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A concise synthesis of indoloquinoline skeletons applying two consecutive Pd-catalyzed reactions

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ABSTRACT

The indoloquinoline alkaloids cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**), and isoneocryptolepine (**4**) are important tools in traditional medicine. Now, their precursors **1a**–**4a** were synthesized in two steps starting from the corresponding bromo-iodoquinolines. Our strategy is based on palladium-catalyzed reactions, applying regioselective Buchwald–Hartwig amination on 2,3- and 3,4-dihaloquinolines followed by an intramolecular Heck-type reaction. Both steps were carried out under microwave irradiation.

1. Introduction

Quinolines and related heterocyclic skeletons are important target molecules in pharmaceutical chemistry since they occur in numerous biologically active natural products.[1] During the last few decades the family of indoloquinoline alkaloids has attracted considerable attention due to their broad spectrum of biological activities.[2] 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**) have been isolated from *Cryptolepis sanguinolenta*; the decoction of this plant has been used in traditional medicine against malaria, jaundice, hypertension, hepatitis, and inflammation in West and Central Africa.[3] The wide range of interesting pharmacological properties is continually growing as these compounds exhibit strong antiplasmodial activity and behave as DNA intercalating agents, thereby inhibiting DNA replication, transcription, and topoisomerase activities.[4] Therefore these molecules are promising anticancer agents in modern health care, as well. The fourth isomer, i.e., isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]quinoline) (**4**), has never been found in nature; however, two research groups have described its synthesis and biological importance.[5–7]

Since properties of indoloquinolines represent an extensively investigated topic in organic chemistry, several routes have been developed for their synthesis.[8–14] In recent years organometallic catalysis has become a common tool to synthesize the target precursors **1a**–**4a** mentioned above; however, regioselectivity remained one of the main problems to be solved.[5–7,15,16] Mohan et al. has published a two-step route for the preparation of the four scaffolds **1a**–**4a**, however in the case of the reaction of 3-bromoquinoline with aniline, the resulting intermediate using 'heteroatom directed photoannulation technique' gave both linear and angular products, i.e., **1a** and **4a**, respectively.[7] Ablordeppey et al. also reported on a palladium-catalyzed intramolecular arylation reaction starting from 3-aminoquinoline, which afforded the mixture of **1a** and **4a**.[15] Maes et al. described a 'Suzuki-intramolecular nitrene insertion' four-step approach starting from 4-chloroquinoline and a 'Buchwald–Hartwig amination-intramolecular Heck-type reaction' approach from 3-bromoquinoline in two steps; in both cases a small amount of the undesired regioisomer was also detected after the ring closure.[5,6] Ila et al. also published a palladium-catalyzed Buchwald–Hartwig aryl-amination methodology, where not only the targeted benzo[4,5]imidazo[1,2-*a*]quinoline but also a significant amount of **2a** was formed as a by-product during the intramolecular cyclization step[16] (Fig. 1).

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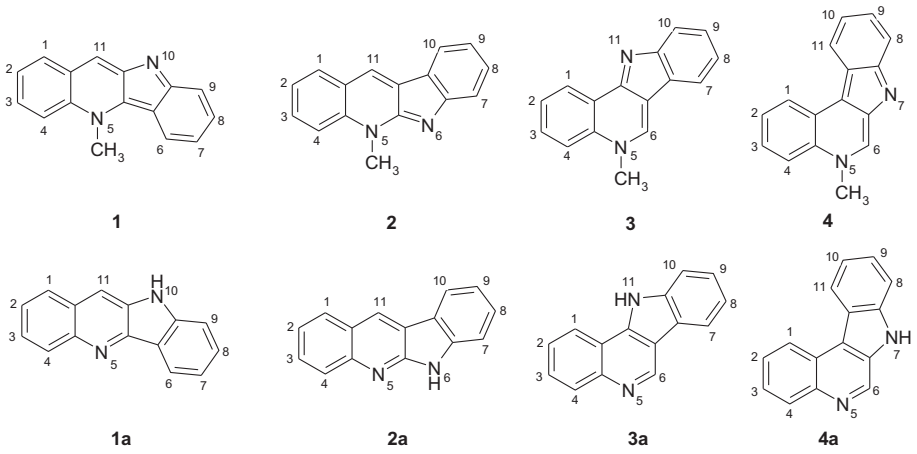
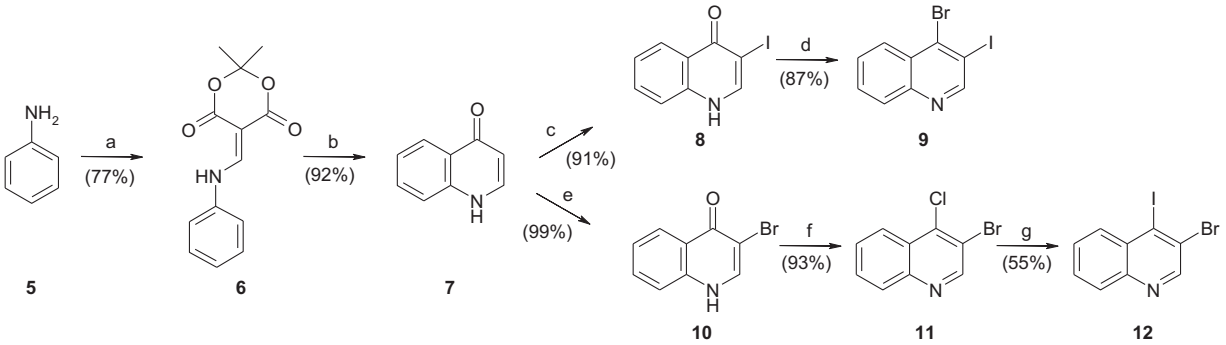


Fig. 1.

2. Results and discussion

Our work focused on the synthetic challenge to identify a regioselective pathway towards the synthesis of benzo-α,β,γ,δ-carbolines **1a**–**4a** involving Pd-catalyzed reactions.

To achieve our aim we synthesized the requisite dihaloquinolines, i.e., bromoiodoquinolines **9**, **12**, **17**, **21**. To our best knowledge, only the preparation of 3-bromo-2-iodoquinoline (**17**) is known in the literature[17] but the syntheses of the other three regioisomers have never been described. On the route to **9** and **12** first the key intermediate 1*H*-quinolin-4-one (**7**) was prepared by condensation of aniline (**5**) with Meldrum's acid in the presence of trimethyl orthoformate, followed by thermolysis in diphenyl ether[18] (Scheme 1).



(a) Meldrum's acid, trimethyl ortoformate, reflux; (b) diphenyl ether, 250 °C; (c) NIS, DMF, RT; (d) $POBr_3$, DMF, 70 °C; (e) Br_2, AcOH, reflux; (f) $POCl_3$, MeCN, reflux; (g) NaI, MeCN, reflux

Scheme 1.

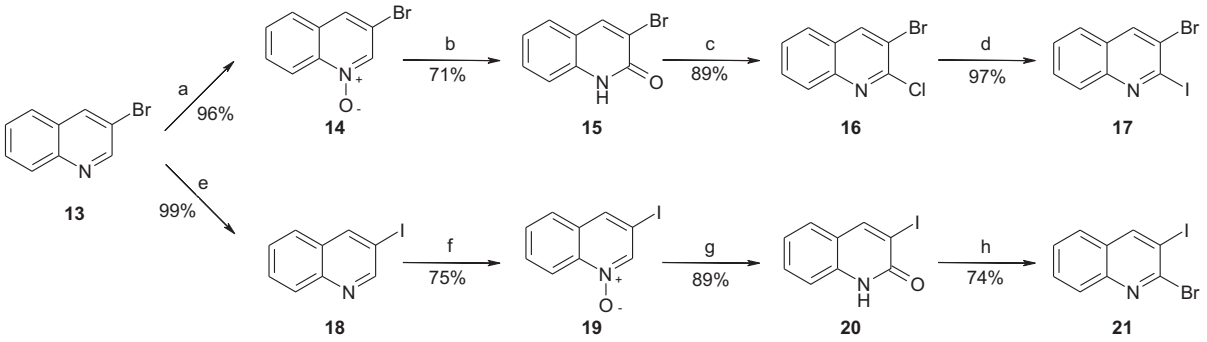
The direct halogenation of **7** with *N*-iodosuccinimide[19] and with bromine,[20] respectively, resulted in 3-iodo-1*H*-quinolin-4-one (**8**) and 3-bromo-1*H*-quinolin-4-one (**10**). Treatment of **8** with phosphorus oxybromide gave the desired isomer **9** in high yield. The synthesis of **12** was carried out in two steps: the 3-bromoquinolin-4-one **10** was converted to 3-bromo-4-chloroquinoline (**11**), and finally Cl/I displacement afforded the desired compound **12**[21,22] (Scheme 1).

The syntheses of 3-bromo-2-iodoquinoline (**17**) and 2-bromo-3-iodoquinolne (**21**) started from the readily available 3-bromoquinoline (**13**) (Scheme 2). In the first step towards the formation of 3-bromo-2-iodoquinoline (**17**) 3-bromoquinoline (**13**) was transformed into its *N*-oxide derivative with Oxone. Rearrangement of **14** in the presence of benzoyl chloride and potassium carbonate afforded 3-bromo-1*H*-quinolin-2-one (**15**).[23] Subsequently, chlorination and Cl/I displacement as mentioned above for the sequence **10**–**11**–**12** generated the desired 3-bromo-2-iodoquinoline (**17**) with excellent yield (97%).

The synthesis of 2-bromo-3-iodoquinoline (**21**) started with a halogen-exchange reaction to give 3-iodoquinoline (**18**) from 3-bromoquinoline (**13**).[24] The *N*-oxide derivative of **18** and its rearrangement were both carried out similarly to the preparation of **15**, with the difference that 3-chloroperoxybenzoic acid was used instead of Oxone in the oxidation step. Finally, bromination of the obtained **20** was performed by application of the same method as in the case of **8**, **9**. The desired compound **21** was obtained in good yield (74%) (Scheme 2).

Next, the targeted benzocarbolines **1a**–**4a** were prepared from the above dihaloquinolines **9**, **12**, **17**, **21** by following a two-step strategy based on a Buchwald–Hartwig amination as a first step followed by an intramolecular Heck-type reaction to execute the ring closure. By using the above bromo-iodoquinolines high regioselectivity was achieved that was one of the main goals of our work.

Based upon our earlier investigations on Buchwald–Hartwig reactions on 3,4-dihaloquinolines with aminoheteroarenes,[25] here anilines were used as amine reactants. 4-Bromo-3-iodoquinoline (**9**) was chosen as a representative substrate for the amination step. As a first approach we applied an established protocol ($Pd(OAc)_2$, Xantphos, Cs_2CO_3 in toluene at reflux) with the



(a) MeOH, Oxone, H_2O, 50 °C; (b) CH_2Cl_2, benzoyl chloride, K_2CO_3-solution, RT; (c) $POCl_3$, MeCN, reflux; (d) NaI, MeCN, reflux; (e) *N,N*-dimethylethylene diamine, CuI, NaI, 1,4-dioxane, 100 °C; (f) *m*-CPBA, CH_2Cl_2, RT; (g) CH_2Cl_2, benzoyl chloride, K_2CO_3-solution, RT; (h) $POBr_3$, toluene, reflux

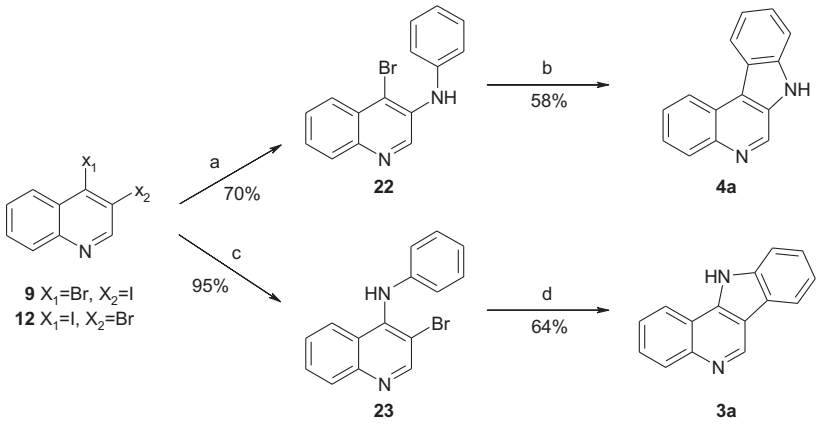
Scheme 2.

modification employing microwave irradiation was employed with shorter reaction time instead of conventional heating.[25] In some preliminary optimization studies the effects of solvents (toluene, 1,4-dioxane, and 1,2-dimethoxyethane), ligands (Xantphos, Binap), and temperatures (100 °C, 120 °C) were investigated. Then, the four available dihaloquinolines **9**, **12**, **17**, **21** were coupled with aniline according to the optimized protocol (toluene, $Pd(OAc)_2$, Xantphos, and Cs_2CO_3, microwave irradiation at 120 °C for 90 min) to yield the key intermediates **22**–**25** required for the preparation of the desired indoloquinoline skeletons **1a**–**4a** (Schemes 3 and 4). The yields, along with those of the subsequent cyclizations, are summarized in Table 2.

instead of Na_2CO_3 the desired indoloquinoline became the main component of the reaction mixture (entry 5). The best results were obtained with the system $PdCl_2(PPh_3)_2$/NaOAc in DMA at 150 °C[5,6] where conversion became complete (entry 6).

The indoloquinoline precursors **1a**–**4a** were then synthesized under the above optimal conditions, with good yields received (58–64%) (Table 2).

The efficacy of the microwave irradiation under the optimized conditions was compared to that of the traditional oil bath heating on the representative substrates **9** and **22** in the Buchwald–Hartwig amination and Heck-type reaction, as well. Microwave irradiation was found to result in higher conversion in both

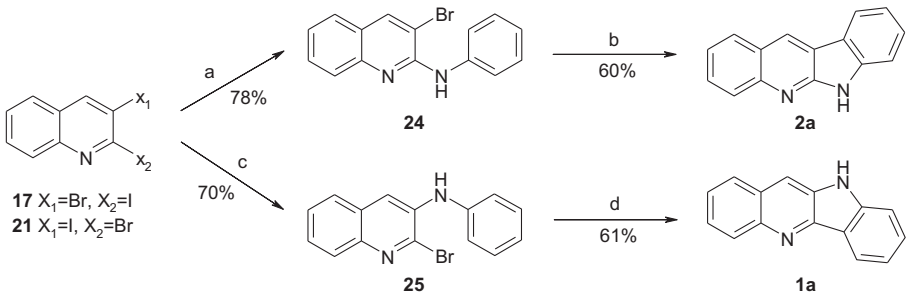


(a) aniline, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 120 °C, Mw; (b) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, Mw; (c) aniline, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 120 °C, Mw; (d) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, Mw,

Scheme 3.

Next, cyclization to the indoloquinoline skeletons **1a**–**4a** was performed in an intramolecular Heck-type reaction under microwave irradiation. The influence of various parameters, such as solvent (acetonitrile, 1,4-dioxane, DMF, DMA), base (sodium carbonate, sodium acetate), catalyst ($Pd(OAc)_2$, $PdCl_2(PPh_3)_2$), and temperature was studied by starting from 4-bromo-(3-phenylamino)quinoline (**22**) as a representative substrate. The use of $Pd(OAc)_2$ with Na_2CO_3[26] in DMF, 1,4-dioxane or acetonitrile at 100–150 °C (Table 1, entries 1, 2, 3) resulted in low conversions and at 100 °C a small amount of a debrominated anilinoquinoline was also detected in the reaction mixture. The same system in DMA worked better (entry 4) and upon using the weaker base NaOAc reactions (100% vs 80% in the amination while 100% vs 30% in the cyclization).

In view of these results we extended our study to substituted anilines, too (Scheme 5). It was found that anilines with electron withdrawing substituents (4-nitroaniline (**26a**), 4-fluoroaniline (**26b**)) needed longer reaction times to achieve good yields both in the Buchwald–Hartwig amination and Heck-type reaction (Table 3, entries 1, 2). Faster conversion was detected in the amination reaction with an aniline bearing an electron donating substituent (4-methoxyaniline (**26c**)) (Table 3, entry 3) compared to the reaction with aniline (Table 2, entry 1). However, for the subsequent ring closure the same reaction time was needed (Table 2, entry 1).



(a) aniline, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 120 °C, Mw; (b) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, Mw; (c) aniline, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 120 °C, Mw; (d) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, Mw

Scheme 4.

Table 1
Reaction conditions and yields in the Heck-type reaction on 4-bromo-(3-phenylamino)quinoline (**22**) under microwave irradiation

Entry	Catalyst	Base	Solvent	T (°C)	**22**:**4a**[a]
1	$Pd(OAc)_2$	Na_2CO_3	DMF	150	6:1
2	$Pd(OAc)_2$	Na_2CO_3	1,4-Dioxane	100	90:1
3	$Pd(OAc)_2$	Na_2CO_3	Acetonitrile	150	15:1
4	$Pd(OAc)_2$	Na_2CO_3	DMA	150	4:1
5	$Pd(OAc)_2$	NaOAc	DMA	150	2:3
6	$PdCl_2(PPh_3)_2$	NaOAc	DMA	150	0:1

[a] Ratio was determined by LCMS analysis.

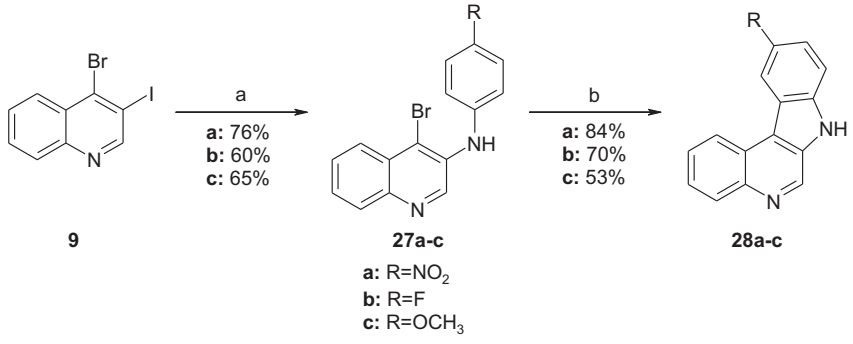
Table 2
Reaction conditions and yields in the regioselective Buchwald–Hartwig amination on dihaloquinolines (**9**, **12**, **17**, **21**) and subsequent Heck-type reaction on the obtained phenylaminoquinolines (**22**–**25**) under microwave irradiation

Entry	Dihaloquinoline[a]	Yield (%)	Phenylamino intermediate[b]	Yield (%)	Indolo-quinoline
1	**9**	70	**22**	58	**4a**
2	**12**	95	**23**	64	**3a**
3	**17**	78	**24**	60	**2a**
4	**21**	70	**25**	61	**1a**

[a] Buchwald–Hartwig amination: t=90 min, T=120 °C.
[b] Heck-type reaction: t=60 min, T=150 °C.

3. Conclusion

The synthesis of three hitherto unknown bromo-iodoquinoline regioisomers **9**, **12**, **21**, has been described. A regioselective two-step strategy based on palladium chemistry was developed for the preparation of the four indoloquinoline precursors **1a**–**4a** of cryptolepine, neocryptolepine, isocryptolepine, and isoneocryptolepine. The first step is a regioselective Buchwald–Hartwig amination starting from 2,3- and 3,4-substituted dihaloquinolines, followed by an intramolecular Heck-type reaction to produce the ring-closed indoloquinoline scaffolds. The palladium-catalyzed reactions were carried out under microwave irradiation ensuring both higher reaction rates and product yields compared to oil-bath heating in the case of compound **9** and **22** (Table 2 entry 1). In summary, a concise and regioselective procedure was elaborated for the synthesis of benzo-α,β,γ,δ-carbolines **1a**–**4a**.



(a) **26a-c**, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 120 °C, Mw; (b) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 150 °C, Mw

Scheme 5.

Table 3
Reaction conditions and yields in the regioselective Buchwald–Hartwig amination on 4-bromo-3-iodoquinoline (**9**) with substituted anilines **26a**–**c** and Heck-type reaction on the obtained phenylaminoquinolines **27a**–**c** under microwave irradiation

Entry	R–$C_6H_4NH_2$	t (min)	T (°C)	Yield (%)	Phenylamino intermediate	t (min)	T (°C)	Yield (%)	Indolo-quinoline
1	**26a**	180	130	76	**27a**	120	150	84	**28a**
2	**26b**	180	130	60	**27b**	120	150	70	**28b**
3	**26c**	60	120	65	**27c**	60	150	53	**28c**

4. Experimental section

4.1. General

All melting points were measured on a Büchi-540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz instrument using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shift values are reported in δ (parts per million), all coupling constants (J values) are given in Hertz. Multiplicity is indicated using the following abbreviations: br for broad, d for doublet, t for triplet, m for multiplet, s for singlet. LCMS analyses were performed on an instrument consisting of an Agilent 1200 liquid chromatograph and an Agilent 6140 Simple Quadrupole mass spectrometer using electrospray ionization (ESI) technique. Elemental analyses were carried out on a VARIO EL III instrument. Reactions were monitored by LCMS and/or TLC on silica gel plates (Type 60 F_{254}, Merck) and the spots were detected by exposure to a UV-lamp at 254/366 nm for a few seconds. Column chromatography was performed on silica gel (230–400 mesh). Certain reactions were carried out in a Biotage Initiator EXP EU microwave oven. All materials were purchased from Aldrich except 3-bromoquinoline, which was ordered from Alfa Aesar. All the solvents were of the highest analytical grade.

4.2. 1*H*-Quinolin-4-one (7)

*4.2.1. 5-Anilinomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**).* A stirred mixture of Meldrum's acid (51.07 g, 0.35 mol) and trimethyl orthoformate (150.69 g, 1.42 mol) was refluxed for 30 min. Then aniline (30.00 g, 0.32 mol) was added dropwise at the same temperature, and the solution was stirred for 40 min. After cooling to room temperature the resulting precipitate was filtered off, washed with *n*-hexane, and dried in vacuo. The title compound was obtained as an orange solid (61.71 g, 77%), mp 155–157 °C (lit.,[27] mp 156–157 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.25 (d, 1H, J=14 Hz), 8.58 (d, 1H, J=14.4 Hz), 7.56 (d, 2H, J=7.6 Hz), 7.47–7.40 (m, 2H), 7.27 (t, 1H, J=7.2 Hz), 1.68 (s, 6H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 163.8, 162.6, 153.1, 138.4, 129.5, 126.2, 118.9, 104.0, 86.5, 26.4; $C_{13}H_{13}NO_4$ (247.25); LCMS (ESI$^+$) m/z 246 [M−H]$^-$. Anal. Calcd for $C_{13}H_{13}NO_4$ (247.25) C, 63.15; H, 5.30; N, 5.66. Found: C, 62.93; H, 5.28; N, 5.70.

*4.2.2. 1H-Quinolin-4-one (**7**).* Diphenylether (140 mL) was heated to 250 °C and stirred vigorously under nitrogen atmosphere. 5-Anilinomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**) (26.30 g, 0.11 mol) was added portionwise at the same temperature, and the reaction mixture was stirred for 30 min. The resulting solution was allowed to cool to 70 °C and diluted with *n*-hexane (200 mL). The precipitate was filtered off, washed with *n*-hexane, and dried in vacuo. The title compound was obtained as a brown solid (14.26 g, 92%), mp 200–202 °C (lit.,[28] mp 199–203 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.72 (br s, 1H), 8.08 (dd, 1H, J=0.8, 8.0 Hz), 7.88 (d, 1H, J=7.2 Hz), 7.66–7.60 (m, 1H), 7.53 (d, 1H, J=8.4 Hz), 7.34–7.27 (m, 1H), 6.02 (d, 1H, J=7.6 Hz); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 176.7, 139.8, 139.2, 131.5, 125.7, 124.8, 122.9, 118.1, 108.6; C_9H_7NO (145.16); LCMS (ESI$^+$) m/z 146 [M+H]$^+$. Anal. Calcd for C_9H_7NO (145.16) C, 74.47; H, 4.86; N, 9.65. Found: C, 74.19; H, 4.84; N, 9.68.

4.3. 4-Bromo-3-iodoquinoline (9)

*4.3.1. 3-Iodo-1H-quinolin-4-one (**8**).* To a stirred solution of 1*H*-quinolin-4-one (**7**) (10.00 g, 68.89 mmol) in DMF (100 mL) *N*-iodosuccinimide (16.74 g, 74.40 mmol) was added portionwise at room temperature. The reaction mixture was stirred for 3 h. The solvent was evaporated and the residue was boiled in water (100 mL). The precipitate was filtered off, washed with water, and dried in vacuo. The title compound was obtained as a beige solid (16.92 g, 91%), mp 296–298 °C (lit.,[29] mp 296–299 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.18 (br s, 1H), 8.50 (d, 1H, J=6.4), 8.11 (d, 1H, J=8.0 Hz), 7.72–7.65 (m, 1H), 7.59 (d, 1H, J=8.0 Hz), 7.42–7.35 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 172.9, 144.5, 139.3, 131.8, 125.3, 124.0, 122.3, 118.3, 80.5; C_9H_6INO (271.06); LCMS (ESI$^+$) m/z 272 [M+H]$^+$. Anal. Calcd for C_9H_6INO (271.06) C, 39.88; H, 2.23; N, 5.17. Found: C, 39.73; H, 2.22; N, 5.18.

*4.3.2. 4-Bromo-3-iodoquinoline (**9**).* To a stirred solution of 3-iodo-1*H*-quinolin-4-one (**8**) (8.00 g, 29.51 mmol) in DMF (80 mL) phosphorus oxybromide (10.15 g, 35.42 mmol) was added portionwise at 0–10 °C. The reaction mixture was stirred at 70 °C for 3 h. After completion of the reaction the mixture was poured on crushed ice (200 mL) and the pH was adjusted to 9 with potassium carbonate solution (10%, 50 mL). The resulting precipitate was filtered off, washed with water, and dried in vacuo. The title compound was obtained as a brown solid (8.62 g, 87%), mp 109–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.08 (s, 1H), 8.26 (dd, 1H, J=0.8, 8.4 Hz), 8.07 (d, 1H, J=8.4 Hz), 7.80–7.73 (m, 1H), 7.65–7.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 156.3, 147.0, 140.4, 130.5, 129.9, 129.5, 128.9, 128.2, 99.3; C_9H_5BrIN (333.96); LCMS (ESI$^+$) m/z 334, 336 [M+H]$^+$. Anal. Calcd for C_9H_5BrIN (333.96) C, 32.37; H, 1.51; N, 4.19. Found: C, 32.25; H, 1.51; N, 4.20.

4.4. 3-Bromo-4-iodoquinoline (12)

*4.4.1. 3-Bromo-1H-quinolin-4-one (**10**).* The stirred solution of 1*H*-quinolin-4-one (**7**) (15.00 g, 0.10 mol) in acetic acid (90 mL) was refluxed for 10 min and bromine (16.51 g, 0.10 mol) was added dropwise at the same temperature. The reaction mixture was stirred for 2 h, then it was allowed to cool to room temperature. The resulting suspension was poured on crushed ice (340 mL) and diluted further with sodium thiosulfate solution (1 N, 50 mL). The resulting precipitate was filtered off, washed with water and dried in vacuo. The title compound was obtained as a beige solid (22.94 g, 99%), mp 199–201 °C (lit.,[30] mp 278–279 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.27 (br s, 1H), 8.47 (d, 1H, J=6.4 Hz), 8.14 (dd, 1H, J=0.8, 8.0 Hz), 7.72–7.66 (m, 1H), 7.60 (d, 1H, J=8.0 Hz), 7.42–7.36 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 171.2, 140.0, 139.1, 131.8, 125.1, 124.1, 123.9, 118.4, 104.0; C_9H_6BrNO (224.06); LCMS (ESI$^+$) m/z 224, 226 [M+H]$^+$. Anal. Calcd for C_9H_6BrNO (224.06) C, 48.25; H, 2.70; N, 6.25. Found: C, 48.08; H, 2.69; N, 6.27.

*4.4.2. 3-Bromo-4-chloroquinoline (**11**).* To a stirred suspension of 3-bromo-1*H*-quinolin-4-one (**10**) (22.44 g, 0.10 mol) in acetonitrile (100 mL) phosphorus oxychloride (18.43 g, 0.12 mol) was added dropwise at room temperature. The reaction mixture was refluxed for 7 h. After cooling to room temperature it was poured on crushed ice (400 mL) and the pH was adjusted to 9 with potassium carbonate solution (10%, 220 mL). The resulting precipitate was filtered off, washed with water, and dried in vacuo. The title compound was obtained as a brown solid (22.58 g, 93%), mp 182–188 °C (lit.,[31] mp 69–69,5 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.08 (s, 1H), 8.25 (dd, 1H, J=0.8, 8.4 Hz), 8.12 (d, 1H, J=8.0 Hz), 7.95–7.89 (m, 1H), 7.86–7.80 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 151.6, 146.5, 140.2, 130.9, 129.5, 129.2, 126.4, 124.0, 117.7; C_9H_5BrClN (242.50); LCMS (ESI$^+$) m/z 242, 244 [M+H]$^+$. Anal. Calcd for C_9H_5BrClN (242.50) C, 44.58; H, 2.08; N, 5.78. Found: C, 44.43; H, 2.09; N, 5.79.

*4.4.3. 3-Bromo-4-iodoquinoline (**12**).* To a stirred solution of 3-bromo-4-chloroquinoline (**11**) (10.00 g, 41.24 mmol) in dichloromethane (50 mL) HCl/diethyl ether (1 M, 40 mL) was added below 5 °C and stirred for 60 min, while the reaction mixture was

allowed to warm to room temperature. The resulting white precipitate was filtered off, washed with diethyl ether and dried in vacuo (10.18 g, 88%). The obtained HCl salt was used in crude form without further purification.

The stirred suspension of 3-bromo-4-chloroquinoline hydrochloride (10.18 g, 36.49 mmol) and sodium iodide (27.35 g, 182.44 mmol) in acetonitrile (130 mL) was refluxed for 5 h. The solvent was evaporated off, the residue was dissolved in dichloromethane (200 mL), and the solution was washed with potassium carbonate solution (10%, 100 mL) and water (100 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography using dichloromethane/ethyl acetate (100/0.5) as eluent. The title compound was obtained as an off-white solid (7.79 g, 55%), mp 148–149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (s, 1H), 8.12 (dd, 1H, J=0.8, 8.4 Hz), 8.03 (d, 1H, J=8.0 Hz), 7.77–7.71 (m, 1H), 7.65–7.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 150.3, 145.5, 133.1, 132.4, 130.2, 130.0, 129.3, 127.6, 118.1; C_9H_5BrIN (333.96); LCMS (ESI$^+$) m/z 334, 336 $[M+H]^+$. Anal. Calcd for C_9H_5BrIN (333.96) C, 32.37; H, 1.51; N, 4.19. Found: C, 32.27; H, 1.51; N, 4.20.

4.5. 3-Bromo-2-iodoquinoline (17)

*4.5.1. 3-Bromoquinoline-1-oxide (**14**).* To a stirred solution of 3-bromoquinoline (**13**) (8.50 g, 40.85 mmol) in methanol (100 mL) was added a solution of Oxone (25.14 g, 4.81 mmol) in water (250 mL). The reaction mixture was stirred at 50 °C for 3 h. The resulting suspension was filtered, the filter cake was washed with methanol, and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane (170 mL) and washed with water (80 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The title compound was obtained as an off-white solid (8.81 g, 96%), mp 97–99 °C (lit.,[32] mp 95–97 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.67 (d, 1H, J=8.8 Hz), 8.62 (s, 1H), 7.89 (s, 1H), 7.82–7.71 (m, 2H), 7.70–7.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 140.6, 137.1, 130.4, 130.3, 129.8, 127.5, 127.3, 119.9, 114.4; C_9H_6BrNO (224.06); LCMS (ESI$^+$) m/z 224, 226 $[M+H]^+$. Anal. Calcd for C_9H_6BrNO (224.06) C, 47.82; H, 3.57; N, 6.20. Found: C, 47.98; H, 3.56; N, 6.18.

*4.5.2. 3-Bromo-1H-quinolin-2-one (**15**).* To a stirred solution of 3-bromoquinoline-1-oxide (**14**) (6.69 g, 29.88 mmol) in dichloromethane (80 mL), benzoyl chloride (5.04 g, 35.86 mmol), and potassium carbonate solution (10%, 80 mL) were added at 0–10 °C. The resulting two phase system was stirred vigorously at room temperature for 3 h. After completion of the reaction the resulting precipitate was filtered off and washed with dichloromethane. The title compound was obtained as an off-white solid (4.76 g, 71%), mp 261–264 °C (lit.,[33] mp 265–269 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.24 (br s, 1H), 8.50 (s, 1H), 7.67 (dd, 1H, J=0.8, 8.0 Hz), 7.58–7.50 (m, 1H), 7.33 (d, 1H, J=8.4 Hz), 7.26–7.18 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 157.5, 141.6, 138.0, 130.6, 127.2, 122.2, 119.3, 116.9, 115.1; C_9H_6BrNO (224.06); LCMS (ESI$^+$) m/z 224, 226 $[M+H]^+$. Anal. Calcd for C_9H_6BrNO (224.06) C, 48.25; H, 2.70; N, 6.25. Found: C, 48.09; H, 2.69; N, 6.26.

*4.5.3. 3-Bromo-2-chloroquinoline (**16**).* To a stirred suspension of 3-bromo-1*H*-quinolin-2-one (**15**) (4.16 g, 18.57 mmol) in acetonitrile (30 mL) phosphorus oxychloride (3.42 g, 22.28 mmol) was added dropwise at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature it was poured on crushed ice (70 mL) and the pH was adjusted to 9 with potassium carbonate solution (10%, 40 mL). The resulting precipitate was filtered off, washed with water and dried in vacuo. The title compound was obtained as a white solid (4.00 g, 89%), mp 101–103 °C (lit.,[34] mp 96–98 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.95 (s, 1H), 8.03 (d, 1H, J=8.0 Hz), 7.98 (d, 1H, J=8.8 Hz), 7.90–7.84 (m, 1H), 7.74–7.69 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 148.1, 145.4, 142.1, 131.3, 128.1, 127.8, 127.6, 127.2, 115.6; C_9H_5BrClN (242.50); LCMS (ESI$^+$) m/z 242, 244 $[M+H]^+$; Anal. Calcd for C_9H_5BrClN (242.50) C, 44.58; H, 2.08; N, 5.78. Found: C, 44.46; H, 2.07; N, 5.79.

*4.5.4. 3-Bromo-2-iodoquinoline (**17**).* To a stirred solution of 3-bromo-2-chloroquinoline (**16**) (3.95 g, 16.29 mmol) in dichloromethane (20 mL) HCl/diethyl ether (15 mL) was added below 5 °C and stirred for 60 min, while the reaction mixture was allowed to warm to room temperature. The resulting white precipitate was filtered off, washed with diethyl ether and dried in vacuo (3.80 g, 83%). The obtained HCl salt was used in crude form without further purification.

The stirred suspension of 3-bromo-2-chloroquinoline hydrochloride (3.80 g, 13.62 mmol) and sodium iodide (10.21 g, 68.10 mmol) in acetonitrile (50 mL) was refluxed for 5 h. The solvent was evaporated off, the residue was dissolved in dichloromethane (80 mL) and the solution was washed with potassium carbonate solution (10%, 40 mL) and water (40 mL). After concentration the crude product was recrystallized from isopropyl alcohol. The title compound was obtained as a white solid (4.24 g, 97%), mp 119–121 °C (lit.,[35] mp 120–122 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.75 (s, 1H), 7.98 (d, 2H, J=8.4 Hz), 7.86–7.80 (m, 1H), 7.72–7.67 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 146.6, 138.5, 130.9, 128.1, 127.8, 127.6, 127.4, 125.5, 124.3; C_9H_5BrIN (333.96); LCMS (ESI$^+$) m/z 334, 336 $[M+H]^+$. Anal. Calcd for C_9H_5BrIN (333.96) C, 32.37; H, 1.51; N, 4.19. Found: C, 32.29; H, 1.51; N, 4.18.

4.6. 2-Bromo-3-iodoquinoline (21)

*4.6.1. 3-Iodoquinoline (**18**).* 3-Bromoquinoline (**13**) (8.50 g, 40.85 mmol), *N*,*N*-dimethylethylenediamine (720 mg, 8.17 mmol), copper(I) iodide (389 mg, 2.04 mmol), and sodium iodide (12.25 g, 81.71 mmol) in 1,4-dioxane (30 mL) were stirred under argon at 100 °C for 8 h. The reaction mixture was allowed to cool to room temperature, diluted with dichloromethane (40 mL), and washed with ammonia solution (25 mL) and water (25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The title compound was obtained as a yellow solid (10.30 g, 99%), mp 56–58 °C (lit.,[36] mp 58–59 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (br s, 1H), 8.54 (d, 1H, J=1.6 Hz) 8.06 (d, 1H, J=8.4 Hz), 7.77–7.69 (m, 2H), 7.59–7.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 155.6, 146.4, 143.7, 130.0, 129.9, 129.5, 127.4, 126.8, 89.8; C_9H_6IN (255.06); LCMS (ESI$^+$) m/z 256 $[M+H]^+$. Anal. Calcd for C_9H_6IN (255.06) C, 42.38; H, 2.37; N, 5.49. Found: C, 42.25; H, 2.36; N, 5.51.

*4.6.2. 3-Iodoquinoline-1-oxide (**19**).* To a stirred solution of 3-iodoquinoline (**18**) (5.87 g, 23.01 mmol) in dichloromethane (100 mL) 3-chloroperoxybenzoic acid (10.32 g, 46.03 mmol) was added portionwise at room temperature. The reaction mixture was stirred at the same temperature overnight. The resulting suspension was filtered, the filtrate was washed with sodium bicarbonate solution (10%, 30 mL) and water (30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography using dichloromethane/ethyl acetate (9/1) as eluent. The title compound was obtained as an off-white solid (4.67 g, 75%), mp 137–140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (d, 1H, J=1.2 Hz), 8.67 (d, 1H, J=8.8 Hz), 8.10 (s, 1H), 7.80–7.72 (m, 2H), 7.68–7.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 141.2, 140.8, 134.1, 131.0, 130.7, 129.6, 127.0, 119.9, 84.1; C_9H_6INO (271.06); LCMS (ESI$^+$) m/z 272 $[M+H]^+$. Anal. Calcd for C_9H_6INO (271.06) C, 39.59; H, 2.95; N, 5.13. Found: C, 39.72; H, 2.96; N, 5.15.

*4.6.3. 3-Iodo-1H-quinolin-2-one (**20**).* To a stirred solution of 3-iodoquinoline-1-oxide (**19**) (4.56 g, 16.82 mmol) in

dichloromethane (50 mL) benzoyl chloride (2.84 g, 20.18 mmol) and potassium carbonate solution (10%, 50 mL) were added at 0–10 °C. The resulting two phase system was stirred vigorously at room temperature overnight. The resulting precipitate was filtered off and washed with dichloromethane. The title compound was obtained as an off-white solid (2.03 g, 89%), mp 256–258 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.09 (br s, 1H), 8.70 (s, 1H), 7.64 (d, 1H, J=7.6 Hz), 7.56–7.50 (m, 1H), 7.31 (d, 1H, J=8.4 Hz), 7.22–7.16 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 158.7, 148.7, 138.7, 130.7, 126.9, 122.0, 120.2, 115.1, 95.7; C_9H_6INO (271.06); LCMS (ESI$^+$) m/z 272 $[M+H]^+$. Anal. Calcd for C_9H_6INO (271.06) C, 39.88; H, 2.23; N, 5.17. Found: C, 39.74; H, 2.24; N, 5.18.

*4.6.4. 2-Bromo-3-iodoquinoline (**21**).* To a stirred suspension of 3-iodo-1*H*-quinolin-2-one (**20**) (1.90 g, 6.99 mmol) in toluene (20 mL) phosphorus oxybromide (2.01 g, 6.99 mmol) was added in small portions at 0–10 °C. The reaction mixture was refluxed for 3 h. After completion of the reaction the solvent was evaporated off, the residue was dissolved in dichloromethane (40 mL) then washed with potassium carbonate solution (10%, 20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was recrystallized from isopropyl alcohol. The title compound was obtained as a beige solid (1.74 g, 74%), mp 126–128 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.02 (s, 1H), 7.99–7.92 (m, 2H), 7.87–7.81 (m, 1H), 7.72–7.66 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 148.3, 146.3, 146.2, 131.2, 127.9, 127.8, 127.6, 127.1, 96.1; C_9H_5BrIN (333.96); LCMS (ESI$^+$) m/z 334, 336 $[M+H]^+$. Anal. Calcd for C_9H_5BrIN (333.96) C, 32.37; H, 1.51; N, 4.19. Found: C, 32.25; H, 1.51; N, 4.20.

4.7. General procedure for the Buchwald–Hartwig reactions

A microwave vial (2–5 mL) was charged with palladium acetate (6.7 mg, 0.03 mmol), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (34.7 mg, 0.06 mmol), the requisite dihaloquinoline, i.e., **9**, **12**, **17** or **21** (200.0 mg, 0.60 mmol), cesium carbonate (782.0 mg, 2.40 mmol) and aniline (59.0 mg, 0.63 mmol) followed by toluene (3 mL) and flushed with argon. The reactions were run at 120 or 130 °C for 60, 90 or 180 min (see Tables 2 and 3). After completion of the reaction the solvent was evaporated and the residue was purified by column chromatography.

*4.7.1. 4-Bromo-(3-phenylamino)quinoline (**22**).* Prepared from **9**. Eluent: hexane/ethyl acetate (9/1). Green solid (126 mg, 70%), mp 103–105 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.76 (s, 1H), 8.17 (br s, 1H), 8.06 (dd, 1H, J=8.4, 8.0 Hz), 8.00–7.96 (m, 1H), 7.72–7.63 (m, 2H), 7.29 (t, 2H, J=8.0 Hz), 7.10 (d, 2H, J=7.6 Hz), 6.98–6.93 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 145.0, 143.6, 142.5, 136.0, 129.2, 129.1, 128.4, 127.9, 127.3, 125.2, 121.2, 119.6, 117.9; for $C_{15}H_{11}BrN_2$ (299.17); LCMS (ESI$^+$) m/z 299, 301 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.17) C, 60.22; H, 3.71; N, 9.36. Found: C, 60.05; H, 3.72; N, 9.33.

*4.7.2. 3-Bromo-(4-phenylamino)quinoline (**23**).* Prepared from **12**. Eluent: dichloromethane (100%). Yellow solid (170 mg, 95%), mp 138–140 °C (lit.,[37] mp 136.5–137.5 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.89 (s, 1H), 8.66 (br s, 1H), 8.04–7.95 (m, 2H), 7.79–7.72 (m, 1H), 7.57–7.50 (m, 1H), 7.24–7.16 (m, 2H), 6.91–6.85 (m, 1H), 6.80–6.75 (m, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 152.7, 147.7, 144.0, 143.3, 129.6, 129.4, 128.7, 126.3, 124.7, 123.7, 120.5, 117.1, 110.7; $C_{15}H_{11}BrN_2$ (299.17); LCMS (ESI$^+$) m/z 299, 301 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.17) C, 60.22; H, 3.71; N, 9.36. Found: C, 60.11; H, 3.71; N, 9.39.

*4.7.3. 3-Bromo-(2-phenylamino)quinoline (**24**).* Prepared from **17**. Eluent: hexane/ethyl acetate (9/1). Pale pink foam (140 mg, 78%), ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.59 (s, 1H), 8.36 (br s, 1H), 7.91 (d, 2H, J=7.6 Hz), 7.77 (d, 1H, J=8.0 Hz), 7.67–7.59 (m, 2H), 7.39–7.32 (m, 3H), 7.09–7.03 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 149.5, 145.2, 140.1, 139.9, 130.0, 128.2, 126.7, 126.0, 124.6, 123.5, 122.4, 120.6, 107.7; $C_{15}H_{11}BrN_2$ (299.17); LCMS (ESI$^+$) m/z 299, 301 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.17) C, 60.22; H, 3.71; N, 9.36. Found: C, 60.13; H, 3.70; N, 9.38.

*4.7.4. 2-Bromo-(3-phenylamino)quinoline (**25**).* Prepared from **21**. Eluent: hexane/ethyl acetate (95/5). Yellow oil (126 mg, 70%), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, 1H, J=8.0 Hz), 7.69 (s, 1H), 7.60–7.55 (m, 1H), 7.52–7.38 (m, 4H), 7.28 (s, 1H), 7.18–7.12 (m, 1H), 6.32 (br s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 142.8, 140.3, 136.3, 136.2, 129.8, 128.7, 128.2, 127.5, 126.9, 126.0, 123.9, 121.2, 115.6; $C_{15}H_{11}BrN_2$ (299.17); LCMS (ESI$^+$) m/z 299, 301 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2$ (299.17) C, 60.22; H, 3.71; N, 9.36. Found: C, 60.08; H, 3.70; N, 9.39.

*4.7.5. 4-Bromo-3-(4-nitrophenylamino)quinoline (**27a**).* Prepared from **9** and **26a** by irradiation at 130 °C for 180 min. Eluent: hexane/ethyl acetate (3/2). Yellow solid (156 mg, 76%), mp 189–190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.94 (s, 1H), 8.19 (d, 2H, J=8.8 Hz), 8.14 (d, 1H, J=8.4 Hz), 8.10 (d, 1H, J=8.0 Hz), 7.75–7.65 (m, 2H), 7.07 (d, 2H, J=9.2 Hz), 6.54 (br s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 148.3, 145.7, 145.0, 141.6, 132.7, 129.8, 129.0, 128.7, 128.1, 126.2, 124.6, 115.2, 110.0; $C_{15}H_{10}BrN_3O_2$ (344.17); LCMS (ESI$^+$) m/z 344, 346 $[M+H]^+$. Anal. Calcd for $C_{15}H_{10}BrN_3O_2$ (344.17) C, 52.35; H, 2.93; N, 12.21. Found: C, 52.48; H, 2.92; N, 12.24.

*4.7.6. 4-Bromo-3-(4-fluorophenylamino)quinoline (**27b**).* Prepared from **9** and **26b** by irradiation at 130 °C 180 min. Eluent: hexane/ethyl acetate (9/1). Yellow solid (114 mg, 60%), mp 120–122 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.68 (s, 1H), 8.13 (br s, 1H), 8.04 (dd, 1H, J=1.2, 8.4 Hz), 7.99–7.93 (m, 1H), 7.72–7.60 (m, 2H), 7.19–7.10 (m, 4H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 158.7, 156.3, 144.2, 143.5, 138.8, 138.7, 136.5, 129.2, 128.5, 127.9, 127.2, 125.1, 120.6, 120.6, 118.4, 116.0, 115.8; $C_{15}H_{10}BrFN_2$ (317.16); LCMS (ESI$^+$) m/z 317, 319 $[M+H]^+$. Anal. Calcd for $C_{15}H_{10}BrFN_2$ (317.16) C, 56.81; H, 3.18; N, 8.83. Found: C, 56.65; H, 3.19; N, 8.80.

*4.7.7. 4-Bromo-3-(4-methoxyphenylamino)quinoline (**27c**).* Prepared from **9** and **26c** by irradiation for 60 min. Eluent: hexane/ethyl acetate (3/2) Yellow oil (129 mg, 65%), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (s, 1H), 8.05–7.95 (m, 2H), 7.60–7.48 (m, 2H), 7.18 (d, 2H, J=8.8 Hz), 6.93 (d, 2H, J=8.8 Hz), 6.17 (br s, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 157.0, 143.3, 141.2, 137.2, 133.4, 129.6, 128.2, 128.2, 126.3, 125.0, 124.4, 115.1, 55.6; $C_{16}H_{13}BrN_2O$ (329.20); LCMS (ESI$^+$) m/z 329, 331 $[M+H]^+$. Anal. Calcd for $C_{16}H_{13}BrN_2O$ (329.20) C, 58.38; H, 3.98; N, 8.51. Found: C, 58.21; H, 3.99; N, 8.49.

4.8. General procedure for the Heck-type reactions

A microwave vial (2–5 mL) was charged with bis(-triphenylphosphine)palladium(II) dichloride (23.2 mg, 0.03 mmol), the corresponding phenylaminoquinoline: **22**–**25** (100 mg, 0.33 mmol) or **27a**–**c** (0.33 mmol) and sodium acetate (108.3 mg, 1.32 mmol) followed by *N*,*N*-dimethylacetamide (4.8 mL) and flushed with argon. The reactions were run at 150 °C for 60 or 120 min (see Tables 2 and 3). After completion of the reaction the solvent was evaporated and the residue was purified by column chromatography.

*4.8.1. 7H-Indolo[2,3-c]quinoline (**4a**).* Prepared from **22**. Eluent: dichloromethane/methanol (95/5). Yellow solid (42.5 mg, 58%), mp 253–255 °C (lit.,[15] mp 242–244 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.150 (s, 1H), 9.29 (s, 1H), 8.79 (d, 1H, J=7.6 Hz), 8.67

(d, 1H, *J*=8.0 Hz), 8.19 (d, 1H, *J*=8.0 Hz), 7.80–7.72 (m, 2H), 7.70–7.64 (m, 1H), 7.62–7.56 (m, 1H), 7.43–7.37 (m, 1H);^{13}C NMR (DMSO-d_6, 400 MHz) δ 142.1, 139.3, 138.6, 132.6, 129.8, 126.9, 126.6, 125.1, 124.1, 123.1, 122.8, 121.1, 120.2, 119.3, 112.6; $C_{15}H_{10}N_2$ (218.26); LCMS (ESI$^+$) *m*/*z* 219 [M+H]$^+$. Anal. Calcd for $C_{15}H_{10}N_2$ (218.26) C, 82.55; H, 4.62; N, 12.83. Found: C, 82.76; H, 4.63; N, 12.88.

*4.8.2. 11H-Indolo[3,2-c]quinoline (**3a**).* Prepared from **23**. Eluent: dichloromethane/methanol (95/5). Beige solid (46.5 mg, 64%), mp 316–318 °C (lit.,[38] mp 320 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.70 (s, 1H), 9.60 (s, 1H), 8.53 (d, 1H, *J*=7.2 Hz), 8.32 (d, 1H, *J*=8.0 Hz), 8.14 (d, 1H, *J*=8.0 Hz), 7.78–7.66 (m, 3H), 7.50 (t, 1H, *J*=7.6 Hz), 7.34 (t, 1H, *J*=7.6 Hz); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 145.3, 144.7, 139.6, 138.6, 129.4, 127.8, 125.5, 125.4, 121.9, 121.7, 120.4, 119.9, 117.0, 114.2, 111.7; $C_{15}H_{10}N_2$ (218.26); LCMS (ESI$^+$) *m*/*z* 219 [M+H]$^+$. Anal. Calcd for $C_{15}H_{10}N_2$ (218.26) C, 82.55; H, 4.62; N, 12.83. Found: C, 82.69; H, 4.60; N, 12.86.

*4.8.3. 6H-Indolo[2,3-b]quinoline (**2a**).* Prepared from **24**. Eluent: dichloromethane/methanol (9/1). Yellow foam (25.2 mg, 60%), ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.74 (br s, 1H), 9.04 (s, 1H), 8.26 (d, 1H, *J*=7.6 Hz), 8.11 (d, 1H, *J*=8.0 Hz), 7.97 (d, 1H, *J*=8.4 Hz), 7.75–7.68 (m, 1H), 7.56–7.45 (m, 3H), 7.29–7.23 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 152.8, 146.2, 141.4, 128.5, 128.0, 127.4, 126.9, 123.6, 122.6, 121.7, 120.2, 119.5, 117.8, 110.8; $C_{15}H_{10}N_2$ (218.26); LCMS (ESI$^+$) *m*/*z* 219 [M+H]$^+$. Anal. Calcd for $C_{15}H_{10}N_2$ (218.26) C, 82.55; H, 4.62; N, 12.83. Found: C, 82.86; H, 4.63; N, 12.81.

*4.8.4. 10H-Indolo[3,2-b]quinoline (**1a**).* Prepared from **25**. Eluent: dichloromethane/ethyl acetate (95/5). Beige solid (44.3 mg, 61%), mp 252–254 °C (lit.,[15] mp 249–251 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.39 (br s, 1H), 8.36 (d, 1H, *J*=8.0 Hz), 8.28 (s, 1H) 8.19 (d, 1H, *J*=8.4 Hz), 8.10 (d, 1H, *J*=8.0 Hz), 7.68–7.52 (m, 4H), 7.32–7.26 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 145.6, 143.9, 143.3, 132.3, 129.6, 128.6, 127.4, 126.6, 125.9, 124.7, 121.2, 120.9, 119.2, 112.9, 111.4; $C_{15}H_{10}N_2$ (218.26); LCMS (ESI$^+$) *m*/*z* 219 [M+H]$^+$. Anal. Calcd for $C_{15}H_{10}N_2$ (218.26) C, 82.55; H, 4.62; N, 12.83. Found: C, 82.79; H, 4.63; N, 12.87.

*4.8.5. 10-Nitro-7H-indolo[2,3-c]quinoline (**28a**).* Prepared from **27a**. Reaction time: 120 min. Eluent: dichloromethane/methanol (95/5). Beige solid (73.0 mg, 84%), mp >340 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.43 (d, 1H, *J*=2.0 Hz), 9.35 (s, 1H), 8.78 (d, 1H, *J*=8.0 Hz), 8.39 (dd, 1H, *J*=2.0, 8.8 Hz), 8.20 (d, 1H, *J*=8.0 Hz), 7.89 (d, 1H, *J*=9.2 Hz), 7.84–7.77 (m, 1H), 7.73–7.67 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 143.6, 142.3, 140.4, 139.7, 135.7, 130.0, 127.5, 125.8, 123.6, 123.0, 121.1, 120.6, 120.2, 119.5, 113.6; $C_{15}H_9N_3O_2$ (263.26); LCMS (ESI$^+$) *m*/*z* 264 [M+H]$^+$. Anal. Calcd for $C_{15}H_9N_3O_2$ (263.26) C, 68.44; H, 3.45; N, 15.96. Found: C, 68.66; H, 3.44; N, 15.93.

*4.8.6. 10-Fluoro-7H-indolo[2,3-c]quinoline (**28b**).* Prepared from **27b**. Reaction time: 120 min. Eluent: hexane/ethyl acetate (9/1). Yellow solid (54.6 mg, 70%), mp >340 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.33 (br s, 1H), 9.30 (s, 1H), 8.77 (d, 1H, *J*=8.0 Hz), 8.48 (dd, 1H, *J*=2.0, 10.0 Hz), 8.18 (d, 1H, *J*=8.4 Hz), 7.81–7.71 (m, 2H), 7.69–7.63 (m, 1H), 7.50–7.42 (m, 1H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 158.3, 156.0, 141.9, 139.0, 135.9, 133.7, 129.9, 127.2, 125.3, 124.0, 123.2, 121.2, 121.1, 119.1, 119.1, 115.1, 114.9, 113.9, 113.8, 108.0, 107.7, $C_{15}H_9FN_2$ (236.25), LCMS (ESI$^+$) *m*/*z* 237 [M+H]$^+$. Anal. Calcd for $C_{15}H_9FN_2$ (236.25) C, 76.26; H, 3.84; N, 11.86. Found: C, 76.01; H, 3.85; N, 11.89.

*4.8.7. 10-Methoxy-7H-indolo[2,3-c]quinoline (**28c**).* Prepared from **27c**. Eluent: dichloromethane/methanol (95/5). Yellow solid, (43.4 mg, 53%), mp 223–225 °C (lit.,[15] mp 142–144 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.0 (s, 1H), 9.24 (s, 1H), 8.79 (d, 1H, *J*=8.0 Hz), 8.16 (d, 1H, *J*=8.0 Hz), 8.05 (d, 1H, *J*=2.4 Hz), 7.78–7.72 (m, 1H), 7.70–7.62 (m, 2H), 7.25 (dd, 1H, *J*=2.0, 9.2 Hz), 3.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 154.0, 141.8, 138.8, 134.3, 133.1, 129.7, 126.8, 124.9, 124.2, 123.2, 121.3, 118.9, 117.0, 113.4, 104.2, 55.7; $C_{16}H_{12}N_2O$ (248.29); LCMS (ESI$^+$) *m*/*z* 249 [M+H]$^+$. Anal. Calcd for $C_{16}H_{12}N_2O$ (248.29) C, 77.40; H, 4.87; N, 11.28. Found: C, 77.15; H, 4.89; N, 11.31.

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