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Synthesis of quinolinyl and isoquinolinyl phenyl ketones as novel agonists for the cannabinoid CB₂ receptor

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ABSTRACT

A series of quinolinyl and isoquinolinyl phenyl ketones was synthesized and their CB₂ receptor-dependent G-protein activities were determined using the [³⁵S]GTPγS binding assay. Both quinoline and isoquinoline derivatives exhibited similar CB₂ receptor agonist activity, the most potent ligands being the 2-(Me₂N)-phenyl substituted derivatives, which were also full agonists at the CB₂-receptor.

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1. Introduction

The CB₂ receptor is a seven-transmembrane-domain G-protein-coupled receptor.¹ It is part of the endocannabinoid system which consists of another cannabinoid receptor (CB₁), 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 CB₂ receptor was cloned in 1993.³ The CB₁ 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 CB₂ receptor is absent from the CNS and it is abundant in the immune system.⁵ More recent studies have suggested that CB₂ 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 CB₂ has increased. It has been shown that the expression of CB₂ receptors increases with the degree of malignancy in glial⁷ and breast⁸ 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 osteoporosis¹² or sclerosis.¹³ These observations have spurred wide spread interest in synthetic CB₂-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 CB₂ 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 [³⁵S]GTPγS G-protein activations assays showed that one of them acted as a selective CB₂ 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 CB₂ agonist properties and no sign of CB₁ 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

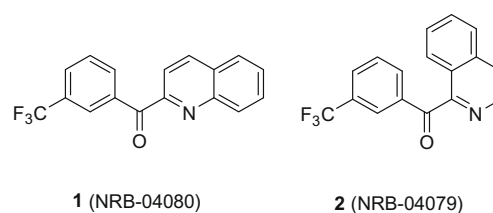
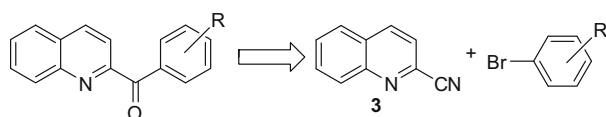
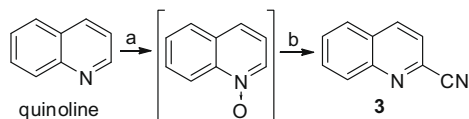


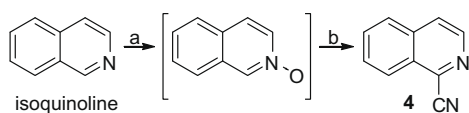
Figure 1. The structures of the hit compounds.



Scheme 1. Synthetic plan.



Scheme 2. Reagents and conditions: (a) *m*-CPBA, CH₂Cl₂, 2 h; (b) benzoyl chloride, KCN, MeOH, CH₃CN, overnight, 82% overall.



Scheme 3. Reagents and conditions: (a) *m*-CPBA, CH₂Cl₂, 2 h; (b) benzoyl chloride, KCN, MeOH, CH₃CN, 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 CB₂ receptor (hCB₂) via a [³⁵]GTPγS binding assay according to the procedure described by Savinainen et al.²⁰ The receptors used were hCB₂ 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 ana-

logue [³⁵]GTPγS. The relative efficacy responses of the molecules are expressed as percentage of the full (both CB₁ and CB₂) 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 EC₅₀ and E_{max} values were calculated by nonlinear regression analysis with the equation for a sigmoidal concentration–response curve (GRAPHPAD PRISM 4). The possible CB₁ receptor agonist and antagonism of all the compounds was screened at 10 μM concentration in rat cerebellar membranes as previously described²¹ to estimate the CB₂ 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

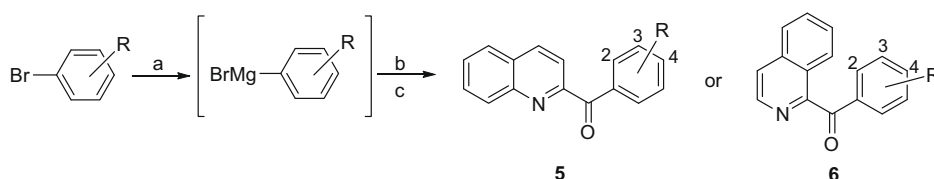
Both electron donating and electron withdrawing substituents were evaluated. Of the 4-substituted molecules, the best compound (**5k**, $-\log EC_{50} = 5.4$, $E_{max} = 62$) possesses an electron donating NMe₂ group. An electron-withdrawing 4-chloro substituent (**5m**) and electron-donating 4-methoxy substituent (**5e**) also maintain considerable relative activity, whereas electron-withdrawing 4-CF₃ (**5b**) and 4-F substituents (**5o**) showed weaker activity.

Moving the CF₃ group from the 4-position to the 3-position (**2**) led to slight improvement in CB₂ activity whereas introducing CF₃ 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 CB₂ efficacy and potency is even better when 4-NMe₂ 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 CB₂ activity.

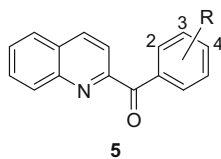
Elongation of the alkoxy group at the 4-position (**5h**, **5i** and **5j**) leads to loss of CB₂ activity. Those observations suggest that the binding area of the CB₂ receptor is not sensitive to the electronic nature of the compounds but more likely to the size and shape and is intolerant to steric bulk. This assertion is supported by the bis-functionalized molecules **5d** (3,5-CF₃) and **5n** (3,4-Cl) which lose almost all activity.

3.2. Isoquinolines

The 4-CF₃ analogue **6b** ($-\log EC_{50} = 5.5$, $E_{max} = 57$) seems to be equipotent with the 3-CF₃ hit **2** ($-\log EC_{50} = 5.3$, $E_{max} = 53$) but like in the quinoline series, the 2-CF₃ analogue **6c** has higher CB₂ potency and efficacy ($-\log EC_{50} = 6.3$, $E_{max} = 72$). A further 3-CF₃ 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, Et₂O.

Table 1CB₂ receptor activity data of the quinolinyl phenyl ketones^a

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-NMe₂ analogue **6h** has higher potency and efficacy (-log EC₅₀ = 6.2, E_{max} = 95) than the 4-NMe₂ analogue **6g** (-log EC₅₀ = 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 EC₅₀ >5.3 for the quinoline series; E_{max} >53, -log EC₅₀ >5.3 for the isoquinoline series). However, only compounds **5l**, **6h** and **5c** are full CB₂ agonists (respectively E_{max} = 91, 95 and 87). None of these compounds showed any significant CB₁ receptor activation.

In conclusion, the quinolinyl and isoquinolinyl phenyl ketones represent a new class of CB₂-selective receptor ligands, which revealed full or partial CB₂ cannabinoid receptor agonistic properties in the [³⁵S]-GTPγS binding assay. Both isoquinoline and quinoline derivatives showed more or less same efficacy and potency. The most potent ligands were the 2-NMe₂ substituted compounds (**5l** and **6h**).

5. Experimental

5.1. General methods

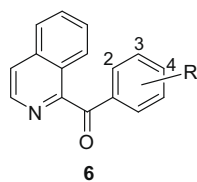
All reactions were carried out under an atmosphere of argon in flame-dried glassware. Non-aqueous reagents were transferred under argon via syringe or cannula and dried prior to use. THF was distilled from Na/benzophenone ketyl. CH₂Cl₂ and MeOH were dis-

tilled from CaH₂. 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 ¹H and ¹³C NMR spectra were recorded in a CDCl₃ solution on a Bruker Avance 400 (¹H 399.98 MHz; ¹³C 100.59 MHz) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (δ 0) for ¹H NMR. For the ¹³C NMR spectra, the signal for CDCl₃ (δ 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 CH₂Cl₂ was added *m*-CPBA (70% with water, 2.87 g, 11.6 mmol, 100 mol %) portionwise. After 2 h, the solution was dried with Na₂SO₄, 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 CH₂Cl₂ and washed twice with a solution of saturated NaHCO₃. The organic layer was dried over Na₂SO₄, 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. ¹H NMR (CDCl₃) δ 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
CB₂ receptor activity of the isoquinolinyl phenyl ketones^a



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. ¹H NMR (CDCl₃) δ 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 NH₄Cl. The organic layer was separated and extracted twice with CH₂Cl₂. After evaporation, the organic layer was redissolved in Et₂O (10 mL) and 1 M HCl (4 mL) was added. After 20 min, the organic layer was separated; the aqueous layer basified with saturated NaHCO₃ and then extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ 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) ν 1671, 1338, 1318, 1103, 777 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₀F₃NO·0.2H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₁F₃NO (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) ν 1678, 1315, 1161, 1126, 927, 771 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₀F₃NO·0.1H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₁F₃NO (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) ν 1668, 1285, 1148, 1127, 775 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₉F₆NO) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₀F₆NO (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) ν 1659, 1605, 1328, 1257, 1164, 925, 773 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₃NO₂·0.1H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₄NO₂ (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) ν 1662, 1598, 1462, 1318, 1143, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₃NO₂) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₄NO₂ (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) ν 1682, 1599, 1315, 1251, 921 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₃NO₂) C, H, N.

HRMS (ESI⁺) calcd for C₁₇H₁₄NO₂ (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; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₅NO₂) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₆NO₂ (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) ν 2962, 2874, 1650, 1599, 1316, 1257, 1158, 780 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₉H₁₇NO₂) C, H, N. HRMS (ESI⁺) calcd for C₁₉H₁₈NO₂ (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) ν 2983, 2967, 1647, 1597, 1322, 1256, 1156, 774 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₉H₁₇NO₂) C, H, N. HRMS (ESI⁺) calcd for C₁₉H₁₇NO₂Na (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) ν 2909, 2821, 1632, 1590, 1371, 1330, 1157, 776 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₆N₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₇N₂O (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; mp 84 °C (diisopropyl ether); IR (KBr) ν 1655, 1596, 1558, 1501, 917 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₆N₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₇N₂O (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-bromo-chlorobenzene in 81%. White needles; mp 133 °C (hexane/EtOAc); IR (KBr) ν 1665, 1591, 1318, 1091, 924, 772 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₆H₁₀ClNO·0.1 H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₁ClNO (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) ν 1670, 1584, 1313, 1295, 1166, 764 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₆H₉Cl₂NO) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₀Cl₂NO (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-bromo-fluorobenzene in 93% yield. White needles; mp 131 °C (hexane/EtOAc); IR (KBr) ν 1664, 1598, 1506, 1322, 1236, 766 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₆H₁₀FNO·0.1H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₁FNO (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-bromo-fluorobenzene in 98%. Pale yellow needles; mp 116 °C (hexane/EtOAc); IR (KBr) ν 1666, 1586, 1438, 1316, 768 cm⁻¹; ¹H NMR (CDCl₃) δ 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, 1H, *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); ¹³C NMR (CDCl₃) δ 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. (C₁₆H₁₁FNO·0.1H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₁FNO (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) ν 1665, 1450, 1252, 924, 711 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR

(CDCl₃) δ 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. (C₁₆H₁₁NO·0.1H₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₁NO-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) ν 1670, 1332, 1120, 1068, 926, 830 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₀F₃NO) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₀F₃NONa (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) ν 1674, 1318, 1242, 1114, 924 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₀F₃NO) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₀F₃NO (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) ν 1678, 1278, 1190, 1126, 681 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₀F₆NO) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₀F₆NO (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 (Et₂O); IR (KBr) ν 1651, 1601, 1249, 1155, 1023, 925 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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 C₁₇H₁₃NO₂: C, 77.55; H, 4.98; N, 5.32. Found: C, 76.94; H, 4.86; N, 5.18. HRMS (ESI⁺) calcd for C₁₇H₁₄NO₂ (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) ν 1674, 1595, 1463, 1279, 1263, 747 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₇H₁₃NO₂) C, H, N. HRMS (ESI⁺) calcd for C₁₇H₁₄NO₂ (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 (Et₂O); IR (KBr) ν 3053, 2913, 1638, 1587, 1386, 1286, 1181, 925 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₆N₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₇N₂O (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) ν 1661, 1593, 1489, 1284, 920 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₈H₁₆N₂O) C, H, N. HRMS (ESI⁺) calcd for C₁₈H₁₇N₂O (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) ν 1664, 1596, 1247, 1151, 925 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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 C₁₆H₁₀FNO: C, 76.49; H, 4.01; N, 5.57. Found: C, 76.85; H, 3.85; N, 5.55. HRMS (ESI⁺) calcd for C₁₆H₁₁FNO (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) ν 1666, 1586, 1441, 1256, 1136, 871 cm⁻¹; ¹H NMR (CDCl₃) δ 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); ¹³C NMR (CDCl₃) δ 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. (C₁₆H₁₀FNO) C, H, N. HRMS (ESI⁺) calcd for C₁₆H₁₁FNO (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) ν 1664, 1585, 1245, 1092, 922 cm^{-1} ; ^1H NMR (CDCl_3) δ 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) δ 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. ($\text{C}_{16}\text{H}_{10}\text{ClNO}$) C, H, N. HRMS (ESI⁺) calcd for $\text{C}_{16}\text{H}_{11}\text{ClNO}$ (M+H), 268.0529; found, 268.0520.

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

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) ν 1666, 1557, 1248, 935, 756 cm^{-1} ; ^1H NMR (CDCl_3) δ 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) δ 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. ($\text{C}_{16}\text{H}_9\text{Cl}_2\text{NO}$) C, H, N. HRMS (ESI⁺) calcd for $\text{C}_{16}\text{H}_9\text{Cl}_2\text{NONa}$ (M+Na), 323.9959; found, 323.9967.

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Supplementary data

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

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