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RESEARCH ARTICLE

Correlation of binding affinity of β-carbolines on benzodiazepines receptor with UV-and IR-Spectroscopic data

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Abstract

50% displacement of [^{3}H]Flunitrazepam on benzodiazepines receptor (BzR) by β-Carboline derivatives in term of binding affinity has been correlated using λ_{max} and stretching frequencies viz. υ(C-H), υ(N-H), υ(C=C) and υ(C=N). The above data were evaluated by modeling and optimizing the fourteen derivatives of β-carboline on workspace program of CAChe Pro software of Fujitsu, using PM3 method. To obtain a correlation between biological activity and UV-data and IR-data, multiple linear regressions (MLR) analysis were done on Project Leader Program associated with CAChe, using above data as independent variables and biological activity as dependent variables. The reliability of correlation through MLR equations have been judged by correlation coefficient ($r^2 \geq 0.5$) and cross-validated correlation coefficient ($r^2_{CV} \geq 0.25$).The study revealed that λ_{max} and υ(C-H) (r^2= 0.546; r^2_{CV}= 0.382) can be used as descriptor to predict the binding affinity of new derivatives of this series before their synthesis.

INTRODUCTION

The pharmacological action of β-carbolines is due to its affinity for benzodiazepine receptor (BzR), which is present in the central nervous system (Venault and Chapouthier, 2007). Biological activities of β-carboline's derivatives have been reported in literature (Hadjipavlou-Litina et al., 2004) and the survey of the literature also indicates that no QSAR study of β-carboline's derivatives has been made with the UV- and IR-spectroscopic data. The aim of this study is to correlate the binding affinities of selected β-carboline derivatives on BzR with electronic spectral data and vibrational frequencies.

Material and methods

The study materials of this paper are β-carboline and its fourteen derivatives, and are presented in Table-1 alongwith their observed biological activity (OBA) reported in term of IC_{50} binding affinities to displace 50% of [^{3}H]Flunitrazepam on benzodiazepines receptor (Hadjipavlou-Litina et al., 2004). For the study, the 3D modeling and geometry optimization (Thiel, 1988; Stewart, 1989) of all the fifteen compounds were performed on MOPAC 2002 (Stewart, 1990) software as implemented in CAChe Pro 5.04 software of Fijitsu by opting PM3 method. UV-visible spectrum for each compound was created by electron transition between molecular orbitals as electromagnetic radiation in the visible and ultraviolet (UV-visible) region is absorbed by the molecule. After obtaining approximate minimum energy structures, the UV-visible electronic transitions of the each compound were generated by a ZINDO configuration interaction. IR spectrum of transitions for each compound was created by

coordinated motions of the atoms as electromagnetic radiation in the infrared region is absorbed by the molecule. The force necessary to distort the molecule from its equilibrium geometry and predict the frequency of vibrational transitions was predicted (Essa et al., 2008).

Result and discussion

Many types of compounds either BDZs (benzodiazepines, figure 1) or Non-BDZs (arylpyrazolo-quinolines, β-carbolines, imidazopyridazines, and cyclo-pyrrolones) have been shown to bind at the BzR on γ-aminobutyric acid receptor ($GABA_A$) family (Sharma et al, 1992; Hadjipavlou-Litina et al., 2004).The β-carbolines, non-BDZs and inverse agonists of BDZ, possess a broad spectrum of pharmacological actions (as muscle relaxants) mediated via occupation of BzR in the central nervous system (Cooper, 1986; Klockgether et al., 1985). Biological activities of β –carboline's derivatives have been reported in literature (Hadjipavlou-Litina et al., 2004) in term of (a) IC_{50} inhibition of [^{3}H]diazepam binding to the benzodiazepine receptor, (b) IC_{50} antagonistic activity on benzodiazepine receptor and (c) IC_{50} binding affinities to displace 50% of [^{3}H]Flunitrazepam on BzR and have been subjected to extensive quantitative structure-activity relationship (QSAR) studies (Sharma et al, 1992; Hadjipavlou-Litina et al., 2004; Singh et al., 2009; Sahu et al., 2010, Soni et al., 2011). Our work is based on inhibition of [^{3}H]Flunitrazepam binding to BzR.

Structure of β-carboline as showed in figure 2 have two ring nitrogens viz. one in indole ring and the other in pyridine ring. Replacement of hydrogen atom(s) of ring A or ring C or both the ring at specific site(s) by various substituents, as presented in Table 1, were reoptimized in comparison to β-carboline. Generally, the molecular point group (C_1) is retained. In order to investigate the direct effect of auxochromes and chromophores on β-carboline and their effects on the binding affinity of β-carboline's derivatives to the BzR, we have computed HOMO-LUMO gap (Sahu, et al., 2010) and λ_{max} (Singh, et al, 2014). These data are presented in Table 2. For comparative study the UV-visible spectra of all the compounds are placed in scheme 1, while the effect of substituents on electronic spectral data is placed in scheme 2. A close look at the scheme 2 shows increment in the HOMO-LUMO gap occurred in all the compounds, except compound no. 7 (-0.037 eV) and 9 (-0.029 eV). In compounds 3 to 6 the change is small (0.004-0.007 eV), while in the compounds 8, 11 and 14 the change is large, 0.249, 0.285 and 0.310 eV, respectively. All the compounds show bathochromic shift (red shift). Highest shift is shown by compound no. 15 (25.88 nm) and lowest by compound no. 2 (1.82nm) ≈ compound no. 4 (1.96 nm) ≈ compound no. 5 (1.99 nm). The highest shift is due to substitution of carboxylic group at position 3 i.e. on ring C, and the lowering in shift is due to substitution of hydroxymethyl group (compound no. 2) at the same position. Further, if the hydrogen of the carboxyl group (compound no. 15) is replaced by ethyl (compound no. 4) or n-propyl group (compound no. 5), there is a decreases in bathochromic shift.

Further, to investigate changes in binding affinity of β-carboline on at the level of substitutions, vibrational spectrum of β-carboline was calculated beyond the harmonic approximation (Essa et al., 2008). For comparative study the IR spectra of all the compounds are also placed in scheme 1, while the effect of substituents on vibrational frequencies is placed on scheme 2. β-Carboline shows symmetric C-H stretching at 3179.24 cm^{-1} and introduction of various substituents lowered this stretching, except compound no. 7, 8, 9 and 14. Further, an increase in antisymmetric stretching of this bond was shown by all the compounds, except the six compounds (1 to 6). The reference compound (β-carboline) shows a characteristic N-H stretching at 3508.15 cm^{-1}, except compound no.1 and 9; all the compounds reflect an increment in this stretching. Among them compound no. 2 having hydroxyl methyl group at site 3 shows highest N-H stretching at 3547.66 cm^{-1}. Increment in frequency of aromatic C=C bond is shown by only five compounds namely 7, 8, 11, 12, 14, while all the other compounds show a decrease with respect to β-carboline. In β-carboline C=N stretching occurs at 1562.44 cm^{-1} and an increase in frequency is reflected by all the compounds except compound no. 11 (1547.90 cm^{-1}) and 13 (1560.51 cm^{-1}).

To correlate binding affinity of the compounds with UV- and IR spectral data, we have performed MLR analysis (Myers, 1990) and various regression equations have been developed. For this electronic spectral data (HOMO-LUMO gap and λ_{max}) and vibration frequencies (υ_{sym} (C-H), υ_{asym} (C-H), υ(N-H), υ(C=C) and υ(C=N)) were used as independent variables and the experimental binding affinities of the compounds as dependent variables. MLR analysis has been made by Project Leader software associated with CAChe, using the descriptors in various combinations with a limit of $k \leq 3$. A number of models were generated and among them following model was found reliable.

$PBA = -0.12449 \times \boldsymbol{\lambda_{max}} - 0.134855 \times \boldsymbol{\upsilon_{sym}}\ \textbf{(C-H)} + 459.493$
$r^2_{CV} = 0.382$
$r^2 = 0.546$

where λ_{max} is the first descriptor and υ_{sym} (C-H) is the second descriptors. Both have negative descriptor coefficient magnitudes that show indirect relationship with binding affinity of the molecule. The predicted binding affinities values as obtained from this model are also given in Table 2, while the trend of observed (OBA) and predicted biological activity (PBA) is shown in figure 3. The study revealed that λ_{max} and υ(C-H) (r^2= 0.546; r^2_{CV}= 0.382) can be used as descriptor to predict the binding affinity of new derivatives of this series before their synthesis.

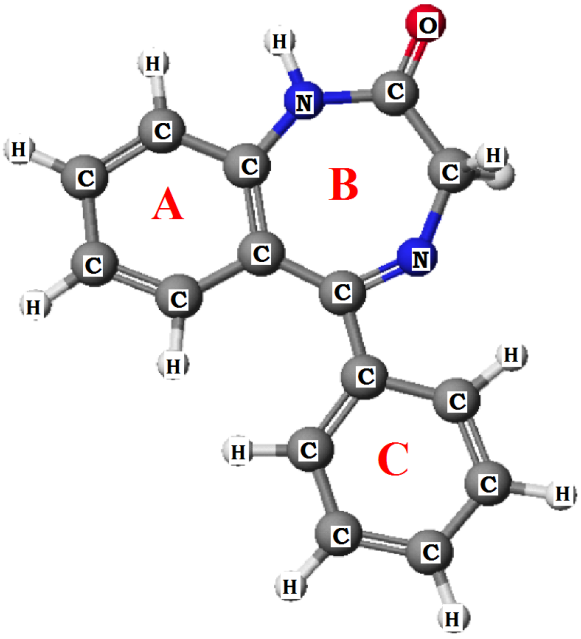


Figure 1. Structure of Benzodiazepine (BDZ)

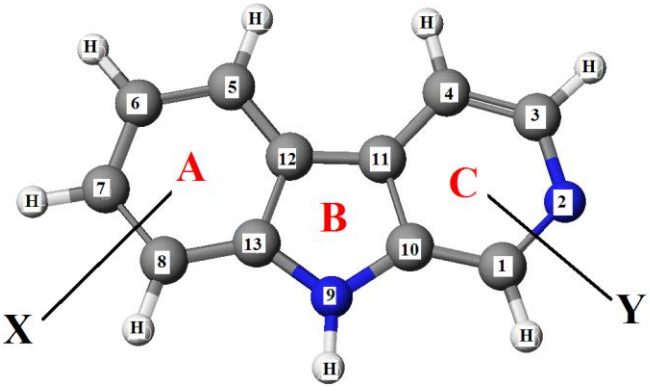


Figure 2. Parent skeleton of β-Carboline

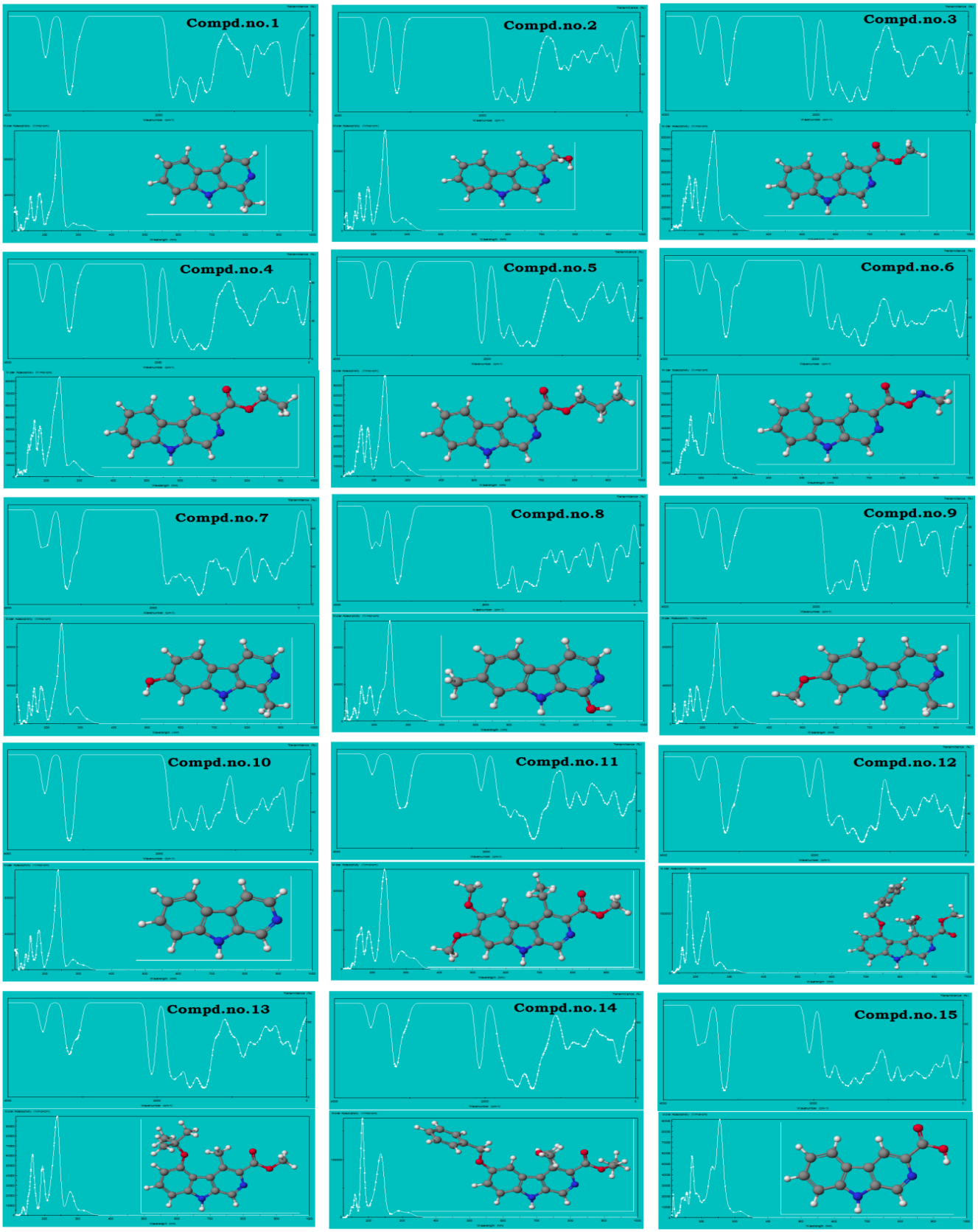
Table 1. β-Carboline derivatives with their observe biological activity in terms of IC_{50} binding affinities to displace 50% of [^{3}H]Flunitrazepam on benzodiazepines receptor (Hadjipavlou-Litina et al., 2004)

Compd. No.	X	Y	OBA
1	H	1-CH_3	-1.86
2	H	3-CH_2OH	1.67
3	H	3-$COOCH_3$	2.00
4	H	3-$COOC_2H_5$	2.26
5	H	3-$COOC_3H_7$	2.53
6	H	3-$COONHCH_3$	1.61
7	7-OH	1-CH_3	-2.20
8	7-CH_3	1-OH	-2.20
9	7-OCH_3	1-CH_3	-1.81
10	H	H	2.01
11	6,7-di-OCH_3	3-$COOCH_3$, 4-C_2H_5	2.37
12	5-$OCH_2C_6H_5$	3-$COOCH_3$, 4-CH_2OCH_3	2.71
13	5-$OCH(CH_3)_2$	3-$COOCH_3$, 4-CH_3	2.96
14	6-$OCH_2C_6H_5$	3-$COOC_2H_5$, 4-CH_2OCH_3	2.71
15	H	3-COOH	-1.03

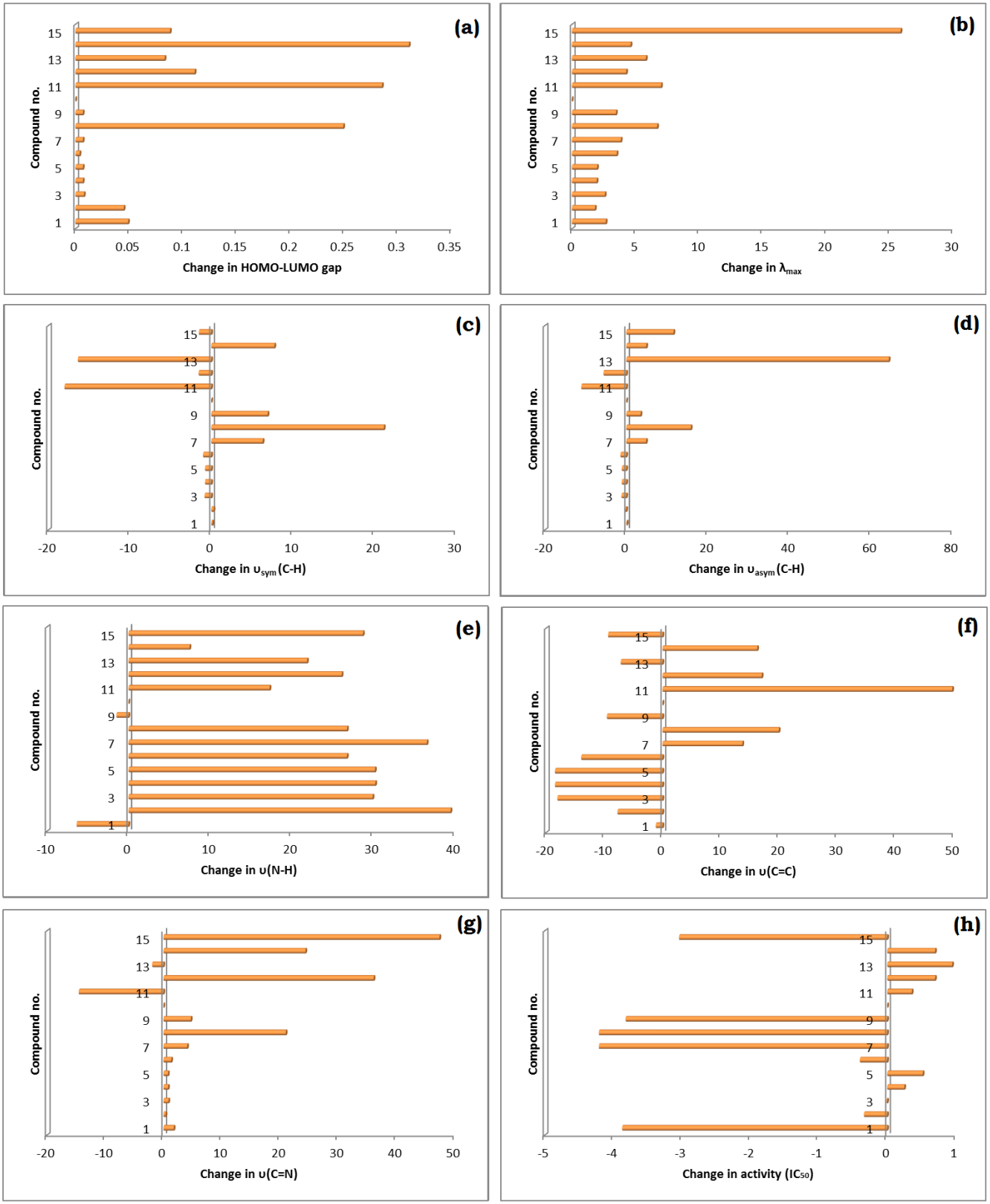
Table 2. Calculated HOMO-LUMO gap, λ_{max} from UV-visible spectra and frequencies from IR spectra of β-carboline (compd.no.10) and its derivatives

Compd. No.	HOMO-LUMO gap	λ_{max} (nm)	υ_{sym} (C-H)	Y_{asym} (C-H)	υ(N-H)	υ(C=C)	υ(C=N)	OBA	PBA
1[a]	-8.060	235.548	3179.40	3196.43	3501.79	1544.86	1564.22	-1.86	1.411
2	-8.064	234.699	3179.53	3196.06	3547.66	1538.28	1562.83	1.67	1.500
3	-8.101	235.474	3178.41	3195.10	3538.10	1527.96	1563.31	2.00	1.554
4	-8.102	234.834	3178.47	3195.18	3538.43	1527.55	1563.25	2.26	1.626
5	-8.102	234.865	3178.46	3195.17	3538.39	1527.55	1563.23	2.53	1.623
6	-8.105	236.409	3178.22	3194.85	3534.95	1532.05	1563.79	1.61	1.463
7	-8.146	236.734	3185.55	3201.16	3544.75	1559.74	1566.52	-2.20	0.434
8	-7.860	239.591	3200.41	3212.12	3534.96	1565.99	1583.46	-2.20	-1.925
9	-8.138	236.349	3186.16	3199.81	3506.67	1536.46	1567.16	-1.81	0.400
10[a]	-8.109	232.878	3179.24	3196.29	3508.15	1546.02	1562.44	2.01	1.765
11	-7.824	239.901	3161.23	3185.24	3525.47	1595.77	1547.90	2.37	3.320
12	-7.998	237.156	3177.68	3190.69	3534.31	1563.07	1598.55	2.71	1.443
13	-8.026	238.708	3162.86	3260.68	3530.06	1538.84	1560.51	2.96	3.248
14	-7.799	237.501	3186.99	3201.20	3515.65	1562.28	1586.83	2.71	0.145
15	-8.021	258.754	3177.72	3184.70	3536.92	1536.68	1609.84	-1.03	-1.251

[a]Data point not used in derive the equation, compound no. 10 is β-carboline, OBA is observed biological activity, i.e., the experimental activity of the compounds in terms of IC_{50} binding affinities to displace 50% of [^{3}H]Flunitrazepam on benzodiazepines receptor and PBA is the predicted biological activity as obtained by solving the MLR equation



Scheme 1. IR and UV-visible spectra of β-carboline (compd. no. 10) and its derivatives



Scheme 2. Effect of substituent's on HOMO-LUMO gap, λ_{max}, vibrational frequencies and experimental activity

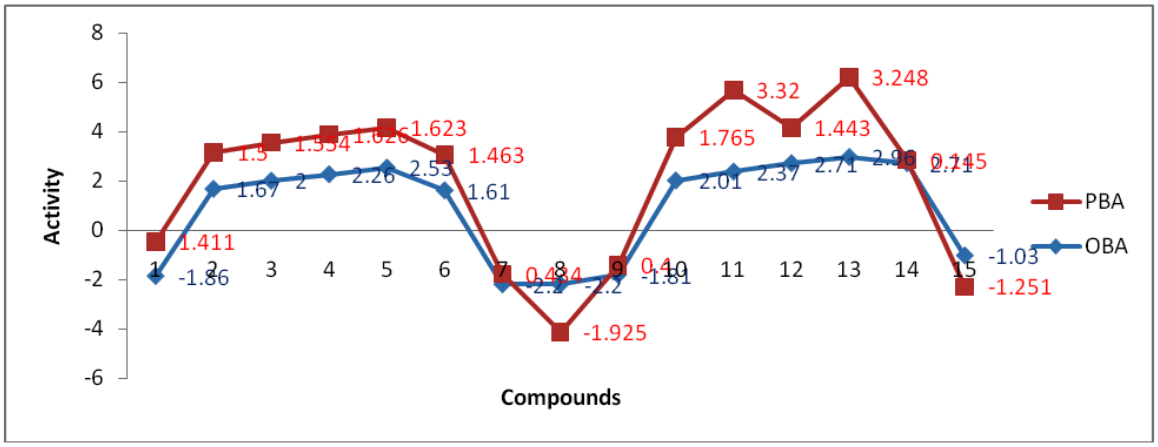


Figure 3. Trends of observed biological activity (OBA) and predicted bilogical activity (PBA)

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