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A REVIEW ON THE BIOLOGICAL ACTIVITY OF *β*-CARBOLINE DERIVATIVES

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Abstract – *β*-Carboline ring is one of the most important scaffolds in drug discovery owing to its abundance in nature and its various biological activity. A large number of *β*-carboline alkaloids were isolated from plants, mammals, marine organisms, fungi and bacteria. Various biological activities have been identified for synthetic *β*-carboline compounds like anticancer, antimicrobial, antileishmanial, antimalarial, anti-Alzheimer, anti-inflammatory, analgesic and vasorelaxant activity. The present review describes the method of synthesis of *β*-carboline and highlights the recent progress achieved in the last decade in the development of biologically active *β*-carboline derivatives.

INTRODUCTION

The *β*-carboline alkaloids are widely distributed in nature (Figure 1). For example, seeds[1] and fruits[2] of *Peganum harmala* L, roots of *Psammosilene tunicoides*,[3] *Evodiae fructus* herb,[4] *Picrasma quassioides*,[5] *Vochysia divergens*,[6] marine sponge *Hyritos reticulatus*,[7] marine tunicate *Cnemidocarpa stolonifera*[8] and marine bryozoan *Pterocella vesiculosa*.[9] Figure 1 displayed the structures of some important naturally occurring carboline containing alkaloids **1-9**. The *β*-carboline scaffold is present in many biologically active compounds. Thus, *β*-carboline derivatives exhibited anticancer,[10–14] antimicrobial,[15–21] anti-Alzheimer[22–24] and antimalarial[25–27] activities. The present review summarized the most important

biological application of β-carboline derivatives in the last decade. The biological activities included the anticancer, antimicrobial, antimalarial, anti-Alzheimer, anti-inflammatory, analgesic and vasorelaxant activities. The mechanism inherited behind the activity and a brief description of the structure-activity relationship (SAR) were provided whenever possible. The structures of the most active compounds in each study together with their inhibitory activity (IC_{50}) were also presented.

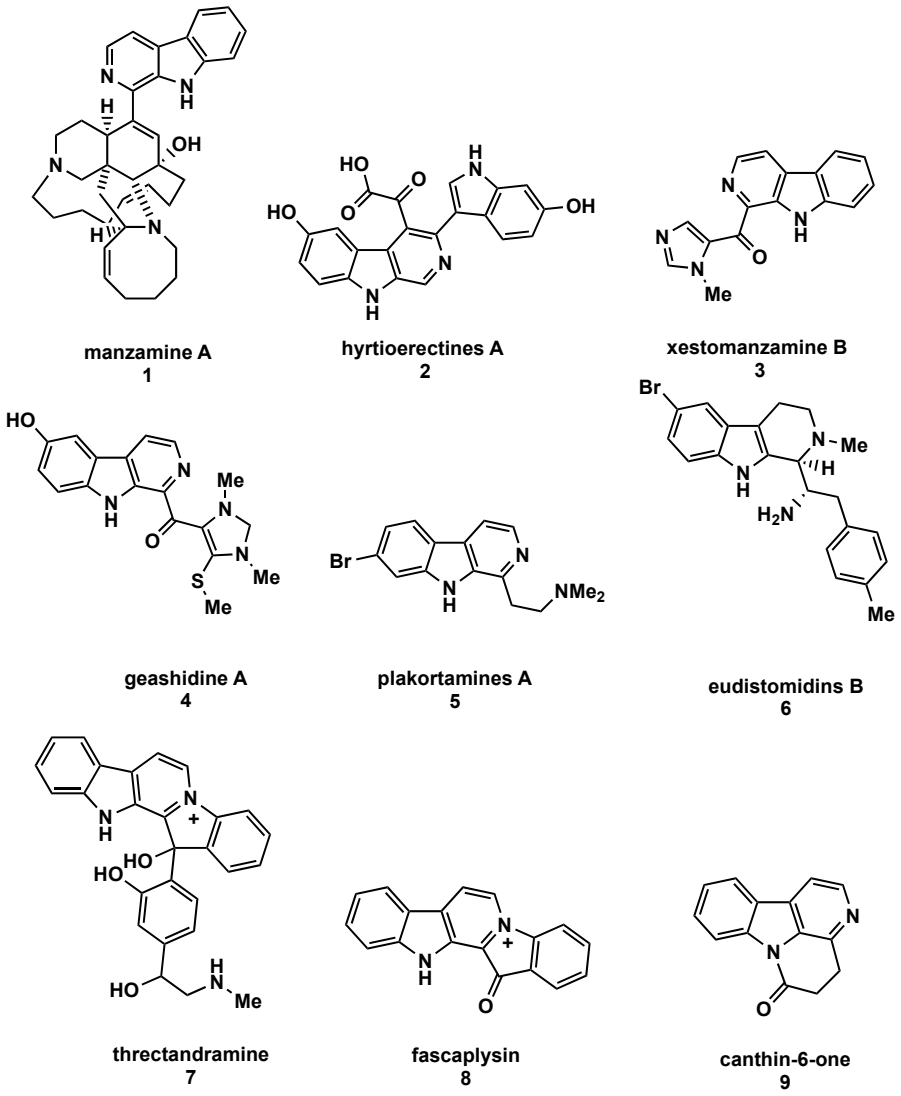
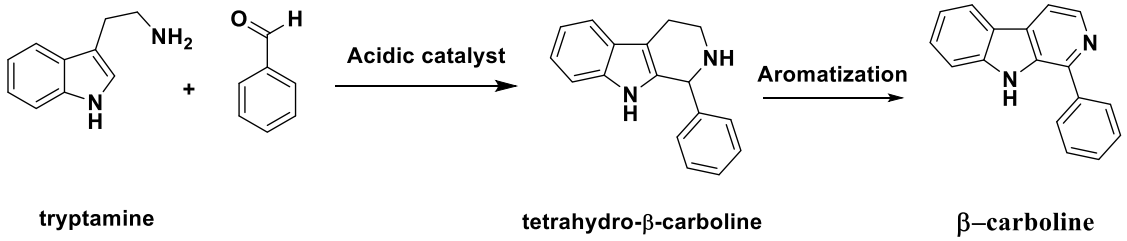


Figure 1. Biologically active β-carboline alkaloids

SYNTHESIS OF β-CARBOLINE RING

The most commonly used method for the synthesis of β-carboline ring is *via* Pictet-Spengler reaction of tryptamine and aliphatic or aromatic aldehydes.[28] The reaction may be carried out in one step or in two steps where tryptamine reacted with aldehyde to give Schiff base which was then cyclized in acidic medium to afford β-carboline derivative (Scheme 1). Different acidic catalysts were used including trifluoroacetic acid[29] and HCl.[8] The reaction can be also catalyzed using heterogeneous catalysts like

β-cyclodextrin-SO_3H[30] and Fe(III)-montmorillonite.[31] The reaction was enzymatically catalyzed using strictosidine synthase enzyme[32] as well as Pictet-Spenglerase enzymes.[33]



Scheme 1. Pictet-Spengler synthesis of *β*-carboline

BIOLOGICAL ACTIVITY OF *β*-CARBOLINES

I. Anticancer activity

a) Anticancer activity of *β*-carboline hybrids

Molecular hybridization of *β*-carboline and chalcone pharmacophore resulted in compounds **10** and **11** with potent antiproliferative activity against eight cell lines especially against breast cancer with IC_{50} 2.25 and 3.29 μM respectively. Moreover, compound **10** had induced DNA fragmentation and apoptosis in breast cancer cells. It was observed that the presence of electron donating group (like methoxy group) substituted on chalcone increased the anticancer activity (compounds **10** and **11**) while introducing electron withdrawing group (like halogens) decreased the anticancer activity[34] (Figure 2).

Shankaraiah *et al*. synthesized and evaluated the anticancer activity of tetrahydro-*β*-carboline-hydantoin hybrids against lung, cervical, prostate and breast cancer cell lines. The hybrid derivative **12** showed the most potent anticancer activity against prostate cancer (PC-3 cell line) with IC_{50} 6.08 ± 0.2 μM[35] (Figure 2). The *β*-carboline-4-thiazolidinone hybrid **13** displayed highly potent antitumor activity against MCF-7, NCI/ADR-RES, 786-0, NCI-H460, OVCAR-3 and HT-29 cell lines with IC_{50} values 2.93, 0.48, 1.60, 1.44, 1.27 and 5.04 μM, respectively[36] (Figure 2).

The hybrids of *β*-carboline and acylhydrazone derivatives were designed to overcome drug resistance and their anticancer activity was examined by Li *et al*. The synthesized compounds had good activity especially compound **14** that showed high antiproliferative activity against all cancer cell lines especially against MCF-7 with IC_{50} 0.93 ± 0.03 μM[37] (Figure 2).

N^9-Substituted acylhydrazone-*β*-carbolines were synthesized and their anticancer activity was evaluated by Jeyapal *et al*. The compounds showed moderate to strong cytotoxic activity against NCI-60 panel cells. The most potent cytotoxic compound in this study was compound **15** especially against colon cancer with GI_{50}

values 3 μM to 45 μM. The anticancer activity was attributed to inhibition of polo-like kinase 1 (*PLK-1)* and induction of apoptosis[38] (Figure 2). Likewise, the hybrids of *N*-acylhydrazone linked to heterobivalent β-carbolines were evaluated as anticancer agents against five cancer cell lines and one normal cell line (EA.HY926). Compound **16** showed highly potent cytotoxic activity with IC_{50} values 4.2 ± 0.7 μM to 18.5 ± 3.1 μM against all cancer cell lines and antiproliferative activity with IC_{50} 2.4 ± 0.8 μM against EA-HY926. SAR analysis of the synthesized compounds suggested that the order of cytotoxic activity of substituent at position 9 was 2,3,4,5,6-perfluorophenylmethyl > 4-fluorobenzyl > 3-phenylpropyl group[39] (Figure 2).

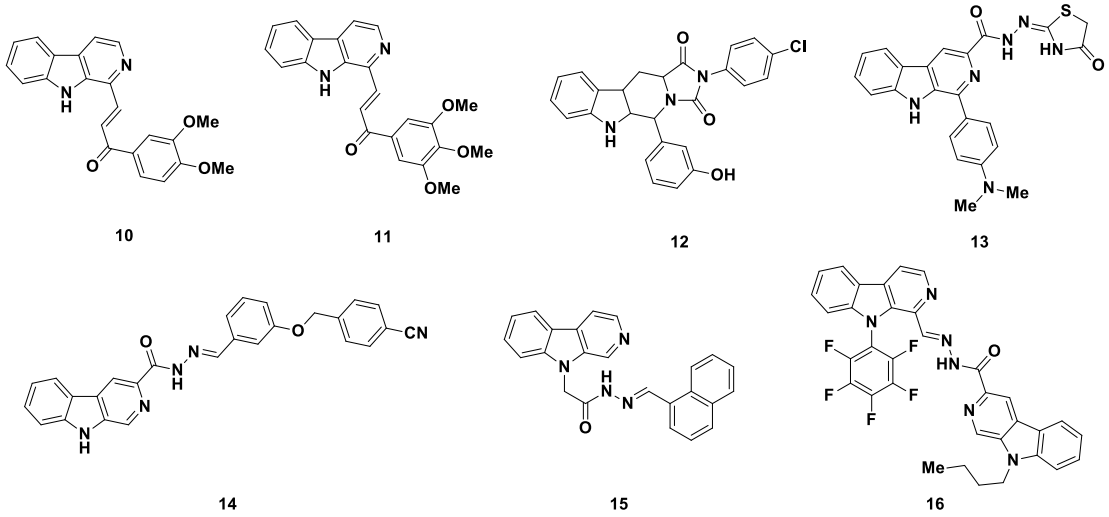


Figure 2. β-Carboline hybrids **10-16** with anticancer activity

The hybrids formed of podophyllotoxin linked β-carbolines were prepared as potential anticancer agents. The study showed that the hybrids had high activity against DU-145 cell line especially compounds **17a** and **17b** with IC_{50} 1.07 ± 0.07 and 1.14 ± 0.16 μM, respectively. They exhibited their cytotoxic activity through inhibition of topoisomerase II enzyme[40] (Figure 3).

In 2019, Ling *et al*. reported the synthesis of derivatives of β-carboline and *N*-hydroxycinnamamide hybrids and studied their anticancer activity and inhibition of histone deacetylase (HADC). Compound **18** showed the highest inhibitory activity of HDAC1 with IC_{50} 1.3 ± 0.2 μM and the best antiproliferative activity against HepG2 with IC_{50} 0.41 ± 0.06 μM[41] (Figure 3). Hu *et al*. investigated the cytotoxic effect of β-carboline-(phenylsulfonyl)furoxan hybrids against breast cancer cell lines. The study showed that compound **19** was the most potent against breast cancer cell lines MCF-7 (IC_{50} 0.89 μM) and MDA-MB-231 (IC_{50} 0.62 μM). Their antiproliferative effect was accompanied by induction of G2/M phase arrest and induction of apoptosis[42] (Figure 3).

In 2021, Sireesha *et al*. synthesized and evaluated the anticancer activity of benzimidazole/benzoxazole

linked *β*-carboline derivatives. The synthesized compounds were tested against four cancer cell lines and all of them showed good anticancer activity against all tested cells especially against breast cancer cells (MCF-7). Compounds **20a**, **20b** (benzimidazole derivatives) and compound **20c** (benzoxazole derivative) were the most potent against MCF-7 with IC_{50} values 0.092 ± 0.001 μM, 0.81 ± 0.062 μM and 2.40 ± 1.85 μM, respectively[43] (Figure 3). Namballa *et al*. studied the cytotoxic activity of *β*-carboline cinnamoyl-2-aminobenzamides that showed inhibition to histone deacetylase (HDAC) more than the controlled drug Entinostat. Compound **21** was the most potent against HCT-15 cell line with IC_{50} 0.7 ± 0.15 μM while Entinostat IC_{50} was 3.87 ± 0.62 μM. The suggested mechanism of action was inhibition of proliferation, apoptosis induction, increase of G2/M and sub-G1/S phase arrest and inhibition of class 1 HDAC 2 and 3 isoforms expression[44] (Figure 3).

The antitumor activity of *β*-carboline derivatives containing nitrogen mustard moieties against breast cancer was assessed by Sun *et al*. Compound **22** showed potent antiproliferative activity against MCF-7 and MDA-MB-231 cell lines with IC_{50} 1.79 and 4.96 μM, respectively with high selectivity against cancer cells and low selectivity against normal breast cell line MCF-10A[45] (Figure 3).

Novel 1,3,4-oxadiazole-*β*-carboline hybrids were synthesized by Tian *et al.* in 2022 and their anticancer efficacy was assessed. Compound **23** was the most potent cytotoxic compound against all tested cancer cell lines especially HCT116 cells with IC_{50} 0.173 ± 0.018 μM. It displayed this effect through inhibition of proliferation and inhibition of HDAC6 with IC_{50} 6 *n*M[46] (Figure 3).

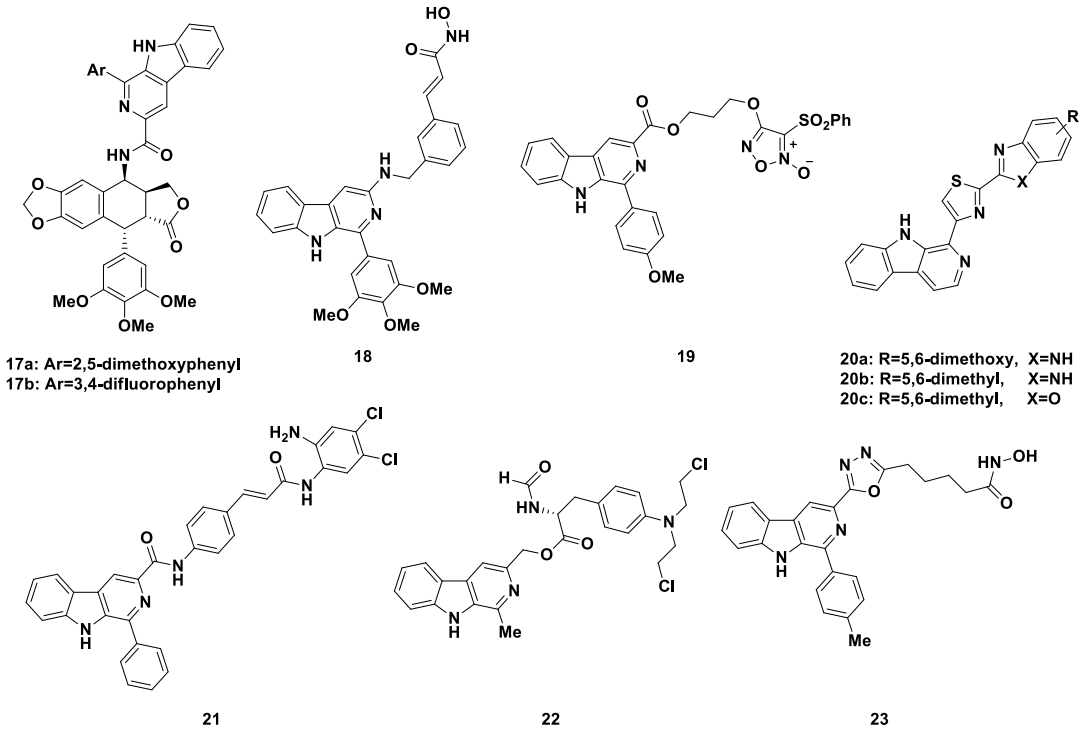


Figure 3. *β*-Carboline hybrids **17-23** with anticancer activity

b) Substituted β-carbolines

New β-carbolines bearing an aryl group at C^1 and an alcohol substituent at C^3 were synthesized by Bai *et al.* The anticancer activities of these compounds were then examined against five tumor-cell lines (HL-60, SMMC7721, A-549, MCF-7 and SW-480). Compounds **24**, and **25a-d**, showed potent cytotoxic activity with IC_{50} lower than 10 μM. SAR analysis revealed that compounds containing H or methyl substituent at the indole nitrogen and compounds containing naphthalen-2-yl linked structures displayed strong anticancer activity[47] (Figure 4).

The 3,9-disubstituted-β-carboline derivatives were synthesized by Chen *et al.* using bioisosterism hypothesis. The compounds had good anticancer activity especially upon substitution at N^9 with benzyl group and in C^3 with carboxylic acid group. Compound **26** (9-(2-methoxybenzyl)-β-carboline-3-carboxylic acid) showed potent anticancer activity through induction of apoptosis with IC_{50} value 4.0 μM against HL-60 cell line[48] (Figure 4).

The anticancer efficacy of 1,3,6-trisubstituted-β-carboline derivatives against four human cancer cells was evaluated by Lunagariya *et al*. The result indicated that compounds **27a** and **27b** showed the most potent cytotoxic effect with IC_{50} values 4.72, 3.59, 3.65 and 4.17 μM for compound **27a** and 15.47, 5.30, 6.15 and 13.39 μM for compound **27b** against A-549, HeLa, HepG2 and MCF-7 cell lines, respectively. The apoptotic activity increased with the presence of bulky substituents at position 6 like 4-*tert*-butylbenzamido **27a** and 3,4-bis(trifluoromethyl)benzamido derivatives **27b**[49] (Figure 4).

The anticancer activity of N^9-substituted harmine derivatives was investigated by Du *et al*. The results revealed that N^9-haloalkyl derivatives (like compounds **28a** and **28b**) and N^9-benzenesulfonyl derivatives (like compounds **29a** and **29b**) had the most potent anticancer activity with IC_{50} values less than 1 μM against A-549 and MCF-7 cell lines. Compound **29b** bearing methylbenzenesulfonyl group at N^9-position induced apoptosis and cell cycle arrest in G_2/M phase[50] (Figure 4).

Zhao *et al*. examined the antitumor activity of 1,9-disubstituted-β-carboline derivatives against ten human cancer cell lines. The synthesized compounds showed good antitumor activity especially compound **30** that showed potent inhibition of proliferation of BGC-923, A375 and HT-29 cell lines with IC_{50} 23.9, 9.3 and 3.6 μM, respectively[11] (Figure 4).

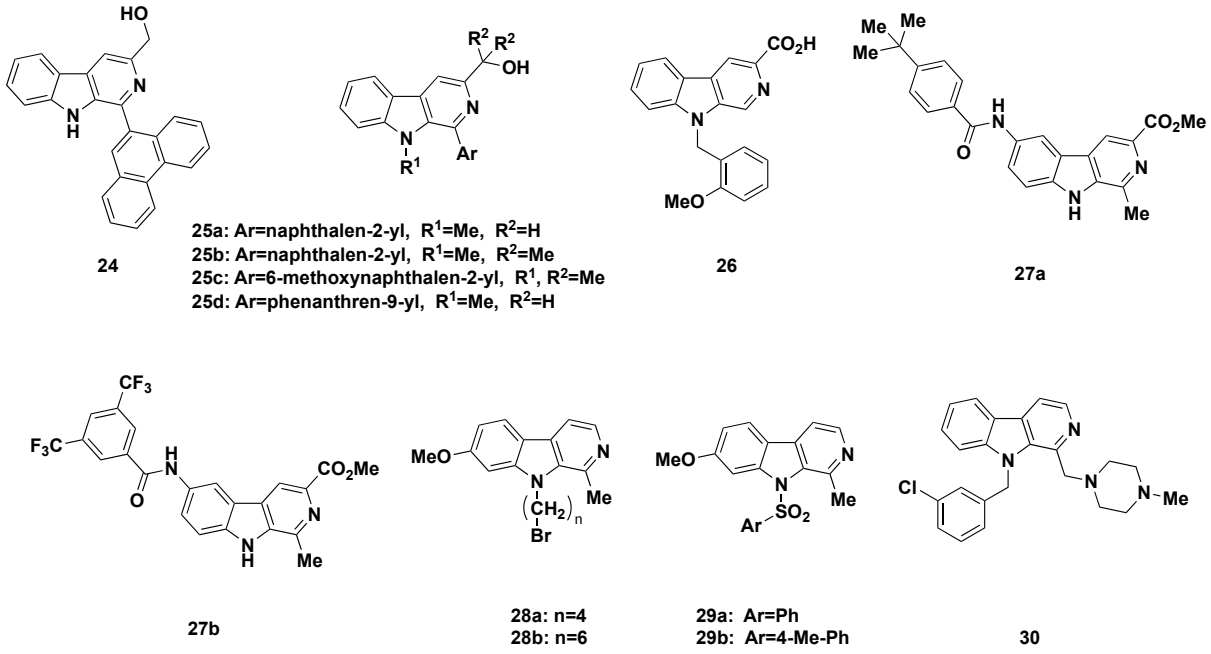


Figure 4. Substituted *β*-carbolines with anticancer activity

c) *β*-Carboline isolates

Figueiredo and his colleagues isolated two *β*-carboline alkaloids namely: 1-methyl-3-(2-hydroxypropan-2-yl)-2-(5-methoxy-9*H*-*β*-carbolin-1-yl)cyclopentanol **31** and 1-(hydroxymethyl)-3-(2-hydroxypropan-2-yl)-2-(5-methoxy-9*H*-*β*-carbolin-1-yl)cyclopentanol **32** from the roots of *Galianthe thalictroides.* Both compounds exhibited potent topoisomerase I and II*α* inhibitory activity. Compound **31** displayed potent cytotoxic activity with IC_{50} values of 3.0, 3.0, 2.5 and 19.5 μM against 786-0, MCF-7, UACC-62 and B16-F10 cell lines, respectively. While, compound **32** was more potent with IC_{50} values of 0.22, 1.80 and 1.70 μM against 786-0, MCF-7 and UACC-62 cell lines, respectively[51] (Figure 5).

Zhao *et al.* isolated a new *β*-carboline dimer from the stem of *Picrasma quassioides* and investigated the cytotoxic effect of the obtained compounds' enantiomers. The authors indicated that compound **33a** ((-)-kumudine B) had anti-hepatoma effect and was more potent than compound **33b** ((+)-kumudine B) against Hep3B cell line[52] (Figure 5).

Owing to its promising anticancer action, Xu *et al*. synthesized derivatives of *β*-carboline alkaloid called pityriacitrin that was isolated from *Burkholderia* sp. The synthesized compounds showed good cytotoxic activity especially compound **34**, which had a better inhibitory effect against SGC-7901, A875, HepG2 and MARC145 cell lines[53] (Figure 5).

Evodiamine **35**; a naturally occurring substance; was simplified by Ma *et al.* to a new

tetrahydro-β-carboline derivatives that had higher activity and fewer adverse effects. Compound **36** showed significant cytotoxic activity through inhibition of topoisomerase I/II and induction of caspase dependent cell apoptosis against cell lines HCT116 with IC_{50} 0.16 μM, A549 with IC_{50} 0.76 μM and MDA-MB-231 with IC_{50} 0.16 μM[4] (Figure 5).

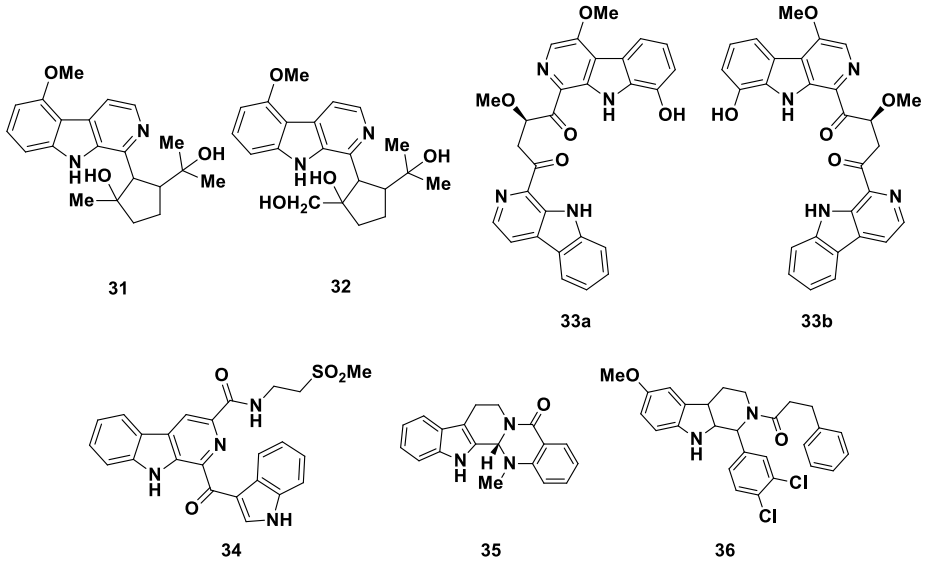


Figure 5. β-Carboline isolates with anticancer activity

d) β-Carboline dimers

The semisynthetic β-carboline derivative formed of two β-carboline rings linked through butyl group showed strong cytotoxic activity against lung, breast and colon cancer through antiproliferative effect and induction of apoptosis. Compound **37** was more potent cytotoxic agent on colon cancer with IC_{50} values 3.58 μM to 5.09 μM than on lung cancer with IC_{50} values 9.58 μM to 10.89 μM or breast cancer with IC_{50} values 8.82 μM to 9.88 μM[54] (Figure 6).

The mechanism of action of β-carboline alkaloid in the treatment of non-small cell lung cancer (NSCLC) was studied by Chatwichien *et al*. The authors found that dimeric β-carboline **38** was lysosomotropic agent and induced apoptosis by increasing transcription of p53 upregulated modulator of apoptosis (PUMA) protein. Moreover, dimeric β-carboline **38** was more potent than monomeric β-carboline **39** as anticancer agent in the treatment of NSCLC with IC_{50} values 0.7 μM to 5.6 μM against NSCLC and IMR90, respectively[55] (Figure 6).

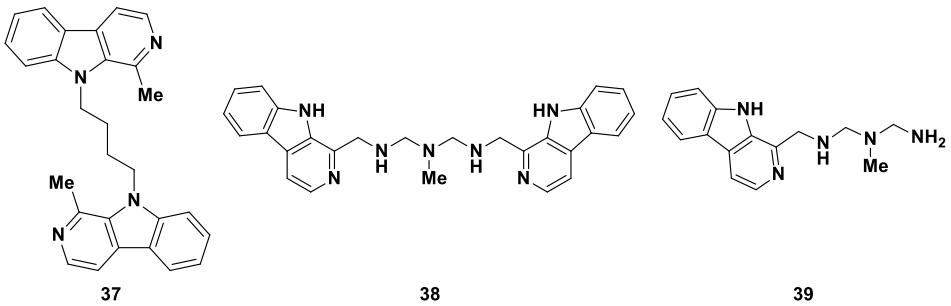


Figure 6. *β*-Carboline dimers with anticancer activity

e) *β*-Carboline metal complexes

Alharbi *et al*. prepared the metal complex of *β*-carboline with tryptophan-based copper (compound **40**) and tryptophan-based zinc (compound **41**) and evaluated their anticancer activity against MCF-7 and HepG2 cancer cell lines. The result showed that compound **40** was more active against MCF-7 cell line with IC_{50} 7.8 ± 0.4 μM[56] (Figure 7).

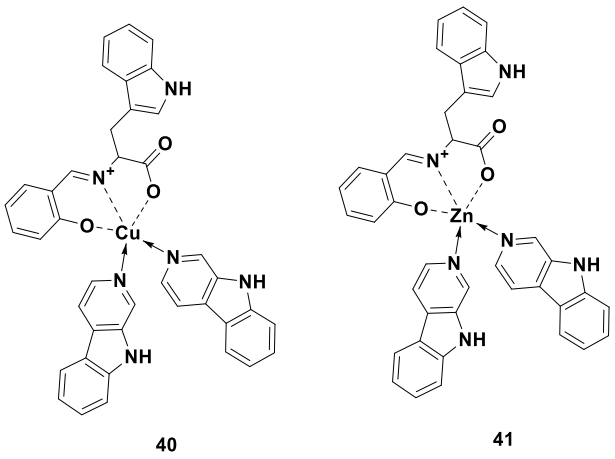


Figure 7. *β*-Carboline metal complexes with anticancer activity

II. Antimicrobial activity

Derivatives of 1,2,3,4-tetrahydro-*β*-carboline-3-carboxylic acid were reported to exhibit anti-TMV (tobacco mosaic virus), fungicide and insecticide activities. Compounds **42** and **43** showed the highest anti-TMV activity with inhibition rate 48.2% and 50.0%, respectively which were superior to ribavirin. Compound **42** was also the most potent fungicide against *Cercospora arachidicola* Hori, *Alternaria solani*, *Bipolaris maydis* and *Rhizoctonia solani* with more than 70% inhibitory activity[57] (Figure 8).

In order to test the effectiveness of their human immunodeficiency virus (HIV-1) and (HIV-2) inhibitory

action, Ashok *et al.* developed and synthesized a series of *β*-carboline derivatives. HIV-2 strain was inhibited selectively by compounds **44a-d** with EC_{50} values 3.3 ± 0.02, 3.2 ± 0.22, 2.6 ± 0.02 and 5.4 ± 0.23 μM, respectively[58] (Figure 8).

The molecular hybrids of piperazinyl-*β*-carboline were evaluated as anti-leishmanial agents against *Leishmania infantum* and *Leishmania donovan*i. Compound **44e** was the most potent against *L. infantum* with EC_{50} 2.89 ± 0.34 μM; while compound **44d** was the most potent against *L. donovani* with EC_{50} 3.47 ± 0.17 μM. Study of the SAR showed that the anti-leishmanial activity increased with the presence of electron donating substituents on the phenyl ring at the *ortho* and *meta* positions[59] (Figure 8).

The antiviral activity of *β*-carboline-4-thiazolidinones against *Herpes simplex* virus type-1 (HSV-1) was studied by Barbosa *et al.* The study showed that compounds **45a-c** displayed the most potent activity with EC_{50} values 0.80, 2.15 and 2.02 μM, respectively. The SAR study revealed that the antiviral activity depended on the nature of 4-thiazolidinone ring and substituents at position 1 and 4 in *β*-carboline ring[36] (Figure 8).

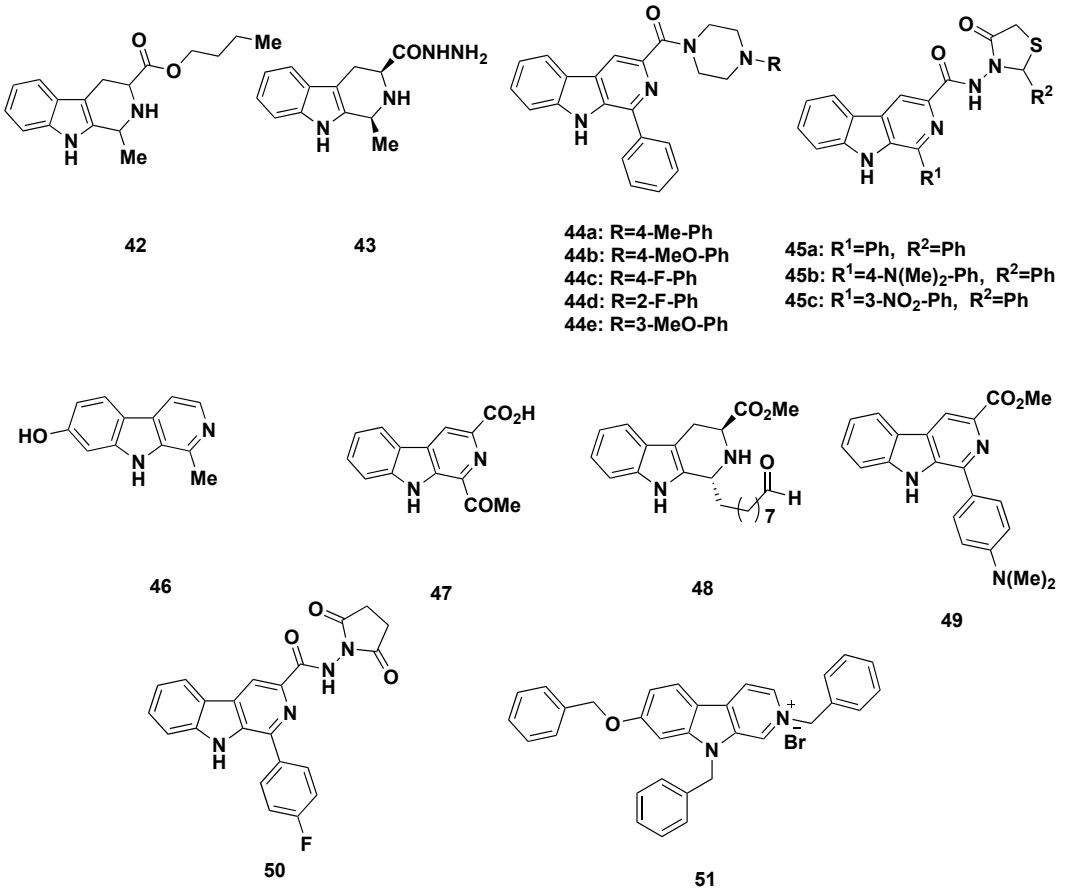


Figure 8. *β*-Carboline derivatives with antimicrobial activity

Olmedo *et al*. studied the antifungal activity of six *β*-carboline compounds against *Penicillium digitatum* and *Botrytis cinerea*. All aromatic *β*-carboline compounds showed good activity, but harmol (**46**) had the most potent fungicide activity against *B. cinerea* and fungistatic activity against *P. digitatum* at concentration 1 μM[60] (Figure 8).

By crude fermentation of isolates of yak milk, Kaur *et al.* prepared *β*-carboline derivative from *Pseudomonas koreensis*. The obtained compound **47** (1-acetyl-9*H*-*β*-carboline-3-carboxylic acid) showed good antimicrobial activity with MIC 62.5- 125 μM/mL against all Gram-negative bacteria tested and 250 μM/mL against *S. aureus*[61] (Figure 8).

The antifungal activity of C^1 alkylated tetrahydro-*β*-carboline derivatives was assessed in 2020 by Singh and collaborators. Compound **48** showed the highest antifungal activity against *Candida glabrata* and *Candida kefyr* with MIC values 9.70 and 9.70 μM, respectively[62] (Figure 8).

The anti-*Mycobacterium tuberculosis* activity of imide-*β*-carboline and carbomethoxy-*β*-carboline was investigated by Lopez-Ortiz *et al.* Compounds **49** (carbomethoxy-*β*-carboline) and **50** (imide-*β*-carboline) showed the highest inhibitory activity against *M. tuberculosis* and against the resistant clinical isolates with MIC values 362.16 μM and 310.86 μM, respectively[63] (Figure 8). Breine *et al.* studied the effect of harmine derivatives on *Acinetobacter baumannii* which is resistant to carbapenem. Among the derivatives investigated, compound **51** had good bactericidal activity with IC_{50} 48.23 μM on multidrug-resistant AB5075-VUB reference strain and caused growth impairment of 43 clinical *A. baumannii* isolates[64] (Figure 8).

III. Antimalarial activity

The antimalarial effect of harmine-analogues against *Plasmodium falciparum* was investigated both *in vitro* and *in vivo* by Bayih *et al*. Compounds **52a** and **52b** had good inhibitory activity and effective binding to *Pf*Hsp90 with IC_{50} values 12.2 ± 2.3 and 23.1 ± 8.8 μM, respectively and to *P. falciparum* W2 strain with IC_{50} values 4.2 ± 1.3 and 5.7 ± 1.7 μM, respectively[65] (Figure 9). The hybrids of harmine and ferrocene were synthesized and their antimalarial effectiveness was assessed by Poje *et al*. The study showed that compound **53** had the most potent inhibitory activity against *Pf*3D7 with IC_{50} 0.15 ± 0.05 μM and this activity was due to direct attachment of triazole ring to ferrocene. In addition, compound **54** was the most active against *Pf*Dd2 with IC_{50} 0.66 ± 0.01 μM[66] (Figure 9).

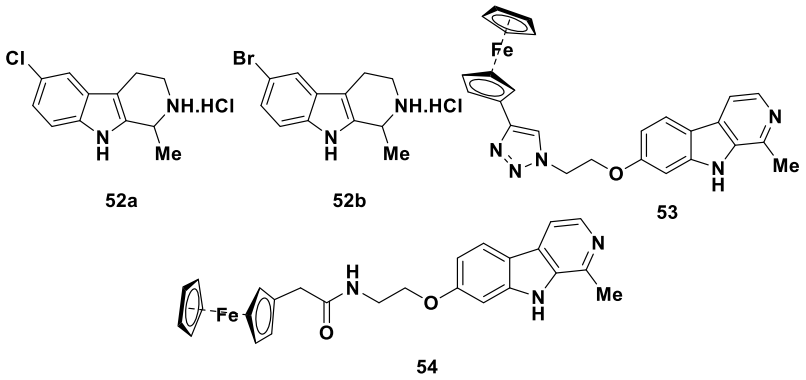


Figure 9. *β*-Carboline derivatives with antimalarial activity

IV. Anti-Alzheimer activity

The effectiveness of tacrine-*β*-carboline hybrid derivatives in treating Alzheimer's disease was evaluated by Lan *et al.*[67] All the synthesized compound showed good activity especially compound **55** that showed potent inhibitory activity of *ee* acetylcholinesterase (*ee*AChE), *h* acetylcholinesterase (*h*AChE) and butyrylcholinesterase (BuChE) with IC_{50} values 21.6 *n*M, 63.2 *n*M and 39.8 *n*M, respectively and 65.8% A*β* aggregation inhibition at 20 μM[67] (Figure 10). In order to study the inhibitory action of AChE and BuChE, Yang *et al*. extracted compounds from *Peganum harmala* Linn. seeds. The study showed that compound **56** (tetrahydroharmine-2-formamide) was the most potent anti-AChE and anti-BuChE with IC_{50} values 12.35 ± 0.24 and 5.51 ± 0.33 μM, respectively. SAR analysis revealed that pyridine ring's saturation and substitution at the indole ring at C^1, C^3, C^7 and N^2 were necessary for effective inhibition of both AChE and BuChE.[68] Harmin (**57**), that was studied by Filali *et al.* demonstrated strong anticholinesterase inhibitory action with IC_{50} 10.4 μM[69] (Figure 10).

The anti-Alzheimer action of *β*-carboline derivatives was also studied by Horton *et al.* The study discovered compound **58** as the most effective derivative with 39% A*β* inhibition, 95% BuChE inhibition and BuChE IC_{50} 0.22 ± 0.03 μM[70] (Figure 10). In 2018, Zhao *et al*. reported the synthesis of a series of bivalent *β*-carboline derivatives and evaluated their efficacy as therapeutic agents for Alzheimer's disease. Compounds **59b** and **59c** displayed the most potent and selective inhibitory activity against BuChE with IC_{50} values 1.7 and 2.7 μM, respectively and inhibition of $A\beta_{1\text{-}42}$ aggregation with inhibitory rate 82.7% and 85.7%, respectively. Compounds **59a-c** also showed good neuroprotective activity[71] (Figure 10)

A number of *β*-carboline-1,2,3-triazole hybrids were synthesized by Liu and his colleagues, and their anti-Alzheimer activity was assessed. Compound **60** demonstrated good permeability to blood brain barrier (BBB) and excellent inhibition of *ee*AChE, *h*AChE and glycogen synthase kinase-3*β* (GSK-3*β*) with IC_{50}

values 0.2 ± 0.02, 0.34 ± 0.01 and 1.14 ± 0.05 μM, respectively[72] (Figure 10). Compound **61** was also discovered by the same research team and it exhibited IC_{50} values 0.27, 20.82 and 6.78 μM against AChE, BuChE and GSK-3β respectively[24] (Figure 10).

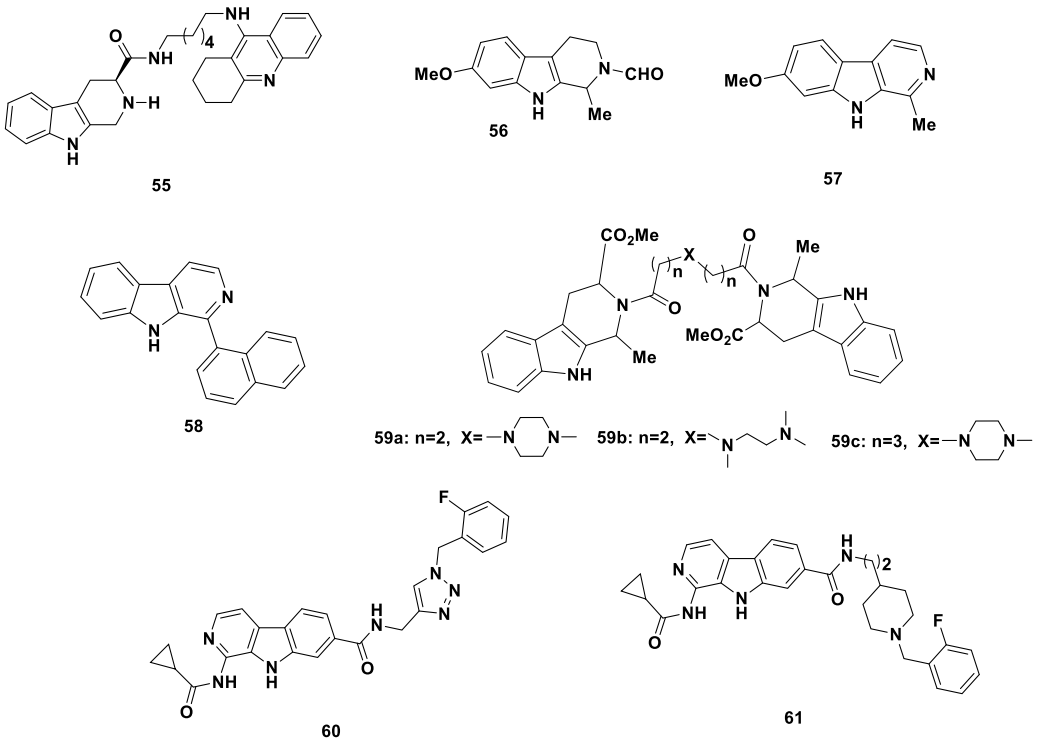


Figure 10. β-Carboline derivatives with anti-Alzheimer activity

V. Anti-inflammatory activity

The antineutrophilic inflammatory activity of variety of β-carboline/combretastatin hybrid compounds was assessed by Kumar *et al*. in 2021. The study showed that compounds **62** and **63** were the most potent to cause significant inhibition of *N*-formylmethionyl-leucyl-phenylalanine (FMLF)-induced superoxide anion generation with IC_{50} values 5.58 ± 0.56 and 2.81 ± 0.07 μM, respectively[73] (Figure 11).

In vitro and *in silico* inhibitory action of compounds extracted from *Peganum harmala* L. was investigated in 2022 by Abdel Bar *et al.* Compounds **64** and **65** had the most potent inhibitory activity against cyclooxygenase-2 enzyme (COX-2) *in vitro* with IC_{50} values 2.638 and 9.924 μM, respectively. Moreover, compounds **64-67** had potent inhibitory activity against 5-lipooxygenase enzyme (5-LOX) with IC_{50} values 1.63, 4.596, 6.174 and 3.237 μM, respectively[74] (Figure 11).

The harmine derivatives **68** and **69** showed potent inhibitory activity against 5-lipoxygenase enzyme with IC_{50} values 29.2 and 55.5 μM, respectively[69] (Figure 11).

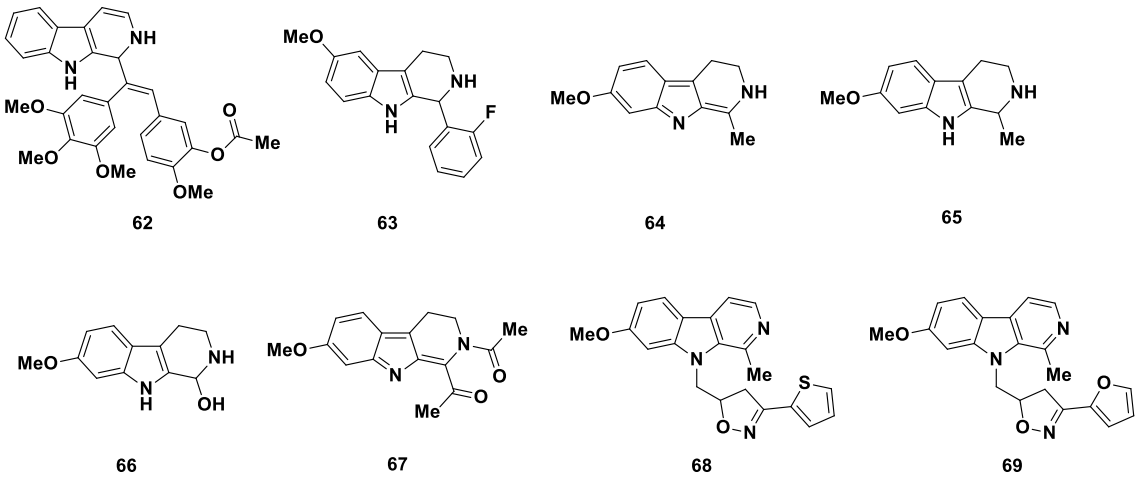


Figure 11. *β*-Carboline derivatives with anti-inflammatory activity

VI. Analgesic activity

Four *β*-carboline derivatives that were isolated from roots of *Psammosilene tunicoides* were examined for their analgesic properties. Compounds **70-73** showed potent analgesic activity through antinociceptive effect and good anti-inflammatory activity through inhibition of nitric oxide (NO) production in lipopolysaccharide-induced RAW264.7 cells with IC_{50} values 23.3 ± 1.4, 4.2 ± 0.9, 1.7 ± 0.4 and 1.1 ± 0.5 μM, respectively. SAR analysis of the compounds revealed that substitution at C^1 with acetyl group increased both analgesic and anti-inflammatory activity while substitution at C^3 position with CO_2Me, $CONH_2$ and CO_2H groups increased only the anti-inflammatory activity[3] (Figure 12).

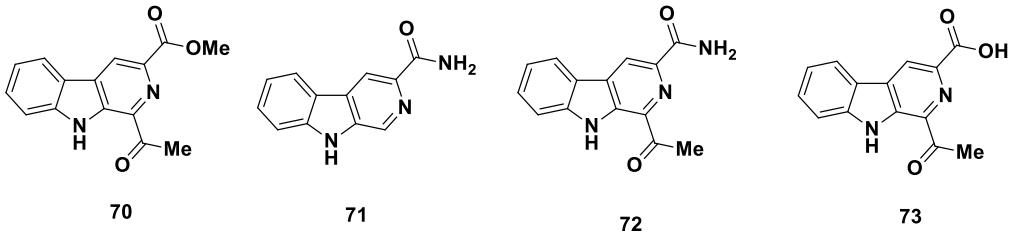


Figure 12. *β*-Carboline derivatives with analgesic activity

VII. Vasorelaxant activity

The vasorelaxant activity of furyl/thienyl-*β*-carboline derivatives was assessed by Zheng *et al.* The compounds exerted their action by inhibition of phosphodiesterase 5 enzyme (PDE5). Compounds **74** and **75** displayed the highest PDE5 inhibitory activity with IC_{50} values 3.87 ± 0.61 and 2.92 ± 0.17 *n*M,

respectively[75] (Figure 13).

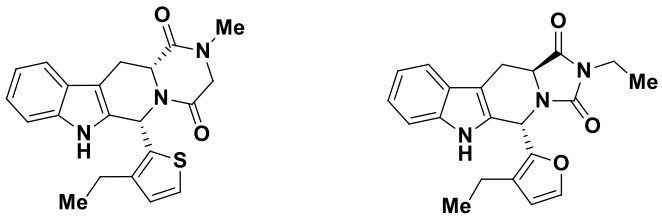


Figure 13. *β*-Carboline derivatives with vasorelaxant activity

CONCLUSION

The *β*-carboline derivatives displayed variable biological activities. The ring is present in many natural alkaloids. The ring is also characterized by being easily prepared using conventional and green synthetic approaches. More efforts needs to be done to explore the mechanism of action and the structure-activity relationship of each biological activity. The present review may be helpful to develop further study on each of the biologically active compounds to enhance their biological activities and method of synthesis.

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