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Synthesis of the benzo-β-carboline isoneocryptolepine: the missing indoloquinoline isomer in the alkaloid series cryptolepine, neocryptolepine and isocryptolepine

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Cordially dedicated to Professor Kálmán Hideg on the occasion of his 70th birthday

Abstract—7*H*-Indolo[2,3-*c*]quinoline has been synthesized in two steps via a new approach starting from commercially available 3-bromoquinoline and 2-bromoaniline. The new methodology consists of two consecutive palladium-catalyzed reactions: a selective Buchwald/Hartwig amination followed by an intramolecular Heck-type reaction. Alternatively, the same skeleton has also been prepared via the combination of a Suzuki arylation with an intramolecular nitrene insertion starting from 4-chloroquinoline and {2-[(2,2-dimethylpropanoyl)amino]phenyl}boronic acid. Selective methylation of 7*H*-indolo[2,3-*c*]quinoline yielded 5-methyl-5*H*-indolo[2,3-*c*]quinoline (Isoneocryptolepine) which is an interesting new lead compound in the search for new antiplasmodial drugs.
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1. Introduction

Every year between 300 and 500 million people worldwide are infected by the malaria parasite (*Plasmodium*). One to two million of them die as a direct consequence of this disease. These shocking figures are estimations of the World Health Organization (WHO) and put malaria besides tuberculosis and AIDS on the top list of infection diseases in the world.[1] Although several drugs are available to treat malaria, the increasing resistance of the parasite becomes really problematic. Consequently, the development of new and efficient drugs to treat and prevent malaria is of great importance in order to stop the proliferation of *Plasmodia*.

Besides available synthetic drugs (e.g. chloroquine, halofantrine and mefloquine) also nature has shown to be an interesting source of antiplasmodial compounds. The best known examples are of course quinine and artemisinine isolated from *Cinchona* bark and the leafy portions of *Artemisia annua*, respectively.[2,3] In the last decade our laboratories have been active in the field of antimalarial natural products. In the Department of Pharmaceutical Sciences of the University of Antwerp several alkaloids have been isolated from the root of the West African plant *Cryptolepis sanguinolenta*.[4] In traditional folk medicine, a decoction of the root of this plant is used to treat fevers (including fever caused by malaria). Cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**), neocryptolepine (cryptotackieine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**2**) and isocryptolepine (cryptosanguinolentine, 5-methyl-5*H*-indolo[3,2-*c*]quinoline) (**3**) are three of the 13 characterized alkaloids (Fig. 1).[4a,5] Chemically, these compounds are isomeric indoloquinolines, but more importantly the two linearly (**1**,**2**) as well as the angularly fused isomers (**3**) possess an interesting antiplasmodial activity.[4b,6] In Antwerp and Budapest efficient synthetic strategies have been developed for all three benzocarbolines based on palladium-catalyzed reactions (Suzuki, Heck, Buchwald–Hartwig).[7–9] Interestingly, the benzo-β-carboline (5-methyl-5*H*-indolo[2,3-*c*]quinoline, for which we have adopted the name isoneocryptolepine) (**4**) (Fig. 1) has hitherto never been found in nature. In order to be able to study the antiplasmodial activity and cytotoxicity of this

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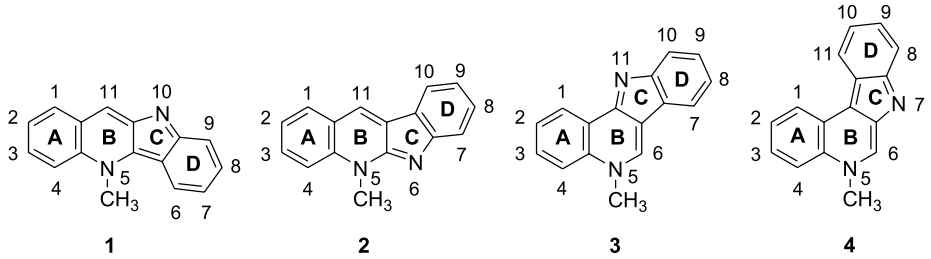


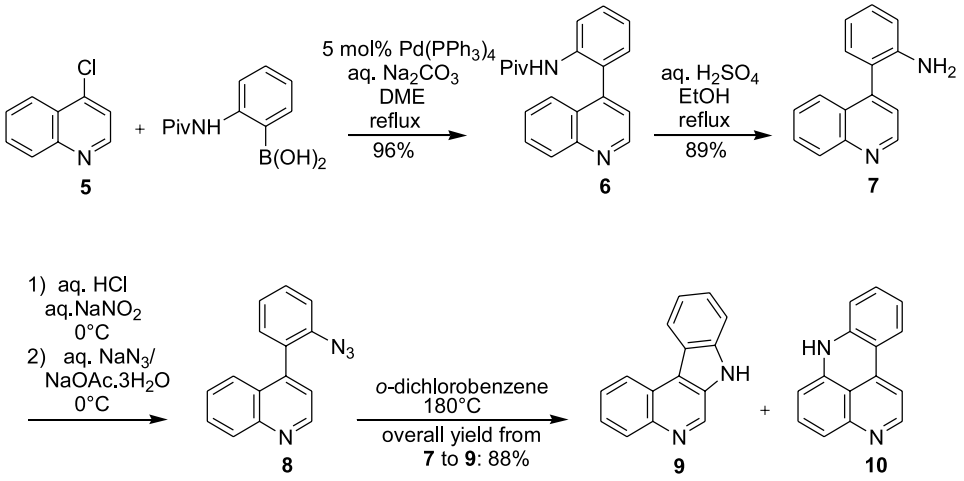
Figure 1. Cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**) and isoneocryptolepine (**4**).

isomer and to compare it with the three naturally occurring ones we decided to develop an efficient synthetic route for the 7*H*-indolo[2,3-*c*]quinoline skeleton of 5-methyl-5*H*-indolo[2,3-*c*]quinoline.

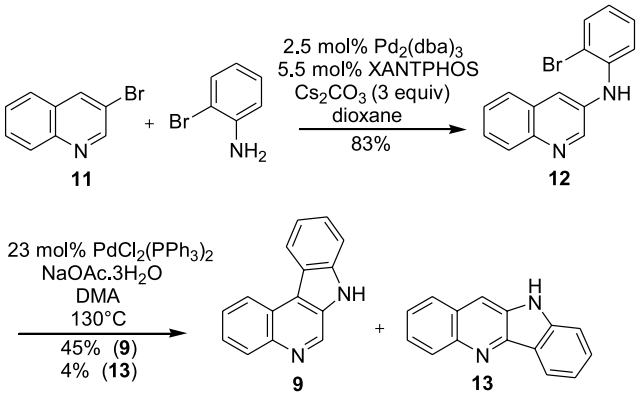
2. Discussion

As a first approach towards the synthesis of the 7*H*-indolo[2,3-*c*]quinoline skeleton we investigated the combination of a Suzuki arylation reaction with an intramolecular nitrene insertion (Scheme 1). A similar approach has already been used in our laboratories for the synthesis of other indolo fused ring systems (11*H*-indolo[3,2-*c*]quinoline,[7a,7c] 2,5-dihydro-1*H*-pyridazino(4,5-*b*(indol-1-one[7c,10] and indolo[3,2-*c*]isoquinoline[7c,11]). Suzuki reaction of commercially available 4-chloroquinoline[12] (**5**) with {2-[(2,2-dimethylpropanoyl)-amino]phenyl}boronic acid[13] under Gronowitz conditions[14] yielded 2,2-dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (**6**) in 96%. Acid hydrolysis of the pivalamide in 20% aq H_2SO_4 gave 2-quinolin-4-ylaniline (**7**) in a moderate yield only (51%). The reaction could be further optimized to 89% by using 40% aq H_2SO_4 in combination with ethanol as a co-solvent. Subsequent diazotization of the amine **7** followed by introduction of the azido group via an ArS_N1 type reaction on the diazonium salt gave 4-(2-azidophenyl)quinoline (**8**). Finally, thermal decomposition of the azide in boiling *o*-dichlorobenzene yielded the target indoloquinoline skeleton **9** in 88%. When the lower boiling *o*-xylene was used as solvent for the thermolysis of **8** a longer reaction time (48 h instead of 3 h) was required and a slightly lower yield was obtained (80%). The mechanism of this reaction presumably occurs via the formation of a nitrene from the azide which formally inserts into the C3–H bond.[15,16] Interestingly, the intramolecular nitrene insertion is C-3 regioselective and only a trace amount of the C-5 ring closed product (7*H*-pyrido[2,3,4-*kl*]acridine, **10**)[17] could be observed in a chromatographic fraction during purification of **9**. This selectivity can be explained by taking into account the kinetic preference for 5- versus 6-membered rings.[18]

Next, we investigated the synthesis of 7*H*-indolo[2,3-*c*]quinoline via an alternative approach (Scheme 2) since the 'Suzuki—intramolecular nitrene insertion' strategy is a quite lengthy route (four steps) which does not allow an easy introduction of substituents on the A and D ring. Recently, our laboratories published two examples (11*H*-indolo[3,2-*c*]quinoline[7d] and 2,5-dihydro-1*H*-pyridazino(4,5-*b*(indol-1-one[19]) where indolo fused ring systems were prepared via the combination of a selective Buchwald–Hartwig amination with an intramolecular Heck-type reaction. Commercially available 3-bromoquinoline and 2-bromoaniline seemed to be ideal starting materials for such a route since 3-bromoquinolines substituted in the benzene ring are easily accessible via regioselective C-3 bromination[20] and several substituted 2-bromoanilines can be obtained from commercial sources. In this way easy A and D ring functionalization can be obtained, respectively. First, we investigated the Pd-catalyzed amination of 3-bromoquinoline (**11**) with 2-bromoaniline using a Pd(0)/XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) catalyst.[21] Interestingly, regioselective amination was observed although each coupling partner contains an



Scheme 1. Synthesis of 7*H*-indolo[2,3-*c*]quinoline via a 'Suzuki—intramolecular nitrene insertion' approach.



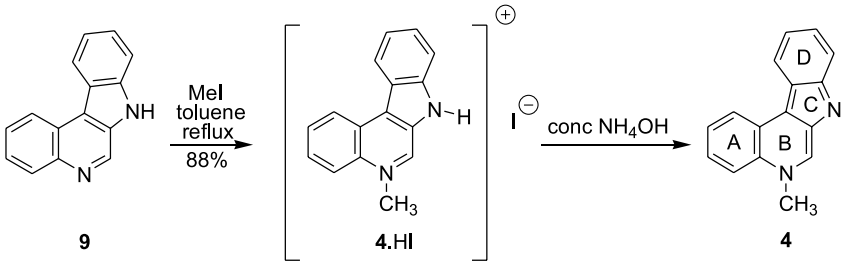
Scheme 2. Synthesis of 7*H*-indolo[2,3-*c*]quinoline via a 'Buchwald–Hartwig amination–intramolecular Heck type reaction' approach.

unactivated C–Br bond. Clearly, the C–Br bond of 3-bromoquinoline is more reactive than the C–Br bond of 2-bromoaniline due to the amino substituent of the latter which sterically and electronically deactivates the C2–Br bond for oxidative addition. Subsequent Heck-type cyclization of *N*-(2-bromophenyl)quinolin-3-amine (**12**) gave predominantly 7*H*-indolo[2,3-*c*]quinoline (**9**) and only a small amount of the undesired regioisomer quindoline (**13**). The mechanism of a Pd-catalyzed cyclodehydrohalogenation involving C–H bond activation is often considered to occur via the intramolecular electrophilic attack of the oxidative addition complex on a π system.[22] If one accepts this model the preferential C4–H activation can be explained by taking into account that in this case three resonance contributors, which do not break the aromatic character of the benzene ring in the carbocationic intermediate, can be drawn versus only one in the case of C2–H activation. In addition, the electron density is larger on C-4 than on C-2.[23]

A literature search revealed that only a very limited number of synthetic approaches for the 7*H*-indolo[2,3-*c*]quinoline (**9**) ring system have been reported up to now. In 1928, Kermack and Slater published a six step route with an overall yield of less than 36%.[24,25] In their route, the indole ring was built up via a Fischer[26] synthesis on 3-(2-nitrophenyl)-2-(phenylhydrazono)propanoic acid. Subsequent decarboxylation of the Fischer indole reaction product 3-(2-nitrophenyl)-1*H*-indole-2-carboxylic acid followed by reduction of the nitro group and formamide formation, using formic acid, yielded 2-(1*H*-indol-3-yl)-phenylformamide. Finally, the quinoline ring was obtained via a Bischler–Napieralski[27] type ring closure yielding the desired 7*H*-indolo[2,3-*c*]quinoline. In 1951, Clemo and Felton published a modified version of the method developed by Kermack and Slater with an equal number of synthetic steps but a better overall yield (<59%).[28,29] Fischer synthesis was executed on ethyl 3-(2-nitrophenyl)-2-(phenylhydrazono)propanoate instead of the free acid. Reduction of the nitro group of ethyl 3-(2-nitrophenyl)-1*H*-indole-2-carboxylate afforded a quinolin-2(1*H*)-one ring via spontaneous lactamization. Subsequent chlorodehydroxylation and hydrodehalogenation gave **9**. In the same paper, another approach based on the Fischer synthesis on cyclohexanone quinolin-3-ylhydrazone is also mentioned. The required 3-hydrazinoquinoline for hydrazone synthesis was obtained from the corresponding 3-aminoquinoline. Dehydrogenation of the reaction product of the Fischer indole synthesis (8,9,10,11-tetrahydro-7*H*-indolo[2,3-*c*]-quinoline) also gave access to the 7*H*-indolo[2,3-*c*]quinoline skeleton. Unfortunately, no experimental details and yields have been reported for the latter route mentioned by Clemo and Felton. More recently, Fan and Ablordeppey reported a short route also based on 3-aminoquinoline.[30] Phenylation of 3-aminoquinoline with triphenylbismuth diacetate in the presence of metallic copper yielded *N*-phenylquinolin-3-amine in 94% yield. Subsequent oxidative cyclization with an excess of $Pd(OAc)_2$ in trifluoroacetic acid gave a mixture of quindoline (**13**) (10*H*-indolo[3,2-b]quinoline) (23%) and **9** (50%). These two indoloquinoline isomers result from a non-selective palladation at C-2 and C-4 of the quinoline nucleus. Interestingly, Fan and Ablordeppey were only interested in the development of a new strategy for quindoline and the major compound formed in the oxidative cyclization was only an undesired side product. Unwittingly, they obtained a concise synthesis for the indoloquinoline **9** with an overall yield of 47%. Recently, Kannadasan and Srinivasan published a new five step route towards 3,4-benzo-β-carboline (**9**) starting from 2-methylindole. The obtained overall yield of **9** is only 20%. The method used to build up the tetracyclic skeleton is based on a radical cyclization of *N*-(3-bromo-1-phenylsulfonylindol-2-ylmethyl)aniline.[31]

Although our 'Suzuki—intramolecular nitrene insertion' consists of four steps, which is longer than the two step route developed by Fan and Ablordeppey (overall yield: 47%) and also longer than our 'Buchwald–Hartwig—intramolecular Heck-type reaction' procedure (overall yield: 37%), it gives access to the target skeleton in the highest overall yield (75%) hitherto reported in the literature. Our 'Buchwald–Hartwig amination—intramolecular Heck type reaction' strategy on the other hand has an equal number of steps and a similar overall yield as the procedure of Fan and Ablordeppey but uses substantially cheaper reagents.[32] In addition, in our Pd-catalyzed cyclodehydrohalogenation 23 mol% palladium is used whereas Fan and Ablordeppey's oxidative cyclization is not catalytic and requires 200 mol% of palladium. Moreover, D ring substituted 7*H*-indolo[2,3-*c*]quinolines will require substituted triphenylbismuth diacetates which are not commercially available in contrast to the 2-bromoanilines.

For the selective *N*-5 methylation of 7*H*-indolo[2,3-*c*]quinoline (**9**) we first tried to use the conditions (CH_3I, DMF, 80 °C; then aq Na_2CO_3) we previously reported for the selective methylation of 6*H*-indolo[2,3-*b*]quinolines and 11*H*-indolo[3,2-*c*]quinoline.[7d,33,34] However, under these reaction conditions and after work-up with aqueous Na_2CO_3 and extraction with dichloromethane, MS-data of the reaction mixture clearly revealed the formation of undesired 5,7-dimethyl-5*H*-indolo[3,2-*b*]quinolinium iodide. To avoid this selectivity problem we decided to perform the methylation in refluxing toluene (Scheme 3). In this way, the formed isoneocryptolepinium hydroiodide immediately precipitated and the formation of 7-methylisoneocryptolepinium iodide (**14**) (Fig. 2) could be avoided. After cooling down the reaction mixture to room temperature the yellow precipitate was filtered off and subsequently it was



Scheme 3. Selective N-5 methylation of 7*H*-indolo[2,3-*c*]quinoline.[34]

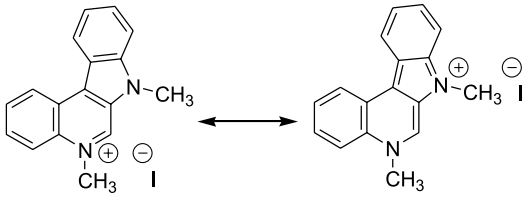


Figure 2. 7-Methylisoneocryptolepinium iodide (**14**).

purified by flash column chromatography on silicagel yielding pure **4**·HI in 88%. Finally, the desired free base **4** could be obtained via an acid–base reaction using ammonia in water (28%–30%).[35]

In conclusion, we have developed two new synthetic strategies for the 7*H*-indolo[2,3-*c*]quinoline (**9**) skeleton. Upon selective methylation of **9** the desired 5-methyl-5*H*-indolo[2,3-*c*]quinoline (**4**) was obtained. Preliminary in vitro screening results indicate that the selectivity index (ratio antiplasmodial activity/cytotoxicity) of isoneocryptolepine is superior to the reported indices of the three naturally occurring isomeric methylated indoloquinolines (**1**–**3**). Consequently, **4** can be regarded as an important new lead compound for future research. A detailed description of the antiplasmodial activity and cytotoxicity of **4** will be published in a pharmaceutical journal in due course.

3. Experimental

3.1. General

All melting points were determined on a Büchi apparatus and are uncorrected The ^{1}H- and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer in the solvent indicated with TMS as the internal standard. All coupling constants are given in Hertz and chemical shifts are given in ppm. For mass-spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min CH_3OH (0.1% formic acid), using a CapLC HPLC system (Waters, Millford). Accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (Q-Tof-II, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimised on one compound and used for all others. For the determination of the high-resolution *m*/*z*-values of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as lock mass for the measurement of the accurate mass values of the samples. 4-Chloroquinoline (Aldrich), 3-bromoquinoline (Acros), XANTPHOS (Aldrich), $Pd(PPh_3)_4$ (Acros), $PdCl_2(PPh_3)_2$ (Acros) and $Pd_2(dba)_3$ (Acros) were obtained from commercial sources and used as such. For the Buchwald–Hartwig amination Cs_2CO_3 (99%) (Aldrich) and freshly distilled dioxane (dried over sodium benzophenone) were used. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm).

3.1.1. 2,2-Dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (6). 4-Chloroquinoline (**5**) (4.0 mmol, 0.654 g) was dissolved in DME (24 mL). $Pd(PPh_3)_4$ (0.20 mmol, 0.24 g) was added and the solution subsequently stirred for 10 min under a N_2 atmosphere. Next, {2-[(2,2-dimethylpropanoyl)-amino]phenyl}boronic acid (5.0 mmol, 1.105 g) and aq Na_2CO_3 (10%, 4 mL) were added. The mixture was magnetically stirred and heated at reflux in an oil bath (oil bath temperature: 110 °C) under an inert atmosphere (N_2) for 20 h. After cooling the reaction mixture to room temperature, water (60 mL) was added and the reaction mixture was extracted with dichloromethane (3×60 mL). The combined organic phase was dried over $MgSO_4$, filtered and subsequently evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/ethyl acetate (95/5) and dichloromethane/ethyl acetate (9/1) as the eluent yielding the title compound in 96%.

Yellow solid; mp 115 °C; δ_H ($CDCl_3$): 9.02 (d, J=4.4 Hz, 1H, H-2″), 8.34 (d, J=8.4 Hz, 1H, H-6′), 8.22 (d, J=8.4 Hz, 1H, H-8″), 7.77 (ddd, J=8.4, 6.7, 1.6 Hz, 1H, H-7″), 7.57 (dd, J=8.6, 1.6 Hz, 1H, H-5″), 7.52 (ddd, J=8.4, 7.3, 1.7 Hz, 1H, H-5′), 7.51 (dd, J=8.6, 6.7 Hz, 1H, H-6″), 7.37 (d, J=4.4 Hz, 1H, H-3″), 7.32 (dd, J=8.0, 1.7 Hz, 1H, H-3′), 7.28 (dd, J=8.0, 7.3 Hz, 1H, H-4′), 6.87 (brs, 1H, NH), 0.76 (s, 9H, CH_3); δ_c ($CDCl_3$): 176.3, 150.4, 148.6, 144.7, 135.5, 130.3, 130.0, 129.8, 129.7, 128.3, 127.5, 126.5, 125.6, 124.5, 122.2, 122.0, 39.5, 27.0; HRMS (ESI) for $C_{20}H_{21}N_2O$ $[M+H]^+$: calcd: 305.1654, found: 305.1650.

3.1.2. 2-Quinolin-4-ylaniline (7). 2,2-Dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (**6**) (2.0 mmol, 0.609 g) was dissolved in ethanol (150 mL). Next, aq H_2SO_4 (40%, 150 mL) was added dropwise. The obtained mixture was

stirred and refluxed in an oil bath (oil bath temperature: 130 °C) for 24 h. Subsequently, the pH of the reaction mixture was adjusted to 8–9 with 28–30% NH_4OH under cooling in an ice bath. Next, the aqueous phase was extracted with chloroform (3×100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/ethyl acetate (1/1) as the eluent yielding the title compound in 89%.

Pale brown solid; mp 119 °C; δ_H ($CDCl_3$): 8.98 (d, J=4.4 Hz, 1H, H-2′), 8.18 (d, J=8.3 Hz, 1H, H-8′), 7.74 (ddd, J=8.3, 6.8, 1.4 Hz, 1H, H-7′), 7.71 (dd, J=8.5, 1.4 Hz, 1H, H-5′), 7.50 (dd, J=8.5, 6.8 Hz, 1H, H-6′), 7.39 (d, J=4.4 Hz, 1H, H-3′), 7.30 (ddd, J=8.1, 7.4, 1.6 Hz, 1H, H-5), 7.14 (dd, J=6.8, 1.6 Hz, 1H, H-3), 6.90 (ddd, J=7.4, 6.8, 1.1 Hz, 1H, H-4), 6.85 (dd, J=8.1, 1.1 Hz, 1H, H-6), 3.50 (brs, 2H, NH_2); δ_c ($CDCl_3$): 150.5, 148.8, 146.1, 143.9, 130.6, 130.0, 129.7, 129.6, 127.0, 126.8, 126.1, 123.1, 122.2, 118.5, 115.7; HRMS (ESI) for $C_{15}H_{13}N_2$ $[M+H]^+$: calcd: 221.1079, found: 221.1086.

3.1.3. *N*-(2-Bromophenyl)quinolin-3-amine (12). A round-bottomed flask was charged with $Pd_2(dba)_3$ (0.069 g, 0.075 mmol, 2.5 mol%) and XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) (0.096 g, 0.165 mmol, 5.5 mol%) followed by dry dioxane (12 mL) (freshly distilled). The mixture was flushed with N_2 for 10 min. Meanwhile, in another round-bottomed flask 3-bromoquinoline (**11**) (0.624 g, 3 mmol), 2-bromoaniline (0.619 g, 3.6 mmol) and caesium carbonate (2.932 g, 9 mmol) (Aldrich, 99%) were weighed. To this mixture, the Pd-catalyst was added and the flask was flushed with N_2 for 5 min. The resulting mixture was heated at reflux (oil bath temperature: 110 °C) for 30 h under magnetic stirring. After cooling down to room temperature dichloromethane (25 mL) was added and the suspension filtered over a path of celite and rinsed with dichloromethane (75 mL). The solvent was removed under reduced pressure and the residue purified by column chromatography on silicagel using dichloromethane as the eluent yielding the title compound in 83%.

White solid; mp 109 °C; δ_H ($CDCl_3$): 8.78 (d, J=2.7 Hz, 1H, H-2), 8.05 (d, J=8.4 Hz, 1H, H-8), 7.79 (d, J=2.7 Hz, 1H, H-4), 7.68 (dd, J=8.0, 1.2 Hz, 1H, H-3′), 7.59 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.58 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, H-7), 7.50 (dd, J=8.1, 6.9 Hz, 1H, H-6), 7.32 (dd, J=8.3, 1.6 Hz, 1H, H-6′), 7.23 (ddd, J=8.3, 7.0, 1.2 Hz, 1H, H-5′), 6.85 (ddd, J=8.0, 7.0, 1.6 Hz, 1H, H-4′), 6.27 (brs, 1H, NH); δ_c ($CDCl_3$): 146.2, 144.6, 140.5, 135.6, 133.4, 129.3, 128.7, 128.4, 127.4, 127.3, 126.7, 122.4, 120.9, 116.7, 113.3; HRMS (ESI) for $C_{15}H_{12}BrN_2$ $[M+H]^+$: calcd: 299.0184, found: 299.0192.

3.1.4. 7*H*-Indolo[2,3-*c*]quinoline (9). *Method A*. 2-Quinolin-4-ylaniline (**7**) (4.0 mmol, 0.881 g) was dissolved in aq HCl (37%, 35 mL) and the mixture cooled to 0 °C using an ice bath. Subsequently, ice cooled aq $NaNO_2$ (0.4 M, 22 mL) was added dropwise keeping the temperature below 3 °C. The mixture was stirred for 1.5 h at 0 °C. Ice cooled aq NaN_3/NaOAc solution (8.46 mmol NaN_3 and 56 mmol $NaOAc \cdot 3H_2O$ in 20 mL water) was added dropwise keeping the temperature below 3 °C. Next, the mixture was stirred for another 1 h at 0 °C. The reaction mixture was neutralized with saturated aq Na_2CO_3 while keeping the temperature below 3 °C and subsequently extracted with EtOAc (5×100 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was dissolved in 150 mL *o*-dichlorobenzene and flushed with Ar. The mixture was stirred and heated in an oil bath at 180 °C for 3 h under Ar atmosphere. After cooling down to room temperature, the solvent was removed under reduced pressure. Finally, the obtained residue was purified via column chromatography on silicagel using ethyl acetate/methanol (95/5) as the eluent yielding the title compound **9** in 88%.

Only a trace amount of the C-5 ring closed product (7*H*-pyrido[2,3,4-*kl*]acridine, **10**) could be observed in a chromatographic fraction during purification of **9**.

Compound **10**. δ_H (400 MHz, DMSO-d_6): 10.58 (brs, 1H, NH), 8.49 (d, J=5.0 Hz, 1H), 7.98 (dd, J=7.8, 1.3 Hz, 1H), 7.44 (t, J=8.2 Hz, 1H), 7.41 (d, J=5.0 Hz, 1H), 7.40 (ddd, J=7.7, 7.0, 1.3 Hz, 1H), 7.09 (dd, J=8.2, 0.9 Hz, 1H), 7.03 (dd, J=8.2, 0.9 Hz, 1H), 6.98 (ddd, J=7.8, 7.0, 1.0 Hz, 1H), 6.65 (dd, J=7.7, 1 Hz, 1H).[36]

Method B. A round-bottomed flask was charged with $Pd(PPh_3)_2Cl_2$ (0.097 g, 0.138 mmol, 23 mol%), *N*-(2-bromophenyl)quinolin-3-amine (**12**) (0.180 g, 0.6 mmol), $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol) followed by dimethyl acetamide (DMA) (10 mL). The mixture was flushed with Ar for 5 min and then stirred at 130 °C under Ar atmosphere for 48 h. Subsequently, the mixture was evaporated to dryness in vacuo and the residue was filtered over celite using dichloromethane/methanol (95/5) (300 mL). The filtrate was evaporated to dryness and the residue dissolved in dichloromethane (100 mL). The organic phase was extracted with 0.6 M HCl (10×50 mL) and the aqueous phase was subsequently washed with toluene (3×100 mL). Next, 10 M NaOH (30 mL) was added to the aqueous phase until the colour changed from yellow to white. The water phase was extracted with dichloromethane (3×100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/methanol (97/3) as the eluent yielding the title compound (**9**) in 45%. The fractions with R_f value between 0.35 and 0.58 contained quindoline (**13**), starting material (**12**) and *N*-phenylquinolin-3-amine (dehalogenated starting material). Evaporation of these fractions, followed by a second column on silicagel using dichloromethane/ethyl acetate (95/5) as the eluent yielded a mixture of **12** (2%) and **13** (4%). Calculation of the yield of **13** was done based on the ^1H NMR spectrum of the mixture of **12** and **13**. The obtained NMR data of **13** were identical with those reported in the literature.[7b,8]

For the work-up of the reaction mixture an alternative approach can be used yielding the title compound in essentially the same yield.

The mixture was evaporated to dryness in vacuo. The obtained residue was taken up in some dichloromethane/

methanol (95/5) and filtered over celite (using the same solvent combination (total volume: 300 mL)) and the filtrate subsequently evaporated to dryness in vacuo. Amberlyst 15 (1.2 g resin washed with 30 mL dichloromethane) was added to the residue (for the complete transfer 60 mL dichloromethane was used to rinse). The resulting mixture was stirred for 16 h. Next, the dichloromethane was decanted. Subsequently, the amberlyst was washed with dichloromethane (3×60 mL), toluene (3×60 mL) and diethyl ether (60 mL). 7 N NH_3 in MeOH (60 mL) was added to the amberlyst and the mixture was stirred for 1 h. The amberlyst was filtered over a glass filter and then rinsed with 7 N NH_3 in MeOH (1×60 mL) and MeOH (1×60 mL). Next, the filtrate was concentrated to dryness in vacuo. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/methanol (97/3) as the eluent yielding the title compound (**9**).

Compound **9**. White solid; mp>240 °C (decomp.); δ_H (DMSO-d_6): 12.15 (brs, 1H, NH), 9.29 (s, 1H, H-6), 8.80 (dd, J=8.2, 1.3 Hz, 1H, H-4), 8.67 (d, J=8.1 Hz, 1H, H-11), 8.19 (dd, J=8.2, 1.1 Hz, 1H, H-1), 7.70 (dd, J=8.2 1.1 Hz, 1H, H-8), 7.76 (ddd, J=8.2, 7.1, 1.1 Hz, 1H, H-3), 7.67 (ddd, J=8.2, 7.1, 1.3 Hz, 1H, H-2), 7.60 (dd, J=8.3, 7.1 Hz, 1H, H-9), 7.40 (ddd, J=8.1, 7.1, 1.1 Hz, 1H, H-10); δ_c (DMSO-d_6): 142.1, 139.4, 138.7, 132.6, 129.9, 126.9, 126.6, 125.1, 124.2, 123.2, 122.8, 121.2, 120.2, 119.3, 112.6; HRMS (ESI) for $C_{15}H_{11}N_2$ $[M+H]^+$: calcd: 219.0922, found: 219.0929.

3.1.5. Isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]-quinoline) (4). In a round-bottomed flask 7*H*-indolo[2,3-*c*]quinoline (**9**) (0.109 g, 0.5 mmol), toluene (7.5 mL) and CH_3I (3 mL) were heated at reflux under N_2 atmosphere (oil bath temperature: 120 °C) for 2 h under magnetic stirring. Then the precipitated material was filtered off and rinsed well with toluene (100 mL). The residue was dissolved in methanol (300 mL), to remove it from the filter, and the solvent subsequently evaporated to dryness under reduced pressure. The crude product was purified via column chromatography on silica gel (eluent: chloroform/methanol (9/1)) (the residue was brought on column as a suspension in a minimal amount of acetonitrile) giving isoneocryptolepine hydroiodide (**4**·HI) as a yellow solid in 88% yield. To obtain the free base, **4**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to quantitatively yield **4** as a red solid.

mp>220 °C (decomp.); δ_H (DMSO-d_6): 9.55 (s, 1H, H-6), 8.91 (dd, J=8.3, 1.3 Hz, 1H, H-1), 8.61 (brd, J=8.4 Hz, 1H, H-11), 8.28 (dd, J=8.6, 1.0 Hz, 1H, H-4), 7.85 (ddd, J=8.3, 7.0, 1.0 Hz, 1H, H-2), 7.81 (brd, J=8.4 Hz, 1H, H-8), 7.71 (ddd, J=8.6, 7.0, 1.3 Hz, 1H, H-3), 7.45 (ddd, J=8.4, 6.6, 1.1 Hz, 1H, H-9), 7.18 (ddd, J=8.4, 6.6, 1.0 Hz, 1H, H-10), 4.57 (s, 3 H, NCH_3); δ_c (DMSO-d_6): 156.7 (C-7a), 141.2 (C-6), 141.1 (C-6a), 130.2 (C-4a), 127.2 (C-2), 126.4 (C-9), 125.1 (C-3), 125.0 (C-11c), 124.2 (C-11b), 123.8 (C-1), 123.4 (C-11), 122.1 (C-11a), 120.2 (C-8), 118.6 (C-4), 118.5 (C-10), 44.0 (CH_3); HRMS (ESI) for $C_{16}H_{13}N_2$ $[M+H]^+$: calcd: 233.1079, found: 233.1069.

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36. Based on this ^{1}H NMR spectrum we can not conclude which tautomer is obtained (3*H*-pyrido[2,3,4-*kl*]acridine or 7*H*-pyrido[2,3,4-*kl*]acridine). We did not use any additional NMR-techniques to try to find out which tautomer we prepared since only one chromatographic fraction contained the pyridoacridine skeleton mixed with **9**. Based on PM3 calculations 7*H*-pyrido[2,3,4-*kl*]acridine is the most stable tautomer.