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Design and Strategic Synthesis of Some β -Carboline-Based Novel Natural Products of Biological Importance

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Abstract

β -Carboline compounds and their derivatives have attracted strong interest in medicinal chemistry due to their biological and pharmacological properties. Many bioactive β -carboline-based natural products have been found to be an important source of drugs and drug leads. β -Carboline has major players in natural products chemistry, which plays an important role in drug discovery. β -Carboline represents the core unit of several natural products, alkaloids, and bioactive compounds. The unusual and complex molecular architectures of natural products pose significant challenges to organic chemists and are a source of inspiration for the development of new organic reactions and innovative synthetic strategies. However, in many cases, β -carboline natural products are isolated in only minute quantities, and their constant supply from natural sources is problematic or virtually impossible. In addition, chemoselective derivatization of natural products themselves is usually quite difficult because of their sensitive and elaborate molecular structures, and access to their structural analogs is severely restricted in many cases. Since chemical synthesis is expected to be the only way to overcome these shortcomings, β -carboline natural products are rewarding synthetic targets for organic chemists. This chapter assimilates the reports pertaining to the synthetic applications of some β -carbolines for the synthesis of substituted and fused β -carbolines.

Keywords: β -carboline, scaffold, organic synthesis, natural product, biological importance

1. Introduction

The need for efficient and practical synthesis of biologically active molecules remains one of the greatest intellectual challenges with which chemists are faced in the twenty-first century.

Organic synthesis is a compound-creating activity often focused on biologically active molecules and occupies a central role in any pharmaceutical development endeavor. The field of organic synthesis has made phenomenal advances in the past 50 years, yet chemists still struggle to design synthetic routes that will enable them to obtain sufficient quantities of complex molecules for biological and medicinal studies. The diversity of β -carboline compounds offers a great advantage for being

developed into new drugs because of their unique and complex structures, developed through old and underexplored species evolution.

The drive to develop methodology allowing improved access to such compounds has arisen after the demonstration of the useful physical and chemical properties possessed by this class of compounds such as improved lipophilicity and decrease in oxidative metabolism.

Naturally occurring compounds have always played a vital role in medicine and, in particular, β -carboline has progressively become real players in recent drug discovery. The β -carboline moiety represents core structure of several natural compounds and pharmaceutical agents. Compounds containing this subunit are pervasively present in plants, marine organisms, insects, mammalian including human tissues and body fluids in the form of alkaloids or hormones [1–7]. Several β -carboline-based compounds of natural or synthetic origin are ascribed with different pharmacological properties [8] which include antimalarial [9, 10], anti-neoplastic [11, 12], anticonvulsive [13], hypnotic and anxiolytic [14], antiviral [15], antimicrobial [16], as well as topoisomerase-II inhibitors [17, 18] and cGMP inhibitors [19] (**Figure 1**).

Further, the significance of β -carboline-based compound is underscored by the way that two of the β -carboline-based mixes Tadalafil and Abecarnil (**Figure 2**) are clinically utilized for erectile brokenness and CNS issue, individually [20–22].

Many bioactive β -carboline-based natural products have been found to be an important source of drugs and drug leads. Most of the natural products of interest to the pharmaceutical industry are secondary metabolites and several such β -carbolines, derived from marine invertebrates, have been in clinical trials as experimental anti-cancer drugs. The significant favorable position offered by utilizing these metabolites as valuable formats, is that they are as such exceedingly dynamic and specific. Being created ordinarily to secure a specific living being, they have been exposed to evolutive pressure for a few a huge number of years and have been chosen to achieve ideal action and to perform particular capacities.

Synthesis of medicinally important β -carboline-based natural products is challenging in synthetic organic chemistry. Current research activities while primarily with the academic laboratories, have generated convincing evidence that these natural products have an exceedingly bright future in discovery of life saving drugs

Figure 1.
Bioactive β -carboline-based compounds.

Figure 2.
 β -Carboline-based drugs.

[23] included antibacterial, analgesic, anti-inflammatory, antimalarial, anticancer, antiparasitic and antiviral agents [24]. Although large numbers of novel β -carboline compounds have been isolated from plants, marine organisms, insects, mammalian including human tissues.

Furthermore, huge numbers of these substances have articulated natural action, without a doubt, not many have been advertised as pharmaceutical products. Some of the compounds have also been valuable as “lead” compounds, which have led to derivatives of them being marketed [25, 26].

In addition, the biological diversity of many of the β -carboline compounds still partially unknown. A considerable lot of them have indicated fascinating bioactivities both in vitro and in vivo measures, although just couple of molecules have been up to this point brought into facilities and onto the pharmaceutical market. Be that as it may, precedents are realized where cutting-edge clinical or preclinical preliminaries, did by utilizing common β -carboline items have prompted promising outcomes in the investigation of new prescriptions a variety of diseases including cancer and infective pathologies. Synthetic organic chemistry is able to produce sufficient amounts for a broad biological application and to provide access to synthetic analogs for structure-activity relationships (SAR) studies.

In particular, alkaloids establish one of the biggest classes of natural products and are synthesized by terrestrial and marine organisms on every transformative dimension and a standout amongst the most encouraging being indole alkaloids. Indole alkaloids, their action, synthesis, and potential use in medicines have been as of now inspected in a few articles [27–29]. Marine indole alkaloids speak to a rich gathering of characteristic natural compounds and can possibly turned out to be new medicinal chemistry leads for different psychiatric disorders, just as to give better bits of knowledge into the comprehension of serotonin receptor work. These atoms are sensible synthetic targets, which further improve their incentive as conceivable medicinal chemistry studies; be that as it may, hardly any, have been set up as a feature of manufactured or therapeutic science thinks about intended to produce advanced leads.

In this class, β -carbolines that consist of a pyridine ring that is fused to an indole skeleton and biological activity of their derivatives is also well established [30].

Also, substance blend might be utilized to illuminate normal procedures at the atomic dimension through biomimetic approaches, to affirm the structures of natural compounds which are typically settled depending just on spectral information, or to develop new synthetic methods for tackling the challenge of the complex chemical templates designed by nature. Significant endeavors are identified with the structure of particles that in nature are created by metabolic changes happening with high return and rate, and furthermore with high regio-, diastereo- and enantio-particularity.

2. Synthesis of β -carboline

During the last two decades, β -carboline-based natural products have been the focus of many investigations [31]. The β -carboline is a core-unit of several natural compounds and pharmaceutical agents. Compounds containing this core-unit are pervasively present in plants, marine animals, insects, mammalian including human tissues and body fluids in the form of alkaloids or hormones. Several β -carboline-based compounds of natural or synthetic origin are ascribed with different pharmacological properties which include antimalarial, antineoplastic, anticonvulsive, hypnotic and anxiolytic, antiviral, antimicrobial, as well as topoisomerase-II inhibitors and cGMP inhibitors.

The Pictet-Spengler reaction since its discovery in 1911 has been the key step of the synthetic strategies formulated for obtaining either substituted or fused β -carboline [32]. The utility of Pictet-Spengler reaction is immense as it allows the option to either construct the tetrahydro- β -carboline (THBC) core first with appropriate substitution which could be extended after cyclization or to install the different substitutions which undergo cascade reactions during cyclization to afford the new THBC derivatives. These THBCs can then be oxidized to generate the desired β -carboline-derivative. However due to major significance associated with this heterocyclic moiety, alternate strategies for generating new β -carboline are desired. In this context one of the possible strategies could be generation of a β -carboline core that bears a functional group at a suitable position that could be synthetically designed for producing substituted or fused β -carboline. The presence of an electrophilic site in the form of formyl group in close proximity of the indole NH which is a nucleophilic site makes it an attractive template for the synthesis of substituted and 1–9 annulated β -carboline. Alternatively, intramolecular cyclization could also be achieved with the N-2 to generate 1–2 annulated β -carboline.

The synthesis of 1-formyl-9*H*- β -carboline was firstly reported by Gatta and Misiti [33] while carrying out the studies toward SeO₂ mediated oxidation of variously substituted THBCs. During the synthesis of carboline he unexpectedly obtained the 1-formyl-9*H*- β -carboline instead of the expected 1-methyl,1-phenyl-3-(methoxycarbonyl)-1,4-dihydro-4-oxo- β -carboline when the reaction of the diastereomeric mixture of 1-methyl,1-phenyl THBC was carried out with SeO₂ in dioxane. Probably the reaction was preceded through the oxidation of the benzylic moiety affording the benzaldehyde, followed by the aromatization of C-ring and finally the oxidation of the C-1-methyl to the formyl group (**Figure 3**).

Later Gatta and co-workers [34] reported an improved synthesis of methyl 1-formyl-9-*H*-pyrido [3,4-*b*] indole-3-carboxylate from 1-methyl-3-methoxycarbonyl- β -carboline via oxidation with SeO₂ in dioxane. These workers further reported the application of 1-formyl-9*H*- β -carboline for the synthesis of canthin-6-one [35]. They extended the synthetic utility of for the generation of pyrimido-[3,4,5-*lm*]-pyrido-[3,4-*b*]-indole derivatives in the synthesis of different derivatives of this carboline moiety.

Suzuki et al. [36] reported the total synthesis of various naturally occurring 4,8-dioxygenated β -carboline alkaloids (**Figure 4**). The synthetic route involved two methodologies (i) an improved Fischer indolization for affording 7-oxygenated indole via protecting the phenolic group with a tosyl group and (ii) construction of a 4-methoxy- β -carboline skeleton by the C-3 selective cyclization of the C-2 substituent of the indole. Then, 4-methoxy- β -carboline was converted into 1-nitrile derivative with diethylphosphoryl cyanide (DEPC) via *N*-oxide by a modified Reissert-Henze reaction.

Figure 3.
Synthesis of 1-formyl-9H- β -carboline.

Figure 4.
Total synthesis of naturally occurring 4,8-dioxygenated β -carboline alkaloids.

Takasu et al. [37] also reported the synthesis of different β -carboline-based compounds including the natural products Kumujancine, MVC (4-methoxy vinyl β -carboline), Creatine and their corresponding salts. They followed the synthetic strategies which involved the Pictet-Spengler reaction of tryptamine hydrochloride with ethyl glyoxylate in ethanol, followed by acylation with acetyl chloride which furnished THBC in 44% yields (**Figure 5**).

Condie and Bergman [38] reported the condensation of 1-formyl-9H- β -carboline with ethyl azidoacetate which produced a non-isolable intermediate which immediately underwent intramolecular cyclization via the attack of nitrogen of indole subunit at the ester functionality. The resulting 5-azido-canthin-6-one was further transformed to 5-aminocanthin-6-one via catalytic reduction (**Figure 6**).

Figure 5.
Synthesis of tosyl salt of β -carboline-based compounds.

Figure 6.
Synthesis of 5-aminocanthin-6-one via intramolecular cyclization process.

Suzuki et al. [39] reported the synthesis of canthin-6-one derivative from 1-formyl-9H- β -carboline and its 4-methoxy derivative. In addition many researchers are continuous trying to do more research in this field. Because the β -carboline gives more interest to natural product chemist and it is a huge scope for researchers (Figure 7).

The Morita-Baylis-Hillman (MBH) reaction have also been used by Singh et al. [40] for 1-formyl-9H- β -carbolines (**38**) with various activated alkenes led to the formation of expected MBH product (**40**) as well as unnatural canthin-6-one derivatives (**41**). It was discovered that exclusive formation of either product **40** or **41** could be achieved by modulating the amount of DABCO used in the reaction as well as the reaction time (Figure 8).

In an extension of this study, they disclosed the potential of substituted 1-formyl-9H- β -carboline for achieving the synthesis of indolizinoindole derivatives as depicted in Figure 9. The N-alkylated derivatives (**42**) were subjected to MBH reaction with various acrylates and cycloalkenones in the presence of DABCO or DMAP to afford the MBH adducts (**43**) which were transformed into indolizinoindole derivatives **45** ($\text{R}_1 = \text{CO}_2\text{Me}$) via reaction with PBr_3 . The reaction was preceded through the formation of allyl bromide **44**.

A Claisen rearrangement have also been used for the synthesis of different β -carbolines by using of allyl alcohol in the presence of p -toluenesulfonic acid, which upon heating at 200°C for 30 min resulted the final product in 84% yield [41].

Figure 7.
Synthesis of 5-aminocanthin-6-one.

Figure 8.
Morita-Baylis-Hillman reaction of 1-formyl-9H- β -carbolines.

Figure 9.
Synthesis of indolizinoindole derivatives of 1-formyl-9H- β -carbolines.

Alternatively, 4-amino- β -carboline synthesized by Fischer indole synthesis reaction when the hydrazine was used as a reactant, which is postulated to occur via initial hydrazone formation, followed by isomerization and loss of ammonia (Figure 10).

Another oxidant for changing over tetrahydro- β -carbolines to the completely fragrant framework is elemental sulfur, which is usually utilized when utilization of palladium or platinum is not feasible. For example, in Still's synthesis of

Figure 10.
Claisen rearrangement for the synthesis of different β -carbolines.

Figure 11.
Oxidation of tetrahydro- β -carbolines.

Figure 12.
Synthesis of 4-alkoxy- β -carbolines.

eudistomins **52**, aromatic esters **53** were produced by heating **52** with sulfur in xylenes at reflux condition [42] (**Figure 11**).

For the synthesis of 4-alkoxy- β -carbolines **61**, Oxidation of tetrahydro- β -carbolines **57** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has also found one of the best way of synthetic method [43] (**Figure 12**).

3. Conclusion

Using different reaction conditions and reports, it is evident from the past years in medicinal chemistry filed that a wide range of synthetic methods have been reported for the generation of β -carboline moiety and its analogs. However with the new strategy developed for the synthesis of the β -carboline substrate this chapter demonstrated the extensive utility of this prototype design and synthesis of new β -carboline analogs. We believe that this substrate has great potential in medicinal chemistry division and would be more beneficial for pharmaceutical industry.

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