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A copper(II)-mediated radical cross-dehydrogenative coupling/sulfinic acid elimination approach to 2-quinolones

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Dedicated to Professor Steve Davies to acknowledge his many seminal research achievements, his contributions to Tetrahedron: Asymmetry – and his unfailing friendship over the years

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ABSTRACT

A new cyclisation procedure to prepare 4-carboxy-quinolin-2-ones via a one-pot Cu(II)-mediated radical cross-dehydrogenative coupling/sulfinic acid elimination of linear anilides is described. Extensions to more complex substrates are also reported as are applications in target synthesis allowing access to natural products isolated from *Oryza sativa* and HOFQ.

1. Introduction

The 2-quinolone scaffold is an attractive synthetic target due to its presence in a diverse array of both naturally occurring and biologically active molecules (Fig. 1) [1]. Examples of 2-quinolone containing natural products range from simple congeners such as **1a**-**b** (isolated from *Oryza sativa*, also known as purple rice) [2], to more complex members such as isaindigotidione **2**, isolated from the roots of *Isatis indigotica* which has found broad utility in traditional Chinese medicine [3]. Furthermore, 2-quinolones have been shown to possess potent bioactivity, including as inhibitors of farnesyl protein transferase (e.g. Zarnestra) [4], as FMS and P38 MAP kinase inhibitors [5], as well as possessing anti-Hepatitis B [6], anti-bacterial [7], and anti-cancer [8] activities and as a potential treatment for Chagas disease [9]. In addition, 4-hydroxymethyl-1,6,8-trimethylfuro[2,3-h]quinolin-2(1*H*)-one (HOFQ, **3**) has been identified as a promising new member of the furocoumarins (psoralens), a class of active sensitisers used in PUVA (psoralen plus UVA) photochemotherapy and photopheresis for the treatment of various skin diseases, T-cell lymphoma and organ transplant rejection [10].

Given their promiscuous bioactivity and utility as synthetic intermediates (e.g. as ligand precursors) [11], it is therefore of no surprise that the synthesis of 2-quinolones has been widely explored by a variety of methods. In particular, formation of the C4–C4a bond has emerged as a powerful tool in the preparation of 2-quinolones. Examples include via Friedländer cyclisation [12], iodocyclisation [13], isatin ring expansion [14], metal-free oxidative

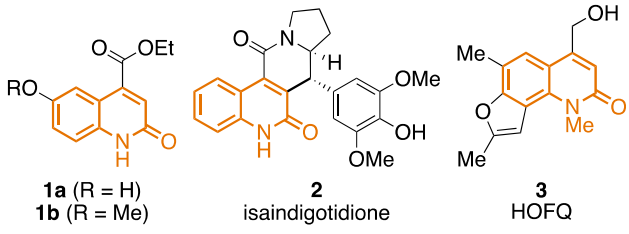

Fig. 1. Examples of naturally occurring and biologically active quinolones.

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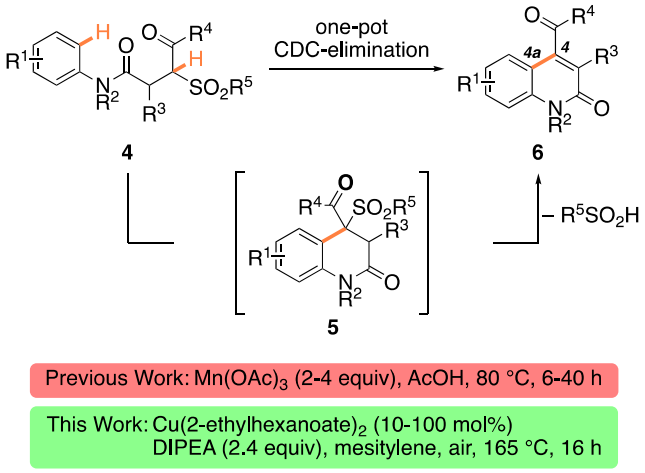


Scheme 1. Synthesis of quinolones via a one-pot cross-dehydrogenative coupling/sulfinic acid elimination strategy.

cyclisation [15], and superelectrophilic activation [16].

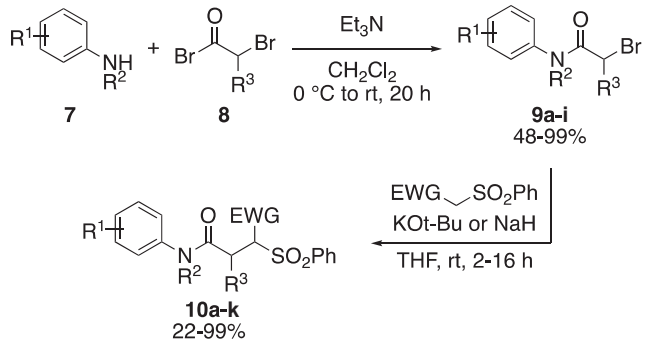
In a related approach, Chuang and coworkers have reported the manganese(III) acetate mediated oxidative free radical cyclisation of linear anilides **4** to give 4-carboxy-2-quinolones **6** (Scheme 1) [17]. The cyclisation itself may be considered as a radical cross-dehydrogenative coupling (CDC) to give key intermediate **5**, which subsequently undergoes rapid β-elimination of the sulfinic acid *in situ* to deliver the 2-quinolone **6**. In terms of the substrate scope, higher yields and lower reaction times were observed when ketones were used as the substrate (R^4 = Alk or Ar, 6 h, 62–88% yield) compared to the corresponding esters (R^4 = OEt, 40 h, 41–53% yield). Furthermore, a large excess of manganese(III) acetate is required (up to 4 equiv), especially in the case of ester substrates. Finally, the reaction must be performed in acetic acid as the solvent, thereby limiting the potential functional group compatibility.

In light of our recent work on the copper-catalysed synthesis of varied 5- and 6-membered nitrogen heterocycles under mild conditions, we sought to develop a copper(II)-mediated approach to quinolones [18]. In particular, we hoped to reduce the amount of transition metal salt required and avoid the use of neat acid as a solvent, while improving the yields and reducing the reaction times with respect to ester substrates. As such, we wish to report the synthesis of 4-carboxy-quinolin-2-ones via a one-pot Cu(II)-mediated radical cross-dehydrogenative coupling/sulfinic acid elimination of linear anilides (Scheme 1) and its extension to related quinolones and to target synthesis.

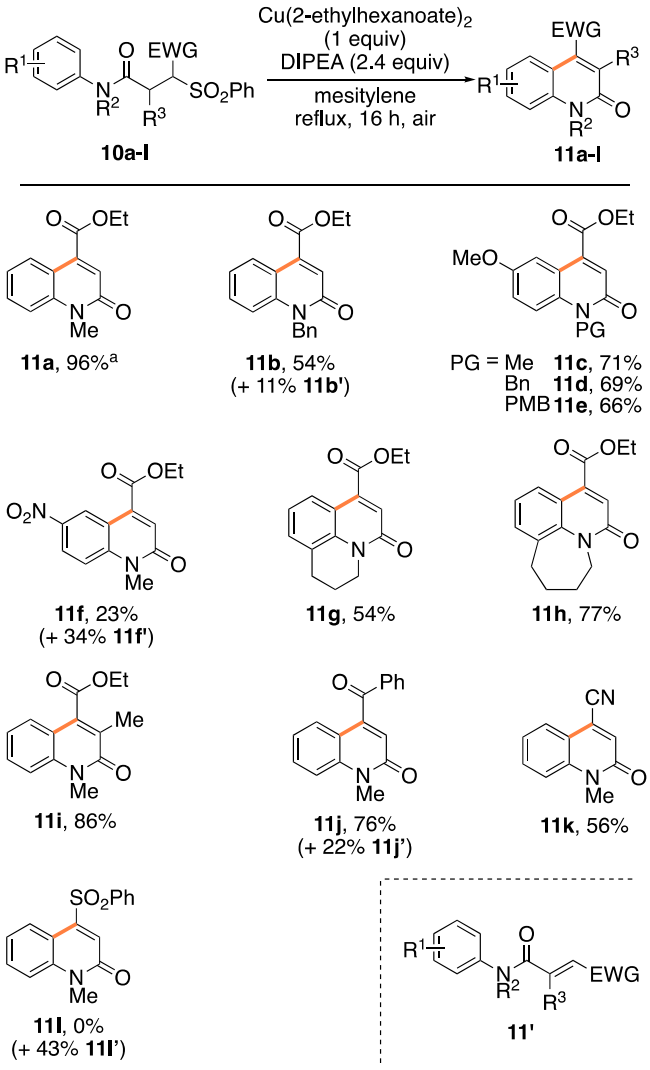
2. Results and discussion

The linear substrates required to test the cyclisation were readily prepared in 2 steps from commercially available materials. Coupling of anilines **7** with bromoacetyl bromide derivatives **8** gave the bromoacetamides **9a-l**, which underwent alkylation upon treatment with the appropriate activated methylene compound under basic conditions to deliver the anilide cyclisation precursors **10a-l** (Scheme 2).

With the linear anilide precursors in hand, attention turned to the key cyclisation/elimination reaction (Scheme 3). Upon treatment of sulfone-containing anilide **10a** under our previously established [18] conditions (10 mol% commercially-available copper(II) 2-ethylhexanoate, 2.4 equiv DIPEA, toluene, reflux under air), only unreacted starting material was isolated. However, the



Scheme 2. Synthesis of anilide cyclisation precursors.



Scheme 3. Substrate scope in the Cu(II)-mediated synthesis of 2-quinolones **11a-l**. [a] **11a** was isolated in 84% yield when 10 mol% copper(II) 2-ethylhexanoate was used.

desired quinolone **11a** was obtained in 84% yield upon changing the solvent to mesitylene and increasing the reaction temperature to 165 °C. The yield of **11a** was further improved to 96% by increasing the copper salt loading to 1 equiv (Scheme 3). Although not directly comparable, the yield of **11a** is considerably improved compared to an almost identical substrate (51% yield with NEt instead of NMe) prepared under the previously reported Mn(III)-mediated process

[17].

With conditions for the one-pot cyclisation/elimination established, the substrate scope was next investigated. Incorporation of a benzyl protecting group on nitrogen led to isolation of quinolone **11b** in 54% yield, along with 11% of a by-product that was identified as α,β-unsaturated anilide **11b′** arising from elimination of phenylsulfinic acid instead of cyclisation.

The effect of electron-donating and electron-withdrawing groups on the cyclisation reaction were next examined. *N*-Methyl-6-methoxyquinolone **11c** was isolated in 71% yield, representing a minor drop in yield relative to the unsubstituted system **11a**. Pleasingly, removable protecting groups on nitrogen were also tolerated, with **11d** and **11e** isolated in 69% and 66% yield, respectively.

In contrast, incorporation of the strongly electron-withdrawing nitro group on the aromatic ring gave the desired quinolone **11f** in only 23% yield, with the elimination by-product **11f′** isolated as the major component. Although distant to the site of elimination, the acidifying effect of the nitro group on the anilide α-hydrogen appears sufficient to promote elimination over cyclisation in this case.

The introduction of further substitution into the quinolone scaffold was next investigated. For example, the synthesis of fused tricyclic quinolones **11g-h** bearing an additional 6- or 7-membered ring was accomplished in good yields using our method. Furthermore, alkyl substituents were also well-tolerated in the 3-position of the final product (**11i**).

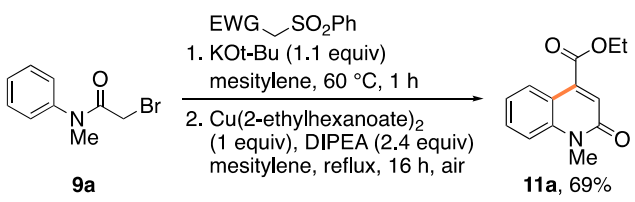
Finally, in this initial scoping study, the potential to incorporate electron-withdrawing groups other than an ester into the final product was also investigated. In analogous fashion to the reported manganese(III) acetate mediated procedure, replacement of the ester with a ketone was well-tolerated in the one-pot cyclisation/elimination reaction. In the event, exposure of anilide **10j** to the standard reaction conditions afforded quinolone **11j** in 76% yield, along with elimination by-product **11j′** in 22% yield. While nitrile-containing anilide **10k** was also a suitable substrate in the reaction giving quinolone **11k**, attempted incorporation of a sulfone gave only the elimination by-product **11l′**. Again, it should be noted that the copper(II) procedure avoids the requirement for super-stoichiometric quantities of metal salt and acetic acid as a solvent, as used in the Mn(III) variant.

In light of our previous one-pot synthesis of oxindoles [18g], a similar one-pot route to 2-quinolones seemed attainable. Thus, treatment of α-bromoanilide **9a** with the potassium salt of ethyl 2-(phenylsulfonyl)acetate in mesitylene at 60 °C for 1 h, followed by addition of the copper salt/DIPEA and further heating delivered quinolone **11a** in a respectable 69% yield over the 2 steps (Scheme 4).

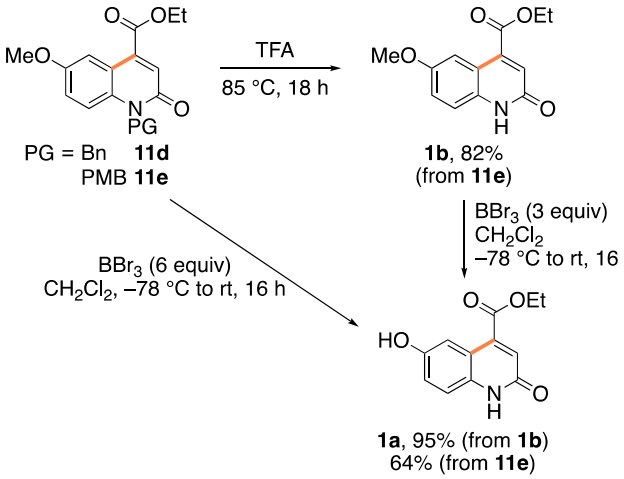
With conditions for the copper-mediated route to 2-quinolones successfully established, extension of this methodology to the preparation of several target molecules was investigated.

First, simple natural products **1a** and **1b**, isolated from the purple rice species *Oryza sativa* [2], were prepared. Although attempted removal of the benzyl group in **11d** with TFA gave only recovered starting material, PMB protected quinolone **11e** was smoothly converted into the natural product **1b** under the same conditions (Scheme 5). Further conversion of **1b** into the related natural product **1a** was accomplished by demethylation using excess BBr_3 (3 equiv). Simultaneous deprotection of both protecting groups in **11e** could also be achieved in one-pot through the use of a greater excess of BBr_3 (6 equiv), giving **1a** in 64% yield.

Finally, the furocoumarin HOFQ **3** was identified as a more complex candidate to validate our copper-mediated quinolone procedure. The required linear anilide **12** was prepared in the same manner as before, via acylation of the aniline derivative with bromoacetyl bromide followed by alkylation. Treatment of anilide **12** under the previously optimised conditions (1 equiv copper salt) delivered the cyclised product **13** in a disappointing 15% yield, along with 32% of the corresponding alkene **13′** resulting from premature elimination of phenylsulfinic acid. However, the yield of the desired product could be increased to 29% (along with 36% of the elimination by-product **13′**) by raising the amount of copper salt to 2 equiv (Scheme 6). In the final step of the synthesis, reduction of the ester was accomplished by addition of $LiAlH(Ot\text{-}Bu)_3$, giving the target molecule HOFQ **3** in 60% yield.



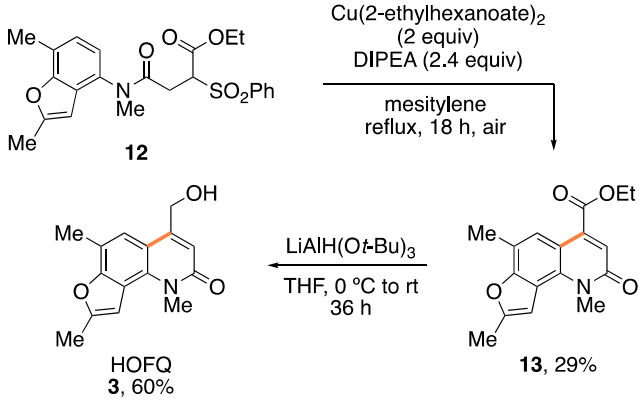
Scheme 4. Telescoped alkylation/CDC/elimination sequence.



Scheme 5. Total synthesis of simple natural products **1a** and **1b**.

3. Conclusions

A new cyclisation procedure has been developed to prepare 4-carboxy-quinolin-2-ones from linear anilides via a one-pot Cu(II)-mediated radical cross-dehydrogenative coupling/sulfinic acid



Scheme 6. Total synthesis of furocumarin HOFQ **3**.

elimination sequence. This improved method removes the need to employ super-stoichiometric quantities of metal salt and acetic acid as a solvent. Scoping studies have been carried out to prepare substituted 4-carboxy-quinolin-2-ones, related 4-keto- and 4-cyano- systems, and related tricyclic analogues. The copper-based methodology has been validated in target synthesis by preparing quinolin-2-one natural products isolated from *Oryza sativa* and HOFQ.

4. Experimental section

Except where stated, all reagents were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX400 or ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.27 and δ_C 77.0 for $CDCl_3$ was used as a reference. Coupling constants (J) are reported in Hertz (Hz). The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using a Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system.

4.1. General procedure A. Synthesis of α-bromoanilides **9a-i**

To a stirred solution of the aniline **7** and triethylamine (1 equiv) in CH_2Cl_2 (~0.9 mM) at 0 °C was added acid bromide **8** (1 equiv) in CH_2Cl_2 (~0.6 M) via cannula. The solution was allowed to warm to rt and stirred for 20 h. Further CH_2Cl_2 was added and the organics washed with 10% HCl solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compounds **9a-i** which could be used without further purification.

4.1.1. 2-Bromo-N-methyl-N-phenylacetamide [19] (**9a**)

N-Methylaniline **7a** (1.30 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), CH_2Cl_2 (14 mL) and bromoacetyl bromide **8a** (1.04 mL, 12.0 mmol) in CH_2Cl_2 (20 mL) were subjected to general procedure A to afford the title compound **9a** (2.15 g, 9.43 mmol, 78%) as a brown solid; R_f: 0.72 (1:1 Petrol/EtOAc); m.p. 45–46 °C (Lit [19]. 47 °C); ν_{max}/cm^{-1} (solid): 2997, 2926, 2328, 1622 (C=O), 1570, 1474; δ_H (400 MHz, $CDCl_3$): 7.44 (2H, tt, $J = 7.2$, 1.6 Hz), 7.38 (1H, tt, $J = 7.2$, 1.6 Hz), 7.27 (2H, dt, $J = 7.2$, 1.6 Hz), 3.65 (2H, s), 3.29 (3H, s); δ_C (100 MHz, $CDCl_3$): 166.4 (C), 143.0 (C), 130.0 (CH), 128.5 (CH), 126.9 (CH), 38.0 (Me), 26.8 (CH_2); HRMS [ES^+] found MH^+, 228.0019. $C_9H_{11}^{79}BrNO$ requires 228.0019.

4.1.2. N-Benzyl-2-bromo-N-phenylacetamide [20] (**9b**)

N-Benzylaniline **7b** (2.07 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), CH_2Cl_2 (14 mL) and bromoacetyl bromide **8a** (1.04 mL, 12.0 mmol) in CH_2Cl_2 (20 mL) were subjected to general procedure A to afford the title compound **9b** (2.49 g, 8.18 mmol, 68%) as a brown/yellow crystalline solid; R_f: 0.25 (4:1 Petrol/EtOAc); m.p. 64–65 °C (Lit [20]. 70 °C); ν_{max}/cm^{-1} (solid): 2325, 1634 (C=O), 1567, 1470, 1366, 1176; δ_H (400 MHz, $CDCl_3$): 7.35–7.32 (3H, m), 7.28–7.24 (3H, m), 7.20–7.17 (2H, m), 7.07–7.03 (2H, m), 4.89 (2H, s), 3.66 (2H, s); δ_C (100 MHz, $CDCl_3$): 166.5 (C), 141.3 (C), 136.7 (C), 129.9 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 53.8 (CH_2), 27.5 (CH_2); HRMS [ES^+] found MH^+, 304.0321. $C_{15}H_{15}^{79}BrNO$ requires 304.0332.

4.1.3. 2-Bromo-N-(4-methoxyphenyl)-N-methylacetamide [21] (**9c**)

4-Methoxy-*N*-methylaniline **7c** (927 mg, 6.76 mmol), triethylamine (0.95 mL, 6.76 mmol), CH_2Cl_2 (8 mL) and bromoacetyl bromide **8a** (589 μL, 6.76 mmol) in CH_2Cl_2 (12 mL) were subjected to general procedure A to afford the title compound **9c** (1.53 g, 5.93 mmol, 87%) as a brown oil; R_f: 0.38 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2914, 1638 (C=O), 1489, 1419, 1359, 1281, 1230; δ_H (400 MHz, $CDCl_3$): 7.20 (2H, d, $J = 8.8$ Hz), 6.94 (2H, d, $J = 8.8$ Hz), 3.84 (3H, s), 3.66 (2H, s), 3.27 (3H, s); δ_C (100 MHz, $CDCl_3$): 166.9 (C), 159.3 (C), 135.7 (C), 128.1 (CH), 115.0 (CH), 55.5 (Me), 38.2 (Me), 26.8 (CH_2); HRMS [ES^+] found MH^+ 258.0132. $C_{10}H_{13}^{79}BrNO_2$ requires 258.0124.

4.1.4. N-Benzyl-2-bromo-N-(4-methoxyphenyl)acetamide (**9d**)

N-Benzyl-4-methoxyaniline **7d** (1.28 g, 6.00 mmol), triethylamine (835 μL, 6.00 mmol), CH_2Cl_2 (7 mL) and bromoacetyl bromide **8a** (521 μL, 6.00 mmol) in CH_2Cl_2 (10 mL) were subjected to general procedure A to afford the title compound **9d** (1.76 g, 5.25 mmol, 88%) as a brown oil; R_f: 0.37 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 3010, 2934, 2837, 1653 (C=O), 1509, 1434, 1401, 1293, 1251; δ_H (400 MHz, $CDCl_3$): 7.29–7.22 (3H, m), 7.20–7.13 (2H, m), 6.94 (2H, d, $J = 8.8$ Hz), 6.81 (2H, d, $J = 8.8$ Hz), 4.84 (2H, s), 3.79 (3H, s), 3.66 (2H, s); δ_C (100 MHz, $CDCl_3$): 166.8 (C), 159.3 (C), 136.5 (C), 133.6 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 127.5 (CH), 114.7 (CH), 55.3 (Me), 53.7 (CH_2), 27.3 (CH_2); HRMS [ES^+] found MH^+ 334.0426. $C_{16}H_{17}^{79}BrNO_2$ requires 334.0437.

4.1.5. 2-Bromo-N-(4-methoxybenzyl)-N-(4-methoxyphenyl) acetamide (**9e**)

4-Methoxy-*N*-(4-methoxybenzyl)aniline **7a** (2.00 g, 8.22 mmol), triethylamine (1.14 mL, 8.22 mmol), CH_2Cl_2 (10 mL) and bromoacetyl bromide **8a** (714 μL, 8.22 mmol) in CH_2Cl_2 (14 mL) were subjected to general procedure A. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded the title compound **9e** (2.64 g, 7.25 mmol, 88%) as a brown oil; R_f: 0.22 (4:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2934, 1658 (C=O), 1509, 1300, 1247, 1175; δ_H (400 MHz, $CDCl_3$): 7.05 (2H, d, $J = 8.5$ Hz), 6.88 (2H, d, $J = 8.8$ Hz), 6.78 (2H, d, $J = 8.8$ Hz), 6.74 (2H, d, $J = 8.5$ Hz), 4.73 (2H, s), 3.75 (3H, s), 3.72 (3H, s), 3.61 (2H, s); δ_C (100 MHz, $CDCl_3$): 166.5 (C), 159.2 (C), 158.9 (C), 133.5 (CH), 130.2 (CH), 129.2 (CH), 128.7 (C), 114.6 (CH), 113.6 (CH), 55.3 (Me), 55.0 (Me), 53.0 (CH_2), 27.5 (CH_2); HRMS [ES^+] found MNa^+ 386.0354. $C_{17}H_{18}^{79}BrNNaO_3$ requires 386.0362.

4.1.6. 2-Bromo-N-methyl-N-(4-nitrophenyl)acetamide [22] (**9f**)

4-Nitro-*N*-methylaniline **7f** (1.82 g, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), CH_2Cl_2 (14 mL) and bromoacetyl bromide **7a** (1.04 mL, 12.0 mmol) in CH_2Cl_2 (20 mL) were subjected to general procedure A. Purification by flash column chromatography (13:7 Petrol/EtOAc) afforded the title compound **9f** (1.59 g, 5.82 mmol, 48%) as a colourless powder; R_f: 0.34 (1:1 petrol/EtOAc); m.p. 84–85 °C (Lit.[22] 88–89 °C); ν_{max}/cm^{-1} (solid): 1654 (C=O), 1587, 1518, 1341, 1104, 866; δ_H (400 MHz, $CDCl_3$): 8.33 (2H, d, $J = 9.0$ Hz), 7.51 (2H, d, $J = 9.0$ Hz), 3.74 (2H, s), 3.39 (3H, s); δ_C (100 MHz, $CDCl_3$): 166.1 (C), 148.5 (C), 146.3 (C), 127.5 (CH), 125.2 (CH), 38.1 (Me), 26.2 (CH_2); HRMS [ES^+] found MH^+ 272.9873. $C_9H_{10}^{79}BrN_2O_3$ requires 272.9869.

*4.1.7. 2-Bromo-1-(3,4-dihydroquinolin-1(2H)-yl)ethanone [23] (**9g**)*

1,2,3,4-Tetrahydroquinoline **7g** (1.25 mL, 10.0 mmol), triethylamine (1.39 mL, 6.00 mmol), CH_2Cl_2 (12 mL) and bromoacetyl bromide **7a** (869 μL, 10.0 mmol) in CH_2Cl_2 (16 mL) were subjected to general procedure A to afford the title compound **9g** (2.25 g, 8.91 mmol, 88%) as a brown oil; R_f: 0.52 (1:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2948, 1654 (C=O), 1581, 1491, 1458, 1428, 1389; δ_H (400 MHz, $CDCl_3$): 7.23–7.08 (4H, m), 4.03 (2H, s), 3.80 (2H, t, J = 6.5 Hz), 2.76–2.65 (2H, m), 2.02–1.90 (2H, m); δ_C (100 MHz, $CDCl_3$): 166.3 (C), 138.5 (C), 134.3 (C), 128.6 (CH), 126.5 (CH), 126.1 (CH), 123.4 (CH), 43.4 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 23.7 (CH_2); HRMS [ES^+] found MNa^+ 275.9984. $C_{11}H_{12}^{79}BrNNaO$ requires 275.9994.

*4.1.8. 2-Bromo-1-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl) ethanone [24] (**9h**)*

2,3,4,5-Tetrahydro−1*H*-benzo[*b*]azepine **7h** (525 mg, 3.57 mmol), triethylamine (480 μL, 3.57 mmol), CH_2Cl_2 (5 mL) and bromoacetyl bromide **7a** (310 μL, 3.57 mmol) in CH_2Cl_2 (6.5 mL) were subjected to general procedure A. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded the title compound **9h** (679 mg, 2.53 mmol, 71%) as a colourless solid; R_f: 0.21 (4:1 Hexane/EtOAc); m.p. 93–95 °C; ν_{max}/cm^{-1} (neat): 2938, 1654 (C=O), 1492, 1440, 1399, 1311; δ_H (400 MHz, $CDCl_3$): 7.27–7.18 (4H, m), 4.69–4.62 (1H,m), 3.73(1H,d,J = 10.8 Hz), 3.65(1H,d,J = 10.8 Hz), 2.94–2.85(1H, m), 2.73–2.61(2H,m), 2.03–1.87(2H,m), 1.82–1.73(1H,m), 1.43–1.31 (1H, m); δ_C (100 MHz, $CDCl_3$): 165.3 (C), 142.3 (C), 140.7(C), 130.5 (CH), 128.6(CH), 127.4(CH), 126.8(CH), 48.0(CH_2), 34.4(CH_2), 28.7(CH_2), 26.9 (CH_2), 26.3 (CH_2); HRMS [ES^+] found MH^+ 268.0329. $C_{12}H_{15}^{79}BrNO$ requires 268.0332.

*4.1.9. 2-Bromo-N-methyl-N-phenylpropanamide [25,26] (**9i**)*

N-Methylaniline **7a** (1.30 mL, 12.0 mmol), triethylamine (1.67 mL, 12.0 mmol), CH_2Cl_2 (14 mL) and 2-bromopropionyl bromide **7b** (1.26 mL, 12.0 mmol) in CH_2Cl_2 (20 mL) were subjected to general procedure A to afford the title compound **9i** (2.87 g, 11.8 mmol, 99%) as an orange oil; R_f: 0.60 (1:1 petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1641 (C=O), 1571, 1472, 1368, 1250, 1104; δ_H (400 MHz, $CDCl_3$): 7.48–7.47 (2H, m), 7.40 (1H, tt, J = 7.2, 1.2 Hz), 7.29 (2H, d, J = 7.2 Hz), 4.26 (1H, q, J = 6.8 Hz), 3.29 (3H, s), 1.73 (3H, d, J = 6.8 Hz); δ_C (100 MHz, $CDCl_3$): 169.6 (C), 142.8 (C), 129.9 (CH), 128.4 (CH), 127.1 (CH), 39.0 (CH), 38.1 (Me), 21.8 (Me); HRMS [ES^+] found MH^+ 242.0172. $C_{10}H_{13}^{79}BrNO$ requires 242.0175.

*4.2. General procedure B. Synthesis of linear anilides **10a-k***

To a stirred solution of activated methylene compound (1–2 equiv) in THF (~0.26 M) was added KO*t*Bu (1–2 equiv). The reaction mixture was stirred for 5 min, then the anilide (1–2 equiv) in THF (~0.94 M) was added via cannula. Stirring was continued for 2 h at room temperature. The reaction mixture was quenched (sat. NH_4Cl solution), the aqueous extracted (EtOAc), and the combined organics washed (brine), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

*4.2.1. Ethyl 4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl) butanoate (**10a**)*

Ethyl 2-(phenylsulfonyl)acetate (2.00 g, 8.76 mmol) and KO*t*Bu (982 mg, 8.76 mmol) in THF (32 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **9a** (1.00 g, 4.38 mmol) in THF (6 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **10a** (1.53 g, 4.07 mmol, 93%) as a colourless solid; R_f: 0.25 (1:1 Hexane/EtOAc); m.p. 120–123 °C; ν_{max}/cm^{-1} (neat): 2936, 1736 (C=O), 1649 (C=O), 1595, 1497, 1449, 1309 (S=O), 1226, 1145 (S=O); δ_H (400 MHz, $CDCl_3$): 7.79 (2H, dd, J = 8.2, 1.0 Hz), 7.66 (1H, tt, J = 7.5, 1.2 Hz), 7.55–7.49 (2H, m), 7.48–7.37 (3H, m), 7.24–7.21 (2H, m), 4.56 (1H, dd, J = 6.7, 3.9 Hz), 4.10–3.98 (2H, m), 3.24 (3H, s), 2.97 (1H, dd, J = 16.8, 10.7 Hz), 2.84 (1H, dd, J = 10.7, 3.9 Hz), 1.06 (3H, t, J = 7.1 Hz); δ_C (100 MHz, $CDCl_3$): 168.4 (C), 165.3 (C), 142.8 (C), 137.8 (C), 134.2 (CH), 130.1 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.2 (CH), 66.9 (CH), 62.2 (CH_2), 37.5 (Me), 30.8 (CH_2), 13.6 (Me); HRMS [ES^+] found MNa^+, 398.1030. $C_{19}H_{21}NNaO_5S$ requires 398.1033.

*4.2.2. Ethyl 4-(benzyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl) butanoate (**10b**)*

Ethyl 2-(phenylsulfonyl)acetate (422 mg, 1.85 mmol) and KO*t*Bu (227 mg, 2.03 mmol) in THF (20 mL) and 2-bromo-*N*-benzyl-*N*-phenylacetamide **9b** (727 mg, 2.40 mmol) in THF (4 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (7:3 Hexane/EtOAc) afforded the title compound **10b** (830 mg, 1.84 mmol, 99%) as a colourless oil; R_f: 0.18 (7:3 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1736 (C=O), 1651 (C=O), 1595, 1494, 1407, 1322 (S=O), 1146 (S=O); δ_H (400 MHz, $CDCl_3$): 7.78 (2H, dd, J = 7.2, 1.4 Hz), 7.65 (1H, tt, J = 7.4, 1.1 Hz), 7.51 (2H, t, J = 7.9 Hz), 7.36–7.29 (3H, m), 7.26–7.19 (3H, m), 7.15–7.11 (2H, m), 7.03–6.99 (2H, m), 4.88 (2H, d, J = 14.3 Hz), 4.80 (2H, d, J = 14.3 Hz), 4.62 (1H, dd, J = 10.4, 4.1 Hz), 4.14–4.00 (2H, m), 2.94 (1H, dd, J = 16.9, 10.4 Hz), 2.85 (1H, dd, J = 16.9, 4.1 Hz), 1.07 (3H, t, J = 7.1 Hz); δ_C (100 MHz, $CDCl_3$): 168.4 (C), 165.2 (C), 141.1 (C), 137.8 (C), 136.8 (C), 134.1 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 66.9 (CH), 62.2 (CH_2), 53.3 (CH_2), 31.1 (CH_2), 13.6 (Me); HRMS [ES^+] found MNa^+, 474.1337. $C_{25}H_{25}NNaO_5S$ requires 474.1346.

*4.2.3. Ethyl 4-((4-methoxyphenyl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**10c**)*

Ethyl 2-(phenylsulfonyl)acetate (575 mg, 2.52 mmol) and KO*t*Bu (282 mg, 2.52 mmol) in THF (11 mL) and 2-bromo-*N*-(4-methoxyphenyl)-*N*-methylacetamide **9c** (325 mg, 1.26 mmol) in THF (2 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (55:45 Hexane/EtOAc) afforded the title compound **10c** (361 mg, 891 μmol, 71%) as a brown semi-solid; R_f: 0.12 (55:45 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1738 (C=O), 1655 (C=O), 1512, 1448, 1392, 1323 (S=O), 1249, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2H, dd, J = 7.2, 1.3 Hz), 7.66 (1H, tt, J = 7.5, 1.2 Hz), 7.53 (2H, t, J = 7.5 Hz), 7.15–7.11 (2H, m), 6.96–6.92 (2H, m), 4.54 (1H, dd, J = 10.7, 3.9 Hz), 4.15–3.97 (2H, m), 3.86 (3H, s), 3.20 (3H, s), 2.97 (1H, dd, J = 16.8, 10.7 Hz), 2.83 (1H, dd, J = 16.8, 3.8 Hz), 1.05 (3H, t, J = 7.2 Hz); δ_C (100 MHz, $CDCl_3$): 168.8 (C), 165.3 (C), 159.3 (C), 137.9 (C), 135.5 (C), 134.1 (CH), 129.0 (CH), 128.8 (CH), 128.3 (CH), 115.2 (CH), 66.9 (CH), 62.2 (CH_2), 55.5 (Me), 37.6 (Me), 30.7 (CH_2), 13.6 (Me); HRMS [ES^+] found MNa^+, 428.1139. $C_{20}H_{23}NNaO_6S$ requires 428.1138.

*4.2.4. Ethyl 4-(benzyl(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**10d**)*

Ethyl 2-(phenylsulfonyl)acetate (1.36 g, 5.98 mmol) and KO*t*Bu (670 mg, 5.98 mmol) in THF (42 mL) and *N*-benzyl-2-bromo-*N*-(4-methoxyphenyl)acetamide **9d** (1.00 g, 2.99 mmol) in THF (9 mL) were subjected to general procedure B for 4 h. Purification by flash column chromatography (13:7 Hexane/EtOAc) afforded the title compound **10d** (1.06 g, 2.20 mmol, 74%) as an orange gum; R_f: 0.22 (13:7 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1324 (S=O), 1250, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2H, dd, J = 8.4, 1.2 Hz), 7.66 (1H, tt, J = 7.5, 1.8 Hz), 7.53 (2H, t, J = 7.4 Hz), 7.27–7.21 (3H, m), 7.15–7.12 (2H, m), 6.90 (2H, d, J = 9.0 Hz), 6.83 (2H, d, J = 9.0 Hz), 4.84 (1H, d, J = 14.2 Hz), 4.73 (1H,

d, J = 14.2 Hz), 4.60 (1H, dd, J = 10.6, 4.0 Hz), 4.13–3.98 (2H, m), 3.81 (3H, s), 2.95 (1H, dd, J = 16.9, 10.6 Hz), 2.84 (1H, dd, J = 16.9, 4.0 Hz), 1.06 (3H, t, J = 7.2 Hz); δ_C (100 MHz, $CDCl_3$): 168.9 (C), 165.4 (C), 159.4 (C), 138.0 (C), 137.0 (C), 134.3 (CH), 133.8 (C), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 115.1 (CH), 67.1 (CH), 62.4 (CH_2), 55.6 (Me), 53.5 (CH_2), 31.0 (CH_2), 13.7 (Me); HRMS [ES^+] found MH^+, 482.1637. $C_{26}H_{28}NO_6S$ requires 482.1632.

4.2.5. Ethyl 4-((4-methoxybenzyl)(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**10e**)

Ethyl 2-(phenylsulfonyl)acetate (1.00 g, 4.40 mmol) and KO*t*Bu (492 mg, 4.40 mmol) in THF (32 mL) and 2-bromo-*N*-(4-methoxybenzyl)-*N*-(4-methoxyphenyl)acetamide **9e** (800 mg, 2.20 mmol) in THF (6 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **10e** (960 mg, 1.89 mmol, 85%) as an orange gum; R_f: 0.21 (3:2 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2937, 1738 (C=O), 1654 (C=O), 1512, 1447, 1408, 1323 (S=O), 1248, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.80 (2H, d, J = 7.5 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.53 (2H, t, J = 7.5 Hz), 7.04 (2H, d, J = 8.6 Hz), 6.89–6.81 (4H, m), 6.76 (2H, d, J = 8.6 Hz), 4.79 (1H, d, J = 14.1 Hz), 4.66 (1H, d, J = 14.1 Hz), 4.59 (1H, dd, J = 10.6, 4.0 Hz), 4.12–3.98 (2H, m), 3.82 (3H, s), 3.77 (3H, s), 2.93 (1H, dd, J = 16.9, 10.6 Hz), 2.82 (1H, dd, J = 16.9, 4.0 Hz), 1.06 (3H, t, J = 7.2 Hz); δ_C (100 MHz, $CDCl_3$): 168.6 (C), 165.3 (C), 159.3 (C), 158.9 (C), 137.9 (C), 134.1 (CH), 133.6 (C), 130.1 (CH), 129.4 (CH), 129.1 (C), 129.0 (CH), 128.8 (CH), 115.0 (CH), 113.7 (CH), 66.9 (CH), 62.2 (CH_2), 55.4 (Me), 55.2 (Me), 52.7 (CH_2), 31.0 (CH_2), 13.6 (Me); HRMS [ES^+] found MNa^+, 534.1530. $C_{27}H_{29}NNaO_7S$ requires 534.1557.

4.2.6. Ethyl 4-(methyl(4-nitrophenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**10f**)

Ethyl 2-(phenylsulfonyl)acetate (399 mg, 1.75 mmol) and KO*t*Bu (196 mg, 1.75 mmol) in THF (8 mL) and 2-bromo-*N*-(4-nitrophenyl)-*N*-methylacetamide **9f** (361 mg, 1.26 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (1:1 Petrol/EtOAc) afforded the title compound **10f** (364 mg, 867 μmol, 66%) as a colourless oil; R_f: 0.19 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 1737 (C=O), 1663 (C=O), 1593, 1522, 1496 1448, 1342 (S=O), 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 8.31 (2H, d, J = 8.3 Hz), 7.83 (2H, d, J = 7.8 Hz), 7.69 (1H, t, J = 7.8 Hz), 7.59 (2H, t, J = 7.8 Hz), 7.45 (2H, d, J = 8.3 Hz), 4.59 (1H, dd, J = 10.2, 4.2 Hz), 4.14–3.96 (2H, m), 3.30 (3H, s), 3.02 (2H, br s), 1.03 (3H, t, J = 7.2 Hz3); δ_C (100 MHz, $CDCl_3$): 168.4 (C), 165.3 (C), 148.6 (C), 146.9 (C), 137.9 (C), 134.5 (CH), 129.3 (CH), 129.0 (CH), 128.0 (CH), 125.5 (CH), 66.8 (CH), 62.6 (CH_2), 37.8 (Me), 30.9 (CH_2), 13.7 (Me); HRMS [ES^+] found MNa^+, 443.0890. $C_{19}H_{20}N_2NaO_7S$ requires 443.0883.

4.2.7. Ethyl 4-(3,4-dihydroquinolin-1(2H)-yl)-4-oxo-2-(phenylsulfonyl)butanoate (**10g**)

Ethyl 2-(phenylsulfonyl)acetate (381 mg, 1.67 mmol) and KO*t*Bu (187 mg, 1.67 mmol) in THF (9 mL) and 2-bromo-1-(3,4-dihydroquinolin-1(2*H*)-yl)ethanone **9g** (316 g, 1.25 mmol) in THF (2 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (13:7 Hexane/EtOAc) afforded the title compound **10g** (339 mg, 845 μmol, 68%) as a yellow oil; R_f: 0.23 (13:7 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2942, 1737 (C=O), 1650 (C=O), 1492, 1400, 1323 (S=O), 1240, 1147 (S=O); δ_H (400 MHz, $CDCl_3$): 7.87–7.75 (2H, m), 7.68–7.61 (1H, m), 7.56–7.49 (2H, m), 7.22–7.03 (4H, m), 4.64–4.56 (1H, m), 4.08–3.96 (2H, m), 3.83–3.64 (2H, m), 3.45–3.16 (2H, m), 2.75–2.63 (2H, m), 2.01–1.79 (2H, m), 1.07–0.99 (3H, m); δ_C (100 MHz, $CDCl_3$): 168.1 (C), 165.2 (C), 138.1 (C), 137.6 (CH), 134.2 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 126.3 (CH), 126.0 (CH) 124.4 (C), 67.1 (CH), 62.2 (CH_2), 43.0 (CH_2), 31.3 (CH_2), 26.5 (CH_2), 23.7 (CH_2), 13.5 (Me); HRMS [ES^+] found MH^+, 402.1369. $C_{21}H_{24}NO_5S$ requires 402.1370.

4.2.8. Ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)butanoate (**10h**)

Ethyl 2-(phenylsulfonyl)acetate (204 mg, 896 μmol) and KO*t*Bu (100 mg, 896 μmol) in THF (5 mL) and 2-bromo-1-(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)ethanone **9h** (120 mg, 448 μmol) in THF (2 mL) were subjected to general procedure B for 16 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **10h** (119 g, 286 μmol, 64%) as a colourless oil; R_f: 0.22 (3:2 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2938, 1737 (C=O), 1650 (C=O), 1408, 1400, 1322 (S=O), 1145 (S=O); δ_H (400 MHz, $CDCl_3$): 7.81–7.77 (2H, m), 7.68–7.62 (1H, m), 7.52 (2H, t, J = 7.8 Hz), 7.26–7.12 (4H, m), 4.63–4.56 (2H, m), 4.13–3.96 (2H, m), 3.24–3.02 (1H, m), 2.89–2.76 (1H, m), 2.73 (3H, m), 2.01–1.69 (3H, m), 1.41–1.27 (1H, m), 1.08–1.02 (3H, m); δ_C (100 MHz, $CDCl_3$): Mixture of rotamers: 167.5 (C), 167.4 (C), 165.5 (C), 165.2 (C), 142.0 (C), 141.9 (C), 140.9 (C), 140.7 (C), 138.0 (C), 137.9 (C), 134.2 (CH), 130.6 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 66.9 (CH), 62.28 (CH_2), 62.25 (CH_2), 47.70 (CH_2), 47.65 (CH_2), 34.4 (CH_2), 34.2 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 29.0 (CH_2), 28.96 (CH_2), 26.4 (CH_2), 13.7 (Me); HRMS [ES^+] found MH^+, 438.1349. $C_{22}H_{25}NNaO_5S$ requires 438.1346.

4.2.9. Ethyl 3-methyl-4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**10i**)

Ethyl 2-(phenylsulfonyl)acetate (839 mg, 3.68 mmol) and KO*t*Bu (448 mg, 3.68 mmol) in THF (14 mL) and 2-bromo-*N*-methyl-*N*-phenylpropanamide **9i** (594 mg, 2.45 mmol) in THF (4 mL) were subjected to general procedure B for 16 h. Purification by flash column chromatography (17:3 → 3:1 Hexane/EtOAc) afforded the title compound **10i** (208 mg, 535 μmol, 22%) as an orange oil which was an inseparable (1:1.6) mixture of diastereoisomers; R_f: 0.23 (1:1 Petrol/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1732 (C=O), 1651 (C=O), 1595, 1495, 1448, 1392, 1323 (S=O), 1144 (S=O); δ_H (400 MHz, $CDCl_3$): Major diastereoisomer: 7.68 (2H, d, J = 7.6 Hz), 7.57 (2H, t, J = 7.6 Hz), 7.44–7.25 (4H, m), 7.18 (2H, d, J = 7.6 Hz), 4.25 (1H, d, J = 10.7 Hz), 3.98–3.90 (2H, m), 3.37–3.24 (1H, m), 3.09 (3H, s), 1.29–1.25 (3H, m), 1.05–0.94 (3H, m); Minor diastereoisomer: 7.82 (2H, d, J = 6.8 Hz), 7.47 (2H, t, J = 6.8 Hz), 7.44–7.25 (6H, m), 4.72 (1H, d, J = 10.7 Hz), 3.85–3.75 (2H, m), 3.37–3.24 (1H, m), 3.23 (3H, s), 1.29–1.25 (3H, m), 1.05–0.94 (3H, m); δ_C (100 MHz, $CDCl_3$): Major diastereoisomer; 173.2 (C), 166.3 (C), 142.8 (C), 137.5 (C), 133.9 (CH), 129.7 (CH), 128.73 (CH), 128.7 (CH), 127.8 (CH), 127.0 (CH), 73.5 (CH), 61.9 (CH_2), 37.3 (Me), 36.3 (CH), 16.5 (Me), 13.3 (Me); Minor diastereoisomer: 172.3 (C), 164.5 (C), 143.0 (C), 139.0 (C), 133.8 (CH), 129.7 (CH), 128.8 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 72.7 (CH), 61.7 (CH_2), 37.8 (Me), 34.6 (CH), 16.4 (Me), 13.5 (Me); HRMS [ES^+] found MNa^+, 412.1179. $C_{20}H_{23}NNaO_5S$ requires 412.1189.

4.2.10. N-Methyl-4-oxo-N,4-diphenyl-3-(phenylsulfonyl)butanamide (**10j**)

1-Phenyl-2-(phenylsulfonyl)ethanone (274 mg, 1.05 mmol) and KO*t*Bu (118 mg, 1.05 mmol) in THF (4 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **9a** (120 mg, 0.526 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded the title compound **10j** (213 mg, 523 μmol, 99%) as a colourless solid; R_f: 0.22 (4:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 3061, 1681 (C=O), 1654 (C=O), 1596, 1496, 1448, 1377, 1310 (S=O), 1150 (S=O); δ_H (400 MHz, $CDCl_3$): 7.90 (2H, d, J = 7.3 Hz), 7.54–7.30 (11H, m), 7.21 (2H, d, J = 7.3 Hz), 5.61 (1H, dd, J = 10.9, 3.1 Hz), 3.17–3.09 (1H, m),

3.16 (3H, s), 2.89 (1H, dd, $J = 16.7$, 3.1 Hz); δ_C (100 MHz, $CDCl_3$): 191.8 (C), 168.6 (C), 142.7 (C), 136.7 (C), 134.1 (CH), 133.5 (CH), 130.1 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.2 (CH), 66.4 (CH), 37.4 (Me), 33.3 (CH_2); HRMS [ES^+] found MNa^+, 430.1070. $C_{23}H_{21}NNaO_4S$ requires 430.1083.

4.2.11. 3-Cyano-N-methyl-N-phenyl-3-(phenylsulfonyl) propanamide (**10k**)

2-(Phenylsulfonyl)acetonitrile (191 mg, 1.05 mmol) and KO*t*Bu (118 mg, 1.05 mmol) in THF (4 mL) and 2-bromo-*N*-methyl-*N*-phenylacetamide **9a** (120 mg, 0.526 mmol) in THF (1.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded the title compound **10k** (123 mg, 302 μmol, 57%) as a colourless solid; R_f: 0.24 (4:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2925, 1656 (C═O), 1596, 1496, 1333 (S═O), 1157 (S═O); δ_H (400 MHz, $CDCl_3$): 7.97–7.93 (2H, m), 7.83–7.73 (1H, m), 7.68–7.59 (2H, m), 7.54–7.40 (3H, m), 7.23 (2H, d, $J = 7.6$ Hz), 4.73–4.65 (1H, m), 3.31 (3H, s), 3.06 (1H, dd, $J = 16.4$, 4.6 Hz), 2.73 (1H, dd, $J = 16.4$, 9.2 Hz); δ_C (100 MHz, $CDCl_3$): 166.0 (C), 142.2 (C), 135.6 (C), 135.4 (CH), 130.4 (CH), 129.6 (CH), 129.4 (CH), 127.8 (CH), 127.2 (CH), 114.0 (C), 53.8 (CH), 37.8 (Me), 31.5 (CH_2); HRMS [ES^+] found MH^+, 329.0947. $C_{17}H_{17}N_2O_3S$ requires 329.0954.

4.3. General procedure C. Copper mediated synthesis of quinolones **11a-k**

To a stirred solution of the anilide **10a-k** and copper(II) 2-ethylhexanoate (10 mol% to 100 mol%) in mesitylene (0.03 M) was added DIPEA (2.4 eq). The reaction was stirred at reflux under an atmosphere of air. Upon completion of the reaction, the solvent was removed under reduced pressure and EtOAc was added. The solution was washed with 10% HCl solution, 10% aqueous NH_4OH solution, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compounds.

4.3.1. Ethyl 1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate [27] (**11a**)

From **10a**: Ethyl 4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10a** (100 mg, 266 μmol), copper(II) 2-ethylhexanoate (93.3 mg, 100 mol%) and DIPEA (111 μL, 638 μmol) in mesitylene (8 mL) were subjected to general procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **11a** (59.0 mg, 255 μmol, 96%) as a brown solid; R_f: 0.19 (3:2 Hexane/EtOAc); m.p. 132 °C (Lit [27]. 134–135 °C); ν_{max}/cm^{-1} (neat): 2919, 1714 (C═O), 1643 (C═O), 1583, 1454, 1416, 1399, 1334, 1235; δ_H (400 MHz, $CDCl_3$): 8.35 (1H, dd, $J = 8.2$, 1.1 Hz), 7.64–7.58 (1H, m), 7.41 (1H, d, $J = 8.6$ Hz), 7.24–7.18 (1H, m), 7.16 (1H, s), 4.43 (2H, q $J = 7.1$ Hz), 3.73 (3H, s), 1.41 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.3 (C), 161.4 (C), 140.3 (C), 138.9 (C), 131.1 (CH), 127.1 (CH), 124.2 (CH), 122.7 (CH), 117.5 (C), 114.5 (CH), 62.0 (CH_2), 29.8 (Me), 14.1 (Me); HRMS [ES^+] found MH^+, 232.0965. $C_{13}H_{14}NO_3$ requires 232.0968.

One-pot synthesis from **7a**: To a stirred solution of ethyl 2-(phenylsulfonyl)acetate (50 mg, 219 μmol) in mesitylene (2.25 mL) was added KO*t*Bu (27.0 mg, 241 μmol) and held for 5 min. 2-Bromo-*N*-methyl-*N*-phenylacetamide **7a** (50 mg, 439 μmol) in mesitylene (0.5 mL) was added and stirring continued for 1 h at 60 °C under an atmosphere of air. Copper(II) 2-ethylhexanoate (77 mg, 100 mol%), DIPEA (89 μL, 526 μmol) and mesitylene (1.75 mL) were added to the reaction mixture and stirred at 165 °C for 16 h under an atmosphere of air. The solvent was removed under reduced pressure and EtOAc (10 mL) was added. The solution was washed with 10% HCl solution (8 mL), 10% aqueous NH_4OH solution (8 mL), brine (8 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **11a** (42 mg, 182 μmol, 83%) as a brown solid.

4.3.2. Ethyl 1-benzyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (**11b**)

Ethyl 4-(benzyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10b** (162 mg, 0.359 mmol), copper(II) 2-ethylhexanoate (126 mg, 100 mol%) and DIPEA (150 μL, 0.862 mmol) in mesitylene (11 mL) were subjected to general procedure C at 165 °C for 18 h. Purification by flash column chromatography (5:1 Hexane/EtOAc) afforded the title compound **11b** (60 mg, 195 μmol, 54%) as a colourless oil; R_f: 0.17 (5:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2978, 1736 (C═O), 1656 (C═O), 1595, 1495, 1449, 1407; δ_H (400 MHz, $CDCl_3$): 8.25 (1H, d, $J = 8.2$ Hz), 7.39 (1H, t, $J = 8.2$ Hz), 7.28–7.04 (8H, m), 5.51 (2H, s), 4.40 (2H, q, $J = 7.3$ Hz), 1.37 (3H, t, $J = 7.3$ Hz); δ_C (100 MHz, $CDCl_3$): 165.3 (C), 161.5 (C), 139.7 (C), 139.5 (C), 135.7 (C), 131.0 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 123.7 (CH), 122.7 (CH), 117.7 (C), 115.5 (CH), 62.0 (CH_2), 46.2 (CH_2), 14.2 (Me); HRMS [ES^+] found MH^+, 308.1282. $C_{19}H_{18}NO_3$ requires 308.1281.

Also isolated was ethyl (*E*)-4-(benzyl(phenyl)amino)-4-oxobut-2-enoate [28] **11b′** (19 mg, 61 μmol, 11%) as a yellow oil; R_f: 0.21 (5:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2980, 1720 (C═O), 1659 (C═O), 1634, 1594, 1494, 1389, 1293, 1160; δ_H (400 MHz, $CDCl_3$): 7.36–7.16 (8H, m), 7.01–6.96 (2H, m), 6.90 (1H, d, $J = 15.3$ Hz), 6.80 (1H, d, $J = 15.3$ Hz), 4.98 (2H, s), 4.14 (2H, q, $J = 7.1$ Hz), 1.23 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.7 (C), 164.1 (C), 141.1 (C), 136.9 (C), 134.4 (CH), 131.6 (CH), 129.8 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 61.1 (CH_2), 53.6 (CH_2), 14.2 (Me); HRMS [ES^+] found MNa^+, 332.1251. $C_{19}H_{19}NNaO_3$ requires 332.1257.

4.3.3. Ethyl 6-methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-4-carboxylate [29] (**11c**)

Ethyl 4-((4-methoxyphenyl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10c** (166 mg, 410 μmol), copper(II) 2-ethylhexanoate (144 mg, 100 mol%) and DIPEA (171 μL, 984 μmol) in mesitylene (15 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (1:1 Hexane/EtOAc) afforded the title compound **11c** (77 mg, 293 μmol, 71%) as a yellow solid; R_f: 0.17 (1:1 Petrol/EtOAc); m.p. 99–100 °C (Lit [29]. 105 °C); ν_{max}/cm^{-1} (neat): 1723 (C═O), 1658 (C═O), 1620, 1586, 1563, 1463, 1430; δ_H (400 MHz, $CDCl_3$): 7.97 (1H, d, $J = 2.9$ Hz), 7.34 (1H, d, $J = 9.3$ Hz), 7.29 (1H, s), 7.23 (1H, dd, $J = 9.3$, 2.9 Hz), 4.44 (2H, q, $J = 7.1$ Hz), 3.87 (3H, s), 3.74 (3H, s), 1.43 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.4 (C), 160.9 (C), 155.0 (C), 137.6 (C), 135.0 (C), 125.2 (CH), 120.1 (CH), 118.3 (C), 115.7 (CH), 108.8 (CH), 61.9 (CH_2), 55.6 (Me), 29.9 (Me), 14.1 (Me); HRMS [ES^+] found MH^+, 262.1069. $C_{14}H_{16}NO_4$ requires 262.1074.

4.3.4. Ethyl 1-benzyl-6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate (**11d**)

Ethyl 4-(benzyl(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10d** (241 mg, 501 μmol), copper(II) 2-ethylhexanoate (175 mg, 100 mol%) and DIPEA (209 μL, 1.20 mmol) in mesitylene (15 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (7:3 Hexane/EtOAc) afforded the title compound **11d** (117 mg, 344 μmol, 69%) as an orange solid; R_f: 0.18 (7:3 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 1723 (C═O), 1655 (C═O), 1617, 1590, 1563, 1496, 1454, 1431; δ_H (400 MHz, $CDCl_3$): 7.91 (1H, d, $J = 2.8$ Hz), 7.34 (1H, s), 7.30–7.13 (5H, m), 7.04 (1H, dd, $J = 9.3$, 2.9 Hz), 5.54 (2H, br s), 4.44 (2H, q, $J = 7.1$ Hz), 3.80 (3H, s), 1.42 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.3 (C), 161.0 (C), 154.9 (C), 138.2 (C), 135.8

(C), 134.2 (C), 128.7 (CH), 127.3 (CH), 126.4 (CH), 124.8 (CH), 119.9 (CH), 118.5 (C), 116.5 (CH), 108.8 (CH), 61.9 (CH_2), 55.5 (Me), 46.2 (CH_2), 14.1 (Me); HRMS [ES^+] found MNa^+, 360.1211. $C_{20}H_{19}NNaO_4$ requires 360.1206.

4.3.5. Ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate (**11e**)

Ethyl 4-((4-methoxybenzyl)(4-methoxyphenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10e** (491 mg, 960 μmol), copper(II) 2-ethylhexanoate (336 mg, 100 mol%) and DIPEA (400 μL, 2.30 mmol) in mesitylene (27 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (7:3 Hexane/EtOAc) afforded the title compound **11e** (232 mg, 631 μmol, 66%) as an orange solid; R_f: 0.19 (7:3 Hexane/EtOAc); m.p. 84–86 °C; ν_{max}/cm^{-1} (neat): 2937, 1725 (C=O), 1656 (C=O), 1513, 1431, 1247; δ_H (400 MHz, $CDCl_3$): 7.91 (1H, d, $J = 2.9$ Hz), 7.33 (1H, s), 7.25 (1H, d, $J = 9.5$ Hz), 7.11 (2H, d, $J = 8.7$ Hz), 7.07 (1H, dd, $J = 9.5$, 2.9 Hz), 6.80 (2H, d, $J = 8.7$ Hz), 5.48 (2H, s), 4.44 (2H, q, $J = 7.1$ Hz), 3.82 (3H, s), 3.73 (3H, s), 1.43 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.4 (C), 161.0 (C), 158.8 (C), 154.9 (C), 138.2 (C), 134.3 (C), 127.9 (C), 127.8 (CH), 125.0 (CH), 120.0 (CH), 118.6 (C), 116.6 (CH), 114.2 (CH), 108.8 (CH), 62.0 (CH_2), 55.6 (Me), 55.2 (Me), 45.7 (CH_2), 14.1 (Me); HRMS [ES^+] found MNa^+, 390.1301. $C_{21}H_{21}NNaO_5$ requires 390.1312.

4.3.6. Ethyl 1-methyl-6-nitro-2-oxo-1,2-dihydroquinoline-4-carboxylate (**11f**)

Ethyl 4-(methyl(4-nitrophenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10f** (141 mg, 336 μmol), copper(II) 2-ethylhexanoate (117 mg, 100 mol%) and DIPEA (140 μL, 336 μmol) in mesitylene (10 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **11f** (21 mg, 76 μmol, 23%) as a yellow solid; R_f: 0.26 (1:1 Hexane/EtOAc); m.p. 147–151 °C; ν_{max}/cm^{-1} (neat): 1725 (C=O), 1671 (C=O), 1607, 1524, 1342, 1301; δ_H (400 MHz, $CDCl_3$): 9.44 (1H, d, $J = 2.6$ Hz), 8.44 (1H, dd, $J = 9.4$, 2.6 Hz), 7.50 (1H, d, $J = 9.4$ Hz), 7.40 (1H, s), 4.49 (2H, q, $J = 7.1$ Hz), 3.80 (3H, s), 1.46 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 171.3 (C), 164.2 (C), 161.2 (C), 144.1 (C), 137.8 (C), 126.7 (CH), 125.6 (CH), 123.8 (CH), 117.2 (C), 115.1 (CH), 62.6 (CH_2), 30.4 (Me), 14.1 (Me); HRMS [ES^+] found MH^+, 277.0820. $C_{13}H_{13}N_2O_5$ requires 277.0819.

Also isolated was ethyl (*E*)-4-(methyl(4-nitrophenyl)amino)-4-oxobut-2-enoate **11f′** (32 mg, 115 μmol, 34%) as a brown solid; R_f: 0.37 (1:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2983, 1720 (C=O), 1665 (C=O), 1592, 1521, 1496, 1341, 1301, 1177; δ_H (400 MHz, $CDCl_3$): 8.30 (2H, d, $J = 8.3$ Hz), 7.35 (2H, d, $J = 8.3$ Hz), 6.86 (2H, s), 4.16 (2H, q, $J = 7.3$ Hz), 3.44 (3H, s), 1.25 (3H, t, $J = 7.3$ Hz); δ_C (100 MHz, $CDCl_3$): 165.2 (C), 163.8 (C), 148.2 (C), 146.2 (C), 133.3 (CH), 132.4 (CH), 127.2 (CH), 125.2 (CH), 61.2 (CH_2), 37.5 (Me), 14.0 (Me); HRMS [ES^+] found MH^+, 279.0971. $C_{13}H_{15}N_2O_5$ requires 279.0975.

4.3.7. Ethyl 5-oxo-2,3-dihydro-1H,5H-pyrido[3,2,1-ij]quinoline-7-carboxylate (**11g**)

Ethyl 2-(benzenesulfonyl)-4-oxo-4-(1,2,3,4-tetrahydroquinolin-1-yl)butanoate **10g** (230 mg, 574 μmol), copper(II) 2-ethylhexanoate (201 mg, 100 mol%) and DIPEA (240 μL, 1.38 mmol) in mesitylene (12 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (1:1 Hexane/EtOAc) afforded the title compound **11g** (80 mg, 311 μmol, 54%) as an orange solid; R_f: 0.24 (1:1 Hexane/EtOAc); m.p. 134–136 °C; ν_{max}/cm^{-1} (neat): 2937, 1718 (C=O), 1641 (C=O), 1582, 1431, 1232, 1066; δ_H (400 MHz, $CDCl_3$): 8.13 (1H, d, $J = 8.0$ Hz), 7.32 (1H, d, $J = 7.7$ Hz), 7.16 (1H, t, $J = 7.7$ Hz), 7.15 (1H, s), 4.42 (2H, q, $J = 7.1$ Hz), 4.19 (2H, t, $J = 6.0$ Hz), 2.98 (2H, t, $J = 6.0$ Hz), 2.09 (2H, quint, $J = 6.0$ Hz), 1.41 (3H, t, $J = 7.1$ Hz); δ_C (100 MHz, $CDCl_3$): 165.5 (C), 160.9 (C), 138.9 (C), 137.0 (C), 130.5 (CH), 125.0 (CH), 124.9 (CH), 123.4 (CH), 122.2 (C), 117.3 (C), 61.9 (CH_2), 42.7 (CH_2), 27.9 (CH_2), 20.4 (CH_2), 14.1 (Me); HRMS [ES^+] found MH^+, 258.1125. $C_{15}H_{16}NO_3$ requires 258.1125.

4.3.8. Ethyl 3-oxo-5,6,7,8-tetrahydro-3H-azepino[3,2,1-ij]quinoline-1-carboxylate (**11h**)

Ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro−1H-benzo[*b*]azepin-1-yl)butanoate ethyl 4-oxo-2-(phenylsulfonyl)-4-(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)butanoate **10h** (72 mg, 173 μmol), copper(II) 2-ethylhexanoate (60.0 mg, 100 mol%) and DIPEA (72.3 μL, 416 μmol) in mesitylene (5.5 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 Hexane/EtOAc) afforded the title compound **10h** (36 mg, 311 μmol, 77%) as an orange oil; R_f: 0.22 (13:7 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2937, 1728 (C=O), 1655 (C=O), 1587, 1448, 1243; δ_H (400 MHz, $CDCl_3$): 8.01 (1H, d, $J = 7.6$ Hz), 7.30 (1H, d, $J = 7.6$ Hz), 7.12 (1H, t, $J = 7.6$ Hz), 7.07 (1H, s), 4.46–4.38 (4H, m), 3.17–3.11 (2H, m), 2.14–2.05 (2H, m), 2.02–1.93 (2H, m), 1.39 (3H, t, $J = 7.3$ Hz); δ_C (100 MHz, $CDCl_3$): 165.7 (C), 162.4 (C), 141.7 (C), 139.8 (C), 133.7 (CH), 130.7 (C), 124.7 (CH), 123.4 (CH), 122.7 (CH), 118.7 (C), 61.9 (CH_2), 44.8 (CH_2), 33.2 (CH_2), 25.4 (CH_2), 23.8 (CH_2), 14.1 (Me); HRMS [ES^+] found MNa^+, 294.1093. $C_{16}H_{17}NNaO_3$ requires 294.1101.

4.3.9. Ethyl 1,3-dimethyl-2-oxo-1,2-dihydroquinoline-4-carboxylate (**11i**)

Ethyl 3-methyl-4-(methyl(phenyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **10i** (167 mg, 429 μmol), copper(II) 2-ethylhexanoate (150 mg, 100 mol%) and DIPEA (179 μL, 1.03 mmol) in mesitylene (12 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (5:2 Hexane/EtOAc) afforded the title compound **11i** (90 mg, 367 μmol, 86%) as an orange solid; R_f: 0.34 (1:1 Hexane/EtOAc); m.p. 68–70 °C; ν_{max}/cm^{-1} (neat): 2982, 1730 (C=O), 1646 (C=O), 1600, 1590, 1464, 1226; δ_H (400 MHz, $CDCl_3$): 7.52 (1H, t, $J = 8.5$ Hz), 7.42 (1H, d, $J = 8.5$ Hz), 7.34 (1H, d, $J = 8.5$ Hz), 7.22 (1H, t, $J = 8.5$ Hz), 4.50 (2H, q, $J = 7.2$ Hz), 3.74 (3H, s), 2.23 (3H, s), 1.43 (3H, t, $J = 7.2$ Hz); δ_C (100 MHz, $CDCl_3$): 167.0 (C), 162.0 (C), 139.0 (C), 138.7 (C), 130.0 (CH), 126.9 (C), 125.5 (CH), 122.4 (CH), 117.1 (C), 114.4 (CH), 61.9 (CH_2), 30.0 (Me), 14.9 (Me), 14.2 (Me); HRMS [ES^+] found MNa^+, 368.0943. $C_{14}H_{15}NNaO_3$ requires 268.0944.

4.3.10. 4-Benzoyl-1-methylquinolin-2(1H)-one [30] (**11j**)

N-Methyl-4-oxo-*N*,4-diphenyl-3-(phenylsulfonyl)butanamide **10j** (100 mg, 245 μmol), copper(II) 2-ethylhexanoate (85.9 mg, 100 mol%) and DIPEA (102 μL, 589 μmol) in mesitylene (7 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 Hexane/EtOAc) afforded the title compound **11j** (49 mg, 186 μmol, 76%) as an orange solid; R_f: 0.19 (13:7 Hexane/EtOAc); m.p. 83–85 °C; ν_{max}/cm^{-1} (neat): 1656 (C=O), 1589, 1452, 1250; δ_H (400 MHz, $CDCl_3$): 7.94 (2H, d, $J = 8.0$ Hz), 7.67–7.59 (2H, m), 7.56–7.44 (4H, m), 7.19 (1H, t, $J = 8.0$ Hz), 6.72 (1H, s), 3.79 (3H, s); δ_C (100 MHz, $CDCl_3$): 194.7 (C), 161.2 (C), 147.2 (C), 140.3 (C), 135.7 (C), 134.5 (CH), 131.4 (CH), 130.2 (CH), 128.8 (CH), 127.0 (CH), 122.6 (CH), 120.5 (CH), 118.1 (C), 114.7 (CH), 29.7 (Me); HRMS [ES^+] found MNa^+, 286.0833. $C_{17}H_{13}NNaO_2$ requires 286.0838.

Also isolated was (*E*)-*N*-methyl-4-oxo-*N*,4-diphenylbut-2-enamide [31] **11j′** (14 mg, 52.8 μmol, 22%) as an orange solid; R_f: 0.26 (13:7 Hexane/EtOAc); m.p. 65–68 °C; ν_{max}/cm^{-1} (neat): 1644 (C=O), 1594, 1495, 1374, 1306; δ_H (400 MHz, $CDCl_3$): 7.98 (1H, d, $J = 15.3$ Hz), 7.98 (2H, d, $J = 7.6$ Hz), 7.59 (1H, t, 7.6 Hz), 7.48 (2H, t,

$J = 7.6$ Hz), 7.45 (2H, t, $J = 7.6$ Hz), 7.37 (1H, t, $J = 7.6$ Hz), 7.20 (2H, d, $J = 7.6$ Hz), 6.93 (1H, d, $J = 15.3$ Hz), 3.44 (3H, s); δ_C (100 MHz, $CDCl_3$): 189.8 (C), 164.7 (C), 142.8 (C), 137.0 (C), 133.8 (CH), 133.7 (CH), 133.4 (CH), 130.0 (C), 128.91 (C), 128.88 (C), 128.3 (CH), 127.2 (CH), 38.0 (CH); HRMS [ES^+] found MNa^+, 288.0989. $C_{17}H_{15}NNaO_2$ requires 288.0995.

4.3.11. 1-Methyl-2-oxo-1,2-dihydroquinoline-4-carbonitrile [32] (**11k**)

3-Cyano-*N*-methyl-*N*-phenyl-3-(phenylsulfonyl)propanamide **10k** (76 mg, 231 μmol), copper(II) 2-ethylhexanoate (81.0 mg, 100 mol%) and DIPEA (96.6 μL, 555 μmol) in mesitylene (7 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound **11k** (24 mg, 130 μmol, 56%) as an orange solid; R_f: 0.22 (3:2 Hexane/EtOAc); m.p. 127–129 °C (Lit [32]. 165–166 °C); ν_{max}/cm^{-1} (neat): 1659 (C=O), 1593, 1457; δ_H (400 MHz, $CDCl_3$): 7.96 (1H, dd, $J = 7.6$, 1.5 Hz), 7.72 (1H, t, $J = 8.4$ Hz), 7.46 (1H, d, $J = 8.4$ Hz), 7.41 (1H, t, $J = 7.6$ Hz), 7.17 (1H, s), 3.76 (3H, s); δ_C (100 MHz, $CDCl_3$): 159.8 (C), 140.0 (C), 132.5 (CH), 128.8 (CH), 126.8 (CH), 123.3 (CH), 122.5 (C), 117.6 (C), 114.8 (C), 114.3 (C-5), 29.8 (C-7); HRMS [ES^+] found MNa^+, 207.0531. $C_{11}H_8N_2NaO$ requires 207.0529.

4.3.12. Ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate [2] (**1b**)

Ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate **11e** (100 mg, 272 μmol) in TFA (2 mL) was stirred at 85 °C for 18 h. The reaction mixture was added dropwise to cold saturated $NaHCO_3$ solution (20 mL) then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and concentrated *in vacuo*. Purification by flash column chromatography (3:1 Hexane/EtOAc) afforded the title compound **1b** (55 mg, 0.22 mmol, 82%) as a yellow solid; R_f: 0.27 (1:3 Hexane/EtOAc); m.p. 140–143 °C (Lit [2]. 183–186 °C); ν_{max}/cm^{-1} (neat): 2991, 1726 (C=O), 1681 (C=O), 1623, 1503, 1448, 1234; δ_H (400 MHz, DMSO-d_6): 12.04 (1H, s), 7.60 (1H, d, $J = 2.6$ Hz), 7.31 (1H, d, $J = 8.9$ Hz), 7.24 (1H, dd, $J = 8.9$, 2.6 Hz), 6.92 (1H, s), 4.38 (2H, q, $J = 6.9$ Hz), 3.33 (3H, s), 1.35 (3H, t, $J = 6.9$ Hz); δ_C (100 MHz, DMSO-d_6): 165.6 (C), 160.9 (C), 154.9 (C), 139.8 (C), 134.6 (C), 125.4 (CH), 120.8 (CH), 117.8 (CH), 116.6 (C), 108.0 (CH), 62.4 (CH_2), 55.9 (Me), 14.5 (Me); HRMS [ES^+] found MNa^+, 270.0743. $C_{13}H_{13}NNaO_4$ requires 270.0737.

4.3.13. Ethyl 6-hydroxy-2-oxo-1,2-dihydroquinoline-4-carboxylate [2] (**1a**)

From **1b**: To a stirred solution of ethyl 6-methoxy-2-oxo-1,2-dihydroquinoline-4-carboxylate **1b** (28 mg, 113 μmol) in CH_2Cl_2 (1.13 mL) at −78 °C was added BBr_3 (1 M solution in CH_2Cl_2, 340 μL, 340 μmol). The solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **1a** (25 mg, 107 μmol, 95%) as a colourless solid; R_f: 0.22 (19:1 Hexane/EtOAc); m.p. > 200 °C; ν_{max}/cm^{-1} (neat): 3289 (O–H), 1712 (C=O), 1654 (C=O), 1615, 1423, 1254; δ_H (400 MHz, DMSO-d_6): 11.93 (1H, s), 9.54 (1H, s), 7.46 (1H, d, $J = 2.6$ Hz), 7.22 (1H, d, $J = 8.9$ Hz), 7.06 (1H, dd, $J = 8.9$, 2.6 Hz), 6.85 (1H, s), 4.36 (2H, q, $J = 6.9$ Hz), 1.34 (3H, t, $J = 6.9$ Hz); δ_C (100 MHz, DMSO-d_6): 166.1 (C), 161.1 (C), 153.4 (C), 140.2 (C), 133.7 (C), 125.0 (CH), 121.6 (CH), 117.8 (CH), 117.2 (C), 110.4 (CH), 62.7 (CH_2), 14.8 (Me); HRMS [ES^+] found MNa^+, 256.0577. $C_{12}H_{11}NNaO_4$ requires 256.0580.

From **11e**: To a stirred solution of ethyl 6-methoxy-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-4-carboxylate **11e** (37 mg, 101 μmol) in CH_2Cl_2 (1.01 mL) at −78 °C was added BBr_3 (1 M solution in CH_2Cl_2, 605 μL, 605 μmol). The solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound **1a** (15 mg, 64.4 μmol, 64%) as a colourless solid.

4.4. 2-Bromo-N-(2,7-dimethylbenzofuran-4-yl)-N-methylacetamide

N,2,7-Trimethylbenzofuran-4-amine (1.13 g, 6.42 mmol), triethylamine (971 μL, 6.98 mmol), CH_2Cl_2 (7 mL) and bromoacetyl bromide (607 μL, 6.98 mmol) in CH_2Cl_2 (10 mL) were subjected to general procedure A. Purification by flash column chromatography (3:2 Hexane/EtOAc) afforded the title compound (1.670 g, 5.64 mmol, 88%) as a colourless solid; R_f: 0.21 (3:2 Hexane/EtOAc); m.p. 64–66 °C; ν_{max}/cm^{-1} (neat): 3107, 2917, 1672 (C=O), 1505, 1371, 1186; δ_H (400 MHz, $CDCl_3$): 7.02 (1H, d, $J = 7.8$ Hz), 6.98 (1H, d, $J = 7.8$ Hz), 6.31 (1H, s), 3.66–3.64 (2H, m), 3.31 (3H, s), 2.51 (3H, s), 2,48 (3H, s); δ_C (100 MHz, $CDCl_3$): 166.9 (C), 156.8 (C), 154.3 (C), 131.9 (C), 125.9 (C), 124.5 (CH), 121.7 (C), 121.1 (CH), 100.1 (CH), 37.3 (Me), 27.1 (CH_2), 14.8 (Me), 14.1 (Me); HRMS [ES^+] found MH^+ 296.0281. $C_{13}H_{15}^{79}BrNO_2$ requires 296.0281.

4.5. Ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate (**12**)

Ethyl 2-(phenylsulfonyl)acetate (578 mg, 2.54 mmol) and KO*t*Bu (303 mg, 2.70 mmol) in THF (20 mL) and 2-bromo-*N*-(2,7-dimethylbenzofuran-4-yl)-*N*-methylacetamide (500 mg, 1.69 mmol) in THF (7.5 mL) were subjected to general procedure B for 18 h. Purification by flash column chromatography (7:3 Hexane/EtOAc) afforded the title compound **12** (678 mg, 1.53 μmol, 90%) as a colourless gum; R_f: 0.35 (1:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2925, 1738 (C=O), 1658 (C=O), 1324 (S=O), 1188, 1148 (S=O); δ_H (400 MHz, $CDCl_3$): 7.72 (2H, d, $J = 7.8$ Hz), 7.62 (1H, t, $J = 7.8$ Hz), 7.47 (2H, t, $J = 7.8$ Hz), 7.01 (1H, d, $J = 7.8$ Hz), 6.96–6.89 (1H, m), 6.27 (1H, s), 4.54–4.47 (1H, m), 4.12–3.96 (2H, m), 3.23 (3H, s), 3.10–3.61 (2H, m), 2.52 (3H, s), 2.46 (3H, s), 1.04 (3H, t, $J = 7.15$ Hz); δ_C (100 MHz, $CDCl_3$): 168.7 (C), 165.2 (C), 156.6 (C), 154.3 (C), 137.6 (C), 134.0 (CH), 131.6 (C), 128.8 (CH), 128.7 (CH), 126.0 (C), 124.7 (CH), 121.4 (C), 121.2 (CH), 100.0 (CH), 66.7 (CH), 62.1 (CH_2), 36.7 (Me), 30.6 (CH_2), 14.8 (Me), 14.1 (Me), 13.6 (Me); HRMS [ES^+] found MH^+, 444.1479. $C_{23}H_{26}NO_6S$ requires 444.1475.

4.6. Ethyl 1,6,8-trimethyl-2-oxo-1,2dihydrofuro[2,3-h]quinoline-4-carboxylate (**13**)

Ethyl 4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxo-2-(phenylsulfonyl)butanoate **12** (270 mg, 609 μmol), copper(II) 2-ethylhexanoate (416 mg, 200 mol%) and DIPEA (254 μL, 1.46 mmol μmol) in mesitylene (18 mL) were subjected to standard procedure C at 165 °C for 18 h. Purification by flash column chromatography (13:7 Hexane/EtOAc) afforded the title compound **13** (52 mg, 174 μmol, 29%) as an orange oil; R_f: 0.22 (1:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2924, 1726 (C=O), 1652 (C=O), 1590, 1236; δ_H (400 MHz, $CDCl_3$): 7.86 (1H, s), 7.06 (1H, s), 6.91 (1H, s), 4.46 (2H, q, $J = 7.3$ Hz), 4.03 (3H, s), 2.53 (6H, s), 1.44 (3H, t, $J = 7.3$ Hz); δ_C (100 MHz, $CDCl_3$): 166.4 (C), 162.0 (C), 155.9 (C), 154.6 (C), 140.4 (C), 134.4 (C), 122.5 (CH), 120.4 (CH), 117.8 (C), 113.0 (C), 104.5 (CH), 62.2 (CH_2) 33.5 (Me), 15.2 (Me), 14.4 (Me), 14.1 (Me); HRMS [ES^+] found MNa^+, 322.1043. $C_{17}H_{17}NNaO_4$ requires 322.1050.

Also isolated was ethyl (*E*)-4-((2,7-dimethylbenzofuran-4-yl)(methyl)amino)-4-oxobut-2-enoate **13′** (66 mg, 285 μmol, 36%) as an orange oil; R_f: 0.61 (1:1 Hexane/EtOAc); ν_{max}/cm^{-1} (neat): 2927, 1720 (C=O), 1661 (C=O), 1508, 1369, 1293; δ_H (400 MHz, $CDCl_3$): 7.00 (1H, d, $J = 7.6$ Hz), 6.86 (1H, d, $J = 7.6$ Hz), 6.86 (1H, d, $J = 15.3$ Hz), 7.68 (1H, d, $J = 15.3$ Hz), 6.24 (1H, s), 4.12 (2H, q, $J = 7.3$ Hz), 3.38 (3H, s), 2.51 (3H, s), 2.46 (3H, s), 1.21 (3H, t, $J = 7.3$ Hz); δ_C (100 MHz, $CDCl_3$): 165.6 (C), 164.3 (C), 156.6 (C), 154.2 (C), 134.2 (CH) 131.5 (C), 130.8 (CH), 125.9 (C), 124.5 (CH), 121.4 (C), 121.3 (CH), 100.1 (CH), 60.8 (CH_2) 36.9 (Me), 14.8 (Me), 14.1 (Me), 13.9 (Me); HRMS [ES^+] found MNa^+, 324.1206. $C_{17}H_{19}NNaO_4$ requires 324.1212.

*4.7. 4-Hydroxymethyl-1,6,8-trimethylfuro[2,3-h]quinolin-2(1H)-one (HOFQ, **3**) [10]*

To a solution of ethyl 1,6,8-trimethyl-2-oxo-1,2dihydrofuro[2,3-h]quinoline-4-carboxylate 13 (40 mg, 0.13 mmol) in dry THF (5 mL) at 0 °C under Ar atmosphere, was added in one portion, $LiAlH(OtBu)_3$ (70 mg, 0.27 mmol). The reaction was warmed slowly to room temperature and stirred for 36 h. A solution of 10% aqueous HCl (6 mL) was then added and the mixture stirred at this temperature for 1 h before the THF was removed *in vacuo*. The solid was filtered and washed with cold MeOH afford the title compound (20 mg, 77.7 μmol, 60%) as a colourless solid. δ_H (400 MHz, DMSO-d_6): 7.40 (1H, s), 7.24 (1H, s), 6.64 (1H, s), 5.50 (1H, t, $J = 5.6$ Hz), 4.78 (2H, dd, $J = 5.6$, 1.1 Hz), 3.90 (3H, s), 2.52 (3H, br s), 2.49 (3H, br s); HRMS [ES^+] found 258.1114. $C_{15}H_{16}NO_3$ requires 258.1125. The data obtained was consistent with those previously reported in the literature [10].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130711.

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