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# Stability Index Based Quantitative Structure-Activity Relationship Study of β-Carbolines

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Quantitative structure-activity relationship (QSAR) study of derivatives of β-carboline has been made with the help of quantum chemical parameter: stability index (HOMO-LUMO gap). For QSAR study, the molecular modeling and geometry optimization for all the derivatives were carried out with CAChe Pro software and the HOMO/LUMO energies were evaluated by a MOPAC/PM3 wave function for the chemical sample, at a geometry determined by MOPAC using PM3 parameters. The study has shown that there is inverse relationship between stability index and observed biological activity *i.e.*, as stability index increases reactivity of the β-carboline derivatives decrease because a large HOMO-LUMO gap implies high stability for the molecule in the sense of its lower reactivity in chemical reactions. Thus stability index provides valuable information to explore the interaction of β-carboline with the receptor and to distinguish between the agonistic, antagonistic and inverse agonistic activities of the ligands.

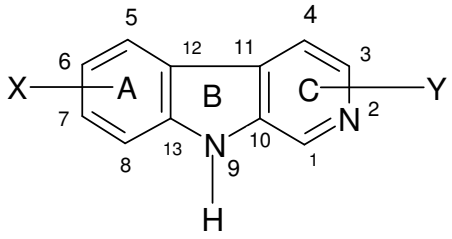
**Key Words: β-Carboline, HOMO-LUMO energies, PM3, BzR.**

## INTRODUCTION

In our recent communications, we have made QSAR (quantitative structure-activity relationship) study of β-carbolines using electronegativity and absolute hardness as reactive parameters[1]. The development of a QSAR model[2-5] requires these three components: first of all a data set that provides experimental measures of a biological activity for a group of chemicals, secondly molecular structure and/or property data (*i.e.* the descriptors, variables or predictors) for this group of chemicals and finally statistical methods, to find the relationship between these two data sets. In this paper quantitative structure-activity relationship between stability index (HOMO-LUMO) and biological activity have been studied. Energies of the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are very popular quantum chemical descriptors[6]. It has been shown[7] that these orbitals play a major role in governing many chemical reactions and determining electronic band gaps in solids. They are also responsible for the formation of many charge transfer complexes[8,9]. According to the frontier molecular orbital theory (FMO) of chemical reactivity, the formation of a transition state is due to an interaction between the frontier orbitals (HOMO and LUMO) of reacting species[10].

Thus, the treatment of orbitals is based on the general principles governing the nature of chemical reactions. The energy of the HOMO is directly related to the ionization potential and characterizes the susceptibility of the molecule toward attack by electrophiles. The energy of LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule toward attack by nucleophiles. Both the HOMO and the LUMO energies are important in radical reactions[11,12]. The concept of hard and soft nucleophiles and electrophiles has also been directly related to the relative energy of the HOMO/LUMO orbitals. Hard nucleophiles have a low energy HOMO while soft nucleophiles have a high energy HOMO[13]. The HOMO-LUMO gap, *i.e.*, the difference in energy between the HOMO and LUMO, is an important stability index[14]. A large HOMO-LUMO gap implies high stability for the molecule in the sense of its lower reactivity in chemical reactions. The HOMO-LUMO gap has also been used as an approximation to the lowest excitation energy of the molecule[15].

The general structure of β-carboline is based on the following parent skeleton structure, which has 13 sites (**Scheme-I**).




**Scheme-I**

β-Carbolines posssess a broad spectrum of pharmacological actions (as muscle relaxants) mediated *via* occupation of benzodiazepine receptor (BzR) in the central nervous system[16-18]. They follow an alternative alignment rule when they bind into the pharmacophore/receptor site of BzR. In search for receptor-specific ligands, several groups of compounds active for the GABAA/BzR have been synthesized based on pharmacophore receptor models for BzR sub types. All compounds that bind to benzodiazepines receptor should have certain common characteristics that allow for recognition by the receptor regardless of the type of activity.

## EXPERIMENTAL

The study materials of this paper are 43 derevaties of β-carboline and are presented in Tables 1-3. For QSAR study, the molecular modeling and geometry optimization[19-22] for all the derivatives were carried out with CAChe Pro software by applying semiempirical PM3[23] method using MOPAC 2002. The HOMO energy is the energy required to remove an electron from the highest occupied molecular orbital (HOMO), while LUMO energy is the energy gained when an electron is

added to the lowest unoccupied molecular orbital (LUMO). Thus HOMO and LUMO energies are the energies of frontier orbitals of the chemical sample and were generated by a MOPAC/PM3 wave function for the chemical sample, at a geometry determined by MOPAC using PM3 parameters.

## RESULTS AND DISCUSSION

The biological activity of β-carboline derivatives has been measured by three different methods: $IC_{50}$ inhibition of [$^3$H]diazepam[24,25], $IC_{50}$ antagonistic activity[26-28] and $IC_{50}$ binding affinities to displace 50 % of [$^3$H]flunitrazepam on benzodiazepines receptor[29]. The derivatives accordingly have been studied in three different sets and are given in Tables 1-3. The HOMO-LUMO gap, *i.e.*, the difference in energy between the HOMO and LUMO, is an important stability index. A large HOMO-LUMO gap implies high stability for the molecule in the sense of its lower reactivity in chemical reactions. The HOMO-LUMO gap has also been used as an approximation to the lowest excitation energy of the molecule. This concept, however, neglects the electronic reorganization in the excited state and therefore may often lead to conceptually incorrect results. The values of reactivity parameters of the compounds of the Tables 1-3 are presented in Tables 4-6, respectively. The structure activity relationship study of each set has been discussed as below:

TABLE-1
FIRST SET OF β-CARBOLINE DERIVATIVES WITH THEIR OBSERVED BIOLOGICAL ACTIVITY IN TERMS OF $IC_{50}$ INHIBITION ACTIVITY (IA) OF [$^3$H]DIAZEPAM BINDING TO THE BENZODIAZEPINE RECEPTOR[14,15]

| S. No. | X | Y | IA |
|---|---|---|---|
| 1 | 6-H | 3-H | 5.79 |
| 2 | 6-H | 3-OH | 5.40 |
| 3 | 6-H | 3-OMe | 6.91 |
| 4 | 6-H | 3-OEt | 7.62 |
| 5 | 6-H | 3-$OC_3H_7$ | 7.96 |
| 6 | 6-H | 3-Cl | 7.35 |
| 7 | 6-H | 3-$NO_2$ | 6.90 |
| 8 | 6-H | 3-$NH_2$ | 4.60 |
| 9 | 6-H | 3-NCS | 8.10 |
| 10 | 6-H | 3-COOMe, | 8.30 |
| 11 | 6-OH | 3-COOEt, 4-$CH_2OMe$ | 9.05 |
| 12 | 6-OMe | 3-COOEt, 4-$CH_2OMe$ | 9.30 |
| 13 | 6-OEt | 3-COOEt, 4-$CH_2OMe$ | 8.64 |
| 14 | 6-$OCH_2C_6H_5$ | 3-COOEt | 8.05 |
| 15 | 6-$OCH_2C_6H_5$ | 3-COOEt, 4-$C_2H_5$ | 7.66 |
| 16 | 6-$OCH_2C_6H_5$ | 3-COOEt, 4-$CH_2OMe$ | 9.00 |

**First set:** The activity of the first set has been measured in terms of 50 % inhibition of [$^3$H]diazepam binding to benzodiazepines receptor ($IC_{50}$)[24,25]. The values of $IC_{50}$ along with reactivity indices (εHOMO, εLUMO and their difference-stability

TABLE-2
SECOND SET OF β-CARBOLINE DERIVATIVES WITH THEIR OBSERVED BIOLOGICAL ACTIVITY IN TERMS OF $IC_{50}$ ANTAGONISTIC ACTIVITY (AA) ON BENZODIAZEPINE RECEPTOR[16-18]

| S. No. | X | Y | IA |
|---|---|---|---|
| 1 | H | 3-H | 5.790 |
| 2 | H | 3-$OCH_3$ | 6.910 |
| 3 | H | 3-OEt | 7.620 |
| 4 | H | 3-$OC_3H_7$ | 7.960 |
| 5 | H | 3-$OCHMe_2$ | 6.290 |
| 6 | H | 3-$OC_4H_9$ | 7.010 |
| 7 | H | 3-$C_4H_9$ | 6.640 |
| 8 | H | 3-Cl | 7.350 |
| 9 | H | 3-$NO_2$ | 6.900 |
| 10 | H | 3-COOMe | 8.300 |
| 11 | H | 3-COOEt | 8.300 |
| 12 | H | 3-$COOCMe_3$ | 8.000 |
| 13 | H | 3-$COCH_3C_4H_9$ | 7.640 |

TABLE-3
THIRD SET OF β-CAROLINE DERIVATIVES WITH THEIR OBSERVED BIOLOGICAL ACTIVITY IN TERMS OF $IC_{50}$ BINDING AFFINITIES (BA) TO DISPLACE 50 % OF [$^3$H]FLUNITRAZEPAM ON BENZODIAZEPINES RECEPTOR[19]

| S. No. | X | Y | IA |
|---|---|---|---|
| 1 | H | 1-$C_2H_5$ | -1.860 |
| 2 | H | 3-$CH_2OH$ | 1.670 |
| 3 | H | 3-$COOCH_3$ | 2.000 |
| 4 | H | 3$COOC_2H_5$ | 2.260 |
| 5 | H | 3-$COOC_3H_7$ | 2.530 |
| 6 | H | 3-$COONHCH_3$ | 1.610 |
| 7 | 7-OH | 1-$CH_3$ | -2.200 |
| 8 | 7- $CH_3$ | 1-OH | -2.200 |
| 9 | 7-$OCH_3$ | 1-$CH_3$ | -1.810 |
| 10 | 7-$CH_3$ | 1-$OCH_3$ | -1.810 |
| 11 | 6,7-di-$OCH_3$ | 3-$COOCH_3$, 4-$C_2H_5$ | 2.370 |
| 12 | 5-$OCH_2C_6H_5$ | 3-$COOCH_3$, 4-$CH_2OCH_3$ | 2.710 |
| 13 | 5-$OCH(CH_3)_2$ | 3-$COOCH_3$,4-$CH_3$ | 2.960 |
| 14 | 6-$OCH_2C_6H_5$ | 3-$COOC_2H_5$, 4-$CH_2OCH_3$ | 2.710 |

index) are placed in Table-4. A close look of the table indicates following points. Compared to compound-1, the compound-2 has less inhibition activity *i.e.* addition of a 3-hydroxy group in compound-2 both inhibition of [$^3$H]diazepam binding to benzodiazepines receptor and stability index decrease and becomes 5.40 from 5.79, -7.774 from -7.714, respectively. On addition of a 3-methoxy group in compound-1 (*i.e.* compound-3) the inhibition activity increases and becomes 6.91 from 5.40, while stability index decreases and becomes -7.772 from -7.774. On addition of

TABLE-4
RELATIONSHIP BETWEEN STABILITY INDEX
AND BIOLOGICAL ACTIVITY OF FIRST SET

| S. No. | εHOMO | εLUMO | Stability index | IA |
|---|---|---|---|---|
| 1 | –7.863 | –0.149 | –7.714 | 5.79 |
| 2 | –8.011 | –0.237 | –7.774 | 5.40 |
| 3 | –8.011 | –0.239 | –7.772 | 6.91 |
| 4 | –8.007 | –0.232 | –7.775 | 7.62 |
| 5 | –7.899 | –0.210 | –7.689 | 7.96 |
| 6 | –8.200 | –0.449 | –7.751 | 7.35 |
| 7 | –8.512 | –1.273 | –7.239 | 6.90 |
| 8 | –7.877 | –0.176 | –7.701 | 4.60 |
| 9 | –8.294 | –1.068 | –7.226 | 8.10 |
| 10 | –8.116 | –0.342 | –7.774 | 8.30 |
| 11 | –8.182 | –0.433 | –7.749 | 9.05 |
| 12 | –8.158 | –0.394 | –7.764 | 9.30 |
| 13 | –8.146 | –0.383 | –7.763 | 8.64 |
| 14 | –8.069 | –0.341 | –7.728 | 8.05 |
| 15 | –8.116 | –0.364 | –7.752 | 7.66 |
| 16 | –8.156 | –0.392 | –7.764 | 9.00 |

TABLE-5
RELATIONSHIP BETWEEN STABILITY INDEX
AND BIOLOGICAL ACTIVITY OF SECOND SET

| S. No. | εHOMO | εLUMO | Stability index | IA |
|---|---|---|---|---|
| 1 | –8.422 | –0.470 | –7.952 | 5.790 |
| 2 | –8.500 | –0.619 | –7.881 | 6.910 |
| 3 | –8.200 | –0.494 | –7.706 | 7.620 |
| 4 | –8.478 | –0.607 | –7.871 | 7.960 |
| 5 | –8.462 | –0.599 | –7.863 | 6.290 |
| 6 | –8.479 | –0.608 | –7.871 | 7.010 |
| 7 | –8.312 | –0.419 | –7.893 | 6.640 |
| 8 | –8.437 | –0.616 | –7.821 | 7.350 |
| 9 | –8.836 | –1.836 | –7.000 | 6.900 |
| 10 | –8.883 | –0.783 | –8.100 | 8.300 |
| 11 | –8.876 | –0.773 | –8.103 | 8.300 |
| 12 | –8.842 | –0.739 | –8.103 | 8.000 |
| 13 | –8.672 | –0.580 | –8.092 | 7.640 |

2-ethoxy (*i.e.* compound-4), the inhibition activity increases and becomes 7.62 from 5.79, while stability index decreases and becomes -7.775 from -7.714. On addition of a 3-*n*-propoxy group in compound-1 (*i.e.* compound-5) both inhibition activity and stability index increase and become 7.96 from 5.40 and -7.689 from -7.714, respectively. On addition of a 3-chloro group in compound-1 (*i.e.* compound-6) the inhibition activity increases and becomes 7.35 from 5.40, while stability index decreases and becomes -7.751 from -7.714. On addition of a 3-nitro group in compound-1

TABLE-6
RELATIONSHIP BETWEEN STABILITY INDEX
AND BIOLOGICAL ACTIVITY OF THIRD SET

| S. No. | εHOMO | εLUMO | Stability index | IA |
|---|---|---|---|---|
| 1 | -8.621 | -0.552 | -8.069 | -1.860 |
| 2 | -8.302 | -0.393 | -7.909 | 1.670 |
| 3 | -8.883 | -0.783 | -8.100 | 2.000 |
| 4 | -8.870 | -0.768 | -8.102 | 2.260 |
| 5 | -8.748 | -0.697 | -8.051 | 2.530 |
| 6 | -8.870 | -0.767 | -8.103 | 1.610 |
| 7 | -8.417 | -0.428 | -7.749 | -2.200 |
| 8 | -8.219 | -0.470 | -7.769 | -2.200 |
| 9 | -8.381 | -0.396 | -7.989 | -1.810 |
| 10 | -8.187 | -0.418 | -7.985 | -1.810 |
| 11 | -8.541 | -0.717 | -7.824 | 2.370 |
| 12 | -8.785 | -0.826 | -7.959 | 2.710 |
| 13 | -8.831 | -0.844 | -7.987 | 2.960 |
| 14 | -8.598 | -0.798 | -7.800 | 2.710 |

(*i.e.* compound-7) both inhibition activity and stability index increase and become 6.90 from 5.40 and -7.239 from -7.714, respectively. On addition of a 3-amino group in compound-1 (*i.e.* compound-8) the inhibition activity decreases and becomes 4.60 from 5.40, while stability index increases and becomes -7.701 from -7.714. On addition of a 3-thiocyanate group in compound-1 (*i.e.* compound-9) both inhibition activity and stability index increase and become 8.10 from 5.40 and -7.226 from -7.714, respectively. On addition of a 3-ethylformate group in compound-1 (*i.e.* compound-10) the inhibition activity increases and becomes 8.30 from 5.40, while stability index decreases and becomes -7.774 from -7.714. On addition of a 3-ethylformate, 4-methoxymethyl and 6-hydroxyl group in compound-1 (*i.e.* compound-11) the inhibition activity increases and becomes 9.05 from 5.40, while stability index decreases and becomes -7.749 from -7.714. On addition of a 3-ethylformate, 4-methoxymethyl and 6-methoxy group in compound-1 (*i.e.* compound-12) the inhibition activity increases and becomes 9.30 from 5.40, while stability index decreases and becomes -7.764 from -7.714. On addition of a 3-ethylformate, 4-methoxymethyl and 6-methoxy group in compound-1 (*i.e.* compound-12) the inhibition activity increases and becomes 9.30 from 5.40, while stability index decreases and becomes -7.764 from -7.714. On addition of a 3-ethylformate, 4-methoxymethyl and 6-ethoxy group in compound-1 (*i.e.* compound-13) the inhibition activity increases and becomes 8.64 from 5.40, while stability index decreases and becomes -7.763 from -7.714. On addition of a 3-ethylformate and 6-benzyloxy group in compound-1 (*i.e.* compound-14) the inhibition activity increases and becomes 8.05 from 5.40, while stability index decreases and becomes -7.728 from -7.714. On addition of a 3-ethylformate, 4-ethyl and 6-benzyloxy group in compound-1 (*i.e.* compound-15) the inhibition activity increases and becomes 7.66 from 5.40, while stability index decreases and

becomes -7.752 from -7.714. On addition of a 3-ethylformate, 4-methoxymethyl and 6-benzyloxy group in compound-1 (*i.e.* compound-16) the inhibition activity increases and becomes 9.00 from 5.40, while stability index decreases and becomes -7.764 from -7.714. The above discussion indicates that substitutions on site-2 are responsible for high inhibition activity. The discussion also indicates that there is inverse relation between stability index and inhibition activity except compounds 2, 5, 7 and 9. So on this basis an assumption arises that stability index is inversely proportional to inhibition activity (Fig. 1).

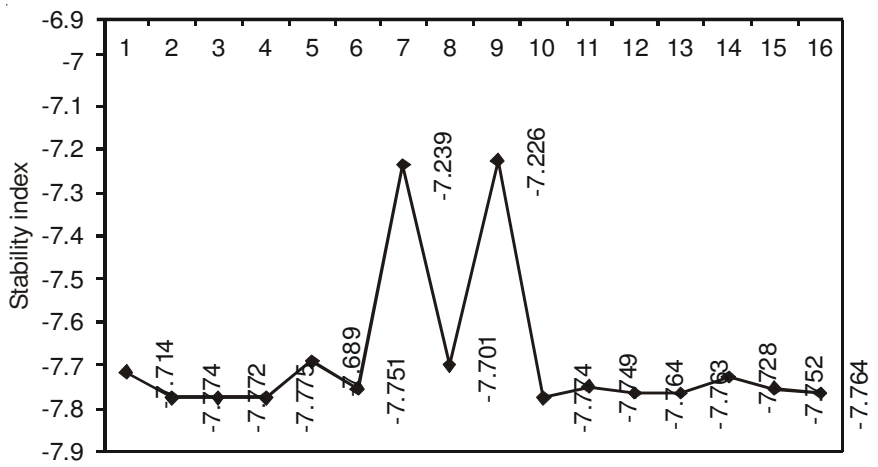



Fig. 1. The stability index of first set

**Second set:** The activity of the second set has been measured in terms of $IC_{50}$ antagonistic activity on benzodiazepine receptor[26-28]. The values of antagonistic activity along with reactivity indices (εHOMO, εLUMO and their difference-stability index) are given in Table-5. A close look of the Table-5 indicates following points. Compared to compound-1, the compound-2 has more inhibition activity *i.e.* addition of a 3-methoxy group in compound-2 antagonistic activity on benzodiazepine receptor increases and becomes 6.91 from 5.79, stability index increases and becomes -7.881 from -7.952. On addition of a 3-ethoxy group in compound-1 (*i.e.* compound-3) the inhibition activity increases and becomes 7.620 from 5.79, while stability index increases and becomes -7.772 from -7.952. On addition of 3-*n*-propoxy (*i.e.* compound-4), the inhibition activity increases and becomes 7.960 from 5.79, while stability index increases and becomes -7.871 from -7.952. On addition of 3-*iso*-propoxy group in compound-1 (*i.e.* compound-5) the inhibition activity increases and becomes 6.290 from 5.79, while stability index decreases and becomes -7.863 from -7.714. On addition of a 3-*n*-butyloxy group in compound-1 (*i.e.* compound-6) the inhibition activity increases and becomes 7.010 from 5.79, while stability index increases and becomes -7.871 from -7.952. On addition of a 3-butyl group in com-

pound-1 (*i.e.* compound-7) the inhibition activity increases and becomes 6.640 from 5.79, while stability index increases and becomes -7.893 from -7.952. On addition of 3-chloro group in compound-1 (*i.e.* compound-8) the inhibition activity decreases and becomes 7.350 from 5.79, while stability index increases and becomes -7.821 from -7.952. On addition of a 3-nitro group in compound-1 (*i.e.* compound-9) the inhibition activity increases and becomes 6.900 from 5.79, while stability index increases and becomes -7.000 from -7.952. On addition of a 2-methylformate group in compound-1 (*i.e.* compound-10) the inhibition activity increases and becomes 8.300 from 5.79, while stability index decreases and becomes -8.100 from -7.952. On addition of a 3-ethylformate group in compound-1 (*i.e.* compound-11) the inhibition activity increases and becomes 8.300 from 5.79, while stability index decreases and becomes -8.103 from -7.952. On addition of a 3-*tert*-butylformate group in compound-1 (*i.e.* compound-12) the inhibition activity increases and becomes 8.000 from 5.79, while stability index decreases and becomes -8.103 from -7.952. On addition of a 3-$COCH_2C_4H_9$ group in compound-1 (*i.e.* compound-13) the inhibition activity increases and becomes 7.640 from 5.79, while stability index decreases and becomes -8.092 from -7.952. The above discussion indicates that substitutions on site-2 are responsible for high antagonistic activity. The discussion also indicates that there is inverse relation between stability index and inhibition activity except compounds 10, 11, 12 and 13. So on this basis an assumption arises that stability index is inversely proportional to antagonistic activity (Fig. 2).

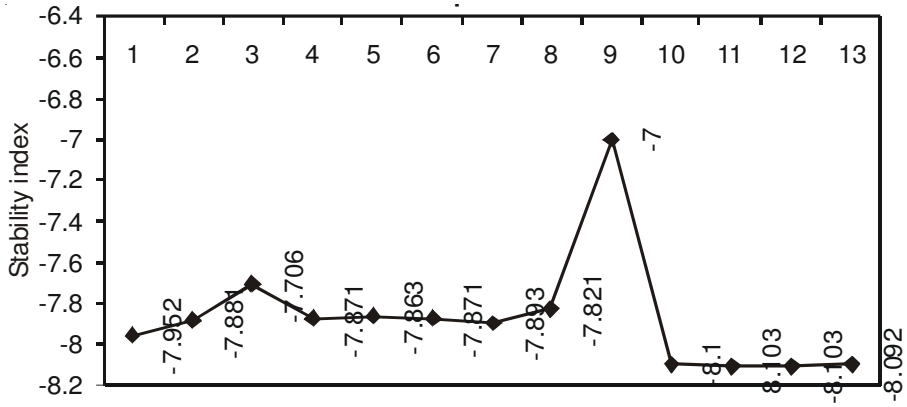



Fig. 2. The stability index of second set

**Third set:** The activity of the third set has been measured in terms of $IC_{50}$ binding affinities to displace 50 % of [$^3$H]flunitrazepam on benzodiazepines receptor[29]. The values of binding affinities along with reactivity indices (εHOMO, εLUMO and their difference-stability index) are placed in Table-6. A close look of the table indicates following points. Compared to compound-2, the compound-3 has more $IC_{50}$ binding affinity to displace 50 % of [$^3$H]flunitrazepam on benzodiazepines

receptor *i.e.* replacement of 3-methyl alcohol group by 3-methylformate group in compound-2, the binding affinity increases and becomes 2.000 from 1.670, while stability index decreases and becomes -8.100 from -7.909. On replacement of 3-methyl alcohol group by 3-ethylformate group in compound-2 (*i.e.* compound-4) the binding affinity increases and becomes 2.260 from 1.670, while stability index decreases and becomes -8.102 from -7.774. On replacement of 3-methylalcohol group by 3-*n*-propylformate group in compound-2 (*i.e.* compound-5), the binding affinity increases and becomes 2.530 from 1.670, while stability index decreases and becomes -8.051 from -7.909. On replacement of 3-methylalcohol group by 3-(N-methyl)formamidyl group in compound-2 (*i.e.* compound-6) both binding affinity and stability index decrease and becomes 1.610 from 1.670 and -8.103 from -7.909, respectively. On removal of 3-methylalcohol group and addition of 1-ethyl group in compound-2 (*i.e.* compound-1), both binding affinity and stability index decrease and becomes -1.860 from 1.670 and -8.069 from -7.909, respectively. On removal of 3-methylalcohol group and addition of 7-hydroxy and 1-methyl group in compound-2 (*i.e.* compound-7), the binding affinity decreases and becomes -2.200 from 1.670, while stability index increases and becomes -7.749 from -7.909. On removal of 3-methylalcohol group and addition of 7-methyl and 1-hydroxy group in compound-2 (*i.e.* compound-8), the binding affinity decreases and becomes -2.200 from 1.670, while stability index increases and becomes -7.769 from -7.909. On removal of 3-methylalcohol group and addition of 7-methoxy and 1-methyl group in compound-2 (*i.e.* compound-9), both binding affinity and stability index decrease and becomes -1.810 from 1.670 and -7.985 from -7.909, respectively. On removal of 3-methylalcohol group and addition of 7- methyl and 1-methoxy group in compound-2 (*i.e.* compound-10), both binding affinity and stability index decrease and becomes -1.810 from 1.670 and -8.146 from -7.909, respectively. On removal of 3-methylalcohol group and addition of 6,7-dimethoxy, 3-methylformate and 4-ethyl group in compound-2 (*i.e.* compound-11), the binding affinity increases and becomes 2.370 from 1.670, while stability index decreases and becomes -7.824 from -7.909. On removal of 3-methylalcohol group and addition of 5-benzyloxy, 3-methylformate and 4-methoxymethyl group in compound-2 (*i.e.* compound-12), the binding affinity increases and becomes 2.710 from 1.670, while stability index decreases and becomes -7.959 from -7.909. On removal of 3-methylalcohol group and addition of 5-*iso*-propoxy, 3-methylformate and 4-methyl group in compound-2 (*i.e.* compound-13), the binding affinity increases and becomes 2.960 from 1.670, while stability index decreases and becomes -7.987 from -7.909. On removal of 3-methylalcohol group and addition of 6-benzyloxy, 3-ethylformate and 4-methoxymethyl group in compound-2 (*i.e.* compound-14), both binding affinity and stability index increase and becomes 2.710 from 1.670 and -7.800 from -7.909, respectively. The above discussion indicates that there is inverse relation between stability index and binding affinity except compound-1, 6, 9, 10 and 14. So on this basis an assumption arises that stability index is inversely proportional to binding affinity (Fig. 3).

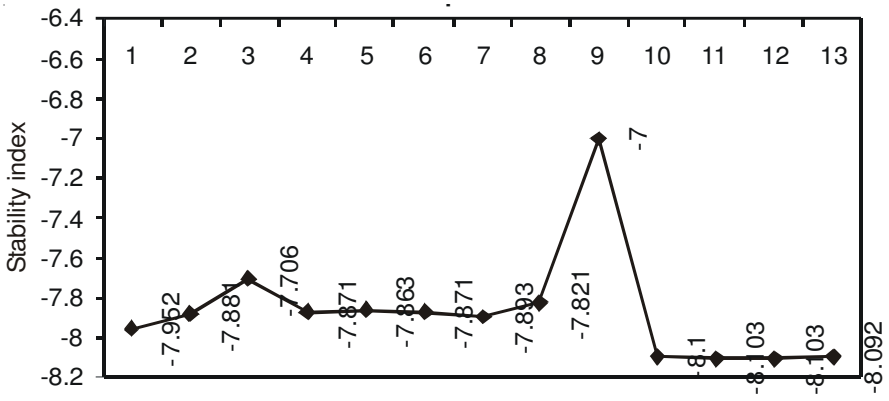



Fig. 3. The stability index of third set

The study has shown that there is inverse relationship between stability index and observed biological activity *i.e.*, as stability index increases reactivity of the β-carboline derivatives decrease because a large HOMO-LUMO gap implies high stability for the molecule in the sense of its lower reactivity in chemical reactions. Thus, stability index provides valuable information to explore the interaction of β-carboline with the receptor and to distinguish between the agonistic, antagonistic and inverse agonistic activities of the ligands. On the basis of this one can build up theoretical background for approximate activity of any desired compound before its synthesis in laboratory.

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