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SYNTHESIS OF A 6*H*-CHROMENO[3,4-*b*]QUINOLINE AND A 6*a*,12*a*-DEHYDRO-7-AZAROTENOID

Andrew L. C. Morris and Yvette A. Jackson*

Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, W.I. Tel: (876)-927-1910
E-mail: yvette.jackson@uwimona.edu.jm

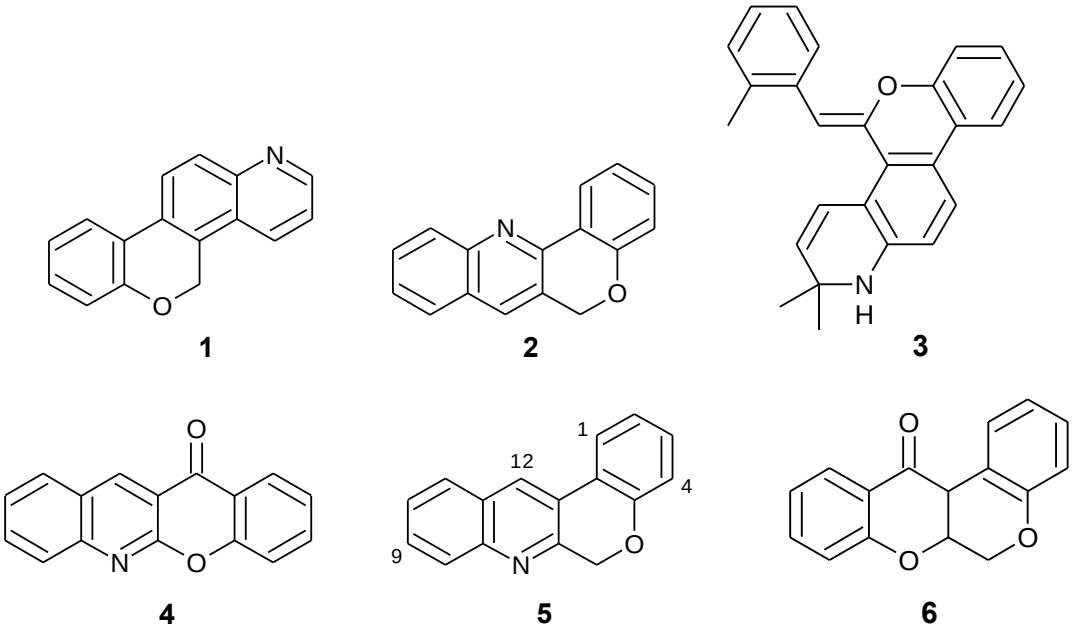
Abstract – The preparation of a 6*H*-chromeno[3,4-*b*]quinoline *via* a palladium-mediated coupling reaction, and the first synthesis of a nitrogenous dehydro-analogue of the naturally occurring rotenoids are reported.

INTRODUCTION

The presence of planar aromatic and heteroaromatic polycyclic systems is usually a key feature of compounds possessing DNA intercalating properties, an important characteristic of antitumor drugs.[1] Chromenoquinolines, in particular, are attractive molecules for drug discovery as many compounds of this type have been shown to exhibit excellent biological activity.[2] Steroidal natural products used as therapeutic agents also have undesirable side effects, and these have been averted by the use of synthetic chromenoquinoline analogues.[3] For example, 5*H*-chromeno[3,4-*f*]quinolines (**1**) have been shown to mimic the effects of natural glucocorticoids such as cortisone and cortisol, used as anti-inflammatory agents,[4] and are the first reported non-steroidal agents which possess these properties. 6*H*-Chromeno[4,3-*b*]quinolines (**2**) show inhibition of estrogens by binding to estrogen receptor beta (ERβ) sites.[5] It has also been demonstrated that 5-benzylidene-1,2-dihydrochromeno[3,4-*f*]quinolines (**3**) behave as highly potent progestins[6] and that the 5-oxo-5*H*-chromeno[2,3-*b*]quinolines (**4**) are highly potent inhibitors of the passive cutaneous anaphylaxis.[7] The development of simple protocols for the preparation of functionalized quinoline derivatives, therefore, represents an interesting challenge for synthetic chemists.

There have been only few reports on the preparation of chromenoquinolines. These include (i) condensation of 2-aminobenzaldehyde with chroman-4-one[8a,b] and (ii) treatment of *N*-phenyl-2-(prop-2-

ynyloxy)benzamide with $POCl_3$.[8c] The synthesis of chromeno[3,4-*b*]quinolines have even less prevalent in the literature. The only reported preparation of chromeno[3,4-*b*]quinolines has been *via* the Friedlander-Kempter reaction of chroman-3-one with 2-aminobenzaldehyde or 2-aminoacetophenone. This, to the best of our knowledge, is the only reported synthesis of this unique heterocyclic system. Preliminary tests showed these compounds to be mild carcinogens.[9]

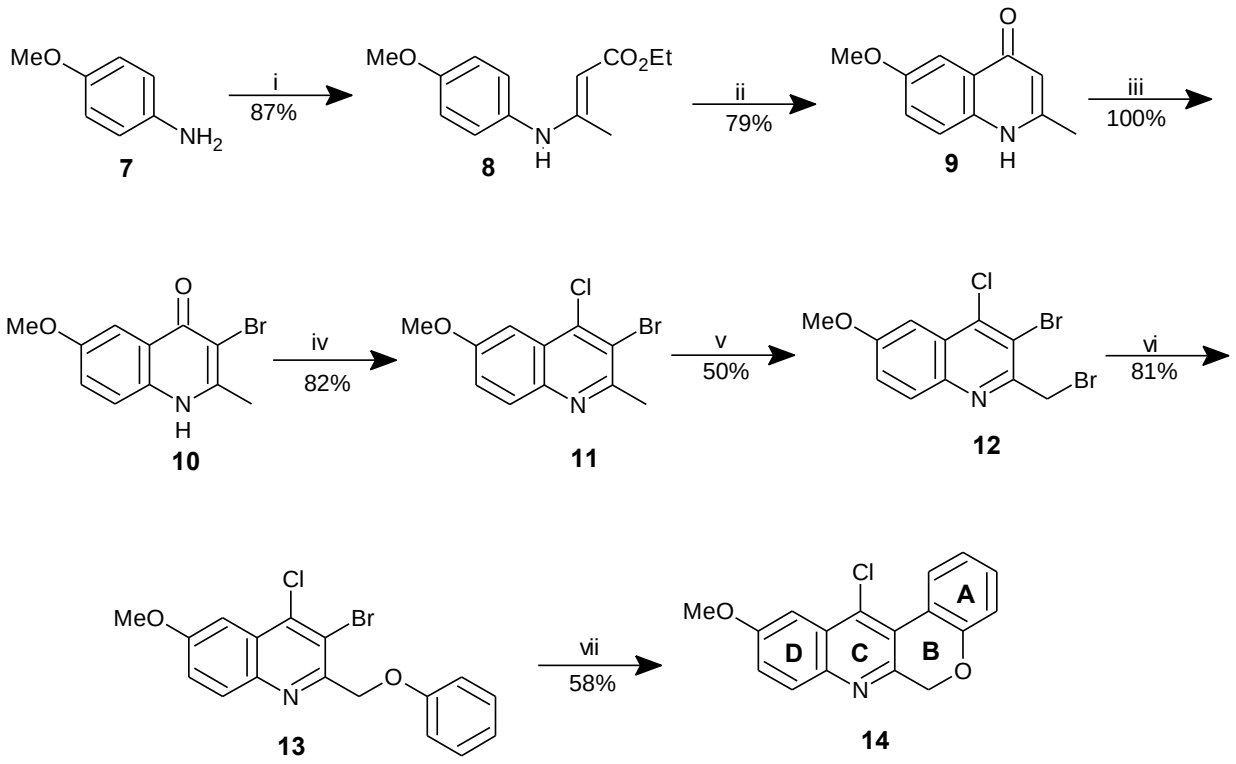


Our interest in the synthesis of polycyclic heteroatomic molecules with potential biological activity led us to explore methods for the preparation of the chromeno[3,4-*b*]quinoline (**5**) ring system. It seemed that success here could also give us access to the aza-rotenoids – nitrogen analogues of the insecticidal rotenoids of basic skeleton (**6**). The rotenoids, compounds bearing the 12-oxo-chromanochromene core (**6**), possess a wide range of biological activities including insecticidal, antifeedant, antimicrobial and piscicidal properties.[10,11] Other beneficial biological effects associated with the rotenoids include inhibition of the formation of microtubules from tubulin, a prelude to anti-cancer activity. The biological activity associated with rotenoids has been attributed to the intact A/B/C/D core.[12] Herein, we report the first palladium-mediated synthesis of a chromeno[3,4-*b*]quinoline (**14**) as well as synthesis of a 12-oxo-dihydro-analogue (**24**), representing the first report of a 7-aza-analogue of the rotenoids.

RESULTS AND DISCUSSION

The preparation of compound **14** was achieved as outlined in Scheme 1. Heating commercially available *p*-anisidine (**7**) at reflux in EtOH for 4 hours in the presence of ethyl acetoacetate provided ester **8** in 87% yield. Thermally-induced cyclization of compound **8** in Ph_2O at 250 °C then afforded quinolin-4*H*-one **9**

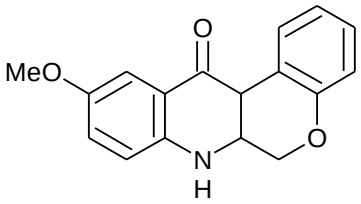
(79%). With the palladium-mediated reaction in mind, the 3-bromo- derivative of compound **9** was prepared without incident following its treatment with NBS in a mixture of acetic acid/CH_2Cl_2. Stirring the mixture at room temperature for 30 minutes produced 3-bromoquinolin-4*H*-one (**10**) in quantitative yield. Initial treatment of compound **10** with MsCl in dichloromethane, DMAP and lutidine at ambient temperatures provided chloroquinoline **11** in only 34% yield. Starting material was, however, recovered in 49% yield. In an effort to improve the yield, quinolone **10** was subsequently treated with PCl_5 in the presence of excess organic base for 4 hours in refluxing DMF. 4-Chloroquinoline **11** was thus obtained in 82% yield from compound **10**. No starting material was recovered.



Scheme 1. Reagents and conditions: i) ethyl acetoacetate, AcOH, $CaSO_4$, reflux ii) Ph_2O, 250 °C iii) NBS, AcOH/CH_2Cl_2, rt iv) PCl_5, 2,6-lutidine, DMAP, DMF, reflux v) NBS, CCl_4, hν vi) K_2CO_3, PhOH, acetone, reflux vii) $Pd(OAc)_2$, PPh_3, Et_3N, DMF, microwave.

Light-promoted bromination of compound **11** resulted in dibromide **12** in 50% yield (see EXPERIMENTAL). Larger-scaled reactions (in excess of 600 mg starting material) resulted in lower yields. Reaction of **12** with phenol then afforded ether **13** (81%). 12-Chloro-10-methoxychromeno[3,4-*b*]quinoline (**14**) was then prepared in 58% yield when a mixture of **13**, $Pd(OAc)_2$, PPh_3 and triethyl amine in DMF was allowed to react under microwave conditions for 15 minutes. Compound **14** was also obtained from **13** under thermal conditions with $Pd(OAc)_2$, PPh_3, K_2CO_3 in refluxing acetonitrile (45%).[13]

Having successfully obtained chromeno[3,4-*b*]quinoline **14**, reduction of ring C and subsequent benzylic oxidation seemed to be a ready route to 7-azarotenoid **15**. All attempts at reduction of ring C, however – $NaBH_4$/AcOH, $NaCNBH_3/BF_3{\cdot}OEt_2$/MeOH, $NaBH_4/NiCl_2$/MeOH,[14] ammonium formate/Pd-C/MeOH,[15] hydrogenation in the presence of Pd/C and Raney Ni catalysts and LAH/Et_2O[16] – yielded either starting material or the product of hydrogenolysis (compound **16**).



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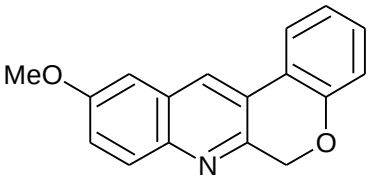

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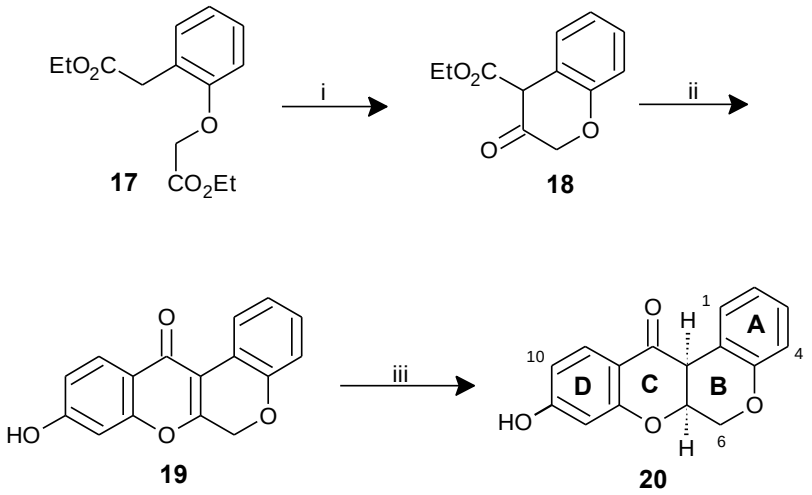
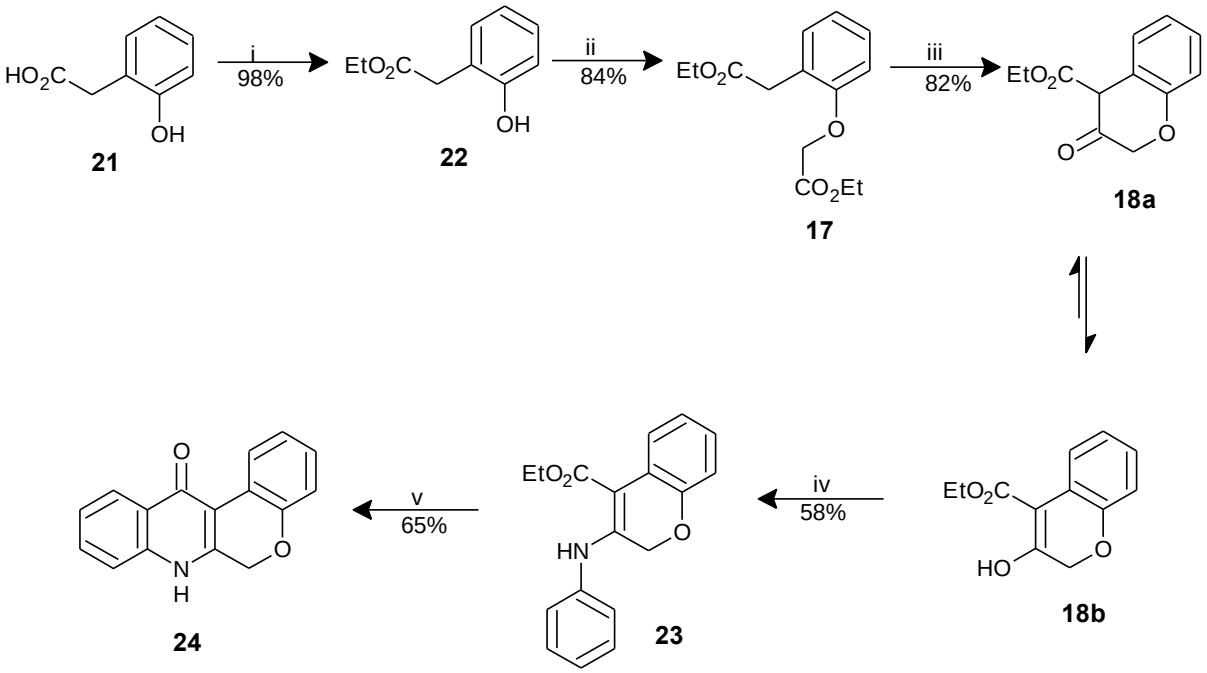
The synthesis of a azarotenoid **24** was achieved *via* a Dieckmann condensation reaction and makes use of an intermediate prepared, and an idea developed, by Crombie in the preparation of rotenoid **20** (Scheme 2).[17] Crombie and his group treated keto ester **18** with phloroglucinol dehydrate and produce dehydrorotenoid **19** which was then reduced by DIBAL to produce rotenoid **20**. We explored this pathway, anticipating that use of aniline in lieu of phloroglucinol, would give rise to the aza-compound **24**. Success at this would lead to a novel heteroatomic analogue of the rotenoids. Thio-derivatives have been previously reported.[18]

Ester **22** was prepared from readily available 2'-hydroxyphenylacetic acid (**21**) under acidic conditions in excellent yield, *c.a.* 98% (Scheme 3). Subsequent alkylation of compound **22** with ethyl bromoacetate resulted in the diester **17** which was subjected to base-induced cyclisation with sodium methoxide. ^{1}H NMR and ^{13}C NMR data confirmed that cyclisation of diester **17** had produced enol **18b** in 82% yield. With enol **18b** in hand, it was subjected to condensation with aniline to produce amine **23** (68% yield), which was then cyclized in refluxing Ph_2O to afford dehydro-7-azarotenoid **24** in 65% yield. Reduction of the unsaturated 6*a*,12*a*-bond of compound **24** with a view to producing the azarotenoid in its natural oxidation state has so far been unsuccessful. Reduction has been attempted with DIBAL in THF, at -78 °C and at room temperature, conditions which have been used successfully for reduction of the 4-chromone-type system in reported syntheses of rotenoids.[17,19] Reduction using $NaBH_4$ and $NaCNBH_3$ in refluxing MeOH and EtOH has also been attempted without success.

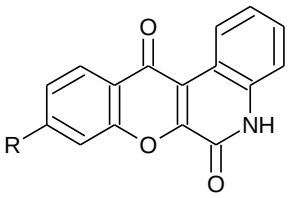


Scheme 2. **Reagents and conditions**: i) Na, toluene/EtOH, reflux ii) resorcinol, 150-160 °C (22 mmHg) iii) DIBAL, THF, -78 °C.



Scheme 3. **Reagents and conditions.** i) EtOH, H_2SO_4, reflux ii) $BrCH_2CO_2Et$, K_2CO_3, acetone iii) NaOEt, EtOH, 4Å mol. sieves iv) aniline, AcOH, $CaSO_4$, reflux v) Ph_2O, 250 ^oC.

To the best of our knowledge, the only previous report of a nitrogen analogue of the rotenoids has been the synthesis of the 5-aza-compound **25** by Srimanarayana and Kumar.[20] Our synthesis of compound **24** represents the first 7-aza-analogue of the rotenoids. This paves the way for structure-activity relationship (SAR) studies on the rotenoids, the previously reported 5-thio and now, the aza-derivatives.



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R = H, Me, OMe

ACKNOWLEDGEMENTS

Partial support of this work by the Royal Society of Chemistry is gratefully acknowledged.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Thomas Hoover Melting Point Apparatus and are uncorrected. IR (KBr) spectra were recorded on a Bruker Vector 22 FTIR instrument. NMR spectra were recorded using a Bruker Avance 200 MHz or a Bruker Avance 500 MHz spectrometer and, unless stated otherwise, were determined in $CDCl_3$ solution. Resonances are reported in δ units downfield from TMS; *J*-Values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, United Kingdom. A 150 W tungsten bulb was used as the source for light-promoted bromination. Chromatography was carried out using silica as support.

Ethyl (*2Z*)-3-[(4-methoxyphenyl)amino]-2-butenoate (8)

A mixture of *p*-anisidine **7** (1.76g, 13.5 mmol), ethyl acetoacetate (1.96 g, 14.9 mmol), glacial acetic acid (0.5 mL) and calcium sulfate (4 g) in dry EtOH (15 mL) was heated at reflux for 3 h. The reaction mixture was filtered and the filtercake washed with EtOH. The filtrate was concentrated under reduced pressure then diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and H_2O (2 x 10 mL), dried and concentrated *en vacuo*. The resulting yellow oil was purified *via* chromatography to give pure **8** (2.75 g, 87%); mp 41 - 42 °C (hexanes) (lit.,[21] mp 43 - 44 °C); ν_{max}/cm^{-1} 3443, 2947, 1656, 1612; δ_H: 1.28 (3H, t, *J* = 7 Hz, -$CH_2\underline{CH_3}$), 1.88 (3H, d, *J* = 0.5 Hz, -CH_3), 3.80 (3H, s, -OCH_3), 4.14 (2H, q, *J* = 7 Hz, -$\underline{CH_2}CH_3$), 4.65 (1H, d, *J* = 0.5 Hz, vinylic H), 6.85 (2H, dd, *J* = 9, 2 Hz, 3- and 5-H), 7.02 (2H, dd, *J* = 9, 2 Hz, 2- and 6-H), 10.16 (1H, s, -NH-). δ_C: 14.6, 20.1, 55.4, 58.6, 84.7, 114.2, 126.8, 132.1, 157.4, 160.0, 170.5.

6-Methoxy-2-methylquinolin-4(1*H*)-one (9)

Ph_2O (2 mL) was preheated under an atmosphere of nitrogen at 120 °C at which point ester **3** (496 mg, 2.11 mmol) was added as a solution in Ph_2O (1 mL) and the temperature rapidly increased to 260 ºC. This temperature was maintained for 15-20 min with continuous stirring. Upon cooling, an off-white slurry

was formed, hexanes (10 mL) was added and the mixture was filtered. The residue was then boiled in acetone to give the desired quinolone **9** as an off-white amorphous solid (314 mg, 79%), mp >300 ºC (decomp.); IR ν_{max}/cm^{-1} 3260, 2800, 1630, 1540; δ_H (DMSO): 2.33 (3H, s, -CH_3), 3.82 (3H, s, -OCH_3), 5.88 (1H, s, 3-H) 7.23 (1H, dd, *J* = 9, 3 Hz, 7-H), 7.43 (1H, d, *J* = 2 Hz, 5-H), 7.45 (1H, d, *J* = 4 Hz, 8-H), 11.54 (1H, s, NH). δ_C: 20.2, 56.2, 105.3, 108.3, 120.3, 122.5, 126.4, 135.6, 149.4, 156.1, 177.0. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40%. Found: C, 69.81; H, 5.81; N, 7.23%.

3-Bromo-6-methoxy-2-methylquinolin-4(1*H*)-one (10)

4-Quinolone **9** (2.04 g, 10.8 mmol) was dissolved in a mixture of HOAc:CH_2Cl_2 (40 mL, 3:7). *N*-Bromosuccinimide (1.97 g, 11.0 mmol) was then added in small portions over 5 min with continuous stirring at ambient temperatures. After stirring for a further 15 min the mixture was poured into H_2O (30 mL) and neutralized with 3 M NaOH (8 mL). The mixture was then filtered, the residue boiled in EtOH and filtered to give pure 3-bromo-4-quinolone **10** (2.88 g, 100%) as a white powder: mp >300 ºC (decomp.); IR ν_{max}/cm^{-1} 3264, 2760, 1637; δ_H ($CDCl_3$/TFA): 2.73 (3H, s, -CH_3), 3.92 (3H, s, -OCH_3), 7.38 (2H, m, 5- and 8-H), 7.72 (1H, dd, *J* = 9, 1 Hz, 7-H). δ_C: 21.9, 56.0, 101.4, 120.1, 121.0, 126.8, 133.1, 152.4, 159.0, 164.8, 178.6.

3-Bromo-4-chloro-6-methoxy-2-methylquinoline (11)

Compound **9** (3.74 g, 14.0 mmol) was heated in a mixture of 2,6-lutidine (4.50 g, 42.0 mmol) and DMAP (171 mg, 1.40 mmol) in DMF (20 mL) until dissolved. PCl_5 (3.65 g, 17.5 mmol) was then added in small portions over 5 min and the resulting mixture heated at reflux for 2 h. After cooling, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl (3 x 20 mL). The organic layer was then washed with H_2O (5 x 15 mL), dried (Na_2SO_4) and concentrated *en vacuo*. The residue was then purified *via* column chromatography (hexanes: CH_2Cl_2, 7:3) to give the desired 4-chloroquinoline **11** (3.30 g, 82%) as yellow needles: mp 107 - 108 °C (acetone). IR ν_{max}/cm^{-1} 1620, 1561, 1489 δ_H: 2.86 (3H, s, -CH_3), 3.97 (3H, s, -OCH_3), 7.37 (2H, m, 5- and 8-H), 7.90 (1H, dd, *J* = 9, 3 Hz, 7-H); δ_C: 27.0, 55.7, 102.4, 120.2, 123.0, 127.0, 130.6, 140.4, 142.5 155.3, 158.7. Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89%. Found: C, 46.31; H, 3.05; N, 4.94%.

3-Bromo-2-(bromomethyl)-4-chloro-6-methoxyquinoline (12)

Compound **11** (250mg, 0.872 mmol) was dissolved in CCl_4 (4 mL) and irradiated. NBS (217 mg, 1.22 mmol) was added in small portions over 10 min and the mixture heated at reflux for a further 2-4 h while being irradiated. The mixture was then filtered and the filtrate concentrated, diluted with CH_2Cl_2 (15 mL) and washed with 30% aqueous $NaHSO_3$ solution (3 x 10mL). The organic layer was dried over Na_2SO_4,

concentrated and recrystallized to give dibromide **12** (159 mg, 50%) as off-white plates; mp 148 - 150 °C (acetone); ν_{max}/cm^{-1} 1618, 1561, 1488; δ_H: 3.99 (3H, s, -OCH_3), 4.90 (2H, s, -CH_2Br), 7.40 (2H, m, 5-H and 7-H), 7.92 (1H, d, *J* = 8 Hz, 8-H); δ_C: 35.1, 55.8, 102.3, 118.9, 123.8, 128.1, 131.4, 141.5, 142.1, 152.6, 159.9.

3-Bromo-4-chloro-6-methoxy-2-(phenoxymethyl)quinoline (13)

Bromomethylquinoline **12** (300 mg, 0.821 mmol) was dissolved in acetone (5 mL), K_2CO_3 (204 mg, 1.48 mmol) added and the mixture was stirred at rt for 15 min. Phenol (93 mg, 0.985 mmol) was added as a solution in acetone (5 mL) and the mixture heated at reflux for 4 h. The mixture was then filtered to remove inorganic material, concentrated, diluted with CH_2Cl_2 (20 mL) and washed with 2 M NaOH (2 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated to give ether **13** (252 mg, 81%) as pale brown needles: mp 109 - 111 °C (EtOH); IR ν_{max}/cm^{-1} 1618, 1600, 1489, 1228; δ_H: 3.98 (3H, s, -OCH_3), 5.43 (2H, s, -CH_2O-), 6.99 (1H, tt, *J* = 7, 1 Hz, 4'-H), 7.08 (2H, dd, *J* = 9, 1 Hz, 2'- and 6'-H), 7.34 (4H, m, 3'-, 5'-, 5- and 7-H), 8.00 (1H, td, *J* = 10, 1 Hz, 8-H); δ_C: 55.8, 72.0, 102.2, 115.1, 121.3, 128.3, 128.2, 129.5, 131.6, 142.4, 151.8, 159.7. Anal. Calcd for $C_{17}H_{13}BrClNO_2$: C, 53.92; H, 3.46; N, 3.70%. Found: C, 53.88; H, 3.44; N, 3.60%.

12-Chloro-10-methoxy-*6H*-chromeno[*3,4-b*]quinoline (14)

Method 1:

A mixture of quinoline **13** (190 mg, 0.502 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), PPh_3 (10 mg, 0.038 mmol) and Et_3N (36 mg, 0.502 mmol) in DMF (1 mL) was irradiated (microwave, 70 W) for 15 min in a sealed tube. The crude mixture was then purified *via* flash chromatography (CH_2Cl_2: hexanes 2:1) to give compound **14** as a white crystalline solid (87 mg, 58%): mp 61 - 63 °C; IR ν_{max}/cm^{-1} 1618, 1600, 1489; δ_H: 4.00 (3H, s, -OCH_3), 5.20 (2H, s, –CH_2O-), 7.15 (1H, dd, *J* = 8, 1 Hz, 9-H), 7.18 (1H, dt, *J* = 8, 1 Hz, 4-H), 7.38 (2H, m, 2 and 3-H), 7.60 (1H, d, *J* = 2 Hz, 11-H) 7.93 (1H, d, *J* = 2 Hz, 8-H), 8.58 (1H, dd, *J* = 8, 1 Hz, 1-H); δ_C: 55.8, 71.4, 102.8, 107.1, 113.5, 118.0, 122.0, 122.9, 128.6, 129.0, 130.6, 130.7, 141.8, 142.7, 156.7, 158.92. Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.58; H, 4.06; N, 4.70%. Found: C, 68.68; H, 4.17; N, 4.59%.

Method 2:

A mixture of quinoline **13** (100 mg, 0.264 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), PPh_3 (14 mg, 0.053 mmol) and K_2CO_3 (73 mg, 0.528 mmol) in MeCN (3 mL) was stirred at reflux for 8 h under a steady stream of nitrogen. The mixture was filtered and the residue concentrated. The mixture was then purified *via* flash chromatography (CH_2Cl_2: hexanes 2:1) to give compound **14** as a white crystalline solid (41 mg, 45%).

Ethyl 3-Anilino-2*H*-chromene-4-carboxylate (23)

A mixture of aniline (280 mg, 3.00 mmol), hydroxychromene **18b** (600mg, 2.72 mmol), $CaSO_4$ (1.5g), EtOH (10 mL) and acetic acid (200 mg) was heated at reflux for 4 h with continuous stirring. The mixture was then filtered, the filter cake washed with EtOH, and the ethanolic solution concentrated. CH_2Cl_2 (30 mL) was added and the mixture was washed with saturated aqueous $NaHCO_3$ (2 x 10mL) then concentrated *in vacuo* to give **23**, which crystallized as yellow needles (467 mg, 58%): mp 80 - 82 °C (EtOH); IR ν_{max}/cm^{-1} 2985, 1644, 1519, 1232; δ_H: 1.41 (3H, t, *J* = 7 Hz, $-CH_3$), 4.36 (2H, q, *J* = 7 Hz, $-CH_2-$), 4.65 (2H, s, $-CH_2O-$), 6.95 (4H, m, 3'-, 5'-, 4'-, 8-H), 7.18 (2H, m, 2'-, 6'-H), 7.37 (2H, m, 6-, 8-H), 7.89 (1H, dd, *J* = 5, 3 Hz, 5-H), 11.05 (1H, s, NH); δ_C: 14.4, 60.1, 64.0, 92.6, 115.8, 122.2, 123.1, 124.2, 124.9, 125.6, 126.4, 129.4, 137.9, 151.9, 153.7, 168.8. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74%. Found: C, 73.38; H, 5.91; N, 4.72%.

6*H*-Chromeno[3,4-*b*]quinolin-12*H*-one (24)

Ph_2O (3 mL) was preheated under an atmosphere of nitrogen at 120 °C. Ester **23** (200 mg, 0.677 mmol) was then added as a solution in Ph_2O (1 mL) and the temperature of the mixture rapidly increased to 260 ºC and maintained for 15-20 min with continuous stirring. Upon cooling, an off-white slurry was formed. Hexanes (5 mL) were added and the mixture was filtered. The residue was then boiled in acetone to give the desired compound **24** as a white amorphous solid (112 mg, 65%): mp >300 ºC (decomp.); IR ν_{max}/cm^{-1} 2919, 1640, 1559, 1510; δ_H (DMSO): 5.12 (2H, s, $-CH_2-$), 6.94 (1H, d, *J* = 8 Hz, 4-H), 7.03 (1H, t, *J* = 8 Hz, 2-H), 7.14 (1H, td, *J* = 8, 2 Hz, 3-H), 7.37 (1H, t, *J* = 8 Hz, 10-H), 7.54 (1H, d, *J* = 8 Hz, 8-H), 7.67 (1H, t, *J* = 7 Hz, 9-H), 8.22 (1H, d, *J* = 8 Hz, 11-H), 8.93 (1H, dd, *J* = 8, 2 Hz, 1-H), 12.2 (1H, broad, NH); δ_C: 64.7, 108.0, 116.2, 118.7, 122.1, 122.3, 124.1, 126.0, 126.3, 126.7, 127.5, 132.2, 138.6, 144.4, 152.1, 174.0. Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62%. Found: C, 77.45; H, 4.34; N, 5.34%.

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