Original Article

In Silico Estrogen Receptor Activity Evaluation of Some *β*-Carboline Derivatives Through Molecular Docking Approach and Target Prediction by ADME Study

Bapusaheb S. Wadje[a,b,*] |Pawar Devidas[c] |Swapnil Navhate[a] | Vijay N. Bhosale[a]

[a]*Department Of Chemistry, Yeshwant Mahavidyalaya, Nanded- 431602 (MS); affiliated to SRTM University Nnanded, India*
[b]*Department of Chemistry, Sambhajirao Kendre Mahavidyalay Jalkot tq. Jalkot Dist. Latur, India*
[c]*Gramin (Art's, commerce and science) Mahavidyalaya, Vasant Nagar (Kotgyal), TQ.Mukhed, Dist.Nanded- 431715, India*

Use your device to scan and read the article online

Citation Bapusaheb S. Wadje, Pawar Devidas, Swapnil Navhate, Vijay N. Bhosale. ***In Silico* Estrogen Receptor Activity Evaluation of Some *β*-Carboline Derivatives Through Molecular Docking Approach and Target Prediction by ADME Study**. *J. Appl. Organomet. Chem.*, **2023**, *3*(1), 28-38.

https://doi.org/10.22034/jaoc.2023.356944.1060

Article info:
Received: 2022-08-20
Accepted: 2022-09-17
Available Online: 2022-09-30
ID: JAOC-2208-1060
Checked for Plagiarism: Yes
Language Editor checked: Yes

Keywords:
Insilco; CADD; b-carboline; Estrogen Receptor; Swiss target prediction; ADME.

ABSTRACT

A series of *β*-carboline derivatives have been modified at C-1 sites of the aryl ring and tested for the Insilco Estrogen Receptor inhibitary study. All of the designed molecules show the excellent bonding score with 5ACC Estrogen Receptor protein. The position of proposed ligand BC-6, BC-12 in the binding site of protein is superimposable with the native ligand and indicates the hydrogen bonding with the LEU: 346 amino acid residues. The ADME studies reveal that groups BC-6 and BC-12 show good human intestinal CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP3A4 inhibitor, and CYP3A4 inhibitor activity with Log Kp (skin permeation)-5.43 cm/s, while *ramachandran plot* for BC-6 indicate, molecules shows the 100% favourable region in the pocket of enzyme 5ACC, while the BC-6 and BC-12 can cross the BBB barrier. This study indicates that from all the synthesized molecules, the scaffolds BC-6 and BC-12 illustrate the excellent activity.

Introduction

Naturally, tricyclic alkaloids is an β-carboline with a pyridoindoles heterocyclic scaffolds presented in the broad range of natural products and bioactive molecules [1]. The classification of *β*-carboline is based on the nitrogen position at *α*, *β*, *γ*, and *δ*- site of TH*β*C. The tricyclic pyrido [3,4-*b*] indole ring system [2], presented in a broad range natural products isolated from natural sources like marine sponge [3], territorial plants [4], fast food [5], and mammals [6]. *β*-carbolines are named based on the saturation percentage of the pyridine ring, compounds with fully unsaturated aromatic pyridine ring are named as *β*-carbolines (*β*-Cs), partly unsaturated compounds, and fully saturated compounds are known as dihydro-*β*-carbolines (DH *β*-Cs)

***Corresponding Author: Bapusaheb S. Wadje** (wadjebapu2014@gmail.com)

and tetrahydro-*β*-carbolines (TH *β*-Cs), respectively [7]. The product of Pictet-Spengler reaction tetrahydro-*β*-carboline (tryptoline) moiety found in the numerous biologically important synthetic and natural compounds. The TH*β*-Cs have been known to have a broad range of medicinal activities such as anticonvulsant, anticancer, antiviral, antifungal, and anticancer activities, and are of high significance in the synthesis of these compounds (Figure 1) [8-15]. Molecular docking with CADD methods are used to screen different possible compounds, searching for new compounds with desired binding application or testing a range of tempering of an existing compound. The presence of a large amount of pharmaceutical data available [16], the computer-aided analysis of molecular interactions becomes more realistic in addition to which as of now the CADD is an study of binding study which can easily predict the biochemical mechanism of the designed molecules for the drug development and the docking results also give the desire conformation of the molecule in the binding pocket of the enzyme [17-18].

In this study, molecular docking is performed between receptor, i.e. protein molecule and ligand, i.e. novel *β*-carboline molecules has been studies. The novel derivatives of *β*-carboline which belong to an important group of heterocyclic compounds, the modification of the *β*-carboline at the C-1, C-2, C- -C-4, C-7, C-8, and C-9 sites could enhance the anticancer activity of the proposed molecules [19-20]. In the literature, there are broad range of natural products that are isolated worldwide and have the potential application which can be the good target for the anticancer activity (Figure 1) [20-24].

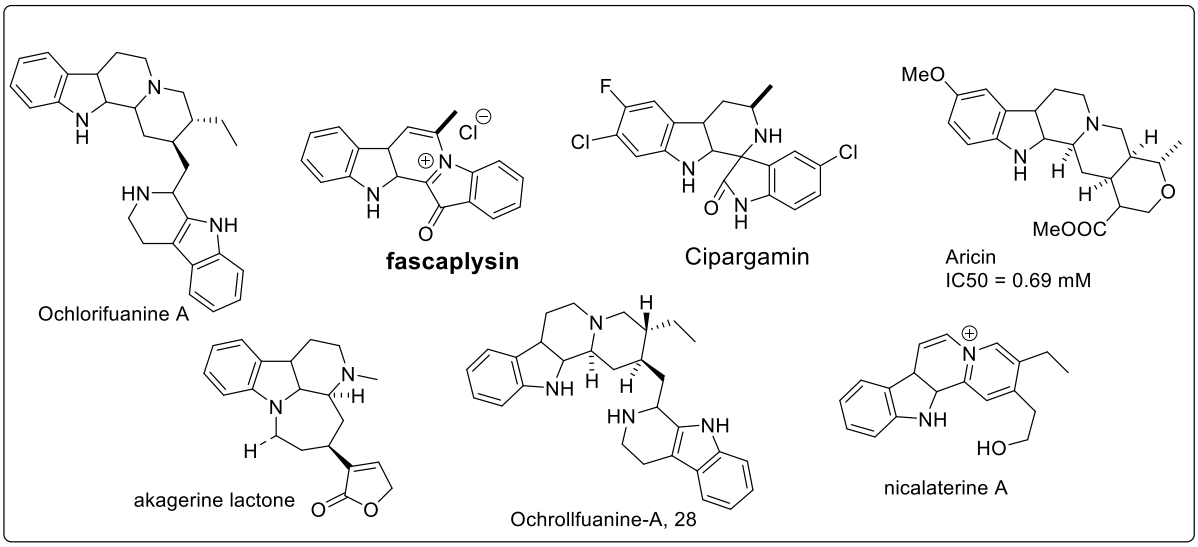


Figure 1. Bioactive *β*-carboline

The *β*-carboline, as the important class of bioactive molecules, has diverse biological activities so that it attracted great attention due to the diversity of their biological effects such as anti-diarrheal, anti-diabetic, anti-histaminic, cardio-protective, anti-ischemic, cyclooxygenases inhibitory, anti-platelet activating factor, antimicrobial, and anticancer [25-26].

Experimental

Docking studies

Protein selection

According to the SAR study, through the modification at C-1, C-3 N-9 position will enhance the anticancer activity. As per literature search, some *β*-carboline compounds are specific inhibitors of selective Estrogen Receptor Down-regulator. Based on the literature survey and structural modification, we have selected PDB: 5ACC protein for the docking analysis.

Protein preparation

The three-dimensional crystal structure of crystal structure of PDB: 5ACC protein was retrieved from the Protein Data Bank (http://www.rscb.org/pdb) for the molecular docking study (Figure 2).

Active site identification of PDB: 5ACC inhibitor

The catalytic sites of PDB: 5ACC inhibitor along with the area and volume of binding pocket was carried out with Computed Atlas of Surface Topography of Proteins (Castro) program (http: //cast.engr.uic.edu) (Binkowski TA *et al.,* 2003). The protein has ASP:351, PRO:535, HIS:524, THR:347, LEU:525, GLY:521, ILE:424, LEU:428, MET:421, PHE:404, LEU:387, LEU:349, ALA:350, GLU:353, VAL:534, and LEU-346 amino acids.

Validation of Glide docking

The validation of "Auto dock" docking protocol was performed by re-docking the ligand co-crystalline with PDB: 5ACC. The validation result shows the similar result with the original, this indicate the designed molecule could be a potential candidate for the anti-cancer drug discovery.

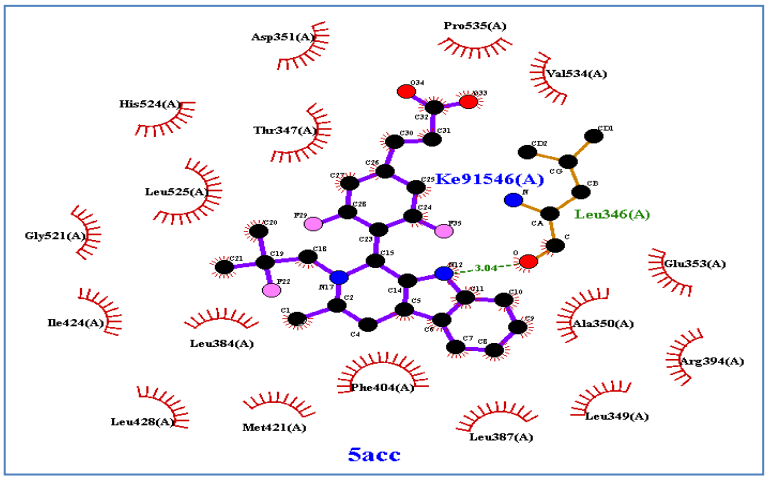


Figure 2. The 2D view of the native ligand shows the binding interaction with desire amino acid residues.

Docking protocol

The structures of the examined compounds were drawn by using Chem Draw Ultra 7.0 and Lig-Plus which were later saved by using PDB formats. All the 3D structure of the molecules was drawn in the Chem Draw pro16.0 and saved in the PDB format. The protein preparation was performed with the Pymol software, all the unwanted water molecules was removed, co-crystalline ligand also remove and macromolecules was saved in the pdb format. The configuration file was created containing the receptor name, ligand name, output file name, X, Y, and Z coordinates of the grid box, and also the size X, Y, and Z of the

grid box. Furthermore, the docking of proposed ligand was docked with the selected protein molecule with Auto Dock Vina software. The result output in a 3D and 2D has been performed with Pymol and Ligplus Software [27-29].

Results and Discussion

Molecular docking

The molecular docking for the synthesized/selected molecules has been performed with the estrogens receptor protein Pdb:5ACC [30]. From the docking results, all the molecules display the desired minimum energy score with Auto Dock Software. The ligand were well accommodated in the protein socket and display an excellent hydrogen bonding with the desire amino acid in the active position of the 5ACC protein.

The ligand BC-12 display Vander Waals force of interaction, alkyl Pi- interaction with the amino acids residues HIS:524, MET:421, ILE:424, LEU:384, LEU:428, MET:343, THR:347, MET:528, GLU:353, ARG:394, LEU:525, PHE:404, MET:388, LEU:391, LEU:349, and ALA:350, along with the BC-12 display hydrogen bonding interaction with the LEU:346 amino acid residues, which is similar to the native ligand (Figure 2). The ligand BC-6 also display very good binding interaction and the excellent ramachandran plod with the BC-6 ligand and docked macromolecules (Figure 7). Likewise, the ligand BC-6 display hydrogen bond with the THR: 347 amino acid residues and Vander Waals interaction with LEU: 346 amino acid residues, this indicates that out of all the synthesized/proposed b-carboline derivatives, the ligand BC-6 and BC-12 could be the potential candidate for the drug discovery (Figure 3).

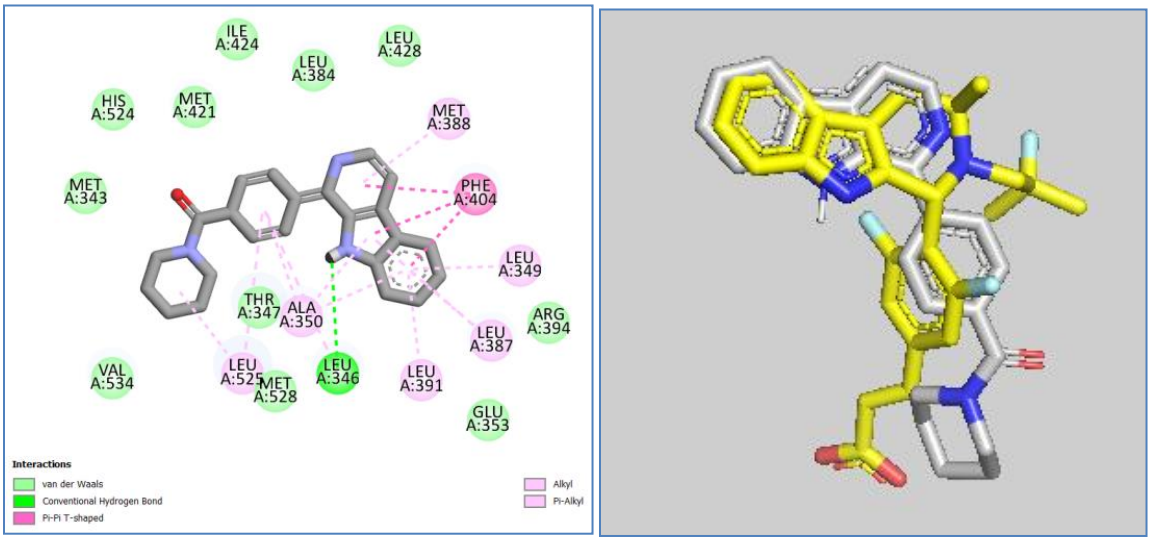
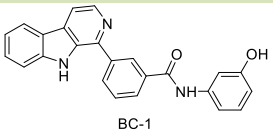
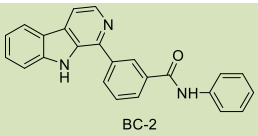
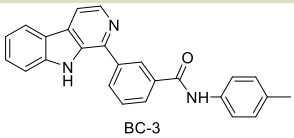
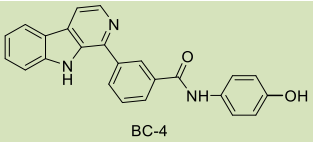
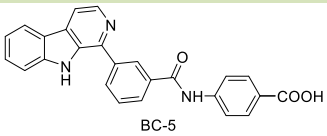
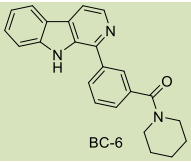
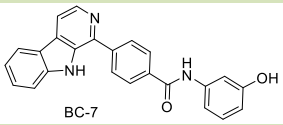
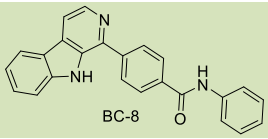
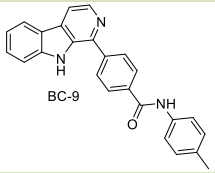
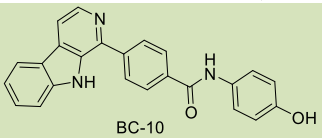
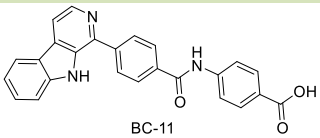
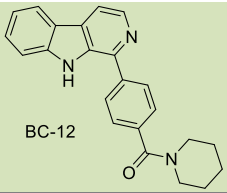


Figure 2. a) 2D view of compound BC-12, b) Validation 3D view of native ligand (yellow) with BC-12 ligand (silver)

Table 1. Physicochemical properties

Sr./No.	Structure of molecules	Affinity (kcal/mol)	No. of Hydrogen bonds	Van der Waals/alkyl, Pi-Pi interaction
1	 BC-1	-9.2	1 LEU:387	GLU:353, ARG:394, TRP:383, LEU:525, LEU:384, MET:421, ASP:351, PHE:404, LEU:391, MET:388, ALA:350 ILE:424, LEU:428, LEU:346, and LEU:349.
2	 BC-2	-9.2	1 MET:421	LEU:384, LEU:391, MET:388, LEU:387, ALA:350, ILE:424, LEU:428, LEU:346, LEU:349, ASP:351, and PHE:404.
3	 BC-3	-9.2	0	LEU:384, LEU:391, MET:388, LEU:387, LEU:346, LEU:349, MET:421, ASP:351, ALA:350 ILE:424, LEU:428, and PHE:404.
4	 BC-4	-8.9	1 LEU:402	ILE:424, LEU:428, LEU:384, MET:421, ASP:351, LEU:346, LEU:349, LEU:391, MET:388, LEU:387, ALA:350, GLU:353, ARG:394, TRP:383, LEU:525, PHE:404.
5	 BC-5	-9.2	1 LEU:387	ILE:424, LEU:391, MET:388, ARG:394, TRP:383, LEU:525, PHE:404, LEU:428, LEU:384, MET:421, ALA:350, GLU:353, ASP:351, LEU:346, and LEU:349.
6	 BC-6	-10.8	1 THR:347	ILE:424, LEU:428, LEU:384, MET:421, ASP:351, LEU:346, LEU:349, GLU:353, ARG:394, TRP:383, LEU:525, PHE:404, LEU:391, MET:388, LEU:387, and ALA:350.
7	 BC-7	-9.3	1	MET:421, ASP:351, ALA:350 ILE:424, LEU:428, PHE:404, LEU:384, LEU:391, MET:388, LEU:387, LEU:346, LEU:349.
8	 BC-8	-10.7	1	LEU:346, LEU:349, MET:421, ASP:351, LEU:384, LEU:391, MET:388, LEU:387, ALA:350 ILE:424, LEU:428, PHE:404.
9	 BC-9	-9.3	0	HIS:524, MET:528, GLU:353, ARG:394, LEU:525, PHE:404, MET:421, ILE:424, LEU:428, MET:343, LEU:384, and MET:388.
10	 BC-10	-9.1	1 THR:347,	PHE:425, PHE:404, MET:528, THR:347, SP:351, TRP:383, LEU:384, LEU:428, LEU:391, LEU:525, LEU:387, A, and MET:388.
11	 BC-11	-8.2	2 ILE:424,	PHE:425, PHE:404, MET:528, THR:347, LEU:525, LEU:387, ASP:351, TRP:383, LEU:384, LEU:428, LEU:391, and MET:388.

12	 BC-12	-10.5	1 **LEU:346**	HIS:524, MET:421, ILE:424, LEU:384, LEU:428, MET:343, THR:347, MET:528, GLU:353, ARG:394, LEU:525, PHE:404, MET:388, LEU:391, LEU:349, and ALA:350.

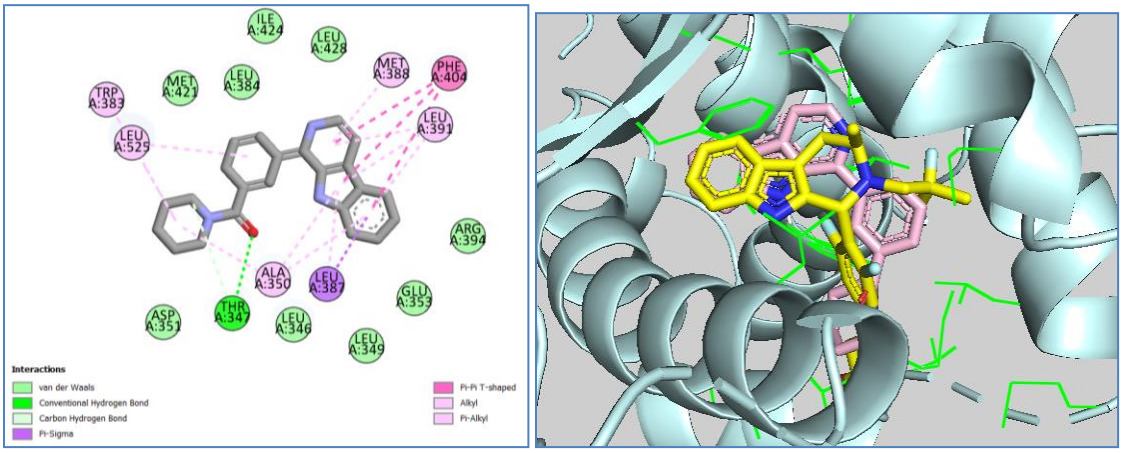


Figure 3. (a,b) The 2D view of molecule BC-6 in the active sites of 5ACC enzyme

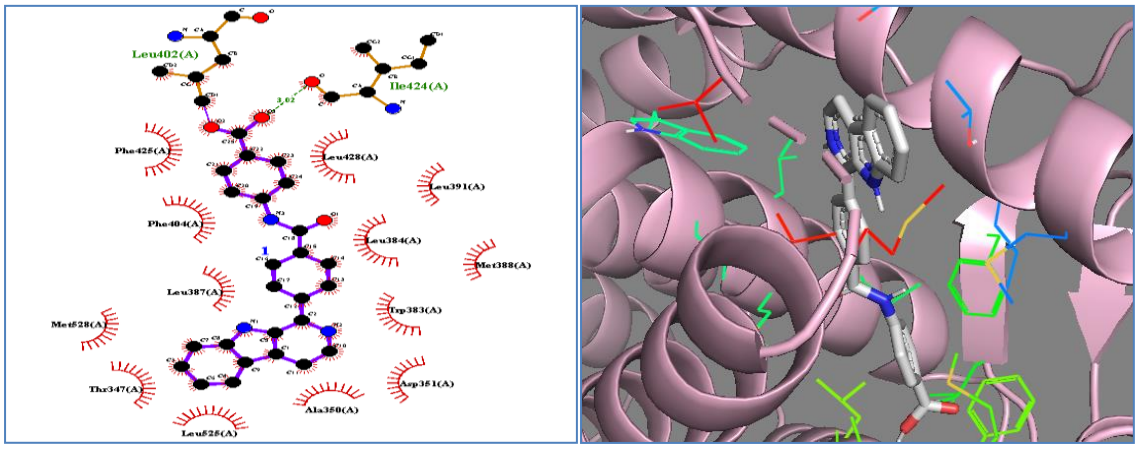


Figure 4. a) The 2D view of molecule BC-11 in the active sites of 5ACC enzyme, b) the cartoon model represents the ligand BC-11 packed in the active site of protein

Molecular Prediction ADME Parameters and Swiss Target Prediction

The results of ADME studies of the **12** compounds have been depicted (Tables 2, 3, and 4). Molecules with the potential of being absorbed through the intestine appear in the white portion, while the absorbed molecules with the potential to cross the BBB barrier appear in the yellow portion. The study shows that molecules BC-1, BC-2, BC-3, BC-6, BC-11, and BC-12 are capable of being absorbed through the human intestine (HIA). Out of these 12 molecules, only molecule 2 is observed to be capable of crossing the BBB barrier.

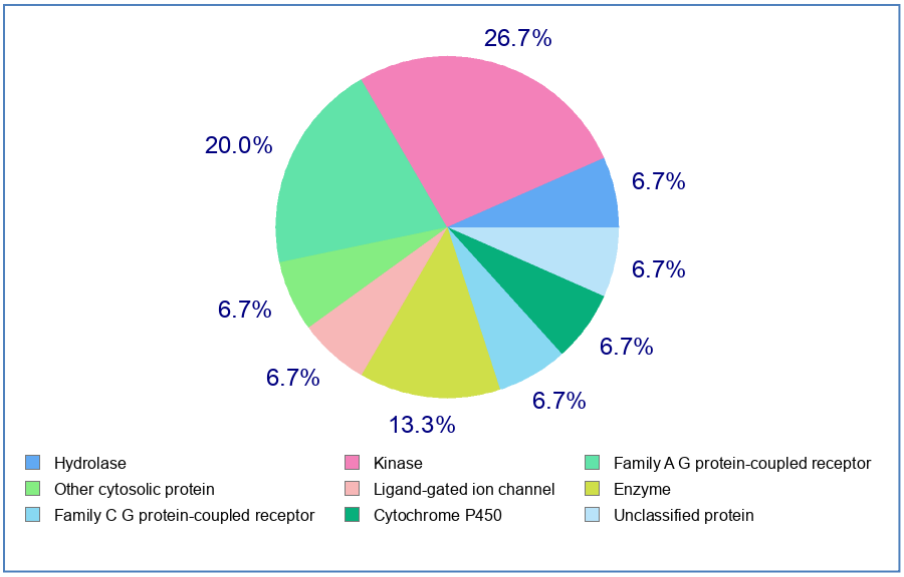


Figure 5. Swiss target prediction

Table 2. Physicochemical properties

Sr./No.	Formula	MW	#H-bond acceptors	#H-bond donors	MR	TPSA
BC-1	$C_{24}H_{17}N_3O_2$	379.41	3	3	115.27	78.01
BC-2	$C_{24}H_{17}N_3O$	363.41	2	2	113.25	57.78
BC-3	$C_{25}H_{19}N_3O$	377.44	2	2	118.22	57.78
BC-4	$C_{24}H_{17}N_3O_2$	379.41	3	3	115.27	78.01
BC-5	$C_{25}H_{17}N_3O_3$	407.42	4	3	120.21	95.08
BC-6	$C_{23}H_{21}N_3O$	355.43	2	1	113.16	48.99
BC-7	$C_{24}H_{17}N_3O_2$	379.41	3	3	115.27	78.01
BC-8	$C_{24}H_{17}N_3O$	363.41	2	2	113.25	57.78
BC-9	$C_{25}H_{19}N_3O$	377.44	2	2	118.22	57.78
BC-10	$C_{24}H_{17}N_3O_2$	379.41	3	3	115.27	78.01
BC-11	$C_{25}H_{17}N_3O_3$	407.42	4	3	120.21	95.08
BC-12	$C_{23}H_{21}N_3O$	355.43	2	1	113.16	48.99

Table 3. Pharmacokinetics

GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)
High	No	Yes	Yes	Yes	No	Yes	Yes	-5.45
High	Yes	Yes	Yes	Yes	No	Yes	Yes	-5.1
High	No	Yes	Yes	Yes	No	Yes	Yes	-4.92
High	No	Yes	Yes	Yes	No	Yes	Yes	-5.45
High	No	No	Yes	Yes	No	Yes	No	-5.7
High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-5.43
High	No	Yes	Yes	Yes	No	Yes	Yes	-5.45
High	Yes	Yes	Yes	Yes	No	Yes	Yes	-5.1
High	No	Yes	Yes	Yes	No	Yes	Yes	-4.92
High	No	Yes	Yes	Yes	No	Yes	Yes	-5.45
High	No	No	Yes	Yes	Yes	Yes	No	-5.7
High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-5.43

Table 4. Water solubility

ESOL Solubility (mg/mL)	ESOL Solubility (mol/l)	ESOL Class	Ali Log S	Ali Solubility (mg/mL)	Ali Solubility (mol/l)
1.60E-03	4.21E-06	Moderately soluble	-5.82	5.78E-04	1.52E-06
1.10E-03	3.02E-06	Moderately soluble	-5.76	6.38E-04	1.75E-06
5.75E-04	1.52E-06	Moderately soluble	-6.14	2.74E-04	7.25E-07
1.60E-03	4.21E-06	Moderately soluble	-5.82	5.78E-04	1.52E-06
1.75E-03	4.30E-06	Moderately soluble	-6.05	3.62E-04	8.88E-07
3.08E-03	8.65E-06	Moderately soluble	-5.02	3.38E-03	9.52E-06
1.60E-03	4.21E-06	Moderately soluble	-5.82	5.78E-04	1.52E-06
1.10E-03	3.02E-06	Moderately soluble	-5.76	6.38E-04	1.75E-06
5.75E-04	1.52E-06	Moderately soluble	-6.14	2.74E-04	7.25E-07
1.60E-03	4.21E-06	Moderately soluble	-5.82	5.78E-04	1.52E-06
1.75E-03	4.30E-06	Moderately soluble	-6.05	3.62E-04	8.88E-07
3.08E-03	8.65E-06	Moderately soluble	-5.02	3.38E-03	9.52E-06

The molecule BC-6 and BC-12 shows the excellent pharmacokinetics, as per ADME study, the designed molecules BC-6 and BC-8 have capability of passing BBB barrier, which have a high GI absorption rate. Likewise, the molecules exhibit CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP3A4 inhibitor, and CYP3A4 inhibitor activity with Log-Kp (skin permeation)-5.43 cm/s, as compared with the other designed molecules (Table 3). Almost all the molecules shoe the drug likeness characters with obeying Lipinski with zero violation and bioavailability Score is nearly similar. BC-1, BC-5, and BC-11 indicate an H-bond acceptors functional group of and 3 H-bond donor functional groups, while molecules BC-6 and BC-12 display two H-bond acceptors functional group of and 1 functional group H-bond donor, which is equal to the stand co-crystal presented in the protein 5ACC (Table 2).

The Ramachandran plot [31] performed with the BC-6 molecules, the designed molecule indicates the following observation. Black, dark grey, light grey among which grey represents highly preferred conformations. Delta >= -2, while the highly preferred observations shown as Green crosses: 205 (100.000%). There are no questionable observations shown as Red circles: 0 (0.000%), as observed in the plot (Figure 5).

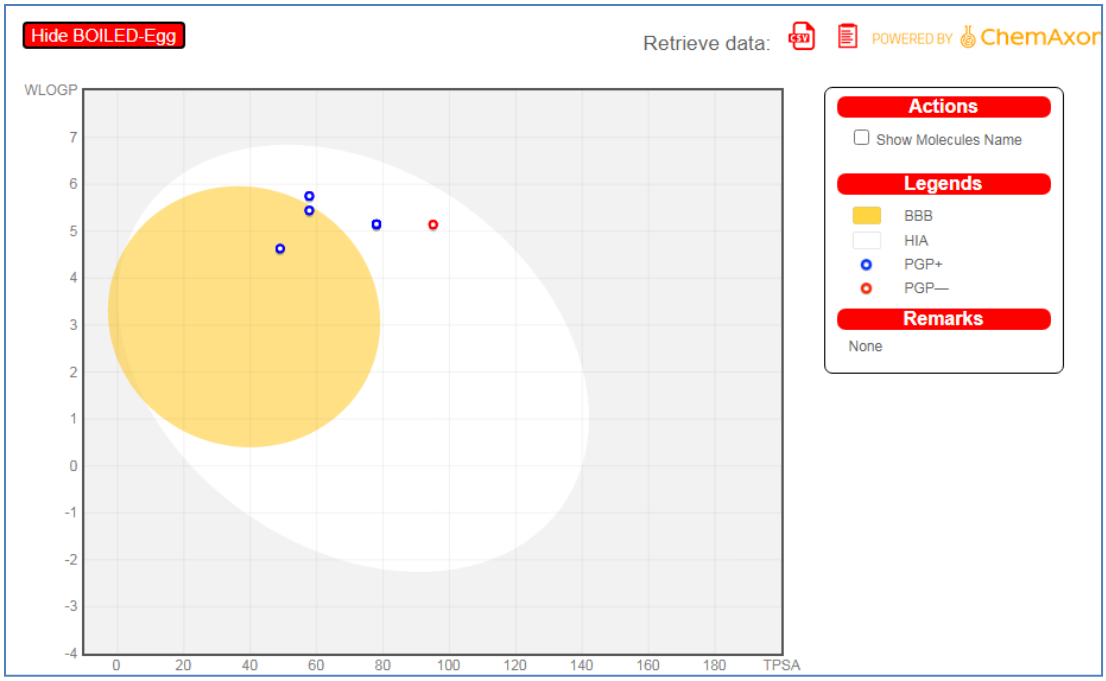


Figure 6. ADME Boiled egg diagram

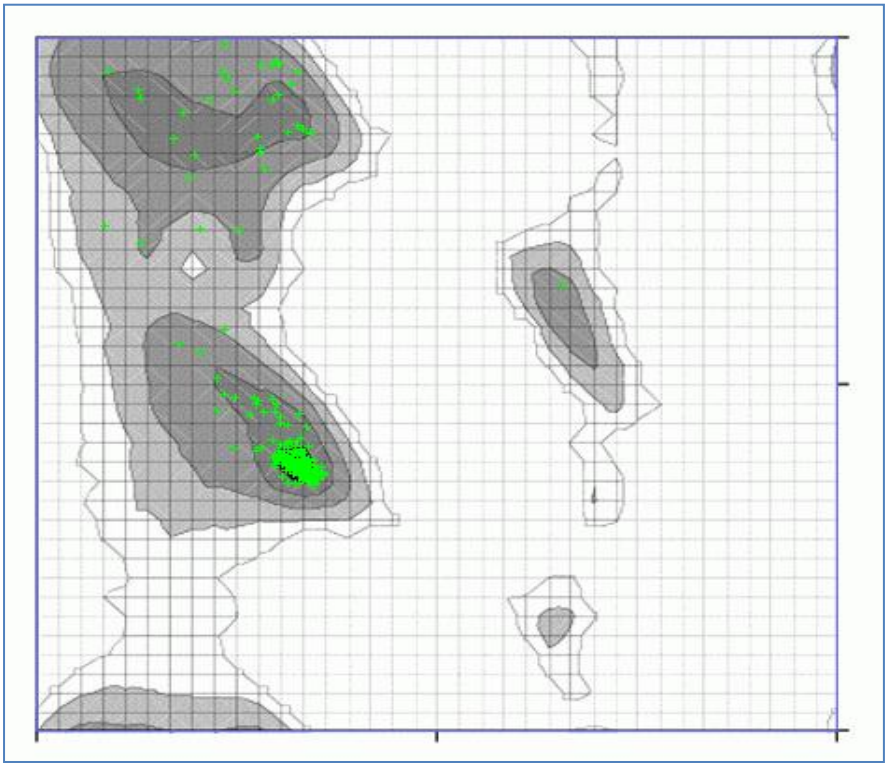


Figure 7. Ramachandran Plot

Conclusion

The synthesized *β*-carboline derivatives indicated the good interactions with the estrogens receptor protein and the interaction with the required active amino acid residues, which is responsible for the biochemical mechanism. The ADME studies reveal that BC-6 and BC-12 exhibited CYP1A2 inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP3A4 inhibitor, and CYP3A4 inhibitor properties along with Log Kp (skin permeation)-5.43 cm/s. The *ramachandran plot* for BC-6 molecule indicates 100% favourable region in the pocket of enzyme 5ACC, while the BC-6 and BC-12 can cross the BBB barrier. This study indicates that scaffolds BC-6 and BC-12 could be the prompting candidates for further drug discovery.

The authors declare that they have no known competing financial interest.

Acknowledgements

The authors are very thankful to the Principal Sambhajirao Kendre Mahavidyalay Jalkot and Yeshwant College, Nanded for giving required facility for research.

Orcid

Bapusaheb S. Wadje:
https://orcid.org/0000-0003-3722-0376
Pawar D C:
https://orcid.org/0000-0001-9636-9985
Swapnil Navhate:
https://orcid.org/0000-0003-1040-1935
V. N. Bhosale:
https://orcid.org/0000-0003-0084-6631

References

[1] P. Piechowska, R. Zawirska-Wojtasiak, S. Mildner-Szkudlarz, *Nutrients*., **2019**, *11*, 814. [Crossref],[Google Scholar], [Publisher]

[2] T. Szabó, B. Volk, M. Milen, *Molecules*., **2021**, *27*, 663. [Crossref], [Google Scholar], [Publisher]

[3] P.H. França, D.P. Barbosa, D.L. da Silva, E.A. Ribeiro, A.E. Santana, B.V. Santos, J.M. Barbosa-Filho, J.S. Quintans, R.S. Barreto, L.J. Quintans-Júnior, J.X. de Araújo-Júnior, *Biomed Res Int.*, **2014**, 375423. [Crossref], [Google Scholar], [Publisher]

[4] E. Sakai, H. Kato, H. Rotinsulu, F. Losung, R. E. Mangindaan, N. J. de Voogd, H. Yokosawa, S. Tsukamoto S., *J Nat Med.,* **2014**, *68*, 215-9. [Crossref], [Google Scholar], [Publisher]

[5] A. Lourdes, C. Peña-Farfal, P. Yáñez-Sedeño, J.M. Pingarrón, *Analytica Chimica Acta,* **2007**, *585*, 323-330. [Crossref], [Google Scholar], [Publisher]

[6] M.M. Iraksinen, I. Kari, *Effects. Med Biol*., **1981**. [Publisher]

[7] T. Herraiz, A. Peña, H. Mateo, M. Herraiz, A. Salgado, *J. Agric. Food Chem.*, **2022**, *70*, 9143–9153. [Crossref], [Google Scholar], [Publisher]

[8] Faheem, B.K. Kumar, K.V.G. C.Sekhar, S. Kunjiappan, J. Jamalis, R. Balaña-Fouce, M. Sankaranarayanan, Recent Update on the Anti-infective Potential of *β*-carboline Analogs, **2021**, *21*, 398-425. [Crossref], [Google Scholar], [Publisher]

[9] S. Kumar, A. Singh, K. Kumar, V. Kumar, *European Journal of Medicinal Chemistry,* **2017**, *142*, 48-73. [Crossref], [Google Scholar], [Publisher]

[10] P. Max Headley, D. Lodge, *Brain Research*, **1976**, *01*, 479-488. [Crossref], [Google Scholar], [Publisher]

[11] P.M. Quan, H.B.Q.G. Anh, N.T.N. Hang, D.H. Toan, D.V. Ha, P.Q.C. Long, *Regional Studies in Marine Science*, **2022**, 102619. [Crossref], [Google Scholar], [Publisher]

[12] M.V. Gaikwad, S.V. Gaikwad, R.D. Kamble, *Current Research in Green and Sustainable Chemistry*, **2022**, *5*, 100268. [Crossref], [Google Scholar], [Publisher]

[13] S. Gaikwad, D. Kamble, P. Lokhande, *Tetrahedron Lett.*, **2018**, *59*, 2387–2392. [Crossref], [Google Scholar], [Publisher].
[14] S.V. Gaikwad, M.V. Gaikwad, P.D. Lokhande, *J. Heterocycl. Chem.*, **2021**, *58*, 1408-1414. [Crossref], [Google Scholar], [Publisher]
[15] S.V. Gaikwad, D.N. Nadimetla, M. Al Kobaisi, M. Devkate, R. Joshi, R. G. Shinde, M.V. Gaikwad, M.D. Nikalje, S.V. Bhosale, P.D. Lokhande, *Chemistry Select*, **2019**, *4*, 10054-10059. [Crossref], [Google Scholar], [Publisher]
[16] S.J.Y. Macalino, V. Gosu, S. Hong, *Arch. Pharm. Res.*, **2015**, *38*, 1686–1701. [Crossref], [[Google Scholar], [[Publisher]
[17] W. Yu, A.D. MacKerell, *Methods in Molecular Biology*, **2017**, *1520*, 85-106. [Crossref], [Google Scholar], [Publisher]
[18] J.H. Van Drie, *J Comput Aided Mol Des,* **2007,** *21*, 591–601. [Crossref], [Google Scholar], [Publisher]
[19] S. Gaikwad, M. Gaikwad, P. Lokhande, *Eurasian Chemical Communications*, **2020**, *2*, 945-952. [Crossref], [Google Scholar], [Publisher]
[20] S. Gaikwad, M. Basavanag Unnamatla, *Journal of Applied Organometallic Chemistry*, **2022**, *2*, 24-30. [Crossref], [Google Scholar], [Publisher]
[21] M. Gaikwad, S. Gaikwad, R. Kamble, *J. Med. Chem. Sci.,* **2022**, *5*, 239-248. [Crossref], [Google Scholar] [Publisher]
[22] G. Mohammadi Ziarani, S. Afsharnia, A. Badiei, P. Gholamzadeh. *J. Appl. Organomet. Chem.*, **2021**, *1*, 202-206 [Crossref], [Google Scholar], [Publisher]
[23] S.V. Gaikwad, M.V. Gaikwad, P.D. Lokhande, *J. Appl. Organomet. Chem.*, **2021**, *1*, 1-8. [Crossref], [Google Scholar], [Publisher]
[24] G.S. Khansole, D. Prasad, J.A. Angulwar, A.B. Atar, B.M. Nagaraja, A.H. Jadhav, Vijay N. Bhosale, *Materials Today: Proceedings*, **2019**, *9*, 653-660. [Crossref], [Google Scholar], [Publisher]
[25] R. Abinaya, S. Srinath, S. Soundarya, R, Sridhar, K.K. Balasubramanian, B. Baskar, *Journal of Molecular Structure*, **2022**, *1261*, 132750. [Crossref], [Google Scholar], [Publisher]
[26] S. Takahashi, *J Antibiot,* **2022**, *75*, 432–444. [Crossref], [Google Scholar], [Publisher]
[27] W.W.T. Lam, S.W.I. Siu, *Biochemistry and Molecular Biology*, **2017**, *45***,** 76-83. [Crossref], [Google Scholar], [Publisher]
[28] H. Li, K.S. Leung, M.H. Wong, P.J. Ballester, *Molecular Informatics*, **2015**, *34*, 115-126. [Crossref], [Google Scholar], [Publisher]
[29] BIOVIA, Dassault Systèmes, BIOVIA Discovery Studio Visualizer, San Diego: Dassault Systems, 2021. [Publisher]
[30] C. De Savi, R.H. Bradbury, A.A. Rabow, R.A. Norman, *J Med Chem,* **2015**, *58*, 8128. [Crossref], [Google Scholar], [Publisher]]
[31] S.A. Hollingsworth, P.A. Karplus, *Biomol Concepts.*, **2010**, *1*, 271-283. [Crossref], [Google Scholar], [Publisher]