W -1.29518*η+0.253716
rCV^2=0.441688
r^2=0.628166
RE12=-0.00611816*ΔH_f^0 -0.0264481* E_T -0.971903*εHOMO -2.21826
rCV^2=0.385883
r^2=0.564586
RE13=-0.012107*ΔH_f^0 -0.010764* E_T -1.46992*εLUMO +6.10165
rCV^2=0.417495
r^2=0.648228
RE14=-0.011898*ΔH_f^0 -0.00978273* E_T -2.97721*χ+18.5419
rCV^2=0.417749
r^2=0.549355
RE15=-0.00885162*ΔH_f^0 -0.0194264* E_T -1.32928*η+0.43915
rCV^2=0.458941
r^2=0.611355
RE16=-0.0156572*ΔH_f^0 +0.918113*εHOMO -2.26807*εLUMO +14.0115
rCV^2=0.417126
r^2=0.662311
RE17=-0.0156572*ΔH_f^0 -1.34996*εHOMO -4.53614*χ+14.0115
rCV^2=0.417126
r^2=0.662311
RE18=-0.0148895*ΔH_f^0 -0.00309168* E_T +3.00592*εHOMO -4.34099*η+13.1769
rCV^2=0.351374
r^2=0.662896
RE19=-0.0156572*ΔH_f^0 -1.34996*εLUMO -1.83623*χ+14.0115
rCV^2=0.417126
r^2=0.662311
RE20=-0.0156572*ΔH_f^0 -3.18618*εLUMO +1.83623*η+14.0115
rCV^2=0.417126
r^2=0.662311
RE21=-0.0156572*ΔH_f^0 -3.18618*χ-1.34996*η+14.0115
rCV^2=0.417126
r^2=0.662311
RE22=-0.00843275*ΔH_f^0 +0.0440006* M_W +0.139404* E_T -0.932622*εHOMO -2.44003
rCV^2=0.314168
r^2=0.635304
RE23=-0.0141829*ΔH_f^0 +0.0428252* M_W +0.150185* E_T -1.42607*εLUMO +5.56043
rCV^2=0.54325
r^2=0.715188
RE24=-0.0142169*ΔH_f^0 +0.0452384* M_W +0.160528* E_T -2.94296*χ+17.831
rCV^2=0.376308
r^2=0.624216

RE25=-0.011035*ΔH_f^0 +0.0432515* M_W +0.143361* E_T -1.28413*η+0.0841066
rCV^2=0.456911
r^2=0.67966
RE26=-0.0134226*ΔH_f^0 +0.00252592* M_W +0.664466*εHOMO -1.96606*εLUMO +11.4188
rCV^2=0.397208
r^2=0.668063
RE27=-0.0134226*ΔH_f^0 +0.00252592* M_W -1.30159*εHOMO -3.93211*χ+11.4188
rCV^2=0.397208
r^2=0.668063
RE28=-0.0134226*ΔH_f^0 +0.00252592* M_W +2.63052*εHOMO -3.93211*η+11.4188
rCV^2=0.397208
r^2=0.668063
RE29=-0.0134226*ΔH_f^0 +0.00252592* M_W -1.30159*εLUMO -1.32893*χ+11.4188
rCV^2=0.397208
r^2=0.668063
RE30=-0.0134226*ΔH_f^0 +0.00252592* M_W -2.63052*εLUMO +1.32893*η+11.4188
rCV^2=0.397208
r^2=0.668063
RE31=-0.0134226*ΔH_f^0 +0.00252592* M_W -2.63052*χ-1.30159*η+11.4188
rCV^2=0.397208
r^2=0.668063
RE32=-0.0148895*ΔH_f^0 -0.00309168* E_T +0.835423*εHOMO -2.17049*εLUMO +13.1769
rCV^2=0.351374
r^2=0.662896

In order to explore the reliability of the proposed model we have used correlation coefficient (r^2) and cross-validation coefficient (rCV^2). Best QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first, molecular weight as second, total energy as third and LUMO energy as fourth descriptor. The values of the predicted activities PA23 of all the compounds are listed in the Table-1. The regression equation is given below:
RE23=-0.0141829*ΔH_f^0 + 0.0428252* M_W +0.150185* E_T -1.42607*εLUMO +5.56043
rCV^2=0.54325
r^2=0.715188

The reliability of this QSAR models is very clear from their high values of correlation coefficient and cross-validation coefficient. The trend of observed and predicted activity is shown in Fig. 2.

Concluding remarks: (i) QSAR model, "RE23 = -0.0141829*ΔH_f^0 +0.0428252* M_W +0.150185* E_T -1.42607* εLUMO +5.56043" can be useful for predicting the activity of new β-carbolines prior to their synthesis. (2) ΔH_f^0, M_W, E_T and εLUMO are reliable descriptor for predicting activity. (3) QSAR model indicates that these descriptors have significant relationships with observed bioactivity.

TABLE-1
VALUES OF QUANTUM CHEMICAL DESCRIPTORS OF β-CARBOLINE DERIVATIVES, THEIR OBSERVED AND PREDICTED ACTIVITY

S. No.	Descriptors								PA23
	ΔH_f^0	M_W	E_T	εHOMO	εLUMO	χ	η	OA	
1	55.732	204.659	-45.927	-8.200	-0.449	3.876	-4.324	7.35	7.28
2	152.144	215.211	-54.103	-8.512	-1.273	3.620	-4.892	6.90	6.31
3	126.741	227.283	-50.737	-8.294	-1.068	3.613	-4.681	8.10	7.40
4	-23.323	228.250	-57.878	-8.116	-0.342	3.887	-4.229	8.30	7.46
5	58.273	170.213	-42.043	-7.863	-0.149	3.857	-4.006	5.79	5.92
6	55.016	200.240	-50.555	-8.011	-0.239	3.886	-4.125	6.91	6.10
7	51.241	214.266	-54.448	-8.007	-0.232	3.888	-4.119	7.62	6.16
8	83.167	185.228	-46.187	-7.877	-0.176	3.850	-4.027	4.60	5.63
9	50.416	186.213	-46.646	-8.011	-0.237	3.887	-4.124	5.40	6.15
10	-75.333	392.454	-100.87	-8.156	-0.392	3.882	-4.274	9.00	8.85
11	-112.130	302.329	-78.794	-8.182	-0.433	3.874	-4.308	9.05	8.88
12	-105.090	316.356	-82.707	-8.158	-0.394	3.882	-4.276	9.30	8.74
13	-109.600	330.383	-86.599	-8.146	-0.383	3.881	-4.264	8.64	8.80
14	-46.871	376.454	-96.232	-8.116	-0.364	3.876	-4.240	7.66	8.41
15	-36.243	348.401	-88.466	-8.069	-0.341	3.864	-4.205	8.05	8.20
16	-19.584	226.234	-56.603	-8.883	-0.783	4.050	-4.833	8.30	8.14
17	-24.428	240.261	-60.496	-8.876	-0.773	4.051	-4.825	8.30	8.21
18	18.690	212.251	-53.223	-8.200	-0.494	3.853	-4.347	7.62	7.10
19	11.374	226.277	-57.111	-8.462	-0.599	3.931	-4.531	6.29	7.37
20	6.750	240.304	-60.999	-8.479	-0.608	3.935	-4.543	7.01	7.46
21	22.089	198.224	-49.331	-8.500	-0.619	3.940	-4.560	6.91	7.21
22	12.133	226.277	-57.111	-8.478	-0.607	3.935	-4.542	7.96	7.37
23	-11.850	296.411	-76.545	-8.672	-0.580	4.046	-4.626	7.64	7.75
24	38.888	224.305	-56.345	-8.312	-0.419	3.946	-4.366	6.64	6.75
25	62.277	168.198	-40.793	-8.422	-0.470	3.976	-4.446	5.79	6.43
26	-33.736	268.315	-68.271	-8.842	-0.739	4.052	-4.791	8.00	8.33
27	55.119	202.643	-44.708	-8.437	-0.616	3.910	-4.526	7.35	7.62
28	142.764	213.195	-52.842	-8.836	-1.836	3.500	-5.336	6.90	7.35

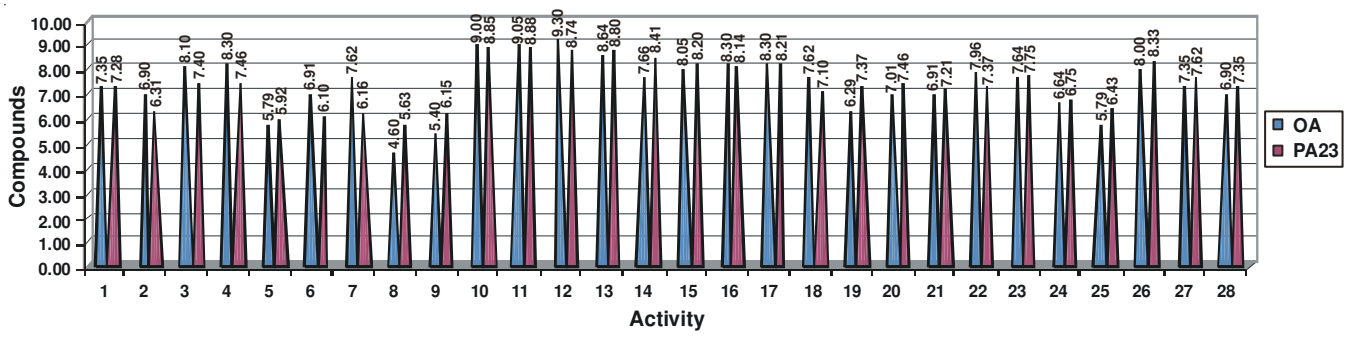

Fig. 2.

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