Supplementary Information:

Chelation-assisted de-aryloxylative 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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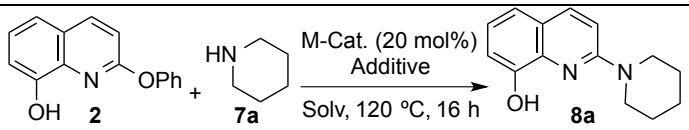
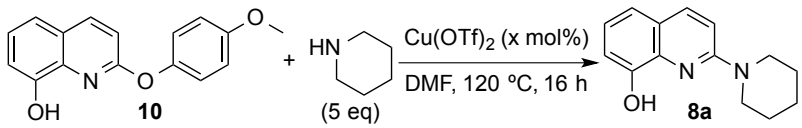
Table S1. Optimization of the reaction conditions for the de-aryloxylative amination[a]



Entry	M-Cat	Additive (Equiv.)	Solvent	Temp (˚C)	8a (%)
1[b]	$Pd(OAc)_2$	–	DMF	120	12
2[b]	$PdCl_2$	–	DMF	120	21
3	$NiBr_2$	–	DMF	120	0
4	$Mg(OTf)_2$	–	DMF	120	0
5	$CuBr_2$	–	DMF	120	25
6	$CuCl_2$	–	DMF	120	28
7	$Cu(OTf)_2$	–	DMF	120	85
8	$Cu(OAc)_2$	–	DMF	120	68
9	$Cu(OTf)_2$	–	DMSO	120	41
10	$Cu(OTf)_2$	–	Toluene	110	61
11	$Cu(OTf)_2$	–	THF	70	73
12	$Cu(OTf)_2$	–	H_2O	100	55
13	$Cu(OTf)_2$	N_2 balloon	DMF	120	84
14[c]	$Cu(OTf)_2$	Cs_2CO_3	DMF	120	<5
15[c]	$Cu(OTf)_2$	K_2CO_3	DMF	120	21
16[d]	$Cu(OTf)_2$	–	DMF	120	84
17[e]	$Cu(OTf)_2$	–	DMF	120	55
18[b]	**$Cu(OTf)_2$**	**–**	**DMF**	**120**	**84**
19[f]	$Cu(OTf)_2$	–	DMF	120	55
20	$Cu(OTf)_2$	–	DMF	100	75
21	$Cu(OTf)_2$	–	DMF	70	80
22[g]	$Cu(OTf)_2$	–	DMF	r.t.	41
23[b,g]	$Cu(OTf)_2$	–	DMF	120	84
24[g]	–	–	DMF	120	nd

[a] *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-aryloxylative amination of 9 with piperidine by varying $Cu(OTf)_2$ loading

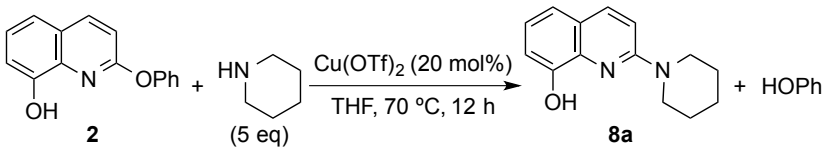


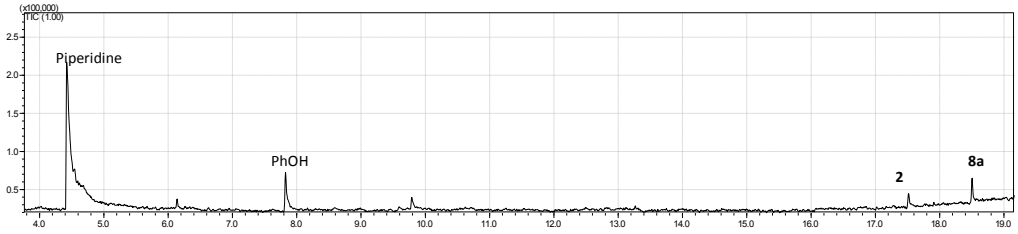
Entry	$Cu(OTf)_2$ (x mmol)	8a (%)
1	10	64
2	15	72
3	**20**	**82**
4	25	82
5	30	83

[a] *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.

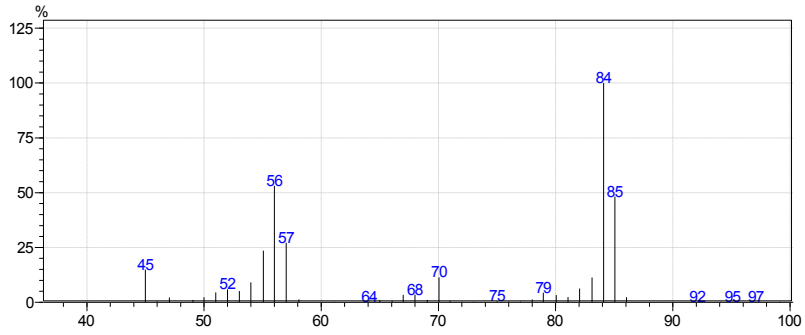
GC-MS Analysis:

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 ºC 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 Na_2SO_4, and subsequently submitted to GC-MS, which shows the formation of **8a** (m/z = 228) and phenol (m/z = 94).

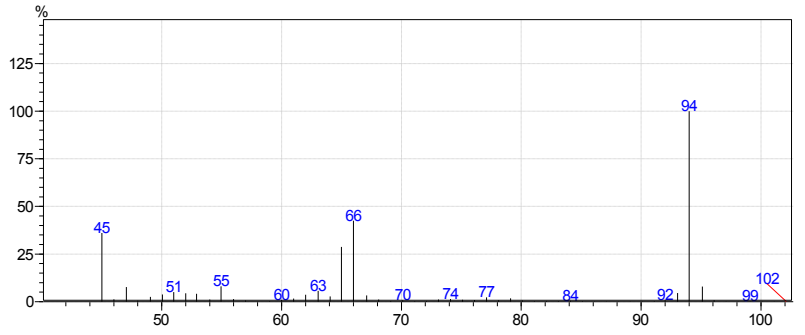




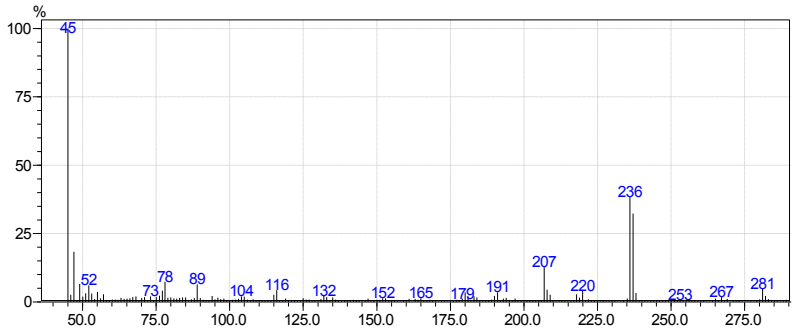
GC-MS spectrum of Piperidine (m/z = 85, R_t = 4.5 min):



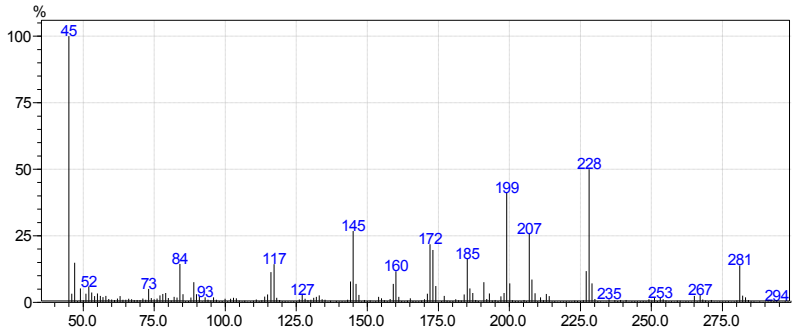
GC-MS spectrum of PhOH (m/z = 94, R_t = 7.9 min):



GC-MS spectrum of 2 (m/z = 237, R_t = 17.5 min):



GC-MS spectrum of 8a (m/z = 228, R_t = 18.5 min):



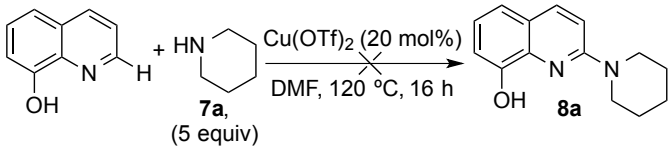
Mechanistic Studies:

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 Na_2SO_4, 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:

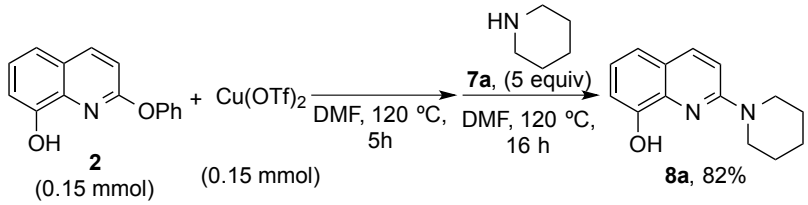
A reaction pathway consisting of dephenoxylation of **2** and a subsequent C–H amination of the resulting compound was excluded as 8-hydroxyquinoline was not converted into **8a** under the optimized condition.



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 Na_2SO_4, filtered, and concentrated in vacuum. The reaction did not provide any aminated product **8a** and 8-hydroxyquinoline was recovered exclusively (20 mg, 91%).

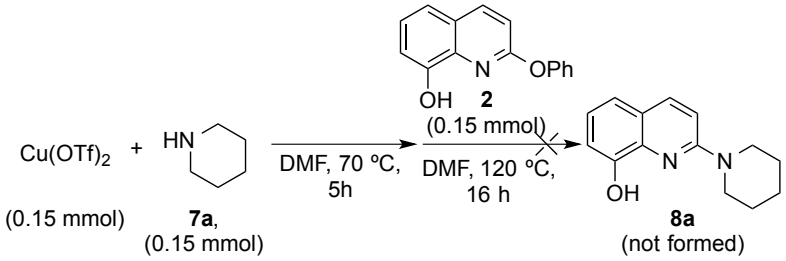
Experiments with preformed complexes:

1. With the preformed copper-complex of 2 and $Cu(OTf)_2$:



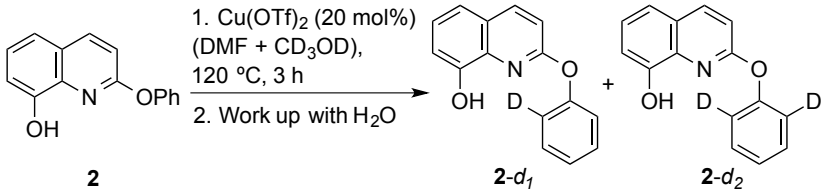
A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline **2** (35.6 mg, 0.15 mmol, 1.0 equiv) and copper(II) triflate (54.3 mg, 0.15 mmol, 1.0 eq). The tube was evacuated and backfilled with N_2 (x 3). To it, anhydrous DMF (2.5 mL) was added by syringe and the reaction mixture was heated with vigorous stirring at 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 Na_2SO_4, 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:

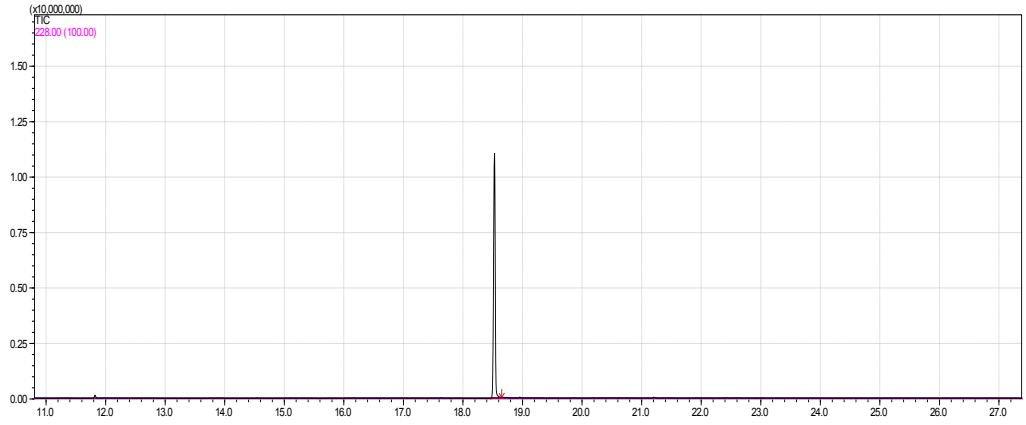


A 20 mL Schlenk tube was charged with copper(II) triflate (54.3 mg, 0.15 mmol, 1.0 eq) and piperidine (15 μL, 0.15 mmol, 1 equiv). The tube was evacuated and backfilled with N_2 (x 3). To it, anhydrous DMF (2.5 mL) was added by syringe and the reaction mixture was heated with vigorous stirring at 70 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_2SO_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:

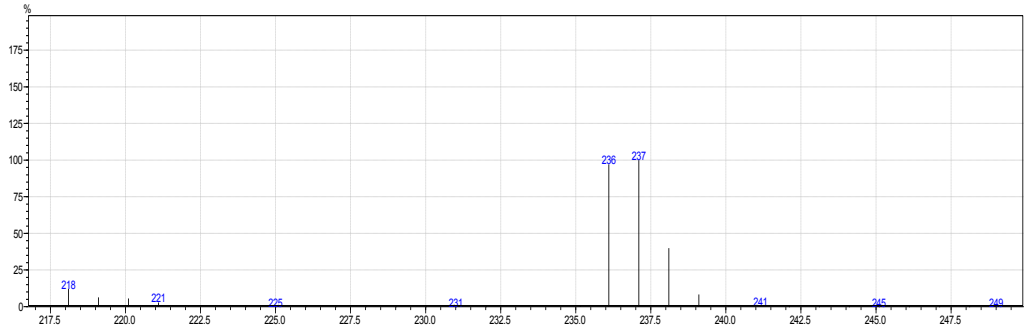


A 20 mL reaction vessel was charged with 2-phenoxy-8-hydroxyquinoline **2** (24 mg, 0.1 mmol) and $Cu(OTf)_2$ (10.8 mg, 0.03 mmol, 20 mol%). To it, 0.5 mL DMF and 0.5 mL methanol-d_4 were added and the reaction mixture was stirred at 70 ºC for 3 h under air. After cooling to room temperature, 0.2 mL 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**-*d_1* (m/z = 238) and 2-phenoxy-8-hydroxyquinoline-d_2 **2**-*d_2* (m/z = 239).



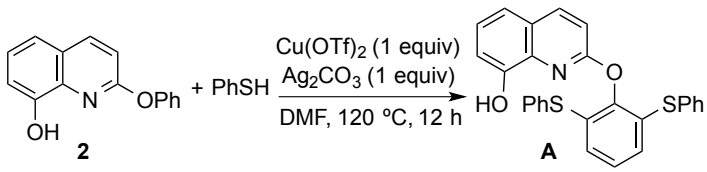
Raw Spectrum 18.535 (scan : 2608)
Background No Background Spectrum

Base Peak m/z 237.10 (Inten : 1,988,663)
Event# 1



m/z	Absolute Intensity	Relative Intensity
231.00	150	0.01
232.00	106	0.01
232.95	1873	0.09
234.10	1662	0.08
235.15	17473	0.88
236.10	1930532	97.08
237.10	1988663	100.00
238.10	794890	39.97
239.10	165679	8.33
241.15	2262	0.11
242.10	242	0.01
243.10	207	0.01
244.10	188	0.01
245.10	145	0.01
246.10	116	0.01
247.10	103	0.01
248.10	140	0.01
249.00	204	0.01
250.00	4418	0.22

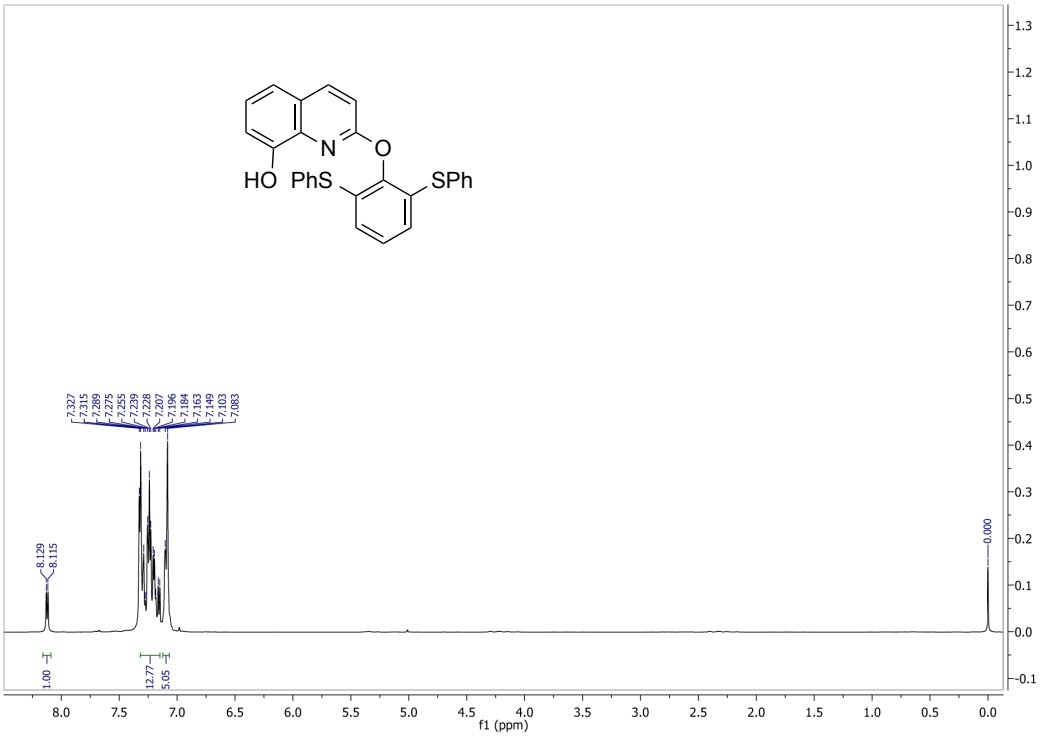
***ortho*-Thiolation in the phenoxy substituent:**



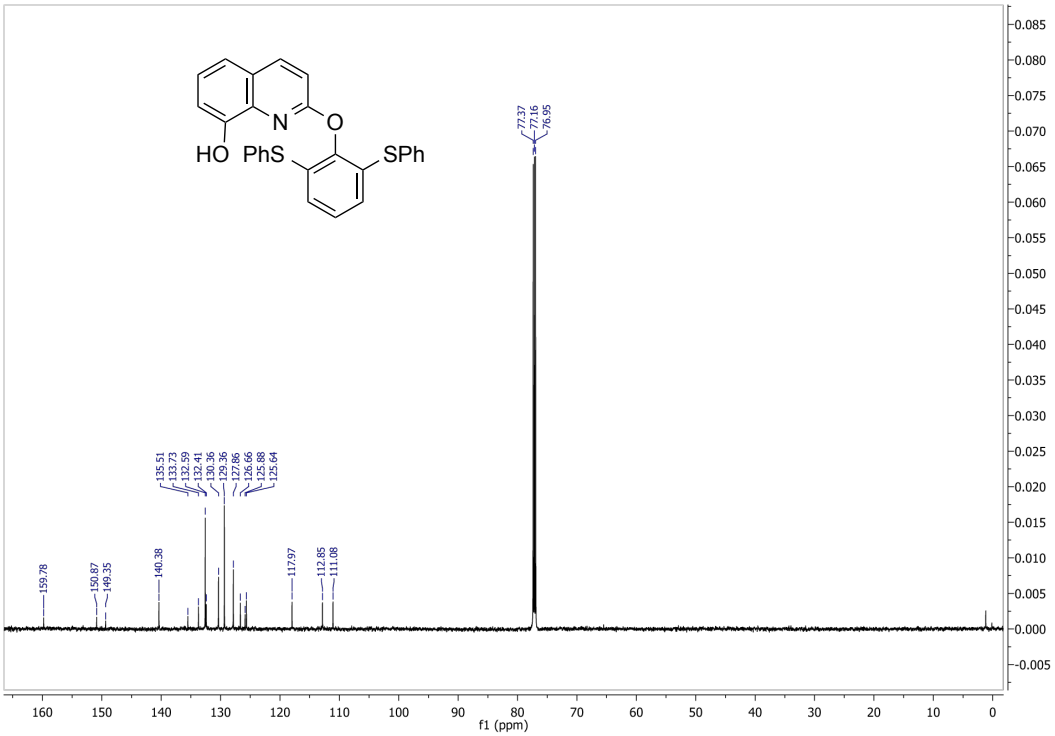
A 20 mL reaction vessel was charged with 2-phenoxy-8-hydroxyquinoline **2** (35.6 mg, 0.15 mmol, 1 equiv), $Cu(OTf)_2$ (54.3 mg, 0.15 mmol, 1 equiv) and Ag_2CO_3 (41.4 mg, 0.15 mmol, 1 equiv). The vessel was evacuated and back-filled with nitrogen (x 3). To it, anhydrous DMF (2 mL) and PhSH (50 mg, 0.45 mmol, 3 equiv) were added and the reaction mixture was stirred at 120 ºC for 12 h. After cooling, the reaction mixture was diluted with diethyl ether (10 mL) and washed with water (5 mL) and 10% NaOH solution (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_2SO_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_2O = 9:1). mp = 92 ºC. IR (neat): ν = 3409, 2963, 1588, 1127, 744 cm^{-1}. ^1H 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),

127.9 (2C), 126.7, 125.9, 125.6, 118.0, 112.9, 111.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{27}H_{20}NO_2S_2$ $[M + H]^+$, 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

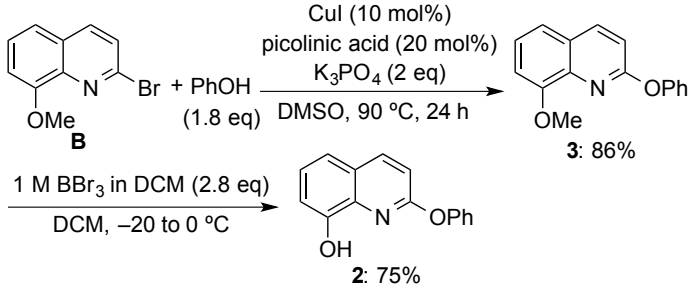
General Methods. NMR spectra were recorded on Jeol Resonance ECZ 600R spectrometer (600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR, 564 MHz for ^{19}F) and Bruker AvanceII 500 spectrometer (500 MHz for ^{1}H NMR, 121 MHz for ^{13}C NMR). Chemical shifts were reported in ppm on the δ scale relative to Me_4Si (δ = 0.00 for ^{1}H-NMR) and $CDCl_3$ (δ = 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.[1] All other solvents and commercially available compounds were used without further purification.

Preparation of Substrates:

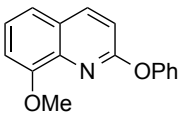
Substrates **1** and **4** were prepared by reported methods.[2,3] Substrates **2**, **3**, and **10–25** were prepared as follows:

General procedure A:

Preparation of 2:



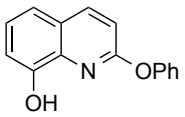
Step 1. Synthesis of 2-phenoxy-8-methoxyquinoline (3):



3

An oven-dried Schenk 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_3PO_4 (636.8 mg, 3.0 mmol, 2.0 eq).[4] 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_2SO_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): ν = 3440, 2920, 2155, 1582, 1086 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 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:



2

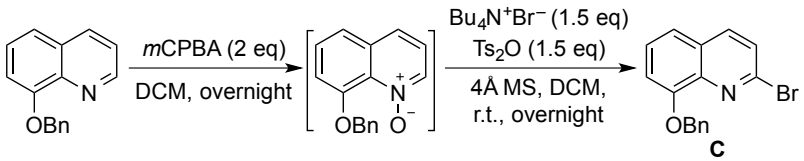
To a solution of **3** (297 mg, 1.18 mmol) in 45 mL CH_2Cl_2, 1 M BBr_3 solution in CH_2Cl_2 (3.3 mL, 3.3 mmol) was added dropwise at –20 ºC. The reaction was allowed to stir at that temperature for 1 h and then warmed up to 0 ºC and stirred for 12 h. It was then further warmed up to room temperature and stirred for additional 1 h before quenching with ice-water mixture. The reaction mixture was then extracted with CH_2Cl_2 (3 x 30 mL), washed with brine solution (10 mL), dried over Na_2SO_4 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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.9, 153.5, 150.9, 140.3, 135.6, 129.7 (2C), 125.8, 125.7, 125.2, 121.7 (2C), 117.9, 113.4, 111.2 ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}NO_2$ $[M + H]^+$, 238.0868; found, 238.0857.

General procedure B:

<u>Preparation of 10:</u>

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

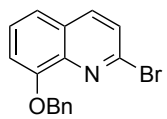
2-Bromo-8-benzyloxyquinoline was prepared according to the literature procedure[3] as follows:



C

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 Na_2SO_4 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.

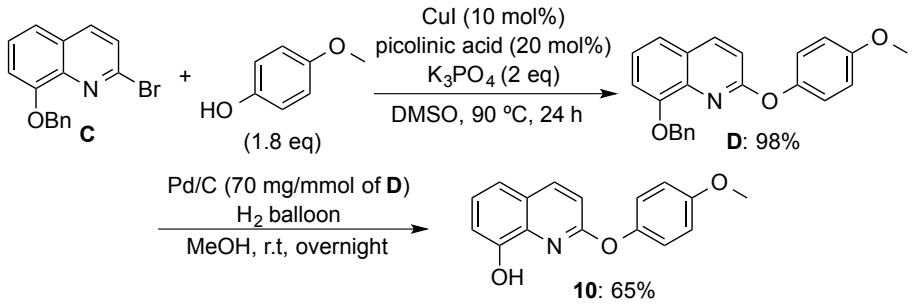
To a mixture of the *N*-oxide (1.81 g, 7.2 mmol), tetrabutylammonium bromide (3.48 g, 10.8 mmol, 1.5 equiv), and 4 Å molecular sieves (7.2 g) was added anhydrous DCM (0.01M) and the mixture was stirred at room temperature for 10 min. To it, *p*-toluenesulfonic anhydride (3.53 g, 10.8 mmol, 1.5 equiv) was added and the reaction was stirred at room temperature overnight. The reaction mixture was filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexanes/Et_2O solvent mixtures to afford the title compound **C** as a white solid (1.38 g, 61% yield).

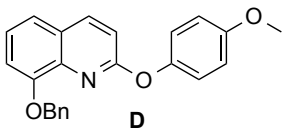


C

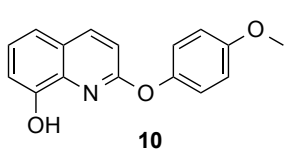
IR (neat): ν = 3415, 3048, 2928, 1589, 1079, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.8 Hz, 1H), 7.49–7.52 (m, 3H), 7.25–7.37 (m, 5H), 7.04 (d, J = 7.2 Hz, 1H), 5.41 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 141.0, 140.8, 138.3, 136.9, 128.7 (2C), 128.4, 127.9, 127.3, 127.1 (2C), 126.5, 119.8, 111.8, 71.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{16}H_{13}BrNO$ $[M + H]^+$, 314.0181; found 314.0168.

Step 2. Synthesis of 2-(4-methoxyphenyl)-8-hydroxyquinoline[4] 10:



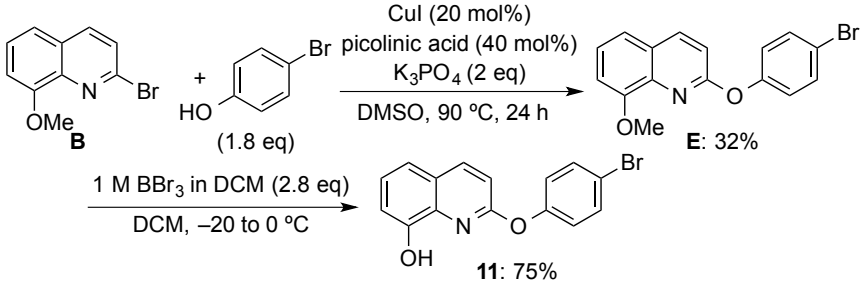

D

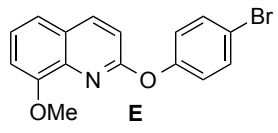
An oven-dried 50 mL round bottomed flask was charged with a magnetic stirring bar, copper(I) iodide (20.9 mg, 0.11 mmol, 10 mol%), picolinic acid (27.1 mg, 0.22 mmol, 20 mol%), 2-bromo-8-benzyloxyquinoline (350 mg, 1.1 mmol, 1.0 eq), 4-methoxyphenol (245.8 mg, 1.98 mmol, 1.8 eq), and K_3PO_4 (467 mg, 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_2SO_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, 1596, 1334 cm^{-1}. ^1H 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%).


10

An oven-dried 50 mL round bottomed flask was charged with a magnetic stirring bar, 2-(4-Methoxyphenyl)-8-benzyloxyquinoline **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_2O 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}. ^1H 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).

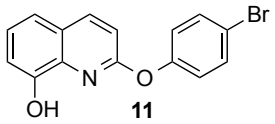
Preparation of 11:





E

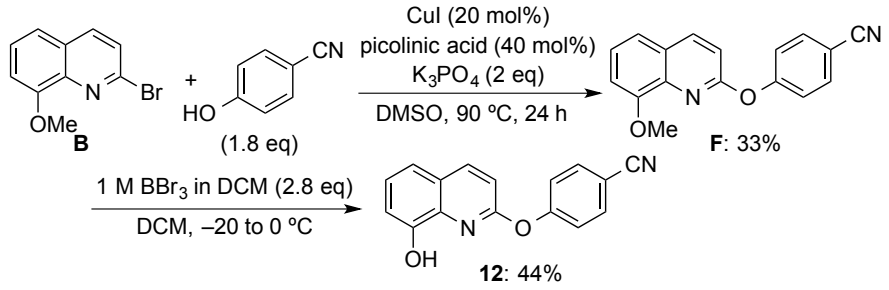
Compound **E** was prepared according to the general procedure A as described for the preparation of **3** using 20 mol% CuI and 40 mol% picolinic acid starting from 1.6 mmol 2-bromo-8-methoxyquinoline **B**. Colorless solid, (169 mg, 32%): IR (KBr): ν = 3408, 2827, 1604, 1250, 1094, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{16}H_{13}BrNO_2$ $[M + H]^+$, 330.0130; found, 330.0132.

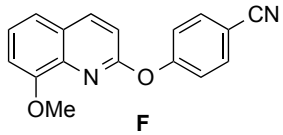


11

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 CH_2Cl_2, 1 M BBr_3 solution in CH_2Cl_2 (1.2 mL, 1.2 mmol) was added dropwise at 0 ºC. 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 CH_2Cl_2 (3 x 20 mL), washed with brine solution (5 mL), dried over Na_2SO_4 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, 2807, 1604, 1257, 747 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{15}H_{11}BrNO_2$ $[M + H]^+$, 315.9973; found, 315.9971.

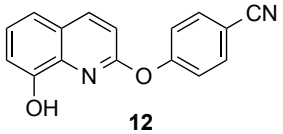
Preparation of 12:





F

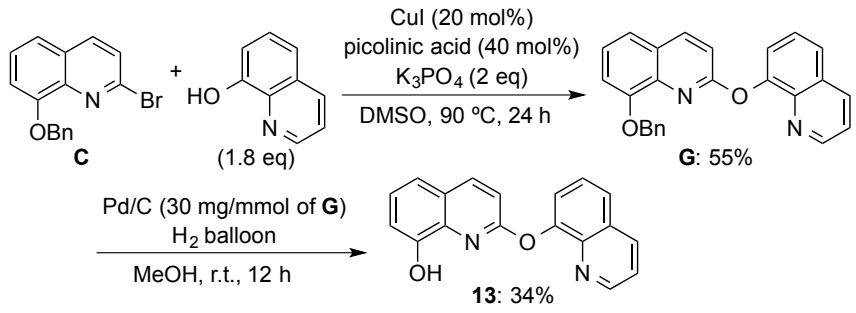
Compound **F** was prepared according to the general procedure A as described for the preparation of **3** using 20 mol% CuI and 40 mol% picolinic acid starting from 2.1 mmol of **B**. Colorless solid, (191 mg, 33%): IR (KBr): ν = 2928, 2223, 1595, 1497, 1260, 828 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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).

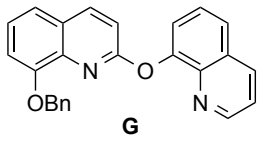


12

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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7, 157.2, 150.9, 141.0, 135.3, 134.0 (2C), 126.5, 126.2, 122.4 (2C), 118.6, 118.1, 113.5, 111.7, 108.8 ppm. MS (70 eV), m/z (%) 262 (91) [M+], 261 (100), 116 (25), 89 (24).

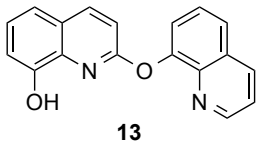
Preparation of 13:





G

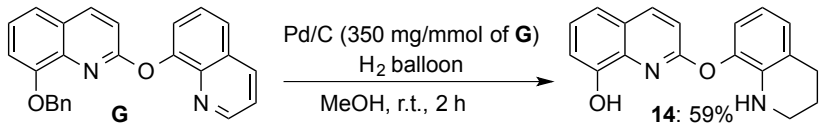
Compound **G** was prepared according to the general procedure B as described for the preparation of **D** using 20 mol% CuI and 40 mol% picolinic acid starting from 1.26 mmol **C**. Colorless solid, (262 mg, 55%): IR (KBr): ν = 3430, 2821, 2354, 1589, 1250, 754 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 8.81–8.82 (m, 1H), 8.15–8.18 (m, 2H), 7.73–7.77 (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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{25}H_{19}N_2O_2$ $[M + H]^+$, 379.1447; found, 379.1448.



13

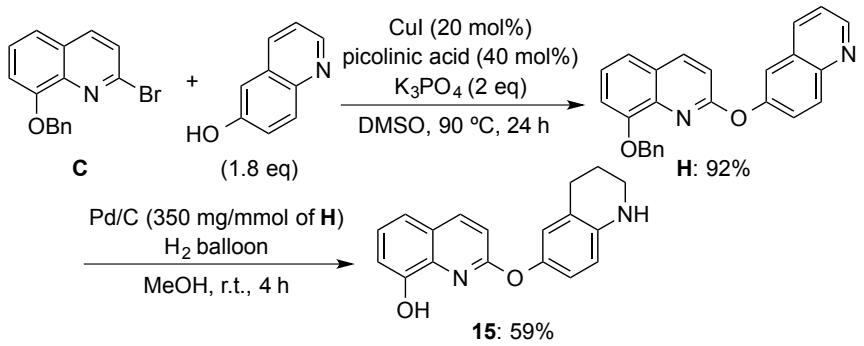
Compound **13** was prepared according to the general procedure B as described for the preparation of **10** using 16 mg 10 wt% Pd/C as the catalyst starting from 0.53 mmol **G**: Colorless viscous liquid, (53 mg, 34%): IR (KBr): ν = 3430, 2969, 1604, 1080, 797 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 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. ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{18}H_{13}N_2O_2$ $[M + H]^+$, 289.0977; found, 289.0972.

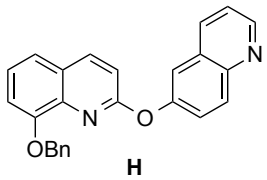
Preparation of 14:



Compound **14** was prepared according to the general procedure B as described for the preparation of **10** using 185.5 mg of 10 wt% Pd/C as the catalyst starting from 0.53 mmol of **G**. Colorless viscous liquid, (91 mg, 59%): IR (neat): ν = 3415, 2927, 1589, 1348, 1256, 740 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 1H), 7.31 (bs, 1H), 7.25–7.31 (m, 2H), 7.08–7.12 (m, 2H), 6.88–6.91 (m, 2H), 6.62 (t, J = 7.8 Hz, 1H), 4.10 (bs, 1H), 3.28–3.29 (m, 2H), 2.83–2.85 (m, 2H), 1.95–1.96 (m, 2H) ppm.^{13}C NMR (151 MHz, $CDCl_3$) δ 160.7, 151.0, 140.3, 139.5, 137.5, 135.9, 126.4, 125.8, 125.7, 123.5, 119.7, 117.9, 116.0, 112.7, 111.2, 41.7, 27.0, 22.0 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1290; found, 293.1287.

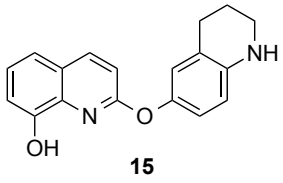
Preparation of 15:





H

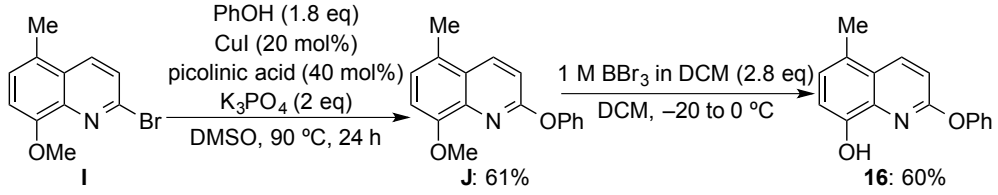
Compound **H** was prepared according to the general procedure B as described for the preparation of **D** using 20 mol% CuI and 40 mol% picolinic acid starting from 1.26 mmol of **C**. Colourless viscous liquid, (439 mg, 92%): IR (KBr): ν = 3430, 2813, 2354, 1589, 1334, 1249, 733 cm^{-1}. ^{1}H NMR (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 $C_{25}H_{19}N_2O_2$ $[M + H]^+$, 379.1447; found, 379.1434.

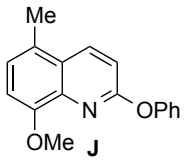


15

Compound **15** was prepared according to the general procedure B as described for the preparation of **10** using 406 mg 10 wt% Pd/C as the catalyst starting from 1.16 mmol of **H**. Light yellow viscous liquid (200 mg, 59%): IR (neat): ν = 3423, 2927, 2857, 2332, 1038, 669 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 1H), 7.29 (bs,1H), 7.26–7.28 (m, 2H), 7.06–7.10 (m, 2H), 6.81–6.82 (m, 2H), 6.51 (d, J = 8.4 Hz, 1H), 3.33 (t, J = 5.4 Hz, 2H), 2.78 (t, J = 6.0 Hz, 2H), 1.95–1.99 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$)δ 161.8, 150.9, 144.3, 142.3, 139.9, 135.8, 125.5, 125.4, 122.6, 122.4, 120.1, 117.8, 114.9, 113. 3, 111.0, 42.2, 27.2, 22.2 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{19}N_2O_2$ $[M + H]^+$, 293.1290; found, 293.1284.

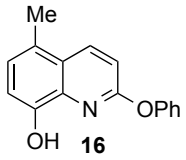
Preparation of 16:





J

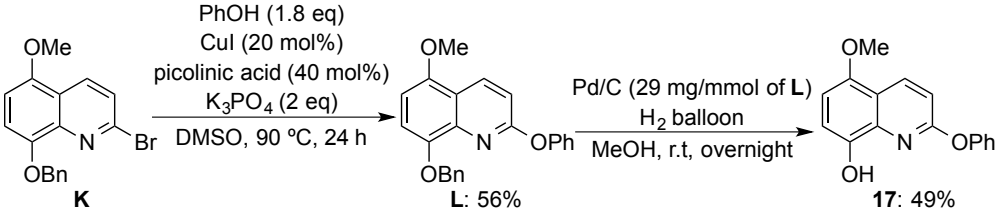
Compound **J** was prepared according to the general procedure A as described for the preparation of **3** using 20 mol% CuI and 40 mol% picolinic acid starting from 2.5 mmol of **I**. Colorless solid, (403 mg, 61%): IR (KBr): ν = 2935, 1595, 1484, 1400, 1253, 1099, 827 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17–8.19 (m, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.22 (d, J = 7.8Hz, 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 (%) 266 (99), 265 (99) [M+], 264 (100), 246 (47), 236 (99), 235 (84), 115 (88), 77 (99).



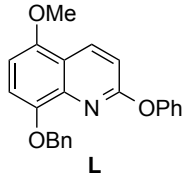
16

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): ν =3395, 2920, 1588, 1491, 1400, 1323, 1253 786 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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* calcd. for $C_{16}H_{14}NO_2$ $[M + H]^+$, 252.1025; found, 252.1030.

Preparation of 17:

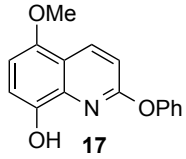


K **L**: 56% **17**: 49%



L

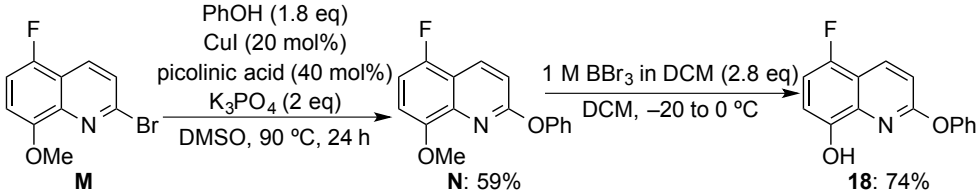
Compound **L** was prepared according to the general procedure B as described for the preparation of **D** using 20 mol% CuI and 40 mol% picolinic acid starting from 0.81 mmol of **K**. Colourless solid, (200 mg, 56%): IR (KBr): ν = 3064, 1595, 1469, 1407, 1260, 1092, 813 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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).



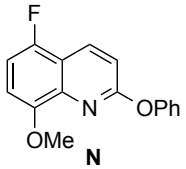
17

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): ν = 3430, 2920, 1581, 1400, 1253, 1079 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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* calcd. for $C_{16}H_{14}NO_3$ $[M + H]^+$, 268.0974; found, 268.0967.

Prepararion of 18:



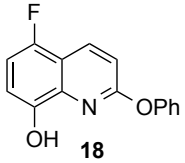
M **N**: 59% **18**: 74%



N

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): ν = 3423, 1609, 1484, 1407, 1260, 1092, 771 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 161.7, 154.1, 152.2 (d, $J_{C\text{-}F}$ = 246.5 Hz), 151.0 (d, $J_{C\text{-}F}$ = 2.7 Hz), 138.6, 133.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.9 (2C), 125.0, 121.2 (2C), 117.0 (d, $J_{C\text{-}F}$ = 17.7 Hz), 112.6, 108.7 (d, $J_{C\text{-}F}$ = 8.8 Hz),

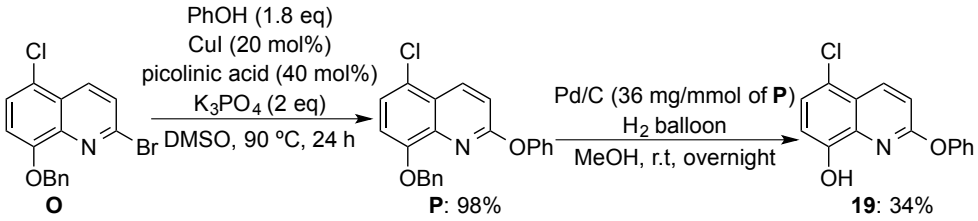
108.2 (d, $J_{C\text{-}F}$ = 20.7 Hz) ppm. MS (70 eV), m/z (%) 269 (88) [M+], 268 (100), 240 (51), 146 (15), 77 (18), 51 (12).

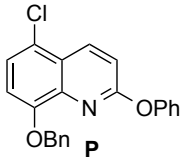


18

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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.60, 153.2, 151.2 (d, $J_{C\text{-}F}$ = 245.8 Hz), 147.1, 135.5, 134.1, 129.8(2C), 125.5, 121.8 (2C), 115.8 (d, $J_{C\text{-}F}$ = 19.0 Hz), 113.6, 110.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 109.1 (d, $J_{C\text{-}F}$ = 20.5 Hz) ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{11}FNO_2$ $[M + H]^+$, 256.0774; found, 256.0777.

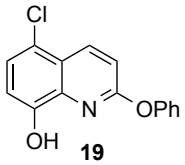
Preparation of 19:





P

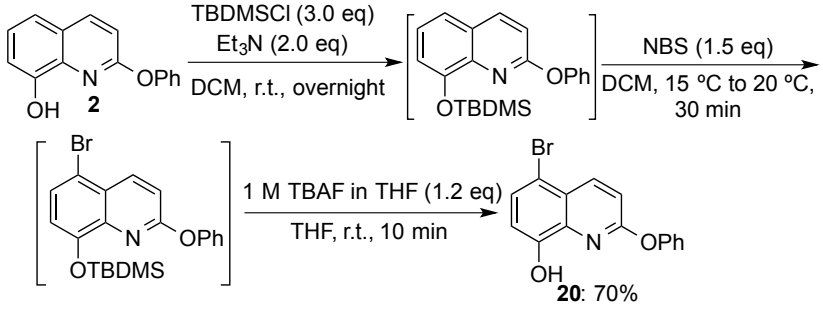
Compound **P** was prepared according to the general procedure B as described for the preparation of **D** using 20 mol% CuI and 40 mol% picolinic acid starting from 1.6 mmol of **O**. Colourless solid, (567 mg, 98%): IR (KBr): ν = 3415, 2962, 1582, 1384, 768 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 8.50 (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 = 8.4Hz, 1H), 5.17 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{22}H_{17}ClNO_2$ $[M + H]^+$, 362.0948; found, 362.0930.



19

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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{15}H_{11}ClNO_2$ $[M + H]^+$, 272.0478; found, 272.0471.

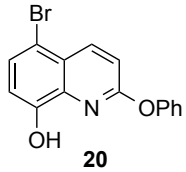
Preparation of 20:



A 25 mL round bottom flask with magnetic stirring bar was charged with substrate **2** (279 mg, 1.2 mmol), and *tert*-butyldimethylsilyl chloride (TBDMSCl) (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 Na_2SO_4, filtered and removed the solvent in vacuo to get the crude TBDMS-protected product which was used for the next step without further purification. Yield: 136 mg, 32%

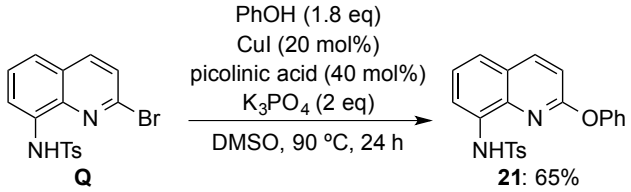
To a mixture of TBDMS-protected substrate (136 mg, 0.39 mmol) in DCM (3 mL), freshly recrystallized NBS (106.8 mg, 0.59 mmol, 1.5 equiv) was added slowly at 15 ºC and the reaction mixture was allowed to stir at 20 ºC for 30 min. Reaction mixture was successively washed with 1% Na_2SO_3 solution and water, organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated in vacuo to give the brominated TBDMS-protected compound. Yield: 136 mg, 81%.



20

To a mixture of brominated TBDMS-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 strirred 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 Na_2SO_4 and the solvent was evaporated vacuo. The crude product was purified by flash column chromatography using hexanes/Et_2O 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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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).

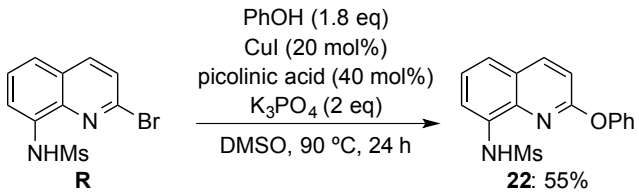
Preparation of 21:



Q **21**: 65%

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, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{22}H_{19}N_2O_3S$ $[M + H]^+$, 391.1116; found, 391.1110.

Preparation of 22:

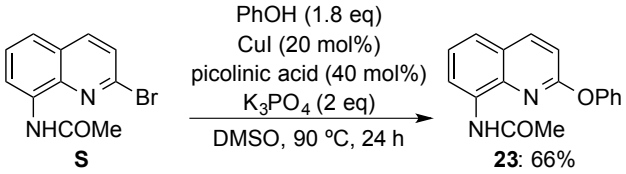


R **22**: 55%

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, $CDCl_3$) 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 =

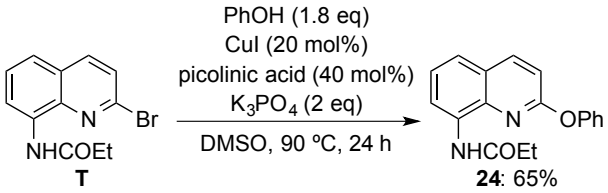
7.8 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 8.4 Hz,3H), 2.82 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 161.7, 153.3, 140.5, 136.9, 132.6, 129.9 (2C), 125.8, 125.7, 125.3, 122.9, 121.7(2C), 118.1, 113.7, 39.3 ppm. MS (70 eV), m/z (%) 314 (39) [M+], 236 (20), 235 (100), 234 (20), 206 (15), 77 (10).

Preparation of 23:



Compound **23** 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): ν = 3359, 2807, 2354, 1674, 1250, 761 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) *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. ^{13}C NMR (151 MHz, $CDCl_3$) *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 $C_{17}H_{15}N_2O_2$ $[M + H]^+$, 279.1134; found, 279.1125.

Preparation of 24:



Compound **24** 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): ν = 3387, 2934, 2835, 2361, 1667, 1030, 662 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) *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. ^{13}C NMR (151 MHz, $CDCl_3$) *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 $C_{18}H_{17}N_2O_2$ $[M + H]^+$, 293.1290; found, 293.1285.

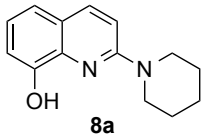
Preparation of 25:

Compound **25** 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): ν = 2816, 1595, 1344, 1253, 841 cm-^{1}. ^{1}H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.6, 154.8, 150.3, 145.5, 145.2, 140.0, 135.9, 130.0 (2C), 129.2, 125.9, 125.6,

124.9, 124.7, 123.0, 120.8 (2C), 112.7 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{13}N_2O$ $[M + H]^+$, 273.1028; found, 273.1022.

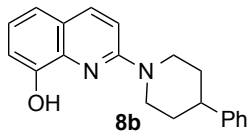
General Procedure C: Dearyloxylative Amination of 2-phenoxy-8-hydroxyquinoline (2) with various amines (7a–7i). A 20 mL Schlenk tube was charged with 2-phenoxy-8-hydroxyquinoline **2** (36 mg, 0.15 mmol, 1.00 equiv) and copper(II) triflate (5.4 mg, 0.015 mmol, 10 mol% or 10.8 mg, 0.03 mmol, 20 mol%). 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_2SO_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).



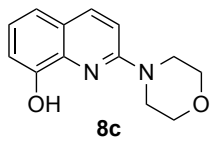
8a

2-(Piperidin-1-yl)quinolin-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 ºC. Light yellow solid (29 mg, 84%). R_f = 0.4 (Hexane: Et_2O = 19:1). mp = 63 ºC. IR (neat): ν = 3430, 2920, 1256, 1037, 797 cm^{-1}. ^1H 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 $C_{14}H_{17}N_2O$ $[M + H]^+$, 229.1341; found, 229.1342.



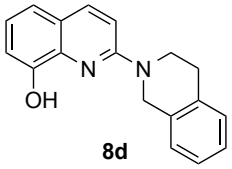
8b

2-(4-Phenylpiperidin-1-yl)quinolin-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 ºC. Light yellow solid (34 mg, 75%). R_f = 0.5 (Hexane:Et_2O = 18:2). mp = 87 ºC. IR (KBr): ν = 3387, 2927, 2354, 1596, 1249, 754 cm^{-1}. ^1H 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), 1.80–1.83 (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 $C_{20}H_{21}N_2O$ $[M + H]^+$, 305.1654; found, 305.1660.



8c

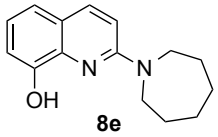
2-Morpholinoquinolin-8-ol (**8c**) was prepared according to the general procedure C using morpholine (65 mL, 0.75 mmol, 5 equiv) as the amine source and $Cu(OTf)_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst at 120 ºC. Light yellow solid (28 mg, 82%). R_f = 0.5 (Hexane:EtOAc = 1:1). mp = 92 ºC. IR (KBr): ν = 3430, 2919, 2354, 1356, 1116, 754 cm^{-1}. ^1H 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, 117.7, 110.5, 110.3, 66.8 (2C), 45.7 (2C) ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{15}N_2O_2$ $[M + H]^+$, 231.1134; found, 231.1129.



8d

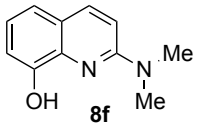
2-(3,4-Dihydroisoquinolin-2(1H)-yl)quinolin-8-ol (**8d**) was prepared according to the general procedure C using 1,2,3,4-tetrahydroisoquinoline (94 mL, 0.75 mmol, 5 equiv) as the amine source, $Cu(OTf)_2$ (5.4 mg, 0.015 mmol, 10 mol%) as the catalyst and Cs_2CO_3 (73.3 mg, 0.225 mmol, 1.5 eq) as an additive at 120 ºC. Viscous liquid (22 mg, 54%). R_f = 0.4 (Hexane:Et_2O = 19:1). IR (neat): ν = 3423, 2935, 2335, 1260, 1023, 729cm^{-1}. ^1H 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,

2H), 6.97–7.01 (m, 2H), 4.79 (s, 2H), 3.90 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 150.2, 137.8, 137.3, 135.3, 134.1, 128.6, 126.8, 126.7, 126.5, 122.8, 122.6, 117.7, 110.4, 110.2, 47.4, 43.0, 29.2 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{17}N_2ONa$ $[M + H]^+$, 299.1160; found, 299.1165.



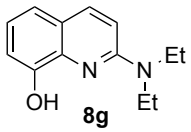
8e

2-(Azepan-1-yl)quinolin-8-ol (**8e**) was prepared according to the general procedure C using hexamethyleneimine (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 ºC. Viscous liquid (31 mg, 86%). R_f = 0.3 (Hexane:Et_2O = 19:1). IR (neat): ν = 3401, 2934, 2325, 1448, 1080, 740 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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 (s, 4H), 1.45 (s, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.3, 149.9, 137.7, 137.4, 121.9, 121.8, 117.6, 109.8, 109.7, 48.1 (2C), 27.8 (2C), 27.0 (2C) ppm. HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}N_2O$ $[M + H]^+$, 243.1497; found, 243.1501.



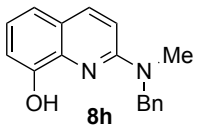
8f

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 ºC 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_2SO_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:Et_2O = 9:1). mp = 71 ºC. IR (KBr): ν = 3366, 2927, 1640, 1385, 1250, 747 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 1H), 7.08–7.13 (m, 2H), 7.04–7.05 (m, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 3.21 (s, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 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 $C_{11}H_{13}N_2O$ $[M + H]^+$, 189.1028; found, 189.1028.



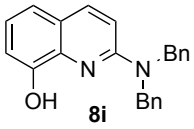
8g

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 ºC. Brown solid (24 mg, 73%). R_f = 0.3 (Hexane:Et_2O = 19:1). mp = 75 ºC. IR (neat): ν = 3438, 2933, 2341, 1738, 1164, 668 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{13}H_{16}N_2ONa$ $[M + H]^+$, 239.1160; found, 239.1158.



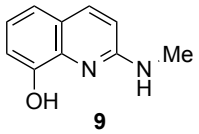
8h

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 ºC. Brown solid (35 mg, 88%). R_f = 0.4 (Hexane:Et_2O = 19:1). mp = 78 ºC. IR (KBr): ν = 3430, 2947, 1589, 1257, 768 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1341; found, 265.1348.



8i

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 ºC and the reaction was continued for 72 h. Light yellow solid (28 mg, 55%). R_f = 0.5 (Hexane:Et_2O = 19:1). mp = 91 ºC. IR (KBr): ν = 3422, 2920, 2361, 1589, 1242, 740 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{23}H_{21}N_2O$ $[M + H]^+$, 341.1654; found, 341.1651.



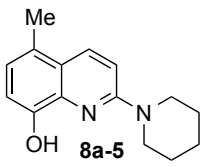
9

*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 N_2 (3 times) and then again evacuated and back filled with H_2 (3 times). To the flask, anhydrous MeOH (2.5 mL) was added and the reaction mixture was stirred under hydrogen atmosphere using a 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:Et_2O = 3:2), mp = 115–120 ºC. IR (KBr): ν = 3415, 2920, 1611, 1392, 818 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{10}H_{10}N_2ONa$ $[M + Na]^+$, 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 ºC 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_2SO_4, filtered, and concentrated in vacuum. The residue was purified by flash column chromatography on silica-gel to give the corresponding *N*-heteroaryl amine.

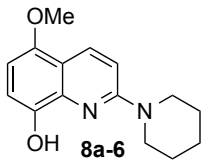
Characterization of N-heteroaryl amines.

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, ^1H and ^{13}C NMR, and HRMS was found to be identical with the one as described above.



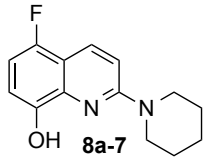
8a-5

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 ºC. IR (KBr): ν = 3438, 2928, 2844, 1609, 1427, 1253, 828 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{18}N_2ONa$ $[M + Na]^+$, 265.1317; found, 265.1317.



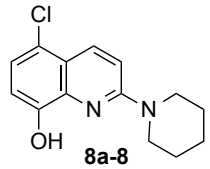
8a-6

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:Et_2O = 4:1). IR (KBr): ν = 3423, 2921, 2349, 912, 730, 646 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{19}N_2O_2$ $[M + H]^+$, 259.1447; found, 259.1435.



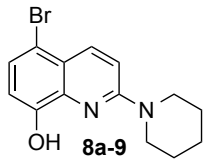
8a-7

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:Et_2O = 19:1). mp = 72 ºC. IR (KBr): ν = 3423, 2935, 1623, 1434, 1233, 813, 575 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{14}H_{16}FN_2O$ $[M + H]^+$, 247.1247; found, 247.1256.



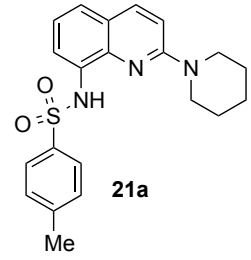
8a-8

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:Et_2O = 19:1). mp = 52 ºC. IR (KBr): ν = 3387, 2906, 1604, 1356, 783 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{14}H_{16}ClN_2O$ $[M + H]^+$, 263.0951; found, 263.0947.



8a-9

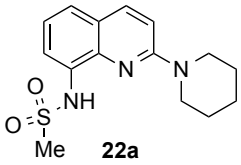
5-Bromo-2-(piperidin-1-yl)quinolin-8-ol (**8a-9**) was prepared according to the general procedure D starting from **20** (47 mg, 0.15 mmol, 1 equiv) as the *N*-heteroaryl ether substrate. Light yellow solid (32 mg, 70%). R_f = 0.3 (Hexane:Et_2O = 49:1). mp = 81 ºC. IR (KBr): ν = 3368, 2920, 2850, 1735, 1602, 1267, 1099, 799 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{14}H_{16}BrN_2O$ $[M + H]^+$, 307.0446; found, 307.0462.



21a

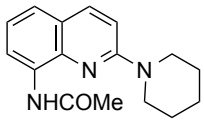
*4-Methyl-N-(2-(piperidin-1-yl)quinolin-8-yl)benzenesulfonamide (**21a**)* was prepared according to the general procedure D starting from **21** (59 mg, 0.15 mmol, 1 equiv) as the *N*-heteroaryl ether substrate Colourless solid (35 mg, 62%). R_f = 0.3 (Hexane:Et_2O = 3:2). mp = 164 ºC. IR (neat): ν = 3416, 2928, 2349, 1162, 904, 744 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 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,

$CDCl_3$) δ 156.5, 143.5, 138.2, 137.7, 136.8, 131.2, 129.5 (2C), 127.3 (2C), 122.3, 122.1, 121.9, 116.5, 110.6, 46.5 (2C), 25.7 (2C), 24.9, 21.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{21}H_{23}N_3O_2SNa$ $[M + Na]^+$, 404.1409; found, 404.1410.



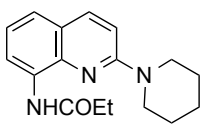
22a

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%). R_f = 0.6 (Hexane:Et_2O = 3:2). mp = 128 ºC. IR (neat): ν = 3430, 2920, 1622, 1162, 904 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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), 2.97 (s, 3H), 1.69–1.70 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{15}H_{19}N_3O_2SNa$ $[M + Na]^+$, 328.1096; found, 328.1100.



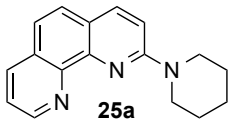
23a

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%). R_f = 0.3 (Hexane:Et_2O = 7:3). mp = 79 ºC. IR (KBr): ν = 3423, 3302, 2927, 2354, 1632, 1235, 740 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{16}H_{19}N_3ONa$ $[M + Na]^+$, 292.1426; found, 292.1430.

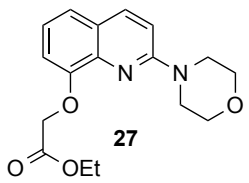


24a

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%). R_f = 0.4 (Hexane:Et_2O = 4:1). mp = 90 ºC. IR (neat): ν = 3402, 2928, 1637, 1037, 632 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{17}H_{22}N_3O$ $[M + H]^+$, 284.1763; found, 284.1759.


25a

2-(Piperidin-1-yl)-1,10-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, 64%). R_f = 0.6 (CH_2Cl_2:MeOH = 19:1). IR (neat): ν = 2942, 2837, 2244, 2041, 1037, 730 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) 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. ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{17}H_{17}N_3Na$ $[M + Na]^+$, 286.1320; found, 286.1310.


27

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 K_2CO_3 (186.6 mg, 1.4 mmol). The mixture was stirred at 80 °C for 4 h. After filtration, the filtrate was concentrated to give crude product, which

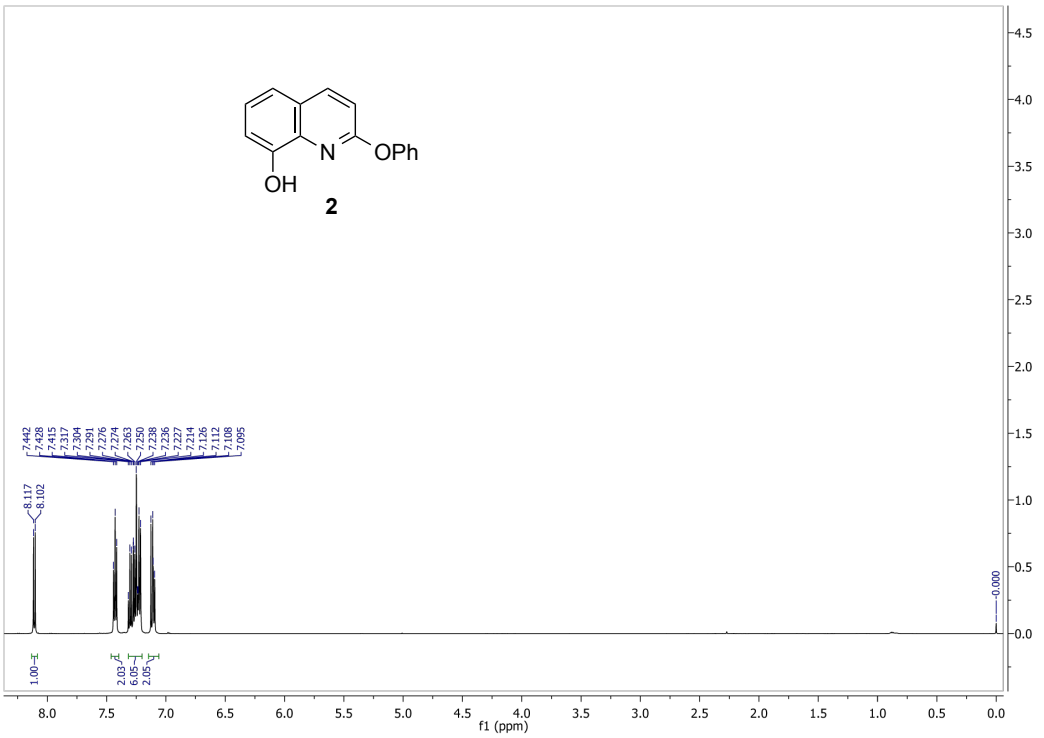
was purified by flash column chromatography on silica-gel to give **27** as a colorless viscous liquid (125 mg, 88%). R_f = 0.5 (Hexane:EtOAc = 1:1). IR (neat): ν = 3465, 2963, 2935, 2844, 1756, 1441, 1121 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 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, $CDCl_3$) δ 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 $C_{17}H_{21}N_2O_4Na$ $[M + H]^+$, 317.1501; found, 317.1500.

References:

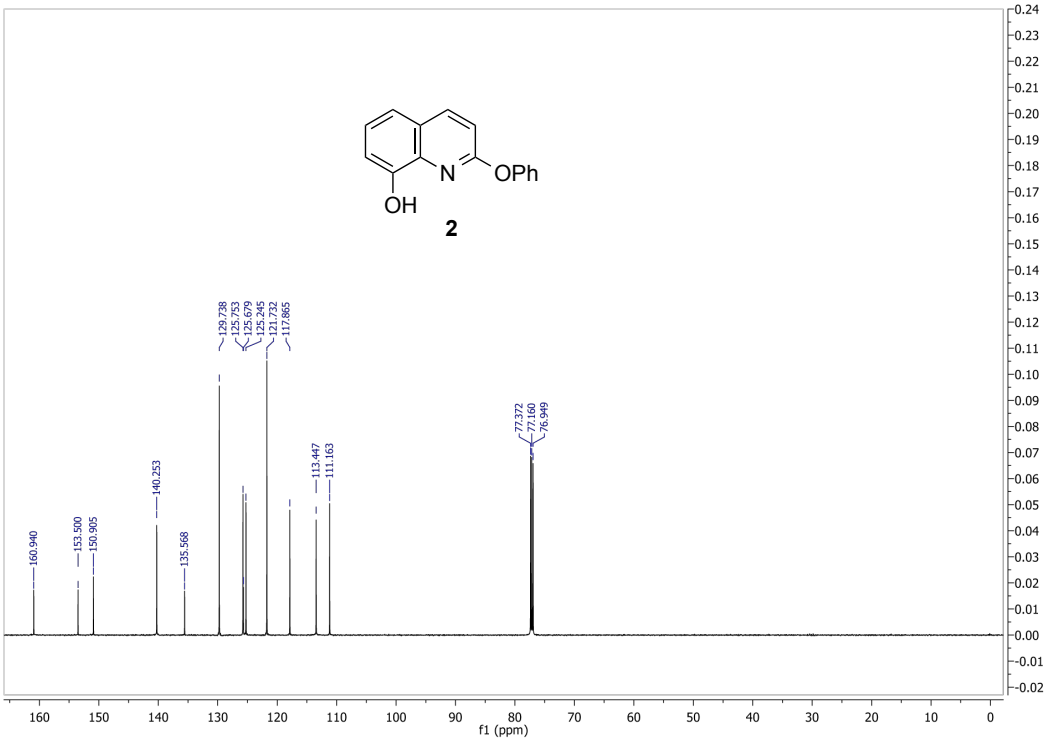
1. W. L. F. Armarego and D. D. Perrin In *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford: USA, **2000.**
2. J. M. Axten, R. A.Daines, D. T. Davies, T. F. Gallagher, G. E. Jones, W. H. Miller, N. D. Pearson and I. A. Pendrak *PCT Int. Appl.* 2004002490, 08 Jan **2004**.
3. S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate and P. S. Baran *Org. Lett.*, 2013, **15**, 792–795.
4. D. Maiti and S. L. Buchwald, *J. Org. Chem.*, 2010, **75**, 1791–1794.

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

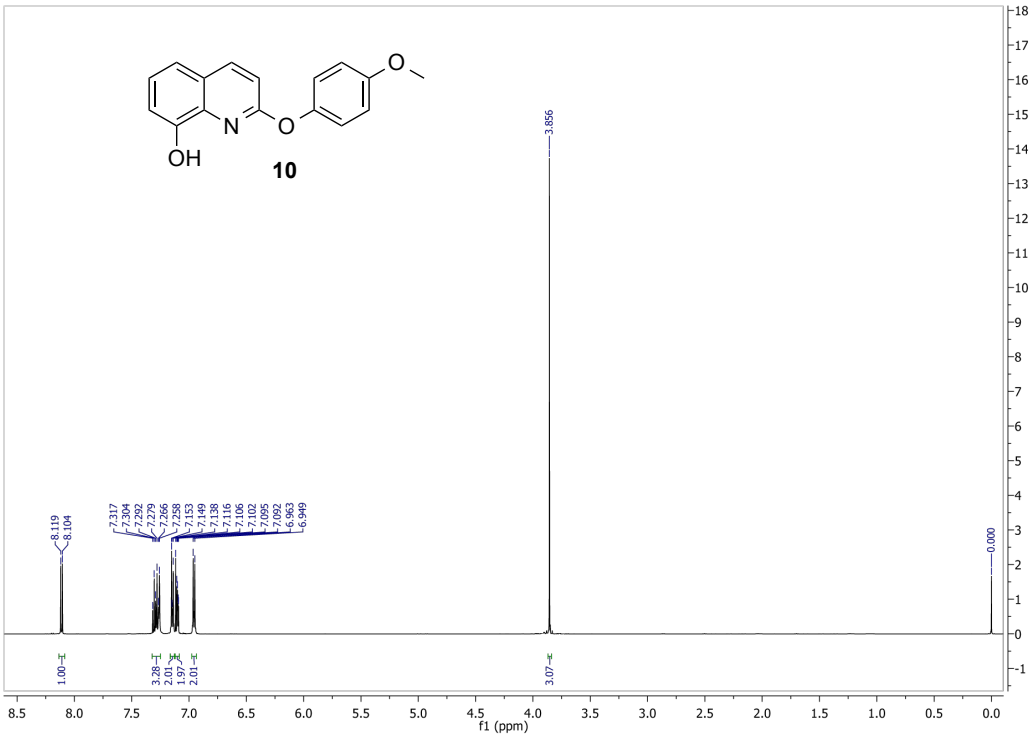
^{1}H NMR (600 MHz, $CDCl_3$):



^{13}C NMR (151 MHz, $CDCl_3$):



^{1}H NMR (600 MHz, $CDCl_3$):



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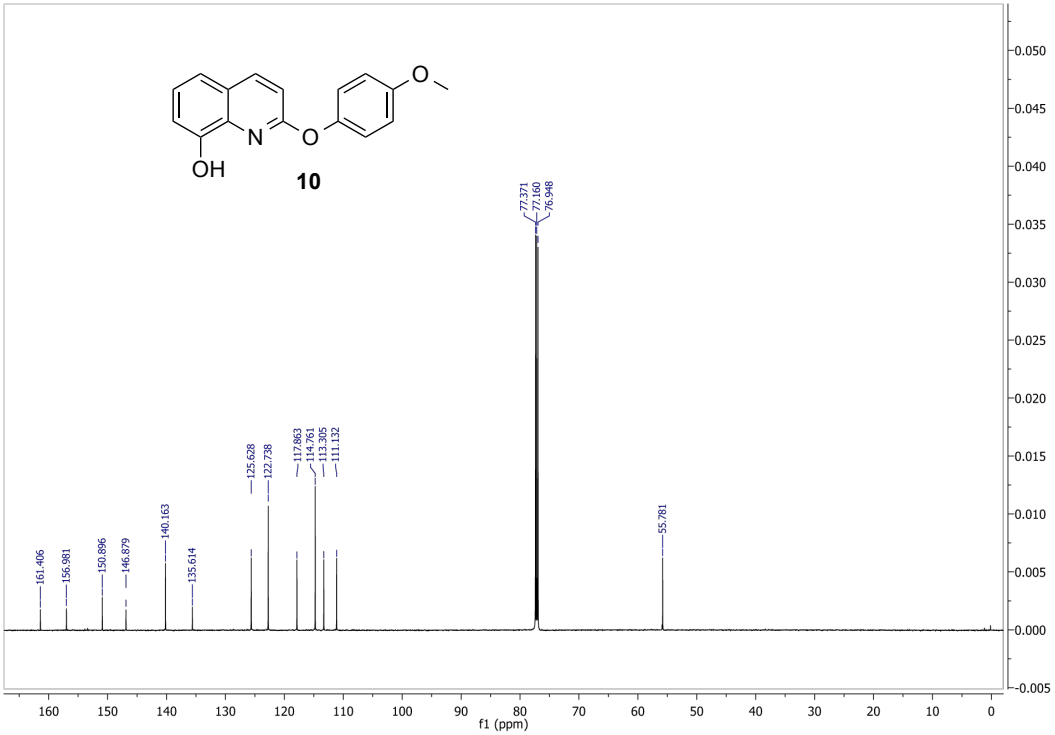
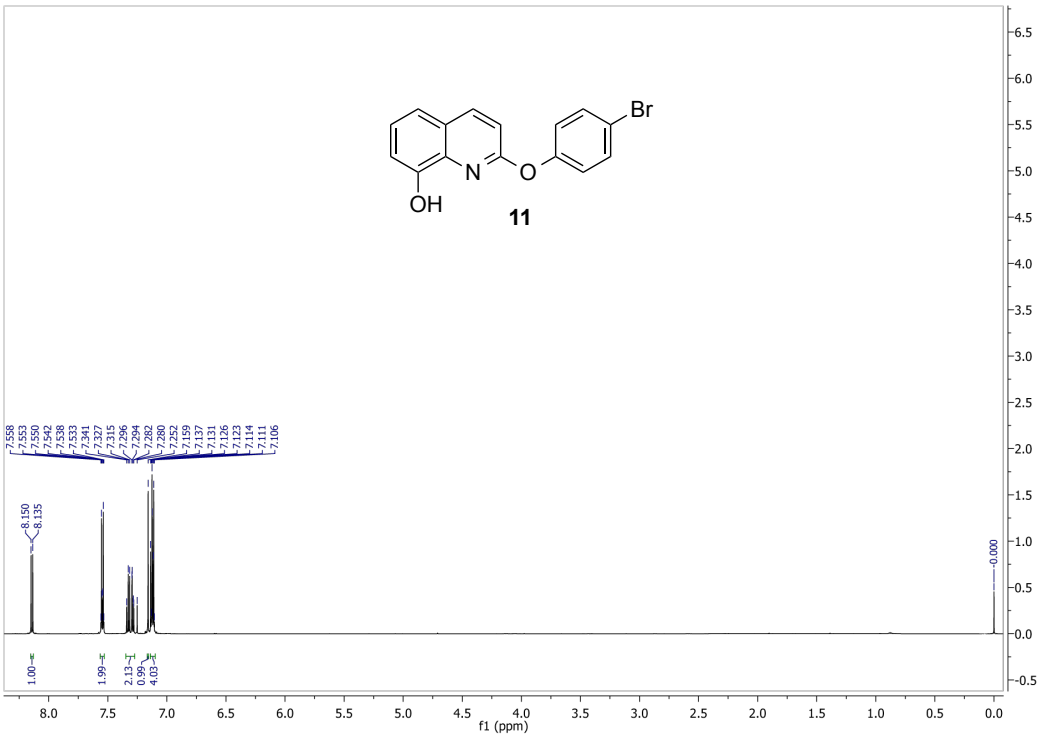
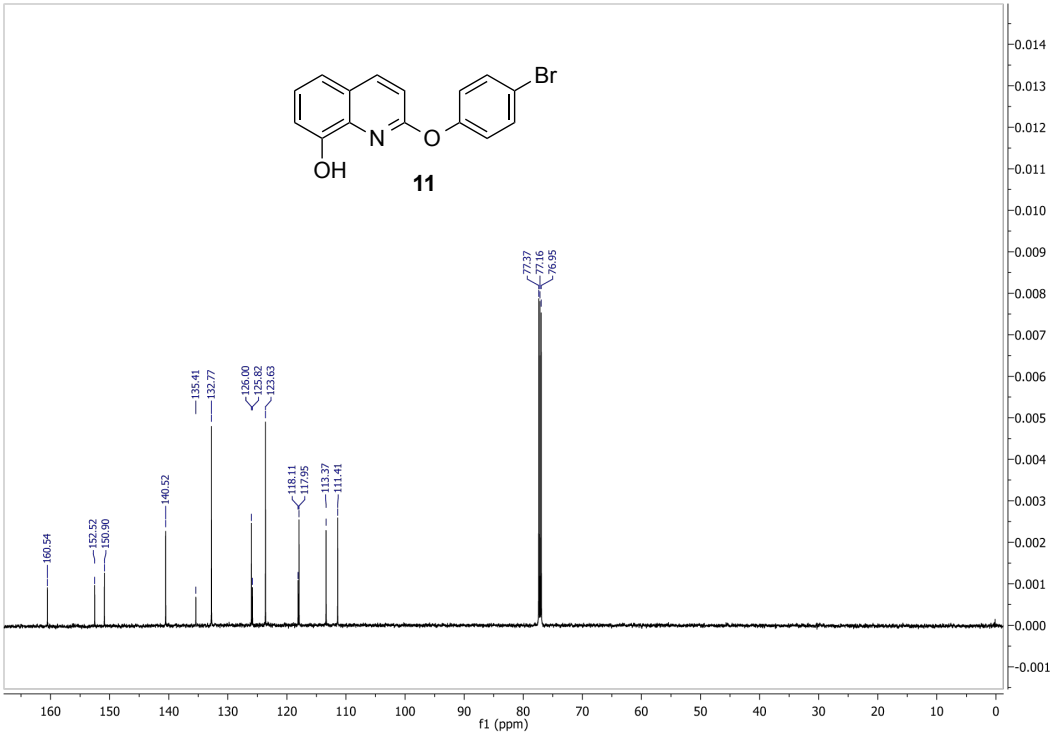


^{1}H NMR (600 MHz, $CDCl_3$):



^{13}C NMR (151 MHz, $CDCl_3$):



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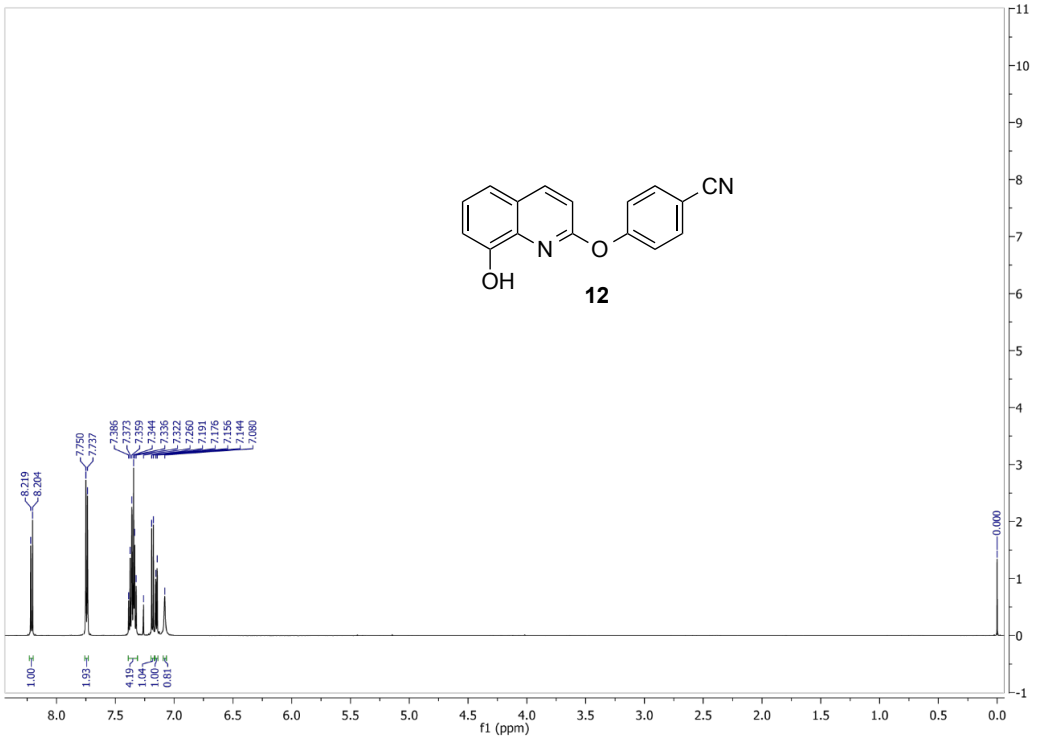
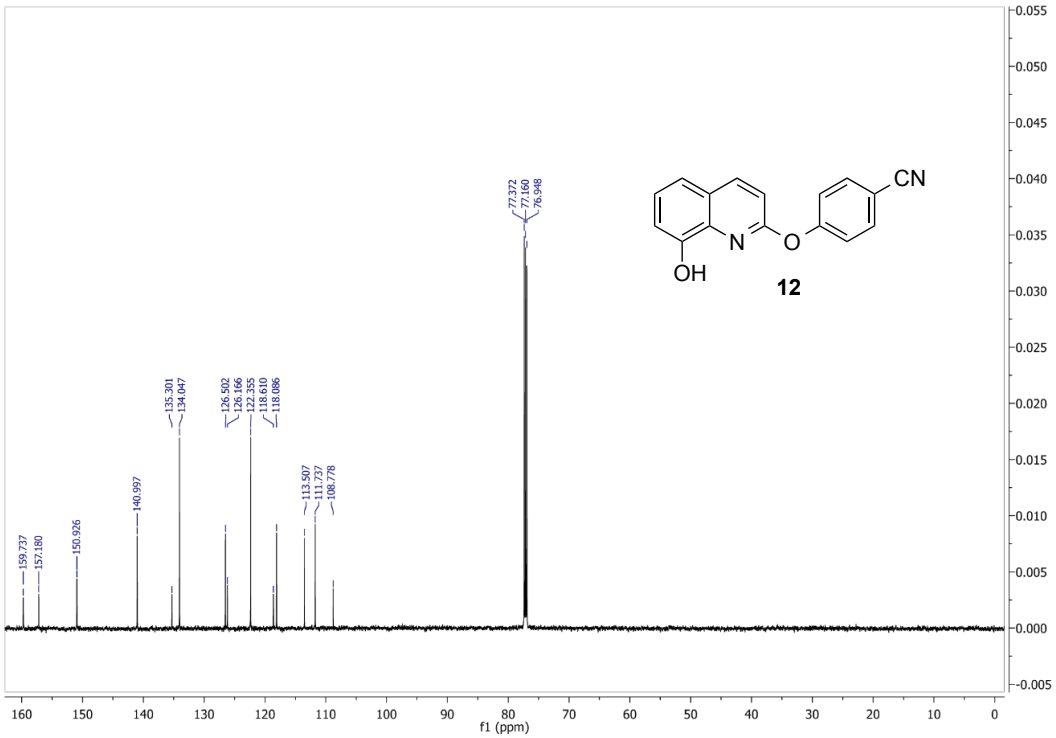
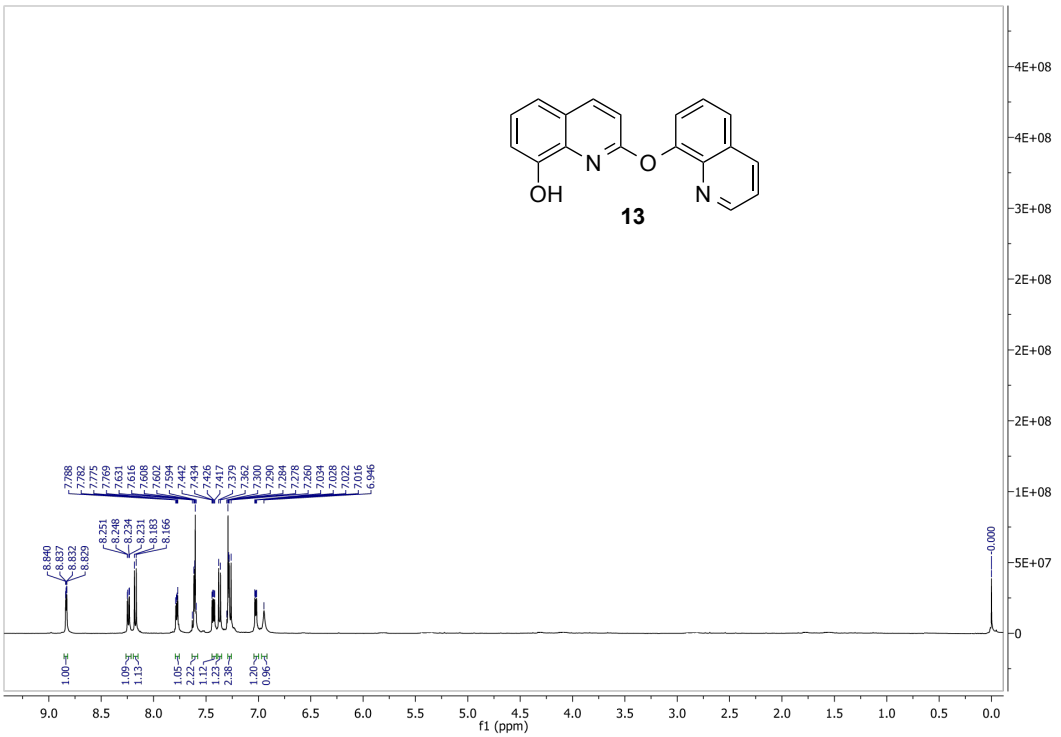


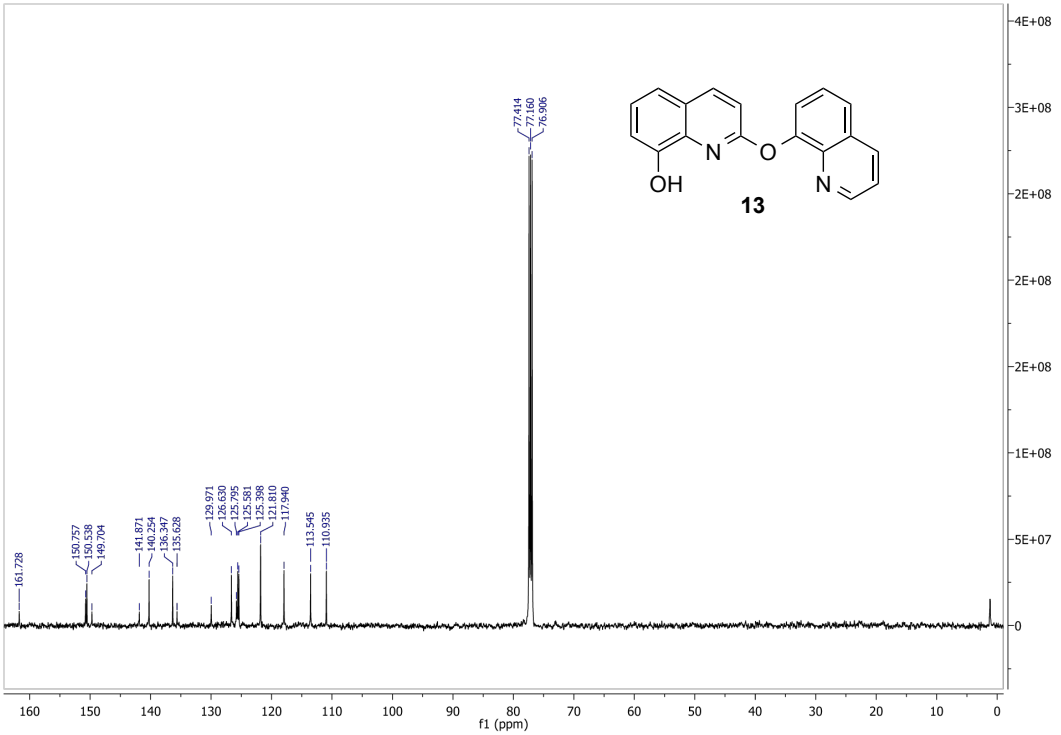
^{13}C NMR (151 MHz, $CDCl_3$):



^{1}H NMR (500 MHz, $CDCl_3$):



^{13}C NMR (126 MHz, $CDCl_3$):



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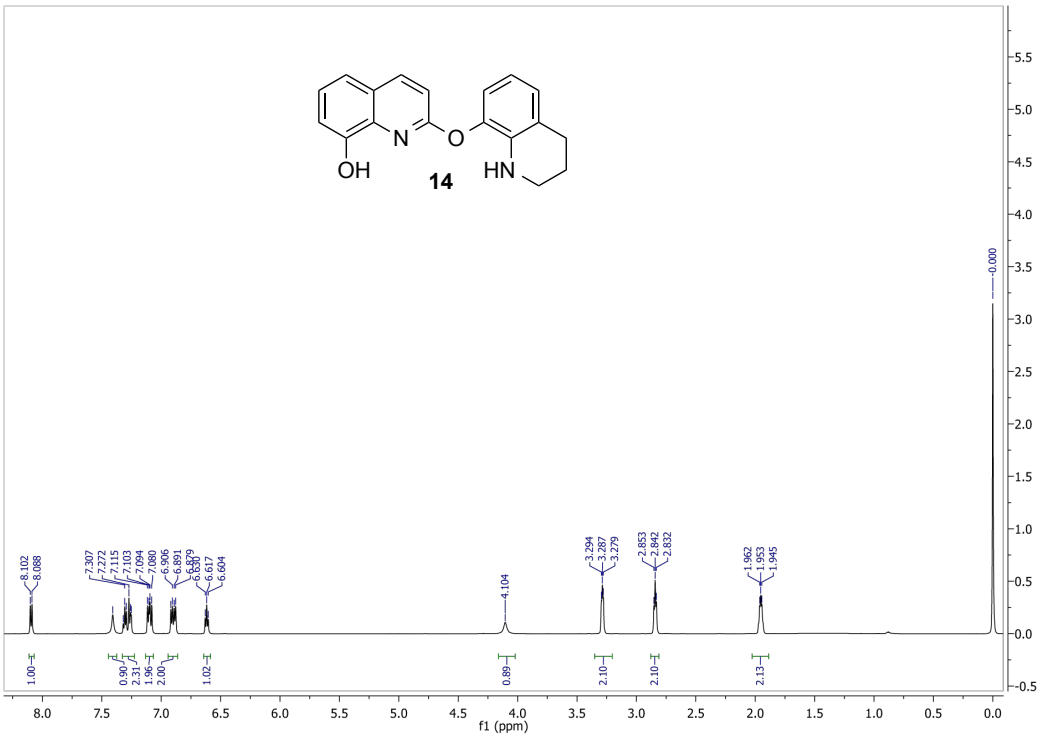
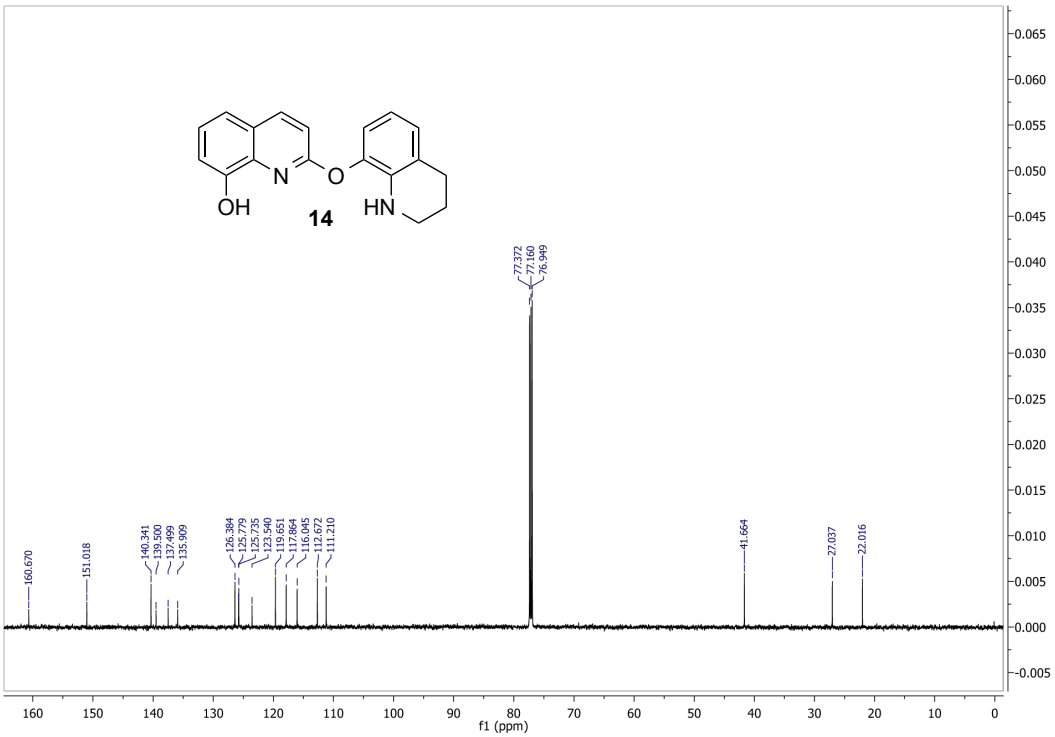


^{13}C NMR (151 MHz, $CDCl_3$):



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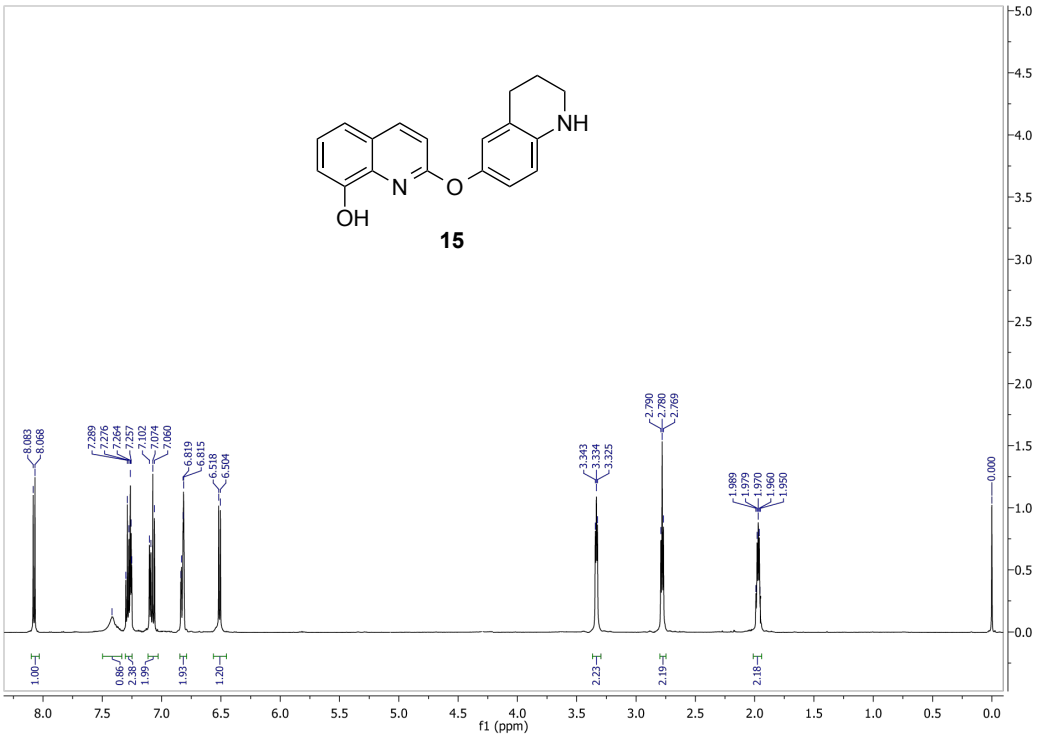
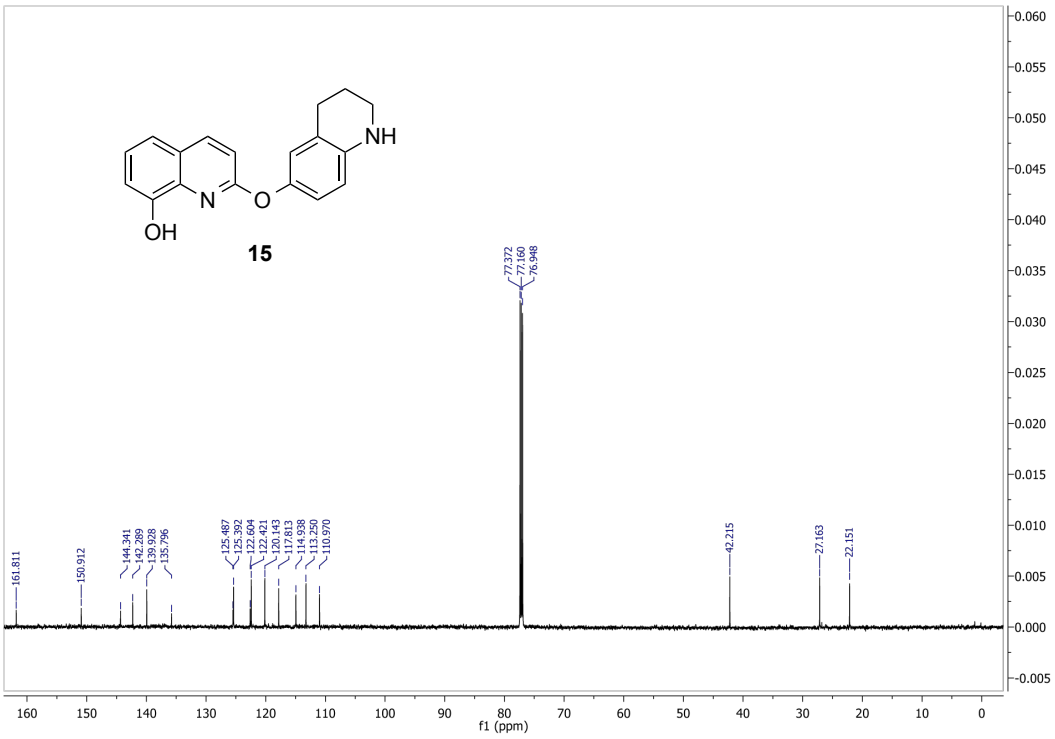


^{13}C NMR (151 MHz, $CDCl_3$):



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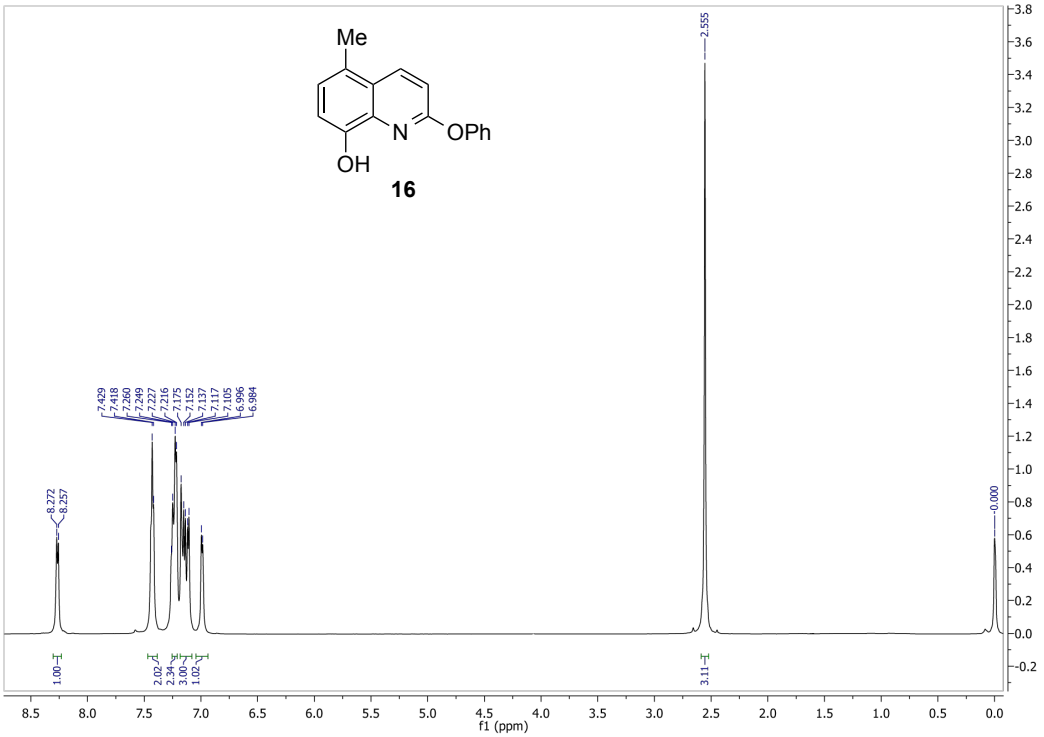
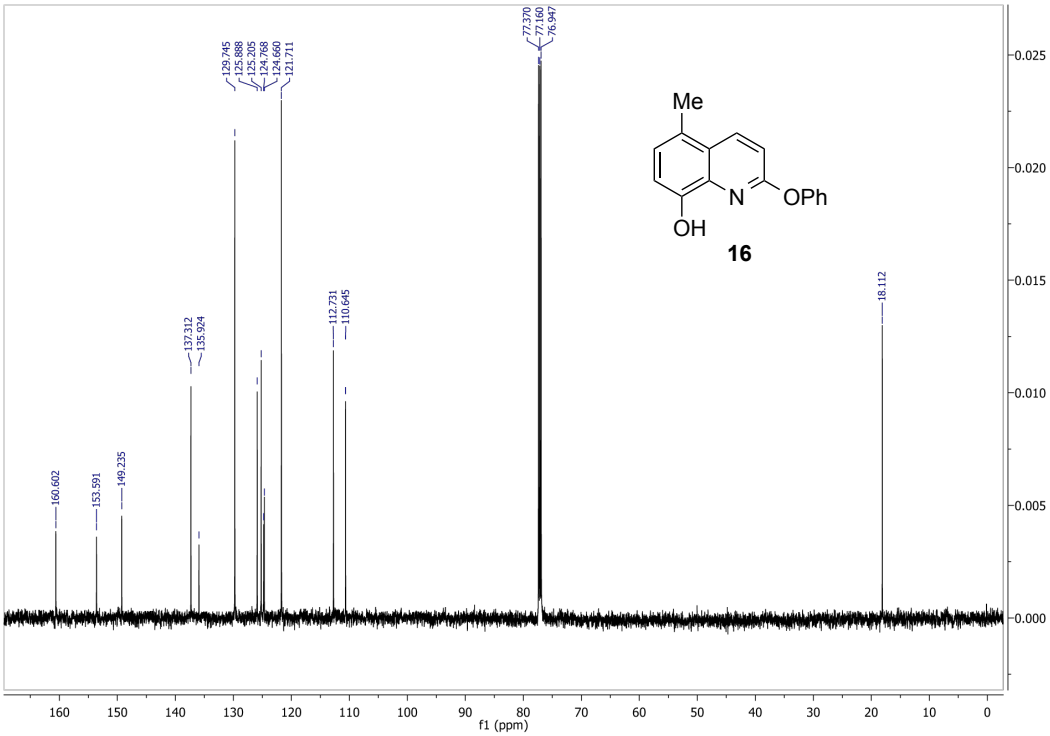


^{13}C NMR (151 MHz, $CDCl_3$):



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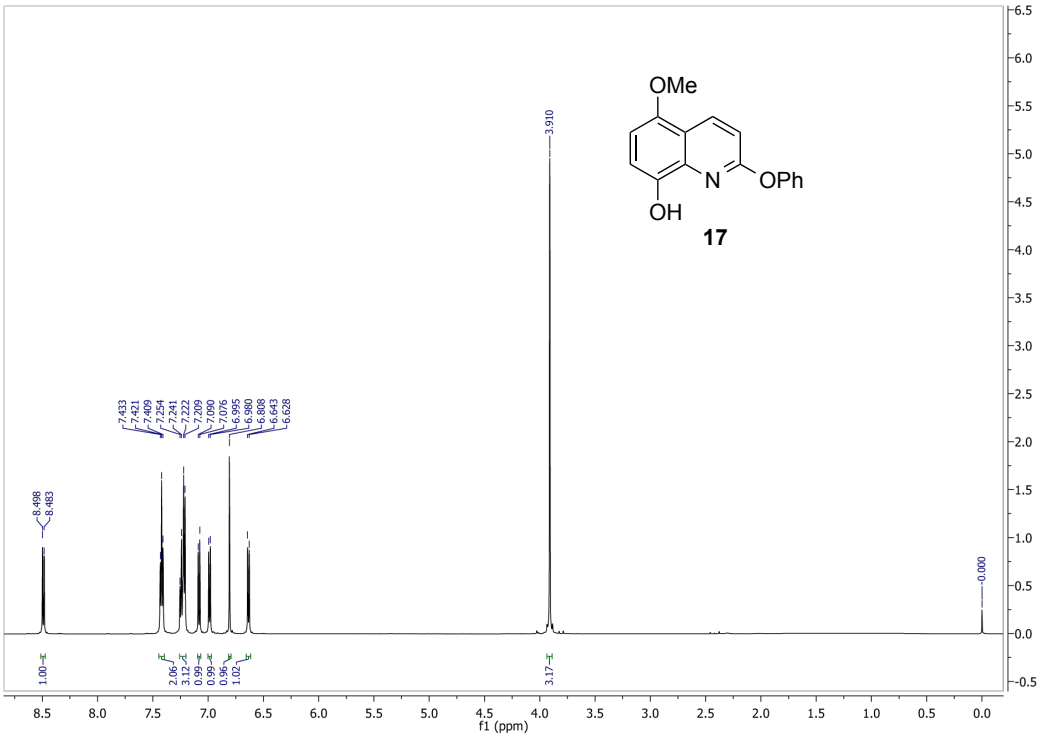
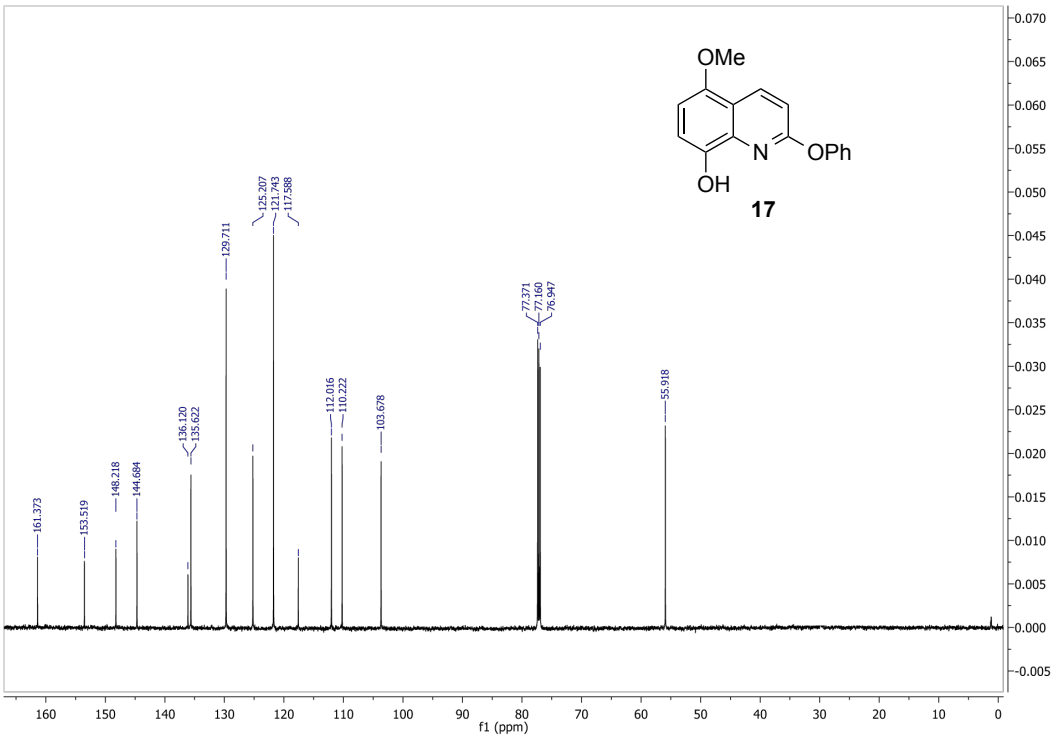


^{13}C NMR (151 MHz, $CDCl_3$):



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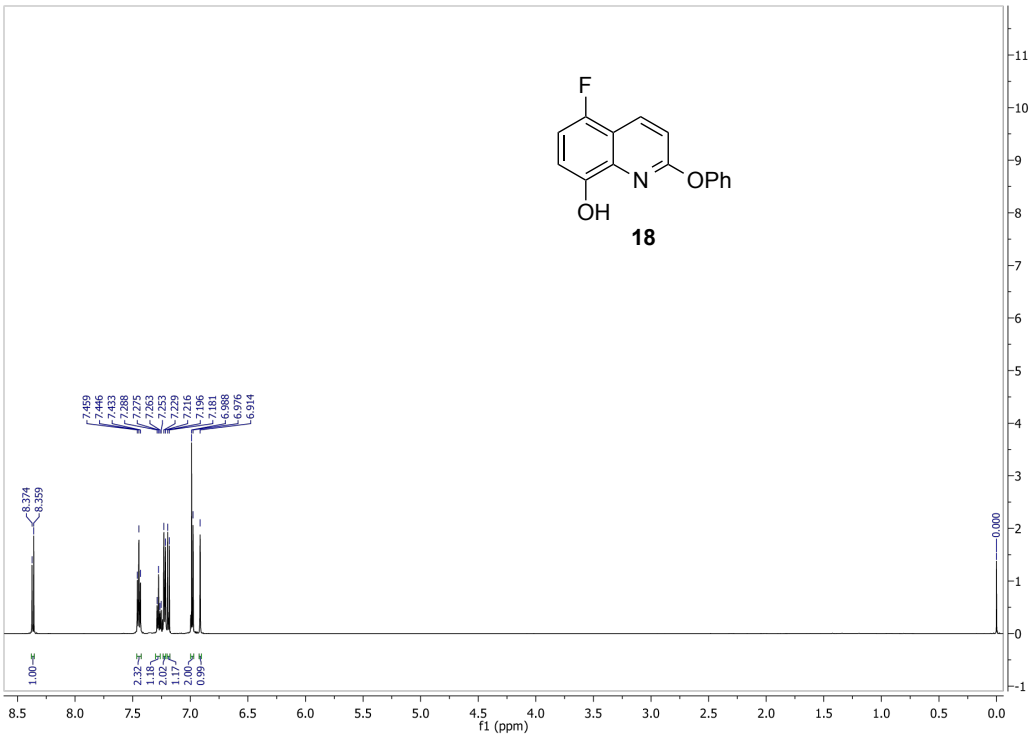
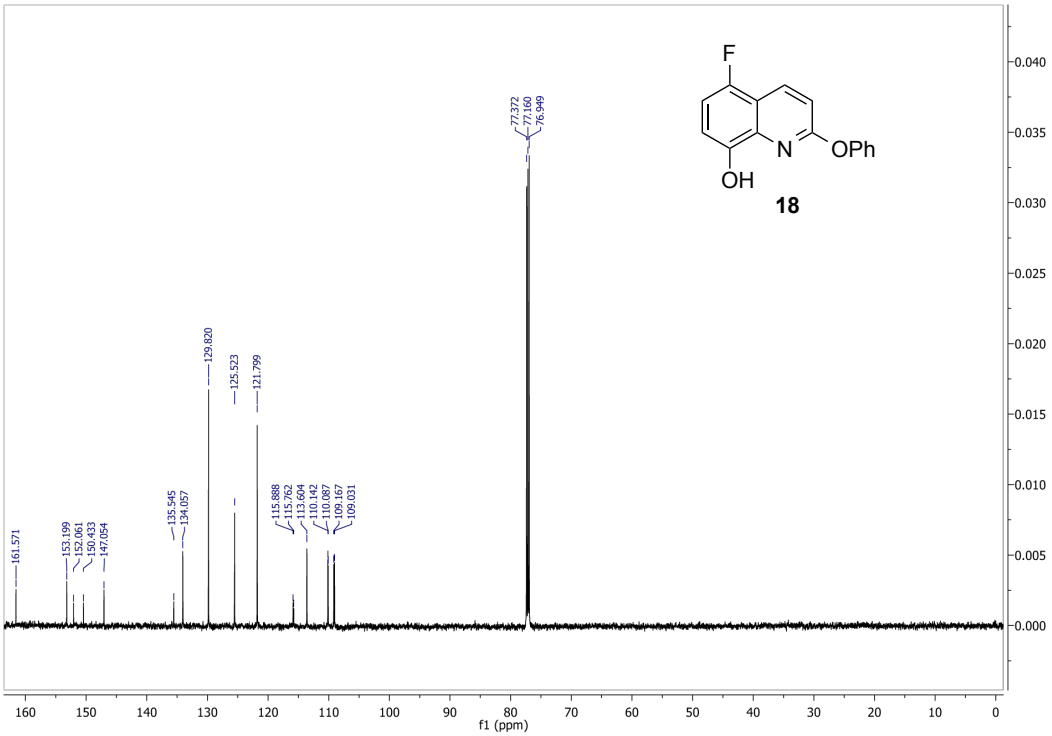


^{13}C NMR (151 MHz, $CDCl_3$):



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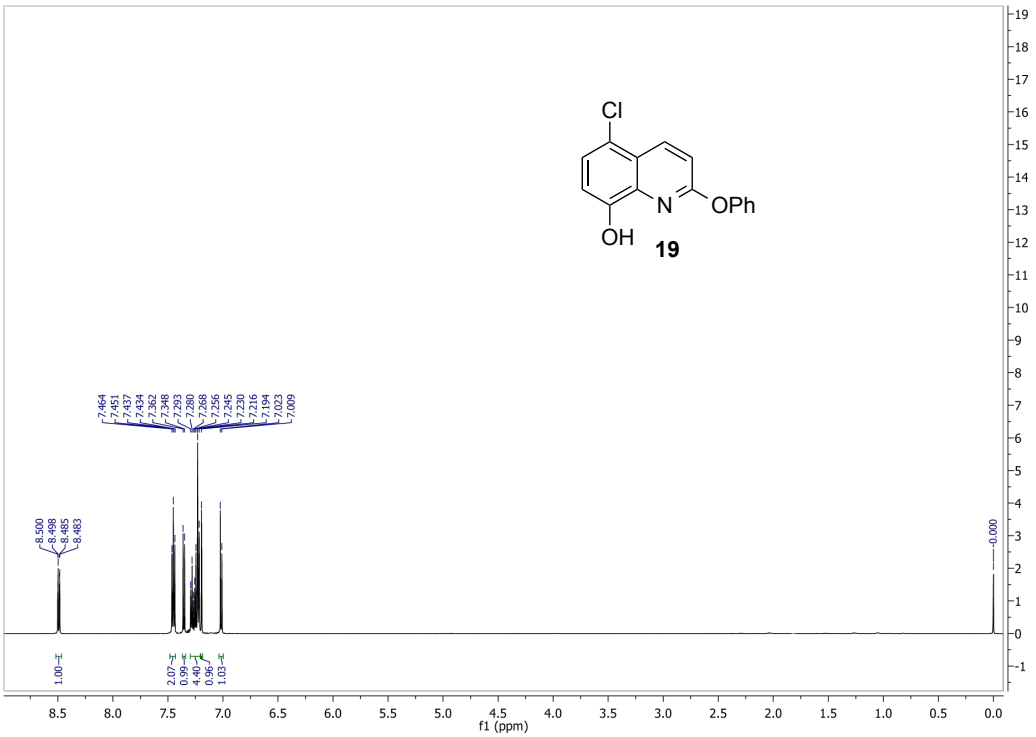

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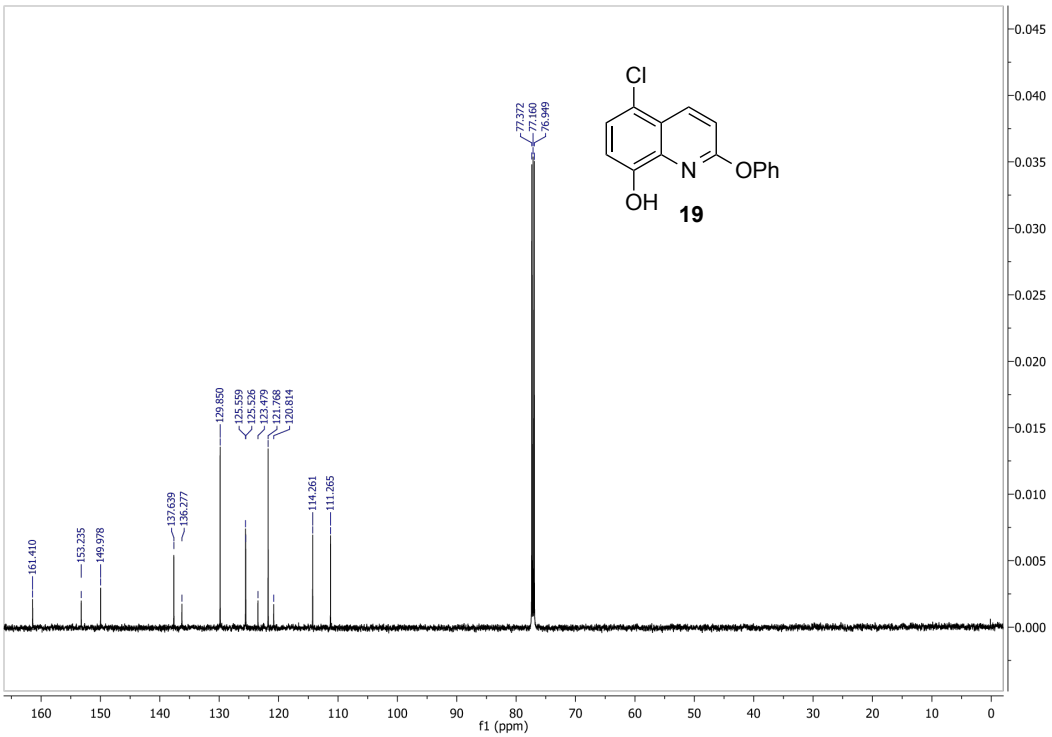

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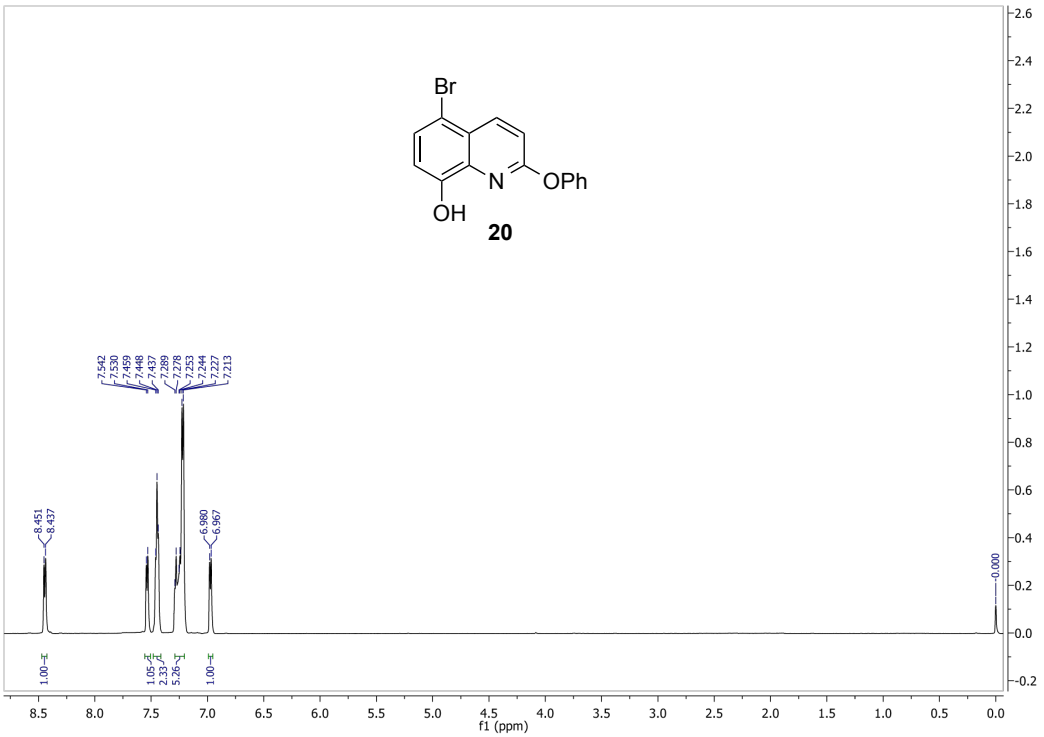

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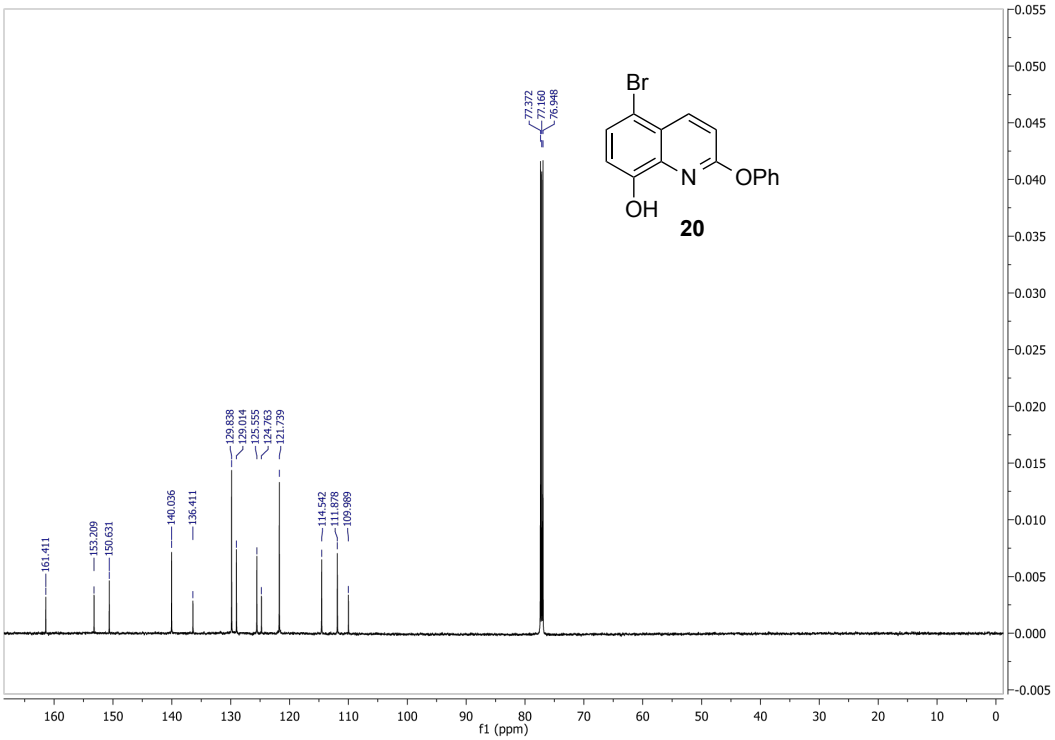

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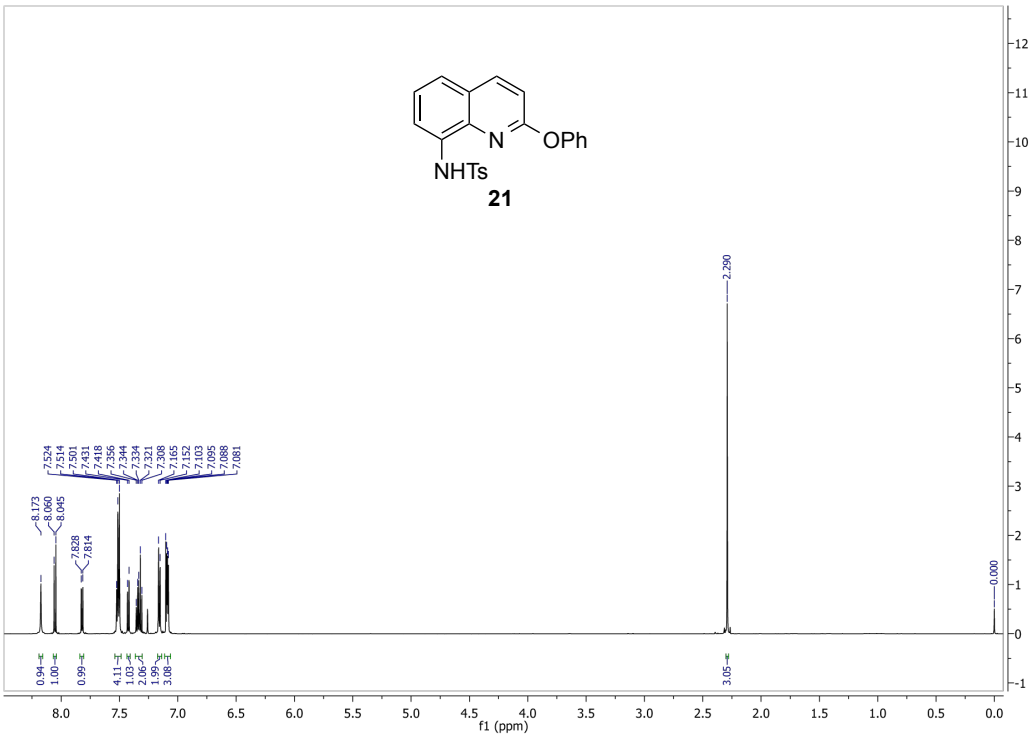

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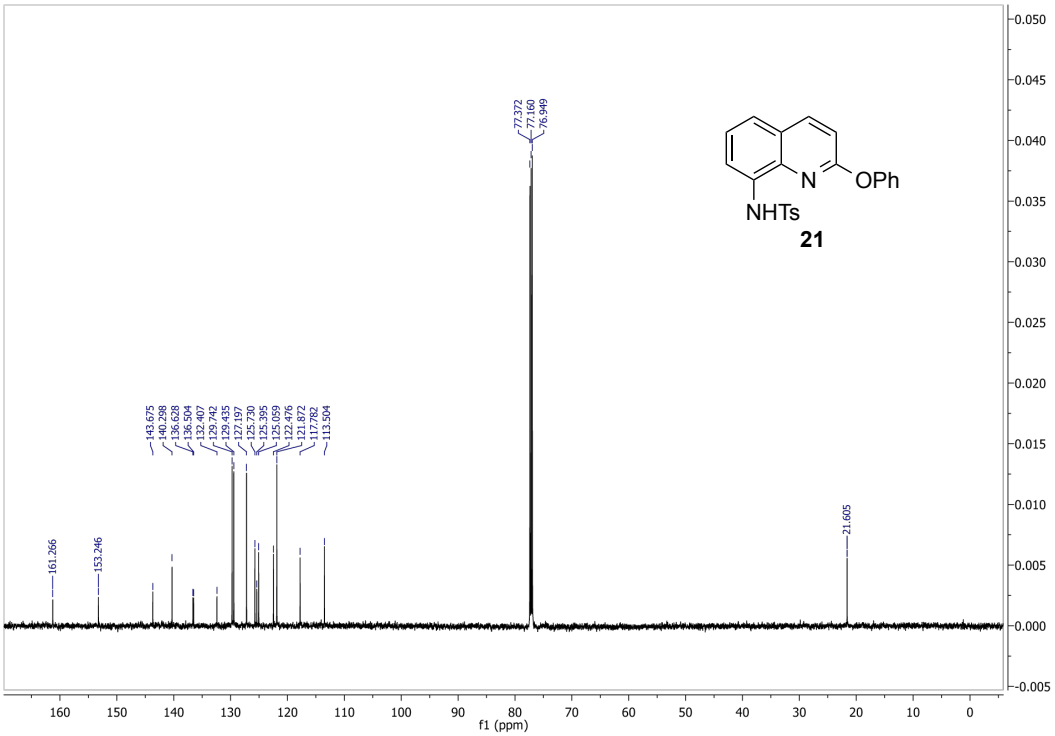

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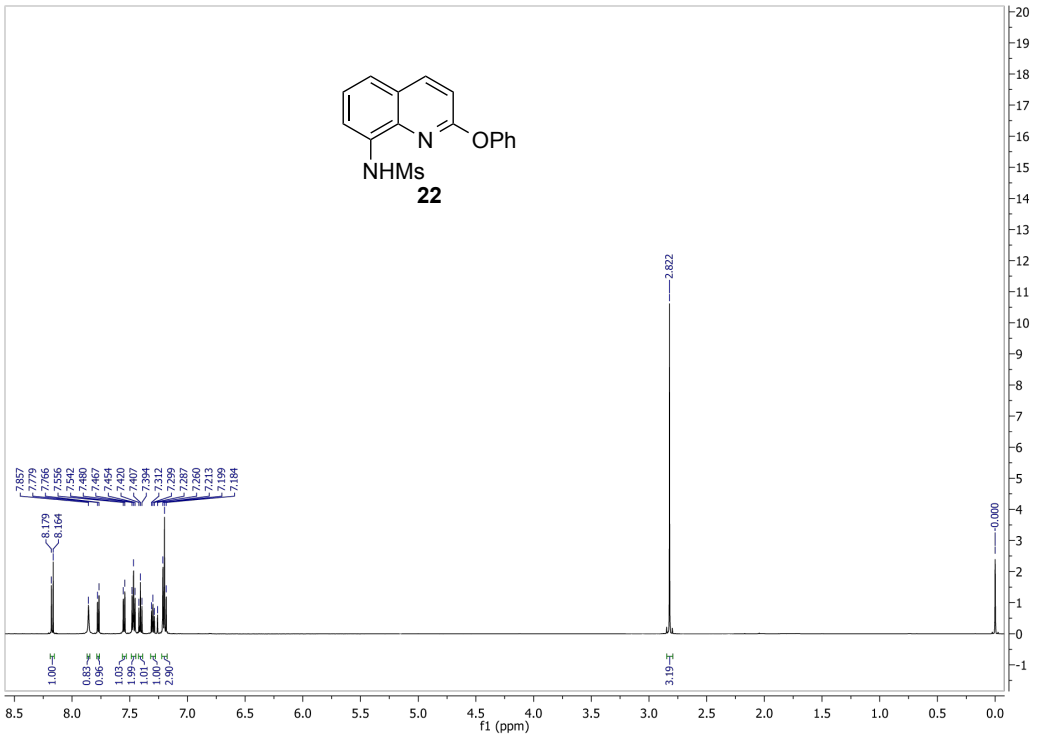

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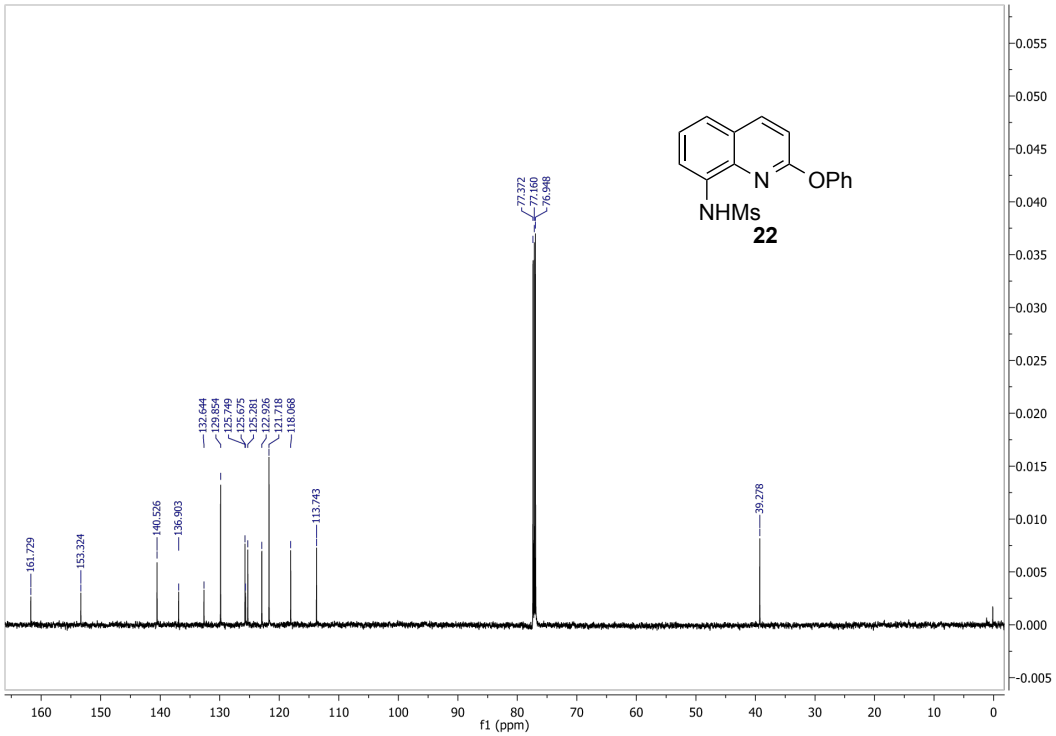

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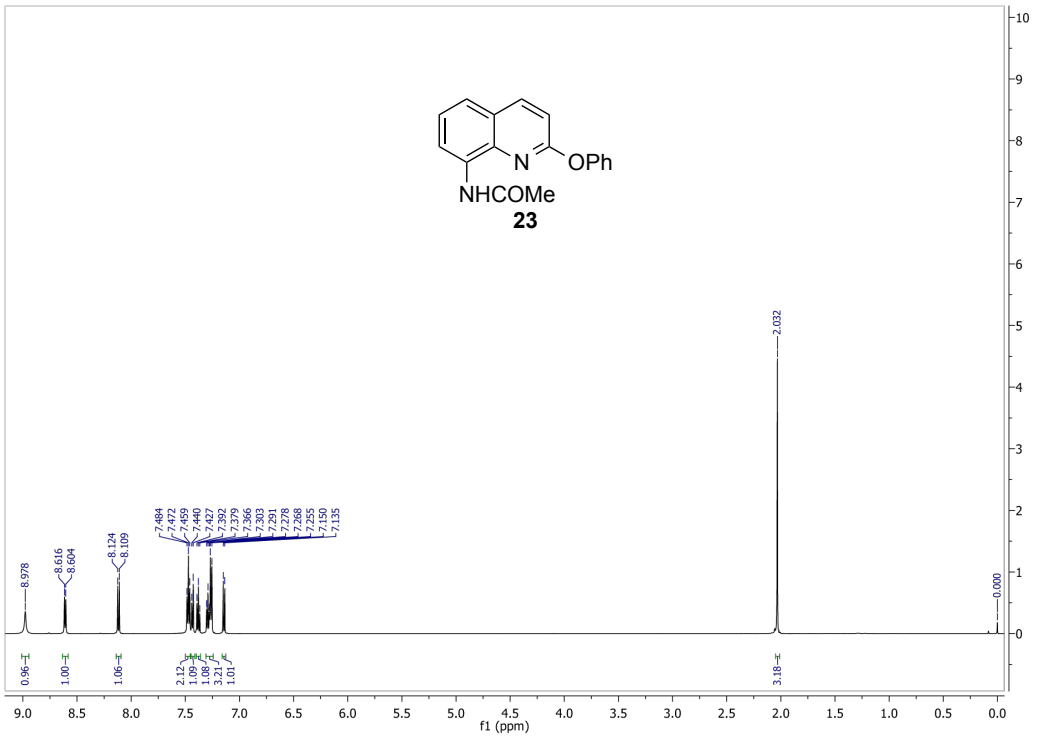
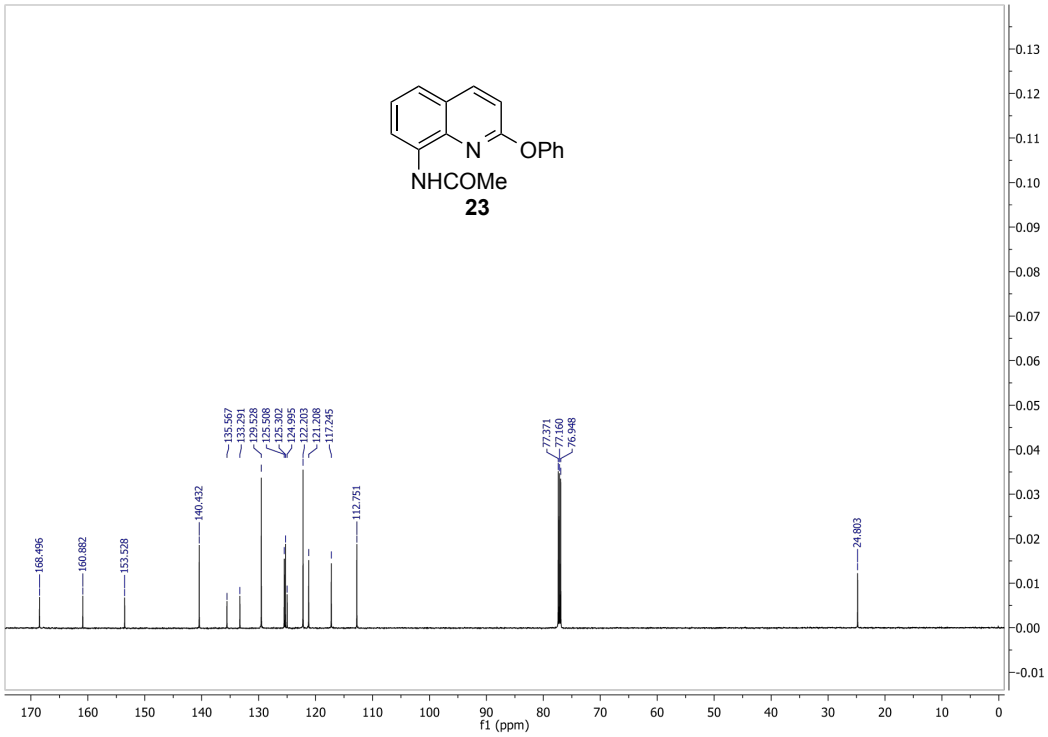
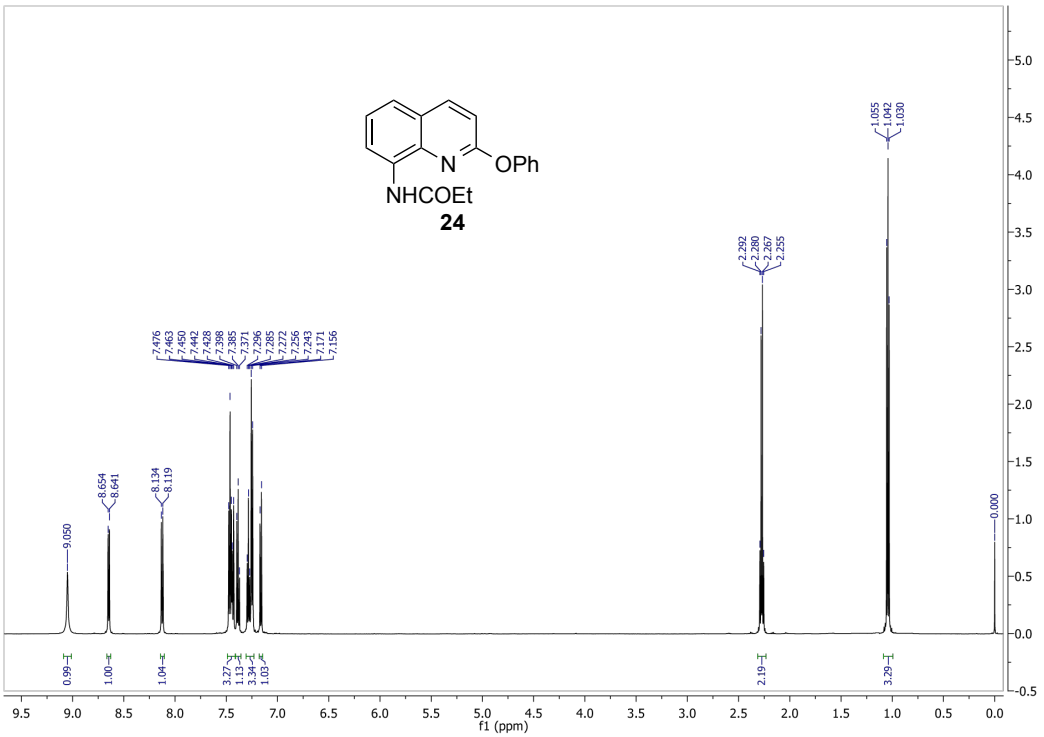


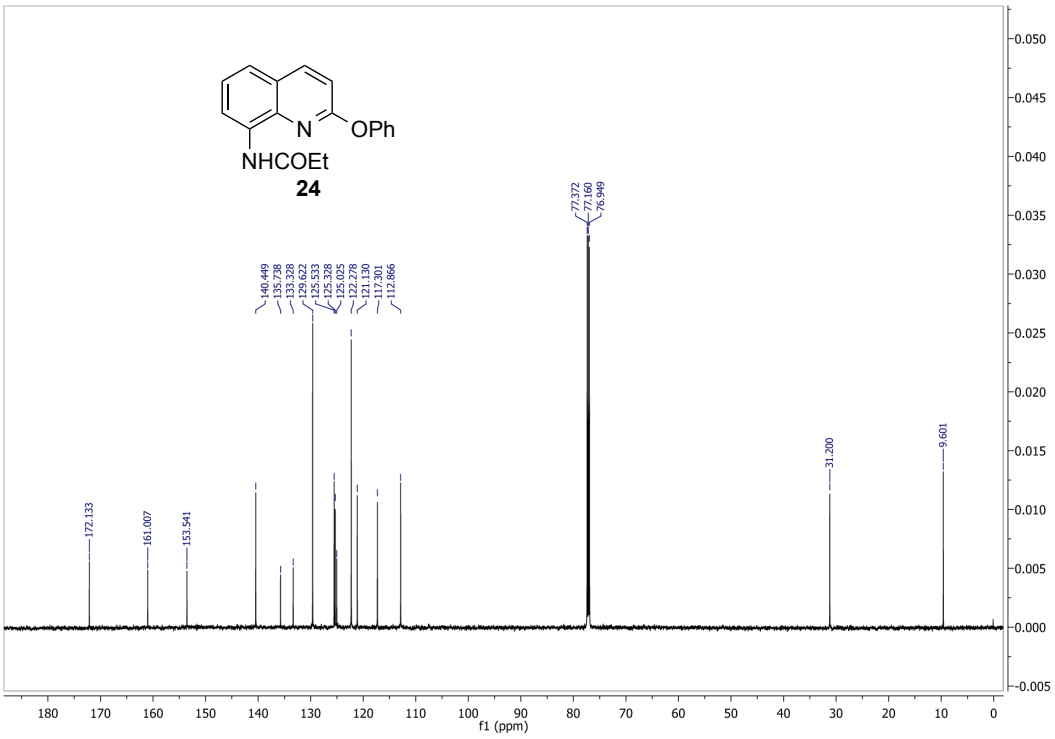
^{13}C NMR (151 MHz, $CDCl_3$):



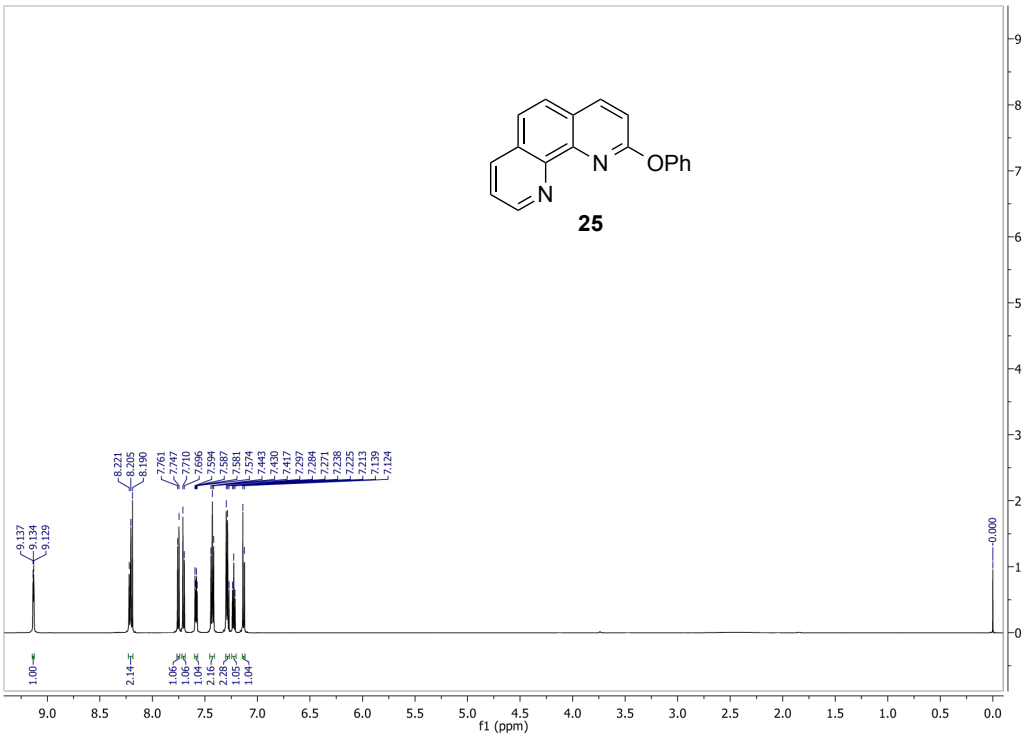
^{1}H NMR (600 MHz, $CDCl_3$):



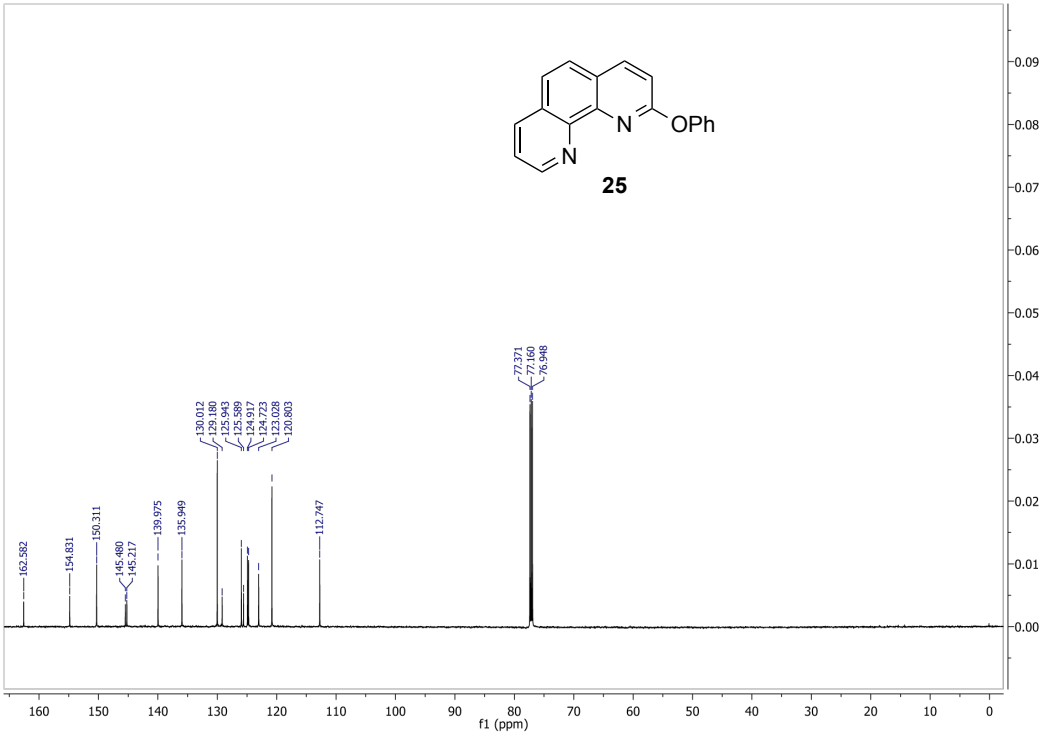
^{13}C NMR (151 MHz, $CDCl_3$):



^{1}H NMR (600 MHz, $CDCl_3$):

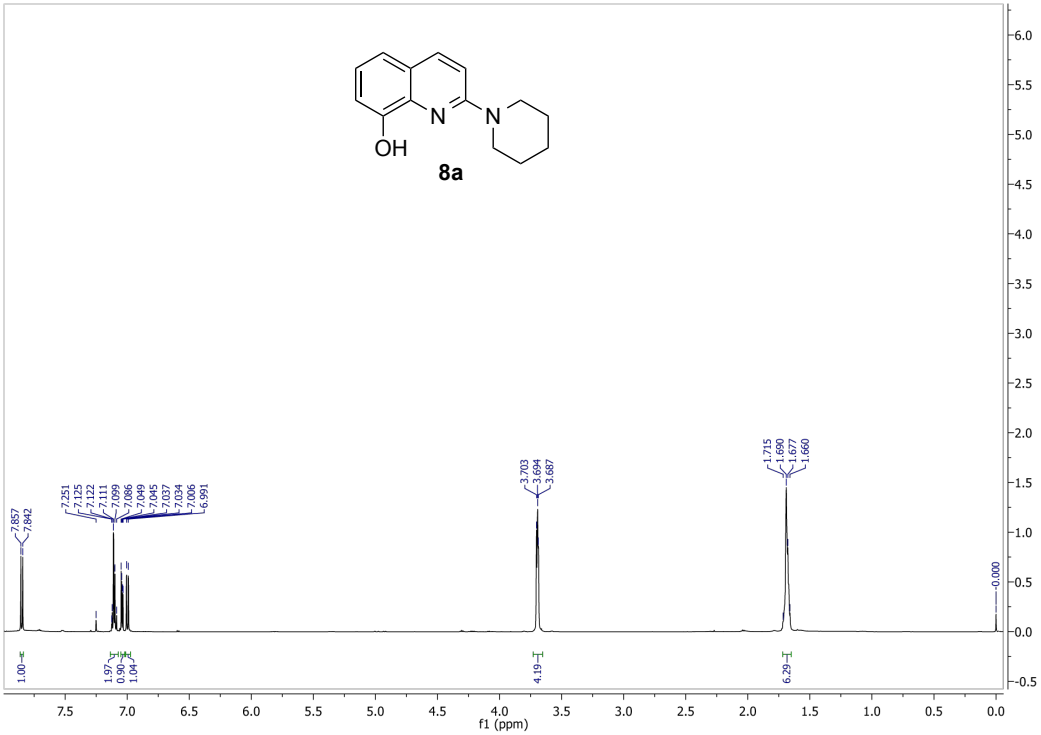


^{13}C NMR (151 MHz, $CDCl_3$):

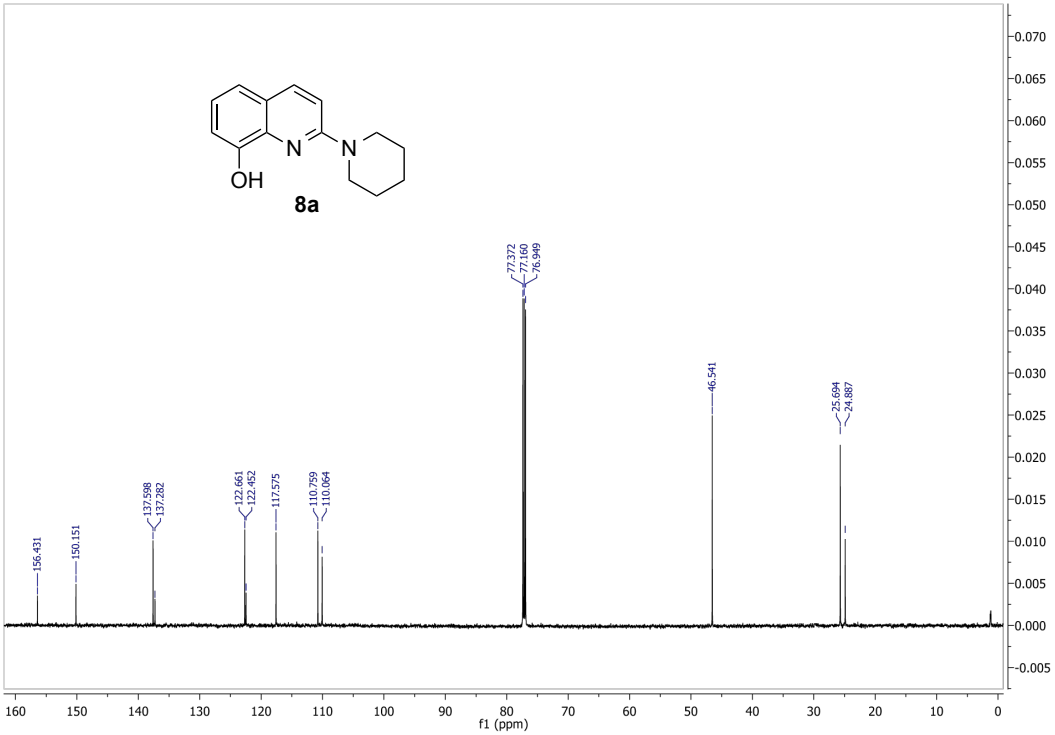


^{1}H and ^{13}C NMR spectra of all products

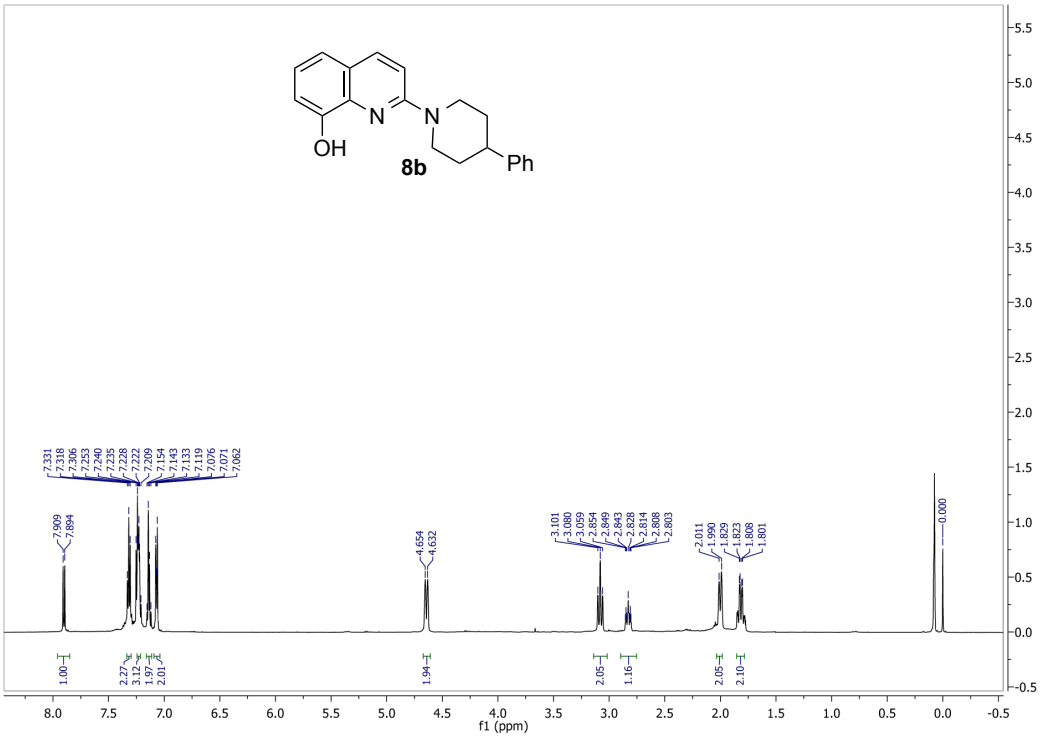
^{1}H NMR (600 MHz, $CDCl_3$):



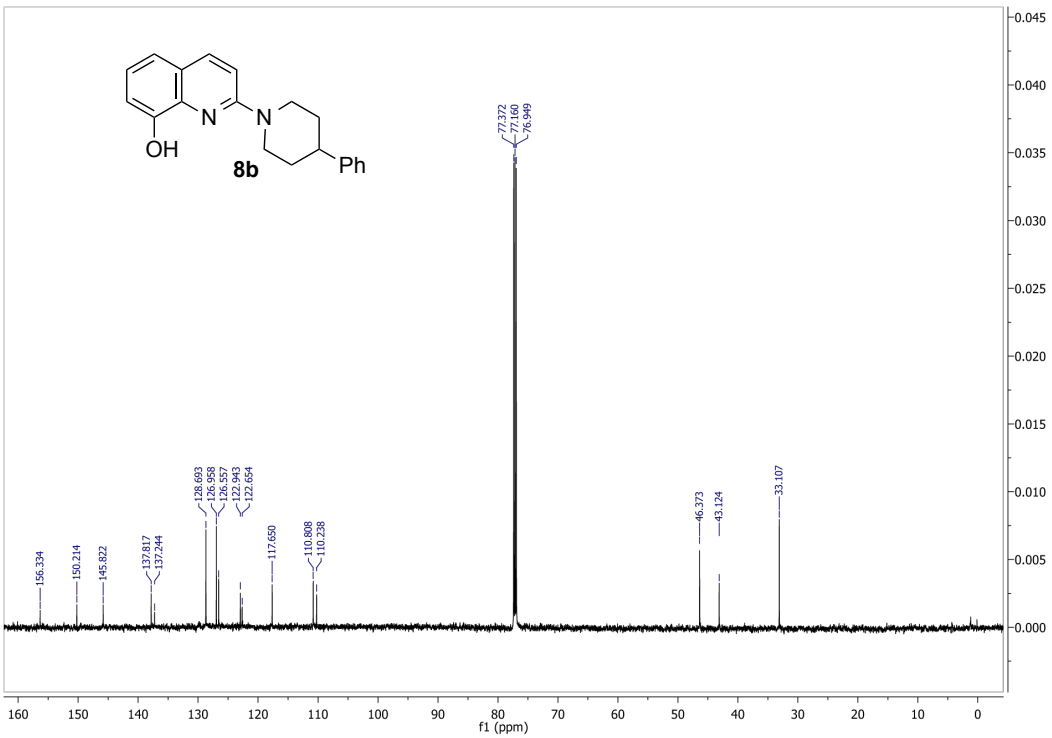
^{13}C NMR (151 MHz, $CDCl_3$):



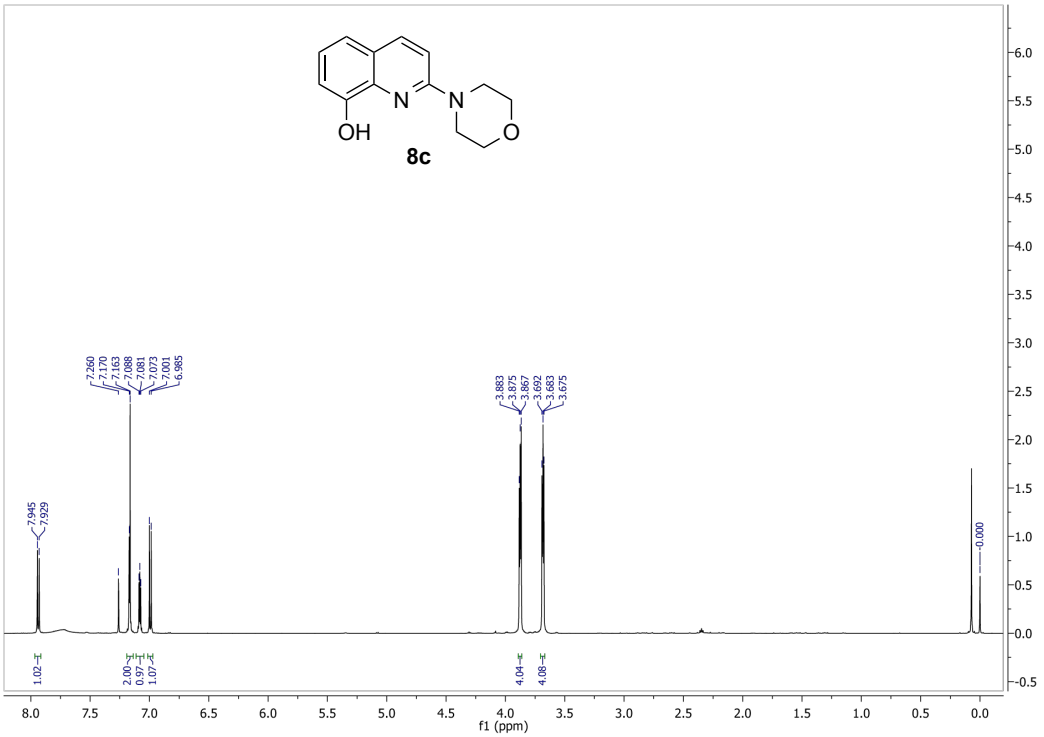
^{1}H NMR (600 MHz, $CDCl_3$):



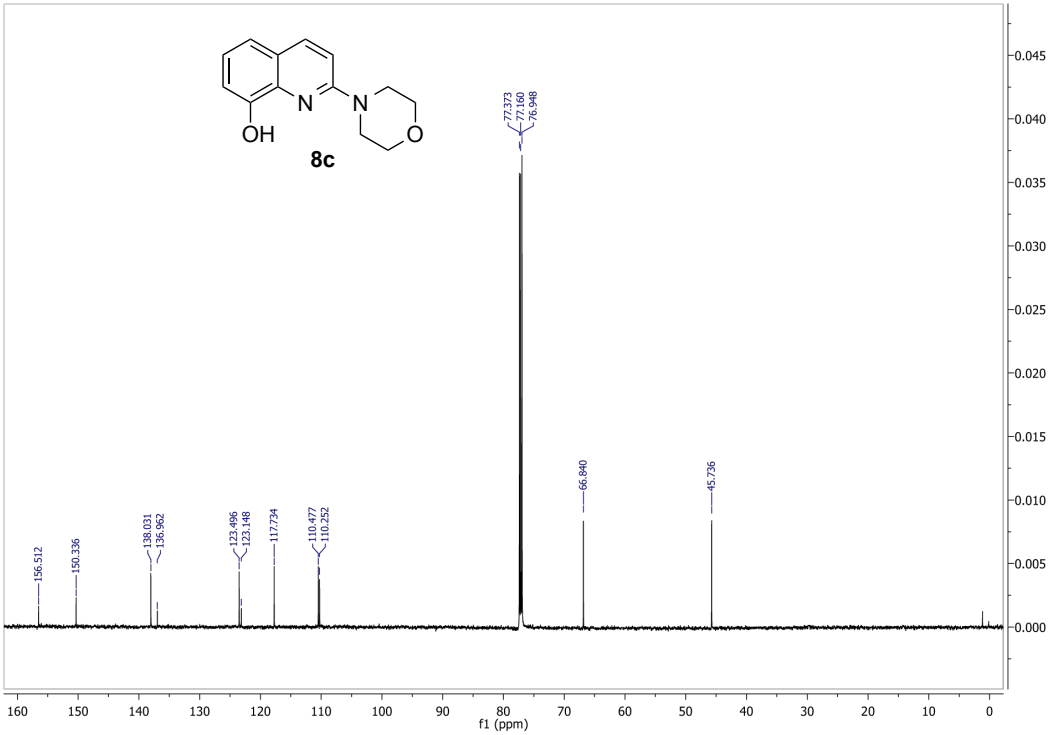
^{13}C NMR (151 MHz, $CDCl_3$):



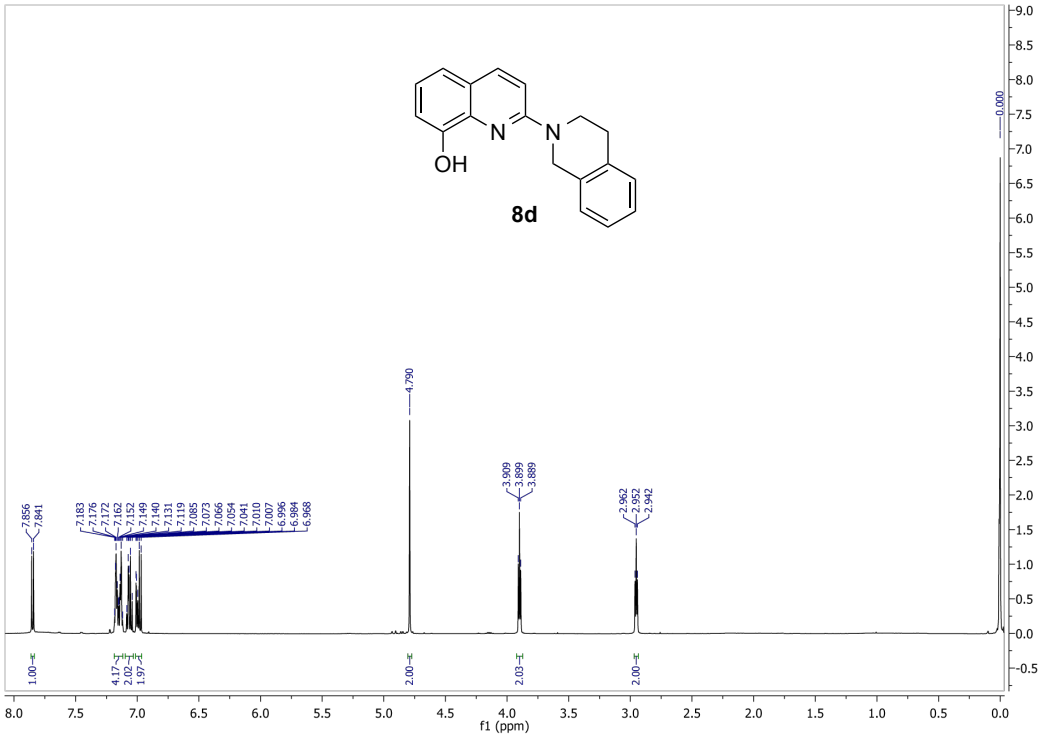
^{1}H NMR (600 MHz, $CDCl_3$):



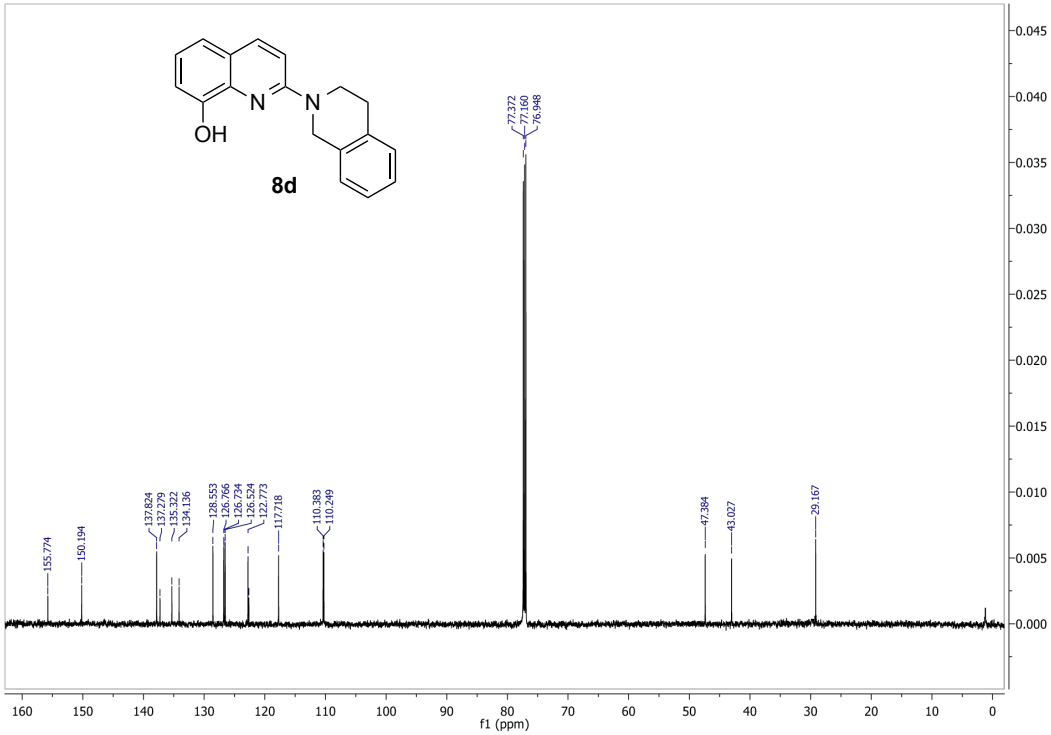
^{13}C NMR (151 MHz, $CDCl_3$):



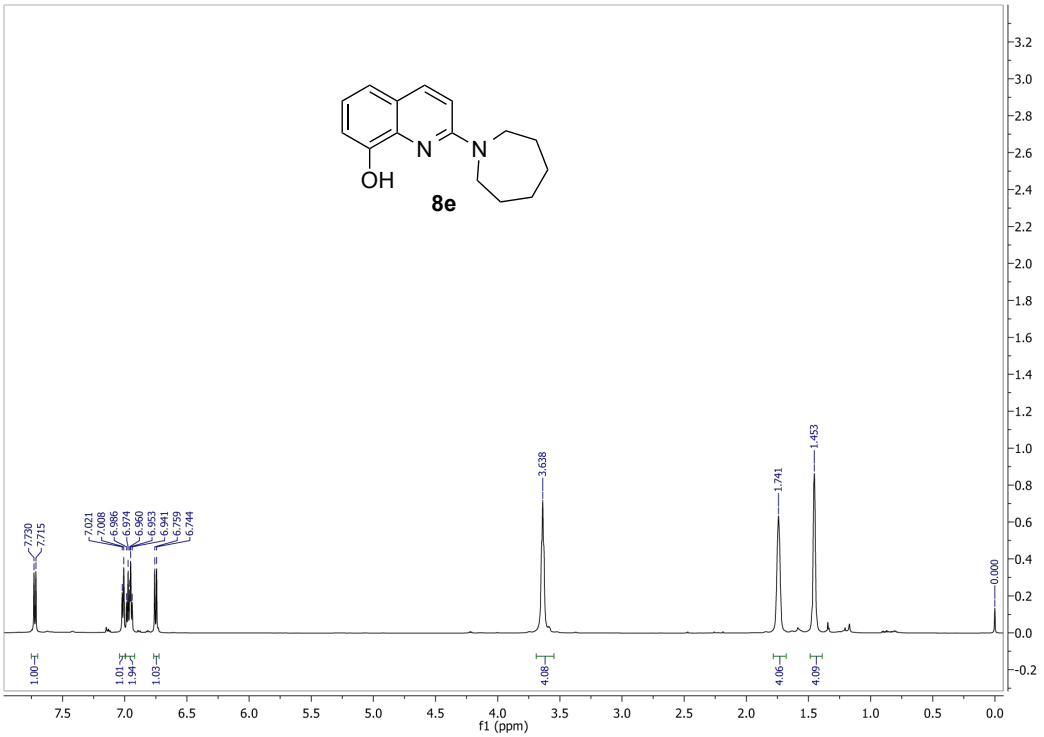
^{1}H NMR (600 MHz, $CDCl_3$):



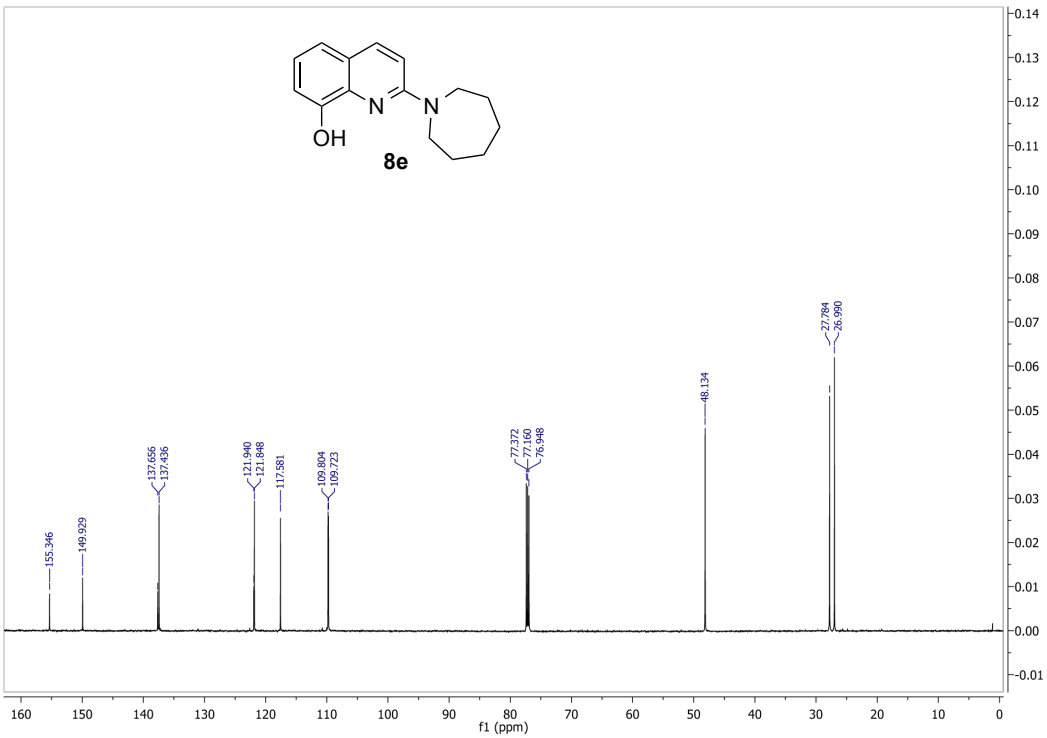
^{13}C NMR (151 MHz, $CDCl_3$):



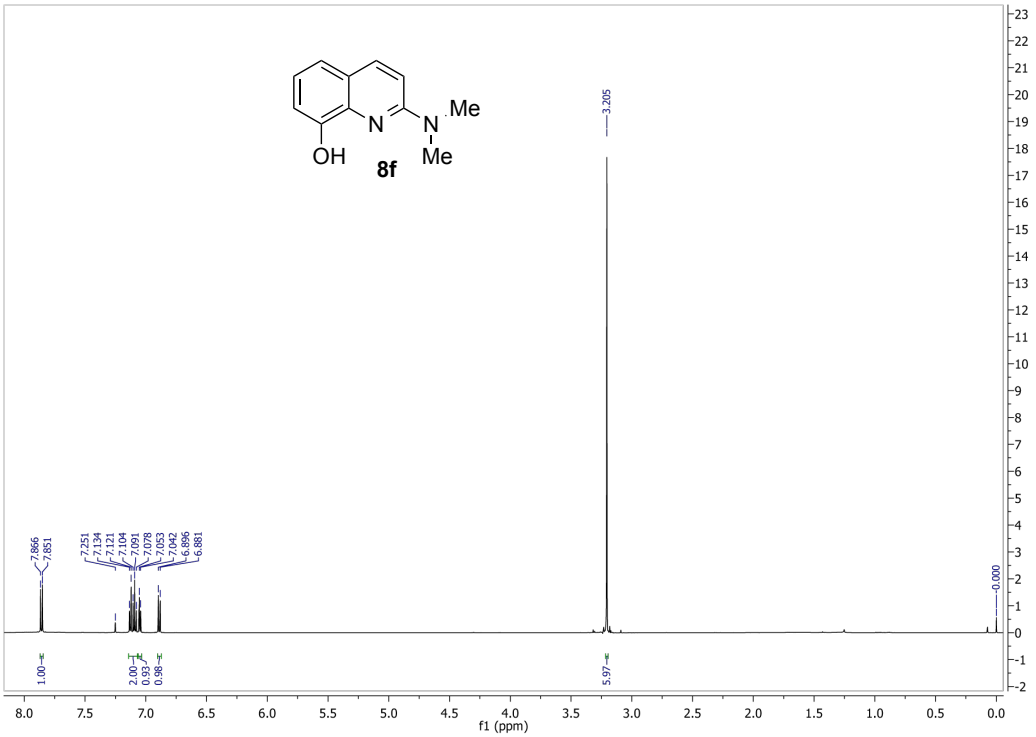
^{1}H NMR (600 MHz, $CDCl_3$):



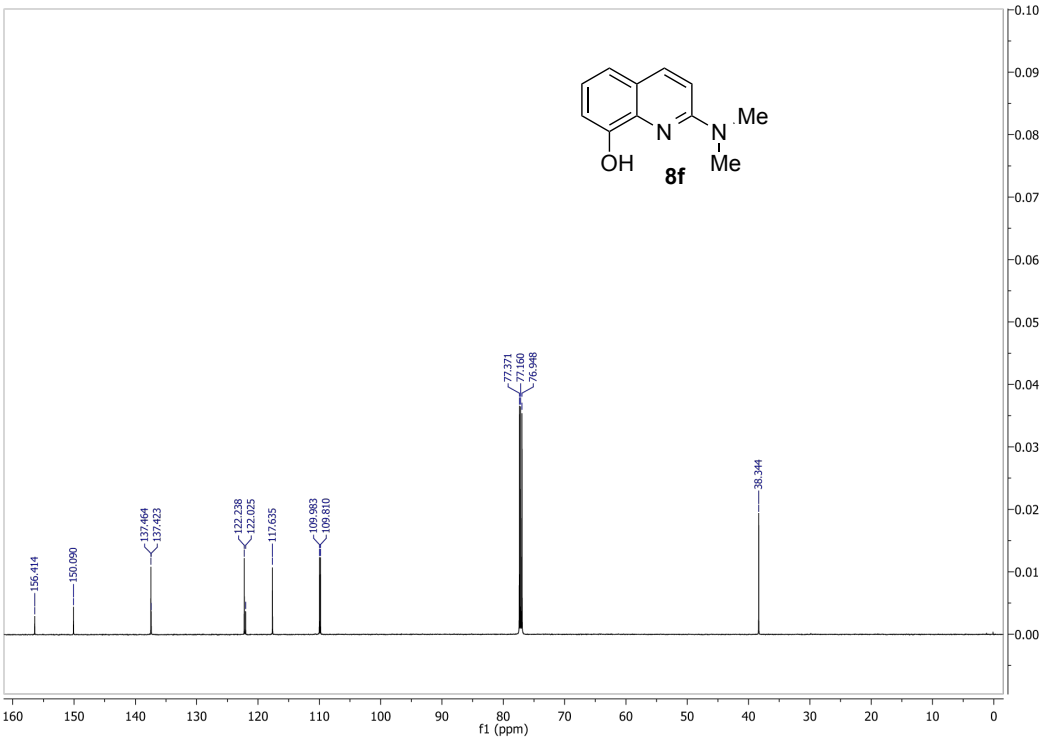
^{13}C NMR (151 MHz, $CDCl_3$):



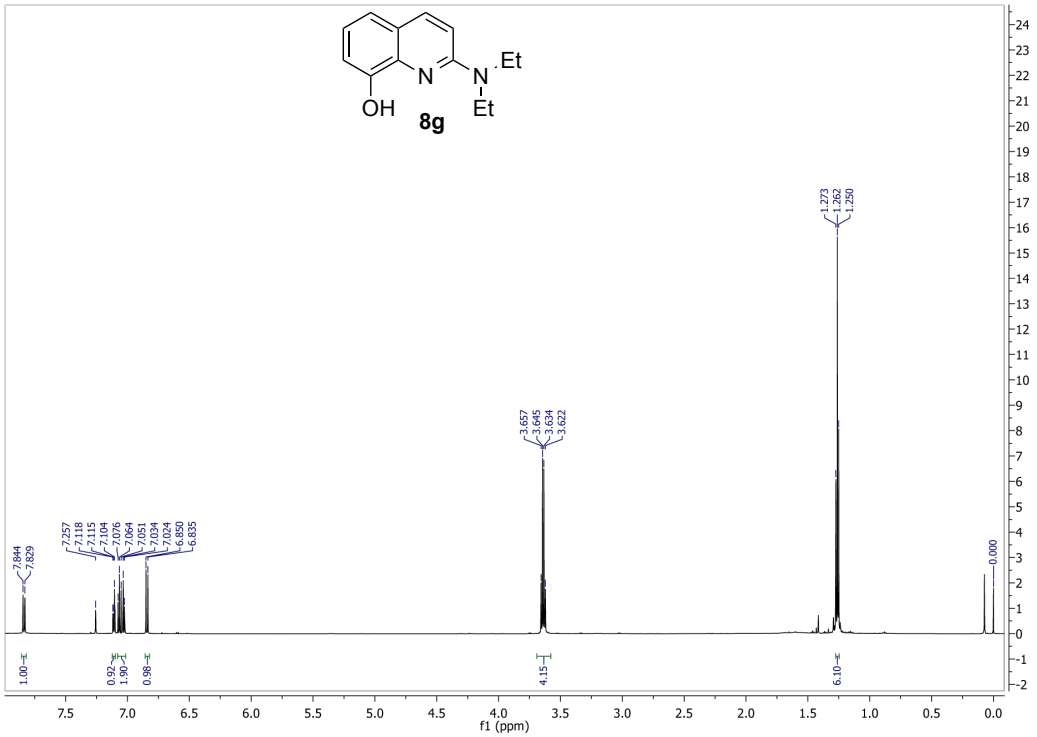
^{1}H NMR (600 MHz, $CDCl_3$):



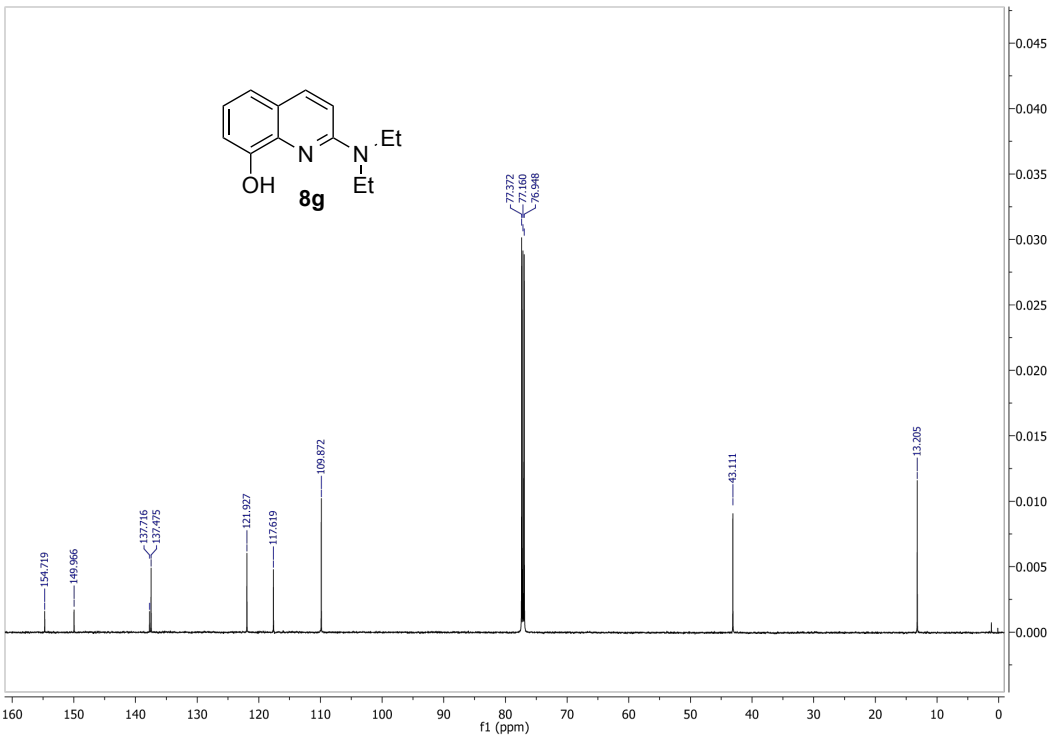
^{13}C NMR (151 MHz, $CDCl_3$):



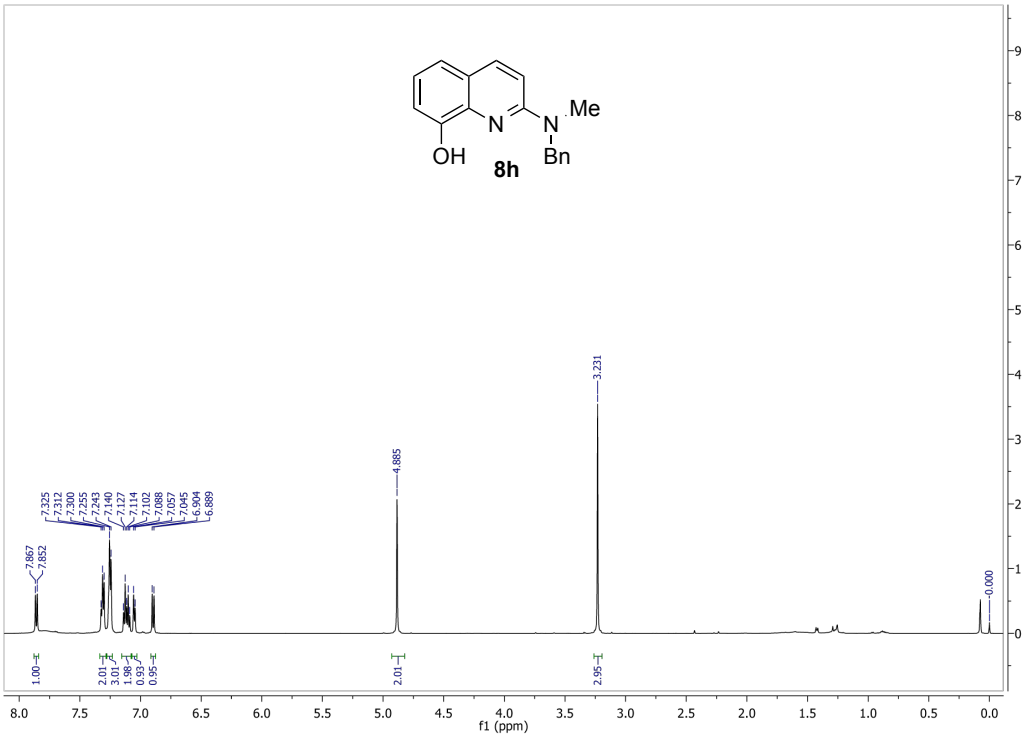
^{1}H NMR (600 MHz, $CDCl_3$):



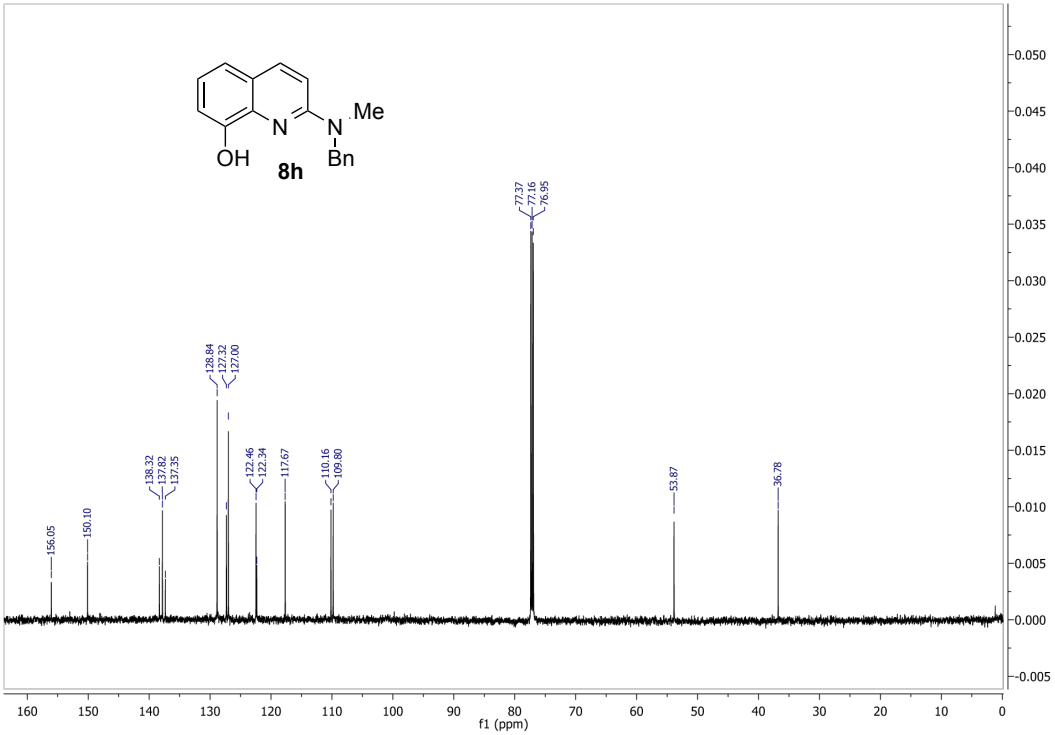
^{13}C NMR (151 MHz, $CDCl_3$):



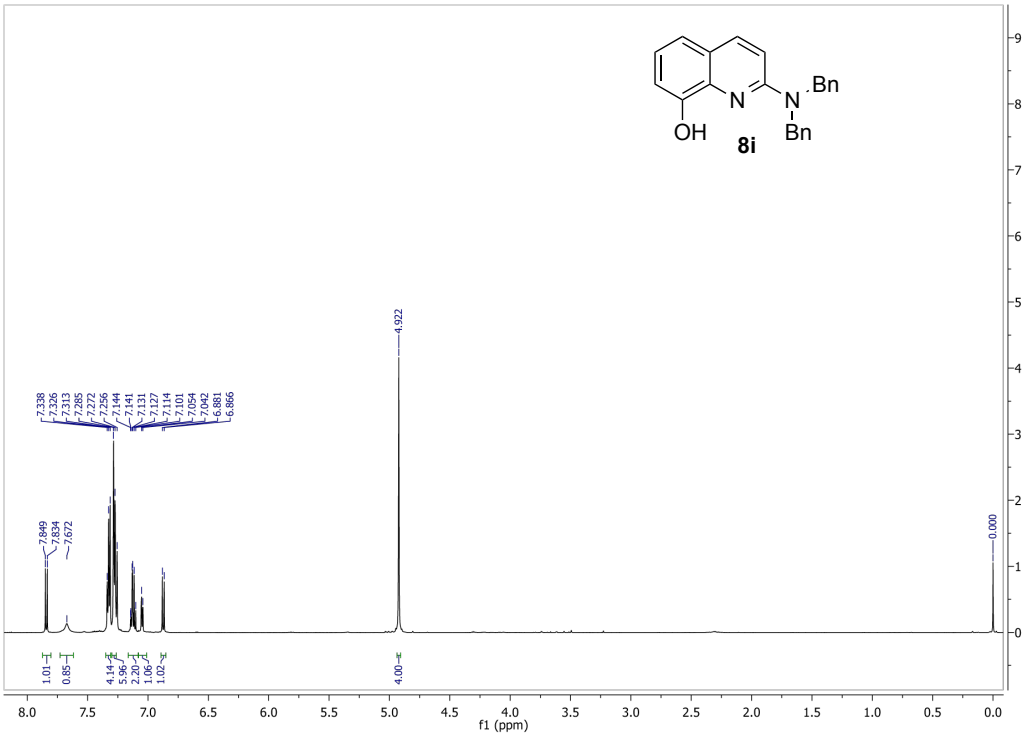
^{1}H NMR (600 MHz, $CDCl_3$):



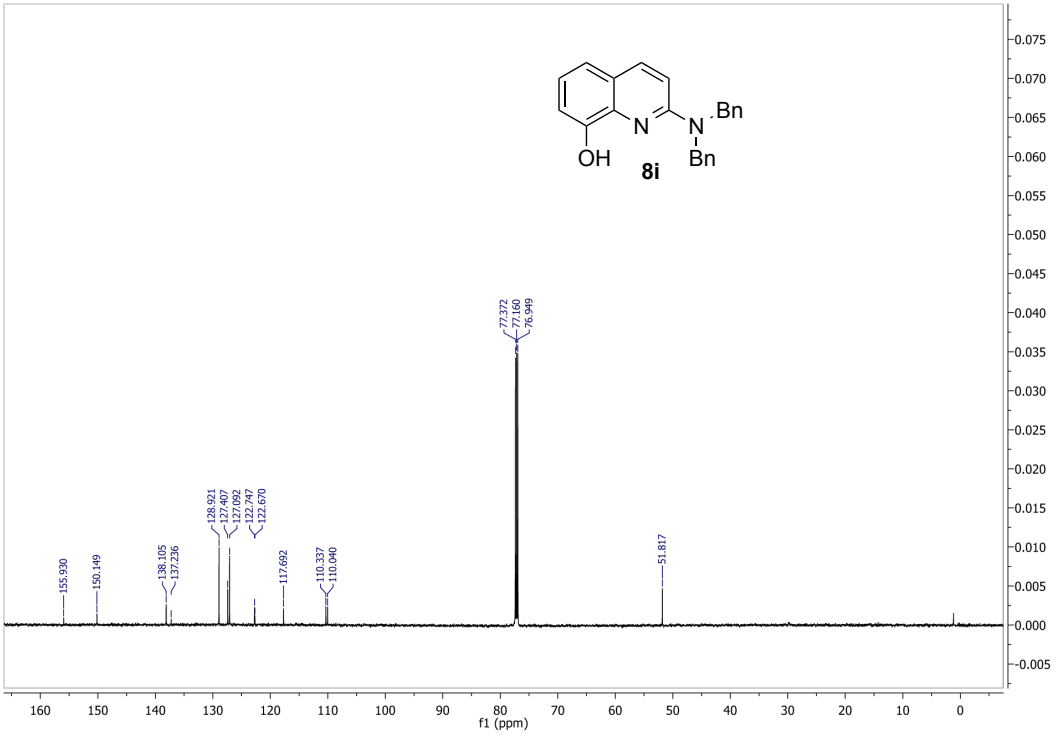
^{13}C NMR (151 MHz, $CDCl_3$):



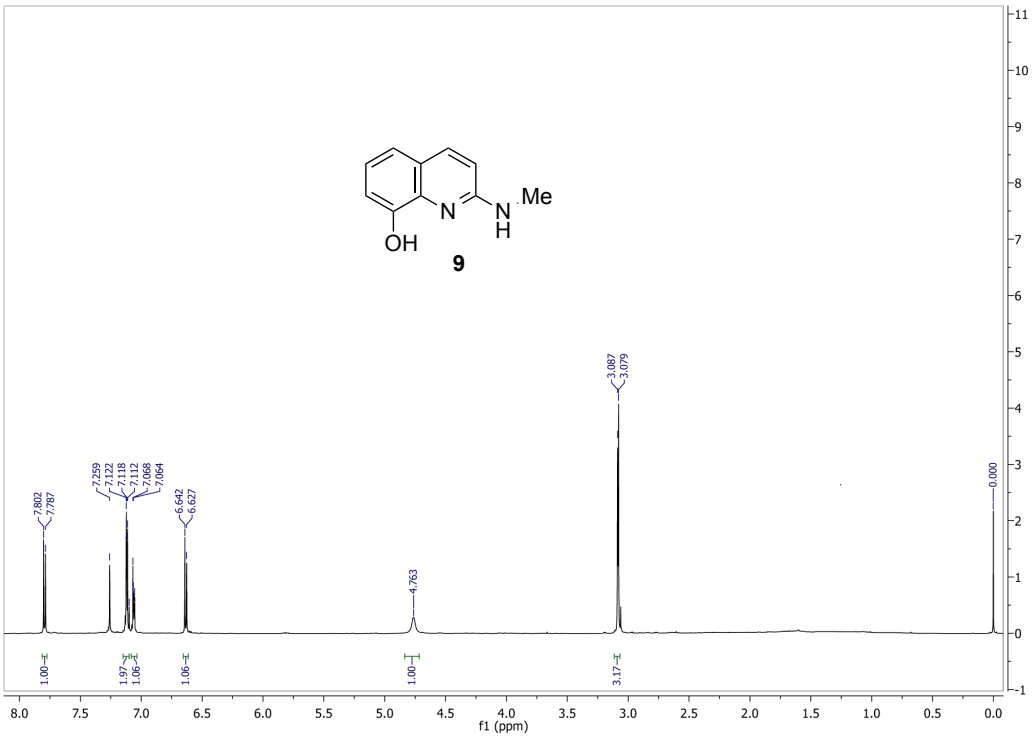
^{1}H NMR (600 MHz, $CDCl_3$):



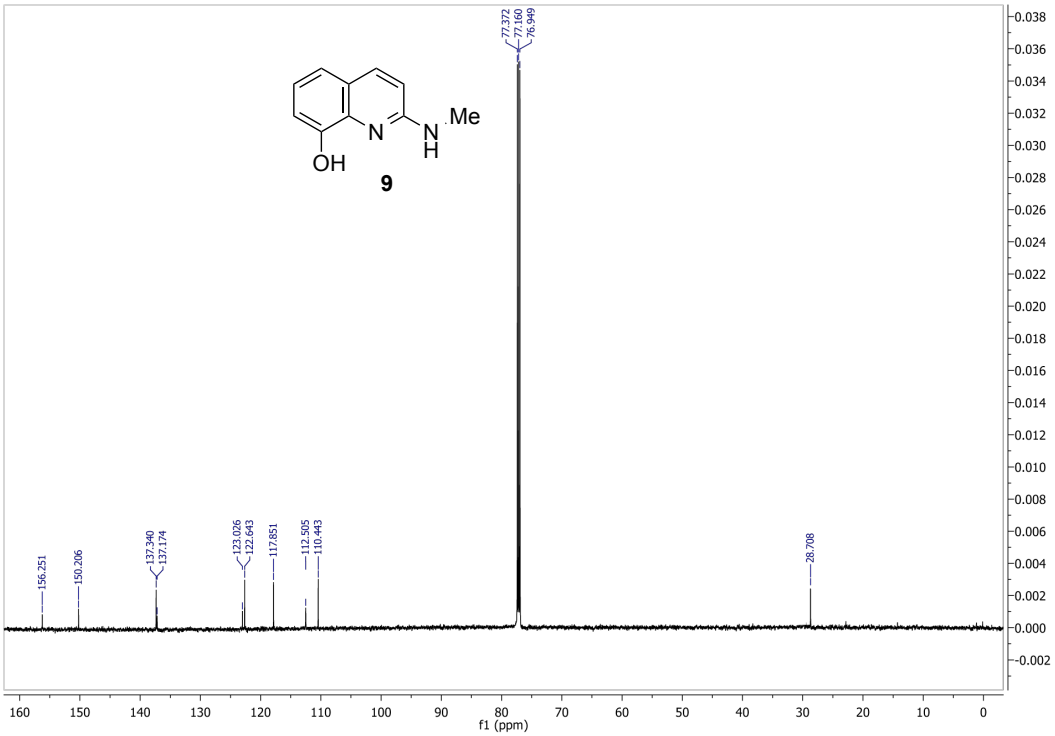
^{13}C NMR (151 MHz, $CDCl_3$):



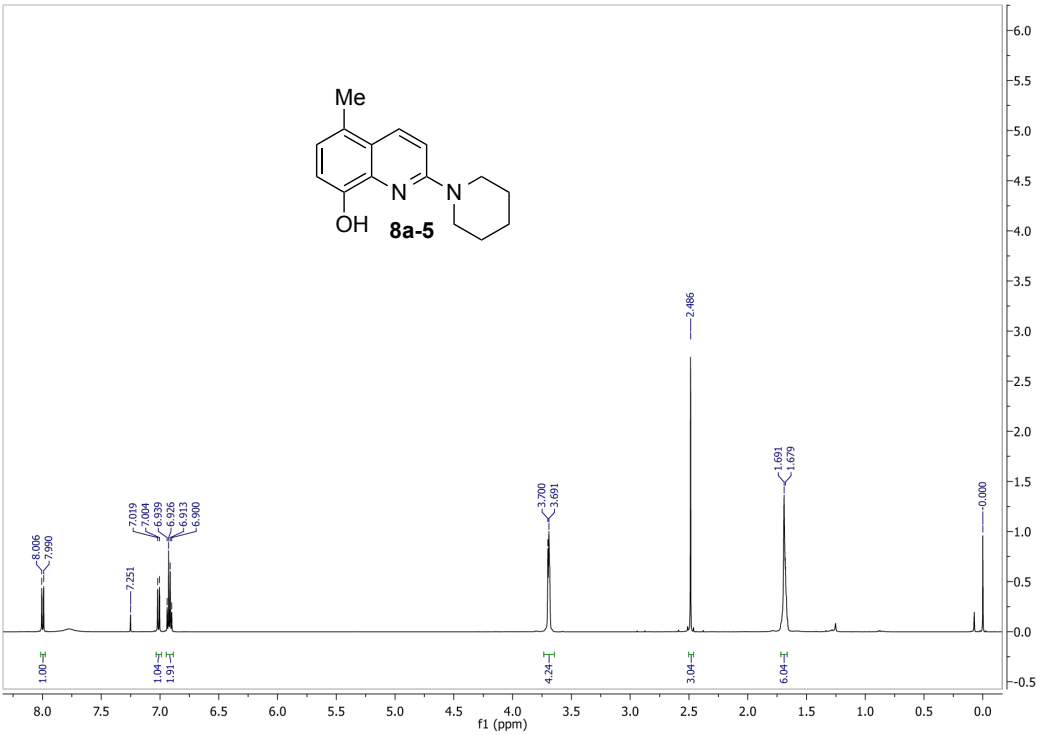
^{1}H NMR (600 MHz, $CDCl_3$):



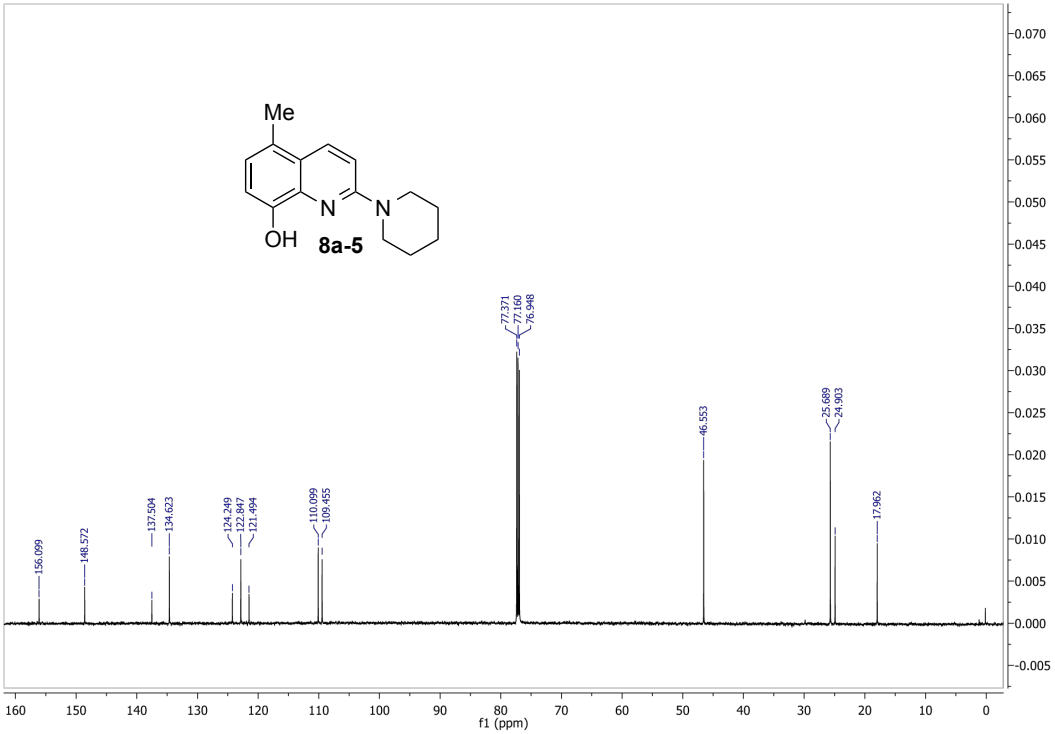
^{13}C NMR (121 MHz, $CDCl_3$):



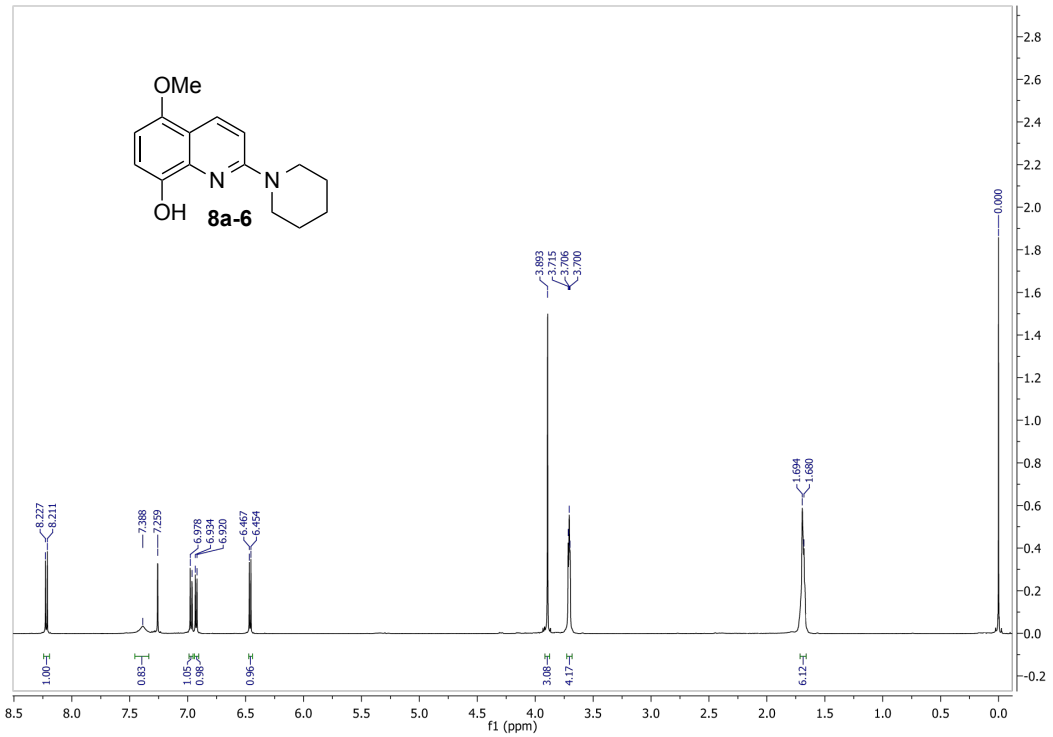
^{1}H NMR (600 MHz, $CDCl_3$):



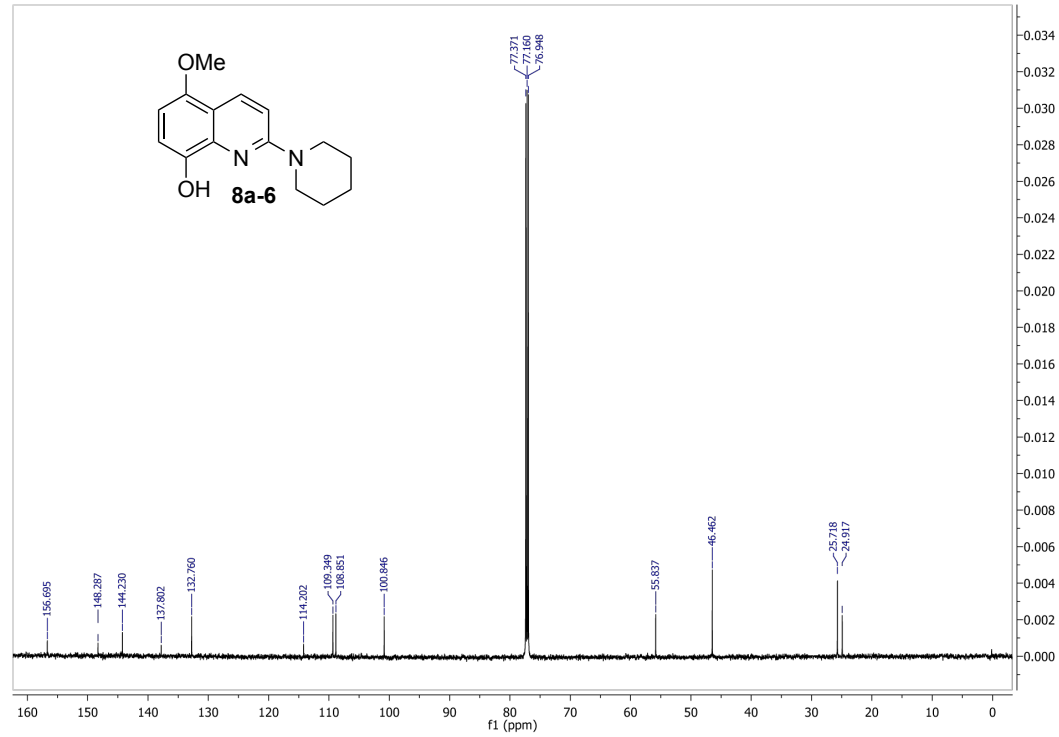
^{13}C NMR (151 MHz, $CDCl_3$):



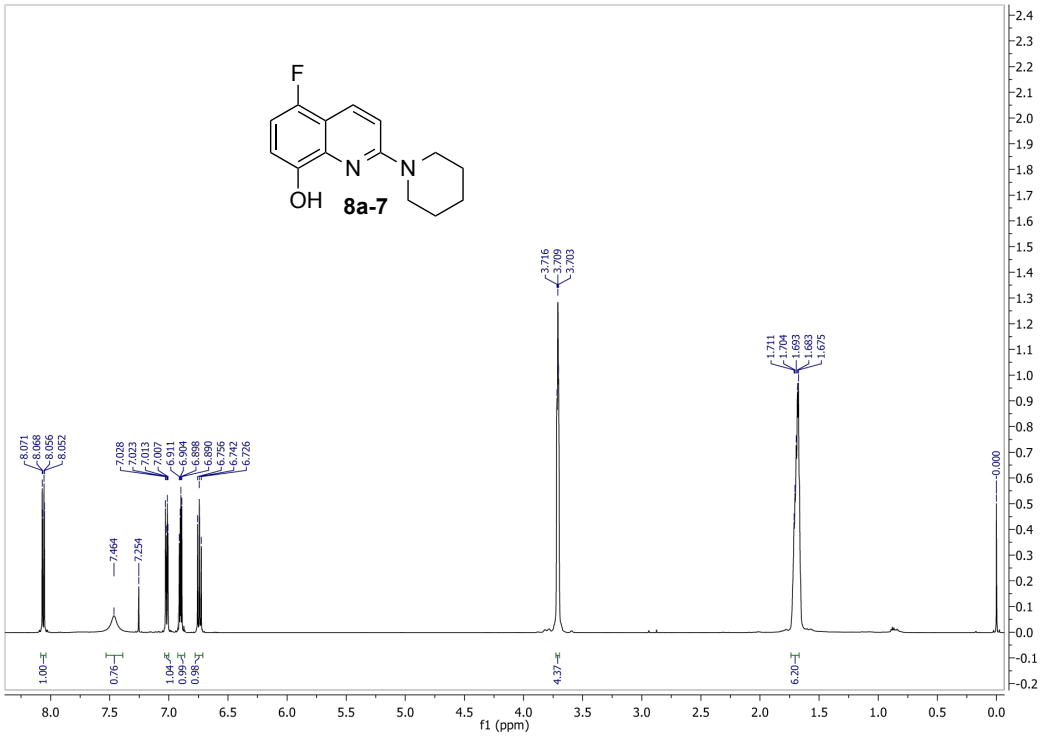
^{1}H NMR (600 MHz, $CDCl_3$):



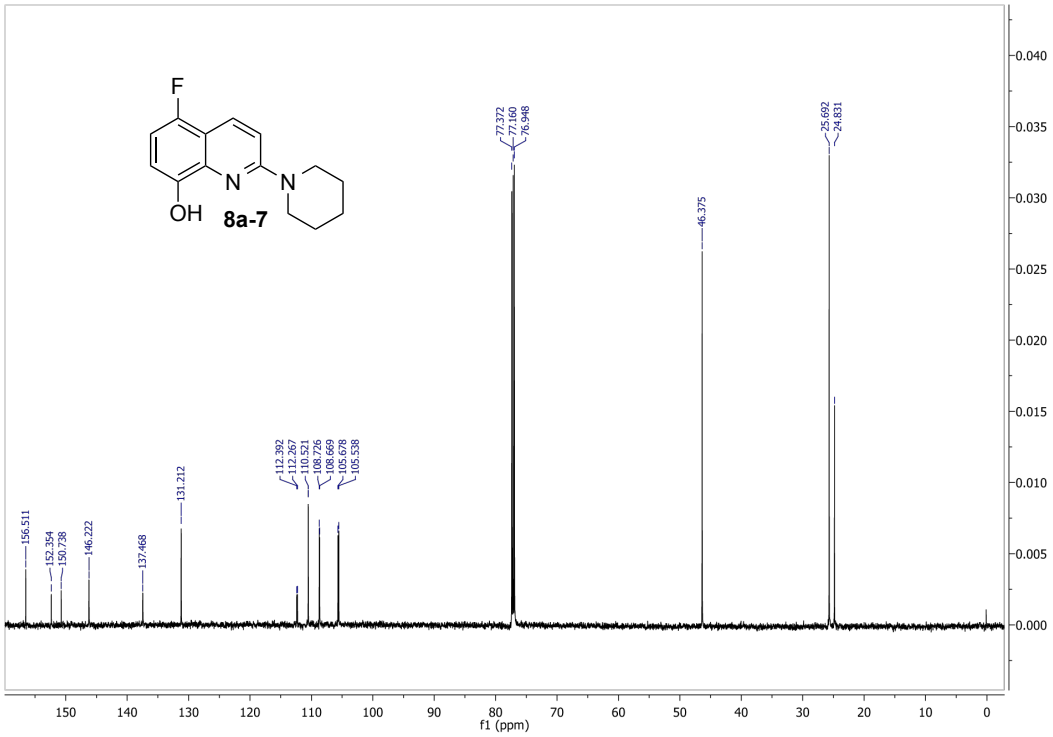
^{13}C NMR (151 MHz, $CDCl_3$):



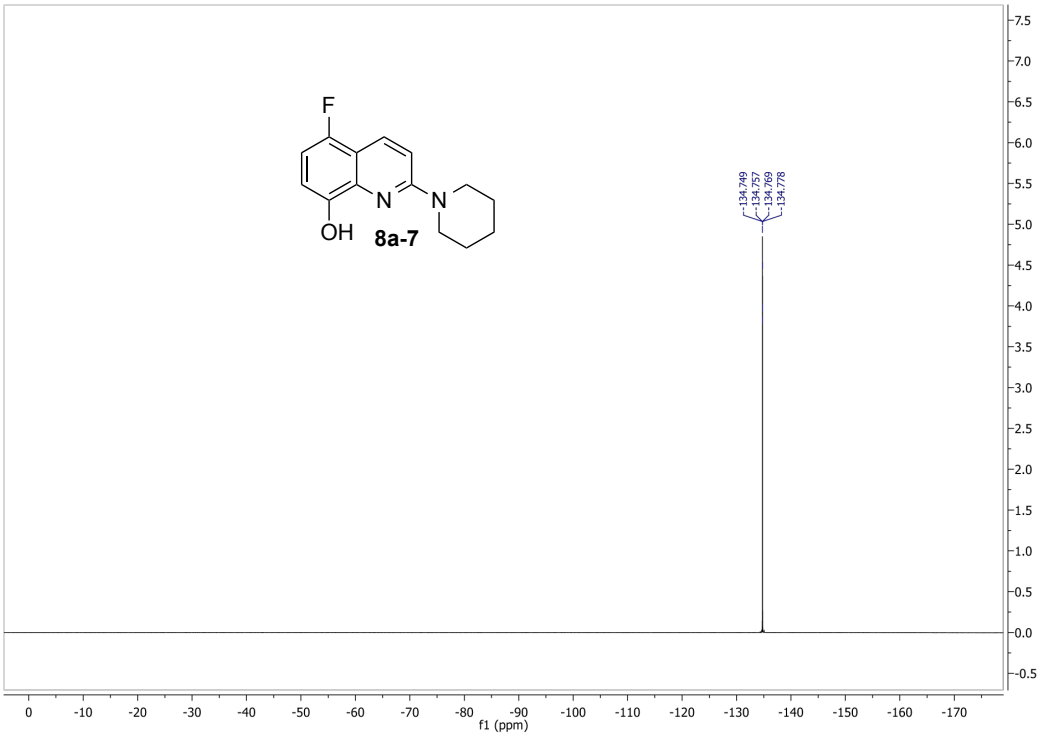
^{1}H NMR (600 MHz, $CDCl_3$):



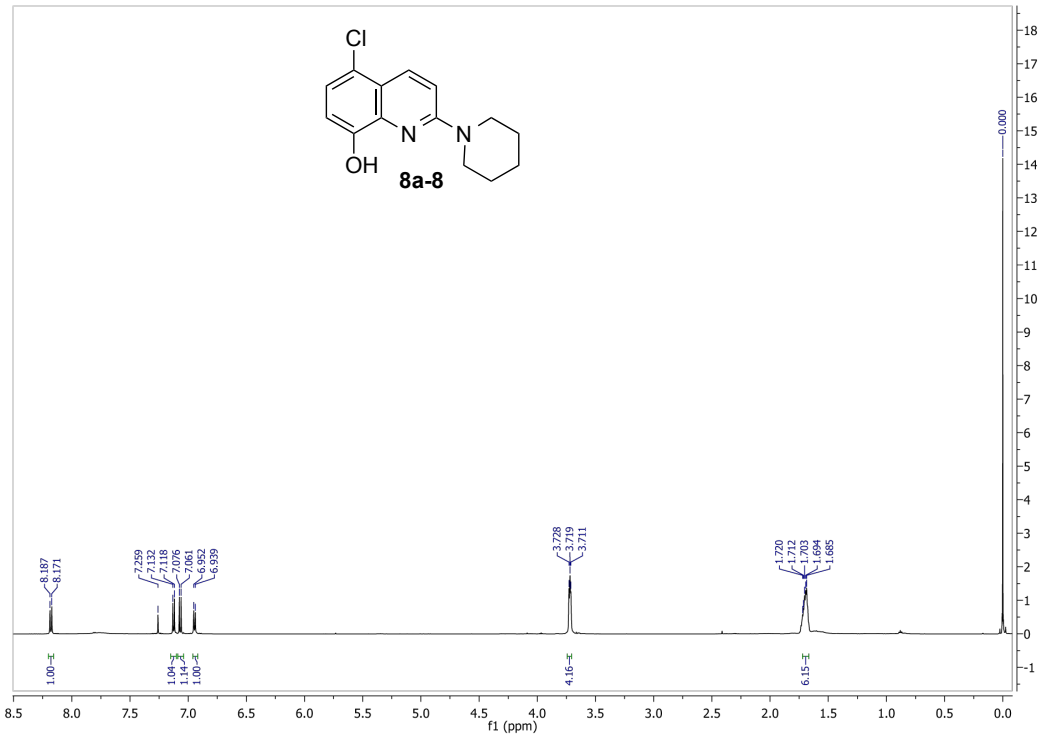
^{13}C NMR (151 MHz, $CDCl_3$):



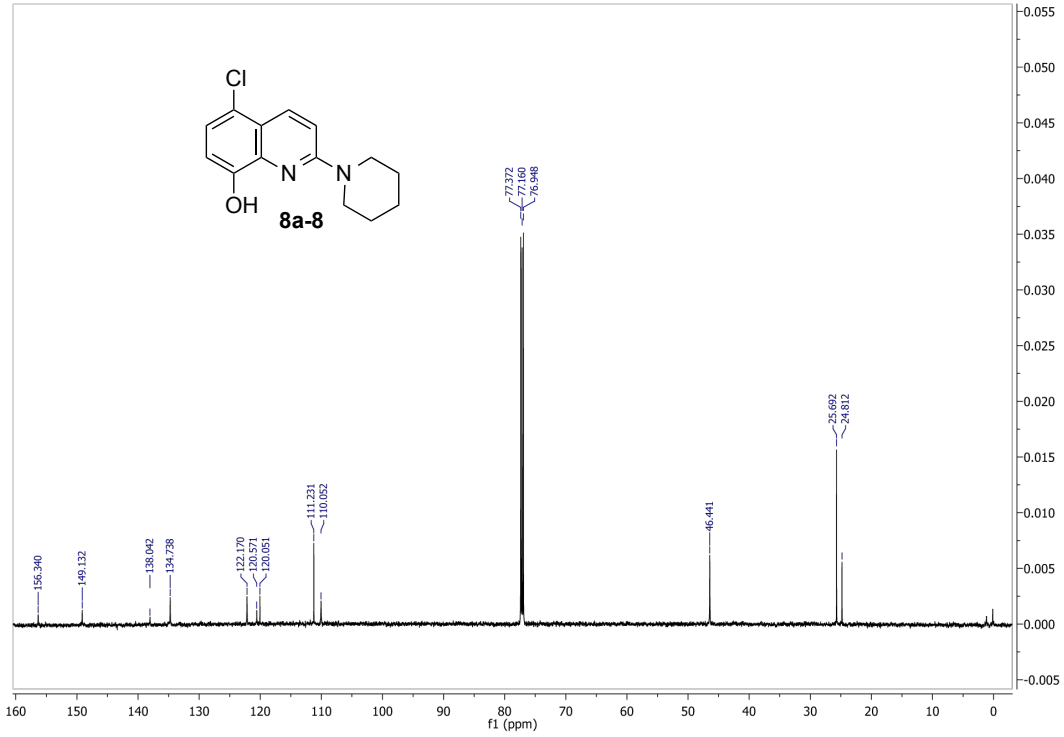
^{19}F NMR (564 MHz, $CDCl_3$):



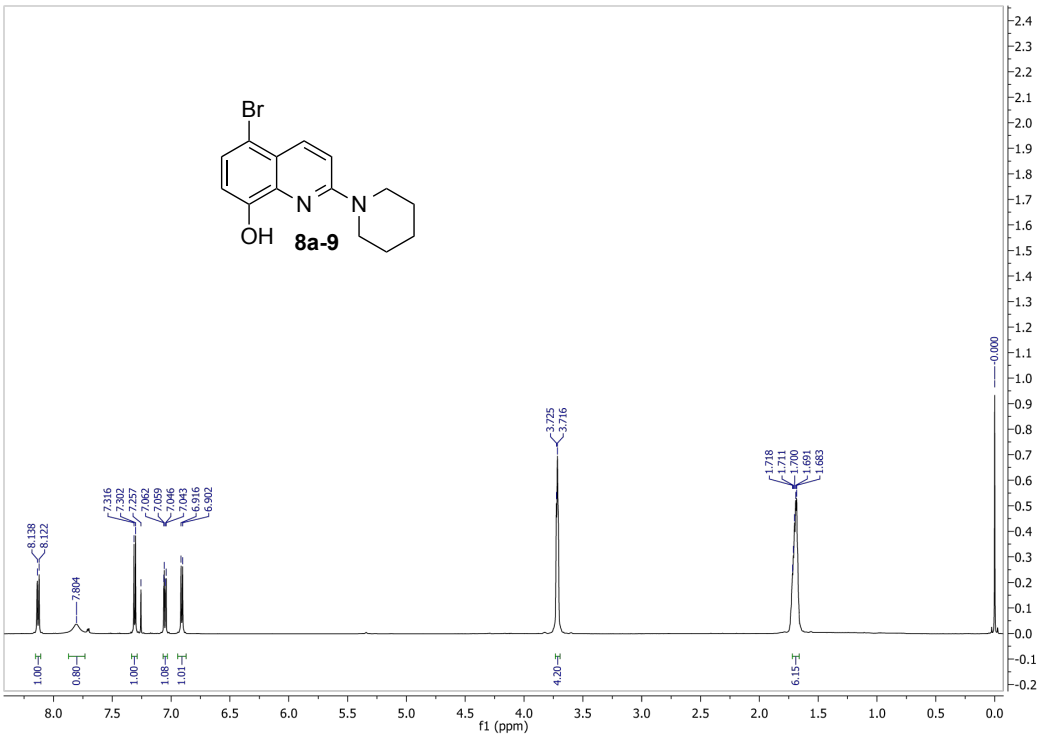
^{1}H NMR (600 MHz, $CDCl_3$):



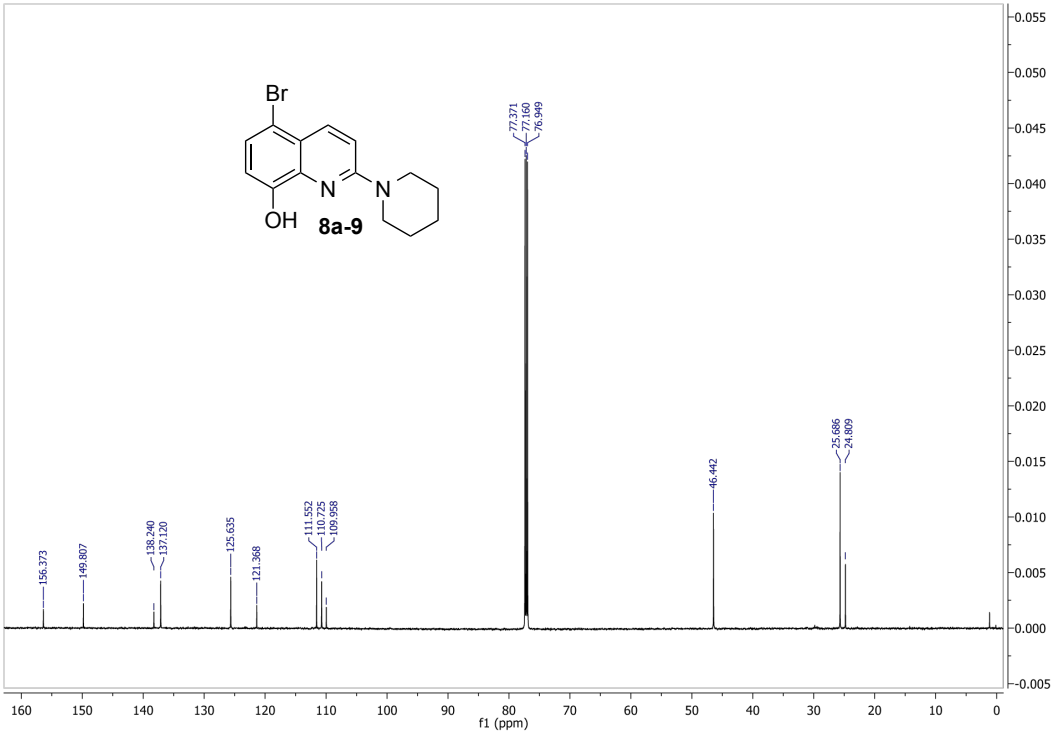
^{13}C NMR (151 MHz, $CDCl_3$):



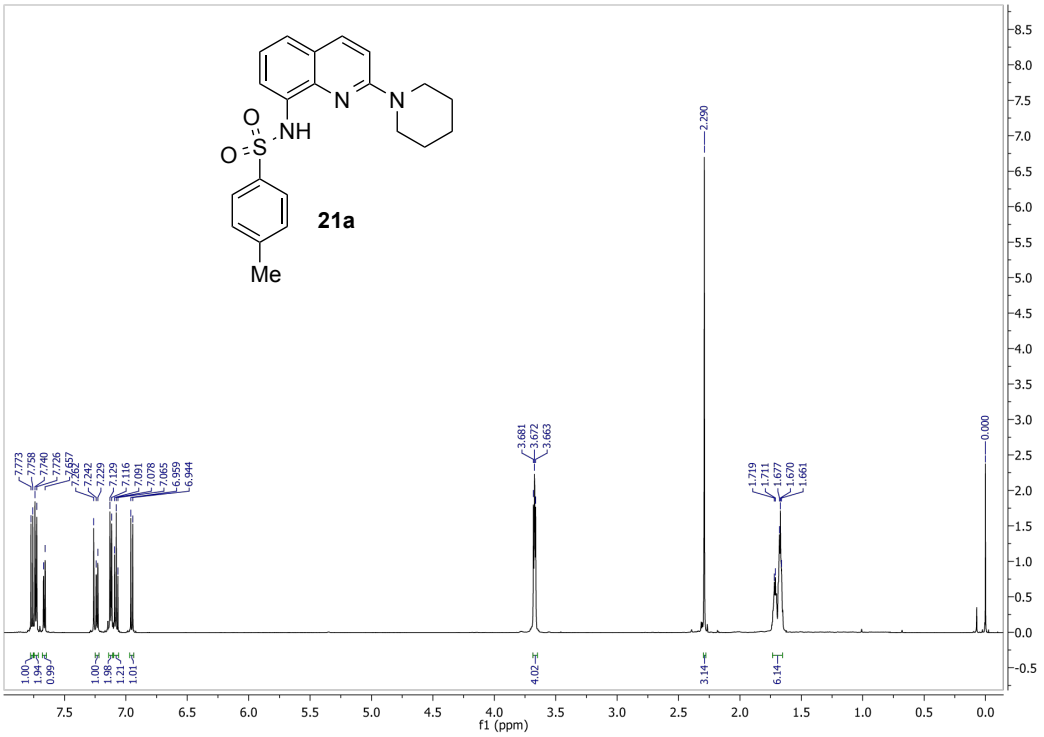
^{1}H NMR (600 MHz, $CDCl_3$):



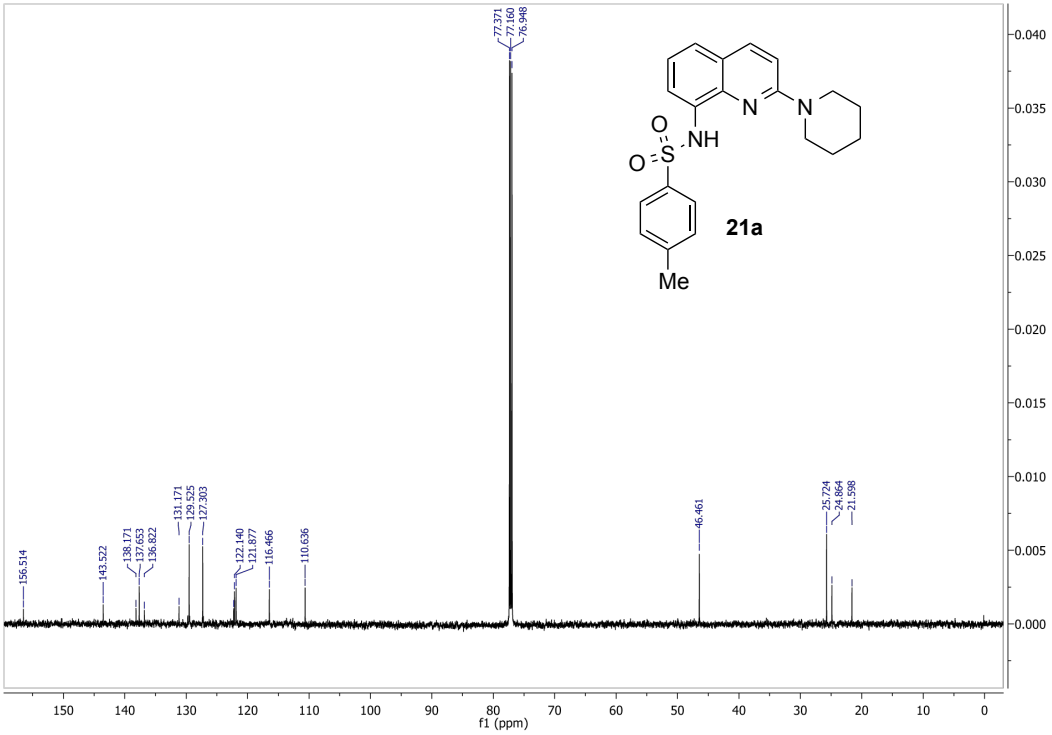
^{13}C NMR (151 MHz, $CDCl_3$):



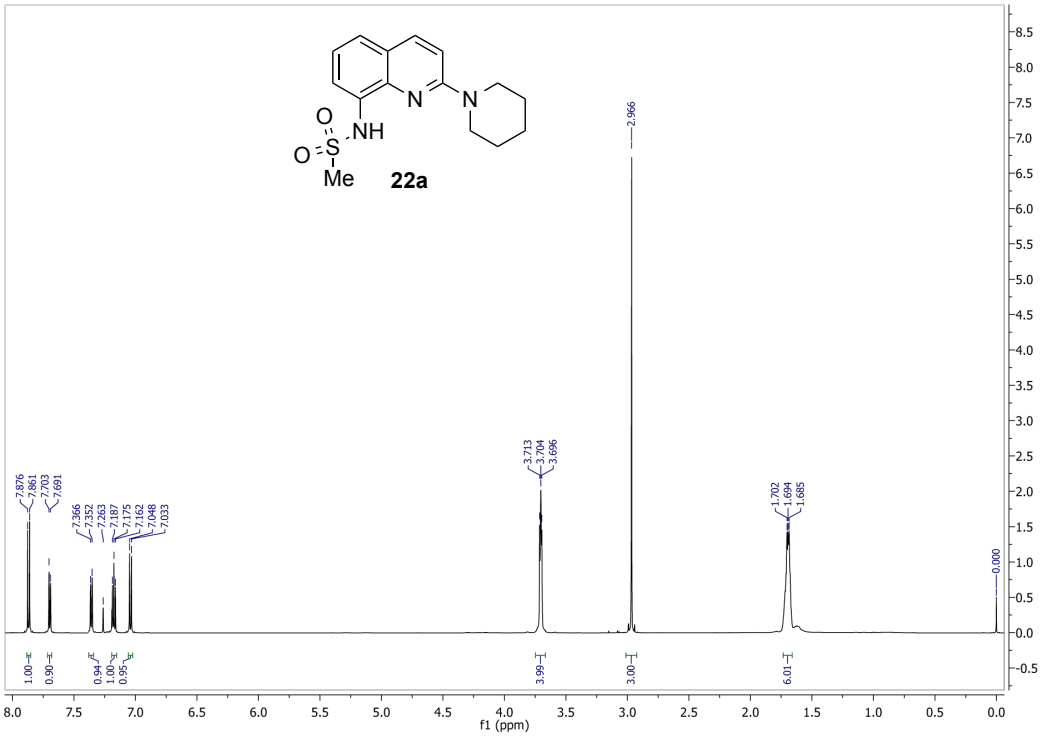
^{1}H NMR (600 MHz, $CDCl_3$):



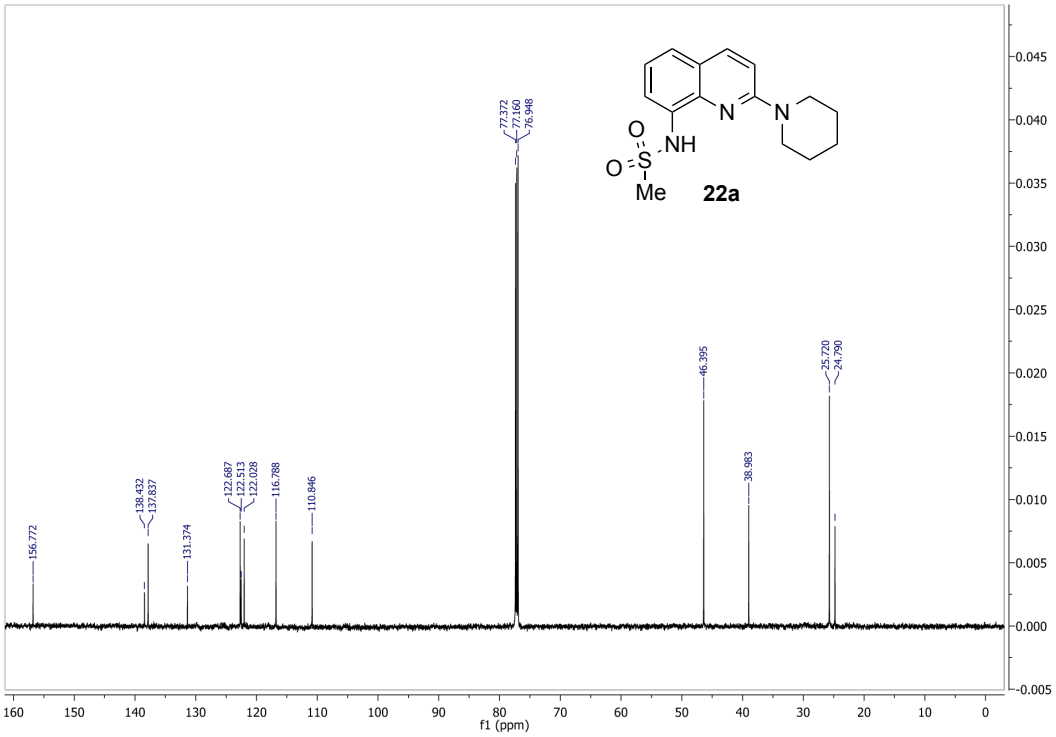
^{13}C NMR (151 MHz, $CDCl_3$):



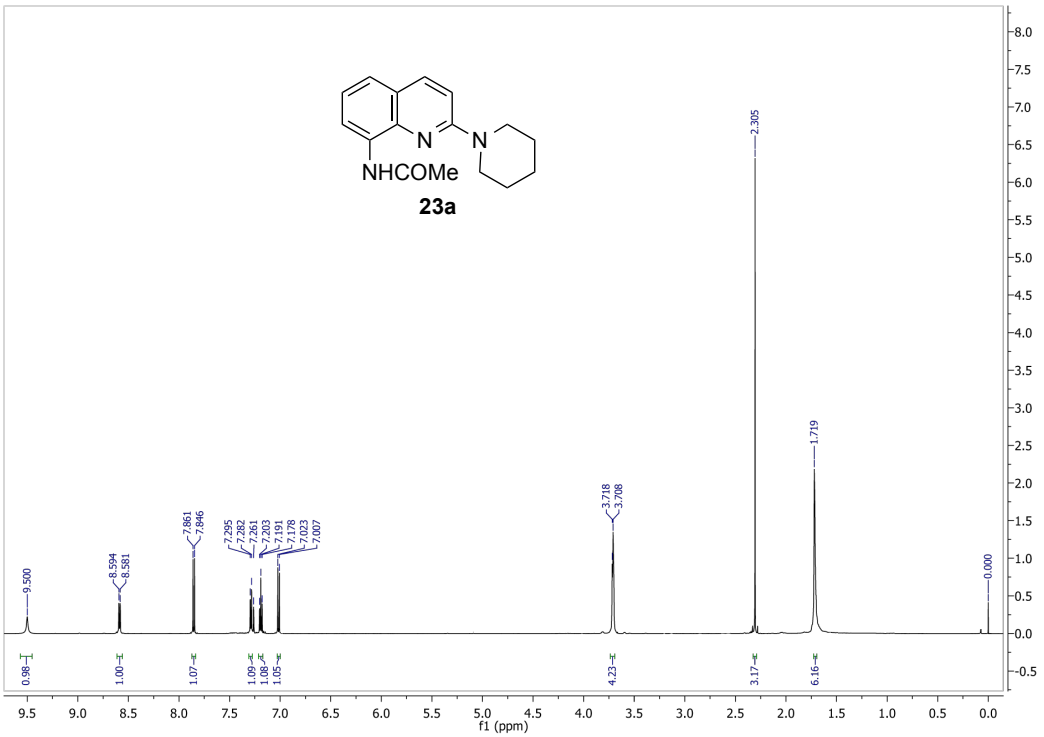
^{1}H NMR (600 MHz, $CDCl_3$):



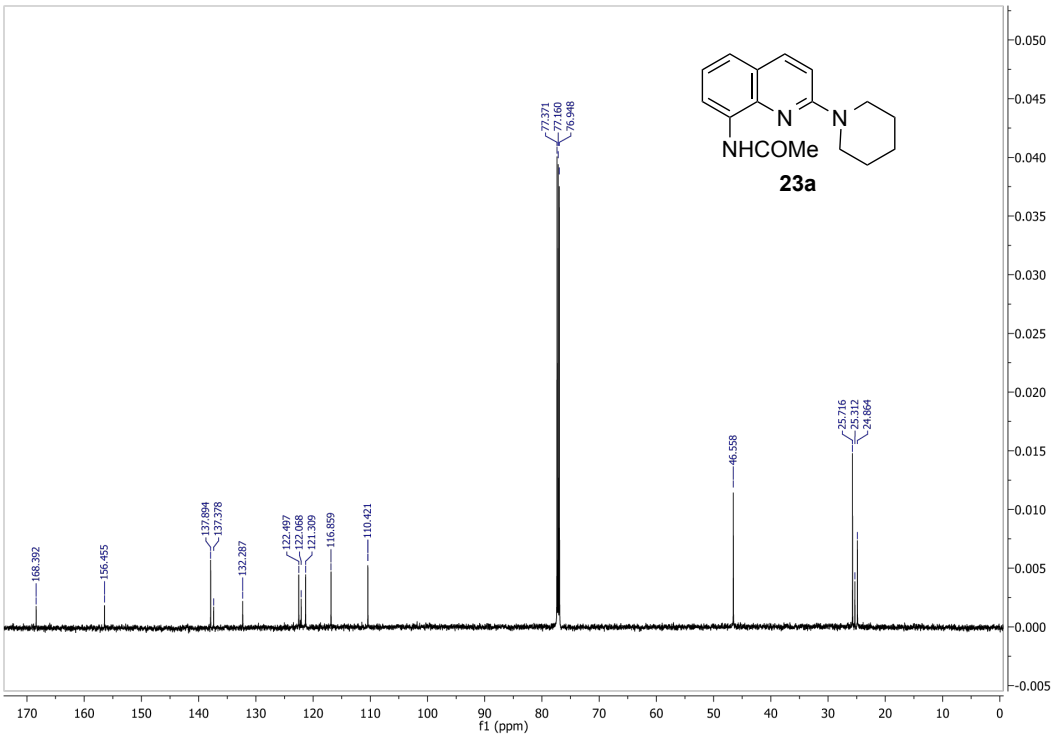
^{13}C NMR (151 MHz, $CDCl_3$):



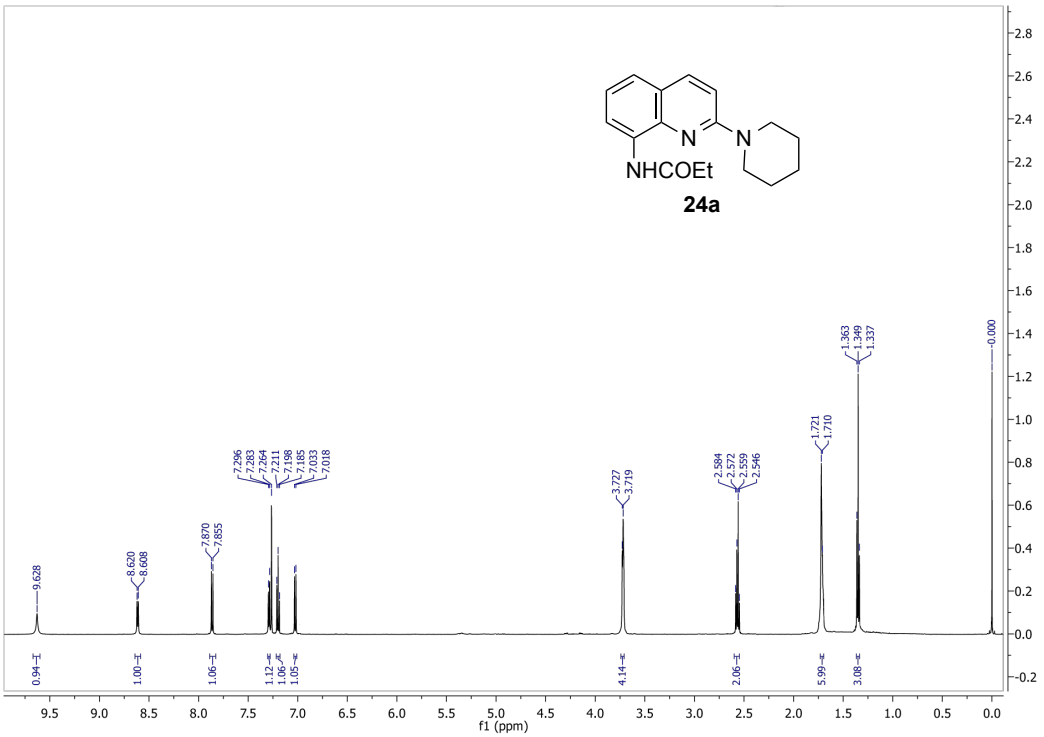
^{1}H NMR (600 MHz, $CDCl_3$):



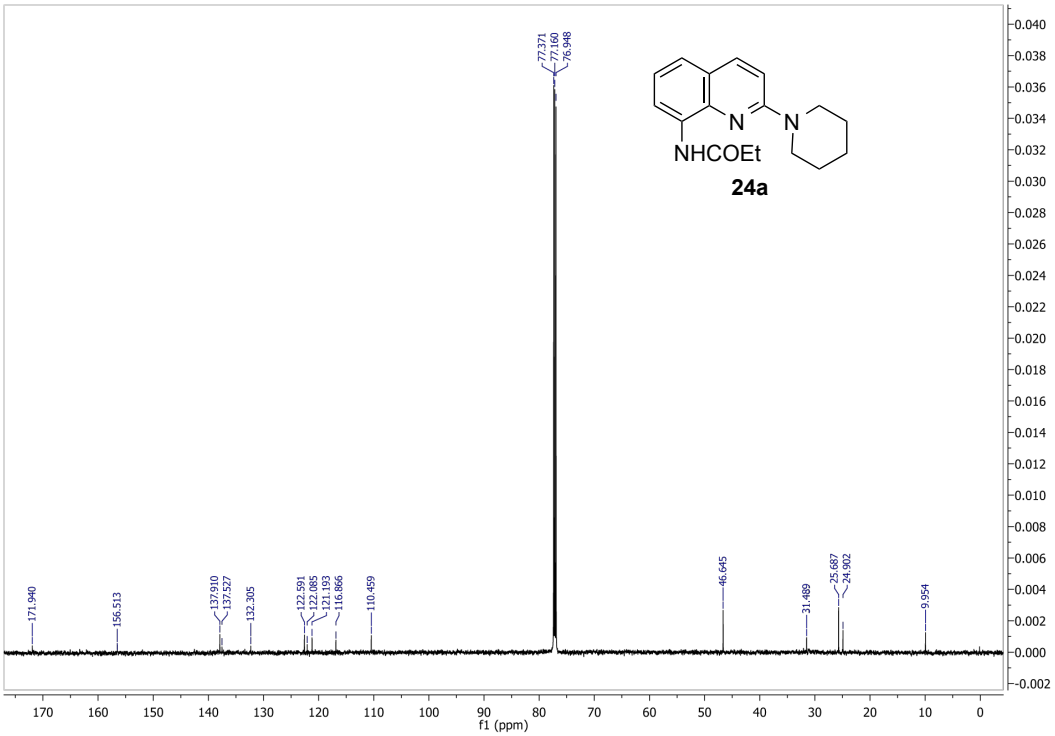
^{13}C NMR (151 MHz, $CDCl_3$):



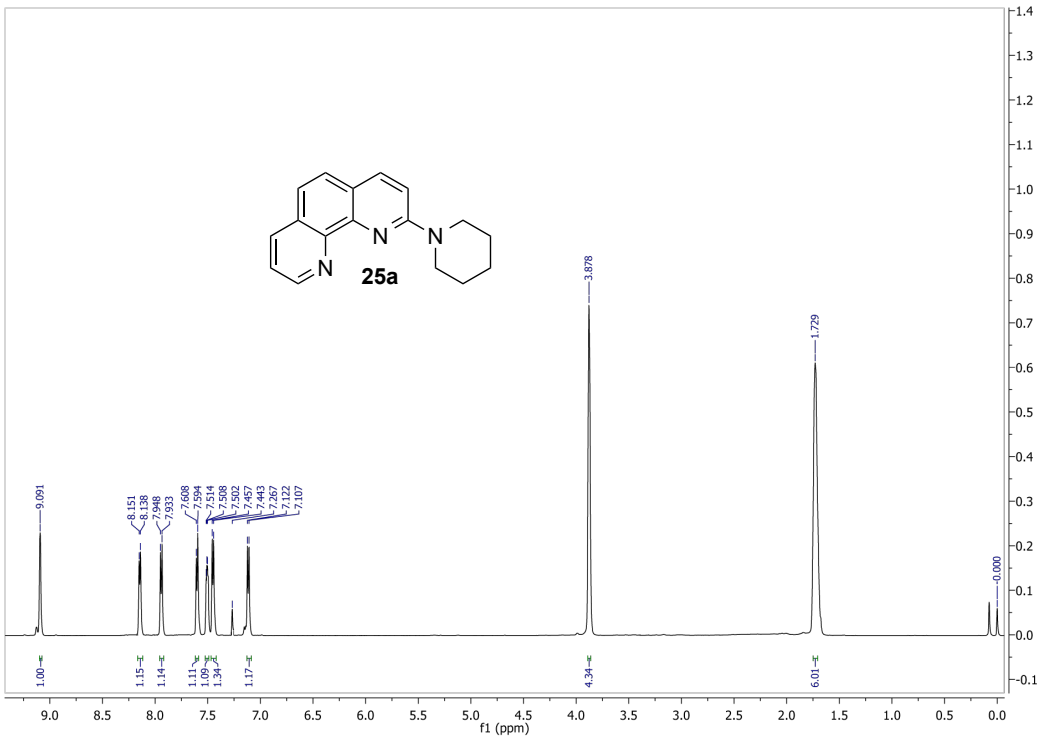
^{1}H NMR (600 MHz, $CDCl_3$):



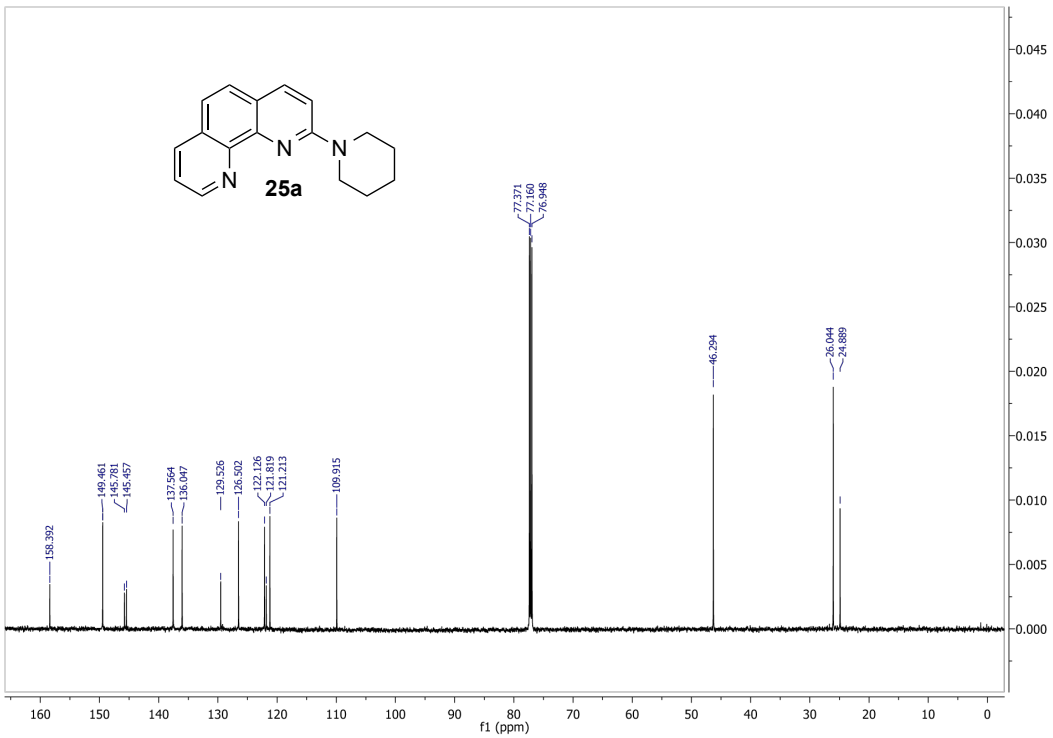
^{13}C NMR (151 MHz, $CDCl_3$):



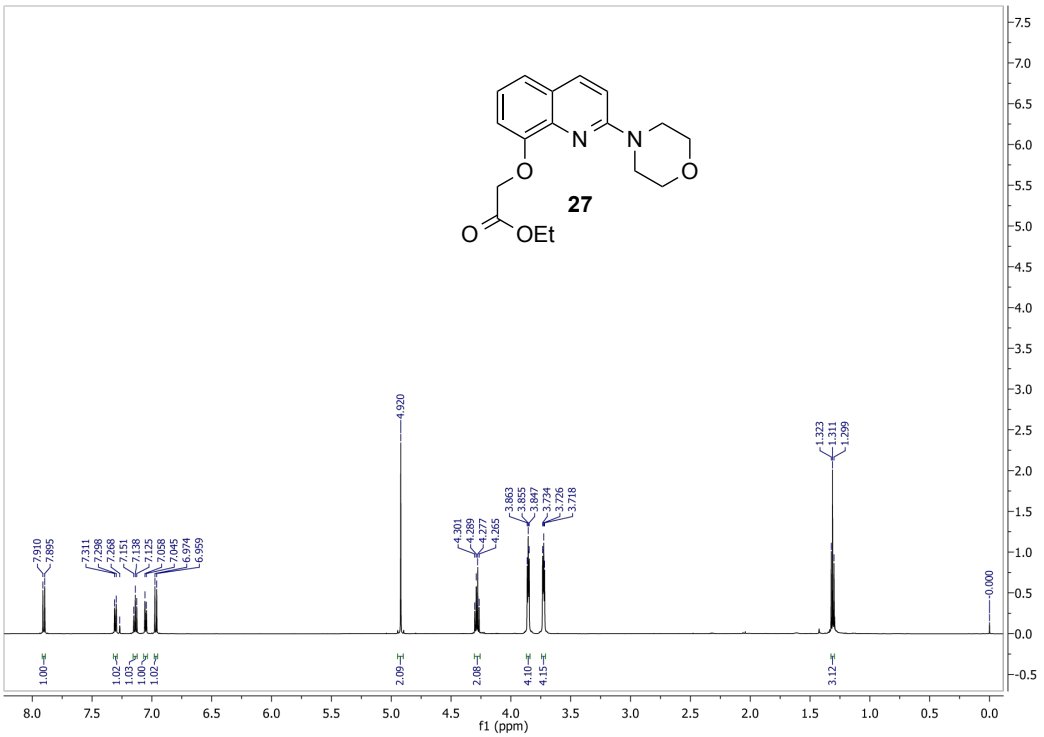
^{1}H NMR (600 MHz, $CDCl_3$):



^{13}C NMR (151 MHz, $CDCl_3$):



^{1}H NMR (600 MHz, $CDCl_3$):



^{13}C NMR (151 MHz, $CDCl_3$):