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Microwave-assisted synthesis of quinoline, isoquinoline, quinoxaline and quinazoline derivatives as CB2 receptor agonists

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ABSTRACT

Quinoline, isoquinoline, quinoxaline, and quinazoline derivatives were synthesized using microwave-assisted synthesis and their CB1/CB2 receptor activities were determined using the [^{35}S]GTPγS binding assay. Most of the prepared quinoline, isoquinoline, and quinoxalinyl phenyl amines showed low-potency partial CB2 receptor agonists activity. The most potent CB2 ligand was the 4-morpholinylmethanone derivative (compound **40e**) (−log EC_{50} = 7.8; E_{max} = 75%). The isoquinolin-1-yl(3-trifluoromethyl-phenyl)amine (compound **26c**) was a high efficacy CB2 agonist (−log EC_{50} = 5.8; E_{max} = 128%). No significant CB1 receptor activation or inactivation was shown in these studies, except **40e**, which showed weak CB1 agonist activity (CB1 −log EC_{50} = 5.0). These ligands serve as novel templates for the development of selective CB2 receptor agonist.

1. Introduction

Recent research evidence has demonstrated the therapeutic potential for the selective CB2 receptor ligands. CB2 selective cannabinoids are expected to devoid of undesired CB1-mediated psychotropic side effects and would have therapeutic value in the pain relief, inflammation, osteoporosis, and in treating cancers. In recent years, structurally diverse CB2 selective agonists exhibiting analgesic activity in various pain models have been discovered and recently reviewed.[1–3] These CB2 selective agonists include tetrahydrocannabinol mimetics such as JWH-133 (**1**), which was shown to inhibit inflammatory and neuropathic pain.[4] AM1241 (**2**) is a widely studied CB2 agonist from the aminoalkylindole family, which has also shown efficacy in inflammatory and neuropathic pain models.[5,6] NESS400 is a CB2 selective pyrazolecarboxamide derivative,[7] which inhibits neuropathic pain through downregulation of microglial activation.[8] Many other chemically heterogeneous CB2 selective agonists have been developed recently. Representative examples of novel chemotypes include pyrimidinecarboxamide based structure **4** (GW842166X)[9] and 5-azaindole **5** (GSK554418A)[10] disclosed by GlaxoSmithKline. Other examples of recently published CB2 selective agonists are A-836339 (**6**) developed by Abbott Laboratories,[11] pyridine-based compounds by Adolor Corporation, (**7**)[12] and 3-amino-6-arylpyridazines (**8**) by GlaxoSmithKline[13] (Fig. 1).

Our previously reported CB2 agonist NRB04079 (isoquinolin-1-yl-[3-(trifluoromethyl)phenyl]-methanone, **9**) (Fig. 2) served as a lead structure in our search for more potent CB2 agonists.[14] NRB04079 was found in a molecular database search study using a CB2 receptor model and it act as a partial agonist at the human CB2 receptor (−log EC_{50} = 5.3; E_{max} = 53%). Later we found that *N*-phenyl-2-naphthylamine (**10**) (Fig. 2) show full CB2 agonist activity (−log EC_{50} = 5.2; E_{max} = 93%), which inspired us to synthesize diarylketone and -amine derivatives. In our previous paper, we discussed structure–activity relationships of quinolinyl and isoquinolinyl phenyl ketones as novel agonists for the cannabinoid CB2 receptor.[15] Here, we present series of quinolinyl, isoquinolinyl, quinoxalinyl, and quinazoline phenyl amines, phenylsulfanylquinolines and phenoxyquinolines, which were synthesized using microwave irradiation and their CB2 receptor-dependent G-protein activities were determined using the [^{35}S]GTPγS binding assay.

2. Results and discussion

2.1. Chemistry

In general, microwave-assisted synthesis was used in all coupling reactions of aryl amines and aryl halides to reduce reaction times and increase yields. The quinoline-, quinazoline- quinoxa-

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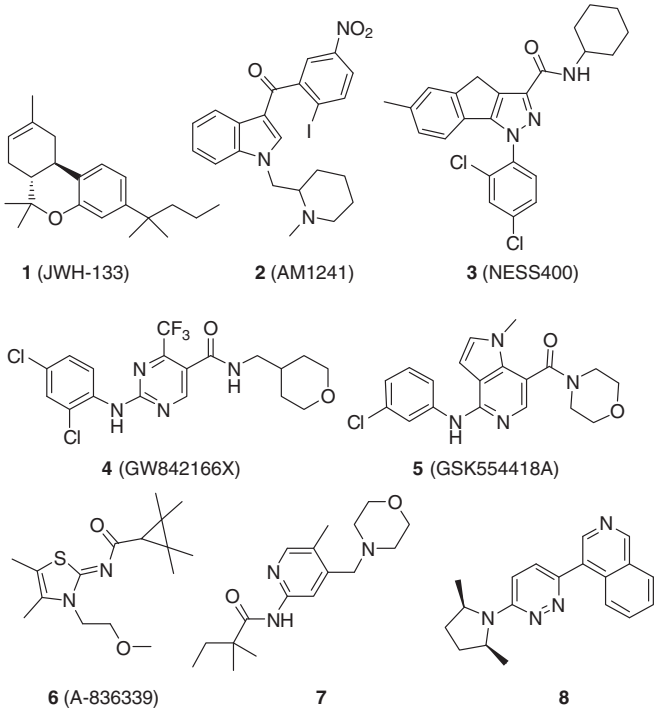


Figure 1. Structures of CB2 selective agonists.

line-, and isoquinolineamines were prepared by reacting chlorides (**17**, **13**, **15**, **17**, **19**, and **21**) with 4–5 equiv of amine under microwave irradiation without solvent (Scheme 1).

The 2-chloroquinazoline **15** was synthesized in two steps from commercially available 1*H*,3*H*-quinazoline 2,4-dione **23** by a modification of the previously published procedure.[16] The starting material was reacted with $POCl_3$ under microwave irradiation in *N*,*N*-diethylamine to provide 2,4-dichloroquinazoline **24**, which is then selectively reduced by activated zinc to yield 2-chloroquinazoline **15**[17] (Scheme 2).

The 4-chloroquinazoline **21** was prepared from 2-aminobenzonitrile **25**, which was first converted to quinazolin-4(3*H*)-one **26** by acid-catalyzed cyclization with formic acid under microwave irradiation.[18] Treatment of **26** under microwave irradiation with an excess amount of $POCl_3$ in *N*,*N*-diethylamine yielded the 4-chloroquinazoline **21**[19] (Scheme 3).

1-(Phenylamino)-isoquinoline-3-carboxylic acid derivatives (**32** and **33a–c**) were prepared from methyl 1-chloroisoquinoline-3-carboxylate **31**. 2-Formyl benzoic acid **27** was converted to its methyl ester **28** using methyl iodide under microwave irradiation. Oxazolone **29** was formed by condensation of hippuric acid with the methyl 2-formylbenzoate **28** under microwave irradiation applying the literature procedure.[20] Cyclization with KOH in MeOH again under microwave irradiation gave the methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate **30**, which on treatment with $POCl_3$ is chlorinated and aromatized to the methyl 1-chloroisoquinoline-3-carboxylate **31**.[21] The substitution reaction of **30** with

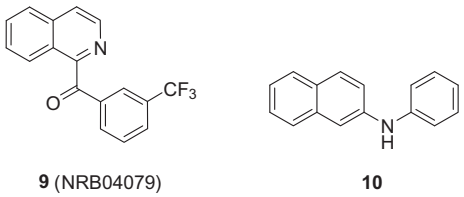
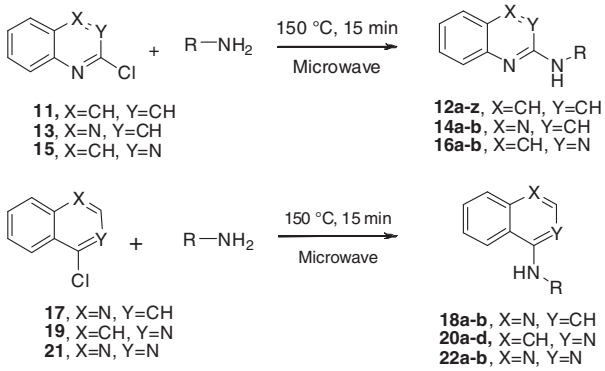
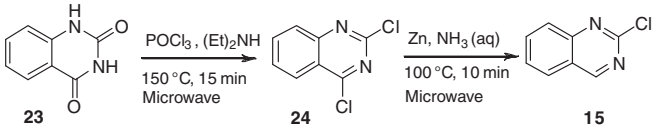


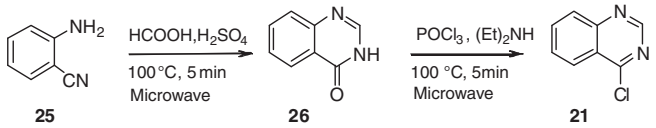
Figure 2. The chemical structures of the CB2 agonist lead structures.



Scheme 1. Synthesis of quinoline-, quinazoline- quinoxaline, and isoquinolineamines.



Scheme 2. Synthesis of 2-chloroquinazoline (**15**).



Scheme 3. Synthesis of 4-chloroquinazoline (**21**).

3-trifluoromethylaniline produced methyl 1-(phenylamino)-isoquinoline-3-carboxylate **32**, which was subjected to potassium *tert*-butoxide-induced aminolysis under microwave irradiation to yield the amides **33a–c** (Scheme 4).

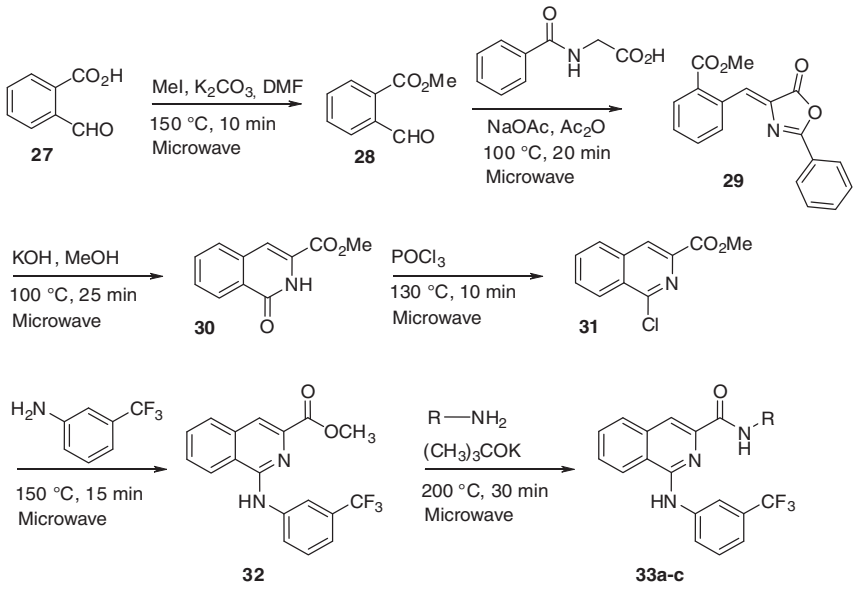
In case of 1-(3-trifluoromethylphenylamino)-isoquinoline-4-carboxamides (**40a–e**) synthetic route starts from the commercially available 4-bromoisoquinoline **34**, which was first oxidized to the corresponding *N*-oxide **35** with aqueous H_2O_2 in the presence of Na_2WO_4 and then treated with $POCl_3$ in DMF to give the 4-bromo-1-chloroisoquinoline **36**.[22] Lithiation of the remaining bromide **36** and subsequent quenching with dry ice delivers the 1-chloroisoquinoline-4-carboxylic acid **37**. The acid was treated with thionyl chloride to give substituted acid chloride **38**, which was further substituted with amines to yield 1-chloroisoquinoline-4-carboxamides **39a–e** which were treated with 3-trifluoromethylaniline to give the desired products **40a–e** (Scheme 5).

Phenylsulfanylquinolines (**41a** and **41e**), 1-phenylsulfanylquinoline **41e** (Scheme 6), 3-phenoxyquinoline **41b**, and 1-phenoxyisoquinoline **41d** (Scheme 7) were synthesized by microwave irradiation of haloquinoline with PhSNa or phenol at 150 °C for 15 min to give the desired products.[23]

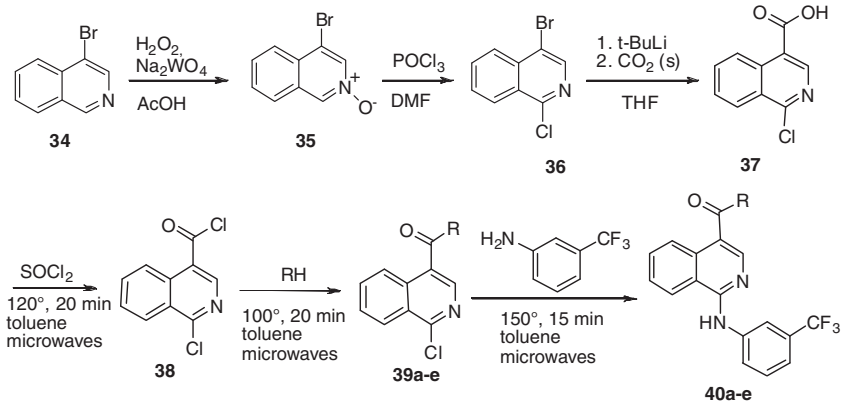
2.2. Biological testing

The quinoline-, quinazoline- quinoxaline-, and isoquinolineamines were tested for their capacity to induce G-protein activation of the human recombinant CB2 receptor (hCB2) via a [^{35}S]GTPγS binding assay according to the procedure described by Savinainen et al.[25] (Tables 1–4). The receptors used were hCB2 stably expressed in Chinese hamster ovary (CHO) cells.

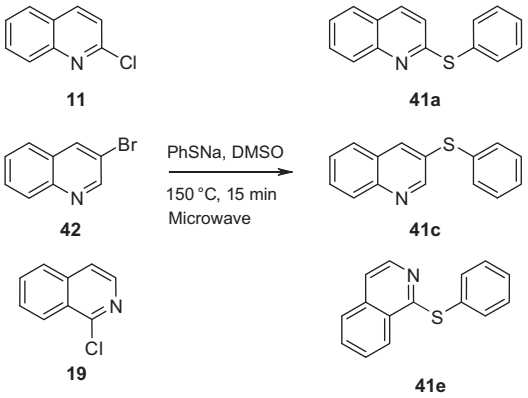
All the synthesized compounds were also screened at 10 μM concentration for their CB1 agonist activity and for their ability



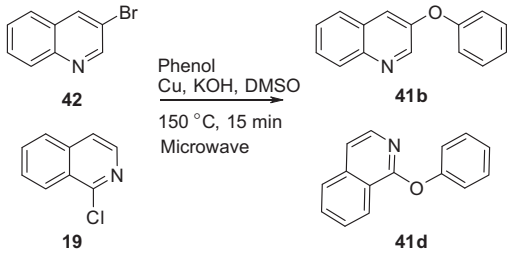
Scheme 4. Synthesis of 1-[3-(trifluoromethyl)phenylamino]-isoquinoline-3-carboxylic acid derivatives (**32** and **33a–c**).



Scheme 5. Synthesis of 1-[3-(trifluoromethyl)phenylamino]-isoquinoline-4-carboxamides (**40a–e**).



Scheme 6. Synthesis of phenylthioquinolines (**48a** and **48c**) and 1-(phenylthio)-isoquinoline **48e**.



Scheme 7. Synthesis of 3-phenoxyquinoline **41b** and 1-phenoxyisoquinoline **41d**.[24]

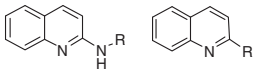
to antagonize agonist (10 nM HU-210) response in rat cerebellar membranes as previously described.[26] No significant CB1 receptor activation or inactivation was shown in these studies, except compound **40e**, which showed weak CB1 agonist activity (CB1 $-\log EC_{50} = 5.0$).

All the compounds were first evaluated for CB2 at 10 μM concentration. For the compounds that showed over 50% relative activity, the dose–response curves were generated and the $\log EC_{50}$ and E_{max} values were calculated by nonlinear regression analysis with the equation for a sigmoidal concentration–response curve (GraphPad Prism 4).

2.3. Results

In general the CF_3-, OMe-, and Cl-substituted phenyl quinoline amines showed partial or full agonist activity at the human CB2

Table 1
CB2 receptor activity data of the quinoline-2-amines (**12a–z**).

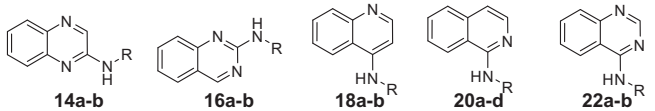


12a-x **12y, 12z**

Entry	R =	Yield	CB2 agonism at 10 μM[a,b]	Relative E_{max}[b]	−log EC_{50}
12a	Phenyl	49	39 ± 5	—	—
12b	Benzyl	42	20 ± 3	—	—
12c	2-CF_3-Phenyl	61	63 ± 4	103 ± 3	5.2 ± 0.1
12d	3-CF_3-Phenyl	42	64 ± 4	65 ± 3	5.9 ± 0.1
12e	4-CF_3-Phenyl	75	48 ± 1	—	—
12f	2-OMe-Phenyl	25	69 ± 4	102 ± 3	5.3 ± 0.1
12g	3-OMe-Phenyl	69	50 ± 3	61 ± 2	5.6 ± 0.1
12h	4-OMe-Phenyl	85	49 ± 4	51 ± 4	5.7 ± 0.2
12i	2-Cl-Phenyl	33	56 ± 2	91 ± 3	5.2 ± 0.1
12j	3-Cl-Phenyl	85	58 ± 3	70 ± 2	5.6 ± 0.1
12k	4-Cl-Phenyl	67	75 ± 5	80 ± 4	5.7 ± 0.1
12l	3-Br-Phenyl	58	64 ± 2	69 ± 3	5.7 ± 0.1
12m	3-CN-Phenyl	57	25 ± 2	—	—
12n	4-$(Me)_2N$-phenyl	87	20 ± 2	—	—
12o	4-OH-Phenyl	93	8 ± 1	—	—
12p	4-EtO_2C-Phenyl	44	3 ± 2	—	—
12q	4-$(HOCH_2CH_2)$-Phenyl	86	20 ± 2	—	—
12r	2-(Benzyl)phenyl	33	18 ± 4		
12s	2-MeO-4-CF_3-Phenyl	97	33 ± 3		
12t	Cyclohexyl	47	57 ± 3	88 ± 2	5.2 ± 0.1
12u	Cyclohexylmethyl	68	44 ± 1	—	—
12v	Cyclopentyl	65	22 ± 2	—	—
12x	*n*-Hexyl	79	10 ± 2	—	
12y	Ppiperidinyl	62	10 ± 2		—
12z	Morpholinyl	53	7 ± 1	—	—

[a] CB2 agonism at 10 μM ligand concentration. Values are mean ± SEM of at least three experiments performed in duplicate.
[b] Relative responses as percentage of the 10 nM HU-210 agonist response.

Table 2
CB2 receptor activity data of the quinoxalineamines (**14a–b**), quinazoline-2-amines (**16a–b**), quinoline-4-amines, (**18a–b**), isoquinoline-1-amines (**20a–d**), and quinazoline-4-amines (**22a–b**).



14a-b **16a-b** **18a-b** **20a-d** **22a-b**

Entry	R =	Yield	CB2 agonism at 10 μM[a,b]	Relative E_{max}[b]	−log EC_{50}
14a	Phenyl	95	30 ± 1	—	—
14b	3-CF_3-Phenyl	95	52 ± 3	69 ± 2	5.4 ± 0.1
16a	Phenyl	75	38 ± 3	—	—
16b	3-CF_3-Phenyl	91	53 ± 2	67 ± 2	5.5 ± 0.1
18a	Phenyl	96	9 ± 1	—	—
18b	3-CF_3-Phenyl	98	50 ± 3	58 ± 3	5.5 ± 0.1
20a	Phenyl	14	7 ± 1	—	—
20b	2-CF_3-Phenyl	42	43 ± 2	—	—
20c	3-CF_3-Phenyl	93	102 ± 2	124 ± 4	5.8 ± 0.1
20d	4-CF_3-Phenyl	53	25 ± 3	—	—
22a	Phenyl	61	10 ± 2	—	—
22b	3-CF_3-Phenyl	46	68 ± 6	79 ± 4	5.6 ± 0.1

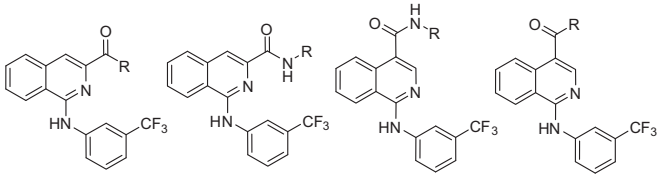
[a] CB2 agonism at 10 μM ligand concentration. Values are mean ± SEM of at least three experiments performed in duplicate.
[b] Relative responses as percentage of the 10 nM HU-210 agonist response.

receptor. The *ortho*-substituted quinoline 2-amines (**12c**, **12f**, **12i**, Table 1) had weak potency (−log EC_{50} = 5.2–5.3) but high efficacy (E_{max} = 91–103%). The most potent compound in this series was the meta CF_3-substituted amine **12d** with −log EC_{50} of 5.9.

Non-aromatic cycloalkyl and heteroalkyl derivatives were only weakly active or inactive, except cycloalkyl (**12t**), which showed good efficacy E_{max} = 88%) but low potency (−log EC_{50} = 5.2). Phenyl derivatives with large substituents (**12p–s**) had low efficacy. The substituted phenyl derivatives (**12c–l**) showed increased activity at 10 μM concentration when compared to the unsubstituted **12a**. Both electron withdrawing (CF_3) and electron donating (OMe) substituents had similar efficacy and potency. The data clearly indicates that, derivatives with polar residues (e.g., **12n–q**) show very low or no activity.

Of the quinazoline- quinoxaline-, and isoquinoline-amines, the CF_3-substituted ones were more potent than their parent compounds. The 3-CF_3-substituted analogues (**14b**, **16b**, **18b**, and **22b)** exhibited moderate partial agonist activity. Of the CF_3-substi-

Table 3
CB2 receptor activity data of 1-[(3-trifluoromethyl)-phenylamino]-isoquinoline-3-carboxylic acid derivatives (**32**, **33a–c**) and -isoquinoline-4-carboxylic acid derivatives (**40a–e**).

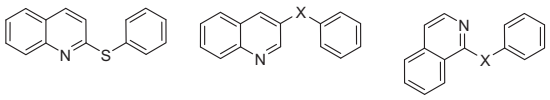


32 **33a-c** **40a-d** **40e**

Entry	R =	Yield	CB2 agonism at 10 μM)[a,b]	Relative E_{max}[b]	−log EC_{50}
32	MeO	73	4 ± 1	—	—
33a	Cyclohexylmethyl	47	−2 ± 2	—	—
33b	Cyclohexyl	95	13 ± 2	—	—
33c	Benzyl	55	0 ± 2	—	—
40a	Benzyl	53[c]	21 ± 4	—	—
40b	Cyclohexylmethyl	73[d]	58 ± 3	67 ± 2	5.8 ± 0.1
40c	Cyclohexyl	24[c]	54 ± 4	73 ± 4	5.7 ± 0.1
40d	2-MeO-Phenyl	18[c]	1 ± 1	—	—
40e		41[c]	76 ± 4	75 ± 1	7.8 ± 0.1

[a] CB2 agonism at 10 μM ligand concentration. Values are mean ± SEM of at least three experiments performed in duplicate.
[b] Relative responses as percentage of the 10 nM HU-210 agonist response.
[c] Yield for 3 steps from **37**.
[d] Yield from **39b**.

Table 4
Phenylsulfanyl-quinolines (**41a**, **41c**, **41e**) and phenoxyquinolines (**41b**, **41d**).



41a **41b** (X=O), **41c** (X=S) **41d** (X=O), **41e** (X=S)

Entry	Yield	CB2 agonism at 10 μM[a,b]	Relative E_{max}[b]	−log EC_{50}
41a	83	47 ± 3	61 ± 1	5.4 ± 0.1
41b	75	17 ± 1	—	—
41c	86	13 ± 1	—	—
41d	79	31 ± 4	—	—
41e	92	33 ± 4	—	—

[a] CB2 agonism at 10 μM ligand concentration. Values are mean ± SEM of at least three experiments performed in duplicate.
[b] Relative responses as percentage of the 10 nM HU-210 agonist.

tuted isoquinolineamines, the meta CF_3-substituted isoquinolinyl amine **20c** exhibited the highest efficacy with reasonable potency (E_{max} = 128%; −log EC_{50} = 5.8, Table 2).

The 3-substituted carboxamide derivatives (**33a–c**) were inactive, whereas 4-substituted cycloalkyl derivatives (**40b**, **40c**, and **40e**) were active (Table 3). However, the aromatic 2-MeO-phenyl-substituted analogue **40d** was inactive. The most potent analogue was 4-morpholinylmethanone **40e**, which showed nanomolar potency (−log EC_{50} = 7.8) and fairly good affinity (E_{max} = 75%). This is not surprising since the previously discovered potent and selective CB2 agonist **5** (GSK554418A) has similar morpholinylmethanone structure.

The unsubstituted phenylsulfanyl-quinoline **41a** exhibited moderate partial agonist activity. The phenoxyquinoline **41b** and the phenylsulfanyl-quinoline **41c** showed faint, and phenoxyisoquinoline **41d** and phenylsulfanyl-quinoline **41b** equipotent weak activation of CB2 (Table 4).

3. Conclusion

The purpose of this study was to determine both the affinity and agonist efficacy of novel heterocyclic diarylamines using ligand-induced [^{35}S]GTPγS binding assay at human CB2 and rat CB1 receptors. Most of the prepared quinoline, isoquinoline, quinaxolinyl, and quinoxalinyl phenyl amines showed low-potency partial CB2 receptor agonists activity. The isoquinolin-1-yl(3-trifluoromethylphenyl)amine **20c** and 4-morpholinylmethanone derivative **40e** appear to be the most promising ligands. The amine **20c** showed to be a high efficacy CB2 agonist (−log EC_{50} =5.8; E_{max} = 128%) and the derivative **40e** show considerable potency at CB2 (−log EC_{50} = 7.8; E_{max} = 75%). All the synthesized compounds were also screened at 10 μM concentration for their CB1 agonist activity and for their ability to antagonize agonist (10 nM HU-210) response in rat cerebellar membranes as previously described.[25] In this GTPγS binding assay we used non-recombinant membrane fractions from CB1 rat cerebellar membranes, which display 97% homology to corresponding human CB1. No significant CB1 receptor activation or inactivation was shown in these studies, except the most potent CB2 agonist **40e**, which also showed weak CB1 agonist activity (CB1 −log EC_{50} = 5.0), exhibiting 600-fold selectivity for the CB2 receptor. These ligands serve as novel templates for the development of selective CB2 receptor agonist.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance instrument operating at 500.1 and 25.8 MHz, respectively. Chemical shifts are reported as δ values (ppm) relative to an internal standard of tetramethylsilane (TMS) or to the solvent line of DMSO (δH = 2.50 ppm quintuplet, δC = 39.43 ppm septuplet). Electrospray ionization mass spectra were determined on Finnigan MAT LCQ quadrupole ion trap mass spectrometer. Elemental analyses were performed on ThermoQuest CE instrument (EA 1110 CHNS-O). The Biotage Initiator 2.0 was used for microwave-assisted synthesis. All chemicals and solvents were of commercial quality and were used without further purification. Most intermediate and end products were purified by flash chromatography using 30–60 μm silica gel and an appropriate eluent.

4.1.1. Phenyl-quinolin-2-yl-amine (12a)

A mixture of 2-chloroquinoline **17** (200 mg, 1.22 mmol) and aniline (455 mg, 4.89 mmol) was heated 15 min at 150 °C using microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with saturated Na_2CO_3 (2× 50 ml) and H_2O (2× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to leave a clear oil. This oil was purified by flash chromatography (silica gel) eluting with dichloromethane to give **12a** as a light brown solid (133 mg, 49%). ^{1}H NMR (DMSO-d_6): δ 9.39 (s, 1H); 8.05–7.99 (m, 3H); 7.72–7.68 (m, 2H); 7.59–7.55 (m, 1H); 7.34–7.27 (m, 3H); 7.07 (d, 1H, J = 8.9 Hz); 6.97–6.94 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 154.6; 147.4; 141.9; 137.3; 129.8; 129.0 (2C); 127.9; 126.8; 124.0; 123.1; 121.4; 118.8 (2C); 114.6. ESI-MS 221.2 (M+H). Anal. Calcd for $C_{15}H_{12}N_2{\cdot}0.1H_2O$: C, 81.13; H, 5.54; N, 12.61. Found: C, 81.26; H, 5.59; N, 12.69.

The following analogues (**12b–z**) were prepared using the procedure outlined for **12a** above.

4.1.2. Benzyl-quinolin-2-yl-amine (12b)

^{1}H NMR (DMSO-d_6): δ 7.85 (d, 1H, J = 8.9 Hz); 7.61–7.59 (m, 1H); 7.50–7.39 (m, 5H); 7.33–7.30 (m, 2H); 7.24–7.21 (m, 1H); 7.15–7.12 (m, 1H); 6.84 (d, 1H, J = 8.9 Hz); 4.65–4.64 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 157.2; 148.2; 140.8; 136.7; 129.4; 128.7 (2C); 128.0 (2C); 127.9; 126.1; 123.5: 121.6; 113.5; 44.3. ESI-MS 235.1 (M+H). Anal. Calcd for $C_{16}H_{14}N_2{\cdot}0.1H_2O$: C, 81.40; H, 6.06; N, 11.86. Found: C, 81.24; H, 6.13; N, 11.59.

4.1.3. Quinolin-2-yl-(2-trifluoromethyl-phenyl)-amine (12c)

^{1}H NMR (DMSO-d_6): δ 8.63 (s, 1H); 8.07 (d, 1H, J = 8.5 Hz); 7.92 (m, 1H); 7.73 (m, 2H); 7.68 (t, 1H, J = 7.8 Hz); 7.55–7.46 (m, 2H); 7.36 (t, 1H, J = 7.5 Hz); 7.27 (t, 1H, J = 7.2 Hz); 7.16 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 155.1; 146.8; 138.2; 137.3; 131.6; 129.3; 128.3; 127.4 (q, $^3J_{CF}$ = 5.2 Hz); 126.4; 126.1; 125.1; 124.5; 123.8; 122.9; 122.6; 120.5; 113.1. ESI-MS 289.1 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.1H_2O{\cdot}0.05$ hexane: C, 66.51; H, 4.07; N, 9.52. Found: C, 66.77; H, 4.23; N, 9.22.

4.1.4. Quinolin-2-yl-(3-trifluoromethyl-phenyl)-amine (12d)

^{1}H NMR (DMSO-d_6): δ 9.78 (s, 1H); 8.64 (s, 1H); 8.16 (d, 1H, J = 8.2 Hz); 8.11 (d, 1H, J = 8.9 Hz); 7.77 (d, 1H, J = 7.9 Hz); 7.71 (d, 1H, J = 8.2 Hz); 7.63–7.61 (m, 1H); 7.57–7.53 (m, 1H); 7.35–7.32 (m, 1H); 7.27 (d, 1H, J = 7.6 Hz); 7.09 (d, 1H, J = 8.9 Hz). ^{13}C NMR (DMSO-d_6): δ 153.8; 146.5; 142.1; 137.2; 129.5 (2C); 129.3 (q, $^2J_{CF}$ = 31.3 Hz); 127.5; 126.4; 124.3 (q, $^1J_{CF}$ = 270.0 Hz); 123.7; 123.1; 121.4; 116.8 (q, $^3J_{CF}$ = 3.7 Hz); 114.1(q, $^3J_{CF}$ = 4.0 Hz); 114.0. ESI-MS 289.1 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.15\ H_2O$: C, 66.05; H, 3.91; N, 9.63. Found: C, 66.25; H, 4.17; N, 9.24.

4.1.5. Quinolin-2-yl-(4-trifluoromethyl-phenyl)-amine (12e)

^{1}H NMR (DMSO-d_6): δ 9.83 (s, 1H); 8.22 (d, 2H, J = 8.6 Hz); 8.12 (d, 1H, J = 8.9 Hz); 7.77–7.76 (m, 2H); 7.66–7.60 (m, 3H); 7.36–7.32 (m, 1H); 7.12 (d, 1H, J = 8.9 Hz). ^{13}C NMR (DMSO-d_6): δ 153.6; 146.5; 144.9; 137.2; 129.5; 127.5; 126.5; 125.7 (q, 2C, $^3J_{CF}$ = 3.2 Hz); 124.6 (q, $^1J_{CF}$ = 270.7 Hz); 123.7; 123.1; 120.6 (q, $^2J_{CF}$ = 31.9 Hz); 117.7 (2C); 114.1. ESI-MS 289.2 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.1\ H_2O$: C, 66.25; H, 3.89; N, 9.66. Found: C, 66.12; H, 4.17; N, 9.29.

4.1.6. (2-Methoxy-phenyl)-quinolin-2-yl-amine (12f)

^{1}H NMR ($CDCl_3$): δ 8.72 (dd, 1H, J = 7.9, 1.5 Hz); 7.82 (m, 2H); 7.59–7.53 (m, 2H); 7.31–7.22 (m, 2H); 7.02 (td, 1H, J = 7.7, 1.5 Hz); 6.96 (td, 1H, J = 7.7, 1.5 Hz); 7.32 (dd, 1H, J = 8.0, 1.3 Hz); 6.85 (d, 1H, J = 8.8 Hz); 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 153.7; 148.2; 147.5; 137.1; 130.0; 129.5; 127.2; 126.9; 123.9; 122.9; 121.6; 120.9; 119.9; 118.7; 113.1; 55.5 (3C). ESI-MS 251.2 (M+H). Anal. Calcd for ($C_{16}H_{14}N_2O{\cdot}0.02$ toluene, based on ^{1}H NMR): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.88; H, 5.66; N, 11.11.

4.1.7. (3-Methoxy-phenyl)-quinolin-2-yl-amine (12g)

^{1}H NMR (DMSO-d_6): δ 9.42 (s, 1H); 8.02 (d, 1H, J = 8.8 Hz); 7.95 (t, 1H, J = 2.2 Hz); 7.71 (m, 2H); 7.58 (t, 1H, J = 8.3 Hz); 7.45 (d, 1H, J = 7.9 Hz); 7.28 (t, 1H, J = 7.9 Hz); 7.22 (t, 1H, J = 8.1 Hz); 7.09 (d, 1H, J = 8.8 Hz); 6.55 (ddd, 1H, J = 8.1, 2.4, 0.6 Hz); 3.82 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 153.7; 148.2; 147.5; 137.1; 130.0; 129.5; 127.2; 126.9; 123.9; 122.9; 121.6; 120.9; 118.7; 113.1; 109.9: 55.5 (3C). ESI-MS 251.3 (M+H). Anal. Calcd for ($C_{16}H_{14}N_2O{\cdot}0.1$ toluene, based on ^{1}H NMR): C, 77.29; H, 5.75; N, 10.79. Found: C, 77.11; H, 6.06; N, 10.98.

4.1.8. (4-Methoxy-phenyl)-quinolin-2-yl-amine (12h)

^{1}H NMR ($CDCl_3$): δ 7.85 (d, 2H, J = 8.8 Hz); 7.72 (d, 1H, J = 8.5 Hz); 7.61 (dd, 1H, J = 7.9, 1.0 Hz); 7.55 (m, 1H); 7.40 (m, 2H); 7.26 (m, 1H); 6.91(m, 2H); 6.85 (d, 1H, J = 8.8 Hz), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 156.4; 155.3; 147.2; 137.9; 132.7; 129.8; 127.4; 126.0; 124.0 (2C); 123.8; 122.8; 114.5 (2C); 110.9; 55.5 (3C). ESI-MS 251.3 (M+H). Anal. Calcd for ($C_{16}H_{14}N_2O{\cdot}0.03$ toluene, based on ^{1}H NMR): C, 76.94; H, 5.67; N, 11.07. Found: C, 77.29; H, 5.67; N, 11.28.

4.1.9. (2-Chloro-phenyl)-quinolin-2-yl-amine (12i)

^{1}H NMR (DMSO-d_6): δ 8.69 (s, 1H); 8.49 (d, 1H, J = 8.1 Hz); 8.07 (d, 1H, J = 8.8 Hz); 7.74 (d, 1H, J = 8.8 Hz); 7.64 (m, 1H); 7.56 (t, 1H, J = 8.0 Hz); 7.49 (dd, 1H, J = 7.9, 1.5 Hz); 7.36 (t, 1H, J = 8.0 Hz); 7.31 (d, 1H, J = 8.8 Hz); 7.30 (m, 1H); 7.07 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 154.0; 146.5; 137.1; 137.0; 129.2 (2C); 127.3; 127.1; 126.2; 124.1; 123.8; 123.3 (2C); 122.7; 113.8. ESI-MS 255.2 (M+H). Anal. Calcd for ($C_{15}H_{11}ClN_2$): C, 70.73; H, 4.35; N, 11.00. Found: C, 70.36; H, 4.29; N, 10.80.

4.1.10. (3-Chloro-phenyl)-quinolin-2-yl-amine (12j)

^{1}H NMR (DMSO-d_6): δ 9.**65** (s, 1H); 8.39 (t, 1H, J = 2.0 Hz); 8.10 (d, 1H, J = 8.8 Hz); 7.83 (dd, 1H, J = 8.2, 1.2 Hz); 7.75 (t, 1H, J = 8.1 Hz); 7.62 (m, 1H); 7.36 (d, 1H, J = 8.2 Hz); 7.33 (m, 1H); 7.10 (d, 1H, J = 8.8 Hz); 7.00 (dd, 1H, J = 7.9, 2.0 Hz). ^{13}C NMR (DMSO-d_6): δ 153.7; 146.5; 142.8; 137.0; 133.0; 130.0; 129.4; 127.4; 126.3; 123.6; 122.9; 120.2; 117.4; 116.5; 114.0. ESI-MS 255.2 (M+H). Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.57; H, 4.30; N, 10.79.

4.1.11. (4-Chloro-phenyl)-quinolin-2-yl-amine (12k)

^{1}H NMR ($CDCl_3$): δ 7.91 (d, 2H, J = 8.7 Hz); 7.79 (d, 1H, J = 8.4 Hz); 7.64 (dd, 1H, J = 8.0, 1.2 Hz); 7.61–7.56 (m, 3H); 7.33–7.28 (m, 3H); 6.88 (d, 1H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 153.7; 147.4; 138.8; 129.9; 129.1 (2C); 127.4; 126.8; 124.1; 123.4; 121.2 (2C); 111.9. ESI-MS 255.3 (M+H). Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 71.00; H, 4.32; N, 11.11.

4.1.12. (3-Bromo-phenyl)-quinolin-2-yl-amine (12l)

^{1}H NMR ($CDCl_3$): δ 7.91 (m, 2H); 7.81 (d, 1H, J = 8.4 Hz); 7.64 (dd, 1H, J = 8.0, 1.2 Hz); 7.59 (t, 1H, J = 8.4 Hz); 7.50–7.46 (m, 1H); 7.31 (t, 1H, J = 8.0 Hz); 7.33 (m, 1H); 7.18–7.15 (m, 2H); 6.89 (d, 1H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 153.5; 147.3; 141.7; 137.9; 130.3; 129.9; 127.4; 126.9; 125.5; 124.2; 123.6; 122.8; 122.5; 118.2; 112.1. ESI-MS 299.2 (M). Anal. Calcd for $C_{15}H_{11}BrN_2{\cdot}0.02$toluene: C, 60.41; H, 3.74; N, 9.31. Found: C, 60.73; H, 3.75; N, 9.25.

4.1.13. 3-(Quinolin-2-ylamino)-benzonitrile (12m)

^{1}H NMR (DMSO-d_6): δ 9.77 (s, 1H); 8.70 (t, 1H, J = 1.8 Hz); 8.16 (ddd, 1H, J = 8.4, 2.2, 1.0 Hz); 8.09 (dd, 1H, J = 8.8 Hz); 7.77 (t, 1H,

J = 8.5 Hz); 7.62 (t, 1H, J = 8.4 Hz); 7.52 (t, 1H, J = 7.9 Hz); 7.38–7.30 (m, 2H); 7.10 (d, 1H, J = 8.9 Hz). ^{13}C NMR (DMSO-d_6): δ 153.5; 146.4; 142.1; 137.1; 129.6; 129.3; 127.3; 126.4; 123.8; 123.6; 123.6; 123.0; 122.4; 120.4; 119.0; 113.9; 111.4. ESI-MS 246.3 (M+H). Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.60; H, 4.59; N, 16.98.

4.1.14. *N*,*N*-Dimethyl-*N*′-quinolin-2-yl-benzene-1,4-diamine (12n)

^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1H); 7.92 (d, 1H, J = 8.9 Hz); 7.77 (d, 2H, J = 9.0 Hz); 7.64 (dd, 1H, J = 7.9, 1.2 Hz); 7.61 (d, 1H, J = 8.4 Hz); 7.51 (t, 1H, J = 8.3 Hz); 7.20 (t, 1H, J = 8.0 Hz); 6.97 (d, 1H, J = 8.9 Hz); 6.76 (d, 2H, J = 9.0 Hz); 2.85 (s, 6H). ^{13}C NMR (DMSO-d_6): δ 154.5; 147.3; 145.8; 131.4; 129.0; 127.2; 125.8; 123.1; 121.7; 120.3 (2C); 113.6; 113.0 (2C); 40.6 (6C). ESI-MS 264.2 (M+H). Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.21; H, 6.47; N, 15.81.

4.1.15. 4-(Quinolin-2-ylamino)-phenol (12o)

^{1}H NMR (DMSO-d_6): δ 8.63 (s, 1H); 8.07 (d, 1H, J = 8.7 Hz); 7.92 (m, 1H); 7.80–7.60 (m, 3H); 7.55–7.45 (m, 2H); 7.36 (t, 1H, J = 7.6 Hz); 7.27 (t, 1H, J = 7.0 Hz); 7.16 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 155.1; 146.7; 138.1; 137.3; 132.8; 129.3; 127.4; 126.3; 126.1; 124.5; 123.8; 122.0 (2C); 113.1 (2C). ESI-MS 237.2 (M+H). Anal. Calcd for $C_{15}H_{12}N_2O{\cdot}0.1\ H_2O{\cdot}0.02$ EtOAc: C, 74.92; H, 5.31; N, 11.35. Found: C, 74.88; H, 5.47; N, 10.99.

4.1.16. 4-(Quinolin-2-ylamino)-benzoic acid ethyl ester (12p)

^{1}H NMR ($CDCl_3$): δ 8.05 (d, 2H, J = 8.7 Hz); 7.97 (d, 1H, J = 8.8 Hz); 7.85 (d, 1H, J = 8.4 Hz); 7.76 (d, 2H, J = 8.6 Hz); 7.67 (d, 1H, J = 8.0 Hz); 7.62 (t, 1H, J = 7.7 Hz); 7.35 (t, 1H, J = 7.5 Hz); 7.06 (bs, 1H); 6.96 (d, 1H, J = 8.8 Hz); 4.37 (q, 2H, J = 7.1 Hz); 1.39 (q, 3H, J = 7.1 Hz). ^{13}C,NMR ($CDCl_3$): δ 166.4 (C═O); 153.0; 147.3; 144.7; 137.9; 131.0 (2C); 129.9; 127.4; 127.2; 124.4; 123.8; 123.7; 117.8 (2C); 112.7; 60.6; 14.4. ESI-MS 293.2 (M+H). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.86; H, 5.50; N, 9.69,

4.1.17. 2-[4-(Quinolin-2-ylamino)-phenyl]-ethanol (12q)

^{1}H NMR ($CDCl_3$): δ 7.87 (d, 2H, J = 8.9 Hz); 7.75 (d, 1H, J = 8.3 Hz); 7.62 (d, 1H, J = 8.0 Hz); 7.57 (t, 1H, J = 8.4 Hz); 7.44 (d, 2H, J = 8.3 Hz); 7.28 (t, 1H, J = 7.9 Hz); 7.20 (d, 2H, J = 8.3 Hz); 6.93 (d, 1H, J = 8.9 Hz); 3.86 (t, 2H, J = 6.5 Hz); 2.85 (t, 2H, J = 6.5 Hz). ^{13}C,NMR ($CDCl_3$): δ 154.5; 147.3; 138.3; 137.8; 133.6; 129.9; 129.8 (2C); 127.4; 126.2; 124.0; 123.1; 121.2 (2C); 111.5; 63.5: 38.6. ESI-MS 265.2 (M+H). Anal. Calcd for $C_{17}H_{16}N_2O{\cdot}0.1H_2O{\cdot}0.4$EtOAc: C, 74.13; H, 6.49; N, 9.30. Found: C, 73.74; H, 6.25; N, 9.55.

4.1.18. (2-Benzyl-phenyl)-quinolin-2-yl-amine (12r)

^{1}H NMR (DMSO-d_6): δ 8.66 (s, 1H); 7.98 (d, 1H, J = 8.8 Hz); 7.87 (dd, 1H, J = 8.0, 1.0 Hz); 7.68 (dd, 1H, J = 8.0, 1.0 Hz); 7.58 (d, 1H, J = 8.4 Hz); 7.51 (t, 1H, J = 8.4 Hz); 7.28–7.18 (m, 4H); 7.18–7.03 (m, 4H); 4.10 (m, 2H). ^{13}C,NMR (DMSO-d_6): δ 155.2; 147.1; 140.3; 138.3; 136.8; 134.6; 130.0; 129.1; 128.7 (2C); 128.1 (2C); 127.3; 126.4; 125.9; 125.7; 124.3; 123.8; 123.5; 122.0; 112.9; 36.7. ESI-MS 311.3 (M+H). Anal. Calcd for $C_{22}H_{18}N_2{\cdot}0.07H_2O$: C, 84.79; H, 5.87; N, 8.99. Found: C, 84.70; H, 5.85; N, 8.80.

4.1.19. (2-Methoxy-5-trifluoromethyl-phenyl)-quinolin-2-yl-amine (12s)

^{1}H NMR (DMSO-d_6): δ 9.49 (d, 1H, J = 2.2 Hz); 8.81 (s, 1H); 8.09 (d, 1H, J = 8.9 Hz); 7.76 (dd, 1H, J = 8.0, 1.0 Hz); 7.68 (d, 1H, J = 8.6 Hz); 7.62 (t, 1H, J = 8.3 Hz); 7.45 (d, 1H, J = 8.9 Hz); 7.36–7.30 (m, 2H); 7.20 (d, 1H, J = 8.4 Hz); 4.00 (s, 3H). ^{13}C,NMR (DMSO-d_6): δ 153.8; 150.6 (q, $^5J_{CF}$ = 1.4 Hz); 146.6; 136.8; 130.4; 129.4; 127.3; 126.2; 124.7 (q, $^2J_{CF}$ = 271.1 Hz); 123.7; 123.0; 120.9 (q, $^2J_{CF}$ = 31.7 Hz); 118.1 (q, $^3J_{CF}$ = 4.4 Hz); 115.2 (q, $^3J_{CF}$ = 3.9 Hz); 114.7; 110.2; 55.9. ESI-MS 319.2 (M+H). Anal. Calcd for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12; N, 8.80. Found: C, 63.99; H, 4.46; N, 8.59.

4.1.20. Cyclohexyl-quinolin-2-yl-amine (12t)

^{1}H NMR (DMSO-d_6): δ 7.78 (d, 1H, J = 8.9 Hz); 7.56 (dd, 1H, J = 7.8, 0.9 Hz); 7.46 (d, 1H, J = 8.1 Hz); 7.42 (t, 1H, J = 8.1 Hz); 7.10 (t, 1H, J = 7.9 Hz); 6.82 (bd, 1H, J = 7.6 Hz); 6.74 (d, 1H, J = 8.9 Hz); 3.95 (m, 1H); 2.01–1.94 (m, 2H); 1.78–1.70 (m, 2H); 1.65–1.58 (m, 1H); 1.43–1.31 (m, 2H); 1.29–1.17 (m, 3H). ^{13}C,NMR (DMSO-d_6): δ 156.2; 147.9; 135.9; 128.7; 127.2; 125.4; 122.6; 120.7; 113.2; 48.2; 32.5 (2C); 25.5 (2C); 24.6. ESI-MS 227.2 (M+H). Anal. Calcd for $C_{15}H_{18}N_2{\cdot}0.1H_2O$: C, 78.98; H, 8.04; N, 12.28. Found: C, 79.36; H, 8.28; N, 11.93.

4.1.21. Cyclohexylmethyl-quinolin-2-yl-amine (12u)

^{1}H NMR (DMSO-d_6): δ 7.78 (d, 1H, J = 8.9 Hz); 7.56 (dd, 1H, J = 7.8, 0.9 Hz); 7.47 (d, 1H, J = 8.2 Hz); 7.42 (t, 1H, J = 8.2 Hz); 7.10 (t, 1H, J = 7.9 Hz); 6.92 (bt, 1H, J = 5.5 Hz); 6.78 (d, 1H, J = 8.9 Hz); 3.25 (t, 2H, J = 6.1 Hz); 1.85–1.75 (m, 2H); 1.75–1.55 (m, 4H); 1.30–1.10 (m, 3H); 1.05–0.90 (m, 2H). ^{13}C,NMR (DMSO-d_6): δ 157.1; 147.9; 135.8; 128.7; 127.3; 125.4: 122.7; 120.7; 113.1; 46.8; 37.2; 30.7 (2C); 26.1; 25.5 (2C). ESI-MS 241.2 (M+H). Anal. Calcd for $C_{16}H_{20}N_2{\cdot}0.12\ H_2O$: C, 79.24; H, 8.41; N, 11.55. Found: C, 79.47; H, 8.61; N, 11.16.

4.1.22. Cyclopentyl-quinolin-2-yl-amine (12v)

^{1}H NMR (DMSO-d_6): δ 7.86 (d, 1H, J = 8.9 Hz); 7.62 (d, 1H, J = 7.9 Hz); 7.58 (d, 1H, J = 8.3 Hz); 7.42 (bs, 1H); 7.48 (t, 1H, J = 8.0 Hz); 7.17 (t, 1H, J = 7.3 Hz); 6.81 (d, 1H, J = 8.9 Hz); 4.38 (m, 1H); 2.00 (m, 2H); 1.71 (m, 2H); 1.65–1.45 (m, 4H). ESI-MS 213.2 (M+H). Anal. Calcd for $(C_{14}H_{16}N_2{\cdot}0.3H_2O{\cdot}0.1$ EtOAc: C, 76.36; H, 7.74; N, 12.37. Found: C, 76.39; H, 7.67; N, 12.24.

4.1.23. Hexyl-quinolin-2-yl-amine (12x)

^{1}H NMR (DMSO-d_6): δ 7.78 (d, 1H, J = 8.9 Hz); 7.57 (d, 1H, J = 7.9 Hz); 7.48 (d, 1H, J = 8.0 Hz); 7.43 (t, 1H, J = 8.0 Hz); 7.11 (t, 1H, J = 8.0 Hz); 6.91 (bt, 1H, J = 5.1 Hz); 6.74 (d, 1H, J = 8.9 Hz); 3.38 (q, 2H, J = 7.1, 5.5 Hz); 1.59 (p, 2H, J = 7.2 Hz); 1.42–1.24 (m, 6H); 0.88 (t, 6H, J = 7.1 Hz). ^{13}C,NMR (DMSO-d_6): δ 156.9; 147.8; 135.7; 128.6; 127.2; 125.4; 122.6; 120.7; 112.9; 40.3; 31.0; 28.8; 26.2; 22.0; 13.8. ESI-MS 229.2 (M+H). Anal. Calcd for $C_{15}H_{20}N_2{\cdot}0.147H_2O$: C, 78.00; H, 8.86; N, 12.13. Found: C, 78.40; H, 9.09; N, 11.73.

4.1.24. 2-Piperidin-1-yl-quinoline (12y)

^{1}H NMR (DMSO-d_6): δ 7.97 (d, 1H, J = 9.1 Hz); 7.65 (d, 1H, J = 7.9 Hz); 7.54 (d, 1H, J = 7.8 Hz); 7.49 (t, 1H, J = 8.3 Hz); 7.21–7.15 (m, 2H); 3.70 (m, 4H); 1.70–1.50 (m, 6H). ^{13}C,NMR (DMSO-d_6): δ 156.8; 147.3; 137.0; 129.0; 127.1; 125.7; 122.3; 121.4; 109.9; 45.4 (2C); 25.1 (2C); 24.3. ESI-MS 213.3 (M+H). Anal. Calcd for $C_{14}H_{16}N_2{\cdot}0.1\ H_2O$: C, 78.54; H, 7.63; N, 13.08. Found: C, 78.80; H, 7.75; N, 12.75.

4.1.25. 2-Morpholin-4-yl-quinoline (12z)

^{1}H NMR (DMSO-d_6): δ 8.04 (d, 1H, J = 9.1 Hz); 7.70 (d, 1H, J = 8.0 Hz); 7.59 (d, 1H, J = 7.9 Hz); 7.53 (t, 1H, J = 8.3 Hz); 7.25–7.19 (m, 2H); 3.74 (m, 4H); 3.65 (m, 4H). ^{13}C,NMR (DMSO-d_6): δ 157.0; 147.0; 137.2; 129.2; 127.2; 126.0; 122.8; 122.0; 109.7; 65.9 (2C); 44.9 (2C). ESI-MS 215.2 (M+H). Anal. Calcd for $C_{13}H_{14}N_2O{\cdot}0.05H_2O{\cdot}0.01$EtOAc: C, 72.49; H, 6.62; N, 12.37. Found: C, 72.82; H, 6.84; N, 12.57.

The following analogues (**18a–b**) were prepared using the procedure outlined for **12a** above (**23** as starting material)

4.1.26. Phenyl-quinolin-4-yl-amine (18a)

^{1}H NMR (DMSO-d_6): δ 8.97 (br, 1H); 8.45 (d, 1H, $^3J_{HH}$ = 5.2 Hz); 8.40–8.39 (m, 1H); 7.88 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 7.71–7.68 (m, 1H); 7.54–7.51 (m, 1H); 7.44–7.37 (m, 4H); 7.16–7.13 (m, 1H); 6.94 (d, 1H, $^3J_{HH}$ = 5.2 Hz). ^{13}C,NMR (DMSO-d_6): δ 150.5; 148.8; 147.7; 140.5; 129.2 (2C); 129.1; 129.0; 124.5; 123.6; 122.3; 122.0; 119.7; 101.4. ESI-MS 221.2 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.1$ H_2O: C, 81.13; H, 5.54; N, 12.61. Found: C, 81.15; H, 5.47; N, 12.37.

4.1.27. Quinolin-4-yl-(3-trifluoromethyl-phenyl)-amine (18b)

^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H); 8.55 (d, 1H, $^3J_{HH}$ = 4.3 Hz); 8.37–8.35 (m, 1H); 7.93 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 7.74–7.55 (m, 5H); 7.41 (d, 1H, $^3J_{HH}$ = 7.7 Hz); 7.10–9.09 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 156.4; 151.1; 140.2; 134.7; 131.3 (q, $^2J_{CF}$ = 32.1 Hz); 129.4 (2C); 127.5; 126.4; 125.4; 124.4; 124.2 (q, $^1J_{CF}$ = 272.3 Hz); 121.8 (q, $^5J_{CF}$ = 1.3 Hz); 121.1; 118.9 (q, $^3J_{CF}$ = 3.8 Hz); 115.6 (q, $^3J_{CF}$ = 4.0 Hz). ESI-MS 289.2 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}$ $0.1H_2O$: C, 66.25; H, 3.89; N, 9.66. Found: C, 66.57; H, 4.02; N, 9.32.

The following analogues (**20a–d**) were prepared using the procedure outlined for **12a** above (**19** as starting material).

4.1.28. Isoquinolin-1-yl-phenyl-amine (20a)

^{1}H NMR (DMSO-d_6): δ 9.13 (s, 1H); 8.54 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.99–7.98 (m, 1H); 7.91–7.88 (m, 2H); 7.81 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.72–7.69 (m, 1H); 7.63–7.60 (m, 1H); 7.33–7.30 (m, 2H); 7.17 (d, 1H, $^3J_{HH}$ = 5.8 Hz); 7.00–6.97 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 152.6; 141.2; 140.5; 136.9; 129.9; 128.1 (2C); 126.7; 126.1; 123.2; 121.2; 120.3; 120.2; 118.5; 112.4. ESI-MS 221.2 (M+H). Anal. Calcd for $C_{15}H_{12}N_2{\cdot}0.1$ H_2O: C, 81.13; H, 5.54; N, 12.61. Found: C, 81.18; H, 5.77; N, 12.28.

4.1.29. Isoquinolin-1-yl-(2-trifluoromethyl-phenyl)-amine (20b)

^{1}H NMR ($CDCl_3$): δ 8.43 (d,1H, $^3J_{HH}$ = 7.9 Hz); 8.10 (bd, 1H, $^3J_{HH}$ = 4.6 Hz); 7.87 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 7.77 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.70–7.63 (m, 2H); 7.61–7.51 (m, 2H); 7.20 (d, 1H, $^3J_{HH}$ = 5.5 Hz); 7.13 (t, 1H, $^3J_{HH}$ = 7.6 Hz). ESI-MS 289.1 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.1H_2O{\cdot}0.13$ hexane: C, 66.90; H, 4.36; N, 9.30. Found: C, 67.12; H, 4.73; N, 8.94.

4.1.30. Isoquinolin-1-yl-(3-trifluoromethyl-phenyl)-amine (20c)

^{1}H NMR (DMSO-d_6): δ 9.46 (s, 1H); 8.56 (d, 1H, $^3J_{HH}$ = 8.6 Hz); 8.38–8.37 (m, 1H); 8.27–8.25 (m, 1H); 8.06 (d, 1H, $^3J_{HH}$ = 5.8 Hz); 7.86 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 7.76–7.73 (m, 1H); 7.67–7.64 (m, 1H); 7.56–7.52 (m, 1H); 7.29–7.25 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 152.1; 142.0; 140.2; 136.9; 130.1; 129.2; 129.1 (q, $^2J_{CF}$ = 31.3 Hz); 126.8; 126.3; 124.3 (q, $^1J_{CF}$ = 272.2 Hz); 123.2; 123.1; 118.5 (2C); 117.3 (q, $^3J_{CF}$ = 3.8 Hz); 115.7 (q, $^3J_{CF}$ = 4.3 Hz); 113.4. ESI-MS 289.2 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}0.1$ H_2O: C, 66.25; H, 3.89; N, 9.66. Found: C, 66.62; H, 4.29; N, 9.33.

4.1.31. Isoquinolin-1-yl-(4-trifluoromethyl-phenyl)-amine (20d)

^{1}H NMR (DMSO-d_6): δ 9.51 (br, 1H, 9.51); 8.56 (d, 1H, 3JHH = 8.5 Hz); 8.15 (m, 2H); 8.07 (d, 1H, $^3J_{HH}$ = 5.7 Hz); 7.86 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 7.74 (t, 1H, $^3J_{HH}$ = 7.5 Hz); 7.70–7.60 (m, 3H); 7.29 (d, 1H, $^3J_{HH}$ = 5.7 Hz). ^{13}C NMR (DMSO-d_6): δ 151.9; 145.0; 140.2; 137.0; 130.2; 126.8; 126.4; 125.4 (q, 2C, $^3J_{CF}$ = 3.9 Hz); 124.6 (q, $^1J_{CF}$ = 270.7 Hz); 123.3; 121.0 (q, $^2J_{CF}$ = 31.3 Hz); 119.2 (2C); 118.8; 113.7. ESI-MS 289.2 (M+H). Anal. Calcd for $C_{16}H_{11}F_3N_2{\cdot}$ $0.15H_2O$: C, 66.05; H, 3.91; N, 9.63. Found: C, 66.40; H, 4.29; N, 9.37.

4.1.32. 3H-Quinazolin-4-one (26)

A mixture of 2-cyanoaniline **25** (300 mg, 2.53 mmol), formic acid (175 mg, 3.80 mmol) and sulfuric acid (373 mg, 3.80 mmol) was heated 5 min at 100 °C using Biotage Initiator microwave synthesizer. Saturated Na_2CO_3 (50 ml) was added to the resulting reaction mixture and then extracted with CH_2Cl_2 (3× 50 ml) and EtOAc (3× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:2 to give **26** (235 mg, 64%). ^{1}H NMR (DMSO-d_6): δ 12.26 (bs, 1H); 8.16 (dd, 1H, J = 7.9, 1.2 Hz); 8.12 (s, 1H); 7.82 (t, 1H, J = 7.6 Hz); 7.69 (d, 1H, J = 7.8 Hz); 7.54 (t, 1H, J = 7.5 Hz). ^{13}C NMR (DMSO-d_6): δ 161.2; 149.2; 145.8; 134.6; 127.6; 127.1; 126.3; 123.1.

4.1.33. 4-Chloro-quinazoline (21)

26 (230 mg, 1.57 mmol) was heated with $POCl_3$ (362 mg, 2.36 mmol) and *N,N*-diethylamine (1.0 ml) 10 min at 100 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with HCl (1 M) (3× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:10 to give **21** (187 mg, 72%). ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1H); 8.18 (dd, 1H, J = 7.9, 0.9 Hz); 7.87 (t, 1H, J = 7.6 Hz); 7.77 (d, 1H, J = 8.1 Hz); 7.59 (t, 1H, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6): δ 160.0; 146.5; 145.6; 134.6; 127.2; 126.0; 125.0; 122.0.

The following analogues (**22a–b**) were prepared using the procedure outlined for **12a** above (**21** as starting material).

4.1.34. Phenyl-quinazolin-4-yl-amine (22a)

^{1}H NMR (DMSO-d_6): δ 9.81 (s, 1H); 8.64 (s, 1H); 8.60 (d, 1H, $^3J_{HH}$ = 7.9 Hz); 7.92 (d, 2H, $^3J_{HH}$ = 7.7 Hz); 7.87–7.80 (m, 2H); 7.63 (t, 2H, $^3J_{HH}$ = 8.2 Hz); 7.41 (m, 2H); 7.15 (t, 1H, $^3J_{HH}$ = 7.4 Hz); 7.17 (d, 1H, $^3J_{HH}$ = 5.8 Hz). ^{13}C NMR (DMSO-d_6): δ 158.3; 154.9; 150.2: 139.7; 133.3; 128.8 (2C); 128.2; 126.5; 124.1; 123.4: 122.9 (2C); 115.706. ESI-MS 222.3 (M+H). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.85; H, 5.16; N, 18.66.

4.1.35. Quinazolin-4-yl-(3-trifluoromethylphenyl)-amine (22b)

^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H); 8.72 (s, 1H); 8.61 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 8.40 (s, 1H); 8.31 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 7.92–7.82 (m, 2H); 7.68 (t, 2H, $^3J_{HH}$ = 8.2 Hz); 7.63 (t, 1H, $^3J_{HH}$ = 794 Hz); 7.45 (d, 1H, $^3J_{HH}$ = 7.7 Hz). ^{13}C NMR (DMSO-d_6): δ 157.4; 154.0; 149.6; 140.1; 132.9; 129.3; 129.2 (q, $^2J_{CF}$ = 31.5 Hz); 127.8; 126.2; 125.2; 124.1 (q, $^1J_{CF}$ = 272.4 Hz); 122.8; 119.3 (q, $^3J_{CF}$ = 4.2 Hz); 117.8 (q, $^3J_{CF}$ = 4.2 Hz); 115.0. ESI-MS 290.2 (M+H). Anal. Calcd for $C_{15}H_{10}F_3N_2$: C, 62.29; H, 3.48; N, 14.53. Found: C, 62.58; H, 3.52; N, 14.26.

4.1.36. 2,4-Dichloro-quinazoline (24)

A mixture of 1H,3H-quinazoline 2,4-dione **23** (1.00 g, 6.15 mmol), $POCl_3$ (2.83 g, 18.5 mmol) and *N,N*-diethylamine (3.0 ml) was heated 15 min at 150 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (100 ml) and washed with H_2O (2× 100 ml) and saturated Na_2CO_3 (2× 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:20 to give **24** (754 mg, 62%). ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, J = 8.4 Hz); 8.02–8.00 (m, 2H); 7.75 (m, 1H).

4.1.37. 2-Chloro-quinazoline (15)

A mixture of **24** (900 mg, 0.502 mmol), Zn-powder (900 mg, 1.53 mmol), saturated NaCl with 9% NH_3 (2 ml) and CH_2Cl_2 (2 ml) was heated 15 min at 100 °C using microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (100 ml) and washed with HCl (1 M) (2× 100 ml) and H_2O (2× 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:10 to give **15** (82 mg, 13%). ^{1}H

NMR ($CDCl_3$): δ 9.31 (s, 1H); 8.02–7.95 (m, 3H); 7.70 (t, 1H, J = 7.4 Hz); 7.77 (d, 1H, J = 8.1 Hz); 7.59 (t, 1H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 163.0; 157.6; 151.9; 135.5; 128.3; 127.6; 127.3; 123.4.

The following analogues (**16a–b**) were prepared using the procedure outlined for **12a** above.

4.1.38. Phenyl-quinazolin-2-yl-amine (16a)

^{1}H NMR ($CDCl_3$): δ 9.08 (s, 1H); 7.82 (m, 2H); 7.76–7.70 (m, 3H); 7.57 (bs, 1H); 7.38 (m, 2H); 7.33 (m, 1H); 7.07 (t, 1H, $^3J_{HH}$ = 7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 161.9; 156.8; 151.4; 139.6; 134.4; 128.9 (2C); 127.4; 126.3; 123.8; 122.6; 120.8; 119.1 (2C). ESI-MS 222.3 (M+H). Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.17; H, 5.11; N, 18.83.

4.1.39. Quinazolin-2-yl-(3-trifluoromethylphenyl)-amine (16b)

^{1}H NMR ($CDCl_3$): δ 9.12 (s, 1H); 8.29 (s, 1H); 7.93 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 7.81–7.74 (m, 3H); 7.72 (bs, 1H); 7.46 (t, 1H, $^3J_{HH}$ = 7.9 Hz); 7.38 (m, 1H); 7.30 (d, 1H, $^3J_{HH}$ = 7.7 Hz). ^{13}C NMR ($CDCl_3$): δ 162.1; 156.4; 151.1; 140.2; 134.7; 131.3 (q, $^2J_{CF}$ = 31.5 Hz); 129.4; 127.5; 126.4; 124.4; 124.2 (q, $^1J_{CF}$ = 272.4 Hz); 121.8 (q, $^5J_{CF}$ = 1.4 Hz); 121.1; 118.9 (q, $^3J_{CF}$ = 3.7 Hz); 115.6 (q, $^3J_{CF}$ = 4.2 Hz). ESI-MS 290.2 (M+H). Anal. Calcd for $C_{15}H_{10}F_3N_3$: C, 62.29; H, 3.48; N, 14.53. Found: C, 62.40; H, 3.70; N, 14.43.

The following analogues (**14a–b**) were prepared using the procedure outlined for **12a** above (**13** as starting material).

4.1.40. *N*-Phenylquinoxalin-2-amine (14a)

^{1}H NMR (DMSO-d_6): δ 9.94 (s, 1H); 8.58 (s, 1H); 8.01 (m, 2H); 7.86 (dd, 1H, $^3J_{HH}$ = 8.1, 1.1 Hz); 7.74 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 7.65 (t, 1H, $^3J_{HH}$ = 8.3 Hz); 7.47 (t, 1H, $^3J_{HH}$ = 8.2 Hz); 7.39 (m, 2H). 7.04 (t, 1H, $^3J_{HH}$ = 7.3 Hz). ^{13}C NMR (DMSO-d_6): δ 149.6; 140.5; 140.5; 140.3; 136.7; 129.8; 128.7 (2C); 128.3; 126.3; 124.8; 121.8; 118.5 (2C); 118.4. ESI-MS 222.2 (M+H). Anal. Calcd for $C_{14}H_{11}N_3 \cdot 0.1\ H_2O \cdot 0.06$ hexane: C, 75.57; H, 5.32; N, 18.41. Found: C, 75.71; H, 5.34; N, 18.05.

4.1.41. *N*-3-(Trifluoromethylphenyl)quinoxalin-2-amine (14b)

^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H); 8.60 (s, 1H); 8.54 (s, 1H); 7.18 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 7.90 (dd, 1H, $^3J_{HH}$ = 8.2, 1.1 Hz); 7.75 (dd, 1H, $^3J_{HH}$ = 8.2, 1.0 Hz); 7.69 (t, 1H, $^3J_{HH}$ = 8.2 Hz); 7.61 (t, 1H, $^3J_{HH}$ = 8.0 Hz). 7.52 (t, 1H, $^3J_{HH}$ = 8.2 Hz): 7.36 (d, 1H, $^3J_{HH}$ = 7.7 Hz). ^{13}C NMR (DMSO-d_6): δ 149.3; 141.1; 140.4; 140.1; 137.0; 130.2; 129.9; 129.5 (q, $^2J_{CF}$ = 31.2 Hz); 128.5; 126.5; 125.4; 124.2 ($^1J_{CF}$ = 272.1 Hz); 121.9; 117.9 (q, $^3J_{CF}$ = 3.9 Hz); 114.4 (q, $^3J_{CF}$ = 4.4 Hz). ESI-MS 290.2 (M+H). Anal. Calcd for $C_{15}H_{10}F_3N_3 \cdot 0.1H_2O \cdot 0.08$EtOAc: C, 61.73; H, 3.67; N, 14.10. Found: C, 61.86; H, 3.27; N, 13.69.

4.1.42. Methyl 2-formylbenzoate (28)

A mixture of **27** (100 mg, 0.666 mmol), MeI (189 mg, 1.33 mmol), K_2CO_3 (55 mg, 0.400 mmol), and DMF (0.5 ml) was heated 10 min at 150 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with HCl (1 M, 3× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:10 to give **28** (104 mg, 95%). ^{1}H NMR (DMSO-d_6): δ 10.42 (s, 1H); 7.94–7.85 (m, 2H), 7.80–7.75 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 192.8 (CHO); 166.9 (CO_2Me); 136.7; 133.7; 132.8; 132.4; 130.2; 128.8; 53.1.

4.1.43. Methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate (30)

A mixture of **28** (1.63 g, 9.93 mmol), hippuric acid (2.13 g, 11.9 mmol), NaOAc (977 mg, 11.9 mmol), and Ac_2O (10 ml) was heated 20 min at 100 °C using microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (100 ml) and washed with saturated Na_2CO_3 (2× 100 ml) and H_2O (2× 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude (*Z*)-methyl 2-[(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)-methyl]-benzoate **29** was used in the next step without purification. A mixture of the crude **29** (3.05 g, 9.92 mmol) from the previous step, KOH (1.11 g, 19.8 mmol) and MeOH (10 ml) was heated 25 min at 100 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (100 ml) and washed with saturated Na_2CO_3 (2× 100 ml) and H_2O (2× 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:5 to 1:1 to give **30** (1.53 g, 76% calculated from **28**). ^{1}H NMR (DMSO-d_6): δ 10.70 (s, 1H); 8.25 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 7.80–7.68 (m, 2H), 7.54 (t, 1H, $^3J_{HH}$ = 8.1 Hz); 6.82 (s, 1H), 3.20 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 162.5; 136.8; 135.3; 132.94; 127.5; 127.4; 127.1; 126.5; 112.4; 105.7; 49.9.

4.1.44. Methyl 1-chloroisoquinoline-3-carboxylate (31)

A mixture of **30** (594 mg, 2.92 mmol) and $POCl_3$ (3 ml, 32.8 mmol) was heated 10 min at 130 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (100 ml) and washed with HCl (1 M, 3× 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:3 to give **31** (585 mg, 90%). ^{1}H NMR (DMSO-d_6): δ 8.59 (s, 1H); 8.27 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 8.23 (d, 1H, $^3J_{HH}$ = 7.3 Hz); 7.94 (m, 2H); 3.99 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 163.9; 150.1; 139.3; 136.6; 132.0; 131.2; 128.7; 127.1; 125.4; 124.0; 52.2.

4.1.45. Methyl 1-[3-(trifluoromethyl)phenylamino]-isoquinoline-3-carbo-xylate (32)

A mixture of **31** (200 mg, 0.902 mmol) and 3-trifluoromethylanilin**e** (582 mg, 3.61 mmol) was heated 15 min at 150 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with saturated Na_2CO_3 (2× 50 ml) and H_2O (2× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with CH_2Cl_2 to give **32** (229 mg, 73%). ^{1}H NMR (DMSO-d_6): δ 9.62 (s, 1H); 9.03 (s, 1H); 8.69 (d, 1H, $^3J_{HH}$ = 7.2 Hz); 8.31 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 8.06 (s, 1H), 8.03 (m, 1H); 7.79 (m, 2H); 7.54 (t, 1H, $^3J_{HH}$ = 7.9 Hz); 7.31 (d, 1H, $^3J_{HH}$ = 7.7 Hz); 3.94 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 166.2; 152.1; 142.3; 139.0; 136.9; 131.1; 129.9 (q, $^2J_{CF}$ = 31.2 Hz); 129.4; 129.1 (2C); 124.9 (q, $^1J_{CF}$ = 272.5 Hz); 123.7; 123.3; 120.4; 118.0 (q, $^3J_{CF}$ = 3.5 Hz); 116.8; 116.5 (q, $^3J_{CF}$ = 3.5 Hz); 52.4. ESI-MS 347.1 (M+H). Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09. Found: C, 62.35; H, 3.71; N, 8.11.

4.1.46. *N*-(Cyclohexylmethyl)-1-[3-(trifluoromethyl)-phenylamino]-isoquinoline-3-carboxamide (33a)

A mixture of **32** (145 mg, 0.419 mmol), cyclohexanemethylamine (285 mg, 2.51 mmol) and potassium *tert*-butoxide (94 mg, 0.837 mmol) was heated 60 min at 250 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with saturated Na_2CO_3 (2× 50 ml) and H_2O (2× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:5 to give **33a** (85 mg, 47%). ^{1}H NMR (DMSO-d_6): δ 9.70 (s, 1H); 8.59 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 8.16 (s, 1H); 8.09 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 8.06 (d, 1H, $^3J_{HH}$ = 8.0 Hz); 8.97 (m, 2H); 7.79 (m, 2H); 7.82 (t, 1H, $^3J_{HH}$ = 7.5 Hz); 7.77 (t, 1H, $^3J_{HH}$ = 8.2 Hz); 7.58 (t, 1H, $^3J_{HH}$ = 7.9 Hz); 7.39 (d, 1H, $^3J_{HH}$ = 7.7 Hz); 3.19 (t, 2H, $^3J_{HH}$ = 8.3 Hz); 1.72–1.54 (m,

5H); 1.50 (m, 1H), 1.29–1.10 (m, 3H); 1.00–0.88 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 163.0; 151.1; 141.3; 140.8; 137.0; 130.7; 129.3; 129.2 (q, $^2J_{CF}$ = 31.4 Hz); 128.4; 127.8; 124.2 (q, $^1J_{CF}$ = 272.1 Hz); 124.2; 123.4; 119.7; 118.3 (q, $^3J_{CF}$ = 3.7 Hz); 116.5 (q, $^3J_{CF}$ = 3.6 Hz); 112.5; 44.7; 37.4; 30.2 (2C); 25.9; 25.2 (2C). ESI-MS 428.2 (M+H). Anal. Calcd for $C_{24}H_{24}F_3N_3O_2$·0.1 toluene: C, 67.94; H, 5.72; N, 9.62. Found: C, 67.90; H, 5.99; N, 9.56.

The following analogues (**33b–c**) were prepared using the procedure outlined for **33a** above (**32** as starting material).

4.1.47. *N*-(Cyclohexyl)-1-[3-(trifluoromethyl)phenyl-amino]-isoquinoline-3-carboxamide (33b)

^{1}H NMR (DMSO-d_6): δ 9.73 (s, 1H); 8.62 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 8.26 (s, 1H); 8.07–7.98 (m, 3H); 7.84–7.73 (m, 3H); 7.61 (t, 1H, $^3J_{HH}$ = 7.9 Hz); 7.40 (d, 1H, $^3J_{HH}$ = 7.6 Hz); 3.84 (m, 1H); 1.94–1.83 (m, 2H); 1.73–1.53 (m, 3H); 1.44–1.15 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 164.0; 151.2; 141.3; 140.9; 137.0; 130.8; 129.3; 129.2 (q, $^2J_{CF}$ = 31.4 Hz); 128.4; 127.9; 124.3 (q, $^1J_{CF}$ = 272.6 Hz); 124.8; 123.4; 119.7; 118.3 (q, $^3J_{CF}$ = 3.9 Hz); 116.8 (q, $^3J_{CF}$ = 4.4 Hz); 112.4; 47.1; 32.1 (2C); 25.0; 24.1 (2C). ESI-MS 414.2 (M+H). Anal. Calcd for $C_{23}H_{22}F_3N_3O$: C, 66.82; H, 5.36; N, 10.16. Found: C, 66.48; H, 5.66; N, 10.01.

4.1.48. *N*-(Benzyl)-1-[3-(trifluoromethyl)phenyl-amino]-isoquinoline-3-carboxamide (33c)

^{1}H NMR (DMSO-d_6): δ 9.72 (s, 1H); 8.63 (d, 1H, $^3J_{HH}$ = 8.3 Hz); 8.40 (t, 1H, $^3J_{HH}$ = 6.1 Hz); 8.20 (s, 1H); 8.13 (d, 1H, $^3J_{HH}$ = 7.8 Hz); 8.08–8.03 (m, 2H); 7.82 (t, 1H, $^3J_{HH}$ = 7.5 Hz); 7.76 (t, 1H, $^3J_{HH}$ = 7.6 Hz); 7.50 (t, 1H, $^3J_{HH}$ = 7.9 Hz); 7.40–7.30 (m, 5H); 7.28 (m, 1H); 4.59 (d, 2H, $^3J_{HH}$ = 6.1 Hz). ^{13}C NMR (DMSO-d_6): δ 164.3; 151.2; 141.3; 140.9; 138.9; 136.9; 130.8; 129.3; 129.2 (q, $^2J_{CF}$ = 31.4 Hz); 128.4; 128.2 (2C); 127.9; 127.0 (2C); 126.5; 124.1 (q, $^1J_{CF}$ = 272.8 Hz); 124.8; 123.4; 119.8; 118.0 (q, $^3J_{CF}$ = 4.0 Hz); 116.5 (q, $^3J_{CF}$ = 3.7 Hz); 112.8; 42.5; ESI-MS 422.1 (M+H). Anal. Calcd for $C_{24}H_{18}F_3N_3O$: C, 68.40; H, 4.31; N, 9.97. Found: C, 68.02; H, 4.26; N, 9.80.

4.1.49. 4-Bromo-1-chloroisoquinoline (36)

4-Bromoisoquinoline (**34**) (200 mg, 0.961 mmol), Na_2WO_4·H_2O (32 mg, 0.096 mmol), AcOH (5 ml) and 30% H_2O_2 (297 μl, 88 mmol) were added in the reaction flask and the mixture was stirred at 80 °C for 3 h. After cooling 50 ml of CH_2Cl_2 was added and the organic phase washed with saturated $NaHCO_3$ and water. After drying the organic phase with anhydrous Na_2SO_4 and removal of the solvent under vacuum, 240 mg of crude *N*-oxide **35** was obtained. The crude **35** was dissolved in mixture of dimethylformamide (1.5 ml) and toluene (4.5 ml) and phosphorus oxychloride (176 μl, 1.92 mmol,) was added in ice cooled reaction mixture under argon. The reaction mixture was stirred at rt for 1 h and then partitioned between EtOAc and water. The organic layer was washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and solvent removed under vacuum. The residue (270 mg) was purified by silica gel flash chromatography (2.5% EtOAc–petroleum ether) to give 115 mg (total yield 49%) of **36** as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H); 8.35 (d, 1H, J = 8.5 Hz); 8.20 (d, 1H, J = 8.5 Hz); 7.87 (t, 1H, J = 7.6 Hz); 7.77 (t, 1H, J = 7.6 Hz).

4.1.50. 1-Chloroisoquinoline-4-carboxylic acid (37)

1.40 g (5.77 mmol) of **36** in dry THF (30 ml) was cooled to −80 °C under argon then and solution of *t*-BuLi (12.70 mmol, 7.47 ml of 1.7 M solution in hexane) was added dropwise via syringe and stirred at −80 °C for 20 min. The reaction mixture was poured onto crushed dry ice under nitrogen, 50 ml of water was added and solution was made basic using 1 M NaOH solution. The aqueous solution was washed with EtOAc (3× 50 ml) and acidified with concd HCl (a white precipitate was immediately formed). The precipitate was filtered off and dried under vacuum to yield 900 mg of acid **37** (yield 75%). ^{1}H NMR (DMSO-d_6): δ 13.68 (s, 1H); 8.97 (d, 1H, J = 8.55 Hz); 8.86 (s, 1H); 8.41 (d, 1H, J = 8,30 Hz); 8.05–8.01 (m, 1H); 7.92–7.89 (m, 1H). ^{13}C NMR (DMSO-d_6): δ 167.3; 155.0; 145.2; 135.6; 133.6; 129.9; 126.8; 126.3; 126.0; 122.2.

4.1.51. *N*-Benzyl-1-chloroisoquinoline-4-carboxamide (39a)

1-Chloroisoquinoline-4-carboxylic acid (**37**) (150 mg, 0.66 mmol), toluene (1.5 ml) and $SOCl_2$ (96.9 μl, 1.33 mmol) were placed in a 2 ml microwave reaction vessel, and the vessel was sealed with a septum and placed into the microwave cavity (Biotage Initiator). Microwave irradiation was used to increase the temperature to 120 °C; the reaction mixture was then kept at this temperature for 10 min. Another portion of $SOCl_2$ (97 μl, 1.33 mmol) was placed in a microwave reaction vessel and heated at 120 °C for 10 min. The $SOCl_2$ and toluene was removed under vacuum and the crude acid chloride **38** was used in the next reaction without further purification. Aforementioned acid chloride **38**, benzylamide (193 μl, 1.77 mmol) and toluene (1.5 ml) were heated for 10 min at 80 °C under microwave irradiation. The resultant mixture was diluted with H_2O and EtOAc. The organic layer was extracted with saturated $NaHCO_3$, water, dried over Na_2SO_4, and solvent removed under vacuum to yield 227 mg crude **39a**.

4.1.52. *N*-Benzyl-1-[3-(trifluoromethyl)phenyl-amino]isoquinoline-4-carboxamide (40a)

Crude **39a** and 3-(trifluoromethyl)-aniline (500 μl, 4.02 mmol) were mixed in a closed microwave reaction vessel. The vessel was placed in a microwave oven and irradiated at 150 °C for 15 min. The reaction mixture was dissolved in EtOAc and washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and dried under vacuum. The residue was recrystallized from toluene to give 147 mg of product **40a** as a white solid (53% yield for 3 steps from **37**). ^{1}H NMR (DMSO-d_6): δ 9.71 (s, 1H); 9.05 (t, 1H, J = 5.93 Hz); 8.62 (d, 1H); 8.45–8.43 (m, 2H); 8.35 (s, 1H); 8.21 (10, d, 1H, J = 8.15 Hz); 7.81–7.78 (m, 1H); 7.71–7.68 (m, 1H); 7.59–7.56 (m, 1H); 7.41–7.34 (m, 6H); 7.27–7.25 (m, 1H); 4.55–4.54 (d, 1H, J = 5.8 Hz). ^{13}C NMR (DMSO-d_6): δ 166.9; 153.4; 141.4; 140.6; 139.5: 134.4; 131.7; 129.3; 129.1 (q, $^2J_{CF}$ = 31.3 Hz); 128.2 (2C); 127.0 (2C); 126.6; 126.5; 124.3 (q, $^1J_{CF}$ = 272.3 Hz); 125.0; 123.9; 119.5; 118.1 (q, $^3J_{CF}$ = 3.8 Hz); 117.8; 116.5 (q, $^3J_{CF}$ = 4.3 Hz); 42.4. ESI-MS 422.3 (M+H). Anal. Calcd for $C_{24}H_{18}F_3N_3O$: C, 68.40; H, 4.31; N, 9.97. Found: C, 68.23; H, 4.56; N, 9.71.

4.1.53. *N*-(Cyclohexylmethyl)-1-chloroisoquinoline-4-carboxamide (39b)

A mixture of crude 1-chloroisoquinoline-4-carboxylic acid chloride **38** (prepared from 0.66 mmol of **37** as described above), cyclohexanemethylamine (173 μl, 1.33 mmol) and toluene (1.5 ml) were introduced into a pressurised microwave reaction tube (2 ml) equipped with a magnetic stirrer, which was irradiated first at 80 °C for 10 min and then 100 °C for 10 min in a Biotage Initiator microwave synthesizer. The reaction mixture was diluted with H_2O and EtOAc and the organic layer was extracted twice with saturated $NaHCO_3$, once with water, dried over Na_2SO_4, and solvent removed under vacuum. The residue was purified by flash chromatography using 20% EtOAc–petroleum ether to give 82 mg (41% yield from **37**) of **39b**. ^{1}H NMR (DMSO-d_6): δ 8.34–8.30 (m, 3H); 7.79 (t, 1H, J = 8.1 Hz); 7.71 (t, 1H, J = 8.1 Hz); 6.38 (s, 1H); 3.36 (t, 2H, J = 6.4 Hz); 1.84–1.55 (m, 5H); 1.35–1.15 (m, 4H); 1.07–1.00 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 166.6; 153.7; 139.5; 135.0; 132.3; 129.2; 128.5; 126.7; 126.7; 125.5; 46.4; 38.1; 31.0; 26.4; 25.9.

4.1.54. *N*-(Cyclohexylmethyl)-1-[3(trifluoromethyl)-phenylamino]-isoquinoline-4-carboxamide (40b)

39b (82 mg, 0.270 mmol) and 3-(trifluoromethyl)-aniline (350 μl, 2.80 mmol) were mixed in a closed microwave reaction vessel. The vessel was placed in a microwave oven and irradiated at 150 °C for 15 min. The reaction mixture was dissolved in EtOAc and washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and dried under vacuum. The residue (116 mg) was recrystallized from toluene to give 84 mg of product **40b** as a white solid (yield 73%). ^{1}H NMR (DMSO-d_6): δ 9.70 (s, 1H); 8.61 (d, 1H, J = 8.40 Hz); 8.44 (s, 1H); 8.38 (d, 1H, J = 8.40 Hz); 8.31 (s, 1H); 8.25 (s, 1H); 8.21 (d, 1H, J = 8.25 Hz); 7.81–7.78 (m, 1H); 7.71–7,68 (5, m, 1H); 7.59–7.56 (m,1H); 7.35 (d, 1H, J = 7.70 Hz); 3.17–3.15 (m, 2H); 1.79–0.94 (m, 11 H). ^{13}C NMR (DMSO-d_6): δ 166.8; 153.2; 141.4; 140.3; 134.4; 130.6; 129.3; 129.1 (q, $^2J_{CF}$ = 31.3 Hz); 126.5; 125.1; 124.3 (q, $^1J_{CF}$ = 272.3 Hz); 123.8; 123.2; 120.1; 118.0; 117.8; 116.3; 45.1; 37.5; 30.5 (2C); 26.0; 25.4 (2C). ESI-MS 428.3 (M+H). Anal. Calcd for $C_{24}H_{24}F_3N_3O{\cdot}0.6\ H_2O$: C, 65.77; H, 5.80; N, 9.59. Found: C, 65.64; H, 5.50; N, 9.47.

4.1.55. *N*-(Cyclohexyl)-1-chloroisoquinoline-4-carboxamide (39c)

A mixture of 1-chloroisoquinoline-4-carboxylic acid chloride **38** (prepared from 0.885 mmol of **37** as described above), cyclohexylamine (202 μl, 1.77 mmol) and toluene (1.5 ml) were introduced into a pressurised microwave reaction vessel (2 ml) equipped with a magnetic stirrer, which was irradiated at 80 °C for 10 min in a Biotage Initiator microwave synthesizer. The reaction mixture was diluted with H_2O and EtOAc and the organic layer was washed with saturated $NaHCO_3$ (twice), water, dried over Na_2SO_4, and solvent removed under vacuum to yield 131 mg crude **39c**.

4.1.56. *N*-(Cyclohexyl)-1-[3-(trifluoromethyl)phenyl-amino]isoquinoline-4-carboxamide (40c)

Crude **40c** 3-(trifluoromethyl)-aniline (500 μl, 4.02 mmol) were mixed in a closed microwave reaction vessel. The vessel was placed in a microwave oven and irradiated at 150 °C for 15 min. The reaction mixture was dissolved in EtOAc and washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and dried under vacuum. The residue (116 mg) was purified by flash chromatography using 15–20% EtOAc–petroleum ether to give 86 mg (24% yield from **37**) **40c** as a white solid. ^{1}H NMR (DMSO-d_6): δ 9.68 (s, 1H); 8.60 (d, 1H, J = 8.40 Hz); 8.44 (s, 1H); 8.36–8.30 (m, 2H); 8.3 (s, 1H); 8.26–8.24 (m, 1H); 7.85–7.83 (m, 1H); 7.71–7.68 (m, 1H); 7.59–7.56 (m, 1H); 7.35 (d, 1H, J = 7.65); 3.83–3.81 (m, 1H); 1.90–1.89 (m, 2H); 1.76–1.73 (m, 2H); 1.60 (d, 1H, J = 12.35 Hz); 1.37–1.27 (m, 4H); 1.17–1.11 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 165.6; 153.8; 142.2; 140.9; 135.0; 131.3; 130.0; 129.8 (q, $^2J_{CF}$ = 31.3 Hz); 127.2; 125.7; 124.9 (q, $^2J_{CF}$ = 272,3 Hz); 124.4; 123.9; 121.0; 118.7; 118.5; 117.0; 48.7; 33.0 (2C); 25.8; 25.4 (2C). ESI-MS 414.2 (M+H). Anal. Calcd for $C_{23}H_{22}F_3N_3O$: C, 66.82; H, 5.36; N, 10.16. Found: C, 66.48; H, 5.62; N, 10.23.

4.1.57. *N*-(2-Methoxyphenyl)-1-chloroisoquinoline-4-carboxamide (39d)

A mixture of 1-chloroisoquinoline-4-carboxylic acid chloride **38** ((prepared from 0.885 mmol of **37** as described above), *m*-anisidine (198 μl, 1.77 mmol) and toluene (1.5 ml) were introduced into a pressurised microwave reaction vessel (2 ml) equipped with a magnetic stirrer, which was irradiated at 80 °C for 10 min in a Biotage Initiator microwave synthesizer. The reaction mixture was partitioned between H_2O and EtOAc and the organic layer was washed with saturated $NaHCO_3$ (twice), water, dried over Na_2SO_4, and solvent removed under vacuum to yield 381 mg crude **39d**.

4.1.58. *N*-(2-Methoxyphenyl)-1-[3-(trifluoromethyl)-phenylamino]iso-quinoline-4-carboxamide (40d)

Crude **39d** and 3-(trifluoromethyl)-aniline (500 μl, 4.02 mmol) were mixed in a closed microwave reaction vessel. The vessel was placed in a microwave oven and irradiated at 150 °C for 15 min. The reaction mixture was dissolved in EtOAc and washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and dried under vacuum. The residue was purified by flash chromatography using 5–20% EtOAc–petroleum ether and then recrystallized from toluene to give 69 mg (18% yield from **37**) **40d** as a white solid. ^{1}H NMR (DMSO-d_6): δ 10.43 (s, 1H); 9.78 (s, 1H); 8.65 (d, 1H, J = 8.45 Hz); 8.45–8.40 (m, 3H); 8.24 (d, 1H, J = 8.25 Hz); 7.86–7.82 (m, 1H); 7.75–7.72 (m, 1H); 7.61–7.58 (m, 1H); 7.53 (s, 1H); 7.39–7.36 (m, 1H); 7.27–7.24 (m, 1H); 6.69 (dd, 1H, J = 8.18 Hz, J = 2.03 Hz); 3.77 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 166.2; 159.9; 154.2; 142.0; 141.7; 141.1; 134.8; 131.6; 129.8 (2C); 129.8 (q, $^2J_{CF}$ = 31.3 Hz); 127.4; 125.5; 124.9 (q, $^2J_{CF}$ = 272.3 Hz); 124.7; 124.1; 120.4; 119.0; 118.5; 117.3; 112.7; 109.5; 106.1; 55.5. ESI-MS 438.3 (M+H). Anal. Calcd for $C_{24}H_{18}F_3N_3O_2{\cdot}0.1\ H_2O$: C, 65.90; H, 4.15; N, 9.61. Found: C, 65.49; H, 3.94; N, 9.38.

4.1.59. *N*-(Morpholinyl)-1-chloroisoquinoline-4-carboxamide (39e)

1-Chloroisoquinoline-4-carboxylic acid (**37**) (200 mg, 0.884 mmol), toluene (1.5 ml), and $SOCl_2$ (258 μl, 3.54 mmol) were placed in a 2 ml microwave reaction vessel, and the vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation was used to increase the temperature to 120 °C; the reaction mixture was then kept at this temperature for 15 min. The $SOCl_2$ and toluene was removed under vacuum and the crude acid chloride **38** was used in the next reaction without further purification. Aforementioned acid chloride **38**, morpholine (154 μl, 1.77 mmol) and toluene (1.5 ml) were heated for 10 min at 80 °C and then another 10 min at 100 °C. The resultant mixture was partitioned between H_2O and EtOAc. The organic layer was extracted with saturated $NaHCO_3$, water, dried over Na_2SO_4, and solvent removed under vacuum to yield 171 mg crude **39e**.

4.1.60. *N*-(Morpholinyl)-1-[3-(trifluoromethyl)phenyl-amino]isoquinoline-4-carboxamide (40e)

Crude **39e** and 3-(trifluoromethyl)aniline (500 μl, 4.02 mmol) were mixed in a closed microwave reaction vessel. The vessel was placed in a microwave oven and irradiated at 150 °C for 15 min. The reaction mixture was dissolved in EtOAc and washed with saturated $NaHCO_3$ (twice), water, dried over anhydrous Na_2SO_4, and dried under vacuum. The residue (203 mg) was purified by flash chromatography using 13–100% EtOAc–petroleum ether and then recrystallized from toluene to give 146 mg (41% yield from **37**) **40e** as a white solid. ^{1}H NMR (DMSO-d_6): δ 9.67 (s, 1H); 8.64 (d, 1H, J = 8.45 Hz); 8.35 (s, 1H); 8.27 (d, 1H, J = 8.20 Hz); 8.04 (s, 1H); 7.83–7.79 (m, 2H); 7.73–7.70 (m, 1H); 7.58–7.55 (m, 1H); 7.34 (d, 1H, J = 7.65 Hz); 3.74–3.30 (m, 8H) ^{13}C NMR (DMSO-d_6): δ 166.7; 152.7; 141.5; 138.6; 133.7; 130.9; 129.2; 129.1 (q, $^2J_{CF}$ = 31.4 Hz); 126.8; 124.2 (q, $^1J_{CF}$ = 272.2 Hz); 124.2; 123.8; 123.6; 119.6; 117.9 (q, $^3J_{CF}$ = 4.0 Hz); 117.8; 116.4 (q, $^3J_{CF}$ = 4.0 Hz); 117.1; 66.2 (4C). ESI-MS 402.3 (M+H). Anal. Calcd for $C_{21}H_{18}F_3N_3O_2{\cdot}0.1\ H_2O$: C, 62.84; H, 4.52; N, 10.47. Found: C, 62.34; H, 4.66; N, 10.41.

4.1.61. 2-Phenylsulfanyl-quinoline (41a)

A mixture of 2-chloroquinoline **11** (200 mg, 1.22 mmol), sodium thiophenolate (455 mg, 4.89 mmol) and DMSO (1.0 ml) was heated 15 min at 150 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with saturated Na_2CO_3 (2× 50 ml) and

H_2O (2× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with dichloromethane to give **41a** (180 mg, 83%). ^1H NMR (DMSO-d_6): δ 8.19 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 7.55 (d, 1H, $^3J_{HH}$ = 7.9 Hz); 7.81 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.73–7.66 (m, 3H); 7.56–7.51 (m, 4H); 7.07 (d, 1H, $^3J_{HH}$ = 7.1 Hz). ^{13}C NMR (DMSO-d_6): δ 160.2; 147.4; 136.9; 134.7 (2C); 130.2; 129.8 (2C); 129.7; 129.4; 127.9; 127.5; 125.8; 125.6; 119.2. ESI-MS 238.1 (M+H). Anal. Calcd for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.9; S, 13.51. Found: C, 75.91; H, 4.63; N, 5.71; S, 13.20.

The following molecules (**41c** and **41e**) were prepared using the procedure outlined for **41a** above (**42** and **19** as starting materials).

4.1.62. 3-Phenylsulfanyl-quinoline (41c)

^1H NMR (DMSO-d_6): δ 8.79 (d, 1H, $^4J_{HH}$ = 2.2 Hz); 8.38 (d, 1H, $^4J_{HH}$ = 2.0 Hz); 8.04 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.94 (d, 1H, $^3J_{HH}$ = 8.1 Hz); 7.80–7.76 (m, 1H); 7.65–7.62 (m, 1H); 7.41–7.33 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 151.9; 146.2; 137.6; 134.1; 130.6 (2C); 129.9; 129.7 (2C); 128.7 (2C); 127.8; 127.7 (2C); 127.4. ESI-MS 238.2 (M+H). Anal. Calcd for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.90. Found: C, 75.63; H, 4.63; N, 5.70.

4.1.63. 1-Phenylsulfanyl-isoquinoline (41e)

^1H NMR ($CDCl_3$): δ 8.37 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 8.24 (d, 1H, $^3J_{HH}$ = 5.6 Hz); 7.77 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 7.68 (t, 1H, $^3J_{HH}$ = 8.1 Hz); 7.62–7.67 (m, 3H); 7.43–7.37 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 159.3; 142.4; 136.0; 134.6 (2C); 130.8; 129.1 (2C); 128.5; 127.3; 127.2 (2C); 125.0; 118.4. ESI-MS 238.2 (M+H). Anal. Calcd for $C_{15}H_{11}NS$: C, 75.92; H, 4.67; N, 5.90. Found: C, 76.25; H, 4.79; N, 5.83.

4.1.64. 3-Phenoxy-quinoline (41b)

A mixture of 3-bromoquinoline **42** (250 mg, 1.20 mmol), phenol (226 mg, 2.40 mmol), KOH (135 mg, 2.40 mmol), Cu-powder (43 mg, 0.67) and 1,4-dioxane (4.0 ml) was heated 45 min at 200 °C using Biotage Initiator microwave synthesizer. The resulting reaction mixture was dissolved in ethyl acetate (50 ml) and washed with saturated Na_2CO_3 (2× 50 ml) and H_2O (2× 50 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by flash chromatography (silica gel) eluting with EtOAc/PE 1:30 to give **41b** (199 mg, 75%). ^1H NMR ($CDCl_3$): δ 8.82 (d, 1H, $^3J_{HH}$ = 2.7 Hz); 8.11 (d, 1H, $^3J_{HH}$ = 8.4 Hz); 7.67 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 7.63 (t, 1H, $^3J_{HH}$ = 8.3 Hz); 7.54–7.49 (m, 2H); 7.41 (m, 2H); 7.20 (t, 1H, $^3J_{HH}$ = 7.4 Hz); 7.10 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 156.3; 151.1; 145.1; 144.6; 130.1 (2C); 129.2; 128.6; 127.9; 127.3; 127.0; 124.3; 120.2; 119.2 (2C). ESI-MS 222.2 (M+H). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.39; H, 5.01; N, 6.34.

Compound **41d** was prepared using the procedure outlined for **41b** using **19** as starting material.

4.1.65. 1-Phenoxy-isoquinoline (41d)

^1H NMR ($CDCl_3$): δ 8.44 (d, 1H, $^3J_{HH}$ = 9.1 Hz); 7.97 (d, 1H, $^3J_{HH}$ = 5.8 Hz); 7.79 (d, 1H, $^3J_{HH}$ = 8.2 Hz); 7.72 (t, 1H, $^3J_{HH}$ = 8.2 Hz); 7.62 (t, 1H, $^3J_{HH}$ = 8.2 Hz); 7.62–7.67 (m, 3H); 7.45 (m, 2H); 7.30 (d, 1H, $^3J_{HH}$ = 6.1 Hz); 7.28–7.22 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 160.6; 153.9; 139.8; 138.5; 130.8; 129.6 (2C); 127.1; 126.3; 125.0; 124.3; 121.8 (2C); 119.9; 116.3. ESI-MS 222.2 (M+H). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.32; H, 5.14; N, 6.14.

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