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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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_{3}CO_{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 Csp²–Csp² 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)(PPh₃)₄ as a precursor of palladium(0) complex is attributed to the inhibiting role of the extra PPh₃ generated in the 2nd equilibrium \{SPd(0)(PPh₃)₂ → SPd(0)(PPh₃)₂ + PPh₃ (K₂/[PPh₃] << 1); S = solvent\} to afford the reactive low ligated 14-electron species (Pd(0)(PPh₃)₂) [7]. The oxidative addition performed from palladium(0) complex (Pd(0)(PPh₃)₃Cl⁺) generated by the reduction of dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂) is reported to be more than 30 times faster than that performed from Pd(0)(PPh₃)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 PdCl₂(PPh₃)₂–catalyzed Suzuki cross-coupling with arylboronic acid derivatives (2.5 equiv.) in the presence of tricyclohexylphosphine (PCy₃) and K₂CO₃ in dioxane-water (3:1, v/v) (Scheme 1). The reaction in the presence of PdCl₂(PPh₃)₂–PCy₃ 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, CH₃, NH₂, CO₂H 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 (ERβ) [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.

\[
\begin{align*}
\text{Cl} & \quad \text{I} \\
\text{C}_6\text{H}_4\text{R} & \\
\text{N} & \quad \text{Cl} & \quad \text{C}_6\text{H}_4\text{R} \\
1a - d & \quad 2a - h \\
\end{align*}
\]

| Comp | 4-R | Ar     | % Yield (3) |
|------|-----|--------|-------------|
| a    | H   | -C6H5  | 59          |
| b    | F   | -C6H5  | 55          |
| c    | Cl  | -C6H5  | 61          |
| d    | OMe | -C6H5  | 58          |
| e    | H   | p-FC6H4 | 72          |
| f    | F   | p-FC6H4 | 75          |
| g    | Cl  | p-FC6H4 | 62          |
| h    | OMe | p-FC6H4 | 62          |

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; $\alpha = 103.289(1)^\circ$, $\beta = 99.454(1)^\circ$, $\gamma = 96.939(1)^\circ$] 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)$^\cdot$N(1) 2.11 Å; O(1)$^\cdot$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.

| Property                               | Value                                      |
|----------------------------------------|--------------------------------------------|
| 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) Å³                             |
| Z                                      | 2                                          |
| Density (calculated)                   | 1.333 Mg/m³                                |
| Absorption coefficient                 | 0.097 mm⁻¹                                 |
| F(000)                                 | 900                                        |
| Crystal size                           | 0.44 × 0.37 × 0.37 mm³                     |
| 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 F²           |
| Data / restraints / parameters         | 9440 / 0 / 588                             |
| Goodness-of-fit on F²                  | 1.055                                      |
| Final R indices [I>2sigma(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.

![Scheme 2](image)

| 4-R | % Yield (2) | % Yield (4) |
|-----|-------------|-------------|
| H   | 60 (e)      | 53 (a)      |
| F   | 55 (f)      | 52 (b)      |
| Cl  | 61 (g)      | 69 (c)      |
| OMe | 79 (h)      | 61 (d)      |

Reagents (i) $p$-FC$_6$H$_4$B(OH)$_2$, Pd(PPh$_3$)$_3$, 2M K$_2$CO$_3$, DMF, heat, 48 h; (ii) NH$_2$Ph, 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(1H)-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 $^1$H-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(1H)-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(1H)-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 70eV 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); Rf (10% ethyl acetate/hexane) 0.26; νmax (neat) 1026, 1074, 1347, 1441, 1481, 1549, 2923 cm⁻¹; 1H-NMR δH (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 δC (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); R₇ (10% ethyl acetate/hexane) 0.38; νmax (neat) 836, 1158, 1232, 1345, 1479, 1509, 1601, 3052 cm⁻¹; ¹H-NMR δH (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 δC (75 MHz, CDCl₃) 114.6 (d, 2JCF 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, 3JCF 8.3 Hz), 132.8, 136.8, 137.2 (d, 4JCF 3.4 Hz), 138.2, 147.3, 147.8, 157.8, 162.4 (d, 1JCF 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); R₇ (10% ethyl acetate–hexane) 0.46; νmax (neat) 833, 1014, 1093, 1347, 1482, 1546, 2926 cm⁻¹; ¹H-NMR δH (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 δC (75 MHz, CDCl₃) 126.5, 126.6, 126.7, 126.8, 127.4, 127.6, 127.8, 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. C₂₇H₁₉N₃Cl⁺ 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); R₇ (30% ethyl acetate/hexane) 0.79; νmax (neat) 831, 1026, 1248, 1514, 1607 cm⁻¹; ¹H-NMR δH (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 δC (75 MHz, CDCl₃) 55.2, 113.1, 126.2, 126.3, 126.5, 126.6, 127.2, 127.4, 127.6, 127.9, 129.5, 129.7, 130.2, 131.2, 131.3, 132.7, 133.8, 136.7, 138.0, 139.6, 147.3, 147.6, 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); R₇ (10% ethyl acetate/hexane) 0.27; νmax (neat) 839, 1224, 1487, 1511, 1605, 3059 cm⁻¹; ¹H-NMR δH (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), 7.32–7.37 (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 δC (75 MHz, CDCl₃) 114.6 (d, 2JCF 21.4 Hz), 115.1 (d, 2JCF 21.4 Hz), 126.3, 126.6, 126.8, 127.7, 127.8,
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), PdCl₂(PPh₃)₂ (0.02 g, 0.03 mmol), PCy₃ (0.01 g, 0.05 mmol), and K₂CO₃ (0.21 g, 1.50 mmol) in dioxane/water (12 mL) afforded (3f) as a solid (0.153 g, 75%), mp 158–163 °C (ethanol); Rf (10% ethyl acetate/hexane) 0.27; νmax (neat) 833, 1157, 1219, 1509, 1601 cm⁻¹; ¹H-NMR δH (300 MHz, CDCl₃) 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 1.5 and 7.8 Hz, 1H), 8.23 (d, J 8.7 Hz, 1H); ¹³C-NMR δC (75 MHz, CDCl₃) 114.8 (d, JCF 21.4 Hz, 2xC), 115.2 (d, JCF 21.4 Hz), 126.3, 126.6, 126.9, 129.7, 129.8 (2xC), 131.7 (d, JCF 8.3 Hz), 131.8, 131.9 (d, JCF 8.3 Hz), 132.0, 132.5 (d, JCF 3.5 Hz), 132.8 (d, JCF 8.4 Hz), 134.0 (d, JCF 3.5 Hz), 136.9 (d, JCF 3.4 Hz), 157.8, 161.4 (d, JCF 245.6 Hz), 162.0 (d, JCF 246.2 Hz), 162.5 (d, JCF 246.4 Hz); MS m/z (100, MH⁺) 412; HRMS (ES): MH⁺, found 412.1314. C₂₇H₁₇F₃N⁺ 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), 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 (12 mL) afforded (3g) as a solid (0.20 g, 62%), mp 183–185 °C (ethanol); Rf (10% ethyl acetate/hexane) 0.29; νmax (neat) 832, 1093, 1157, 1223, 1509, 1604 cm⁻¹; ¹H-NMR δH (300 MHz, CDCl₃) 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); ¹³C-NMR δC (75 MHz, CDCl₃) 114.9 (d, JCF 21.3 Hz), 115.2 (d, JCF 21.7 Hz), 126.3, 126.6, 127.1, 128.1, 129.7, 131.2 (2xC), 131.8 (d, JCF 8.0 Hz), 132.4 (d, JCF 3.4 Hz), 132.8 (d, JCF 8.1 Hz), 133.9 (d, JCF 3.5 Hz), 134.0, 139.3, 147.1, 147.4, 157.9, 161.4 (d, JCF 245.9 Hz), 162.0 (d, JCF 245.9 Hz); MS m/z (100, MH⁺) 428; HRMS (ES): MH⁺, found 428.0999. C₂₇H₁₇F₃N₅Cl⁺ 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), PdCl₂(PPh₃)₂ (0.03 g, 0.04 mmol), PCy₃ (0.02 g, 0.08 mmol), and K₂CO₃ (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); Rf (30% ethyl acetate/hexane) 0.79; νmax (neat) 829, 1222, 1251, 1510, 1604 cm⁻¹; ¹H-NMR δH (300 MHz, CDCl₃) 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); ¹³C-NMR δC (75 MHz, CDCl₃) 55.2, 113.3, 114.7 (d, JCF 21.4 Hz), 115.1 (d, JCF 21.4 Hz), 126.3, 126.4, 126.6, 129.5, 129.7, 131.3, 131.9 (d, JCF 8.3 Hz), 132.0 (d, JCF 3.4 Hz), 132.8 (d, JCF 8.0 Hz), 133.3, 134.4 (d, JCF 3.7 Hz), 146.7, 147.4, 158.4, 159.2 (2xC), 161.3 (d, JCF 245.6 Hz), 161.9 (d, JCF 246.2 Hz); MS m/z (100, MH⁺) 424; HRMS (ES): MH⁺, found 424.1499. C₂₈H₂₀F₂NO⁻ 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; ν_max (neat) 839, 1157, 1211, 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, J =CF 21.7Hz), 124.7, 125.4, 127.8, 127.9, 128.1, 129.7, 130.5, 132.0, 132.5 (d, J =CF 8.3 Hz), 132.9 (d, J =CF 3.5 Hz), 140.1, 142.1, 147.7, 159.2, 162.2 (d, J =CF 246.5 Hz); MS m/z (100, MH+) 334; HRMS (ES): MH+, found 334.0817. C₂₁H₁₄FN₃SCl+ 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; ν_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, J_CF 21.4 Hz), 115.3 (d, J_CF 21.6 Hz), 124.7, 125.4, 127.9, 129.8, 130.6, 131.6 (d, J_CF 8.3 Hz), 131.8, 132.4 (d, J_CF 8.3 Hz), 132.8 (d, J_CF 3.4 Hz), 136.1 (d, J_CF 3.4 Hz), 142.3, 147.6, 158.0, 162.2 (d, J_CF 246.8 Hz), 162.6 (d, J_CF 247.0 Hz); MS m/z (100, MH⁺) 352; HRMS (ES): MH⁺, found 352.0709. C₂₁H₁₄F₂N₃SCl+ requires 352.0799.

4-Chloro-2-(4-chlorophenyl)-3-(4-fluorophenyl)quinoline (2g). A mixture of 1c (0.50 g, 1.30 mmol), 4-fluorophenylboronic acid (0.21 g, 1.50 mmol), Pd(PPh₃)₄ (0.07 g, 0.07 mmol), and 2M K₂CO₃ (2.6 mL) in DMF (7 mL) afforded (2g) as a solid (0.28 g, 61%), mp 168–171 °C (ethanol); R_f (10% ethyl acetate–hexane) 0.42; ν_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), 8.19 (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, J_CF 21.4 Hz), 115.3 (d, J_CF 21.6 Hz), 124.7, 125.4, 127.9, 129.8, 130.6, 131.6 (d, J_CF 8.3 Hz), 131.8, 132.4 (d, J_CF 8.3 Hz), 132.8 (d, J_CF 3.4 Hz), 136.1 (d, J_CF 3.4 Hz), 142.3, 147.6, 158.0, 162.2 (d, J_CF 246.8 Hz), 162.6 (d, J_CF 247.0 Hz); MS m/z (100, MH⁺) 352; HRMS (ES): MH⁺, found 352.0709. C₂₁H₁₄F₂N₃SCl+ requires 352.0795.
8.3 Hz), 132.6 (d, \(^{1}J_{CF} 3.4\) Hz), 134.4, 138.6, 142.3, 147.7, 157.8, 162.3 (d, \(^{1}J_{CF} 246.45\) Hz); MS m/z (100, MH\(^{+}\)) 368; HRMS (ES): MH\(^{+}\), found 368.0395. C\(_{21}\)H\(_{13}\)FN\(_{3}\)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), Pd(PPh\(_{3}\))\(_{4}\) (0.07 g, 0.06 mmol), and 2M K\(_{2}\)CO\(_{3}\) (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; \(\nu_{\text{max}}\) (neat) 828, 1032, 1175, 1245, 1337, 1513, 1607, 2835 cm\(^{-1}\); \(^{1}\)H-NMR \(\delta\)\(^{H}\) (300 MHz, CDCl\(_{3}\)) 3.78 (s, 3H), 6.76 (dd, \(J_{HF} 2.1\) and 8.7 Hz, 2H), 7.04 (t, \(J_{HF} 8.4\) Hz, 2H), 7.14–7.21 (m, 2H), 7.28 (d, \(J_{HF} 2.1\) and 8.7 Hz, 2H), 7.65 (dt, \(J_{HF} 1.2\) and 7.8 Hz, 1H), 7.78 (dt, \(J_{HF} 1.2\) and 7.5 Hz, 1H), 8.19 (d, \(J_{HF} 8.1\) Hz, 1H), 8.24 (dd, \(J_{HF} 0.9\) and 8.4 Hz, 1H); \(^{13}\)C-NMR \(\delta\)\(^{C}\) (75 MHz, CDCl\(_{3}\)) 55.2, 113.3, 115.2 (d, \(^{2}J_{CF} 21.4\) Hz), 124.6, 125.2, 127.5, 129.6, 131.2, 131.8, 132.5 (d, \(^{3}J_{CF} 8.3\) Hz), 142.0, 147.7, 158.7, 159.5, 159.6, 162.1 (d, \(^{1}J_{CF} 246.2\) Hz); MS m/z (100, MH\(^{+}\)) 364; HRMS (ES): MH\(^{+}\), found 364.0905. C\(_{22}\)H\(_{16}\)FNO\(_{3}\)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; \(\nu_{\text{max}}\) (neat) 744, 833, 1213, 1234, 1372, 1399, 1490, 1573, 3393 cm\(^{-1}\); \(^{1}\)H-NMR \(\delta\)\(^{H}\) (300 MHz, CDCl\(_{3}\)) 5.80 (br s, 1H), 6.76 (d, \(J_{HF} 7.8\) Hz, 2H), 6.96 (t, \(J_{HF} 8.7\) Hz, 1H), 7.06–7.11 (m, 2H), 7.18–7.25 (m, 5H), 7.29–7.33 (m, 2H), 7.34 (dt, \(J_{HF} 1.5\) and 7.7 Hz, 1H), 7.67 (dt, \(J_{HF} 1.5\) and 7.7 Hz, 1H), 7.77 (dd, \(J_{HF} 0.6\) and 8.4 Hz, 1H), 8.17 (dd, \(J_{HF} 0.6\) and 8.4 Hz, 1H); \(^{13}\)C-NMR \(\delta\)\(^{C}\) (75 MHz, CDCl\(_{3}\)) 116.0 (d, \(^{2}J_{CF} 21.3\) 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, \(^{4}J_{CF} 3.8\) Hz), 132.4 (d, \(^{3}J_{CF} 8.0\) Hz), 140.9, 145.0, 145.1, 148.6, 159.5, 162.2 (d, \(^{1}J_{CF} 246.5\) Hz); MS m/z (100, MH\(^{+}\)) 391; HRMS (ES): MH\(^{+}\), found 391.1611. C\(_{27}\)H\(_{20}\)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 (0.03 g, 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; \(\nu_{\text{max}}\) (neat) 748, 758, 834, 946, 1214, 1232, 1491, 1509, 1575, 1599, 3391 cm\(^{-1}\); \(^{1}\)H-NMR \(\delta\)\(^{H}\) (300 MHz, CDCl\(_{3}\)) 5.80 (br s, 1H), 6.77 (d, \(J_{HF} 7.8\) Hz, 2H), 6.91 (t, \(J_{HF} 8.7\) Hz, 2H), 6.94–7.02 (m, 3H), 7.06–7.12 (m, 2H), 7.20 (t, \(J_{HF} 7.8\) Hz, 2H), 7.27–7.33 (m, 2H), 7.34 (dt, \(J_{HF} 1.2\) and 7.5 Hz, 1H), 7.67 (dt, \(J_{HF} 1.5\) and 7.4 Hz, 1H), 7.76 (dd, \(J_{HF} 0.6\) and 8.6 Hz, 1H), 8.14 (dd, \(J_{HF} 0.6\) and 8.7 Hz, 1H); \(^{13}\)C-NMR \(\delta\)\(^{C}\) (75 MHz, CDCl\(_{3}\)) 114.8 (d, \(^{2}J_{CF} 21.4\) Hz), 116.2 (d, \(^{2}J_{CF} 21.4\) Hz), 118.3, 121.7, 122.0, 124.4, 125.2, 125.6, 129.3, 129.7, 130.0, 131.5 (d, \(^{3}J_{CF} 8.0\) Hz), 131.6 (d, \(^{4}J_{CF} 3.7\) Hz), 132.3 (d, \(^{3}J_{CF} 8.0\) Hz), 136.8 (d, \(^{4}J_{CF} 3.2\) Hz), 145.0, 145.2, 148.5, 158.3, 162.3 (d, \(^{1}J_{CF} 247.0\) Hz), 162.4 (d, \(^{1}J_{CF} 246.2\) Hz); MS m/z (100, MH\(^{+}\)) 409; HRMS (ES): MH\(^{+}\), found 409.1523. C\(_{27}\)H\(_{20}\)FN\(_{2}\) 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; \( \nu_{\text{max}} \) (neat) 747, 762, 831, 1091, 1218, 1400, 1498, 1569, 3391 cm\(^{-1}\); \( ^1\)H-NMR \( \delta_H \) (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); \( ^{13}\)C-NMR \( \delta_C \) (75 MHz, CDCl\(_3\)) 116.3 (d, \( ^2\)JC 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, \( ^4\)JC 3.8 Hz), 132.4 (d, \( ^3\)JC 8.0 Hz), 133.9, 139.1, 144.8 (2xC), 145.4, 148.4, 158.1, 162.2 (d, \( ^1\)JC 247.2 Hz); \( m/z \) (100, MH\(^+\)) 425; HRMS (ES): MH\(^+\), found 425. 1315. C\(_{22}\)H\(_{19}\)FN\(_2\)Cl\(_3\) 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; \( \nu_{\text{max}} \) (neat) 767, 834, 1026, 1214, 1243, 1399, 1492, 1508, 1573, 3388 cm\(^{-1}\); \( ^1\)H-NMR \( \delta_H \) (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); \( ^{13}\)C-NMR \( \delta_C \) (75 MHz, CDCl\(_3\)) 55.2, 113.2, 116.1 (d, \( ^2\)JC 242.8 Hz), 118.1, 121.6, 121.7, 124.7, 125.2, 125.4, 129.2, 130.0, 131.1, 132.0 (d, \( ^4\)JC 3.4 Hz), 132.3 (d, \( ^3\)JC 8.0 Hz), 133.3, 144.9, 145.2, 148.5, 159.0, 159.2, 162.2 (d, \( ^1\)JC 246.2 Hz); MS \( m/z \) (100, MH\(^+\)) 421; HRMS (ES): MH\(^+\), found 421.1722. C\(_{23}\)H\(_{18}\)FN\(_2\)Cl\(_2\) 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); \( \nu_{\text{max}} \) (neat) 1213, 1352, 1495, 1251, 1552, 1624, 3095 cm\(^{-1}\); \( ^1\)H-NMR \( \delta_H \) (300 MHz, 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); \( ^{13}\)C-NMR \( \delta_C \) (75 MHz, DMSO-d\(_6\)) 114.2 (d, \( ^2\)JC 21.1 Hz), 118.5, 119.8, 123.2, 125.0, 125.7, 128.1, 129.0, 129.6, 131.5 (d, \( ^4\)JC 3.4 Hz), 131.6, 133.3 (d, \( ^3\)JC 8.1 Hz), 135.4, 139.9, 148.6, 161.0 (d, \( ^1\)JC 242.8 Hz), 176.4; MS \( m/z \) (100, MH\(^+\)) 316; HRMS (ES): MH\(^+\), found 316.1138. C\(_{21}\)H\(_{15}\)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); \( \nu_{\text{max}} \) (neat) 829, 1159, 1221, 1351, 1351, 1500, 1521, 1604, 1625, 3065 cm\(^{-1}\); \( ^1\)H-NMR \( \delta_H \) (300 MHz, 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); \( ^{13}\)C-NMR \( \delta_C \) (75 MHz, CDCl\(_3\)) 114.7 (d, \( ^2\)JC 20.8 Hz), 115.7 (d, \( ^2\)JC 21.6 Hz), 118.9, 120.0, 123.8, 125.1, 125.8, 131.9 (d, \( ^4\)JC 3.2 Hz), 132.3 (d, \( ^4\)JC 3.1 Hz), 132.3, 132.5 (d, \( ^3\)JC 8.6 Hz), 134.0 (d, \( ^3\)JC 8.0 Hz), 140.1, 148.2, 161.1 (d, \( ^1\)JC 241.4 Hz), 162.7 (d,
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, 1600, 1624, 3089 cm⁻¹; 1H-NMR δ_H (300 MHz, DMSO-d₆) 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); 13C-NMR δ_C (75 MHz, CDCl₃) 114.5 (d, 2J_CF 21.1 Hz), 118.3, 119.9, 123.3, 125.0, 125.8, 128.3, 131.1, 131.7, 131.8 (d, 4J_CF 3.2 Hz), 133.3 (d, 3J_CF 8.0 Hz), 133.9, 134.8, 147.2, 161.2 (d, 1J_CF 243.1 Hz), 176.5; MS m/z (100, MH⁺) 350; HRMS (ES): MH⁺, found 350.0748. C21H14F2NO35Cl⁺ 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); 1H-NMR δ_H (300 MHz, DMSO-d₆) 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); 13C-NMR δ_C (75 MHz, DMSO-d₆) 55.6, 113.9, 114.4 (d, 2J_CF 21.1 Hz), 118.8, 119.8, 123.5, 125.0, 125.7, 127.6, 131.4, 131.6 (d, 4J_CF 3.4 Hz), 132.0, 133.9 (d, 3J_CF 8.1 Hz), 140.1, 148.8, 161.2 (d, 1J_CF 242.8 Hz), 161.3, 175.3; MS m/z (100, MH⁺) 346; HRMS (ES): MH⁺, found 346.1246. C22H17FNO2⁺ 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 Kα 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 F² 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 carbozole–
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.

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

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