Supporting Information

Cooperative Silver-Base Catalysis for Multi-Deuteration of Heterocyclic *N*-Oxides with D_2O

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1. General Information

1.1 Experiments and Reagents

Unless noted otherwise, all experiments were carried out under the protection of nitrogen atmosphere, with oven-dried glassware and magnetic stirring bar. All laboratory reagents are purchased from market suppliers, including Bide, Aladdin, Sigma Aldrich, Ningbo Cuiying Chemicals. All reagents are used directly without further purification unless otherwise specified. The deuteroxide (D_2O) used in the experiment was purchased from Ningbo Cuiying Chemicals.

1.2 TLC and Chromatography

Analytic thin-layer chromatography (Leyan chemicals) was used for checking the formation of unexpected side reactions. Visualization was achieved by ultraviolet light (254 nm and 365 nm) and iodine staining. Flash chromatography was performed on silica gel (200-300 mesh) with the indicated solvent systems.

1.3 Spectroscopy Analysis

The gas chromatography-mass spectroscopy (GC-MS) are recorded on an Agilent 6890N GC-system with an Agilent 5973 Network Mass Selective Detector (electron ionization), and a HP-5MS column (30 m, 0.25 mm × 0.25 μm).

^1H NMR (400 MHz) is recorded on a Bruker Ascend 400 spectrometer and chemical shifts are reported in ppm down field from TMS and are referenced to residual proton in $CDCl_3$ or Chloroform-d. The spectra for deuterated substrates are reported as observed, while the integration difference less than 5% are ignored. The NMR data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet with J = coupling constant in Hz, and the deuterated position are marked as“Labelled”.

2. Calculation methods for deuterium-incorporation

The ratio of deuterium-incorporation is based on GC-MS and ^{1}H-NMR. Firstly, the total D-incorporation of the material is by GC-MS, and then its deuterium distribution is determined by nuclear magnetic resonance detection. For some materials that have positions not deuteration, this position can be directly used as an internal standard to calculate the deuterium-incorporation at other positions through ^{1}H-NMR (calculated by comparing with undetermined hydrogen).

2.1 Calculation method of D-incorporation by GC-MS

The calculation of averaged D-incorporation ($\%\ average\ D$) :

$$\%\ avertage\ D = \frac{Mw(D) - Mw(S)}{N} \times 100\%$$

The calculation of total D-incorporation ($\%\ total\ D$) :

$$\%\ total\ D = Mw(D) - Mw(S) \times 100\%$$

Here into

$$Mw(D) = \frac{(M-1) \times A(M-1) + M \times A(M) + (M+1) \times A(M+1) + \cdots + (M+N+1) \times A(M+N+1)}{\sum A}$$

$$Mw(S) = \frac{(M-1) \times A(M-1) + M \times A(M) + (M+1) \times A(M+1)}{\sum A}$$

N = The number of hydrogen atoms actually deuterated
A = The relative abundance of the peak of interest
$Mw(D)$ = The weighted average molecular weight of the deuterated product
$Mw(S)$ = The weighted average molecular weight of the substrate

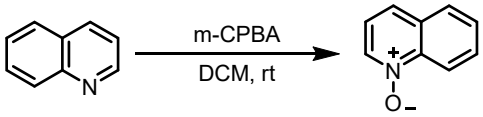
2.2 Calculation method of D-incorporation by ^{1}H-NMR

The calculation of averaged D-incorporation ($\%\ average\ D$) :

$$\%\ average\ D = (1 - \frac{residual\ integral\ of\ deuterated\ producN}{corresponding\ integral\ of\ start\ material}) \times 100\%$$

3. Synthesis of substrates

3.1 The synthesis of Pyridine N-Oxides[1]



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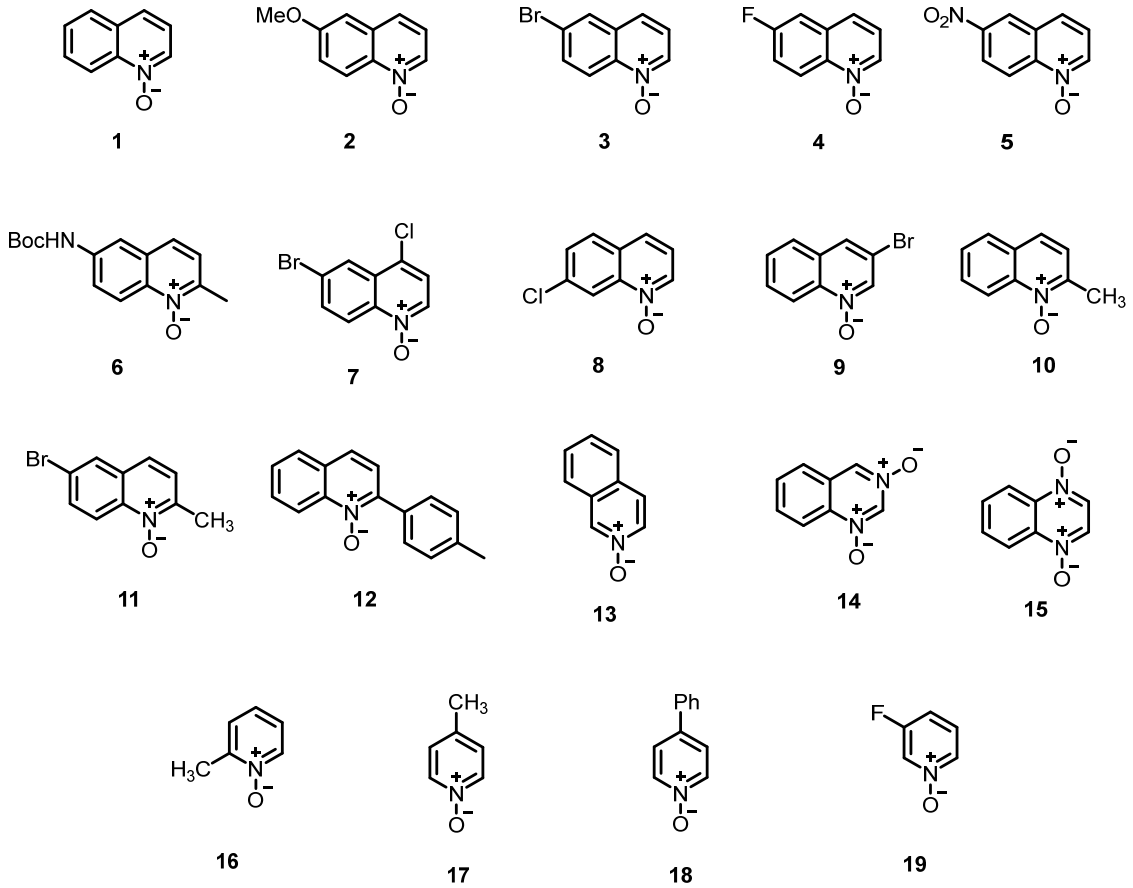
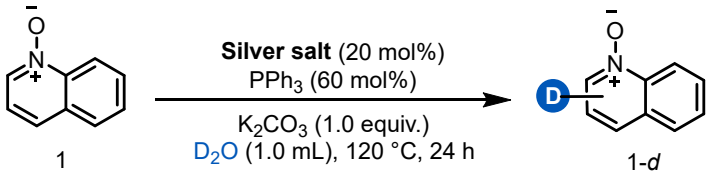
Quinoline (1.29 g, 10 mmol) and dichloromethane (25 mL) were added in a 25 mL single mouthed reaction flask, then cool down to 0℃. Slowly add 3-Chloroperoxybenzoic acid (2.59 g, 15 mmol, 85%) in 10 minutes. Stirred at room temperature for 24 hours. Then, excess potassium carbonate was added to adjust the pH greater than 9, and stirred for 20 minutes. After filtration, the mother liquor was dried with anhydrous sodium sulfate, filtered, and the solvent was removed by rotary evaporation. After purification by chromatography on silica gel (EA, R_f = 0.25), 1.35g of light brown solid was obtained with a yield of about 93%.

3.2 Table S1. The table of substrates



4. Optimization of the reaction conditions

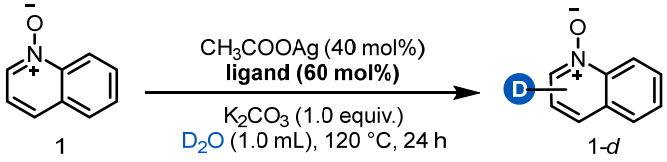
4.1 Table S2. optimization of metal catalysts and ligand ratios



Entry	Catalyst (mol%)	Ligand (mol%)	D_{MS}
1	CH_3COOAg (40)	PPh_3 (60)	3.08
2	Ag_3PO_4 (13.3)	PPh_3 (60)	1.43
3	Ag_2O (20)	PPh_3 (60)	1.43
4	C_6H_5COOAg (40)	PPh_3 (60)	1.10
5	CF_3COOAg (40)	PPh_3 (60)	0.97
6	$AgBF_4$ (40)	PPh_3 (60)	1.31
7	Ag_2CO_3 (20)	PPh_3 (0)	0.98
8	Ag_2CO_3 (20)	PPh_3 (10)	1.41
10	Ag_2CO_3 (20)	PPh_3 (20)	1.67
11	Ag_2CO_3 (20)	PPh_3 (30)	2.10
12	Ag_2CO_3 (20)	PPh_3 (60)	2.87
13	Ag_2CO_3 (20)	PPh_3 (80)	2.31
14	Ag_2CO_3 (20)	PPh_3 (100)	1.66

[a] The reaction conducted with quinoline-*N*-oxides 2.0 mmol, N_2; [b] D_{MS} was determined by GC-MS analysis;

4.2 Table S3. Optimization of ligand

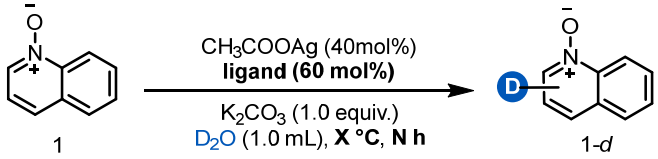


1 1-*d*

Entry	Ligand (mol%)	D_{MS}
1	Triphenylphosphane oxide	0.96
2	1,3-dimesitylimidazol-2-ylidene	0.97
3	Cyclohexyldiphenylphosphine	3.18
4	Triphenylphosphine	3.08
5	2-dicyclohexylphosphino-2' 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl	2.37
6	5-diphenylphosphanylpentyl(diphenyl) phosphane	2.46
7	1,4-bis(diphenylphosphino)butane	2.40
8	1,3-bis(diphenylphosphino)propane	2.36
9	1-dihexylphosphorylhexane	1.94
9	1,2-bis(diphenylphosphino)ethane	1.54
10	Tri(o-tolyl)phosphine	1.22
11	tris(P-trifluoromethylphenyl)benzene	1.10
12	Tri(1-naphthyl)phosphine	0.94
13	1,1'-Bis(diphenylphosphino)ferrocene	0.94

[a] The reaction conducted with quinoline-*N*-oxides 2.0 mmol, N_2; [b] D_{MS} was determined by GC-MS analysis;

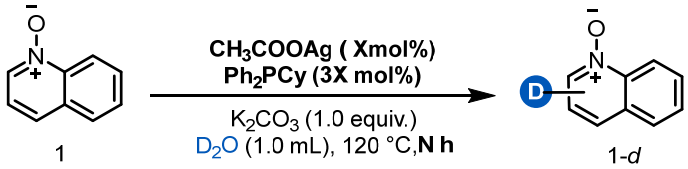
4.3 Table S4. Optimization of ligand, reaction time and temperature



Entry	Time (h)	T (°C)	Ligand	D_{MS}	Yield (%)
1	12	120	Ph_2PCy	2.68	91%
2	24	120	Ph_2PCy	3.18	88%
3	48	120	Ph_2PCy	3.45	80%
4	72	120	Ph_2PCy	3.81	93%
5	96	120	Ph_2PCy	3.98	91%
6	12	120	Ph_3P	2.26	85%
7	24	120	Ph_3P	3.08	91%
8	48	120	Ph_3P	3.55	88%
9	72	120	Ph_3P	3.96	80%
10	24	140	Ph_2PCy	3.07	91%
11	48	140	Ph_2PCy	3.41	98%
12	72	140	Ph_2PCy	3.68	91%
13	24	140	Ph_3P	3.47	85%
14	48	140	Ph_3P	3.96	90%
15	72	140	Ph_3P	4.15	90%
16	24	160	Ph_2PCy	3.65	90%
17	48	160	Ph_2PCy	3.87	88%
18	72	160	Ph_2PCy	4.00	93%
19	24	160	Ph_3P	3.98	94%
20	48	160	Ph_3P	4.25	89%
21	72	160	Ph_3P	4.79	97%

[a] The reaction conducted with quinoline-*N*-oxides 2.0 mmol, N_2; [b] D_{MS} was determined by GC-MS analysis; [c] Isolated yield.

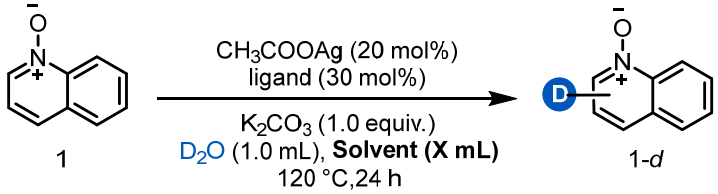
4.4 Table S5. Optimization of Quantity of catalyst



Entry	Time (h)	Catalyst (mol%)	D_{MS}
1	24	20	1.88
2	48	20	3.02
3	72	20	3.50
4	24	40	2.26
5	48	40	3.08
6	72	40	3.55

[a] The reaction conducted with quinoline-*N*-oxides 2.0 mmol, N_2; [b] D_{MS} was determined by GC-MS analysis; [c] Isolated yield.

4.5 Table S6. Selection of reaction solvents and deuterium sources

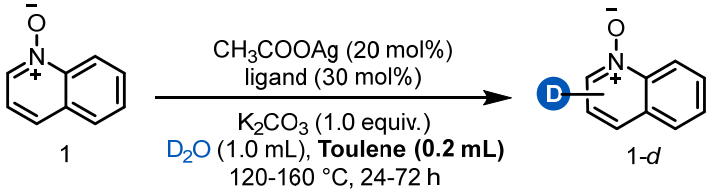


Entry	Deuterium source (1.0 mL)	Solvent (0.2 mL)	D_{MS}
1	D_2O	DCM	0.24
2	D_2O	Dioxane	1.04
3	D_2O	MTBE	1.11
4	D_2O	Cyclohexane	1.38
5	D_2O	CPME	1.84
6	D_2O	Toluene	2.22
7	D_2O	-	1.50
8	CH_3CH_2OD	-	0.91
9	Acetone-d_6	-	0.23
10	DMSO-d_6	-	0.33
11	Bromobenzene-d_5	-	0
12	Toluene-d_8	-	0
13	D_2O	Toluene (0.1 mL)	1.74
14	D_2O	Toluene (0.4 mL)	1.78
15	D_2O	Toluene (0.8 mL)	1.01
16	D_2O	Toluene (1.2 mL)	0.86

[a] The reaction conducted with quinoline-*N*-oxides 2.0 mmol, N_2; [b] D_{MS} was determined by GC-MS analysis.

5. The synthesis of deuterated compounds

5.1 General methods for Deuteration



Method A:

According to the optimized reaction conditions, reaction substrate (1.0 mmol), silver acetate (34 mg, 0.2 mmol), triphenylphosphine (79 mg, 0.3 mmol), potassium carbonate (138 mg, 1.0 mmol), toluene (0.1 mL), and D_2O (1.0 mL) were sequentially added into a 15 mL sealed tube. The vessel was purged with nitrogen stream and sealed by Teflon bushing with a Viton O-ring. Next, the mixture is heated to 120 ℃ using a metal module equipped with a Haydn heating magnetic stirrer. After a constant temperature reaction of 24-72 hours, it is cooled down and quenched with a saturated NH_4Cl solution. Extract with ethyl acetate three times, using approximately 20 mL of solvent each time. Combine the organic phases, wash with saturated sodium chloride, dry with anhydrous sodium sulfate, filter, purify via column chromatography on silica gel to obtain the target product, then rotary evaporate and perform GC-MS and ^{1}H-NMR detection. The D-incorporation of each site was determined by ^{1}H-NMR detection (since there is hydrogen inside the substrate that does not undergo deuterium, it can be used as a position to calculate the D-incorporation of the deuterated site).

Method B:

According to the optimized reaction conditions, reaction substrate (1.0 mmol), silver acetate (34 mg, 0.2 mmol), triphenylphosphine (79 mg, 0.3 mmol), potassium carbonate (138 mg, 1.0 mmol), toluene (0.1 mL), and D_2O (1.0 mL) were sequentially added into a 15 mL sealed tube. The vessel was purged with nitrogen stream and sealed by Teflon bushing with a Viton O-ring. Next, the mixture was heated to 160 ℃ using a metal module equipped with a Haydn heating magnetic stirrer. After 24 hours of constant temperature reaction, it was cooled down and quenched with a saturated NH_4Cl solution. Then extract with ethyl acetate three times, using about 20 mL of solvent each time. Combine the organic phases, wash with saturated sodium chloride, dry with anhydrous sodium sulfate, filter, purify via column chromatography on silica gel to obtain the target product, and perform GC-MS and ^{1}H-NMR detection. The D-incorporation of each site was determined by ^{1}H-NMR detection (since there is hydrogen inside the substrate that does not undergo deuterium, it can be used as a position to calculate the D-incorporation of the deuterated site).

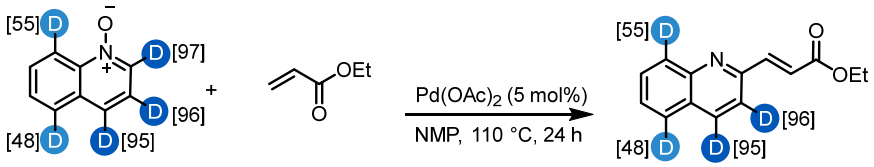
Method C:

According to the optimized reaction conditions, reaction substrate (1.0 mmol), silver acetate (34 mg, 0.2 mmol), triphenylphosphine (79 mg, 0.3 mmol), potassium carbonate (138 mg, 1.0 mmol), toluene (0.1 mL), and D_2O (1.0 mL) were sequentially added into a 15 mL sealed tube. The vessel was purged with nitrogen stream and sealed by Teflon bushing with a Viton O-ring. Next, the mixture is heated to 100 ℃ using a metal module equipped with a Haydn heating magnetic stirrer. After a constant temperature reaction of 24-72 hours, it is cooled down and quenched with a saturated NH_4Cl solution. Then extract with ethyl acetate

three times, using about 20 mL of solvent each time. Combine the organic phases, wash with saturated sodium chloride, dry with anhydrous sodium sulfate, filter, purify via column chromatography on silica gel to obtain the target product, and perform GC-MS and ^{1}H-NMR detection. The D-incorporation of each site was determined by ^{1}H-NMR detection (since there is hydrogen inside the substrate that does not undergo deuterium, it can be used as a position to calculate the D-incorporation of the deuterated site).

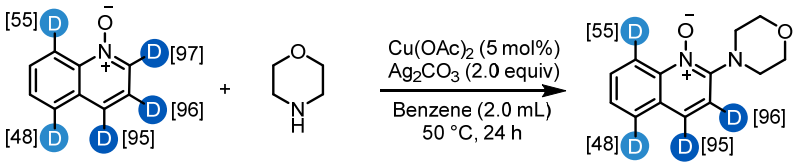
5.2 Synthesis of Deuterated Compounds

5.2.1 Synthesis of compound 20 (introduction of ethyl acrylate at C2)[2]



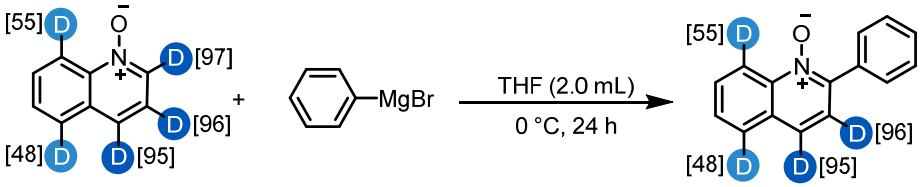
Deuterated quinoline-*N*-oxides (50 mg, 0.33 mmol), ethyl acrylate (165 mg, 0.65 mmol), Pd $(OAc)_2$ (5 mg, 5 mol%), and 1.0 mL N-Methylpyrrolidone added into a 15 mL sealed tube reactor. After nitrogen substitution, sealed and heated to 120 ℃ for 24 hours. Cooled down to room temperature, add saturated NH_4Cl solution to quench the reaction, and then extract three times with 20 mL of ethyl acetate each time. Combine the organic phases, wash with saturated NaCl solution, dry with anhydrous sodium sulfate, filter, and purify by chromatography on silica gel (PE/EA=20/1) to obtain 57 mg of white solid with a yield of 71%.^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.74 **(d, *J* = 8.7 Hz, 0.45H, Labelled)**, 8.54 **(s, 0.03H, Labelled),** 7.86 **(d, *J* = 7.8 Hz, 0.52H, Labelled)**, 7.79 – 7.70 **(m, 1.05H, Labelled)**, 7.63 (dt, J = 7.4, 3.9 Hz, 1H), 7.35 **(s, 0.04H, Labelled)**.

5.2.2 Synthesis of compound 21 (introduction of morpholine at C2)[3]



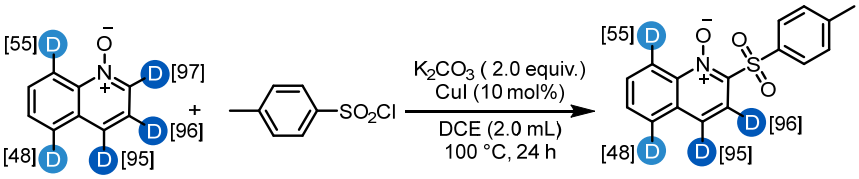
Deuterated quinoline-*N*-oxides (50 mg, 0.33 mmol), morpholine (90 mg, 1.03 mmol), copper acetate (3 mg, 5 mol%), silver carbonate (182 mg, 0.66 mmol), and 2.0 mL benzene added into a 15 mL sealed tube reactor. After nitrogen substitution, sealed and heated to 50 ℃ for 24 hours of reaction. Cooled down to room temperature, added saturated NH_4Cl solution to quench the reaction, and then extract three times with 20 mL of ethyl acetate each time. Combine the organic phases, wash with saturated NaCl solution, dry with anhydrous sodium sulfate, filter, and purify by chromatography on silica gel (PE/EA=12/1) to obtain 54 mg of pale solid with a yield of 72%.^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 **(s, 0.04H, Labelled)**, 7.73 **(d, *J* = 8.2 Hz, 0.45H, Labelled)**, 7.61 **(d, *J* = 7.8 Hz, 0.52H, Labelled)**, 7.55 (d, *J* = 4.1 Hz, 1.00H), 7.25 (d, *J* = 3.0 Hz, 1.00H), 6.95 (**s, 0.05H, Labelled)**, 3.94 – 3.81 (m, 4H), 3.65 – 3.78 (m, 4H).

5.2.3 Synthesis of compound 22 (introduction of phenyl at C2)[4]



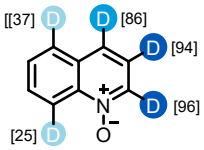
Deuterated quinoline-*N*-oxides (50 mg, 0.33 mmol), add 1.0 mL of THF solvent to a 10 mL reactor, stir and dissolve, replaced with nitrogen, cooled to 0 ℃, slowly added 1.2 mL of 1.0 M phenyl reagent dropwise, and then react at 0℃ for 24 hours at constant temperature. Cooled down to room temperature, the reaction was quenched by adding saturated NH_4Cl solution, and then extracted three times with 20 mL of ethyl acetate each time. The organic phases were combined, washed with saturated NaCl solution, dried over anhydrous sodium sulfate, filtered, and purify by chromatography on silica gel (PE/EA = 3/1) to obtain 54 mg of pale solid with a yield of 72%.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 **(dd, *J* = 8.2 1.0 Hz, 0.45H, Labelled)**, 8.03 – 7.93 (m, 2H), 7.89 **(dd, *J* = 8.1, 1.3 Hz, 0.52H, Labelled)**, 7.84 – 7.76 **(m, 1H, Labelled)**, 7.66 (dt, *J* = 7.5, 4.0 Hz, 1H), 7.52 **(dt, *J* = 13.9, 7.0 Hz, 3H, Labelled)**.

5.2.4 Synthesis of compound 23 (introduction of phenylsulfonyl at C2)[5]



Deuterated quinoline-*N*-oxides (75 mg, 0.50 mmol), p-Toluenesulfonyl Chloride (382 mg, 2.00 mmol), cuprous iodide (9.5 mg, 10 mol%), potassium carbonate (138 mg, 1.00 mmol), and 6.0 mL dichloroethane added into a 15 mL sealed tube reactor. After nitrogen replacement, sealed and heated to 100 ℃ for 24 hours. Cooled to room temperature, NH_4Cl saturated solution was added to quench the reaction, and then extracted three times with 20 mL of ethyl acetate each time. The organic phases were combined, washed with saturated NaCl solution, dried over anhydrous sodium sulfate, filtered, and purify by chromatography on silica gel (PE/EA = 6/1) to obtain 132 mg of pale solid with a yield of 85%.^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.18 **(dd, *J* = 8.7, 1.1 Hz, 0.45H, Labelled)**, 8.02 (d, *J* = 8.3 Hz, 2H), 7.88 **(dd, *J* = 8.2, 1.4 Hz, 0.52H, Labelled)**, 7.82 – 7.76 (m, 1H), 7.70 – 7.59 (m, 1H), 7.55 **(s, 0.05H, Labelled)**, 7.33 (d, *J* = 8.1 Hz, 2H), 7.14 **(d, *J* = 2.5 Hz, 0.06H, Labelled)**.

6. Experimental characterization data for products



1-*d*

Compound **1-*d*** (quinoline-*N*-oxides):

Yellow solid, 136 mg, yield 94%; The D-incorporation at C2, C3, C4, C5, and C8 determined by ^{1}H-NMR is 96%, 94%, 86%, 37%, and 25%, respectively; R_f = 0.20 (PE/EA = 1/1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (**s, 0.04H, Labelle**), 8.54 (**d, *J* = 8.7 Hz, 0.63H, Labelled**), 8.07 (**dd, *J* = 8.1, 1.4 Hz, 0.75H, Labelled**), 7.92 (**s, 0.14H, Labelled**), 7.84 – 7.77 (m, 2H), 7.71 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.46 (**s, 0.06H, Labelled**).

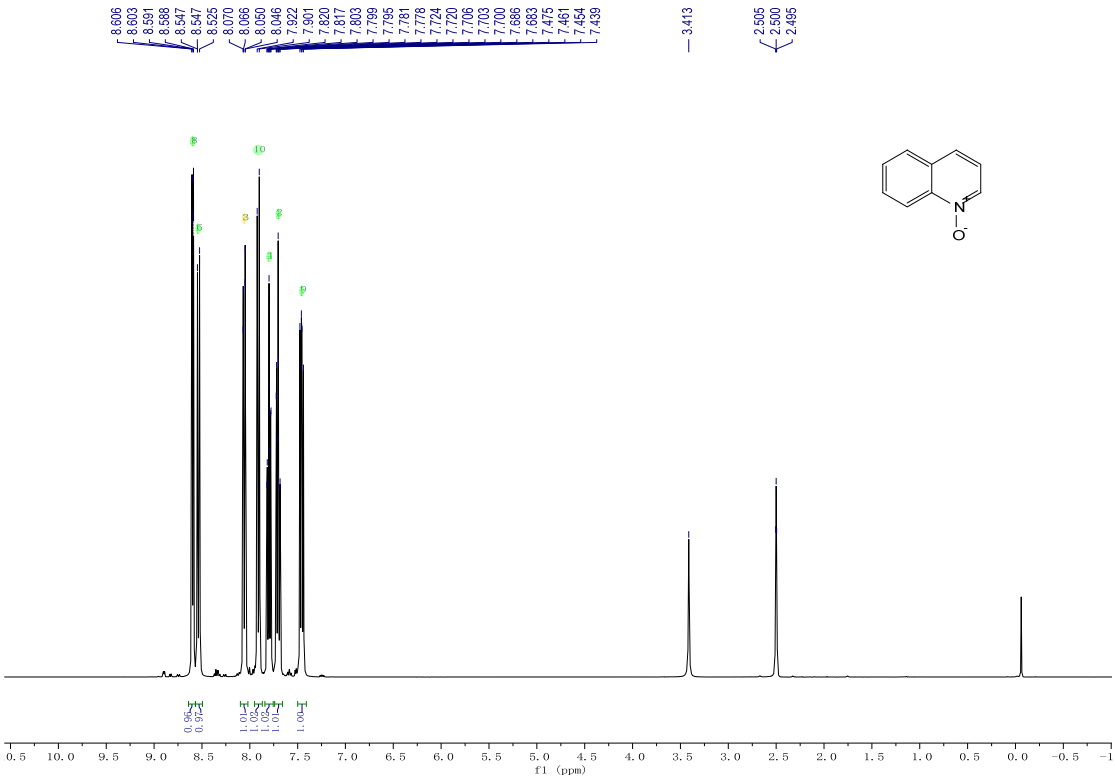


Figure S1 ^{1}H NMR (400 MHz, $CDCl_3$) of 1

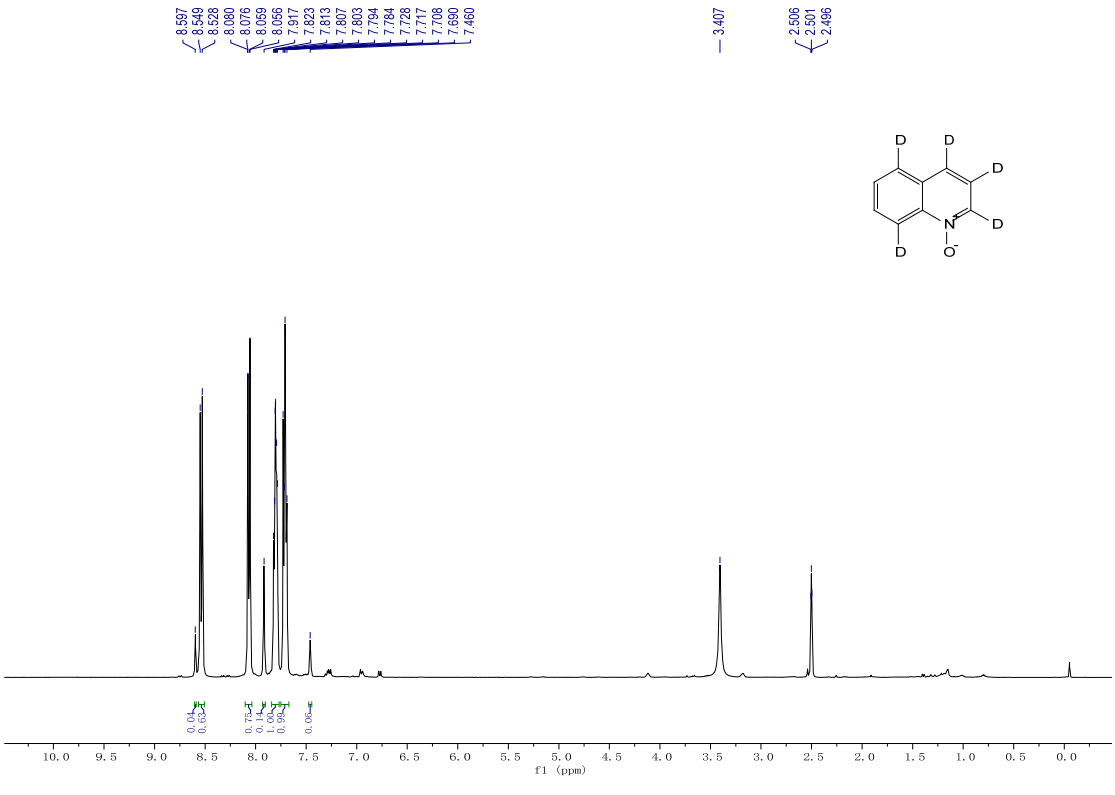


Figure S2 ^{1}H NMR (400 MHz, $CDCl_3$) of 1-*d*

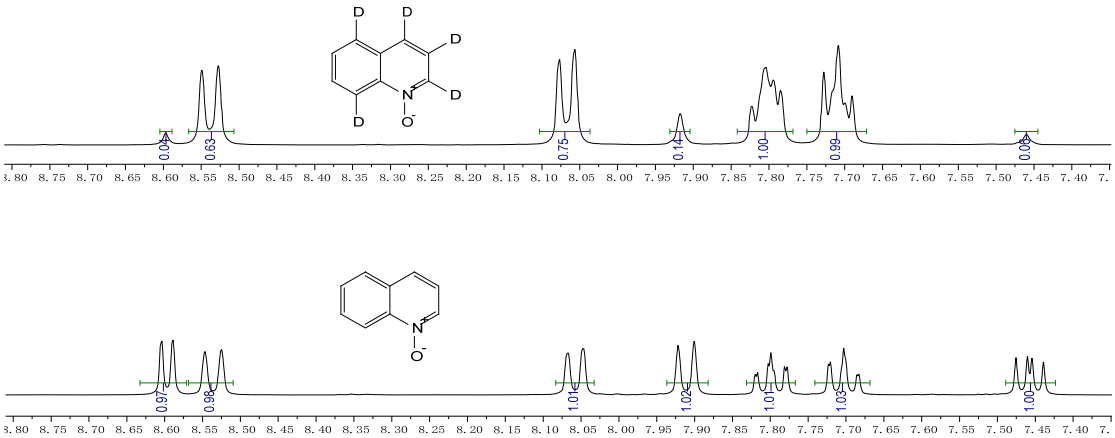
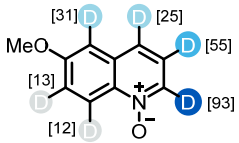


Figure S3 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 1-*d* and 1



2-*d*

Compound **2-*d*** (6-methoxyquinoline-*N*-oxides):

Yellow solid, 164 mg, yield 94%; The D-incorporation at C2, C3, C4, C5, C6, and C8 determined by ^{1}H-NMR is 93%, 55%, 25%, 13%, and 12%, respectively; R_f = 0.10 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 9.5 Hz, 0.88H, Labelled), 8.39 (d, J = 6.0 Hz, 0.02H, Labelled), 7.62 (m, 0.75H, Labelled), 7.35 (**m,0.87H, Labelled**), 7.23 (dd, J = 8.5, 6.0 Hz, 0.44H, Labelled), 7.09 (d, J = 2.6 Hz, 0.69H, Labelled).

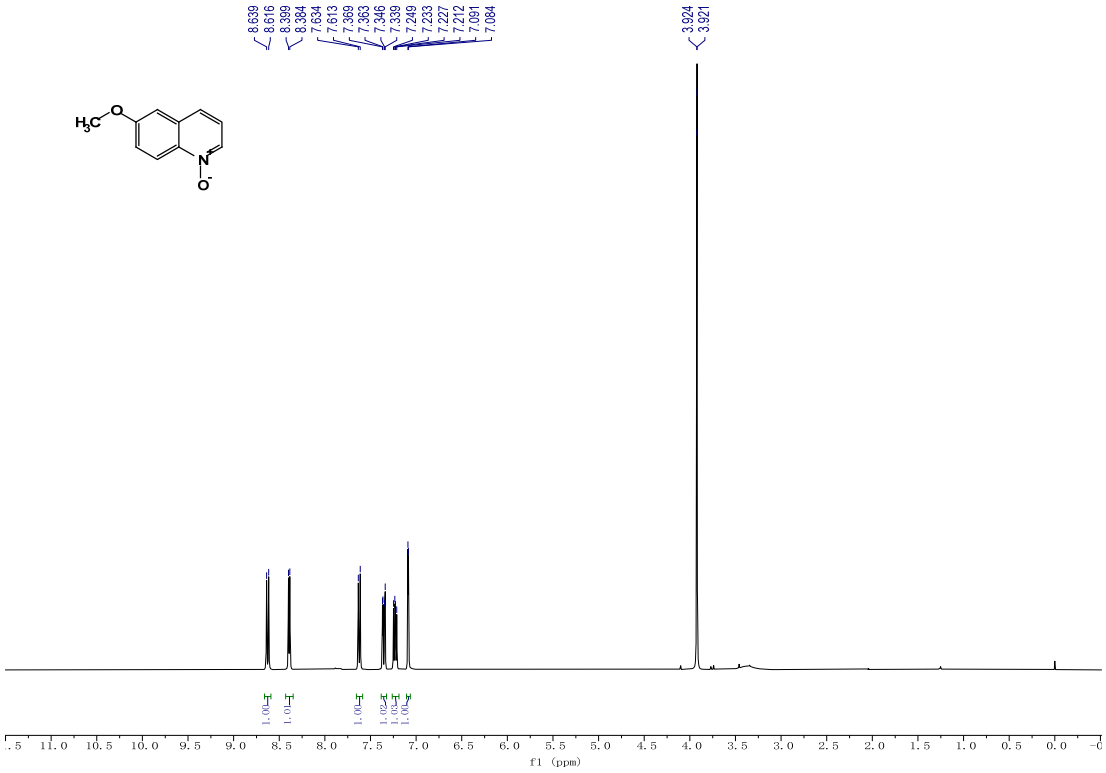


Figure S4 ^{1}H NMR (400 MHz, $CDCl_3$) of 2

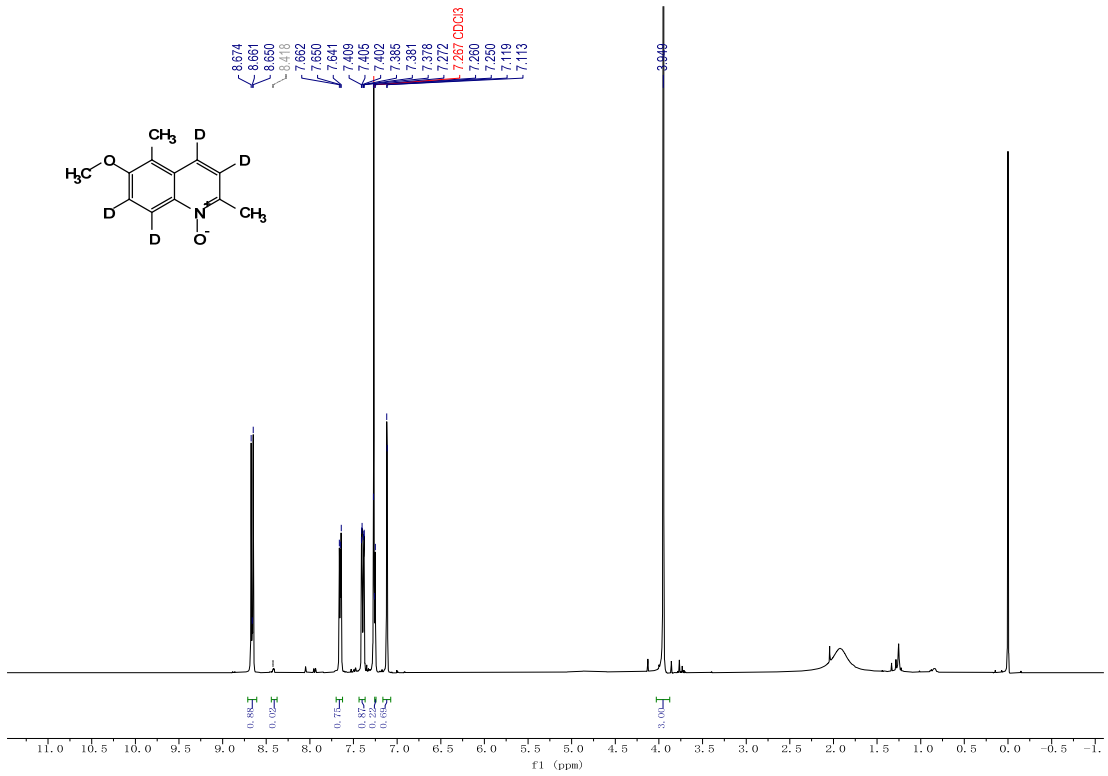


Figure S5 ^{1}H NMR (400 MHz, $CDCl_3$) of 2-*d*

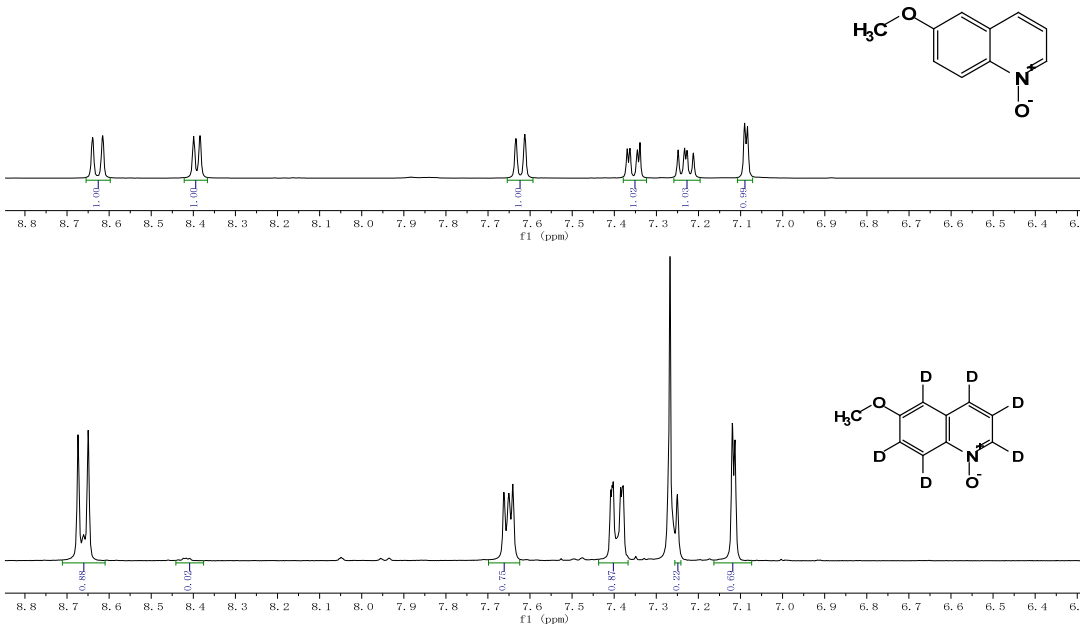
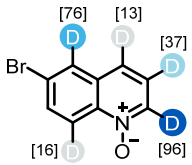


Figure S6 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 2-*d* and 2



3-*d*

Compound **3-*d*** (6-bromoquinoline-*N*-oxides):

Yellow solid, 50 mg, yield 87%; The D-incorporation at C2, C3, C4, C5, and C8 determined by ^{1}H-NMR is 96%, 37%, 13%, 78%, and 16%, respectively; R_f = 0.25 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.63 (m, 0.84H, Labelled), 8.59 (d, J = 6.0 Hz, 0.04H, Labelled),8.07 (d, J = 1.8 Hz, 0.24H, Labelled), 7.85 (m, 1H), 7.70 (t, J = 4.2 Hz,0.87H, Labelled), 7.36 (m, 0.63H, Labelled).

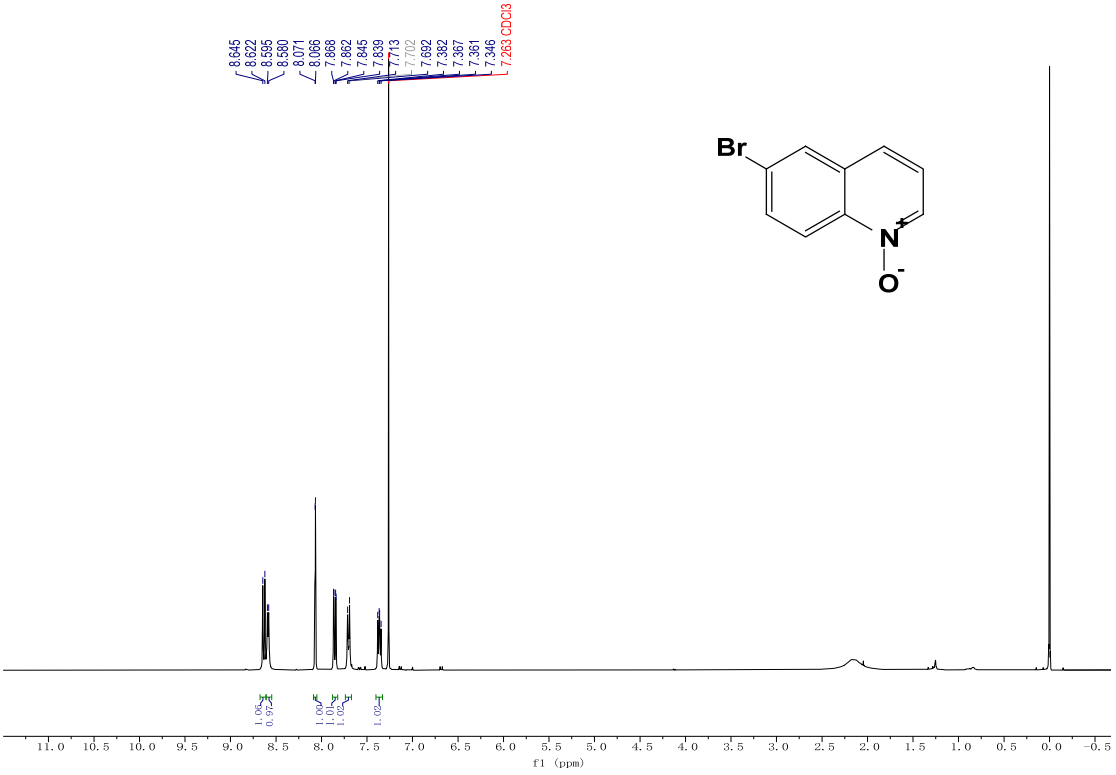


Figure S7 ^{1}H NMR (400 MHz, $CDCl_3$) of 3

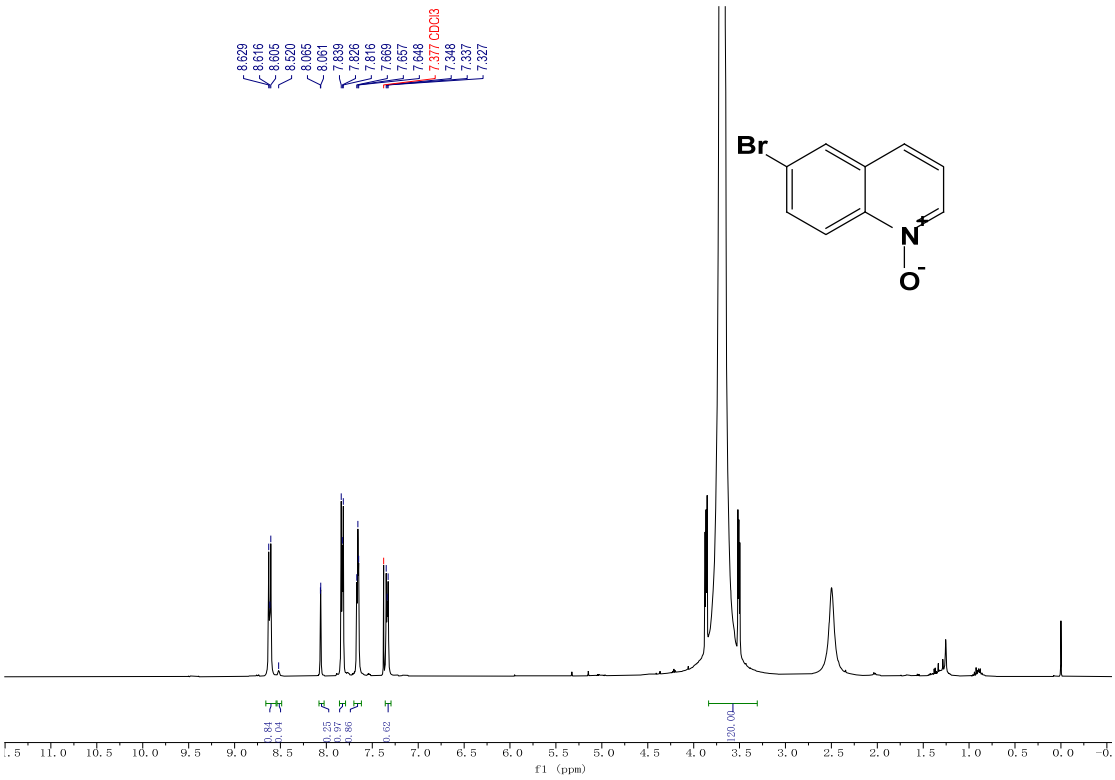


Figure S8 ^{1}H NMR (400 MHz, $CDCl_3$) of 3-*d*

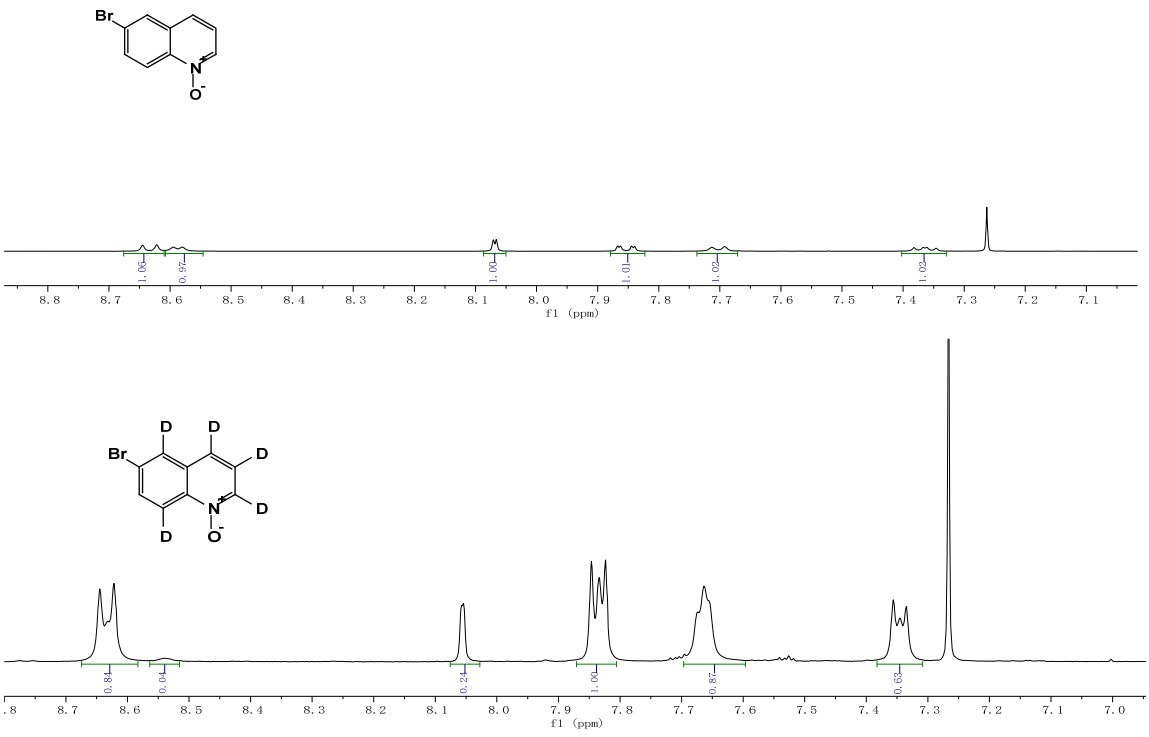
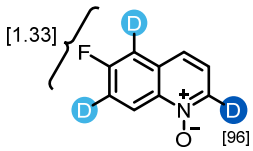


Figure S9 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 3-*d* and 3



4-*d*

Compound **4-*d*** (6-fluoroquinoline-*N*-oxides):

Yellow solid, 58 mg, yield 85%; The D-incorporation at C2 determined by ^{1}H-NMR is 96%, and the average D-incorporation at the two ortho-position of fluorine is 33%; R_f = 0.40 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.79 (q, J = 5.0 Hz, 1H), 8.49 (**dd, *J* = 6.1, 0.9 Hz, 0.04H, Labelled**),7.72 – 7.65 (m, 1H), 7.56 – 7.47 (**m, 0.67H, Labelled**), 7.34 (d, J = 8.4 Hz, 1H).

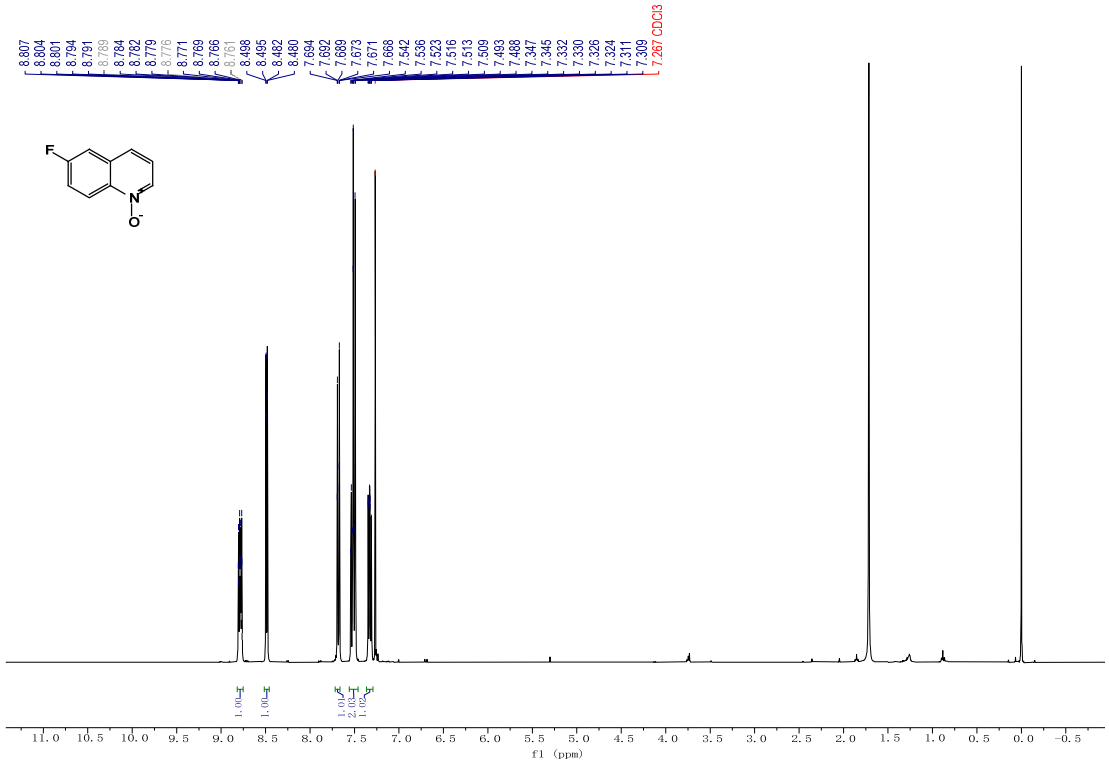


Figure S10 ^{1}H NMR (400 MHz, $CDCl_3$) of 4

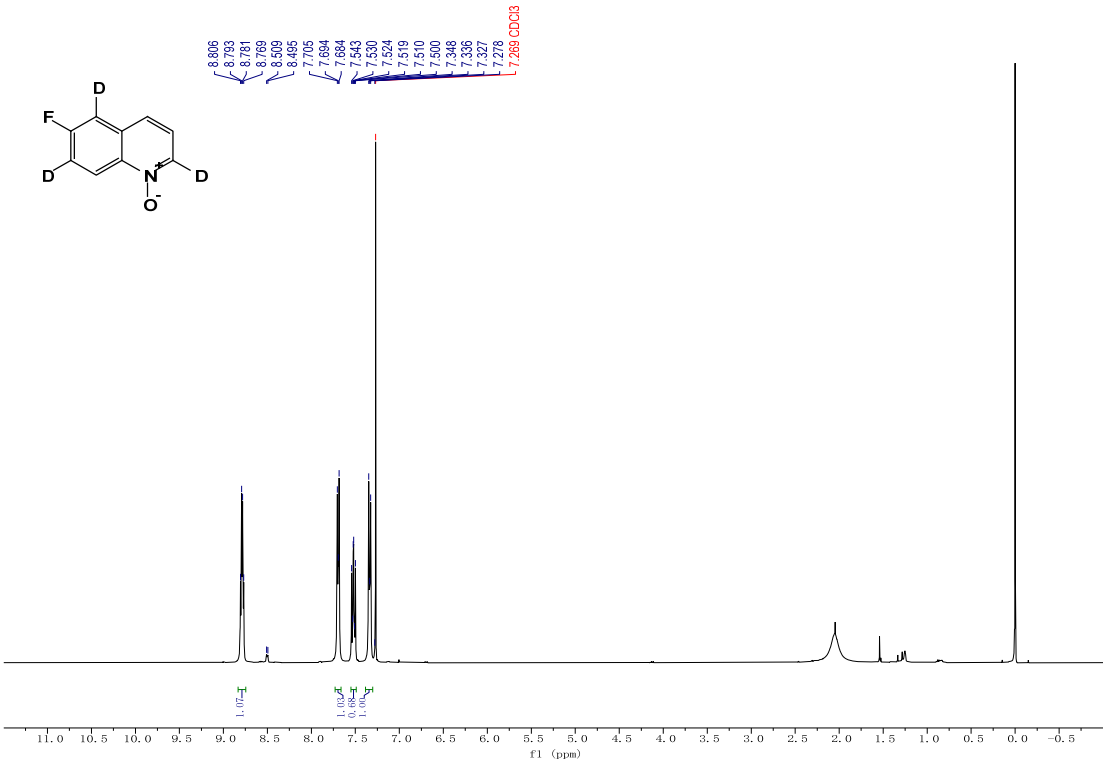


Figure S11 ^{1}H NMR (400 MHz, $CDCl_3$) of 4-*d*

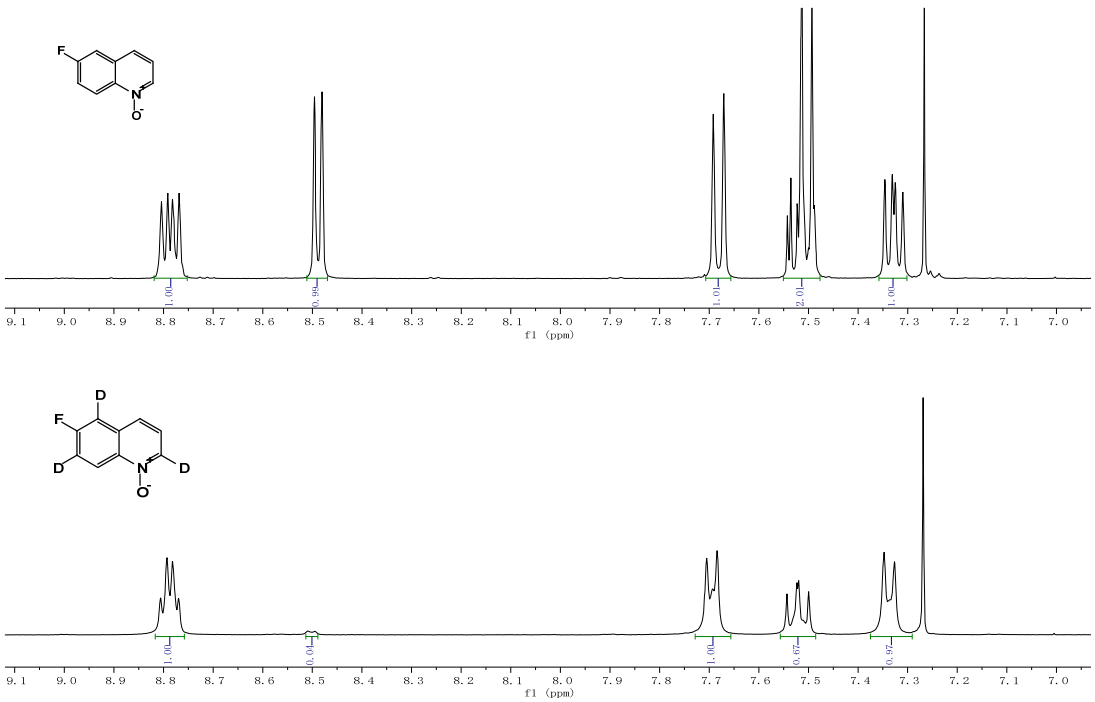
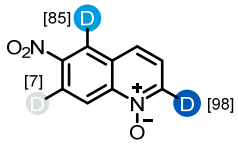


Figure S12 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 4-*d* and 4



5-*d*

Compound **5-*d*** (6-Nitroquinoline-*N*-oxides):

Yellow solid, 147 mg, yield 77%; The D-incorporation at C2, C5, and C7 determined by ^{1}H-NMR is 98%, 85%, and 7%, respectively; R_f = 0.15 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, DMSO-d6) δ 9.17 (**d, *J* = 2.5 Hz,0.15H, Labelled**), 8.78 (**dd, *J* = 6.1, 0.9 Hz, 0.02H, Labelled**),8.72 (d, *J* = 9.5 Hz, 1H), 8.49 (**d, *J* = 9.5 Hz, 0.93H, Labelled**), 8.25 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H).

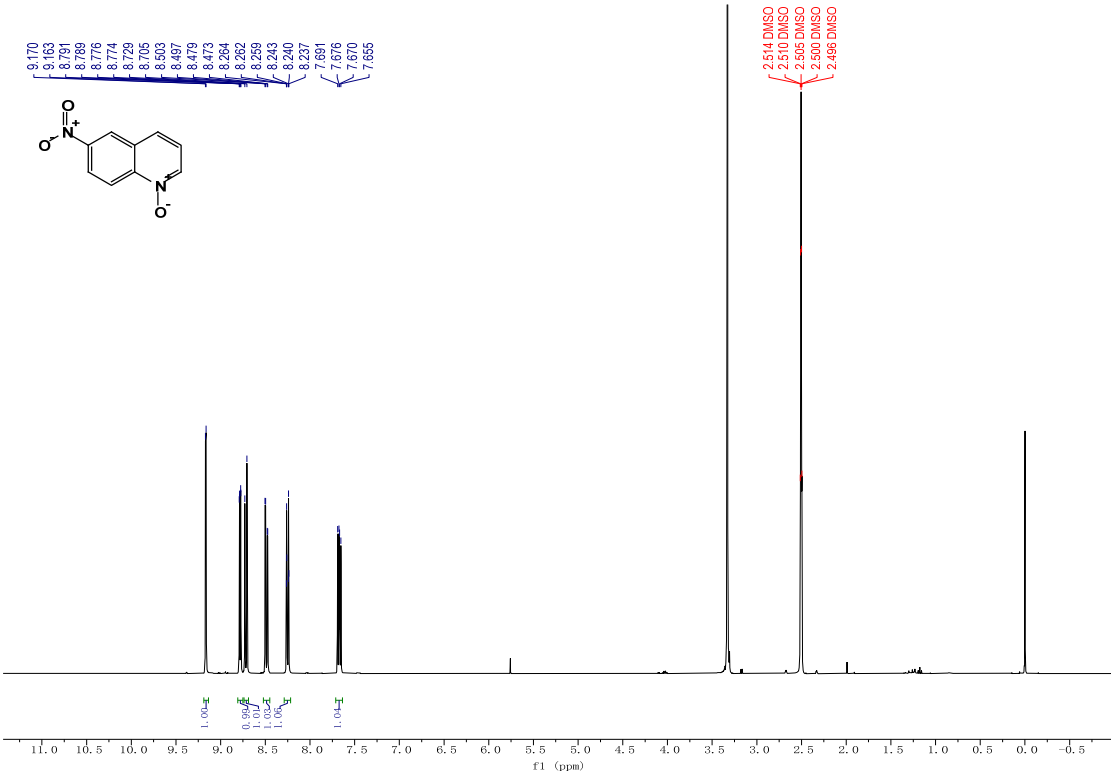


Figure S13 ^{1}H NMR (400 MHz, $CDCl_3$) of 5

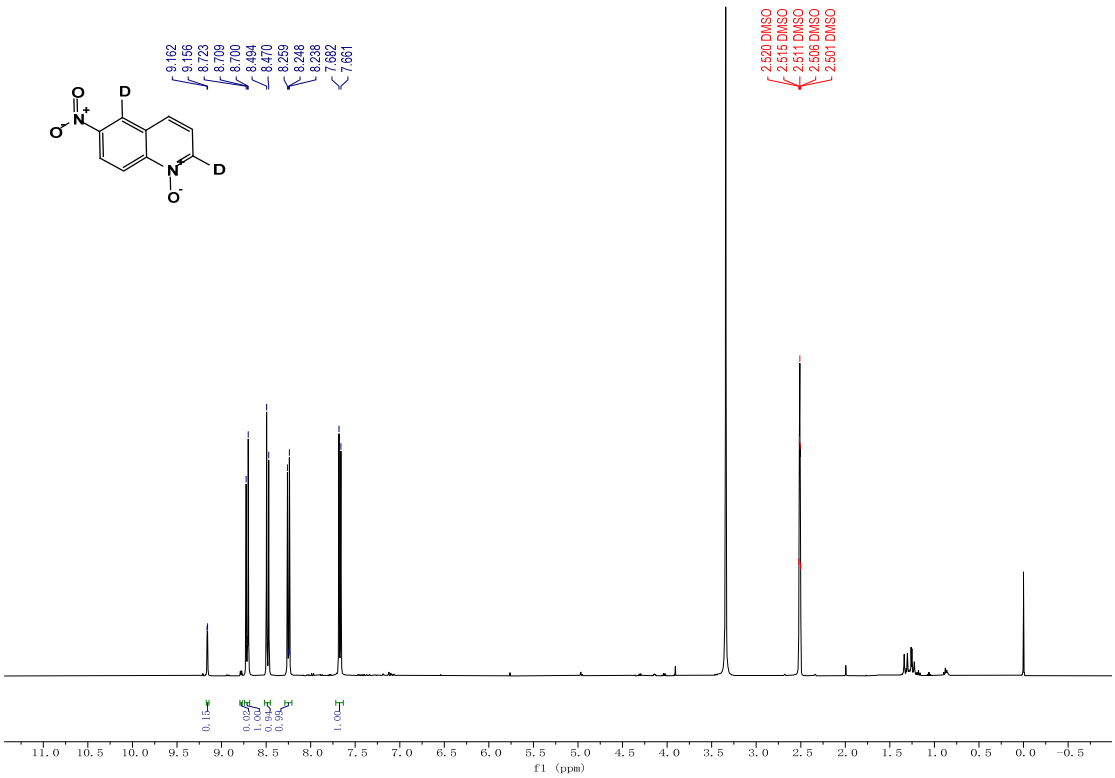


Figure S14 ^{1}H NMR (400 MHz, $CDCl_3$) of 5-*d*

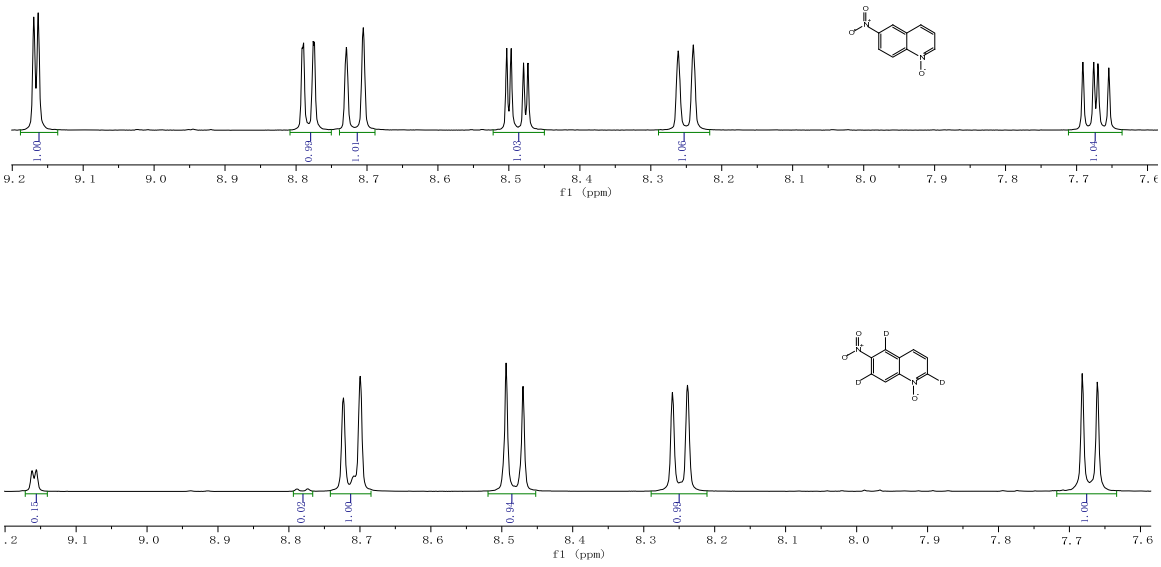
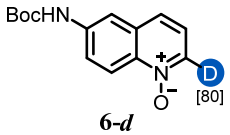


Figure S15 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 5-*d* and 5



6-*d*

Compound **6-*d*** (6- (N-BOC-amino)-quinoline-*N*-oxides):

White solid, 99 mg, yield 38%; The D-incorporation at C2 determined by ^{1}H-NMR is 80%; R_f = 0.25 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (**dd, *J* = 5.9, 1.0 Hz, 0.22H s, 0.03H, Labelled**), 8.10 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.48 (dd, *J* = 8.8, 7.6 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.83 (dd, *J* = 7.6, 1.0 Hz, 1H), 1.54 (s, 9H).

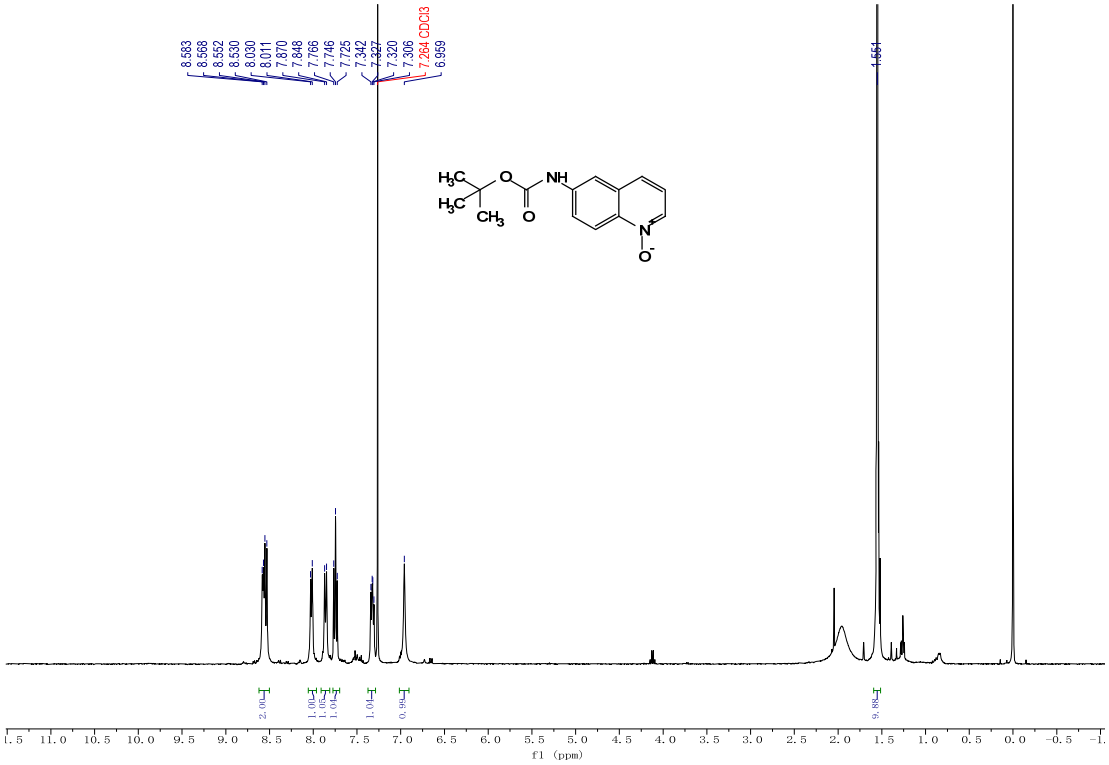


Figure S16 ^{1}H NMR (400 MHz, $CDCl_3$) of 6

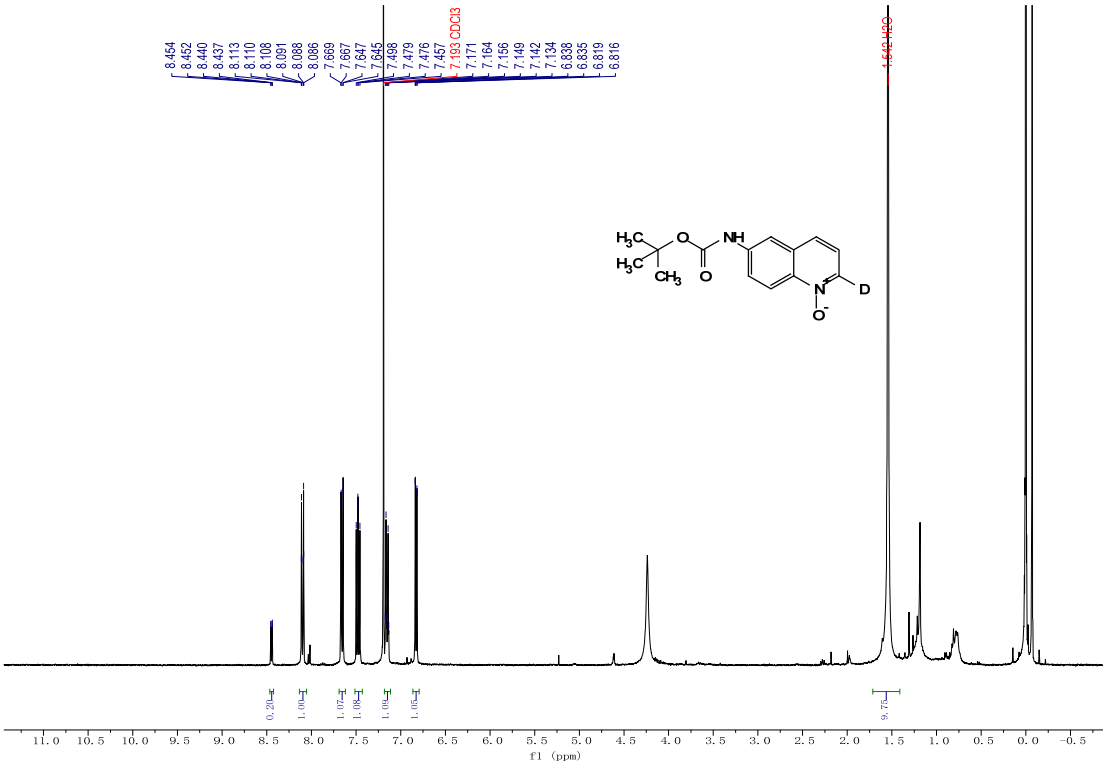


Figure S17 ^{1}H NMR (400 MHz, $CDCl_3$) of 6-*d*

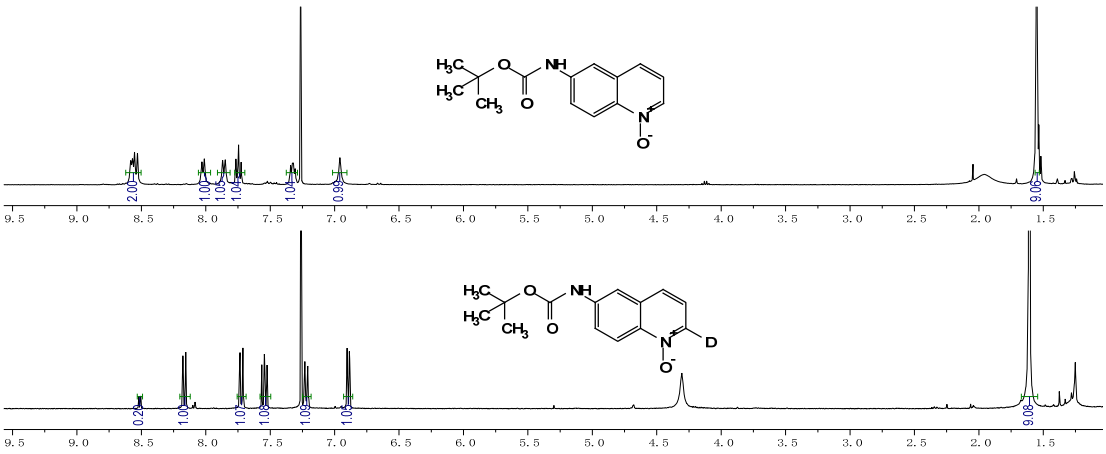
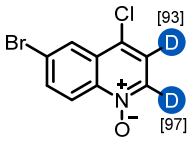


Figure S18 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 6-*d* and 6



7-*d*

Compound **7-*d*** (6-bromo-4-chloroquinoline-*N*-oxides):

Yellow solid, 167 mg, yield 65%; The D-incorporation at C2 and C3 determined by ^{1}H-NMR is 97% and 93%, respectively; R_f = 0.40 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) 8.64 (d, J = 9.2 Hz, 1H), 8.42 (**d, *J* = 6.6 Hz, 0.03H, Labelled**), 8.38 (d, J = 2.1 Hz, 1H), 7.90 (dd, J = 9.3, 2.0 Hz, 1H), 7.40 (**d, *J* = 6.6 Hz, 0.07H, Labelled**).

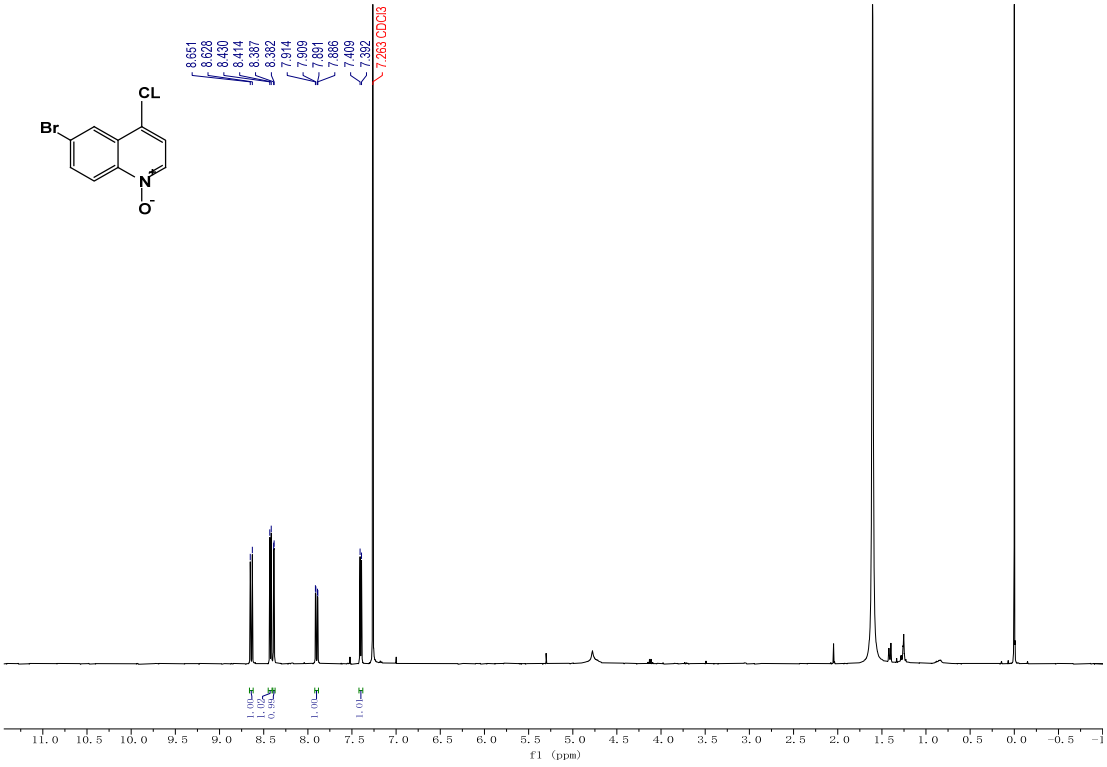


Figure S19 ^{1}H NMR (400 MHz, $CDCl_3$) of 7

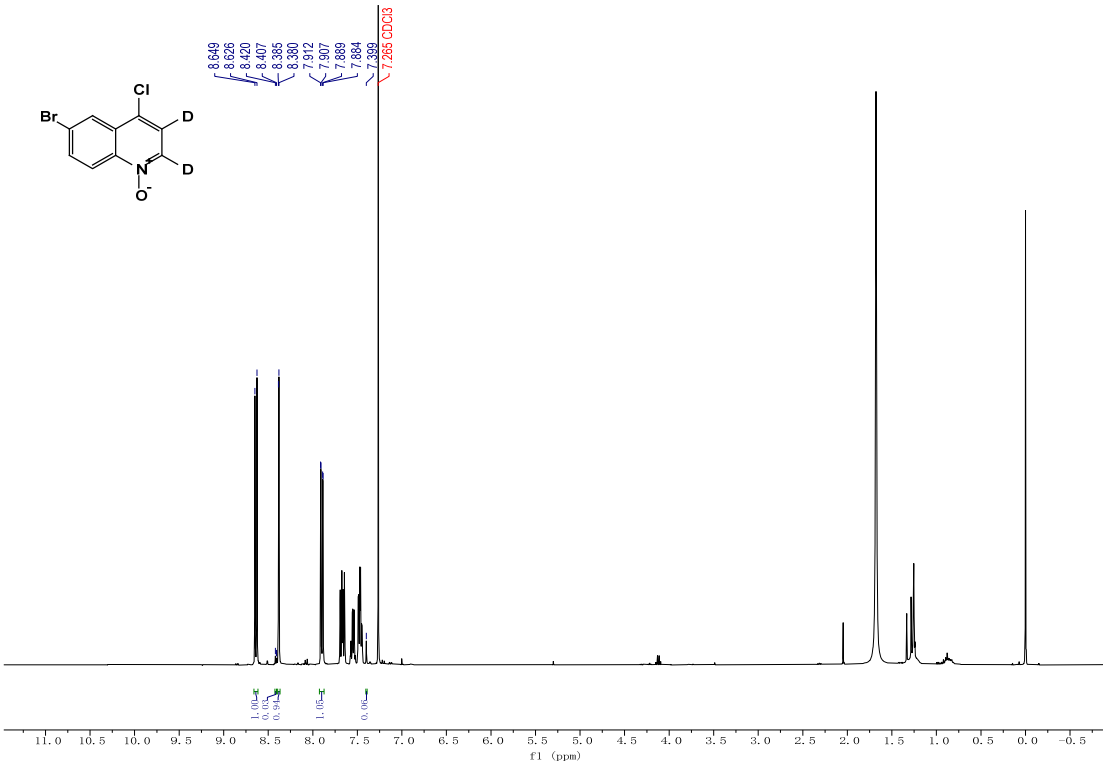


Figure S20 ^{1}H NMR (400 MHz, $CDCl_3$) of 7-*d*

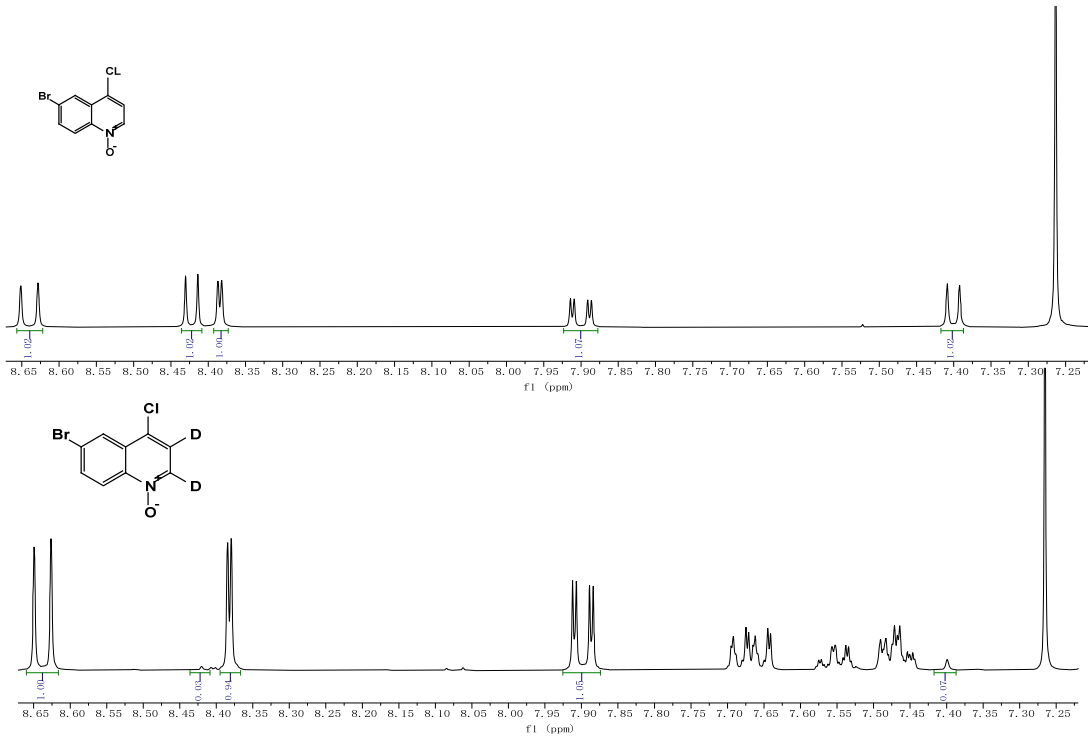
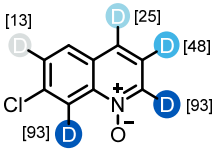


Figure S21 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 7-*d* and 7



8-*d*

Compound **8-*d*** (7-chloroquinoline-*N*-oxides):

Yellow solid, 160 mg, yield 89%; The D-incorporation at C2, C3, C4, C6, and C8 determined by ^{1}H-NMR is 93%, 48%, 25%, 13%, and 93%, respectively; R_f = 0.25 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.64 (**s, 0.07H, Labelled**), 8.53 (**s, 0.07H, Labelled**), 8.17 (t, *J* = 4.4 Hz, 0.75H, Labelled), 7.99 (**m, 0.87H, Labelled**), 7.80(m, 1H), 7.52 (**m, 0.52H, Labelled**).

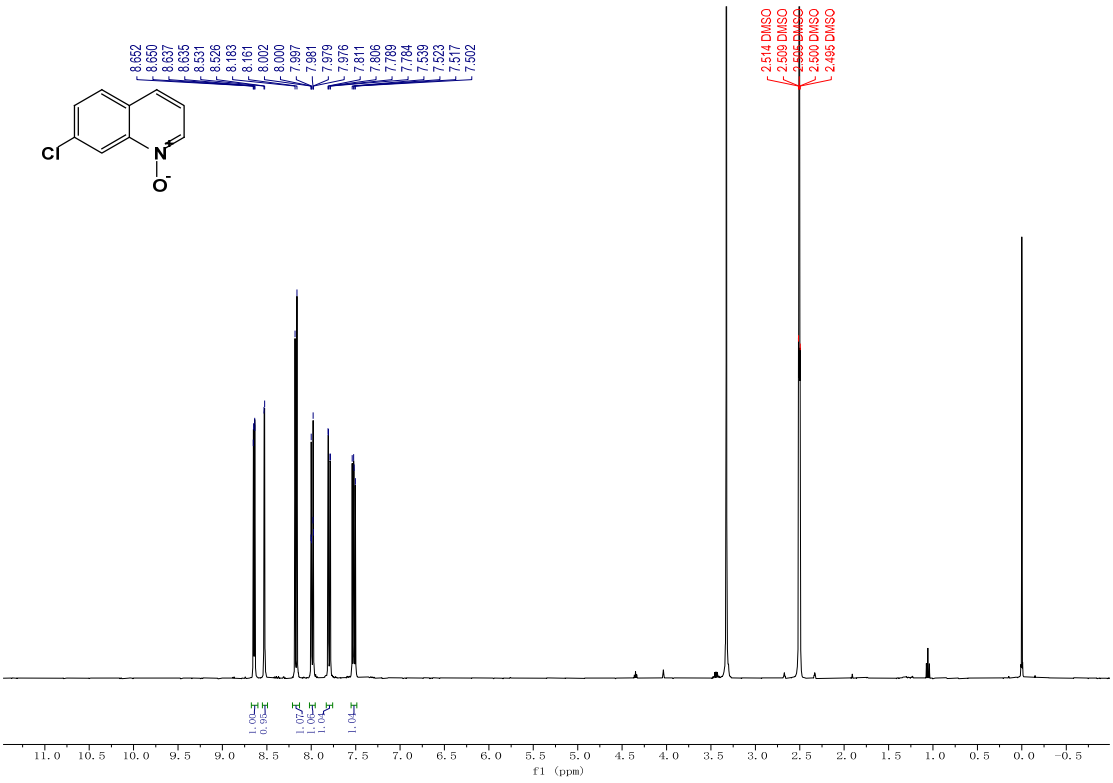


Figure S22 ^{1}H NMR (400 MHz, DMSO-*d*$_6$) of 8

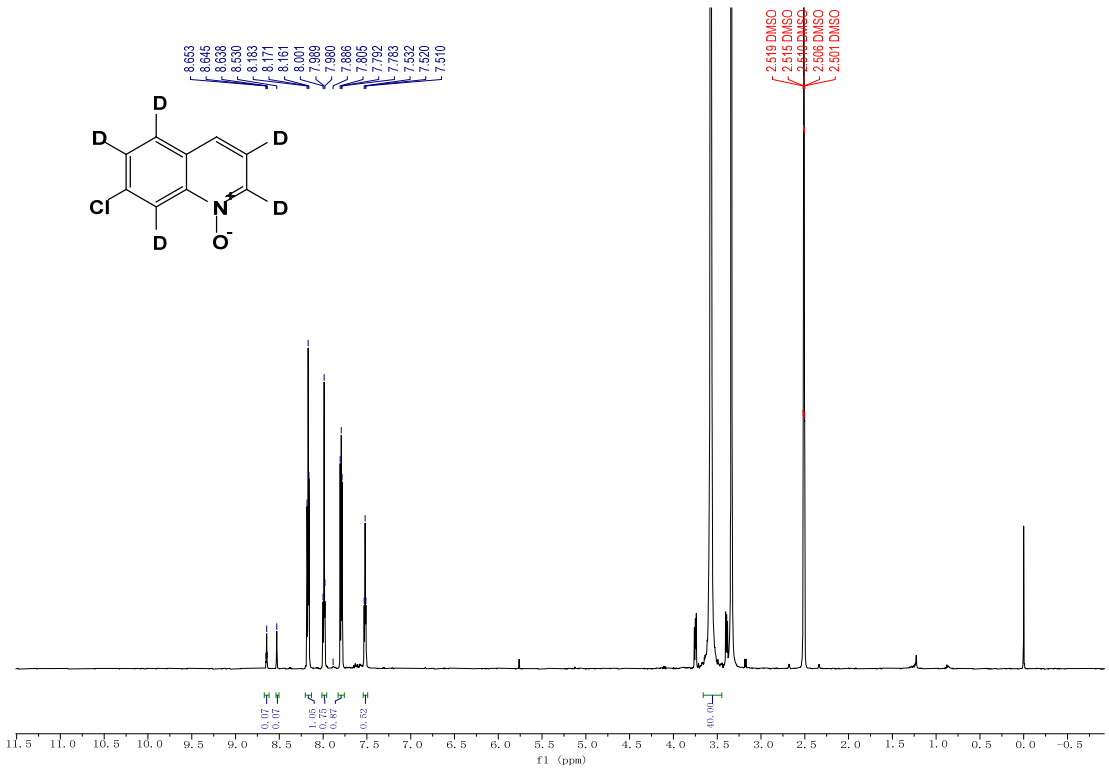


Figure S23 ^{1}H NMR (400 MHz, DMSO-d_6) of 8-*d*

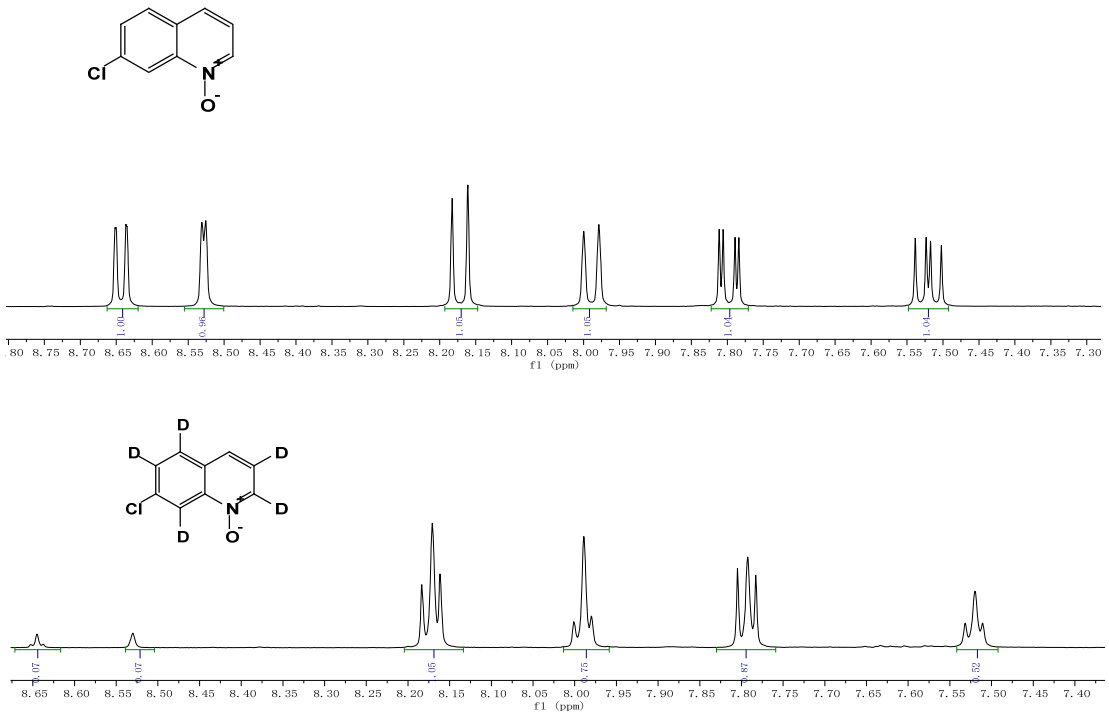
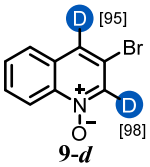


Figure S24 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 8-*d* and 8



9-*d*

Compound **9-*d*** (3-bromoquinoline-*N*-oxides):

Light yellow solid, 166 mg, yield 74%; The D-incorporation at C2 and C4 determined by ^{1}H-NMR is 98% and 95%, respectively; R_f = 0.25 (PE/EA = 5/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.7 Hz, 1H), 8.63 (**s, 0.02H, Labelled**), 7.89 (**s, 0.05H, Labelled**), 7.83 – 7.72 (m, 1H), 7.72 – 7.63 (m, 1H).

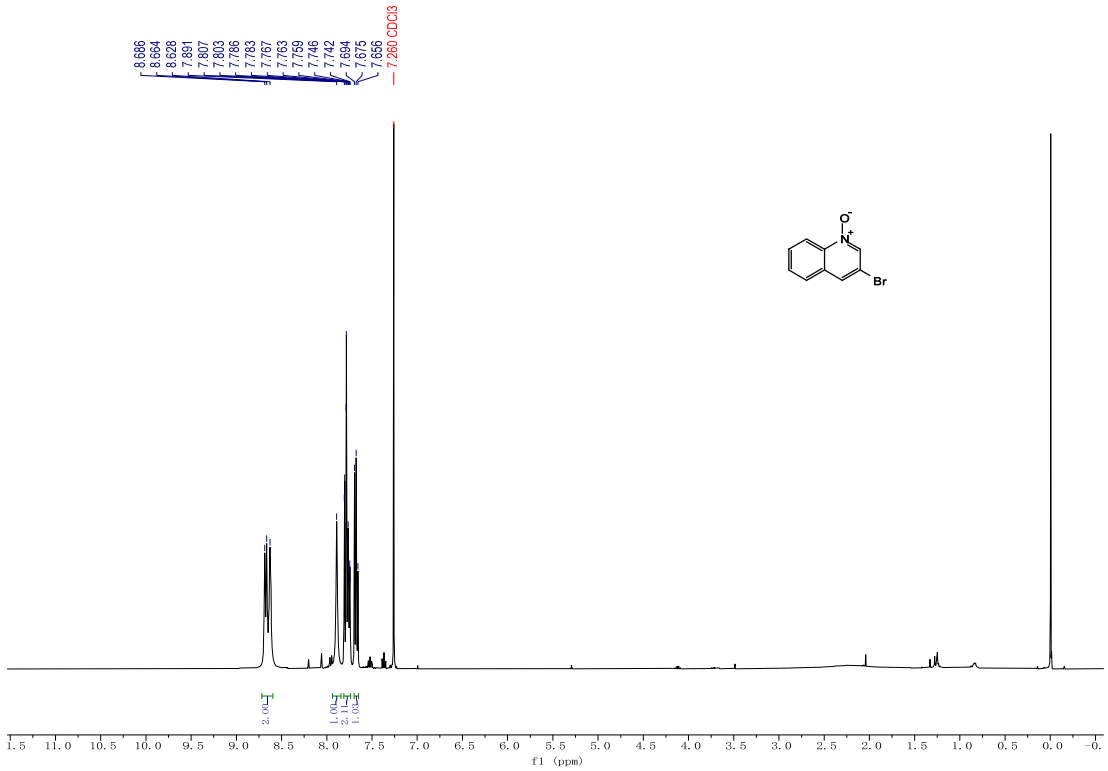


Figure S25 ^{1}H NMR (400 MHz, $CDCl_3$) of 9

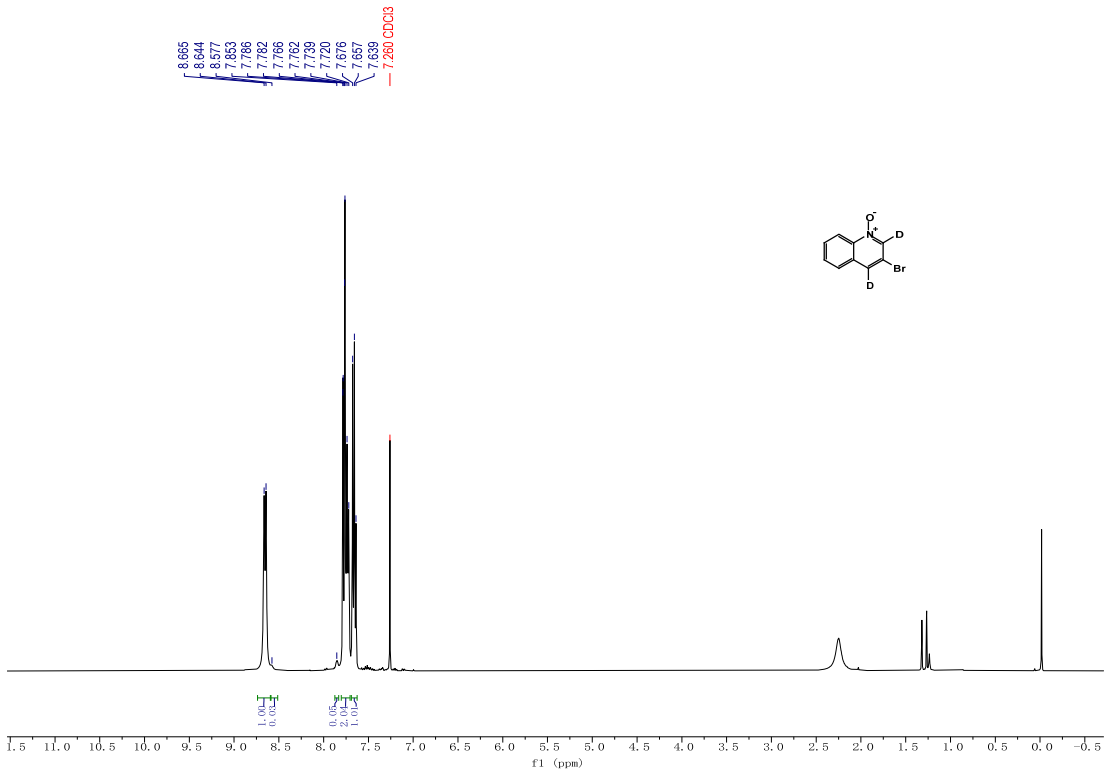


Figure S26 ^{1}H NMR (400 MHz, $CDCl_3$) of 9-*d*

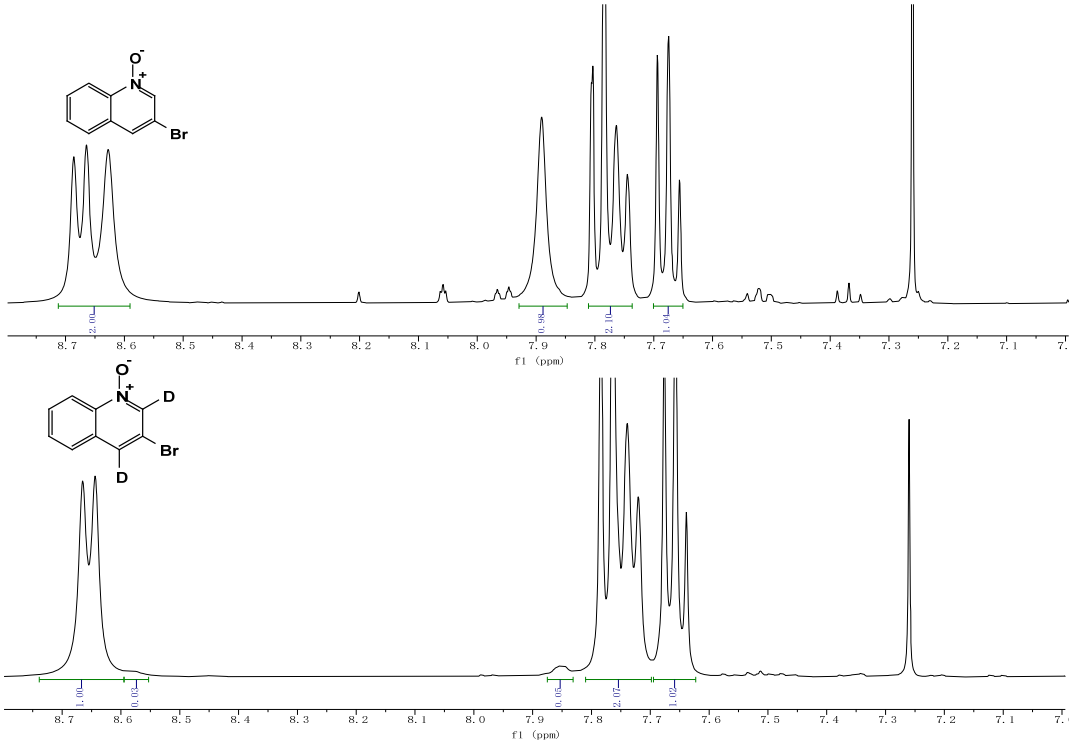
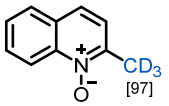


Figure S27 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 9 and 9-*d*



10-*d*

Compound **10-*d*** (2-methylquinoline-*N*-oxides):

Black solid, 116 mg, yield 74%; The D-incorporation determined by ^{1}H-NMR is 97%; R_f = 0.20 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, J = 8.9, 1.1 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.76 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 2.77 – 2.63 (**m, 0.08H, Labelled**).

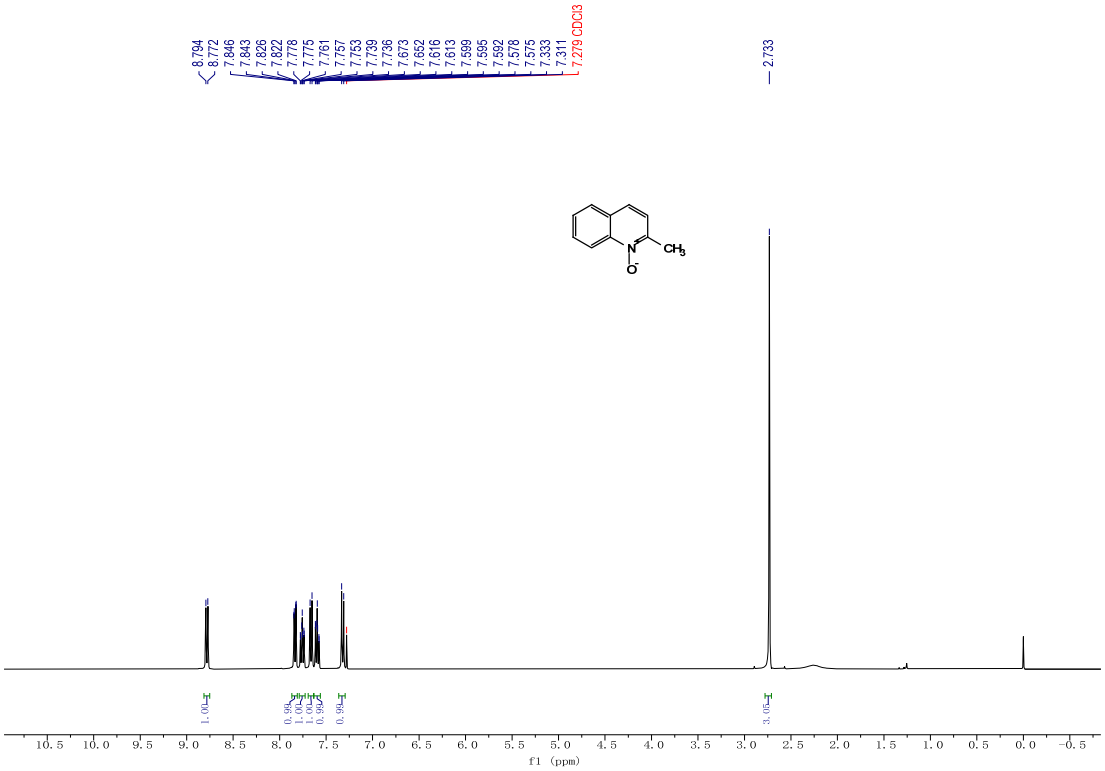


Figure S28 ^{1}H NMR (400 MHz, $CDCl_3$) of 10

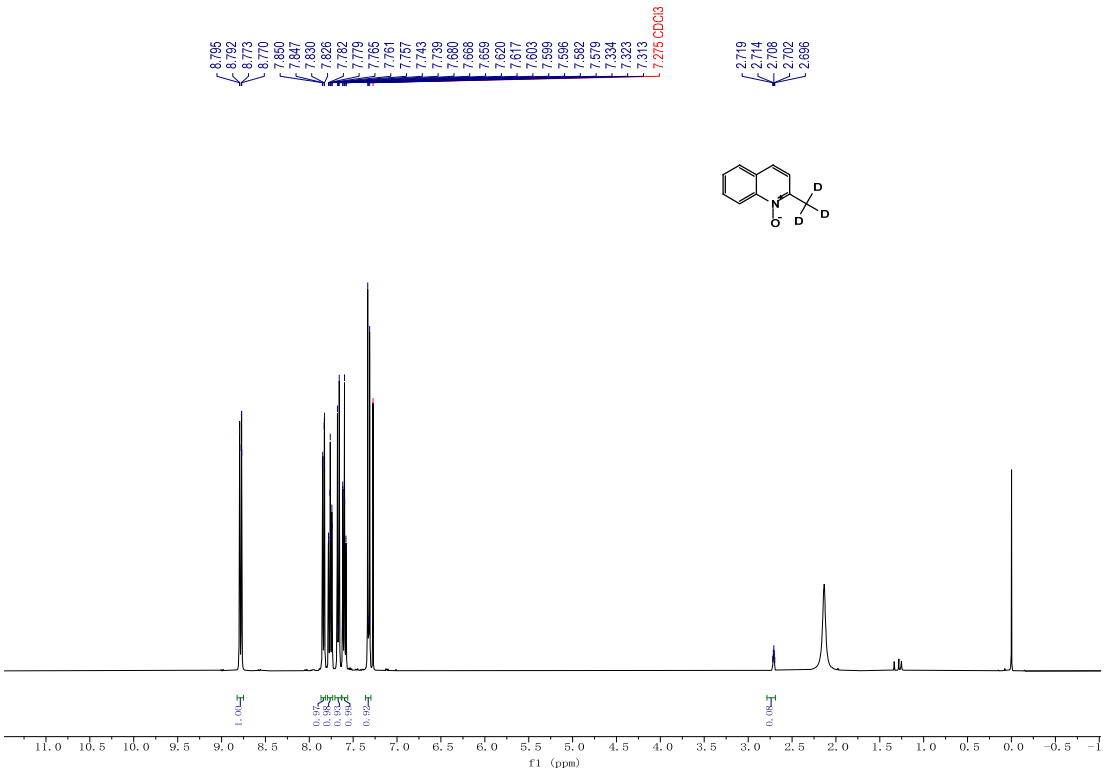


Figure S29 ^{1}H NMR (400 MHz, $CDCl_3$) of 10-*d*

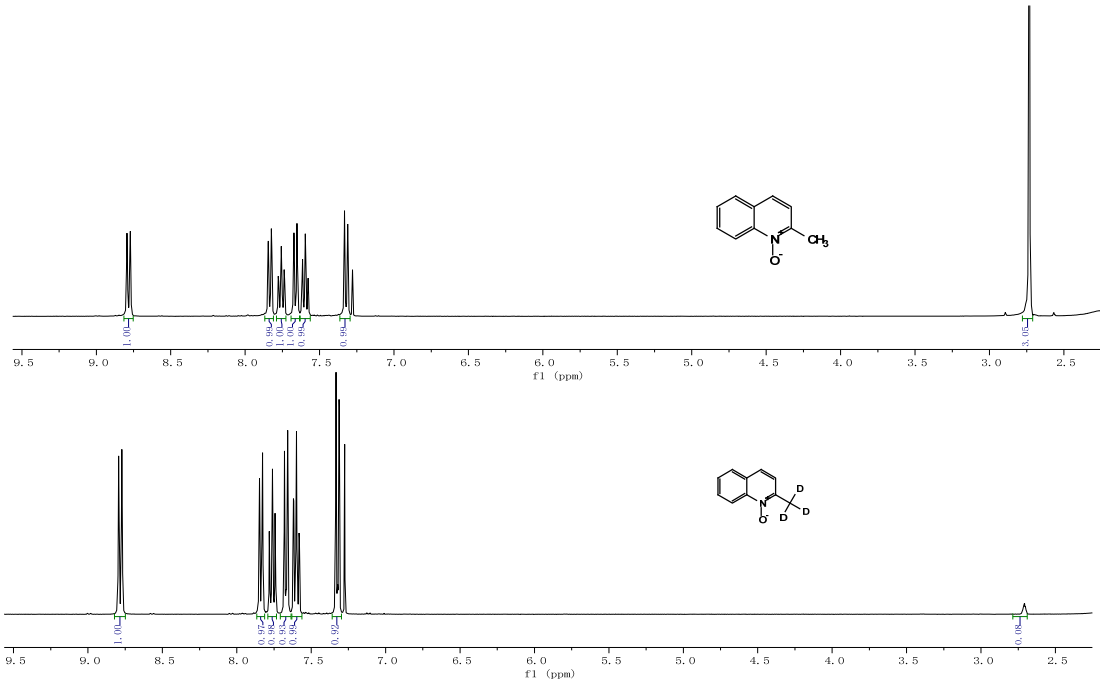
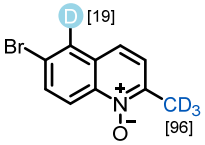


Figure S30 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 10-*d* and 10



11-*d*

Compound **11-*d*** (6-bromo-2-methylquinoline-*N*-oxides):

Yellow solid, 87 mg, yield 37%; The D-incorporation at C5 determined by ^{1}H-NMR is 19%, and The D-incorporation of methyl is 96%; R_f = 0.30 (PE/EA = 3/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 9.2 Hz, 1H), 8.01 (**<u>d, *J* = 2.0 Hz, 0.81H, Labelled</u>**), 7.82(dd, J = 9.2, 1.9 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 2.74 (**<u>m, 0.02H, Labelled</u>**).

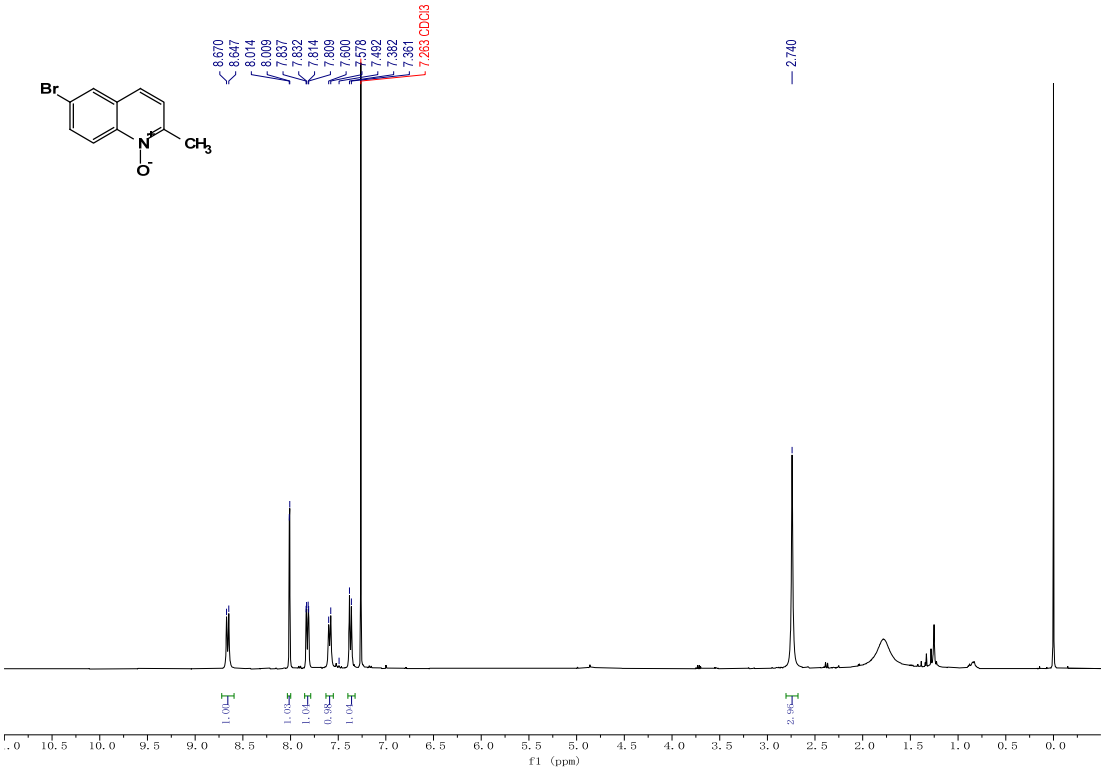


Figure S31 ^{1}H NMR (400 MHz, $CDCl_3$) of 11

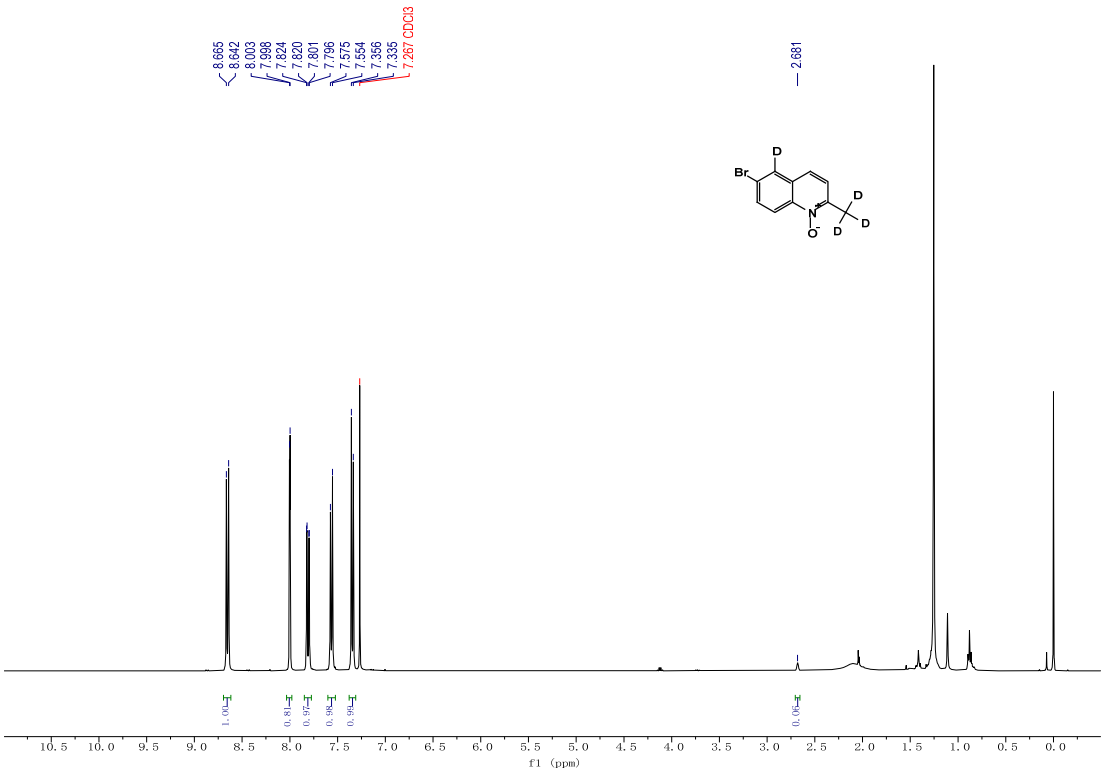


Figure S32 ^{1}H NMR (400 MHz, $CDCl_3$) of 11-*d*

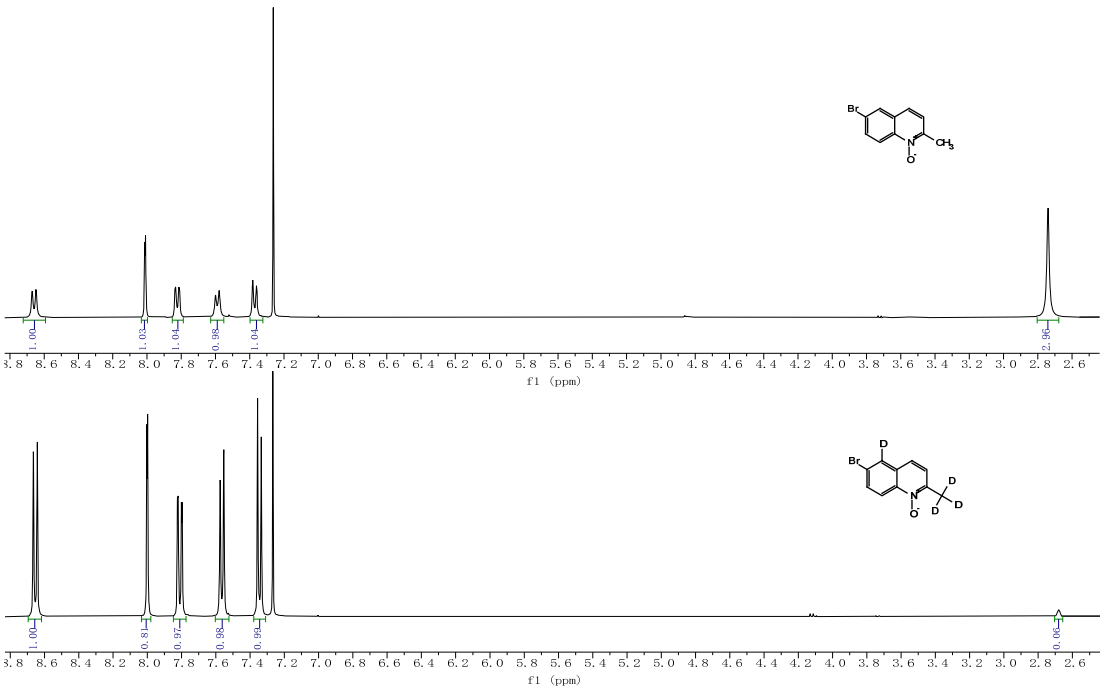
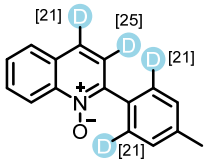


Figure S33 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 11-*d* and 11



12-*d*

Compound **12-*d*** (2-(4-methylphenyl) quinoline-*N*-oxides):

Yellow solid, 131 mg, yield 56%; The D-incorporation at C3 and C4 determined by ^{1}H-NMR is 25% and 21%, and the D-incorporation of the two ortho-position of the phenyl is 21%; R_f = 0.20 (PE/EA = 1/1)

^{1}H-NMR (400 MHz, CDCl3) δ 8.87 (**s, 0.79H, Labelled**), 7.91 (**d, *J* = 7.8 Hz, 1.58H, Labelled**), 7.87 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.74 (**d, *J* = 8.8 Hz, 0.50H, Labelled**), 7.66 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 2.45 (s, 3H).

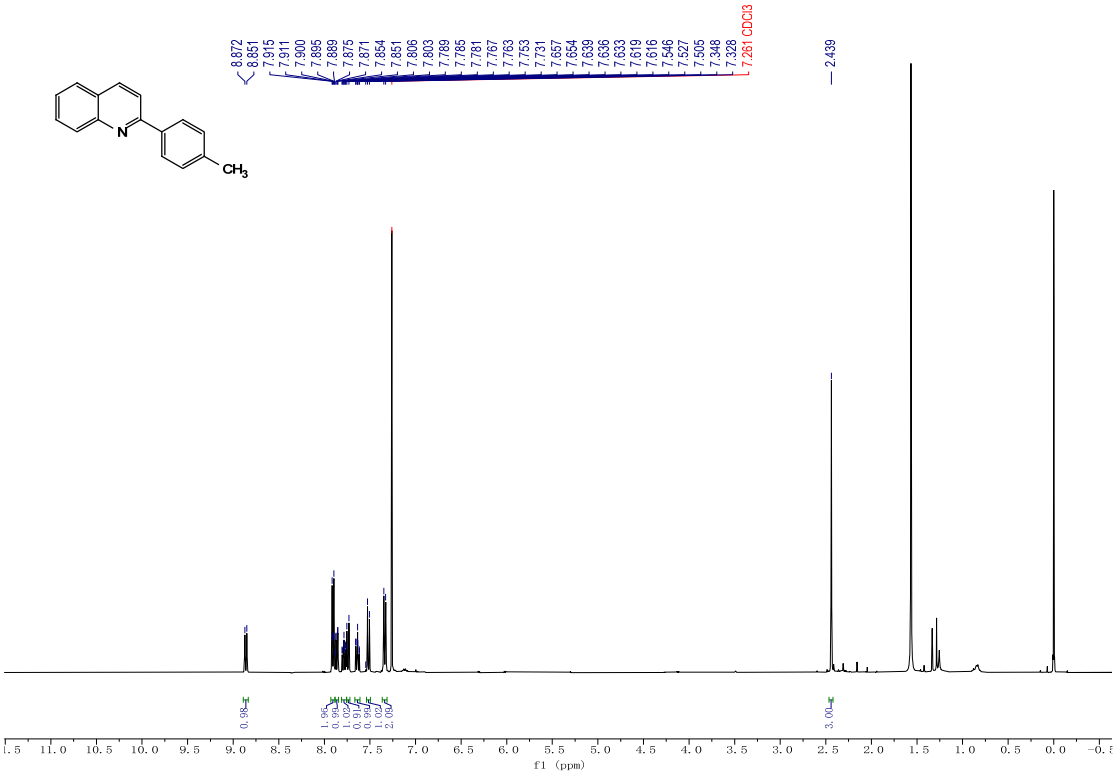


Figure S34 ^{1}H NMR (400 MHz, $CDCl_3$) of 12

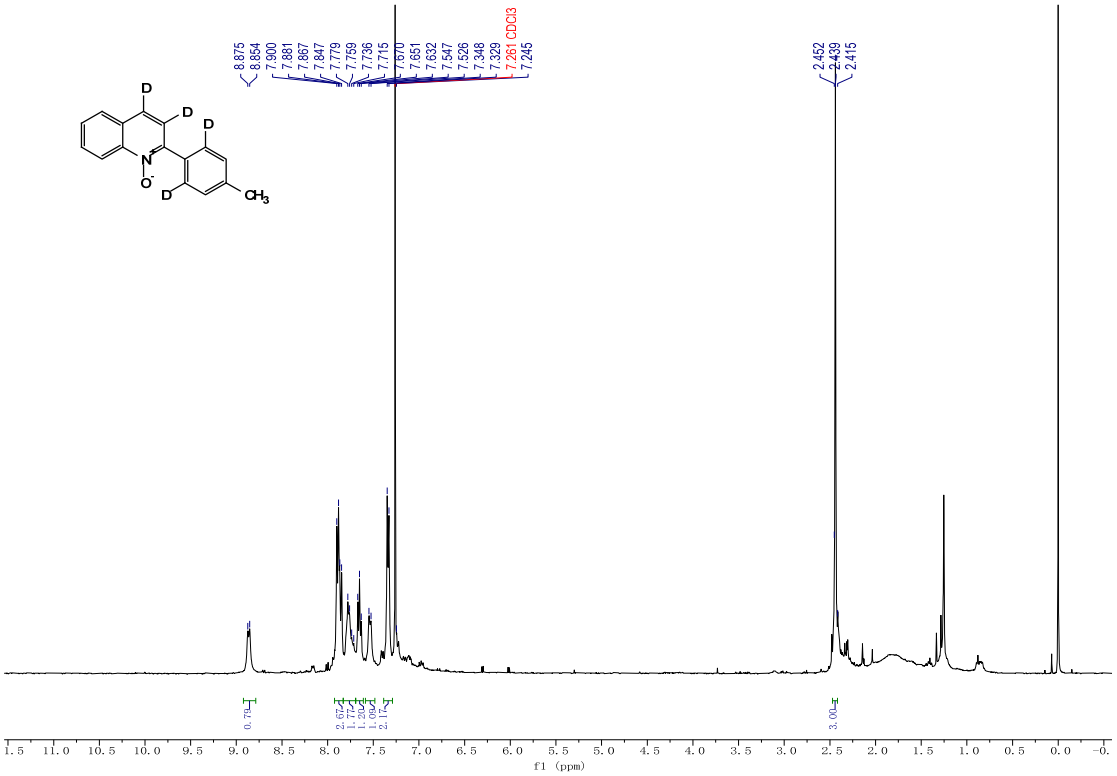


Figure S35 ^{1}H NMR (400 MHz, $CDCl_3$) of 12-*d*

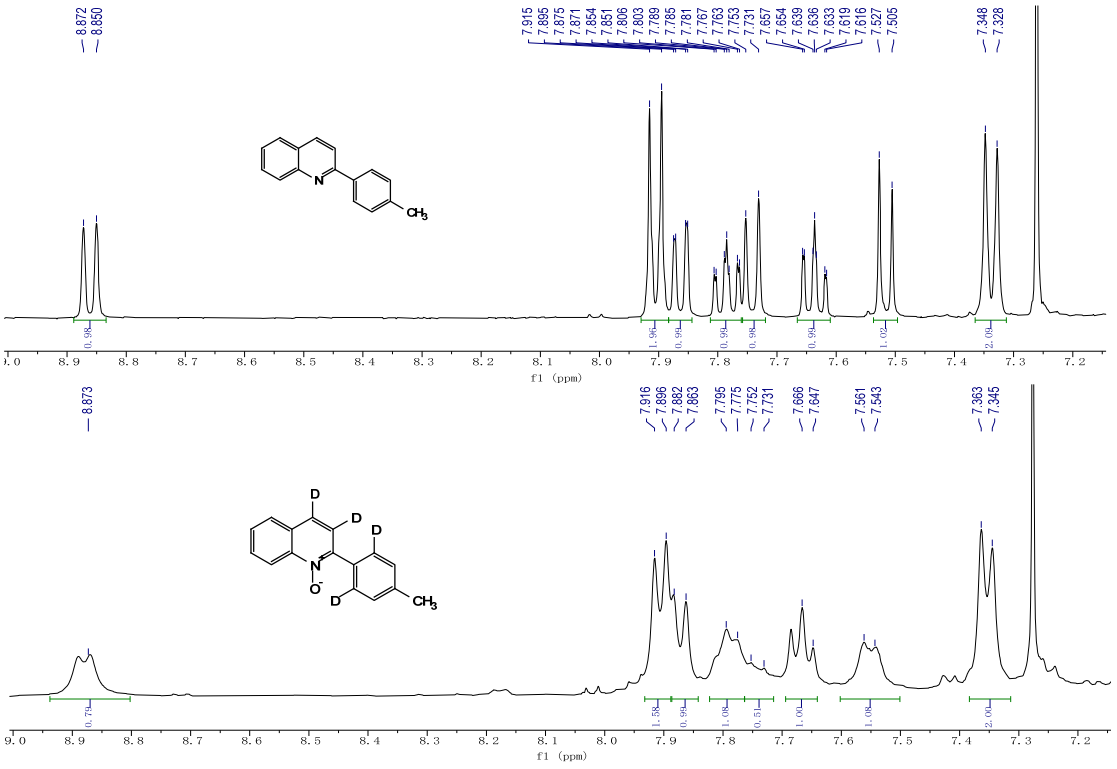
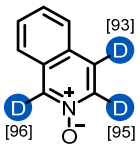


Figure S36. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 12-*d* and 12



13-*d*

Compound **13-*d*** (isoquinoline-*N*-oxides):

Yellow solid, 112 mg, yield 77%; The D-incorporation at C1, C3, and C4 determined by ^{1}H-NMR is 96%, 95%, and 93%, respectively; R_f = 0.20 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.79 (**s, 0.04H, Labelled**), 8.15 (**s, 0.05H, Labelled**), 7.78 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.68 (**s, 0.03H, Labelled**), 7.58 (p, *J* = 6.9 Hz, 2H).

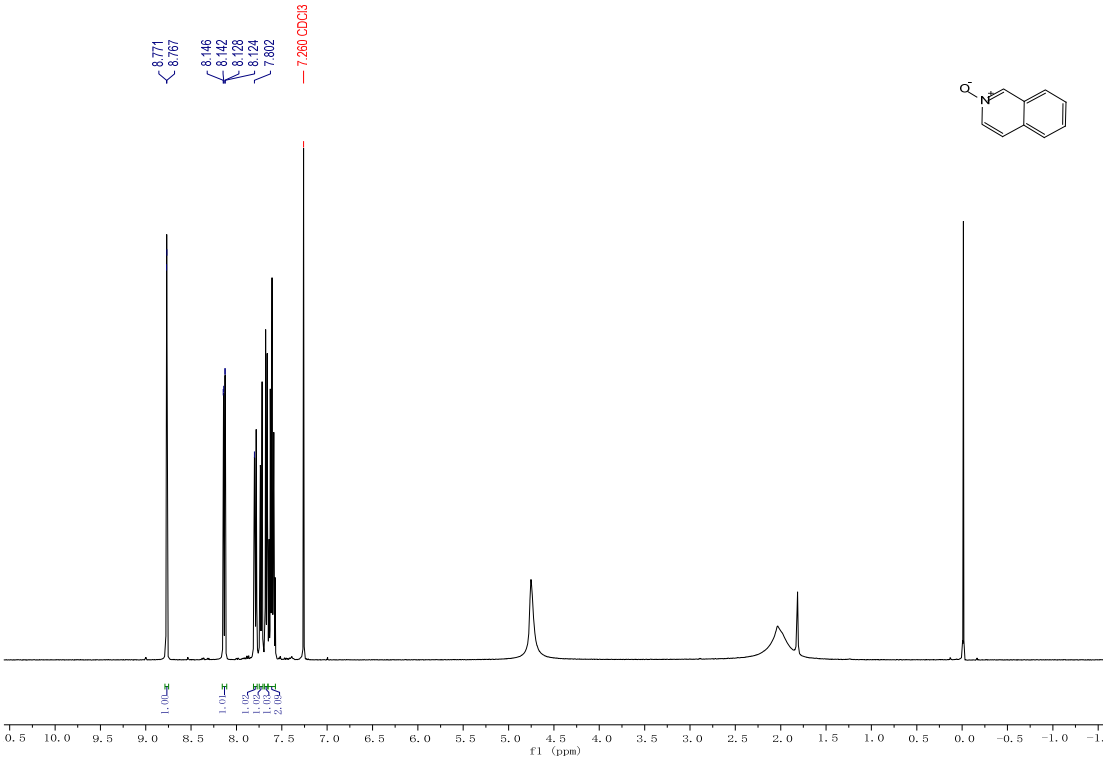


Figure S37 ^{1}H NMR (400 MHz, CDCl3) of 13

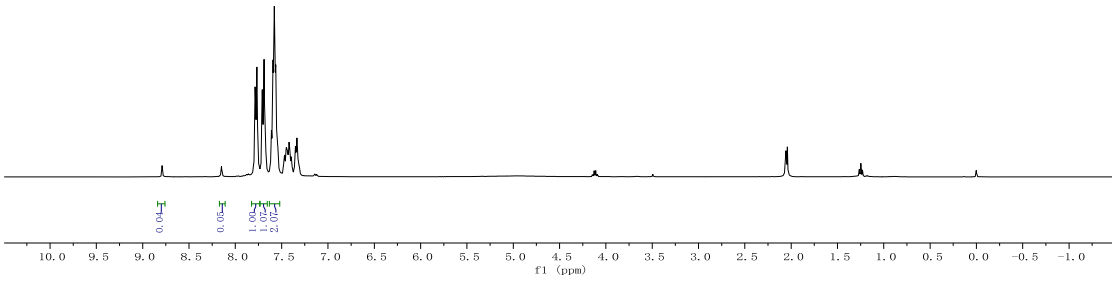


Figure S38 ^{1}H NMR (400 MHz, $CDCl_3$) of 13-*d*

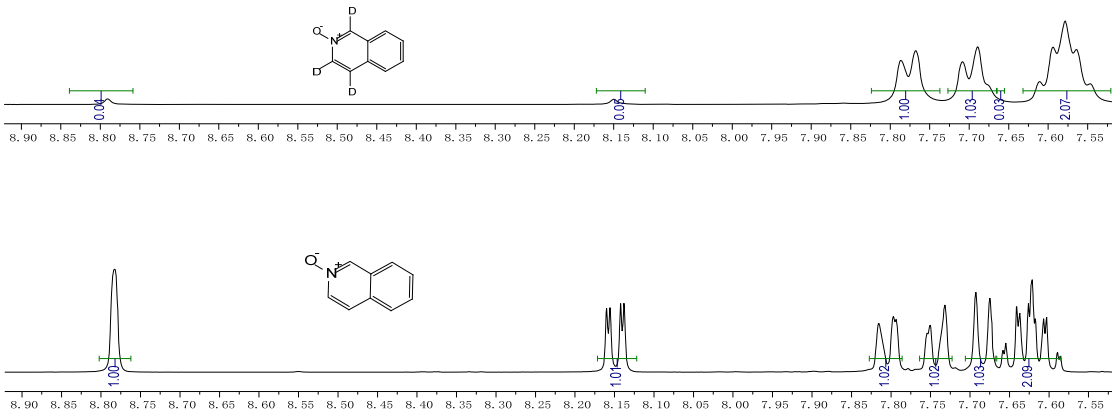
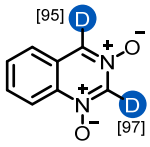


Figure S39 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 13-*d* and 13



14-*d*

Compound **14-*d*** (quinazoline-1,3-*N*-oxides):

White solid, 52 mg, yield 32%; The D-incorporation at C2 and C4 determined by ^{1}H-NMR is 99% and 95%, respectively; R_f = 0.25 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 8.10 (**s, 0.03H, Labelled**), 7.81 (dt, J = 14.1, 7.9 Hz, 2H), 7.71 – 7.51 (**m, 1.05H, Labelled**).

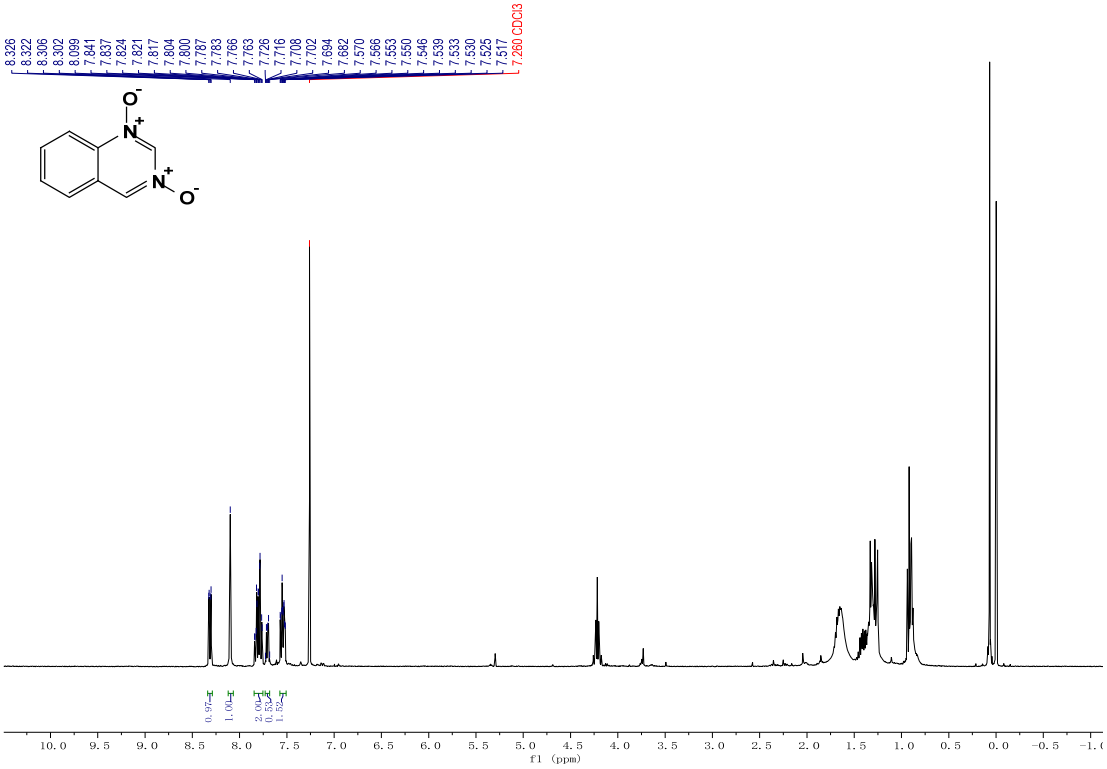


Figure S40 ^{1}H NMR (400 MHz, $CDCl_3$) of 14

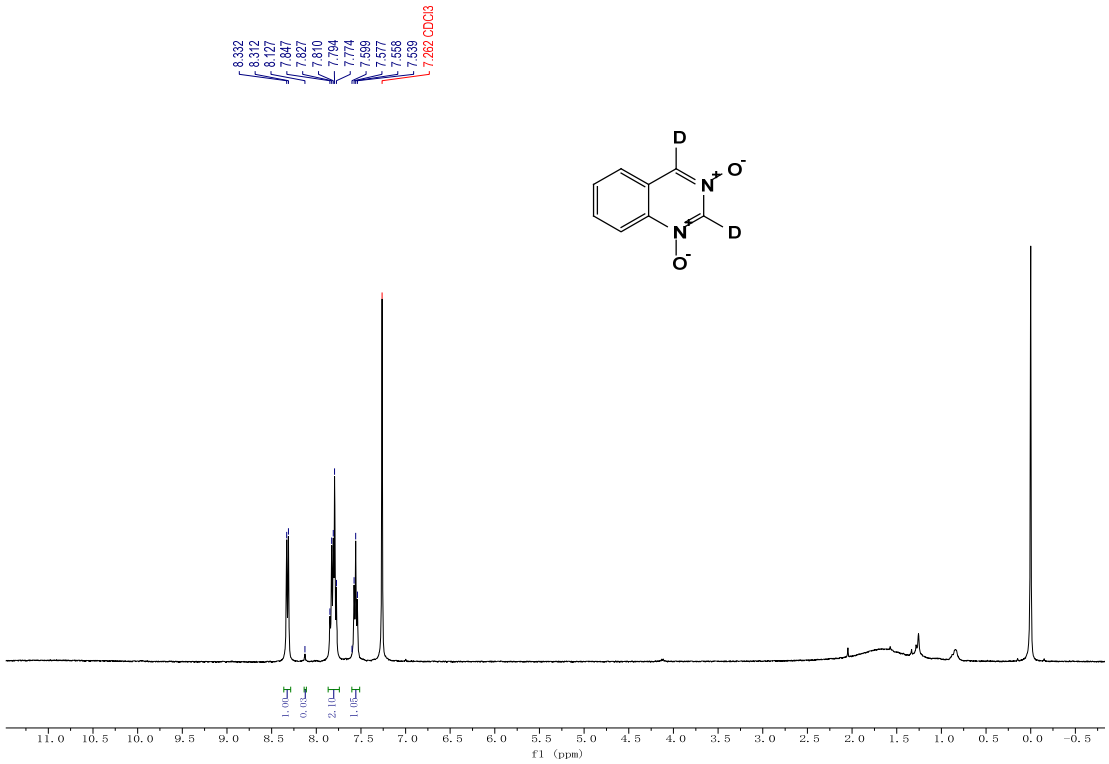


Figure S41 ^{1}H NMR (400 MHz, $CDCl_3$) of 14-*d*

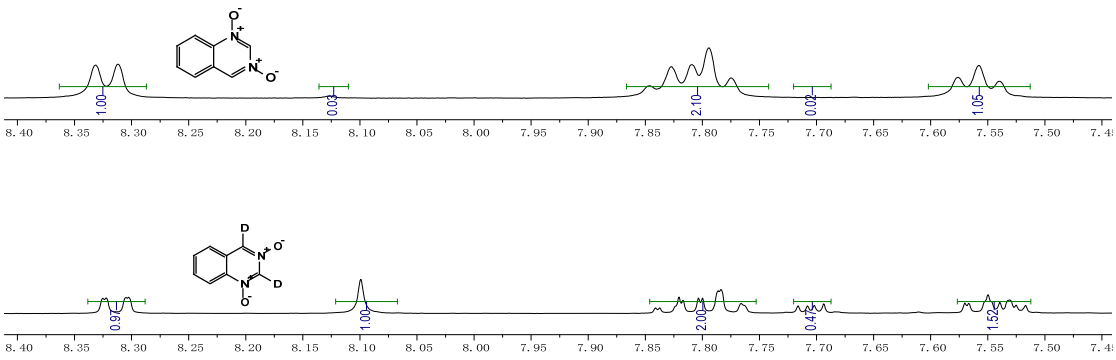
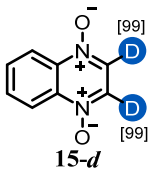


Figure S42 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 14-*d* and 14



15-*d*

Compound **15-*d*** (quinoxaline-1,4-*N*-oxides):

Yellow solid, 136 mg, yield 94%; The D-incorporation at C2, C3, determined by ^{1}H-NMR is 99%, respectively; R_f = 0.20 (PE/EA = 1/1).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.64-8.58 (m, 2H), 8.23 (<u>s, 0.03H, **Labelled**</u>), 7.91-7.87 (m, 2H).

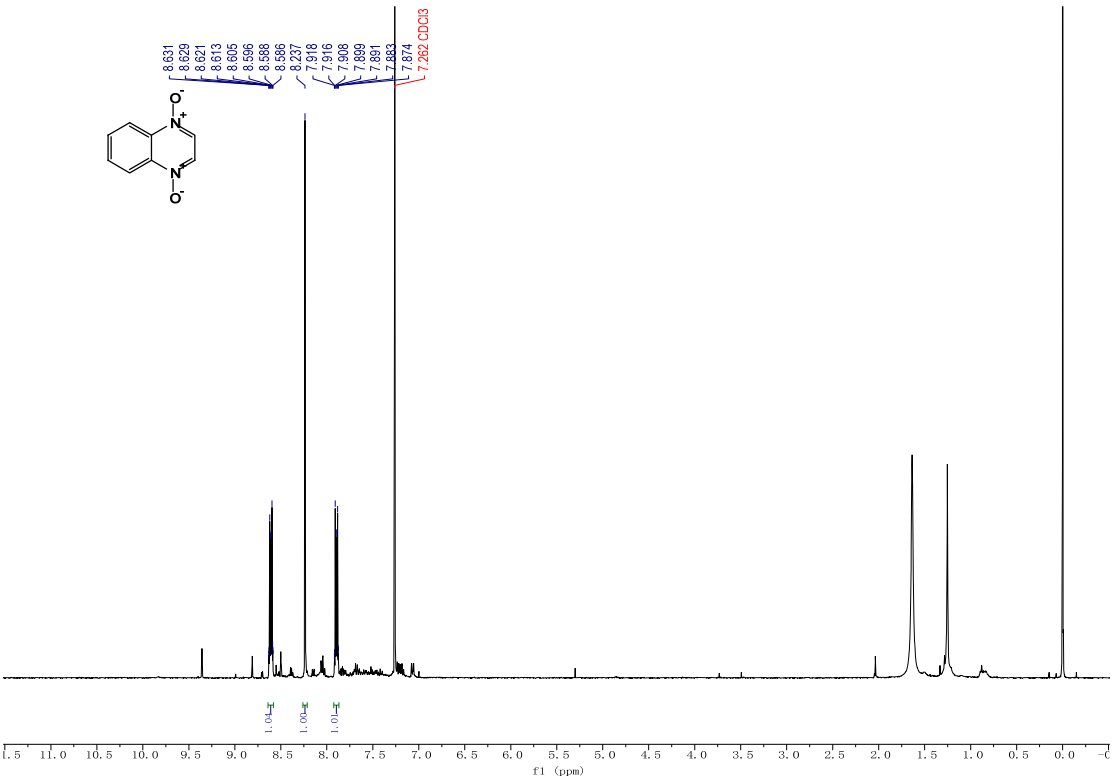


Figure S43 ^{1}H NMR (400 MHz, $CDCl_3$) of 15

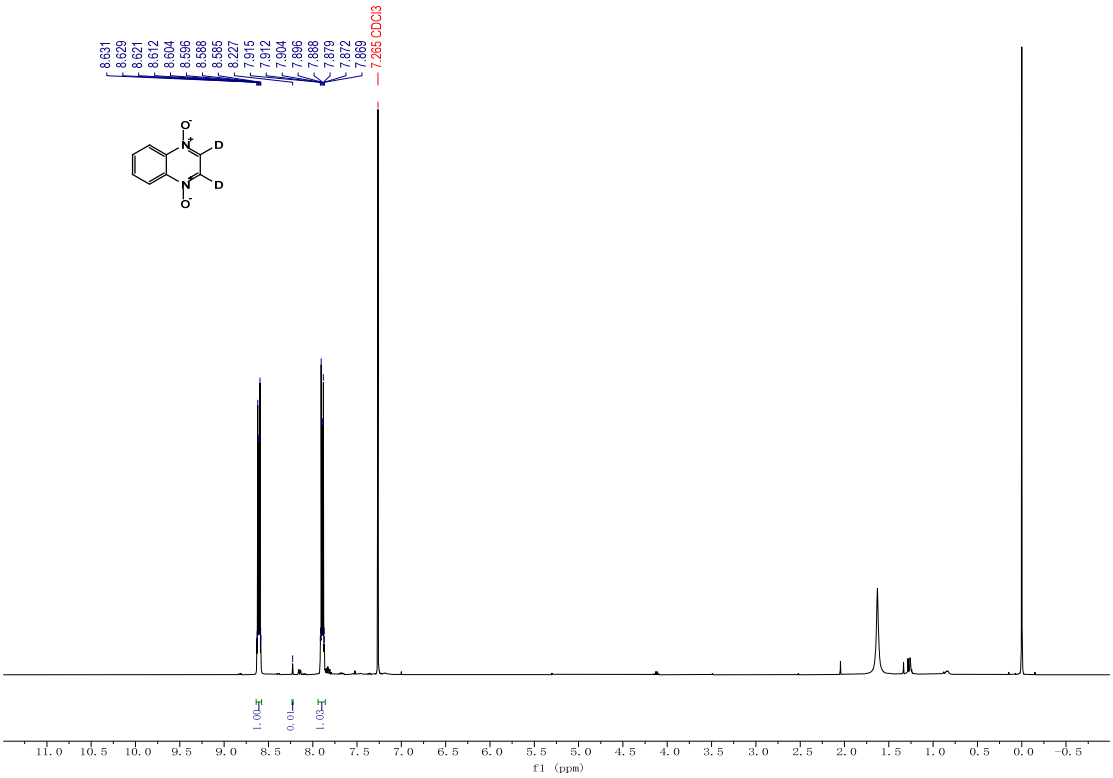


Figure S44 ^{1}H NMR (400 MHz, $CDCl_3$) of 15-*d*

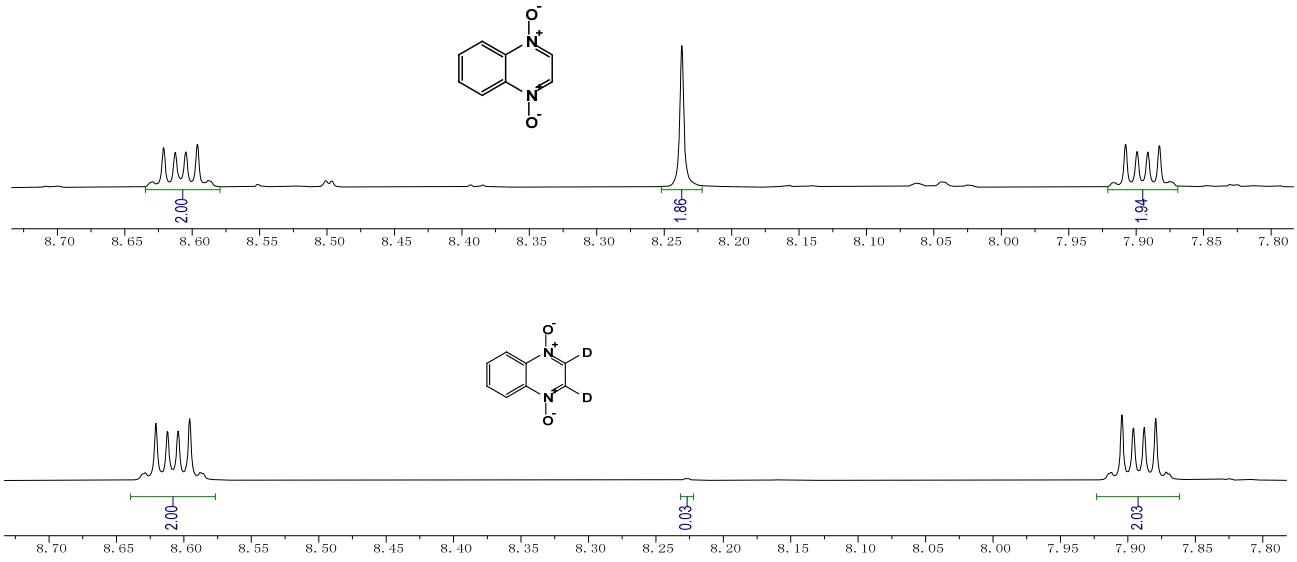
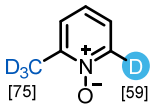


Figure S45 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 15-*d* and 15



16-*d*

Compound **16-*d*** (2-methylpyridine-*N*-oxides):

Yellow solid, 105 mg, yield 96%; The D-incorporation at C2 determined by ^{1}H-NMR is 59%, and its D-incorporation of methyl is 93%; R_f = 0.20 (EA).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (**dd, *J* = 6.1, 1.6 Hz, 0.41H, Labelled**), 7.27 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.21 (td, *J* = 7.8, 1.4 Hz, 1H), 7.16 (dd, *J* = 7.7, 3.1 Hz, 1H), 2.52 (**tt, *J* = 4.6, 2.8 Hz, 0.76H, Labelled**).

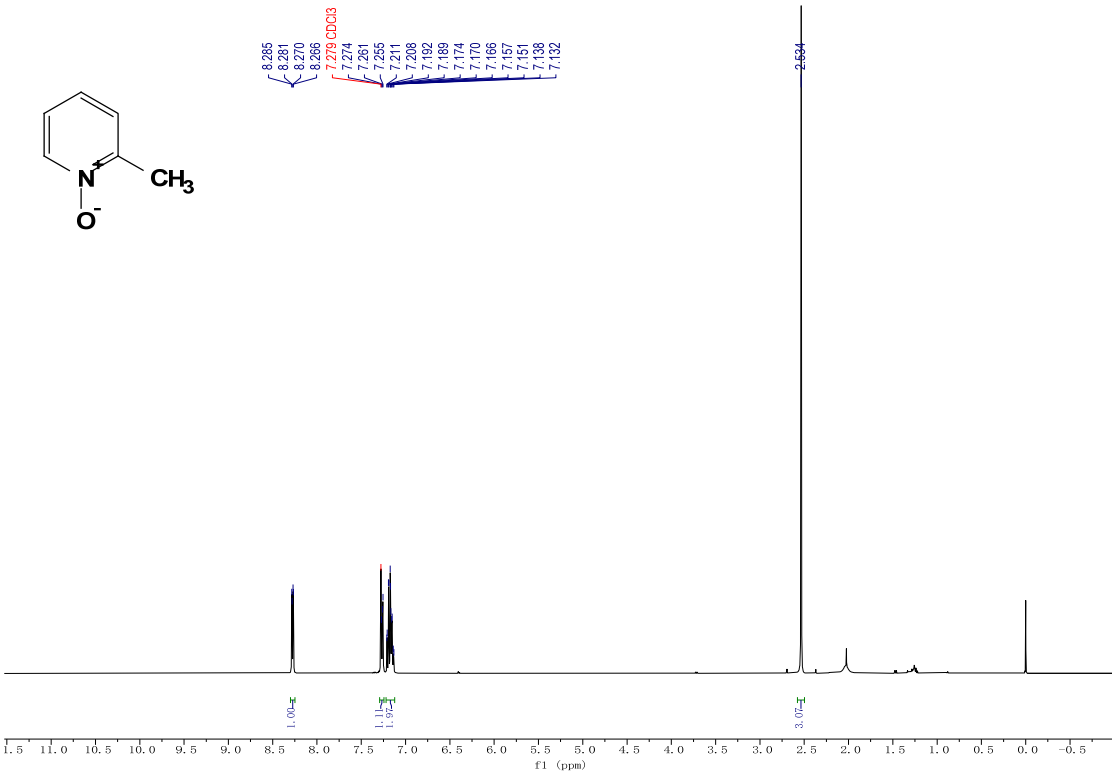


Figure S46 ^{1}H NMR (400 MHz, $CDCl_3$) of 16

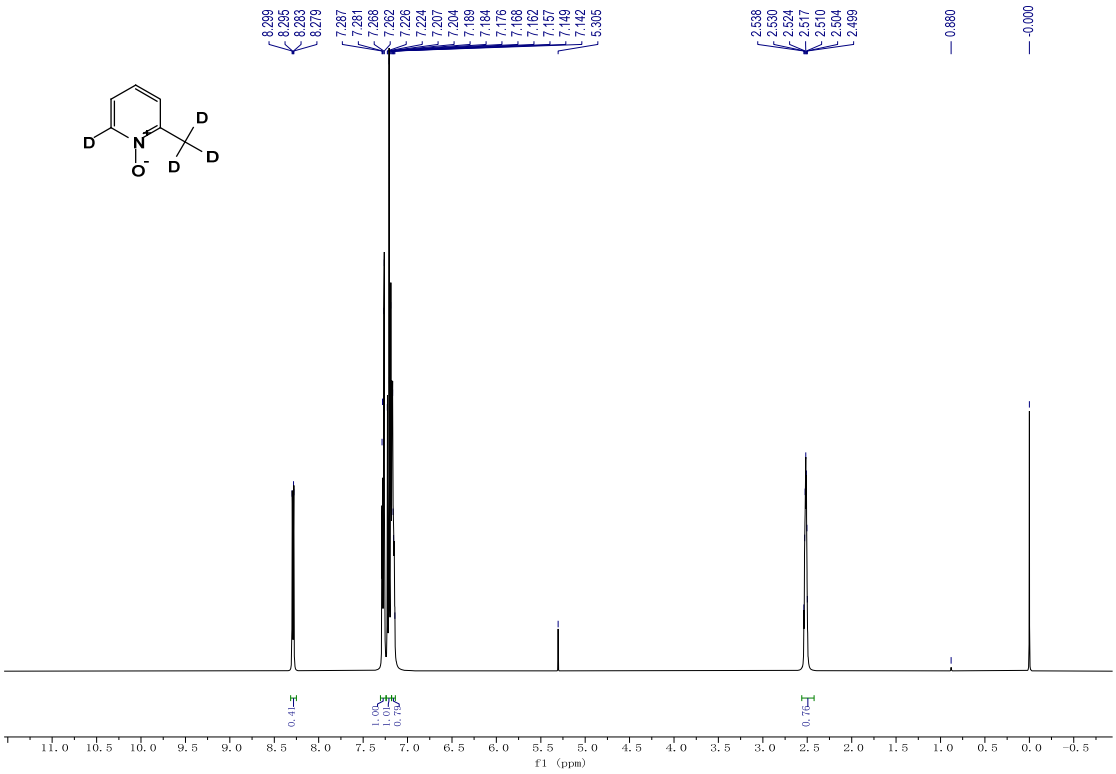


Figure S47 ^{1}H NMR (400 MHz, $CDCl_3$) of 16-*d*

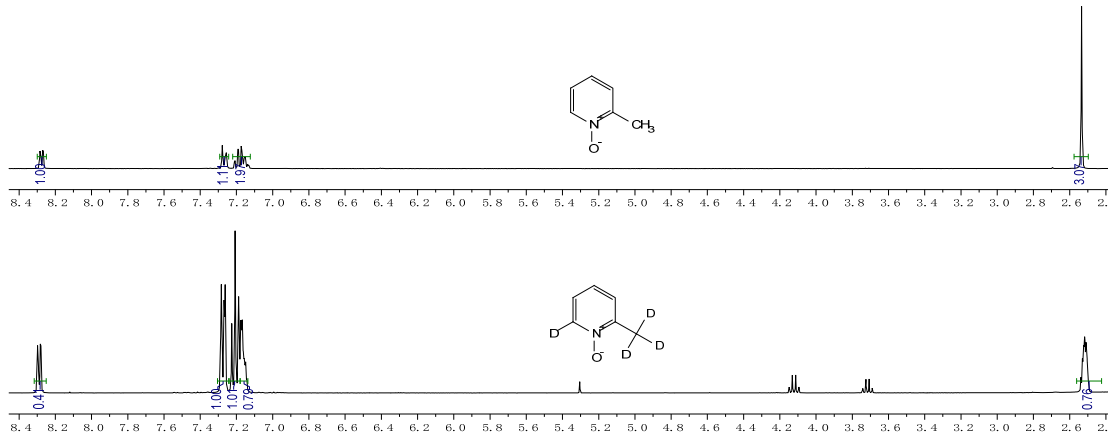
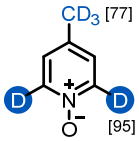


Figure S48 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 16-*d* and 16



17-*d*

Compound **17-*d*** (4-methylpyridine-*N*-oxides):

Yellow solid, 105 mg, yield 96%; The D-incorporation at C2 determined by ^{1}H-NMR is 59%, and its D-incorporation of methyl is 93%; R_f = 0.10 (EA).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.08 (**<u>m, 0.10H, Labelled</u>**), 7.09 (d, J = 6.5 Hz, 2H), 2.36 (**<u>s, 0.87H, Labelled</u>**).

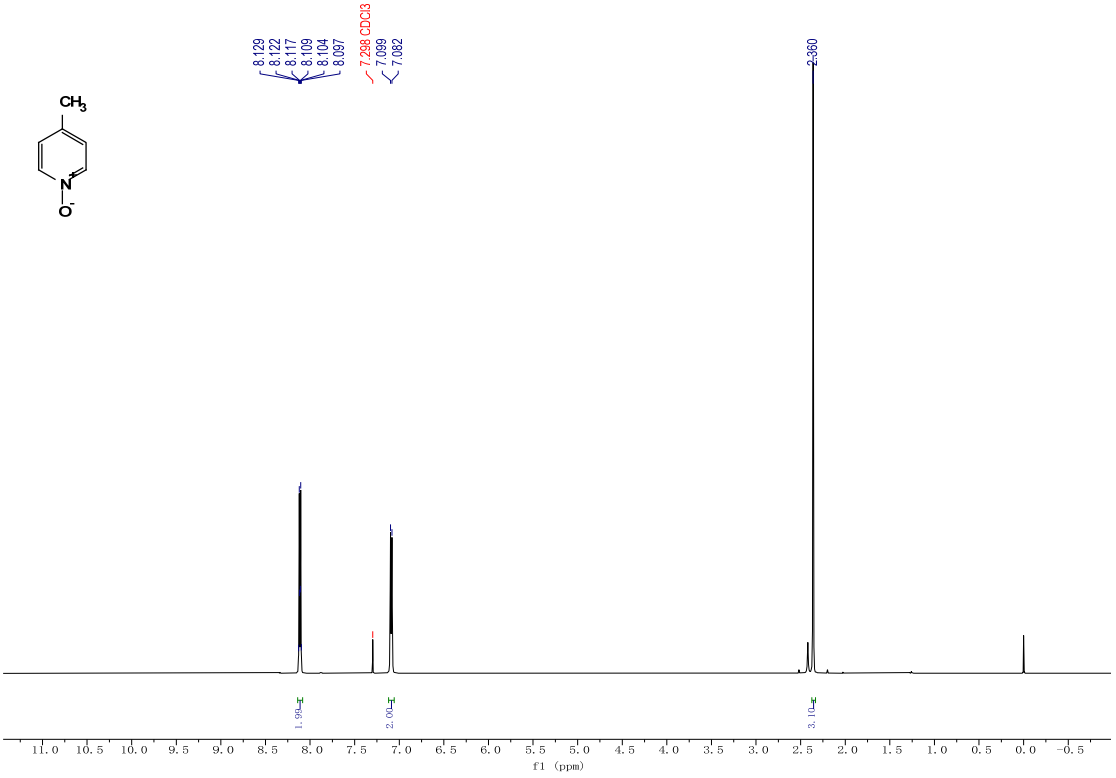


Figure S49 ^{1}H NMR (400 MHz, $CDCl_3$) of 17

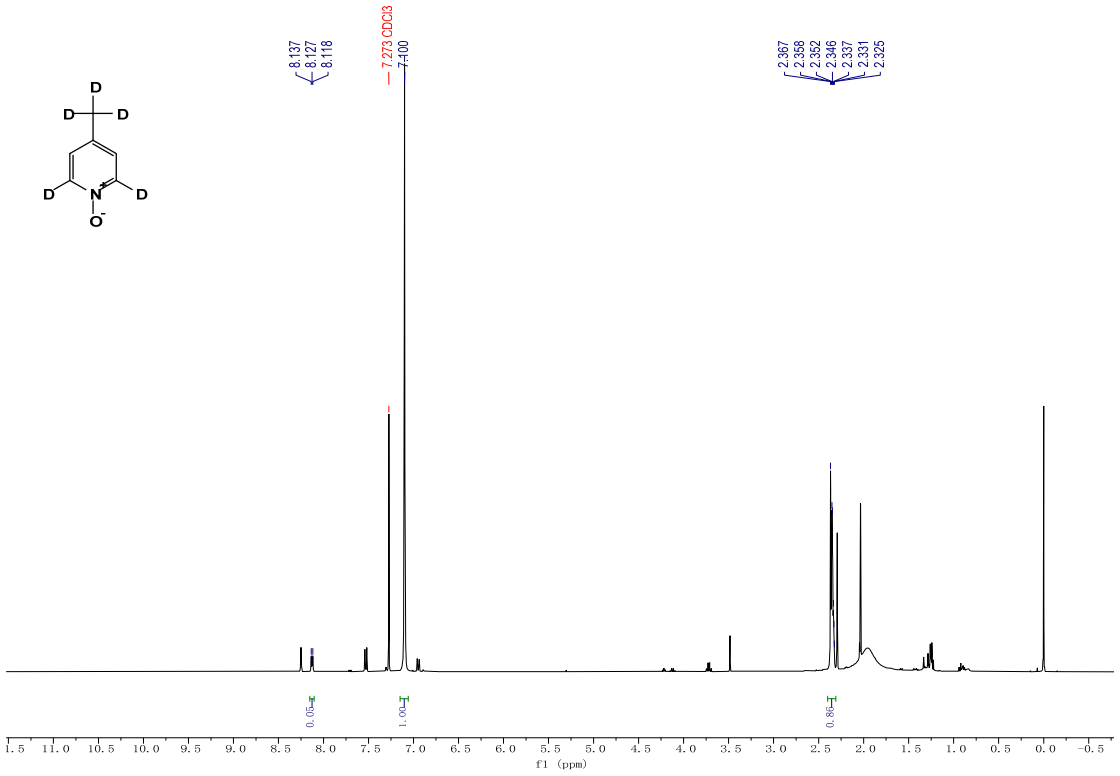


Figure S50 ^{1}H NMR (400 MHz, $CDCl_3$) of 17-*d*

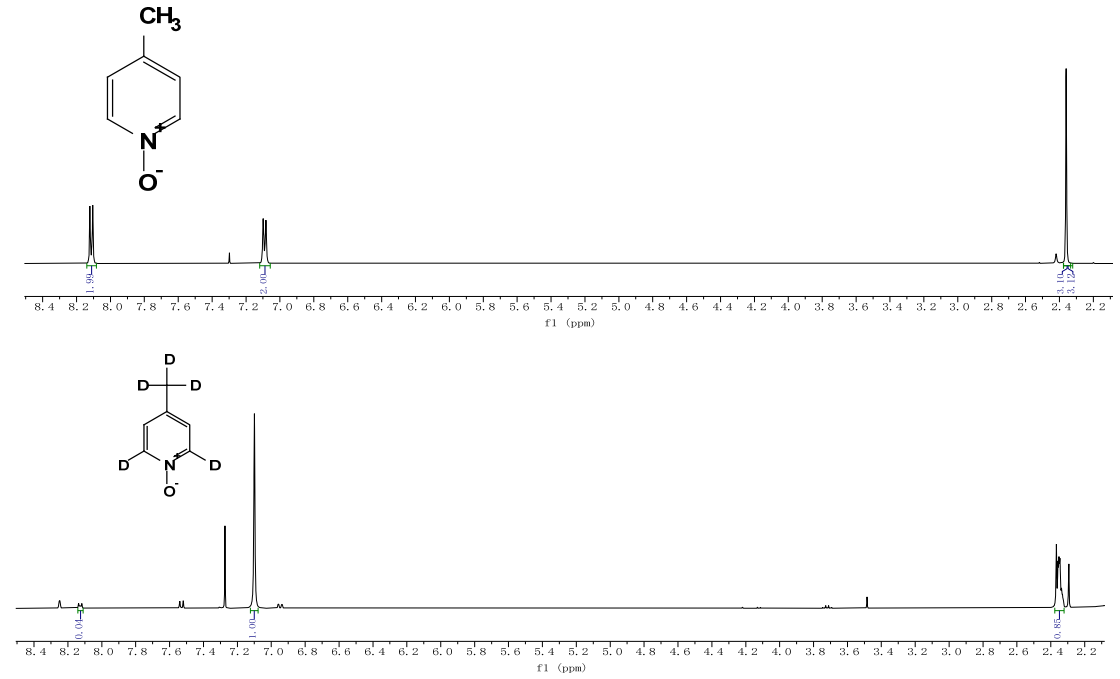
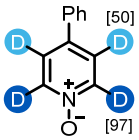


Figure S51 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 17-*d* and 17



18-*d*

Compound **18-*d*** (4-phenylpyridine-*N*-oxides):

White solid, 192 mg, yield 87%; The D-incorporation at ortho-position of N-oxide bond is 97% and 50%, respectively; R_f = 0.10 (EA).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.23 (**m, 0.06H, Labelled**), 7.62 – 7.56 (m, 2H), 7.54 – 7.41 (**m, 3H, Labelled**).

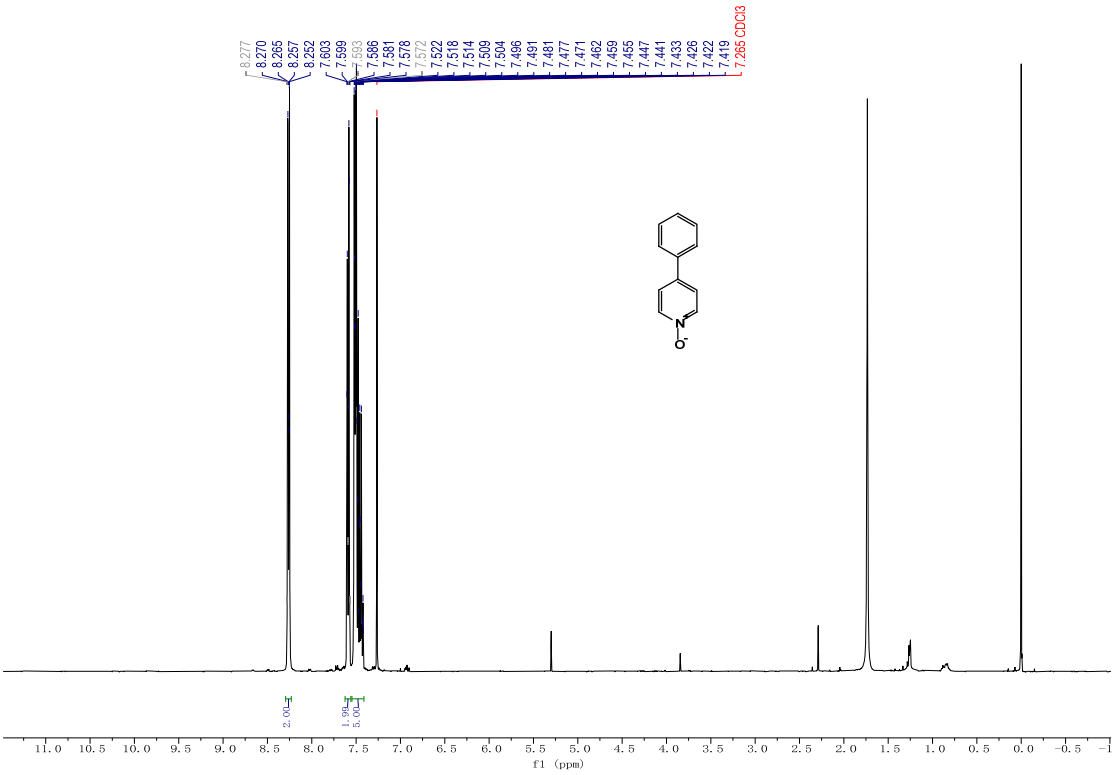


Figure S52 ^{1}H NMR (400 MHz, $CDCl_3$) of 18

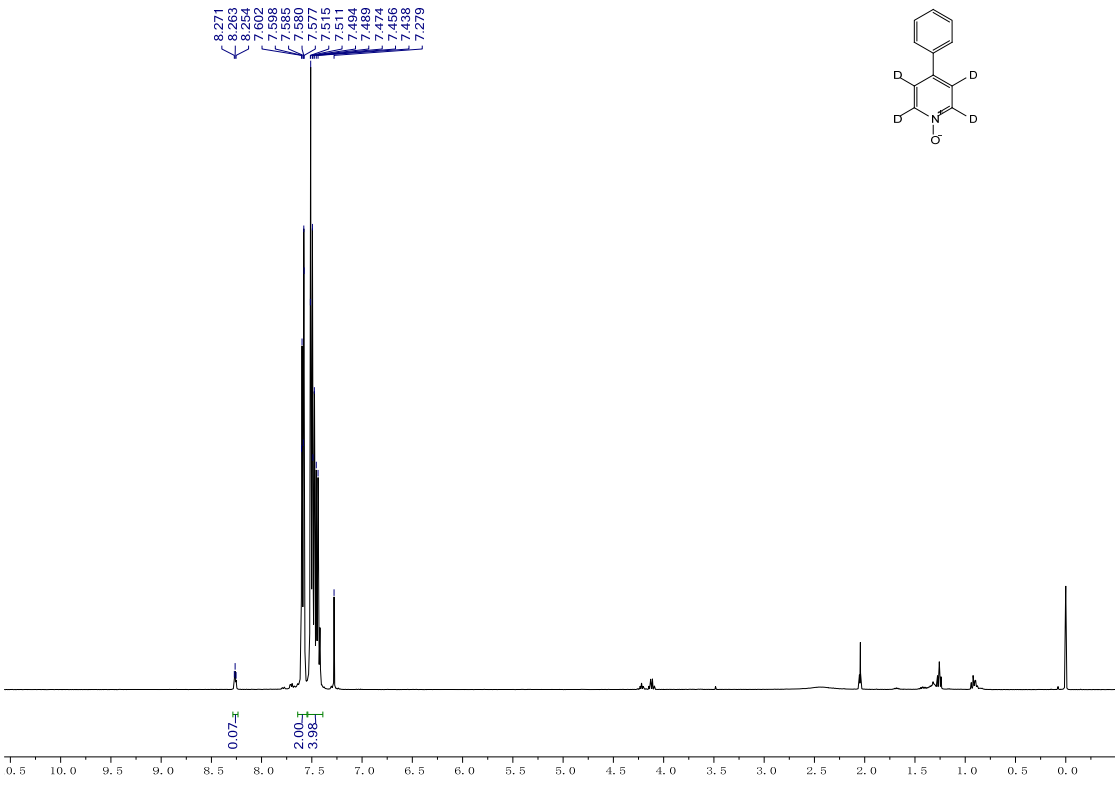


Figure S53 ^{1}H NMR (400 MHz, $CDCl_3$) of 18-*d*

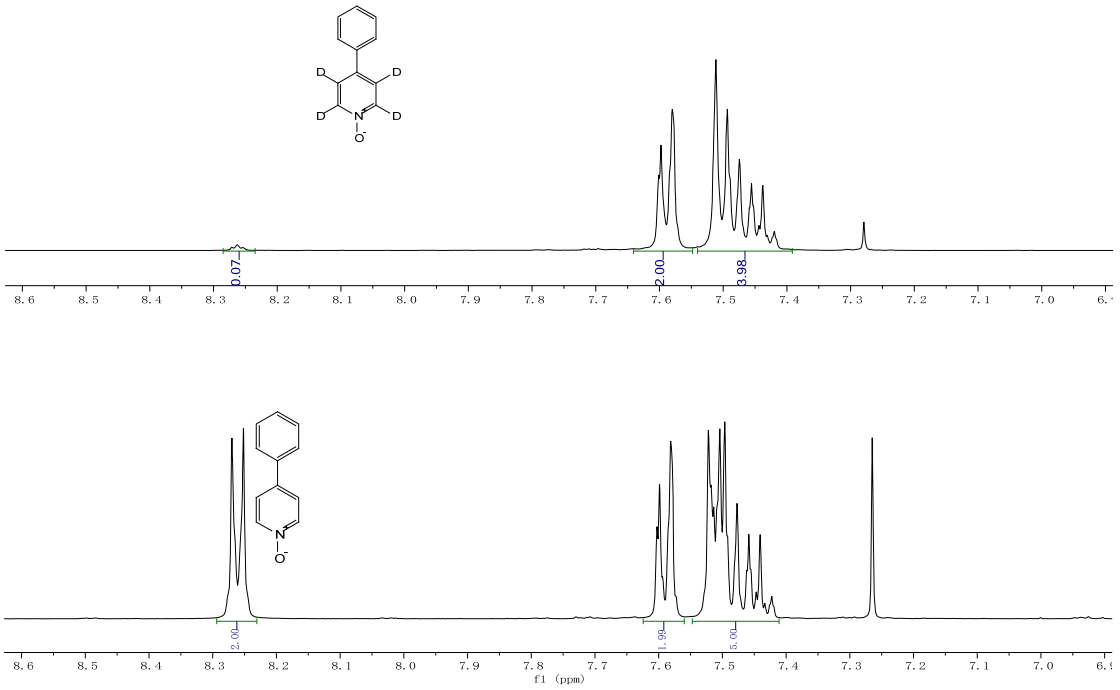
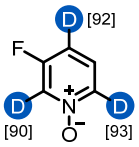


Figure S54 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 18-*d* and 18



19-*d*

Compound **19-*d*** (3-fluoropyridine-*N*-oxides):

Yellow liquid, 110 mg, yield 97%; The D-incorporation at C2, C4, and C6 determined by ^{1}H-NMR is 93%, 92%, and 90%, respectively; R_f = 0.10 (EA).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (**d, *J* = 4.2 Hz, 0.10H, Labelled**), 8.08 (**m, 0.07H, Labelled**), 7.27 (d, *J* = 6.2 Hz, 1H),7.09 (**ddd, *J* = 8.9, 6.6, 2.2 Hz,0.08H, Labelled**)。

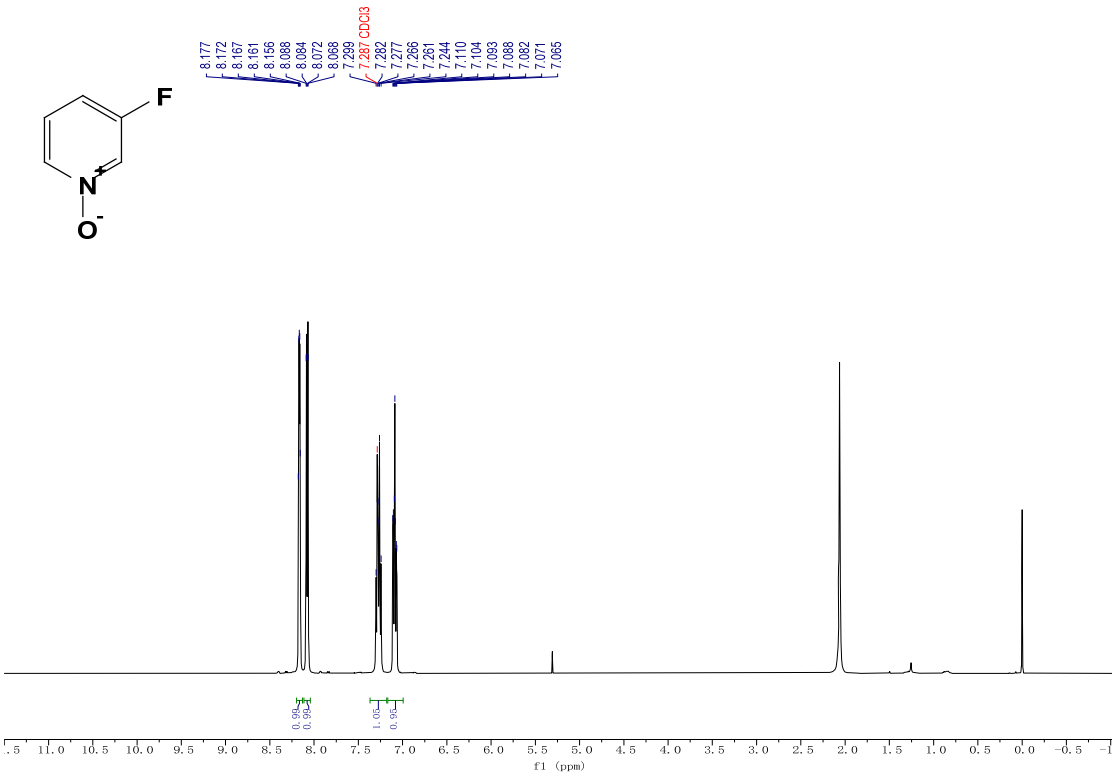


Figure S55 ^{1}H NMR (400 MHz, $CDCl_3$) of 19

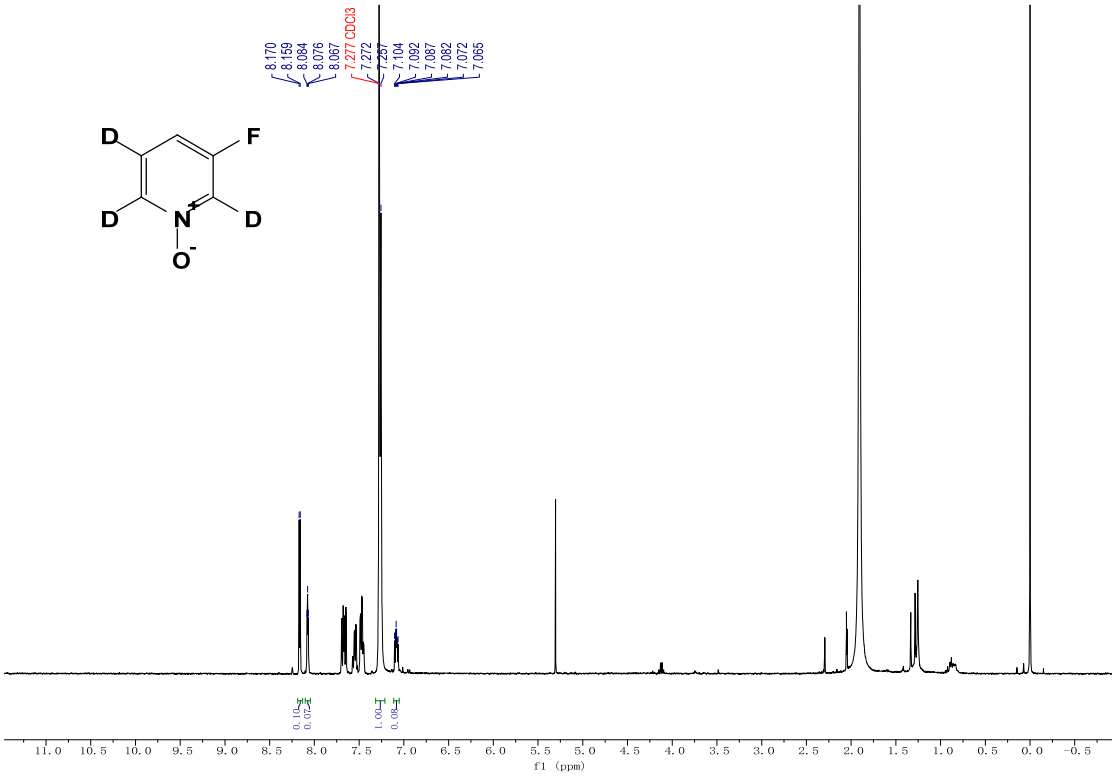


Figure S56 ^{1}H NMR (400 MHz, $CDCl_3$) of 19-*d*

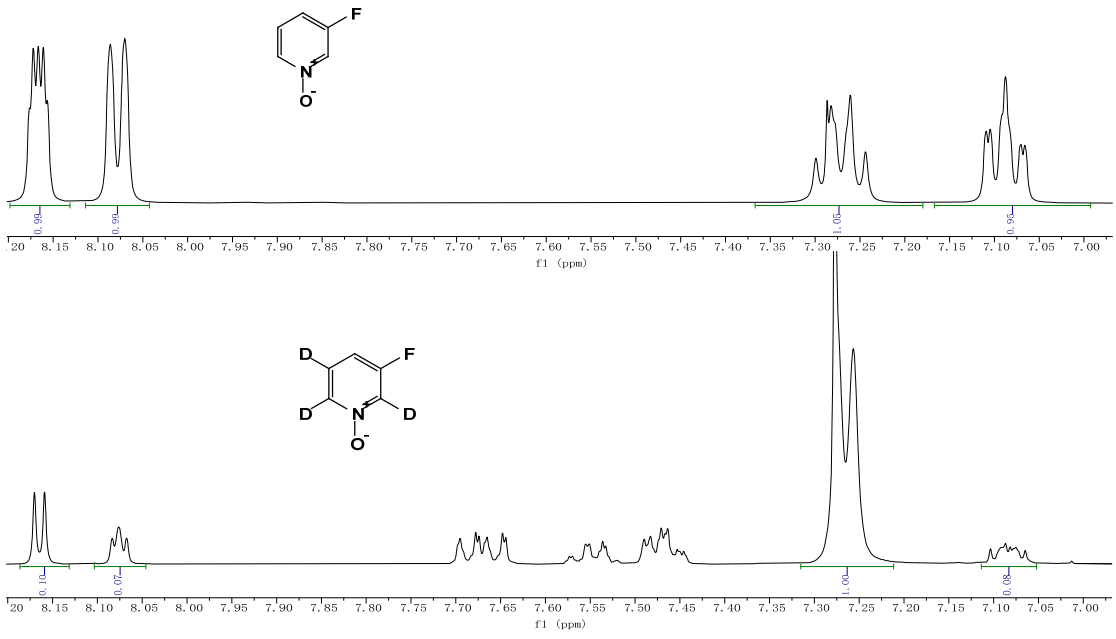


Figure S57 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 19-*d* and 19

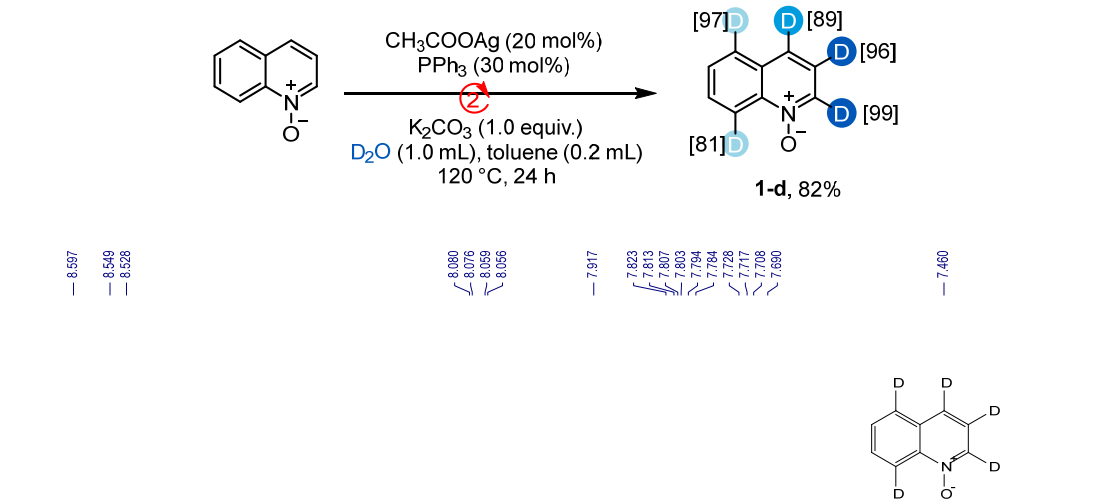


Figure S58 ^{1}H NMR (400 MHz, $CDCl_3$) of Iterative H/D exchange

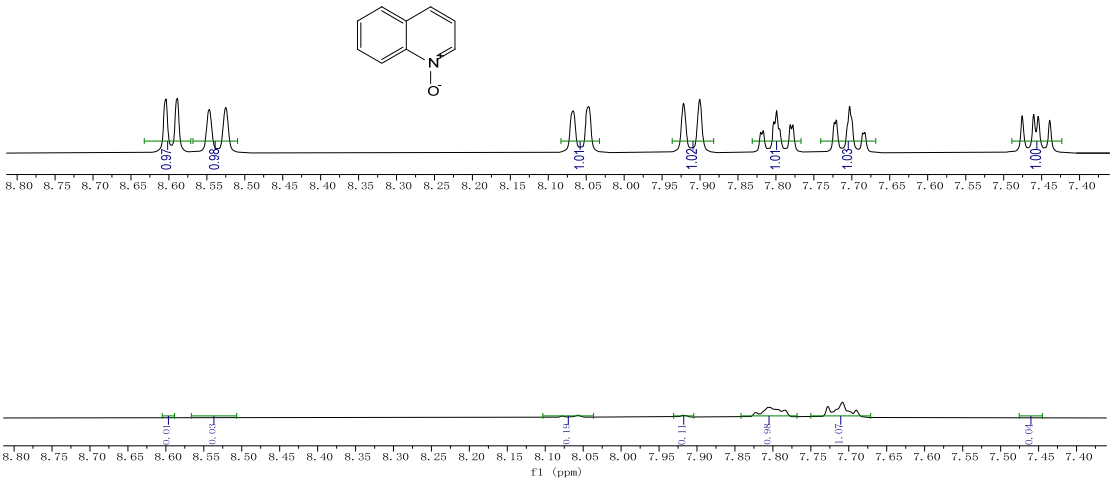


Figure S59 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of Iterative H/D exchange

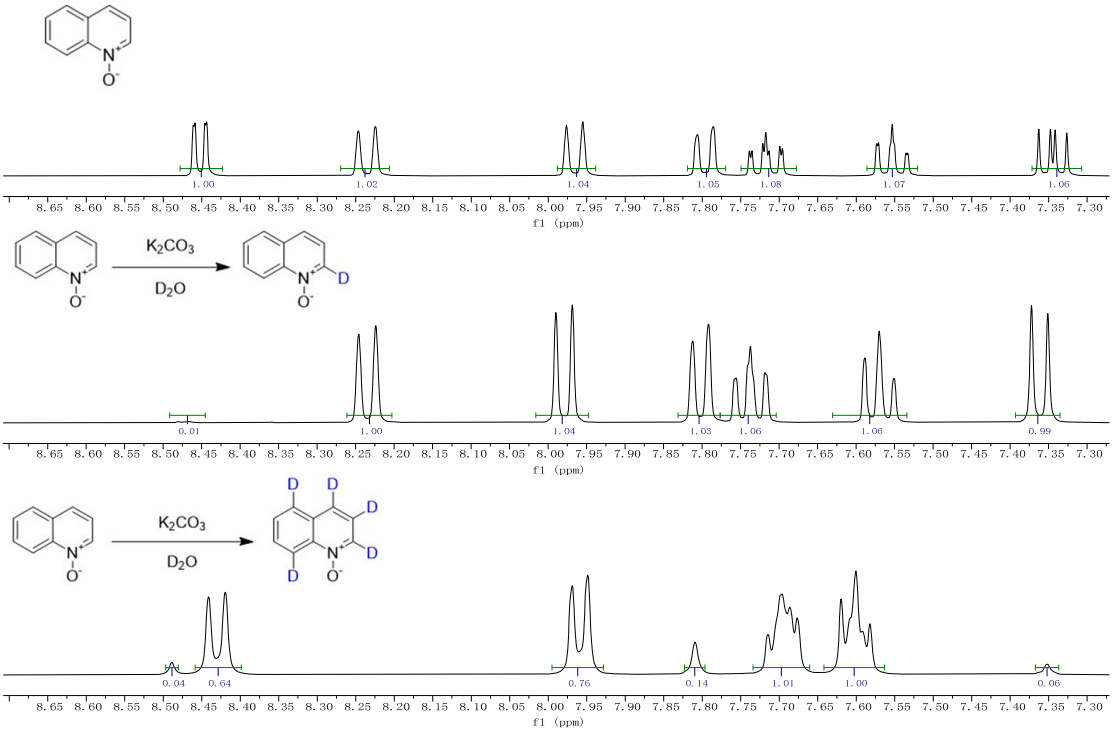


Figure S60 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 1-d and 1'-d

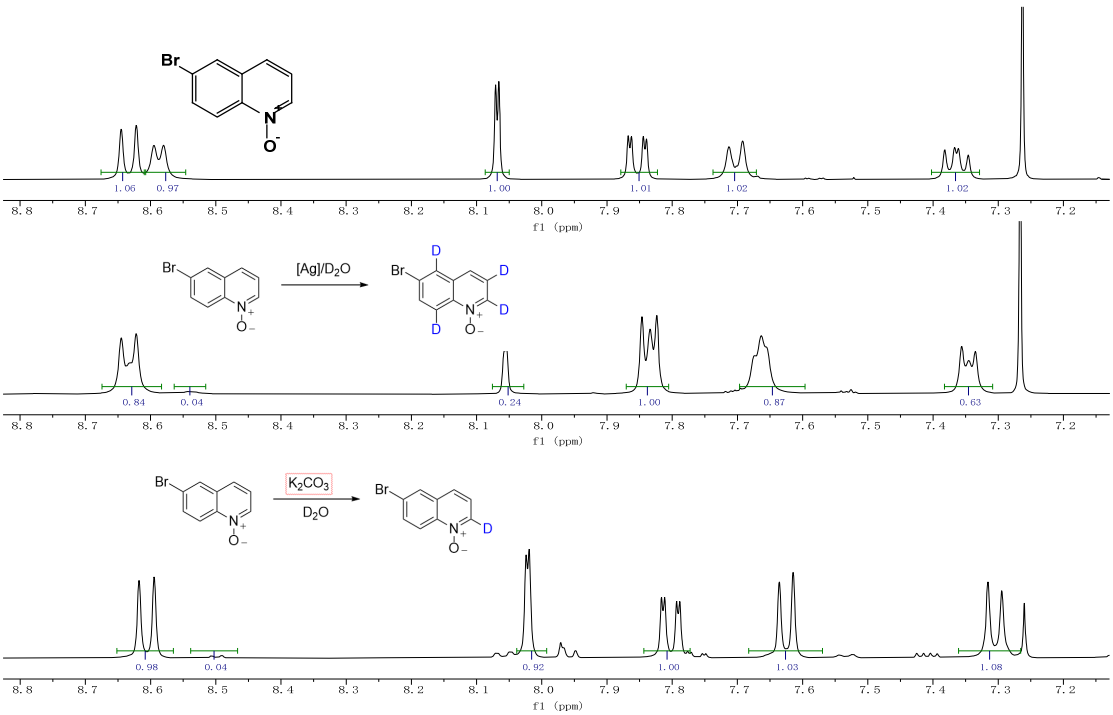


Figure S61 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 3-d and 3'-d

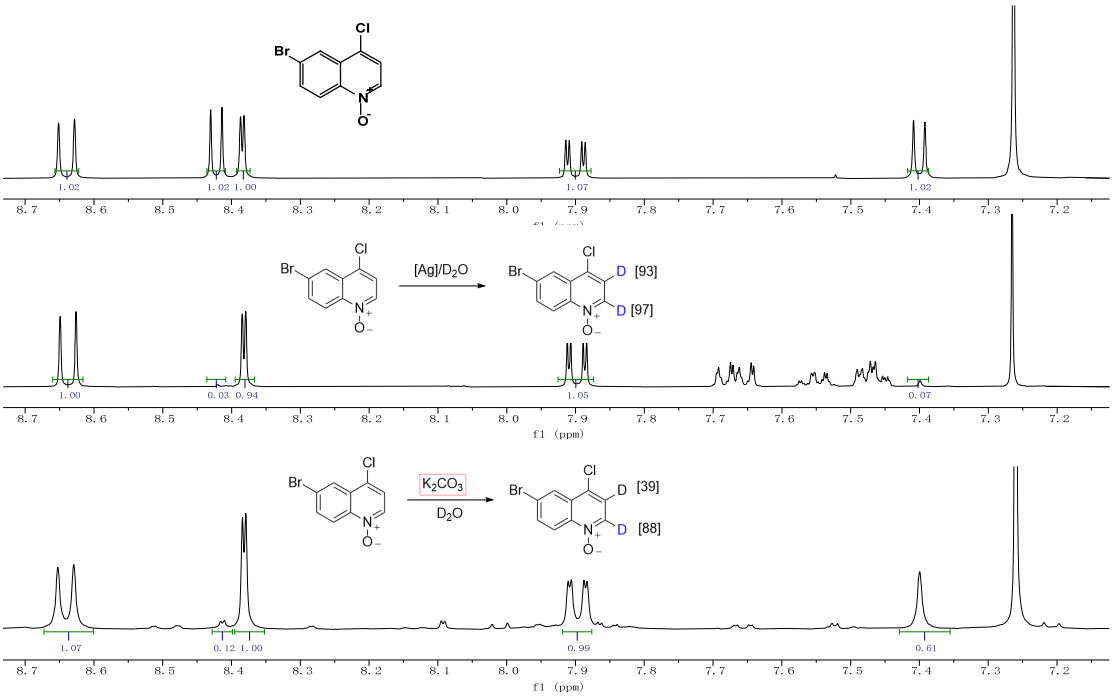


Figure S62 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 7-d and 7'-d

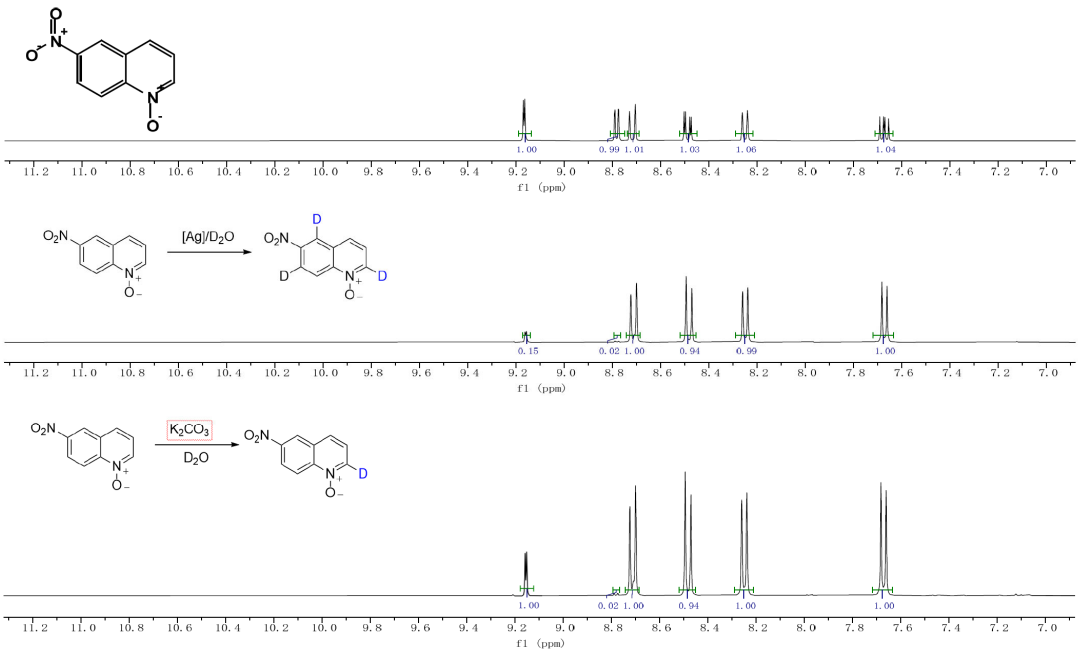


Figure S63 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 5-d and 5'-d

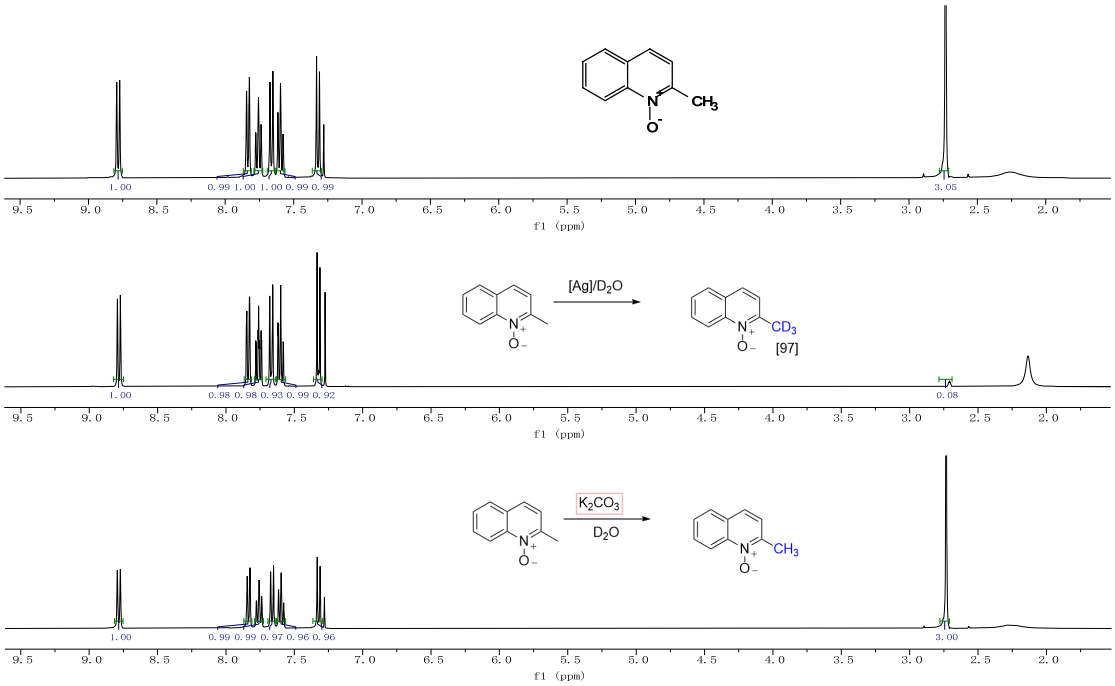


Figure S64 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 10-d and 10'-d

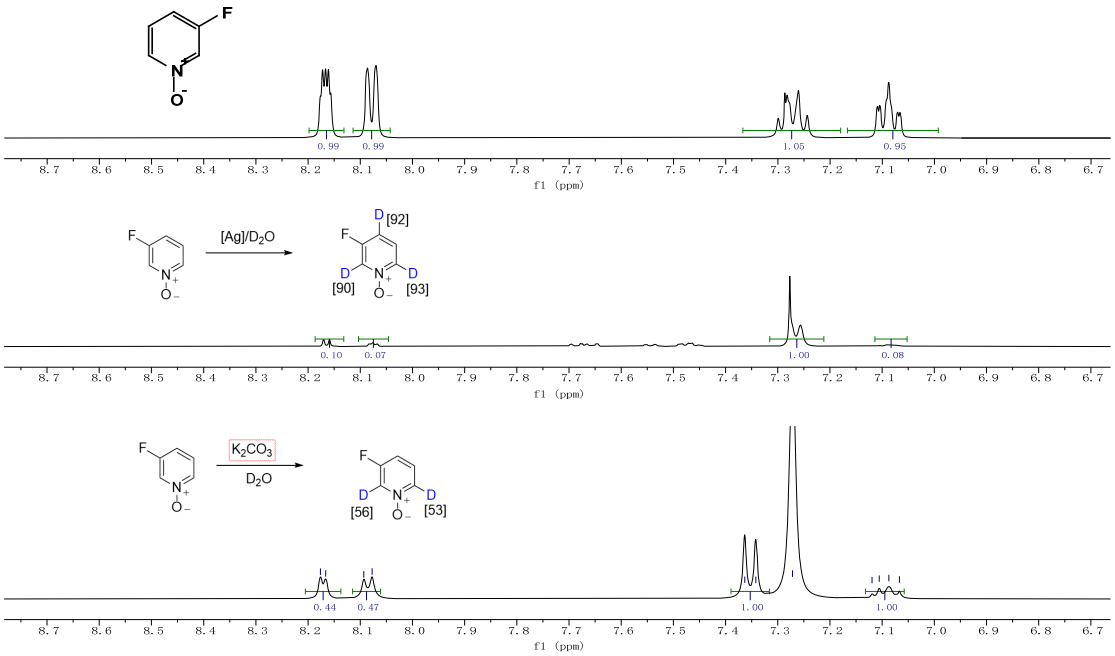


Figure S65 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum comparison of 19-d and 19'-d

7. References

[1] Jha, A. K.; Jain, N., The microwave-assisted ortho-alkylation of azine N-oxides with N-tosylhydrazones catalyzed by copper (i) iodide. *Chem. Commun.* **2016,** *52* (9), 1831-1834.

[2] Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y., Palladium-catalyzed alkenylation of quinoline-N-oxides via C-H activation under external-oxidant-free conditions. *J. Am. Chem. Soc.* **2009,** *131* (39), 13888-9.

[3] Li, G.; Jia, C.; Sun, K., Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline N-Oxides with Lactams/Cyclamines. *Org. Lett.* **2013,** *15* (20), 5198-5201.

[4] Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G., Direct, Catalytic, and Regioselective Synthesis of 2-Alkyl-, Aryl-, and Alkenyl-Substituted N-Heterocycles from N-Oxides. *Org. Lett.* **2014,** *16* (3), 864-867.

[5] Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y., Sulfonylation of Quinoline N-Oxides with Aryl Sulfonyl Chlorides via Copper-Catalyzed C–H Bonds Activation. *Org. Lett.* **2013,** *15* (6), 1270-1273.