ISOLATION, BIOLOGICAL ACTIVITIES AND SYNTHESIS OF INDOLOQUINOLINE ALKALOIDS: CRYPTOLEPINE, ISOCRYPTOLEPINE AND NEOCRYPTOLEPINE

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Running Title:
Recent Development in Indoloquinoline Alkaloids

Abstract: The tetracyclic heteroaromatic compounds cryptolepine, isocryptolepine and neocryptolepine are all naturally occurring indoloquinoline alkaloids isolated from the shrub Cryptolepis sanguinolenta and are important due to their wide spectrum of biological properties. This review describes the isolation, brief biological activities and various synthetic methodologies developed during recent years for the preparation of this important class of alkaloids, with special emphasis on preparation and properties of cryptolepine 1, isocryptolepine 2 and neocryptolepine 3.

Keywords: Alkaloid, cryptolepine, heteroaromatic, indoloquinoline, isocryptolepine, and neocryptolepine.
1. INTRODUCTION

1.1. General

In recent years, indoloquinoline alkaloids have received considerable attention due to their promising DNA intercalating [1] and antimalarial properties [2 - 4]. According to World Health Organization (WHO), about 3.3 billion people are at risk of malaria. Every year, this leads to about 250 million malaria cases, causing nearly a million deaths, mostly of children under 5 years, justifying its classification as a dreaded infectious disease along with tuberculosis and AIDS [5].

The roots of the West African plant Cryptolepis sanguinolenta [6 - 19] has long been used in folk medicine for the treatment of infectious diseases, amoebiasis, fever and malaria. Since 1974, a decoction of this plant is being used in the clinical therapy of rheumatism, urinary tract infections, malaria and other diseases [20 - 23]. Chemical examination indicated this plant to be a rich source of several indoloquinoline alkaloids [6 - 19].

1.2. Isolation

So far 13 alkaloids including cryptolepine 1, isocryptolepine 2 and neocryptolepine 3 have been reported from the roots of the West African plant C. sanguinolenta (Figure 1).

![Fig. (1).](image-url)

Among these, cryptolepine 1 is a rare example of natural product whose synthesis was reported prior to its isolation from nature. It was synthesized in 1906 by Fichter and Boehringer [24] for possible use as a dye while its isolation from C. triangularis was reported only in 1929 [25]. Subsequently, in 1951, Gellert et al. [6] reported this compound from the roots of C. sanguinolenta.

In 1995, two research groups, i.e., Pousset et al. [10] and Sharaf et al. [26] independently reported a related alkaloid 2 and named it as isocryptolepine and cryptosanguinolentine, respectively. Isocryptolepine 2 is an angularly-fused alkaloid with indolo[3,2-c]quinoline ring system whereas cryptolepine 1 is a linearly-fused alkaloid with indolo[3,2-b]quinoline ring system.

Subsequently in 1996, a new linearly-fused indolo[2,3-b]quinoline alkaloid 3 was reported by two independent research groups and named it as neocryptolepine by Pieter's group [9] and cryptotackieine by Schiff's group [26].
Other alkaloids reported from the plant *C. sanguinolenta* include quindoline 4 [7], cryptospirolepine 5 [13], cryptolepicarboline 6 [27], cryptomisrine 7 [28], 11-isopropyl/cryptolepine 8 [17], cryptolepinone 9 [13 - 15], and bis-cryptolepine 10 [9] (Figure 2).

**Fig. (2).**

1.3. Brief Biological activities

The tetracyclic heteroaromatic compounds 1 and 3 are linearly fused indoloquinolines, while compound 2 has angularly-fused ring system. All the three compounds exhibit promising antiplasmodial activity [2 - 4, 29] against chloroquine-resistant *P. falciparum* and cryptolepine has been used as a lead compound for synthetic antiplasmodial agents [30 – 31]. Initially, neocryptolepine was reported to show an activity comparable to cryptolepine [2 - 3], more recent studies have shown that, it was 7 times less active against the chloroquine-resistant *P. falciparum* Ghana-strain [32]. These alkaloids also intercalate with DNA double helix, causing dramatic changes in DNA conformation leading to inhibition of DNA replication and transcription [1]. The strength and mode of binding of these alkaloids to DNA have been investigated by spectroscopy and X-ray analysis [33 - 34]. Cryptolepine binds 10-fold more tightly to DNA than other alkaloids and proves to be much more cytotoxic toward B16 melanoma cells [33]. In addition, these compounds as well as some of their methyl derivatives have also shown promising antimuscarinic, antibacterial, antiviral, antimicotic, antihyperglycemic and cytotoxic properties *in vitro* and antitumor activity *in vivo* [19, 23, 35 - 38].

These alkaloids, due to their wide spectrum of biological activities, have been targets of synthetic chemists in recent years.
2. SYNTHESIS

The synthetic methods used for the preparation of indoloquinoline alkaloids may be classified under the following six major categories based on the method of formation of the ring system – palladium-catalyzed coupling reaction, aza-Wittig reaction, transition-metal mediated reductive cyclization, photochemical reactions, Graebe-Ullmann reaction and other miscellaneous methods.

2.1. Palladium-catalyzed coupling reaction

Pd-catalyzed coupling reactions [39 - 43] have become a powerful tool for the synthetic chemists particularly for the synthesis of biologically active natural products and for the preparation of versatile organic building blocks. Palladium catalysts possess a higher activity than other metal alternatives (Cu, Ni or Fe) enabling the conversion of less reactive substrates and performance at relatively low temperature.

Timari et al. [44] reported the synthesis of isocryptolepine and neocryptolepine using Suzuki procedure (Scheme 1 & 2).

![Scheme 1.](image)

The reaction of 3-bromoquinoline 11 with N-pivaloylaminophenyl boronic acid 12 in presence of Pd(0) catalyst afforded the desired biaryl compound 13 which, on hydrolysis with sulfuric acid gave amine 14. The compound 14 was converted to azide 15 which, on nitrene insertion, gave exclusively the indolo[3,2-c]quinoline 16.
16. Regioselective methylation on quinoline nitrogen using dimethyl sulfate yielded the target molecule isocryptolepine 2 (Scheme 1).

\[ \text{Scheme 1} \]

3-Bromo-1H-2-quinoline 18 was prepared from 3-bromo-quinoline 11 via its N-oxide 17 which, on treatment with methyl iodide, gave N-methyl compound 19. Coupling reaction of 19 with 12 in the presence of Pd(0) catalyst afforded the biaryl compound 20. Hydrolysis of 20 with sulfuric acid followed by cyclization using POCl₃ furnished neocryptolepine 3 (Scheme 2).

Fan and Ablordeppy [45] described the synthesis of 10H-indolo[3,2-b]quinoline 4 via N-arylation of 3-bromoquinoline 22 with triphenylbismuth diacetate using metallic copper, followed by oxidative cyclization of the resultant anilinoquinoline 23 using palladium acetate (Scheme 3).

\[ \text{Scheme 3} \]

Arzel et al. [46] described the first halogen-dance reaction [47] in quinoline series and its application to a synthesis of quindoline (Scheme 4).
Pd-catalyzed cross-coupling reaction between boronic acid 12 and 3-fluoro-2-iodoquinoline 24 using Suzuki procedure [48 - 51] afforded the biaryl compound 25 which, underwent cyclization on treatment with boiling pyridinium hydrochloride [52] to give quindoline 4 in 83% yield. The intramolecular nucleophilic displacement of fluorine with amino group is facilitated by the formation of quinoline hydrochloride.

Murray et al. [53] achieved the synthesis of isocryptolepine as depicted in scheme 5.

Csanyi et al. [54] accomplished the synthesis of quindoline 4 by a regioselective coupling reaction of 2,3-dibromoquinoline [55] 30 with 12 taking into consideration the fact that the α-heteroaryl halogen atom is more reactive than the β-halogen atom [56] to give N-pivaloyl-2-(2’-anilino)-3-bromoquinoline 31. Hydrolysis of 31
afforded the free amine 32 which underwent cyclization when heated at 200-220°C in presence of pyridinium hydrochloride to give quindoline 4 (Scheme 6).

Scheme 6.

Jonckers et al. [57] described the Pd-catalyzed 'amination-arylation' approach for the synthesis of isocryptolepine (Scheme 7).

Scheme 7.


Hostyn et al. [67] reported the synthesis of isoneocryptolepine, a missing indoloquinoline isomer in the alkaloid series cryptolepine, neocryptolepine and isocryptolepine via two routes – 1. Suzuki arylation with an intramolecular nitrene insertion (Scheme 8) and 2. With a combination of a selective Buchwald-Hartwig-amination with an intramolecular Heck-type reaction (Scheme 9).
Scheme 8.

Suzuki reaction of 33 with 12 under Grönowitz conditions \([68-69]\) yielded compound 36 which on hydrolysis provided amine 37. Diazotization of the resulting amine 37 followed by introduction of azido group and then thermal decomposition of azide 38 in boiling o-dichlorobenzene yielded the target molecule 39 as the major product and 40 in trace amount (Scheme 8).

Scheme 9.

Regioselective amination of 11 with 41 in presence of Pd(0) catalyst gave compound 42 which on Heck-type cyclization yielded predominantly 7H-indolo[2,3-c]quinoline 39 and small amount of quindoline 4. Selective N-methylation \([70]\) of 39 using methyl iodide in refluxing toluene afforded the isoneocryptolepine 43 (Scheme 9).

Venkatesh \textit{et al.} \([71]\) reported the synthesis of benzimidazo[1,2-a]quinoline 47 \textit{via} Pd-catalyzed intramolecular heterocyclization of 2-(2-bromoanilino)quinoline 46 in which 6H-indolo[2,3-b]quinoline 48 (precursor to neocryptolepine) was formed as a minor product (Scheme 10).
Scheme 10.

Miki and co-workers [72] have developed a simple approach towards isocryptolepine by applying Myers method [73 - 75] (Scheme 11).

Scheme 11.

Reaction of 49 with N-methyl aniline 50 in acetonitrile afforded a mixture of acids 51 and 52 respectively. The decarboxylative Heck-type cyclization of 51 was achieved using Pd(OCOCF₃)₂ and Ag₂CO₃ to give the required compound 53 in 71% yield and decarboxylated product 54 in 12% yield. The compound 53 was converted to 2 by treatment with LiAlH₄ in hot dioxane.

Mori and Ichikawa [76] reported the synthesis of 11-alkylated cryptolepines via radical cyclization and Stille coupling reaction (Scheme 12).
Scheme 12.

α-Isocyano-substituted β,β-difluorostyrenes 55 on treatment with tributyltin hydride in presence of catalytic amount of AIBN and subsequent Pd-catalyzed coupling reaction with 56 afforded the 2,4-disubstituted-3-fluoroquinolines 57 which, on cyclization followed by methylation furnished the 11-n-butyl and 11-isopropyl cryptolepines 1b-c.

1.2. Aza-Wittig reaction

Aza-Wittig reaction [77 - 78] has become one of the important reactions in organic synthetic strategies directed towards the construction of acyclic and cyclic compounds as the reaction is mostly carried out in neutral conditions, in the absence of catalyst, generally at mild temperature and usually proceeds in high yield.

Shi et al. [80] prepared various derivatives of 6H-indolo[2,3-b]quinoline 48 using the above methodology [79] (Scheme 14).
Scheme 14.

The introduction of trimethylsilyl group at the acetylenic terminus provided an efficient route to 48 by suppressing the competing pathway toward the 2-anilinoquinoline 62 as the trimethylsilyl group serve as a surrogate for the hydrogen atom in directing the reaction toward the indoloquinoline. A subsequent protodesilylation using NaOH furnished 48 in good yield. Similarly, the derivatives of 48 with substituents at C-11 position are prepared by treating the corresponding iminophosphoranes with phenyl isocyanate.

Using the methodology of Alajarin et al. [79], Jonckers and co-workers [32] also prepared various cryptolepines with substituents on A-ring or D-ring and were evaluated for their cytotoxicity, antiplasmodial and antitrypanosomal activities.

Molina and co-workers [81] reported the synthesis of neocryptolepine via Staudinger, aza-Wittig and electrocyclization reactions (Scheme 15).
The iminophosphorane 69 was prepared by condensing 2-(nitrobenzyl)triphenylphosphonium bromide 63 with 2-bromobenzaldehyde 64 in the presence of K₂CO₃ followed by reduction of nitro group with iron and then treatment of the resultant amino-stilbene derivative 67 with triphenylphosphine dibromide 68. An aza-Wittig reaction of 69 with tosyl isocyanate 70 afforded the carbodiimide 71 which on heating underwent electrocyclic ring closure to give compound 72. Treatment of 72 with NaH in presence of CuI and subsequent detosylation using TBAF yielded 48. Microwave-promoted methylation with DMS in DMF provided the target molecule 3.

Fresneda and co-workers [82] devised a divergent synthetic approach to the alkaloids isocryptolepine and neocryptolepine which was based on the formation of key common intermediate 1-methyl-(α-azidophenyl)quinoline-2-one 83 (Scheme 16).
Scheme 16.

The key intermediate 83 was prepared using 63 and 2-azidobenzaldehyde 74 as the starting materials which underwent Wittig reaction in presence of K$_2$CO$_3$ to give compound 75. Reaction of 75 with n-Bu$_3$P followed by hydrolysis of the resultant iminophosphorane 76 and Z$\rightarrow$E isomerization of the C=C bond afforded amino-stilbene derivative 77 which, on treatment with triphosgene 78 yielded the corresponding o-vinylsubstituted isocyanate 79. Electrocyclic ring closure of 79 was achieved via microwave irradiation to give quinoline-2-one derivative 80 which, was converted to 83 by a four step sequence – methylation, catalytic hydrogenation and diazotization followed by reaction with sodium azide. Selective indolization was achieved either by intramolecular aza-Wittig reaction of the iminophosphorane derived from 83 and PPh$_3$ under microwave irradiation to give neocryptolepine 3 or by nitrene-insertion process followed by reduction with Red-Al to give isocryptolepine 2.
1.3. Transition-metal mediated reductive cyclization

Reductive cyclization [83] using transition metals is an effective protocol for the synthesis of compounds containing quinoline ring and thus is being used by several research groups for the synthesis of indoloquinolines.

Ho and co-workers [84] reported the synthesis of cryptolepine and neocryptolepine from common intermediate 1,3-bis-(2-nitrophenyl)propan-2-one 86 (Scheme 17).

Scheme 17.

The key intermediate 86 was readily obtained from 2-nitrophenyl acetic acid 85 by reaction with DCC in presence of DMAP. The approach to 1 involved the reduction of nitro groups with Fe powder followed by oxidative cyclization and subsequent N-methylation. On the other hand, 3 was obtained via bromination, Favorskii rearrangement of the resultant bromo compound 88 followed by reduction-cyclization using Fe powder and finally N-methylation using methyl iodide.

Amiri-Attou et al. [85] described the synthesis of analogues of neocryptolepine via one-pot reduction-cyclization-dehydration reaction (Scheme 18).
Reaction of \( o \)-nitrobenzyl chlorides \( 90a-e \) with 1-methylisatin \( 91 \) in the presence of tetrakis(dimethylamino)ethylene (TDAE) \([86 \text{–} 87]\) afforded the corresponding \( \alpha \)-hydroxy lactams \( 92a-e \) which, on treatment with iron underwent reduction-cyclization and dehydration in one-pot to give the respective 6-methyl-6\( H \)-indolo[2,3-\( b \)]quinolines \( 93a-e \).

We reported \([88]\) the synthesis of neocryptolepine using the Perkin reaction and double reduction – double cyclization as the main steps (Scheme 19).

Condensation of 2-nitrobenzaldehyde \( 94 \) with 2-nitrophenyl acetic acid \( 85 \) in refluxing acetic anhydride in presence of \( \text{Et}_3\text{N} \) gave the \( \alpha,\beta \)-unsaturated acid which on esterification afforded the required ester \( 95 \) in good yield. Reduction with \( \text{Fe} \) powder furnishes the 6\( H \)-indolo[2,3-\( b \)]quinoline \( 48 \) via double reduction-double cyclization reactions in one-pot.
Sharma and Kundu [89] achieved the synthesis of neocryptolepine using indole 96 and 2- nitrobenzyl bromide 97 as the starting materials (Scheme 20)

Alkylation of indole with 2-nitrobenzyl bromide 97 yielded compound 98 which, on treatment with SnCl₂·2H₂O afforded 48 in 35% yield along with other two compounds 99 and 100 in 27% and 10% respectively.

1.4. Photochemical reactions

Photochemical reactions [90] are valuable in organic chemistry as they proceed differently than thermal reactions and have the advantage of forming thermodynamically disfavored products by overcoming large activation barriers and allow reactivity otherwise inaccessible by thermal methods. Photochemical substrate activation often occurs without additional reagents which prevents the formation of any by-products and thus become important in the context of green chemistry.

Kumar et al. [91] described the synthesis of isocryptolepine using photo-cyclization as the main step (Scheme 21)
Schiff's base 103, obtained by heating indole-3-carboxaldehyde 101 with aniline 102 in acetic acid, when irradiated at 253.7 nm underwent cyclization to give 11H-indolo[3,2-c]quinoline 16 via initial photoisomerization of the Schiff's base 103 from E- to Z-isomer followed by conrotatory ring closure and subsequent oxidation by iodine.

Dhanabal et al. [92] reported the synthesis of cryptolepine 1, isocryptolepine 2 and neocryptolepine 3 via heteroatom directed photoannulation technique (Scheme 22 - 24).
Scheme 23.

Nucleophilic substitution of 3-bromoquinoline 11 with aniline 102 was achieved by heating at 200°C and the resultant anilinoquinoline 23 was subjected to photochemical cyclization. Interestingly, both linearly-fused and angularly-fused products 4 and 39 were obtained, which on methylation gave cryptolepine 1 and isoneocryptolepine 43 respectively (Scheme 22).

Synthesis of isocryptolepine 2 and neocryptolepine 3 were obtained by photocyclization of the respective anilinoquinolines 105a and 105b and subsequent methylation at the quinoline nitrogen. Anilinoquinolines 105a-b were obtained from the corresponding chloroquinolines 104a-b (Scheme 23 and 24).
Pitchai et al. [93] reported a simple photo-induced method for the synthesis of the methyl derivative of isocryptolepine (Scheme 25).

![Scheme 25.](image)

4-Hydroxy-2-methyl quinoline 107 was prepared by microwave irradiation of β-anilinocrotonate 106 and then converted to 3-iodo-4-hydroxy-2-methylquinoline 108 using a known procedure [94], which on treatment with POCl₃ afforded the corresponding chlorinated compound 109. The amination reaction of 109 with aniline afforded the compound 110 which on photo irradiation and subsequent N-methylation yielded the methyl derivative of isocryptolepine.

1.5. Graebe-Ullmann reaction

Graebe-Ullmann reaction [95 - 96] has been widely used for the synthesis of carbazoles as the phenyl benzotriazoles formed in the reaction are unstable and readily undergo cyclization upon pyrolysis (catalyzed by acid) or on photolysis. Few research groups have exploited this reaction for the synthesis of indoloquinolines using haloquinolines instead of halopyridines as one of the starting materials.

Peczynska-Czoch and co-workers [36] reported the synthesis of various derivatives of neocryptolepines via Graebe-Ullmann reaction (Scheme 26) and these were evaluated for their in vitro antimicrobial and cytotoxic activities.
Triazoles 114a-d were prepared by heating the corresponding chloroquinolines 104a-d with benzotriazoles 113 at 110-120°C. Decomposition of the triazoles 114a-d by heating at 130-180°C in presence of PPA yielded the respective indoloquinolines 48a-d, which on methylation using DMS afforded the neocryptolepines 3a-d.

Godlewska et al. [97] reported the synthesis of nitro-substituted 6H-indolo[2,3-b]quinolines 115 using the above methodology [36] and then indole nitrogen was methylated using NaH and DMS to give the corresponding analogue of neocryptolepines 116. The nitro group was reduced to the corresponding amine using SnCl₂, which on treatment with p-toluenesulfonyl chloride afforded sulfonamide 118. Alkylation with (dialkylamino)alkyl chlorides and subsequent reaction with naphthylsodium yielded the 9-amino substituted neocryptolepine 121 (Scheme 27). Similarly, the 2-amino substituted neocryptolepine was prepared using 6-nitro-benzotriazole and 2-chloro-4-methyl-quinoline as the starting materials.
Sayed et al. [98] described the synthesis of neocryptolepines with A or D-ring substitutions using the methodology of Peczynska-Czoch and co-workers [36] and the side chain was introduced on the 2-, 3-, 8- and 9-positions using Pd-catalyzed amination reaction (Scheme 28). All these compounds were screened for in vitro antiplasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity on a human cell (MRC5) line.
Vera-Luque et al. [99] achieved the synthesis of 6H-indolo[2,3-b]quinolines via modified Graebe-Ullmann reaction under microwave irradiation (Scheme 29).
Microwave irradiation of benzotriazoles 113 and 2-chloroquinoline 104 afforded the respective triazoles 114a-d. The subsequent microwave irradiation of the resultant triazoles 114a-d in the presence of acid gave the respective 6H-indolo[2,3-b]quinolines 48a-d.

1.6. Other miscellaneous methods

Cooper et al. [100] described the synthesis of quindoline utilizing the intramolecular $\beta$-nucleophilic substitution as the main step (Scheme 30).

Scheme 30.

Amido ketone 127 was prepared by directed lithiation of 126 followed by addition of 94, subsequent oxidation of the resultant alcohol with MnO$_2$, reduction of nitro group using catalytic hydrogenation and N-benzylation using benzylichloride. The cyclized product 128 was obtained from 127 in 80% yield by initial 1,4-addition of amido anion followed by expulsion of the phenyl sulfonate. N-deprotection of 128 using NaOH in MeOH and subsequent reaction with POCl$_3$ followed by catalytic hydrogenolysis of the resultant chlorinated compound 130 afforded quindoline 4 in good yield.

Bierer and co-workers [23, 101] reported the synthesis of cryptolepine and its analogues by utilizing the procedures of Holt and Petrow [102] and Degutis and Ezerskaite [103] (Scheme 31).
Reaction of substituted indolyl acetates 131 with isatin derivatives 132 gave the respective quindoline carboxylic acids 133 which were decarboxylated by heating at 255°C in Ph2O and the subsequent quindolines 4 were alkylated using the method of Fichter and Boehringer [24] to give the respective cryptolepines 1. All these compounds were evaluated for their antihyperglycemic activities in vitro and in an non-insulin-dependent diabetes mellitus (NIDDM) mouse model.

Several other research groups [30, 104 – 105] have reported the synthesis of cryptolepine analogues using the above methodology [23, 101] and were screened for their antimalarial and cytotoxic activities.

Bierer and co-workers [101] have reported the synthesis of 4-methoxy cryptolepine hydrochloride and a series of 11-chlorocryptolepine analogues as shown below (Scheme 32 and 33) and evaluated for their antimalarial and antihyperglycemic activities.

Scheme 31.

Scheme 32.
Scheme 33.

Condensation of 134 with 135 using catalytic amount of piperidine gave compound 136 as a mixture of E/Z isomers which on hydrogenation and subsequent deprotection using KOH followed by alkylation afforded the methoxy cryptolepine hydrochloride 139 (Scheme 32).

Compound 142 formed by stirring anthranilic acids 140 and bromoacetyl bromide on treatment with substituted anilines 102 provided the anthranilic acid derivatives 143. Acid-promoted cyclization of 143 with PPA gave quindolones 144 which when refluxed in POCl₃ afforded the corresponding 11-chloroquindolines 145. N-Methylation of 145 was achieved using methyl triflate to give the respective hydrotriflate salts which, was converted to free base and subsequently treated with HCl to provide the corresponding 11-chlorocryptolepine hydrochloride salts 146 (Scheme 33).

Radl and co-workers [106] reported the synthesis of quindoline 4 via intermediate 149 by treating anthranilonitrilo derivative 147 with phenacyl bromide 148 in presence of K₂CO₃ (Scheme 34).

Scheme 34.
Nucleophilic denitrocyclization [107] of 149 with NaH gave the required tetracyclic compound 129 which on treatment with PCl₅ afforded the corresponding chloro compound 130 in 70% yield. The compound 129 may have formed by initial intramolecular 1,4-addition, followed by expulsion of nitro group as nitrous acid and subsequent N-deprotection of carboethoxy group during work-up.

Engqvist and Bergman [108] achieved the synthesis of neocryptolepine by simply heating the chloroindole derivative 150 with excess of N-methylaniline at reflux temperature (Scheme 35).

\[
\begin{align*}
\text{R} &= \text{H or Me} \\
\text{Scheme 35.}
\end{align*}
\]

Sundaram et al. [109] reported the synthesis of 6H-indolo[2,3-b]quinoline 48 using conjugate addition-elimination and the heterocyclization as the main steps (Scheme 36).

\[
\begin{align*}
\text{Scheme 36.}
\end{align*}
\]

Reaction of 151 with cyclohexanones 152 in presence of NaH underwent conjugate addition-elimination to give the corresponding adduct 153 which on heterocyclization with ammonium acetate yielded compound 154. Dethiomethylation of 154 with Ra-Ni and subsequent dehydrogenation with DDQ afforded 48. The 11-
sustituted 6H-indolo[2,3-b]quinolines 48c and 48e were prepared by treating compound 154 with DDQ and subsequent nickel-catalyzed cross-coupling reaction of resultant compound 156 with Grignard reagent.

Dhanabal et al. [110] described the synthesis of isocryptolepene using a Fischer indole cyclization as the key step (Scheme 37).

\[
\begin{align*}
\text{Fischer indole reaction of 157 with 158 gave indoloquinoline 84 which exist predominantly in the hydroxy form 159 as confirmed by IR. The enol 159 when refluxed in POCl}_3 \text{ afforded the corresponding chloride 160 which on catalytic hydrogenation yielded isocryptolepene 2.}
\end{align*}
\]

Dutta et al. [111] developed a general method for the synthesis of various 2-substituted cryptolepines which involves regioselective thermal cyclization and reductive cyclization using triethyl phosphite as the key steps (Scheme 38).
Scheme 38.

2-Nitroacetophenone 161 underwent Vilsmeier-Haack reaction when treated with POCl₃ in DMF to give the β-chlorocinnamaldehyde 162 which, on treatment with excess arylamines 102a-d in presence of 2N ethanolic HCl afforded the corresponding enaminoimine hydrochlorides 163a-d. Thermal cyclization of 163a-d at 200-250°C provided the respective 2-(2-nitrophenyl)quinoline derivatives 164a-d. The quindolines 4a-d was prepared by heating 164a-d with triethyl phosphite at 160°C.

Portela-Cubillo et al. [112] described the microwave-mediated formal synthesis of neocryptolepine via radical intermediate (Scheme 39).

Scheme 39.
The indolo-ketone 165 was treated with O-phenylhydroxylamine hydrochloride and the resultant O-phenyl oxime ether 166 was subjected to microwave irradiation in ionic liquid emimPF₆ to give tetrahydroindolo[2,3-b]quinoline 155 in 69% yield.

Sayed et al. [98] reported the synthesis of aminoalkylamino-substituted neocryptolepines using the procedure of Bergman and co-workers [113] (Scheme 40) and evaluated for their in vitro antiplasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity on a human cell line (MRC5).

Scheme 40.

The key intermediate 169 was obtained via chlorination of 168 with NCS in presence of 1,4-dimethylpiperazine followed by addition of aniline which underwent cyclization when refluxed in Ph₂O to give compound 129 [113] and then converted to 11-chloro-6H-indolo[2,3-b]quinolines 130 using POCl₃. Methylation using methyl iodide and subsequent amination via S_NAr reaction yielded the corresponding aminoalkylamino-substituted neocryptolepine derivatives.

Recently, we reported [114] the synthesis of series of novel 6H-indolo[2,3-b]quinolines using iodine as a catalyst in one-pot via Schiff's base intermediate (Scheme 41).
Scheme 41.

The reaction of indole-3-carboxaldehyde 101 with aryl amines 102 in presence of catalytic amount of iodine in refluxing diphenyl ether yielded indolo[2,3-b] quinolines 48 in a one-pot experiment via sequential imination, nucleophilic addition and subsequent annulation.

Kraus and Guo [115] achieved a formal synthesis of neocryptolepine 3 and isocryptolepine 2 from a common intermediate 83 using an intramolecular Wittig reaction and regioselective methylation as the key steps (Scheme 42).

Scheme 42.

The acid 173, prepared from isatin [116] was converted to acid chloride 174 by two different methods, one using thionyl chloride and the other using oxalyl chloride. Condensation of 2-
(aminobenzyl)triphenylphosphonium bromide with 174, followed by intramolecular Wittig reaction in presence of potassium tert-butoxide at room temperature afforded lactam 177 in 62% overall yield from compound 173. Methylation of 177 gave a known intermediate 83 which constitutes the formal synthesis of isocryptolepine 2 and neocryptolepine 3, respectively.

3. CONCLUSION

Indoloquinoline alkaloids show remarkable biological activities and constitute important scaffolds for drug development. Due to this, synthesis of indoloquinoline alkaloids forms, one of the important fields of research in medicinal chemistry. This review presents a collection of highly interesting and useful methods for the synthesis of different types of indoloquinoline alkaloids which includes cryptolepine, isocryptolepine and neocryptolepine. Several synthetic strategies are now available which provides flexibility for introducing various substituents into the ring system.

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