Synthesis and Photophysical Property Studies of the 2,6,8-Triaryl-4-(phenylethynyl)quinazolines

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Received: 29 October 2013; in revised form: 30 December 2013 / Accepted: 6 January 2014 / Published: 10 January 2014

Abstract: The 2-aryl-6,8-dibromo-4-chloroquinazolines derived from the 2-aryl-6,8-dibromoquinazolin-4(3H)-ones were subjected to the Sonogashira cross-coupling with terminal acetylenes at room temperature to afford novel 2-aryl-6,8-dibromo-4-(alkynyl)quinazoline derivatives. Further transformation of the 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines via Suzuki-Miyaura cross-coupling with arylboronic acids occurred without selectivity to afford the corresponding 2,6,8-triaryl-4-(phenylethynyl)quinazolines. The absorption and emission properties of these polysubstituted quinazolines were also determined.

Keywords: 2-aryl-6,8-dibromoquinazolin-4(3H)-ones; 2-aryl-6,8-dibromo-4-chloroquinazolines; Sonogashira cross-coupling; 2-aryl-6,8-dibromo-4-(alkynyl)quinazolines; Suzuki cross-coupling; 2,6,8-triaryl-4-(phenylethynyl)quinazolines; photophysical properties
1. Introduction

Halogenated quinazolines constitute important substrates for structural elaboration via metal-catalyzed carbon–carbon bond formation to afford novel polysubstituted quinazoline derivatives. It has been established that the order of reactivity of carbon-halogen bonds, C-I > C-Br >> C-Cl, in transition metal-mediated cross-coupling of aryl/heteroaryl halides allows selective coupling with iodides or bromides in the presence of chlorides [1,2]. Although the bond dissociation energy (BDE) of the C-Cl bond at the 4-position (84.8 kcal/mol at B3LYP) of 6-bromo-2,4-dichloroquinazoline is larger than that of the weaker C-Br bond (83 kcal/mol at B3LYP) [3], the selectivity of Pd-catalyzed cross-coupling favours C-4 substitution due to $\alpha$-nitrogen effect [4,5]. For cross-coupling reactions employing 2,4-dichloroquinazoline, for example, exclusive selectivity for the most electrophilic C-4 position is favoured [3,4,6]. Likewise, regioselective Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 2,4,7-trichloroquinazoline with aryl- and heteroarylboronic acids favours coupling at C-4 position albeit in low yield due to competitive hydrolysis at this site [7]. Attempts to achieve monosubstitution via the Stille cross-coupling with 6-bromo-2,4-dichloroquinazoline, on the other hand, resulted in mixtures of the C-4 (major) and C-6 (minor) cross-coupled products [4]. However, Sonogashira cross-coupling of 6-bromo-2,4-dichloroquinazoline with stoichiometric amount of terminal alkynes led to exclusive replacement of the 4-chloro atom [5]. During our research on the development of novel polysubstituted heterocycles [8,9], we became interested in the synthesis of polysubstituted quinazolines in which the electron-deficient quinazoline framework is linked to the 4-phenyl ring via $\pi$-conjugated spacer and to the 6- and 8-aryl rings directly to comprise donor-$\pi$-acceptor systems. We envisioned that the 2-aryl-6,8-dibromo-4-chloroquinazolines represent suitable candidates for sequential Pd-catalyzed Sonogashira and Suzuki cross-coupling to afford the requisite polysubstituted quinazolines with potential photophysical properties.

2. Results and Discussion

2.1. Synthesis of the 2-Aryl-6,8-dibromoquinazolin-4(3H)-ones

The first task was to synthesize the 2-aryl-6,8-dibromoquinazolin-4(3H)-ones to serve as substrates for the requisite 2-aryl-6,8-dibromo-4-chloroquinazolines. The potentially tautomeric quinazolin-4(3H)-one moiety itself is readily accessible via dehydrogenation of the corresponding 2,3-dihydroquinazolin-4(1H)-one precursors using oxidants such as KMnO$_4$ [10], CuCl$_2$ [11], DDQ [12] and MnO$_2$ [13] in stoichiometric or large access. The 2-substituted quinazolin-4(3H)-ones have also been synthesized directly from anthranilamide and aldehydes using NaHSO$_3$ [14], DDQ [15], CuCl$_2$ (3 equiv.) [16], FeCl$_3$.6H$_2$O [17] or I$_2$ [18]. In this investigation, we exploited the combined electrophilic (cyclocondensation) and oxidative (dehydrogenation) properties of iodine on 3,5-dibromobenzamide 1 and benzaldehyde derivatives 2a–d in ethanol under reflux for 7 h to afford products 3a–d in a single-pot operation (Scheme 1). A series of the analogous 2,3-disubstituted 6,8-dibromoquinazolin-4(3H)-ones have been prepared before via the reaction of 6,8-dibromo-2-methyl-1-benzoxazin-4(3H)-one with nitrogen nucleophiles such as hydrazine hydrate, sulphamides and 4-aminoacetoephone [19]. Likewise, the 6-fluoro-8-iodo/bromo-2-methyl-1-benzoxazin-4(3H)-ones reacted with aqueous ammonia under reflux to yield the 6-fluoro-8-(iodo/bromo)-2-methylquinazolin-4(3H)-ones [20].
Scheme 1. (i) Iodine-promoted cyclocondensation.

| R   | % Yield |
|-----|---------|
| 3a  | 80      |
| 3b  | 89      |
| 3c  | 94      |
| 3d  | 91      |

Reagents and conditions: (i) I$_2$ (2 equiv.), ethanol, heat, 7 h.

2.2. Oxidative Aromatization of 2-Aryl-6,8-dibromoquinazolin-4(3H)-Ones

The oxidative aromatization of quinazolin-4(3H)-one moiety into 4-chloroquinazoline derivatives is often effected by refluxing the NH-4-oxo compound in an excess of POCl$_3$ [21] or POCl$_3$-PCl$_5$ mixture [22]. Oxidative aromatization of compounds 3a–d with POCl$_3$, POCl$_3$-amine or POCl$_3$-DMF mixture under reflux led to incomplete conversion (tlc monitoring) to the requisite 4-chloroquinazolines. The 4-chloroquinazolines 4a–d were prepared in high yields and purity using thionyl chloride in the presence of DMF under reflux for 2 h (Scheme 2).

Scheme 2. Oxidative aromatization of 3a–d to afford the 4-chloroquinazolines.

| R    | % Yield |
|------|---------|
| 4a   | 77      |
| 4b   | 81      |
| 4c   | 77      |
| 4d   | 91      |

Reagents and conditions: (i) DMF, SOCl$_2$, reflux, 2 h.

With the halogenated quinazolines 4a–d in hand, we next focused our attention on their reactivity in Sonogashira cross-coupling with terminal alkynes as models for C-C bond formation.

2.3. Sonogashira Cross-Coupling of the 2-Aryl-6,8-dibromo-4-chloroquinazolines

Sonogashira cross-coupling of 4a with phenylacetylene (1.5 equiv.) in the presence of tetrakis(triphenylphosphine)palladium(0), CuI and Cs$_2$CO$_3$ in THF at room temperature for 24 h
afforded product 5a, exclusively. The reaction conditions were extended to other substrates using phenylacetylene, 2-ethynylpyridine and 3-butyln-2-ol to afford products 5b–h (Scheme 3). The analogous 2-substituted quinazolines bearing alkynyl substituent on the C-4 or C-6 position exhibit excellent EGFR or Aurora A kinase inhibition activity [23].

Scheme 3. Sonogashira cross-coupling of 4a–d with terminal alkynes.

\[
\begin{array}{ccc}
\text{R} & \text{R'} & \% \text{ Yield 5} \\
5a & 4-\text{H} & -\text{C}_2\text{H}_5 & 60 \\
5b & 4-\text{F} & -\text{C}_2\text{H}_5 & 72 \\
5c & 4-\text{Cl} & -\text{C}_2\text{H}_5 & 69 \\
5d & 4-\text{OMe} & -\text{C}_2\text{H}_5 & 72 \\
5e & 4-\text{H} & 2-\text{pyridyl}- & 65 \\
5f & 4-\text{F} & 2-\text{pyridyl}- & 67 \\
5g & 4-\text{OMe} & 2-\text{pyridyl}- & 53 \\
5h & 4-\text{H} & -\text{CH(OH)}\text{CH}_3 & 56 \\
\end{array}
\]

Reagents and conditions: (i) R'\equiv\text{CH}, \text{Pd(PPh}_3)_4, \text{CuI, Cs}_2\text{CO}_3, \text{THF, rt., 24 h.}

The presence of the two bromine atoms in compounds 5 makes them suitable candidates for further transformation through transition metal-catalyzed cross-coupling or metal exchange reactions to enable adequate diversity on the heterocycle. This prompted us to explore the reactivity of compounds 5 in palladium catalyzed Suzuki-Miyaura cross-coupling with arylboronic acids as models for Csp2–Csp2 bond formation.

2.4. Suzuki-Miyaura Cross-Coupling of the 2-Aryl-6,8-dibromo-4-(phenylethynyl)quinazolines

We first subjected compounds 5a–d to 1–1.5 equiv. of the arylboronic acid using PdCl2(PPh3)2/PCy3 as catalyst complex, K2CO3 as a base in dioxane (aq) under reflux. We isolated after 4 h the dicoupled product in low to moderate yields (30–50%) along with the starting material without any traces of the mono cross-coupled derivative. This observation was found to compare with previous literature results for the Suzuki-Miyaura cross-coupling reactions of the analogous 2-arylquinolines bearing two bromine atoms on the fused benzo ring [9] and 3,6,8-tribromoquinoline which occur without selectivity [24]. Computed bond dissociation energies at B3LYP and G3B3 levels reveal that all of the positions on the fused benzo ring of various heterocycles bearing identical halogen atoms have comparable C–X bond dissociation energies [3]. This presumably accounts for the observed lack of selectivity. In analogy with the literature precedents on the analogous
di/tribromoquinolines, we opted for the use of an excess arylboronic acid (2.5 equiv.) on compounds 5a–d and we isolated the corresponding tetrasubstituted quinazolines 6a–h in more than 50% yields (Scheme 4).

Scheme 4. Suzuki-Miyaura cross-coupling of 5a–d with arylvinylboronic acid.

| 5a–d | 6a–h |
|------|------|
| R | Ar | % Yield 6 |
| 6a | 4-H | -C₆H₅ | 61 |
| 6b | 4-F | -C₆H₅ | 69 |
| 6c | 4-Cl | -C₆H₅ | 88 |
| 6d | 4-OMe | -C₆H₅ | 68 |
| 6e | 4-H | 4-FC₆H₄- | 64 |
| 6f | 4-F | 4-FC₆H₄- | 76 |
| 6g | 4-Cl | 4-FC₆H₄- | 77 |
| 6h | 4-OMe | 4-FC₆H₄- | 58 |
| 6i | 4-H | 4-MeOC₆H₄- | 70 |
| 6j | 4-F | 4-MeOC₆H₄- | 62 |
| 6k | 4-Cl | 4-MeOC₆H₄- | 76 |
| 6l | 4-OMe | 4-MeOC₆H₄- | 52 |

Reagents and conditions: (i) ArB(OH)₂, PdCl₂(PCy₃)₂, K₂CO₃, dioxane (aq), reflux, 4 h.

The molecular backbone of compounds 6a–l comprises of the electron-deficient quinazoline framework as an electron-acceptor linked to the 4-phenyl ring via π-conjugated spacer and to the 6- and 8-aryl rings directly to comprise donor-π-acceptor systems.

2.5. Photophysical Property Studies of Compounds 6

To understand the influence of substituents on intramolecular charge transfer (ICT), absorption and emission spectra were measured in solution for compounds 6a–l. Electronic properties of compounds 6a–l were studied by UV/Vis and fluorescence spectroscopy in conjunction with quantum chemical calculations to establish the effect of substituents on the absorption and emission properties of these polysubstituted quinazoline derivatives.

2.5.1. UV-Vis Absorption Properties of the 2,6,8-Triaryl-4-(phenylethynyl)quinazolines 6a–l

The electronic absorption spectra of compounds 6a–l (Figures 1–3) were acquired in CHCl₃ and are characterized by intense broad bands in the ultraviolet region λ 270–295 nm. These bands are
attributed to the $\pi$-$\pi^*$ transition and the intramolecular donor-acceptor charge transfer absorption, respectively [25]. Both the absorption maxima and wavelength within each series are influenced by the variation of substituents on the para position of the aryl groups on the fused benzo ring and the 2-aryl substituents. In the case of the 2-phenyl derivatives $6a$, $6e$ and $6i$, intensity of the absorption bands decreases with increasing conjugative effect of the substituent on the 2-aryl ring, $6a > 6e > 6i$, and is accompanied by the reverse trend in peak broadening ($6a < 6e < 6i$). Moreover, the absorption wavelengths for $6e$ and $6i$ bearing the moderately and strongly donating 4-fluorophenyl- and 4-methoxyphenyl substituents are blue shifted relative to $6a$. Increased intensity of the absorption maxima is observed in the spectra of all the 2-(4-fluorophenyl) substituted derivatives $6b$, $6f$ and $6j$. The trend in molar extinction coefficients, $6j > 6f > 6b$, reflects the electron donating effect of the 6- and 8-aryl rings. The presence of a strong electron withdrawing 2-(4-chlorophenyl) group in compounds $6g$ and $6k$ causes the moderately resonance donating 4-fluorophenyl and strongly donating 4-methoxyphenyl groups to increase the $\pi$-$\pi^*$ transition resulting in increased absorption intensities for these compounds. Reduced intensity of the absorption maxima due to reduced $\pi$-$\pi^*$ transition accompanied by increased broadening are observed for $6c$ bearing the 6- and 8-phenyl groups. A combination of the 2-(4-methoxyphenyl) substituent with phenyl groups in $6d$ or with the 4-methoxyphenyl groups at the 6- and 8-positions in compounds $6h$ and $6l$ resulted in reduced intensity of the absorption maxima and increased broadening. Increased peak broadening and reduced intensity indicate that the strong electron donating methoxy groups interfere with the conjugation of the $\pi$ electrons presumably restricting the transition from bonding orbital to antibonding orbital. The additional low intensity band observed for compound $6l$ at $\mu ca. 320$ nm is probably the consequence of poor through-space charge transfer by the strongly electron donating 4-methoxyphenyl groups at the 6- and 8-positions.

**Figure 1.** UV-Vis spectra of $6a$–$d$ in CHCl$_3$ (0.022 mmol/L).
2.5.2. Emission properties of the 2,6,8-triaryl-4-(phenylethynyl)quinazolines 6a–l

The emission properties of compounds 6a–l have also been studied at room temperature in the moderately polar chloroform (Figures 4–6) and strongly polar DMF (Figures 7–9) at the excitation wavelengths, \( \lambda_{ex} = 380 \) nm and 400 nm, respectively. Their emission spectra in both solvents are characterized by intense single emission bands attributed to increased \( \pi-\pi^* \) transition resulting from direct \( \pi \)-electron delocalization by the aryl groups and through the conjugate bridge towards the electron-deficient quinazoline ring. Moreover, within each series the emission wavelengths, Stokes shift and the fluorescence quantum yields are influenced by the variation of substituents on either the para position of the 2-aryl or the 6- and 8-aryl groups (Table 1). Compounds 6a and 6e, for example, exhibit relatively reduced emission intensities in CHCl₃ than 6i bearing the 4-methoxyphenyl groups at
6- and 8-positions. Moreover, the following trends in Stokes shift and quantum yields: $6i > 6e > 6a$ are consistent with the conjugative effects of the 6- and 8-aryl substituents. Likewise, compound $6j$ exhibits larger Stokes shift than $6b$ and $6f$, but with lower quantum yield.

**Figure 4.** The emission spectra of compounds $6a$–$d$ ($\lambda_{ex} = 380$ nm) in CHCl$_3$ (0.022 mmol/L) at rt.

![Emission spectra of compounds 6a–d](image)

**Figure 5.** The emission spectra of compounds $6e$–$h$ ($\lambda_{ex} = 380$ nm) in CHCl$_3$ (0.022 mmol/L) at rt.

![Emission spectra of compounds 6e–h](image)
Figure 6. The emission spectra of compounds 6i–l (λex = 380 nm) in CHCl3 (0.022 mmol/L) at rt.

Since the π,π* state is much more polarizable than the ground state, a change in polarity of the medium has been previously found to cause measurable displacements of the π-π* transition towards the red bands [26]. The emission spectra of compounds 6a–l in DMF are also characterized by intense single emission bands (Figures 7–9). For the 4-phenylethynylquinazolines 6a, 6f and 6l bearing similar aryl groups at the 2-, 6- and 8-positions, the presence of strongly electron donating 4-methoxyphenyl groups in compound 6l leads to reduced emission intensity, which is accompanied by higher emission wavelength. A similar trend in intensity is observed for compounds 6c, 6g and 6k bearing a strong electron withdrawing chloro group on the 2-phenyl ring. However, a combination of the 2-(4-chlorophenyl) and 6- and 8-(4-fluorophenyl) groups leads to decreased emission wavelength. For the 2-(4-methoxyphenyl) derivatives 6d, 6h and 6l the emission intensity seems to be influenced by the electron donating effect of the 6- and 8-(4-ethoxyphenyl) rings. Additional interaction of DMF with the methoxy group of 6d would reduce the propensity of the 2-(4-methoxyphenyl) substituent for π-electron pair delocalization into the quinazoline ring. Such interaction would probably result in relatively less pronounced ICT and therefore reduced maxima for 6d (Figure 7). Relatively increased emission maxima observed in the spectra of compounds 6h (Figure 8) and 6l (Figure 9) in DMF are presumably due to increased π-electron delocalization into the quinazoline ring by the moderately and strongly donating 4-fluorophenyl and 4-methoxyphenyl groups, respectively. A combination of the 2-(4-methoxyphenyl) group and the 4-fluorophenyl groups at the 6- and 8-positions in 6h, on the other hand, leads to red shift of the emission maxima (Figure 8). An additional undesired red-shifted emission band of reduced intensity exhibited by 6h in DMF is presumably due to the re-absorption of light emitted and/or molecular excited state interaction with a ground state molecule leading to a partial transfer of charge in the molecule [27]. The emission spectra of compounds 6i–l showed pronounced red shifts with increasing solvent polarity and the intensities of their emission maxima in DMF seem to be influenced by the electronic effect of the substituent on the para position of the 2-phenyl group: MeO>H>F>Cl (Figure 9). The solvent-dependent emission characteristics may result from the dipolar interaction with DMF thus suggesting the ICT character of the emission state [28].
Figure 7. The emission spectra of compounds 6a–d (λex = 400 nm) in DMF (0.022 mmol/L) at rt.

Figure 8. The emission spectra of compounds 6e–h (λex = 400 nm) in DMF (0.022 mmol/L) at rt.

Figure 9. The emission spectra of compounds 6i–l (λex = 400 nm) in DMF (0.022 mmol/L) at rt.
Table 1. The absorption and emission data for compounds 6a–l.

| Compounds | \( \lambda_{\text{max}} \) (nm) | (\( \varepsilon \)) \( \times 10^3 \) | \( \lambda_{\text{em}} \) (nm) | \( \lambda_{\text{em}} \) (nm) | (a) Quantum yields (\( \Phi \)) | Stokes shift |
|-----------|--------|----------------|----------|----------|----------------|----------|
| CHCl3     | CHCl3  | DMF            | DMF      | CHCl3    |                |          |
| 6a        | 298.0  | 11.216         | 454.5    | 456.5    | 0.071          | 156.5    |
| 6b        | 295.6  | 11.163         | 455.0    | 459.0    | 0.078          | 159.4    |
| 6c        | 285.7  | 8.798          | 462.5    | 467.0    | 0.102          | 176.8    |
| 6d        | 280.3  | 8.601          | 455.0    | 458.0    | 0.105          | 174.7    |
| 6e        | 285.7  | 11.216         | 454.5    | 457.5    | 0.071          | 168.8    |
| 6f        | 284.5  | 11.181         | 456.0    | 457.0    | 0.081          | 171.5    |
| 6g        | 278.5  | 11.754         | 455.0    | 458.5    | 0.076          | 176.5    |
| 6h        | 286.6  | 10.271         | 463.0    | 466.5    | 0.088          | 176.4    |
| 6i        | 292.9  | 9.725          | 478.5    | 503.0    | 0.088          | 185.6    |
| 6j        | 276.4  | 12.063         | 479.0    | 504.5    | 0.072          | 202.6    |
| 6k        | 276.7  | 12.268         | 480.0    | 505.5    | 0.070          | 203.3    |
| 6l        | 273.4  | 10.422         | 479.5    | 496.0    | 0.081          | 206.1    |

(a) The relative quantum yields in CHCl3 were calculated according to the equation indicated under Experimental section using quinine sulfate as the standard (\( \Phi_q = 0.55 \)) in 0.5 M H2SO4.

2.5.3. Quantum Chemical Calculations

To further establish the structural features and molecular orbitals of compounds 6, we carried out a theoretical approach using density functional theory at the B3LYP/6-31G* level. The geometries were optimized using CAM-B3LYP/6-31G(d,p) [29] as implemented in Gaussian 09 suite [30] to obtain reasonable structures for the subsequent electronic structure computations. Based upon the CAM-B3LYP geometries, single-point ZINDO/S calculations were performed in chloroform as inexpensive, rapid and relatively accurate computations [31]. Compound 6a was chosen as a representative model to assign the absorption bands in the electronic spectra. The lowest energy band at 373 nm which represents \( S_1 \) state has moderate oscillator strength of \( ca. 0.5 \). This band is assigned mainly to the electronic transition between the frontier orbitals, where the HOMO→LUMO transition is the main contribution to the first excited state (\( S_1 \)). The HOMO is delocalized over the entire molecule whereas the LUMO shrinks toward the quinazoline core (Figure 10) and these represent \( \pi \) and \( \pi^* \) orbitals, respectively. The band located at 328 nm with oscillator strength of 0.3 is based on \( S_4 \) singlet state. This state consists of HOMO→LUMO (55%), HOMO-1→LUMO (15%) and HOMO→LUMO+1 (15%). The HOMO-1 is mainly localized over the 6- and 8-aryl groups, while the LUMO-1 is mainly localized on the quinazoline framework, 2- and 8-aryl moieties. The most intense band at 298 nm, on the other hand, arises from the electronic excitation to \( S_7 \) singlet state, which consists predominantly of HOMO-1→LUMO (47%) and HOMO→LUMO+1 (25%) transitions. Similar results were observed for the other compounds. Figure 10 shows the HOMO and LUMO of 6a, 6f and 6k and no great changes were observed on the electron density distributions.
Figure 10. Selected frontier molecular orbitals, HOMO-1, HOMO, LUMO and LUMO+1 of some representative compounds.
The computed spectral profiles of 6a, 6f and 6k were chosen and are presented in Figure 11 in order to reveal the effect of substitution on the para position of the 2-, 6- and 8-phenyl groups on the electronic spectra. The presence of electron donating group on the para positions of the phenyl ring causes a blue shift (ca. 15 nm) in compounds 6a to 6l. The calculated spectral data compares favourably with the experimental ones. The 4-methoxy groups in compound 6l, on the other hand, enhance the intramolecular charge transfer from the aryl groups into the quinazoline core more than the 4-fluoro substituents in 6f and the parent compound 6a. This could explain the appearance of CT-band in 6l compared to 6f. In the case of 6a, the CT-band at the longer wavelength is merged with the most intense band presumably due to the relatively poor resonance donation by the phenyl groups that are not able to make charge separation with the acceptor core.

**Figure 11.** The computed electronic absorption spectra of 6a, 6f and 6l.

### 3. Experimental

#### 3.1. 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. The UV-vis spectra were recorded on a Cecil CE 9500 (9000 Series) UV-Vis spectrometer while emission spectra were taken using a Perkin Elmer LS 55 fluorescence spectrometer. The quantum efficiencies of fluorescence ($\Phi_\text{fl}$) were obtained with the following equation:

$$\Phi_\lambda = \Phi_\text{st} \times \left( \frac{F_\lambda}{F_\text{st}} \right) \times \left( \frac{A_\text{st}}{A_\lambda} \right) \times \left( \frac{n_{\text{st}}^2}{n_\lambda^2} \right)$$

$F$ denotes the area under the fluorescence band ($F = \int I_\text{fl}(\lambda) \, d\lambda$, where $I_\text{fl}(\lambda)$ is the fluorescence intensity at each emission wavelength), $A$ denotes the absorbance at the excitation wavelength, and $n$ is the refractive index of the solvent [32]. NMR spectra were obtained as DMSO-$d_6$ or CDCl$_3$ 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 the University of Stellenbosch Mass Spectrometry Unit using Synapt G2 Quadrupole Time-of-flight mass spectrometer.

3.2. I$_2$–Promoted Cyclocondensation of 3,5-Dibromoanthranilamide and Arylaldehydes

Typical Procedure

A stirred mixture of 2-amino-3,5-dibromobenzamide 1 (1 equiv.), benzaldehyde derivative 2 (1.4 equiv.) and iodine (2 equiv.) in ethanol (20 mL per mmol of 1) was refluxed for 7 h. The mixture was allowed to cool to room temperature and then quenched with an ice-cold saturated sodium thiosulfate solution. The resulting precipitate was filtered on a sintered funnel and then washed with an ice-cold water. The solid product was recrystallized from acetonitrile to afford the corresponding quinazolin-4(3H)-one 3. The following products were prepared in this fashion:

6,8-Dibromo-2-phenylquinazolin-4(3H)-one (3a). A mixture of 1 (1.00 g, 3.37 mmol), benzaldehyde (2a) (0.43 g, 4.06 mmol) and iodine (1.19 g, 6.74 mmol) in ethanol (100 mL) afforded 3a as a white solid (1.08 g, 80%), m.p. 332–335 °C; $\nu$$_{\text{max}}$(ATR) 698, 742, 1147, 1486, 1599, 1681, 3174, 3380 cm$^{-1}$; $\delta$$_{\text{H}}$(300 MHz, DMSO-$d_6$) 7.56–7.64 (m, 3H), 8.21–8.25 (m, 2H), 8.26 (d, $J$ = 3.0 Hz, 1H), 8.38 (d, $J$ = 3.0 Hz, 1H), 12.93 (s, 1H); m/z 379 (100, MH$^+$); HRMS (ES): MH$^+$, found 378.9087. C$_{14}$H$_9$N$_2$O$_7$Br$_2$ requires 378.9082.

6,8-Dibromo-2-(4-fluorophenyl)quinazolin-4(3H)-one (3b). A mixture of 1 (1.00 g, 3.37 mmol), 4-fluorobenzaldehyde (2b) (0.50 g, 4.06 mmol) and iodine (1.19 g, 6.74 mmol) in ethanol (100 mL) afforded 3b as a white solid (1.20 g, 89%), m.p. > 350 °C; $\nu$$_{\text{max}}$(ATR) 875, 1155, 1230, 1487, 1599, 1686, 3374 cm$^{-1}$; $\delta$$_{\text{H}}$(300 MHz, DMSO-$d_6$) 7.43 (t, $J$ = 8.7 Hz, 2H), 8.19 (d, $J$ = 3.0 Hz, 1H), 8.31 (t, $J$ = 8.7 Hz, 2H), 8.34 (d, $J$ = 3.0 Hz, 1H), 12.94 (s, 1H); m/z 397 (100, MH$^+$); HRMS (ES): MH$^+$, found 396.8975. C$_{14}$H$_8$N$_2$OFBr$_2$ requires 396.8987.

6,8-Dibromo-2-(4-chlorophenyl)quinazolin-4(3H)-one (3c). A mixture of 1 (1.00 g, 3.37 mmol), 4-chlorobenzaldehyde (2c) (0.56 g, 4.06 mmol) and iodine (1.19 g, 6.74 mmol) in ethanol (100 mL) afforded 3c as a white solid (1.37 g, 94%), m.p. > 350 °C; $\nu$$_{\text{max}}$(ATR) 724, 823, 1408, 1487, 1671, 3138, 3362 cm$^{-1}$; $\delta$$_{\text{H}}$(300 MHz, DMSO-$d_6$) 7.64 (d, $J$ = 9.3 Hz, 2H), 8.19 (d, $J$ = 3.0 Hz, 1H), 8.27 (d, $J$ = 9.3 Hz, 2H), 8.34 (d, $J$ = 3.0 Hz, 1H), 12.98 (s, 1H); m/z 413 (100, MH$^+$); HRMS (ES): MH$^+$, found 412.8683. C$_{14}$H$_8$N$_2$OClBr$_2$ requires 412.8692.

6,8-Dibromo-2-(4-methoxyphenyl)quinazolin-4(3H)-one (3d). A mixture of 1 (1.00 g, 3.37 mmol), 4-methoxybenzaldehyde (2d) (0.54 g, 4.06 mmol) and iodine (1.19 g, 6.74 mmol) in ethanol (100 mL) afforded 3d as a white solid (1.28 g, 91%), m.p. 302–304 °C; $\nu$$_{\text{max}}$(ATR) 818, 1032, 1251, 1556, 1675, 3177, 3381 cm$^{-1}$; $\delta$$_{\text{H}}$(300 MHz, DMSO-$d_6$) 7.12 (d, $J$ = 8.7 Hz, 2H), 8.19 (d, $J$ = 3.0 Hz, 1H), 8.26 (d, $J$ = 8.7 Hz, 2H), 8.34 (d, $J$ = 3.0 Hz, 1H), 12.77 (s, 1H); m/z 409 (100, MH$^+$); HRMS (ES): MH$^+$, found 408.9190. C$_{15}$H$_{11}$N$_2$O$^{15}$ClBr$_2$ requires 408.9187.
3.3. Oxidative Aromatization of 3a–d with SOCl2-DMF Mixture

Typical Procedure

6,8-Dibromo-4-chloro-2-phenylquinazoline (4a). DMF (1 mL) was added dropwise to a stirred suspension of 3a (1.00 g, 2.60 mmol) in thionyl chloride (30 mL) at room temperature. The mixture was heated under reflux for 2 h and then allowed to cool to room temperature. The mixture was quenched with an ice-cold water and the resulting precipitate was filtered and taken up into chloroform. The chloroform layer was washed with water, dried over MgSO$_4$, filtered and evaporated under reduced pressure to afford 4a as a white solid (0.80 g, 77%), m.p. 169–171 °C; $\nu_{\text{max}}$ (ATR) 706, 771, 1023, 1409, 1456, 1551, 1582 cm$^{-1}$; $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 7.51–7.56 (m, 3H), 8.30 (d, $J = 2.1$ Hz, 1H), 8.36 (d, $J = 2.1$ Hz, 1H), 8.61–8.65 (m, 2H); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 121.2, 123.9, 125.6, 127.6, 128.7, 129.0, 131.8, 135.7, 140.9, 148.1, 160.6, 161.6; $m/z$ 397 (100, MH$^+$); HRMS (ES): MH$^+$, found 396.8733. C$_{14}$H$_8$N$_2$Cl$_7$Br$_2$ requires 396.8743.

6,8-Dibromo-4-chloro-2-(4-fluorophenyl)quinazoline (4b). A stirred suspension of 3b (1.00 g, 2.48 mmol) and DMF (1 mL) in thionyl chloride (30 mL) was treated as above to afford 4b as a white solid (0.84 g, 81%), mp. 206–208 °C; $\nu_{\text{max}}$ (ATR) 721, 1150, 1251, 1300, 1313, 1413, 1508, 1555, 1597 cm$^{-1}$; $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 7.19 (t, $J = 8.7$ Hz, 2H), 8.30 (d, $J = 2.1$ Hz, 1H), 8.35 (d, $J = 2.1$ Hz, 1H), 8.63 (t, $J = 8.7$ Hz, 2H); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 115.8 (d, $J_{\text{CF}} = 21.7$ Hz), 121.3, 123.8, 125.5, 127.6, 131.3 (d, $J_{\text{CF}} = 8.3$ Hz), 132.0 (d, $J_{\text{CF}} = 3.2$ Hz), 141.0, 148.1, 159.6, 161.6, 165.3 (d, $J_{\text{CF}} = 251.2$ Hz); $m/z$ 415 (100, MH$^+$); HRMS (ES): MH$^+$, found 414.8641. C$_{14}$H$_7$N$_2$FCl$_7$Br$_2$ requires 414.8649.

6,8-Dibromo-4-chloro-2-(4-chlorophenyl)quinazoline (4c). A stirred suspension of 3c (1.00 g, 2.39 mmol) and DMF (1 mL) in thionyl chloride (30 mL) was treated as above to afford 4c as a white solid (0.80 g, 77%), m.p. 239–240 °C; $\nu_{\text{max}}$ (ATR) 744, 786, 1012, 1211, 1298, 1332, 1414, 1553, 1587 cm$^{-1}$; $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 7.50 (t, $J = 7.8$ Hz, 2H), 8.31 (d, $J = 2.1$ Hz, 1H), 8.36 (d, $J = 2.1$ Hz, 1H), 8.57 (d, $J = 7.8$ Hz, 2H); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 121.6, 124.1, 125.6, 127.7, 129.1, 130.3, 134.4, 138.2, 141.1, 148.1, 159.7, 161.8; $m/z$ 431 (100, MH$^+$); HRMS (ES): MH$^+$, found 430.8339. C$_{14}$H$_7$N$_2$Cl$_2$Br$_2$ requires 430.8353.

6,8-Dibromo-4-chloro-2-(4-methoxyphenyl)quinazoline (4d). A stirred suspension of 3d (1.00 g, 2.41 mmol) and DMF (1 mL) in thionyl chloride (30 mL) was treated as above to afford 4d as a white solid (1.02 g, 91%), m.p. 200–202 °C; $\nu_{\text{max}}$ (ATR) 767, 792, 1026, 1164, 1253, 1335, 1422, 1555, 1583 cm$^{-1}$; $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 3.89 (s, 3H), 7.00 (d, $J = 8.7$ Hz, 2H), 8.25 (d, $J = 2.1$ Hz, 1H), 8.30 (d, $J = 2.1$ Hz, 1H), 8.56 (d, $J = 8.7$ Hz, 2H); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 55.4, 114.1, 120.5, 123.6, 125.3, 127.6, 128.5, 130.9, 140.8, 148.2, 160.5, 161.4, 162.8; $m/z$ 427 (100, MH$^+$); HRMS (ES): MH$^+$, found 426.8841. C$_{15}$H$_{10}$N$_2$OCl$_2$Br$_2$ requires 426.8848.
3.4. Sonogashira Cross-Coupling of 4a–d with Terminal Acetylenes

Typical Procedure

A mixture of 4 (1 equiv.), Pd(PPh₃)₄ (5% of 4), CuI (5% of 4) and Cs₂CO₃ (1.5 equiv.) in THF (ca. 5 mL/mmol of 4) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser equipped with a balloon was flushed for 20 min with argon gas. Terminal acetylene (1.2 equiv.) was added to the flask via a syringe and the mixture was flushed for additional 10 min. The mixture was stirred for 24 h at room temperature under argon atmosphere and then quenched with an cold water. The precipitate was filtered on a sintered funnel and then taken-up into chloroform. The solution was dried with MgSO₄, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the 2-aryl-6,8-dibromo-4-(aryl/alkylethynyl)quinazoline 5. The following products were prepared in this fashion:

6,8-Dibromo-2-phenyl-4-(phenylethynyl)quinazoline (5a). A mixture of 4a (0.50 g, 1.30 mmol), phenylacetylene (0.14 g, 1.40 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5a (0.35 g, 60%), m.p. 192–195 °C;  Rf (1:1 toluene–petroleum ether) 0.58; ν_max (ATR) 684, 730, 777, 870, 1303, 1379, 1525, 2215 cm⁻¹; δ_H (300 MHz, CDCl₃) 7.42–7.54 (m, 6H), 7.76 (dd, J = 1.2 and 7.5 Hz, 2H), 8.26 (d, J = 2.1 Hz, 1H), 8.43 (d, J = 2.1 Hz, 1H), 8.67–8.70 (m, 2H); δ_C (75 MHz, CDCl₃) 84.9, 99.1, 120.7, 120.8, 125.4, 125.9, 128.3, 128.6, 128.7, 129.0, 130.5, 131.3, 132.7, 136.9, 140.2, 147.2, 152.3, 161.5; m/z 463 (100, MH⁺); HRMS (ES): MH⁺, found 462.9435. C₂₂H₁₃N₂Br₂ requires 462.9445.

6,8-Dibromo-2-(4-fluorophenyl)-4-(phenylethynyl)quinazoline (5b). A mixture of 4b (0.50 g, 1.20 mmol), phenylacetylene (0.14 g, 1.40 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5b (0.42 g, 72%), m.p. 217–220 °C;  Rf (1:1 toluene–petroleum ether) 0.62; ν_max (ATR) 688, 721, 760, 801, 842, 866, 1146, 1219, 1308, 1407, 1441, 1491, 1525, 1601, 2210 cm⁻¹; δ_H (300 MHz, CDCl₃) 7.20 (t, J = 8.7 Hz, 2H), 7.44–7.49 (m, 3H), 7.76 (d, J = 7.5 Hz, 2H), 8.29 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.70 (t, J = 8.7 Hz, 2H); δ_C (75 MHz, CDCl₃) 84.8, 99.3, 115.6 (d, J_CF = 21.6 Hz), 120.6, 120.7, 125.3, 125.7, 128.3, 128.5, 1130.6, 131.2 (d, J_CF = 8.8 Hz), 132.7, 133.1 (d, J_CF = 3.4 Hz), 140.4, 147.2, 152.4, 160.6, 165.1 (d, J_CF = 250.2 Hz); m/z 481 (100, MH⁺); HRMS (ES): MH⁺, found 480.9347. C₂₂H₁₂N₂FBr₂ requires 480.9351.

6,8-Dibromo-2-(4-chlorophenyl)-4-(phenylethynyl)quinazoline (5c). A mixture of 4c (0.50 g, 1.16 mmol), phenylacetylene (0.13 g, 1.29 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5c (0.40 g, 69%), m.p. 223–226 °C;  Rf (1:1 toluene–petroleum ether) 0.62; ν_max (ATR) 682, 735, 748, 801, 870, 1089, 1308, 1375, 1408, 1525, 1544, 2210 cm⁻¹; δ_H (300 MHz, CDCl₃) 7.45–7.51 (m, 5H), 7.77 (d, J = 6.0 Hz, 2H), 8.29 (d, J = 1.8 Hz, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.64 (d, J = 8.7 Hz, 2H); δ_C (75 MHz, CDCl₃) 84.8, 99.4, 120.7, 121.0, 125.5, 125.8, 128.3, 128.8, 128.9, 130.3, 130.6, 132.7, 135.4, 137.7, 140.4, 147.2, 152.4, 160.6; m/z 497 (100, MH⁺); HRMS (ES): MH⁺, found 496.8040. C₂₂H₁₂N₂ClBr₂ requires 496.8056.
6,8-Dibromo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinazoline (5d). A mixture of 4d (0.50 g, 1.20 mmol), phenylacetylene (0.12 g, 1.20 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5d (0.42 g, 72%), m.p. 195–198 °C; δH (300 MHz, CDCl₃) 3.90 (s, 3H), 7.03 (d, J = 7.8 Hz, 2H), 7.39–7.49 (m, 3H), 7.76 (d, J = 7.0 Hz, 2H), 8.24 (s, 1H), 8.42 (s, 1H), 8.64 (d, J = 7.8 Hz, 2H); δC (75 MHz, CDCl₃) 55.4, 85.0, 98.7, 114.0, 120.0, 120.8, 125.1, 125.6, 128.3, 128.7, 129.5, 130.5, 130.8, 132.7, 140.1, 147.4, 152.2, 161.4, 162.4; m/z 493 (100, MH⁺); HRMS (ES): MH⁺, found 492.9541. C₂₃H₁₅N₂O₇₉Br₂⁺ requires 492.9551.

6,8-Dibromo-2-phenyl-4-(pyridin-2-ethynyl)quinazoline (5e). A mixture of 4a (0.50 g, 1.30 mmol), 2-ethynylpyridine (0.14 g, 1.30 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5e (0.36 g, 65%), m.p. 207–209 °C; δH (300 MHz, CDCl₃) 7.54–7.55 (m, 4H), 7.77–7.85 (m, 2H), 8.30 (d, J = 1.8 Hz, 1H), 8.54 (d, J = 1.8 Hz, 1H), 8.68–8.82 (m, 2H), 8.76 (d, J = 4.8 Hz, 1H); δC (75 MHz, CDCl₃) 83.5, 96.4, 121.1, 124.5, 125.5, 125.9, 128.2, 128.6, 128.7, 130.0, 131.4, 136.5, 140.6, 141.5, 147.4, 150.6, 151.7, 161.5; m/z 464 (100, MH⁺); HRMS (ES): MH⁺, found 463.9398. C₂₁H₁₂N₃₇₉Br₂⁺ requires 463.9398.

6,8-Dibromo-2-(4-fluorophenyl)-4-(pyridin-2-ethynyl)quinazoline (5f). A mixture of 4b (0.50 g, 1.16 mmol), 2-ethynylpyridine (0.14 g, 1.30 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5f (0.38 g, 67%), m.p. 216–218 °C; δH (300 MHz, CDCl₃) 7.20 (d, J = 8.7 Hz, 2H), 7.39–7.44 (m, 1H), 7.77–7.85 (m, 2H), 8.29 (d, J = 1.8 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 8.70 (d, J = 8.7 Hz, 2H), 8.75 (d, J = 4.5 Hz, 1H); δC (75 MHz, CDCl₃) 83.4, 96.6, 115.6 (d, J CF = 21.6 Hz), 121.1, 124.6, 125.4, 125.7, 128.3, 128.6, 131.3 (d, J CF = 8.8 Hz), 133.1 (d, J CF = 3.4 Hz), 136.5, 140.7, 141.4, 147.4, 150.7, 151.7, 160.6, 165.1 (d, J CF = 250.2 Hz); m/z 482 (100, MH⁺); HRMS (ES): MH⁺, found 481.9301. C₂₁H₁₁N₃F₇₉Br₂⁺ requires 481.9304.

6,8-Dibromo-2-(4-methoxyphenyl)-4-(pyridin-2-ethynyl)quinazoline (5g). A mixture of 4d (0.50 g, 1.18 mmol), 2-ethynylpyridine (0.14 g, 1.30 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5g (0.32 g, 55%), m.p. 204–206 °C; δH (300 MHz, CDCl₃) 83.6, 96.1, 114.0, 120.3, 124.5, 125.1, 125.6, 128.2, 128.5, 130.5, 130.8, 136.4, 140.4, 141.5, 147.4, 150.7, 151.4, 161.3, 162.4; m/z 494 (100, MH⁺); HRMS (ES): MH⁺, found 493.9517. C₂₂H₁₄N₃O₇₉Br₂⁺ requires 493.9504.

6,8-Dibromo-2-(4-hydroxybutynyl)-2-phenylquinazoline (5h). A mixture of 4a (0.42 g, 1.10mmol), 3-butyln-2-ol (0.09 g, 1.32 mmol), Pd(PPh₃)₄ (0.07 g, 0.06 mmol), CuI (0.012 g, 0.06 mmol), Cs₂CO₃ (0.60 g, 1.70 mmol) in THF (30 mL) afforded 5h (0.28 g, 56%), m.p. 162–165 °C; Rf (1:1, ethyl acetate–hexane) 0.70; δmax (ATR) 683, 703, 735, 777, 868, 1025, 1073, 1304, 1364, 1458, 1529, 2222,
3373 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 1.68 (dq, $J = 5.1$ and 6.6 Hz, 3H), 2.97 (d, $J = 5.1$ Hz, 1H), 4.91 (q, $J = 6.6$ Hz, 1H), 7.50–7.53 (m 3H), 8.26 (d, $J = 1.8$ Hz, 1H), 8.30 (d, $J = 1.8$ Hz, 1H), 8.62–8.66 (m, 2H); $\delta_C$ (75 MHz, CDCl$_3$) 23.6, 58.7, 79.4, 100.9, 120.8, 125.0, 125.7, 128.0, 128.6, 128.9, 131.4, 136.6, 140.3, 147.0, 151.6, 161.3; $m/z$ 433 (100, MH$^+$); HRMS (ES): MH$^+$, found 432.9371. C$_{18}$H$_{14}$N$_3$O$_7$Br$_2^+$ requires 432.9371.

3.5. Typical Procedure for the Suzuki-Miyaura Cross-Coupling of 5a–d with Arylboronic Acids

2,6,8-Triphenyl-4-(phenylethynyl)quinazoline (6a). A mixture of 5a (0.30 g, 0.64 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.022 g, 0.03 mmol), PCy$_3$ (0.02 g, 0.06 mmol) and K$_2$CO$_3$ (0.23 g, 1.60 mmol) in dioxane-water (3:1, v/v; 20 mL) in a three-necked flask equipped with a stirrer, condenser and a rubber septum was flushed with nitrogen gas for 20 min. Phenylboronic acid (0.19 g, 1.50 mmol) was added to the flask via a syringe. The mixture was flushed for additional 10 min and a balloon filled with argon gas was connected to the top of the condenser. The mixture was heated with stirring at 100 °C for 5 h under nitrogen atmosphere and then allowed to cool to room temperature. The cooled mixture was added to a beaker containing an ice-cold water and the product was extracted into ethyl acetate. The combined organic layers were dried over anhydrous MgSO$_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford 6a as a solid (0.179 g, 61%), m.p. 184–186 °C; $R_f$ (1:1 toluene–hexane) 0.41; $\nu_{\text{max}}$ (ATR) 688, 756, 1396, 1491, 1535, 1562, 2208 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 7.46–7.61 (m, 12H), 7.77–7.82 (m, 4H), 7.90 (d, $J = 7.5$ Hz, 2H), 8.25 (d, $J = 2.1$ Hz, 1H), 8.57–8.60 (m, 3H); $\delta_C$ (75 MHz, CDCl$_3$) 86.0, 97.8, 121.4, 123.3, 124.6, 127.5, 127.8, 128.0, 128.2, 128.5, 128.6, 128.7, 129.2, 130.1, 130.6, 131.0, 132.7, 134.3, 137.8, 137.9, 139.9, 140.1, 140.7, 148.0, 153.1, 160.0; $m/z$ 459 (100, MH$^+$); HRMS (ES): MH$^+$, found 459.1870. C$_{34}$H$_{23}$N$_2^+$ requires 459.1861.

2-(4-Fluorophenyl)-6,8-diphenyl-4-(phenylethynyl)quinazoline (6b). A mixture of 5b (0.20 g, 0.43 mmol), phenylboronic acid (0.10 g, 1.60 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.022 g, 0.03 mmol), PCy$_3$ (0.02 g, 0.06 mmol) and K$_2$CO$_3$ (0.23 g, 1.60 mmol) in dioxane-water (20 mL) afforded 6b (0.12 g, 57%), m.p. 250–252 °C; $R_f$ (1:1 toluene–hexane) 0.54; $\nu_{\text{max}}$ (ATR) 686, 741, 846, 1148, 1218, 1409, 1536, 1536, 1598, 2210 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 7.14 (d, $J = 8.7$ Hz, 2H), 7.42–7.60 (m, 9H), 7.75–7.81 (m, 4H), 7.87 (d, $J = 6.9$ Hz, 2H), 8.22 (d, $J = 1.8$ Hz, 1H), 8.55 (t, $J = 8.7$ Hz, 2H), 8.56 (d, $J = 1.8$ Hz, 1H); $\delta_C$ (75 MHz, CDCl$_3$) 85.9, 98.0, 115.3 (d, $J_{\text{CF}} = 21.6$ Hz), 121.3, 123.3, 124.4, 127.5, 128.0, 128.2, 128.7, 129.2, 130.2, 130.8 (d, $J_{\text{CF}} = 3.3$ Hz), 134.4, 137.9, 139.8, 140.1, 140.7, 147.9, 153.1, 159.1, 164.5 (d, $J_{\text{CF}} = 248.8$ Hz); $m/z$ 477 (100, MH$^+$); HRMS (ES): MH$^+$, found 477.1772. C$_{34}$H$_{22}$N$_2$F$^+$ requires 477.1765.

2-(4-Chlorophenyl)-6,8-diphenyl-4-(2-phenylethynyl)quinazoline (6c). A mixture of 5c (0.20 g, 0.41 mmol), phenylboronic acid (0.12 g, 1.00 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.022 g, 0.03 mmol), PCy$_3$ (0.02 g, 0.06 mmol) and K$_2$CO$_3$ (0.23 g, 1.60 mmol) in dioxane-water (20 mL) afforded 6c (0.18 g, 88%), m.p. 246–248 °C; $R_f$ (1:1 toluene–hexane) 0.60; $\nu_{\text{max}}$ (ATR) 687, 739, 752, 1012, 1087, 1533, 1576, 2211 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 7.41–7.60 (m, 11H), 7.75–7.81 (m, 4H), 7.90 (d, $J = 6.9$ Hz, 2H), 8.22 (d, $J = 1.8$ Hz, 1H), 8.50 (d, $J = 8.4$ Hz, 2H), 8.55 (d, $J = 1.8$ Hz, 1H); $\delta_C$ (75 MHz, CDCl$_3$) 85.9, 98.0, 121.3, 123.3, 124.5, 127.5, 127.9, 128.0, 128.3, 128.6, 128.7, 129.2, 130.0, 130.2, 130.9, 132.6, 134.4,
136.3, 136.7, 137.8, 139.8, 140.3, 140.7, 147.8, 153.1, 159.0; \textit{m/z} 493 (100, MH\textsuperscript{+}); HRMS (ES): MH\textsuperscript{+}, found 493.1475. C\textsubscript{3}H\textsubscript{22}N\textsubscript{2}O\textsubscript{5} requires 493.1472.

2-(4-Methoxyphenyl)-6,8-diphenyl-4-(phenylethynyl)quinazoline (6d). A mixture of 5d (0.20 g, 0.42 mmol), phenylboronic acid (0.100 g, 1.20 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (0.015 g, 0.02 mmol), PCy\textsubscript{3} (0.013 g, 0.04 mmol) and K\textsubscript{2}CO\textsubscript{3} (0.15 g, 1.30 mmol) in dioxane-water (20 mL) afforded 6d (0.14 g, 68%), m.p. 220–223 °C; \textit{R} \textsubscript{f} (1:1 toluene–hexane) 0.17; \nu \textsubscript{max} (ATR) 685, 699, 752, 1028, 1161, 1247, 1411, 1533, 1602, 2205 cm\textsuperscript{-1}; \delta\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.23 (t, 1H); 7.26 (t, 1H); 7.46–7.50 (m, 6H), 7.72–7.80 (m, 4H), 7.85 (t, J = 8.7 Hz, 2H), 8.12 (d, J = 2.1 Hz, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.56 (t, J = 8.7 Hz, 2H), 8.89 (d, J = 8.7 Hz, 2H), 132.4, 137.7, 139.1, 139.8, 147.8, 153.1, 160.1, 162.7 (d, \textit{J}\textsubscript{CF} = 249.5 Hz), 163.0 (d, \textit{J}\textsubscript{CF} = 247.0 Hz); \textit{m/z} 495 (100, MH\textsuperscript{+}); HRMS (ES): MH\textsuperscript{+}, found 495.1685. C\textsubscript{3}H\textsubscript{22}N\textsubscript{2}O\textsubscript{5} requires 495.1673.

2,6,8-Tris(4-fluorophenyl)-4-(phenylethynyl)quinazoline (6f). A mixture of 5b (0.20 g, 0.41 mmol), 4-fluorophenylboronic acid (0.15 g, 1.07 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (0.015 g, 0.021 mmol), PCy\textsubscript{3} (0.012 g, 0.04 mmol) and K\textsubscript{2}CO\textsubscript{3} (0.12 g, 1.30 mmol) in dioxane-water (20 mL) afforded 6f (0.14 g, 64%), m.p. 228–230 °C; \textit{R} \textsubscript{f} (1:1 toluene–hexane) 0.48; \nu \textsubscript{max} (ATR) 691, 725, 825, 1158, 1232, 1466, 1510, 1561, 1605, 2206 cm\textsuperscript{-1}; \delta\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.23 (t, J = 8.7 Hz, 2H), 7.26 (t, J = 8.7 Hz, 2H); \delta\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 85.9, 98.0, 115.0 (d, \textit{J}\textsubscript{CF} = 21.4 Hz), 116.2 (d, \textit{J}\textsubscript{CF} = 21.4 Hz), 121.3, 123.2, 124.5, 128.6 (d, \textit{J}\textsubscript{CF} = 8.3 Hz), 128.7, 129.1 (d, \textit{J}\textsubscript{CF} = 8.3 Hz), 130.2, 130.7, 132.5, 132.6, 133.7 (d, \textit{J}\textsubscript{CF} = 3.2 Hz), 133.8, 135.9 (d, \textit{J}\textsubscript{CF} = 3.2 Hz), 137.7, 139.1, 139.8, 147.8, 153.1, 160.1, 162.7 (d, \textit{J}\textsubscript{CF} = 249.5 Hz), 163.0 (d, \textit{J}\textsubscript{CF} = 247.0 Hz); \textit{m/z} 495 (100, MH\textsuperscript{+}); HRMS (ES): MH\textsuperscript{+}, found 495.1685. C\textsubscript{3}H\textsubscript{22}N\textsubscript{2}O\textsubscript{5} requires 495.1673.

2-(4-Chlorophenyl)-6,8-bis(4-fluorophenyl)-4-(phenylethynyl)quinazoline (6g). A mixture of 5c (0.20 g, 0.42 mmol), 4-fluorophenylboronic acid (0.15 g, 1.07 mmol), PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (0.015 g, 0.02 mmol), PCy\textsubscript{3} (0.01 g, 0.04 mmol) and K\textsubscript{2}CO\textsubscript{3} (0.12 g, 1.30 mmol) in dioxane-water (20 mL) afforded 6g (0.17 g,
77%), m.p. 243–245 °C; Rf (1:1 toluene–hexane) 0.72; νmax (ATR) 747, 809, 820, 1011, 1088, 1158, 1231, 1509, 1605, 2205 cm−1; δH (300 MHz, CDCl3) 7.24 (t, J = 8.7 Hz, 2H), 7.26 (t, J = 8.7 Hz, 2H), 7.43–7.51 (m, 3H), 7.74 (t, J = 8.7 Hz, 2H), 7.75–7.80 (m, 2H), 7.82 (t, J = 8.7 Hz, 2H), 8.12 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.48–8.49 (m, 2H); δC (75 MHz, CDCl3) 85.7, 98.2, 114.9 (d, JCF = 21.3 Hz), 116.2 (d, JCF = 21.4 Hz), 121.2, 123.1, 124.4, 128.7, 128.8, 129.1 (d, JCF = 8.3 Hz), 129.9, 130.3, 132.4 (d, JCF = 8.3 Hz), 132.5, 133.6 (d, JCF = 3.4 Hz), 133.9, 135.8 (d, JCF = 3.4 Hz), 136.1, 136.9, 139.2, 139.7, 147.6, 153.1, 159.1, 162.8 (d, JCF = 246.2 Hz), 163.0 (d, JCF = 247.0 Hz); m/z 529 (100, MH+); HRMS (ES): MH+, found 529.1282. C34H20N2F235Cl+ requires 529.1283.

6,8-Bis(4-fluorophenyl)-2-(4-methoxyphenyl)-4-(phenylethynyl)quinazoline (6h). A mixture of 5d (0.20 g, 0.42 mmol), 4-fluorophenylboronic acid (0.15 g, 1.07 mmol), PdCl2(PPh3)2 (0.015 g, 0.02 mmol), PCy3 (0.01 g, 0.04 mmol) and K2CO3 (0.12 g, 1.30 mmol) in dioxane-water (20 mL) afforded 6h (0.18 g, 58%), m.p. 211–230 °C; Rf (1:1 toluene–hexane) 0.50; νmax (ATR) 684, 750, 810, 1028, 1157, 1227, 1252, 1507, 1537, 1605, 2203 cm−1; δH (300 MHz, CDCl3) 3.88 (s, 3H), 7.00 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.44–7.50 (m, 2H), 7.75–7.84 (m, 5H), 8.09 (d, J = 2.1 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.59 (dd, J = 2.4 and 7.5 Hz, 2H); δC (75 MHz, CDCl3) 55.4, 85.9, 97.7, 113.9, 114.9 (d, JCF = 21.4 Hz), 116.1 (d, JCF = 21.4 Hz), 121.4, 123.2, 124.2, 128.7, 129.1 (d, JCF = 8.3 Hz), 130.1, 130.3, 131.8, 132.5, 132.6 (d, JCF = 8.4 Hz), 133.7, 133.8 (d, JCF = 3.0 Hz), 136.1 (d, JCF = 3.0 Hz), 138.5, 139.5, 147.9, 153.0, 160.0, 161.9, 162.8 (d, JCF = 245.9 Hz), 162.9 (d, JCF = 246.5 Hz); m/z 525 (100, MH+); HRMS (ES): MH+, found 525.1785. C35H22N2O2F2+ requires 525.1778.

6,8-Bis(4-methoxyphenyl)-2-phenyl-4-(phenylethynyl)quinazoline (6i). A mixture of 5a (0.30 g, 0.64 mmol), 4-methoxyphenylboronic acid (0.20 g, 1.60 mmol), PdCl2(PPh3)2 (0.022 g, 0.03 mmol), PCy3 (0.02 g, 0.06 mmol) and K2CO3 (0.23 g, 1.60 mmol) in dioxane-water (20 mL) afforded 6i (0.23 g, 69%), m.p. 209–211 °C; Rf (2:1 toluene–hexane) 0.28; νmax (ATR) 691; 831, 1032, 1174, 1243, 1393, 1460, 1510, 1608, 2209 cm−1; δH (300 MHz, CDCl3) 3.88 (s, 3H), 3.93 (s, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.44–7.50 (m, 6H), 7.73 (d, J = 8.7 Hz, 2H), 7.77–7.81 (m, 2H), 7.86 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 2.1 Hz, 1H); 8.48 (d, J = 2.1 Hz, 1H), 8.59 (dd, J = 2.4 and 7.5 Hz, 2H); δC (75 MHz, CDCl3) 55.3 (2×C), 86.1, 97.5, 113.4, 114.5, 121.4, 121.7, 124.6, 126.4 (2×C), 128.6 (2×C), 130.0, 130.3, 130.4, 132.1, 132.2, 132.5, 133.4, 137.8, 139.5, 140.0, 147.6, 152.7, 159.4, 159.5, 159.7; m/z 519 (100, MH+); HRMS (ES): MH+, found 519.2071. C36H27N2O2+ requires 519.2073.

2-(4-Fluorophenyl)-6,8-bis(4-methoxyphenyl)-4-(phenylethynyl)quinazoline (6j). A mixture of 5b (0.40 g, 0.86 mmol), 4-methoxyphenylboronic acid (0.26 g, 2.15 mmol), PdCl2(PPh3)2 (0.03 g, 0.04 mmol), PCy3 (0.024 g, 0.08 mmol) and K2CO3 (0.30 g, 2.15 mmol) in dioxane-water (30 mL) afforded 6j (0.29 g, 62%), m.p. 236–238 °C; Rf (2:1 toluene–hexane) 0.33; νmax (ATR) 831, 1017, 1150, 1222, 1287, 1508, 1605, 2208 cm−1; δH (300 MHz, CDCl3) 3.89 (s, 3H), 3.94 (s, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.44–7.49 (m, 3H), 7.73 (d, J = 8.7 Hz, 2H), 7.75–7.80 (m, 2H), 7.83 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 2.4 Hz, 1H), 8.46 (d, J = 1.8 Hz, 1H), 8.57 (t, J = 8.7 Hz, 2H); δC (75 MHz, CDCl3) 55.3, 55.4, 86.0, 97.8, 113.5, 114.6,
115.3 (d, \(J_{CF} = 21.3\) Hz), 121.4, 124.6, 128.5, 128.7, 130.1, 130.3, 130.7 (d, \(J_{CF} = 8.5\) Hz), 132.1, 132.3, 132.5, 133.7, 134.1 (d, \(J_{CF} = 3.2\) Hz), 139.7, 140.1, 147.6, 152.8, 158.7, 159.4, 159.8, 164.6 (d, \(J_{CF} = 248.7\) Hz); m/z 537 (100, MH\(^+\)); HRMS (ES): MH\(^+\), found 537.1986. C\(_{36}\)H\(_{26}\)N\(_2\)F\(_2\)O\(_2\) requires 537.1978.

2-(4-Chlorophenyl)-6,8-bis(4-methoxyphenyl)-4-(phenylethynyl)quinazoline (6k). A mixture of 5c (0.30 g, 0.64 mmol), 4-methoxyphenylboronic acid (0.20 g, 1.60 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.023 g, 0.03 mmol), PCy\(_3\) (0.020 g, 0.06 mmol) and K\(_2\)CO\(_3\) (0.23 g, 1.60 mmol) in dioxane-water (20 mL) afforded 6k (0.27 g, 76%), m.p. 233–235 °C; \(R_f\) (2:1 toluene–hexane) 0.38; \(\nu_{max}\) (ATR) 746, 807, 830, 1016, 1178, 1248, 1491, 1511, 1605, 2210 cm\(^{-1}\); \(\delta_H\) (300 MHz, CDCl\(_3\)) 3.88 (s, 3H), 3.92 (s, 3H), 7.05 (d, \(J = 8.7\) Hz, 2H), 7.10 (d, \(J = 8.7\) Hz, 2H), 7.41–7.47 (m, 5H), 7.71 (d, \(J = 8.7\) Hz, 2H), 7.76 (dd, \(J = 1.8\) and 7.8 Hz, 2H), 7.81 (d, \(J = 8.7\) Hz, 2H), 8.15 (d, \(J = 1.8\) Hz, 1H); 8.44 (d, \(J = 1.8\) Hz, 1H), 8.49 (d, \(J = 8.4\) Hz, 2H); \(\delta_C\) (75 MHz, CDCl\(_3\)) 55.3, 55.4, 86.0, 97.9, 113.5, 114.6, 121.4, 121.9, 124.7, 128.5, 128.6, 128.7, 129.9, 130.1, 130.3, 132.1, 132.3, 132.1, 132.3, 132.5, 133.7, 136.4, 136.6, 139.9, 140.2, 147.6, 152.9, 158.6, 159.5, 159.9; m/z 553 (100, MH\(^+\)); HRMS (ES): MH\(^+\), found 553.1689. C\(_{36}\)H\(_{26}\)N\(_2\)O\(_2\)Cl requires 553.1683.

2,6,8-Tris(4-methoxyphenyl)-4-(phenylethynyl)quinazoline (6l). A mixture of 5d (0.30 g, 0.64 mmol), 4-methoxyphenylboronic acid (0.20 g, 1.60 mmol), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 g, 0.03 mmol), PCy\(_3\) (0.02 g, 0.06 mmol) and K\(_2\)CO\(_3\) (0.24 g, 1.61 mmol) in dioxane-water (20 mL) afforded 6l (0.18 g, 52%), m.p. 237–239 °C; \(R_f\) (2:1 toluene–hexane) 0.20; \(\nu_{max}\) (ATR) 753, 808, 832, 1018, 1162, 1176, 1243, 1507, 1605, 2207 cm\(^{-1}\); \(\delta_H\) (300 MHz, CDCl\(_3\)) 3.87 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 6.99 (d, \(J = 8.7\) Hz, 2H), 7.04 (d, \(J = 8.7\) Hz, 2H), 7.10 (d, \(J = 8.7\) Hz, 2H), 7.10–7.14 (m, 3H), 7.71 (d, \(J = 1.8\) Hz, 1H); 8.42 (d, \(J = 1.8\) Hz, 1H), 8.52 (d, \(J = 8.7\) Hz, 2H); \(\delta_C\) (75 MHz, CDCl\(_3\)) 55.3, 55.4, 55.5, 86.1, 97.3, 113.4, 113.7, 114.5, 121.5, 121.9, 124.3, 128.4, 128.6, 129.9, 130.2, 130.4, 130.6, 132.1, 132.4, 132.5, 133.4, 139.1, 139.8, 147.7, 152.7, 159.3, 159.4, 159.7, 161.6; m/z 549 (100, MH\(^+\)); HRMS (ES): MH\(^+\), found 549.2192. C\(_{37}\)H\(_{29}\)N\(_2\)O\(_3\)Cl\(_{35}\) requires 549.2178.

4. Conclusions

Elaboration of the 6,8-dibromo-4-chloroquinazoline scaffold via sequential Sonogashira and Suzuki-Miyaura cross-coupling reactions with terminal alkynes and arylboronic acids afforded novel polysubstituted quinazoline derivatives that would not be readily accessible otherwise. Exclusive replacement of 4-chloro atom of the 6,8-dibromo-4-chloroquinazolines via Sonogashira cross-coupling with stoichiometric amount of terminal alkynes is attributed to the \(\alpha\)-nitrogen effect, which makes the 4-position highly activated than other positions. Lack of selectivity during Suzuki cross-coupling of the 2-aryl-4-alkynyl-6,8-dibromoquinazolines with arylboronic acids, on the other hand, is presumably the consequence of comparable C(6)–Br and C(8)–Br bond dissociation energies. The polyaryl substituted heterocycles 6 comprise an electron-deficient quinazoline framework as an electron-acceptor linked to the aryl rings directly or through a \(\pi\)-conjugated bridge to comprise donor-\(\pi\)-acceptor systems. Preliminary photophysical (absorption and emission) properties of these compounds showed a strong correlation with the substituents on the 2-, 6- and 8-phenyl groups. Based on the orbital
diagrams, the electronic transitions of compounds 6 can be attributed to ICT from the aryl substituents to the quinazoline ring. Due to its electron deficiency, the quinazoline moiety may provide a site for reduction in this D-π-A system. This makes quinazolines 6a–l suitable candidates for further studies using cyclic voltametry to probe oxidation and reduction potentials and the stability of the oxidized and reduced forms. Compounds 6a–l, on the other hand, can be used as substrates for the synthesis of metal complexes with iridium, palladium or platinum, for example, as a prelude to compounds with potential application as organic light-emitting diode in materials. Moreover, the analogous 2-substituted quinazolines bearing alkynyl substituent on the C-4 or C-6 position exhibit excellent EGFR or Aurora A kinase inhibition activity [23].

Acknowledgments

The authors are grateful to the University of South Africa for financial assistance and to A.O. Adeloye for UV-Vis and fluorescence spectral data acquisition.

Author Contributions

H.K. Paumo carried out all the synthesis at UNISA under the supervision of M.J. Mphahlele who is the lead author. Quantum chemical calculations and interpretation of the corresponding data are joint contribution by A.M. El-Nahas and M.M. El-Hendawy.

Conflicts of Interest

The authors hereby declare that there is no conflict of interest.

References

1. Grushin, V.V.; Alper, H. Transformations of chloroarenes, catalyzed by transition-metal complexes. Chem. Rev. 1994, 94, 1047–1062.
2. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. Chem. Rev. 2002, 102, 1359–1469.
3. Garcia, Y.; Schoenebeck, F.; Legault, C.Y.; Merlic, C.A.; Houk, K.N. Theoretical bond dissociation energies of halo-heterocycles: Trends and relationships to regioselectivity in palladium-catalyzed cross-coupling reactions. J. Am. Chem. Soc. 2009, 131, 6632–6639.
4. Mangalagiu, I.; Benneche, T.; Undheim, K. Trialkylalanes in palladium-catalyzed chemo- and regioselective alkylations. Tetrahedron Lett. 1996, 37, 1309–1312.
5. Mangalagiu, I.; Benneche, T.; Undheim, K. Ethenylation and alkynylation in palladium-catalyzed carbosubstitution in heteroaazines. Acta Chem. Scand. 1996, 50, 914–917.
6. Charpiot, B.; Brun, J.; Donze, I.; Naef, R.; Stefani, M.; Mueller, T. Quinazolines: Combined type 3- and 4-phosphodiesterase inhibitors. Bioorg. Med. Chem. Lett. 1998, 8, 2891–2896.
7. Wipf, P.; George, K.M. Regioselective palladium-catalyzed cross-coupling reactions of 2,4,7-trichloroquinazoline. SynLett. 2010, 644–648.
8. Mphahlele, M.J. Regioselective alkynylation of 2-aryl-4-chloro-3-iodoquinolines and subsequent arylation or amination of the 2-aryl-3-(alkynyl)-4-chloroquinolines. *Tetrahedron* 2010, 66, 8261–8266.

9. Khoza, T.A.; Maluleka, M.M.; Mama, N.; Mphahlele, M.J. Synthesis and photophysical properties of the 2-aryl-6,8-bis(arylethenyl)-4-methoxyquinolines. *Molecules* 2012, 17, 14186–14204.

10. Hisano, T.; Ichikawa, M.; Nakagawa, A.; Tsuji, M. Organosulfur compounds. XII. Syntheses and pharmacological activities of 2-heterocyclic-substituted 4(3H)-quinazolinones. *Chem. Pharm. Bull.* 1975, 23, 1910–1916.

11. Abdel-Jalil, R.J.; Aldoqum, H.M.; Ayoub, M.T.; Voelter, W. Synthesis and antitumor activity of 2-aryl-7-fluoro-6-(4-methyl-1-piperazinyl)-4(3H)-quinazolinones. *Heterocycles* 2005, 65, 2061–2070.

12. Mitobe, Y.; Ito, S.; Mizutani, T.; Nagase, T.; Sato, N.; Tokita, S. Development of a selective and potent radioactive ligand for histamine H3 receptors: A compound potentially useful for receptor occupancy studies. *Bioorg. Med. Chem. Lett.* 2009, 19, 4075–4078.

13. Balakumar, C.; Lamaba, P.; Kishore, D.P.; Narayana, B.L.; Rao, K.V.; Rajwinder, K.; Rao, A.R.; Shireesha, B.; Narsaiah, B. Synthesis, Anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. *Eur. J. Med. Chem.* 2010, 45, 4904–4913.

14. López, S.E.; Rosales, M.E.; Urdenata, N.; Godoy, M.V.; Charris, J.E. The synthesis of substituted 2-aryl-4(3H)-quinazolinones using NaHSO₃/DMA. Steric effect upon the cyclization-dehydrogenation step. *J. Chem. Res.* 2000, 258–259.

15. Naleway, J.J.; Fox, C.J.M.; Robinhold, D.; Terpetsching, E.; Olsen, N.A.; Haugland, R.P. Synthesis and use of new fluorogenic precipitating substrates. *Tetrahedron Lett.* 1994, 35, 8569–8572.

16. Abdel-Jalil, R.J.; Voelterb, W.; Saeed, M. A novel method for the synthesis of 4(3H)-quinazolinones. *Tetrahedron* 2004, 45, 3475–3476.

17. Wang, G.-W.; Miao, C.-B.; Kang, H. Benign and efficient synthesis of 2-substituted 4(3H)-quinazolinones mediated by iron(III) chloride hexahydrate in refluxing water. *Bull. Chem. Soc. Jpn.* 2006, 79, 1426–1430.

18. Bakavoli, M.; Rahimizadeh, M.; Shiri, A.; Ebrahimpour, Z. Molecular iodine oxidative cyclocondesation of ortho-aminobenzamide with aryl aldehydes: A new and efficient access to quinazolin-4(3H)-ones. *Iran. J. Org. Chem.* 2009, 1, 39–42.

19. Barlaam, B.; Harris, C.S.; Lecog, J.; Nguyen, H.T.H. Preparation of 6-aminooquinazolin-4(3H)-ones via direct SNAr on the quinazoline ring. *Tetrahedron* 2012, 68, 534–543.

20. Jiang, J.B.; Hesson, D.P.; Dusak, B.A.; Dexter, D.L.; Kang, G.J.; Hamel, E. Synthesis and biological evaluation of 2-styrylquinazolin-4(3H)-ones, a new class of antimitotic anticancer agents which inhibit tubulin polymerization. *J. Med. Chem.* 1990, 33, 1721–1728.

21. Arnott, E.A.; Chan, L.C.; Cox, B.G.; Meyrick, B.; Phillips, A. POCl₃ chlorination of 4-quinazolinones. *J. Org. Chem.* 2011, 76, 1653–1661.

22. El-Badry, Y.A.-M. Synthesis and reactions of 2-carboxyvinyl-4-chloro-6,8-dibromoquinazoline and some new fused triazolo-quinazoline derivatives. *Acta Chim. Slov.* 2010, 57, 836–841.

23. Kitano, Y.; Suzuki, T.; Kawahara, E.; Yamashita, T. Synthesis and inhibitory activity of 4-alkynyl and 4-alkenylquinazolines: Identification of new scaffolds for potent EGFR tyrosine kinase inhibitors. *Bioorg. Med. Chem. Lett.* 2007, 17, 5863–5867.
24. Akrawi, O.A.; Mohammed, H.H.; Langer, P. Synthesis and Suzuki-Miyaura reactions of 3,6,8-tribromoquinoline: A structural revision. *SynLett.* **2013**, 1121–1124.

25. Ho-Joon, L.; Hao, X.; Seong-Min, P.; Seog-IL, P.; Taek, A.; Dong-Kyu, P.; Samson, A.J.; Tae-Woo, K. Synthesis and properties of diarylmino-substituted linear and dendritic oligoquinolines for organic light-emitting diodes. *Bull. Korean Chem. Soc.* **2012**, *33*, 1627–1637.

26. Diaz, A.N.J. Absorption and emission spectroscopy and photochemistry of 1,10-anthraquinone derivatives: A review. *Photochem. Photobiol. A* **1990**, *53*, 141–167.

27. Kalinowski, J. Excimers and exciplexes in organic electroluminescence. *Mat. Sci.-Poland* **2009**, *27*, 735–756.

28. Chen, G.S.; Talekar, R.S.; Wong, K.-T.; Chi, L.-C.; Chern, J.-W. Physical properties of 8-substituted 5,7-dichloro-2-styrylquinolines as potential light emitting materials. *J. Chin. Chem. Soc.* **2007**, *54*, 1387–1394.

29. Yanai, T.; Tew, D.; Handy, N. A new hybrid exchange-correlation functional using the Coulomb-attenuating method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, *393*, 51–57.

30. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; *et al.* Gaussian 09, Revision B.01; Gaussian, Inc.: Wallingford, CT, USA, 2010.

31. Zerner, M.C. Semiempirical Molecular Orbital Methods. In *Reviews in Computational Chemistry*; Lipkowitz, K.B., Boyd, D.B., Eds.; VCH Publishing: New York, NY, USA, 1991; Volume 2, pp. 313–366.

32. Sunahara, H.; Urano, Y.; Kojima, H.; Nagano, T. Design and synthesis of a library of BODIPY-based environmental polarity sensors utilizing photoinduced electron-transfer-controlled fluorescence on/off switching. *J. Am. Chem. Soc.* **2007**, *129*, 5597–5604.

*Sample Availability:* Samples of the compounds 3a–d, 4a–d, 5a–h and 6a–l are available from the authors.

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