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Neocryptolepine (Cryprotackieine), A Unique Bioactive Natural Product: Isolation, Synthesis, and Profile of Its Biological Activity

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The widely varying different approaches to the total synthesis of the indoloquinoline alkaloid neocryptolepine are discussed. Aspects relating to the isolation of the natural product from *Cryptolepis sanguinolenta*, as well as its performance in various biological tests and spectroscopic studies involving the natural product, are also reviewed.

Introduction

Natural products are still one of the most relevant sources of lead structures and, because of their vast structural diversity, they represent a permanent source of stimulus and inspiration for the development of pharmaceutically useful small organic synthetic molecules.[1] Our current pharmaceutical arsenal is abundant in natural products, their analogues, and their derivatives.

Furthermore, half of the new chemical entities approved for their use in human medicine during the last quarter of century have some relationship or connection to a natural product. Accordingly, finding new drug candidates requires both the screening of extracts in search of the presence of new compounds and a thorough investigation of the useful biological activities within the bioactivity profiles of these compounds.

Among the known producers of pharmacologically relevant small-molecule natural products, microorganisms represent a rich source of biologically active metabolites.[2] However, plants still remain among the most important resources for the discovery of new drugs.

The potential of natural compounds as a source of new drugs is clearly illustrated by the development of chloroquine (**1**), primaquine (**2**), mepacrine (**3**), and mefloquine (**4**) as quinine (**5**) analogues (Figure 1), following centuries of use of the Cinchona alkaloid as an antimalarial.[3]

Another example is the discovery of artemisinin (**6**) as an antimalaric (Figure 2), the resulting development of its analogues dihydroartemisinin (**7**), artemether (**8**), arteether (**9**), and artesunate (**10**) as more suitable antimalarial agents, and the study of different endoperoxides inspired by its singular motif for their ability to act as antimalarics. Moreover, the importance of artemisinin has encouraged the investigation of other plants, bacteria, fungi, and even marine organisms as a source of new antimalarial lead structures and other antiparasitic agents.[4]

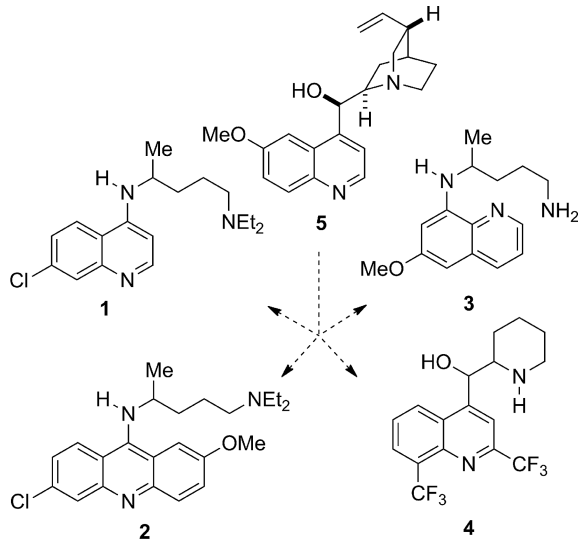

Figure 1. Chemical structures of quinine and structurally related antimalarial agents.

The isolation of bioactive compounds from plants used in traditional medicine as drug leads remains one of the most straightforward and effective strategies in the search for new drugs.[5] Plant alkaloids employed in folk medicine have contributed greatly over the centuries to curing deadly diseases; later, they became the focus of attention for the discovery of new molecules that proved to be indispensable for fighting disease, both simply as therapeutic agents and more sophisticatedly as lead structures for new pharmaceuticals.

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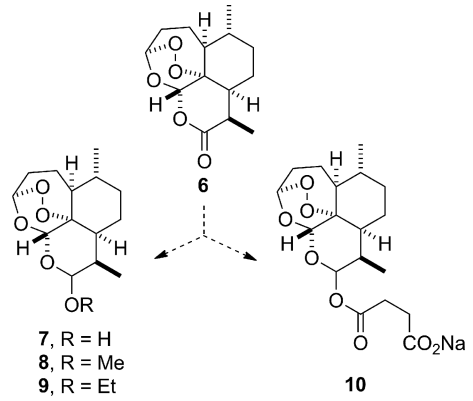

Figure 2. Chemical structures of artemisinin and structurally related antimalarial agents.

In more recent times, they have also helped in unveiling the most intricate plant biochemical pathways and in elucidating pharmacological modes of action. In turn, this accumulated body of knowledge allowed the development of the modern pharmaceutical industry.[6]

The roots of the shrub *Cryptolepis sanguinolenta*, which grows in West and Central Africa,[7] and is locally known as nibima, kadze, and gangamau, have long been employed by Ghanian traditional healers as a medicinal plant material for use in therapy against various fevers, including malaria. They proved to be a rich source of indoloquinoline alkaloids.

Cryptolepine, the first example of these alkaloids, was isolated in 1951.[8] For a long time, it was regarded as the paradigm example of an indoloquinoline alkaloid; however, further developments were hindered by different studies that established that cryptolepine is too toxic. Therefore, more recently, attention has become focused on neocryptolepine, which is now considered a promising naturally occurring indoloquinoline alkaloid with interesting properties.

Here we review aspects of the isolation of neocryptolepine (**11**, Figure 3, below) and diverse approaches directed towards its synthesis. Results of different tests designed to explore the bioactivity profile of the natural product, its analogues, and its derivatives, as well as spectroscopic studies involving the natural product, are also discussed.

2. Naturally Occurring Indoloquinolines – Isolation of Neocryptolepine

The indoloquinolines are a family of relatively rare and unusual alkaloids characterized by possessing two fused rings: an indole and a quinoline. They are found almost exclusively in the climbing vine *Cryptolepis sanguinolenta* (Lindl.) Schlachter (Periplocaceae).[9] However, scattered reports disclose that indoloquinolines have also been isolated

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from other sources, such as *Cryptolepis triangularis* N. E. Br., *Sida acuta* Burm. (Malvaceae), *Microphilis guyanensis* (A. DC) Pierre (Sapotaceae), and *Genipa Americana* L. (Rubiaceae).[10]

To date, 13 known alkaloids have been isolated from *Cryptolepis sanguinolenta*; they include neocryptolepine (cryptotackieine, **11**),[11,11a] cryptolepine (**12**),[7,11b,11c] quindoline (**13**),[12] quindolinone (**14**),[13] cryptosanguinolentine (isocryptolepine, **15**),[14] 11-isopropylcryptolepine (**16**),[15] biscryptolepine (**17**),[16] cryptoquindoline (**18**),[17] cryptospirolepine (**19**),[18] cryptolepicarboline (**20**),[19] 11-hydroxycryptolepine (**21**),[17,20] cryptomisrine (**22**),[21] and quindolinocryptotackieine (**23**),[22] as shown in Figure 3.

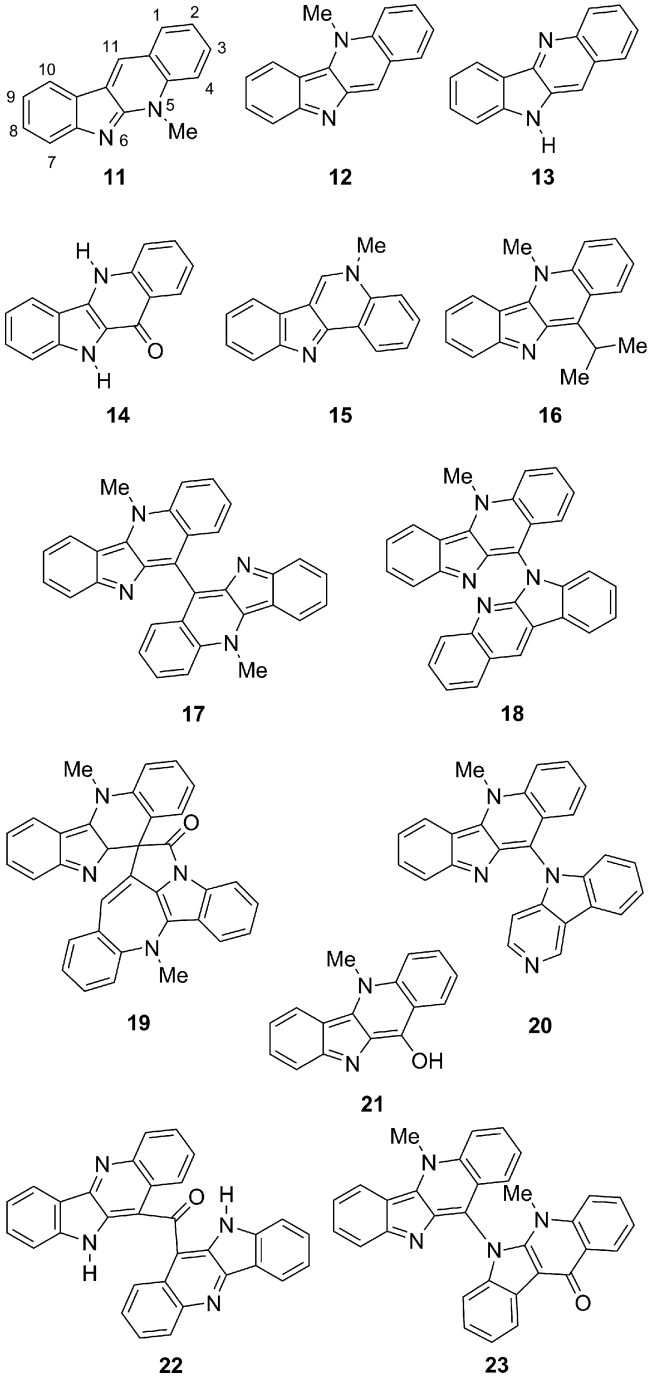


Figure 3. Chemical structures of the naturally occurring indoloquinoline alkaloids: neocryptolepine (cryptotackieine, **11**), cryprolepine (**12**), quindoline (**13**), quindolinone (**14**), biscryptolepine (**17**), cryptoquindoline (**18**), cryptosanguinolentine (isocryptolepine, **15**), 11-isopropylcryptolepine (**16**), cryptospirolepine (**19**), cryptolepicarboline (**20**), 11-hydroxycryptolepine (cryptolepinone, **21**), cryptomisrine (**22**), and quindolinocryptotackieine (**23**).

Decoctions of *Cryptolepis sanguinolenta* have been used in traditional West and Central African medicine against malaria, jaundice, hypertension, hepatitis, and inflammation.[23]

Neocryptolepine was first reported as a natural product in 1996. Its isolation, in small amounts as an amorphous yellowish powder, from the bark of the roots of *Cryptolepis sanguinolenta* was performed simultaneously and independently by the groups of Schiff and Pieters. The Schiff group termed the new alkaloid cryptotakieine.[11a] This is not the sole case of dual naming of the same alkaloid isolated from this plant.[21] The isolation of the natural product by Schiff and co-workers required repeated chromatographic separations (through alumina) of the alkaloid fraction of an ethanolic extract of the roots of the plant, followed by preparative RP-HPLC separations. This complex process afforded only 0.7 mg of pure alkaloid.

On the other hand, the isolation by the group of Pieters was performed by column chromatography on silica gel followed by preparative TLC, yielding 13 mg of pure compound. In both cases, the structure of **11** was elucidated by use of 1D- and 2D-NMR spectroscopy,[16] defining the natural product as an *N*-methylated indolo[3,2-*b*]quinoline, isomeric with cryptolepine and isocryptolepine.[14]

Interestingly enough, *N*-methylation and subsequent deprotonation of quinindoline (norcryptotackieine, **24**) with Me_2SO_4 in nitrobenzene at 160 °C for 1 h, followed by treatment with aqueous NaOH to yield **11**, had already been described before the isolation of neocryptolepine from natural sources.[24]

The 6*H*-indolo[2,3-*b*]quinoline **24** (norcryptotackieine, quinindoline, see Scheme 1) is also a natural product, isolated from the leaves of *Justicia betonica*.[25] It shares many biological properties with neocryptolepine, including the ability to interact with DNA as an intercalator and to inhibit topoisomerase II activity.

3. Total Syntheses of Neocryptolepine

The interest of chemists in the synthesis of the 6*H*-indolo[2,3-*b*]quinoline skeleton and related structures preceded the isolation of neocryptolepine by many decades.[26] Two preparations of this product were recorded before its isolation from natural sources.

Analysis of the literature shows that three different approaches have been employed for the synthesis of the basic 6*H*-indolo[2,3-*b*]quinoline framework and the natural product itself. In the first case, the indoloquinoline skeleton is built from an indole derivative as starting material, upon which the quinoline moiety is formed. The second strategy

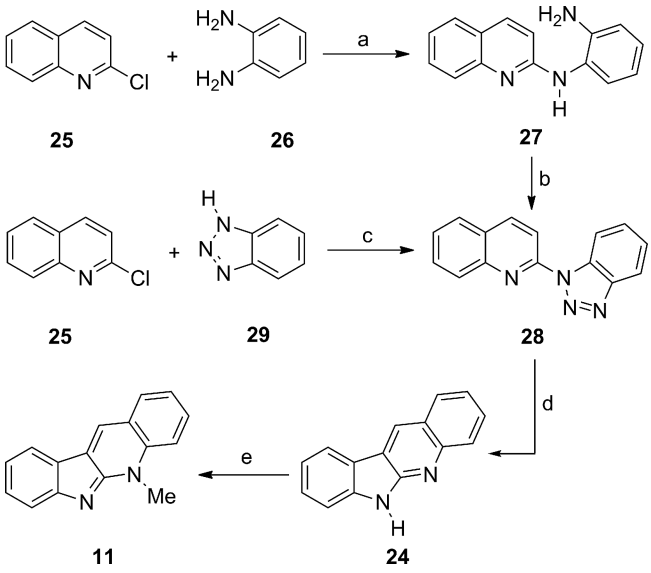
involves starting with a quinoline derivative, and then building up the indole motif. In the third approach, simple benzenoids are employed as starting materials; the indole and quinoline heterocyclic moieties are then constructed through consecutive cyclization stages.

3.1. Syntheses of Neocryptolepine Before Its Isolation from Natural Sources

The first synthesis of the 6*H*-indolo[2,3-*b*]quinoline skeleton was performed in 1897 by Gabriel and Eschenbach,[27] during the process of reducing *o,o′*-dinitro-α-cyanodi benzyl, and the natural product was synthesized twice before being found in nature.

The first synthesis of **11** was achieved by Holt and Petrow in 1948, 40 years before its identification as a natural product,[24a] when their structure–activity studies moved from azacarbazoles to quinindoline (**13**) derivatives.

Although **11** was then a known heterocycle,[28] the authors devised a Graebe–Ullmann-based alternative preparation, in which 1-(2-quinolyl)-1*H*-benzotriazole (**28**) was prepared and pyrolytically decomposed to yield quinindoline (**24**). The required 2-quinolylbenzotriazole (**28**) intermediate was prepared by treating 2-chloroquinoline (**25**) with a slight excess of *ortho*-phenylenediamine (**26**), in the presence of copper powder and a small amount of HCl, followed by nitrous acid treatment of the resulting aminoquinoline product **27** (Scheme 1).



Scheme 1. *Reagents and conditions:* (a) Cu, HCl (cat.), 155 °C/30 Torr, 30 min; (b) 2 N HCl, $NaNO_2$, 0 °C (65% overall); (c) 100–120 °C, 15 min (68%); (d) PPA, 100–150 °C, 30 min, 150–200 °C, 20 min (30–36%); (e) 1. Me_2SO_4, $PhNO_2$, 160 °C, 1 h; 2. HCl, PhMe; 3. H_2O, 2 N NaOH, or 1. MeI, EtOH, 100 °C (closed tube), 12 h; 2. H_2O, 20% NaOH (41%).

The authors discovered that pyrolysis of **28** failed to occur in neutral or basic solvents (nitrobenzene, quinoline, liquid paraffin) under reflux, but did take place under less drastic conditions in syrupy phosphoric acid to afford **24** (norcryptotackieine). *N*-Methylation of **24** with dimethyl sulfate in nitrobenzene at reflux, followed by anion exchange to yield the chloride and final basic treatment furnished **11**. This methylation occurs at N-5 because H-6, the proton at N-6, is quite acidic and therefore does not constitute a good nucleophilic site for methylation.

The second total synthesis of neocryptolepine was carried out in 1988,[24b] eight years before the alkaloid was found in nature, by the group of Peczynska-Czoch. They studied the chemistry and biological activity of fused nitrogen heteroaromatic compounds, gaining experience in the synthesis of α-carbolines and iso-α-carbolines,[29] and prepared a series of benzo-iso-α-carbolines, among them **11**. The compound was resynthesized by the authors in 1994 to examine its potential antineoplastic activity.[24c]

The synthesis of **11** (Scheme 1) entailed a small modification of the Holt and Petrow sequence, involving heating 2-chloroquinoline (**25**) with benzotriazole (**29**) to afford the 2-quinolinotriazole intermediate (**28**, 68%) more directly. Next, a Graebe–Ullmann reaction[30] with polyphosphoric acid effected the key thermal decomposition of **28** with loss of nitrogen, giving a 30% yield of tetracyclic compound **24**. Finally, treatment with methyl iodide and basification furnished the tetracyclic natural product **11** in 41% yield, adding up to a four-step synthesis that proceeded in 9% overall yield.

In addition, Peczynska-Czoch studied the conversion of 2,3-benzo-α-carboline and related compounds into the corresponding N_1-methylated derivatives by *Kitasatosporia setae*. It was found that the heterocycle was methylated only to 4–5% extent, affording neocryptolepine.[31]

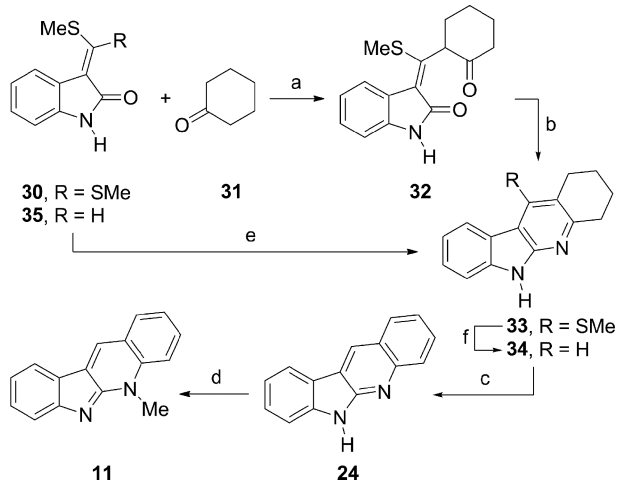
3.2. Indoles as Starting Materials

An attractive way of generating new indole-containing molecular frameworks is the annulation of preformed and readily available indoles. Indole itself, as well as several of its functionalized derivatives, including isatin, have been employed as starting materials for the preparation of **11**.

Recognizing the α-carboline (pyrido[2,3-*b*]indole) moiety as a key part of **11**,[32] in 2004 Ila's group reported two five-step total syntheses of neocryptolepine from oxindole derivatives.[33] To that end, 3-bis[(methylsulfanyl)methylene]-1,3-dihydroindol-2-one[34] (**30**) was subjected to a conjugate addition with the enolate of cyclohexanone (**31**), to provide an 81% yield of diketo intermediate **32**, followed by heterocyclization with ammonium acetate in DMSO in the presence of molecular sieves (4 Å) to afford the indoloquinoline **33** (52%, Scheme 2).

Dethiomethylation of the tetracycle with Raney nickel in ethanol gave a 90% yield of tetrahydro-6*H*-indolo[2,3-*b*]-quinoline (**34**), which was dehydrogenated with DDQ in dioxane at reflux, in 88% yield, to give the related 6*H*-indolo[2,3-*b*]quinoline **24**. Final *N*-methylation of quinindoline with dimethyl sulfate and NaOH, as described previously, furnished the natural product.[24c,35]

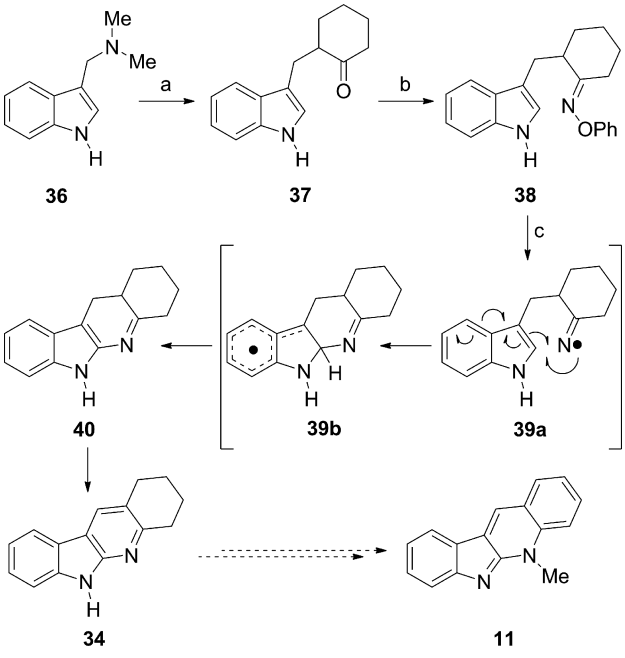
Considering that the bulky methylsulfanyl group in the indolyl-cyclohexanone adduct may have been hindering the



Scheme 2. *Reagents and conditions:* (a) NaH, DMF, PhH, room temp. (81%); (b) 1. NH_4OAc, DMSO, 4 Å MS, 120–130 °C, 10–12 h (52%); 2. Raney Ni, EtOH (90%); (c) DDQ, dioxane, Δ (88%); (d) Me_2SO_4, NaOH (42%); (e) 1. NaH, DMF, PhH, room temp.; 2. NH_4OAc, DMSO, 4 Å MS, 120–130 °C, 10–12 h (54%); (f) Raney Ni, EtOH (90%).

cyclization, an alternative route was designed. Thus, enol sulfide **35** was subjected to the conjugate addition with cyclohexanone and the resulting adduct **32** was cyclized. However, only comparable yields of product **33** were realized.

Cyclohexanone derivative **37**, a desulfenated analogue of compound **32**, is available from gramine (**36**).[36] It was a key intermediate in the synthesis of neocryptolepine reported by Walton's group (Scheme 3).[37]

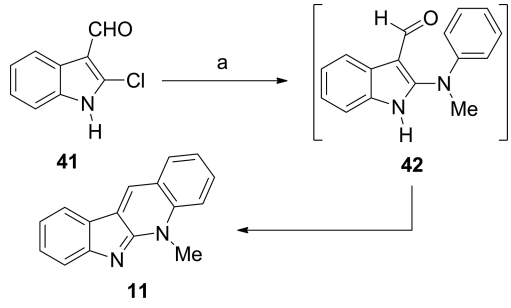


Scheme 3. *Reagents and conditions:* (a) cyclohex-1-enylpyrrolidine (78%); (b) $PhONH_2$·HCl, Py (70%); (c) *t*BuPh, emimPF_4, MW, 160 °C, 30 min (69%).

Indolo ketone **37** was prepared in 78% yield from the reaction between gramine and cyclohex-1-enylpyrrolidine, and the corresponding *O*-phenyl oxime ether **38** was then obtained in 70% yield. Microwave irradiation of **38** in *t*BuPh afforded a 69% yield of tricyclic derivative **40**, through the intermediacy of **39**. In turn, **40** underwent a second in situ dehydrogenation step, resulting in aromatization of the newly formed pyridine ring to provide **34**, formally affording a total synthesis of neocryptolepine in five steps from **36**.[36]

According to the proposed mechanism, microwave irradiation of the oxime **38** affords the indolopyridine derivative **40** in which both the acceptor ring and the pyridyl ring become aromatic. The 6-*endo* cyclization seems to be favored against the alternative *5-exo* mode because it entails the intermediacy of a resonance-stabilized benzyl-type radical.

A straightforward and improved synthesis of neocryptolepine based on a previous report by the group of Stoess[38] was reported in 2004 by Engqvist and Bergman (Scheme 4).[39] It hinged upon the condensation of 2-chloroindole-3-carbaldehyde (**41**)[40] with *N*-methylaniline to yield anilinoaldehyde **42**, which cyclized in situ to the natural product **11** in 75% overall yield.



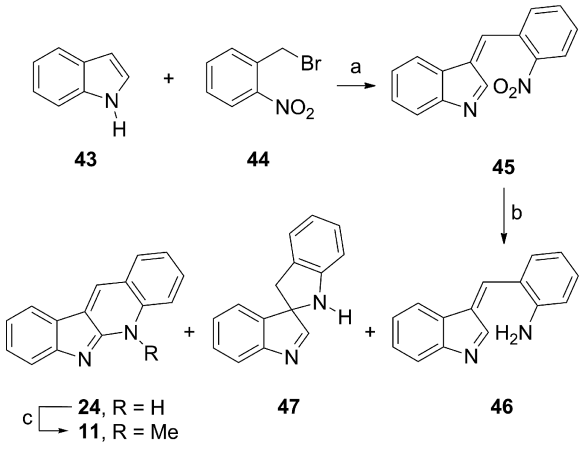
Scheme 4. *Reagents and conditions:* (a) PhNHMe (5 equiv.), 15 min, $NaHCO_3$ (satd.), 25 °C, 1 h (75%).

In 2008, Sharma and Kindu disclosed their approach to neocryptolepine, based on a $SnCl_2$-mediated intramolecular cyclization of nitroarenes with concomitant C–N bond formation (Scheme 5).[41]

Treatment of indole (**43**) with 2-nitrobenzyl bromide (**44**) in the presence of sodium carbonate afforded **45**.[42] Upon subjection of the nitro derivative to reduction with $SnCl_2$ in MeOH at reflux, three components were detected by HPLC (1:2.3:3 ratio) and isolated; they included spiroindole **47**, amine **46** and **24**.[25c]

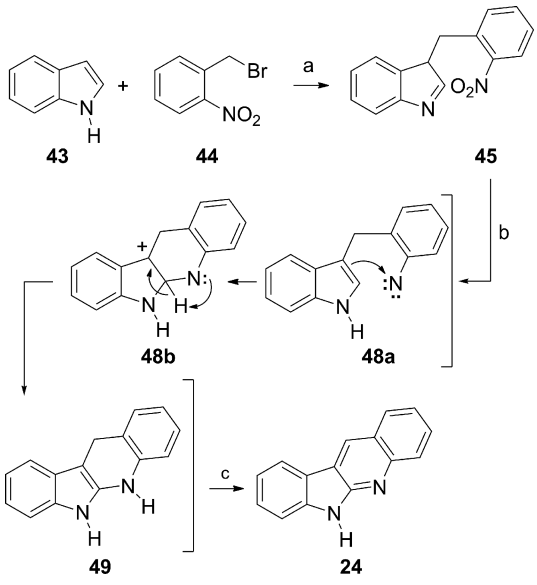
The isolation of the spiroindole points to a mechanism[43] involving participation of C-3 in the indole as the preferred position for an initial intramolecular electrophilic attack leading to an unstable "spiroindolenine", which then quickly undergoes rearrangement to the C-2 of the indole.

Interestingly, the use of other procedures for the reduction of the nitro moiety, involving metallic zinc, failed to offer any improvement in terms of yield or selectivity.[44]



Scheme 5. *Reagents and conditions:* (a) Na_2CO_3, acetone/H_2O (4:1), 70 °C, 36 h (83%); (b) $SnCl_2{\cdot}2H_2O$, MeOH, reflux, 1 h (**24**, 35%; **46**, 27%; **47**, 10%); (c) MeI, PhMe, 130 °C, sealed tube, 4 h (82%).

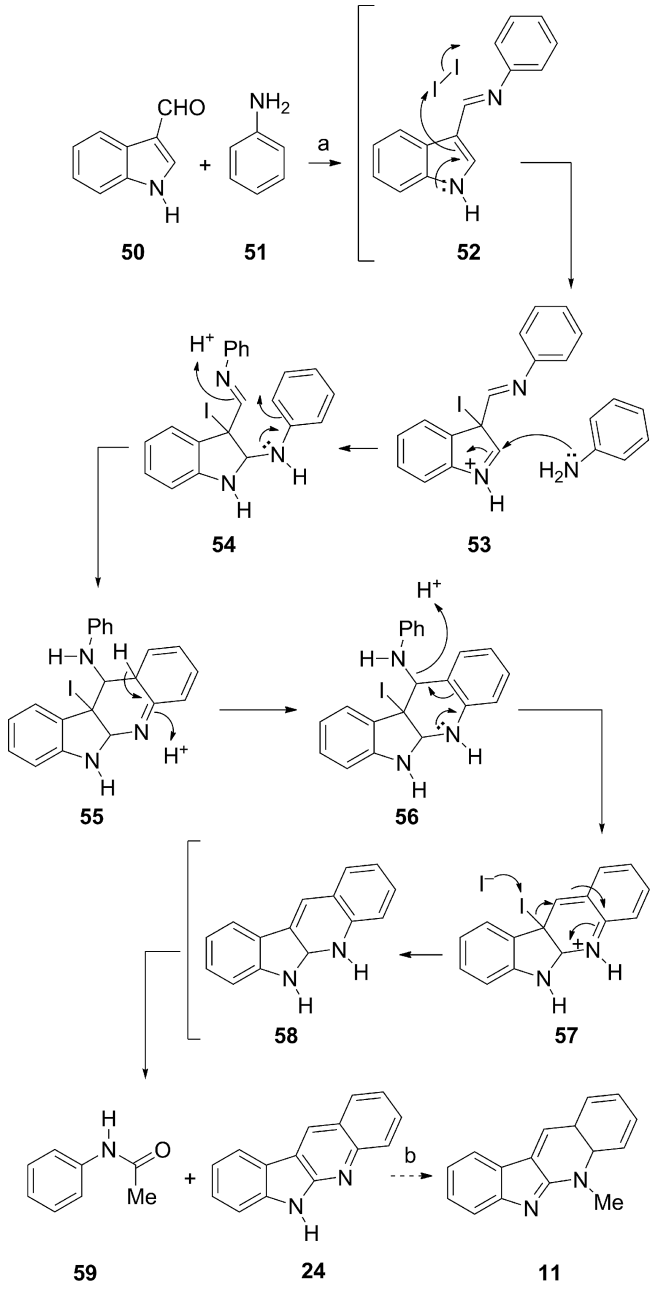
In 2012, Tilve reported a formal total synthesis of neocryptolepine[45] by a similar approach that included the 3-alkylation of indole (**43**) with 2-nitrobenzyl bromide (**44**) in 68–72% yield (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) Na_2CO_3, acetone/H_2O (4:1), 80 °C, 40 h or H_2O, MW, 200 W, 150 °C, 10 min or MeMgBr, PhMe, room temp., 12 h (65–72%); (b) PPh_3, Ph_2O, 4–6 h; (c) [O] (63% overall).

Reductive cyclization of the resulting product **45**[41,46] with PPh_3 in Ph_2O at reflux[47] afforded a 63% yield of the tetracycle **49**, through the intermediacy of **48**. Upon oxidation in the same reaction medium, **49** was converted into the final product **24**. The authors proposed a mechanism for the transformation.

In 2009, the groups of Tilve and of Ghorbani-Vaghei[48] developed the synthesis of a series of 6*H*-indolo[2,3-*b*]-quinolines bearing various substituents on the quinoline ring, including quinindoline (**24**), by employing iodine and NBS, respectively, as catalysts. These syntheses are formal total syntheses of **11** (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) 1. $AcOH_{gl}$, Ph_2O, reflux, 3 h; 2. I_2 (0.1 equiv.), Ph_2O, reflux, 10 h (23%) or I_2 (0.1 equiv.), Ph_2O, reflux, 12 h (45%); (b) *N*-methylation.

Their approach involved the reaction between indole-3-carboxyaldehyde (**50**) and aniline derivatives in diphenyl ether at reflux, in the presence of catalytic amounts of iodine. Iodine is a mild Lewis acid, well suited for various chemical transformations.[49] These authors observed that the condensation was most efficient when 0.1 mol-% of the promoter was employed, in the presence of 2 equiv. aniline. Replacement of I_2 by HI does not led to the tetracyclic product, confirming that HI, generated during the transformation, is not the real catalyst.

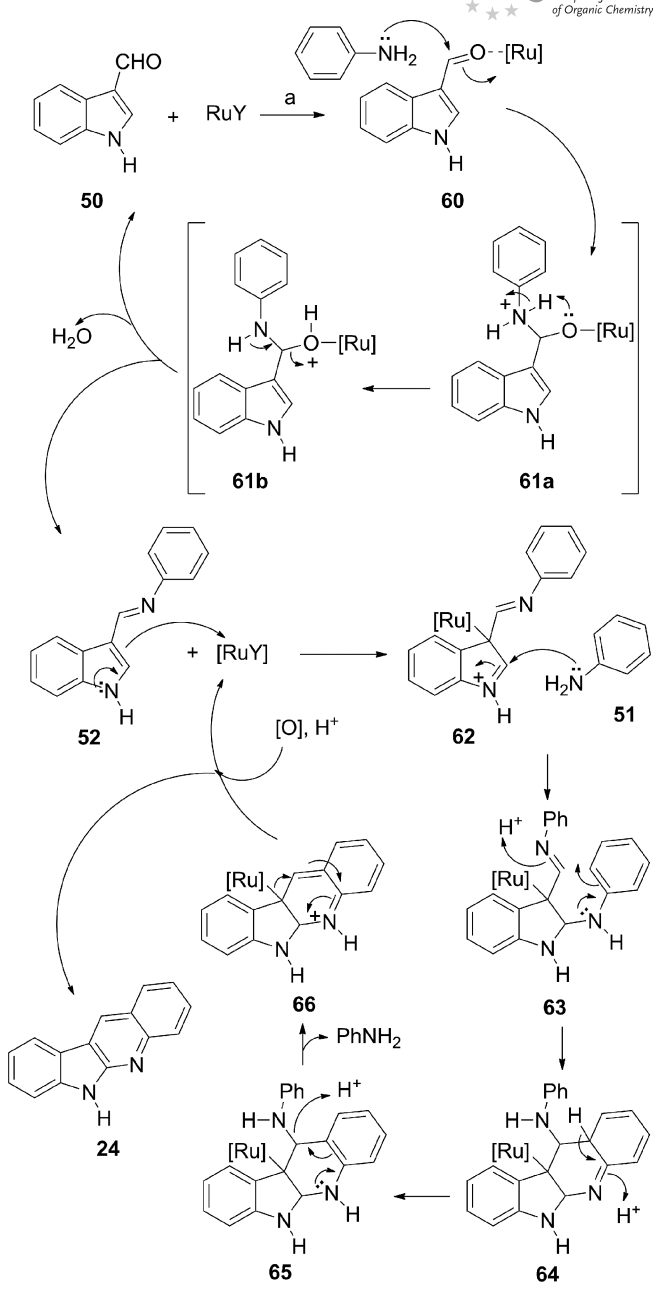
The authors proposed that heating of the reactants at reflux in Ph_2O, to which glacial acetic acid was added,

served to condense the aldehyde and the aniline, yielding imine **52**. Electrophilic attack of iodine on imine **52** would generate the 3-iodoindolinium cation **53**, which upon nucleophilic attack by aniline (**51**) would lead to the 2-*N*-phenyl-substituted indole derivative **54**. Then, an intramolecular electrophilic substitution would lead to tetracyclic structure **55**, which should provide **57** through the intermediacy of **56**, after releasing aniline (**51**). Iodide-mediated nucleophilic attack on the tertiary iodide would regenerate the catalyst, furnishing **58**, and oxidation of **58** should afford the aromatized heterocycle **24**.[50]

Acetanilide (**59**) is formed as a side product as a result of the use of AcOH to promote formation of the Schiff base **52**. It was observed that in the absence of AcOH the imine could still be generated, albeit at a slower pace, taking 18 h to go to completion, but the transformation led to **24** as the sole product, in 45% yield. Interestingly enough, addition of iodine from the beginning of the transformation gave **24** in 12 h and 45% yield. Decomposition of the starting Schiff base during the reaction was the main cause of the diminished yields.

More recently, Khorshidi and Tabatabaeian reported that a ruthenium-exchanged FAU-Y zeolite (RuY) is capable of improving the synthesis of norneocryptolepine (**24**) and other 6*H*-indolo[2,3-*b*]quinolones,[51] affording a 65% yield of **24** after 4 h in dioxane at reflux. The optimum loading was found to be 0.1 g of RuY per mmol of the aldehyde substrate. The catalyst could be used in up to five runs without appreciable loss of catalytic activity.

The proposed mechanism of the reaction is shown in Scheme 8. It involves Ru activation of the aldehyde to provide **60**, followed by attack of the aniline to afford imine **52** through the intermediacy of protonated hemiaminals **61**. Ruthenium-mediated activation of **52** would prepare the field for attack of the resulting intermediate **62** by aniline (**51**), to afford **63**. In turn, the aromatic ring of the incoming aniline in **63** would attack the imino moiety, undergoing cyclization to intermediate **64**, with assistance from an electron pair of the attached amino group. Aromatization of the A-ring to give **65**, followed by loss of aniline, would afford the ruthenium intermediate **66**. Oxidation of this in the reaction medium would then release both the ruthenium promoter and the final product **24**. This mechanism strongly resembles that put forward by Tilve et al. for an analogous reaction promoted by iodine (Scheme 7).

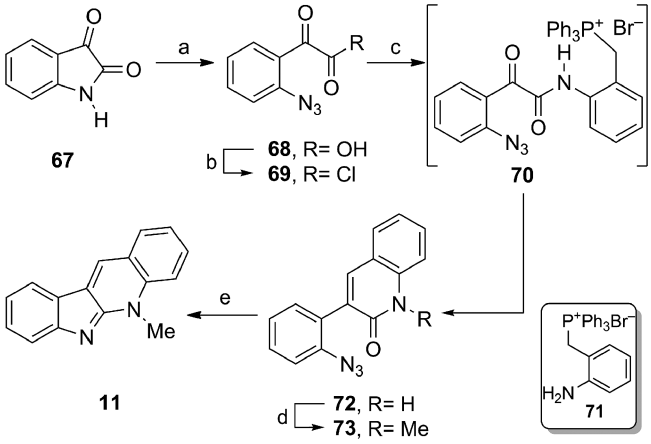


Scheme 8. Proposed mechanism for the ruthenium-mediated synthesis of **24**. Reagents and conditions: (a) ruthenium-exchanged FAU-Y zeolite (RuY, 0.1 g mmol^{-1}), 4 h (65%).

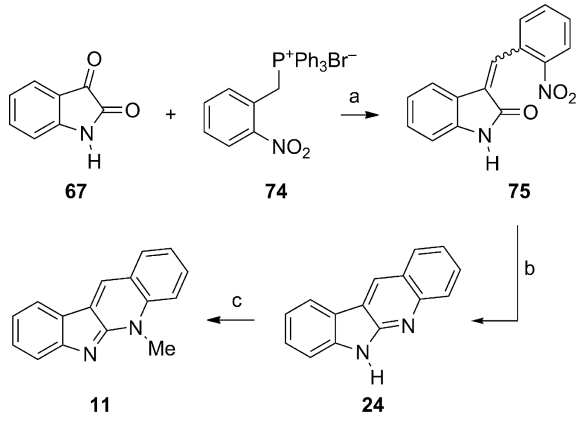
In 2010, Kraus and Guo reported a total synthesis of neocryptolepine employing an intramolecular Wittig reaction as key step.[52] In their approach, (2-azidophenyl)glyoxylic acid (**68**), easily available in 92% yield from isatin (**67**),[53] was converted into the acid chloride **69** and condensed with (2-aminobenzyl)triphenylphosphonium bromide (**71**) to afford **70**. This was followed by an intramolecular Wittig reaction of the resulting **70** by treatment with potassium *tert*-butoxide, leading to lactam **72** in 62% overall yield (one-pot, three steps from **68**). Methylation of **72** with methyl iodide in the presence of potassium carbonate in DMF gave the known intermediate **73** in 98% yield (60% over four steps). Neocryptolepine was finally obtained from **73** through a microwave-assisted intramolecular aza-Wittig reaction (Scheme 9).

In 2011, Parvatkar and Tilve[54,54a] reported a short, simple, and high-yielding synthesis of neocryptolepine (Scheme 10) based on a retrosynthetic analysis that called for a reduction/cyclization/dehydration sequence from a stilbenic key intermediate. The stilbene derivative was easily obtained in 92% yield through a Wittig-type condensation between (2-nitrobenzyl)triphenylphosphonium bromide (**74**) and isatin (**67**).

Treatment of **75** with metallic iron in acetic acid in the presence of a catalytic amount of HCl resulted in the sequential reduction of the nitro group, isomerization of the



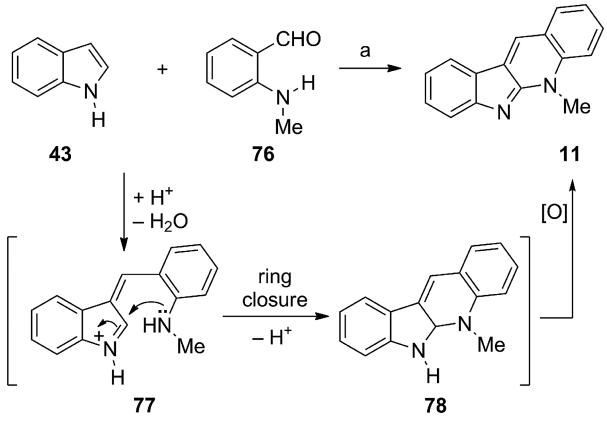
Scheme 9. *Reagents and conditions:* (a) 1. NaOH (1.0 equiv.); 2. $NaNO_2$, H_2SO_4, 0 °C, 2 h; 3. NaN_3 0 °C, 30 min (85%); (b) $SOCl_2$, PhH, reflux, 1 h or $(COCl)_2$, CH_2Cl_2, room temp., 3 h; (c) 1. **71**, CH_2Cl_2, room temp., 11 h; 2. KO*t*Bu, THF, room temp., 5 h (62% from acid **68**) ; (d) MeI, K_2CO_3, DMF, 60 °C, 8 h (98%); (e) MW, Me_3P, $PhNO_2$, 180 °C (40%).



Scheme 10. *Reagents and conditions:* (a) Et_3N, $CHCl_3$, room temp., 3 h (92%); (b) Fe, HCl (cat.), AcOH, 120 °C, 24 h (77%); (c) MeI, THF, reflux, 12 h (96%).

C=C double bond, cyclization, and then dehydration, affording a 77% yield of 6*H*-indolo[2,3-*b*]quinoline (**24**). Regioselective methylation of the product furnished **11** in 68% overall yield. The reductive cyclization of **75** to **24** with PPh_3 or $P(OEt)_3$ under thermal and microwave-assisted conditions has recently been reported by the same group;[54b] however, the transformation took place to afford **24** in disappointing yields (3–22%) as part of mixtures with other products.

Another facile one-pot synthesis of neocryptolepine was that published in 2011 by Seidel's group.[55] As depicted in Scheme 11, these authors proposed the reaction between indole and 2-(methylamino)benzaldehyde (**76**)[56] as an alternative approach to the natural product. In their sequence, condensation of **76** with indole would form azafulvenium ion **77**, which in turn could undergo ring-closure to form **78**. Final oxidation of **78** would lead to the natural product.



Scheme 11. *Reagents and conditions:* (a) TsOH (1.0 equiv.), EtOH (0.1 M), reflux, open to air, 2 h (77%).

Analogously, a series of neocryprolepine analogues was prepared by employing substituted indoles and aminobenzaldehydes. The overall sequence bears some resemblance to the synthesis of benzazepine-fused indoles, disclosed by the same group.[57]

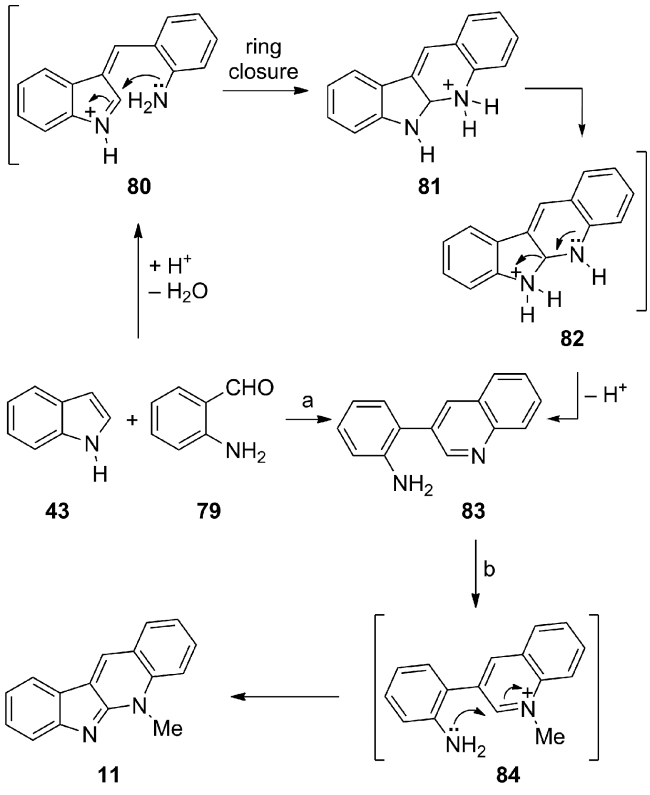
In this process, the reaction between tetrakis(dimethylamino)ethylene (TDAE) and *o*-nitrobenzyl chloride yields the nitrobenzyl carbanion, which is able to react with various electrophiles.[58] Accordingly, reactions between *o*-nitrobenzyl chlorides, 1-methylisatin, and TDAE, followed by one-pot reduction/cyclization/dehydration reaction sequences, were employed to prepare analogues of neocryptolepine.[59]

Interestingly, these authors also found that both indole reactivity and the outcome of the reaction strongly depend on the nature of the aminobenzaldehyde component. When 2-aminobenzaldehyde (**79**) was employed instead of the *N*-methyl derivative **76**, 3-(2-aminophenyl)quinoline (**83**) was isolated in good yield, after a quinoline ring closing/indole ring opening sequence (Scheme 12), through the intermediacy of **80**, **81**, and **82**, in a process in which indole served as an equivalent of 2-(2-aminophenyl)acetaldehyde.

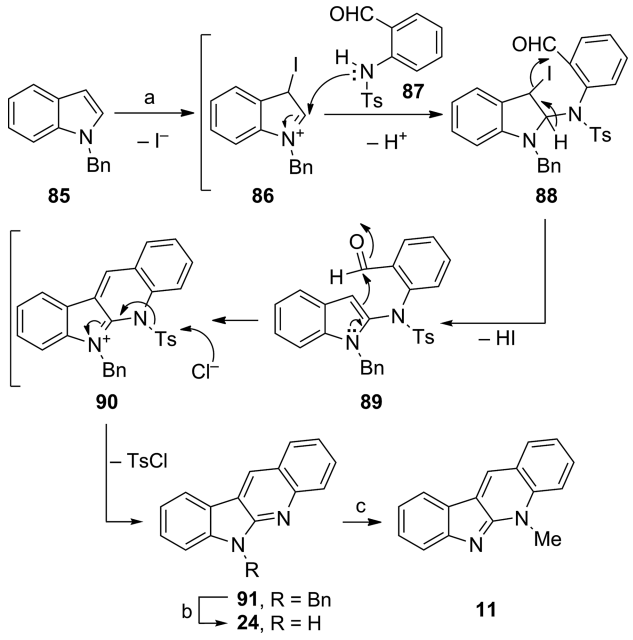
The heterocycle **83** could be converted into the natural product by quaternarization of the quinoline nitrogen to give **84**, which was followed by an intramolecular nucleophilic attack by the pendant amino group and oxidation to yield the tetracycle final product. Two neocryptolepine analogues were prepared by changing the alkylation agent.

An analogous approach to neocryptolepine and its derivatives, involving an iodine-based and metal-free cross-amination/alkylation cascade of indoles with 1-(2-tosylaminophenyl)aldehydes and ketones, was disclosed by Liang's group.[60]

As shown in Scheme 13, the synthesis involves the reaction between *N*-benzylindole (**85**) and 2-(tosylamino)benzaldehyde (**87**).[61]



Scheme 12. *Reagents and conditions:* (a) TsOH (1.0 equiv.), PhMe (0.1 M), reflux, 30 min (83%); (b) MeI, MeCN, reflux, open to air, 12 h (64%).



Scheme 13. *Reagents and conditions:* (a) 1 I_2, Cs_2CO_3, MeCN, room temp.→90 °C; 2. 12 N HCl (78%); (b) 1. $AlCl_3$, PhH, reflux, 8 h; 2. HCl (99%); (c) Me_2SO_4, K_2CO_3, MeCN, reflux, 11 h (88%).

The authors optimized the conditions for accessing the initial tetracycle, concluding that I_2/Cs_2CO_3 is the most efficient reagent system with which to carry out the initial C–N coupling. In model experiments, they also observed that addition of HCl in the second stage ensured completion of the C–C coupling to produce the tetracyclic product.

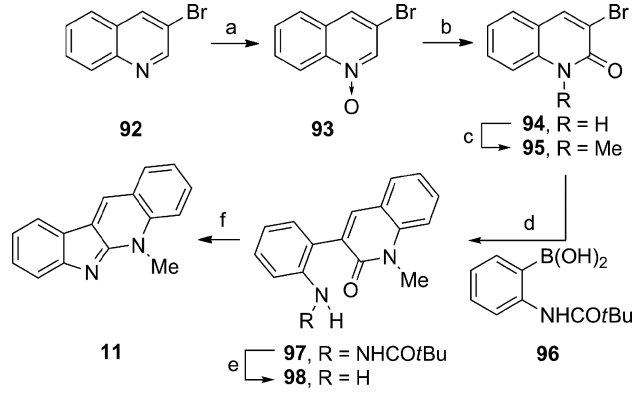
The small structural differences between the reactants in Seidel's and Liang's syntheses of neocryptolepine may be translated into differences in scope and limitations of both syntheses. Liang's group demonstrated that their synthesis is able to afford 11-substituted neocryptolepine derivatives in similar yields when aryl ketones are employed instead of the substituted benzaldehyde.

The proposed mechanism (Scheme 13) involves the electrophilic addition of iodonium ion to the starting indole **85** to yield iminium ion **86**, which undergoes a 2-amination with the tosyl aldehyde **87** to afford **88**. In the presence of base, the intermediate **88** loses HI to afford indole **89**. Next, HCl-assisted intramolecular alkylation and subsequent detosylation of **90** gives **91** (78% overall yield). In order to install the required methyl group, intermediate **91** was debenzylated with $AlCl_3$ in 99% yield and the resulting **24** was further subjected to conventional *N*-methylation with Me_2SO_4 (88% yield).

3.3. Quinolines as Starting Materials

Quinolines, mainly 2-mono-, 3-mono-, and 2,3-dihalogenated derivatives, were the first starting materials used for the preparation of neocryptolepine. However, they have been employed rather scarcely.

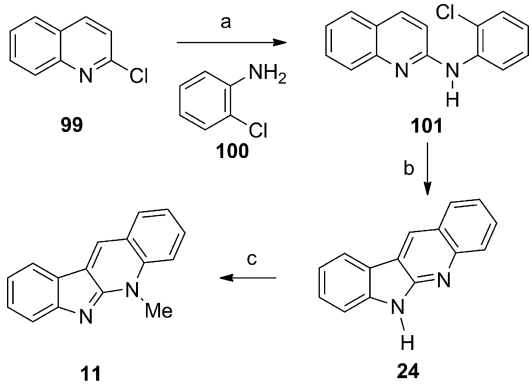
As shown in Scheme 14, in 1997 Timári's group reported a synthesis of **11** from 3-bromo-1*H*-quinolin-2-one (**94**), readily available in two steps and 55% yield from 3-bromoquinoline (**92**), through the intermediacy of N-oxide derivative **93**.[62] The quinolone was *N*-methylated with methyl iodide in the presence of potassium carbonate, yielding **95** (81%). Suzuki cross-coupling[63] between **95** and 2-(pivaloylamino)phenylboronic acid (**96**)[64] attached the remaining aromatic ring, affording an 85% yield of the expected biaryl derivative **97**, which was quantitatively hydrolyzed to the key intermediate **98**. Treatment of **98** with $POCl_3$ in



Scheme 14. *Reagents and conditions:* (a) *m*-CPBA, $CHCl_3$, room temp., 24 h (98%); (b) TsCl, K_2CO_3, $CHCl_3$, room temp., 6 h (55%); (c) MeI, K_2CO_3, DMF, 60 °C, 3 h (81%); (d) Pd^0, DME, $NaHCO_3$, 3 h (85%); (e) 20% H_2SO_4, EtOH (1:1), reflux, 2 d (100%); (f) $POCl_3$ (2 equiv.), PhH, reflux, 3 h (65%).

benzene at reflux triggered the indolization between the amine and the amide, furnishing the ring-closed product **11** in moderate yield (65%).

After previous reports indicating that aniline condenses with 2-chloroquinolines and other haloquinoline derivatives[65] on cautious heating at temperatures ranging from 100 to 200 °C, in 2006 Mohan's group reported a total synthesis of **11**,[66] starting with the regioselective amination of 2-chloroquinoline (**99**) with 2-chloroaniline (**100**) and depicted in Scheme 15. Despite the availability of new catalysts for this reaction,[67] the classical procedure proved more effective, even in relation to the Buchwald–Hartwig amination, which requires expensive palladium catalysts. Compound **101** was obtained in 72% yield.

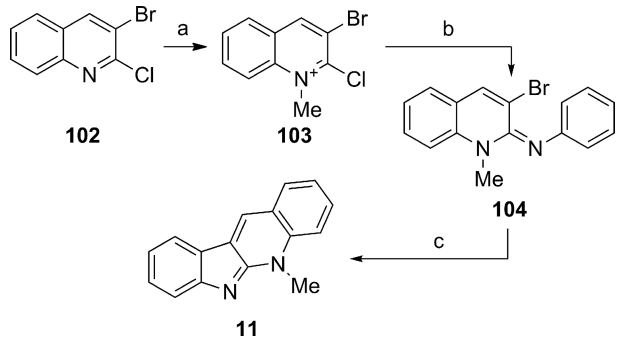


Scheme 15. *Reagents and conditions:* (a) 200 °C, 5 h (72%); (b) hν, PhH/MeOH/H_2SO_4 (60:30:1, v/v/v), I_2 (cat.), room temp. (70%); (c) Me_2SO_4, K_2CO_3, MeCN, reflux, 6 h (83%).

Subjection of anilinoquinoline **101** to irradiation with ultraviolet light in PhH/MeOH (60:30, v/v), to which traces of iodine and 1% in volume of H_2SO_4 had been added, effected the expected heteroatom-directed photoannulation, furnishing a 70% yield of the linear photoproduct **24**, together with a certain amount of the angular isomer **13**. An acidic medium is needed in order to ensure suitable yields of the cyclization. This photochemically initiated electrocyclic reaction is based on the rearrangement of the available electron pair in the nitrogen and the electron pair of at least one aromatic π-bond. Interestingly; the transformation is regiospecific with regard to the aromatic substitution *ortho* to the heteroatom.

Interestingly, the oxidative cyclization took place exclusively at the C-3 position and not at N-1 of the quinoline moiety; this is because cyclization at the latter position would require carbon–nitrogen bond formation, which would entail a net loss of aromaticity. Finally, selective *N*-methylation of **24** with methyl sulfate gave access to the natural product in 83% yield.[68]

Employing their previous experience in the synthesis of 1-methyl-1*H*-α-carbolines from 2,3-dichloropyridine,[69] in 2011 the group of Maes disclosed a new strategy directed towards neocryptolepine,[70] which was also useful for the preparation of various chlorinated analogues. In their synthesis (Scheme 16), the commercially available 3-bromo-2-chloroquinoline (**102**)[71] was subjected to *N*-methylation with methyl triflate, affording a 90% yield of the corresponding 1-methylquinolinium triflate **103**.



Scheme 16. *Reagents and conditions:* (a) MeOTf, PhMe, room temp. 48 h (90%); (b) 1. $PhNH_2$, THF, –10 °C→room temp.; 2. DBU, 30 min; (c) $Pd(PPh_3)_2Cl_2$, $NaOAc{\cdot}3H_2O$, DMA, 130 °C, 17 h; 2. NH_4OH (98%).

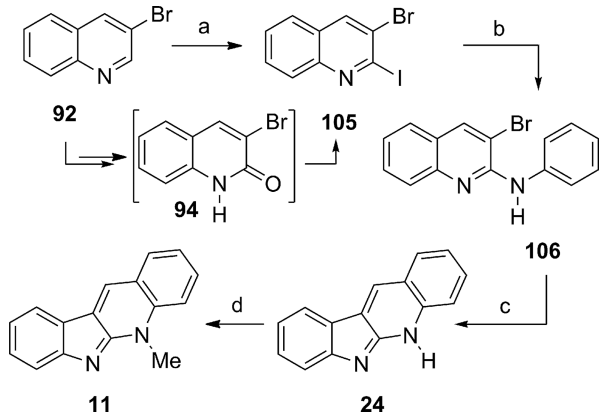
In turn, this was treated with aniline, yielding *N*-[3-bromo-1-methylquinolin-2(1*H*)-yliden]aniline (**104**), which proved to be unstable and prone to hydrolysis, and hence difficult to purify. After optimization of the transformation by slow addition of the quinolinium salt to the aniline and use of DBU to deprotonate the resulting anilinium salt, it was found that the product could be used for the next step without purification. This step consisted of a direct arylation reaction catalyzed by $PdCl_2(PPh_3)_2$ in DMA, with $NaOAc{\cdot}3H_2O$ as base,[67a] and proceeded in 98% yield.

This three-reaction, two-step synthesis of neocryptolepine is the most efficient route so far reported in terms of overall yields (88%). 3-Bromo-2-chloroquinoline was ideal as starting material in comparison with the 2,3-dichloro[69] and the 2,3-dibromo alternatives. It provided the required selectivity, because the brominated derivative, being more reactive, could participate in the direct arylation step under milder conditions. On the other hand, the presence of a chlorine atom on C-2, as in **103**, afforded a heterocycle that proved to be more reactive towards the condensation than the 2-bromoquinolinium analogue.

Interestingly, Maes et al. described a two-step route to norneocryptolepine by means of a Buchwald–Hartwig amination of 2,3-dichloroquinoline[72] with aniline, which proceeded in 90% yield, followed by a microwave-assisted Pd-catalyzed intramolecular direct arylation reaction to afford the final product, which took place in 89% yield.[69]

An approach similar to that of Maes was followed by Bóganyi and Kámán (Scheme 17), starting from 3-bromo-2-iodoquinoline (**105**), easily available from 3-bromoquinoline (**92**) through the intermediacy of 3-bromo-1*H*-quinolin-2-one (**94**).[73] They devised a two-step strategy based on microwave-assisted palladium chemistry and entailing a regioselective Buchwald–Hartwig amination of the quinoline **105** with aniline under Xantphos-$Pd(OAc)_2$ catalysis conditions, followed by a $PdCl_2(PPh_3)_2$-catalyzed intramolecular Heck-type reaction of the resulting intermediate **106** to produce the ring-closed indoloquinoline scaffold **24** after

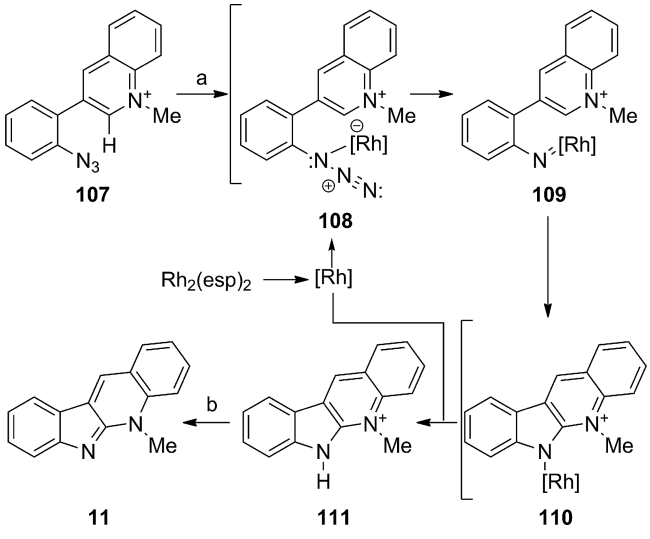
double bond rearrangement. Final *N*-methylation of **24** afforded **11**.



Scheme 17. *Reagents and conditions:* (a) 1. oxone, MeOH, H_2O, 50 °C (96%); 2. BzCl, K_2CO_3, CH_2Cl_2/H_2O, room temp. (71%); 3. $POCl_3$, MeCN, reflux (89%); 4. NaI, MeCN, reflux (97%); (b) $PhNH_2$, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, PhMe, 120 °C, MW (78%); (c) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, MW (60%); (d) selective *N*-methylation.

The activation of C–H bonds by dirhodium(II) carbenoids and nitrenoids allows access to valuable carbocycles and heterocycles efficiently and stereoselectively.[74] Driver's group recently reported a study of the Rh_2^{II}-catalyzed synthesis of various heterocycles by taking advantage of rhodium-mediated controlled decomposition of aryl and vinyl azides.[75]

They demonstrated that treatment of azide **107** with $[Rh_2(esp)_2]$ in 1,2-DCE at 80 °C (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate) resulted in exclusive amination of the carbon atom next to the quinolinium nitrogen (Scheme 18), to produce neocryptolepine as a single regioisomer in 68% yield after basification of quinolinium derivative **111** with Na_2CO_3.



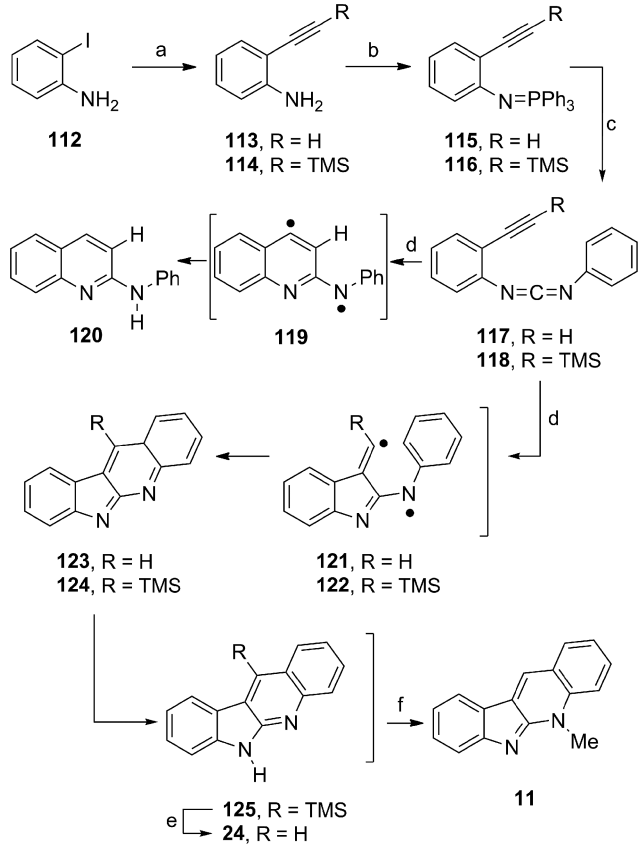
Scheme 18. *Reagents and conditions:* (a) $Rh_2(esp)_2$ (1 mol-%), 1,2-DCE, 80 °C; (b) Na_2CO_3, H_2O (98% overall); esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate.

The starting material was conveniently obtained through a Suzuki-type arylation of 2-bromoaniline with the corresponding boronic acid, followed by diazotization and azidation of the resulting amino biaryl derivative.[76]

On the other hand, the proposed reaction mechanism is similar to that suggested for the Rh^{II}-mediated C–H bond functionalization by α-diazo esters,[77] in which initial coordination of the dirhodium(II) carboxylate with the α-nitrogen of the azide produces **108**, the presumed resting state of the catalyst.[78] Upon formation of the rhodium nitrenoid **109**, generation of the C–N bond to form **110** takes place, either through a concerted insertion into the *ortho*-C–H bond of the quinolinium or through a stepwise electrophilic aromatic substitution via arenium ion **111**.[79]

3.4. Benzenoids as Starting Materials

While studying the pericyclic reactivity of C=C-conjugated carbodiimides, Molina's group was able to prepare various indolo[2,3-*b*]-quinolines.[26a,26b,80] The insight gained by these and other authors was employed (Scheme 19) for the development of a short formal total



Scheme 19. *Reagents and conditions:* (a) H–≡–R (R = H, TMS), $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF (R = H, 100%; R = TMS, 99%); (b) PPh_3Br_2, Et_3N, PhH, room temp., 4 h (R = H, 71%; R = TMS, 79%); (c) PhNCO, PhMe, room temp., 1 h (R = H, 83%; R = TMS, 71%); d) PhMe, 160 °C (sealed tube), 14 h (R = H, 19%) or xylene, reflux, 5 h (R = TMS, 86%); (e) NaOH, EtOH, reflux, 12 h (92%); (f) Me_2SO_4, NaOH (42%).

synthesis of neocryptolepine (**11**), through the synthesis of quinindoline (**24**).[81] An aza-Wittig-type reaction between iminophosphorane **115** (R = H) and phenyl isocyanate afforded carbodiimide **117**, which upon subjection to strong heating (160 °C) gave a mixture of 19% of quinindoline (**24**) and 40% of 2-anilinoquinoline (**120**). The latter compound was obtained through the intermediacy of diradical **119**.

Wang's group studied the use of iminophosphoranes **115** resulting from reactions between 2-(1-alkynyl)anilines **113** and Ph_3PBr_2 as substrates for aza-Wittig reactions of ketenes to produce ketenimines.[82] Employing an isocyanate as cumulene counterpart, they obtained carbodiimides.[26c] This finding became the basis of a strategy that was employed in 1999 for a total synthesis of neocryptolepine featuring a thermally induced biradical-forming cycloaromatization reaction.

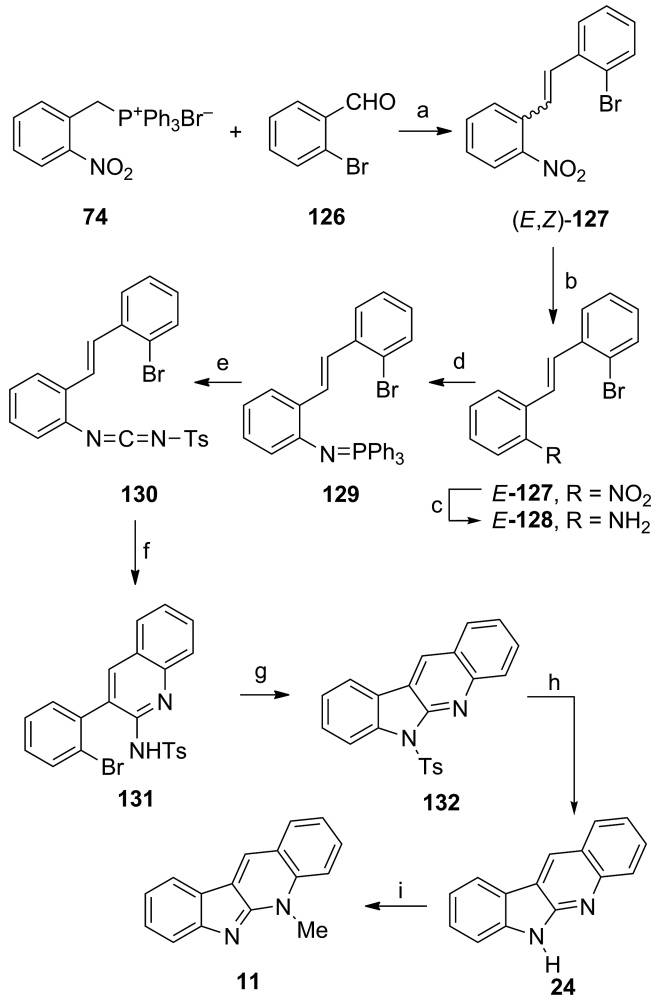
In their sequence, *ortho*-iodoaniline (**112**) was subjected to a Sonogashira reaction with acetylene to furnish 2-(1-alkynyl)aniline **113**, which was converted into the iminophosphorane **115** and then treated with phenyl isocyanate to furnish *N*-phenylcarbodiimide **117**. Upon heating in toluene or γ-terpinene, this compound underwent either a two-step biradical pathway through **121/122**, or a one-step intramolecular Diels–Alder[26e] reaction leading to intermediates **123/124**, which after tautomerization resulted in a 14–19% yield of the tetracycles **24/125**. Compound **125** could be easily transformed into the final product **24**, in 92% yield, by treatment with NaOH in ethanol at reflux.

Depending on the nature of the substituents on the indole moiety, diradicals such as **121** have been shown to undergo reaction through several different pathways, including formal [4+2][83] and [2+2][84] cycloadducts, as well as ene intermediates.[85] Analogously, the keteneimines are able to switch reactivity according to their substitution pattern,[86] which would explain the low yield attained and the side-product observed.

Because blocking the free side of the acetylene might avoid side reactions, silyl derivative **114** was prepared in an analogous fashion by employing TMS-acetylene. Compound **116** was transformed in 71% yield into the intermediate carbodiimide **118** and then into the tetracycle **125** in high yield (86%). Treatment of **125** with 0.5 N NaOH at reflux accomplished the required protodesilylation in 92% yield and, finally, selective *N*-methylation of **24** with Me_2SO_4 and NaOH furnished the natural product in 42% yield.

Molina's group reported that iminophosphoranes derived from anilines and containing an unsaturated side chain at the *ortho* position are able to react with isocyanates to yield carbodiimides. Upon strong heating, these underwent either electrocyclic ring-closure to afford quinoline derivatives or intramolecular hetero-Diels–Alder cycloaddition to yield indolo[2,3-*b*]quinolines.[26a,26b] Turning their attention to an aza-Wittig electrocyclic ring-closure strategy,[35] Molina et al. employed this protocol in 1999 for an improved synthesis of neocryptolepine, in view of the meager yields of their previous synthesis of the natural product.[81a]

To that end, (2-nitrobenzyl)triphenylphosphonium bromide (**74**) and *ortho*-bromobenzaldehyde (**126**) were subjected to a Wittig reaction, affording a 4:1 (*Z*/*E*) mixture of stilbenes **127** in 95% yield (Scheme 20). Thiophenol/AIBN-catalyzed isomerization to the *E* isomer proceeded in 89% yield, and this was followed by reduction with iron in AcOH, which gave access to (*E*)-2-amino-2′-bromostilbene derivative **128** in 85% yield.



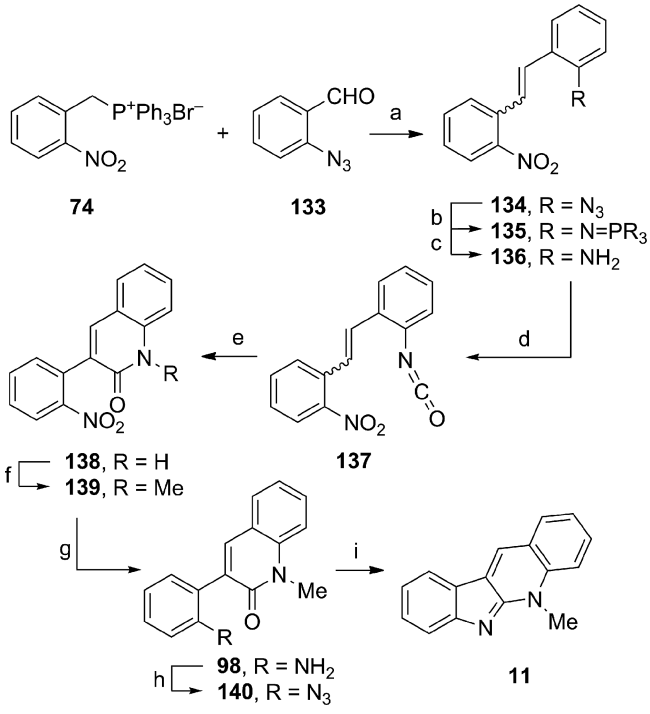
Scheme 20. Reagents and conditions: (a) K_2CO_3, dibenzo-18-crown-6, CH_2Cl_2, room temp. (95%); (b) PhSH, AIBN, PhH, reflux (89%); (c) Fe, AcOH, EtOH, reflux (85%); (d) $Ph_3P{\cdot}Br_2$, Et_3N, PhH, 0 °C→room temp. (87%); (e) TsNCO, PhMe, 0 °C→room temp. (72%); (f) PhMe, reflux (72% from **129**); (g) NaH, CuI, diglyme, room temp. (85%); (h) TBAF, THF, room temp. (90%); (i) Me_2SO_4, DMF, MW (140 °C, 5 min, 75%).

The required iminophosphorane **129** was obtained in 87% yield by treatment of **128** with $Ph_3P{\cdot}Br_2$, in the presence of triethylamine as base. Subjection of iminophosphorane **129** to an aza-Wittig type reaction with tosyl isocyanate gave carbodiimide **130**, which upon heating at reflux in toluene gave a 72% yield of the 2-amino-3-arylquinoline derivative **131**. Treatment of **131** with NaH, in the presence of CuI, completed the assembly of the carbon framework

of the natural product, giving an 85% yield of indolo[2,3-*b*]quinoline **132**.

Unexpectedly, however, attempted direct conversion of sulfonamide **132** into neocryprolepine by treatment with Meerwein's salt (trimethyloxonium tetrafluoroborate)[87] followed by methanolysis of the intermediate salt met with failure. Therefore, the sulfonyl moiety had to be released by treatment with TBAF (90%);[88] this was followed by the microwave-promoted selective methylation of **24** with dimethyl sulfate in DMF, which afforded a 75% yield of the natural product **11**. In an improvement on previous work, the synthesis took place in eight steps, with an overall yield of 25%.

Molina's group also reported that arylheterocumulenes containing unsaturated side chains at their *ortho*-positions undergo thermal cyclization to afford quinoline derivatives.[26a,26b] In 2001, Molina and Fresneda devised another improved approach for the preparation of **11**,[89] based on the formation and selective indolization of 3-(*o*-azidophenyl)-1-methylquinoline-2-one (**140**, Scheme 21).



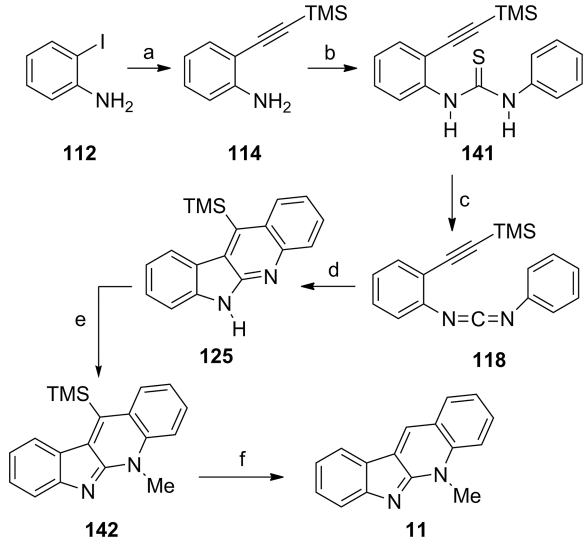
Scheme 21. Reagents and conditions: (a) K_2CO_3, dibenzo-18-crown-6, CH_2Cl_2, room temp. (85%); (b) 1. Ph_3P, CH_2Cl_2, room temp.; 2. PhSH, AIBN (cat.), PhH, reflux [(*E*)-**135**, 70%]; (c) 1. from **135** (R = N=PBu$_3$), THF/H_2O, room temp. (84%); 2. PhSH, AIBN (cat.), PhH, reflux (92%); (d) triphosgene, CH_2Cl_2, 0 °C→room temp.; (e) MW, $PhNO_2$ (80%); (f) CH_3I, DMF, 60 °C (82%); (g) H_2, Pd/C, EtOH, room temp. (91%); (h) 1. $NaNO_2$, H_2SO_4, H_2O; 2. NaN_3 (85%); (i) MW, Me_3P, $PhNO_2$, 180 °C (40%).

To that end, in a rather long sequence, (2-nitrobenzyl)-triphenylphosphonium bromide (**74**) was condensed with *ortho*-azidobenzaldehyde (**133**)[90] in the presence of anhydrous potassium carbonate and catalytic amounts of dibenzo-18-crown-6, to afford stilbene derivative **134** (85%) as a 4:1 (*Z*/*E*) isomeric mixture. A Staudinger reaction between triphenylphosphine and the azide **134** gave a 92% yield of iminophosphorane (*E*/*Z*)-**135**, which was isomerized in 70% yield to (*E*)-**135** by treatment with thiophenol and catalytic AIBN.

Next, hydrolysis of **135** and an aza-Wittig reaction between the resulting (*E*)-**136** and triphosgene gave the corresponding isocyanate **137**, which was subjected, without isolation, to a microwave-promoted cyclization to the quinolin-2-one **138**. Methylation of **138** gave an 82% yield of **139**, which was catalytically hydrogenated over Pd/C to afford a 91% yield of **98**. Diazotization followed by treatment with sodium azide finally afforded access to azide **140** in 85% yield.

Cyclization of the iminophosphorane derived from azide intermediate **140** failed when PPh_3 was employed and gave only a 5% yield of **11** with the use of the more reactive nBu$_3$P, even in boiling xylene. However, use of PMe_3 in nitrobenzene at reflux gave a 24% yield of the final product, and this was increased to 40% when the reaction was subjected to microwave irradiation (150–180 °C) for 30 min.

The group of Pieters, one of the research teams involved in the original isolation of neocryptolepine, became interested in studying the cytotoxicity and the antiplasmodial and antitrypanosomal activities of neocryptolepine derivatives. Therefore, in 2002 they devised a synthesis of the natural product useful for the preparation of analogues on both benzenoid rings (Scheme 22).[91]



Scheme 22. Reagents and conditions: (a) H–≡–TMS, Pd(PPh$_3$)$_2$Cl$_2$, CuI, Et_3N, THF (99%); (b) PhNCS, DMAP, EtOH, 40 °C, 4 h (72%); (c) MsCl, DMAP, Et_3N, CH_2Cl_2, room temp., 10 min (91%); (d) cyclohexa-1,4-diene, mesitylene, reflux, 18 h (60%) or xylene, reflux, 5 h (86%); (e) 1. MeI, DMF, reflux, 18 h (76%); 2. 1 M K_2CO_3; (f) 6 N NaOH, 70 °C, 3 h (99%).

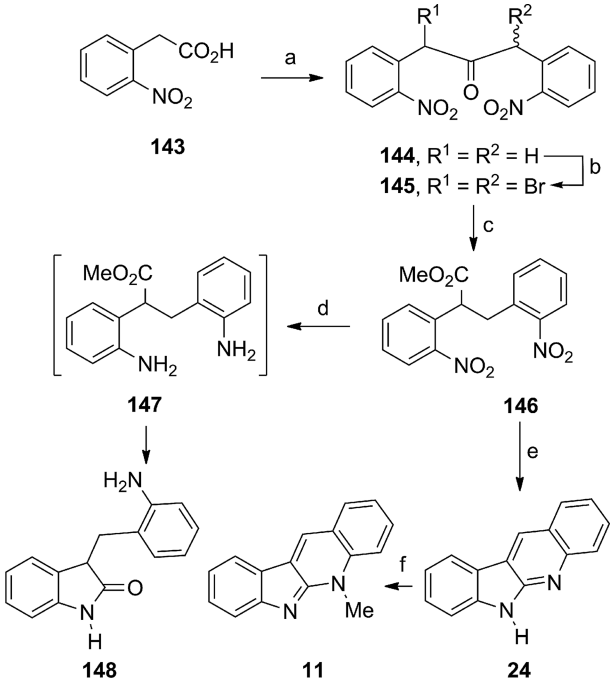
Their strategy was inspired by previous work by Wang's group and by the findings of Schmittel et al.[92] relating to the biradical cyclization reaction of *N*-[4-methyl-2-(2-trimethylsilylethynyl)phenyl]-*N*′-phenylcarbodiimide.

The initial step of the synthetic sequence was a Sonogashira reaction between 2-iodoaniline (**112**) and TMS-acetylene to yield the corresponding 2-trimethylsilylethynylaniline

(**114**). Access to the intermediate unstable carbodiimides **118**[93] was performed through the corresponding thioureas **141**, by treatment with mesyl chloride.[94]

The best conditions for the formation of the thioureas involved the use of catalytic amounts of DMAP in EtOH. After biradical cyclization in the presence of cyclohexa-1,4-diene, 11-trimethylsilyl-6*H*-indolo[2,3-*b*]quinoline (**125**) was obtained and converted into **142** by selective methylation of the 5-nitrogen atom in DMF, followed by desilylation.[26c] This order of transformations proved relevant for a satisfactory yield of the sequence.

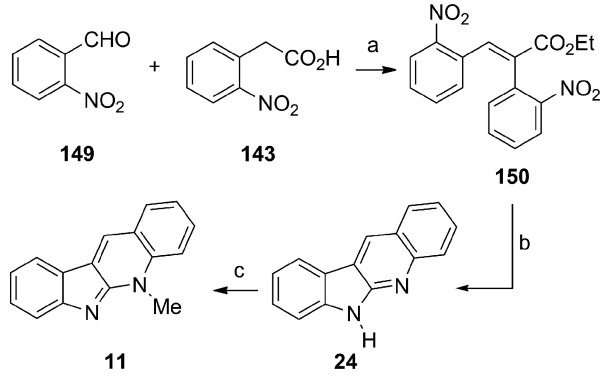
In 2002, Ho and Jou reported their total synthesis of neocryptolepine, designed on the basis of symmetry considerations (Scheme 23). Accordingly, 1,3-bis(2-nitrophenyl)-propan-2-one (**144**), readily available through the reaction between *ortho*-nitrophenylacetic acid (**143**) and dicyclohexyl carbodiimide,[95] was chosen as starting material.[25a]



Scheme 23. Reagents and conditions: (a) DCC, DMAP, THF, reflux, 3 h (86%); (b) Br_2, $CHCl_3$, room temp., reflux, 1.5 h (98%); (c) NaOMe, $CHCl_3$, 0 °C, 20 min; room temp., overnight (57%); (d) $Na_2S_2O_6$, MeOH, reflux, 18 h (32%); (e) Fe, AcOH, EtOH, reflux, 3.5 h (72%); (f) MeI, THF, reflux, 18 h (72%).

Bromination of **144** afforded a 95% yield of the bromo ketone **145**, which, once subjected to a Favorskii rearrangement by treatment with NaOMe, furnished a 57% yield of methyl ester **146**. Reduction of the ester with sodium dithionite gave oxindole **148** in rather low yield (32%) by way of bis(2-aminophenyl) ester **147**. However, iron-powder-mediated reduction of the nitro moieties in **146** in hot AcOH gave a 72% yield of quinindoline (**24**), which after *N*-methylation completed the sequence to **11** (72%).

In 2007, Tilve's group reported a highly efficient total synthesis of neocryptolepine, proceeding in 42% yield and consisting of only three steps (Scheme 24).[96] Their sequence employed a Perkin reaction, followed by a tandem double reduction/double cyclization and final regioselective *N*-methylation.



Scheme 24. Reagents and conditions: (a) 1. Ac_2O, Et_3N, reflux, 5 h; 2. EtOH, H_2SO_4, reflux, 24 h (71%); (b) Fe, HCl, AcOH/EtOH/H_2O, 120 °C, 24 h (74%); (c) Me_2SO_4, DMF, MW (140 °C), 5 min (75%) or Me_2SO_4, K_2CO_3, CH_3CN, reflux, 6 h (80%).

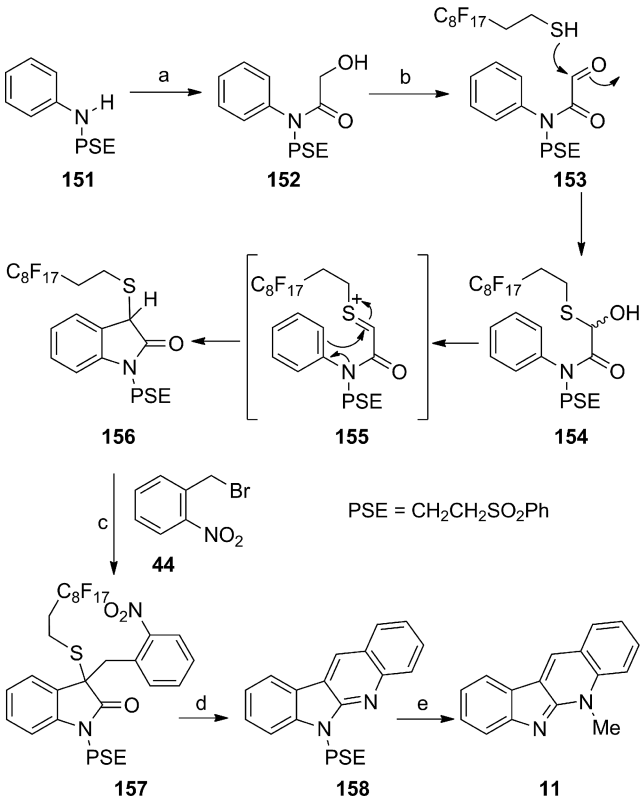
The synthesis commenced with the reaction between *o*-nitrobenzaldehyde (**149**) and *o*-nitrophenylacetic acid (**143**) in the presence of Ac_2O and Et_3N, under Perkin conditions, followed by Fischer esterification to provide α,β-unsaturated ester **150** (71% overall yield). Reduction of the nitro moieties with iron in AcOH, in the presence of HCl, gave a 74% yield of 6*H*-indolo[2,3-*b*]quinoline (**24**).

The synthesis of **24** entails a domino sequence of four reactions, initiated by the reduction of both nitro groups and continuing with a first cyclization, followed by double bond isomerization of the intermediate (*E*)-amide to the corresponding (*Z*)-amide and a second cyclization. The final step is the known regioselective methylation of **24** on its quinoline nitrogen, in 80% yield.

Procter's group studied the formation of N-heterocycles with the aid of reactions between thiols and glyoxamides. In 2009 they explored the usefulness of a connective Pummerer-type cyclization[97] for the synthesis of neocryptolepine.[98] Their synthesis (Scheme 25) began with *N*-[2-(phenylsulfonyl)ethyl]aniline (**151**), easily accessible in 76% yield from the microwave-assisted reaction between aniline and phenyl vinyl sulfone in MeOH.[99]

This was transformed into the related β-hydroxyamide **152** by Bartlett's method,[100] and then it was oxidized to the corresponding glyoxamide **153** under Swern conditions. Addition of $C_8F_{17}CH_2CH_2SH$ to the glyoxamide[101] resulted in the connective Pummerer-type cyclization, giving a 67% yield of **154**, which in turn was purified by fluorous solid-phase extraction, taking advantage of its fluorous tag.[102]

Alkylation of oxindole **156** with 2-nitrobenzyl bromide to yield **157** (75%) was facilitated by the presence of the alkylsulfanyl group introduced during the Pummerer-type cyclization of intermediate **155**. Subsequently, a sequential reductive removal of the fluorous moiety[103] and reduction of the nitro group was carried out with SmI_2,[104] followed by acid-mediated cyclization, furnishing **158** in 83% yield. Finally, the one-pot removal of the sulfone protecting group



Scheme 25. Reagents and conditions: (a) 1. $AcOCH_2CO_2H$, EDCI, HOBt, CH_2Cl_2; 2. K_2CO_3, MeOH, H_2O, room temp. (67%); (b) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C→room temp.; 2. $C_8F_{17}(CH_2)_2SH$, TFAA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp. (67%); (c) K_2CO_3, MeOH, **44** (75%); (d) 1. SmI_2, THF, MeOH, room temp.; 2. AcOH, EtOH, 100 °C (83%); (e) 1. ^{t}BuOK, THF, –40 °C; 2. CF_3CH_2OH, MeI, THF, Δ (69%).

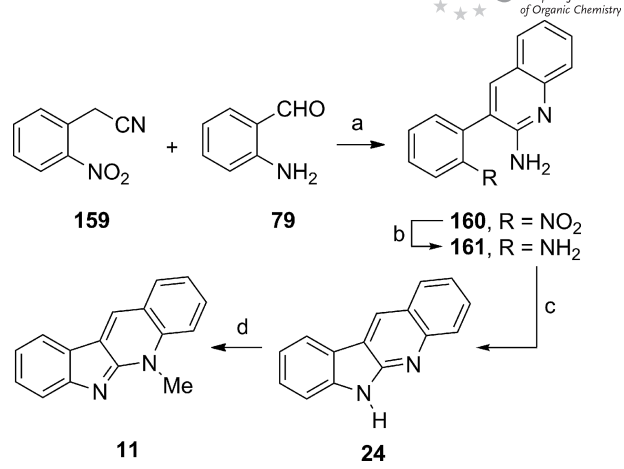
and selective *N*-methylation afforded a 69% yield of neocryptolepine.

In 2010 Haddadin's group disclosed an efficient four-step total synthesis of neocryptolepine and related compounds based on a variation of the Friëdlander reaction[105] for the synthesis of the quinolone moiety and a diazotization reaction to form the indole heterocycle.[25b]

As shown in Scheme 26, condensation of *o*-aminobenzaldehyde (**79**) with (*o*-nitrophenyl)acetonitrile (**159**) in methanolic potassium methoxide at reflux afforded 2-amino-3-(2-nitrophenyl)quinoline (**160**) in 73% yield, as an easy to purify yellow solid.

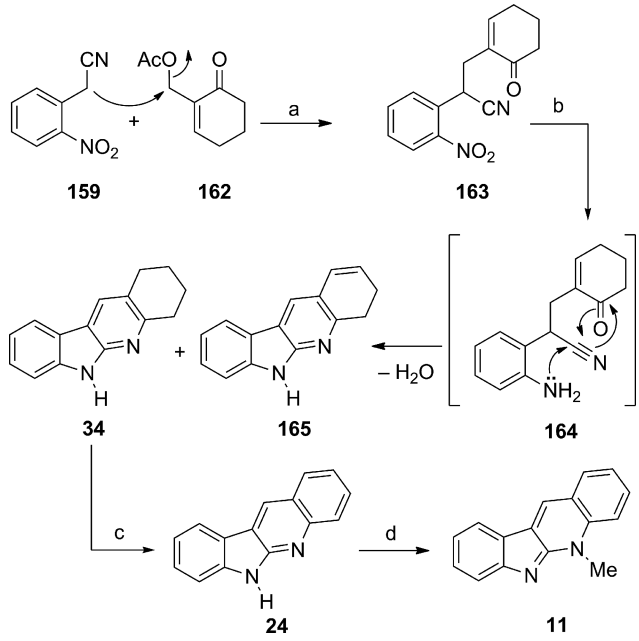
Reduction of the nitro moiety in **160** with zinc in AcOH to afford the diamine derivative **161** proceeded in moderate yield. Diazotization and cyclization of **161** with sodium nitrite and HCl afforded 6*H*-indolo[2,3-*b*]quinoline (**24**) in 54% overall yield. Although diazotization of either site can lead to **24**, it can be assumed that the 2-aminoquinolone, being more basic (pK_a = 7.2) is diazotized preferentially to the aminophenyl system (pK_a = 5.2).[106] Final selective *N*-methylation of **24** with dimethyl sulfate in acetonitrile[107] provided the natural product in 70% yield.

In 2012, Basavaiah and Mallikarjuna Reddy[108] reported a methodology for the synthesis of pyrido[2,3-*b*]indole de-



Scheme 26. Reagents and conditions: (a) KOH, pyrrolidine (cat.), MeOH (73%); (b) Zn, AcOH, 10–15 min; (c) $NaNO_2$, HCl, MeOH (54% overall); (d) Me_2SO_4, MeCN (70%).

rivatives from Baylis–Hillman acetates (Scheme 27). Their protocol involves the monoalkylation of conveniently substituted 2-nitroarylacetonitriles with the BH-acetates, the reduction of the nitro group, and formation of the five- and six-membered rings in an operationally simple one-pot procedure.



Scheme 27. Reagents and conditions: (a) K_2CO_3, THF, room temp., 48 h; (b) Fe, AcOH, reflux, 1 h (40% overall); (c) DDQ, dioxane, reflux, 8 h (68%); (d) MeI, THF, reflux, 11 h (82%).

Accordingly, the Baylis–Hillman alcohol resulting from the condensation of formaldehyde and cyclohex-2-enone was acetylated and the thus-obtained ester **162** was used for alkylation of (2-nitrophenyl)acetonitrile (**159**), affording nitrile **163**. Next, the iron-mediated reduction of the nitro moiety triggered the cyclization, which afforded a 2:1 mixture of tetracycles **34** and **165** in 40% overall yield through the intermediacy of aniline **164**, after cyclization, double

bond isomerization, and partial dehydrogenation. Fortunately, full dehydrogenation of the mixture[33] with DDQ in dioxane at reflux furnished a 68% yield of **24**,[24a] which was finally methylated to afford **11** (82% yield). Although the overall yield of **11** was not too high, the protocol demonstrated the importance of the Baylis–Hillman reaction as a source of precursors for the synthesis of heterocyclic compounds.

Table 1 summarizes the performances of the most relevant syntheses of the natural product, before (Entries 1 and 2) and after its discovery as a natural product, the latter spanning the period from 1997 to 2013. Thirty-two different syntheses are included. The reaction characteristics are expressed in terms of class of starting materials (strategic approach to the target), classified as in the above synthetic section, number of steps involved, and overall yield of the synthetic sequence. The corresponding literature references are also given.

Table 1. Summary of the performances of the most relevant syntheses of neocryptolepine.

Entry	Year of publication	Strategy or approach[a]	Number of steps	Overall yield [%]	Reference number
1	1948	B	4	9.5	[24a]
2	1988	B	3	8.4	[24b,24c]
3	1997	B	7	24.1	[62c]
4	1997	C	5	11.2[b]	[81a]
5	1999	C	9	25.8	[35]
6	2001	C	9	9.3	[89]
7	2002	C	6	18.5	[82b]
8	2002	C	6	25.2	[91]
9	2002	C	5	24.9	[25a]
10	2004	A	5	16.9	[33]
11	2004	A	4	17.9	[33]
12	2004	A	1	75.0	[39]
13	2006	B	3	58.1	[66]
14	2007	C	3	42.0	[96]
15	2008	A	3	37.7[b]	[37]
16	2008	A	3	23.8	[41]
17	2008	B	2	80.1[b]	[69]
18	2009	A	1	45.0[b]	[48a]
19	2009	C	5	19.3	[98]
20	2010	A	6	20.6	[52]
21	2010	C	4	27.6	[25b]
22	2011	A	1	65.0[b]	[51]
23	2011	A	3	68.0	[54a]
24	2011	A	1	77.0	[55]
25	2011	A	2	53.1	[57]
26	2011	B	3	88.2	[70]
27	2011	B	2	98.0	[75]
28	2012	A	3	43.0[b]	[45]
29	2012	A	1	45.0[b]	[48b]
30	2012	A	3	68.0	[60]
31	2012	C	4	22.3	[108]
32	2013	B	4	27.6[b]	[73]

[a] A: From indoles; B: from quinolones; C: from benzenoids. [b] Formal total synthesis.

Table 1 also contains a few formal total syntheses (Entries 4, 15, 17, 18, 22, 28, 29, and 32) and approaches that, through the employment of more complexly functionalized starting materials (Entries 12, 23, and 25), efficiently reached the natural products in only few steps.

Some sequences were highly step-efficient, employing three or fewer stages (Entries 13, 14, 16, 23, 25–27, and 30), whereas others exhibited overall yields exceeding 85% (Entries 26 and 27). Very long sequences, with up to nine steps, have also been reported (Entries 3, 5, and 6), being included among the first syntheses of the natural product, whilst the literature records a handful of approaches that afforded neocryptolepine in less than 20% overall yield (Entries 1, 2, 6, 7, 10, 11, and 19).

4. Biological Activity of Neocryptolepine and Its Derivatives

The biological activity of the indoloquinoline alkaloids has recently been reviewed.[109] Compounds containing this ring system have been reported as antimuscarinics, antibacterials, antivirals, antifungals, and cytotoxics, also displaying antihyperglycemic and antitumor activity with low toxicity. Therefore, they are currently considered interesting scaffolds for drug discovery.

4.1. Ethnomedical Uses of *Cryptolepis sanguinolenta*

Cryptolepis sanguinolenta is a thin-stemmed twining and scrambling shrub, up to 8 m in length,[110] which contains a yellow-orange juice that becomes red upon drying. The plant is native to the West African coast, being found in Ghana, Cote d'Ivoire, Guinea, Guinea-Bissau, Mali, Nigeria, Senegal, Sierra Leone, Angola, Congo, Uganda, and Cameroon. It is known under the names of nibima, kadze, gangamau, or yellow-dye root, and in the Yoruba-speaking areas of Nigeria it is called "paran pupa".

The plant has long been employed in the dyeing of textiles and leather,[111] and is also used by traditional herbalists in Ghana, Nigeria, Congo, Zaire, and Senegal. It has been proposed that the root and leaf extracts have hypotensive, antipyretic, antiinflammatory, antidiarrheal, antibacterial, and antimalarial effects.[112]

The roots of the plant are employed in traditional medicine in Central Africa[113] in the form of an aqueous macerate of the root bark, whereas in West Africa the entire root is used as an aqueous decoction. In Ghana, *C. sanguinolenta* has been used in clinical therapeutics since 1974, to treat upper respiratory tract and urinary disorders, fevers, and malaria;[114] in Congo it is employed as stomachic, whereas in Nigeria it is prescribed for rheumatism and urogenital infections.

The plant is also employed for treatment of various disorders, including intestinal conditions, amebiasis, colics, hepatitis, and spasms.[115] In addition, antibacterial and vasodilation activities have also been reported.[18] A tea containing the powdered roots of the plant, with the name of Phyto-Laria,[116] is available and prescribed for the treatment of malaria and fever.[117]

4.2. DNA-Binding Activity

The therapeutic potential of small organic molecules is often the result of a balance between the output of their

interference with physiological and pathological processes. DNA has been a major target for anticancer drugs because they can be structurally tuned to interfere with transcription and DNA replication.[118]

Peczynska-Czoch et al. prepared a series of analogues of neocryptolepine that were demonstrated to stimulate the formation of cleavable complexes between topoisomerase II and calf thymus DNA at concentrations between 0.4 and 10 μM.[24c]

The interaction of the analogues with DNA was studied by measuring the increase in the denaturating temperature (ΔT_m) of calf thymus DNA. The ΔT_m values for the compounds bearing a methyl group on the pyridine ring were found to be about 10 times higher than those for compounds lacking this feature. In addition, it was observed that the higher the number of methyl groups in the molecule, the greater the contribution to the increase in the T_m of calf thymus DNA, reaching 19 °C in the case of the most substituted compound **166**. For neocryptolepine, ΔT_m = 5.2 °C.

Dialysis competition and MS experiments confirmed that neocryptolepine binds to DNA, preferring GC- over AT-rich duplex sequences, but also recognizes triplex and quadruplex structures, exhibiting a significant preference for triplexes over quadruplexes or duplexes. The natural product is also a weak telomerase inhibitor.[119]

When a series of linear, methyl-substituted derivatives of 5*H*-indolo[2,3-*b*]quinolines were tested for their mutagenic activity with the battery of Ames test strains, it was observed that the activity was strongly influenced by the positions and number of methyl groups. The tested compounds acted like DNA frame-shift mutagens.[120]

4.3. Topoisomerase-II-Inhibiting Activity

Protein–ligand interactions are a product of their mutual recognition. The pharmacological and toxicological effects that define the therapeutic potential of small molecules are a consequence of the ability of the latter to interact with functionally different targets.

Neocryptolepine stimulates DNA cleavage by the human DNA-relaxing enzyme topoisomerase II. The natural product exhibits an affinity for DNA five times lower than that of cryptolepine, and the poisoning activity is slightly more pronounced with cryptolepine than with neocryptolepine. These observations provide a molecular basis to account for the reduced cytotoxicity of neocryptolepine in relation to cryptolepine.[121]

Godlewska et al. prepared a series of ω-(dialkylamino)-alkyl derivatives of neocryptolepine and tested their ability to act as topoisomerase II inhibitors.[122] They observed that 6*H*-indolo[2,3-*b*]quinolines substituted with (dialkylamino)alkyl chains at C-2, C-9, or N-6 are able to bind to DNA and to interfere with the topoisomerase II catalytic activity in vitro.

These and other authors[123] also found that the cytotoxicity of the neocryptolepine derivatives corresponded well with their ability to arrest cell proliferation in the G2M phase of the cell cycle. In these tests, the analogues substituted at N-6 behave as the most effective compounds. These compounds exhibited the ability to overcome multidrug resistance generated by various cellular mechanisms in three different cell lines. The results suggested that topoisomerase II may not be the only cellular target for these compounds.[124]

These bioactivity data were employed in a computational study, in which the calculated molar refractivity was used as a parameter for estimating molecular polarizability.[125] The polarizability of a molecule is a physical property relevant in the area of quantitative structure–activity relationships for analysis of chemical–biological interactions.

4.4. Cytotoxic Activity

In early investigations, it was found that 5,11-dimethyl-5*H*-indolo[2,3-*b*]quinoline (DiMIQ, **167**), an 11-methylated analogue of neocryptolepine, is the most promising lead compound for potential anticancer agents among different indoloquinoline derivatives (Figure 4).[24b]

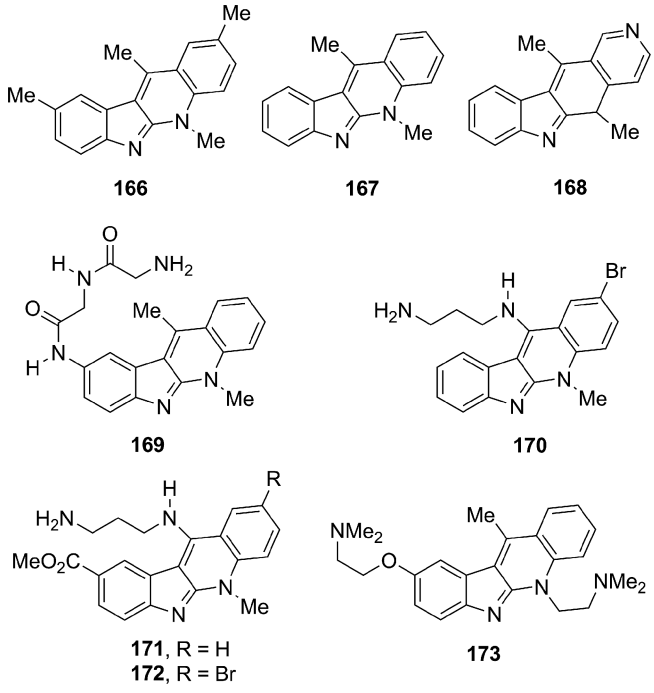


Figure 4. Chemical structures of DiMIQ, ellipticine, and C-9 derivatives.

DiMIQ has a great structural similarity to ellipticine (**168**), a DNA intercalator with analogous physicochemical properties.[126] Unlike its 6,11-dimethyl-6*H* analogue, DiMIQ has potent antiproliferative activity in vitro, resulting from its ability to intercalate the DNA and to create a drug–DNA–topoisomerase II complex.[24c,127]

Peczynska-Czoch et al. studied the cytotoxic activities of a series of analogues of neocryptolepine.[24c] They found that the activities were strongly influenced by the positions and number of the methyl substituents; in addition, they

observed that the presence of a methyl group on the N-5 pyridine nitrogen was essential for good levels of cytotoxicity. Their cytotoxicities against KB cells (ID_{50}) was in the 2–9 μM range.

Because DiMIQ has low aqueous solubility, its practical application for the treatment of cancer is rather limited;[128] however, differently substituted 5*H*- and 6*H*-indolo[2,3-*b*]-quinolines were synthesized.[122,129] As a result, it has been concluded that 5-methylated derivatives are more cytotoxic than their 6-methylated analogues.[130] It was also found that attachment of hydrophilic moieties increased the hydrophilic properties and decreased the hemolytic activity of DiMIQ.

The 9-glycylglycine conjugate **169** inhibited tumor growth in mice and was less toxic than DiMIQ, confirming that amino acid derivatives of **11** may be promising lead compounds for the development of new, highly potent, and selective agents against cancer.[131]

Amino-functionalization of C-11 improves potency and selectivity. Bromo derivative **170** exhibited an IC_{50} = 0.12 μM against the human leukemia MV4–11 cell line, with a binding constant to salmon fish sperm DNA of 2.93×10^5 L mol^{-1}.[130] Introduction of an ester moiety at C-9 improves the antiproliferative activity and selectivity. Compound **171** exhibited IC_{50} = 0.044 μM against the MV4–11 human leukemia cell line, whereas **172** was 28 times more potent against the human colon cancer cell line HCT116 than against BALB/3T3, a normal mice fibroblast cell line.[132]

11-Methyl-N^6-substituted neocryptolepine derivatives functionalized at C-2 or C-9 with dimethylaminoethyl chains linked to the heteroaromatic core by ether, amide, or amine bonds – such as compound **173** – were recently prepared as more soluble analogues of DiMIQ.[133] They were demonstrated to be cytotoxic against various cell lines including multidrug resistant ones (LoVo/DX, MES-SA/DX5, and HL-60 sublines). These compounds inhibit topoisomerase II activity and induce arrest of the G2M phase cell cycle in Jurkat cells.

4.5. Antibacterial and Antifungic Activities

The roots of *C. sanguinolenta* have long been used in African folk medicine for the treatment of infectious diseases. In view of the continuing need for new antibacterial and antifungic agents, plants have been under constant scrutiny during the last decades, in the search for new chemotherapeutic agents.

After the initial report by Boakye-Yiadom[134] on the antibacterial activity of cryptolepine against *Staphylococcus aureus*, Pieters et al. examined the antibacterial and antifungic activities of neocryptolepine. They observed that the natural product exhibited antibacterial activity against a wide range of Gram-positive bacteria (MIC < 100 μg mL^{-1}), inhibiting *B. cereus, M. fortuitum*, *P. vulgaris*, and *S. aureus*, among others. However, the natural product was less active against Gram-negative bacteria such as *K. pneumoniae*, *P. aeruginosa* and *E. coli*.

The antibacterial activity of neocryptolepine is bacteriostatic in nature rather than bactericidal. No antifungal activity against *E. floccosum*, *T. rubrum*, or *A. fumigatus* could be observed at a test concentration of 100 μg mL^{-1}.[135]

Peczynska-Czoch et al. prepared a series of alkyl-substituted analogues of neocryptolepine and studied their antibacterial and antifungal activities.[24c] The analogues exhibited significant activity against prokaryotic and eukaryotic organisms, inhibiting the growth of Gram-positive bacteria (MIC ≈ 5 μM), and their antimicrobial activity was strongly influenced by the positions and number of methyl substituents.

Kazmareck et al.[136] also prepared a series of 5*H*-indolo[2,3-*b*]quinoline derivatives with methoxy and methyl groups at C-2 and C-9 and evaluated their activity against several bacterial strains. These derivatives exhibited significant activity against Gram-positive bacteria and no antimicrobial activity was observed for Gram-negative bacteria, thus confirming the behavior of neocryptolepine. In addition, a series of ω-(dialkylamino)alkyl derivatives of neocryptolepine synthesized by Godlewska et al. also exhibited antimicrobial activity against Gram-positive bacteria.[122]

Neocryptolepine was evaluated against several fungal strains. Despite inhibiting the growth of the yeast *C. albicans*, the natural product proved to be essentially inactive at the 100 μg mL^{-1} level. Alkyl-substituted derivatives of neocryptolepine prepared by Peczynska-Czoch inhibited the growth of some pathogenic fungi (MIC = 0.03–0.25 μM).[24c]

4.6. Antiprotozoal Activity

Among the parasite-borne diseases, protozoa are responsible for causing leishmaniasis, Chagas disease, malaria, African trypanosomiasis, schistosomiasis, giardiasis, and amebiasis. Caused by *Trypanosoma cruzi*, Chagas disease is currently one of the most serious health problems of parasitic origin, taking third place in the number of deaths per year, after malaria and schistosomiasis. The poor effectiveness of the available drugs and the number of deaths caused by the disease demand urgent pharmaceutical solutions.

Neocryptolepine itself has antiprotozoal activity against *T. brucei rhod* and *T. cruzi*, exhibiting IC_{50} values of 2.23 ± 0.82 μM and 2.01 ± 1.30 μM, respectively. However, the natural product is less active than the corresponding drug references melarsoprol ($IC_{50} = 0.004 \pm 0.002$ μM) and benznidazole ($IC_{50} = 1.50 \pm 0.58$ μM).[67a,137]

It was observed that some 2-substituted neocryptolepine analogues (2-bromo-, 2-nitro-, and 2-methoxy-9-cyano-) also exhibited good antitrypanosomal activity against *T. brucei* and *T. cruzi*, without being cytotoxic to MRC-5 cells.[91]

Because of these precedents, neocryptolepine was included in different sets of compounds used for developing computational models for classification of antitrypanosomals and for rational design of new drugs.[138] The natu-

ral product was also studied in docking experiments into validated drug targets of *T. brucei*, which include trypanothione reductase, rhodesain, farnesyl diphosphate synthase, and triosephosphate isomerase.[139]

Interestingly, neocryptolepine also exhibited weak activity against *Leishmania donovani*, with IC_{50} = 49.5 ± 3.7 μM, almost two orders of magnitude higher than the standard miltefosine (IC_{50} = 0.56 ± 0.07 μM).[137] Leishmaniasis is a vector-transmitted protozoal disease that currently affects 12 million people in 88 countries.

4.6.1. Antimalarial Activity

Malaria is a tropical disease caused by parasitic protozoa of the genus Plasmodium. The most serious infections are those provoked by *Plasmodium falciparum*. Despite considerable efforts, the disease remains one of the most important infectious diseases worldwide. Therefore, the WHO has placed malaria next to tuberculosis and AIDS as a major contagious disease.

Malaria is endemic in wide areas in the tropics, but it is also present in temperate regions and it is expected to increase in prevalence due to global climate change. Because of increasing resistance to antimalarial drugs, there is a continuous and unavoidable need for new therapeutic agents against this disease.[140]

Following clues resulting from ethnomedical use of the plant and based on literature precedents relating to other indoloquinolines,[141] Cimanga's group carried out one of the first series of studies on the antimalarial activity of neocryptolepine.[142] They demonstrated that the natural product exhibited a strong antiplasmodial activity against chloroquine-resistant *P. falciparum* strains (IC_{50} = 35 ± 0.7 ng mL^{-1}, 51 ± 0.1 ng mL^{-1}, and 65 ± 1.3 ng mL^{-1} against D-6, K-1, and W-2 strains, respectively), significantly higher than the antiplasmodial potency of chloroquine (IC_{50} = 72 ± 0.1 and 68 ± 0.1 ng L^{-1} against K-1 and W-2 strains, respectively).

It was then speculated that substitution of neocryptolepine could favor potency and selectivity of the antimalarial activity. Therefore, several sets of substituted neocryptolepines were synthesized. The group of Pieters[91] prepared a series of derivatives of neocryptolepine by the biradical cyclization approach, and these were evaluated for their biological activity against chloroquine-sensitive (Ghana) and -resistant (W2) strains of *Plasmodium falciparum*.

In initial work with these analogues, it was found that 2-bromoneocryptolepine (**175**, Figure 5) exhibited one of the best profiles, with low toxicity, good potency for inhibiting β-hematin formation, and good activity against chloroquine-resistant *P. falciparum*. This compound displayed low affinity for DNA and no inhibition of topoisomerase II; therefore, it was considered a promising lead for new antimalarial agents.[143] It was also observed that 1-methyl-1*H*-pyrido[2,3-*b*]indole (**174**), which lacks one of the benzenoid rings, proved to be much less active and less cytotoxic than neocryptolepin and its derivatives.[144]

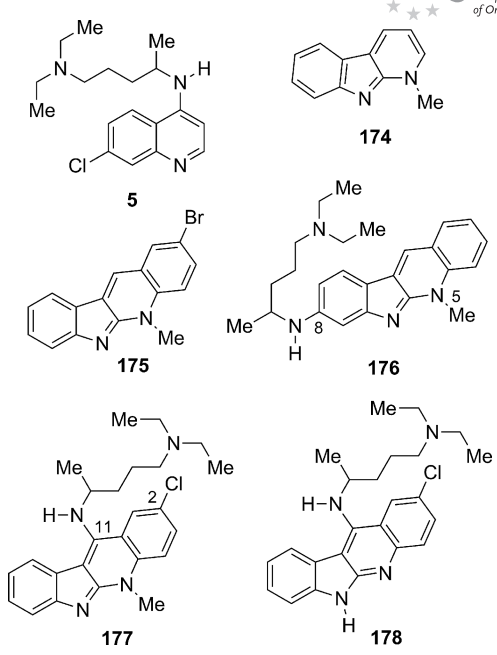


Figure 5. Chloroquine and relevant halo and aminoalkylamino derivatives of neocryptolepine.

It was demonstrated that the antiplasmodial mechanism of action of chloroquine as a relevant antimalarial agent is based on inhibiting the transformation of hematin into hemozoin.[145] This can be evaluated in vitro by measuring the conversion of hemin (hematin as chloride) to β-hematin (synthetic hemozoin). Accordingly, functional assays and in vitro tests were used to obtain additional information on the mechanism of action of neocryptolepine and its derivatives. These included the inhibitory assay of formation of β-hematin (heme detoxification), inhibition of topoisomerase II, and the methyl green displacement assay (interaction with DNA).

Some studies have demonstrated that, although their in vitro antiplasmodial activities are lower than that of chloroquine,[146] 2- or 3-substituted neocryptolepine derivatives have about the same ability as chloroquine to inhibit the formation of β-hematin. This indicates that inhibition of the formation of hemozoin makes at least an important contribution to their antiplasmodial activity. Mathematical models for the classification of neocryptolepine analogues as inhibitors of β-hematin formation have also been developed.[147]

Inspired by the structure of chloroquine, El Sayed's group[30c] synthesized a series of chloro-, aminoalkylamino-, and aminoalkylamino-chloro-substituted neocryptolepine derivatives and evaluated their activity as antiplasmodial agents. Mono- and dichloro-substituted neocryptolepines displayed poor potency, showing lower activity than neocryptolepine.

On the other hand, neocryptolepine analogues bearing aminoalkylamino moieties attached at C-2, C-3, C-8, C-9, and C-11 were prepared. It was observed that introduction of these chains substantially increased the antiplasmodial activity of the compounds, and the most efficient analogues

exhibited antiplasmodial activities in the nanomolar range. Compound **176** displayed IC_{50} = 0.01 μM and a high selectivity index (SI = 1800).

The neocryptolepine derivatives bearing alkylamino side chains inhibited β-hematin formation; the same was observed in the case of chlorinated derivatives bearing an N^1,N^1-diethylpentane-1,4-diamino substituent at C-11. Furthermore, removal of the N^5-methyl group increased the activity.

Introduction of the aminoalkylamino side chains did not result in a marked loss of DNA-interacting properties. Furthermore, all compounds showing interaction with DNA were also cytotoxic to various degrees. However, compounds that were inactive in both functional assays did not show pronounced antiplasmodial activity.

Heterocycles **177** and **178** were also tested in a Swiss mice model against *Plasmodium berghei*. After daily intraperitoneal injection of 50 mg kg^{-1} for five consecutive days, **177** showed 100% reduction in parasitemia on day 4, but half of the animals had died by day 7, due to its toxicity. An intraperitoneal dose of 20 mg kg^{-1} was ineffective. On the other side, the nor-compound **178** was less potent, and 100% reduction in parasitemia could not be obtained, emphasizing the role of methyl groups as nitrogen substituents.

The synthesis and in vitro antimalarial activity of analogues bearing linear and branched dibasic side chains at C-11 revealed that a branched structural motif is not superior for antimalarial activity over a linear side chain in the antimalarial test against the chloroquine-sensitive *P. falciparum* strain NF54.[148]

It was also observed that thioureido derivatives such as **179** (Figure 6) showed lower cytotoxicity but higher selectivity than the linear precursor and stronger β-hematin inhibition than the corresponding free amines. Combinations of ureido derivatives bearing 2-Cl and 2-OMe functions also exhibited good antimalarial potency.[149]

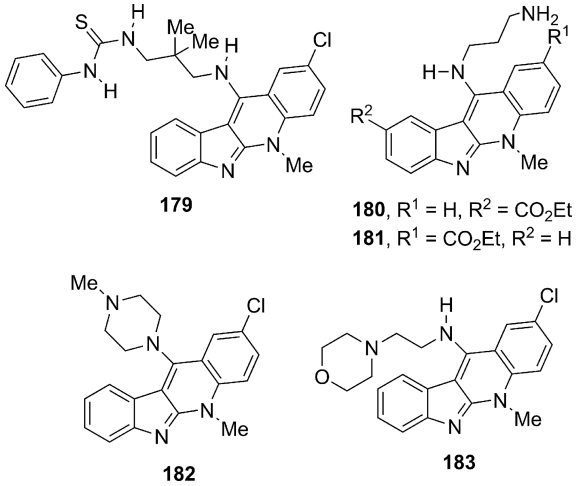


Figure 6. Thioureido and ester derivatives of neocryptolepine.

Introducing ester groups at C-2 and/or C-9 of neocryptolepine (Figure 6) and functionalizing C-11 with 3-aminopropylamino substituents end-capped with urea/thiourea units afforded compounds with augmented antiplasmodial activity against two different *Plasmodium berghei* strains (NF54 and K1) and a low cytotoxic activity against normal cells.[150]

In vivo testing of compounds **180** and **181** against the NF54 strain of *Plasmodium berghei* on female mice showed that the introduction of the ester group substantially increased the antiplasmodial activity of the neocryptolepine core. Similarly, the thiourea group attached to the terminal amino function of the group at C-11 also showed a contribution to the antiplasmodial activity.

In addition, in this series, structure–activity relationship studies revealed a weak correlation between antiplasmodial activity and β-hematin activity and a linear correlation between the polar surface areas of the molecules and β-hematin inhibition. Therefore, factors likely to be involved in the uptake of these compounds into the parasite appeared to be most important predictors of this biological activity.[151]

4.7. Molluscicidal Activity

Several neocryptolepine derivatives such as **182** (Figure 6) have been found to cause 100% snail mortality of *Biomphalaria alexandrina* at a 5 ppm level, with LC_{50} values between 0.63 and 3.9 ppm (LC_{50} for niclosamide is 0.2 ppm) after 24 h.

Other neocryptolepine derivatives displayed in vitro schistosomicidal activity. The most effective compound – **183** – had IC_{50} = 1.26 and 4.05 μM against the Egyptian and Puerto Rican strains of *Schistosoma mansoni*, respectively.[152]

5. Spectroscopic Studies Involving Neocryptolepine

Kamienska-Trela's group prepared a set of ^{13}C NMR spectroscopic data, including one-bond spin–spin coupling constants obtained for a large series of heteroaromatic compounds.[153] These compounds included 6-substituted quinolines, their *N*-oxides, and 2- and 5-methoxyindoles, among others. The results obtained for these basic molecules were compared with those determined for a series of variously substituted 5*H*- and 6*H*-indolo[2,3-*b*]quinolones in order to understand the electronic structures of the last two sets of compounds.

On the other hand, Marek's group studied the ability of indoloquinolines, including neocryptolepine, to enter into intermolecular interactions with solvents, with the aid of ^{13}C and ^{15}N NMR spectroscopy and density functional theory (B3LYP/6–31G**) calculations.[154] They found that the anisotropy of the electron distribution underwent significant changes, reflected in the span of the chemical shielding tensor ($\Omega = \sigma_{11} - \sigma_{33}$). The solvent effects on the span of the ^{13}C and ^{15}N shielding tensor reflected a significant influence of solute–solvent interactions, which depended on the type of atom.

For alkaloids, acid–base dissociation constants are an important characteristic, thought to be associated with biological activity. Therefore, the same group studied the pK_a values, and their structural dependence, for several natural and synthetic indoloquinoline alkaloids, including cryptolepine and its isomers neocryptolepine, isocryptolepine, and isoneocryptolepine,[137] as well as some substituted neocryptolepine derivatives.[155]

The evaluation was carried out by ^{1}H NMR spectroscopy in a mixture of solvents. The data were recalculated for water solutions by use of suitable correction factors.[156] It was observed that H-11 of cryptolepine exhibits a pH-dependent chemical shift and that the NMR shieldings of the hydrochloride salt were different from those of the base.

Kania et al. studied the concentration-dependent variation of ^{1}H NMR chemical shifts in spectra of 5*H*- and 6*H*-indolo[2,3-*b*]quinolines. For some proton resonances they observed upfield shifts with increasing concentration of the alkaloids. The findings were explained as the result of self-association of the indoloquinolines in solution. Assuming the existence of a dimer–monomer equilibrium, they determined the dimerization constant of the process.[157]

StrucEluc is an expert system that functions as a tool to allow automated and assisted natural product structure elucidation with the aid of 1D and 2D NMR spectra. Indoloquinoline alkaloids have been used to demonstrate the potential of the system for structural elucidation of natural products when there is a lack of connectivity information, a characteristic of proton-deficient compounds.[158]

The strategy included using a ^{13}C NMR spectrum as input to search a database for fragments to fill gaps in the data. 2D NMR spectroscopic data analysis allows embedding of the fragments found in the library or proposed by the user in molecular connectivity diagrams for further analysis.

Gabelica's group carried out a systematic investigation of duplex DNA complexes with minor groove binders and intercalators, such as neocryptolepine, by ESI-MS and ESI-MS/MS in the negative and positive ion modes.[159] They were able to determine the apparent solution-phase equilibrium binding constants by measuring relative intensities in the ESI-MS spectrum. Negative ion mode gave the most reliable results.

Neocryptolepine is a neutral nonpolar intercalator that interacts only through stacking between the base pairs. It is a ligand for which the complex dissociates mainly through the loss of the neutral drug. However, no complex could be observed in the positive ion mode whatever the sequence of the double-stranded DNA used. This is in contradiction with the ESI-MS negative ion mode results, and also with the literature data demonstrating that neocryptolepine binds to DNA.

ESI-MS allowed probing of subtle differences in the drug–DNA intermolecular interactions. Cryptolepine and neocryptolepine are positional isomers, with the former having higher binding constants than the latter.[121,123] MS/MS for both complexes with Dk66 at a collision voltage of 10 V revealed that the complex with neocryptolepine dissociates more rapidly than that with cryptolepine. This reflects their relative solution-phase binding affinities, which are due to specific intermolecular interactions.

Furthermore, superimposition of the chemical structures of cryptolepine and neocryptolepine onto a GC pair revealed that for cryptolepine the NH group and the N–Me group can each interact with a C=O group of the base pair because they are on opposite sides of the molecule. However, in the case of neocryptolepine, which has both groups on the same side, one of these interactions is lost. In addition, steric hindrance was observed between the N–Me group of the alkaloid and one of the NH_2 groups of the base pairs.

Conclusions

As a chemical structure of academic interest, neocryptolepine was prepared in the laboratory at least twice before its isolation from a natural source, in 1996. Then it became a new member of the indoloquinoline alkaloids, a small family of natural products originating from a few natural sources. Exhaustively studied during the last two decades, neocryptolepine became a highly regarded objective, which was synthetically targeted from three different main flanks in approximately 20 imaginative and usually short total syntheses.

The natural product was demonstrated to possess several interesting biological activities, including its ability to interact with DNA and to inhibit the enzyme topoisomerase II, these being probably the causes of the observed antiproliferative, cytotoxic, and antitumor effects. It has also shown to be endowed with antifungal and selective antibiotic properties, as well as with molluscicidal and antiprotozoal activities, being particularly interesting as an antimalarial. Some of these properties could prove valuable to human medicine.

This wide range of potentially useful properties of the natural product drove synthetic attention to the preparation of derivatives for bioactivity testing. Currently, neocryptolepine and some of its more potent analogues still command great interest from the synthetic and medicinal chemistry points of view.

The modes of action of numerous natural products are considered to be complicated. Decoding the mechanism of action of neocryptolepine and its derivatives against its various targets and improving its desired effects through a rational design approach may be at the heart of the development of new therapeutic strategies.

In view of the continuous evolution of this area, it is almost certain that more findings relating to its usefulness await; the future also holds the promise of unveiling more surprisingly active derivatives, especially in the antitumor and antimalarial drug discovery arenas.

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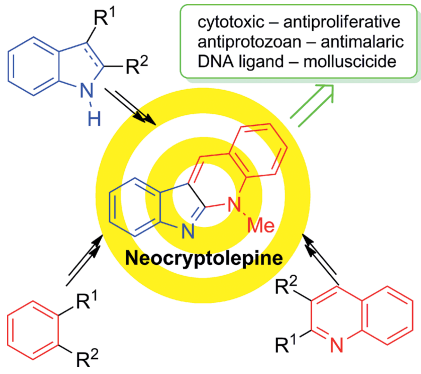
Neocryptolepine is an indoloquinoline alkaloid, isolated from *Cryptolepis sanguinolenta*. The isolation of the natural product and the numerous and different approaches directed towards its total synthesis, as well as its biological activity profile and spectroscopic studies, are discussed.



Natural Product Synthesis

Keywords: Total synthesis / Natural products / Medicinal chemistry / Alkaloids / Nitrogen heterocycles / Cyclization

