

Review

Recent Advances in the Synthesis of the Marine-Derived Alkaloid Fascaplysin and Its Metabolites Homofascaplysin A–C

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Abstract: The fascaplysin and homofascaplysin class of marine natural products has a characteristic 12H-pyrido[1,2-a:3,4-b']diindole pentacyclic structure. Fascaplysin was isolated in 1988 from the marine sponge *Fascaplysinopsis bergquist* sp. The analogs of fascaplysin, such as homofascaplysin A, B, and C, were discovered late in the Fijian sponge *F. reticulata*, and also have potent antimicrobial activity and strong cytotoxicity against L-1210 mouse leukemia. In this review, the total synthesis of fascaplysin and its analogs, such as homofascaplysin A, B, and C, will be reviewed, which will offer useful information for medicinal chemistry researchers who are interested in the exploration of marine alkaloids.

Keywords: marine natural products; sponge; fascaplysin; homofascaplysin A, B, and C; alkaloids

1. Introduction

The β -carboline group is a valuable structural motif found in many plants, marine organisms, insects, and mammals, and compounds in this family show a broad range of biological activities [1–4]. In particular, the 12H-pyrido[1,2-a:3,4-b']diindole ring system is an important component of various marine alkaloids, such as fascaplysin and homofascaplysin A–C (Figure 1) [5]. Among compounds derived from the sponge *Fascaplysinopsis bergquist* sp., fascaplysin, which was first isolated in 1988, is the most studied [6]. This natural product was later isolated by several other researchers from *Hyrtios erecta* [7] as well as from *Thorectandra* sp. *tunicate* [8], *Didemnum* sp. [9], and sponge *Fascaplysinopsis* [10].

In 1988, Ireland et al. first isolated and determined the structure of the red pigment fascaplysin, a pentacyclic quaternary salt from the Fijian sponge *Fascaplysinopsis bergquist* sp., which was collected near Dravuni Island, Fiji [6]. The lyophilized sponge was extracted with methanol, and then fractionation was performed using the Kupchan partitioning method. The above methanol/water fraction was washed with CCl_4 and then extracted with chloroform. This CHCl_3 partition exhibited substantial cytotoxicity and high antimicrobial activity. The chloroform fraction was chromatographed over Sephadex LH-20 using methanol, and subsequent purification by crystallization from methanol yielded fascaplysin. The structure of fascaplysin (13-oxo-12,13-dihydropyrido[1,2-a:3,4-b'] diindol-5-ium chloride) was determined using ^1H and ^{13}C NMR spectroscopy, X-ray analysis, and EI and FAB mass spectrometry (Figure 1).

In 1990, Crews et al. isolated the bioactive constituents from *F. reticulata* collected from the Benga Lagoon, Fiji. *F. reticulata* was found to contain new 12H-pyrido[1,2-a:3,4-b']diindole alkaloids such as homofascaplysin A–C as well as the known natural products fascaplysin and (+)-octopamine [11]. Four separate specimens of *F. reticulata* sponge were collected by SCUBA at 10–20 m between 1985 and 1989 from the Benga Lagoon, Fiji. The specimens were preserved for long periods before extraction. The viscous crude oil obtained by methanol extraction of the sponge specimens contained three alkaloids as major constituents, as determined by ^1H and ^{13}C NMR spectroscopy. The crude oil was then



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successively partitioned using equal volumes of aqueous methanol and a series of solvents including hexanes, CCl_4 , and dichloromethane. The CCl_4 fraction was chromatographed over Sephadex LH₂₀ using methanol and then purified by repeated reversed-phase HPLC. This fraction afforded a mixture of homofascaplysins A–C.

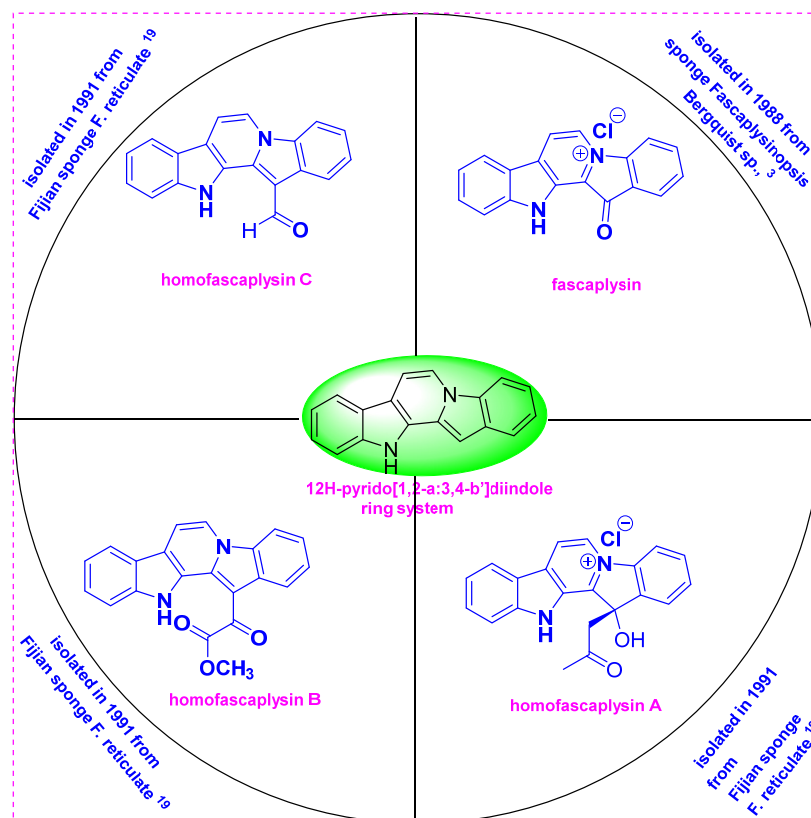


Figure 1. Structures of fascaplysins and homofascaplysins A–C.

Fascaplysins inhibit the growth of several microbes [12] and have been widely studied for the selective inhibition of CDK4, a cyclin-dependent kinase (CDK), as reported by Sony et al. [13]. The inhibition of CDKs by small molecules is an area of recent interest in anticancer research [14]. Fascaplysins are the first biologically active planar, toxic anticancer agents. Unfortunately, fascaplysins cannot be used as anticancer drugs because they are extremely toxic due to their planar structure that intercalates with DNA [15]. As a key element in the cell division cycle, CDKs are essential for cell proliferation and healthy cell growth. Consequently, various nonplanar analogs of fascaplysins have been synthesized and studied. Amongst these compounds, the CDK4 inhibitors BPT and CA224 inhibit tubulin polymerization *in vitro* and exhibit antitumor activity in the colon cancer tumor model HCT-116 *in vivo* [16].

Chen et al. revealed that fascaplysins inhibit angiogenesis by suppressing the vascular endothelial growth factor (VEGF) and inducing apoptosis in human umbilical vein endothelial cells (HUVECs) [17]. In addition, Oh et al. demonstrated that fascaplysins inhibit VEGFR2, TRKA, HIF-1 α , and survivin, thereby preventing cancer cell growth [18]. Hamilton et al. examined the cytotoxic effects of fascaplysins against non-small cell and small cell lung cancer. Fascaplysins were found to induce tumor cell apoptosis through several mechanisms, including G1/S cell cycle arrest [19]. Furthermore, fascaplysins significantly upregulate the expression of PD-L1 in lung cancer cells, thus improving the sensitivity of anti-PD-1 immunotherapy *in vivo*.

The enzyme acetylcholinesterase (AChE) is responsible for the death of neurons in Alzheimer's disease. Fascaplysins inhibit AChE noncompetitively, with IC₅₀ and K_i values of 1.49 and 2.28 μM , respectively [20]. At 1 mM, fascaplysins display promising P-gp

activation and AChE inhibition, which together with good medication safety demonstrates the potential of this compound as an anti-Alzheimer agent [21]. Furthermore, fascaplysin shows potential antiplasmodial activity, inhibiting *Plasmodium falciparum* strains NF54 and K1 with IC₅₀ values of 34 and 50 ng/mL, respectively [22]. Thus, fascaplysin is a potent in vitro inhibitor of chloroquine-resistant *P. falciparum* and chloroquine-susceptible (NF54) strains. Due to the potent antiplasmodial activity, fascaplysin demonstrates the potential to be a leading structure. In addition, the fascaplysin analogs homofascaplysin A–C, which were isolated from the Fijian sponge *Fascaplysinopsis reticulata* in 1991, have strong cytotoxicity against L-1210 mouse leukemia cells and potent antimicrobial activity [11].

Although fascaplysin has a wide-ranging bioactive spectrum, its advance study has been disturbed by the limited number of compounds isolated from marine microorganism sources. In the future, modifying the planar structure of fascaplysin to reduce its toxicity could play a huge role in chemistry discoveries. These encouraging biological activities linked with fascaplysin have already led to the discovery of a few synthetic targets, and there is much unexplored medicinal chemistry space that may further lead to the discovery of novel biological active lead compounds. Investigations on nonplanar fascaplysin derivatives can form the starting point for elaboration of novel lead compounds, and therefore require finding effective procedures for their syntheses. As a result, many research groups have enthusiastically put their effort into total synthesis. This review may help to find the suitable total synthesis method for a nontoxic, nonplanar structure of fascaplysin derivatives in future synthesis.

Many methods have been established for the synthesis of fascaplysin, but there are limited reports on the synthesis of homofascaplysin B and C. Moreover, to the best of our knowledge, the synthetic methods for obtaining fascaplysin and related analogs, such as homofascaplysin A–C, have not yet been comprehensively reviewed. Herein, we systematically review important advances in synthetic strategies for obtaining fascaplysin and its metabolites homofascaplysin A–C, focusing on a selection of representative examples.

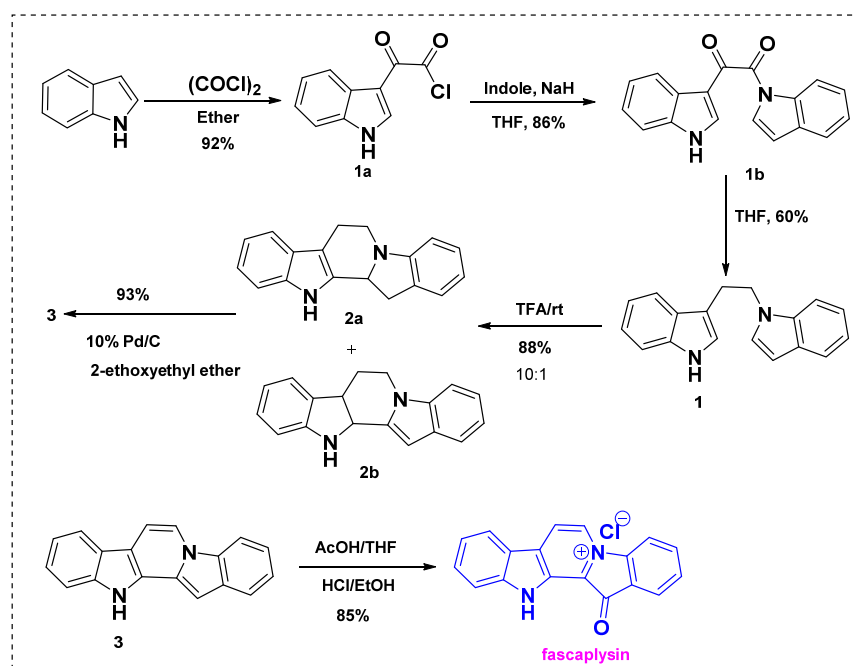
2. Discussion

2.1. Total and Formal Synthesis of Fascaplysin

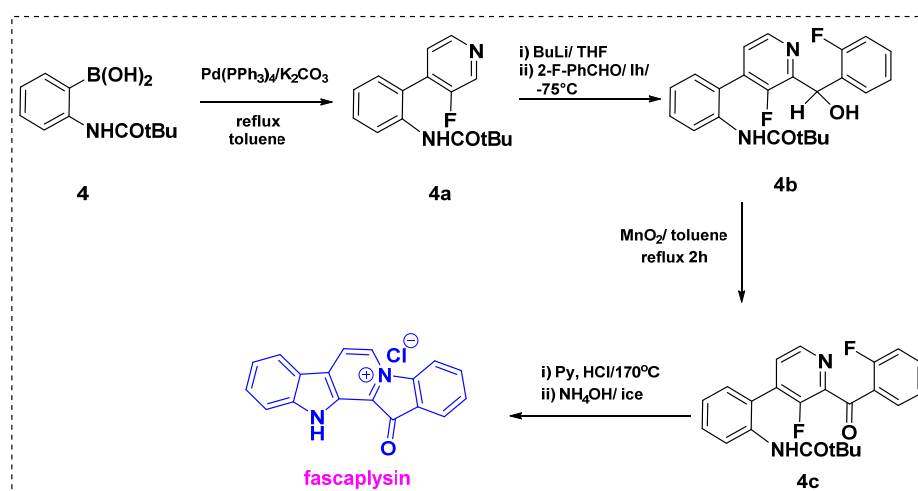
In 1990, Gribble et al. described the first total synthesis of fascaplysin from indole (Scheme 1) [23]. This approach involved peracid oxidation followed by reaction with oxalyl chloride/methanol or Vilsmeier formylation of the key diindole intermediate. Initially, the indole was treated with oxalyl chloride in ether and gave 3-indolyl glyoxylyl chloride **1a** at 92%, as shown in Scheme 1. Then, 3-indolylglyoxylyl chloride **1a** was permitted to react with I-indolylsodium to give keto amide **1b** in an 86% yield. The next step was reduction of **1b** with sodium (mono)trifluoroacetoxyborohydride, which afforded diindole **1** in a 60% yield and a 47% overall yield from the starting indole. Further, diindole **1** was then treated with trifluoro acetic acid to obtain a mixture of cyclized products **2a** and **2b** in a 10:1 ratio. Direct oxidation of this mixture with 10% Pd/C in refluxing 2-ethoxyethyl ether gave fully aromatic pentacycle **3** as a pale green solid. The reaction of **3** with peracetic acid in cold THF followed by treatment with con. HCl/EtOH afforded fascaplysin in an 85% yield. Thus, fascaplysin was efficiently synthesized from indole in seven steps with an overall yield of 65%. The main advantage of this method is that none of the steps, except the final one, involve chromatography, and the overall yield was very high.

In 1993, Qukguiner et al. developed a strategy for the total synthesis of fascaplysin from simple benzene and pyridine derivatives (Scheme 2) [24]. Palladium-catalyzed Suzuki cross-coupling between boronic acid **4** and iodopyridine gave bis aryl product **4a**. Regioselective coupling of **4a** with 2-fluorobenzaldehyde in the presence of n-BuLi afforded corresponding pyridine **4b** in a 95% yield. Further, oxidation of **4b** with MnO₂ in refluxing toluene provided carbonyl derivative **4c** in a 99% yield. The one-pot double cyclization of **4c** by treatment with pyridinium chloride at 170 °C followed by a basic workup gave fascaplysin in an 82% yield. The reported synthesis of fascaplysin relies on key steps such

as cross-coupling, metalation, and cyclization. This method is fully regioselective and provides a 76% overall yield from starting material **4**.

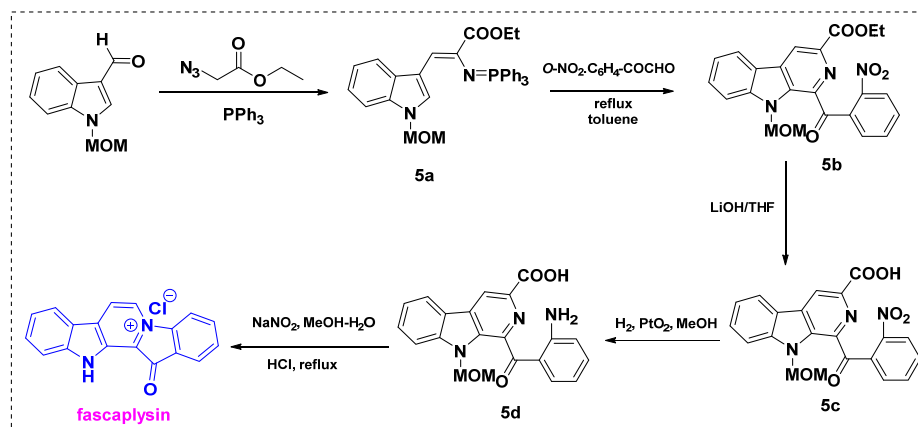


Scheme 1. First total synthesis of fascaplysin by Gribble et al. [23].



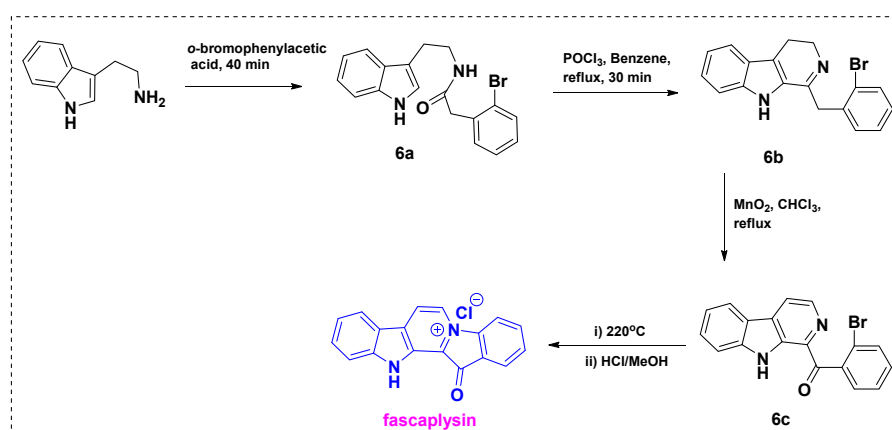
Scheme 2. Total synthesis of fascaplysin by Qukguiner et al. [24].

In 1994, Molina et al. described the synthesis of fascaplysin from *N*-methoxymethyl-3-formylindole in four steps (Scheme 3) [25]. *N*-Methoxymethyl-3-formylindole was converted into intermediate iminophosphorane **5a** by treatment with ethyl azidoacetate followed by triphenylphosphine. Iminophosphorane **5a** was treated with a nitro-substituted aryl glyoxal in toluene at 160°C in a sealed tube to give 1-aryl- β -carboline derivative **5b** in a 60–65% yield. Subsequent hydrolysis of **5b** with LiOH/THF at room temperature provided **5c** in a 90% yield. The nitro group was then selectively reduced by PtO_2 /catalytic hydrogenation to give **5d** in an 80% yield. Finally, deprotection and decarboxylation by diazotization and further heating afforded fascaplysin in a 60% yield. This method provides a 72% overall yield from the starting material.



Scheme 3. Total synthesis of fascaplysin by Molina et al. [25].

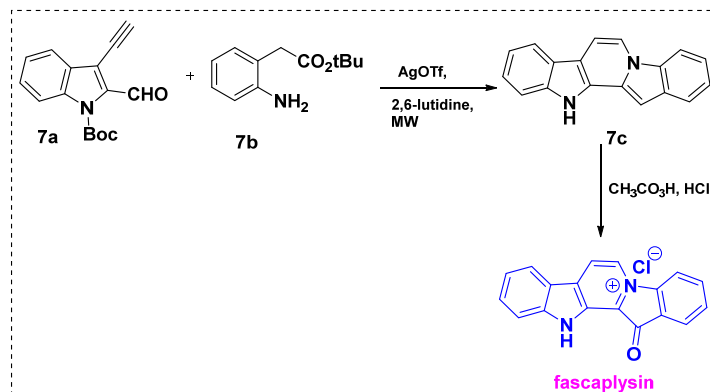
In 1997, Novikov et al. obtained a 44% overall yield for the total synthesis of fascaplysin from tryptamine in five steps (Scheme 4) [26]. Acylation of tryptamine with *o*-bromophenylacetic acid gave corresponding amide **6a**, which was converted into dihydro-13-carboline **6b** using POCl_3 . Subsequent reaction of **6b** with MnO_2 in CHCl_3 under reflux conditions gave α -acyl-substituted β -carboline **6c**. Heating of **6c** yielded pyridodiindole quaternary salt **6d**, which was treated with dry HCl in methanol to give fascaplysin in an overall yield of 44%.



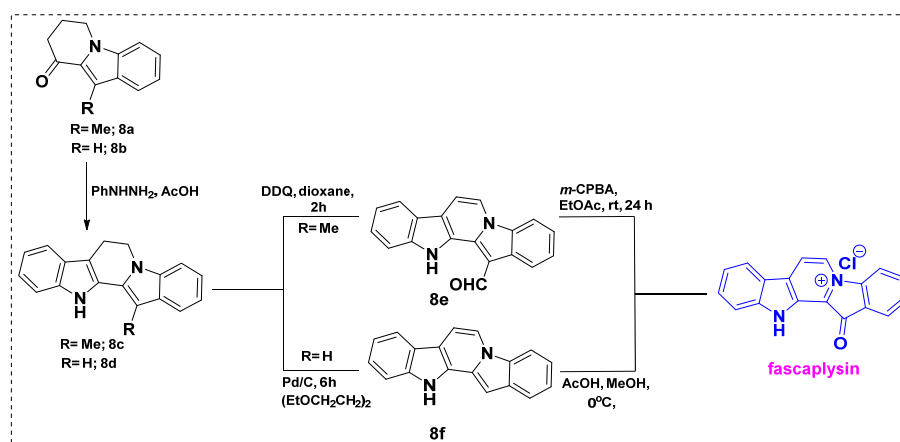
Scheme 4. Total synthesis of fascaplysin from tryptamine.

In 2010, Waldmann et al. developed a silver-catalyzed cascade reaction, which was then applied in the total synthesis of fascaplysin (Scheme 5) [27]. In this method, commercially available Boc-protected 3-ethynyl-indole-2-carbaldehyde **7a** was used as a precursor. The microwave-assisted silver-catalyzed cascade cyclization of **7a** with aniline **7b** yielded pentacyclic core **7c** in a high yield after acidic workup. Peracetic acid oxidation of diindole **7c** followed by salt formation with con. HCl provided a 52% overall yield.

Also in 2010, Zhidkov et al. developed a short synthetic route to fascaplysin from 3-methyl indole/indole ketone **8a/8b** using the popular Fischer indole synthesis reaction as a key step (Scheme 6) [28]. Fischer cyclization of **8a** or **8b** gave corresponding bisindole **8c** or **8d** in a 90–91% yield, which were further converted into **8e** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation or **8f** by dehydrogenation over Pd/C. The yield was 50% for **8e** and 75% for **8f**. Finally, the reaction of **8e** with mCPBA provided fascaplysin in a 67% yield and **8f** with acetic acid in methanol gave fascaplysin in 85% yields. Therefore, fascaplysin can be synthesized from commercially available ethyl indole-2-carboxylate in seven steps with overall yields of 69% through **8e** and 82% through intermediate **8f**.

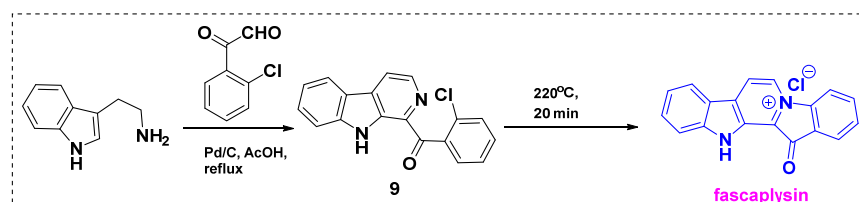


Scheme 5. Total synthesis of fascaplysin via a silver-catalyzed cascade reaction.



Scheme 6. Total synthesis of fascaplysin using Fischer cyclization as a key step.

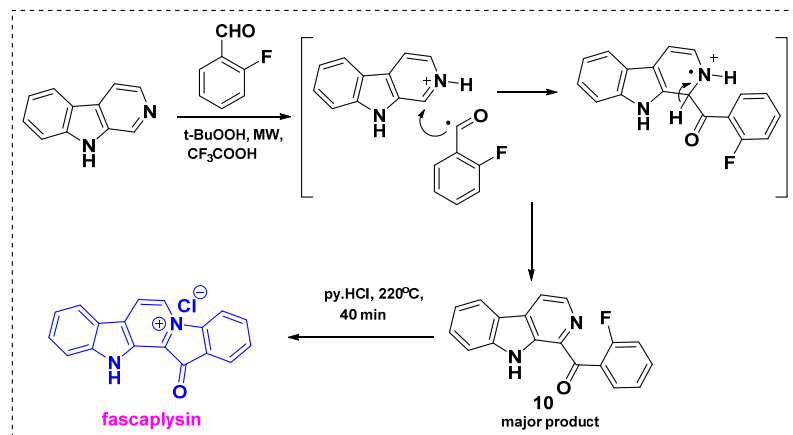
In 2012, Bharate et al. described a two-step total synthesis of fascaplysin from commercially available tryptamine in a 68% overall yield (Scheme 7) [29]. As well as being shorter, less expensive, and more efficient than previously reported synthetic methods, this approach has potential for the large-scale synthesis of fascaplysin. A key step in this strategy is tandem dehydrative condensation between ortho-chloro-substituted glyoxal and tryptamine followed by dehydrogenation. Initially, tryptamine was reacted with glyoxal in acetic acid in the presence of Pd/C to give cyclized product **9** in an 85% yield. Next, β -carboline **9** was heated at 220 °C for 20 min to induce ring closure and produce fascaplysin in an 80% yield.



Scheme 7. Total synthesis of fascaplysin from tryptamine.

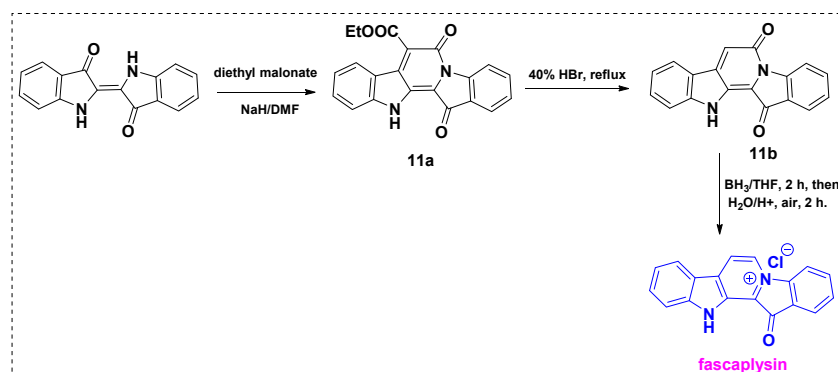
In 2013, Zhidkov et al. developed a two-step method for the synthesis of fascaplysin via a microwave-assisted Minisci reaction of β -carboline followed by intramolecular quaternization (Scheme 8) [30]. Initially, the reaction of β -carboline with *o*-fluorobenzaldehyde and *t*-BuOOH in TFA under microwave irradiation gave β -carboline **10** in a 65% yield as well as trace amounts of byproducts. This report presents the first microwave-assisted Minisci reaction. In this reaction, TFA can act as an acid catalyst and *t*-BuOOH is involved in the radical generation in the aldehyde moiety. Therefore, TFA was catalyzed to initiate

nucleophilic radical substitution to an electron-deficient aromatic compound of β -carboline, resulting in the introduction of an alkyl group of the aldehyde moiety to a nitrogen containing β -carboline, as shown in Scheme 8. Heating of **10** with pyridinium chloride at 220 °C and a subsequent workup gave faspaplysin in an 80% yield. This method provides faspaplysin in a 72% overall yield from commercially available β -carboline.



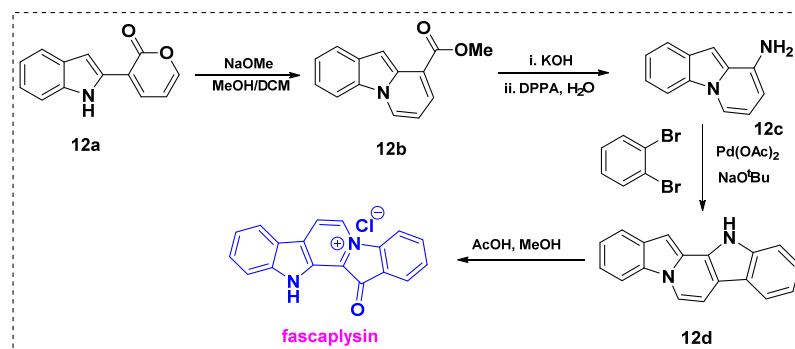
Scheme 8. Two-step synthesis of faspaplysin under microwave conditions.

The same research group reported a novel three-step method involving indigo and methylene active compounds for the total synthesis of faspaplysin and its derivatives in 2018 (Scheme 9) [31]. Indigo was reacted with diethyl malonate in DMF/NaH to produce **11a** in a 75% yield. Subsequent hydrolysis and decarboxylation of **11a** via refluxing in 40% hydrobromic acid for 2 h gave **11b** in a 95% yield. Finally, **11b** was refluxed with a BH₃/THF complex for 2 h and then oxidized in air to afford faspaplysin in a 43% yield and, overall, a 71% yield from indigo.



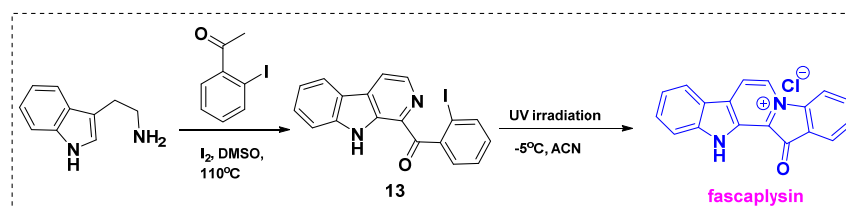
Scheme 9. Total synthesis of faspaplysin from indigo.

In 2020, Sarpong et al. described the synthesis of diverse N-fused heterocycles, including the pyrido[1,2-*a*] indole scaffold, using an effective pyrone remodeling strategy [32]. To demonstrate its utility, this methodology was applied in the synthesis of faspaplysin (Scheme 10). Initially, indole-pyrone **12a** was reacted with sodium methoxide as a nucleophile in dichloromethane/methanol to furnish **12b** in a 61% yield. Then, hydrolysis of ester **12a** with KOH provided an intermediate carboxylic acid in a 99% yield, which efficiently underwent Curtius rearrangement in the presence of DPPA/H₂O to generate amine **12c** in a 94% yield. Next, the palladium-catalyzed amination/C–H arylation domino coupling reaction of **12c** and 1,2-dibromobenzene in the presence of dppf ligand gave the product **12d** at 55%, which was further converted to faspaplysin via a previously reported procedure using acetic acid/methanol.



Scheme 10. Formal synthesis of fascaplysin via pyrone remodeling.

In 2023, Tryapkin et al. described a novel two-step synthesis of fascaplysin derivatives based on low-temperature UV quaternization (Scheme 11) [33]. The first step of this method was a modification of the synthetic routes from tryptamine and acetophenones previously reported by Zhu et al. and Battini et al. The reaction of tryptamine with 2-iodoacetophenone in DMSO/ I_2 at 110 °C gave isoquinoline **13** in a 40% yield. Next, UV quaternization was performed in acetonitrile at −5 °C to prevent side product formation, and fascaplysin was obtained in a 50% yield. The usage of acetonitrile with the temperature decreasing to −50 °C hinders the side reactions to allow obtaining fascaplysin in a good yield. Notably, only the starting material and quaternization product (fascaplysin) were observed in the reaction mixture. After fascaplysin was isolated, three-times-repeated irradiation of the starting material remaining in the reaction mixture increased the product yield to 91%.



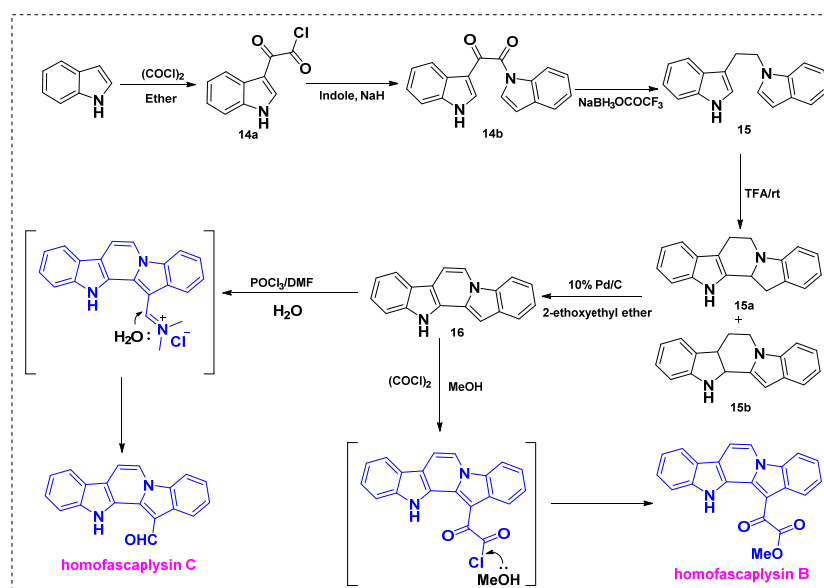
Scheme 11. Total synthesis of fascaplysin from tryptamine by UV irradiation.

2.2. Total and Formal Synthesis of Homofascaplysin B–C

The therapeutic potential of homofascaplysin A–C is based on a broad range of bioactivities, including anticancer, antibacterial, antifungal, antiviral, and antimalarial properties. Homofascaplysin A–C have effective cytotoxicity against L-1210 mouse leukemia cells and potent antimicrobial activity [7,34]. Although fascaplysin has been synthesized by several groups, as detailed in Section 1, only a few syntheses of homofascaplysin B and C have been reported. A total of five synthetic routes have been reported for total synthesis of fascaplysin C and three synthetic routes for homofascaplysin B since 1992. Here, we are going to briefly discuss each and every total synthesis of homofascaplysin A–C reported in the literature up to 2023.

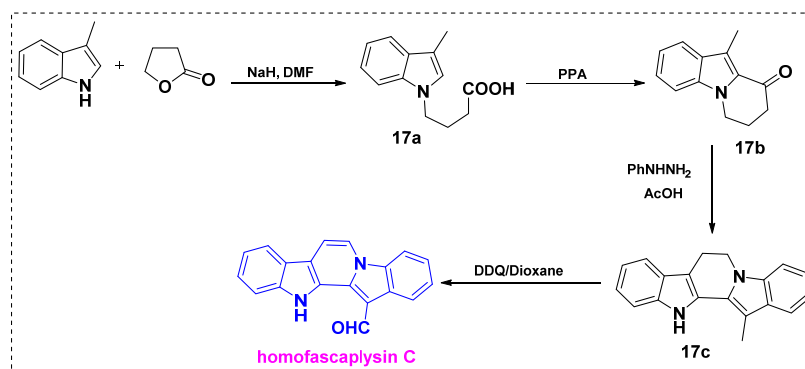
The first total synthesis was described in 1992 by Gribble et al., who obtained homofascaplysin B and C from indole in seven steps with overall yields of 76% and 67%, respectively (Scheme 12) [35]. These compounds were synthesized by peracid oxidation followed by reaction of the key diindole intermediate with oxalyl chloride/methanol or Vilsmeier formylation. In the first step, indole was reacted with oxalyl chloride under mild reaction conditions to give 3-indolyl glyoxylyl chloride **14a**, which was further treated with the sodium salt of indole to afford keto amide **14b** in an 86% yield. Treatment of keto amide **14b** with sodium trifluoroacetoxyborohydride provided diindole **15** in a 47% overall yield. Next, the neat reaction of diindole **15** in CF_3CO_2H at room temperature provided a 10:1 mixture of **15a** and **15b** in a good yield. The crude mixture of **15a** and **15b** was dehydrogenated with 10% Pd/C in EtOAc under reflux to give diindole **16** in a 98% yield. Finally, **16** was treated with the Vilsmeier reagent $POCl_3/DMF$ to obtain homofascaplysin

C in an 88% yield or with oxalyl chloride followed by methanol to obtain homofascaplysin B in a 99% yield. In both reactions, intermediate **16** provided the regioselective products homofascaplysin B and C.



Scheme 12. First total synthesis of homofascaplysin B and C from indole.

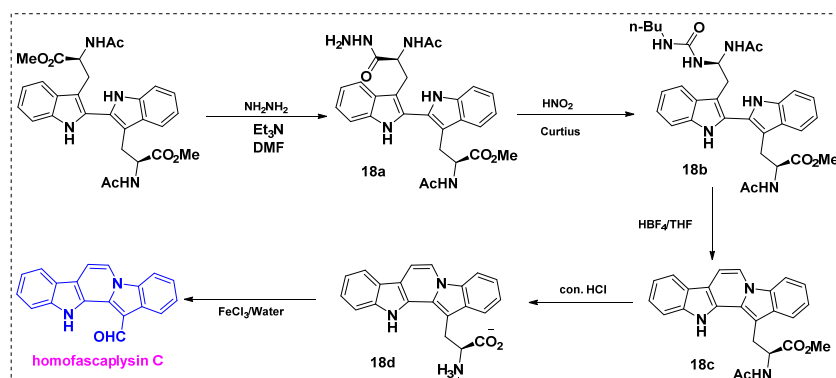
In 1996, Dubovitskii et al. developed an efficient protocol for the total synthesis of homofascaplysin C from commercially available 3-methylindole in only four steps (Scheme 13) [36]. In the first step, the reaction of 3-methylindole with γ -butyrolactone in the presence of NaH/DMF provided acid **17a** in a 95% yield. Next, cyclization of acid **17a** in PPA at 100 °C gave pyrido[1,2-a] indole **17b** in a 90% yield. Using the Fischer indole synthesis method, **17b** was treated with phenylhydrazine hydrochloride in refluxing acetic acid to obtain 6,7-dihydro-13-methyl-12H-pyrido[1,2-a:3,4-b']diindole **17c** in a 91% yield. Finally, oxidative dehydrogenation and oxidation of the methyl group to a formyl group by DDQ in dioxane under reflux for 2 h gave homofascaplysin C in a 50% yield and an 81% overall yield from the 3-methyl indole in four steps. This route is highly favorable for scaling up reactions because of the easy availability of the starting materials, like 3-methyl-indole.



Scheme 13. Total synthesis of homofascaplysin C from 3-methylindole.

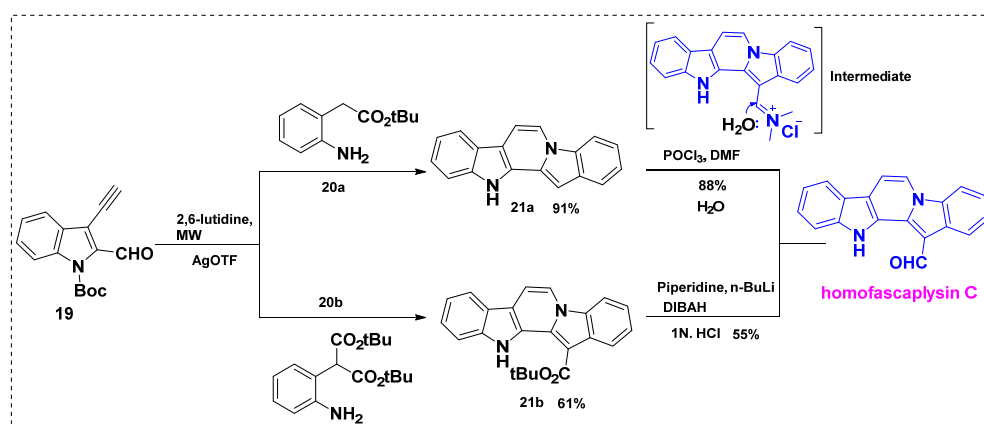
In 1999, Van Vranken et al. described the total synthesis of homofascaplysin C from peptides via the Mannich dimerization of tryptophan side chains (Scheme 14) [37]. This novel and efficient method relies on peptide chemistry. Initially, ditryptophan was converted into monohydrazide **18a** using 1.5 equiv of hydrazine in DMF, and the product yield was 30%. Triethylamine was added to the reaction mixture to facilitate proton-transfer

steps. Subsequently, acyl hydrazide **18a** was converted into an acyl azide using a mixture of NaNO_2 , 1 N HCl, and glacial acetic acid in chloroform. After extraction and drying, the acyl azide was trapped by *n*-butylamine to give urea **18b** in a 48% yield. Unexpectedly, ionization of **18b** in THF with anhydrous HBF_4 gave the cyclized product **18c** in an 83% yield instead of the expected product of uncyclized aldehyde. The structure of **18c** was interesting because it contained the indolo[1,2-*a*] carbazole ring system found in faspaplysins. Finally, compound **18c** was hydrolyzed to amino acid **18d**. The reaction was first performed under basic conditions, giving **18d** only in a 25% yield, but it was later found that the corresponding carboxamide hydrolyses under acidic conditions could give **18d** in a 43% yield, and then oxidative cleavage of the amino acid moiety with aqueous ferric chloride provided homofaspaplysins C in a 23% yield, and the overall yield was 45% from tryptophan.



Scheme 14. Total synthesis of homofaspaplysins C from ditryptophan esters.

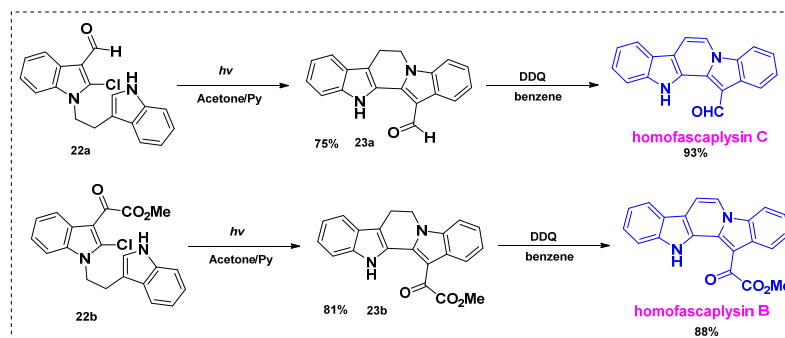
In 2010, Waldmann et al. described a silver-catalyzed cascade reaction and its application in the total synthesis of homofaspaplysins C from Boc-protected 3-ethynyl-indole-2-carbaldehyde **19** (Scheme 15) [27]. The microwave-assisted silver-catalyzed cascade cyclization of **19** with aniline **20a** or **20b** yielded pentacyclic core **21a** or **21b** in a 91% yield or a 61% yield, respectively. Partial reduction of the tert-butyl ester of **21b** with in situ generated lithium diisobutyl piperidino hydroaluminat provided homofaspaplysins C in a 55% yield and a 58% overall yield from **19** (two steps). In contrast, diindole **21a** was effectively converted into homofaspaplysins C in an 88% yield by formylation with POCl_3 in DMF, and the overall yield was 89% from **19** (two steps). This reaction proceeded regioselectively to produce homofaspaplysins C, and no other isomers were observed, as shown in Scheme 15.



Scheme 15. Total synthesis of homofaspaplysins C via a silver-catalyzed cascade reaction.

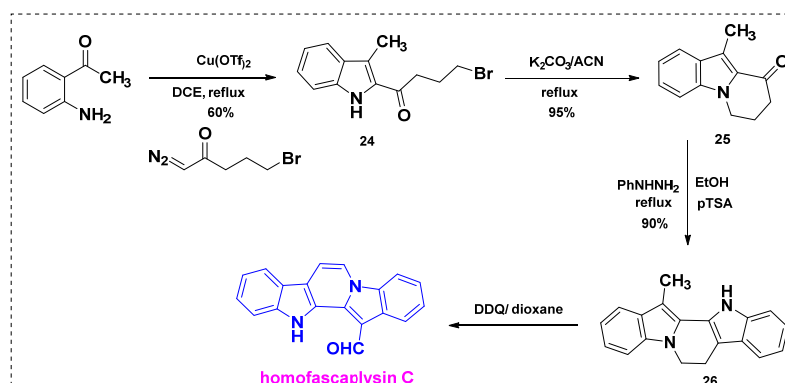
In 2012, Zhang et al. developed a two-step photocyclization/dehydrogenation reaction for the synthesis of homofaspaplysins B and C from indole derivatives (Scheme 16) [38]. Ir-

radiation of 2-chloro-1-[2-(indol-3-yl)-ethyl] indole-3-carbaldehyde **22a** or **22b** in deaerated anhydrous acetone containing pyridine at an ambient temperature for 12–13 h provided photocyclized products **23a** in a 75% yield or **23b** in an 81% yield. Subsequent dehydrogenation of **23a** or **23b** by DDQ in benzene for 2–3 h at room temperature gave homofascaplysin C and B in 93% and 88% yields, respectively. The overall yield was 84% for homofascaplysin C from **22a** and 84% for homofascaplysin C from **22b**. This group also developed a one-step sequential photocyclization and photochemical dehydrogenation reaction in $\text{Cu}(\text{OAc})_2$ - and air-saturated acetone to synthesize homofascaplysin C and B directly from **22a** or **22b**, but the yields were very low. Therefore, the two-step photocyclization/dehydrogenation route is more efficient for the synthesis of homofascaplysin B and C and other analogs.



Scheme 16. Total synthesis of homofascaplysin B and C through photocyclization/dehydrogenation reactions.

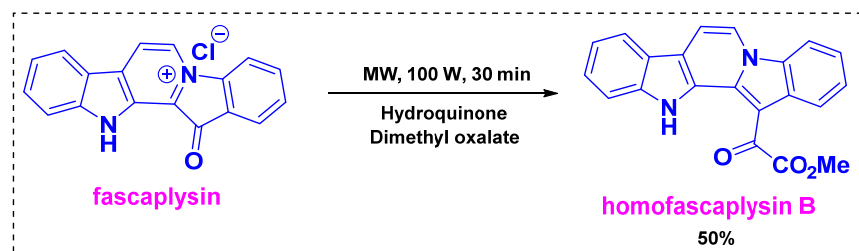
In 2013, Reddy et al. applied an α -diazoketone-based methodology to the formal synthesis of homofascaplysin C [39]. Initially, 2,4,5-trisubstituted pyrrole derivatives were synthesized by coupling α -diazoketones with β -enaminoketones and esters using 10 mol% $\text{Cu}(\text{OTf})_2$. In addition, a wide range of 2,3-disubstituted indole derivatives were prepared from α -diazoketones and 2-aminoaryl or alkyl ketones. Finally, homofascaplysin C was synthesized by coupling an alkyl diazoketone with 2-aminoacetophenone (Scheme 17). Specifically, the coupling of 2-aminoacetophenone with bromo butyric diazoketone in the presence of 10% $\text{Cu}(\text{OTf})_2$ afforded 2,3-disubstituted indole **24** in a 60% yield. Subsequent intramolecular cyclization of **24** in $\text{K}_2\text{CO}_3/\text{acetonitrile}$ under reflux afforded compound **25** in a 95% yield. Further treatment of **25** with phenylhydrazine in the presence of pTSA in ethanol at 80 °C gave Fischer indole product **26** regioselectively in a 90% yield. The oxidation of **26** under the conventional DDQ/dioxane conditions reported in the literature provided homofascaplysin C in a 50% yield and a 74% overall yield from 2-aminoacetophenone in four steps.



Scheme 17. Total synthesis of homofascaplysin C from α -diazoketones.

In 2018, Zhidkov et al. developed a one-step transformation of the marine alkaloid fascaplysin into homofascaplysin B using traditional heating or microwave conditions [40].

In the heating method, the reaction of faspaplysin with excess dimethyl oxalate and $\text{Na}_2\text{S}_2\text{O}_3$ (10 equiv) in an autoclave at 200 °C for 30 min produced homofaspaplysin B in a 30% yield. The presence of $\text{Na}_2\text{S}_2\text{O}_3$ (10 equiv) increased the yield from 24% to 30%. To further improve the yield, microwave irradiation was employed. Under irradiation at 100 W, the reaction of faspaplysin with dimethyl oxalate was complete after 30 min and provided a similar yield of homofaspaplysin B. Subsequently, faspaplysin was reacted with excess dimethyl oxalate under microwave irradiation at 100 W for 30 min in the presence of dihydroquinone as a reducing agent, and these optimal conditions provided homofaspaplysin B in a 50% yield (Scheme 18). The mechanism of this reaction was not investigated properly in the manuscript, but the reaction proceeded regioselectively.



Scheme 18. One-step transformation of the marine alkaloid faspaplysin into homofaspaplysin B.

3. Conclusions

Owing to its anticancer and antimicrobial properties, faspaplysin and its derivatives have potential for therapeutic applications. Moreover, faspaplysin exhibits potent antiplasmodial, antioxidant, and anti-inflammatory activities, highlighting new paths for the development of biomedical applications and paving the way for developing novel faspaplysin analogs. All the above discussed methods except Bharate et al.'s method have some drawbacks like harsh reaction conditions, difficulty scaling up, and limited faspaplysin analog synthesis. The total synthesis developed by Bharate et al. has significant scope for scaling up to the kilogram scale and synthesis of various faspaplysin derivatives using commercially available starting materials.

However, owing to its unusual planar structure, faspaplysin can intercalate in DNA, which results in extreme toxicity and may affect drug product formation. To reduce these toxic effects, the development of related targeted drugs via the structural modification of faspaplysin is essential. Surprisingly, no synthetic methods have yet been reported for homofaspaplysin A. In our opinion, development of a new synthetic route to total synthesis of homofaspaplysin A and its derivatives is worth further study in terms of its DNA intercalation and toxic effects. This review, which summarizes the advances in the total synthesis of faspaplysin and its metabolites over the past 30 years, will aid in promoting the development of efficient, scalable, and ecofriendly methods for generating these compounds as well as new derivatives.

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