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Recent syntheses of ellipticine and its derivatives

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Abstract

The pyrido[4,3-b]carbazole alkaloid, ellipticine, was attracting considerable interest for many years due to its pronounced antitumor activity. We review the most important achievements in the field of ellipticine synthesis and its derivatives since 2012.

Keywords: Ellipticine, ellipticine derivatives, alkaloids, synthesis
1. Introduction

The natural plant product ellipticine\textsuperscript{1-7} was isolated in 1959 from the Australian evergreen tree, Ochrosia elliptica, of the Apocynaceae Apocynaceae. This compound was found to be a promising anticancer drug. So, the syntheses of ellipticine and its derivatives have been reported by many groups.\textsuperscript{8-27}

The planar polycyclic structure was found to interact with DNA through intercalation, exhibiting a high DNA binding affinity (10^6 M\textsuperscript{-1}). The presence of protonatable ring nitrogens distinguished ellipticine from other simple intercalators. Both monocationic and uncharged species were found to be present under physiological conditions. The position charge stabilized the binding of ellipticine to nucleic acids, while the more lipophilic uncharged compound was shown to readily penetrate membrane barriers. The structural nature of these compounds offers a plausible basis for the implication of multiple modes of action, including DNA binding, interactions with membrane barriers, oxidative bioactivation and modification of enzyme function; most notably that of topoisomerase II and telomerase. Pharmaceutically, a number of toxic side effects have been shown to be problematic, but the amenability of ellipticine towards systematic structural modification has permitted the extensive application of rational drug design. A number of successful ellipticine analogs have been designed and synthesized with improved toxicities and anticancer activities.\textsuperscript{28-29} More recently the synthetic focus has broadened to include the design of hybrid compounds, as well as drug delivery conjugates. Considerable research efforts have been directed towards gaining a greater understanding of the mechanism of action of these drugs that will aid further in the optimization of drug design.

This article provide an overview of the various syntheses of ellipticine from the years 2013 to 2017. Although a previous review by McCarthy \textit{et al.} has appeared in 2012,\textsuperscript{30} some reports were missing from their compilation. Thus, we have chosen to cover the literature under one section up to December 2017, omitting those works which have already been reported in the previous review.

2. Synthesis of Ellipticine and Derivatives

In 2014, Meesala \textit{et al.}\textsuperscript{31} have developed a simple and an efficient method to synthesize a new series of ellipticine analogues using the Vilsmeier–Haack reagent (Scheme 1). They described the synthesis of pyrido[3,2-\textit{b}]carbazoles and pyrido[2,3-\textit{c}]carbazoles by treating N-(carbazol-3-yl)acetamides 1a-e with DMF (2.5 equiv) and POCl\textsubscript{3} (10.0 equiv) at 70 °C for 12 hours. The reaction works well with different types of N-(carbazol-3-yl)acetamide derivatives and provides the corresponding linear and angular products. The angular products were obtained as the major isomers compared to the linear products.

Since the pyridocarbazoles contain the reactive substituents chlorine and aldehyde, these can be utilized for further heteroannulations to develop novel pyridocarbazole-based heterocyclic systems which may exhibit interesting biological properties.
Scheme 1. Synthesis of pyridocarbazoles 2 and 3.

Nagarajan et al.\textsuperscript{32} reported a simple and efficient route to the synthesis of ellipticine quinone 12 (Scheme 3) from isatin 4. The first key step is the synthesis of 7 from isatin using various alkylating reagents (Scheme 2). They performed reaction between sodium 2-[(2-aminophenyl)-2-oxoacetate 5 and 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide in DMF at 70 °C for 5 h affording 7 in 17% yield. The next step is the rearrangement of 7 to carboxylic acid 9. Hydrolysis of compound 7 afforded 9 through an intermediate 8 along with easily separable decarboxilated product 10 in 76% and 24% yield respectively (Scheme 3).

Scheme 2. Synthesis of 7.

The key intermediate 9 was subjected to esterification with ethanol to give corresponding ester 11 in 92% yield. The ortho-lithiation of 11 by utilizing of LiHMDS/TMEDA produced the target ellipticine quinone 12 in good yield (Scheme 4).

In 2014, Nagarajan et al.\textsuperscript{33} reported an expedient synthesis of the pyrido[4,3-b]carbazole alkaloids, ellipticine 29 and 9-methoxyellipticine 30 (Scheme 7) over seven steps from known 1,4-dimethylcarbazoles 13.
and 14 with 23% and 25% overall yields, respectively. For the first time, they have utilized the H₃PO₄-mediated Friedel–Crafts cyclodehydration as a key step to construct these pyrido[4,3-b]carbazole alkaloids.

Scheme 3. Indoliodione-indole rearrangement of 7 to carboxylic acid 9.

Scheme 4. Synthesis of ellipticine quinone 12.

Their synthesis commenced with the preparation of 9-benzyl-1,4-dimethylcarbazoles 15 and 16 from the corresponding 1,4-dimethylcarbazoles, which can be readily prepared by literature methods (Scheme 5). N-Benzylation of 13 and 14 afforded 15 and 16 in excellent yields. Next, Vilsmeier–Haack formylation of 15 and 16 with DMF and POCl₃ at 70 °C furnished aldehydes 17 and 18. Subsequent Pinnick oxidation, using 30% aqueous H₂O₂, NaClO₂, and KH₂PO₄ in THF–H₂O (2:1), transformed 17 and 18 into acids 19 and 20 in 94% and 97% yields, respectively. Acids 19 and 20 were converted into the corresponding acid chlorides using SOCl₂, followed by amidation with 2-aminoethanol afforded the desired amides 21 and 22 along with esters 23 and 24 in smaller amounts (Scheme 5).
Scheme 5. Synthesis of 9-benzyl-N-(2-hydroxyethyl)-1,4-dimethyl-9H-carbazole-3-carboxamides 21 and 22.

Treatment of 21 or 22 with H₃PO₄ in air at 150 °C furnished dihydropyridocarbazolones 25 and 26 in 73% and 71% yields, respectively. Under these rather forcing conditions, they also observed the formation of the oxidative cleavage products 15 or 16 in trace amounts (Scheme 6).

Scheme 6. The key H₃PO₄-mediated Friedel-Crafts cyclodehydration.

Having assembled the tetracyclic scaffold of the natural products, two simple transformations remained in order to access ellipticine 29 and 9-methoxyellipticine 30. This would involve conversion of the amide group.
into an imine followed by the cleavage of the \( N \)-benzyl group in the intermediates 25 and 26. As shown in Scheme 7, the first of these challenges was achieved by reductive amination using mild reagents Tf\(_2\)O and Et\(_3\)SiH. This generated \( N \)-benzylellipticines 27 and 28 in good yields. Next, the \( N \)-benzyl group was removed from 27 and 28 by using 10% palladium on carbon to furnish ellipticines 29 and 30.

\[
\begin{align*}
\text{Scheme 7. Synthesis of ellipticine 29 and 9-methoxyellipticine 30.}
\end{align*}
\]

The same authors reported later a novel and concise total synthesis of biologically important ellipticine quinone and calothrixin B in three-step sequences of 67\% and 38\% good overall yields, respectively. They have also extended this route to the synthesis of olivacine in 16\% overall yield over 6 steps. Their synthetic approach for these compounds is superior to that of previously reported methods in terms of availability of starting materials, overall yields, and the number of steps used.

\[
\begin{align*}
\text{Scheme 8. Synthesis of ellipticine quinone.}
\end{align*}
\]
They treated commercially available ethyl 1H-indole-2-carboxylate 31 with pyridine-3-carboxaldehyde 32 in presence of AlCl$_3$ followed by oxidation using IBX in DMSO, giving ketone 34 in 94% yield. The carbinol formed 33 was not isolated from the reaction mixture, and subsequently they carried out oxidation after the reaction workup. The ketone 34 was then subjected to directed o-lithiation reaction using LiTMP (lithium tetramethylpiperidide) as a base to afford a single regioisomer 12 in 72% yield. Thus, ellipticine quinone 12 was obtained in 3 steps and 67.6% overall yield (Scheme 8).

Similarly, isoellipticine quinones 39 and 40 can be obtained by varying pyridine part 36 as shown in Scheme 9. Also the other isomer of ellipticine quinone 43 was synthesized by using pyridine-2-carboxaldehyde 41.

Scheme 9. Synthesis of isomeric ellipticine quinones.
They have successfully applied their synthetic route to the synthesis of olivacine 48 and calothrixin B 51. Treatment of 31 with 2-methylnicotinaldehyde in the presence of 1,1,3,3-tetramethylguanidine (TMG) in MeOH at room temperature followed by oxidation using IBX afforded the ketone 45 in 84% yield. Wolff–Kishner reduction of the ketone 45 gave reduced compound 46. The cyclized compound 47 was obtained by treating 46 with LDA/HMPA at −78 °C. Finally, the addition of MeMgI into 47 followed by treatment upon NaBH₄/AlCl₃ (3:1) in dry THF at room temperature produced 48 in 58% yield. Thus, olivacine 48 was obtained in 6 steps and 15.6% overall yield as shown in Scheme 10.

Scheme 10. Synthesis of olivacine 48

The synthesis of calothrixin B 50 is outlined in Scheme 11. The reaction of 31 with quinoline-3-carboxaldehyde in the presence of TMG in MeOH followed by oxidation with Dess–Martin periodinane (DMP) in DCM/ AcOH (9:1) at room temperature gave the ketone 49 in 80% yield. Then intramolecular directedolithiation reaction of 49 in the presence of LiTMP afforded 50 in 48% yield. Thus, calothrixin B 50 was obtained in three steps and 38.4% overall yield.

In 2014, Konakahara et al. developed a simple and efficient synthetic method of novel four ellipticine derivatives in good to high yields. Moreover three kinds of novel pyridocarbazole-5-carboxylate derivatives were synthesized. All these new compounds exhibited higher solubility in water than ellipticine itself.
Scheme 11. Synthesis of Calothrixin B 50.

2-alkyl-5-methoxycarbonyl-11-methyl-6H-pyrido[4,3-b]carbazol-2-ium chloride derivatives were prepared from indole 51. First, the NH group of 51 was protected with benzensulfonyl group to give 52 which was oxalylated on the C-2 atom to give compound 53 in a 61% yield. Removal of benzene sulfonyl protecting group and hydrolysis of the ester group of 53 give the corresponding carboxylic acid 54 in an 85% yield. The carbonyl group of 54 was reduced with hydrazine leading to the formation of 2-indolylacetic acid 55. The crude product was treated with trimethylsilyldiazomethane to give the corresponding methyl ester 56. Finally, a mixture of 56 and 3-acetylpyridine was heated in the presence of concentrated sulfuric acid leading to methyl 2-(3-(1-(pyridin-yl)vinyl)-1H-indol-2-yl)acetate 57 in 65% yield (Scheme 12).

Scheme 12. Synthesis of 57.
To construct a pyridocarbazole ring, the compound 57 was treated with 58 and 59 in the presence of 3-ethoxycarbonyl-1-methylpyridinium chloride 62 leading to 2-alkylpyridocarbazolium derivatives 64a,b in a yield of 10% (Scheme 13). Alternatively, the 2-alkylpyridocarbazolium derivatives 64a, 64b and 64d were prepared in good yields in two steps via treatment of 57 with 61a, 61b and 61d respectively, in the presence of NaOMe and 62 followed by the action of Amberlite IRA-900 (Scheme 13). The stability of the quaternary salts of these molecules increases by converting them into the corresponding tosylate and chloride salts.

**Scheme 13.** Synthesis of 2-alkylellipticinium analogue 65.

Ellipticine 29, hydroxyellipticine 70, 6-methylellipticine 67 and 9-hydroxy-6-methylellipticine 69 were prepared via a modification of a previously reported method, as shown in Scheme 14 for 67 and 69 and followed by Dakin oxidation leading to the formation of 9-hydroxyellipticine 70 in 55% yield.
Scheme 14. Synthesis of 6-methyllumpicine 67 and 9-hydroxy-6-methyllumpicine 69.

Scheme 15. Synthesis of 2-alkyl analogues of ellipticine 73a-d.
Ellipticine 29, 9-hydroxyellipticine 70, and 9-hydroxy-6-methylellipticine 69 were treated with 61d to form the corresponding ellipticinium tosylate quaternary salts 71a-c (Scheme 15). In a similar manner, tosylate salts 71a-d were then treated with Amberlite IRA-900 to give the corresponding chloride salts 72a-d. These chloride salts were then refluxed in HCl (12M) to give the 2-alkyellipticinium analogues 73a-d in good yields.

The obtained 2-(2-aminoethoxy)ethoxy)ethyl-5-methoxycarbonyl-11-methyl-6H-[4,3-b]carbazol-2-ium chloride 65 and its analogues 73a-d were treated with p-nitrophenyl N-methylcarbamate 74a and its N-nitroso derivative 74b to get the corresponding urea derivatives 75a-e and N-nitrosourea derivatives 76a-e (Scheme 16).

Scheme 16. Synthesis of urea and nitrosourea analogues of ellipticine derivatives 75a-e, 76a-e.

Finally, 2-(2-aminoethyl)- and 2-(3-aminopropyl)-pyridocarbazol-2-ium chlorides 81-88 were synthesized by a method analogous to the synthesis of 75e and 76e in poor to high yields (Scheme 17).

In 2016, Ergün et al. reported a new synthetic route for the synthesis of 5-methyl-6H-pyrido[4,3-b]carbazole 96, so called 11-demethylellipticine (Scheme 18). They have used tetrahydrocarbazole acid 89 as a starting material and synthesized according to the literature. Then, acid 89 was converted to glycine 90 derivative using ethyl chloroformate and methyl glycinate. The reduction of glycine 90 with lithium aluminium hydride gave amine alcohol 91. Amine alcohol 91 was reacted with benzene sulfonyl chloride and gave protected compound 92. The oxidation of the compound 92 at position 1 with periodic acid yielded tetrahydrocarbazolone 93. Then, reaction of 93 in the presence of sodium hydride led to the tetracyclic structure 94. Finally, pyridocarbazole 96 was synthesized by aromatization of compound 95, which was obtained from reaction between compound 94 and methyl lithium. One of the syntheses of pyridocarbazole alkaloid olivacine had been achieved via the reaction between pyridocarbazole 96 and methyl lithium in the literature previously. Tetracyclic structure 94 can also allow the synthesis of several ellipticine derivatives.
Scheme 17. Synthesis of urea and nitrosourea derivatives of pyridocarbazole-5-carboxylates 85-88.
Scheme 18. Synthesis of 11-demethylellipticine 96.

The same year Konakahara and al.\textsuperscript{40} succeeded in developing the simple and efficient synthesis of three novel 9-hydroxyellipticine derivatives linked with a glucose moiety by a triazole ring-succinate tether at the position 9 of an ellipticine nucleus (Scheme 19).

9-Hydroxysuccinate 97 was synthesized by a previously reported method,\textsuperscript{41} and then treated with monopropargyl succinate 98 leading to the formation of ellipticin-9-yl propargyl succinate 99 in a 78% yield.

Scheme 19. Synthesis of ellipticin-9-yl propargyl succinate 99.
Reaction of ellipticin-9-yl propargyl succinate 99 and 2-azidoethyl β-D-glucopyranoside 100a was performed and the best yields were obtained using CuI as catalyst in the presence of diisopropylethylamine (DIPEA) (Scheme 20).

![Scheme 20](image)

**Scheme 20.** Huisgen reaction of 2-azidoethyl β-D-glucopyranoside 100a and ellipticin-9-yl propargyl succinate 99.

The reaction of 99 with β-D-glucopyranosyl azide 100b and 2-acetamido-2-deoxy-β-D-glucopyranosyl azide 100c gave the corresponding products 101b-c, in 94 and 90% yields, respectively (Scheme 21).

![Scheme 21](image)

**Scheme 21.** Huisgen reaction of 2-azidoethyl β-D-glucopyranoside 101b-c and ellipticin-9-yl propargyl succinate 100.

These compounds exhibited potent antitumor activity. The introduction of glucose conjugaison at the 9-position enhanced its solubility in water compared with those of ellipticine alone. This is the first report of the synthesis and evaluation of the antitumor activity of the uncharged glucose-conjugates of 9-hydroxyellipticine with increased water solubility.
An efficient and simple Ni-catalyzed C(aryl)-OMe bond cleavage and subsequent C(aryl)-Me bond formation by treating carbazoles with MeMgBr has been developed in 2016 by Das et al. This protocol was successfully applied to the synthesis of the natural product ellipticine from readily available starting materials.

They used commercially available 2,5-dimethoxybenzaldehyde 102 as the starting material and introduced the methyl group through a Ni-catalyzed Kumada-type coupling reactions at a late stage of the synthesis. They began the synthesis with the nitration reaction (CuSO$_4$·6H$_2$O/HNO$_3$) of 2,5-dimethoxybenzaldehyde 102 to afford nitration product 103 in 80% yield (Scheme 22). The condensation reaction of 103 with aminoacetaldehyde diethyl acetal in dry benzene gave imine product 104. The subsequent reduction of 104 with sodiumborohydride in methanol afforded amine 105 in 85% yield. The protection of amine 105 with a tosyl group gave protected compound 106, which underwent cyclization in an acidic medium to furnish isoquinoline 107 in 54% yield (two steps). In the next step, the reduction of the nitro group was achieved by using Pd/C in methanol, and amine 108 was isolated in 80% yield. This product was then subjected to a Cu-

Scheme 22. Total synthesis of ellipticine.
catalyzed Chan–Lam-type coupling with phenylboronic acid \( \text{109} \) to afford \( \text{N-arylated product 110} \).\(^\text{43}\)

Subsequently, the preparation of carbazole \( \text{111} \) was achieved in 70% yield by using a Pd-catalyzed cross-dehydrogenative (CDC) coupling reaction. Finally, they applied their optimized Ni-catalyzed protocol to replace the methoxy with a methyl group to afford ellipticine in 85% yield.

This protocol demonstrates that the lipophilicity of bioactive carbazoles can be easily modified by replacing a methoxy with a methyl group, which is important in the regulation of drug properties such as bioavailability and metabolic stability.

Topçu et al.\(^\text{44}\) synthesized in 2016 two novel ellipticine derivatives, \( \text{N-methyl-5-demethyl ellipticine (ET-1)} \) and \( \text{2-methyl-N-methyl-5-demethyl ellipticinium iodide (ET-2)} \), via a novel pathway shown in Scheme 23.

\( \text{ET-1} \) and \( \text{ET-2} \) were generated using a nine-step synthetic pathway with a 12% overall yield. First, 4,9-dimethyl-9\( \text{H} \)-carbazole-3-carbaldehyde \( \text{112} \)\(^\text{45}\) was treated with aminoacetaldehyde diethylacetal to yield imine \( \text{113} \). The imine was reduced with sodium borohydride to produce amine \( \text{114} \), which was treated with benzene sulfonyl chloride to produce sulfonamide \( \text{115} \). Finally, cyclization of \( \text{ET-1} \) was achieved by treating sulfonamide \( \text{115} \) with hydrochloric acid. \( \text{ET-2} \) was obtained by treating \( \text{ET-1} \) with iodomethane in DMF. \( \text{ET-1} \) and \( \text{ET-2} \) were more soluble than ellipticine.

Scheme 23. Synthetic pathway of novel ellipticine derivatives.

A series of 3-(alkyl)(dialkyl)amino)benzofuro[2,3-\( f \)]quinazolin-1(2\( H \))-ones \( \text{119} \) has been synthesized as new ellipticine analogs by Ando and al.\(^\text{46}\) in 2016.

3-Aminodibenzofurans \( \text{116a-b} \) were used as starting materials (Scheme 24). The amino derivatives \( \text{116a-b} \) were reacted with ethoxycarbonylisothiocyanate to give the thiourea intermediates \( \text{117} \), followed by the addition of the appropriate alkylamine or dialkylamine and \( \text{HgCl}_2 \) to give the ethoxycarbonylguanidine
intermediates 118. The latter intermediates were subjected to thermal cyclization followed by filtration of the HgS-by-product to give the 3-(alkyl)(dialkyl)amino)benzofuro[2,3-f]quinazolin-1(2H)-ones 119, respectively.

![Scheme 24. Synthesis of 3-(alkyl)(dialkyl)amino)benzofuro[2,3-f]quinazolin-1(2H)-ones 119.](image)

Ishikura et al.\textsuperscript{47} reported the total syntheses of 9-methoxyellipticine 30, 3,4-dihydroellipticine 128, 1,2,3,4-tetrahydroellipticine 129, 2-methyl1,2,3,4-tetrahydroellipticine 131, olivacine 142, 3,4-dihydroolivacine 141, (±)-janetine 138, and (±)-guatambuine 136 using triene 120 as a key intermediate. The cyclization of triene 120 to pyridocarbazole 122 was successfully performed by taking advantage of Cu-mediated 6π-electrocyclization, enabling a gram-scale reaction (Scheme 25).

![Scheme 25. Cu-mediated cyclization of indole 120.](image)

9-methoxyellipticine 30 was synthesized starting from carbazole 122b (Scheme 26). The N-Cbz group was removed by catalytic hydrogenation, and resulting amine 123 was subjected, without further purification, to oxidation with MnO\textsubscript{2} in dioxane at 100 °C, to afford 124 in 70% yield. Removal of the N-Boc group with BBr\textsubscript{3} afforded 30 in 75% yield.
Scheme 26. Synthesis of 9-methoxyellipticine 30.

Scheme 27. Synthesis of 128 and 130.
Next, carbazole 122a was converted to 3,4-dihydroellipticine (μ-alkaloid D) 127, 1,2,3,4-tetrahydroellipticine 128 and 2-methyl-1,2,3,4-tetrahydroellipticine 130 (Scheme 27). Removal of the N-Cbz group of 122a by catalytic hydrogenation provided amine 125, which was then treated with BBr₃. This sequence of transformations gave 1,2,3,4-tetrahydroellipticine 129 in 65% yield from 122a. Moreover, catalytic reduction of carbazole 122d produced 129 in a one-pot reaction. Additionally, amine 125 was oxidized with MnO₂ to give imine 126. Treatment of 126 with BBr₃ provided 3,4-dihydroellipticine 127 in 75% yield. The N-Cbz group of 122a was readily reduced to the N-Me group with DIBAL in THF at room temperature, leading to compound 129 in 75% yield. The N-Boc group was then removed with BBr₃ to give 2-methyl-1,2,3,4-tetrahydroellipticine 130.

The total syntheses of olivacine 48, 3,4-dihydroolivacine 140, (±)-janetine 137 and (±)-gutambuine 135 were undertaken starting from carbazole 122f. To transform 122f into carbazole 133, the N-Cbz group of 122f was removed by catalytic hydrogenation, and resulting amine 131 was subjected, without purification, to oxidation with MnO₂ to yield 132 in 70% yield from 122f. Next, the Me group was introduced into the C-1 position of 132. Treatment of 132 with ClCO₂Bn in THF at room temperature, followed by the addition of MeMgBr, readily provided 133 in 80% yield. Conversion of 133 to (±)-gutambuine 135 was carried out (Scheme 28) by first converting the N-Cbz group of 133 to its NMe congener with DIBAL; 134 was generated in 80% yield. Removal of the N-Boc group in 134 was effected with BBr₃ to provide (±)-gutambuine 135 in 60% yield. Additionally, the N-Boc group in 133 was cleaved by treatment with Cs₂CO₃ in refluxing MeOH/THF to render 135a. A conformational inversion of the D-ring, accompanied by inversion of the nitrogen at the 2-position was observed.

Scheme 28. Synthesis of (±)-135.
Next, 133 was converted to (±)-janetine 137 (Scheme 29) by removal of the N-Cbz group using catalytic hydrogenation. Resulting amine 136 was subjected, without purification, to reaction with BBr₃ to produce (±)-janetine 137 in 50% yield. Additionally, amine 136 was oxidized with a fivefold excess of MnO₂. This oxidation provided imine 138 in 70% yield and 139 in 5% yield from 133. A 20-fold excess of MnO₂ and prolonged reaction time (7 d) sufficed for the oxidation of 136 at room temperature, affording 139 in 72% yield from 133. Removal of the N-Boc group in 139 with BBr₃ provided olivacine 48 in 60% yield. On the other hand, 3,4-dihydroolivacine 140 was generated by treatment of 138 with BBr₃.

Scheme 29. Synthesis of 140, 48 and (±)-137.

In 2017, Hatae et al. developed a concise protocol for the synthesis of ellipticine quinone as outlined in scheme 31. The three-component Pd-catalyzed cross-coupling reaction between 3-iodoindole-2-carbaldehyde 144 and alkenyl tributyltin 143 under CO (1 atm) atmosphere was conducted in DMF at 70 °C to provide 3-acryloylindole 145 in 64% yield. The alkenyl tributyltin required 143 is obtained by treatment of aminoacetalddehyde diethyl acetal with p-toluene sulfonyl chloride and NEt₃ leading to the p-toluene sulfonamide 141 in 76% yield. This latter was subjected to alkylation with propargyl bromide to give
the propargylamine 142 in 74% yield. Subsequently, 142 was subjected to Pd-catalyzed hydrostannylation with tributyltin hydride to afford the desired alkenyl tributyltin 143 in 97% yield (Scheme 30).

![Scheme 30](image)

**Scheme 30.** Synthesis of alkenyl tributyltin.

The Grignard reaction of 145 with vinylmagnesium bromide afforded the allyl alcohol 146. Treatment of 146 with grubbs 2nd generation catalyst directly afforded the carbazole-1,4-quinone 147 in 66% yield. Finally, compound 147 was subjected to cyclization with 6M HCl by conventional heating. The desired ellipticine quinone 12 was obtained in 35% yield. Under microwave irradiation, the yield improved and 12 was obtained in 67% yield. Furthermore, cyclization of 147 with 6M HCl under microwave irradiation gave ellipticine quinone 12 as the sole product in 90% yield. Thus, the synthesis of ellipticine quinone 12 was achieved in 34.6% overall yield in four steps (Scheme 31).
Recently, in 2017, ellipticine, olivacine and their five reduced natural variants were synthesized via a palladium-catalyzed tandem cyclization/cross-coupling reaction as the key step by Ishikura et al.\textsuperscript{49}

The syntheses of pyridocarbazole alkaloids \textsuperscript{29, 30, 48, 122, 127-128, 135, 137, 140} were reported by the one-pot tandem cyclization/cross-coupling reaction of bromide \textsuperscript{150} with indolyborate \textsuperscript{149}, which was generated \textit{in situ} from indole \textsuperscript{148}, to produce hexatriene intermediate \textsuperscript{120}. This was followed by 6\pi-electrocyclization of \textsuperscript{120} to produce pyridocarbazole core \textsuperscript{121}. Carbazole intermediates \textsuperscript{121a} were transformed into ellipticine \textsuperscript{29}, 9-methoxyellipticine \textsuperscript{30}, 3,4-dihydroellipticine \textsuperscript{127}, and 1,2,3,4-tetrahydroellipticine \textsuperscript{128}. Olivacine \textsuperscript{48}, (\pm)-guatambuine \textsuperscript{135}, (\pm)-janetine \textsuperscript{137}, and 3,4-dihydroolivacine \textsuperscript{140} were synthesized from common intermediate \textsuperscript{122} derived from \textsuperscript{121b} (Scheme 32).

The cytotoxicities of the synthetic alkaloids and their derivatives against HCT-116 and HL-60 cells were determined. Structural properties, such as the aromaticity of the D ring and the presence of a Me group at the \textit{N}(6)- and \textit{C}(11)-positions, affected the activities of the compounds.
3. Conclusions

The present review offers an up-to-date literature on the latest syntheses of ellipticine and ellipticine derivatives reported during the last years. Several of these syntheses may be useful, and in particular Hatae et
al.\textsuperscript{48} offers an attractive, short and efficient preparation of ellipticine quinone and its analogs. Overall, the interest in ellipticines and related pyridocarbazoles continue to expand given the diversity of structure and emerging bioactivity inherent in this compound class.

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