SUPPORTING INFORMATION

Undirected, Pd-catalyzed deuteration of indoles with programmable regioselectivity.

Liam S. Fitzgerald,[a] Rachael L. McNulty,[a] Andrew Greener,[b] Miriam L. O'Duill[b]*

a School of Chemistry, National University of Ireland Galway, University Road, Galway, H91 TK33, Ireland.
b School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK.

** Corresponding author: miriam.oduill@nottingham.ac.uk*

TABLE OF CONTENTS

GENERAL INFORMATION

All solvents and chemicals were used as purchased unless stated otherwise; all solvents were dried according to conventional methods. Anhydrous 1,4-dioxane was purchased from Sigma Aldrich and further dried over molecular sieves. CD_3CO_2D was purchased from Deutero. NaOAc was dried at room temperature under vacuum for 4 hours prior to use. All reactions were performed in oven dried apparatus with magnetic stirring under an inert atmosphere of argon or nitrogen. The reactions were followed by thin layer chromatography (TLC) carried out on aluminium-foil backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). The products were visualized using UV fluorescence (254 nm) or potassium permanganate stain. Silica flash column chromatography was performed over Merck silica gel C60 (40-60 μm) using eluent systems as described for each experiment.

All NMR spectra were recorded on Varian VNMRS 500 MHz or Jeol 400 MHz spectrometer. NMR data were processed using MNova 12.0.4 software. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to residual undeuterated solvent peak or TMS. Coupling constants (*J*) are reported in units of hertz (Hz) and are rounded to the nearest 0.5 ppm. The following abbreviations are used to describe multiplets: s (singlet), d (doublet), ad (apparent doublet), q (quartet), p (pentet), m (multiplet), br (broad). Known compounds have been checked against literature references and only relevant analytical data are given.

Determination of Deuteration Incorporation. Deuterium incorporation was quantified by comparing the ^{1}H NMR integral intensity at the deuterated position with the starting material (see Fig. S1). ^{1}H NMR experiments were run with a T1 relaxation time of 1 second and integral intensities were calibrated against hydrogen signals that did not undergo H/D-exchange.

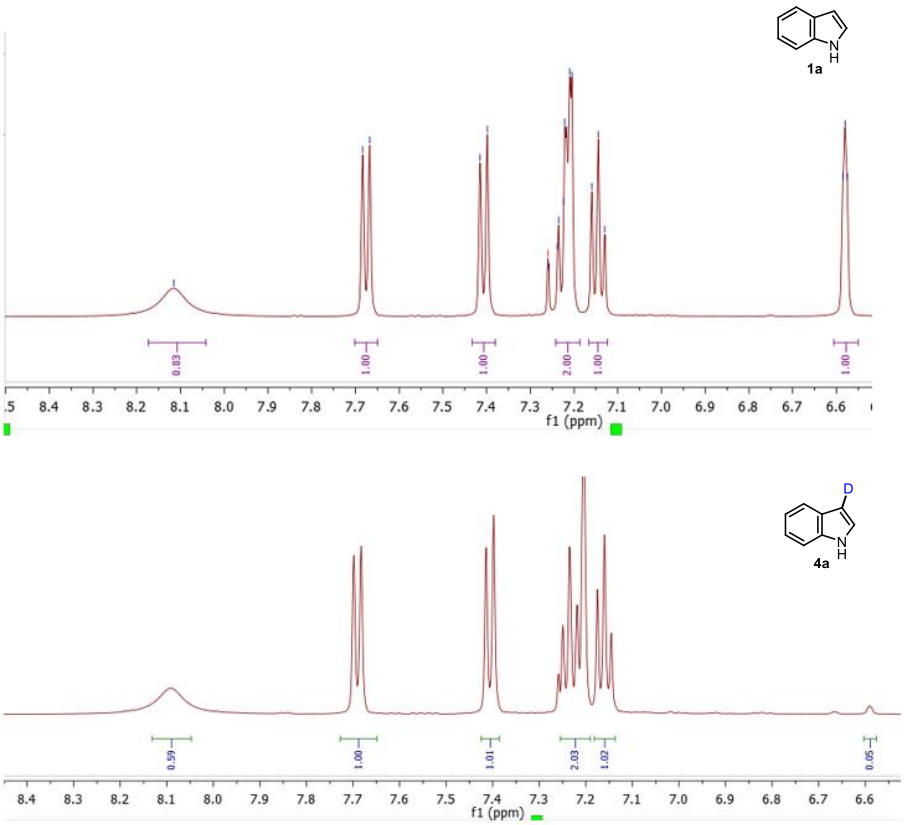
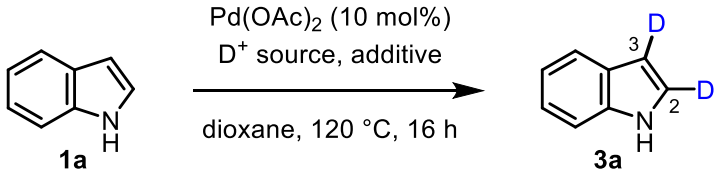


Figure S1: ^{1}H NMR spectra of unlabelled (top) and labelled/deuterated (bottom) indole in $CDCl_3$. Integration of the signal at 6.47 ppm decreases from 100% (**1a**) to 5% intensity (**4a**), indicating 95% deuterium incorporation.

REACTION INFORMATION

Reaction Optimisation

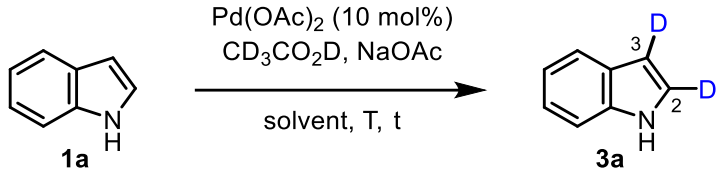
Table S1. Deuterium source & additive screen



Entry	D+ Source	Additive	C2 deuteration [%]	C3 deuteration [%]
1	CD_3CO_2D (1.14 mL)	-	68	60
2	CD_3CO_2D (1.14 mL)	NaOAc (1.5 equiv)	81	72
3	CH_3CO_2D (1.14 mL)	NaOAc (1.5 equiv)	50	15
4[a]	**CD_3CO_2D (0.6 mL)**	**NaOAc (1.5 equiv)**	**73**	**70**
5	CD_3CO_2D (0.6 mL)	NaOAc (1.5 equiv)	80	40
6	CD_3CO_2D (0.6 mL)	NaOAc (4 equiv)	64	69
7	CD_3CO_2D (0.3 mL)	NaOAc (1.5 equiv)	70	25
8[b]	CD_3CO_2D (0.2 mL)	NaOAc (1.5 equiv)	51	14
9	D_2O (1 mL)	NaOAc (1.5 equiv)	42	87
10	D_2O (1 mL)	NaOAc (1.5 equiv), AcOH (0.5 mL)	41	72

Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), D^+ source, additive, 1,4-dioxane (1.5 mL, 0.13M), 120 °C, 16 h. Deuterium incorporation determined by ^1H NMR. [a] 1,4-Dioxane dried over molecular sieves (for the importance of anhydrous solvents in this reaction, see Table S4 below). [b] 0.8 mL dioxane (0.25M); 47% deuterium incorporation at C7.

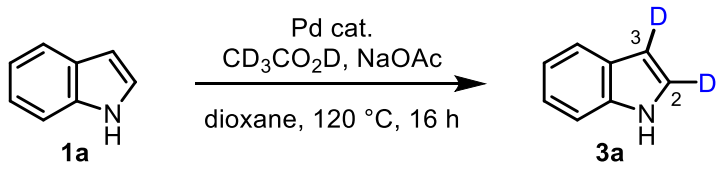
Table S2. Solvent, temperature & time screen



Entry	Solvent	Temperature [°C], time	C2 deuteration [%]	C3 deuteration [%]
1	dioxane	80 °C, 16 h	58	13
2	dioxane	120 °C, 16 h	81	72
3	dioxane	120 °C, 4 h	60	20
3	no solvent	120 °C, 16 h	60	63
4	MeCN	80 °C, 16 h	27	43

Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), CD_3CO_2D (1.14 mL), NaOAc (1.5 equiv.), solvent (1.5 mL, 0.13M), temperature, time. Deuterium incorporation determined by ^1H NMR.

Table S3. Catalyst screen



Entry	Pd cat.	C2 deuteration [%]	C3 deuteration [%]
1	$Pd(OAc)_2$ (10 mol%)	81	72
2	$Pd(OAc)_2$ (5 mol%)	15	47
3	none	0	50

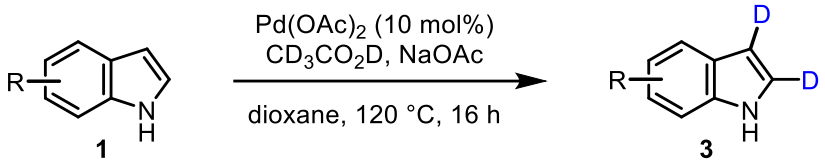
Reaction conditions: **1a** (0.2 mmol), Pd cat., CD_3CO_2D, NaOAc (1.5 equiv.), 1,4-dioxane (1.5 mL, 0.13M), 120 °C, 16 h. Deuterium incorporation determined by ^1H NMR.

As the palladium loading is decreased, the uncatalyzed acid-base background reaction becomes dominant.

The importance of dry solvents

The use of strictly anhydrous 1,4-dioxane proved instrumental to avoid acid/base background reactions causing isotopic dilution at C3 (Table S4). When an older bottle of dioxane was used, deuterium incorporation at C3 was markedly lower than with a new bottle of anhydrous 1,4-dioxane (stored over molecular sieves).

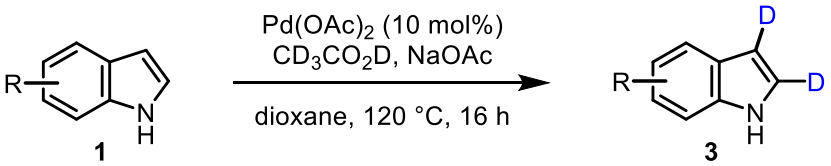
Table S4. Effect of anhydrous solvent



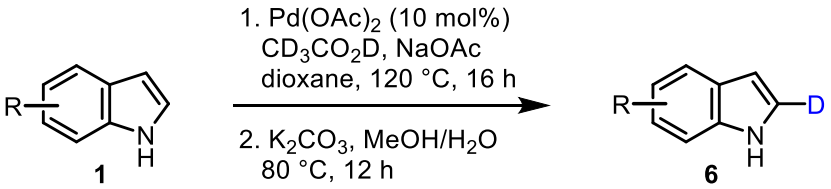
anhydrous dioxane	old (wet) dioxane	anhydrous dioxane	old (wet) dioxane
[70%] [73%] **3a**	[60%] [81%] **3a**	F [76%] [85%] **3e**	F [70%] [90%] **3e**
[70%] [70%] Me **3c**	[21%] [85%] Me **3c**	NO_2 [90%] [32%] **3f**	NO_2 [63%] [33%] **3f**
[70%] [70%] MeO [30%] **3d**	[50%] [85%] MeO [36%] **3d**	[95%] **6h**	[63%] **6h**

Conditions: **1** (0.4 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (1.5 equiv.), CD_3CO_2D/dioxane (1.2 mL/3 mL), 120 °C, 16 h. Grey circles show the labelling positions, with values in brackets denoting isotope incorporation, as determined by ^1H NMR, before purification on silica.

Optimised Reaction Conditions

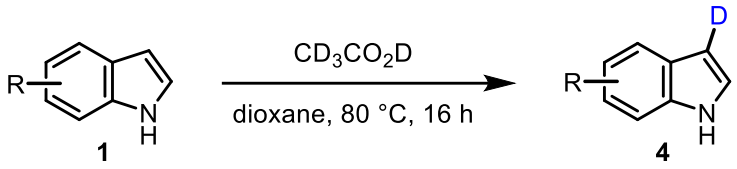


Method 1: Pd-catalysed C2- and C3-deuteration. To a mixture of indole (0.4 mmol), $Pd(OAc)_2$ (9 mg, 10 mol%) and NaOAc (50 mg, 0.6 mmol) in anhydrous 1,4-dioxane (3 mL, 0.13 M) was added deuterated acetic acid (CD_3CO_2D) (1.2 mL, 10 mmol). The reaction was heated at 120 °C for 16 h, after which it was allowed to cool to rt. The crude mixture was filtered over celite, and solvent was removed under vacuum. The compounds were purified via silica flash column chromatography.



Method 2: C2-deuteration. d_2-Deuterated indole **3** (0.2 mmol) was dissolved in a solution of MeOH (1.2 ml) and H_2O (0.4 ml). K_2CO_3 (28 mg, 0.2 mmol) was added, and the reaction was heated at 80 °C for 16 h, after which it was allowed to cool to rt. The reaction was diluted with H_2O and extracted 3 times with CH_2Cl_2 (30ml). The organic layer was dried using $MgSO_4$ and

solvent was removed under reduced pressure to provide the pure product. In some cases, further purification by silica flash column chromatography was required.

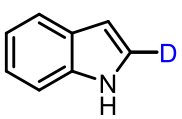


Method 3: C3-deuteration. To a mixture of indole (0.2 mmol) in anhydrous 1,4-dioxane (0.6 mL, 0.3M) was added deuterated acetic acid (CD_3CO_2D) (1.2 mL, 10 mmol). The reaction was allowed to stir for 16 h at 80 °C after which it was cooled to room temperature and solvents were removed under vacuum. No further purification was required, unless stated otherwise.

CHARACTERISATION OF COMPOUNDS

C2-deuterated indoles

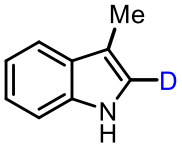
2-deuterio-1*H*-indole (6a)



6a was synthesised from **3a** (0.2 mmol) according to method 2 to give 19 mg (80% yield, 72% deuterium incorporation) of the title compound as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (brs, 1H, N*H*), 7.65 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.41 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.22 – 7.17 (m, **1.28H**), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H). Analytical data matches literature values.[1]

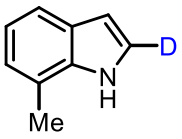
3-methyl-1*H*-indole-2-*d* (6b)



6b was synthesised from **3b** (0.2 mmol) according to method 2. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 44 mg (83% yield, 80% deuterium incorporation) of the title compound as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (brs, 1H, N*H*), 7.59 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.15 – 7.11 (m, 1H), 6.98 (s, **0.2H**), 2.35 (s, 3H). Analytical data matches literature values.[2]

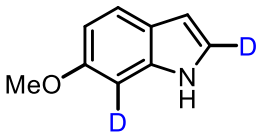
7-methyl-1*H*-indole-2-*d* (6c)



6c was synthesised from **3c** (0.2 mmol) according to method 2 to yield 18 mg (68% yield, 55% deuterium incorporation) of the title compound as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (brs, 1H, N*H*), 7.52 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 3.0, 2.5 Hz, **0.45H**), 7.08 – 6.99 (m, 2H), 6.60 – 6.55 (m, 1H), 2.51 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.5, 127.5, 123.9, 122.6, 120.3, 120.1, 118.6, 103.3, 16.8 (deuterated carbon signal not observed); **FT-IR (neat):** 3412, 2900, 2852, 1750, 1595, 1452, 1377, 1340, 1245, 1072, 803, 783, 745, 698, 666 cm^{-1}.

6-methoxy-1*H*-indole-2,7-d_2 (6d)

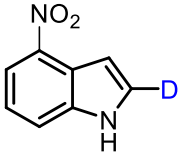


6d was synthesised from **3d** (0.2 mmol) according to method 2 to afford 21 mg (71% yield, 65% deuterium incorporation at C2, 25% deuterium incorporation at C7) of the title compound as a pink solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.10 (dd, *J* = 3.0, 2.5 Hz, **0.35H**), 6.88 (d, *J* = 2.0 Hz**, 0.75H**), 6.83 – 6.80 (m, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 3.85 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.5, 136.6, 123.1, 122.2, 121.4, 110.0, 102.4, 94.6, 55.8.

FT-IR (neat): 3389, 3009, 2961, 2835, 2528, 1620, 1579, 1501, 1455, 1463, 1290, 1161, 1111, 1058, 1026, 954, 810, 422, 661 cm^{-1}.

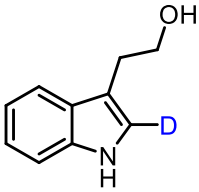
4-nitro-1*H*-indole-2-*d* (6f)



6f was synthesised from **3f** (0.2 mmol) according to method 2 to yield 22 mg (67% yield, 65% deuterium incorporation) of the title compound as a yellow solid.

^{1}H NMR (600 MHz, CD_3OD) δ 8.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.80 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.57 (d, *J* = 3.0 Hz, **0.35H**), 7.26 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.07 (m, 1H); **^{13}C NMR** (151 MHz, CD_3OD) δ 139.9, 138.6, 129.2, 121.7, 119.7, 118.1, 116.5, 101.4; **FT-IR (neat):** 3310, 2918, 1560, 1530, 1450, 1306, 1220, 770, 650 cm^{-1}.

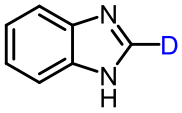
2-(1*H*-indol-3-yl-2-*d*)ethan-1-ol / tryptophol-2-*d* (6g)



6g was synthesised from tryptophol (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: 100% cyclohexane to 100% ethyl acetate) to afford 25 mg (39% yield, 60% deuterium incorporation) of the title compound as a beige solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (brs, 1H, N*H*), 7.64 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.16 – 7.11 (m, 1H), 7.05 (s, **0.4H**), 4.36 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.3, 127.6, 122.3, 122.1, 119.6, 118.9, 112.3, 111.3, 64.7, 24.9; **FT-IR (neat):** 3404, 3056, 2955, 2922, 2855, 1724, 1448, 1257, 1076, 984, 745 cm^{-1}.

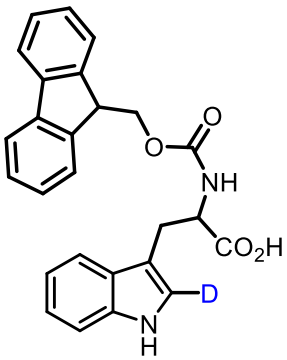
1*H*-benzoimidazole-2-*d* (6h)



Method 1 (Pd catalysis): **6h** was synthesised from benzimidazole (0.4 mmol). The crude product was purified by silica flash column chromatography (gradient: cyclohexane to 1:1 cyclohexane:ethyl acetate) to afford 45 mg (94% yield, 92% deuterium incorporation) of the title compound as a white solid.
Method 3 (Pd-free): **6h** was synthesised from benzimidazole (0.2 mmol) to afford 23 mg (97% yield, 96% deuterium incorporation).

^{1}H NMR (500 MHz, CD_3OD) δ 8.15 (s, 0.08H), 7.64 – 7.57 (m, 2H), 7.28 – 7.23 (m, 2H). Analytical data matches literature values.[3]

***N*-Fmoc-2-deuterotryptophan / (((9*H*-fluoren-9-yl)methoxy)carbonyl)tryptophan-2-*d* (6k)**



6k was synthesised from Fmoc-Trp(Boc)-OH (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: ethyl acetate to 9:1 ethyl acetate:methanol) to afford 141 mg (83% yield, 56% deuterium incorporation) of the title compound as a beige solid.

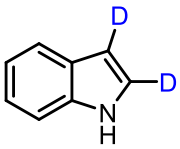
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H, N*H*), 7.76 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 9.0 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.31 – 7.27 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.96 (s, **0.44H**), 5.32 (d, *J* = 8.0 Hz, 1H), 4.77 (d, *J* = 8.0 Hz, 1H), 4.46 – 4.34 (m, 2H), 4.19 (t, *J* = 7.0 Hz, 1H), 3.36 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.53, 156.02, 143.66, 141.30, 136.09, 127.72, 127.08, 125.10, 122.33, 119.98, 119.96, 119.90, 118.56, 111.31, 77.26, 77.00, 76.75, 67.14, 54.47, 47.10,

27.60.**FT-IR (neat):** 3361, 3060, 1717, 1664, 1512, 1450, 1412, 1335, 1224, 1139, 1083, 1048, 905, 758 cm^{-1}.

C2- and C3-deuterated indoles

Note: While every effort was made to *keep the compounds on silica for the minimum amount of time possible* to avoid protonation (isotopic dilution) at C3, all compounds in this section showed a reduction in deuteration during column chromatography (compared to the crude product). *E.g.* for compound **3a**, deuterium incorporation was 70% at C3 prior to purification, but dropped to 44% after silica flash column chromatography on silica (see Table S4 above for more C3 deuteration values before silica flash column chromatography).

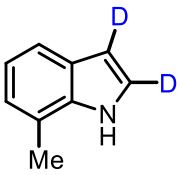
1*H*-indole-2,3-d_2 (3a)



3a was synthesised from indole (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 40 mg (83% yield, 80% deuterium incorporation at C2, 44% deuterium incorporation at C3) of the title compound as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (brs, 1H, N*H*), 7.67 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.19 (m, **1.2H**), 7.14 (at, *J* = 7.5 Hz, 1H), 6.57 (s, **0.56H**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.9, 128.0, 124.2, 122.1, 120.9, 119.9, 111.1, 102.8. **FT-IR (neat):** 3400, 3053, 2917, 2849, 1698, 1615, 1454, 1335, 1243, 1092, 1009, 931, 710, 669 cm^{-1}.

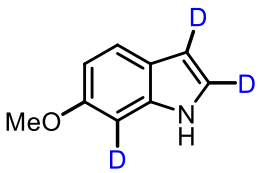
7-methyl-1*H*-indole-2,3-d_2 (3c)



3c was synthesised from 7-methylindole (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 48 mg (90% yield, 75% deuterium incorporation at C2, 45% deuterium incorporation at C3) of the title compound as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (brs, 1H, N*H*), 7.52 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.21 (m, **0.25H**), 7.06 (t, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.58 – 6.57 (m, **0.55H**), 2.52 (s, 3H). Analytical data matches literature values.[4]

6-methoxy-1*H*-indole-2,3,7-d_3 (3d)

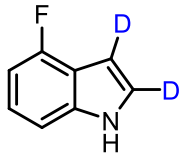


3d was synthesised from 6-methoxyindole (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 45 mg (58% yield, 80% deuterium incorporation at C2, 45% deuterium incorporation at C3, 30% deuterium incorporation at C7) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (brs, 1H, N*H*), 7.53 (d, *J* = 8.5 Hz, 1H), 7.09 (s, **0.2H**), 6.88 (s, **0.7H**), 6.82 (d, *J* = 8.5 Hz, 1H), 6.49 (s, **0.55H**), 3.86 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4, 136.5, 122.9, 121.2, 109.9, 102.5, 94.5, 55.7 (deuterated carbon signal not

observed); **FT-IR (neat):** 3391, 3042, 3007, 2959, 2921, 2835, 1617, 1499, 1451, 1441, 1427, 1388, 1346, 1289, 1160, 1026, 810, 663 cm^{-1}.

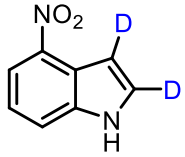
4-fluoro-1*H*-indole-2,3-d_2 (3e)



3e was synthesised from 4-fluoroindole (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 41 mg (75% yield, 85% deuterium incorporation at C2, 75% deuterium incorporation at C3) of the title compound as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.19 (ad, *J* = 8.0 Hz, **1.15H**), 7.14 – 7.09 (m, 1H), 6.80 (dd, *J* = 10.0, 8.0 Hz, 1H), 6.65 (s, **0.25H**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6 (d, *J* = 247.0 Hz), 138.5 (d, *J* = 11.5 Hz), 124.1, 122.6 (d, *J* = 8.0 Hz), 117.2 (d, *J* = 22.5 Hz), 107.2, 104.6 (d, *J* = 19 Hz), 98.7; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -122.06 – -122.20 (m); **FT-IR (neat):** 3396, 2922, 2852, 1723, 1629, 1578, 1504, 1466, 1438, 1402, 1349, 1226, 1034, 768 cm^{-1}.

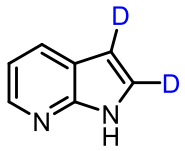
4-nitro-1*H*-indole-2,3-d_2 (3f)



3f was synthesised from 4-nitroindole (0.4 mmol) according to a modified method 1, where the reaction time was extended to 36 h. It was purified by silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) to afford 45 mg (69% yield, 65% deuterium incorporation at C2, 91% deuterium incorporation at C3) of the title compound as a yellow solid. (After 16 h, only 32% deuterium incorporation at C2 and 90% deuterium incorporation at C3 were observed.)

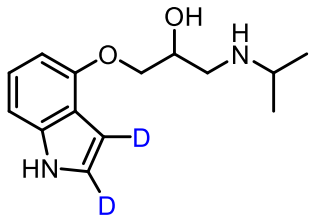
^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.58 (s, **0.35H**), 7.26 (t, *J* = 8.0 Hz, 1H), 7.15 – 7.13 (m, **0.09H**); **^{13}C NMR** (126 MHz, CD_3OD) δ 141.3, 140.1, 130.6, 123.2, 121.2, 119.5, 117.9, 102.9; **FT-IR (neat):** 3313, 2956, 2917, 2849, 1560, 1503, 1413, 1359, 1303, 1252, 1099, 1059, 811, 748, cm^{-1}.

7-Aza-1*H*-indole-2,3-d_2 (3i)



3i was synthesised from 7-azaindole.
Method 1 (0.4 mmol) followed by purification on silica flash column chromatography (gradient: cyclohexane to 7:3 cyclohexane:ethyl acetate) afforded 27 mg (57% yield, 11% deuterium incorporation at C2, 90% deuterium incorporation at C3) of the title compound as an off-white solid.
A modified method 2 (conditions applied twice) did not lead to complete protonation at C3, instead affording 20 mg (83% yield, 8% deuterium incorporation at C2, 6% deuterium incorporation at C3) of the title compound as an off-white solid. Analytical data is provided for the product from method 1:
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.44 (brs, 1H, N*H*), 8.36 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.40 (s, **0.89H**), 7.11 (dd, *J* = 8.0, 4.5 Hz, 1H), 6.52 (d, *J* = 3.4 Hz, **0.10H**); **^{13}C NMR** (126 MHz, CDCl3) δ 148.9, 142.5, 129.2, 125.3, 120.6, 115.9, 100.8; **FT-IR (neat):** 3670, 2969, 2904, 1599, 1563, 1500, 1496, 1417 1329, 1278, 1111, 913, 885, 747 cm^{-1}.

Pindolol-2,3-*d*$_2$ (3l)

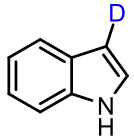


3l was synthesised from pindolol (0.4 mmol) according to method 1. It was purified by silica flash column chromatography (gradient: 100% cyclohexane to 100% ethyl acetate) to afford 70 mg (70% yield, 57% deuterium incorporation at C2, 34% deuterium incorporation at C3) of the title compound as an off-white solid. Method 2 did not lead to a significant reduction of deuterium incorporation at C3.

^{1}H NMR (400 MHz, CD_3COD) δ 7.14 (d, *J* = 3.0 Hz, **0.46H**), 7.08 – 6.97 (m, 2H), 6.57 – 6.54 (m, 1H), 6.52 (d, *J* = 7.0 Hz, **0.7H**), 4.36 – 4.28 (m, 1H), 4.20 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.11 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.41 (p, *J* = 6.5 Hz, 1H), 3.16 (dd, *J* = 12.5, 9.5 Hz, 1H), 1.35 (dd, *J* = 6.5, 4.0 Hz, 6H), (one of the proton peaks is hidden under the CD_3COD solvent peak); **^{13}C NMR** (101 MHz, CD_3COD) δ 153.1, 139.2, 124.2, 122.9, 120.0, 106.4, 101.2, 99.2, 70.9, 67.2, 51.8, 48.9, 19.5, 19.1; **FT-IR (neat):** 3210, 3116, 2973, 2472, 2330, 1637, 1550, 1504, 1471, 1400, 1351, 1269, 1284, 1248, 1228, 1092, 740 cm^{-1}.

C3-deuterated indoles

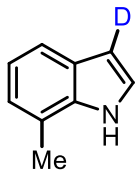
1*H*-indole-3-*d* (4a)



4a was synthesised from indole (0.2 mmol) according to method 3 to afford 24 mg (quantitative yield, 95% deuterium incorporation) of the title compound as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (brs, 1H, N*H*), 7.57 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.14 – 7.08 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, **0.05H**). Analytical data matches literature values.[5]

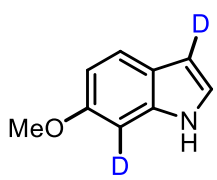
7-methyl-1*H*-indole-3-*d* (4c)



4c was synthesised from 7-methylindole (0.2 mmol) according to method 3 to afford 26 mg (quantitative yield, 94% deuterium incorporation) of the title compound as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (brs, 1H, N*H*), 7.56 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, **0.06H**), 2.53 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.3, 127.3, 123.6, 122.5, 120.2, 120.0, 118.5, 103.0, 16.7; **FT-IR (neat):** 3388, 3063, 2948, 2904, 2845, 1676, 1615, 1478, 1458, 1425, 1339, 1107, 782 cm^{-1}.

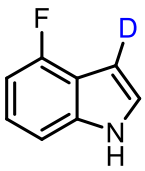
6-methoxy-1*H*-indole-3,7-*d*$_2$ (4d)



4d was synthesised from 7-methylindole (0.2 mmol) according to method 3 to afford 29 mg (97% yield, 95% deuterium incorporation at C3, 27% deuterium incorporation at C7) of the title compound an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (brs, 1H, N*H*), 7.51 (d, *J* = 8.5 Hz, 1H), 7.10 (s, **0.73H**), 6.89 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, **0.05H**), 3.85 (s, 3H). Analytical data matches literature values.[5]

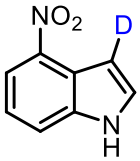
4-fluoro-1*H*-indole-3-*d* (4e)



4e was synthesised from 4-fluoroindole (0.2 mmol) according to method 3 to afford 27 mg (quantitative yield, 93% deuterium incorporation) of the title compound as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (brs, 1H, N*H*), 7.20 – 7.16 (m, 2H), 7.11 (td, *J* = 7.9, 5.0 Hz, 1H), 6.80 (dd, *J* = 10.3, 7.7 Hz, 1H), 6.65 (t, *J* = 2.6 Hz, **0.07H**); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.6 (d, *J* = 247.0 Hz), 138.6 (d, *J* = 11.0 Hz), 124.1, 122.6 (d, *J* = 8.0 Hz), 117.2 (d, *J* = 22.5 Hz), 107.22, 104.7 (d, *J* = 19.0 Hz), 98.9; **^{19}F NMR** (470 MHz, $CDCl_3$) δ -122.07 – -122.13 (m). FT-IR (neat): 3363, 2918, 2850, 1560, 1419, 1226, 1030, 873, 710, 662 cm^{-1}.

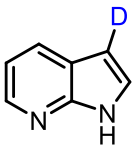
4-nitro-1*H*-indole-3-*d* (4f)



4f was synthesised from 4-nitroindole (0.2 mmol) according to method 3 to afford 32 mg (97% yield, 74% deuterium incorporation) of the title compound as a yellow solid.

^{1}H NMR (500 MHz, CD_3OD) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 3.0 Hz, **0.26H**); **^{13}C NMR** (126 MHz, CD_3OD) δ 139.8, 138.6, 129.2, 121.8, 119.8, 118.2, 116.5, 101.4; **FT-IR (neat):** 3297, 2912, 1708, 1496, 1466, 1351, 1314, 1296, 1238, 1105, 1066, 986, 820, 715 cm^{-1}.

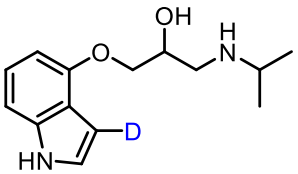
7-aza-1*H*-indole-3-*d* (4i)



4i was synthesised from 7-azaindole (0.2 mmol) according to method 3 to afford 24 mg (quantitative yield, 98% deuterium incorporation) of the title compound as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.37 (brs, 1H, N*H*), 8.34 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.98 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.39 (s, 1H), 7.10 (dd, *J* = 8.0, 5.0 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, **0.02H**). Analytical data matches literature values.[4]

Pindolol-3-*d* (4l)



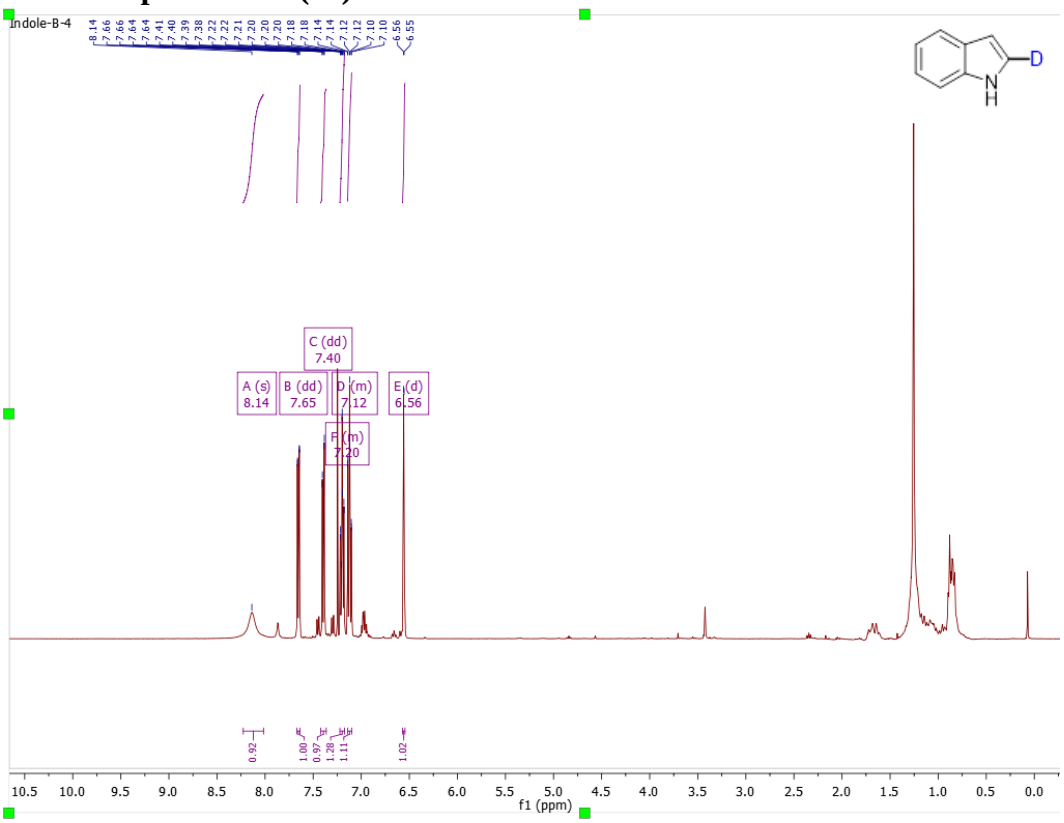
4l was synthesised from pindolol (0.2 mmol) according to method 3 to afford 49 mg (98% yield, 86% deuterium incorporation) of the title compound as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.13 (d, *J* = 3.0 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.55 (d, *J* = 3.0 Hz, 1H), 6.50 (d, *J* = 2.9 Hz, **0.14H**), 4.36 – 4.29 (m, 1H), 4.20 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.10 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.41 (p, *J* = 6.5 Hz, 1H), 3.33 (ad, *J* = 3.0 Hz, 1H), 3.17 (dd, *J* = 12.5, 9.5 Hz, 1H), 1.35 (dd, *J* = 6.5, 5.0 Hz, 6H).**^{13}C NMR** (101 MHz, CD_3OD**)** δ 153.1, 139.3, 124.2, 122.8, 120.1, 106.4, 101.2, 99.5, 70.9, 67.0, 51.9, 48.7, 19.4, 18.8; **FT-IR (neat):** 3310, 3115, 2973, 2924, 2689, 2470, 2330, 1550, 1471, 1400, 1321, 1229, 1092, 929, 739 cm^{-1}.

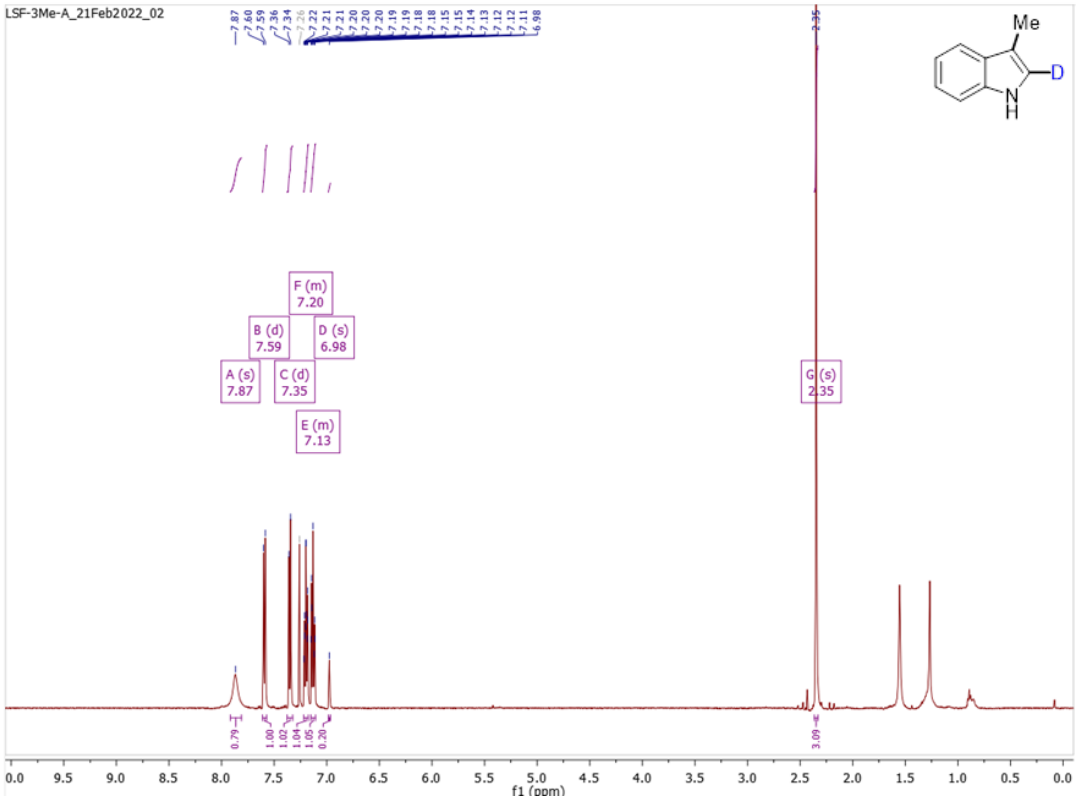
NMR SPECTRA

C2-deuterated indoles

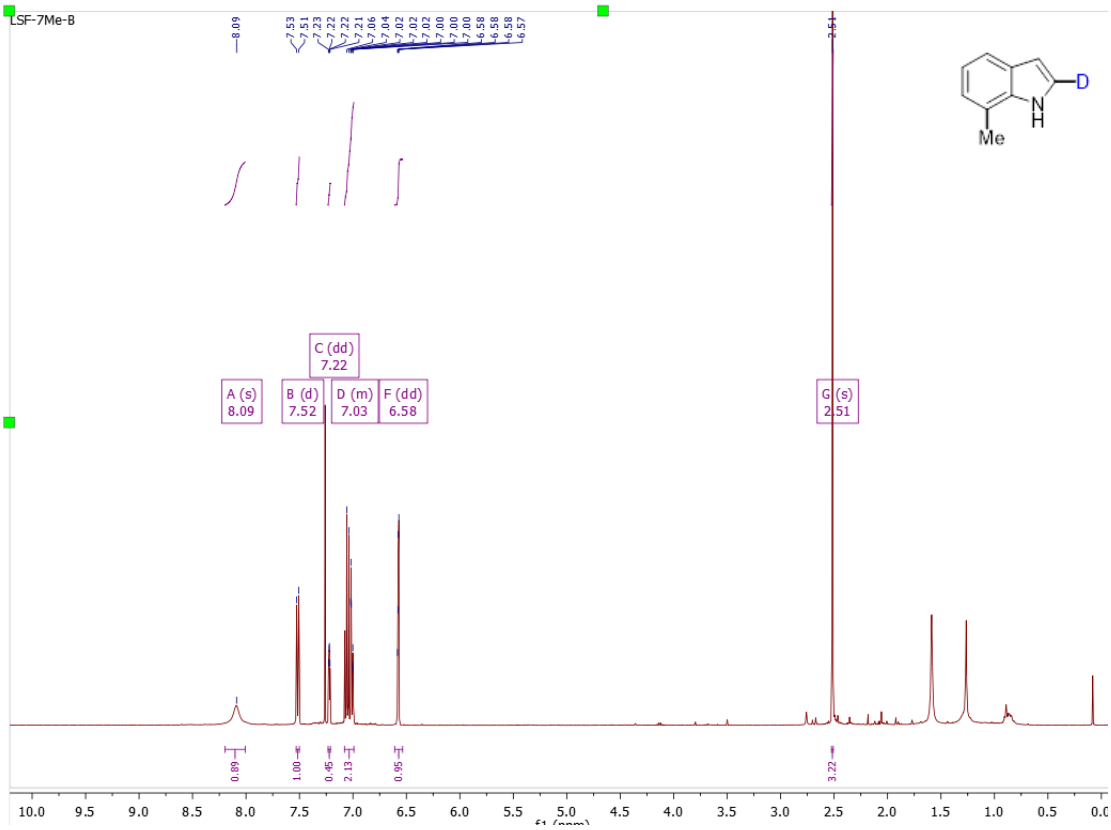
^{1}H NMR spectrum of (6a)



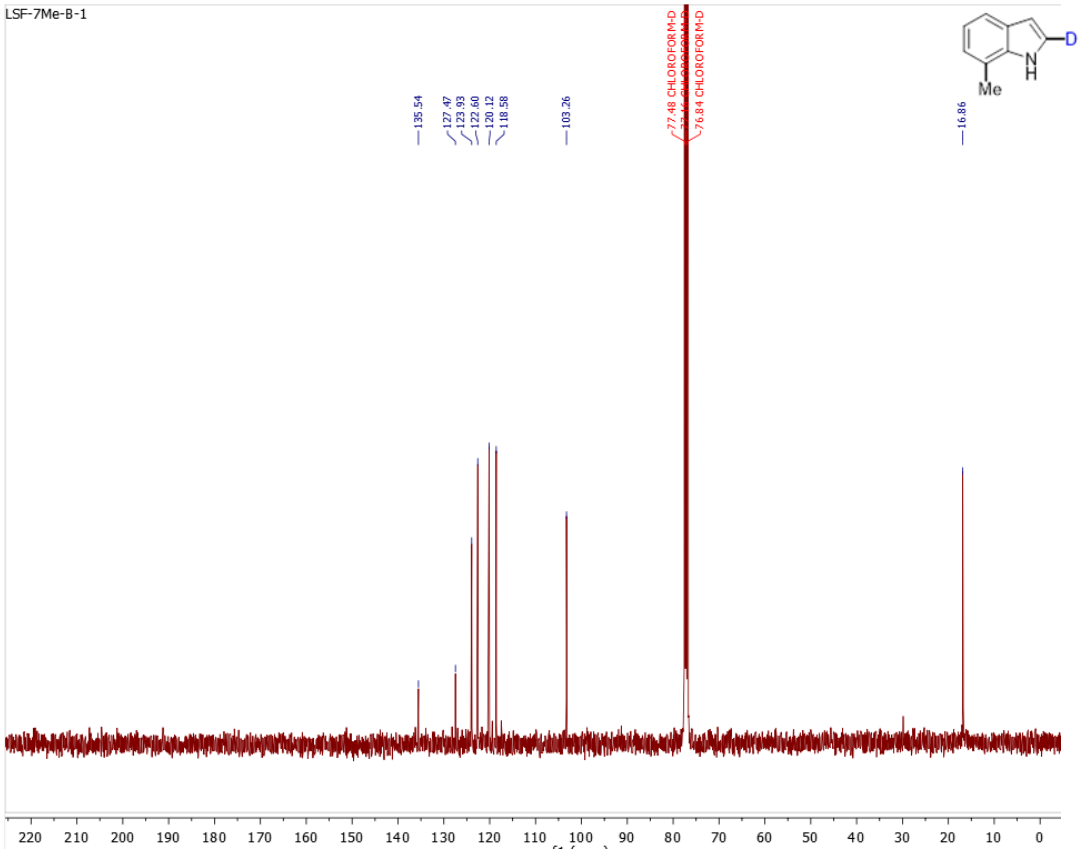
^{1}H NMR spectrum of (6b)



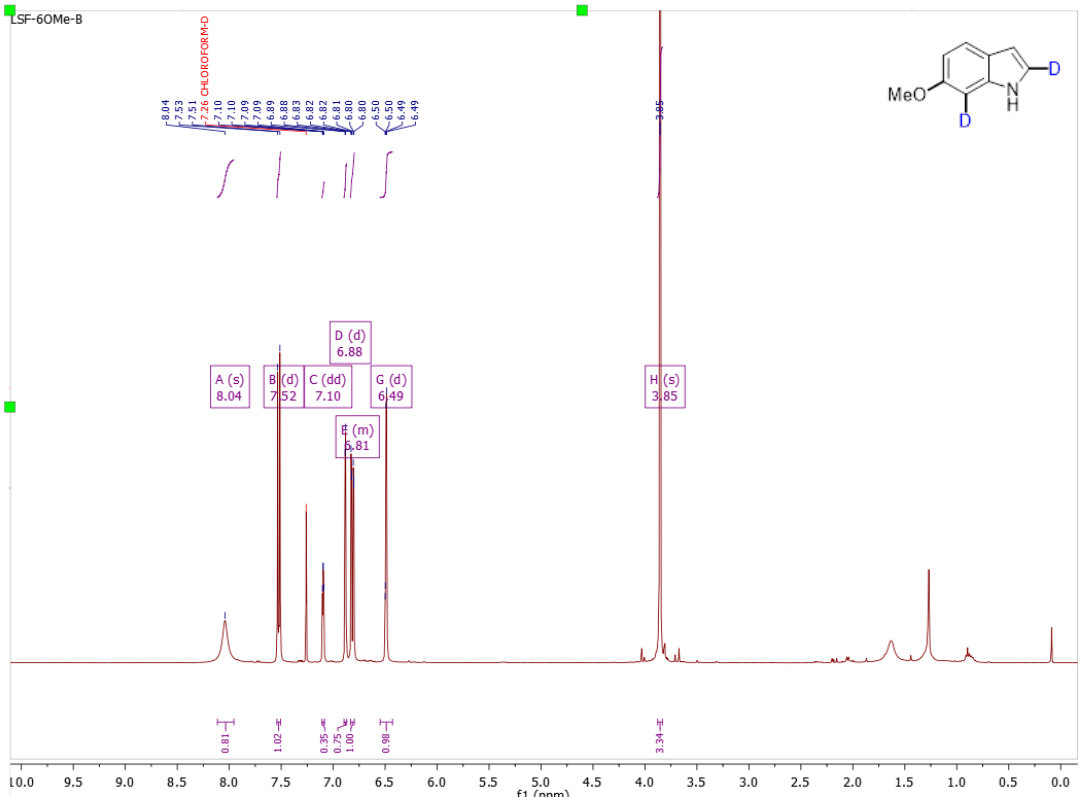
^{1}H NMR spectrum of (6c)



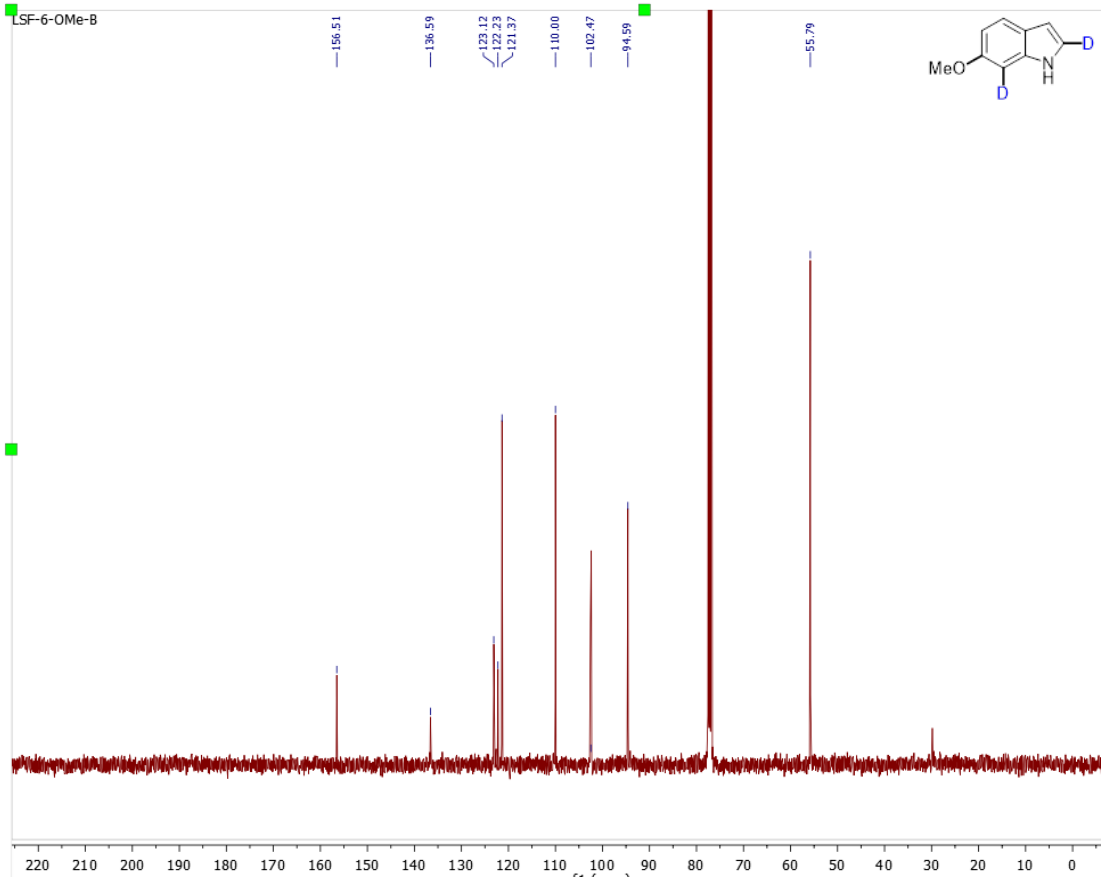
^{13}C NMR spectrum of (6c)



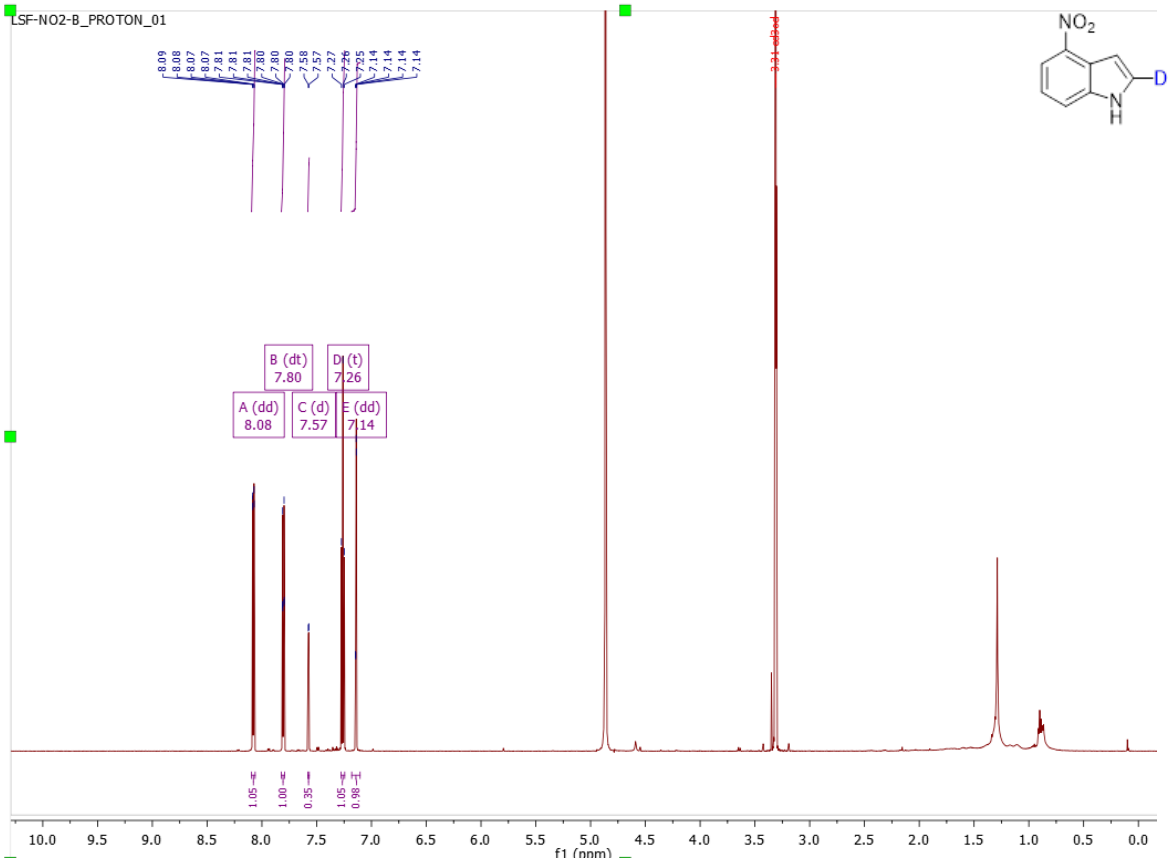
^{1}H NMR spectrum of (6d)



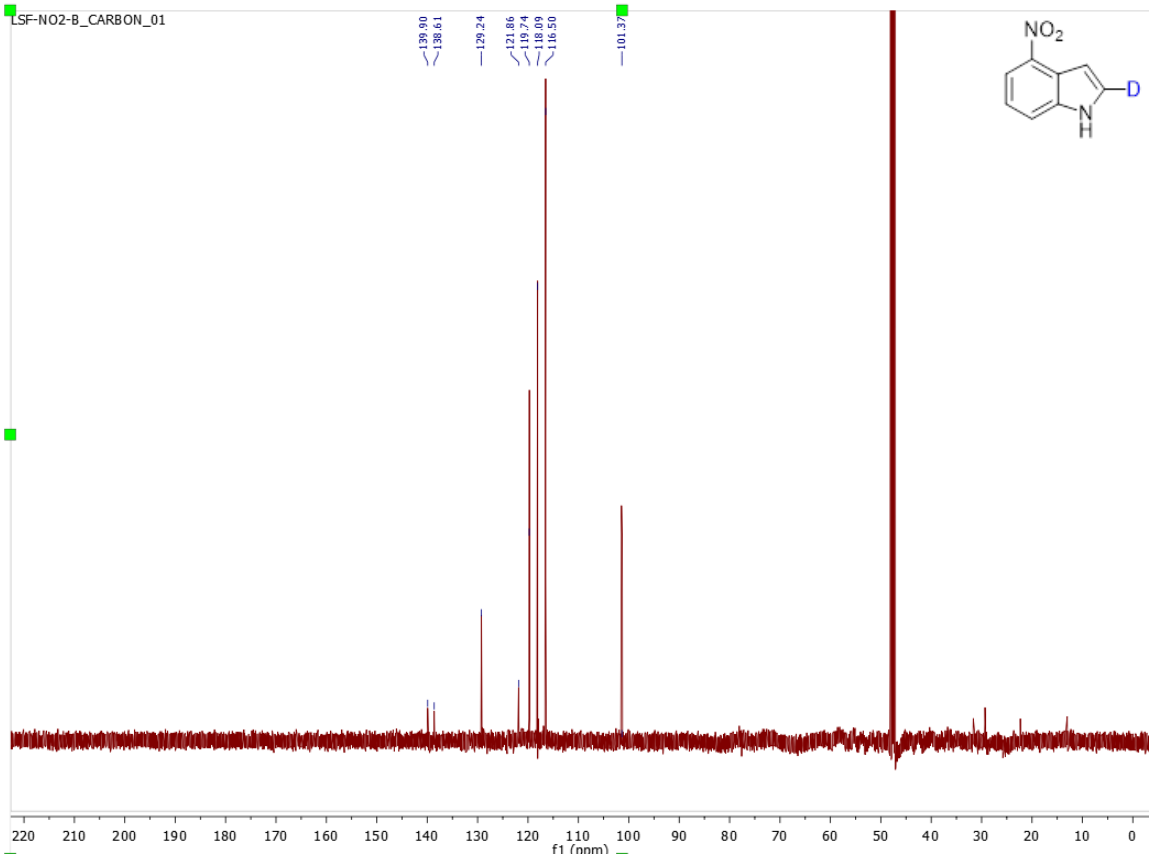
^{13}C NMR spectrum of (6d)



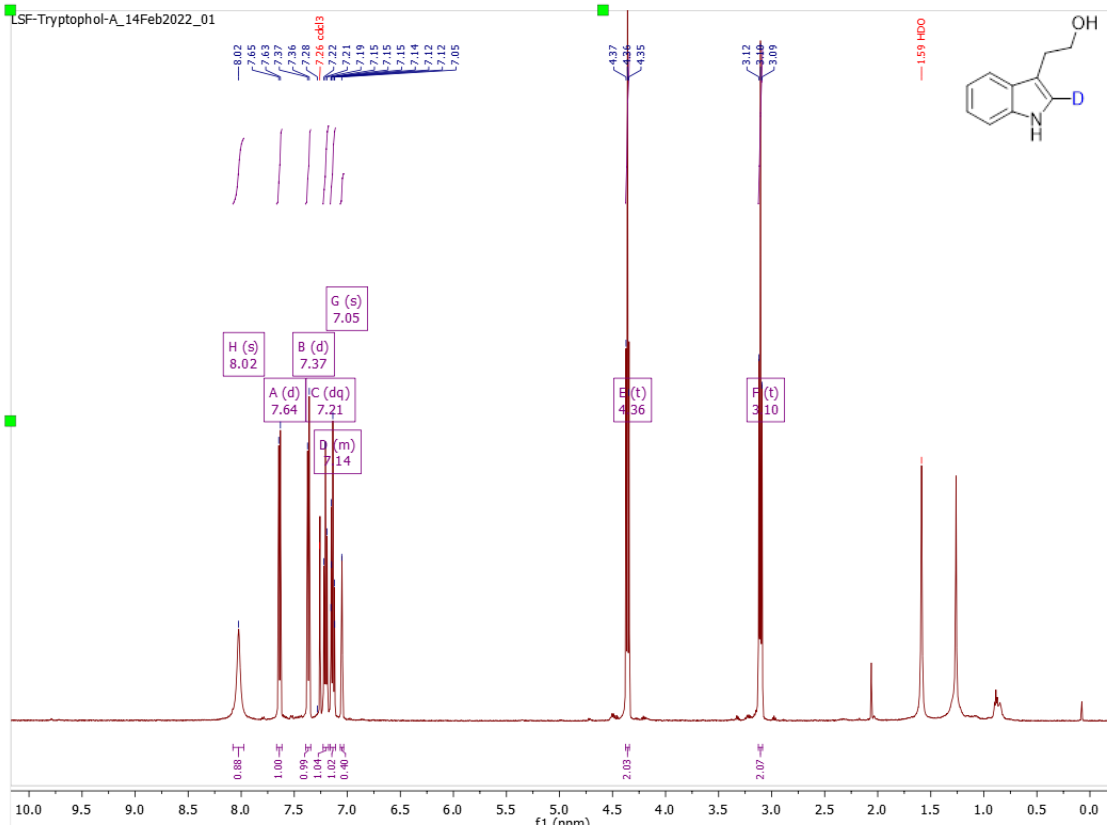
^{1}H NMR spectrum of (6f)



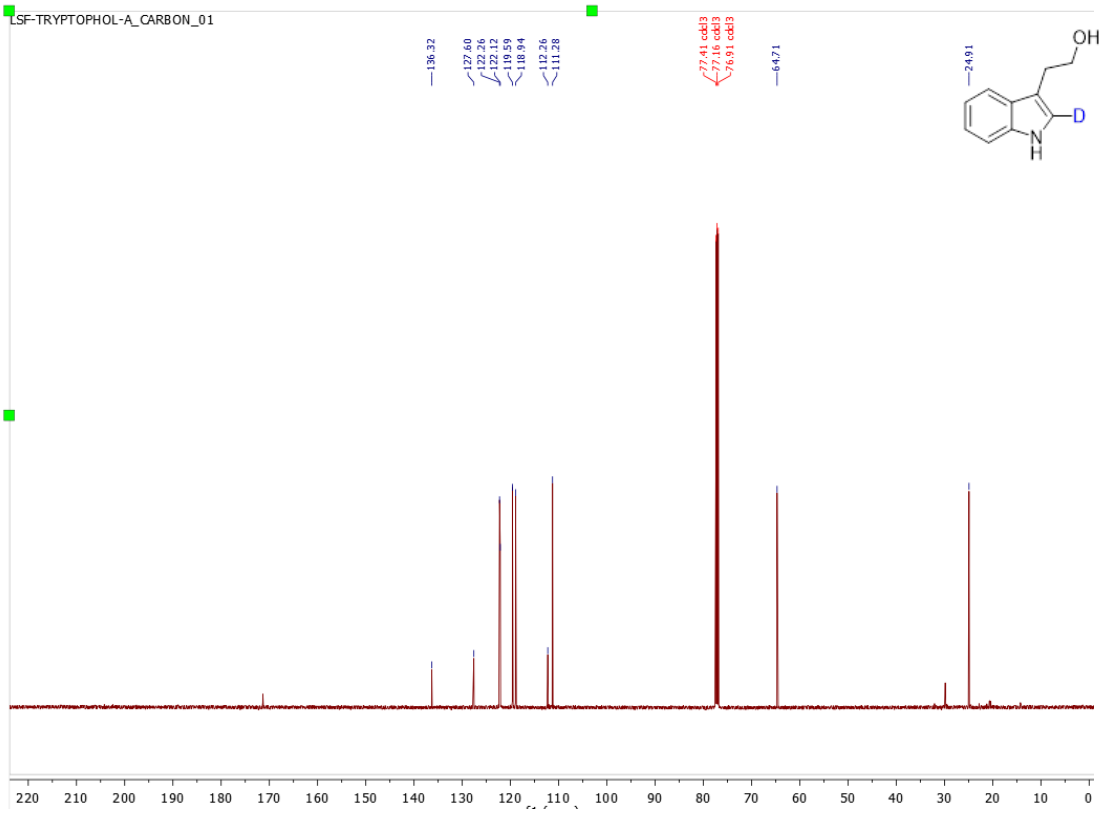
^{13}C NMR spectrum of (6f)



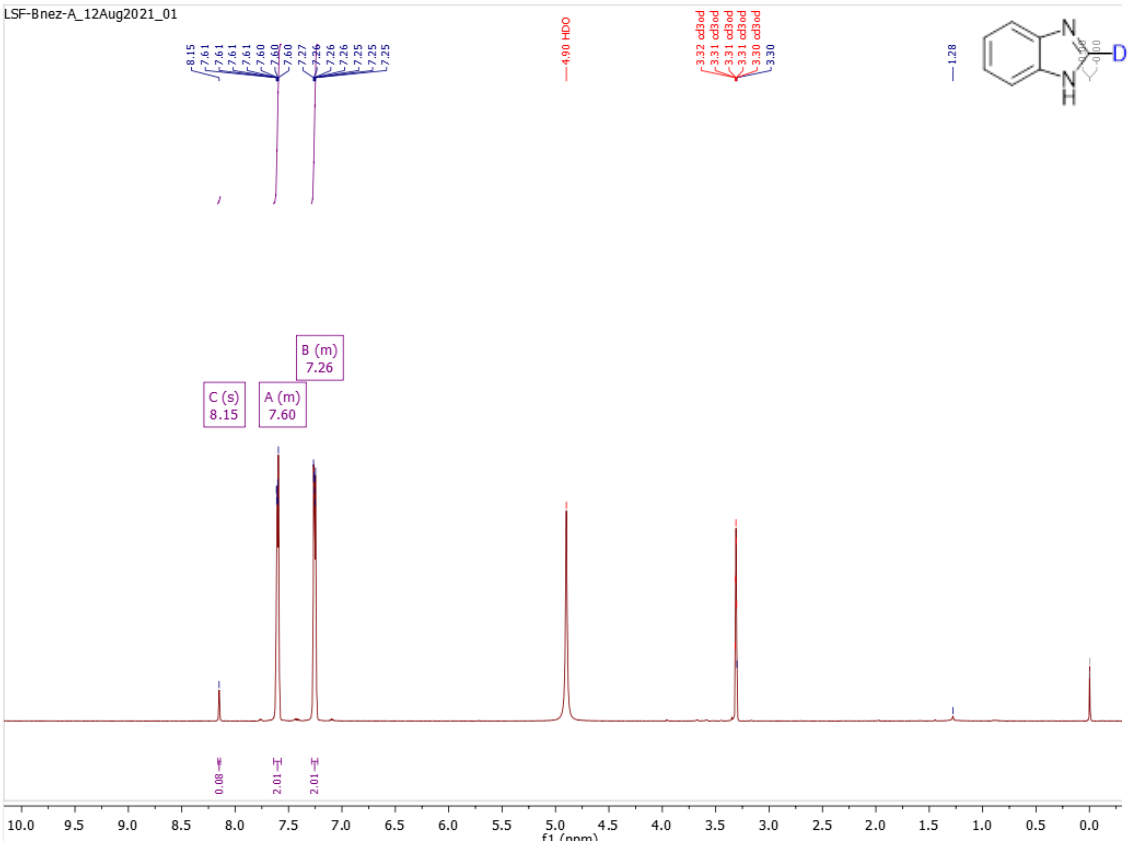
^{1}H NMR spectrum of (6g)



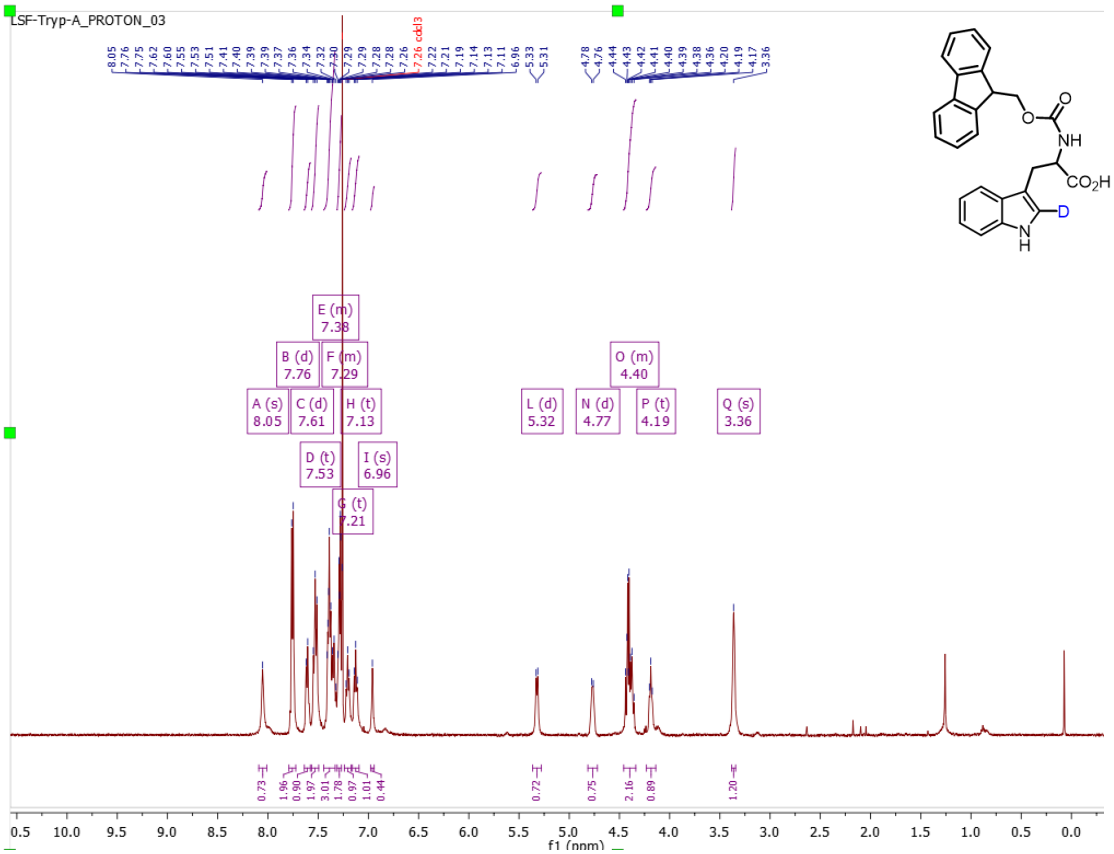
^{13}C NMR spectrum of (6g)



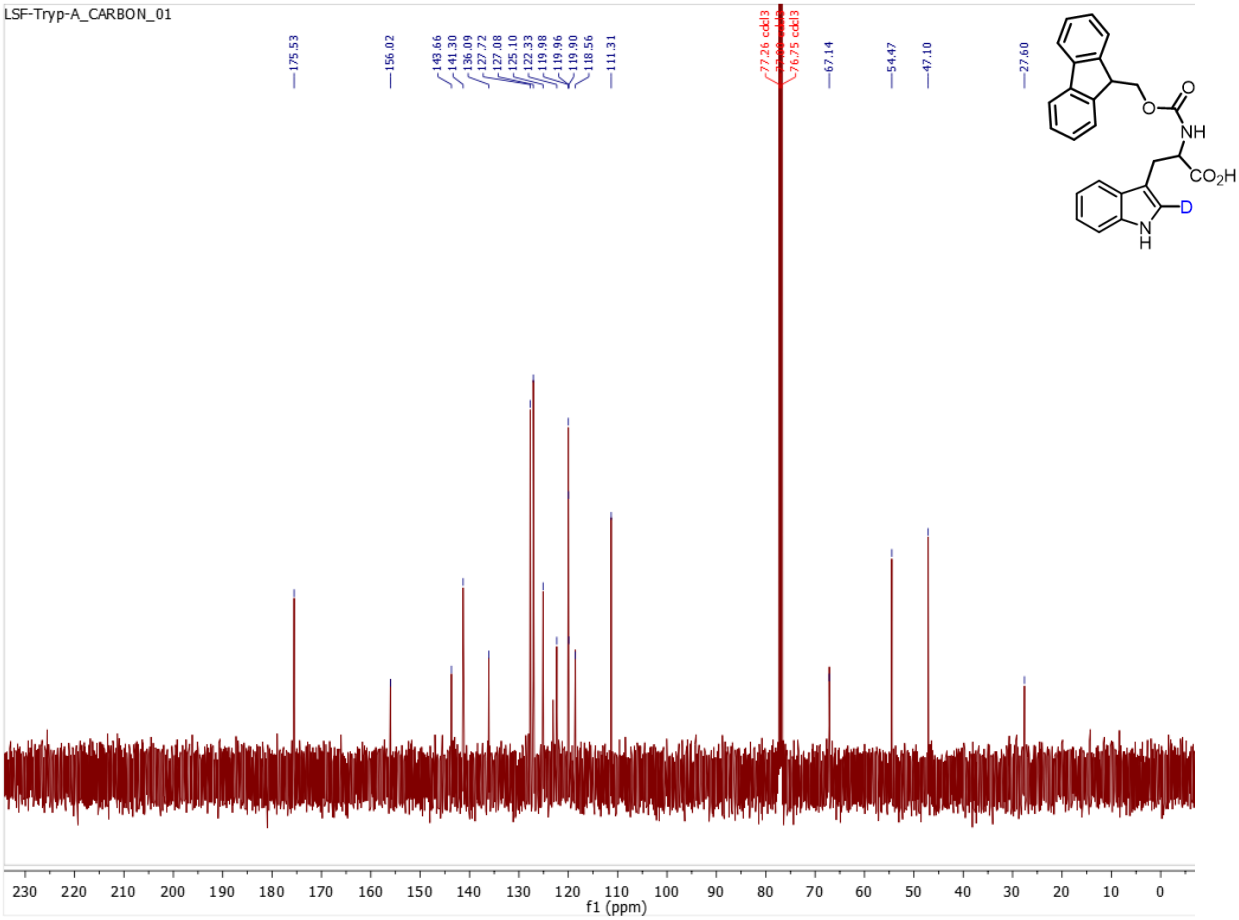
^{1}H NMR spectrum of (6h)



^{1}H NMR spectrum of (6k)

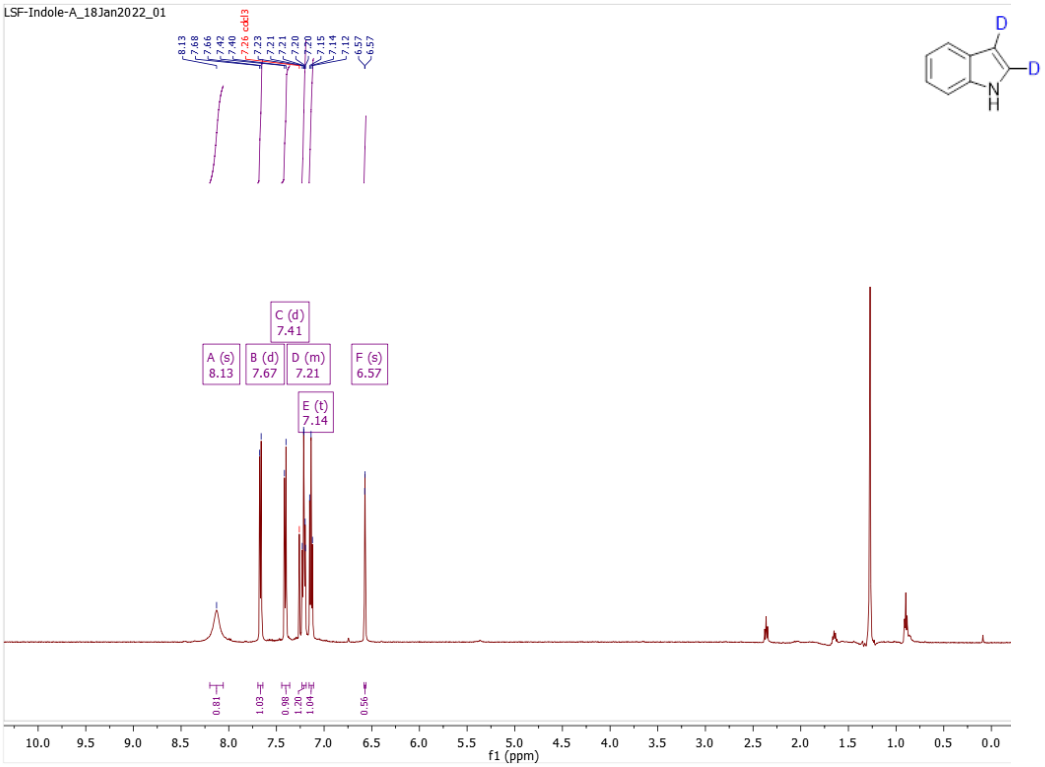


^{13}C NMR spectrum of (6k)

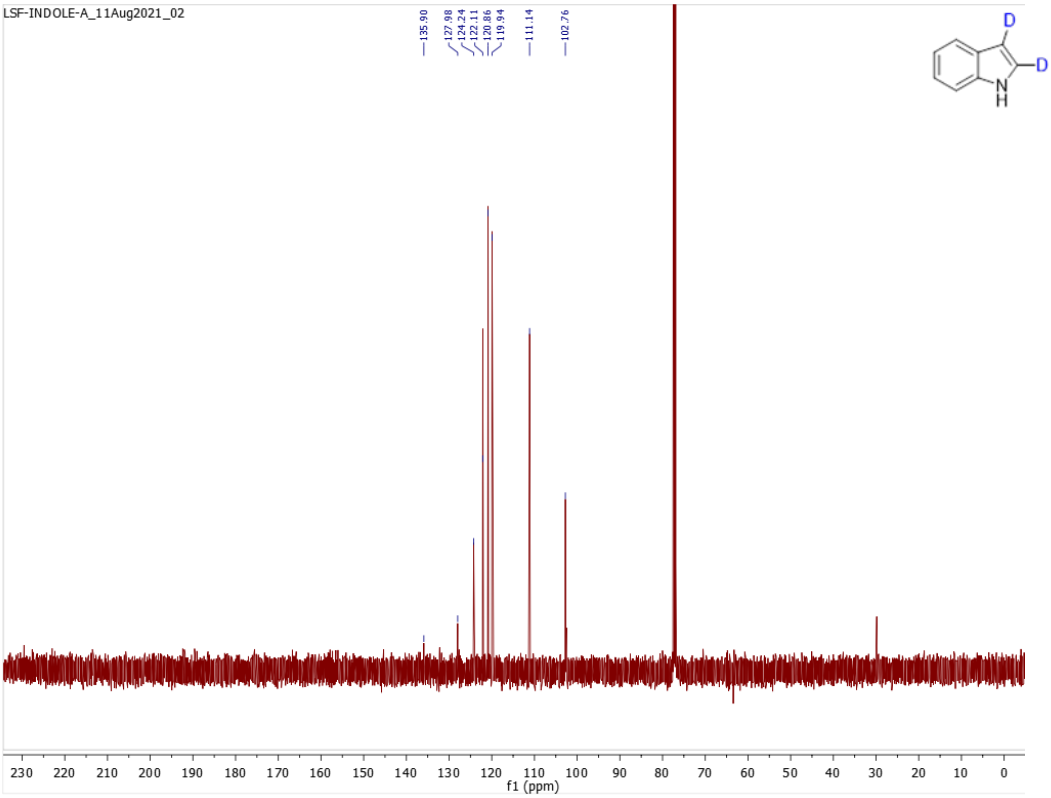


C2- and C3-deuterated indoles

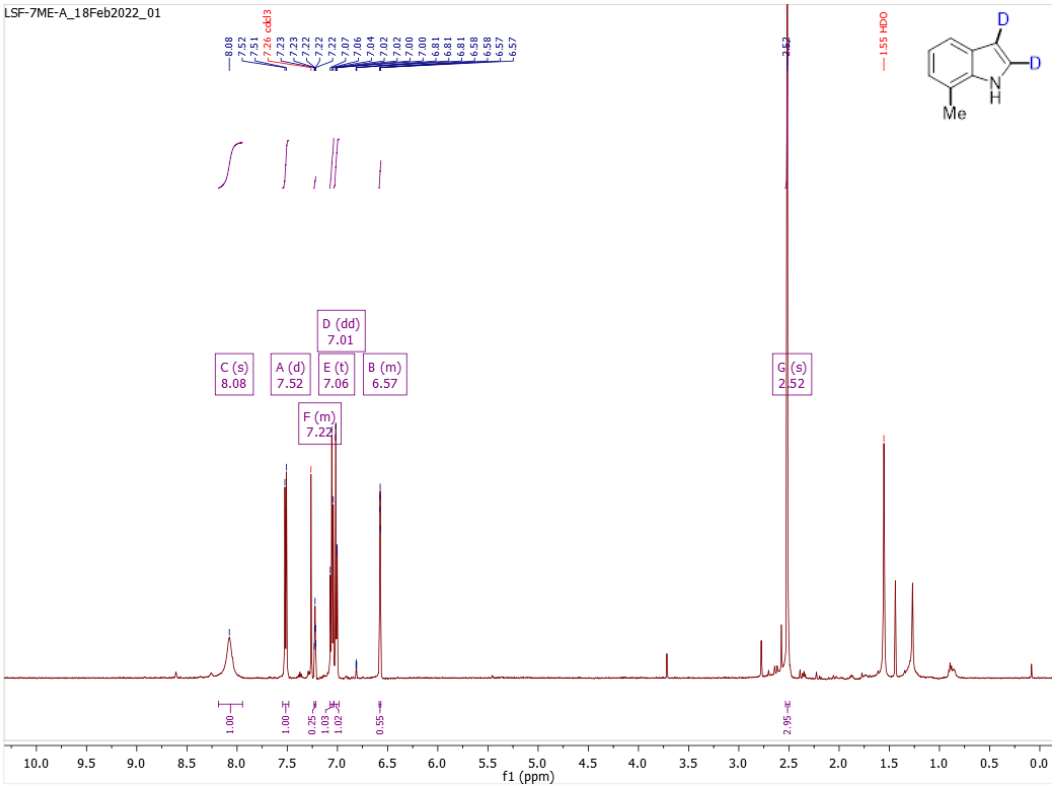
^{1}H NMR spectrum of (3a)



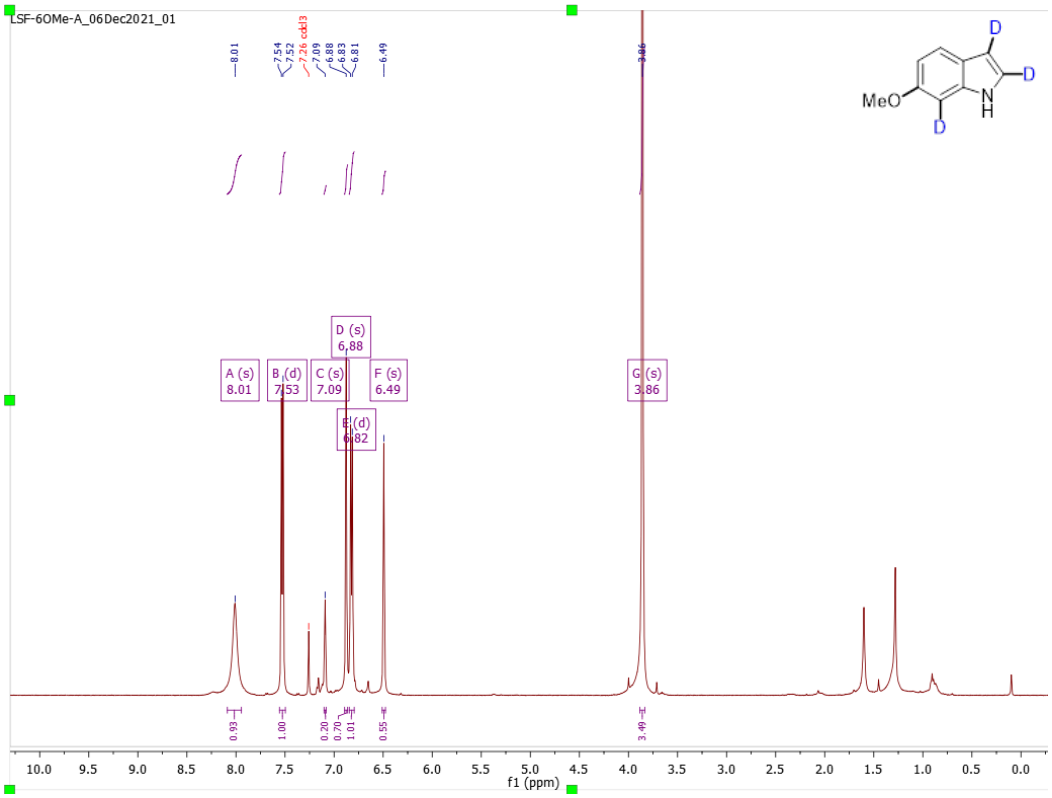
^{13}C NMR spectrum of (3a)



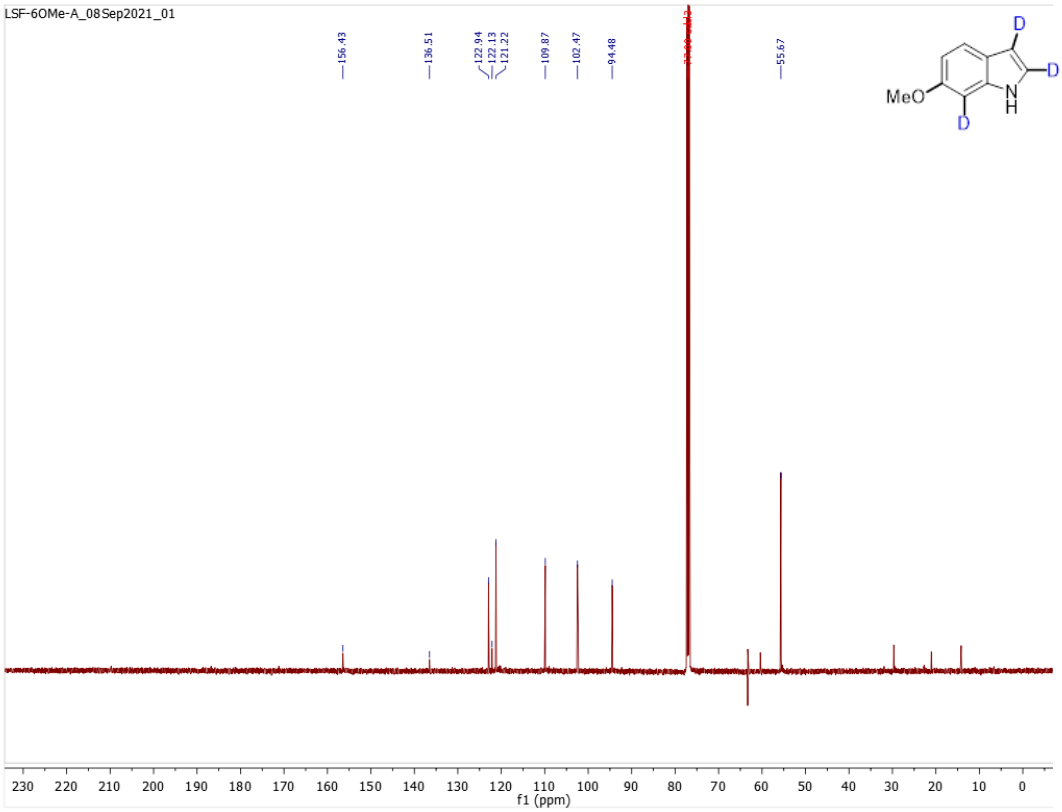
^{1}H NMR spectrum of (3c)



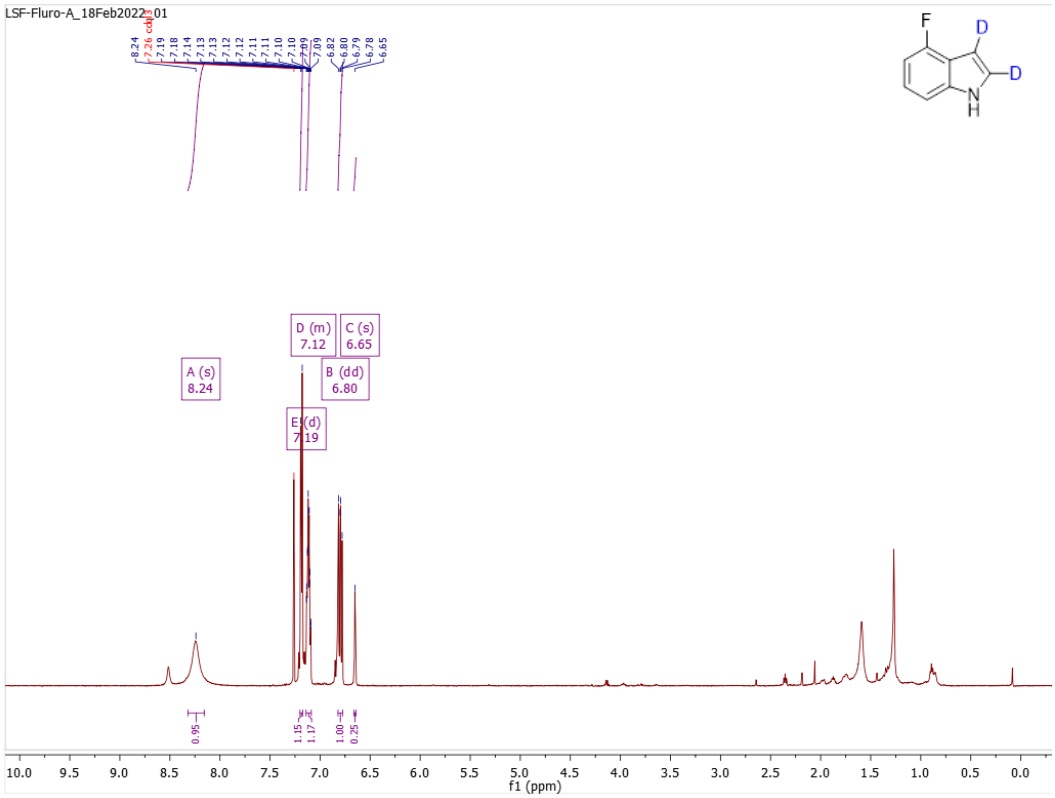
^{1}H NMR spectrum of (3d)



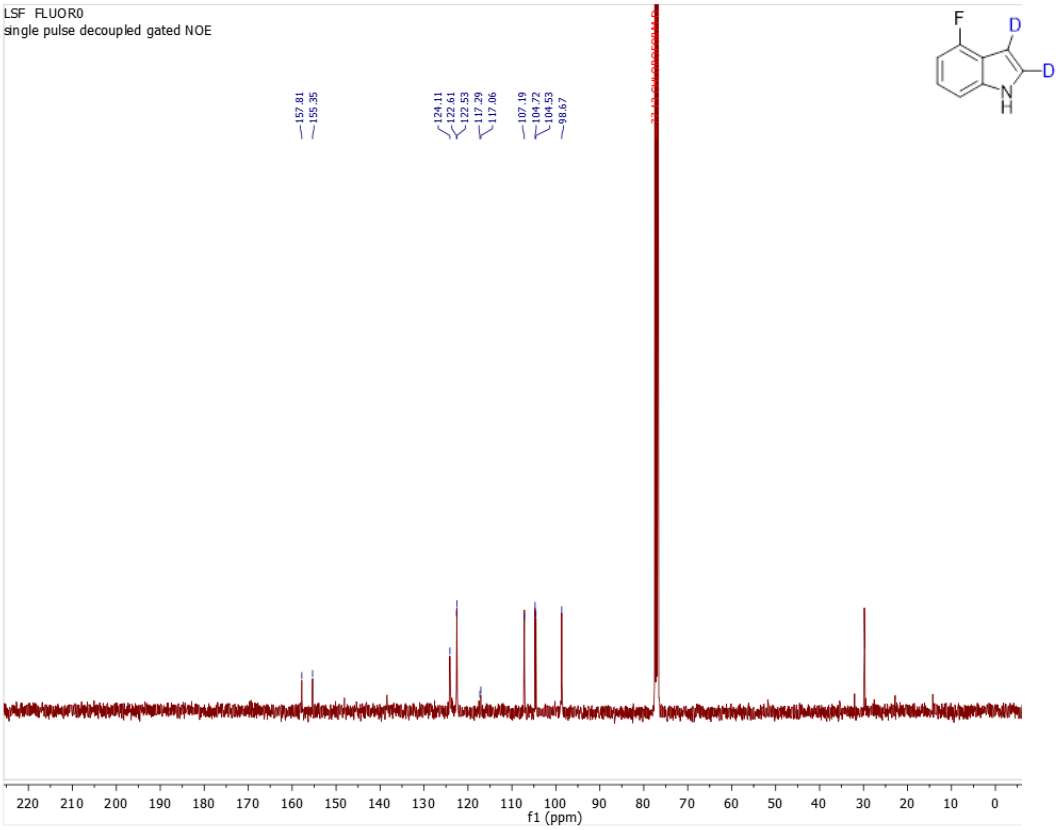
^{13}C NMR spectrum of (3d)



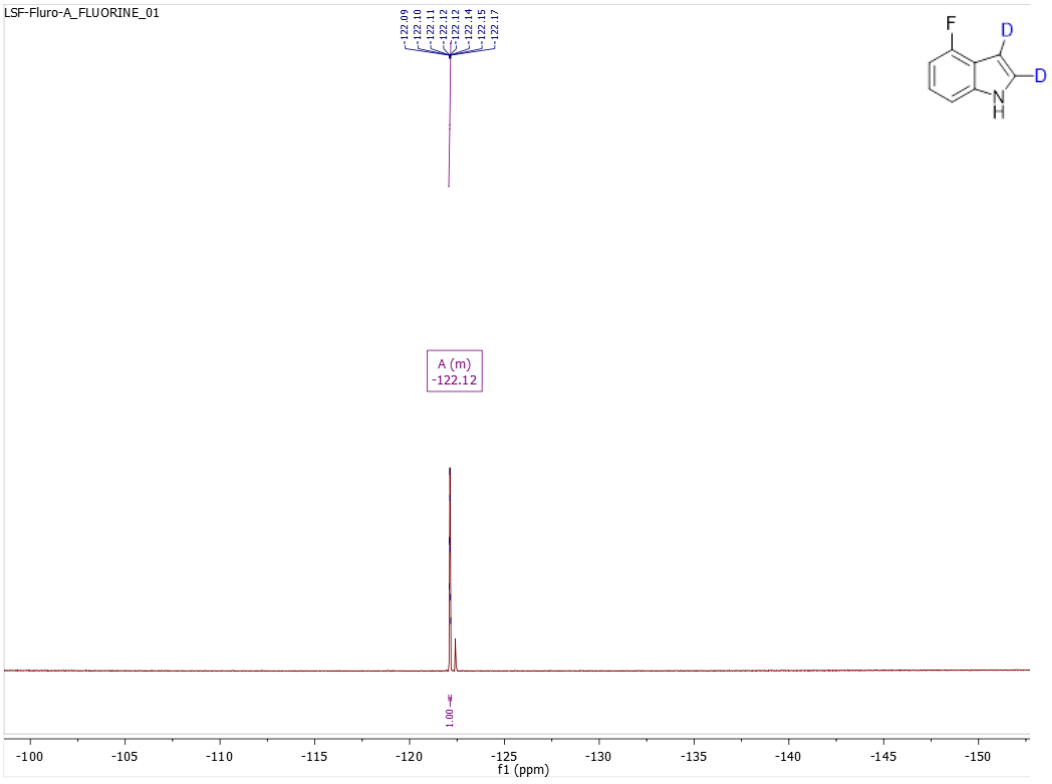
^{1}H NMR spectrum of (3e)



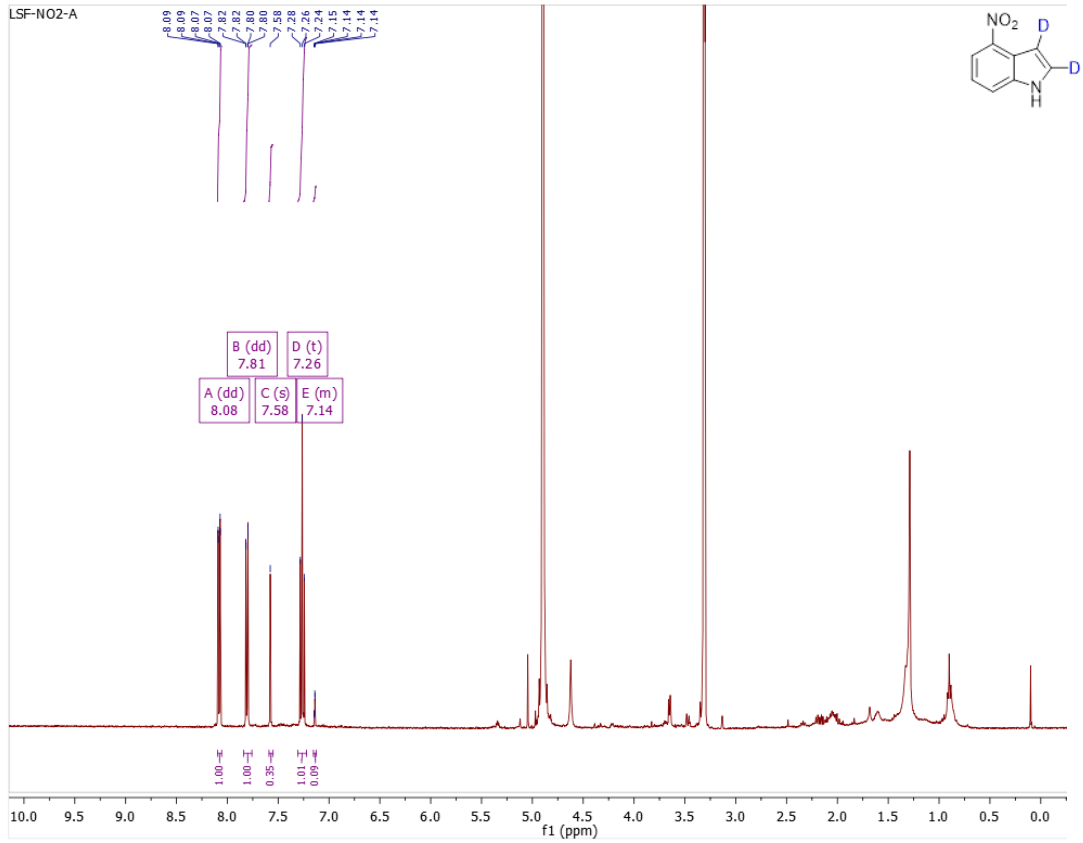
^{13}C NMR spectrum of (3e)



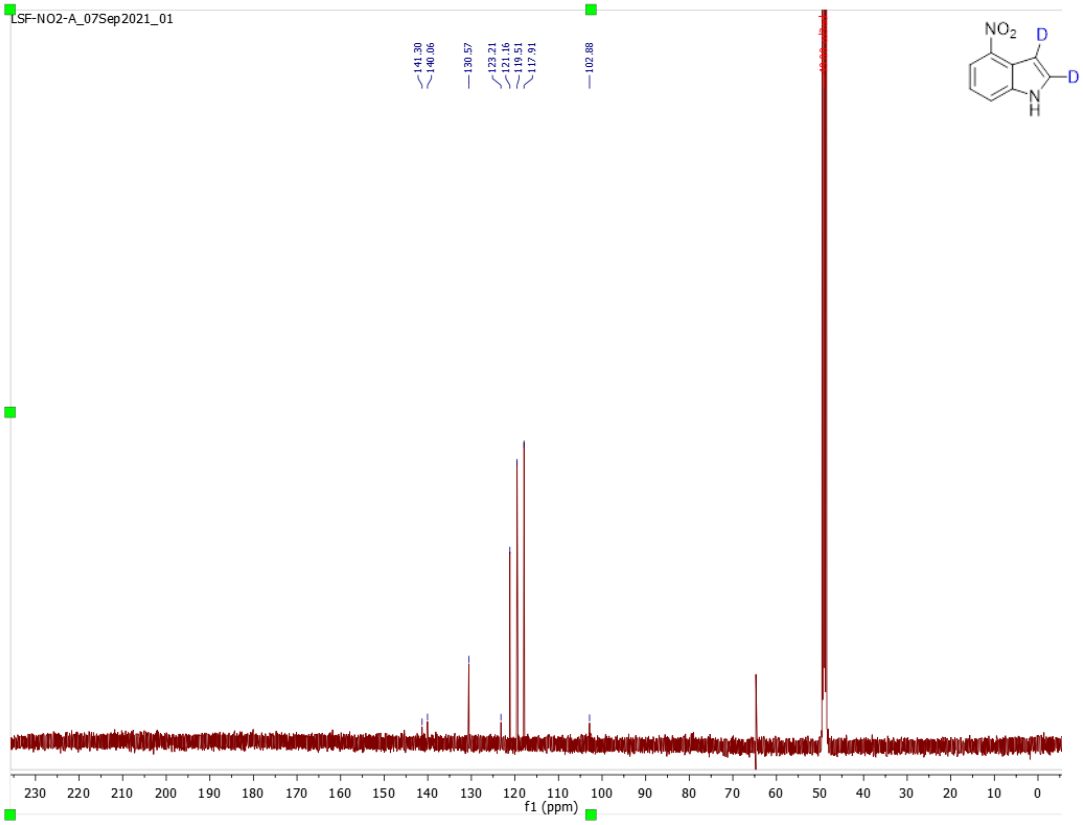
^{19}F NMR spectrum of (3e)



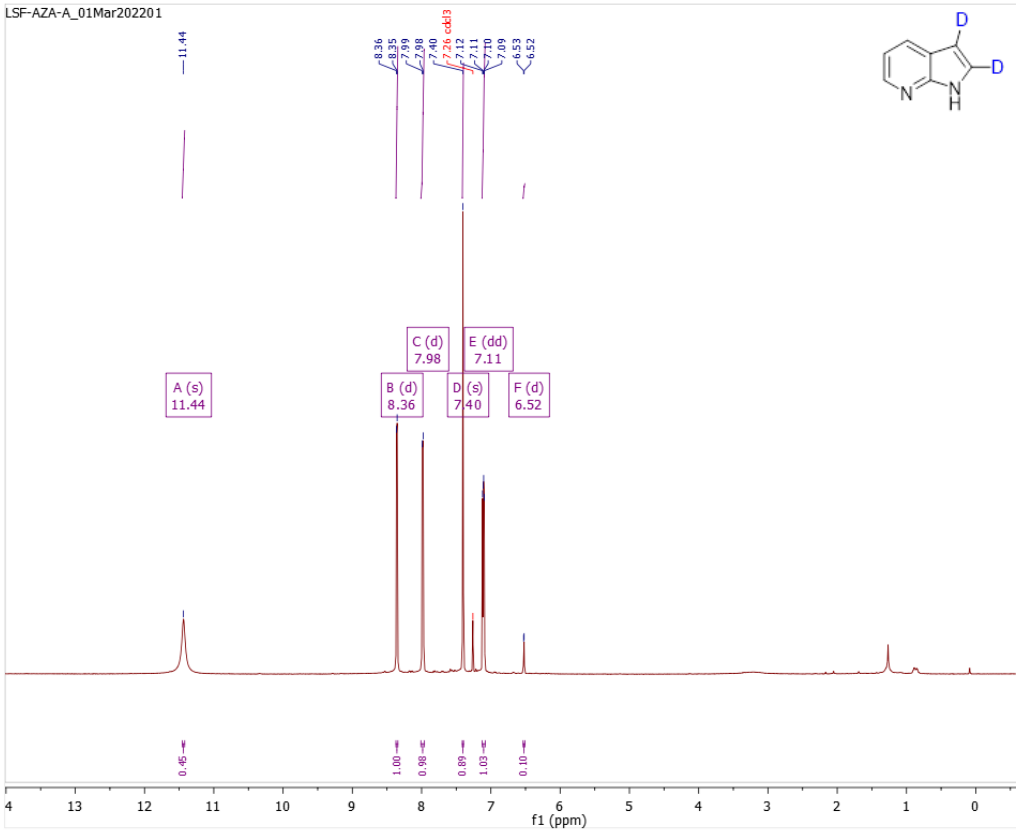
^{1}H NMR spectrum of (3f)



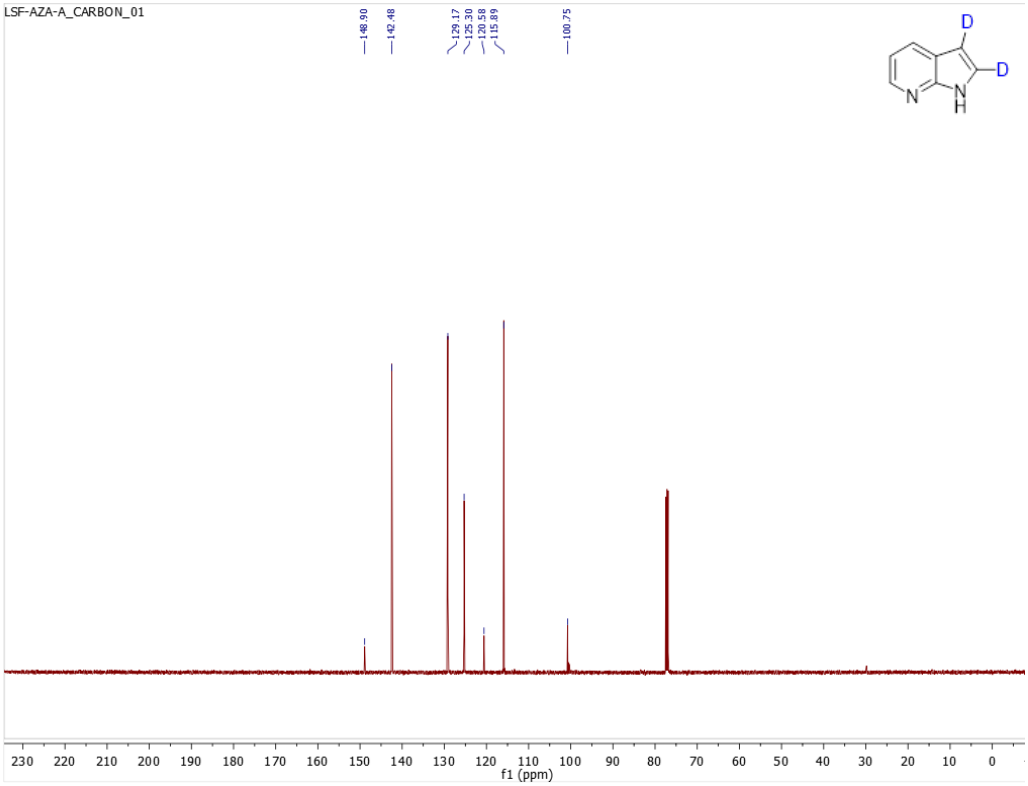
^{13}C NMR spectrum of (3f)



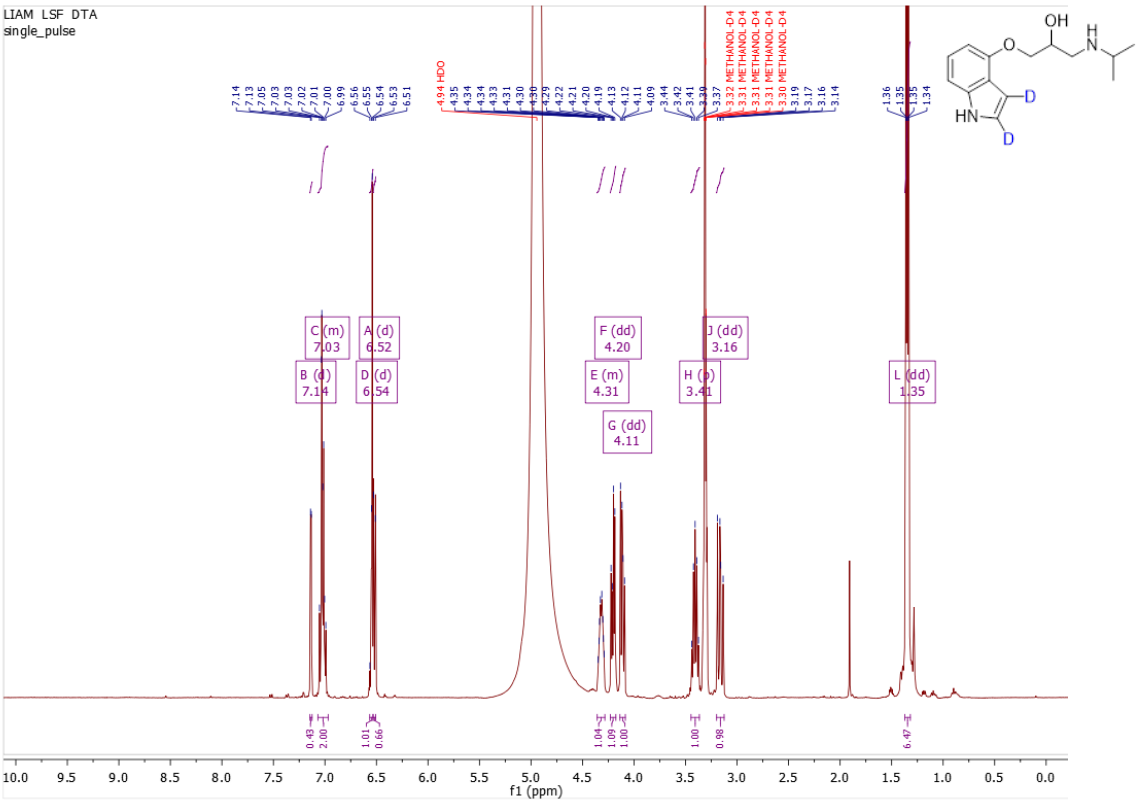
^{1}H NMR spectrum of (3i)



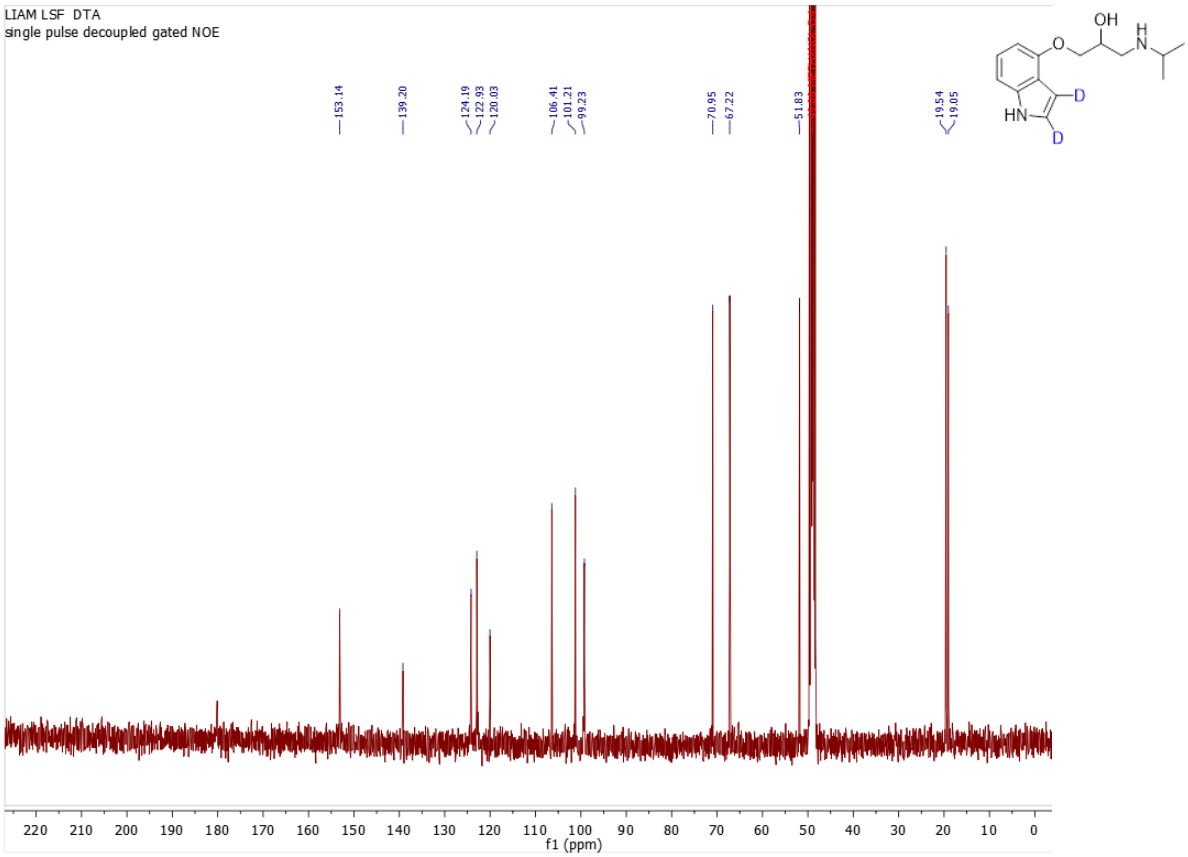
^{13}C NMR spectrum of (3i)



^{1}H NMR spectrum of (3l)

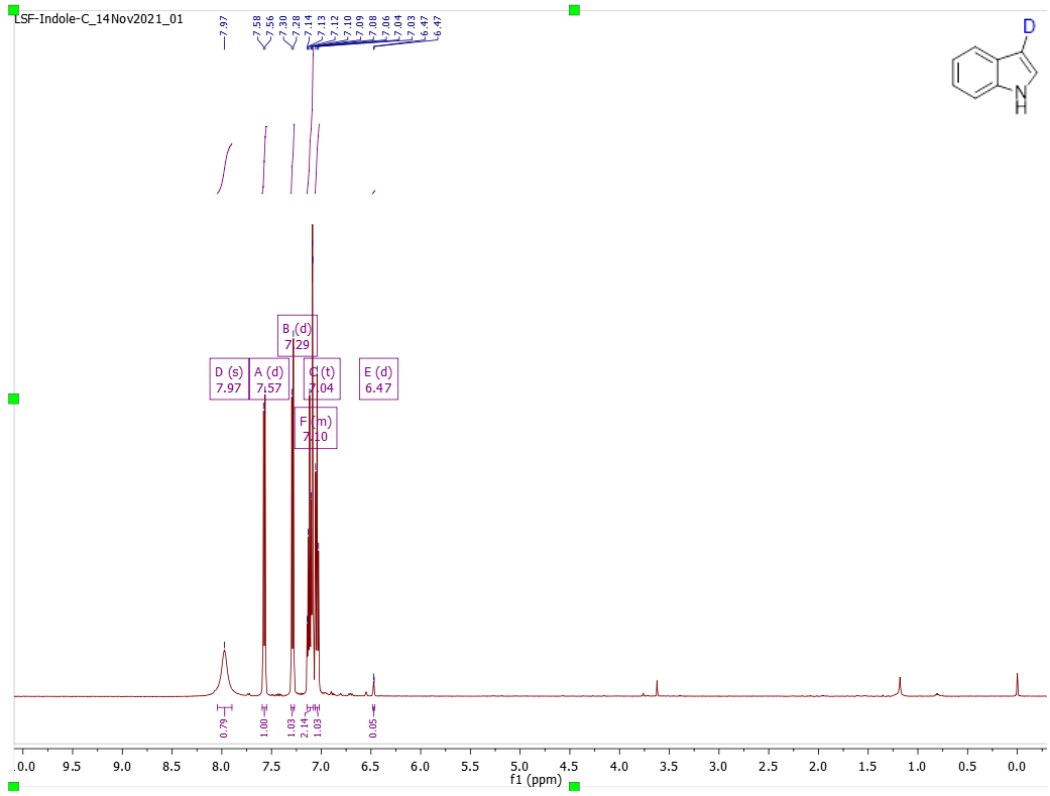


^{13}C NMR spectrum of (3l)

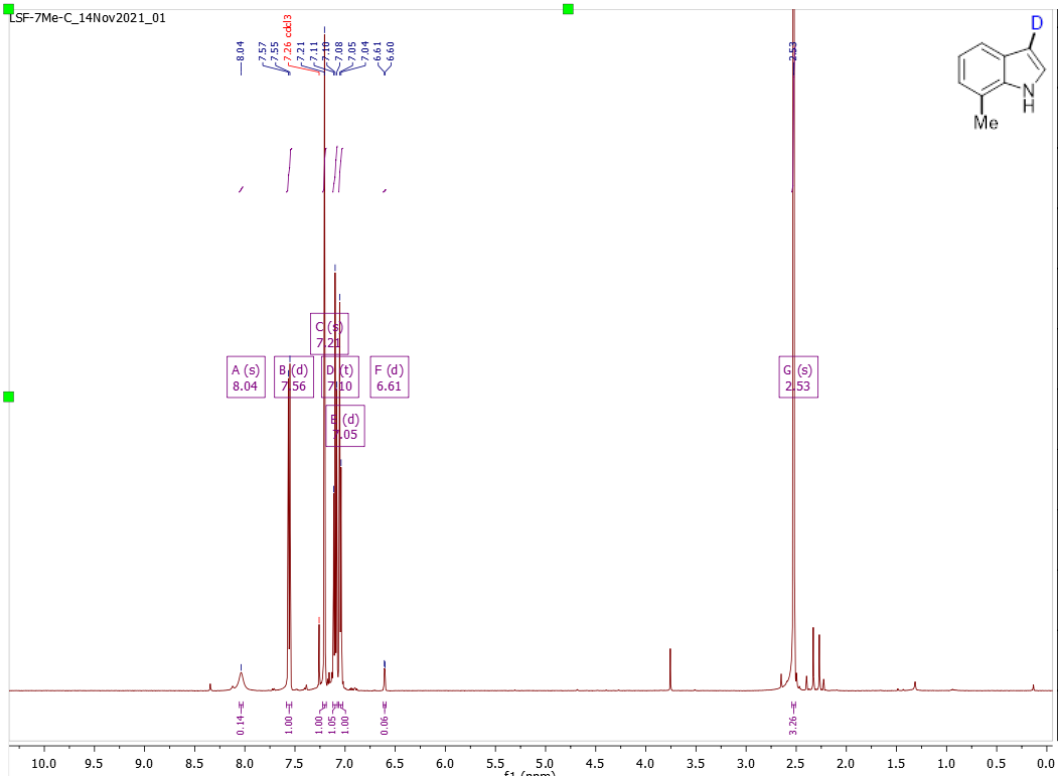


C3-deuterated indoles

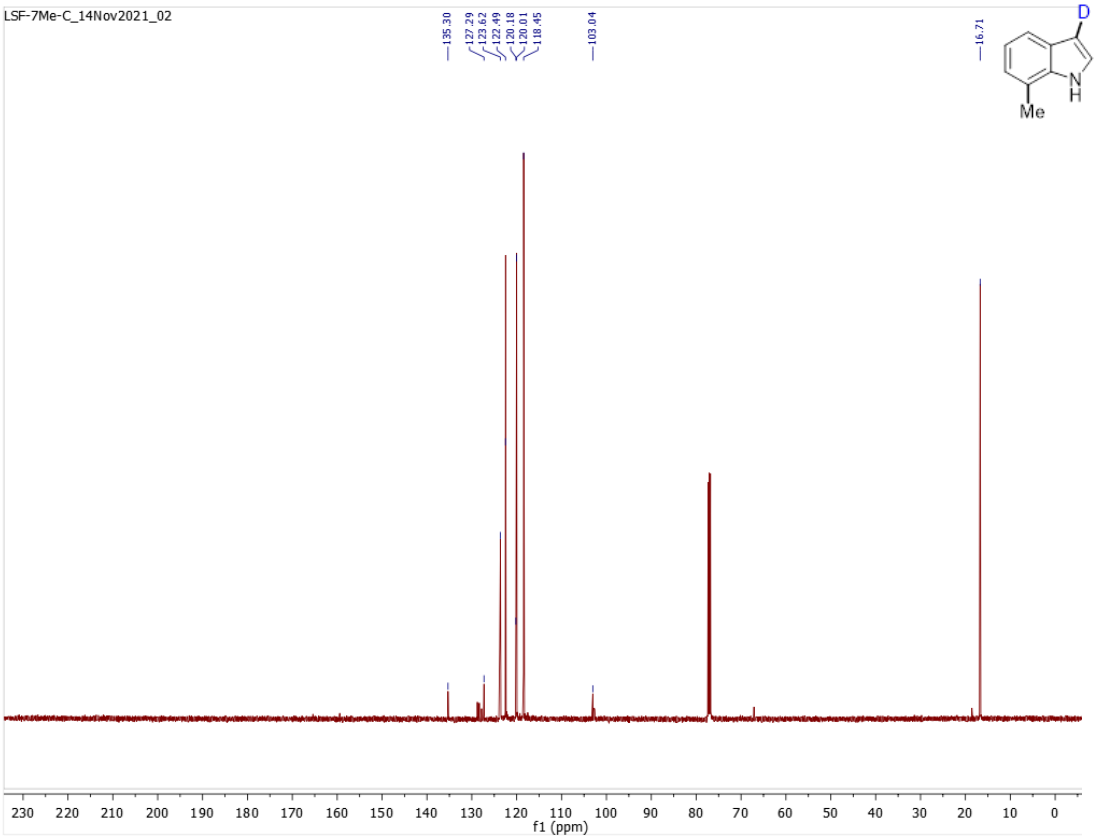
^{1}H NMR spectrum of (4a)



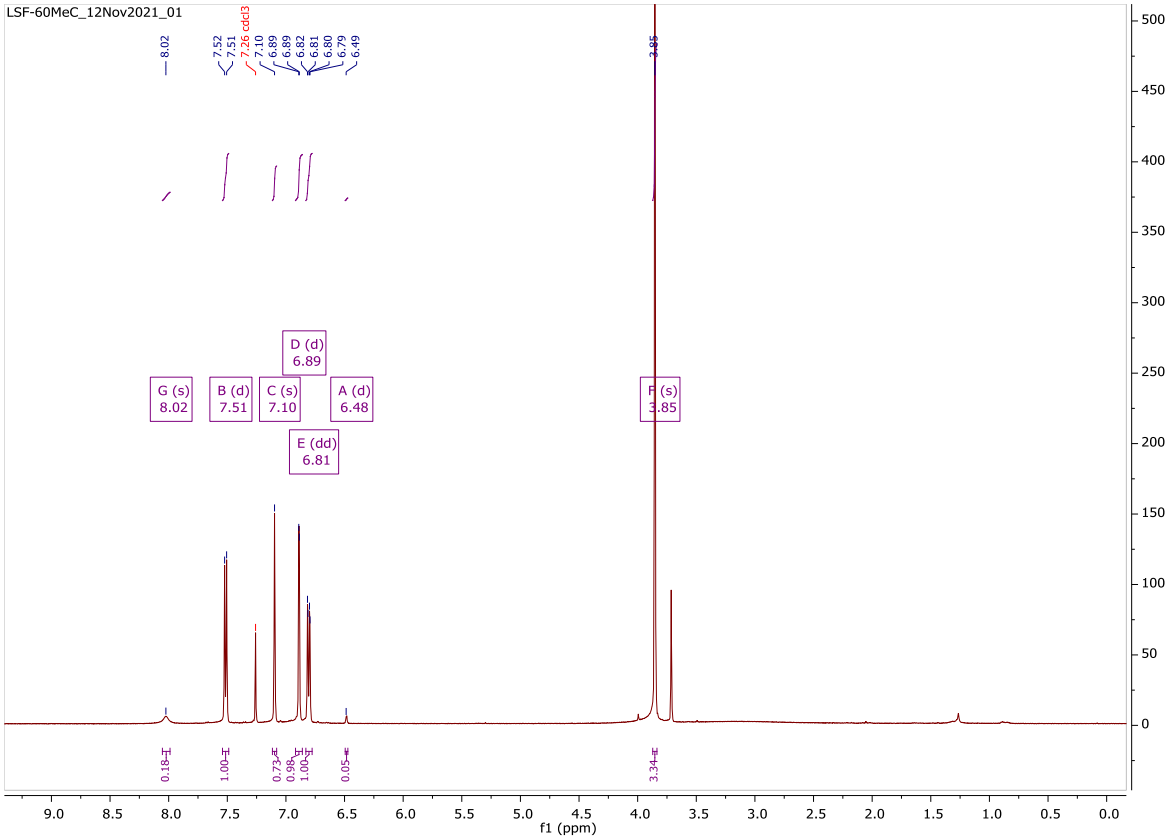
^{1}H NMR spectrum of (4c)



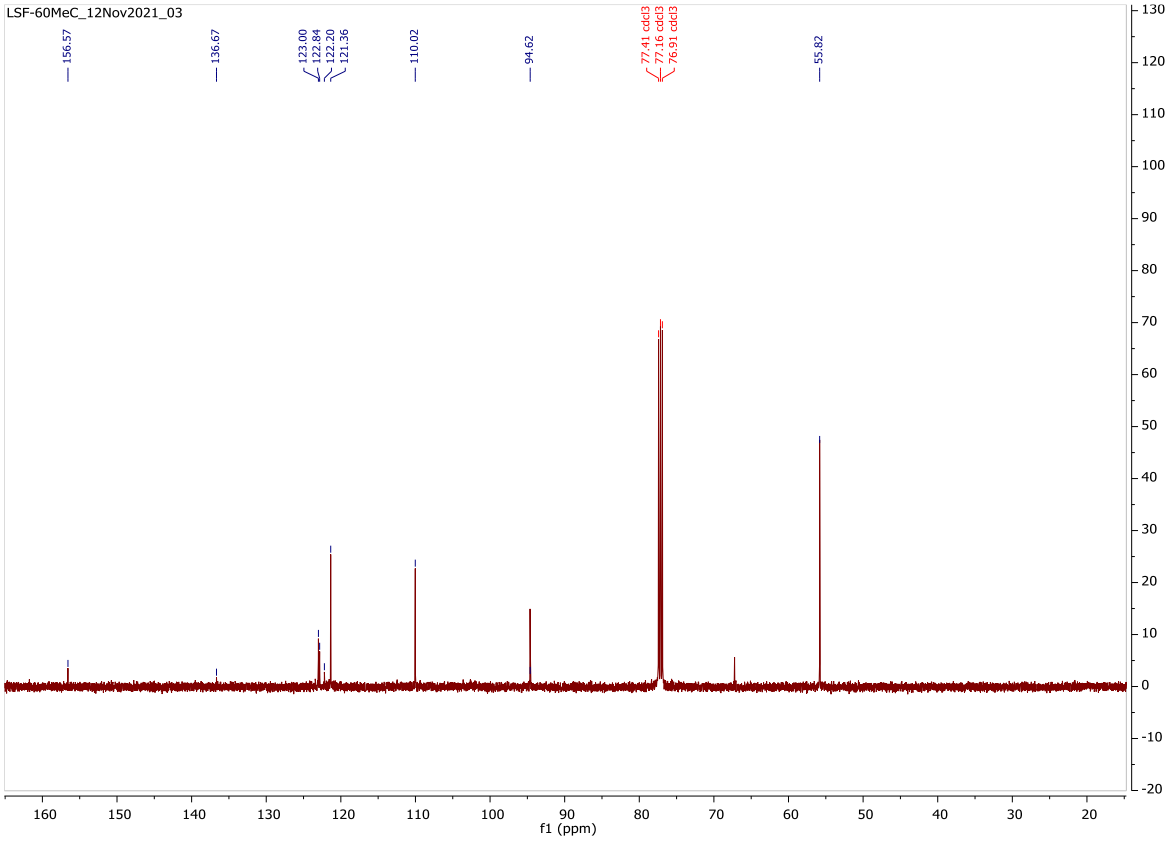
^{13}C NMR spectrum of (4c)



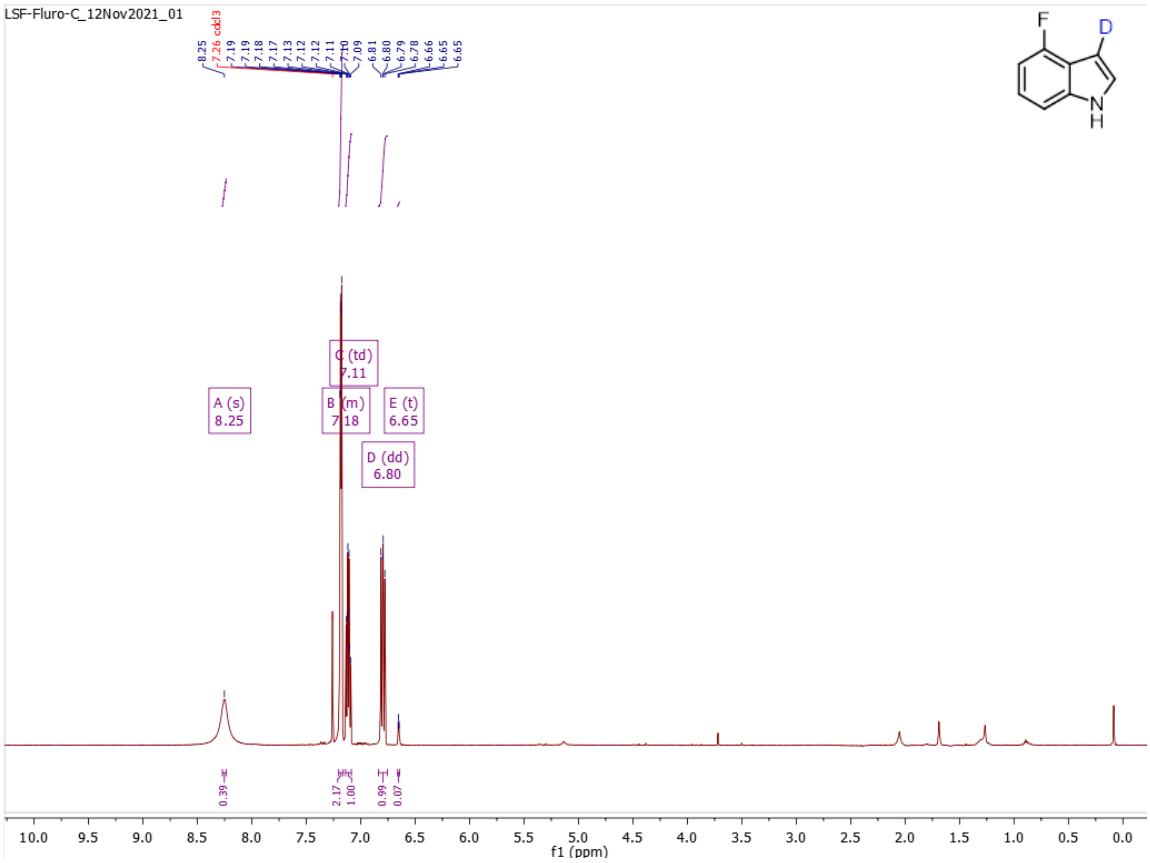
^{1}H NMR spectrum of (4d)



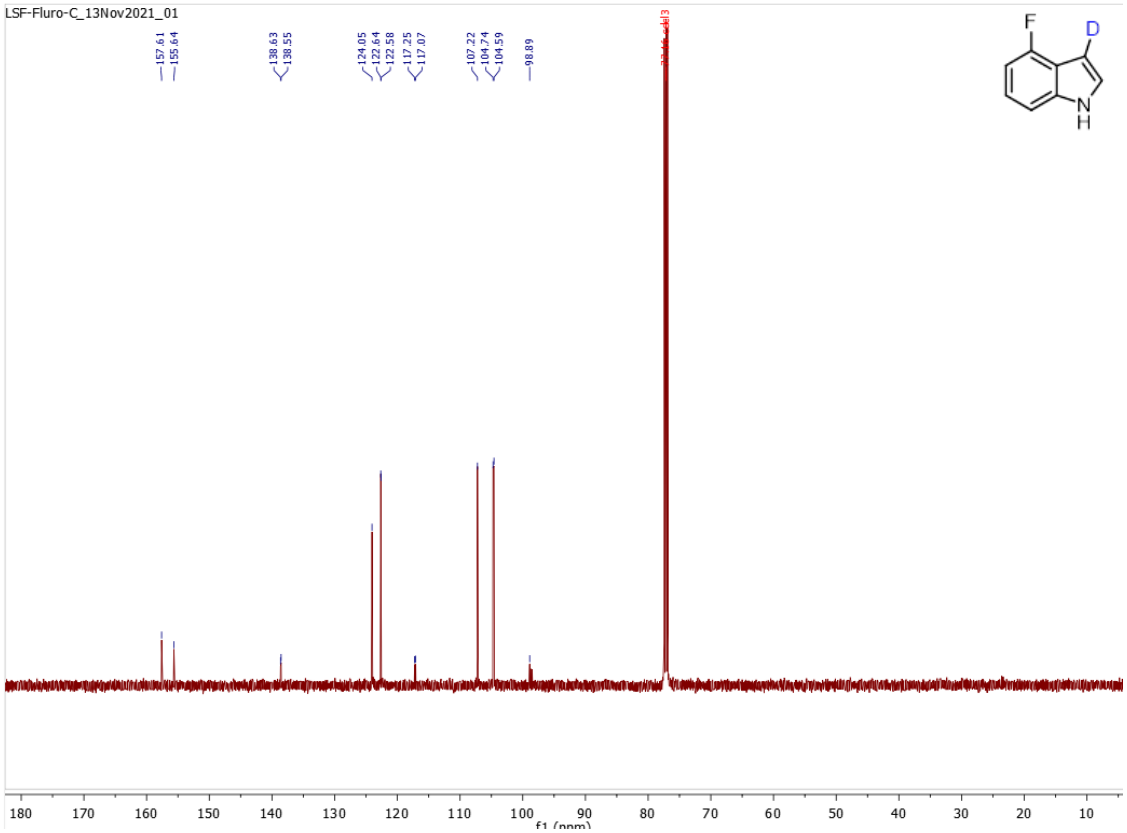
^{13}C NMR spectrum of (4d)



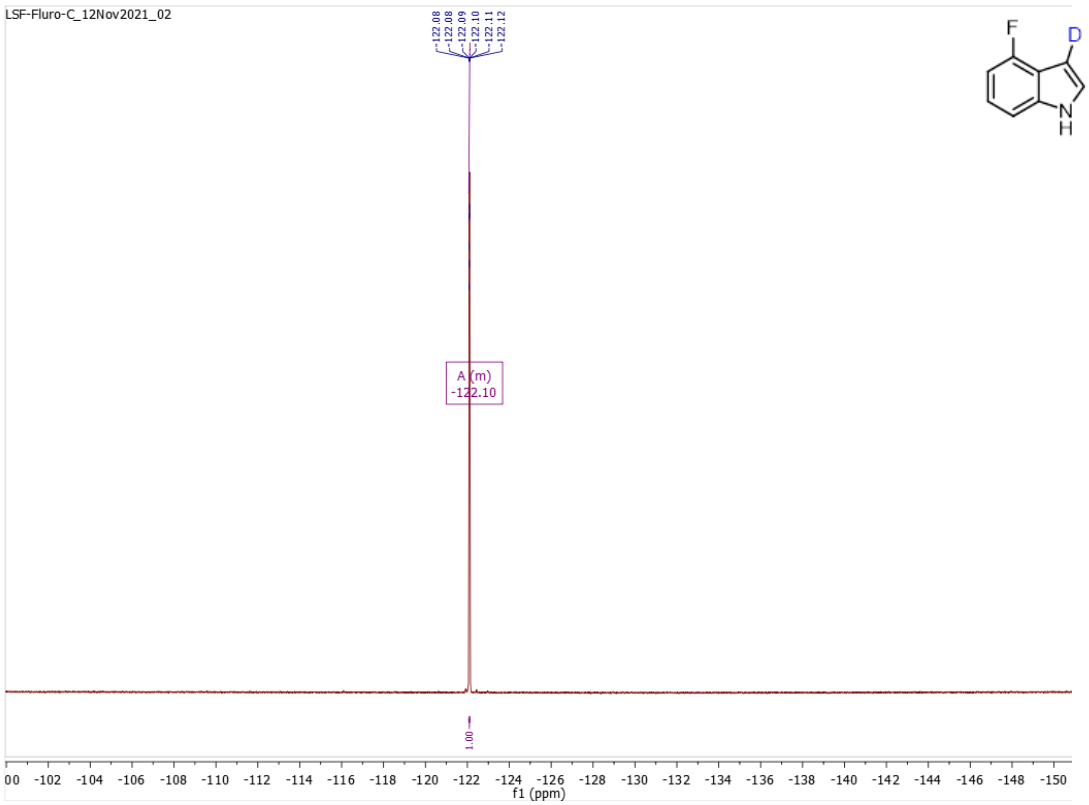
^{1}H NMR spectrum of (4e)



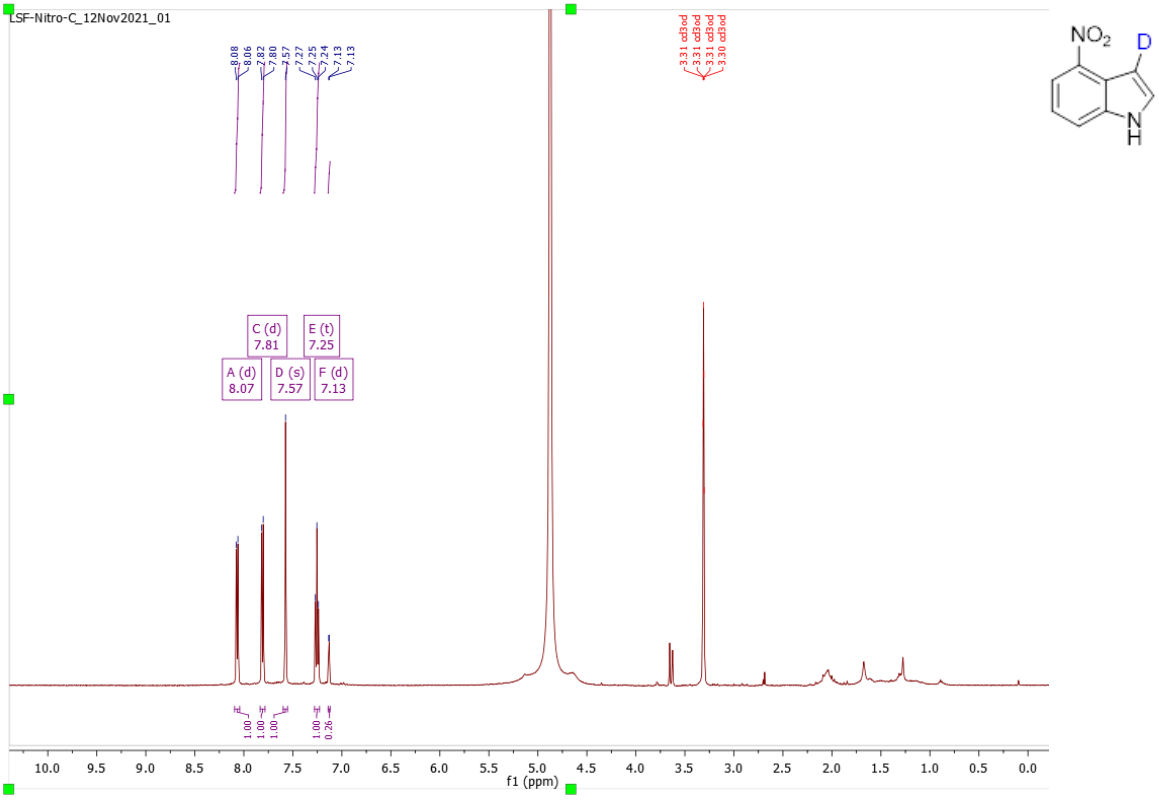
^{13}C NMR spectrum of (4e)



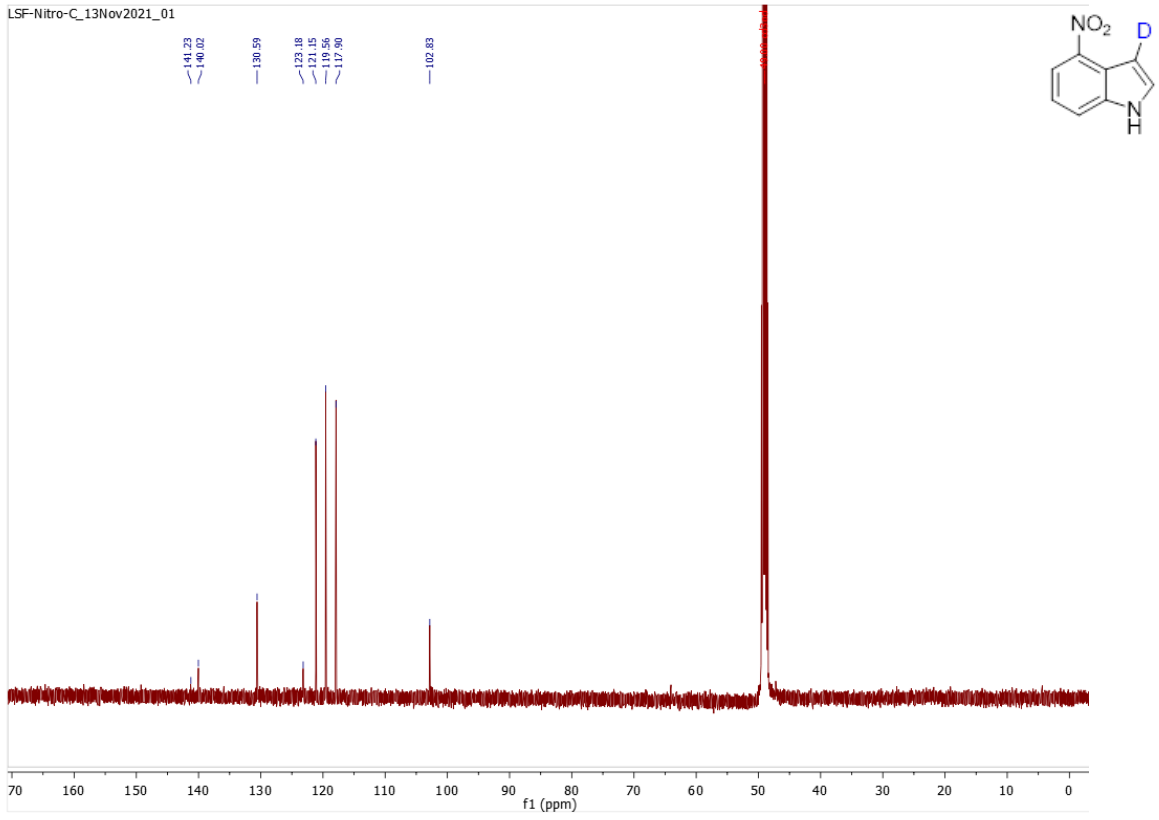
^{19}F NMR spectrum of (4e)



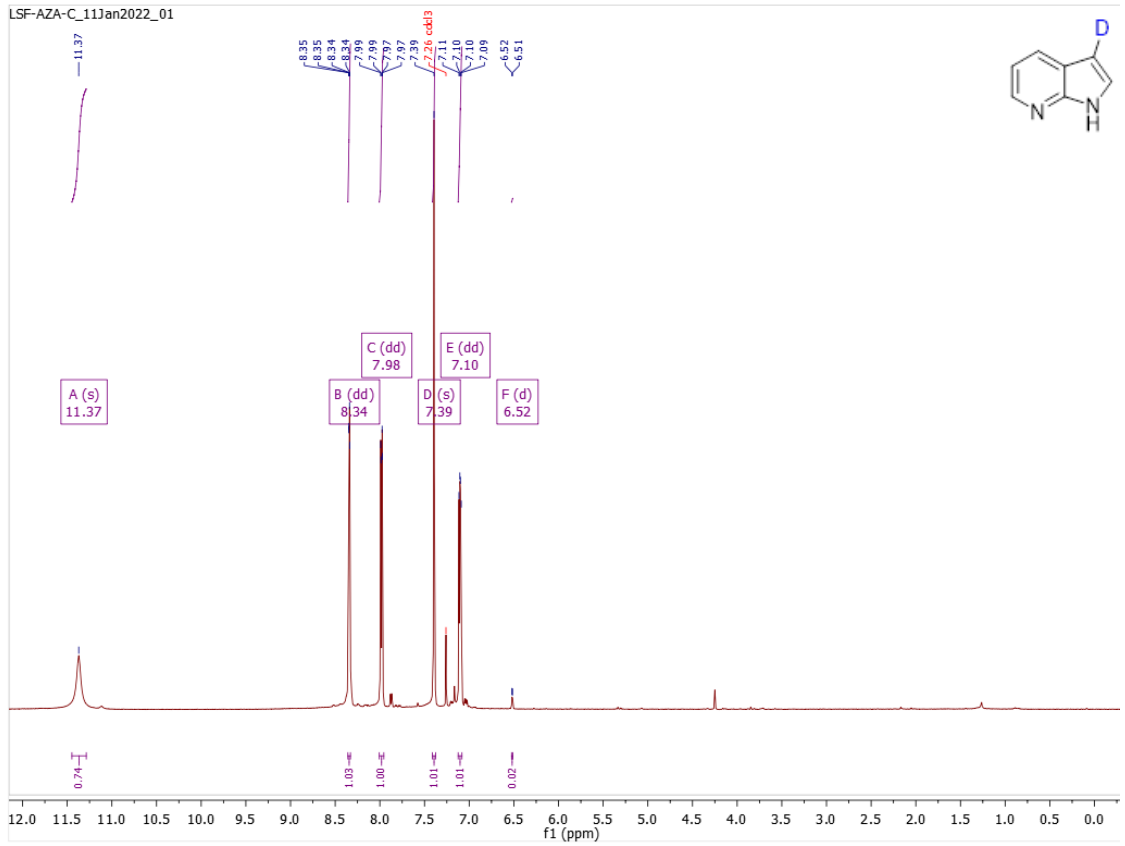
^{1}H NMR spectrum of (4f)



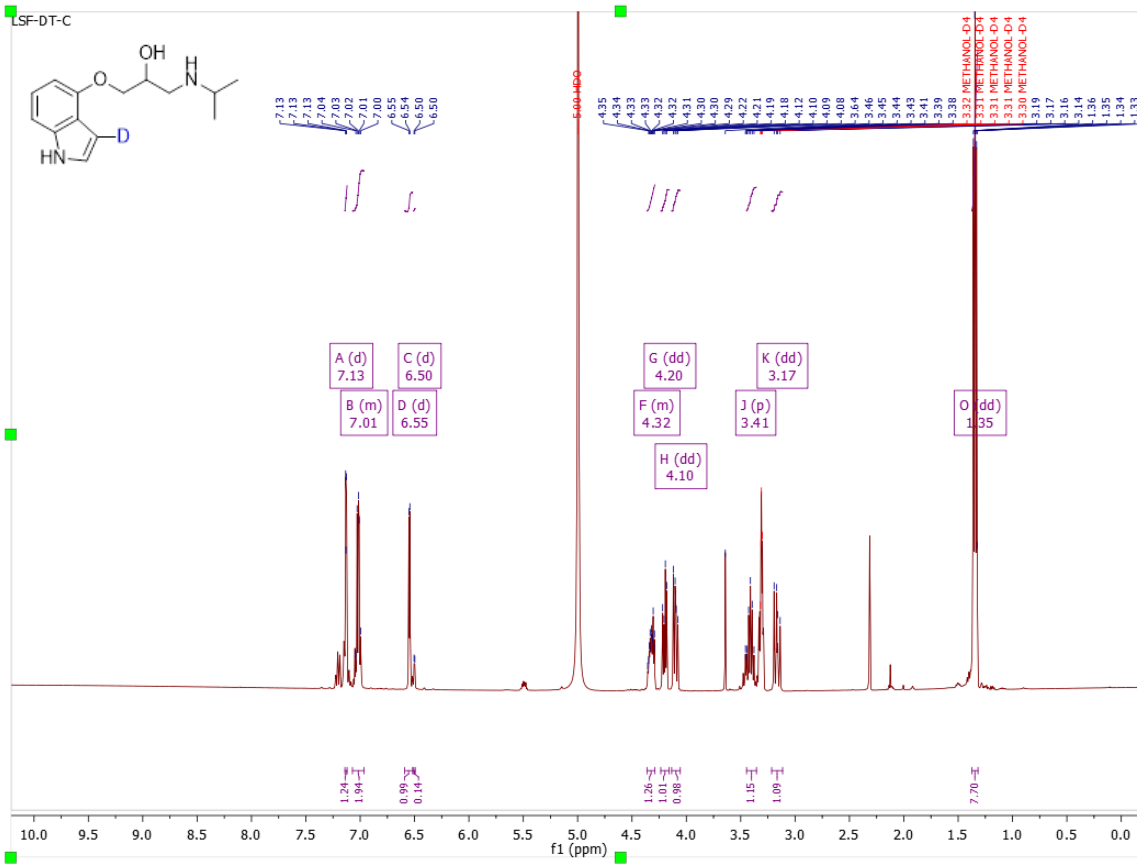
^{13}C NMR spectrum of (4f)



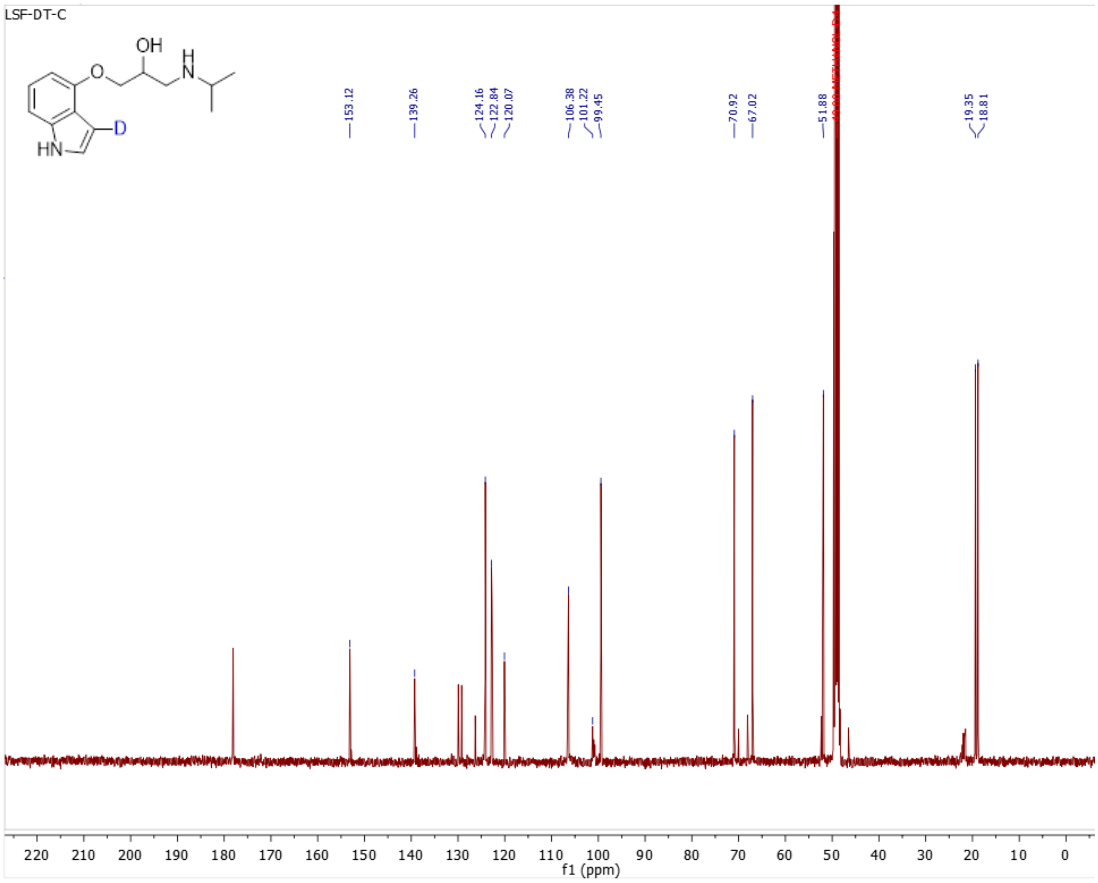
^{1}H NMR spectrum of (4i)



^{1}H NMR spectrum of (4l)



^{13}C NMR spectrum of (4l)



References

[1] X. Liu, J. Huang, H. Xu, D. Zhang, Q. Sun, L. He, *European J. Org. Chem.* **2019**, *2019*, 900–906.

[2] G. Pieters, C. Taglang, E. Bonnefille, T. Gutmann, C. Puente, J. C. Berthet, C. Dugave, B. Chaudret, B. Rousseau, *Angew. Chemie - Int. Ed.* **2014**, *53*, 230–234.

[3] P. Thapa, S. Hazoor, B. Chouhan, T. T. Vuong, F. W. Foss, *J. Org. Chem.* **2020**, *85*, 9096–9105.

[4] B. Dong, X. Cong, N. Hao, *RSC Adv.* **2020**, *10*, 25475–25479.

[5] D. Darshana, S. Sureram, C. Mahidol, S. Ruchirawat, P. Kittakoop, *Org. Biomol. Chem.* **2021**, *19*, 7390–7402.