

Article

One-Pot Synthesis of 2,3,4-Triarylquinolines via Suzuki-Miyaura Cross-Coupling of 2-Aryl-4-chloro-3-iodoquinolines with Arylboronic Acids

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Received: 16 September 2010; in revised form: 12 October 2010 / Accepted: 18 October 2010 /
Published: 22 October 2010

Abstract: Palladium-catalyzed Suzuki cross-coupling of 2-aryl-4-chloro-3-iodoquinolines with excess arylboronic acids (2.5 equiv.) in the presence of tricyclohexylphosphine afforded the 2,3,4-triarylquinolines in one-pot operation. The incipient 2,3-diaryl-4-chloroquinolines were also prepared and transformed to the primary 4-amino-2,3-diarylquinolines and 2,3-diarylquinolin-4(1H)-ones.

Keywords: 2-aryl-4-chloro-3-iodoquinolines; Suzuki-Miyaura cross-coupling; 2,3-diaryl-4-chloroquinolines; 2,3,4-triarylquinolines

1. Introduction

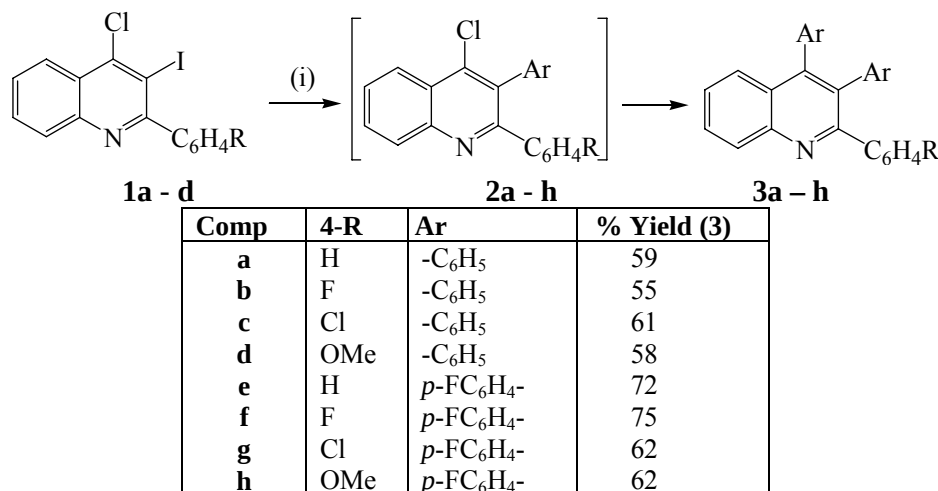
The high reactivity of the aryl-iodo bond toward oxidative addition with palladium in Suzuki [1–4], Sonogashira [4,5], Stille [4] and Heck [4] cross-coupling reactions has been found to allow successive substitution of the halogen atoms ($I > Br > Cl > F$) in dihaloquinolines. The observed trend relates to the Ar–X bond strength, which increases as follows: $I < Br < Cl < F$ (D_{Ph-X} values 65, 81, 96 and 126 Kcal/mol, respectively) and makes the oxidative addition step increasingly difficult [6]. We have previously subjected a series of 2-aryl-4-chloro-3-iodoquinolines to Suzuki cross-coupling with phenylboronic acid (1.2–2.0 equiv.) using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst and 2M K_2CO_3 in dimethyl formamide (DMF) under reflux to afford the 2,3-diaryl-4-

chloroquinolines in moderate yields [1]. Hitherto our investigation, the analogous 4-chloro-6-(bromo/iodo)quinolines were subjected to successive replacement of the two halogen atoms via Suzuki cross-coupling to afford the Csp^2-Csp^2 cross-coupled products [2,3]. The second arylboronic acid was in this case added to the reaction mixture after completion of the first step (tlc monitoring) without isolating the incipient 6-substituted derivative. Despite the successes in sequential metal-catalyzed halogen substitution reactions [2-4], the development of versatile and efficient methods for the synthesis of polysubstituted quinolines from dihaloquinolines in a single operation remains a challenge in organic synthesis. We are interested in the synthesis of 3,4-disubstituted 2-arylquinoline derivatives as a prelude to derivatives with potential biological activity or photoelectronic properties and the 2-aryl-4-chloro-3-iodoquinolines appeared suitable candidates for palladium-catalyzed Suzuki cross-coupling to afford such systems.

As we have previously communicated, Suzuki cross-coupling of the 2-aryl-4-chloro-3-iodoquinolines with phenylboronic acid did not proceed beyond C-3 substitution after 48 hours [1]. The slow oxidative addition step using $Pd(0)(PPh_3)_4$ as a precursor of palladium(0) complex is attributed to the inhibiting role of the extra PPh_3 generated in the 2nd equilibrium $\{SPd(0)(PPh_3)_3 \rightleftharpoons SPd(0)(PPh_3)_2 + PPh_3 (K_2/[PPh_3] \ll 1); S = \text{solvent}\}$ to afford the reactive low ligated 14-electron species $(Pd(0)(PPh_3)_2)$ [7]. The oxidative addition performed from palladium(0) complex $(Pd(0)(PPh_3)_2Cl^-)$ generated by the reduction of dichlorobis(triphenylphosphine)palladium(II) $(PdCl_2(PPh_3)_2)$ is reported to be more than 30 times faster than that performed from $Pd(0)(PPh_3)_4$ [7]. Likewise, alkylphosphine ligands are known to coordinate with palladium and increase its electron density than arylphosphines and, in turn, accelerate the oxidative addition and reductive elimination steps in the catalytic cycle [8,9]. Based on this postulate we decided to investigate the possibility for the direct one-pot synthesis of 2,3,4-triarylquinolines via palladium-catalyzed Suzuki-Miyaura cross-coupling of 2-aryl-4-chloro-3-iodoquinolines with arylboronic acids as models for C–C bond formation.

2. Results and Discussion

We subjected the known 2-aryl-4-chloro-3-iodoquinolines **1** [1] to $PdCl_2(PPh_3)_2$ -catalyzed Suzuki cross-coupling with arylboronic acid derivatives (2.5 equiv.) in the presence of tricyclohexylphosphine (PCy_3) and K_2CO_3 in dioxane-water (3:1, v/v) (Scheme 1). The reaction in the presence of $PdCl_2(PPh_3)_2-PCy_3$ catalyst mixture was complete within 18 hours without any trace of the starting material. We isolated in all cases by column chromatography a single product characterized using a combination of spectroscopic techniques (NMR, IR, MS) as the corresponding 2,3,4-triarylquinoline **3**. In some cases, the 2,3-diaryl-4-chloroquinoline **2** was detected in the reaction mixture by thin layer chromatography, but could not be isolated by column chromatography. The 2,3-diarylquinolines substituted at the C-4 position with H, CH_3 , NH_2 , CO_2H or Ph have been found to serve as selective cyclooxygenase-1/-2 (COX-1 or COX-2) inhibitors [10]. 2-Arylquinolines bearing vinyl, alkynyl, halogen (Cl, Br) or phenyl substituent on the C-4 position, on the other hand, were found to display high affinity (3–5 nM) and significant selectivity (up to 83-fold) for estrogen receptor β (ER β) [11]. Moreover, the analogous 2,4-diarylquinolines show intense blue emission upon UV excitation [12].

Scheme 1. Suzuki-Miyaura cross-coupling of 2-aryl-4-chloro-3-iodoquinolines.

Reagents (i) ArB(OH)₂ (2.5 equiv.), PdCl₂(PPh₃)₂, PCy₃, K₂CO₃, dioxane-water (3:1, v/v); heat, 18 h

Crystals of quality suitable for X-ray diffraction were obtained for **3f** and the molecular structure of these novel systems were further confirmed by X-ray diffraction. Compound **3f** crystallizes in the triclinic space group *P*-1 [*a* = 10.2571(2), *b* = 13.2887(2), *c* = 16.7681(3) Å; α = 103.289(1)°, β = 99.454(1)°, γ = 96.939(1)°] with two independent molecules (**A** and **B**) and an ethanol molecule in the asymmetric unit (Fig. 1). One of the molecules (**A**) is hydrogen bonded to ethanol: O(1)–H(1) 0.84 Å; H(1)···N(1) 2.11 Å; O(1)···N(1) 2.919(2) Å; <O(1)H(1)N(1) 161°. The 2-, 3- and 4-aryl rings of both molecules in the unit are strongly deformed out of plane of the quinoline ring as evidenced by the large torsion angles (Table 1) [13]. The 2-aryl substituent of molecule (**A**) is however relatively less deformed (N(1)–C(1)–C(22)–C(23) = 42.09°) due to the hydrogen bonded ethanol molecule. Crystal data and experimental details for compound **3f** are shown in Table 2.

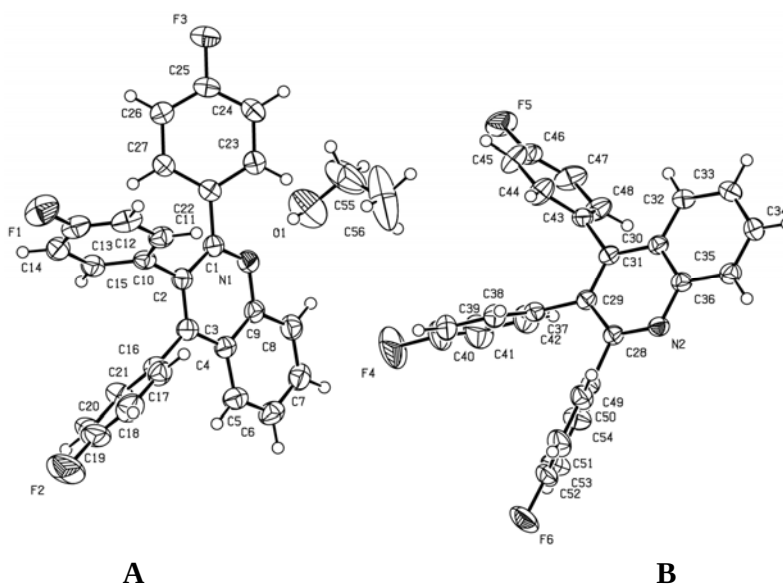
Figure 1. X-ray crystal structure of 2,3,4-tris(4-fluorophenyl)quinoline **3f** showing crystallographic numbering. For clarity, hydrogen atoms are not labelled.

Table 1. Selected torsion angles (°) for **3f**. For atom labelling see Figure 1.

Ring	Torsion angles/deg (molecule A)		Torsion angles/deg (molecule B)	
2-Ar	N(1)-C(1)-C(22)-C(23)	42.09°	N(2)-C(28)-C(49)-C(50)	60.22°
	C(2)-C(1)-C(22)-C(27)	45.80°	C(29)-C(28)-C(49)-C(54)	60.07°
3-Ar	C(1)-C(2)-C(10)-C(11)	68.03°	C(30)-C(29)-C(37)-C(42)	68.93°
	C(3)-C(2)-C(10)-C(15)	67.27°	C(28)-C(29)-C(37)-C(38)	66.95°
4-Ar	C(2)-C(3)-C(16)-C(17)	68.08°	C(31)-C(30)-C(43)-C(48)	74.75°
	C(4)-C(3)-C(16)-C(21)	68.29°	C(29)-C(30)-C(43)-C(44)	71.34°

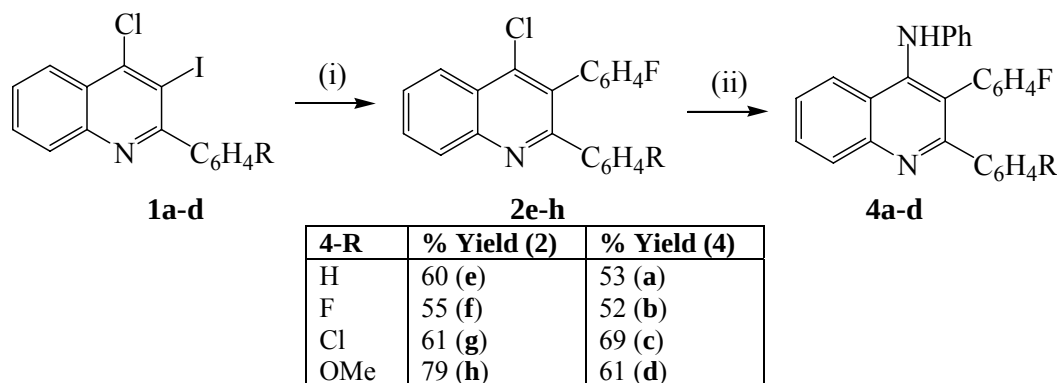
Table 2. Crystal data and structure refinement for compound **3f**.

Empirical formula	C ₅₆ H ₃₈ F ₆ N ₂ O
Formula weight	868.88
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.2571(2) Å α = 103.2890(10)°. b = 13.2887(2) Å β = 99.4540(10)°. c = 16.7681(3) Å γ = 96.9390(10)°.
Volume	2164.00(7) Å ³
Z	2
Density (calculated)	1.333 Mg/m ³
Absorption coefficient	0.097 mm ⁻¹
F(000)	900
Crystal size	0.44 × 0.37 × 0.37 mm ³
Theta range for data collection	1.27 to 27.00°.
Index ranges	-13 ≤ h ≤ 13, -16 ≤ k ≤ 16, -21 ≤ l ≤ 21
Reflections collected	40665
Independent reflections	9440 [R(int) = 0.0484]
Completeness to theta = 27.00°	100.0 %
Absorption correction	None
Max. and min. transmission	0.9650 and 0.9586
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	9440 / 0 / 588
Goodness-of-fit on F ²	1.055
Final R indices [I > 2σ(I)]	R1 = 0.0424, wR2 = 0.1057
R indices (all data)	R1 = 0.0640, wR2 = 0.1158
Largest diff. peak and hole	0.218 and -0.379 e.Å ⁻³

Since the 2-aryl-4-chloro-3-(4-fluorophenyl)quinolines **2e-h** have not been described before and were in some cases only detected in the reaction mixtures, we decided to prepare these systems from **1**. We followed a similar procedure previously employed for the synthesis of **2a-d** [1] and subjected systems **1** to 4-fluorophenylboronic acid (1.2 equiv.) in the presence of Pd(0)(PPh₃)₄ and 2M K₂CO₃ as a base in DMF. We isolated in all cases the corresponding 3-(4-fluorophenyl) derivatives **2e-h** as sole products (Scheme 2). The presence of a fluorine atom in quinolones and quinoline derivatives is known to have a profound effect on their biological, chemical and physical properties [1,14,15]. With

this consideration in mind, we took advantage of the known ease of displacement of the 4-chloro atom on the quinoline ring by nucleophiles and subjected systems **2e-h** to aniline in dioxane under reflux (Scheme 2). We isolated the corresponding primary 4-amino 2,3-diarylquinolines **4** with potential antimalarial [16–18], anti-inflammatory [19], and antihypertensive activities [20]. The primary 4-amino-2-arylquinolines also represent a novel class of NR1/2B subtype selective *N*-methyl-D-aspartate (NMDA) receptor antagonists [21].

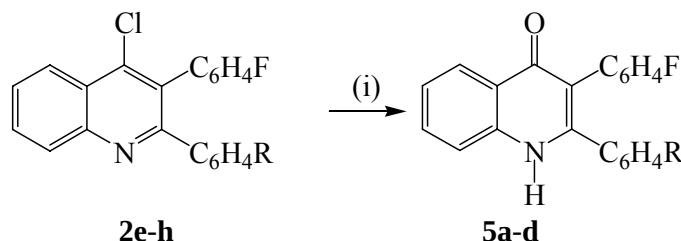
Scheme 2. Successive C-3 arylation and amination of **1**.



Reagents (i) *p*-FC₆H₄B(OH)₂, Pd(PPh₃)₄, 2M K₂CO₃, DMF, heat, 48 h; (ii) NH₂Ph, dioxane, heat, 18 h

To further demonstrate the versatility of the 4-chloroquinoline derivatives in synthesis in the last part of this investigation, we decided to investigate the possibility of transforming systems **2e-f** to the NH-4-oxo derivatives. Whereas the NMe-4-oxo [22] or NPh-4-oxo [23] derivatives undergo Suzuki cross-coupling with arylboronic acids with ease to afford the corresponding *N*-substituted 2,3-diarylquinolinones, under similar reaction conditions the NH-4-oxo precursors afford complex mixtures of products [22]. Although demethylation of 2,3-diaryl-4-methoxyquinolines with boron tribromide in dichloromethane afforded the 2,3-diarylquinolin-4(1*H*)-ones, under these reaction conditions the 4-methoxy-2-(4-methoxyphenyl)-3-phenylquinoline led to a complex mixture of products lacking the methoxy signals in the ¹H-NMR spectrum [1]. Consequently, in this investigation we subjected systems **2e-h** to acetic acid/water (4:1, v/v) under reflux and we isolated the corresponding previously undescribed 2-aryl-3-(4-fluorophenyl)quinolin-4(1*H*)-ones **5a-d** in high yield and purity (Scheme 3). The smooth hydrolysis of the 4-chloroquinolines to afford the NH-4-oxo derivatives without affecting the 4-methoxy group make this a convenient synthetic strategy for the construction of 2,3-diarylquinolin-4(1*H*)-ones that are difficult to synthesize otherwise.

Scheme 3. Hydrolysis of **2** to NH-4-oxo derivatives **5**.



Scheme 3. Cont.

Comp	4-R	% Yield (5)
a	H	70
b	F	70
c	Cl	55
d	OMe	65

Reagents: (i) AcOH-Water (4:1, v/v), heat, 6 h

3. Experimental

3.1. General

Melting points were recorded on a Thermocouple digital melting point apparatus. IR spectra were recorded as powders using FTS 7000 Series Digilab Win-IR Pro ATR (attenuated total reflectance) spectrometer. For column chromatography, Merck Kieselgel 60 (0.063–0.200 mm) was used as stationary phase. NMR spectra were obtained using a Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are measured relative to the solvent peaks. Low and high-resolution mass spectra were recorded at an ionization potential of 70 eV using a Micromass Autospec-TOF (double focusing high resolution) instrument. The synthesis and characterization of substrates **1** have been described before [1].

3.2. Typical procedure for the one-pot synthesis of 2,3,4-triarylquinolines **2**

2-Aryl-4-chloro-3-iodoquinoline **1** (1 equiv.), arylboronic acid (2.5 equiv.), PdCl₂(PPh₃)₂ (5% of **1**), PCy₃ (10% of **1**), K₂CO₃ (2 equiv.) and 3:1 dioxane–water (*ca.* 5 mL/mmol of **1**) were added to a two-necked flask equipped with a stirrer bar, rubber septum and a condenser. The mixture was flushed for 20 minutes with argon gas and a balloon filled with argon gas was connected to the top of the condenser. The mixture was heated with stirring at 80–90 °C under argon atmosphere for 18 hours and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water and the product was taken-up into chloroform. The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography to afford the 2,3,4-triarylquinoline **3**. The following products were prepared in this fashion:

2,3,4-Triphenylquinoline (3a). A mixture of **1a** (0.50 g, 1.37 mmol), phenylboronic acid (0.42 g, 3.42 mmol), PdCl₂(PPh₃)₂ (0.05 g, 0.07 mmol), PCy₃ (0.04 g, 0.14 mmol), and K₂CO₃ (0.38 g, 2.74 mmol) in dioxane/water (20 mL) afforded (**3a**) as a solid (0.29 g, 59%), mp 197–198 °C (ethanol); *R*_f (10% ethyl acetate/hexane) 0.26; *v*_{max} (neat) 1026, 1074, 1347, 1441, 1481, 1549, 2923 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 6.86–6.90 (m, 2H), 6.97–7.01 (m, 3H), 7.11–7.15 (m, 2H), 7.19–7.22 (m, 3H), 7.25–7.30 (m, 3H), 7.35–7.39 (m, 2H), 7.45 (dt, *J* 1.5 and 7.4 Hz, 1H), 7.58 (td, *J* 0.6 and 8.4 Hz, 1H), 7.73 (dt, *J* 1.5 and 7.4 Hz, 1H), 8.26 (dd, *J* 0.6 and 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 126.3, 126.5, 126.6, 126.7, 127.2, 127.3, 127.5, 127.7, 127.8, 129.3, 129.7, 129.9, 130.3, 131.3, 132.9, 136.9, 138.3, 141.1, 147.3, 147.6, 159.0; MS *m/z* (100, MH⁺) 358; HRMS (ES): MH⁺, found 358.1585. C₂₇H₂₀N⁺ requires 358.1596.

2-(4-Fluorophenyl)-3,4-diphenylquinoline (3b). A mixture of **1b** (0.50 g, 1.30 mmol), phenylboronic acid (0.40 g, 3.26 mmol), PdCl₂(PPh₃)₂ (0.05 g, 0.07 mmol), PCy₃ (0.04 g, 0.13 mmol), and K₂CO₃ (0.36 g, 2.61 mmol) in dioxane/water (20 mL) afforded (**3b**) as a solid (0.27 g, 55%), mp 181–183 °C (ethanol); *R_f* (10% ethyl acetate/hexane) 0.38; *v*_{max} (neat) 836, 1158, 1232, 1345, 1479, 1509, 1601, 3052 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 6.86–6.92 (m, 4H), 7.00–7.05 (m, 3H), 7.11–7.15 (m, 2H), 7.24–7.30 (m, 3H), 7.36 (dd, *J* 5.4 and 9.0 Hz, 2H), 7.45 (dt, *J* 1.2 and 7.8 Hz, 1H), 7.58 (dd, *J* 1.5 and 8.4 Hz, 1H), 7.73 (dt, *J* 1.2 and 7.8 Hz, 1H), 6.23 (d, *J* 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 114.6 (d, ²*J*_{CF} 21.9 Hz), 126.4, 126.6, 126.7 (2xC), 127.3, 127.5, 127.8, 129.5, 129.6, 130.2, 131.3, 131.8 (d, ³*J*_{CF} 8.3 Hz), 132.8, 136.8, 137.2 (d, ⁴*J*_{CF} 3.4 Hz), 138.2, 147.3, 147.8, 157.8, 162.4 (d, ¹*J*_{CF} 245.9 Hz); MS *m/z* (100, MH⁺) 376; HRMS (ES): MH⁺, found 376.1491. C₂₇H₁₉FN⁺ requires 376.1502.

2-(4-Chlorophenyl)-3,4-diphenylquinoline (3c). A mixture of **1c** (0.30 g, 0.75 mmol), phenylboronic acid (0.23 g, 1.88 mmol), PdCl₂(PPh₃)₂ (0.03 g, 0.04 mmol), PCy₃ (0.02 g, 0.08 mmol), and K₂CO₃ (0.21 g, 1.50 mmol) in dioxane/water (11 mL) afforded (**3c**) as a solid (0.18 g, 61%), mp 148–151 °C (ethanol); *R_f* (10% ethyl acetate–hexane) 0.46; *v*_{max} (neat) 833, 1014, 1093, 1347, 1482, 1546, 2926 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 6.85–6.89 (m, 2H), 7.00–7.04 (m, 3H), 7.09–7.13 (m, 2H), 7.32 (d, *J* 8.4 Hz, 2H), 7.24–7.28 (m, 3H), 7.32 (d, *J* 8.4 Hz, 2H), 7.45 (t, *J* 8.4 Hz, 1H), 7.57 (d, *J* 7.5 Hz, 1H), 7.73 (t, *J* 7.5 Hz, 1H), 8.22 (d, *J* 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 126.5, 126.6, 126.7, 126.8, 127.4, 127.6, 127.8, 127.9, 129.5, 129.7, 130.2, 131.2, 131.3, 132.7, 133.8, 136.7, 138.0, 139.6, 147.3, 147.9, 157.6; MS *m/z* (100, MH⁺) 392; HRMS (ES): MH⁺, found 392.1200. C₂₇H₁₉N³⁵Cl⁺ requires 392.1206.

2-(4-Methoxyphenyl)-3,4-diphenylquinoline (3d). A mixture of **1d** (0.30 g, 0.77 mmol), phenylboronic acid (0.24 g, 1.93 mmol), PdCl₂(PPh₃)₂ (0.03 g, 0.04 mmol), PCy₃ (0.02 g, 0.08 mmol), and K₂CO₃ (0.21 g, 1.55 mmol) in dioxane/water (20 mL) afforded (**3d**) as a solid (0.17 g, 58%), mp 177–179 °C (ethanol); *R_f* (30% ethyl acetate/hexane) 0.79; *v*_{max} (neat) 831, 1026, 1248, 1514, 1607 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 3.76 (s, 3H), 6.73 (d, *J* 9.3 Hz, 2H), 6.87–6.92 (m, 2H), 7.00–7.03 (m, 3H), 7.10–7.13 (m, 2H), 7.24–7.28 (m, 3H), 7.35 (d, *J* 8.4 Hz, 2H), 7.42 (t, *J* 7.5 Hz, 1H), 7.55 (d, *J* 8.4 Hz, 1H), 7.71 (t, *J* 8.4 Hz, 1H), 8.23 (d, *J* 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 55.2, 113.1, 126.2, 126.3, 126.5, 126.6, 127.2, 127.4, 127.7, 129.2, 129.6, 130.3, 131.3 (2xC), 132.8, 133.6, 137.0, 138.6, 147.3, 147.6, 158.4, 159.2; MS *m/z* (100, MH⁺) 388; HRMS (ES): MH⁺, found 388.1711. C₂₈H₂₂NO⁺ requires 388.1701.

3,4-Bis(4-fluorophenyl)-2-phenylquinoline (3e). A mixture of **1a** (0.50 g, 1.37 mmol), 4-fluorophenylboronic acid (0.48 g, 3.42 mmol), PdCl₂(PPh₃)₂ (0.05 g, 0.07 mmol), PCy₃ (0.04 g, 0.14 mmol), and K₂CO₃ (0.38 g, 2.74 mmol) in dioxane/water (20 mL) afforded (**3e**) as a solid (0.39 g, 72%), mp 183–185 °C (ethanol); *R_f* (10% ethyl acetate/hexane) 0.27; *v*_{max} (neat) 839, 1224, 1487, 1511, 1605, 3059 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 6.74 (t, *J* 8.7 Hz, 2H), 6.80–6.86 (m, 2H), 7.01 (t, *J* 8.7 Hz, 2H), 7.07–7.12 (m, 2H), 7.22–7.26 (m, 3H), 7.33–7.37 (m, 2H), 7.48 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.56 (td, *J* 1.2 and 8.4 Hz, 1H), 7.75 (dt, *J* 1.5 and 7.8 Hz, 1H), 8.26 (d, *J* 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 114.6 (d, ²*J*_{CF} 21.4 Hz), 115.1 (d, ²*J*_{CF} 21.4 Hz), 126.3, 126.6, 126.8, 127.7, 127.8,

129.6, 129.8 (2xC), 131.9 (d, $^3J_{\text{CF}}$ 8.3 Hz), 132.1, 132.6 (d, $^4J_{\text{CF}}$ 3.5 Hz), 132.8 (d, $^3J_{\text{CF}}$ 8.3 Hz), 134.1 (d, $^4J_{\text{CF}}$ 3.4 Hz), 140.9, 146.8, 147.4, 159.0, 161.3 (d, $^1J_{\text{CF}}$ 245.3 Hz), 162.0 (d, $^1J_{\text{CF}}$ 245.9 Hz); MS m/z (100, MH^+) 394; HRMS (ES): MH^+ , found 394.1389. $\text{C}_{27}\text{H}_{18}\text{F}_2\text{N}^+$ requires 394.1407.

2,3,4-Tris(4-fluorophenyl)quinoline (3f). A mixture of **1b** (0.20 g, 0.52 mmol), 4-fluorophenylboronic acid (0.18 g, 1.30 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.02 g, 0.03 mmol), PCy_3 (0.01 g, 0.05 mmol), and K_2CO_3 (0.14 g, 1.04 mmol) in dioxane/water (12 mL) afforded (**3f**) as a solid (0.153 g, 75%), mp 158–163 °C (ethanol); R_f (10% ethyl acetate/hexane) 0.27; ν_{max} (neat) 833, 1157, 1219, 1509, 1601 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 6.75 (t, J 8.7 Hz, 2H), 6.77–6.85 (m, 2H), 6.92 (t, J 8.7 Hz, 2H), 7.00 (t, J 8.7 Hz, 2H), 7.05–7.11 (m, 2H), 7.31–7.36 (m, 2H), 7.48 (dt, J 1.2 and 7.5 Hz, 1H), 7.53 (t, J 1.2 and 7.5 Hz, 1H), 7.75 (dt, J 1.5 and 7.8 Hz, 1H), 8.23 (d, J 8.7 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 114.8 (d, $^2J_{\text{CF}}$ 21.4 Hz, 2xC), 115.2 (d, $^2J_{\text{CF}}$ 21.4 Hz), 126.3, 126.6, 126.9, 129.7, 129.8 (2xC), 131.7 (d, $^3J_{\text{CF}}$ 8.3 Hz), 131.8, 131.9 (d, $^3J_{\text{CF}}$ 8.3 Hz), 132.0, 132.5 (d, $^4J_{\text{CF}}$ 3.5 Hz), 132.8 (d, $^3J_{\text{CF}}$ 8.4 Hz), 134.0 (d, $^4J_{\text{CF}}$ 3.5 Hz), 136.9 (d, $^4J_{\text{CF}}$ 3.4 Hz), 157.8, 161.4 (d, $^1J_{\text{CF}}$ 245.6 Hz), 162.0 (d, $^1J_{\text{CF}}$ 246.2 Hz), 162.5 (d, $^1J_{\text{CF}}$ 246.4 Hz); MS m/z (100, MH^+) 412; HRMS (ES): MH^+ , found 412.1314. $\text{C}_{27}\text{H}_{17}\text{F}_3\text{N}^+$ requires 412.1313.

2-(4-Chlorophenyl)-3,4-bis(4-fluorophenyl)quinoline (3g). A mixture of **1c** (0.30 g, 0.75 mmol), 4-fluorophenylboronic acid (0.26 g, 1.88 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.03 g, 0.04 mmol), PCy_3 (0.02 g, 0.08 mmol), and K_2CO_3 (0.21 g, 1.50 mmol) in dioxane/water (12 mL) afforded (**3g**) as a solid (0.20 g, 62%), mp 183–185 °C (ethanol); R_f (10% ethyl acetate/hexane) 0.29; ν_{max} (neat) 832, 1093, 1157, 1223, 1509, 1604 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 6.72–6.85 (m, 4H), 6.97–7.10 (m, 4H), 7.21 (d, J 9.0 Hz, 2H), 7.29 (d, J 9.0 Hz, 2H), 7.45–7.56 (m, 2H), 7.75 (dt, J 1.8 and 7.5 Hz, 1H), 8.23 (dd, J 0.9 and 8.4 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 114.9 (d, $^2J_{\text{CF}}$ 21.3 Hz), 115.2 (d, $^2J_{\text{CF}}$ 21.7 Hz), 126.3, 126.6, 127.1, 128.1, 129.7, 129.8, 131.2 (2xC), 131.8 (d, $^3J_{\text{CF}}$ 8.0 Hz), 132.4 (d, $^4J_{\text{CF}}$ 3.4 Hz), 132.8 (d, $^3J_{\text{CF}}$ 8.1 Hz), 133.9 (d, $^4J_{\text{CF}}$ 3.5 Hz), 134.0, 139.3, 147.1, 147.4, 157.9, 161.4 (d, $^1J_{\text{CF}}$ 245.9 Hz), 162.0 (d, $^1J_{\text{CF}}$ 245.9 Hz); MS m/z (100, MH^+) 428; HRMS (ES): MH^+ , found 428.0999. $\text{C}_{27}\text{H}_{17}\text{F}_2\text{N}^{35}\text{Cl}^+$ requires 428.1018.

3,4-Bis(4-fluorophenyl)-2-(4-methoxyphenyl)quinoline (3h). A mixture of **1d** (0.30 g, 0.76 mmol), 4-fluorophenylboronic acid (0.27 g, 1.89 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.03 g, 0.04 mmol), PCy_3 (0.02 g, 0.08 mmol), and K_2CO_3 (0.21 g, 1.52 mmol) in dioxane/water (12 mL) afforded (**3h**) as a solid (0.20 g, 62%), mp 169–182 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.79; ν_{max} (neat) 829, 1222, 1251, 1510, 1604 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 3.76 (s, 3H), 6.76 (dd, J 1.5 and 8.7 Hz, 4H), 6.84 (dd, J 5.4 and 8.7 Hz, 2H), 6.99 (t, J 8.7 Hz, 2H), 7.08 (dd, J 5.4 and 8.7 Hz, 2H), 7.31 (d, J 9.0 Hz, 2H), 7.44 (dt, J 1.5 and 7.8 Hz, 1H), (td, J 0.9 and 8.7 Hz, 1H), 7.72 (dt, J 1.8 and 7.5 Hz, 1H), 8.23 (dd, J 0.6 and 7.8 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 55.2, 113.3, 114.7 (d, $^2J_{\text{CF}}$ 21.4 Hz), 115.1 (d, $^2J_{\text{CF}}$ 21.4 Hz), 126.3, 126.4, 126.6, 129.5, 129.7, 131.3, 131.9 (d, $^3J_{\text{CF}}$ 8.3 Hz), 132.0 (d, $^4J_{\text{CF}}$ 3.4 Hz), 132.8 (d, $^3J_{\text{CF}}$ 8.0 Hz), 133.3, 134.4 (d, $^3J_{\text{CF}}$ 3.7 Hz), 146.7, 147.4, 158.4, 159.2 (2xC), 161.3 (d, $^1J_{\text{CF}}$ 245.6 Hz), 161.9 (d, $^1J_{\text{CF}}$ 246.2 Hz); MS m/z (100, MH^+) 424; HRMS (ES): MH^+ , found 424.1499. $\text{C}_{28}\text{H}_{20}\text{F}_2\text{NO}^+$ requires 424.1513.

3.3. Synthesis of 2-aryl-4-chloro-3-(4-fluorophenyl)quinolines 2e-h. typical procedure

A mixture of 2-aryl-4-chloro-3-iodoquinoline **1** (1 equiv.), arylboronic acid (1.2 equiv.) and Pd(PPh₃)₄ (5% of **1**) in DMF (5 mL/mmol of **1**) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser was flushed with nitrogen gas. After 10 minutes 2M K₂CO₃ (2 mL/mmol of **1**) was added and the mixture was flushed for additional 10 minutes with nitrogen gas. A balloon filled with nitrogen gas was connected to the top of the condenser and the mixture was heated with stirring at 80–90 °C for 48 hours. The mixture was allowed to cool to room temperature and then quenched with ice-cold water. The product was extracted with chloroform and the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography to afford the 2-aryl-4-chloro-3-(4-fluorophenyl)quinoline **2**. The following products were prepared:

4-Chloro-3-(4-fluorophenyl)-2-phenylquinoline (2e). A mixture of **1a** (0.55 g, 1.50 mmol), 4-fluorophenylboronic acid (0.25 g, 1.81 mmol), Pd(PPh₃)₄ (0.09 g, 0.08 mmol), and 2M K₂CO₃ (3 mL) in DMF (8 mL) afforded (**2e**) as a solid (0.30 g, 60%), mp 147–149 °C (ethanol); *R_f* (10% ethyl acetate/hexane) 0.42; *v*_{max} (neat) 839, 1157, 12111, 1337, 1337, 1475, 1507, 1565; ¹H-NMR δ_H (300 MHz, CDCl₃) 7.01 (t, *J* 9.0 Hz, 2H), 7.13–7.18 (m, 2H), 7.20–7.26 (m, 3H), 7.28–7.33 (m, 2H), 7.67 (dt, *J* 1.5 and 7.8 Hz, 1H), 7.80 (dt, *J* 1.5 and 7.4 Hz, 1H), 8.20 (d, *J* 2.4 and 7.5 Hz, 1H), 8.31 (dt, *J* 0.3 and 8.7 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 115.2 (d, ²*J*_{CF} 21.7 Hz), 124.7, 125.4, 127.8, 127.9, 128.1, 129.7, 130.5, 132.0, 132.5 (d, ³*J*_{CF} 8.3 Hz), 132.9 (d, ⁴*J*_{CF} 3.5 Hz), 140.1, 142.1, 147.7, 159.2, 162.2 (d, ¹*J*_{CF} 246.5 Hz); MS *m/z* (100, MH⁺) 334; HRMS (ES): MH⁺, found 334.0817. C₂₁H₁₄FN³⁵Cl⁺ requires 334.0799.

4-Chloro-2,3-bis(4-fluorophenyl)quinoline (2f). A mixture of **1b** (0.50 g, 1.30 mmol), 4-fluorophenylboronic acid (0.22 g, 1.56 mmol), Pd(PPh₃)₄ (0.08 g, 0.07 mmol), and 2M K₂CO₃ (2.6 mL) in DMF (7 mL) afforded (**2f**) as a solid (0.25 g, 55%), mp 183–185 °C (ethanol); *R_f* (10% ethyl acetate/hexane) 0.42; *v*_{max} (neat) 831, 1158, 1219, 1337, 1474, 1509, 1597 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 6.92 (t, *J* 8.7 Hz, 2H), 7.04 (t, *J* 8.7 Hz, 2H), 7.16 (dd, *J* 5.4 and 8.8 Hz, 2H), 7.30 (dd, *J* 5.4 and 8.8 Hz, 2H), 7.68 (dt, *J* 1.2 and 7.8 Hz, 1H), 7.81 (dt, *J* 1.2 and 7.8 Hz, 1H), 8.19 (dddd, *J* 0.6, 1.2 and 8.4 Hz, 1H), (dddd, *J* 0.6, 1.6 and 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 114.9 (d, ²*J*_{CF} 21.4 Hz), 115.3 (d, ²*J*_{CF} 21.6 Hz), 124.7, 125.4, 127.9, 129.8, 130.6, 131.6 (d, ³*J*_{CF} 8.3 Hz), 131.8, 132.4 (d, ³*J*_{CF} 8.3 Hz), 132.8 (d, ⁴*J*_{CF} 3.4 Hz), 136.1 (d, ⁴*J*_{CF} 3.4 Hz), 142.3, 147.6, 158.0, 162.2 (d, ¹*J*_{CF} 246.8 Hz), 162.6 (d, ¹*J*_{CF} 247.0 Hz); MS *m/z* (100, MH⁺) 352; HRMS (ES): MH⁺, found 352.0709. C₂₁H₁₃F₂N³⁵Cl⁺ requires 352.0705.

4-Chloro-2-(4-chlorophenyl)-3-(4-fluorophenyl)quinoline (2g). A mixture of **1c** (0.50 g, 1.25 mmol), 4-fluorophenylboronic acid (0.21 g, 1.50 mmol), Pd(PPh₃)₄ (0.07 g, 0.07 mmol), and 2M K₂CO₃ (2.5 mL) in DMF (6.5 mL) afforded (**2g**) as a solid (0.28 g, 61%), mp 168–171 °C (ethanol); *R_f* (10% ethyl acetate–hexane) 0.51; *v*_{max} (neat) 827, 1092, 1341, 1474, 1509 cm^{−1}; ¹H-NMR δ_H (300 MHz, CDCl₃) 7.04 (t, *J* 8.4 Hz, 2H), 7.13–7.28 (m, 6H), 7.69 (dt, *J* 1.2 and 7.8 Hz, 1H), 7.81 (dt, *J* 1.2 and 7.8 Hz, 1H), 8.18 (dd, *J* 0.6 and 7.8 Hz, 1H), 8.31 (td, *J* 0.9 and 8.4 Hz, 1H); ¹³C-NMR δ_C (75 MHz, CDCl₃) 115.4 (d, ²*J*_{CF} 21.6 Hz), 124.7, 125.5, 128.0, 128.1, 129.9, 130.6, 131.1, 131.8, 132.4, (d, ³*J*_{CF}

8.3 Hz), 132.6 (d, $^4J_{\text{CF}}$ 3.4 Hz), 134.4, 138.6, 142.3, 147.7, 157.8, 162.3 (d, $^1J_{\text{CF}}$ 246.45 Hz); MS m/z (100, MH^+) 368; HRMS (ES): MH^+ , found 368.0395. $\text{C}_{21}\text{H}_{13}\text{FN}^{35}\text{Cl}_2^+$ requires 368.0409.

4-Chloro-3-(4-fluorophenyl)-2-(4-methoxyphenyl)quinoline (2h). A mixture of **1d** (0.50 g, 1.26 mmol), 4-fluorophenylboronic acid (0.21 g, 1.52 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.07 g, 0.06 mmol), and 2M K_2CO_3 (2.5 mL) in DMF (7 mL) afforded (**2h**) as a solid (0.36 g, 79%), mp 155–157 °C (ethanol); R_f (10% ethyl acetate/hexane) 0.23; ν_{max} (neat) 828, 1032, 1175, 1245, 1337, 1513, 1607, 2835 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 3.78 (s, 3H), 6.76 (dd, J 2.1 and 8.7 Hz, 2H), 7.04 (t, J 8.4 Hz, 2H), 7.14–7.21 (m, 2H), 7.28 (d, J 2.1 and 8.7 Hz, 2H), 7.65 (dt, J 1.2 and 7.8 Hz, 1H), 7.78 (dt, J 1.2 and 7.5 Hz, 1H), 8.19 (d, J 8.1 Hz, 1H), 8.24 (dd, J 0.9 and 8.4 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 55.2, 113.3, 115.2 (d, $^2J_{\text{CF}}$ 21.4 Hz), 124.6, 125.2, 127.5, 129.6, 131.2, 131.8, 132.5 (d, $^3J_{\text{CF}}$ 8.3 Hz), 133.2 (d, $^4J_{\text{CF}}$ 3.4 Hz), 142.0, 147.7, 158.7, 159.5, 159.5, 162.1 (d, $^1J_{\text{CF}}$ 246.2 Hz); MS m/z (100, MH^+) 364; HRMS (ES): MH^+ , found 364.0905. $\text{C}_{22}\text{H}_{16}\text{FNO}^{35}\text{Cl}^+$ requires 364.0904.

3.4. Reaction of 2e-h with aniline. typical procedure

A mixture of **2** (1 equiv.) and aniline (2.5 equiv.) was heated under reflux for 18 hours. The cooled mixture was quenched with ice-cold water and then extracted with chloroform. The combined organic phase was dried over MgSO_4 , filtered and then evaporated under reduced pressure. The residue was purified by column chromatography to afford (**4**).

3-(4-Fluorophenyl)-2-phenyl-4-(phenylamino)quinoline (4a). A mixture of **2e** (0.08 g, 0.24 mmol) and aniline (0.06 g, 0.60 mmol) afforded (**4a**) as a solid (0.05 g, 53%), mp 189–192 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.64; ν_{max} (neat) 744, 833, 1213, 1234, 1372, 1399, 1490, 1573, 3393 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 5.80 (br s, 1H), 6.76 (d, J 7.8 Hz, 2H), 6.96 (t, J 8.7 Hz, 3H), 7.06–7.11 (m, 2H), 7.18–7.25 (m, 5H), 7.29–7.33 (m, 2H), 7.34 (dt, J 1.5 and 7.7 Hz, 1H), 7.67 (dt, J 1.5 and 7.7 Hz, 1H), 7.77 (dd, J 0.6 and 8.4 Hz, 1H), 8.17 (dd, J 0.6 and 8.4 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 116.0 (d, $^2J_{\text{CF}}$ 21.3 Hz), 118.3, 121.8, 121.9, 124.7, 125.2, 125.6, 127.7, 127.8, 129.3, 129.6, 129.7, 130.1, 131.8 (d, $^4J_{\text{CF}}$ 3.8 Hz), 132.4 (d, $^3J_{\text{CF}}$ 8.0 Hz), 140.9, 145.0, 145.1, 148.6, 159.5, 162.2 (d, $^1J_{\text{CF}}$ 246.5 Hz); MS m/z (100, MH^+) 391; HRMS (ES): MH^+ , found 391.1611. $\text{C}_{27}\text{H}_{20}\text{FN}_2^+$ requires 391.1617.

2,3-Bis(4-fluorophenyl)-4-(phenylamino)quinoline (4b). A mixture of **2f** (0.05 g, 0.14 mmol) and aniline (0.03g, 0.35 mmol) afforded (**4b**) as a solid (0.03 g, 52%), mp 178–181 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.70; ν_{max} (neat) 748, 758, 834, 946, 1214, 1232, 1491, 1509, 1575, 1599, 3391 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 5.80 (s, 1H), 6.77 (d, J 7.8 Hz, 2H), 6.91 (t, J 8.7 Hz, 2H), 6.94–7.02 (m, 3H), 7.06–7.12 (m, 2H), 7.20 (t, J 7.8 Hz, 2H), 7.27–7.33 (m, 2H), 7.34 (dt, J 1.2 and 7.5 Hz, 1H), 7.67 (dt, J 1.5 and 7.4 Hz, 1H), 7.76 (dd, J 0.6 and 8.6 Hz, 1H), 8.14 (dd, J 0.6 and 8.7 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 114.8 (d, $^2J_{\text{CF}}$ 21.4 Hz), 116.2 (d, $^2J_{\text{CF}}$ 21.4 Hz), 118.3, 121.7, 122.0, 124.4, 125.2, 125.6, 129.3, 129.7, 130.0, 131.5 (d, $^3J_{\text{CF}}$ 8.0 Hz), 131.6 (d, $^4J_{\text{CF}}$ 3.7 Hz), 132.3 (d, $^3J_{\text{CF}}$ 8.0 Hz), 136.8 (d, $^4J_{\text{CF}}$ 3.2 Hz), 145.0, 145.2, 148.5, 158.3, 162.3 (d, $^1J_{\text{CF}}$ 247.0 Hz), 162.4 (d, $^1J_{\text{CF}}$ 246.2 Hz); MS m/z (100, MH^+) 409; HRMS (ES): MH^+ , found 409.1523. $\text{C}_{27}\text{H}_{19}\text{F}_2\text{N}_2^+$ requires 409.1516.

2-(4-Chlorophenyl)-3-(4-fluorophenyl)-4-(phenylamino)quinoline (4c). A mixture of **2g** (0.10 g, 0.27 mmol) and aniline (0.06 g, 0.66 mmol) afforded (**4c**) as solid (0.08 g, 69%), mp 200–203 °C (ethanol); R_f (3:7, ethyl acetate/hexane) 0.74; $\nu_{\max}$ (neat) 747, 762, 831, 1091, 1218, 1400, 1498, 1569, 3391 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 5.85 (br s, 1H), 6.79 (d, J 9.0 Hz, 2H), 7.01 (t, J 8.4 Hz, 3H), 7.07–7.13 (m, 2H), 7.18–7.29 (m, 6H), 7.36 (dt, J 1.5 and 7.7 Hz, 1H), 7.69 (dt, J 1.5 and 7.7 Hz, 1H), 7.76 (dd, J 0.6 and 8.4 Hz, 1H), 8.16 (d, J 8.4 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 116.3 (d, $^2J_{\text{CF}}$ 21.3 Hz), 118.5, 121.6, 122.1, 124.3, 125.2, 125.7, 128.0, 129.3, 129.9, 131.0, 131.4 (d, $^4J_{\text{CF}}$ 3.8 Hz), 132.4 (d, $^3J_{\text{CF}}$ 8.0 Hz), 133.9, 139.1, 144.8 (2xC), 145.4, 148.4, 158.1, 162.2 (d, $^1J_{\text{CF}}$ 247.2 Hz); m/z (100, MH^+) 425; HRMS (ES): MH^+ , found 425. 1313. $\text{C}_{27}\text{H}_{19}\text{FN}_2^{35}\text{Cl}^+$ requires 425. 1315.

3-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4-(phenylamino)quinoline (4d). A mixture of **2h** (0.10 g, 0.28 mmol) and aniline (0.07 g, 0.70 mmol) afforded (**4d**) as a solid (0.07 g, 61%), mp 180–182 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.57; $\nu_{\max}$ (neat) 767, 834, 1026, 1214, 1243, 1399, 1492, 1508, 1573, 3388 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, CDCl_3) 3.77 (s, 3H), 5.78 (s, 1H), 6.73–6.77 (m, 4H), 6.93–7.01 (m, 3H), 7.07–7.12 (m, 2H), 7.19 (t, J 7.8 Hz, 2H), 7.26 (d, J 8.7 Hz, 2H), 7.32 (dt, J 1.2 and 7.5 Hz, 1H), 7.65 (dt, J 1.5 and 7.4 Hz, 1H), 7.75 (dd, J 0.6 and 8.6 Hz, 1H), 8.14 (dd, J 0.6 and 8.7 Hz, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 55.2, 113.2, 116.1 (d, $^2J_{\text{CF}}$ 21.4 Hz), 118.1, 121.6, 121.7, 124.7, 125.2, 125.4, 129.2, 129.5, 130.0, 131.1, 132.0 (d, $^4J_{\text{CF}}$ 3.4 Hz), 132.3 (d, $^3J_{\text{CF}}$ 8.0 Hz), 133.3, 144.9, 145.2, 148.5, 159.0, 159.2, 162.2 (d, $^1J_{\text{CF}}$ 246.2 Hz); MS m/z (100, MH^+) 421; HRMS (ES): MH^+ , found 421.1722. $\text{C}_{28}\text{H}_{22}\text{N}_2\text{FO}^+$ requires 421.1716.

3.5. Hydrolysis of 4 with acetic acid: typical procedure

A suspension of **2** (1 equiv.) in acetic acid-water (5:1, v/v) was refluxed for 6 hours. The mixture was quenched with ice-cold water and the precipitate was filtered and recrystallized to afford **5**.

3-(4-Fluorophenyl)-2-phenylquinolin-4(1H)-one (5a). A suspension of **2e** (0.06 g, 0.18 mmol) in 5:1 acetic acid-water (10 mL) afforded (**5a**) as a solid (0.04 g, 70%), mp 340–342 °C (ethanol); $\nu_{\max}$ (neat) 1213, 1352, 1495, 1251, 1552, 1624, 3095 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, $\text{DMSO}-d_6$) 6.78 (t, J 9.0 Hz, 2H), 7.02 (dd, J 6.0 and 8.4 Hz, 2H), 7.24 (s, 5H), 7.26 (d, J 7.8 Hz, 1H), 7.51 (t, J 7.5 Hz, 1H), 7.62 (d, J 7.8 Hz, 1H), 8.21 (d, J 7.8 Hz, 1H), 11.54 (br s, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, $\text{DMSO}-d_6$) 114.2 (d, $^2J_{\text{CF}}$ 21.1 Hz), 118.5, 119.8, 123.2, 125.0, 125.7, 128.1, 129.0, 129.6, 131.5 (d, $^4J_{\text{CF}}$ 3.4 Hz), 131.6, 133.3 (d, $^3J_{\text{CF}}$ 8.1 Hz), 135.4, 139.9, 148.6, 161.0 (d, $^1J_{\text{CF}}$ 242.8 Hz), 176.4; MS m/z (100, MH^+) 316; HRMS (ES): MH^+ , found 316.1138. $\text{C}_{21}\text{H}_{15}\text{FNO}^+$ requires 316.1125.

2,3-Bis(4-fluorophenyl)quinolin-4(1H)-one (5b). A suspension of **2f** (0.06 g, 0.171 mmol) in acetic acid-water (10 mL) afforded **5b** as a solid (0.04 g, 70%), mp 347–349 °C (ethanol); $\nu_{\max}$ (neat) 829, 1159, 1221, 1351, 1351, 1500, 1521, 1604, 1625, 3065 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, $\text{DMSO}-d_6$) 7.01 (t, J 9.0 Hz, 2H), 7.041–7.11 (m, 2H), 7.21 (t, J 9.0 Hz, 2H), 7.33–7.41 (m, 3H), 7.68 (d, J 3.0 Hz, 2H), 8.15 (d, J 9.0 Hz, 1H), 11.85 (br s, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 114.7 (d, $^2J_{\text{CF}}$ 20.8 Hz), 115.7 (d, $^2J_{\text{CF}}$ 21.6 Hz), 118.9, 120.0, 123.8, 125.1, 125.8, 131.9 (d, $^4J_{\text{CF}}$ 3.2 Hz), 132.3 (d, $^4J_{\text{CF}}$ 3.1 Hz), 132.3, 132.5 (d, $^3J_{\text{CF}}$ 8.6 Hz), 134.0 (d, $^3J_{\text{CF}}$ 8.0 Hz), 140.1, 148.2, 161.1 (d, $^1J_{\text{CF}}$ 241.4 Hz), 162.7 (d,

$^1J_{\text{CF}}$ 245.0 Hz), 175.8; MS m/z (100, MH^+) 334; HRMS (ES): MH^+ , found 334.1046. $\text{C}_{21}\text{H}_{14}\text{F}_2\text{NO}^+$ requires 334.1043.

2-(4-Chlorophenyl)-3-(4-fluorophenyl)quinolin-4(1H)-one (5c). A suspension of **2g** (0.06 g, 0.172 mmol) in acetic acid-water (10 mL) afforded **5c** as a solid (0.03 g, 55%), mp 309–312 °C (ethanol); ν_{max} (neat) 822, 1091, 1210, 1350, 1491, 1519, 1551, 1600, 1624, 3089 cm^{-1} ; $^1\text{H-NMR}$ δ_{H} (300 MHz, $\text{DMSO-}d_6$) 6.81 (t, J 9.0 Hz, 2H), 7.02 (dd, J 6.0 and 8.4 Hz, 2H), 7.18 (d, J 9.0 Hz, 2H), 7.23 (d, J 9.0 Hz, 2H), 7.51 (t, J 7.5 Hz, 1H), 7.56 (t, J 7.5 Hz, 2H), 8.23 (d, J 7.8 Hz, 1H), 11.42 (br s, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, CDCl_3) 114.5 (d, $^2J_{\text{CF}}$ 21.1 Hz), 118.3, 119.9, 123.3, 125.0, 125.8, 128.3, 131.1, 131.7, 131.8 (d, $^4J_{\text{CF}}$ 3.2 Hz), 133.3 (d, $^3J_{\text{CF}}$ 8.0 Hz), 133.9, 134.8, 139.8, 147.2, 161.2 (d, $^1J_{\text{CF}}$ 243.1 Hz), 176.5; MS m/z (100, MH^+) 350; HRMS (ES): MH^+ , found 350.0748. $\text{C}_{21}\text{H}_{14}\text{F}_2\text{NO}^{35}\text{Cl}^+$ requires 350.0748.

3-(4-Fluorophenyl)-2-(4-methoxyphenyl)quinolin-4(1H)-one (5d). A suspension of **2h** (0.10 g, mmol) in acetic acid (5 mL) afforded **5d** as a solid (0.05 g, 65%), mp 375–377 °C (ethanol); $^1\text{H-NMR}$ δ_{H} (300 MHz, $\text{DMSO-}d_6$) 3.75 (s, 3H), 6.90 (d, J 9.0 Hz, 2H), 6.98–7.11 (m, 4H), 7.23 (d, J 9.0 Hz, 2H), 7.34 (t, J 7.5 Hz, 1H), 7.67 (1H, J 7.5 Hz, 1H), 7.68 (d, J 7.5 Hz, 1H), 8.13 (d, J 7.8 Hz, 1H), 11.78 (br s, 1H); $^{13}\text{C-NMR}$ δ_{C} (75 MHz, $\text{DMSO-}d_6$) 55.6, 113.9, 114.4 (d, $^2J_{\text{CF}}$ 21.1 Hz), 118.8, 119.8, 123.5, 125.0, 125.7, 127.6, 131.4, 131.6 (d, $^4J_{\text{CF}}$ 3.4 Hz), 132.0, 133.9 (d, $^3J_{\text{CF}}$ 8.1 Hz), 140.1, 148.8, 161.2 (d, $^1J_{\text{CF}}$ 242.8 Hz), 161.3, 175.3; MS m/z (100, MH^+) 346; HRMS (ES): MH^+ , found 346.1246. $\text{C}_{22}\text{H}_{17}\text{FNO}_2^+$ requires 346.1243.

4. Crystal Structure Solution and Refinement

X-ray quality crystals of the title compound **3f** were obtained by slow crystallization from ethanol solution. Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_{α} radiation (50 kV, 30 mA) using the Bruker APEX 2 [30] data collection software. The collection method involved ω -scans of width 0.5° and 512×512 bit data frames. Data reduction was carried out using the program Bruker SAINT+ [31]. The crystal structure was solved by direct methods using Bruker SHELXTL [32]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using SHELXTL. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON [33] and ORTEP-3 [34].

5. Conclusions

Overall, the results described in this investigation present another example showing the potential of 2-aryl-4-chloroquinolines in the synthesis of novel 2,3,4-trisubstituted quinolines and the 2,3-diarylquinolin-4(1H)-ones with potential to serve as molecular organic materials in nanomaterials or as selective cyclooxygenase-1/-2 (COX-1/-2) inhibitors. Polyarylquinoline-based compounds constitute an important component in optoelectronic materials [24–26]. This moiety constitutes a π -conjugated bridge in nonlinear optical polymers [27] and also serves as electron-acceptor unit in carbazole–

quinoline and phenothiazine–quinoline copolymers and oligomers found to exhibit intramolecular charge transfer [28]. The 2,3,4-triarylquinoline derivatives prepared in this investigation can also serve as substrates for metalation with iridium, for example, to form cyclometalated iridium complexes with potential application in organic light-emitting diodes (OLEDs) [25,26] or novel red-emitting electrophosphorescent devices [29]. Studies are currently underway in our laboratory to investigate the biological and photophysical properties of the polysubstituted quinolones and their quinoline derivatives.

Acknowledgements

The authors thank M.A. Fernandes and M. Stander of the University of the Witwatersrand and University of Stellenbosch for X-ray and mass spectral data, respectively. Financial support from the University of South Africa and the National Research Foundation (NRF) in South Africa is gratefully acknowledged.

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Sample Availability: Samples of the compounds are available from the authors.

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