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Mapping the Reactivity of the Quinoline Ring-System – Synthesis of the Tetracyclic Ring-System of Isocryptolepine and Regioisomers

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Abstract Bromoquinolines (2-bromoquinoline – 8-bromoquinoline and 5-bromo-3-methoxyquinoline) and 2-aminophenylboronic acid hydrochloride were subjected to Suzuki-Miyaura cross-coupling conditions resulting in formation of the desired biaryl systems in good yields. The resulting biaryls were then subjected to palladium catalyzed C-H activation/C-N bond formation utilizing $PdCl_2$(dppf). The reactions revealed large differences in reactivity depending on the attachment point for the 2-aminophenyl group on the quinoline. The variation in the reactivity was rationalized based on the electron distribution around the quinoline ring-system.

Introduction

Nitrogen containing heterocycles are immensely important appearing in 59% of the Food and Drug Administration (FDA) approved small-molecule drugs.[1] Heterocycles containing one or more nitrogen atoms are also commonly found in nature,[2] with many of these compounds being based on the quinoline core.[2c,2d] Cryptolepine, neocryptolepine, and isocryptolepine belonging to the indoloquinoline family of natural products represents examples of such compounds (Figure 1).[3] The antimalarial activity of these three compounds has made them

attractive synthetic targets.[4] In particular isocryptolepine has been the focus of studies in several research groups throughout the world resulting in a range of total syntheses,[5,6] including our own synthesis.[7] Lately it has also been found that neocryptolepine has activity towards neglected topical diseases caused by trypanosomatid parasites, increasing the interest for this natural product amongst medicinal chemists.[8] The three mentioned natural products have also been targeted for analogue synthesis with the aim to enhance the antimalarial and anticancer activity.[9]

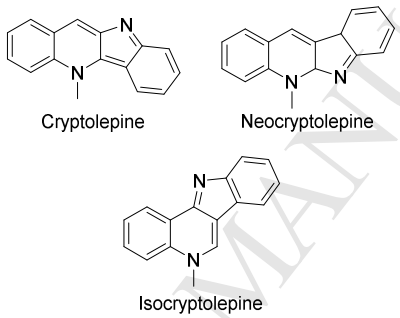


Figure 1. The structure of cryptolepine, neocryptolepine, and isocryptolepine.

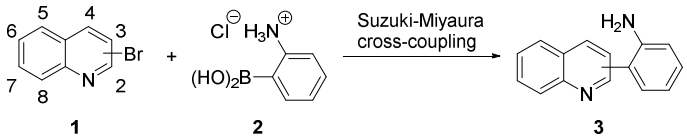
As a continuation of our own synthesis of isocryptolepine,[7] we became interested in mapping the reactivity around the quinoline ring-system in terms of the ability to engage in the Suzuki-Miyaura cross-coupling and the following C-H activation/C-N bond formation leading up to the formation of the core structure of the natural products neocryptolepine and isocryptolepine and regioisomers thereof. Although several of these compounds have been prepared previously (compounds **4a**,[10,11] **4b**,[7,11] **4c**,[10,11] **4d**,[12] **4e**,[13] **4f**,[14] and **4g**[15]), in particular the natural product precursors (compound **4a** and **4b**), it is the first time that the same reaction conditions have been utilized in order to study the reactivity around the quinoline ring-system.

Herein, we present the results of these studies highlighting the difference in reactivity around the quinoline ring-system in particular towards ring formation.

Result and Discussion

In our reported synthesis of isocryptolepine, $PdCl_2$(dppf) was utilized as catalyst in order to facilitate the Suzuki-Miyaura cross-coupling reaction.[7] Naturally, this catalyst was an obvious starting point for our further studies. Treating 2-bromoquinoline (**1a**) and boronic acid **2** with $PdCl_2$(dppf) under our previously used reaction conditions gave quick conversion (1 h) to the desired product **3a** in 65% isolated yield (Table 1, Entry 1). Prolonging the reaction time only resulted in the formation of unwanted byproducts. The drop in yield compared to the yield obtained for the cross-coupling in C3,[7a] which gave compound **3b** in 84% yield, prompted us to try $Pd(PPh_3)_4$ as catalyst. Switching catalyst to $Pd(PPh_3)_4$ resulted in formation of compound **3a** in 94% yield (Table 1, Entry 1). The great difference in yields obtained with the two catalysts in these two reactions prompted us to utilize both reaction conditions in the continuation of the work.

Table 1. Suzuki-Miyaura cross-coupling of bromoquinoline **1** with 2-aminophenylboronic acid hydrochloride (**2**).



1 2 3

Entry	Substrate	Catalyst $PdCl_2$(dppf)[a] (Reaction time)	Catalyst $Pd(PPh_3)_4$[b] (Reaction time)

1	2-bromoquinoline (**1a**)	**3a** 65% (1 h)	**3a** 94% (16 h)
2	3-bromoquinoline (**1b**)	**3b** 84%[c] (20 h)	**3b** 53% (20 h)
3	4-bromoquinoline (**1c**)	**3c** 91% (21 h)	**3c** 96% (1.75 h)
4	5-bromoquinoline (**1d**)	**3d** 54% (overnight)	**3d** 90% (overnight)
5	6-bromoquinoline (**1e**)	**3e** 81% (overnight)	**3e** 82% (overnight)
6	7-bromoquinoline (**1f**)	**3f** 30% (29 h)	**3f** 82% (20 h)
7	8-bromoquinoline (**1g**)	**3g** 45% (22 h)	**3g** 87% (16 h)

[a]Method A: $PdCl_2$(dppf) (dppf = 1,1'-bis(diphenylphosphino)ferrocene) (5 mol%), K_2CO_3, EtOH/H_2O (5:1), 60 ^oC; [b]Method B: $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3, DME/H_2O (5:1), 80 ^oC; [c]Slightly increased yield compared to our previously reported yield is due to optimization of the purification of the crude material.

The remaining bromoquinolines were subjected to Suzuki-Miyaura cross-coupling reaction using $PdCl_2$(dppf) (Method A) and $Pd(PPh_3)_4$ (Method B). Both methods successfully yielded all the desired Suzuki-Miyaura cross-coupling products **3b-g** in predominantly good yields (Table 1). Overall, tetrakis(triphenylphosphine)palladium(0) (Method B) generally resulted in the best yields and the reaction times were mostly shorter (Table 1). In particular, the coupling reaction with 4-bromoquinoline worked remarkably well resulting in the formation of the desired cross-coupling product **3c** in close to quantitative yield (96%) in less than 2 h (Table 1, Entry 3).

Based on the results obtained for the Suzuki-Miyaura cross-coupling reactions it is obvious that the reactivity around the quinoline ring varies. It has been known for some time that the two least electron dense positions of the quinoline ring-system are the C2 and C4.[16,17] This is clearly demonstrated by electron density calculations by Coulson and Longuet-Higgins (Figure 2a),[18] however, other calculations suggest that the data for the C2 and C4 should be reversed.[10,18] Indeed, Brower *et al.*[17] observed lower activation energies at the C2 of quinoline

in the aromatic substitution with piperidine (Figure 2b) and PM3 calculations carried out by Hostyn *et al.*[10] revealed a significantly higher electron density at the C4 of quinoline.

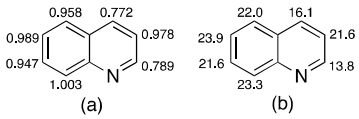


Figure 2. (a) Electron densities of the quinoline ring-system;[18] (b) Energies of activation (ΔE) for reactions of haloquinolines with piperidine.[17]

It was noted by Brower *et al.* that this deviation in electron density could be the result of the chosen model employed by Coulson and Longuet-Higgins, as the calculations are based on the occurrence of a certain substitution reaction being made.[17,18] While there seems to be an agreement that C3 is the least active of the pyridyl carbons,[17,19] there is some debate regarding which position is the most active between C2 and C4, as evident by the preceding discussion. Schröter *et al.* argue that the annelated benzol ring in quinoline makes C2 the only carbon with any significant electrophilicity,[20] while Almond-Thynne *et al.* claims that in dihalogenated quinolines, the electrophilicity is highest at C2, C4 and C3, in decreasing order.[19]

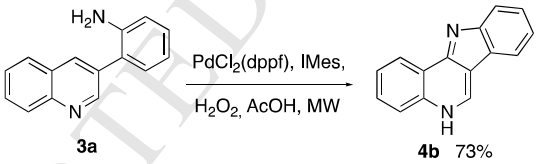
In the Suzuki-Miyaura cross-coupling reactions of heteroaryl halides it has been remarked that the oxidative addition step proceeds in a similar mechanistic fashion to S_NAr reactions.[19] From this, it can be inferred that the reaction occurs at the most electrophilic carbon given the choice between multiple reaction sites.[19-21] This trend was not quite representative for our cross-couplings, with the reactions at C5 and C8 performing better than at C3 when $Pd(PPh_3)_4$ was used as catalyst (Table 1, Entries 2, 4, and 7). As can be seen from Table 1 the reactivity was not only determined by the relative electron density, but also by the employed catalyst.

Keeping the previous discussion in mind, when it came to testing the reactivity of our Suzuki-Miyaura cross-coupling products towards cyclization, we expected that when two positions

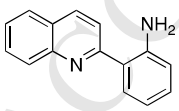
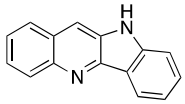
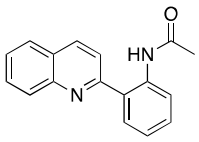
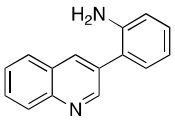
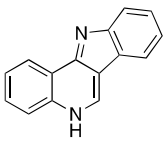
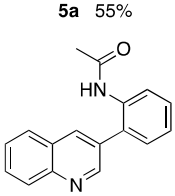
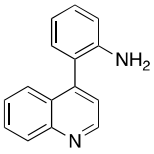
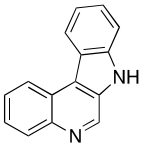
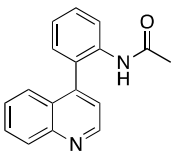
were available to form a C-N bond it would selectively occur at the most electron deficient carbon. This is based on the assumption that the cyclization proceeds *via* an oxidative addition-type mechanism with the palladium species, which was proposed by Bjørsvik and Elumalai as a likely reaction pathway for the cyclization of 2-aminobiphenyl to form the carbazole scaffold under conditions similar to the ones used in this work.[22]

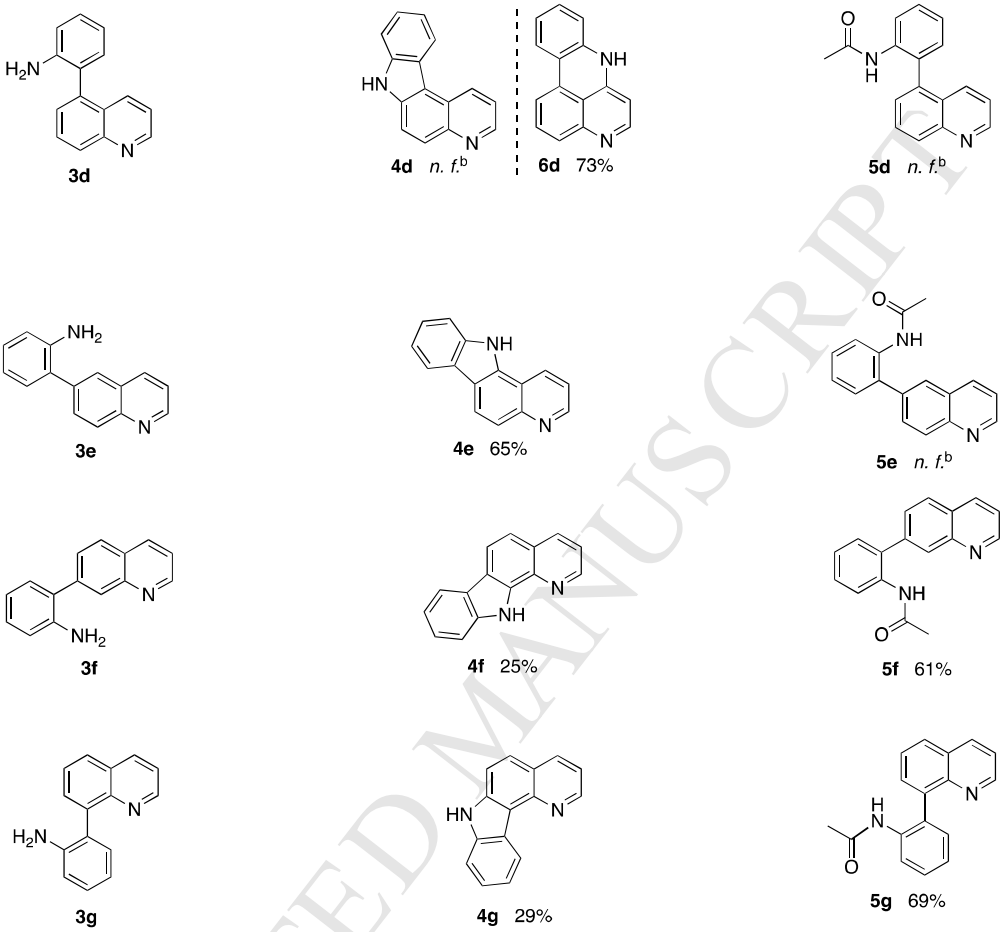
Rerunning the cyclization of compound **3b** using our previously reported chemistry,[7a] proceeded regiospecific to give indoloquinoline **4b** in 73% yield (Table 2, Entry 2). The increased yield (62% → 73%) for the cyclization reaction compared to our previous report[7a] is due to the discovery of a better solvent combination for purification of the crude product by flash chromatography.

Table 2. Summary of the C-H activation/C-N bond formation resulting in the formation of the tetracyclic ring-systems **4b**, **4e**, **4f, 4g** and **6c**.[a]



3a **4b** 73%

Entry	Substrate	Cyclization product	Acetylation product
1	 **3a**	 **4a** *n. f.*[b]	 **5a** 55%
2	 **3b**	 **4b** 73%	 **5b** *n. f.*[b]
	 **3c**	 **4c** *n. f.*[b]	 **5c** 54%

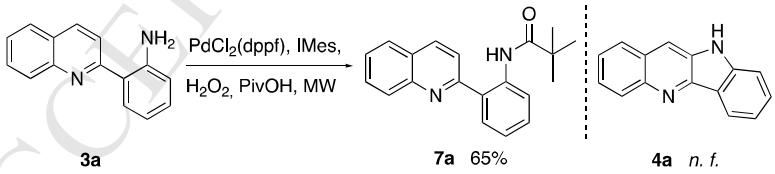


[a]Conditions: $PdCl_2$(dppf) (20 mol%), 1,3-bis(2,4,6-trimethylphenyl)-imidazolium (IMes) (5 mol%), H_2O_2 (35 wt%, 29 mol%), AcOH, MW sealed reactor tube 118 □; [b]*n. f.* = not formed.

Upon cyclization of substrate **3b** no trace of its regioisomer 6*H*-indolo[2,3-*b*]quinoline was observed in the crude reaction mixture despite the resonance forms of compound **3b** bearing a negative charge at both the C2 and C4 as outlined in Scheme 3a. The observed regioselectivity towards C-N bond formation at the C4 over C2 is presumably governed by favorable relative electrostatic effects. Similar observations has also been reported for C-C bond formations, although in those examples small amounts of the product resulting from reaction at C2 was also isolated.[10,17]

Much to our disappointment, subjecting biaryls **3a** and **3c** to our standard cyclization conditions did not yield the expected products 7*H*-indolo[2,3-*c*]quinoline (**4a**) and 10*H*-indolo[3,2-*b*]quinoline (**4c**), respectively. Instead, these reactions resulted in acetylation of the starting materials to give **5a** and **5c** in 55% and 54% yield, respectively (Table 2, Entries 1 and 3). The resonance structures of **3a** and **3c** show that the C3 of the quinoline moiety can bear a negative charge and additional inductive effects exhibited by the nuclear nitrogen may make this position particularly unreactive.[17] With the aid of ESI-MS, traces of a mass corresponding to the expected mass of protonated species **4c** was detected, however, ^{1}H NMR analysis on a minute amount of compound post purification by silica gel column chromatography failed to provide evidence of its formation.

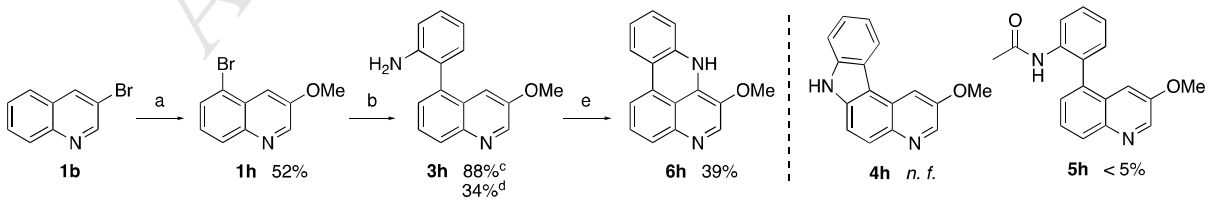
Acetic acid is known to act as an acetylating agent when employed in microwave-assisted syntheses.[23] Efforts were therefore made to avoid the formation of the acetylation product by replacing acetic acid with a more sterically hindered acid, viz. pivalic acid. Attempts to carry out the cyclization of **3a** in pivalic acid unfortunately only lead to the formation of *N*-(2-(quinolin-2-yl)phenyl)pivalamide (**7a**) in 65% yield, thus no further experiments were conducted using this solvent (Scheme 1).



Scheme 1. Attempted formation of compound **4a** utilizing pivalic acid as solvent.

Cyclization of compound **3d** gave only phenanthridine **6d** in 73% yield with no trace of cyclization into C6 (Table 2, Entry 4). It can be seen from the resonance structures of compound **3d** that C6 of quinoline can have a negative charge while C4 cannot (Scheme 3b). Formation of compound **6d** is in agreement with cyclization into the most electron deficient position.

Despite the resonance structures for compound **3d** favoring cyclization into C4 (Scheme 3b), the kinetic preference is to form 5- over 6-membered rings[24] and the regioselective formation of phenanthridine **6d** warranted further exploration. We became interested in altering the electron distribution of biaryl **3d** by introducing a methoxy group at C3 to examine if the electron donating properties of the alkoxide would affect the regioselectivity (Scheme 3b). Following the procedure outlined by Landagaray *et al.*[25] 5-bromo-3-methoxyquinoline (**1h**) was synthesized starting from 3-bromoquinoline (**1b**) (Scheme 2). Subsequent Suzuki-Miyaura cross-coupling of quinoline **1h** with boronic acid **2** using methods A and B yielded 2-(3-methoxyquinolin-5-yl)aniline (**3h**) in poor yields (method A: 47%; method B: 34%). Unreacted starting material (**1h**) (29%) and 19% of 2,2'-biphenyldiamine was also isolated when method A was used. Method A could be further optimized by adjusting the equivalents of boronic acid **2** from 1.5 eq. to 3 eq., which increased the yield of the desired coupling product **3h** from 47% → 88%. Finally, cyclization of biaryl **3h** surprisingly yielded phenanthridine **6h** in 39% yield in addition to a small quantity of the acetylated product **5h** (< 5%) together with several unidentified impurities. Analyzing the crude mixture by ESI-MS, traces of a mass corresponding to the protonated mass of the 5-membered ring product **4h** was detected but this was not verifiable by ^{1}H NMR. Consequently, it is clear that the inductive effect exhibited by the methoxy moiety affects the system, however, it is not sufficient to completely reverse the regioselectivity observed for the cyclization of biaryl **3d**.

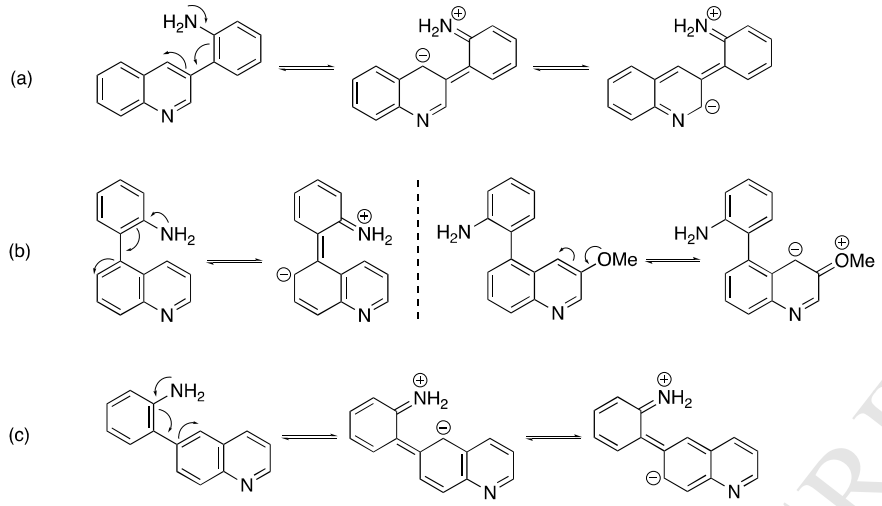


Scheme 2. Synthesis of 2-(3-methoxyquinolin-5-yl)aniline (**3h**) and subsequent ring closure to yield 6-methoxy-7*H*-pyrido[4,3,2-*gh*]phenanthridine (**6h**). Conditions: a) (i) NaOMe

(30%), CuI (5 mol%), DMF, reflux, overnight; (ii) NBS, H_2SO_4 (conc.), 0 □ to rt, overnight; b) [c]Method A: **2** (0.48 mmol), $PdCl_2$(dppf) (5 mol%), K_2CO_3, EtOH/H_2O (5:1), 60 ^oC, overnight; [d]Method B: **2** (0.24 mmol), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3, DME/H_2O (5:1), 80 ^oC, overnight; e) $PdCl_2$(dppf) (20 mol%), IMes (5 mol%), H_2O_2 (35 wt%, 29 mol%), AcOH, MW 118 ℃ 1 h.

A literature search revealed no synthetic strategies for the synthesis of systems such as phenanthridines **6d** and **6h** at present time. Hostyn *et al.*[10] describes the synthesis of 7*H*-indolo[2,3-*c*]quinoline (**4a**) and 7*H*-pyrido[2,3,4-*kl*]acridine by thermal collapse of 4-(2-azidophenyl)quinoline, where the indoloquinoline was the major product and only traces of the acridine was observed. The authors rationalize the selectivity in terms of kinetics, moreover, the cyclization is thought to be the result of a nitrene insertion which presumably plays a role in determining the regioselectivity.

Turning to the cyclization of compounds **3e** and **3f** (Table 2, Entries 5 and 6), it did not seem immediately obvious where the C-N bond would be formed. Unlike the resonance form of compound **3b**, there is no adjacent heteroatom to delocalize the negative charge in these cases (Scheme 3c). Instead, we examined the chemical shifts for the protons adjacent to the tethered aniline to see which of the two protons experienced the most deshielding, a method advocated for by Handy and Zhang for the prediction of regioselectivity in cross-coupling reactions.[21] However, it is noted that when $\Delta\delta_H < 0.03$ ppm this technique should be used with caution as they demonstrated that it failed to accurately predict the selectivity in such cases. In compound **3e**, H-5 has a shift of 7.91 ppm while H-7 is at 7.85 ppm ($\Delta\delta_H$ = 0.06 ppm), favoring cyclization into C5, which in fact was the outfall of the reaction resulting in a 65% isolated yield of compound **4e** (Table 2, Entry 5). No trace of the H-7 regioisomer, 10*H*-pyrido[2,3-*b*]carbazole, was observed.



Scheme 3. Resonance structures for compounds **3b**, **3d**/**3h** and **3e**.

Similarly, cyclization of compound **3f** occurred at H-8, which displayed a higher chemical shift than H-6, to furnish **4f** in 25% yield (Table 2, Entry 6). This reaction was also regioselective towards cyclization at H-8, however, undesired acetylation product **5f** was also formed in 61% yield. The cyclization of biaryl **3g** returned a similar outcome, with target compound **4g** formed in 29% yield while the acetylation product was furnished in 69% yield (Table 2, Entry 7). It seems that acetylation of biaryls **3** is the outcome when the electron flow of the quinoline ring-system is congested, i.e. it is energetically unfavorable to form the tetracyclic ring-system due to high electron densities at the adjacent protons.

Conclusion

In conclusion, the reactivity of the quinoline ring-system has been mapped by subjecting bromoquinolines **1a**-**h** to a Suzuki-Miyaura cross-coupling reaction with 2-aminophenylboronic acid hydrochloride (**2**). The resulting cross-coupling products were then subjected to an intramolecular cyclization *via* tandem C-H activation and C-N bond formation to furnish tetracyclic ring-systems **4b** and **4e**-**4g** and **6d** and **6h**. Our findings were congruent

with earlier reports that C2 and C4 of the quinoline scaffold is the most active and it appears that the electron densities at the various carbons determined the regioselectivity of the cyclization. Our synthetic efforts also resulted in an improved yield for the formation of the tetracyclic ring-system required for the formation of isocryptolepine.

Experimental

General experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ascend^{TM} 400 series, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are expressed in ppm relative to residual chloroform (^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm), DMSO-d_6 (^{1}H, 2.50 ppm; ^{13}C, 39.52 ppm) or methanol (^{1}H, 3.31 ppm; ^{13}C, 49.00 ppm). The assignments of signals in various NMR spectra was often assisted by conducting correlation spectroscopy (COSY), heteronuclear single-quantum correlation spectroscopy (HSQC) and/or heteronuclear multiple bond correlation spectroscopy (HMBC).

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel 60 F_{254} coated aluminium sheets using UV light as visualizing agent. Silica gel 60 (particle size 40-63 μm) was used for silica flash chromatography and alumina gel (particle size 30-48 μm) was used for alumina flash chromatography. Automated flash chromatography was carried out using an Interchim puriFlash® 215 chromatography system. The sample was evaporated onto celite and then dry-loaded onto a specialized column which was attached to an SI-HP Interchim column filled with silica gel (particle size 40-50 μm). The appropriate eluent was flushed through the columns using an applied pressure of 22-26 bar.

In addition to TLC, low resolution mass spectrometry (LRMS) was routinely used to monitor and identify the various components of reaction mixtures. The LRMS spectra were obtained on an Advion expression^{s} CMS mass spectrometer operating at 3.5 kV in electrospray ionization (ESI) mode.

Infrared spectroscopy (IR) was performed on a Cary 360 FTIR spectrophotometer. Solids were dissolved in $CHCl_3$ or DCM and absorbed on a NaCl plate, or by placing the sample directly onto the crystal of an attenuated total reflectance (ATR) module. Melting points were measured using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. High resolution mass spectroscopy (HRMS) were conducted externally at the University of Bergen or the University of Tromsø, using electron spray ionization (ESI). The microwave-assisted experiments were performed in a CEM Focused Microwave^{TM} Synthesis System, model type Discover, operating at 0-300 W at a temperature of 118 ˚C, a pressure range of 0-290 psi, with reactor vial volumes of either 10 or 35 mL. Commercially chemicals were used as delivered from the supplier unless otherwise noted.

5-Bromo-3-methoxyquinoline (1h). [25] Following the procedure reported by Landagaray *et al.* the title compound **1h** was obtained as off-white crystals (52%), mp 76-77 ^{o}C (lit.[25] 81-83 ^{o}C); IR (ATR): ν_{max} 3067, 3004, 2995, 2964, 2853, 1599, 1407, 1161, 859 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 8.61 (d, *J* = 2.8 Hz, 1H), 7.99-7.96 (m, 1H), 7.87 (dd, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.4 Hz, 7.6 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 155.9, 146.2, 144.6, 132.3, 129.7, 129.3, 128.3, 121.5, 113.2, 56.3. In accordance with previously reported data.[25]

Method A: General method for Suzuki-Miyaura cross-coupling using [$PdCl_2$(dppf)] as catalyst. 2-Aminophenylboronic acid hydrochloride (**2**) (62.5 mg, 0.36 mmol), an aqueous solution of potassium carbonate (116.1 mg, 0.84 mmol in 0.2 mL H_2O), and $PdCl_2$(dppf) (8.9 mg, 0.012 mmol, 5 mol%) was added to a stirred solution of bromoquinoline **1a-h** (0.24 mmol) in EtOH (1 mL) under an argon atmosphere and the reaction mixture was stirred at 60 ˚C until completion of the reaction as indicated by TLC analysis. The reaction mixture was then allowed to cool to room temperature and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by silica gel column chromatography using the chromatographic technique and eluent as indicated for each compound in order to give compound **3a-h**.

Method B: General method for Suzuki-Miyaura cross-coupling using $Pd(PPh_3)_4$ as catalyst. To a solution of bromoquinoline **1a-h** (0.24 mmol) in dimethoxyethane (2 mL) under an argon atmosphere was added 2-aminophenylboronic acid hydrochloride (**2**) (62.5 mg, 0.36 mmol), an aqueous solution of cesium carbonate (273.7 mg, 0.84 mmol in 0.4 mL H_2O), and tetrakis(triphenylphosphine)palladium(0) (13.9 mg, 0.012 mmol, 5 mol%). The resulting reaction mixture was stirred at 80 ˚C until completion as indicated by TLC. The reaction mixture was then allowed to cool to room temperature and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by silica gel column chromatography using the chromatographic technique and eluent as indicated for each compound in order to give compound **3a-h**.

2-(Quinolin-2-yl)aniline (3a). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 9:1 v/v) and concentration of the relevant

fractions [R_f = 0.17 (pet. ether/EtOAc, 9:1 v/v)] gave the title compound **3a** as bright yellow crystals (method A: 65%; method B: 94%), mp 152-155 ^oC; IR (ATR): ν_{max} 2922, 2852, 1718, 1465, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.82-7.80 (m, 1H), 7.73-7.69 (m, 2H), 7.54-7.49 (m, 1H), 7.24-7.19 (m, 1H), 6.85-6.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 147.2, 146.9, 136.9, 130.5, 129.9, 129.8, 128.9, 127.5, 126.4, 126.3, 121.8, 120.6, 117.9, 117.7. In accordance with previously reported data.[26]

Utilizing method A, the desired product **3a** had to undergo recrystallization (*n*-heptane/EtOAc, 9:1 v/v) to remove overlapping impurities.

2-(Quinolin-3-yl)aniline (3b). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 7:3 → 1:1 v/v) and concentration of the relevant fractions [R_f = 0.27 (pet. ether/EtOAc, 7:3 v/v)] gave the title compound **3b** as a yellow crystalline solid (method A: 84%; method B: 53%), mp 132-135 ˚C (lit.[7a] 130-132 ^oC). IR (NaCl): ν_{max} 3438, 3331, 3208, 3061, 1619, 1575, 1497, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.0 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.83-7.81 (m, 1H), 7.75-7-71 (m, 1H), 7.59-7.55 (m, 1H), 7.25-7.19 (m, 2H), 6.92-6.88 (m, 1H), 6.84-6.82 (m, 1H), 3.80 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 147.1, 144.1, 135.5, 132.5, 130.9, 129.6, 129.5, 129.2, 127.9, 127.8, 127.1, 123.7, 119.1, 116.0. In accordance with previously reported data.[7a]

2-(Quinolin-4-yl)aniline (3c). Following methods A and B; the crude was purified by an Interchim puriFlash chromatography system (pet. ether/EtOAc, 95:5 → 55:45 v/v) and concentration of the relevant fractions [R_f = 0.29 (pet. ether/EtOAc, 1:1 v/v)] gave the title

compound **3c** as a yellow solid (method A: 91%; method B: 96%), mp 128-129 ^{o}C (lit.[13] 119 ^{o}C). IR (NaCl): ν_{max} 3454, 3328, 3210, 3061, 3033, 1617, 1494, 1451, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 4.4 Hz, 1H), 8.18-8.15 (m, 1H), 7.74-7.69 (m, 2H), 7.50-7.46 (m, 1H), 7.37 (d, *J* = 4.4 Hz, 1H), 7.28 (ddd, *J* = 7.5 Hz, 1.6 Hz, 0.6 Hz, 1H), 7.12 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.88 (td, *J* = 7.4 Hz, 1.0 Hz, 1H), 6.83 (dd, *J* = 8.1 Hz, 0.8 Hz, 1H), 3.83 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.7, 146.2, 143.9, 130.6, 129.9, 129.8, 129.7, 126.9, 126.9, 126.1, 122.9, 122.3, 118.5, 115.8. In accordance with previously reported data.[13]

2-(Quinolin-5-yl)aniline (3d). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 7:3 → 6:4 v/v) and concentration of the relevant fractions [R_f = 0.23 (pet. ether/EtOAc, 1:1 v/v)] gave the title compound **3d** as light brown crystals (method A: 54%; method B: 90%), mp 163-166 ^{o}C. IR (ATR) ν_{max} 3410, 3318, 3209, 2924, 1618, 1491, 959, 803, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (dd, *J* = 4.1 Hz, 1.7 Hz, 1H), 8.16-8.14 (m, 1H), 8.02-7.99 (m, 1H), 7.81-7.77 (m, 1H), 7.53 (dd, *J* = 6.9 Hz, 0.9 Hz, 1H), 7.35 (dd, *J* = 8.5 Hz, 4.2 Hz, 1H), 7.30-7.25 (m, 1H), 7.13 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.88 (td, *J* = 7.5 Hz, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.0 Hz, 0.7 Hz, 1H), 3.44 (bs, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.7, 144.4, 137.5, 134.9, 131.4, 129.6, 129.5, 129.3, 128.2, 127.1, 124.4, 121.4, 118.56, 115.6; HRMS (ESI): calcd. for $C_{15}H_{12}N_2H^+$ 221.1073, found 221.1071.

2-(Quinolin-6-yl)aniline (3e). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 4:6 v/v) and concentration of the relevant fractions [R_f = 0.16 (pet. ether/EtOAc, 6:4 v/v)] gave the title compound **3e** as an off-white

solid (method A: 81%; method B: 82%), mp 130-132 ^{o}C. IR (NaCl) ν_{max} 3462, 3327, 3203, 3020, 2925, 2854, 1618, 1570, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 2.4 Hz, 1H), 8.20-8.18 (m, 2H), 7.91(s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.45-7.42 (m, 1H), 7.26-7.19 (m, 2H), 6.88-6.81 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.62 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.4, 143.8, 138.1, 136.3, 131.3, 130.8, 129.9, 129.1, 128.6, 127.8, 126.7, 121.6, 119.0, 115.9; HRMS (ESI): calcd. for $C_{15}H_{12}N_2H^+$ 221.1073, found 221.1072.

2-(Quinolin-7-yl)aniline (3f). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 6:4 v/v) and concentration of the relevant fractions [R_f = 0.21 (pet. ether/EtOAc, 6:4 v/v] gave the title compound **3f** as a pale yellow oil (method A: 30%; method B: 82%). IR (ATR): ν_{max} 3453, 3330, 3200, 3050, 3019, 2923, 2858, 1618, 1488, 1301, 839, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (d, *J* = 3.1 Hz, 1H), 8.22 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.40 (dd, *J* = 8.2 Hz, 4.2 Hz, 1H), 7.24 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.20 (td, *J* = 7.9 Hz, 1.5 Hz, 1H), 6.87 (td, *J* = 7.4 Hz, 1.0 Hz, 1H), 6.80 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 3.73 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.5, 143.7, 141.2, 135.9, 130.7, 129.1, 129.0, 128.4, 128.3, 127.3, 126.6, 121.2, 118.9, 115.9; HRMS (ESI): calcd. for $C_{15}H_{12}N_2H^+$ 221.1073, found 221.1073.

2-(Quinolin-8-yl)aniline (3g). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 9:1 v/) and concentration of the relevant fractions [R_f = 0.30 (pet. ether/EtOAc, 7:3 v/v)] gave the title compound **3g** as an off-white solid (method A: 45%; method B: 87%), mp 103-105 ^{o}C (lit.[27] 100-102 ^{o}C). IR (ATR): ν_{max} 3424, 3330, 3206, 3026, 1615, 1491, 793, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (dd,

J = 4.1 Hz, 1.8 Hz, 1H), 8.19 (dd, *J* = 8.3 Hz, 1.9 Hz, 1H), 7.83 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.70 (dd, *J* = 7.1 Hz, 1.5 Hz, 1H), 7.62-7.58 (m, 1H), 7.39 (dd, *J* = 8.3 Hz, 4.2 Hz, 1H), 7.25-7.21 (m, 2H), 6.90 (td, *J* = 7.5 Hz, 1.1 Hz, 1H), 6.85-6.82 (m, 1H), 3.67 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 146.2, 144.8, 139.4, 136.7, 131.7, 131.6, 128.9, 127.9, 126.8, 121.1, 118.8, 116.4. In accordance with previously reported data.[27]

2-(3-Methoxyquinolin-5-yl)aniline (3h). Following methods A and B; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 1:1 v/v) followed by alumina gel column chromatography (CH_2Cl_2/pet. ether, 8:2 v/v) and concentration of the relevant fractions [R_f = 0.33 (CH_2Cl_2/pet. ether, 8:2 v/v)] gave the title compound **3h** as an orange solid (method A: 88%; method B: 34%) along with recovered starting material (**1h**) (method B: 18%), mp 142-144 ^{o}C. IR (ATR): ν_{max} 3059, 3018, 2957, 2933, 2857, 1604, 1249, 819 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.9 Hz, 1H), 8.11-8.08 (m, 1H), 7.62 (dd, *J* = 8.4 Hz, 7.1 Hz, 1H), 7.49 (dd, *J* = 7.0 Hz, 1.2 Hz, 1H), 7.27 (ddd, *J* = 7.9 Hz, 7.5 Hz, 1.6 Hz, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.14 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.88 (dt, *J* = 7.4 Hz, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 3.79 (s, 3H), 3.58 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ153.4, 144.3, 143.6, 136.2, 131.3, 129.3, 128.9, 128.8, 127.6, 126.8, 124.6, 118.5, 115.6, 111.4, 55.6; HRMS (ESI): calcd. for $C_{16}H_{15}N_2OH^+$ 251.1179, found 251.1188.

Method C: General method for palladium-initiated intramolecular C-H activation/C-N bond formation. The appropriate biaryl (**3a-h**) (0.23 mmol) in acetic acid (0.8 mL) was added to a premixed solution of $PdCl_2$(dppf) (33.6 mg, 0.046 mmol), 1,3-bis(2,4,6-trimethylphenyl)-imidazolium (IMes) (3.5 mg, 0.011 mmol), H_2O_2 (35 wt%, 5.6 µL, 0.067 mmol) and acetic acid (0.2 mL). The reaction mixture was placed in a sealed reactor tube and

immersed into the cavity of the microwave oven and heated at 118 ˚C until completion as indicated by TLC. The reaction mixture was then transferred to a 25 mL round bottom flask with the aid of EtOAc/$CHCl_3$ and the volatiles were removed under reduced pressure. The reaction mixture was evaporated onto celite and purified by silica gel column chromatography, with the chromatographic technique and eluent gradient as indicated.

5*H*-Indolo[3,2-*c*]quinoline (4b). Following method C; the crude was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 8:2 → 6:4 v/v) to give the title compound **4b** (R_f = 0.25 (CH_2Cl_2/EtOAc, 1:1 v/v)) as an off-white solid (73%), mp 333-336 ˚C (lit.[7a] 340-341 ˚C). IR (NaCl): λ_{max} 3060, 2958, 2854, 1682,1582, 1515, 1493 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.71 (bs, 1H), 9.59 (s, 1H), 8.52 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 8. 32 (d, *J* = 7.9 Hz, 1H), 8.13 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.77-7-67 (m, 3H), 7.52-7.48 (m, 1H), 7.36-7.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.4, 144.8, 139.7, 138.7, 129.4, 128.0, 125.7, 125.5, 122.1, 121.8, 120.6, 120.1, 117.1, 114.3, 111.8. In accordance with previously reported data.[7a]

11*H*-Pyrido[3,2-*a*]carbazole (4e). Following method C; the crude was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 8:2 + 5% Et_3N v/v) and concentration of the relevant fractions [R_f = 0.06 (pet. ether/EtOAc, 6:4 v/v)] gave the title compound **4e** as an off-white solid (65%) along with recovered starting material (**3e)** (12%), mp 135-139 ˚C. IR (NaCl): λ_{max} 3133, 3075, 2923, 2852, 1731, 1574, 1372, 808, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 12.48 (bs, 1H), 8.94 (ddd, *J* = 8.3 Hz, 1.6 Hz, 0.6 Hz, 1H), 8.91 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.46 (d, *J* = 8.7 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.74 (dd, *J* = 8.7 Hz, 0.5 Hz, 1H), 7.68-7.63 (m, 2H), 7.46-7.42 (m, 1H), 7.29-7.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-

d_6): δ 148.9, 147.2, 139.1, 134.6, 130.1, 124.9, 122.9, 122.7, 120.5, 119.9, 119.5, 117.3, 116.4, 111.5. In accordance with previously reported data.[24]

11*H*-Pyrido[2,3-*a*]carbazole (4f). Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 1:1 + 0.2% Et_3N → 2/8 v/v) and concentration of the relevant fractions [R_f = 0.27 (pet. ether/ CH_2Cl_2, 1:1 v/v)] gave the title compound **4f** as pale yellow crystals (25%), mp 165-167 ˚C (lit.[14] 164-165 ˚C). IR (ATR): ν_{max} 3263, 3043, 2923, 2854, 1523, 1369, 820, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (bs, 1H), 8.92 (dd, *J* = 4.4 Hz, 1.5 Hz, 1H), 8.35 (dd, *J* = 8. 3 Hz, 1.5 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.19-8.17 (m, 1H), 7.62-7.60 (m, 2H), 7.51-7.47 (m, 2H), 7.35-7.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 139.2, 137.4, 136.8, 134.9, 127.3, 125.9, 123.8, 121.7, 120.8, 120.5, 120.4, 120.2, 118.8, 111.8. In accordance with previously reported data.[14]

7*H*-Pyrido[3,2-*c*]carbazole (4g). Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 1:1 + 0.2% Et_3N v/v) and concentration of the relevant fractions [R_f = 0.06 (pet. ether/EtOAc, 6:4 v/v] gave the title compound **4g** as a pale yellow solid (29%), mp 150-152 ˚C (lit.[15] 173-174 ˚C). IR (ATR): ν_{max} 3207, 2976, 2919, 2850, 2740, 2605, 2499 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.92 (bs, 1H), 9.02 (dd, *J* = 4.4 Hz, 1.8 Hz, 1H), 8.90-8.88 (m, 1H), 8.46 (dd, *J* = 8.1 Hz, 1.4 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.66-7.64 (m, 1H), 7.49 (dd, *J* = 8.0 Hz, 4.3 Hz, 1H), 7.46-7.42 (m, 1H), 7.33-7.29 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.8, 145.3, 139.6, 138.5, 136.5, 126.0, 124.5, 123.1, 122.9, 122.8, 119.7, 118.3, 115.3, 114.2, 111.4.

***N*-(2-(Quinolin-2-yl)phenyl)acetamide (5a).** Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 9:1 → 7:3 v/v) and concentration of the relevant fractions [R_f = 0.24 (pet. ether/EtOAc, 7:3 v/v)] gave the title compound **5a** as orange crystals (55%), mp 124-125 ˚C. IR (NaCl): ν_{max} cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.97 (bs, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 8.06-8.04 (m, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.86 (dd, *J* = 8.2 Hz, 1.0 Hz, 1H), 7.83 (dd, *J* = 7.9 Hz, 1.5 Hz, 1H), 7.80-7.76 (m, 1H), 7.48-7.43 (m, 1H), 7.20 (td, *J* = 7.9 Hz, 1.2 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 158.2, 146.2, 138.6, 137.7, 130.7, 130.5, 129.4, 128.4, 127.8, 127.1, 126.6, 124.9, 123.4, 121.8, 120.9, 25.5; HRMS (ESI): calcd. for $C_{17}H_{14}N_2OH^+$ 263.1179, found 263.1182.

***N*-(2-(Quinolin-4-yl)phenyl)acetamide (5c).** Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 6:4 → 3:7 v/v) and concentration of the relevant fractions [R_f = 0.44 (pet. ether/EtOAc, 3:7 v/v)] gave the title compound **5c** as a dark yellow solid (54%), mp 183-185 ˚C. IR (NaCl): ν_{max} 3253, 3033, 2925, 2853, 1685, 1526, 1295, 850 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.08 (bs, 1H), 8.95 (d, *J* = 4.4 Hz, 1H), 8.09-8.07 (m, 1H), 7.78-7.74 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.52-7.49 (m, 3H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.35-7.33 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 150.1, 148.0, 145.0, 135.8, 131.4, 130.7, 129.4, 129.2, 128.8, 126.4, 126.3, 126.2, 125.6, 125.2, 122.3, 22.3; HRMS (ESI): calcd. for $C_{17}H_{14}N_2OH^+$ 263.1179, found 263.1187.

***N*-(2-(Quinolin-7-yl)phenyl)acetamide (5f).** Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 1:1 + 0.2% Et_3N v/v) and concentration of the relevant fractions [R_f = 0.16 (pet. ether/EtOAc, 8:2 v/v)] gave the title compound **5f** as

a red oil (61%). IR (NaCl): ν_{max} 3418, 3249, 3051, 2966, 2924, 2852, 1676, 1526, 1301, 840, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 8.85 (d, *J* = 3.3 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.04 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.55-7.53 (m, 2H), 7.48-7.35 (m, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 172.1, 151.2, 148.4, 142.4, 138.0, 137.6, 135.3, 131.5, 129.5, 129.2, 128.9, 128.7, 128.5, 128.0, 127.7, 122.4, 22.9; HRMS (ESI): calcd. for $C_{17}H_{14}N_2OH^+$ 263.1179, found 263.1181.

***N*-(2-(Quinolin-8-yl)phenyl)acetamide (5g).** Following method C; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 9:1 → 4:6 + 1% Et_3N) and concentration of the relevant fractions [R_f = 0.21 (pet. ether/EtOAc, 1:1 v/v)] gave the title compound **5f** as dark yellow crystals (69%), mp 128-130 ˚C. IR (ATR): ν_{max} 3247, 3195, 3059, 3026, 2926, 2854, 1678, 1522, 1439, 1295, 789, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (dd, *J* = 3.9 Hz, 1.4 Hz, 1H), 8.48 (bs, 1H), 8.31 (dd, *J* = 8.2 Hz, 1.3 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 7.74-7.66 (m, 2H), 7.52-7.45 (m, 2H), 7.35 (dd, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.29-7.25 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 150.7, 145.8, 138.8, 137.7, 135.7, 133.1, 132.9, 131.9, 128.9, 128.6, 128.6, 127.2, 125.3, 124.4, 121.4, 24.4; HRMS (ESI): calcd. for $C_{17}H_{14}N_2OH^+$ 263.1179, found 263.1183.

7*H*-Pyrido[4,3,2-*gh*]phenanthridine (6d). Following method C; the crude was purified by silica gel column chromatography (EtOH/MeOH, 100:0 → 8:2 v/v) and concentration of the relevant fractions [R_f = 0.19 (EtOH)] gave the title compound **6d** as a yellow gel (73%). IR (NaCl): ν_{max} 3274, 3167, 3112, 3049, 2919, 2851, 2762, 1614, 1576, 1460, 669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 8.27 (d, *J* = 6.6 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 8.4 Hz, 0.6 Hz, 1H), 7.59-7.55

(m, 1H), 6.78-6.76 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2, 143.3, 141.1, 135.5, 134.1, 131.6, 130.9, 124.9, 123.8, 120.4, 118.1, 117.2, 115.9, 115.0, 99.7; HRMS (ESI): calcd. for $C_{15}H_{10}N_2H^+$ 219.0917, found 219.0917.

6-Methoxy-7*H*-pyrido[4,3,2-*gh*]phenanthridine (6h). Following method C; the crude was purified by silica gel column chromatography (CH_2Cl_2/EtOAc/EtOH, 1:1:0 → 1:0:1 → 0:0:1 v/v) followed by a second purification by silica gel (CH_2Cl_2/EtOH, 7:3 → 1:1 v/v) and concentration of the relevant fractions [R_f = 0.33 (CH_2Cl_2/EtOH, 7:3 v/v)] gave the title compound **6h** as a bright yellow gel (39%). IR (ATR): ν_{max} 2958, 2926, 2860, 1609, 1464, 1278, 764 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (bs, 1H), 8.30 (dd, *J* = 8.4 Hz, 1.0 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.80 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.56-7.52 (m, 1H), 7.38-7.34 (m, 1H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.2, 138.3, 135.5, 132.8, 131.0, 130.8, 127.0 (2C), 125.2, 123.6, 120.7, 118.8, 116.5, 115.7, 113.8, 57.8; HRMS (ESI): calcd. for $C_{16}H_{13}N_2OH^+$ 249.1028, found 249.1029.

***N*-(2-(Quinolin-2-yl)phenyl)pivalamide (7a).** Following method C, take for the solvent being pivalic acid; the crude was purified by silica gel column chromatography (pet. ether/EtOAc, 9/1 v/v) and concentration of the relevant fractions [R_f = 0.25 (pet. ether/EtOAc, 9:1 v/v)] gave the title compound **7a** as white crystals (65%), mp 107-108 ˚C (lit.[28] 99-100 ˚C). IR (ATR): ν_{max} 3181, 2954, 2928, 2865, 1676, 1582, 1501, 1297, 1158, 829, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.28 (bs, 1H), 8.64 (dd, *J* = 8.4 Hz, 1.0 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.86 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.79-7.75 (m, 1H), 7.73 (dd, *J* = 7.9 Hz, 1.5 Hz, 1H), 7.60-7.56 (m, 1H), 7.47-7.43 (m, 1H),

7.20 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 158.5, 146.4, 138.1, 137.8, 130.4, 130.3, 129.9, 128.4, 127.9, 126.9, 126.8, 126.7, 123.4, 122.3, 121.5, 40.2, 27.9. In accordance with previously reported data.[28]

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References

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitroge Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem*. **2014**, *57*, 10257-10274.

(2) a) Davidson, E. K.; Sperry, J. Natural Products with Heteroatom-Rich Ring Systems. *J. Nat. Prod*. **2017**, *80*, 3060-3079; b) Homer, J. A.; Sperry, J. Mushroom-Derived Indole Alkaloids. *J. Nat. Prod*. **2017**, *80*, 2178-2187; c) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep*. **2008**, *25*, 166-187; d) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep*. **2003**, *20*, 476-493.

(3) a) Pousset, J. L.; Martin, M. T.; Jossang, A.; Bodo, A. Isocryptolepine from Cryptolepis sanguinolenta. *Phytochemistry* **1995**, *39*, 735-736; b) Sharaf, M. H. H.; Schiff, P. L.; Tackie,

Jr. A. N.; Phoebe, C. H.; Johnson, Jr. R. L.; Minick, D.; Andrews, C. W.; Crouch, R. C.; Martin, G. E. the isolation and structure determination of cryptomisrine, a novel indolo[3,2-*b*]quinoline dimeric alkaloid from *cryptolepis sanguinolenta*. *J. Heterocycl. Chem*. **1996**, *33*, 789-797.

(4) a) Aroonkit, P.; Thongsornkleeb, C.; Tummatorn, J.; Karjangsri, S.; Mungthin, M.; Ruchirawat, S. Synthesis of isocryptolepine analogues and their structure-activity relationship studies as antiplasmodial and antiproliferatice agents. *Eur. J. Med. Chem*. **2015**, *94*, 56-62; b) Wang, N.; Wicht, K. J.; Imai, K.; Wang, M.; Ngoc, T. A.; Kiguchi, R.; Kaiser, M.; Egan, T. J.; Inokuchi, T. Synthesis, β-haematin inhibition, and *in vitro* antimalarial testing of isocryptolepine analogues: SAR study of indolo[3,2-*c*]quinolones with various substituents at C2, C6, and N11. *Bioorg. Med. Chem*. **2014**, *22*, 2629-2642; c) Whittell, L. R.; Batty, K. T.; Wong, R. P. M.; Bolitho, E. M.; Fox, S. A.; Davis, T. M. E.; Murray, P. E. Synthesis and antimalarial evaluation of novel isocryptolepine derivatives. *Bioorg. Med. Chem*. **2011**, *19*, 7519-7525.

(5) For synthesis prior to 2016 see the following three review articles; a) Parvatkar, P. T.; Parameswaran, P. S. Indoloquinolines: Possible biogenesis from common indole precursors and their synthesis using domino strategies. *Curr. Org. Synth*. **2016**, *13*, 58-72; b) Prakash, P.; Parash, T.; Tilve, S. G. Bioactivities and synthesis of indoloquinoline alkaloids: Cryptolepine, isocryptolepine and neocryptolepine. *Biact. Heterocycl*. **2013**, 217-234; c) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. Isolation, biological activities, and synthesis of indoloquinoline alkaloids: cryptolepine, isocryptolepine, and neocryptolepine. *Curr. Org. Chem*. **2011**, *15*, 1036-1057.

(6) a) Aksenov, A. V.; Aksenov, D. A.; Griaznov, G. D.; Aksenov, N. A.; Voskressensky, L. G.; Rubin, M. Unexpected cyclization of 2-(2-aminophenyl)indoles with nitroalkenes to

furnish indole[3,2-*c*]quinolones. *Org. Biomol. Chem*. **2018**, *16*, 4325-4332; b) Zhang, T.-Y.; Liu, C.; Chen, C.; Liu, J.-X.; Xiang, H.-Y.; Jiang, W.; Ding, T.-M.; Zhang, S.-Y. *Org. Lett*. Copper-Mediated Cascade C-H/N-H Annulation of Indolocarboxamides with Arynes: Construction of Tetracyclic Indoloquinoline Alkaloids. **2018**, *20*, 220-223; c) Murugan, A.; Vidyacharan, S.; Ghosh, R.; Duddu, S. M. Metal-Free Regioselective Dual C-H Functionalization in a Cascade Fashion: Access to Isocryptolepine Alkaloid Analogues. *ChemistrySelect* **2017**, *2*, 3511-3515; d) Aksenov, A. V.; Aksenov, D. A.; Orazova, N. A.; Aksenov, N. A.; Griaznov, G. D.; De Carvalho, A.; Kiss, R.; Mathieu, V.; Kornienko, A.; Rubin, M. One-Pot, Three-Component Assembly of Indoloquinolines: Total Synthesis of Isocryptolepine. *J. Org. Chem*. **2017**, *82*, 3011-3018; e) Mahajan, P. S.; Humne, V. T.; Tanpure, S. D.; Mhaske, S. B. Radical Beckmann Rearrangement and Its Application in the Formal Total Synthesis of Antimalarial Natural Product Isocryptolepine via C-H Activation. *Org. Lett*. **2016**, *18*, 3450-3453; f) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. Electrochemical C-H/N-H Functionalization for Synthesis of Highly Functionalized (Aza)indoles. *Angew. Chem., Int. Ed. Engl*. **2016**, *55*, 9168-9172; g) Volvoikar, P. S.; Tilve, S. G. Iodine-Mediated Intramolecular Dehydrogenative Coupling: Synthesis of N-Alkylindole[3,2-*c*]- and -[2,3-*c*]quinoline Iodides. *Org. Lett*. **2016**, *18*, 892-895.

(7) a) Helgeland, I. T. U.; Sydnes, M. O. A Concise Synthesis of Isocryptolepine by C-C Cross-Coupling Followed by a Tandem C-H Activation and C-N Bond Formation. *SynOpen* **2017**, *1*, 41-44; b) Sydnes, M. O. One-pot Strategies for the Synthesis of Nitrogen-containing Heteroaromatics. *Curr. Green Chem*. **2018**, *5*, 22-39.

(8) Cockram, P. E.; Smith, T. K. Active Natural Product Scaffolds against Trypanosomatid Parasites: A Review. *J. Nat. Prod*. **2018**, *81*, 2138-2154.

(9) a) Whittell, L.R.; Batty, K.T.; Wong, R.P.M.; Bolitho, E.M.; Fox, S.A.; Davis, T.M.E.; Murray, P.E. Synthesis and antimalarial evaluation of novel isocryptolepine derivatives. *Bioorg. Med. Chem*. **2011**, *19*, 7519-7525; b) Aroonkit, P.; Thongsornkleeb, C.; Tummatorn, J.; Karjangsri, S.; Mungthin, M.; Ruchirawat, S. Synthesis of isocryptolepine analogues and their structure-activity relationship studies as antiplamodial and antiproliferative agents. *Eur. J. Med. Chem*. **2015**, *94*, 56-62; c) Wang, N.; Wicht, K.J.; Imai, K.; Wang, M.; Ngoc, T.A.; Kiguchi, R.; Kaiser, M.; Egan, T.J.; Inokuchi, T. Synthesis, β-haematin inhibition, and in vitro antimalarial testing of isocryptolepine analogues: SAR study of indolo[3,2-*c*]quinolines with various substituents at C2, C6, and N11. *Bioorg. Med. Chem*. **2014**, *22*, 2629-2642.

(10) Hostyn, S.; Maes, B. U. W.; Pieters, L.; Lemiére, G. L. F.; Mátyus, P.; Hajós, G.; Dommisse, R. A. Synthesis of the benzo-β-carboline isoneocryptolepine: the missing indoloquinoline isomer in the alkaloid series cryptolepine, neocryptolepine and isocryptolepine. *Tetrahedron* **2005**, *61*, 1571-1577.

(11) Dhanabal, T.; Sangeetha, R.; Mohan, P. S. Heteroatom directed photoannulation: synthesis of indoloquinoline alkaloids: cryptolepine, cryptotackieine, cryptosanguinlentine, and their methyl derivatives. *Tetrahedron* **2006**, *62*, 6258-6263.

(12) Mallory, F. B.; Mallory, C. W. Photocyclization of stilbenes and related molecules. *Organic Reactions* **1981**, *30*, 1-456.

(13) Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Roques, B. P.; Le Pecq, J.-B. Synthesis of 11*H*-Pyridocarbazoles and Derivatives. Comparison of Their DNA Binding and Antitumor Activity with Those of 6*H*- and 7*H*-Pyridocarbazoles. *J. Med. Chem.* **1986**, *29*, 1731-1737.

(14) Wu, F.; Hardesty, J.; Thummel, R. P. Preparation and Study of Tautomers Derived from 2-(2´-Pyridyl)indole and Related Compounds. *J. Org. Chem.* **1998**, *63*, 4055-4061.

(15) Kulka, M.; Manske, R. H. F. The Synthesis of Pyridocarbazoles. *Can. J. Chem.* **1952**, *30*, 711-719.

(16) Jansen, H. E.; Wibaut, J. P. Some Reactions of 2-Bromo- and 3-Bromoquinolines. *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 709-713.

(17) Brower, K. R.; Samuels, W. P.; Way, J. W.; Amstutz, E. D. Halogen reactivities. III. Kinetic study of displacement reactions of haloquinolines with piperidine. *J. Org. Chem.* **1953**, *18*, 1648-1654.

(18) Coulson, C. A.; Longuet-Higgins, H.C. The electronic structure of conjugated systems II. Unsaturated hydrocarbons and their hetero-derivatives. *Proc. Royal Soc. Lond.* **1947**, *192*, 16-32.

(19) Almond-Thynne, J.; Blakemore, D. C.; Pryde, D. C.; Spivey A. C. Site-selective Suzuki-Miyaura coupling of heteroaryl halides – understanding the trends for pharmaceutically important classes. *Chem. Sci.* **2017**, *8*, 40-61.

(20) Schröter, S.; Stock, C.; Bach, T. Regioselective cross-coupling reactions of multiple halogenated nitrogen-, oxygen-, and sulfur-containing heterocycles. *Tetrahedron*, **2005**, *61*, 2245-2267.

(21) Handy, S. T.; Zhang, Y. A simple guide for predicting regioselectivity in the coupling of polyheteroaromatics. *Chem. Commun.* **2006**, 299-301.

(22) Bjørsvik, H.-R.; Elumalai, V. Synthesis of the carbazole scaffold directly from 2-aminobiphenyl by means of tandem C-H activation and C-N bond formation. *Eur. J. Org. Chem*. **2016**, 5474–5479.

(23) a) Wang, X.-J.; Yang, Q.; Liu, F.; You, Q.-D. Microwave-assisted synthesis of amide under solvent-free conditions. *Synth. Commun.* **2008**, *38*, 1028–1035; b) Chakraborty, M.;

Umrigar, V.; Parikh, P. A. Microwave irradiated acetylation of p-anisidine: a step towards green chemistry. *Int. J. Chem. React. Eng*. **2008**, *6*, 1–12.

(24) Ciufolini, M. A.; Byrne, N. E. The total synthesis of cystodytins. *J. Am. Chem. Soc.* **1991**, *113*, 8016-8024.

(25) Landagaray, E.; Ettaoussi, M.; Rami, M.; Boutin, J. A.; Caignard, D.-H.; Delagrange, P.; Melnyk, P.; Berthelot, P.; Yous, S. New quinolinic derivatives as melatonergic ligands: Synthesis and pharmacological evaluation. *Eur. J. Med. Chem.* **2017**, *127*, 621-631.

(26) Wippich, J.; Truchan, N.; Bach, T. Rhodium-catalyzed *N-tert*-Butyloxycarbonyl (Boc) Amination by Directed C-H Bond Activation. *Adv. Synth. Catal.* **2016**, *358*, 2083-2087.

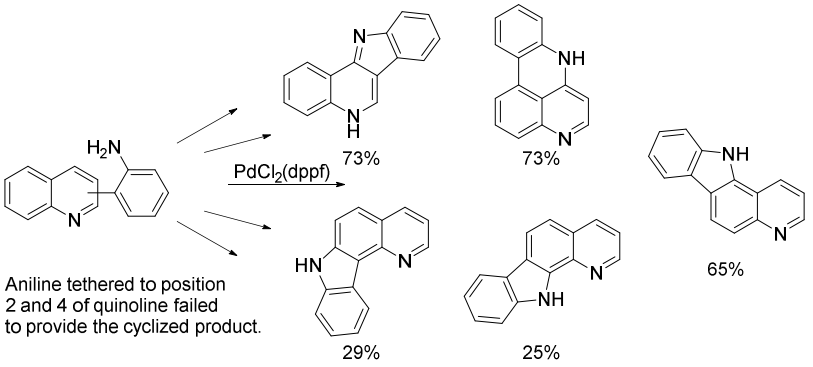
(27) Chatterjee, T.; Choi, M. G.; Kim, J.; Chang, S.-K.; Cho, E. J. Visible-Light-Induced Regioselective Synthesis of Polyheteroaromatic Compounds. *Chem. Commun.* **2016**, *52*, 4203-4206.

(28) Csányi, D.; Timári, G.; Hajós, G. An alternative synthesis of quindoline and one of its closely related derivatives. *Synth. Commun.* **1999**, *29*, 3959-3969.

Supplementary Material

Supplementary material including ^{1}H and ^{13}C NMR charts can be found in the online version at doi:…..

Graphical abstract



Aniline tethered to position 2 and 4 of quinoline failed to provide the cyclized product.