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# Convergent synthesis of dihydroquinolones from *o*-aminoarylboronates

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ABSTRACT

An efficient and convergent one-step synthesis of substituted dihydroquinolin-2-ones from α,β-unsaturated esters and aminoaryl pinacolboronates under rhodium catalysis is reported. The reaction is easily applicable in parallel synthesis format and provides convenient access to this pharmaceutically-relevant motif.



## 1. Introduction

The dihydroquinolin-2-one (dihydroquinolone) structure is found in a large number of interesting natural and man-made compounds. Simple 5-, 6- and 7-alkoxydihydroquinolones respectively form the core of the commercial drugs carteolol **1** (a β-adrenergic blocker used in the treatment of glaucoma),[1] cilostazol **2** (a PDE3 phosphodiesterase inhibitor used in the treatment of peripheral vascular disease)[2] and aripiprazole **3** (an anti-psychotic used in the treatment of schizophrenia) (Fig. 1).[3] The structure is also embedded within alkaloids of the *Melodinus* family, exemplified by meloscine **4**,[4] as well as the structurally unique insecticidal microbial metabolites yaequinolone J1 (**5**) and J2.[5]

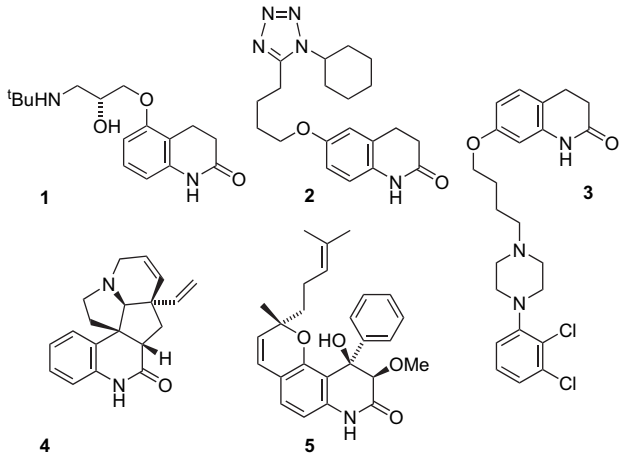


**Figure 1.** Pharmaceuticals and natural products containing the dihydroquinolin-2-one structure.

Methods for the synthesis of dihydroquinolin-2-ones are therefore of significant interest. Alongside classical Friedlander/Friedel–Crafts cyclisation approaches,[6] more recent methods include oxidative cyclisation of 2-(3-hydroxypropyl)anilines,[7] radical reactions (6-*exo* cyclisations of aryl radicals[8] and cyclisation by addition of radicals to the aromatic ring[9]), 6π-photocyclisations of acrylanilides,[10] and palladium-catalysed cyclocarbonylation of 2-alkenylanilines.[11] We recently reported[12] a novel, regiospecific rhodium-catalysed synthesis of quinolines from enones and *ortho*-aminophenylboronates.[13] In this process, the rhodium catalyst mediates a 1,4-addition of the boronic acid to the enone, with the resulting keto-aniline undergoing self-condensation to generate a labile 3,4-dihydroquinoline which is aerobically oxidised to the quinoline on addition of palladium on charcoal. The reaction offers a mild and regiocomplentary route from enones to substituted quinolines compared with the classical Skraup–Doebner–von Miller reaction,[14] wherein the product is one of formal aza-Michael addition of an aniline nucleophile to the enone, followed by intramolecular Friedel–Crafts alkylation. We therefore considered whether we might be able to exploit similar Michael addition/condensation chemistry to directly access dihydroquinolones by addition of the aminoarylboronates to α,β-unsaturated esters. We report herein the successful attainment of this goal.

## 2. Results and discussion

Our initial work focused on the condensation of commercially available 2-aminophenylboronic acid **6** with α,β-unsaturated esters **7** of varying substitution patterns and electronic properties. Under the initially chosen conditions (3 mol % $[Rh(cod)Cl]_2$ and 12 mol % KOH in aqueous dioxane at reflux), we were pleased to find that the

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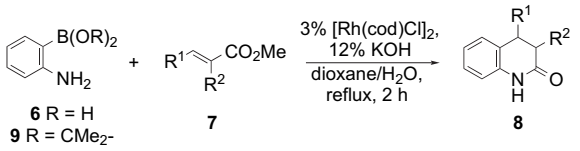
**Table 1**
Comparison of boronic acids and pinacolboronate esters in addition to α,β-unsaturated esters




| Entry | Boronate | Enoate | $R^1$ | $R^2$ | Product | Yield, % |
|---|---|---|---|---|---|---|
| 1 | **6** | **7a** | H | H | **8a** | 86 |
| 2 | **6** | **7b** | H | Me | **8b** | 56 |
| 3 | **6** | **7c** | Me | H | **8c** | 47 |
| 4 | **6** | **7d** | Me | Me | **8d** | 0 |
| 5 | **6** | **7e** | Ph | H | **8e** | 0 |
| 6 | **6** | **7f** | $CO_2Me$ | H | **8f** | 0 |
| 7 | **9** | **7a** | H | H | **8a** | 69 |
| 8 | **9** | **7b** | H | Me | **8b** | 45 |
| 9 | **9** | **7c** | Me | H | **8c** | 48 |
| 10 | **9** | **7d** | Me | Me | **8d** | 0 |
| 11 | **9** | **7e** | Ph | H | **8e** | 46 |
| 12 | **9** | **7g** | 4-$MeOC_6H_4$ | H | **8g** | 32 |
| 13 | **9** | **7f** | $CO_2Me$ | H | **8f** | 7 |
| 14[a] | **9** | **7f** | $CO_2Me$ | H | **8f** | 40 (10)[b] |
| 15 | **9** | **7h** | H | NHAc | **8h** | 71 |

[a] Using 10% $[Rh(cod)Cl]_2$, 200% KOH.
[b] Yield of methyl (2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate by-product.

condensation proceeded smoothly with methyl acrylate **7a** to generate the desired dihydroquinolone **8a** in good yield (Table 1, entry 1). The presumed intermediate 3-(2-aminophenyl)propionate ester was not observed, suggesting that cyclisation to the lactam proceeds rapidly following the initial 1,4-addition. The reaction was also successful using both methyl crotonate and methyl methacrylate; dihydroquinolones **8b** and **8c** were formed in moderate yield (entries 2 and 3), demonstrating that substituents at the α- and β-positions, although detrimental to the reaction, were tolerated. Attempted reactions with the more hindered/less electrophilic methyl tiglate **7d**, the conjugated methyl cinnamate **7e**, and the electron-deficient dimethyl fumarate **7f**, however, all met with failure (entries 4–6). In all cases, the product of protodeboronation of the boronic acid (aniline) was observed as the sole product of the reaction. We therefore examined the use of commercial 2-aminophenyl pinacolboronate **9** in place of **6**. In our previous work,[12] **9** was shown to be a competent nucleophile in addition to enones, though less reactive than **6** (higher catalyst loadings were required to effect addition on comparable timescales). However, the slower rate of conjugate addition need not be detrimental to the overall reaction efficiency provided that protodeboronation is also slowed significantly with this reagent. In the event, we were pleased to find that **9** proved to be an effective nucleophilic aryl donor across a much wider range of electrophiles. Reaction with methyl acrylate gave a slightly lower yield of **8a**, but the yields for addition/cyclisation with crotonate and methacrylate to give **8b** and **8c** were comparable to those with boronic acid **6** (entries 7–9). Methyl tiglate, however, remained unreactive (entry 10). The previously unsuccessful phenyl cinnamate gave a promising 48% yield of **8e** and the less electrophilic *p*-methoxycinnamate also gave the desired dihydroquinolone **8g** (entries 11 and 12). Dimethyl fumarate was found to still be poorly reactive, giving just a 7% yield of the desired target **8f**; we found however that this could be increased to 40% if the catalyst loading was increased to 10% $[Rh(cod)Cl]_2$ (entries 13 and 14). The latter reaction also gave a 10% yield of methyl (2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate, the product of ring closure to the proximal ester of the intermediate 2-(2-aminophenyl)succinate derivative. Finally, the relatively electron-rich dehydroalanine methyl ester **7h** was converted to the 2-acetamidodihydroquinolinone **8h** in a pleasing 71% yield.

**Table 2**
Optimisation of the formation of 4-phenyldihydroquinolin-2-one **8e**[a]

| Entry | Base | Solvent | Yield, % |
|---|---|---|---|
| 1 | 12% KOH | Dioxane/$H_2O$ | 46 |
| 2 | 200% KOH | Dioxane/$H_2O$ | 65 |
| 3 | 400% KOH | Dioxane/$H_2O$ | 64 |
| 4 | 12% KOH[b] | Dioxane/$H_2O$ | 43 |
| 5 | 200% KOH[b] | Dioxane/$H_2O$ | 67 |
| 6 | 400% KOH[b] | Dioxane/$H_2O$ | 66 |
| 7 | 400% LiOH | Dioxane/$H_2O$ | 47 |
| 8 | 200% $Ba(OH)_2$ | Dioxane/$H_2O$ | 64 |
| 9 | 100% $Et_3N$ | Dioxane/$H_2O$ | 0 |
| 10 | 200% $K_2CO_3$ | THF/$^i$PrOH | 0 |
| 11[c] | 200% KOH | Dioxane/$H_2O$ | 27 |
| 12[d] | 200% KOH | Dioxane/$H_2O$ | 32 |
| 13 | 200% KOH | Dioxane/$^i$PrOH | 57 |
| 14 | 200% KOH | 2-Butanol | 39 |
| 15 | 200% KOH | Toluene/$H_2O$ | 18 |

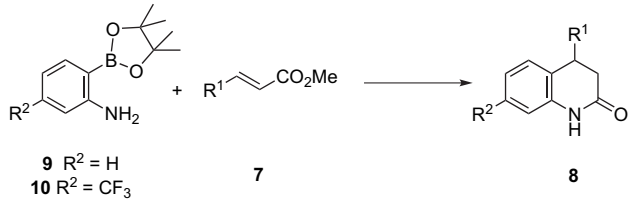
[a] Basic reaction conditions: 1 equiv of methyl cinnamate **7e**, 2 equiv of 2-aminophenyl pinacolboronate **9**, 3% $[Rh(cod)Cl]_2$, indicated base, solvent, reflux, 2 h.
[b] Reaction also contains 200% KF.
[c] Reaction carried out at 70 °C.
[d] Reaction on *iso*-propyl cinnamate.

With this preliminary substrate scoping exercise complete, we next sought to identify optimised conditions for the reaction using methyl cinnamate **7e** as the model substrate. Specifically, we focused on the choice of reaction solvent and the nature and stoichiometry of the base additive, and the results are shown in Table 2. We had been employing a 12 mol % loading of potassium hydroxide to ensure formation of the active catalyst [Rh(cod)OH],[15] but wished to investigate the effect of adding stoichiometric basic or nucleophilic additives for boronate activation. Increasing the quantity of hydroxide to 200 mol % (i.e., 1 equiv to the boronate reagent **9**) lead to a significant increase in yield to 65% (entries 1 and 2); increasing this to 400 mol % gave no further improvement (entry 3). Fluoride is also commonly used to activate boronates towards transmetalation, including in conjugate addition reactions,[16] but the addition of potassium fluoride had no beneficial effect on either reaction (entries 4–6). Substitution of other metal hydroxide salts for KOH was not successful (entries 7 and 8). In some of the reactions using the higher base loadings, we were able to observe cinnamic acid as a by-product in the NMR spectrum of the crude reaction mixture. While this clearly arises by hydrolysis of the ester, we were concerned as to whether this event occurred competitively with Michael addition/cyclisation, or was simply occurring slowly once all of the boronate **9** had been consumed (either by the desired Michael addition or protodeboronation)—in the former case, the species liberated in the reaction would be the potassium cinnamate salt, which would likely be too poorly electrophilic to act as a competent Michael acceptor and hence would compromise the overall reaction yield. In an attempt to probe this, we investigated the use of weaker inorganic or organic bases, but these gave no reaction (entries 9 and 10). Decreasing the reaction temperature from reflux to 70 °C gave a lower yield of addition (entry 11), while the use of the bulkier *iso*-propyl cinnamate ester also gave a poor 32% yield of **8e** (entry 12). In this latter case, no cinnamic acid was observable in the NMR spectrum of the crude reaction mixture, with only unreacted *iso*-propyl cinnamate being present. This suggests that the incomplete conversion of the enoates to dihydroquinolin-2-ones is due to the competition between protodeboronation and Michael addition of the boronate, rather than hydrolytic consumption of the electrophile itself. Finally, the use of alternative solvent systems was investigated, though no improvements on the aqueous dioxane regime were found (entries 13–15).

With the optimised reaction conditions (200 mol % KOH in aqueous dioxane) in hand, we next turned our attention to the synthesis of a range of substituted dihydroquinolin-2-ones in parallel. Using a Radleys GreenHouse parallel reactor, we treated pinacolboronate **9**

with methyl acrylate and eleven other β-substituted α,β-unsaturated esters under the standard reaction conditions. To probe the influence of substitution in the ring of the boronate nucleophile, we also prepared the 4-trifluoromethyl-2-aminophenyl pinacolboronate **10**[12] by palladium-catalysed cross-coupling of the corresponding aryl bromide with pinacolborane using the method of Baudoin,[17] and investigated its reaction with eight representative Michael acceptors using the GreenHouse. The aim of the series was to establish the generality of the protocol and no attempt was made to optimise individual reactions. The results are summarised in Table 3.

**Table 3**
Synthesis of diverse 4-substituted dihydroquinolin-2-ones[a]




**9** $R^2$ = H
**10** $R^2$ = $CF_3$ **7** **8**

| Entry | Boronate | Enoate | $R^1$ | $R^2$ | Product | Yield, % |
|---|---|---|---|---|---|---|
| 1 | **9** | **7a** | H | H | **8a** | 64 |
| 2 | **9** | **7c** | Me | H | **8c** | 46 |
| 3 | **9** | **7e** | Ph | H | **8e** | 58 |
| 4 | **9** | **7g** | 4-$MeOC_6H_4$ | H | **8g** | 30 |
| 5 | **9** | **7i** | 4-$NO_2C_6H_4$ | H | **8i** | 37 |
| 6 | **9** | **7j** | 4-$BrC_6H_4$ | H | **8j** | 37 |
| 7 | **9** | **7k** | 3-$BrC_6H_4$ | H | **8k** | 34 |
| 8 | **9** | **7l** | 2-$BrC_6H_4$ | H | **8l** | 29 |
| 9 | **9** | **7m** | *N*-Et-Indol-3-yl | H | **8m** | 39 |
| 10 | **9** | **7n** | 3-Quinolinyl | H | **8n** | 39 |
| 11 | **9** | **7o** | 2-Thienyl | H | **8o** | 38 |
| 12 | **9** | **7p** | 2-Pyridyl | H | **8p** | 49 |
| 13 | **10** | **7a** | H | $CF_3$ | **8q** | 50 |
| 14[a] | **10** | **7c** | Me | $CF_3$ | **8r** | 39 |
| 15 | **10** | **7e** | Ph | $CF_3$ | **8s** | 43 |
| 16 | **10** | **7g** | 4-$MeOC_6H_4$ | $CF_3$ | **8t** | 46 |
| 17 | **10** | **7m** | *N*-Et-Indol-3-yl | $CF_3$ | **8u** | 0 |
| 18 | **10** | **7n** | 3-Quinolinyl | $CF_3$ | **8v** | 47 |
| 19 | **10** | **7o** | 2-Thienyl | $CF_3$ | **8w** | 19 |
| 20 | **10** | **7p** | 2-Pyridyl | $CF_3$ | **8x** | 33 |

[a] Reaction conditions: 1 equiv **7**, 2 equiv **9** or **10**, 3% $[Rh(cod)Cl]_2$, 200% KOH, 14:1 dioxane/water, reflux, 6–20 h.

We were pleased to find a 95% success rate for the reactions, with significant quantities of product being formed in all cases except one (the reaction of **10** with methyl *N*-ethylindol-3-yl acrylate **7m**, entry 17). We repeated this latter reaction using a round-bottomed flask and condenser and again observed none of the desired product, confirming that this is a result of poorly matched reactivity rather than an artefact of the experimental set-up. Amongst the successful reactions, the following trends emerged. Firstly, the reaction of methyl cinnamate **7e** provides a benchmark for the reaction against a standard experimental set-up. From this, we see that the experiment in the GreenHouse reactor is slightly lower yielding at 58% (Table 3, entry 3) compared with 65% under standard conditions (Table 2, entry 2) but that the difference is small. Secondly, a wide range of substituents are tolerated on the ester. For both nucleophiles **9** and **10** the unsubstituted Michael acceptor methyl acrylate is most reactive (entries 1 and 13), but both alkyl- and aryl-substituted electrophiles participate successfully. The aryl substituents can be electron-donating (entries 4 and 16), electron-withdrawing (entry 5) or heteroaryl (entries 9–12 and 18–20). Additionally, the rhodium catalyst tolerates the presence of aryl bromide substituents of any regiochemistry (entries 6–8), generating products that could potentially be further functionalised under, for example, palladium catalysis. Finally, with respect to the aminophenyl boronate nucleophile, a longer reaction time was found to be required (20 h versus 6 h) and slightly lower yields were generally observed with the trifluoromethyl-substituted boronate **10** than the parent boronate **9**, likely reflecting the lower nucleophilicity of the reagent bearing the electron-withdrawing group.

In summary, we have developed an efficient and convergent one-step synthesis of substituted dihydroquinolin-2-ones from α,β-unsaturated esters and aminophenyl pinacolboronates under rhodium catalysis. The reaction is easily applicable in parallel synthesis format and provides convenient access to this pharmaceutically-relevant motif.

## 3. Experimental section

### 3.1. General information

All experiments were conducted under an atmosphere of nitrogen unless otherwise stated. Column chromatography was carried out using Fisher Matrix silica gel 60. Aluminium-backed plates, pre-coated with silica gel 60 ($UV_{254}$), were used for thin layer chromatography and were visualized by UV and staining either with anisaldehyde, $KMnO_4$, vanillin or phosphomolybdate.

$^1H$ and $^{13}C$ NMR spectra have chemical shift values reported in ppm relative to residual protic solvent as internal standards unless otherwise stated.

### 3.2. General experimental procedures

#### 3.2.1. *General procedure A: (Table 1)*

To a suspension of chloro(1,5-cyclooctadiene)rhodium(I) dimer (8 mg, 0.015 mmol, 0.03 equiv), 2-aminophenylboronic acid pinacol boronate (219 mg, 1.00 mmol, 2.00 equiv) and α,β-unsaturated ester (0.50 mmol, 1.00 equiv) in dioxane (1.4 mL, ca. 0.33 M) was added 2.5 M KOH (24 μL, 0.12 mmol, 0.25 equiv). The mixture was heated under reflux conditions for 2 h. The solvent was removed in vacuo. The residue was dissolved in EtOAc and washed with 1 N HCl (twice), satd $NaHCO_3$, brine and then dried ($MgSO_4$). The organic layer was concentrated in vacuo to give the crude product which was purified by flash column chromatography.

#### 3.2.2. *General procedure B: (Table 3)*

Reactions were carried out in a Radleys GreenHouse Parallel Synthesiser. To a suspension of chloro(1,5-cyclooctadiene)rhodium(I) dimer (8 mg, 0.015 mmol, 0.03 equiv), 2-aminoarylboronic acid pinacol ester (**9**: 219 mg or **10**: 287 mg, 1.00 mmol, 2.00 equiv) and α,β-unsaturated ester (0.50 mmol, 1 equiv) in dioxane (1.4 mL, ca. 0.33 M) was added 10 M KOH (0.1 mL, 1 mmol, 2 equiv). The mixture was heated at reflux temperature for 6 h (entries 1–12) or 20 h (entries 13–20). The solvent was removed in vacuo give the crude product which was purified by flash column chromatography.

### 3.3. Compound data

#### 3.3.1. *3,4-Dihydro-1H-quinolin-2-one **8a***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as brown oil. This was purified by column chromatography (3:1 to 3:2 petrol–ethyl acetate) to yield **8a** as pale yellow crystals (45 mg, 64%). $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 9.21 (1H, br s, NH), 7.17 (1H, t, $J$=7.5 Hz, C7-H), 7.15 (1H, d, $J$=7.5 Hz, C5-H), 6.98 (1H, dt, $J$=1.2, 7.5 Hz, C6-H), 6.85 (1H, d, $J$=7.5 Hz, C8-H), 2.97 (2H, t, $J$=7.5 Hz, C3-$H_2$), 2.65 (2H, t, $J$=7.5 Hz, C4-$H_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 172.6, 137.8, 128.3, 127.9, 124.0, 123.5, 116.0, 31.2, 25.6; ESIHRMS for $C_9H_9NONa$ ($[M+Na]^+$): calcd 170.0576; found 170.0570; melting point=160–162 °C ($CH_2Cl_2/Et_2O$), (lit.,[18] mp=163–164 °C; EtOH/$H_2O$); IR (NaCl, thin film): $\nu_{max}$ 3400, 1643, 1492, 1463, 1384, 1340, 1281, 1246 $cm^{-1}$. $^1H$ and $^{13}C$ NMR data are consistent with the reported values.[19]

*3.3.2. 4-Methyl-3,4-dihydro-1H-quinolin-2-one **8b***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:1 to 3:2 petrol/ethyl acetate) to yield **8b** as pale yellow crystals (37 mg, 46%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.55 (1H, br s, NH), 7.19–7.13 (2H, m, C7-H and C5-H), 6.95 (1H, t, $J$=7.5 Hz, C6-H), 6.80 (1H, d, $J$=7.5 Hz, C8-H), 3.00 (1H, dd, $J$=15.0, 6.0 Hz, C4-$H_A$), 2.74–2.62 (2H, m, C4-$H_B$ and C3-H), 1.30 (3H, d, $J$=6.5 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 173.5, 136.2, 127.1, 126.4, 122.6, 121.9, 114.1, 34.0, 32.5, 14.3; ESIHRMS for $C_{10}H_{12}NO$ ($[M+H]^+$) and $C_{10}H_{11}NONa$ ($[M+Na]^+$): calcd 162.0913, 184.0733; found 162.0913, 184.0741; melting point=128–129 °C ($CH_2Cl_2$), (lit.,[20] mp=126–127 °C); IR (NaCl, thin film): $\nu_{max}$ 3434, 2955, 1686, 1593, 1487, 1379, 1339, 1311 cm$^{-1}$. $^1$H and $^{13}$C NMR data are consistent with the reported values.[20]

*3.3.3. 4-Methyl-3,4-dihydro-1H-quinolin-2-one **8c***

Synthesised according to general procedure **A** on a 0.1 mmol scale. The crude product was purified by flash column chromatography to yield **8c** as colourless crystals (8 mg, 48%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.88 (1H, br s, NH), 7.19 (1H, d, $J$=7.8 Hz, C5-H), 7.18 (1H, t, $J$=7.5 Hz, C7-H), 7.02 (1H, t, $J$=7.5 Hz, C6-H), 6.83 (1H, d, $J$=7.8 Hz, C8-H), 3.17–3.10 (1H, m, C4-H), 2.74 (1H, dd, $J$=15.9, 6.0 Hz, C3-$H_A$), 2.43 (1H, dd, $J$=15.9, 7.2 Hz, C3-$H_B$), 1.32 (3H, d, $J$=6.9 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.9, 136.9, 129.2, 127.9, 126.9, 123.7, 116.0, 38.8, 33.1, 20.2; ESIHRMS for $C_{10}H_{12}NO$ ($[M+H]^+$) and $C_{10}H_{11}NONa$ ($[M+Na]^+$): calcd 162.0913, 184.0733; found 162.0917, 184.0739; melting point=98–99 °C ($CH_2Cl_2$), (lit.,[20] mp=92–95 °C); IR (NaCl, thin film): $\nu_{max}$ 3434, 2964, 2923, 1674, 1593, 1487, 1379, 1332, 1312, 1282, 1245, 1219 cm$^{-1}$. $^1$H and $^{13}$C NMR data are consistent with the reported values.[20]

*3.3.4. 4-Phenyl-3,4-dihydro-1H-quinolin-2-one **8e***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:1 petrol/ethyl acetate) to yield **8e** as pale yellow crystals (65 mg, 58%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.48 (1H, br s, NH), 7.37–7.18 (6H, m, phenyl C3-H, phenyl C2-H, C7-H and C6-H), 6.99–6.84 (3H, m, phenyl C4-H, C8-H and C5-H), 4.30 (1H, t, $J$=7.5 Hz, C4-H), 2.96–2.92 (2H, app. dd, $J$=8.5, 6.0 Hz, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.6, 141.5, 137.1, 128.9, 128.4, 128.0, 127.8, 127.2, 126.8, 123.4, 115.6, 42.1, 38.4; ESIHRMS for $C_{15}H_{14}NO$ ($[M+H]^+$): calcd 224.1070; found 224.1061; melting point=181–182 °C ($CH_2Cl_2$/MeOH), (lit.,[20] mp=177–178 °C); IR (NaCl, thin film): $\nu_{max}$ 3429, 1648, 1485, 1376 cm$^{-1}$. $^1$H and $^{13}$C NMR data are consistent with the reported values.[21]

*3.3.5. 2-Oxo-1,2,3,4-tetrahydroquinoline-4-carboxylic acid methyl ester **8f** and (2-oxo-2,3-dihydro-1H-indol-3-yl)-acetic acid methyl ester*

Synthesis according to general procedure **A** but using 10 mol % $[Rh(cod)Cl]_2$ and 200 mol % KOH on a 0.5 mmol scale gave the crude products as a brown oil. Purification by column chromatography (3:2 petrol/ethyl acetate) yielded **8f** as pale yellow crystals (41 mg, 40%) and (2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetic acid methyl ester as a pale yellow oil (12 mg, 10%). Date for **8f**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.08 (1H, br s, NH), 7.21–7.13 (2H, m, C7-H and C5-H), 6.94 (1H, dt, $J$=0.9, 7.5 Hz, C6-H), 6.81 (1H, dd, $J$=7.8, 0.9 Hz, C8-H), 3.88 (1H, dd, $J$=6.8, 4.1 Hz, C4-H), 3.63 (3H, s, COOMe), 2.91 (1H, dd, $J$=16.5, 4.1 Hz, C3-$H_A$), 2.71 (1H, dd, $J$=16.5, 6.8 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.0, 169.7, 136.2, 129.1, 128.9, 123.2, 119.0, 115.1, 51.5, 45.4, 33.1; ESIHRMS for $C_{11}H_{12}NO_3$ ($[M+H]^+$) and $C_{11}H_{11}NO_3Na$ ($[M+H]^+$): calcd 206.0812, 228.0631; found 206.0815, 228.0621; melting point=168–170 °C ($CH_2Cl_2$/MeOH), (lit.,[22] mp=170–171 °C; DMSO); IR (NaCl, thin film): $\nu_{max}$ 3446, 1740, 1661, 1617 cm$^{-1}$. $^1$H and $^{13}$C NMR data consistent with reported values.[22] Data for (2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetic acid methyl ester: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.85 (1H, br s, NH), 7.22 (2H, m, C6-H and C4-H), 7.00 (1H, dt, $J$=1.2, 7.5 Hz, C5-H), 6.90 (1H, d, $J$=7.8 Hz, C7-H), 3.82 (1H, dd, $J$=7.9, 4.5 Hz, C3-H), 3.70 (3H, s, COOMe), 3.09 (1H, dd, $J$=17.1, 4.5 Hz, C-$H_A$), 2.83 (1H, dd, $J$=17.1, 7.9 Hz, C-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 178.1, 170.1, 140.6, 127.7, 127.3, 123.1, 121.5, 108.9, 51.0, 41.3, 33.6; ESIHRMS for $C_{11}H_{12}NO_3$ ($[M+H]^+$) and $C_{11}H_{11}NO_3MNa$ ($[M+Na]^+$): calcd 206.0812, 228.0631; found 206.0805, 228.0621; melting point=186–187 °C ($CH_2Cl_2$/MeOH), (lit.,[22] mp=187–188 °C; MeOH); IR (NaCl, thin film): $\nu_{max}$ 3224, 1710, 1625 cm$^{-1}$. $^1$H and $^{13}$C NMR data consistent with reported values.[22]

*3.3.6. 4-(4-Methoxyphenyl)-3,4-dihydro-1H-quinolin-2-one **8g***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8g** as pale brown crystals (38 mg, 30%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.25 (1H, br s, NH), 7.18 (1H, dt, $J$=2.1, 7.5 Hz, C7-H), 7.11 (2H, d, $J$=8.4 Hz, methoxyphenyl C2-H), 6.98–6.88 (3H, m, C8-H, C6-H and C5-H), 6.86 (2H, dt, $J$=8.4 Hz, methoxyphenyl C3-H), 4.24 (1H, t, $J$=7.5 Hz, C4-H), 3.78 (3H, s, $OCH_3$), 2.90 (2H, app. d, $J$=7.5 Hz, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.8, 159.1, 137.5, 134.0, 129.2, 128.5, 127.6, 123.7, 116.3, 114.7, 114.3, 55.7, 41.6, 39.0; ESIHRMS for $C_{16}H_{16}NO_2$ ($[M+H]^+$) and $C_{16}H_{15}NO_2Na$ ($[M+Na]^+$): calcd 254.1176, 276.0995; found 254.1168, 276.0986; melting point=184–185 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3429, 1673, 1512, 1485, 1377, 1250 cm$^{-1}$.

*3.3.7. N-(2-Oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetamide **8h***

Synthesised according to general procedure **A** on a 0.5 mmol scale. The product precipitated from the reaction solution when ethyl acetate was added. The product was filtered off from the solution and washed with diethyl ether to give **8h** as a white solid (72 mg, 71%). $^1$H NMR (300 MHz, DMSO) $\delta$: 10.30 (1H, br s, 1N-H), 8.17 (1H, d, $J$=7.8 Hz, C3-NH), 7.19 (1H, d, $J$=7.6 Hz, C5-H), 7.17 (1H, t, $J$=7.6 Hz, C7-H), 6.94 (1H, t, $J$=7.6 Hz, C6-H), 6.87 (1H, d, $J$=7.6 Hz, C8-H), 4.45 (1H, app. q, $J$=7.1 Hz, C3-H), 3.02 (1H, dd, $J$=15.3, 6.6 Hz, C4-$H_A$), 2.86 (1H, app. t, $J$=15.3 Hz, C4-$H_B$), 1.91 (3H, s, $CH_3$); $^{13}$C NMR (75 MHz, DMSO) $\delta$: 169.6, 169.1, 137.9, 128.4, 127.9, 122.8, 122.5, 115.4, 48.2, 31.9, 22.9; ESIHRMS for $C_{11}H_{12}N_2O_2Na$ ($[M+Na]^+$): calcd 227.0791; found 227.0787; melting point=227–229 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1683, 1639, 1535, 1491, 1437, 1402, 1341, 1293, 1266, 1243, 1219 cm$^{-1}$.

*3.3.8. 4-(4-Nitrophenyl)-3,4-dihydro-1H-quinolin-2-one **8i***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8i** as yellow solid (50 mg, 37%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.79 (1H, br s, NH), 8.18 (2H, d, $J$=8.7 Hz, nitrophenyl C3-H), 7.36 (2H, d, $J$=8.7 Hz, nitrophenyl C2-H), 7.26 (1H, dt, $J$=1.2, 7.6 Hz, C7-H,), 7.02 (1H, dt, $J$=1.2, 7.6 Hz, C6-H), 6.94 (1H, d, $J$=7.6 Hz, C5-H), 6.92 (1H, d, $J$=7.6 Hz, C8-H), 4.43 (1H, t, $J$=6.9 Hz, C4-H), 3.03 (1H, dd, $J$=16.2, 6.3 Hz, C3-$H_A$), 2.91 (1H, dd, $J$=16.2, 7.5 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.0, 149.5, 147.6, 137.4, 130.3, 129.2, 128.8, 125.2, 124.6, 124.2, 116.5, 42.3, 38.5; ESIHRMS for $C_{15}H_{12}N_2O_3Na$ ($[M+Na]^+$): calcd 291.0740; found 291.0736; melting point=203–204 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1641, 1219 cm$^{-1}$.

*3.3.9. 4-(4-Bromophenyl)-3,4-dihydro-1H-quinolin-2-one **8j***

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8j** as pale brown crystals (56 mg, 37%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.93 (1H, br s, NH), 7.45 (2H, d, $J$=8.4 Hz, bromophenyl C3-H), 7.22 (1H, dd, $J$=7.5, 1.5 Hz, C7-H), 7.06 (2H, d, $J$=8.4 Hz, bromophenyl C2-H), 6.98 (1H, dt, $J$=1.5, 7.5 Hz, C6-H), 6.89 (2H, m, C8-H and C5-H), 4.26 (1H, dd, $J$=7.8,

6.8 Hz, C4-H), 2.95 (1H, dd, $J$=16.2, 6.8 Hz, C3-$H_A$), 2.86 (1H, dd, $J$=16.2, 7.8 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.8, 140.9, 137.4, 132.5, 130.0, 128.7, 126.4, 123.9, 121.6, 116.3, 42.0, 38.7; 12 of 13 expected signals observed; EIHRMS for $C_{15}H_{12}{}^{79/81}BrNO$ ($[M]^+$): calcd 301.0102, 303.0082; found 301.0109, 303.0087; melting point=184–185 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3435, 1644, 1486, 1377 cm$^{-1}$.

### 3.3.10. 4-(3-Bromophenyl)-3,4-dihydro-1H-quinolin-2-one **8k**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8k** as pale brown crystals (51 mg, 34%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.51 (1H, br s, NH), 7.39 (1H, dt, $J$=7.8, 1.5 Hz, bromophenyl C4-H), 7.33 (1H, t, $J$=1.8 Hz, bromophenyl C2-H), 7.25–7.16 (2H, m, C7-H and bromophenyl C5-H and C7-H), 7.11 (1H, dt, $J$=7.5, 1.2 Hz, bromophenyl C6-H), 6.97 (1H, dt, $J$=1.2, 7.5 Hz, C6-H), 6.94–6.89 (2H, m, C8-H and C5-H), 4.26 (1H, t, $J$=7.8 Hz, C4-H), 2.96 (1H, dd, $J$=16.2, 6.3 Hz, C3-$H_A$), 2.86 (1H, dd, $J$=16.2, 8.1 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.2, 144.4, 137.5, 131.3, 130.9, 130.8, 128.8, 128.7, 126.9, 126.1, 123.9, 123.4, 116.5, 42.2, 38.8; ESIHRMS for $C_{15}H_{13}{}^{79/81}BrNO$ ($[M+H]^+$) and $C_{15}H_{12}Br^{79/81}NONa$ ($[M+Na]^+$): calcd 302.0175/304.1555, 323.9994/325.9992; found 302.0176/304.0160, 323.9987/325.9980; melting point=162–164 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1675, 1649, 1594, 1486, 1428, 1376, 1245, 1219 cm$^{-1}$.

### 3.3.11. 4-(2-Bromophenyl)-3,4-dihydro-1H-quinolin-2-one **8l**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8l** as pale brown crystals (43 mg, 29%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.89 (1H, br s, NH), 7.62 (1H, dd, $J$=7.8, 1.5 Hz, bromophenyl C3-H), 7.26–7.19 (2H, m, bromophenyl C5-H and C7-H), 7.12 (1H, dt, $J$=1.8, 7.8 Hz, bromophenyl C4-H), 7.01–6.95 (2H, m, bromophenyl C6-H and C6-H), 6.94–6.89 (2H, m, C8-H and C5-H), 4.84 (1H, t, $J$=7.2 Hz, C4-H), 2.94 (2H, app. dd, $J$=7.5, 6.9 Hz, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.3, 140.6, 137.5, 133.4, 129.1, 128.8, 128.5, 128.4, 128.1, 125.3, 124.5, 123.6, 115.8, 41.2, 37.2; ESIHRMS for $C_{15}H_{12}{}^{79/81}BrNONa$ ($[M+Na]^+$): calcd 323.9994/325.9992; found 323.9980/325.9982; melting point=216–217 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3435, 1676, 1487, 1437, 1379, 1247 cm$^{-1}$.

### 3.3.12. 4-(1-Ethyl-1H-indol-3-yl)-3,4-dihydro-1H-quinolin-2-one **8m**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate to neat ethyl acetate) to yield **8m** as pale yellow crystals (56 mg, 39%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.47 (1H, br s, NH), 7.52 (1H, d, $J$=7.8 Hz, indolyl C4-H or indolyl C7-H), 7.34 (1H, d, $J$=8.1 Hz, indolyl C4-H or indolyl C7-H), 7.24–7.16 (2H, m, C7-H and indolyl C5/C6-H), 7.11–7.06 (2H, m, C5-H and indolyl C5/C6-H), 6.93 (1H, dt, $J$=0.9, 7.6 Hz, C6-H), 6.85 (1H, d, $J$=7.8 Hz, C8-H), 6.80 (1H, s, indolyl C2-H), 4.63 (1H, dd, $J$=8.7, 6.0 Hz, C4-H), 4.09 (2H, q, $J$=7.2 Hz, N-$CH_2$), 3.11 (1H, dd, $J$=16.1, 8.7 Hz, C3-$H_A$), 2.95 (1H, dd, $J$=16.1, 6.0 Hz, C3-$H_B$), 1.41 (3H, t, $J$=7.2 Hz, $CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.7, 137.2, 136.9, 128.7, 128.1, 127.5, 127.2, 125.3, 123.7, 122.1, 119.8, 119.5, 115.9, 114.9, 110.0, 41.3, 38.3, 34.3, 15.8; ESIHRMS for $C_{19}H_{18}N_2ONa$ ($[M+Na]^+$): calcd 313.1311; found 313.1315; melting point=182–183 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1641, 1379, 1219 cm$^{-1}$.

### 3.3.13. 3′,4′-Dihydro-1′H-[3,4′]biquinolinyl-2′-one **8n**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate to neat ethyl acetate) to yield **8n** as pale yellow crystals (53 mg, 39%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.68 (1H, br s, NH), 8.87 (1H, br s, quinoline C2-H), 8.10 (1H, d, $J$=8.1 Hz, quinoline C8-H), 7.86 (1H, s, quinoline C4-H), 7.73–7.49 (3H, m, quinoline C5-H, C6-H and C7-H), 7.24 (1H, t, $J$=7.8 Hz, C7-H), 6.98–6.97 (3H, m, C8-H, C6-H and C5-H), 4.53 (1H, t, $J$=6.8 Hz, C4-H), 3.07–3.05 (2H, app. d, $J$=6.8 Hz, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.9, 151.3, 147.9, 137.7, 134.7, 134.6, 129.9, 129.6, 129.0, 128.6, 128.3, 128.1, 127.4, 125.6, 124.0, 116.6, 40.2, 38.5; ESIHRMS for $C_{18}H_{15}N_2O$ ($[M+H]^+$): calcd 275.1179; found 275.1176; melting point=182–183 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1644, 1488, 1420, 1376, 1245 cm$^{-1}$.

### 3.3.14. 4-Thien-2-yl-3,4-dihydro-1H-quinolin-2-one **8o**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8o** as pale yellow crystals (43 mg, 38%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.22 (1H, br s, NH), 7.23–7.17 (2H, m, C7-H and thienyl C5-H), 7.12 (1H, d, $J$=7.5 Hz, C5-H), 7.02 (1H, dt, $J$=1.2, 7.5 Hz, C6-H), 6.92 (1H, dd, $J$=5.1, 3.6 Hz, thienyl C4-H), 6.88 (1H, dd, $J$=7.5, 1.3 Hz, C8-H), 6.82 (1H, d, $J$=3.6 Hz, thienyl C3-H), 4.54 (1H, t, $J$=6.3 Hz, C4-H), 3.01 (1H, d, $J$=6.3 Hz, C3-$H_A$), 3.01 (1H, d, $J$=6.8 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 170.8, 145.5, 137.0, 128.9, 128.5, 127.4, 126.7, 125.3, 125.0, 123.9, 116.4, 39.2, 38.0; ESIHRMS for $C_{13}H_{12}NOS$ ($[M+H]^+$) and $C_{13}H_{11}NONaS$ ($[M+Na]^+$): calcd 230.0634, 252.0454; found 230.0638, 252.0457; melting point=175–176 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1643, 1490, 1434, 1389, 1311, 1269, 1252 cm$^{-1}$.

### 3.3.15. 4-Pyridin-2-yl-3,4-dihydro-1H-quinolin-2-one **8p**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate to neat ethyl acetate) to yield **8p** as pale yellow crystals (55 mg, 49%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.84 (1H, br s, NH), 8.54 (1H, ddd, $J$=4.8, 1.8, 0.9 Hz, pyridyl C6-H), 7.59 (1H, dt, $J$=1.8, 7.5 Hz, pyridyl C4-H), 7.20 (1H, dt, $J$=1.8, 7.5 Hz, C7-H), 7.15 (1H, ddd, $J$=7.5, 4.8, 0.9 Hz, pyridyl C5-H), 7.08–6.95 (3H, m, C6-H, C5-H and pyridyl C3-H), 6.87 (1H, d, $J$=7.5 Hz, C8-H), 4.44 (1H, t, $J$=6.6 Hz, C4-H), 3.22 (1H, dd, $J$=16.2, 6.3 Hz, C3-$H_A$), 2.97 (1H, dd, $J$=16.2, 6.6 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.3, 161.4, 150.3, 137.6, 137.2, 129.0, 128.7, 125.6, 123.7, 122.5, 116.3, 44.5, 36.8; 13 of 14 expected signals observed; ESIHRMS for $C_{14}H_{13}N_2O$ ($[M+H]^+$): calcd 225.1022; found 225.1020; melting point=178–179 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1671, 1593, 1487, 1433, 1378, 1219 cm$^{-1}$.

### 3.3.16. 7-Trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8q**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8q** as pale yellow crystals (54 mg, 50%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.72 (1H, br s, NH), 7.27 (1H, d, $J$=8.0 Hz, C6-H), 7.24 (1H, d, $J$=8.0 Hz, C5-H), 7.10 (1H, s, C8-H), 3.03 (2H, t, $J$=7.7 Hz, C3-$H_2$), 2.69 (2H, t, $J$=7.7 Hz, C4-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 172.6, 138.4, 130.5 (q, $J$=33 Hz, C7), 128.8, 127.9, 124.2 (q, $J$=271 Hz, $CF_3$), 120.1, 112.8, 30.6, 25.6; EIHRMS for $C_{10}H_8F_3NO$ ($[M]^+$): calcd 215.0558; found 215.0551; melting point=149–150 °C ($CH_2Cl_2$); IR (NaCl, thin film): $\nu_{max}$ 3412, 1683, 1642, 1492, 1439, 1408, 1385, 1331, 1234 cm$^{-1}$.

### 3.3.17. 4-Methyl-7-trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8r**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8r** as pale yellow crystals (45 mg, 39%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.62 (1H, br s, NH), 7.31 (1H, d, $J$=8.3 Hz, C6-H), 7.28 (1H, d, $J$=8.3 Hz, C5-H), 7.11 (1H, s, C8-H), 3.23–3.17 (1H, m, C4-H), 2.78 (1H, dd, $J$=16.0, 5.5 Hz, C3-$H_A$), 2.48 (1H, dd, $J$=16.0, 7.0 Hz, C3-$H_B$), 1.35 (3H, d, $J$=7.0 Hz,

C4-$CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 172.0, 137.5, 132.9, 130.5 (q, $J$=33 Hz, C7), 127.5, 124.2 (q, $J$=270 Hz, $CF_3$), 120.4, 112.9, 38.2, 31.2, 20.0; ESIHRMS for $C_{11}H_{11}F_3NO$ ($[M+H]^+$) and $C_{11}H_{10}F_3NONa$ ($[M+Na]^+$): calcd 230.0787, 252.0607; found 230.0788, 252.0617; melting point=158–159 °C ($CH_2Cl_2$); IR (NaCl, thin film): $\nu_{max}$ 3412, 1682, 1637, 1485, 1405, 1377, 1339, 1219 $cm^{-1}$.

### 3.3.18. 4-Phenyl-7-trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8s**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (1:3 petrol/diethyl ether) to yield **8s** as pale yellow crystals (62 mg, 43%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.76 (1H, br s, NH), 7.37–7.28 (3H, m, phenyl C2-H and C6-H), 7.21–7.18 (3H, m, phenyl C3-H and phenyl C4-H), 7.16 (1H, s, C8-H), 7.02 (1H, d, $J$=7.5 Hz, C5-H), 4.34 (1H, t, $J$=7.5 Hz, C4-H), 2.97 (2H, app. d, $J$=7.5 Hz, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.6, 147.1, 140.9, 130.5 (q, $J$=38 Hz, C7), 130.3, 129.6, 129.3, 128.2, 128.0, 124.1 (q, $J$=270 Hz, $CF_3$), 120.4, 113.1, 42.4, 38.3; ESIHRMS for $C_{16}H_{12}F_3NONa$ ($[M+Na]^+$): calcd 314.0763; found 314.0756; melting point=153–154 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3400, 1685, 1638, 1481, 1332, 1219 $cm^{-1}$.

### 3.3.19. 4-(4-Methoxyphenyl)-7-trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8t**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (1:3 petrol/diethyl ether) to yield **8t** as pale yellow crystals (74 mg, 46%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.45 (1H, br s, NH), 7.21 (1H, d, $J$=8.0 Hz, C6-H), 7.13–7.10 (3H, m, methoxyphenyl C2-H and C8-H), 7.03 (1H, d, $J$=8.0 Hz, C7-H), 6.89 (2H, d, $J$=8.5 Hz, methoxyphenyl C3-H), 4.30 (1H, t, $J$=7.5 Hz, C4-H), 3.04 (3H, s, $OCH_3$), 2.95–2.93 (2H, m, C3-$H_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.4, 159.4, 138.0, 132.8, 131.9 (q, $J$=33 Hz, C7), 131.5, 131.3, 129.3, 124.1 (q, $J$=271 Hz, $CF_3$), 120.4, 114.9, 113.0, 55.7, 41.6, 38.5; ESIHRMS for $C_{17}H_{14}F_3NONa$ ($[M+Na]^+$): calcd 344.0869; found 344.0853; melting point=184–186 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3434, 1642, 1331, 1254 $cm^{-1}$.

### 3.3.20. 7′-Trifluoromethyl-3′,4′-dihydro-1′H-[3,4′]biquinolinyl-2′-one **8v**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate to neat ethyl acetate) to yield **8v** as pale yellow crystals (82 mg, 47%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.63 (1H, br s, NH), 8.86 (1H, d, $J$=2.4 Hz, quinolinyl C2-H), 8.12 (1H, d, $J$=8.4 Hz, quinolinyl C8-H), 7.88 (1H, d, $J$=2.4 Hz, quinolinyl C4-H), 7.78–7.70 (2H, m, quinolinyl C5-H and C6/C7-H), 7.56 (1H, t, $J$=7.6 Hz, quinolinyl C6/C7-H), 7.26 (1H, s, C8-H), 7.22 (1H, d, $J$=8.1 Hz, C6-H), 7.10 (1H, d, $J$=8.1 Hz, C5-H), 4.59 (1H, t, $J$=7.2 Hz, C4-H), 3.09 (2H, d, $J$=7.2 Hz, C3-$CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 171.9, 152.2, 149.3, 139.5, 135.9, 134.9, 132.7 (q, $J$=33 Hz, C7), 131.5, 131.0, 130.5, 130.3, 130.1, 129.5, 129.4, 125.3 (q, $J$=271 Hz, $CF_3$), 121.9, 114.6, 41.4, 39.3; ESIHRMS for $C_{19}H_{14}F_3N_2O$ ($[M+H]^+$): calcd 343.1053; found 343.1039; melting point=190–191 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3401, 1638, 1331, 1331, 1219 $cm^{-1}$.

### 3.3.21. 4-Thien-2-yl-7-trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8w**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate) to yield **8w** as pale yellow crystals (23 mg, 19%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.35 (1H, br s, NH), 7.29–7.24 (3H, m, C5-H, C6-H and thienyl C5-H), 7.07 (1H, s, C8-H), 6.96 (1H, dd, $J$=5.0, 3.5 Hz, thienyl C4-H), 6.85 (1H, d, $J$=3.5 Hz, thienyl C3-H), 4.61 (1H, t, $J$=6.5 Hz, C4-H), 3.04 (2H, app. d, $J$=6.5 Hz, C3-$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 171.0, 145.2, 138.7, 132.1, 132.5 (q, $J$=33 Hz, C7), 130.4, 128.7, 126.9, 126.7, 125.4 (q, $J$=280 Hz, $CF_3$), 121.8, 114.2, 39.9, 39.1; ESIHRMS for $C_{14}H_{11}F_3NOS$ ($[M+H]^+$): calcd 320.0327; found 320.0323; melting point=179–180 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3413, 1642, 1333, 1219 $cm^{-1}$.

### 3.3.22. 4-Pyridin-2-yl-7-trifluoromethyl-3,4-dihydro-1H-quinolin-2-one **8x**

Synthesis according to general procedure **B** on a 0.5 mmol scale gave the crude product as a brown oil. This was purified by column chromatography (3:2 petrol/ethyl acetate to neat ethyl acetate) to yield **8x** as pale yellow crystals (52 mg, 33%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.35 (1H, br s, NH), 8.59 (1H, d, $J$=4.5 Hz, pyridyl C6-H), 7.64 (1H, dt, $J$=1.5, 7.0 Hz, pyridyl C4-H), 7.23 (1H, d, $J$=7.0 Hz, pyridyl C3-H), 7.19 (1H, ddd, $J$=7.0, 4.5, 1.5 Hz, pyridyl C5-H), 7.13–7.11 (3H, m, C8-H, C6-H and C5-H), 4.49 (1H, t, $J$=6.5 Hz, C4-H), 3.25 (1H, dd, $J$=16.5, 6.5 Hz, C3-$H_A$), 2.98 (1H, dd, $J$=16.5, 6.5 Hz, C3-$H_B$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 171.0, 160.0, 150.1, 137.8, 137.0, 130.7 (q, $J$=33 Hz, C7), 129.0, 123.9 (q, $J$=271 Hz, $CF_3$), 122.4, 122.1, 119.9, 119.7, 112.8, 43.9, 35.9; ESIHRMS for $C_{15}H_{12}F_3N_2O$ ($[M+H]^+$): calcd 293.0896; found 293.0897; melting point=186–187 °C ($CH_2Cl_2$/MeOH); IR (NaCl, thin film): $\nu_{max}$ 3429, 2099, 1642, 1473, 1331 $cm^{-1}$.

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## References and notes

1. Morita, S.; Irie, Y.; Saitoh, Y.; Kohri, H. *Biochem. Pharmacol.* **1976**, *25*, 1836.
2. Nishi, T.; Tabusa, F.; Tanaka, T.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 1151.
3. Semba, J.; Watanabe, A.; Kito, S.; Toru, M. *Neuropharmacology* **1995**, *34*, 785.
4. Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886.
5. Uchida, R.; Imasoto, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701.
6. (a) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2, Chapter 8; (b) Johnston, K. M. *Tetrahedron* **1968**, *24*, 5595; (c) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881.
7. Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785.
8. Clark, A. J.; Jones, K.; McCarthy, C.; Storey, J. M. D. *Tetrahedron Lett.* **1991**, *32*, 2829.
9. (a) Wu, Y. L.; Chuang, C. P.; Lin, P. Y. *Tetrahedron* **2000**, *56*, 6209; (b) Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 7503.
10. (a) Chapman, O. L.; Adams, W. R. *J. Am. Chem. Soc.* **1968**, *90*, 2333; (b) Ogata, Y.; Takagi, K.; Ishino, I. *J. Org. Chem.* **1971**, *36*, 3975; (c) For a recent example utilising Ugi condensation to establish the photocyclisation precursor, see: Akritopolou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Tetrahedron Lett.* **2007**, *48*, 3549.
11. (a) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264; (b) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307.
12. Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117.
13. For examples of heterocycle formation from aminophenylboronates or *N*-protected derivatives by Suzuki coupling/condensation, see: (a) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463; (b) Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 979; (c) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179; (d) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2003**, *5*, 2911; (e) Gug, F.; Blondel, M.; Desban, M.; Bouaziz, S.; Vierfond, J.-M.; Galons, H. *Tetrahedron Lett.* **2005**, *46*, 3725.
14. Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. W. F., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 167–243; For a recent mechanistic study on this reaction, see: Denmark, S. E.; Venkataraman, S. *J. Org. Chem.* **2006**, *71*, 1668.
15. (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000; (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
16. Navarro, C.; Morena, A.; Csaky, A. G. *J. Org. Chem.* **2009**, *74*, 466.
17. Baudoin, O.; Guénard, D.; Guérrite, F. *J. Org. Chem.* **2000**, *65*, 9268.
18. Koltunov, K. Y.; Prakash, G. K.; Rasul, G.; Olah, G. A. *Heterocycles* **2004**, *62*, 757.
19. Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218.
20. Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 35.
21. Paquin, J. F.; Stephenson, C. R.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821.
22. Becerril, E. R.; Hernández, N. P.; Nathan, P. J.; Ríos, M. S. *Heterocycles* **2007**, *68*, 1459.