IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 3 Ser. IV (May –June 2020), PP 01-27
www.Iosrjournals.Org

The *β*-carboline alkaloids in cancer therapy- recent advancements in this area

Kesari Lakshmi Manasa,*[a] Sanam Swetha Yadav,[a] Narayana Nagesh*[b]
[a]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad-500037, India.*
[b]*CSIR - Centre for Cellular and Molecular Biology, Medical Biotechnology Complex, ANNEXE- II, Uppal Road, Hyderabad 500007, India*
[*]*Corresponding author: Narayana Nagesh.*

Abstract: *Nature inspired new drug molecules are developed through the medicinal chemistry approach has a great success in drug discovery. Efforts of chemists have succeeded in developing semi-synthetic derivatives to dominate the authentic natural product in terms of drug-likeness properties include increased potency, high affinity, selectivity, reduced toxicity and patient compliance. β-carbolines a family of indole-based alkaloids, remained as a privileged scaffold known to exhibit anticancer potential through various mechanisms. This review attracts the readers towards the ongoing developments (2017-2020) of β-Carboline with an significance on structure based rational drug design, multiparameter lead optimization strategies, SAR studies and its cytotoxic potential.*

Keywords: *β-Carbolines, Harmine, DNA binding studies, Cytotoxicity, Topoisomerase inhibition activity and Molecular Docking.*

Date of Submission: 04-06-2020 Date of Acceptance: 20-06-2020

I. Introduction

Natural products have a protracted history as therapeutics for broad range of diseases. Indelible co-evolution between biological communities and humans has tried to explain the baffle of biological significance of natural products in humans and other species [1-7]. Many chemists and biologists in both industrial and academic sector have commenced and proved clinical potentiality of natural compounds as a prolific source of chemical inspiration for the evolution of new drugs. The impact of plant-derived drugs on mankind become enormous in the recent daysand is proved by the development of plant-derived drugs such as vinblastine, vincristine, paclitaxel, quinine, etoposide, artemisinin, teniposide, morphine, and the camptothecin derivatives topotecan and irinotecan. Even though, natural products derived from microbial origin have made significant contribution, marine derived natural products are also having an increasing impact on the treatment of human disease, particularly as anticancer agents [8-10]. Evolution of semi-synthetic modifications of natural products as a source of bioactive-lead compounds to improve drug-likeness and clinical utility is one of the transitions taken an advanced role in drug discovery and drug development. Hence, further research regarding the development of new chemotherapeutic agents that are more effectively combat cancer is an active area of research in medicinal chemistry [11-13].

Carbolines are nature-derived heterocyclic compounds containing indole ring fused with pyridine (fused benzene-pyrrole-pyridine system) system [14]. Carbolines were first found in harmala alkaloids and were found to be widespread in both plant as well as animals. Carbolines are classified based on the position of nitrogen on pyridine ring as α-, *β*-, γ- and δ- carbolines (**Fig. 1**) [15]. Among all the carbolines, *β*-carbolines have been observed as major-stock holder, due to their dynamic use in the treatment of various diseases including psychopharmacological and oncological properties [16].

β-Carbolines are a group of alkaloids having a planar tricyclic pyrido [3,4-*b*] indole ring system [17] and are originally isolated from seeds of *Peganum harmala*; Zygophillaceae family and has been used traditionally for the treatment of alimentary tract cancers and malaria [18]. These are widely distributed in plant (leaves, barks and roots), microorganisms, insects, marine invertebrates (bryozoans, hydroids, soft corals, sponges), marine ascidians (genus Eudistoma) [17], mammalians (human tissues and body fluids like blood, cerebro-spinal fluid, etc.) [19], various food products (tomatoes, kiwi, fruit juice, fish, grilled bacon, etc) [20], coffee, alcoholic beverages and tobacco smoke [21]. These exhibits various pharmacological properties include anticonvulsant, antifungal, antimicrobial, antiviral, antiplasmodial, antiparkinson, antialzheimer, anxiolytic and antitumor property [22]. The best known natural products which contain *β*-carboline skeleton include norharmane, harmine, harmane and harmaline. Harmine type of *β*-carbolines are found to possess profound

anticancer effects through multiple mechanisms such as inhibition of CDK's [23], topoisomerase I & II [24], MK-2 [25], PLKs [26], DYRK1A [27] and DNA intercalation or binding through minor groove [28]. Besides, Harmane like *β* -carbolines interact with multiple neuro-receptors, such as that of serotonin, dopamine, benzodiazepine, opiate, nicotine, histamine and imidazoline binding sites (I-BS) and thus mediate numerous psychopharmacological effects. *β*-carboline alkaloids are isolated from many other plants as given in **Table 1**.

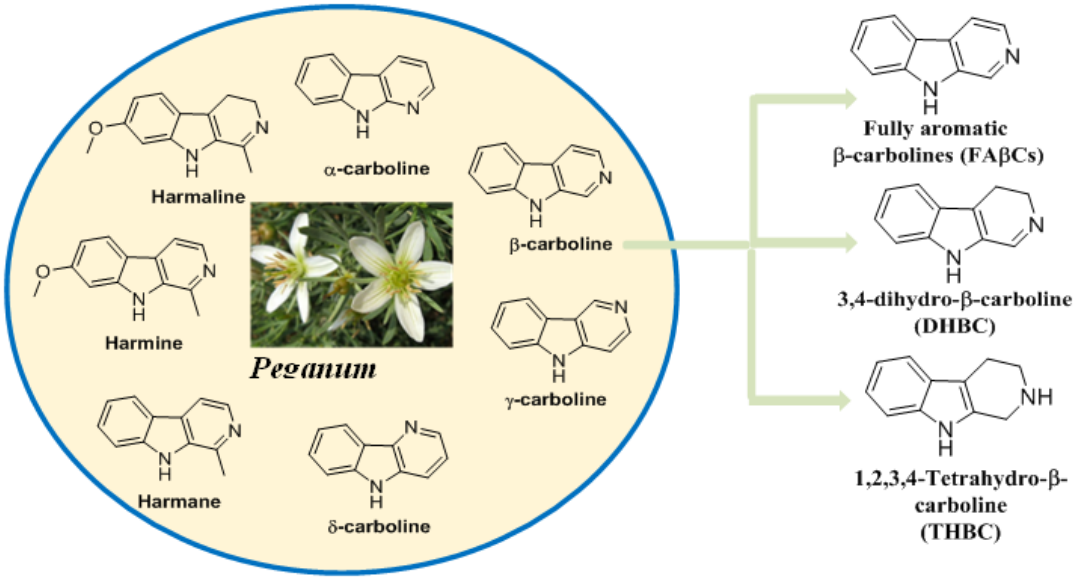


Fig. (1). *β*-carbolines and their derivatives.

II. Classification of *β*-carbolines

β-carbolines are further classified based on the saturation of the *N*-containing 6-membered ring (pyridine ring). Unsaturated pyridine ring containing compounds (**Fig. 1**) are named as Fully Aromatic Beta-Carbolines (FA*β*Cs), partially and fully saturated compounds are named as 3,4-dihydro-*β*-carbolines (DH*β*Cs) and 1,2,3,4-tetra hydro-*β*-carbolines (TH*β*Cs) respectively.

- FA*β*Cs: A large group of natural and synthetic indole alkaloids that possess a common tricyclic pyrido[3,4-*b*]indole ring with unsaturated pyridine ring system. These derivatives were generally synthesized *via* two-step process in a step-wise fashion. Generally synthesized by Pictet-Spengler reaction followed by *in situ* decarboxylation and then aromatization [29, 30].
- DH*β*Cs: These type of alkaloids possess a tricyclic pyrido[3,4-*b*]indole ring as common but with partially saturated pyridine ring system, hence called as 3,4-dihydro-*β*-carbolines (DH*β*Cs). These can be synthesized *via* Pictet-Spengler reaction followed by dehydrogenation [31].
- TH*β*Cs: These tricyclic systems usually contain saturated pyridine ring in the tricyclic pyrido[3,4-*b*]indole ring system The most traditional methods to synthesize TH*β*C frameworks are Pictet-Spengler and Bischler-Napieralski reaction. Among the huge number of *β*-carbolines, TH*β*Cs found to present in large number of natural products and exhibit different biological properties [32].

III. Structural-Activity Relationship (SAR) Studies of β-Carboline

All the recent developments on β-carboline based derivatives have some insights into the Structure-Activity Relationships (SARs), which have been greatly benefited in the design and synthesis of new β-carboline derivatives as potential antitumor agents. β-Carbolines are potent anticancer agents and the potency was correlated to both the structural planarity and the nature of the ring substituents. Introducing suitable substituent on appropriate positions of β-carboline scaffold played a crucial role in the modulation of their antitumor efficacies. The introduction of appropriate groups at the positions-1 and -3 of the β-carboline ring accentuated anticancer activity as well as DNA binding ability and also significantly reduced acute toxicity of β-carboline derivatives. Further, introducing an appropriate substituent at position-9 and -2 of β-carboline ring enhances greatly their anticancer activities. Similarly, introducing benzyl group on position-2 resulted in quaternary β-carbolines that exhibited the most interesting anticancer activities. Introducing an appropriate substituent at position-9 of β-carboline nucleus, improvement in the affinity of the drug to DNA interaction and remarkable DNA topo I inhibition effects were observed. As well, the phenylpropyl or n-butyl substituent at position-9 was suitable pharmacophoric group which reveals some potent anticancer agents. Likewise, the benzyl substituents at position-9 of β-carboline ring were the favourable substituent which resulted significant anticancer agents [24].

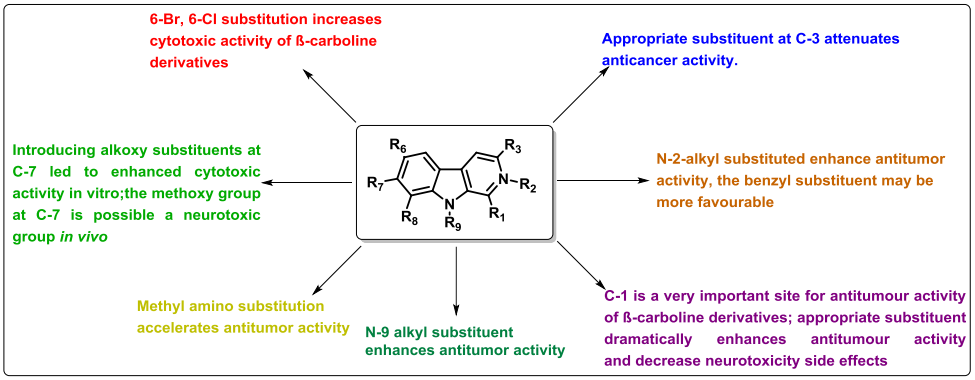
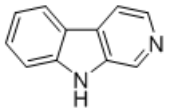
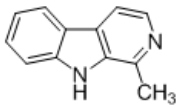
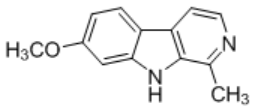
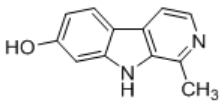
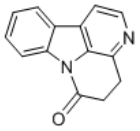
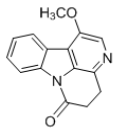
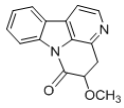
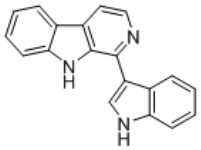
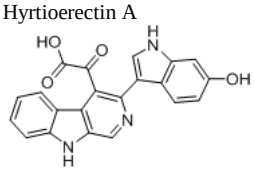
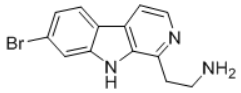
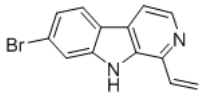
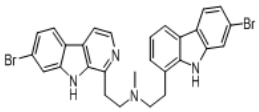
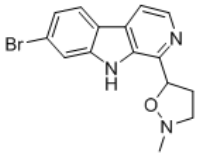
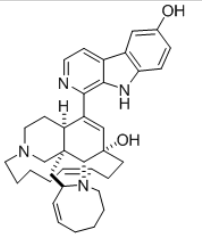
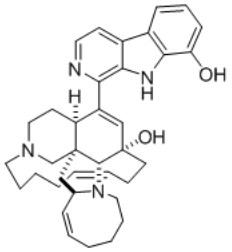
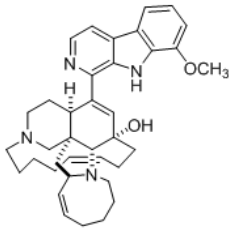
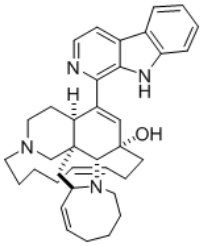
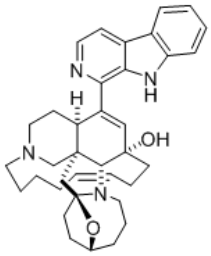
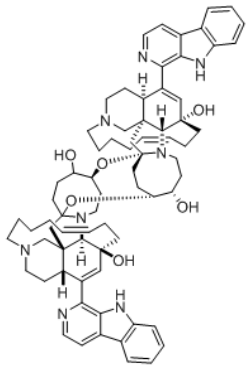
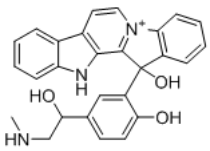


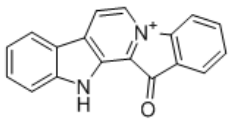
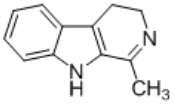
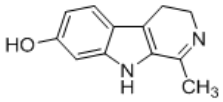
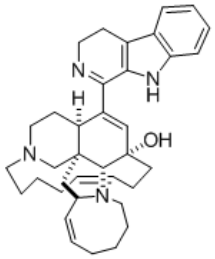
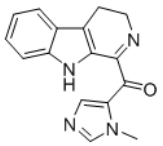
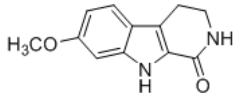
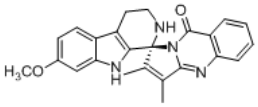
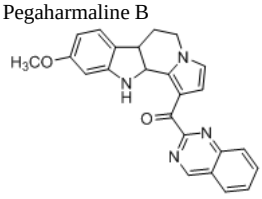
Fig. (2). The structure-activity relationships (SARs) of β-carboline.

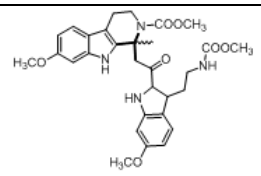
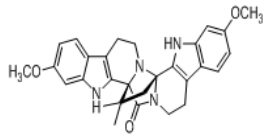
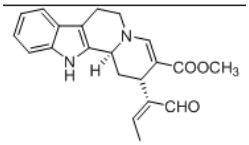
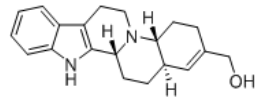
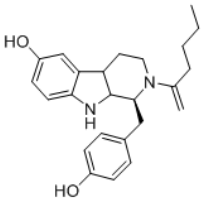
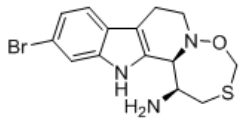
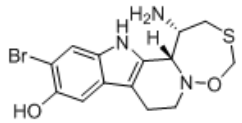
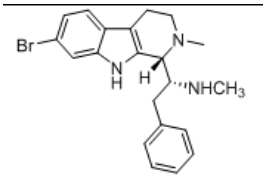
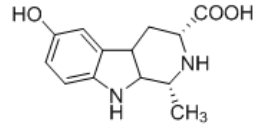
Table 1. List of some natural *β*-carboline derivatives.

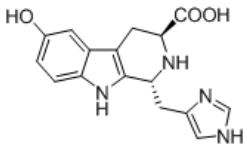
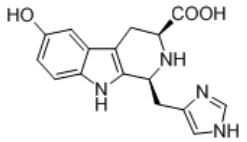
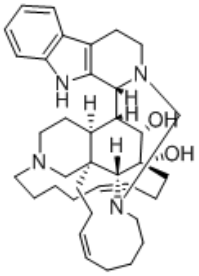
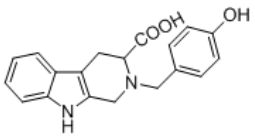
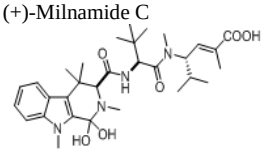
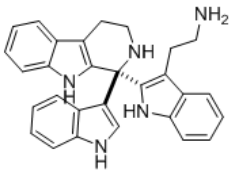
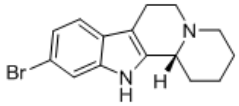
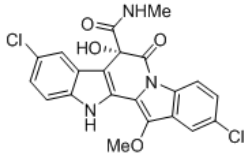
S.No	Compound	Source	Mechanism of Action
		FA*β*Cs	
1	Norharmane 	*Peganum harmala* (Syrian rye) *Tribulus terrestris*.	1. DNA intercalation [33]. 2. Inhibits the transcription of isolated DNA [34]. 3. Enhances both the DNA strand breaks and cytotoxicity induced by 4HAQO [35]. 4. Inhibits DNA excision repair and causes an increase in UV induced mutations [36]. 5. Inhibits the activity of Topoisomerase I & II [33]. 6. Inhibits the activity MAO-B [38]. 7. Interacts with CYP11 and CYP17 [39].
2	Harmane 	*Peganum harmala*, Passifloraincarnata, Symplocosracemosa.	1. Inhibits Topoisomerase I & II [40]. 2. DNA intercalation [33]. 3. Inhibits the activity MAO-A [41]. 4. Inhibition of the AP endonuclease activity of phage T4 [42]. 5. Inhibition of HIV replication in H9 lymphocyte cells [43]. 6. Interaction with DNA metabolism and significant accumulation of parasites in the S–G2/M phases of the cell cycle (Anti-leishmanial against promastigotes & amastigotes) [44].
3	Harmine 	*Peganum harmala*	1. DNA intercalation [45]. 2. Inhibits DNA excision repair [46]. 3. Causes DNA strand breaks upon UV light irradiation [45]. 4. Inhibition of MAO-A activity [41]. 5. Potent and specific inhibitors of CDKs [47]. 6. Inhibit synthesis of viral DNA, RNA and blocks gene expression [48]. 7. Interaction with DNA metabolism and significant accumulation of parasites in the S–G2/M phases of the cell cycle (anti-leishmanial against promastigotes & amastigotes) [44].
4	Harmol 	*Passiflora incarnata*	Induces autophagy and cell death in human NSCLC A549 cells [49].
5	Canthin-6-one 	*Picrasma quassoids* (wood)	Causes accumulation of cancer cells in the G2/M Phase [50].

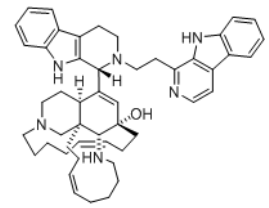
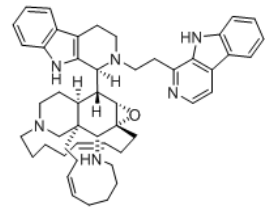
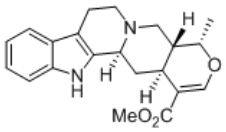
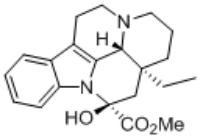
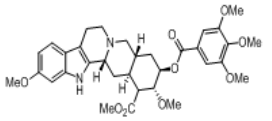
6	1-Methoxycanthinone  5-Methoxycanthinone 	*Ailanthus altissima* and *Leitneria floridana*	Induces c-Jun NH_2-terminal kinase–dependent apoptosis and synergizes with tumor necrosis factor–related apoptosis-inducing ligand activity in human neoplastic cells of hematopoietic or endodermal origin [51].
7	Eudistomin U 	Caribbean *Lissoclinum fragile*	1. Strong Antibacterial activity. 2. Anticancer activity: High binding affinity with DNA, strong KSP (kinesin spindle protein) inhibitor 3. No Antifungal activity [52].
8	Hyrtioerectin A 	*Hyrtios erectus* (Red sea sponge)	Cytotoxic against HeLa cell lines [53].
9	Plakortamine A  Plakortamine B  Plakortamine C  Plakortamine D 	*Plakortis nigra*	Cytotoxic activity against HCT-116 [54].
10	6-Hydroxymanzamine A (Manzamine Y) 	Amphimedon species (Okinawan marine sponge).	Inhibit DNA synthesis through intercalation of DNA base pairs [55].
11	8-Hydroxymanzamine A	Pachypellina species (Marine sponge).	1. Inhibits asexual erythrocytic stages of *Plasmodium beighei*. 2. Inhibit DNA synthesis through intercalation of DNA base pairs [55].

	 8-Methoxymanzamine A 		
12	Manzamine A 	(Okinawan marine sponges) Xestospongia species and Haliclona species.	1. Inhibits asexual erythrocytic stages of *Plasmodium beighei*. 2. Inhibit DNA synthesis through intercalation of DNA base pairs [55].
13	6-Deoxymanzamine X 	Haliclona genus (Indo-Pacific sponge)	Inhibit DNA synthesis through intercalation of DNA base pairs [55].
14	Neo-Kauluamine 	Indo-Pacific sponge	Accumulates in lysosomes and mediates apoptosis by upregulating a pro-apoptotic protein, PUMA (p53 upregulated modulator of apoptosis).
15	Thorectandramine 	Thorectandra species (Marine sponge).	Induction of caspase-8, -9, -3-dependent apoptosis [56].

16	Fascaplysin 	Fascaplysinopsis species.	1. DNA intercalator. 2. Selective inhibitor of Cdk4. 3. Inhibit phosphorylation of the retinoblastoma protein R_b, resulting in G0/G1 phase cycle arrest of cancerous cells [57].
	DHβCs		
17	Harmaline 	*Peganum harmala*	1. Inhibits the activity of DNA Topoisomerase 2. Inhibit DNA excision repair [58]. 3. Inhibits the Na^+-dependent I uptake [59]. 4. Inhibits the activity of PKC [60]. 5. Interactions with DNA metabolism and significant accumulation of parasites in the S–G2/M phases of the cell cycle [60].
18	Harmalol 	*Peganum harmala*	Inhibits the dioxin mediated induction of CYP1A1 (carcinogen activating enzyme) [61].
19	3,4-dihydromanzamine A 	Pachypellina species (Marine sponge).	
20	Xestomanzamine B 	(Okinawan marine sponges) Xestospongia species and Haliclona species.	Not reported
	THβCs		
21	Harmalacidine 	*Peganum harmala, Banisteriopsis caapi*	Cytotoxic against human leukemia cells.
22	Pegaharmaline A  Pegaharmaline B 	*Peganum harmala* Seeds of *peganum harmala*	Cytotoxic activity against human cancer cell line (L-60) [62]. Cytotoxic activity against human cancer cell line (L-60) [62].
23	Pegaharmine D	*Peganum harmala*	Interacts with G-quadruplex complex [63].

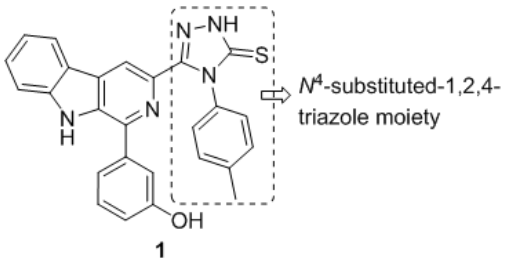
			
24	Peganumine A 	*Peganum harmala*	Cytotoxic activity against MCF-7, PC-3 and HepG2 cells and selective effects on HL-60 cells [64].
25	Z-Vallesiachotamine 	(Z-Vallesiachotamine) *Rhazya stricta*	Promoting G0/G1 cell cycle arrest, apoptosis and necrosis [65].
26	Tangutorine 	*Nitraria tangutorum*	Induces p21 expression and abnormal mitosis in human colon cancer HT-29 cells [66].
27	Sacleuximine A 	*Triclisia sacleuxii*	Cytotoxic against human adenocarcinoma, hepatocarcinoma and breast carcinoma cell lines [67].
28	Eudistomin K 	*Eudistoma glaucus* (Okinawan marine tunicate), Lissoclinium fragile (Ascidian),	1. Antitumour activity against L1210, A549, HCT-8 and P388 cell lines [68]. 2. Active against Herpes simplex Type I and Polio vaccine Type I viruses [69]. Target 40S ribosome and inhibit the protein translation [70].
	Eudistomin C 	*Eudistoma olivaceum*	Not reported
	Eudistomin G 	*Eudistoma olivaceum*	
29	Hyrtioerectin B 	*Hyrtios erectus* (Red sea sponge)	Cytotoxic against HeLa cell lines [53].

30	Hyrtioreticuline A  Hyrtioreticuline B 	*Hystios reticulatus*	Inhibit ubiquitin activating enzyme and ubiquitin-proteasome pathway [71].
31	Ma'ganedin A 	Amphimedon species (Okinawan marine sponge).	Inhibit DNA synthesis through intercalation of DNA base pairs [72].
32	Callophycin A 	*Callophycus oppositifolius* (Red algae).	Induces quinone reductase 1 (QR1) and inhibits aromatase, nitric oxide (NO) production, tumor necrosis factor (TNF)-α-induced NFκB activity, and MCF7 breast cancer cell proliferation [73].
33	(+)-Milnamide C 	Marine sponge Auletta species	Cytotoxic activity by causing microtubule depolymerization and microfilament disruption [74].
34	Bengacarboline 	Marine Ascidian Didemnum species.	Inhibit topoisomerase II [75].
35	(+)-Arborescidine A 	Marine tunicate Pseudodistoma arborescens.	Inhibit topoisomerase-II [76].
36	Cladoniamide G 	Actinomycete *Streptomyces uncialis*	Cytotoxic activity against human breast cancer MCF-7 cells [77].
37	Zamamidine A	Okinawan marine sponge Amphimedon species	Cytotoxic against P388 murine leukemia [78].

	 Zamamidine B 	Fruits of *Evodia rutaecarpa*	Not reported
38	Ajmalicine 	*Raulfia serpentine*; *Catharanthus roseus*; *Mitragyna speciosa*.	Antihypertensive activity [79].
39	Vincaamine 	*Vinca minor*	Primary degenerative; vascular dementia [80].
40	Reserpine 	*Raulfia serpentina*	Antihypertensive and Antipsychotic activity [81].

IV. *β*-carboline and its derivatives

4.1 Triazole-β-carboline derivatives



1

Fig. (3). *β*-carboline-linked 1,2,4-triazole as cytotoxic agents.

Abdelsalam *et al.* have reported a series of 24 novel 1-(3-hydroxyphenyl)-9*H*-*β*-carboline (**Fig. 3**) possessing oxadiazoles and triazoles at C3-position and assayed against various cancer cell lines. Replacement of 1,3,4-oxadiazole with its bioisostere N^4-substituted-1,2,4-triazole moiety enhanced the cytotoxic activity. Moreover, the presence of 4-tolyl substituent on 1,2,4-triazole moiety showed potent anticancer activity. Further, retention of cytotoxic activity by the *S*-methylation of the sulfanyl group. S-alkylation using bulkier groups such as ethoxycarbonyl methylene or 4-substituted phenacyl moieties dramatically decreased the antitumor activity. Compound **1** was found to be potent among the series. Further mechanistic studies demonstrated that compound **1** elicits sub-G1 apoptosis and arrest the cell cycle at G_2/M phase in MDA-MB-435 cells. *In silico* physicochemical and ADME parameters revealed that potent compounds have acceptable bioavailability and pharmacokinetic parameters upon oral administration. Also authors reported the binding affinity of compound **1** with topo-I and KSP ATPase. Thus this study revealed a potential lead for the topoisomerase I and KSP ATPase inhibitors [82].

4.2 Triazole-tetrahydro-β-carboline derivatives

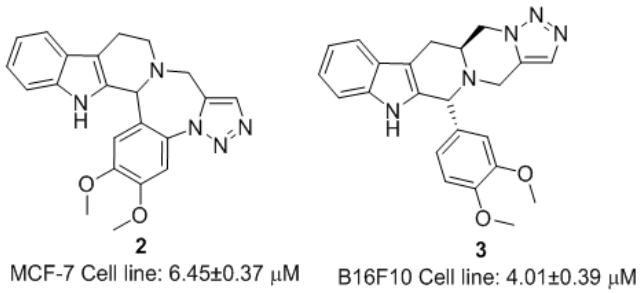


Fig. (4). Tetrahydro-*β*-carboline-linked 1,2,3-triazoles derivatives.

Shankaraiah *et al.* has reported a series of 1,2,3-Triazolo-linked-tetrahydro-*β*-carboline derivatives (**Fig. 4**) *via* intramoecular 1,3-Dipolar cycloaddition reaction. Compound **2** and **3** having free indole NH and electron donating group substituted at C_6 phenyl ring showed potent cytotoxicity. Thus, polyheterocyclic annulated molecules displayed synergistic mechanism of action [83].

4.3 1,3,4-oxadiazole-*β*-carboline derivative

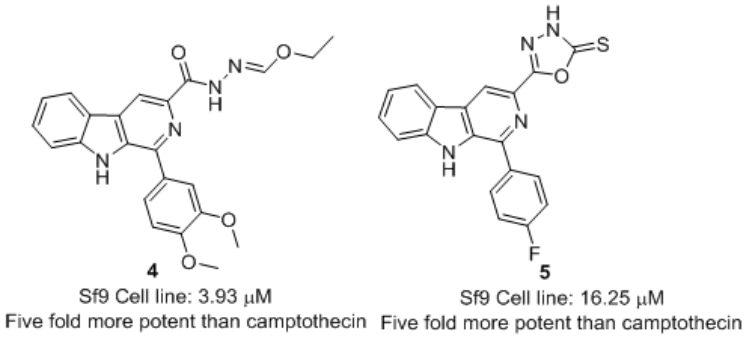


Fig. (5). *β*-carboline-linked 1,3,4-oxadiazoles as insect growth regulators.

Zhong *et al*. disclosed a series of insect growth inhibitors by combining the core pharmacophore *β*-carboline with 1,3,4-oxadiazole and tested against Sf9 cells. SAR analysis revealed that substitution at C_2-position on oxadiazole motif and electron withdrawing groups at C_1-*β*-carbolines were crucial for activity. Compound **4** and **5** (**Fig. 5**) were found to be fivefold more potent than standard molecule camptothecin via activating Sf-caspase-1 and significantly inhibit the growth of larvae of *S. litura in vivo.* Further these compounds can serve as a potential leads in the development of insect growth regulators [84].

4.4 Acyl hydrazone-*β*-carboline derivative

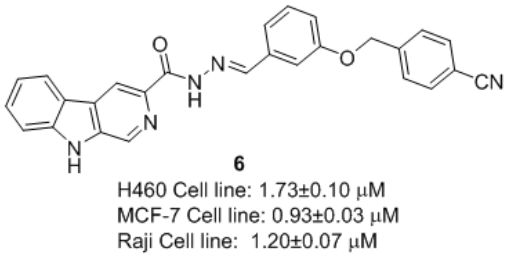
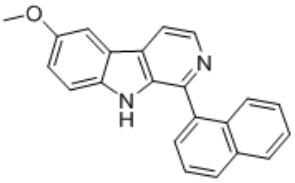


Fig. (6). *β*-carboline based acylhydrazones.

Compound **6** a novel *β*-carboline/acyl hydrazone (**Fig. 6**) based antitumor agent has been reported by *Chen et al*. was shown to be active against resistant cancer cell lines and inhibited tumor growth with low side effects, toxicity, without significant loss of body wt. Compound **6** showed drug resistance index low when compared to the standard colchicines, paclitaxel, vinblastine and adriamycin. Further studies has underwent on nude mice to monitor the antitumor effects on H460 xenograft model. Therefore acylhydrazones which can be further explored to improve the solubility and biological activity [85].

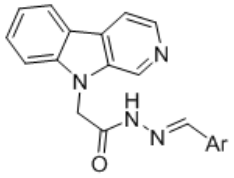
4.5 Naphthalene-*β*-carboline derivative



SP141 (**7**)

Fig. (7). SP141based derivatives.

Zhang *et al*. developed SP141 (**Fig. 7**), a dual target molecule for cancer therapy. SP141 (*β*-carboline derivative) exerts its effect activity by directly bounding to *β*-catenin. Therefore, the authors disclosed SP141 as a potential scaffold having dual inhibitory activity on *β*-catenin and MDM2 [86].



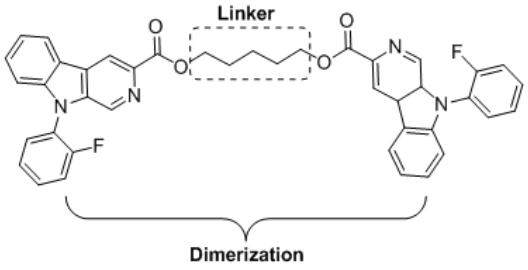
Ar = 1-Naphthaldehyde

SB-2 (**8**)

Fig. (8). *N*9-substituted *β*-Carbolines as PLK-1 inhibitors.

Chandrasekar *et al*. have reported a series of *N*9-substituted *β*-Carbolines (**Fig. 8**) as PLK-1inhibitors. SAR studies disclosed that cytotoxic activity was more prominent in *β*-carboline moiety substituted with naphthalene as well as indole rings. The order of reactivity towards cytotoxic potential was naphthalene > indole > 6-membered heterocyclic > 5-membered heterocyclic rings. Compound **8** was found to be most potent with a GI_{50} 3-45 µM on NCI-60 panel cancer cell lines and selectively inhibits *PLK-1* at 15 µM. It arrests the cell cycle at S/G2 phase on HCT-116 cell line and induced apoptosis by the activation of procaspase-3 and cleaved PARP. SB-2 subjected to *in vivo* models and considerably increased their average lifespan. *In silico* studies revealed that inhibition of PLK-1 was due to the interaction between SB-2 and unusual residues, Arg136 and Leu132 present in the hinge region of PLK-1 protein [87].

4.6 β-carboline dimers



9

IC_{50}: A549 Cell line: 5.61 µM

Fig. (9). Bivalent *β*-carboline derivatives.

Wang *et al*. disclosed the synthesis and structure activity relationship of bivalent *β*-carboline derivatives modified at the N^9 position and dimerized at the C_3-position. Compound **9** (**Fig. 9**) was found to be most potent anticancer compound with an IC_{50} value 5.61 µM. Study revealed that dimers with linker size four to six methylene units were more active compared to monomers, concluding that influence of size of the linker for antitumor activity. Also demonstrated the enhanced antitumor activity by the modification of the *β*-carboline structure (i.e, from monomer to dimer). Compound **9** could serve as a lead molecule for the development of potential DNA intercalating agents [20].

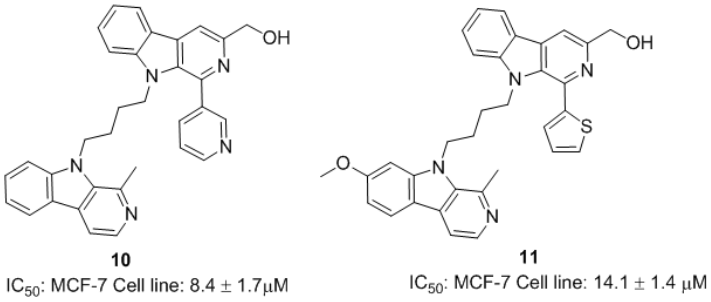


Fig. (10). N^9-heterodimeric *β*-carbolines as cytotoxic agents.

Dai *et al*. have reported compound **10** and **11** a novel N^9-heterobivalent *β*-carbolines (**Fig. 10**) with an IC_{50} value 8.4 and 14.1 μM respectively against MCF-7 cell line. *In vivo* studies were performed for the compound **10** and **11** against mice, with tumor inhibition rate 40% bearing Sarcoma 180 and Lewis lung cancer. Compound **10** also reported for angiogenetic activity and was more potent compared to its standard CA4P. SAR studies revealed that C_1 methylation and C_7 methoxylation are more favorable to enhance the activity. 3-Pyridyl or 2-thienyl group at C1-position of *β*-carboline core and aryl substitution at another *β*-carboline ring can reduced the cytotoxic activity. Structural modification studies of N^9-heterodimeric *β*-carbolines would serve for designing most potent compounds [88].

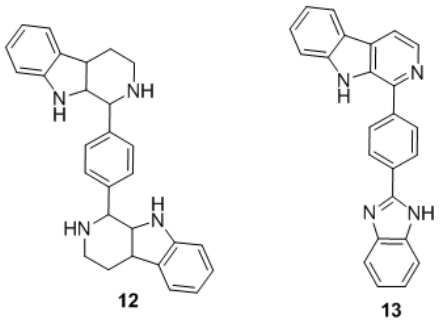


Fig. (11). *β*-carboline conjugates as DNA intercalative agents.

Shastri *et al*. (**Fig. 11**) reported compound **12** and **13** a series of *β*-carbolines with other heterocycles linked by phenyl ring with an anticancer activity (GI_{50} values range from 1.00 to 7.10 μM) against all the cell lines. CT-DNA intercalation and protein binding studies showed that molecules are highly potent. Authors also demonstrated binding of compound **12** and **13** to DNA by docking studies. Compound **12** and **13** showed hydrogen bonding interactions with oxygen atom of carbonyl group of MET547 and hydrogen of amine group makes a hydrogen bonding interaction with LYS524. Both the compounds are surrounded by hydrophobic interactions (LEU528, LEU531, ALA527, GLY401, LEU505, PHE506, PHE508, LEU543, MET547, LEU582, ALA583, VAL575, and GLY571) and hydrophilic interactions (GLU503, ASN549, GLU548, THR578, SER577, THR507, LYS524, THR526, TYR400, GLN525, and LYS523). Hydrophobic and hydrophilic interactions play a major role in binding [89].

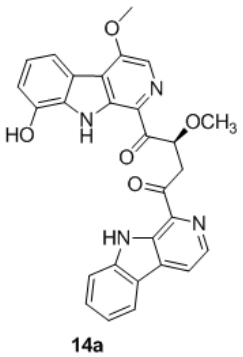
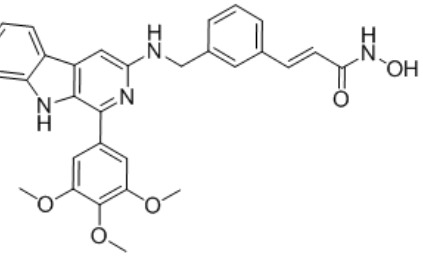


Fig. (12). (+)-Kumudine.

Later the same research group has explored potency of (+) and (−)-kumudine A (**Fig. 12**), kumudine B-D and kumudine E against Hep3B and HepG2 cells by SRB assay. **14a** ((+)-Kumudine B) and **14b** ((-)-Kumudine B) were most potent and selective towards Hep3B cells whereas **14b** showed superior cytotoxicity

compared to **14a** at same concentration. Thus **14b** may be a lead candidate for the development of anti hepatoma agents [90].

4.7 Cinnamide-β-carboline derivatives

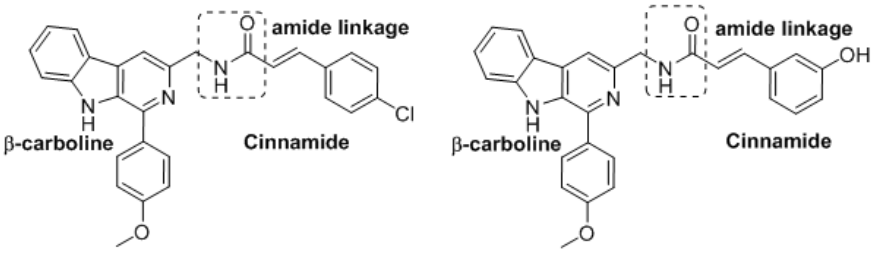


15

IC_{50}: HDAC1: 1.3 nM
HDAC6: 3.1 nM
Bel7402: 0.85 μM
Bel7402/5-FU: 2.09 μM

Fig. (13). Cinnamide linked *β*-carboline derivatives as HDAC inhibitors.

Ling *et al.* investigated *β*-carboline based *N*-hydroxy cinnamide derivatives (**Fig. 13**) for histone deacetylase inhibitory effect. Authors demonstrated that, the HDAC1 inhibitory activity of the synthesized compounds clearly depends on the substitution at C1 position of *β*-carboline. Aryl group substitution at C1 position of *β*-carboliine highly influences the inhibitory activity, where electrons donating groups like mono-methoxyl or di/tri-methoxyl groups are more favorable compared to the electron withdrawing groups. Compound **15** was the most potent analogue with an IC_{50} value 0.85, 2.09 μM against drug-sensitive Bel7402, drug-resistant Bel7402/5-FU cell lines and 1.3 nM against HDAC1 were 5 to 6 fold better than SAHA (IC_{50} = 4.72-9.83 μM) and 18-30 fold more potent than 5-FU (IC_{50} = 15.6-61.7 μM). Compound **15** induce apoptosis by enhancing the expression of cleaved caspase-3 and PARP. **15** up regulate the LC3-II and down regulate the P62 and LC3-I. Thus the author discloses *β*-carboline/*N*-hydroxycinnamamide hybrids as potential leads for the treatment of drug-resistant hepatocellular carcinoma [91].



16
MCF7 Cell line: 14.05 nM

17
MCF7 Cell line: 13.84 nM

Fig. (14). C3-trans-cinnamide based *β*-carbolines as Topo-I inhibitors.

Kamal *et al*. disclosed C_3-trans-cinnamide linked *β*-carboline motifs and evaluated its cytotoxic potential (**Fig. 14**). Authors states that, 4-methoxyphenyl group at position-1 and 3,4,5-trimethoxy on cinnamide part at position-3 were most active when compared to other conjugates and are crucial for *in vitro* cytotoxic activity whereas acrylamide containing congeners were less potent. **16** and **17** were potent against MCF-7 with an IC_{50} value 14.05 nM and 13.84 nM and catalytically inhibit topo-I. **16** and **17** are considered as potential candidates for anticancer therapy [92].

4.8 Bisindole-β-carboline derivative

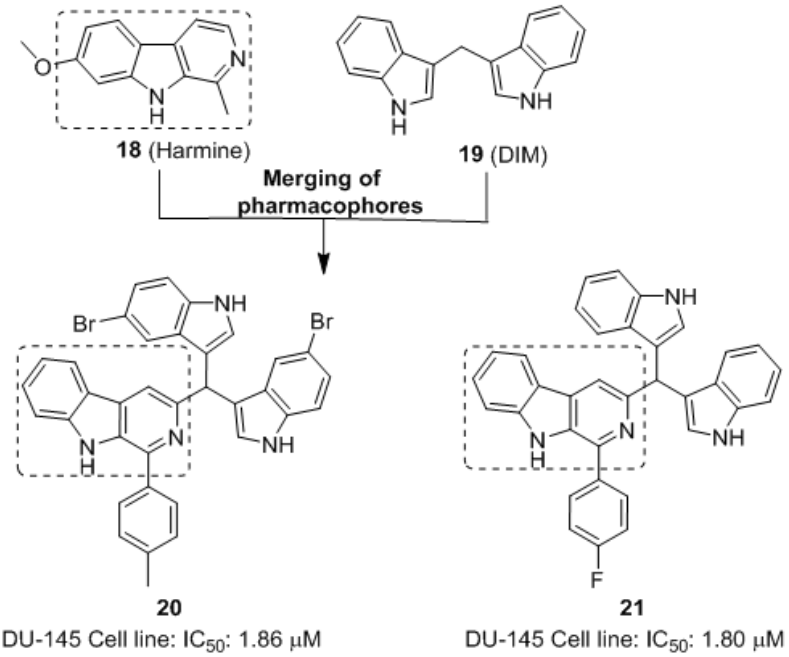


Fig. (15). Lead optimization of *β*-carboline linked bisindole derivatives.

Kamal *et al.* disclosed *β*-carboline linked bisindole congeners (**Fig. 15**) for topo I inhibitory activity. SAR analysis revealed that substitutions like fluoro and methyl on the phenyl ring at C-1 position displayed potent cytotoxicity. Replacement of methyl by methoxy displayed 1.4 fold decreased in the activity. Therefore electron deficient substituents enhanced the cytotoxicity compared to electron rich substituents. Electron deficient substituents at C-5 position on indole ring enhances the activity compared to electron rich substituents. Compounds **20** and **21** inhibited the topoisomerase I at 20 μM concentration. Therefore the authors disclosed a potential scaffolds **20** and **21** having combilexin type of interactions with DNA [93].

4.9 Coumarin-β-carboline derivative

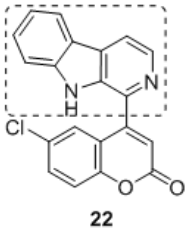


Fig. (16). Amalgamation of THBC linked Coumarin.

Amalgamation of tetrahydro-*β*-carboline (KSP protein inhibitor and antimitotic agent) and coumarin (tubulin inhibitor) may lead to the development of coumarin-*β*-carboline hybrids. Compound **22** showed good cytotoxic results compared to tetrahydro-*β*-carboline. Compound **22** (**Fig. 16**) cleaves the CT-DNA in a conc. dependent manner. Molecular docking results revealed that coumarin ring in the compound **22** interacted with tubulin rather than *β*-carboline. Additionally, the authors docked compound **22** with KSP (Kinesin spindle protein), it shows interactions with *β*-carboline and there is no interaction with the coumarin. Therefore these results revealed that structural modifications of compound **22** could be further explored for enhancing the selectivity and cytotoxicity [94].

3.10. Furan –β-carboline derivative

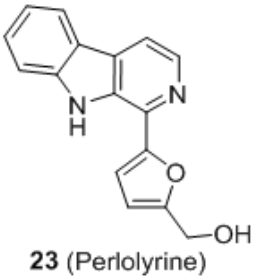


Fig. (17). Perlolyrine.

By using chromatographic separation techniques, Minh *et al*. isolated crinane type alkaloids from the leaves of *crinum latifolium* and evaluated its cytotoxic potential on human cancer cell lines. Among the tested compounds, perlolyrine (**Fig. 17**) showed potent cytotoxicity. Thus the author discloses perlolyrine as a lead candidate for anti-tumor property [95].

3.11. Pharmacological importance of Eudistomin U

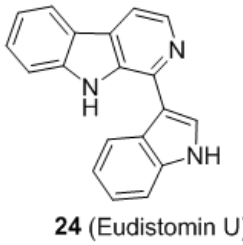


Fig. (18). Eudistomin U.

DNA binding studies of natural *β*-carboline alkaloid eudistomin U was examined by Mulcahy *et al*. Further, mechanistic studies were carried out and states that eudistomin U binds weakly when compared to other alkaloids. Thus eudistomin U (**Fig. 18**) can be a promising lead for the development of newer cytotoxic agents [96].

3.12. Salicylic acid-β-carboline derivative

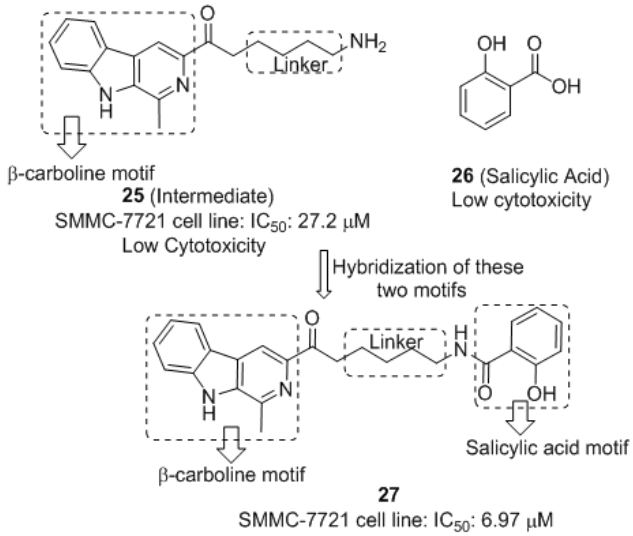


Fig. (19). *β*-carboline linked salicylic acid derivatives.

Xu *et al*. synthesized novel hybrids of *β*-carboline and salicylic acid (**Fig. 19**). SAR studies revealed that methyl group at position-1 of the *β*-carboline unveiled strong anticancer activity than with hydrogen or *p*-methoxyphenyl. Length of the linker can influence the cytotoxic activity. Hybrids linked with butanediamine (n = 3) and amyl diamine (n = 4) exhibited greater potency than hexanediamine (n = 5). Most of the compounds in the series showed profound cytotoxicity than the standards 5-Fluorouracil and Harmine. Compound **27** selectively suppress the liver cancer cells (SMMC-7721). Mechanistic studies have shown that they decrease the mitochondrial membrane potential which was associated with the down regulation of Bcl-2 and up regulation of

Bax in dose dependent manner. **27** can be considered as a novel molecule for the intervention of various cancers [14].

3.13. Hydantoin, thiohydantoin and urea-THBC derivative

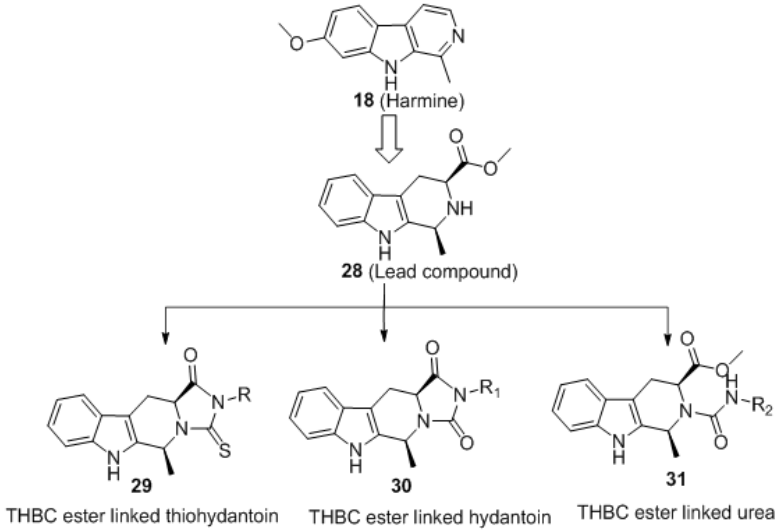


Fig. (20). Lead optimization of THBC linked thiohydantoin, hydantoin and urea derivatives.

By employing structural diversity oriented synthesis, Wang *et al.* designed and synthesized a series of tetrahydro-*β*-carboline ester linked with hydantoin, thiohydantoin and urea motifs. Compounds **29, 30** and **31** (**Fig. 20**) exhibited higher anti-TMV activity *in vitro* and *in vivo* than that of commercial plant virucide ribavirin. Some of the compounds showed good fungicidal and insecticidal activity against *Plutella xylostella* and *Culex pipiens pallens.* Hydantoin, thiohydantoin and urea motifs of these hybrids can improve the activities of the natural products. SAR studies states that substituents on thiohydantoin moiety have a great influence on anti-TMV activity. Sterically hindered substituents (R = isopropyl ≈ cyclohexyl > cyclopentyl > n-butyl) on thiohydantoin possesses better anti-TMV activity. Anti-TMV activity of the compound was increased if we change the substituent from phenyl to benzyl. In case of *N*-phenyl hydantoin, the compounds substituted with electron withdrawing groups shows profound activity compared to electron donating groups. The order of reactivity of substituents on ureas was isopropyl > cyclopentyl > t-butyl ≈ cyclohexyl. Hydantoin and urea compounds exhibit higher insecticidal property rather than thiohydantoin. Whereas, tetrahydro-*β*-carboline ester linked with hydantoin, thiohydantoin and urea derivatives are the potent scaffolds for possessing anti-TMV activity rather than the standard (ribavirin) [97].

3.14. Hydroxamate-β-carboline derivatives

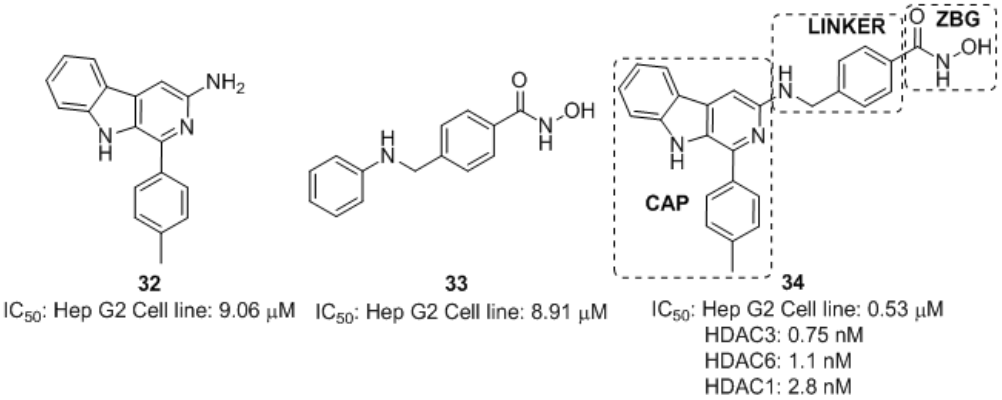
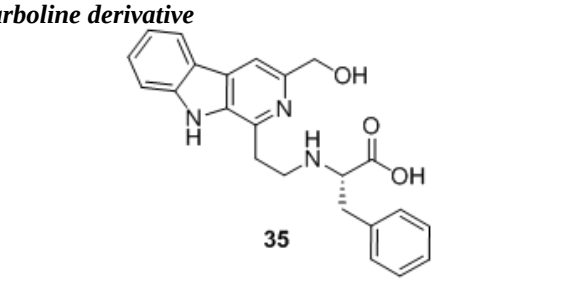


Fig. (21). *β*-carboline hydroxamates.

β-carboline based hydroxamate hybrids comprised of *β*-carboline as cap, benzylic as linker and hydroxamate as ZBG were tested against various cancer cell lines. SAR studies states that C_1 substitution had significant effect on HDAC1 inhibitory activity. Compounds with electron rich groups (methoxy, methyl) at C_1 position was more potent compared to electron deficient groups such as nitro. Compound **34** showed most potent activity with an IC_{50} value 0.53-1.56 μM than standard drug Harmine (IC_{50}: 46.7-55.3 μM). Potency of **34** (**Fig. 21**) against HepG2 cells was 15 and 16 fold lower than **33** and **32** (**Fig. 21**). Further mechanistic studies revealed that **34** inhibit histone H3 and α-tubulin acetylation in dose dependent manner. Moreover it arrest G2/M phase in HepG2 cells through inhibiting the cell cycle related protein CDK1 and cyclin B in dose

dependent manner. **34** reduced the protein level of MMP2 and MMP9 thereby inhibit MAPK pathway. Thus **34** can be considered as a potential candidate for the development of antitumor agents in case of Hepatocellular carcinoma [98].

3.15. Phenylalanine-β-carboline derivative



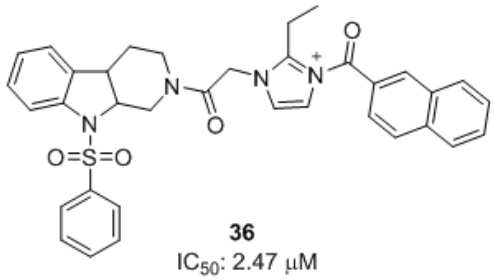
35

N-(3-hydroxymethyl-β-carboline-1-yl-ethyl-2-yl)-l-Phe
(HMCEF)

Fig. (22). HMCEF as P-selectin inhibitor.

Wu *et al*. developed a P-selectin inhibitor (**Fig. 22**) capable of inhibiting thrombosis and inflammation. HMCEF is a nanoscaled antitumor drug, forms nanoparticles with a diameter of <120 nm that promote delivery in blood circulation. HMCEF intercalates with DNA and inhibit the proliferation of cells. Thus the author discloses HMCEF is a promising antitumor drug used in thrombosis and inflammation patients [99].

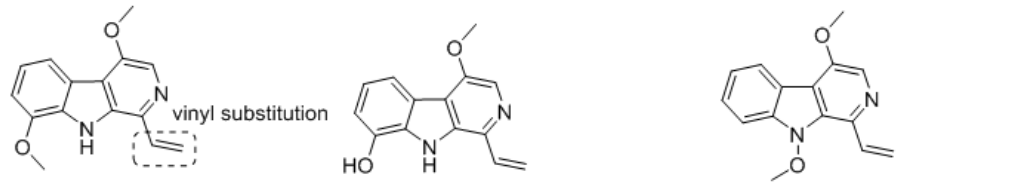
3.16. Imidazolium –THBC derivative



36
IC_{50}: 2.47 μM

Fig. (23). Tetrhydro-*β*-carboline imidazolium salt as MEK-1 inhibitor.

To design MEK-1 inhibitors, Meng *et al*. employed *in silico* approaches for the construction of *N*-substituted tetrahydro-*β*-carboline imidazolium salt (**Fig. 23**) derivatives and its potential target was identified by QASR, PharmMapper and molecular docking studies. Molecular docking studies demonstrated that target protein was stable for 0.8–5 ns. Benzenesulfonylated substitution in compound **36** showed ligand receptor interaction with Lys192, naphthyl ring showed aromatic interactions with Asp208 or Phe209. Thus suggesting *N*-substituted tetrahydro-*β*-carboline and imidazole as promising scaffolds for the development of MEK-1 inhibitors [100].



37
IC_{50}: HepG2 cell line: 3.21±0.08 μM
Hep3B cell line: 19.41±0.64 μM

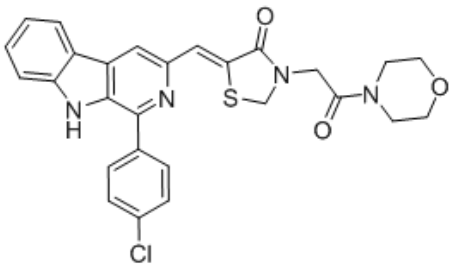
38
IC_{50}: HepG2 cell line: 8.47±0.87 μM
Hep3B cell line: 16.28±0.68 μM

39
IC_{50}: HepG2 cell line: 14.85±1.28 μM
Hep3B cell line: 66.60±5.23 μM

Fig. (24). *β*-carboline derivatives.

Huang *et al*. identified 39 *β*-carboline alkaloids from *picrasma quassioides*. Compound **37**, **38** and **39** (**Fig. 24**) were the most potent compounds comparable with sorafinib (IC_{50}: 8.35 μM) and shows better activity than 5-FU (IC_{50}: 27.06 μM). SAR studies revealed that double bond at C-3 position enhances the activity and order of reactivity: vinyl > acetyl > aldehyde > ester group. Two oxygen substitutions in the structure displayed better activity. Potent compounds induce apoptosis *via* activating caspase-3. These hybrids represent valuable complement to existing chemotherapies [101].

3.17. Thiazolidinedione-β-carboline derivative



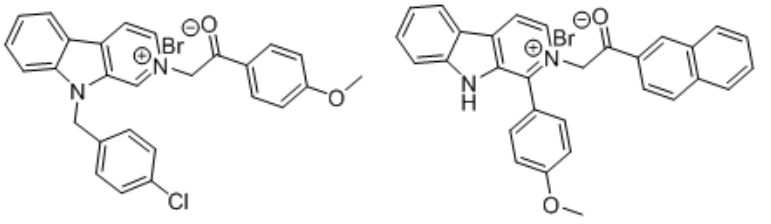
40

IC_{50}: MDA-MB-231 cell line: 0.97±0.13 μM

Fig. (25). *β*-carboline based thiazolidinedione derivatives.

Shankaraiah *et al*. (**Fig. 25**) designed a series of *β*-carboline-thiazolidinedione hybrids and tested against various cancer cell lines. SAR analysis clearly indicated that C_1 position of *β*-carboline bearing benzaldehyde substituted with electron withdrawing group at para position displayed better cytotoxic activity rather than electron donating groups. Compound **40** was the most potent against MDA-MB-231 with an IC_{50} value 0.97±0.13 μM. Further, pharmacological studies states that compound **40** arrest the cell cycle at subG1 phase. Spectroscopic and molecular modelling studies showed the classical interaction with CT-DNA bearing the binding constant value 1×10^5 M^{-1} [102].

3.18. β-carbolinium bromide derivatives



41

IC_{50}: HeLa cell line: 3.2±0.9 μM
HEK293T cell line: 3.8±1.1 μM

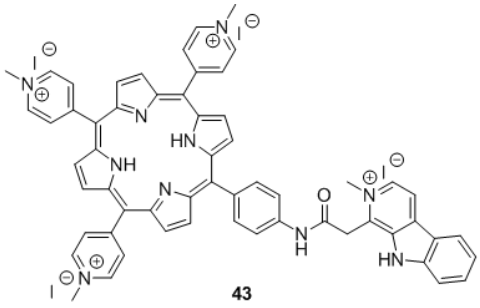
42

IC_{50}: HeLa cell line: 15.5±2.0 μM
HEK293T cell line: 11.6±1.9 μM

Fig. (26). *β*-carbolinium bromides as tubulin inhibitors.

Dalip kumar *et al*. synthesized *β*-carbolinium bromides (**Fig. 26**) from easily available starting materials *i.e*, *β*-carbolines and 1-aryl-2-bromoethanones. Most potent derivative **41** tested against BxPC-3, HeLa, C4-2, PC-3, HEK293T and MDA-MB-231cancer cell line with an IC_{50} value 3.16-7.93 μM. In order to understand the in depth mechanism of action, **41** and **42** were exposed to castration resistant prostate cancer cell line (C4–2) and resulted in increased levels of cleaved PARP1 as well as inhibited the tubulin polymerization. From the results, it can be observed that modifications in the structure of *β*-carbolinium bromides may ensue potent cytotoxic agents [103].

3.19. **Porphyrin-*β*-carboline derivative**



43

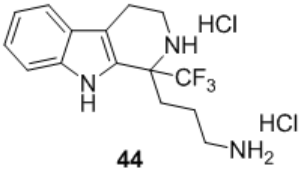
IC_{50}: Colon26 cell line: 47 nM
A549 cell line: 39 nM
Binding constant value: 2.3×10^6 M^{-1}

Fig. (27). Porphyrin linked *β*-carbolines.

Dalip kumar *et al.* developed a microwave assisted approach to prepare water-soluble cationic porphyrin-*β*-carboline conjugates (**Fig. 27**) by coupling *β*-carboline acid and 5-(4-aminophenyl)tripyridyl porphyrin. *N*-Methylation of porphyrin-*β*-carboline conjugate rapidly afforded to form cationic porphyrin-*β*-carboline. Compound **43** was the most potent against colon26 and A549 cell line with an IC_{50} value: 47 nM and

39 nM. Additionally, porphyrin-*β*-carboline conjugate **43** possess binding constant (K_b) value 2.3×10^6 M^{-1} similar to H_2TMPyP (2.5×10^6 M^{-1}) displayed visible light induced DNA cleavage and triggered efficient cell death. Thus compound **43** was proved to be a novel and potent photosensitizing agent and likely to be a potential candidate for PDT [104].

3.20. Trifluoromethylated –THBC derivative



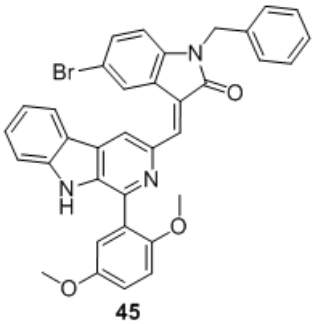
44

GI_{50} : HCT-116: 6.2 μM

Fig. (28). Trifluoromethylated carboline derivatives.

Kakali Bhadra *et al*. reported a series of trifluoromethylated carboline (**Fig. 28**) compounds with an additional amino alkyl (α- or δ-position) and guanidine (α-position) alkyl chains of varying length. SAR analysis revealed that incorporation of trifluoromethyl group could significantly improve the metabolic stability, lipophilicity and other physicochemical properties of target molecules. Binding affinity with CT-DNA decreases with increase chain length because of its bulky nature. Order of reactivity towards DNA binding: γ-carboline > *β* with amino alkyl chain > guanidine alkyl chain. Compound **44** showed potent cytotoxicity with GI_{50} 6.2 μM against HCT-116 cell line. *β*-carboline with amino alkyl chain possess poor cytotoxicity. Mode of binding and partial interaction was supported by viscosity studies and FTIR. These results may be useful for designing novel carboline derivatives for improved therapeutic applications in future [16].

3.21. Indolinone-β-carboline derivative



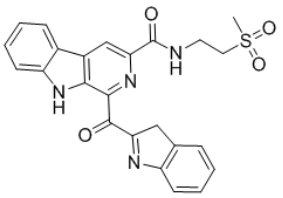
45

GI_{50} : HCT-116: 0.89±0.06 μM
IC_{50} : HCT-116: 1.43±0.26 μM

Fig. (29). *β*-carboline linked indolinone conjugates.

Shankaraiah *et al*. synthesized a series of (*E*)-3-((1-aryl-9*H*-pyrido[3,4-*b*]indol-3yl)methylene)indolin-2-one congeners (**Fig. 29**) and evaluated for their *in vitro* cytotoxic activity. Compound **45** showed potent cytotoxicity with an IC_{50} of 1.43±0.26 μM and GI_{50} value of 0.89±0.06 μM respectively. Further, mechanistic studies was performed by using various assays such as annexin V-FITC/PI, DCFDA, and JC-1to understand the in depth mechanism of action. Compound **45** arrested the cell cycle at G0/G1 phase. Additionally, western blot analysis indicated that compound **45** on HCT-15 cancer cells led to decreased expression of Bcl-2 and increased protein expression of pro-apoptotic proteins such as Bax, caspase-3, 8, 9 and cleaved PARP with reference to actin [105].

3.22. Indole-β-carboline derivative



46

IC_{50}: SGC-7901: 6.82 ± 0.98 μM
MARC145: 7.19 ± 1.43 μM

Fig. (30). *β*-carboline amides as cytotoxic agents.

Ke *et al*. synthesized a series of *β*-carboline amide derivatives (**Fig. 30**) from natural marine alkaloid Pityriacitrin and evaluated their *in vitro* cytotoxic potential. Compound **46** with sulfonyl group possess highest inhibitory activity against SGC-7901 (IC_{50}: 6.82±0.98 μM), A875 (IC_{50}: 8.43±1.93 μM), HepG2 (IC_{50}:

7.69±2.17 μM), MARC145 (IC_{50}: 7.19±1.43 μM) respectively. The author discloses compound **46** might be a lead molecule for development of novel cytotoxic agents [106].

3.23. Podophyllotoxin-β-carboline derivative

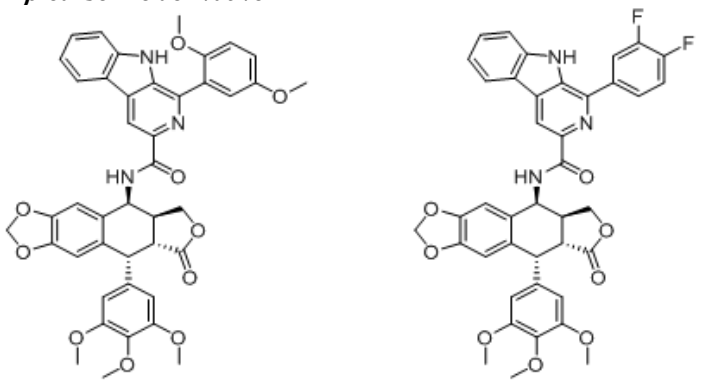


Fig. (31). Podophyllotoxin based *β*-carbolines as Topo-II inhibitors.

By utilizing the molecular hybridization strategy, kamal *et al*. (**Fig. 31**) has synthesized a series of podophyllotoxin linked *β*-carboline conjugates and evaluated their cytotoxic potential and Topo II inhibitory activity. **47** and **48** were the most potent among the series of compounds. External binding affinity of compounds **47** and **48** was disclosed by DNA binding studies. Detailed biological studies such as cell cycle analysis, Comet assay, DNA binding studies and topoisomerase II inhibition studies have revealed that these congeners are DNA interacting topoisomerase II inhibitors. Molecular docking studies states that all the interactions strengthen through minor groove binding affinity [107].

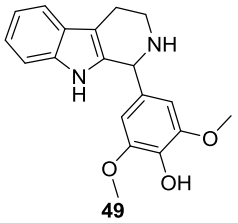


Fig. (32). Tetrahydro-*β*-carboline derivative.

Byeon *et al.* reported a new method for the synthesis of four tetrahydro-β-carbolines (tryptolines, **Fig. 32**) by using Pictet-Spengler reaction followed by evaluation of cytotoxic potential against EJ cells for anticancer-activity. Compound **49** showed highest inhibitory activity against EJ cells whereas least cytotoxicity with an LC_{50} value of 1.49 mg/mL in the brine shrimp lethality assay [108].

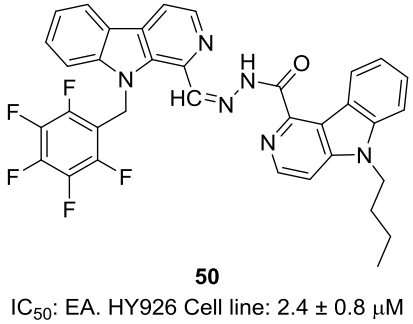
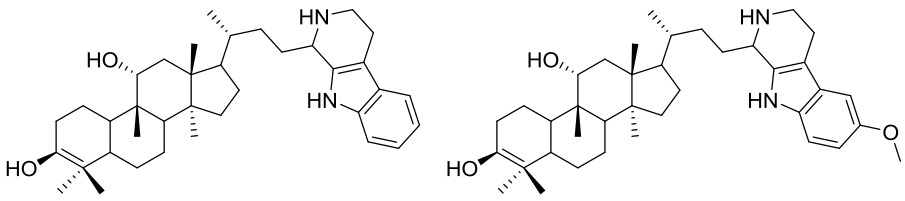


Fig. (33). *N*-acylhydrazone-linked hetero bivalent *β*-carboline derivative (**Fig. 33**)as cytotoxic agents.

Guo *et al.* synthesized a series of *N*-acylhydrazone-linked hetero bivalent β-carboline derivatives and evaluation of its cytotoxic potential against EA.HY926 cells and 5other cancer cell lines (LLC, BGC-823, CT-26, Bel-7402 and MCF-7). SAR studies disclosed the impact of the substituent in the R9′-position of β-carboline ring on cytotoxic activities are in the order: 2,3,4,5,6-perfluorophenylmethyl > 4-fluorobenzyl > 3-phenyl propyl group. The compound **50** was found to show anti-proliferative activity with an IC_{50} value of 2.4±0.8 μM against EA.HY926 cells. It was also found to exhibit most potent cytotoxic activity with IC_{50} values ranging from 4.2 ± 0.7 to 18.5 ± 3.1μM on cancer cell lines [109].



51

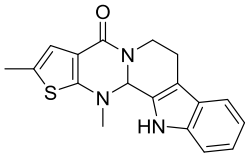
IC_{50}: A549 cell line: 9.21±0.77 μM
CNE1 cell line: 9.07±1.50 μM

52

IC_{50}: A549 cell line: 2.58±0.31 μM
CNE1 cell line: 3.28±0.27 μM

Fig. (34). *β*-carboline linked morgol derivatives as cytotoxic agents.

Wang *et al.* separated four metabolites of mogrol and then synthesized amines, alcohols and rigid planar derivatives of mogrol. These molecules were evaluated for cytotoxic activity and among them compound **51** and **52** were found to be most potent compared to mogrol (IC_{50} = 80–90 μM, **Fig. 34**). Compound **51** exhibited IC_{50} values of 9.21±0.77 and 9.07±1.50against A549 and CNE1 cell respectively. Compound **52** exhibited IC_{50} values of 2.58±0.31 and 3.28±0.27 against A549 and CNE1 cell respectively. Authors found that perhydro cyclo pentanophenanthrene moiety and the tetrahydro-*β*-carboline moiety were responsible for the increased cytotoxic activity [110].

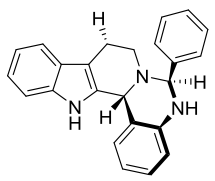


53

IC_{50}: A549 cell line: 10.45±1.27 μM
PC-9 cell line: 9.46±0.24 μM
MCF-7 cell line: 9.02±1.12 μM
PC-3 cell line: 7.77±0.77 μM

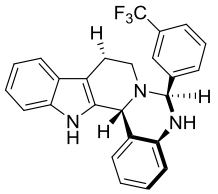
Fig. (35). *β*-carboline derivatives as cytotoxic agents.

12 hybrids of natural alkaloid evodiamine/rutaecarpine and thieno[2,3-d]pyrimidinones were synthesized by Nie *et al.* Further, evaluated these compounds for cytotoxic activity. Compound **53** showed potential cytotoxic activity on MCF-7, A549, PC-9 and PC-3 cell lines (with IC_{50} of 10.45±1.27, 9.46±0.24, 9.02±1.12 and 7.77±0.77μM respectively, **Fig. 35**). Colony formation assay confirmed that it could dose-dependently inhibit the proliferation of cancer cells [111].



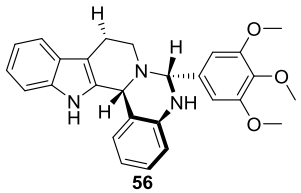
54

IC_{50}: PANC-1 cell line: 7.0 ± 1.9 μM
COLO-205 cell line: 5.6 ± 0.56 μM
A2058 cell line: 14 ± 3.2 μM
EBC-1 cell line: 6.4 ± 1.1 μM



55

IC_{50}: PANC-1 cell line: 2.8 ± 1.0 μM
COLO-205 cell line: 1.5 ± 0.59 μM
A2058 cell line: 2.5 ± 0.4 μM
EBC-1 cell line: 4.7 ± 0.41 μM



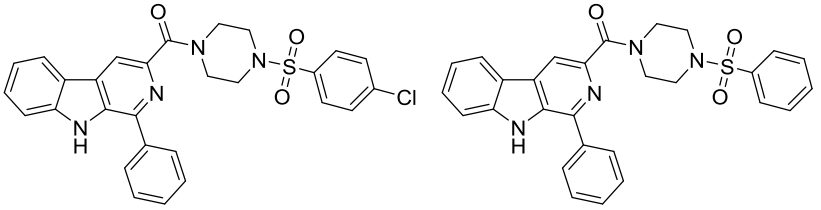
56

IC_{50}: PANC-1 cell line: 5.2 ± 2.3 μM
COLO-205 cell line: 2.5 ± 0.094 μM
A2058 cell line: 2.1 ± 0.19 μM
EBC-1 cell line: 4.1 ± 0.78 μM

Fig. (36). Partly saturated poly-condensed *β*-carboline derivatives as anti-tumor agents.

Fodor *et al.* synthesized a series of partly saturated novel poly-condensed β-carbolines (**Fig. 36**) and evaluated them for cytotoxic activity on four human tumour cell lines PANC-1, COLO-205, A2058 and EBC-1. DFT calculations were performed to determine the suitable mechanisms for the characteristic substituent-dependent diastereoselective formation of the products. Potent cytotoxic activity was exhibited by the trans

diastereomers having phenyl substituent **54** (IC_{50} values 7.0±1.9, 5.6±0.56, 14±3.2 and 6.4±1.1μM) and3-trifluoromethylphenyl substituent **55** (IC_{50} values 2.8±1.0, 1.5±0.59, 2.5±0.4 and 4.7±0.41μM) against PANC-1, COLO-205, A2058 and EBC-1 cell lines respectively. Compound **56,** a racemic cis-pentacycle showed highest potency with IC_{50} values of 5.2±2.3, 2.5±0.094, 2.1±0.19 and 4.1±0.78 against PANC-1, COLO-205, A2058 and EBC-1 cell lines respectively whereas it's trans form was found inactive [112].

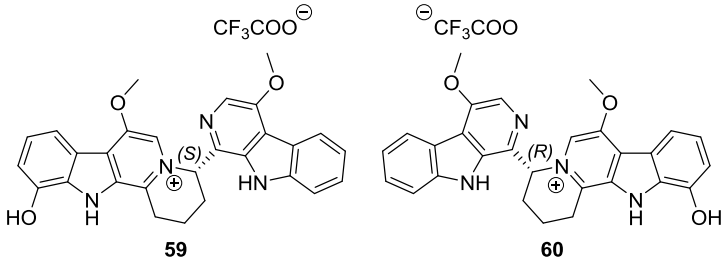


57 IC_{50}: MG-63 cell line: 2.80±0.10 μM

58 IC_{50}: MG-63 cell line: 0.59±0.28 μM

Fig. (37). *β*-carbolinelinked aryl sulfonyl piperazine derivatives as human TopoIIα inhibitors.

Babu *et al.* reported the synthesis of novel β-carboline linked aryl sulfonyl piperazine derivatives (**Fig. 37**) and evaluated for cytotoxic activity against HT-29, MDA-MB-231, MG-63, U87 MG, PC- 3 and Vero cell lines. Compound **57** and **58** was found to exhibit least IC_{50} values of 2.80±0.10 μM and 0.59±0.28 μM respectively against MG-63 cell line. Specific Topo II inhibition assay confirmed that compounds **57** and **58** inhibited Topo II. Molecular docking studies revealed that both the compounds bind in the ATP binding domain of hTopoIIα and at the minor groove of duplex DNA. β-carboline NH and carbonyl groups in compound **58** showed two H-bond interactions, sulfonyl phenylmoiety showed π-cation interaction with ATP binding domain residues of hTopoIIα. It also showed many hydrophobic interactions with Ile33, Tyr34, Pro100, Pro126 and Tyr186residues. β-carboline NH and carbonyl groups in compound **57** showed H-bond interaction with back bone and side chain of Arg98, β-carboline moiety also formed π-cation contact with Arg98 and many hydrophobic interactions with ATP binding domain residues of hTopoIIα [113].



59 IC_{50}: HeLa cell line: 1.58 μM

60 IC_{50}: HeLa cell line: 0.59±0.28 μM

Fig. (38). bis-β-carboline alkaloid enantiomers as cytotoxic agents.

By using chromatographic techniques, Guo *et al*. isolated a pair of new bis-β-carboline (**Fig. 38**) alkaloid enantiomers,(±)-Quassidine K. Among them, Compound **59** and **60** showed potent activity with an IC_{50} value 15.8 and 20.1μMrespectively against HeLa cells [114].

V. Conclusion and Outlook

Natural products act as a creative source for drug-leads and are deep-seated in drug discovery due to their biological activity and wider chemical space. Synthetic renewal of these natural products to semi-synthetic derivatives and natural-product like molecules with clinical significance is an attractive area for chemists. *β*-carbolines represent an importance class of indole-based alkaloids with wide spectrum of anticancer activities exerting through varied mechanisms by interacting with different enzymes/targets/receptors. The prerequisite for the development of novel *β*-carbolines as a potential anticancer agents include site specificity, enhancing potency with improved pharmacokinetic profile, metabolic stability with minimal side effects, improvement in the bioavailability and incidence of drug resistance. In this review, attempts have been taken to focus the occurrence, structural diversity, highlighted the latest information available on anticancer attributes of *β*-carbolines with the addition of relevant SAR and binding interactions studied through molecular docking, mainly covering the years 2017-19. Further, we believe that variedly functionalized *β*-carboline derivatives and *β*-carboline hybrids integrated in this review will help to improve the status of this privileged scaffold in its future synthesis for drug discovery applications.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

Acknowledgements

The authors thank the Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers Govt. of India, New Delhi for the award of NIPER fellowship.

References

[1]. Newman, D. J.; Cragg, G. M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod. 2012, 75, 311−335.
[2]. Brahmachari, G. Natural products in drug discovery: impacts and Opportunities-an assessment, Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry, 2011, 1−199.
[3]. Chen, Y.; Garcia de Lomana, M.; Friedrich N.O.; Kirchmair, J. Characterization of the Chemical Space of Known and Readily Obtainable Natural Products. J. Chem. Inf. Model. 2018, 58(8), 1518-1532.
[4]. Butler, M.S. The role of natural product chemistry in drug discovery. J. Nat. Prod. 2004, 67, 2141−2153.
[5]. Siddiqui, A.A.; Iram, F.; Siddiqui, S.; Sahu, K. Role of Natural Products in Drug Discovery Process. Int. J. Drug Dev. & Res. 2014, 6(2), 172-204.
[6]. Cragg, G.M.; Grothaus, P.G.; Newman, D.J. Impact of natural products on developing new anti-cancer agents. Chem. Rev. 2009, 109, 3012−3043.
[7]. Koehn, F.E.; Carter, G.T. The evolving role of natural products in drug discovery. Nat Rev Drug Discov. 2005, 4(3), 206-220.
[8]. DeCorte, B.L. Underexplored Opportunities for Natural Products in Drug Discovery. J. Med. Chem. 2016, 59(20), 9295-9304.
[9]. Lee, K.H. Discovery and Development of Natural Product-Derived Chemotherapeutic Agents Based on a Medicinal Chemistry Approach. J. Nat. Prod. 2010, 73, 500–516.
[10]. Newman, D.J. Natural Products as Leads to Potential Drugs: An Old Process or the NewHope for Drug Discovery? J. Med. Chem. 2008, 51, 2589–2599.
[11]. Vasilevich, N.I.; Kombarov, R.V.; Genis, D.V.; Kirpichenok, M.A. Lessons from Natural Products Chemistry Can Offer Novel Approaches for Synthetic Chemistry in Drug Discovery. J. Med. Chem. 2012, 55(16), 7003-7009.
[12]. Ertl, P.; Roggo, S.; Schuffenhauer, A. Natural product-likeness score and its application for prioritization of compound libraries. J. Chem. Inf. Model. 2008, 48, 68−74.
[13]. Walters, W.P.; Green, J.; Weiss, J.R.; Murcko, M.A. What do medicinal chemists actually make? A 50-year retrospective. J. Med. Chem. 2011, 54, 6405−6416.
[14]. Xu, Q.B.; Chen, X.F.; Feng, J.; Miao, J.F.; Liu, J.; Liu, F.T.; Niu, B.X.; Cai, J.Y.; Huang, C.; Zhang, Y.; Ling, Y. Design, synthesis and biological evaluation of hybrids of β-carboline and salicylic acid as potential anticancer and apoptosis inducing agents. Scientific reports. 2016, 6(1), 36238.
[15]. Smirnova, O.B.; Golovko, T.V.; Granik, V.G. Carbolines. Part 2: comparison of some of the properties of α-, γ- and δ-carbolines (Review), Pharmaceut. Chem. J. 2011, 45, 389-400.
[16]. Sarkar, S.; Shmatova, O.I.; Nenajdenko, V.G.; Bhadra, K. Trifluoromethylated carboline compounds targeting DNA: Synthesis, binding and anti-proliferative effects on human cancer cell lines. Bioorg. Chem. 2019, 86, 61-79.
[17]. Cao, R.; Peng, W.; Wang, Z.; Xu, A. Carboline Alkaloids: Biochemical and Pharmacological Functions. Curr. Med. Chem. 2007, 14(4), 479-500.
[18]. Huang, H.; Yao, Y.; He, Z.; Yang, T.; Ma, J.; Tian, X.; Li, Y.; Huang, C.; Chen, X.; Li, W.; Zhang, S.; Zhang, C.; Ju, J. Antimalarial β-Carboline and Indolactam Alkaloids from Marinactinosporathermotolerans, a Deep Sea Isolate. J. Nat. Prod. 2011, 74, 2122-2127.
[19]. Li, Y.; Yan, W.; Yang, J.; Yang, Z.; Hu, M.; Bai, P.; Tang, M.; Chen, L. Discovery of novel β-carboline/acylhydrazone hybrids as potent antitumor agents and overcome drug resistance. Eur. J. Med. Chem. 2018, 152, 516-526.
[20]. Gu, H.; Li, N.; Dai, J.; Xi, Y.; Wang, S.; Wang, J. Synthesis and In Vitro Antitumor Activity of Novel Bivalent β-Carboline-3-carboxylic Acid Derivatives with DNA as a Potential Target. Int. J. Mol. Sci. 2018, 19(10), 3179.
[21]. Louis, E.D.; Zheng, W. β-Carboline alkaloids and essential tremor: exploring the environmental determinants of one of the most prevalent neurological diseases. The Scientific World Journal. 2010, 10, 1783-1794.
[22]. (a) Polanski, W.; Reichmann, H.; Gille, G. Stimulation, protection and regeneration of dopaminergic neurons by 9-methyl-β-carboline: a new anti-Parkinson drug? Expert Rev. Neurother. 2011, 11(6), 845-860; (b) Rook, Y.; Schmidtke, K.U.; Gaube, F.; Schepmann, D.; Wünsch, B.; Heilmann, J.; Lehmann, J.; Winckler, T. Bivalent β-carbolines as potential multitarget anti-Alzheimer agents. J. Med. Chem. 2010, 53(9), 3611-3617; (c) Volk, R.B.; Furkert, F.H. Antialgal, antibacterial and antifungal activity of two metabolites produced and excreted by cyanobacteria during growth. Microbiological Res. 2006, 161(2), 180-186. (d) Shin, H.J.; Lee, H.S.; Lee, D.S. The synergistic antibacterial activity of 1-acetyl-beta-carboline and beta-lactams against methicillin-resistant Staphylococcus aureus (MRSA). J. Microbiol. Biotechnol. 2010, 20(3), 501-505; (e) Rao, K.V.; Kasanah, N.; Wahyuono, S.; Tekwani, B.L.; Schinazi, R.F.; Hamann, M.T. Three new manzamine alkaloids from a common Indonesian sponge and their activity against infectious and tropical parasitic diseases. J. Nat. Prod. 2004, 67(8), 1314-1318; (f) Rinehart Jr, K.L.; Kobayashi, J.; Harbour, G.C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Lafargue, F. Eudistomins A-Q .beta.-carbolines from the antiviral Caribbean tunicate Eudistomaolivaceum. J. Am. Chem. Soc. 1987, 109(11), 3378-3387; (g) Frédérick, R.; Bruyère, C.; Vancraeynest, C.; Reniers, J.; Meinguet, C.; Pochet, L.; Backlund, A.; Masereel, B.; Kiss, R.; Wouters, J. Novel trisubstituted harmine derivatives with original in vitro anticancer activity. J. Med. Chem. 2012, 55(14), 6489-6501.
[23]. (a) Li, Y.; Liang, F.; Jiang, W.; Yu, F.; Cao, R.; Ma, Q.; Dai, X.; Jiang, J.; Wang, Y.; Si, S. DH334, a β-carboline anti-cancer drug, inhibits the CDK activity of budding yeast. Cancer Biol. Ther. 2007, 6(8), 1204-1210; (b) Barsanti, P.A.; Wang, W.; Ni, Z.J.; Duhl, D.; Brammeier, N.; Martin, E.; Bussiere, D.; Walter, A.O. The discovery of tetrahydro-β-carbolines as inhibitors of the kinesin Eg5. Bioorg. Med. Chem. Lett. 2010, 20(1), 157-160.
[24]. (a) Kamal, A.; Srinivasulu, V.; Nayak, V.L.; Sathish, M.; Shankaraiah, N.; Bagul, C.; Reddy, N.S.; Rangaraj, N.; Nagesh, N. Design and Synthesis of C3-Pyrazole/Chalcone-Linked Beta-Carboline Hybrids: Antitopoisomerase I, DNA-Interactive, and Apoptosis-Inducing Anticancer Agents. Chem. Med. Chem. 2014, 9(9), 2084-2098; (b) Jimenez, J.; Riveron-Negrete, L.; Abdullaev, F.; Espinosa-Aguirre, J.; Rodríguez-Arnaiz, R. Cytotoxicity of the β-carboline alkaloids harmine and harmaline in human cell assays in vitro. Exp. Toxicol. Pathol. 2008, 60(4-5), 381-389.
[25]. Trujillo, J.I.; Meyers, M.J.; Anderson, D.R.; Hegde, S.; Mahoney, M.W.; Vernier, W.F.; Buchler, I.P.; Wu, K.K.; Yang, S.; Hartmann, S.J.; Reitz, D.B. Novel tetrahydro-β-carboline-1-carboxylic acids as inhibitors of mitogen activated protein kinase-activated protein kinase 2 (MK-2). Bioorg. Med. Chem. Lett. 2007, 17(16), 4657-4663.

[26]. (a) Zhang, J.; Li, Y.; Guo, L.; Cao, R.; Zhao, P.; Jiang, W.; Ma, Q.; Yi, H.; Li, Z.; Jiang, J.; Wu, J. DH166, a beta-carboline derivative, inhibits the kinase activity of PLK1. Cancer. Biol. Ther. 2009, 8(24), 2374-2383; (b) Li, X.; Bai, B.; Liu, L.; Ma, P.; Kong, L.; Yan, J.; Zhang, J.; Ye, Z.; Zhou, H.; Mao, B.; Zhu, H. Novel β-carbolines against colorectal cancer cell growth via inhibition of Wnt/β-catenin signaling. Cell. Death. Dis. 2015, 1, 15033.

[27]. (a) Göckler, N.; Jofre, G.; Papadopoulos, C.; Soppa, U.; Tejedor, F.J.; Becker, W. Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation. The FEBS journal. 2009, 276(21), 6324-6337. (b) Seifert, A.; Allan, L.A.; Clarke, P.R. DYRK1A phosphorylates caspase 9 at an inhibitory site and is potently inhibited in human cells by harmine. The FEBS journal. 2008, 275(24), 6268-6280.

[28]. Wu, J.; Zhao, M.; Qian, K.; Lee, K.H.; Morris-Natschke, S.; Peng, S. Novel N-(3-carboxyl-9-benzyl-β-carboline-1-yl) ethylamino acids: synthesis, anti-tumor evaluation, intercalating determination, 3D QSAR analysis and docking investigation. Eur. J. Med. Chem. 2009, 44(10), 4153-4161.

[29]. Hagen, T.J.; Skolnick, P.; Cook, J.M. Synthesis of 6-substituted beta-carbolines that behave as benzodiazepine receptor antagonists or inverse agonists. J. Med. Chem. 1987, 30, 4750-753.

[30]. Manasa, K.L.; Tangella, Y.; Ramu, G.; Babu, B.N. TCCA; A Mild Reagent for Decarboxylative/Dehydrogenative Aromatization of Tetrahydro-β-carbolines: Utility in the Total Synthesis of Norharmane, Harmane, Eudistomin U, I and N. ChemistrySelect. 2017, 2, 9162-9167.

[31]. Grella, B.; Teitler, M.; Smith, C.; Herrick-Davis, K.; Glennon, R.A. Binding of β-Carbolines at 5-HT2 serotonin receptors. Bioorg. Med. Chem. Lett. 2003, 13, 4421-4425.

[32]. Zheng, H.; Li, L.; Sun, B.; Gao, Y.; Song, W.; Zhao, X.; Gao, Y.; Xie, Z.; Zhang, N.; Ji, J.; Yuan, H.; Lou, H. Design and synthesis of furyl/thienyl pyrroloquinolones based on natural alkaloid perlolyrine, lead to the discovery of potent and selective PDE5 inhibitors. Eur. J. Med. Chem. 2018, 150, 30-38.

[33]. Hayashi, K.; Nagao, M.; Sugimura, T. Interactions of norharman and harman with DNA. Nucleic Acids Res. 1977, 4(11), 3679-3686.

[34]. Madle, E.; Obe, G.; Hansen, J.; Ristow, H. Harman and norharman: induction of sister-chromatid exchanges in human peripheral lymphocytes in vitro and interaction with isolated DNA. Mutat. Res.Genet. Toxicol. 1981, 90(4), 433-442.

[35]. Mita, S.; Kamataki, T.; Kato, R. Effect of norharman on DNA strand breaks and mutation of Chinese hamster V79 cells by chemical carcinogens. Carcinogenesis. 1984, 5(6), 715-718.

[36]. Shimoi, K.; Kawabata, H.; Tomita, I. Enhancing effect of heterocyclic amines and ß-carbolines on UV or chemically induced mutagenesis in E. coli. Mutat. Res. Fund. Mol. M. 1992, 268(2), 287-295.

[37]. Funayama, Y.; Nishio, K.; Wakabayashi, K.; Nagao, M.; Shimoi, K.; Ohira, T.; Hasegawa, S.; Saijo, N. Effects of β-and γ-carboline derivatives on DNA topoisomerase activities. Mutat. Res. Fund. Mol. M. 1996, 349(2), 183-191.

[38]. Herraiz, T.; Chaparro, C. Human monoamine oxidase enzyme inhibition by coffee and β-carbolines norharman and harman isolated from coffee. Life Sci. 2006, 78(8), 795-802.

[39]. Kühn-Velten, W.N. Norharman (β-carboline) as a potent inhibitory ligand for steroidogenic cytochromes P450 (CYP11 and CYP17). Eur. J. Pharmacol. 1993, 250(1), R1-R3.

[40]. Okereke, C.S. Role of integrative pharmacokinetic and pharmacodynamic optimization strategy in the management of Parkinson's disease patients experiencing motor fluctuations with levodopa. J. Pharm. Sci. 2002, 5(2), 146-61.

[41]. Kim, H.; Sablin, S.O.; Ramsay, R.R. Inhibition of monoamine oxidase A by β-carboline derivatives. Arch. Biochem. Biophys. 1997, 337(1), 137-142.

[42]. Warner, H.R.; Persson, M.L.; Bensen, R.J.; Mosbaugh, D.W.; Linn, S. Selective inhibition by harmane of the apurinic/apyrimidinic endonuclease activity of phage T4-induced UV endonuclease. Nucleic. Acids. Res. 1981, 9(22), 6083-6092.

[43]. Ishida, J.; Wang, H.K.; Oyama, M.; Cosentino, M.L.; Hu, C.Q.; Lee, K.H. Anti-AIDS agents. 46. Anti-HIV activity of harman, an anti-HIV principle from Symplocossetchuensis, and its derivatives. J. Nat. Prod. 2001, 64(7), 958-960.

[44]. Di Giorgio, C.; Delmas, F.; Ollivier, E.; Elias, R.; Balansard, G.; Timon-David, P. In vitro activity of the β-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species Leishmania infantum. Exp. Parasitol. 2004, 106(3-4), 67-74.

[45]. Cao, R.; Peng, W.; Chen, H.; Ma, Y.; Liu, X.; Hou, X.; Guan, H.; Xu, A. DNA binding properties of 9-substituted harmine derivatives. Biochem. Biophys. Res. Commun. 2005, 338(3), 1557-1563.

[46]. Shimoi, K.; Kawabata, H.; Tomita, I. Enhancing effect of heterocyclic amines and ß-carbolines on UV or chemically induced mutagenesis in E. coli. Mutat. Res. Fund. Mol. M. 1992, 268(2), 287-295.

[47]. Song, Y.; Wang, J.; Teng, S. F.; Kesuma, D.; Deng, Y.; Duan, J.; Wang, J. H.; Qi, R. Z.; Sim, M. M. β-Carbolines as specific inhibitors of cyclin-Dependent kinases. Bioorg. Med. Chem. Lett. 2002 12(7), 1129-1132.

[48]. Hudson, J. B.; Graham, E. A.; Fong, R.; Hudson, L. L.; Towers, G. H. N. Further studies on the antiviral activity of harmine, a photoactive β-carboline alkaloid. Photochem. Photobiol. 1986, 44(4), 483-487.

[49]. Abe, A.; Yamada, H.; Moriya, S.; Miyazawa, K. The β-carboline alkaloid harmol induces cell death via autophagy but not apoptosis in human non-small cell lung cancer A549 cells. Biol. Pharm. Bull. 2011, 34(8), 1264-1272.

[50]. Dejos, C.; Voisin, P.; Bernard, M.; Régnacq, M.; Bergès, T. Canthin-6-one displays antiproliferative activity and causes accumulation of cancer cells in the G2/M phase. J. Nat. Prod. 2014, 77(11), 2481-2487.

[51]. Xu, Z.; Chang, F.R.; Wang, H.K.; Kashiwada, Y.; McPhail, A.T.; Bastow, K.F.; Tachibana, Y.; Cosentino, M.; Lee, K.H. Anti-HIV Agents 45 and Antitumor Agents 205. Two New Sesquiterpenes, Leitneridanins A and B, and the Cytotoxic and Anti-HIV Principles from Leitneriafloridana. J. Nat. Prod. 2000, 63(12), 1712-1715.

[52]. Kolodina, A.A.; Serdyuk, O.V. Eudistomin U, Isoeudistomin U, and related indole compounds: synthesis and biological activity. Heterocycles. 2018, 96(7), 1171-96.

[53]. Youssef, D.T. Hyrtioerectines A− C, Cytotoxic Alkaloids from the Red Sea Sponge Hyrtios e rectus. J. Nat. Prod. 2005, 68(9), 1416-1419.

[54]. Sandler, J.S.; Colin, P.L.; Hooper, J.N.; Faulkner, D.J. Cytotoxic β-Carbolines and Cyclic Peroxides from the Palauan Sponge Plakortisnigra. J. Nat. Prod. 2002, 65(9), 1258-1261.

[55]. Ashok, P.; Ganguly, S.; Murugesan, S. Manzamine alkaloids: isolation, cytotoxicity, antimalarial activity and SAR studies. Drug Discovery Today. 2014, 19(11), 1781-1791.

[56]. Bharate, S.; Manda, S.; Mupparapu, N.; Bathini, N.; A Vishwakarma, R. Chemistry and biology of fascaplysin, a potent marine-derived CDK-4 inhibitor. Mini. Rev. Med. Chem. 2012, 12(7), 650-664.

[57]. Soni, R.; Muller, L.; Furet, P.; Schoepfer, J.; Stephan, C.; Zumstein-Mecker, S.; Fretz, H.; Chaudhuri, B. Inhibition of cyclin-dependent kinase 4 (Cdk4) by fascaplysin, a marine natural product. Biochem. Biophys. Res. Comm. 2000, 275(3), 877-884.

[58]. Shimoi, K.; Kawabata, H.; Tomita, I. Enhancing effect of heterocyclic amines and ß-carbolines on UV or chemically induced mutagenesis in E. coli. Mutat. Res. Fund. Mol. M. 1992, 268(2), 287-295.

[59]. Kaminsky, S.M.; Levy, O.; Garry, M.T.; Carrasco, N. Inhibition of the Na+/I-symporter by harmaline and 3-amino-1-methyl-5H-pyrido (4, 3-b) indole acetate in thyroid cells and membrane vesicles. Eur. J. Biochem. 1991, 200(1), 203-207.

[60]. Di Giorgio, C.; Delmas, F.; Ollivier, E.; Elias, R.; Balansard, G.; Timon-David, P. In vitro activity of the β-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species Leishmania infantum. Exp. parasitol. 2004, 106(3-4), 67-74.

[61]. El Gendy, M.A.; Soshilov, A.A.; Denison, M.S.; El-Kadi, A.O. Harmaline and harmalol inhibit the carcinogen-activating enzyme CYP1A1 via transcriptional and posttranslational mechanisms. Food. Chem. Toxicol. 2012, 50(2), 353-362.

[62]. Wang, K.B.; Yuan, C.M.; Xue, C.M.; Li, D.H.; Jing, Y.K.; He, H.P.; Hao, X.J.; Di, Y.T.; Li, Z.L.; Hua, H.M. Pegaharmalines A and B, two novel β-carboline alkaloids with unprecedented carbon skeletons from Peganum harmala. RSC Advances. 2014, 4(96), 53725-53729.

[63]. Wang, K.B.; Li, D.H.; Hu, P.; Wang, W.J.; Lin, C.; Wang, J.; Lin, B.; Bai, J.; Pei, Y.H.; Jing, Y.K.; Li, Z.L. A series of β-carboline alkaloids from the seeds of Peganum harmala show G-quadruplex interactions. Org. Lett. 2016, 18(14), 3398-3401.

[64]. Wang, K.B.; Di, Y.T.; Bao, Y.; Yuan, C.M.; Chen, G.; Li, D.H.; Bai, J.; He, H.P.; Hao, X.J.; Pei, Y.H.; Jing, Y.K. Peganumine A, a β-carboline dimer with a new octacyclic scaffold from Peganum harmala. Org. Lett. 2014, 16(15), 4028-4031.

[65]. Soares, P.R.; De Oliveira, P.L.; De Oliveira, C.M.; Kato, L.; Guillo, L.A. In vitro antiproliferative effects of the indole alkaloid vallesiachotamine on human melanoma cells. Arch. Pharmacal. Res. 2012, 35(3), 565-571.

[66]. Liu, B.P.L.; Chong, E.Y.Y.; Cheung, F.W.K.; Duan, J.A.; Che, C.T.; Liu, W.K. Tangutorine induces p21 expression and abnormal mitosis in human colon cancer HT-29 cells. Biochem. Pharmacol. 2005, 70(2), 287-299.

[67]. Samita, F.; Ochieng, C.O.; Owuor, P.O.; Manguro, L.O.A.; Midiwo, J.O. Isolation of a new β-carboline alkaloid from aerial parts of Triclisiasacleuxii and its antibacterial and cytotoxicity effects. Nat. Prod. Res. 2017, 31(5), 529-536.

[68]. Lake, R.J.; Blunt, J.W.; Munro, M.H.G. Eudistomins from the New Zealand ascidian Ritterellasigillinoides. Aust. J. Chem. 1989, 42(7), 1201-1206.

[69]. Gul, W.; Hamann, M.T. Indole alkaloid marine natural products: An established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases. Life Sci. 2005, 78(5), 442-453.

[70]. Ota, Y.; Chinen, T.; Yoshida, K.; Kudo, S.; Nagumo, Y.; Shiwa, Y.; Yamada, R.; Umihara, H.; Iwasaki, K.; Masumoto, H.; Yokoshima, S. Eudistomin C, an antitumor and antiviral natural product, targets 40S ribosome and inhibits protein translation. Chem Bio Chem. 2016, 17(17), 1616-1620.

[71]. Yamanokuchi, R.; Imada, K.; Miyazaki, M.; Kato, H.; Watanabe, T.; Fujimuro, M.; Saeki, Y.; Yoshinaga, S.; Terasawa, H.; Iwasaki, N.; Rotinsulu, H. Hyrtioreticulins A–E, indole alkaloids inhibiting the ubiquitin-activating enzyme, from the marine sponge Hyrtiosreticulatus. Bioorg. Med. Chem. 2012, 20(14), 4437-4442.

[72]. Ashok, P.; Lathiya, H.; Murugesan, S. Manzamine alkaloids as antileishmanial agents: a review. Eur. J. Med. Chem. 2015, 97, 928-936.

[73]. Ovenden, S.P.; Nielson, J.L.; Liptrot, C.H.; Willis, R.H.; Tapiolas, D.M.; Wright, A.D.; Motti, C.A. Callophycin A, a cytotoxic tetrahydro-β-carboline from the red algae Callophycusoppositifolius. Phytochem. Lett. 2011, 4(2), 69-71.

[74]. Sonnenschein, R.N.; Farias, J.J.; Tenney, K.; Mooberry, S.L.; Lobkovsky, E.; Clardy, J.; Crews, P.A further study of the cytotoxic constituents of a milnamide-producing sponge. Org. Lett., 2004, 6(5), 779-782.

[75]. Foderaro, T.A.; Barrows, L.R.; Lassota, P.; Ireland, C.M. Bengacarboline, a New β-Carboline from a Marine Ascidian Didemnum sp. J. Org. Chem. 1997, 62(17), 6064-6065.

[76]. Santos, L.S.; Theoduloz, C.; Pilli, R.A.; Rodriguez, J. Antiproliferative activity of arborescidine alkaloids and derivatives. Eur. J. Med. Chem. 2009, 44(9), 3810-3815.

[77]. Williams, D.E.; Davies, J.; Patrick, B.O.; Bottriell, H.; Tarling, T.; Roberge, M.; Andersen, R. J. Cladoniamides A−G, tryptophan-derived alkaloids produced in culture by Streptomyces uncialis. Org. Lett. 2008, 10(16), 3501-3504.

[78]. Takahashi, Y.; Kubota, T.; Fromont, J.; Kobayashi, J.I. Zamamidines A and B, new manzamine alkaloids from the sponge Amphimedon species. Org. Lett. 2008, 11(1), 21-24.

[79]. Stavrinides, A.; Tatsis, E.C.; Foureau, E.; Caputi, L.; Kellner, F.; Courdavault, V.; O'Connor, S.E. Unlocking the diversity of alkaloids in Catharanthus roseus: nuclear localization suggests metabolic channeling in secondary metabolism. Chem. Biol. 2015, 22(3), 336-341.

[80]. Fischhof, P.K.; Möslinger-Gehmayr, R.; Herrmann, W.M.; Friedmann, A.; Ruβmann, D.L. Therapeutic efficacy of vincamine in dementia. Neuropsychobiology. 1996, 34(1), 29-35.

[81]. Rajapaksa, N.S.; McGowan, M.A.; Rienzo, M.; Jacobsen, E. N. Enantioselective total synthesis of (+)-reserpine. Org. Lett. 2013, 15(3) 706-709.

[82]. Abdelsalam, M.A.; AboulWafa, O.M.; Badawey, E.S.A.; El-Shoukrofy, M.S.; El-Miligy, M.M.; Gouda, N. Design and synthesis of some β-carboline derivatives as multi-target anticancer agents. Fut. Med. Chem. 2018, 10(24), 2791-2814.

[83]. Nekkanti, S.; Pooladanda, V.; Veldandi, M.; Tokala, R.; Godugu, C.; Shankaraiah, N. Synthesis of 1, 2, 3-Triazolo-fused-tetrahydro-β-carboline Derivatives via 1, 3-Dipolar Cycloaddition Reaction: Cytotoxicity Evaluation and DNA-Binding studies. ChemistrySelect, 2017, 2(24), 7210-7221.

[84]. Zhang, Z.J.; Zhang, J.J.; Jiang, Z.Y.; Zhong, G.H. Design, synthesis and bioactivity evaluation of novel β-carboline 1, 3, 4-oxadiazole derivatives. Molecules 2017, 22(11), 1811.

[85]. Li, Y.; Yan, W.; Yang, J.; Yang, Z.; Hu, M.; Bai, P.; Tang, M.; Chen, L. Discovery of novel β-carboline/acylhydrazone hybrids as potent antitumor agents and overcome drug resistance. Eur. J. Med. Chem. 2018, 152, 516-526.

[86]. Qin, J.J.; Wang, W.; Li, X.; Deokar, H.; Buolamwini, J.K.; Zhang, R. Inhibiting β-Catenin by β-Carboline-Type MDM2 Inhibitor for Pancreatic Cancer Therapy. Front. Pharmacol. 2018, 9, 5.

[87]. Jeyapal, G.P.; Krishnasamy, R.; Suzuki, C.K.; Venkatesh, S.; Chandrasekar, M.J.N. In-silico design and synthesis of N9-substituted β-Carbolines as PLK-1 inhibitors and their in-vitro/in-vivo tumor suppressing evaluation. Bioorg. Chem. 2019, 88, 102913.

[88]. Guo, L.; Ma, Q.; Chen, W.; Fan, W.; Zhang, J.; Dai, B. Synthesis and biological evaluation of novel N 9-heterobivalent β-carbolines as angiogenesis inhibitors. J. Enzyme. Inhib. Med. Chem. 2019, 34(1), 375-387.

[89]. Samundeeswari, S.; Chougala, B.; Holiyachi, M.; Shastri, L.; Kulkarni, M.; Dodamani, S.; Jalalpur, S.; Joshi, S.; Dixit, S.; Sunagar, V.; Hunnur, R. Design and synthesis of novel phenyl-1, 4-beta-carboline-hybrid molecules as potential anticancer agents. Eur. J. Med. Chem. 2017, 128, 123-139.

[90]. Zhao, W.Y.; Zhou, W.Y.; Chen, J.J.; Yao, G.D.; Lin, B., Wang, X.B.; Huang, X.X.; Song, S.J. Enantiomeric β-carboline dimers from Picrasmaquassioides and their anti-hepatoma potential. Phytochemistry. 2019, 159, 39-45.

[91]. Ling, Y.; Gao, W.J.; Ling, C.; Liu, J.; Meng, C.; Qian, J.; Liu, S.; Gan, H.; Wu, H.; Tao, J.; Dai, H. β-Carboline and N-hydroxycinnamamide hybrids as anticancer agents for drug-resistant hepatocellular carcinoma. Eur. J. Med. Chem. 2019, 168, 515-526.

[92]. Sathish, M.; Dushantrao, S.C.; Nekkanti, S., Tokala, R.; Thatikonda, S.; Tangella, Y.; Srinivas, G.; Cherukommu, S.; Krishna, N.H.; Shankaraiah, N.; Nagesh, N. Synthesis of DNA interactive C3-trans-cinnamide linked β-carboline conjugates as potential cytotoxic and DNA topoisomerase I inhibitors. Bioorg. Med. Chem. 2018, 26(17), 4916-4929.
[93]. Kovvuri, J.; Nagaraju, B.; Nayak, V.L.; Akunuri, R.; Rao, M.N.; Ajitha, A.; Nagesh, N.; Kamal, A. Design, synthesis and biological evaluation of new β-carboline-bisindole compounds as DNA binding, photocleavage agents and topoisomerase I inhibitors. Eur. J. Med. Chem. 2018, 143, 1563-1577.
[94]. Samundeeswari, S.; Kulkarni, M.V.; Joshi, S.D.; Dixit, S.R.; Jayakumar, S.; Ezhilarasi, R. M. Synthesis and human anticancer cell line studies on coumarin-β-carboline hybrids as possible antimitotic agents. ChemistrySelect. 2016, 1(15), 5019-5024.
[95]. Hanh, T.T.H.; Huong, P.T.T.; Van Thanh, N.; Trung, N.Q.; Van Cuong, T.; Mai, N.T.; Cuong, N.T.; Cuong, N.X.; Nam, N.H.; Van Minh, C. Crinane, augustamine, and β-carboline alkaloids from Crinum latifolium. Phytochem. Lett. 2018, 24, 27-30.
[96]. Giulietti, J.M.; Tate, P.M.; Cai, A.; Cho, B.; Mulcahy, S.P. DNA-binding studies of the natural β-carboline eudistomin U. Bioorg. Med. Chem. Lett. 2016, 26(19), 4705-4708.
[97]. Huang, Y.; Guo, Z.; Song, H.; Liu, Y.; Wang, L.; Wang, Q. Design, Synthesis, and Biological Activity of β-Carboline Analogues Containing Hydantoin, Thiohydantoin, and Urea Moieties. J. Agric. Food. Chem. 2018, 66(31), 8253-8261.
[98]. Ling, Y.; Guo, J.; Yang, Q.; Zhu, P.; Miao, J.; Gao, W.; Peng, Y.; Yang, J.; Xu, K.; Xiong, B.; Liu, G. Development of novel β-carboline-based hydroxamate derivatives as HDAC inhibitors with antiproliferative and antimetastatic activities in human cancer cells. Eur. J. Med. Chem. 2018, 144, 398-409.
[99]. Wu, J.; Zhao, M.; Wang, Y.; Wang, Y.; Zhu, H.; Zhao, S.; Gui, L.; Zhang, X.; Peng, S. N-(3-hydroxymethyl-β-carboline-1-yl-ethyl-2-yl)-L-Phe: development toward a nanoscaled antitumor drug capable of treating complicated thrombosis and inflammation. Drug. Des. Devel. Ther. 2017, 11, 225-239.
[100]. Liang, J.; Wang, M.; Li, X.; He, X.; Cao, C.; Meng, F. Determination of Structural Requirements of N-Substituted Tetrahydro-β-Carboline Imidazolium Salt Derivatives Using in silico Approaches for Designing MEK-1 Inhibitors. Molecules 2017, 22(6), 1020.
[101]. Zhao, W.Y.; Shang, X.Y.; Zhao, L.; Yao, G.D.; Sun, Z.; Huang, X.X.; Song, S.J. Bioactivity-guided isolation of β-Carboline alkaloids with potential anti-hepatoma effect from Picrasmaquassioides (D. Don) Benn. Fitoterapia. 2018, 130, 66-72.
[102]. Tokala, R.; Thatikonda, S.; Sana, S.; Regur, P.; Godugu, C.; Shankaraiah, N. Synthesis and in vitro cytotoxicity evaluation of β-carboline-linked 2, 4-thiazolidinedione hybrids: potential DNA intercalation and apoptosis-inducing studies. New. J. Chem. 2018, 42(19), 16226-16236.
[103]. Reddy, P.V.; Mishra, S.; Tantak, M.P.; Nikhil, K.; Sadana, R.; Shah, K.; Kumar, D. Design, synthesis and in vitro cytotoxicity studies of novel β-carbolinium bromides. Bioorg. Med. Chem. Lett. 2017, 27(6), 1379-1384.
[104]. Reddy, P.V.; Shekar, K.C.; Khandagale, S.B.; Hara, D.; Son, A.; Ito, T.; Tanabe, K.; Kumar, D. Easy Access to Water-Soluble Cationic Porphyrin-β-Carboline Conjugates as Potent Photocytotoxic and DNA Cleaving Agents. Asian. J. Org. Chem. 2019, 8(2), 269-274.
[105]. Tokala, R.; Thatikonda, S.; Vanteddu, U.S.; Sana, S.; Godugu, C.; Shankaraiah, N. Design and Synthesis of DNA-Interactive β-Carboline–Oxindole Hybrids as Cytotoxic and Apoptosis-Inducing Agents. Chem. Med. Chem. 2018, 13(18), 1909-1922.
[106]. Xu, T., Shi, L.; Zhang, Y.; Wang, K.; Yang, Z.; Ke, S. Synthesis and biological evaluation of marine alkaloid-oriented β-carboline analogues. Eur. J. Med. Chem. 2019, 168, 293-300.
[107]. Sathish, M.; Kavitha, B.; Nayak, V.L.; Tangella, Y.; Ajitha, A.; Nekkanti, S.; Alarifi, A.; Shankaraiah, N.; Nagesh, N.; Kamal, A. Synthesis of podophyllotoxin linked β-carboline congeners as potential anticancer agents and DNA topoisomerase II inhibitors. Eur. J. Med. Chem. 2018, 144, 557-571.
[108]. Byeon, H.J.; Jung, K.H.; Moon, G.S.; Moon, S.K.; Lee, H.Y. A facile and efficient method for the synthesis of crystalline tetrahydro-β-carbolines via the Pictet-Spengler reaction in water. Sci. Rep. 2020, 10(1),1-6.
[109]. Guo, L.; Chen, X.; Chen, W.; Ma, Q.; Fan, W.; Zhang, J.; Dai, B. Molecular hybrid design, synthesis, in vitro and in vivo anticancer evaluation, and mechanism of action of N-acylhydrazone linked, heterobivalent β-carbolines. Bioorg. Chem. 2020, 96,103612.
[110]. Wang, L.; Li, L.; Fu, Y.; Li, B.; Chen, B.; Xu, F.; Li, D.; Separation, synthesis, and cytotoxicity of a series of mogrol derivatives. J. Asian Nat. Prod. Res.2020, 22(7), 663-677.
[111]. Nie, L. F.; Wang, S. S.; Cao, J.G.; Liu, F.Z.;Xiamuxi, H.;Aisa, H. A.; Huang, G. Z. Straightforward synthesis, characterization, and cytotoxicity evaluation of hybrids of natural alkaloid evodiamine/rutaecarpine and thieno [2,3-d] pyrimidinones. J. Asian Nat. Prod. Res. 2020,22(1), 69-82.
[112]. Fodor, K.J.;Hutai, D.;Jernei, T.;Takács, A.;Szász, Z.;Sulyok-Eiler, M.;Harmat, V.;OláhSzabó, R.; Schlosser, G.;Hudecz, F.;Kőhidai, L. Novel Polycondensed Partly Saturated β-Carbolines Including Ferrocene Derivatives: Synthesis, DFT-Supported Structural Analysis, Mechanism of Some Diastereoselective Transformations and a Preliminary Study of their In Vitro Antiproliferative Effects. Molecules, 2020, 25(7), 1599.
[113]. Manasa, K.L.;Thatikonda, S.;Sigalapalli, D.K.; Sagar, A.;Kiranmai, G.;Kalle, A.M.; Alvala, M.;Godugu, C.; Nagesh, N.; Babu, B.N. Design and Synthesis of β-carboline linked aryl sulfonyl piperazine derivatives: DNA topoisomerase II inhibition with DNA binding and apoptosis inducing ability. Bioorg. Chem. 2020, 1,103983.
[114]. Guo, X.M.; Li, F.; Zheng, F.F.; Gong, N.N.; Li, Y.; Feng, W.Z.; Tian, L. (±)-Quassidine K, a pair of cytotoxic bis-β-carboline alkaloid enantiomers from Picrasmaquassioides. Natural product research.2020, 34(4),489-93.