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*Published in:*
Bioorganic and Medicinal Chemistry

*DOI:*
10.1016/j.bmc.2009.05.013

Published: 01/01/2009

*Document Version*
Peer-reviewed accepted author manuscript, also known as Final accepted manuscript or Post-print

*Author's accepted manuscript, published in Bioorganic & Medicinal Chemistry 17 (2009) 4441–4447*

# Synthesis of quinolinyl and isoquinolinyl phenyl ketones as novel agonists for the cannabinoid $CB_2$ receptor

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ARTICLE INFO

*Keywords:* Cannabinoid receptor $CB_2$ Quinoline Isoquinoline

ABSTRACT

A series of quinolinyl and isoquinolinyl phenyl ketones was synthesized and their $CB_2$ receptor-dependent G-protein activities were determined using the [$^{35}$S]GTPγS binding assay. Both quinoline and isoquinoline derivatives exhibited similar $CB_2$ receptor agonist activity, the most potent ligands being the 2-($Me_2N$)-phenyl substituted derivatives, which were also full agonists at the $CB_2$-receptor.



## 1. Introduction

The $CB_2$ receptor is a seven-transmembrane-domain G-protein-coupled receptor.[1] It is part of the endocannabinoid system which consists of another cannabinoid receptor ($CB_1$), endogenous agonist ligands derived from arachidonic acid (endocannabinoids) and a mechanism of deactivation involving enzymes and membrane transport system.[2] The gene encoding the human cannabinoid $CB_2$ receptor was cloned in 1993.[3] The $CB_1$ receptor is largely present in the central nervous system (CNS) with high density in the brain causing the well known psychotropic side-effects associated with the use of cannabis derivatives which are agonists to the receptor.[4] It has been thought for some time that the $CB_2$ receptor is absent from the CNS and it is abundant in the immune system.[5] More recent studies have suggested that $CB_2$ is also expressed in certain subpopulations of the CNS.[6]

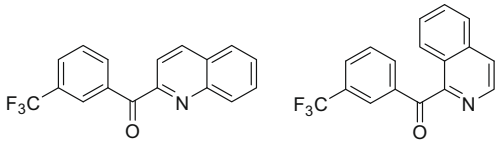
Together with this discovery and the understanding of the mechanism involved, the potential of therapeutic uses for $CB_2$ has increased. It has been shown that the expression of $CB_2$ receptors increases with the degree of malignancy in glial[7] and breast[8] tumors and that activation of the receptor could stop the tumor progression[7,9] or induce apoptosis of the cancerous cells.[5] Cannabinoid receptor activation has also been suggested in therapeutic approaches in the treatment of pain,[10] inflammation,[11] osteoporosis[12] or sclerosis.[13] These observations have spurred wide spread interest in synthetic $CB_2$-selective cannabinoid receptor specific molecules that act as agonists, inverse agonists, antagonists or simply new drugs for clinical use.[14–17]

Recently, Salo et al.[18] have used a comparative model of $CB_2$ receptor constructed using the bovine rhodopsin X-ray structure to identify new hit compounds. After virtual screening of chemical databases for hit molecules, the results of [$^{35}$]GTPγS G-protein activations assays showed that one of them acted as a selective $CB_2$ agonist (**NRB-04079**, **2**). This rather small isoquinolinyl phenyl ketone was suitable for pharmacomodulation together with its quinoline analogue **NRB-04080** (**1**) which also showed $CB_2$ agonist properties and no sign of $CB_1$ activity (Fig. 1). We report here the synthesis and the biological evaluation of such derivatives.

## 2. Results

### 2.1. Chemistry

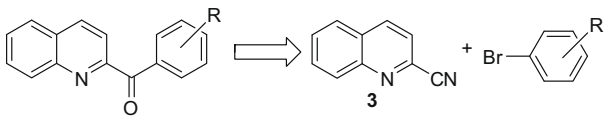
In this study we investigated the modifications on the benzene ring of the phenyl quinolinyl ketones, which can be synthesized by



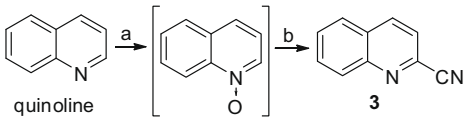

**1** (NRB-04080) **2** (NRB-04079)

**Figure 1.** The structures of the hit compounds.

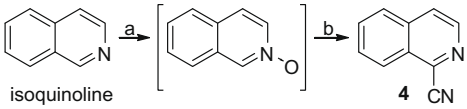
doi:10.1016/j.bmc.2009.05.013



**Scheme 1.** Synthetic plan.



**Scheme 2.** Reagents and conditions: (a) *m*-CPBA, $CH_2Cl_2$, 2 h; (b) benzoyl chloride, KCN, MeOH, $CH_3CN$, overnight, 82% overall.



**Scheme 3.** Reagents and conditions: (a) *m*-CPBA, $CH_2Cl_2$, 2 h; (b) benzoyl chloride, KCN, MeOH, $CH_3CN$, overnight, 68% overall.

a Grignard coupling of an appropriate arylmagnesium halide and quinoline-2-carbonitrile **3** (Scheme 1).

The carbonitrile **3** was obtained from quinoline through N-oxidation followed by in situ conversion to an N-benzoate and addition of cyanide (Scheme 2). The oxidation of quinoline was more efficient with *m*-CPBA (after 30 min no more starting material was detected by TLC, 74% yield) than with hydrogen peroxide (3 days, 60% yield). The N-oxide was used without purification and **3** was obtained in high yield. Similarly, the isoquinolinyl carbonitrile **4** was obtained by oxidation of isoquinoline with *m*-CPBA and treatment with potassium cyanide and benzoyl chloride (Scheme 3).

The coupling reaction to give the isoquinolinyl aryl ketones involved the formation of a Grignard reagent from adequately substituted bromobenzenes (Scheme 4). Addition to the carbonitrile (**3** or **4**) led to the corresponding imine which gave the desired ketone upon hydrolysis with 1 M HCl. The reaction was conducted in a mixture of THF/toluene 1:2 in order to enhance the reactivity of the nucleophile toward the nitrile.[19]

### 2.2. Pharmacology

The new quinolinyl and isoquinolinyl phenyl ketones have been tested for their capacity of G-protein activation of the human $CB_2$ receptor ($hCB_2$) via a [$^{35}$]GTPγS binding assay according to the procedure described by Savinainen et al.[20] The receptors used were $hCB_2$ stably expressed in Chinese hamster ovary (CHO) cells. In this assay, the effects of the tested cannabinoid agonists are obtained from agonist-induced binding of the nonhydrolyzable GTP analogue [$^{35}$]GTPγS. The relative efficacy responses of the molecules are expressed as percentage of the full (both $CB_1$ and $CB_2$) potent cannabinoid agonist HU-210. All the compounds were first evaluated at 10 μM concentration. For the compounds that showed over 50% relative activity, the dose response curves were generated and the $EC_{50}$ and $E_{max}$ values were calculated by nonlinear regression analysis with the equation for a sigmoidal concentration–response curve (GRAPHPAD PRISM 4). The possible $CB_1$ receptor agonist and antagonism of all the compounds were screened at 10 μM concentration in rat cerebellar membranes as previously described[21] to estimate the $CB_2$ selectivity of the compounds.

## 3. Discussion

We have synthesized two series of compounds that are listed together with their yields and their efficacy results in Table 1 (quinolines) and Table 2 (isoquinolines).

### 3.1. Quinolines

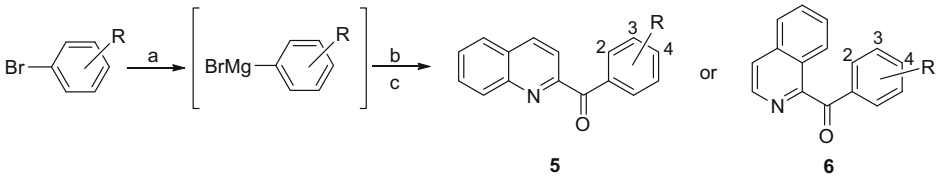
Both electron donating and electron withdrawing substituents were evaluated. Of the 4-substituted molecules, the best compound (**5k,** $-\log EC_{50} = 5.4$, $E_{max} = 62$) possesses an electron donating $NMe_2$ group. An electron-withdrawing 4-chloro substituent (**5m**) and electron-donating 4-methoxy substituent (**5e)** also maintain considerable relative activity, whereas electron-withdrawing 4-$CF_3$ (**5b)** and 4-F substituents (**5o**) showed weaker activity.

Moving the $CF_3$ group from the 4-position to the 3-position (**2**) led to slight improvement in $CB_2$ activity whereas introducing $CF_3$ to the 2-position (**5c**) gives a potent high efficacy ligand ($-\log EC_{50} = 5.7$, $E_{max} = 87$). That pattern is also apparent with electron-donating substituents. Moving a methoxy group from the 4-position (**5e**) to the 3-position (**5f**) and then to the 2-position (**5g**) leads to improved activity. The gain in $CB_2$ efficacy and potency is even better when 4-$NMe_2$ substituent is moved to 2-position (**5l**, $-\log EC_{50} = 6.1$, $E_{max} = 91$). Moving 4-chloro (**5m**) to 2-position (data not shown) or 4-fluoride (**5j**) to 3-position (**5i**) does not noticeably improve the $CB_2$ activity.

Elongation of the alkoxy group at the 4-position (**5h**, **5i** and **5j**) leads to loss of $CB_2$ activity. Those observations suggest that the binding area of the $CB_2$ receptor is not sensitive to the electronic nature of the compounds but more likely to the size and shape and is intolerant to steric bulk. This assertion is supported by the bis-functionalized molecules **5d** (3,5-$CF_3$) and **5n** (3,4-Cl) which lose almost all activity.

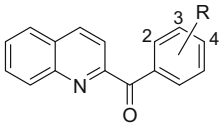
### 3.2. Isoquinolines

The 4-$CF_3$ analogue **6b** ($-\log EC_{50} = 5.5$, $E_{max} = 57$) seems to be equipotent with the 3-$CF_3$ hit **2** ($-\log EC_{50} = 5.3$, $E_{max} = 53$) but like in the quinoline series, the 2-$CF_3$ analogue **6c** has higher $CB_2$ potency and efficacy ($-\log EC_{50} = 6.3$, $E_{max} = 72$). A further 3-$CF_3$ is still responsible for a dramatically drop of the activity (**6d**). Overall, the isoquinoline compounds show approximately the same efficacy and potency as the quinoline analogues with the exception



**Scheme 4.** Reagents and conditions: (a) Mg, THF; (b) **3** or **4**, toluene, 0 °C then rt; (c) 1 M HCl, $Et_2O$.

**Table 1**
$CB_2$ receptor activity data of the quinolinyl phenyl ketones[a]




**5**

| Compound | R= | Yield (%) | $CB_1$ agonism at 10 μM ligand concd[b] | $CB_2$ agonism at 10 μM ligand concd[c] | $CB_2$ Relative $E_{max}$[c] | $CB_2$ $-\log EC_{50}$ |
|---|---|---|---|---|---|---|
| **5a**, **BTB14404** | H | 97 | 103 ± 1 | 29 ± 1 | 52 ± 5 | 5.1 ± 0.2 |
| **5b** | 4-$CF_3$ | 80 | 105 ± 5 | 20 ± 1 | n.d. | n.d. |
| **1**, **NRB-04080**[d] | 3-$CF_3$ | — | 102 ± 1 | 42 ± 3 | 42 ± 3 | 5.3 ± 0.2 |
| **5c** | 2-$CF_3$ | 46 | 102 ± 1 | 80 ± 6 | 87 ± 3 | 5.7 ± 0.1 |
| **5d** | 3,5-$CF_3$ | 76 | 108 ± 3 | 11 ± 1 | n.d. | n.d. |
| **5e** | 4-OMe | 98 | 108 ± 7 | 45 ± 2 | n.d. | n.d. |
| **5f** | 3-OMe | 90 | 102 ± 4 | 52 ± 12 | 54 ± 4 | 5.7 ± 0.2 |
| **5g** | 2-OMe | 96 | 106 ± 5 | 46 ± 7 | 53 ± 3 | 5.6 ± 0.1 |
| **5h** | 4-OEt | 67 | 100 ± 2 | 19 ± 4 | n.d. | n.d. |
| **5i** | 4-OPr | 87 | 108 ± 3 | 7 ± 1 | n.d. | n.d. |
| **5j** | 4-OiPr | 64 | 102 ± 5 | 10 ± 2 | n.d. | n.d. |
| **5k** | 4-$NMe_2$ | 94 | 101 ± 6 | 45 ± 6 | 62 ± 2 | 5.2 ± 0.1 |
| **5l** | 2-$NMe_2$ | 81 | 101 ± 3 | 85 ± 8 | 91 ± 2 | 6.1 ± 0.1 |
| **5m** | 4-Cl | 81 | 101 ± 3 | 47 ± 2 | 63 ± 2 | 5.4 ± 0.1 |
| **5n** | 3,4-Cl | 64 | 100 ± 3 | 18 ± 2 | n.d. | n.d. |
| **5o** | 4-F | 93 | 99 ± 2 | 34 ± 2 | n.d. | n.d. |
| **5p** | 3-F | 98 | 106 ± ± 2 | 34 ± 5 | n.d. | n.d. |

[a] Values are mean ± SEM of at least three experiments performed in duplicate.
[b] The data are presented as % basal.
[c] Relative responses as percentage of the 10 nM HU-210 agonist response.
[d] Ordered from Maybridge. n.d. = not determined.

of the 4-methoxy analogue **6e** which has very weak potency. The same observations can be made regarding the non-influence of the electronic nature of the substituents (**6b** and **6g** have the same relative agonist activity) and the large impact of its position on the benzene ring as can be seen by comparing the compounds **6h** and **6g**. We finally observe that the 2-$NMe_2$ analogue **6h** has higher potency and efficacy ($-\log EC_{50} = 6.2$, $E_{max} = 95$) than the 4-$NMe_2$ analogue **6g** ($-\log EC_{50} = 5.6$, $E_{max} = 68$) as was the case in quinoline series.

## 4. Conclusions

The pharmacomodulation of the hit compounds **1** and **2** was achieved to give better agonist capacity ($E_{max}$ >42, $-\log EC_{50}$ >5.3 for the quinoline series; $E_{max}$ >53, $-\log EC_{50}$ >5.3 for the isoquinoline series). However, only compounds **5l**, **6h** and **5c** are full $CB_2$ agonists (respectively $E_{max} = 91$, 95 and 87). None of these compounds showed any significant $CB_1$ receptor activation.

In conclusion, the quinolinyl and isoquinolinyl phenyl ketones represent a new class of $CB_2$-selective receptor ligands, which revealed full or partial $CB_2$ cannabinoid receptor agonistic properties in the [$^{35}$]-GTP$\gamma$S binding assay. Both isoquinoline and quinoline derivatives showed more or less same efficacy and potency. The most potent ligands were the 2-$NMe_2$ substituted compounds (**5l** and **6h**).

## 5. Experimental

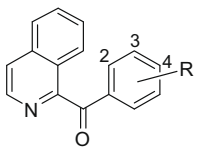
### 5.1. General methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware. Non-aqueous reagents were transferred under argon via syringe or cannula and dried prior to use. THF was distilled from Na/benzophenone ketyl. $CH_2Cl_2$ and MeOH were distilled from $CaH_2$. All other solvents and reagents were used as obtained from the supplier. Analytical TLC was performed on Merck silica gel F254 (230–400 mesh) plates and visualized under UV light. Flash chromatography was performed on Merck Silica Gel 60 (230–400 mesh) and p.a. grade solvents. Infrared spectra were measured on a Perkin Elmer Spectrum One FT-IR spectrometer using KBr disc. The $^1$H and $^{13}$C NMR spectra were recorded in a $CDCl_3$ solution on a Bruker Avance 400 ($^1$H 399.98 MHz; $^{13}$C 100.59 MHz) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane ($\delta$ 0) for $^1$H NMR. For the $^{13}$C NMR spectra, the signal for $CDCl_3$ ($\delta$ 77.16) was used as the internal standard. High-resolution mass spectrometric data were obtained on Waters LCT Premier—spectrometer. Melting points were obtained on Gallenkamp and Stuart SMP3 melting point apparatuses. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

#### 5.1.1. Quinoline-2-carbonitrile (3)

To a solution of quinoline (1.50 g, 11.6 mmol, 100 mol %) in 15 mL of $CH_2Cl_2$ was added *m*-CPBA (70% with water, 2.87 g, 11.6 mmol, 100 mol %) portionwise. After 2 h, the solution was dried with $Na_2SO_4$, filtered and evaporated. The solid obtained was dissolved in acetonitrile (51 mL) and added to a solution of KCN (1.51 g, 23.2 mmol, 200 mol %) in methanol (39 mL). Benzoyl chloride (2.70 mL, 23.2 mmol, 200 mol %) was added dropwise and the reaction was stirred overnight. After evaporation of the solvent, the residue was taken up in $CH_2Cl_2$ and washed twice with a solution of saturated $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography (hexane/EtOAc, 9:1) affording compound **3** (1.47 g, 82%) as a white solid. $^1$H NMR ($CDCl_3$) $\delta$ 8.32 (d, 1H, $J$ = 8.4 Hz), 8.17 (br d, 1H, $J$ = 8.6 Hz), 7.91 (br d, 1H, $J$ = 8.2 Hz), 7.85 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.4 Hz), 7.72 (m, 2H).

**Table 2**
$CB_2$ receptor activity of the isoquinolinyl phenyl ketones[a]




**6**

| Compound | R= | Yield (%) | $CB_1$ agonism at 10 μM ligand concd[b] | $CB_2$ agonism at 10 μM ligand concd[c] | $CB_2$ relative $E_{max}$[c] | $CB_2$ −log $EC_{50}$ |
|---|---|---|---|---|---|---|
| **6a** | H | 94 | 102 ± 7 | 24 ± 15 | n.d. | n.d. |
| **6b** | 4-$CF_3$ | 89 | 95 ± 7 | 46 ± 3 | 57 ± 1 | 5.5 ± 0.1 |
| **2**, **NRB-04079**[d] | 3-$CF_3$ | — | 106 ± 3 | — | 53 ± 4[e] | 5.3 ± 0.2[e] |
| **6c** | 2-$CF_3$ | 44 | 112 ± 6 | 63 ± 3 | 72 ± 2 | 6.3 ± 0.1 |
| **6d** | 3,5-$CF_3$ | 55 | 101 ± 1 | 16 ± 4 | n.d. | n.d. |
| **6e** | 4-OMe | 93 | 85 ± 1 | 17 ± 3 | n.d. | n.d. |
| **6f** | 3-OMe | 90 | 112 ± 4 | 41 ± 4 | n.d. | n.d. |
| **6g** | 4-$NMe_2$ | 54 | 99 ± 3 | 56 ± 5 | 68 ± 5 | 5.6 ± 0.2 |
| **6h** | 2-$NMe_2$ | 96 | 116 ± 5 | 90 ± 5 | 95 ± 2 | 6.2 ± 0.1 |
| **6i** | 4-F | 86 | 104 ± 2 | 20 ± 5 | n.d. | n.d. |
| **6j** | 3-F | 92 | 99 ± 2 | 17 ± 2 | n.d. | n.d. |
| **6k** | 4-Cl | 98 | 101 ± 3 | 40 ± 4 | n.d. | n.d. |
| **6l** | 3,4-Cl | 83 | 111 ± 9 | 45 ± 4 | n.d. | n.d. |

[a–d] See the corresponding footnotes in Table 1.
[e] Ref. 18.

#### 5.1.2. Isoquinoline-1-carbonitrile (4)

This was prepared from isoquinoline (1.50 g, 11.6 mmol) following the same procedure as for quinoline-2-carbonitrile **3** to give isoquinoline-1-carbonitrile **4** (1.23 g, 68%) as a white solid. $^1$H NMR ($CDCl_3$) $\delta$ 8.64 (d, 1H, $J$ = 5.7 Hz), 8.30 (br d, 1H, $J$ = 8.2 Hz), 7.95 (br d, 1H, $J$ = 7.8 Hz), 7.91 (d, 1H), 7.81 (m, 2H).

### 5.2. General procedure for the quinolinyl and isoquinolinyl phenyl ketones

A solution of the appropriate bromophenyl derivative (1.43 mmol, 200 mol %) in 1.5 mL of THF was treated with magnesium (1.71 mmol, 240 mol %). After the formation of the Grignard reagent, the solution was added to a solution of the appropriate carbonitrile (0.713 mmol, 100 mol %) in toluene (3 mL) at 0 °C. When TLC showed no more starting material, the reaction was quenched by addition of a solution of satd $NH_4Cl$. The organic layer was separated and extracted twice with $CH_2Cl_2$. After evaporation, the organic layer was redissolved in $Et_2O$ (10 mL) and 1 M HCl (4 mL) was added. After 20 min, the organic layer was separated; the aqueous layer basified with saturated $NaHCO_3$ and then extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and evaporated in vacuo. The residue was purified by column chromatography (hexane/EtOAc) and crystallized.

#### 5.2.1. Quinolin-2-yl-(4-trifluoromethylphenyl)-methanone (5b)

This was prepared from quinoline-2-carbonitrile and 4-bromobenzotrifluoride in 80% yield. White needles; mp 99 °C (hexane); IR (KBr) $\nu$ 1671, 1338, 1318, 1103, 777 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.37 (m, 3H), 8.19 (d, 1H, $J$ = 8.5 Hz), 8.18 (d, 2H, $J$ = 8.2 Hz), 7.92 (br d, 1H, $J$ = 8.2 Hz), 7.79 (m, 3H), 7.69 (ddd, 1H, $J$ = 1.1 Hz, $J$ = 7.0, $J$ = 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.70, 153.77, 146.85, 139.36, 137.46, 134.12 (q, $J$ = 32.3 Hz), 131.82 (2C), 130.69, 130.43, 129.23, 128.97, 127.82, 125.14 (q, 2C, $J$ = 3.6 Hz), 123.92 (q, $J$ = 271.0 Hz), 120.73. Anal. ($C_{17}H_{10}F_3NO{\cdot}0.2H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{11}F_3NO$ (M+H), 302.0793; found, 302.0782.

#### 5.2.2. Quinolin-2-yl-(2-trifluoromethylphenyl)-methanone (5c)

This was prepared from quinoline-2-carbonitrile and 2-bromobenzotrifluoride in 46%. White solid mp; 87 °C (hexane); IR (KBr) $\nu$ 1678, 1315, 1161, 1126, 927, 771 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.34 (d, 1H, $J$ = 8.6 Hz), 8.29 (d, 1H), 8.01 (br d, 1H, $J$ = 8.5 Hz), 7.88 (dd, 1H, $J$ = 1.1 Hz, $J$ = 8.0 Hz), 7.78 (m, 1H), 7.71 (ddd, 1H, $J$ = 1.5 Hz, $J$ = 6.9 Hz), 7.64 (m, 3H), 7.56 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 196.20, 153.09, 147.24, 138.16 (d, $J$ = 2.2 Hz), 137.18, 131.16, 130.95, 130.14, 129.95, 129.51, 129.25, 129.09, 128.75 (q, 1C, $J$ = 32.1 Hz), 127.71, 126.52 (q, 1C, $J$ = 4.3 Hz), 123.96 (q, 1C, $J$ = 272.0 Hz), 119.31. Anal. ($C_{17}H_{10}F_3NO{\cdot}0.1H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{11}F_3NO$ (M+H), 302.0793; found, 302.0790.

#### 5.2.3. (3,5-Bis-trifluoromethylphenyl)-quinolin-2-yl-methanone (5d)

This was prepared from quinoline-2-carbonitrile and 3,5-bis(trifluoromethyl) bromobenzene in 76% yield. Pale yellow crystals; mp 86 °C (hexane); IR (KBr) $\nu$ 1668, 1285, 1148, 1127, 775 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.87 (s, 2H), 8.39 (d, 1H, $J$ = 8.5 Hz), 8.26 (d, 1H), 8.16 (br d, 1H, $J$ = 8.4 Hz), 8.12 (br s, 1H), 7.93 (br d, 1H), 7.82 (ddd, 1H, $J$ = 1.2 Hz, $J$ = 7.0 Hz), 7.70 (ddd, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 190.21, 152.85, 146.83, 138.04, 137.74, 1321.83 (br s, 2C), 131.65 (q, 2C, $J$ = 33.7 Hz), 130.72 (2C), 129.41, 127.84, 125.90 (sept., 1C, $J$ = 3.6 Hz), 123.29 (q, 2C, $J$ = 271.1 Hz), 120.62. Anal. ($C_{18}H_9F_6NO$) C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{10}F_6NO$ (M+H), 370.0667; found, 370.0650.

#### 5.2.4. (4-Methoxyphenyl)-quinolin-2-yl-methanone (5e)

This was prepared from quinoline-2-carbonitrile and 4-bromoanisole in 98% yield. White solid; mp 87 °C (hexane/EtOAc); IR (KBr) $\nu$ 1659, 1605, 1328, 1257, 1164, 925, 773 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.34 (d, 1H, $J$ = 8.5 Hz), 8.29 (d, 2H, $J$ = 9.0 Hz), 8.21 (br d, 1H, $J$ = 8.4 Hz), 8.06 (d, 1H), 7.91 (br d, 1H), 7.79 (ddd, 1H, $J$ = 1.4 Hz, $J$ = 6.9 Hz), 7.66 (ddd, 1H), 7.00 (d, 2H), 3.90 (s, 3H); $^{13}$C ($CDCl_3$) $\delta$ 192.31, 163.83, 155.48, 146.74, 137.12, 134.01 (2C), 130.51, 130.12, 129.03, 128.86, 128.29, 127.74, 120.98, 113.63 (2C), 55.59. Anal. ($C_{17}H_{13}NO_2{\cdot}0.1H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{14}NO_2$ (M+H), 264.1025; found, 264.1018.

#### 5.2.5. (3-Methoxyphenyl)-quinolin-2-yl-methanone (5f)

This was prepared from quinoline-2-carbonitrile and 3-bromoanisole in 90% yield. White solid; mp 77 °C (hexane/EtOAc); IR (KBr) $\nu$ 1662, 1598, 1462, 1318, 1143, 760 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.34 (d, 1H, $J$ = 8.5 Hz), 8.20 (br d, 1H, $J$ = 8.5 Hz), 8.09 (d, 1H), 7.91 (br d, 1H, $J$ = 8.2 Hz), 7.80 (m, 3H), 7.66 (m, 1H), 7.41 (t, 1H, $J$ = 8.3 Hz), 7.18 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 193.50, 159.43, 154.76, 146.72, 137.37, 137.08, 130.52, 130.12, 129.14, 128.87, 128.42, 127.66, 124.44, 120.80, 119.78, 115.43, 55.45. Anal. ($C_{17}H_{13}NO_2$) C, H, N. HRMS (ESI$^+$) calcd for $C_{17}H_{14}NO_2$ (M+H), 264.1025; found, 264.1015.

#### 5.2.6. (2-Methoxyphenyl)-quinolin-2-yl-methanone (5g)

This was prepared from quinoline-2-carbonitrile and 2-bromoanisole in 96% yield. White solid; mp 93 °C (diisopropyl ether); IR (KBr) $\nu$ 1682, 1599, 1315, 1251, 921 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.28 (d, 1H, $J$ = 8.4 Hz), 8.09 (br d, 1H, $J$ = 8.5 Hz), 8.05 (d, 1H), 7.86 (dd, 1H, $J$ = 8.1 Hz, $J$ = 1.0 Hz), 7.70 (ddd, 1H, $J$ = 6.9 Hz), 7.65 (dd, 1H, $J$ = 7.5 Hz, $J$ = 1.7 Hz), 7.60 (ddd, 1H, $J$ = 1.2 Hz), 7.52 (ddd, 1H, $J$ = 8.3 Hz, $J$ = 7.5 Hz), 7.09 (td, 1H, $J$ = 0.9 Hz), 7.00 (d, 1H), 3.59 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 196.35, 158.96, 155.28, 147.27, 136.78, 133.05, 131.09, 130.71, 129.85, 129.15, 128.24, 128.18, 127.67, 120.63, 119.82, 112.03, 55.91. Anal. ($C_{17}H_{13}NO_2$) C, H, N.

HRMS (ESI$^+$) calcd for $C_{17}H_{14}NO_2$ (M+H), 264.1025; found, 264.1024.

#### 5.2.7. (4-Ethoxyphenyl)-quinolin-2-yl-methanone (5h)

This was prepared from quinoline-2-carbonitrile and 1-bromo-4-ethoxybenzene in 67% yield. White solid; mp 68 °C (diisopropyl ether); IR (KBr) ν 2983, 2943, 1657, 1605, 1275, 1257, 1163, 7.62 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.28 (m, 3H), 8.20 (br d, 1H, $J$ = 8.5 Hz), 8.04 (d, 1H, $J$ = 8.5 Hz), 7.88 (br d, 1H, $J$ = 8.1 Hz), 7.76 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.4 Hz), 7.63 (ddd, 1H, $J$ = 1.2 Hz), 6.97 (d, 2H, $J$ = 9.0 Hz), 4.12 (q, 2H, $J$ = 7.0 Hz), 1.44 (t, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.29, 163.26, 155.54, 146.72, 137.09, 134.00 (2C), 130.49, 130.09, 128.82, 128.80, 128.25, 127.73, 120.98, 114.06 (2C), 63.84, 14.78. Anal. ($C_{18}H_{15}NO_2$) C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{16}NO_2$ (M+H), 278.1181; found, 278.1179.

#### 5.2.8. (4-Propoxyphenyl)-quinolin-2-yl-methanone (5i)

This was prepared from quinoline-2-carbonitrile and 1-bromo-4-propoxybenzene in 87% yield. Beige crystals; mp 89 °C (hexane/EtOAc); IR (KBr) $\nu$ 2962, 2874, 1650, 1599, 1316, 1257, 1158, 780 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.33 (d, 1H, $J$ = 8.5 Hz), 8.27 (d, 2H, $J$ = 9.0 Hz), 8.21 (br d, 1H, $J$ = 8.4 Hz), 8.05 (d, 1H), 7.90 (dd, 1H, $J$ = 8.2 Hz, $J$ = 1.2 Hz), 7.78 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.5 Hz), 7.65 (ddd, 1H, $J$ = 1.2 Hz), 6.98 (d, 2H), 4.02 (t, 2H, $J$ = 6.6 Hz), 1.85 (sext, 2H), 1.06 (t, 3H, $J$ = 7.4 Hz); $^{13}$C ($CDCl_3$) $\delta$ 192.33, 163.49, 155.57, 146.75, 137.09, 134.01 (2C), 130.52, 130.10, 128.85, 128.77, 128.25, 127.74, 121.01, 114.10 (2C), 69.83, 22.55, 10.57. Anal. ($C_{19}H_{17}NO_2$) C, H, N. HRMS (ESI$^+$) calcd for $C_{19}H_{18}NO_2$ (M+H), 292.1338; found, 292.1333.

#### 5.2.9. (4-Isopropoxyphenyl)-quinolin-2-yl-methanone (5j)

This was prepared from quinoline-2-carbonitrile and 1-bromo-4-isopropoxybenzene in 64%. Pale yellow crystals; mp 66 °C (diisopropyl ether); IR (KBr) $\nu$ 2983, 2967, 1647, 1597, 1322, 1256, 1156, 774 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.31 (d, 1H, $J$ = 8.4 Hz), 8.26 (d, 2H, $J$ = 9.0 Hz), 8.20 (br d, 1H, $J$ = 8.2 Hz), 8.04 (d, 1H), 7.88 (dd, 1H, $J$ = 8.1 Hz, $J$ = 1.2 Hz), 7.77 (ddd, 1H, $J$ = 6.9 Hz), 7.63 (ddd, 1H, $J$ = 1.2 Hz), 6.96 (d, 2H), 4.68 (sept, 1H, $J$ = 6.1 Hz), 1.38 (d, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.24, 162.38, 155.57, 146.72, 137.08, 134.03 (2C), 130.49, 130.07, 128.82, 128.51, 128.22, 127.72, 120.98, 114.97 (2C), 70.15, 22.02 (2C). Anal. ($C_{19}H_{17}NO_2$) C, H, N. HRMS (ESI$^+$) calcd for $C_{19}H_{17}NO_2Na$ (M+Na), 314.1157; found, 314.1167.

#### 5.2.10. (4-Dimethylaminophenyl)-quinolin-2-yl-methanone (5k)

This was prepared from quinoline-2-carbonitrile and 4-bromo-*N*,*N*-dimethylaniline in 94% yield. Yellow needles; mp 120 °C (hexane/EtOAc); IR (KBr) $\nu$ 2909, 2821, 1632, 1590, 1371, 1330, 1157, 776 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.30 (d, 1H, $J$ = 8.2 Hz), 8.21 (m, 3H), 7.99 (d, 1H), 7.89 (dd, 1H, $J$ = 8.2 Hz, $J$ = 1.1 Hz), 7.77 (ddd, 1H, $J$ = 8.5 Hz, $J$ = 6.9 Hz), 7.63 (ddd, 1H, $J$ = 1.2 Hz), 6.71 (d, 2H, $J$ = 9.2 Hz), 3.09 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 191.73, 156.66, 153.74, 146.75, 136.84, 133.88 (2C), 130.40, 129.88, 128.61, 127.83, 127.69, 123.70, 121.09, 110.67 (2C), 40.09 (2C). Anal. ($C_{18}H_{16}N_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{17}N_2O$ (M+H), 277.1341; found, 277.1348.

#### 5.2.11. (2-Dimethylaminophenyl)-quinolin-2-yl-methanone (5l)

This was prepared from quinoline-2-carbonitrile and 2-bromo-*N*,*N*-dimethylaniline in 81% yield. Orange solid; 84 °C (diisopropyl ether); IR (KBr) $\nu$ 1655, 1596, 1558, 1501, 917 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.24 (d, 1H, $J$ = 8.5 Hz), 8.16 (br d, 1H, $J$ = 8.4 Hz), 7.95 (d, 1H), 7.85 (dd, 1H, $J$ = 8.1 Hz, $J$ = 1.0 Hz), 7.71 (ddd, 1H, $J$ = 6.9 Hz), 7.60 (ddd, 1H, $J$ = 1.2 Hz), 7.52 (dd, 1H, $J$ = 7.7 Hz, $J$ = 1.6 Hz), 7.43 (ddd, 1H, $J$ = 8.4 Hz, $J$ = 7.2 Hz), 7.03 (d, 1H), 6.91 (td, 1H, $J$ = 1.0 Hz), 2.69 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 196.90, 155.44, 152.85, 147.37, 136.55, 132.29, 132.01, 130.80, 129.86, 129.02, 128.42, 128.16, 127.57, 120.65, 118.89, 116.87, 43.79. Anal. ($C_{18}H_{16}N_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{18}H_{17}N_2O$ (M+H), 277.1341; found, 277.1348.

#### 5.2.12. (4-Chlorophenyl)-quinolin-2-yl-methanone (5m)

This was prepared from quinoline-2-carbonitrile and 4-bromochlorobenzene in 81%. White needles; mp 133 °C (hexane/EtOAc); IR (KBr) $\nu$ 1665, 1591, 1318, 1091, 924, 772 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.35 (d, 1H, $J$ = 8.4 Hz), 8.24 (d, 2H, $J$ = 8.6 Hz), 8.19 (br d, 1H, $J$ = 8.5 Hz), 8.13 (d, 1H), 7.91 (br d, 1H, $J$ = 8.1 Hz), 7.80 (ddd, 1H, $J$ = 1.3 Hz, $J$ = 6.9 Hz), 7.67 (ddd, 1H), 7.49 (d, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.41, 154.30, 146.75, 139.63, 137.32, 134.61, 133.02 (2C), 130.61, 130.30, 129.07, 128.71, 128.54, 127.77, 120.81. Anal. ($C_{16}H_{10}ClNO{\cdot}0.1\ H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{16}H_{11}ClNO$ (M+H), 268.0529; found, 268.0520.

#### 5.2.13. (3,4-Dichlorophenyl)-quinolin-2-yl-methanone (5n)

This was prepared from quinoline-2-carbonitrile and 4-bromo-1,2-dichlorobenzene in 64% yield. White solid; mp 146 °C (hexane/EtOAc); IR (KBr) $\nu$ 1670, 1584, 1313, 1295, 1166, 764 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.45 (d, 1H, $J$ = 2.0 Hz), 8.37 (d, 1H, $J$ = 8.4 Hz), 8.20 (br d, 1H, $J$ = 8.4 Hz), 8.15 (m, 2H), 7.92 (dd, 1H, $J$ = 8.2 Hz, $J$ = 1.1 Hz), 7.82 (ddd, 1H, $J$ = 6.9 Hz), 7.69 (ddd, 1H, $J$ = 1.2 Hz), 7.60 (d, 1H, $J$ = 8.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 191.12, 153.74, 146.77, 137.63, 137.48, 135.94, 133.53, 132.73, 130.70 (2C), 130.45, 130.30, 129.20, 128.97, 127.80, 120.74. Anal. ($C_{16}H_9Cl_2NO$) C, H, N. HRMS (ESI$^+$) calcd for $C_{16}H_{10}Cl_2NO$ (M+H), 302.0139; found, 302.0150.

#### 5.2.14. (4-Fluorophenyl)-quinolin-2-yl-methanone (5o)

This was prepared from quinoline-2-carbonitrile and 4-bromofluorobenzene in 93% yield. White needles; mp 131 °C (hexane/EtOAc); IR (KBr) ν 1664, 1598, 1506, 1322, 1236, 766 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.34 (m, 3H), 8.20 (br d, 1H, $J$ = 8.5 Hz), 8.12 (d, 1H, $J$ = 8.5 Hz), 7.92 (dd, 1H, $J$ = 1.1 Hz), 7.80 (ddd, 1H, $J$ = 6.9 Hz), 7.67 (ddd, 1H), 7.19 (t, 2H, $J$ = 8.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.10, 165.96 (d, 1C, $J$ = 253.7 Hz), 154.59, 146.75, 137.33, 134.36 (d, 2C, $J$ = 9.3 Hz), 132.58 (d, 1C, $J$ = 2.9 Hz), 130.59, 130.30, 129.04, 128.65, 127.79, 120.90, 115.41 (d, 2C, $J$ = 21.6 Hz). Anal. ($C_{16}H_{10}FNO{\cdot}0.1H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{16}H_{11}FNO$ (M+H), 252.0825; found, 252.0821.

#### 5.2.15. (3-Fluorophenyl)-quinolin-2-yl-methanone (5p)

This was prepared from quinoline-2-carbonitrile and 3-bromofluorobenzene in 98%. Pale yellow needles; mp 116 °C (hexane/EtOAc); IR (KBr) $\nu$ 1666, 1586, 1438, 1316, 768 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.36 (d, 1H, $J$ = 8.4 Hz), 8.21 (br d, 1H, $J$ = 8.3 Hz), 8.14 (d, 1H), 8.06 (td, 1H, $J$ = 1.2 Hz, $J$ = 7.9 Hz), 8.01 (ddd, 1H, $J$ = 2.6 Hz, $J$ = 9.7 Hz), 7.92 (dd, 1 h, $J$ = 1.0 Hz, $J$ = 8.2 Hz), 7.80 (ddd, 1H, $J$ = 1.5 Hz, $J$ = 6.9 Hz), 7.67 (ddd, 1H), 7.49 (td, 1H, $J$ = 5.6 Hz), 7.34 (tdd, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 192.28, 162.46 (d, 1C, $J$ = 245.1 Hz), 154.17, 146.79, 138.25 (d, 1C, $J$ = 6.7 Hz), 137.36, 130.68, 130.33, 129.81 (d, 1C, $J$ = 7.7 Hz), 129.11, 128.77, 127.77, 127.37 (d, 1C, $J$ = 2.9 Hz), 120.80, 120.07 (d, 1C, $J$ = 21.2 Hz), 118.35 (d, 1C, $J$ = 22.8 Hz). Anal. ($C_{16}H_{11}FNO{\cdot}0.1H_2O$) C, H, N. HRMS (ESI$^+$) calcd for $C_{16}H_{11}FNO$ (M), 252.0825; found, 252.0823.

#### 5.2.16. Isoquinolin-1-yl-phenyl-methanone (6a)

This was prepared from isoquinoline-1-carbonitrile and phenyl magnesium bromide in 94% yield. White solid; mp 81 °C (hexane/EtOAc); IR (KBr) $\nu$ 1665, 1450, 1252, 924, 711 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.60 (d, 1H, $J$ = 5.6 Hz), 8.22 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.9 Hz), 7.96 (m, 2H), 7.91 (br d, 1H, $J$ = 8.3 Hz), 7.80 (d, 1H), 7.73 (ddd, 1H, $J$ = 6.9 Hz), 7.60 (m, 2H), 7.47 (m, 2H); $^{13}$C NMR

($CDCl_3$) $\delta$ 194.79, 156.47, 141.21, 136.72, 136.67, 133.71, 130.79 (2C), 130.76, 128.51 (2C), 128.36, 127.15, 126.44, 126.17, 122.64. Anal. ($C_{16}H_{11}NO{\cdot}0.1H_2O$) C, H, N. HRMS ($ESI^+$) calcd for $C_{16}H_{11}NO$-Na (M+Na), 256.0738; found, 256.0732.

#### 5.2.17. Isoquinolin-1-yl-(4-trifluoromethylphenyl)-methanone (6b)

This was prepared from isoquinoline-1-carbonitrile and 4-bromobenzotrifluoride in 89% yield. White needles; mp 96 °C (hexane/EtOAc); IR (KBr) $\nu$ 1670, 1332, 1120, 1068, 926, 830 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.61 (d, 1H, $J$ = 5.6 Hz), 8.35 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.6 Hz), 8.08 (d, 2H, $J$ = 8.1 Hz), 7.94 (br d, 1H, $J$ = 8.3 Hz), 7.85 (d, 1H), 7.75 (m, 3H), 7.67 (ddd, 1H, $J$ = 7.00 Hz, $J$ = 1.2 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.58, 154.96, 141.17, 139.84, 136.98, 134.61 (q, $J$ = 32.6 Hz), 131.16 (2C), 130.99, 128.87, 127.32, 126.73, 126.10, 125.48 (q, 2C, $J$ = 13.8 Hz), 123.74 (q, $J$ = 271.1 Hz), 123.51. Anal. ($C_{17}H_{10}F_3NO$) C, H, N. HRMS ($ESI^+$) calcd for $Cg_{17}H_{10}F_3NONa$ (M+Na), 324.0612; found, 324.0624.

#### 5.2.18. Isoquinolin-1-yl-(2-trifluoromethylphenyl)-methanone (6c)

This was prepared from isoquinoline-1-carbonitrile and 2-bromobenzotrifluoride in 44% yield. Pale green crystals; mp 109 °C (hexane/EtOAc); IR (KBr) $\nu$ 1674, 1318, 1242, 1114, 924 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.01 (m, 1H), 8.51 (d, 1H, $J$ = 5.5 Hz), 7.90 (m, 1H), 7.81 (d, 1H), 7.74 (m, 3H), 7.62 (m, 2H), 7.55 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 197.05, 152.92, 141.21, 139.94, 137.05, 131.48, 130.75, 130.22, 129.58, 129.53, 128.12 (q, 1C, $J$ = 32.1 Hz), 127.22, 126.96, 126.61 (q, 1C, $J$ = 272.3 Hz), 126.57, 126.55 (q, 1C, $J$ = 4.5 Hz), 124.83. Anal. ($C_{17}H_{10}F_3NO$) C, H, N. HRMS ($ESI^+$) calcd for $C_{17}H_{11}F_3NO$ (M+H), 302.0793; found, 302.0785.

#### 5.2.19. (3,5-Bis-trifluoromethylphenyl)-isoquinolin-1-yl-methanone (6d)

This was prepared from isoquinoline-1-carbonitrile and 3,5-bis(trifluoromethyl) bromobenzene in 55% yield. White solid; mp 118 °C (hexane); IR (KBr) $\nu$ 1678, 1278, 1190, 1126, 681 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.63 (d, 1H, $J$ = 5.6 Hz), 8.49 (dd, 1H, $J$ = 8.6 Hz, $J$ = 0.8 Hz), 8.47 (br s, 2H), 8.10 (br s, 1H), 7.98 (br d, 1H, $J$ = 8.2 Hz), 7.91 (d, 1H), 7.81 (ddd, 1H, $J$ = 6.9 Hz), 7.73 (ddd, 1H, $J$ = 1.2 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 191.52, 153.34, 141.14, 138.91, 137.27, 132.05 (q, 2C, $J$ = 33.6 Hz), 131.21, 131.02 (q, 2C, $J$ = 3.4 Hz), 129.36, 127.51, 127.07, 126.40 (sept, $J$ = 3.6 Hz), 126.07, 124.43, 123.13 (q, 2C, $J$ = 271.3 Hz). Anal. ($C_{18}H_9F_6NO$) C, H, N. HRMS ($ESI^+$) calcd for $C_{18}H_{10}F_6NO$ (M+H), 370.0667; found, 370.0669.

#### 5.2.20. Isoquinolin-1-yl-(4-methoxyphenyl)-methanone (6e)

This was prepared from isoquinoline-1-carbonitrile and 4-bromoanisole in 93% yield. Pale yellow solid; mp 74 °C ($Et_2O$); IR (KBr) $\nu$ 1651, 1601, 1249, 1155, 1023, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.58 (d, 1H, $J$ = 5.6 Hz), 8.16 (br d, 1H, $J$ = 8.5 Hz), 7.94 (d, 2H, $J$ = 8.9 Hz), 7.89 (br d, 1H, $J$ = 8.3 Hz), 7.77 (d, 1H), 7.71 (br t, 1H, $J$ = 7.1 Hz), 7.58 (br t, 1H), 6.94 (d, 2H), 3.85 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.46, 164.19, 157.16, 141.26, 136.70, 133.22 (2C), 130.72, 129.60, 128.19, 127.11, 126.38, 126.33, 122.31, 113.87 (2C), 55.61. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 76.94; H, 4.86; N, 5.18. HRMS ($ESI^+$) calcd for $C_{17}H_{14}NO_2$ (M+H), 264.1025; found, 264.1023.

#### 5.2.21. Isoquinolin-1-yl-(3-methoxyphenyl)-methanone (6f)

This was prepared from isoquinoline-1-carbonitrile and 3-bromoanisole in 90% yield. Beige crystals; mp 59 °C (diisopropyl ether); IR (KBr) $\nu$ 1674, 1595, 1463, 1279, 1263, 747 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.60 (d, 1H, $J$ = 5.64 Hz), 8.20 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.8 Hz), 7.92 (br d, 1H, $J$ = 8.2 Hz), 7.80 (d, 1H), 7.75 (ddd, 1H, $J$ = 6.9 Hz), 7.62 (ddd, 1H, $J$ = 1.2 Hz), 7.58 (dd, 1H, $J$ = 2.5 Hz, $J$ = 1.5 Hz), 7.41 (td, 1H, $J$ = 7.6 Hz), 7.35 (t, 1H), 7.16 (ddd, 1H), 3.86 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 194.73, 159.85, 156.64, 141.32, 138.06, 136.79, 130.84, 129.58, 128.43, 127.22, 126.49, 126.26, 124.10, 122.68, 120.57, 114.41, 55.61. Anal. ($C_{17}H_{13}NO_2$) C, H, N. HRMS ($ESI^+$) calcd for $C_{17}H_{14}NO_2$ (M+H), 264.1025; found, 264.1012.

#### 5.2.22. Isoquinolin-1-yl-(4-dimethylaminophenyl)-methanone (6g)

This was prepared from isoquinoline-1-carbonitrile and 4-bromo-*N*,*N*-dimethylaniline in 54% yield. Pale green needles; mp 102 °C ($Et_2O$); IR (KBr) $\nu$ 3053, 2913, 1638, 1587, 1386, 1286, 1181, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.58 (d, 1H, $J$ = 5.7 Hz), 8.12 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.8 Hz), 7.87 (br d, 1H, $J$ = 8.3 Hz), 7.83 (d, 2H, $J$ = 9.1 Hz), 7.73 (d, 1H), 7.69 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.1 Hz), 7.55 (ddd, 1H), 6.63 (d, 2H), 3.04 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 192.97, 158.48, 154.01, 141.42, 136.60, 133.09 (2C), 130.55, 127.86, 126.99, 126.66, 126.35, 124.36, 121.66, 110.75 (2C), 40.09 (2C). Anal. ($C_{18}H_{16}N_2O$) C, H, N. HRMS ($ESI^+$) calcd for $C_{18}H_{17}N_2O$ (M+H), 277.1341; found, 277.1346.

#### 5.2.23. Isoquinolin-1-yl-(2-dimethylaminophenyl)-methanone (6h)

This was prepared from isoquinoline-1-carbonitrile and 2-bromo-*N*,*N*-dimethylaniline in 96% yield. Orange solid; mp 73 °C (diisopropyl ether); IR (KBr) $\nu$ 1661, 1593, 1489, 1284, 920 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.50 (d, 1H, $J$ = 5.6 Hz), 8.42 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.7 Hz), 7.89 (br d, 1H, $J$ = 8.3 Hz), 7.70 (m, 2H), 7.61 (ddd, 1H, $J$ = 7.0 Hz, $J$ = 1.2 Hz), 7.41 (m, 2H), 7.04 (d, 1H, $J$ = 8.2 Hz), 6.86 (td, 1H, $J$ = 7.9 Hz, $J$ = 0.9 Hz), 2.74 (s, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 196.42, 157.72, 153.15, 141.27, 136.76, 133.12, 132.57, 130.49, 129.25, 128.27, 127.07, 126.64, 126.47, 122.60, 119.12, 117.33, 44.05. Anal. ($C_{18}H_{16}N_2O$) C, H, N. HRMS ($ESI^+$) calcd for $C_{18}H_{17}N_2O$ (M+H), 277.1341; found, 277.1353.

#### 5.2.24. Isoquinolin-1-yl-(4-fluorophenyl)-methanone (6i)

This was prepared from isoquinoline-1-carbonitrile and 4-bromofluorobenzene in 86% yield. Beige crystals; mp 92 °C (hexane/EtOAc); IR (KBr) $\nu$ 1664, 1596, 1247, 1151, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.60 (d, 1H, $J$ = 5.6 Hz), 8.23 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.9 Hz), 8.01 (dd, 2H, $J$ = 9.0 Hz, $J$ = 5.5 Hz), 7.93 (br d, 1H, $J$ = 8.3 Hz), 7.82 (d, 1H), 7.76 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.1 Hz), 7.64 (ddd, 1H, $J$ = 1.2 Hz), 7.15 (t, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.14, 166.21 (d, $J$ = 254.3 Hz), 156.07, 141.19, 136.86, 133.63 (d, 2C, $J$ = 9.3 Hz), 133.13 (d, $J$ = 2.8 Hz), 130.89, 128.54, 127.24, 126.52, 126.19, 122.90, 115.75 (d, 2C, $J$ = 21.8 Hz). Anal. Calcd for $C_{16}H_{10}FNO$: C, 76.49; H, 4.01; N, 5.57. Found: C, 76.85; H, 3.85; N, 5.55. HRMS ($ESI^+$) calcd for $C_{16}H_{11}FNO$ (M+H), 252.0825; found, 252.0835.

#### 5.2.25. Isoquinolin-1-yl-(3-fluorophenyl)-methanone (6j)

This was prepared from isoquinoline-1-carbonitrile and 3-bromofluorobenzene in 92% yield. White crystals; mp 99 °C (hexane/EtOAc); IR (KBr) $\nu$ 1666, 1586, 1441, 1256, 1136, 871 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.61 (d, 1H, $J$ = 5.6 Hz), 8.26 (dd, 1H, $J$ = 8.5 Hz, $J$ = 0.9 Hz), 7.93 (br d, 1H, $J$ = 8.3 Hz), 7.83 (d, 1H), 7.75 (m, 2H), 7.69 (ddd, 1H, $J$ = 9.4 Hz, $J$ = 2.5 Hz, $J$ = 1.5 Hz), 7.64 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.2 Hz), 7.45 (td, 1H, $J$ = 8.1 Hz, $J$ = 5.5 Hz), 7.31 (tdd, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.37, 162.73 (d, 1C, $J$ = 246.2 Hz), 155.60, 141.22, 138.88 (d, 1C, $J$ = 6.5 Hz), 136.92, 130.95, 130.21 (d, 1C, $J$ = 7.6 Hz), 128.69, 127.31, 126.82 (d, 1C, $J$ = 3.1 Hz), 126.59, 126.15, 123.17, 120.74 (d, 1C, $J$ = 21.6 Hz), 117.44 (d, 1C, $J$ = 22.5 Hz). Anal. ($C_{16}H_{10}FNO$) C, H, N. HRMS ($ESI^+$) calcd for $C_{16}H_{11}FNO$ (M+H), 252.0825; found, 252.0837.

#### 5.2.26. Isoquinolin-1-yl-(4-chlorophenyl)-methanone (6k)

This was prepared from isoquinoline-1-carbonitrile and 4-chlorofluorobenzene in 98% yield. Pale yellow crystals; mp 103 °C (hex-

ane/EtOAc); IR (KBr) $\nu$ 1664, 1585, 1245, 1092, 922 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.59 (d, 1H, $J$ = 5.6 Hz), 8.25 (br d, 1H, $J$ = 8.5 Hz), 7.91 (m, 3H), 7.81 (d, 1H), 7.74 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 0.9 Hz), 7.63 (ddd, 1H, $J$ = 1.0 Hz), 7.44 (d, 2H, $J$ = 8.6 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 193.44, 155.70, 141.16, 140.22, 136.85, 135.13, 132.25 (2C), 130.89, 128.85 (2C), 128.60, 127.24, 126.54, 126.14, 123.04. Anal. ($C_{16}H_{10}ClNO$) C, H, N. HRMS ($ESI^+$) calcd for $C_{16}H_{11}ClNO$ (M+H), 268.0529; found, 268.0520.

#### 5.2.27. (3,4-Dichlorophenyl)-isoquinolin-1-yl-methanone (6l)

This was prepared from isoquinoline-1-carbonitrile and 4-bromo-1,2-dichlorobenzene in 83% yield. White solid; mp 147 °C (hexane/EtOAc); IR (KBr) $\nu$ 1666, 1557, 1248, 935, 756 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.61 (d, 1H, $J$ = 5.6 Hz), 8.30 (br d, 1H, $J$ = 8.6 Hz), 8.07 (d, 1H, $J$ = 2.0 Hz), 7.94 (br d, 1H, $J$ = 8.2 Hz), 7.86 (d, 1H), 7.82 (dd, 1H, $J$ = 8.4 Hz), 7.77 (ddd, 1H, $J$ = 6.9 Hz, $J$ = 1.1 Hz), 7.67 (ddd, 1H, $J$ = 1.2 Hz), 7.56 (d, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 192.26, 154.80, 141.16, 138.22, 136.99, 136.54, 133.15, 132.74, 131.01, 130.62, 129.93, 128.86, 127.34, 126.66, 126.07, 123.51. Anal. ($C_{16}H_9Cl_2NO$) C, H, N. HRMS ($ESI^+$) calcd for $C_{16}H_9Cl_2NONa$ (M+Na), 323.9959; found, 323.9967.

## Acknowledgments

This work was supported by the National Technology Agency of Finland and the Academy of Finland (Grant 110277). We are grateful to Mrs. Minna Glad for technical assistance.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.05.013.

## References and notes

1. Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. *Pharmacol. Rev.* **2002**, *54*, 161.
2. Mackie, K. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101.
3. Munro, S.; Thomas, K. L.; Abu-Shaar, M. *Nature* **1993**, *365*, 61.
4. Pertwee, R. G. *Pharmacol. Ther.* **1997**, *74*, 129.
5. Di Marzo, V.; Bifulco, M.; De Petrocellis, L. *Nat. Rev. Drug Disc.* **2004**, *3*, 771.
6. Fernández-Ruiz, J.; Romero, J.; Velasco, G.; Tolón, R. M.; Ramos, J. A.; Guzmán, M. *Trends Pharmacol. Sci.* **2007**, *28*, 39.
7. Sánchez, C.; de Ceballos, M. L.; Gómez del Pulgar, T.; Rueda, D.; Corbacho, C.; Velasco, G.; Galve-Roperh, I.; Huffman, J. W.; Ramón y Cajal, S.; Guzmán, M. *Cancer Res.* **2001**, *61*, 5784.
8. Caffarel, M. M.; Sarrió, D.; Palacios, J.; Guzmán, M.; Sánchez, C. *Cancer Res.* **2006**, *66*, 6615.
9. De Petrocellis, L.; Melck, D.; Palmisano, A.; Bisogno, T.; Laezza, C.; Bifulco, M.; Di Marzo, V. *Proc. Natl. Acad. Sci.* **1998**, *95*, 8375.
10. Malan, T. P., Jr.; Ibrahim, M. M.; Lai, J.; Vanderah, T. W.; Makriyannis, A.; Porreca, F. *Curr. Opin. Pharmacol.* **2003**, *3*, 62.
11. Iwamura, H.; Suzuki, H.; Ueda, Y.; Kaya, T.; Inaba, T. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 420.
12. Ofek, O.; Karsak, M.; Leclerc, N.; Fogel, M.; Frenkel, B.; Wright, K.; Tam, J.; Attar-Namdar, M.; Kram, V.; Shohami, E.; Mechoulam, R.; Zimmer, A.; Bab, I. *Proc. Natl. Acad. Sci.* **2006**, *103*, 696.
13. Kim, K.; Moore, D. H.; Makriyannis, A.; Abood, M. E. *Eur. J. Pharmacol.* **2006**, *542*, 100.
14. Ashton, J. C.; Wright, J. L.; McPartland, J. M.; Tyndall, J. D. *Curr. Med. Chem.* **2008**, *15*, 1428.
15. Poso, A.; Huffman, J. W. *Br. J. Pharmacol.* **2008**, *153*, 335.
16. Whitesides, G. T.; Lee, G. P.; Valenzano, K. J. *Curr. Med. Chem.* **2007**, *14*, 917.
17. Marriott, K. S.; Huffman, J. W. *Curr. Top. Med. Chem.* **2008**, *8*, 187.
18. Salo, O. M. H.; Raitio, K. H.; Savinainen, J. R.; Nevalainen, T.; Lahtela-Kakkonen, M.; Laitinen, J. T.; Järvinen, T.; Poso, A. *J. Med. Chem.* **2005**, *48*, 7166.
19. Canonne, P.; Foscolos, G. B.; Lemay, G. *Tetrahedron Lett.* **1980**, *21*, 155.
20. Savinainen, J. R.; Kokkola, T.; Salo, O. M. H.; Poso, A.; Järvinen, T.; Laitinen, J. T. *Br. J. Pharmacol.* **2005**, *145*, 636.
21. Savinainen, J. R.; Saario, S. M.; Niemi, R.; Järvinen, T.; Laitinen, J. T. *Br. J. Pharmacol.* **2003**, *140*, 1451.