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

Prakash T. Parvatkar,[a,b] Perunninakulath S. Parameswaran,*[,c] and Santosh G. Tilve*[,b]

[a]National Institute of Oceanography, Dona Paula, Goa 403 004, India

[b]Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India

[c]National Institute of Oceanography, Regional Centre, Kochi 682 018, India

Tel.: 91-(0)-484-2390814 / 832-6519317

Fax: 91-(0)-484-2390618 / 832-2452886

E-mail: param@nio.org; stilve@unigoa.ac.in

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).

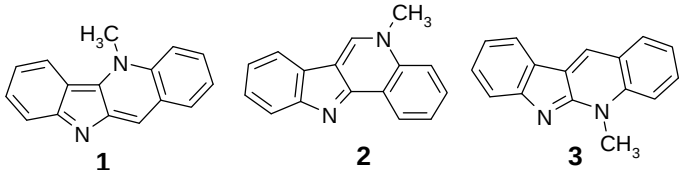


Fig. (1).

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-isopropylcryptolepine **8** [17], cryptolepinone **9** [13 - 15], and bis-cryptolepine **10** [9] (Figure 2).

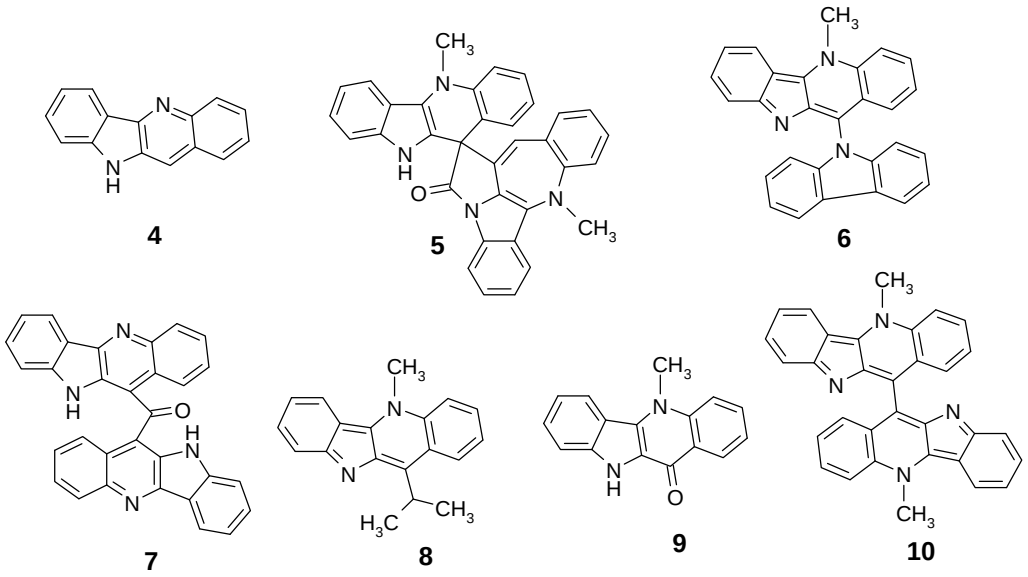


Fig. (2).

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.

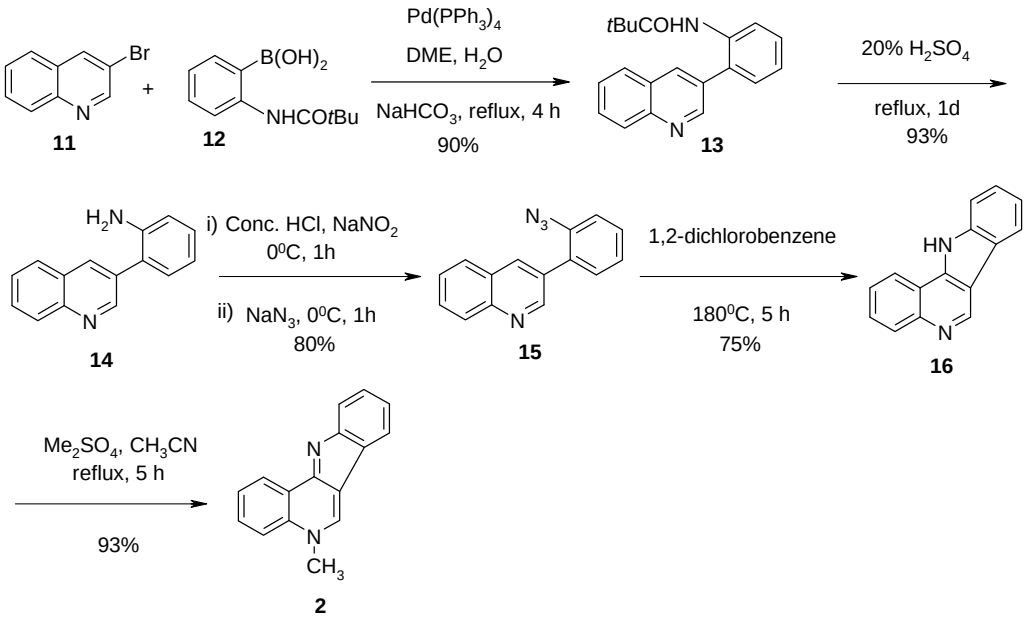
2. SYNTHESIS

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.

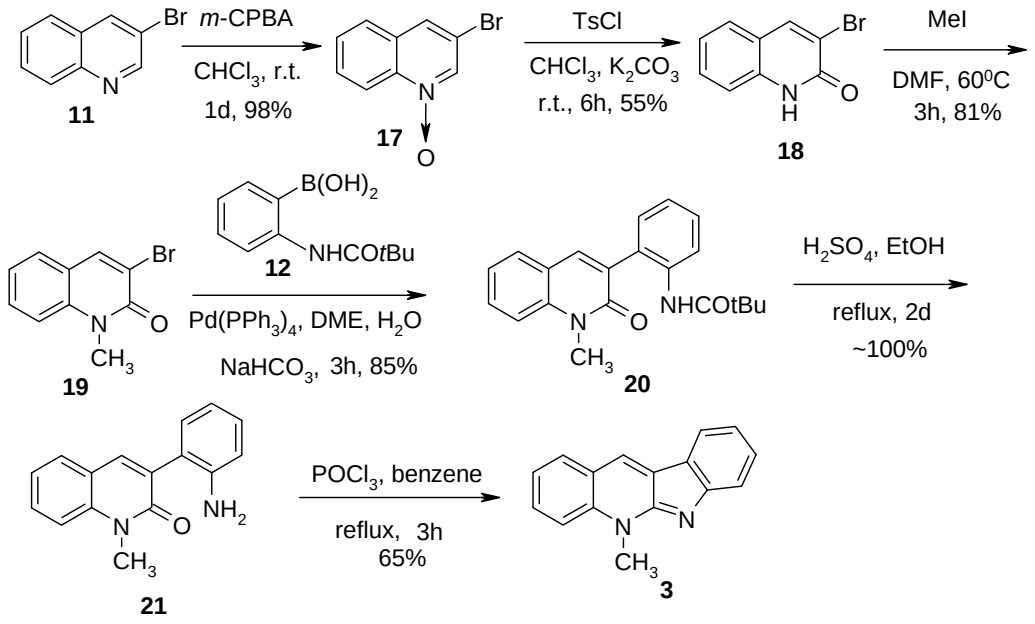
Timari *et al*. [44] reported the synthesis of isocryptolepine and neocryptolepine using Suzuki procedure (Scheme **1** & **2**).



Scheme 1.

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

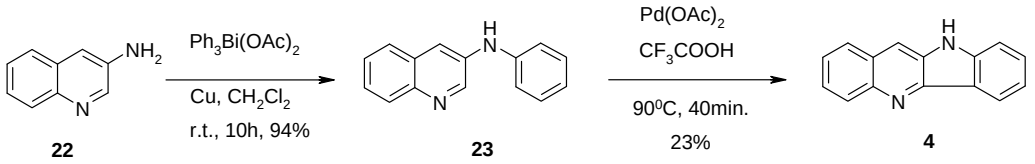
16. Regioselective methylation on quinoline nitrogen using dimethyl sulfate yielded the target molecule isocryptolepine **2** (Scheme **1**).



Scheme 2.

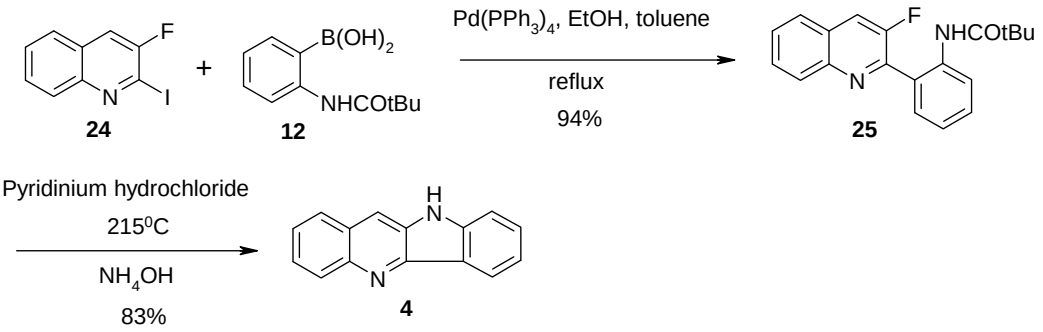
3-Bromo-1*H*-2-quinoline **18** was prepared from 3-bromo-quinoline **11** *via* its *N*-oxide **17** which, on treatment with methyl iodide, gave *N*-methyl compound **19**. Coupling reaction of **19** with **12** in the presence of Pd(0) catalyst afforded the biaryl compound **20**. Hydrolysis of **20** with sulfuric acid followed by cyclization using $POCl_3$ furnished neocryptolepine **3** (Scheme **2**).

Fan and Ablordeppy [45] described the synthesis of 10*H*-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**).



Scheme 3.

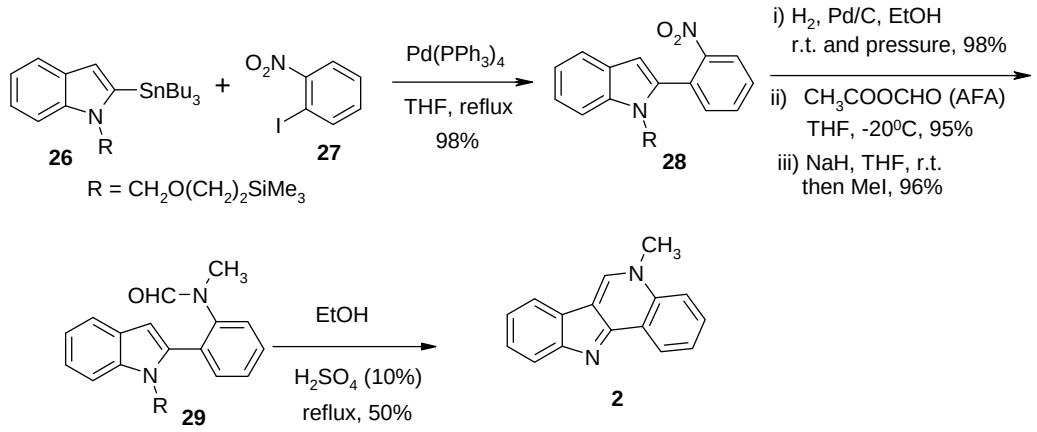
Arzel *et al*. [46] described the first halogen-dance reaction [47] in quinoline series and its application to a synthesis of quindoline (Scheme **4**).



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**.

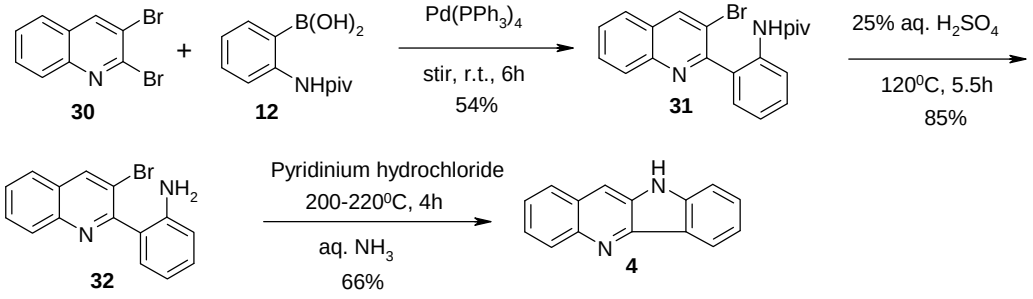


Scheme 5.

Pd(0)-catalyzed Stille coupling reaction of 2-tributylstannyl-*N*-protected indole **26** with 2-iodonitrobenzene **27** gave 2-(*o*-nitrophenyl)indole **28** which on reduction, *N*-formylation and *N*-methylation afforded the desired formamide **29**. Final ring closure was achieved by refluxing compound **29** in ethanol in presence of sulfuric acid to give isocryptolepine **2**.

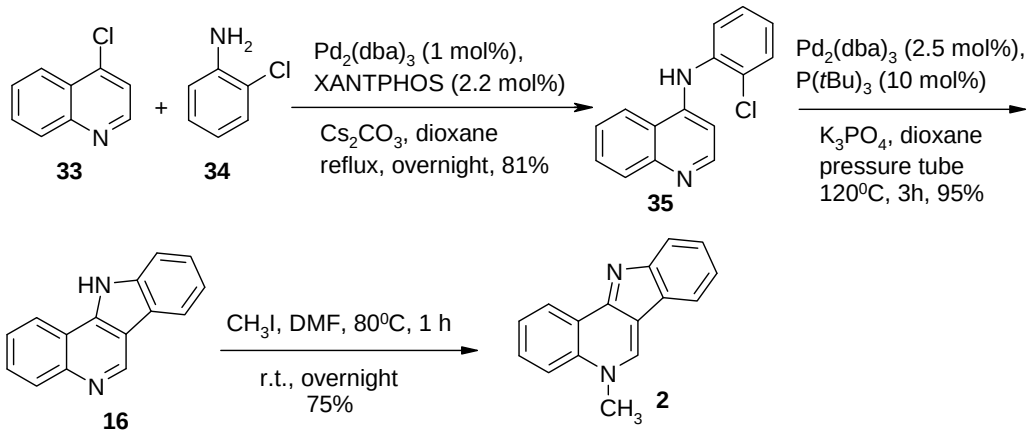
Csanyi *et al*. [54] accomplished the synthesis of quindoline **4** by a regioselective coupling reaction of 2,3-dibromoquinoline [55] **30** with **12** taking into consideration the fact that the α-heteroaryl halogen atom is more reactive than the β-halogen atom [56] to give *N*-pivaloyl-2-(2'-anilino)-3-bromoquinoline **31**. Hydrolysis of **31**

afforded the free amine **32** which underwent cyclization when heated at 200-220^{0}C in presence of pyridinium hydrochloride to give quindoline **4** (Scheme **6**).



Scheme 6.

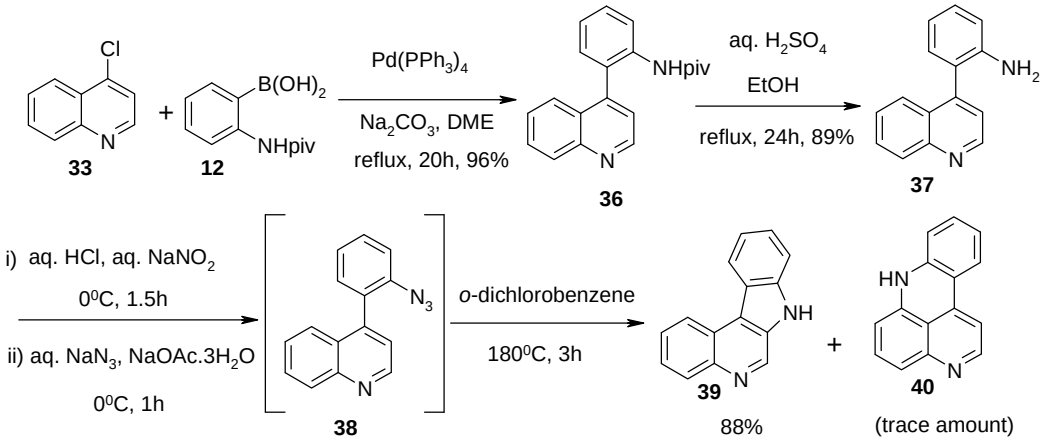
Jonckers *et al*. [57] described the Pd-catalyzed 'amination-arylation' approach for the synthesis of isocryptolepine (Scheme **7**).



Scheme 7.

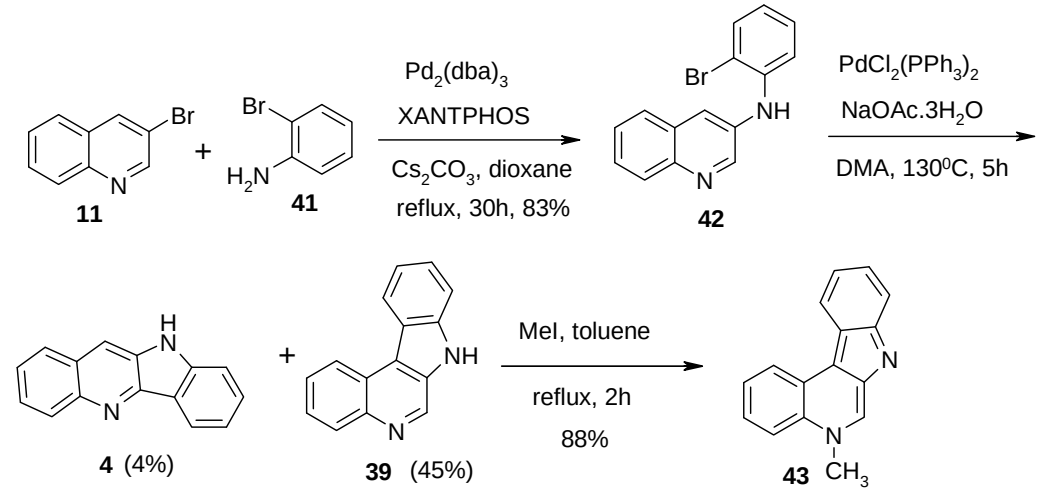
This approach consists of two consecutive Pd-catalyzed reactions – a selective Buchwald-Hartwig [58 – 63] reaction of 2-chloroaniline **34** with 4-chloroquinoline **33** followed by an intramolecular arylation [64 – 66] of the resulting compound **35** to afford the 11*H*-indolo[3,2-*c*]quinoline **16**.

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.

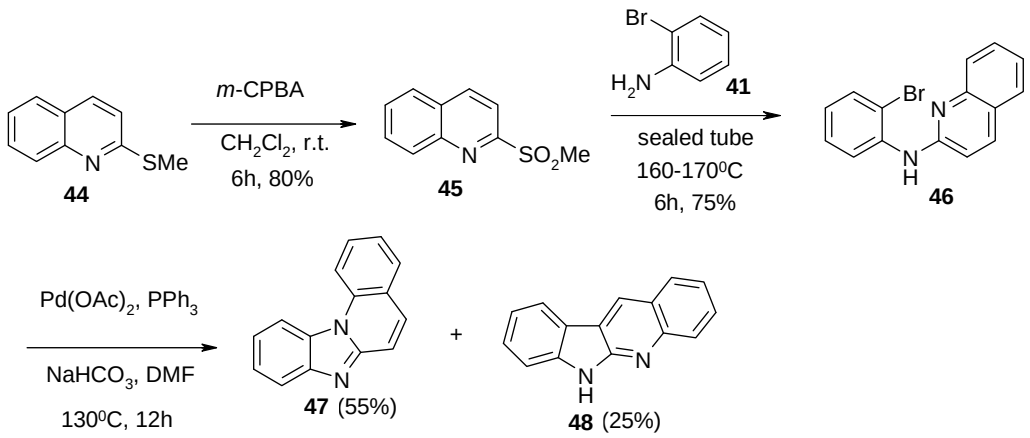
Suzuki reaction of **33** with **12** under Gronowitz conditions [68 – 69] yielded compound **36** which on hydrolysis provided amine **37**. Diazotization of the resulting amine **37** followed by introduction of azido group and then thermal decomposition of azide **38** in boiling *o*-dichlorobenzene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



Scheme 9.

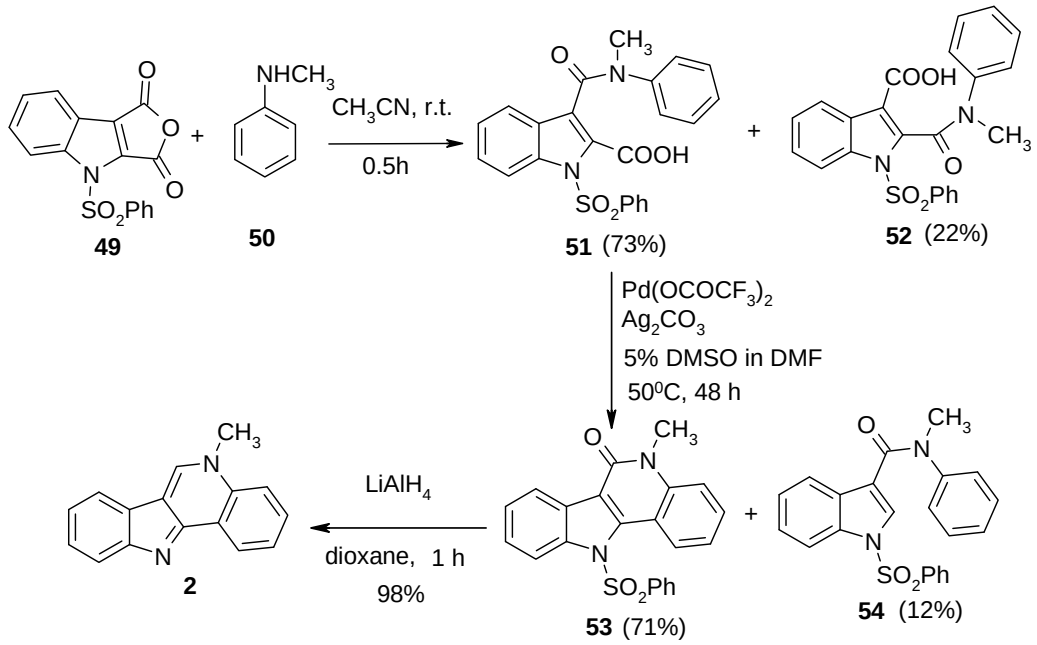
Regioselective amination of **11** with **41** in presence of Pd(0) catalyst gave compound **42** which on Heck-type cyclization yielded predominantly 7*H*-indolo[2,3-*c*]quinoline **39** and small amount of quindoline **4**. Selective *N*-methylation [70] of **39** using methyl iodide in refluxing toluene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

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



Scheme 10.

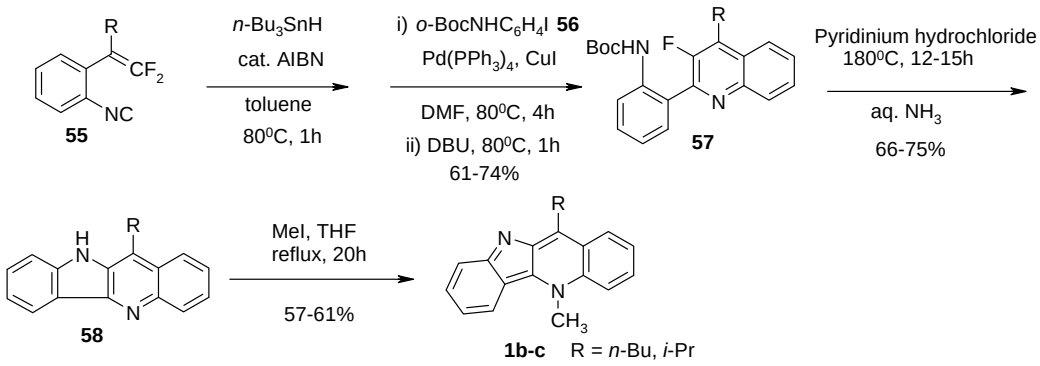
Miki and co-workers [72] have developed a simple approach towards isocryptolepine by applying Myers method [73 - 75] (Scheme **11**).



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 $Pd(OCOCF_3)_2$ and Ag_2CO_3 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 $LiAlH_4$ in hot dioxane.

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



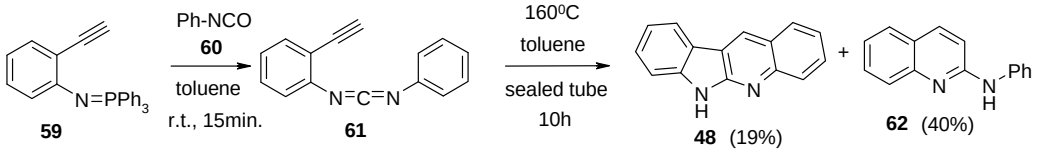
Scheme 12.

o-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-disustituted-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

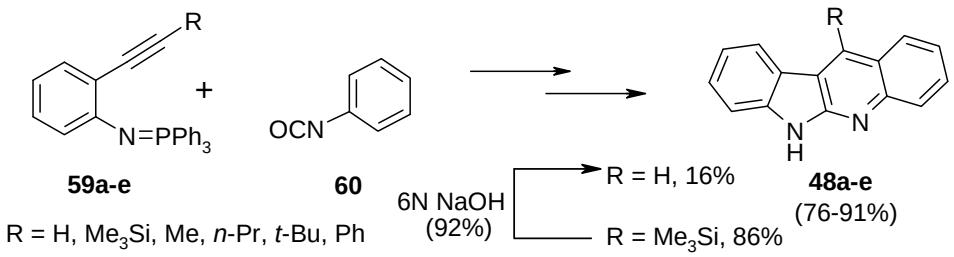
Aza-Wittig reaction [77 - 78] has become one of the important reactions in organic synthetic strategies directed towards the construction of acyclic and cyclic compounds as the reaction is mostly carried out in neutral conditions, in the absence of catalyst, generally at mild temperature and usually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

Alajarin and co-workers [79] described the synthesis of neocryptolepine using aza-Wittig reaction of the iminophosphorane **59** with phenyl isocyanate **60** to yield carbodiimide **61** and triphenylphosphine oxide which, without purification, was subjected to thermal treatment to give **48** and 2-anilinoquinoline **62** in 19% and 40% yield, respectively (Scheme **13**).



Scheme 13.

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

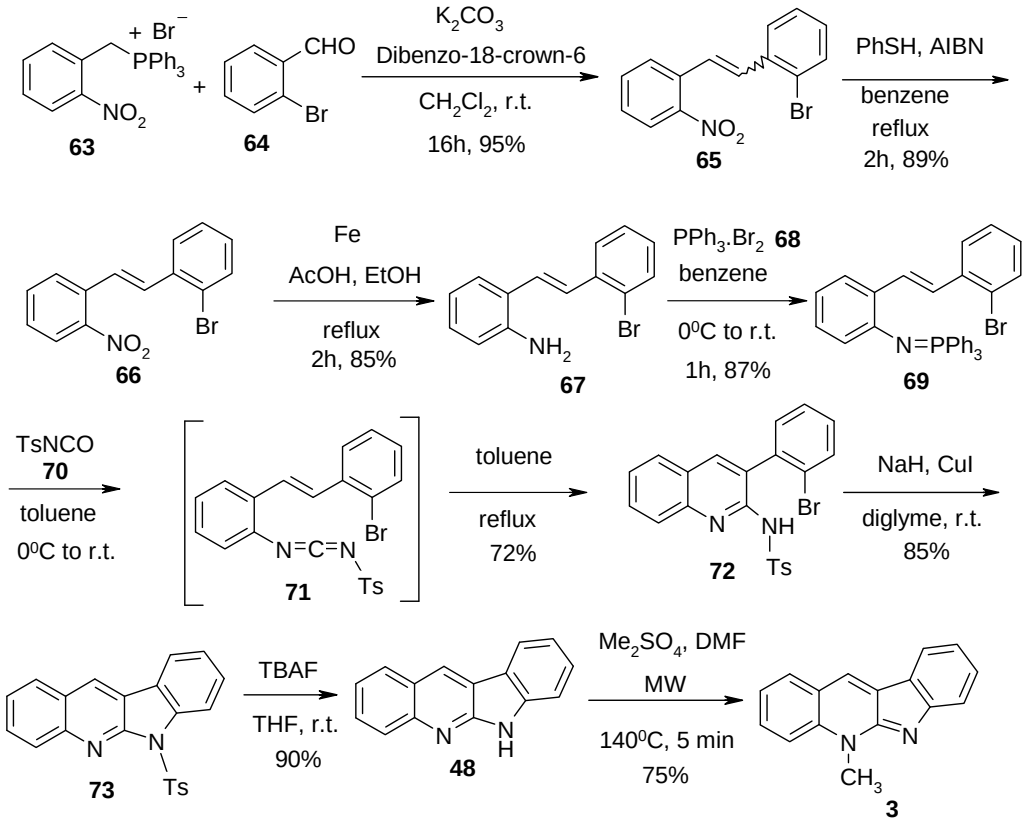


Scheme 14.

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 substitutents 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.

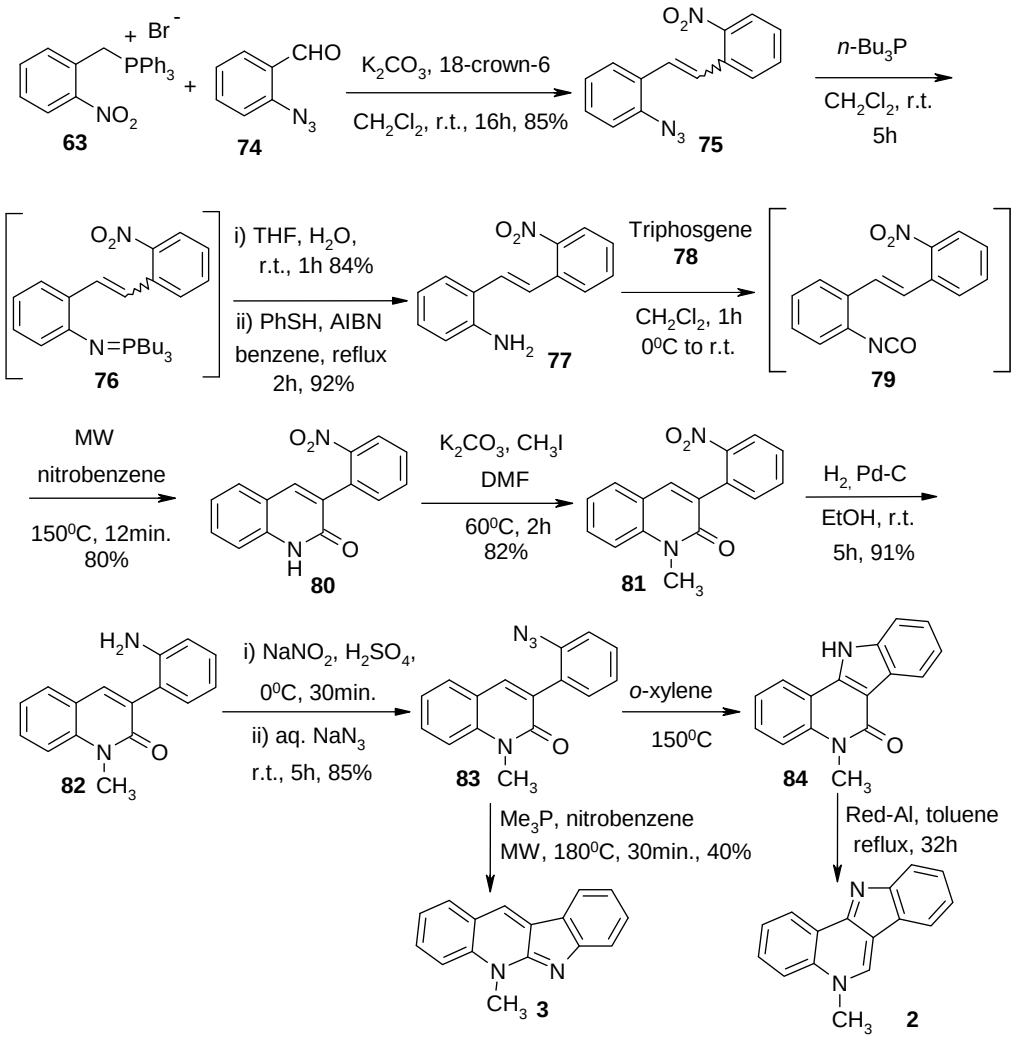
Molina and co-workers [81] reported the synthesis of neocryptolepine *via* Staudinger, aza-Wittig and electrocyclization reactions (Scheme **15**).



Scheme 15.

The iminophosphorane **69** was prepared by condensing 2-(nitrobenzyl)triphenylphosphonium bromide **63** with 2-bromobenzaldehyde **64** in the presence of K_2CO_3 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-(*o*-azidophenyl)quinoline-2-one **83** (Scheme **16**).



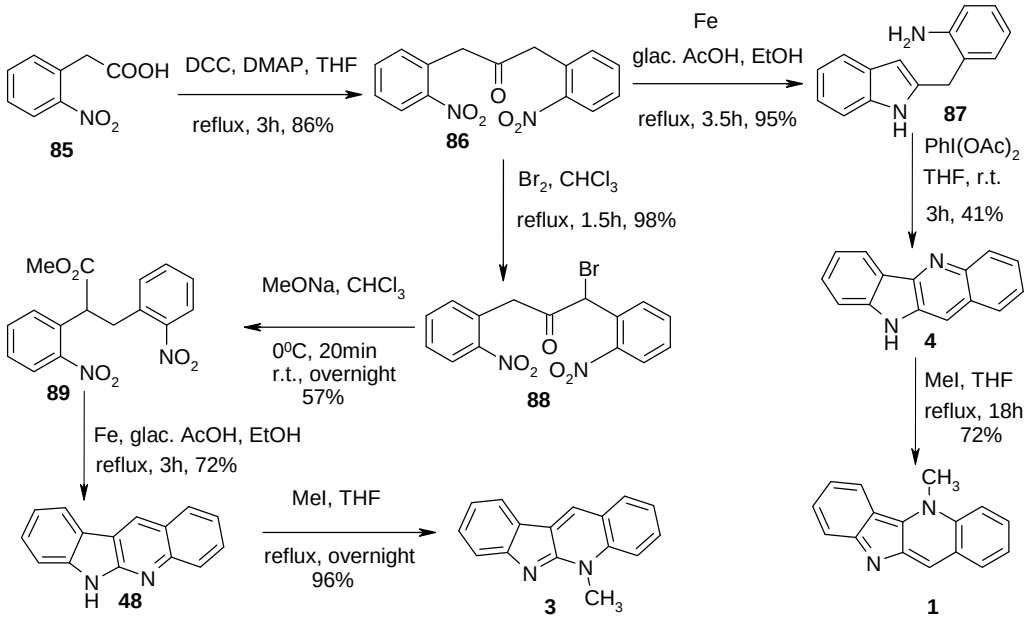
Scheme 16.

The key intermediate **83** was prepared using **63** and 2-azidobenzaldehyde **74** as the starting materials which underwent Wittig reaction in presence of K_2CO_3 to give compound **75**. Reaction of **75** with *n*-Bu_3P followed by hydrolysis of the resultant iminophosphorane **76** and *Z*→*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. Trasition-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.

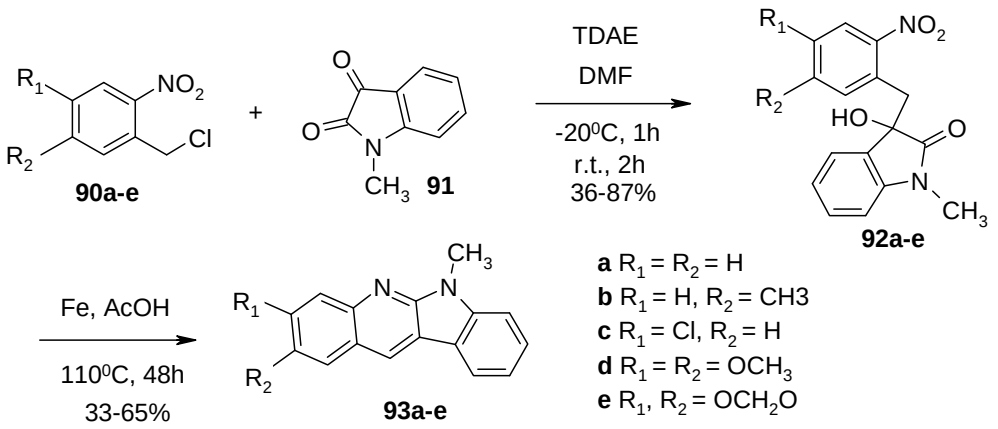
Ho and co-workers [84] reported the synthesis of cryptolepine and neocryptolepine from common intermediate 1,3-bis-(2-nitrophenyl)propan-2-one **86** (Scheme **17**).



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.

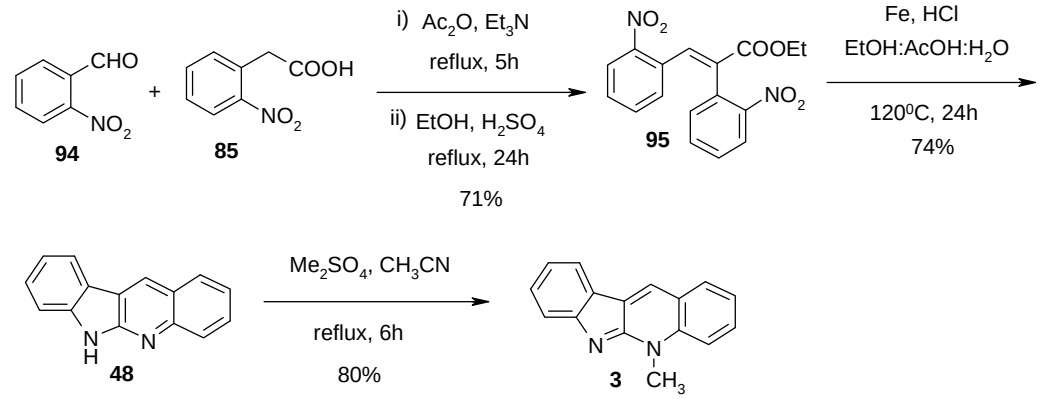
Amiri-Attou *et al*. [85] described the synthesis of analogues of neocryptolepine *via* one-pot reduction-cyclization-dehydration reaction (Scheme **18**).



Scheme 18.

Reaction of *o*-nitrobenzyl chlorides **90a-e** with 1-methylisatin **91** in the presence of tetrakis(dimethyl-amino)ethylene (TDAE) [86 – 87] afforded the corresponding α-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**.

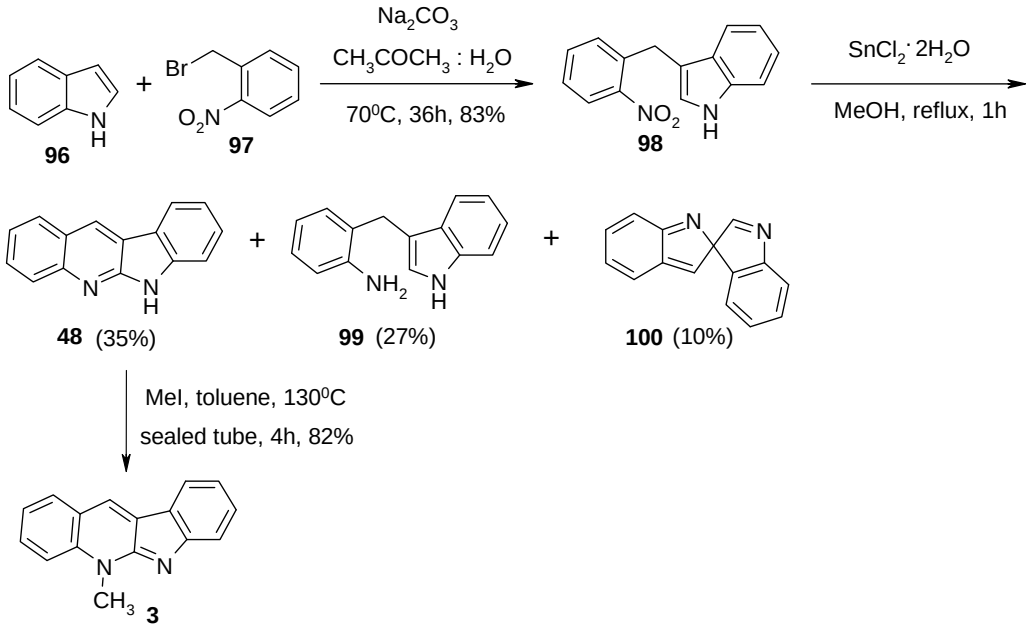
We reported [88] the synthesis of neocryptolepine using the Perkin reaction and double reduction – double cyclization as the main steps (Scheme **19**).



Scheme 19.

Condensation of 2-nitrobenzaldehyde **94** with 2-nitrophenyl acetic acid **85** in refluxing acetic anhydride in presence of Et_3N gave the α,β-unsaturated acid which on esterification afforded the required ester **95** in good yield. Reduction with 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**)



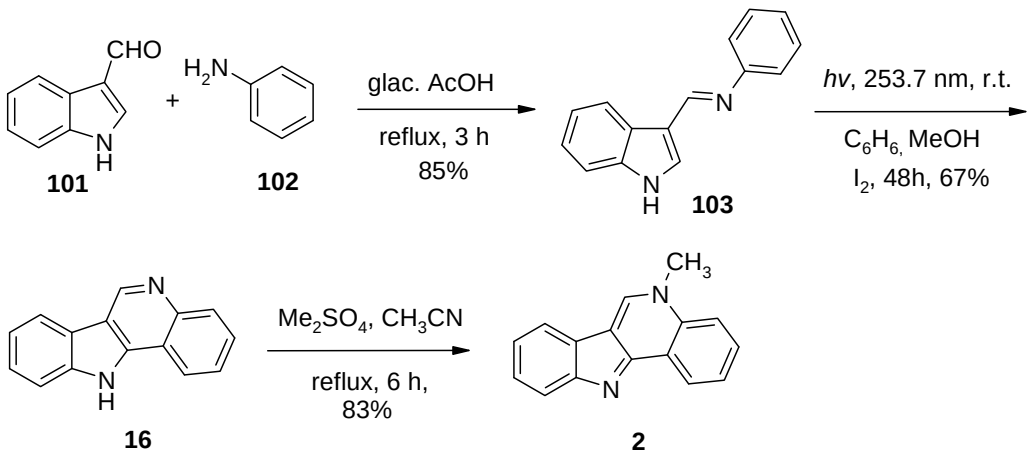
Scheme 20.

Alkylation of indole with 2-nitrobenzyl bromide **97** yielded compound **98** which, on treatment with $SnCl_2 \cdot 2H_2O$ 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.

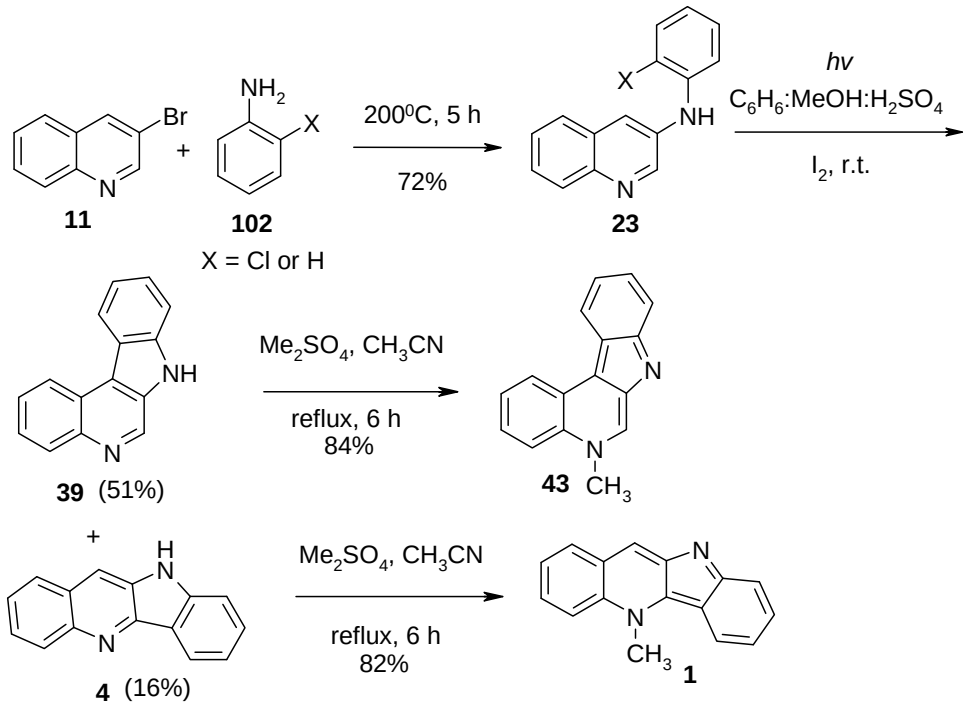
Kumar *et al*. [91] described the synthesis of isocryptolepine using photo-cyclization as the main step (Scheme **21**)



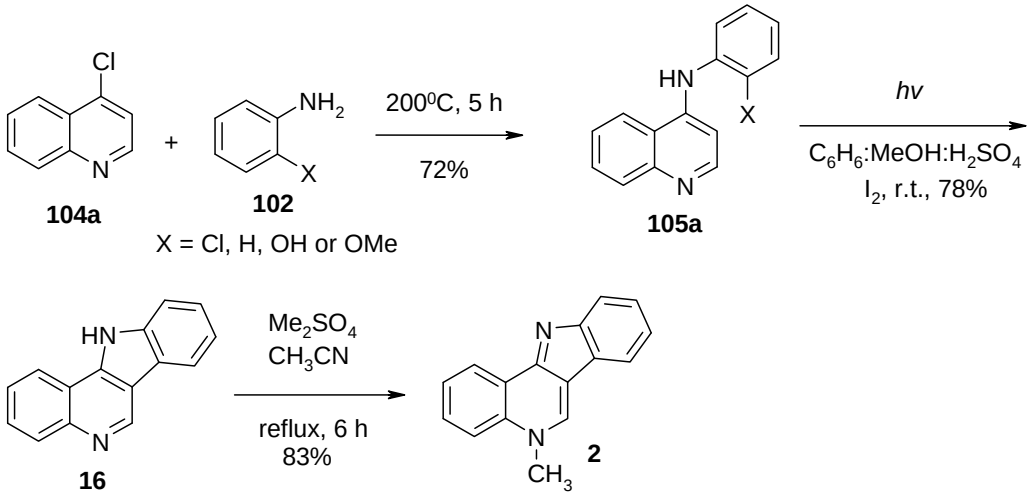
Scheme 21.

Schiff's base **103**, obtained by heating indole-3-carboxaldehyde **101** with aniline **102** in acetic acid, when irradiated at 253.7nm underwent cyclization to give 11*H*-indolo[3,2-*c*]quinoline **16** *via* initial photo-isomerization of the Schiff's base **103** from *E*- to *Z*-isomer followed by conrotatory ring closure and subsequent oxidation by iodine.

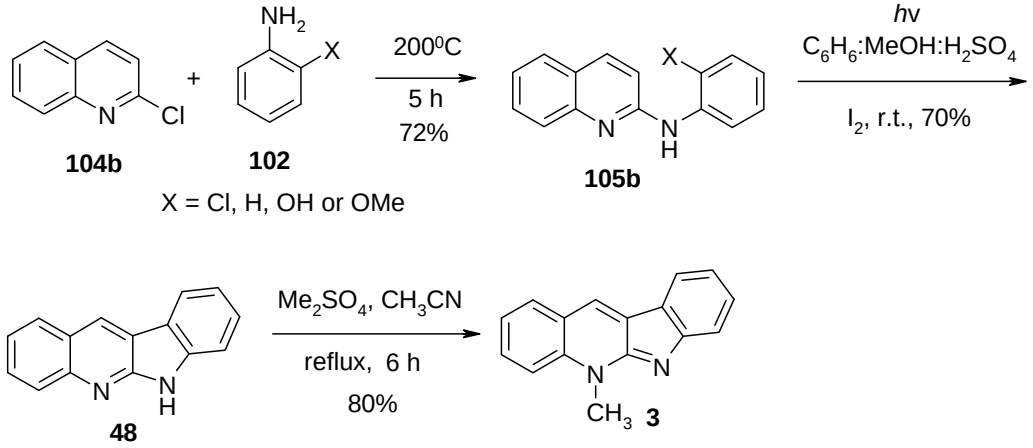
Dhanabal *et al*. [92] reported the synthesis of cryptolepine **1**, isocryptolepine **2** and neocryptolepine **3** *via* heteroatom directed photoannulation technique (Scheme **22** - **24**).



Scheme 22.



Scheme 23.

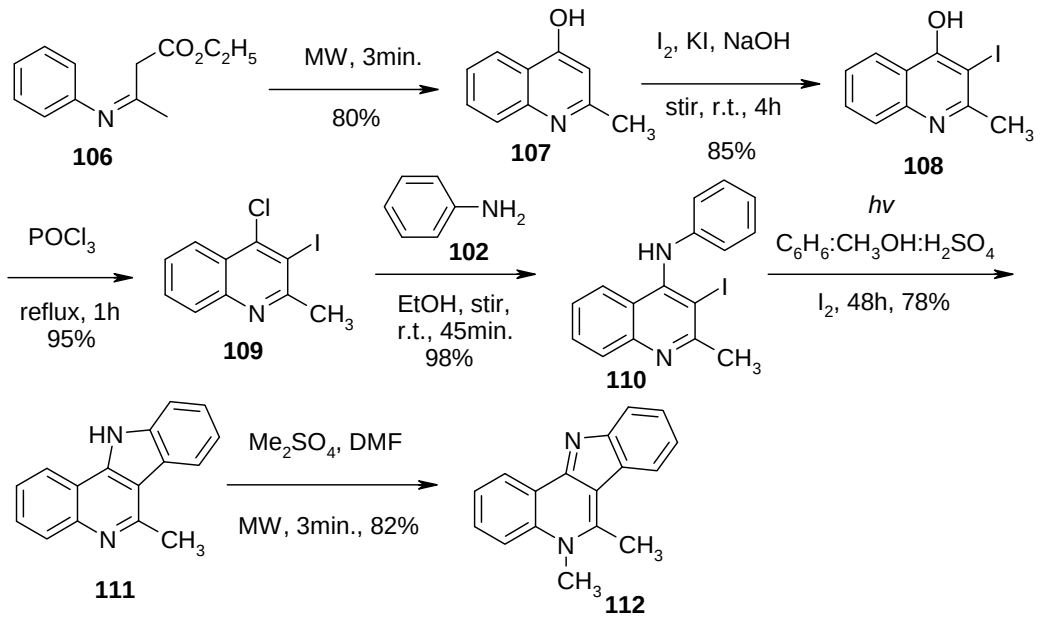


Scheme 24.

Nucleophilic substitution of 3-bromoquinoline **11** with aniline **102** was achieved by heating at 200^{0}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**).



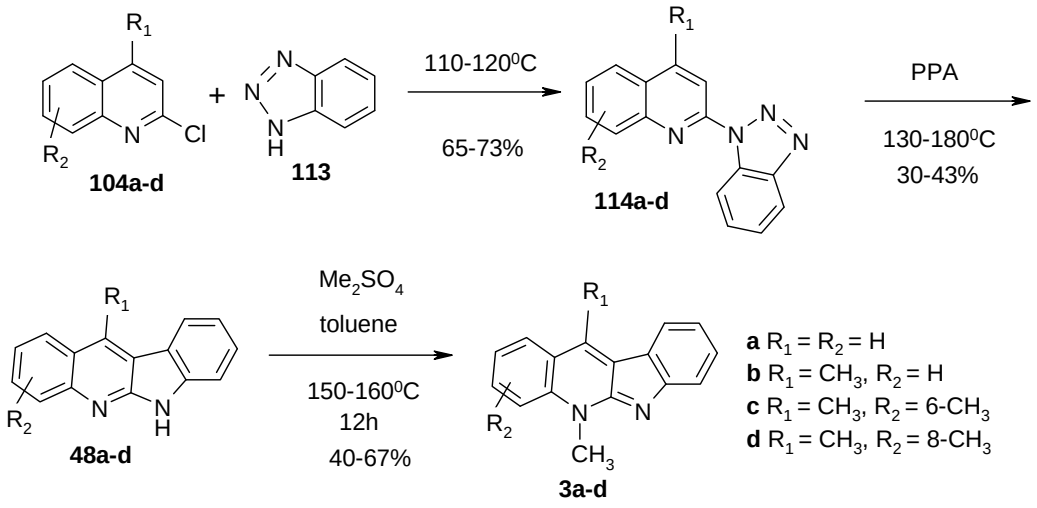
Scheme 25.

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 $POCl_3$ 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.

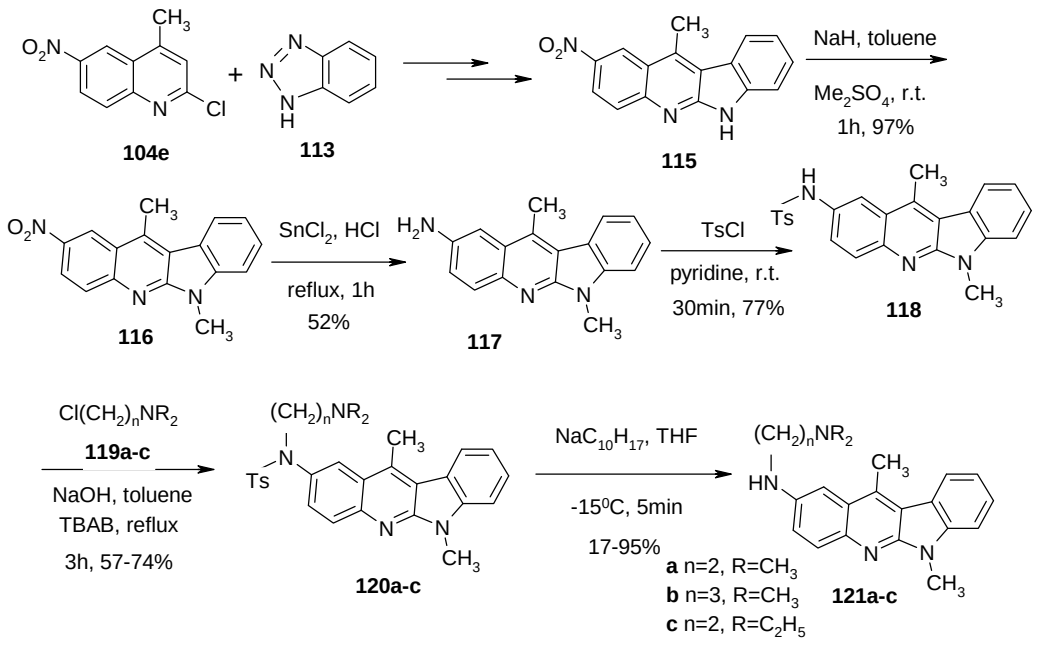
Peczynska-Czoch and co-workers [36] reported the synthesis of various derivatives of neocryptolepines via Graebe-Ullmann reaction (Scheme **26**) and these were evaluated for their in vitro antimicrobial and cytotoxic activities.



Scheme 26.

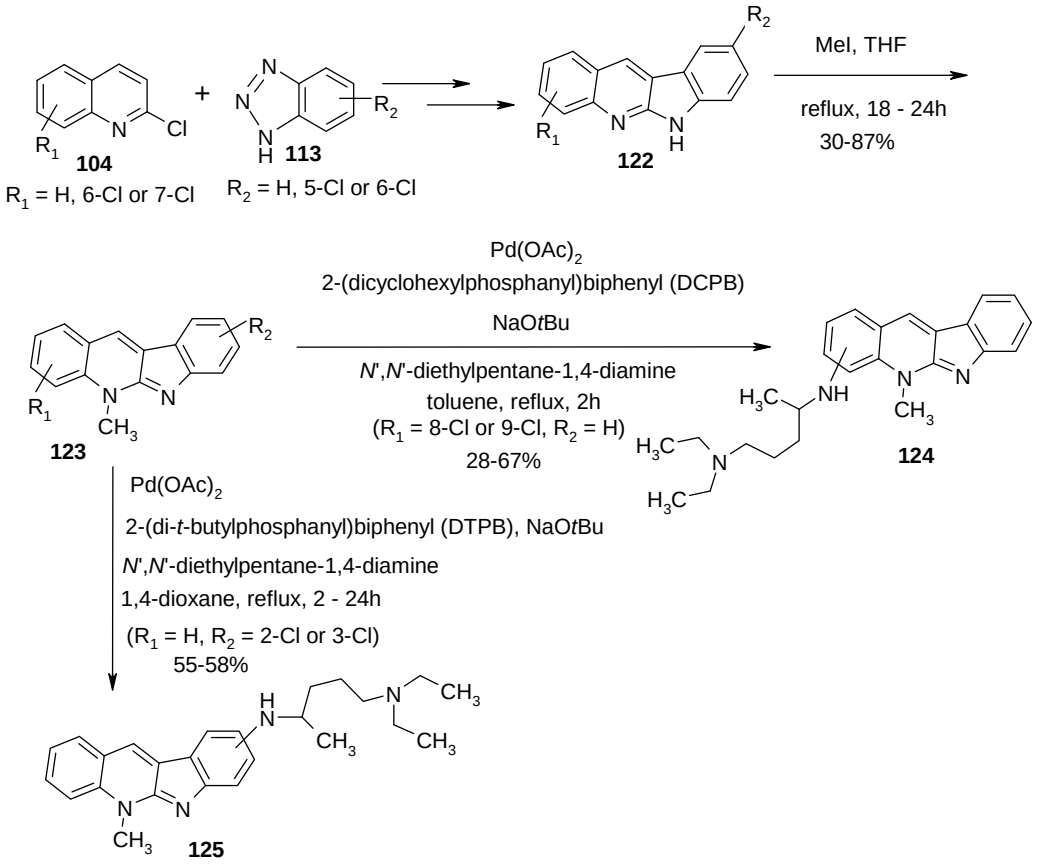
Triazoles **114a-d** were prepared by heating the corresponding chloroquinolines **104a-d** with benzotriazoles **113** at 110-120^{0}C. Decomposition of the triazoles **114a-d** by heating at 130-180^{0}C in presence of PPA yielded the respective indoloquinolines **48a-d**, which on methylation using DMS afforded the neocryptolepines **3a-d**.

Godlewska *et al*. [97] reported the synthesis of nitro-substituted 6*H*-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 $SnCl_2$, 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.



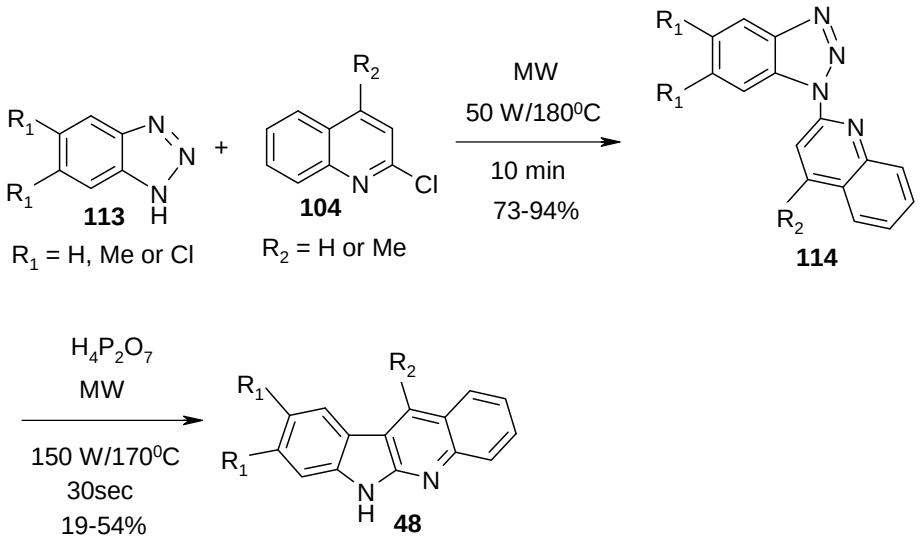
Scheme 27.

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.



Scheme 28.

Vera-Luque *et al*. [99] achieved the synthesis of 6*H*-indolo[2,3-*b*]quinolines *via* modified Graebe-Ullmann reaction under microwave irradiation (Scheme **29**).

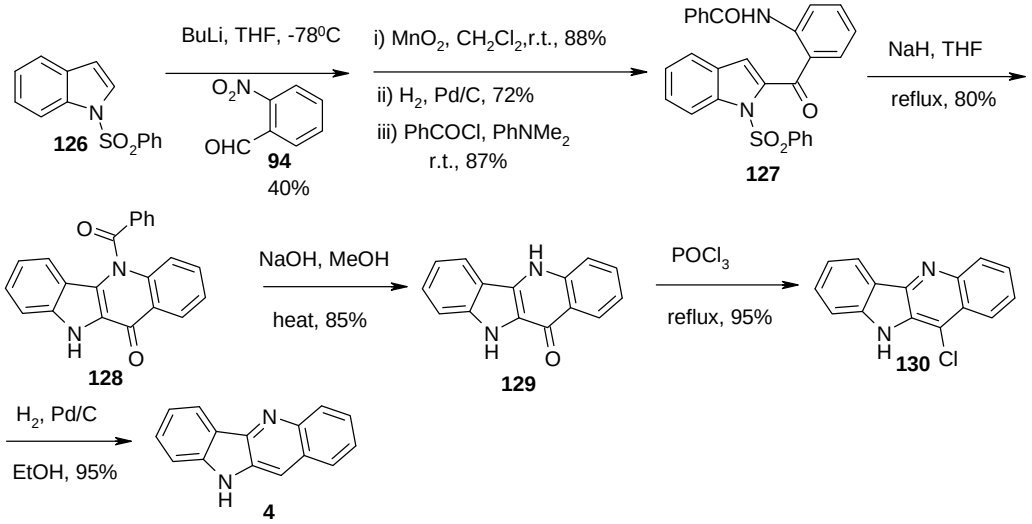


Scheme 29.

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 6*H*-indolo[2,3-*b*]quinolines **48a-d**.

1.6. Other miscellaneous methods

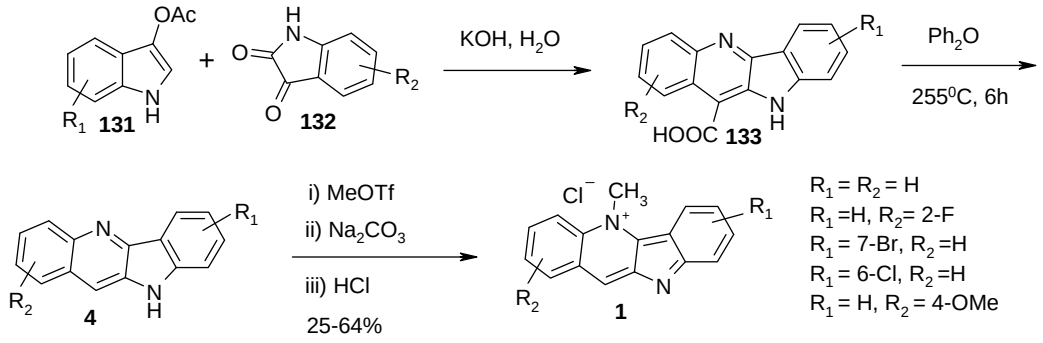
Cooper *et al*. [100] described the synthesis of quindoline utilizing the intramolecular β-nucleophilic substitution as the main step (Scheme **30**).



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*-benzoylation using benzoylchloride. 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**).

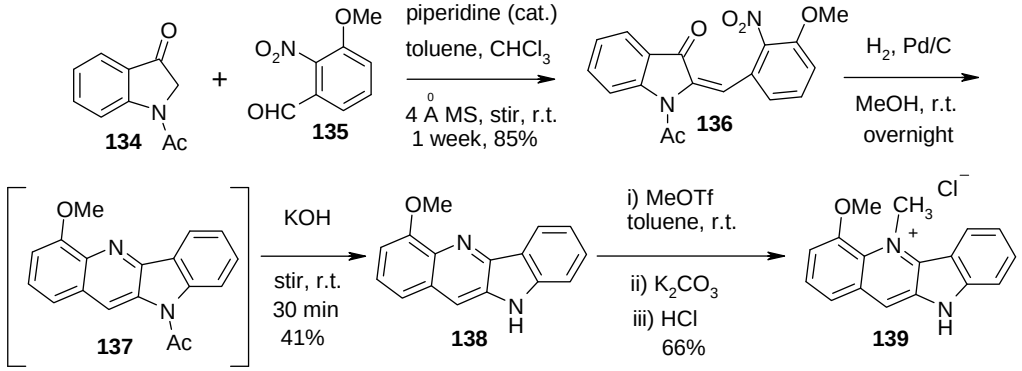


Scheme 31.

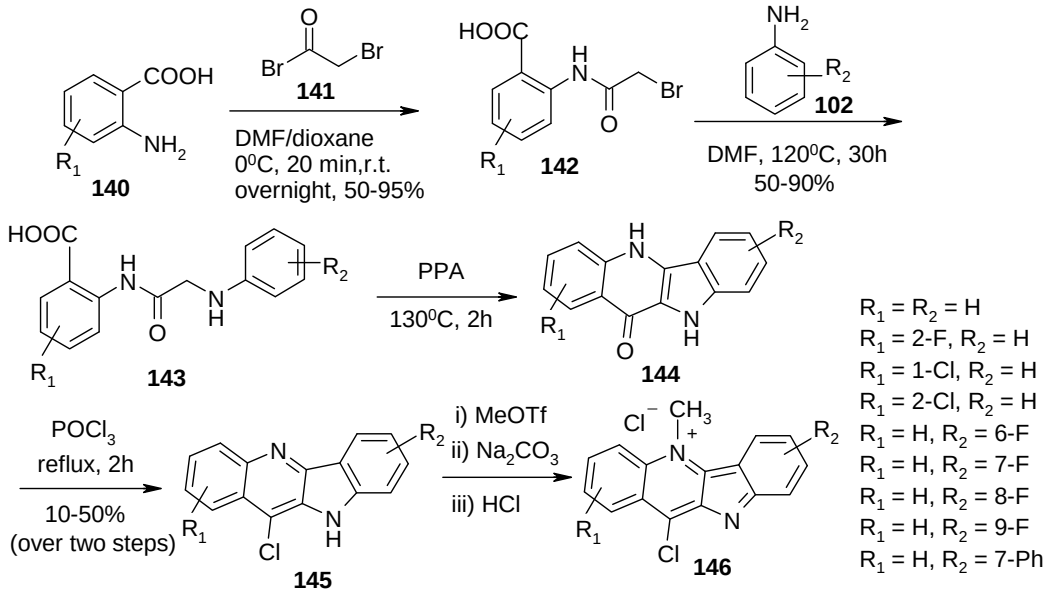
Reaction of substituted indolyl acetates **131** with isatin derivatives **132** gave the respective quindoline carboxylic acids **133** which were decarboxylated by heating at 255^0C in Ph_2O and the subsequent quindolines **4** were alkylated using the method of Fichter and Boehringer [24] to give 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 32.

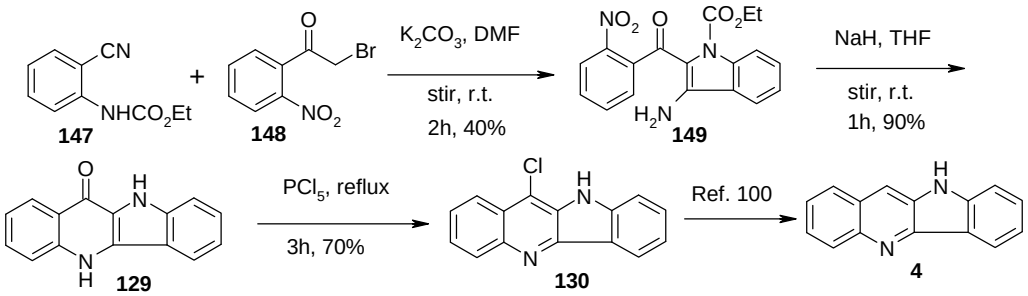


Scheme 33.

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 $POCl_3$ 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**).

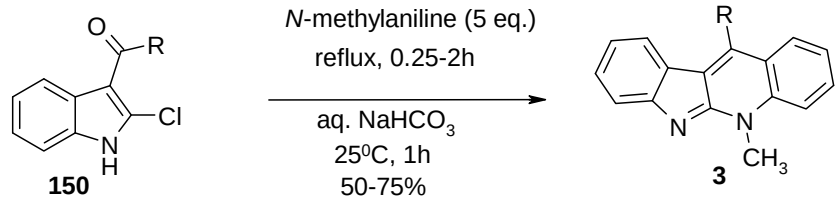
Radl and co-workers [106] reported the synthesis of quindoline **4** *via* intermediate **149** by treating anthranilonitrilo derivative **147** with phenacyl bromide **148** in presence of K_2CO_3 (Scheme **34**).



Scheme 34.

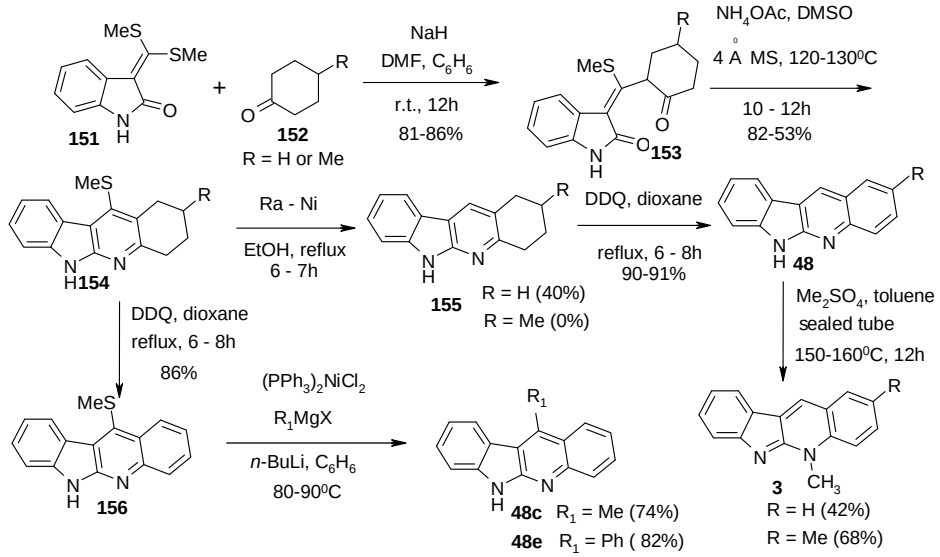
Nucleophilic denitrocyclization [107] of **149** with NaH gave the required tetracyclic compound **129** which on treatment with PCl_5 afforded the corresponding chloro compound **130** in 70% yield. The compound **129** may have formed by initial intramolecular 1,4-addition, followed by expulsion of 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**).



Scheme 35.

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

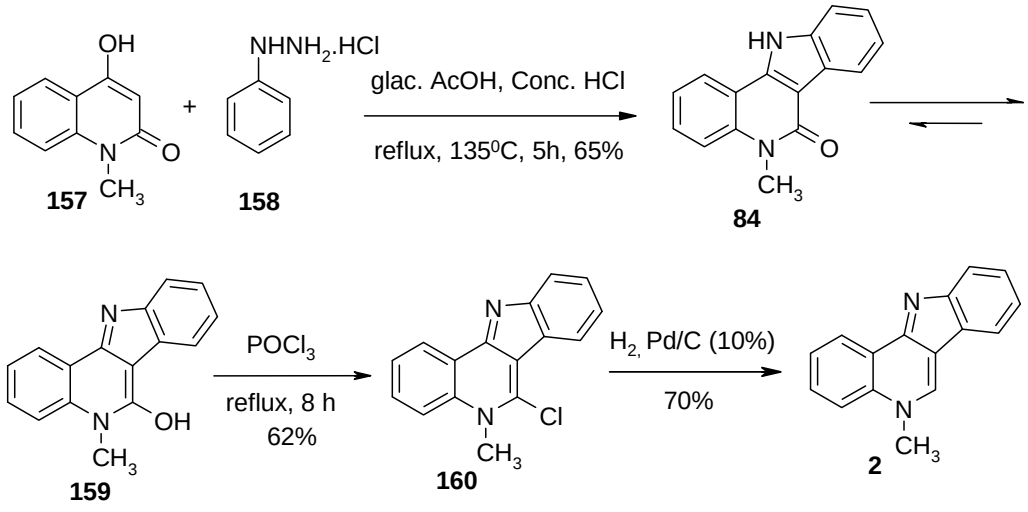


Scheme 36.

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 6*H*-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.

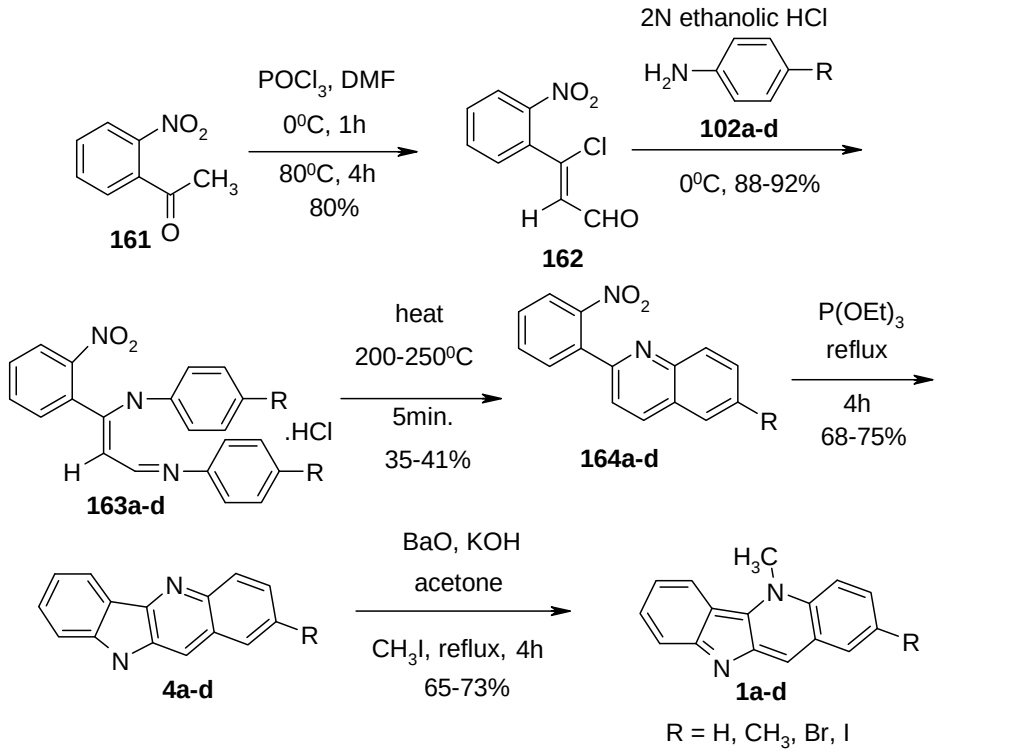
Dhanabal *et al*. [110] described the synthesis of isocryptolepine using a Fischer indole cyclization as the key step (Scheme **37**).



Scheme 37.

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 $POCl_3$ afforded the corresponding chloride **160** which on catalytic hydrogenation yielded isocryptolepine **2**.

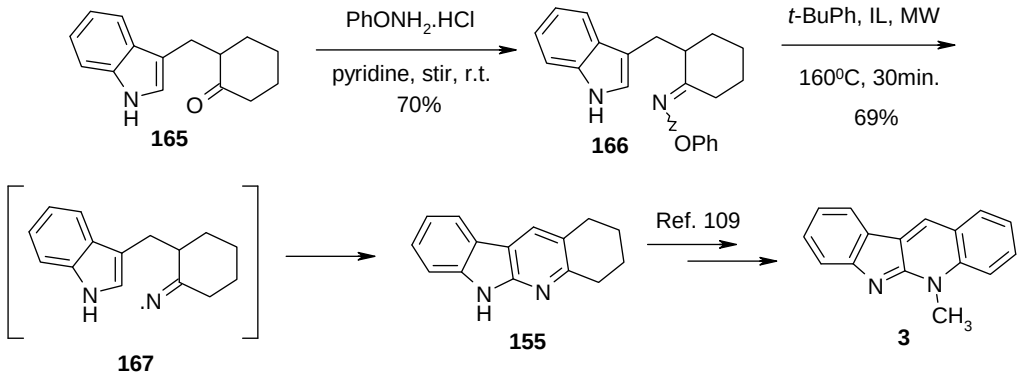
Dutta *et al*. [111] developed a general method for the synthesis of various 2-substituted cryptolepines which involves regioselective thermal cyclization and reductive cyclization using triethyl phosphite as the key steps (Scheme **38**).



Scheme 38.

2-Nitroacetophenone **161** underwent Vilsmeier-Haack reaction when treated with $POCl_3$ 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^{0}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^{0}C.

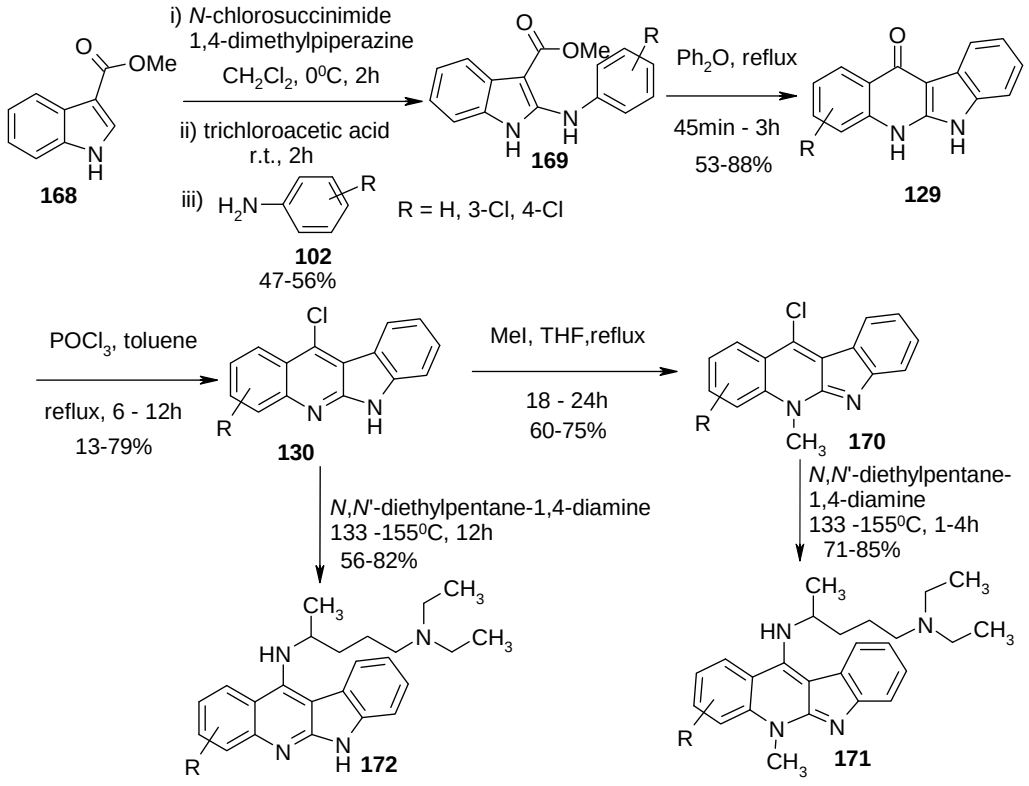
Portela-Cubillo *et al*. [112] described the microwave-mediated formal synthesis of neocryptolepine *via* radical intermediate (Scheme **39**).



Scheme 39.

The indolo-ketone **165** was treated with *O*-phenylhydroxylamine hydrochloride and the resultant *O*-phenyl oxime ether **166** was subjected to microwave irridiation in ionic liquid emimPF_6 to give tetrahydroindolo[2,3-*b*]quinoline **155** in 69% yield.

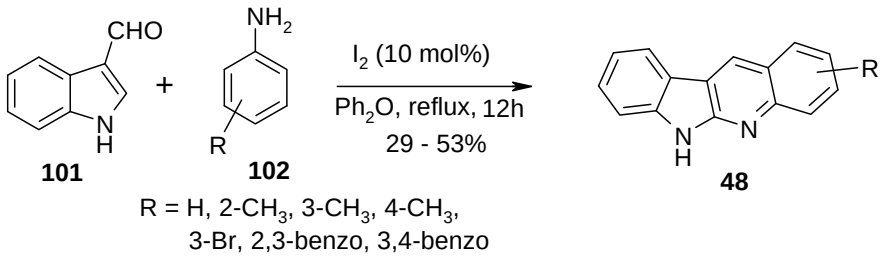
Sayed *et al*. [98] reported the synthesis of aminoalkylamino-substituted neocryptolepines using the procedure of Bergman and co-workers [113] (Scheme **40**) and evaluated for their in *vitro* antiplasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity on a human 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 Ph_2O to give compound **129** [113] and then converted to 11-chloro-6*H*-indolo[2,3-*b*]quinolines **130** using $POCl_3$. Methylation using methyl iodide and subsequent amination *via* S_NAr reaction yielded the corresponding aminoalkylamino-substituted neocryptolepine derivatives.

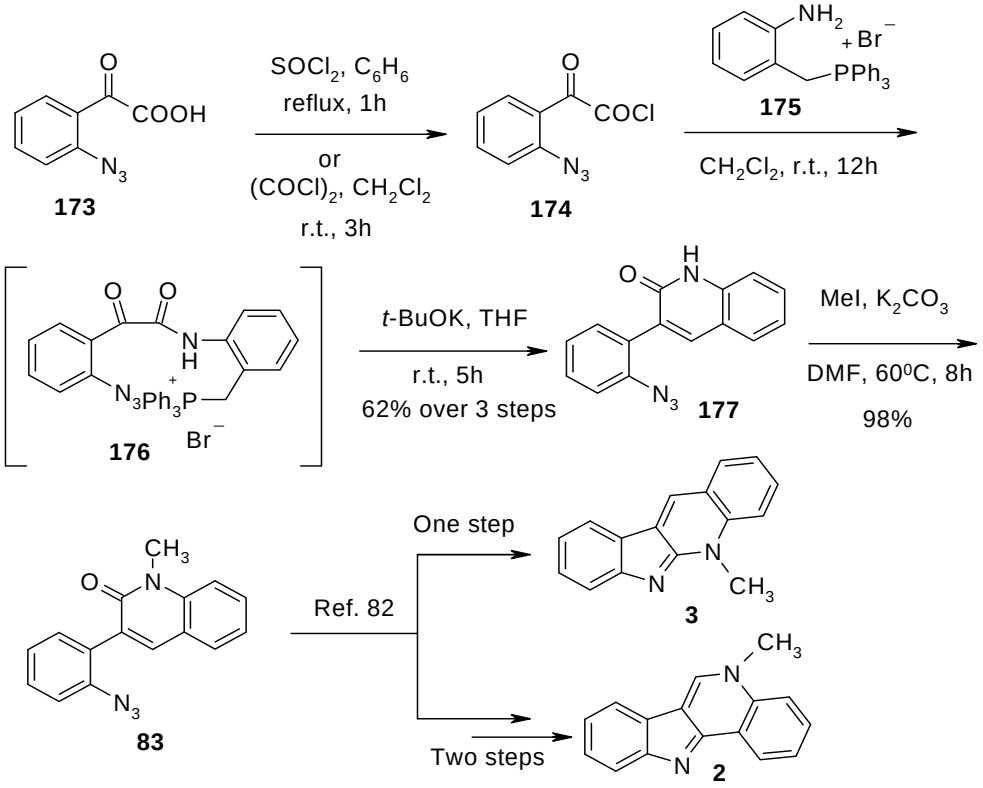
Recently, we reported [114] the synthesis of series of novel 6*H*-indolo[2,3-*b*]quinolines using iodine as a catalyst in one-pot *via* Schiff's base intermediate (Scheme **41**).



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.

ACKNOWLEDGMENTS

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