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# Iridium catalysed alkylation of 4-hydroxy coumarin, 4-hydroxy-2-quinolones and quinolin-4(1*H*)-one with alcohols under solvent free thermal conditions

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ABSTRACT

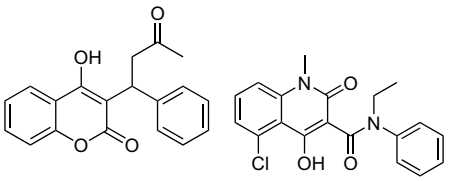
Ir catalysed alkylation of 4-hydroxy coumarin, 4-hydroxy-2-quinolones and quinolin-4(1*H*)-one with a range of substituted benzyl and aliphatic alcohols under solvent free thermal conditions afforded the corresponding monoalkylated products in high to excellent yield and in certain cases produced bis-(3,3′-1-methyl-4-hydroxy)methenes.



## 1. Introduction

Coumarins and quinolones are of great interest due to their roles in natural product chemistry, their biological activity and presence in many compounds of pharmaceutical interest.[1] 3-(Benzyl/alkyl)-substituted 4-hydroxycoumarins include a range of bioactive compounds such as warfarin **1** and also serve as useful scaffolds.[1a] The latter include the Hsp90 inhibitor novobiocin **2** a member of the coumermycin family of antibiotics and laquinimod **3**, a novel oral immunomodulator, developed as a disease-modifying drug for relapsing-remitting multiple sclerosis (RRMS)[2] is a further topical example.

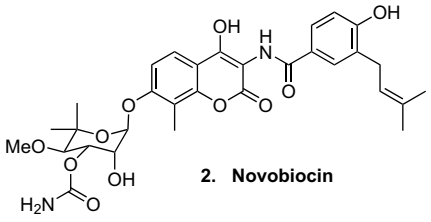
Environmental legislation has highlighted the need for processes using efficient (high atom economy), selective, high yielding and environmentally benign methods.[3] C–C bond formation is a pivotal method in organic synthesis and the indirect functionalisation of alcohols using catalytic amounts of a metal complex and base, which generates only water as a by-product is an attractive green alternative to standard C–C bond forming reactions. These cascades are termed redox-neutral, hydrogen autotransfer or 'borrowing hydrogen' processes. We have previously reported the alkylation of active methylene and methine compounds with




1. Warfarin




3. Laquinimod




2. Novobiocin

alcohols catalysed by iridium, rhodium and ruthenium complexes. Thus alkylation of arylacetonitriles was achieved by using rhodium[4] and more recently iridium catalysts.[5] We have also reported microwave assisted redox-neutral processes for the selective C-monoalkylation of 1,3-dimethylbarbituric acid, oxindole and *tert*-butyl cyanoacetate by alcohols.[5–7] C-3 (Methine) alkylation of indoles was also successfully carried out utilising alcohols and iridium catalysts as was cascade indole ring formation—C-3

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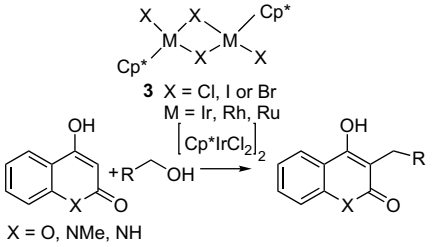
alkylation.[8] This general approach is attracting much current interest with many thoughtful contributions. Cho et al. have reported the direct α-alkylation of ketones with alcohols, using a Ru catalyst, to afford saturated alcohols via α-alkylated ketones.[9] The same reaction can be performed in the presence of a sacrificial hydrogen acceptor, such as 1-dodecene, when α-alkylated ketones are obtained.[10] Alternative catalysts for the α-alkylation of ketones with alcohols include the use of the phosphine free catalyst $Ru(DMSO)_4Cl_2$[11] and palladium nanoparticles.[12] Ishi et al. reported the selective direct α-alkylation of ketones with alcohols using an Ir catalyst,[13] and Williams et al. reported indirect Wittig reactions with alcohols using $[Ir(cod)Cl]_2$[14] or a ruthenium carbene complex[15] and variants of the aldol condensation.[16] Krische et al. reported a series of Ir catalysed C–C coupling processes via hydrogen autotransfer processes involving alcohols and π-unsaturated reactants (1,3-dienes, 1,2-dienes, 1,3-enynes, 1,2 diynes).[17–20] Milstein et al. have reported the direct conversion of alcohols to acetals by the use of a ruthenium pincer complex catalyst.[21] Reddy et al. [1a] have reported solid supported acid catalysed C-3 alkylation of 4-hydroxycoumarins with secondary benzyl alcohols. This process however failed to work with primary benzyl alcohols. We and others reported the *N*-alkylation of amines with alcohols using iridium and rhodium catalysts[22] whilst Beller et al. achieved the N-alkylation of anilines with aliphatic amines using Shvo's catalyst.[23] N-Acylation of amines with alcohols has been achieved from a ruthenium precursor catalyst, an *N*-heterocyclic carbene and a phosphine ligand.[24] A ruthenium pincer complex catalyst was also utilised for this transformation.[25] N-Alkylation of sulfonamides with alcohols has been achieved using either a homogeneous Ru catalyst or a heterogeneous nano-$Ru/Fe_3O_4$ catalyst.[26,27] Aromatic heterocycles such as furans, pyrroles, indoles, quinolines and benzazoles have all been constructed via redox-neutral processes.[8,28–31]

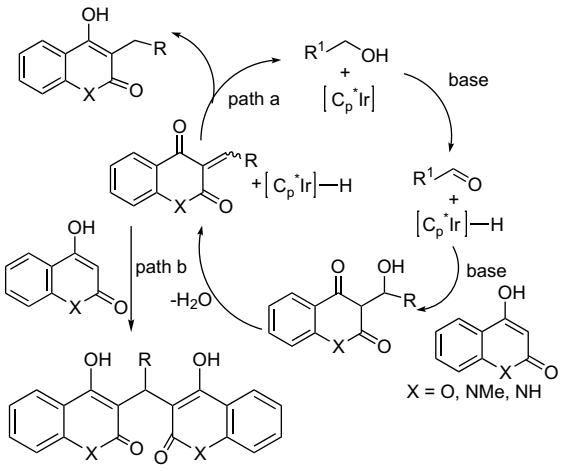
## 2. Results and discussion

Early extensive pioneering work by the Maitlis group[32] established simple routes to a series of halide bridged dimers **3** and highlighted their catalytic potential. Recently Fujita's group[22c–f] and others have reported applications of **3** in redox-neutral processes. The alkylation of 4-hydroxy coumarin/quinolone with alcohols (Scheme 1) is of interest as it provides a potential 'green' route to C-3 substituted derivatives of 4-hydroxy coumarin and 4-hydroxy 1-methyl quinolone. We initially surveyed a range of catalysts and identified the iridium chloro-bridged compound **3** [X=Cl, M=Ir(III)] as an effective catalyst for this transformation (Scheme 1).




**Scheme 1.**

The proposed mechanism for this transformation involves dehydrogenation of the primary alcohol to generate an aldehyde and metal hydride species. Knoevenagel type condensation occurs followed by hydrogenation of the double bond by the in situ formed metal hydride to give the C-3 alkylated product (Scheme 2, path a).




**Scheme 2.**

However there is the potential for a competing Michael addition process leading to the 3,3′-bis(heterocyclyl)methenes (Scheme 2, path b).

Further optimisation showed that the reaction could be achieved under essentially solvent free conditions and identified potassium hydroxide as the base of choice. Initially we carried out the alkylation reaction of 4-hydroxy-1-methyl-2(1*H*)-quinoline (1 mmol) with benzyl alcohol (5 mmol), KOH (20 mol %) and $[Cp^*IrCl_2]_2$ (2.5 mol %) at 110 °C for 48 h in a sealed tube, which afforded the monoalkylated product **5** in 68% yield (Table 1, entry 1). The conversion and the yield of *C*-alkylated product varied greatly depending on the alcohol in question. Electron rich aromatic alcohols (Table 1, entries 2, 3) and aliphatic alcohols (Table 1, entries 6, 7) gave high conversion and high yields of the desired *C*(3)-alkylated products. However aromatic benzylic alcohols with inductively withdrawing substituents such as 3-bromo or 4-chlorobenzyl alcohol gave very poor yields of the desired C-3 alkylated products (Table 1, entries 3, 4). In these cases the major products isolated were the 3,3′ bis-(heterocyclyl) methene products **8** and **10** arising from addition of 4-hydroxy-1-methylquinolin-2(1*H*)-one to the Michael acceptor intermediate (Scheme 2, path b). The formation of two different products demonstrates that the rate of hydrogenation of the Michael acceptor is affected by the nature of the alcohol. In the case of electron rich alcohols it appears that hydrogenation of the Michael acceptor is fast and therefore the expected 3-substituted product is observed. However, in the case of electron deficient alcohols, hydrogenation of the Michael acceptor is slow indicating this intermediate is longer lived and therefore prone to nucleophilic attack.

Next we briefly studied the alkylation of 4-hydroxy coumarin and 4-hydroxy-2(1*H*)-quinolone with benzyl alcohol. In both cases C-3 alkylated products were obtained in excellent yield (Table 1, entries 8, 9) but excess benzyl alcohol (7–10 mol equiv) was required in both cases. Finally, quinolin-4-(1*H*)-one was also investigated in the alkylation cascade with benzyl alcohol under more forcing conditions using an excess of benzyl alcohol (5 mol equiv). After heating for 48 h at 120 °C the C-3 alkylated product **15** was isolated in 37% yield (Table 1, entry 10). With longer reactions times (>72 h) the reaction remained incomplete.

## 3. Conclusion

In conclusion 4-hydroxy-quinolones, coumarin and 4-(1*H*)-quinolone were successfully *C*-alkylated with a range of substituted

**Table 1**
Alkylation of 4-hydroxy coumarin and 4-hydroxy-quinolones with alcohols[a]

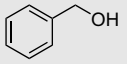
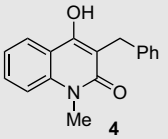
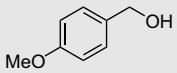
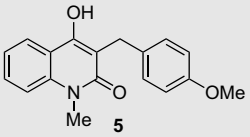
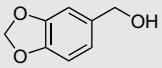
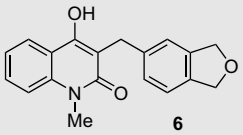
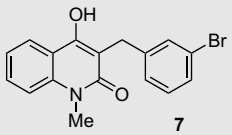
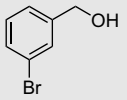
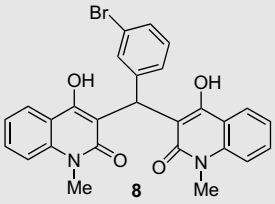
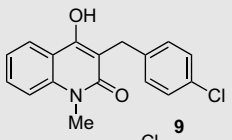
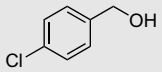
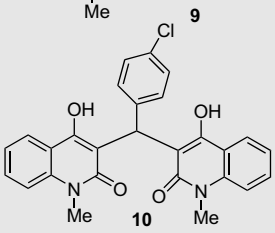
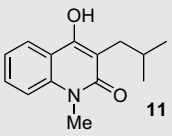
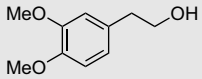
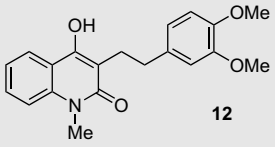
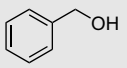
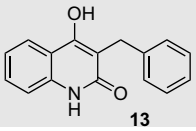
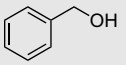
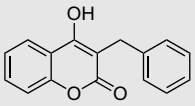
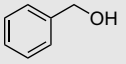
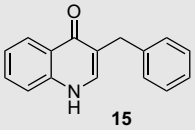
| Entry | Alcohol | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  |  **4** | 68 |
| 2 |  |  **5** | 88 |
| 3 |  |  **6** | 71 |
| | |  **7** | 11 |
| 4 |  |  **8** | 82 |
| | |  **9** | 19 |
| 5 |  |  **10** | 59 |
| 6 |  |  **11** | 92 |
| 7 |  |  **12** | 82 |
| 8 |  |  **13** | 94[c] |

**Table 1** (*continued*)

| Entry | Alcohol | Product | Yield[b] (%) |
|---|---|---|---|
| 9 |  |  **14** | 87[c] |
| 10 |  |  **15** | 37 |

[a] Heterocycle (1.1 mmol), alcohol (5 mmol), $[IrCp^*Cl_2]_2$ (2.5 mol %), KOH (20 mol %), $N_2$ (1 atm), 110 °C, 48 h.
[b] Isolated yield.
[c] Alcohol (10 mmol) was used.

benzyl and aliphatic alcohols to afford the corresponding C-3 alkylated products in high yield. In certain cases 3,3′-bis (heterocyclyl) methane products arising via a Michael addition pathway were also observed.

## 4. Experimental

### 4.1. General

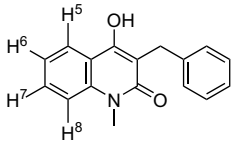
Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. Chromatography columns were prepared using Fisher Chemicals 60Å 35–70 micron silica gel. Nuclear magnetic resonance spectra were recorded using Bruker DPX300 and DPX500 MHz spectrometers. Chemical shifts are reported in parts per million ($\delta$) downfield relative to the internal reference tetramethylsilane. Unless otherwise specified NMR spectra were recorded in deuterochloroform at room temperature. Abbreviations used: Ar=aromatic, d=doublet, dd=doublet of doublets, dq=doublet of quartets, dt=doublet of triplets, m=multiplet, q=quartet, s=singlet, t=triplet. Mass spectra were recorded using a micromass ZMD 2000 spectrometer employing the electrospray ($ES^+$) ionisation technique. Accurate molecular masses were obtained from Walters LCT, GCT or Bruker MicroTof spectrometers. Infra-red spectra were recorded using a Perkin–Elmer FT-IR spectrometer. IR spectra of liquids were recorded as thin films on sodium chloride plates. IR spectra of solids were recorded using the 'golden gate' apparatus. Petrol refers to the fraction of petroleum ether with bp 40–60 °C and ether refers to diethyl ether. Accurate masses refer to $^{35}Cl$ and $^{79}Br$ isotopes.

### 4.2. General procedure for the alkylation of oxindoles with alcohols

#### *4.2.1. General procedure*

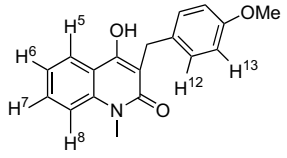
The heterocycle (1.0 mmol), $[Cp^*IrCl_2]_2$ (0.020 g, 2.5 mol %), KOH (0.011 g, 0.2 mmol) and the alcohol (5.0 mmol) were combined in a thick walled glass tube. The tube was sealed with a rubber septum, purged with nitrogen and the mixture was magnetically stirred at 110 °C with conventional heating for 48 h then allowed to cool to room temperature. The reaction mixture was analysed by $^1H$ NMR and thereafter purified by silica gel column chromatography.

*4.2.2. 3-Benzyl-4-hydroxy-1-methylquinolin-2(1H)-one (**4**)*



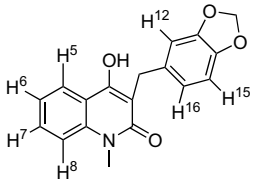
Prepared by the general procedure from 4-hydroxy-1-methylquinolin-2(1*H*)-one (0.161 g, 1.0 mmol) and benzyl alcohol (0.540 g, 5.0 mmol). Chromatography, eluting with 3:97 v/v methanol and DCM followed by crystallisation of the residue from methanol gave the product (0.184 g, 68%) as colourless prisms. Mp 226.0–228.0 °C (lit. mp 219.0–220.0 °C);[33] $\delta_H$ (500 MHz, $CDCl_3$); 7.92 (d, 1H, *J* 7.8, $H^8$), 7.57 (appar t, 1H, *J* 7.8, $H^7$), 7.36–7.21 (m, 7H, 7×ArH), 5.96 (s, 1H, OH), 4.14 (s, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$); $\nu_{max}/cm^{-1}$ (solid) 1627, 1583, 1498, 1455, 1093, 1011, 913, 818; HRMS [$ES^+$] found M+1, 266.1171. $C_{17}H_{16}NO_2$ requires 266.1176.

*4.2.3. 3-(4-Methoxybenzyl)-4-hydroxy-1-methylquinolin-2(1H)-one (**5**)*



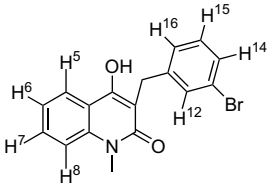
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 4-methoxy benzyl alcohol (0.414 g, 5.0 mmol). Chromatography eluting with 1:1 v/v ethyl acetate and hexane gave the product (0.260 g, 88%) as colourless micro needles. Mp 194.0–195.0 °C; (Found: C, 73.20; H, 5.70; N, 4.80. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80; N, 4.74%.) $\delta_H$ (500 MHz, $CDCl_3$); 7.94 (d, 1H, *J* 7.3, $H^8$), 7.56 (appar t, 1H, *J* 7.3, $H^7$), 7.34 (d, 1H, *J* 8.5, $H^5$), 7.23 (d, 2H, *J* 8.6, $H^{12}$), 7.22 (appar t, 1H, *J* 7.7, $H^6$), 6.80 (d, 2H, *J* 8.6, $H^{13}$), 6.42 (br s, 1H, OH), 4.07 (s, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$); 163.66 (CO), 158.42 (ArC), 156.86 (ArC), 138.76 (ArC), 130.66 (ArCH), 130.42 (2×ArCH), 129.45 (ArCH), 123.20 (ArCH), 121.71 (ArCH), 116.01 (ArC), 114.38 (2×ArCH), 113.90 (ArCH), 110.28 (ArC), 55.23 ($OCH_3$), 29.85 ($NCH_3$), 29.32 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1607 (CO), 1511, 1463, 1301, 1038, 940, 820, 748; HRMS [$ES^+$] found M+1, 296.1282. $C_{18}H_{18}NO_3$ requires 296.1281.

*4.2.4. 3-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-hydroxy-1-methylquinolin-2(1H)-one (**6**)*



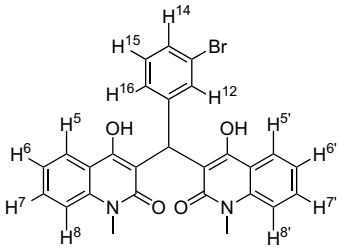
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)quinolone (0.175 g, 1.0 mmol) and 3,4-(methylenedioxy) benzyl alcohol (0.760 g, 5.0 mmol). Chromatography, eluting with 1:1 v/v petroleum ether and diethyl ether, followed by crystallisation from methanol gave the product (0.220 g, 71%) as colourless micro needles. Mp 207.0–208.0 °C; (Found: C, 69.90; H, 4.85; N, 4.4. $C_{18}H_{15}NO_4$ requires: C, 69.89; H, 4.89; N, 4.53%.) $\delta_H$ (500 MHz, DMSO-$d_6$); 10.40 (s, 1H, OH), 8.03 (d, 1H, *J* 7.9, $H^8$), 7.60 (appar t, 1H, *J* 8.6, $H^6$), 7.48 (d, 1H, *J* 8.6, $H^5$), 7.27 (1H, *J* 7.9, $H^7$), 6.84 (s, 1H, $H^{12}$), 6.76 (d, 1H, *J* 7.7, $H^{15}$), 6.74 (d, 1H, *J* 7.7, $H^{16}$), 5.92 (s, 2H, $OCH_2O$), 3.90 (s, 2H, $CH_2$), 3.60 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, DMSO-$d_6$); 163.00 (CO), 156.60 (ArC), 147.24 (ArC), 145.44 (ArC), 138.83 (ArC), 134.92 (ArC), 130.83 (ArCH), 123.48 (ArCH), 121.61 (ArCH), 121.33 (ArCH), 116.48 (ArC), 114.70 (ArCH), 111.19 (ArC), 109.24 (ArCH), 108.16 (ArCH), 100.85 ($CH_2$), 29.56 ($CH_3$), 29.323 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1639, 1609, 1569, 1486, 1442, 1331, 1037, 931; HRMS [$ES^+$] found M+Na, 332.0891. $C_{18}H_{15}NO_4Na$ requires 332.0893.

*4.2.5. 3-(3-Bromobenzyl)-4-hydroxy-1-methylquinolin-2(1H)-one (**7**)*



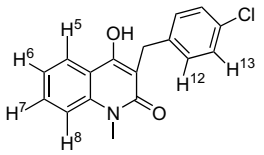
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 3-bromobenzyl alcohol (0.935 g, 5.0 mmol). Chromatography eluting with DCM followed by crystallisation from methanol gave the product (0.39 g, 11.0%) as colourless micro needles. Mp >230.0 °C; $\delta_H$ (500 MHz, DMSO-$d_6$); 10.55 (br s, 1H, OH), 8.08 (d, 1H, *J* 8.1, ArH), 7.62 (appar t, 1H, *J* 7.7, ArH), 7.50 (d, 1H, *J* 8.1, ArH), 7.44 (s, 1H, $H^{12}$), 7.34 (d, 1H, *J* 7.7, ArH), 7.30–7.26 (m, 2H, 2×ArH), 7.21 (appar t, 1H, *J* 7.7, ArH), 3.98 (s, 2H, $CH_2$), 3.60 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, DMSO-$d_6$); 162.94 (CO), 157.08 (ArC), 144.05 (ArC), 138.93 (ArC), 131.26 (ArCH), 131.03 (ArCH), 130.57 (ArCH), 128.84 (ArCH), 127.78 (ArCH), 123.57 (ArCH), 121.71 (ArCH), 121.67 (ArC), 116.38 (ArC), 114.81 (ArCH), 110.16 (ArC), 29.60 ($CH_3$), 29.59 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1639, 1608, 1508, 1421, 1394, 1329, 951, 753; HRMS [$ES^+$] found M+Na, 366.0108. $C_{17}H_{14}BrNO_2Na$ requires 366.0100.

*4.2.6. 3,3′-Bis(3-bromobenzylidene)2,2′-dioxo-4,4′-hydroxyl-1,1′-dimethylquinolyl methane (**8**)*



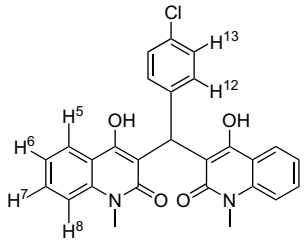
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 3-bromobenzyl alcohol (0.935 g, 5.0 mmol). Chromatography eluting with DCM followed by crystallisation from methanol gave the product (0.212 g, 82%) as a colourless solid. Mp >230.0 °C; $\delta_H$ (500 MHz, $CDCl_3$); 8.25 (d, 1H, *J* 8.1, ArH), 8.21 (d, 1H, *J* 7.7, ArH), 7.65–7.60 (m, 2H, 2×ArH), 7.42 (d, 2H, *J* 8.6, 2×ArH), 7.36–7.29 (m, 4H, 4×ArH), 7.13 (d, 2H, *J* 4.7, 2×ArH), 6.40 (s, 1H, CH), 3.82 (s, 3H, $CH_3$), 3.72 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, DMSO-$d_6$); 166.66 (CO), 164.78 (CO), 162.32 (ArC), 161.19 (ArC), 140.55 (ArC), 138.61 (ArC), 138.46 (ArC), 131.38 (ArCH), 129.63 (ArCH), 129.58 (ArCH), 129.11 (ArCH), 125.33 (ArCH), 124.98 (ArCH), 124.85 (ArCH), 122.73 (ArCH), 122.67 (ArCH), 122.46 (ArC), 118.05 (ArC), 117.74 (ArC), 114.28 (ArCH), 114.14 (ArCH), 110.91 (ArC), 109.15 (ArC), 37.05 (CH), 30.52 ($CH_3$), 30.06 ($CH_3$); $\nu_{max}/cm^{-1}$ (solid) 1624 (CO), 1554, 1496, 1373, 1344, 1176, 866, 755; HRMS [$ES^+$] found M+1, 517.0785. $C_{27}H_{22}BrN_2O_4$ requires 517.0757.

*4.2.7. 3-(4-Chlorobenzyl)-4-hydroxy-1-methylquinolin-2(1H)-one (**9**)*



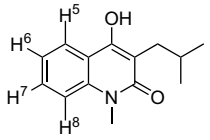
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 4-chlorobenzyl alcohol (0.710 g, 5.0 mmol). Chromatography eluting with 1:1 v/v ethyl acetate and hexane followed by crystallisation from methanol gave the product (0.057 g, 19.0%) as colourless micro needles. Mp 227.0–228.0 °C; $\delta_H$ (500 MHz, DMSO-$d_6$); 10.5 (br s, 1H, OH), 8.04 (d, 1H, *J* 8.1, ArH), 7.62 (appar t, 1H, *J* 8.1, ArH), 7.50 (d, 1H, *J* 8.1, ArH), 7.30–7.26 (m, 5H, 5×ArH), 3.97 (s, 2H, $CH_2$), 3.60 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, DMSO-$d_6$); 162.95 (CO), 156.96 (ArC), 140.15 (ArC), 138.90 (ArC), 130.96 (ArCH), 130.48 (2×ArCH), 128.25 (2×ArCH), 123.54 (ArCH), 121.66 (ArCH), 116.42 (ArC), 114.76 (ArCH), 110.41 (ArC), 29.56 ($CH_3$), 29.15 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1609 (CO), 1494, 1428, 1017, 965, 898, 749, 552; HRMS [ES$^+$] found M+Na, 322.0595. $C_{17}H_{14}NClO_2Na$ requires 322.0605.

*4.2.8. 3,3′-Bis(4-chlorobenzylidene)-1,1′-methylquinolin-2,2′-(1H)-one (**10**)*



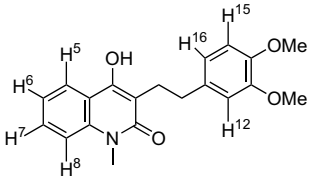
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 4-chlorobenzyl alcohol (0.710 g, 5.0 mmol). Chromatography eluting with 1:1 v/v ethyl acetate and hexane gave the product (0.140 g, 59%) as a colourless solid. Mp 174.0–175.0 °C. (Found: C, 68.65; H, 4.75; N, 5.75; Cl, 7.55. $C_{27}H_{20}ClN_2O_4$ requires: C, 68.57; H, 4.48; N, 5.92; Cl, 7.50%.) $\delta_H$ (500 MHz, $CDCl_3$); 8.25 (d, 1H, *J* 7.7, ArH), 8.19 (d, 1H, *J* 7.7, ArH), 7.65–7.60 (m, 2H, 2×ArH), 7.42 (d, 2H, *J* 8.5, 2×ArH), 7.37–7.30 (m, 2H, 2×ArH), 7.22 (d, 2H, *J* 8.6, H$^{13}$), 7.11 (d, 2H, *J* 8.6, H$^{12}$), 6.38 (s, 1H, CH), 3.83 (s, 3H, $CH_3$), 3.71 (s, 3H, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$); 166.70 (CO), 164.82 (CO), 162.32 (ArC), 161.12 (ArC), 138.58 (ArC), 138.44 (ArC), 136.47 (ArC), 131.65 (ArC), 131.35 (ArCH), 128.25 (ArCH), 128.02 (ArCH), 124.91 (ArCH), 124.84 (ArCH), 122.74 (ArCH), 122.66 (ArCH), 118.06 (ArC), 117.77 (ArC), 114.25 (ArCH), 114.15 (ArCH), 111.08 (ArC), 109.50 (ArC), 36.99 (CH), 30.52 ($CH_3$), 30.06 ($CH_3$); $\nu_{max}/cm^{-1}$ (solid) 1627 (CO), 1490, 1366, 1217, 1116, 1014, 827, 756; HRMS [ES$^+$] found M+1, 473.1262. $C_{27}H_{22}ClN_2O_4$ requires 473.1263.

*4.2.9. 4-Hydroxy-3-isobutyl-1-methylquinolin-2(1H)-one (**11**)*



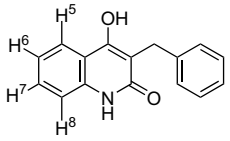
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 2-methyl propanol (1.0 mL, 5.0 mmol). Chromatography eluting with 1:1 v/v ethyl acetate and hexane followed by crystallisation of the residue from DCM and methanol gave the product (0.260 g, 88%) as colourless micro prisms. Mp 186.0–187.0 °C; $\delta_H$ (500 MHz, $CDCl_3$); 8.05 (d, 1H, *J* 8.1, H$^8$), 7.61 (appar t, 1H, *J* 8.6, H$^6$), 7.51 (d, 1H, *J* 8.6, H$^5$), 7.29 (appar t, 1H, *J* 7.5, H$^7$), 4.90 (br s, 1H, OH), 3.71 (s, 1H, $NCH_3$), 2.59 (d, 2H, *J* 7.7, $CH_2$), 2.05–1.95 (m, 1H, CH), 0.95 (d, 6H, *J* 6.7, 2×$CH_3$); $\delta_C$ (75 MHz, $CDCl_3$); 166.23 (CO), 159.39 (ArC), 140.00 (ArC), 131.84 (ArCH), 124.66 (ArCH), 123.28 (ArCH), 118.34 (ArC), 115.68 (ArCH), 111.95 (ArC), 34.03 ($CH_2$), 30.43 ($CH_3$), 29.20 (CH), 22.98 (2×$CH_3$); $\nu_{max}/cm^{-1}$ (solid) 1581 (CO), 1395, 1252, 1164, 1085, 987, 876, 758; HRMS [ES$^+$] found M+1, 232.1333. $C_{14}H_{18}NO_2$ requires 232.1332.

*4.2.10. 3-(3,4-Dimethoxyphenethyl)-4-hydroxy-1-methylquinolin-2(1H)-one (**12**)*



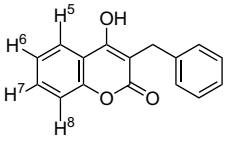
Prepared by the general procedure from 4-hydroxy-1-methyl-2(1*H*)-quinolone (0.175 g, 1.0 mmol) and 3,4-dimethoxyphenyl ethyl alcohol (0.910 g, 5.0 mmol). Chromatography, eluting with ether, followed by crystallisation of the residue from DCM and methanol gave the product (0.278 g, 82%) as colourless micro needles. Mp 173.0–174.0 °C; (Found: C, 70.70; H, 6.25; N, 4.0. $C_{20}H_{21}NO_4$ requires: C, 70.78; H, 6.24; N, 4.13%); $\delta_H$ (500 MHz, DMSO-$d_6$); 10.20 (br s, 1H, OH), 8.01 (d, 1H, *J* 7.9, H$^8$), 7.59 (appar t, 1H, *J* 8.6, H$^7$), 7.48 (d, 1H, *J* 8.6, H$^5$), 7.26 (appar t, 1H, *J* 7.7, H$^6$), 6.91 (d, 1H, *J* 1.6, H$^{12}$), 6.86 (d, 1H, *J* 8.2, H$^{15}$), 6.79 (dd, 1H, *J* 1.6, 8.2, H$^{16}$), 3.75 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.62 (s, 3H, $NCH_3$); $\delta_C$ (75 MHz, $CDCl_3$); 160.68 (CO), 153.89 (ArC), 146.56 (ArC), 144.98 (ArC), 136.37 (ArC), 132.77 (ArC), 128.28 (ArCH), 121.09 (ArCH), 119.22 (ArCH), 118.12 (ArCH), 114.27 (ArC), 112.24 (ArCH), 110.33 (ArCH), 109.89 (ArCH), 108.65 (ArC), 53.58 ($OCH_3$), 53.39 ($OCH_3$), 31.44 ($CH_2$), 27.14 ($NCH_3$), 24.30 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1637 (CO), 1516, 1330, 1388, 1224, 1024, 927, 800, 645; HRMS [ES$^+$] found M+Na, 262.1355. $C_{20}H_{21}NNaO_4$ requires 262.1362.

*4.2.11. 3-Benzyl-4-hydroxyquinolin-2(1H)-one (**13**)*



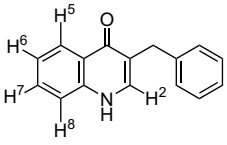
4-Hydroxyquinolin-2(1*H*)-one (0.161 g, 1.0 mmol), $[Cp^*IrCl_2]_2$ (0.02 g, 2.5 mol%), KOH (0.011 g, 0.2 mmol) and benzyl alcohol (0.756 g, 7.0 mmol) were combined in a thick walled glass tube. The tube was sealed with a rubber septum and purged with nitrogen. The reaction mixture was heated with stirring at 110 °C for 48 h. Chromatography eluting with 1:1 v/v ethyl acetate and hexane gave the product (0.234 g, 94%) as a colourless solid. Mp 214.0–216.0 °C (lit. Mp 218.0–220.0 °C);[34] $\delta_H$ (500 MHz, DMSO-$d_6$); 11.36 (br s, 1H, NH), 7.94 (d, 1H, *J* 7.7, H$^8$), 7.46 (appar t, 1H, *J* 7.3, H$^7$), 7.30–7.20 (m, 5H, 5×ArH), 7.18–7.10 (m, 2H, 2×ArH), 3.94 (s, 2H, $CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1629, 1603, 1498, 1382, 1273, 1098, 914, 756; HRMS [ES$^+$] found M+Na, 274.0846. $C_{16}H_{13}NO_2Na$ requires 274.0838.

*4.2.12. 3-Benzyl-4-hydroxy-2H-chromen-2-one (**14**)*




4-Hydroxy coumarin (0.162 g, 1.0 mmol), $[Cp^*IrCl_2]_2$ (0.020 g, 2.5 mol %), KOH (0.011 g, 0.2 mmol) and benzyl alcohol (1.08 g, 10.0 mmol) were combined in a thick walled glass tube. The tube was sealed with a rubber septum and purged with nitrogen. The reaction mixture was heated with stirring at 110 °C for 48 h. Chromatography eluting with 1:99 v/v methanol and DCM gave the product (0.219 g, 87%) as a colourless solid. Mp 207.0–208.0 °C (lit. Mp 207.0–209.0 °C);[35] $\delta_H$ (500 MHz, $CDCl_3$); 7.74 (dd, 1H, *J* 1.3, 8.1, $H^5$), 7.54 (ddd, 1H, *J* 1.3, 7.3, 8.5, $H^7$), 7.37–7.33 (m, 5H, 5×ArH), 7.31–7.27 (m, 2H, 2×ArH), 6.12 (br s, 1H, OH), 4.04 (s, 2H, $CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1662, 1614, 1567, 1494, 1392, 1185, 1108, 750; HRMS [$ES^+$] found M+Na, 275.0679. $C_{16}H_{12}O_3Na$ requires 275.0679.

*4.2.13. 3-Benzylquinolin-4(1H)-one (**15**)*




Quinolin-4(1*H*)-one (0.145 g, 1.0 mmol), $[Cp^*IrCl_2]_2$ (0.02 g, 2.5 mol %), KOH (0.112 g, 2.0 mmol) and benzyl alcohol (0.540 g, 5.0 mmol) were combined in a thick walled glass tube and sealed with a rubber septum. The reaction vessel was purged with nitrogen and heated with stirring at 110 °C for 48 h. The reaction mixture was allowed to cool. Chromatography eluting with 3:97 v/v methanol and DCM followed by crystallisation from methanol gave the product (0.087 g, 37%) as colourless micro plates. Mp 218.0–219.0 °C; $\delta_H$ (500 MHz, DMSO-$d_6$); 11.69 (br s, 1H, NH), 8.12 (d, 1H, *J* 7.7, $H^5$), 7.86 (s, 1H, $H^2$), 7.62 (appar t, 1H, *J* 7.7, $H^6$), 7.52 (d, 1H, *J* 8.3, $H^8$), 7.32–7.23 (m, 4H, 4×ArH), 7.15 (appar t, 1H, *J* 7.5, $H^7$), 3.78 (s, 2H, $CH_2$); $\delta_C$ (75 MHz, DMSO-$d_6$); 176.25 (CO), 141.72 (ArC), 140.01 (ArC), 137.81 (ArCH), 131.60 (ArCH), 128.90 (2×ArCH), 128.43 (2×ArCH), 125.96 (ArCH), 125.44 (ArCH), 125.05 (ArC), 123.08 (ArCH), 120.74 (ArC), 118.43 (ArCH), 33.32 ($CH_2$); $\nu_{max}/cm^{-1}$ (solid) 1629, 1549, 1526, 1474, 1455, 1367, 1208, 761; HRMS [$ES^+$] found M+1, 236.1079. $C_{16}H_{14}NO$ requires 236.1070.

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