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# **Supporting Information**

# Mechanochemical Silver-Catalyzed Direct H/D Exchange on Heteroarenes

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## 1. General Information

## 1) Experiments and Reagents

Unless otherwise stated, all experiments were carried out in an air atmosphere using oven-dried glassware and a magnetic stirring bar. The ball milling reaction was carried out on a Retsch MM 400 hybrid ball mill, and a MITR QM-QX planetary ball mill was used for gram-scale experiment and iterative deuteration. Stainless steel grinding jars and stainless steel grinding balls were used unless otherwise stated. Temperature is reported as the temperature of the digital display of a heat gun apparatus.

Commercially available reagents were purchased from Aladdin, Bidepharm and Leyan Chemicals and used directly without further purification unless otherwise stated. Deuterated solvents were supplied by Ningbo Cuiying Chemicals. The  $D_2O$  for the reaction was collected and transferred to the reaction in a glove box with a 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

<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>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<sub>3</sub> or DMSO-*d*<sub>6</sub>. 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".

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  $\times$  0.25  $\mu$ m).

## 4) <u>Calculation of Deuterium Incorporation</u>

The degree of deuterium-incorporation was calculated based on both GC-MS and <sup>1</sup>H-NMR methods, which had been described in our previous work<sup>1</sup>. The theoretical deuterium degree was calculated as follow.

$$D_{theo} = \frac{2 \times n(D_2 O)}{2 \times n(D_2 O) + n(thiophene)} = \frac{2 \times 5 \ mmol}{2 \times 5 \ mmol + 1 \ mmol} = 0.91$$

## 2. Experimental procedures

## 1) <u>General procedure for the mechanochemical H/D exchange of thiophenes</u>



An oven-dried 10 mL stainless steel vessel was charged with a substrate (1.0 mmol), Ag<sub>2</sub>CO<sub>3</sub> (27.6 mg, 10 mol%), Johnphos **L12** (59.7 mg, 20 mol%), K<sub>2</sub>CO<sub>3</sub> (138.2 mg, 1.0 equiv.) and D<sub>2</sub>O (91  $\mu$ L, 5.0 equiv.). The stainless steel vessel was sealed with a circular silicone gasket and placed in the robotic arm of the Retsch MM 400 hybrid ball mill and ground at 30 Hz for 1 hour in a room temperature air environment. After grinding, the mixture was filtered over Celite and the residue was washed with dichloromethane (2 x 5 mL). The mixture was diluted with saturated NaCl solution (10 mL) and extracted with dichloromethane (20 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, sampled for GC-MS analysis and then concentrated under reduced pressure. The crude product was then purified by chromatography to afford purified product.



Figure S1 Thermo-grinding setup according to Browne's work.<sup>2</sup>

## 3. Condition Optimization

## 1) Table S1 Optimization of catalytic system.<sup>a</sup>



entry	Ag-source	Ligand	Base	D <sub>MS</sub> <sup>b</sup>	%Recov. <sup>c</sup>
1	Ag <sub>2</sub> CO <sub>3</sub>	L12	/	0.78	71
2	/	L12	/	0.05	94
3	Ag <sub>2</sub> CO <sub>3</sub>	Ι	/	0.02	95
4	Ag <sub>2</sub> O	L12	/	0.29	93
5	AgOAc	L12	K <sub>2</sub> CO <sub>3</sub>	0.02	70
6	AgF	L12	K <sub>2</sub> CO <sub>3</sub>	n.d.	/
7	AgTFA	L12	K <sub>2</sub> CO <sub>3</sub>	n.d.	/
8	AgBF <sub>4</sub>	L12	K <sub>2</sub> CO <sub>3</sub>	n.d.	/
9	$Ag_2SO_4$	L12	K <sub>2</sub> CO <sub>3</sub>	n.d.	/
10	Ag <sub>2</sub> O	L12	K <sub>2</sub> CO <sub>3</sub>	0.48	78
11	Ag <sub>2</sub> O	L12	Na <sub>2</sub> CO <sub>3</sub>	0.36	/
12	Ag <sub>2</sub> O	L12	NaOAc	0.03	/
13	Ag <sub>2</sub> O	L12	NaOH	0.02	/
14	Ag <sub>2</sub> CO <sub>3</sub>	L12	K <sub>2</sub> CO <sub>3</sub>	0.84	93
15	Ag <sub>2</sub> CO <sub>3</sub>	L12	Na <sub>2</sub> CO <sub>3</sub>	0.60	71
16	Ag <sub>2</sub> CO <sub>3</sub>	L12	NaOH	0.43	85
17	Ag <sub>2</sub> CO <sub>3</sub>	L12	NaOAc	0.03	88
18	Ag <sub>2</sub> CO <sub>3</sub>	L12	K <sub>3</sub> PO <sub>4</sub>	0.79	91
19	Ag <sub>2</sub> CO <sub>3</sub>	L12	t-BuOK	0.35	87
20 <sup>d</sup>	Ag <sub>2</sub> CO <sub>3</sub>	L12	K <sub>2</sub> CO <sub>3</sub>	0.66	91

<sup>a</sup> Reaction condition: Substrate (1.0 mmol), Ag-source (10 mol%), Ligand (20 mol%), Base (1.0 equiv.) and D<sub>2</sub>O (5.0 equiv.), room temperature in 10 mL Stainless-Steel vessel with 1 ball (1.5 cm) for 30 Hz and 1 h. <sup>b</sup> D<sub>MS</sub> was determined by GC-MS analysis. <sup>c</sup> %Recov. Determined by HPLC analysis. <sup>d</sup>Silica gel (0.2 g) added.

#### Ligand Examination



#### 2) Table S2 Detailed optimization of components loading.<sup>a</sup>



entry	Ag <sub>2</sub> CO <sub>3</sub> (mol%)	L12 (mol%)	K <sub>2</sub> CO <sub>3</sub> (equiv.)	D₂O (equiv.)	D <sub>MS</sub> <sup>b</sup>	%Recov. <sup>c</sup>
1	5	20	1.0	5.0	0.82	95
2	10	20	1.0	5.0	0.84	93
3	15	20	1.0	5.0	0.83	96
4	20	20	1.0	5.0	0.82	90
5	10	5	1.0	5.0	0.79	80
6	10	10	1.0	5.0	0.78	83
7	10	15	1.0	5.0	0.82	88
8	10	20	1.0	5.0	0.84	93
9	10	30	1.0	5.0	0.82	83
10	10	50	1.0	5.0	0.84	90
11	10	20	0.5	5.0	0.80	94
12	10	20	0.8	5.0	0.80	95
13	10	20	1.0	5.0	0.84	93
14	10	20	1.2	5.0	0.81	86
15	10	20	1.5	5.0	0.81	84
16	10	20	2.0	5.0	0.79	88
17	10	20	3.0	5.0	0.74	92
18	10	20	1.0	2.0	0.59	79
19	10	20	1.0	3.0	0.68	87
20	10	20	1.0	5.0	0.84	93
21	10	20	1.0	10.0	0.84	84
22	10	20	1.0	15.0	0.83	85
23	10	20	1.0	20.0	0.87	82

<sup>a</sup> Reaction condition: Substrate (1.0 mmol), Ag<sub>2</sub>CO<sub>3</sub> (10 mol%), Johnphos (20 mol%), K<sub>2</sub>CO<sub>3</sub> (1.0 equiv.), and D<sub>2</sub>O (5.0 equiv.), r.t. in Ball-milling for 30 Hz and 1 h. <sup>b</sup> D<sub>MS</sub> was determined by GC-MS analysis. <sup>c</sup> %Recov. Determined by HPLC analysis.

#### 3) Table S3 Optimization of mechanochemical parameters.<sup>a</sup>

entry	diameter (cm)	ball number	freq. (Hz)	t (min)	D <sub>MS</sub> <sup>b</sup>	%Recov. <sup>c</sup>
1	1.5	1	30	60	0.84	93
2	1.2	1	30	60	0.76	83
3	1.2	2	30	60	0.80	88
4	1.0	2	30	60	0.74	87
5	1.0	3	30	60	0.75	90
6	1.5	1	15	60	0.56	95
7	1.5	1	15	99	0.64	91
8	1.5	1	20	60	0.72	92
9	1.5	1	20	99	0.75	88
10	1.5	1	25	60	0.77	95
11	1.5	1	25	99	0.79	89
12	1.5	1	30	45	0.75	95
13	1.5	1	30	60	0.84	93
14	1.5	1	30	99	0.84	84

<sup>a</sup> Reaction condition: Substrate (1.0 mmol), Ag<sub>2</sub>CO<sub>3</sub> (10 mol%), Johnphos (20 mol%), K<sub>2</sub>CO<sub>3</sub> (1.0 equiv.), and D<sub>2</sub>O (5.0 equiv.), r.t. under specific Ball-milling condition. <sup>b</sup> D<sub>MS</sub> was determined by GC-MS analysis. <sup>c</sup> %Recov. Determined by HPLC analysis.

## 4. Additional Experiments

#### 1) Gram-scale preparation in planetary miller



An oven-dried 50 mL stainless steel bowl was charged with substrate 1 (2.41 g, 15.0 mmol, 1.0 equiv.),  $Ag_2CO_3$  (413.7 mg, 10 mol%), Johnphos (895.0 mg, 20 mol%),  $K_2CO_3$  (2.08 g, 1.0 equiv.) and  $D_2O$  (1.36 mL, 5.0 equiv.). The stainless steel bowl was sealed with a round silicone pad and placed in the planetary ball mill and grind for 2 hours at 750 rpm under room temperature. After the grinding finished, the mixture was filtered over Celite and the residue was washed with dichloromethane (4 x 20 mL). The mixture was diluted with saturated NaCl solution (50 mL) and extracted with dichloromethane (100 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, sampled for GC-MS analysis and then concentrated under reduced pressure. The crude product was purified with column chromatography on silica gel, eluting with petroleum ether to afford the product 1-[d] as a white crystals (1.89 g, 79% yield).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.69 – 7.62 (m, 2H), 7.54 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.69 – 7.63 (m, 2H), <u>7.55 (dd, J = 5.1, 1.2 Hz, 0.19H, Labelled)</u>, 7.51 (d, J = 3.6 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.34 – 7.27 (m, 1H), 7.14 (t, J = 3.6 Hz, 1H).





### Figure S3 <sup>1</sup>H NMR of 1 in DMSO-d<sub>6</sub>



. 0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0. f1 (ppm)

#### 2) Iterative deuteration of 1 in planetary miller



An oven-dried 50 mL stainless steel bowl was charged with a substrate 1 (0.80 g, 5.0 mmol, 1.0 equiv.),  $Ag_2CO_3$  (137.9 mg, 10 mol%), Johnphos (298.4 mg, 20 mol%),  $K_2CO_3$  (691.1 mg, 1.0 equiv.) and  $D_2O$  (181.0 µL, 2.0 equiv.). The stainless steel bowl was sealed with a round silicone pad and placed in the planetary ball mill and grind for 2 hours at 750 rpm under room temperature. The mixture was washed with DCM, and the solvent in filtrate was removed under vacuum. The reaction was then repeated with crude product obtained with with fresh  $D_2O$  (2.0 equiv.). After the grinding, the mixture was filtered over Celite and the residue was washed with dichloromethane (4 x 20 mL). The mixture was diluted with saturated NaCl solution (50 mL) and extracted with dichloromethane (100 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, sampled for GC-MS analysis and then concentrated under reduced pressure. The crude product use purified with column chromatography on silica gel, eluting with petroleum ether to afford the product 1-[d] as a white crystals (688.4 mg, 86% yield).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.69 – 7.62 (m, 2H), 7.54 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.69 – 7.63 (m, 2H), <u>7.55 (d, *J* = 5.1</u> <u>Hz, 0.22H, Labelled)</u>, 7.51 (d, *J* = 3.5 Hz, 1H), 7.42 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.15 (t, *J* = 3.6 Hz, 1H).

Figure S5 <sup>1</sup>H NMR spectrum comparison



## 5. Results of Substrate deuteration

### Deuteration of 2-Phenylthiophene (1)<sup>4</sup>



The corresponding substrate was ground under standard condition to afford **1-[d]** as white crystals (148.5 mg, 93%) with D-incorporation 83% for 5-position by <sup>1</sup>H NMR; 0.84 D by GC-MS;  $R_f = 0.70$  (Petroleum ether).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.69 – 7.62 (m, 2H), 7.54 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.51 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.69 – 7.63 (m, 2H), <u>7.55 (dd, J = 5.1, 1.2 Hz, 0.17H, Labelled)</u>, 7.51 (d, J = 3.6 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.34 – 7.27 (m, 1H), 7.14 (t, J = 3.6 Hz, 1H).

Figure S6 <sup>1</sup>H NMR spectrum comparison







### Figure S8 <sup>1</sup>H NMR of 1 in DMSO-d<sub>6</sub>





#### Deuteration of 2,3-Dihydrothieno[3,4-b][1,4]dioxine (2) 4



The corresponding substrate was ground under standard condition for 99 minutes to afford **2-[d]** as transparent liquid (96.1 mg, 68%) with D-incorporation 75% for 2,5-position by <sup>1</sup>H NMR; 1.48 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 50/1).

**NMR** data for starting material: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  6.32 (s, 2H), 4.20 (s, 4H). **NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  <u>6.32 (d, *J* = 2.0 Hz, 0.51H, Labelled)</u>, 4.20 (s, 4H).

#### Figure S10 <sup>1</sup>H NMR spectrum comparison







## Figure S12 <sup>1</sup>H NMR of 2 in Chloroform-d



# Figure S13 <sup>1</sup>H NMR of 2-[d] in Chloroform-d



#### Deuteration of Ethyl 2-thiophenecarboxylate (3) 4



The corresponding substrate was ground under standard condition to afford **3-[d]** as yellow liquid (51.2 mg, 33%) with D-incorporation 81% for 5-position by <sup>1</sup>H NMR; 0.81 D by GC-MS;  $R_f = 0.45$  (Petroleum ether/Ethyl acetate = 25/1).

**NMR** data for starting material: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.80 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.54 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). **NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.80 (d, *J* = 3.7 Hz, 1H), <u>7.54</u> (dd, *J* = 5.0, 1.2 Hz, 0.19H, Labelled), 7.09 (d, *J* = 3.7 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). Hz, 3H).









### Figure S16 <sup>1</sup>H NMR of 3 in Chloroform-d



# Figure S17 <sup>1</sup>H NMR of 3-[d] in Chloroform-d



#### Deuteration of Diethyl thiophene-3,4-dicarboxylate (4) 5



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **4-[d]** as transparent liquid (86.4 mg, 82%) with D-incorporation 62% for 2,5-position by <sup>1</sup>H NMR; 1.14 D by GC-MS;  $R_f = 0.20$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.83 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 4H), 1.34 (t, *J* = 7.1 Hz, 6H).–

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  <u>7.83 (d, *J* = 1.6 Hz, 0.76H,</u> <u>Labelled</u>), 4.33 (q, *J* = 7.1 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 6H).









## Figure S20 <sup>1</sup>H NMR of 4 in Chloroform-d







### Deuteration of Phenyl(thiophen-2-yl)methanone (5) 4



The corresponding substrate was ground under standard condition for 99 minutes to afford 5**-[d]** as yellow solid (171.0 mg, 91%) with D-incorporation 79% for 5-position by <sup>1</sup>H NMR; 0.72 D by GC-MS;  $R_f = 0.80$  (Petroleum ether/Ethyl acetate = 10/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.83 (m, 2H), 7.73 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.65 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.54 – 7.43 (m, 2H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.83 (m, 2H), <u>7.73 (dd, J</u> <u>= 4.9, 1.1 Hz, 0.21H, Labelled)</u>, 7.65 (d, *J* = 3.8 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.54 – 7.46 (m, 2H), 7.16 (d, *J* = 3.7 Hz, 1H).

Figure S22 <sup>1</sup>H NMR spectrum comparison







86.0 186.4 186.8 187.2 187.6 188.0 188.4 188.8 189.2 189.6 190.0 190.4 190.8 191.2 191.6 192.0 m/z. (Da)

## Figure S24 <sup>1</sup>H NMR of 5 in Chloroform-d







#### Deuteration of 2-Thiophenecarbonitrile (6) <sup>6</sup>



The corresponding substrate was ground under standard condition for 99 minutes to afford **6-[d]** as yellow liquid (65.8 mg, 60%) with D-incorporation 81% for 5-position by <sup>1</sup>H NMR; 0.90 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 50/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) *δ* 7.67 – 7.63 (m, 1H), 7.61 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dd, *J* = 5.1, 3.7 Hz, 1H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 3.7 Hz, 1H), <u>7.61</u> (dd, *J* = 5.1, 1.2 Hz, 0.19H, Labelled), 7.14 (t, *J* = 3.6 Hz, 1H).

Figure S26 <sup>1</sup>H NMR spectrum comparison







106.6 107.0 111.8 112.2 109.0 109.8 110.2 111.0 113.0 107.4 107.8 108.2 108.6 109.4 110.6 111.4 112.6

## Figure S28 <sup>1</sup>H NMR of 6 in Chloroform-d





### Deuteration of 2-Bromo-3-methylthiophene (7) 7



The corresponding substrate was ground under standard condition to afford **7-[d]** as yellow liquid (121.0 mg, 68%) with D-incorporation 81% for 5-position by <sup>1</sup>H NMR; 0.86 D by GC-MS;  $R_f = 0.80$  (Petroleum ether).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.50 (d, J = 5.6 Hz, 1H), 6.91 (d, J = 5.6 Hz, 1H), 2.14 (s, 3H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ <u>7.51 (d, *J* = 5.5 Hz, 0.19H, Labelled)</u>, 6.91 (d, *J* = 1.7 Hz, 1H), 2.15 (s, 3H).

#### Figure S30 <sup>1</sup>H NMR spectrum comparison







## Figure S32 <sup>1</sup>H NMR of 7 in Chloroform-d



.0 10.5 10.0 9.5 7.5 7.0 -0. 6.5 5.5 5.0 f1 (ppm) 2.5 2.0 1.5 0.0 9.0 8.5 8.0 6.0 4.5 4.0 3, 5 3.0 1.0 0.5

#### Deuteration of Morpholino(thiophen-2-yl)methanone (9)



The corresponding substrate was ground under 150 °C heating for 99 minutes to afford **9-[d]** as transparent liquid (91.0mg, 92%) with D-incorporation 76% for 5-position by <sup>1</sup>H NMR; 0.82 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 2/1).

**Characterization of starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.45 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.28 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.6 Hz, 1H), 3.79 – 3.67 (m, 8H); <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)  $\delta$  163.67, 136.61, 128.96, 128.86, 126.77, 66.87; HRMS (ESI): calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>SNa<sup>+</sup> (M + Na)<sup>+</sup>: 220.0408, found: 220.0412.

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>7.46 (dd, *J* = 5.0, 1.2 Hz, 0.24H,</u> <u>Labelled</u>), 7.29 (d, *J* = 3.6 Hz, 1H), 7.04 (d, *J* = 3.5 Hz, 1H), 3.80 – 3.69 (m, 8H).

Figure S34 <sup>1</sup>H NMR spectrum comparison







192. 5 193. ο 193. 5 194. ο 194. 5 195. ο 195. 5 196. ο 196. 5 197. ο 197. 5 198. ο 198. 5 199. ο 199. 5 200. ο 200. 5 201. ο 201. 5 202. ο 202. 5 203. ο 203. 5 204. ο 204. 5 205 m/z (Da)

### Figure S36 <sup>1</sup>H NMR of 9 in Chloroform-d







210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 f1 (ppm)

# Figure S38 <sup>1</sup>H NMR of 9-[d] in Chloroform-d



. 0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -( f1 (ppm)

#### Deuteration of 2-(2-Thienyl)benzothiazole (10) 8



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **10-[d]** as white solid (202.7 mg, 93%) with D-incorporation 79% for 5-position of Thiophene, 14% for 3-position of Thiophene by <sup>1</sup>H NMR;  $R_f = 0.45$  (Petroleum ether/Ethyl acetate = 50/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.11 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.87 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.85 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.53 (td, *J* = 8.2, 7.7, 1.3 Hz, 1H), 7.44 (td, *J* = 7.7, 1.2 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.7 Hz, 1H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.13 – 8.06 (m, 1H), 8.03 – 7.96 (m, 1H), **<u>7.87 (dd, J = 5.0, 1.2 Hz, 0.21H, Labelled)</u>**, **<u>7.84 (d, J = 3.7 Hz, 0.86H)</u>**, 7.52 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1H), 7.25 (dd, *J* = 4.4, 2.9 Hz, 1H).

Figure S39 <sup>1</sup>H NMR spectrum comparison



#### Figure S40 <sup>1</sup>H NMR of 10 in DMSO-d<sub>6</sub>



1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -( f1 (ppm)

#### Deuteration of 2-(Thiophen-2-yl)pyridine (11) 4



The corresponding substrate was ground under standard condition for 99 minutes to afford **11-[d]** as white solid (130.0 mg, 81%) with D-incorporation 80% for 5-position by <sup>1</sup>H NMR; 0.79 D by GC-MS;  $R_f = 0.80$  (Petroleum ether/Ethyl acetate = 10/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.57 (dt, *J* = 4.9, 1.4 Hz, 1H), 7.73 – 7.62 (m, 2H), 7.60 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.40 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.20 – 7.08 (m, 2H).– **NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.57 (dt, *J* = 5.0, 1.4 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.60 (d, *J* = 3.7 Hz, 1H), <u>7.40 (dd, *J* = 5.1, 1.1 Hz, 0.20H, Labelled)</u>, 7.20 – 7.08 (m, 2H).

#### Figure S42 <sup>1</sup>H NMR spectrum comparison







### Figure S44 <sup>1</sup>H NMR of 11 in Chloroform-d



Figure S45 <sup>1</sup>H NMR of 11-[d] in Chloroform-d



### Deuteration of 2,2':5',2"-Terthiophene (12) 9



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **12-[d]** as yellow solid (175.4 mg, 71%) with D-incorporation 52% for 5-position by <sup>1</sup>H NMR;  $R_f = 0.50$  (Petroleum ether).

**NMR** data for starting material: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.22 (dd, *J* = 5.1, 1.1 Hz, 2H), 7.18 (dd, *J* = 3.6, 1.1 Hz, 2H), 7.08 (s, 2H), 7.05 – 7.01 (dd, *J* = 5.1, 3.6 Hz, 2H). **NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  <u>7.22 (dd, *J* = 5.1, 1.1 Hz, 0.96H, Labelled)</u>, 7.18 (dd, *J* = 3.6, 1.1 Hz, 2H), 7.08 (s, 2H), 7.05 – 7.01 (m, 2H).

Figure S46 <sup>1</sup>H NMR spectrum comparison



## Figure S47 <sup>1</sup>H NMR of 12 in Chloroform-d





### Deuteration of 1,3,5-Tri(2-thienyl)benzene (13) 10



The corresponding substrate was ground under standard condition to afford **13-[d]** as white solid (124.5 mg, 77%) with D-incorporation 67% for 5-position by <sup>1</sup>H NMR; 2.13 D by GC-MS;  $R_f = 0.70$  (Petroleum ether).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) *δ* 7.75 (s, 3H), 7.42 (dd, *J* = 3.6, 1.2 Hz, 3H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 3H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 3H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.75 (s, 3H), 7.42 (dd, *J* = 3.6, 1.2 Hz, 3H), <u>7.35 (dd, *J* = 5.1, 1.2 Hz, 0.99H, Labelled)</u>, 7.13 (dd, *J* = 5.1, 3.5 Hz, 3H).



Figure S49 <sup>1</sup>H NMR spectrum comparison





## Figure S51 <sup>1</sup>H NMR of 13 in Chloroform-d



Figure S52 <sup>1</sup>H NMR of 13-[d] in Chloroform-d



### Deuteration of Thianaphthene (14) 6



The corresponding substrate was ground under standard condition for 99 minutes to afford **14-[d]** as white solid (80.1 mg, 60%) with D-incorporation 83% for 2-position by <sup>1</sup>H NMR; 0.84 D by GC-MS;  $R_f = 0.70$  (Petroleum ether).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.90 (ddd, *J* = 6.8, 2.3, 0.9 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.45 (d, *J* = 5.5 Hz, 1H), 7.41 – 7.32 (m, 3H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.85 (m, 1H), 7.85 – 7.79 (m, 1H), 7.44 (d, *J* = 5.5 Hz, 0.17H, Labelled), 7.40 – 7.28 (m, 3H).

### Figure S53 <sup>1</sup>H NMR spectrum comparison



#### Figure S54 GC-MS spectrum comparison



130.5 137.5 130.0 131.0 131.5 132.0132.5 133.0 133 34.0 134.5 135. 0 135.5 136.0 136.5 137.0 138.0 138.5 n/z (Da)

# Figure S55 <sup>1</sup>H NMR of 14 in Chloroform-d





S36
#### Deuteration of Thieno[3,2-b]thiophene (15) 11



The corresponding substrate was ground under standard condition for 99 minutes to afford 1**5-[d]** as white solid (115.3 mg, 82%) with D-incorporation 68% for 2-position by <sup>1</sup>H NMR; 1.62 D by GC-MS;  $R_f = 0.80$  (Petroleum ether).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.66 (d, J = 5.0 Hz, 2H), 7.44 (d, J = 5.0 Hz, 2H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  <u>7.66 (d, J = 5.2 Hz, 0.64H, Labelled</u>), 7.44 (d, J = 5.1 Hz, 2H).

#### Figure S57 <sup>1</sup>H NMR spectrum comparison







36. 5 137. 0 137. 5 138. 0 138. 5 139. 0 139. 5 140. 0 140. 5 141. 0 141. 5 142. 0 142. 5 143. 5 144. 0 144. 5 145. 0 145. 5 146. 0 146. 5 147. 0 147. 5 148. 0 148. 5 m/z (Da)







5.5 5.0 fl (ppm) 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.

۲ حر 0.64 2.00

. 0 10. 5 10. 0 9. 5 9. 0 8. 5 8. 0 7. 5 7. 0 6. 5 6. 0



The corresponding substrate was ground under standard condition for 99 minutes to afford **18-[d]** as white solid (127.5 mg, 79%) with D-incorporation 81% for 2-position by <sup>1</sup>H NMR; 0.78 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.77 (s, 1H), 8.09 (s, 1H), 7.62 – 7.54 (m, 2H), 7.46 – 7.37 (m, 2H), 7.39 – 7.31 (m, 1H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>8.76 (s, 0.19H, Labelled)</u>, 8.08 (s, 1H), 7.62 – 7.53 (m, 2H), 7.46 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H).









### Figure S63 <sup>1</sup>H NMR of 18 in Chloroform-d





#### Deuteration of Ethyl thiazole-4-carboxylate (19) 13



The corresponding substrate was ground under standard condition for 99 minutes to afford **19-[d]** as yellow solid (128.2 mg, 82%) with D-incorporation 69% or 74% for 2,5-position by <sup>1</sup>H NMR;  $R_f = 0.3$  (Petroleum ether/Ethyl acetate = 5/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.85 (d, *J* = 2.1 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  <u>8.84 (d, *J* = 2.6 Hz, 0.31H,</u> <u>Labelled</u>), <u>8.24 (d, *J* = 2.2 Hz, 0.26H, Labelled)</u>, 4.43 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).

Figure S65 <sup>1</sup>H NMR spectrum comparison



### Figure S66 <sup>1</sup>H NMR of 19 in Chloroform-d



Figure S67 <sup>1</sup>H NMR of 19-[d] in Chloroform-d



#### Deuteration of Benzo[d]thiazole (20) 4



The corresponding substrate was ground under standard condition for 99 minutes to afford **20-[d]** as transparent liquid (126.4mg, 93%) with D-incorporation 82% for 2-position by <sup>1</sup>H NMR; 0.80 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 100/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.40 (s, 1H), 8.17 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.10 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.51 (m, *J* = 24.2, 7.2, 1.3 Hz, 2H).–

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ <u>9.40 (s, 0.18H, Labelled)</u>, 8.21 – 8.14 (m, 1H), 8.13 – 8.06 (m, 1H), 7.51 (m, *J* = 24.2, 8.4, 7.2, 1.3 Hz, 2H).

#### Figure S68 <sup>1</sup>H NMR spectrum comparison







### Figure S70 <sup>1</sup>H NMR of 20 in DMSO-d<sub>6</sub>







The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **21-[d]** as yellow solid (129.9 mg, 79%) with D-incorporation 83% for 2-position by <sup>1</sup>H NMR; 0.79 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.91 (s, 1H), 7.53 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.06 (s, 3H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>8.88 (s, 0.17H, Labelled)</u>, 7.49 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 4.03 (s, 3H).









<sup>9. 5 160. 0 160. 5 161. 0 161. 5 162. 0 162. 5 163. 0 163. 5 164. 0 164. 5 165. 0 165. 5 166. 0 166. 5 167. 0 167. 5 168. 0 168. 5 169. 0 169. 5 170. 0 170. 5</sup> m/z (Da)

### Figure S74 <sup>1</sup>H NMR of 21 in Chloroform-d



Figure S75 <sup>1</sup>H NMR of 21-[d] in Chloroform-d



#### Deuteration of ethyl benzothiazole-5-carboxylate (22) 15



The corresponding substrate was ground under 150 °C heating for 99 minutes to afford **22-[d]** as white solid (164.9 mg, 79%) with D-incorporation 79% for 2-position by <sup>1</sup>H NMR; 0.62 D by GC-MS;  $R_f = 0.25$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.53 (s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). **NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  <u>9.53 (s, 0.21H, Labelled)</u>, 8.60 (d, *J* = 1.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.04 (dd, *J* = 8.5, 1.6 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

#### Figure S76 <sup>1</sup>H NMR spectrum comparison







Figure S78 <sup>1</sup>H NMR of 22 in DMSO-d<sub>6</sub>



Figure S79 <sup>1</sup>H NMR of 22-[d] in DMSO-d<sub>6</sub>





The corresponding substrate was ground under standard condition for 99 minutes to afford 23-[d] as white solid (193.7 mg, 90%) with D-incorporation 40% for 2-position by <sup>1</sup>H NMR; 0.30 D by GC-MS;  $R_f = 0.30$ (Petroleum ether/Ethyl acetate = 20/1).

**NMR** data for starting material: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.49 (s, 1H), 8.20 (dd, J = 8.1, 1.0 Hz, 1H), 7.80 (dd, J = 7.7, 1.0 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H).-

NMR data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.49 (s, 0.60H, Labelled), 8.19 (dd, J = 8.1, 1.0 Hz, 1H), 7.79 (dd, J = 7.8, 1.0 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H).









Figure S82 <sup>1</sup>H NMR of 23 in DMSO-d<sub>6</sub>





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번 0.60



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **24-[d]** as yellow solid (143.7 mg, 84%) with D-incorporation 76% for 2-position by <sup>1</sup>H NMR; 0.83 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.49 (s, 1H), 8.15 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H).–

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ <u>9.49 (s, 0.24H, Labelled)</u>, 8.15 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H).









# Figure S86 <sup>1</sup>H NMR of 24 in DMSO-d<sub>6</sub>



# Figure S87 <sup>1</sup>H NMR of 24-[d] in DMSO-d<sub>6</sub>



#### Deuteration of Methyl 2-phenyloxazole-4-carboxylate (27) 18



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **27-[d]** as white solid (174.1 mg, 86%) with D-incorporation 80% for 5-position by <sup>1</sup>H NMR; 0.76 D by GC-MS;  $R_f = 0.20$  (Petroleum ether/Ethyl acetate = 20/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.29 (s, 1H), 8.17 – 8.07 (m, 2H), 7.57 – 7.43 (m, 3H), 3.96 (s, 3H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>8.29 (s, 0.20H, Labelled)</u>, 8.17 – 8.07 (m, 2H), 7.57 – 7.43 (m, 3H), 3.96 (s, 3H).

#### Figure S88 <sup>1</sup>H NMR spectrum comparison







Figure S90 <sup>1</sup>H NMR of 27 in Chloroform-d



Figure S91 <sup>1</sup>H NMR of 27-[d] in Chloroform-d





The corresponding substrate was ground under standard condition for 99 minutes to afford **28-[d]** as yellow liquid (120.3 mg, 83%) with D-incorporation 78% for 2,5-position by <sup>1</sup>H NMR; 1.39 D by GC-MS;  $R_f = 0.35$  (Petroleum ether/Ethyl acetate = 100/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 2H), 7.79 – 7.72 (m, 2H), 7.55 – 7.38 (m, 2H), 7.37 – 7.29 (m, 1H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>**7.94 (d, J = 2.0 Hz, 0.44H,**</u> <u>Labelled</u>), 7.79 – 7.72 (m, 2H), 7.42 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.37 – 7.29 (m, 1H).

Figure S92 <sup>1</sup>H NMR spectrum comparison







10.5 141. 6 141. 5 142. 6 142. 5 143. 6 143. 5 144. 6 144. 5 145. 6 145. 5 146. 6 146. 5 147. 6 147. 5 148. 6 148. 5 149. 6 149. 5 150. 6 150. 5 151. 6 151. 5 152. 6 152. 5 153. 6 m/z (Da)

#### Figure S94 <sup>1</sup>H NMR of 28 in Chloroform-d





#### Deuteration of Benzoxazole (29) 6



The corresponding substrate was ground under 100 °C heating for 99 minutes to afford **29-[d]** as white solid (76.0 mg, 64%) with D-incorporation 81% for 2-position by <sup>1</sup>H NMR; 0.77 D by GC-MS;  $R_f = 0.30$  (Petroleum ether/Ethyl acetate = 100/1).

**NMR data for starting material**: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.85 – 7.75 (m, 1H), 7.64 – 7.54 (m, 1H), 7.44 – 7.33 (m, 2H).

**NMR data for deuterated product**: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>8.10 (s, 0.19H, Labelled)</u>, 7.86 – 7.74 (m, 1H), 7.63 – 7.51 (m, 1H), 7.44 – 7.32 (m, 2H).

Figure S96 <sup>1</sup>H NMR spectrum comparison







#### Figure S98 <sup>1</sup>H NMR of 29 in Chloroform-d



#### Deuteration of 1-Methylbenzimidazole (31) 6



The corresponding substrate was ground under standard condition for 99 minutes to afford **31-[d]** as white solid (120.6 mg, 91%) with D-incorporation 84% for 2-position by <sup>1</sup>H NMR; 0.72 D by GC-MS;  $R_f = 0.35$  (Ethyl acetate).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.17 (s, 1H), 7.65 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.31 – 7.16 (m, 2H), 3.84 (s, 3H).

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ <u>8.17 (s, 0.16H, Labelled)</u>, 7.64 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.56 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.23 (m, *J* = 25.2, 8.3, 7.2, 1.2 Hz, 2H), 3.83 (s, 3H).

Figure S100 <sup>1</sup>H NMR spectrum comparison







29.6 130.0 130.4 130.8 131.2 131.6 132.0 132.4 132.8 m/z (Da) 133.2 133.6 134.0 134.4 134.8 135.2 135.6

### Figure S102 <sup>1</sup>H NMR of 31 in DMSO-d<sub>6</sub>



Figure S103 <sup>1</sup>H NMR of 31-[d] in DMSO-d<sub>6</sub>



#### Deuteration of tert-butyl (S)-methyl(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)carbamate (34)



The corresponding substrate was ground under standard condition to afford **34-[d]** as transparent liquid (105.2 mg, 66%) with D-incorporation 80% for 2-position by <sup>1</sup>H NMR;  $R_f = 0.15$  (Petroleum ether/Ethyl acetate = 20/1).

**Characterization of starting material:** <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.28 – 8.21 (m, 1H), 7.88 – 7.79 (m, 1H), 7.55 – 7.46 (m, 2H), 7.43 (dd, *J* = 7.0, 1.9 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.25 (d, J = 3.5 Hz, 1H), 7.04 – 6.94 (m, 2H), 5.87 (s, 1H), 3.42 (s, 1H), 2.78 (s, 3H), 2.41 – 2.31 (m, 1H), 2.19 (s, 1H), 1.43 – 1.13 (m, 9H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  155.18, 152.97, 145.00, 134.64, 127.90, 127.11, 126.83, 126.35, 126.12, 125.98, 125.87, 125.75, 122.10, 120.72, 107.49, 78.85, 45.51, 28.38, 26.82; **HRMS** (ESI): calcd. for C<sub>23</sub>H<sub>27</sub>NO<sub>3</sub>SNa<sup>+</sup> (M+Na)+: 420.1609, found: 420.1615.

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.27 – 8.19 (m, 1H), 7.88 – 7.79 (m, 1H), 7.55 – 7.45 (m, 2H), <u>7.42 (d, *J* = 8.2 Hz, 1.20H, Labelled)</u>, 7.31 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.03 – 6.94 (m, 2H), 5.86 (s, 1H), 3.47 (s, 1H), 2.77 (s, 3H), 2.34 (dt, *J* = 14.1, 7.0 Hz, 1H), 2.18 (s, 1H), 1.40 – 1.10 (m, 9H).

#### Figure S104 <sup>1</sup>H NMR spectrum comparison



### Figure S105 <sup>1</sup>H NMR of 34 in DMSO-d<sub>6</sub>



Figure S106 <sup>13</sup>C NMR of 34 in DMSO-d<sub>6</sub>



# Figure S107 <sup>1</sup>H NMR of 34-[d] in DMSO-d<sub>6</sub>



5.5 5.0 fl (ppm)

### Deuteration of Vagistat (37) 4



The corresponding substrate was ground under 150 °C heating for 99 minutes to afford **37-[d]** as white solid (183.9 mg, 95%) with D-incorporation 26% for 2-position of Thiophene, 64%, 21% and 59% for 2,4,5-position of Imidazole, 56% for 3-position of Benzene by <sup>1</sup>H NMR;  $R_f = 0.30$  (Dichloromethane/Methanol = 50/1).

**NMR data for starting material**: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.44 – 7.34 (m, 2H), 7.02 (d, *J* = 1.3 Hz, 1H), 6.88 – 6.80 (m, 2H), 4.97 (dd, *J* = 6.9, 3.9 Hz, 1H), 4.41 – 4.14 (m, 4H).

NMR data for deuterated product: <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  <u>7.65 (d, J = 2.0 Hz, 0.74H, Labelled)</u>, <u>7.51 – 7.44 (m, 1.44H, Labelled)</u>, <u>7.43 – 7.35 (m, 1.41H, Labelled)</u>, <u>7.02 (d, J = 1.4 Hz, 0.36H, Labelled)</u>, <u>6.84 (dd, 1.79H, Labelled)</u>, 4.97 (dd, J = 7.0, 3.9 Hz, 1H), 4.41 – 4.11 (m, 4H).

Figure S108 <sup>1</sup>H NMR spectrum comparison



### Figure S109 <sup>1</sup>H NMR of 37 in DMSO-d<sub>6</sub>



# Figure S110 <sup>1</sup>H NMR of 37-[d] in DMSO-d<sub>6</sub>



#### Deuteration of Fluconazole (38)<sup>4</sup>



The corresponding substrate was ground under 150 °C heating for 99 minutes to afford **38-[d]** as white solid (142.8 mg, 93%) with D-incorporation 62% for 5-position of Triazole, 31% for 3-position of Benzene by <sup>1</sup>H NMR;  $R_f = 0.20$  (Dichloromethane/Methanol = 50/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.06 (s, 2H), 7.85 (s, 2H), 7.42 (td, J = 9.6, 9.2, 6.3 Hz, 1H), 6.84 – 6.73 (m, 2H), 4.74 (d, J = 14.3 Hz, 2H), 4.46 (d, J = 14.3 Hz, 2H).

**NMR data for deuterated product:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>8.05 (s, 0.76H, Labelled)</u>, 7.83 (s, 2H), 7.41 (td, *J* = 9.2, 6.4 Hz, 1H), <u>6.84 – 6.72 (m, 1.69H, Labelled)</u>, 4.73 (d, *J* = 14.3 Hz, 2H), 4.45 (d, *J* = 14.3 Hz, 2H).

Figure S111 <sup>1</sup>H NMR spectrum comparison



### Figure S112 <sup>1</sup>H NMR of 38 in Chloroform-d



# Figure S113 <sup>1</sup>H NMR of 38-[d] in Chloroform-d



#### Deuteration of 3,7-Dimethyl-1-(5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (39) 4



The corresponding substrate was ground under standard condition for 99 minutes to afford **39-[d]** as white solid (222.4 mg, 80%) with D-incorporation 26% for 2-position of Imidazole, 29% for Methyl adjacent to the carbonyl group, 22% for Methylene adjacent to the carbonyl group by <sup>1</sup>H NMR;  $R_f = 0.50$  (Ethyl acetate/Methanol = 25/1).

**NMR** data for starting material: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.49 (s, 1H), 4.00 (t, *J* = 6.8 Hz, 2H), 3.97 (s, 3H), 3.55 (s, 3H), 2.49 (t, *J* = 6.9 Hz, 2H), 2.13 (s, 3H), 1.65 (qt, *J* = 8.7, 4.0 Hz, 4H).– **NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  <u>7.48 (s, 0.74H, Labelled)</u>, 3.96 (d, *J* = 6.8 Hz, 2H), 3.94 (s, 3H), 3.52 (s, 3H), <u>2.45 (t, *J* = 6.9 Hz, 1.57H, Labelled)</u>, <u>2.08 (d, *J* = 8.8 Hz, 2.13H, Labelled)</u>, 1.61 (ddt, *J* = 11.8, 9.3, 4.6 Hz, 4H).



#### Figure S115 <sup>1</sup>H NMR of 39 in Chloroform-d



# Figure S116 <sup>1</sup>H NMR of 39-[d] in Chloroform-d





#### Deuteration of 7-((1,3-Dioxolan-2-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione (40) 4



The corresponding substrate was ground under 150 °C heating for 99 minutes to afford **40-[d]** as white solid (128.3 mg, 96%) with D-incorporation 79% for 2-position by <sup>1</sup>H NMR;  $R_f = 0.30$  (Ethyl acetate/Methanol = 50/1).

**NMR data for starting material:** <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.65 (s, 1H), 5.22 (t, *J* = 3.2 Hz, 1H), 4.58 (d, *J* = 3.2 Hz, 2H), 3.92 – 3.78 (m, 4H), 3.59 (s, 3H), 3.41 (s, 3H).–

**NMR** data for deuterated product: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ <u>7.65 (s, 0.21H, Labelled)</u>, 5.22 (t, *J* = 3.2 Hz, 1H), 4.58 (d, *J* = 3.2 Hz, 2H), 3.92 – 3.78 (m, 4H), 3.59 (s, 3H), 3.41 (s, 3H).

Figure S117 <sup>1</sup>H NMR spectrum comparison



### Figure S118 <sup>1</sup>H NMR of 40 in Chloroform-d



# Figure S119 <sup>1</sup>H NMR of 40-[d] in Chloroform-d



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