Supplementary Information:

Chelation-assisted de-aryloxylylative amination of 2-aryloxy quinolines: A new synthetic route to a key fragment of a bioactive PRMT5 inhibitor

Aniket Gupta, Jogendra Kumar and Sukalyan Bhadra*

Inorganic Materials and Catalysis Division, Academy of Scientific and Innovative Research, CSIR-Central Salt and Marine Chemicals Research Institute, G.B. Marg, Bhavnagar 364002, Gujarat, India

Email: sbhadra@csmcri.res.in

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Table S1. Optimization of the reaction conditions for the de-aryloxyative amination

<table>
<thead>
<tr>
<th>Entry</th>
<th>M-Cat</th>
<th>Additive (Equiv.)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>8a (%)</th>
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<td>nd</td>
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* Reaction condition: substrate (0.15 mmol), piperidine (5 equiv), M-cat (0.03 mmol, 20 mol%), in solvent (2.5 mL) under air at a given temp. for 16 h; Isolated yields of pure products. b 10 mol% M-cat. c 1.5 equiv additive. d Using 10 equiv piperidine. e Using 2.5 equiv piperidine. f 5 mol% Cu(OTf)$_2$. g For 36 h. nd = not detected

Table S2: De-aryloxyative amination of 9 with piperidine by varying Cu(OTf)$_2$ loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OTf)$_2$ (x mmol)</th>
<th>8a (%)</th>
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</thead>
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* Reaction condition: 10 (40 mg, 0.15 mmol, 1 equiv), piperidine (74 µL, 0.75 mmol, 5 equiv), Cu(OTf)$_2$ (x mol%), in DMF (2.5 mL) under air at 120 ºC for 16 h; Isolated yields of pure products.
GC-MS Analysis:

A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline (35.6 mg, 0.15 mmol, 1 equiv, m/z = 237.0) and copper(II) triflate (10.8 mg, 0.03 mmol, 20 mol%). To it, THF (2.5 mL) and piperidine (0.75 mmol, 5 equiv, m/z = 85.0) were added. The reaction mixture was stirred at 70 °C for 12 h. After cooling, an aliquot (0.2 mL) from the reaction mixture was withdrawn and diluted with EtOAc (2 mL) and washed with water (1 mL). The organic layer was dried over Na2SO4, and subsequently submitted to GC-MS, which shows the formation of 8a (m/z = 228) and phenol (m/z = 94).

\[
\begin{align*}
\text{GC-MS spectrum of Piperidine (m/z = 85, R_t = 4.5 min):} \\
\text{GC-MS spectrum of PhOH (m/z = 94, R_t = 7.9 min):}
\end{align*}
\]
GC-MS spectrum of 2 (m/z = 237, R<sub>t</sub> = 17.5 min):

![GC-MS spectrum of 2](image1)

GC-MS spectrum of 8a (m/z = 228, R<sub>t</sub> = 18.5 min):

![GC-MS spectrum of 8a](image2)
Mechanistic Studies:

Experiments with TEMPO:

A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline 2 (35.6 mg, 0.15 mmol, 1 equiv), copper(II) triflate (10.8 mg, 0.03 mmol, 20 mol%) and TEMPO (35.2 mg, 0.225 mmol, 1.5 equiv). To it, DMF (2.5 mL) and piperidine (0.75 mmol, 5 equiv) were added. The reaction mixture was stirred under air at 120 ºC for 16 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding N-heteroaryl amine 8a (82%).

Evidence against a dehydrogenative C–H amination process:

A reaction pathway consisting of dephenoxylation of 2 and a subsequent C–H amination of the resulting compound was excluded as 8-hydroxyquinoline was not converted into 8a under the optimized condition.

A 20 mL Schlenk tube was charged with 8-hydroxyquinoline (22 mg, 0.15 mmol, 1 equiv), and copper(II) triflate (10.8 mg, 0.03 mmol, 20 mol%). To it, DMF (2.5 mL) and piperidine (0.75 mmol, 5 equiv) were added. The reaction mixture was stirred under air at 120 ºC for 16 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The reaction did not provide any aminated product 8a and 8-hydroxyquinoline was recovered exclusively (20 mg, 91%).

Experiments with preformed complexes:

1. With the preformed copper-complex of 2 and Cu(OTf)₂:

A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline 2 (35.6 mg, 0.15 mmol, 1.0 equiv) and copper(II) triflate (54.3 mg, 0.15 mmol, 1.0 eq). The tube was evacuated and backfilled with N₂ (x 3). To it, anhydrous DMF (2.5 mL) was added by syringe and the reaction mixture was heated with vigorous stirring at 120 ºC for 5 h. After cooling to room temperature, piperidine (74 µL, 0.75 mmol, 5 equiv) was added to it. The reaction mixture was stirred at 120 ºC for additional 16 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding 2-aminoquinoline 8a (82%).
2. With preformed Cu-complex of Cu(OTf)$_2$ and piperidine:

A 20 mL Schlenk tube was charged with copper(II) triflate (54.3 mg, 0.15 mmol, 1.0 eq) and piperidine (15 µL, 0.15 mmol, 1 equiv). The tube was evacuated and backfilled with N$_2$ (x 3). To it, anhydrous DMF (2.5 mL) was added by syringe and the reaction mixture was heated with vigorous stirring at 70 ºC for 5 h. After cooling to room temperature, 2-phenoxy-8-hydroxyquinoline 2 (35.6 mg, 0.15 mmol, 1.0 equiv) was added to it and was further heated at 120 ºC for additional 16 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to recover the starting material 2 (98%).

**Deuterium exchange experiments:**

A 20 mL reaction vessel was charged with 2-phenoxy-8-hydroxyquinoline 2 (24 mg, 0.1 mmol) and Cu(OTf)$_2$ (10.8 mg, 0.03 mmol, 20 mol%). To it, 0.5 mL DMF and 0.5 mL methanol-d$_4$ were added and the reaction mixture was stirred at 70 ºC for 3 h under air. After cooling to room temperature, 0.2 mL of the reaction mixture was diluted with ethyl acetate (1 mL) and washed with water (1 mL). The organic layer was filtered through a plug of sodium sulphate and the solution was used for the GC-MS analysis, which shows a mixture of 2-phenoxy-8-hydroxyquinoline 2 (m/z = 237), 2-phenoxy-8-hydroxyquinoline-d$_1$ 2-$_{d1}$ (m/z = 238) and 2-phenoxy-8-hydroxyquinoline-d$_2$ 2-$_{d2}$ (m/z = 239).
organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding bis-thiolated product A as a colorless liquid (30 mg, 44%). R$_f$ = 0.5 (Hexane: Et$_2$O = 9:1). mp = 92 °C. IR (neat): v = 3409, 2963, 1588, 1127, 744 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ = 8.12 (d, J = 8.4 Hz, 1H), 7.15–7.33 (m, 12H), 7.08–7.10 (m, 5H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.8, 150.9, 149.4, 140.4, 135.5, 133.7 (2C), 132.6 (4C), 132.4 (2C), 130.4 (2C), 129.4 (4C), 250.00 (0.01), 248.10 (0.01), 247.10 (0.01), 244.10 (0.01), 242.10 (0.01), 241.15 (0.01), 238.10 (0.01), 237.10 (0.01), 236.10 (0.01), 235.15 (0.01), 234.10 (0.01), 232.10 (0.01), 231.10 (0.01), 229.10 (0.01), 227.10 (0.01), 225.10 (0.01), 223.10 (0.01), 221.10 (0.01), 219.10 (0.01), 217.10 (0.01), 215.10 (0.01), 213.10 (0.01), 211.10 (0.01), 209.10 (0.01), 207.10 (0.01), 205.10 (0.01), 203.10 (0.01), 201.10 (0.01), 199.10 (0.01), 197.10 (0.01), 195.10 (0.01), 193.10 (0.01), 191.10 (0.01), 189.10 (0.01), 187.10 (0.01), 185.10 (0.01), 183.10 (0.01), 181.10 (0.01), 179.10 (0.01), 177.10 (0.01), 175.10 (0.01), 173.10 (0.01), 171.10 (0.01), 169.10 (0.01), 167.10 (0.01), 165.10 (0.01), 163.10 (0.01), 161.10 (0.01), 159.10 (0.01), 157.10 (0.01), 155.10 (0.01), 153.10 (0.01), 151.10 (0.01), 149.10 (0.01), 147.10 (0.01), 145.10 (0.01), 143.10 (0.01), 141.10 (0.01), 139.10 (0.01), 137.10 (0.01), 135.10 (0.01), 133.10 (0.01), 131.10 (0.01), 129.10 (0.01), 127.10 (0.01), 125.10 (0.01), 123.10 (0.01), 121.10 (0.01), 119.10 (0.01), 117.10 (0.01), 115.10 (0.01), 113.10 (0.01), 111.10 (0.01), 109.10 (0.01), 107.10 (0.01), 105.10 (0.01), 103.10 (0.01), 101.10 (0.01), 99.10 (0.01), 97.10 (0.01), 95.10 (0.01), 93.10 (0.01), 91.10 (0.01), 89.10 (0.01), 87.10 (0.01), 85.10 (0.01), 83.10 (0.01), 81.10 (0.01), 79.10 (0.01), 77.10 (0.01), 75.10 (0.01), 73.10 (0.01), 71.10 (0.01), 69.10 (0.01), 67.10 (0.01), 65.10 (0.01), 63.10 (0.01), 61.10 (0.01), 59.10 (0.01), 57.10 (0.01), 55.10 (0.01), 53.10 (0.01), 51.10 (0.01), 49.10 (0.01), 47.10 (0.01), 45.10 (0.01), 43.10 (0.01), 41.10 (0.01), 39.10 (0.01), 37.10 (0.01), 35.10 (0.01), 33.10 (0.01), 31.10 (0.01), 29.10 (0.01), 27.10 (0.01), 25.10 (0.01), 23.10 (0.01), 21.10 (0.01), 19.10 (0.01), 17.10 (0.01), 15.10 (0.01), 13.10 (0.01), 11.10 (0.01), 9.10 (0.01), 7.10 (0.01), 5.10 (0.01), 3.10 (0.01), 1.10 (0.01), 0.10 (0.01), -0.10 (0.01).
127.9 (2C), 126.7, 125.9, 125.6, 118.0, 112.9, 111.1 ppm. HRMS (ESI): m/z calcd. for C_{27}H_{20}NO_{2}S_{2} [M + H]^+ , 454.0935; found 454.0931.

^{1}H NMR (600 MHz, CDCl_{3}):

^{13}C NMR (151 MHz, CDCl_{3}):
Preparative methods and characterization of all substrates and products

General Methods. NMR spectra were recorded on Jeol Resonance ECZ 600R spectrometer (600 MHz for $^1$H NMR, 151 MHz for $^{13}$C NMR, 564 MHz for $^{19}$F) and Bruker AvanceII 500 spectrometer (500 MHz for $^1$H NMR, 121 MHz for $^{13}$C NMR). Chemical shifts were reported in ppm on the $\delta$ scale relative to Me$_4$Si ($\delta = 0.00$ for $^1$H-NMR) and CDCl$_3$ ($\delta = 77.160$ for $^{13}$C-NMR). Multiplicities are indicated as: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Infrared (IR) spectra were recorded on Perkin Elmer Spectrum GX FT-IR system. HRMS (SI) spectra were recorded on a Micromass Q-Tof microTM instrument. GCMS spectral data were acquired on a Shimadzu GC-2010 Plus coupled with GCMS-TQ8040 instrument. All low temperature reactions were performed in a Siskin Profichill RFC-90 immersion cooler instrument. For thin-layer chromatography (TLC) analysis throughout this work, Macherey-Nagel pre-coated TLC plates (silica gel 60 F254 0.25 mm) were used. Solvents e.g. DMF, DMSO, Toluene, THF, Dioxan and DCM were dried by standard drying techniques. All other solvents and commercially available compounds were used without further purification.

Preparation of Substrates:

Substrates 1 and 4 were prepared by reported methods.$^{2,3}$ Substrates 2, 3, and 10–25 were prepared as follows:

General procedure A:

Preparation of 2:

An oven-dried Schenck tube was charged with a magnetic stirring bar, copper(I) iodide (28.6 mg, 0.15 mmol, 10 mol%), picolinic acid (36.9 mg, 0.3 mmol, 20 mol%), 2-bromo-8-methoxyquinoline B (357.2 mg, 1.5 mmol, 1.0 eq), PhOH (254.1 mg, 2.7 mmol, 1.8 eq), and K$_3$PO$_4$ (636.8 mg, 3.0 mmol, 2.0 eq). The tube was then evacuated and backfilled with nitrogen (x 3). To it, dimethyl sulfoxide (9.0 mL) was added by syringe. The reaction mixture was stirred vigorously at 90 ºC for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL), the organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give title compound 3 as a colorless solid (324 mg, 86%). IR (KBr): $\nu = 3440, 2920, 2155, 1582, 1086$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.08 (d, $J = 10.2$ Hz, 1H), 7.39–7.42 (m, 2H), 7.34–7.36 (m, 2H), 7.24–7.26 (m, 2H), 7.20 (t, $J = 8.4$ Hz, 1H), 7.03–7.05 (m, 1H), 6.99 (d, $J = 10.2$ Hz, 1H), 3.98 (s, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 161.0, 154.6 (2C), 140.0, 138.3, 129.8 (2C), 126.8, 125.2, 124.6, 120.9 (2C), 119.4, 112.5, 109.2, 56.2 ppm. HRMS (ESI): $m/z$ calcd. for C$_{16}$H$_{14}$NO$_2$ [M + H]$^+$, 252.1025; found, 252.1015.
Step 2: Demethylation of 2-phenoxy-8-methoxyquinoline 3:

To a solution of 3 (297 mg, 1.18 mmol) in 45 mL CH₂Cl₂, 1 M BBr₃ solution in CH₂Cl₂ (3.3 mL, 3.3 mmol) was added dropwise at –20 ºC. The reaction was allowed to stir at that temperature for 1 h and then warmed up to 0 ºC and stirred for 12 h. It was then further warmed up to room temperature and stirred for additional 1 h before quenching with ice-water mixture. The reaction mixture was then extracted with CH₂Cl₂ (3 x 30 mL), washed with brine solution (10 mL), dried over Na₂SO₄ and the solvent was evaporated in vacuo. The crude product was purified by column chromatography over silica gel to obtain the title compound 2 as a pale yellow solid (210 mg, 75% yield). IR (neat): ν = 3429, 2927, 2332, 1263, 1023, 740 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.11 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 8.4 Hz, 2H), 7.21–7.32 (m, 6H), 7.10–7.13 (m, 2H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 160.9, 153.5, 150.9, 140.3, 135.6, 129.7 (2C), 128.4, 127.9, 127.3, 127.1 (2C), 117.9, 113.4, 111.2 ppm. HRMS (ESI): m/z calcd. for C₁₅H₁₂NO₂ [M + H]⁺, 238.0868; found, 238.0857.

General procedure B:

Preparation of 10:

Step 1. Synthesis of 2-bromo-8-benzyloxyquinoline C:

2-Bromo-8-benzyloxyquinoline was prepared according to the literature procedure³ as follows:

To an ice cooled solution of 8-benzyloxyquinoline (4.97 g, 31.3 mmol) in DCM (0.5 M) was added m-CPBA (10.8 g, 62.6 mmol, 2.0 equiv) and the reaction was allowed to stir overnight at room temperature. The reaction mixture was then diluted with DCM and washed with aq. KOH (6 N, 3 x 30 mL), the organic layer was dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The N-oxide was obtained as brown solid (4.32 g, 55% yield), which was thoroughly washed with hexane (5 x 25 mL) and used without further purification for the next step.

To a mixture of the N-oxide (1.81 g, 7.2 mmol), tetrabutylammonium bromide (3.48 g, 10.8 mmol, 1.5 equiv), and 4 Å molecular sieves (7.2 g) was added anhydrous DCM (0.01M) and the mixture was stirred at room temperature for 10 min. To it, p-toluenesulfonic anhydride (3.53 g, 10.8 mmol, 1.5 equiv) was added and the reaction was stirred at room temperature overnight. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexanes/Et₂O solvent mixtures to afford the title compound C as a white solid (1.38 g, 61% yield).

IR (neat): ν = 3415, 3048, 2928, 1589, 1079, 747 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 7.91 (d, J = 7.8 Hz, 1H), 7.49–7.52 (m, 3H), 7.25–7.37 (m, 5H), 7.04 (d, J = 7.2 Hz, 1H), 5.41 (s, 2H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 153.7, 141.0, 140.8, 138.3, 136.9, 128.7 (2C), 128.4, 127.9, 127.3, 127.1 (2C), 126.5, 119.8, 111.8, 71.0 ppm. HRMS (ESI): m/z calcd. for C₁₆H₁₃BrNO [M + H]⁺, 314.0181; found 314.0168.
Step 2. Synthesis of 2-(4-methoxyphenyl)-8-hydroxyquinoline 10:

An oven-dried 50 mL round bottomed flask was charged with a magnetic stirring bar, copper(I) iodide (20.9 mg, 0.11 mmol, 10 mol%), picolinic acid (27.1 mg, 0.22 mmol, 20 mol%), 2-bromo-8-benzoxylquinoline (350 mg, 1.1 mmol, 1.0 eq), 4-methoxyphenol (245.8 mg, 1.98 mmol, 1.8 eq), and K$_2$PO$_4$ (467 mg, 2.2 mmol, 2.0 eq). The flask was then evacuated and backfilled with nitrogen (x 3). To it, dimethyl sulfoxide (6.6 mL) was added by syringe. The reaction mixture was stirred vigorously at 90 ºC for 24 h. After cooling, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (8 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL), the organic layers were washed with 10% NaOH solution (8 mL), brine (8 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The title compound D was obtained as a colorless solid (385 mg, 98%) which was used for the next step without further purification. IR (KBr): ν = 3423, 2963, 2354, 1589, 1504, 1094, 754 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ 8.07 (d, $J = 9.0$ Hz, 1H), 7.32–7.37 (m, 5H), 7.24–7.30 (m, 4H), 7.07–7.09 (m, 2H), 6.95 (d, $J = 9.0$ Hz, 2H), 5.20 (s, 2H), 3.83 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 161.6, 156.7, 153.5, 147.5, 139.8, 138.6, 137.5, 128.4 (2C), 127.6, 126.94 (2C), 126.9, 124.8, 122.9 (2C), 120.2, 114.6 (2C), 112.7, 112.6, 71.0, 55.7 ppm. MS (70 eV), m/z (%) 359 (40), 358 (17), 357 (68) [M$^+$], 356 (28), 197 (68), 103 (37), 91 (100%).

An oven-dried 50 mL round bottomed flask was charged with a magnetic stirring bar, 2-(4-Methoxyphenyl)-8-benzoxylquinoline D (337 mg, 0.94 mmol, 1.0 eq), 10 wt% Pd/C (66 mg). The flask was then evacuated and backfilled with nitrogen (x 3) and finally backfilled with hydrogen gas (using a hydrogen balloon). To it, anhydrous MeOH (15 mL) was added by syringe. The reaction mixture was stirred vigorously at room temperature for 12 h. Then MeOH was evaporated to get a black residue, which was directly subjected to column chromatography over silica gel using hexane and Et$_2$O as eluents to give the title compound 10 as a colorless solid (174 mg, 65%). IR (KBr): ν = 3415, 2927, 1589, 1504, 1094, 754 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ 8.11 (d, $J = 9.0$ Hz, 1H), 7.27–7.32 (m, 3H), 7.14–7.15 (m, 2H), 7.10–7.12 (m, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 3.86 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 161.4, 157.0, 150.9, 146.9, 140.2, 135.6, 125.6 (2C), 122.7 (2C), 117.9, 114.7 (2C), 113.3, 111.1, 55.8 ppm. MS (70 eV), m/z (%) 268 (23), 267 (100) [M$^+$], 266 (91), 252 (33), 116 (16), 89 (16).

Preparation of 11:

Cul (20 mol%) + picolinic acid (40 mol%) + K$_2$PO$_4$ (2 eq) in DMSO, 90 ºC, 24 h.
Compound E was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% CuI and 40 mol% picolinic acid starting from 1.6 mmol 2-bromo-8-methoxyquinoline B. Colorless solid, (169 mg, 32%): IR (KBr): ν = 3408, 2827, 1604, 1250, 1094, 747 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.11 (d, J = 9.0 Hz, 1H), 7.50–7.52 (m, 2H), 7.36–7.39 (m, 2H), 7.17–7.19 (m, 2H), 7.03–7.06 (m, 2H), 3.98 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 160.4, 154.6, 153.6, 140.3, 138.1, 132.7 (2C), 127.0, 125.4, 122.7 (2C), 119.5, 117.2, 112.8, 109.4, 56.3 ppm. HRMS (ESI): m/z calcd. for C₁₆H₁₃BrNO₂ [M + H⁺], 330.0130; found, 330.0132.

Compound 11 was prepared according to the general procedure A as described for the preparation of 2 with a little modification: To a solution of E (143 mg, 0.43 mmol) in 16 mL CH₂Cl₂, 1 M BBr₃ solution in CH₂Cl₂ (1.2 mL, 1.2 mmol) was added dropwise at 0 °C. The reaction was allowed to stir at that temperature for 1 h and then warmed up to room temperature and stirred for 12 h before quenching with ice-water mixture. The reaction mixture was then extracted with CH₂Cl₂ (3 x 20 mL), washed with brine solution (5 mL), dried over Na₂SO₄ and the solvent was evaporated in vacuo. The crude product was purified by column chromatography over silica gel to obtain the title compound 11 as a colorless viscous liquid (102 mg, 75% yield). IR (KBr): ν = 3471, 2928, 2223, 1604, 1257, 747 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.14 (d, J = 9.0 Hz, 1H), 7.53–7.56 (m, 2H), 7.28–7.34 (m, 2H), 7.16 (s, 1H) 7.11–7.14 (m, 4H), ppm. ¹³C NMR (151 MHz, CDCl₃) δ 160.5, 152.5, 150.9, 140.5, 135.4, 132.8 (2C), 126.0, 125.8, 123.6 (2C), 118.1, 118.0, 113.4, 111.4 ppm. HRMS (ESI): m/z calcd. for C₁₅H₁₂BrNO₂ [M + H⁺], 315.9973; found, 315.9971.

Preparation of 12:

Compound F was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% CuI and 40 mol% picolinic acid starting from 2.1 mmol of B. Colorless solid, (191 mg, 33%): IR (KBr): ν = 2928, 2223, 1595, 1497, 1260, 828 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.18 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.38–7.43 (m, 4H), 7.13 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 6.6 Hz, 1H), 3.98 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 159.3, 158.2, 154.6, 140.6, 137.8, 133.9 (2C), 127.4, 126.0, 121.0 (2C), 119.5, 119.0, 113.5, 109.4, 107.5, 56.3 ppm. MS (70 eV, m/z (%): 276 (100) [M⁺], 275 (88), 247 (61), 246 (27), 128 (49), 127 (24).

Compound 12 was prepared according to the general procedure A as described for the preparation of 2 starting from 0.6 mmol of F. Colourless solid (69 mg, 44%): IR (KBr): ν = 3458, 2920, 2223, 1602, 1504, 1274, 827 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.21 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 7.8 Hz, 2H), 7.32–7.39 (m, 4H), 7.18 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.08 (bs, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 159.7, 157.2, 150.9, 141.0, 135.3, 134.0 (2C), 126.5, 126.2, 122.4 (2C), 118.0, 118.1, 113.5, 111.7, 108.8 ppm. MS (70 eV, m/z (%): 262 (91) [M⁺], 261 (100), 116 (25), 89 (24).
Preparation of 13:

Compound G was prepared according to the general procedure B as described for the preparation of D using 20 mol% CuI and 40 mol% picolinic acid starting from 1.26 mmol C. Colorless solid, (262 mg, 55%): IR (KBr): ν = 3430, 2927, 1589, 1348, 1256, 740 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.81–8.82 (m, 1H), 8.15–8.18 (m, 2H), 7.33–7.77 (m, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.39–7.40 (m, 2H), 7.34–7.36 (m, 1H), 7.22–7.27 (m, 4H), 7.02–7.03 (m, 3H), 4.87 (s, 2H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.8, 153.4, 150.3, 150.2, 142.2, 139.9, 138.8, 137.6, 136.1, 129.9, 128.2 (2C), 127.4, 127.2, 126.8 (2C), 126.7, 124.8, 124.7, 121.9, 121.5, 120.7, 113.9, 113.2, 71.4 ppm. HRMS (ESI): m/z calcd. for C₂₃H₁₉N₂O₂ [M + H]^⁺, 379.1447; found, 379.1448.

Preparation of 14:

Compound 14 was prepared according to the general procedure B as described for the preparation of 10 using 16 mg 10 wt% Pd/C as the catalyst starting from 0.53 mmol G. Colorless viscous liquid, (53 mg, 34%): IR (KBr): ν = 3430, 2969, 1604, 1080, 797 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 8.83–8.84 (m, 1H), 8.23–8.25 (m, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.77–7.79 (m, 1H), 7.60–7.63 (m, 2H), 7.42–7.44 (m, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.28–7.30 (m, 2H), 7.02–7.03 (m, 1H), 6.95 (bs, 1H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 161.7, 150.8, 150.5, 149.7, 141.9, 140.3, 136.3, 135.6, 130.0, 126.6, 125.8, 125.6, 125.4, 121.8 (2C), 117.9, 113.5, 110.9 ppm. HRMS (ESI): m/z calcd. for C₁₈H₁₁N₂O₂ [M + H]^⁺, 289.0797; found, 289.0972.

Preparation of 14:
Preparation of 15:

![Chemical structure of compound H](image)

Compound H was prepared according to the general procedure B as described for the preparation of D using 20 mol% Cu and 40 mol% picolinic acid starting from 1.26 mmol of C. Colourless viscous liquid, (439 mg, 92%). IR (KBr): ν = 3430, 2813, 2354, 1589, 1334, 1249, 733 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.92–8.93 (m, 1H), 8.17 (t, J = 8.4 Hz, 2H), 8.00 (d, J = 7.8 Hz, 1H), 7.92–7.93 (m, 1H), 7.74–7.75 (m, 1H), 7.33–7.41 (m, 3H), 7.20–7.25 (m, 4H), 7.11 (t, J = 7.2 Hz, 3H), 5.16 (s, 2H) ppm. \(^13\)C NMR (151 MHz, CDCl\(_3\)) δ 160.9, 153.6, 152.0, 149.7, 146.1, 140.1, 138.3, 137.1, 136.0, 130.8, 129.1, 128.4 (2C), 127.6, 127.1, 126.8 (2C), 125.8, 125.2, 121.4, 120.1, 117.7, 113.2, 112.1, 70.9 ppm. HRMS (ESI): m/z calcd. for C\(_{25}H_{20}N_2O_2^+ [M + H]^+\), 379.1447; found, 379.1434.

Preparation of 16:

![Chemical structure of compound J](image)

Compound J was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% Cu and 40 mol% picolinic acid starting from 2.5 mmol of I. Colorless solid, (403 mg, 61%). IR (KBr): ν = 2935, 1595, 1484, 1400, 1253, 1099, 827 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) δ 8.17–8.19 (m, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.22 (d, J = 7.8 Hz, 2H), 7.17 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 3.92 (s, 3H), 2.52 (s, 3H) ppm. \(^13\)C NMR (151 MHz, CDCl\(_3\)) δ 160.6, 154.5, 152.9, 138.5, 136.7, 129.7 (2C), 125.8, 125.7, 125.2, 124.4, 120.7 (2C), 111.7, 108.9, 56.0, 18.18 ppm. MS (70 eV), m/z (%) 238 (99), 268 (99) [M+], 264 (100), 246 (47), 236 (99), 235 (84), 115 (88), 77 (99).
Compound 16 was prepared according to the general procedure A as described for the preparation of 2 starting from 1.5 mmol of J. Colourless thick liquid (225 mg, 60%): IR (KBr): v = 3395, 2920, 1588, 1491, 1400, 1323, 1253 786 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.26 (d, \(J = 9.0\) Hz, 1H), 7.42-7.43 (m, 2H), 7.22-7.25 (m, 2H), 7.12-7.18 (m, 3H), 6.99 (d, \(J = 7.2\) Hz, 1H), 2.56 (s, 1H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 160.6, 153.6, 149.2, 137.3, 135.9, 129.7 (2C), 125.9, 125.2, 124.8, 124.7, 121.7 (2C), 112.7, 110.6, 18.1 ppm. HRMS (ESI): \(m/z\) calc. for C\(_{16}\)H\(_{15}\)NO\(_2\) [M + H]\(^+\), 252.1025; found, 252.1030.

**Preparation of 17:**

Compound L was prepared according to the general procedure B as described for the preparation of D using 20 mol% CuI and 40 mol% picolinic acid starting from 0.81 mmol of K. Colourless solid, (200 mg, 56%): IR (KBr): v = 3064, 1595, 1469, 1407, 1260, 1092, 813 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.51 (d, \(J = 9.0\) Hz, 1H), 7.42 (t, \(J = 7.8\) Hz, 2H), 7.25-7.34 (m, 8H), 7.08 (d, \(J = 9.0\) Hz, 1H), 7.01 (d, \(J = 8.4\) Hz, 1H), 6.60 (d, \(J = 7.8\) Hz, 1H), 5.11 (s, 2H), 3.92 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 161.7, 154.1, 150.1, 147.5, 139.7, 137.9, 135.1, 129.6 (2C), 128.4 (2C), 127.3, 124.8, 122.0 (2C), 118.7, 114.1, 111.6, 102.6, 72.3, 55.8 ppm. MS (70 eV), \(m/z\) (%) 357 (28) [M+], 342 (15), 266 (60), 251 (67), 167 (100), 91 (49).

Compound 17 was prepared according to the general procedure B as described for the preparation of 10 with slight modification using 16 mg 10 wt% Pd/C as the catalyst starting from 0.56 mmol of L and the reaction mixture was stirred vigorously at room temperature for 3 h. Yellow viscous liquid (130 mg, 49%). IR (KBr): v = 3430, 2920, 1581, 1400, 1253, 1079 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.49 (d, \(J = 9.0\) Hz, 1H), 7.42 (t, \(J = 7.2\) Hz, 2H), 7.21-7.24 (m, 3H), 7.08 (d, \(J = 8.4\) Hz, 1H), 6.99 (d, \(J = 9.0\) Hz, 1H), 6.81 (s, 1H), 6.64 (d, \(J = 9.0\) Hz, 1H), 3.91 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 161.4, 153.5, 148.2, 144.7, 136.1, 135.6, 129.7 (2C), 125.2, 121.7 (2C), 117.6, 112.0, 110.2, 103.7, 55.9 ppm. HRMS (ESI): \(m/z\) calc. for C\(_{16}\)H\(_{15}\)NO\(_2\) [M + H]\(^+\), 268.0974; found, 268.0967.

**Preparation of 18:**

Compound N was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% CuI and 40 mol% picolinic acid starting from 0.75 mmol M. Colourless solid, (119 mg, 59%): IR (KBr): v = 3423, 1609, 1484, 1407, 1260, 1092, 771 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.32 (d, \(J = 9.0\) Hz, 1H), 7.41 (t, \(J = 8.4\) Hz, 2H), 7.20-7.25 (m, 3H), 7.05 (d, \(J = 9.0\) Hz, 1H), 7.0 (t, \(J = 9.0\) Hz, 1H), 6.89-6.91 (m, 1H), 3.93 (s, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 161.7, 154.1, 152.2 (d, \(J_{CF} = 246.5\) Hz), 151.0 (d, \(J_{CF} = 2.7\) Hz), 138.6, 133.6 (d, \(J_{CF} = 3.0\) Hz), 129.9 (2C), 125.0, 121.2 (2C), 117.0 (d, \(J_{CF} = 17.7\) Hz), 112.6, 108.7 (d, \(J_{CF} = 8.8\) Hz), 77.1 ppm.
Compound 18 was prepared according to the general procedure A as described for the preparation of 2 starting from 0.94 mmol of N. Colourless viscous liquid (177 mg, 74%): IR (KBr): ν = 3409, 1595, 1483, 1400, 1253, 778 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.37 (d, J = 9.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 9.0 Hz, 1H), 6.97-6.99 (m, 2H), 6.91 (s, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.60, 153.2, 151.2 (d, J = 245.8 Hz), 147.1, 135.5, 134.1, 129.8 (2C), 125.5, 121.8 (2C), 115.8 (d, J = 19.0 Hz), 113.6, 110.1 (d, J = 8.3 Hz), 109.1 (d, J = 20.5 Hz) ppm. HRMS (ESI): m/z calcd. for C₁₉H₁₄FNO₂ [M + H]⁺, 256.0774; found, 256.0777.

**Preparation of 19:**

Compound P was prepared according to the general procedure B as described for the preparation of D using 20 mol% Cul and 40 mol% picolinic acid starting from 1.6 mmol of O. Colourless solid, (567 mg, 98%): IR (KBr): ν = 3415, 2962, 1582, 1384, 768 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.50 (d, J = 9.0 Hz, 1H), 7.44 (t, J = 8.4 Hz, 2H), 7.34–7.36 (m, 3H), 7.31–7.32 (m, 3H), 7.25–7.29 (m, 3H), 7.22 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.17 (s, 2H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.7, 153.9, 152.7, 139.5, 137.1 (2C), 129.7 (2C), 128.5 (2C), 127.7, 126.9 (2C), 125.0, 124.7, 124.6, 123.2, 121.9 (2C), 113.7, 112.5, 71.3 ppm HRMS (ESI): m/z calcd. for C₂₃H₁₉ClN₂O₂ [M + H]⁺, 362.0948; found, 362.0930.

Compound 19 was prepared according to the general procedure B as described for the preparation of 10 using 50 mg of 10 wt% Pd/C as the catalyst starting from 1.43 mmol of P. Colorless solid (132 mg, 34%): IR (neat): ν = 3415, 2807, 2361, 1589, 1377, 1264, 768 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.48–8.50 (m, 1H), 7.43–7.46 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.19–7.29 (m, 4H), 7.19 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 161.4, 153.2, 150.0, 137.6, 136.3, 129.9 (2C), 125.6, 125.5, 123.5, 121.8 (2C), 120.8, 114.3, 111.3 ppm. HRMS (ESI): m/z calcd. for C₁₉H₁₄ClNO₂ [M + H]⁺, 372.0478; found, 272.0471.

**Preparation of 20:**

A 25 mL round bottom flask with magnetic stirring bar was charged with substrate 2 (279 mg, 1.2 mmol), and tert-butyldimethylsilyl chloride (TBDMSCI) (542.6 mg, 3.6 mmol, 3.0 equiv) in DCM (7
mL). To it, triethyl amine (333 µL, 2.4 mmol, 2.0 equiv) was added and the reaction mixture was stirred for overnight at room temperature. After completion of the reaction (TLC), the reaction mixture was washed with water (3 x 2 mL), organic layer was dried over Na2SO4, filtered and removed the solvent in vacuo to get the crude TBDMС-protected product which was used for the next step without further purification. Yield: 136 mg, 32%

To a mixture of TBDMС-protected substrate (136 mg, 0.39 mmol) in DCM (3 mL), freshly recrystallized NBS (106.8 mg, 0.59 mmol, 1.5 equiv) was added slowly at 15 °C and the reaction mixture was allowed to stir at 20 °C for 30 min. Reaction mixture was successively washed with 1% Na2SO3 solution and water, organic layer was dried over Na2SO4, filtered, and the solvent was evaporated in vacuo to give the brominated TBDMС-protected compound.

Yield: 136 mg, 81%

To a mixture of brominated TBDMС-protected compound (136 mg, 0.32 mmol) in THF (5 mL), tetrabutylammonium fluoride (1.0 M in THF, 384 µL, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 10 minutes at room temperature. After completion, the reaction mixture was diluted with DCM (20 mL), washed with water (3 x 3 mL), the organic layer was dried over Na2SO4 and the solvent was evaporated vacuo. The crude product was purified by flash column chromatography using hexanes/Et2O solvent mixtures to afford the title compound 20 as a colorless solid (71 mg, 70%): IR (KBr): ν = 3440, 1624, 1383, 1251 cm⁻¹. 1H NMR (600 MHz, CDCl3) δ 8.44 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.44–7.46 (m, 2H), 7.21–7.29 (m, 4H), 6.97 (d, J = 7.8 Hz, 1H) ppm. 13C NMR (151 MHz, CDCl3) δ 161.4, 153.2, 150.6, 140.0, 136.4, 129.8 (2C), 129.0, 125.6, 124.8, 121.7 (2C), 114.5, 111.9, 110.0 ppm. MS (70 eV), m/z (%): 317 (93), 316 (90), 315 (100) [M⁺], 314 (80), 236 (13), 180 (18), 77 (26), 51 (21).

**Preparation of 21:**

![Diagram](image)

Compound 21 was prepared according to the general procedure B as described for the preparation of D using 20 mol% CuI and 40 mol% picolinic acid starting from 4.8 mmol of Q. Colorless solid (1.17 g, 65%): IR (neat): ν = 3452, 1624, 1372, 614 cm⁻¹. 1H NMR (600 MHz, CDCl3) δ 8.17 (bs, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.50–7.52 (m, 4H), 7.42 (d, J = 7.8 Hz, 1H), 7.31–7.36 (m, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.08–7.10 (m, 3H), 2.29 (s, 3H) ppm. 13C NMR (151 MHz, CDCl3) δ 161.3, 153.2, 143.7, 140.3, 136.6, 136.5, 132.4, 129.7 (2C), 129.4 (2C), 127.2 (2C), 125.7, 125.4, 125.1, 122.5, 121.9 (2C), 117.8, 113.5, 21.6 ppm. HRMS (ESI): m/z calcd. for C23H19N2O2S [M + H]⁺, 391.1116; found, 391.1110.

**Preparation of 22:**

![Diagram](image)

Compound 22 was prepared according to the general procedure B as described for the preparation of D using 20 mol% CuI and 40 mol% picolinic acid starting from 3.5 mmol of R. Colorless solid (605 mg, 55%): IR (neat): ν = 3241, 2920, 1588, 1407, 1330, 1246, 1155, 757 cm⁻¹. 1H NMR (600 MHz, CDCl3) δ 8.17 (d, J = 9.0 Hz, 1H), 7.86 (bs, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.47 (t, J =
7.8 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 8.4 Hz, 3H), 2.82 (s, 3H) ppm. 

13C NMR (151 MHz, CDCl₃) δ 161.7, 153.3, 140.5, 136.9, 132.6, 129.9 (2C), 125.8, 125.7, 125.3, 122.9, 121.7(2C), 118.1, 113.7, 39.3 ppm. MS (70 eV), m/z (%): 314 (39) [M+], 236 (20), 235 (100), 234 (20), 206 (15), 77 (10).

**Preparation of 23:**

<table>
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<th>S</th>
<th>PhOH (1.8 eq)</th>
<th>CuI (20 mol%)</th>
<th>picolinic acid (40 mol%)</th>
<th>K₃PO₄ (2 eq)</th>
<th>DMSO, 90 ºC, 24 h</th>
<th>NHCOMe</th>
<th>NPh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 23</td>
<td>was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% CuI and 40 mol% picolinic acid starting from 1.7 mmol of S. Colorless solid, (310 mg, 66%): IR (KBr): v = 3359, 2807, 2354, 1674, 1250, 761 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.98 (bs, 1H), 8.61 (d, J = 7.2 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.26–7.30 (m, 3H), 7.14 (d, J = 9.0 Hz, 1H), 2.03 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 168.5, 160.9, 153.5, 140.4, 135.6, 133.3, 129.5 (2C), 125.5, 125.3, 125.0, 122.2 (2C), 121.2, 117.2, 112.8, 24.8 ppm. HRMS (ESI): m/z calcd. for C₁₃H₁₃N₂O₂ [M + H]+, 279.1134; found, 279.1125.</td>
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**Preparation of 24:**

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<th>T</th>
<th>PhOH (1.8 eq)</th>
<th>CuI (20 mol%)</th>
<th>picolinic acid (40 mol%)</th>
<th>K₃PO₄ (2 eq)</th>
<th>DMSO, 90 ºC, 24 h</th>
<th>NHCOMe</th>
<th>NPh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 24</td>
<td>was prepared according to the procedure for the synthesis of 23 starting from 2.0 mmol of T. Colorless solid (379 mg, 65%): IR (neat): v = 3387, 2934, 2835, 2361, 1667, 1030, 662 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.05 (bs, 1H), 8.65 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.43–7.48 (m, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.24–7.30 (m, 3H), 7.16 (d, J = 9.0 Hz, 1H), 2.27 (q, J = 7.8 Hz, 2H), 1.04 (t, J = 7.8 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 172.1, 161.0, 153.5, 140.5, 135.7, 133.3, 129.6 (2C), 125.5, 125.3, 125.0, 122.3 (2C), 121.1, 117.3, 112.9, 31.2, 9.6 ppm. HRMS (ESI): m/z calcd. for C₁₃H₁₃N₂O₂ [M + H]+, 293.1290; found, 293.1285.</td>
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**Preparation of 25:**

<table>
<thead>
<tr>
<th>U</th>
<th>PhOH (1.8 eq)</th>
<th>CuI (20 mol%)</th>
<th>picolinic acid (40 mol%)</th>
<th>K₃PO₄ (2 eq)</th>
<th>DMSO, 90 ºC, 24 h</th>
<th>NHCOMe</th>
<th>NPh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 25</td>
<td>was prepared according to the general procedure A as described for the preparation of 3 using 20 mol% CuI and 40 mol% picolinic acid starting from 1.25 mmol of U. Brownish white solid, (300 mg, 91%): IR (KBr): v = 2816, 1595, 1344, 1253, 841 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.13–9.14 (m, 1H), 8.19–8.22 (m, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.57–7.59 (m, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.27–7.30 (m, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.12–7.14 (m, 1H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 162.6, 158.4, 150.3, 145.5, 145.2, 140.0, 135.9, 130.0 (2C), 129.2, 125.9, 125.6, 122.9, 118.1, 113.7, 39.3 ppm. MS (70 eV), m/z (%): 314 (39) [M+], 236 (20), 235 (100), 234 (20), 206 (15), 77 (10).</td>
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124.9, 124.7, 123.0, 120.8 (2C), 112.7 ppm. HRMS (ESI): m/z calcd. for C_{13}H_{17}N_{2}O [M + H]^+, 273.1028; found, 273.1022.

**General Procedure C: Dearlyoxyative Amination of 2-phenoxy-8-hydroxyquinoline (2) with various amines (7a–7i).** A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline 2 (36 mg, 0.15 mmol, 1.0 equiv) and copper(II) triflate (5.4 mg, 0.015 mmol, 10 mol%) or 10.8 mg, 0.03 mmol, 20 mol%). To it, DMF (2.5 mL) and an amine (0.75 mmol, 5 equiv) were added sequentially. The reaction mixture was stirred under air at the specified temperature for the required time (TLC). After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding 2-amino-8-hydroxyquinoline.

**Characterization of 2-amino-8-hydroxyquinolines (8a–8i).**

2-(Piperidin-1-yl)quinolinol-8-ol (8a) was prepared according to the general procedure C using piperidine (74 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst at 120 °C. Light yellow solid (29 mg, 84%). R$_f$ = 0.4 (Hexane: Et$_2$O = 19:1). mp = 63 °C. IR ( neat): ν = 3430, 2920, 1256, 1037, 797 cm$^{-1}$. $^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.85 (d, J = 9.0 Hz, 1H), 7.09–7.13 (m, 2H), 7.03–7.05 (m, 1H), 7.00 (d, J = 9.0 Hz, 1H), 3.69–3.70 (m, 4H), 1.66–1.72 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.4, 150.2, 137.6, 137.3, 122.7, 122.5, 117.6, 110.8, 110.1, 46.5 (2C), 25.7 (2C), 24.9 ppm. HRMS (ESI): m/z calcd. for C$_{14}$H$_{15}$N$_2$O [M + H]$^+$, 229.1341; found, 229.1342.

2-(4-Phenylpiperidin-1-yl)quinolinol-8-ol (8b) was prepared according to the general procedure C using 4-phenylpiperidine (121 mg, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst at 120 °C. Light yellow solid (34 mg, 75%). R$_f$ = 0.5 (Hexane:Et$_2$O = 18:2). mp = 87 °C. IR (KBr): ν = 3387, 2927, 2354, 1596, 1249, 754 cm$^{-1}$. $^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.90 (d, J = 9.0 Hz, 1H), 7.31–7.33 (m, 2H), 7.21–7.24 (m, 3H), 7.12–7.15 (m, 2H), 7.06–7.08 (m, 2H), 4.63–4.65 (m, 2H), 3.06–3.10 (m, 2H), 2.80–2.85 (m, 1H), 1.99–2.01 (m, 2H). 18.0–1.83 (m, 2H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.3, 150.2, 145.8, 137.8, 137.2, 128.7 (2C), 127.0 (2C), 126.6, 122.9, 122.7, 117.6, 110.8, 110.2, 46.4 (2C), 43.1, 33.1 (2C) ppm. HRMS (ESI): m/z calcd. for C$_{20}$H$_{17}$N$_2$O [M + H]$^+$, 305.1664; found, 305.1660.

2-Morpholinoquinolinol-8-ol (8c) was prepared according to the general procedure C using morpholine (65 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst at 120 °C. Light yellow solid (28 mg, 82%). R$_f$ = 0.5 (Hexane:EtOAc = 1:1). mp = 92 °C. IR (KBr): ν = 3430, 2919, 2354, 1356, 1116, 754 cm$^{-1}$. $^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.94 (d, J = 9.6 Hz, 1H), 7.16–7.17 (m, 2H), 7.07–7.09 (m, 1H), 6.99 (d, J = 9.6 Hz, 1H), 3.87–3.88 (m, 4H), 3.67–3.69 (m, 4H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.5, 150.3, 138.0, 137.0, 123.5, 123.1, 123.1, 117.7, 110.5, 110.3, 66.8 (2C), 45.7 (2C) ppm. HRMS (ESI): m/z calcd. for C$_{13}$H$_{15}$N$_2$O$_2$ [M + H]$^+$, 231.1134; found, 231.1129.

2-(3,4-Dihydroisoquinolin-2(1H)-yl)quinolinol-8-ol (8d) was prepared according to the general procedure C using 1,2,3,4-tetrahydroisoquinoline (94 mL, 0.75 mmol, 5 equiv) as the amine source, Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst and Cs$_2$CO$_3$ (73.3 mg, 0.225 mmol, 1.5 eq) as an additive at 120 °C. Viscous liquid (22 mg, 54%). R$_f$ = 0.4 (Hexane:Et$_2$O = 19:1). IR ( neat): ν = 3423, 2935, 2335, 1260, 1023, 729 cm$^{-1}$. $^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.85 (d, J = 9.0 Hz, 1H), 7.12–7.18 (m, 4H), 7.04–7.09 (m,
2-(Azepan-1-yl)quinolin-8-ol (8e) was prepared according to the general procedure C using hexamethylenimine (85 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst at 120 °C. Viscous liquid (31 mg, 86%). $R_f = 0.3$ (Hexane:EtO = 19:1). IR (neat): $\nu = 3401, 2934, 2325, 1448, 1080, 740$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 9.0$ Hz, 1H), 7.00–7.02 (m, 1H), 6.94–6.99 (m, 2H), 6.75 (d, $J = 9.0$ Hz, 1H), 3.64 (s, 4H), 1.74 ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 155.3, 149.9, 137.7, 137.4, 121.9, 121.8, 117.6, 109.8, 109.7, 48.1 (2C) ppm. HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{16}$N$_2$O [M + H]$^+$, 299.1160; found, 299.1165.

2-(Dimethylamino)quinolin-8-ol (8f) was prepared according to the general procedure C with a little modification: A 20 mL Schlenk tube was charged with 2 (36 mg, 0.15 mmol, 1.00 equiv) and copper(II) triflate (10.8 mg, 0.03 mmol, 20 mol%). To it, DMF (2.5 mL) and a freshly prepared solution of dimethylamine in methanol [prepared in a separate vessel by mixing dimethylamine hydrochloride (61 mg, 0.75 mmol) and triethylamine (105 mL, 0.75 mmol) in 1:1 ratio] were added sequentially. The reaction mixture was stirred under air at 100 °C for 16 h and subsequently at r.t for 12 h. Then it was cooled, diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give 8f as a Brown solid (17 mg, 61%). $R_f = 0.3$ (Hexane:EtO = 9:1). mp = 71 °C. IR (KBr): $\nu = 3366, 2927, 1640, 1385, 1250, 747$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 9.0$ Hz, 1H), 7.04–7.05 (m, 1H), 6.89 (d, $J = 9.0$ Hz, 1H), 3.21 (s, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 156.4, 150.1, 137.5, 137.4, 122.2, 122.0, 117.6, 110.0, 109.8, 38.3 (2C) ppm. HRMS (ESI): $m/z$ calcd. for C$_{15}$H$_{10}$N$_2$O [M + H]$^+$, 243.1497; found, 243.1501.

2-(Diethylamino)quinolin-8-ol (8g) was prepared according to the general procedure C using diethylamine (78 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (10.8 mg, 0.03 mmol, 20 mol%) as the catalyst at 100 °C. Brown solid (24 mg, 73%). $R_f = 0.3$ (Hexane:EtO = 19:1). mp = 75 °C. IR (neat): $\nu = 3438, 2933, 2341, 1738, 1164, 668$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 9.0$ Hz, 1H), 7.10–7.12 (m, 1H), 7.02–7.08 (m, 2H), 6.84 (d, $J = 9.0$ Hz, 1H), 3.64 (q, $J = 7.2$ Hz, 4H), 1.26 (t, $J = 6.6$ Hz, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 154.7, 150.0, 137.7, 137.5, 121.9 (2C), 117.6, 109.9 (2C), 43.1 (2C), 13.2 (2C) ppm. HRMS (ESI): $m/z$ calcd. for C$_{16}$H$_{18}$N$_2$O [M + H]$^+$, 239.1160; found, 239.1158.

2-(Benzyl(methyl)amino)quinolin-8-ol (8h) was prepared according to the general procedure C using N-benzylmethylamine (97 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (10.8 mg, 0.03 mmol, 20 mol%) as the catalyst at 120 °C. Brown solid (35 mg, 88%). $R_f = 0.4$ (Hexane:EtO = 19:1). mp = 78 °C. IR (KBr): $\nu = 3430, 2947, 1589, 1257, 768$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 9.0$ Hz, 1H), 7.30–7.32 (m, 2H), 7.24–7.26 (m, 3H), 7.09–7.14 (m, 2H), 7.05–7.06 (m, 1H), 6.90 (d, $J = 9.0$ Hz, 1H), 4.89 (s, 2H), 3.23 (s, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 156.1, 150.1, 138.3, 137.8, 137.4, 128.8 (2C), 127.3, 127.0 (2C), 122.5, 122.3, 117.7, 110.2, 109.8, 53.9, 36.8 ppm. HRMS (ESI): $m/z$ calcd. for C$_{18}$H$_{13}$N$_2$O [M + H]$^+$, 265.1341; found, 265.1348.
2-(Dibenzylamino)quinolin-8-ol (8i) was prepared according to the general procedure C using dibenzylamine (144 mL, 0.75 mmol, 5 equiv) as the amine source and Cu(OTf)$_2$ (10.8 mg, 0.03 mmol, 20 mol%) as the catalyst at 120 °C and the reaction was continued for 72 h. Light yellow solid (28 mg, 55%). $R_f = 0.5$ (Hexane:EtOAc = 19:1); mp = 91 °C. IR (KBr): $\nu = 3422$, 2920, 2361, 1589, 1242, 740 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 9.0$ Hz, 1H), 7.67 (bs, 1H), 7.31–7.34 (m, 4H), 7.27–7.29 (m, 6H), 7.10–7.14 (m, 2H), 7.05 (d, $J = 7.2$ Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 1H), 4.92 (s, 4H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 155.9, 150.1, 138.1 (2C), 137.2 (2C), 128.9 (4C), 127.4 (2C), 127.1 (4C), 122.8, 122.7, 117.7, 110.3, 110.0, 51.8 (2C) ppm. HRMS (ESI): $m/z$ calcd. for C$_{25}$H$_{21}$N$_2$O [M + H]$^+$, 341.1654; found, 341.1651.

Synthesis of 2-(methylamino)quinolin-8-ol (9) via hydrogenolysis of N-benzylated amine product 8h. A 25 mL round bottom flask equipped with a magnetic stirring bar and rubber septum was charged with 8h (90 mg, 0.34 mmol), and Pd/C (61 mg). The flask was evacuated and back filled with H$_2$-balloon at room temperature for 24 h (TLC). Next, MeOH was evaporated using rotary evaporator and the black residue was directly purified by flash column chromatography on silica-gel to give the corresponding secondary N-heteroaryl amine 9. Greenish yellow solid (31 mg, 52%). $R_f = 0.3$ (Hexane:EtOAc = 3:2); mp = 115–120 °C. IR (KBr): $\nu = 3415$, 2920, 1611, 1392, 818 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 9.0$ Hz, 1H), 7.11–7.12 (m, 2H), 7.06–7.07 (m, 1H), 6.63 (d, $J = 9.0$ Hz, 1H), 4.76 (bs, 1H), 3.08 (d, $J = 4.8$ Hz, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 156.3, 150.2, 137.3, 137.2, 123.0, 122.6, 117.9, 112.5, 110.4, 28.7 ppm. MS (70 eV), $m/z$ (%) 174 (100) [M$^+$], 173 (32), 145 (51), 117 (43). HRMS (ESI): $m/z$ calcd. for C$_{10}$H$_{16}$N$_2$O$^+$ [M + Na]$^+$, 197.0691; found, 197.0682.

General Procedure D: Dearyloxylative amination of various N-heteroaryl ethers with piperidine. A 20 mL Schlenk tube was charged with the N-heteroaryl ether (0.15 mmol, 1.00 equiv) and copper(II) triflate (10.8 mg, 0.03 mmol, 20 mol%). To it, DMF (2.5 mL) and piperidine (74 µL, 0.75 mmol, 5 equiv) were added sequentially. The reaction mixture was stirred under air at 120 °C for the required time (TLC). After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding N-heteroaryl amine.

Characterization of N-heteroaryl amines.

Compound 8a was prepared according to the general procedure D starting from 10–15 (0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. All characterization data including IR, $^1$H and $^{13}$C NMR, and HRMS was found to be identical with the one as described above.

5-Methyl-2-(piperidin-1-yl)quinolin-8-ol (8a-5) was prepared according to the general procedure D starting from 16 (38 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (26 mg, 72%). $R_f = 0.4$ (Hexane:EtOAc = 9:1); mp = 78 °C. IR (KBr): $\nu = 3438$, 2928, 2844, 1609, 1427, 1253, 828 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.0 (d, $J = 9.6$ Hz, 1H), 7.01 (d, $J = 9.0$ Hz, 1H), 6.90–6.94 (m, 2H), 3.69–3.70 (m, 4H), 2.49 (s, 3H), 1.68–1.69 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 156.1, 148.6, 137.5, 134.6, 124.2, 122.8, 121.5, 110.1, 109.5, 46.6 (2C), 25.7 (2C), 24.9, 18.0 ppm. HRMS (ESI): $m/z$ calcd. for C$_{12}$H$_{19}$N$_2$O$^+$ [M + Na]$^+$, 265.1317; found, 265.1317.
5-Methoxy-2-(piperidin-1-yl)quinolin-8-ol (8a-6) was prepared according to the general procedure D starting from 17 (40 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Brown viscous liquid (25 mg, 65%). $R_f = 0.4$ (Hexane:EtO$\alpha$ = 4:1). IR (KBr): $\nu$ = 3423, 2921, 2349, 91, 730, 646 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.22 (d, $J$ = 9.6 Hz, 1H), 7.39 (bs, 1H), 6.97 (d, $J$ = 9.6 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 6.46 (d, $J$ = 7.8 Hz, 1H), 3.89 (s, 3H), 3.70–3.72 (m, 4H), 1.66–1.69 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 156.7, 148.3, 144.2, 137.8, 132.8, 114.2, 109.3, 108.9, 100.8, 55.8, 46.5 (2C), 25.7 (2C), 24.9 ppm. HRMS (ESI): $m/z$ calcd. for C$_{15}$H$_{10}$N$_2$O$_2$ [M + H]$^+$, 259.1447; found, 259.1435.

5-Fluoro-2-(piperidin-1-yl)quinolin-8-ol (8a-7) was prepared according to the general procedure D starting from 18 (38 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (28 mg, 76%). $R_f = 0.4$ (Hexane:EtO$\alpha$ = 19:1). mp = 72 °C. IR (KBr): $\nu$ = 3423, 2935, 1623, 1434, 1233, 813, 575 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.05–8.07 (m, 1H), 7.46 (bs, 1H), 7.01–7.03 (m, 1H), 6.89–6.91 (m, 1H), 6.73–6.76 (m, 1H), 3.70–3.72 (m, 4H), 1.68–1.71 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 156.5, 151.5 (d, $J_{C,F}$ = 244.0 Hz), 146.2, 137.5, 131.2, 112.3 (d, $J_{C,F}$ = 18.9 Hz), 110.5, 108.7 (d, $J_{C,F}$ = 8.6 Hz), 105.6 (d, $J_{C,F}$ = 21.1), 46.4 (2C), 25.7 (2C), 24.8 ppm. $^{19}$F (564 MHz) –134.76 (m, 1F). HRMS (ESI): $m/z$ calcd. for C$_{16}$H$_{11}$FNO [M + H]$^+$, 247.1247; found, 247.1256.

5-Chloro-2-(piperidin-1-yl)quinolin-8-ol (8a-8) was prepared according to the general procedure D starting from 19 (41 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (30 mg, 76%). $R_f = 0.5$ (Hexane:EtO$\alpha$ = 19:1). mp = 52 °C. IR (KBr): $\nu$ = 3387, 2906, 1604, 1356, 783 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.18 (d, $J$ = 9.6 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 1H), 7.07 (d, $J$ = 9.0 Hz, 1H), 6.95 (d, $J$ = 7.8 Hz, 1H), 3.71–3.73 (m, 4H), 1.69–1.72 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 156.3, 149.1, 138.0, 134.7, 122.2, 120.6, 120.1, 111.2, 110.1, 46.4 (2C), 25.7 (2C), 24.8 ppm. HRMS (ESI): $m/z$ calcd. for C$_{15}$H$_{10}$ClN$_2$O [M + H]$^+$, 263.0951; found, 263.0947.

5-Bromo-2-(piperidin-1-yl)quinolin-8-ol (8a-9) was prepared according to the general procedure D starting from 20 (47 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (32 mg, 70%). $R_f = 0.3$ (Hexane:EtO$\alpha$ = 49:1). mp = 81 °C. IR (KBr): $\nu$ = 3368, 2920, 2850, 1735, 1602, 1267, 1099, 799 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 8.13 (d, $J$ = 9.6 Hz, 1H), 7.80 (bs, 1H), 7.31 (d, $J$ = 8.4 Hz, 1H), 7.04–7.06 (m, 1H), 6.91 (d, $J$ = 8.4 Hz, 1H), 3.72–3.73 (m, 4H), 1.68–1.72 (m, 6H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ = 156.4, 149.8, 138.2, 137.1, 125.6, 121.4, 111.6, 110.7, 110.0, 46.4 (2C), 25.7 (2C), 24.8 ppm. HRMS (ESI): $m/z$ calcd. for C$_{16}$H$_{10}$BrN$_2$O [M + H]$^+$, 307.0446; found, 307.0462.

4-Methyl-N-(2-(piperidin-1-yl)quinolin-8-yl)benzenesulfonamide (21a) was prepared according to the general procedure D starting from 21 (59 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate Colourless solid (35 mg, 62%). $R_f = 0.3$ (Hexane:EtO$\alpha$ = 3:2). mp = 164 °C. IR (neat): $\nu$ = 3416, 2928, 2349, 1162, 904, 744 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ = 7.77 (d, $J$ = 9.0 Hz, 1H), 7.73 (d, $J$ = 8.4 Hz, 2H), 7.67 (d, $J$ = 6.6 Hz, 1H), 7.24 (d, $J$ = 8.4 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 2H), 7.07–7.09 (m, 1H), 6.95 (d, $J$ = 9.0 Hz, 1H), 3.66–3.68 (m, 4H), 2.29 (s, 3H), 1.66–1.72 (m, 6H) ppm. $^{13}$C NMR (151 MHz,
N-(2-(Piperidin-1-yl)quinolin-8-yl)methanesulfonamide (22a) was prepared according to the general procedure D starting from 22 (47 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Colorless solid (30 mg, 66%). Rf = 0.6 (Hexane:EtO = 3:2). mp = 128 ºC. IR (neat): ν = 3430, 2920, 1622, 1162, 904 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 7.87 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 3.70–3.71 (m, 4H), 2.31 (s, 3H), 1.72 (s, 6H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 156.8, 138.4, 137.8, 131.4, 122.7, 122.5, 122.0, 116.8, 110.8, 46.4 (2C), 39.0, 25.7 (2C), 24.8 ppm. HRMS (ESI): m/z calcd. for C₁₈H₁₆N₂O₂SNa [M + Na]⁺, 328.1096; found, 328.1100.

N-(2-(Piperidin-1-yl)quinolin-8-yl)acetamide (23a) was prepared according to the general procedure D starting from 23 (42 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (13 mg, 32%). Rf = 0.3 (Hexane:EtO = 7:3). mp = 79 ºC. IR (KBr): ν = 3423, 3302, 2927, 2354, 1632, 1235, 740 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.50 (bs, 1H), 8.59 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.18–7.20 (m, 1H), 7.02 (d, J = 9.6 Hz, 1H), 3.71–3.72 (m, 4H), 2.31 (s, 3H), 1.72 (s, 6H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 168.4, 156.5, 137.9, 137.4, 132.3, 122.5, 122.1, 121.3, 116.9, 110.4, 46.6 (2C), 25.7 (2C), 25.3, 24.9 ppm. HRMS (ESI): m/z calcd. for C₁₈H₁₆N₂O₂Na [M + Na]⁺, 292.1426; found, 292.1430.

N-(2-(Piperidin-1-yl)quinolin-8-yl)propionamide (24a) was prepared according to the general procedure D starting from 24 (44 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate. Light yellow solid (14 mg, 34%). Rf = 0.4 (Hexane:EtO = 4:1). mp = 90 ºC. IR (neat): ν = 3402, 2928, 1637, 1037, 632 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.63 (bs, 1H), 8.61 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.19–7.21 (m, 1H), 7.03 (d, J = 9.0 Hz, 1H), 3.72–3.73 (m, 4H), 2.55–2.58 (m, 2H), 1.71–1.72 (m, 6H), 1.35 (t, J = 7.2 Hz, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 171.9, 156.5, 137.9, 137.5, 132.3, 122.6, 122.1, 121.2, 116.9, 110.5, 46.6 (2C), 31.5, 25.7 (2C), 24.9, 10.0 ppm. HRMS (ESI): m/z calcd. for C₁₈H₁₆N₂O₂ [M + H]⁺, 284.1763; found, 284.1759.

2-(Piperidin-1-yl)-10-phenanthroline (25a) was prepared according to the general procedure D starting from 25 (41 mg, 0.15 mmol, 1 equiv) as the N-heteroaryl ether substrate using THF as the solvent at 70 ºC. Viscous liquid (25 mg, 66%). Rf = 0.6 (CH₂Cl₂:MeOH = 19:1). IR (neat): ν = 2942, 2837, 2244, 2041, 1037, 730 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.09 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50–7.51 (m, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 3.88 (s, 4H), 1.73 (s, 6H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 158.4, 149.5, 145.8, 145.5, 137.6, 136.0, 129.5, 126.5, 122.1, 121.8, 121.2, 109.9, 46.3 (2C), 26.0 (2C), 24.9 ppm. HRMS (ESI): m/z calcd. for C₁₉H₁₇N₃Na [M + Na]⁺, 286.1320; found, 286.1310.

Synthesis of ethyl 2-((2-morpholinoquinolin-8-yl)oxy)acetate (27). To a stirred mixture of 2-morpholinoquinolin-8-ol 8c (104 mg, 0.45 mmol) in MeCN (2.6 mL) was added ethyl bromoacetate (113 mg, 0.68 mmol) and K₂CO₃ (186.6 mg, 1.4 mmol). The mixture was stirred at 80 ºC for 4 h. After filtration, the filtrate was concentrated to give crude product, which
was purified by flash column chromatography on silica-gel to give 27 as a colorless viscous liquid (125 mg, 88%). $R_f = 0.5$ (Hexane:EtOAc = 1:1). IR (neat): $\nu = 3465, 2963, 2935, 2844, 1756, 1441, 1121$ cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J = 9.0$ Hz, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 7.8$ Hz, 1H), 7.05 (d, $J = 7.8$ Hz, 1H), 6.97 (d, $J = 9.0$ Hz, 1H), 4.92 (s, 2H), 4.27–4.30 (m, 2H), 3.86 (t. $J = 4.8$ Hz, 4H), 3.73 (t, $J = 4.8$ Hz, 4H), 1.31 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.6, 156.9, 151.9, 139.7, 137.9, 124.6, 122.3, 121.6, 114.1, 109.6, 67.5, 67.0 (2C), 61.2, 45.5 (2C), 14.3 ppm. HRMS (ESI): $m/z$ calcd. for C$_{17}$H$_{21}$N$_2$O$_4$Na $[M + H]^+$, 317.1501; found, 317.1500.

References:
$^1$H and $^{13}$C NMR spectra of all substrates

$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (500 MHz, CDCl$_3$):

![NMR spectrum of compound 13](image)

$^{13}$C NMR (126 MHz, CDCl$_3$):

![C-NMR spectrum of compound 13](image)
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

13C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

![NMR spectrum image]

$^{13}$C NMR (151 MHz, CDCl$_3$):

![NMR spectrum image]
$^1H$ NMR (600 MHz, CDCl$_3$):

$^{13}C$ NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl₃):

![H NMR spectrum image]

$^{13}$C NMR (151 MHz, CDCl₃):

![C NMR spectrum image]
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

![H NMR spectrum](image1)

$^{13}$C NMR (151 MHz, CDCl$_3$):

![C NMR spectrum](image2)
$^1$H and $^{13}$C NMR spectra of all products

$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl₃):

$^{13}$C NMR (151 MHz, CDCl₃):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (121 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^{19}$F NMR (564 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

\[ \text{N} \quad \text{NHCOMe} \quad \text{N} \quad 23a \]

$^{13}$C NMR (151 MHz, CDCl$_3$):

\[ \text{N} \quad \text{NHCOMe} \quad \text{N} \quad 23a \]
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):
$^1$H NMR (600 MHz, CDCl$_3$):

$^{13}$C NMR (151 MHz, CDCl$_3$):