Efficient Syntheses of New Chromone- and Chromanequinoline Hybrids and their Aza-analogs

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Abstract: Some novel chromone- and chromanequinoline hybrids and their aza-analogs were synthesized from 2-chloro-3-quinolinecarboxaldehydes as starting materials. The cyclization of 2-hydroxychalcones in the presence of AcONa yielded chroman-4-ones, while, in the typical AFO conditions, the 2-corresponding quinolyl-3-hydroxyflavonols were obtained. These approaches were extended to 2-aminochalcones, which delivered the 3-hydroxy-2,3-dihydroquinolin-4(1*H*)-one *via* an epoxy-ketone and 2-quinolyl-2,3-dihydroquinoline-4(1*H*)-one under microwave irradiation in the presence of silica gel impregnated with indium (III) chloride.

Keywords: Quinoline, chalcones, flavonoid, quinolinone, bis-heterocycles.

Flavonoids are naturally occurring polyphenol derivatives present in substantial amounts in plants, fruits and vegetables [1]. Since food products derived from plants are an integral part of the human diet, the potential bioactivity of these compounds has been largely investigated ever since their discovery. Flavonoids exert various effects on health that explains the considerable interest aroused by this family. Numerous studies have shown their capacity to absorb oxygen radicals, their antioxidant potential and radical-scavenging properties [2]. Other benefits have since been described: anti-viral, anti-allergic, anti-platelet, anti-inflammatory, anti-tumor activities [3]. Flavonoids have been classified into several subgroups, such as flavonols and flavanones (Fig. **1**).

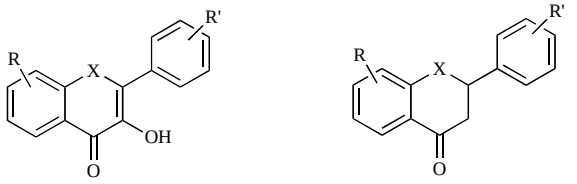

Fig. (1). Some subgroups of the flavonoid family.

From a chemical point of view, 2,3-dihydro-2-aryl-4(1*H*)-quinolinones can be considered as aza-analogs of flavanones (X=NH instead of X=O, Fig. **1**). They are known for the wide-range of their biological activity, as anticancer and immunosuppressive agents [4]. They also serve as valuable precursors for the synthesis of other medicinally important compounds [5]. To improve the pharmacological profile of these important families of bioactive molecules, a number of investigations have been carried out which involved the replacement of the 2-aryl substituent by various heterocycles [6]. The introduction of quinoline nucleus has already been used successfully in a number of pharmacomodulations [7]. In relation to these endeavours,

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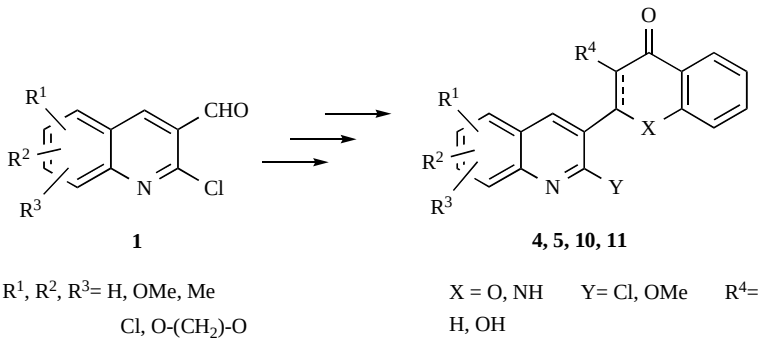


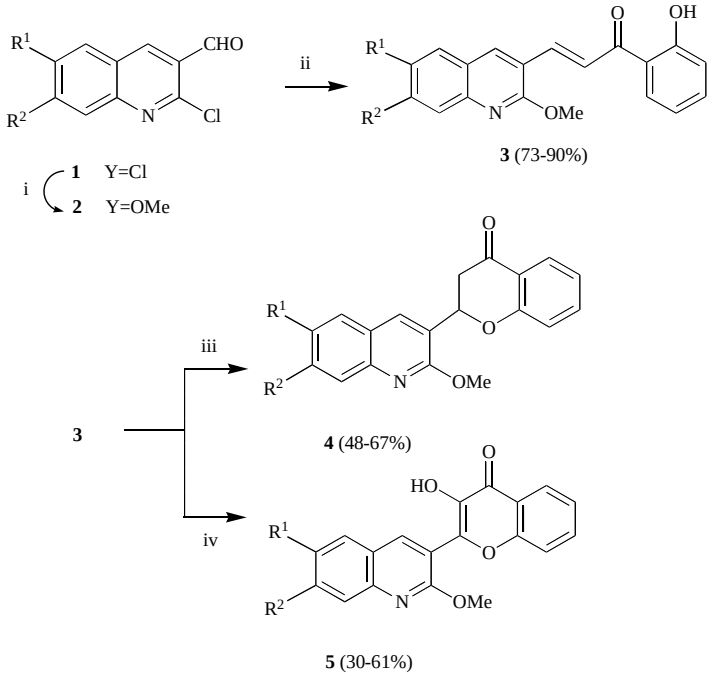
Scheme 1. Synthesis of chromone- and chromanequinoline hybrids and analogues.

Ibrahim *et al*. have recently published the synthesis of a 2-(3-quinolinyl)-substituted chromone [8]. Analogously, Chang *et al*. have reported the synthesis and evaluation of antitubulin activity of a 2-(quinolin-3-yl)quinolin-4(1*H*)-one [9].

Following our previous works related to the use of substituted 2-chloro-3-formylquinolines **1** as precursors of different quinoline-containing heterocycles, [10] we wish to report herein our preliminary results concerning the synthesis of chromone- and chromanequinoline hybrids and their aza-analogs (Scheme **1**).

We first chose 2-methoxy-3-formylquinolines **2** as starting material. They were easily prepared in good yields from the corresponding 2-chloro-3-formylquinolines **1** in refluxing methanol in the presence of sodium methoxide (2.0 equiv) [11]. Their conversion to the corresponding 2-hydroxychalcones **3** proceeded cleanly in 73–90% yields by treatment with 2-hydroxyacetophenone in the presence of $Ba(OH)_2$/MeOH. The flavanones **4a-e** were synthesized on treatment with AcONa in refluxing ethanol *via* intramolecular attack of the phenoxide moiety at the β-position of the α,β-unsaturated ketone [12], while **5a-e** were obtained albeit in lower yields, when subjected to the typical Algar-Flynn-Oymanda (AFO) conditions, [13] aqueous hydrogen peroxide in the presence of sodium hydroxide (Scheme **2**, Table **1**) [14]. Both ^1H and ^{13}C NMR spectra are in full agreement with those reported in the literature for similar structures [15].

In contrast, if the base-catalyzed condensation of 2-hydroxy-4,6-dimethoxyacetophenone effectively yielded the desired chalcone **6**, the major product detected after treatment with H_2O_2/NaOH was a benzofuran-3(2*H*)-one **7** (aurone). The structure of **7** was established by detailed examination of ^1H and ^{13}C spectra which showed characteristic signals at 7.28 ppm assigned to the vinylic proton and at 104.0 ppm for the corresponding carbon [16-17]. In agreement with the literature, this result suggests that the cyclization occurred at the α-position of an epoxide intermediate due to the presence of a substituent at the

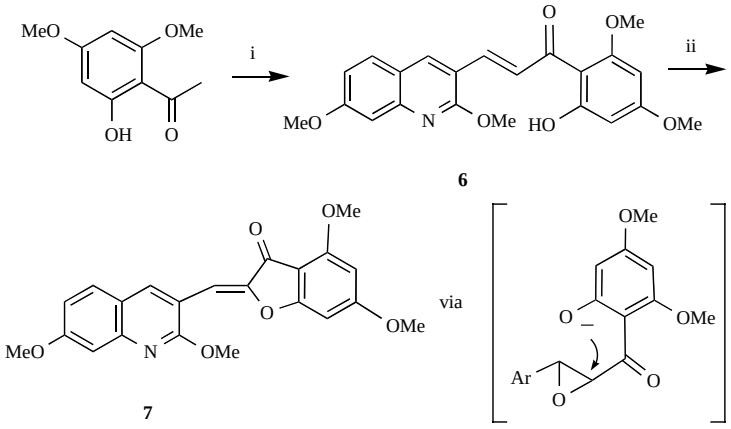


Scheme 2. Reagents and conditions: (i) MeONa (2.0 eq.), MeOH, reflux. (ii) 2-hydroxyacetophenone, $Ba(OH)_2$, MeOH, 40°C, 24h. (iii) AcONa, EtOH, reflux, 48h. (iv) H_2O_2, NaOH, MeOH-THF, rt, 24h.

Table 1. Synthesis of Substituted Flavanones (4) and Flavonols (5) from 2-hydroxychalcones (3)

Entry	R^1	R^2	Yield 3 (%)	Yield 4 (%)[a]	Yield 5 (%)[a]
a	H	H	90	50	49
b	H	OMe	73	56	45
c	OMe	H	76	67	61
d	-O-(CH_2)-O-		74	51	30
e	H	Cl	86	48	50

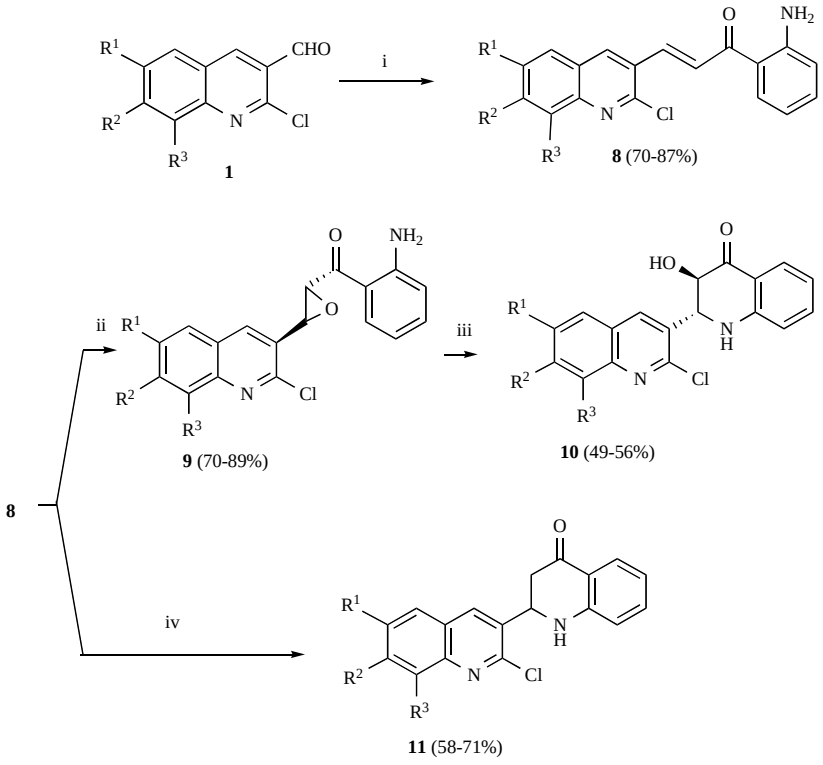
[a]Yield of isolated product after purification by column chromatography.



Scheme 3. Reagents and conditions: (i) **2b**, $Ba(OH)_2$, MeOH, 40°C, 24h, 80%. (ii) H_2O_2, NaOH, MeOH-THF, rt, 24h, 36%.

6'position to yield exclusively the *Z*-geometrical isomer (Scheme **3**) [17-18].

Another aim of this study was to expand this work to some aza-analogs of flavanones. First, 2-aminoacetophenone was condensed with 2-chloro-3-formylquinolines **1a-d** to deliver the 2-aminochalcones **8a-d** in 70-87% yields according to the procedure described by Schlenoff and co-workers [19]. Oxidation with hydrogen peroxide performed



Scheme 4. Reagents and conditions: (i) 2-aminoacetophenone, NaOH, EtOH, r.t., 24h. (ii) H_2O_2, NaOH, MeOH, THF, rt, 24h. (iii) H_2O, MeOH, reflux, 24h. (iv) $InCl_3$, silica gel, μw, 5 min.

Table 2. Synthesis of Substituted 3-hydroxy-2,3-dihydroquinolin-4(1*H*)-ones (10) and 2,3-dihydroquinolin-4(1*H*)-ones (11) from 2-aminochalcones (3)

Entry	R^1	R^2	R^3	Yield 8 (%)	Yield 9 (%)	Yield 10 (%)[a]	Yield 11 (%)[a]
a	H	H	H	80	81	56	58
b	H	H	Me	70	70	49	71
c	Me	H	H	74	77	51	69
d	Me	Me	H	87	89	53	63

[a]Yield of isolated product after purification by column chromatography.

in the presence of sodium hydroxide afforded epoxides **9a-d** (Scheme **4**, Table **2**).

The structure of compound **9a-d** has been established by spectroscopic methods. In the epoxy ring, the quinoline group at C-2 and the aroyl group at C-3 adopt a 2,3-*trans* arrangement. Suitable crystal of **9b** compound was obtained by recrystallization and X-ray crystallographic analysis confirmed the structural assignment (Fig. **2**).

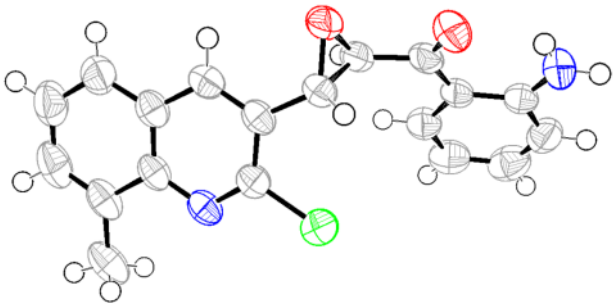


Fig. (2). ORTEP plot of the X-ray crystal structure of **9b** [20].

Upon heating in refluxing methanol/water, intramolecular cyclization occurred at the β-position of epoxides to give the corresponding 3-hydroxy-2,3-dihydroquinolin-4(1*H*)-ones **10a-d** [21]. The relative position of the hydroxyl and quinoline unit on the new heterocyclic ring could not be determined efficiently by NMR spectroscopy ($J_{H2\text{-}H3}$ = 12.5-12.8 Hz). However, an X-ray structure determination of quinolone **10b** (Fig. **3**) revealed a *trans*-configuration which showed that the new ring was formed with inversion of configuration at C-2 [22]. X-ray crystallography of **10b** showed an asymmetric unit which contains only one stereoisomer and the analysis of the unit cell demonstrate that the second stereoisomer is generated *via* a symmetry element. The two stereoisomers have for each one, the absolute stereochemistry *2S*, *3S* and *2R*, *3R* of the new stereocenters created in the cyclization reactions.

Finally, we turned our attention to the synthesis of the 2,3-dihydroquinolin-4(1*H*)-ones. Most of the reported procedures dealing with the synthesis of such compounds involved the use of corrosive reagents, such as orthophosphoric acid, acetic acid or strong alkalis [23]. The high efficiency of $InCl_3$ as catalyst in the synthesis of the 2,3-dihydroquinolin-4(1*H*)-ones [24] and the ease of product isolation prompted us to investigate its use in the synthesis of **11**. The reaction of the 2-aminochalcones **8a-d** with $InCl_3$ in CH_3CN was firstly examined. The corresponding 2,3-dihydroquinolin-4(1*H*)-ones **11c-d** were indeed obtained, but in relatively low yields (40-43%).

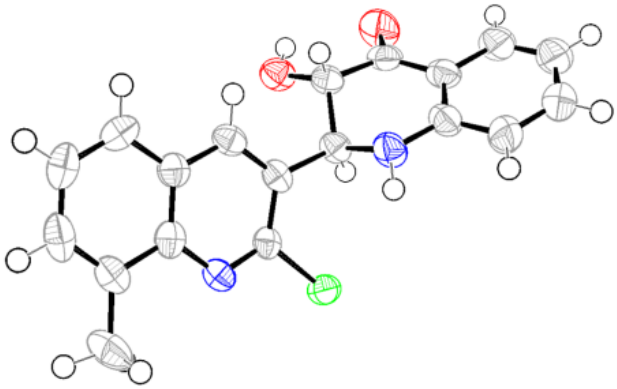


Fig. (3). ORTEP plot of the X-ray crystal structure of **10b** [20].

Recent studies on the Lewis acid catalyzed reactions with indium halides revealed that $InCl_3$ adsorbed on silica gel has often better catalytic properties than $InCl_3$ in solution [24]. In this context, a mixture of 2-aminochalcones **8a-d** and silica gel impregnated with indium (III) chloride (20 mol%) was irradiated in domestic microwave oven at 360 W for 5 minutes. Under these conditions, **11a-d** was successfully synthesized in good yields (58-71%) (Scheme **4**, Table **2**) [25].

Single crystal of compound **11b** was obtained and X-ray crystallographic analysis confirmed the structural assignments (Fig. **4**). The unit cell contains two independent molecules and the analysis demonstrates that the two stereoisomers have for each one, the absolute stereochemistry (*2R*) and (*2S*).

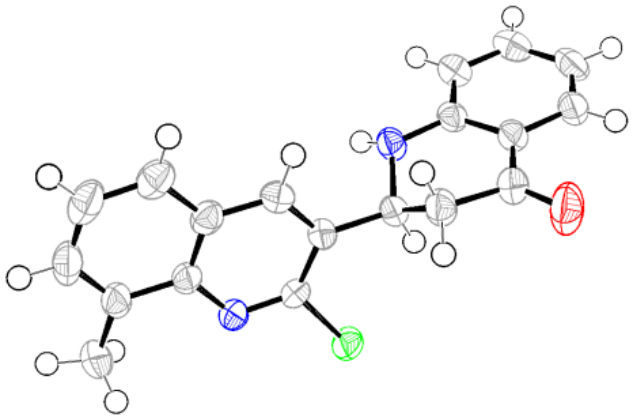


Fig. (4). ORTEP plot of the X-ray crystal structure of **11b** [20].

In conclusion, as demonstrated herein, the approaches developed in this work allow an easy and efficient access to structural analogs of flavonols and flavanones combining these important substructures with quinolyl moieties. Further biological evaluation of these compounds is currently underway and will be reported in due course.

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[12] Selected data for *2-(2,7-dimethoxyquinolin-3-yl)chroman-4-one* **4b** (yellow solid, mp. 160-163°C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.98 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.54 (td, *J* = 8.7 Hz, 1.8 Hz, 1H), 7.26 (m, 1H), 7.15-7.06 (m, 1H), 5.80 (dd, *J* = 13.0, 3.2 Hz, 1H), 4.11 (s, 3H), 3.96 (s, 3H), 3.15 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.91 (dd, *J* = 17.0, 13.2 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 192.1, 162.1, 161.6, 159.5, 140.7, 136.5,

135.1, 129.1, 127.5, 125.6, 123.7, 122.1, 121.4, 121.1, 118.4, 106.6, 75.2, 55.9, 54.2, 43.5. HRMS (EI): m/z [M^+] Calc. for $C_{20}H_{17}NO_4$: 335.1158; found: 335,1174**.**

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[14] Typical procedure for the synthesis of *3-hydroxy-2-(2,7-dimethoxyquinolin-3-yl)-4H-chromen-4-one* **5c**: To a stirring solution of chalcone **3c** (200 mg, 0.59 mmol) in MeOH-THF (10 mL, 1/1) was added NaOH 16% (2 mL) at 0°C, followed by the solution of 30% H_2O_2 (2 mL). The solution was stirred for 24 h at rt. The reaction mixture was acidified with 2 N HCl and extracted with DCM. The extracts were washed with water, brine, and dried over anhydrous Na_2SO_4. Purification by silica gel column chromatography (CH_2Cl_2), afforded **5c** as a yellow solid (112 mg, 0.32 mmol, 61%) mp. 195°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33-8.30 (m, 2H), 7.73-7.70 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.12-7.08 (m, 2H), 6.50 (s, 1H), 4.13 (s, 3H), 4.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 161.2, 158.5, 154.9, 148.2, 143.4, 139.4, 138.1, 132.4, 128.2, 124.5, 123.4, 120.2, 118.0, 117.4, 116.0, 111.5, 105.2, 54.5, 52.8. HRMS (EI): m/z [M^+] Calc. for $C_{20}H_{15}NO_5$: 349.0950; found: 349.0945.

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[16] Spectral data for selected products: *2-[(2,7-dimethoxyquinolin-3-yl)methylene]-4,6-dimethoxy-1-benzofuran-3(2H)-one* **7** (yellow solid: mp. 237°C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.28 (s, 1H) 7.21 (s, 1H), 7.06 (dd, *J* = 8.9 and 2.4 Hz, 1H), 6.46 (s, 1H), 6.17 (s, 1H), 4.15 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 168.9, 168.8, 161.9, 160.7, 159.4, 148.7, 148.3, 139.7, 129.4, 120.0, 116.8, 114.9, 106.2, 105.4, 104.0, 94.0, 89.3, 56.2, 56.1, 55.5, 53.7. HRMS (EI): m/z [M+H]$^+$ Calc. for $C_{22}H_{20}NO_6$: 394.12906; found: 394.1291.

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[20] Crystallographic data (excluding structure factors) for compounds **9b**, **10b** and **11b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC786116, CCDC786117, CCDC786115. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[21] Selected data for *2'-chloro-3-hydroxy-6'-methyl-2,3-dihydro-2,3'-biquinolin-4(1H)-one* **10c** (mp. 172°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.89 (m, 2H), 7.59-7.29 (m, 3H), 6.90-6.83 (m, 2H), 5.15 (d, *J* = 12.8 Hz, 1H), 4.94 (s, 1H), 4.67 (d, *J* = 12.8 Hz, 1H), 3.75 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 151.4, 145.7, 137.7, 137.5, 137.4, 136.3, 133.4, 129.5, 128.2, 127.9, 127.6, 126.6, 119.2, 116.5, 116.0, 74.9, 60.2, 21.6. HRMS (EI): m/z [M^+] Calc. for $C_{19}H_{15}ClN_2O_2$: 338.0822; found: 338.0820.

[22] (a) Chen, W. P.; Egar, A. L.; Hursthouse, M. B.; Abdul Malik, K.M.; Mathews J. E.; Roberts S. M. Synthesis of optically active 2,3-substituted-1,2,3,4-tetrahydro-4-quinolones using polyleucine. *Tetrahedron Lett.* **1998**, *39(46)*, 8495-8498. (b) Donnelly, J. A.; Farrell D. F. The chemistry of 2'-amino analogs of 2'-hydroxychalcone and its derivatives. *J. Org. Chem.* **1990**, *55(6)*, 1757-1761.

[23] (a) Donnelly, J. A.; Farrell, D. F. Chalcone derivatives as precursors of 1,2,3,4-tetrahydro-4-quinolones. *Tetrahedron* **1990**, *46(3)*, 885. (b) Tokes, A. L.; Litkei, G. Schmidt Reaction on 2-Aryl-1,2,3,4-tetrahydro-4-quinolone. *Synth. Commun.* **1993**, *23(7)*, 895-902 and references cited therein.

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[25] Typical procedure for the synthesis of 2,3-dihydro-2-(2-chloro-6-methylquinolin-3-yl)quinolin-4(1*H*)-one **11c**: To 2-aminochalcone **8c** (100 mg, 0.31 mmol) in DCM (5 mL) was added silica gel impregnated with $InCl_3$ (13.6 mg, 20% mol), prepared by addition of a solution of $InCl_3$ in a minimum of THF to silica gel (1 g, 100-200 mesh activated by heating for 4 h at 150°C before use). The resulting mixture was homogenized by stirring for 5 min. After complete evaporation of the solvent, it was transferred to a glass tube which was inserted in an alumina bath (100 g, 60 GF254, fisher scientific bath 6.5 cm diameter) inside the microwave oven. The compound was irradiated at 350 W for 5 min. On completion, the resulting product was directly charged on a small pad of silica gel and eluted with DCM to afford **11c** as yellow solid (65 mg, 0.20 mmol, 69%, mp. 205°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.59-7.55 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 6.87-6.75 (m, 2H), 5.28 (dd, *J* = 11.2, 4.0 Hz, 1H), 4.90 (s, 1H), 3.12 (dd, *J* = 13.3, 3.5 Hz, 1H), 2.82 (dd, *J* = 16.2, 11.8 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 151.0, 148.0, 145.5, 137.6, 135.4, 133.1, 132.4, 127.8, 127.7, 127.5, 127.1, 126.5, 119.0, 118.9, 116.2, 53.9, 43.8, 21.6. HRMS (EI): m/z [M^+] Calc. for $C_{19}H_{15}ClN_2O$: 322.0872; found: 322.0864.