Synthesis M. V. Méndez et al. Short Review

Isolation, Synthesis, and Biological Activity of Quindoline, a Valuable Indoloquinoline Natural Product and Useful Key Intermediate

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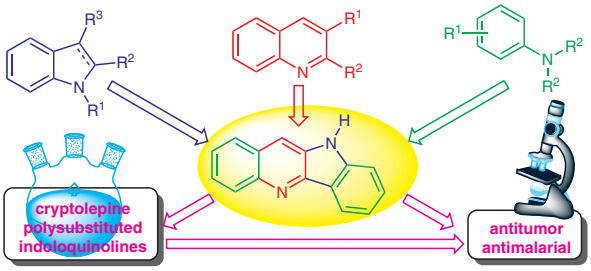

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Abstract Quindoline is one of the simplest naturally occurring monomeric indoloquinoline alkaloids. Chemists exhibited interest in this compound before it was isolated from a natural source. The different approaches toward the total synthesis of the natural product and its performance in various biological tests are discussed. Aspects related to the isolation of quindoline from different ethnomedicinally relevant plants around the world are also reviewed.

Key words quindoline, heterocyclic natural products, chemical synthesis, indoloquinolines, bioactive alkaloids, synthetic approaches

1 Introduction

Historically, humankind has used plants to supply almost all of its basic needs, such as foods, clothing, shelter, and medicines. In this process, over several millennia, indigenous cultures around the world were exposed to the huge diversity of the plant kingdom and gathered an enormous amount of empirical knowledge about the suitability of various plants for different medicinal purposes.[1]

Thus, plants became the basis of sophisticated traditional medicine systems that have been in existence for thousands of years. The World Health Organization (WHO) has estimated that approximately 80% of the world's inhabitants rely mainly on such traditional medicines for their primary health care.[2]

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Natural products and their derivatives have a long-standing reputation as being a rich source of bioactive compounds suitable for therapeutics. Their impact on the modern pharmaceutical drug arsenal has been so important that approximately 25% of the currently available prescription drugs are plant derived.

The fact that many of these compounds were discovered as a result of chemical studies directed at the isolation of the active substances from plants used in traditional medicine is proof of the strong evolutive link between ethnomedicine and modern pharmacy.[3]

The alkaloids from traditional herbal medicines have made many of the most substantial contributions to the discovery of new therapeutic agents and to the elucidation of biochemical pathways,[4] beginning with the landmark isolation of quinine in 1820, which gave birth to the modern pharmaceutical industry.[5]

The naturally occurring indoloquinolines are a small family of alkaloids, isolated mainly from *Cryptolepis sanguinolenta* (Lind.), family Asclepiadaceae.[6] These unique heterocycles bear indole and quinoline rings fused through their pyrrole and pyridine rings.

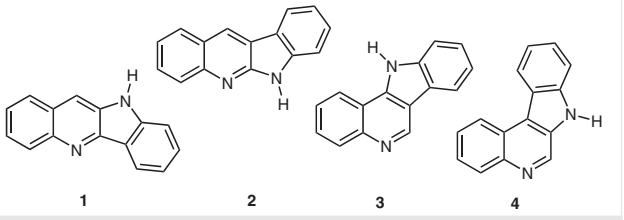

Figure 1 Some isomers of the indoloquinoline skeleton

Considering these characteristics, only four isomeric ring systems are possible (Figure 1), namely indolo[3,2-*b*]quinoline (quindoline, **1**), indolo[2,3-*b*]quinoline (quinindoline, **2**), indolo[3,2-*c*]quinoline (**3**), and indolo[2,3-*c*]quinoline (**4**). The cores of the natural indoloquinolines correspond to isomers **1**, **2**, and **3**. There are no natural examples of compounds of class **4**; however, the skeleton has been synthesized.[7]

Quindoline (**1**),[8] quinindoline (**2**),[9] quindolinone (**5**),[10] neocryptolepine (**6**),[11] cryptosanguinolentine (isocryptolepine, **7**),[12] cryptolepine (**8**),[13] 11-isopropylcryptolepine (**9**),[14] and cryptolepinone (hydroxycryptolepine, **10**)[15] are monomeric members of this family (Figure 2). Dimeric indoloquinolines have also been reported.[15,16,22a]

Several articles describe the pharmacological activity of different indoloquinoline alkaloids, their analogues and derivatives, revealing their antitumoral and antiparasitic activities as the most relevant ones.[17]

Quindoline (**1**) is one of the simplest indoloquinoline alkaloids, and according to molecular simulations, is a flat tetracyclic aromatic compound.[18] Its structural simplicity coupled to its bioactivity profile have converted the natural

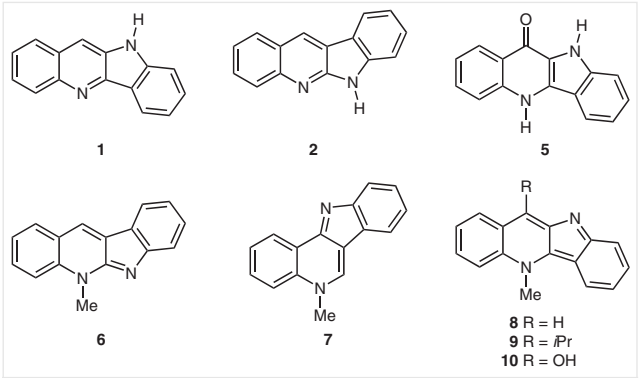

Figure 2 Naturally occurring indoloquinolines

product into an interesting synthetic target, a useful precursor for the preparation of its much-studied congener cryptolepine (**8**),[19] and also into a useful key intermediate toward more functionalized indoloquinolines.[20]

Therefore, the objective of this work is to review some key aspects of quindoline, including its isolation, the multiple synthetic approaches to its structure, and the biological activities exhibited by the natural product. Emphasis is placed on the most relevant developments of the last 25 years.

2 Isolation and Biogenetic Considerations

As with some other indoloquinolines, quindoline (**1**) was chemically synthesized before its discovery as a natural product. Compound **1** was not isolated from a plant source until 1978, when Slatkin and co-workers described the compound as a minor heterocyclic metabolite obtained from the roots of *Cryptolepis sanguinolenta*.[8] The alkaloid was re-isolated from the same source in 1991, when its structure was unequivocally assigned by NMR spectroscopy,[21] as well as in 1996 and in 2000.[22]

C. sanguinolenta is a tropical twinning and scrambling shrub indigenous to West and Central Africa,[23] where a decoction of its roots is used in traditional folk medicine to treat fevers, malaria, upper respiratory infections, and venereal diseases.[24]

In 2004, its isolation was reported from the leaves of *Justicia betonica* L. (Acanthaceae), collected from Balinaidu Kandriga (India).[9] Interestingly, this plant is found natively from India to tropical East Africa[25] and was introduced into Central America. The roots, leaves, and flowers of the plant are employed in the treatment of various gastrointestinal complaints. In India it is used in the treatment of diarrhea, whereas in Ethiopia it is indicated to treat snakebites in cattle. A combination of flower ash and leaves is prescribed in Kenia as a cough remedy, while in Uganda, it is employed to treat malaria.[26]

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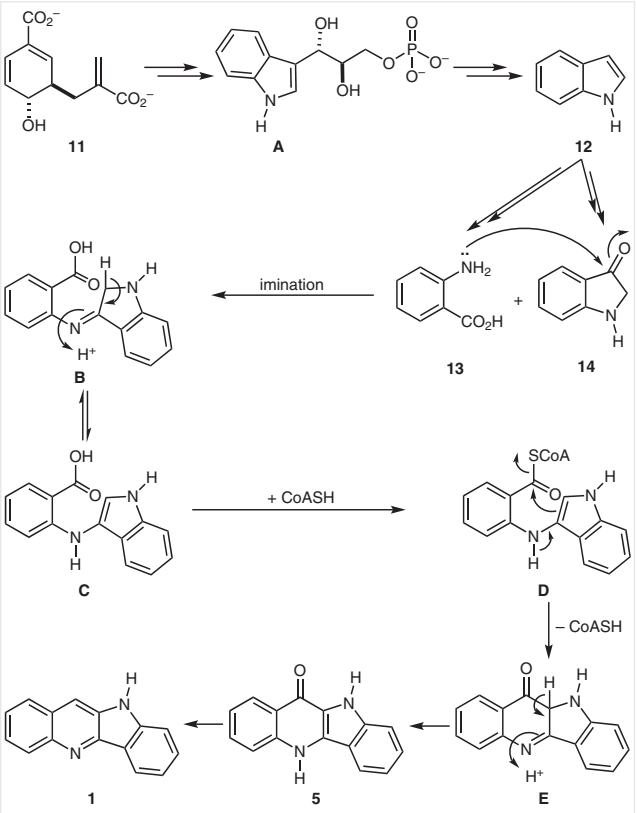
In 2013, quindoline was isolated from the CH_2Cl_2 extract of the dried stems of *Justicia secunda* (Acanthaceae),[27] collected from the Anton Valley in Panama, and identified by LC–DAD–APCI–MS analysis. The plant is used in Venezuela and other countries as a sanguineous depurative and antipyretic, and for the treatment of anemia,[28] hypertension,[29] chicken pox, diabetes, and amenorrhea.[30] Interestingly, compound **1** could not be found in the related *Justicia refractifolia* and *J. graciliflora*.

It was reported in 2017 that the natural product was also isolated from the aerial parts of *Sida rhombifolia* L. (Malvaceae), collected in Santa Rita city (Brazil).[31] This plant is widely distributed in tropical regions worldwide. In many African countries and islands of the Indian Ocean it is used to treat an ample variety of conditions.[32]

No biosynthetic studies have been carried out on the indoloquinolines. However, in 2016 Parvatkar and Parameswaran proposed that quindoline results from chorismate (**11**), through the intermediacy of indole-3-glycerol phosphate **A**, an intermediate of the metabolism of the amino acid tryptophan (Scheme 1).[6]



Scheme 1 Possible biogenesis of quindoline

Compound **A** is proposed to provided indole (**12**) as a known precursor of both, anthranilic acid (**13**) and 3-hydroxyindole (indoxyl, **14**).[33] Condensation of the latter with anthranilic acid results in the imine **B**,[34] which after isomerization to its more stable indole-type form **C** reacts with coenzyme A (CoASH) to afford the thioester intermediate **D**. This activated ester then cyclizes to **E** (freeing CoASH) and further isomerizes to furnish the more stable natural product quindolinone (**5**); finally, NADPH-assisted reduction and subsequent dehydration of the carbonyl moiety of **5** furnishes quindoline (**1**).

3 Total Syntheses of Quindoline

3.1 Early Synthetic Studies

Quindoline is a rare example of a natural product whose synthetic access was reported prior to its isolation from a natural source. Oddly, far more than a single effort was made to the synthesis of **1**, reflecting a feverish interest in this compound, as part of the then highly valued chemistry of indigo. Furthermore, the compound was obtained through both synthetic and degradative strategies.

It is currently recognized that the alkaloid was first well-described and structurally well-characterized as a synthetic product ($C_{15}H_{10}N_2$) by Fichter and Boehringer in 1906.[35a] However, the authors noticed that their compound was identical to 'indoline' ($C_{16}H_{14}N_2$) reported in 1877 by Schützenberger;[35b] 'indoline' was obtained by autoclaving indigotin at 180 °C with an aqueous mixture of $Ba(OH)_2$ and zinc powder. In turn, indigotin (**15**) was prepared by air-mediated oxidation of a basic solution of indigo-white (**16**, Figure 3).

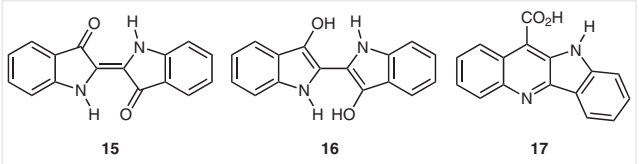


Figure 3 Chemical structures of indigotin, indigo-white, and quindoline-11-carboxylic acid

Giraud identified Schützenberger's indoline precursor as flavindine ($C_{32}H_{22}N_4O_4$) and introduced reduction with sodium amalgam as a superior method.[36a,b] This reduction procedure was later used by Armit and Robinson.[36c] On the other hand, Fichter and Rohner corrected the formula of flavindine to $C_{16}H_{10}N_2O_2$ and established its structure as quindoline-11-carboxylic acid (**17**),[37] as shown in Figure 3.

The exact details of the mechanism leading from indigo-white (**16**) to quindoline remain unknown, and no reaction mechanism has been proposed for this transformation. However, a plausible mechanistic picture can be drawn on the basis of present day knowledge.

In this sequence (Scheme 2), it is known that air-mediated oxidation of indigo-white (**16**) results in indigotin (**15**), which can be isomerized to intermediate **F** under the

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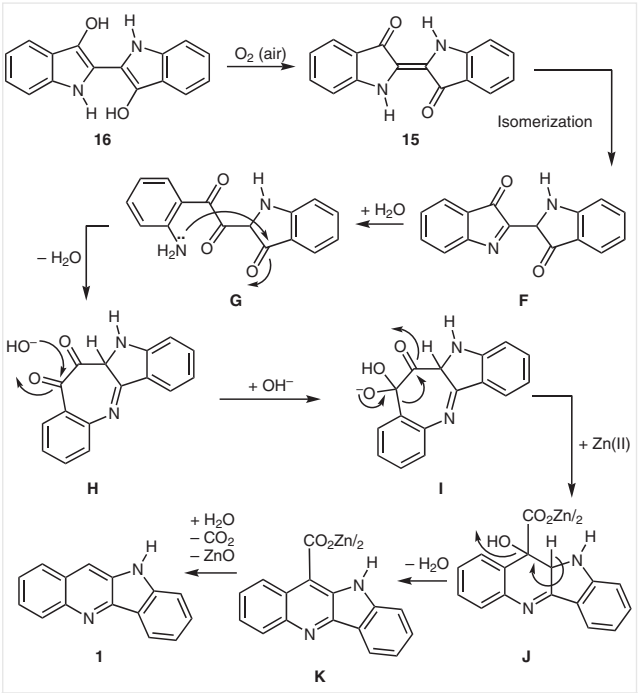
strong basic conditions of the reaction. In turn, this intermediate undergoes a hydrolytic ring opening, affording the tricarbonylic aniline **G**, which suffers imination by condensation with the indolic ring carbonyl to give the α-dicarbonyl intermediate **H**.

It is known that this class of compounds can undergo a benzilic acid rearrangement,[38] triggered by addition of hydroxide anion to the benzylic carbonyl to afford intermediate **I**, which then rearranges to intermediate **J** after migration of the phenyl moiety onto the adjacent carbonyl.

Next, base-mediated dehydration of **J** furnishes quindoline-11-carboxylic acid (**17**). The driving force for the rearrangement is the conversion of the less stable anionic intermediate **J** into a more stable one (carboxylate form of **I**). In the presence of Zn and a strongly alkaline medium, the zinc carboxylate is formed and dehydrated, resulting in intermediate **K**, which further decarboxylates to afford quindoline (**1**). Recent research has shown that zinc carboxylates exhibit a lower temperature for the onset of the decarboxylation.[39]



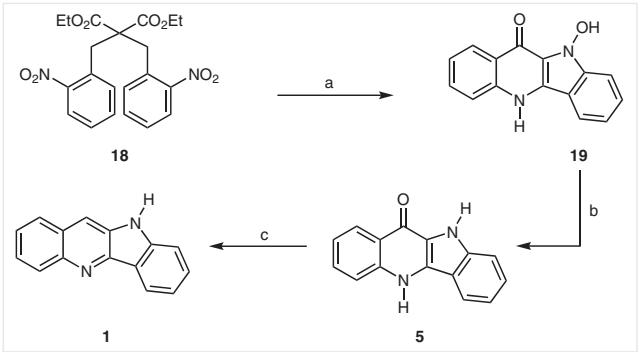
Scheme 2 Proposed sequence of reactions leading from indigotin to quindoline via quindoline-11-carboxylic acid under the conditions of Schützenberger

Interestingly, in 1947, quindoline was prepared again by Holt and Petrow, together with other indoloquinolines.[40] At the same time, it was observed that **1** was structurally related to the alkaloid cryptolepine (**8**), and that the UV-Vis spectra of both natural products were found to be similar.[41]

We have previously classified the synthetic approaches toward the indoloquinoline alkaloid neocryptolepine (**6**) in three main groups, according to the chemical structure of the involved starting materials, including: (a) benzenoids, (b) indoles, and (c) quinolines.[42] Accordingly, the total syntheses of quindoline are grouped into these three categories.

3.2 Syntheses from Benzenoids

Examples of the use of this strategy have been published over the span of a century. The first synthesis of quindoline by Fichter and Boehringer in 1906[35a] was from benzenoid derivatives (Scheme 3), through the base-mediated ring closure of bis-2-nitrobenzylmalonyl ester **18** into dioxyquindoline (**19**). In turn, this was reduced with phenylhydrazine to give oxyquindoline (quindolinone, **5**) and then reductively deoxygenated with HI/phosphorus to give quindoline (**1**).



Scheme 3 *Reagents and conditions*: (a) NaOH, EtOH; (b) $PhNHNH_2$; (c) HI, phosphorus, 150 °C, 4 h.

Another benzenoid-based strategy was presented in 2000 by Rádl and co-workers (Scheme 4).[43] They coupled benzonitrile **20** with the phenacyl bromides **21** and **22** to obtain 3-aminoindole derivatives **23** and **24**, respectively, in rather low yield (25 and 40%). Cyclization of the so-obtained 3-aminoindoles with NaH in THF furnished good to excellent yields of quindolinone (**5**), a known precursor of quindoline. Next, quindolinone was hydrogenolytically deoxygenated through the corresponding 11-chloroquindoline (**25**), furnishing quindoline in 4 steps and up to 20% overall yield.

In an alternative approach, Ho and Jou reported in 2002 a synthesis of quindoline from 2-nitrophenylacetic acid (**26**).[44] In their sequence (Scheme 5), the self-condensation of **26** with DCC was used to provide ketone **27** in 86% yield,[45] which upon simultaneous selective reduction of both nitro moieties cyclized to afford the indole derivative **28** (95%). Oxidative cyclization of the aniline moiety onto the indole completed the sequence and afforded **1** in 41% yield.

In 2006, Ray and co-workers[46a] reported a synthesis of quindoline, starting from 2-nitroacetophenone (**29**). In their sequence (Scheme 6), the acetophenone was exposed

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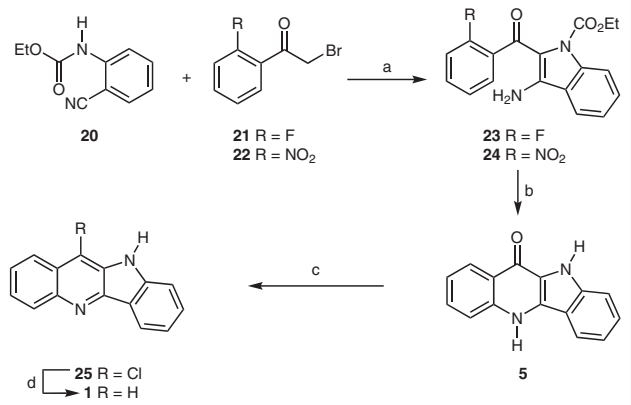
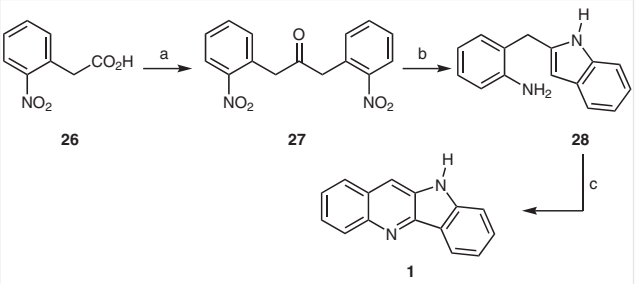


Scheme 4 *Reagents and conditions*: (a) NaH, DMF, 1 h, rt (R = F, 25%); K_2CO_3, DMF, 30 min, rt (R = NO_2, 40%); (b) NaH, THF, 1 h, rt (R = F, 77%; R = NO_2, 90%); (c) $POCl_3$, PCl_5, reflux, 3 h (70%); (d) H_2 (1 atm), 10% Pd/C, HCl, MeOH, rt, 1 h (80%).

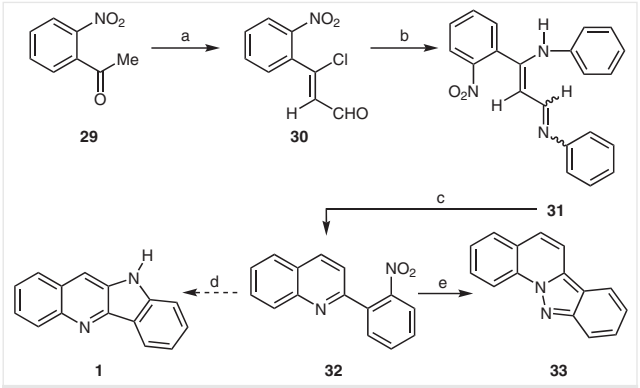
to Vilsmeier–Haack conditions[46b] with $POCl_3$ in DMF, to produce the β-chlorocinnamaldehyde **30** in 80% yield.[46a] Then, the reaction of the α,β-unsaturated aldehyde **30** with excess aniline under acid conditions produced a sequential Michael addition–elimination and further condensation of the aniline with the formyl moiety to afford the intermediate enaminoimine **31**. Next, thermal cyclization of the enaminoimine gave the substituted quinoline **32**, which was heated with triethyl phosphite to obtain the desired quindoline. It is proposed that this reaction affords a reactive nitrene intermediate,[47] able to undergo an intramolecular annulation furnishing quindoline.



Scheme 5 *Reagents and conditions*: (a) DCC, DMAP, THF, reflux, 3 h (86%); (b) Fe, glacial AcOH, EtOH, reflux, 3.5 h (95%); (c) $PhI(OAc)_2$, THF, rt, 3 h (41%).

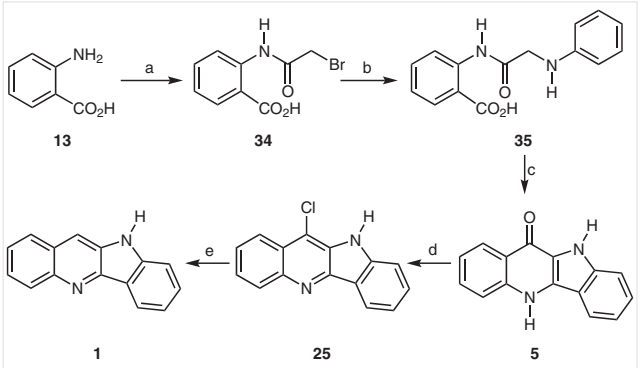
In our hands, however, treatment of **32** with Ph_3P gave the known bioactive[48] indazolo[2,3-*a*]quinoline **33** in 60% yield.[49] Formation of the latter has been observed under similar conditions.[50]

In 2011, Moreira and co-workers prepared quindoline and related heterocycles en route to the synthesis of analogues of cryptolepine (**8**).[51] Their approach was based on the procedure developed by Görlitzer and Weber[52] and adapted by Bierer.[53] To this end, anthranilic acid (**13**) was



Scheme 6 *Reagents and conditions*: (a) $POCl_3$, DMF, 0 °C, 1 h then 80 °C, 4 h (80%); (b) 2 M HCl in EtOH, $PhNH_2$, 0 °C; (c) 200–250 °C, 5 min; (d) $P(OEt)_3$, reflux, 4 h; (e) Ph_3P, 1,2-dichlorobenzene (60%).

treated with bromoacetyl bromide to give the corresponding bromoacetyl derivative **34** in 96% yield (Scheme 7). In turn, this was coupled with aniline in DMF to afford the aminoacetic intermediate **35** in 70% yield. Double cyclodehydration of the latter with PPA furnished quindolinone (**5**), which was transformed into 11-chloroquindoline (**25**, 60% yield) by reaction with $POCl_3$ at 130 °C. Final dehalogenation by catalytic hydrogenolysis with 10% Pd/C in AcOH at 4 atm,[54] gave quindoline (**5**) in 85% yield. This synthetic scheme was also used to access cryptolepine derivatives to test as cytotoxic and anti-plasmodium agents,[55] as well as other tetracyclic compounds to test as anti-infective agents.[56]



Scheme 7 *Reagents and conditions*: (a) $BrCH_2COBr$, DMF/dioxane (1:1), rt (96%); (b) $PhNH_2$, DMF, 100 °C (70%); (c) PPA, 130 °C (66%); (d) $POCl_3$, 130 °C (60%); (e) H_2, 10% Pd/C, NaOAc, AcOH, 4 atm (85%).

3.3 Syntheses from Indoles

The use of indoles as starting materials is fundamental to the synthesis of quindoline; however, the diversity of strategies within this approach is rather limited. Among the different alternatives, the first route was that of Fichter and Rohner in 1910 (Scheme 8).[37] They effected the Pfitzinger

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condensation of indoxyl (**14**, 3-hydroxyindole) and isatinic acid (**36**) to afford quindoline-11-carboxylic acid (**17**), and this was reduced with zinc or sodium amalgam to give a dihydro compound that was further oxidized to **1** with a current of air.

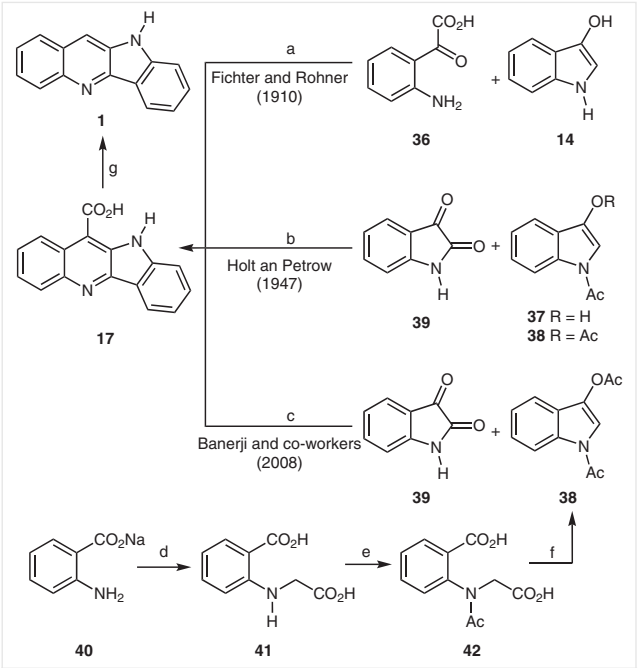
The procedure was later modified and improved by Holt and Petrow (Scheme 8), who introduced the use of the less easily oxidizable derivatives, 1-acetoxy-3-hydroxyindole (**37**) and indoxyl-1,3-diacetate (**38**).[40] Either **37** or **38** was condensed with isatin (**39**) for 10 days under basic conditions to give the intermediate quindoline-11-carboxylic acid (**17**) in high yields. Then, the resulting carboxylic acid product **17** was decarboxylated at high temperature, to furnish quindoline. The process has been used many times, and in order to withstand the conditions required for this process, different high temperature boiling solvents have been used, such as mineral oil and diphenyl ether;[53b,57] the overall yields are in the range 57–67%.

A further modification of this route was published in 2008 by Banerji and co-workers. This variation entailed the coupling of indoxyl-1,3-diacetate (**38**) with isatin under microwave irradiation as a strategy to accelerate the otherwise long initial condensation process.[58] This approach afforded the tetracyclic carboxylic acid **17** as the key intermediate in 70% yield (Scheme 8). As in the synthesis by Holt and Petrow synthesis, the acid was decarboxylated at high temperature, in an oil bath, furnishing quindoline in 76% yield.

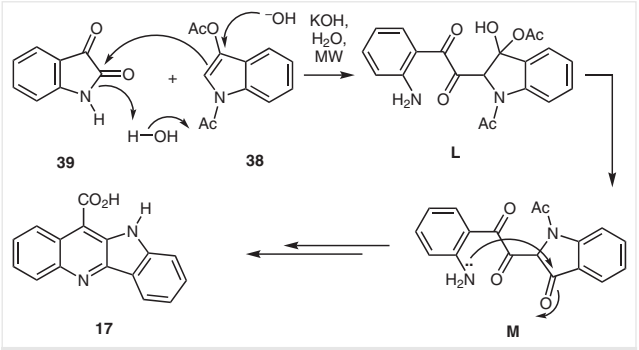
The indoxyl-1,3-diacetate (**38**) employed as starting material was obtained by condensation between sodium anthranilate (**40**), and sodium chloroacetate, in aqueous solution under microwave irradiation, which gave the benzoic acid derivative **41** in 90% yield. In turn, *N*-acetylation of **41** (92% yield) and subsequent microwave-induced cyclization of the so-obtained **42** afforded **38** in 86% yield.

Taking into account previous strategies (Scheme 2), a mechanism is proposed for the transformation. As indicated by Banerji and co-workers, the sequence (Scheme 9) commences with nucleophilic attack of indoxyl-1,3-diacetate (**38**) onto C2 of isatin (**39**) to open the heterocyclic ring of isatin and give the intermediate **L**. Next, loss of the elements of acetic acid provides intermediate **M**, structurally similar to the intermediate **G** of the sequence depicted in Scheme 2, which affords quindoline-11-carboxylic acid (**17**) by way of a benzylic acid rearrangement and *N*-deacetylation.

In 1996, Joule and co-workers devised a rather long sequence for the synthesis of quindoline and related heterocycles, using an amide as nucleophile.[54b] The synthesis was based on their discovery that *N*-phenylsulfonyl-substituted indole derivatives with a carbonyl substituent attached to C-2 undergo intramolecular nucleophilic substitution at the 3-position, with expulsion of phenylsulfinate.



Scheme 8 *Reagents and conditions*: (a) KOH, H_2O, 10 days, rt (> 90%); (b) KOH, H_2O, rt, 10 d (93%); (c) 1. MW, reflux, 16 min; 2. 70 °C, O_2 (air), 20 min (70%); (d) 1. $ClCH_2CO_2Na$, K_2CO_3, H_2O, MW, 14 min; 2. HCl (90%); (e) Ac_2O, K_2CO_3, H_2O, MW, 4 min (92%); (f) Ac_2O, Et_3N, MW, 4 min (86%); (g) Zn, KOH, H_2O (Fichter and Rohner); or (g) oil bath, 290–300 °C (94%, Holt and Petrow); or (g) Ph_2O, 250 °C, 4 h (76%, Banerji and co-workers).



Scheme 9 Proposed mechanism for the synthesis of quindoline-11-carboxylic acid from isatin and indoxyl-1,3-diacetate

In their sequence (Scheme 10), 1-(phenylsulfonyl)indole (**43**) was subjected to selective lithiation on C-2, this species was added to 2-nitrobenzaldehyde (**44**), and the resulting secondary alcohol was oxidized with MnO_2 affording ketone **45**.

Next, the nitro moiety of **45** was subjected to catalytic reduction to give **46** and further *N*-benzoylation to give the key amido ketone **47** in 25% overall yield over 4 steps. Deprotonation of the amide using NaH triggered the ring closure in hot THF to give the tetracycle **48**, which was fur-

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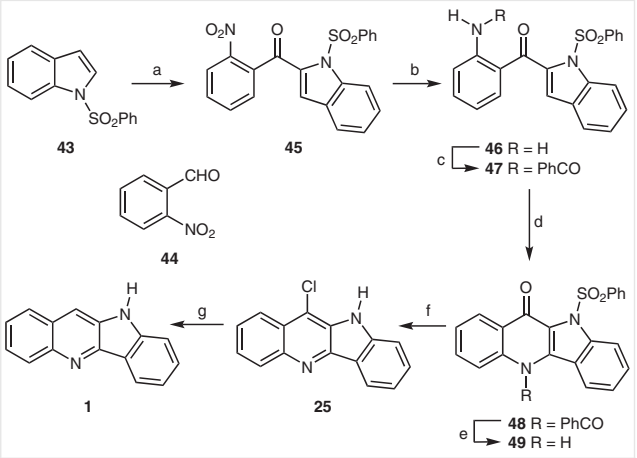
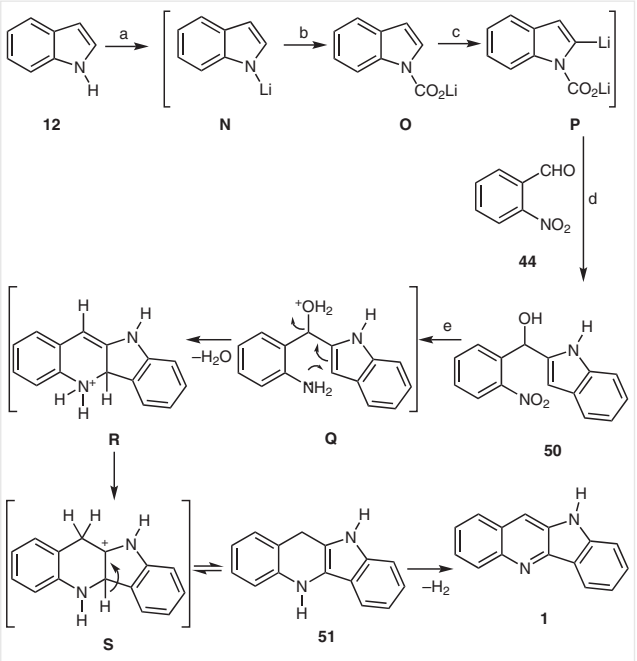


Scheme 10 *Reagents and conditions*: (a) 1. *n*-BuLi, THF, –78 °C; 2. 2-nitrobenzaldehyde (**44**, 40%); 3. MnO_2, CH_2Cl_2, rt (88%); (b) H_2, Pd/C (72%); (c) PhCOCl, $PhNMe_2$, rt (87%); (d) NaH, THF, reflux (80%); (e) NaOH, MeOH, heat (85%); (f) $POCl_3$, reflux (95%); (g) H_2, Pd/C, EtOH (95%).

ther hydrolyzed to **49** in 68% overall yield. Treatment with $POCl_3$ to obtain the chloro derivative **25** (95% yield), followed by Pd/C-mediated catalytic hydrogenation (95% yield) completed the sequence to give **1**.

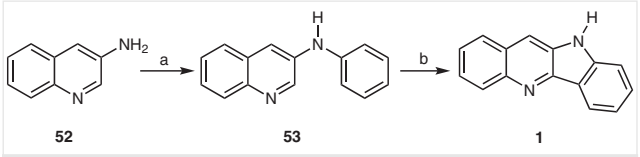
In 2013, Lopes and co-workers reported an efficient two-step total synthesis of quindoline from indole (**12**) and 2-nitrobenzaldehyde (**44**).[59] They sequentially exposed indole (**12**) to *n*-BuLi and the resulting organolithium species **N** was quenched with CO_2 affording intermediate **O**; exposure of the latter to *sec*-BuLi gave intermediate **P**, in which the heteroatom was protected with an easily removable group (Scheme 11), while the heterocycle was activated for a regioselective functionalization at C-2 with **44**, to produce the intermediate alcohol **50** in 92% yield. Catalytic hydrogenation of the nitro group in MeOH, acidic through the addition of $CHCl_3$,[60] caused formation of aniline intermediate **Q**. Then, its nucleophilic attack onto the indole, provoked the intramolecular cyclization with concomitant elimination of water to cyclized intermediate **R**. Subsequently, isomerization of the double bound gave dihydroquinoline **51** via the cationic intermediate **S** with the restoration of aromaticity.[61] Finally, an unusual Pd/C-mediated dehydrogenation gave quindoline (**1**) in 55% overall yield.



Scheme 11 *Reagents and conditions*: (a) *n*-BuLi, THF –70 °C, 30 min; (b) CO_2, THF, 10 min; (c) *sec*-BuLi, THF, –70 °C, 1 h; (d) 2-nitrobenzaldehyde (**44**), THF, –70 °C, 1 h; H_2O; (e) H_2 (35 psi), Pd/C, MeOH, $CHCl_3$ (drops), 12 h (60% overall).

3.4 Syntheses from Quinolines

In 1997, the Ablordeppey group[62] developed a synthetic procedure for quindoline, involving the efficient arylation of 3-aminoquinoline (**52**) with triphenylbismuth diacetate to form 3-anilinoquinoline (**53**) in 94% yield (Scheme 12). Subsequent oxidative cyclization of **53** with $Pd(OAc)_2$ in TFA produced the desired tetracycle in only 23% yield, accompanied by **4** as the major product.



Scheme 12 *Reagents and conditions*: (a) $Ph_3Bi(OAc)_2$, Cu, CH_2Cl_2, 10 h (94%) or $PhB(OH)_2$, $Cu(OAc)_2$, Et_3N, 4-Å MS, CH_2Cl_2, rt, 12–24 h (80–90%); (b) $Pd(OAc)_2$, TFA, 90 °C, 40 min (23%).

The strategy was used in 1999 to study the effects of N-5 functionalization on anticryptococcal activity.[63] Notably, the unsubstituted natural product is devoid of such activity. In 2008 it was disclosed that phenylboronic acid is a more convenient source of an aryl ring for amination, affording **53** in 90% yield when $Cu(OAc)_2$ was used as catalyst (Scheme 12). Further, cyclization of **53** with $Pd(OAc)_2$ and TFA at 60 °C produced a 1:9 mixture of quindoline and the isomeric **4**[64] (nor-isocryptolepine, Figure 1).

In 1998, Rocca and co-workers reported the first halogen-dance reaction among quinolines and applied their discovery to a new synthesis of quindoline, as shown in Scheme 13.[65] Thus, treatment of 3-fluoro-4-iodoquinoline (**54**) with LDA at –75 °C followed by quenching with water as electrophile led to 3-fluoro-2-iodoquinoline (**55**) in 95% yield. Next, palladium-catalyzed Suzuki cross-coupling reaction between boronic acid **56** and quinoline **55** afforded

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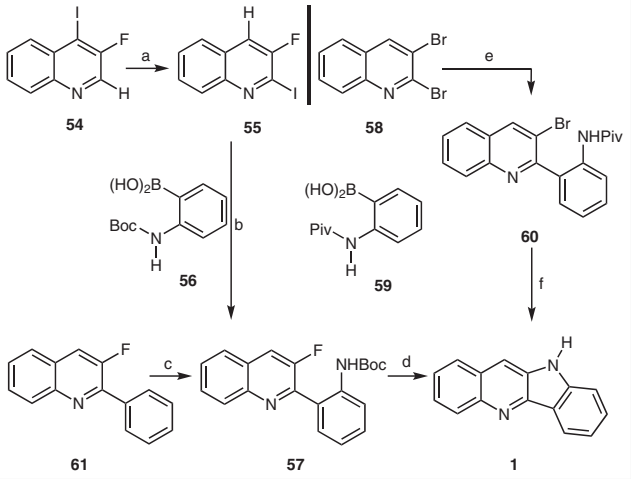
the biaryl derivative **57** in a very good yield, from which quindoline (**1**) was accessed in 83% yield by treatment with melted pyridinium chloride.

A formally similar approach was concomitantly described by Tímari and co-workers (Scheme 13).[66] They reacted 2,3-dibromoquinoline (**58**) with 2-(pivaloylamino)phenylboronic acid (**59**) under palladium(0) catalysis to access biaryl derivative **60**, which was cyclized in boiling 25% H_2SO_4 to afford quindoline (**1**) in 85% yield.

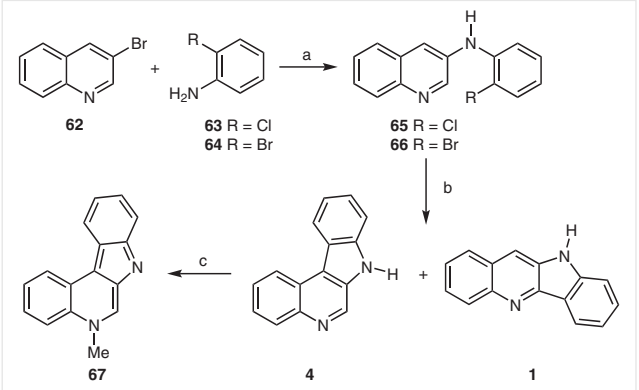


Scheme 13 *Reagents and conditions*: (a) 1. LDA, THF, –78 °C, 2 h; 2. I_2 (95%); (b) **56**, $Pd(PPh_3)_4$, EtOH, PhMe, reflux (94%); (c) $BocN_3$, K_3PO_4, $(Cp^*RhCl_2)_2$ (5 mol%), $AgSbF_6$ (20 mol%), DCE, 80 °C, 14 h (90%); (d) Py·HCl, 220 °C, 4 h (83%); (e) **59**, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, reflux, 6 h (54%); (f) 25% H_2SO_4, 120 °C, 5.5 h (85%).

On the other hand, the fluorinated biaryl **61** was also employed, by Bach and co-workers in 2016,[67] as an intermediate in the synthesis of quindoline through the intermediacy of **57**. With the knowledge that azides are a good nitrogen source in transition-metal catalysis,[68] they demonstrated that Boc-azide ($BocN_3$) is an efficient and economic source for the directed introduction of *N*-Boc-protected amino groups into arenes by the use of C–H activation chemistry.

The facile removal of the Boc protecting group facilitated the application of their development to a short total synthesis of quindoline. The synthetic procedure was initiated from the easily available fluoroquinoline **61**,[69] which was aminated in 90% yield to afford the *N*-Boc-protected product **57**. In turn, this compound was cyclized in melted pyridinium chloride furnishing quindoline in almost quantitative yield.[65,66,70]

In 2005, Mohan and co-workers reported that the thermally promoted amination of 3-bromoquinoline (**62**) with 2-chloroaniline (**63**) gave intermediate **65** (Scheme 14) which upon subjected to heteroatom-directed photoannulation furnished quindoline (**1**) as a minor product in 16% yield.[7b] On the other hand, the angularly fused indoloquinoline **4** was obtained in better yield (51%).



Scheme 14 *Reagents and conditions*: (a) R = Br: $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, dioxane, reflux (83%); R = Cl: 200 °C, 5 h (72%); (b) R = Br: $PdCl_2(PPh_3)_2$, NaOAc·$3H_2O$, DMA, 130 °C (**4**, 45%; **1**, 4%); R = Cl: (b) hv, PhH/MeOH/H_2SO_4 (60:30:1), I_2, rt (**1**, 16%; **4**, 51%); (c) 1. MeI, PhMe, reflux (88%); 2. NH_3/H_2O (28–30%).

Quite similar results were obtained in 2006 by Maes and co-workers. They reported the production of quindoline as a minor side product during the synthesis of 5-methyl-5*H*-indolo[2,3-*c*]quinoline (**67**),[71] as a result of a combined regioselective Buchwald–Hartwig/intramolecular Heck-type reaction.[72] Their synthesis commenced with the selective Buchwald–Hartwig amination of 3-bromoquinoline (**62**) with 2-bromoaniline (**64**) employing Cs_2CO_3 as base, to afford **66** in 83% yield, followed by reaction of the latter with $PdCl_2(PPh_3)_2$ and NaOAc in DMA at 130 °C (Scheme 14). Under these conditions, quindoline was isolated in only 4% yield, accompanied by **4** which was the preferred indoloquinoline isomer. In turn, **4** was selectively *N*-methylated with MeI in toluene, and the resulting methyl iodide was treated with aqueous ammonia to give **67** as the final product.

Interestingly, in 2013 Bogányi and Kámán devised a synthesis of 2,3-dihaloquinolines from 3-bromoquinoline (**62**) and used their route for a synthesis of quindoline sequentially using Buchwald–Hartwig and Heck reactions.[73] The synthesis of 2-bromo-3-iodoquinoline (**68**) started with a copper(I)-catalyzed halogen-exchange reaction of **62** to give 3-iodoquinoline (**69**) almost quantitatively (Scheme 15). This was oxidized with *m*-CPBA (75%) and the resulting *N*-oxide derivative **70** was rearranged to furnish the 3-iodoquinolinone **71** in 89% yield. Final dehydrative bromination was performed with $POBr_3$ to afford **68** in 74% yield.

Next, the Buchwald–Hartwig reaction was put in place, under $Pd(OAc)_2$/Xantphos catalysis and microwave irradiation,[74] thus **68** afforded the diarylamine **72** in 70% yield, which was then cyclized under Heck conditions affording quindoline in 61% yield. In contrast to the work of Maes and co-workers,[71] where the bromine atom was attached to the pendant benzene ring, offering two alternative cyclization

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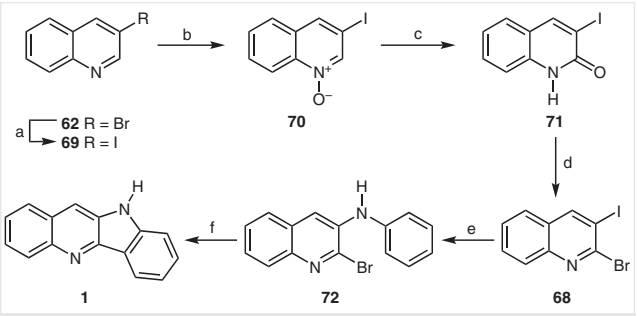
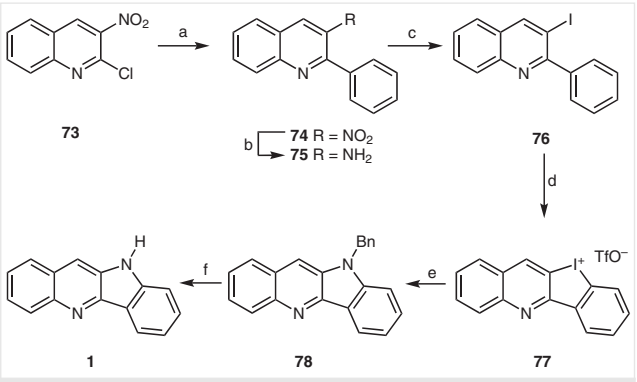
pathways, in **72** the bromine was attached to C-2 of the heterocyclic skeleton, commanding the cyclization toward this position.



Scheme 15 *Reagents and conditions*: (a) *N*,*N*-dimethylethylenediamine, CuI, NaI, dioxane, 100 °C (99%); (b) *m*-CPBA, CH_2Cl_2, rt (75%); (c) Bz, K_2CO_3, CH_2Cl_2, rt (89%); (d) $POBr_3$, PhMe, reflux (74%); (e) $PhNH_2$, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, PhMe, 120 °C, MW (70%); (f) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, MW (61%).

In 2012, Detert and Letessier[75] used the Olofsson group's synthesis of diaryliodonium triflates[76] for the preparation of dibenzoiodolium as a new class of iodolium heterocycles that are useful to construct the δ-carboline core. They applied their development to a new synthesis of quindoline.[75]

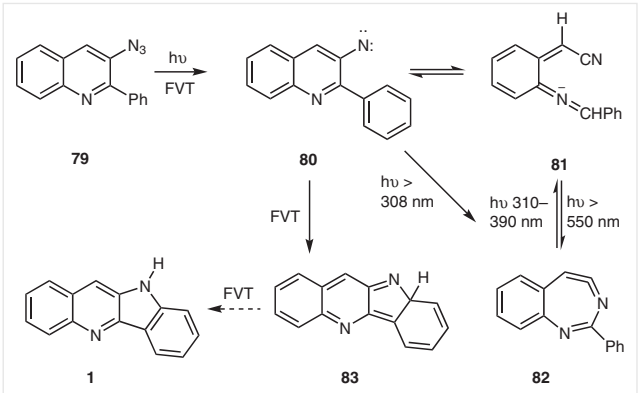


Scheme 16 *Reagents and conditions*: (a) $PhB(OH)_2$, Pd/C, Ph_3P, Na_2CO_3, DME, 80 °C (95%); (b) H_2, Pd/C, THF, rt (67%); (c) TsOH, $NaNO_2$, KI, MeCN, 0 °C (35%); (d) *m*-CPBA, TfOH, CH_2Cl_2, 0 °C (96%); (e) $BnNH_2$, $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, PhMe, 100 °C (49%); (f) *t*-BuOK, DMSO, air (98%).

Their sequence commenced with 2-chloro-3-nitroquinoline (**73**), which was prepared in three steps from quinoline.[77] The heterocycle was then submitted to Suzuki coupling with phenylboronic acid to give the nitroquinoline **74** almost quantitatively (Scheme 16).[78] Hydrogenation of the nitro group with Pd/C at room temperature gave **75**, which was subject to diazotization and the Sandmeyer reaction[79] with iodide to give iodoquinoline **76** in 35% overall yield.

Oxidation of the iodoquinoline **76** with *m*-CPBA in the presence of three equivalents of TfOH selectively gave benzoquinoloiodolium triflate **77** in excellent yield (96%) as a highly hygroscopic salt. Next, $Pd_2(dba)_3$/Xantphos and benzylamine were used to perform a palladium-catalyzed double amination reaction, to afford the expected *N*-benzylquindoline **78** in moderate yield (49%). Finally, aerobic deprotection with potassium *tert*-butoxide in DMSO[80] gave quindoline (**1**) quantitatively.

Wentrup and co-workers studied the matrix photolysis of 3-azido-2-phenylquinoline (**79**) under different conditions (Scheme 17).[83] It was observed that irradiation at λ = 308 nm or in the range of 310–390 nm resulted in a blue nitrile ylide **81** that could be converted into the seven-membered ring ketenimine **82** on photolysis above 550 nm. The latter reverted to ylide **81** on photolysis at 310–390 nm. Under these conditions, they assumed that nitrene **80** was formed initially but it was converted into **81** and **82** at the same wavelength. It was conjectured that the ring opening to the ylide **81** may take place either from the nitrene **80** or from the cyclic ketenimine **82**, although only the latter reaction was observed directly.



Scheme 17 Photolysis of 3-azido-2-phenylquinoline

It was possible to cycle many times between these two intermediates before signal intensity was lost, probably because the cyclization to the isocarbazole **83**, a potential precursor of quindoline, took place. Interestingly, preparative flash vacuum thermolysis of azide **79** at 400–800 °C affords quindoline in 52–60% yield.[83]

4 Biological Activity Studies

The biological activity of quindoline has been examined by different authors, and their results are collected in Table 1. It was found that the natural product inhibits acetylcholinesterase,[27] it does not damage DNA,[57] and was claimed to be a telomerase inhibitor, able to reduce hair growth.[84]

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Quindoline also proved to be devoid of significant antifungal activity against *Candida albicans* and *Cryptococcus neoformans*.[63]

Further, the heterocycle has shown to display antiparasitic activity. It exhibited *in vitro* antimalarial activity against *Plasmodium falciparum* K1, when the lactate dehydrogenase activity and the incorporation of ^{3}H-hypoxanthine were determined, being inactive against the multidrug resistant strain and against *P. falciparum* T996.[22b,57a,70]

On the other hand, quindoline exhibited stage-dependent activity against *Trypanosoma cruzi*, being more active against the epimastigote form and inactive against the trypomastigote form.[70]

In addition, the natural product proved to have cytotoxic, antiproliferative, and antitumor activity against different cell lines (human ovarian cancer, mouth epidermoid carcinoma, murine myoblast), being comparatively less active when tested against drug resistant variants of the cell lines.[70,81,82]

Finally, quindoline exhibited no platelet aggregation activity and displayed dose-dependent reduction of the phenylephrine-induced increase in perfusion pressure in Sprague Dawley rats, with a maximum peak at 100 µmol.[18]

5 Conclusions

Most of the active pharmaceutical ingredients of our current pharmacological arsenal are natural products, their derivatives or synthetic compounds inspired in them. Nature has been a continuous source of drug leads that are potentially useful for treating human diseases.

Quindoline is a natural product that has been isolated from many plant sources in different parts of Africa, India, and South America, which has shown to exhibit some interesting biological activities, including as antitumor agent and antiparasitic, against *Plasmodium falciparum* and *Trypanosoma cruzi*.

The simplicity of its structure, its potential as synthetic intermediate toward other natural products, and the possibility of being used as a scaffold toward more functionalized compounds has sparked great interest in the total synthesis of quindoline, leading to the development of various imaginative approaches. As a result, much work has been done to date; however, it seems that the potential of this natural indoloquinoline as a useful intermediate or drug lead is still only barely known and requires a more thorough exploration.

Table 1 Summary of the Biological Activities of Quindoline

Activity	Target	Potency	Ref.
enzyme inhibition	acetylcholinesterase	active at 100 ng; 20% inhibition at 100 mM	27
DNA examination	yeast 1138	IC_{12} = 150 µg/mL	57b
effect on DNA	double-stranded calf thymus DNA	ΔT_m = 0 °C (no effect)	57a
antifungal	*C. neoformans*	MIC >250 µg/mL	63
antifungal	*C. albicans*	MIC >250 µg/mL	63
antimalarial	*P. falciparum* K1 (^{3}H-hypoxanthine incorporation)	IC_{50} = 36.2 µmol/L	70
antimalarial	*P. falciparum* K1 (LDH activity)	IC_{50} = 0.18 µmol/L	57a
antimalarial	*P. falciparum* K1 (multidrug-resistant)	IC_{50} >50.0 µg/mL (inactive)	22b
antimalarial	*P. falciparum* T996	IC_{50} >50.0 µg/mL (inactive)	22b
antiparasitic	*T. cruzi* (epimastigote) (β-galactosidase activity)	IC_{50} = 8.7 µmol/L	70
antiparasitic	*T. cruzi* (amastigote) (β-galactosidase activity)	IC_{50} = 14.2 µmol/L	70
antiparasitic	*T. cruzi* (Trypomastigote)	no effects at 50 µmol/L	70
antiproliferative	KB mouth epidermoid carcinoma	IC_{50} = 45 µmol/L	70
antitumor	SKOV-3 human ovarian cancer	IC_{50} = 66 µmol/L	81,82
antitumor	CH1 human ovarian cancer	IC_{50} = 15.5 µmol/L	81,82
antitumor	CH1 human ovarian cancer (drug resistant line)	IC_{50} = 30 µmol/L	81,82
antitumor	A2780 human ovarian cancer	IC_{50} = 21.5 µmol/L	81,82
antitumor	A2780 human ovarian cancer (drug resistant line)	IC_{50} = 24.5 µmol/L	81,82
cytotoxic	L6 murine myoblasts	IC_{50} = 48.6 µmol/L	70
platelet aggregation	Sprague Dawley rat	no effect at 500 µmol/L	18
renal vasodilation	Sprague Dawley rat (phenylephrine-induced increase in perfusion pressure)	dose-dependent reduction maximum peak at 100 µmol	18

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