Malaysian Journal of Chemistry, 2025, Vol. 27(1), 181-194
(Special Issue: *International Conference in Organic Synthesis, ICOS 2024*)

A Short Review of Daibucarboline A and Its Derivatives: Exploring Tetrahydro-β-Carboline Intermediates for Anti-Inflammatory Potential

Noor Hidayah Pungot[1,2]*, Nur Ain Nabilah Ash'ari[1,2] and Siti Zafirah Zulkifli[1,2]
[1]School of Chemistry and Environment, Faculty of Applied Sciences,
Universiti Teknologi Mara (UiTM), 40450 Shah Alam, Selangor, Malaysia
[2]Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi Mara (UiTM),
Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia
*Corresponding author (e-mail: noorhidayah977@uitm.edu.my)

Daibucarboline A, a notable compound with demonstrated anti-inflammatory properties, has garnered significant interest due to its potential therapeutic applications. This short review explores the synthetic strategies employed to develop Daibucarboline A and its derivatives, focusing on the role of tetrahydro-β-carboline intermediates in their preparation. We summarize recent advancements in the synthesis of these intermediates, which are crucial for constructing the daibucarboline scaffold. The review highlights key methodologies used to achieve efficient and selective synthesis of tetrahydro-β-carboline derivatives and their subsequent transformation into bioactive daibucarboline compounds. Additionally, we review the anti-inflammatory potential of Daibucarboline A and its derivatives in vitro and in vivo studies that elucidate their mechanisms of action. By providing a comprehensive overview of the synthesis and bioactivity of these compounds, this review aims to offer insights into the development of novel anti-inflammatory agents based on the daibucarboline framework and to identify future directions for research in this promising area.

Keywords: Daibucarboline A; anti-inflammatory; tetrahydro-β-carboline intermediates

Received: September 2024; Accepted: January 2025

The concept of secondary plant metabolite was originated in 1910, first defined by Albrecht Kossel, the Nobel Prize winner of the year for physiology and medicine [1]. It refers to the numerous chemical compounds produced by plant cells through metabolic pathways derived from the primary metabolic pathways. For centuries, plant secondary metabolites have been used by physicians and lay healers as the active constituents in the medicinal treatment of human diseases. They encompass a massive number of natural compounds with diverse chemical structures and properties [2]. The use of secondary metabolites in manufacturing pharmaceuticals, fine chemicals, fragrances, and food additives are crucially essential for the health care and welfare of human beings [3]. Therefore, the production of these natural plant-derived compounds by cultivation of plants and chemical synthesis have drawn tremendous interest over the past years and now becoming a major agronomic and industrial objective. To date, up to 50% of approved drugs and prescription medicine are still derived from plants [4]. The secondary plant metabolites are classified according to their chemical structures into several classes which include alkaloids, phenolics, saponins, terpenes, lipids, and carbohydrates [5].

The quest for novel anti-inflammatory agents has led researchers to explore various chemical scaffolds with potential therapeutic benefits. One such scaffold is the daibucarboline framework, which has gained attention for its promising anti-inflammatory properties. Daibucarboline A, a compound within this class, has demonstrated significant bioactivity, making it an intriguing subject for further investigation. Understanding the synthesis and functionalization of daibucarboline A and its derivatives is crucial for developing effective anti-inflammatory therapies. Alkaloids are mainly contained in various living organisms, such as animals, plants, bacteria, and fungi. According to Isah et al. (2019), alkaloids are characterized as nitrogen-containing organic compound derived from amino acid. Productions of alkaloids as secondary metabolites in plants are stimulated by the trigger of biotic and abiotic stress, as well as through the changes in their environment [6]. These endow alkaloids with diverse structures and significant biological activities, causing a growing attention among scientists to consider them as a potential new drug [7]. Alkaloids can be classified as indole, quinoline, isoquinoline, pyridine, and pyrrolidine as shown in **Figure 1** [8].

†Paper presented at the International Conference in Organic Synthesis 2024 (ICOS 2024)

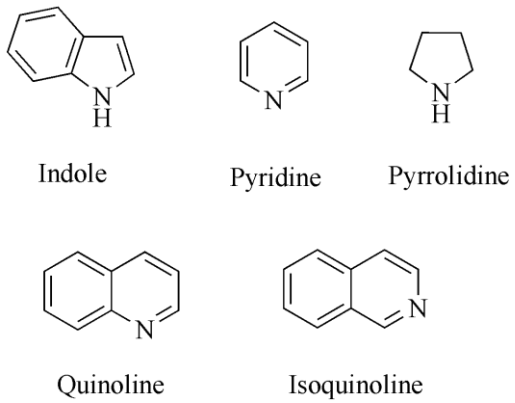


Figure 1. Main classes of alkaloids.

Tetrahydro-β-carbolines serve as key intermediates in the synthesis of Daibucarboline A and its derivatives [9]. These heterocyclic compounds offer a versatile platform for constructing complex molecular frameworks due to their unique structural properties and reactivity. The strategic use of tetrahydro-β-carboline intermediates allows for the precise assembly of the daibucarboline core, facilitating the development of compounds with enhanced bioactivity and selectivity. Recent advancements in synthetic chemistry have led to the development of various methodologies for the efficient preparation of tetrahydro-β-carboline derivatives. These methods include catalytic processes, multi-step syntheses, and novel reaction conditions that improve yield and purity. Understanding these synthetic approaches is essential for optimizing the production of Daibucarboline A and its derivatives, thereby enabling their evaluation as potential anti-inflammatory agents.

The anti-inflammatory potential of Daibucarboline A and its derivatives has been explored through a range of in vitro and in vivo studies [10]. These studies have elucidated their mechanisms of action, highlighting their ability to modulate inflammatory pathways and reduce inflammation-related pathology. By targeting key inflammatory mediators and pathways, these compounds offer a promising approach to managing inflammatory diseases [11].

This review aims to provide a concise overview of the synthetic approaches to Daibucarboline A and its derivatives, with a focus on the role of tetrahydro-β-carboline intermediates. Additionally, it will summarize the current understanding of their anti-inflammatory potential and discuss future research directions. By integrating recent advancements in synthesis with insights into bioactivity, this review seeks to advance the development of novel anti-inflammatory therapies based on the daibucarboline scaffold.

METHOD

A comprehensive literature search was conducted using databases such as PubMed, Google Scholar, and Scopus. Keywords included "Daibucarboline A", "β-carboline", "tetrahydro-β-carboline intermediates", and "anti-inflammatory." Studies published in the past two decades were prioritized to ensure relevance and the inclusion of the most recent advancements.

1. Indole Heterocycle with β-carboline Ring System

β-Carboline (**Figure 2**) or 9*H*-pyrido[3,4-*b*]indole, belongs to the group of indole alkaloids and consist of a pyridine ring that is fused to an indole skeleton. The structure of β-carboline is similar to that of tryptamine, with the ethylamine chain reconnected to the indole ring via an extra carbon atom, to produce a tricyclic ring structure. Commonly known as norharmane, this compound and its derivatives which include tryptoline, pinoline, harmane, harmine, and harmaline (**Figure 2**) are reported to occur in a number of plants, including *Banisteriopsis caapi* and *Peganum harmala* (Malpighiaceae) [12].

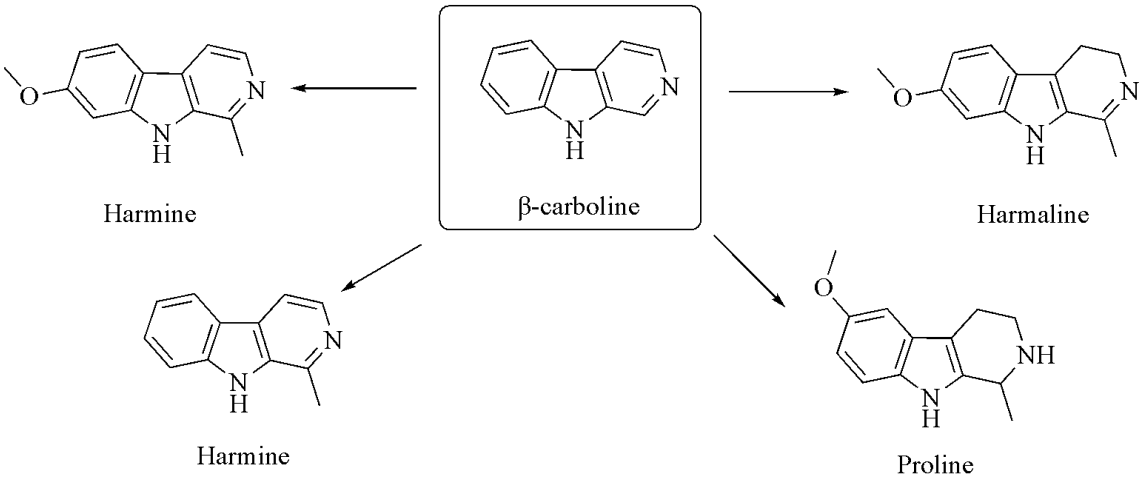


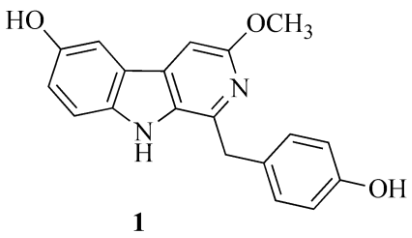
Figure 2. The structure of β-carboline and its derivatives.

The spectrum of biological activities displayed by this natural compound is remarkable in diversity. β-Carboline compounds obtained from various parts of *Peganum harmala*, a medicinal plant with anti-microbial, antioxidant [13], anti-inflammatory, and analgesic properties [14] are used in the treatment of various diseases [15]. For instance, the extract of *Peganum harmala* containing harmine and harmaline are known to possess hypothermic and hallucinogenic properties. It is therefore used as a medical remedy, incense, spice or condiment and employed for the treatment of syphilis, fever, hysteria, malaria, parkinsonism, asthma and eye complaints [16][17] [18][19]. Intrigued by its biological properties, we embarked on the development of a concise and applicable synthetic approach towards a new derivative of β-carboline, named Daibucarboline A.

β-Carbolines can be viewed as indole derivatives with an additional pyridine ring, and thus share some common synthetic routes and reactivity patterns with indole-based compounds. The incorporation of the β-carboline ring into the indole framework can significantly alter the biological properties of the resulting molecules, providing opportunities for designing novel bioactive compounds. Combining the indole and β-carboline ring systems can lead to compounds with enhanced or unique pharmacological profiles, making them attractive candidates for drug development. Research continues to explore how variations in these ring systems influence biological activity, leading to the discovery of new therapeutic agents.

2. Discovery of Daibucarboline A

Daibucarboline A, **1** (**Figure 3**) is a unique derivative of β-carboline, belonging to the indole alkaloid family as well. It is isolated from the Kamikoti (Lauraceae) *Neolitsea daibuensis* by Wong and co-workers in 2011 [20] In their respective research, they conducted bioassay-guided fractionation of the roots of *Neolitsea daibuensis*, which led to the isolation of three new β-carboline alkaloids, and one of them is **1** as well as other 20 known compounds. Further assessment of their anti-inflammatory activity using an inducible nitric oxide synthase (iNOS) assay was performed as well. As a result, four compounds exhibited moderate iNOS inhibitory activity and among them is **1** with IC_{50} values of 18.41 μM.



1

Figure 3. Structure of Daibucarboline A, **1.**

Later in 2018, another **1** compound was isolated by Jani and co-workers from the stems of *Neolitsea kedahensis* in 3.9 mg [37]. The ^{1}H NMR spectrum of the obtained **1** was compared with **1** [34] and the structure were confirmed by displayed similarities including the characteristics signals of phenyl protons with an ABX spin system in the A ring (H-5, H7, H-8), an NH proton in the B ring, a pyridine proton in the C ring (H4), a methoxyl group (3-OCH_3) and a 4- hydroxybenzyl moiety protons (H-2′, H-3′, H-5′, H-6′, H-7′, 4′-OH). To date, there are no reports on the synthesis of **1** or its derivatives. Recent studies from Kim et. al reported that Daibucarboline A, a novel alkaloid, was isolated from the marine sponge *Daibucus* sp. through a combination of chromatographic techniques. The compound's structure was elucidated using advanced spectroscopic methods including NMR and MS.

The recent study by Zhang et al. (2024), Daibucarboline A, discovered natural product, for its potential as an anti-inflammatory agent. It provides insights into the compound's mechanisms of action and its efficacy in reducing inflammation. In vitro assays, the compound was tested using various cell lines, including macrophages and fibroblasts, to assess its impact on inflammatory markers. Cytokine Production: Levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6) were measured using ELISA. Gene Expression: qRT-PCR was used to analyze the expression of genes involved in inflammation, such as COX-2 and iNOS. Cellular Signaling Pathways: Western blotting was performed to evaluate the effects of Daibucarboline A on key signaling pathways, including NF-κB and MAPK [21].

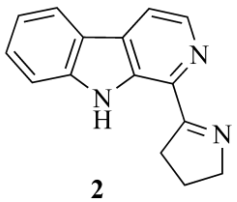
The result for anti-inflammatory activity indicate that Daibucarboline A significantly reduced the production of pro-inflammatory cytokines in treated cell lines. The mechanistic insights show that the compound inhibited NF-κB activation and decreased the expression of COX-2 and iNOS, which are crucial in the inflammatory response. Thus an efficacy in animal models of inflammation, daibucarboline A showed a marked reduction in symptoms, demonstrating its potential effectiveness in vivo. Mechanisms of action for Daibucarboline A's anti-inflammatory effects are primarily mediated through the suppression of NF-κB and MAPK pathways, which play pivotal roles in the regulation of inflammatory responses. Compared to conventional anti-inflammatory drugs, Daibucarboline A exhibited a favorable profile with potentially fewer side effects, although further studies are needed to confirm its safety and efficacy in humans [21][22].

Daibucarboline A represents a promising novel anti-inflammatory agent with significant potential for treating inflammatory diseases. Its unique mechanism of action and effectiveness in preclinical models warrant further investigation in clinical trials. Daibucarboline A also exhibits significant biological activity, including antimicrobial and cytotoxic effects, suggesting its potential as a lead compound for drug development [23]. Therefore, novel derivatives of **1** will be synthesized in which some of them are most likely to display similar or better bioactivities.

3. Total Synthesis of β-carboline Derivatives towards Daibucarboline A.

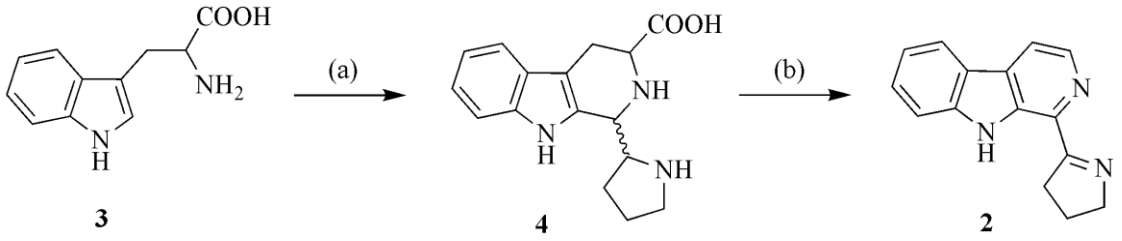
This part will review several synthetic methods towards the syntheses of some naturally bioactive compounds which have the same structural moiety to that of Daibucarboline A. This review provides an insight on how to design and synthesis bioactive daibucarboline A and its derivatives.

Eudistomine I (**Figure 4**), **2** is characterized by a β-carboline unit carrying a 3,4-dihydropyrrole group at C-1 position. Molecules containing this motif exhibit a range of potent bioactivities including antiviral and antitumor properties [24]. Meanwhile, Manasa et al. (2017) was isolated **2** from *Eudistoma Olivaceum* and the results shows strong antiviral and antimicrobial activities [25].



2

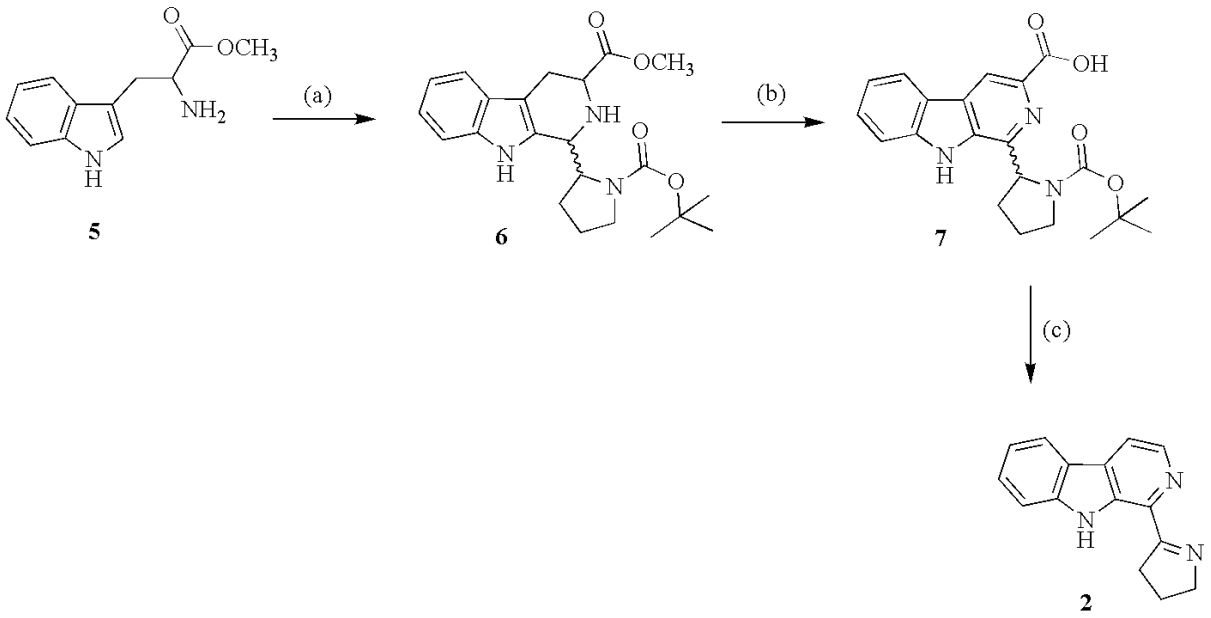
Figure 4. Structure of Eudistomin I, **2**.



Scheme 1. Synthesis of **2** as reported by Kamal et al. (2015).
Reagents and conditions: (a) i. AcOH, 80°C, 1h, ii. 2N dioxane, HCl, 0°C to rt, 3h, 90%, (b) NCS (3.1 equiv.), TEA, DMF, rt, 30 min, 70%.

According to the method employed by Kamal et al. (2015) to synthesize **2**, *N*-boc pyrrolidinyl tetrahydro-β-carboline acid was initially obtained by coupling *L*-tryptophan **3** and *N*-boc prolinal which underwent Pictet-Spengler reaction [26]. The corresponding acid was then directly used for further deprotection of Boc group using 2N HCl in 1,4-dioxane to afford the hydrochloride salt **4**. Compound **2** was produced under optimized reaction conditions by using NCS in 70% yield. Interestingly, it was observed that decarboxylation, aromatization and imine formation were successfully achieved in a one-pot manner as shown in **Scheme 1**.

In another study by Kamal et al. (2015), the total synthesis of **2** was accomplished via three steps. It began with the acid catalyzed Pictet-Spengler condensation of *L*-tryptophan methyl ester **5** with *tert*-butyl 2-formyl pyrrolidine-1- carboxylate to give the corresponding tetrahydro-β-carboline **6** as a diastereomeric mixture in a good yield. Further, saponification of **6** followed by deprotection of the Boc group with 2N HCl in dioxane, afforded the corresponding hydrochloride salt **7** which under the optimized conditions of oxidative decarboxylation, furnished **2** in 63% yield (**Scheme 2**). Here, it is important to note that iodobenzene diacetate mediates three distinct chemical transformations (decarboxylation, aromatization and dehydrogenation of the pyrrolidine ring) in a single, one-pot operation [27].



Scheme 2. Total synthesis of **2** by Kamal et al. (2015).
Reagents and conditions: (a) *tert*-butyl 2-formyl pyrrolidine-1-carboxylate, EtOH, reflux, 12h, 88%, (b) 2M LiOH, THF, reflux, 12h, 91%, (c) i. 2N dioxane, HCl, 0°C to rt, ii. 3 $PhI(OAc)_2$, DMF, rt, 1h, 63%.

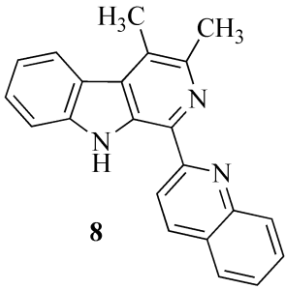
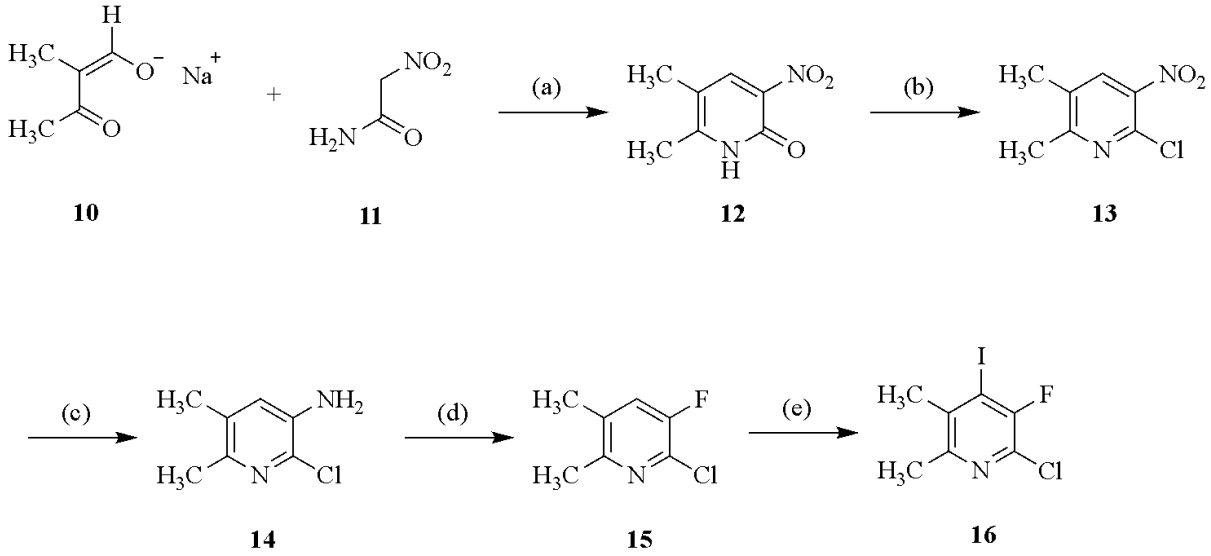


Figure 5. Structure of Lavendamycin, **8**.

Lavendamycin **8** (**Figure 5**) is an important nitrogen containing heterocycle due to its widespread biological and pharmacological applications. This compound has been reported to possess antitumor property [28]. Later, **8** was isolated and characterized by Doyle and co-workers from the fermentation broths of *Streptomyces lavendulae* [29]. Lavendamycin, when used in combination with standard chemotherapeutic agents, shows significant promise in enhancing anti-cancer efficacy. The combination therapy exhibits synergistic effects, providing a strong rationale for further investigation in clinical trials. The study highlights the potential of **8** in enhancing the efficacy of standard chemotherapy agents. The synergistic effects observed suggest that Lavendamycin could be a valuable addition to current treatment regimens, and an observed synergy is likely due to Lavendamycin's ability to modulate apoptotic pathways and enhance the efficacy of conventional drugs, leading to more effective tumor cell killing [30].

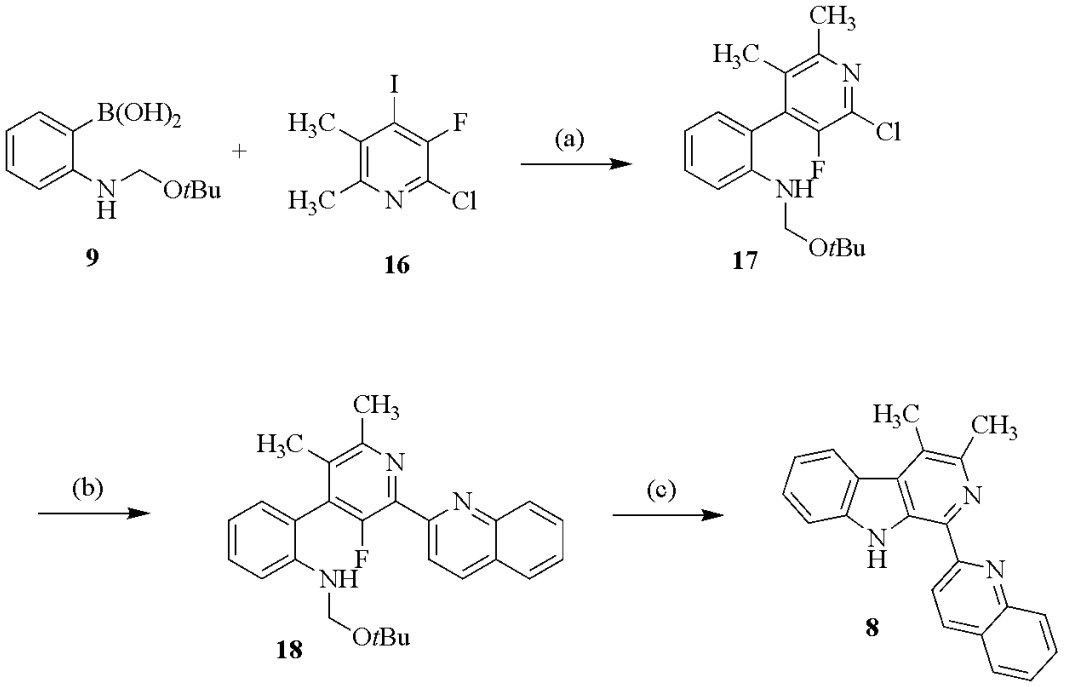
Stimulated by the challenging structure of **8** as well as potential antitumor ability of its derivatives, a study was conducted by Rocca et al. (1993) to establish a new convergent route to α-substituted-β-carbolines starting from simple benzene and pyridine reagents, which led to a fruitful strategy for the construction **8** skeleton [31].

The synthetic route begins with the preparation of boronic acid, **9** by metalation-boronation of pivaloylaminobenxene, which afforded **9** in 58% yield. Subsequently, the pentasubstituted pyridine, **16** was synthetized via four steps from the reaction of sodium salt **10** and nitroacetamide **11**, followed by the chlorination of nitropytidone, **12** in chlorobenxene at 130°C afforded the chloro compound **13** which was reduced to the desired aminochloropyridine, **14**. Proceeding to the next step, diazotation of the amino group with ethylnitrite in tetrafluoroboric acid yielded the fluoro compound, **15**. In a final step to synthesize **16**, metalation of the **15** by LDA in THF at low temperature afforded the corresponding iodo compound **16** in excellent yield (95%). The synthetic route is summarized in **Scheme 3**.



Scheme 3 Preparation of pentasubstituted pyridine **16**, reported by Rocca et al. (1993).

Reagents and conditions: a) piperazine, $AcOH/H_2O$, 70°C, 1h, 82%, b) $POCl_3$, PhCl, reflux, 1h, 92%, c) Fe, HCl, $EtOH/H_20$, 70°C, lh, 93%, d) i. EtONO, Et_2O, HBF_4, ii. Hexane, 60°C, 48%, e) i. LDA, THF, -78°C, 4h, ii. I2, iii. H_3O^+, 95%.



Scheme 4. Synthesis of Lavendamycin, **8** reported by Rocca et al. (1993).
Reagents and conditions: a) $Pd(PPh_3)$, EtOH, $Ba(OH)_2$, toluene, reflux, 16h, 83%, b) 2-trimethylstannylquinoline, toluene, reflux, 67%, c) i. Pyridinium chloride, 215°C, 15min, ii. NH_4OH, 91%.

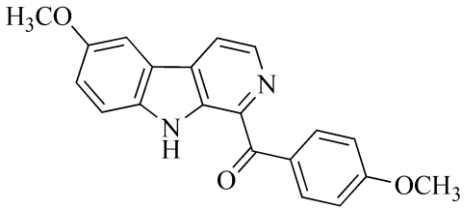


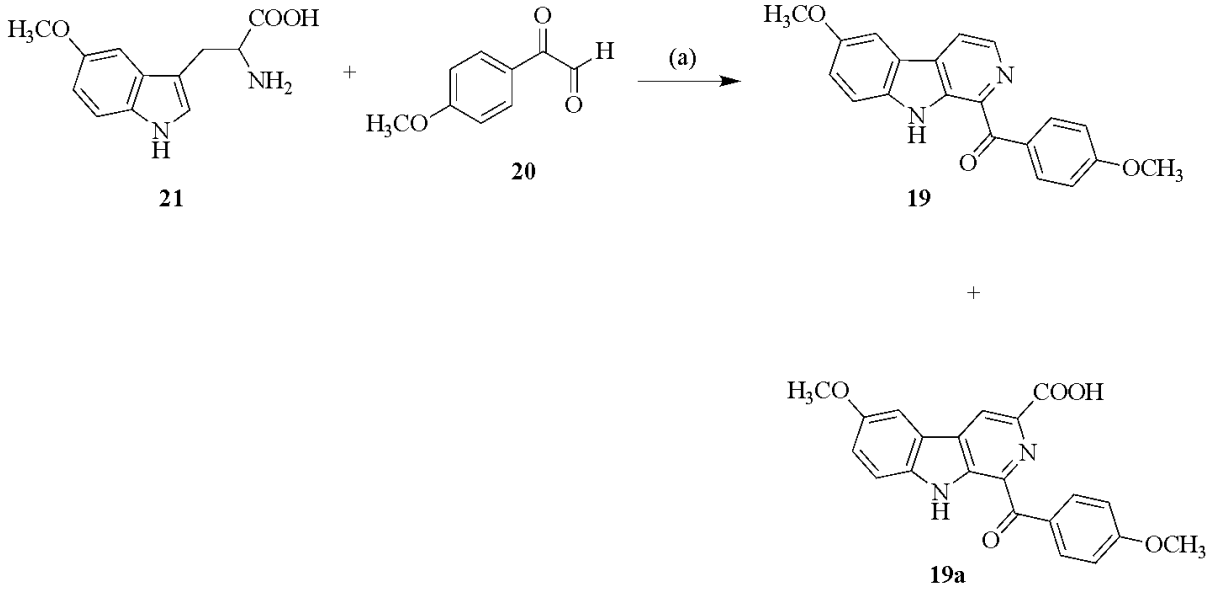
Figure 6. Structure of Luzongerine A, **19**.

The next step involves the palladium-catalyzed cross-coupling between the prepared boronic acid **9** and iodopyridine **16** which yielded the biaryl **17** in high yield (83%). Refluxing mixture of 2-trimethylstan-nylquinoline with the biaryl **17** under the presence of catalytic $Pd(PPh_3)_4$ in toluene led to the poly-substituted triaryl **18**. Cyclization of **18** by treatment with boiling pyridinium chloride at 215°C yielded the β-carboline **8** (**Scheme 4**).

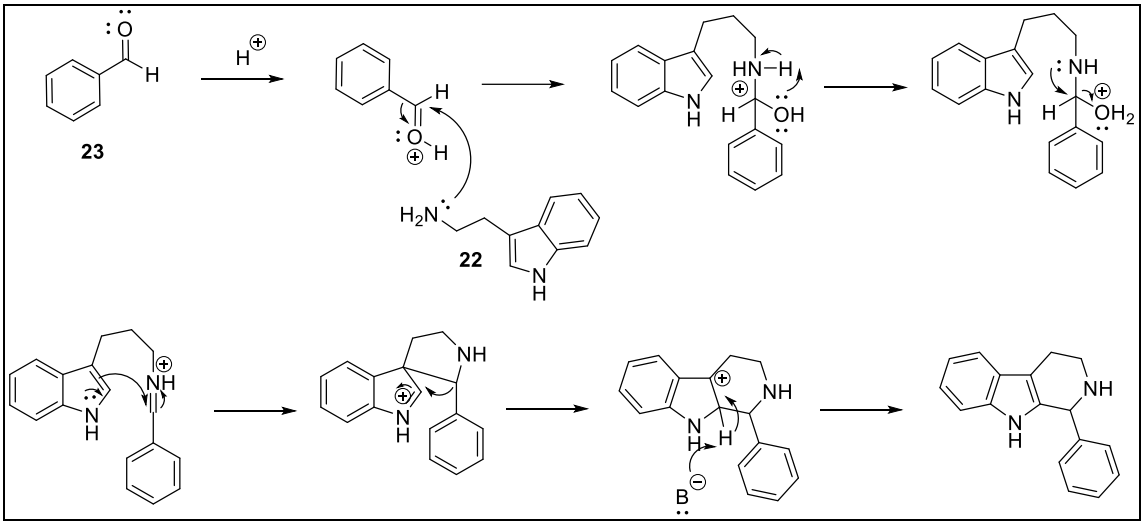
Yang et al. (2006) was synthesized Luzongerine A, **19** (**Figure 6**), by applying the developed methodology, following their success on 1-substituted β-cabolines synthesis. **19**, isolated from Illigera luzonensis, was prepared under optimized condition reactions using 4-methoxyphenyl glyoxal **21** and 5-methoxy-*L*-tryptophan **20** as the starting material (**Scheme 5**). Since the physical and spectral data coincided well with those of the isolated one, it was concluded that the described method is applicable to the synthesis of the natural 1-substituted β-cabolines. Compound **19** was afforded in 40% yield along with a minor product **19a** in 5% yield [32].

Generally, the classical Pictet-Spengler mechanism of action proceeded under two-step reaction that involves acid-catalyzed condensation of an amine bearing a sufficiently reactive aromatic nucleus with aldehydes [32]. It began with the formation of imine, which may be activated by acids, followed by *endo* cyclization between a carbon nucleophile of a sufficiently reactive aromatic moiety and the activated iminium ion *via* a new C-C bond, resulting

in an *N*-heterocyclic ring and forming tetrahydro-β-carboline intermediate (THβC). The THβC led to β-carboline on dehydrogenation. **Scheme 6** below shows the general mechanism of Pictet-Spengler by condensation of tryptamine **22** with benzaldehyde **23**.

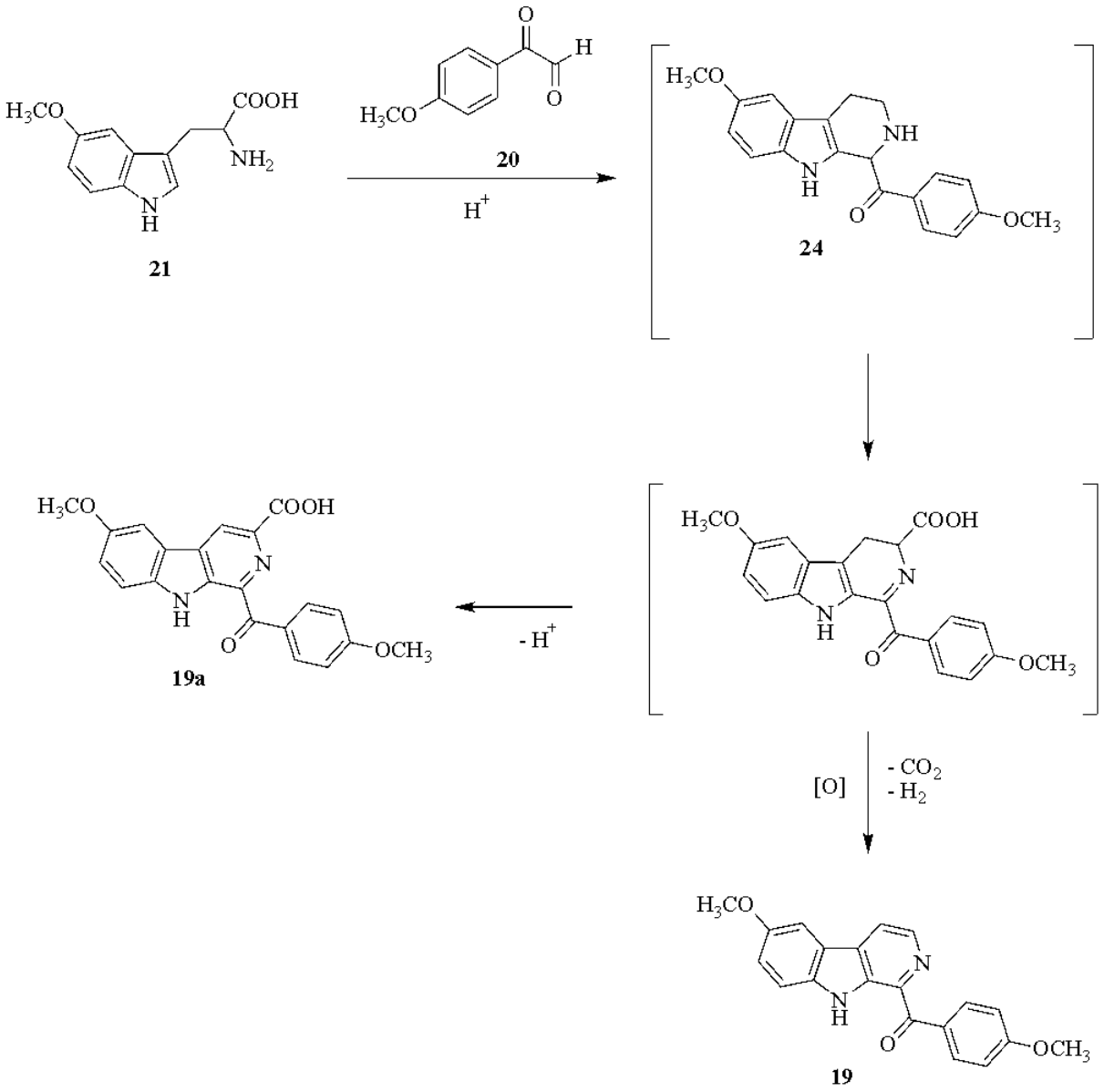


Scheme 5. Synthesis of Luzongerine A, **19** reported by Yang's et al. (2006). Reagents and condition: a) *p*-TsOH, MeOH, 50°C, 2h, **19**: 40%, **19a**: 5%.



Scheme 6. General mechanism of Pictet-Spengler Condensation reaction.

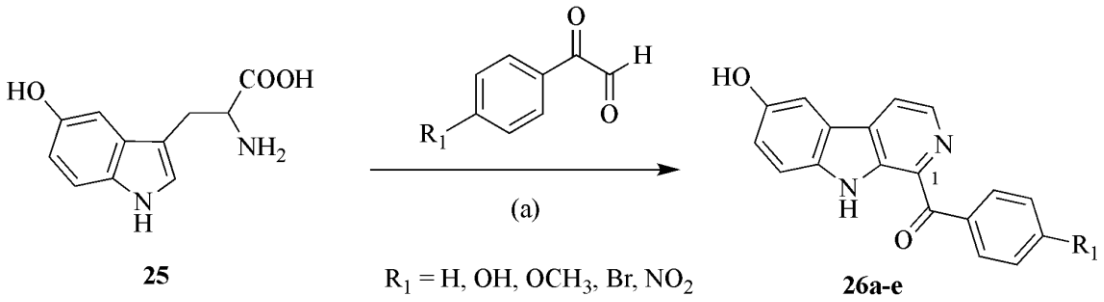
However, it is worth mentioning that in this experiment (**Scheme 7**), the treatment of **21** with **20** did not produce the expected THβC intermediate but rather afforded directly the dehydrogenated β-carboline product **19** as major along with minor amount of **19a** in a single step. These observations were rationalized by the mechanism as proposed in Scheme 7. The aldehyde was activated in the presence of acid to allow the nucleophilic attack of tryptophan, forming tetrahydro-β-carboline-3-carboxylic acid intermediate, **24**. Subsequent successive decarboxylation and oxidative dehydrogenation [33] led to the β-carboline **19** as a major product accompanied by a minor product **19a**.



Scheme 7. Mechanism of Pictet-Spengler as proposed by Yang's et al. (2006*)* to afford product **19** and **19a**.

Recently, Pungot et al. (2024) was attempted in a more practical and convenient synthesis of the aromatic β-carbolines using 5-hydroxytryptophan and various aromatic glyoxals in the desired Pictet-Spengler reaction. The Pictet-Spengler reaction is indeed a valuable chemical transformation for the synthesis of β-carboline ring systems, and is particularly useful when the starting materials are tryptophan or tryptophan derivatives [36]. This reaction involves the process of acid catalyzed condensation of β-carboline with an aldehyde, a ketone or a glyoxal, resulting in the formation of a C-C bond and a series of analogues with a β-carboline ring system. The tetrahydro-β-carboline (THβC) continues to undergo aromatization to form fully aromatic β-carboline [38]. By performing the versatile route of Pictet-Spengler reaction where *p*-TsOH.H_2O is used as a catalyst and methanol as a medium, this simple method produces a fully aromatic β-carboline instead of the tetrahydro β-carboline (**Scheme 8**).

This strategy refines the scope of Pictet-Spengler cyclization as the THβC intermediate directly oxidized to the targeted β-carboline in one-pot oxidation reaction, which also allows for product diversification at C-1 position. This approach is concise and most preferred due to its simplicity since no heat is involved to drive the reaction.



Scheme 8. The synthesis of 5-hydroxy-*L*-tryptophan with different substituted phenylglyoxals by Pungot et al. (2024).
Reagents and condition: a) *p*-TsOH, MeOH, 50°C, 2h, **26a**: 53%, **26b**: 30%, **26c**: 42%, **26d**: 57%, **26e**: 65%.

4. Anti-inflammatory Property and Cytotoxicity

Nitric oxide (NO) is a molecular messenger synthesized by nitric oxide synthase (NOS) enzymes. It is implicated in diverse physiological and pathological processes. Nevertheless, most inflammation reactions, both acute or chronic are speculated to originate from excessive NO generated, produced by inducible nitric oxide synthase (iNOS). It is therefore significant that recent studies have shown the positive effect of naturally occurring 1-substituted-β-carboline alkaloids in suppressing the expression of iNOS in various cell systems [32].

As mentioned in the previous section, the study by Wong et al. (2011) has led to the isolation of three new β-carboline alkaloids. Among them is Daibucarboline A, **1** as well as other 20 known compounds [34]. Further assessment on their anti-inflammatory activity using the iNOS assay was also performed as well and as a result, **1** was shown to exhibit moderate anti-inflammatory activity with IC50 values of 18.41 μM. In addition, four β-carboline compounds, namely, benzalharman, kumujian, 1-ethyl-1,2,3, 4-tetrahydro-β-carboline-3-carboxylic acid, and 1-acetophenone-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (**Figure 7**) exhibited significant inhibitory activity on the overproduction of NO with good dose dependency. Further investigation demonstrated that all the compounds have the ability to down-regulate the high expression of iNOS protein [35, 45].

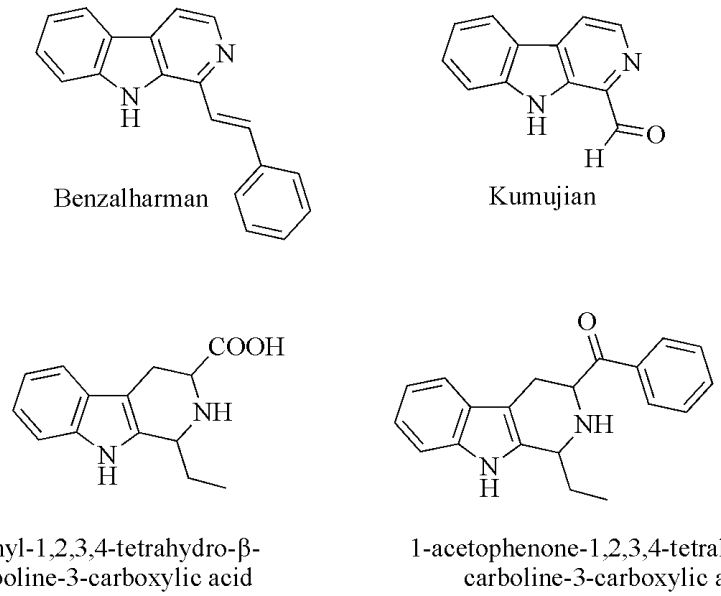


Figure 7. The structure of β-carboline compounds with significant inhibitory activity on the over production of NO.

Another remarkable study led by Yang *et al.* (2006) found that luzongerine A, a natural 1-substituted-β-carboline isolated from *Illigera luzonensis*, has the potent ability to significantly and dose-dependently suppress LPS/IFN-g stimulated nitrite accumulation with IC50 values of 12.67±2.39 μM [32]. Intrigued by the notable finding, in 2010, they enrolled in a natural products research program relating to β-carbolines. This particular time, they had chosen *Stellaria dichotoma* L. var. *lanceolata* Bunge 17. (Caryophyllaceae) as the target plant for new drug discovery since it is known to produce β-carboline alkaloids. Five of the β-carboline derivatives isolated, namely Dichotomide III, Dichotomide X, Stellarines A, Stellarines B, and 1-acetyl-3-methoxycarbonyl-β-carboline were subjected to an examination of their ability to inhibit NO production in LPS-treated RAW 264.7 cells. The results showed that these compounds displayed significant inhibitory effects on NO production with the IC_{50} values of 17.3, 11.3, 19.3, 18.6, and 17.9 μM, respectively as compared to a reference compound, aminoguanidine (IC50 value of 4.6 μM).

Cytotoxicity is the quality of being toxic to cells. Cytotoxicity studies under which in vitro assays are conducted play a vital role in determining the potential toxicity of a test substance, from plant extracts to biologically active compounds isolated from plants. The successful development of a new drug or cosmetic depends not only on its promising biological activity, but also on minimal or negligible cytotoxicity. In this regard, cellular toxicity studies such as MTT and XTT assays are often used to screen potential therapeutic nanostructures [39].

Referring to the previously mentioned study by Yang et al. (2006) [32], it has been proven that the β-carboline derivatives, luzongerine A displayed no detectable cytotoxicity when measured using the MTT assay at all concentrations tested (1, 3, 10, and 30 μM) and that the viability effects of the treated cells were all greater than 95%. β-carbolines modified at C-1 and C-3 position have been reported to increase cytotoxicity towards cancer cells [40]. In addition, a recent report by Xin et al., (2012) suggests that substitutions on A-ring of the structure can improve cytotoxicity towards cancer cells [41]. Therefore, Lunagaria and co-workers synthesized β-carbolines derivatives with 1-methyl and 3-methoxycarbonyl substitutions and the respective compounds were screened for cytotoxic potential. The result showed potent cytotoxicity as compared to docetaxel in four human cancer cell [42].

Eudistalbin A, cytotoxic activity (ED50 < 3.2 μg/mL) in vitro against the growth of KB human buccal carcinoma cells, was first isolated from marine tunicate Eudistoma album [43]. Its first total synthesis was accomplished by Zhang and co-workers in 2010. Interestingly, the synthetic eudistalbin A also showed potent inhibitory activity against the breast carcinoma cell line MDA-231 with an IC_{50} value of 2.1 μM [44].

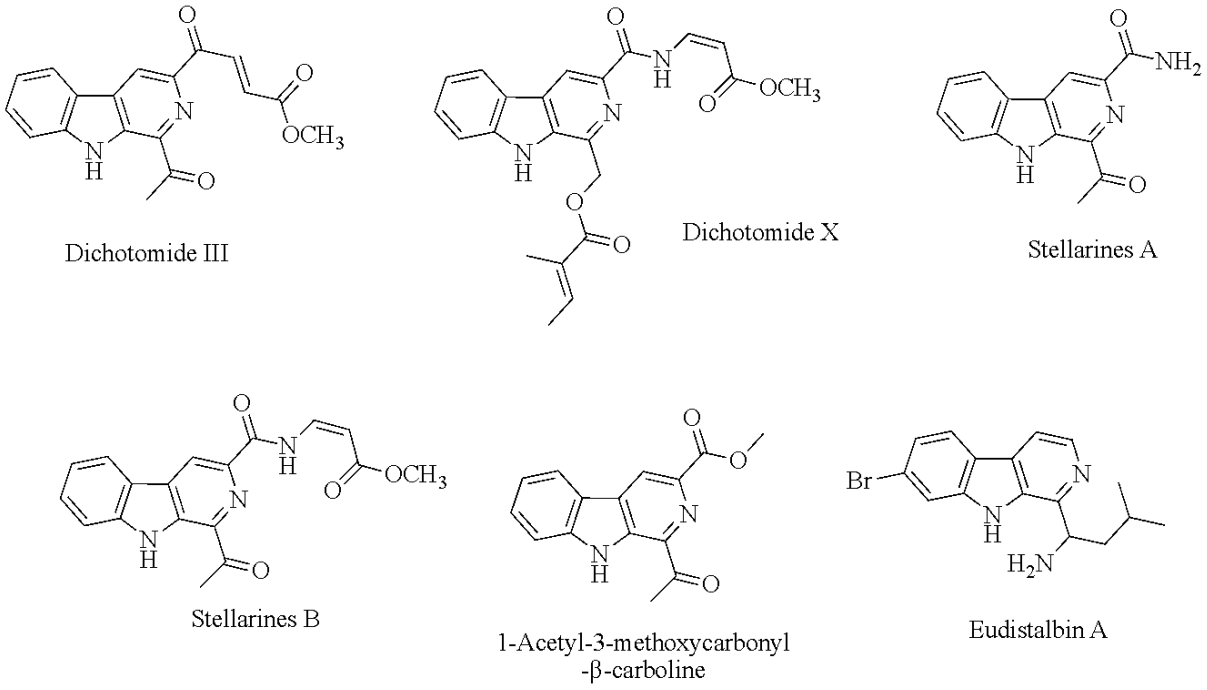


Figure 8. The β-carboline derivatives isolated which has ability to inhibit NO production.

CONCLUSION

In summary, Daibucarboline A and its derivatives represent a promising class of compounds in the search for effective anti-inflammatory agents. This review has highlighted the significance of tetrahydro-β-carboline intermediates in the synthesis of these bioactive molecules. The strategic use of these intermediates facilitates the efficient construction of the daibucarboline scaffold, enabling the development of compounds with potentially enhanced anti-inflammatory properties. Advancements in synthetic methodologies have streamlined the preparation of tetrahydro-β-carboline derivatives, which are pivotal in the synthesis of daibucarboline-based compounds. These advancements not only improve the yield and purity of the target molecules but also enable the exploration of diverse functionalization to optimize bioactivity. The anti-inflammatory potential of Daibucarboline A and its derivatives has been supported by a range of studies demonstrating their ability to modulate key inflammatory pathways and reduce inflammation-related pathology.

Overall, the integration of advanced synthetic techniques with a deeper understanding of bioactivity offers a path toward the development of novel therapeutic agents based on the daibucarboline framework. Future research in this area has the potential to contribute significantly to the advancement of anti-inflammatory therapies, ultimately benefiting patients suffering from chronic inflammatory conditions.

ACKNOWLEDGEMENTS

The authors acknowledge the generous support of Organic Synthesis Research Laboratory, Institute of Science (IOS), Universiti Teknologi MARA, Puncak Alam Campus and Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), Shah Alam in providing required instruments and chemicals. This work was financially supported under the Fundamental Research Grant Scheme (FRGS/1/2022/STG04/UITM/02/7) funded by the Ministry of Education, Malaysia.

REFERENCES

1. Hussein, R. A. and El-Anssary, A. A. (2018) Plants secondary metabolites: the key drivers of the pharmacological actions of medicinal plants. *Herbal Medicine*.

2. Dias, D. A., Urban, S. & Roessner, U. (2012) A historical overview of natural products in drug discovery. *Metabolites*, **2(2)**, 303–336.

3. Thirumurugan, D., Cholarajan, A., Raja, S. S. and Vijayakumar, R. (2018) An introductory chapter: secondary metabolites. *Second Metabsources Appl.*, 1–21.

4. Veeresham, C. (2012) Natural products derived from plants as a source of drugs. *Journal of Advanced Pharmaceutical Technology & Research*, **3(4)**, 200.

5. Hussein, R. A. and El-Anssary, A. A. (2018) Plants secondary metabolites: the key drivers of the pharmacological actions of medicinal plants. *Herbal Medicine*.

6. Isah, T. (2019) Stress and defense responses in plant secondary metabolites production. *Biological Research*, **52(1)**, 39.

7. Gao, H., Li, G. and Lou, H. X. (2018) Structural diversity and biological activities of novel secondary metabolites from endophytes. *Molecules*, **23(3)**, 646.

8. Cushnie, T. T., Cushnie, B. and Lamb, A. J. (2014) Alkaloids: an overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *International Journal of Antimicrobial Agents*, **44(5)**, 377–386.

9. Ash'ari, N. A. N., Pungot, N. H., Shaameri, Z. and Jani, N. A. (2021) A facile synthesis of N-alkylated daibucarboline a derivatives via Pictet-Spengler condensation of tryptamine. *MJAS*, **25(5)**, 706–715.

10. Zulkifli, S. Z., Pungot, N. H., Saaidin, A. S., Jani, N. A. and Mohammat, M. F. (2023) Synthesis and diverse biological activities of substituted indole β-carbolines: a review. *Natural Product Research*, 1–15.

11. Stienstra, R., Joosten, L. A. B. & Netea, M. G. (2020) Targeting Inflammatory Pathways in the Treatment of Inflammatory Disease. *Current Opinion in Pharmacology*, **50**, 28–35.

12. Lima, J. A. and Hamerski, L. (2019) Alkaloids as Potential Multi-Target Drugs to Treat Alzheimer's Disease. *Natural Products Chemistry*, **61**, 301–334.

13. Arshad, N., Zitterl-Eglseer, K., Hasnain, S. and Hess, M. (2008) Effect of Peganum harmala or its β-carboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, **22(11)**, 1533–1538.

14. Monsef, H. R., Ghobadi, A., Iranshahi, M. and Abdollahi, M., (2004) Antinociceptive effects

of Peganum harmala L. alkaloid extract on mouse formalin test. *J. Pharm. Pharm. Sci*., **7**, 65–69.

15. Sobhani, A. M., Ebrahimi, S. A. and Mahmoudian, M. (2002) An in vitro evaluation of human DNA topoisomerase I inhibition by Peganum harmala L. seeds extract and its beta-carboline alkaloids. *J. Pharm. Pharm. Sci.*, **5**, 19–23.

16. Astulla, A., Zaima, K., Matsuno, Y., Hirasawa, Y., Ekasari, W., Widyawaruyanti, A., Zaini, N. C. and Morita, H. (2008) Alkaloids from the seeds of Peganum harmala showing anti-plasmodial and vasorelaxant activities. *J. Nat. Med*., **62**, 470–472.

17. Berrougui, H., Isabelle, M., Cloutier, M., Hmamouchi, M. and Khalil, A. (2006) Protective effects of Peganum harmala L. extract, harmine and harmaline against human low-density lipoprotein oxidation. *J. Pharm. Pharmacol*., **58**, 967–974.

18. Shahverdi, A. R., Monsef-Esfahani, H. R., Nickavar, B., Bitarafan, L., Khodaee, S. and Khoshakhlagh, N. (2005) Antimicrobial activity and main chemical composition of two smoke condensates from Peganum harmala seeds. *Z Naturforsch*, **60**, 707–710.

19. Shahverdi, A., Ostad, S., Khodaee, S., Bitarafan, L., Monsef-Esfahani, H., Jamalifar, H. and Mohseni, M. (2008) Antimicrobial and cytotoxicity potential of Peganum harmala smoke. *Pharmacognosy Magazine*, **4(15)**, 236.

20. Wong, S. L., Chang, H. S., Wang, G. J., Chiang, M. Y., Huang, H. Y., Chen, C. H. and Chen, I. S. (2011) Secondary metabolites from the roots of *Neolitsea daibuensis* and their anti-inflammatory activity. *Journal of Natural Products*, **74(12)**, 2489–2496.

21. Zhang, X., Li, Y., Huang, Z. (2024) Biological Evaluation of Daibucarboline A as an Anti-Inflammatory Agent: Mechanisms and Efficacy. *Bioorganic & Medicinal Chemistry Letters*, **44(8)**, 1383–1390.

22. Wang, Z., Liu, M. and Lin, H. (2023) Daibucarboline A: A Novel Natural Product with Potent Anti-Inflammatory and Anticancer Properties from the Marine-Derived Fungus *Daedalea quercine*. *Journal of Medicinal Chemistry*, **66(12)**, 6930–6942.

23. Kim, S. H., Lee, Y. S. and Park, J. M. (2023) Daibucarboline A, a novel bioactive alkaloid from the marine sponge *Daibucus* sp. *Journal of Natural Products*, **86(7)**, 1456–462.

24. Van Maarseveen, J. H., Hermkens, P. H., De Clercq, E., Balzarini, J., Scheeren, H. W. & Kruse, C. G. (1992) Antiviral and antitumor structure-activity relationship studies on tetracyclic eudistomines. *Journal of Medicinal Chemistry*, **35(17)**, 3223–3230.

25. Manasa, K. L., Tangella, Y., Ramu, G. & Nagendra Babu, B. (2017) 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*, **2(28)**, 9162–9167.

26. Kamal, A., Sathish, M., Prasanthi, A. V. G., Chetna, J., Tangella, Y., Srinivasulu, V. & Alarifi, A. (2015) An efficient one-pot decarboxylative aromatization of tetrahydro-β-carbolines by using N-chlorosuccinimide: total synthesis of norharmane, harmane and eudistomins. *RSC advances*, **5(109)**, 90121–90126.

27. Kamal, A., Tangella, Y., Manasa, K. L., Sathish, M., Srinivasulu, V., Chetna, J. & Alarifi, A. (2015) PhI (OAc) 2-mediated one-pot oxidative decarboxylation and aromatization of tetrahydro-β-carbolines: synthesis of norharmane, harmane, eudistomin U and eudistomin I. Organic & biomolecular chemistry, **13(32)**, 8652–8662.

28. Hibino, S., Okazaki, M., Sato, K., Morita, I. & Ichikawa, M. (1983) Synthetic approach to the antitumor antibiotic lavendamycin: a synthesis of demethyllavendamycin methyl ester. *Heterocycles (Sendai)*, **20(10)**, 1957–1958.

29. Doyle, T. W., Balitz, D. M., Grulich, R. E., Nettleton, D. E., Gould, S. J., Tann, C. H. & Moews, A. E. (1981) Structure determination of lavendamycin-a new antitumor antibiotic from Streptomyces lavendulae. *Tetrahedron letters*, **22(46)**, 4595–4598.

30. Liu, Y., Chen, L. and Zhou, X. (2024) Enhanced Anticancer Efficacy of Lavendamycin in Combination with Standard Chemotherapeutic Agents. *Cancer Chemotherapy and Pharmacology*, **93(2)**, 337–349.

31. Rocca, P., Marsais, F., Godard, A. & Quéguiner, G. (1993) A new approach to the synthesis of lavendamycin analogues. *Tetrahedron letters*, **34(18)**, 2937–2940.

32. Yang, M. L., Kuo, P. C., Damu, A. G., Chang, R. J., Chiou, W. F. & Wu, T. S. (2006) A versatile route to the synthesis of 1-substituted β-carbolines by a single step Pictet–Spengler cyclization. *Tetrahedron*, **62(47)**, 10900–10906.

33. Bobbitt, J. M. & Willis, J. P. (1980) Electrochemistry of natural products. 7. Oxidative

decarboxylation of some tetrahydro-beta-carbolinecarboxylic acids. *The Journal of Organic Chemistry*, **45(10)**, 1978–1984.

34. Wong, S. L., Chang, H. S., Wang, G. J., Chiang, M. Y., Huang, H. Y., Chen, C. H. & Chen, I. S. (2011) Secondary metabolites from the roots of *Neolitsea daibuensis* and their anti-inflammatory activity. *Journal of Natural Products*, **74(12)**, 2489–2496.

35. Liu, P., Li, H., Luan, R., Huang, G., Liu, Y., Wang, M. & Chen, D. (2019) Identification of β-carboline and canthinone alkaloids as anti-inflammatory agents but with different inhibitory profile on the expression of iNOS and COX- 2 in lipopolysaccharide-activated RAW 264.7 macrophages. *Journal of Natural Medicines*, **73(1)**, 124–130.

36. Pungot, N. H., Tarmizi, N. H. M. and Zulkifli, S. Z. (2024) Synthesis of 4-Aryl Substituted Canthin-6-One With B-Carboline Skeleton Via Pictet-Spengler Condensation and Cyclization Reaction. *Malaysian Journal of Analytical Sciences*, **27(6)**, 1183–1191.

37. Jani, N. A., Sirat, H. M., Ahmad, F., Abed, S. A. & Aminudin, N. I. (2018). Chemical constituents of the stems of *Neolitsea kedahensis* Gamble. *Phytochemistry Letters*, **26**, 12–15.

38. Duggineni, S., Sawant, D., Saha, B. and Kundu, B. (2006) Application of modified Pictet–Spengler reaction for the synthesis of thiazolo-and pyrazoloquinolines. *Tetrahedron*, **62(14)**, 3228–3241.

39. Dejous, C., Hallil, H., Raimbault, V., Rukkumani, R. & Yakhmi, J. V. (2017) Using microsensors to promote the development of innovative therapeutic nanostructures. *Nanostructures for Novel Therapy*, 539–566.

40. Cao, R., Peng, W., Wang, Z. & Xu, A. (2007) β-Carboline alkaloids: biochemical and pharmacological functions. *Current Medicinal Chemistry*, **14(4)**, 479–500.

41. Xin, B., Tang, W., Wang, Y., Lin, G., Liu, H., Jiao, Y. & Lu, T. (2012) Design, synthesis and biological evaluation of β-carboline derivatives as novel inhibitors targeting B-Raf kinase. *Bioorganic & Medicinal Chemistry Letters*, **22(14)**, 4783–4786.

42. Lunagariya, N. A., Gohil, V. M., Kushwah, V., Neelagiri, S., Jain, S., Singh, S. & Bhutani, K. K. (2015) Synthesis and biological evaluation of 1, 3, 6- trisubstituted β-carboline derivatives for cytotoxic and anti-leishmanial potential. *Planta Medica*, **81(16)**, 84.

43. Dai, J., Dan, W., Schneider, U. & Wang, J. (2018) β-Carboline alkaloid monomers and dimers: Occurrence, structural diversity, and biological activities. *European Journal of Medicinal Chemistry*, **157**, 622–656.

44. Zhang, P. Y., Wang, J. L., Wan, S. B. & Jiang, T. (2010) First total synthesis of eudistalbin A. *Chinese Chemical Letters*, **21(8)**, 889–891.

45. Zulkifli, S. Z., Asha'ari, N. A. N., Aziz, A. F. A. & Pungot, N. H. (2024) Anti-inflammatory Activity of 1-Substituted Glyoxal β-Carboline Derivatives. *Malaysian Journal of Fundamental and Applied Sciences*, **20(5)**, 1228–1234.