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A mild and metal-free synthesis of 2- and 1-alkyl/aryl/dialkyl-aminoquinolines and isoquinolines†

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A simple synthetic strategy has been developed for the synthesis of 2- and 1-alkyl/aryl/dialkylaminoquinolines and isoquinolines from the easily available quinoline and isoquinoline-*N*-oxides, different amines, triflic anhydride as activating agent and acetonitrile as solvent in a one-pot reaction under metal-free conditions at 0 °C to room temperature.

Introduction

The basic motifs of 2-aminoquinolines and 1-aminoisoquinolines are present in a number of alkaloids[1] that have a broad range of biological activities, including antimicrobial activity,[2] anti-Alzheimer disease,[3] anti-HIV,[4] antihelmintic,[5] antidepressant,[6] and antihypertensive[7] activities. This type of skeleton-containing molecule is an interesting target as potent leads for the medicinal chemist. Some representative examples are given below in Fig. 1. Compound **1** selectively modulates native TRPC4/C5 ion channels and is a potent antagonist. This compound has a broad scope in physiological and pathophysiological studies,[1b] whereas compound **2**, as an antagonist of MCH-1R, is used for the treatment of obesity.[2c]

There are several reports in the literature for the synthesis of 2-aminoquinoline and 1-aminoisoquinoline derivatives.[8] The Chichibabin reaction is one of them, in which amino or alkylamino groups can be incorporated directly into the quinoline and isoquinoline nucleus by the reaction of quinoline and isoquinoline with alkali amide or alkylamide. The Chichibabin reaction does, however, have some drawbacks, such as low yields,

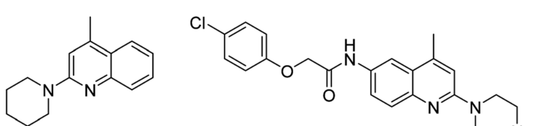
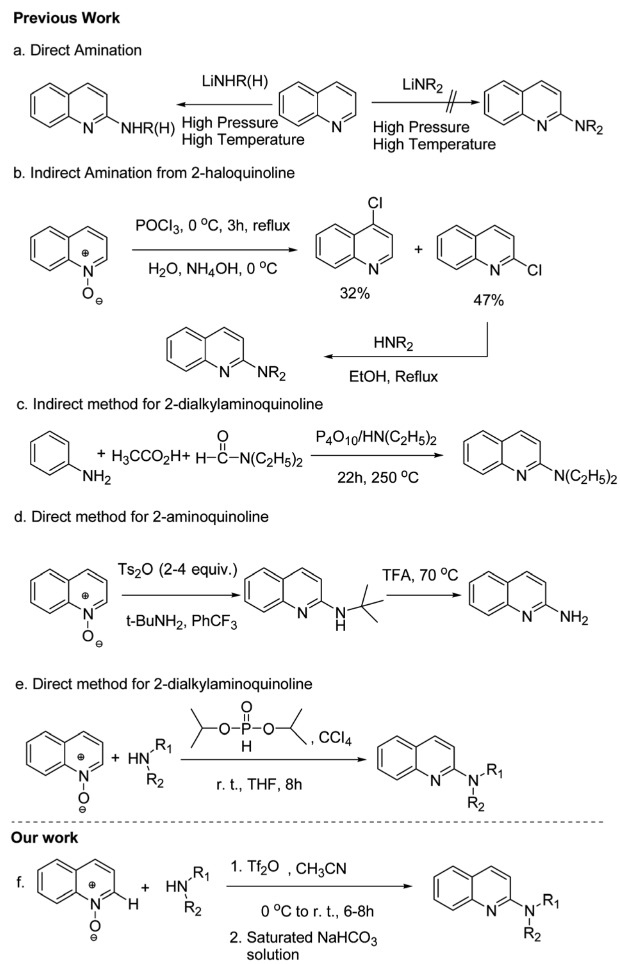


Fig. 1 Representative examples of biologically important 2-aminoquinolines.



Scheme 1 Comparison of earlier work with the present work.

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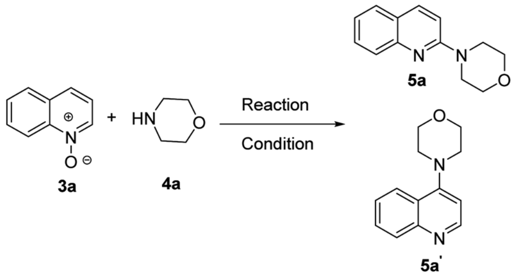
† Electronic supplementary information (ESI) available: For further information of spectra, see the Supporting Information. See DOI: 10.1039/c9ra10397j



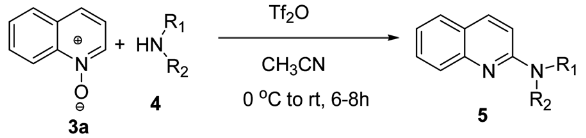
Scheme 2 Synthesis of 2-morpholinoquinoline **5a**.

functional group intolerance and poor regioselectivity due to strong basic conditions, high temperatures and longer reaction times (Scheme 1a).[9] Earlier, it was noted that 2-(dialkylamino) quinolines/(1-dialkylamino)isoquinolines cannot be prepared by other variants of the Chichibabin reaction. This shows that we cannot introduce dialkylamino groups into the quinoline/isoquinoline nucleus by the use of alkali dialkylamides.[10] A literature survey shows that derivatization of the 2-unsubstituted quinoline moiety to the corresponding 2-dialkylaminoquinoline was obtained *via* indirect synthetic methods. The other important approach is amination of 2-haloquinolines with alkyl/dialkylamines.[11] However, to use this approach, first, a halogen atom should be incorporated at the 2-position of quinoline and its derivatives, which is achieved by chlorination of quinoline-*N*-oxides with 2- and 4-regioselectivity and poor yields (Scheme 1b).[11] Londregan reported the amination method for the synthesis of 2-aminopyridines, and when 2-cyclohexylaminoquinoline was made utilising this method, poor yield was observed. They used the phosphonium salt PyBroP as the activating agent in this reaction, which is expensive.[12] Pedersen also described the synthesis of 2-(dialkylamino)quinolines by the reaction of acetanilides and *N*,*N*-dialkylformamides in the presence of phosphorus pentoxide and a dialkylamine at 250 °C.[13a] This method has drawbacks of high temperature, prolonged reaction time, and poor yield (Scheme 1c). Further, Yin and Xiang reported a two-step synthetic route for the synthesis of 2-aminoquinolines in which an expensive solvent, $PhCF_3$, was used, and excess (5–9 equiv.) of *t*-$BuNH_2$ was needed to react with quinoline-*N*-oxide in the first step to form *N*-(*t*-butyl)-substituted 2-aminoquinolines (Scheme 1d).[13b] Zhuo developed

Table 1 Optimization table for the synthesis of 2-morpholinoquinoline **5a**

Entry	Reaction condition	% yield of product **5a**
1	CH_2Cl_2, Tf_2O, 0 °C to rt, 12 h	No reaction
2	Et_2O, Tf_2O, 0 °C to rt, 12 h	No reaction
3	Toluene, Tf_2O, 0 °C to rt, 12 h	[a]Trace product
4	CH_3CN, Tf_2O (2 equiv.), 0 °C to rt, 8 h	80%
5	DMSO, Tf_2O, 0 °C to rt, 12 h	[a]Trace product
6	THF, Tf_2O, 0 °C to rt, 12 h	[a]Trace product
7	THF, *t*-BuOK, 0 °C to rt, 12 h	[a]Trace product
8	THF, NaH, 0 °C to rt, 12 h	[a]Trace product
9	CH_3CN, Tf_2O (1.5 equiv.), 0 °C to rt, 8 h	82%

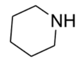
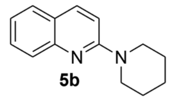
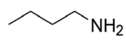
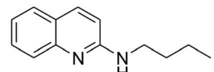
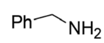
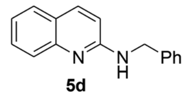
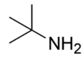
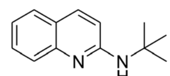
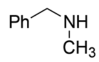
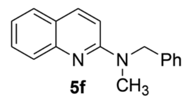
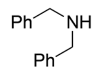
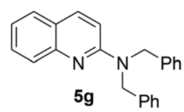
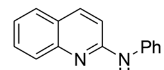
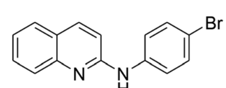
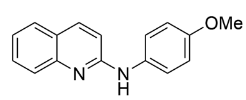
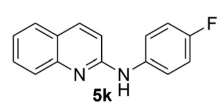
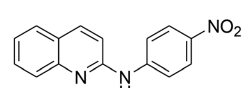
[a] **5a** was observed in TLC and could not be isolated.

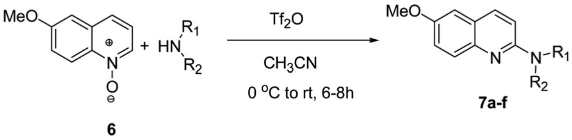


Scheme 3 Synthesis of 2-alkyl/aryl/dialkylaminoquinolines **5b–l**.

a methodology for the preparation of 2-dialkylaminoquinolines from quinoline-*N*-oxides, diisopropyl *H*-phosphonate, tertiary amines and carbon tetrachloride under metal-free reaction conditions at room temperature (Scheme 1e)[14] and the limitation

Table 2 Synthesis of 2-alkyl/aryl/dialkylaminoquinolines **5b–k**

Entry	Amine	Product **5b–k**	% yield of **5b–k**
1		 **5b**	79
2		 **5c**	82
3		 **5d**	84
4		 **5e**	68
5		 **5f**	76
6		 **5g**	74
7	$PhNH_2$	 **5h**	79
8	$BrC_6H_4NH_2$	 **5i**	77
9	$MeOC_6H_4NH_2$	 **5j**	78
10	$FC_6H_4NH_2$	 **5k**	67
11	$NO_2C_6H_4NH_2$	 **5l**	62



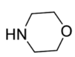
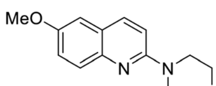
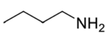
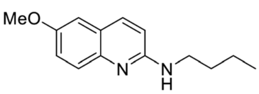
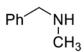
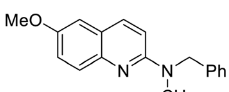
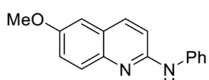
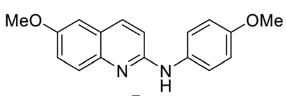
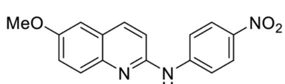
Scheme 4 Synthesis of 2-alkyl/aryl/dialkylamino-6-methoxyquinolines **7a–f**.

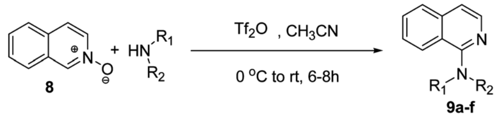
of this reaction is the use of symmetrical tertiary amine. In 2017, Karchava reported a simple, one-pot preparation of *N*-(2-pyridyl)-*N*-ethyl-piperazines[15] from pyridine-*N*-oxide and 1,4-diazabicyclo[2.2.2]octane (DABCO), which generates *N*-(2-pyridyl)-DABCO salt and further ring opening yields the product by nucleophilic attack. Hence, the development of a simple and handy method for the synthesis of 2-(alkyl/aryl/dialkyl-amino)quinolines and 1-(alkyl/aryl/dialkylamino)quinolines from easily available starting materials without the use of metal is still needed.

Results and discussion

Here, we report a synthetic method by which a series of 2- and 1-alkyl/aryl/dialkylaminoquinolines and isoquinolines are easily prepared by reaction of quinoline and isoquinoline-*N*-oxides with different alkyl/aryl/dialkylamines at 0 °C to room temperature in the presence of triflic anhydride as activator and acetonitrile as solvent in a one-pot reaction (Scheme 1f).

Table 3 Synthesis of 2-alkyl/aryl/dialkylamino-6-methoxyquinolines **7a–f**

Entry	Amine	Product **7a–f**	% yield of **7a–f**
1		 **7a**	83
2		 **7b**	66
3		 **7c**	64
4	$PhNH_2$	 **7d**	62
5	$MeOC_6H_4NH_2$	 **7e**	65
6	$NO_2C_6H_4NH_2$	 **7f**	60



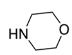
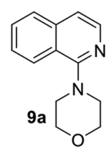
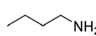
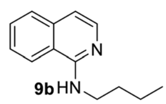
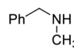
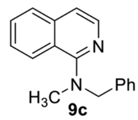
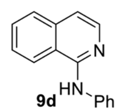
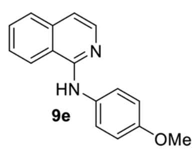
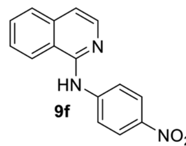
Scheme 5 Synthesis of 1-alkyl/aryl/dialkylaminoisoquinolines **9a–f**.

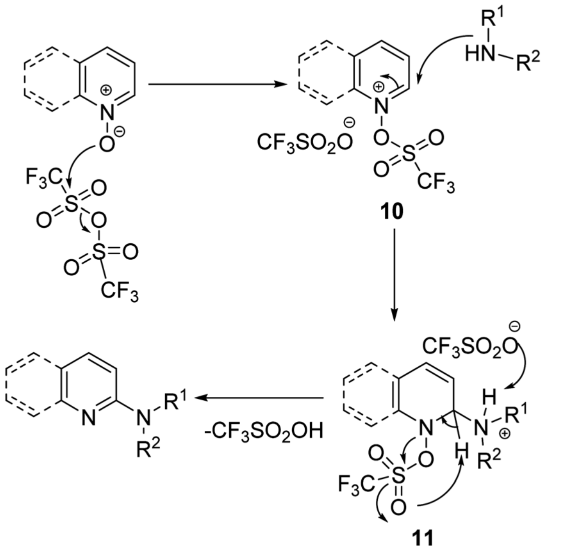
We began our study to optimize reaction conditions for the synthesis of 2-morpholinoquinoline, **5a**, between reaction of quinoline-*N*-oxide, **3a**, and morpholine, **4a**, in the presence of triflic anhydride as activator under different reaction conditions, as shown in Scheme 2 and Table 1 (entries 1–9). It was found that 2-morpholinoquinoline **5a** was obtained in good yield (82%) when the *N*-oxide of quinoline **3a** (1.0 equiv.) was reacted with morpholine **4a** (1.2 equiv.) and triflic anhydride (Tf_2O) (1.5 equiv.) in acetonitrile as solvent at 0 °C to room temperature for 8 h (Table 1, entry 9). There is also the possibility of formation of the isomeric 4-morpholinoquinoline **5a′**. Compound **5a′** was never observed.

The above optimised reaction conditions were employed for the synthesis of other 2-alkyl/aryl/dialkylamino-substituted quinolines (**5b–l**) as shown in Scheme 3 and Table 2.

Further, the optimized methodology was extended for the synthesis of 2-alkyl/aryl/dialkyl-aminosubstituted-6-methoxyquinolines **7a–f** from the reaction of 5-methoxyquinoline-*N*-oxide

Table 4 Synthesis of 1-alkyl/aryl/dialkylaminoisoquinolines **9a–f**

Entry	Amine	Product **9a–f**	% yield of **9a–f**
1			83
2			77
3			74
4	$PhNH_2$		64
5	$MeOC_6H_4NH_2$		62
6	$NO_2C_6H_4NH_2$		60



Scheme 6 Proposed mechanism for amination of quinoline- and isoquinoline-*N*-oxides.

(6) with different amines (Scheme 4 and Table 3). Next, the optimized reaction conditions were utilised for the synthesis of 1-alkyl/aryl/dialkylamino-substituted isoquinolines **9a–f**, when isoquinoline-*N*-oxide 8 was reacted with different alkyl/aryl/dialkyl amines at 0 °C to room temperature for 6–8 h in the presence of triflic anhydride and acetonitrile, as shown in Scheme 5 and Table 4.

In the mechanistic step, triflic anhydride reacts with quinoline-*N*-oxide to produce the activated quinoline-*N*-oxide intermediate **10**. Further, the activated quinoline-*N*-oxide intermediate **10** reacted with amine *via* nucleophilic addition to produce intermediate **11**. The hydrogen of the ammonium intermediate **11** is abstracted by the trifluoromethane sulfonate anion, followed by aromatization to give the 2-amino-substituted quinoline (Scheme 6). Trifluoromethane sulfonic anhydride enhanced the CH-acidity and electrophilicity of the C-2 position by reacting with the *N*-oxide.

Conclusions

In conclusion, we have developed a straightforward and metal-free methodology for the regioselective amination of quinoline-*N*-oxides and isoquinoline-*N*-oxides with different aliphatic and aromatic amines utilising triflic anhydride as activator in a one-pot reaction. A wide range of 2-alkyl/aryl/dialkylamino-substituted quinolines and 1-alkyl/aryl/dialkylamino-substituted isoquinolines were synthesised in up to 84% yield. This amination exposed a good functional group tolerance and proceeds well when electron-donating and -withdrawing substituted amines were used.

Experimental

General

Unless otherwise noted, all the reactions were performed in oven-dried glassware. The solvents used were dried and distilled. The reactions were performed under a nitrogen atmosphere. Acetonitrile was distilled from CaH_2 and stored over 4 Å molecular sieves. The *N*-oxides and amines used were commercially available. All other commercial reagents were used without further purification, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 101 MHz Bruker spectrometers, respectively, using either $CDCl_3$ or DMSO-d_6 as solvent, with tetramethylsilane (TMS) as internal standard.

General experimental procedure

To a solution of quinoline-/isoquinoline-*N*-oxide (1.0 mmol, 1.0 equiv.) and amine (1.2 mmol, 1.2 equiv.) in CH_3CN (8 mL) was added Tf_2O (0.25 mL, 1.5 mmol, 1.5 equiv.) drop by drop at 0 °C. The reaction mixture was stirred for 6–8 h at room temperature and the reaction was monitored by thin layer chromatography. After completion of the reaction, the solvent was evaporated under vacuum, and the residue was quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated and purified by column chromatography on silica gel (60–120 mesh) using a mixture of petroleum ether and ethylacetate as eluent to give pure product.

4-(Quinolin-2-yl)morpholine, 5a[14a]

Yield 82% (175 mg); bone off-white solid; mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, J = 9.1 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 1.1 Hz, 1H), 7.56–7.46 (m, 1H), 7.20–7.16 (m, 1H), 6.90 (d, J = 9.1 Hz, 1H), 3.79 (t, J = 4.8 Hz, 4H), 3.65 (t, J = 5.0 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.6, 147.6, 137.6, 129.7, 127.3, 126.8, 123.3, 122.7, 109.3, 66.9, 45.6; HRMS (ESI) m/z calcd for $C_{13}H_{15}N_2O$: 215.1184, found: 215.1182.

2-(Piperidin-1-yl)quinoline, 5b[16b]

Yield 79% (167.0 mg); mp 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (d, J = 9.2 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 9.2 Hz, 1H), 8.10–8.02 (m, 1H), 7.82–7.73 (m, 1H), 7.55 (d, J = 9.2 Hz, 1H), 4.31–4.26 (m, 4H), 2.25 (brs, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.7, 148.0, 137.5, 129.3, 127.2, 126.5, 122.8, 121.8, 109.8, 46.3, 25.8, 24.8; HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2$: 213.1392, found: 213.1382.

N-Butylquinolin-2-amine, 5c[16b]

Yield 82% (164 mg); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J = 8.9 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.57–7.51 (m, 1H), 7.24–7.18 (m, 1H), 6.65 (d, J = 8.9 Hz, 1H), 4.76 (brs, 1H), 3.50 (q, J = 7.2 Hz, 2H), 1.77–1.55 (m, 2H), 1.53–1.44 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.2, 148.2, 137.3, 129.5, 127.5, 126.0, 123.4, 121.9, 111.2, 41.6, 31.9, 20.3, 13.9.

N-Benzylquinolin-2-amine, 5d[14c]

Yield 84% (196 mg); colourless crystalline solid; mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 8.0, 1.1 Hz, 1H), 7.59–7.55 (m, 1H), 7.47–7.42 (m, 2H), 7.40–7.34 (m, 2H), 7.34–7.28 (m, 1H), 7.28–7.23 (m, 1H), 6.66 (d, $J = 8.9$ Hz, 1H), 5.06 (s, 1H), 4.76 (d, $J = 5.6$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.8, 148.1, 139.5, 137.5, 129.7, 128.7, 127.9, 127.5, 127.4, 126.3, 123.6, 122.2, 111.5, 45.9; HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2$: 235.1235, found: 235.1240.

N-(*tert*-Butyl)quinolin-2-amine, 5e[18]

Yield: 68% (136 mg); light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (s, 9H), 5.49 (brs, 1H), 6.65 (d, $J = 9.0$ Hz, 1H), 7.16–7.21 (m, 1H), 7.48–7.7.53 (m, 1H), 7.55 (dd, $J = 8.0$ Hz, 1.0 Hz, 1H), 7.77 (d, $J = 9.0$ Hz, 1H).

N-Benzyl-*N*-methylquinolin-2-amine, 5f[16c]

Yield 76% (188 mg); colourless crystalline solid; mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, $J = 8.9$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.63 (dd, $J = 8.0$ Hz, 1.3 Hz, 1H), 7.59–7.55 (m, 1H), 7.38–7.20 (m, 6H), 6.91 (d, $J = 9.1$ Hz, 1H), 4.98 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.3, 148.3, 138.7, 137.5, 129.6, 128.7, 127.4, 127.3, 127.2, 126.6, 122.8, 121.9, 109.1, 53.3, 36.3; HRMS (ESI) m/z calcd for $C_{17}H_{17}N_2$: 249.1392, found: 249.1397.

N,*N*-Dibenzylquinolin-2-amine, 5g[14c]

Yield 74% (240 mg); bone off-white solid; mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, $J = 9.1$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.65–7.54 (m, 2H), 7.38–7.20 (m, 11H), 6.85 (d, $J = 9.1$ Hz, 1H), 4.97 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.1, 148.2, 138.6, 137.7, 129.6, 128.7, 127.5, 127.3, 127.2, 126.8, 122.9, 122.0, 109.2, 50.8; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2$: 325.1705, found: 325.1708.

N-Phenylquinolin-2-amine, 5h[14c]

Yield 79% (174 mg); brown solid; mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, $J = 8.9$ Hz, 1H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.66 (dd, $J = 8.0$ Hz, 1.3 Hz, 1H), 7.64–7.59 (m, 1H), 7.57 (dd, $J = 8.6$ Hz, 1.1 Hz, 2H), 7.43–7.35 (m, 2H), 7.33–7.29 (m, 1H), 7.14–7.08 (m, 1H), 7.01 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.5, 147.0, 140.0, 138.2, 130.1, 129.3, 127.6, 126.2, 124.9, 124.0, 123.3, 120.9, 111.7; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_2$: 221.1079, found: 221.1071.

N-(4-Bromophenyl)quinolin-2-amine 5i[14c]

Yield 77% (230 mg); colourless crystalline solid; mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, $J = 8.9$ Hz, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 1H), 7.65–7.58 (m, 3H), 7.49 (d, $J = 8.9$ Hz, 2H), 7.35 (t, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 8.9$ Hz, 1H), 6.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 153.7, 147.4, 139.5, 137.9, 132.1, 129.8, 127.5, 126.9, 124.2, 123.5, 121.4, 115.0, 112.1.

N-(4-Methoxyphenyl)quinolin-2-amine 5j[14c]

Yield 78% (195 mg); colourless crystalline solid; mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, $J = 8.9$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 9.0$ Hz, 1H), 7.59 (t, $J = 7.7$ Hz, 1H), 7.44 (d, $J = 8.9$ Hz, 2H), 7.32–7.26 (m, 1H), 6.96–6.93 (m, 2H), 6.89 (d, $J = 8.9$ Hz, 1H), 6.79 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.3, 155.7, 147.8, 137.7, 133.2, 129.8, 127.5, 126.2, 123.9, 122.5, 114.6, 111.3, 55.4; HRMS (ESI) m/z calcd for $C_{16}H_{15}N_2O$: 251.1184, found: 251.1173.

N-(4-Fluorophenyl)quinolin-2-amine 5k[14c]

Yield 67% (159 mg); colourless crystalline solid; mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, $J = 8.9$ Hz, 1H), 7.66 (d, $J = 4.4$ Hz, 1H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.53–7.48 (m, 1H), 7.46–7.42 (m, 2H), 7.25–7.21 (m, 1H), 6.99 (t, $J = 8.7$ Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.3 (d, $J = 252.5$ Hz), 154.4, 146.4, 138.5, 135.7 (d, $J = 2.7$ Hz), 130.3, 127.6, 126.6 (d, $J = 8.1$ Hz), 125.7, 123.9, 123.5, 123.1 (d, $J = 7.9$ Hz), 116.0 (d, $J = 22.5$ Hz), 115.6 (d, $J = 12.9$ Hz), 111.5; HRMS (ESI) m/z calcd for $C_{15}H_{12}FN_2$: 239.0985, found: 239.0990.

N-(4-Nitrophenyl)quinolin-2-amine 5l[17]

Yield 62% (164 mg); yellow solid; mp 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.28 (d, $J = 8.8$ Hz, 2H), 8.16 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.83–7.76 (m, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.38–7.28 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 150.9, 149.3, 145.3, 140.9, 130.3, 129.6, 126.1, 123.0, 121.8, 118.1, 107.5; HRMS (ESI) m/z calcd for $C_{15}H_{12}N_3O_2$: 266.0930, found: 266.0936.

4-(6-Methoxyquinolin-2-yl)morpholine, 7a[16b]

Yield 83% (203 mg); colourless crystalline solid; mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, $J = 9.0$ Hz, 1H), 7.68 (d, $J = 9.1$ Hz, 1H), 7.30–7.22 (m, 1H), 6.99–6.95 (m, 2H), 3.90 (s, 3H), 3.88 (t, $J = 6.0$ Hz, 4H), 3.66 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.7, 155.3, 143.3, 136.6, 128.3, 123.8, 121.3, 109.7, 106.0, 66.9, 55.5, 45.9; HRMS (ESI) m/z calcd for $C_{14}H_{17}N_2O_2$: 245.1290, found: 245.1294.

N-Butyl-6-methoxyquinolin-2-amine, 7b

Yield 66% (152 mg); brown solid; mp 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, $J = 8.9$ Hz, 1H), 7.52 (d, $J = 9.1$ Hz, 1H), 7.12 (dd, $J = 9.1$ Hz, 2.9 Hz, 1H), 6.86 (d, $J = 2.8$ Hz, 1H), 6.54 (d, $J = 8.9$ Hz, 1H), 4.56 (s, 1H), 3.78 (s, 3H), 3.35 (q, $J = 8.0$ Hz, 2H), 1.64–1.50 (m, 2H), 1.42–1.33 (m, 2H), 0.89 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.1, 154.7, 143.5, 136.4, 127.4, 123.6, 120.9, 111.2, 106.6, 55.5, 41.7, 32.0, 20.2, 13.9; HRMS (ESI) m/z calcd for $C_{14}H_{19}N_2O$: 231.1497, found: 231.1493.

N-Benzyl-6-methoxy-*N*-methylquinolin-2-amine, 7c

Yield 64% (178 mg); colourless crystalline solid; mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, $J = 9.1$ Hz, 1H), 7.69 (d, $J = 9.1$ Hz, 1H), 7.40–7.21 (m, 6H), 6.98 (d, $J = 2.8$ Hz, 1H), 6.89 (d, $J = 9.1$ Hz, 1H), 4.93 (s, 2H), 3.90 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.3, 154.7, 143.7, 138.8, 136.5, 128.6, 127.9, 127.2, 127.0, 122.9, 121.1, 109.3, 106.2, 55.5, 53.4, 36.2; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O$: 279.1497, found: 279.1494.

6-Methoxy-*N*-phenylquinolin-2-amine, 7d[18]

Yield 62% (155 mg); white powder; mp 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 9.1 Hz, 1H), 7.60–7.52 (m, 2H), 7.42–7.33 (m, 2H), 7.30 (dd, *J* = 9.0 Hz, 2.8 Hz, 1H), 7.13–7.06 (m, 1H), 7.01 (t, *J* = 5.8 Hz, 2H), 6.86 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.6, 153.0, 143.2, 140.6, 136.7, 129.2, 128.2, 124.7, 122.7, 121.4, 120.0, 112.0, 106.3, 55.5; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}N_2O$: 251.1184, found: 251.1182.

6-Methoxy-*N*-(4-methoxyphenyl)quinolin-2-amine, 7e[19]

Yield 65% (182 mg); colourless crystalline solid; mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 9.1 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.27 (dd, *J* = 9.1 Hz, 2.9 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.71 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.1, 155.3, 154.1, 143.3, 136.7, 133.5, 127.9, 124.4, 123.5, 121.3, 114.6, 111.2, 106.4, 55.6, 55.6; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}N_2O_2$: 281.1290, found: 281.1291.

6-Methoxy-*N*-(4-nitrophenyl)quinolin-2-amine, 7f

Yield 60% (183 mg); colourless crystalline solid; mp 218–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.50 (s, 1H), 8.58 (d, *J* = 5.0 Hz, 1H), 8.22 (d, *J* = 9.1 Hz, 2H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.60 (d, *J* = 2.6 Hz, 1H), 7.50–7.32 (m, 4H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.5, 149.6, 148.6, 145.6, 143.9, 140.7, 131.5, 126.2, 122.8, 122.2, 117.8, 108.8, 101.6, 56.2; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{14}N_3O_3$: 296.1035, found: 296.1038.

4-(Isoquinolin-1-yl)morpholine, 9a[16c]

Yield 83% (177 mg); colourless crystalline solid; mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, *J* = 5.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 5.7 Hz, 1H), 3.84 (t, *J* = 4.6 Hz, 4H), 3.28 (t, *J* = 4.4 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.1, 140.7, 138.1, 129.7, 127.2, 126.2, 125.3, 121.6, 116.2, 67.1, 51.9; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{15}N_2O$: 215.1184, found: 215.1182.

***N*-Butylisoquinolin-1-amine, 9b**[20a]

Yield 77% (154 mg); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J* = 5.9 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 7.0 Hz, 0.9 Hz, 1H), 7.48–7.34 (m, 1H), 6.90 (d, *J* = 5.8 Hz, 1H), 5.34 (s, 1H), 3.60 (t, *J* = 7.2 Hz, 2H), 1.78–1.63 (m, 2H), 1.49–1.42 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.3, 141.4, 137.0, 129.6, 127.1, 125.8, 121.4, 118.2, 110.6, 41.7, 31.7, 20.4, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{17}N_2$: 201.1392, found: 201.1391.

***N*-Benzyl-*N*-methylisoquinolin-1-amine, 9c**[20b]

Yield 74% (184 mg); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (t, *J* = 6.8 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.49–7.43 (m, 1H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.33–7.24 (m, 3H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 5.7 Hz, 1H), 4.52 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.8, 140.6, 138.8, 138.4, 129.6, 128.6, 127.7, 127.1, 127.1, 125.9, 125.6, 121.6, 115.1, 59.3, 40.1; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}N_2$: 249.1392, found: 249.1387.

***N*-Phenylisoquinolin-1-amine, 9d**[18]

Yield 64% (141 mg); bone off-white solid, mp 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 5.7 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.76–7.73 (m, 3H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 5.7 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.5, 140.9, 140.6, 137.5, 130.0, 129.0, 127.4, 126.5, 122.8, 121.7, 120.6, 119.0, 113.5; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{13}N_2$: 221.1079, found: 221.1074.

***N*-(4-Methoxyphenyl)isoquinolin-1-amine, 9e**[19]

Yield 62% (155 mg); crystalline white solid; mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.60–7.45 (m, 3H), 7.10 (d, *J* = 5.8 Hz, 1H), 7.09 (s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.8, 153.0, 141.1, 137.5, 133.4, 129.8, 127.4, 126.3, 123.2, 121.5, 118.6, 114.3, 112.8, 55.6; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}N_2O$: 251.1184, found: 251.1180.

***N*-(4-Nitrophenyl)isoquinolin-1-amine, 9f**

Yield 60% (159 mg); yellow solid; mp 219–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d *J* = 9.2 Hz, 2H), 8.22 (d *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.34 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.6, 146.7, 141.7, 140.5, 137.6, 130.4, 127.8, 127.3, 125.4, 121.1, 119.2, 118.0, 115.7; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}N_3O_2$: 266.0930, found: 239.0936.

Conflicts of interest

There are no conflicts to declare.

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