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

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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-likeliness 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 antitumor 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-Carboline, Harmine, DNA binding studies, Cytotoxicity, Topoisomerase inhibition activity and Molecular Docking.

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 days and is proved by the development of plant-derived drugs such as vinblastine, vincristine, paclitaxel, quinine, etoposide, artesiminin, 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-likeliness 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].

Carboline are nature-derived heterocyclic compounds containing indole ring fused with pyridine (fused benzene-pyrole-pyridine 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, Zygophyllaceae 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], mammals (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, harmanc and harmaline. Harmine type of β-carbolines are found to possess profound

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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 imidazole 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 Betacarbolines (FAβCs), partially and fully saturated compounds are named as 3,4-dihydro-β-carbolines (DHβCs) and 1,2,3,4-tetrahydro-β-carbolines (THβCs) respectively.
- FAβCs: 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].
- DHβCs: 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 (DHβCs). These can be synthesized via Pictet-Spengler reaction followed by dehydrogenation [31].
- THβCs: These tricyclic systems usually contain saturated pyridine ring in the tricyclic pyrido[3,4-b]indole ring system. The most traditional methods to synthesize THβC frameworks are Pictet-Spengler and Bischler-Napieralski reaction. Among the huge number of β-carbolines, THβCs 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].

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

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

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound</th>
<th>Source</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Norharmane</td>
<td>Peganum harmala (Syrian rye) Tribulus terrestris.</td>
<td>1. DNA intercalation [33].&lt;br&gt;2. Inhibits the transcription of isolated DNA [34].&lt;br&gt;3. Enhances both the DNA strand breaks and cytotoxicity induced by 4HAQO [35].&lt;br&gt;4. Inhibits DNA excision repair and causes an increase in UV induced mutations [36].&lt;br&gt;5. Inhibits the activity of Topoisomerase I &amp; II [33].&lt;br&gt;6. Inhibits the activity MAO-B [38].&lt;br&gt;7. Interacts with CYP11 and CYP17 [39].</td>
</tr>
<tr>
<td>2</td>
<td>Harmane</td>
<td>Peganum harmala, Passifloraincarnata, Symplocosracemosa.</td>
<td>1. Inhibits Topoisomerase I &amp; II [40].&lt;br&gt;2. DNA intercalation [33].&lt;br&gt;3. Inhibits the activity MAO-A [41].&lt;br&gt;4. Inhibition of the AP endonuclease activity of phage T4 [42].&lt;br&gt;5. Inhibition of HIV replication in H9 lymphocyte cells [43].&lt;br&gt;6. Interaction with DNA metabolism and significant accumulation of parasites in the S–G2/M phases of the cell cycle (Anti-leishmanial against promastigotes &amp; amastigotes) [44].</td>
</tr>
<tr>
<td>4</td>
<td>Harmol</td>
<td>Passiflora incarnata</td>
<td>Induces autophagy and cell death in human NSCLC A549 cells [49].</td>
</tr>
<tr>
<td>5</td>
<td>Canthin-6-one</td>
<td>Picrasma quassoids (wood)</td>
<td>Causes accumulation of cancer cells in the G2/M Phase [50].</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1-Methoxycanthinone</td>
<td>Ailanthus altissima</td>
<td>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 hematopoetic or endodermal origin [51].</td>
</tr>
<tr>
<td></td>
<td>5-Methoxycanthinone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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                    | Plakortis nigra                               | Cytotoxic activity against HCT-116 [54].                                                            |
|     | Plakortamine B                    |                                               |                                                                                                       |
|     | Plakortamine C                    |                                               |                                                                                                       |
|     | Plakortamine D                    |                                               |                                                                                                       |
| 10  | 6-Hydroxymanzamine (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 berghei.  
2. Inhibit DNA synthesis through intercalation of DNA base pairs [55]. |
|     |                                   |                                               |                                                                                                       |
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| 8-Methoxymanzamine A | Manzamine A (Okinawan marine sponges) Xestospongia species and Haliclona species. | 1. Inhibits asexual erythrocytic stages of *Plasmodium berghei*.  
2. Inhibit DNA synthesis through intercalation of DNA base pairs [55]. |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>6-Deoxymanzamine X</td>
<td>Haliclona genus (Indo-Pacific sponge)</td>
<td>Inhibit DNA synthesis through intercalation of DNA base pairs [55].</td>
</tr>
<tr>
<td>Neo-Kauluamine</td>
<td>Indo-Pacific sponge</td>
<td>Accumulates in lysosomes and mediates apoptosis by upregulating a pro-apoptotic protein, PUMA (p53 upregulated modulator of apoptosis).</td>
</tr>
<tr>
<td>Thorectandramine</td>
<td>Thorectandra species (Marine sponge).</td>
<td>Induction of caspase-8, -9, -3-dependent apoptosis [56].</td>
</tr>
</tbody>
</table>
| 16 | Fascaplysin | Fascaplysinopsis species. | 1. DNA intercalator.  
2. Selective inhibitor of Cdk4.  
3. Inhibit phosphorylation of the retinoblastoma protein Rb, resulting in G0/G1 phase cycle arrest of cancerous cells [57]. |
| 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]. |
<p>| 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 |
| 21 | Harmalacidine | Peganum harmala, Banisteriopsis caapi | Cytotoxic against human leukemia cells. |
| 22 | Pegaharmaline A | Peganum harmala | Cytotoxic activity against human cancer cell line (L-60) [62]. |
| 23 | Pegaharmine D | Peganum harmala | Interacts with G-quadruplex complex [63]. |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Source</th>
<th>Activity Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Peganumine A</td>
<td>Peganum harmala</td>
<td>Cytotoxic activity against MCF-7, PC-3 and HepG2 cells and selective effects on HL-60 cells [64].</td>
</tr>
<tr>
<td>25</td>
<td>Z-Vallesiachotamine</td>
<td>(Z-Vallesiachotamine) Rhazya stricta</td>
<td>Promoting G0/G1 cell cycle arrest, apoptosis and necrosis [65].</td>
</tr>
<tr>
<td>26</td>
<td>Tangutorine</td>
<td>Nitraria tangutorum</td>
<td>Induces p21 expression and abnormal mitosis in human colon cancer HT-29 cells [66].</td>
</tr>
<tr>
<td>27</td>
<td>Sacleuximine A</td>
<td>Triclisia sacleuxii</td>
<td>Cytotoxic against human adenocarcinoma, hepatocarcinoma and breast carcinoma cell lines [67].</td>
</tr>
</tbody>
</table>
| 28  | Eudistomin K          | Eudistoma glaucus (Okinawan marine tunicate), Lissoclinium fragile (Ascidian), Eudistoma olivaceum | 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]. |
<p>| 29  | Hyrtioerectin B       | Hyrtios erectus (Red sea sponge) | Cytotoxic against HeLa cell lines [53].                                                                                                       |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Source</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Hyrtioreticuline A</td>
<td>Hystios reticulatus</td>
<td>Inhibit ubiquitin activating enzyme and ubiquitin-proteasome pathway [71].</td>
</tr>
<tr>
<td>31</td>
<td>Ma’gamedin A</td>
<td>Amphimedon species (Okinawan marine sponge).</td>
<td>Inhibit DNA synthesis through intercalation of DNA base pairs [72].</td>
</tr>
<tr>
<td>32</td>
<td>Callophycin A</td>
<td>Callophycus oppositifolius (Red algae).</td>
<td>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].</td>
</tr>
<tr>
<td>33</td>
<td>(+)-Mlnamide C</td>
<td>Marine sponge Auletta species</td>
<td>Cytotoxic activity by causing microtubule depolymerization and microfilament disruption [74].</td>
</tr>
<tr>
<td>34</td>
<td>Bengacarboline</td>
<td>Marine Ascidian Didemnum species.</td>
<td>Inhibit topoisomerase II [75].</td>
</tr>
<tr>
<td>35</td>
<td>(+)-Arborescidine A</td>
<td>Marine tunicate Pseudodistoma arborescens.</td>
<td>Inhibit topoisomerase-II [76].</td>
</tr>
<tr>
<td>36</td>
<td>Cladoniamide G</td>
<td>Actinomycete Streptomyces uncialis</td>
<td>Cytotoxic activity against human breast cancer MCF-7 cells [77].</td>
</tr>
<tr>
<td>37</td>
<td>Zamamidine A</td>
<td>Okinawan marine sponge Amphimedon species</td>
<td>Cytotoxic against P388 murine leukemia [78].</td>
</tr>
</tbody>
</table>
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## IV. β-carboline and its derivatives

### 4.1 Triazole-β-carboline derivatives

Abdelsalam *et al.* have reported a series of 24 novel 1-(3-hydroxyphenyl)-9H-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 N4-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 G2/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].

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamamidine B</td>
<td>Fruits of <em>Evodia rutaecarpa</em></td>
<td>Not reported</td>
</tr>
<tr>
<td>38 Ajmalicine</td>
<td><em>Raulfia serpentine</em>; <em>Catharanthus roseus</em>; <em>Mitragyna speciosa</em>.</td>
<td>Antihypertensive activity [79].</td>
</tr>
<tr>
<td>39 Vincaamine</td>
<td><em>Vinca minor</em></td>
<td>Primary degenerative; vascular dementia [80].</td>
</tr>
<tr>
<td>40 Reserpine</td>
<td><em>Raulfia serpentine</em></td>
<td>Antihypertensive and Antipsychotic activity [81].</td>
</tr>
</tbody>
</table>

*Fig. (3).* β-carboline-linked 1,2,4-triazole as cytotoxic agents.
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 C6 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-oxazadiazole and tested against Sf9 cells. SAR analysis revealed that substitution at C2-position on oxadiazole motif and electron withdrawing groups at C1-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

Fig. (7). SP141-based 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 binding to β-catenin. Therefore, the authors disclosed SP141 as a potential scaffold having dual inhibitory activity on β-catenin and MDM2 [86].

Fig. (8). N9-substituted β-Carboline derivatives as PLK-1 inhibitors.

Chandrasekar et al. have reported a series of N9-substituted β-Carboline (Fig. 8) as PLK-1 inhibitors. 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<sub>50</sub> 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

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<sup>9</sup> position and dimerized at the C3-position. Compound 9 (Fig. 9) was found to be most potent anticancer compound with an IC<sub>50</sub> 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].
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Fig. (10). N9-heterodimeric β-carbolines as cytotoxic agents.

Dai et al. have reported compound 10 and 11 a novel N9-heterobivalent β-carbolines (Fig. 10) with an IC50 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 C1 methylation and C7 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 N9-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 (GL50 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 METS47 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, METS47, 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

![Image](image1)

**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-carboline 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\textsubscript{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\textsubscript{50} = 4.72-9.83 µM) and 18-30 fold more potent than 5-FU (IC\textsubscript{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].

![Image](image2)

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

Kamal et al. disclosed C\textsubscript{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\textsubscript{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

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

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].
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3.10. Furan–β-carboline derivative

![Figure 17](image1.png)

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

![Figure 18](image2.png)

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

![Figure 19](image3.png)

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...
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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

![Diagram of lead optimization of THBC linked thiohydantoin, hydantoin and urea derivatives.](image)

**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].


![Diagram of β-carboline hydroxamates.](image)

**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 C1 substitution had significant effect on HDAC1 inhibitory activity. Compounds with electron rich groups (methoxy, methyl) at C1 position was more potent compared to electron deficient groups such as nitro. Compound 34 showed most potent activity with an IC50 value 0.53-1.56 µM than standard drug Harmine (IC50: 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
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3.15. Phenylalanine-β-carboline derivative

\[
N-(3-hydroxymethyl-\beta-carboline-1-yl-ethyl-2-yl)-l-Fhe
\]

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

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].

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 sorafenib (IC₅₀: 8.35 µM) and shows better activity than 5-FU (IC₅₀: 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**

![Image](image_url)

IC₅₀: 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 C₁ 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 IC₅₀ 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 1×10⁵ M⁻¹ [102].

3.18. **β-carbolinium bromide derivatives**

![Image](image_url)

IC₅₀: HeLa cell line: 3.2±0.9 µM
HEK293T cell line: 3.8±1.1 µM

IC₅₀: 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-231 cancer cell line with an IC₅₀ 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**

![Image](image_url)

IC₅₀: Colon26 cell line: 47 nM
A549 cell line: 39 nM
Binding constant value: 2.3 × 10⁵ 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 IC₅₀ value: 47 nM and
39 nM. Additionally, porphyrin-β-carboline conjugate 43 possess binding constant (Kb) value 2.3×10^6 M^-1 similar to H2TMPyP (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**

![Image](image.png)

**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 IC50 of 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**

![Image](image.png)

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

Shankaraiah *et al.* synthesized a series of (E)-3-((1-aryl-9H-pyrido[3,4-b]indol-3-yl)methylene)indolin-2-one congeners (Fig. 29) and evaluated for their *in vitro* cytotoxic activity. Compound 45 showed potent cytotoxicity with an IC50 of 1.43±0.26 μM and GI50 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-1 to 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**

![Image](image.png)

**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 (IC50: 6.82±0.98 μM), A875 (IC50: 8.43±1.93 μM), HepG2 (IC50: 8.43±1.93 μM), MARC145 (IC50: 7.19 ± 1.43 μM), and 786-0 (IC50: 9.70 ± 1.62 μM).
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7.69±2.17 µM), MARC145 (IC\textsubscript{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)](image1)

Fig. (31). Podophyllotoxin based β-carboline derivatives 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)](image2)

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\textsubscript{50} value of 1.49 mg/mL in the brine shrimp lethality assay [108].

![Fig. (33)](image3)

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 5 other 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\textsubscript{50} value of 2.4±0.8 µM against EA.HY926 cells. It was also found to exhibit most potent cytotoxic activity with IC\textsubscript{50} values ranging from 4.2 ± 0.7 to 18.5 ± 3.1µM on cancer cell lines [109].
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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 (IC₅₀ = 80–90 μM, Fig. 34). Compound 51 exhibited IC₅₀ values of 9.21±0.77 and 9.07±1.50 against A549 and CNE1 cell respectively. Compound 52 exhibited IC₅₀ values of 2.58±0.31 and 3.28±0.27 against A549 and CNE1 cell respectively. Authors found that perhydro cyclopentanophenanthrene moiety and the tetrahydro-β-carboline moiety were responsible for the increased cytotoxic activity [110].

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 IC₅₀ 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].

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
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Diastereomers having phenyl substituent 54 (IC<sub>50</sub> values 7.0±1.9, 5.6±0.56, 14±3.2 and 6.4±1.1µM) and trifluoromethylphenyl substituent 55 (IC<sub>50</sub> 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<sub>50</sub> 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 its trans form was found inactive [112].

**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<sub>50</sub> 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 Tyr186 residues. β-carboline NH and carbonyl groups in compound 57 showed H-bond interaction with backbone 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].

**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<sub>50</sub> value 15.8 and 20.1µM respectively 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 important 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.
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References


b) indole acetate

Donor, S.E. Unlocking the diversity of carboline Derivatives via 1, 3-amino-symporter by harmaline and Dipolar Cycloaddition Reaction: Cytotoxicity Evaluation and tetrahydro-fused methyl–mann, D.L. Therapeutic efficacy of vincamine in...
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