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6,8-Dibromo-4-chloroquinoline-3-carbaldehyde as a synthon in the development of novel 1,6,8-triaryl-1*H*-pyrazolo[4,3-*c*]quinolines

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Suzuki–Miyaura cross-coupling
1,6,8-Triaryl-1*H*-pyrazolo[4,3-*c*]quinolines

ABSTRACT

2-Amino-3,5-dibromoacetophenone undergoes Vilsmeier reaction with a phosphoryl chloride–dimethylformamide mixture to afford 6,8-dibromo-4-chloroquinoline-3-carbaldehyde. The latter was reacted with arylhydrazine hydrochlorides in ethanol in the presence of triethylamine to afford the corresponding arylhydrazone derivatives. These hydrazones were, in turn, cyclized with ethanolic KOH (5% in ethanol) to afford the corresponding 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinolines. Suzuki–Miyaura cross-coupling of these 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinolines with arylboronic acids afforded novel 1,6,8-triaryl-1*H*-pyrolo[4,3-*c*]quinolines.

1. Introduction

With their rich biological activity and excellent pharmacological properties, pyrazolo[4,3-*c*]quinoline-based compounds have been the target of a great deal of research.[1] Pyrazolo[4,3-*c*]quinolines are associated with high affinity benzodiazepine receptor ligands,[2,3] selective cyclooxygenase-2 (COX-2) inhibitors,[4] anticancer,[5] and anti-inflammatory agents.[6] The two main approaches for the synthesis of these systems involve either the annulations of the pyrazole onto a quinoline scaffold or annulations of the quinoline ring onto a pyrazole scaffold.[1] Halogenated quinoline precursors such as 2-chloroquinoline-3-carbaldehyde and 2,4-dichloroquinoline-3-carbaldehyde have received considerable attention as key intermediates for various functional group transformation and for further annulations into pyrazolo derivatives.[1,7–10] A few examples involving modification of 4-chloroquinoline-3-carbaldehyde have also been reported in the literature, however, these do not involve annulation.[11–13] Although a wide variety of polysubstituted 1*H*-pyrazolo[4,3-*c*]quinolinones and quinoline derivatives have been reported earlier,[1] a thorough literature search revealed that derivatives containing carbon-bearing substituents (alkyl, aryl, alkenyl, or alkynyl) on the fused benzo ring remain surprisingly unexplored. The arylquinoline moiety, for example, is an important scaffold broadly present in many molecules with a wide array of biological activity[14] and constitute an important structural element in materials chemistry.[15]

During our research on the development of novel annulated quinoline derivatives with potential biological activity,[16] we became interested in the synthesis of pyrazolo[4,3-*c*]quinoline derivatives bearing aryl or alkenyl substituents on the fused benzo ring. We envisioned 6,8-dibromo-4-chloroquinoline-3-carbaldehyde as a potential candidate for the synthesis of the 6,8-dibromo-4-chloroquinoline arylhydrazones to serve as precursors for the requisite 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinolines. The 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinolines appeared suitable substrates for the synthesis of the requisite polyaryl-1*H*-pyrazolo[4,3-*c*]quinolines via palladium-catalyzed Suzuki–Miyaura cross-coupling with arylboronic acids as models for Csp^2–Csp^2 bond formation.

2. Results and discussion

The first task in this investigation was to synthesize the requisite precursor, 6,8-dibromo-4-chloroquinoline-3-carbaldehyde, from the known 1-(2-amino-3,5-dibromophenyl)ethanone. The latter has been

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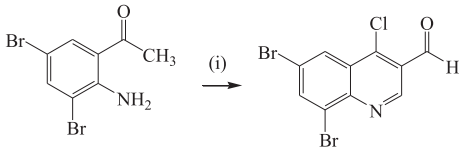
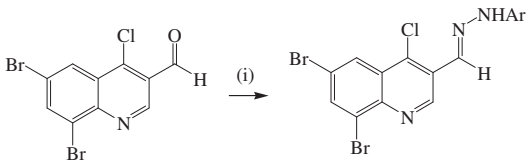
prepared before as a sole product (83%) from 2-aminoacetophenone using NaBr–oxone in CH_3CN–H_2O mixture.[17] Bheemanapalli et al. recently reported the synthesis of a compound described as 1-(2-amino-3,5-dibromophenyl)ethanone (80%) along with a minor product, 1-(2-amino-3,5-dibromophenyl)-2-bromoethanone, which was erroneously reported as 1-(2-amino-5-dibromophenyl)ethanone.[18] Since we required significant amounts of 2-amino-3,5-dibromoacetophenone as starting material for the synthesis of the requisite 6,8-dibromo-4-chloroquinoline-3-carbaldehyde, we employed *N*-bromosuccinimide (NBS) in a chloroform–carbon tetrachloride mixture (3/2, v/v) at room temperature for 78 h to afford 1-(2-amino-3,5-dibromophenyl)ethanone **1** as a single product (90%) without the need for column chromatographic separation. Its ^1H and ^{13}C NMR spectral data were found to compare favorably with the analytical data reported by Lee and co-workers,[17] but to differ from spectral data of the major product described by Bheemanapalli et al. as the 1-(2-amino-3,5-dibromophenyl)ethanone.[16] The analogous commercially available 2-amino-3,5-dibromobenzaldehyde was previously subjected to Friedlander reaction with substituted cyclohexanones[19] and *C*-β-glycosidic ketones,[20] to afford novel multifunctional quinoline derivatives. In our case, we required 6,8-dibromoquinoline bearing a chloro/bromo atom and carbaldehyde at the 4- and 3-position, respectively, and this compound cannot be easily accessible via the known classical methods such as Friedlander or Doebner–von Miller reactions. The Vilsmeier–Haack–Arnold reaction that was initially used for the formylation of carbonyl compounds[21] has now evolved into a powerful synthetic tool for the construction of quinolines[22] including the 2/4-chloroquinoline-3-carbaldehydes.[1,7–13,23] Consequently, we subjected compound **1** to the Vilsmeier reaction conditions with $POCl_3$–DMF mixture under reflux and isolated the corresponding novel 6,8-dibromo-4-chloroquinoline-3-carbaldehyde **2** in reasonable yield (Scheme 1).



1 (90%) **2** (73%)

Scheme 1. Preparation of 6,8-dibromo-4-chloroquinoline-3-carbaldehyde **2**. Reagents and conditions: (i) $POCl_3$, DMF, 60 °C, 4 h.

Compound **2** contains several reactive centers for possible modification with nucleophilic reagents (Cl or –CHO), metal-catalyzed cross-coupling reactions (Br and/or Cl), etc. The carbaldehyde moiety of both 2/4-chloroquinoline-3-carbaldehydes has been found to be more reactive than the C–Cl bond toward nucleophilic attack by ammonia derivatives.[1,9,24] The analogous 2-chloro-3-formylquinolines with hydrazine hydrate/phenylhydrazine hydrochloride in ethanol under reflux (5/7 h), for example, previously afforded pyrrazolo[3,4-*d*] quinolines in 44–82% yield in a single-pot operation.[24] In analogy with this literature precedent, we subjected 6,8-dibromo-4-chloroquinoline-3-carbaldehyde **2** to an arylhydrazine hydrochloride–triethylamine mixture in ethanol under reflux. After 6/12 h we isolated the corresponding 6,8-dibromo-4-chloroquinoline arylhydrazones **3a**–**c** in high yield and purity without the need for column chromatography (Scheme 2). The prepared products were easily distinguished from the corresponding precursors by the increased resonances in the aromatic region of their ^1H NMR and ^{13}C NMR spectra. The molecular ion region of the mass spectra of these polyhalogenated derivatives reveal the presence of the M+ and M+2 peaks in the ratio 3/1 typical for the ^{35}Cl and ^{37}Cl isotopes, thus confirming their β-chlorohydrazone nature. The analogous *N*-[(2-chloroquinolin-3-yl) methylene]benzohydrazides derived from 2-chloroquinoline-3-carboxaldehyde were previously found to exhibit significant cytotoxic activity when tested in vitro.[25]

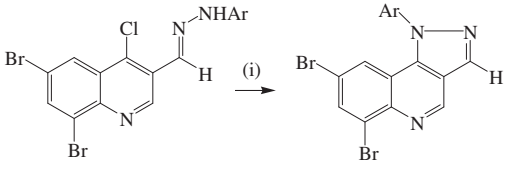


2 **3a-c**

3	Ar	Time	% Yield
3a	4-FC_6H_4-	6 h	80
3b	4-ClC_6H_4-	12 h	83
3c	4-$MeOC_6H_4$-	6 h	88

Scheme 2. Conversion of **2** into 6,8-dibromo-4-chloroquinoline-3-arylhydrazone derivatives **3**. Reagents and conditions: (i) $Cl{\cdot}NH_3NHAr$, NEt_3, EtOH, heat, 6–12 h.

We took advantage of the known ease of displacement of the 4-chloro atom on the quinoline framework by heteroatom-containing (N, O, S) nucleophiles, and subjected the 6,8-dibromo-4-chloroquinoline arylhydrazones **3** to intramolecular cyclization with ethanolic potassium hydroxide (5% in ethanol) under reflux for 3 h. From the cooled mixture, we isolated by simple filtration the corresponding 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinolines **4** in high yield and purity (Scheme 3). These heteroannulated derivatives were characterized using a combination of NMR, IR, and mass spectroscopic techniques and their accurate calculated *m*/*z* values [MH^+–35/37] represent closest fit consistent with the assigned structures.



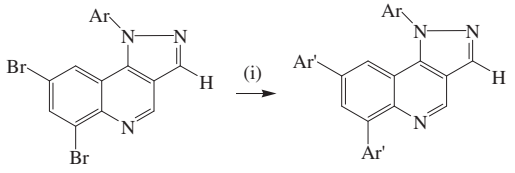
3a-c **4a-c**

4	Ar	% Yield
4a	4-FC_6H_4-	82
4b	4-ClC_6H_4-	89
4c	4-$MeOC_6H_4$-	88

Scheme 3. Base-mediated cyclization of **3** to 1-aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*] quinolines **4**. Reagents and conditions: (i) 5% KOH in EtOH, 80 °C, 3 h.

Bromoquinolines have been of interest for chemists as precursors for heterocyclic compounds with multifunctionality, giving a wide variety of compounds through, e.g., couplings[26] and metal exchange reactions.[27] The presence of the two bromine atoms in compounds **4** makes them suitable candidates for further transformation through transition metal-catalyzed cross-coupling reactions to enable adequate diversity on the fused benzo ring. Prompted by the scarcity of 1*H*-pyrazolo[4,3-*c*]quinolines bearing aryl or alkenyl substituents on the fused benzo ring, we decided to explore the reactivity of **4** in Suzuki–Miyaura cross-coupling reactions with arylboronic acids. While it is possible to control the regioselectivity of Suzuki–Miyaura cross-couplings for dihaloquinolines bearing different halogen atoms (I vs Br/Cl or Br vs Cl), it is relatively difficult to achieve high levels of regioselectivity in the case involving derivatives bearing

similar halogen atoms.[26] It has also been observed that the dibromoquinolines undergo Suzuki cross-coupling with less or no selectivity compared to many of the other dibromoheteroaromatics.[26] The Suzuki–Miyaura cross-coupling reaction of 5,7-dibromoquinoline[26] and 8-benzyloxy-5,7-dibromoquinoline[28] with arylboronic acids, for example, have been found to occur without selectivity to afford the corresponding double coupled derivatives. The most common outcome in Suzuki–Miyaura cross-coupling reactions involving dihaloaromatic precursors bearing similar halogen atoms is exhaustive multiple coupling and an excess of the arylboronic acid or ester coupling partner is often employed to drive the reaction to completion.[28] Based on the literature precedence,[26,28,29] we subjected **4a** to Suzuki–Miyaura cross-coupling with phenylboronic acid (2.5 equiv) using dichlorobis(triphenylphosphine)palladium(II) as Pd(0) catalyst source in dimethyl formamide–water (3/1, v/v) in the presence of K_2CO_3 as a base. After 18 h we isolated by column chromatography on silica gel the 1,6,8-triaryl-1*H*-pyrazolo[4,3-*c*]quinoline **5a** in 40% along with starting material (Scheme 4). Prolonged reaction time and reduced yield prompted us to use dichlorobis(triphenylphosphine) palladium(II)–tricyclohexylphosphine catalyst complex in dimethyl formamide–water (3/1, v/v) in the presence of K_2CO_3 as a base, and the reaction was found to be complete after 3 h to afford **5a** in 77% yield (Scheme 4). Reduced reaction time and complete conversion of the substrate to the products are attributed to addition of tricyclohexylphosphine. Alkylphosphine ligands, are known to coordinate with palladium and increase its electron density more so than arylphosphines and, in turn, accelerate the oxidative addition and reductive elimination steps in the catalytic cycle.[30] The cross-coupling reaction using the $PdCl_2(PPh_3)_2$–PCy_3 catalyst complex was extended to other derivatives using phenylboronic and 4-fluorophenylboronic acids as well as arylvinylboronic acids to afford products **5a**–**l**. In all cases, the products were isolated in reasonable yield by filtration and purified by recrystallization without the need for column chromatography.



4a-c **5a-l**

5	Ar	Ar′	% Yield
5a	4-FC_6H_4-	-C_6H_5	77
5b	4-ClC_6H_4-	-C_6H_5	69
5c	4-$MeOC_6H_4$-	-C_6H_5	69
5d	4-FC_6H_4-	4-FC_6H_4-	71
5e	4-ClC_6H_4-	4-FC_6H_4-	68
5f	4-$MeOC_6H_4$-	4-FC_6H_4-	60
5g	4-FC_6H_4-	4-FC_6H_4CH=CH-	72
5h	4-ClC_6H_4-	4-FC_6H_4CH=CH-	70
5i	4-$MeOC_6H_4$-	4-FC_6H_4CH=CH-	81
5j	4-FC_6H_4-	4-$MeOC_6H_4CH$=CH-	65
5k	4-ClC_6H_4-	4-$MeOC_6H_4CH$=CH-	82
5l	4-$MeOC_6H_4$-	4-$MeOC_6H_4CH$=CH-	70

Scheme 4. Suzuki cross-coupling of **4** to afford the 1,6,8-triaryl-1*H*-pyrazolo[4,3-*c*] quinolines. Reagents and conditions: (i) Ar′$B(OH)_2$ (2.5 equiv), $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, DMF–water (3/1, v/v), heat, 3 h.

3. Conclusions

In summary, the results of this investigation present the readily available 6,8-dibromo-4-chloroquinoline-3-carbaldehyde as a valuable precursor for the synthesis of diversely functionalized polysubstituted and annulated quinoline derivatives through substitution and metal-catalyzed cross-coupling reactions. Polyarylquinoline-based compounds constitute an important component in optoelectronic materials[31] and thus exhaustive metal-catalyzed Suzuki–Miyaura or Sonogashira cross-coupling of 6,8-dibromo-4-chloroquinoline-3-carbaldehyde could lead to poly(aryl/alkynyl)quinolines with potential photophysical properties. Since the analogous 1-phenyl-1*H*-indazole undergoes metal-catalyzed C–H arylation with haloarenes,[32] it is our view that the 1-aryl-1*H*-pyrazole moiety of systems **5** represents a suitable scaffold for possible metal-catalyzed C–H arylation. Studies are currently underway in our laboratory to investigate the reactivity, anticancer, and photophysical properties of the compounds prepared in this investigation.

4. Experimental

4.1. General

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. IR spectra were recorded as powders using a Bruker VERTEX 70 FT-IR Spectrometer with a diamond ATR (attenuated total reflectance) accessory by using the thin-film method. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) was used as stationary phase. NMR spectra were obtained as $CDCl_3$ or DMSO-d_6 solutions using Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks. Low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using Micromass Autospec-TOF (double focusing high resolution) instrument.

*4.1.1. Bromination of 2-aminoacetophenone with NBS. Synthesis of **1***

*4.1.1.1. 1-(2-Amino-3,5-dibromophenyl)ethanone (**1**).* A stirred solution of 2-aminoacetophenone (7.50 g, 55.5 mmol) in $CHCl_3$–CCl_4 (3/2, v/v, 300 mL) was treated with *N*-bromosuccinimide (24.69 g, 138.7 mmol). The mixture was stirred at room temperature for 78 h and then quenched with a saturated solution of $NaHCO_3$ (100 mL). The aqueous phase was extracted with chloroform (2×50 mL) and the combined organic extracts were washed with water (50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and then evaporated under reduced pressure to afford **1** as a solid (14.70 g, 90%), mp 124–125 °C (ethanol) (lit. 119–121 °C,[14] 120–122 °C,[15] 123–124 °C[33]); ν_{max} (ATR) 870.3, 1230.3, 1355.0, 1520.6, 1570.0, 1599.2, 1646.1, 3411.7 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.57 (s, 3H), 6.90 (br s, 2H), 7.68 (d, *J* 2.1 Hz, 1H), 7.79 (d, *J* 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 27.9, 105.8, 111.7, 119.6, 133.7, 139.2, 146.3, 199.1.

*4.1.2. Vilsmeier reaction of **1** with $POCl_3$/DMF mixture. Synthesis of **2***

*4.1.2.1. 6,8-Dibromo-4-chloroquinoline-3-carbaldehyde (**2**).* A two-necked flask equipped with a stirrer, condenser, and rubber septum was charged with dry DMF (30 mL) at 0 °C under a nitrogen atmosphere. Phosphoryl chloride (10 mL, 102.4 mmol) was added dropwise to the flask at 0 °C. The mixture was allowed to warm up to room temperature and stirred at this temperature for 15 min. A

solution of **1** (3.90 g, 13.3 mmol) in DMF (20 mL) was added dropwise by means of a syringe and the mixture was heated at 60 °C for 4 h under nitrogen. The cooled mixture was added to crush ice and then neutralized with saturated $NaHCO_3$ solution. The product was extracted into chloroform and the combined organic phases were washed with water and then dried over anhydrous $MgSO_4$. The mixture was filtered off and the solvent was evaporated under reduced pressure to afford **2** as an off-white solid (3.40 g, 73%), mp 212–214 °C; ν_{max} (ATR) 742.4, 897.2, 1330.9, 1451.8, 1686.5 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.32 (dd, *J* 0.9 and 2.1 Hz, 1H), 8.52 (dd, *J* 0.9 and 2.1 Hz, 1H), 9.34 (s, 1H), 10.68 (s, 1H); δ_C (75 MHz, $CDCl_3$) 122.7, 125.1, 126.7, 127.1, 127.8, 139.5, 146.5, 146.9, 149.4, 188.2; *m*/*z* 350 (100%, $C_{10}H_5NO^{37}Cl^{79}Br_2^+$); HRMS (ES): MH^+, found 347.6421. $C_{10}H_5NO^{35}Cl^{79}Br_2^+$ requires 347.6425.

*4.1.3. Reaction of **2** with arylhydrazine hydrochlorides to afford hydrazones **3**. Typical procedure.* A stirred mixture of **2** (1 equiv), arylhydrazine hydrochloride (1.5 equiv), and triethylamine (1.5 equiv) in ethanol (ca. 10 mL/mmol of **2**) was heated at 60 °C for 6–12 h. The mixture was allowed to cool to room temperature and filtered on a sintered funnel. The product was washed with cold ethanol and dried to afford pure 6,8-dibromo-4-chloroquinoline-3-arylhydrazone **3**. The following products were prepared in this fashion.

*4.1.3.1. N′-[(6,8-Dibromo-4-chloroquinolin-3-yl)methylene]-2-(4-fluorophenyl)hydrazide (**3a**).* A mixture of **2** (1.00 g, 2.80 mmol), 4-fluorophenylhydrazine hydrochloride (0.425 g, 4.20 mmol), and triethylamine (0.68 g, 4.18 mmol) in ethanol (40 mL) was heated for 6 h to afford **2b** as a orange solid (1.05 g, 80%), mp 232–235 °C (ethanol); ν_{max} (ATR) 735.5, 759.5, 823.0, 897.2, 1159.7, 1192.12, 1325.4, 1461.7, 1501.4, 1557.0 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.06 (t, *J* 8.7 Hz, 2H), 7.13 (t, *J* 8.7 Hz, 2H), 8.17 (s, 1H), 8.19 (d, *J* 2.1 Hz, 1H), 8.21 (d, *J* 2.1 Hz, 1H), 9.47 (s, 1H), 11.09 (s, 1H); δ_C (75 MHz, DMSO-d_6) 113.7 (d, $^3J_{CF}$ 6.8 Hz), 115.6 (d, $^2J_{CF}$ 22.5 Hz), 121.3, 121.9, 125.8, 125.9, 128.0, 128.2, 129.2, 135.3, 140.6, 142.7 (d, $^4J_{CF}$ 3.0 Hz), 149.1, 157.2 (d, $^1J_{CF}$ 236.5 Hz); *m*/*z* 458 (100%, $C_{16}H_{10}N_3F^{37}Cl^{79}Br_2^+$); HRMS (ES): MH^+, found 455.8910. $C_{16}H_{10}N_3F^{35}Cl^{79}Br_2^+$ requires 455.8914.

*4.1.3.2. N′-[(6,8-Dibromo-4-chloroquinolin-3-yl)methylene]-2-(4-chlorophenyl)hydrazide (**3b**).* A mixture of **2** (1.00 g, 2.80 mmol), 4-chlorophenylhydrazine hydrochloride (0.75 g, 4.20 mmol), and triethylamine (0.425 g, 4.20 mmol) in ethanol (40 mL) was heated for 12 h to afford **2c** as an yellow solid (1.10 g, 83%), mp 254–256 °C (ethanol); ν_{max} (ATR) 622.1, 638.2, 742.0, 818.5, 1090.7, 1160.7, 1254.4, 1325.2, 1458.5, 1484.7, 1516.2, 1566.6, 1587.1 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.11 (d, *J* 7.8 Hz, 2H), 7.25 (d, *J* 7.8 Hz, 2H), 8.15 (s, 1H), 8.18 (d, *J* 2.1 Hz, 1H), 8.23 (d, *J* 2.1 Hz, 1H), 9.42 (s, 1H), 11.18 (s, 1H); δ_C (75 MHz, DMSO-d_6) 114.5, 121.6, 124.1, 126.0, 126.5, 127.9, 128.2, 129.3, 130.3, 135.4, 135.7, 142.9, 143.3, 149.3; *m*/*z* 474 (100%, $C_{16}H_{10}N_3{}^{35}Cl^{37}Cl^{79}Br_2^+$); HRMS (ES): MH^+, found 471.8621. $C_{16}H_{10}N_3{}^{35}Cl_2^{79}Br_2^+$ requires 471.8619.

*4.1.3.3. N′-[(6,8-Dibromo-4-chloroquinolin-3-yl)methylene]-2-(4-methoxyphenyl)hydrazide (**3c**).* A mixture of **2** (1.00 g, 2.80 mmol), 4-methoxyphenylhydrazine hydrochloride (0.73 g, 4.20 mmol), and triethylamine (0.425 g, 4.20 mmol) in ethanol (40 mL) was heated for 6 h to afford **2d** as an orange solid (1.19 g, 88%), mp 232–234 °C (ethanol); ν_{max} (ATR) 613.3, 643.5, 826.0, 1019.9, 1190.5, 1226.8, 1461.9, 1502.1, 1584.4 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.72 (s, 3H), 6.87 (d, *J* 8.7 Hz, 2H), 7.12 (d, *J* 8.7 Hz, 2H), 8.15 (s, 1H), 8.26 (d, *J* 2.1 Hz, 1H), 8.27 (d, *J* 2.1 Hz, 1H), 9.50 (s, 1H), 11.03 (s, 1H); δ_C (75 MHz, DMSO-d_6) 55.8, 114.3, 115.2, 121.8, 126.0, 126.6, 128.3, 128.4, 128.6, 134.4, 135.5, 138.4, 142.7, 149.5, 154.2; *m*/*z* 470 (100%, $C_{17}H_{13}N_3O^{37}Cl^{79}Br_2^+$); HRMS (ES): MH^+, found 467.9114. $C_{17}H_{13}N_3O^{35}Cl^{79}Br_2^+$ requires 467.9115.

*4.1.4. Cyclization of the 2-arylhydrazone derivatives **3** to afford **4**. Typical procedure*

*4.1.4.1. 6,8-Dibromo-1-(2-fluorophenyl)-1H-pyrazolo[4,3-c]quinoline (**4a**).* A stirred mixture of **3a** (0.50 g, 1.09 mmol) and 5% ethanolic KOH (5% in ethanol, 20 mL) was heated at 80 °C for 3 h and allowed to cool to room temperature. The solid product was filtered, washed with ice-cold ethanol, and then dried on a sintered funnel to afford **4a** as an off-white solid (0.40 g, 82%), mp 299–301 °C; ν_{max} (ATR) 637.9, 787.8, 840.9, 878.9, 1087.2, 1216.7, 1510.3, 1576.8 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35 (t, *J* 8.7 Hz, 2H), 7.57 (t, *J* 8.7 Hz, 2H), 7.66 (s, 1H), 8.14 (s, 1H), 8.41 (d, *J* 2.1 Hz, 1H), 9.35 (s, 1H); δ_C (75 MHz, $CDCl_3$) 117.1 (d, $^2J_{CF}$ 23.0 Hz), 118.1, 119.3, 119.7, 123.7, 127.1, 128.9 (d, $^3J_{CF}$ 8.8 Hz), 135.5, 135.7, 135.8 (d, $^4J_{CF}$ 3.0 Hz), 138.2, 141.8, 146.7, 163.3 (d, $^1J_{CF}$ 250.4 Hz); *m*/*z* 422 (100%, $C_{16}H_9N_3{}^{79}Br^{81}BrF^+$); HRMS (ES): MH^+, found 419.9150. $C_{16}H_9N_3{}^{79}Br_2F^+$ requires 419.9147.

*4.1.4.2. 6,8-Dibromo-1-(2-chlorophenyl)-1H-pyrazolo[4,3-c]quinoline (**4b**).* A mixture of **3b** (0.50 g, 1.05 mmol) and 5% ethanolic KOH (20 mL) afforded **4b** as an off-white solid (0.41 g, 89%), mp 282–284 °C; ν_{max} (ATR) 640.2, 807.7, 880.0, 1039.7, 1088.6, 1390.9, 1460.6, 1505.0, 1597.5 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54 (t, *J* 8.7 Hz, 2H), 7.64 (d, *J* 8.7 Hz, 2H), 7.74 (d, *J* 1.5 Hz, 1H), 8.15 (d, *J* 1.5 Hz, 1H), 8.41 (s, 1H), 9.35 (s, 1H); δ_C (75 MHz, $CDCl_3$) 118.0, 119.5, 119.7, 123.7, 127.1, 128.1, 130.2, 135.6, 136.0, 136.2, 138.0, 138.4, 141.9, 146.7; *m*/*z* 438 (100%, $C_{16}H_9N_3{}^{35}Cl^{79}Br_2^+$); HRMS (ES): MH^+, found 435.8847. $C_{16}H_9N_3{}^{35}Cl^{79}Br_2^+$ requires 435.8852.

*4.1.4.3. 6,8-Dibromo-1-(2-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline (**4c**).* A mixture of **3c** (0.50 g, 1.06 mmol) and 5% ethanolic KOH (20 mL) afforded **4c** as a pink solid (0.405 g, 88%), mp 208–209 °C; ν_{max} (ATR) 637.7, 809.6, 837.0, 860.7, 1023.7, 1044.7, 1181.3, 1246.7, 1516.0, 1608.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.95 (s, 3H), 7.13 (d, *J* 8.7 Hz, 2H), 7.47 (d, *J* 8.7 Hz, 2H), 7.70 (d, *J* 2.1 Hz, 1H), 8.12 (d, *J* 2.1 Hz, 1H), 8.38 (s, 1H), 9.33 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.8, 115.0, 118.3, 119.1, 119.5, 123.9, 126.8, 128.2, 132.6, 135.2, 135.3, 138.2, 141.7, 146.7, 160.8; *m*/*z* 434 (100%, $C_{17}H_{12}N_3O^{79}Br^{81}Br^+$); HRMS (ES): MH^+, found 431.9345. $C_{17}H_{12}N_3O^{79}Br_2^+$ requires 431.9347.

*4.1.5. Suzuki cross-coupling of **4** with arylboronic acids. Typical procedure.* 1-Aryl-6,8-dibromo-1*H*-pyrazolo[4,3-*c*]quinoline **4** (1 equiv), arylboronic acid (2.5 equiv), $PdCl_2(PPh_3)_2$ (5% of **4**), PCy_3 (10% of **4**), K_2CO_3 (2 equiv), and 3/1 DMF–water (ca. 5 mL/mmol of **4**) were added to a two-necked flask equipped with a stirrer bar, rubber septum, and a condenser. The mixture was flushed for 20 min 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 3 h and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water and the precipitate was filtered on a sintered funnel. The solid product was taken-up into chloroform and the solution was dried with $MgSO_4$, filtered, and then evaporated under reduced pressure. The product was recrystallized to afford the 1,6,8-triaryl-1*H*-pyrazolo[4,3-*c*]quinoline **5**. The following products were prepared in this fashion.

*4.1.5.1. 1-(4-Fluorophenyl)-6,8-diphenyl-1H-pyrazolo[4,3-c]quinoline (**5a**).* A mixture of **4a** (0.50 g. 1.19 mmol), phenylboronic acid (0.36 g, 2.97 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.059 mmol), PCy_3 (0.033 g, 0.119 mmol), and K_2CO_3 (0.328 g, 2.38 mmol) in DMF–water (20 mL) afforded **5a** as an off-white solid (0.381 g, 77%), mp 260–262 °C (ethanol); ν_{max} (ATR) 697.7, 759.7, 820.4,

884.6, 1213.6, 1378.9, 1512.8, 1582.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.47 (m, 8H), 7.52 (t, *J* 7.8 Hz, 2H), 7.65–7.73 (m, 4H), 7.81 (d, *J* 2.1 Hz, 1H), 7.97 (d, *J* 2.1 Hz, 1H), 8.37 (s, 1H), 9.26 (s, 1H); δ_C (75 MHz, $CDCl_3$) 116.7 (d, $^2J_{CF}$ 23.0 Hz), 116.8, 118.4, 118.8, 127.0, 127.6, 127.9, 128.0, 129.0, 129.2 (d, $^3J_{CF}$ 8.8 Hz), 129.5, 130.6, 135.6, 136.9 (d, $^3J_{CF}$ 3.0 Hz), 138.3, 139.8 (2×C), 140.2, 142.5, 142.9, 145.2, 163.1 (d, $^1J_{CF}$ 249.3 Hz); *m*/*z* 416 (100%, MH^+); HRMS (ES): MH^+, found 416.1560. $C_{28}H_{19}N_3F^+$ requires 416.1563.

*4.1.5.2. 1-(4-Chlorophenyl)-6,8-diphenyl-1H-pyrazolo[4,3-c]quinoline (**5b**).* A mixture of **4b** (0.50 g. 1.15 mmol), phenylboronic acid (0.35 g, 2.87 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.058 mmol), PCy_3 (0.032 g, 0.115 mmol), and K_2CO_3 (0.317 g, 2.30 mmol) in DMF–water (20 mL) afforded **5b** as an off-white solid (0.320 g, 65%), mp 280–282 °C (ethanol); ν_{max} (ATR) 797.7, 822.3, 833.4, 866.9, 1090.1, 1223.7, 1379.1, 1507.3, 1582.9 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.55 (m, 8H), 7.65 (s, 4H), 7.71 (d, *J* 8.1 Hz, 2H), 7.83 (d, *J* 2.1 Hz, 1H), 7.98 (d, *J* 2.1 Hz, 1H), 8.38 (s, 1H), 9.26 (s, 1H); δ_C (75 MHz, $CDCl_3$) 116.7, 118.6, 118.9 (2×C), 127.0, 127.6, 127.9, 128.0, 128.5, 129.1, 129.4, 129.9, 130.6, 135.7, 135.8, 138.3, 139.3, 139.8, 140.2, 142.5, 142.9, 145.2; *m*/*z* 434 (38%, $C_{28}H_{19}N_3{}^{35}Cl^+$), 432 (100%, MH^+); HRMS (ES): MH^+, found 432.1266. $C_{28}H_{19}N_3{}^{35}Cl^+$ requires 432.1266.

*4.1.5.3. 1-(4-Methoxyphenyl)-6,8-diphenyl-1H-pyrazolo[4,3-c]quinoline (**5c**).* A mixture of **4c** (0.50 g, 1.154 mmol), phenylboronic acid (0.35 g, 2.88 mmol), $PdCl_2(PPh_3)_2$ (0.041 g, 0.057 mmol), PCy_3 (0.032 g, 0.115 mmol), and K_2CO_3 (0.319 g, 2.308 mmol) in DMF–water (20 mL) afforded **5c** as a red solid (0.340 g, 69%), mp 238–240 °C (ethanol); ν_{max} (ATR) 696.6, 758.6, 847.7, 883.5, 1019.0, 1027.4, 1177.4, 1528.4, 1583.5 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.95 (s, 3H), 7.16 (d, *J* 9.0 Hz, 2H), 7.31–7.55 (m, 8H), 7.59 (d, *J* 9.0 Hz, 2H), 7.72 (dd, *J* 1.5 and 7.8 Hz, 2H), 7.85 (d, *J* 1.8 Hz, 1H), 7.96 (d, *J* 1.8 Hz, 1H), 8.36 (s, 1H), 9.25 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.8, 114.9, 117.0, 118.2, 119.1, 127.1, 127.5, 127.7, 128.0, 128.6, 128.9, 129.2, 130.6, 133.6, 135.2, 137.9, 139.8, 139.9, 140.4, 142.3, 142.8, 145.3, 160.6; *m*/*z* 428 (100%, MH^+); HRMS (ES): MH^+, found 428.1758. $C_{29}H_{22}N_3O^+$ requires 428.1763.

*4.1.5.4. 1,6,8-Tris(4-fluorophenyl)-1H-pyrazolo[4,3-c]quinoline (**5d**).* A mixture of **4a** (0.50 g, 1.19 mmol), 4-fluorophenylboronic acid (0.42 g, 2.975 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.059 mmol), PCy_3 (0.033 g, 0.119 mmol), and K_2CO_3 (0.328 g, 2.38 mmol) in DMF–water (20 mL) afforded **5d** as a light brown solid (0.380 g, 71%), mp 252–254 °C (ethanol); ν_{max} (ATR) 833.2, 858.0, 936.2, 1157.9, 1221.3, 1503.9, 1601.9 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.11 (t, *J* 8.1 Hz, 2H), 7.20 (t, *J* 7.8 Hz, 2H), 7.36 (t, *J* 8.4 Hz, 2H), 7.37 (m, 4H), 7.39 (d, *J* 8.4 Hz, 2H), 7.73 (d, *J* 2.1 Hz, 1H), 7.87 (d, *J* 2.1 Hz, 1H), 8.38 (d, 1.2 Hz, 1H), 9.26 (d, *J* 1.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 115.0 (d, $^2J_{CF}$ 21.4 Hz), 116.0 (d, $^2J_{CF}$ 21.4 Hz), 116.8 (d, $^2J_{CF}$ 23.04 Hz), 118.5, 118.8, 128.6 (d, $^3J_{CF}$ 8.0 Hz), 129.0, 129.1, 129.2 (d, $^3J_{CF}$ 8.8 Hz), 132.2 (d, $^3J_{CF}$ 8.0 Hz), 135.6, 135.9 (d, $^4J_{CF}$ 3.2 Hz), 136.0 (d, $^4J_{CF}$ 3.2 Hz), 136.9 (d, $^4J_{CF}$ 3.2 Hz), 137.3, 139.7, 141.5, 142.7, 145.3, 162.5 (d, $^1J_{CF}$ 245.2 Hz), 162.7 (d, $^1J_{CF}$ 246.7 Hz), 163.1 (d, $^1J_{CF}$ 249.6 Hz); *m*/*z* 452 (100%, MH^+); HRMS (ES): MH^+, found 452.1372. $C_{28}H_{17}N_3F_3^+$ requires 452.1375.

*4.1.5.5. 1-(4-Chlorophenyl)-6,8-bis(4-fluorophenyl)-1H-pyrazolo[4,3-c]quinoline (**5e**).* A mixture of **4b** (0.50 g, 1.15 mmol), 4-fluorophenylboronic acid (0.402 g, 2.875 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.0575 mmol), PCy_3 (0.032 g, 0.115 mmol), and K_2CO_3 (0.318 g, 2.30 mmol) in DMF–water (20 mL) afforded **5e** as an off-white solid (0.366 g, 68%), mp 260–262 °C (ethanol); ν_{max} (ATR) 799.5, 857.1, 935.9, 1090.1, 1223.7, 1507.3, 1600.4 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.12 (t, *J* 8.4 Hz, 2H), 7.20 (t, *J* 8.4 Hz, 2H), 7.40 (t, *J* 8.4 Hz, 2H), 7.64 (s, 4H), 7.68 (t, *J* 8.4 Hz, 2H), 7.75 (d, *J* 1.8 Hz, 1H), 7.88 (d, *J* 1.8 Hz, 1H), 8.40 (d, *J* 1.2 Hz, 1H), 9.26 (d, *J* 1.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 115.0 (d, $^2J_{CF}$ 21.4 Hz), 116.0 (d, $^2J_{CF}$ 21.4 Hz), 116.8, 118.7, 118.8, 128.5 (2×C), 128.6 (d, $^3J_{CF}$ 8.3 Hz), 129.1, 129.9, 132.2 (d, $^3J_{CF}$ 8.0 Hz), 135.8 (d, $^4J_{CF}$ 3.4 Hz), 135.9, 136.0 (d, $^4J_{CF}$ 3.4 Hz), 137.3, 139.3, 139.7, 141.6, 142.7, 145.3, 162.5 (d, $^1J_{CF}$ 245.3 Hz), 162.8 (d, $^1J_{CF}$ 246.7 Hz); *m*/*z* 470 (37%, $C_{28}H_{17}N_3F_2{}^{37}Cl^+$), 468.1085 (100%, $C_{28}H_{17}N_3F_2{}^{35}Cl^+$); HRMS (ES): MH^+, found $C_{28}H_{17}N_3{}^{35}ClF_2^+$ requires 468.1085.

*4.1.5.6. 6,8-Bis(4-fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline (**5f**).* A mixture of **4c** (0.50 g, 1.14 mmol), 4-fluorophenylboronic acid (0.40 g, 2.86 mmol), $PdCl_2(PPh_3)_2$ (0.041 g, 0.057 mmol), PCy_3 (0.032 g, 0.114 mmol), and K_2CO_3 (0.314 g, 2.308 mmol) in DMF–water (20 mL) afforded **5f** as a pink solid (0.317 g, 60%), mp 256–258 °C (ethanol); ν_{max} (ATR) 802.4, 1220.3, 1378.9, 1515.2, 1584.8, 1601.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.96 (s, 3H), 7.08 (t, *J* 8.4 Hz, 2H), 7.16 (d, *J* 8.7 Hz, 2H), 7.20 (t, *J* 8.4 Hz, 2H), 7.41 (t, *J* 8.4 Hz, 2H), 7.58 (d, *J* 8.7 Hz, 2H), 7.68 (t, *J* 8.4 Hz, 2H), 7.78 (d, *J* 2.1 Hz, 1H), 7.87 (d, *J* 2.1 Hz, 1H), 8.37 (s, 1H), 9.26 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.8, 114.8, 114.9 (d, $^2J_{CF}$ 21.3 Hz), 115.9 (d, $^2J_{CF}$ 21.3 Hz), 117.1, 118.3, 119.0, 128.5 (2×C), 128.7 (d, $^3J_{CF}$ 8.2 Hz), 132.2 (d, $^3J_{CF}$ 8.1 Hz), 133.5, 135.2, 135.9 (d, $^3J_{CF}$ 3.6 Hz), 136.1 (d, $^3J_{CF}$ 3.5 Hz), 137.0, 139.7, 141.3, 142.6, 145.4, 160.6, 162.4 (d, $^1J_{CF}$ 255.1 Hz), 162.7 (d, $^1J_{CF}$ 246.2 Hz); *m*/*z* 464 (100%, MH^+); HRMS (ES): MH^+, found 464.1576. $C_{29}H_{20}N_3OF_2^+$ requires 464.1574.

*4.1.5.7. 1-(4-Fluorophenyl)-6,8-bis[2-(4-fluorophenyl)ethenyl]-1H-pyrazolo[4,3-c]quinoline (**5g**).* A mixture of **4a** (0.50 g, 1.19 mmol), *trans*-2-(4-fluorophenyl)vinylboronic acid (0.49 g, 2.97 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.059 mmol), PCy_3 (0.033 g, 0.119 mmol), and K_2CO_3 (0.328 g, 2.380 mmol) in DMF–water (20 mL) afforded **5g** as a light brown solid (0.43 g, 72%), mp 234–236 °C (ethanol); ν_{max} (ATR) 789.0, 813.1, 844.5, 956.6, 1156.1, 1230.9, 1523.6, 1600.0 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.92 (d, *J* 2.7 Hz, 2H), 7.07 (t, *J* 8.7 Hz, 2H), 7.09 (t, *J* 8.7 Hz, 2H), 7.30 (d, *J* 16.5 Hz, 1H), 7.38 (t, *J* 8.7 Hz, 2H), 7.45 (t, *J* 8.7 Hz, 2H), 7.52 (d, *J* 1.8 Hz, 1H), 7.65 (t, *J* 8.7 Hz, 2H), 7.66 (t, *J* 8.7 Hz, 2H), 8.13 (d, *J* 1.8 Hz, 1H), 8.37 (s, 1H), 8.46 (t, *J* 16.5 Hz, 1H), 9.24 (s, 1H); δ_C (75 MHz, $CDCl_3$) 115.6 (d, $^2J_{CF}$ 21.6 Hz), 115.7 (d, $^2J_{CF}$ 21.6 Hz), 116.4, 116.6 (d, $^2J_{CF}$ 22.8 Hz), 118.3, 118.6, 122.8, 125.2, 127.3, 128.1 (d, $^3J_{CF}$ 8.0 Hz), 128.5 (d, $^3J_{CF}$ 8.0 Hz), 128.9, 129.2 (d, $^3J_{CF}$ 8.9 Hz), 129.6, 132.8 (d, $^4J_{CF}$ 3.5 Hz), 133.7 (d, $^4J_{CF}$ 3.2 Hz), 134.5, 135.6, 136.8 (d, $^4J_{CF}$ 3.4 Hz), 137.0, 139.4, 142.8, 144.2, 162.5 (d, $^1J_{CF}$ 246.2 Hz), 162.6 (d, $^1J_{CF}$ 246.8 Hz), 163.0 (d, $^1J_{CF}$ 248.8 Hz); *m*/*z* 504 (100%, MH^+); HRMS (ES): MH^+, found 504.1688. $C_{32}H_{21}N_3F_3^+$ requires 504.1688.

*4.1.5.8. 1-(4-Chlorophenyl)-6,8-bis[2-(4-fluorophenyl)ethenyl]-1H-pyrazolo[4,3-c]quinoline (**5h**).* A mixture of **4a** (0.50 g, 1.15 mmol), *trans*-2-(4-fluorophenyl)vinylboronic acid (0.476 g, 2.87 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.058 mmol), PCy_3 (0.032 g, 0.115 mmol), and K_2CO_3 (0.320 g, 2.300 mmol) in DMF–water (20 mL) afforded **5h** as a gray solid (0.421 g, 70%), mp 257–259 °C (ethanol); ν_{max} (ATR) 788.8, 811.4, 836.0, 955.6, 1091.5, 1156.9, 1229.2, 1522.9, 1599.8 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.94 (s, 2H), 7.08 (t, *J* 8.7 Hz, 2H), 7.09 (t, *J* 8.7 Hz, 2H), 7.30 (d, *J* 16.5 Hz, 1H), 7.47 (t, 8.7 H, 2H), 7.59 (d, *J* 1.5 Hz, 1H), 7.608–7.69 (m, 6H), 8.13 (d, *J* 1.5 Hz, 1H), 8.38 (s, 1H), 8.46 (d, *J* 16.5 Hz, 1H), 9.23 (s, 1H); δ_C (75 MHz, $CDCl_3$) 115.6 (d, $^2J_{CF}$ 21.3 Hz), 115.8 (d, $^2J_{CF}$ 21.3 Hz), 116.5, 118.3, 118.8, 123.1, 125.3, 127.3, 128.2 (d, $^3J_{CF}$ 8.0 Hz), 128.5, 128.6 (d, $^3J_{CF}$ 8.0 Hz), 129.1, 129.7, 132.8 (d, $^4J_{CF}$ 3.4 Hz), 133.8 (d, $^4J_{CF}$ 3.4 Hz), 134.7, 135.6, 135.9, 137.2, 139.3, 139.4, 142.9, 144.2, 162.5 (d, $^1J_{CF}$ 246.7 Hz), 162.6 (d, $^1J_{CF}$ 246.7 Hz); *m*/*z* 522 (41%, $C_{32}H_{21}N_3{}^{35}ClF_2^+$), 520 (100%, $C_{32}H_{21}N_3{}^{35}ClF_2^+$); HRMS (ES): MH^+, found 520.1392. $C_{32}H_{21}N_3{}^{35}ClF_2^+$ requires 520.1396.

*4.1.5.9. 6,8-Bis[2-(4-fluorophenyl)ethenyl]-1-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline (**5i**).* A mixture of **4a** (0.50 g, 1.14 mmol), *trans*-2-(4-fluorophenyl)vinylboronic acid (0.472 g,

2.85 mmol), $PCl_2(PPh_3)_2$ (0.041 g, 0.057 mmol), PCy_3 (0.032 g, 0.144 mmol), and K_2CO_3 (0.315 g, 2.28 mmol) in DMF–water (20 mL) afforded **5i** as a pink solid (0.48 g, 81%), mp 224–226 °C (ethanol); ν_{max} (ATR) 790.2, 842.3, 955.7, 1227.9, 1505.5, 1585.9, 1599.0 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.97 (s, 3H), 6.91 (s, 2H), 7.07 (d, *J* 8.7 Hz, 2H), 7.08 (d, *J* 8.7 Hz, 2H), 7.17 (d, *J* 8.7 Hz, 2H), 7.26 (d, *J* 16.5 Hz, 1H), 7.44 (d, *J* 7.8 Hz, 2H), 7.56 (d, *J* 8.7 Hz, 2H), 7.58 (s, 1H), 7.66 (d, *J* 8.7 Hz, 2H), 8.10 (d, *J* 1.5 Hz, 1H), 8.35 (s, 1H), 8.46 (d, *J* 16.5 Hz, 1H), 9.23 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.7, 114.8, 115.6 (d, $^2J_{CF}$ 21.4 Hz), 115.7 (d, $^2J_{CF}$ 21.4 Hz), 116.7, 118.4, 118.5, 122.9, 125.4, 127.5, 128.1 (d, $^3J_{CF}$ 8.0 Hz), 128.4 (d, $^3J_{CF}$ 8.0 Hz), 128.5, 128.8, 129.5, 132.9 (d, $^4J_{CF}$ 3.4 Hz), 133.6, 133.8 (d, $^4J_{CF}$ 3.4 Hz), 134.4, 135.2, 136.9, 139.5, 142.8, 144.4, 160.5, 162.4 (d, $^1J_{CF}$ 245.9 Hz), 162.5 (d, $^1J_{CF}$ 246.7 Hz); *m*/*z* 516 (100%, MH^+); HRMS (ES): MH^+, found 516.1887. $C_{33}H_{24}N_3OF_2^+$ requires 516.1887.

*4.1.5.10. 1-(4-Fluorophenyl)-6,8-bis[2-(4-methoxyphenyl) ethenyl]-1H-pyrazolo[4,3-c]quinoline (**5j**).* A mixture of **4a** (0.50 g, 1.19 mmol), *trans*-2-(4-methoxyphenyl)vinylboronic (0.529 g, 2.97 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.057 mmol), PCy_3 (0.033 g, 0.119 mmol), and K_2CO_3 (0.330 g, 2.380 mmol) in DMF–water (20 mL) afforded **5j** as an orange solid (0.404 g, 65%), mp 216–218 °C (ethanol); ν_{max} (ATR) 841.6, 1031.6, 1173.5, 1247.5, 1508.3, 1601.6 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.84 (s, 3H), 3.85 (s, 3H), 6.90 (s, 2H), 6.92 (d, *J* 8.7 Hz, 2H), 6.94 (d, *J* 8.7 Hz, 2H), 7.29 (d, *J* 16.5 Hz, 1H), 7.37 (t, *J* 8.7 Hz, 2H), 7.42 (d, *J* 8.7 Hz, 2H), 7.48 (d, *J* 1.8 Hz, 1H), 7.64 (d, *J* 8.7 Hz, 2H), 7.65 (t, *J* 8.7 Hz, 2H), 8.12 (d, *J* 1.8 Hz, 1H), 8.35 (s, 1H), 8.41 (d, *J* 16.5 Hz, 1H), 9.20 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.3, 55.4, 114.0, 114.2, 116.7 (d, $^2J_{CF}$ 22.7 Hz), 117.7, 118.6, 122.7, 123.4, 125.6, 127.4, 127.9, 128.3, 129.2 (d, $^3J_{CF}$ 8.9 Hz), 129.5, 129.7, 130.4, 130.5, 135.1, 135.6, 136.9 (d, $^3J_{CF}$ 3.2 Hz), 137.4, 139.6, 142.7, 143.9, 159.4, 159.6, 163.0 (d, $^1J_{CF}$ 249.0 Hz); *m*/*z* 528 (100%, MH^+); HRMS (ES): MH^+, found 528.2093. $C_{34}H_{26}N_3O_2F^+$ requires 528.2087.

*4.1.5.11. 1-(4-Chlorophenyl)-6,8-bis[2-(4-methoxyphenyl) ethenyl]-1H-pyrazolo[4,3-c]quinoline (**5k**).* A mixture of **4b** (0.50 g, 1.15 mmol), *trans*-2-(4-methoxyphenyl)vinylboronic acid (0.512 g, 2.87 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.057 mmol), PCy_3 (0.032 g, 0.144 mmol), and K_2CO_3 (0.320 g, 2.380 mmol) in DMF–water (20 mL) afforded **5k** as a light brown solid (0.445 g, 82%), mp 229–231 °C (ethanol); ν_{max} (ATR) 841.1, 954.9, 1173.4, 1508.7, 1601.9 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.84 (s, 3H), 3.85 (s, 3H), 6.89 (s, 2H), 6.92 (d, *J* 8.7 Hz, 2H), 6.93 (d, *J* 8.7 Hz, 2H), 7.29 (d, *J* 16.5 Hz, 1H), 7.44 (d, *J* 7.8 Hz, 2H), 7.54 (s, 1H), 7.61–7.67 (m, 6H), 8.10 (s, 1H), 8.34 (d, *J* 0.9 Hz, 1H), 8.39 (d, *J* 16.5 Hz, 1H), 9.19 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.2, 55.3, 114.1, 114.2, 116.3, 117.4, 118.7, 122.8, 123.3, 125.4, 127.9, 128.3, 128.5, 129.4, 129.7, 129.8, 130.3, 130.5, 135.1, 135.4, 135.7, 137.3, 139.2, 139.3, 142.6, 143.7, 159.4, 159.6; *m*/*z* 544 (100%, $C_{34}H_{27}N_3O_2{}^{35}Cl^+$); HRMS (ES): MH^+, found 544.1790. $C_{34}H_{27}N_3O_2{}^{35}Cl^+$ requires 544.1792.

*4.1.5.12. 1,6,8-Tris[2-(4-methoxyphenyl)ethenyl]-1H-pyrazolo [4,3-c]quinoline (**5l**).* A mixture of **4c** (0.50 g, 1.14 mmol), *trans*-2-(4-methoxyphenyl)vinylboronic acid (0.507 g, 2.80 mmol), $PdCl_2(PPh_3)_2$ (0.041 g, 0.057 mmol), PCy_3 (0.032 g, 0.144 mmol), and K_2CO_3 (0.316 g, 2.28 mmol) in DMF–water (20 mL) afforded **5l** as a red solid (0.427 g, 70%), mp 227–229 °C (ethanol); ν_{max} (ATR) 813.3, 833.8, 844.4, 1026.8, 1172.8, 1242.6, 1507.7, 1600.4 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (s, 3H), 3.86 (s, 3H), 3.98 (s, 3H), 6.89 (s, 2H), 6.93 (d, *J* 8.7 Hz, 2H), 6.94 (d, *J* 8.7 Hz, 2H), 7.18 (d, *J* 8.7 Hz, 2H), 7.30 (d, *J* 16.5 Hz, 1H), 7.42 (d, *J* 8.7 Hz, 2H), 7.54 (d, *J* 1.5 Hz, 1H), 7.57 (d, *J* 8.7 Hz, 2H), 7.64 (d, *J* 8.7 Hz, 2H), 8.10 (d, *J* 1.5 Hz, 1H), 8.34 (s, 1H), 8.42 (d, *J* 16.5 Hz, 1H), 9.21 (s, 1H); δ_C (75 MHz, $CDCl_3$) 55.3, 55.4, 55.7, 114.0, 114.2, 114.8, 116.7, 117.7, 118.4, 122.7, 123.5, 125.7, 127.8, 128.3, 128.6, 129.5, 129.6, 130.2, 130.6, 133.6, 134.9, 135.1, 137.2, 139.6, 142.6, 143.9, 159.5, 160.5; *m*/*z* 540 (100%, MH^+); HRMS (ES): MH^+, found 540.2294. $C_{35}H_{30}N_3O_3^+$ requires 540.2287.

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