# Supporting Information

# Geometric Constraints Regulated Regioselectivity: Pd-catalyzed α-deuteration of Pyridines with Secondary Phosphine Oxide

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**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.

## 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) 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[1].

The theoretical deuterium degree for this reaction was calculated as follow, with pyridine as model:

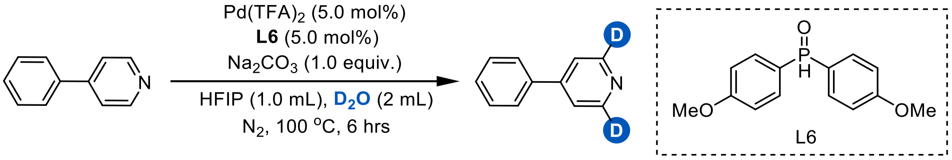
$$\boldsymbol{D_{theo}} = \frac{\mathbf{2} \times \boldsymbol{n}(\boldsymbol{D_2O})}{\mathbf{2} \times \boldsymbol{n}(\boldsymbol{D_2O}) + \boldsymbol{n}(\boldsymbol{HFIP}) + \boldsymbol{n}(\boldsymbol{exchangeable\ hydrogen\ in\ pyridines}) + \boldsymbol{n}(\boldsymbol{Ligand})}$$

$$= \frac{\mathbf{2} \times \mathbf{110}\ \boldsymbol{mmol}}{\mathbf{2} \times \mathbf{110}\ \boldsymbol{mmol} + \mathbf{9.5}\ \boldsymbol{mmol} + \mathbf{2.0}\ \boldsymbol{mmol} + \mathbf{0.05}\ \boldsymbol{mmol}}$$

$$= \mathbf{0.95}$$

## 2. Experimental procedures

### 1) General procedure for standard condition

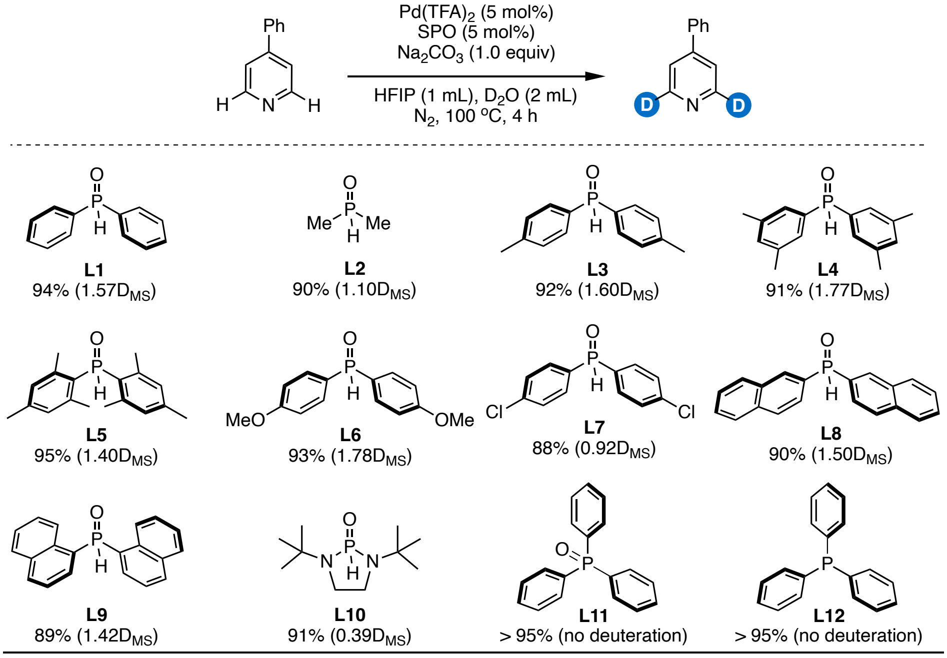


An oven dried 15 mL pressure vessel was charged with a substrate (1.0 mmol), Pd(TFA)$_2$ (16.6 mg, 5 mol%), **L6** (13.1 mg, 5 mol%), Na$_2$CO$_3$ (106.0 mg, 1.0 equiv.), HFIP (1.0 mL), and D$_2$O (2 mL). The vessel was purged with nitrogen stream, and sealed by Teflon bushing with Viton O-ring then placed into the inside circle of a preheated aluminium block on a magnetic stirrer and stirred at 100 °C for 6 hours. After the reaction finished, the vessel was allowed to cool to room temperature in water. The mixture was diluted with saturated NH$_4$Cl solution (2 mL), extracted with ethyl acetate (10 mL). The mixture was filtered over a pad of celite, and the residue was washed with ethyl acetate (2 x 10 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$, sampled for GC-MS analysis, and then concentrated under reduced pressure. The crude product was then purified by chromatography to afford purified product.

## 3. Condition Optimization

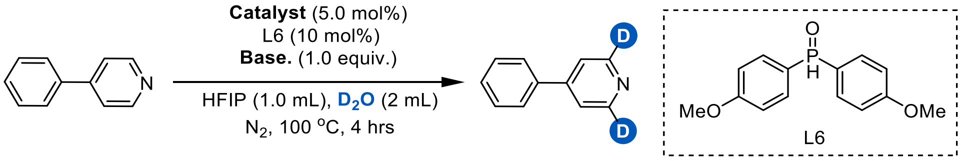
The optimization was conducted with the ligand screening (Table S1) , where the **L4** and **L6** was defined as the most potent ligand for this transformation. Meanwhile, electron-withdrawing ligand

**Table S1 Optimization of Ligand [a,b]**



[a] Reaction condition unless noted otherwise: Substrate (1.0 mmol), Pd(TFA)$_2$ (5.0 mol%), **Ligand** (10 mol%), Na$_2$CO$_3$ (1.0 equiv.), HFIP (1.0 mL) and D$_2$O (2 mL), N$_2$, 100 °C for 4 hrs. [b] D$_{MS}$ and %Recov. were determined by GC-MS and HPLC analysis.

**Table S2 Optimization of Catalytic system [a,b]**



| entry | Catalyst | Base. | $D_{MS}$ | %Recov. |
|---|---|---|---|---|
| 1 | $Pd(TFA)_2$ | $Na_2CO_3$ | 1.78 | 93 |
| 2 | $Pd(OAc)_2$ | $Na_2CO_3$ | 1.19 | 90 |
| 3 | $Pd(OPiv)_2$ | $Na_2CO_3$ | 1.64 | 94 |
| 4 | $PdCl_2$ | $Na_2CO_3$ | 1.67 | 91 |
| 5 | $Pd(dba)_2$ | $Na_2CO_3$ | trace | 95 |
| 6 | Pd/C | $Na_2CO_3$ | trace | 92 |
| 7 | Ru/C | $Na_2CO_3$ | trace | 93 |
| 8 | $Cu(OAc)_2$ | $Na_2CO_3$ | trace | 94 |
| 9 | $Ni(CF_3SO_3)_2$ | $Na_2CO_3$ | trace | 95 |
| 10 | $Fe(CF_3SO_3)_3$ | $Na_2CO_3$ | trace | 91 |
| 11 | $Al(CF_3SO_3)_3$ | $Na_2CO_3$ | trace | 93 |
| 12 | $Pd(TFA)_2$ | $Na_2CO_3$ | 1.78 | 93 |
| 13 | $Pd(TFA)_2$ | $K_2CO_3$ | 1.70 | 94 |
| 14 | $Pd(TFA)_2$ | $Cs_2CO_3$ | 1.76 | 91 |
| 15 | $Pd(TFA)_2$ | NaOAc | 0.76 | 95 |
| 16 | $Pd(TFA)_2$ | NaOPiv | 1.34 | 93 |
| 17 | $Pd(TFA)_2$ | $Na_2C_2O_4$ | 0.48 | 92 |
| 18 | $Pd(TFA)_2$ | NaOH | 1.28 | 90 |
| 19 | $Pd(TFA)_2$ | $Et_3N$ | 1.45 | 88 |

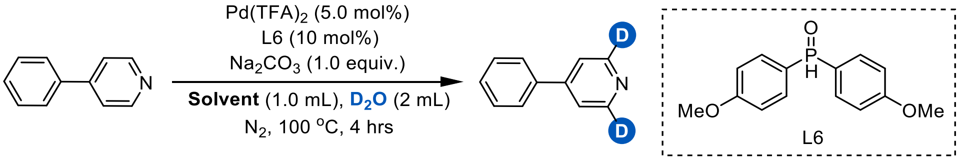
[a] Reaction condition unless noted otherwise: Substrate (1.0 mmol), **Catalyst** (5.0 mol%), L6 (10 mmol%), **Base.** (1.0 equiv.), HFIP (1 mL) and $D_2O$ (2 mL), $N_2$, 100 °C for 4 hrs. [b] $D_{MS}$ and %Recov. were determined by GC-MS and HPLC analysis.

**L7** with chloride substitution rendered considerably lower performance. We also tested the potential of triphenylphosphine and corresponding oxide (**L11** and **L12**), both ligands failed to offer any trace of deuteration.

Subsequently, a detailed optimization was conducted to improve the protocol's performance as listed in Table S2. The initial test with $Pd^{2+}$ rendered considerable labelling efficient. However, the $Pd^0$ catalyst of $Pd(dba)_2$ and Pd/C failed the transformation. A same failure was obtained with Ru/C. Further examination of metal catalysis didn't render any positive results. And the following examination of base showed the $Na_2CO_3$ remained the optimal choice.

Then, we shifted our attention toward the component of solvent system (Table S3). Again, HFIP showed the optimal result, where other solvent failed to render acceptable results. Therefore, the HFIP should not be an innocent bystander for the transformation, but also act as a key player in the reaction, including the protium/deuteron shuffler between organic and aqueous phase, and the recent discussed roles in accelerating the C-H activation.[2]

## Table S3 Optimization of solvent system and control experiment [a, b]

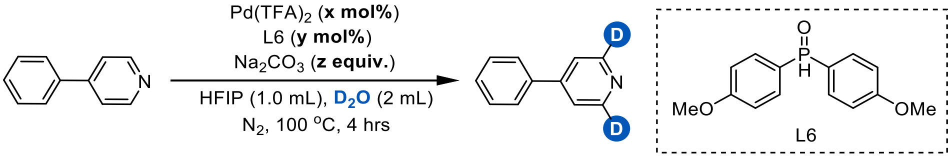


| Entry | Condition Deviation | $D_{MS}$ | %Recov. |
|---|---|---|---|
| 1 | HFIP | 1.78 | 93 |
| 2 | DCE | 0.09 | 96 |
| 3 | PhMe | trace | 90 |
| 4 | $CH_3CN$ | 0.12 | 87 |
| 5 | 1,4- Dioxane | trace | 92 |
| 6 | DMF | trace | 89 |
| 7 | $Pd(TFA)_2$ absence | trace | 94 |
| 8 | **L6** absence | trace | 97 |
| 9 | $Na_2CO_3$ absence | 0.16 | 96 |
| 10 | Without $N_2$ protection | trace | 95 |
| 11 | Add 10 mol% AgTFA | trace | 91 |
| 12 | $PdCl_2$/KOH instead of $Pd(TFA)_2/Na_2CO_3$ | 1.62 | 90 |
| 13 | $Ph_2P(O)OH$ instead of **L6** | trace | 92 |

[a] Reaction condition unless noted otherwise: Substrate (1.0 mmol), Pd source (5.0 mol%), Ligand (10 mol%), Base. (1.0 equiv.), **Solvent** (1.0 mL) and $D_2O$ (2 mL), $N_2$, 100 °C for 4 hrs. [b] $D_{MS}$ and %Recov. were determined by GC-MS and HPLC analysis.

Finally, after a detailed adjustment of components loading (Table S4), the optimal condition comes to $Pd(TFA)_2$ (5 mol%), **L6** (5 mol%), $Na_2CO_3$ (1.0 equiv.), HFIP (1.0 mL), with $D_2O$ (2 mL), heating in a sealed vessel with $N_2$ protection for 6 hours.

## Table S4 Optimization of using of catalytic system [a, b]

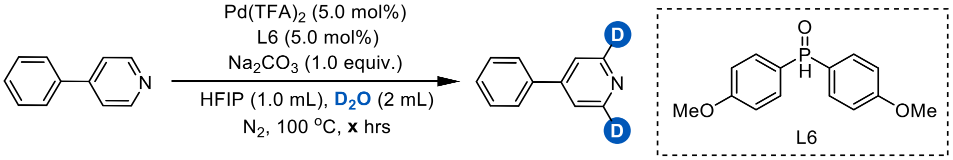


| entry | L6 (mol%) | $Pd(TFA)_2$ (mol%) | $Na_2CO_3$ (mol%) | $D_{MS}$ | %Recov. |
|---|---|---|---|---|---|
| 1 | 2.5 | 5.0 | 1.0 | 1.51 | 96 |
| 2 | 5.0 | 5.0 | 1.0 | 1.85 | 95 |
| 3 | 10 | 5.0 | 1.0 | 1.78 | 93 |
| 4 | 15 | 5.0 | 1.0 | 0.06 | 90 |
| 5 | 20 | 5.0 | 1.0 | trace | 86 |
| 6 | 5.0 | 5.0 | 1.0 | 1.85 | 95 |
| 7 | 5.0 | 10 | 1.0 | 1.88 | 92 |
| 8 | 5.0 | 5.0 | 0.5 | 1.71 | 96 |
| 9 | 5.0 | 5.0 | 1.0 | 1.85 | 95 |
| 10 | 5.0 | 5.0 | 2.0 | 1.86 | 91 |

[a] Reaction condition unless noted otherwise: Substrate (1.0 mmol), $Pd(TFA)_2$ (**x mol%**), L6 (**y mol%**), $Na_2CO_3$ (**z equiv.**), HFIP (1.0 mL) and $D_2O$ (2 mL), $N_2$, 100 °C for 4 hrs. [b] $D_{MS}$ and %Recov. were determined by GC-MS and HPLC analysis.

## 4. Kinetic profile for deuteration process

**Table S5 Reaction kinetics experiment and control experiment** [a, b]



| entry | Reaction Time (h) | $D_{MS}$ | %Recov. |
|---|---|---|---|
| 1 | 0.5 h | 0.10 | / |
| 2 | 1.0 h | 0.25 | / |
| 3 | 1.5 h | 0.52 | / |
| 4 | 2.0 h | 1.07 | / |
| 5 | 3.0 h | 1.59 | / |
| 6 | 4.0 h | 1.85 | / |
| 7 | 5.0 h | 1.89 | / |
| 8 | 6.0 h | 1.90 | 94 |

[a] Reaction condition unless noted otherwise: $Pd(TFA)_2$ (5.0 mol%), L6 (5.0 mmol%), $Na_2CO_3$ (1.0 equiv.), HFIP (1 mL) and $D_2O$ (2 mL), $N_2$, 100 °C for **x hrs**. [b] $D_{MS}$ and %Recov. were determined by GC-MS and HPLC analysis.

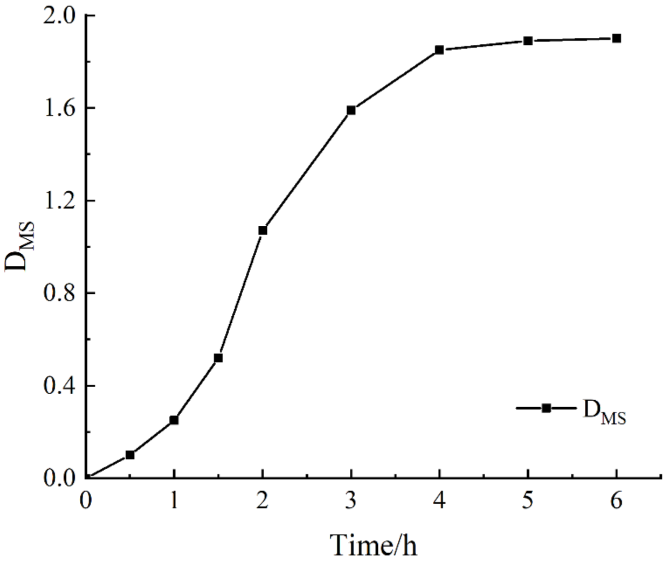


**Figure S1** Kinetic profile of the α-selective deuteration of 4-phenyl pyridine

## 5. Preliminary Mechanistic Investigation

### 1) Radical Trapping Experiment

Since the recent advance in α-selective functionalization of N-heterocycles, the possibility of radical process was examined for the protocol. As expected, no significant influence was observed after TEMPO (1.0 equiv.) addition.

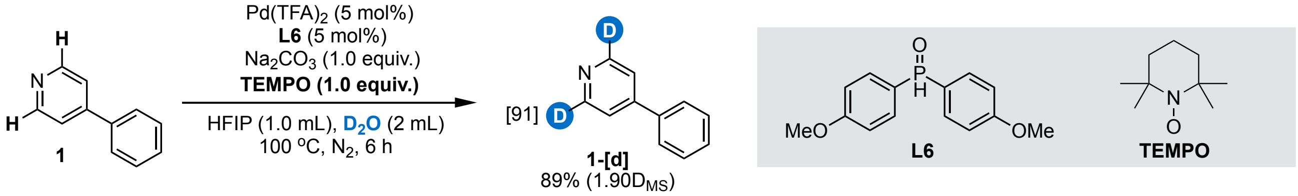


**Figure S2** Radical Trapping Experiment.

### 2) Theoretical Calculation

*Calculation Method:* Density Functional theory (DFT) study was performed with Gaussian 16.[3] Geometry optimization of ground state and transition state were conducted in the gas phases with hybrid-GGA functional PBE0[4] and split valence def2-SVP[5] basis set. Grimme's GFN-xTB program package[6] was used for transition state search, with the assistance of a Gaussain-GFN-xTB interface developed by Lu.[7] Grimme's dispersion correction D3 method was applied for optimization.[8] Both local minima and transition structures are confirmed by vibrational frequencies with 0 and 1 imaginary frequency, respectively. All transition structures are checked by intrinsic reaction coordinate (IRC) calculation. The 3D structures were visualized with CYLview[9].

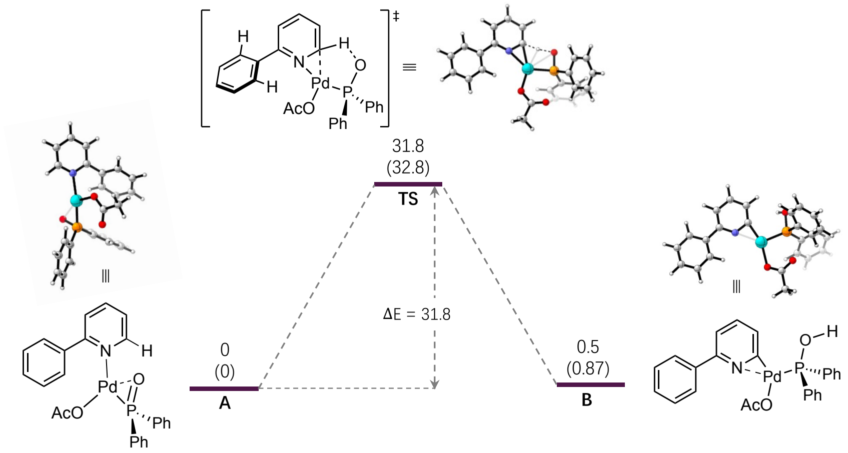


**Figure S3** Results of Preliminary DFT calculation (PBE0D3/def2-SVP)

**Table S6 Energy summary**

| species | EE | ZPE | Energy Corr. | Entropy Corr. | Gibbs Corr. | ΔG | ΔH |
|---|---|---|---|---|---|---|---|
| **A** | -1713.163681 | 0.413802 | 0.442918 | 0.443862 | 0.349662 | 0.0 | 0.0 |
| **TS** | -1713.105362 | 0.408004 | 0.436875 | 0.437819 | 0.342036 | 31.8 | 32.8 |
| **B** | -1713.162248 | 0.413718 | 0.442868 | 0.443812 | 0.349063 | 0.52 | 0.87 |

## Table S7 Coordination for calculated structures

**A**

0 1

| | | | |
|---|---|---|---|
| C | 3.115835 | 2.432932 | -1.205443 |
| C | 3.521008 | 0.312278 | -0.358621 |
| C | 4.899854 | 0.553808 | -0.36541 |
| C | 5.377881 | 1.781024 | -0.807576 |
| C | 4.469676 | 2.743169 | -1.243336 |
| H | 2.360652 | 3.154922 | -1.528064 |
| H | 5.581183 | -0.234413 | -0.041558 |
| H | 6.451725 | 1.98208 | -0.822239 |
| H | 4.797997 | 3.718892 | -1.604575 |
| Pd | 0.522789 | 0.896006 | -0.38762 |
| P | -1.513259 | 0.333773 | -0.689812 |
| O | -0.970156 | 0.782163 | -2.086112 |
| C | -1.933441 | -1.426618 | -0.764349 |
| C | -1.74095 | -2.066539 | -1.995188 |
| C | -2.364133 | -2.155431 | 0.350664 |
| C | -1.984927 | -3.433506 | -2.111977 |
| H | -1.393105 | -1.474899 | -2.845672 |
| C | -2.602455 | -3.521895 | 0.223787 |
| H | -2.47026 | -1.64967 | 1.311621 |
| C | -2.413687 | -4.162023 | -1.002226 |
| H | -1.838446 | -3.932016 | -3.073327 |
| H | -2.933038 | -4.094875 | 1.093595 |
| H | -2.601261 | -5.234969 | -1.092656 |
| C | -2.956431 | 1.255311 | -0.1229 |
| C | -4.239025 | 0.87014 | -0.52631 |
| C | -2.783191 | 2.384572 | 0.682587 |
| C | -5.34378 | 1.621762 | -0.131492 |
| H | -4.373935 | -0.020658 | -1.14531 |
| C | -3.889882 | 3.132447 | 1.073068 |
| H | -1.777546 | 2.660387 | 1.00889 |
| C | -5.169113 | 2.751931 | 0.666087 |
| H | -6.345984 | 1.32164 | -0.446398 |
| H | -3.755564 | 4.012716 | 1.705968 |
| H | -6.037251 | 3.337884 | 0.977878 |
| O | -1.154266 | -0.037304 | 1.984219 |
| C | -0.012744 | 0.258188 | 2.343303 |
| O | 0.914981 | 0.743016 | 1.600697 |
| N | 2.655816 | 1.258261 | -0.768569 |
| C | 2.962243 | -0.976982 | 0.10365 |
| C | 3.377121 | -1.527883 | 1.320376 |
| C | 1.965436 | -1.627485 | -0.638474 |
| C | 2.785364 | -2.692328 | 1.803013 |
| H | 4.132563 | -1.010617 | 1.916553 |
| C | 1.376121 | -2.793009 | -0.155107 |
| H | 1.656949 | -1.223335 | -1.606236 |
| C | 1.778194 | -3.32036 | 1.070817 |
| H | 3.100179 | -3.101519 | 2.765958 |
| H | 0.587363 | -3.279975 | -0.732548 |
| H | 1.301884 | -4.2246 | 1.456717 |
| C | 0.417345 | 0.024247 | 3.775913 |
| H | 1.043318 | -0.881289 | 3.800023 |
| H | 1.030777 | 0.859793 | 4.138684 |
| H | -0.456672 | -0.125682 | 4.420779 |

**TS**

0 1 Nimag =1 (-1702.3392)

| | | | |
|---|---|---|---|
| C | -1.400448 | -1.720929 | 0.988386 |
| C | -3.632798 | -1.09065 | 0.574697 |
| C | -4.076161 | -2.270467 | 1.195845 |
| C | -3.148318 | -3.166083 | 1.7133 |
| C | -1.779894 | -2.90306 | 1.61724 |
| H | -0.024675 | -1.652428 | 1.003035 |
| H | -5.140726 | -2.490769 | 1.268167 |
| H | -3.49603 | -4.083452 | 2.195402 |
| H | -1.027291 | -3.586695 | 2.012948 |
| Pd | -0.393615 | -0.016704 | 0.045945 |
| P | 1.757364 | -0.485021 | 0.310174 |
| O | 1.343667 | -1.785584 | 1.109095 |
| C | 2.778522 | -1.032548 | -1.087553 |
| C | 2.756647 | -2.406493 | -1.359285 |
| C | 3.570541 | -0.177664 | -1.866053 |
| C | 3.521618 | -2.923744 | -2.402458 |
| H | 2.145973 | -3.054652 | -0.726709 |
| C | 4.335736 | -0.7046 | -2.902458 |
| H | 3.565347 | 0.893212 | -1.661758 |
| C | 4.31152 | -2.073612 | -3.174325 |
| H | 3.503884 | -3.996535 | -2.609382 |
| H | 4.955655 | -0.038461 | -3.507485 |
| H | 4.912943 | -2.478621 | -3.992146 |
| C | 2.796477 | 0.574394 | 1.351684 |
| C | 4.151255 | 0.273971 | 1.520923 |
| C | 2.223524 | 1.630853 | 2.06469 |
| C | 4.926576 | 1.030909 | 2.39769 |
| H | 4.602486 | -0.551083 | 0.964073 |
| C | 3.000188 | 2.384295 | 2.939379 |
| H | 1.16552 | 1.866456 | 1.920377 |
| C | 4.352887 | 2.085322 | 3.105982 |
| H | 5.985818 | 0.795608 | 2.52619 |
| H | 2.549983 | 3.213356 | 3.490411 |
| H | 4.963376 | 2.679634 | 3.790255 |
| O | 1.798735 | 1.952927 | -1.013486 |
| C | 0.661968 | 2.33235 | -1.254983 |

|  |  |  |  |
|---|---|---|---|
| O | -0.422513 | 1.710259 | -0.92443 |
| N | -2.316466 | -0.876185 | 0.501865 |
| C | -4.530633 | -0.070217 | -0.008317 |
| C | -5.924785 | -0.171128 | 0.110704 |
| C | -3.993441 | 1.030284 | -0.695838 |
| C | -6.759056 | 0.794799 | -0.442319 |
| H | -6.375373 | -1.007671 | 0.647133 |
| C | -4.831153 | 1.993676 | -1.248107 |
| H | -2.91237 | 1.136644 | -0.799745 |
| C | -6.215344 | 1.881507 | -1.125626 |
| H | -7.841983 | 0.698313 | -0.336435 |
| H | -4.393092 | 2.841244 | -1.780018 |
| H | -6.870411 | 2.640192 | -1.560316 |
| C | 0.399824 | 3.62119 | -2.000766 |
| H | -0.084277 | 3.391569 | -2.961503 |
| H | -0.295086 | 4.251682 | -1.428303 |
| H | 1.340776 | 4.154491 | -2.177347 |

**B**

0 1

|  |  |  |  |
|---|---|---|---|
| C | -1.391603 | 1.081345 | -0.879278 |
| C | -3.710512 | 0.874743 | -0.662289 |
| C | -3.872254 | 2.053026 | -1.409377 |
| C | -2.750634 | 2.731252 | -1.883458 |
| C | -1.463761 | 2.254076 | -1.62726 |
| H | 1.043276 | 1.037377 | -2.384644 |
| H | -4.868109 | 2.450019 | -1.604698 |
| H | -2.885887 | 3.652992 | -2.456026 |
| H | -0.566729 | 2.768179 | -1.974097 |
| Pd | -0.382149 | -0.280261 | 0.01679 |
| P | 1.70464 | 0.34531 | -0.425736 |
| O | 1.657588 | 1.395006 | -1.731257 |
| C | 2.586172 | 1.486389 | 0.677976 |
| C | 2.129937 | 2.808442 | 0.73411 |
| C | 3.689494 | 1.097555 | 1.444111 |
| C | 2.774888 | 3.735745 | 1.548591 |
| H | 1.268927 | 3.111507 | 0.135112 |
| C | 4.338331 | 2.033749 | 2.245036 |
| H | 4.01812 | 0.058844 | 1.424896 |
| C | 3.882964 | 3.350588 | 2.301545 |
| H | 2.410908 | 4.764924 | 1.592293 |
| H | 5.203256 | 1.727441 | 2.838154 |
| H | 4.391751 | 4.078806 | 2.937994 |
| C | 2.869394 | -0.88944 | -1.081151 |
| C | 4.11387 | -0.464698 | -1.557853 |
| C | 2.493837 | -2.229333 | -1.209922 |
| C | 4.987918 | -1.384341 | -2.133665 |
| H | 4.396961 | 0.587787 | -1.478823 |
| C | 3.36607 | -3.14238 | -1.796684 |
| H | 1.516523 | -2.552917 | -0.841619 |
| C | 4.615444 | -2.722709 | -2.253525 |
| H | 5.963992 | -1.051955 | -2.495188 |
| H | 3.069281 | -4.189255 | -1.894986 |
| H | 5.300984 | -3.441762 | -2.708594 |
| O | 2.076815 | -1.182074 | 1.567447 |
| C | 1.159236 | -1.988788 | 1.76887 |
| O | 0.019978 | -1.946974 | 1.196574 |
| N | -2.460465 | 0.454343 | -0.435783 |
| C | -4.826828 | 0.083875 | -0.106074 |
| C | -6.1598 | 0.335445 | -0.461475 |
| C | -4.556424 | -0.951739 | 0.800768 |
| C | -7.193467 | -0.422935 | 0.078948 |
| H | -6.400407 | 1.121855 | -1.179019 |
| C | -5.591091 | -1.707369 | 1.341448 |
| H | -3.520431 | -1.154257 | 1.076909 |
| C | -6.913461 | -1.445909 | 0.984087 |
| H | -8.225704 | -0.215762 | -0.2125 |
| H | -5.3618 | -2.507782 | 2.048625 |
| H | -7.725908 | -2.040564 | 1.408318 |
| C | 1.388512 | -3.151083 | 2.705684 |
| H | 0.448138 | -3.481391 | 3.164458 |
| H | 1.796281 | -3.989351 | 2.11862 |
| H | 2.126626 | -2.883445 | 3.471875 |

## 6. References

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# 7. Results of Substrate Deuteration

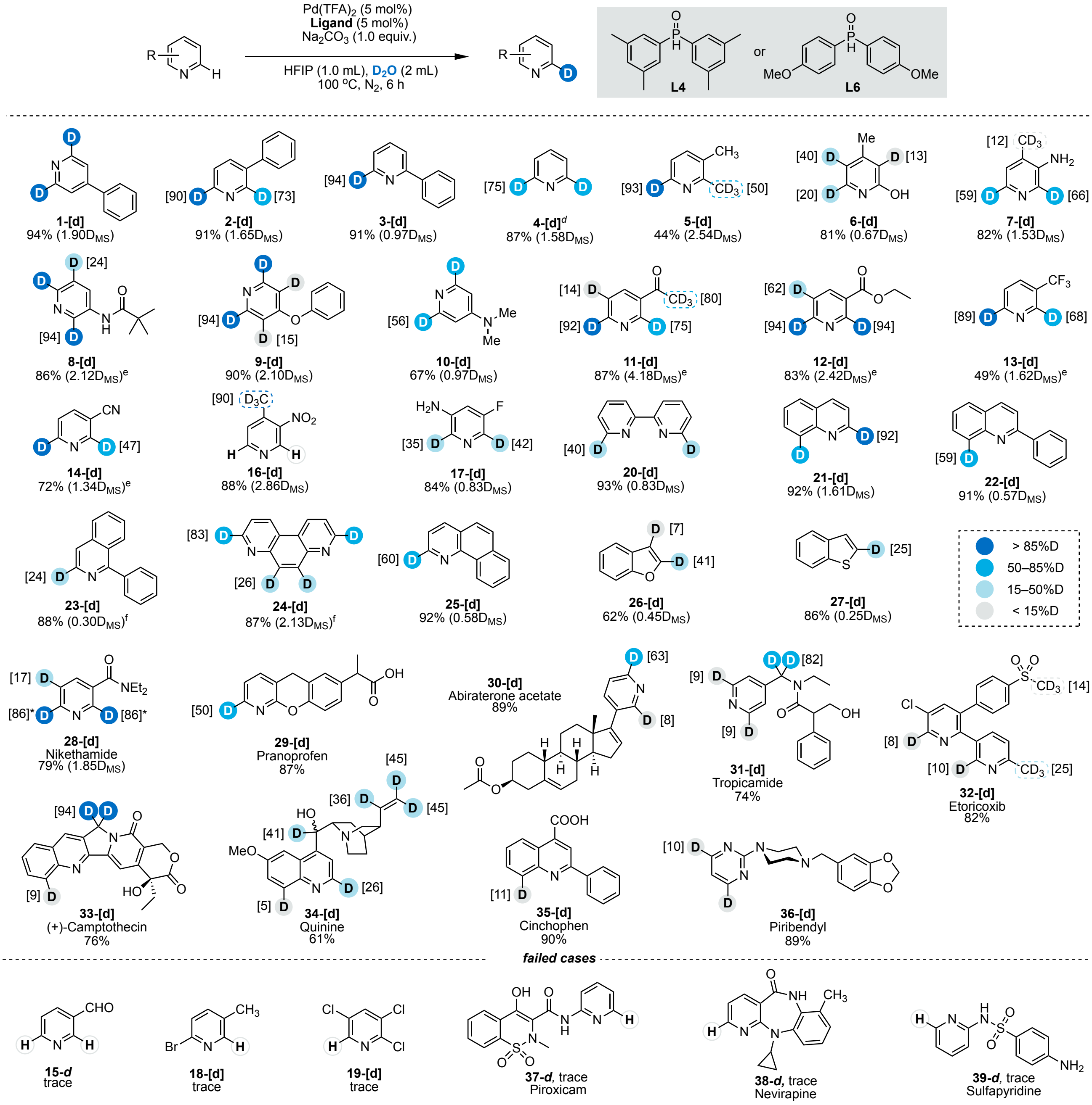
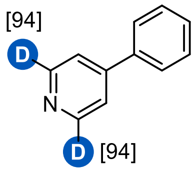


**Figure S4** Substrates tested during the investigation.

## Deuteration of 4-Phenylpyridine (1)



General procedure to afford **1-*d*** as white solid (145.3 mg, 94%) with D-incorporation 94% for 2, 6-position by $^1$H NMR; 1.90 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 6/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.71 – 8.60 (m, 2H), 7.67 – 7.61 (m, 2H), 7.53 – 7.42 (m, 5H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.68 – 8.64 (m, 0.12H, Labelled)**, 7.68 – 7.61 (m, 2H), 7.54 – 7.41 (m, 5H).

**Figure S2** $^1$H NMR spectrum comparison

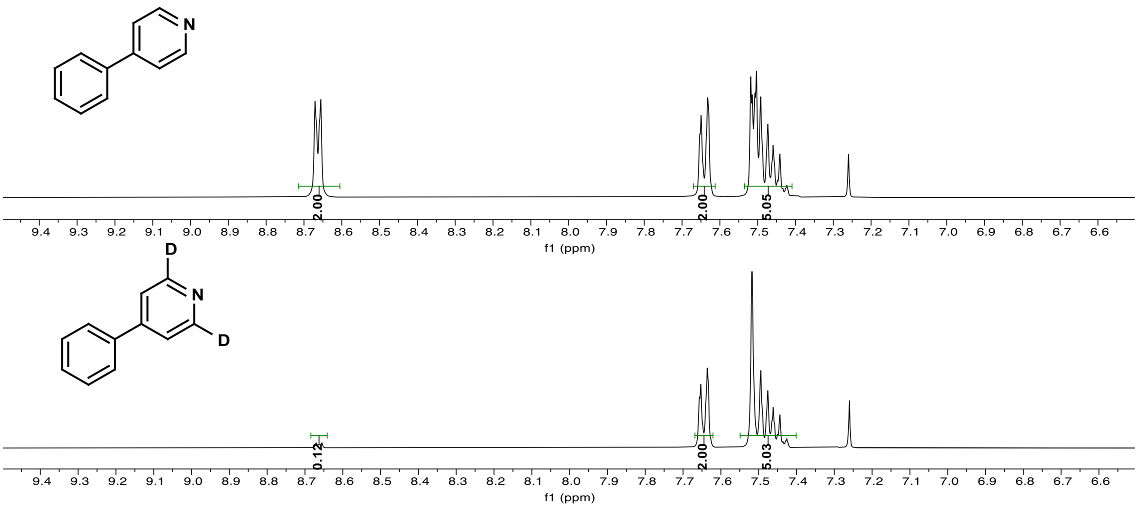


**Figure S3** GC-MS spectrum comparison

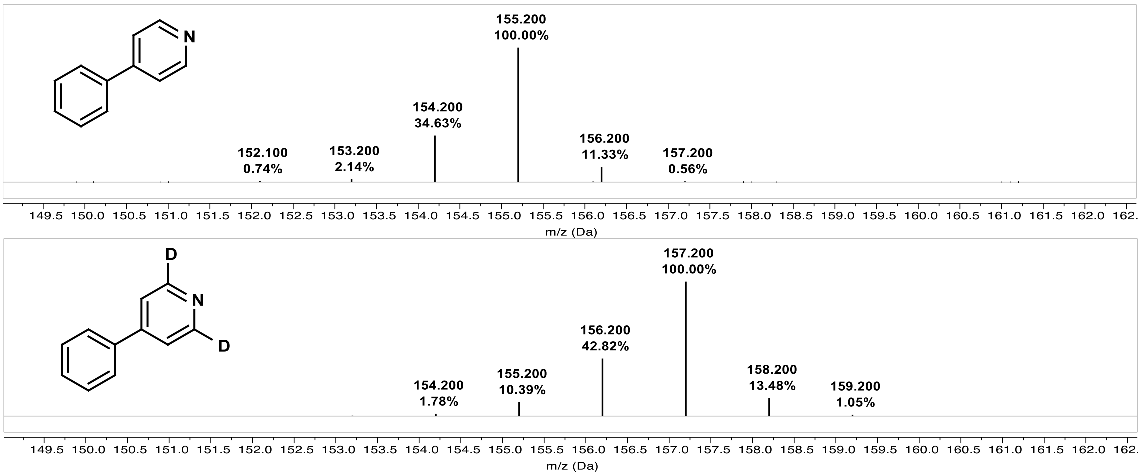


**Figure S4** $^{1}$H NMR of **1** in Chloroform-*d*

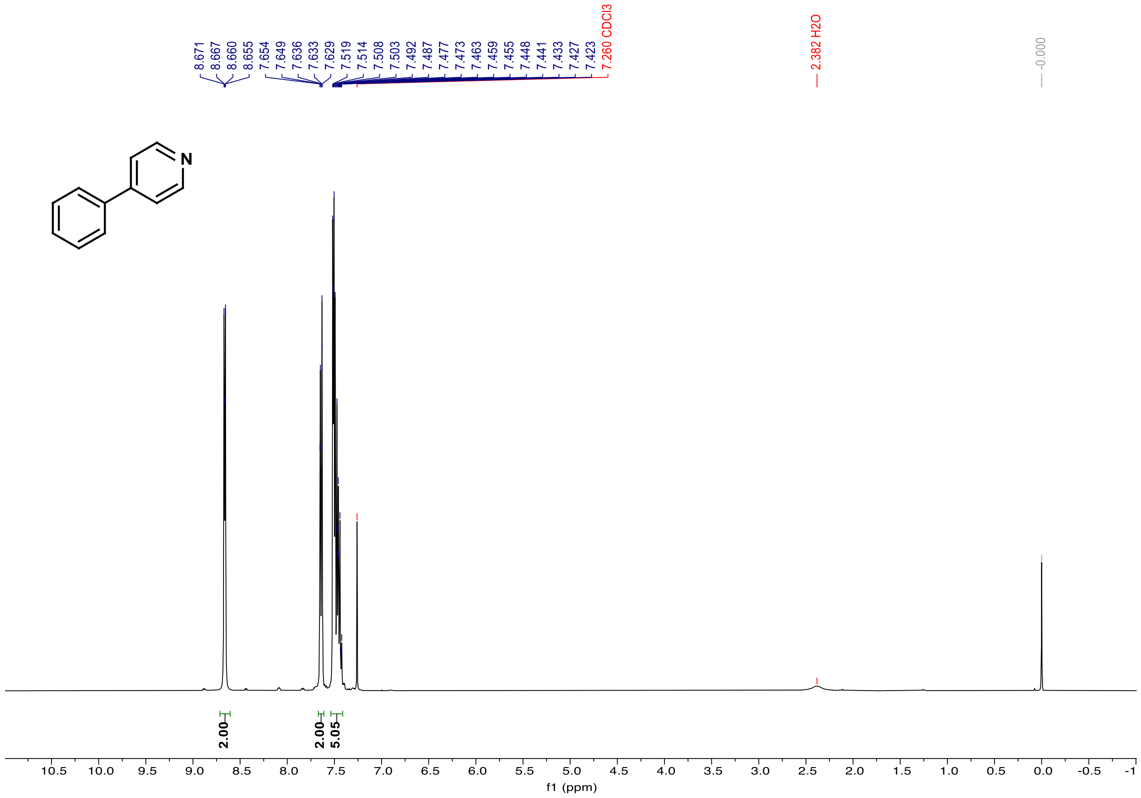
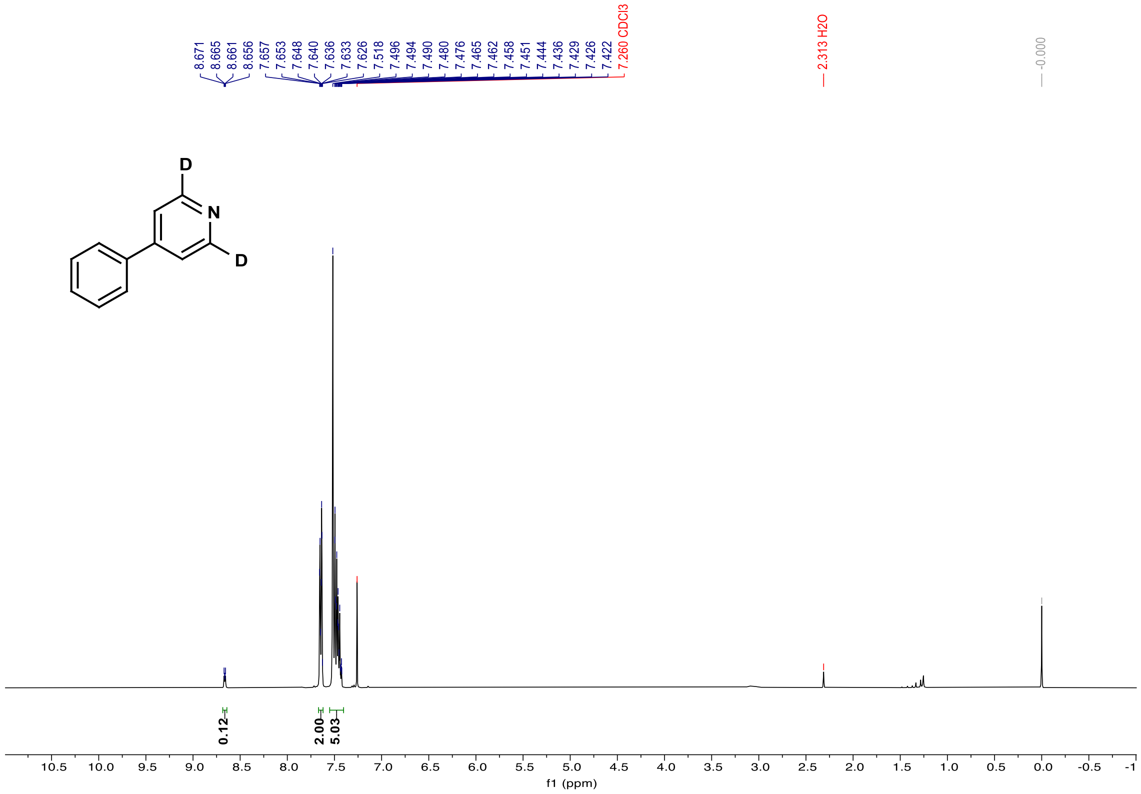
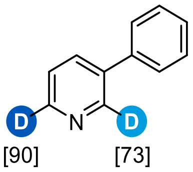


**Figure S5** $^{1}$H NMR of **1-*d*** in Chloroform-*d*



## Deuteration of 3-Phenylpyridine (2)



General procedure to afford **2-*d*** as white solid (141.8 mg, 91%) with D-incorporation 73% for 2-position and 90% for 6-position by $^1$H NMR; 1.65 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 6/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.86 (dd, *J* = 2.5, 0.9 Hz, 1H), 8.60 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.88 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.52 – 7.45 (m, 2H), 7.44 – 7.39 (m, 1H), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.86 (dd, *J* = 2.4, 0.9 Hz, 0.27H, Labelled)**, **8.59 (dd, *J* = 4.8, 1.7 Hz, 0.10H, Labelled)**, 7.88 (dd, *J* = 7.9, 1.7 Hz, 4H), 7.61 – 7.56 (m, 8H), 7.51 – 7.46 (m, 8H), 7.44 – 7.39 (m, 4H), 7.37 (d, *J* = 7.8 Hz, 4H).

**Figure S6** $^1$H NMR spectrum comparison

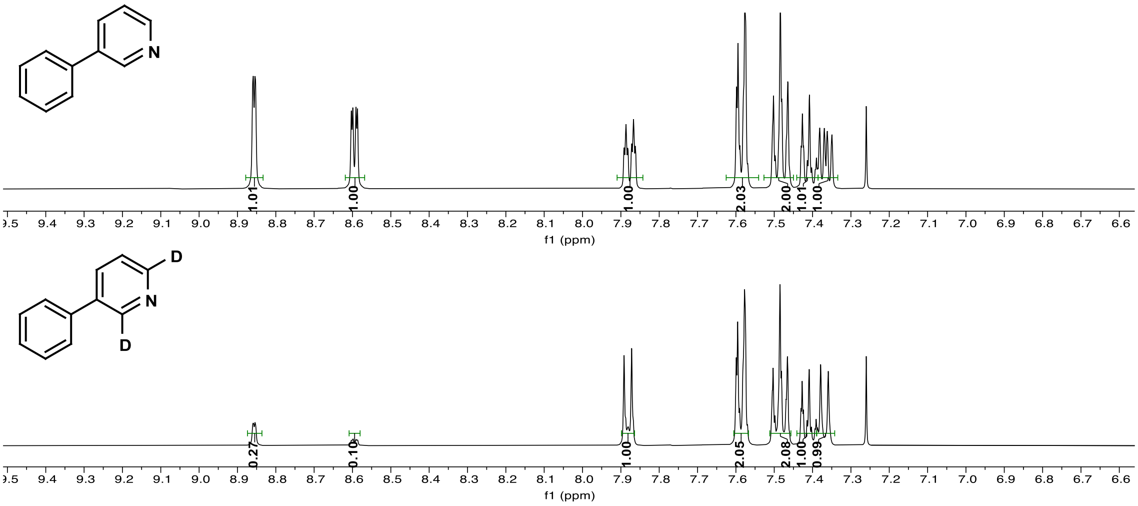


**Figure S7** GC-MS spectrum comparison

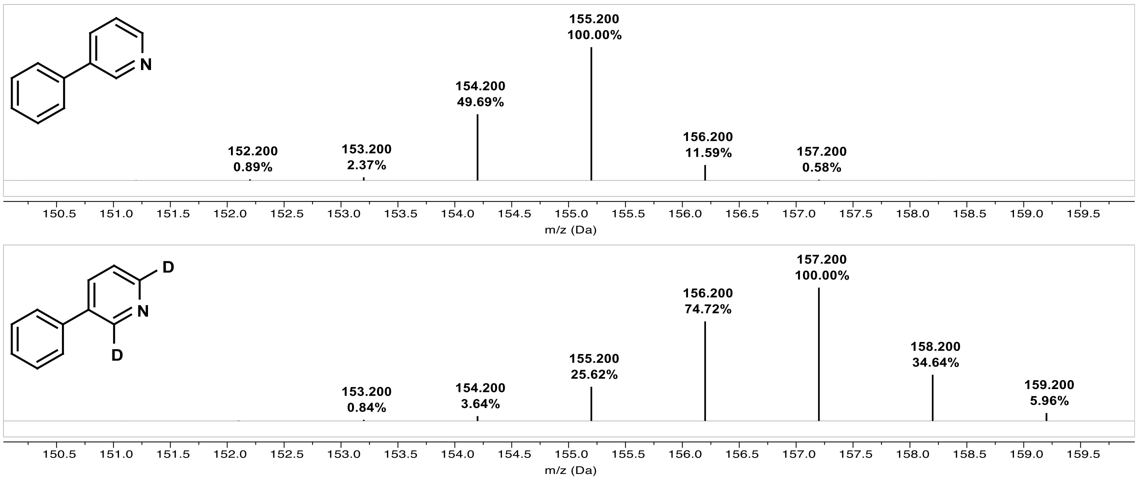


**Figure S8** $^1$H NMR of **2** in Chloroform-*d*

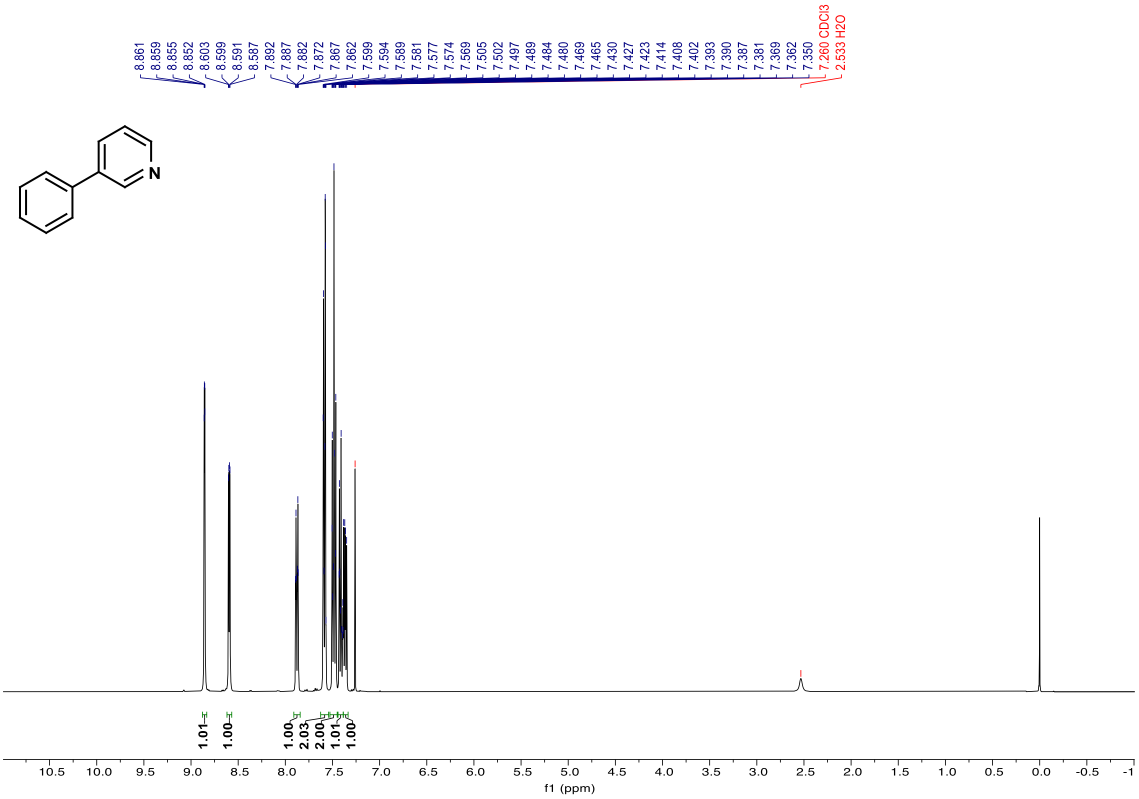
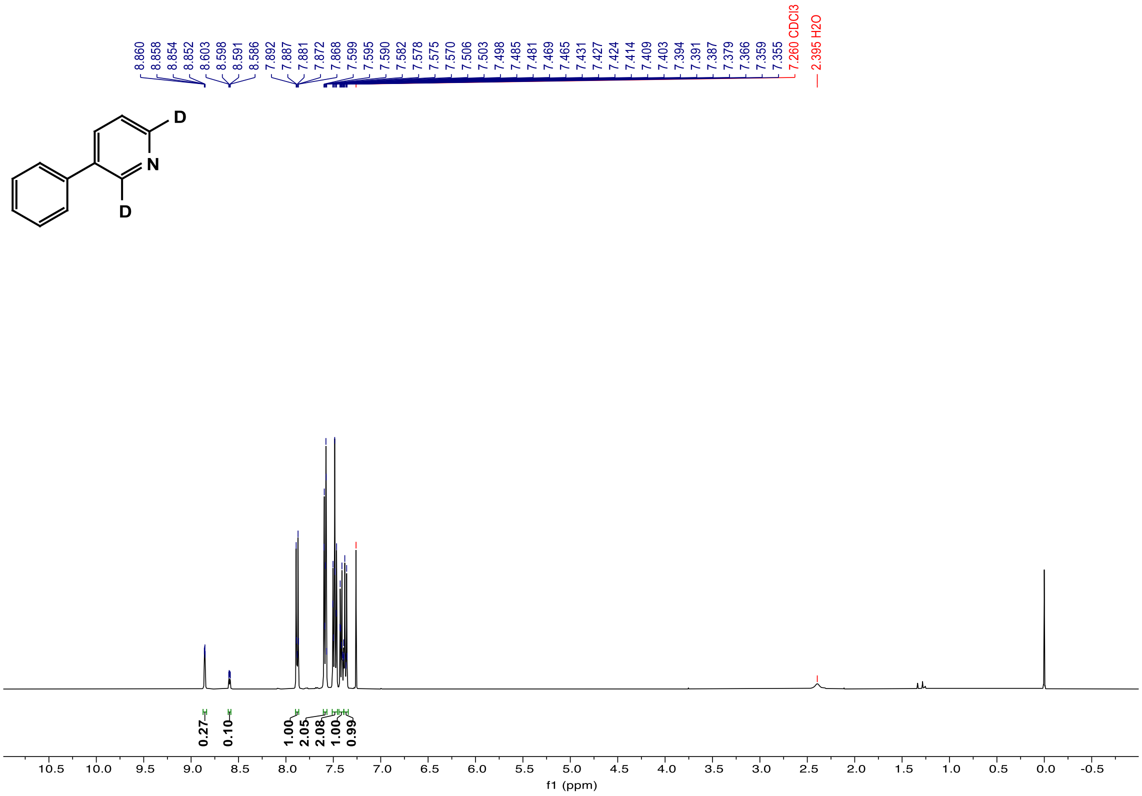
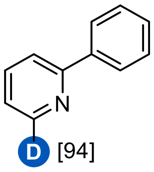


**Figure S9** $^1$H NMR of **2-*d*** in Chloroform-*d*



## Deuteration of 2-Phenylpyridine (3)



General procedure to afford **3-*d*** as slight yellow liquid (142.5 mg, 91%) with D-incorporation 94% for 6-position by $^1$H NMR; 0.97 D by GC-MS; $R_f = 0.35$ (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.73 – 8.67 (m, 1H), 8.02 – 7.97 (m, 2H), 7.79 – 7.71 (m, 2H), 7.51 – 7.45 (m, 2H), 7.45 – 7.39 (m, 1H), 7.23 (ddd, *J* = 6.7, 4.9, 2.2 Hz, 1H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.72 – 8.69 (m, 0.06H, Labelled)**, 8.04 – 7.95 (m, 2H), 7.79 – 7.72 (m, 2H), 7.52 – 7.45 (m, 2H), 7.45 – 7.39 (m, 1H), 7.24 (dd, *J* = 6.6, 2.1 Hz, 1H).

**Figure S10** $^1$H NMR spectrum comparison

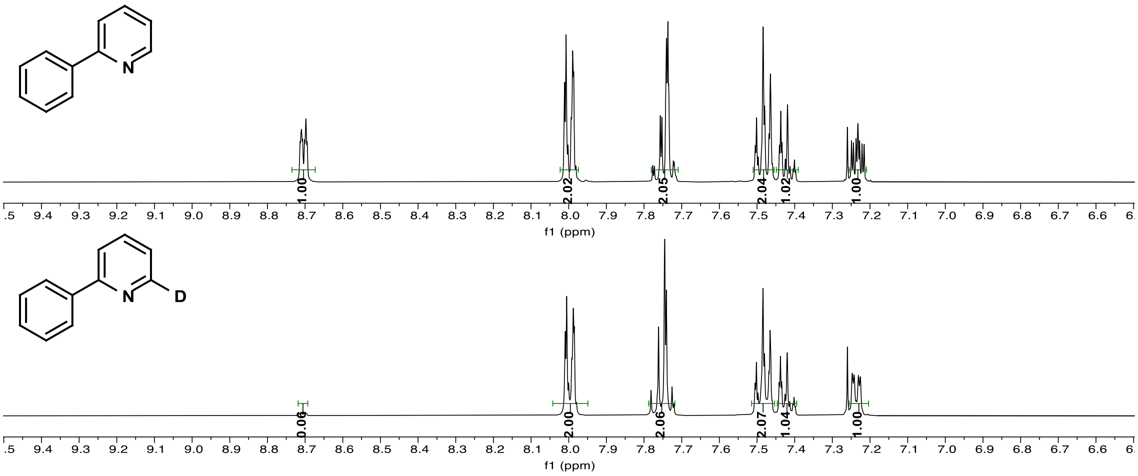


**Figure S11** GC-MS spectrum comparison

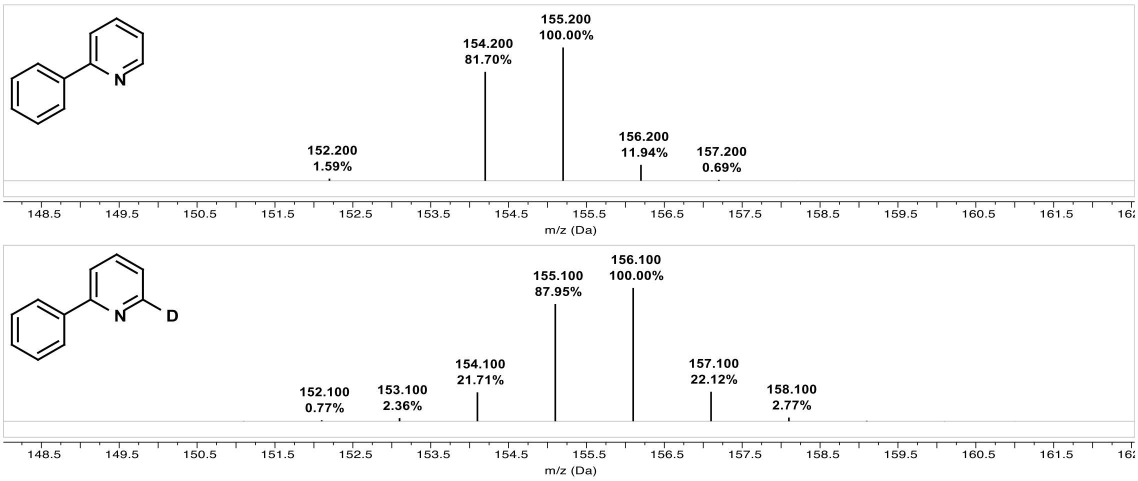


**Figure S12** $^1$H NMR of **3** in Chloroform-*d*

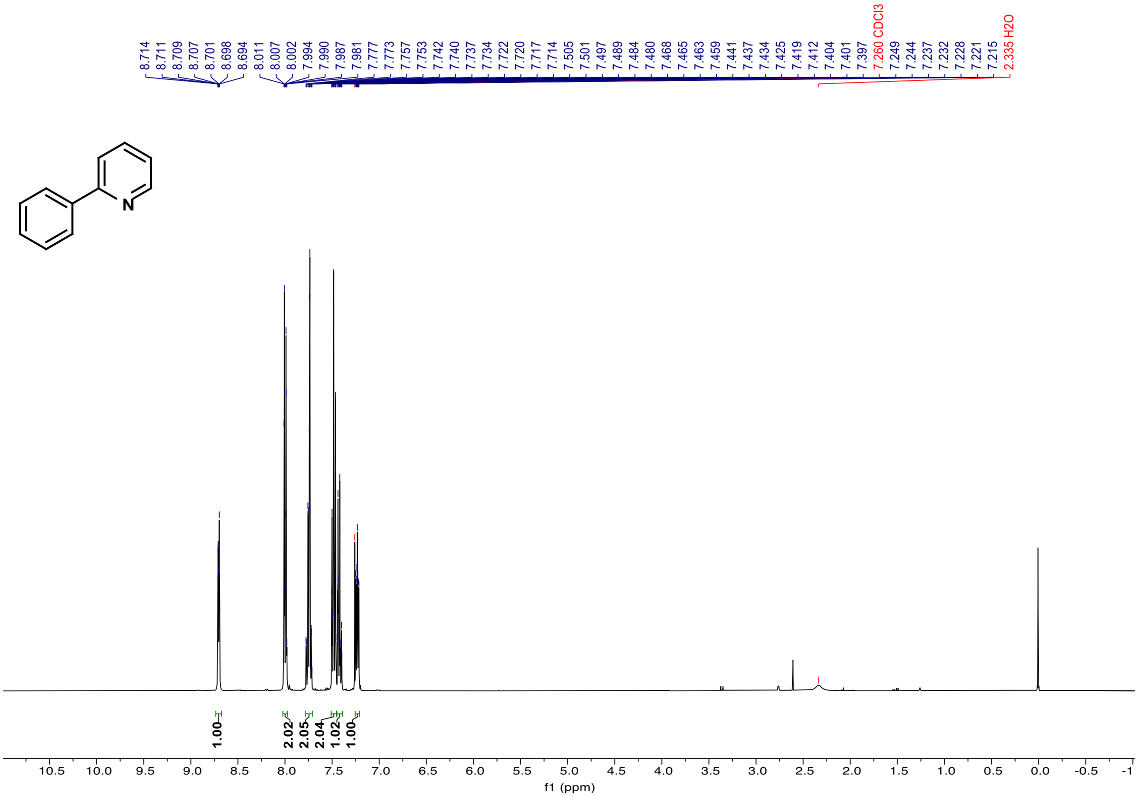
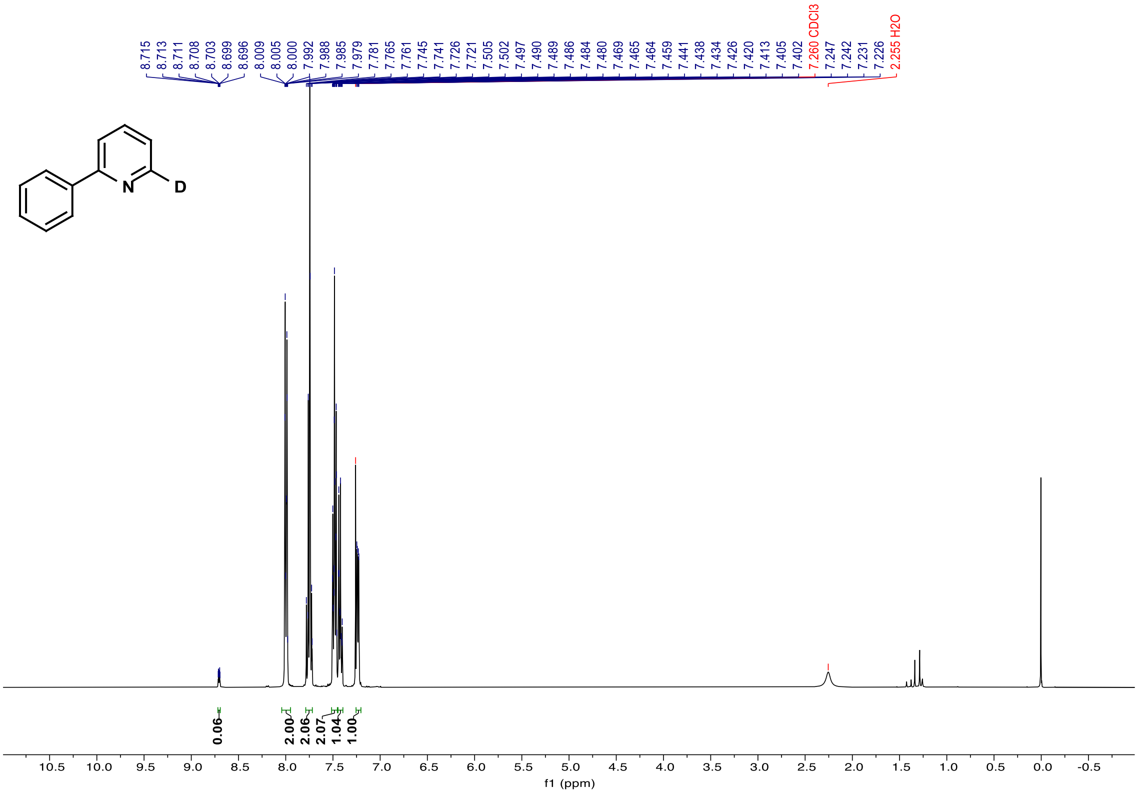
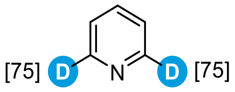


**Figure S13** $^1$H NMR of **3-*d*** in Chloroform-*d*



## Deuteration of Pyridine (4)



General procedure to afford **4-*d*** as slight yellow liquid (87% by GC) with D-incorporation 75% for α-position; 1.58 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.65 – 8.55 (m, 2H), 7.67 (tt, *J* = 7.6, 1.8 Hz, 1H), 7.27 (ddd, *J* = 7.7, 4.3, 1.6 Hz, 2H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.56 – 8.51 (m, 0.50H，Labelled)**, 7.79 (td, *J* = 7.7, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.7, 2.0 Hz, 2H).

**Figure S14** $^1$H NMR spectrum comparison

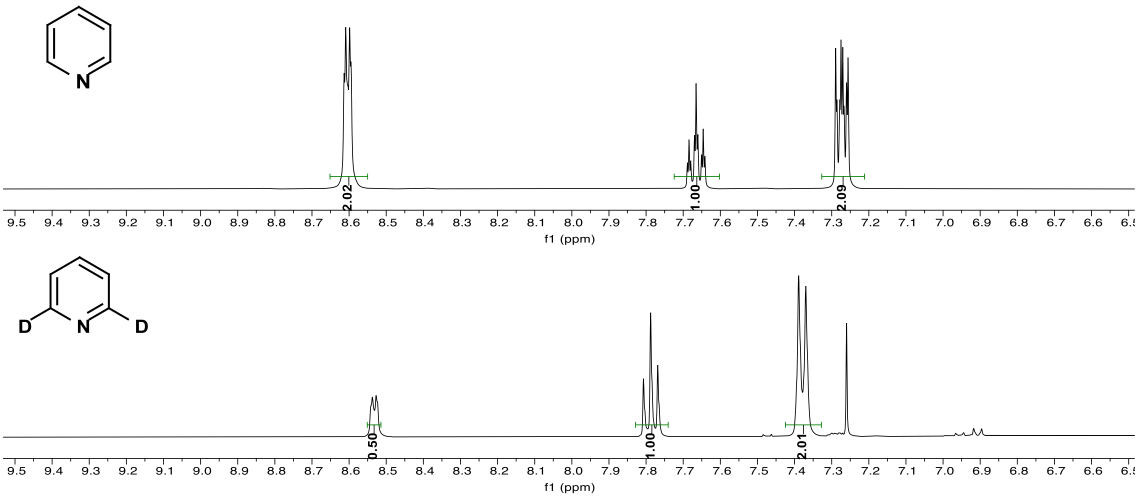


**Figure S15** GC-MS spectrum comparison

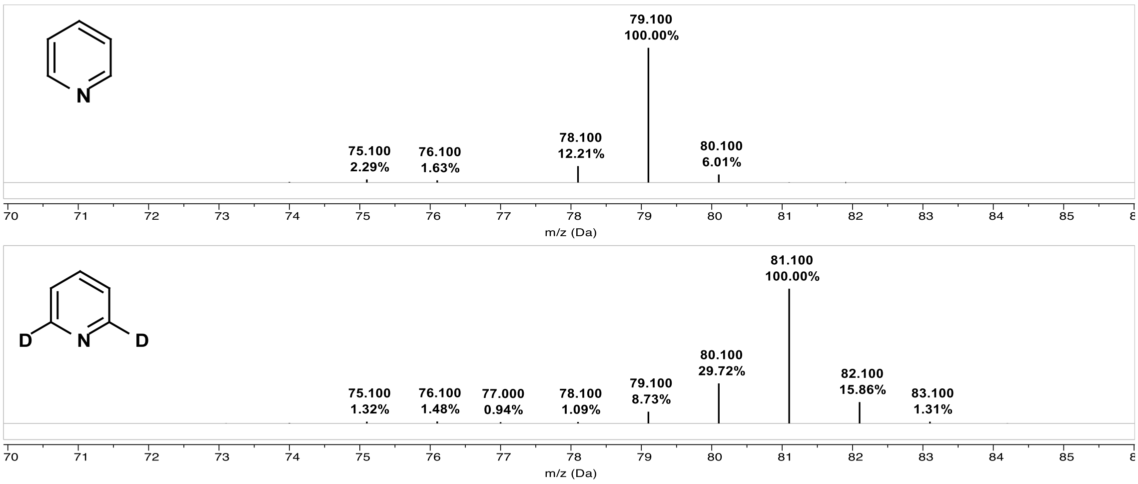


**Figure S16** $^1$H NMR of **4** in Chloroform-*d*

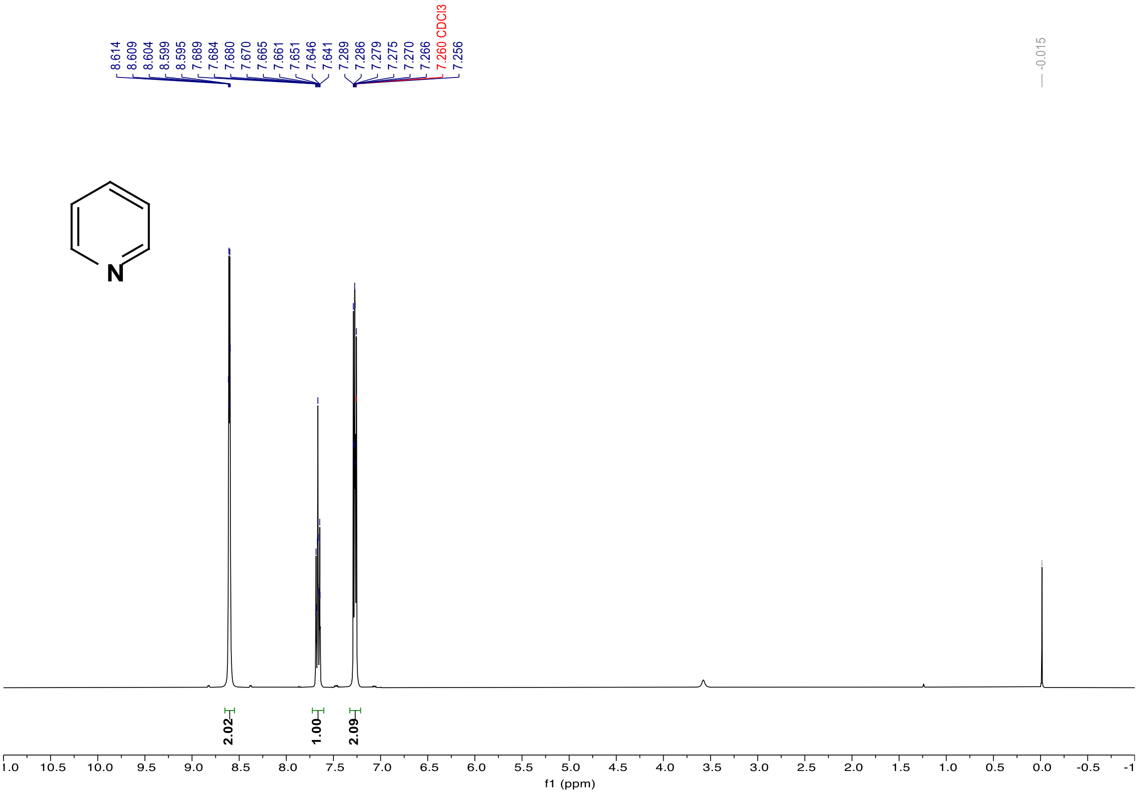
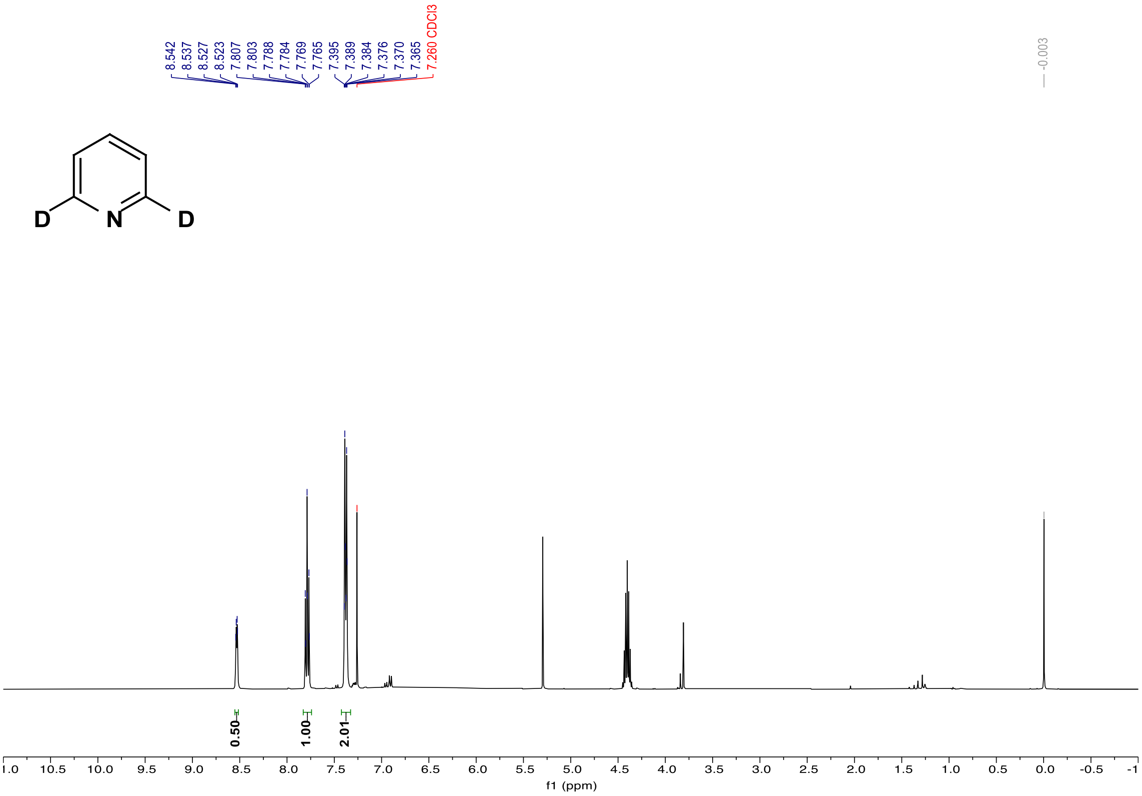
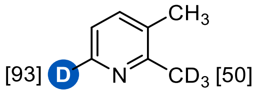


**Figure S17** $^1$H NMR of ***4-d*** in Chloroform-*d*



## Deuteration of 2,3-dimethylpyridine (5)



General procedure to afford **5-*d*** as slight yellow liquid (47.3 mg, 44%) with D-incorporation 93% for 6-position and 50% for 2-methyl by $^{1}$H NMR; 2.54 D by GC-MS; $R_f$ = 0.4 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.02 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.49 (s, 3H), 2.27 (s, 3H).
**NMR data for deuterated product:** $^{1}$H NMR (400 MHz, Chloroform-*d*) δ **8.28 (dd, *J* = 4.9, 1.8 Hz, 0.07H, Labelled)**, 7.35 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), **2.47 – 2.44 (m, 1.5H, Labelled)**, 2.24 (s, 3H).

**Figure S18** $^{1}$H NMR spectrum comparison

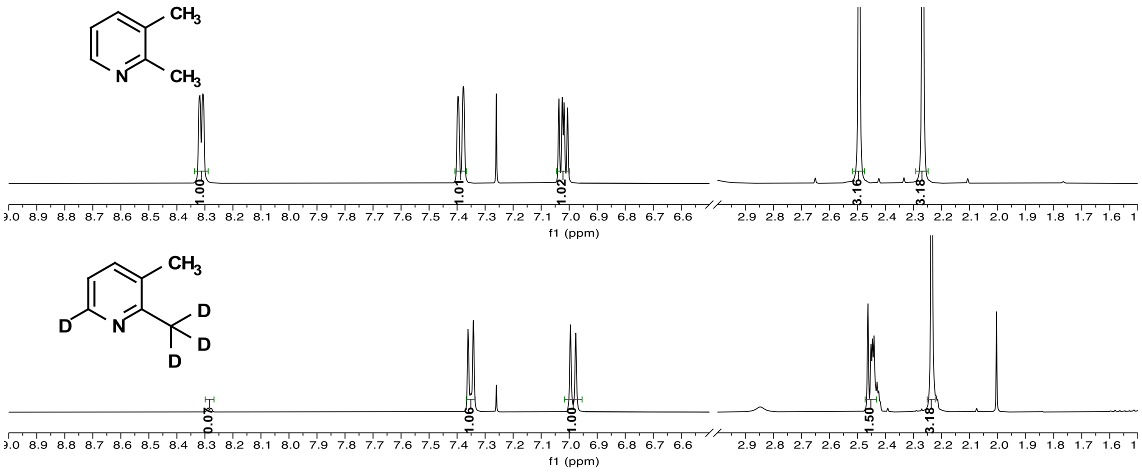


**Figure S19** GC-MS spectrum comparison

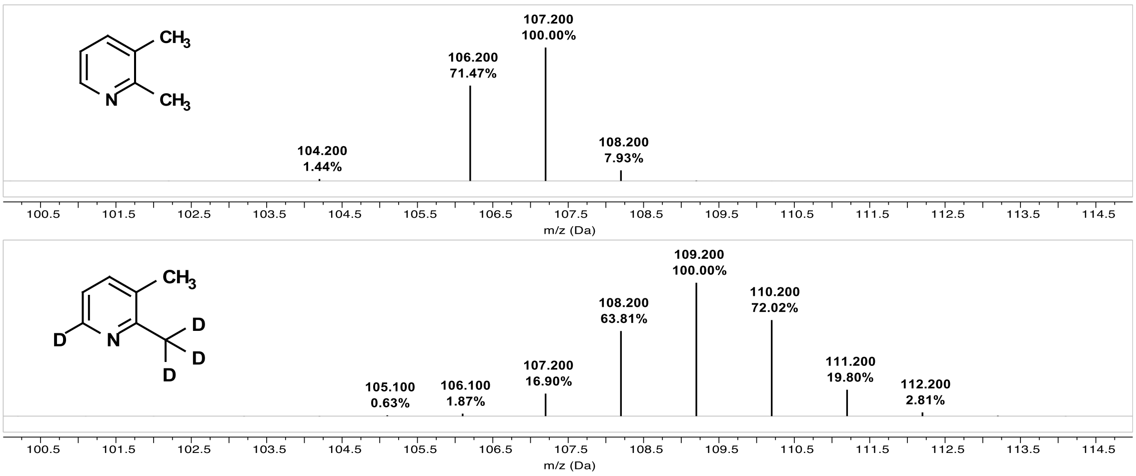


Figure S20 $^1$H NMR of **5** in Chloroform-*d*

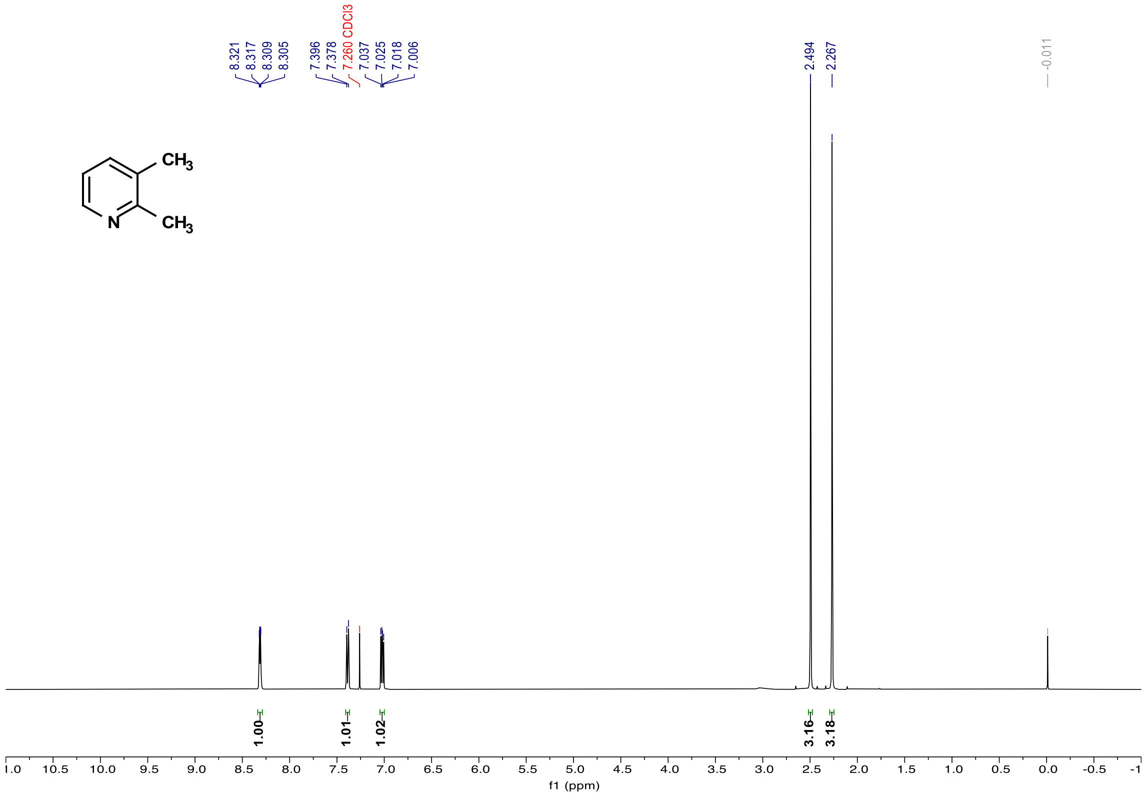
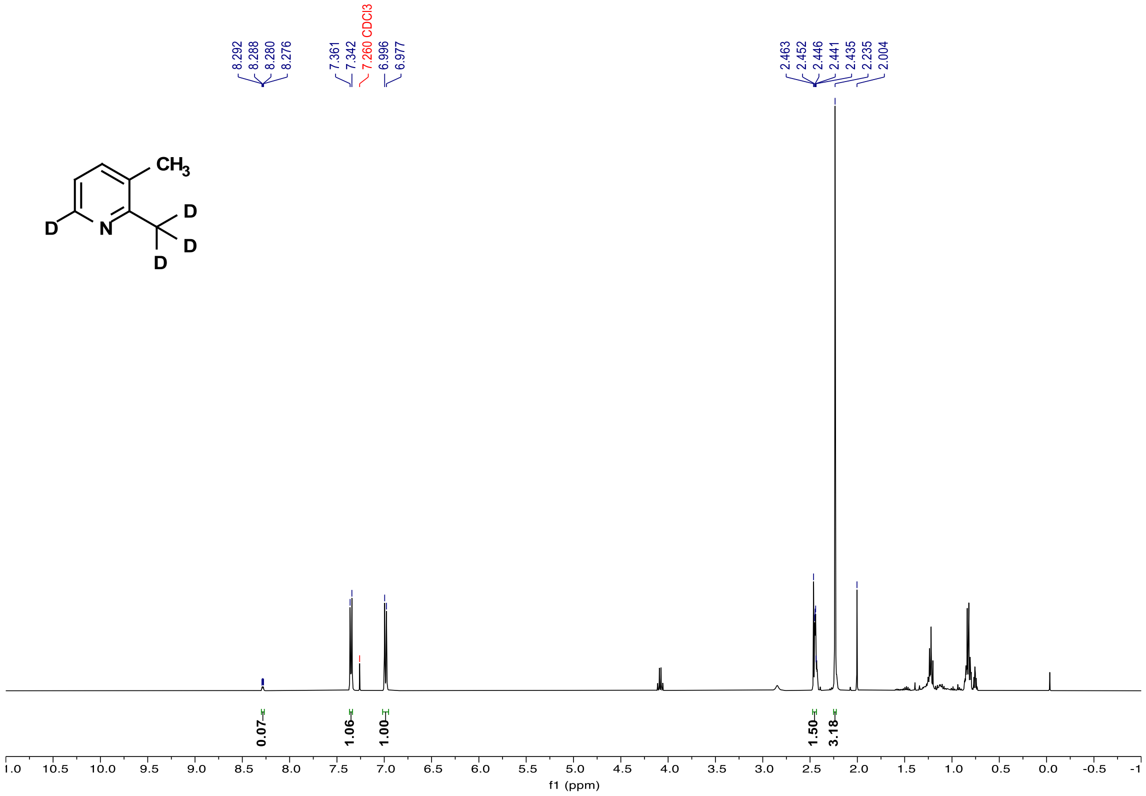
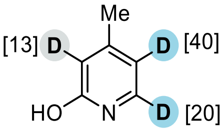


Figure S21 $^1$H NMR of **5-*d*** in Chloroform-*d*



### Deuteration of pyridin-2-ol (6)



General procedure to afford **6-*d*** as white solid (87.9 mg, 81%) with D-incorporation 13% for 3-position, 40% for 5-position, and 20% for 6-position by $^1$H NMR; 0.67 D by GC-MS; $R_f$ = 0.40 (DCM/MeOH = 15/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.32 (s, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 6.13 – 6.08 (m, 1H), 6.00 (dd, *J* = 6.7, 1.7 Hz, 1H), 2.10 (s, 3H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.29 (s, 1H), **7.25-7.19 (m, 0.80H, Labelled)**, **6.10 (s, 0.87H, Labelled)**, **6.02 – 5.97 (m, 0.60H, Labelled)**
, 2.10 (s, 3H).

**Figure S22** $^1$H NMR spectrum comparison

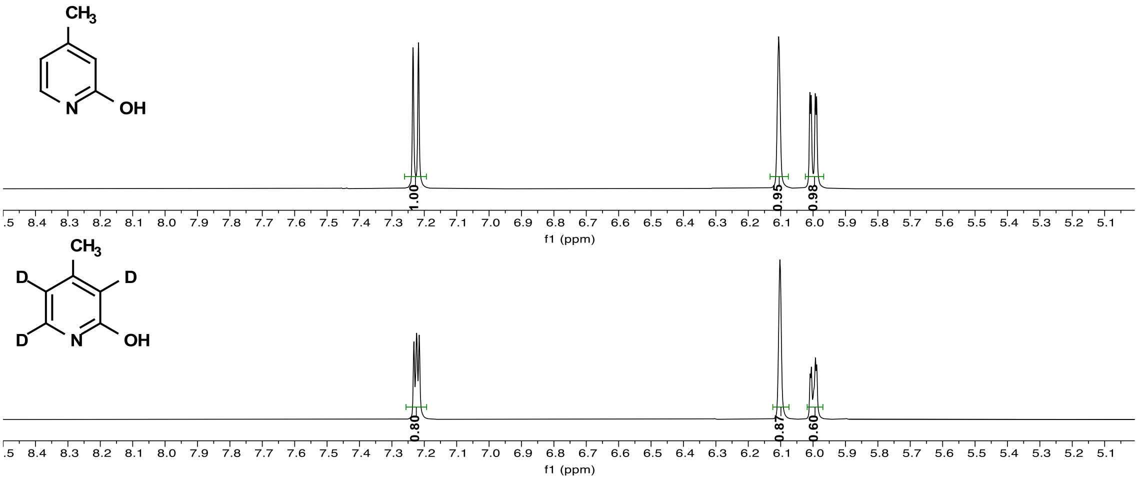


**Figure S23** GC-MS spectrum comparison

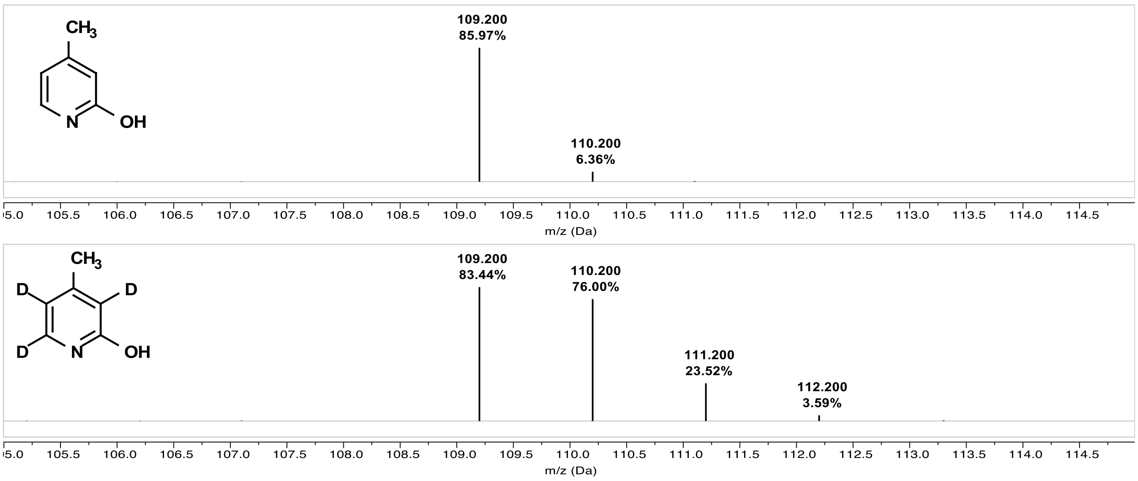


**Figure S24** $^1$H NMR of **6** in DMSO-$d_6$

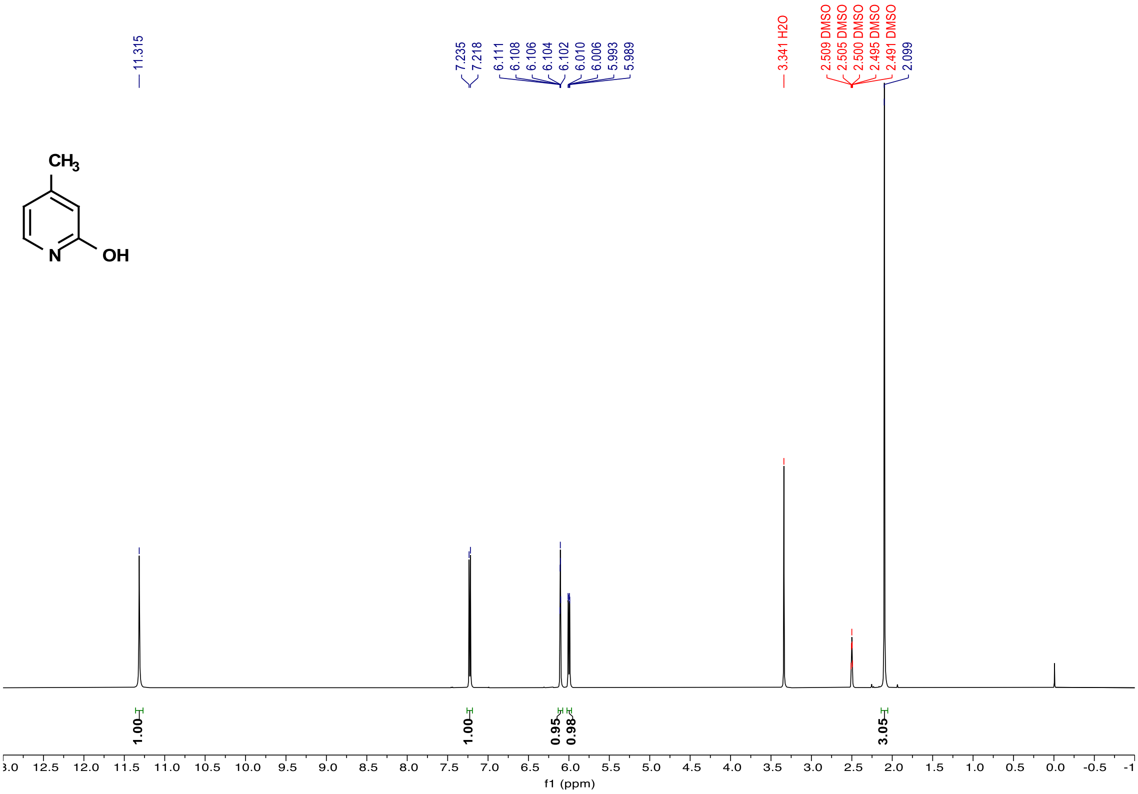
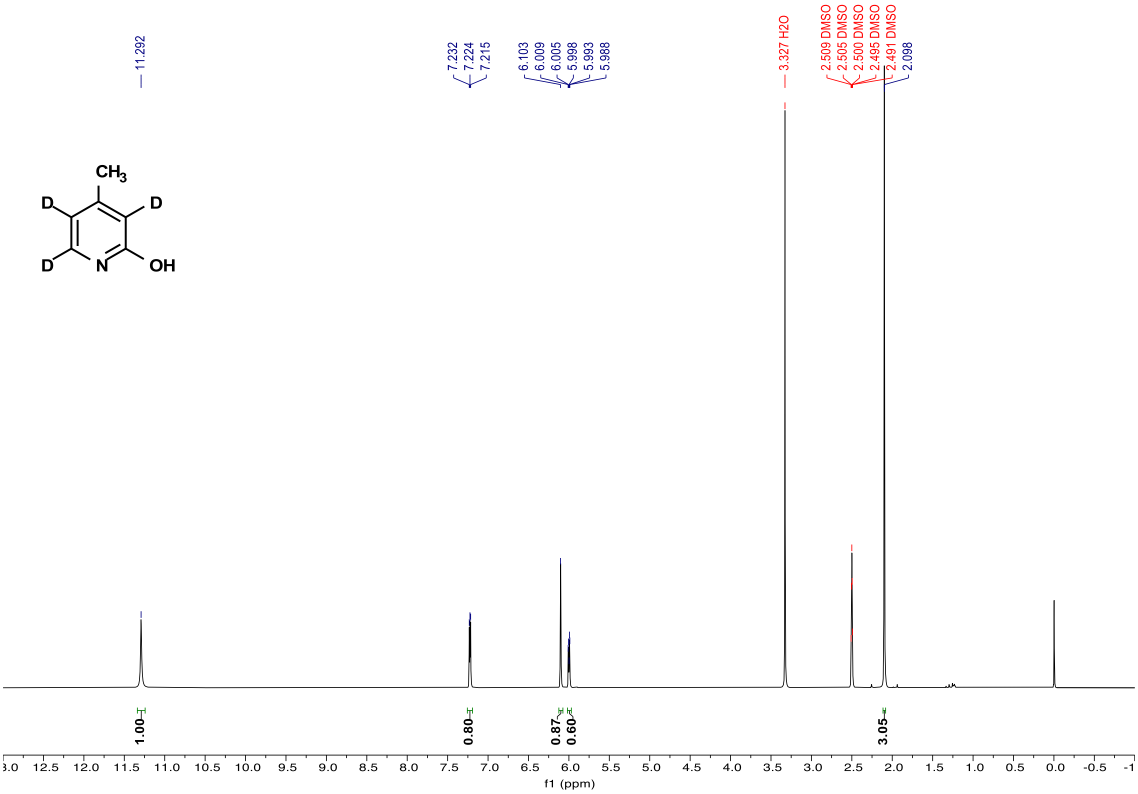
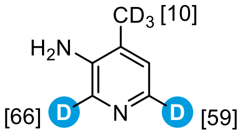


**Figure S25** $^1$H NMR of **6-*d*** in DMSO-$d_6$



### Deuteration of 4-methylpyridin-3-amine (7)



General procedure to afford **7-*d*** as brown solid (87.3 mg, 82%) with D-incorporation 66% for 2-position, 59% for 6-position, and 10% for 4-methyl by $^{1}$H NMR; 1.53 D by GC-MS; $R_f = 0.20$ (Petroleum ether/EtOAc = 1/1, 1% Et$_3$N).

**NMR data for starting material:** $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.93 (d, *J* = 4.8 Hz, 1H), 6.94 (d, *J* = 4.8 Hz, 1H), 3.59 (s, 2H), 2.15 (s, 3H).
**NMR data for deuterated product:** $^{1}$H NMR (400 MHz, Chloroform-*d*) δ **8.02 (s, 0.34H, Labelled)**, **7.93 (d, *J* = 4.8 Hz, 0.41H, Labelled)**, 6.95 (s, 1H), 3.61 (s, 2H), **2.18 – 2.14 (m, 2.72H, Labelled)**.

**Figure S26** $^{1}$H NMR spectrum comparison

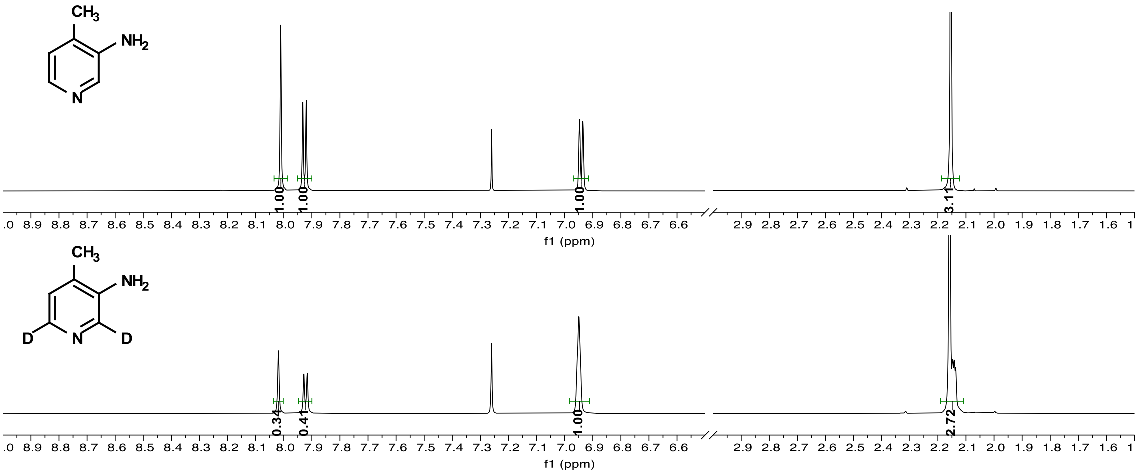


**Figure S27** GC-MS spectrum comparison

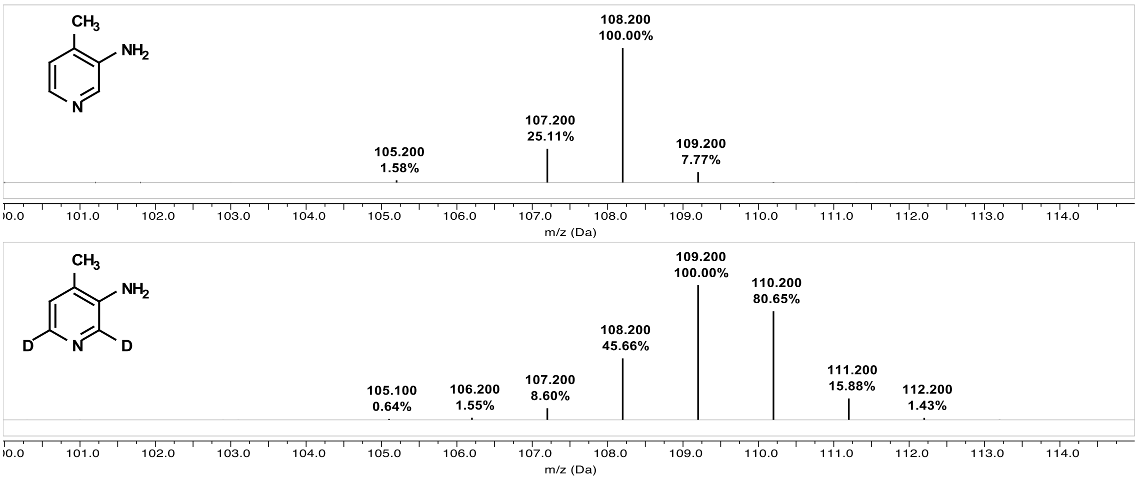


**Figure S28** $^1$H NMR of **7** in Chloroform-*d*

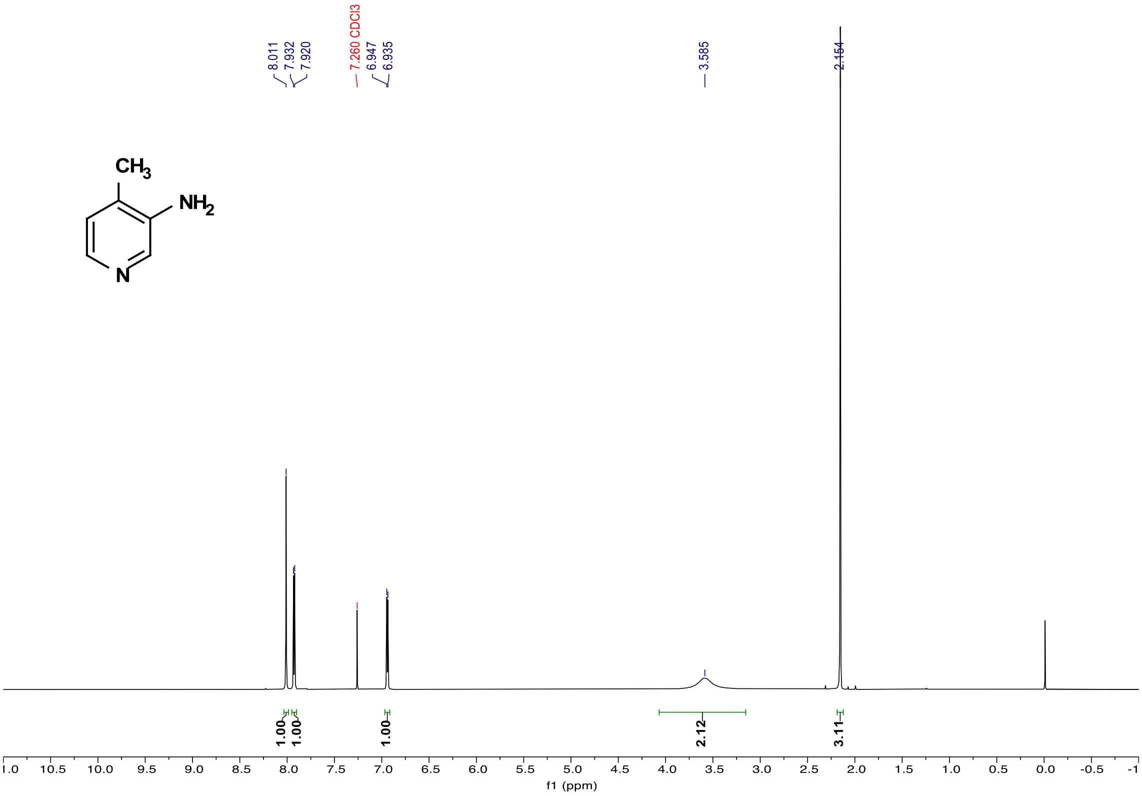
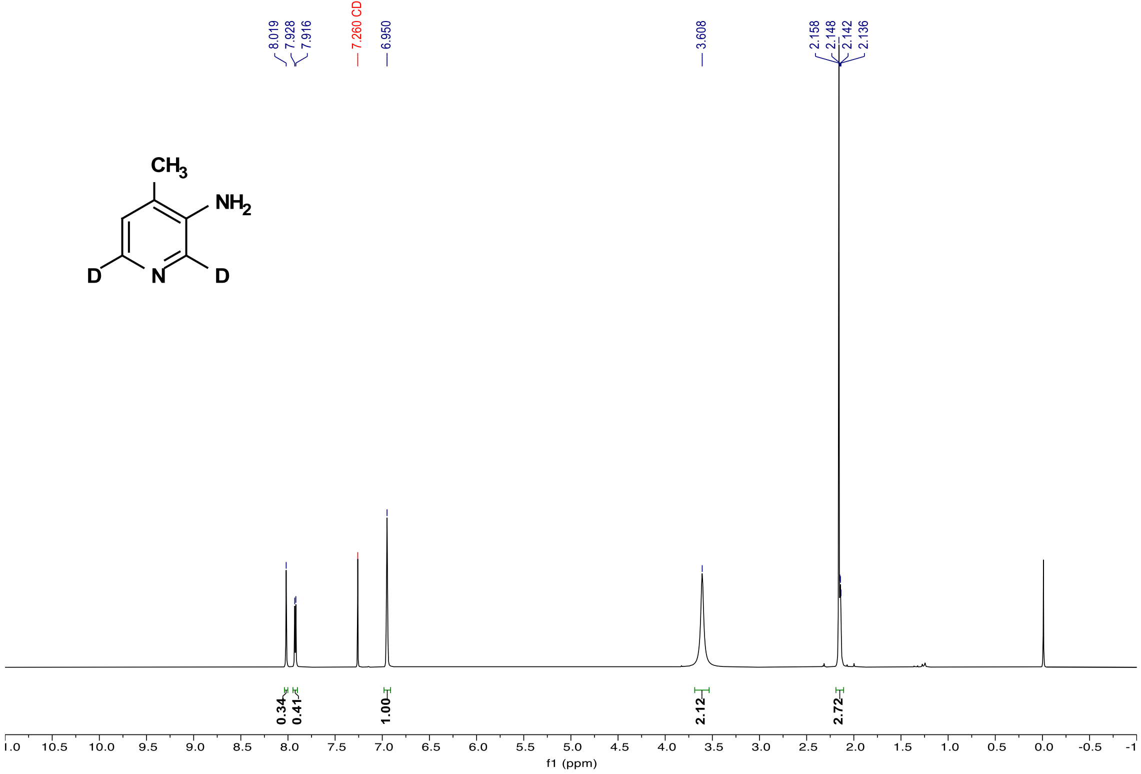
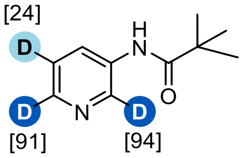


**Figure S29** $^1$H NMR of **7-*d*** in Chloroform-*d*



**Deuteration of N-(pyridin-3-yl)pivalamide (8)**



General procedure to afford **8-*d*** as yellow solid (153.1 mg, 86%) with D-incorporation 94% for 2-position, 24% for 5-position, and 91% for 6-position by $^1$H NMR; 2.12 D by GC-MS; $R_f$ = 0.40 (DCM/MeOH = 15/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.40 (s, 1H), 8.80 (d, *J* = 2.6 Hz, 1H), 8.24 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.1 Hz, 0H), 7.32 (dd, *J* = 8.3, 4.7 Hz, 1H), 1.23 (s, 9H). **NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.40 (s, 1H), **8.80 (d, *J* = 2.5 Hz, 0.06H, Labelled)**, **8.24 (m, 0.09H, Labelled)**, 8.07 – 8.02 (m, 1H), **7.32 (d, *J* = 8.3 Hz, 0.76H, Labelled)**, 1.23 (s, 9H).

**Figure S30** $^1$H NMR spectrum comparison

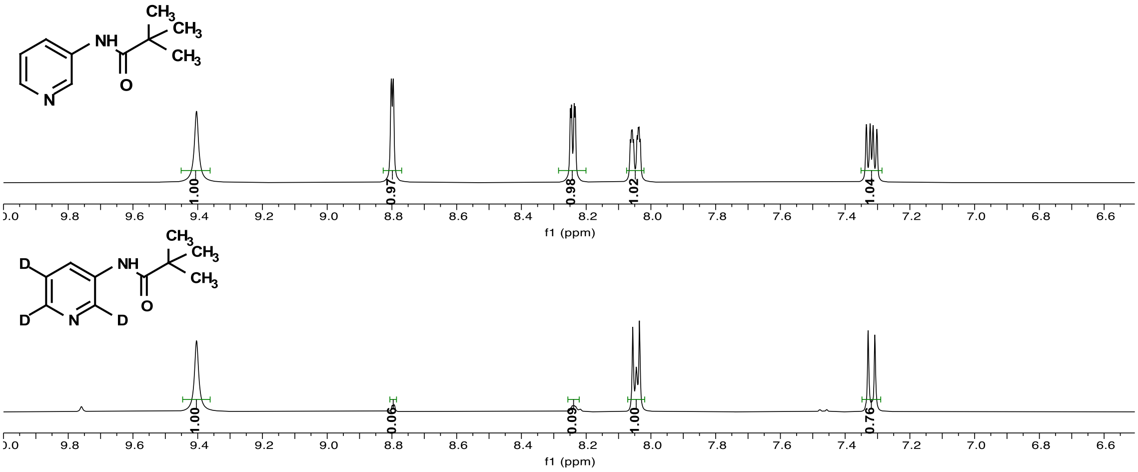


**Figure S31** GC-MS spectrum comparison

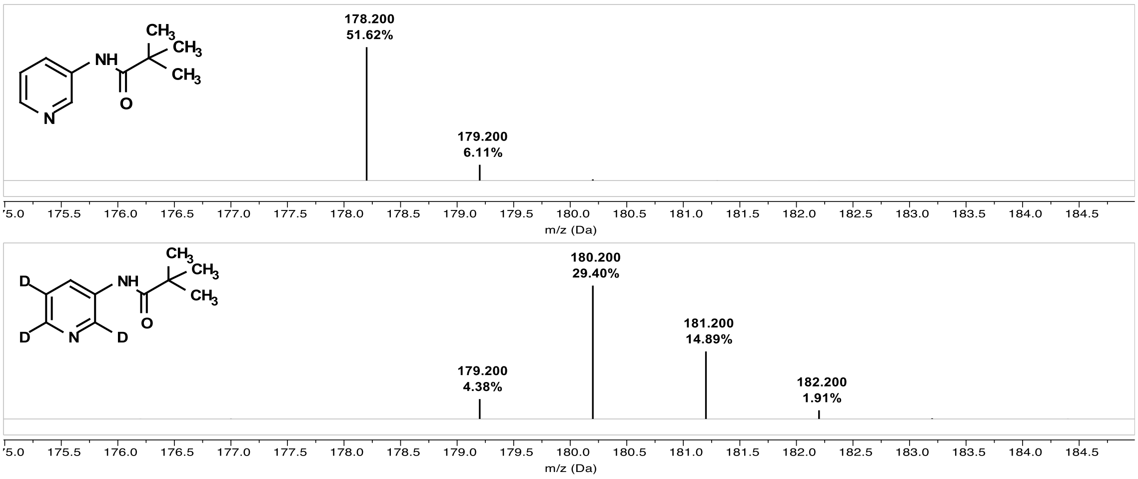


**Figure S32** $^1$H NMR of **8** in DMSO-$d_6$

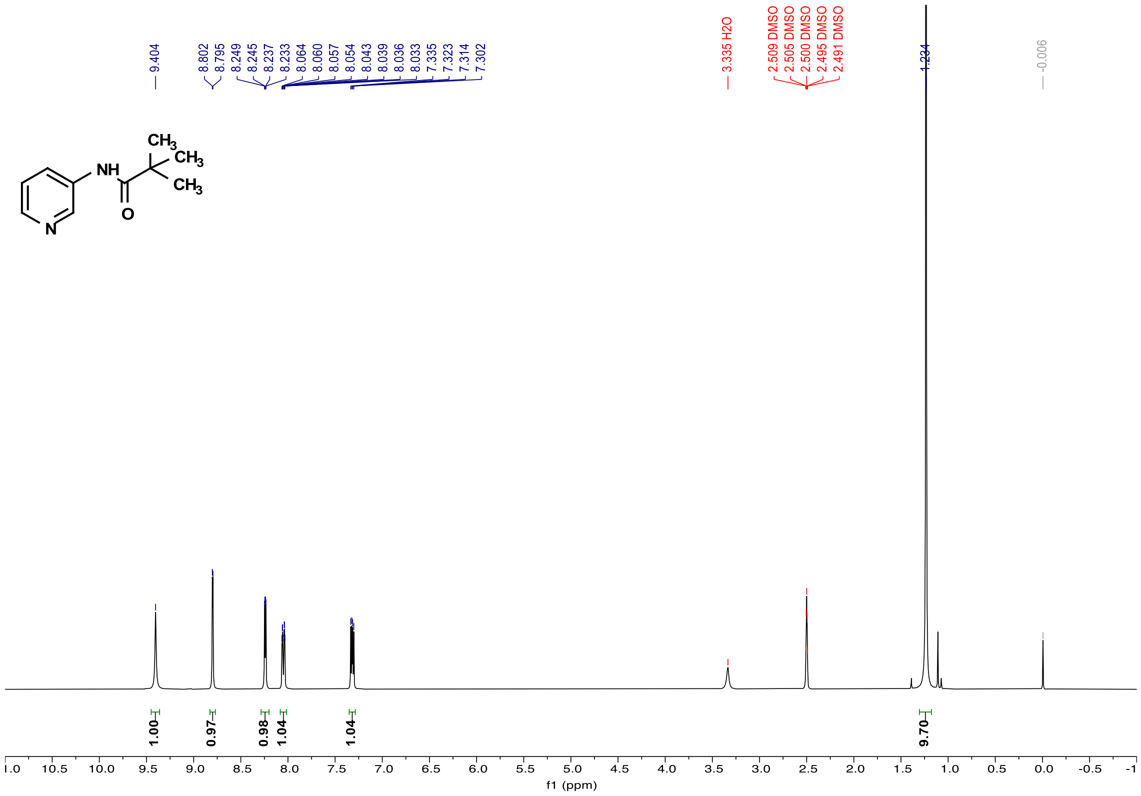
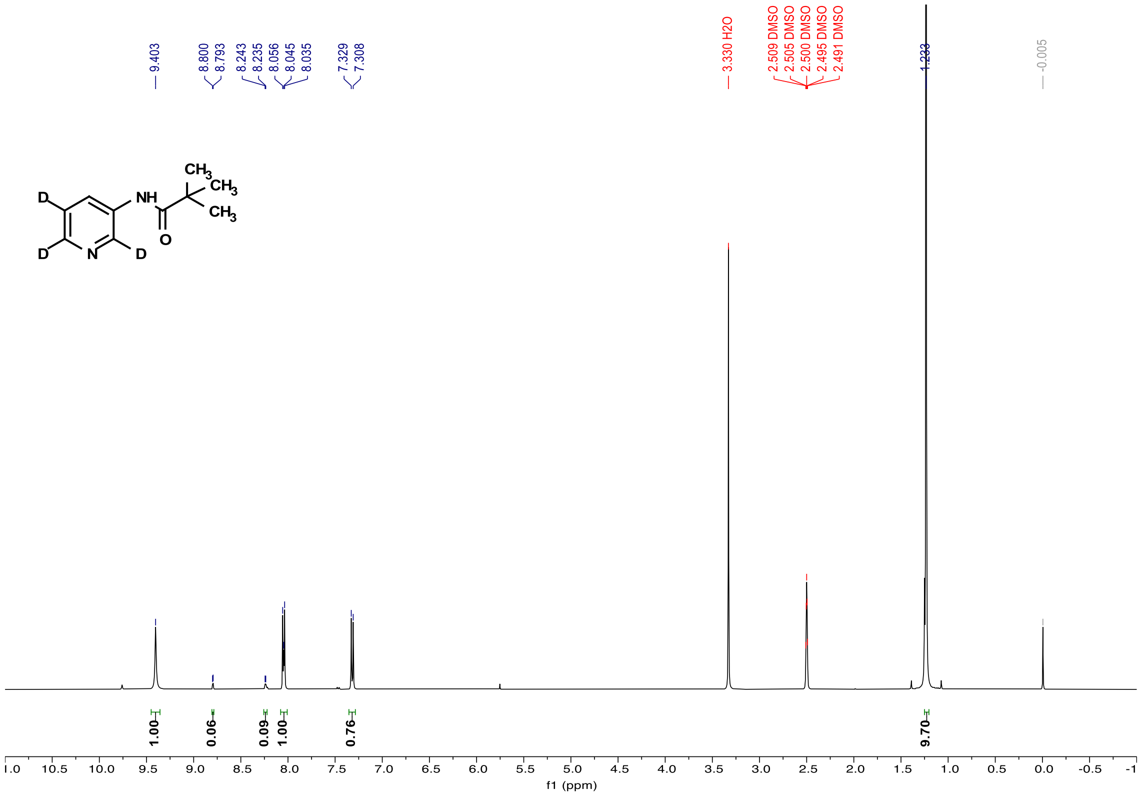
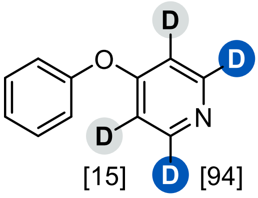


**Figure S33** $^1$H NMR of **8-*d*** in DMSO-$d_6$



## Deuteration of 4-phenoxypyridine (9)



General procedure to afford **9-*d*** as white solid (154.4 mg, 90%) with D-incorporation 94% for 2, 6-position, and 15% for 3, 5-position by $^1$H NMR; 2.10 D by GC-MS; $R_f$ = 0.35 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.46 (dd, *J* = 4.7, 1.6 Hz, 2H), 7.54 – 7.45 (m, 2H), 7.33 – 7.27 (m, 2H), 7.22 – 7.14 (m, 2H), 6.90 (dd, *J* = 4.7, 1.6 Hz, 2H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ **8.48 – 8.44 (m, 0.12H, Labelled)**, 7.54 – 7.46 (m, 2H), 7.34 – 7.28 (m, 1H), 7.22 – 7.16 (m, 2H), **6.91 (s, 1.70H, Labelled)**.

**Figure S34** $^1$H NMR spectrum comparison

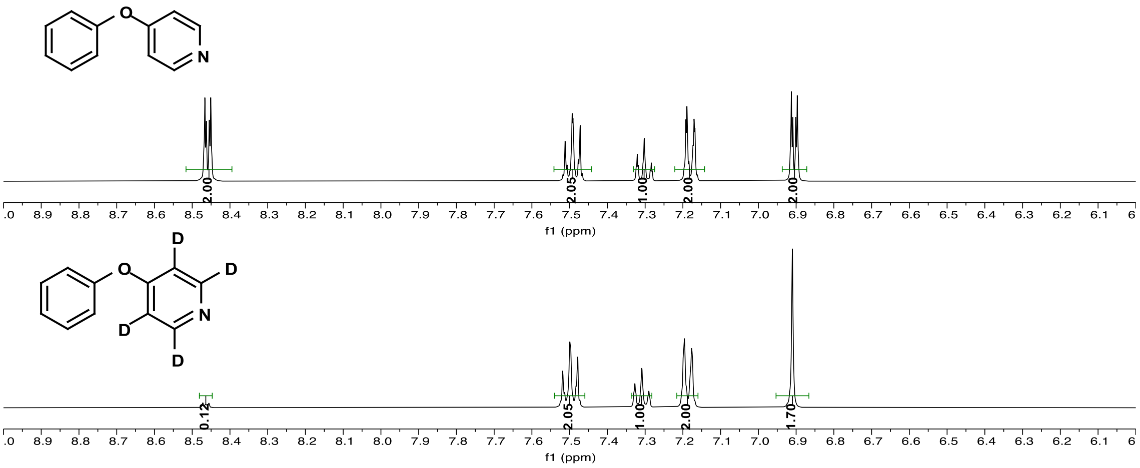


**Figure S35** GC-MS spectrum comparison

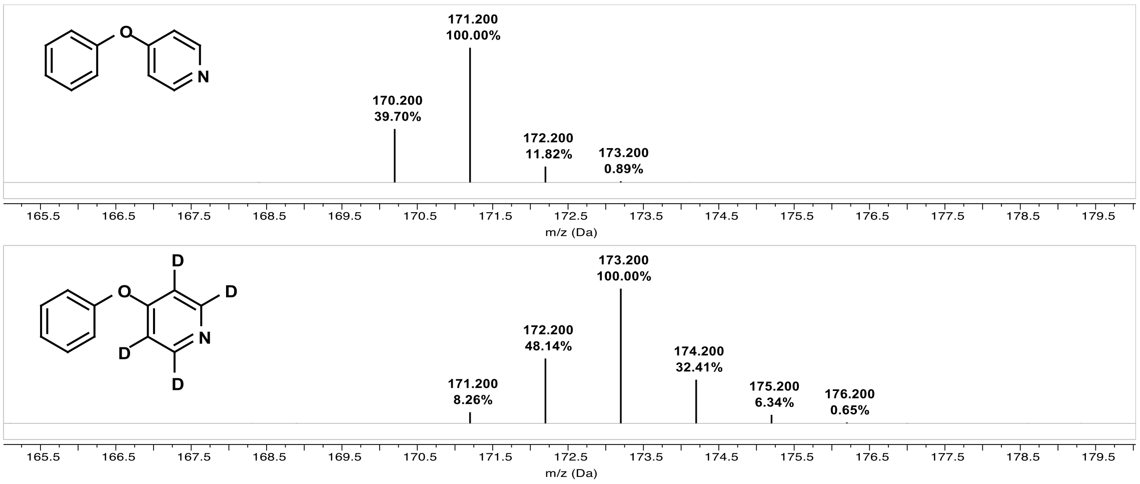


**Figure S36** $^1$H NMR of **9** in DMSO-$d_6$

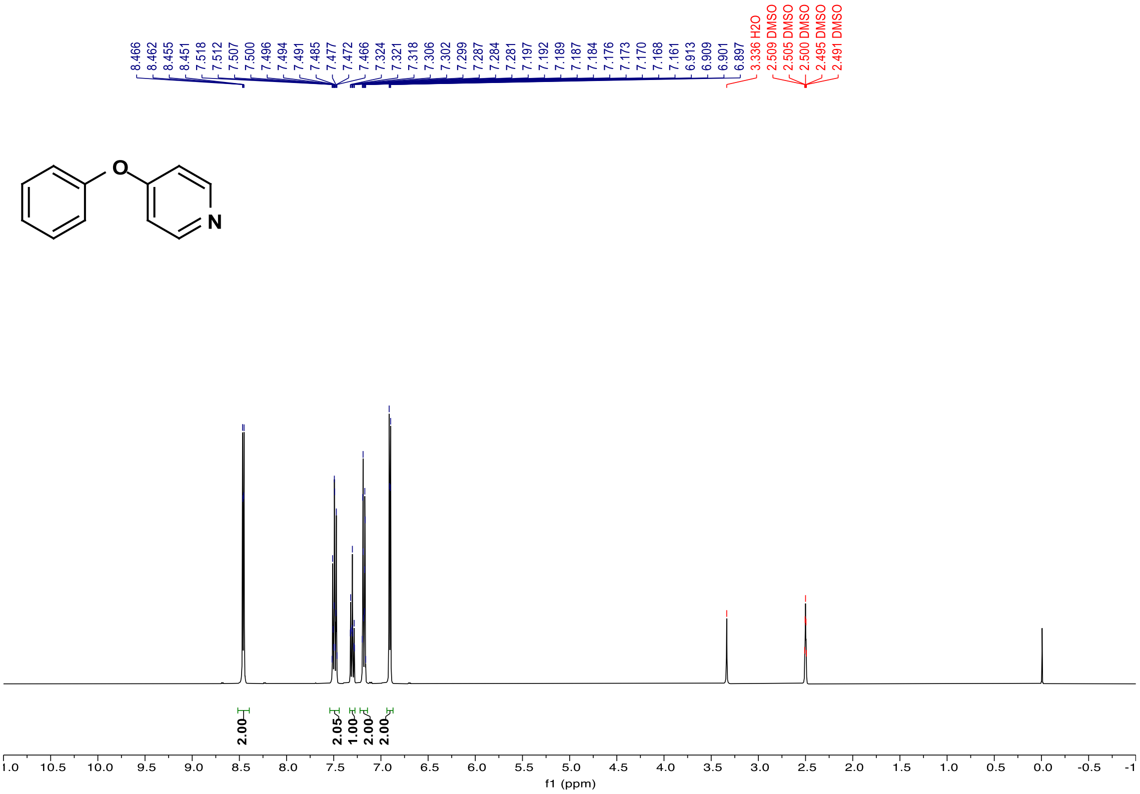
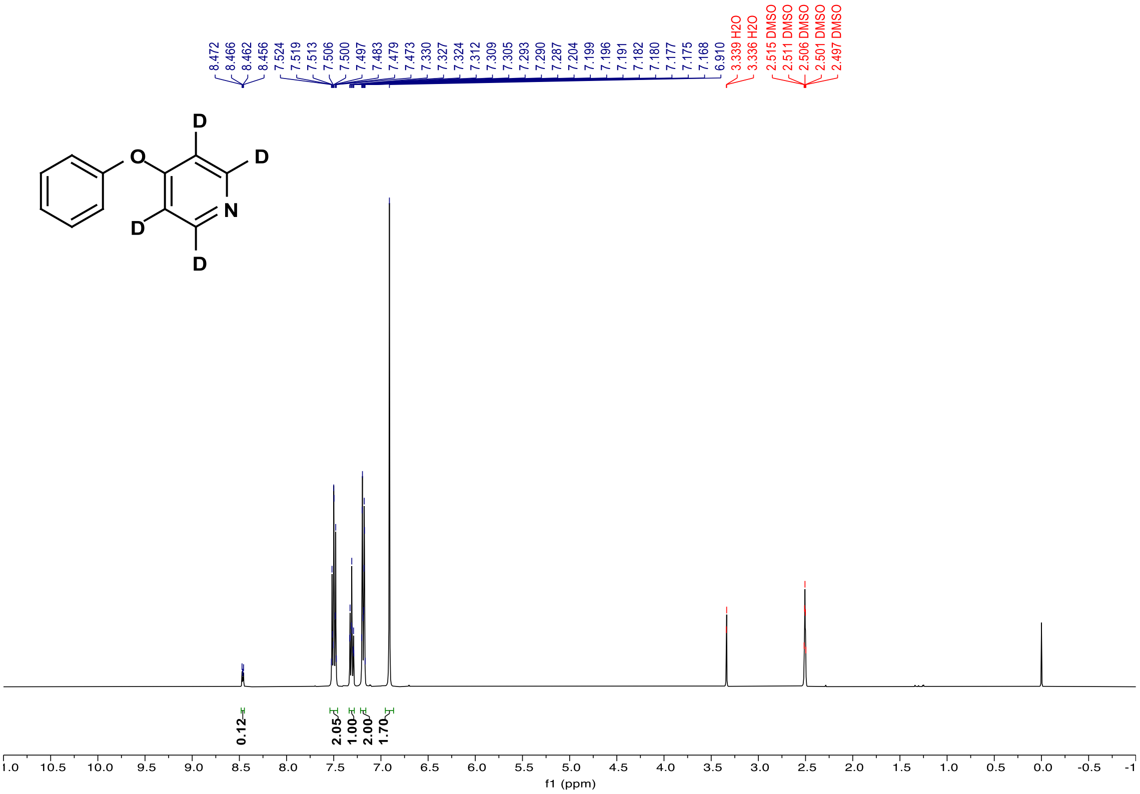
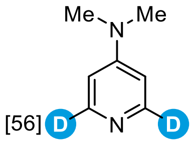


**Figure S37** $^1$H NMR of **9-*d*** in DMSO-$d_6$



### Deuteration of N,N-dimethylpyridin-4-amine (10)



General procedure to afford **10-*d*** as white solid (81.5 mg, 67%) with D-incorporation 56% for 2, 6-position by $^1$H NMR; 0.97 D by GC-MS; $R_f$ = 0.20 (Petroleum ether/EtOAc = 1/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.18 (m, 2H), 6.50 – 6.44 (m, 2H), 2.98 (s, 6H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.24 – 8.17 (m, 0.82H, Labelled)**, 6.48 (t, *J* = 2.3 Hz, 2H), 2.99 (s, 6H).

**Figure S38** $^1$H NMR spectrum comparison

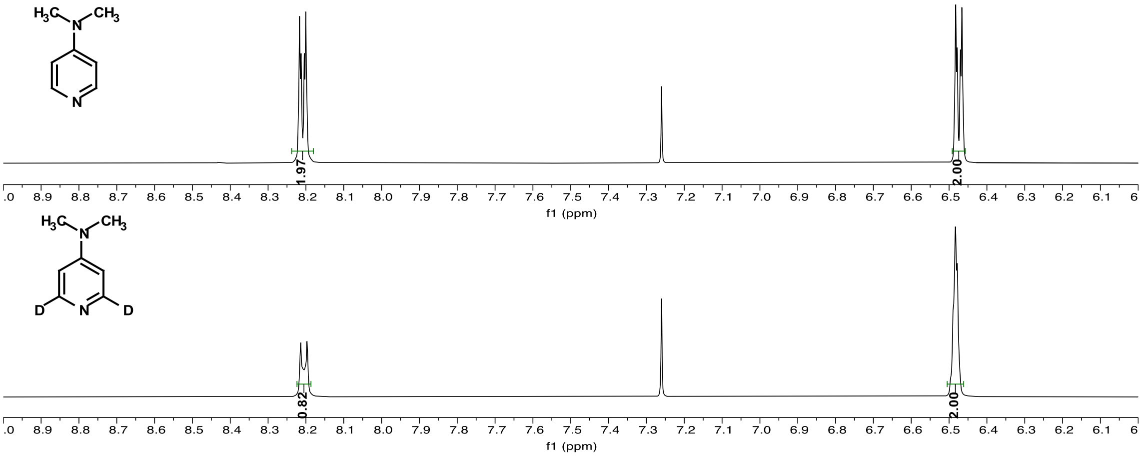


**Figure S39** GC-MS spectrum comparison

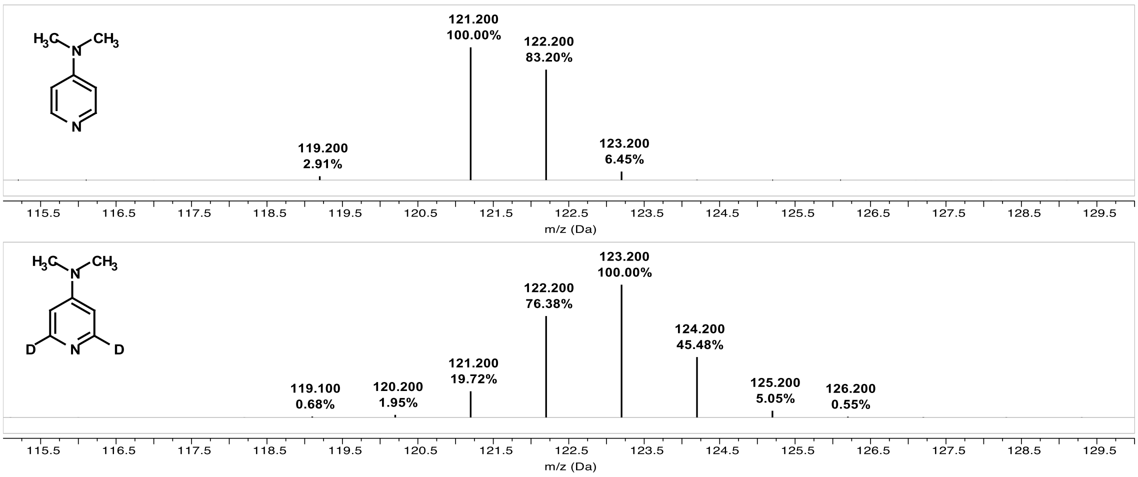


**Figure S40** $^1$H NMR of **10** in Chloroform-*d*

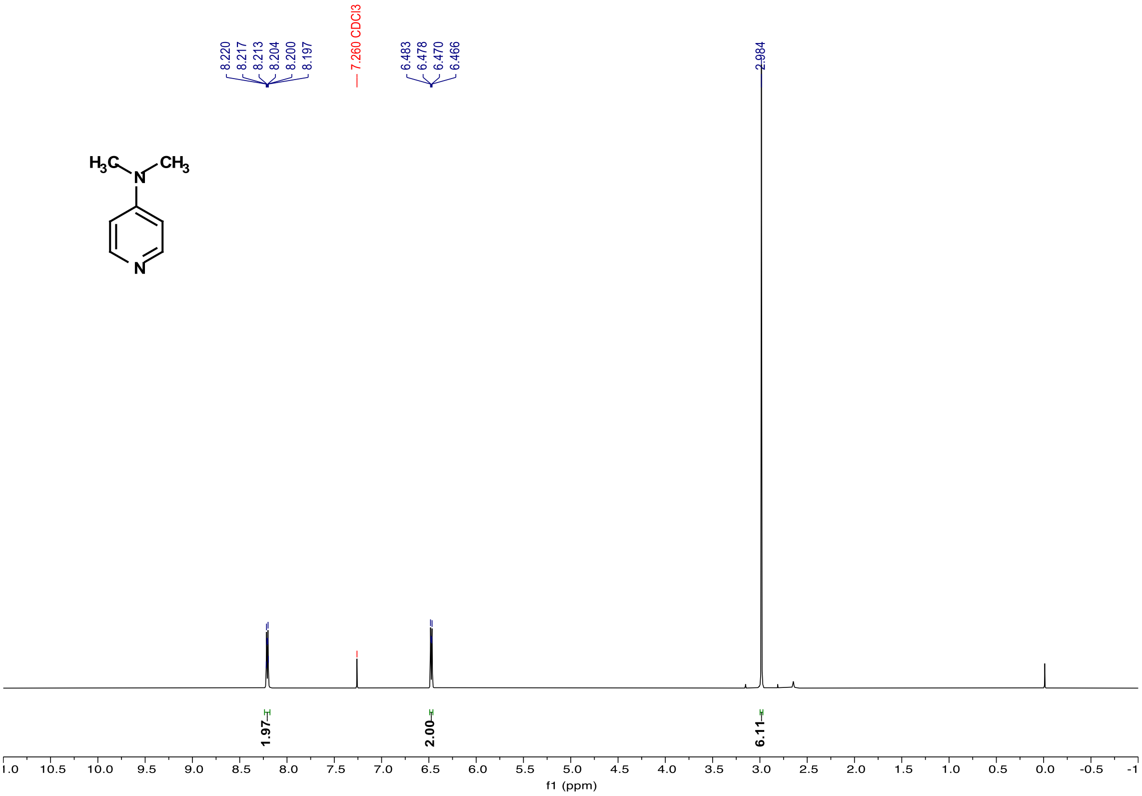
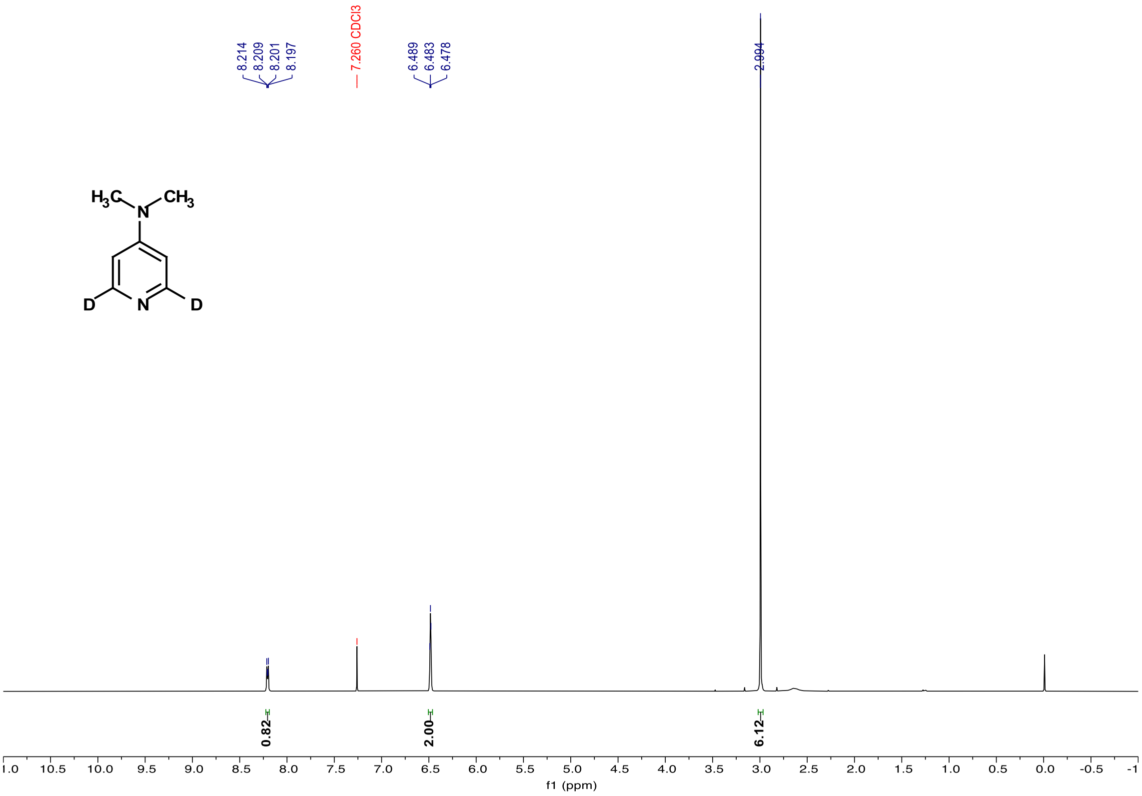
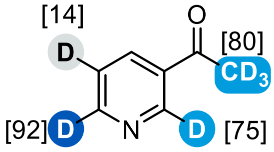


**Figure S41** $^1$H NMR of **10-*d*** in Chloroform-*d*



### Deuteration of 3-Acetylpyridine (11)



General procedure to afford **11-*d*** as slight yellow liquid (104.7 mg, 87%) with D-incorporation 75% for 2-position, 14% for 5-position, 92% for 6-position, and 80% for 3-acetyl group by $^1$H NMR; 4.18 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 2/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.16 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.77 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.23 (ddd, *J* = 8.0, 2.2, 1.7 Hz, 1H), 7.42 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 2.63 (s, 3H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **9.16 (dd, *J* = 2.3, 1.0 Hz, 0.25H, Labelled)**, **8.78 (dd, *J* = 4.8, 1.8 Hz, 0.08H, Labelled)**, 8.27 – 8.21 (m, 1H), **7.43 (d, *J* = 8.0 Hz, 0.86H, Labelled)**, **2.64 – 2.54 (m, 0.60H, Labelled)**.

**Figure S42** $^1$H NMR spectrum comparison

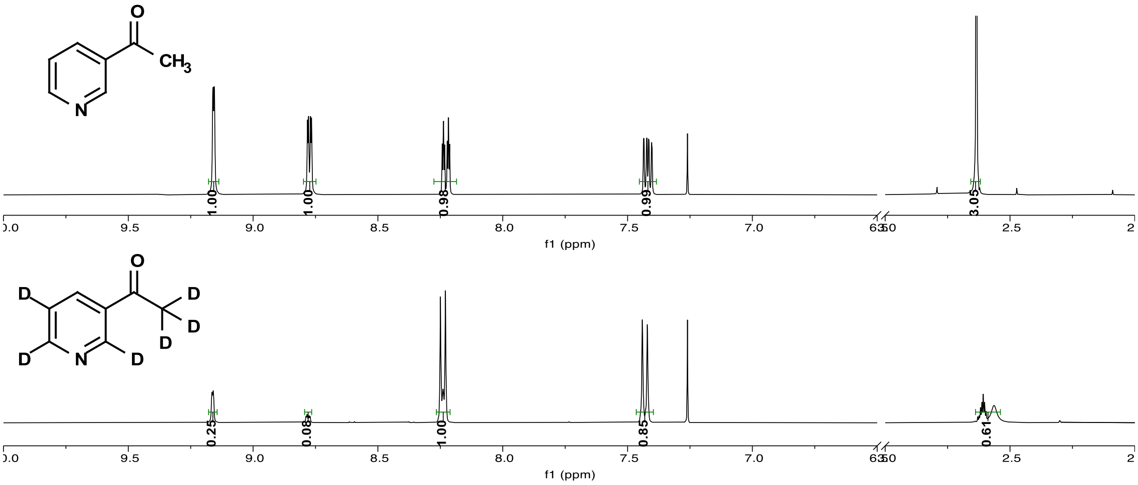


**Figure S43** GC-MS spectrum comparison

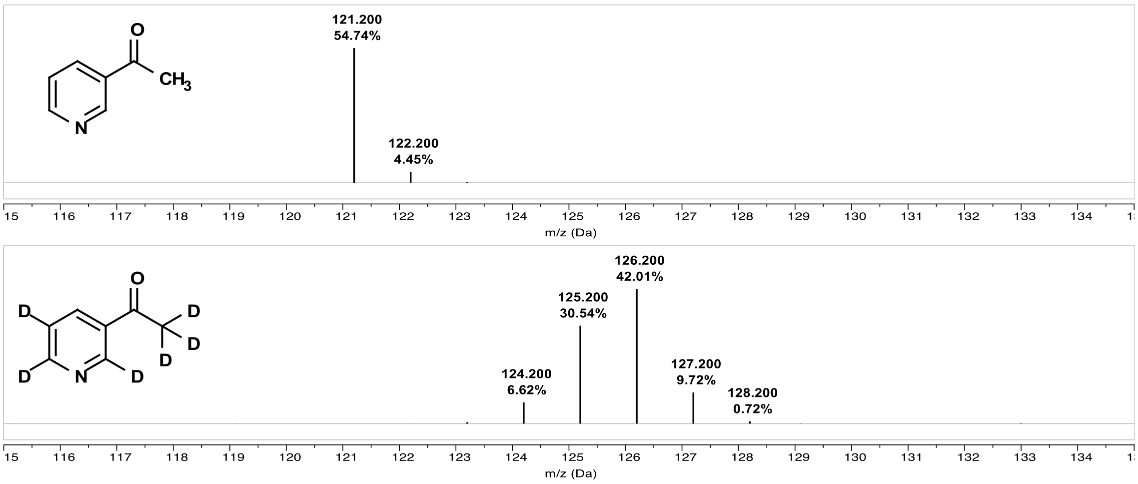


**Figure S44** $^1$H NMR of **11** in Chloroform-*d*

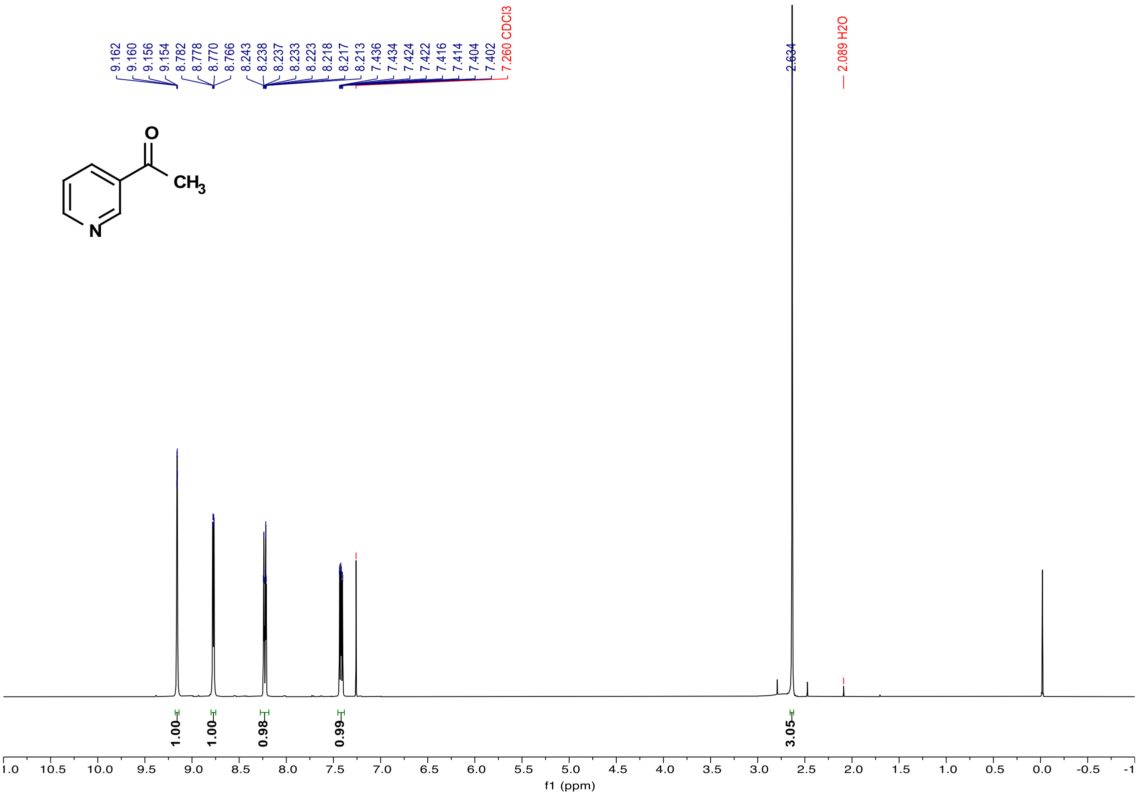
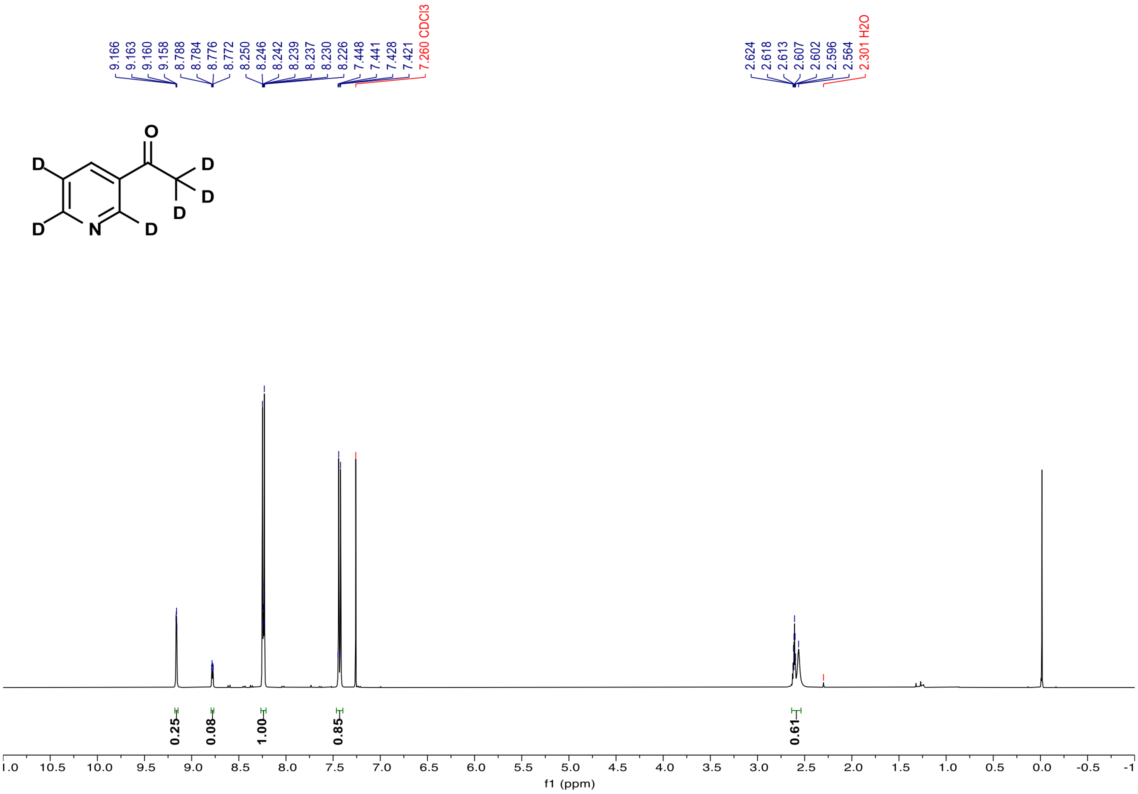
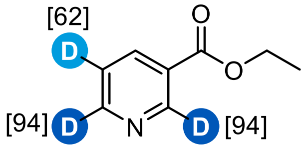


**Figure S45** $^1$H NMR of **11-*d*** in Chloroform-*d*



## Deuteration of Ethyl nicotinate (12)



General procedure to afford **12-*d*** as slight yellow liquid (125.1 mg, 83%) with D-incorporation 94% for 2-position, 62% for 5-position and 94% for 6-position by $^1$H NMR; 2.42 D by GC-MS; $R_f$ = 0.40 (DCM/MeOH = 15/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.24 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.78 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.32 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.40 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **9.23 (d, *J* = 2.1 Hz, 0.06H, Labelled)**, **8.79 – 8.74 (m, 0.06H, Labelled)**, 8.35 – 8.28 (m, 1H), **7.40 (d, *J* = 7.9 Hz, 0.38H, Labelled)**, 4.42 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

**Figure S46** $^1$H NMR spectrum comparison

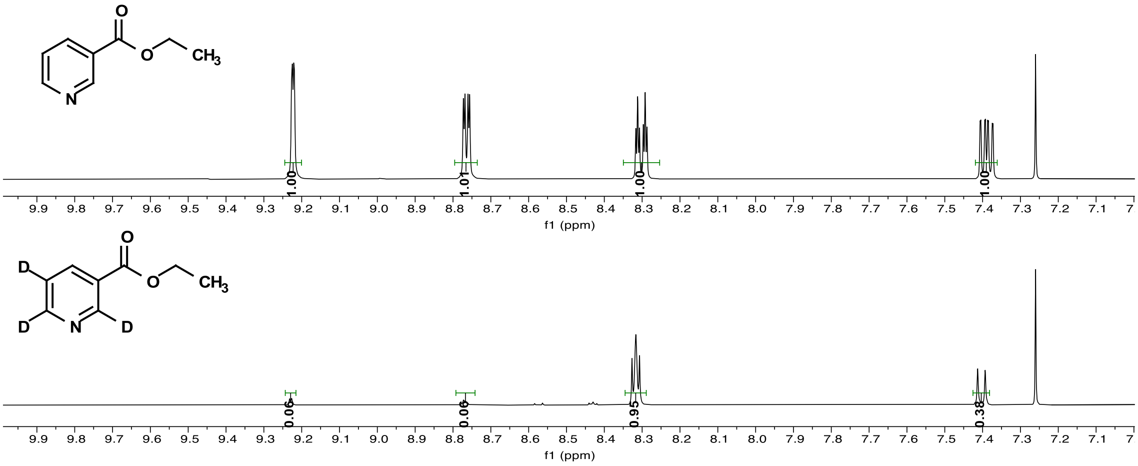


**Figure S47** GC-MS spectrum comparison

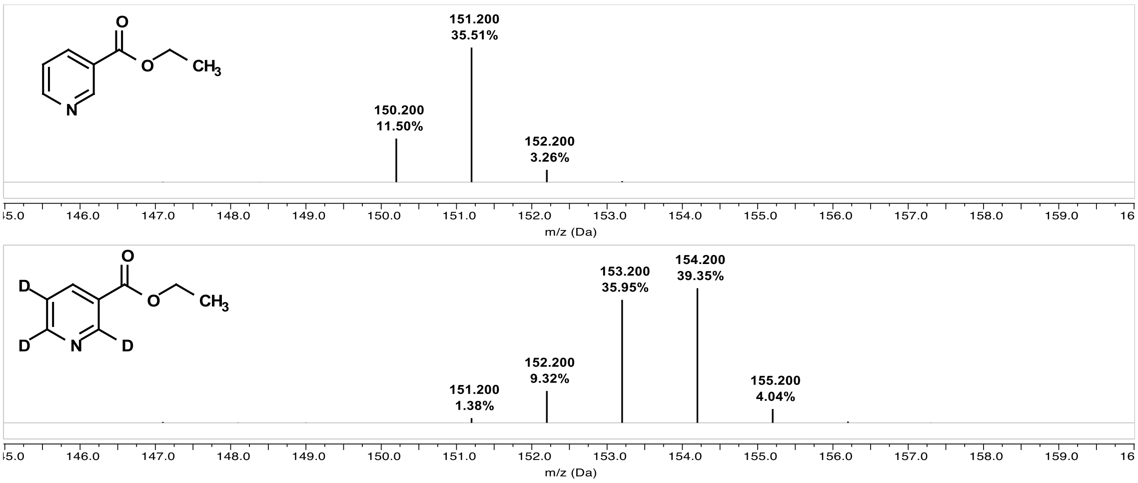


**Figure S48** $^1$H NMR of **12** in Chloroform-*d*

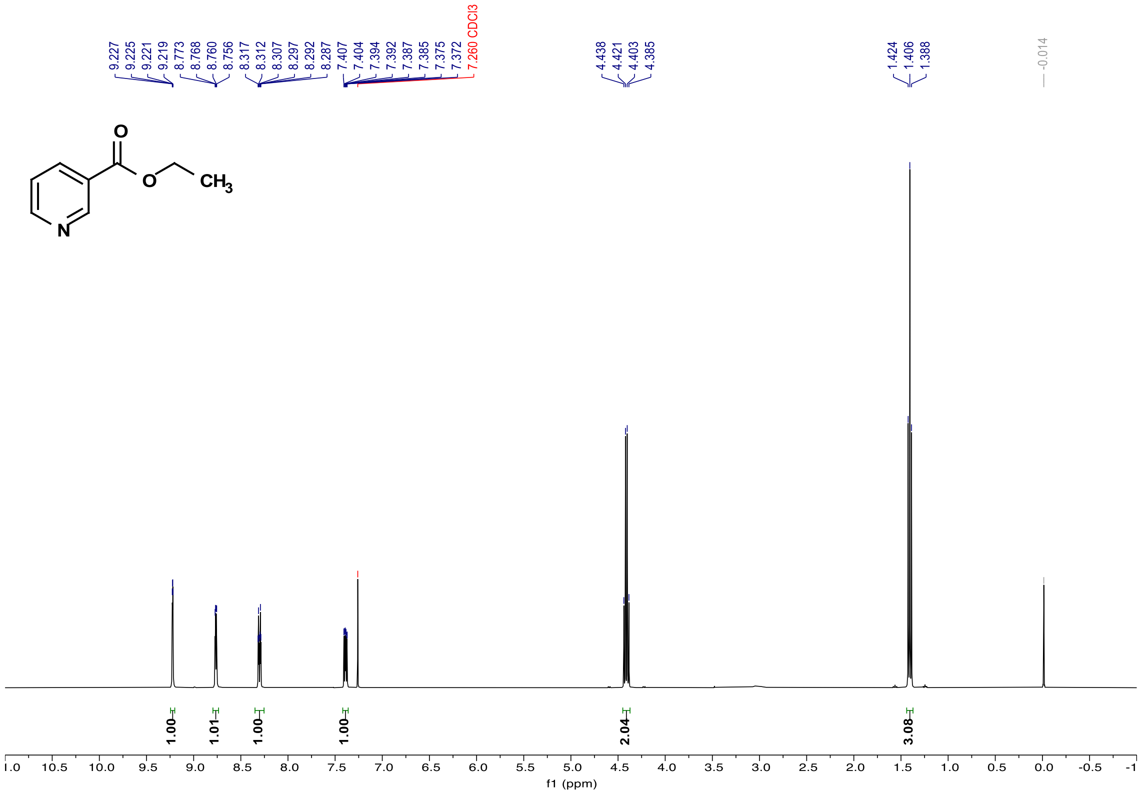
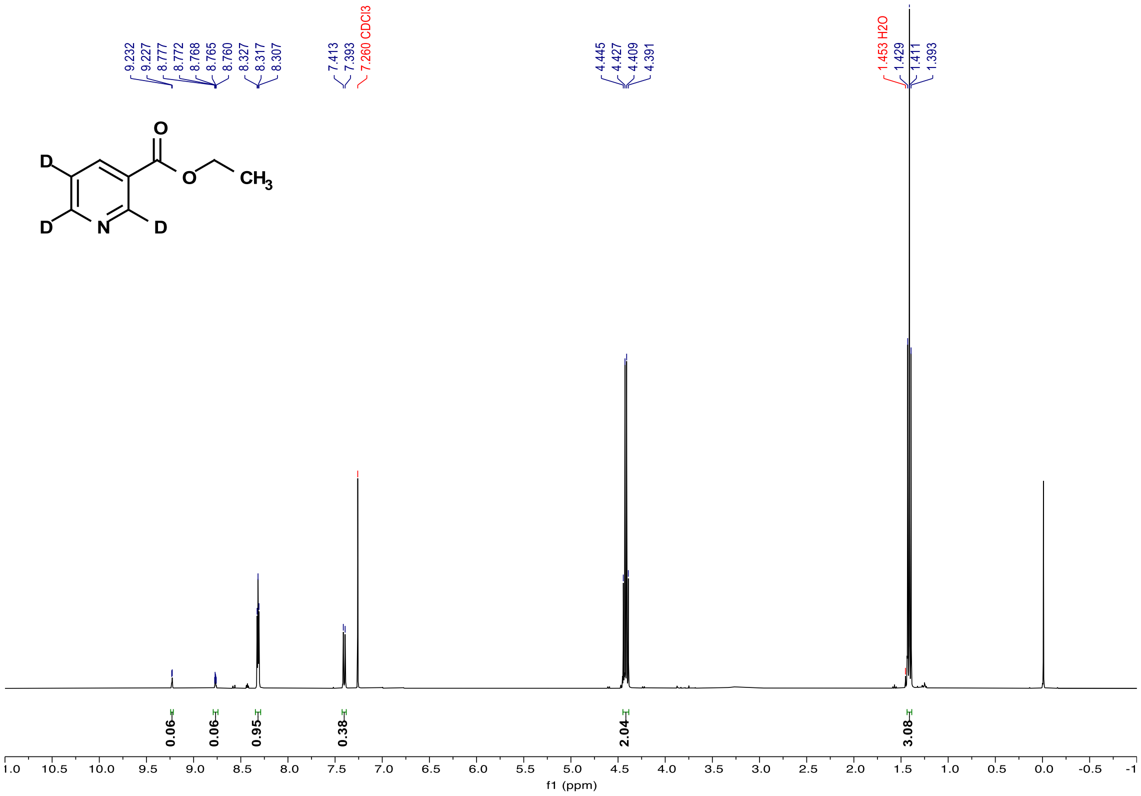
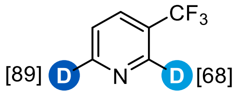


**Figure S49** $^1$H NMR of **12-*d*** in Chloroform-*d*



## Deuteration of 3-Trifluoromethylpyridine (13)



General procedure to afford **13-*d*** as colourless liquid (72.4 mg, 49%) with D-incorporation 68% for 2-position and 89% for 6-position by $^1$H NMR; 1.62 D by GC-MS; $R_f$ = 0.25 (Petroleum ether/EtOAc = 8/1).

**NMR data for starting material:** 1H NMR (400 MHz, Chloroform-d) δ 8.90 (d, J = 2.4 Hz, 1H), 8.81 (dd, J = 4.9, 1.6 Hz, 1H), 7.94 (dt, J = 8.0, 2.1 Hz, 1H), 7.45 (dd, J = 8.0, 4.9 Hz, 1H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.89 – 8.84 (m, 0.32H, Labelled)**, **8.78 (d, *J* = 4.3 Hz, 0.11H, Labelled)**, 8.01 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H).

**Figure S50** $^1$H NMR spectrum comparison

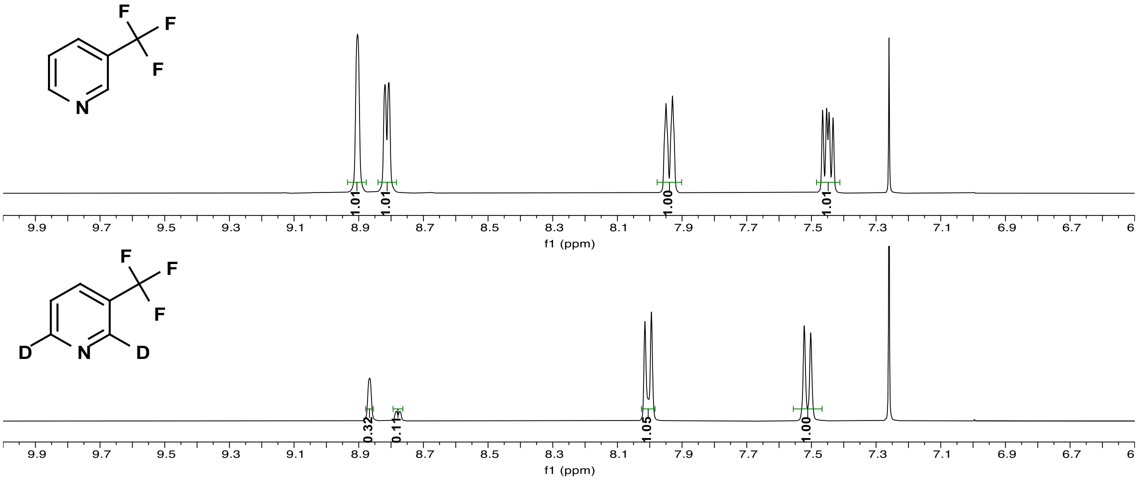


**Figure S51** GC-MS spectrum comparison

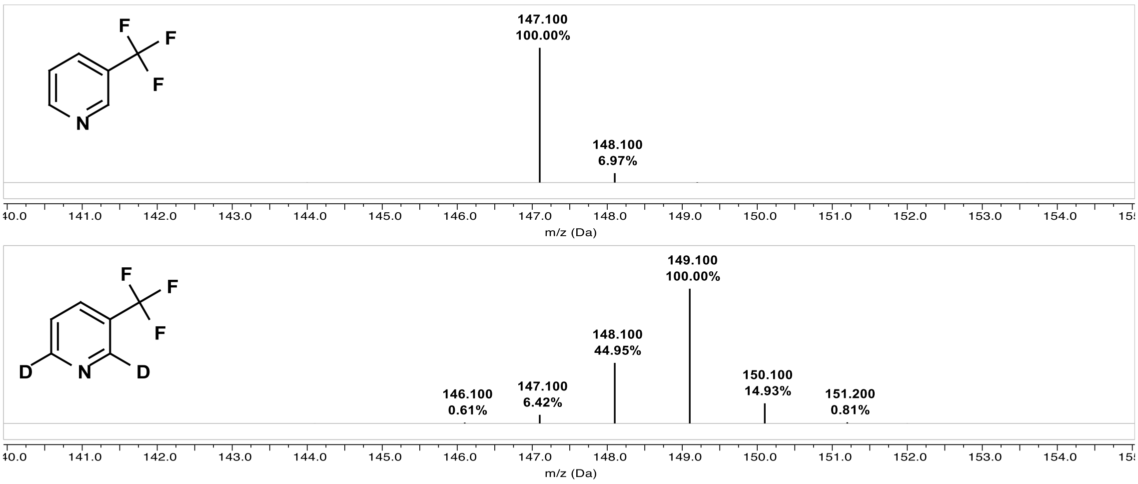


**Figure S52** $^1$H NMR of **13** in Chloroform-*d*

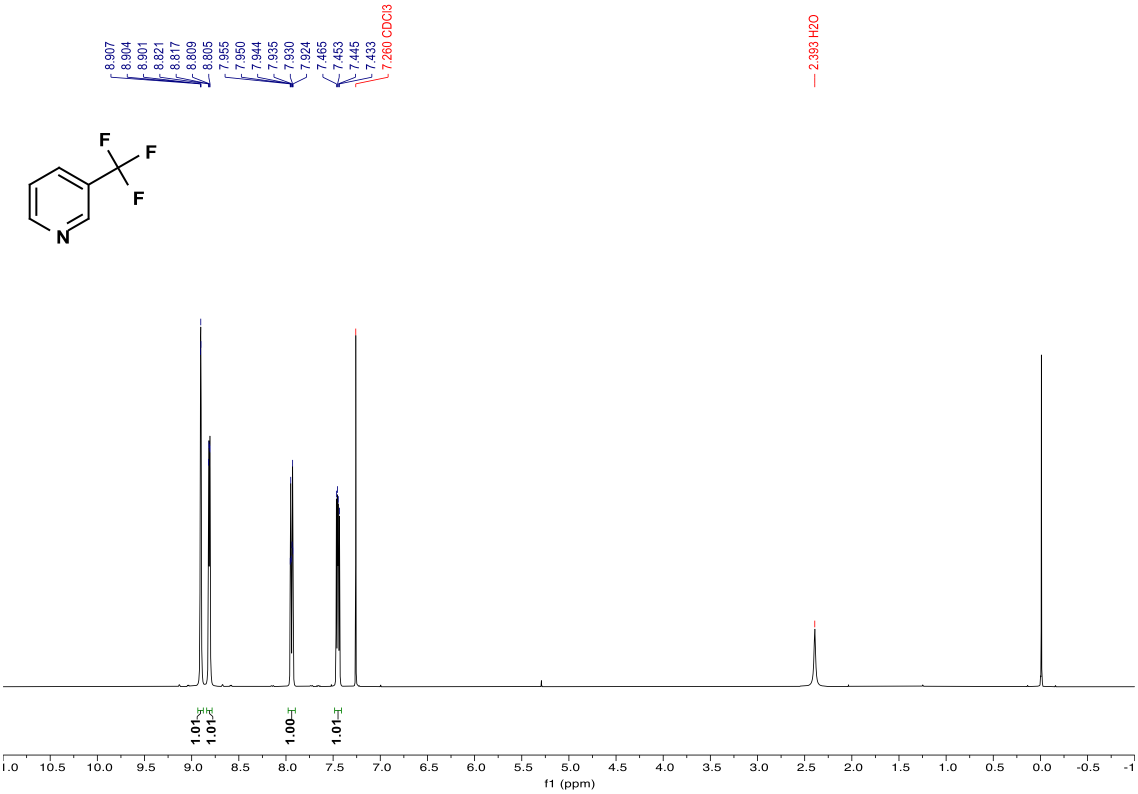
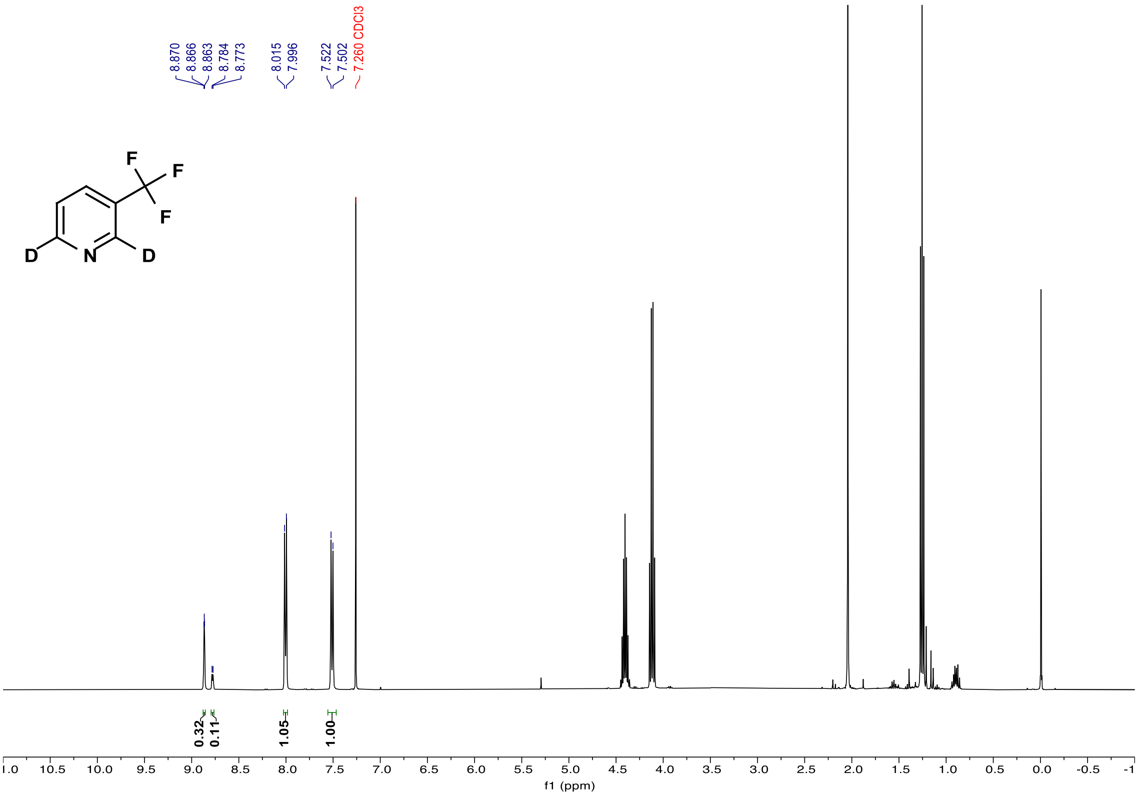
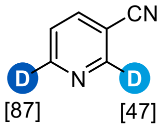


**Figure S53** $^1$H NMR of **13-*d*** in Chloroform-*d*



## Deuteration of 3-Cyanopyridine (14)



General procedure to afford **14-*d*** as white solid (75.1 mg, 72%) with D-incorporation 47% for 2-position and 87% for 6-position by $^1$H NMR; 1.34 D by GC-MS; $R_f$ = 0.20 (Petroleum ether/EtOAc = 1/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.90 (d, *J* = 2.1 Hz, 1H), 8.82 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.97 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.45 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.90 (dd, *J* = 2.2, 0.9 Hz, 0.53H, Labelled)**, **8.82 (dd, *J* = 5.0, 1.7 Hz, 0.13H, Labelled)**, 7.98 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H).

**Figure S54** $^1$H NMR spectrum comparison

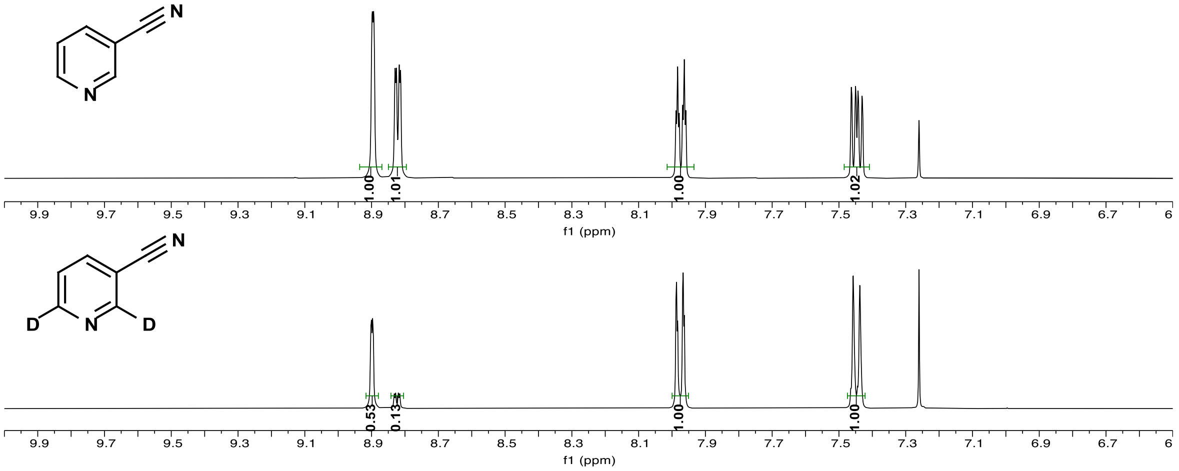


**Figure S55** GC-MS spectrum comparison

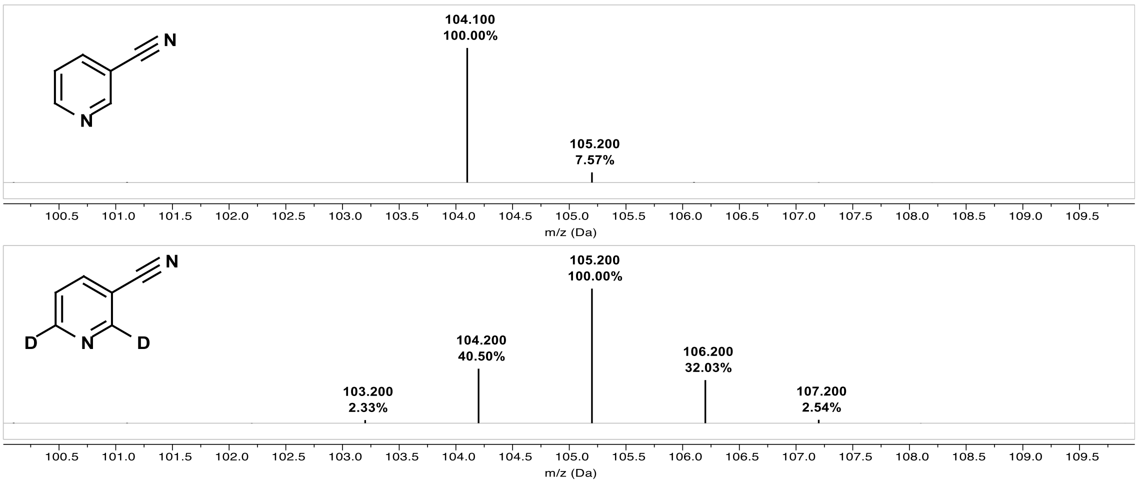


**Figure S56** $^1$H NMR of **14** in Chloroform-*d*

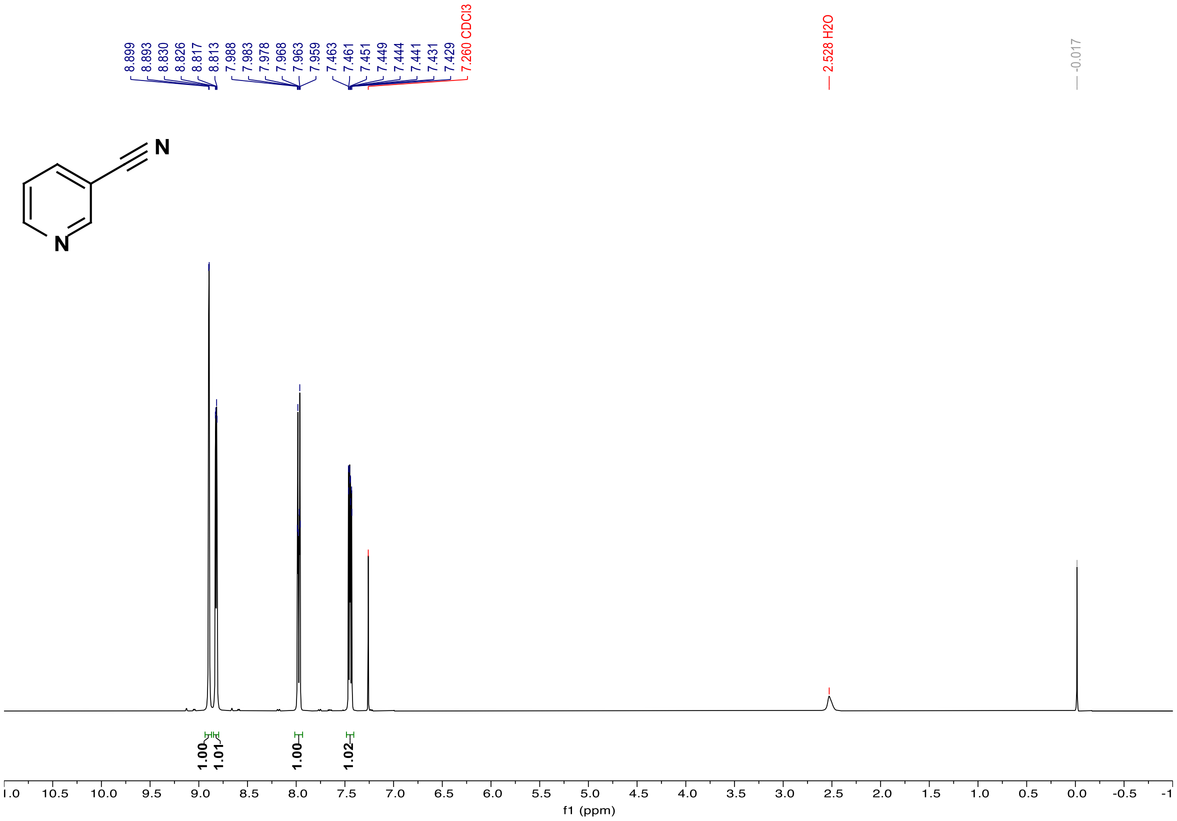
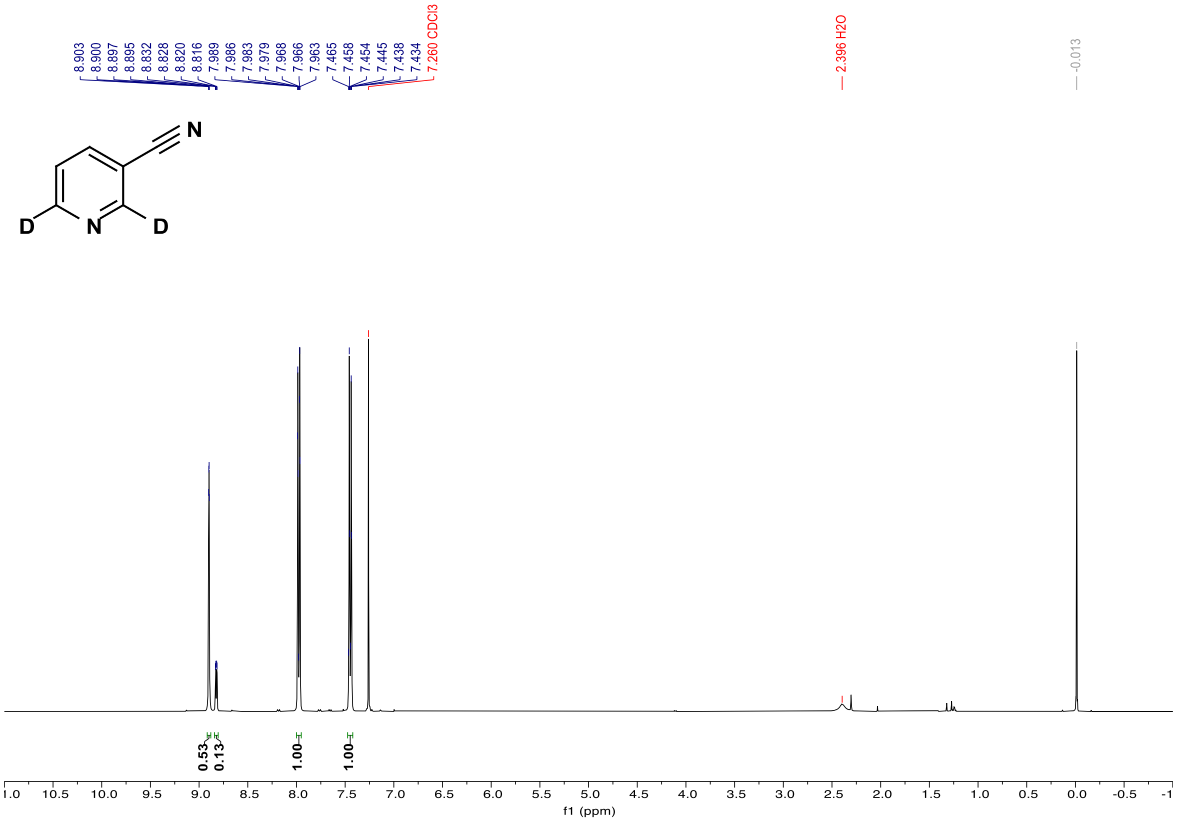
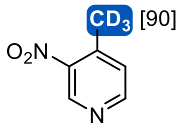


**Figure S57** $^1$H NMR of **14-*d*** in Chloroform-*d*



## Deuteration of 4-methyl-3-nitropyridine (16)



General procedure to afford **16-*d*** s yellow liquid (121.1 mg, 88%) with D-incorporation 90% for 3-methyl by $^1$H NMR; 2.86 D by GC-MS; $R_f$ = 0.35 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.66 (d, *J* = 5.0 Hz, 1H), 7.32 (d, *J* = 5.0 Hz, 1H), 2.66 (s, 3H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 8.66 (d, *J* = 5.0 Hz, 1H), 7.32 (d, *J* = 5.0 Hz, 1H), **2.67-2.60 (m, 0.30H, Labelled)**.

**Figure S58** $^1$H NMR spectrum comparison

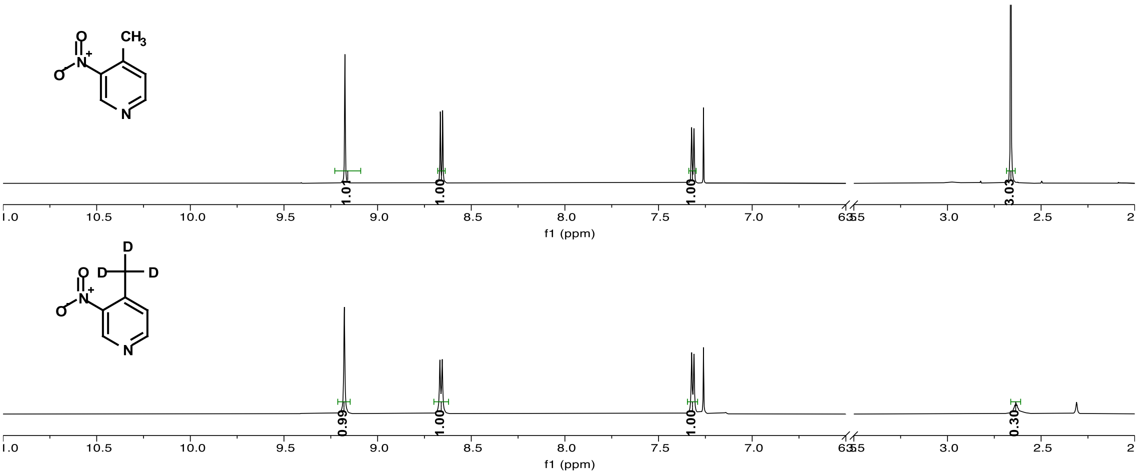


**Figure S59** GC-MS spectrum comparison

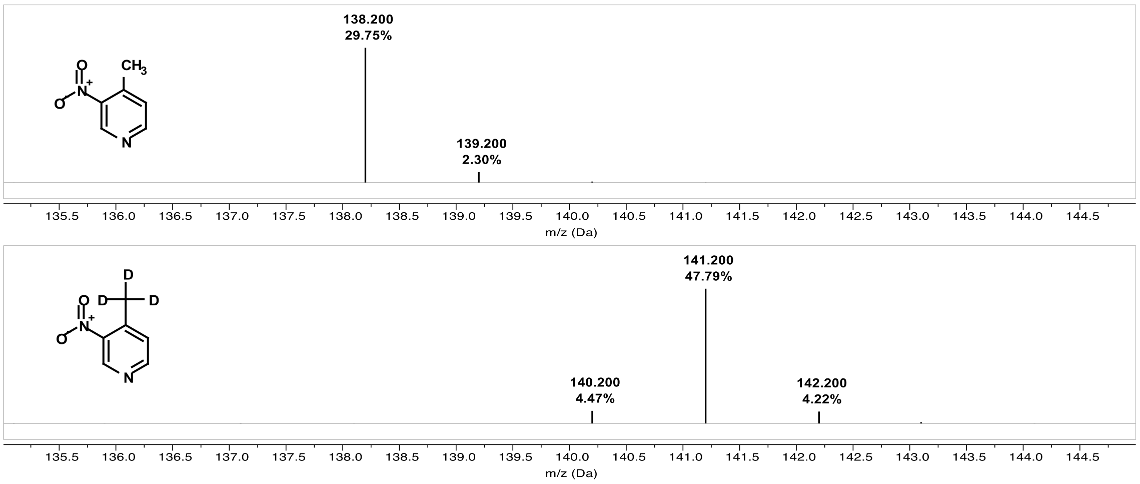


**Figure S60** ${}^{1}$H NMR of **16** in Chloroform-*d*

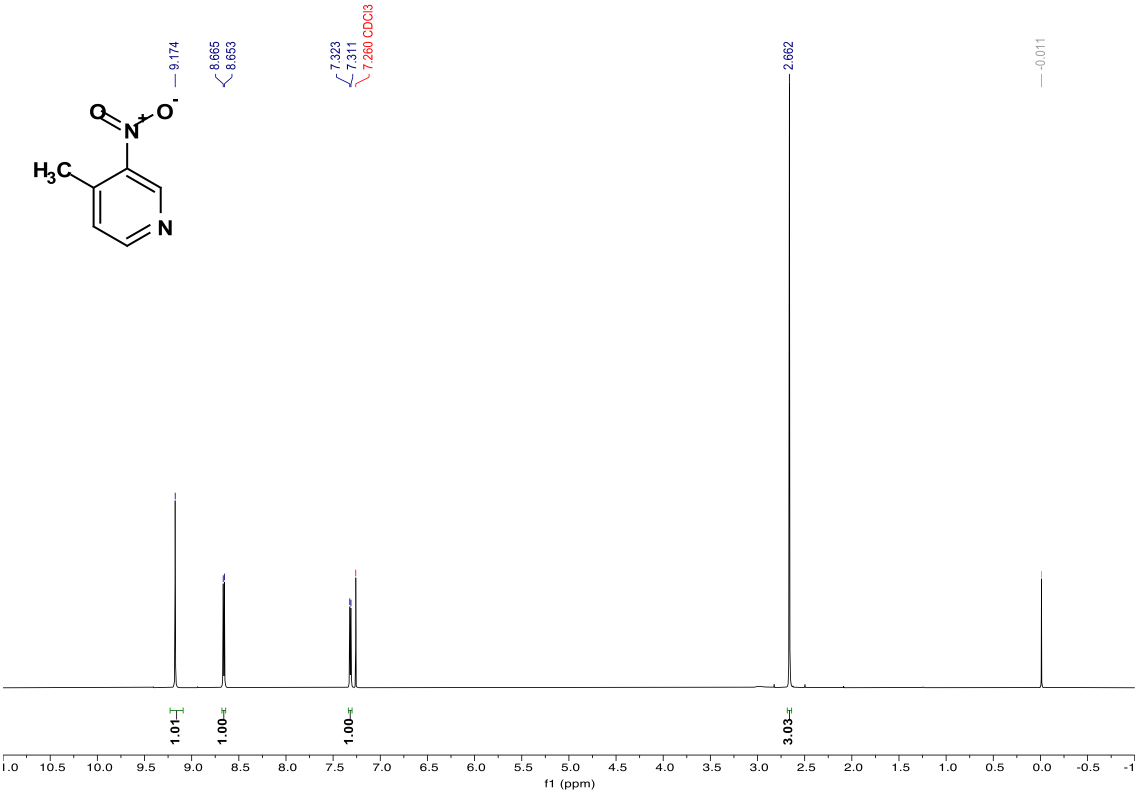
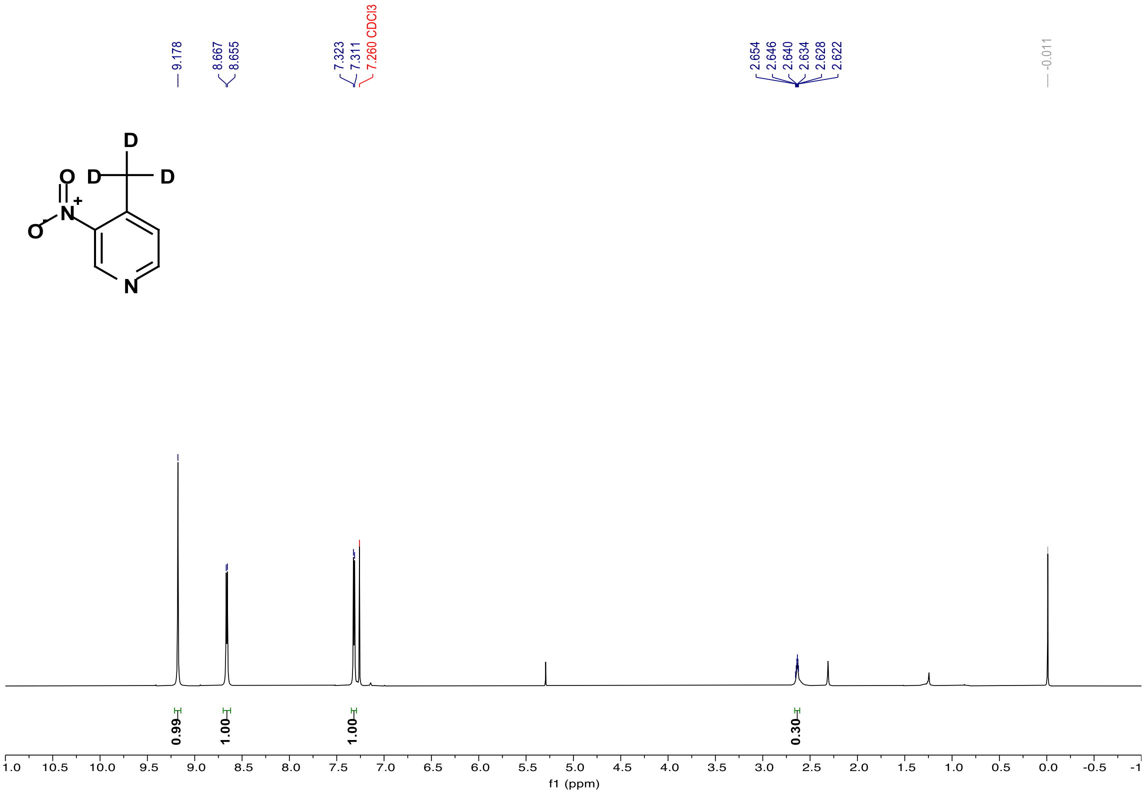
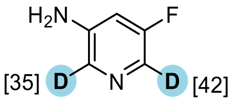


**Figure S61** ${}^{1}$H NMR of ***16-d*** in Chloroform-*d*



**Deuteration of 3-Amino-5-fluoropyridine (17)**



General procedure to afford **17-*d*** as brown solid (94.5 mg, 84%) with D-incorporation 35% for 2-position and 42% for 6-position by $^1$H NMR; 0.83 D by GC-MS; $R_f$ = 0.25 (Petroleum ether/EtOAc = 1/1, 1% $Et_3N$).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.90 (t, *J* = 1.8 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 6.69 (dt, *J* = 10.4, 2.4 Hz, 1H), 3.76 (s, 2H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **7.92 – 7.88 (m, 0.58H, Labelled)**, **7.86 (d, *J* = 2.3 Hz, 0.65H, Labelled)**, 6.69 (dq, *J* = 10.4, 0.9 Hz, 1H), 3.81 (s, 3H).

**Figure S62** $^1$H NMR spectrum comparison

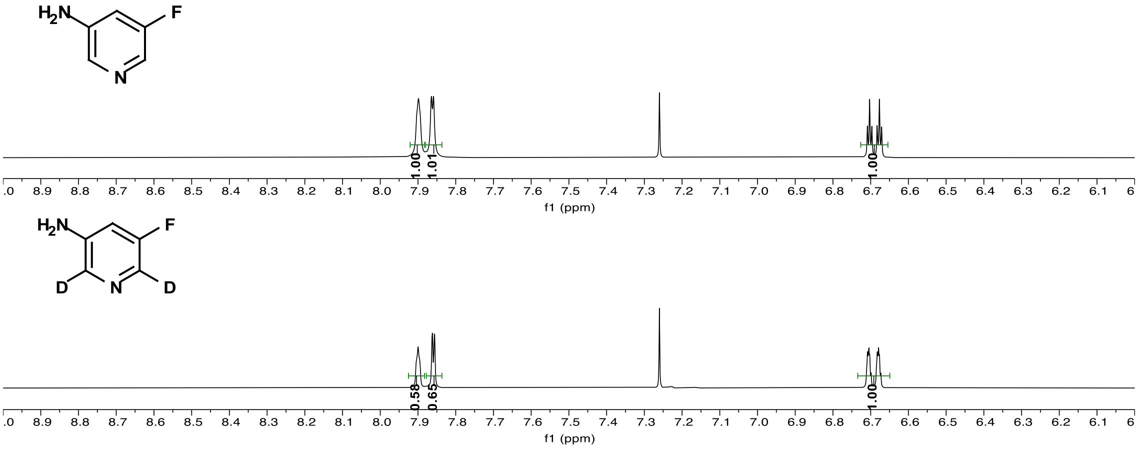


**Figure S63** GC-MS spectrum comparison

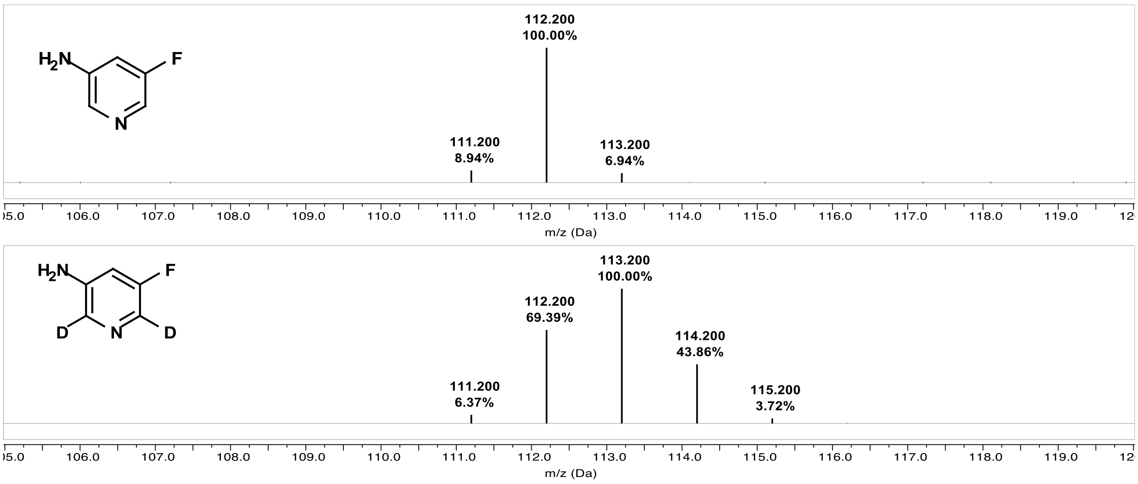


**Figure S64** $^1$H NMR of **17** in Chloroform-*d*

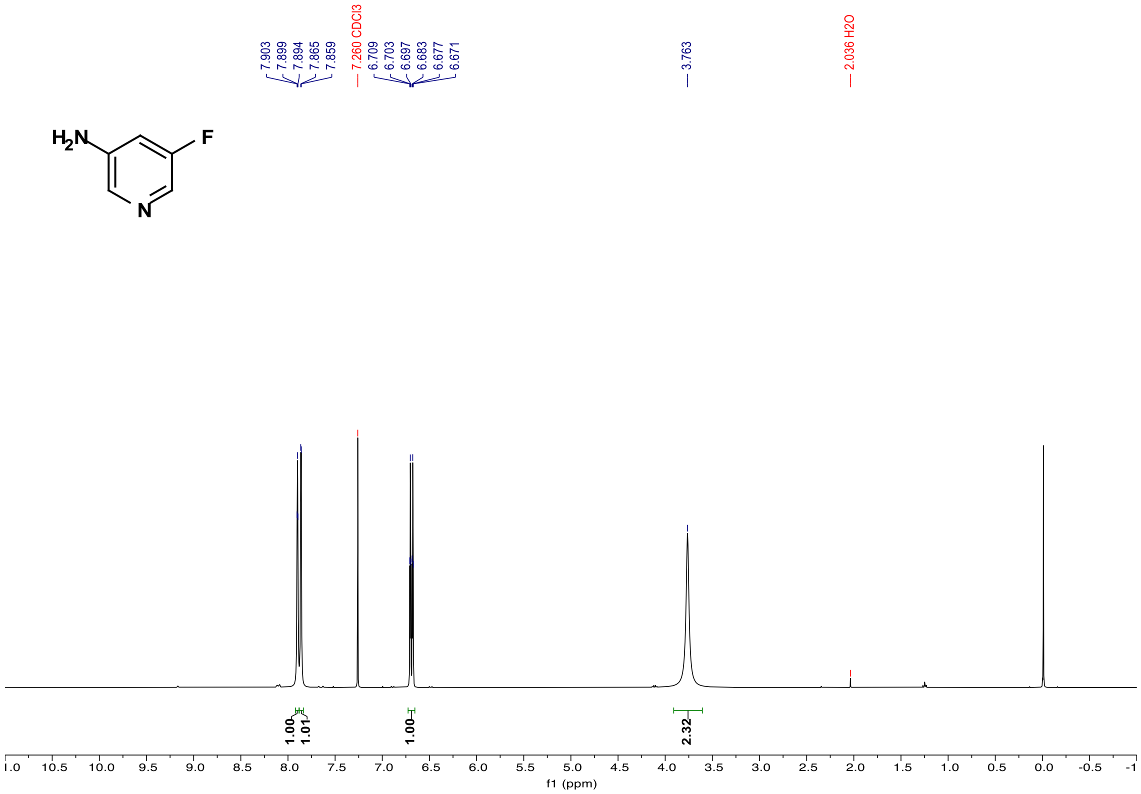
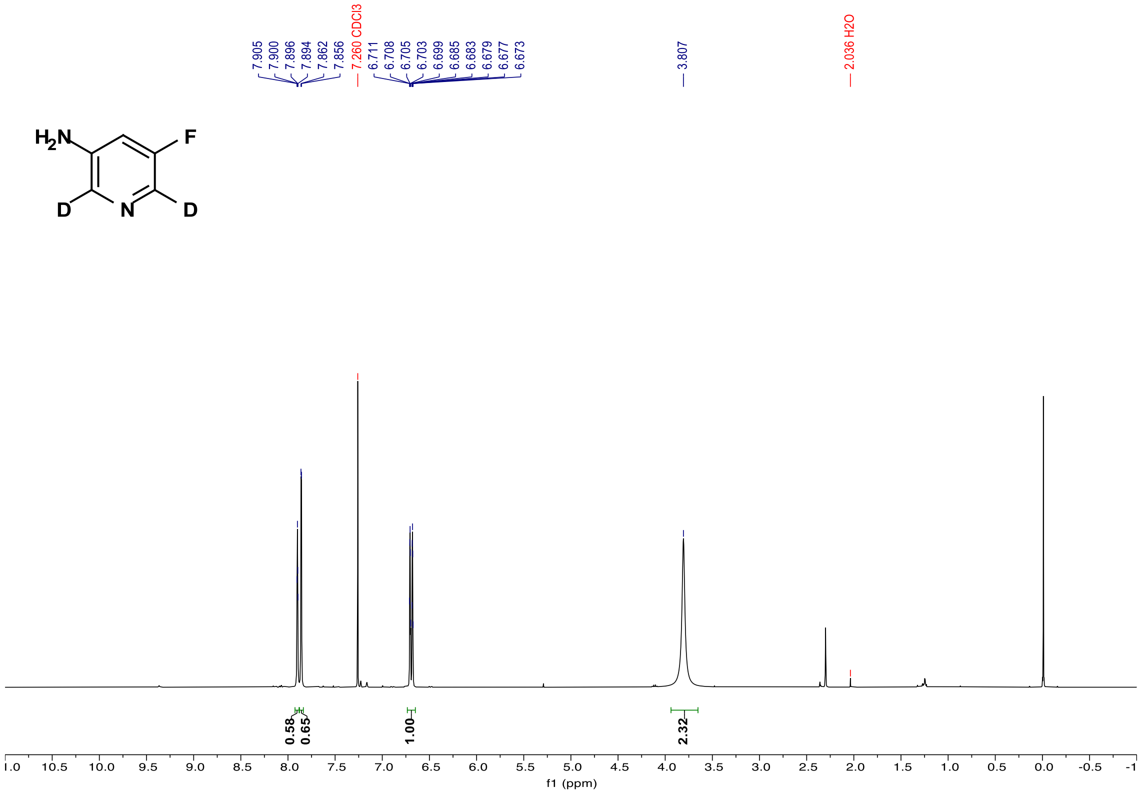
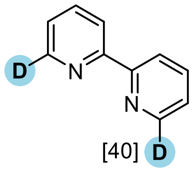


**Figure S65** $^1$H NMR of **17-*d*** in Chloroform-*d*



### Deuteration of 2,2'-Bipyridine (20)



General procedure to afford **20-*d*** as white solid (145.7 mg, 93%) with D-incorporation 40% for 6-position by $^1H$ NMR; 0.83 D by GC-MS; $R_f$ = 0.25 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1H$ NMR (400 MHz, Chloroform-*d*) δ 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.40 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.82 (td, *J* = 7.7, 1.8 Hz, 1H), 7.31 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H).

**NMR data for deuterated product:** $^1H$ NMR (400 MHz, Chloroform-*d*) **δ 8.68 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1.2H, Labelled)**, 8.40 (dt, *J* = 8.0, 1.2 Hz, 2H), 7.82 (td, *J* = 7.7, 1.6 Hz, 2H), 7.31 (ddt, *J* = 7.5, 3.4, 1.3 Hz, 2H).

**Figure S66** $^1H$ NMR spectrum comparison

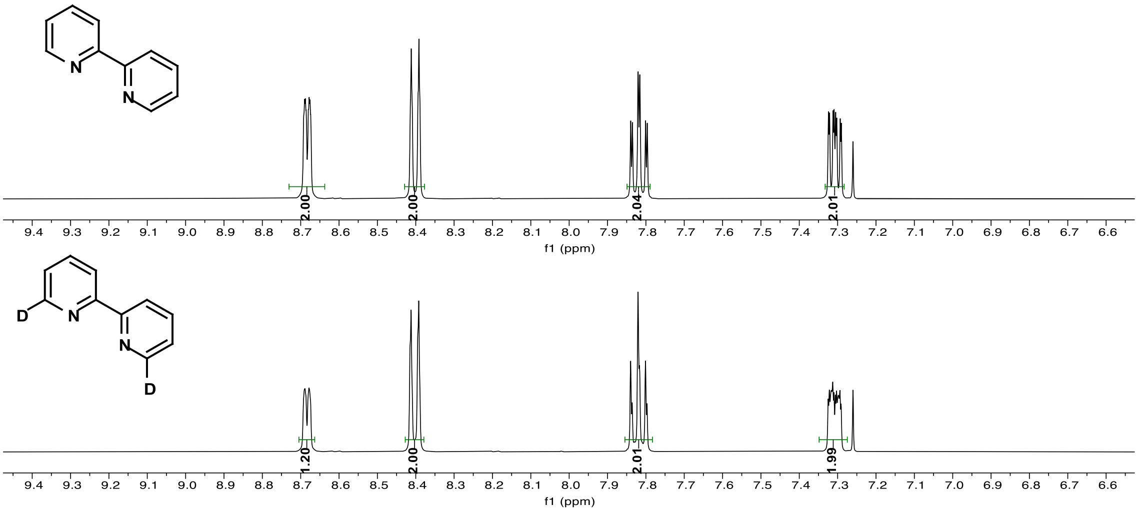


**Figure S67** GC-MS spectrum comparison

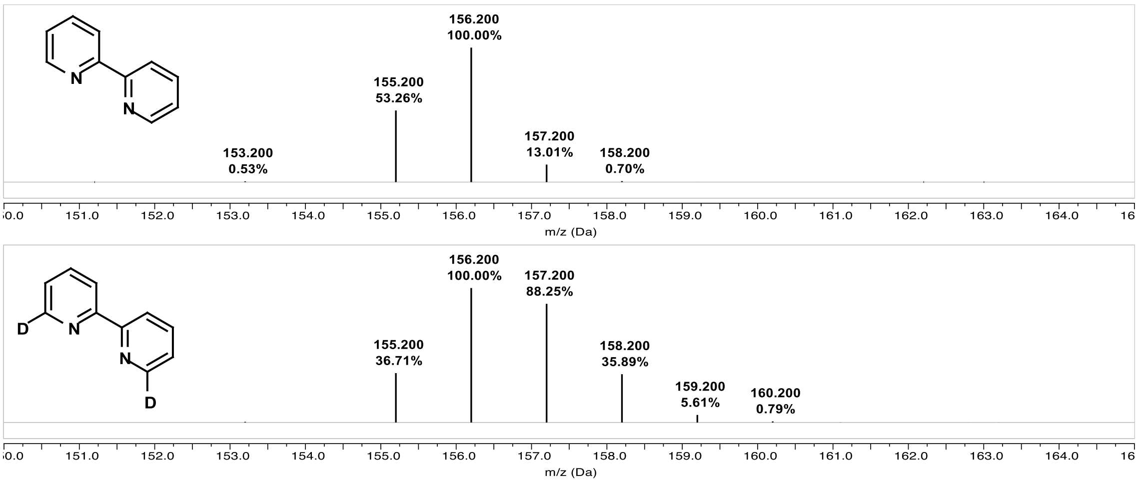


**Figure S68** $^1$H NMR of **20** in Chloroform-*d*

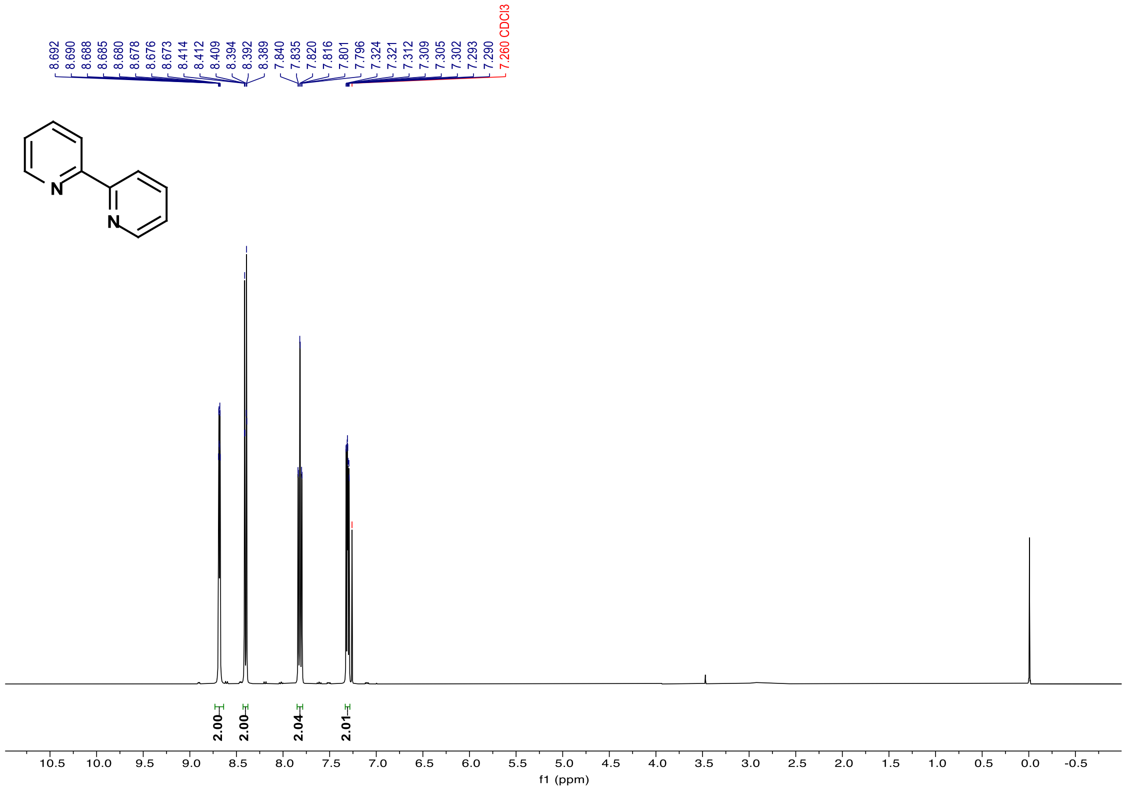
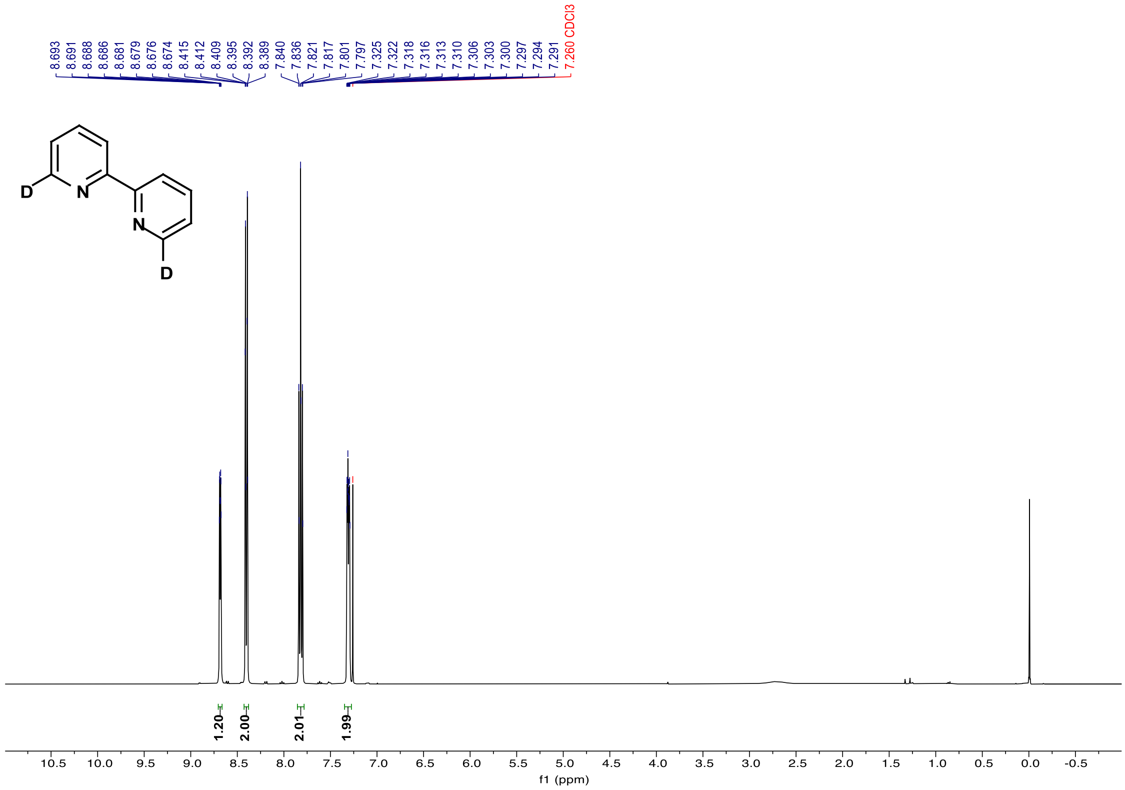
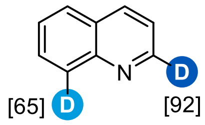


**Figure S69** $^1$H NMR of **20-*d*** in Chloroform-*d*



## Deuteration of Quinoline (21)



General procedure to afford **21-*d*** as slight yellow liquid (118.5 mg, 92%) with D-incorporation 92% for 2-position and 65% 8-position by $^1$H NMR; 1.61 D by GC-MS; $R_f$ = 0.30 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.95 – 8.88 (m, 1H), 8.18 – 8.12 (m, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.71 (ddt, *J* = 8.6, 6.7, 1.6 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.38 (dtd, *J* = 8.1, 2.9, 1.4 Hz, 1H).

**NMR data for deuterated product:**.$^1$H NMR (400 MHz, Chloroform-*d*) δ **8.92 (dd, *J* = 4.2, 1.8 Hz, 0.08H, Labelled)**, 8.17 (d, *J* = 8.3 Hz, 1H), **8.12 (dq, *J* = 8.5, 0.9 Hz, 0.35H, Labelled)**, 7.82 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.72 (dtt, *J* = 6.8, 2.7, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H).

**Figure S70** $^1$H NMR spectrum comparison

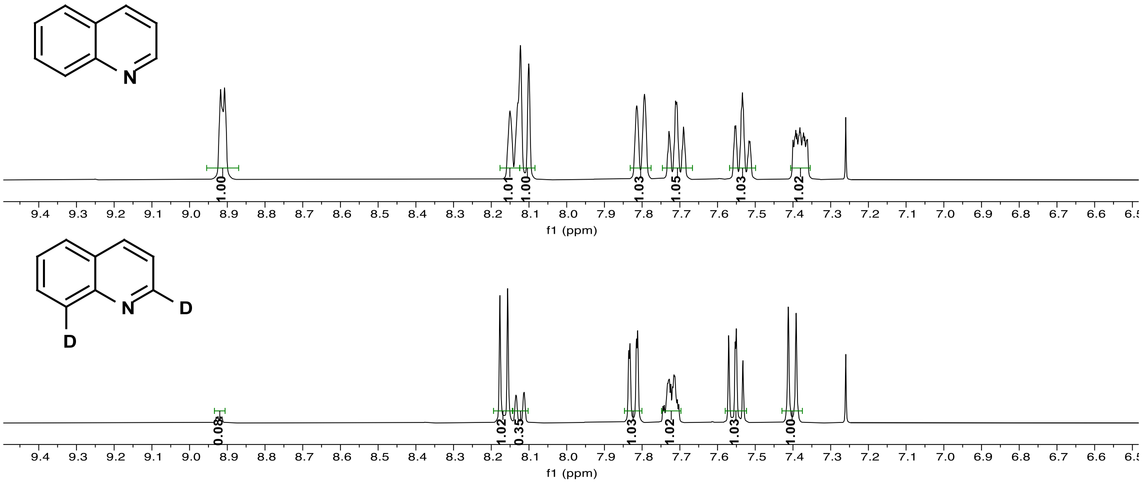


**Figure S71** GC-MS spectrum comparison

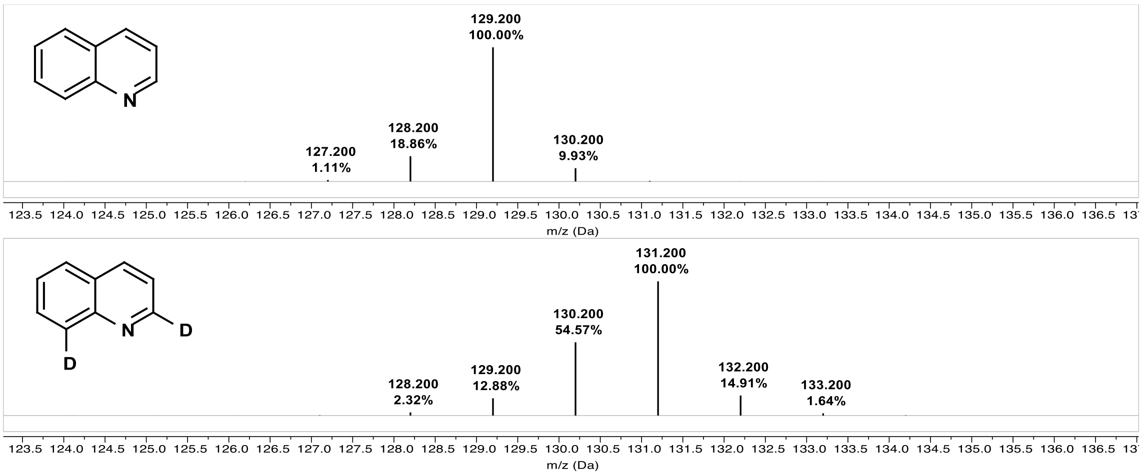


**Figure S72** $^1$H NMR of **21** in Chloroform-*d*

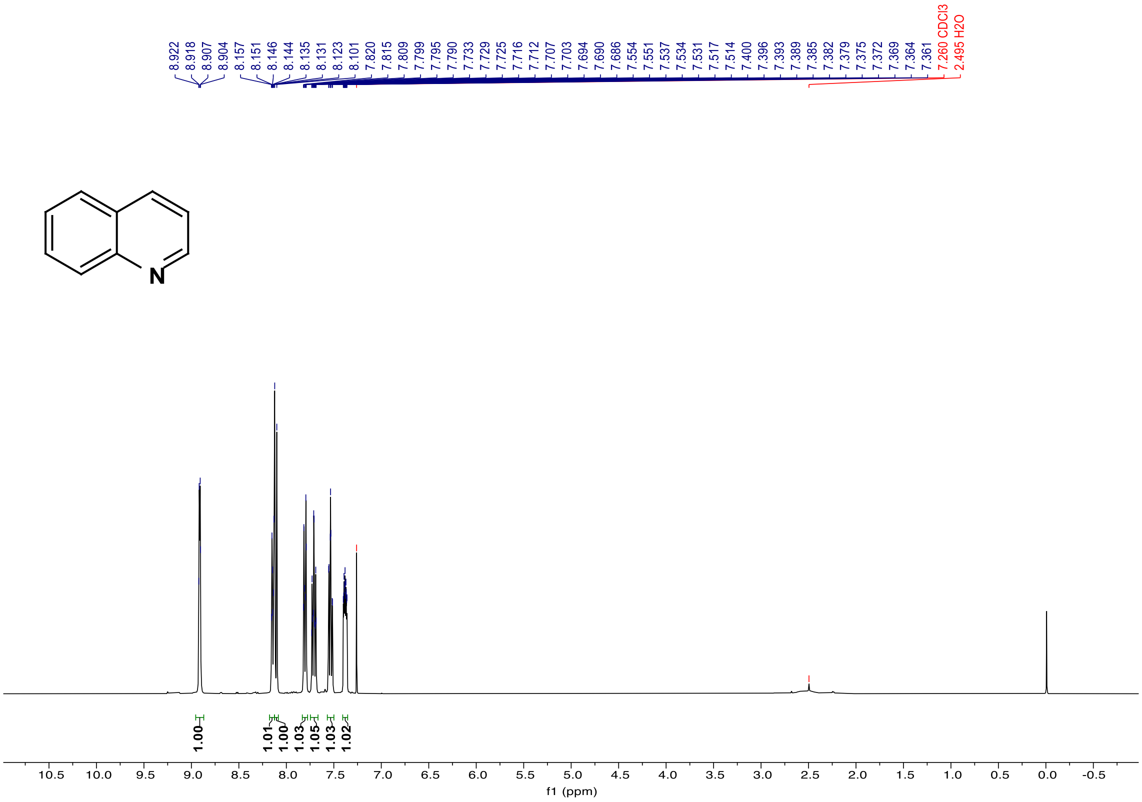
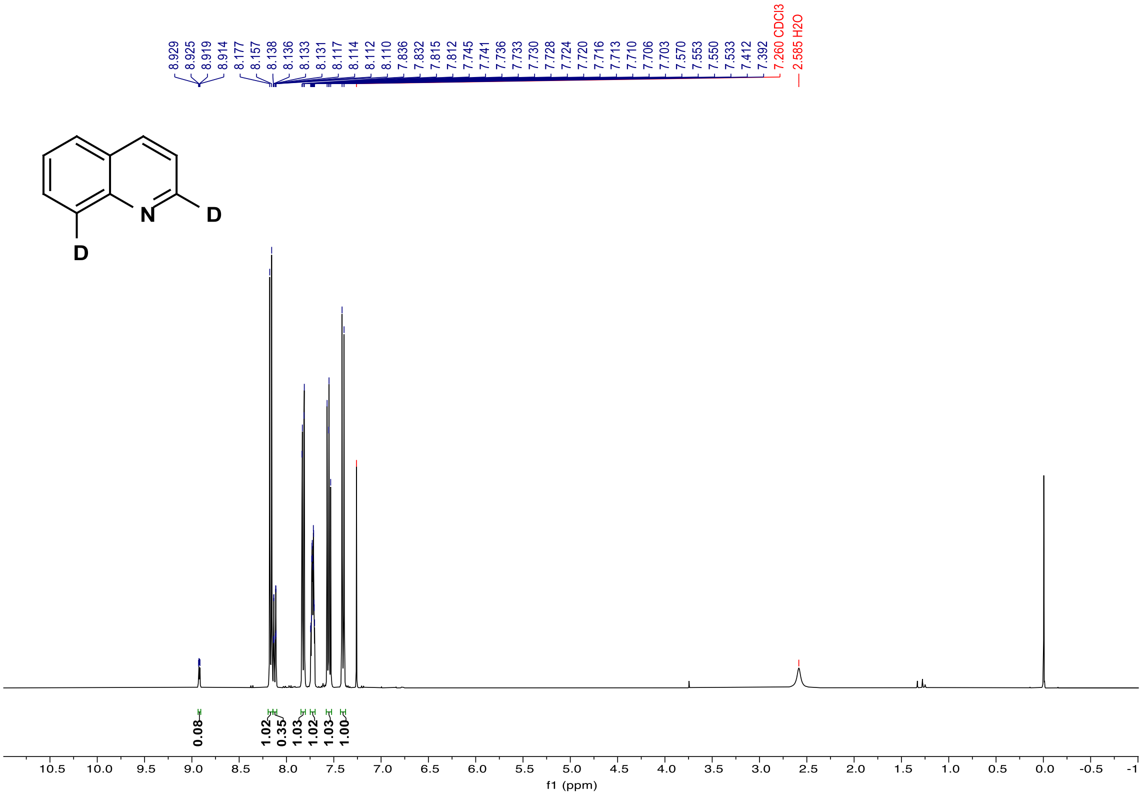
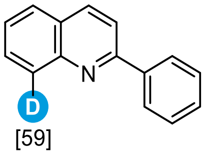


**Figure S73** $^1$H NMR of ***21-d*** in Chloroform-*d*



## Deuteration of 2-phenylquinoline (22)



General procedure to afford **22-*d*** as white solid (187.2 mg, 91%) with D-incorporation 59% for 8-position by $^1$H NMR; 0.57 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 8/1).

**NMR data for starting material**: $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.22 (t, *J* = 9.2 Hz, 2H), 8.18 (d, *J* = 7.1 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.74 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.62 – 7.50 (m, 3H), 7.51 – 7.41 (m, 1H).

**NMR data for deuterated product**: $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.19 (m, 2H), **8.19 – 8.15 (m, 1.41H, Labelled)**, 7.88 (d, *J* = 8.6 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.74 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.51 – 7.45 (m, 1H).

**Figure S74** $^1$H NMR spectrum comparison

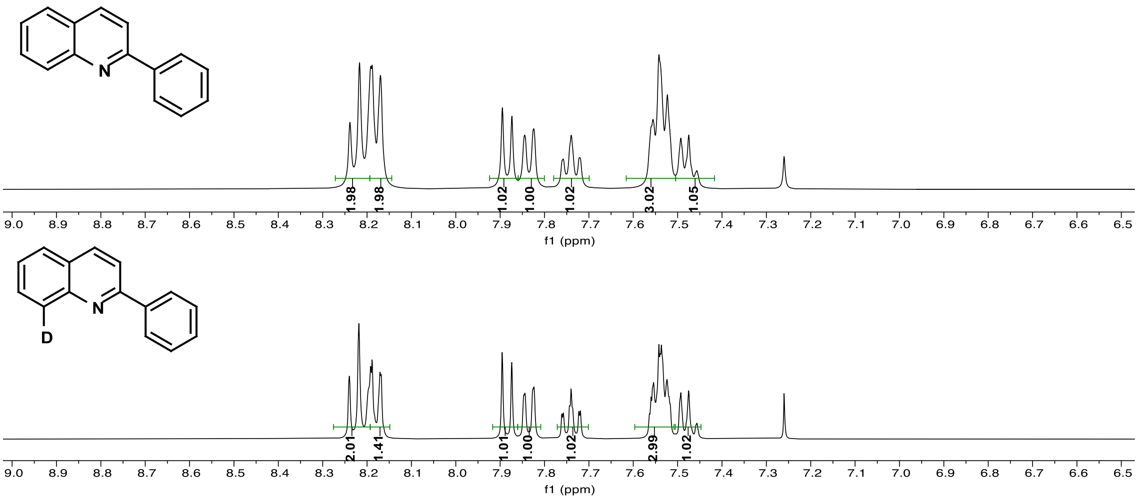


**Figure S75** GC-MS spectrum comparison

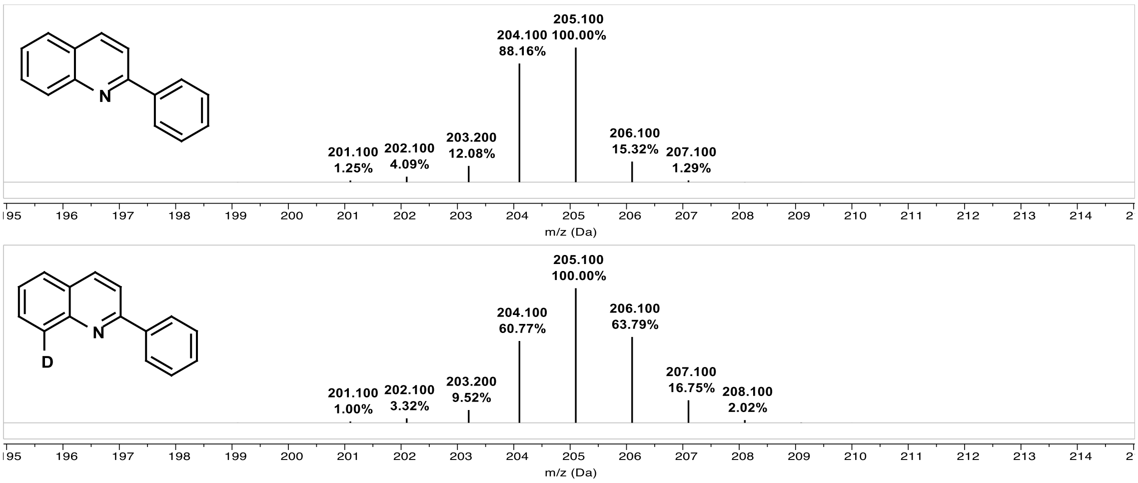


**Figure S76** $^1$H NMR of **22** in Chloroform-*d*

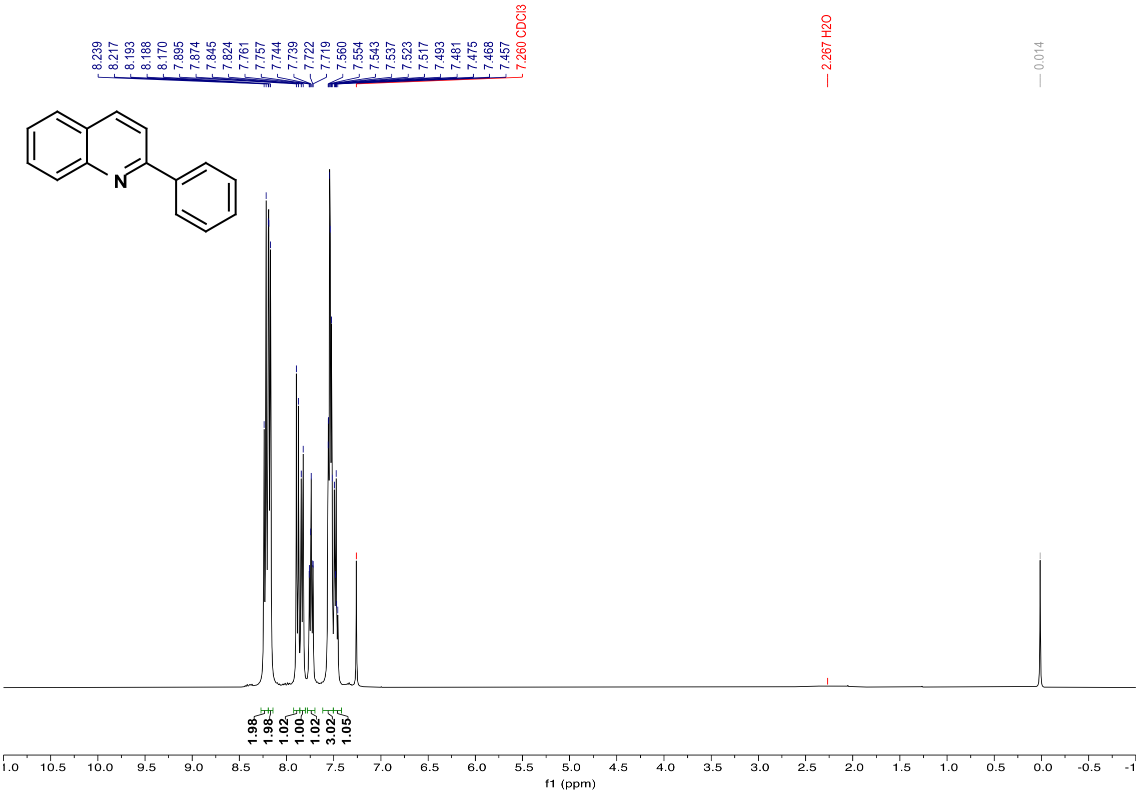
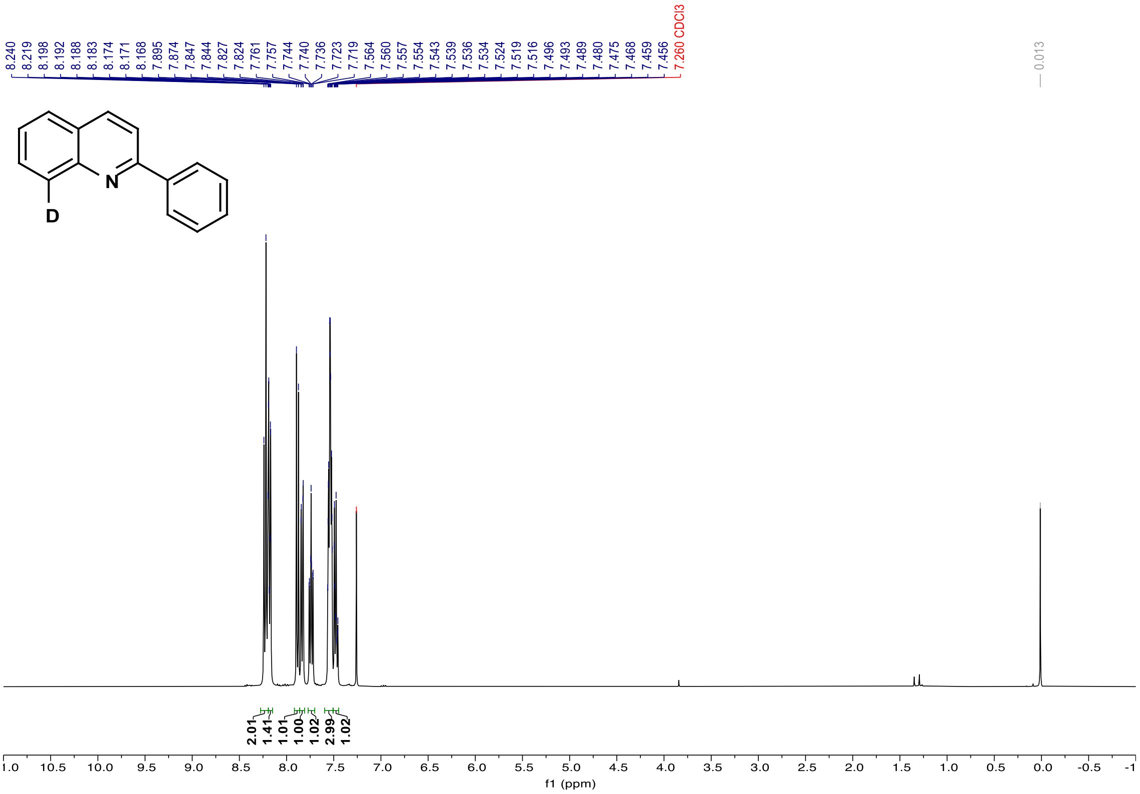
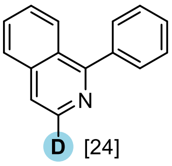


**Figure S77** $^1$H NMR of **22-*d*** in Chloroform-*d*



## Deuteration of 1-phenylisoquinoline (23)



General procedure to afford **23-*d*** as white solid (180.7 mg, 88%) with D-incorporation 24% for 3-position by $^1$H NMR; 0.40 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 8/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 5.7 Hz, 1H), 8.11 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.62 (m, 4H), 7.58 – 7.46 (m, 4H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.62 (d, *J* = 5.7 Hz, 0.76H, Labelled)**, 8.11 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.61 (m, 4H), 7.59 – 7.46 (m, 4H).

**Figure S78** $^1$H NMR spectrum comparison

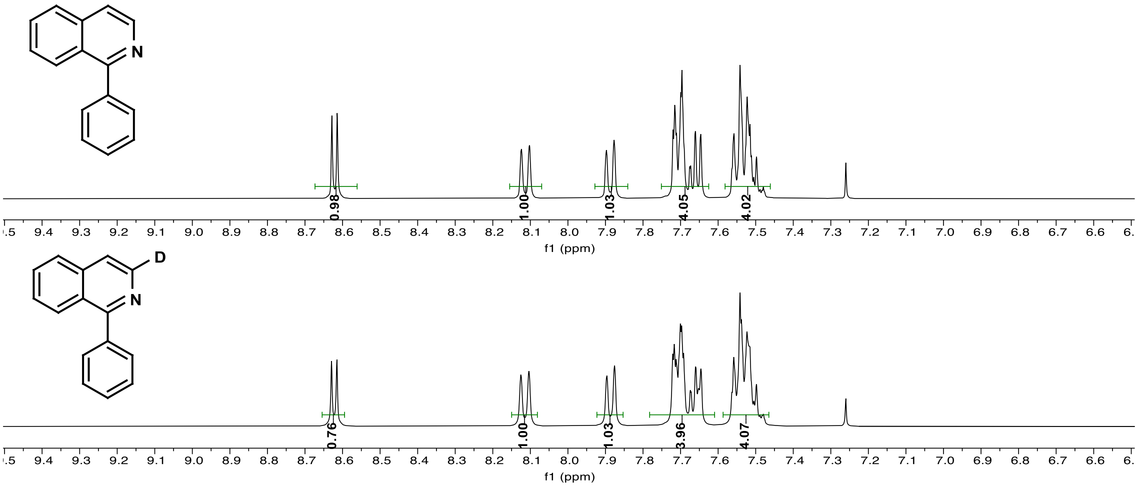


**Figure S79** $^1$H NMR spectrum comparison

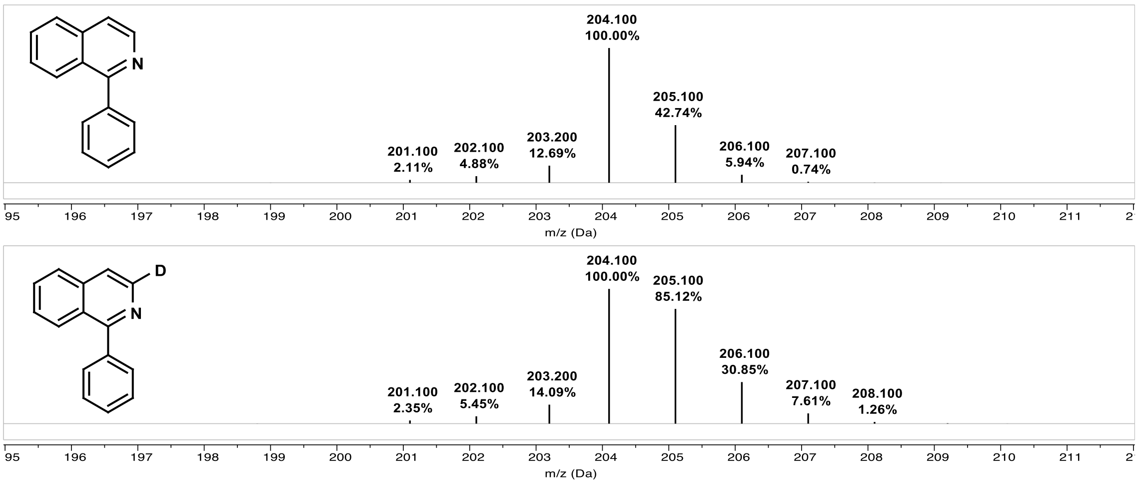


**Figure S80** $^1$H NMR of **23** in Chloroform-*d*

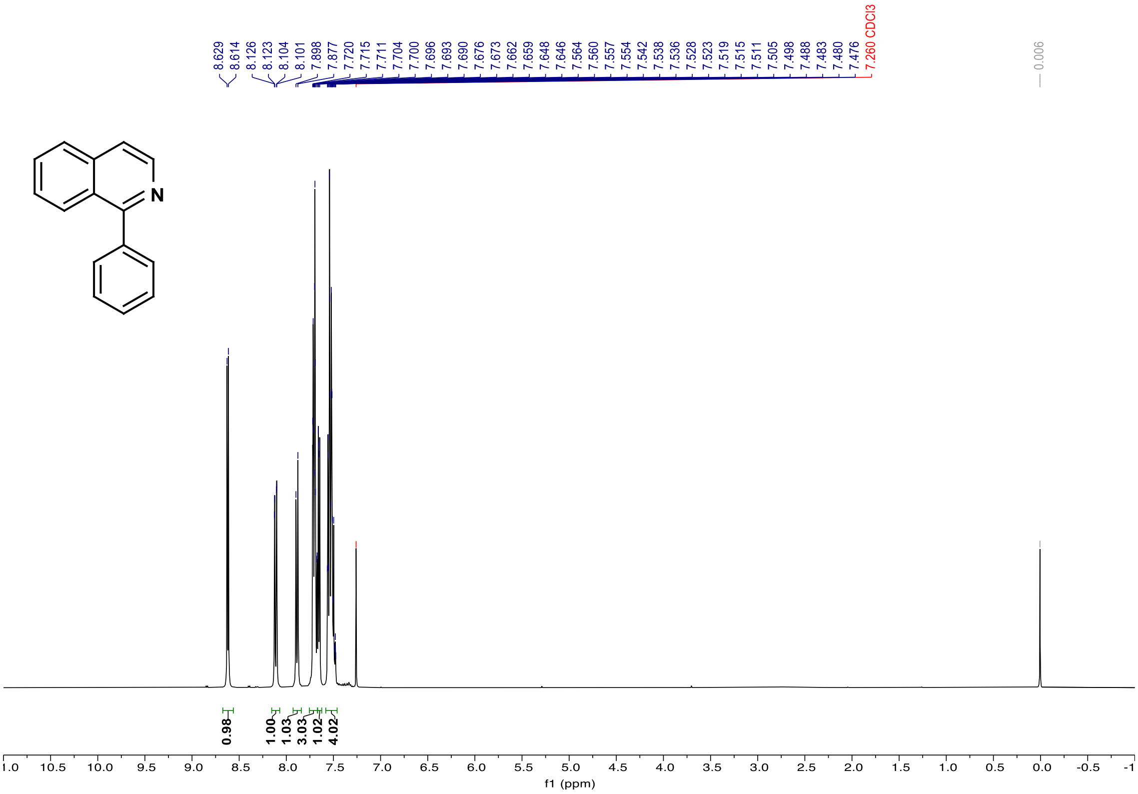
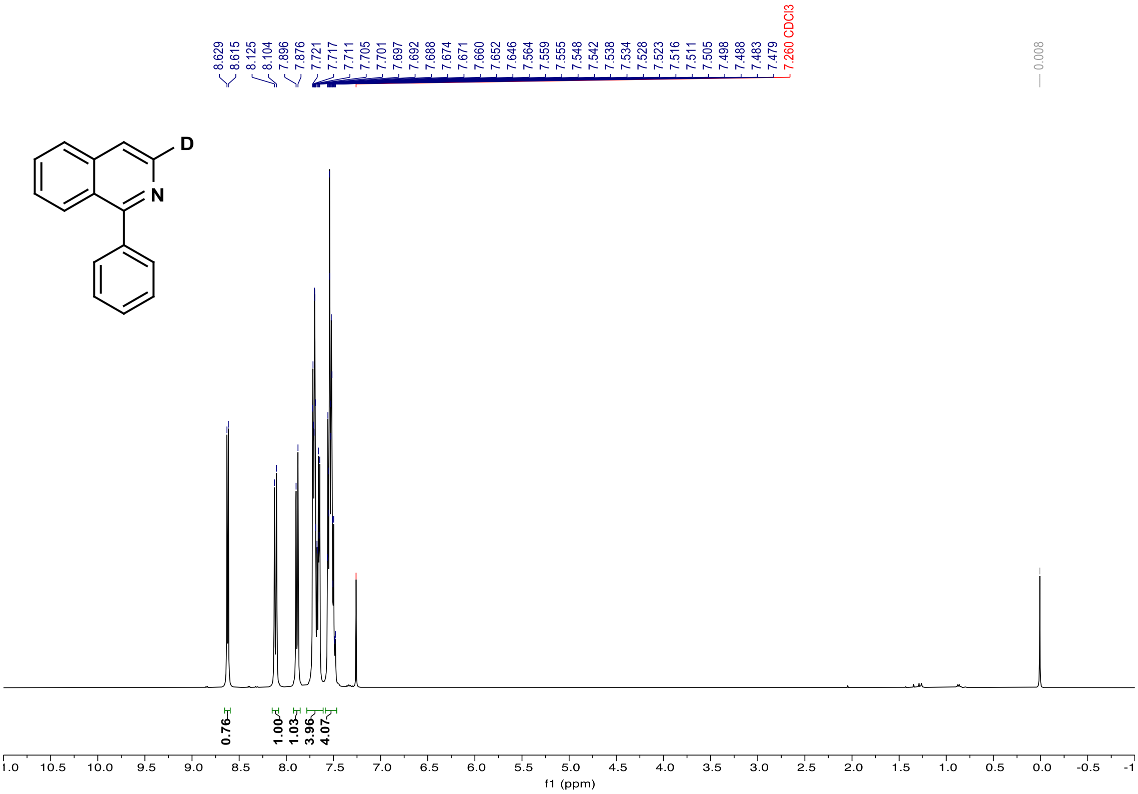
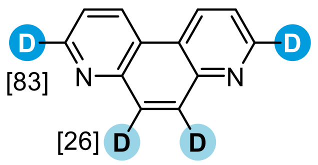


**Figure S81** $^1$H NMR of **23-*d*** in Chloroform-*d*



## Deuteration of 4,7-phenanthroline (24)



General procedure to afford **24-*d*** as white solid (156.3 mg, 87%) with D-incorporation 83% for 2,7-position and 26% for 9,10-position by $^1$H NMR; 2.13 D by GC-MS; $R_f$ = 0.4 (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.01 (dd, *J* = 4.4, 1.6 Hz, 2H), 8.87 (dd, *J* = 8.4, 1.7 Hz, 2H), 8.23 (s, 2H), 7.60 (dd, *J* = 8.3, 4.4 Hz, 2H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **9.01 (dd, *J* = 4.4, 1.6 Hz, 0.34H, Labelled)**, 8.89 (d, *J* = 8.4 Hz, 2H), **8.24 (s, 1.48H, Labelled)**, 7.64 – 7.56 (m, 2H).

**Figure S82** $^1$H NMR spectrum comparison

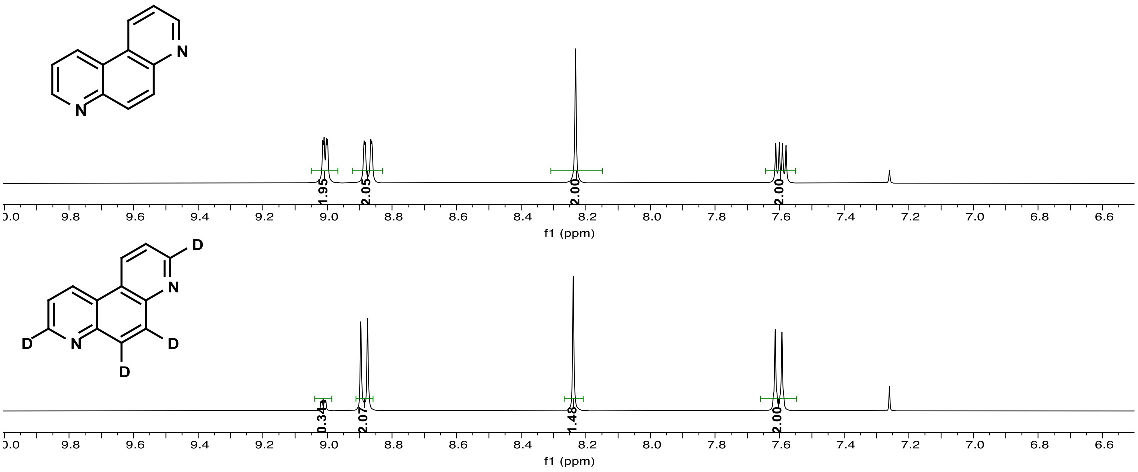


**Figure S83** GC-MS spectrum comparison

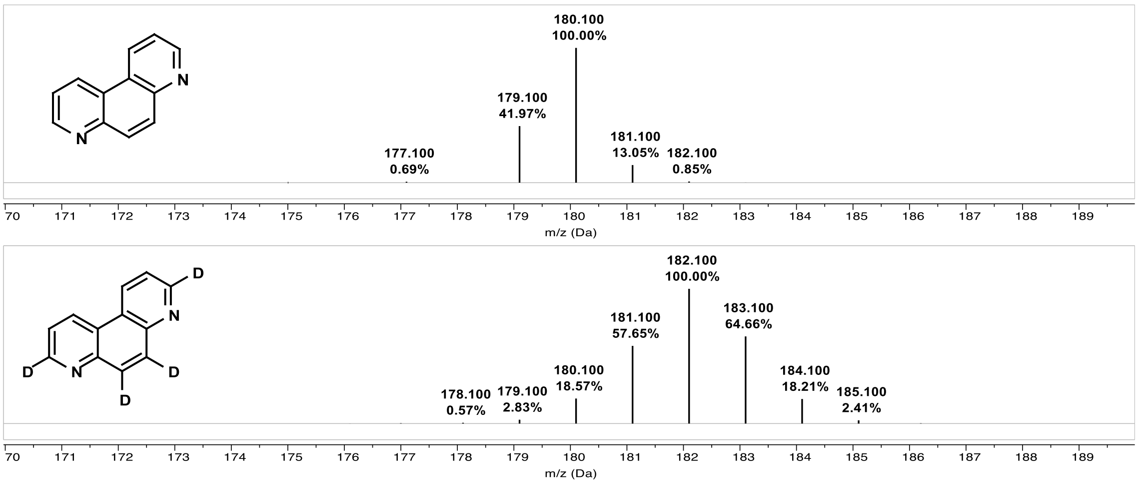


Figure S84 $^1$H NMR of **24** in Chloroform-*d*

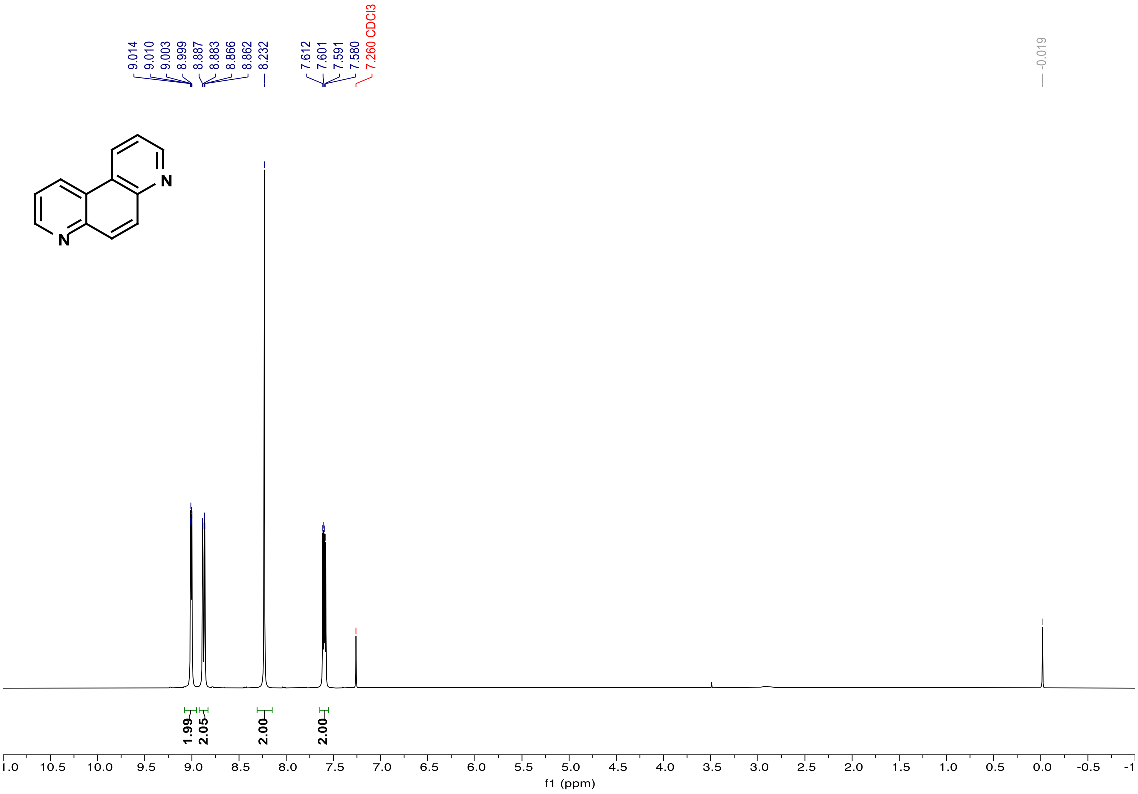
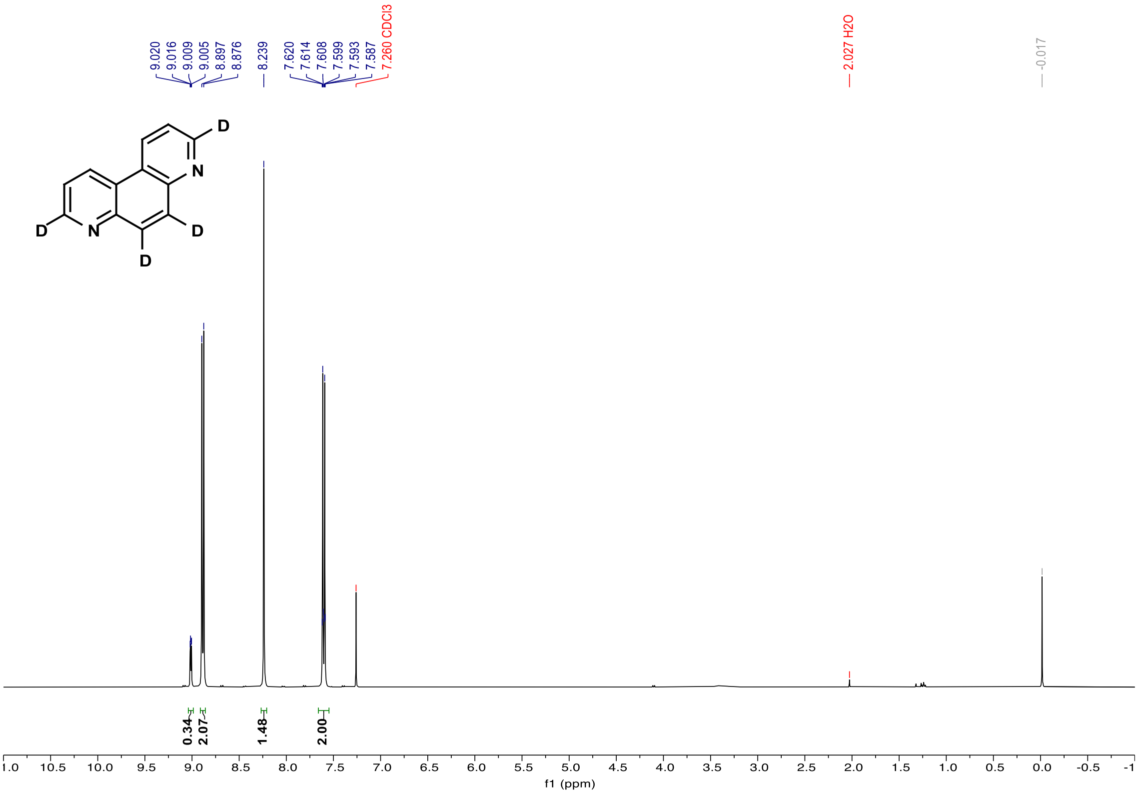
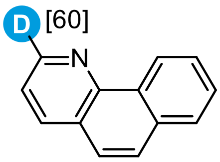


**Figure S85** $^1$H NMR of **24-*d*** in Chloroform-*d*



## Deuteration of benzo[h]quinoline (25)



General procedure to afford **25-*d*** as white solid (164.5 mg, 92%) with D-incorporation 60% for 2-position by $^1$H NMR; 0.58 D by GC-MS; $R_f$ = 0.4 (Petroleum ether/EtOAc = 8/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.32 (dd, *J* = 8.1, 1.5 Hz, 1H), 9.02 (dd, *J* = 4.4, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.92 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.73 – 7.65 (m, 2H), 7.53 (dd, *J* = 8.0, 4.4 Hz, 1H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **9.31 (d, *J* = 7.5 Hz, 0.40H, Labelled)**, 9.02 (dd, *J* = 4.4, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.70 (dd, *J* = 13.3, 8.1 Hz, 2H), 7.53 (dd, *J* = 8.0, 4.4 Hz, 1H).

**Figure S86** $^1$H NMR spectrum comparison

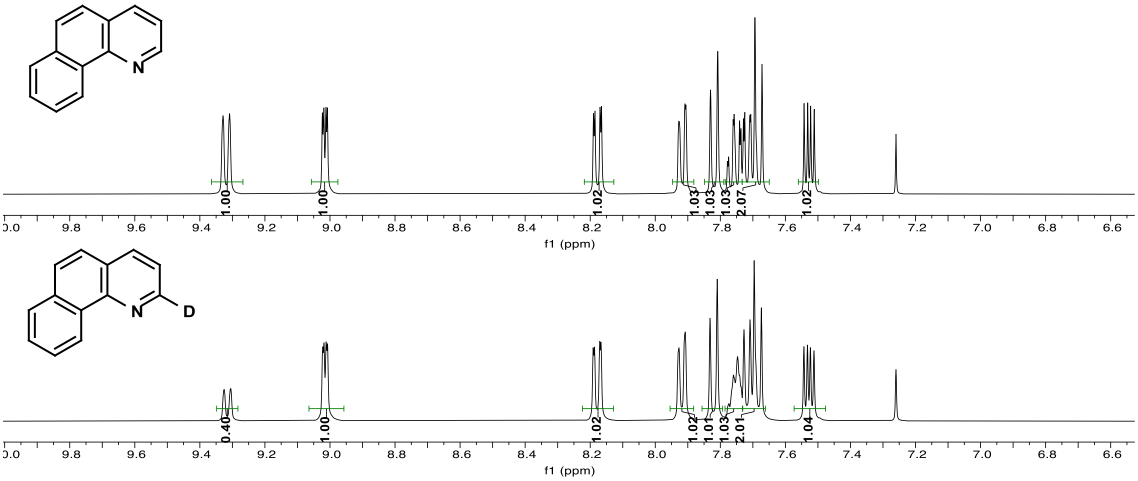


**Figure S87** GC-MS spectrum comparison

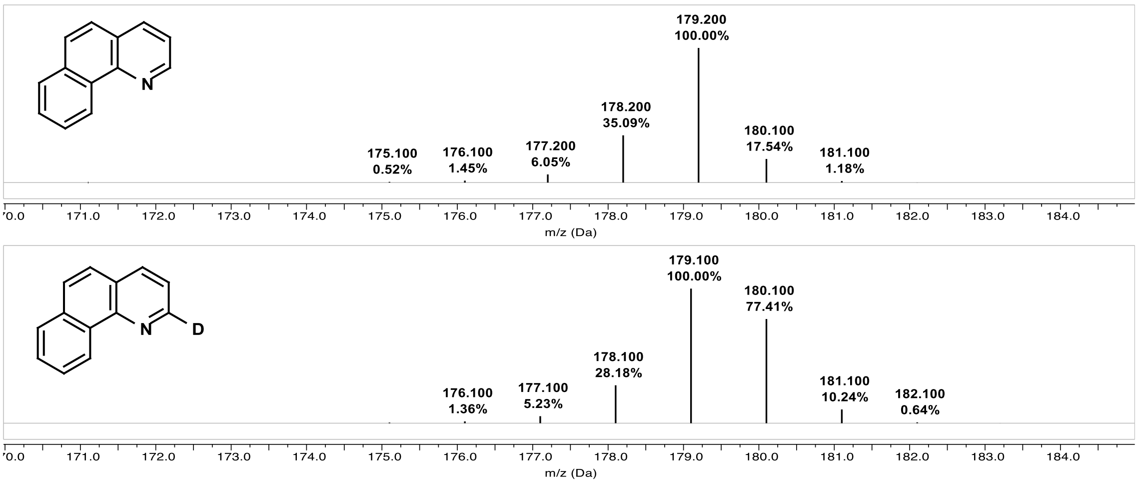


**Figure S88** $^1$H NMR of **25** in Chloroform-*d*

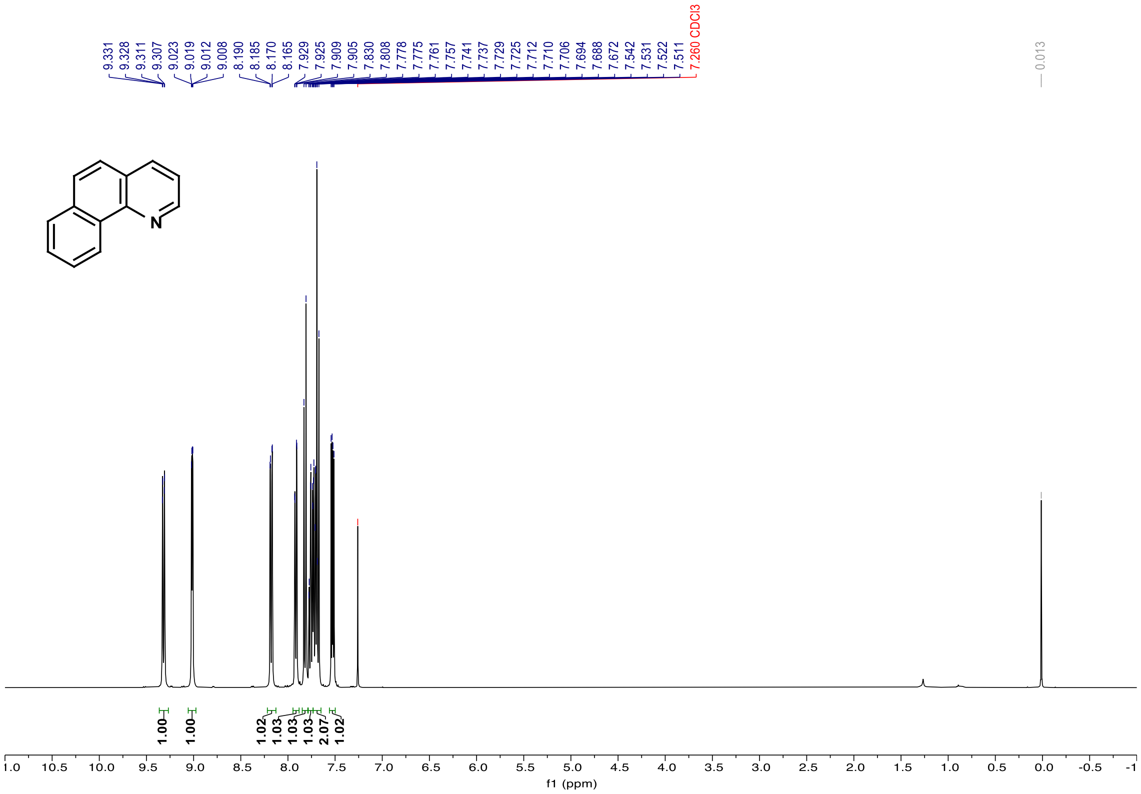
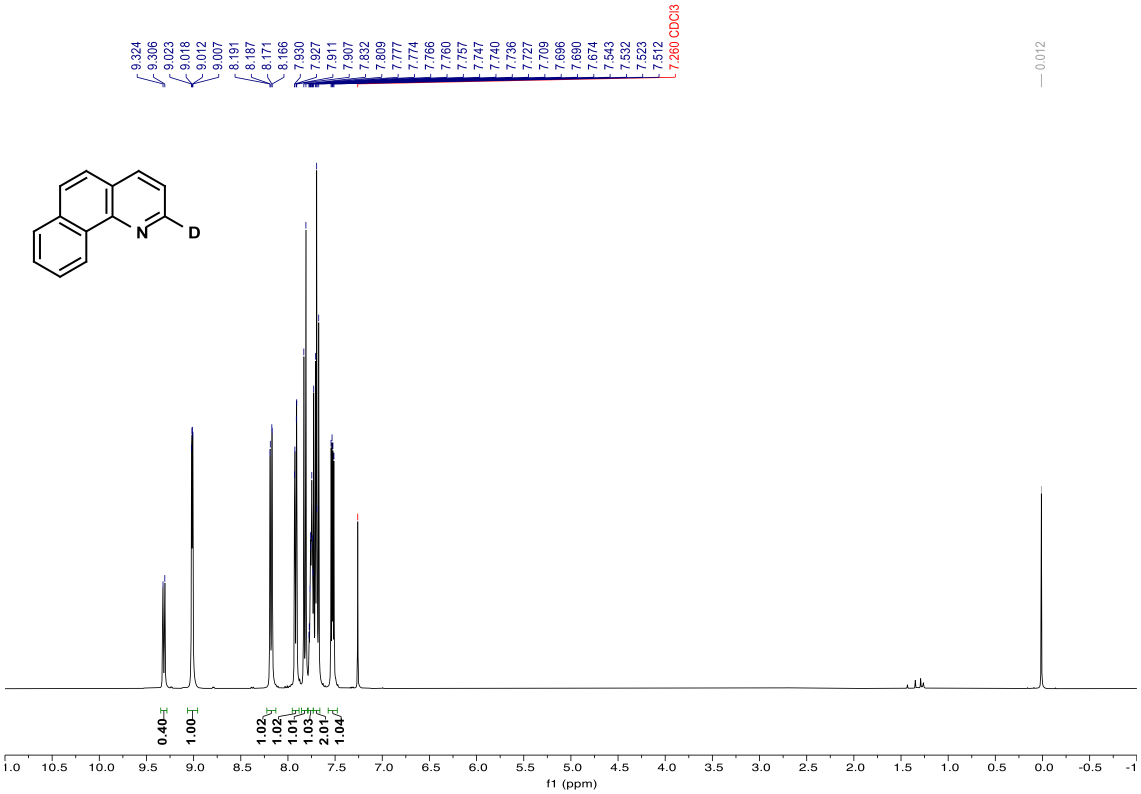
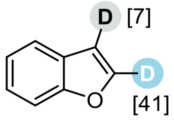


**Figure S89** $^1$H NMR of **25-*d*** in Chloroform-*d*



**Deuteration of benzofuran (26)**



General procedure to afford **26-*d*** as colourless liquid (73.5 mg, 62%) with D-incorporation 41% for 2-position and 7% 3-position by $^1$H NMR; 0.45 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 20/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.98 (d, *J* = 2.2 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.59 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.31 (td, *J* = 8.2, 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.4, 1.2 Hz, 1H), 6.96 (dd, *J* = 2.2, 1.0 Hz, 1H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ **7.98 (d, *J* = 2.2 Hz, 0.59H, Labelled)**, 7.69 – 7.63 (m, 1H), 7.62 – 7.56 (m, 1H), 7.31 (td, *J* = 8.3, 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.4, 1.1 Hz, 1H), **6.99 – 6.92 (m, 0.93H, Labelled)**.

**Figure S90** $^1$H NMR spectrum comparison

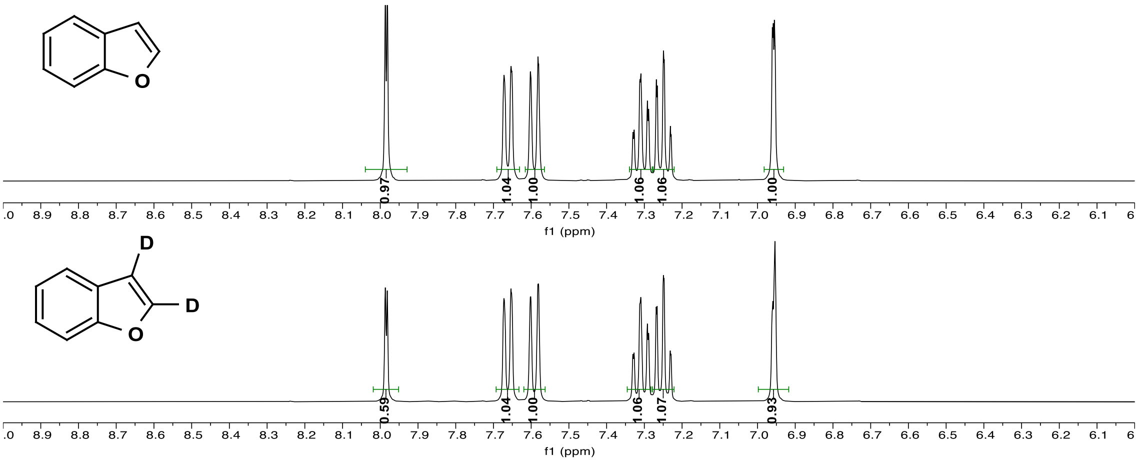
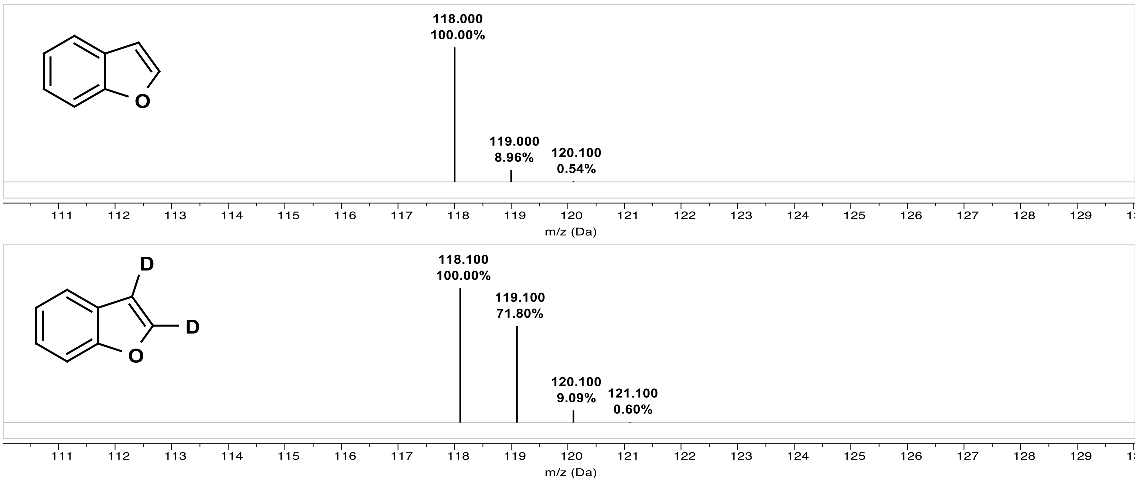
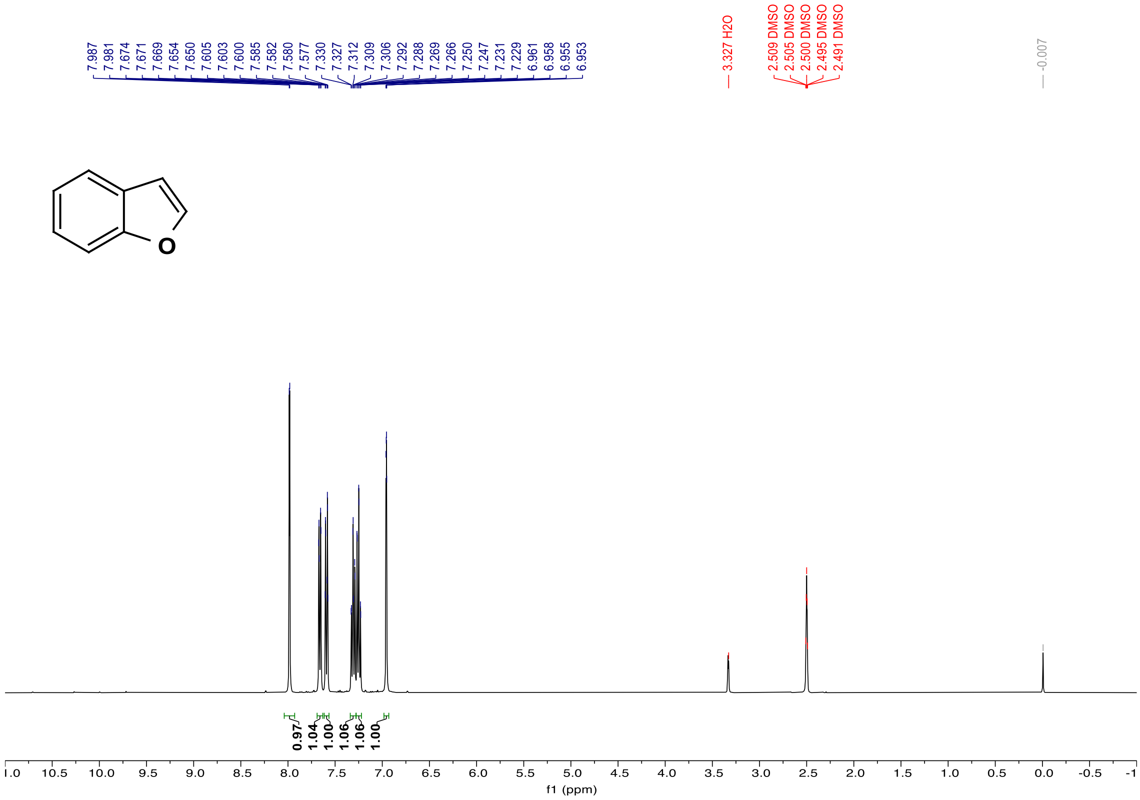


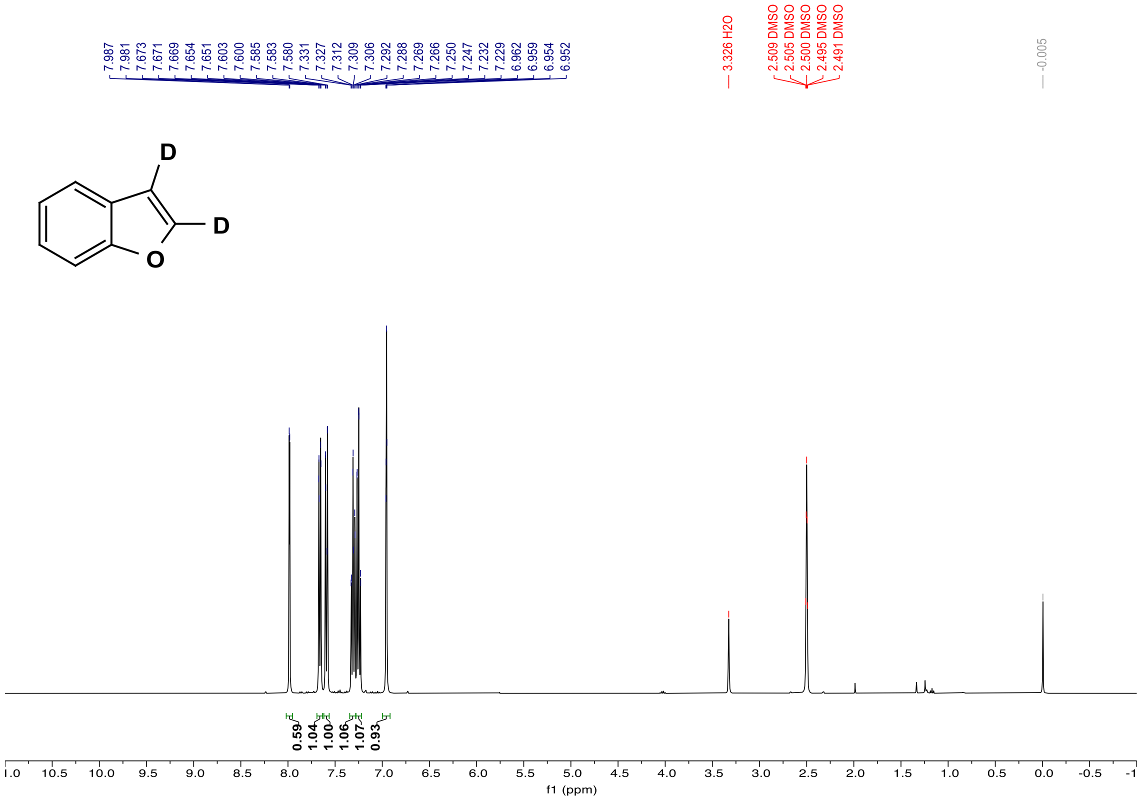
**Figure S91** GC-MS spectrum comparison



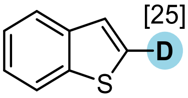
## **Figure S92** $^1$H NMR of **26** in DMSO-$d_6$



## **Figure S93** $^1$H NMR of **26-*d*** in DMSO-$d_6$



**Deuteration of benzo[b]thiophene (27)**



General procedure to afford **27-*d*** as white solid (115.3 mg, 86%) with D-incorporation 25% for 2-position by $^1$H NMR; 0.25 D by GC-MS; $R_f$ = 0.40 (Petroleum ether/EtOAc = 20/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.88 (m, 1H), 7.88 – 7.81 (m, 1H), 7.45 (d, *J* = 5.5 Hz, 1H), 7.42 – 7.31 (m, 3H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.87 (m, 1H), 7.87 – 7.81 (m, 1H), **7.45 (d, *J* = 5.4 Hz, 0.75H, Labelled)**, 7.41 – 7.32 (m, 3H).

**Figure S94** $^1$H NMR spectrum comparison

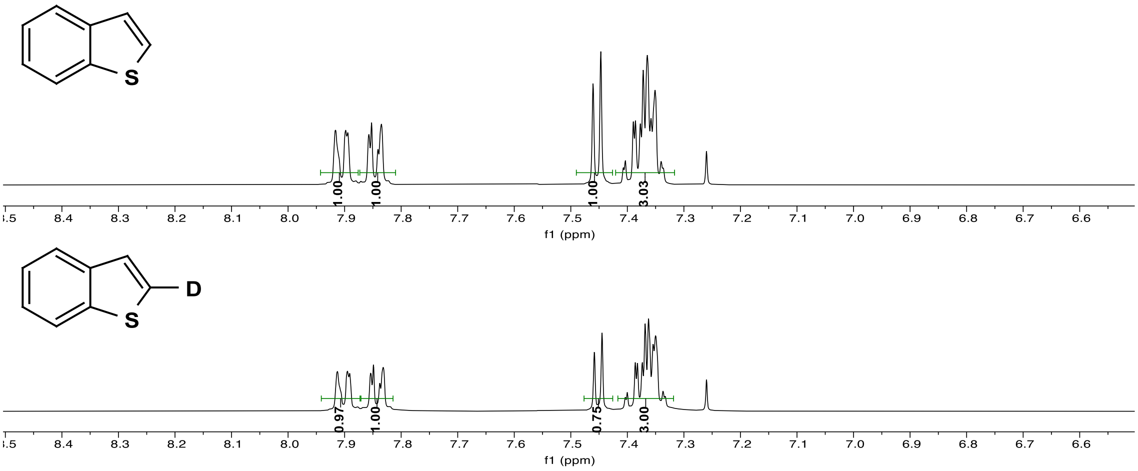


**Figure S95** GC-MS spectrum comparison

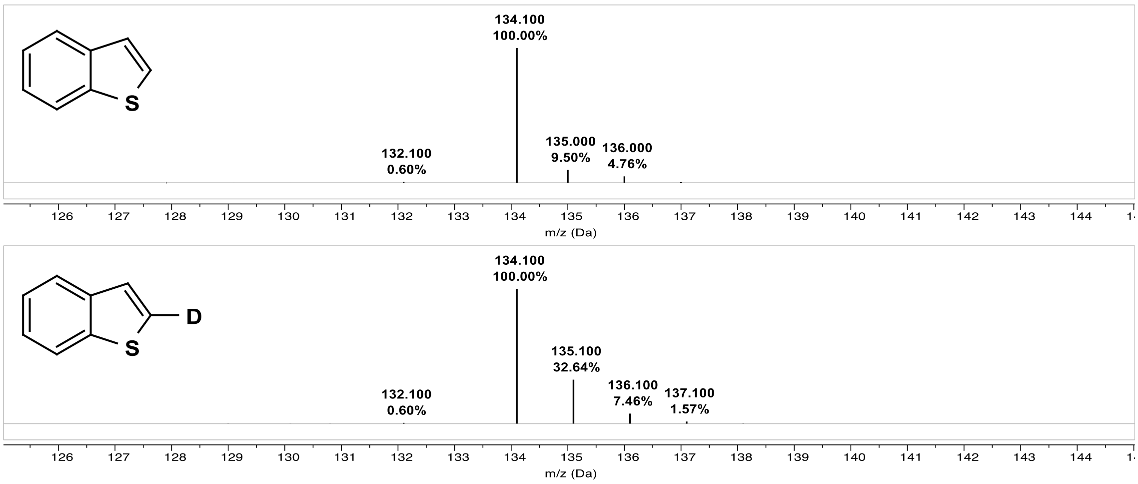


**Figure S96** $^1$H NMR of **27** in *Chloroform-d*

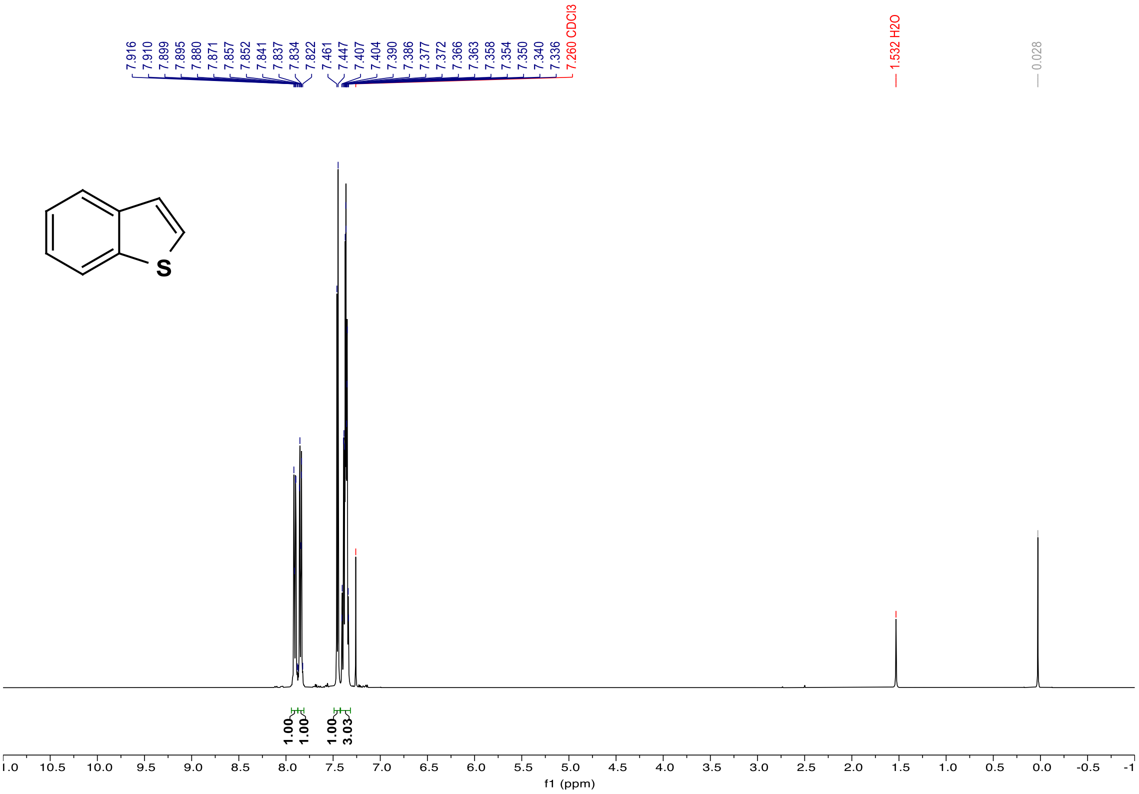
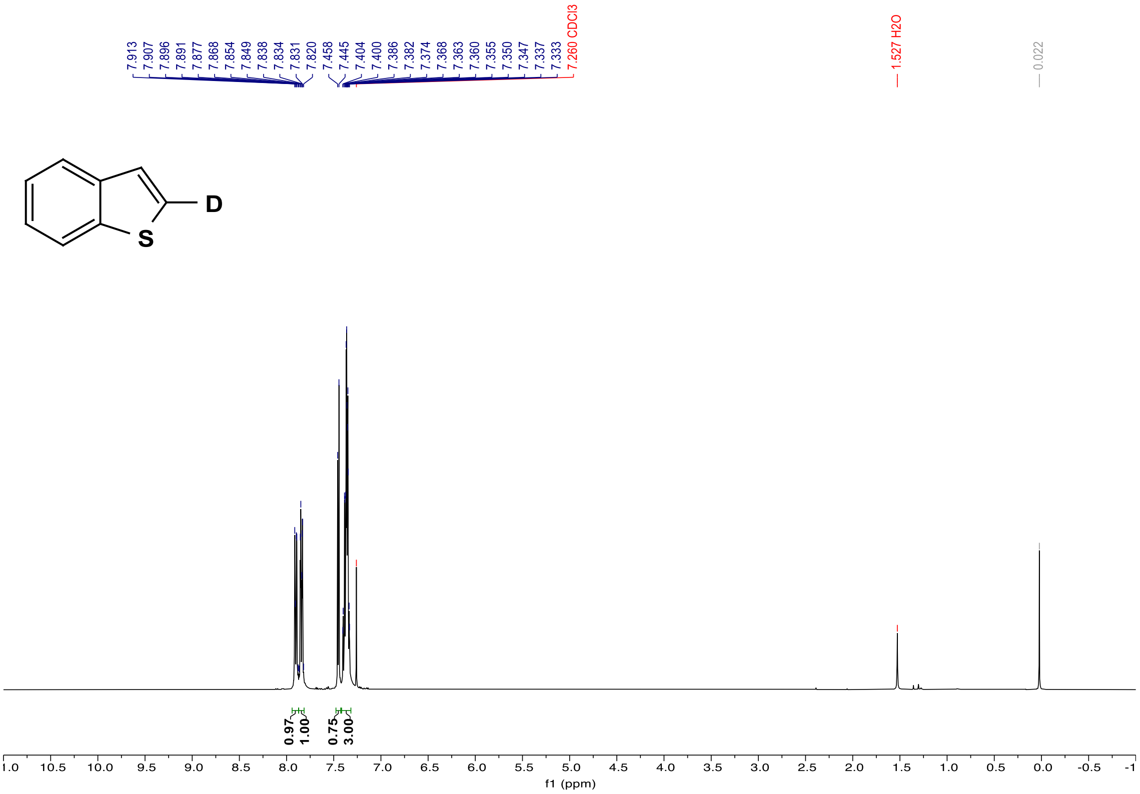
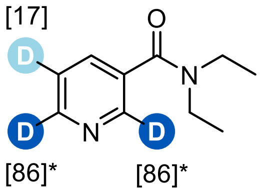


**Figure S97** $^1$H NMR of **27-*d*** in *Chloroform-d*



## Deuteration of Nikethamide (28)



General procedure to afford **28-*d*** as colourless liquid (140.3mg, 79%) with D-incorporation 85% for 2-position, 17% for 5-position and 86% for 6-position by $^1$H NMR; 1.85 D by GC-MS; R$_f$ = 0.40 (DCM/MeOH = 15/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.67 – 8.60 (m, 2H), 7.35 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 3.65 – 3.45 (m, 2H), 3.37 – 3.15 (m, 2H), 1.25 (t, *J* = 6.6 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.67 – 8.61 (m, 0.27H, Labelled)**, 7.76 – 7.70 (m, 1H), **7.35 (d, *J* = 7.8 Hz, 0.83H, Labelled)**, 3.65 – 3.45 (m, 2H), 3.37 – 3.15 (m, 2H), 1.25 (t, *J* = 6.7 Hz, 3H), 1.13 (t, *J* = 7.6 Hz, 3H).

**Figure S98** $^1$H NMR spectrum comparison

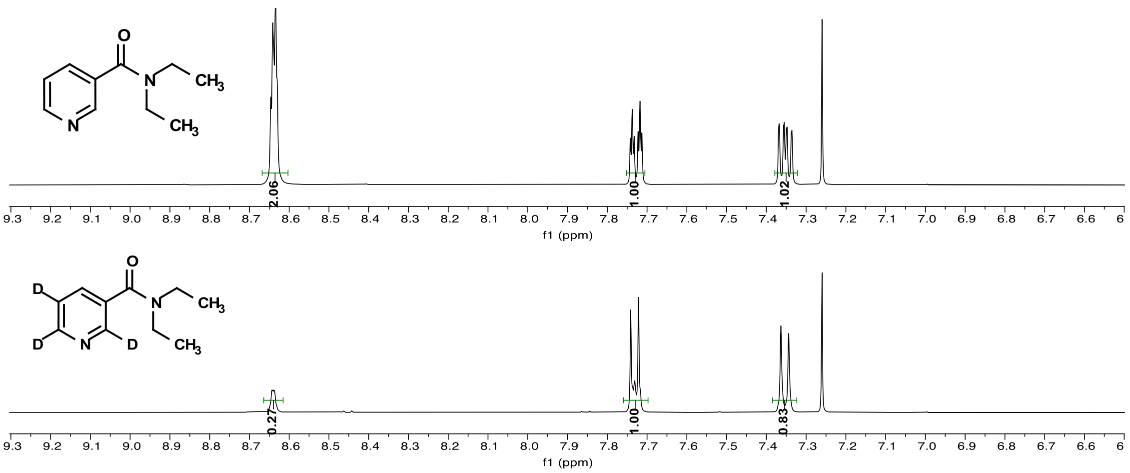


**Figure S99** GC-MS spectrum comparison

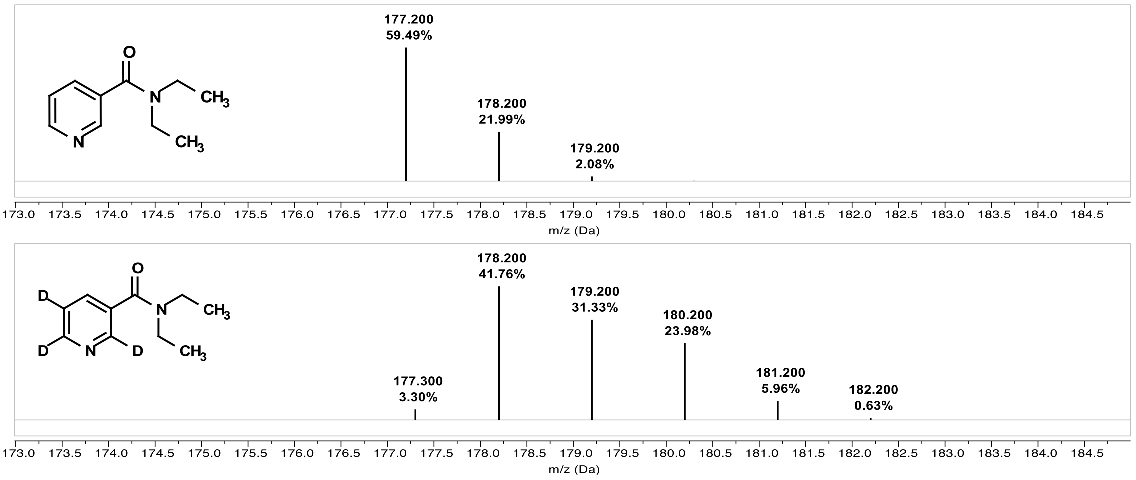


**Figure S100** $^1$H NMR of **28** in Chloroform-*d*

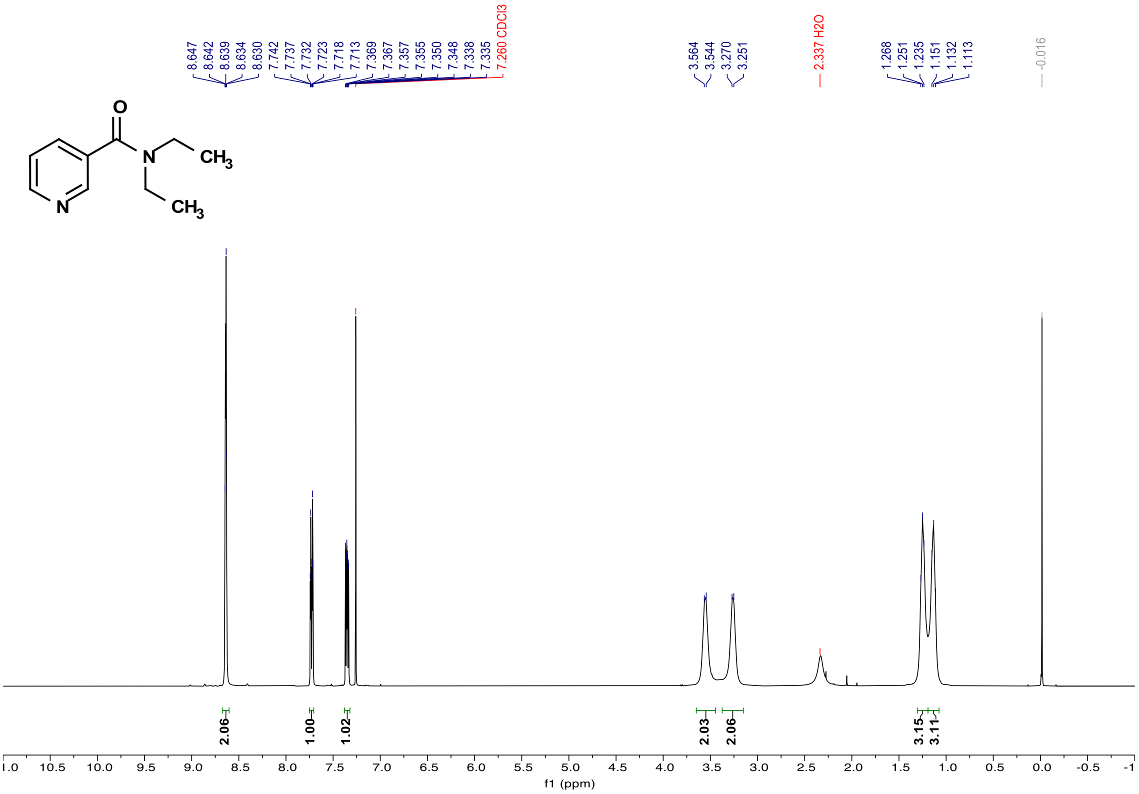
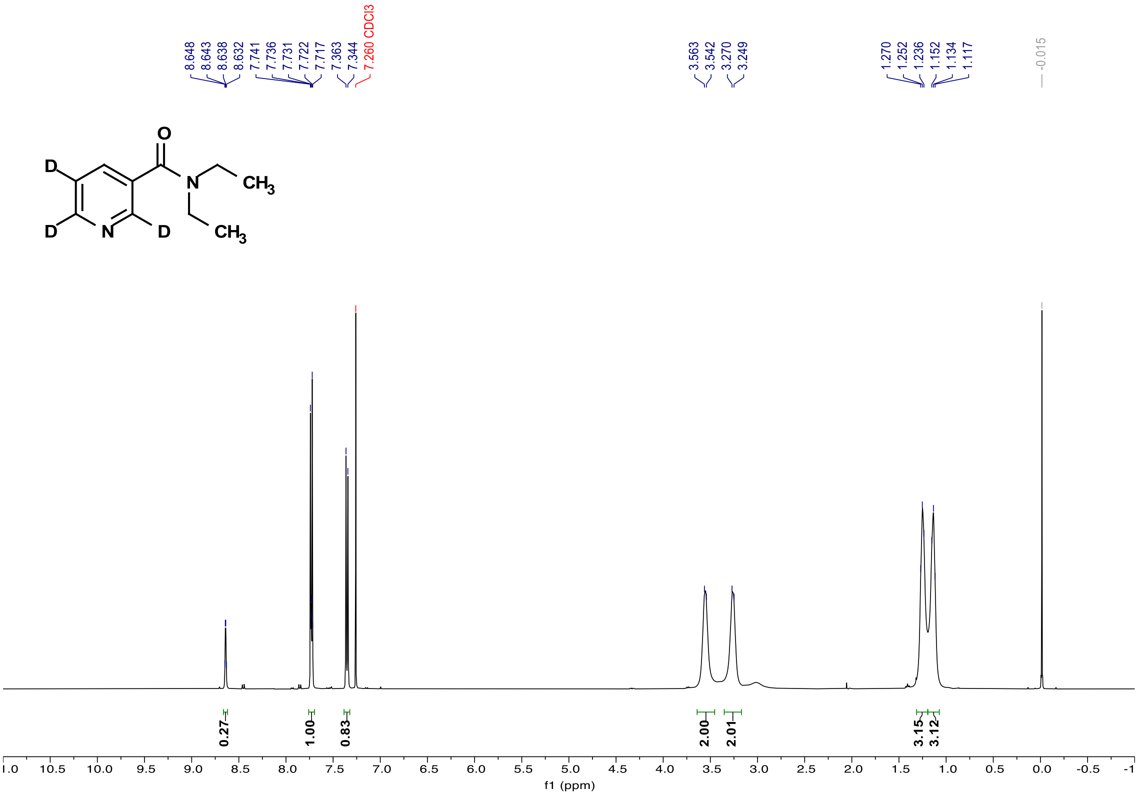
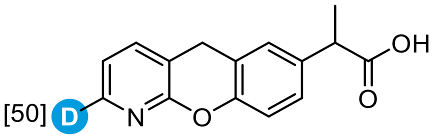


**Figure S101** $^1$H NMR of **28-*d*** in Chloroform-*d*



## Deuteration of Pranoprofen (29)



General procedure to afford **29-*d*** as white solid (221.6 mg, 87%) with D-incorporation 50% for 6-position by $^1$H NMR; $R_f$ = 0.40 (DCM/MeOH = 10/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.13 (dd, $J$ = 4.9, 1.9 Hz, 1H), 7.73 (dd, $J$ = 7.4, 1.8 Hz, 1H), 7.20 – 7.12 (m, 3H), 7.08 (d, $J$ = 8.1 Hz, 1H), 4.12 (s, 2H), 3.66 (q, $J$ = 7.1 Hz, 1H), 1.36 (d, $J$ = 7.1 Hz, 3H).

**NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ **8.13 (dd, $J$ = 4.9, 1.9 Hz, 0.50H, Labelled)**, 7.73 (dt, $J$ = 7.4, 1.1 Hz, 1H), 7.20 – 7.13 (m, 3H), 7.08 (d, $J$ = 8.1 Hz, 1H), 4.12 (s, 2H), 3.66 (q, $J$ = 7.1 Hz, 1H), 1.36 (d, $J$ = 7.2 Hz, 3H).

**Figure S102** $^1$H NMR spectrum comparison

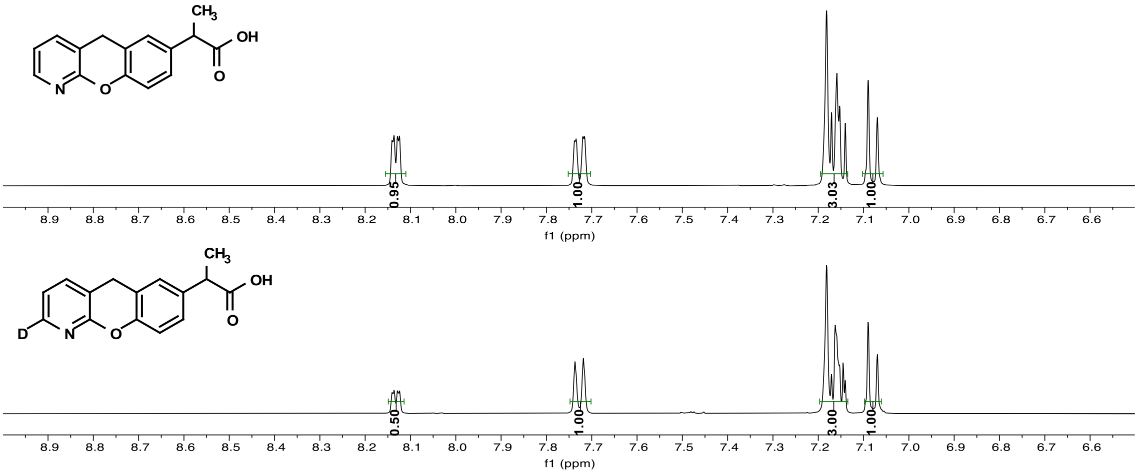


**Figure S103** $^1$H NMR of **29** in DMSO-$d_6$

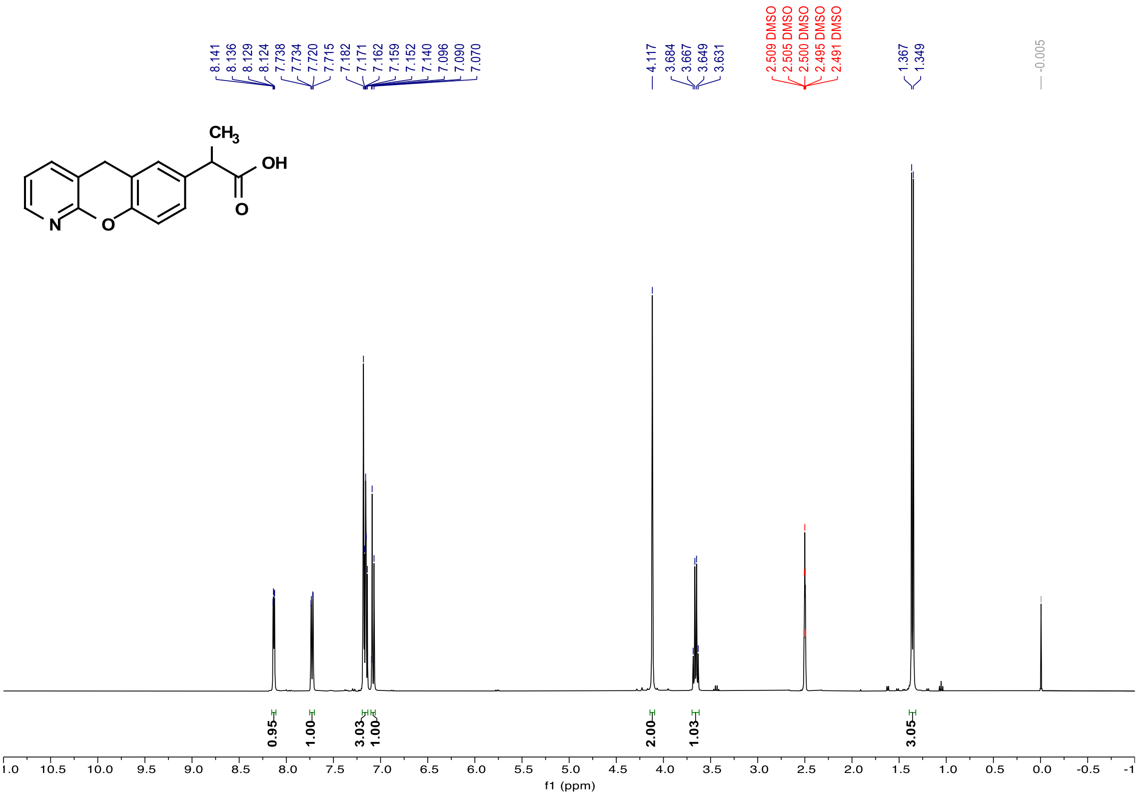
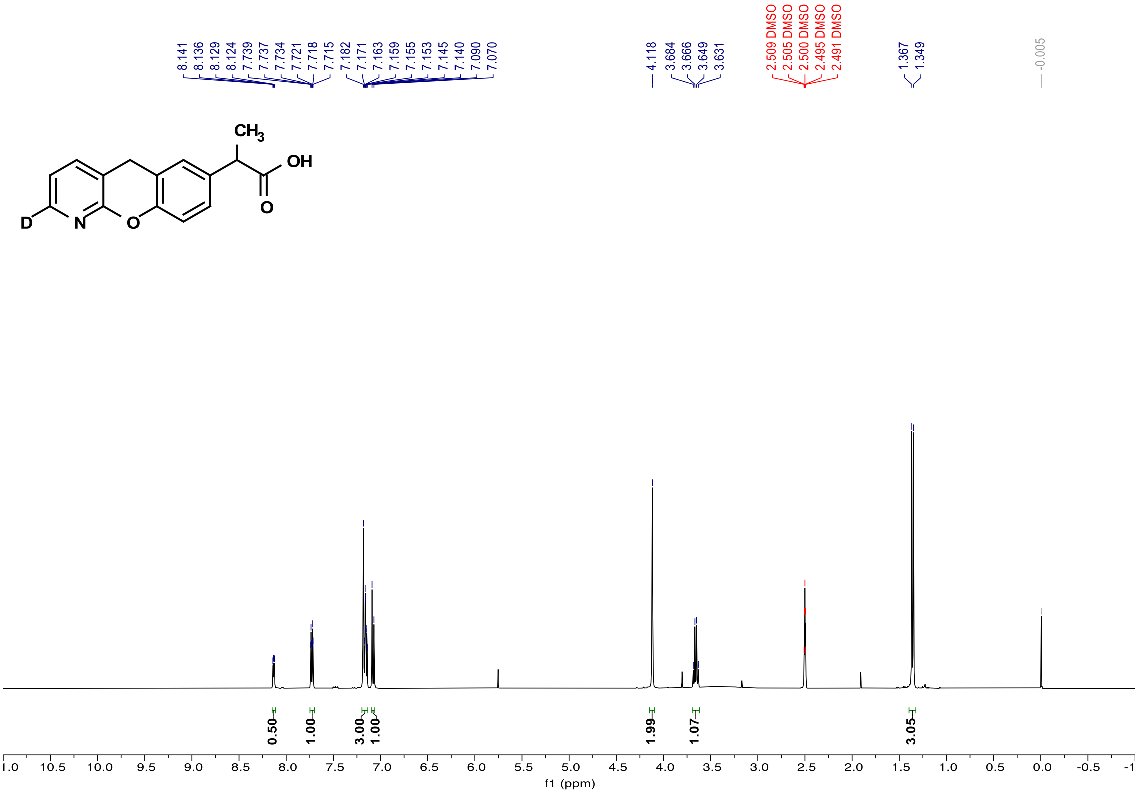
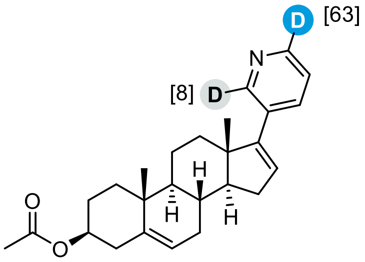


**Figure S104** $^1$H NMR of ***29-d*** in DMSO-$d_6$



## Deuteration of Abiraterone acetate (30)



General procedure to afford **30-*d*** as white solid (310.2 mg, 89%) with D-incorporation 8% for 2-position and 63% for 6-position by $^1$H NMR; $R_f = 0.3$ (Petroleum ether/EtOAc = 4/1).

**NMR data for starting material**: $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.46 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.66 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.23 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 6.00 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.45 – 5.37 (m, 1H), 4.68 – 4.54 (m, 1H), 2.41 – 2.31 (m, 2H), 2.27 (ddd, *J* = 15.8, 6.6, 3.3 Hz, 1H), 2.11 – 2.00 (m, 6H), 1.91 – 1.82 (m, 2H), 1.82 – 1.54 (m, 6H), 1.48 (td, *J* = 12.0, 5.0 Hz, 1H), 1.08 (s, 3H), 1.04 (s, 3H).

**NMR data for deuterated product**: $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.62 (dd, *J* = 2.4, 0.9 Hz, 0.92H, Labelled)**, **8.46 (dd, *J* = 4.8, 1.6 Hz, 0.37H, Labelled)**, 7.67 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.00 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.41 (dt, *J* = 5.2, 1.8 Hz, 1H), 4.68 – 4.55 (m, 1H), 2.39 – 2.31 (m, 2H), 2.27 (ddd, *J* = 15.8, 6.5, 3.3 Hz, 1H), 2.11 – 2.00 (m, 6H), 1.91 – 1.83 (m, 2H), 1.82 – 1.54 (m, 6H), 1.49 (td, *J* = 12.0, 5.0 Hz, 1H), 1.08 (s, 3H), 1.04 (s, 3H).

**Figure S105** $^1$H NMR spectrum comparison

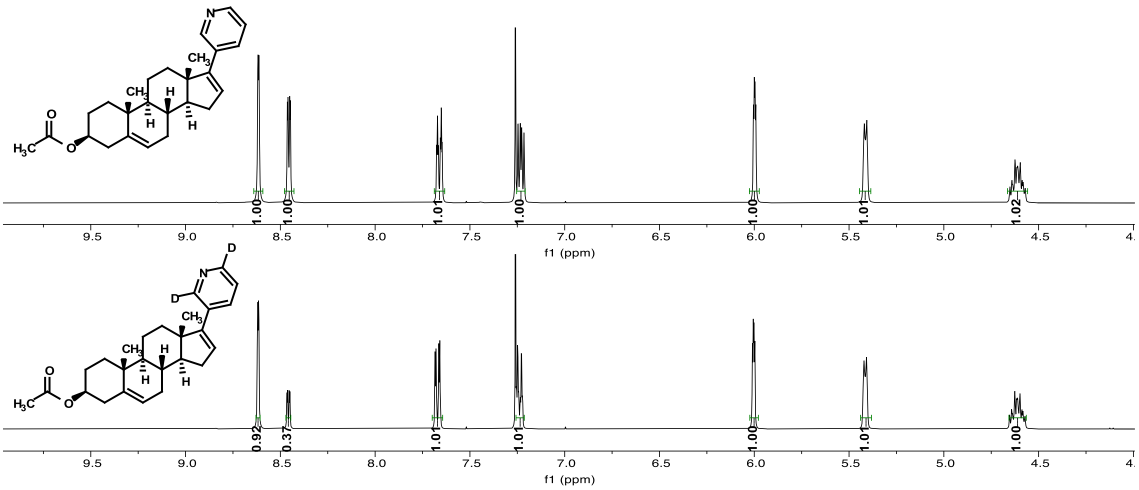


**Figure S106** $^1$H NMR of **30** in Chloroform-*d*

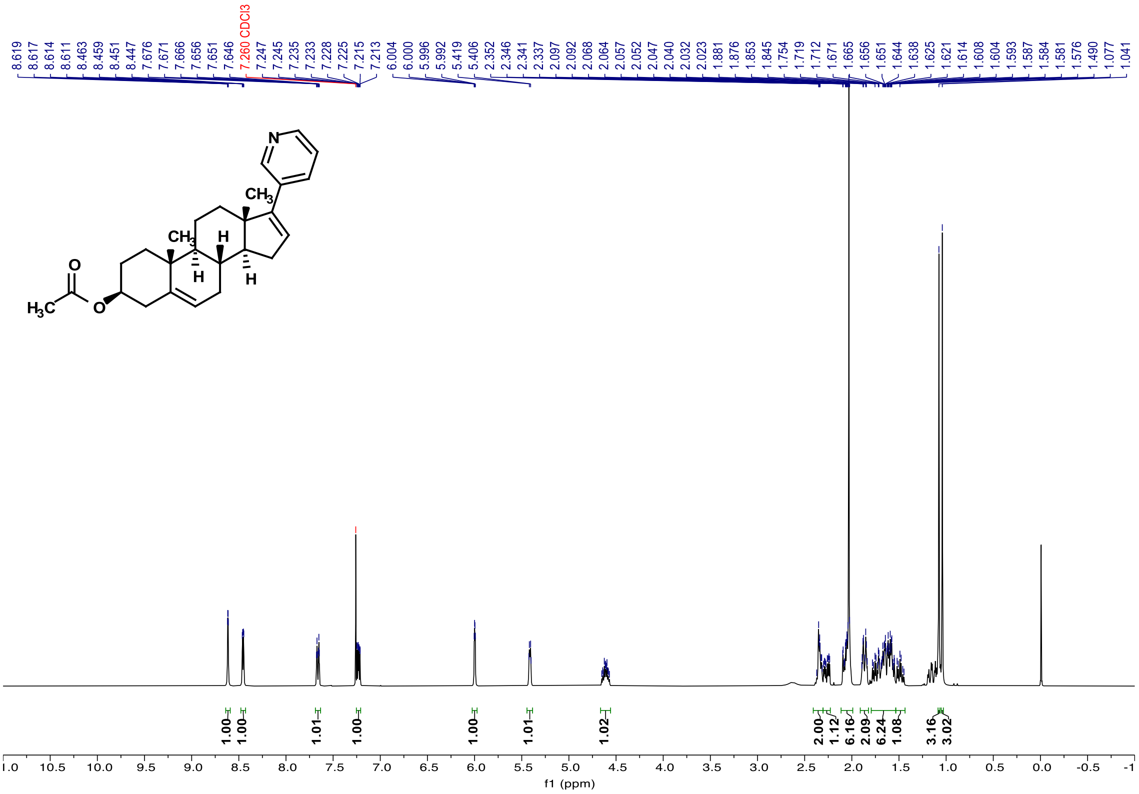
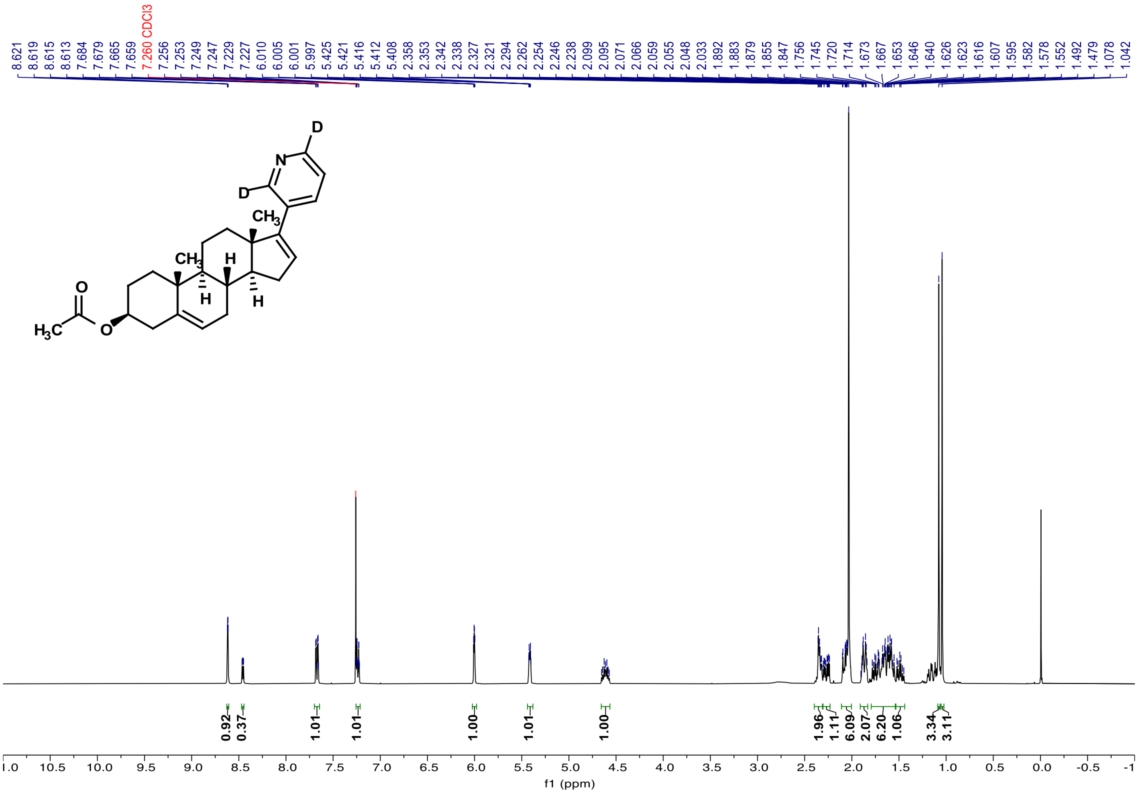
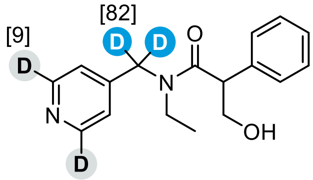


**Figure S107** $^1$H NMR of ***30-d*** in Chloroform-*d*



### Deuteration of Tropicamide (31)



General procedure to afford **30-*d*** as white solid (210.4 mg, 74%) with D-incorporation 9% for 2, 6-position and 82% for 4-methylene by $^1$H NMR; $R_f$ = 0.40 (DCM/MeOH = 10/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.47 (m, 2H), 7.40 – 7.15 (m, 5H), 7.01 (dd, *J* = 53.4, 6.2 Hz, 2H), 4.74 (d, *J* = 15.9 Hz, 1H), 4.46 (d, *J* = 16.7, 1H), 4.16 – 4.00 (m, 2H), 3.83 – 3.61 (m, 2H), 3.23 – 3.05 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 2H).
**NMR data for deuterated product: $^1$H NMR** (400 MHz, Chloroform-*d*) δ **8.51 – 8.46 (m, 1.82H, Labelled)**, 7.41 – 7.15 (m, 5H), 7.03 (dd, *J* = 65.7, 4.5 Hz, 2H), **4.74 (m, *J* = 15.9 Hz, 0.15H, Labelled)**, **4.46 (m, *J* = 16.7, 0.18H, Labelled)**, 4.17 – 4.01 (m, 2H), 3.82 – 3.60 (m, 2H), 3.25 – 3.06 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 1H), 0.95 (t, *J* = 7.1 Hz, 2H).

**Figure S108** $^1$H NMR spectrum comparison

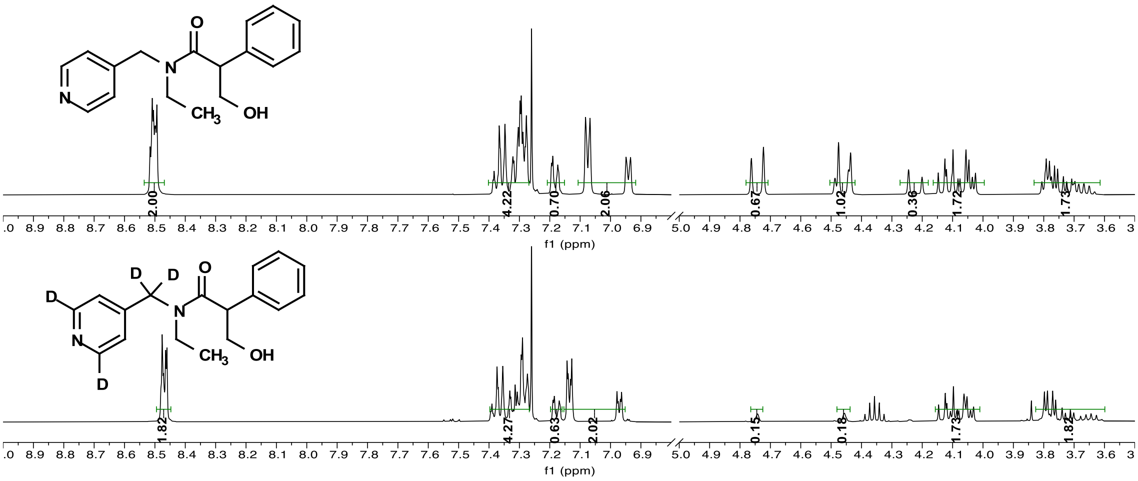


Figure S109 $^1$H NMR of **31** in *Chloroform-d*

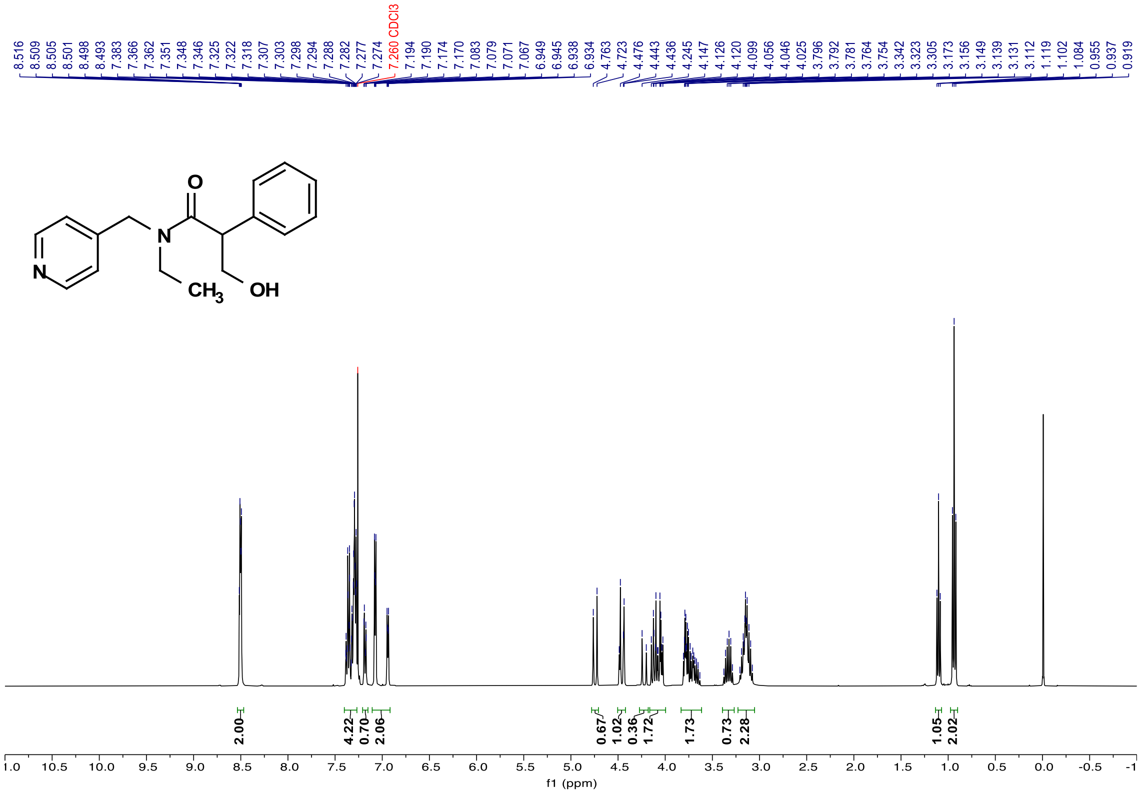
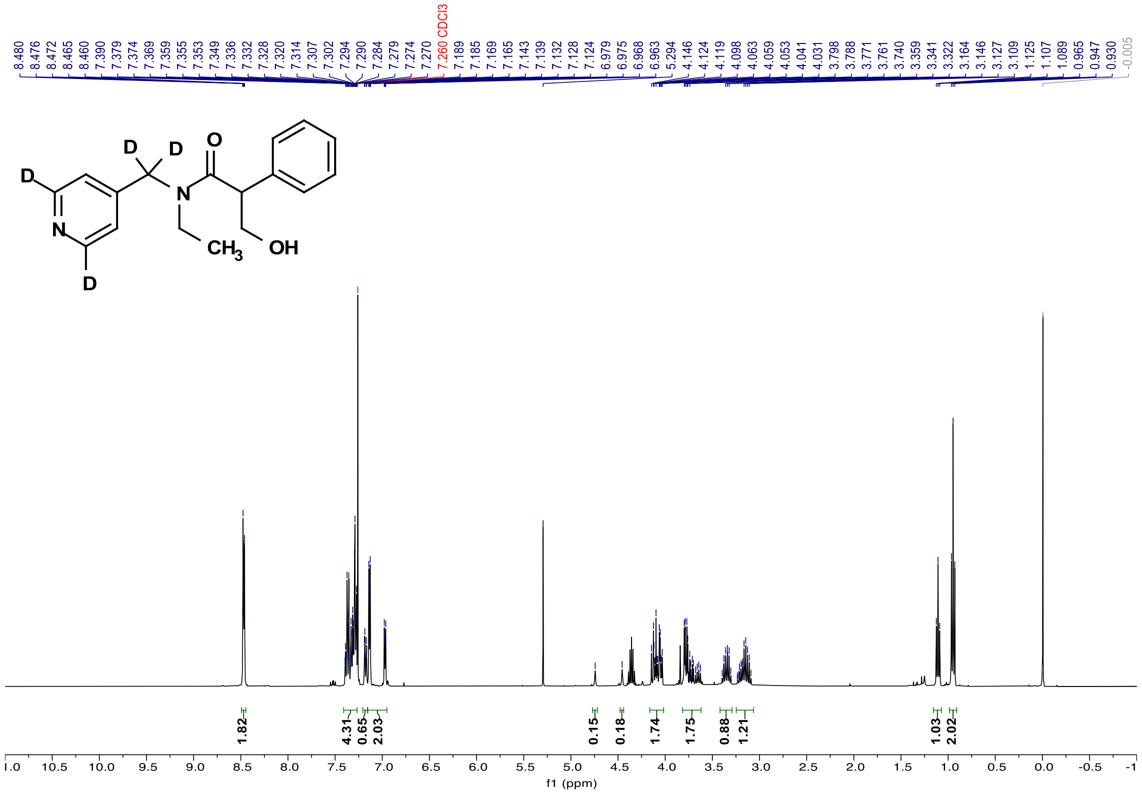
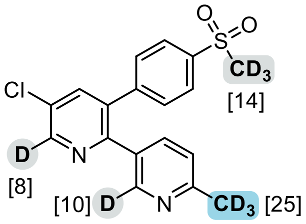


Figure S110 $^1$H NMR of **31**-*d* in *Chloroform-d*



**Deuteration of Etoricoxib (32)**



General procedure to afford **32-*d*** as white solid (293.9 mg, 82%) with D-incorporation 10% for 6-position and 25% for 2-mrthyl on 2-methyl-pyridyl motif, 8% for 2-position on 3-chloro-pyridyl motif, 14% for methylsulfonyl by $^1$H NMR; $R_f$ = 0.30 (Petroleum ether/EtOAc = 1/2).

**NMR data for starting material**: $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.82 (d, *J* = 2.3 Hz, 1H), 8.32 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.60 – 7.51 (m, 3H), 7.20 (d, *J* = 8.1 Hz, 1H), 3.26 (s, 3H), 2.44 (s, 3H).

**NMR data for deuterated product**: $^1$H NMR (400 MHz, DMSO-$d_6$) δ **8.82 (d, *J* = 2.3 Hz, 0.92H, Labelled)**, **8.34 – 8.29 (m, 0.90H, Labelled)**, 8.10 (d, *J* = 2.4 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.60 – 7.51 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), **3.27 – 3.21 (m, 2.58H, Labelled)**, **2.46 – 2.40 (m, 2.26H, Labelled)**.

**Figure S111** $^1$H NMR spectrum comparison

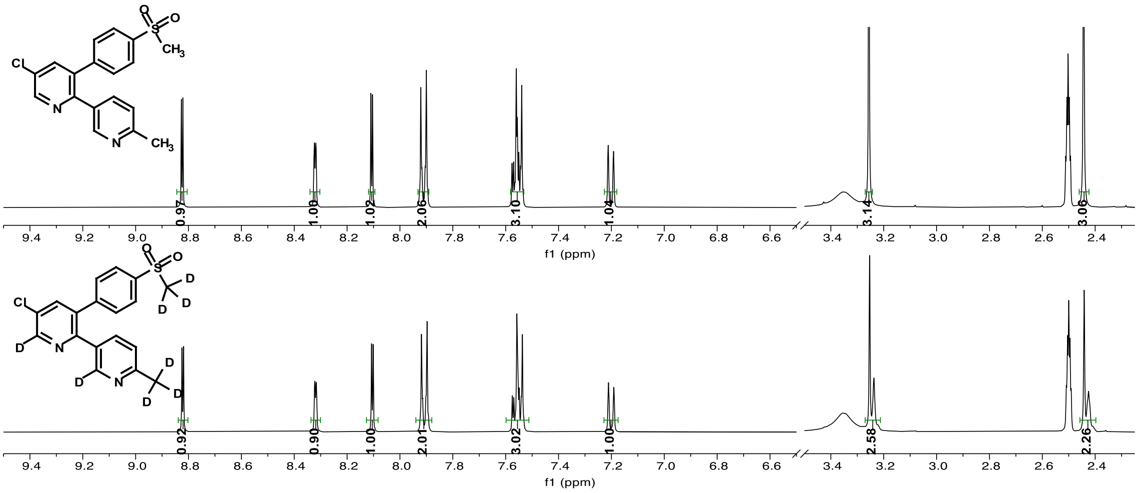


**Figure S112** $^1$H NMR of **32** in DMSO-$d_6$

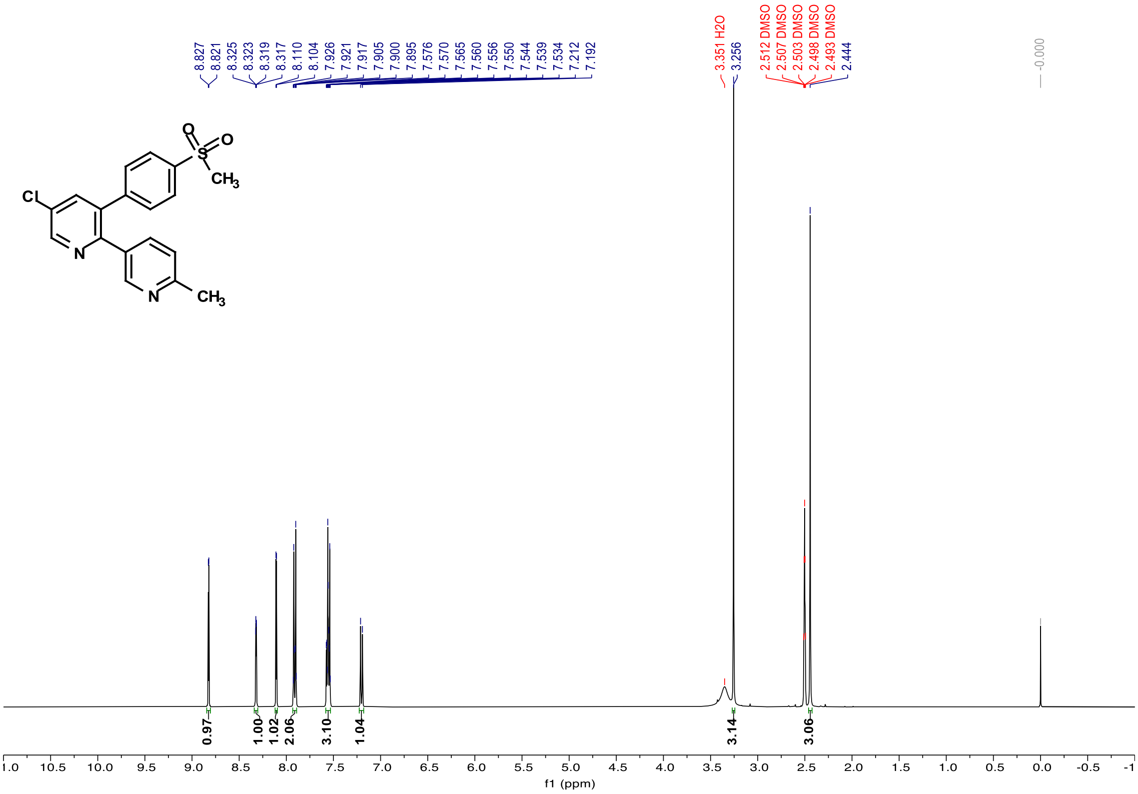
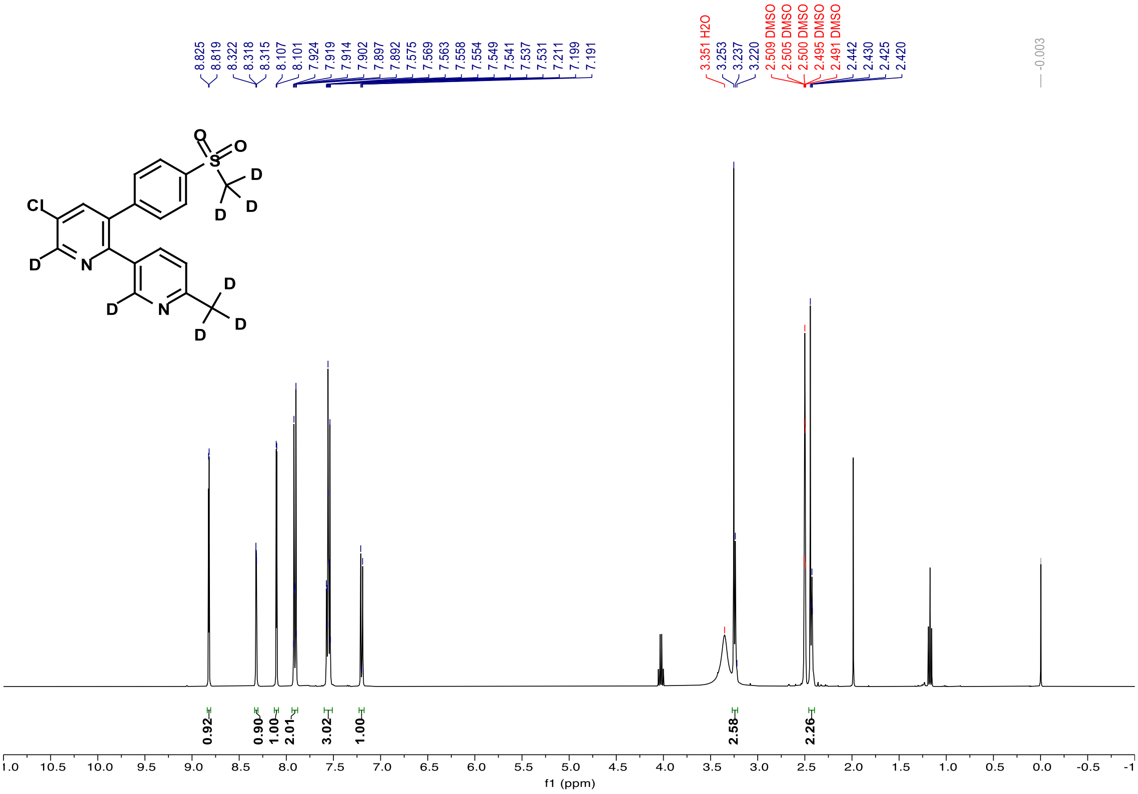
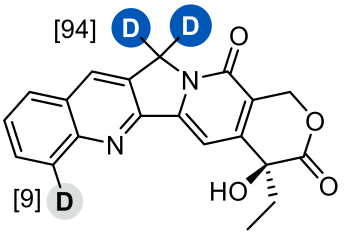


**Figure S113** $^1$H NMR of **32-*d*** in DMSO-$d_6$



## Deuteration of (+)-Camptothecin (33)



General procedure to afford **33-*d*** as white solid (264.9 mg, 76%) with D-incorporation 9% for 8-position and 94% for 3-methylene by $^1$H NMR; $R_f$ = 0.40 (DCM/MeOH = 15/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.68 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.86 (d, *J* = 1.6 Hz, 0H), 7.71 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.35 (s, 1H), 6.53 (s, 1H), 5.43 (s, 2H), 5.28 (s, 2H), 1.97 – 1.78 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.70 (s, 1H), **8.18 (d, *J* = 8.5 Hz, 0.91H, Labelled)**, 8.14 (d, *J* = 8.2 Hz, 1H), 7.88 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.36 (s, 1H), 6.53 (s, 1H), 5.43 (s, 2H), **5.29 (s, 0.12H, Labelled)**, 1.94 – 1.81 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H).

**Figure S114** $^1$H NMR spectrum comparison

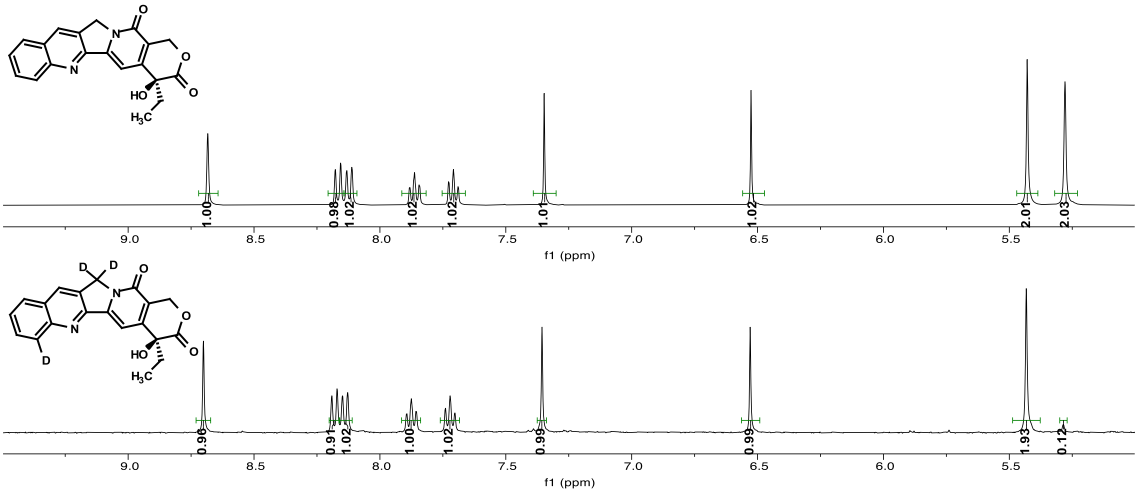


**Figure S115** $^1$H NMR of **33** in DMSO-$d_6$

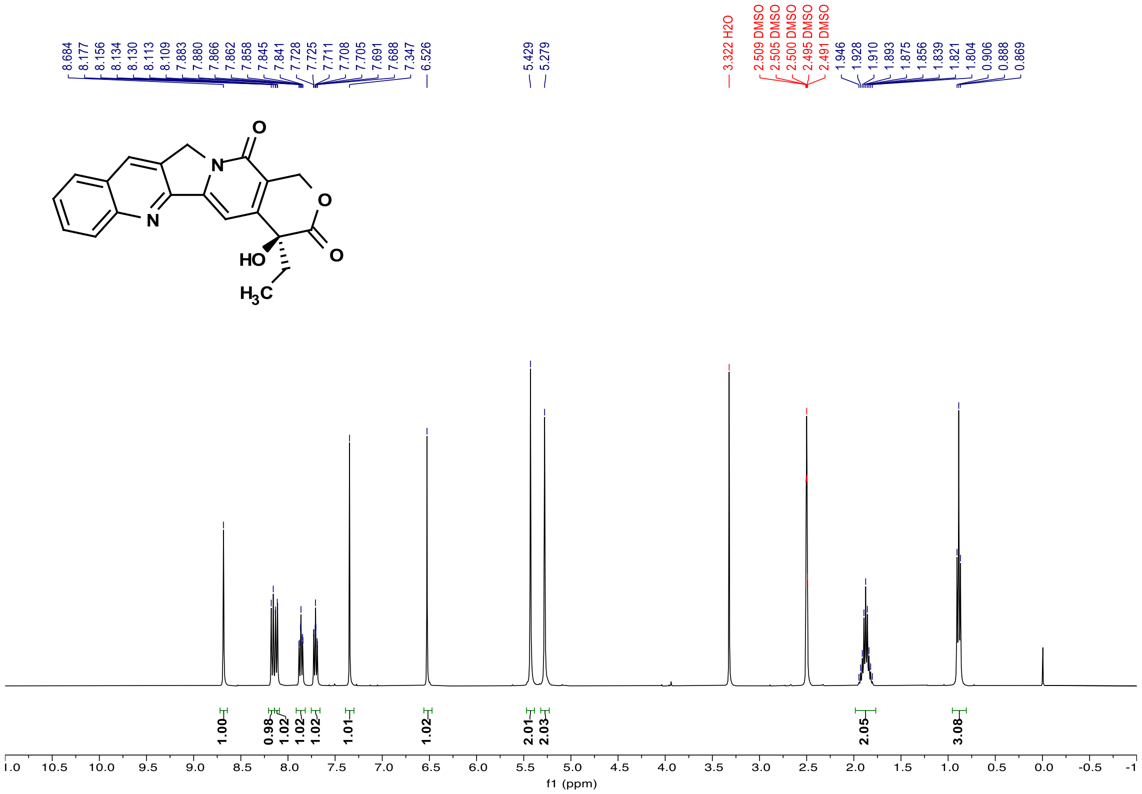
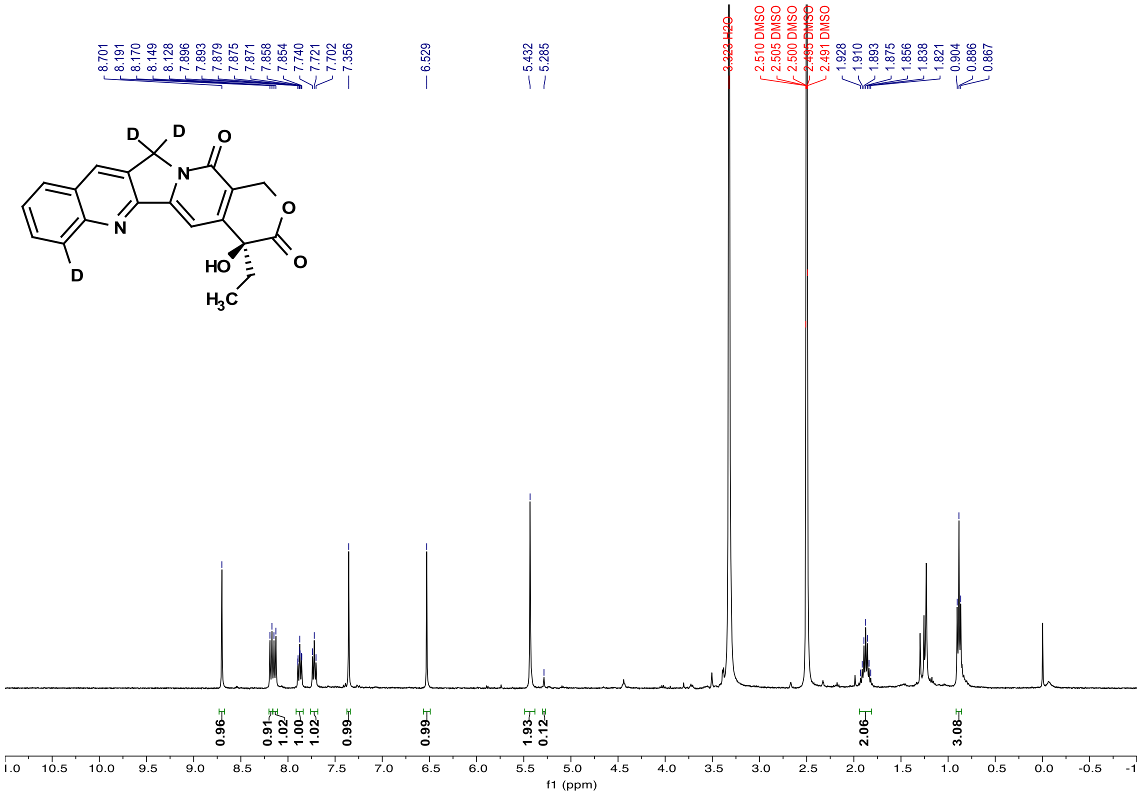
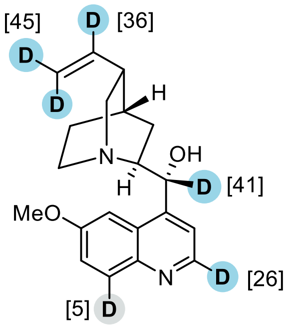


**Figure S116** $^1$H NMR of **33-*d*** in DMSO-$d_6$



## Deuteration of Quinine (34)



General procedure to afford **34-*d*** as white solid (197.3 mg, 61%) with D-incorporation 26% for 2-position, 5% for 8-position and 41% for 4-methyne on quinoline group, 36% for 1-position and 45% for 2-position on vinyl by $^1$H NMR; $R_f$ = 0.40 (DCM/MeOH = 10/1, 1% $Et_3N$).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 4.5 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 4.5 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.22 (d, *J* = 2.7 Hz, 1H), 5.72 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.53 (d, *J* = 4.3 Hz, 1H), 4.98 – 4.87 (m, 2H), 4.00 (s, 1H), 3.88 (s, 3H), 3.44 (dddd, *J* = 12.8, 9.9, 5.2, 2.4 Hz, 1H), 3.17 – 3.02 (m, 2H), 2.70 – 2.59 (m, 2H), 2.32 – 2.21 (m, 1H), 1.85 – 1.78 (m, 1H), 1.78 – 1.67 (m, 2H), 1.59 – 1.45 (m, 2H).
**NMR data for deuterated product:** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.61 (d, *J* = 4.5 Hz, 0.74H, Labelled)**, **7.98 – 7.91 (m, 0.95H, Labelled)**, 7.52 – 7.47 (m, 1H), 7.30 (dt, *J* = 9.2, 2.5 Hz, 1H), 7.22 (d, *J* = 2.8 Hz, 1H), **5.79 – 5.67 (m, 0.64H, Labelled)**, **5.54 (d, *J* = 4.2 Hz, 0.59H, Labelled)**, **4.99 – 4.88 (m, 1.10H, Labelled)**, 4.27 – 3.91 (m, 1H), 3.87 (s, 3H), 3.53 – 3.40 (m, 1H), 3.23 – 2.98 (m, 2H), 2.71 – 2.61 (m, 2H), 2.38 – 2.22 (m, 1H), 1.84 – 1.78 (m, 1H), 1.78 – 1.66 (m, 2H), 1.61 – 1.45 (m, 2H).

**Figure S117** $^1$H NMR spectrum comparison

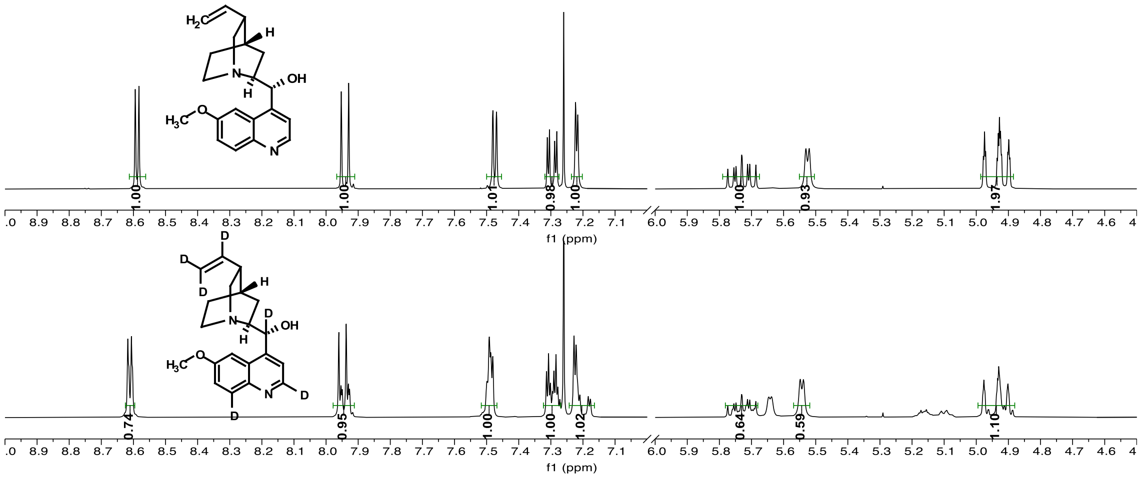


**Figure S118** $^1$H NMR of **34** in Chloroform-*d*

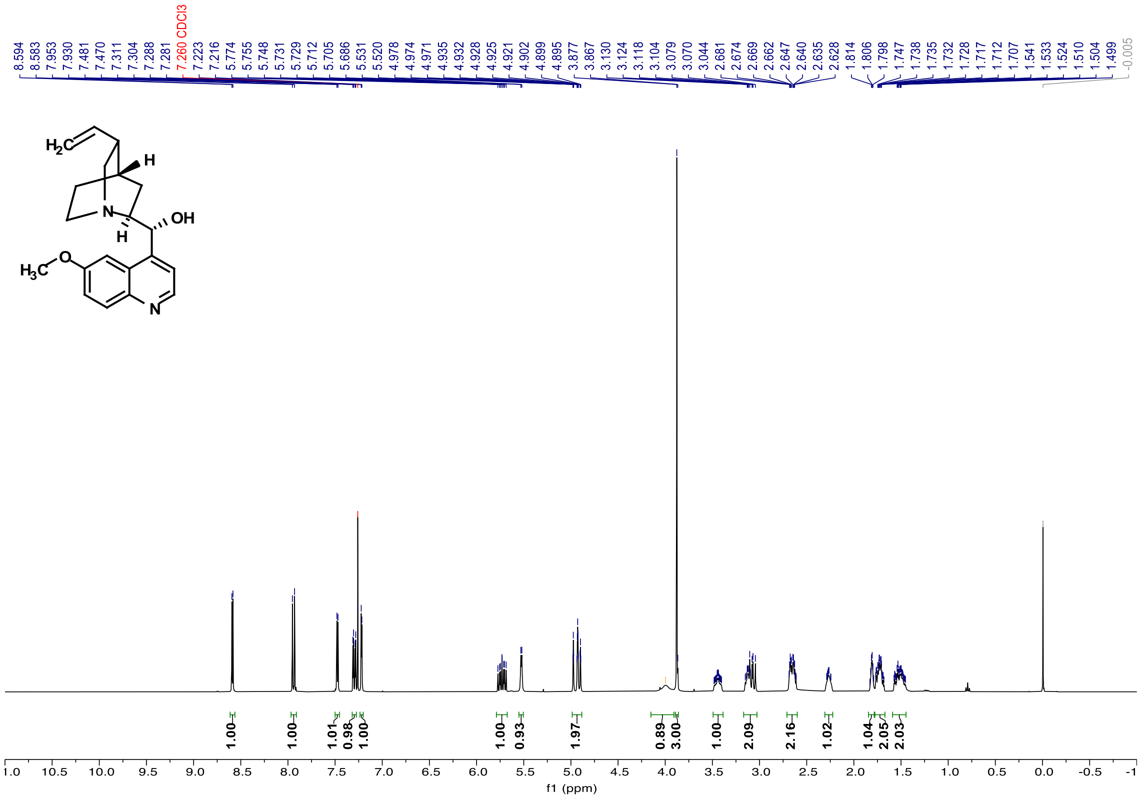
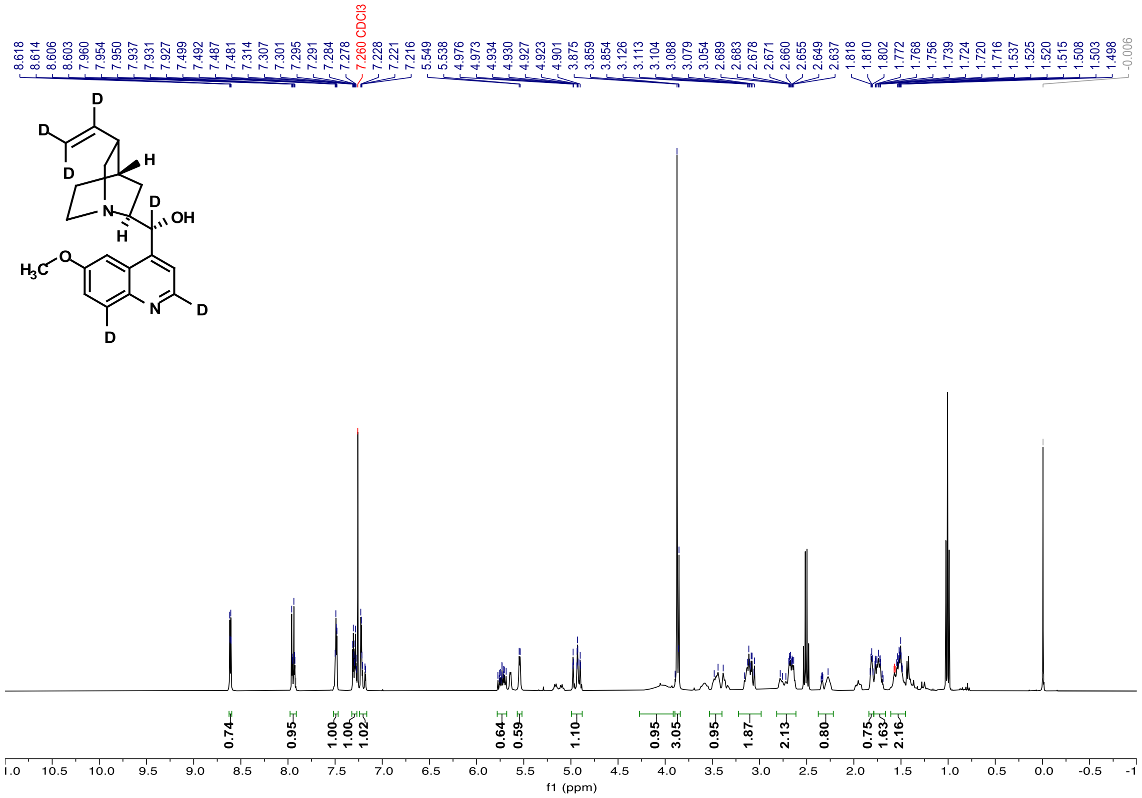
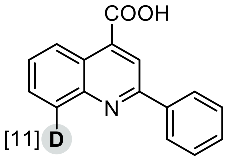


**Figure S119** $^1$H NMR of ***34-d*** in Chloroform-*d*



## Deuteration of Cinchophen (35)



General procedure to afford **35-*d*** as white solid (223.8 mg, 90%) with D-incorporation 11% for 8-position by $^{1}$H NMR; R$_{f}$ = 0.25 (Petroleum ether/EtOAc = 1/1, 1% HOAc).

**NMR data for starting material:** $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.65 (d, *J* = 8.5 Hz, 1H), 8.45 (s, 1H), 8.29 (d, *J* = 7.4 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.64 – 7.48 (m, 3H).

**NMR data for deuterated product:** $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 8.66 (dd, *J* = 8.6, 1.3 Hz, 1H), 8.47 (s, 1H), 8.33 – 8.26 (m, 2H), **8.17 (d, *J* = 7.8 Hz, 0.89H, Labelled)**, 7.85 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1H), 7.71 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.62 – 7.49 (m, 3H).

**Figure S120** $^{1}$H NMR spectrum comparison

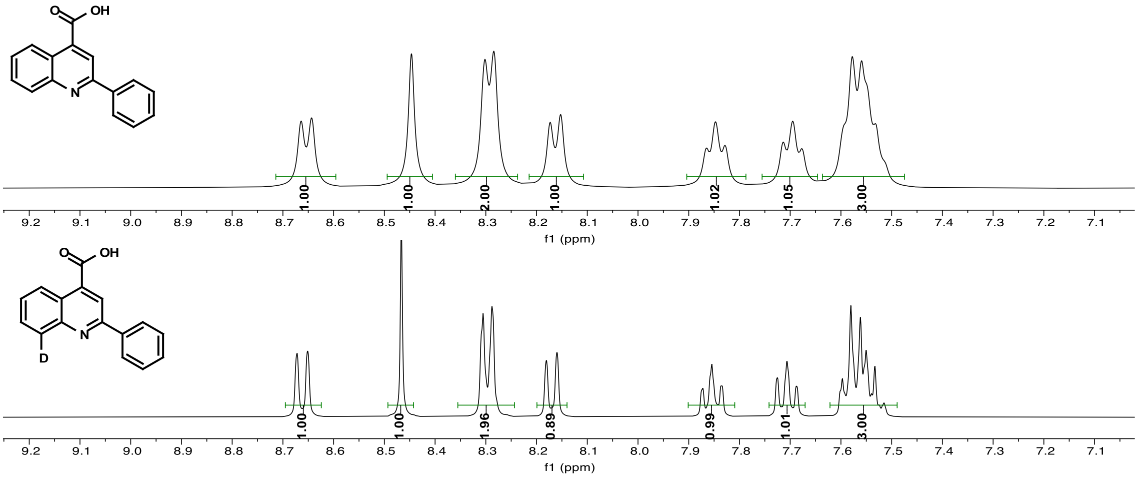


**Figure S121** ¹H NMR of **35** in DMSO-$d_6$

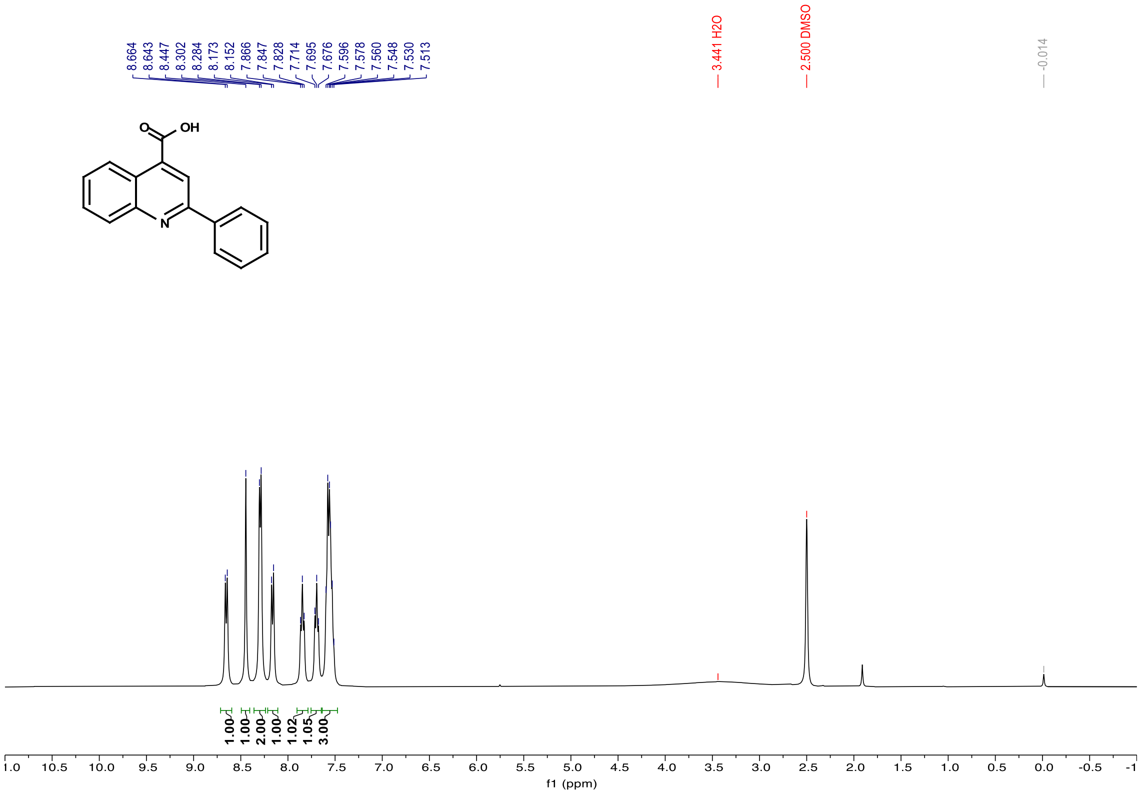
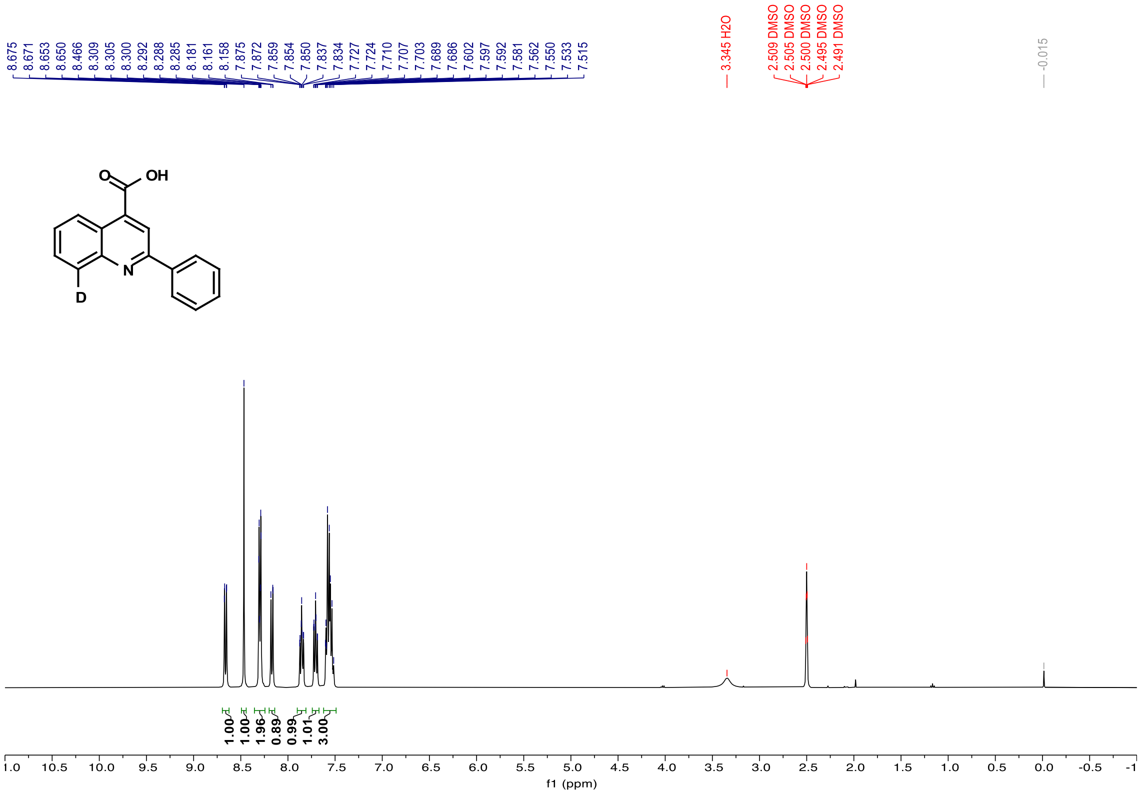
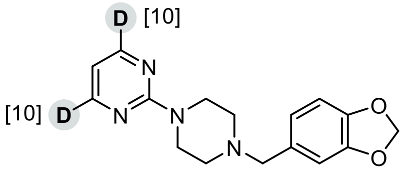


**Figure S122** ¹H NMR of **35-*d*** in DMSO-$d_6$



**Deuteration of Piribendyl (36)**



General procedure to afford **36-*d*** as white solid (264.7 mg, 89%) with D-incorporation 10% for 4, 6-position by $^1$H NMR; $R_f$ = 0.40 (Petroleum ether/EtOAc = 1/1).

**NMR data for starting material:** $^1$H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 4.7 Hz, 2H), 6.89 (s, 1H), 6.76 (s, 2H), 6.46 (t, *J* = 4.7 Hz, 1H), 5.95 (s, 2H), 3.82 (t, *J* = 5.1 Hz, 4H), 3.46 (s, 2H), 2.49 (t, *J* = 5.1 Hz, 4H).

**NMR data for deuterated product :** $^1$H NMR (400 MHz, Chloroform-*d*) δ **8.29 (d, *J* = 4.8 Hz, 1.80H, Labelled)**, 6.90 (s, 1H), 6.76 (s, 2H), 6.50 – 6.43 (m, 1H), 5.95 (s, 2H), 3.83 (t, *J* = 5.1 Hz, 4H), 3.47 (s, 2H), 2.50 (t, *J* = 5.1 Hz, 4H).

**Figure S123** $^1$H NMR spectrum comparison

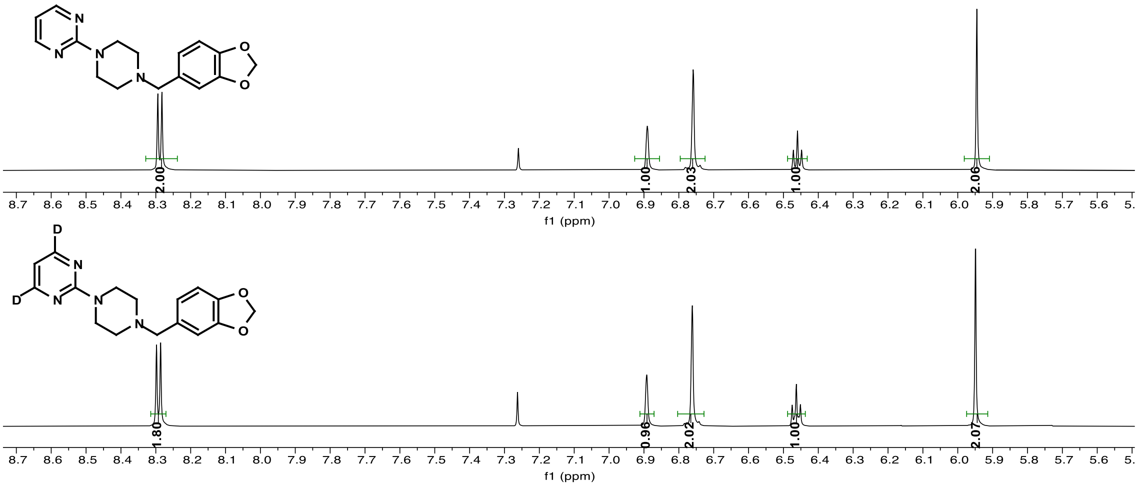


**Figure S124** $^1$H NMR of **36** in *Chloroform-d*

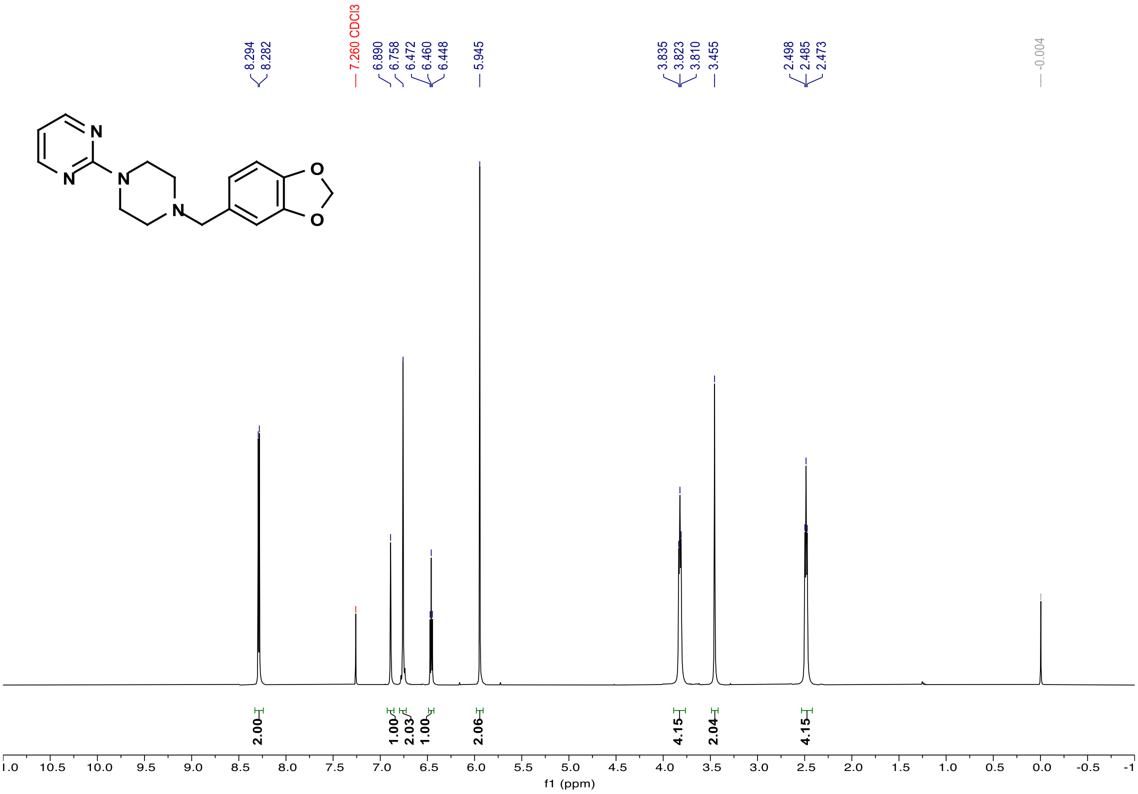


**Figure S125** $^1$H NMR of **36-*d*** in *Chloroform-d*