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Supporting Information

Nickel-Catalyzed Regioselective Hydrogen Isotope Exchange Accelerated by 2-Pyridones

Zhi-Jiang Jiang,*[,1] Si-Han Xu,[1,2] Yuhang Su,[1,2] Erxun Hu,[1] Jiawei Han,[1,2] Jian-Fei Bai,[1] Bencan Tang,[4] Jia Chen,[1,3] Zhanghua Gao*[,1,3]

(Email for corresponding authors: zj.jiang@nbt.edu.cn; z.gao@nbt.edu.cn)

1. NingboTech-Cuiying Joint Laboratory of Stable Isotope Technology, School of Biological and Chemical Engineering, NingboTech University, Ningbo 315100, P. R. China
2. School of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, P. R. China
3. Ningbo Cuiying Chemical Technology Co. Ltd., Ningbo 315100, P. R. China
4. Nottingham Ningbo China Beacons of Excellence Research and Innovation Institute, University of Nottingham Ningbo China, Ningbo, P. R. China

Contents

1. General Information

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. Temperature is reported as the temperature of the metal heating module, with the height of stirring reaction mixture lower than heating module.

Commercially available reagents were purchased from Aladdin, Bidepharm, and Leyan Chemicals, which was used directly without further purification unless stated otherwise. The deuterated solvents were supplied by Ningbo Cuiying Chemicals. The D_2O for reaction was fetched and transferred to the reaction in glovebox with nitrogen atmosphere.

The substrate *N*-(8-aminoquinoline)benzamide was prepared according to the reported literature.[1,2]

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.

3) Spectroscopy Analysis

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

^{1}H NMR (400 MHz) and ^{13}C-NMR (100 MHz) are 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 DMSO-d_6. 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”.

4) Calculation of Deuterium Incorporation

The degree of deuterium-incorporation was calculated based on both GC-MS and ^{1}H-NMR methods, which had been described in our previous work.[3] The theoretical deuterium degree was calculated as follow.

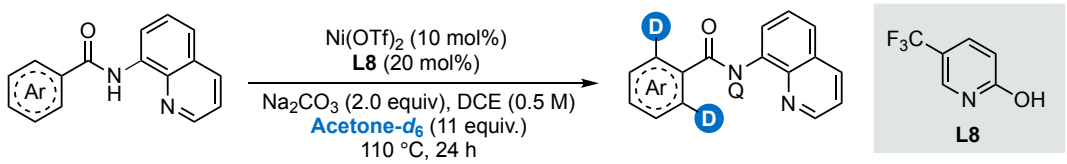
$$D_{theo} = \frac{6 \times n(acetone - d_6)}{6 \times n(acetone - d_6) + 1 \times n(2 - pyridone) + 3 \times n(sub)}$$

$$= \frac{6 \times 12.6\ mmol}{6 \times 12.6\ mmol + 1 \times 0.04\ mmol + 3 \times 0.5\ mmol}$$

$$= 0.98$$

2. Experimental procedures

1) General procedure for standard condition



To an oven dried 10 mL pressure vessel was charged with substrates (0.5 mmol, 1.0 equiv.), $Ni(OTf)_2$ (10 mol%), 5-trifluoromethyl-2-carboxypyridine **L8** (20 mol%), Na_2CO_3 (2.0 equiv.), DCE (1.0 mL, 0.5 M), and acetone-d_6 (1.0 mL). The vessel was purged with nitrogen stream, and was sealed by a Teflon bushing with Viton O-ring. Then, the vessel was placed into a preheated aluminum block on a magnetic stirrer and stirred at 110 °C for 24 hours. After the time ended, the vessel was cooled in water to room temperature. The mixture was diluted with water (5 mL) and extracted by DCM (5 mL) for 3 times. The mixture was then filtrated over a pad of celite, and the residue was washed with DCM. The combined organic layer was dried over anhydrous sodium sulfate, and sampled for GC-MS analysis. The solvent was removed under reduced pressure after filtration, and the crude mixture was purified purified by chromatography to afford purified product.

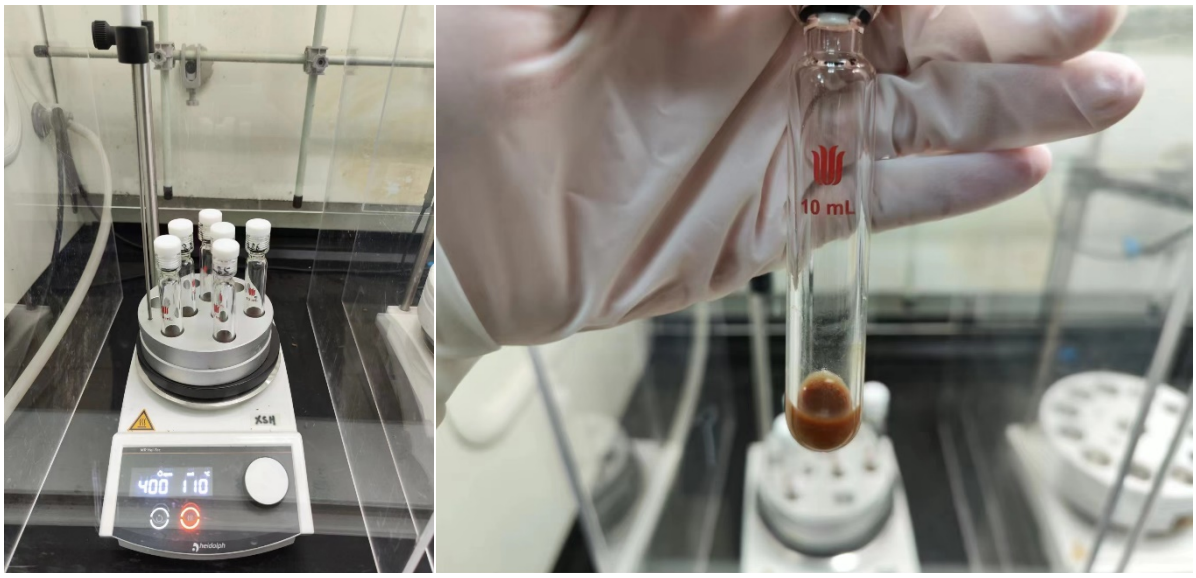


Figure S1 Apparatus and glassware used in the experiments.

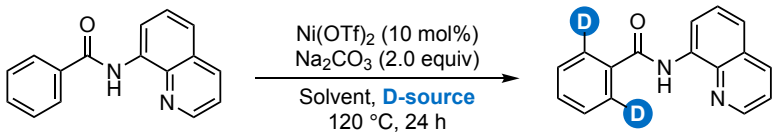
3. Condition Optimization

1) Initial optimization

The initial optimization was commenced with the examination of solvent systems. To achieve the deuterium labelling, conventional solvents were examined with D_2O as deuterium source. Unfortunately, none of such combinations rendered expected labelling result (Table S1 entries 1–5), as the work reported by You.[4] However, all the reactions showed a green-coloured aqueous layer. This observation suggested the nickel catalyst may concentrated into the aqueous layer, which could hardly interact with the substrates.

Therefore, to remove the inference from separated liquid phase, the organic deuterium source was examined. In this case, successive labelling was observed with promising deuterium-incorporation of $1.26D_{MS}$ (Table S1 entry 6). However, extremely poor recovery was found due to the extensive esterlysis, where the amide was replaced to unreactive ester during the reaction period. Thus, the exchange could hardly render a acceptable result with deuterium source with nucleophilicity, where a deuteron provider was required by the mechanistic scheme. Fortunately, acetone-d_6 satisfied the requirement, which could offer the deuteron by tautomerization. Subsequent examination of solvent system suggested its combination with toluene as well as DCE could rendered promising results (Table S1 entries 7–16), and the DCE was chosen for subsequent study due to its higher volatility simplified workups.

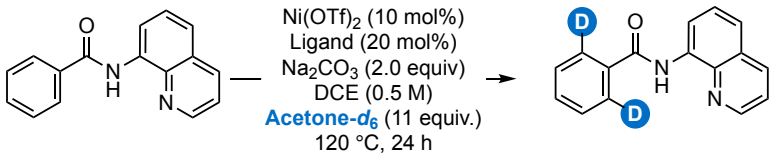
Table S1 Initial tests with solvent systems and deuterium source.[a]



entry	solvent (mL)	D-source (mL)	%Recov[b]	D_{MS}[c]
1	toluene (0.25)	D_2O (0.75)	-	< 0.05
2	MTBE (0.50)	D_2O (1.0)	-	< 0.05
3	THF (1.0)	D_2O (0.30)	-	< 0.05
4	1,4-dioxane (1.0)	D_2O (0.30)	-	< 0.05
5	DMSO (1.0)	D_2O (0.30)	-	< 0.05
6	toluene (0.25)	CD_3OD (0.90)	30	1.26
7	toluene (0.50)	Acetone-d_6 (0.50)	93	1.24
8	1,4-dioxane (0.50)	Acetone-d_6 (0.50)	90	1.21
9	mesitylene (0.50)	Acetone-d_6 (0.50)	94	1.19
10	*c*-hexane (0.50)	Acetone-d_6 (0.50)	91	0.86
11	DCE (0.50)	Acetone-d_6 (0.50)	96	1.18
12	PEG-400 (0.50)	Acetone-d_6 (0.50)	82	0.18
13	DME (0.50)	Acetone-d_6 (0.50)	85	0.80
14	DCE (0.75)	Acetone-d_6 (0.25)	92	0.73
15	DCE (0.25)	Acetone-d_6 (0.75)	91	1.17
16	-	Acetone-d_6 (1.00)	96	0.49

[a] Reaction condition unless noted otherwise: substrate **1** (0.25 mmol), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (2.0 equiv.), solvent and D-source at 120 °C for 24 hours; [b] Recovery after column chromatography; [c] Deuterium incorporation determined by GC-MS.

Table S2 Examination of catalytic system.[a]



entry	catalyst	ligand	%Recov[b]	D_{MS}[c]
1	$Ni(OTf)_2$	-	96	1.18
2	$NiCl_2$	-	95	0.11
3	$Ni(dppf)Cl_2$	-	75	0.11
4	$Ni(OAc)_2{\cdot}4H_2O$	-	89	0.67
5	$Ni(OTf)_2$	**L1**	87	1.23
6	$Ni(OTf)_2$	**L2**	89	1.14
7	$Ni(OTf)_2$	**L3**	94	1.18
8	$Ni(OTf)_2$	**L4**	94	1.13
9	$Ni(OTf)_2$	**L5**	90	1.26
10	$Ni(OTf)_2$	**L6**	95	0.20
11	$Ni(OTf)_2$	**L7**	78	< 0.05
12	$Ni(OTf)_2$	**L8**	91	1.79
13	$Ni(OTf)_2$	**L13**	92	1.78
14	$Cu(OAc)_2{\cdot}H_2O$	**L8**	n/a	0.10
15	$CoSO_4{\cdot}7H_2O$	**L8**	n/a	n.d.
16	$Mn(OAc)_2$	**L8**	n/a	n.d.
17	$FePO_4{\cdot}4H_2O$	**L8**	n/a	n.d.

[a]Reaction condition unless noted otherwise: substrate **1** (0.25 mmol), catalyst (10 mol%), ligand (20 mol%), Na_2CO_3 (2.0 equiv.), DCE (0.5 mL) and Acetone-d_6 (0.5 mL) at 120 °C for 24 hours; [b] Recovery after column chromatography; [c] Deuterium incorporation determined by GC-MS. n.d. = not detected.

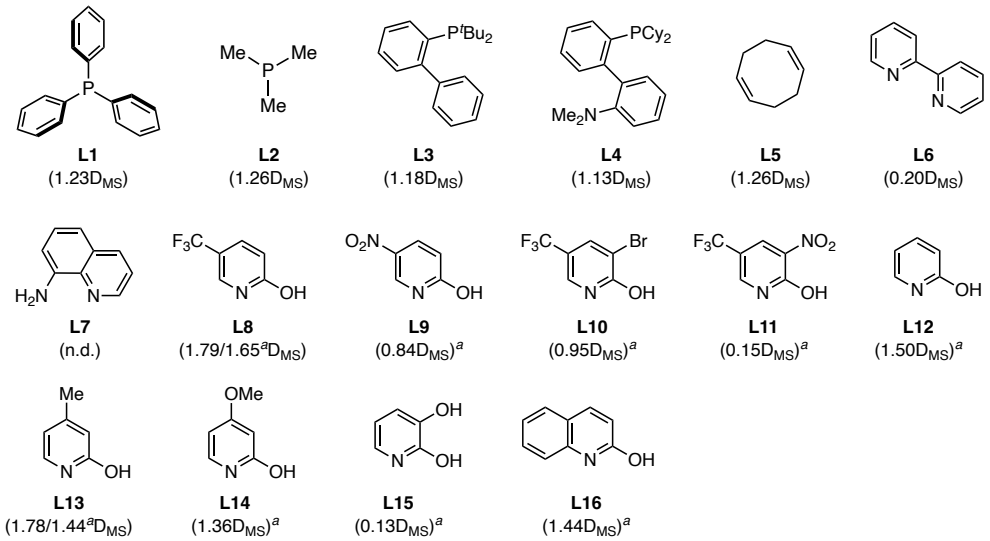
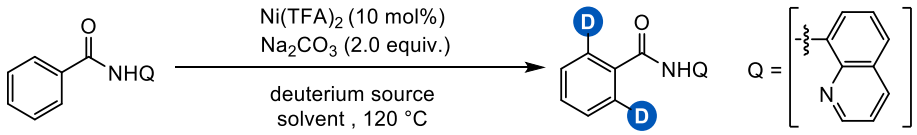


Figure S2 Ligands tested in the work. [a]Deuterium incorporation of 6 hours' exchange.

2) Optimization of reaction condition

After the determination of catalytic system and deuterium source, further optimization was focused to further improve the performance. As shown in Table S3, 20 mol% of ligand loading rendered the highest deuterium incorporation of 1.43D_{MS}, and the sodium sulphate remained the optimal choice. Further adjustment of temperature provided the product with a satisfying labelling degree of 1.83D_{MS} after 24-hour exchange.

Table S3 Condition optimization for HIE of aromatic ring.[a]

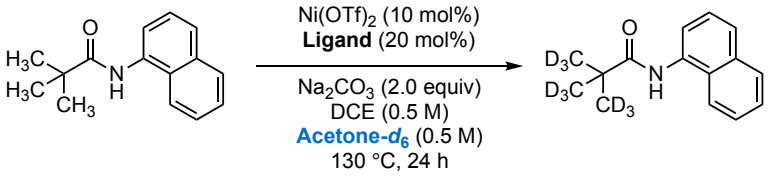


entry	ligand (mol%)	base (equiv.)	T (°C)	time (h)	%Recov[b]	D_{MS}[c]
1	**L8** (2.5)	Na_2CO_3 (2.0)	120	4	96	0.61
2	**L8** (5.0)	Na_2CO_3 (2.0)	120	4	99	0.9
3	**L8** (10)	Na_2CO_3 (2.0)	120	4	97	1.31
4	**L8** (20)	Na_2CO_3 (2.0)	120	4	95	1.43
5	**L8** (30)	Na_2CO_3 (2.0)	120	4	96	1.36
6	**L8** (40)	Na_2CO_3 (2.0)	120	4	98	1.34
7	**L8** (20)	Na_2CO_3 (2.0)	120	4	96	1.65
8	**L8** (20)	K_2CO_3 (2.0)	120	4	93	0.06
9	**L8** (20)	$NaHCO_3$ (2.0)	120	4	92	1.43
10	**L8** (20)	NaOAc (2.0)	120	4	94	0.49
11	**L8** (20)	$K_3PO_4 \cdot H_2O$ (2.0)	120	4	91	< 0.05
12	**L8** (20)	Cs_2CO_3 (2.0)	120	4	93	< 0.05
13	**L8** (20)	TEA (2.0)	120	4	96	1.51
14	**L8** (20)	Na_2CO_3 (1.0)	120	4	94	1.5
15	**L8** (20)	Na_2CO_3 (3.0)	120	4	94	1.56
16	**L8** (20)	-	120	4	94	< 0.05
17	**L8** (20)	Na_2CO_3 (2.0)	120	24	96	1.83
18	**L8** (20)	Na_2CO_3 (2.0)	110	24	94	1.83
19	**L8** (20)	Na_2CO_3 (2.0)	100	24	94	1.64

[a] Reaction condition unless noted otherwise: substrate 1 (0.25 mmol), $Ni(OTf)_2$ (10 mol%), **L8**, base, DCE (0.5 mL) and acetone-d_6 (0.5 mL) at specified temperature; [b]Recovery after column chromatography; [c]Deuterium incorporation determined by GC-MS.

3) Ligand optimization for the HIE of aliphatic substrates

Table S4 Condition optimization for the HIE of aliphatic substrates.[a]



entry	ligand (mol%)	base (equiv.)	T (°C)	D_{MS}[c]
1	**L8** (20)	Na_2CO_3 (2.0)	130	2.04
2	**L11** (20)	Na_2CO_3 (2.0)	130	0.05
3	**L13** (20)	Na_2CO_3 (2.0)	130	7.83
4	**L16** (20)	Na_2CO_3 (2.0)	130	4.99
5	**L17** (20)	Na_2CO_3 (2.0)	130	7.62
6	**L18** (20)	Na_2CO_3 (2.0)	130	2.27
7	**L13** (20)	TEA (2.0)	130	4.86
8	**L13** (20)	DIPEA (2.0)	130	5.28
9	**L13** (20)	$NaHCO_3$ (2.0)	120	5.91

[a]Reaction condition unless noted otherwise: aromatic amides (0.25 mmol), Ni(OTf) 2 (10 mol%), ligand (20 mol%), base (2.0 equiv.), DCE (0.5 mL) and acetone-d_6 (0.5 mL) in a 15 mL tube sealed by Teflon and reacted at 130 ℃ for 24 hours. b Deuterium incorporation determined by GC-MS.

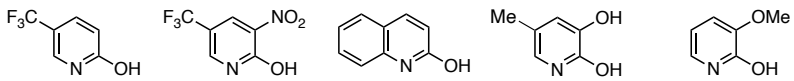


Figure S3 Ligands tested in the work. [a]Deuterium incorporation of 6 hours' exchange.

4. Additional experiments

1) Deuteration kinetic curve

The optimization above rendered a condition with 1.83D_{MS} at 110 °C (Table S3, entry 18). However, the initial success also showed a 1.24D_{MS} incorporation at 120 °C (Table S1, entry 7), which didn't reflect a substantial improvement. Therefore, a kinetic comparison was conducted at 110 °C, and the data was summarized in Table S4 and Figure 2b.

As data indicated, the ligand-free condition showed a dramatically decreased reactivity, which only afford a moderate labelling degree of 0.71D_{MS}. The overall deuterium accumulation was slow, which didn't reach the plateau during the tracking period of 24 hours. In contrast, the reaction with **L8** showed a much faster labelling speed, which reached 0.73D_{MS} in the first 2 hours. Therefore, the addition of **L8** provided a much higher reactivity for nickel catalyzed deuteration.

Table S5 Kinetic profile for labelling under different conditions.[a]

time	D_{MS}		
	ligand-free condition[b]	optimized condition[c]	PPh_3 (20 mol%)
1	0.01	0.19	0.03
2	0.01	0.73	0.12
4	0.04	1.45	0.18
8	0.30	1.82	0.46
12	0.43	1.82	0.76
24	0.71	1.80	1.23

[a]Deuterium incorporation determined by GC-MS; [b]Reaction condition: substrate **1** (0.25 mmol), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (2.0 equiv.), DCE (0.5 mL) and Acetone-d_6 (0.5 mL) at 110 °C; [c]Reaction condition: substrate **1** (0.25 mmol), $Ni(OTf)_2$ (10 mol%), **L8** (20 mol%), Na_2CO_3 (2.0 equiv.), DCE (0.5 mL) and Acetone-d_6 (0.5 mL) at 110 °C.

2) Data for water addition experiments

According to You's mechanistic experiment,[4] the C-H activation of *N*-benzoyl amino acids could hardly be labelled effectively, which employed heavy water as deuterium source (Figure 1b). Therefore, we tested the influence of water to our protocol. As shown in Figure 2c and Table S5, the addition heavy water suppressed the labelling efficiency, which was totally inhibited with 10 equiv. water or more.–

Table S6 Influence of water addition.[a]

entry	D_2O (equiv.)	D_{MS}[b]
1	0	1.78
2	5	0.89
3	10	0.06
4	20	n.d.
5	50	n.d.

[a]Reaction condition: substrate **1** (0.25 mmol), $Ni(OTf)_2$ (10 mol%), **L8** (20 mol%), Na_2CO_3 (2.0 equiv.), DCE (0.5 mL), Acetone-d_6 (0.5 mL) and **D_2O** at 110 °C; [b]Deuterium incorporation determined by GC-MS. n.d. = not detected.

3) Directing group examination

Besides the 8-aminoquinoline, a series directing groups were also tested under the standard condition (Figure S4). However, only the substrate with *N'*-oxide 2-aminopyridine rendered a moderate degree of labelling. *N*-protected benzylamines were also exposed to the protocol, where a moderate degree of labelling was observed on nicotinic amide, which was facilitated by the Thorpe-Ingold effect.

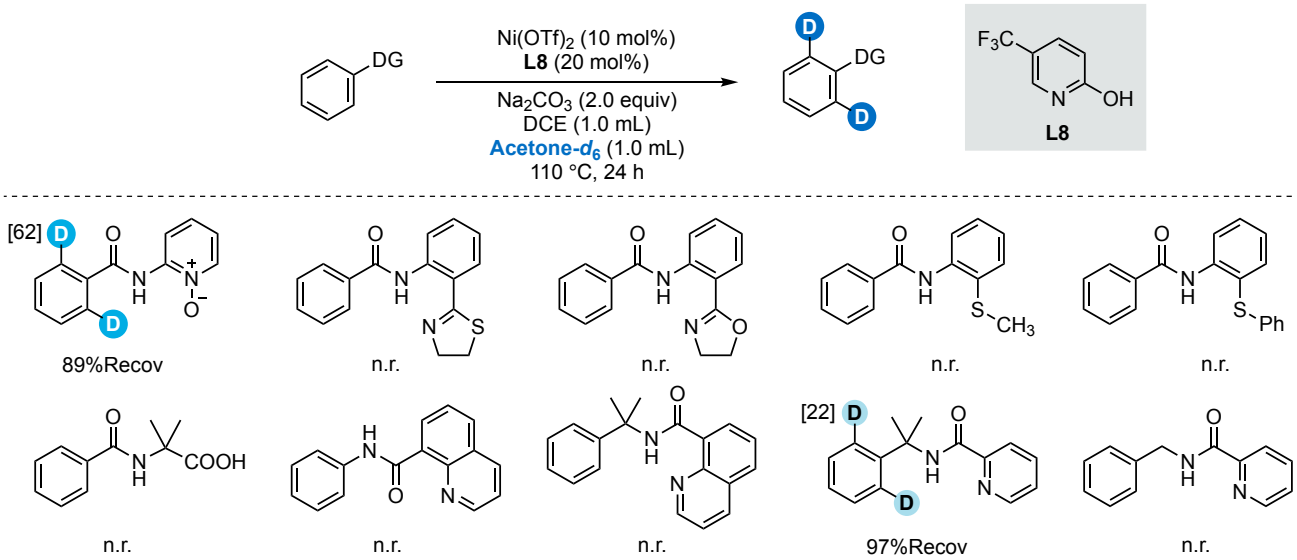
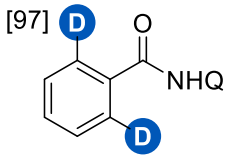


Figure S4 Examination of directing groups.

5. Results of Substrate deuteration

Deuteration of N-(quinolin-8-yl)benzamide (1)



General procedure to afford **1-[d]** as white solid (118.5 mg, 95%) with D-incorporation 97% for 2,6-positions by ^{1}H NMR and 1.86 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.10 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.65 – 7.52 (m, 5H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.12 – 8.08 (m, 0.06H, Labelled)**, 7.68 – 7.52 (m, 5H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H).

Figure S5 ^{1}H NMR spectrum comparison

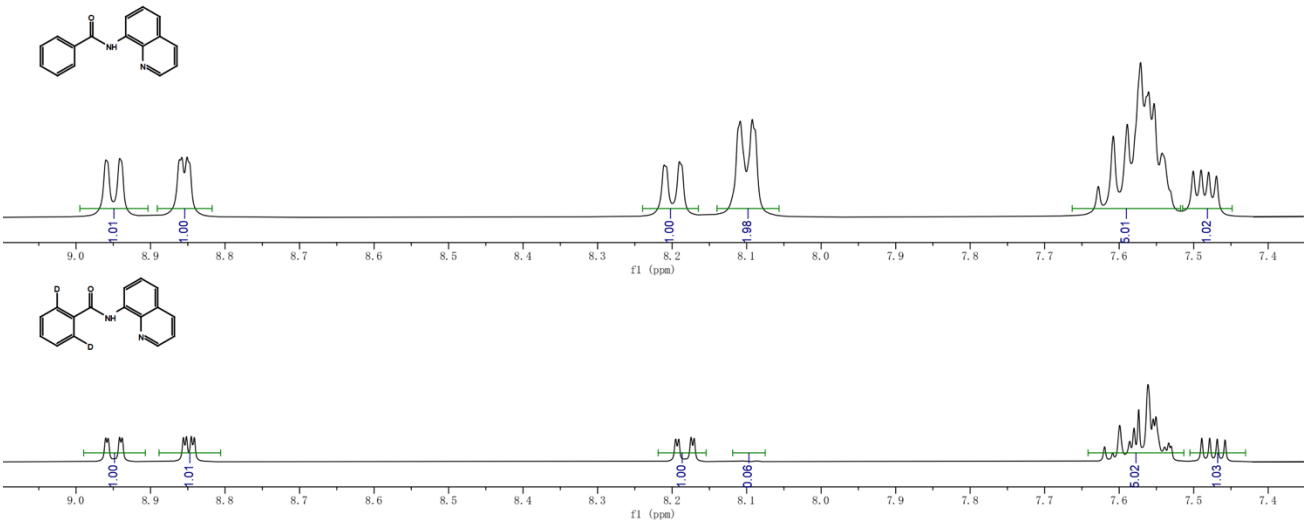


Figure S6 GC-MS spectrum comparison

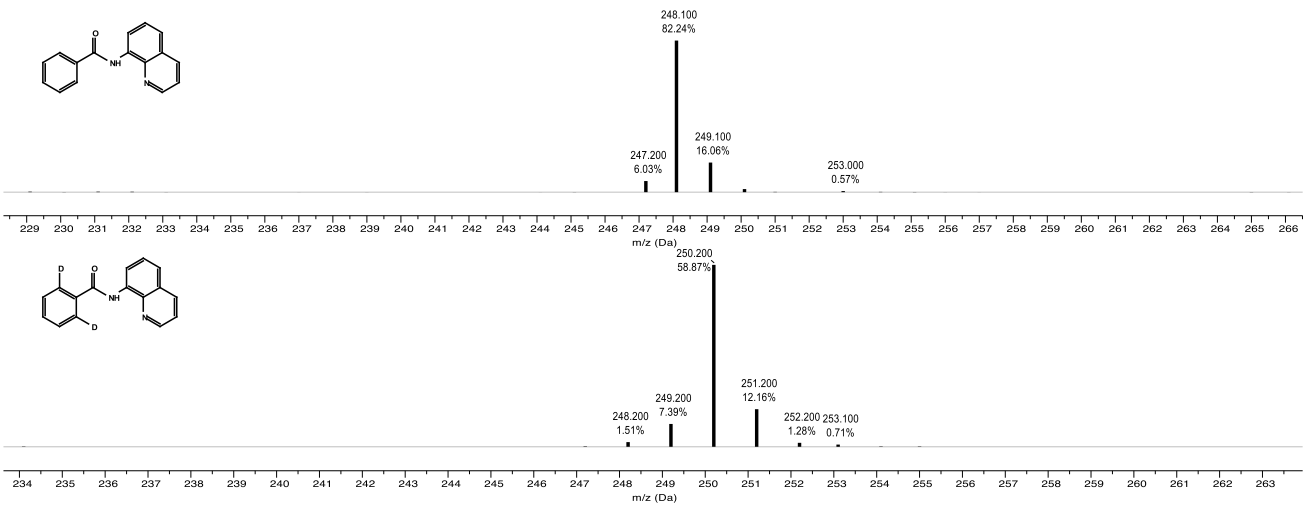


Figure S7 ^{1}H NMR of **1** in $CDCl_3$

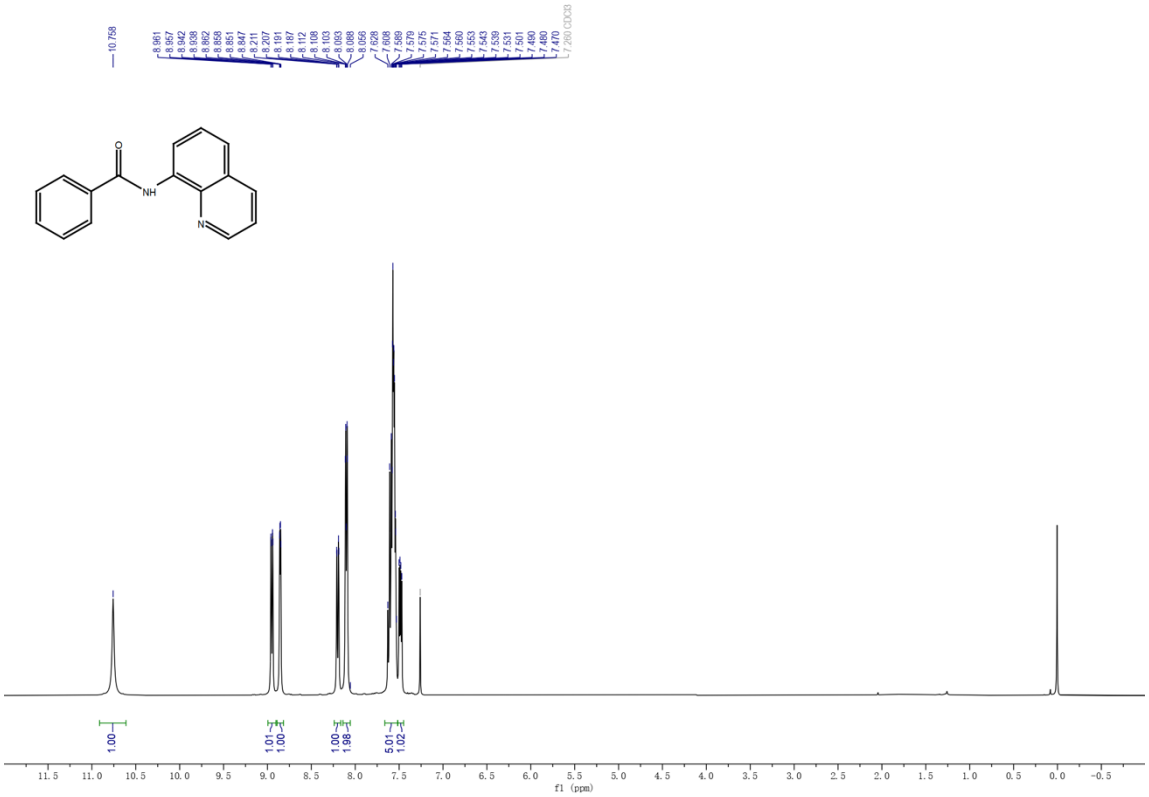
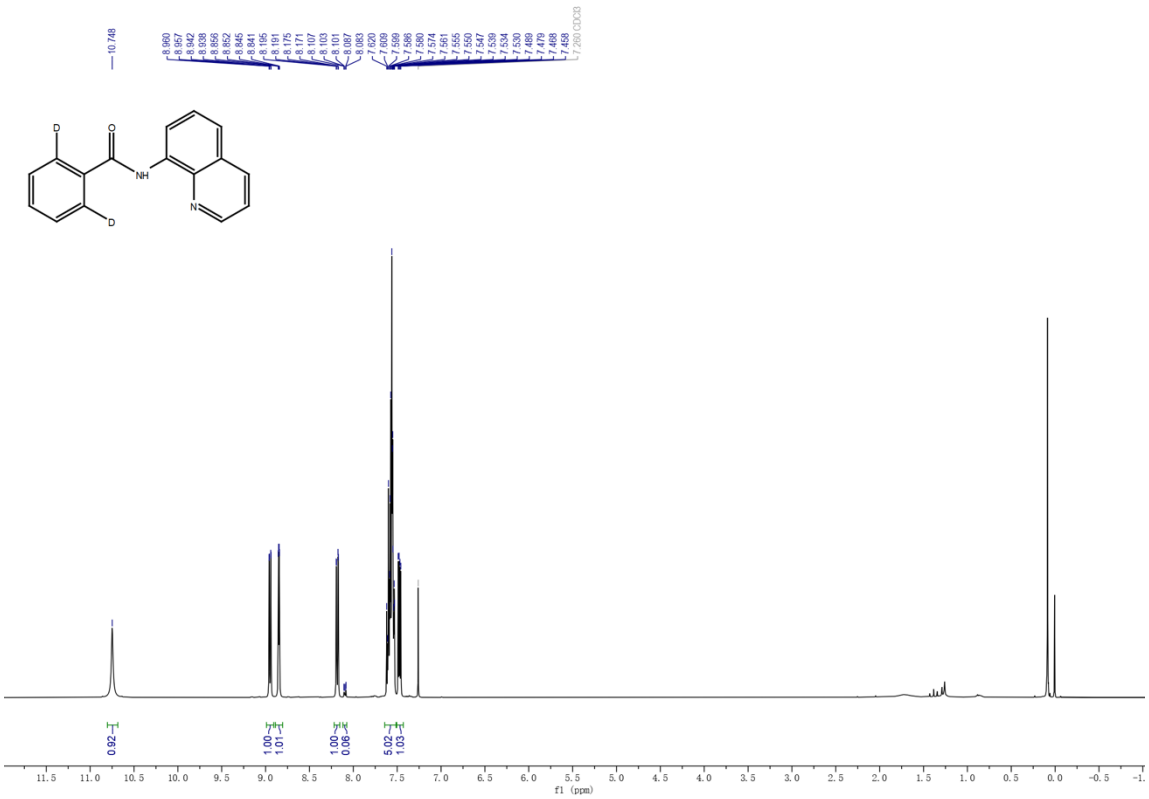
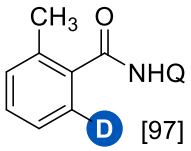


Figure S8 ^{1}H NMR of **1-[d]** in $CDCl_3$



Deuteration of 2-methyl-N-(quinolin-8-yl)benzamide (2)



[97]

General procedure to afford **2-[d]** as white solid (122.5 mg, 94%) with D-incorporation 97% for 6-position by ^{1}H NMR and 0.81 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.96 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.69 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (td, *J* = 7.4, 1.5 Hz, 1H), 7.36 – 7.28 (m, 2H), 2.61 (s, 3H).

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.69 (d, *J* = 7.8 Hz, 0.03H, Labelled)**, 7.67 – 7.52 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.6, 4.0 Hz, 2H), 2.61 (s, 3H).

Figure S9 ^{1}H NMR spectrum comparison

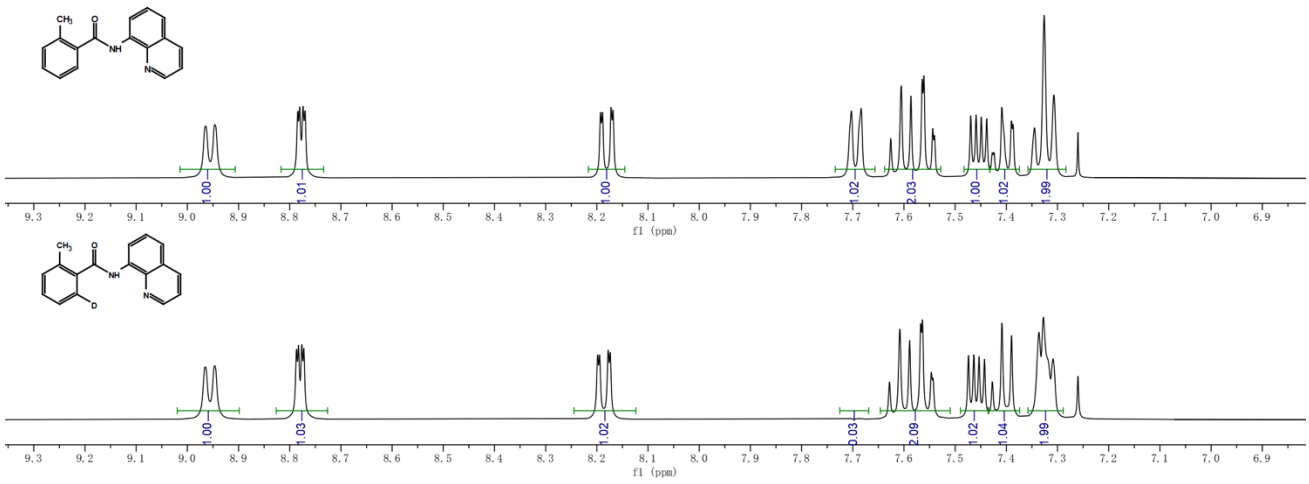


Figure S10 GC-MS spectrum comparison

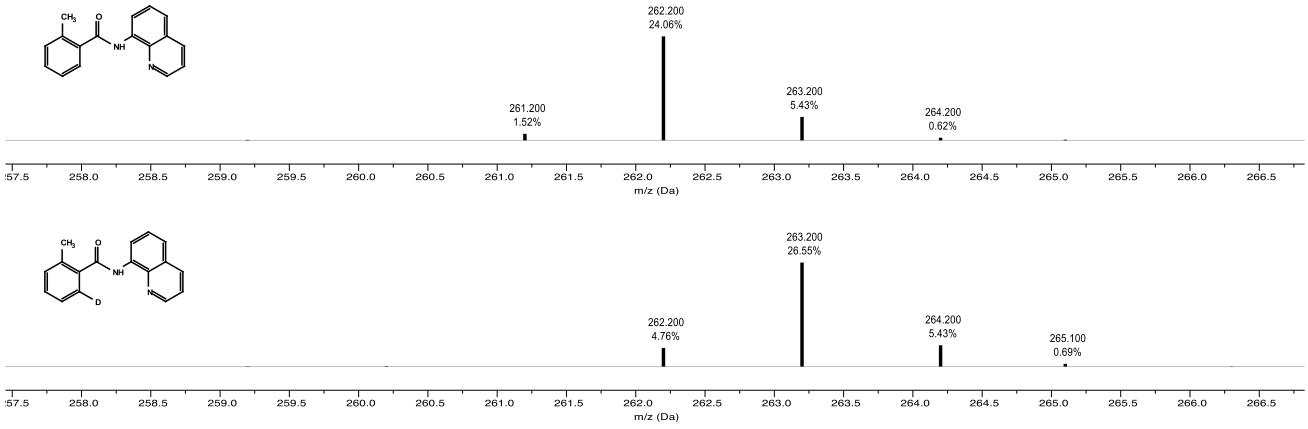


Figure S11 ^{1}H NMR of **2** in $CDCl_3$

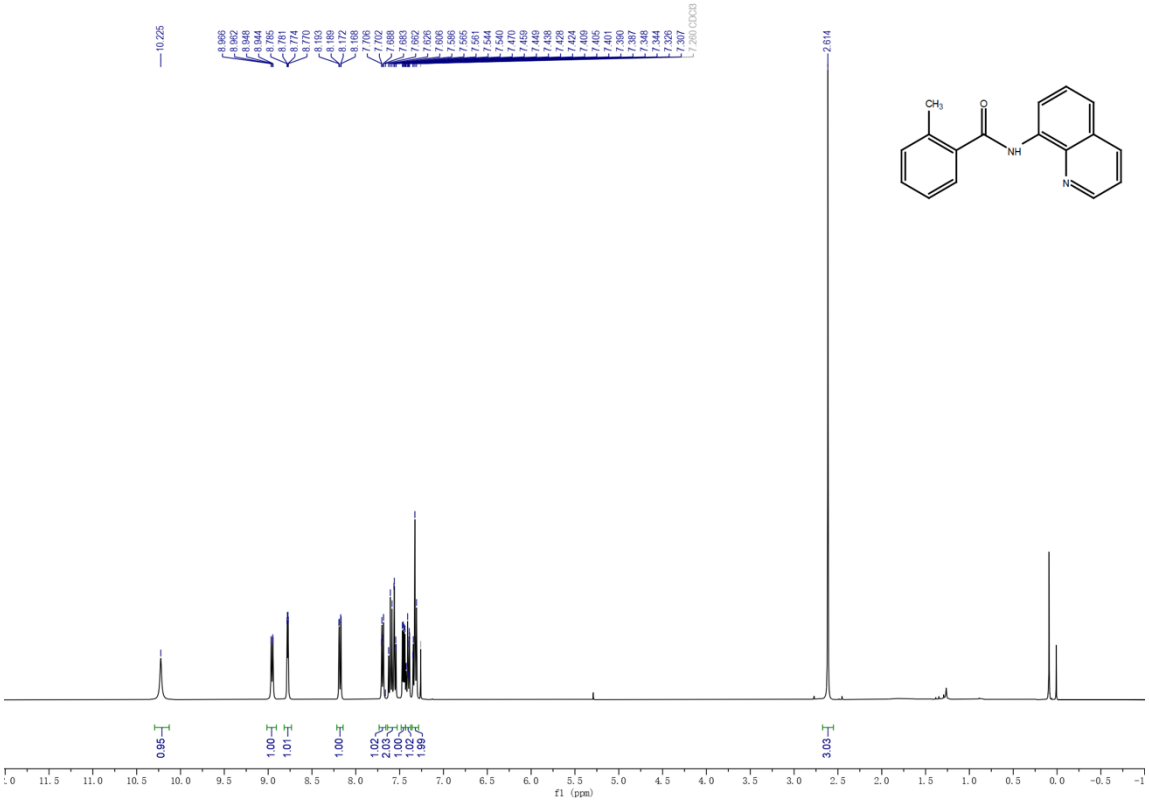
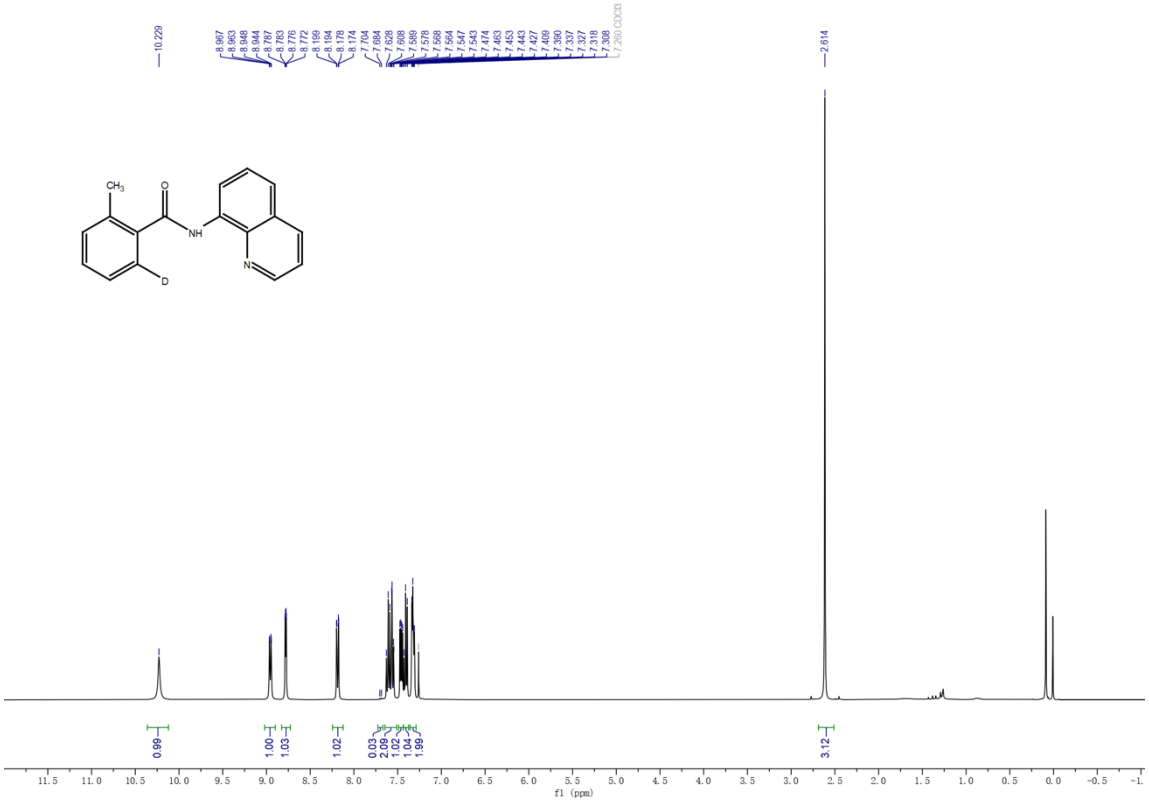
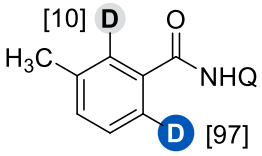


Figure S12 ^{1}H NMR of **2-[d]** in $CDCl_3$



Deuteration of 3-methyl-N-(quinolin-8-yl)benzamide (3)



General procedure to afford **3-[d]** as white solid (124.5 mg, 95%) with D-incorporation 10% for 2-position and 97% for 6-position by ^{1}H NMR and 0.98 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.94 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.51 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.3 Hz, 2H), 7.41 – 7.36 (m, 1H), 2.47 (s, 3H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 8.94 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.83 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.92 – 7.86 (m, 0.93H, Labelled)**, 7.58 (t, *J* = 7.9 Hz, 1H), 7.51 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.37 (ddd, *J* = 7.5, 1.7, 0.8 Hz, 1H), 2.47 (s, 3H).

Figure S13 ^{1}H NMR spectrum comparison

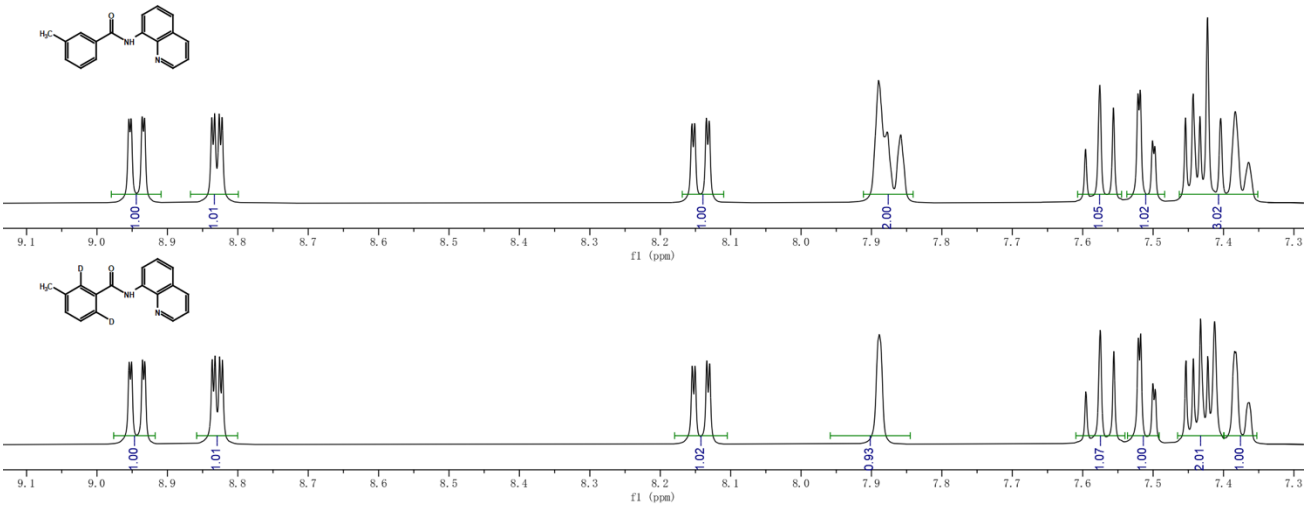


Figure S14 GC-MS spectrum comparison

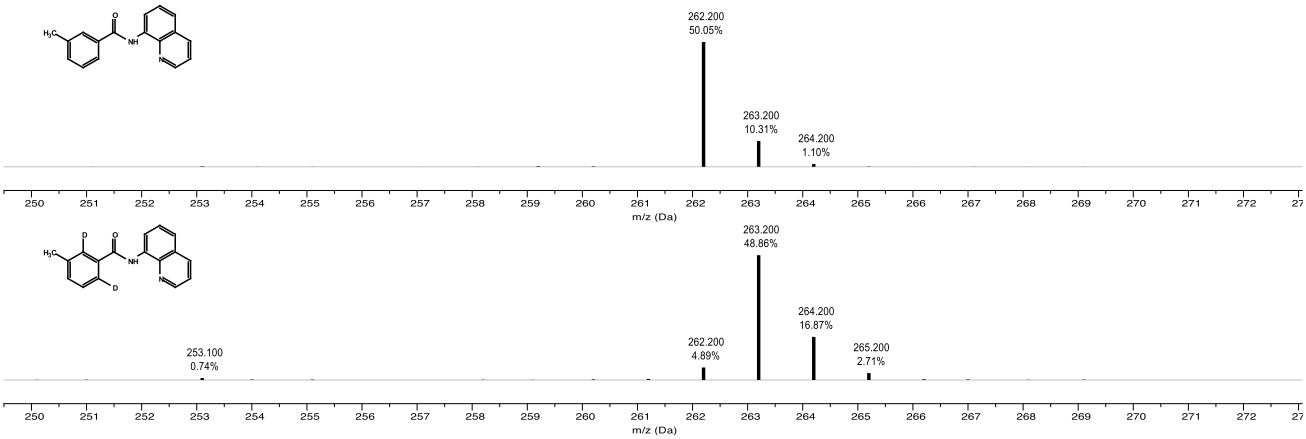


Figure S15 ^{1}H NMR of **3** in $CDCl_3$

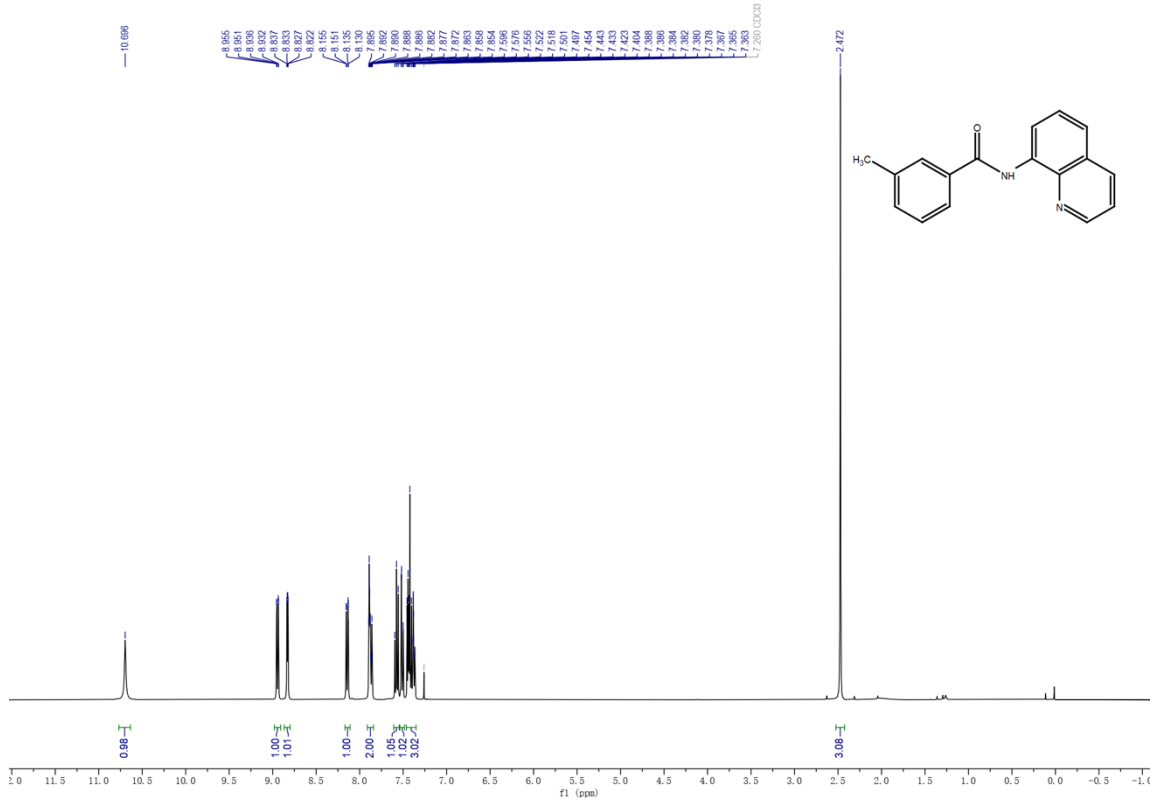
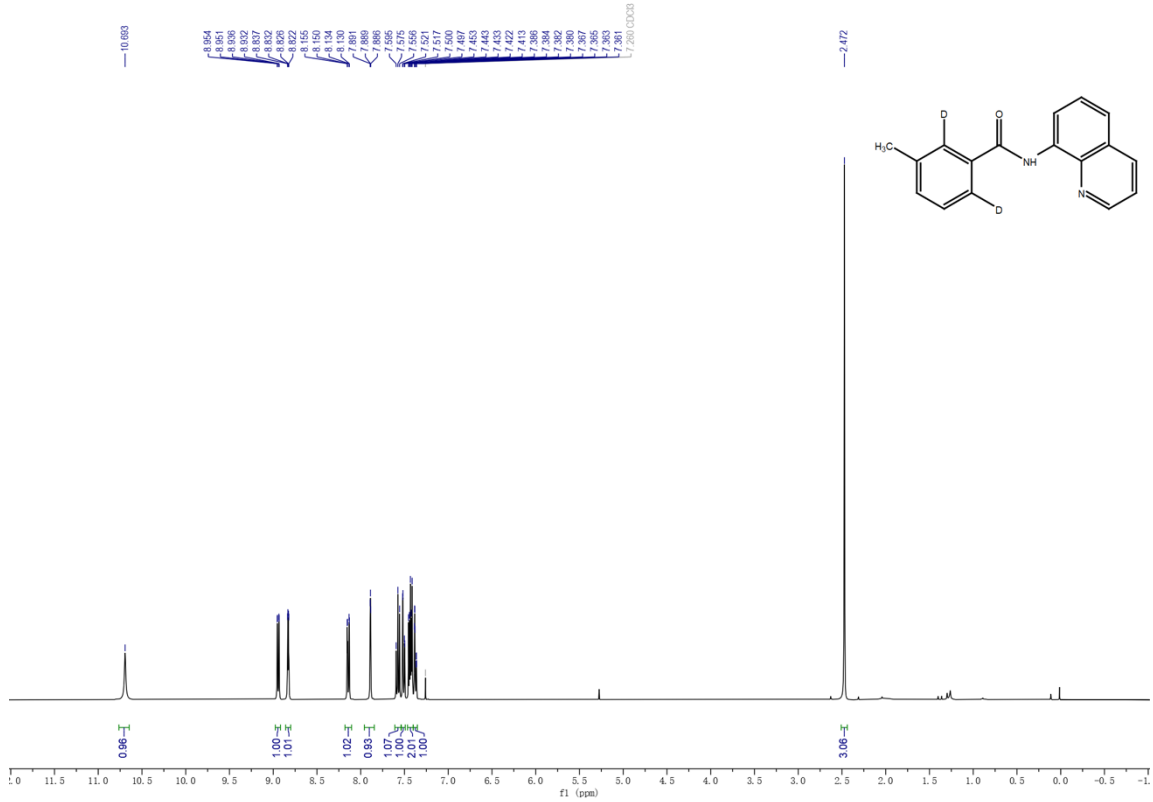
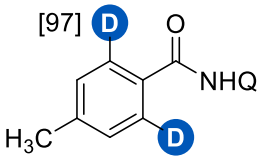


Figure S16 ^{1}H NMR of **3-[d]** in $CDCl_3$



Deuteration of 4-methyl-N-(quinolin-8-yl)benzamide (4)



General procedure to afford **4-[d]** as white solid (123.3 mg, 93%) with D-incorporation 97% for *ortho*-positions by ^{1}H NMR and 1.85 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.85 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.37 – 7.32 (m, 2H), 2.45 (s, 3H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.94 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.99 (d, *J* = 8.4 Hz, 0.06H, Labelled)**, 7.59 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 (s, 2H), 2.45 (s, 3H).

Figure S17 ^{1}H NMR spectrum comparison

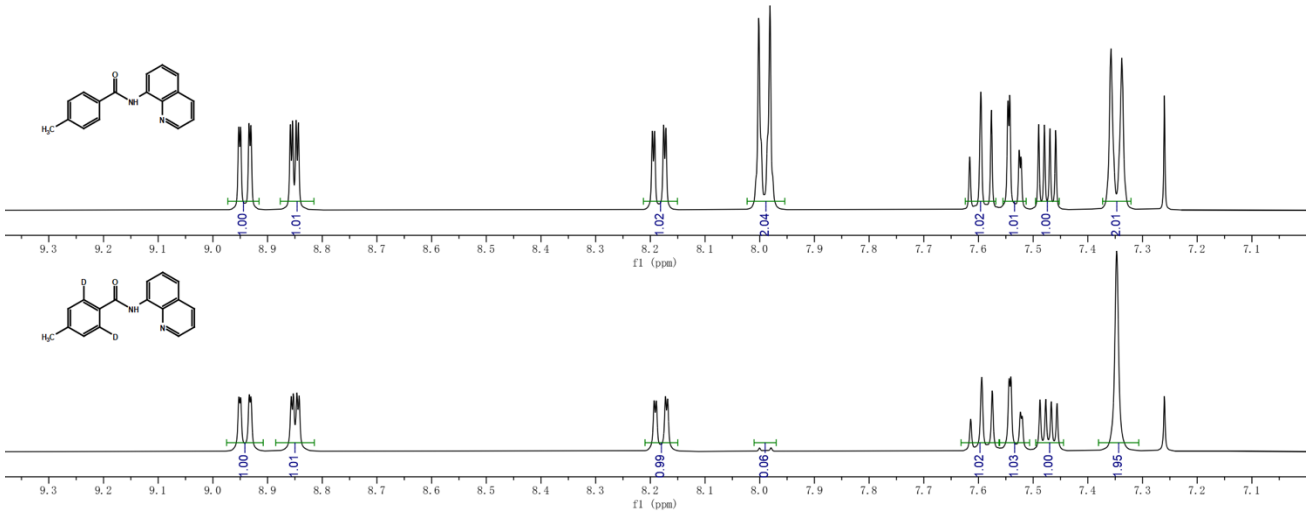


Figure S18 GC-MS spectrum comparison

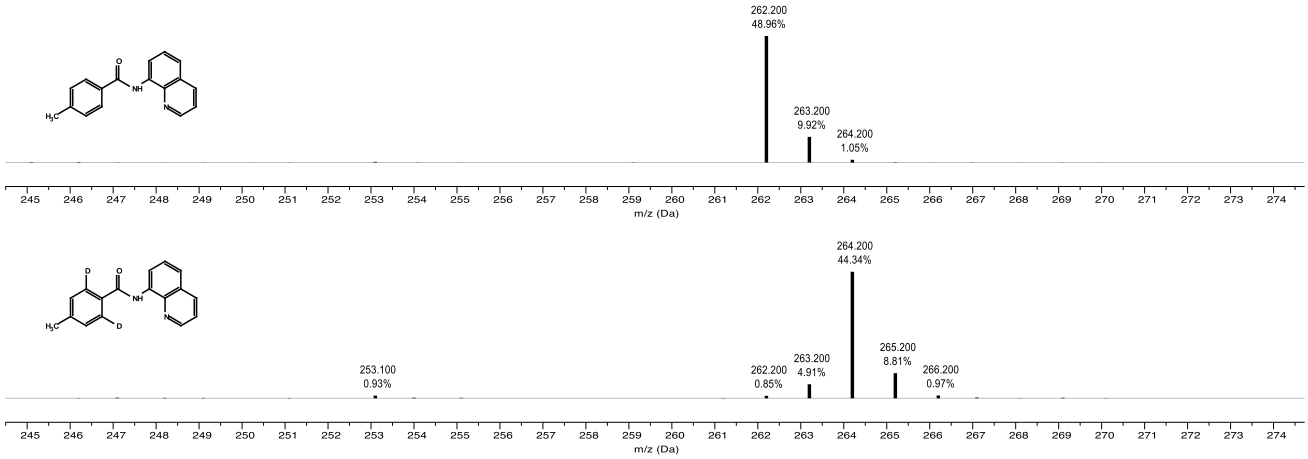


Figure S19 ^{1}H NMR of **4** in $CDCl_3$

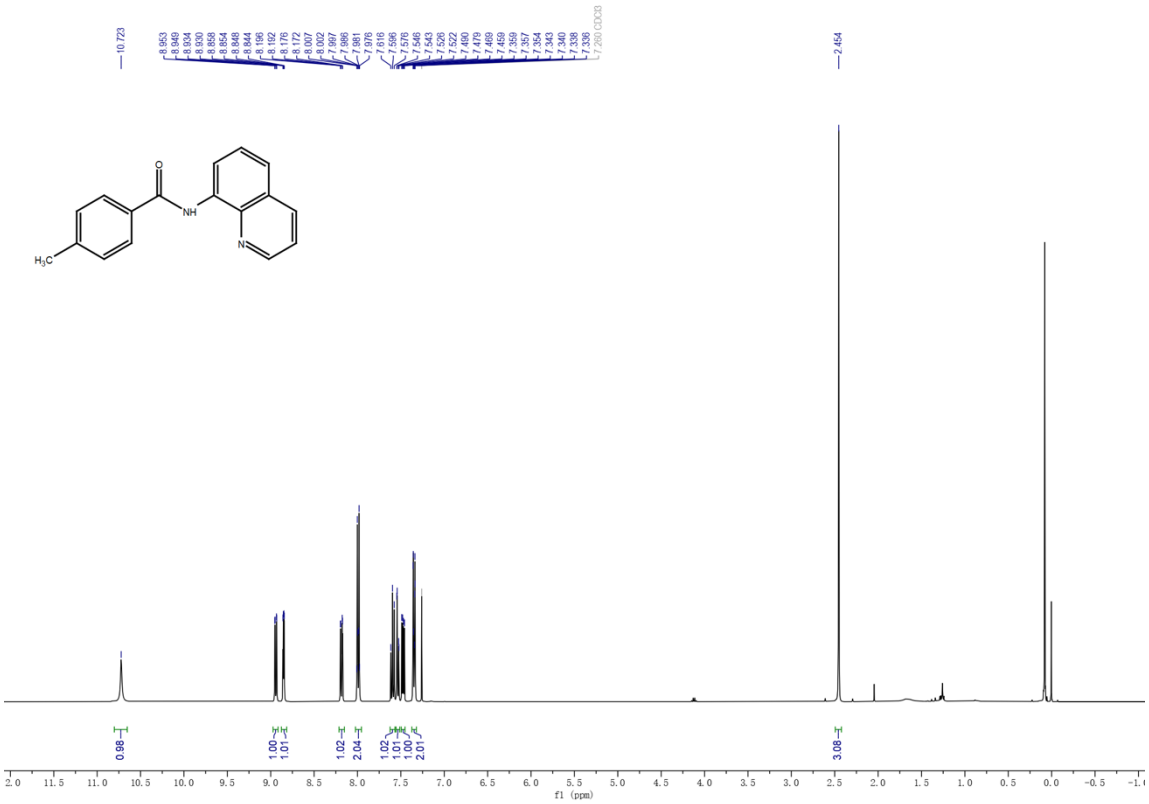
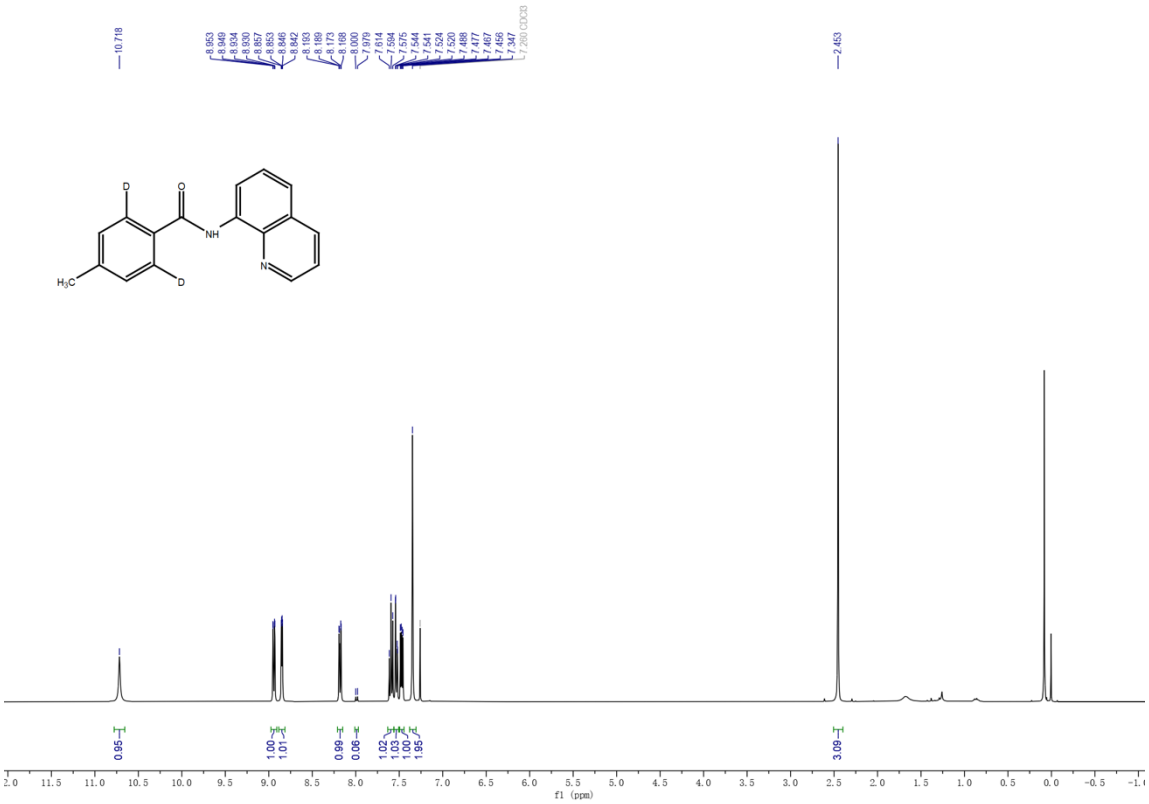
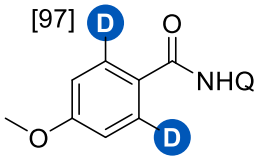


Figure S20 ^{1}H NMR of **4-[d]** in $CDCl_3$



Deuteration of 4-Methoxy-N-(quinolin-8-yl)benzamide-2 (5)



General procedure to afford **5-[d]** as white solid (132.5 mg, 96%) with D-incorporation 97% for *ortho*-positions by ^{1}H NMR; R_f = 0.25 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.92 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.85 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.12 – 8.04 (m, 2H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.08 – 7.01 (m, 2H), 3.90 (s, 3H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.92 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.06 (d, *J* = 9.3 Hz, 0.06H, Labelled)**, 7.58 (t, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.03 (s, 2H), 3.89 (s, 3H).

Figure S21 ^{1}H NMR spectrum comparison

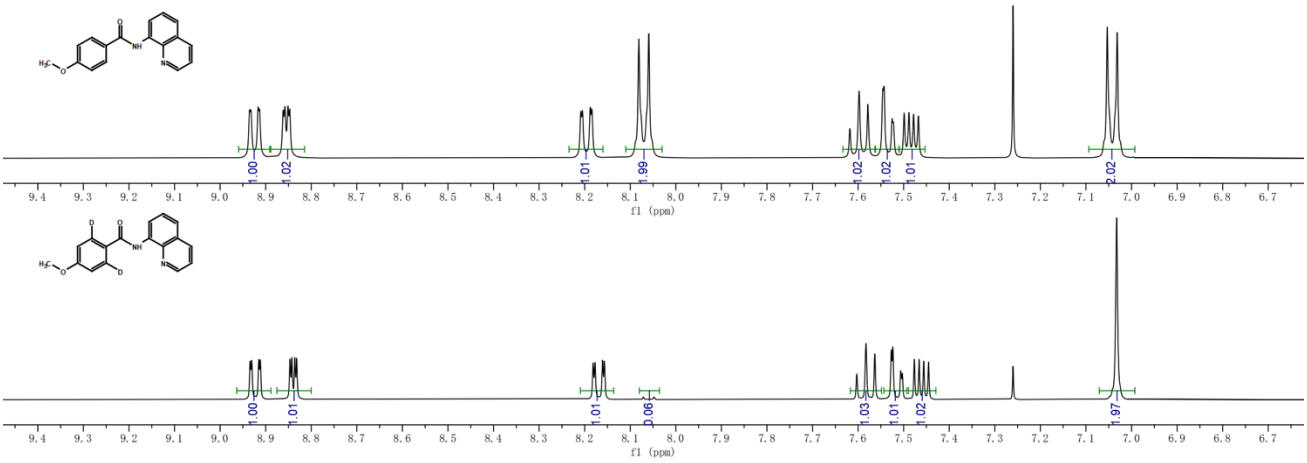


Figure S22 ^{1}H NMR of **5** in $CDCl_3$

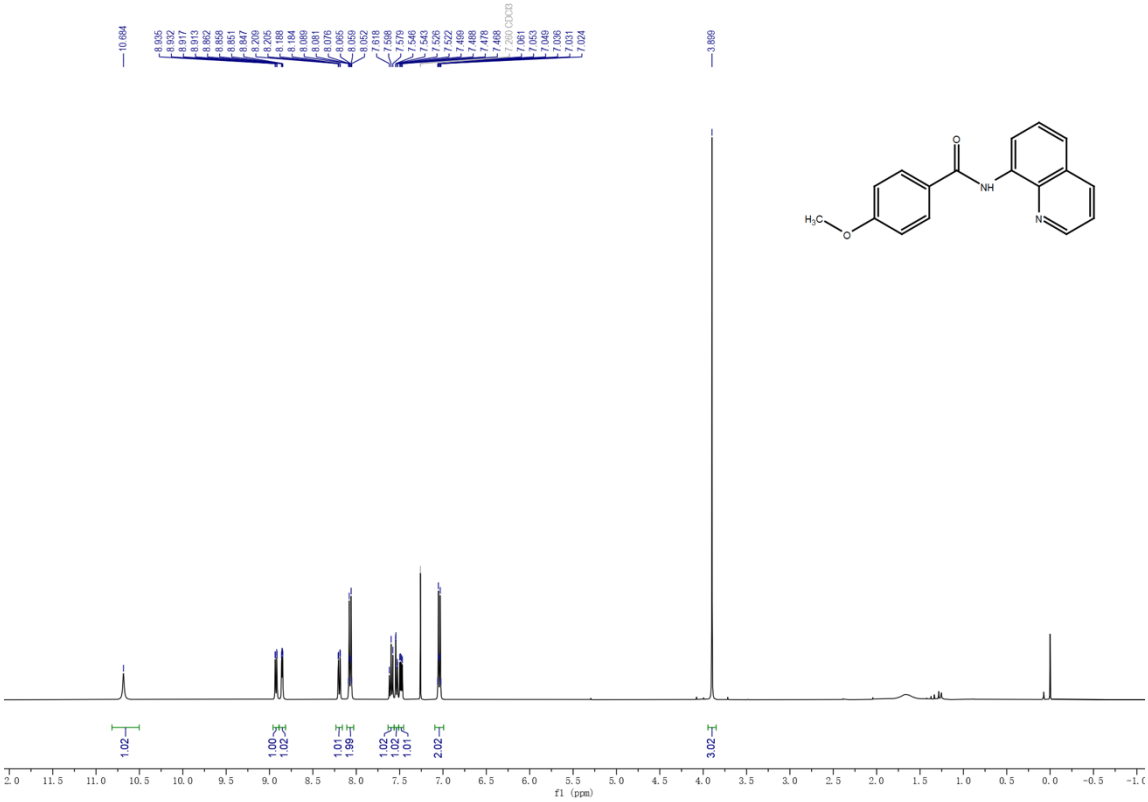
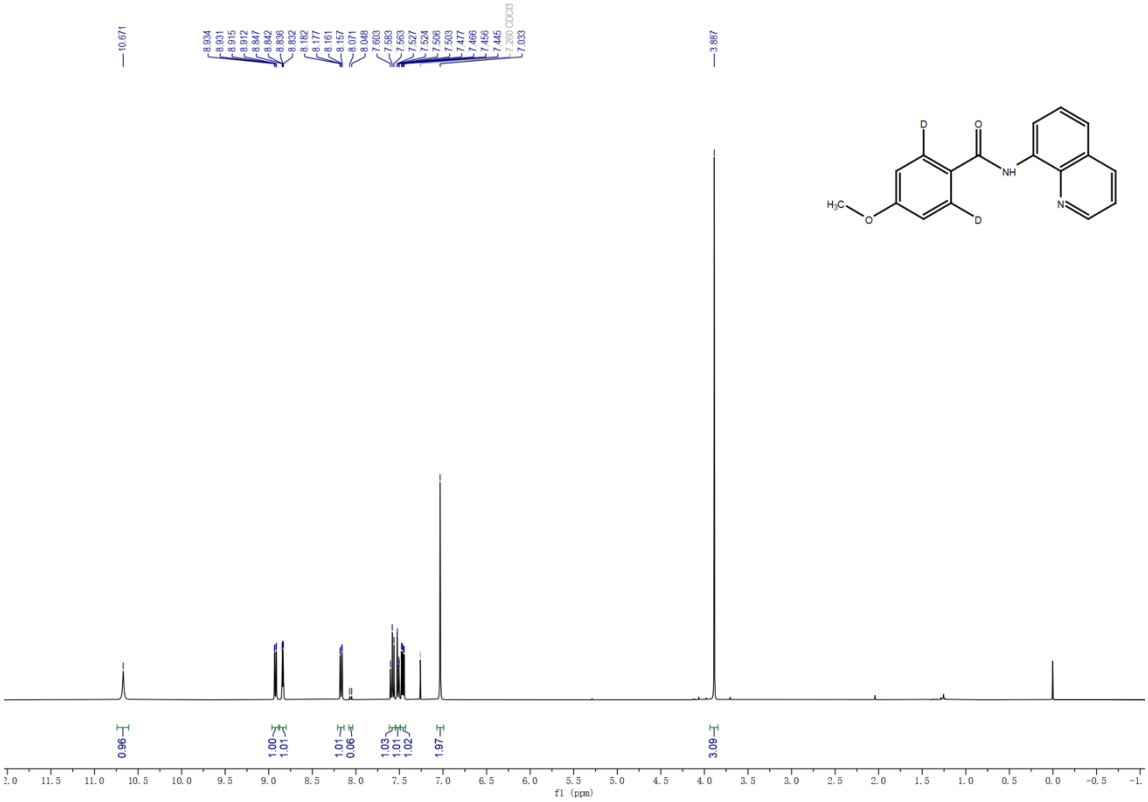
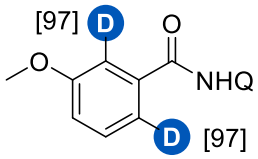


Figure S23 ^{1}H NMR of **5-[d]** in $CDCl_3$



Deuteration of 3-Methoxy-N-(quinolin-8-yl)benzamide-2 (6)



General procedure to afford **6-[d]** as light yellow solid (132.7 mg, 95%) with D-incorporation 97% for 2,6-positions by ^{1}H NMR; R_f = 0.25 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.90 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.77 (dt, *J* = 4.0, 1.9 Hz, 1H), 8.08 (ddd, *J* = 8.3, 2.9, 1.6 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.53 (td, *J* = 8.0, 1.7 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.44 – 7.35 (m, 2H), 7.13 – 7.03 (m, 1H), 3.87 (d, *J* = 1.5 Hz, 3H)..
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.92 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.66 – 7.62 (m, 0.07H, Labelled)**, 7.61 – 7.54 (m, 1H), 7.51 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.44 (dt, *J* = 8.3, 2.1 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H).

Figure S24 ^{1}H NMR spectrum comparison

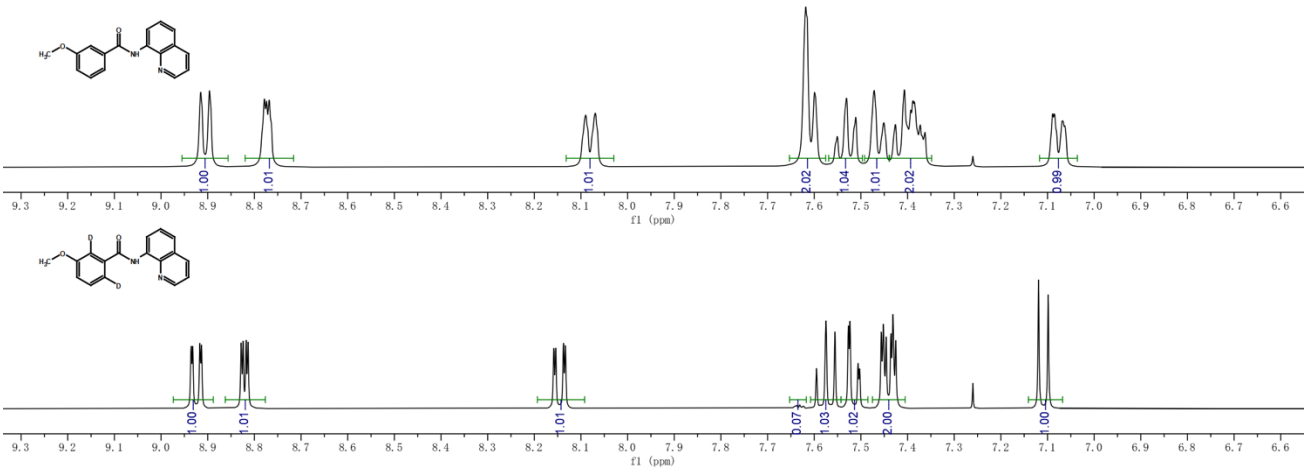


Figure **S25** ^{1}H NMR of **6** in $CDCl_3$

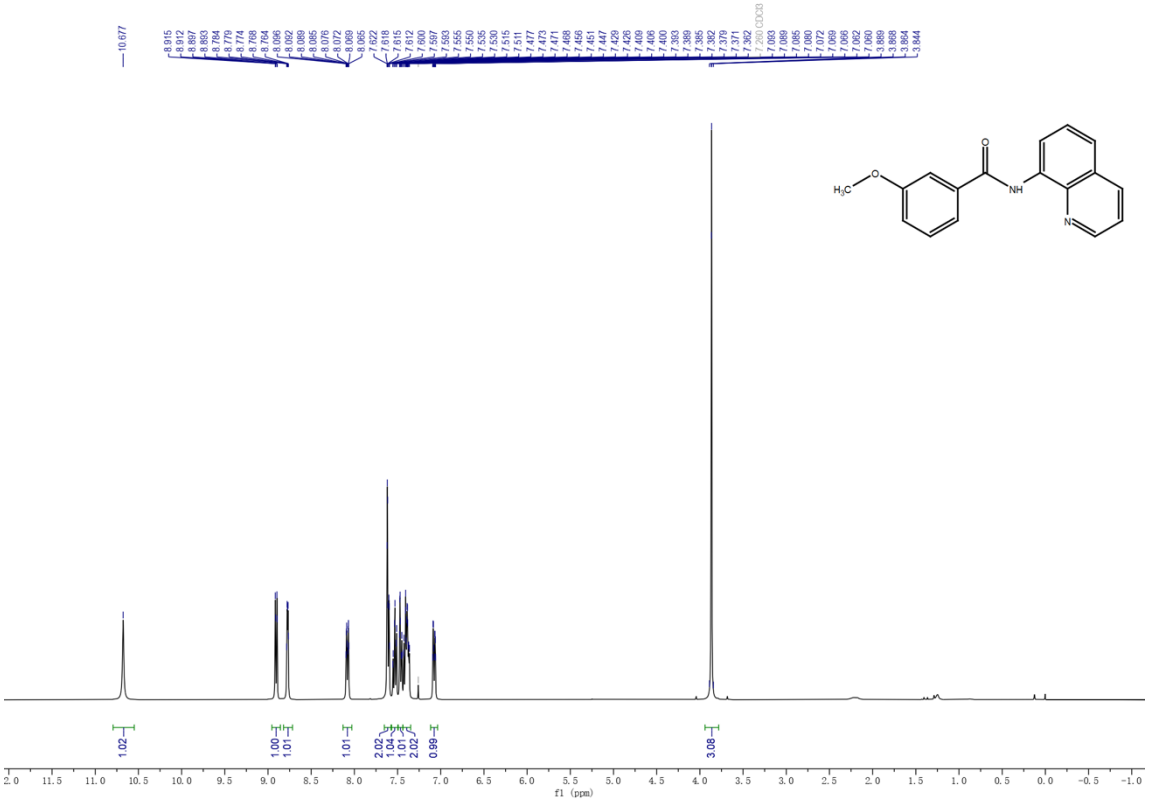
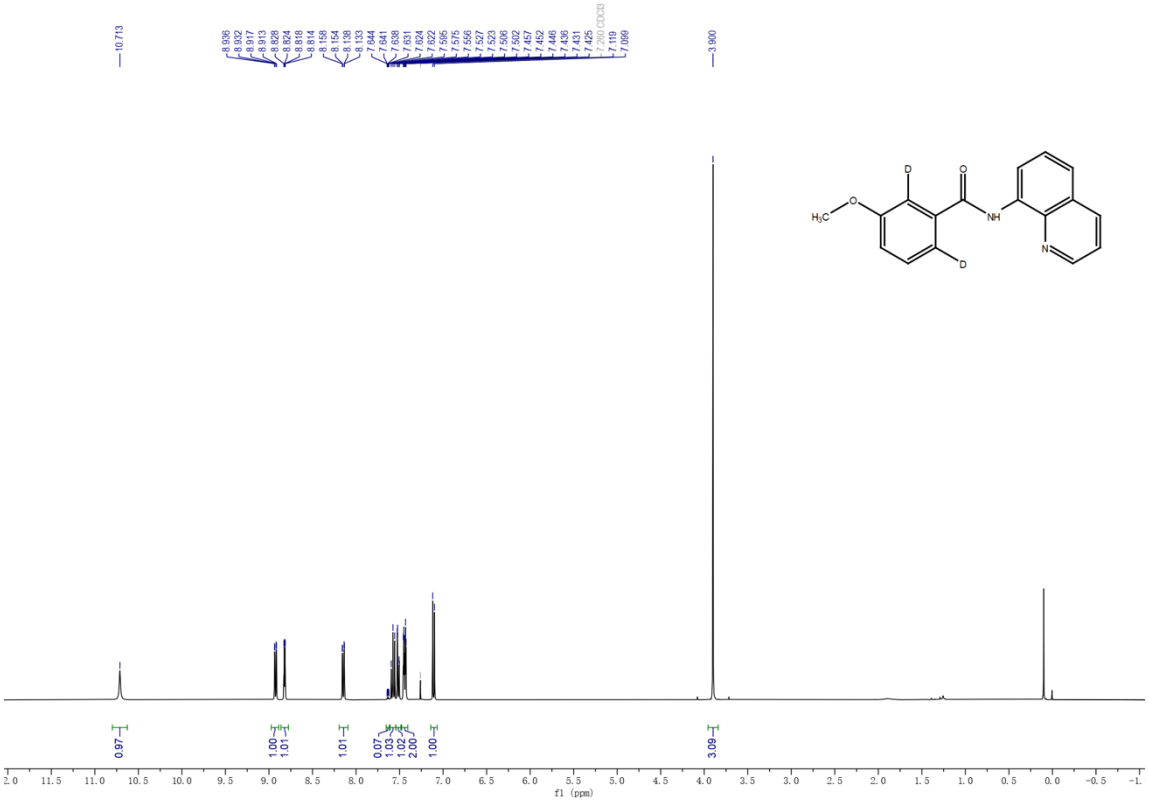
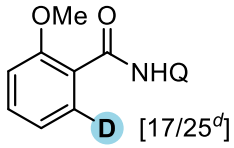


Figure **S26** ^{1}H NMR of **6-[d]** in $CDCl_3$



Deuteration of 2-Methoxy-N-(quinolin-8-yl)benzamide (7)



General procedure to afford **7-[d]** as white solid (131.6 mg, 95%) with D-incorporation 17% for 6-position by ^{1}H NMR and 0.15 D_{MS} by GC-MS; R_f = 0.25 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 9.04 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.36 (dd, *J* = 7.8, 1.9 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.18 – 7.11 (m, 1H), 7.08 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.20 (s, 3H).

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (s, 1H), 9.04 (dd, *J* = 7.7, 1.4 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), **8.36 (dd, *J* = 7.9, 1.9 Hz, 0.83H, Labelled)**, 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.05 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.18 (s, 3H).

Figure S27 ^{1}H NMR spectrum comparison

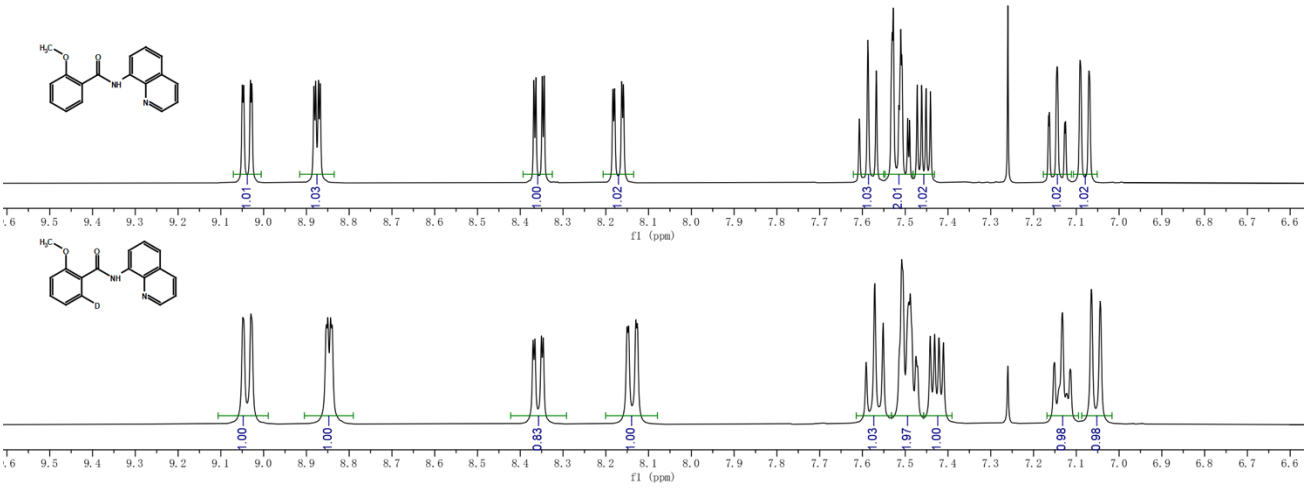


Figure S28 GC-MS spectrum comparison

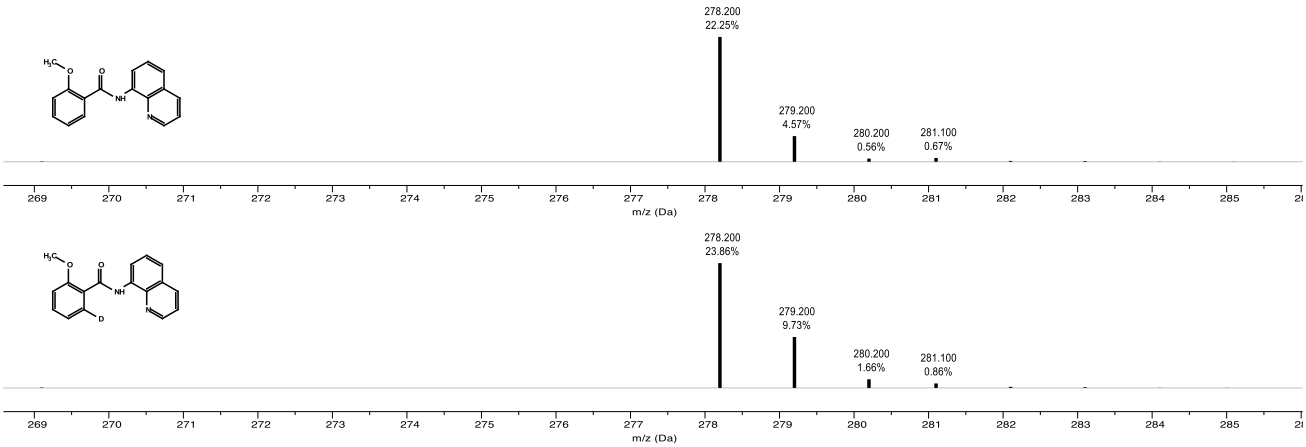


Figure S29 ^{1}H NMR of **7** in $CDCl_3$

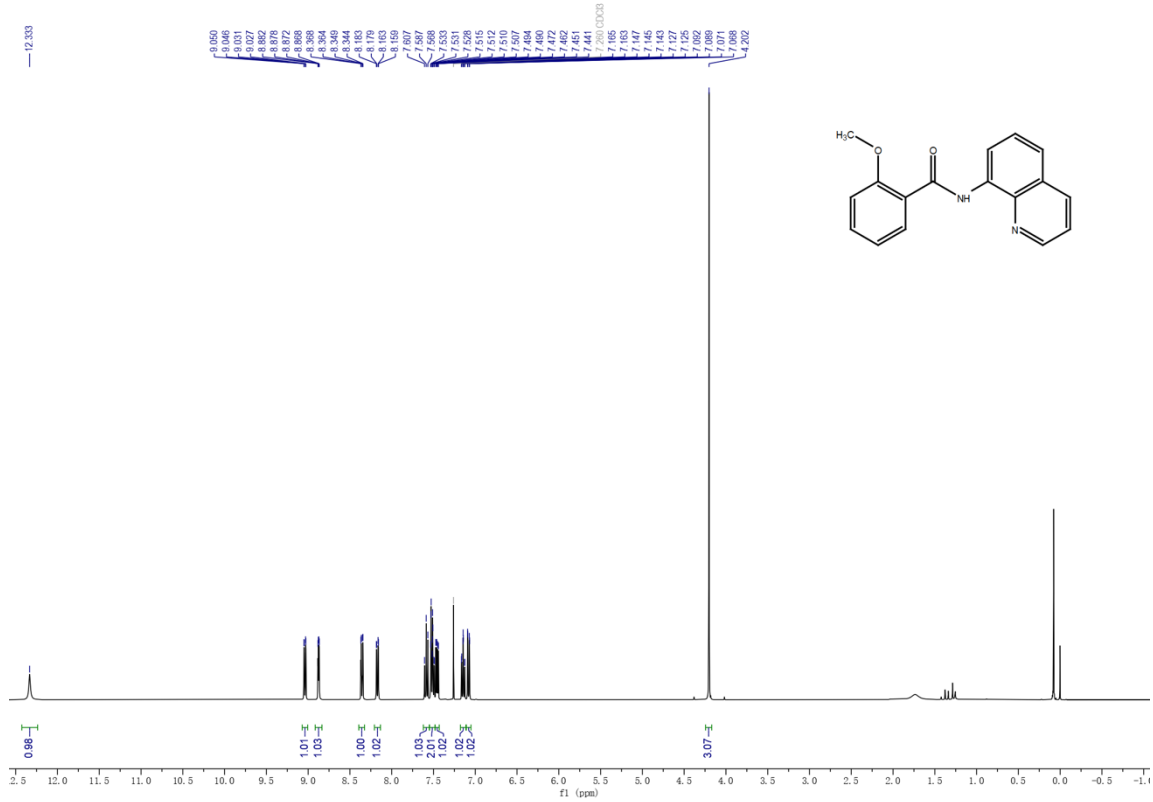
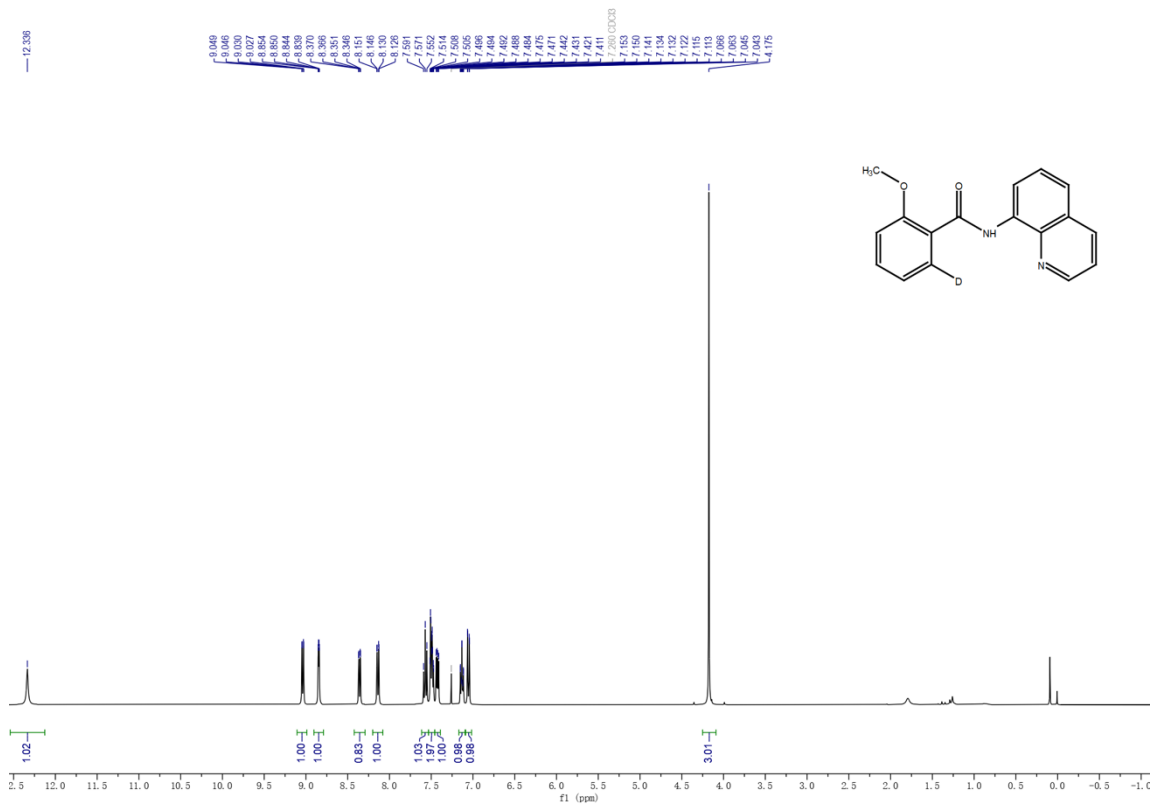
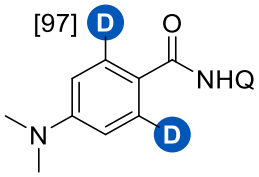


Figure S30 ^{1}H NMR of **7-[d]** in $CDCl_3$



Deuteration of 4-(Dimethylamino)-N-(quinolin-8-yl)benzamide (8)



General procedure to afford **8-[d]** as light yellow solid (135.1 mg, 93%) with D-incorporation 97% for 2,6-positions by ^{1}H NMR; R_f = 0.20 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.94 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.51 – 7.43 (m, 2H), 6.80 – 6.74 (m, 2H), 3.06 (s, 6H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.94 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.01 (d, *J* = 9.5 Hz, 0.06H, Labelled)**, 7.58 (t, *J* = 7.9 Hz, 1H), 7.53 – 7.41 (m, 2H), 6.78 (s, 2H), 3.06 (s, 6H).

Figure S31 ^{1}H NMR spectrum comparison

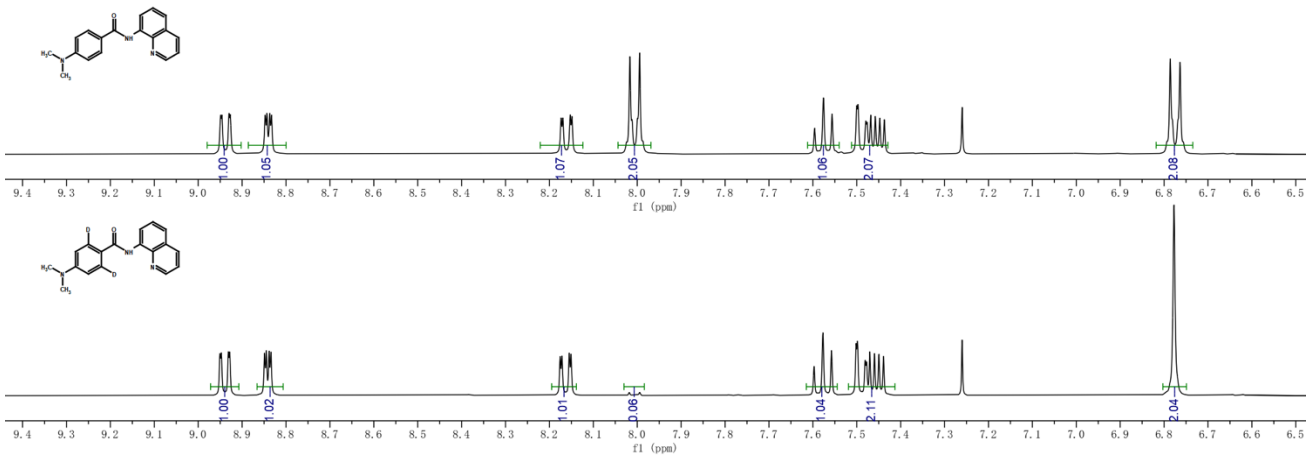


Figure S32 ^{1}H NMR of **8** in $CDCl_3$

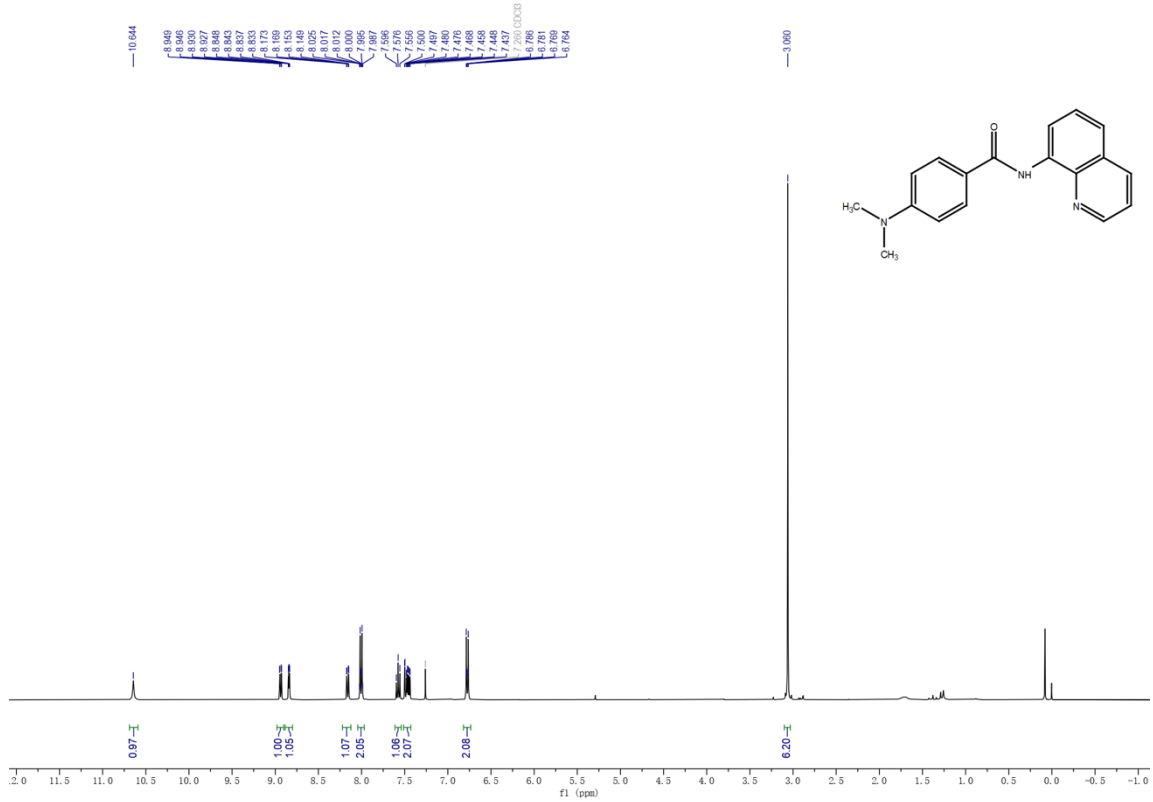
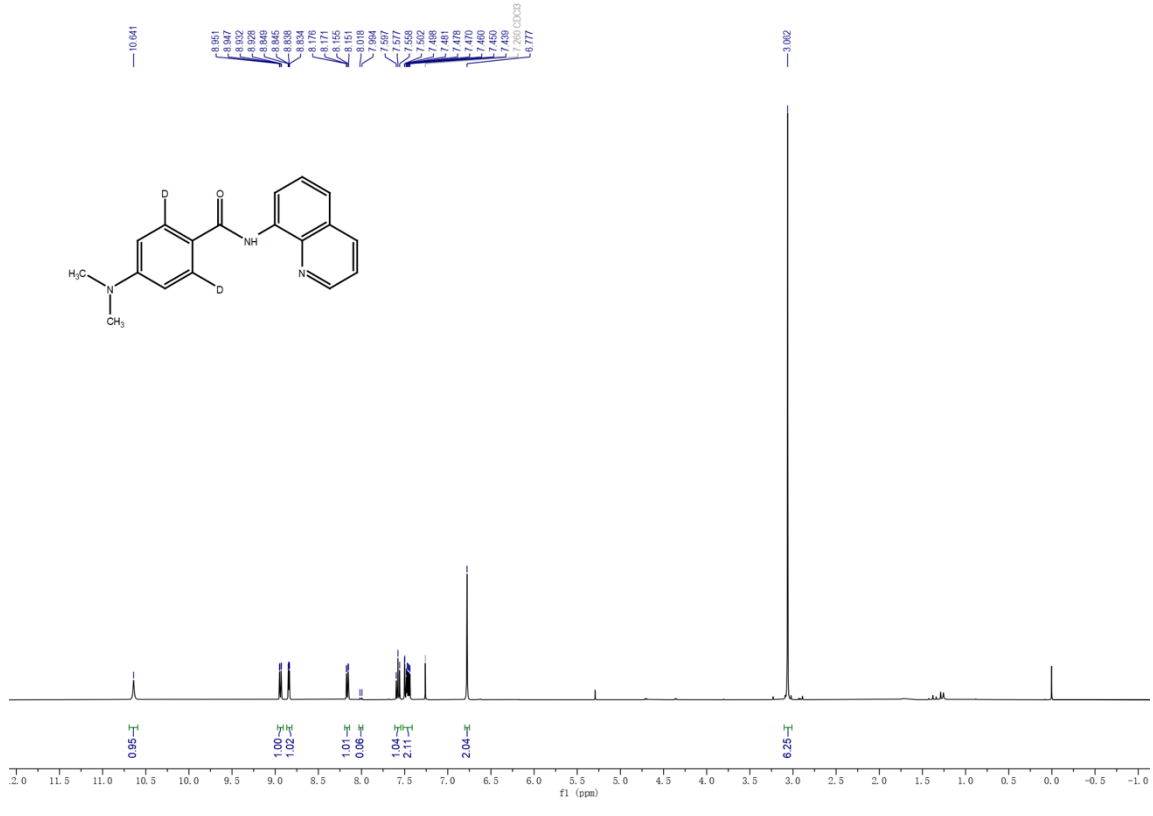
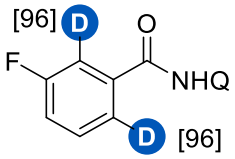


Figure S33 ^{1}H NMR of **8-[d]** in $CDCl_3$



Deuteration of 3-Fluoro-N-(quinolin-8-yl)benzamide (9)



General procedure to afford **9-[d]** as white solid (129.7 mg, 97%) with D-incorporation 96% for 2,6-positions by ^{1}H NMR and 1.77 D_{MS} by GC-MS; R_f = 0.50 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.65 (s, 1H), 8.97 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.68 (d, *J* = 7.6 Hz, 1H), 8.45 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.81 (dt, *J* = 9.7, 2.1 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.67 (qd, *J* = 8.7, 5.2 Hz, 3H), 7.52 (td, *J* = 8.5, 2.7 Hz, 1H)..
NMR data for deuterated product: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.64 (s, 1H), 8.97 (d, *J* = 4.7 Hz, 1H), 8.67 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), **7.91 – 7.59 (m, 4.07H, Labelled)**, 7.51 (t, *J* = 8.6 Hz, 1H).

Figure S34 ^{1}H NMR spectrum comparison

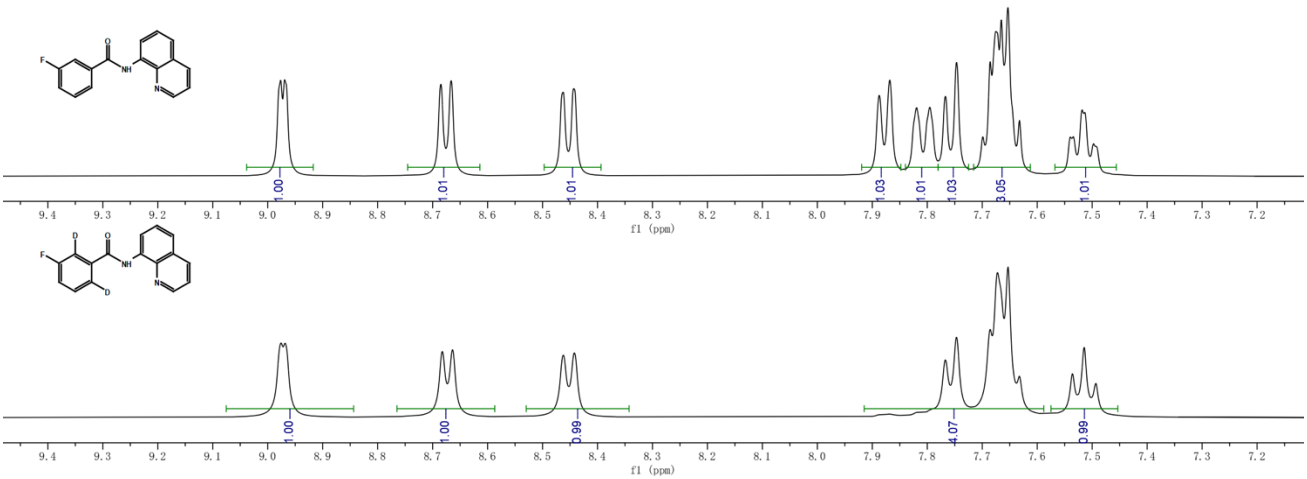


Figure S35 GC-MS spectrum comparison

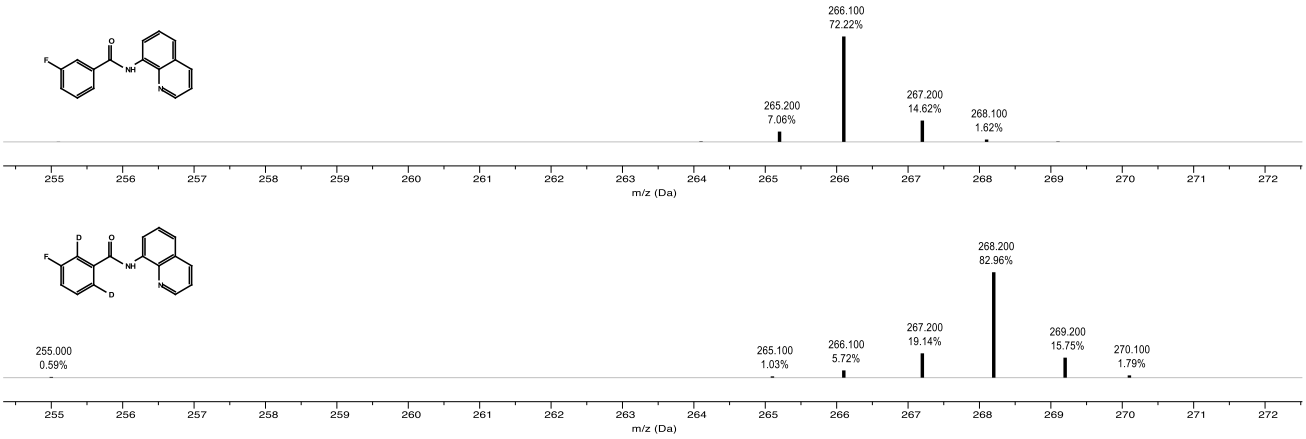


Figure S36 ^{1}H NMR of **9** in DMSO-d_6

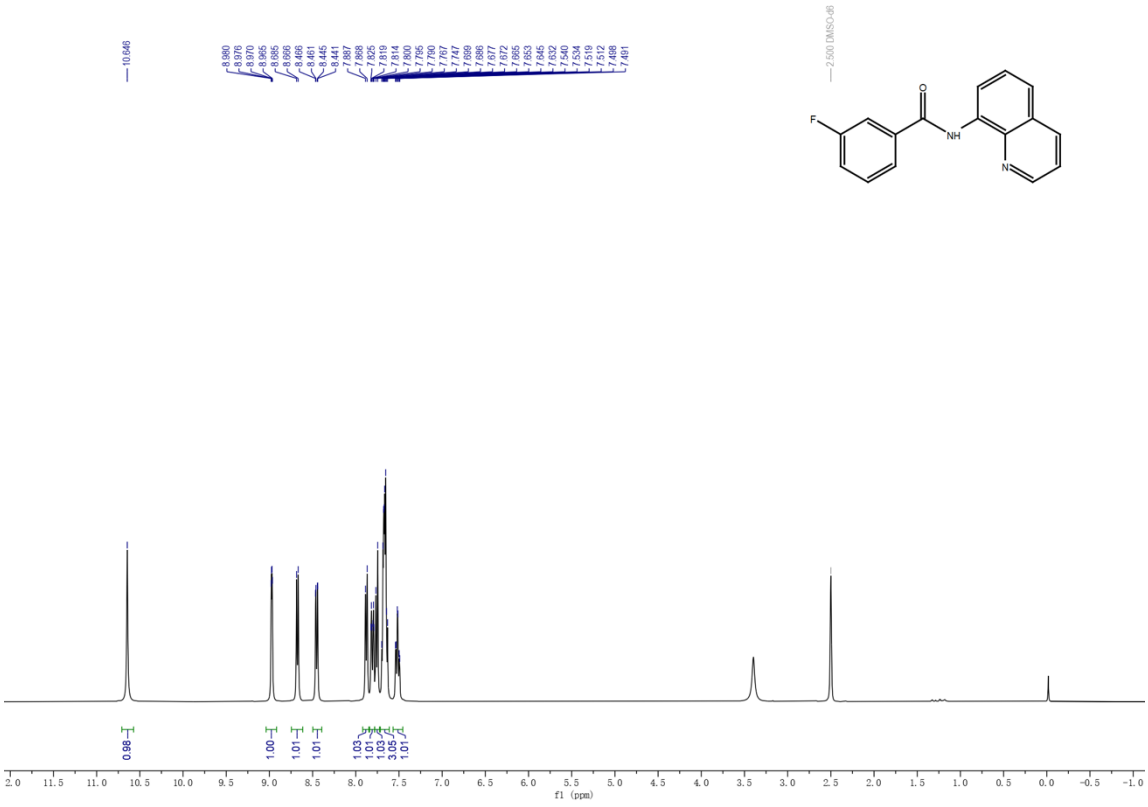
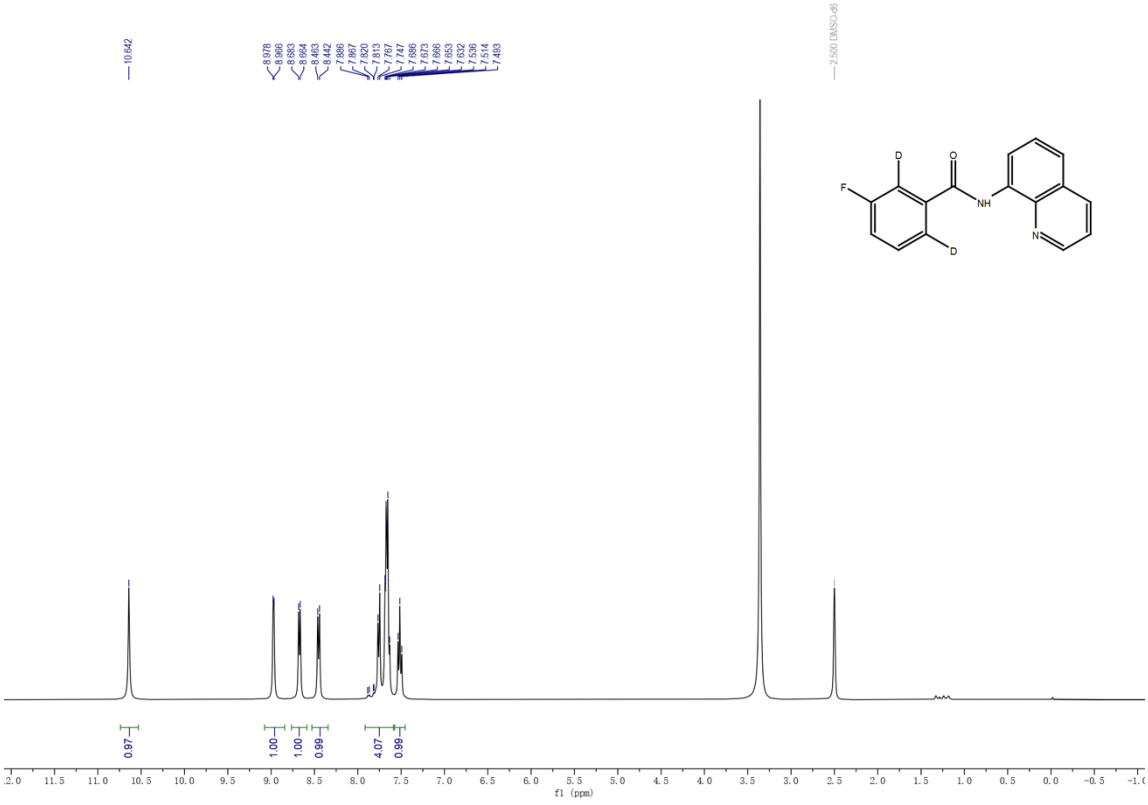
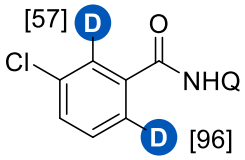


Figure S37 ^{1}H NMR of **9-[d]** in DMSO-d_6



Deuteration of 3-Chloro-N-(quinolin-8-yl)benzamide (10)



General procedure to afford **10-[d]** as white solid (136.2 mg, 96%) with D-incorporation 57% for 2-position and 96% for 6-position by ^{1}H NMR and 1.34 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.90 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.86 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.06 (t, *J* = 1.9 Hz, 1H), 7.95 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.63 – 7.45 (m, 5H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.90 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), **8.06 (d, *J* = 2.1 Hz, 0.43H, Labelled)**, **7.97 – 7.92 (m, 0.04H, Labelled)**, 7.62 – 7.44 (m, 5H).

Figure S38 ^{1}H NMR spectrum comparison

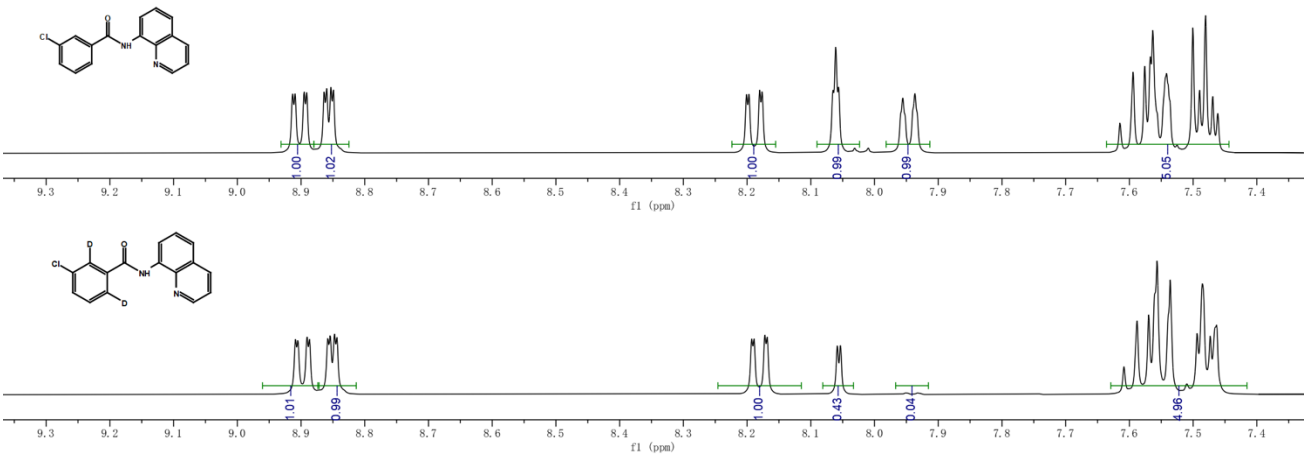


Figure S39 GC-MS spectrum comparison

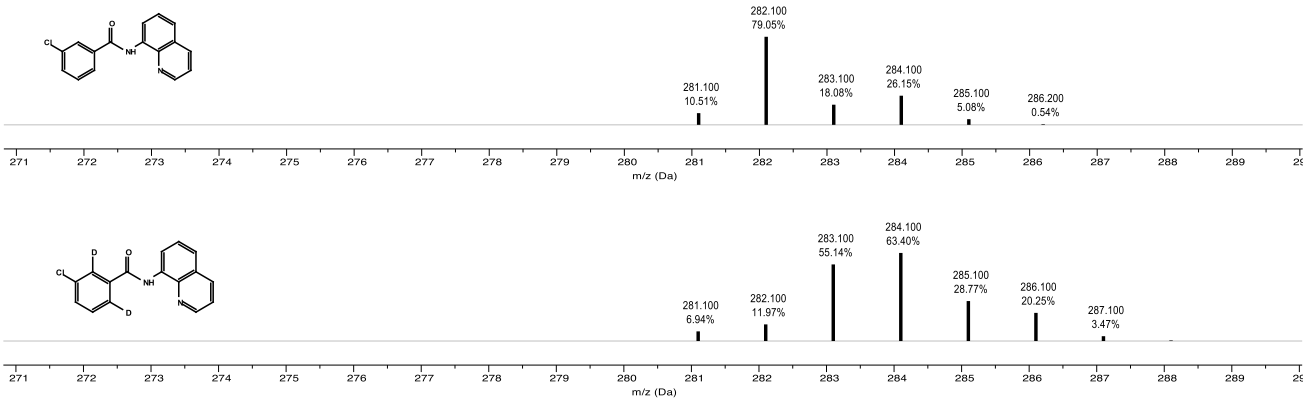


Figure S40 ^{1}H NMR of **10** in $CDCl_3$

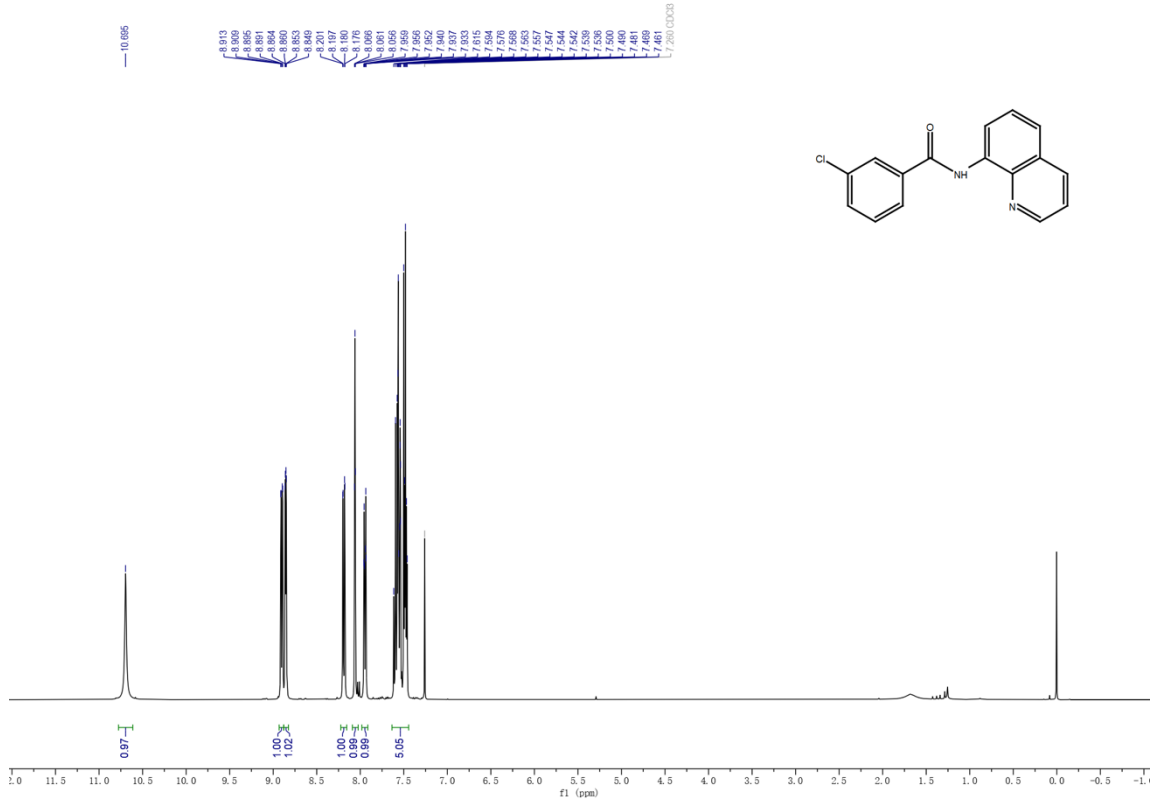
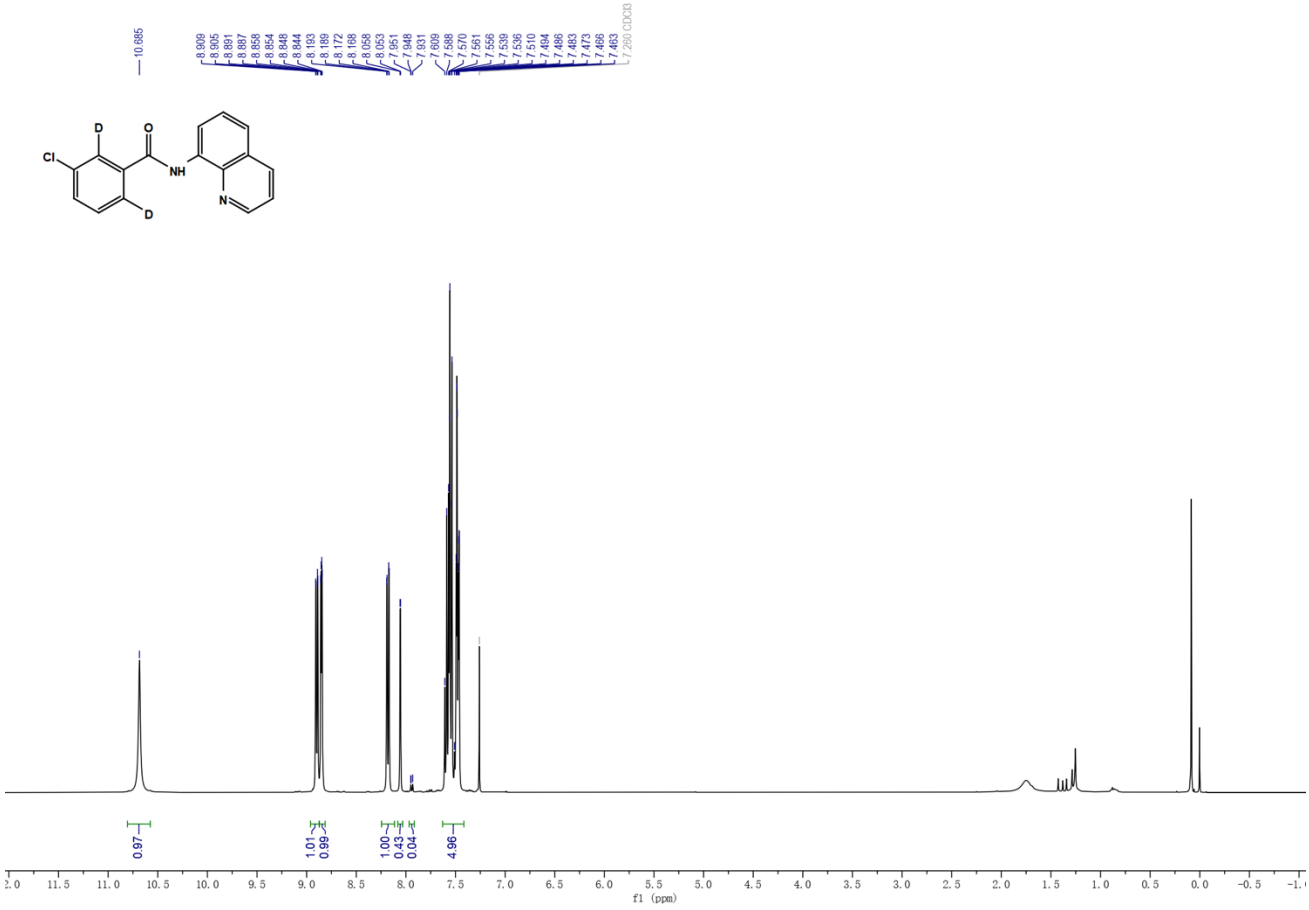
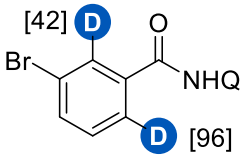


Figure S41 ^{1}H NMR of **10-[d]** in $CDCl_3$



Deuteration of 3-Bromo-N-(quinolin-8-yl)benzamide (11)



General procedure to afford **11-[d]** as white solid (157.3 mg, 96%) with D-incorporation 42% for 2-position and 95% for 6-position by ^{1}H NMR and 1.31 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.86 (dd, *J* = 18.7, 5.8 Hz, 2H), 8.23 – 8.13 (m, 2H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.34 (m, 4H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.88 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.83 (dd, *J* = 4.7 Hz, 1H), **8.20 (d, *J* = 2.0 Hz, 0.58H, Labelled)**, 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.97 (dd, *J* = 7.7, 1.0 Hz, 0.05H, Labelled)**, 7.68 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H).

Figure S42 ^{1}H NMR spectrum comparison

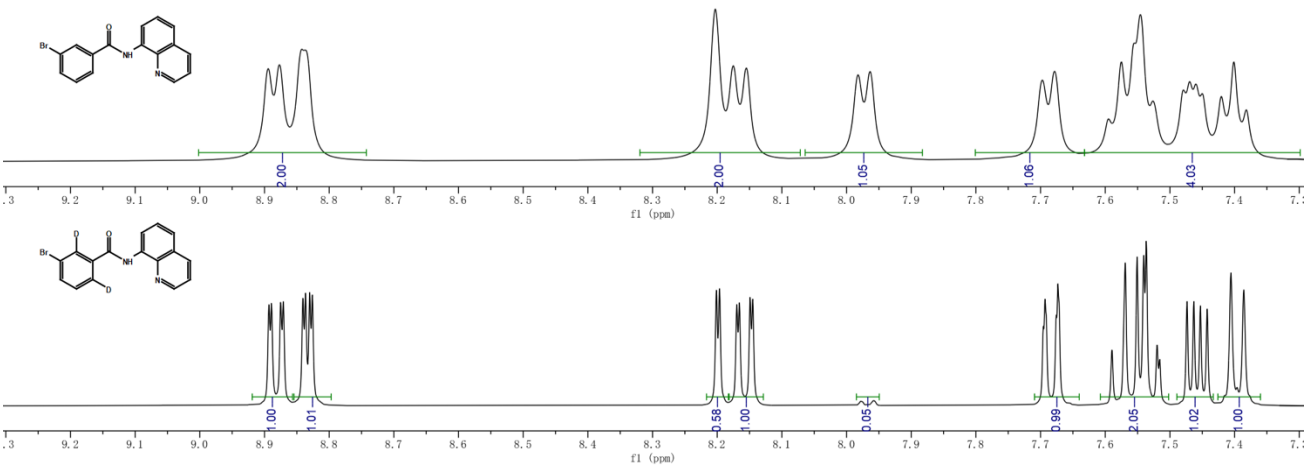


Figure S43 GC-MS spectrum comparison

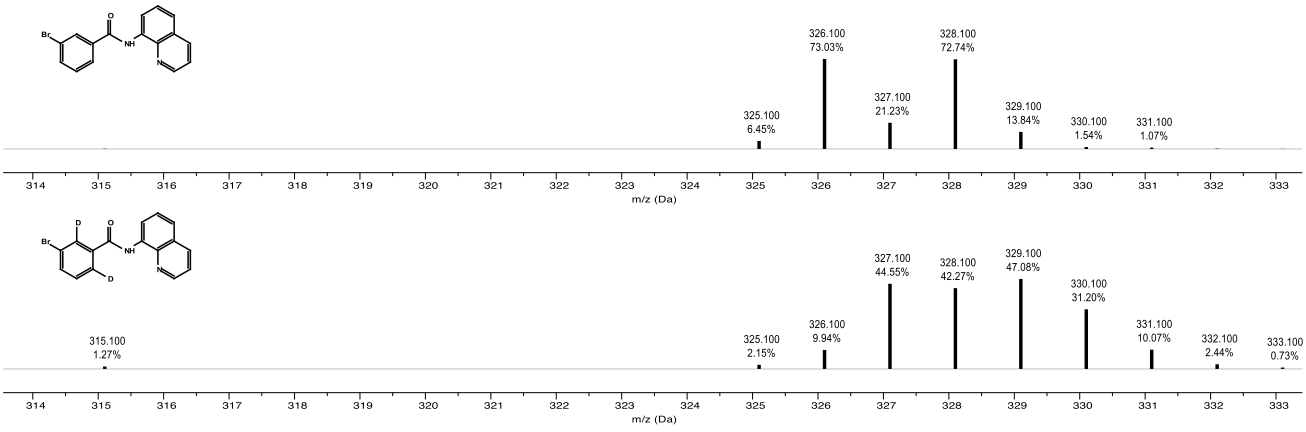


Figure S44 ^{1}H NMR of **11** in $CDCl_3$

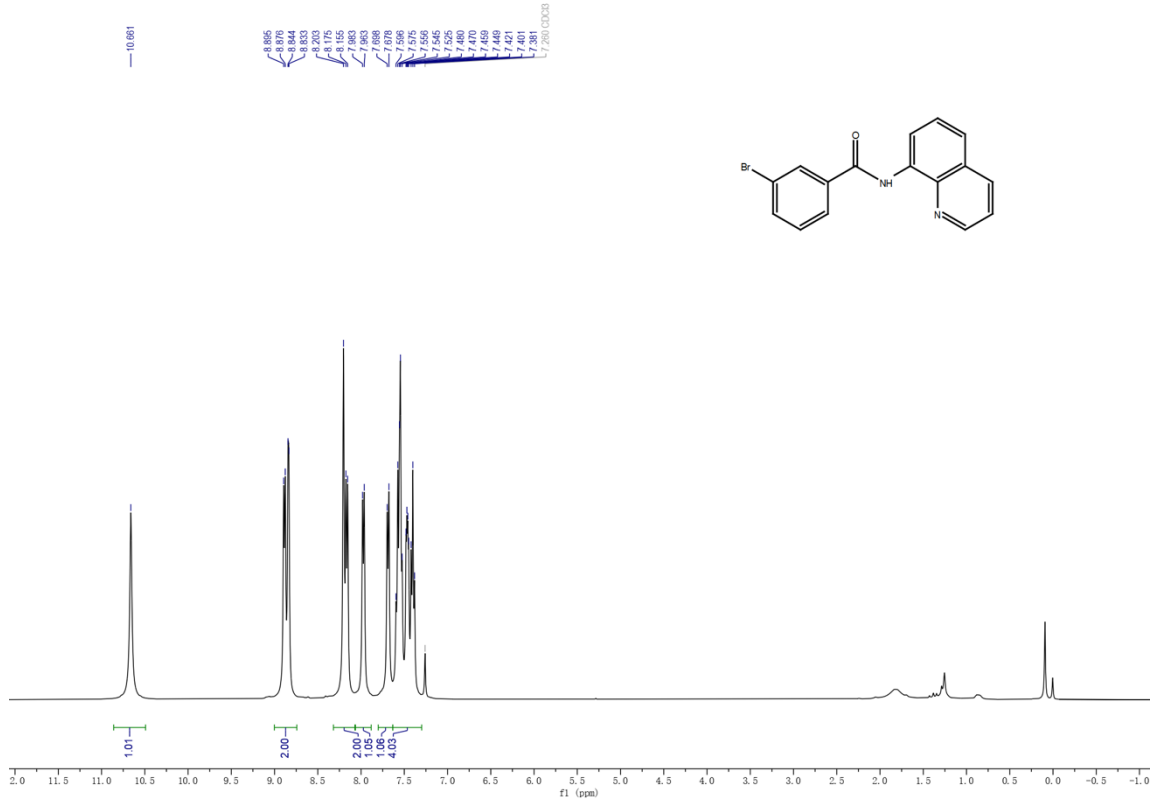
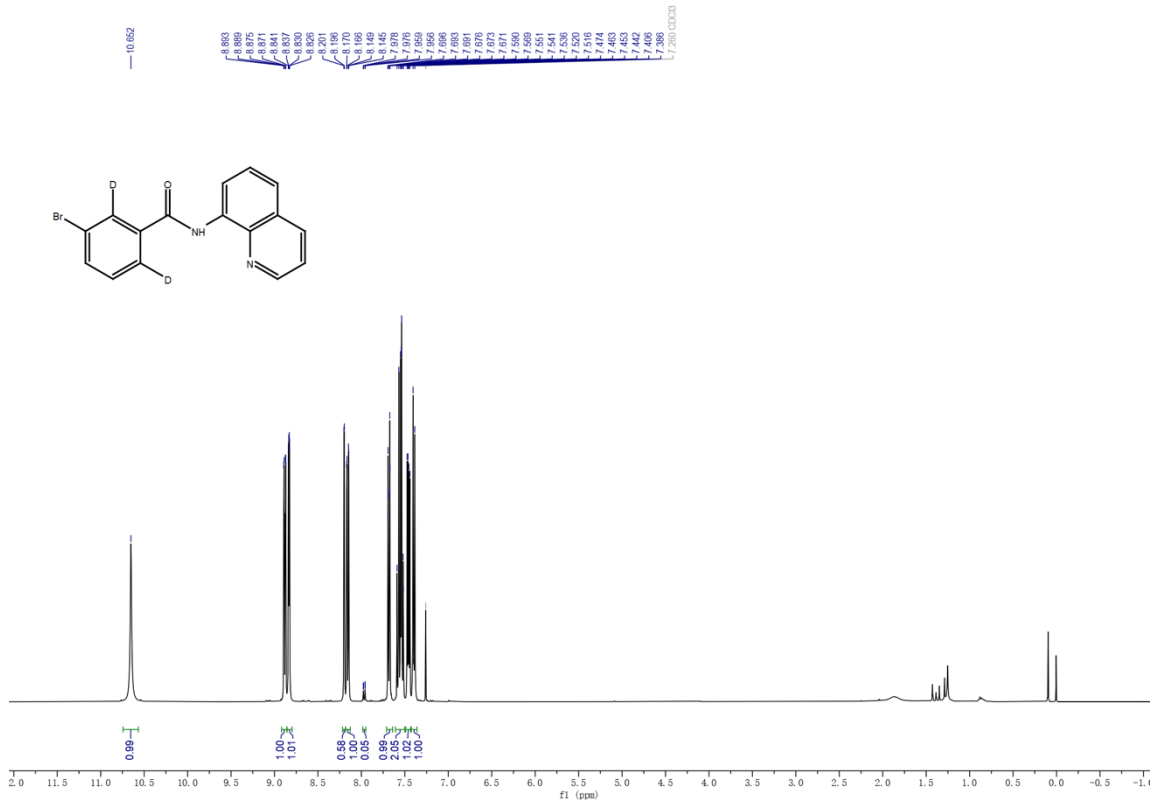
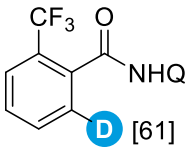


Figure S45 ^{1}H NMR of **11-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)-2-(trifluoromethyl)benzamide (12)



General procedure to afford **12-[d]** as white solid (150.6 mg, 95%) with D-incorporation 61% for 6-position by ^{1}H NMR and 0.59 D_{MS} by GC-MS; R_f = 0.30 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.93 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.69 (td, *J* = 7.6, 1.4 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.93 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.83 – 7.75 (m, 1.39H, Labelled)**, 7.68 (ddt, *J* = 5.4, 4.1, 2.1 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.46 (dd, *J* = 8.3, 4.3 H).

Figure S46 ^{1}H NMR spectrum comparison

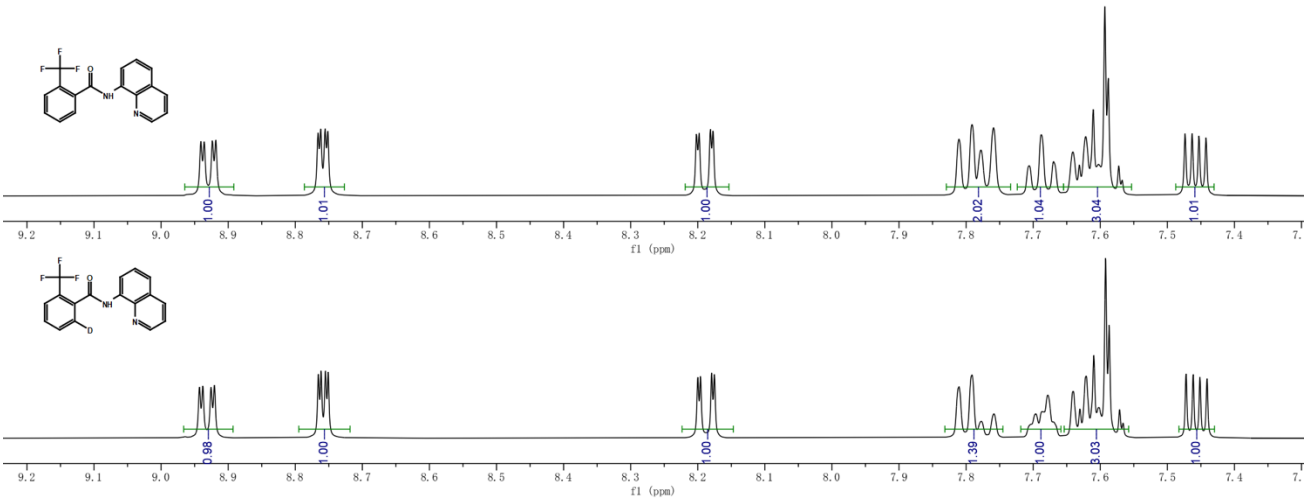


Figure S47 GC-MS spectrum comparison

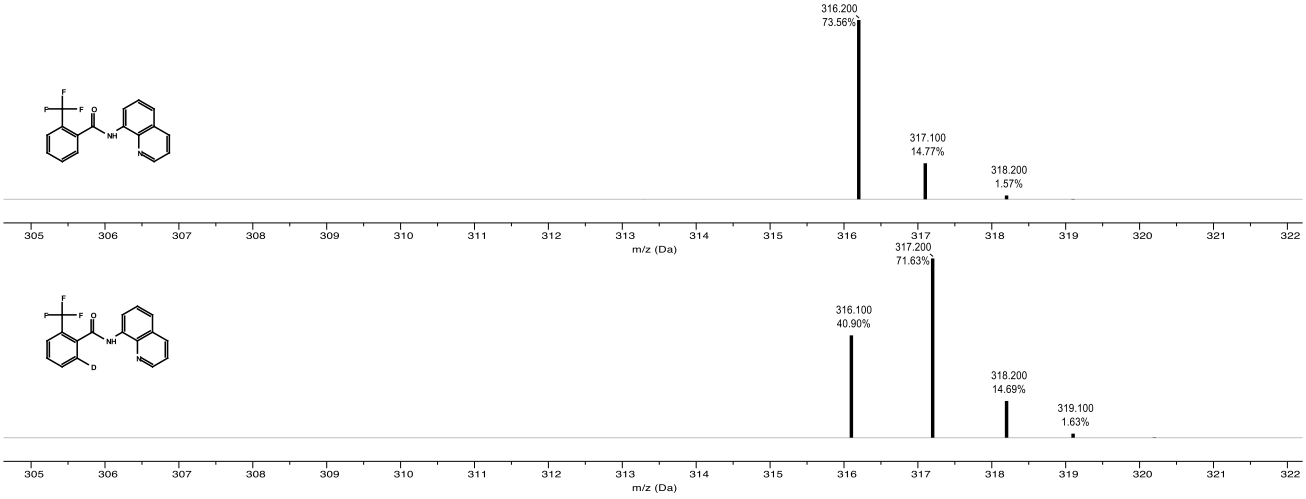


Figure S48 ^{1}H NMR of **12** in $CDCl_3$

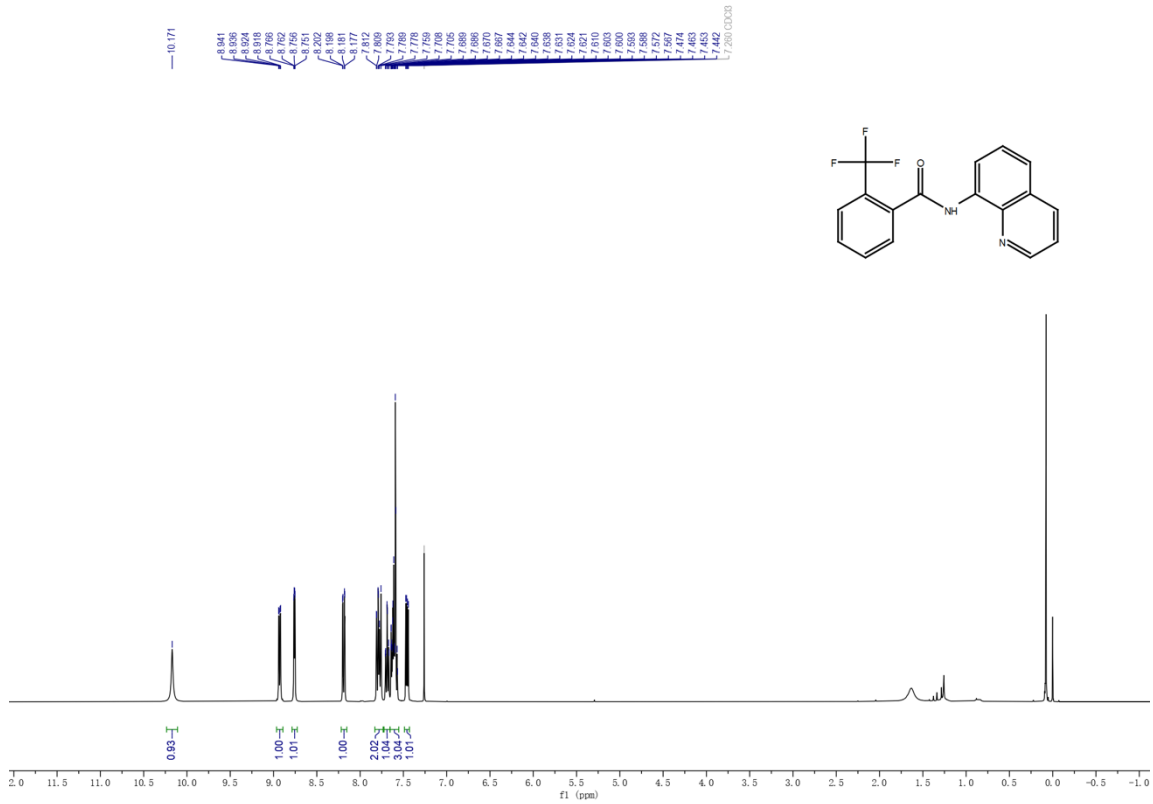
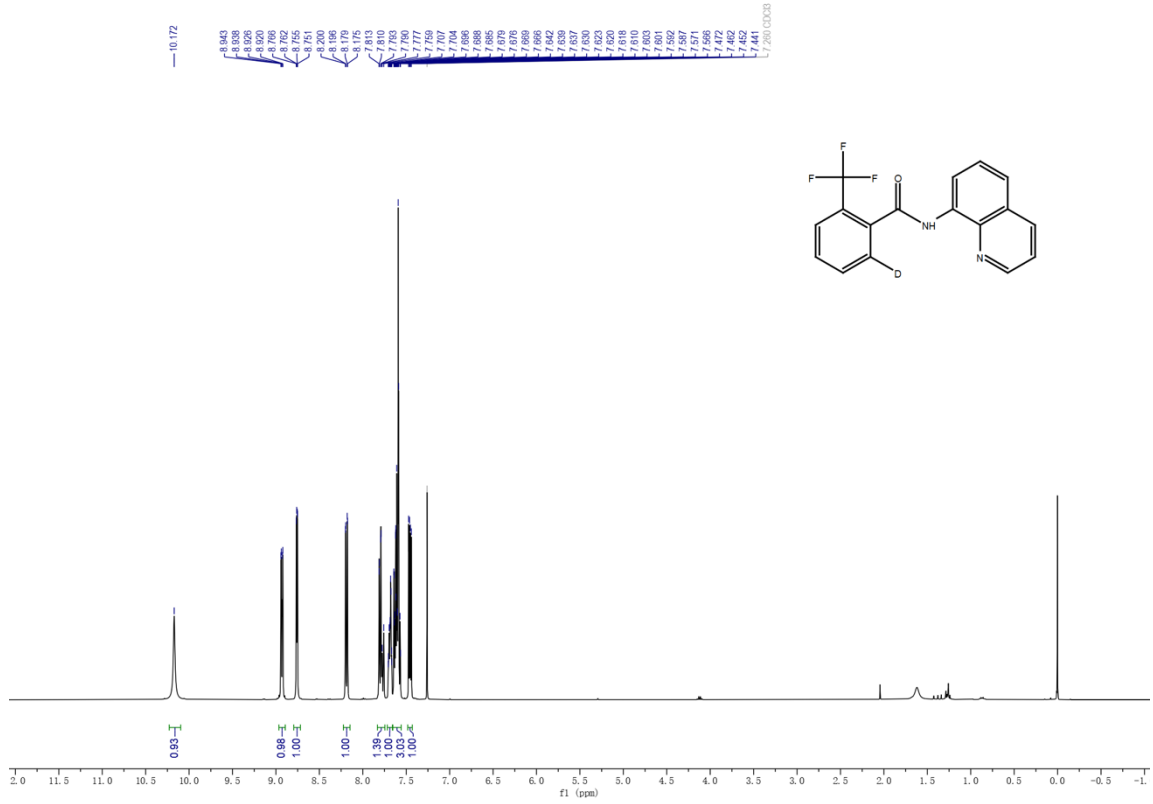
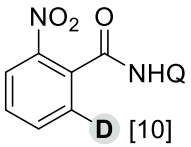


Figure S49 ^{1}H NMR of **12-[d]** in $CDCl_3$



Deuteration of 2-Nitro-N-(quinolin-8-yl)benzamide (13)



General procedure to afford **13-[d]** as light yellow solid (130.2 mg, 90%) with D-incorporation 10% for 6-position by ^{1}H NMR; R_f = 0.10 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.89 (dd, *J* = 6.5, 2.4 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.72 – 7.55 (m, 3H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.90 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.76 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), **7.81 – 7.73 (m, 1.90H, Labelled)**, 7.71 – 7.57 (m, 3H), 7.48 (dd, *J* = 8.3, 4.3 Hz, 1H).

Figure S50 ^{1}H NMR spectrum comparison

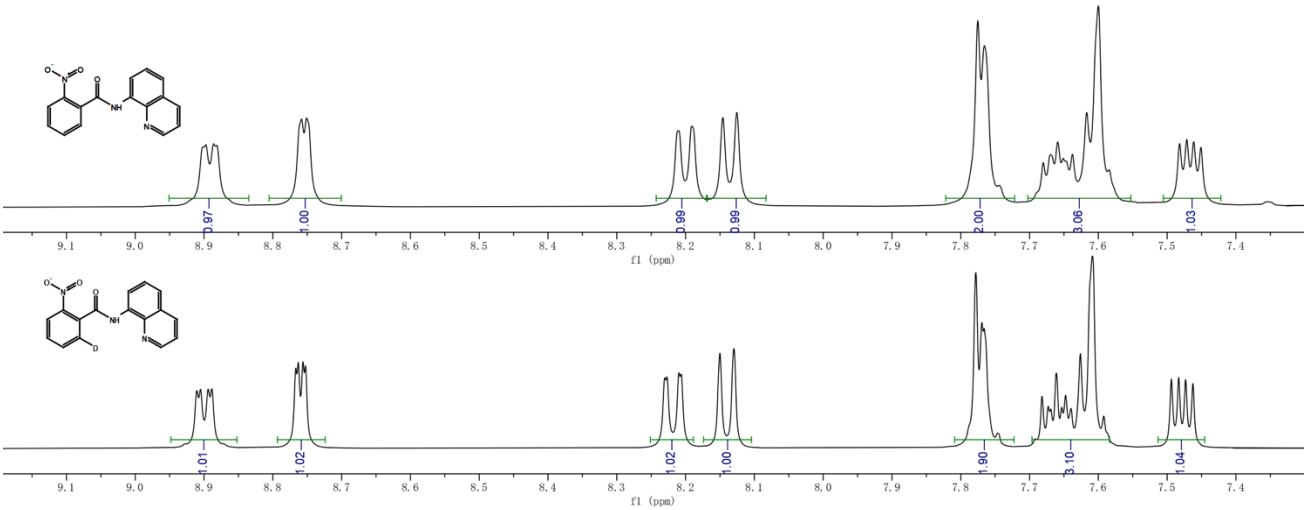


Figure S51 ^{1}H NMR of **13** in $CDCl_3$

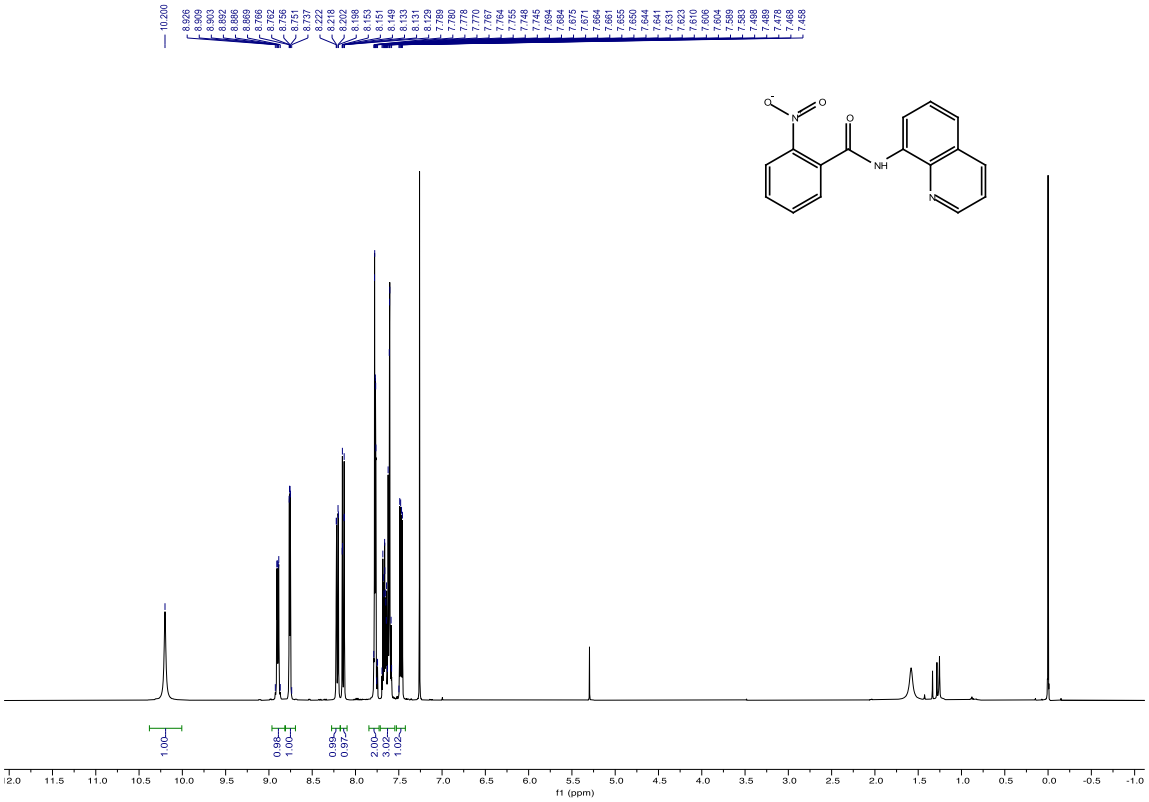
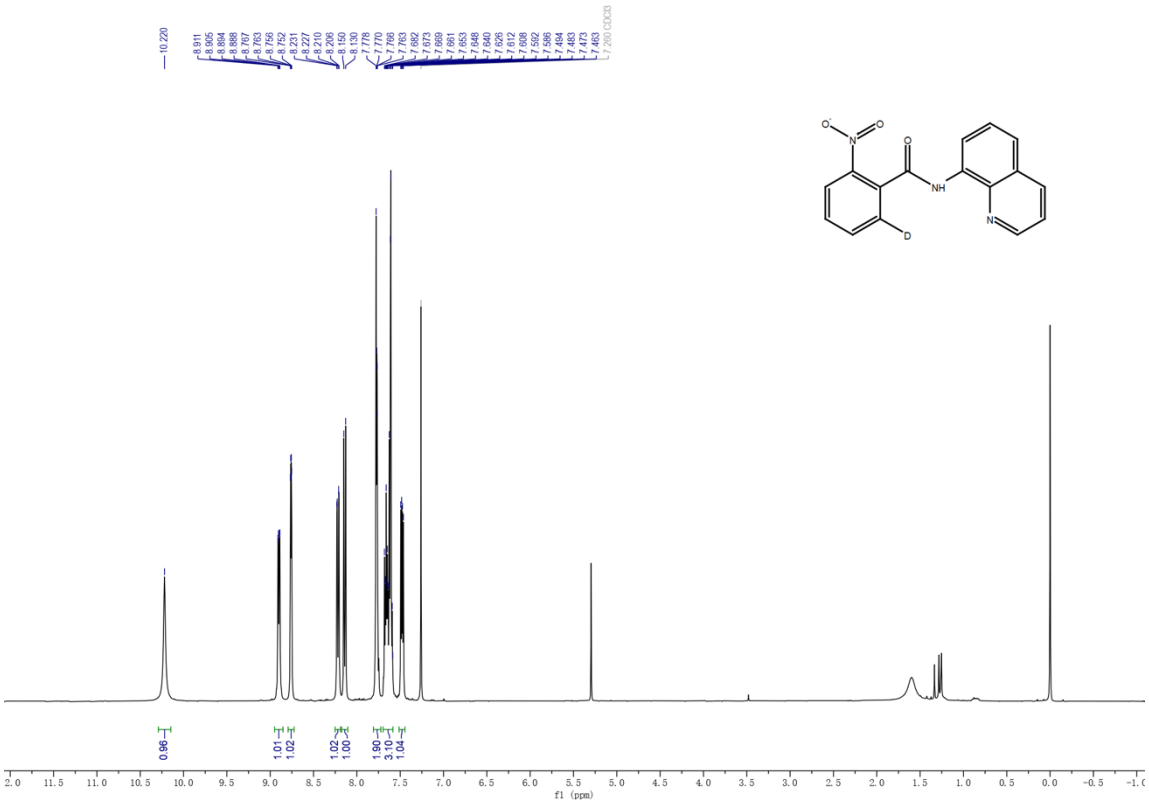
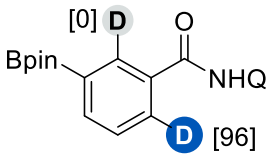


Figure S52 ^{1}H NMR of **13-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (15)



General procedure to afford **15-[d]** as white solid (58.9 mg, 63%, reacted at 0.25 mmol scale) with D-incorporation 96% for 6-position by ^{1}H NMR; R_f = 0.10 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.90 (dd, *J* = 30.2, 5.9 Hz, 2H), 8.50 (s, 1H), 8.17 (dd, *J* = 13.2, 8.1 Hz, 2H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.67 – 7.41 (m, 4H), 1.38 (s, 12H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.94 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.51 (s, 1H), **8.18 (dd, *J* = 8.3, 1.7 Hz, 1.04H, Labelled)**, 8.02 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.63 – 7.51 (m, 3H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.38 (s, 12H).

Figure S53 ^{1}H NMR spectrum comparison

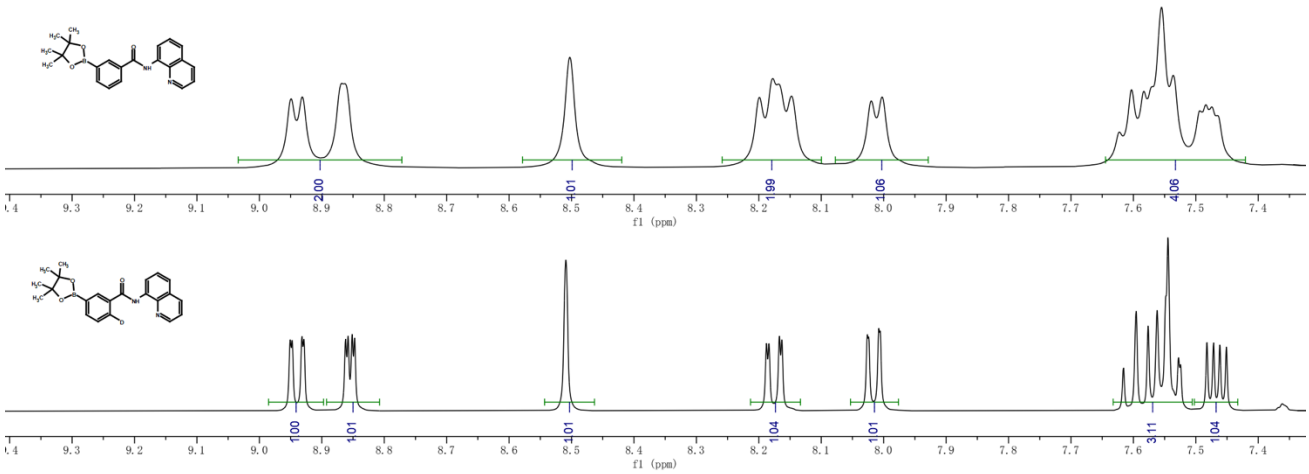


Figure S54 ^{1}H NMR of **15** in $CDCl_3$

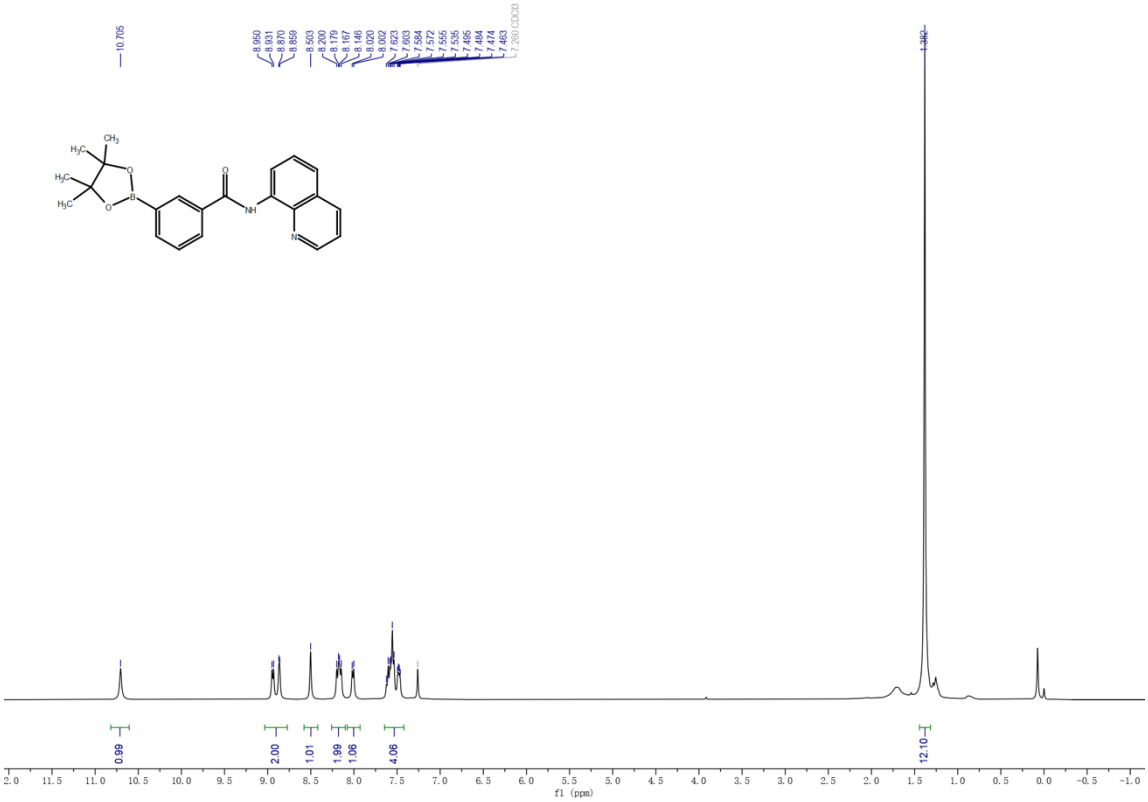
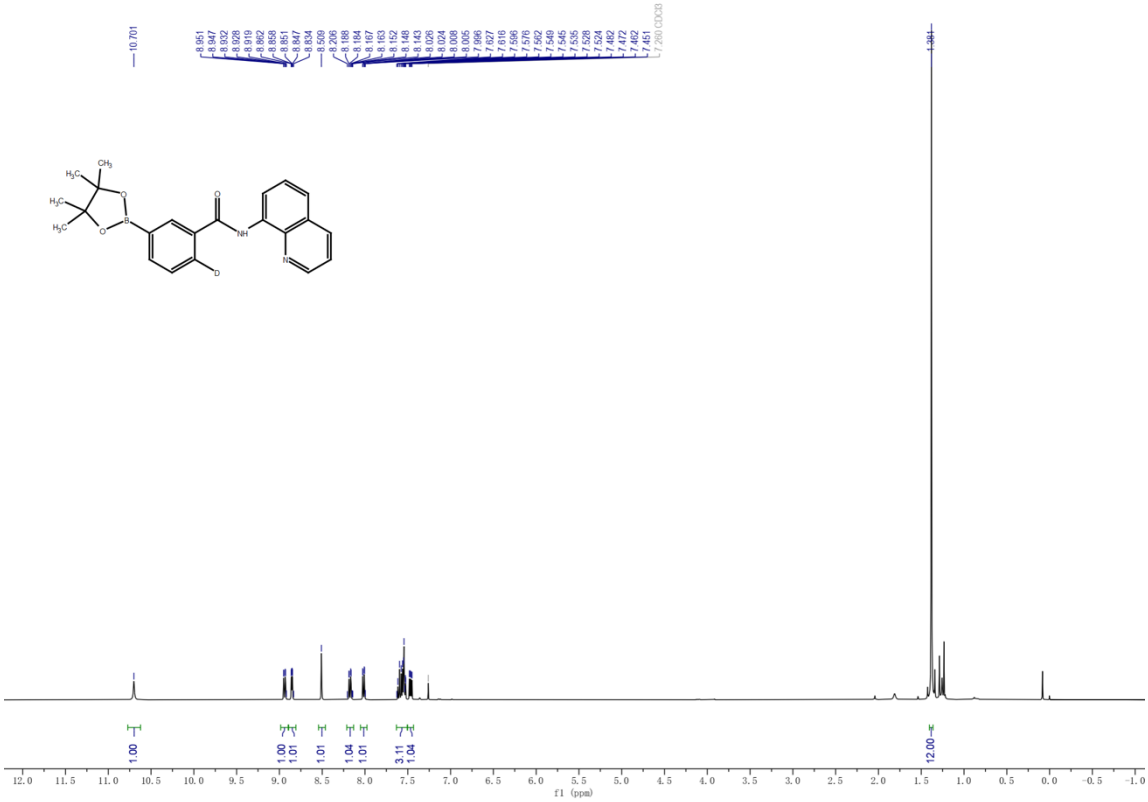
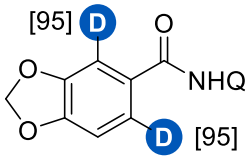


Figure S55 ^{1}H NMR of **15-[d]** in $CDCl_3$



N-(Quinolin-8-yl)benzo[d][1,3]dioxole-5-carboxamide (16)



General procedure to afford **16-[d]** as white solid (62.3 mg, 85%, reacted at 0.25 mmol scale) with D-incorporation 95% for 4,6-position by ^{1}H NMR; R_f = 0.30 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.86 (dd, *J* = 21.1, 5.9 Hz, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.40 (m, 5H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 2H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.87 (dd, *J* = 19.7, 5.9 Hz, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), **7.66 – 7.43 (m, 3.11H, Labelled)**, 6.94 (s, 1H), 6.08 (s, 2H).

Figure S56 ^{1}H NMR spectrum comparison

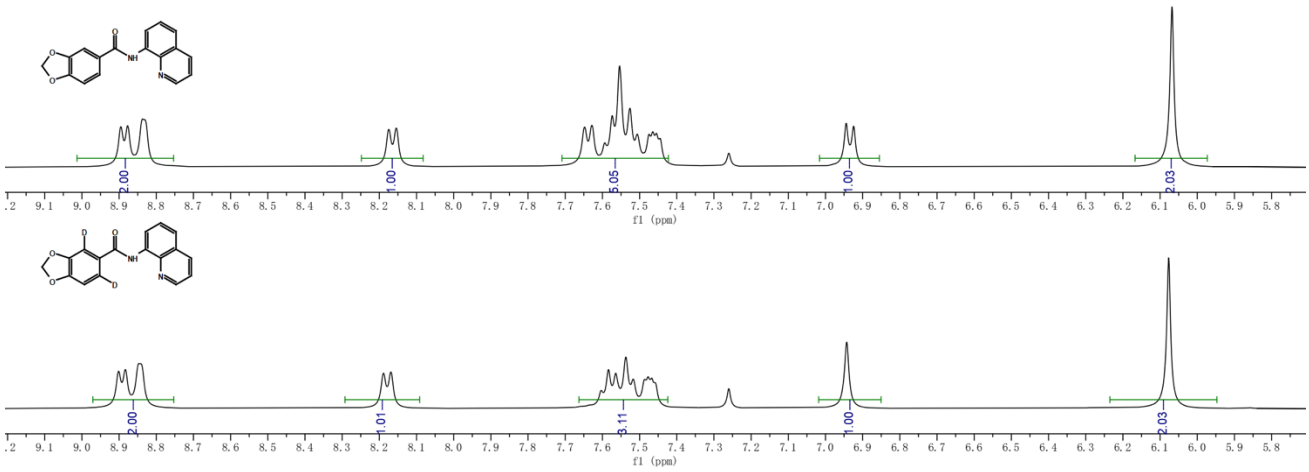


Figure S57 ^{1}H NMR of **16** in $CDCl_3$

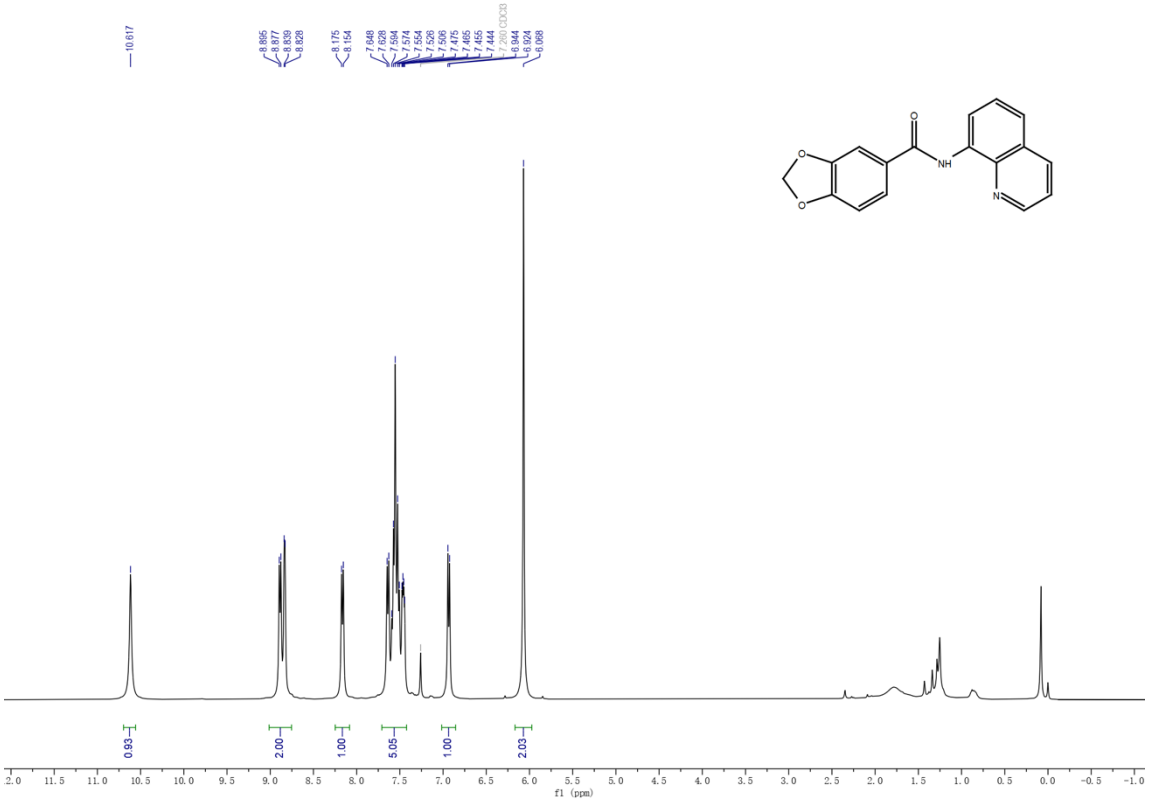
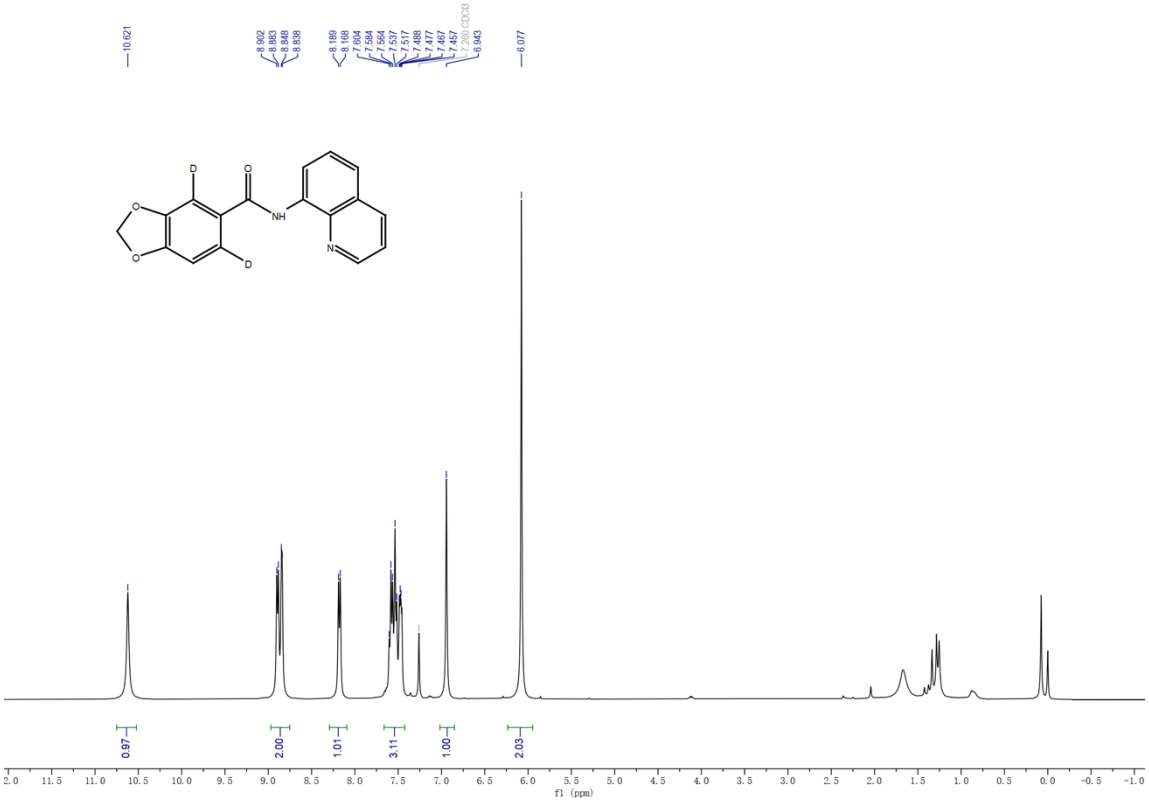
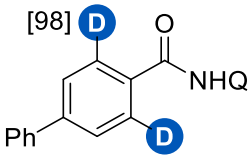


Figure S58 ^{1}H NMR of **16-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (17)



General procedure to afford **17-[d]** as white solid (155.2 mg, 96%) with D-incorporation 98% for 3,5-positions by ^{1}H NMR; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.98 (d, *J* = 7.5 Hz, 1H), 8.91 – 8.81 (m, 1H), 8.17 (d, *J* = 8.1 Hz, 3H), 7.83 – 7.36 (m, 9H)..

NMR data for deuterated product: ^{1}H NMR(400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.97 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), **8.21 (dd, *J* = 8.3, 1.6 Hz, 1.05H, Labelled)**, 7.78 (s, 2H), 7.70 – 7.65 (m, 2H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.56 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.45 – 7.38 (m, 1H).

Figure S59 ^{1}H NMR spectrum comparison

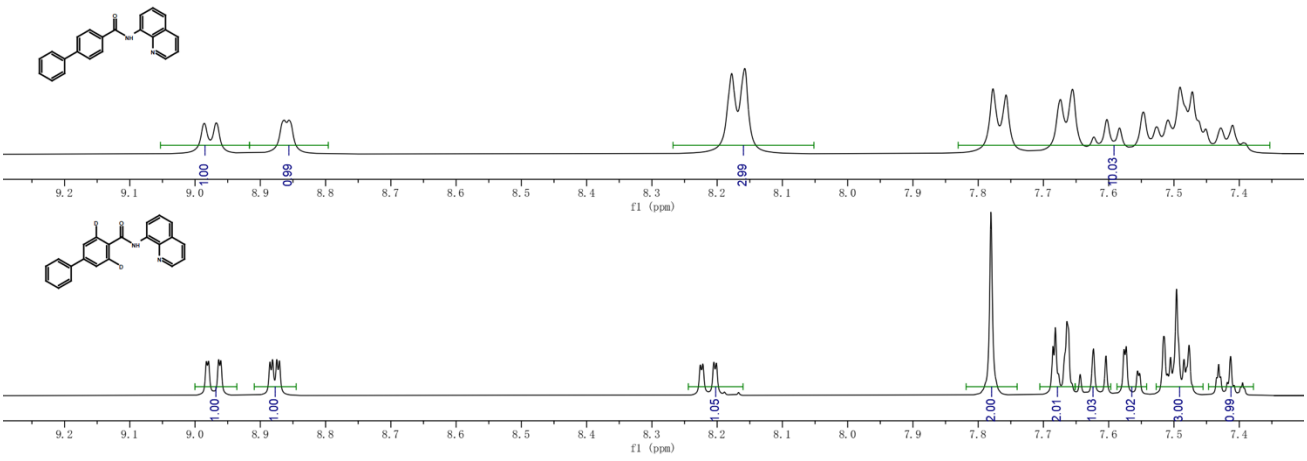


Figure S60 ^{1}H NMR of **17** in $CDCl_3$

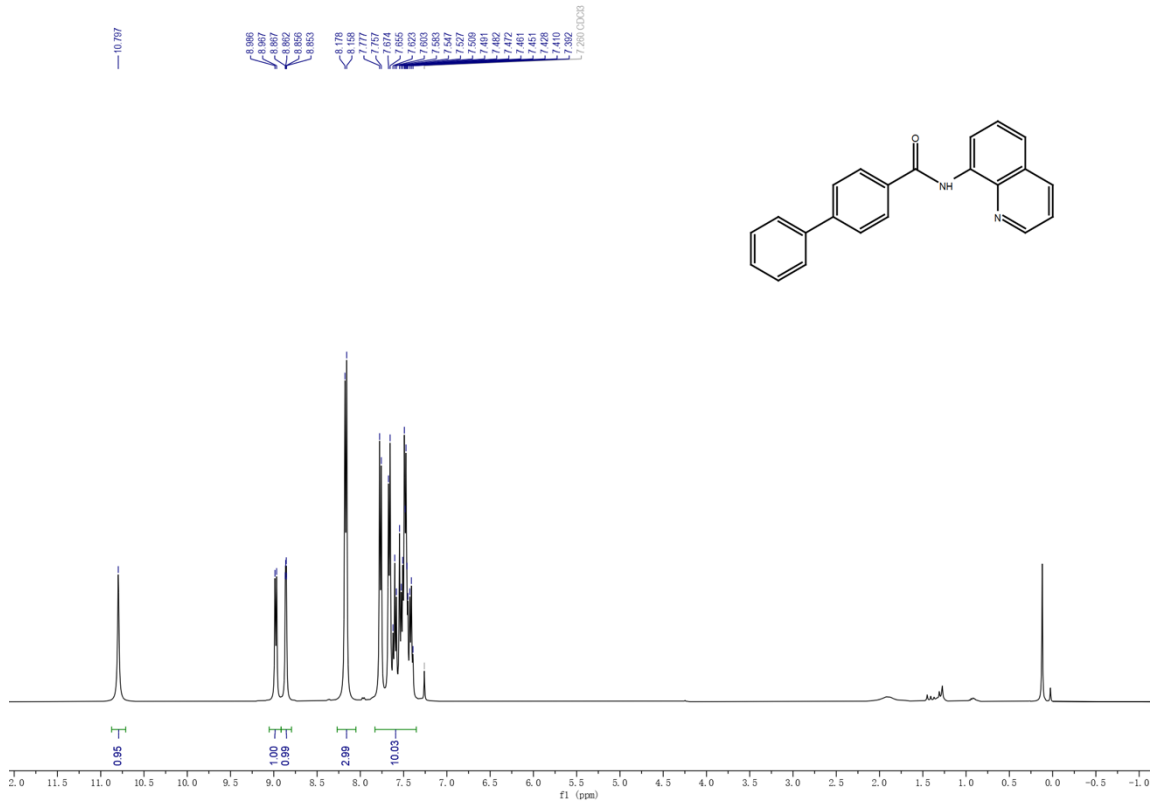
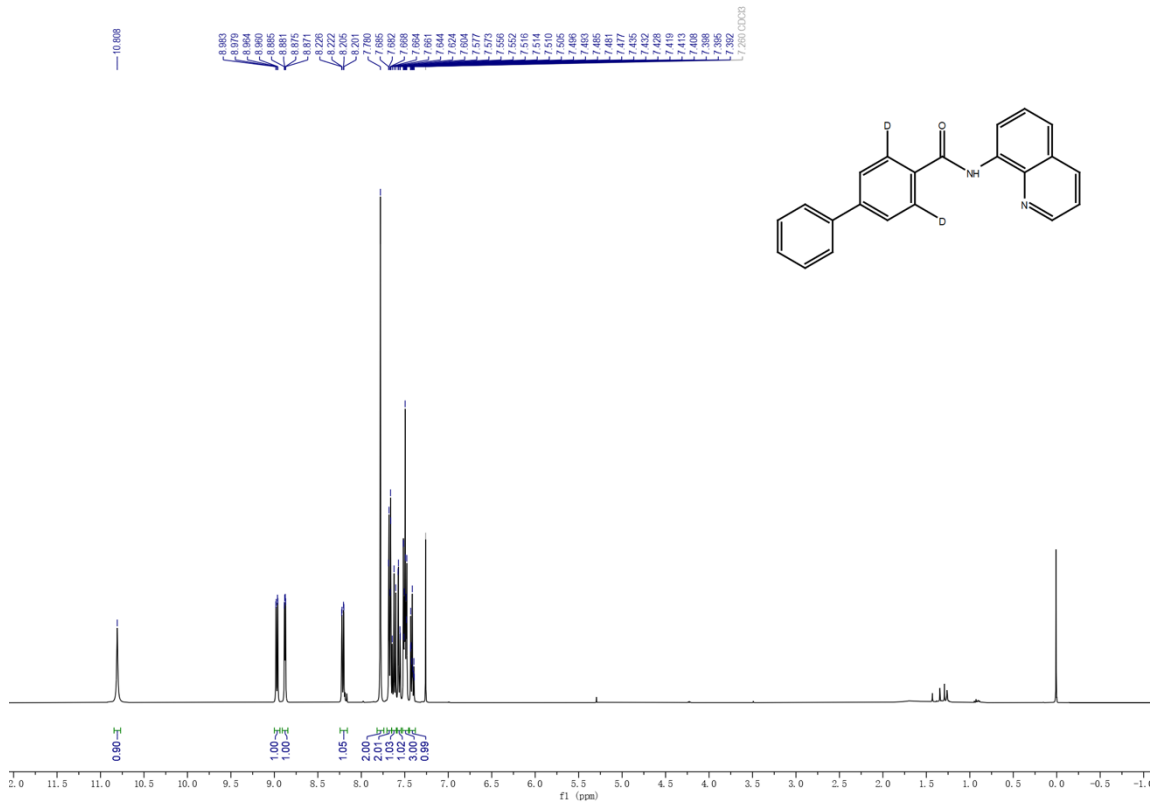
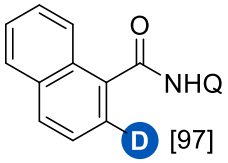


Figure S61 ^{1}H NMR of **17-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)-1-naphthamide (18)



General procedure to afford **18-[d]** as light yellow solid (144.8 mg, 97%) with D-incorporation 97% for 2-position by ^{1}H NMR and 0.78 D_{MS} by GC-MS; R_f = 0.50 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 9.07 (d, *J* = 7.6 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 – 8.49 (m, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.69 – 7.52 (m, 5H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 9.07 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.62 – 8.51 (m, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), **7.96 – 7.90 (m, 1.03H, Labelled)**, 7.69 – 7.53 (m, 5H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H).

Figure S62 ^{1}H NMR spectrum comparison

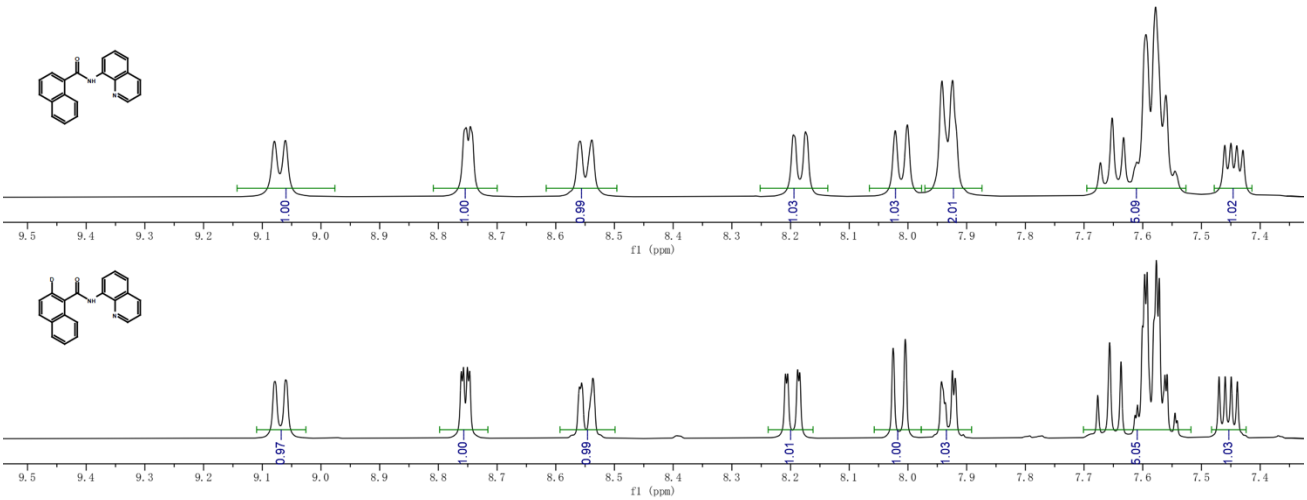


Figure S63 GC-MS spectrum comparison

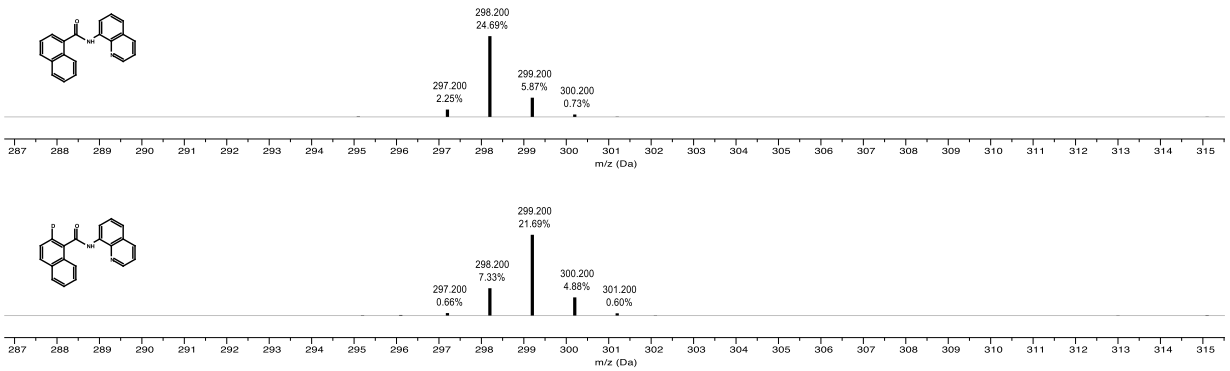


Figure S64 ^{1}H NMR of **18** in $CDCl_3$

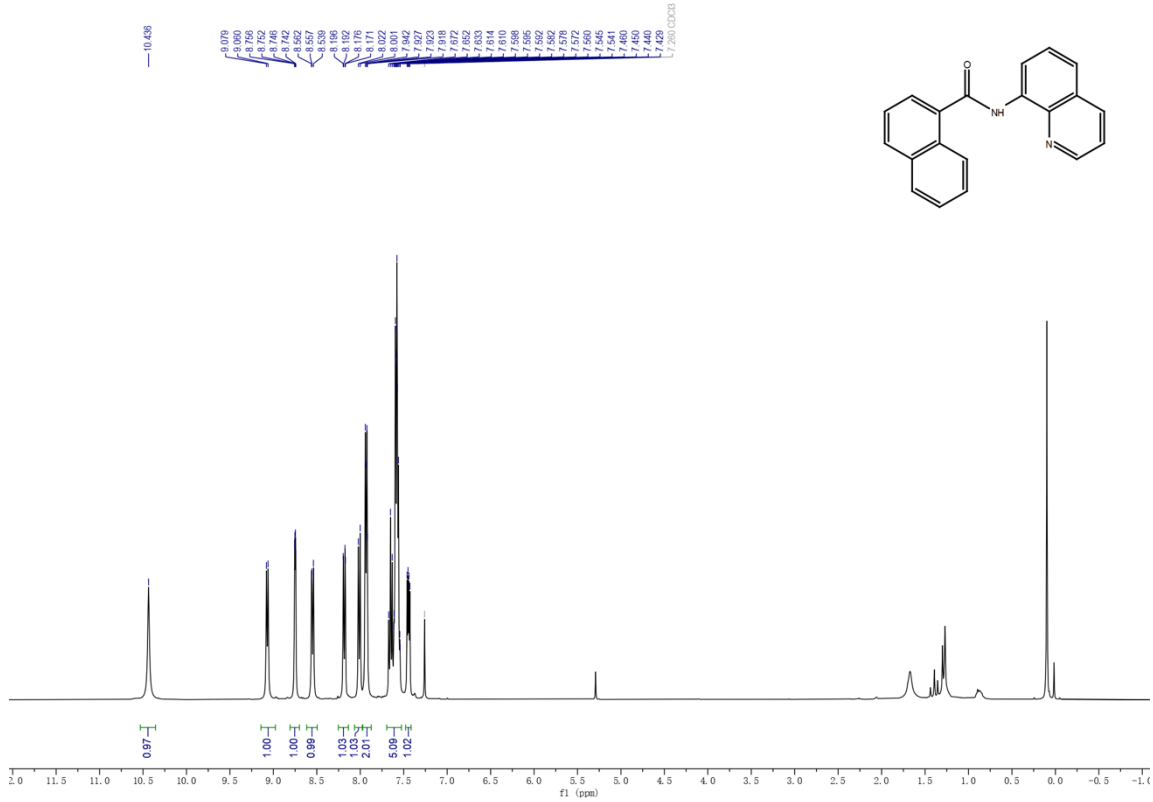
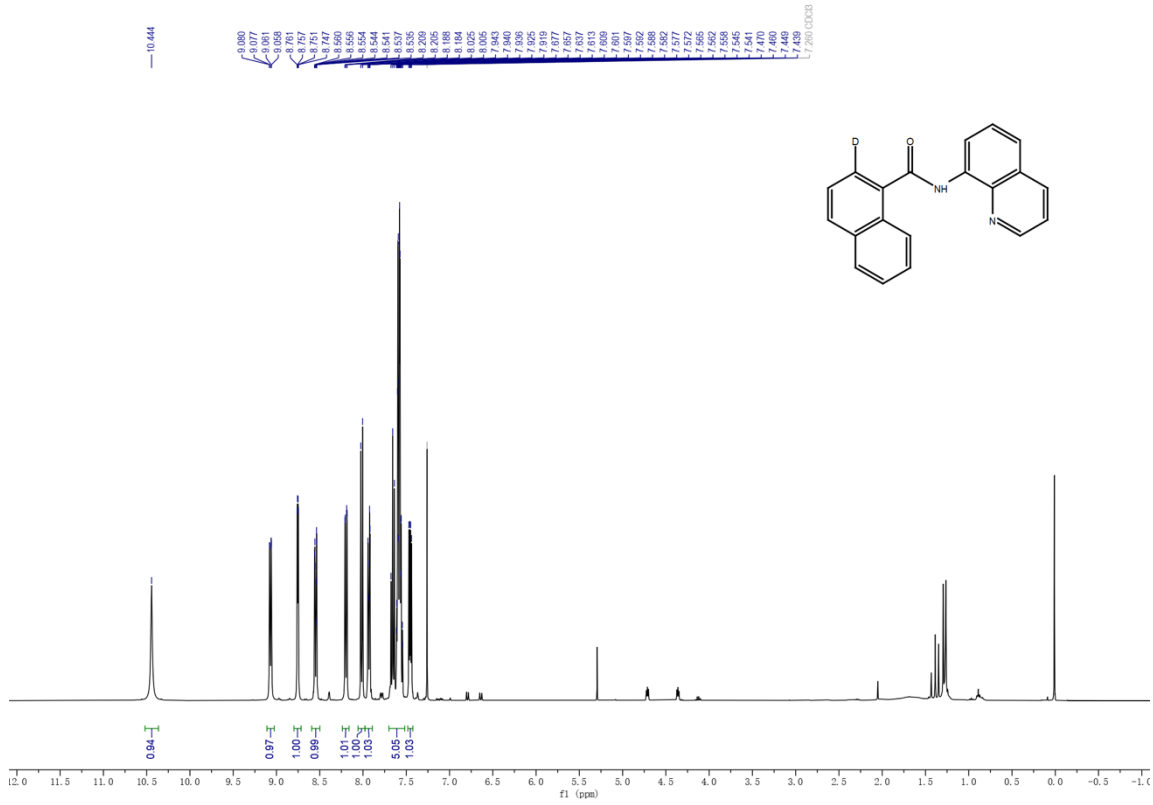
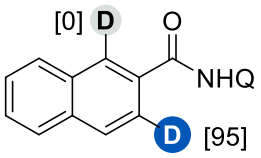


Figure S65 ^{1}H NMR of **18-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)-2-naphthamide (19)



General procedure to afford **19-[d]** as light yellow solid (142.5 mg, 96%) with D-incorporation 0% for 2-position and 97% for 6-position by ^{1}H NMR and 0.86 D_{MS} by GC-MS; R_f = 0.50 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 9.00 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.90 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.62 (d, *J* = 1.9 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.6, 1.9 Hz, 1H), 8.08 – 8.03 (m, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.67 – 7.55 (m, 4H), 7.51 (dd, *J* = 8.3, 4.2 Hz, 1H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 9.00 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.61 (s, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.14 (d, *J* = 9.5 Hz, 0.05H, Labelled)**, 8.09 – 8.02 (m, 1H), 8.00 (s, 1H), 7.95 – 7.87 (m, 1H), 7.68 – 7.53 (m, 4H), 7.49 (dd, *J* = 8.2, 4.2 Hz, 1H).

Figure S66 ^{1}H NMR spectrum comparison

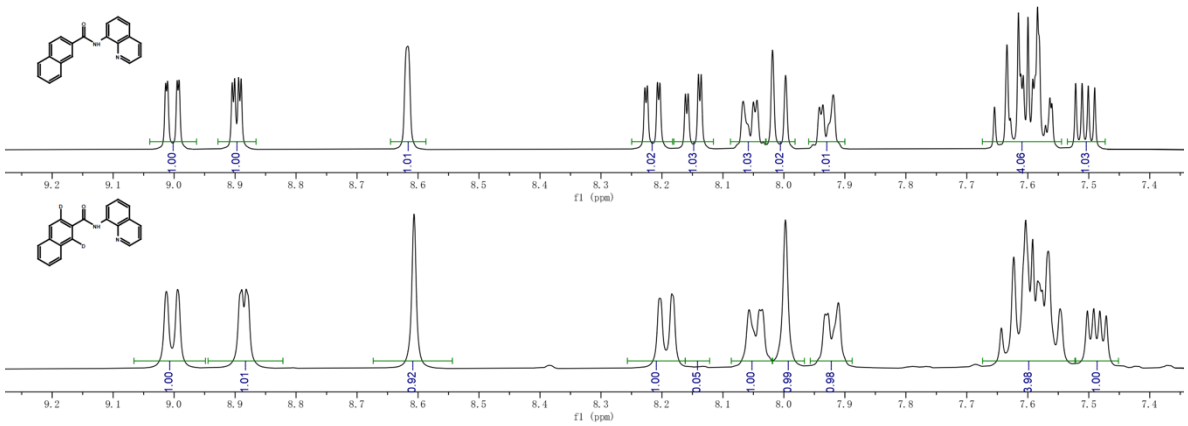


Figure S67 GC-MS spectrum comparison

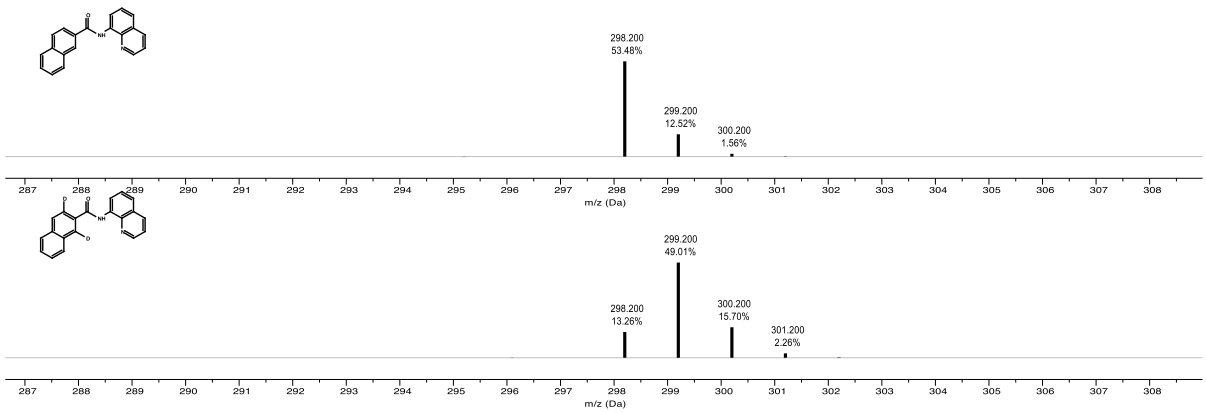


Figure S68 ^{1}H NMR of **19** in $CDCl_3$

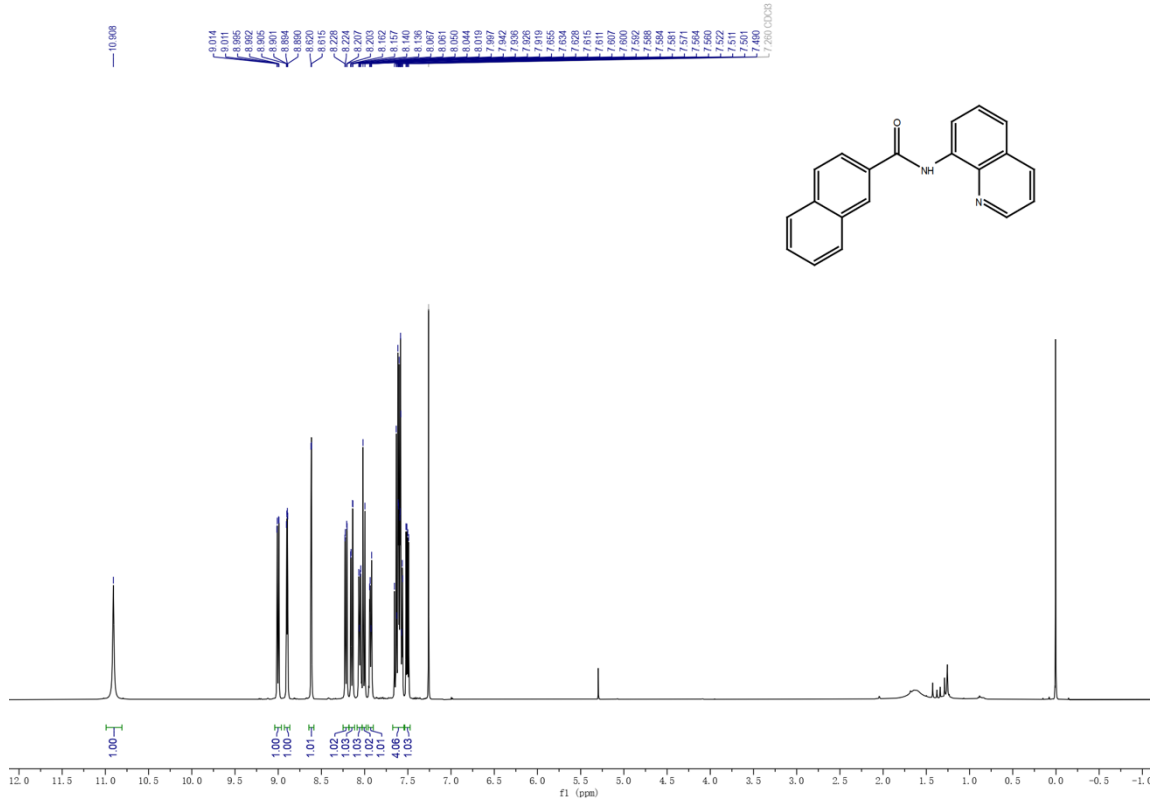
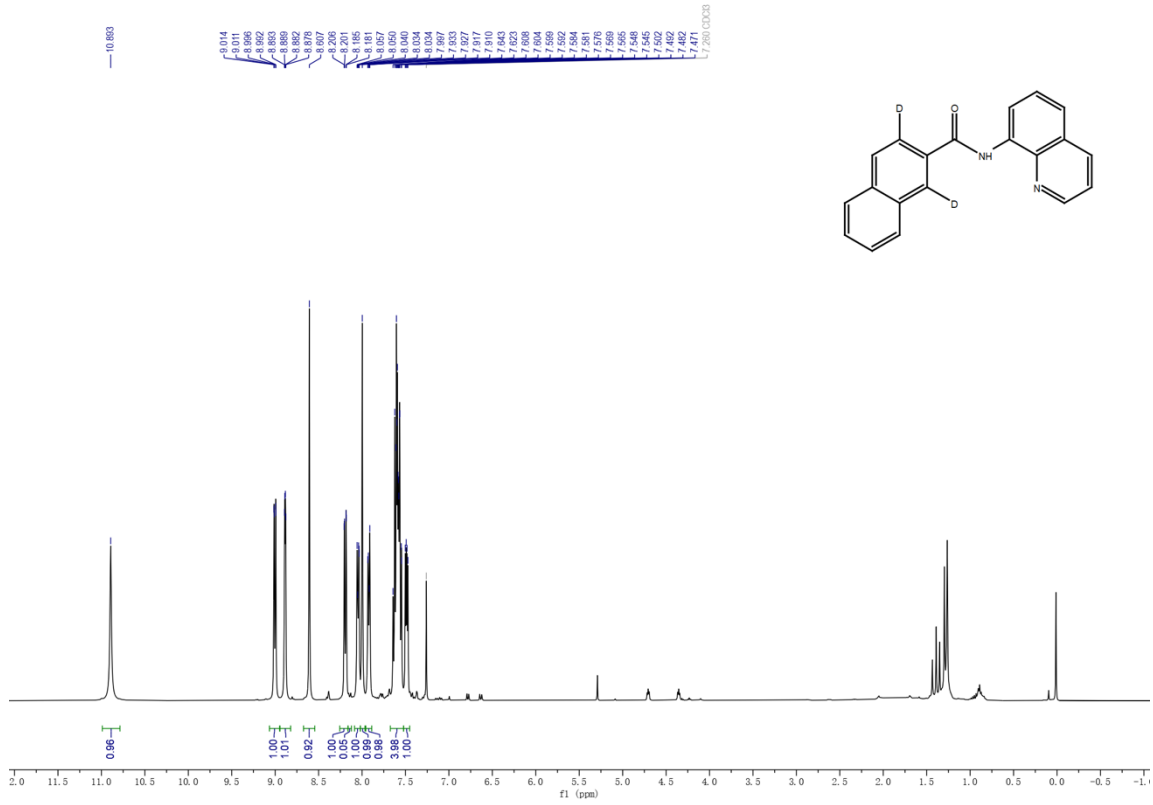
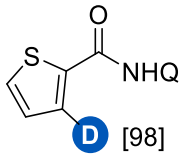


Figure S69 ^{1}H NMR of **19-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)thiophene-2-carboxamide (20)



General procedure to afford **20-[d]** as white solid (123.2 mg, 97%) with D-incorporation 98% for 3-position by ^{1}H NMR and 0.76 D_{MS} by GC-MS; R_f = 0.45 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.84 (d, *J* = 6.2 Hz, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 3.7 Hz, 1H), 7.67 – 7.37 (m, 4H), 7.17 (t, *J* = 4.3 Hz, 1H)..
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.84 (dt, *J* = 5.3, 1.5 Hz, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.84 (dd, *J* = 3.7, 1.1 Hz, 0.02H, Labelled)**, 7.67 – 7.40 (m, 4H), 7.18 (d, *J* = 5.0 Hz, 1H).

Figure S70 ^{1}H NMR spectrum comparison

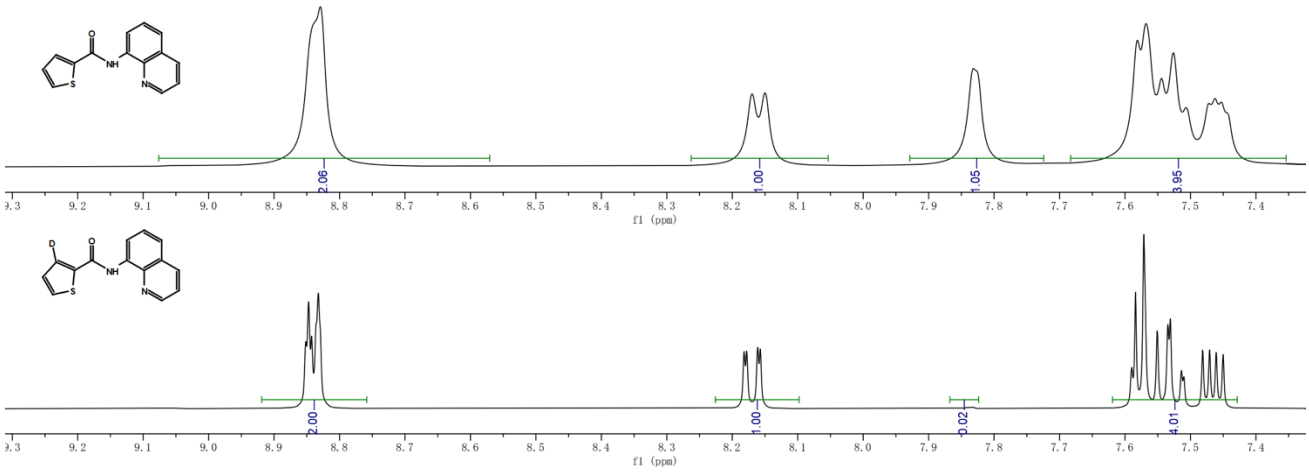


Figure S71 GC-MS spectrum comparison

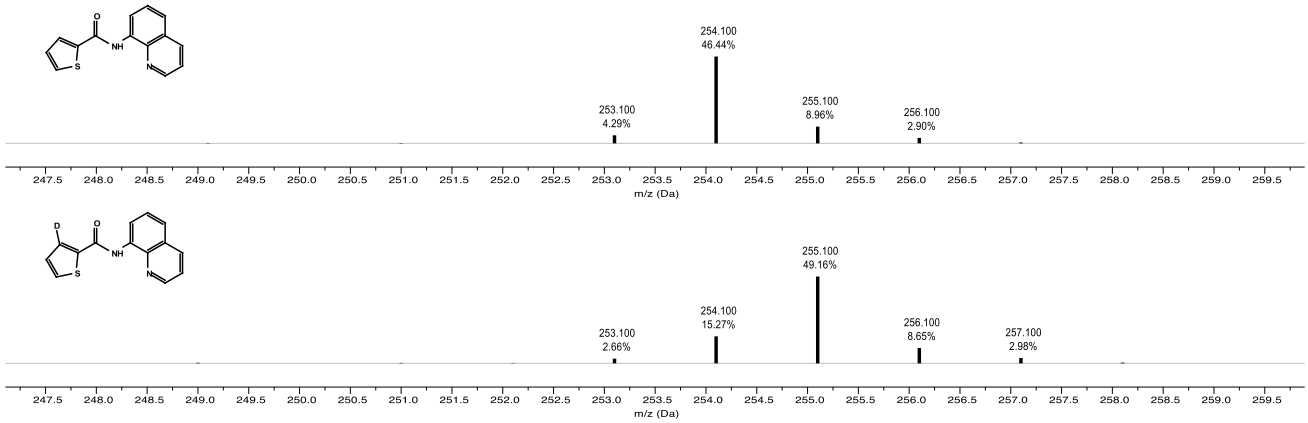


Figure S72 ^{1}H NMR of **20** in $CDCl_3$

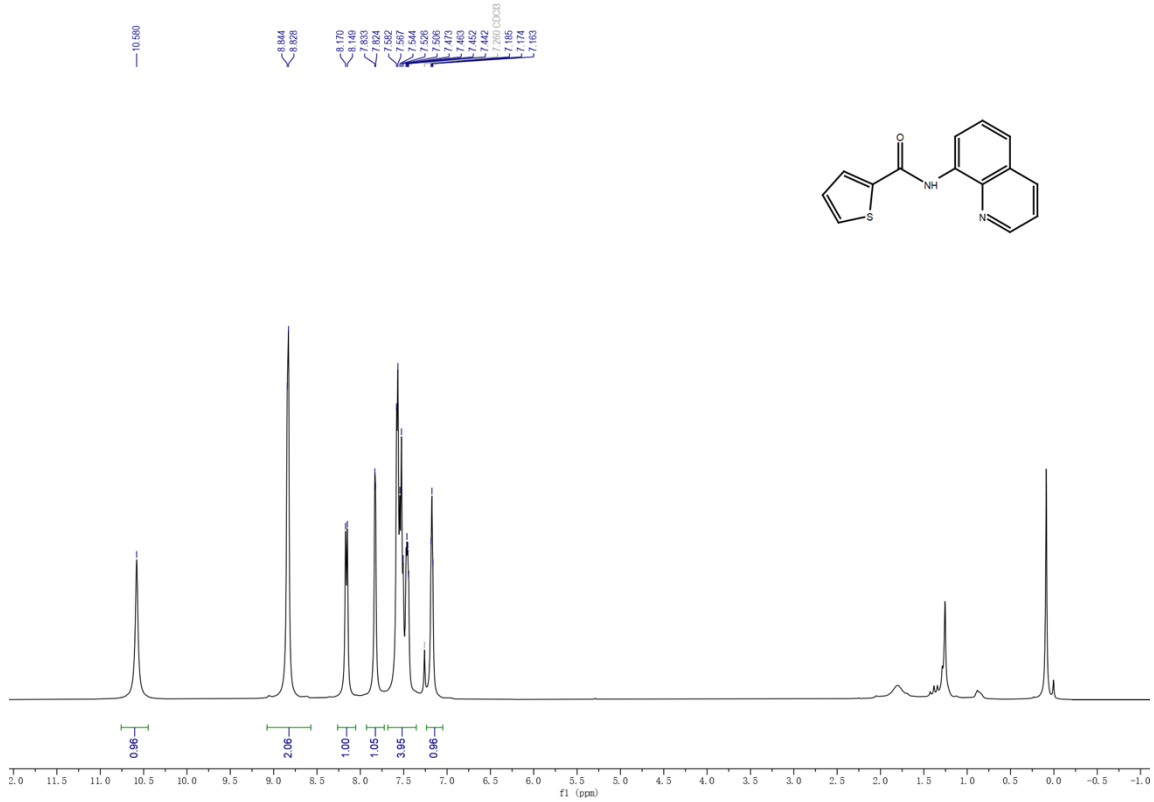
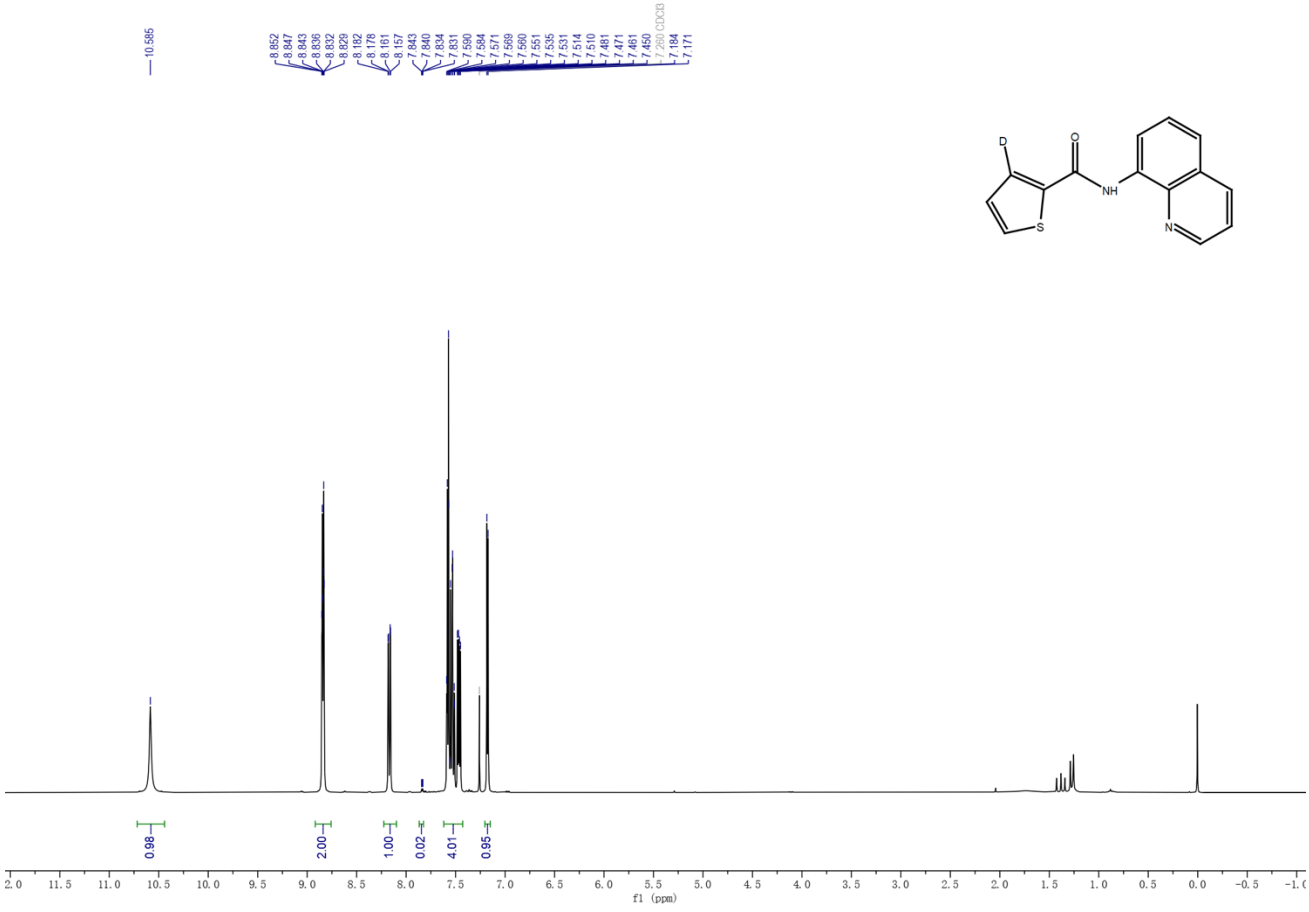
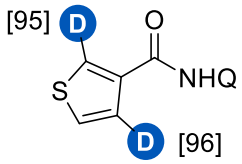


Figure S73 ^{1}H NMR of **20-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)thiophene-3-carboxamide (21)



General procedure to afford **21-[d]** as grey solid (119.0 mg, 94%) with D-incorporation 95% for 2-position and 96% for 4-position by ^{1}H NMR; R_f = 0.45 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.93 – 8.81 (m, 2H), 8.22 – 8.14 (m, 2H), 7.70 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.50 – 7.41 (m, 2H)..
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.92 – 8.81 (m, 2H), **8.19 (dd, *J* = 8.3, 1.7 Hz, 1.05H, Labelled)**, **7.70 (d, *J* = 5.1 Hz, 0.04H, Labelled)**, 7.62 – 7.51 (m, 2H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.43 (s, 1H).

Figure S74 ^{1}H NMR spectrum comparison

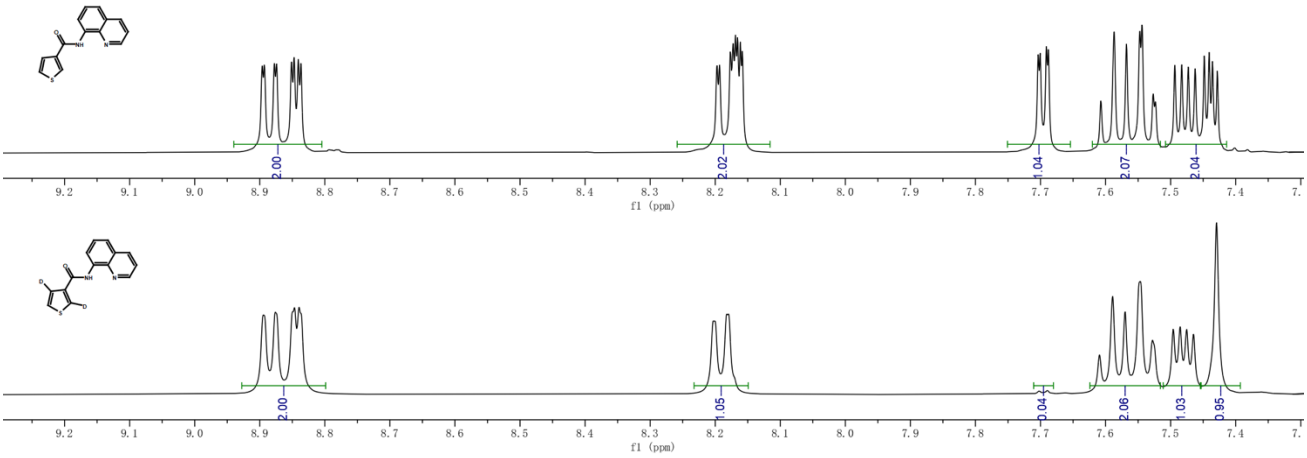


Figure S75 ^{1}H NMR of **21** in $CDCl_3$

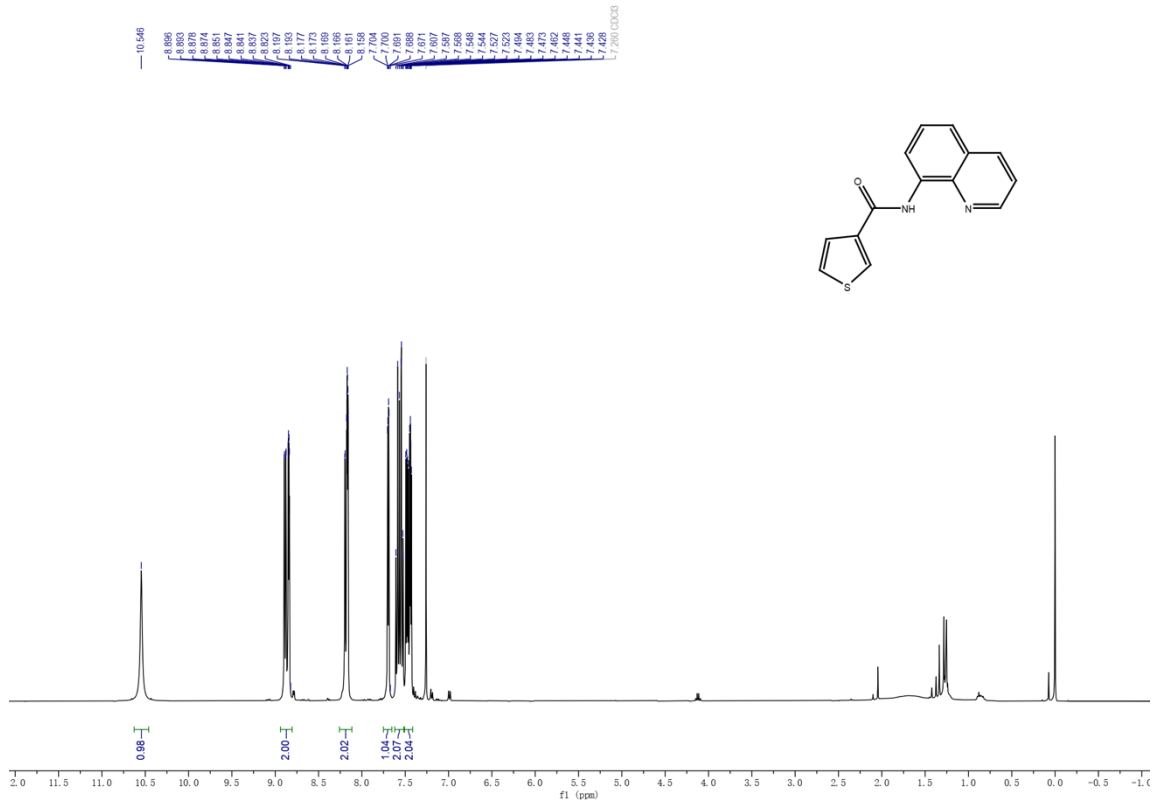
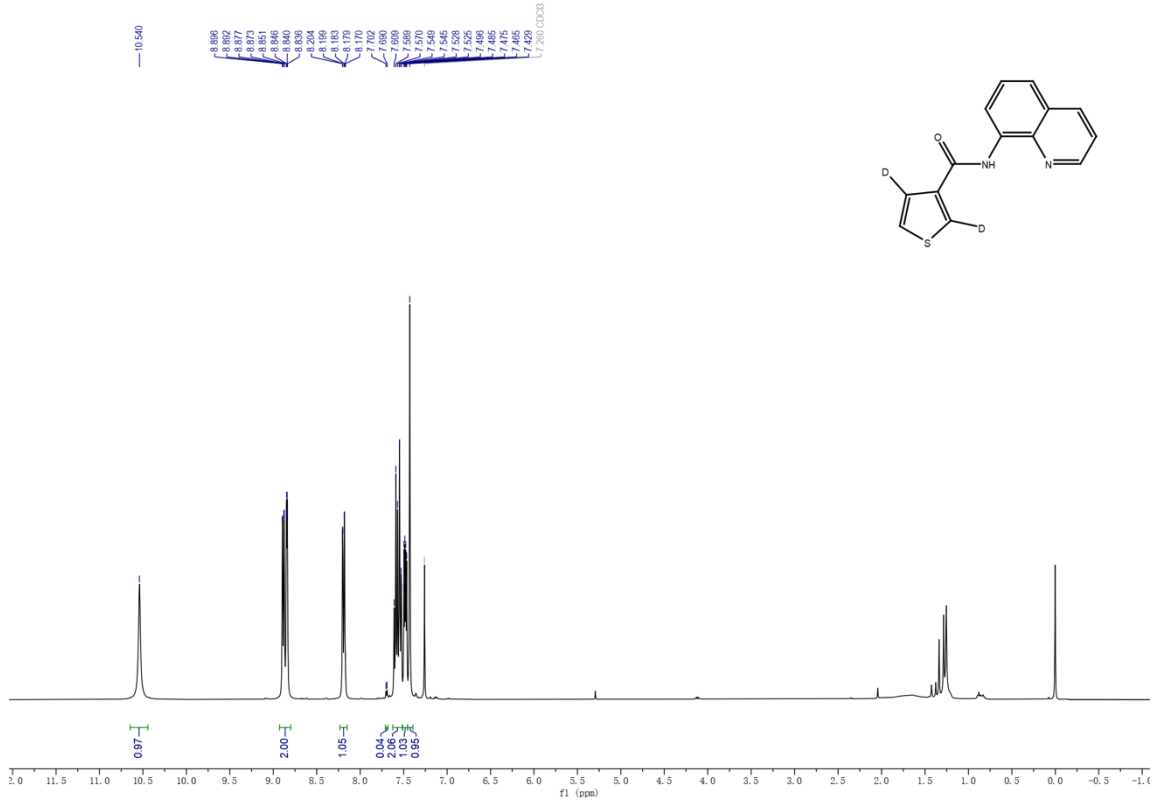
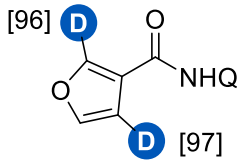


Figure S76 ^{1}H NMR of **21-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)furan-3-carboxamide (22)



General procedure to afford **22-[d]** as light yellow solid (114.9 mg, 97%) with D-incorporation 96% for 2-position and 97% for 4-position by ^{1}H NMR; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.93 – 8.78 (m, 2H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.60 – 7.51 (m, 3H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.93 (dd, *J* = 2.0, 0.9 Hz, 1H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.89 – 8.80 (m, 2H), **8.17 (dd, *J* = 8.3, 1.7 Hz, 1.04H, Labelled)**, 7.61 – 7.50 (m, 3H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), **6.93 (d, *J* = 1.9 Hz, 0.03H, Labelled)**.
Figure S77 ^{1}H NMR spectrum comparison

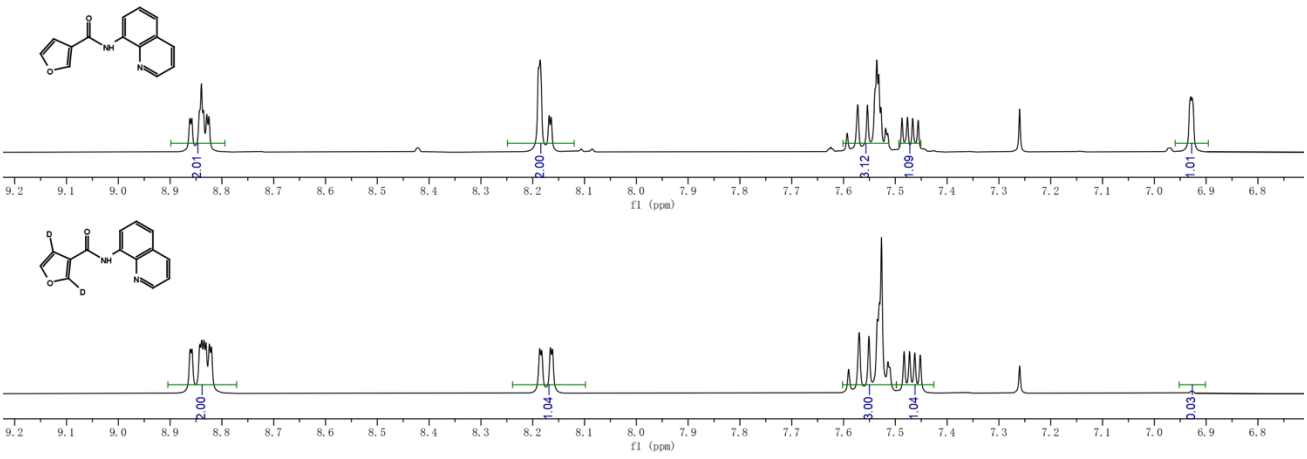


Figure S78 ^{1}H NMR of **22** in $CDCl_3$

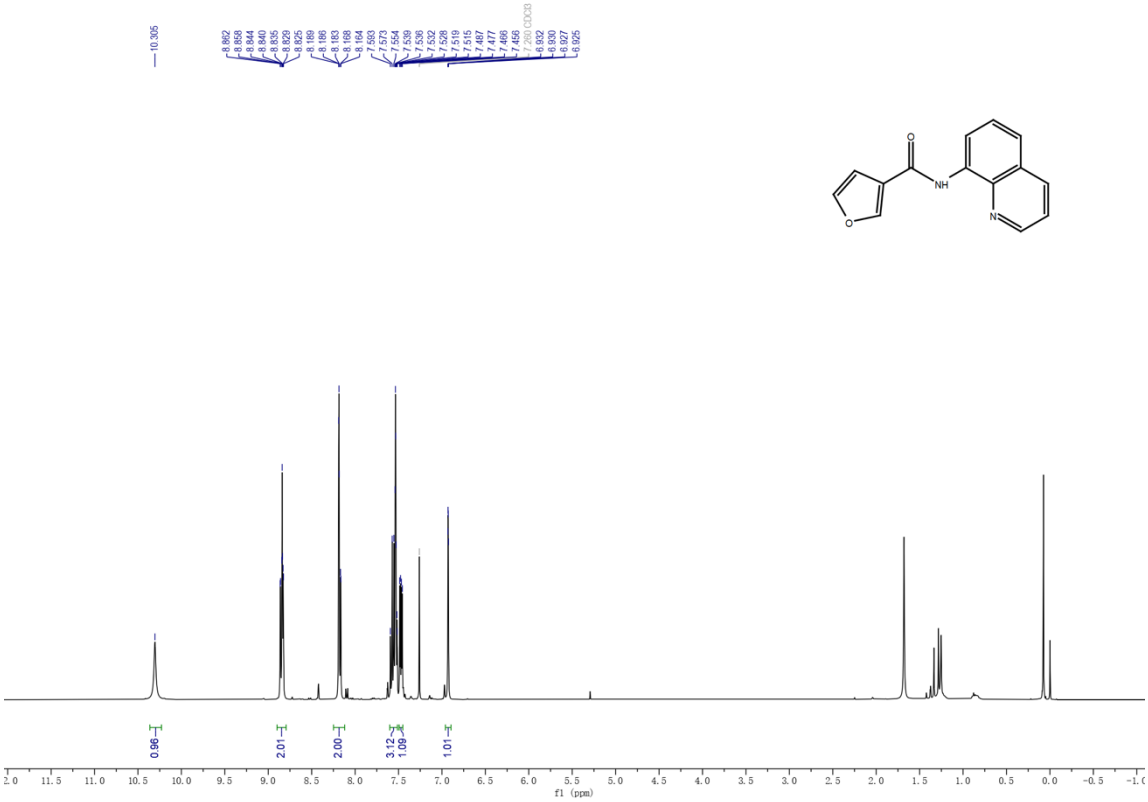
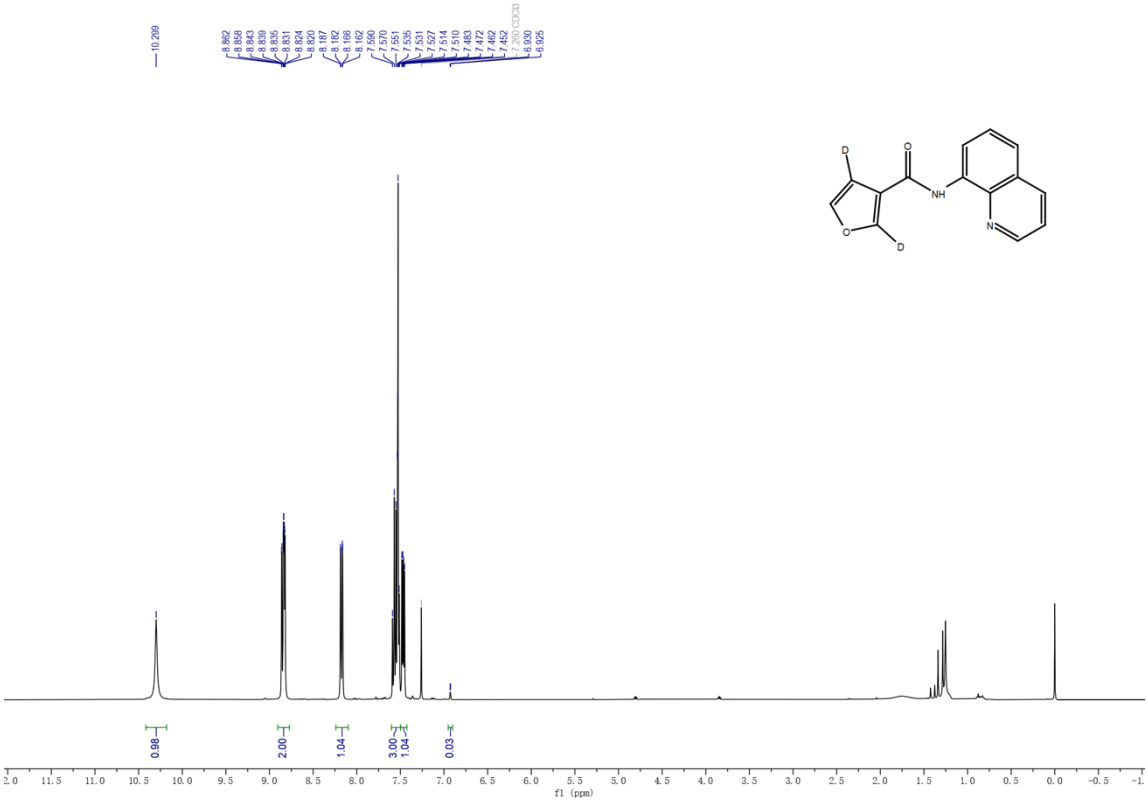
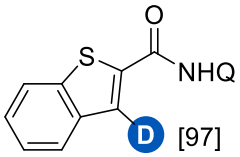


Figure S79 ^{1}H NMR of **22-[d]** in $CDCl_3$



Deuteration of N-(quinolin-8-yl)benzo[b]thiophene-2-carboxamide (24)



[97]

General procedure to afford **24-[d]** as light yellow solid (146.8 mg, 97%) with D-incorporation 97% for 3-position by ^{1}H NMR; R_f = 0.45 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.94 – 8.86 (m, 2H), 8.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.12 (s, 1H), 7.93 (ddd, *J* = 11.5, 7.0, 2.7 Hz, 2H), 7.65 – 7.56 (m, 2H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.45 (tt, *J* = 7.2, 5.5 Hz, 2H)..

NMR data for deuterated product ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 8.95 – 8.81 (m, 2H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.08 (s, 0.03H, Labelled)**, 7.98 – 7.86 (m, 2H), 7.63 – 7.53 (m, 2H), 7.53 – 7.40 (m, 3H).

Figure S80 ^{1}H NMR spectrum comparison

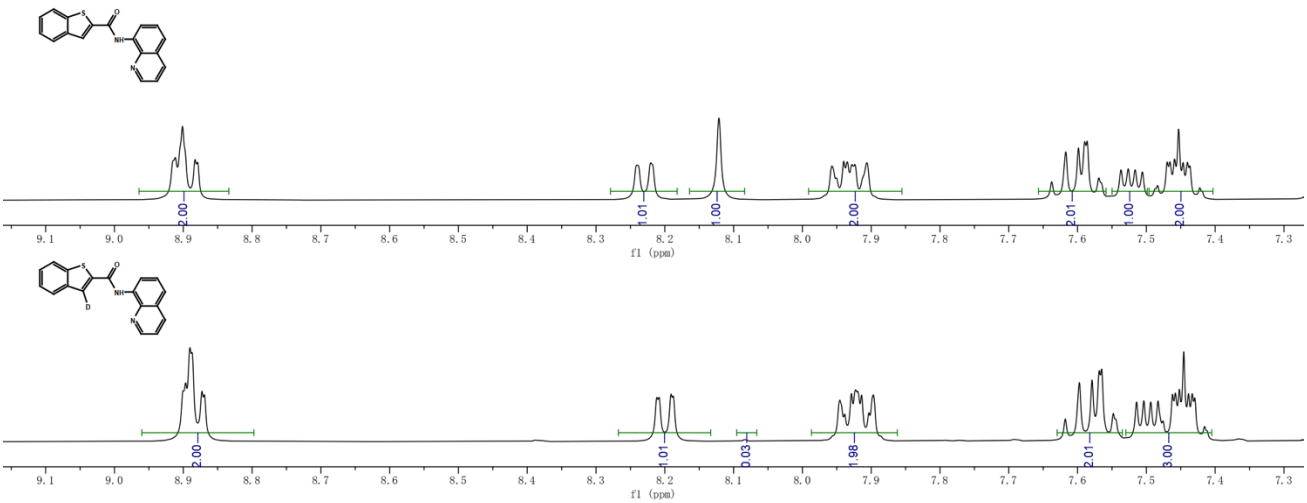


Figure S81 ^{1}H NMR of **24** in $CDCl_3$

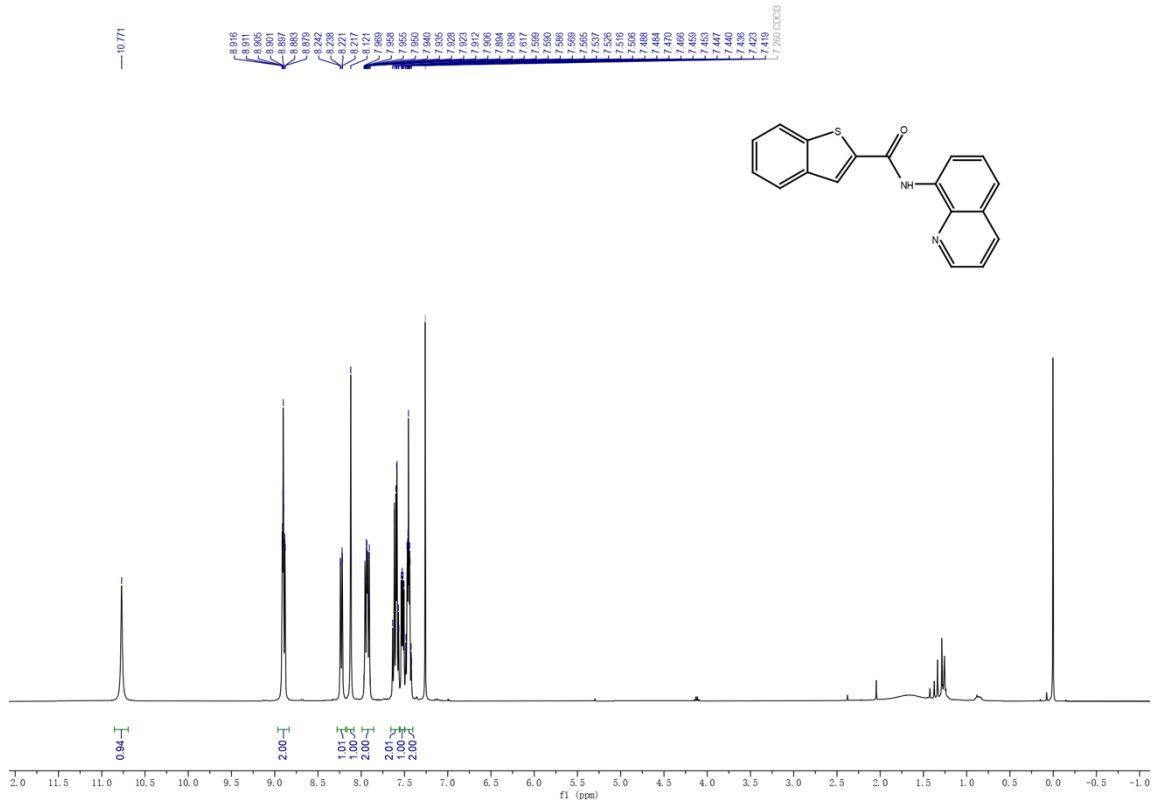
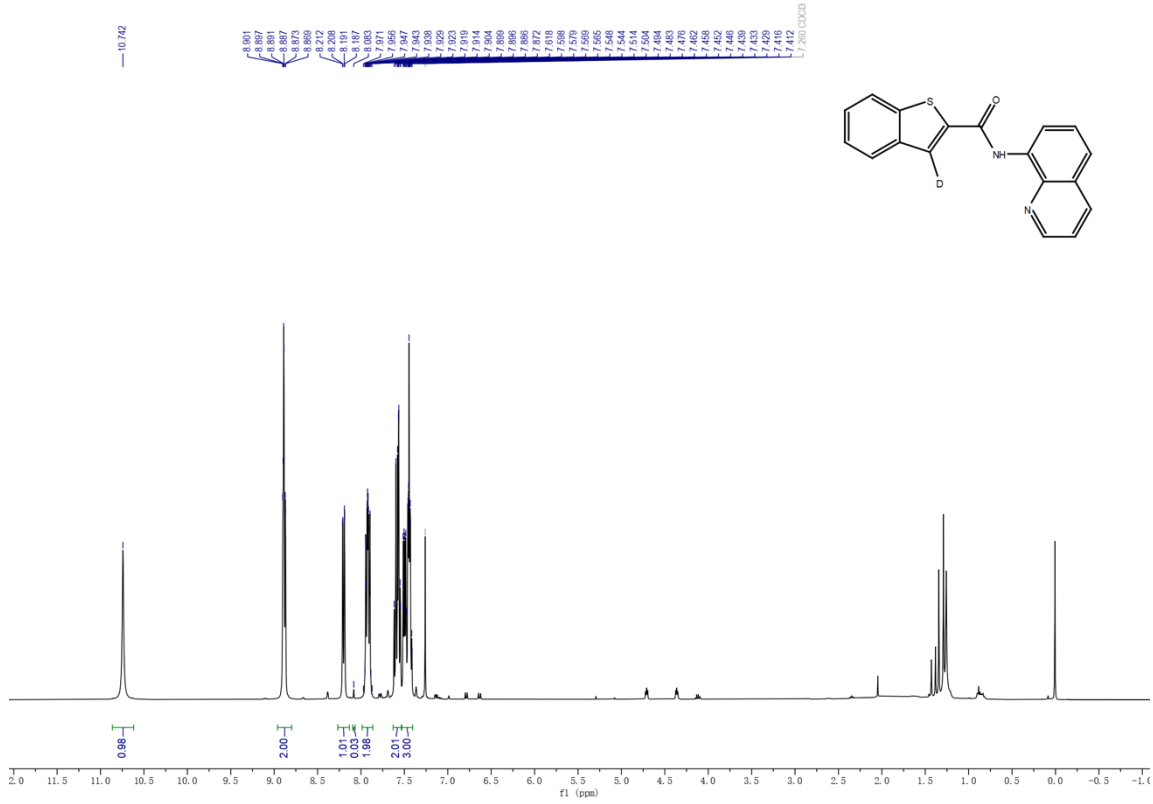
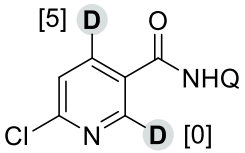


Figure S82 ^{1}H NMR of **24-[d]** in $CDCl_3$



Deuteration of 6-chloro-N-(quinolin-8-yl)nicotinamide (25)



General procedure to afford **25-[d]** as white solid (118.7 mg, 84%) with D-incorporation 5% for 4-position by ^{1}H NMR and 0.05 D_{MS} by GC-MS; R_f = 0.30 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.11 – 9.06 (m, 1H), 8.89 – 8.81 (m, 2H), 8.31 (dd, *J* = 8.3, 2.5 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.53 – 7.48 (m, 2H).

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.09 (d, *J* = 2.5 Hz, 1H), 8.86 (td, *J* = 6.0, 2.3 Hz, 2H), **8.32 (dd, *J* = 8.3, 2.5 Hz, 0.95H, Labelled)**, 8.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.50 (dd, *J* = 8.3, 4.4 Hz, 2H).

Figure S83 ^{1}H NMR spectrum comparison

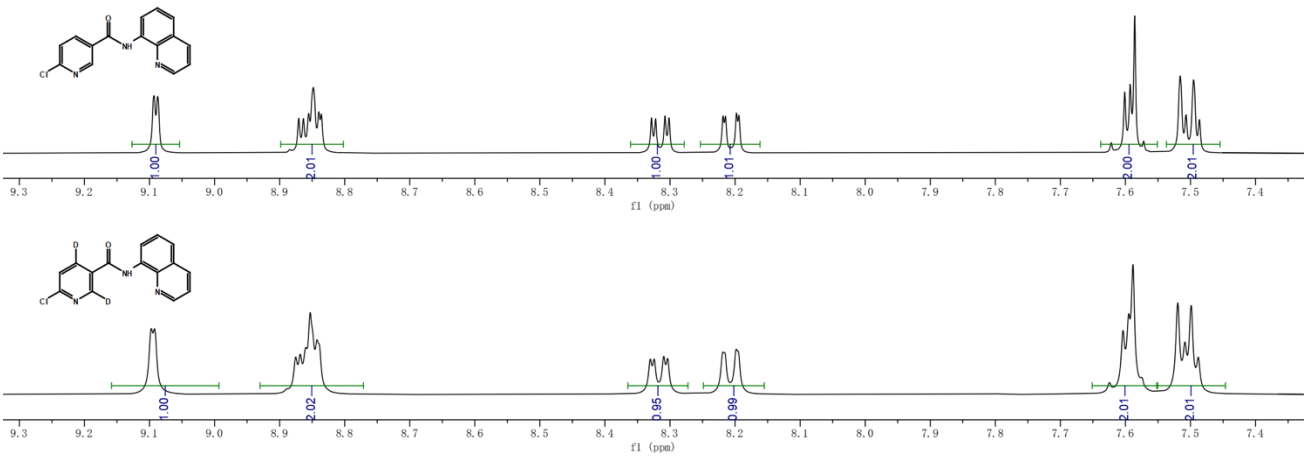


Figure S84 GC-MS spectrum comparison

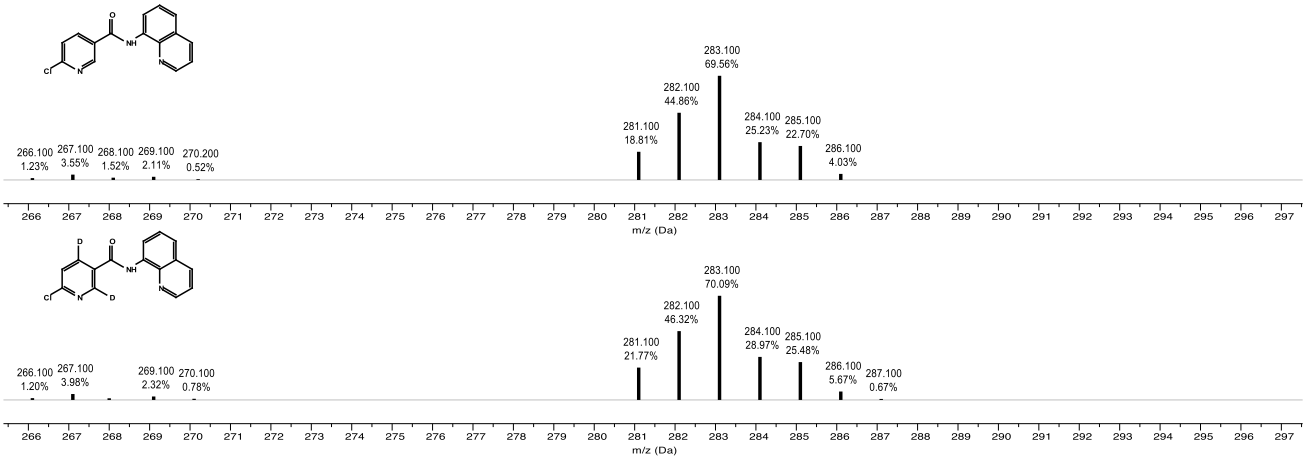


Figure S85 ^{1}H NMR of **25** in $CDCl_3$

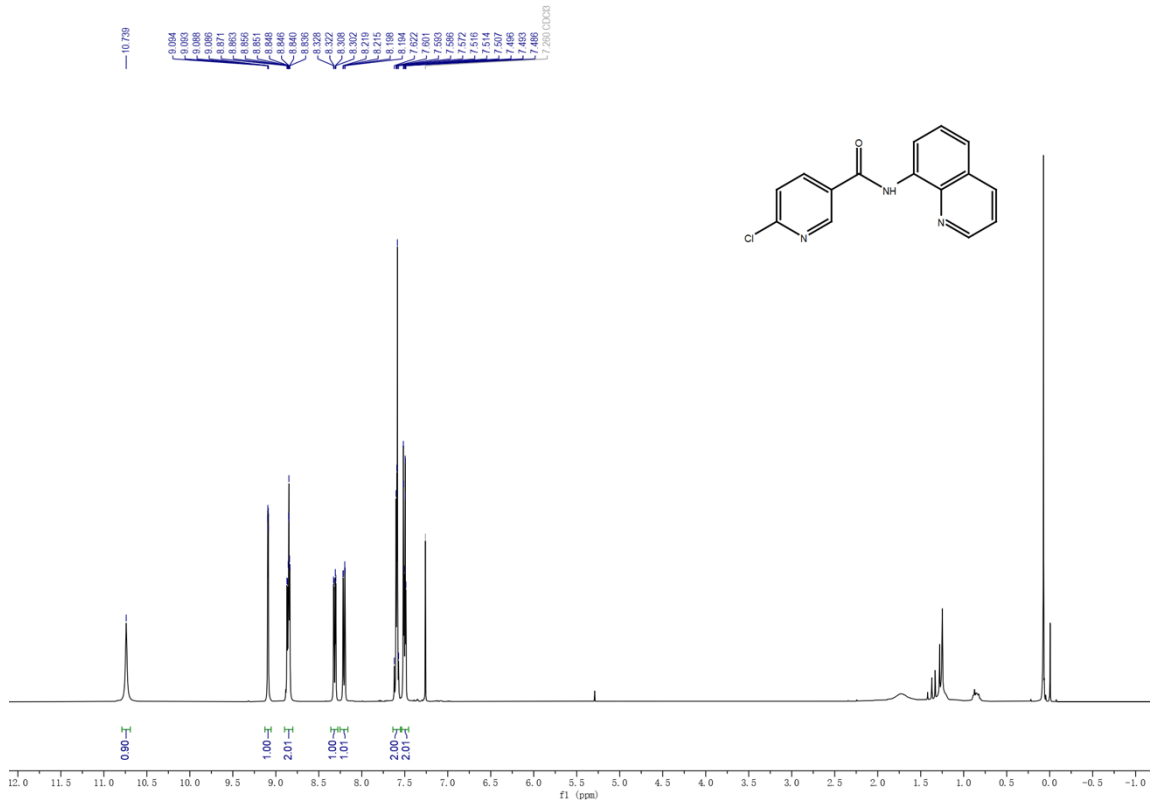
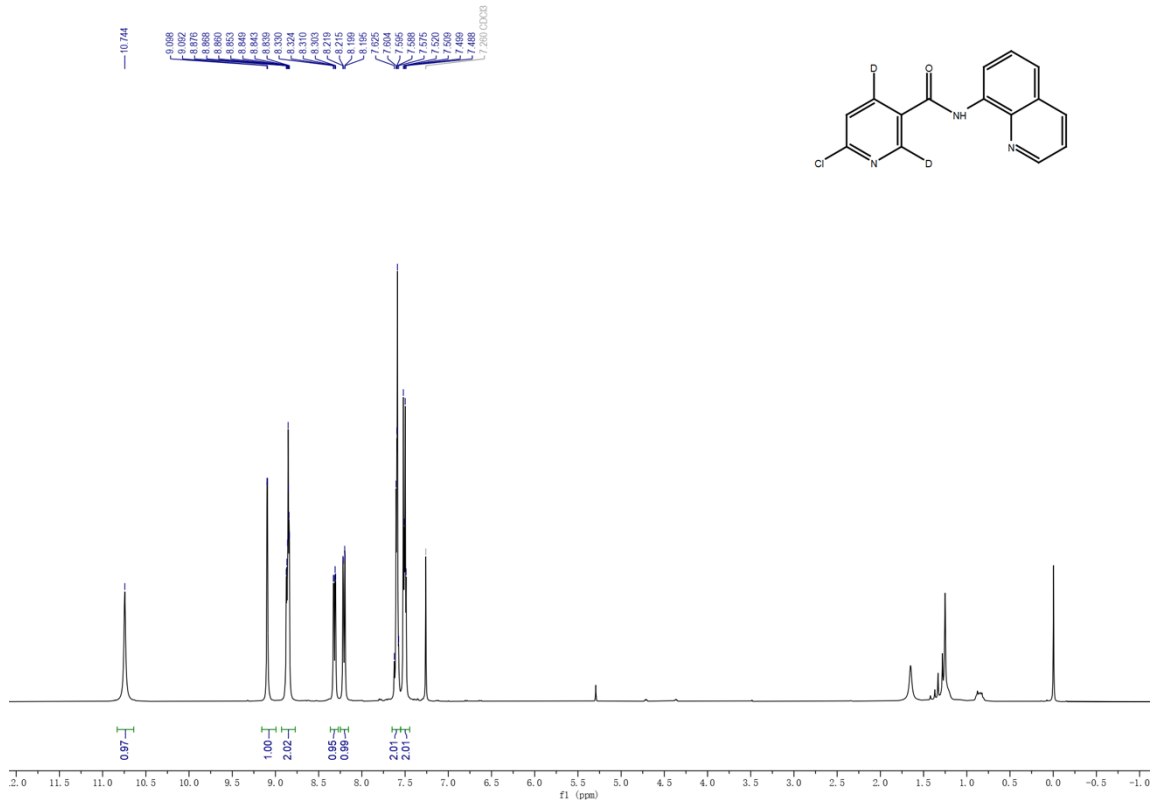
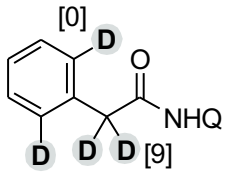


Figure S86 ^{1}H NMR of **25-[d]** in $CDCl_3$



Deuteration of 2-phenyl-N-(quinolin-8-yl)acetamide (26)



General procedure to afford **26-[d]** as grey oily liquid (124.9 mg, 94%) with D-incorporation 12% for α-methylene and 0% for phenyl-2-position by ^{1}H NMR and 0.16 D_{MS} by GC-MS; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.77 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.69 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 – 7.37 (m, 7H), 7.36 – 7.31 (m, 1H), 3.90 (s, 2H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.77 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.70 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.37 (m, 7H), 7.36 – 7.30 (m, 1H), **3.90 (s, 1.83H, Labelled)**.

Figure S87 ^{1}H NMR spectrum comparison

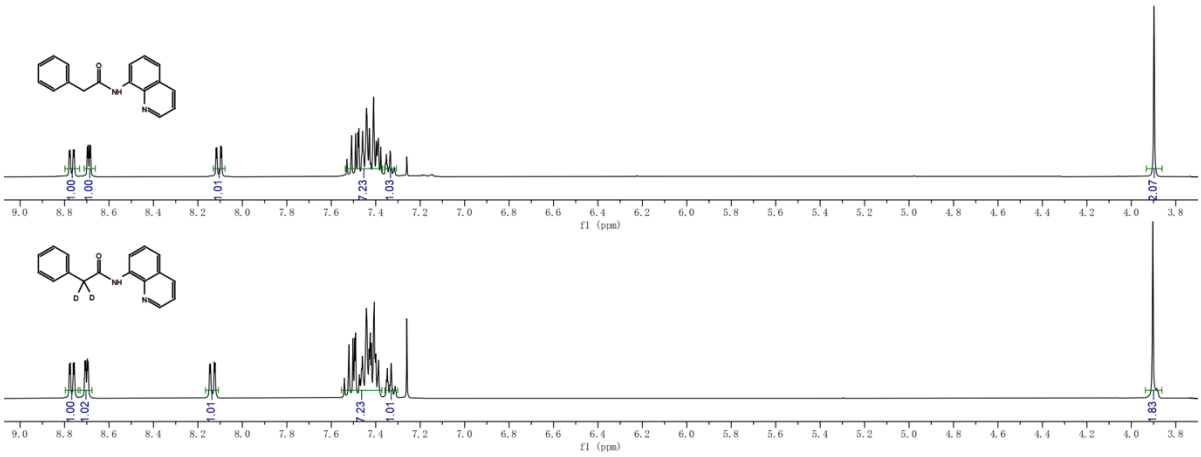


Figure S88 GC-MS spectrum comparison

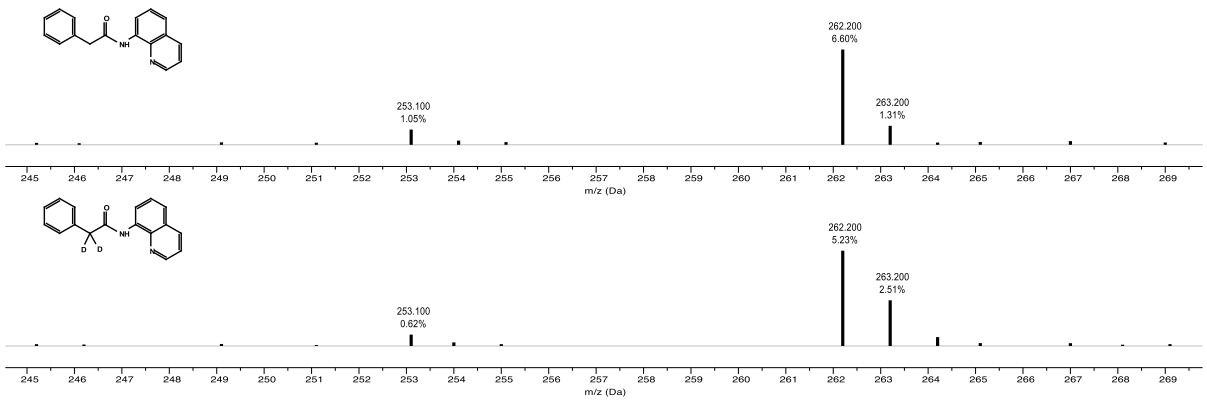


Figure S89 ^{1}H NMR of **26** in $CDCl_3$

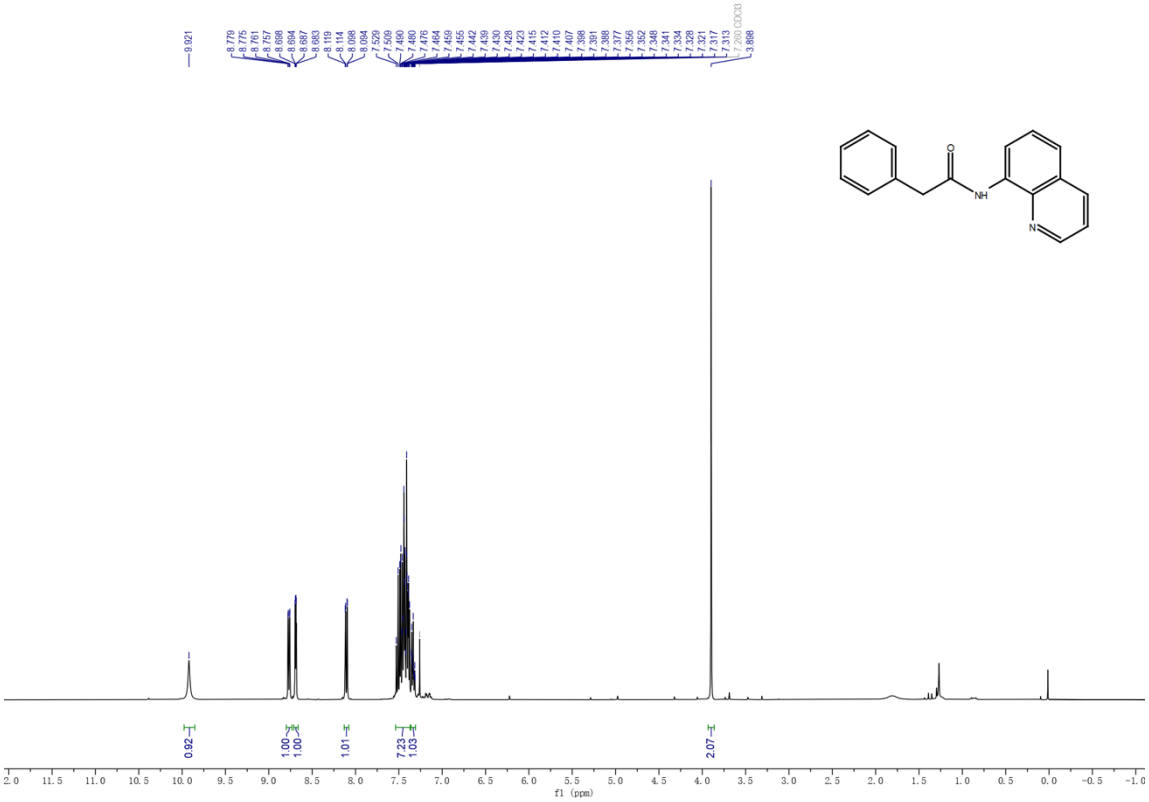
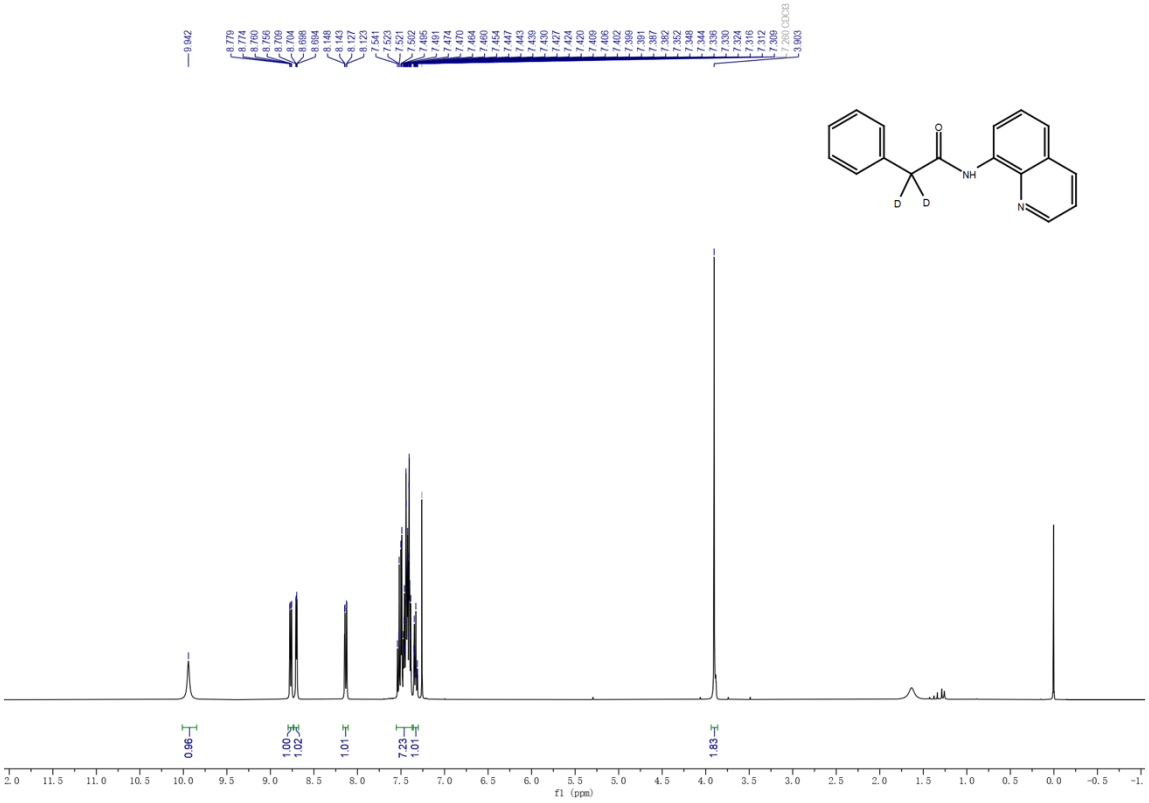
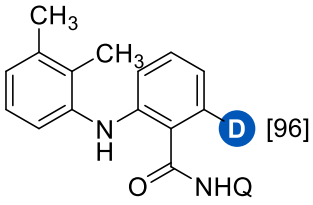


Figure S90 ^{1}H NMR of **26-[d]** in $CDCl_3$



Deuteration of 2-((2,3-dimethylphenyl)amino)-N-(quinolin-8-yl)benzamide (28)



General procedure to afford **28-[d]** as light yellow solid (87.2 mg, 95%) with D-incorporation 96% for 6-position by ^{1}H NMR; R_f = 0.60 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.93 (s, 1H), 8.99 (d, *J* = 62.3 Hz, 2H), 8.71 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 27.3 Hz, 3H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.16 – 6.77 (m, 5H), 2.21 (d, *J* = 40.9 Hz, 6H).
NMR data for deuterated product: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.93 (s, 1H), 9.07 (s, 1H), 8.91 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.70 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.45 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.91 (dd, *J* = 8.0, 1.5 Hz, 0.04H, Labelled)**, 7.73 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.38 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.11 – 7.01 (m, 2H), 6.95 (ddd, *J* = 6.1, 4.6, 1.6 Hz, 2H), 6.87 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 3H).

Figure S91 ^{1}H NMR spectrum comparison

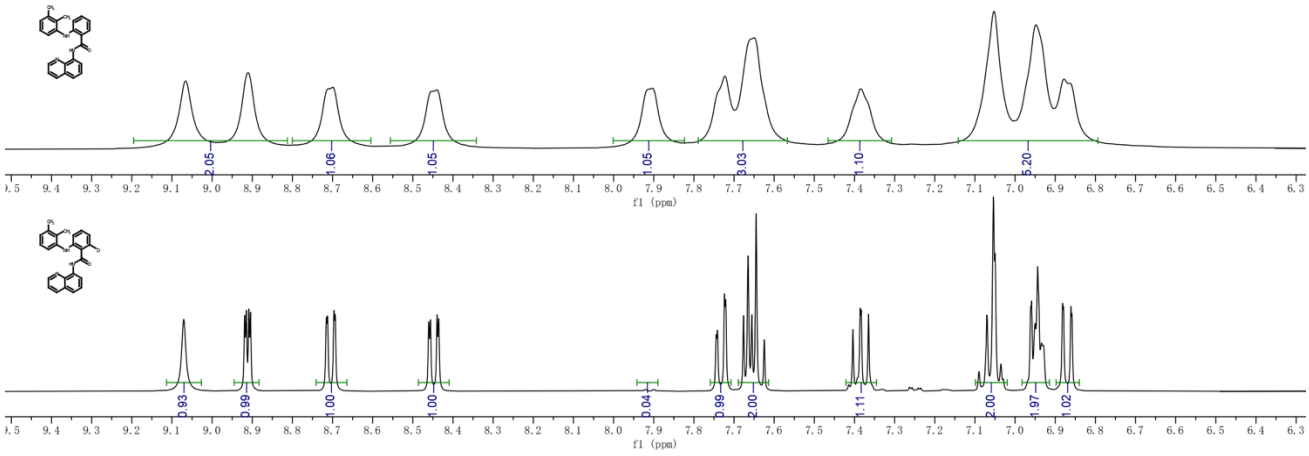


Figure S92 ^{1}H NMR of **28** in DMSO-d_6

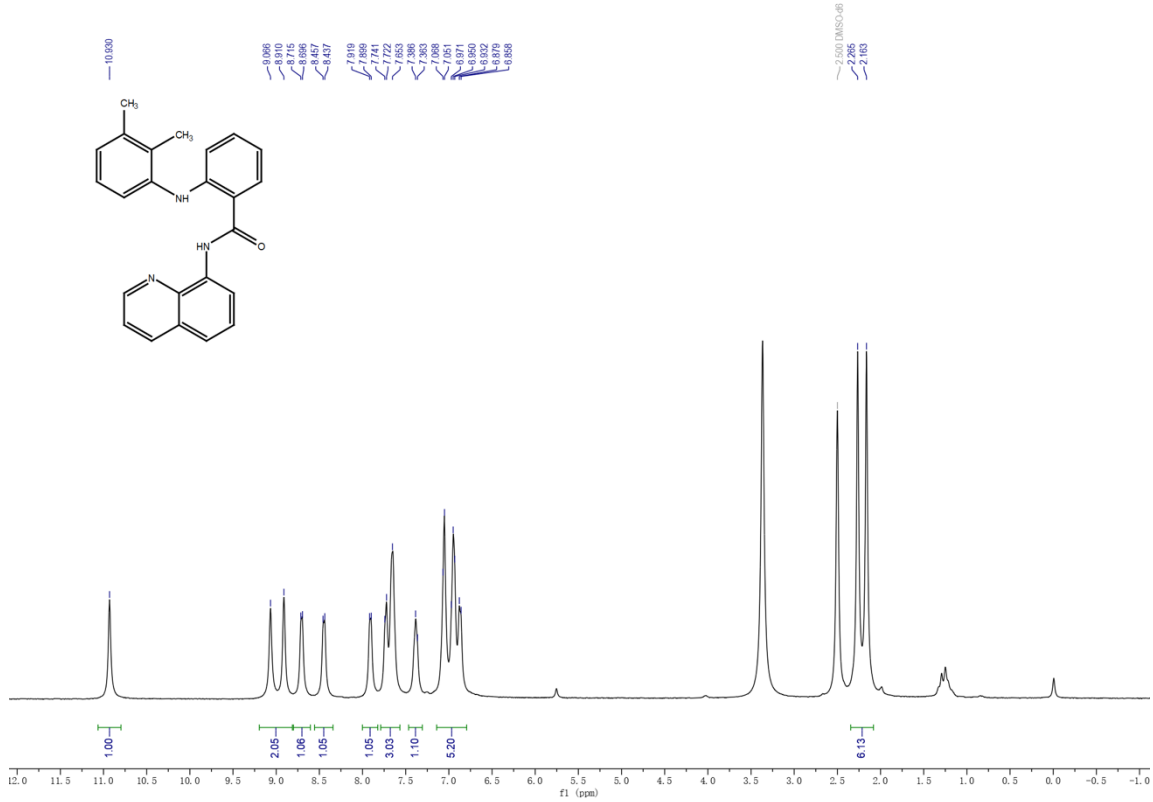
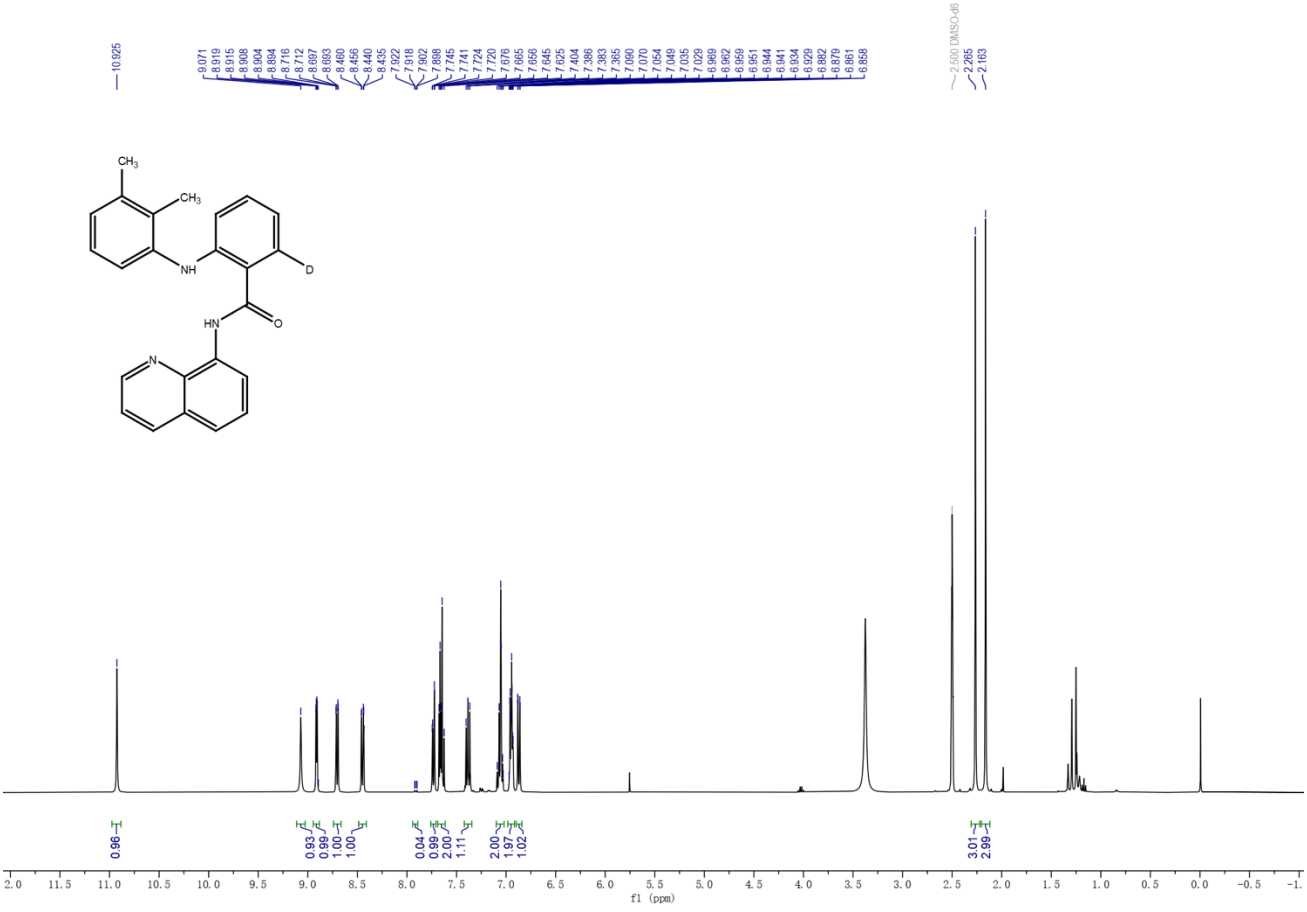
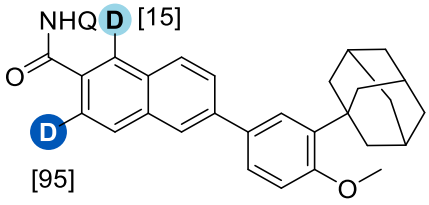


Figure S93 ^{1}H NMR of **28-[d]** in DMSO-d_6



Deuteration of 6-(3-(adamantan-1-yl)-4-methoxyphenyl)-N-(quinolin-8-yl)-2-naphthamide (29)



General procedure to afford **29-[d]** as white solid (126.4 mg, 94%, 3 mL DCE and 1 mL acetone-d_6 was used due to the poor solubility) with D-incorporation 15% for 1-position and 95% for 3-position by ^{1}H NMR; R_f = 0.20 (Pe-troleum ether/EtOAc =8/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 9.01 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.11 – 8.01 (m, 3H), 7.84 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.69 – 7.49 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 2.21 (d, *J* = 3.0 Hz, 6H), 2.12 (t, *J* = 3.1 Hz, 3H), 1.88 – 1.75 (m, 6H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 9.01 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.92 (dd, *J* = 4.3, 1.7 Hz, 1H), **8.63 (s, 0.85H, Labelled)**, 8.23 (dd, *J* = 8.3, 1.6 Hz, 1H), **8.16 (d, *J* = 8.6 Hz, 0.05H, Labelled)**, 8.12 – 8.01 (m, 3H), 7.84 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.68 – 7.48 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 2.21 (d, *J* = 2.9 Hz, 6H), 2.15 – 2.09 (m, 3H), 1.82 (t, *J* = 3.1 Hz, 6H).

Figure S94 ^{1}H NMR spectrum comparison

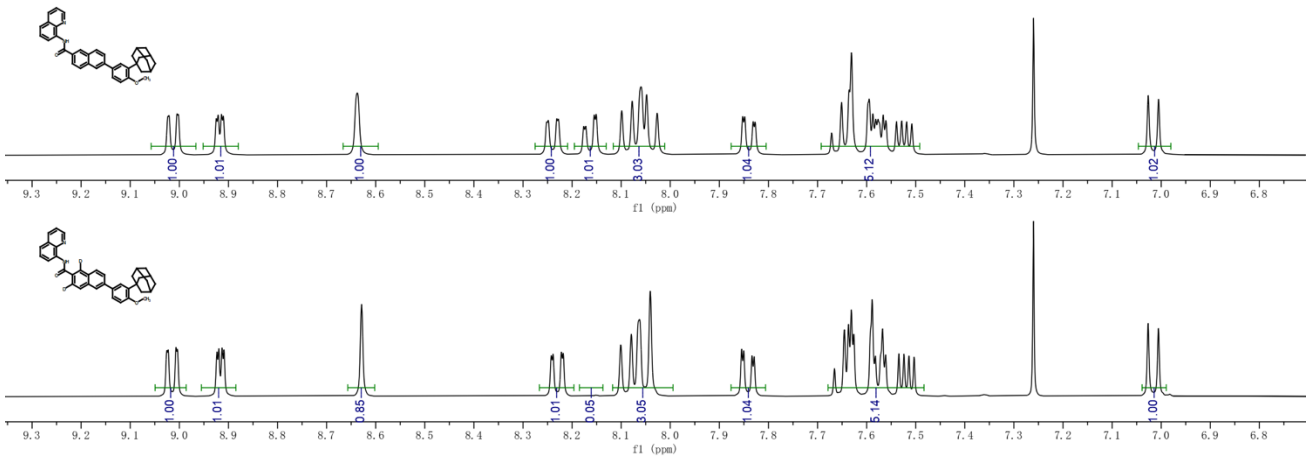


Figure S95 ^{1}H NMR of **29** in $CDCl_3$

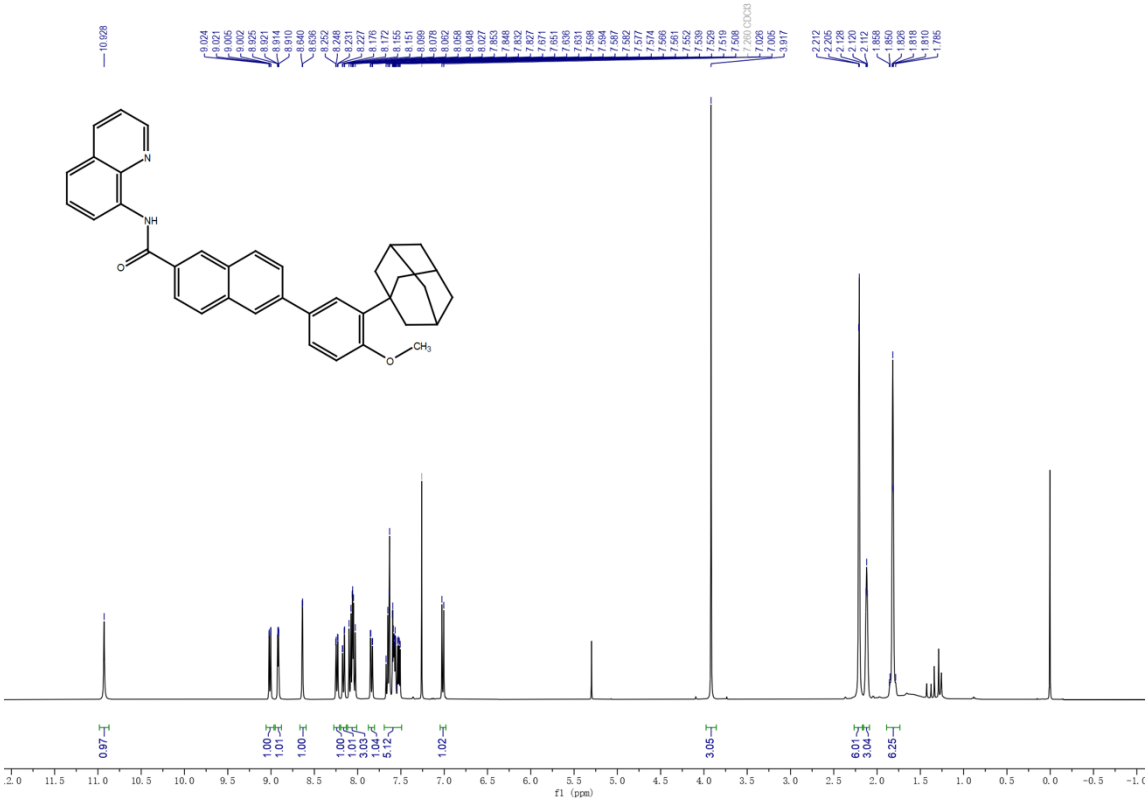
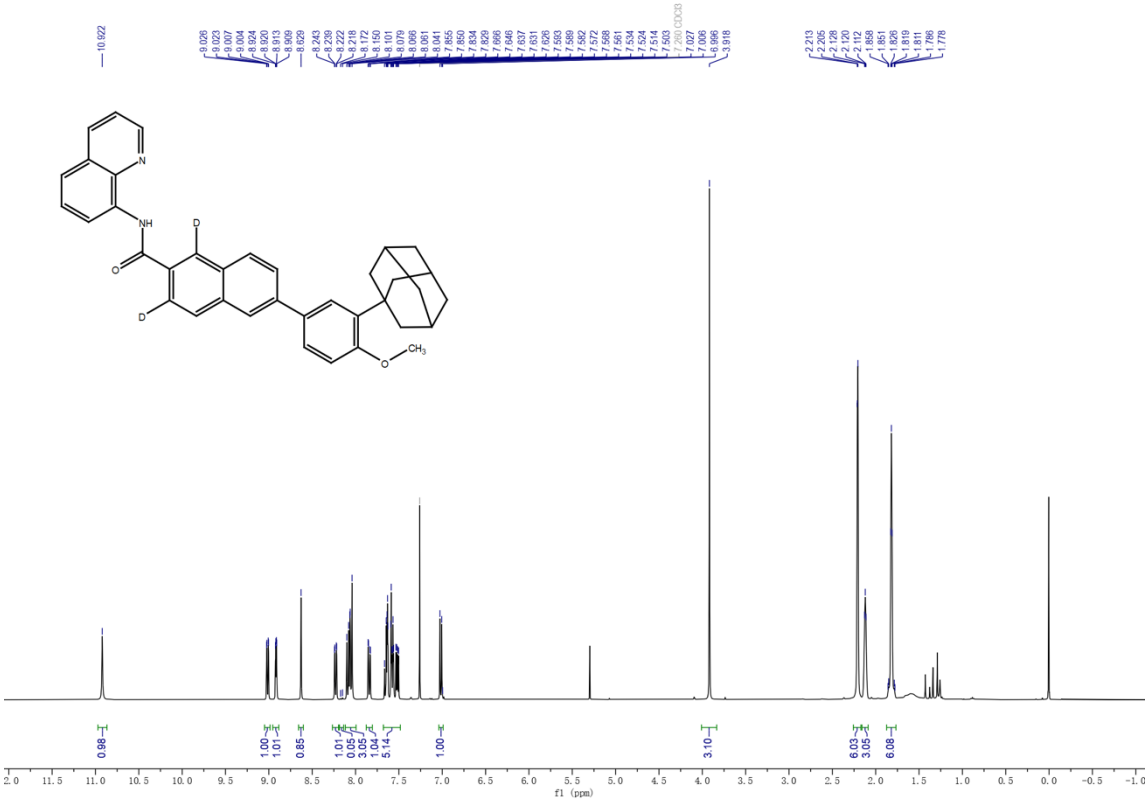
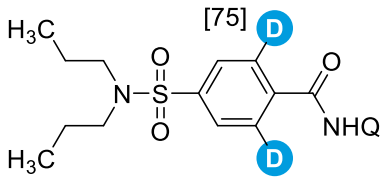


Figure S96 ^{1}H NMR of **29-[d]** in $CDCl_3$



Deuteration of 1-benzoyl-1H-indole-3-carbaldehyde (30)



General procedure to afford **30-[d]** as white solid (95.5 mg, 93%) with D-incorporation 75% for 2,6-positions by ^{1}H NMR; R_f = 0.25 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.74 (s, 1H), 8.98 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.70 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.48 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.26 – 8.19 (m, 2H), 8.06 – 7.99 (m, 2H), 7.79 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.73 – 7.63 (m, 2H), 3.13 – 3.02 (m, 4H), 1.50 (h, *J* = 7.4 Hz, 4H), 0.83 (t, *J* = 7.4 Hz, 6H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 10.74 (s, 1H), 8.98 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.48 (dd, *J* = 8.3, 1.7 Hz, 1H), **8.23 (d, *J* = 8.6 Hz, 0.51H, Labelled)**, 8.03 (d, *J* = 3.9 Hz, 2H), 7.79 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.73 – 7.61 (m, 2H), 3.13 – 3.04 (m, 4H), 1.50 (h, *J* = 7.4 Hz, 4H), 0.83 (t, *J* = 7.3 Hz, 6H).

Figure S97 ^{1}H NMR spectrum comparison

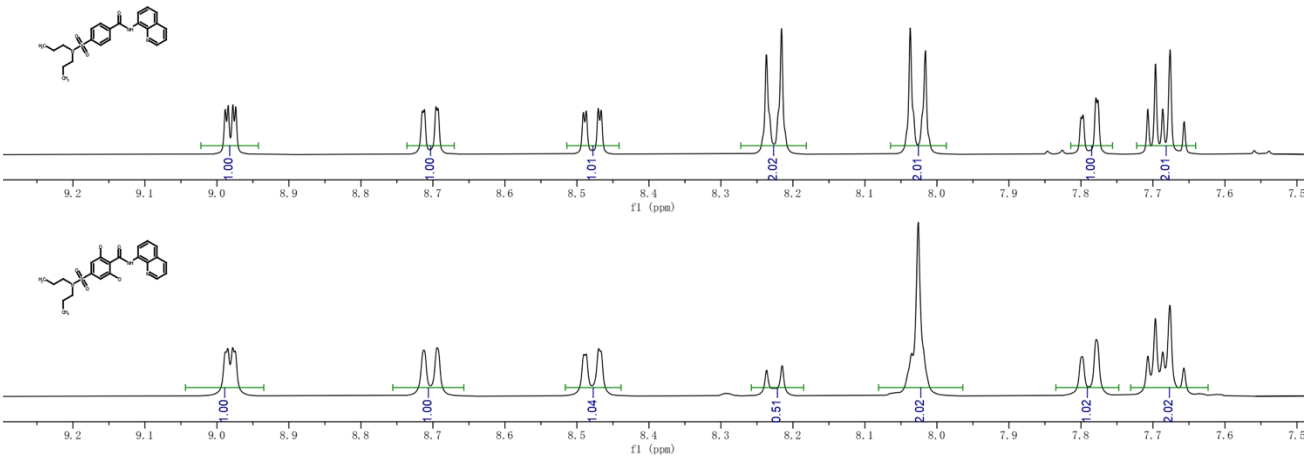
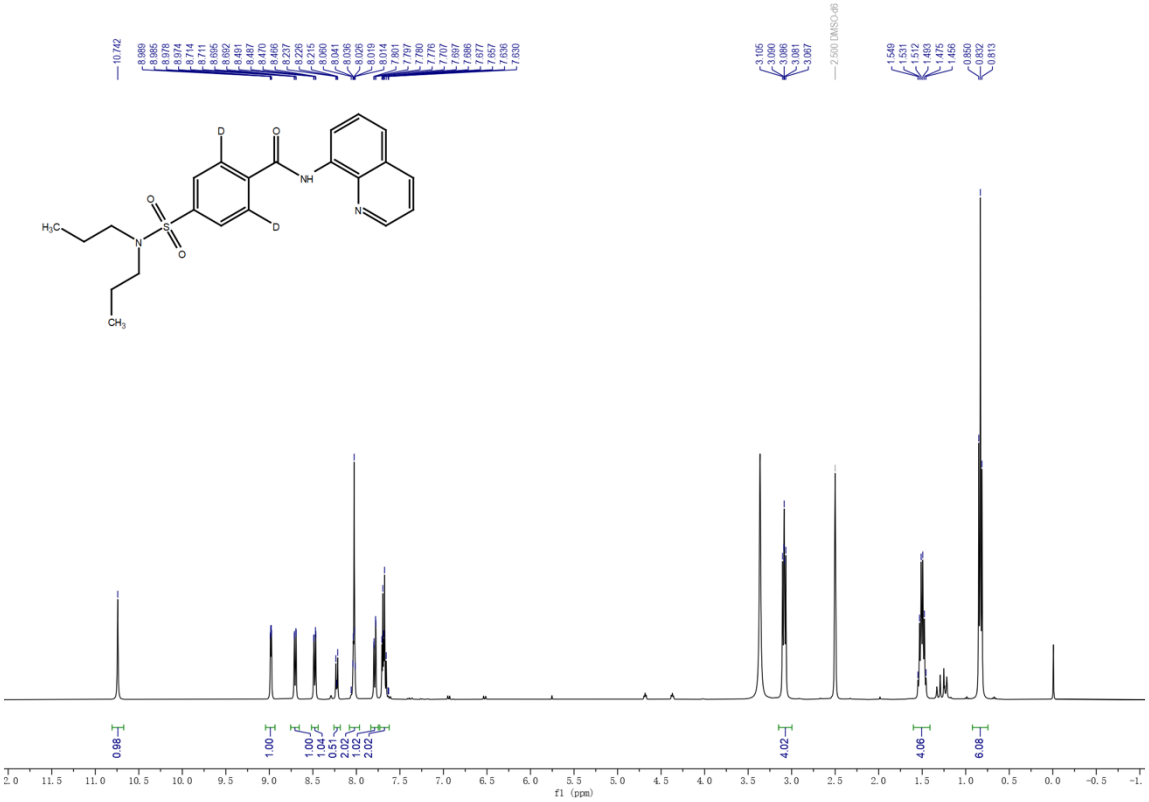
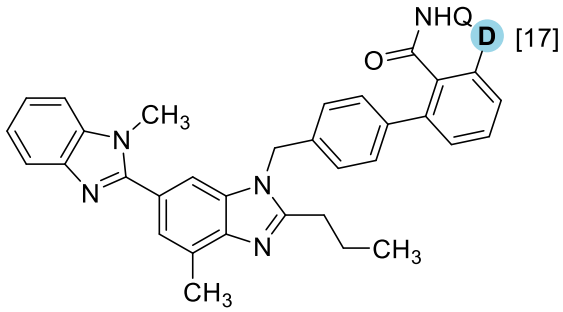


Figure S98 ^{1}H NMR of **30** in DMSO-*d*$_6$

Figure S99 ^{1}H NMR of **30-[d]** in DMSO-*d*$_6$



Deuteration of 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-N-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide (31)



General procedure to afford **31-[d]** as white solid (93.7 mg, 59%) with D-incorporation 17% for 3-position by ^{1}H NMR; R_f = 0.25 (Petroleum ether/EtOAc =1/2).

NMR data for starting material: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 9.85 (s, 1H), 8.62 (d, *J* = 4.9 Hz, 1H), 8.54 (d, *J* = 7.5 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.68 – 7.41 (m, 12H), 7.26 (dt, *J* = 18.1, 7.1 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.47 (s, 2H), 3.77 (s, 3H), 2.60 (d, *J* = 6.8 Hz, 5H), 1.59 (h, *J* = 7.5 Hz, 2H), 0.79 (t, *J* = 7.3 Hz, 3H).

NMR data for deuterated product: ^{1}H NMR (400 MHz, $D_{MS}O$) δ 9.85 (s, 1H), 8.62 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.54 (d, *J* = 7.4 Hz, 1H), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.79 (dd, *J* = 7.5, 1.5 Hz, 0.83H, Labelled)**, 7.69 – 7.42 (m, 12H), 7.33 – 7.20 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.47 (s, 2H), 3.77 (s, 3H), 2.60 (d, *J* = 6.1 Hz, 5H), 1.59 (h, *J* = 7.4 Hz, 2H), 0.79 (t, *J* = 7.3 Hz, 3H).

Figure S100 ^{1}H NMR spectrum comparison

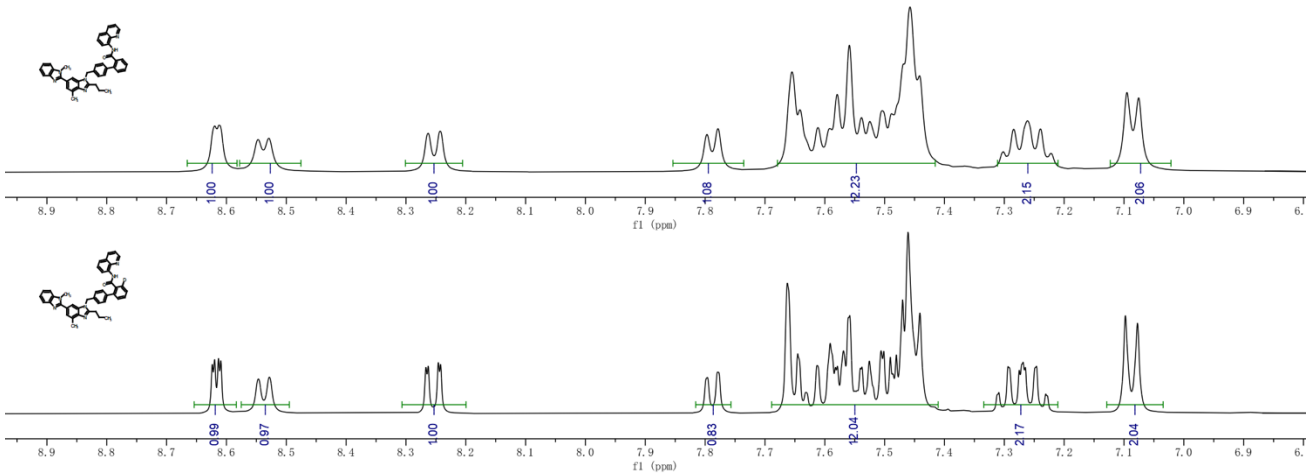


Figure S101 ^{1}H NMR of **31** in DMSO-d_6

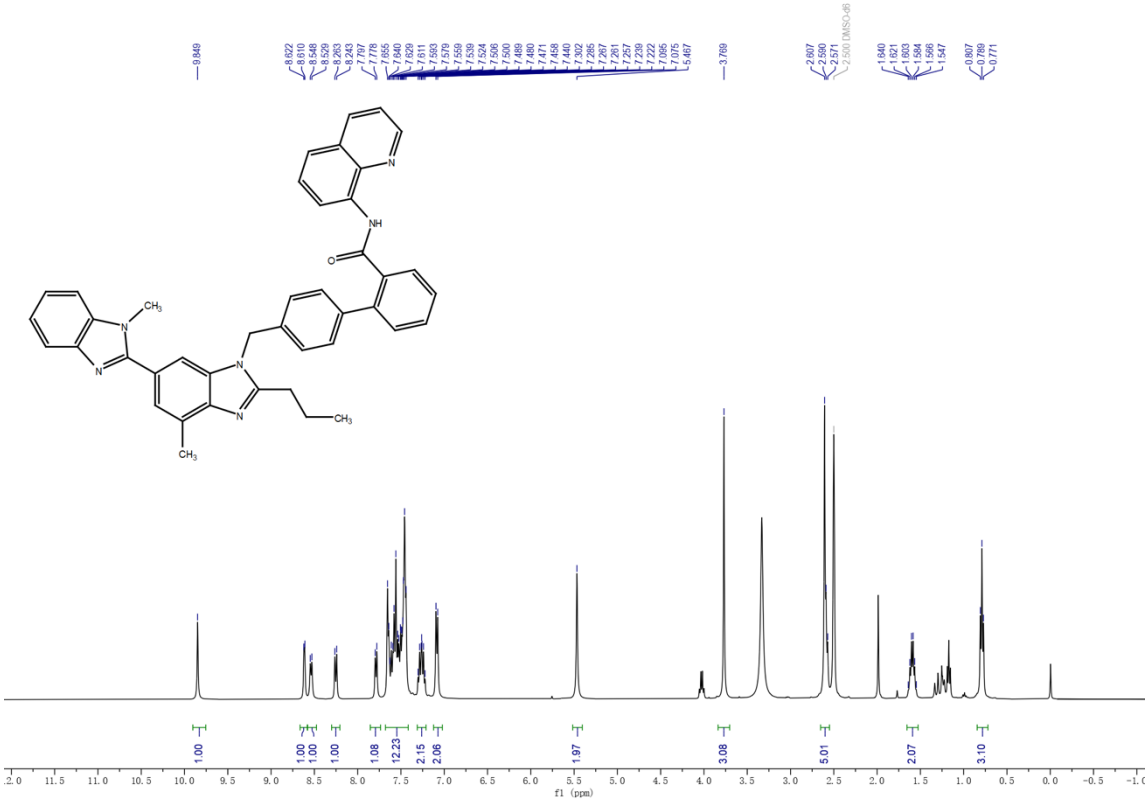
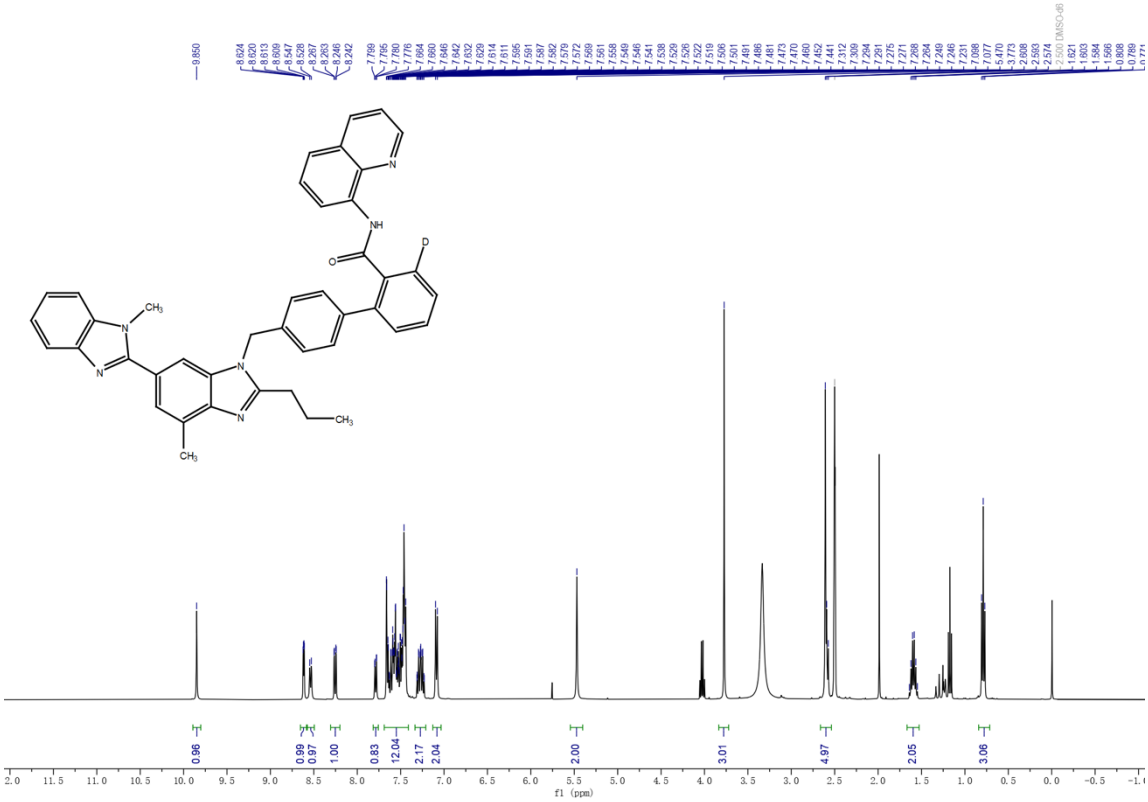
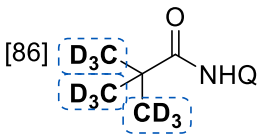


Figure S102 ^{1}H NMR of **31-[d]** in DMSO-d_6



Deuteration of N-(Quinolin-8-yl)pivalamide (32)



General procedure to afford **32-[d]** as colorless oily liquid (114.9 mg, 98%) with D-incorporation 86% for methyl by ^{1}H NMR and 7.80 D_{MS} by GC-MS; R_f = 0.50 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.83 – 8.77 (m, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.47 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.43 (s, 8H)..

NMR data for deuterated product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.85 – 8.77 (m, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58 – 7.42 (m, 3H), **1.40 (dt, *J* = 7.4, 1.9 Hz, 1.27H, Labelled)**; 13C NMR (101 MHz, $CDCl_3$) δ 177.52, 148.26, 138.83, 136.61, 134.82, 128.11, 127.65, 121.65, 121.38, 116.55, 39.94, 28.58 – 25.38 (m).

Figure S103 ^{1}H NMR spectrum comparison

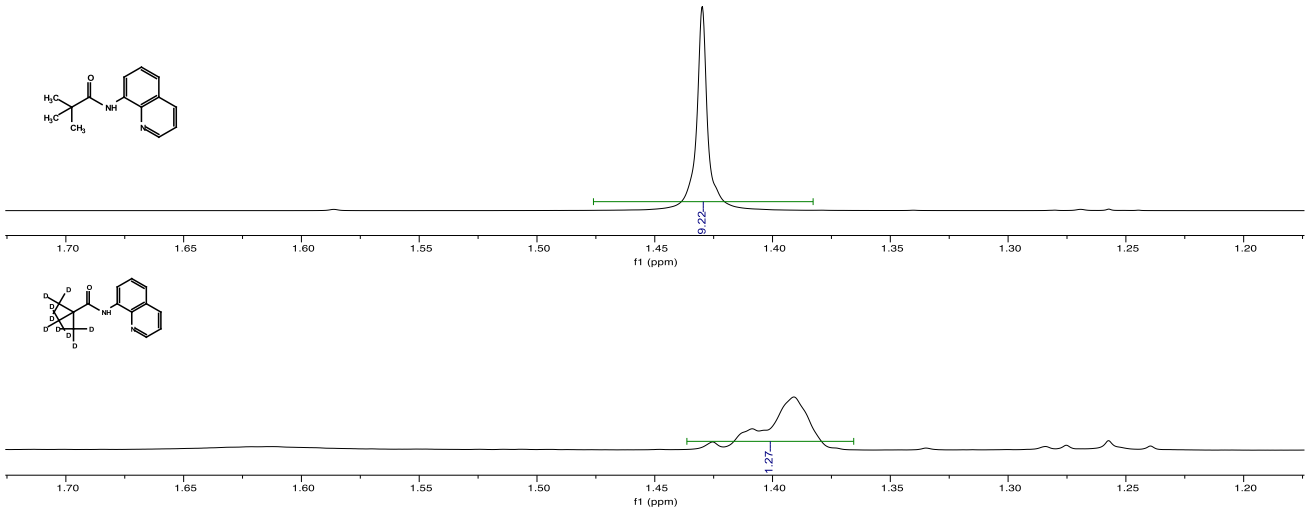


Figure S104 GC-MS spectrum comparison

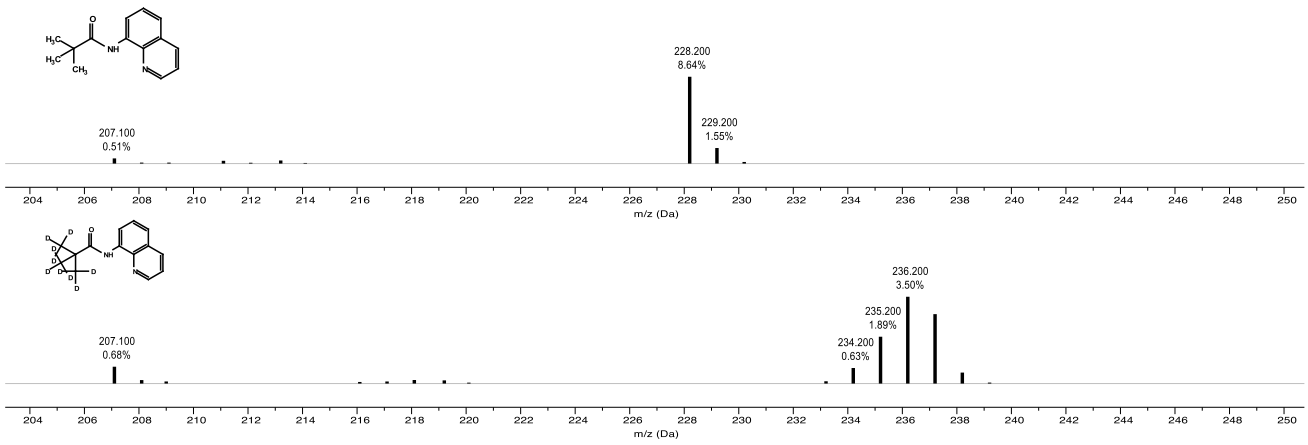


Figure S105 ^{1}H NMR of **32** in $CDCl_3$

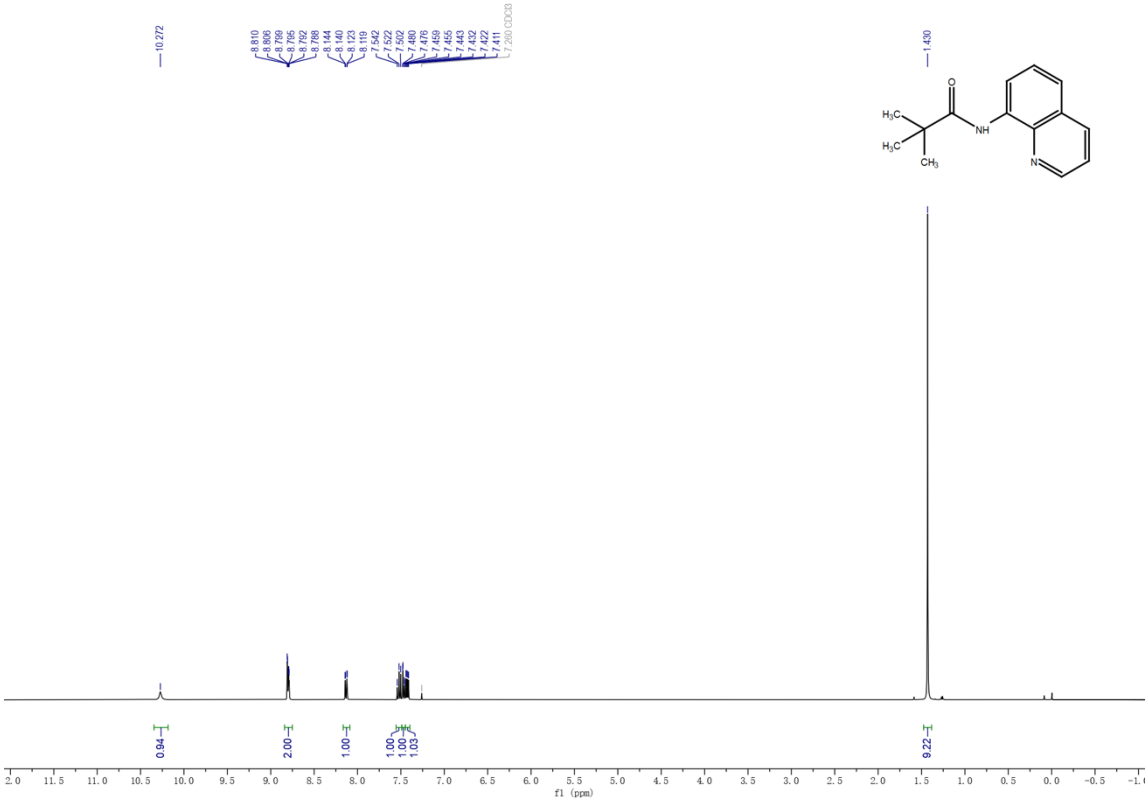
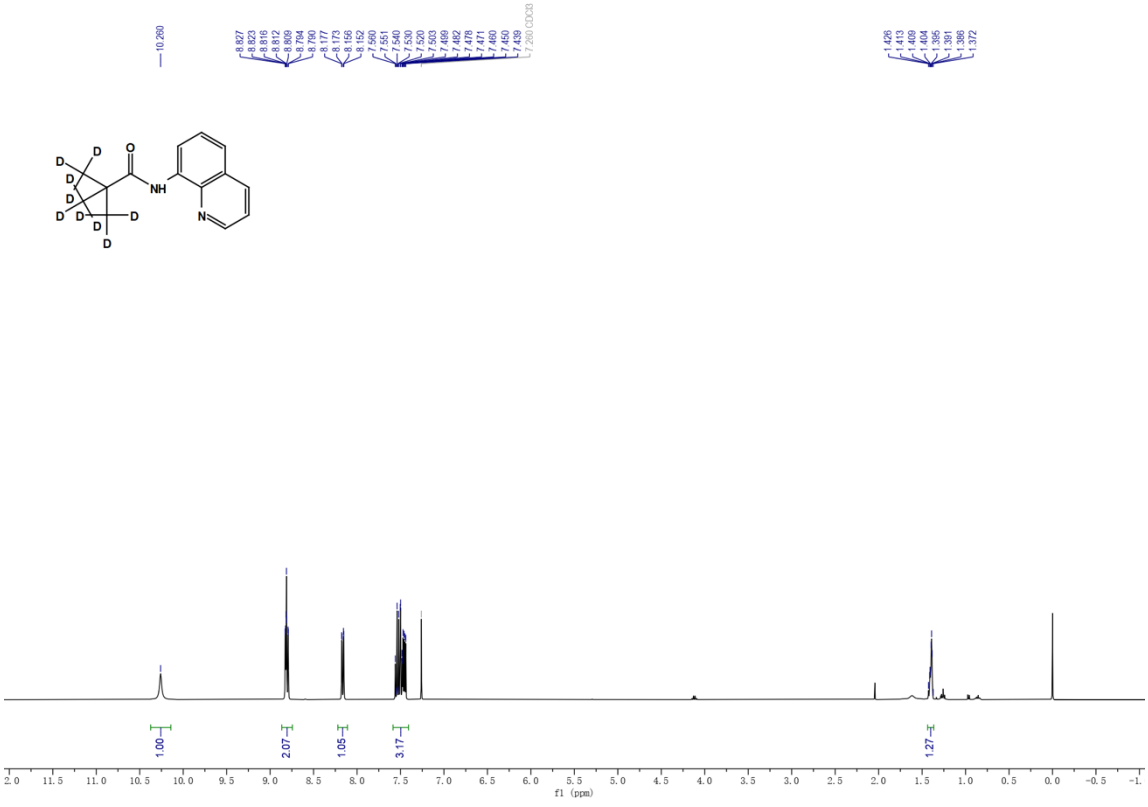
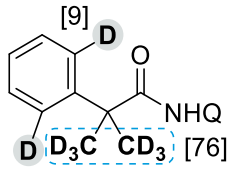


Figure S106 ^{1}H NMR of **32-[d]** in $CDCl_3$



Deuteration of 2-Methyl-2-phenyl-N-(quinolin-8-yl)propenamide (33)



General procedure to afford **33-[d]** as white solid (133.9 mg, 97%) with D-incorporation 76% for gem-methyl and 9% for aromatic ring by ^{1}H NMR; R_f = 0.50 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.77 (d, *J* = 7.6 Hz, 1H), 8.60 (d, *J* = 4.3 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.47 (m, 3H), 7.47 – 7.37 (m, 3H), 7.37 – 7.28 (m, 2H), 1.79 (s, 6H).

NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.76 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.60 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), **7.57 – 7.48 (m, 2.82H, Labelled)**, 7.47 – 7.33 (m, 4H), 7.33 – 7.27 (m, 1H), **1.76 (d, *J* = 6.8 Hz, 1.49H, Labelled)**.

Figure S107 ^{1}H NMR spectrum comparison

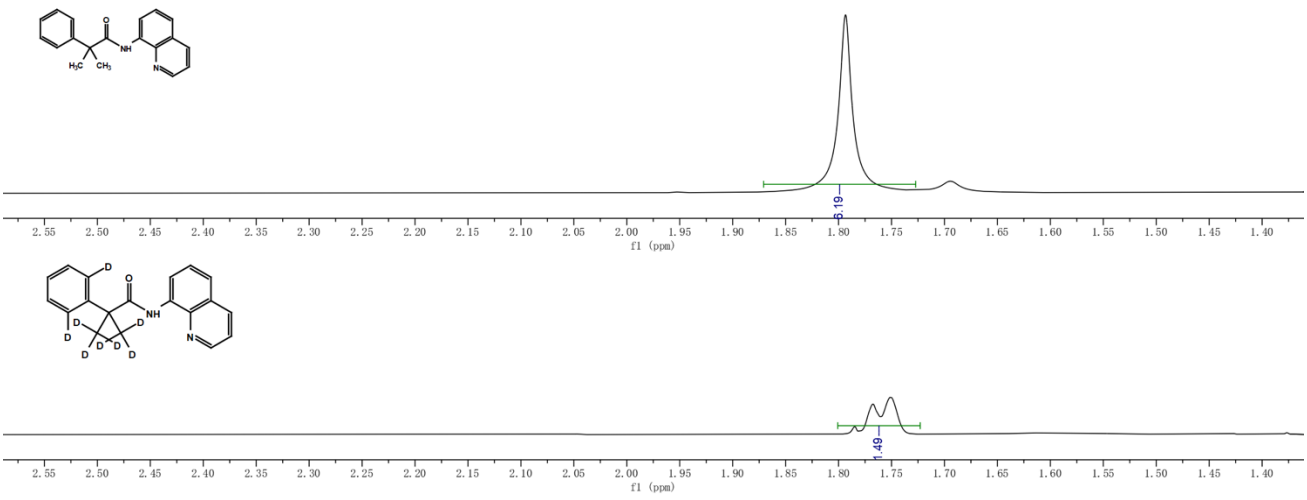


Figure S108 ^{1}H NMR of **33** in $CDCl_3$

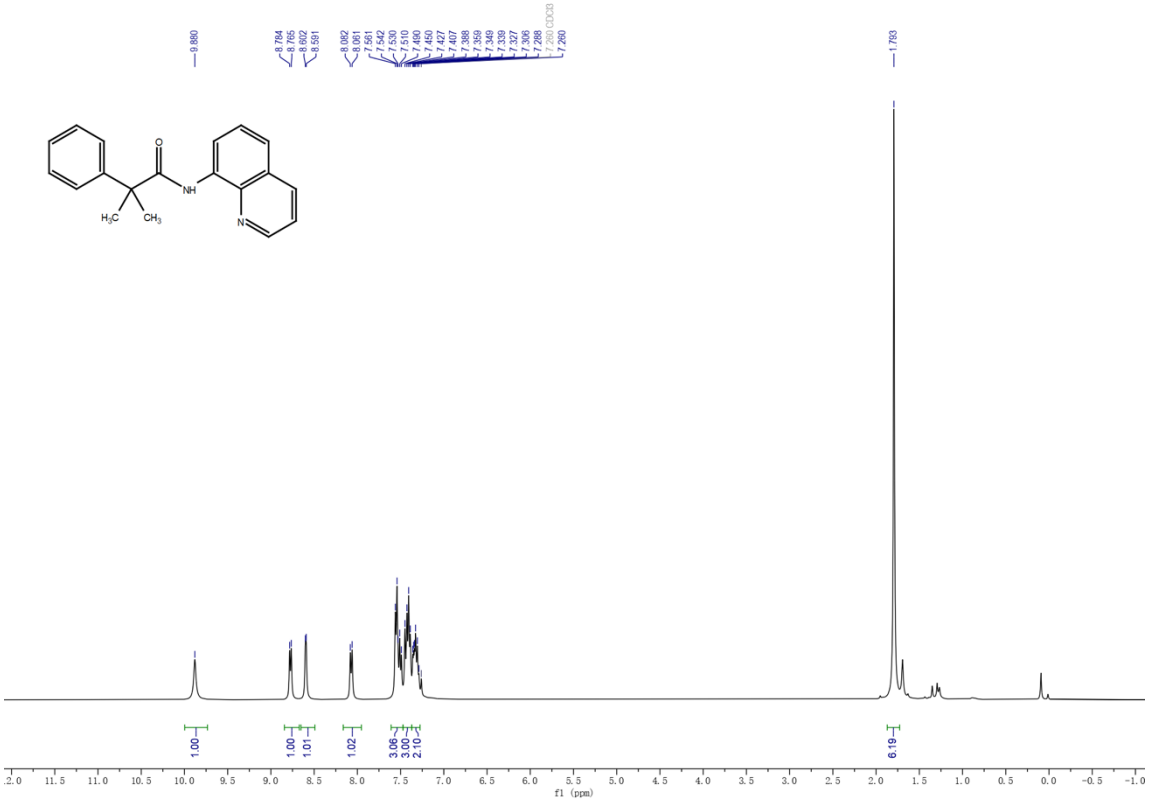
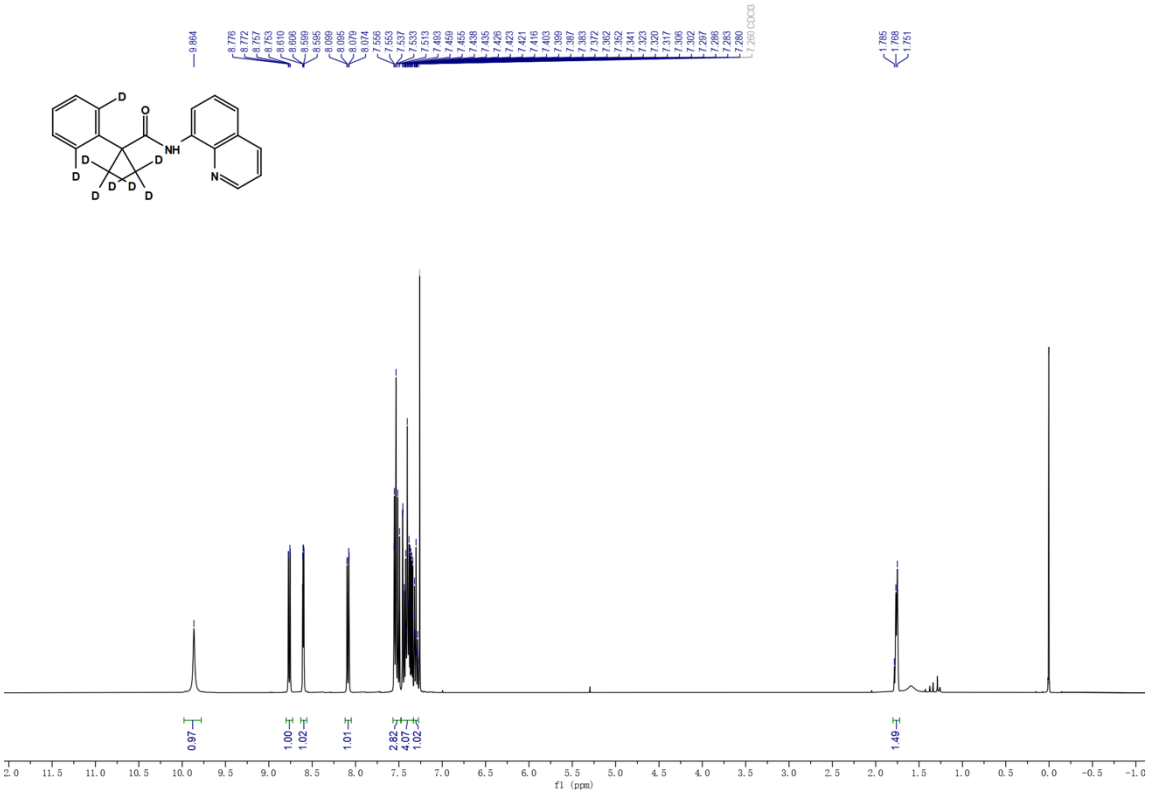
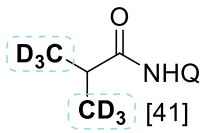


Figure S109 ^{1}H NMR of **33-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)isobutyramide (34)



[41]

General procedure to afford **34-[d]** as colorless oily liquid (104.7 mg, 97%) with D-incorporation 41% for methyl by ^{1}H NMR; R_f = 0.40 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.83 – 8.75 (m, 2H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.45 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.76 (hept, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 6H).
NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.85 – 8.76 (m, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58 – 7.42 (m, 3H), 2.77 (p, *J* = 6.2 Hz, 1H), **1.38 – 1.30 (m, 3.74H, Labelled)**.

Figure S110 ^{1}H NMR spectrum comparison

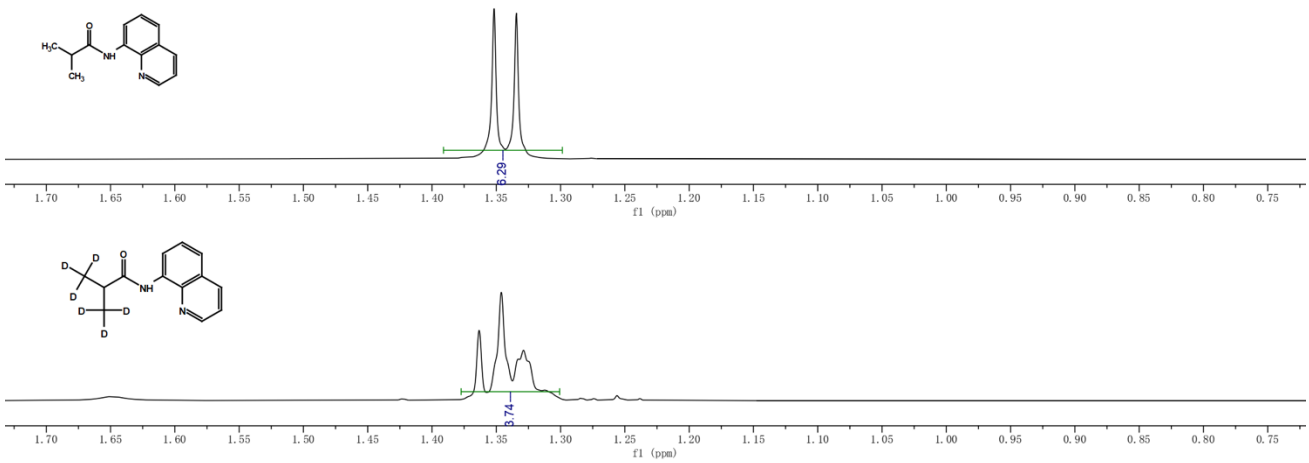


Figure S111 ^{1}H NMR of **34** in $CDCl_3$

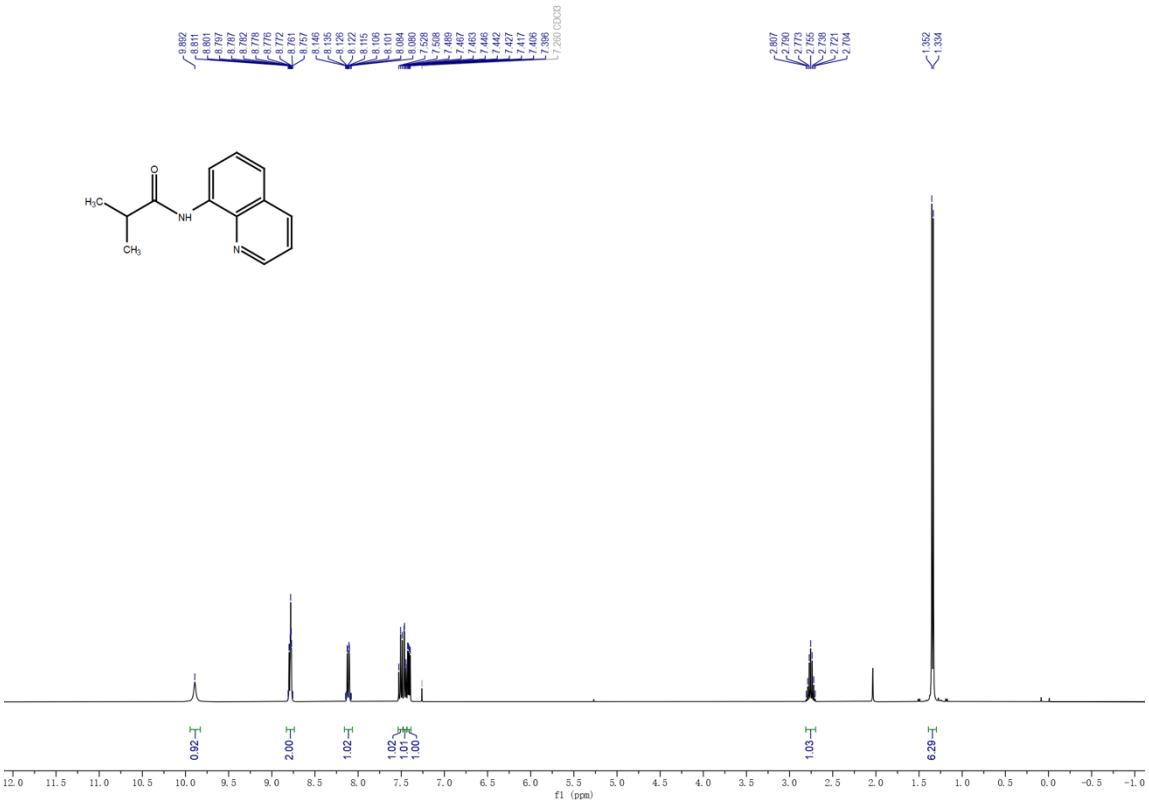
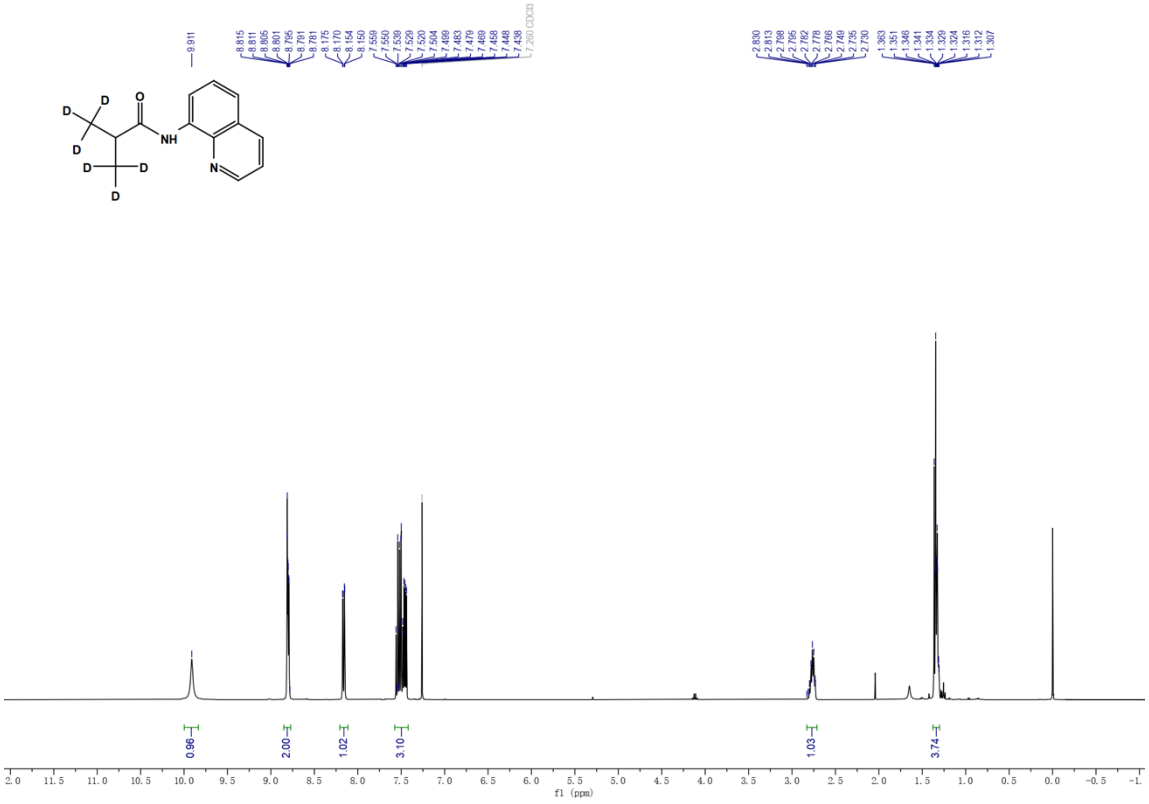
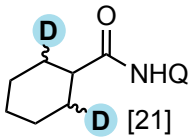


Figure S112 ^{1}H NMR of **34-[d]** in $CDCl_3$



Deuteration of N-(Quinolin-8-yl)cyclohexanecarboxamide (35)



General procedure to afford **35-[d]** as colorless oily liquid (114.0 mg, 90%) with D-incorporation 21% for methylene (equatorial bond) by ^{1}H NMR; R_f = 0.45 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.83 – 8.72 (m, 2H), 8.08 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.44 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.14 – 2.00 (m, 2H), 1.90 – 1.79 (m, 2H), 1.76 – 1.54 (m, 3H), 1.43 – 1.18 (m, 3H)..

NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.85 – 8.76 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58 – 7.41 (m, 3H), 2.55 – 2.43 (m, 1H), **2.14 – 2.02 (m, 1.58H, Labelled)**, 1.88 (dt, *J* = 12.6, 3.3 Hz, 2H), 1.79 – 1.56 (m, 3H), 1.47 – 1.22 (m, 3H).

Figure S113 ^{1}H NMR spectrum comparison

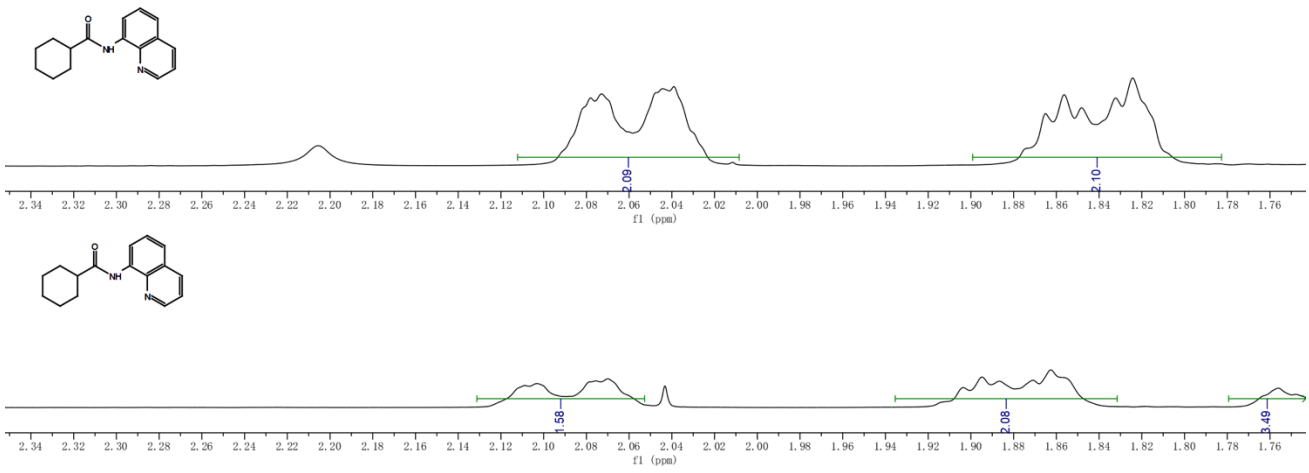


Figure S114 ^{1}H NMR of **35** in $CDCl_3$

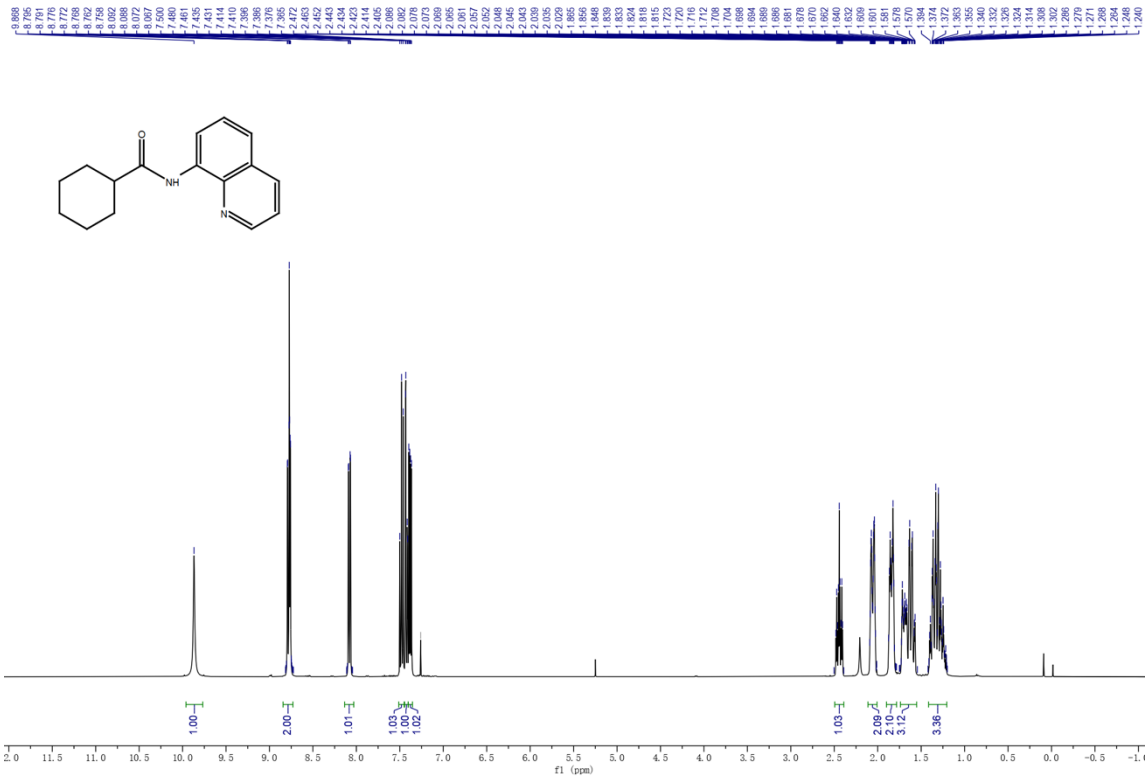
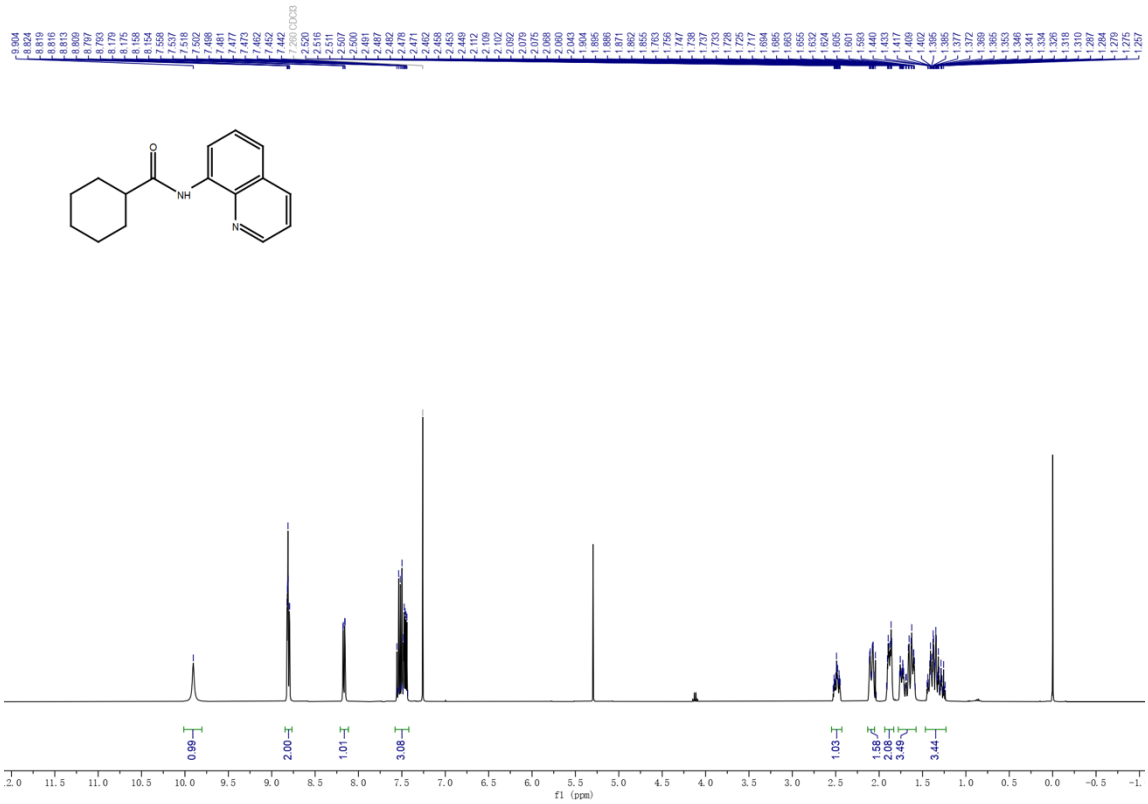
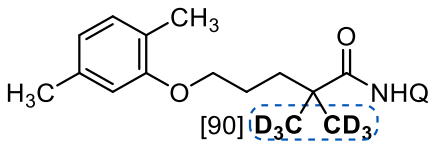


Figure S115 ^{1}H NMR of **35-[d]** in $CDCl_3$



Deuteration of 5-(2,5-dimethylphenoxy)-2,2-dimethyl-N-(quinolin-8-yl)pentanamide (37)



General procedure to afford **37-[d]** as light yellow oily liquid (171.8 mg, 96%) with D-incorporation 90% for methyl by ^{1}H NMR.

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.84 – 8.77 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59 – 7.42 (m, 3H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 1.7 Hz, 1H), 3.95 (t, *J* = 5.8 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.97 – 1.82 (m, 4H), 1.47 (s, 6H).
NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.84 – 8.77 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59 – 7.42 (m, 3H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 1.6 Hz, 1H), 3.95 (t, *J* = 5.8 Hz, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 1.97 – 1.81 (m, 4H), **1.43 (d, *J* = 2.2 Hz, 0.61H, Labelled)**.

Figure S116 ^{1}H NMR spectrum comparison

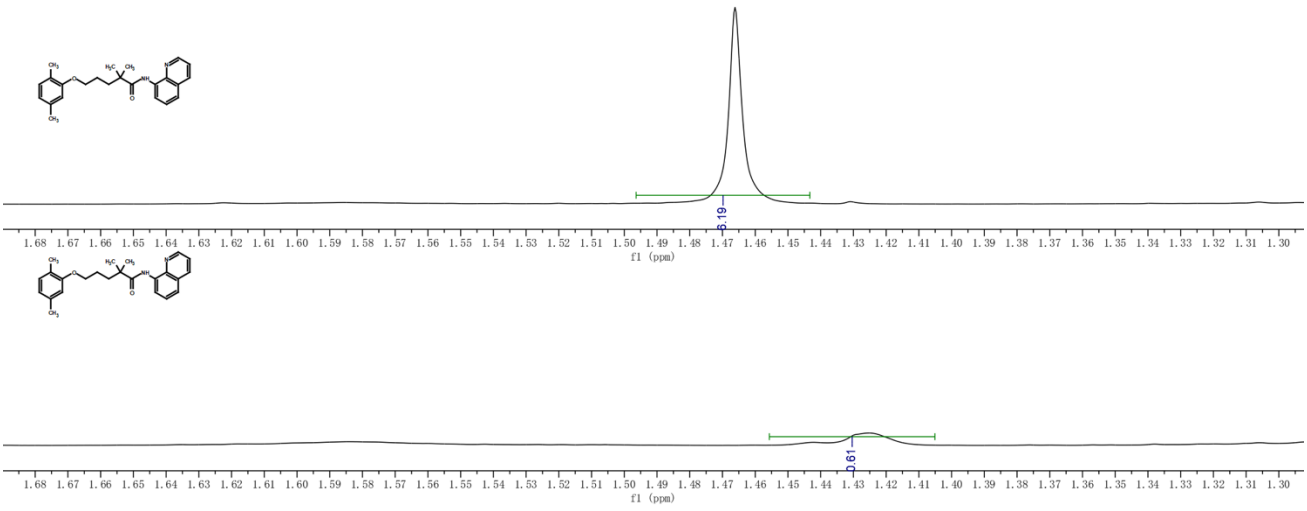


Figure S117 ^{1}H NMR of **37** in $CDCl_3$

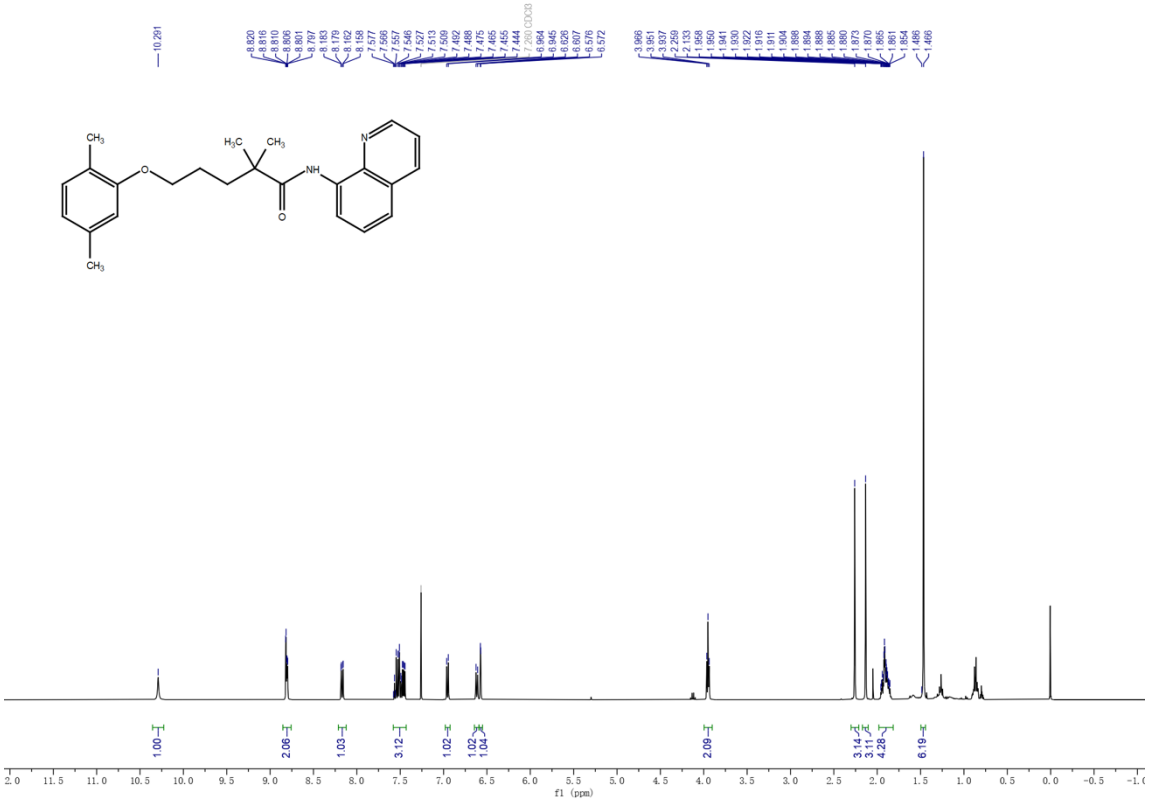
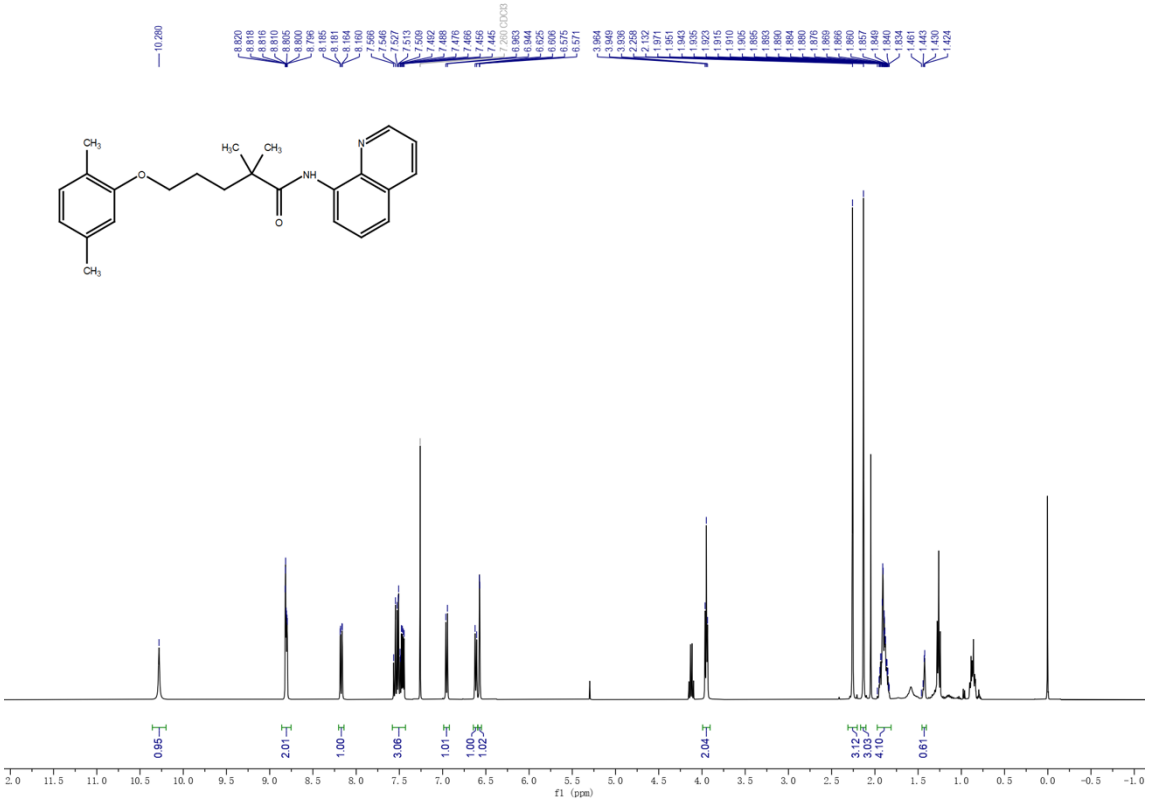
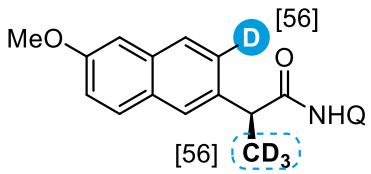


Figure S118 ^{1}H NMR of **37-[d]** in $CDCl_3$



Deuteration of (S)-2-(6-Methoxynaphthalen-2-yl)-N-(quinolin-8-yl)propenamide (38)



General procedure to afford **38-[d]** as white solid (161.2 mg, 91%) with D-incorporation 56% for methyl and 56% for aromatic ring by ^{1}H NMR; R_f = 0.30 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.78 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.61 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.76 (dd, *J* = 8.6, 4.2 Hz, 2H), 7.57 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 1H), 3.91 (s, 3H), 1.76 (d, *J* = 7.1 Hz, 3H).
NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.61 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.87 (s, 1H), 7.76 (q, *J* = 4.2 Hz, 2H), **7.57 (dd, *J* = 8.5, 1.8 Hz, 0.44H, Labelled)**, 7.51 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.36 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.18 – 7.10 (m, 2H), 4.08 (t, *J* = 6.4 Hz, 1H), 3.91 (s, 3H), **1.79 – 1.70 (m, 1.36H, Labelled)**.

Figure S119 ^{1}H NMR spectrum comparison

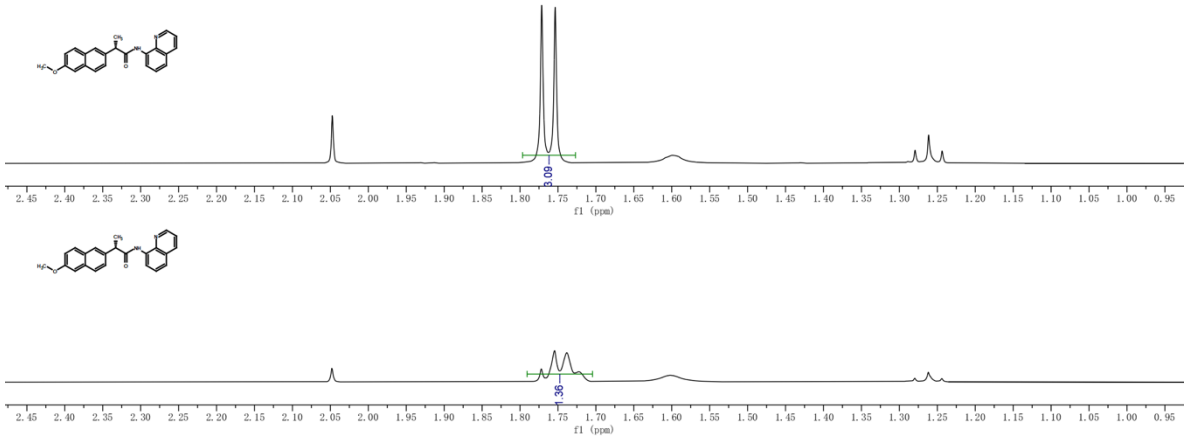


Figure S120 ^{1}H NMR of **38** in $CDCl_3$

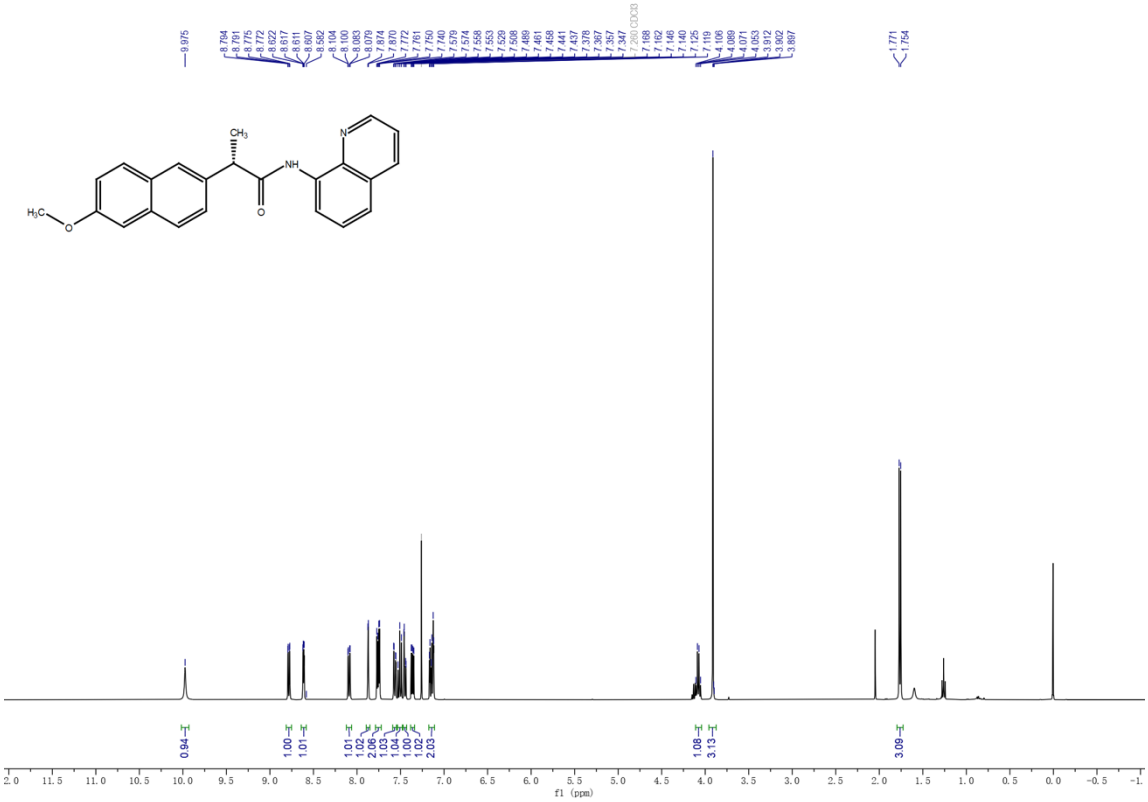
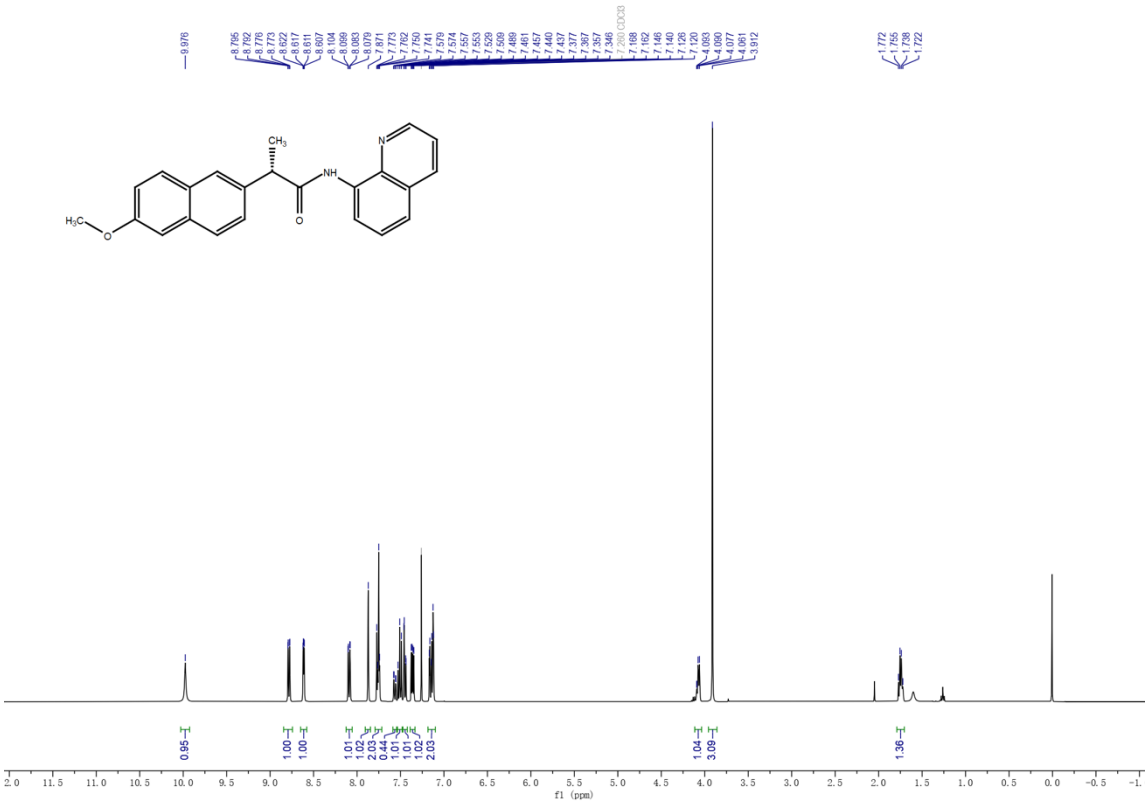
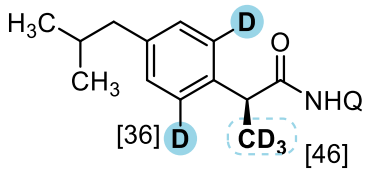


Figure S121 ^{1}H NMR of **38-[d]** in $CDCl_3$



Deuteration of (S)-2-(4-Isobutylphenyl)-N-(quinolin-8-yl)propanamide (39)



General procedure to afford **39-[d]** as white solid (157.2 mg, 95%) with D-incorporation 46% for methyl and 36% for aromatic ring by ^{1}H NMR; R_f = 0.60 (Petroleum ether/EtOAc = 6/1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.78 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.66 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.39 (dt, *J* = 8.3, 2.2 Hz, 3H), 7.20 – 7.14 (m, 2H), 3.92 (q, *J* = 7.2 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.88 (dh, *J* = 13.6, 6.8 Hz, 1H), 1.69 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 6H).
NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.78 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.67 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), **7.20 – 7.13 (m, 2.29H, Labelled)**, 3.91 (t, *J* = 6.5 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.86 (dh, *J* = 13.5, 6.8 Hz, 1H), **1.68 (dd, *J* = 7.8, 5.8 Hz, 1.71H, Labelled)**, 0.91 (d, *J* = 6.6 Hz, 6H).

Figure S122 ^{1}H NMR spectrum comparison

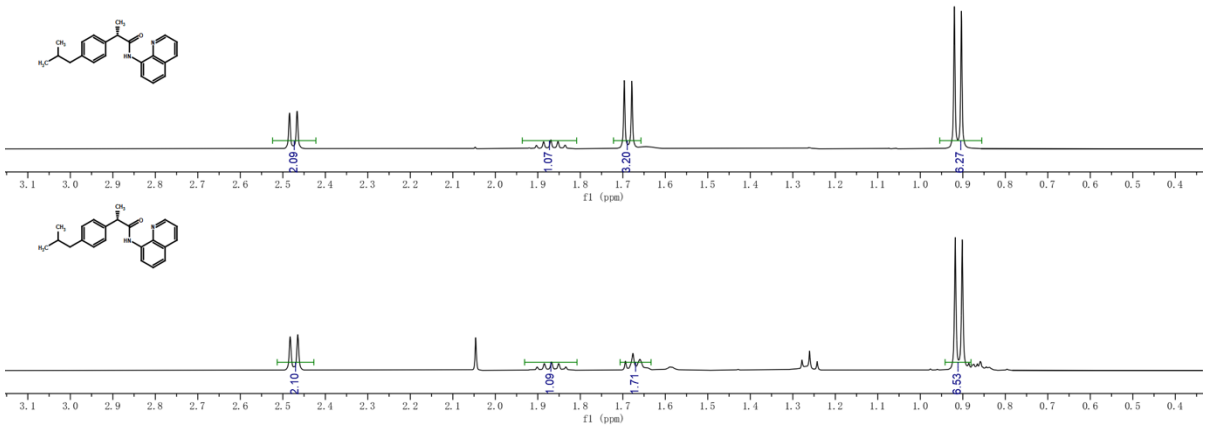


Figure S123 ^{1}H NMR of **39** in $CDCl_3$

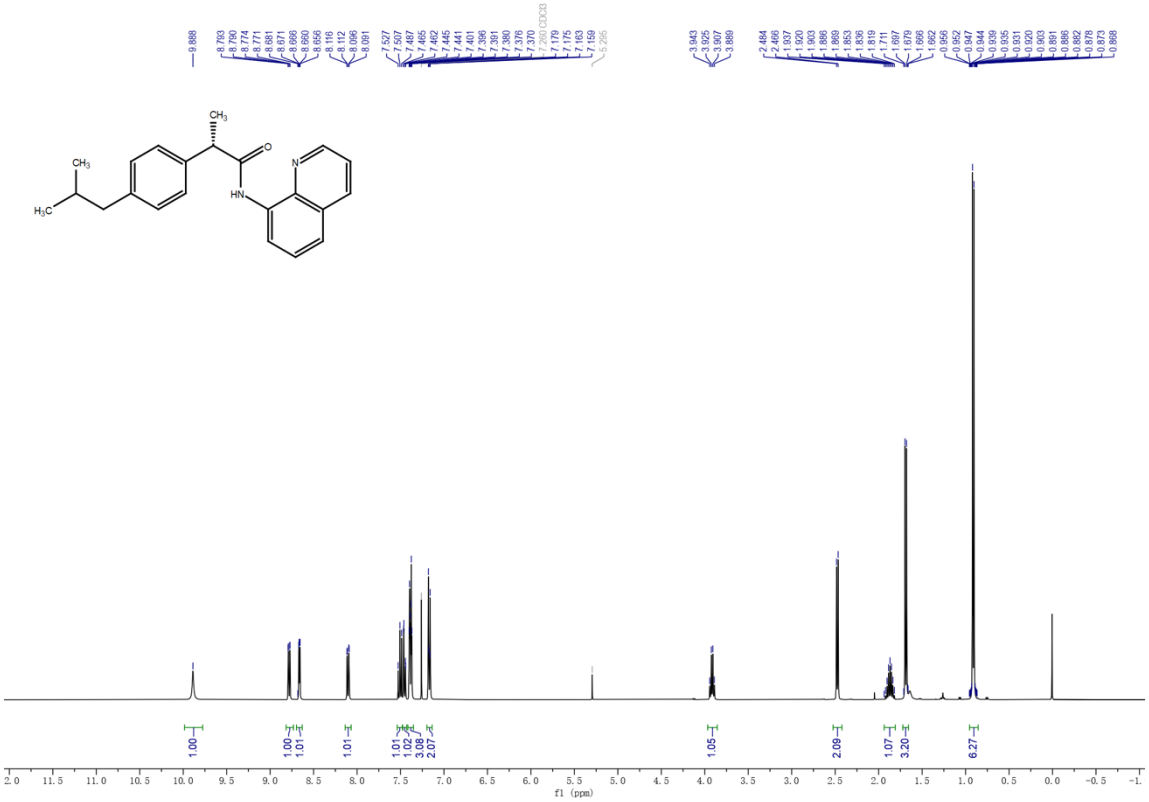
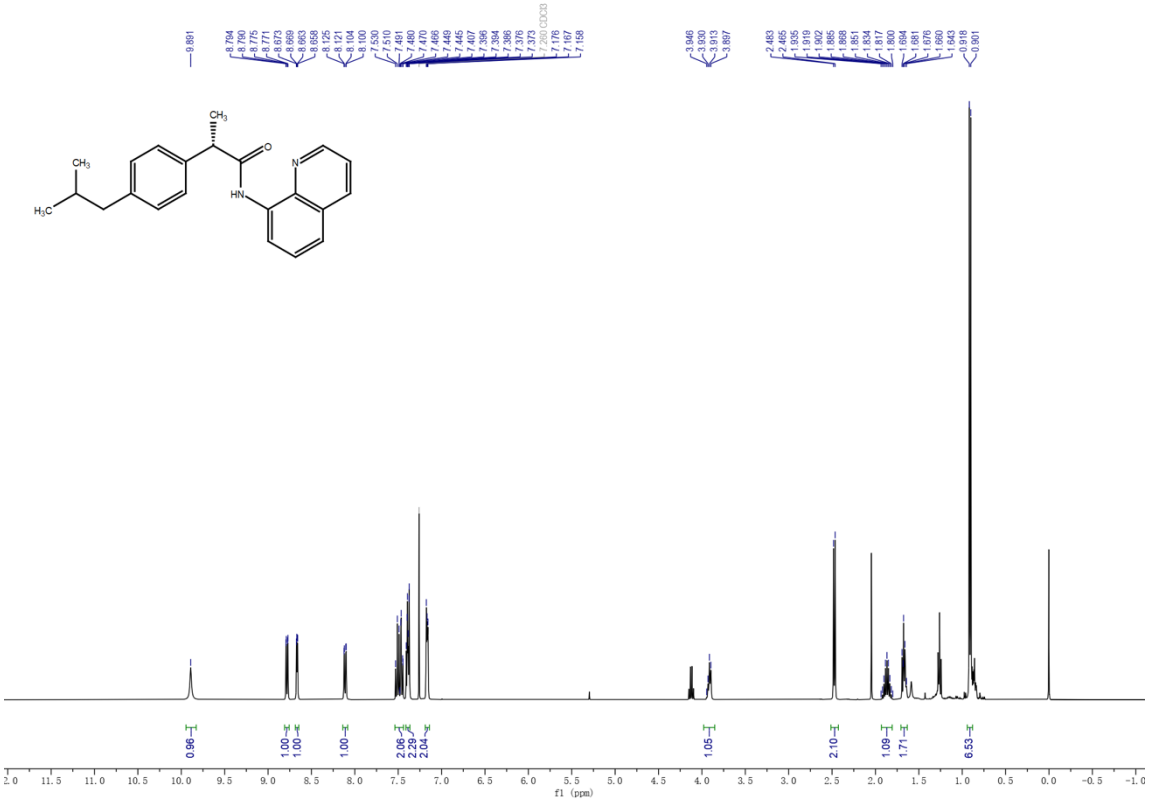
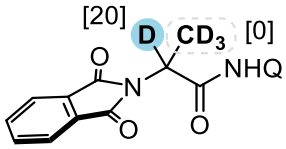


Figure S124 ^{1}H NMR of **39-[d]** in $CDCl_3$



Deuteration of 2-(1-Oxo-1-(quinolin-8-yl)propan-2-yl)isoindoline-1,3-dione (41)



General procedure to afford **41-[d]** as light yellow solid (140.5 mg, 81%, 2 mL DCE and 1 mL acetone-d_6 was used because of solubility) with D-incorporation 0% for methyl and 20% for methine by ^{1}H NMR; R_f = 0.35 (Petroleum ether/DCM/EtOAc = 1.5/1/0.1).

NMR data for starting material: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.77 – 8.66 (m, 2H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.57 – 7.47 (m, 2H), 7.42 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.27 (q, *J* = 7.4 Hz, 1H), 1.98 (d, *J* = 7.3 Hz, 3H).
NMR data for deuterated product : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.77 – 8.66 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.3, 4.3 Hz, 1H), **5.28 (q, *J* = 7.3 Hz, 0.80H, Labelled)**, 1.98 (d, *J* = 7.4 Hz, 2H).

Figure S125 ^{1}H NMR spectrum comparison

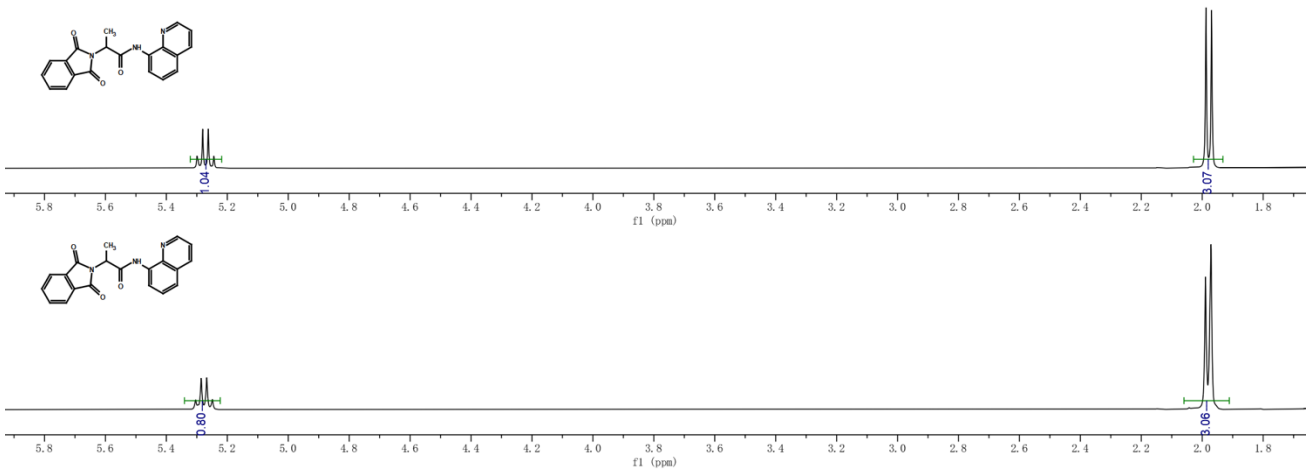


Figure S126 ^{1}H NMR of **41** in $CDCl_3$

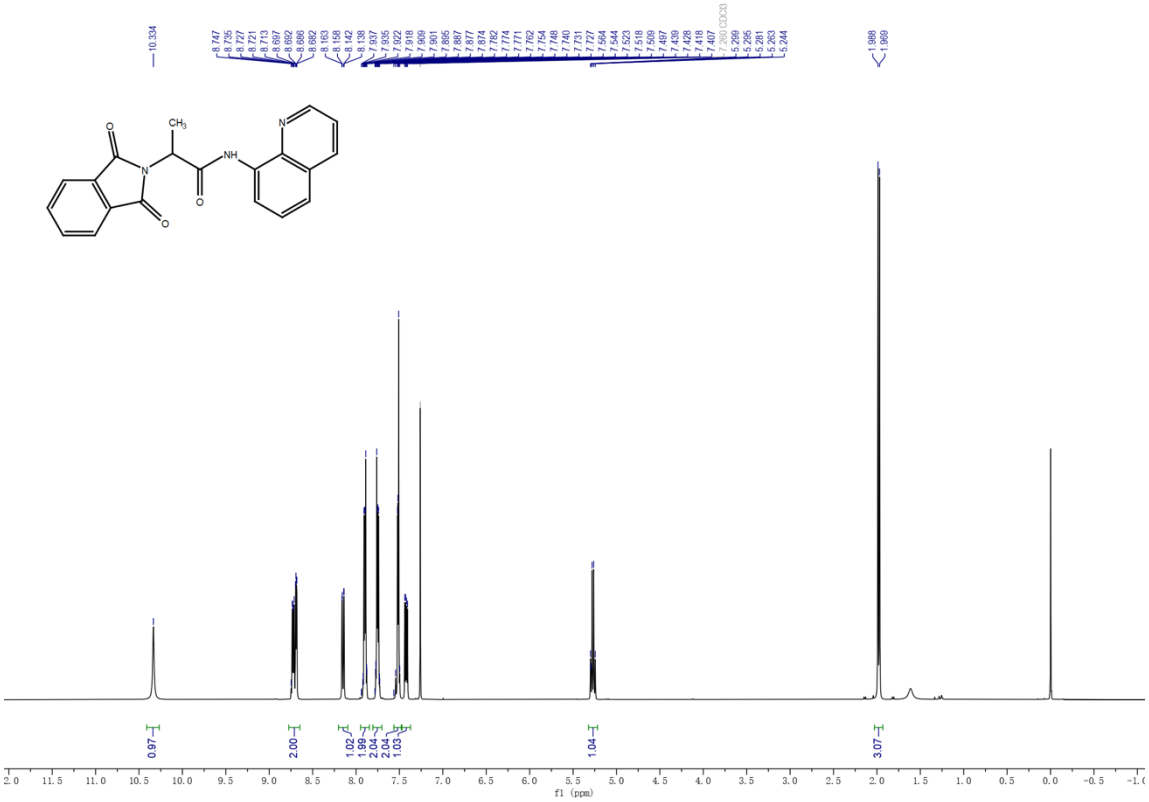
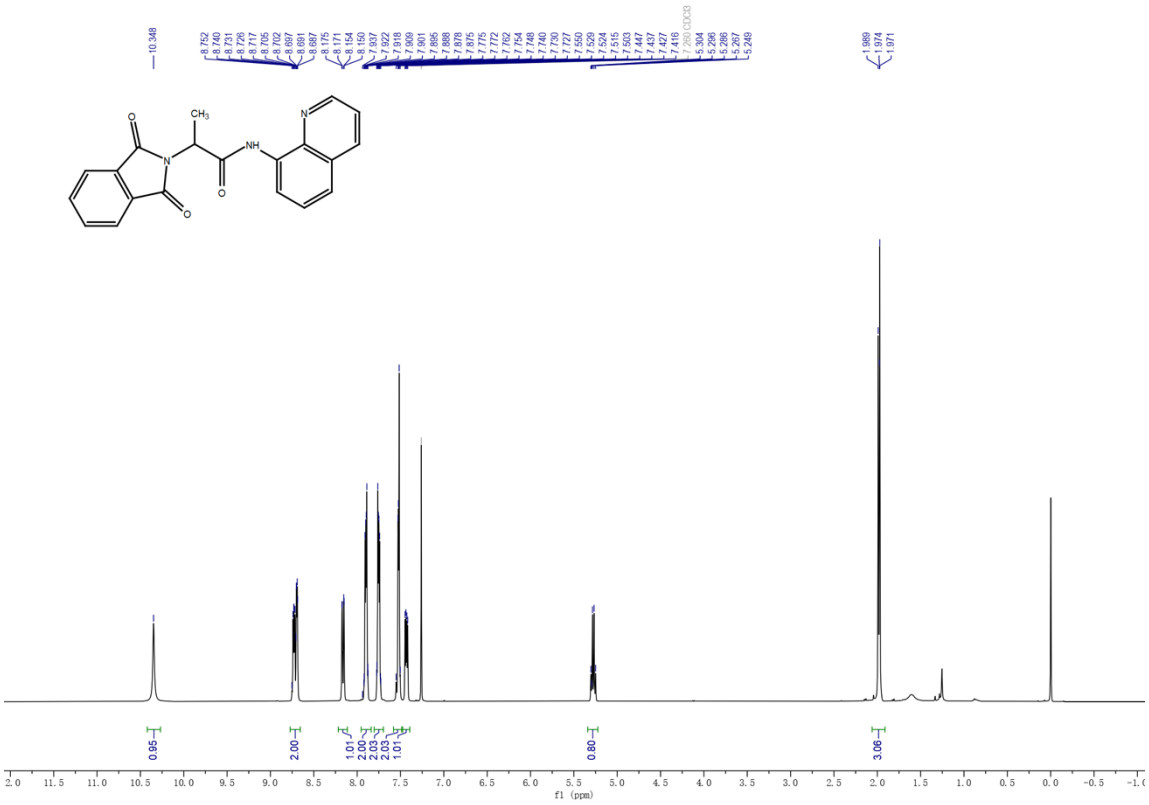


Figure S127 ^{1}H NMR of **41-[d]** in $CDCl_3$



6. References

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[4] Yangyang Cheng, Yimin Wu, Guangyin Tan, Jingsong You. Nickel Catalysis Enables Oxidative C(sp^2)–H/C(sp^2)–H Cross-Coupling Reactions between Two Heteroarenes Angewante Chemie International Edition, 2016, 55, 12275-12279.