Letter - spectral assignments

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Synthesis and structure elucidation of a series of chloroquinoline-2-chalcones by the Doebner–Miller reaction

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Introduction

Quinoline chalcones are a group of compounds in which one of the phenyl rings of the chalcone backbone is substituted with a quinoline moiety, where both the phenyl group and the quinoline moiety are separated by an α,β-unsaturated carbonyl group. The quinoline moiety can either be on the side of the alkene or the ketone. If synthesised from quinoline carbaldehydes, the quinoline is adjacent to the alkene, and when formed from quinoline acetophenones, it is next to the ketone.

The synthesis of quinoline-2-chalcones is rare, and only a few reports exist in the literature.[1–3] In these instances, quinoline-2-carbaldehydes were synthesised as intermediates, which were then condensed with acetophenones, leading to quinoline-2-chalcones with the quinoline moiety adjacent to the alkene. These compounds have shown anticancer activity against lung and breast cancer cells,[2] antileishmanial activity[3] and anti-inflammatory properties.[4] Further to this, a complete NMR elucidation of these compounds is absent in the literature. The only assignment made in the literature is that of the *trans* olefinic protons, probably because they are an indication that the chalcone hybrids have been formed.

Herein we report the synthesis of 15 new quinoline-2-chalcone hybrids via the quinoline-2-carbaldehyde and have carried out a complete structural elucidation of them using 1D and 2D NMR. The effect of containing a fluorine atom in these compounds is also discussed, which results in very characteristic NMR spectra. The manner in which these fluorinated compounds are structurally elucidated is also quite unique in that ^{13}C NMR resonances can be used to identify proton resonances unambiguously.

Experimental

General experimental procedures

All reagents and chemicals used in this study were purchased from Sigma-Aldrich *via* Capital Lab, South Africa and were reagent grade. All organic solvents were redistilled and dried according to standard procedures. Thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} plates. Crude compounds were purified with column chromatography using silica gel (60–120 mesh) as the stationary phase and varying combinations of solvents depending on the sample to be purified. The melting points were measured using a sealed capillary tube in an Electrothermal IA9100 melting point apparatus. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal attenuated total reflectance sampling accessory. UV spectra were obtained on a Shimadzu UV–VIS spectrophotometer in dichloromethane and methanol. High-resolution mass data was obtained using a Waters Micromax LCT Premier TOF-MS instrument, operating at ambient temperatures, with a sample concentration of approximately 1 ppm. The ^{1}H and ^{13}C NMR spectra were recorded at 298 K with 5 to 10-mg samples dissolved in 0.5 ml of $CDCl_3$ in 5-mm NMR tubes using a Bruker Avance 400-MHz NMR spectrometer (9.4 T; Bruker, Germany) (400.22 MHz for ^{1}H, 100.63 MHz for ^{13}C and 376.58 Hz for ^{19}F). The FID resolution was 0.501 Hz/pt for ^{1}H, 0.734 Hz/pt for ^{13}C and 1.36 Hz/pt for ^{19}F spectra. Chemical shifts are reported in ppm and coupling constants (*J*) in Hz. The ^{1}H and ^{13}C chemical shifts of the deuterated solvent were 7.24 and 77.0, respectively, referenced to the internal standard, TMS. For the ^{19}F NMR spectra, the chemical shift of trifluorotoluene (0.05% in $CDCl_3$) was referenced at −62.73. All data was analysed using Bruker TopSpin 3.1 software.

A light yellow plate-like specimen of compound **5k**, recrystallized with hexane and ethyl acetate, with approximate dimensions of 0.150 mm × 0.220 mm × 0.250 mm, was used for the X-ray crystallographic analysis. The data collection and cell refinement were done using Bruker APEX2 and SAINT-Plus software respectively. Data reduction was performed with SAINT-Plus and XPREP. SHELXS-97[5] was used to solve and refine the structure. ORTEP-3[6] was used to prepare the graphic for publication. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB21EZ, UK. Copies of the data can be obtained free of charge on quoting the depository number CCDC 1416785 (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk).

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Synthesis

*Preparation of 6-chloro-2-methylquinoline (**1**)*

Crotonaldehyde (157.60 mmol, 12.95 ml) in toluene was added slowly to a warm solution (~40 °C) of 4-chloroaniline (78.78 mmol, 10.05 g) in aqueous HCl (**Fig**. 1). The reaction mixture was refluxed overnight, cooled and the toluene layer discarded. The aqueous layer was basified and extracted with ethyl acetate, dried over anhydrous $MgSO_4$ and concentrated. The product was purified by column chromatography on silica gel using a mobile phase of hexane: ethyl acetate (98:2). Compound **1** was produced in 74% yield.

*Preparation of 6-chloroquinoline-2-carbaldehyde (**2**)*

Selenium dioxide (87.42 mmol, 9.70 g) was added to a solution of **1** (58.32 mmol, 10.36 g) in 1,4-dioxane and refluxed at 100 °C for 15 min (**Fig**. 1). The reaction was monitored by TLC until completion. Once cooled, the reaction mixture was filtered through celite, diluted with water and extracted with ethyl acetate. The organic extract was dried over anhydrous $MgSO_4$, concentrated and subjected to column chromatography (hexane: ethyl acetate 95:5) which yielded the aldehyde **2** in good yield (82%).

*General procedure for the synthesis of quinoline chalcones (**5a–j**)*

Substituted acetophenones (1.044 mmol) were dissolved in absolute ethanol (20 ml), and 10–15 drops of 40% NaOH (aq) were added at room temperature whilst stirring. 6-Chloroquinoline-2-carbaldehyde (**2**) (1.044 mmol, 200.0 mg) was then added to the solution and allowed to stir for 10–15 min (**Fig**. 1). The reaction mixture was then diluted with ice water which resulted in the quinoline chalcones precipitating out of solution. The product was dried under vacuum and recrystallized from ethyl acetate.

*(E)-3-(6-chloroquinolin-2-yl)-1-phenylprop-2-en-1-one (**5a**)* light yellow crystalline solid; Yield 69%; mp 191–193 °C; IR (neat) υ_{max} 3053, 1657, 1586 cm^{-1}; λ_{max} (log ε): 229 (4.31), 281 (4.34), 343 (4.19); HRMS *m/z* 316.0501 $[M+Na]^+$ (calcd. for $C_{18}H_{12}NOClNa$ 316.0505)

*(E)-3-(6-chloroquinolin-2-yl)-1-(2-fluorophenyl)prop-2-en-1-one (**5b**)* yellow crystalline solid; Yield 57%; mp 154–156 °C; IR (neat) υ_{max} 3087, 1660, 1586 cm^{-1}; λ_{max} (log ε): 229 (4.28), 278 (4.27), 339 (4.17); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.49; HRMS *m/z* 312.0590 $[M+H]^+$ (calcd. for $C_{18}H_{12}NOClF$ 312.0591)

*(E)-3-(6-chloroquinolin-2-yl)-1-(3-fluorophenyl)prop-2-en-1-one (**5c**)* off-white powder; Yield 73%; mp 195–197 °C; IR (neat) υ_{max} 3077, 1660, 1580 cm^{-1}; λ_{max} (log ε): 231 (4.28), 283 (4.24), 344 (4.15); ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.60; HRMS *m/z* 312.0588 $[M+H]^+$ (calcd. for $C_{18}H_{12}NOFCl$ 312.0591)

*(E)-3-(6-chloroquinolin-2-yl)-1-(4-fluorophenyl)prop-2-en-1-one (**5d**)* white powder; Yield 58%; mp 215–216 °C; IR (neat) υ_{max} 2920, 1661, 1587 cm^{-1}; λ_{max} (log ε): 229 (4.30), 281 (4.31), 344 (4.18); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.81; HRMS *m/z* 334.0396 $[M+Na]^+$ (calcd. for $C_{18}H_{11}NOFClNa$ 334.0411)

*(E)-3-(6-chloroquinolin-2-yl)-1-(2-chlorophenyl)prop-2-en-1-one (**5e**)* yellow crystalline solid; Yield 58%; mp 134–135 °C; IR (neat) υ_{max} 3070, 1665, 1589 cm^{-1}; λ_{max} (log ε): 228 (4.24), 276 (4.23), 332 (4.10); HRMS *m/z* 350.0108 $[M+Na]^+$ (calcd. for $C_{18}H_{11}NOCl_2Na$ 350.0115)

*(E)-3-(6-chloroquinolin-2-yl)-1-(3-chlorophenyl)prop-2-en-1-one (**5f**)* off-white powder; Yield 82%; mp 194–196 °C; IR (neat) υ_{max} 3072, 1664, 1589 cm^{-1}; λ_{max} (log ε): 229 (4.34), 284 (4.22), 345 (4.14); HRMS *m/z* 328.0298 $[M+H]^+$ (calcd. for $C_{18}H_{12}NOCl_2$ 328.0296)

*(E)-3-(6-chloroquinolin-2-yl)-1-(4-chlorophenyl)prop-2-en-1-one (**5g**)* light yellow powder; Yield 79%; mp 229–230 °C; IR (neat) υ_{max} 3050, 1659, 1585 cm^{-1}; λ_{max} (log ε): 228 (4.41), 282 (4.37), 342

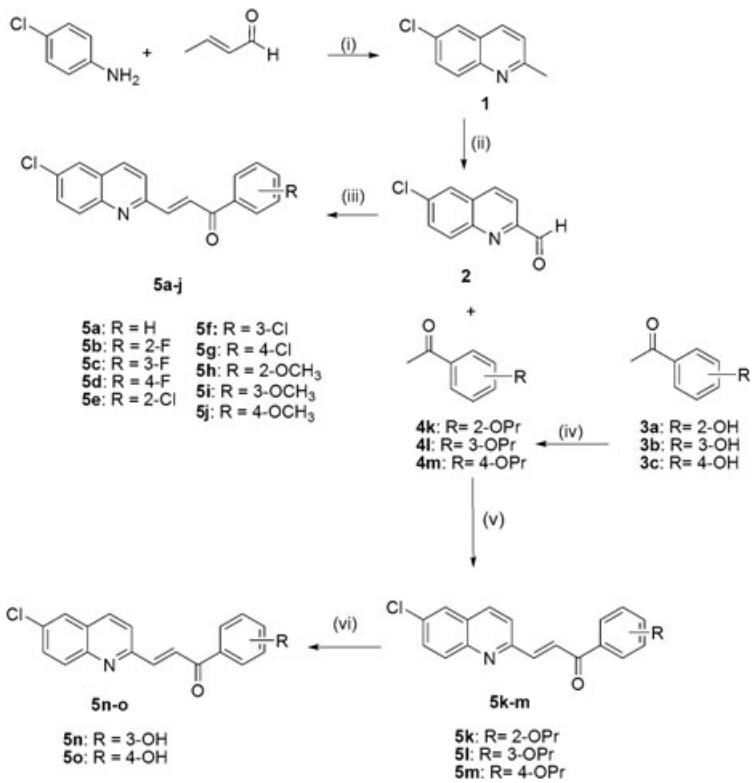

Figure 1. Synthetic scheme for the 6-chloroquinoline-chalcone hybrids **5a–o**. Reagents and conditions: (i) HCl (aq), toluene, reflux, 100 °C; (ii) SeO_2, 1,4-dioxane, reflux, 100 °C; (iii) substituted acetophenones (**4a–j**), 40% NaOH (aq), EtOH, rt; (iv) Prenyl bromide, K_2CO_3, acetone, rt; (v) 40% NaOH (aq), EtOH, rt; (vi) BF_3Et_2O, 1,4-dioxane, rt.

(4.26); HRMS *m/z* 328.0303 $[M+H]^+$ (calcd. for $C_{18}H_{12}NOCl_2$ 328.0296)

(E)-3-(6-chloroquinolin-2-yl)-1-(2-methoxyphenyl)prop-2-en-1-one (***5h***) off-white crystalline solid; Yield 58%; mp 141–143 °C; IR (neat) υ_{max} 1661, 1591 cm^{-1}; λ_{max} (log ε): 228 (4.37), 274 (4.24), 327 (4.16); HRMS *m/z* 346.0597 $[M+Na]^+$ (calcd. for $C_{19}H_{14}NO_2ClNa$ 346.0611)

(E)-3-(6-chloroquinolin-2-yl)-1-(3-methoxyphenyl)prop-2-en-1-one (***5i***) yellow crystalline solid; Yield 80%; mp 155–157 °C; IR (neat) υ_{max} 1663, 1590 cm^{-1}; λ_{max} (log ε): 228 (4.38), 330 (4.16); HRMS *m/z* 324.0790 $[M+H]^+$ (calcd. for $C_{19}H_{15}NO_2Cl$ 324.0791)

(E)-3-(6-chloroquinolin-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (***5j***) off white powder; Yield 68%; mp 183–184 °C; IR (neat) υ_{max} 1655, 1590 cm^{-1}; λ_{max} (log ε): 229 (4.37), 280 (4.30), 330 (4.23); HRMS *m/z* 346.0600 $[M+Na]^+$ (calcd. for $C_{19}H_{14}NO_2ClNa$ 346.0611)

*Preparation of prenylated chalcones (**5k–m**)*

Prenyl bromide (11.02 mmol) was added to a stirred solution of the respective hydroxy acetophenones (7.35 mmol) and K_2CO_3 (14.69 mmol, 2.03 g) in dry acetone. The solution was refluxed at 60 °C for 2 h. The reaction mixture was then filtered to remove unreacted K_2CO_3 and the filtrate concentrated and dried under vacuum, yielding the prenylated acetophenones (**4k–m**) in excellent yields (80–99%) (**Fig**. 1). These prenylated acetophenones (1.04 mmol) were then condensed with 6-chloroquinoline-2-carbaldehyde (**2**) (1.04 mmol, 200.0 mg) as above to yield the chalcones **5k–m** in yields of 72–90%.

*Deprenylation of chalcones **5l** and **5m***

Chalcones **5l** (0.53 mmol, 200.9 mg) and **5m** (0.53 mmol, 201.4 mg) were deprenylated by the addition of BF_3-OEt_2 (0.810 mmol) to the chalcones in 1,4-dioxane (30 ml) at room temperature. The reaction mixture was stirred overnight after which it was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude extract was subjected to column chromatography (hexane: ethyl acetate, 80:20) yielding the deprotected chalcones (**5n** and **5o**) in moderate yields of between 46 and 55% (**Fig**. 1).

(E)-3-(6-chloroquinolin-2-yl)-1-(2-(3-methylbut-2-enyloxy)phenyl) prop-2-en-1-one (***5k***) yellow crystalline solid; Yield 72%; mp 96–97 °C; IR (neat) υ_{max} 1654, 1589 cm^{-1}; λ_{max} (log ε): 229 (4.46), 278 (4.18), 327 (4.13); HRMS *m/z* 378.1268 $[M+H]^+$ (calcd. for $C_{23}H_{21}NO_2Cl$ 378.1261)

(E)-3-(6-chloroquinolin-2-yl)-1-(3-(3-methylbut-2-enyloxy)phenyl) prop-2-en-1-one (***5l***) yellow crystalline solid; Yield 80%; mp 151–153 °C; IR (neat) υ_{max} 1663, 1590 cm^{-1}; λ_{max} (log ε): 228 (4.46), 275 (4.33), 333 (4.24); HRMS *m/z* 378.1273 $[M+H]^+$ (calcd. for $C_{23}H_{21}NO_2Cl$ 378.1261)

(E)-3-(6-chloroquinolin-2-yl)-1-(4-(3-methylbut-2-enyloxy)phenyl) prop-2-en-1-one (***5m***) off-white powder; Yield 90%; mp 181–182 °C; IR (neat) υ_{max} 1655, 1600 cm^{-1}; λ_{max} (log ε): 285 (4.36), 343 (4.32); HRMS *m/z* 378.1271 $[M+H]^+$ (calcd. for $C_{23}H_{21}NO_2Cl$ 378.1261)

(E)-3-(6-chloroquinolin-2-yl)-1-(3-hydroxyphenyl)prop-2-en-1-one (***5n***) yellow powder; Yield 46%; mp 224–225 °C; IR (neat) υ_{max} 3182, 1663, 1592 cm^{-1}; λ_{max} (log ε): 280 (4.36), 337 (4.27); HRMS *m/z* 308.0484 $[M+H]^+$ (calcd. for $C_{18}H_{11}NO_2Cl$ 308.0478)

(E)-3-(6-chloroquinolin-2-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one (***5o***) yellow powder; Yield 55%; mp 236–237 °C; IR (neat) υ_{max} 3069, 1656, 1580 cm^{-1}; λ_{max} (log ε): 278 (4.24), 341 (4.27); HRMS *m/z* 332.0452 $[M+Na]^+$ (calcd. for $C_{18}H_{12}NO_2ClNa$ 332.0454)

Results and Discussion

Synthesis

The quinoline chalcones (**5a–o**) were synthesised from 4-chloroaniline in either three (**5a–j**), four (**5k–m**) or five steps (**5n–o**) depending on the quinoline chalcone synthesised. These reactions involved the Doebner–Miller addition to crotonaldehdye under acidic conditions to produce the 6-chloro-2-methylquinoline (**1**), which was further oxidized to the quinoline carbaldehyde (**2**) using selenium dioxide, before being condensed with various acetophenones to produce the quinoline-chalcone hybrids (**5a–j**) in yields of 57–82% (**Fig**. 1). The prenylated hybrid molecules **5k–m** were synthesised by prenylating the hydroxy group of the acetophenone prior to being condensed with the quinoline carbaldehyde in a Claisen–Schmidt condensation with good yields (72–90%), higher than when the electron withdrawing fluoro and chloro groups were present at the same position (**Fig**. 1). An attempt to deprenylate these compounds was only successful for the *meta* and *para* prenylated quinolines (**5l–m**), yielding the 3′- and 4′-hydroxyquinoline-chalcone hybrids (**5n–o**). These hydroxy quinoline chalcone hybrids could not be synthesised from the hydroxyacetophenones directly, possibly because of interference from the acidic hydroxyl group. Deprenylation of **5k** was unsuccessful, and as such the 2-hydroxyquinoline chalcone hybrid was the only compound of the series that was not synthesised.

Quinoline chalcones bearing substituents at C-4′ were found to have higher melting points than compounds with substituents at C-2′ and C-3′. This could be because of stronger intermolecular forces and better packing of the molecules. The hydroxylated chalcones displayed the highest melting points of the series, thought to be because of intermolecular hydrogen bonding (Table 1).

NMR Structural Elucidation

The full characterisation (^1H and ^{13}C NMR assignments) of the quinoline chalcones (**5a–o**) are presented in **Tables** 2–5. Unambiguous chemical shift assignments were made with the aid of 2D NMR spectra. The structural elucidation of the non-fluorinated quinoline chalcones is divided into three parts, the quinoline moiety, the acetophenone aromatic ring and the α,β-unsaturated moiety linking the two aromatic units together. The fluorinated compounds (**5b–d**) are discussed separately from the other compounds because their spectra are more complicated because of coupling with fluorine.

Table 1. The difference between the chemical shifts of H-9 and H-10 together with the ratio of the outer to inner resonances for each of the doublets

Compound	Δδ (Hz)	Peak ratio (%)
5j	112.76	71
5m	112.52	66
5l	90.52	74
5h	46.32	59
5b	24.64	30
5e	0[a]	

[a]Resonances completely coalesced into a singlet.

Table 2. ^{1}H NMR shifts of quinoline chalcones (**5a–g**)

Pos.	5a	5b	5c	5d	5e	5f	5g
3	7.65 d	7.69 d	7.65 d	7.64 d	7.68 d	7.65 d	7.65 d
4	8.07–8.12 m	8.09 d	8.11 d	8.10–8.16 m	8.09 d	8.10 d	8.12 d
5	7.79 d	7.79 d	7.80 d	7.80 d	7.78 d	7.80 d	7.81 d
7	7.66 dd	7.66 dd	7.67 dd	7.67 dd	7.64 dd	7.67 dd	7.67 dd
8	8.06 d	8.04 d	8.06 d	8.06 d	8.00 d	8.07 d	8.06 d
9	7.90 d	7.83 d	7.90 d	7.89 d	7.59 s	7.90 d	7.90 d
10	8.13 d	7.89 dd	8.09 d	8.14 d	7.59 s	8.08 d	8.12 d
2′	8.07–8.12 m	—	7.76 d	8.10–8.16 m	—	8.05 br s	8.04 d
3′	7.51 dd	7.18 dd	—	7.19 dd	7.45 dd	—	7.49 d
4′	7.60 dd	7.54 dddd	7.29 ddd	—	7.42 ddd	7.57 d	—
5′	7.51 dd	7.26 dd	7.49 ddd	7.19 dd	7.36 ddd	7.46 dd	7.49 d
6′	8.07–8.12 m	7.80–7.84 m	7.88 d	8.10–8.16 m	7.50 dd	7.96 d	8.04 d

5a *J* (Hz): 3,4 = 8.4; 5,7 = 2.2; 7,8 = 9.1; 9,10 = 15.5; 2′,3′ = 7.2; 3′,4′ = 7.2; 4′,5′ = 7.2
5b *J* (Hz): 3,4 = 8.5; 5,7 = 2.3; 7,8 = 9.0; 9,10 = 15.5; 10,2′F = 2.6; 3′,2′F = 8.6; 3′,4′ = 8.5; 4′,5′ = 7.2; 4′,2′F = 5.1; 4′,6′ = 1.8; 5′,6′ = 7.6
5c *J* (Hz): 3,4 = 8.4; 5,7 = 2.2; 7,8 = 9.1; 9,10 = 15.4; 2′,3′F = 9.1; 3′F,4′ = 8.1; 4′,5′ = 8.1; 4′,6′ = 2.4; 3′F,5′ = 5.7; 5′,6′ = 7.7
5d *J* (Hz): 3,4 = 8.7; 5,7 = 2.2; 7,8 = 9.0; 9,10 = 15.4; 2′,3′ = 8.6; 3′,4′F = 8.6; 5′,4′F = 8.6; 5′,6′ = 8.6
5e *J* (Hz): 3,4 = 8.6; 5,7 = 2.3; 7,8 = 9.0; 3′,4′ = 7.9; 4′,5′ = 7.2; 5′,6′ = 7.2; 3′,5′ = 1.5; 4′,6′ = 1.8
5f *J* (Hz): 3,4 = 8.5; 5,7 = 2.1; 7,8 = 9.0; 9,10 = 15.5; 4′,5′ = 7.9; 5′,6′ = 7.8
5g *J* (Hz): 3,4 = 8.6; 5,7 = 2.3; 7,8 = 9.1; 9,10 = 15.4; 2′,3′ = 5′,6′ = 8.6

Table 3. ^{1}H NMR shifts of quinoline chalcones (**5h–o**)

Pos.	5h	5i	5j	5k	5l	5m	5n	5o
3	7.67 d	7.67 d	7.64 d	7.67 d	7.65 d	7.64 d	8.36 d	8.23 d
4	8.07 d	8.13 d	8.09 d	8.06 d	8.10 d	8.08 d	8.59 d	8.44 d
5	7.77 d	7.81 d	7.79 d	7.78 d	7.80 d	7.78 d	8.20 d	8.14 d
7	7.62–7.65 m	7.66–7.68 m	7.66 dd	7.63 dd	7.65–7.69 m	7.66 dd	7.87 dd	7.80 dd
8	8.01 d	8.13 d	8.06 d	8.01 d	8.05 d	8.05 d	8.20 d	8.08 d
9	7.72 d	7.90 d	7.88 d	7.73 d	7.89 d	7.88 d	7.85 d	7.76 d
10	7.83 d	8.18 d	8.16 d	7.96 d	8.12 d	8.16 d	8.34 d	8.30 d
2′	—	7.61 dd	8.11 d	—	7.61 dd	8.10 d	7.50 dd	8.09 d
3′	6.99 d	—	6.99 d	6.99 d	—	6.99 d	—	6.93 d
4′	7.48 ddd	7.15 dd	—	7.45 ddd	7.15 dd	—	7.13 dd	—
5′	7.04 dd	7.43 dd	6.99 d	7.03 dd	7.41 dd	6.99 d	7.40 dd	6.93 d
6′	7.62–7.65 m	7.71 dd	8.11 d	7.69 dd	7.65–7.69 m	8.10 d	7.66 d	8.09 d
OCH_3	3.90 s	3.89 s	3.88 s	—	—	—	—	—
12				4.62 d (2H)	4.59 d (2H)	4.59 d		
13				5.49 t	5.50 t	5.48 t		
15				1.69 s (3H)	1.76 s (3H)	1.75 s (3H)		
16				1.65 s (3H)	1.80 s (3H)	1.80 s (3H)		

5h *J* (Hz): 3,4 = 8.6; 5,7 = 2.2; 7,8 = 9.0; 9,10 = 15.8; 3′,4′ = 8.4; 4′,5′ = 7.9; 5′,6′ = 7.5; 4′,6′ = 1.8
5i *J* (Hz): 3,4 = 8.5; 5,7 = 2.3; 7,8 = 8.4; 9,10 = 15.5; 4′,5′ = 8.3; 5′,6′ = 7.6; 2′,4′ = 2.2; 4′,6′ = 2.2; 2′,6′ = 2.2
5j *J* (Hz): 3,4 = 8.3; 5,7 = 2.3; 7,8 = 8.9; 9,10 = 15.4; 2′,3′ = 5′,6′ = 8.9
5k *J* (Hz): 3,4 = 8.6; 5,7 = 2.3; 7,8 = 9.1; 9,10 = 15.6; 3′,4′ = 8.5; 4′,5′ = 7.8; 5′,6′ = 7.3; 4′,6′ = 2.1; 12,13 = 6.6
5l *J* (Hz): 3,4 = 8.5; 5,7 = 2.2; 7,8 = 9.1; 9,10 = 15.5; 4′,5′ = 8.3; 5′,6′ = 7.9; 2′,4′ = 2.4; 2′,6′ = 2.4, 12,13 = 6.8
5m *J* (Hz): 3,4 = 8.4; 5,7 = 2.3; 7,8 = 9.1; 9,10 = 15.4; 2′,3′ = 5′,6′ = 8.8; 12,13 = 6.7
5n *J* (Hz): 3,4 = 8.6; 5,7 = 2.3; 7,8 = 7.9; 9,10 = 15.5; 4′,5′ = 8.0; 5′,6′ = 7.9; 2′,4′ = 1.9; 4′,6′ = 2.4; 2′,6′ = 1.9
5o *J* (Hz): 3,4 = 8.6; 5,7 = 2.3; 7,8 = 9.0; 9,10 = 15.7; 2′,3′ = 5′,6′ = 8.7

The quinoline moiety

All the quinolines synthesised in this work were 6-chloro substituted. H-3 and H-4 are situated on the pyridine ring whilst H-5, H-7 and H-8 occur on the benzene ring. Because of resonance effects brought about by the nitrogen, the 3-position is more electron dense than 4-position resulting in H-3 being more upfield at δ_H 7.64–7.69 than H-4 at δ_H 8.07–8.13. As expected, H-3 and H-4 are both doublets with *J* ~8 Hz, characteristic of *ortho* coupling. In the same way, resonance electron donation involving Cl at C-6 results in H-5 and H-7 being more shielded than H-8 at δ_H 8.00–8.07. H-5 and H-7 resonate at δ_H 7.78–7.81 and δ_H 7.64–7.67

Table 4. ^{13}C NMR shifts of quinoline chalcones (**5a–j**)

	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j
2	153.7	153.8	153.4	153.5	153.6	153.4	153.5	154.4	153.7	153.9
3	122.4	121.7	122.5	122.6	121.4	122.5	122.6	121.5	122.4	122.5
4	135.9	135.8	135.9	136.0	135.9	136.0	136.0	135.7	135.9	135.9
4a	128.8	128.7	128.8	128.8	128.7	128.8	128.8	128.8	128.7	128.7
5	126.3	126.2	126.3	126.3	126.3	126.3	126.3	126.2	126.3	126.3
6	133.2	133.3	133.4	133.3	133.5	133.4	133.3	133.1	133.2	133.1
7	131.1	131.1	131.2	131.2	131.3	131.2	131.2	130.4	131.5	131.1
8	131.5	131.5	131.5	131.4	131.4	131.5	131.5	131.4	131.1	131.4
8a	146.8	146.8	146.8	146.7	146.7	146.8	146.8	146.7	146.8	146.7
9	143.0	143.4	143.6	143.0	144.9	143.7	143.4	141.9	143.0	142.1
10	127.4	131.0 (d, 2.6)	126.8	126.9	131.2	126.8	126.8	132.3	127.4	127.3
11	190.5	189.2 (d, 2.3)	189.2 (d,1.9)	188.8	194.0	189.1	189.2	193.0	190.2	188.6
1′	137.8	126.8 (d, 13.1)	139.9 (d 6.4)	134.1 (d, 2.9)	138.6	135.1	136.1	128.6	139.1	130.7
2′	128.8	161.4 (d, 253.9)	115.5 (d, 22.4)	131.5 (d, 9.4)	131.5	128.8	130.2	158.4	113.0	131.2
3′	128.7	116.7 (d, 22.9)	163.0 (d, 248.3)	115.9 (d, 21.9)	130.4	139.4	129.1	111.7	160.0	114.0
4′	133.2	134.3 (d, 8.8)	120.2 (d, 21.2)	165.9 (d, 255.3)	131.7	133.1	139.7	133.3	119.8	163.8
5′	128.7	124.6 (d, 3.4)	130.4 (d, 7.6)	115.9 (d, 21.9)	127.0	130.1	129.1	120.8	129.7	114.0
6′	128.8	130.7 (d, 6.2)	124.5 (d, 2.5)	131.5 (d, 9.4)	129.4	126.8	130.2	131.0	121.5	131.2
OCH_3								55.8	55.5	55.5

respectively. The chemical shift and splitting patterns of the protons on the quinoline moiety remain unaffected by the substituents on the phenyl ring B and are similar for all quinoline chalcones **5a–o**.

The nine carbon resonances of the quinoline ring in $CDCl_3$ were present at δ_C 153, 147, 136, 133, 132, 131, 129, 126 and 122 of which five (C-3, C-4, C-5, C-7 and C-8) could be assigned from the HSQC spectrum because these were protonated. The two most deshielded resonances, C-2 and C-8a, occurring at δ_C 153 and 147 respectively (because they are directly bonded to the nitrogen) were distinguished by a HMBC correlation from C-8a to H-5 and H-7 (**Fig.** 2). The remaining C-6 and C-4a resonances occurred at similar chemical shifts at δ_C 133 and δ_C 129 and were identified by a HMBC correlation from C-4a to H-3. Thus, using the HSQC and HMBC spectra, the resonances of the quinoline ring could be unequivocally assigned.

Table 5. ^{13}C NMR shifts of quinoline chalcones (**5k–o**)

	5k	5l	5m	5n	5o
2	154.6	153.7	153.9	153.2	154.4
3	121.3	122.4	122.5	122.0	121.8
4	135.6	135.9	135.8	138.3	136.2
4a	128.5	128.7	128.7	129.5	128.5
5	126.2	126.3	126.3	126.8	126.6
6	132.9	133.2	133.0	132.3	131.7
7	130.9	131.1	131.0	131.6	130.7
8	131.4	131.5	131.4	129.2	131.3
8a	146.8	146.8	146.7	144.0	146.0
9	141.1	143.0	142.1	140.5	141.8
10	132.7	127.4	127.4	128.7	127.6
11	192.5	190.2	188.6	189.0	187.1
1′	128.9	139.1	130.6	138.1	128.7
2′	158.1	113.9	131.2	114.7	131.4
3′	113.1	159.2	114.6	157.9	115.6
4′	133.4	120.4	163.1	120.9	162.6
5′	120.8	129.7	114.6	130.0	115.6
6′	130.8	121.4	131.2	119.8	131.4
12	65.7	65.1	65.1		
13	119.3	119.3	119.0		
14	138.4	138.8	139.0		
15	18.3	18.3	18.3		
16	25.7	25.9	25.8		

The α,β-unsaturated carbonyl group

The H-9 and H-10 resonances are easily identified by their large *trans* coupling constants of ~15 Hz. These resonances can be easily distinguished by the HMBC correlation of H-9 to C-3. It was observed that H-9 is more shielded than H-10 even though resonance effects with the carbonyl group suggest that H-9 should be the more deshielded resonance. This is true for the carbon resonances, C-9 and C-10 where C-9 is more deshielded at δ_C 141–143 than C-10 at δ_C 126–132. The most downfield resonance in the ^{13}C NMR spectrum is the carbonyl resonance (C-11) at δ_C 188–194, which showed HMBC correlations to H-9, H-10 and H-2′/6′. The reason that H-9 is more shielded than H-10 is because of a through space shielding effect by the lone pair on the nitrogen of the quinoline ring similar to that reported for the pyranochromene chalcones in Pawar and Koorbanally.[7]

Considerable second order coupling is observed for H-9 and H-10 in several of the synthesised quinoline chalcones. The distances (in Hz) between the H-9 and H-10 resonances for the various substituents on ring B vary, becoming smaller as the substituent moves from the *para* to the *ortho* position. So too does the ratio of the outer resonance to the inner resonance vary (becoming smaller going toward the *ortho* position), indicating greater

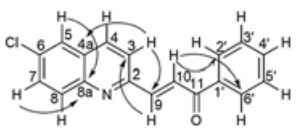

Figure 2. Selected HMBC correlations for **5a** used for the structural assignment.

second-order coupling. This second-order coupling was brought about by the substituents on ring B, wherein lone pairs were involved in shielding H-10. The data in **Table** 1 indicate that this effect is largest when the substituents are in the *ortho* position (**5b** and **5h**). The largest effect is seen with the chlorine atom (**5e**) (**Fig**. 3) (with the largest atomic radius) at C-2′, where the interaction is so pronounced that H-9 and H-10 coalesce into a singlet with the outer peaks being absent in the ^{1}H NMR spectrum.

In many instances, the resonances of either H-9 or H-10 are found to overlap with the aromatic proton resonances, making it difficult to distinguish. However, the resonances can be identified because their coupling constants are known and one can identify these peaks in an overlapping set of resonances. This is illustrated in **Fig**. **S1** (**Supporting Information**) where H-9 and H-10 are completely separate resonances (**5j**), or when either H-10 (**5g**) or H-9 (**5k**) occur in the multiplet along with the aromatic resonances.

The acetophenone ring

In the absence of substituents on the B-ring, as in **5a**, the H-2′/6′ resonance lies downfield in a multiplet with H-4 at δ_H 8.07–8.12 whilst H-3′/5′ and H-4′ are well resolved and resonate upfield at δ_H 7.51 and 7.60 respectively. For the *para* substituted compounds **5g**, **5j**, **5m** and **5o**, a pair of doublets for H-2′/6′ and H-3′/5′ are observed because of *ortho* coupling as expected, with H-3′/5′ occurring more upfield than H-2′/6′ because of resonance effects of the substituent. However, the H-3′/5′ resonance for compound **5d** appears as a triplet rather than a doublet which is because of splitting by both the neighbouring hydrogen and fluorine atoms.

When the phenyl ring is substituted at the *meta* position (**5f**, **5i**, **5l** and **5n**), expected splitting patterns are observed for H-2′, H-4′ and H-5′. H-2′ resonates downfield as a *meta* coupled triplet, whilst H-4′ resonates upfield as a doublet of doublets because of *ortho* and *meta* coupling. H-5′ is split equally by the *ortho* protons, H-4′ and H-6′ and results in a triplet. For compound **5i**, H-6′ resonates downfield as a doublet of doublets as expected, however, this splitting pattern is not observed in **5f** and **5n**. The *meta* coupling between H-6′ and H-2′/4′ is not seen and H-6′ resonates as a doublet. For compound **5l**, the doublet of doublets for H-7 and H-6′ overlap resulting in a multiplet.

For compounds **5e**, **5h** and **5k**, the *ortho* substituted chalcones, H-3′ and H-6′ are expected to be split into doublet of doublets with one large (*ortho*) and one small (*meta*) *J* value and H-4′ and H-5′ into triplets of doublets. This is the case for **5e** but not for **5h** and **5k**. *Meta* coupling for H-3′ and H-5′ is not observed in **5h** and **5k**. H-3′ resonates as a doublet and H-5′ as a triplet; however, H-4′ undergoes *meta* coupling and resonates as a triplet of doublets because it is coupled to two *ortho* protons and a *meta* proton. H-6′ resonates downfield as a doublet of doublets for **5k** as expected, but was unable to be resolved for **5h** as it overlaps with other resonances.

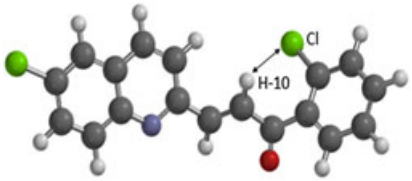

Figure 3. The structure of **5e** showing the interaction of H-10 with the 2-chloro substituent.

The carbon resonances were in the expected aromatic region of the spectrum and were assigned with the aid of the HSQC spectrum. For C-1′, an HMBC correlation to H-10 was used to confirm its assignment. The carbon resonances on the acetophenone ring where the substituents occurred were easy to identify because these carbon resonances had characteristic chemical shifts; the fluorinated carbon resonances appeared as doublets at ~δ 163; the chlorinated carbon resonances appeared at ~δ 139 and the methoxylated carbon resonances appeared at ~δ 160. The fluorinated carbon resonances also had a large characteristic *J* value of ~δ 250 Hz, which made it easier to identify. However, if one is not aware of the C—F coupling, these resonances can be mistaken for impurities.

The fluorinated compounds (5b–5d)

The resonances of the proton and carbon atoms of the quinoline moiety remain unaffected by the fluoro group as it is located away from the quinoline ring, and thus has no influence on its chemical shift. However, the proton and carbon atoms on the acetophenone ring and the ketoethylenic group are affected. The carbon resonances of the B-ring are split into doublets because of C—F coupling with *J* decreasing as the carbon moves further away. These coupling constants may be used to identify the carbon resonances of the B-ring as well as distinguish them from the remaining carbon resonances of the molecule. Once identified, these carbon resonances can then be used to identify their corresponding proton resonances using the HSQC spectrum.

For compounds **5b–d** (the fluorinated quinoline chalcones), the C-2′ (*ipso*) carbon resonates far downfield because of inductive effects by the fluorine atom. This resonance appears as a doublet with a large coupling constant, which may be mistaken for two separate carbon resonances. In **5b**, the *ortho* carbons, C-1′ and C-3′ resonate upfield at δ 126.8 (*J* = 13.1 Hz) and 116.7 (*J* = 22.9 Hz) whilst the *meta* carbons, C-4′ and C-6′ resonate downfield at 134.3 (*J* = 8.8 Hz) and 130.7 (*J* = 6.2 Hz) respectively (**Fig**. **S2**). The difference between the chemical shifts of these carbon atoms is because of resonance effects of the fluorine atom. Even the carbonyl carbon, which is three bonds away from the fluoro group, is split into a doublet with a coupling constant of 2.3 Hz. C-10 and C-5′ resonate as doublets at δ 131.0 (*J* = 2.6 Hz) and δ 124.6 (*J* = 3.4 Hz) respectively (**Fig**. **S2**).

Although some of the resonances coalesce in **5b**, it is possible to identify the *ortho* coupling between H-4′ and H-3′ (*J* = 7.2 Hz), H-4′ and H-5′ (*J* = 7.2 Hz), the *meta* coupling between H-4′ and the fluorine at C-2′ (*J* = 5.1 Hz) and with the proton H-6′ (*J* = 1.8 Hz). The proton of the α,β unsaturated bond, H-10, four bonds away from fluorine, was also split into a dd at δ_H 7.89 (*J* = 15.8, 2.6 Hz) (**Fig**. **S3**).

Interesting splitting patterns are observed in the ^{1}H NMR spectra for the fluorinated compounds. For example, in the ^{1}H NMR spectrum of **5b**, second order coupling and H-F splitting can be seen for H-10 and H-F splitting can be seen for H-3′-6′ (**Fig**. **S3**). For compound **5b**, H-4′ resonates as a dddd initially split by H-3′ and H-5′ with the same *J* value (7.2 Hz) resulting in a triplet (actually a dd), which is further split into a td (actually a ddd) by F (5.1 Hz) and then into a dddd by H-6′ (1.8 Hz) (**Fig**. **S4**). A similar pattern occurs with H-5′ of compound **5c**, which resonates as a ddd, split initially by H-4′ and H-6′ (*J* = 8.0 Hz) resulting in a triplet (actually a dd), which is split further into a td (actually a ddd) by the *meta* fluorine atom (5.7 Hz) (**Fig**. **S4**).

Single Crystal X-ray Diffraction Analysis

A crystal structure of **5k** (2-*O*-prenylated derivative) was solved in the orthorhombic space group $Pna2_1$, with one molecule in the asymmetric unit. H-9 and H-10 are antiperiplanar with a dihedral angle of 178.0°, which is consistent with the large coupling constant ($J = 15.6$ Hz) between H-9 and H-10. The core skeleton of **5k** is planar with the prenyl group lying out of the plane. The crystal structure of compound **5k** confirms that the molecule is in the *E* configuration. An ORTEP diagram of **5k** is provided in **Fig**. **S5**.

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