Turkish Journal of Chemistry
http://journals.tubitak.gov.tr/chem/
Research Article

Turk J Chem
(2015) 39: 1216 – 1231

doi:10.3906/kim-1505-42

Reactivity of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones in a palladium catalyzed Sonogashira cross-coupling reaction

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Received: 14.05.2015 • **Accepted/Published Online:** 01.09.2015 • **Printed:** 25.12.2015

Abstract: Pd/C-PPh_3–CuI catalyzed Sonogashira cross-coupling of the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones with phenyl acetylene or 3-butyn-1-ol afforded the corresponding 8-alkynylated quinolin-4(1*H*)-one derivatives, exclusively. Double carbo-substitution to afford the 6,8-dialkynyl derivatives was observed when $PdCl_2(PPh_3)_2$ was used as Pd(0) source. The monoalkynylated derivatives were, in turn, subjected to $PdCl_2$ in acetonitrile under reflux to afford either the corresponding 2,4-diaryl-8-bromopyrrolo[3,2,1-*ij*]quinolinones or the 8-(4-hydroxybutanoyl)-substituted quinolinone derivatives, exclusively. Suzuki–Miyaura cross-coupling of the 2-aryl-6-bromo-8-(alkynyl)quinolin-4-ones afforded the 2,4,8-trisubstituted pyrrolo[3,2,1-*ij*]quinolin-6-ones.

Key words: 2-Aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones, cross-coupling, pyrrolo[3,2,1-*ij*]quinolin-6-ones

1. Introduction

The elaboration of strategies to efficiently functionalize presynthesized halogenated quinolinones via metal catalyzed cross-coupling to yield novel polysubstituted or heteroannulated derivatives continues to attract considerable attention in synthesis.[1–3] The Sonogashira reaction, which involves palladium catalyzed cross-coupling of terminal alkynes with aryl or heteroaryl halides, has become an important tool for Csp^2–Csp bond formation.[4] Moreover, the proximity of the nucleophilic heteroatom in the case of tethered alkynylated derivatives has been found to facilitate sequential or one-pot intramolecular attack of the metal-activated triple bond to afford heteroannulated derivatives.[5] A two-step synthesis of the 2-substituted 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines involving initial Pd/C-mediated Sonogashira cross-coupling of 6-bromo-8-iodo-1,2,3,4-tetrahydroquinoline with terminal alkynes followed by CuI-promoted intramolecular cyclization of the resulting 8-alkynyl-6-bromo-1,2,3,4-tetrahydroquinolines has been reported before.[6] Palladium(II) chloride has also been found to catalyze heteroannulation of the 8-arylethynyl-1,2,3,4-tetrahydroquinolines to afford the corresponding dihydropyrroloquinolines.[7] A similar strategy involving initial palladium-mediated C–C bond formation and subsequent metal-catalyzed C–N bond formation was employed on the 6-(chloro/methyl)-8-iodo-2,3-dihydroquinolin-4(1*H*)-ones to afford novel 5-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones with potential to activate SIRT1.[8]

Site-selective Sonogashira cross-coupling of dihalogenoquinolinones or dihalogenoquinolines with terminal alkynes to afford heteroannulated derivatives has so far been performed on the less readily accessible

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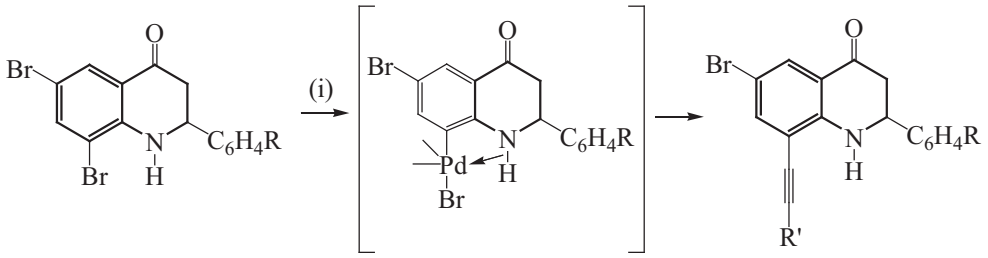
(chloro/bromo)iodo precursors.[6,9] The selectivity in these cases was found to depend largely on the intrinsic reactivity of the halide (I>Br>Cl>>F), which relates to the Ar–X bond strength (D_{Ph-X} values 65, 81, 96, and 126 kcal/mol, respectively) and to a lesser extent the electronic effect of its position.[10] For the dihalogenoquinolinones with two identical halogen atoms on the fused benzo ring, however, site-selective Sonogashira cross-coupling involving conversion of one of the halogen atoms still remains unexplored. This prompted us to investigate the reactivity of the known 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones[11] in Sonogashira cross-coupling with terminal alkynes as coupling partners. We envisioned that the tethered alkynylated moiety would enable further transformation through heteroannulation to afford novel polysubstituted pyrrolo[3,2,1-*ij*]quinolin-1-ones.

2. Results and discussion

It is well known that the efficiency of a palladium catalyst strongly depends on the ligand of palladium atom and the overall reactivity also depends on the precursor of palladium(0) complex.[12] Likewise, selectivity of the palladium-catalyzed cross-coupling reactions of heterocycles bearing multiple identical halogens is mainly determined by the relative ease of oxidative addition related to the C–X bond-dissociation energy and to the interaction of the heterocycle π^* (LUMO) and PdL_2d_σ (HOMO) orbitals.[13] On the other hand, the computed bond dissociation energies of dihalogenated heterocycles at B3LYP and G3B3 levels revealed that all of the positions on the fused benzo ring bearing identical halogen atoms have comparable C–X bond dissociation energies.[13] This literature observation makes it difficult to predict how different the reactivity of the two Csp^2-Br bonds in the 2-aryl-6,8-dibromo-2,3-dihydroquinolin-4(1*H*)-ones would be during Csp^2–Csp bond formation. Hitherto, no selectivity was observed for the Suzuki–Miyaura cross-coupling of compounds **1a**–**d** with arylboronic acids using $PdCl_2(PPh_3)_2$ as Pd(0) source[11] and for the other dihaloarenes bearing *ortho* directing groups, such as –OH, –NH_2, –CH_2OH, or –NHBoc.[14] With these considerations in mind, we subjected compound **1a** to Pd/C-PPh_3 and CuI pre-catalyst mixture and triethylamine as a base in ethanol at 80 °C based on the literature precedent.[6] We isolated after 18 h by column chromatography on silica gel a single product, which was characterized using a combination of ^{1}H NMR and ^{13}C NMR spectroscopic techniques as well as mass spectrometry as the 6-bromo-4-phenyl-8-phenylethynyl-2,3-dihydroquinolin-4-one **2a** (Scheme 1). Incorporation of the alkynyl group at C-8 was confirmed by the significant downfield shift of the resonance corresponding to NH from δ ca. 5.04 ppm in the parent compound **1a** to δ ca. 5.38 ppm in the spectrum of **2a**. The doublet corresponding to 7-H also resonates at high field compared to that in the corresponding precursor. These reaction conditions were extended to other derivatives **1** using phenylacetylene and 3-butyn-1-ol as coupling partners to afford products **2b**–**h**. Since C(6)–Br and C(8)–Br bonds are expected to have comparable bond-dissociation energies,[13] the observed site selective Sonogashira cross-coupling through C-8 is attributed to the *ortho* directing effect of NH in analogy with the literature precedent for the dihalogenated benzo-fused heterocycles having two similar halogen atoms.[6] Selectivity of the Pd-catalyzed cross-coupling reactions of heterocycles bearing multiple identical halogens, on the other hand, has been found to be influenced by the interaction of the heterocycle π^* (LUMO) and PdL_2d_σ (HOMO) orbitals.[13] In our view such coordination would only be possible if the oxidative-addition step takes place through the C(8)–Br bond to form complex **A**. Monoalkynylation, on the other hand, is presumably the consequence of using Pd/C as the Pd(0) source. It is well known that palladium on carbon serves only as a heterogeneous source of Pd(0) catalyst for homogeneous coupling that involves the initial slow leaching of Pd to interact with the ligand to generate the active Pd(0)-PPh_3 species in situ.[15]

The homogeneous Pd(0)-PPh_3 species then undergoes facile transmetallation with copper acetylide followed by reductive elimination and concomitant re-deposition of Pd onto the support.[15,16] The re-adsorption onto the solid support presumably immobilizes Pd and makes it unavailable to promote further cross-coupling with the excess terminal alkyne.



1a-d **A** **2a-h**

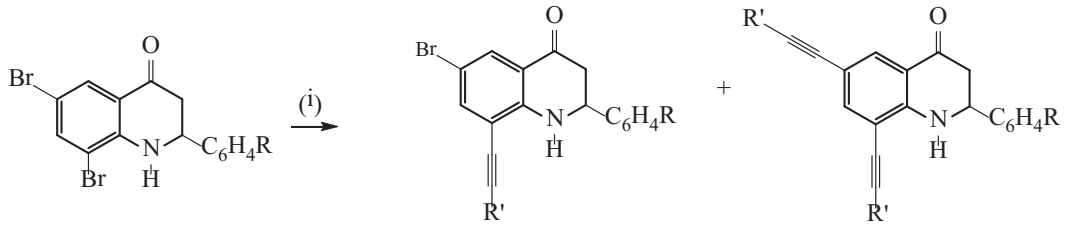
	R	R'	% Yield **2**
2a	4-H	$-C_6H_5$	71
2b	4-F	$-C_6H_5$	74
2c	4-Cl	$-C_6H_5$	73
2d	4-OMe	$-C_6H_5$	78
2e	4-H	$-CH_2CH_2OH$	77
2f	4-F	$-CH_2CH_2OH$	75
2g	4-Cl	$-CH_2CH_2OH$	62
2h	4-OMe	$-CH_2CH_2OH$	74

Reagents: (i) R'-C≡CH (2 equiv.), 10% Pd/C, PPh_3, CuI, NEt_3, ethanol, 80 °C, 18 h

Scheme 1. Monoalkynylation of **1a**–**d** using Pd/C-PPh_3 and CuI as catalyst mixture.

To test the above assumption, we decided to employ a homogeneous Pd(0) source in the presence and absence of activated carbon. Initial attempts to effect alkynylation of **1a** with phenylacetylene in triethylamine–ethanol mixture at 80 °C using tetrakis(triphenyl)phosphine(0)–CuI catalyst mixture in the presence or absence of activated carbon led to poor conversion (tlc monitoring) and the starting material was recovered unchanged. We decided to employ a more reactive Pd(II) pre-catalyst as source of active Pd(0) catalyst in the presence and absence of activated carbon. Alkynylation of **1a** with phenylacetylene in the presence of dichlorobis(triphenylphosphine)palladium(II) [$(PdCl_2(PPh_3)_2$] (0.02 equiv.) and CuI catalyst complex in triethylamine–ethanol mixture at 80 °C in the presence of activated carbon afforded the monoalkynylated **2a** (57%) and dialkynylated derivative **3a** (26%) in sequence without traces of the starting material (Scheme 2). Complete conversion of the substrate was also observed in the absence of activated carbon; however, under these conditions the dialkynylated quinolinone was isolated as the major product with traces of the monoalkynylated derivatives detected (tlc) in the crude reaction mixture. However, the monoalkynylated derivatives could not be

isolated in pure form by column chromatography. The preponderance of the monoalkynylated derivative using $PdCl_2(PPh_3)_2$–CuI catalyst complex as Pd(0) source and activated carbon seems to support our view that the active Pd(0)-PPh_3 species becomes adsorbed onto the solid support and is unavailable to promote further alkynylation. In the absence of the activated carbon, the active Pd(0)-PPh_3 species derived from $PdCl_2(PPh_3)_2$ becomes available in solution to promote further alkynylation and, under these conditions, product **3** predominates. The reaction conditions employing $PdCl_2(PPh_3)_2$–CuI catalyst complex in triethylamine–ethanol mixture at 80 °C in the absence of activated carbon were then extended to other derivatives to afford the dialkynylated products **3a**–**f** (Scheme 2).



1a-d **2a-f** **3a-f**

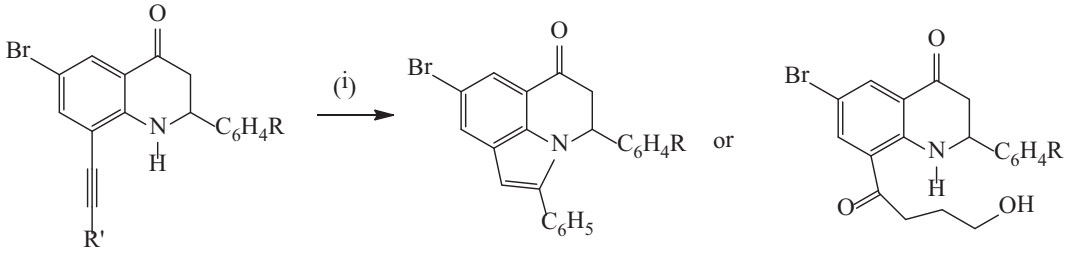
	4-R	R'	% Yield **2**	% Yield **3**
a	4-H	$-C_6H_5$	57	26[a]
			52	24[b]
b	4-F	$-C_6H_5$	-	78[c]
c	4-Cl	$-C_6H_5$	-	73[c]
d	4-OMe	$-C_6H_5$	-	68[c]
e	4-F	$-CH_2CH_2OH$	-	71[c]
f	4-Cl	$-CH_2CH_2OH$	-	69[c]

[a] $PdCl_2(PPh_3)_2$ and activated C (10.0 equiv.) used; [b] $PdCl_2(PPh_3)_2$ and activated C (5.0 equiv.) used
Reagents: (i) R'-C≡CH (3 equiv.), $PdCl_2(PPh_3)_2$, CuI, NEt_3, ethanol, 80 °C, 6 h.[c]

Scheme 2. Dialkynylation of **1a**–**d** using $PdCl_2(PPh_3)_2$–CuI catalyst complex.

The cyclization of alkynes containing proximate nucleophilic centre/s promoted by electrophiles is currently of great interest and represents a very effective strategy for carbo- and heterocyclic ring construction.[17] With the tethered 2,3-dihydroquinolin-4(1*H*)-ones derivatives **2** in hand, we decided to investigate the possibility to cyclize them into the corresponding polysubstituted 1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones. The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline ring occurs in numerous natural products and this moiety constitutes the central core of different series of compounds exerting platelet activating factor production inhibition.[18] Pyrrolo[3,2,1-*ij*]quinoline derivatives have also shown potent histamine and platelet activating factor antagonism and 5-lipoxygenase inhibitory properties.[19] Moreover, some pyrrolo[3,2,1-*ij*]quinolines exhibit antibacterial and antifungal activities for diseases of rice plants.[20] We subjected compounds **2a**–**d** to heteroannulation with

$PdCl_2$ in acetonitrile at 80 °C under argon atmosphere and we isolated products characterized using a combination of spectroscopic techniques as the corresponding 2-substituted 2,4-diaryl-8-bromo-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-ones **4a**–**d** (Scheme 3). Moreover, crystals of quality suitable for X-ray diffraction studies were obtained for compound **4a** and the molecular structure of compounds **4** was also confirmed (Figure) (CCDC 972588 contains the cif file for **4a** and the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif). Under the same reaction conditions employed on **2a**–**d**, the 4-aryl-6-bromo-8-(4-hydroxybutyn-1-yl)-2,3-dihydroquinolin-4-ones **2e**–**h** afforded products characterized using a combination of NMR and IR spectroscopic techniques as well as mass spectrometry as the corresponding 2-aryl-6-bromo-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-ones **4e**–**h**. The outcome of this reaction is surprising because, under similar reaction conditions, the analogous 8-(4-hydroxybut-1-yn-1-yl)-6-methyl-2,3-dihydroquinolin-4(1*H*)-one has previously been reported to afford 2-(2-hydroxyethyl)-8-methyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one in 85% yield.[8] The intriguing results observed in this investigation prompted us to propose a mechanism outlined in Scheme 4 to account for the observed oxidation of **2e**–**h** using $PdCl_2$.



2a-d **4a-d** **4e-h**

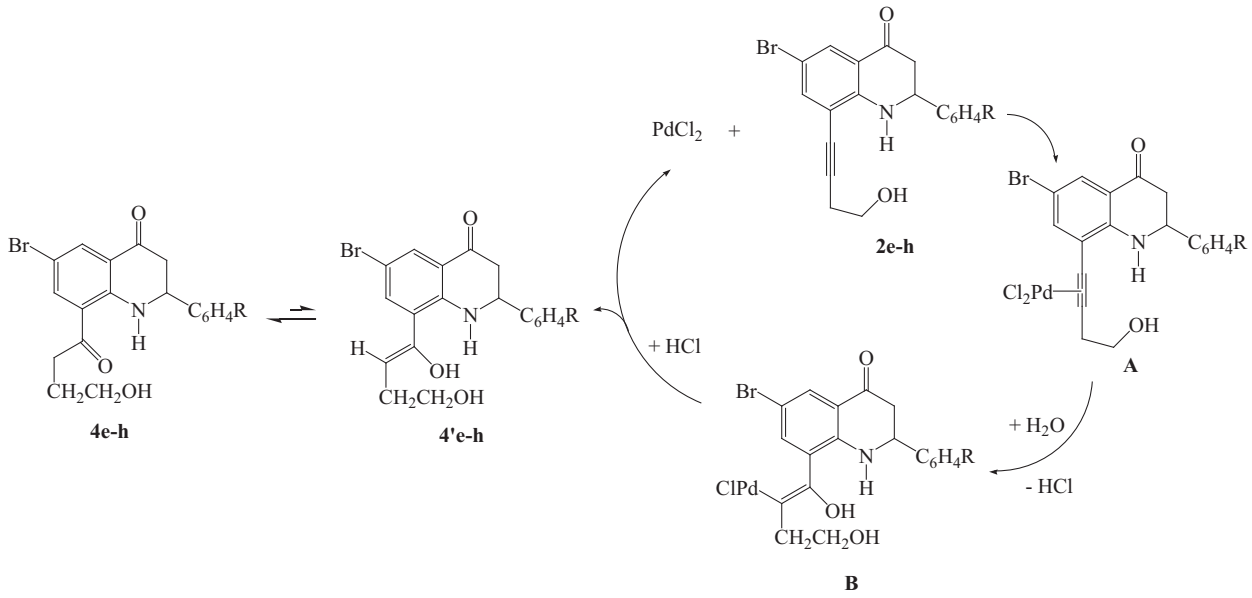
4	4-R	R'	% Yield
4a	4-H	$-C_6H_5$	68
4b	4-F	$-C_6H_5$	77
4c	4-Cl	$-C_6H_5$	70
4d	4-OMe	$-C_6H_5$	64
4e	4-H	$-CH_2CH_2OH$	50
4f	4-F	$-CH_2CH_2OH$	58
4g	4-Cl	$-CH_2CH_2OH$	50
4h	4-OMe	$-CH_2CH_2OH$	54

Reagents: (i) $PdCl_2$, CH_3CN, 80 °C, 3 h

Scheme 3. $PdCl_2$-mediated heteroannulation of **2a**–**d** and oxidation of **2e**–**h**.

Internal alkynes are known to undergo PdX_2 oxidation in the presence of CuX_2 co-catalyst and O_2 as an oxidant followed by hydrolysis to afford dicarbonyl compounds.[21] Palladium catalyzed anti-Markovnikov

addition of water to the carbon–carbon triple bond of arylpropargylic carbonates in the presence of secondary amines to afford α-ketocarbamates has also been observed before.[22] We envision the formation of products **4e**–**h** to involve initial coordination of pi electrons of the triple bond with the d_σ orbitals of $PdCl_2$. The absence of oxidized products from **2a**–**d** under argon atmosphere and the use of catalytic amount of $PdCl_2$ rule out the possibility of participation of water from the workup stage. Although we do not have X-ray crystal data to substantiate our rationale, the hydroxybutyn-1-yl group of compounds **2e**–**h** presumably forms strong intermolecular hydrogen bond/s with moisture during recrystallization. In our view, the hydrogen bonded water would then attack the coordinated intermediate **A** to form **B**. Since the reaction occurs under anhydrous conditions we envision that the released HCl reacts with intermediate **B** to generate the enol intermediate **4'** with concomitant release of $PdCl_2$ into the medium. The enol tautomers **4'** would then undergo tautomerization to generate products **4e**–**h** (Scheme 4). Despite the fact that our proposed mechanism is necessarily speculative, it represents the best option consistent with the formation of the observed products in the presence of $PdCl_2$.



Scheme 4. Plausible mechanism for the $PdCl_2$ catalyzed oxidation of **2e**–**h**.

In the last part of this investigation, we subjected compounds **4a**–**d** to Suzuki–Miyaura cross-coupling with arylboronic acids to afford novel 8-substituted 2,3-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-ones **5a**–**f** (Scheme 5).

In summary, the observed site-selective Csp^2–Csp bond formation through C-8 versus C-6 is attributed to the *ortho* directing effect of the NH and possible molecular orbital interaction between the heterocycle π^* (LUMO) and the PL_2d_σ (HOMO) orbitals in the oxidative addition stage. Monoalkynylation using Pd/C as catalyst is the consequence of the initial slow leaching of Pd from the support to generate the active homogeneous Pd(0) species and subsequent re-deposition of Pd onto the support upon reductive-elimination. In our view, the re-deposition of Pd makes it unavailable to promote further oxidative addition to the incipient 6-bromo-6-(alkynyl)quinolinones and subsequent cross-coupling with excess alkyne to afford the dialkynylated derivatives. Dialkynylation, on the other hand, requires the use of a homogeneous Pd catalyst as a source of the active Pd(0) species. The resultant 2-aryl-6-bromo-8-(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-ones were found to undergo $PdCl_2$-mediated cyclization to afford novel polysubstituted 4*H*-pyrrolo[*3,2,1-ij*]quinolin-6(5*H*)-ones.

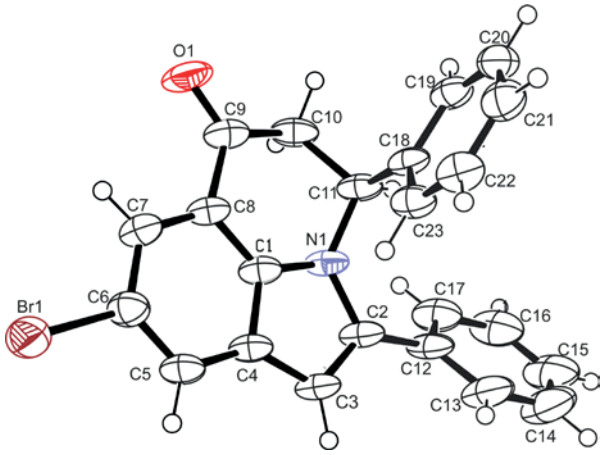
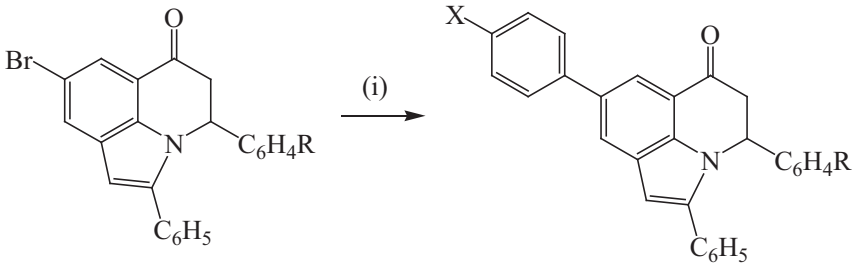


Figure. ORTEP diagram (50% probability level) of **4a** showing crystallographic numbering.



4a-d **5a-f**

	R	X	% Yield **5**
5a	4-H	4-F	67
5b	4-F	4-F	78
5c	4-Cl	4-F	62
5d	4-OMe	4-F	66
5e	4-H	4-OMe	78
5f	4-Cl	4-OMe	73

Reagents: (i) 4-$XC_6H_4B(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, dioxane, 100 °C, 3 h

Scheme 5. Suzuki–Miyaura cross-coupling of **4a**–**d** with arylboronic acids.

Hitherto, the preparation of the 6-oxopyrroloquinolines has generally been based on the cyclodehydration of a suitably functionalized indole derivative.[8] While the observed results for the oxidation of **2e**–**h** to afford products **5a**–**d** show the potential applications of the transformation, understanding of the detailed reaction mechanism would be useful for further expansion. In conclusion, the results of this investigation reveal that the choice of Pd(0) source and the proximity of the C–X bond to the nucleophilic heteroatom influence the

selectivity of the Csp^2–Csp bond formation during Sonogashira cross-coupling of quinolinones bearing two identical halogen atoms on the fused benzo ring.

3. Experimental

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 $CDCl_3$ solutions using a 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 a Synapt G2 Quadrupole Time-of-flight mass spectrometer. The synthesis and characterization of substrates **1a**–**d** have been described elsewhere.[11]

3.1. Typical procedure for Sonogashira coupling of 1 to afford monoalkynylated derivatives 2

3.1.1. 6-Bromo-2-phenyl-8-phenylethynyl-2,3-dihydroquinolin-4(1*H*)-one (2a)

A mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (**1a**) (0.50 g, 1.30 mmol), 10% Pd/C (0.015 g, 0.01 mmol), PPh_3 (0.013 g, 0.05 mmol), and CuI (0.02 g, 0.13 mmol) in EtOH/triethyl amine (2:1; v/v) (30 mL) in a three-necked flask equipped with a stirrer bar, rubber septum, and a condenser was degassed for 30 min. Phenylacetylene (0.29 g, 2.60 mmol) was added via a syringe and the mixture was degassed for an additional 10 min. A balloon filled with argon gas was connected to the top of the condenser and the mixture was heated at 100 °C under argon atmosphere for 18 h. The mixture was evaporated to dryness and the residue was dissolved in $CHCl_3$ (150 mL). The organic solvent was washed with brine (2 × 15 mL) and dried over anhydrous $MgSO_4$. The salt was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **2a** as a yellow solid (0.37 g, 71%), mp 153–155 °C (EtOH); R_f (toluene) 0.28; ν_{max} (ATR) 696, 753, 1475, 1582, 1672, 3373 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.83 (dd, J 5.7 and 16.2 Hz, 1H), 2.86 (dd, J 11.4 and 16.2 Hz, 1H), 4.82 (dd, J 5.7 and 11.4 Hz, 1H), 5.38 (s, 1H), 7.31–7.48 (m, 10H), 7.66 (d, J 2.1 Hz, 1H), 7.95 (d, J 2,1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.8, 57.2, 82.7, 97.5, 109.5, 111.7, 119.7, 122.0, 126.3, 128.5, 128.6, 129.1, 129.2 (2 × C), 130.3, 131.6, 140.0, 140.4, 150.3, 191.5; m/z: 402 (100, MH^+); HRMS (ES): MH^+, found 402.0484. $C_{23}H_{17}NO^{79}Br^+$ requires 402.0494.

3.1.2. 6-Bromo-2-(4-fluorophenyl)-8-(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (2b)

Yield (0.37 g, 74%), mp 151–152 °C (EtOH); R_f (toluene) 0.33; ν_{max} (ATR) 634, 685, 1233, 1491, 1582, 1680, 3373 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.85 (d, J 11.1 Hz, 1H), 2.86 (d, J 5.7 Hz, 1H), 4.81 (dd, J 5.7 and 11.1 Hz, 1H), 5.32 (s, 1H), 7.10 (t, J 8.7 Hz, 2H), 7.31–7.37 (m, 3H), 7.41–7.47 (m, 4H), 7.66 (d, J 2.1 Hz, 1H), 7.95 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.0, 57.0, 82.6, 97.6, 109.7, 111.7, 116.1 (d, $^2J_{CF}$ 21.3 Hz), 119.7, 121.9, 128.1 (d, $^3J_{CF}$ 8.3 Hz), 128.5, 129.1, 130.3, 131.5, 136.1 (d, $^4J_{CF}$ 3.4 Hz), 139.9, 150.1, 162.7 (d, $^1J_{CF}$ 246.2 Hz), 191.3; m/z: 420 (100, MH^+); HRMS (ES): MH^+, found 420.0391. $C_{23}H_{16}NO^{79}BrF^+$ requires 420.0399.

3.1.3. 6-Bromo-2-(4-chlorophenyl)-8-(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (2c).

Yield **2c** (0.38 g, 73%), mp 135–136 °C (EtOH); R_f (toluene) 0.38; ν_{max} (ATR) 684, 751, 822, 1164, 1477, 1570, 1680, 3357 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.85 (d, J 11.1 Hz, 1H), 2.86 (d, J 5.7 Hz, 1H), 4.81 (dd, J 5.7 and 11.1 Hz, 1H), 5.32 (s, 1H), 7.31–7.45 (m, 9H), 7.67 (d, J 2.4 Hz, 1H), 7.95 (d, J 2.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.7, 57.1, 82.5, 97.6, 109.7, 111.8, 119.6, 121.9, 127.7, 128.5, 129.1, 129.4, 130.3, 131.5, 134.4, 138.8, 140.0, 150.1, 191.1; m/z: 436 (100, MH^+); HRMS (ES): MH^+, found 436.0107. $C_{23}H_{16}NO^{79}Br^+$ requires 436.0104.

3.1.4. 6-Bromo-2-(4-methoxyphenyl)-8-(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (2d)

Yield (0.22 g, 78%), mp 133–134 °C (EtOH); R_f (toluene) 0.18; ν_{max} (ATR) 689, 790, 1281, 1512, 1672, 3358, 3613 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.80 (dd, J 4.5 and 16.2 Hz, 1H), 2.89 (dd, J 12.8 and 16.2 Hz, 1H), 3.81 (s, 3H), 4.76 (dd, J 4.5 and 12.8 Hz, 1H), 5.31 (s, 1H), 6.93 (d, J 8.1 Hz, 2H), 7.30–7.45 (m, 7H), 7.65 (d, J 2.1 Hz, 1H), 7.94 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.9, 55.3, 57.1, 82.7, 97.3, 109.4, 111.6, 114.5, 119.6, 122.0, 127.6, 128.5, 129.0, 130.3, 131.6, 132.3, 139.9, 150.4, 159.7, 191.8; m/z: 432 (100, MH^+); HRMS (ES): MH^+, found 432.0584. $C_{24}H_{19}NO_2^{79}Br^+$ requires 432.0599.

3.1.5. 6-Bromo-8-(4-hydroxybutyn-1-yl)-4-phenyl-2,3-dihydroquinolin-4(1*H*)-one (2e).

Yield (0.38 g, 77%), mp 129–130 °C (EtOH); R_f (toluene) 0.38; ν_{max} (ATR) 763, 881, 1055, 1239, 1494, 1579, 1676, 3360, 3387 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.89 (t, J5.4 Hz, 1H), 2.66 (t, J6.3 Hz, 2H), 2.78 (ddd, J 1.5, 6.3 and 16.2 Hz, 1H), 2.86 (dd, J 12.3 and 16.2 Hz, 1H), 3.74 (q, J 6.3 Hz, 2H), 4.74 (dd, J 5.1 and 12.0 Hz, 1H), 5.49 (s, 1H), 7.35–7.46 (m, 5H), 7.51 (d, J 2.7 Hz, 1H), 7.88 (d, J 2.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 23.7, 45.7, 57.5, 60.8, 76.1, 95.7, 109.1, 111.9, 119.3, 126.4, 128.5, 129.1, 129.5, 139.7, 140.4, 150.7, 191.8; m/z: 370 (100, MH^+); HRMS (ES): MH^+, found 370.0444. $C_{19}H_{17}NO_2^{79}Br^+$ requires 370.0443.

3.1.6. 6-Bromo-2-(4-fluorophenyl)-8-(4-hydroxybutyn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one (2f)

Yield (0.38 g, 75%), mp 131–132 °C (EtOH); R_f (40% ethyl acetate–toluene) 0.45; ν_{max} (ATR) 835, 1052, 1157, 1230, 1321, 1488, 1577, 1588, 1642, 3354 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.76 (t, J5.4 Hz, 1H), 2.67 (t, J6.3 Hz, 2H), 2.77 (ddd, J 1.5, 6.3 and 16.2 Hz, 1H), 2.83 (dd, J 12.3 and 16.2 Hz, 1H), 3.75 (q, J 6.3 Hz, 2H), 4.74 (dd, J 5.7 and 12.0 Hz, 1H), 5.44 (s, 1H), 7.08 (t, J8.7 Hz, 2H), 7.41 (t, J8.7 Hz, 2H), 7.51 (d, J 2.4 Hz, 1H), 7.88 (d, J 2.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 23.7, 45.7, 56.9, 60.8, 76.5, 95.8, 109.3, 112.0, 116.0 (d, $^2J_{CF}$ 21.4 Hz), 119.4, 128.2 (d, $^3J_{CF}$ 8.3 Hz), 129.8, 136.1 (d, $^4J_{CF}$ 3.2 Hz), 139.7, 150.6, 162.6 (d, $^1J_{CF}$ 245.9 Hz), 191.5; m/z: 388 (100, MH^+); HRMS (ES): MH^+, found 388.0338. $C_{19}H_{16}NO_2^{79}BrF$ requires 388.0348.

3.1.7. 6-Bromo-2-(4-chlorophenyl)-8-(4-hydroxybutyn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one (2g)

Yield (0.30 g, 77%), mp 151–152 °C (EtOH); R_f (40% ethyl acetate–toluene) 0.46; ν_{max} (ATR) 849, 1012, 1047, 1230, 1486, 1574, 1586, 1642, 3357 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.55 (s, 1H), 2.69 (t, J6.3 Hz, 2H), 2.78 (dd, J 6.3 and 16.2 Hz, 1H), 2.86 (dd, J 12.0 and 16.2 Hz, 1H), 3.77 (q, J 6.3 Hz, 2H), 4.74 (dd, J 6.3 and 12.0 Hz, 1H), 5.44 (s, 1H), 7.39 (m, 4H), 7.53 (d, J 2.7 Hz, 1H), 7.89 (d, J 2.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$)

23.7, 45.6, 56.0, 60.8, 76.0, 95.9, 109.4, 112.0, 119.4, 127.9, 129.3, 129.8, 134.3, 138.9, 139.8, 150.5, 191.4; m/z: 404 (100, MH^+); HRMS (ES): MH^+, found 404.0039. $C_{19}H_{16}NO_2^{35}Cl^{79}Br$ requires 404.0053.

3.1.8. 6-Bromo-8-(4-hydroxybutyn-1-yl)-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (2h)

Yield (0.18 g, 74%), mp 108–110 °C (EtOH); R_f (40% ethyl toluene ether) 0.35; ν_{max} (ATR) 730, 828, 891, 1037, 1231, 1251, 1490, 1572, 1588, 1646, 3349 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.57 (s, 1H), 2.67 (t, J 6.3 Hz, 2H), 2.75 (dd, J 6.3 and 16.2 Hz, 1H), 2.86 (dd, J 12.0 and 16.2 Hz, 1H), 3.76 (q, J 6.3 Hz, 2H), 3.82 (s, 3H), 4.71 (dd, J 6.3 and 12.0 Hz, 1H), 5.41 (s, 1H), 6.92 (d, J 8.7 Hz, 2H), 7.37 (d, J 8.7 Hz, 2H), 7.51 (d, J 2.7 Hz, 1H), 7.90 (d, J 2.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 23.7, 45.8, 55.3, 57.1, 60.8, 76.2, 95.6, 109.1, 111.7, 114.3, 119.4, 127.7, 129.8, 132.3, 139.7, 150.8, 159.7, 192.0; m/z: 400 (100, MH^+); HRMS (ES): MH^+, found 400.0548. $C_{20}H_{19}NO_3^{79}Br$ requires 400.0545.

3.2. $PdCl_2(PPh_3)_2$-CuI mediated Sonogashira cross-coupling of 1a with phenylacetylene in the presence of activated carbon 6-Bromo-4-phenyl-8-phenylethynyl-2,3-dihydroquinolin-4(1*H*)-one (2a)

A mixture of 6,8-dibromo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (**1a**) (0.50 g, 1.3 mmol), $PdCl_2(PPh_3)_2$ (0.023 g, 0.03 mmol), activated carbon (0.004 g, 0.3 mmol), and CuI (0.057 g, 0.3 mmol) in $EtOH/NEt_3$ (30 mL; 2:1) in a three-necked flask equipped with a stirrer bar, rubber septum, and a condenser was degassed for 30 min. Phenyl acetylene (0.22 mL, 2.0 mmol) was added via a syringe and the mixture stirred for another 10 min. A balloon filled with argon gas was connected to the top of the condenser and the mixture was heated at 100 °C for 72 h (tlc monitoring revealed no significant reaction after 18 h). The cooled reaction mixture was concentrated and the residue dissolved in $CHCl_3$ (150 mL). The organic layer was washed with brine (2 × 15 mL), dried, and filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the following products in sequence:

2a solid (0.30 g, 57%); mp 153–155 °C (EtOH); R_f (toluene) 0.28, and **2-Phenyl-6,8-bis(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3a)**, solid (0.13 g, 26%), mp 139–141 °C (EtOH); R_f (toluene) 0.42; ν_{max} (ATR) 688, 753, 1211, 1244, 1489, 1513, 1569, 1592, 1671, 3401 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.82–2.99 (m, 2H), 4.88 (dd, J 6.3 and 10.8 Hz, 1H), 5.53 (s, 1H), 7.32–7.38 (m, 5H), 7.39–7.49 (m, 10H), 7.74 (d, J 2.1 Hz, 1H), 8.03 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.0, 57.6, 83.2, 88.2, 88.3, 96.7, 109.9, 112.5, 118.4, 122.2, 123.3, 126.3, 128.1, 128.3, 128.5, 128.6, 128.9, 129.2, 130.3, 131.2, 131.4, 131.6, 140.5, 150.9, 192.0; m/z: 424 (100, MH^+); HRMS (ES): MH^+, found 424.1709. $C_{31}H_{22}NO^+$ requires 424.1701.

3.3. Typical procedure for $PdCl_2(PPh_3)_2$–CuI mediated Sonogashira cross-coupling of 1a–d in the absence of activated carbon 3

3.3.1. 2-Phenyl-6,8-bis(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3a)

A mixture of **1a** (0.50 g, 1.30 mmol), $PdCl_2(PPh_3)_2$ (0.046 g, 0.066 mmol), and CuI (0.025 g, 0.131 mmol) in triethylamine–ethanol mixture (20 mL) in a three-necked flask equipped with a stirrer, condenser, and rubber septum was flushed with argon gas for 30 min. Phenylacetylene (0.403 g, 3.90 mmol) was added to the flask via a syringe and the mixture was flushed for an additional 10 min with argon and then heated at 80 °C for 6 h under inert atmosphere. The cooled mixture was added to a beaker containing ice-cold water and the product

was extracted into chloroform. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography to afford **3a** as a solid (0.416 g, 76%); R_f (toluene) 0.42.

3.3.2. 2-(4-Fluorophenyl)-6,8-bis(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3b)

Yield (0.412 g, 78%), mp 136–138 °C (EtOH); R_f (toluene) 0.438; ν_{max} (ATR) 687, 751, 834, 1223, 1499, 1592, 1678, 3366 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.83–2.96 (m, 2H), 4.87 (dd, J 6.3 and 10.8 Hz, 1H), 5.47 (s, 1H), 7.11 (t, J 8.7 Hz, 2H), 7.32–7.43 (m, 5H), 7.42–7.50 (m, 7H), 7.74 (d, J 2.1 Hz, 1H), 8.03 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.9, 56.9, 83.1, 88.1. 88.4, 96.8, 109.9, 112.6, 116.1 (d, $^2J_{CF}$ 21.4 Hz), 118.3, 122.1, 123.2, 128.0 (d, $^3J_{CF}$ 3.5 Hz), 128.1, 128.3, 128.5, 128.9, 131.2, 131.4, 131.5, 136.1 (d, $^3J_{CF}$ 3.2 Hz), 140.4, 150.6, 162.6 (d, $^1J_{CF}$ 245.9 Hz), 191.6; m/z: 442 (100, MH^+); HRMS (ES): MH^+, found 442.1599. $C_{31}H_{21}NOF$ requires 442.1607.

3.3.3. 2-(4-Chlorophenyl)-6,8-bis(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3c)

Yield (0.31 g, 73%), mp 143–144 °C (EtOH); R_f (40% ethyl acetate–toluene) 0.50; ν_{max} (ATR) 690, 752, 825, 890, 1237, 1488, 1504, 1591, 1681, 3379 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.81–2.95 (m, 2H), 4.86 (dd, J 6.3 and 10.8 Hz, 1H), 5.46 (s, 1H), 7.31–7.51 (m, 14H), 7.74 (d, J 2.1 Hz, 1H), 8.03 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.9, 57.0, 83.0, 88.1, 88.4, 96.8, 110.0, 112.8, 118.4, 122.1, 123.2, 127.8, 128.1, 128.4, 128.5, 129.0, 129.4, 131.2, 131.4, 131.5, 134.4, 138.9, 140.5, 150.6, 191.6; m/z: 458 (100, MH^+); HRMS (ES): MH^+, found 458.1292. $C_{31}H_{21}NO^{35}Cl^+$ requires 458.1312.

3.3.4. 2-(4-Methoxyphenyl)-6,8-bis(phenylethynyl)-2,3-dihydroquinolin-4(1*H*)-one (3d)

Yield (0.30 g, 68%), mp 162–164 °C (EtOH); R_f (toluene) 0.14; ν_{max} (ATR) 688, 752, 832, 898, 1029, 1235, 1305, 1494, 1591, 1675, 3391 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.82 (dd, J 4.5 and 12.6 Hz, 1H), 2.92 (dd, J 12.6 and 16.2 Hz, 1H), 3.82 (s, 3H), 4.82 (dd, J 4.5 and 12.6 Hz, 1H), 5.47 (s, 1H), 6.94 (d, J 8.4 Hz, 2H), 7.32–7.51 (m, 12H), 7.73 (d, J 1.5 Hz, 1H), 8.03 (d, J 1.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.0, 55.3, 57.0, 83.2, 88.2, 88.3, 96.6, 109.9, 112.4, 114.5, 118.3, 122.2, 123.3, 127.6, 128.1, 128.3, 128.5, 128.9, 131.3, 131.4, 131.6, 132.4, 140.4, 150.9, 159.7, 192.2; m/z: 454 (100, MH^+); HRMS (ES): MH^+, found 454.1809. $C_{32}H_{24}NO_2^+$ requires 454.1807.

3.3.5. 2-(4-Fluorophenyl)-6,8-bis(4-hydroxybutyn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one (3e)

Yield (0.25 g, 71%), mp 115–116 °C (EtOH); R_f (40% ethyl acetate–toluene) 0.16; ν_{max} (ATR) 841, 1038, 1227, 1493, 1507, 1601, 1663, 3393, 3553 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.72 (t, J 5.4 Hz, 1H), 1.91 (t, J 5.4 Hz, 1H), 2.64 (t, J 6.3 Hz, 2H), 2.67 (t, J 6.3 Hz, 2H), 2.75 (ddd, J 1.5, 5.1 and 16.2 Hz, 1H), 2.84 (dd, J 12.0 and 16.2 Hz, 1H), 3.76 (t, J 5.4 Hz, 2H), 3.77 (t, J 5.4 Hz, 2H), 4.78 (dd, J 5.1 and 12.0 Hz, 1H), 5.53 (s, 1H), 7.09 (t, J 8.7 Hz, 2H), 7.43 (t, J 8.7 Hz, 2H), 7.47 (d, J 1.8 Hz, 1H), 7.84 (d, J 1.8 Hz, 1H); (75 MHz, $CDCl_3$) 23.6, 23.7, 45.9, 56.9, 60.8, 61.2, 81.1, 85.0, 94.7, 110.1, 112.4, 116.0 (d, $^2J_{CF}$ 21.6 Hz), 118.0, 128.2 (d, $^3J_{CF}$ 8.0 Hz), 130.8, 132.0, 136.3 (d, $^4J_{CF}$ 3.2 Hz), 140.3, 151.0, 162.6 (d, $^1J_{CF}$ 245.9 Hz) 192.0;m/z: 378 (100, MH^+); HRMS (ES): MH^+, found 378.1509. $C_{23}H_{21}NO_3F^+$ requires 378.1505.

3.3.6. 2-(4-Chlorophenyl)-6,8-bis(4-hydroxybutyn-1-yl)-2,3-dihydroquinolin-4(1*H*)-one (3f)

Yield (0.33 g, 69%), mp 107–108 °C (EtOH); R_f (40% ethyl acetate–toluene) 0.18; ν_{max} (ATR) 827, 1016, 10401, 1239, 1239, 1489, 1600, 1658, 3278, 3354 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.05 (br s, 1H), 2.49 (t, J6.3 Hz, 1H), 2.62 (t, J 6.3 Hz, 2H), 2.66 (t, J 6.3 Hz, 2H), 2.74 (dd, J 5.7 and 16.2 Hz, 1H), 2.86 (dd, J 12.0 and 16.2 Hz, 1H), 3.68–3.77 (m, 4H), 4.74 (dd, J 5.7 and 12.0 Hz, 1H), 5.54 (s, 1H), 7.35 (s, 4H), 7.45 (d, J 1.8 Hz, 1H), 7.81 (d, J 1.8 Hz, 1H); (75 MHz, $CDCl_3$) 23.6, 45.7, 56.9, 60.7, 60.8, 61.1, 76.5, 81.0, 85.1, 94.9, 110.2, 112.5, 118.0, 127.8, 128.6, 129.3, 130.7, 132.0, 139.0, 140.4, 150.9, 191.8; m/z: 394 (100, MH^+); HRMS (ES): MH^+, found 394.1212. $C_{23}H_{21}NO_3^{35}Cl^+$ requires 394.1210.

3.4. Typical procedure for $PdCl_2$ catalyzed heterocyclization of 2a–d

3.4.1. 8-Bromo-2,4-diphenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (4a)

A stirred mixture of **2a** (0.32 g, 0.7 mmol) and $PdCl_2$ (0. 007 g, 0.03 mmol) in MeCN (15 mL) was heated at 90 °C under argon atmosphere for 3 h. The mixture was evaporated to dryness and the residue was dissolved in $CHCl_3$ (100 mL). The organic solvent was washed with brine, dried over $MgSO_4$, and the salt was filtered off. The solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column to afford **4a** as a yellow solid (0.25 g, 78%), mp 169–179 °C; R_f (toluene) 0.34; ν_{max} (ATR) 693, 754, 870, 1111, 1314, 1369, 1445, 1683 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.17 (dd, J 1.8 and 16.2 Hz, 1H), 3.74 (dd, J 6.9 and 16.2 Hz, 1H), 5.96 (d, J 6.9 Hz, 1H), 6.48–6.52 (m, 2H), 6.67 (s, 1H), 7.10–7.13 (m, 3H), 7.36 (s, 5H), 7.80 (d, J 2.1 Hz, 1H), 8.00 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.8, 57.1, 103.0, 114.1, 119.4, 121.1, 125.0, 128.0, 128.7, 128.8, 128.8, 128.9, 129.0, 129.4, 131.1, 140.2, 143.3, 190.6; m/z: 402 (100, MH^+); HRMS (ES): MH^+, found 402.0494. $C_{23}H_{17}NO^{79}Br^+$ requires 402.0491.

3.4.2. 8-Bromo-4-(4-fluorophenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (4b)

Yield (0.27 g, 77%), mp 136–137 °C; R_f (toluene) 0.35; ν_{max} (ATR) 696, 818, 1205, 1223, 1438, 1504, 1600, 1689 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.13 (dd, J 1.8 and 16.2 Hz, 1H), 3.66 (dd, J 6.9 and 16.2 Hz, 1H), 5.95 (d, J 6.9 Hz, 1H), 6.46 (t, J8.7 Hz, 2H), 6.66 (s, 1H), 6.78 (t, J 8.7 Hz, 2H), 7.32–7.40 (m, 5H), 7.81 (d, J 2.1 Hz, 1H), 7.98 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.7, 56.5, 103.2, 114.2, 115.9 (d, $^2J_{CF}$ 21.7 Hz), 119.3, 121.2, 126.8 (d, $^3J_{CF}$ 8.3 Hz), 128.7, 128.8, 128.9, 129.0, 129.4, 130.9, 135.9 (d, $^4J_{CF}$ 3.1 Hz), 138.9, 143.2, 162.2 (d, $^1J_{CF}$ 245.6 Hz), 190.4; m/z: 420 (100, MH^+); HRMS (ES): MH^+, found 420.0388. $C_{23}H_{16}NOF^{79}Br^+$ requires 420.0399.

3.4.3. 8-Bromo-4-(4-chlorophenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (4c)

Yield (0.21 g, 70%), mp 138–139 °C (EtOH); R_f (toluene) 0.45; ν_{max} (ATR) 750, 815, 873, 1090, 1461, 1485, 1687 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.12 (dd, J 1.5 and 16.5 Hz, 1H), 3.65 (dd, J 6.9 and 16.5 Hz, 1H), 5.94 (d, J 6.9 Hz, 1H), 6.41 (d, J8.7 Hz, 2H), 6.67 (s, 1H), 7.07 (d, J 8.7 Hz, 2H), 7.32–7.40 (m, 5H), 7.81 (d, J 2.1 Hz, 1H), 8.00 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.6, 56.5, 103.2, 114.3, 119.3, 121.3, 126.4, 128.7, 128.8, 128.9, 129.1, 129.2, 129.4, 130.8, 133.9, 138.6, 138.9, 143.2, 190.2; m/z: 436 (100, MH^+); HRMS (ES): MH^+, found 436.0104. $C_{23}H_{16}NO^{35}Cl^{79}Br^+$ requires 436.0103.

3.4.4. 8-Bromo-4-(4-methoxyphenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (4d)

Yield (0.13 g, 64%), mp 162–163 °C; R_f (toluene) 0.26; ν_{max} (ATR) 701, 754, 823, 1028, 1247, 1462, 1512, 1685 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.14 (dd, J 1.5 and 16.5 Hz, 1H), 3.62 (dd, J 6.9 and 16.5 Hz, 1H), 3.67 (s, 3H), 5.92 (d, J 6.9 Hz, 1H), 6.43 (d, J8.7 Hz, 2H), 6.62 (d, J 8.7 Hz, 2H), 6.65 (s, 1H), 7.37 (s, 5H), 7.80 (d, J 2.1 Hz, 1H), 7.99 (d, J 2.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.9, 55.1, 56.6, 102.9, 114.0, 114.3, 119.4, 121.0, 126.2, 128.7 (2 × C), 128.8 (2 × C), 129.4, 131.1, 132.2, 139.0, 143.2, 159.2, 190.9; m/z: 432 (100, MH^+); HRMS (ES): MH^+, found 432.0596. $C_{24}H_{19}NO_2^{79}Br^+$ requires 432.0599.

3.4.5. 6-Bromo-8-(4-hydroxybutanoyl)-2-phenyl-2,3-dihydroquinolin-4(1*H*)-one (4e)

Yield (0.08 g, 50%), mp 125–127 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.25; ν_{max} (ATR) 697, 761, 1018, 1053, 1128, 1232, 1324, 1488, 1566, 1590, 1649, 1676, 3288, 3373 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.60 (br s, 1H), 1.96 (q, J 6.0 Hz, 2H), 2.82–2.96 (m, 2H), 3.10 (t, J 6.0 Hz, 2H), 3.73 (t, J 6.0 Hz, 2H), 4.80 (dd, J 4.5 and 12.3 Hz, 1H), 7.39 (s, 5H), 8.11 (d, J 1.2 Hz, 1H), 8.15 (d, J 1.2 Hz, 1H), 9.34 (s, 1H); δ_C (75 MHz, $CDCl_3$) 26.8, 35.8, 44.8, 56.3, 62.0, 107.2, 121.0, 121.7, 126.3, 128.6, 129.2, 136.2, 139.9, 140.2, 151.2, 191.3, 201.6; m/z: 386 (100, MH^+); HRMS (ES): MH^+, found 386.0380. $C_{19}H_{19}NO_3^{79}Br^+$ requires 386.0392.

3.4.6. 6-Bromo-2-(4-fluorophenyl)-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-one (4f)

Yield (0.12 g, 58%), mp 148–149 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.30; ν_{max} (ATR) 642, 831, 857, 888, 1019, 1119, 1219, 1480, 1561, 1643, 1687, 3330, 3375 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.59 (br s, 1H), 1.96 (q, J 6.0 Hz, 2H), 2.80–2.90 (m, 2H), 3.10 (t, J 6.0 Hz, 2H), 3.73 (t, J 6.0 Hz, 2H), 4.80 (dd, J 4.5 and 12.3 Hz, 1H), 7.09 (d, J 8.7 Hz, 2H), 7.39 (d, J 8.7 Hz, 2H), 8.12 (d, J 1.2 Hz, 1H), 8.16 (d, J 1.2 Hz, 1H), 9.31 (s, 1H); δ_C (75 MHz, $CDCl_3$) 26.8, 35.8, 44.9, 55.7, 62.0, 107.4, 116.1 (d, $^2J_{CF}$ 21.4 Hz), 121.0, 121.7, 128.1 (d, $^3J_{CF}$ 8.3 Hz), 135.7 (d, $^4J_{CF}$ 3.2 Hz), 136.2, 140.2, 151.1, 162.6 (d, $^1J_{CF}$ 245.9 Hz), 191.0, 201.7; m/z: 406 (100, MH^+); HRMS (ES): MH^+, found 406.0454. $C_{19}H_{18}NO_3F^{79}Br^+$ requires 406.0436.

3.4.7. 6-Bromo-2-(4-chlorophenyl)-8-(4-hydroxybutanoyl)-2,3-dihydroquinolin-4(1*H*)-one (4g)

Yield (0.13 g, 50%), mp 150–151 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.34; ν_{max} (ATR) 640, 851, 890, 1016, 1122, 1228, 1324, 1485, 1563, 1644, 1688, 3301, 3374 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.63 (br s, 1H), 1.96 (q, J 6.0 Hz, 2H), 2.880–2.88 (m. 2H), 3.10 (t, J 6.3 Hz, 2H), 3.73 (t, J 6.0 Hz, 2H), 4.79 (dd, J 4.5 and 12.3 Hz, 1H), 7.35 (s, 4H), 8.11 (d, J 1.2 Hz, 1H), 8.15 (d, J 1.2 Hz, 1H), 9.32 (s, 1H); δ_C (75 MHz, $CDCl_3$) 26.8, 35.8, 44.7, 55.7, 62.0, 107.5, 121.0, 121.7, 127.7, 129.4, 134.4, 136.1, 138.5, 140.2, 151.0, 190.8, 201.7; m/z: 422 (100, MH^+); HRMS (ES): MH^+, found 422.0159. $C_{19}H_{18}NO_3^{79}Br^+$ requires 422.0139.

3.4.8. 6-Bromo-8-(4-hydroxybutanoyl)-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (4h)

Yield (0.13 g, 54%), mp 117–118 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.19; ν_{max} (neat) 646, 831, 1021, 1122, 1247, 1483, 1562, 1646, 1687, 3298, 3374 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.76 (br s, 1H), 1.95 (q, J 6.0 Hz, 2H), 2.80 (dd, J 4.5 and 16.8 Hz, 1H), 2.88 (dd, J 12.3 and 16.8 Hz, 1H), 3.09 (t, J 6.3 Hz, 2H), 3.72 (t, J 6.0 Hz, 2H), 3.81 (s, 3H), 4.74 (dd, J 4.5 and 12.3 Hz, 1H), 6.91 (d, J 9.3 Hz, 2H), 7.32 (d, J 9.3 Hz, 2H), 8.09 (d, J 1.2 Hz, 1H), 8.14 (d, J 1.2 Hz, 1H), 9.26 (s, 1H); δ_C (75 MHz, $CDCl_3$) 26.8, 35.8, 44.8, 55.4, 55.7,

62.0, 107.1, 114.5, 120.9, 121.7, 127.6, 131.9, 136.1, 140.1, 151.1, 159.7, 191.5, 201.6; m/z: 416 (100, MH^+); HRMS (ES): MH^+, found 416.0494. $C_{20}H_{21}NO_4^{79}Br^+$ requires 416.0497.

3.5. Typical procedure for the Suzuki–Miyaura cross-coupling of 4 to afford 5

3.5.1. 8-(4-Fluorophenyl)-2,4-diphenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5a)

A stirred mixture of **4a** (0.15 g, 0.3 mmol), 4-$FC_6H_4B(OH)_2$ (0.06 g, 0.4 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.01 mmol), PCy_3 (0.01 g, 0.03 mmol), and K_2CO_3 (0.1 g, 0.7 mmol) in dioxane/water (3:1; v/v) (15 mL) was degassed for 0.5 h. The mixture was then heated at 100 °C for 3 h. The mixture was allowed to cool and then quenched with ice-cold water (20 mL). The product was extracted into $CHCl_3$ (3 × 30 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$, and then filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on a silica gel column to afford **5a** as a solid (0.103 g, 67%), mp 195–196 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.78; ν_{max} (ATR) 693, 756, 835, 1215, 1451, 1467, 1589, 1599, 1667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.21 (d, J 0.9 and 16.2 Hz, 1H), 3.71 (dd, J 6.0 and 16.2 Hz, 1H), 6.00 (d, J 6.0 Hz, 1H), 6.56 (t, J 8.7 Hz, 2H), 6.77 (s, 1H), 6.80 (t, J 8.7 Hz, 2H), 7.14 (t, J 8.7 Hz, 2H), 7.11–7.17 (m, 5H), 7.38 (s, 5H), 7.62 (t, J 8.7 Hz, 2H), 7.90 (d, J 0.6 Hz, 1H), 8.05 (d, J 0.6 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.0, 57.1, 103.8, 15.5 (d, $^2J_{CF}$ 21.3 Hz), 117.8, 118.6, 125.1 (d, $^3J_{CF}$ 8.0 Hz), 127.9, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 3.4, 133.4, 137.6 (d, $^4J_{CF}$ 3.0 Hz), 140.0, 140.4, 142.7, 162.2 (d, $^1J_{CF}$ 244.4 Hz), 191.8; m/z: 418 (100, MH^+); HRMS (ES): MH^+, found 418.1606. $C_{29}H_{21}NOF^+$ requires 418.1607.

3.5.2. 4,8-Bis(4-fluorophenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5b)

Yield (0.118 g, 78%), mp 221–222 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.80; ν_{max} (ATR) 527, 835, 1116, 1214, 1407, 1466, 1599, 1668 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.17 (dd, J 1.8 and 16.2 Hz, 1H), 3.71 (dd, J 6.0 and 16.2 Hz, 1H), 5.98 (d, J 6.0 Hz, 1H), 6.52 (t, J 8.7 Hz, 2H), 6.77 (s, 1H), 6.80 (t, J 8.7 Hz, 2H), 7.14 (t, J 8.7 Hz, 2H), 7.39 (s, 5H), 7.62 (t, J 8.7 Hz, 2H), 7.91 (d, J 1.5 Hz, 1H), 8.05 (d, J 1.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.1, 56.6, 103.8, 115.7 (d, $^2J_{CF}$ 21.4 Hz), 115.9 (d, $^2J_{CF}$ 21.6 Hz), 118.0, 118.6, 125.3, 128.8, 126.9, 128.3, 128.7 (d, $^3J_{CF}$ 8.0 Hz), 128.8, 128.9 (d, $^3J_{CF}$ 8.0 Hz), 131.4, 133.6, 136.2 (d, $^4J_{CF}$ 3.2 Hz), 137.6 (d, $^4J_{CF}$ 3.1 Hz), 139.9, 142.7, 162.2 (d, $^1J_{CF}$ 245.5 Hz), 162.3 (d, $^1J_{CF}$ 245.6 Hz), 191.5; m/z: 436 (100, MH^+); HRMS (ES): MH^+, found 436.1518. $C_{29}H_{20}NOF_2^+$ requires 436.1513.

3.5.3. 4-(4-Chlorophenyl)-8-(4-fluorophenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5c)

Yield **5c** (0.052 g, 62%), mp 240–241 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.85; ν_{max} (ATR) 527, 697, 744, 836, 1214, 1469, 1668 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.25 (dd, J 1.8 and 16.2 Hz, 1H), 3.71 (dd, J 6.0 and 16.2 Hz, 1H), 6.00 (d, J 6.0 Hz, 1H), 6.57 (dd, J 1.8 and 7.8 Hz, 2H), 6.77 (s, 1H), 7.13 (dd, J 1.8 and 7.8 Hz, 2H), 7.14 (t, J 8.7 Hz, 2H), 7.38 (s, 5H), 7.62 (t, J 8.7 Hz, 2H), 7.90 (d, J 1.5 Hz, 1H), 8.05 (d, J 1.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.1, 57.2, 103.8, 115.6 (d, $^2J_{CF}$ 21.0 Hz), 117.9, 118.6, 125.1, 125.2, 127.9, 128.2, 128.6, 128.7, 128.8, 128.9 (d, $^3J_{CF}$ 8.1 Hz), 129.0, 131.5, 133.4, 137.6 (d, $^4J_{CF}$ 3.1 Hz), 140.0, 140.5, 142.8, 162.1 (d, $^1J_{CF}$ 244.4 Hz), 191.8; m/z: 452 (100, MH^+); HRMS (ES): MH^+, found 452.1213. $C_{29}H_{20}NOF^{35}Cl^+$ requires 452.1217.

3.5.4. 8-(4-Fluorophenyl)-4-(4-methoxyphenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5d)

Yield (0.068 g, 66%), mp 215–216 °C (EtOH); R_f (20% ethyl acetate–toluene) 0.73; ν_{max} (ATR) 760, 838, 1036, 1115, 1215, 1247, 1467, 1512, 1611, 1663 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.18 (dd, J 1.5 and 16.2 Hz, 1H), 3.67 (s, 3H), 3.68 (dd, J 6.0 and 16.2 Hz, 1H), 5.95 (d, J 6.0 Hz, 1H), 6.49 (d, J 8.7 Hz, 2H), 6.63 (d, J 8.7 Hz, 2H), 6.75 (s, 1H), 7.14 (t, J 8.7 Hz, 2H), 7.33 (s, 5H), 7.62 (t, J 8.7 Hz, 2H), 7.90 (d, J 1.8 Hz, 1H), 8.04 (d, J 1.8 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.2, 55.1, 56.7, 103.7, 114.2, 115.6 (d, $^2J_{CF}$ 21.1 Hz), 117.8, 118.6, 125.1, 126.3, 128.2, 128.5, 128.7 (d, $^3J_{CF}$ 8.0 Hz), 128.8, 128.9, 131.6, 132.6, 133.3, 137.7 (d, $^4J_{CF}$ 3.1 Hz), 139.9, 142.7, 159.0, 162.3 (d, $^1J_{CF}$ 245.2 Hz), 192.0; m/z: 448 (100, MH^+); HRMS (ES): MH^+, found 448.1710. $C_{30}H_{23}NO_2F^+$ requires 448.1713.

3.5.5. 8-(4-Methoxyphenyl)-2,4-diphenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5e)

Yield (0.10 g, 78%), mp 170–171 °C (EtOH); R_f (20% ethyl acetate–toluene) 0.77; ν_{max} (ATR) 695, 754, 826, 1025, 115, 1180, 1224, 1244, 1443, 1469, 1595, 1672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.20 (dd, J 1.5 and 16.2 Hz, 1H), 3.70 (dd, J 6.0 and 16.2 Hz, 1H), 3.86 (s, 3H), 6.04 (d, J 6.0 Hz, 1H), 6.57 (d, J 8.7 Hz, 2H), 6.77 (s, 1H), 7.00 (d, J 8.7 Hz, 2H), 7.11 (s, 1H), 7.12 (s, 2H), 7.38 (s, 5H), 7.62 (t, J 8.7 Hz, 2H), 7.93 (d, J 1.8 Hz, 1H), 8.06 (d, J 1.8 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 46.1, 55.4, 57.1, 103.8, 114.2, 117.8, 118.6, 124.9, 125.1, 127.8, 128.2, 128.4 (2 × C), 128.7, 128.8, 128.9, 131.6, 134.1, 134.2, 139.9, 140.6, 142.5, 158.9, 191.9; m/z: 430 (100, MH^+); HRMS (ES): MH^+, found 430.1815. $C_{30}H_{24}NO_2^+$ requires 430.18107.

3.5.6. 4-(4-Chlorophenyl)-8-(4-methoxyphenyl)-2-phenyl-4*H*-pyrrolo[3,2,1-*ij*]quinolin-6(5*H*)-one (5f)

Yield (0.08 g, 73%), mp 158–159 °C (EtOH); R_f (20% ethyl acetate–hexane) 0.80; ν_{max} (ATR) 698, 755, 828, 1012, 1093, 1112, 1223, 1247, 1469, 1593, 1665 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.15 (dd, J 1.5 and 16.2 Hz, 1H), 3.71 (dd, J 6.0 and 16.2 Hz, 1H), 3.86 (s, 3H), 5.97 (d, J 6.0 Hz, 1H), 6.48 (d, J 8.4 Hz, 2H), 6.76 (s, 1H), 7.00 (d, J 8.4 Hz, 2H), 7.06 (d, J 8.4 Hz, 2H), 7.38 (s, 5H), 7.62 (d, J 8.4 Hz, 2H), 7.93 (d, J 1.5 Hz, 1H), 8.06 (d, J 1.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 45.9, 55.4, 56.6, 104.0, 114.3, 117.9, 118.5, 125.1, 126.6, 128.2, 128.4, 128.6, 128.7, 128.8, 129.1, 131.4, 133.7,0 134.0, 134.3, 139.0, 139.7, 142.5, 158.9, 191.5; m/z: 464 (100, MH^+); HRMS (ES): MH^+, found 464.1404. $C_{30}H_{23}NO_2^{35}Cl^+$ requires 464.1401.

Acknowledgements

The authors are grateful to the University of South Africa and the National Research Foundation (NRF) in South Africa for financial assistance.

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