Selective Deuteration of Heterocycle *N*-Oxides via Iridium-catalyzed Hydrogen Isotope Exchange

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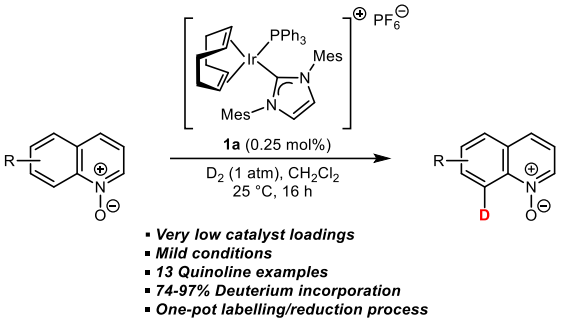

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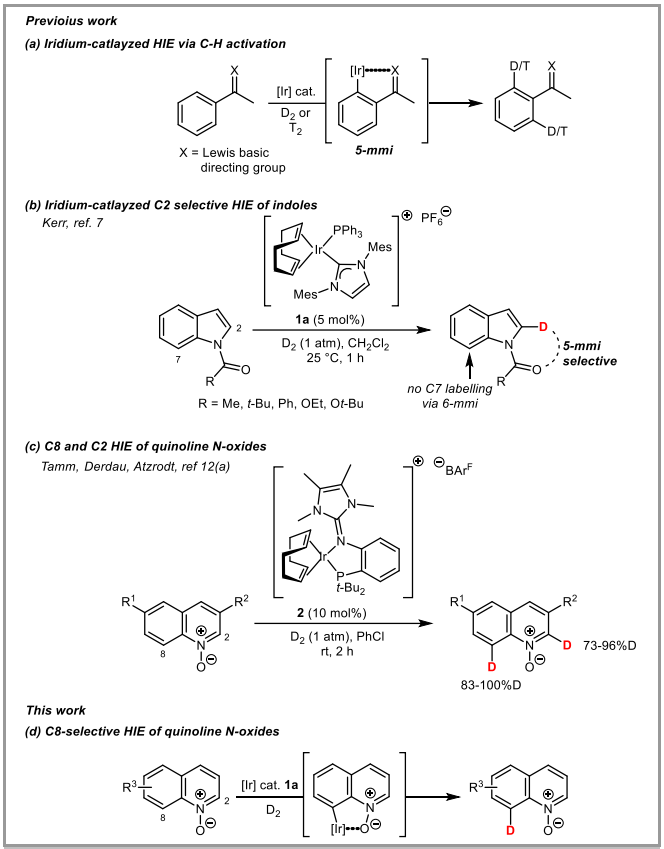
Abstract An iridium(I) *N*-heterocyclic carbene/phosphine complex has been applied to the C-H activation and hydrogen isotope exchange of quinoline *N*-oxides. The isotope labelling proceeds under exceptionally low catalyst loadings of 0.25 mol%, and delivers products with high levels of deuterium incorporation selectively at the C8 position. A broad substrate scope is demonstrated, with the method tolerant of electron-poor and -rich substrates, and of substitution adjacent to the site of C-H activation. The isotope label is fully retained under standard deoxygenation conditions to give the corresponding labelled quinoline, and the labelling and deoxygenation can be combined in a one-pot procedure.

Key words iridium, catalysis, C-H activation, isotope labelling, quinolines, *N*-oxides

Methodology for the incorporation of deuterium or tritium into a drug candidate is of critical importance within the life sciences,[2] due to the crucial role isotopically labelled compounds play within absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies. In this regard, metal-catalyzed hydrogen isotope exchange (HIE), which proceeds via C-H activation,[3] has become established as the mainstay reaction for this process, due to the mild reaction conditions, ready availability of D_2 or T_2 as an isotope source, and applicability to late-stage intermediates and final drug molecules.

In terms of metal-catalyzed HIE, iridium complexes dominate the field.[4] The metal catalyst binds to a Lewis basic directing group, and then activates a proximal C-H bond, giving a 5-membered metallocyclic intermediate (5-mmi) (or more rarely a 6-mmi), which then undergoes C-D or C-T bond formation (Scheme 1a). In recent years, we have demonstrated the broad utility within HIE of iridium(I) catalysts containing a bulky phosphine and *N*-heterocyclic carbene (NHC) ligand,[5] which are able to effect HIE with a broad range of directing groups.[4,6] In terms of pharmaceutically relevant heterocycle motifs, we have reported on the application of a range of such structures,[6] including the labelling of carbonyl-protected indoles using



Scheme 1 Iridium-catalyzed hydrogen isotope exchange and application to the C-H activation and labelling of quinoline *N*-oxides.

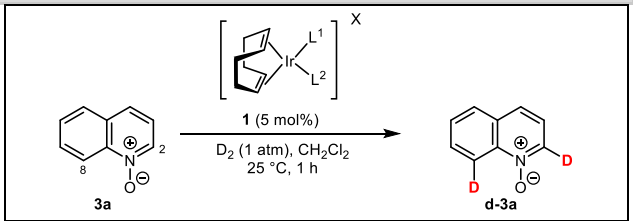
catalyst **1a** (Scheme 1b),[7] where the amide or carbamate directing group leads to highly selective indole C2 labelling via a 5-mmi, with no labelling observed at the C7 position (through any competing 6-mmi).

Based on this, we were motivated to explore other polycyclic aromatic systems where labelling might be directed, in a complementary manner, into the ring adjacent to that bearing the directing group. To this end, we selected the quinoline *N*-oxide[8]

motif for our initial study in this area, based on the ubiquity of quinolines within pharmaceuticals and bioactive natural products.[9] Encouragingly, there are a number of reports on the C-H activation of this system,[10] resulting in selective functionalization at C8.[11] Intriguingly, however, a single HIE study in this area,[12] on a set of three quinoline *N*-oxide substrates, and using 10 mol% of Ir(I) chelate catalyst **2**, reports excellent levels of C8 labelling, alongside similarly high levels of competing labelling at C2 (Scheme 1c). This report provided us with further incentive to apply our iridium(I) NHC/phosphine catalysts to these heterocyclic systems, in order to determine the feasibility of a C8-selective labelling process (Scheme 1d), and we herein report our studies in this area.

To initiate our studies, we evaluated the labelling of model substrate quinoline *N*-oxide **3a**, using a suite of our iridium(I) catalysts, under standard conditions of 1 atm D_2, in CH_2Cl_2 for 1 h at 25 °C (Table 1).[13] Pleasingly, the six IMes-containing catalysts **1a**-**1f** all delivered high levels of labelling at C8, and, crucially, all with good to excellent selectivity over the competing C2 position. Catalyst **1a** was chosen for further optimisation; although several other catalysts gave slightly higher levels of incorporation, no C2 labelling was observed at all with this complex. It should also be noted that catalysts **1d**-**1f**, bearing the BAr^F (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) counterion, also performed exceptionally well, and these complexes have an improved solvent applicability profile[5b] compared to catalysts **1a**-**1c**, should reactions require to be run in solvents other than CH_2Cl_2.

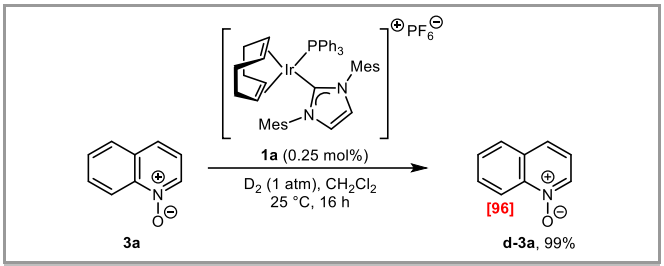
Table 1 Quinoline *N*-oxide labelling: catalyst screen



Entry	Catalyst	L^1	L^2	X	$\%D_{C8}$[a]	$\%D_{C2}$[a]
1	**1a**	PPh_3	IMes	PF_6	80	0
2	**1b**	PMe_2Ph	IMes	PF_6	85	13
3	**1c**	PBn_3	IMes	PF_6	86	9
4	**1d**	PPh_3	IMes	BAr^F	83	3
5	**1e**	PMe_2Ph	IMes	BAr^F	84	5
6	**1f**	PBn_3	IMes	BAr^F	83	7
7	**1g**	PPh_3	IBn	PF_6	10	18
8	**1h**	Cl	IMes	-	45	0

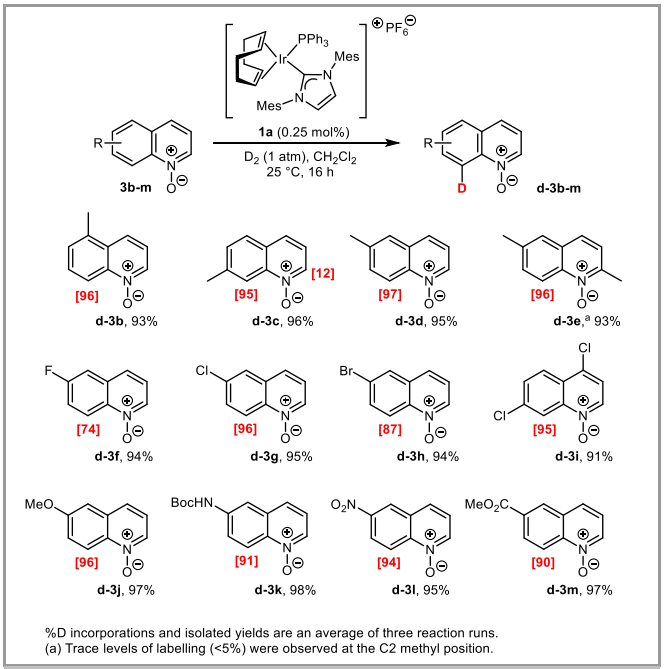
[a] Deuterium incorporations are an average of three reaction runs.

Following further optimisation, we were able to decrease the catalyst loading to a very low level of 0.25 mol% by extending the reaction time to 16 h (Scheme 2). This represents an unusually low catalyst loading for such iridium-catalysed HIE processes, and, coupled with the room temperature reaction, provides an extremely favourable set of conditions for applications in radiolabelling using tritium gas, where radioactive waste is minimized by using as low a catalyst loading as possible, reducing the amount of radiolabelled cyclooctane produced on catalyst activation.



Scheme 2 Optimised deuterium labelling conditions.

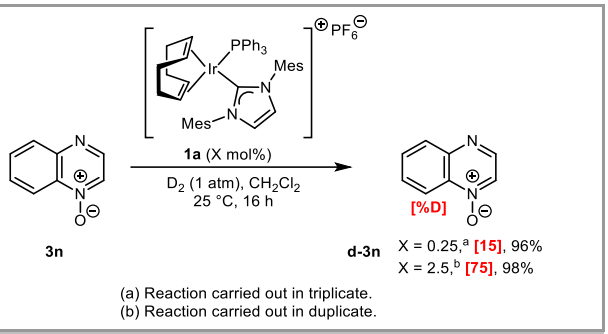
With these notably very mild conditions in hand, we next sought to establish the applicability of this methodology to a range of quinoline *N*-oxide substrates. Derivatives **3b**-**3m** were all labelled to very high deuterium incorporations, with excellent selectivity for the C8 position over C2 (Scheme 3). Methyl isomers **3b**-**3d** all labelled to very high levels, although **3c** was the sole substrate to show any C2 labelling, albeit at very low levels. 2,6-Dimethylquinoline *N*-oxide **3e** also labelled to an excellent level, and we note that trace levels (<5%) of labelling were observed on the 2-methyl group, via a favourable 5-mmi. 6-Halogenated substrates **3f**-**3h** all labelled to very high levels, as did 4,7-dichloro substrate **3i**, demonstrating that the presence of a substituent adjacent to the C-H activation site does not inhibit the desired process. Both electron-rich (**3j** and **3k**) and electron-poor substrates (**3l** and **3m**) also showed excellent levels of deuterium incorporation. Notably, no labelling was observed in substrates **3k**-**3m** as a result of direction by the Lewis basic carbamate, nitro, or ester groups, reflecting their relatively weak directing group power,[14] whilst the *N*-oxide moiety appears to be a very strong directing group, based on the requirement for only 0.25 mol% catalyst loading under the established optimized conditions.



Scheme 3 Quinoline *N*-oxide substrate scope.

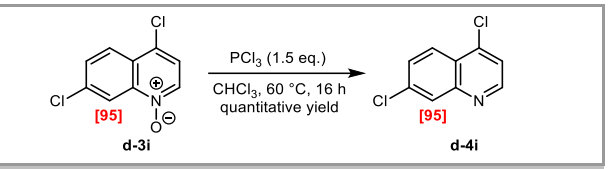
Finally, in a departure from the quinoline moiety, quinoxaline mono-*N*-oxide **3n** was also labelled selectively in the C8 position (Scheme 4). Under the standard conditions of 0.25 mol% of catalyst **1a**, a low 15% incorporation was observed. By raising

the catalyst loading to 2.5 mol%, a 75% deuterium incorporation was achieved. We propose that the requirement of a slightly more elevated catalyst loading with this substrate is related to competitive binding of the second, free, quinoline-type nitrogen.



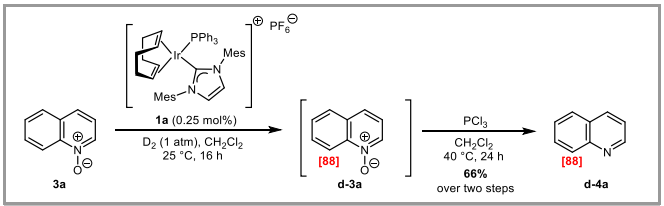
Scheme 4 Extension to the labelling of quinoxaline *N*-oxide **3n**.

With a selective and effective method in hand for the C8-selective labelling of such heterocycle *N*-oxides, we turned our attention to reduction of the labelled *N*-oxide to the parent quinoline, in order to establish that the isotopic label is retained under typical deoxygenation conditions (Scheme 5). Pleasingly, a sample of 4,7-dichloroquinoline *N*-oxide **d-3i**, labelled to 95%D at C8, underwent smooth reduction to labelled 4,7-dichloroquinoline **d-4i** in quantitative yield, using PCl_3 under mildly elevated temperatures, and with complete retention of the isotopic label.



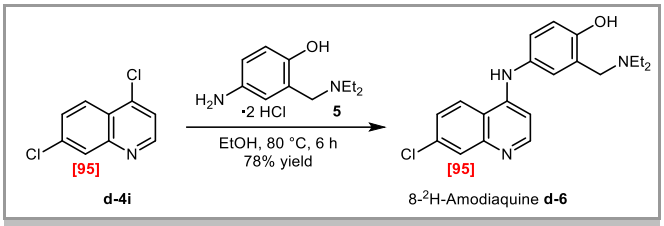
Scheme 5 Deoxygenation of **d-3i** to give the labelled quinolone **d-4i**.

Encouraged by this result, we then investigated the potential for a one-pot labelling/deoxygenation procedure (Scheme 6). Following exposure of quinoline *N*-oxide **d-3a** to the established labelling conditions, NMR spectroscopic analysis of a reaction aliquot indicated a deuterium incorporation of 88%. The reaction atmosphere was exchanged from deuterium to argon, and the mixture was subjected directly to the reduction conditions *in situ*. With a milder temperature than the direct deoxygenation, the reaction still proceeded in good yield, and with complete retention of the deuterium label through this one-pot labelling/reduction process.



Scheme 6 One-pot labelling and deoxygenation.

Finally, we demonstrated the utility of this quinoline *N*-oxide labelling methodology in the synthesis of a selectively labelled analogue of Amodiaquine, **d-6**, an antimalarial and anti-inflammatory agent that is listed on the World Health Organisation's List of Essential Medicines (Scheme 7).[15] Treatment of **d-4i** with aniline dihydrochloride derivative **5** at 80 °C in ethanol gave 8-^{2}H-Amodiaquine **d-6** in 78% yield, with complete retention of the level of isotopic enrichment. To the best of our knowledge, this selectively C-8-labelled analogue of Amodiaquine has not been previously reported.



Scheme 7 Application to a labelled drug molecule.

In conclusion, we have developed a method for the highly efficient and selective C-8 labelling of quinoline *N*-oxides, with catalyst loadings that are at remarkably low levels for this class of hydrogen isotope exchange process. The method tolerates a broad range of functional groups at various positions on the quinoline system. Additionally, the labelled *N*-oxide products are readily deoxygenated to the free quinoline with no loss of the isotopic label, and the utility of these labelled heterocycles has been demonstrated by the application to the preparation of a deuterated analogue of the critical medicine, Amodiaquine. Further, an effective one-pot C8-selective labelling and deoxygenation method has also been realized, which circumvents any requirement to isolate the deuterated *N*-oxide species prior to liberation of the labelled heterocycle.

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All reagents were obtained from commercial suppliers (Alfa Aesar, Sigma Aldrich, Apollo Scientific, Fluorochem, or Strem) and used without further purification, unless otherwise stated. If purification was required, this was carried out following standard laboratory methods. [16]All glassware was flame-dried and cooled under a stream of argon, unless otherwise stated. Tetrahydrofuran was purified by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, before distillation under a nitrogen atmosphere. Dichloromethane was purified by heating to reflux over calcium hydride, before distillation under a nitrogen atmosphere. Diethyl ether was obtained from a PureSolv SPS-400-5 Solvent Purification System. Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. The plates were analysed using a Mineralight UVGL-25 lamp, or developed using vanillin or $KMnO_4$ solution. Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh). IR spectra were obtained on a Shimadzu IRAffinity-1 Spectrophotometer machine, or Perkin Elmer Spectrometer 1. All samples were analysed neat unless otherwise stated, and wavenumbers are reported in cm^{-1}. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz, 101 MHz, and 376 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^3J_{H-H}$ interactions unless stated otherwise. High resolution mass spectrometry was carried out at the Mass Spectrometry facility at the University of Strathclyde, using a ThermoScientific Exactive Plus Orbi-Trap instrument.

Catalysts **1a** (1019853-00-9), **1b** (1019853-03-2), **1c** (1019853-01-0), **1d** (1628471-64-6), and **1e** (1884137-92-1) are commercially available from Strem, Inc. Catalysts **1f**,[17] **1g**[18] and **1h**[18] were prepared according to the reported literature procedures. 4-Amino-2-[(diethylamino)methyl]phenol dihydrochloride (6297-14-9) **5** is commercially available from Fluorochem. 6-((*tert*-Butoxycarbonyl)amino)quinoline **3k** was prepared according to a literature procedure.[19]

Procedures

General Procedure A: the Preparation of Heterocyclic *N*-Oxides

Following a modified literature procedure,[20] in a round-bottom flask the relevant *N*-heterocycle (1.0 eq.) was dissolved in DCM (0.3 M) and subsequently cooled to 0 °C. Following this, *meta*-chloroperoxybenzoic acid (*m*-CPBA) (1.5 eq.) was added, and the reaction mixture was allowed to warm to room temperature and then stirred for 16 h. The reaction mixture was then cooled to 0 °C and saturated sodium bicarbonate solution was added. The resultant solution was then extracted with CH_2Cl_2 (× 3), and the combined extracts washed with water (× 3). The organic phase was then dried over sodium sulfate and the solvent removed *in vacuo*. The residue was loaded onto silica and purified by means of flash column chromatography, eluting with a MeOH/DCM gradient (1-5%). The product-containing fractions were then combined and concentrated under reduced pressure to afford the *N*-oxide product.

General Procedure B: the Deuteration of Heterocyclic *N*-Oxides

Reactions were conducted using a Radley's 12-chamber carousel, with each of the 150 mm × 24 mm Ø carousel tubes oven-dried overnight at 180 °C and then allowed to cool under vacuum. The 12 tubes were purged with an argon atmosphere before the relevant substrate, catalyst, and CH_2Cl_2 (2.5 mL) were added. The tubes were then placed into a dry ice/acetone bath at -78 °C, where the atmosphere in the tubes was exchanged via three vacuum/D_2 cycles. After this, the reaction vessels were sealed, warmed to room temperature and stirred. Upon the reaction time, acetonitrile (0.2 mL) was added to deactivate the catalyst and the solvent was then removed *in vacuo*. The product was isolated by passage through a silica plug, washing with CH_2Cl_2 (× 3), and the product was then eluted using a 10% MeOH in DCM solution. The crude product was concentrated *in vacuo* and the level of incorporation was determined by ^{1}H NMR spectroscopic analysis, with the integrals of the anticipated labelling positions measured against a peak corresponding to a position where labelling was not expected. The percentage deuteration was calculated through use of Eq 1 below.

$$Eq\ (1):\ \%\ Deuteration = 100 - \left[\left(\frac{residual\ integral}{no.\ of\ labelling\ sites}\right) \text{ x } 100\right]$$

Preparation of Heterocycle *N*-Oxide Substrates

Quinoline *N*-oxide (3a)[21]

Following General Procedure A, quinoline (652 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give quinoline *N*-oxide **3a** as a light-brown solid (539 mg, 73% yield).

Melting point: 59–63 °C (lit.[22] 60–62 °C).

IR (ATR): 3100, 3075, 3007, 1567, 1513, 1443, 1398, 1309, 1264, 1229, 1210 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 8.8 Hz, 1H, H8), 8.52 (dd, *J* = 6.1, ^{4}*J* = 1.0 Hz, 1H, H2), 7.88 – 7.83 (m, 1H, H6), 7.80 – 7.69 (m, 2H, H4 &, H5), 7.63 (ddd, *J* = 8.8, *J* = 6.9, ^{4}*J* = 1.2 Hz, 1H, H7), 7.28 (dd, *J* = 8.5 *J* = 6.1 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 135.7, 130.7, 130.5, 128.9, 128.3, 126.0, 121.1, 120.0.

5-Methylquinoline *N*-oxide (3b)[23]

Following General Procedure A, 5-methylquinoline (723 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 5-methylquinoline *N*-oxide **3b** as a white solid (659 mg, 82% yield).

Melting point: 120–122 °C.

IR (ATR): 3075, 3053, 3010, 2923, 1614, 1569, 1517, 1444, 1409, 1299, 1258, 1232 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.7 Hz, 1H, H8), 8.53 (dd, *J* = 6.0, ^{4}*J* = 1.0 Hz, 1H, H2), 7.88 (d, *J* = 8.7 Hz, 1H, H4), 7.63 (dd, *J* = 8.7, *J* = 7.0 Hz, 1H, H7), 7.52 – 7.42 (m, 1H, H6), 7.30 (dd, *J* = 8.7, *J* = 6.0 Hz, 1H, H3), 2.70 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.3, 135.6, 135.5, 130.2, 130.2, 129.4, 122.7, 120.5, 118.1, 19.3.

7-Methylquinoline *N*-oxide (3c)[24]

Following General Procedure A, 7-methylquinoline (723 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 7-methylquinoline *N*-oxide **3c** as a yellow solid (625 mg, 78% yield).

Melting point: 88–92 °C (lit.[25] 129–131 °C).

IR (ATR): 3062, 3021, 2973, 2917, 1625, 1573, 1513, 1426, 1398, 1366, 1297 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (s, 1H, H8), 8.50 (dd, *J* = 6.1, ^{4}*J* = 1.1 Hz, 1H, H2), 7.76 (d, *J* = 8.4 Hz, 1H, H6), 7.70 (d, *J* = 8.4 Hz, 1H, H5), 7.47 (dd, *J* = 8.4, ^{4}*J* = 1.1 Hz, 1H, H4), 7.22 (dd, *J* = 8.4, *J* = 6.1 Hz, 1H, H3), 2.60 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7 (2C), 135.8, 131.1, 128.8, 128.0, 126.0, 120.1, 118.9, 22.2.

6-Methylquinoline *N*-oxide (3d)[26]

Following General Procedure A, 6-methylquinoline (723 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 6-methylquinoline *N*-oxide **3d** as a yellow solid (653 mg, 81% yield).

Melting point: 75–77 °C (lit.[27] 76–78 °C).

IR (ATR): 3051, 3021, 2971, 2919, 1575, 1508, 1463, 1426, 1368, 1281, 1245 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.8 Hz, 1H, H8), 8.46 (dd, *J* = 6.0, ^{4}*J* = 1.0 Hz, 1H, H2), 7.68 – 7.52 (m, 3H, H4, H5 & H7), 7.27 – 7.21 (m, 1H, H3), 2.54 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 139.2, 135.1, 132.8, 130.8, 127.1, 125.6, 121.1, 119.7, 21.6.

2,6-(Dimethyl)quinoline *N*-oxide (3e)[28]

Following General Procedure A, 2,6-(dimethyl)quinoline (794 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 2,6-(dimethyl)quinoline *N*-oxide **3e** as a white solid (729 mg, 83% yield).

Melting point: 90–94 °C (lit.[29] 82.5–82.8 °C).

IR (ATR): 3042, 3025, 2992, 2973, 2943, 2917, 1575, 1512, 1471, 1448, 1331, 1255 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 8.7 Hz, 1H, H8), 7.58 – 7.47 (m, 3H, H3 or H4, H5 & H7), 7.25 (d, *J* = 8.7 Hz, 1H, H3 or H4), 2.69 (s, 3H, 2-CH_3), 2.52 (s, 3H, 6-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.2, 140.3, 137.9, 132.5, 129.5, 127.1, 124.7, 123.1, 119.5, 21.4, 18.8.

6-Fluoroquinoline *N*-oxide (3f)[28]

Following General Procedure A, 6-fluoroquinoline (441 mg, 3.00 mmol) in CH_2Cl_2 (10 mL) was reacted with *m*-CPBA (777 mg, 4.50 mmol) to give 6-fluoroquinoline *N*-oxide **3f** as a white solid (490 mg, 100% yield).

Melting point: 104–108 °C (lit.[30] 102–104 °C).

IR (ATR): 3075, 3051, 2994, 1626, 1566, 1506, 1447, 1431, 1366, 1298, 1264, 1196 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82–8.71 (m, 1H, H8), 8.47 (d, *J* = 6.0 Hz, 1H, H2), 7.66 (d, *J* = 8.5 Hz, 1H, H4), 7.58 – 7.42 (m, 2H, H5 & H7), 7.31 (dd, *J* = 8.5, *J* = 5.6, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0 (d, $^1J_{C\text{-}F}$ = 251.7 Hz), 138.9, 135.2, 131.8 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 125.2 (d, $^4J_{C\text{-}F}$ = 5.0 Hz), 123.1 (d, $^3J_{C\text{-}F}$= 9.3 Hz), 122.4, 120.5 (d, $^2J_{C\text{-}F}$ = 25.9 Hz), 111.7 (d, $^2J_{C\text{-}F}$ = 22.6 Hz).

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -110.3

6-Chloroquinoline *N*-oxide (3g)[24]

Following General Procedure A, 6-chloroquinoline (826 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 6-chloroquinoline *N*-oxide **3g** as a white solid (411 mg, 45% yield).

Melting point: 105–108 °C (lit.[31] 108 °C).

IR (ATR): 3060, 3001, 2994, 1561, 1503, 1441, 1424, 1359, 1301, 1264 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 9.3 Hz, 1H, H8), 8.50 (dd, *J* = 6.1, ^4J = 1.0 Hz, 1H, H2), 7.86 (d, ^4J = 2.2 Hz, 1H, H5), 7.69 (dd, *J* = 9.3, ^4J = 2.2 Hz, 1H, H7), 7.64 (d, *J* = 8.5 Hz, 1H, H4), 7.33 (dd, *J* = 8.5, *J* = 6.1 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 135.2, 134.6, 130.8, 130.7, 126.3, 124.2, 121.8, 121.3.

6-Bromoquinoline *N*-oxide (3h)[28]

Following General Procedure A, 6-bromoquinoline (400 mg, 1.92 mmol) in CH_2Cl_2 (6 mL) was reacted with *m*-CPBA (497 mg, 2.88 mmol). In a deviation from the General Procedure, no column chromatography was carried out, and the product was recrystallized from petroleum ether/ethyl acetate, to give 6-bromoquinoline *N*-oxide **3h** as an off-white solid (339 mg, 79% yield).

Melting point: 130–134 °C (lit.[30] 128–129 °C).

IR (ATR): 3094, 3076, 1562, 1497, 1414, 1356, 1300, 1265, 1227, 1180, 1063 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 9.3 Hz, 1H, H8), 8.50 (d, *J* = 6.1 Hz, 1H, H2), 8.04 (d, ^4J = 2.1 Hz, 1H, H5), 7.82 (dd, *J* = 9.3, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H7), 7.63 (d, *J* = 8.5 Hz, 1H, H4), 7.31 (dd, *J* = 8.5, ^4J = 6.1 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 135.9, 133.9, 131.8, 130.3, 124.7, 123.4, 122.4, 122.0.

4,7-Dichloroquinoline *N*-oxide (3i)[28]

Following General Procedure A, 4,7-dichloroquinoline (1.00 g, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 4,7-dichloroquinoline *N*-oxide **3i** as a white solid (752 mg, 70% yield).

Melting point: 160–162 °C (lit.[32] 164–165 °C).

IR (ATR): 3096, 3042, 1605, 1555, 1497, 1348, 1287, 1240, 1215, 1155, 1086 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (d, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H8), 8.44 (d, *J* = 6.6 Hz, 1H, H2), 8.16 (d, *J* = 9.0 Hz, 1H, H5), 7.70 (dd, *J* = 9.0, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H6), 7.37 (d, *J* = 6.6 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 138.4, 136.1, 131.0, 129.9, 126.9, 126.7, 121.4, 120.2.

6-Methoxyquinoline *N*-oxide (3j)[28]

Following General Procedure A, 6-methoxyquinoline (804 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 6-methoxyquinoline *N*-oxide **3j** as a white solid (639 mg, 72% yield).

Melting point: 84–86 °C (lit.[33] 80–82 °C).

IR (ATR): 3077, 3059, 2997, 2947, 1623, 1577, 1513, 1472, 1441 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 9.5 Hz, 1H, H8), 8.37 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 7.60 (dd, *J* = 8.5, ^4J = 1.0 Hz, 1H, H4), 7.36 (dd, *J* = 9.5, ^4J = 2.7 Hz, 1H, H7), 7.22 (dd, *J* = 8.5, *J* = 6.0 Hz, 1H, H3), 7.09 (d, ^4J = 2.7 Hz, 1H, H5), 3.95 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 137.4, 133.9, 132.1, 125.0, 122.9, 121.6 (2C), 105.9, 55.8.

6-((*tert*-Butoxycarbonyl)amino)quinoline *N*-oxide (3k)[34]

Following General Procedure A, 6-((*tert*-butoxycarbonyl)amino)quinoline (400 mg, 1.64 mmol) in CH_2Cl_2 (5.5 mL) was reacted with *m*-CPBA (425 mg, 2.46 mmol) to give 6-((*tert*-butoxycarbonyl)amino)quinoline *N*-oxide **3k** as a white powder (246 mg, 58% yield).

Melting point: 200–205 °C (lit.[35] 212–213 °C).

IR (ATR): 3237, 3122, 3034, 3014, 2980, 1722, 1597, 1569, 1508, 1394, 1368 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 9.3 Hz, 1H, H8), 8.42 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 8.23 (d, ^4J = 2.3 Hz, 1H, H5), 7.67 (d, *J* = 8.4 Hz, 1H, H4), 7.49 (dd, *J* = 9.3, ^4J = 2.4 Hz, 1H, H7), 7.30 – 7.19 (m, 1H, H3), 7.03 (bs, 1H, NH), 1.54 (s, 9H, *t*Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 138.8, 138.1, 134.4, 131.7, 125.9, 123.1, 121.7, 121.0, 113.8, 81.6, 28.4.

6-Nitroquinoline *N*-oxide (3l)[28]

Following General Procedure A, 6-nitroquinoline (880 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give 6-nitroquinoline *N*-oxide **3l** as a yellow powder (545 mg, 57% yield).

Melting point: 219–222 °C (dec.) (lit.[36] 216–217 °C).

IR (ATR): 3118, 3081, 3059, 1573, 1532, 1500, 1435, 1350 cm^{-1}.

^{1}H NMR (400 MHz, d_6-DMSO): δ = 9.14 (d, ^4J = 2.5 Hz, 1H, H5), 8.77 (dd, *J* = 6.1, ^4J = 0.9 Hz, 1H, H2), 8.70 (d, *J* = 9.5 Hz, 1H, H8), 8.47 (dd, *J* = 9.5, ^4J = 2.5 Hz, 1H, H7), 8.23 (d, *J* = 8.5 Hz, 1H, H4), 7.66 (dd, *J* = 8.5, *J* = 6.1 Hz, 1H, H3).

^{13}C NMR (100 MHz, d_6-DMSO): δ = 146.7, 142.7, 138.1, 129.9, 126.6, 125.5, 124.1, 123.3, 121.4.

6-(Methoxycarbonyl)quinoline *N*-oxide (3m)[28]

Following General Procedure A, 6-(methoxycarbonyl)quinoline (500 mg, 2.67 mmol) in CH_2Cl_2 (9 mL) was reacted with *m*-CPBA (692 mg, 4.01 mmol) to give 6-(methoxycarbonyl)quinoline *N*-oxide **3m** as a white solid (285 mg, 52% yield).

Melting point: 138–142 °C (lit.[30] 134–136 °C).

IR (ATR): 3111, 3057, 2947, 1715, 1574, 1505, 1454, 1358, 1258, 1219, 1175, 1099 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 9.1 Hz, 1H, H8), 8.62 (d, ^4J = 1.8 Hz, 1H, H5), 8.61 – 8.57 (m, 1H, H2), 8.33 (dd, *J* = 9.1, ^4J = 1.8 Hz, 1H, H7), 7.84 (d, *J* = 8.4 Hz, 1H, H4), 7.37 (dd, *J* = 8.4, 6.0 Hz, 1H, H3), 4.01 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 143.4, 137.3, 131.1, 130.7, 130.1, 130.0, 126.9, 122.0, 120.6, 52.9.

Quinoxaline *N*-oxide (3n)[28]

Following General Procedure A, quinoxaline (657 mg, 5.05 mmol) in CH_2Cl_2 (17 mL) was reacted with *m*-CPBA (1.31 g, 7.58 mmol) to give quinoxaline *N*-oxide **3n** as a white solid (458 mg, 62% yield).

Melting point: 150–153 °C (lit.[32] 152–155 °C).

IR (ATR): 3094, 3066, 1577, 1497, 1458, 1426, 1381, 1318 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 3.6 Hz, 1H, H3), 8.60 (dd, *J* = 8.6, ^4J = 1.5 Hz, 1H, H8), 8.36 (d, *J* = 3.6 Hz, 1H, H2), 8.15 (dd, *J* = 8.1, ^4J = 1.5 Hz, 1H H5), 7.84 (ddd, *J* = 8.4, *J* = 7.0, ^4J =1.5 Hz, 1H, H6), 7.77 (ddd, *J* = 8.4, *J* = 7.0, ^4J = 1.5 Hz, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 145.1, 137.7, 131.9, 130.4, 130.3, 129.4, 119.1.

Deuteration of Heterocycle *N*-oxides

The following is given as a representative procedure for the deuteration of the heterocycle *N*-oxides. For full details of the labelling of all other substrates, see the Supporting Information.

Deuteration of 4,7-Dichloroquinoline *N*-oxide (3i)

The labelling was carried out in triplicate. Following General Procedure B, the data are presented as (a) mass of substrate **3i**; (b) mmol of substrate **3i**; (c) mass of catalyst **1a**; (d) μmol of catalyst **1a**; (e) mass of product **d-3i**; (f) mmol of product **d-3i**; (g) product yield; and (h) %D incorporation.

Run 1: (a) 48.2 mg; (b) 0.215; (c) 0.5 mg; (d) 0.538; (e) 42 mg; (f) 0.195; (g) 91%; and (h) 95%.

Run 2: (a) 48.2 mg; (b) 0.215; (c) 0.5 mg; (d) 0.538; (e) 42 mg; (f) 0.195; (g) 91%; and (h) 95%.

Run 3: (a) 48.2 mg; (b) 0.215; (c) 0.5 mg; (d) 0.538; (e) 42 mg; (f) 0.195; (g) 91%; and (h) 95%.

Incorporation expected at δ 8.79 (H8).

Incorporation determined against the integral of the signal at δ 7.37 (H3).

Average yield, 91%; average D incorporation, 95%.

Preparation of 8-^{2}H-4,7-dichloroquinoline (d-4i) by Deoxygenation of 8-^{2}H-4,7-dichloroquinoline *N*-oxide d-3i

Following a literature procedure,[37] to a flame-dried round-bottom flask, cooled under an atmosphere of argon, charged with 8-^{2}H-4,7-dichloroquinoline 1-oxide-8-d (95%D) **d-3i** (100 mg, 0.465 mmol, 1 eq.), was added chloroform (5 mL) and phosphorous trichloride (95.9 mg, 60.9 μL, 0.698 mmol, 1.5 eq.). Following this, the reaction mixture was heated to 60 °C for 16 h, after which time the solvent was removed under reduced pressure. The resulting residue was dissolved in diethyl ether and saturated sodium hydrogen bicarbonate solution was added. The organic phase was then separated and the aqueous phase extracted three times with diethyl ether. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford quinolone **d-4i** as a white solid (93 mg, 0.472 mmol, 100% yield, 95%D).

Melting point: 76-80 °C.

IR (ATR): 3120, 3089, 3059, 2954, 2925, 2856, 1605, 1573, 1534, 1484, 1437, 1351, 1336 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 4.7 Hz, 1H, H2), 8.18 (d, *J* = 9.0 Hz, 1H, H5 or H6), 8.15 – 8.12 (m, 0.05H, H8), 7.60 (d, *J* = 9.0 Hz, 1H, H5 or H6), 7.49 (d, *J* = 4.7 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 149.6, 142.8, 136.6, 128.8 (2C), 125.8, 125.2, 121.6.

HRMS (ESI): m/z calculated for $C_9H_5D^{35}Cl_2N$ $[M+H]^+$: 198.99401; found: 198.99346

Preparation of 8-^{2}H-Quinoline (d-4a)[38] by One-Pot Labelling and Deoxygenation of Quinoline *N*-oxide 3a

A 100 mL round-bottom flask bearing two stopcocks was flame-dried and cooled under argon. Quinoline *N*-oxide **3a** (73 mg, 0.5 mmol), catalyst **1a** (1.26 mg, 0.00125 mmol, 0.25 mol%), and dichloromethane (5 mL) were then added and the flask was cooled to −78 °C in a dry ice/acetone bath. The flask was then evacuated and refilled with deuterium gas from a balloon, and this vacuum/refilling cycle repeated one further time. The stopcocks were closed and the flask was warmed to 25 °C and stirred for 16 h, after which time crude ^{1}H NMR spectroscopic analysis of an aliquot showed 88% deuterium incorporation. The deuterium atmosphere was exchanged for argon and then phosphorous trichloride (65 μL, 0.75 mmol, 1.5 eq.) was added directly to the reaction mixture. The mixture was heated to 40 °C for 24 h, then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with diethyl ether (10 mL) and neutralised with saturated sodium bicarbonate solution (10 mL). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over sodium sulfate and then passed through a silica plug, eluting with diethyl ether. Concentration *in vacuo* yielded [8-^{2}H]-quinoline **d-4a** as a pale yellow oil (43 mg, 66% yield).

Deuterium incorporation in [8-^{2}H]-quinoline **d-4a** was expected at δ 8.14–8.09 (C8) and was determined against the integral at δ 7.72 (H5 or H7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (dd, *J* = 4.3, ^4J =1.8 Hz, 1H, H2), 8.16 (dd, *J* = 8.3, ^4J =1.8 Hz, 1H, H4), 8.14 – 8.09 (m, 0.12H, H8), 7.82 (dd, *J* = 8.2, ^4J = 1.5 Hz, 1H, H5 or H7), 7.72 (dd, *J* = 6.9, ^4J =1.5 Hz, 1H, H5 or H7), 7.55 (dd, *J* = 8.2, ^4J = 6.9 Hz, 1H, H6), 7.40 (dd, *J* = 8.3, *J* =4.2 Hz, 1H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 148.4, 136.2, 129.5, 129.2 (t, $^1J_{C-D}$ = 25 Hz), 128.4, 127.9, 126.7, 122.2.

Preparation of 8-^{2}H-Amodiaquine d-6

To a flame-dried Schlenk flask, cooled under an atmosphere of argon, was added the aniline salt **5** (134 mg, 0.502 mmol, 1.0 eq.), and 8-^{2}H-4,7-dichloroquinoline **d-4i** (100 mg, 0.502 mmol, 1.0 eq.) was then added to the reaction mixture as a solution in ethanol (1.0 mL). The mixture was heated to 80 °C for 6 h. The reaction solution was then neutralised by the addition of a saturated aqueous solution of sodium bicarbonate and the mixture extracted with CH_2Cl_2. The combined organic extracts were washed with water three times, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography, eluting with a 1–7% MeOH/DCM gradient. The product-containing fractions were then combined and concentrated *in vacuo* to give 8-^{2}H-Amodiaquine **d-6** as a light brown solid (140 mg, 0.392 mmol, 78%).

Melting point: 202–206 °C.

IR (ATR): 3300–3200 (br), 3051, 2977, 2936, 2850, 2833, 1608, 1565, 1541, 1493, 1372, 1260 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 5.4 Hz, 1H, H2), 8.01 – 7.99 (m, 0.05H, H8), 7.82 (d, *J* = 8.9 Hz, 1H, H5), 7.42 (d, *J* = 8.9 Hz, 1H, H6), 7.08 (dd, *J* = 8.5, ^4J = 2.7 Hz, 1H, H6'), 6.92 (d, ^4J = 2.7 Hz, 1H, H2'), 6.86 (d, *J* = 8.5 Hz, 1H, H5'), 6.62 (d, *J* = 5.4 Hz, 1H, H3), 6.55 (bs, 1H, NH), 3.78 (s, 2H, CH_2), 2.65 (q, *J* = 7.2 Hz, 4H, 2 × CH_2), 1.14 (t, *J* = 7.2 Hz, 6H, 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 152.1, 149.6, 149.4, 135.2, 130.0, 125.9, 125.7, 125.4, 123.5, 121.1, 117.5, 117.3, 101.5, 57.0, 46.6, 11.4 (C8 carbon not visible).

HRMS (ESI): m/z calculated for $C_{20}H_{22}D^{35}ClN_3O$ $[M+H]^+$: 357.15924; found: 357.15869

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Supporting Information

Supporting Information for this article is available online at

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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Selective Deuteration of Heterocycle *N*-Oxides via Iridium-catalyzed Hydrogen Isotope Exchange

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Supporting Information

Contents

1. General Procedure A: the Deuteration of Heterocyclic *N*-Oxides

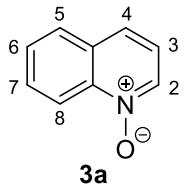
Reactions were conducted using a Radley's 12-chamber carousel, with each of the 150 mm × 24 mm Ø carousel tubes oven-dried overnight at 180 °C and then allowed to cool under vacuum. The 12 tubes were purged with an argon atmosphere before the relevant substrate, catalyst, and CH_2Cl_2 (2.5 mL) were added. The tubes were then placed into a dry ice/acetone bath at -78 °C, where the atmosphere in the tubes was exchanged via three vacuum/D_2 cycles. After this, the reaction vessels were sealed, warmed to room temperature and stirred. Upon the reaction time, acetonitrile (0.2 mL) was added to deactivate the catalyst and the solvent was then removed *in vacuo*. The product was isolated by passage through a silica plug, washing with CH_2Cl_2 (× 3), and the product was then eluted using a 10% MeOH in DCM solution. The crude product was concentrated *in vacuo* and the level of incorporation was determined by ^{1}H NMR spectroscopic analysis, with the integrals of the anticipated labelling positions measured against a peak corresponding to a position where labelling was not expected. The percentage deuteration was calculated through use of Eq 1 below.

$$Eq\ (1): \%\ Deuteration = 100 - \left[\left(\frac{residual\ integral}{no.of\ labelling\ sites}\right) \text{x } 100\right]$$

2. Catalyst Screen (Manuscript, Table 1)

Deuteration of quinoline *N*-oxide **3a**

The reaction was carried out according to *General Procedure A*, using quinoline *N*-oxide **3a** (31 mg, 0.215 mmol), and the specified catalyst (5 mol%, 10.75 μmol), in CH_2Cl_2 (2.7 mL; deviation from the General Procedure) for 1 h. The results are presented in Table S1 below.



3a

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.8 Hz, 1H, H8), 8.52 (dd, *J* = 6.1, ^4J = 1.0 Hz, 1H, H2), 7.88 – 7.83 (m, 1H, H6), 7.80 – 7.69 (m, 2H, H4 & H5), 7.63 (ddd, *J* = 8.8, *J* = 6.9, ^4J = 1.2 Hz, 1H, H7), 7.28 (dd, *J* = 8.5 *J* = 6.1 Hz, 1H, H3)

Incorporation expected at δ 8.74 (H8), and 8.52 (H2).
Incorporation determined against integral at δ 7.63 (H7).

Table S1. Catalyst screen for the HIE of quinoline *N*-oxide **3a**.

Entry	Catalyst	Mass of Catalyst / mg	Deuterium Incorporation / %				
				Run 1	Run 2	Run 3	Avg
1	**1a**	10.1	C8	82	78	80	80
			C2	0	0	0	0
2	**1b**	8.9	C8	85	85	84	85
			C2	13	10	16	13
3	**1c**	10.5	C8	85	89	83	86
			C2	9	8	9	9
4	**1d**	17.3	C8	85	84	81	83
			C2	4	2	4	3
5	**1e**	16.1	C8	85	86	82	84
			C2	4	7	4	5
6	**1f**	17.7	C8	86	81	83	83
			C2	8	9	5	7
7	**1g**	9.5	C8	12	9	10	10
			C2	18	20	15	18
8	**1h**	6.4	C8	46	46	44	45
			C2	0	0	0	0

3. Heterocycle *N*-Oxide Labelling – Substrate Scope

3.1 Deuteration of Quinoline *N*-oxide 3a (Manuscript, Scheme 2)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.

Spectroscopic data for quinoline *N*-oxide **3a** is presented in Section 2 above.

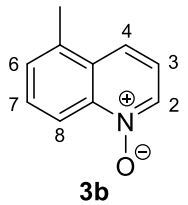
The reaction was carried out in triplicate and the results are given in Table S2 below.

Table S2. Labelling of quinoline *N*-oxide **3a** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	31.2	0.215	0.5	0.538	31	0.212	96	99
2	31.2	0.215	0.5	0.538	31	0.212	94	99
3	31.2	0.215	0.5	0.538	31	0.212	96	99
						Average	**96**	**99**

3.2 Deuteration of 5-Methylquinoline *N*-oxide 3b (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3b

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.7 Hz, 1H, H8), 8.53 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 7.88 (d, *J* = 8.7 Hz, 1H, H4), 7.63 (dd, *J* = 8.7, *J* = 7.0 Hz, 1H, H7), 7.52 – 7.42 (m, 1H, H6), 7.30 (dd, *J* = 8.7, *J* = 6.0 Hz, 1H, H3), 2.70 (s, 3H, CH_3).

Incorporation expected at δ 8.63 (H8)
Incorporation determined against the integral of the signal at δ 7.30 (H3).

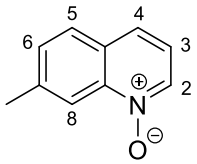
The reaction was carried out in triplicate and the results are given in Table S3 below.

Table S3. Labelling of 5-methylquinoline *N*-oxide **3b** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	34.2	0.215	0.5	0.538	27	0.169	96	79
2	34.2	0.215	0.5	0.538	34	0.212	96	99
3	34.2	0.215	0.5	0.538	35	0.218	96	100
						Average	**96**	**93**

3.3 Deuteration of 7-Methylquinoline *N*-oxide 3c (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3c

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, H8), 8.50 (dd, *J* = 6.1, ^4J = 1.1 Hz, 1H, H2), 7.76 (d, *J* = 8.4 Hz, 1H, H6), 7.70 (d, *J* = 8.4 Hz, 1H, H5), 7.47 (dd, *J* = 8.4, ^4J = 1.1 Hz, 1H, H4), 7.22 (dd, *J* = 8.4, *J* = 6.1 Hz, 1H, H3), 2.60 (s, 3H, CH_3).

Incorporation expected at δ 8.56 (H8). Incorporation also observed at δ 8.50 (H2).
Incorporation determined against the integral of the signal at δ 7.76 (H6).

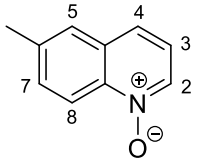
The reaction was carried out in triplicate and the results are given in Table S4 below.

Table S4. Labelling of 7-methylquinoline *N*-oxide **3c** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*C8 %D*	*C2 %D*	*Yield (%)*
1	34.2	0.215	0.5	0.538	34	0.211	95	14	98
2	34.2	0.215	0.5	0.538	32	0.199	95	9	93
3	34.2	0.215	0.5	0.538	34	0.211	95	13	98
						Average	**95**	**12**	**96**

3.4 Deuteration of 6-Methylquinoline *N*-oxide 3d (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3d

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 8.8 Hz, 1H, H8), 8.46 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 7.68 – 7.52 (m, 3H, H4, H5 & H7), 7.27 – 7.21 (m, 1H, H3), 2.54 (s, 3H, CH_3).

Incorporation expected at δ 8.63 (H8).
Incorporation determined against the integral of the signal at δ 7.27-7.21 (H3).

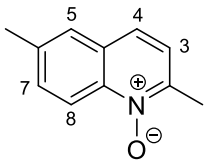
The reaction was carried out in triplicate and the results are given in Table S5 below.

Table S5. Labelling of 6-methylquinoline *N*-oxide **3d** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	34.2	0.215	0.5	0.538	34	0.212	97	99
2	34.2	0.215	0.5	0.538	33	0.206	97	96
3	34.2	0.215	0.5	0.538	31	0.194	96	90
						Average	**97**	**95**

3.5 Deuteration of 2,6-Dimethylquinoline *N*-oxide 3e (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3e

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 8.7 Hz, 1H, H8), 7.58 – 7.47 (m, 3H, H3 or H4, H5 & H7), 7.25 (d, *J* = 8.7 Hz, 1H, H3 or H4), 2.69 (s, 3H, 2-CH_3), 2.52 (s, 3H, 6-CH_3).

Incorporation expected at δ 8.65 (H8). Incorporation also observed at d 2.69 (2-CH_3).
Incorporation determined against the integral of the signal at δ 7.58-7.47 (H3 or H4, H5 & H7).

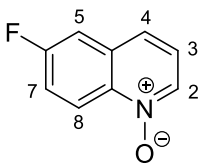
The reaction was carried out in triplicate and the results are given in Table S6 below.

Table S6. Labelling of 2,6-dimethylquinoline *N*-oxide **3e** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*C8 %D*	*C2-Me %D*	*Yield (%)*
1	37.2	0.215	0.5	0.538	34	0.195	96	<5	91
2	37.2	0.215	0.5	0.538	33	0.189	96	<5	88
3	37.2	0.215	0.5	0.538	37	0.212	96	<5	99
						Average	**96**	**<5**	**93**

3.6 Deuteration of 6-Fluoroquinoline *N*-oxide 3f (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3f

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82–8.71 (m, 1H, H8), 8.47 (d, *J* = 6.0 Hz, 1H, H2), 7.66 (d, *J* = 8.5 Hz, 1H, H4), 7.58 – 7.42 (m, 2H, H5 & H7), 7.31 (dd, *J* = 8.5, *J* = 5.6, 1H, H3).

Incorporation expected at δ 8.82-8.71 (H8).
Incorporation determined against the integral of the signal at δ 8.47 (H2).

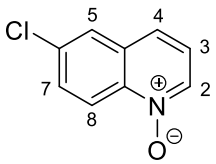
The reaction was carried out in triplicate and the results are given in Table S7 below.

Table S7. Labelling of 6-fluoroquinoline *N*-oxide **3f** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	35.1	0.215	0.5	0.538	34	0.207	71	96
2	35.1	0.215	0.5	0.538	32	0.195	72	91
3	35.1	0.215	0.5	0.538	34	0.207	78	96
						Average	**74**	**94**

3.7 Deuteration of 6-Chloroquinoline *N*-oxide **3g** (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3g

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 9.3 Hz, 1H, H8), 8.50 (dd, *J* = 6.1, ^4J = 1.0 Hz, 1H, H2), 7.86 (d, ^4J = 2.2 Hz, 1H, H5), 7.69 (dd, *J* = 9.3, ^4J = 2.2 Hz, 1H, H7), 7.64 (d, *J* = 8.5 Hz, 1H, H4), 7.33 (dd, *J* = 8.5, *J* = 6.1 Hz, 1H, H3).

Incorporation expected at δ 8.71 (H8).
Incorporation determined against the integral of the signal at δ 7.33 (H3).

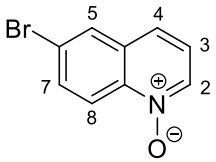
The reaction was carried out in triplicate and the results are given in Table S8 below.

Table S8. Labelling of 6-chloroquinoline *N*-oxide **3g** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	40.9	0.215	0.5	0.538	38	0.210	97	98
2	40.9	0.215	0.5	0.538	35	0.194	96	90
3	40.9	0.215	0.5	0.538	38	0.210	96	98
						Average	**96**	**95**

3.8 Deuteration of 6-Bromoquinoline *N*-oxide 3h (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3h

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 9.3 Hz, 1H, H8), 8.50 (d, *J* = 6.1 Hz, 1H, H2), 8.04 (d, ^4J = 2.1 Hz, 1H, H5), 7.82 (dd, *J* = 9.3, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H7), 7.63 (d, *J* = 8.5 Hz, 1H, H4), 7.31 (dd, *J* = 8.5, ^4J = 6.1 Hz, 1H, H3).

Incorporation expected at δ 8.62 (H8).
Incorporation determined against the integral of the signal at δ 7.31 (H3).

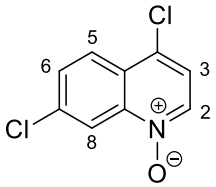
The reaction was carried out in triplicate and the results are given in Table S9 below.

Table S9. Labelling of 6-bromoquinoline *N*-oxide **3h** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	48.2	0.215	0.5	0.538	46	0.210	87	95
2	48.2	0.215	0.5	0.538	44	0.194	87	91
3	48.2	0.215	0.5	0.538	46	0.210	88	95
						Average	**87**	**94**

3.9 Deuteration of 4,7-Dichloroquinoline *N*-oxide 3i (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3i

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H8), 8.44 (d, *J* = 6.6 Hz, 1H, H2), 8.16 (d, *J* = 9.0 Hz, 1H, H5), 7.70 (dd, *J* = 9.0, $^4J_{C\text{-}H}$ = 2.1 Hz, 1H, H6), 7.37 (d, *J* = 6.6 Hz, 1H, H3).

Incorporation expected at δ 8.79 (H8).
Incorporation determined against the integral of the signal at δ 7.37 (H3).

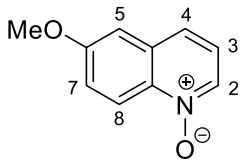
The reaction was carried out in triplicate and the results are given in Table S10 below.

Table S10. Labelling of 4,7-dichloroquinoline *N*-oxide **3i** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	48.2	0.215	0.5	0.538	42	0.210	95	91
2	48.2	0.215	0.5	0.538	42	0.194	95	91
3	48.2	0.215	0.5	0.538	42	0.210	95	91
						Average	**95**	**91**

3.10 Deuteration of 6-Methoxyquinoline *N*-oxide **3j** (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 9.5 Hz, 1H, H8), 8.37 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 7.60 (dd, *J* = 8.5, ^4J = 1.0 Hz, 1H, H4), 7.36 (dd, *J* = 9.5, ^4J = 2.7 Hz, 1H, H7), 7.22 (dd, *J* = 8.5, *J* = 6.0 Hz, 1H, H3), 7.09 (d, ^4J = 2.7 Hz, 1H, H5), 3.95 (s, 3H, OCH_3).

Incorporation expected at δ 8.64 (H8).
Incorporation determined against the integral of the signal at δ 7.09 (H5).

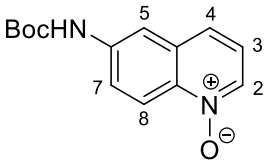
The reaction was carried out in triplicate and the results are given in Table S11 below.

Table S11. Labelling of 6-methoxyquinoline *N*-oxide **3j** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	37.7	0.215	0.5	0.538	37	0.210	95	98
2	37.7	0.215	0.5	0.538	35	0.199	95	93
3	37.7	0.215	0.5	0.538	38	0.216	97	100
						Average	**96**	**97**

3.11 Deuteration of 6-(*tert*-Butoxycarbonyl)amino)quinoline *N*-oxide 3k (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3k

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 9.3 Hz, 1H, H8), 8.42 (dd, *J* = 6.0, ^4J = 1.0 Hz, 1H, H2), 8.23 (d, ^4J = 2.3 Hz, 1H, H5), 7.67 (d, *J* = 8.4 Hz, 1H, H4), 7.49 (dd, *J* = 9.3, ^4J = 2.4 Hz, 1H, H7), 7.30 – 7.19 (m, 1H, H3), 7.03 (bs, 1H, NH), 1.54 (s, 9H, *t*Bu).

Incorporation expected at δ 8.66 (H8).
Incorporation determined against the integral of the signal at δ 7.49 (H7).

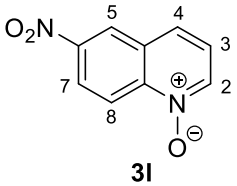
The reaction was carried out in triplicate and the results are given in Table S12 below.

Table S12. Labelling of 6-((*tert*-butoxycarbonyl)amino)quinoline *N*-oxide **3k** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	56.0	0.215	0.5	0.538	54	0.207	87	96
2	56.0	0.215	0.5	0.538	55	0.210	94	98
3	56.0	0.215	0.5	0.538	56	0.214	93	100
						Average	**91**	**98**

3.12 Deuteration of 6-Nitroquinoline *N*-oxide 3l (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time, with the modification that 7.5 mL of CH_2Cl_2 was used instead of 2.5 mL, to aid solubility of this substrate.



3l

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.14 (d, ^4J = 2.5 Hz, 1H, H5), 8.77 (dd, *J* = 6.1, ^4J = 0.9 Hz, 1H, H2), 8.70 (d, *J* = 9.5 Hz, 1H, H8), 8.47 (dd, *J* = 9.5, ^4J = 2.5 Hz, 1H, H7), 8.23 (d, *J* = 8.5 Hz, 1H, H4), 7.66 (dd, *J* = 8.5, *J* = 6.1 Hz, 1H, H3).

Incorporation expected at δ 8.70 (H8).
Incorporation determined against the integral of the signal at δ 7.66 (H3).

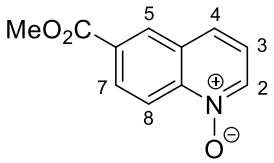
The reaction was carried out in triplicate and the results are given in Table S13 below.

Table S13. Labelling of 6-nitroquinoline *N*-oxide **3l** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	38.6	0.215	0.5	0.538	40	0.209	93	97
2	38.6	0.215	0.5	0.538	38	0.199	94	93
3	38.6	0.215	0.5	0.538	39	0.204	95	95
						Average	**94**	**95**

3.13 Deuteration of 6-(Methoxycarbonyl)quinoline *N*-oxide 3m (Manuscript, Scheme 3)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3m

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 9.1 Hz, 1H, H8), 8.62 (d, ^4J = 1.8 Hz, 1H, H5), 8.61 – 8.57 (m, 1H, H2), 8.33 (dd, *J* = 9.1, ^4J = 1.8 Hz, 1H, H7), 7.84 (d, *J* = 8.4 Hz, 1H, H4), 7.37 (dd, *J* = 8.4, 6.0 Hz, 1H, H3), 4.01 (s, 3H, CH_3).

Incorporation expected at δ 8.80 (H8).
Incorporation determined against the integral of the signal at δ 7.37 (H3).

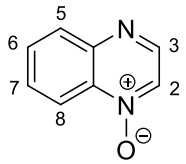
The reaction was carried out in triplicate and the results are given in Table S14 below.

Table S14. Labelling of 6-(methoxycarbonyl)quinoline *N*-oxide **3m** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	43.7	0.215	0.5	0.538	43	0.211	87	98
2	43.7	0.215	0.5	0.538	43	0.211	92	98
3	43.7	0.215	0.5	0.538	42	0.206	91	96
						Average	**90**	**97**

3.14 Deuteration of Quinoxaline *N*-oxide 3n (Manuscript, Scheme 4)

The reaction was carried out according to *General Procedure A* over 16 h reaction time.



3n

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 3.6 Hz, 1H, H2), 8.60 (dd, *J* = 8.6, ^4J = 1.5 Hz, 1H, H8), 8.36 (d, *J* = 3.6 Hz, 1H, H3), 8.15 (dd, *J* = 8.1, ^4J = 1.5 Hz, 1H H5), 7.84 (ddd, *J* = 8.4, *J* = 7.0, ^4J =1.5 Hz, 1H, H6), 7.77 (ddd, *J* = 8.4, *J* = 7.0, ^4J = 1.5 Hz, 1H, H7).

Incorporation expected at δ 8.60 (H8).
Incorporation determined against the integral of the signal at δ 8.68 (H2).

The reaction was carried out in triplicate and the results are given in Table S15 below.

Table S15. Labelling of quinoxaline *N*-oxide **3n** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	31.4	0.215	0.5	0.538	31	0.211	13	98
2	31.4	0.215	0.5	0.538	31	0.211	14	98
3	31.4	0.215	0.5	0.538	29	0.197	17	92
						Average	**15**	**96**

The reaction was then carried out according to *General Procedure A* over 16 h reaction time, but using 2.5 mol% of catalyst **1a**.

The reaction was carried out in duplicate, and the results are given in Table S16 below.

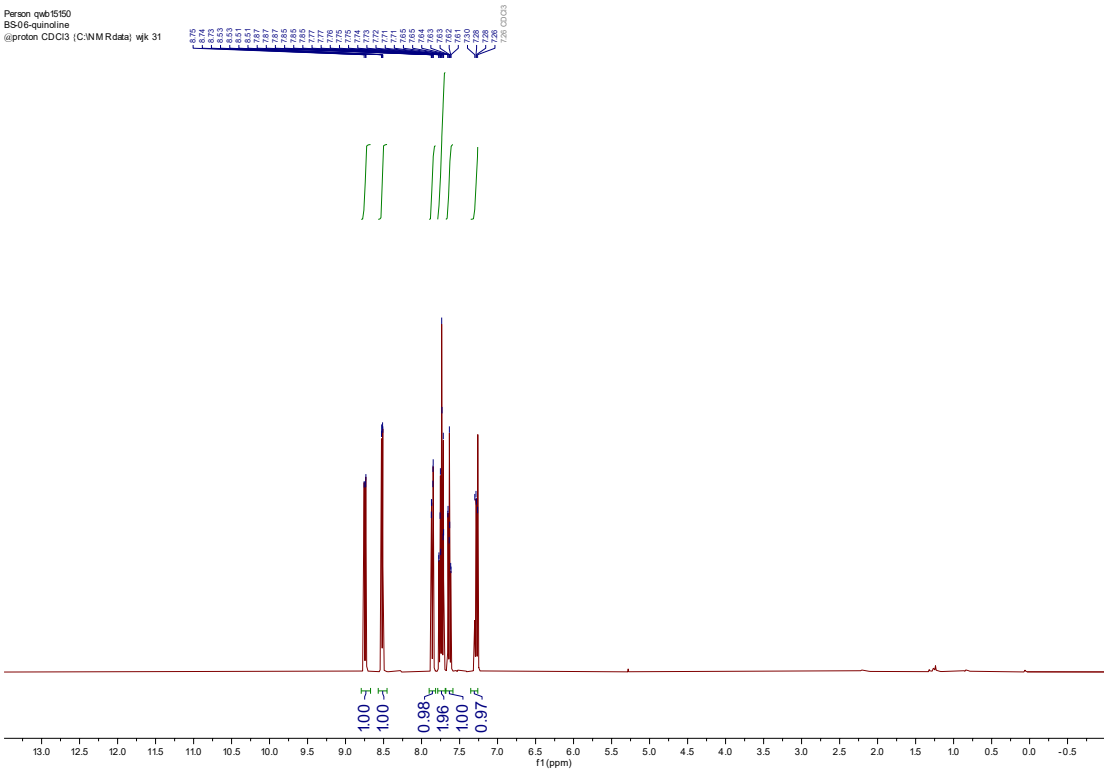
Table S16. Labelling of quinoxaline *N*-oxide **3n** with catalyst **1a**.

Run	*Substrate (mg)*	*Substrate (mmol)*	*Catalyst (mg)*	*Catalyst (μmol)*	*Product (mg)*	*Product (mmol)*	*%D*	*Yield (%)*
1	31.4	0.215	5.5	5.38	31	0.211	76	98
2	31.4	0.215	5.5	5.38	31	0.211	74	98
						Average	**75**	**98**

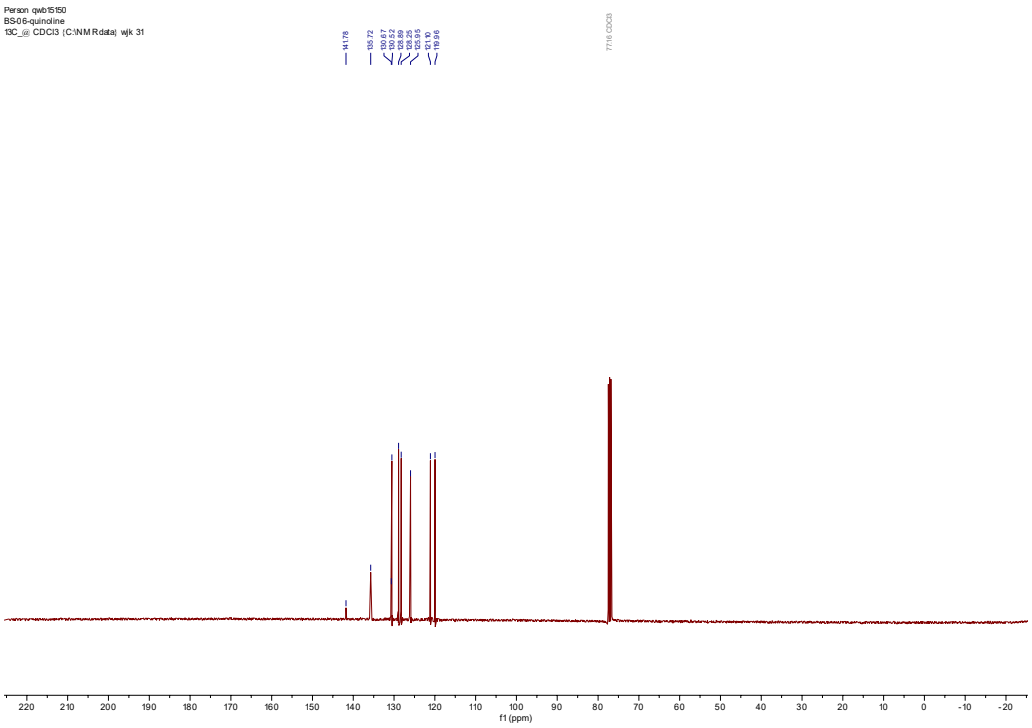
4. NMR Spectra

4.1 Quinoline *N*-oxide **3a**

^{1}H NMR Spectrum

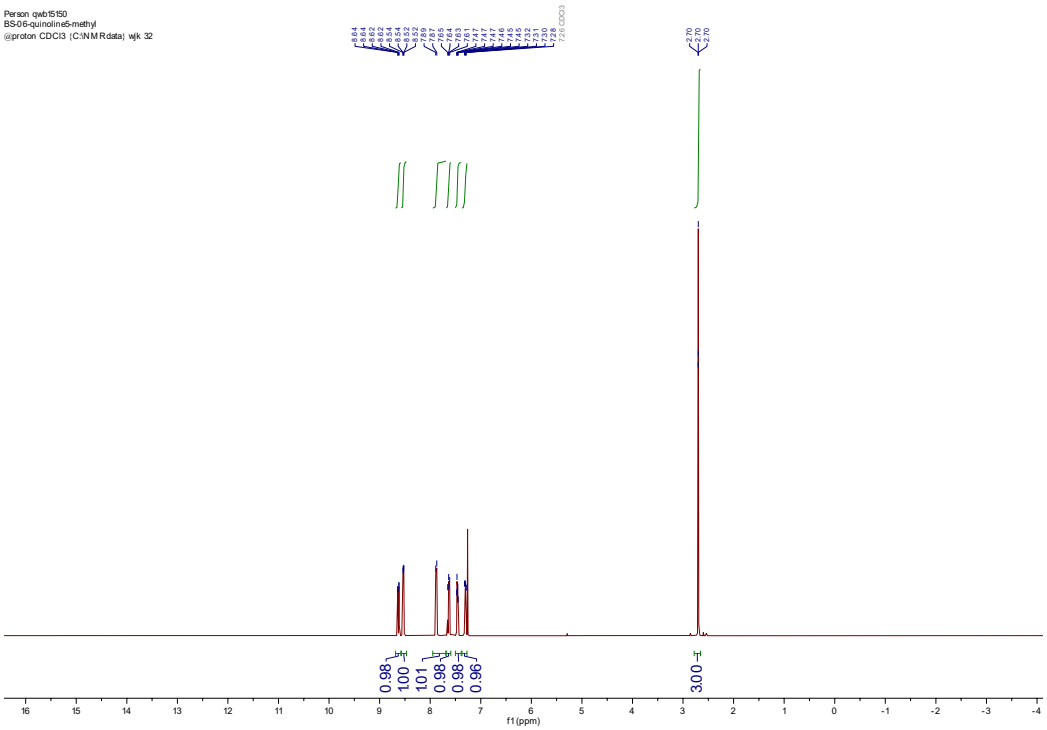


^{13}C NMR Spectrum

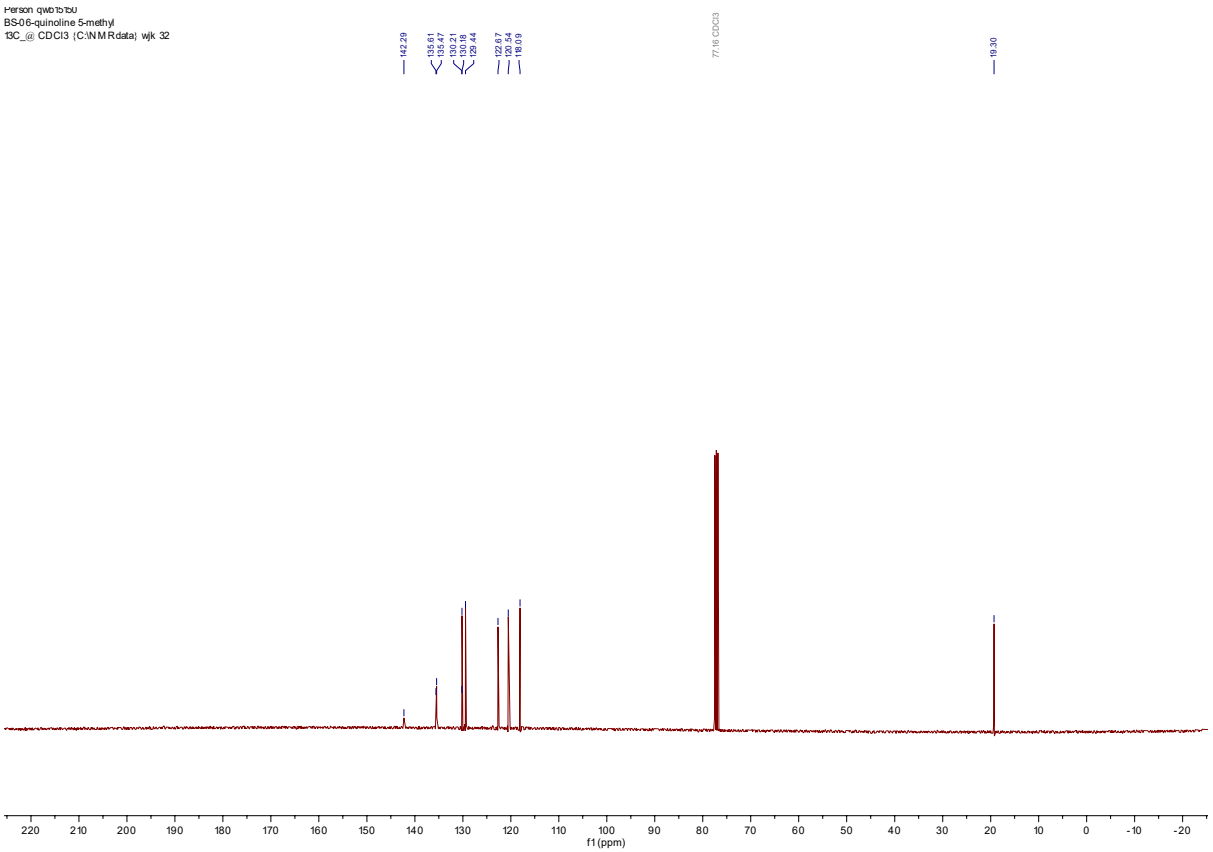


4.2 5-Methylquinoline *N*-oxide **3b**

^{1}H NMR Spectrum

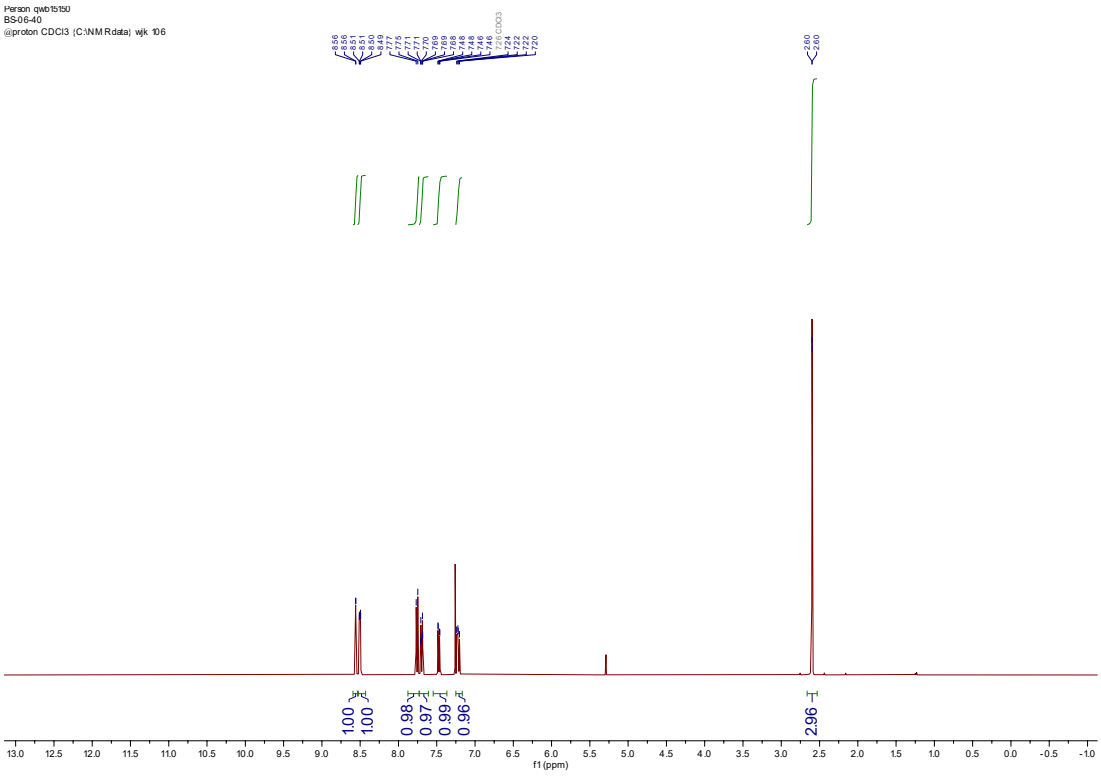


^{13}C NMR Spectrum

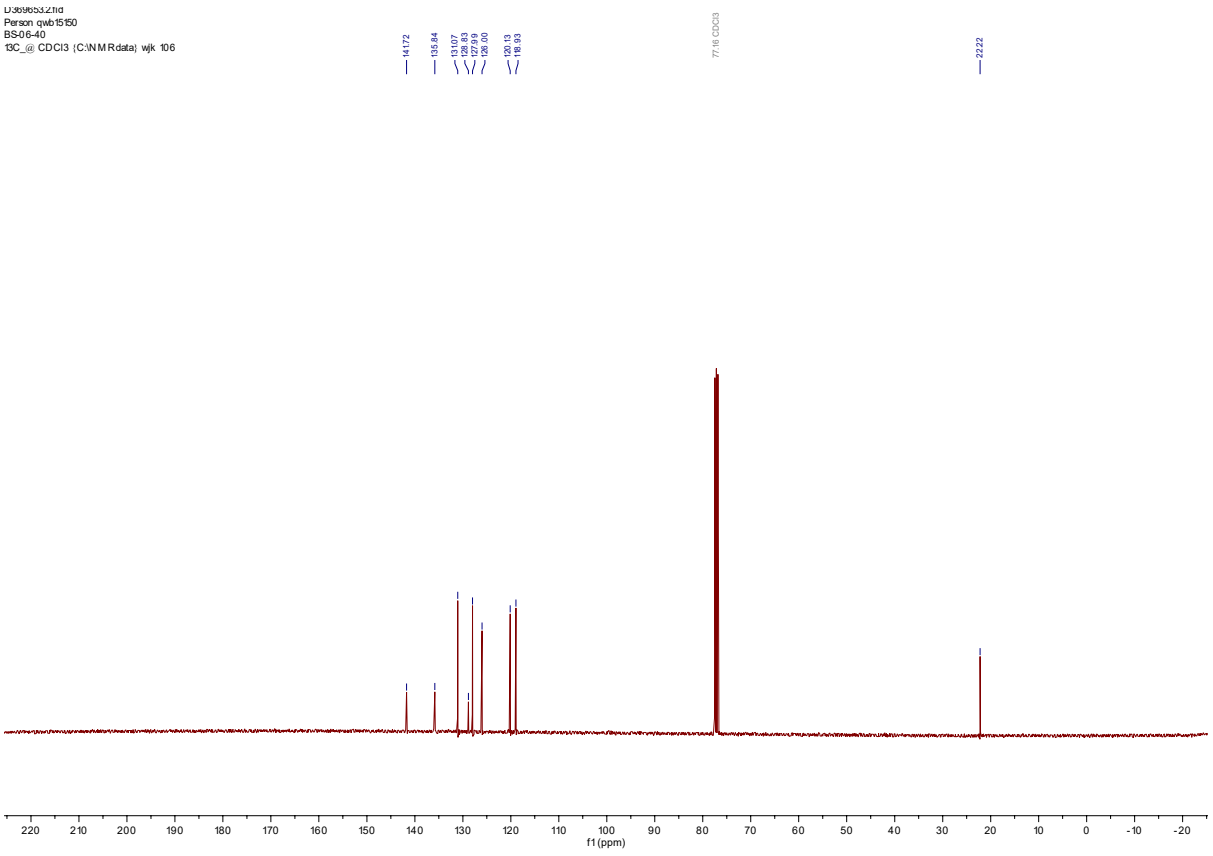


4.3 7-Methylquinoline *N*-oxide **3c**

^{1}H NMR Spectrum

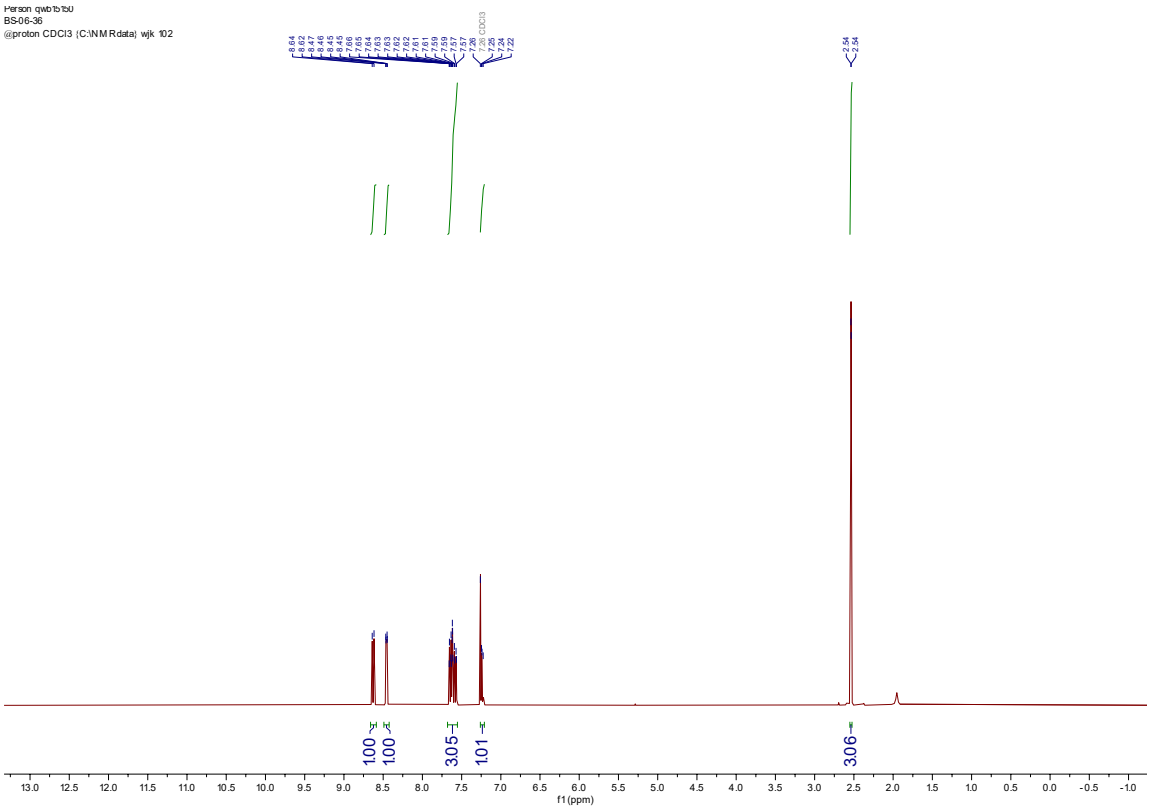


^{13}C NMR Spectrum

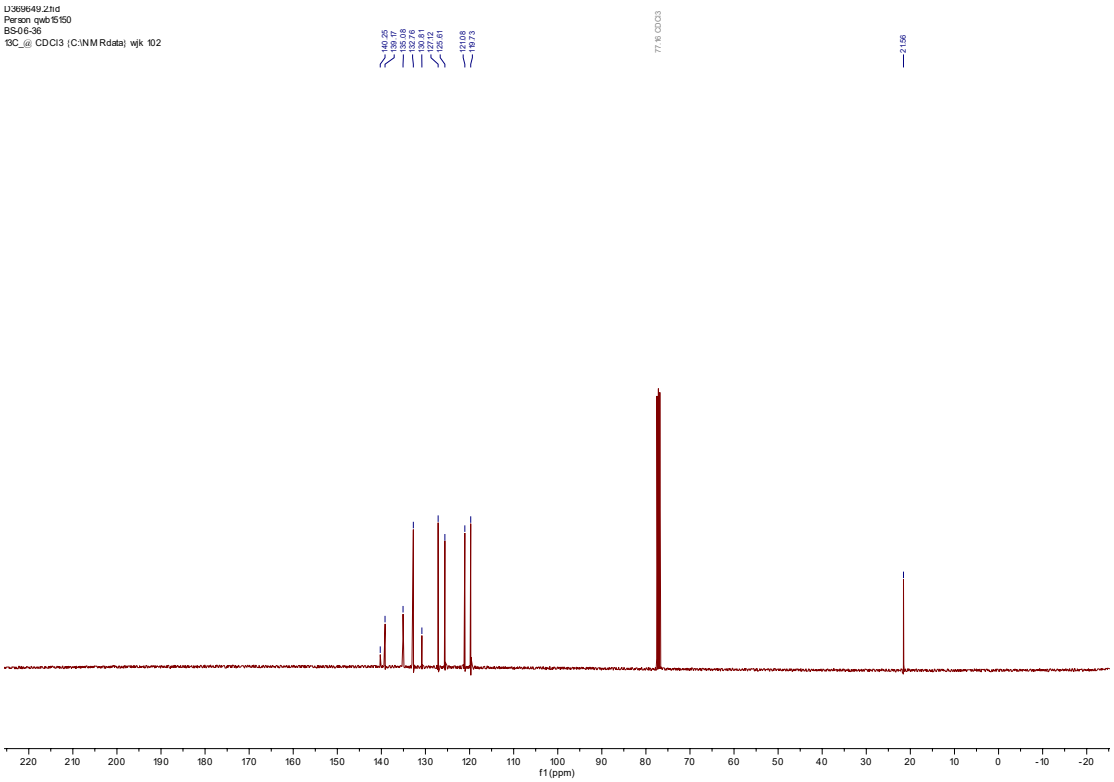


4.4 6-Methylquinoline *N*-oxide **3d**

^{1}H NMR Spectrum

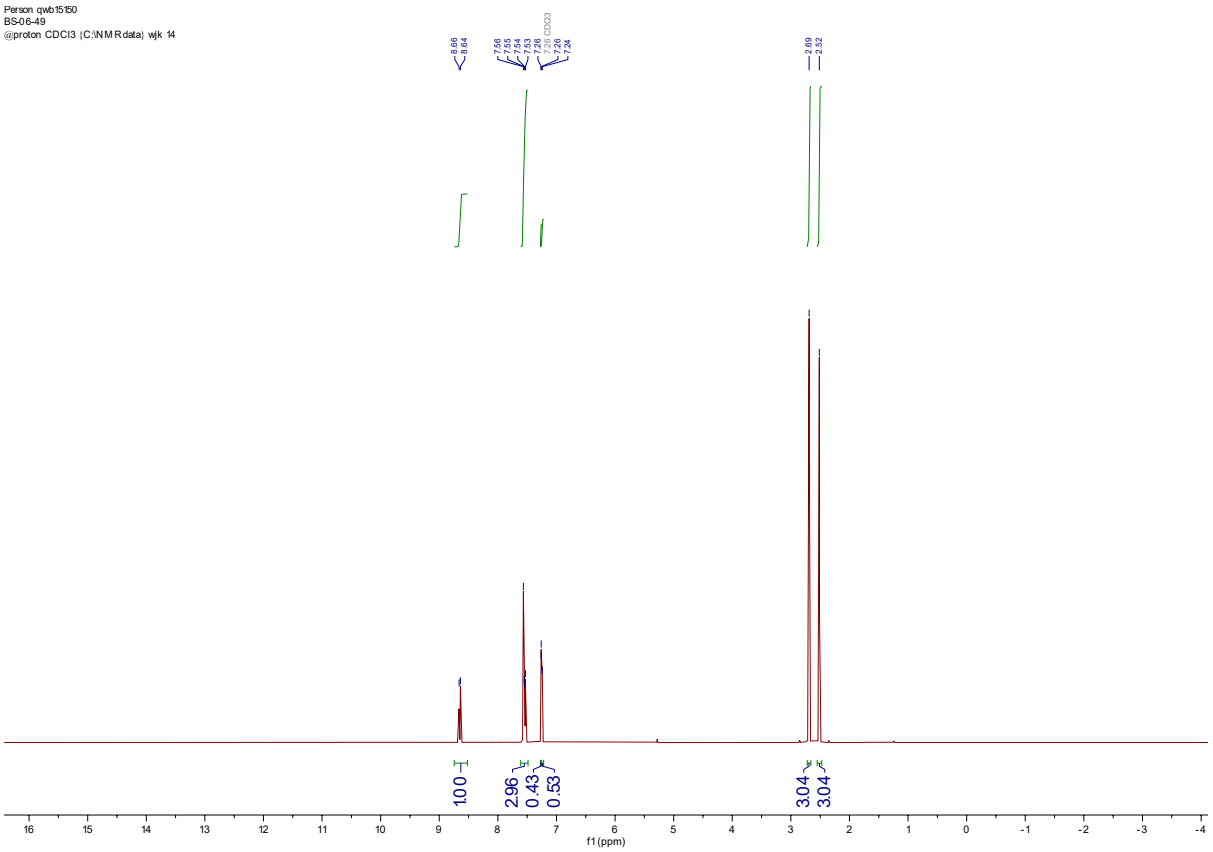


^{13}C NMR Spectrum

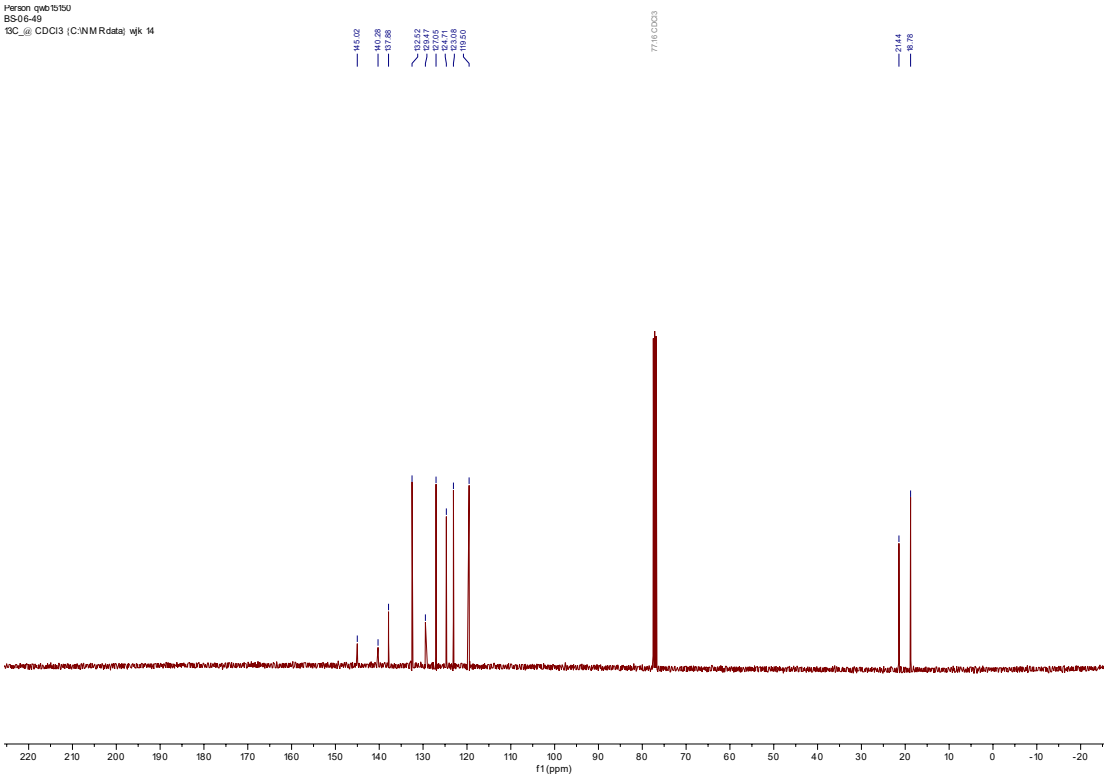


4.5 2-,6-(Dimethyl)quinoline *N*-oxide **3e**

^{1}H NMR Spectrum

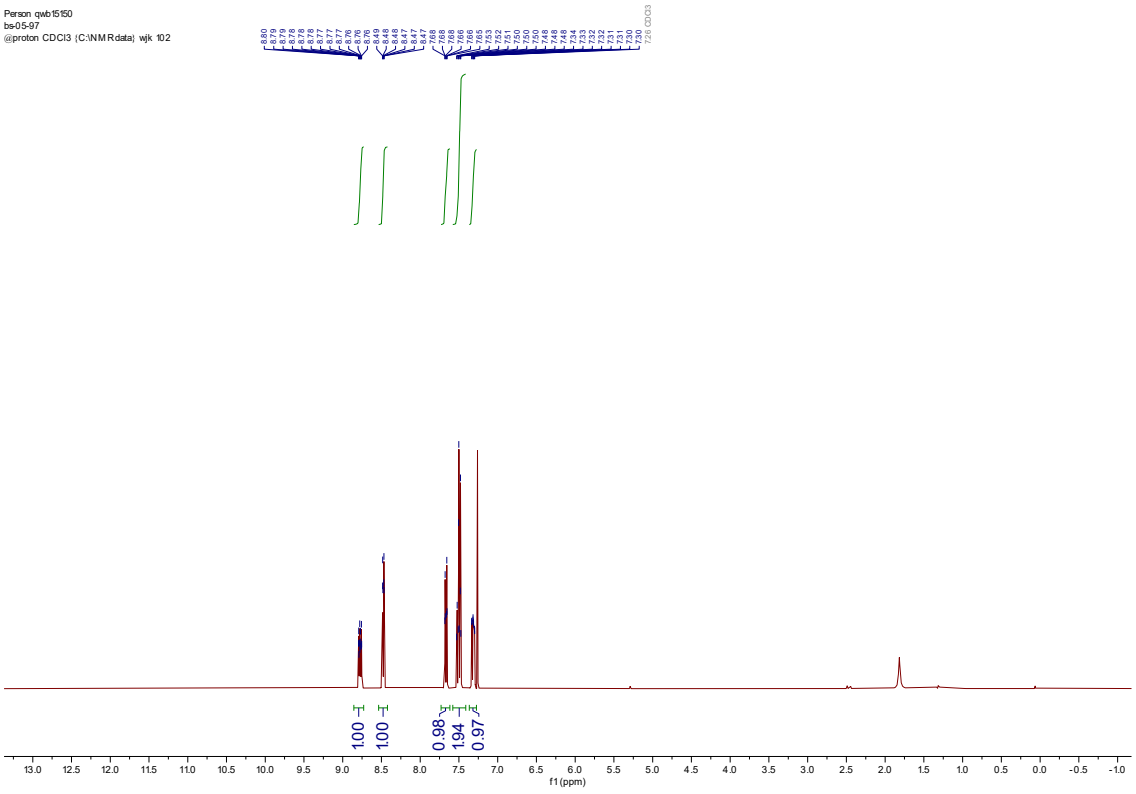


^{13}C NMR Spectrum

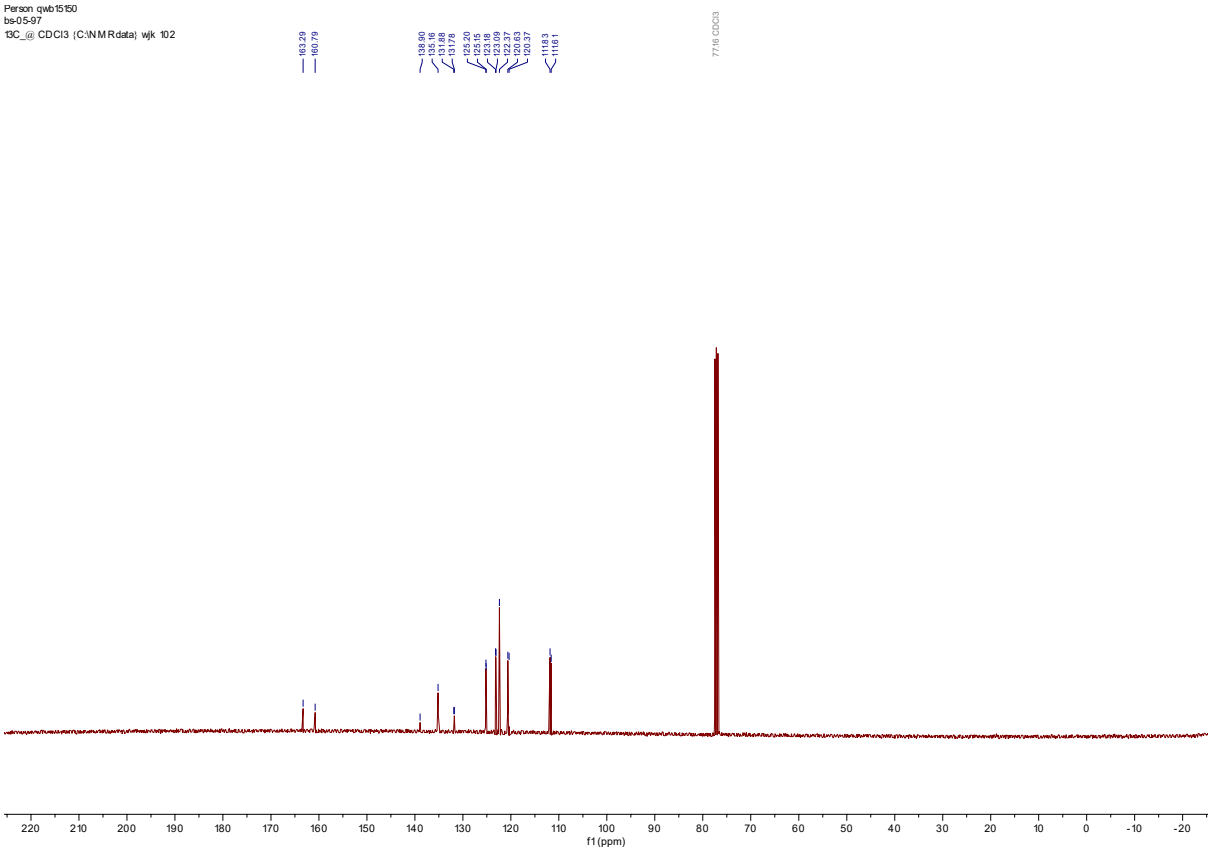


4.6 6-Fluoroquinoline *N*-oxide **3f**

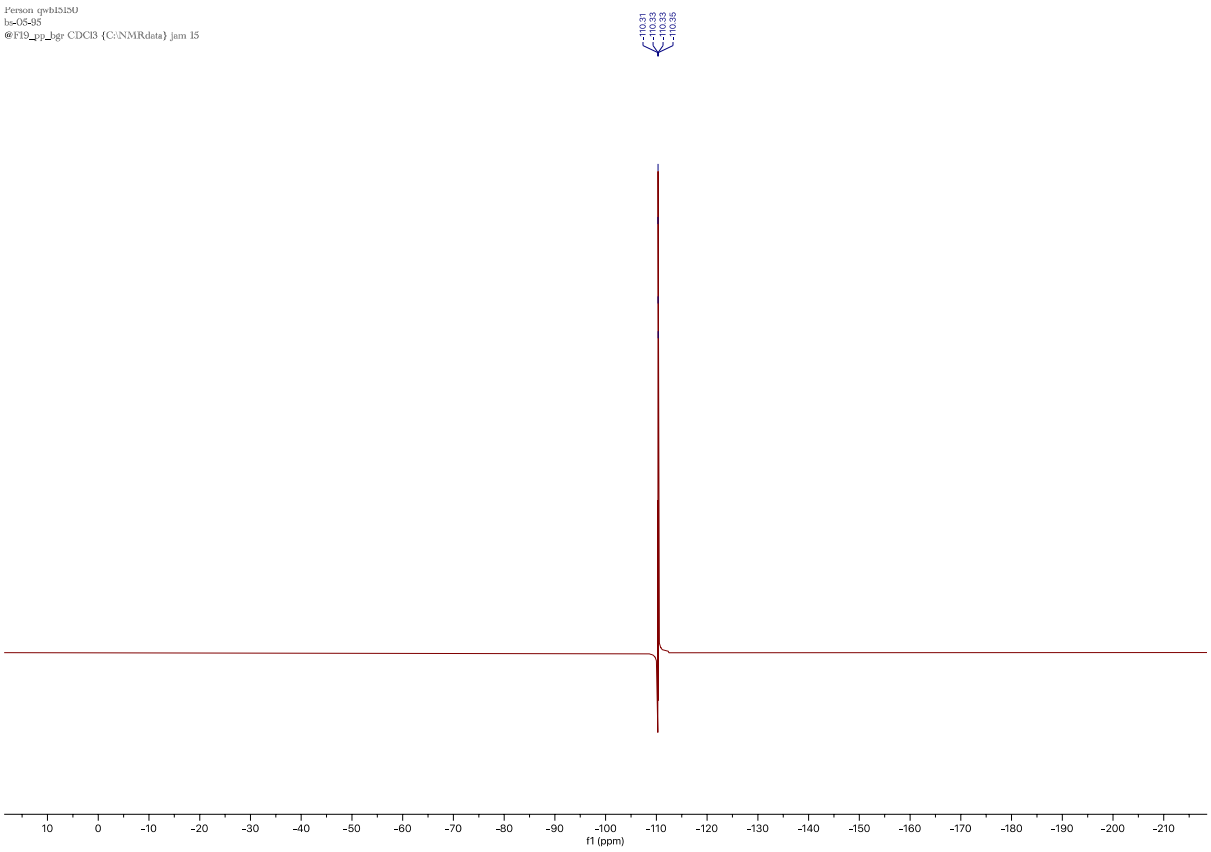
^{1}H NMR Spectrum



^{13}C NMR Spectrum

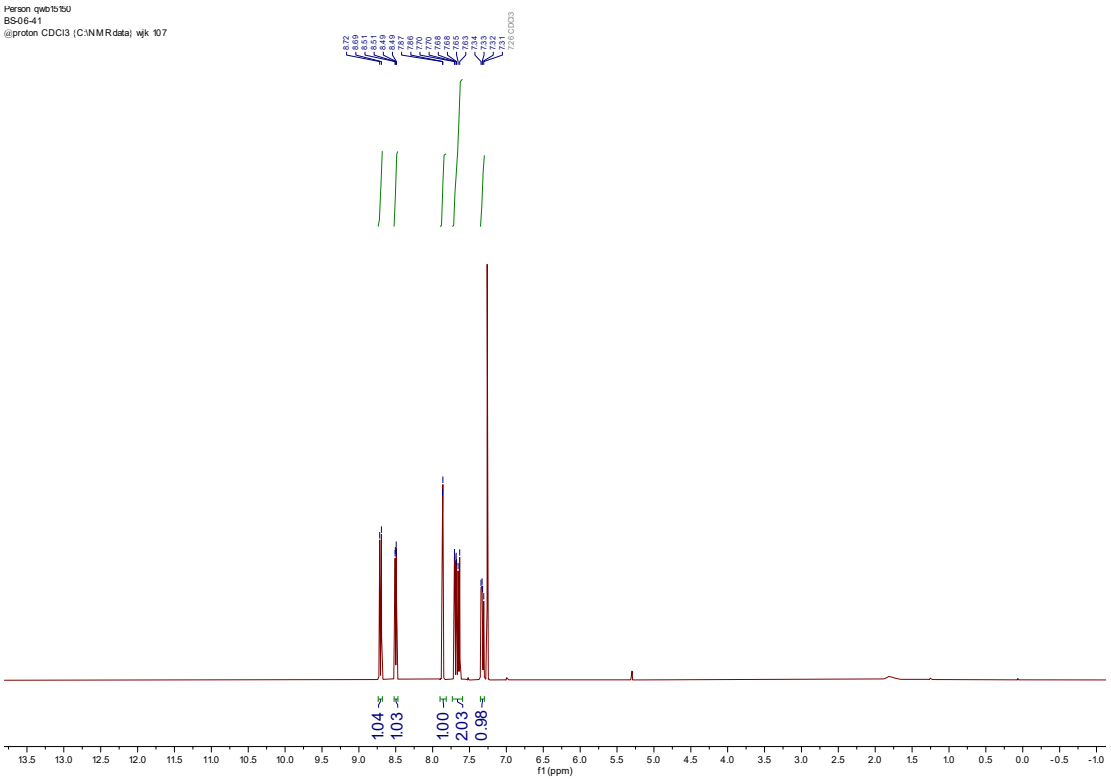


^{19}F NMR Spectrum

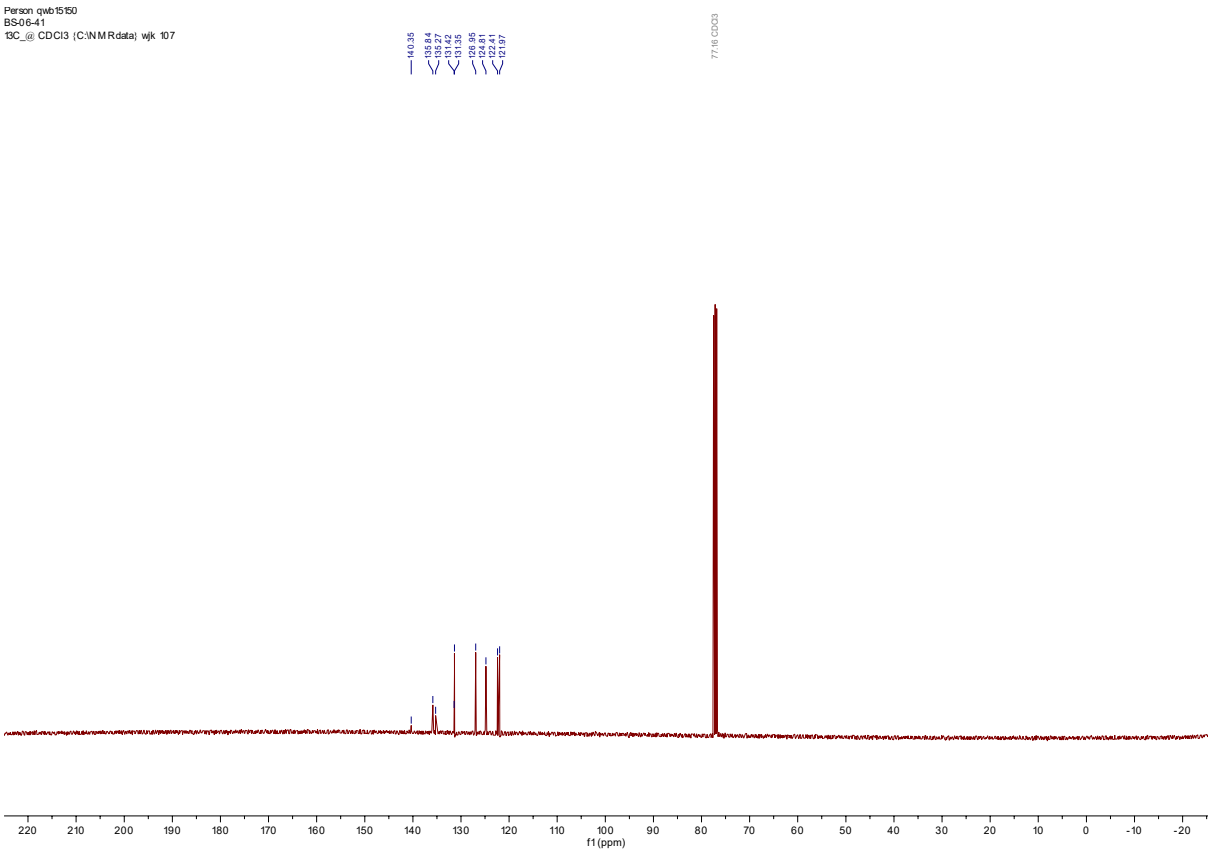


4.7 6-Chloroquinoline *N*-oxide **3g**

^{1}H NMR Spectrum

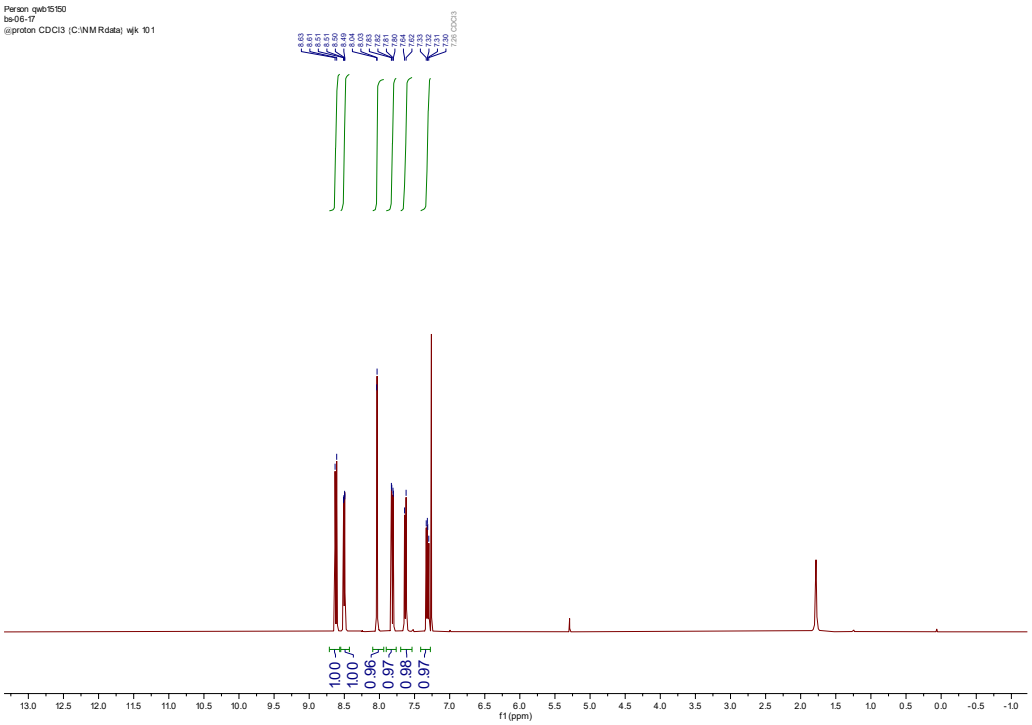


^{13}C NMR Spectrum

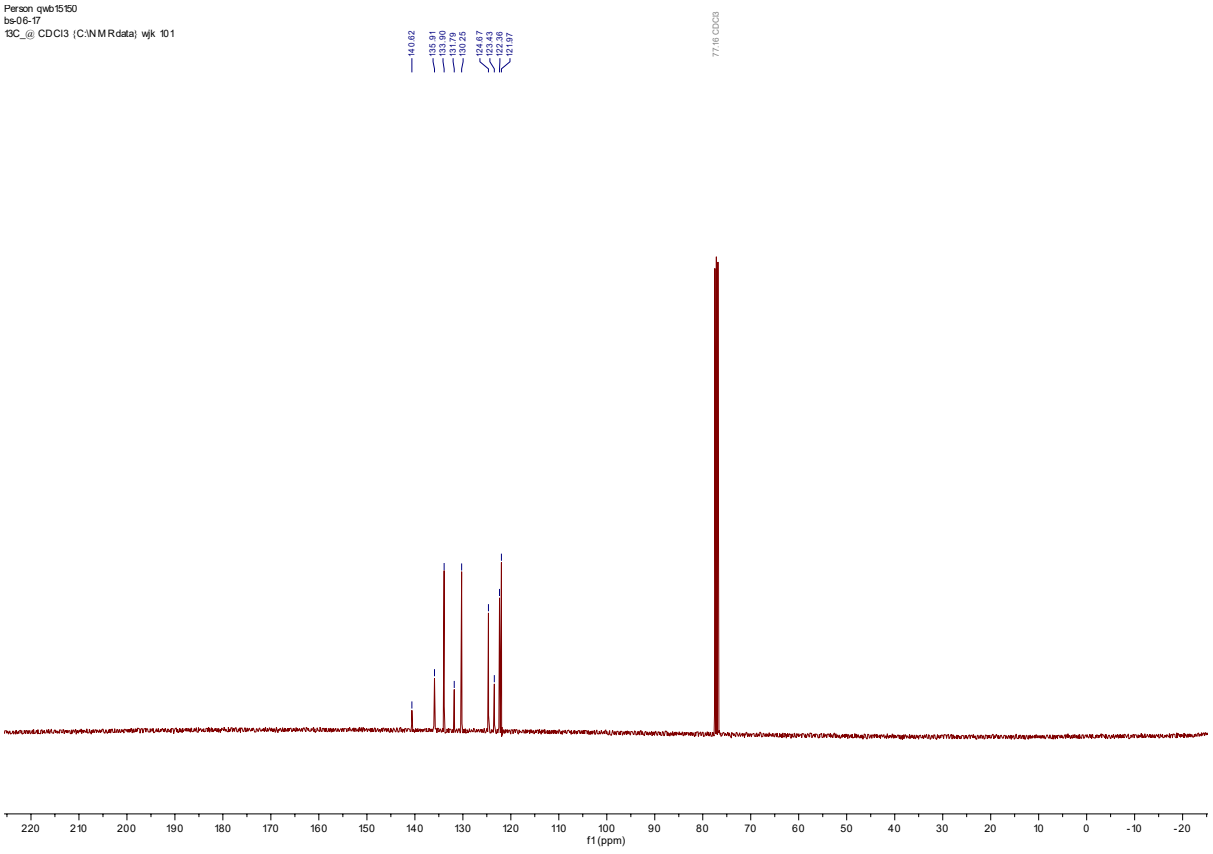


4.8 6-Bromoquinoline *N*-oxide **3h**

^{1}H NMR Spectrum

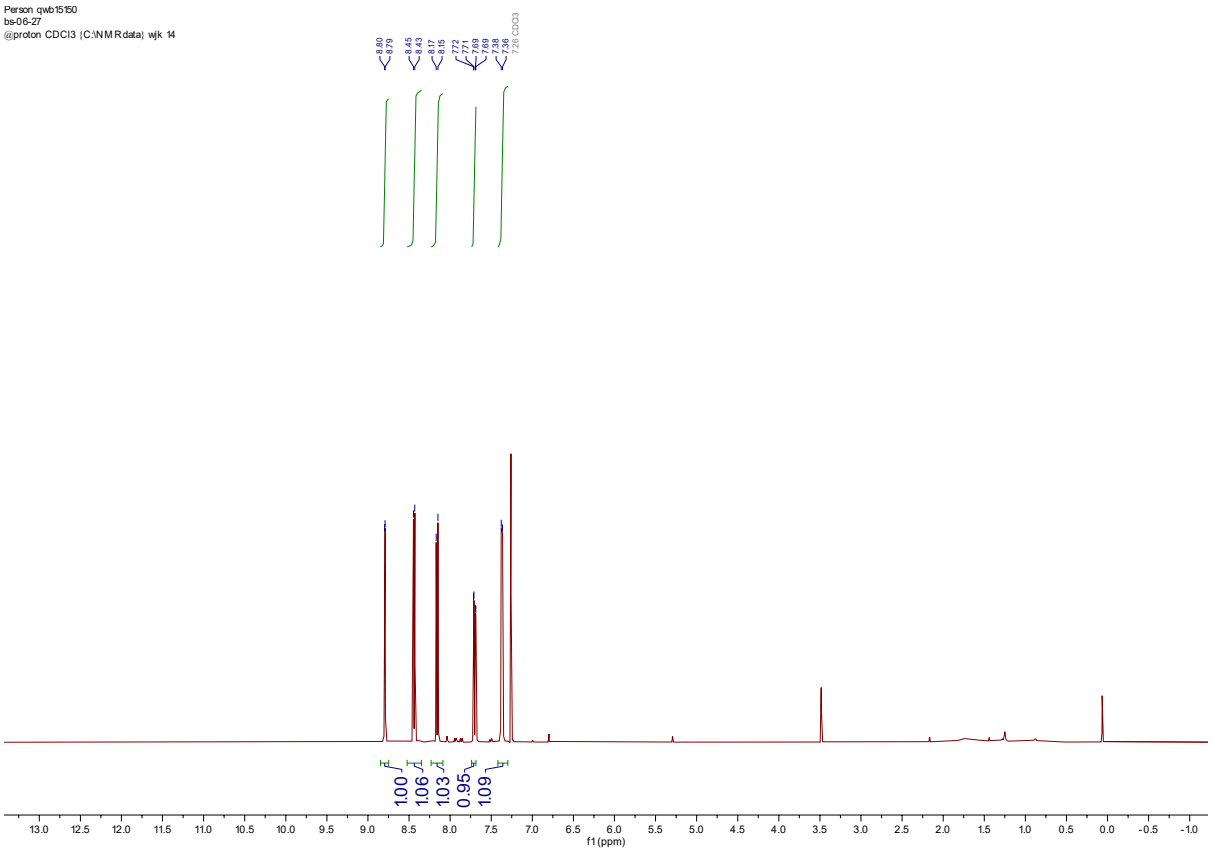


^{13}C NMR Spectrum

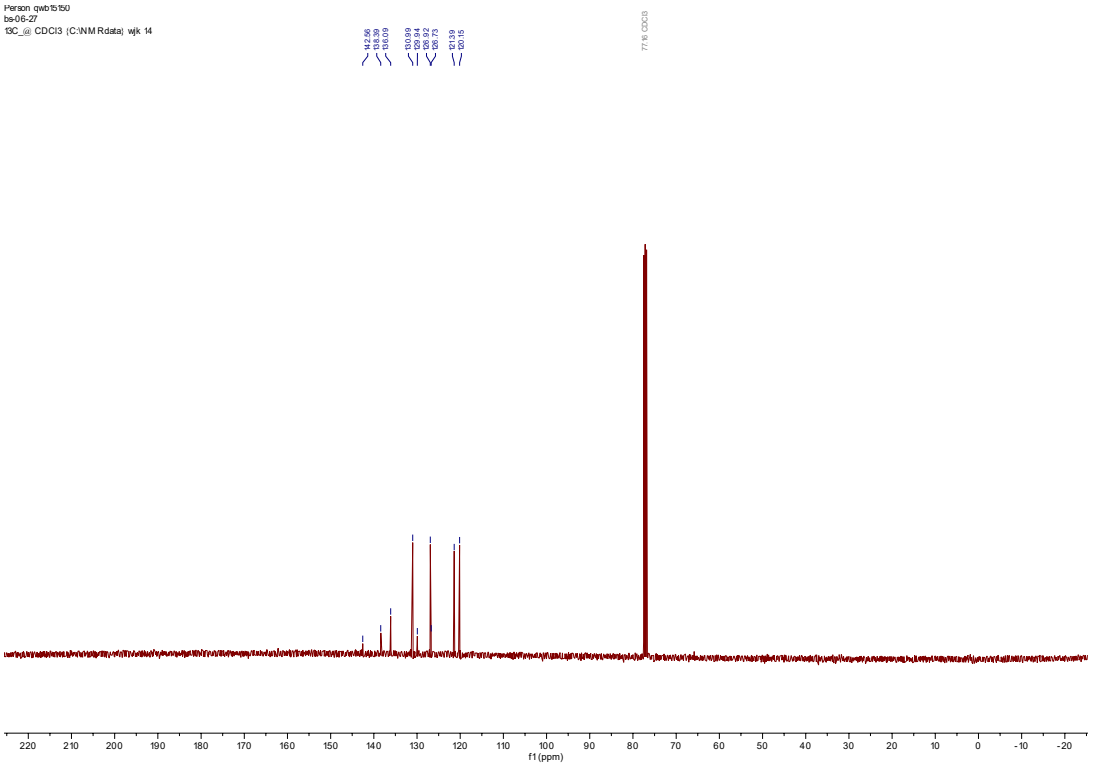


4.9 4,7-Dichloroquinoline *N*-oxide **3i**

^{1}H NMR Spectrum

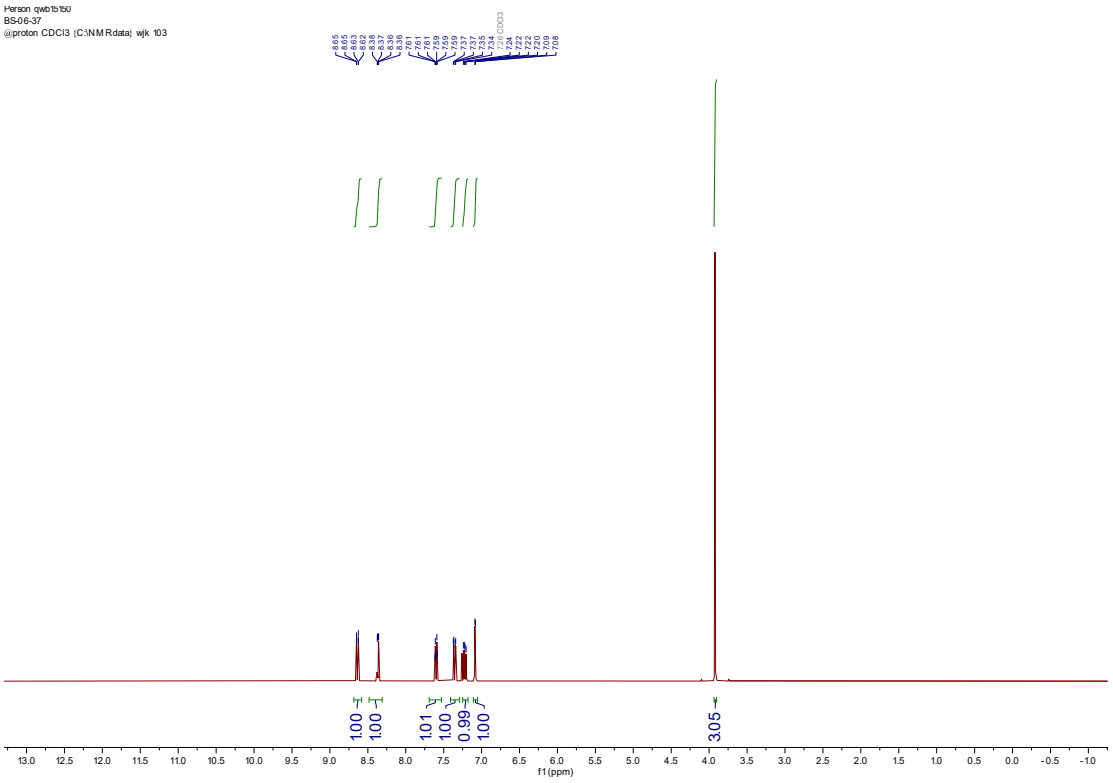


^{13}C NMR Spectrum

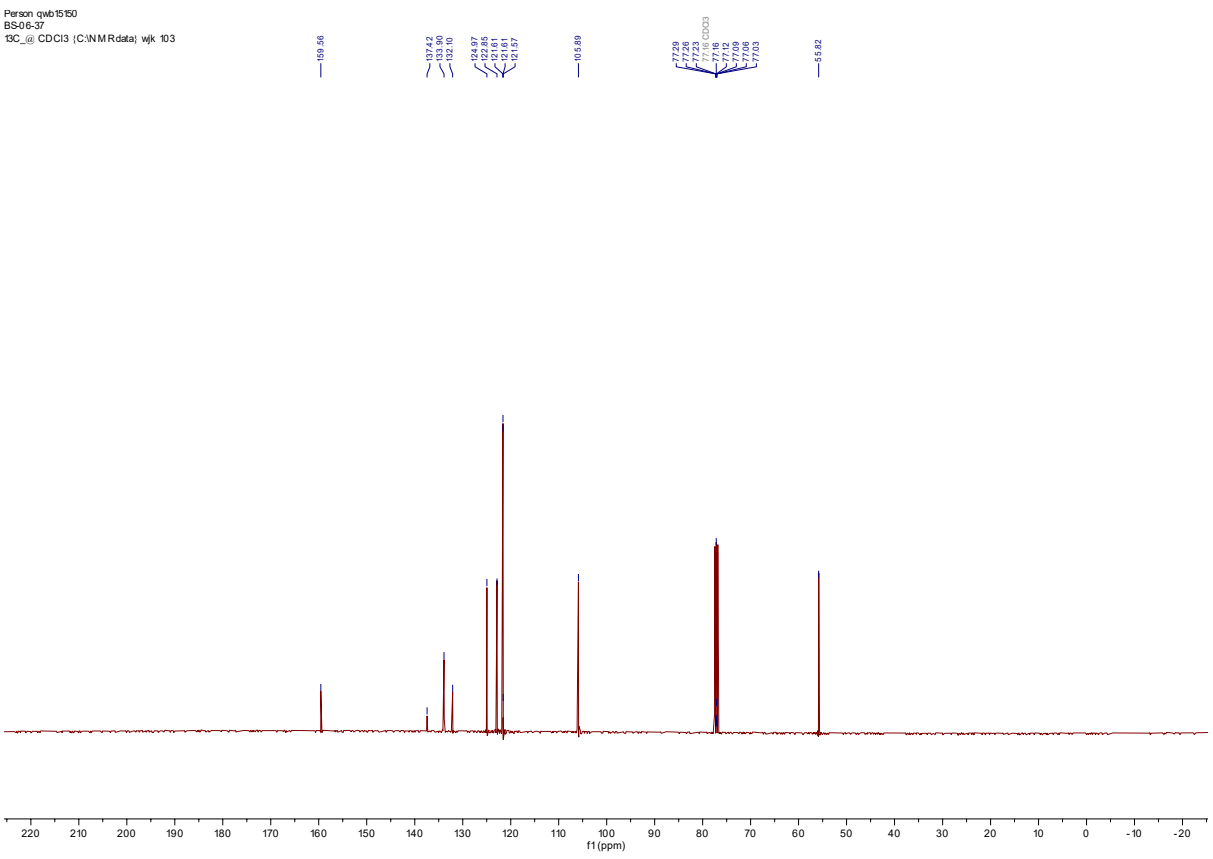


4.10 6-Methoxyquinoline *N*-oxide **3j**

^{1}H NMR Spectrum

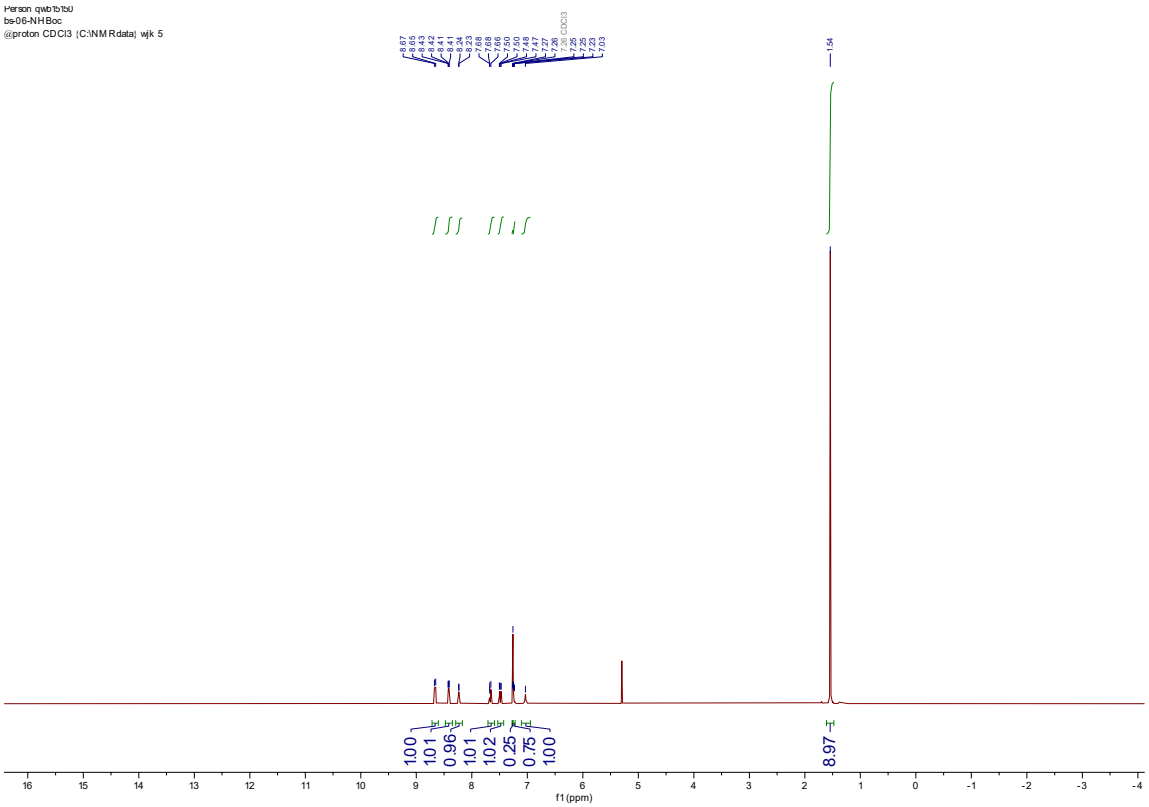


^{13}C NMR Spectrum

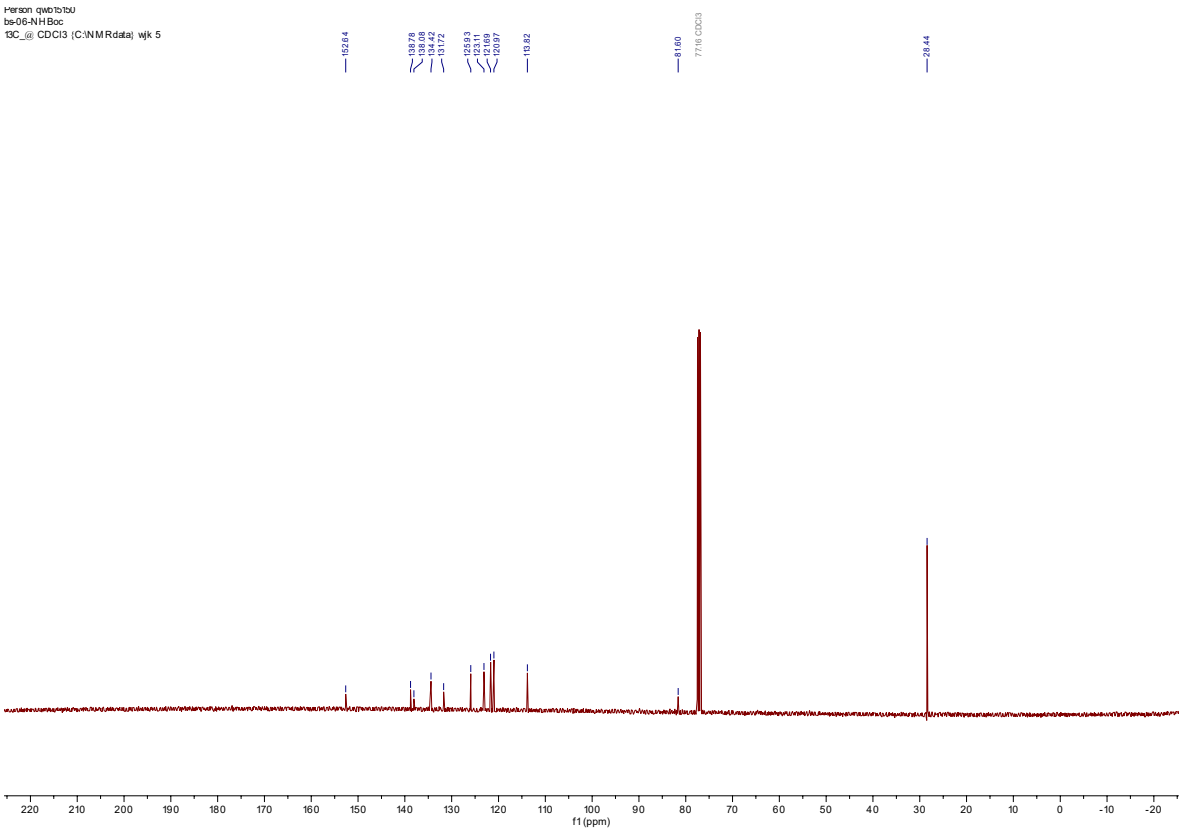


4.11 6-((*tert*-Butoxycarbonyl)amino)quinoline *N*-oxide **3k**

^{1}H NMR Spectrum

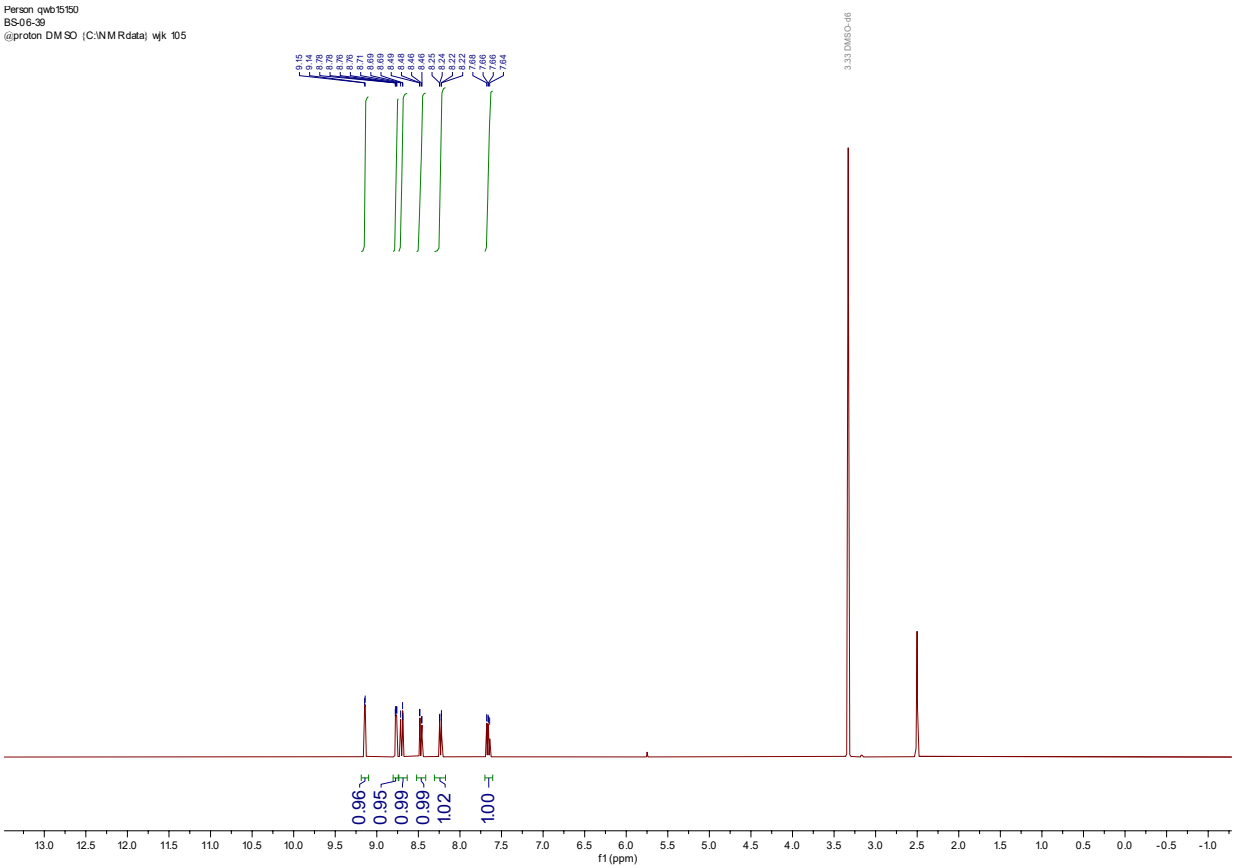


^{13}C NMR Spectrum

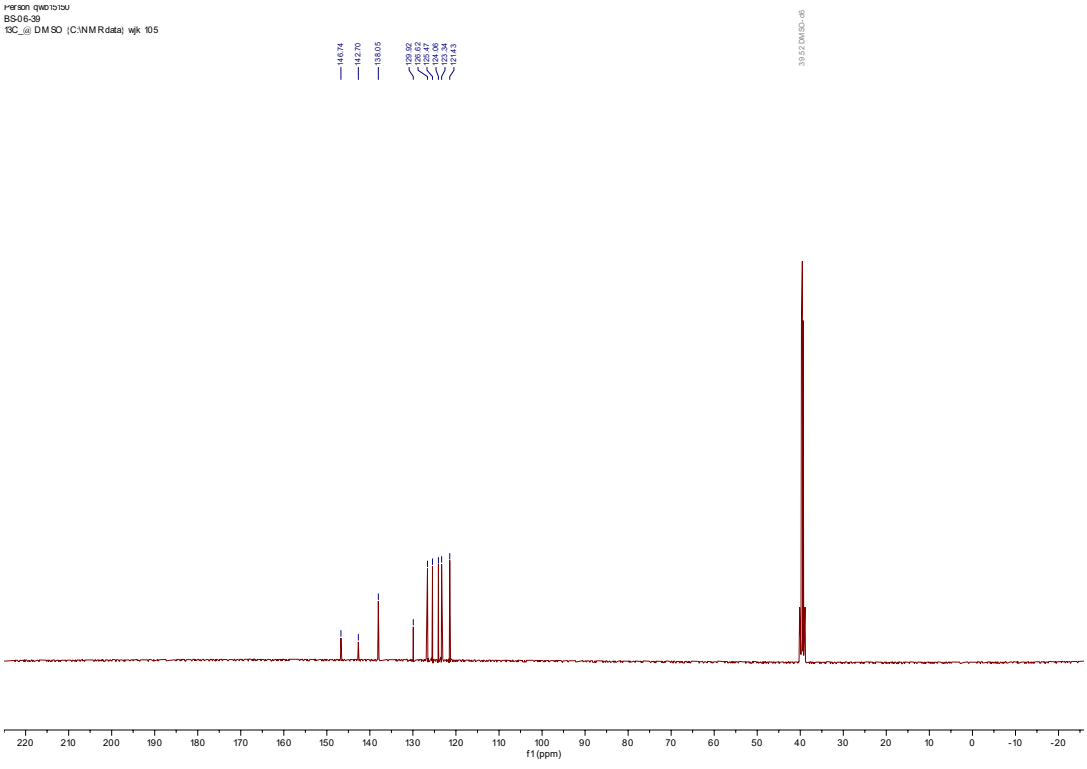


4.12 6-Nitroquinoline *N*-oxide **3l**

^{1}H NMR Spectrum

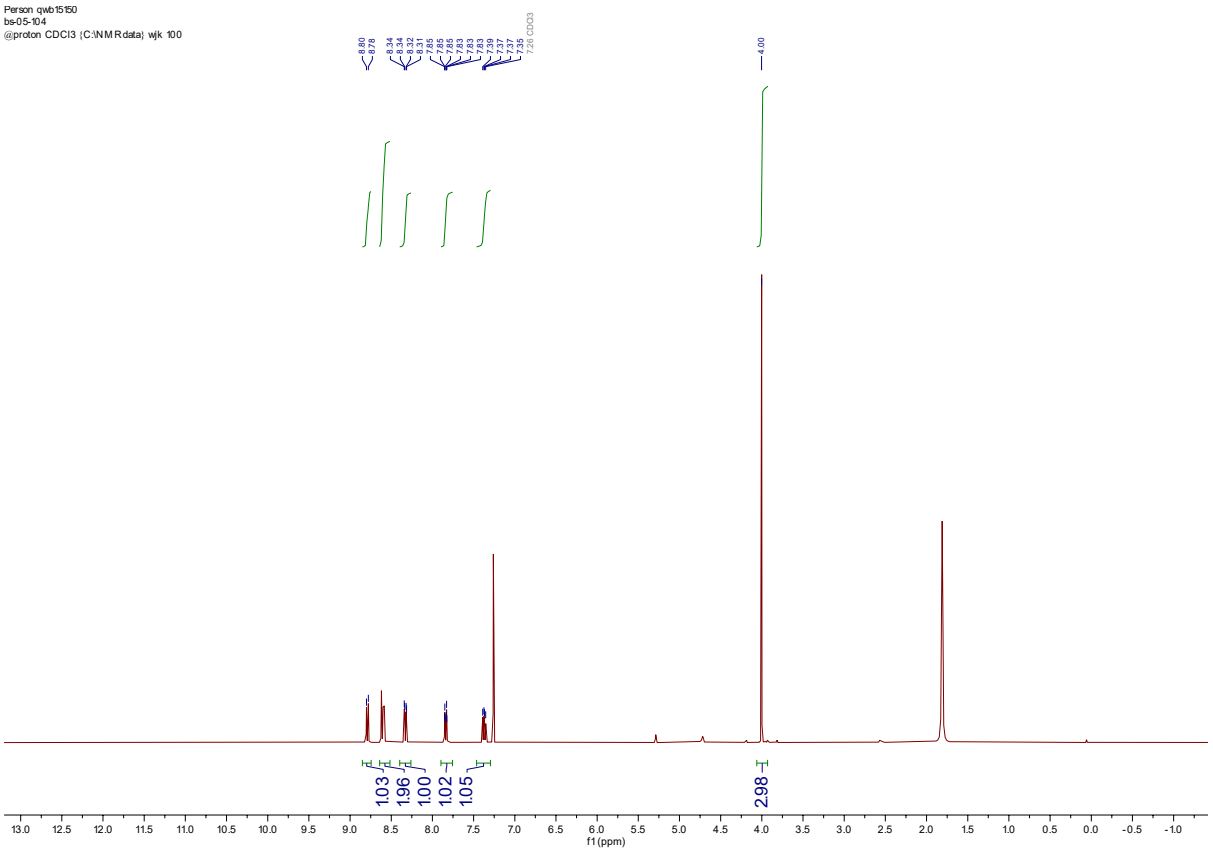


^{13}C NMR Spectrum

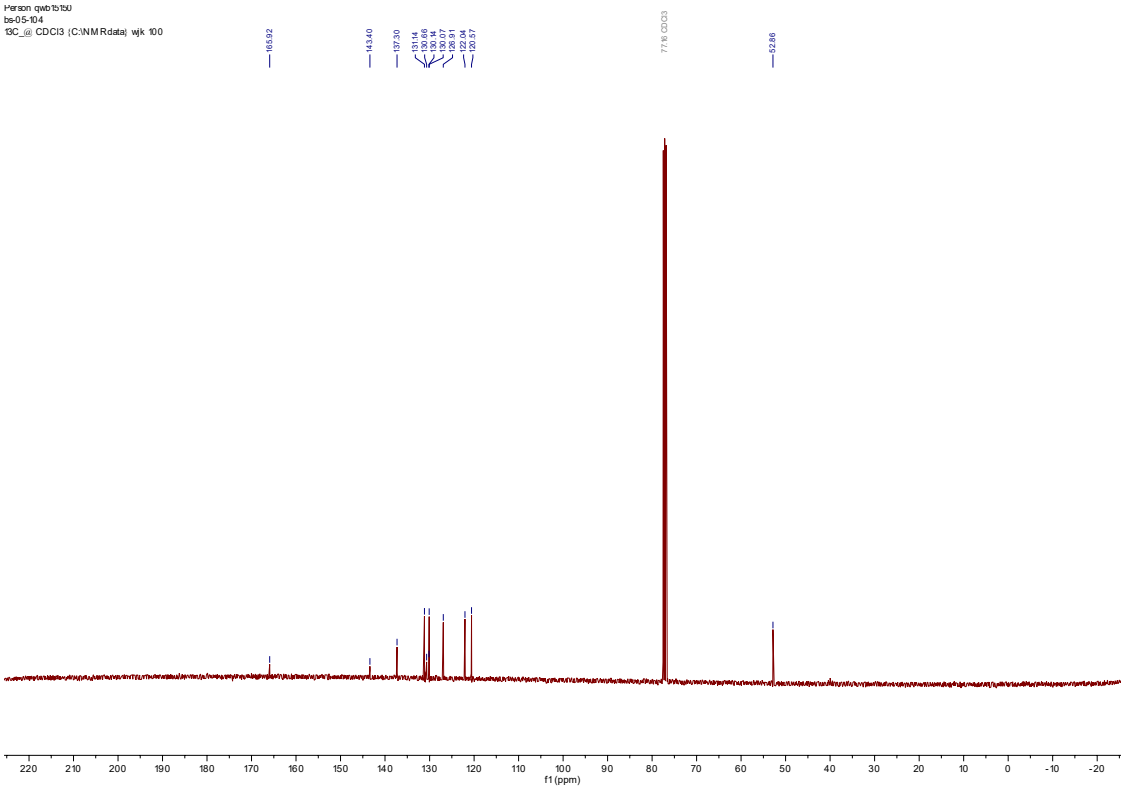


4.13 6-(Methoxycarbonyl)quinoline *N*-oxide **3m**

^{1}H NMR Spectrum

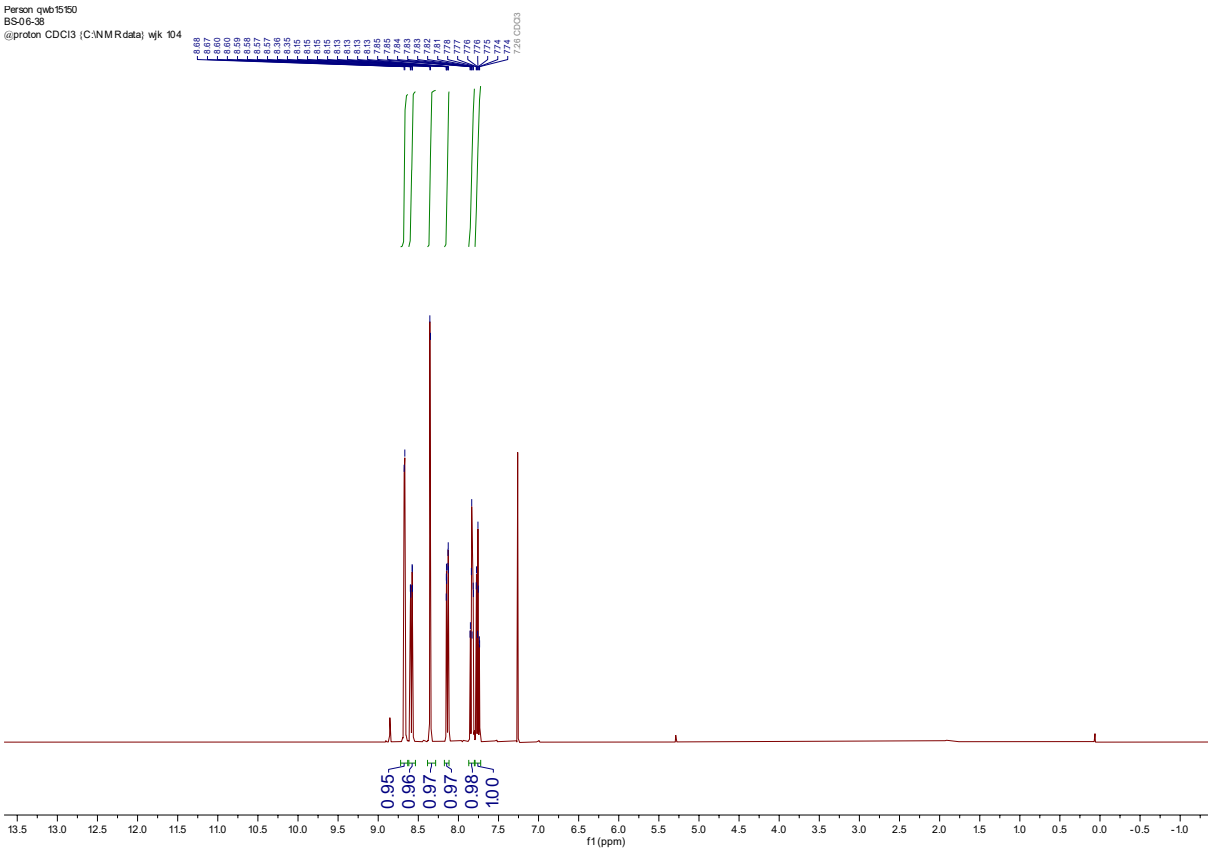


^{13}C NMR Spectrum

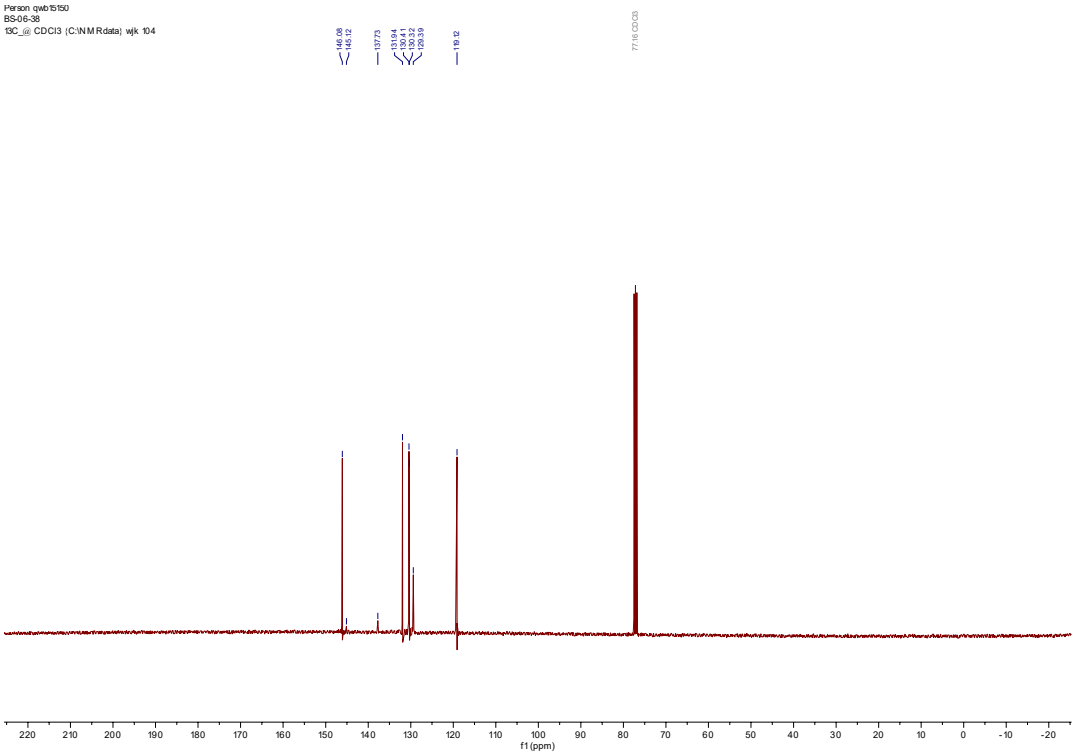


4.14 Quinoxaline *N*-oxide **3n**

^{1}H NMR Spectrum

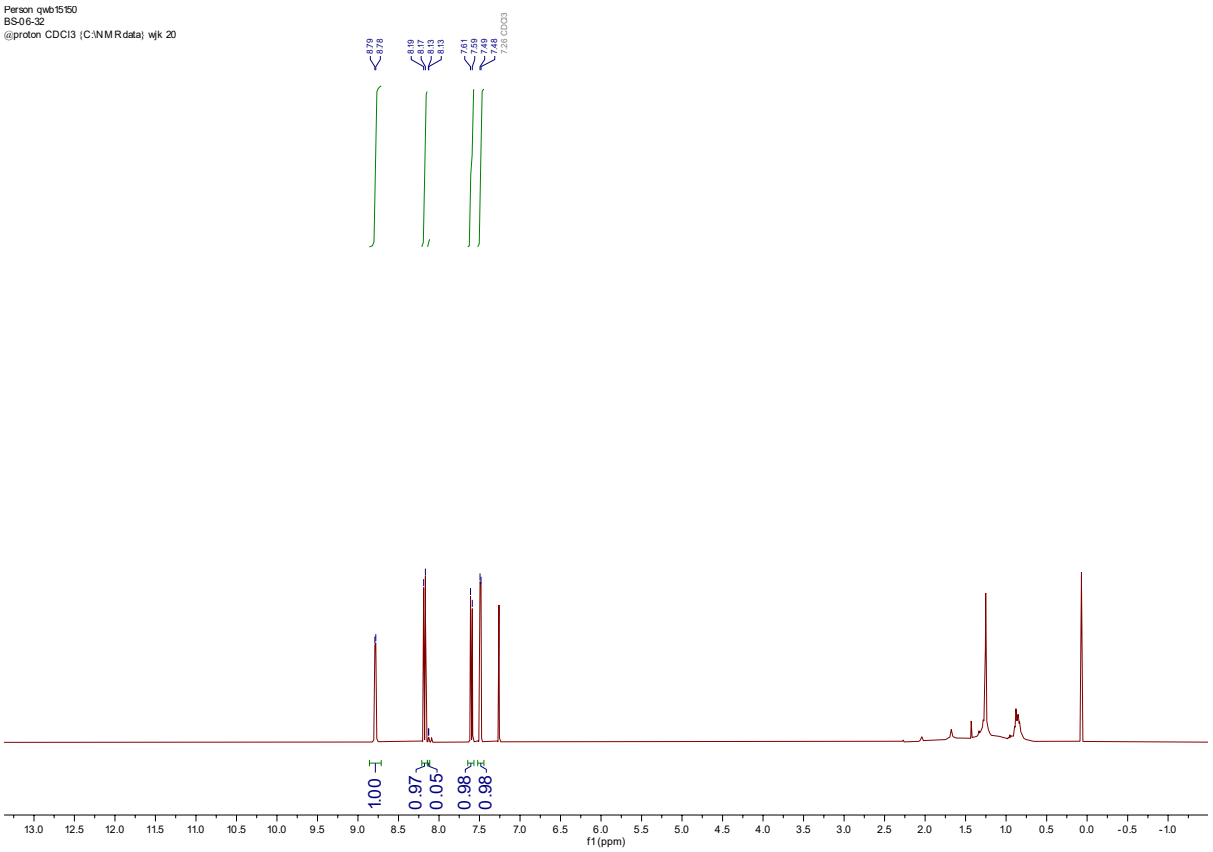


^{13}C NMR Spectrum

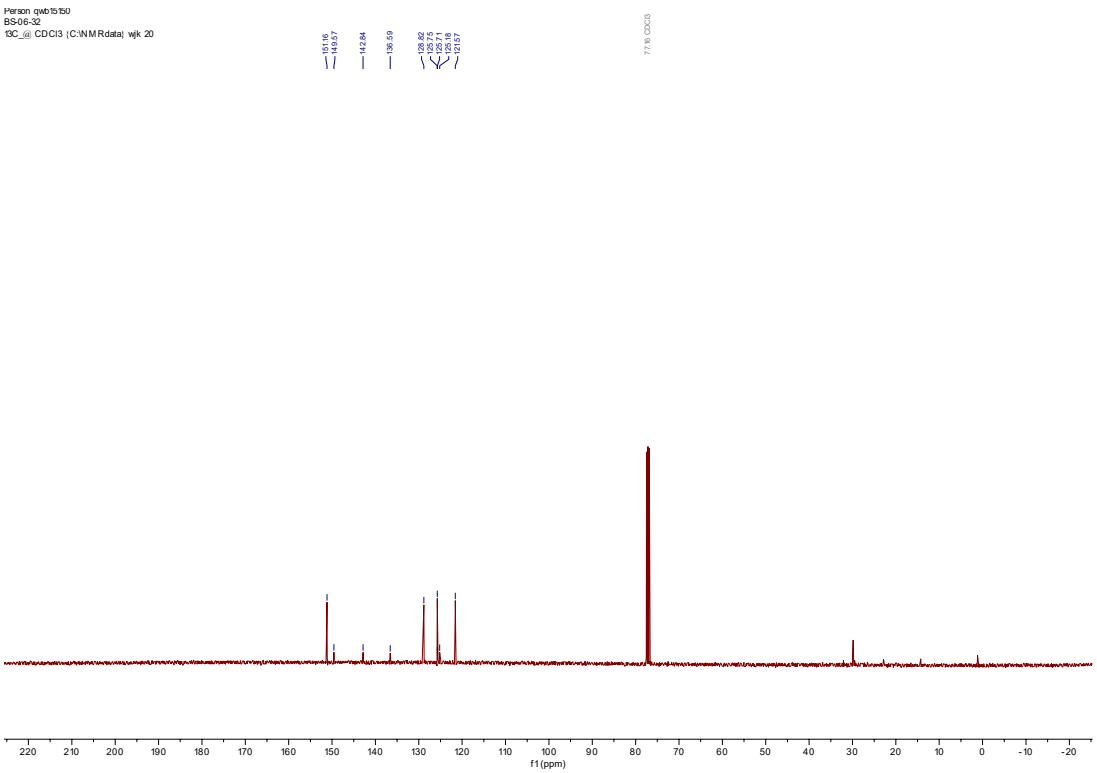


4.15 8-^{2}H-4,7-Dichloroquinoline **d-4i**

^{1}H NMR Spectrum

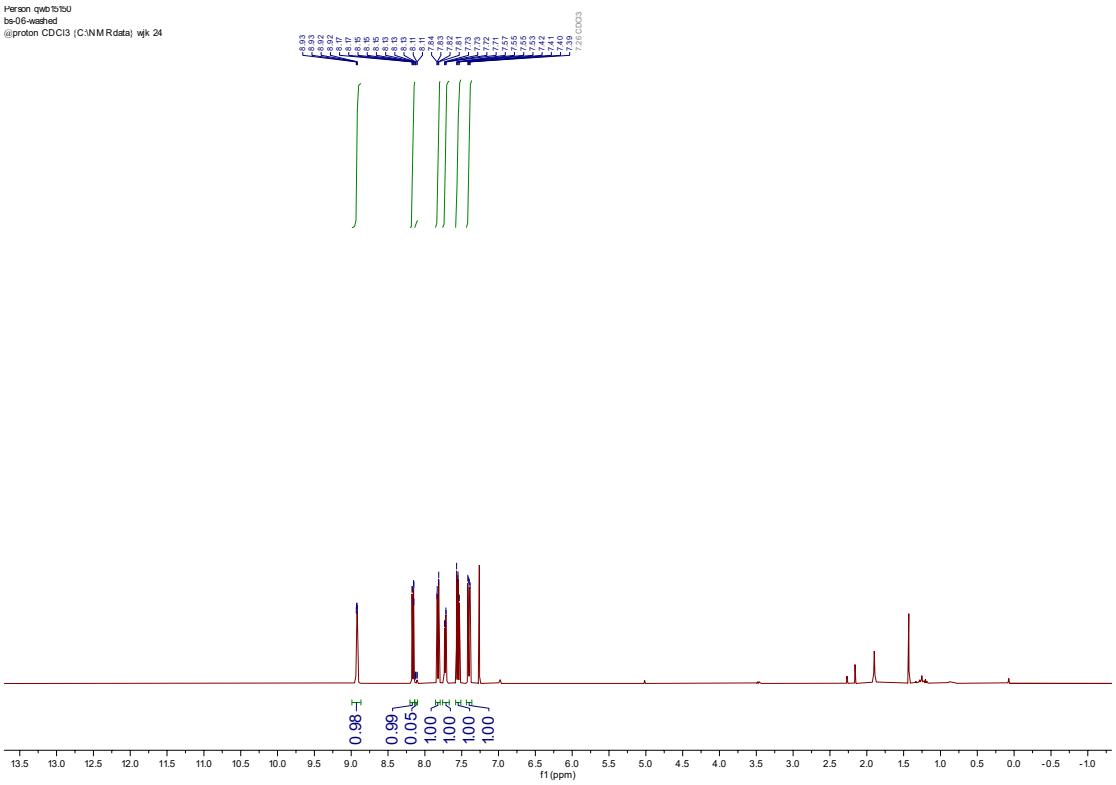


^{13}C NMR Spectrum

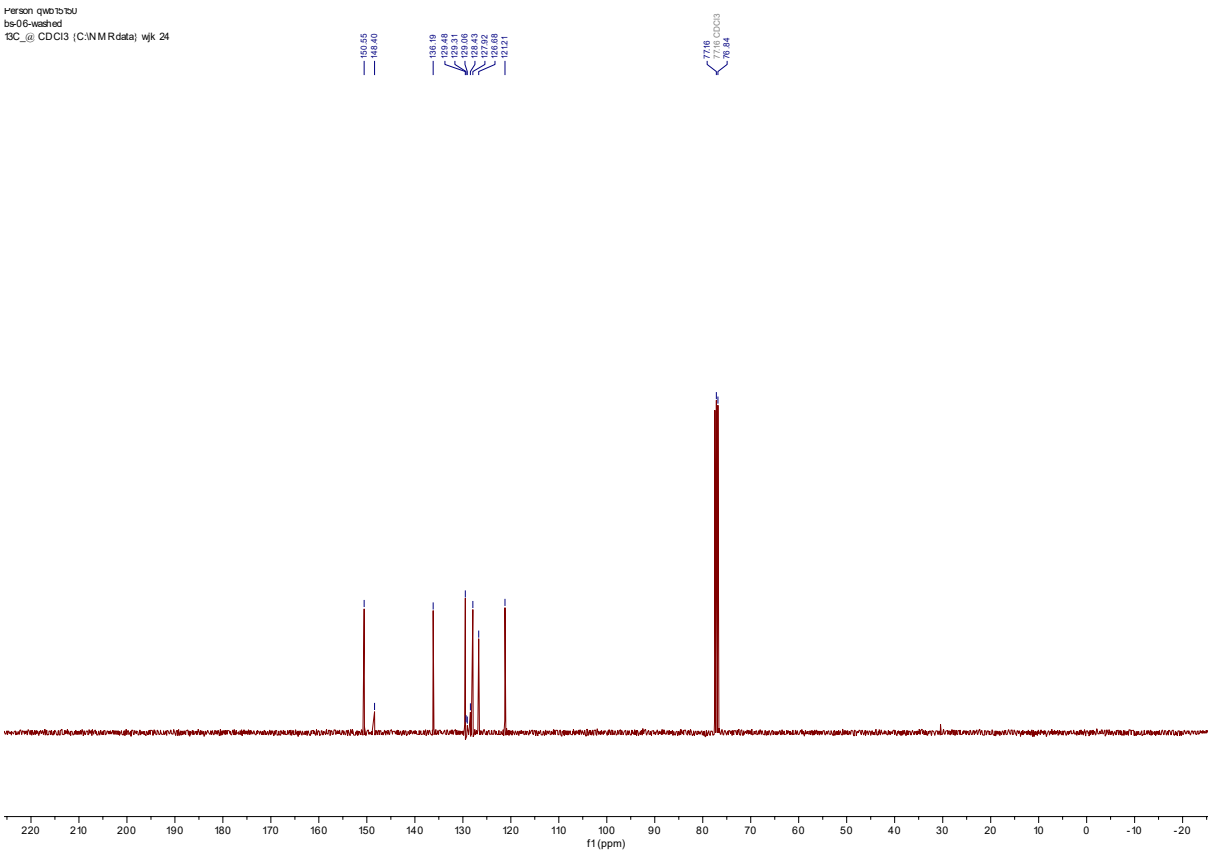


4.16 8-^{2}H-Quinoline **d-4a** (95%D sample)

^{1}H NMR Spectrum

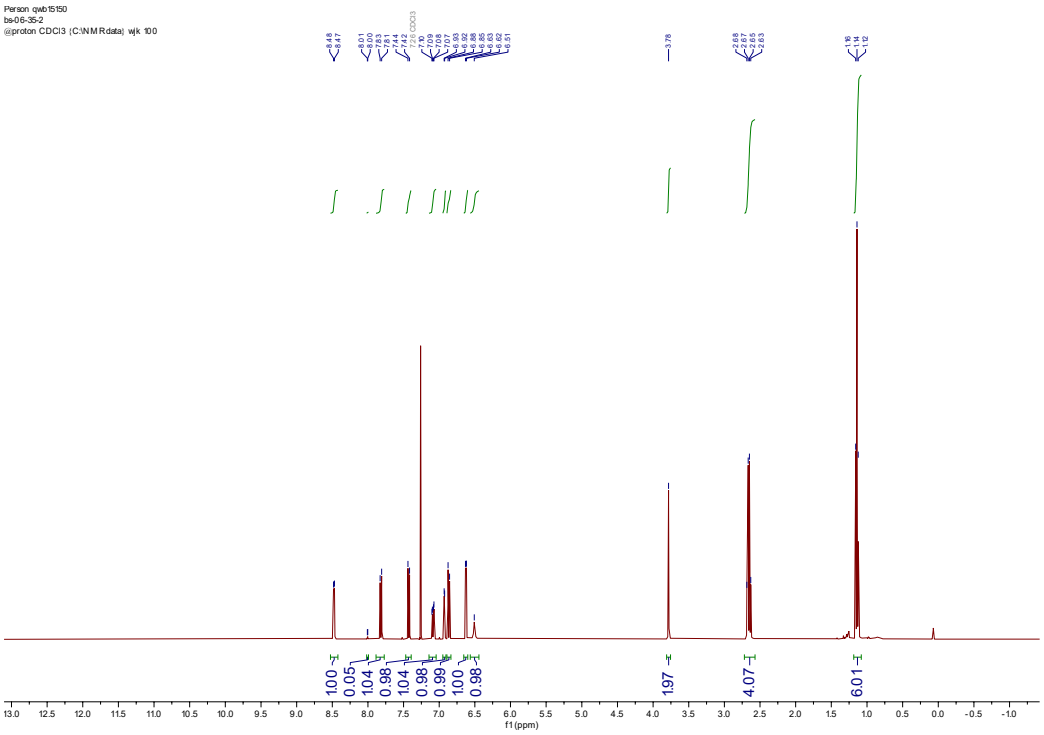


^{13}C NMR Spectrum



4.17 8-^{2}H-Amodiaquine **d-6**

^{1}H NMR Spectrum



^{13}C NMR Spectrum