Supporting Information

O-Difluorodeuteromethylation of phenols using difluorocarbene precursors and deuterium oxide

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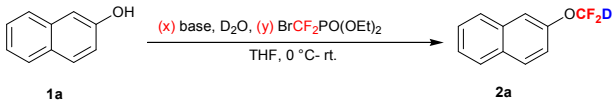
1. Optimization of the reaction conditions

Table S1 Optimization of the reaction conditions.[a]



1a 2a

entry	x eq.	D_2O (eq.)	y eq.	yield (%)[d, e]	d. p. (%)[f]
1[b]	KOH (20)	5 mL	2.0	82/79[e]	91.6
2[c]	KOH (20)	5 mL	2.0	81/78[e]	92.8
3	NaH (1)	1	2.0	trace	-
4	NaH (1)	50	2.0	15	-
5	NaH (3)	50	2.0	45	-
6	NaH (5)	50	2.0	65	-
7	NaH (8)	50	2.0	70	-
8	NaH (10)	50	2.0	83/80[e]	99.3
9	NaH (12)	50	2.0	78/75[e]	99.3
10	NaH (20)	50	2.0	40	-
11	NaH (10)	12	2.0	5	-
12	NaH (10)	30	2.0	20	-
13	NaH (10)	100	2.0	84/81[e]	99.5
14	NaH (10)	200	2.0	83/79[e]	99.5
15	NaH (10)	50	1.5	75/72[e]	98.3
16	NaH (10)	50	2.5	78/74[e]	99.3
17	K_2CO_3 (10)	50	2.0	20	-

[a]Reaction conditions: 2-Naphthol **1a** (1 mmol), base, THF (4 mL), 0 °C, Ar_2, 0.5 h; D_2O, 10 minutes; $BrCF_2PO(OEt)_2$,, 0 °C-rt, 0.5 h.

[b]Reaction conditions: 2-Naphthol **1a** (1 mmol), CH_3CN (5 mL), KOH (20 mmol), -78 °C, Ar_2, 0.5 h; D_2O (5 mL), 10 minutes; $BrCF_2PO(OEt)_2$ (2 mmol), -78 °C-rt, 0.5 h.

[c]THF (5 mL) as solvent.

[d]Yield was determined by GC method using benzophenone as the internal standard substance.

[e]Isolated yield, the product **2a** was purified via silica gel column with petroleum ether as eluent.

[f]d.p. = deuterated purity, was determined by ^1H NMR method.

2. General information

All manipulations were carried out in glass reaction tube equipped with a magnetic stir bar under argon atmosphere. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Melting points were recorded by XT4A micro Melting point Measurement Instruments, thermometer was unrevised. The transformation progress and Mass spectra were indicated by LC-MSD-Trap-XCT instrument or GC-MS (Thermo Fisher Scientific DSQ II). The high

resolution mass spectra were received via Agilent Technologies 6540 UHD Accurate-mass Q-TOF LC/MS, with ESI as ion source and Thermo Scientific Q Exactive GC Orbitrap GC-MS. Moreover, NMR spectra were obtained on Bruker AVANCE III 400 systems using $CDCl_3$ or DMSO-d_6 as solvent, TMS as internal standard substance, with proton, fluorine and carbon resonances at 400, 376 and 100 MHz, respectively. The bioactivity date were supported by Tetranov International, Inc.

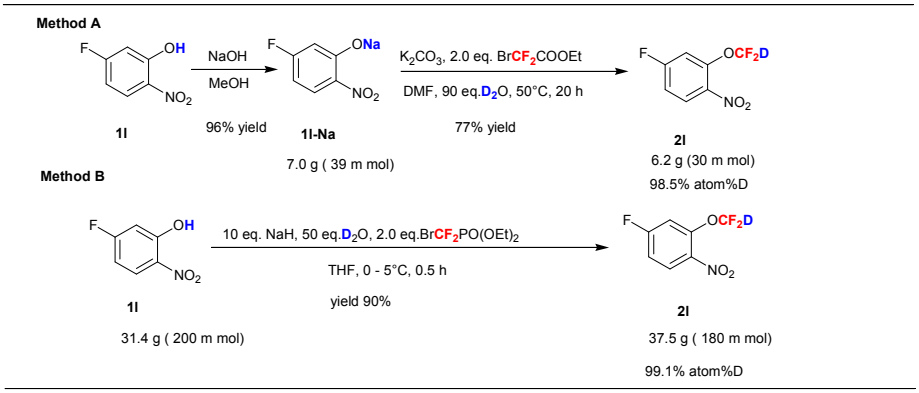
3. Experimental section and analytical date.

3.1 General procedure for preparing difluorodeuteromethyl aryl ethers.

Sodium hydride (400 mg, 10 mmol, 60% in mineral oil) was added to a solution of phenol (1 mmol) in dry THF (4 mL) at 0 °C under argon atmosphere. After 30 min, D_2O (1.0 g, 50 mmol) was slowly added and stirred at 0 °C for 10 minutes. $BrCF_2PO(OEt)_2$ (534 mg, 2 mmol) was added below 0 °C. The reaction mixture was warmed to room temperature (as substrates **1l** and **1t**, the temperature was warmed to 5 °C) and stirred for another 0.5 h. The mixture was added with petroleum ether (or petroleum ether and ethyl acetate mixture) and separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and the resulting residue was purified by flash column chromatograph to give the pure products. The products were characterized by ^1H NMR, ^{13}C NMR, ^{19}F NMR, GC-MS and HRMS.

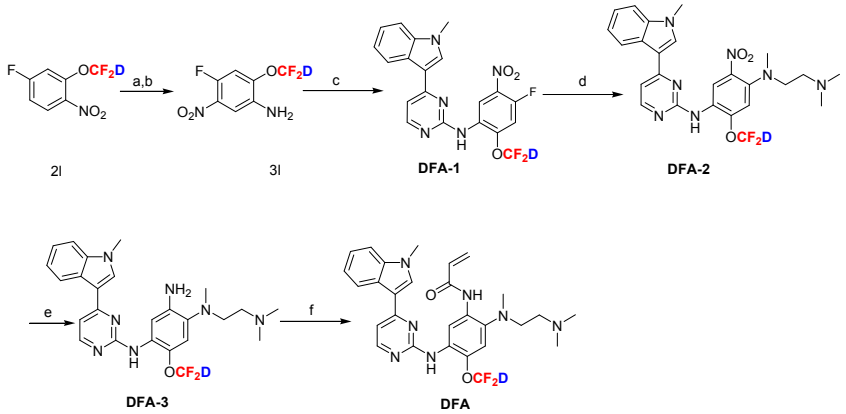
3.2 Procedure for 30 grams scale.

Method B: 5-Fluoro-2-nitrophenol (31.4 g, 200 mmol) and dry THF (800 mL) were added in a 2 L three neck flask equipped with a mechanical agitation and a low-temperature thermometer under argon atmosphere. Sodium hydride (80 g, 2.0 mol, 60% dispersion in mineral oil) was added with multiple batches to the solution under 0 °C. Then, the reaction mixture was stirred for 0.5 h. The D_2O (200 g, 10 mol) was cautiously added drop by drop below 0 °C, and the gas was removed at irregular intervals. The reaction mixture was stirred for 0.5 h, and $BrCF_2PO(OEt)_2$ (106.8 g, 400 mmol) was added below 0 °C. Then, the reaction mixture was warmed to 5 °C and stirred for another 0.5 h. The mixture was added with petroleum ether:ethyl acetate = 10:1. Separation of organic phase and aqueous phase, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and the resulting residue was purified by silica gel column with PE:DCM = 4:1 as eluent to afford the pure product **2l** (37.5 g, 90% yield and 99.1 atom % D).



Scheme S1. Scalability of the difluorodeuteromethylation of 1l

3.3 Procedure of preparation of compound DFA.



Scheme S2. Introduction of the OCF_2D Group into the Drug Molecule

2-(Difluoromethoxy-d_1)-4-fluoro-5-nitrobenzenamine (3l).

Step a[1]: compound **2l** (2-(difluoromethoxy-d_1)-4-fluoro-1-nitrobenzene) (5.0 g, 24 mmol), 10% Pd/C (0.5 g) were dissolved in ethyl acetate (250 mL). Then, the reaction system was stirred under a hydrogen balloon at room temperature for 16 h. The reaction mixture was filtered through a suction funnel filled with diatomite. The solution was concentrated and the crude product 2-(difluoromethoxy-d^1)-4-fluorobenzenamine (3.8 g) was directly used for the next step.

Step b[2]: 2-(difluoromethoxy-d_1)-4-fluorobenzenamine (3.8 g) was added in batches into conc.H_2SO_4 below 10 °C. Then Potassium nitrate (2.2 g, 21.8 mmol) was added. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was poured into ice water and excessive ammonia was added. The mixture was stirred for 30 min and then diluted with EA (100 mL). The organic phase was separated and washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified via silica gel column to afford the product **3l** a yellow solid (3.9g, 17.5 mmol, 73% yield, for two steps).

N-(2-(difluoromethoxy-d_1)-4-fluoro-5-nitrophenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidin-2-amine (DFA-1).

Step c[3]. 4-Methylbenzenesulfonic acid hydrate (4.0 g, 21 mmol) was added in one portion to 3-(2-chloropyrimidin-4-yl)-1-methylindole (4.3 g, 17.5 mmol) and 2-(difluoromethoxy-d_1)-4-fluoro-5-nitrobenzenamine (3.9 g, 17.5 mmol) in 2-pentanol (80 mL). The resulting mixture was stirred at 110 °C for 12 h. The mixture was concentrated and added with 2M Na_2CO_3 solution, then extracted by CH_2Cl_2. The organic phase was dried by anhydrous Na_2SO_4, concentrated and purified via silica gel column to afford the product **DFA-1** a yellow solid (7.1 g, 16.5 mmol, 94% yield).

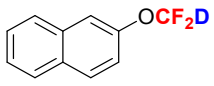
2-(Difluoromethoxy-d_1)-N^4-(2-(dimethylamino)ethyl)-N^4-methyl-N^1-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)-5-nitrobenzene-1,4-diamine (DFA-2)[3] . Compound **DFA-1** (3.2 g, 7.4 mmol**),** N^1, N^1, N^2-trimethylethane-1, 2-diamine (1.52 g, 14.9 mmol), DIEA (2.88 g, 22.3 mmol) were dissolved in DMA (50 mL). The mixture was warmed to 60 °C and stirred overnight. The reaction mixture was cooled to rt, and poured into ice-water, stirred for 0.5 h, filtered and washed with ethyl ether. The solid

was collected and dried to afford the product **DFA-2** an orange solid (3.5 g, 6.8 mmol, 92% yield).

5-(Difluoromethoxy-d_1)-N^1-(2-(dimethylamino)ethyl)-N^1-methyl-N^4-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)benzene-1,2,4-triamine (DFA-3).[3] Compound DFA-2 (3.5 g, 6.8 mmol) was dissolved in EA (300 mL) and DCM (30 mL) added with 0.35 g 10% Pd/C. The reaction mixture was pressurized with a hydrogen balloon and stirred at room temperature for 20 h. The solution was filtered through a suction funnel filled with diatomite and concentrated to afford the reduction product (3.0 g, 6.2 mmol, 91%).

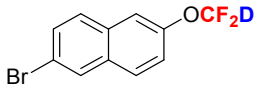
N-(5-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-ylamino)-2-(N-(2-(dimethylamino)ethyl)-N-methylamino)-4-(difluoromethoxy-d_1)phenyl)acrylamide (DFA).[3] The reduction product (0.42 g, 0.87 mmol) and DIEA (0.23 g, 1.74 mmol) were dissolved in DCM (40 mL). The mixture was cooled to 0 °C, slowly added with acryloyl chloride (90 mg) in DCM (10 mL), stirred for 2 h below 10 °C. The mixture was diluted with DCM (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (50 mL). The organics were removed, and the aqueous portion was further extracted with DCM (2 × 30 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified via a silica gel column with elution gradient 1-10% MeOH in DCM. The pure fractions were concentrated to afford the product DFA an offwhite solid (0.32 g, 0.61 mmol, 69%).

3.4 Analytical date of difluorodeuteromethyl aryl ethers.



2a

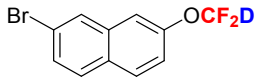
2-(Difluoromethoxy-d_1)naphthalene. (**2a**, 156.1 mg, yield 80%，99.3 atom % D): Using petroleum (PE) as eluent (Rf = 0.3, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.87−7.81 (m, 3H), 7.54−7.48 (m, 3H), 7.31 (dd, J = 2.4 Hz, 8.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.3 (t, J = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.0 (t, $J_{C\text{-}F}$ = 2.6 Hz), 133.8, 131.1, 130.1 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 125.7 (CH), 119.7 (CH), 115.9 (tt, $J_{C\text{-}D}$ = 33.7 Hz, $J_{C\text{-}F}$ = 256.6 Hz), 115.4 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{11}H_7DF_2O$ $[M]^+$：195.06060; Found: 195.06003. GC−MS (EI, *m/z*): $[M]^+$ 195.1.



2b

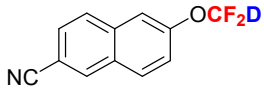
2-Bromo-6-(difluoromethoxy-d_1)naphthalene. (**2b**, 233.8 mg, yield 85%， 98.5 atom % D): Using PE as eluent (Rf = 0.3, PE). White foam; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 (d, J = 1.4 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.50 (dd, J = 1.9 Hz, 8.8 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 2.4 Hz, 8.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.6 (t, J = 11.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.0 (t, $J_{C\text{-}F}$ = 2.8 Hz), 132.2, 132.0, 130.3 (CH), 129.8 (CH), 129.2 (CH), 129.1 (CH), 120.4 (CH), 119.7, 115.6 (tt, $J_{C\text{-}D}$ =

33.8 Hz, $J_{C\text{-}F}$ = 257.3 Hz), 115.3 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{11}H_6DBrF_2O$ $[M]^+$: 272.97111; Found: 272.97089. GC−MS (EI, *m/z*): $[M]^+$ 273.0.



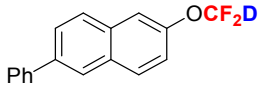
2c

2-Bromo-7-(difluoromethoxy-d$_1$))naphthalene. (**2c**, 225.5 mg, yield 82%，98.3 atom % D): Using PE as eluent (Rf = 0.3, PE). White foam; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.89 (d, J = 1.6 Hz, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.48 (dd, J = 1.9 Hz, 8.8 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 7.24 (dd, J = 2.4 Hz, 8.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.7 (t, J = 11.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.6 (t, $J_{C\text{-}F}$ = 2.8 Hz), 134.9, 130.1 (CH), 129.5 (CH), 129.4 (CH), 129.1 (CH), 121.2, 120.1 (CH), 115.6 (tt, $J_{C\text{-}D}$ = 33.7 Hz, $J_{C\text{-}F}$ = 257.4 Hz), 114.3 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{11}H_6DBrF_2O$ $[M]^+$: 272.97111; Found: 272.97074. GC−MS (EI, *m/z*): $[M]^+$ 273.0.



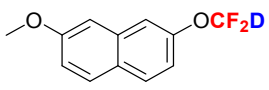
2d

6-(Difluoromethoxy-d$_1$)naphthalene-2-carbonitrile. (**2d**, 132.1 mg, yield 60 %, 98.6 atom % D): Using PE:DCM = 4:1 as eluent (Rf = 0.4, PE:DCM = 1:1). White foam; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.16 (s, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.60 (dd, J = 1.6 Hz, 8.5 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.38 (dd, J = 2.4 Hz, 9.0 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -82.4 (t, J = 11.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 151.1 (t, $J_{C\text{-}F}$ = 2.8 Hz), 135.3, 133.8 (CH), 130.7 (CH), 129.6, 128.8 (CH), 127.5 (CH), 121.4 (CH), 119.0, 115.3 (tt, $J_{C\text{-}D}$ = 34.0 Hz, $J_{C\text{-}F}$ = 258.4 Hz), 115.0 (CH), 109.1. HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{12}H_6DF_2NO$ $[M]^+$: 220.05585; Found: 220.05533. GC−MS (EI, *m/z*): $[M]^+$ 220.1



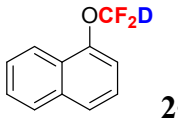
2e

2-(**Difluoromethoxy-d$_1$**)-6-phenylnaphthalene. (**2e**, 230.5 mg, yield 85 %, 98.8 atom % D): Using PE:DCM = 10:1 as eluent (Rf = 0.35, PE:DCM = 10:1). White foam; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.01 (d, J = 0.6 Hz, 1H), 7.88 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.77 (dd, J = 1.8 Hz, 8.5 Hz, 1H), 7.71−7.68 (m, J = 2.0 Hz, 2H), 7.52−7.46 (m, 2H), 7.40−7.36 (m, 1H), 7.29 (dd, J = 2.4 Hz, 8.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.4 (t, J = 11.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.0 (t, $J_{C\text{-}F}$ = 2.7 Hz), 140.7, 138.5, 132.9, 131.3, 130.3 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 125.6 (CH), 120.1 (CH), 115.8 (tt, $J_{C\text{-}D}$ = 33.6 Hz, $J_{C\text{-}F}$ = 256.3 Hz), 115.2 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{17}H_{11}DF_2O$ $[M]^+$: 271.09190; Found: 271.09149. GC−MS (EI, *m/z*): $[M]^+$ 271.2



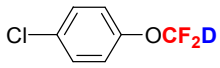
2f

2-(**Difluoromethoxy-d$_1$**)-7-methoxynaphthalene. (**2f**, 157.5 mg, yield 70 %, 99.0 atom % D): Using PE:DCM = 10:1 as eluent (Rf = 0.17, PE:DCM = 10:1). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.61 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.02−6.98 (m, 2H), 6.95 (d, J = 2.4 Hz, 1H), 3.78 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.2 (t, J = 11.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 158.5, 149.7 (t, $J_{C\text{-}F}$ = 2.5 Hz), 135.3, 129.8 (CH), 129.3 (CH), 126.5, 118.8 (CH), 117.0 (CH), 115.9 (tt, $J_{C\text{-}D}$ = 33.6 Hz, $J_{C\text{-}F}$ = 256.2 Hz), 114.4 (CH), 105.5 (CH), 55.3 (CH_3). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{12}H_9DF_2O_2$ $[M]^+$：225.07116; Found: 225.07062. GC−MS (EI, *m/z*): $[M]^+$ 225.0



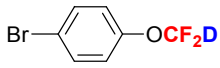
2g

1-(Difluoromethoxy-d$_1$)naphthalene. (**2g**, 152.2 mg, yield 78%，98.2 atom % D): Using PE as eluent (Rf = 0.3, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.19−8.16 (m, 1H), 7.85−7.81 (m, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.56−7.50 (m, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.17 (dd, J = 0.2 Hz, 1.9 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -80.6 (t, J = 11.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 147.5 (t, $J_{C\text{-}F}$ = 2.6 Hz), 134.7, 127.8 (CH), 127.0 (CH), 126.6 (CH), 126.4, 125.4 (CH), 125.3 (CH), 121.6 (CH), 116.3 (tt, $J_{C\text{-}D}$ = 33.6 Hz, $J_{C\text{-}F}$ = 256.1 Hz), 113.8 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{11}H_7DF_2O$ $[M]^+$：195.06060; Found: 195.06006. GC−MS (EI, *m/z*): $[M]^+$ 195.1.



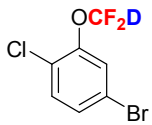
2h

1-Chloro-4-(difluoromethoxy-d$_1$)benzene. (**2h**, 134.2 mg, yield 75 %, 98.3 atom % D): Using PE as eluent (Rf = 0.54, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.35−7.31 (m, 2H), 7.09−7.05 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.96 (t, J = 10.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.4 (t, $J_{C\text{-}F}$ = 2.8 Hz), 130.9, 129.8 (CH), 121.2 (CH), 115.4 (tt, $J_{C\text{-}D}$ = 34.0 Hz, $J_{C\text{-}F}$ = 258.0 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_7H_4DClF_2O$ $[M]^+$：179.00598; Found: 179.00838. GC−MS (EI, *m/z*): $[M]^+$ 179.0.



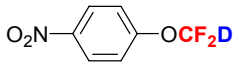
2i

1-Bromo-4-(difluoromethoxy-d$_1$)benzene. (**2i**, 185.1 mg, yield 83 %, 99.1 atom % D): Using PE as eluent (Rf = 0.54, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.49−7.45 (m, 2H), 7.02−6.99 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -82.0 (t, J = 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 150.0 (t, $J_{C\text{-}F}$ = 2.8 Hz), 132.8 (CH), 121.5 (CH), 118.5, 115.3 (tt, $J_{C\text{-}D}$ = 33.9 Hz, $J_{C\text{-}F}$ = 258.3 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_7H_4DBrF_2O$ $[M]^+$：222.95546; Found: 222.95503. GC−MS (EI, *m/z*): $[M]^+$ 223.0



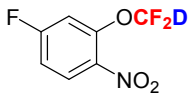
2j

4-Bromo-1-chloro-2-(difluoromethoxy-d$_1$)benzene. (**2j**, 168.3 mg, yield 65 %, 99.0 atom % D): Using PE as eluent (Rf = 0.54, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.41 (t, J = 0.9 Hz 1H), 7.32 (d, J = 1.2 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -82.5 (t, J = 10.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 147.1, 131.7 (CH), 129.8 (CH), 125.7 (CH), 125.2, 120.4, 115.2 (tt, $J_{C\text{-}D}$ = 33.5 Hz, $J_{C\text{-}F}$ = 255.2 Hz), HRMS (EI-Orbitrap) *m/z*: Calcd for $C_7H_3DBrClF_2O$ $[M]^+$: 256.91649; Found: 256.91589. GC−MS (EI, *m/z*): $[M]^+$ 257.0.



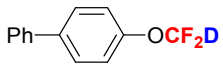
2k

1-(Difluoromethoxy-d$_1$)-4-nitrobenzene. (**2k,** 171.0 mg, yield 90 %, 99.2 atom % D): Using PE:DCM = 4:1 as eluent (Rf = 0.6, PE:DCM = 1:1). White foam; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.29−8.25 (m, 2H), 7.28−7.24 (m, 2H).^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -83.33 (t, J = 10.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 155.5 (t, $J_{C\text{-}F}$ = 2.5 Hz), 144.8, 125.8 (CH), 119.3 (CH), 114.7 (tt, $J_{C\text{-}D}$ = 34.1 Hz, $J_{C\text{-}F}$ = 260.8 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_7H_4DF_2NO_3$ $[M]^+$: 190.03003; Found: 190.02929. GC−MS (EI, *m/z*): $[M]^+$ 190.1



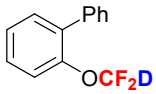
2l

2-(Difluoromethoxy-d$_1$)-4-fluoro-1-nitrobenzene. (**2l**, 191.4 mg, yield 92 %, 98.2 atom % D): Using PE:DCM = 4:1 as eluent (Rf = 0.6, PE:DCM = 1:1). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.03 (dd, J = 5.6 Hz, 9.1 Hz, 2H), 7.15−7.08 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -83.4 (t, J = 10.9 Hz), -99.8 (s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 164.7 (d, J = 257.5 Hz), 144.9−144.8 (m), 139.0, 127.9 (CH) (d, J = 10.6 Hz), 115.1 (CH) (tt, $J_{C\text{-}D}$ = 35.2 Hz, $J_{C\text{-}F}$ = 264.0 Hz). 112.4 (CH) (dd, J = 23.0 Hz, 219.2 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_7H_3DF_3NO_3$ $[M]^+$: 208.02060; Found: 208.02002. GC−MS (EI, *m/z*): $[M]^+$ 208.1.



2m

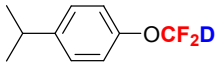
4-(Difluoromethoxy-d$_1$)-4-phenyl-benzene. (**2m**, 205.5 mg, yield 93%, 98.0 atom % D)**:** Using PE as eluent (Rf = 0.25, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.56−7.52 (m, 4H), 7.44−7.40 (m, 2H), 7.36−7.32 (m, 1H), 7.19−7.16 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.4 (t, J = 11.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 150.6 (t, J = 10.1 Hz), 140.1, 138.6, 128.9 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 119.9 (CH), 115.7 (tt, $J_{C\text{-}D}$ = 33.9 Hz, $J_{C\text{-}F}$ = 256.7Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{13}H_9DF_2O$ $[M]^+$: 221.07625; Found: 221.07939. GC−MS (EI, *m/z*): $[M]^+$ 221.1



2n

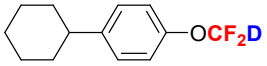
1-(Difluoromethoxy-d$_1$)-2-phenylbenzene. (**2n**, 188 mg, yield 85 %, 98.2 atom % D): Using PE as eluent (Rf = 0.25, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.50−7.47 (m, 2H), 7.44−7.40 (m, 3H), 7.38−7.32 (m, 2H), 7.30−7.26 (m, 1H), 7.24−7.22 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.4 (t, J = 11.9

Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 148.2 (t, $J_{C\text{-}F}$ = 2.7 Hz), 137.0, 134.1, 131.5 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 125.9 (CH), 120.3 (CH), 115.9 (tt, $J_{C\text{-}D}$ = 33.8 Hz, $J_{C\text{-}F}$ = 256.9 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{13}H_9DF_2O$ $[M]^+$：221.07625; Found: 221.07570. GC−MS (EI, *m/z*): $[M]^+$ 221.1.



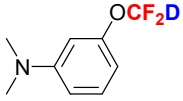
2o

1-(Difluoromethoxy-d$_1$)-4-isopropylbenzene. (**2o**, 103.3 mg, yield 60 %, 98.4 atom % D): Using PE as eluent (Rf = 0.56, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.24−7.19 (m, 2H), 7.05−7.03 (m, 2H), 2.93−2.87 (m, 1H), 1.24 (d, J = 6.9 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.2 (t, J = 12.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.2 (t, $J_{C\text{-}F}$ = 2.7 Hz), 146.1, 127.7 (CH), 119.5 (CH), 115.9 (tt, $J_{C\text{-}D}$ = 33.6 Hz, $J_{C\text{-}F}$ = 256.2 Hz), 33.5 (CH), 24.0 (CH_3). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{10}H_{11}DF_2O$ $[M]^+$：187.09190; Found: 187.09141. GC−MS (EI, *m/z*): $[M]^+$ 187.1.



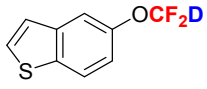
2p

1-Cyclohexyl-4-(difluoromethoxy-d$_1$)benzene. (**2p**, 170.3 mg, yield 75 %, 98.8 atom % D): Using PE as eluent (Rf = 0.56, PE). Colorless oil**;** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.20−7.16 (m, 2H), 7.04−7.02 (m, 2H), 2.52−2.46 (m, 1H), 1.85−1.73 (m, 5H), 1.43−1.21 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.1 (t, J = 11.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.2 (t, $J_{C\text{-}F}$ = 2.6 Hz), 145.4, 128.0 (CH), 119.4 (CH), 115.9 (tt, $J_{C\text{-}D}$ = 33.7 Hz, $J_{C\text{-}F}$ = 256.1 Hz), 43.9 (CH), 34.5 (CH_2), 26.8 (CH_2), 26.1 (CH_2). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{13}H_{15}DF_2O$ $[M]^+$：227.12320; Found: 227.12289.GC−MS (EI, *m/z*): $[M]^+$ 227.2.



2q

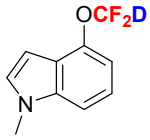
3-(Difluoromethoxy-d$_1$)-N,N-dimethylbenzenamine. (**2q**, 102.9 mg, yield 55 %, 98.8 atom % D): Using PE:DCM = 20:1 as eluent (Rf = 0.18, PE:DCM = 10:1). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.20−7.16 (m, 1H), 6.55−6.52 (m, 1H), 6.44−6.42 (m, 2H), ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -80.6 (t, J = 11.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 152.7 (t, $J_{C\text{-}F}$ = 2.4Hz）, 151.9, 130.0 (CH), 116.1 (tt, $J_{C\text{-}D}$ = 33.4 Hz, $J_{C\text{-}F}$ = 254.9 Hz), 109.4 (CH), 106.2 (CH), 103.3 (CH), 40.3 (CH_3). HRMS (EI-Orbitrap) m/z: Calcd for $C_9H_{10}DF_2NO$. $[M]^+$：188.08715; Found: 188.08652. GC−MS (EI, *m/z*): $[M]^+$ 188.1.



2r

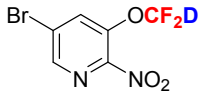
5-(Difluoromethoxy-d$_1$)benzo[b]thiophene. (**2r,** 160.8 mg, yield 80 %, 99.0 atom % D): Using PE as eluent (Rf = 0.38, PE). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.81 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 5.4 Hz, 1H), 7.28 (dd, J =0.4 Hz, 5.5 Hz, 1H), 7.14 (dd, J = 2.1 Hz, 6.4 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.1 (t, J = 11.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$,

ppm): δ = 148.6 (t, $J_{C\text{-}F}$ = 2.6 Hz), 140.5, 136.8, 128.7 (CH), 123.7 (CH), 123.6 (CH), 117.4 (CH), 116.0 (tt, $J_{C\text{-}D}$ = 33.9 Hz, $J_{C\text{-}F}$ = 256.7 Hz), 114.0 (CH). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_9H_5DF_2OS$ $[M]^+$: 201.01702; Found: 201.01646. GC−MS (EI, *m/z*): $[M]^+$ 201.0.



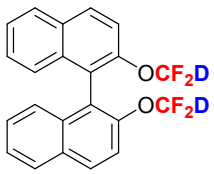
2s

4-(Difluoromethoxy-d$_1$)-1-methyl-1H-indole. (**2s**, 150.6 mg, yield 76 %, 99.0 atom % D): Using PE:DCM =20:1 as eluent (Rf = 0.26, PE:DCM = 10:1). Colorless oil**;** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.17−7.11 (m, 2H), 7.01 (d, J = 3.2 Hz, 1H), 6.82−6.81 (m, 1H), 6.57 (d, J = 3.1 Hz, 1H), 3.75 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -80.3 (t, J = 11.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 144.6 (t, $J_{C\text{-}F}$ = 2.7 Hz）, 138.7, 129.1 (CH), 121.9 (CH), 121.1, 116.5 (tt, $J_{C\text{-}D}$ = 33.5 Hz, $J_{C\text{-}F}$ = 255.2 Hz), 108.6 (CH), 107.0 (CH), 97.9 (CH), 33.1 (CH_3). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{10}H_8DF_2NO$ $[M]^+$：198.07150; Found: 198.07106. GC−MS (EI, *m/z*): $[M]^+$ 198.1.



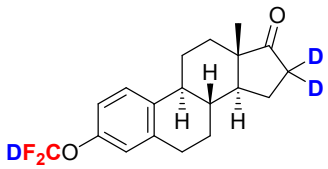
2t

5-Bromo-3-(difluoromethoxy-d$_1$)-2-nitropyridine. (**2t**, 244.8 mg, yield 90 %, 99.0 atom % D): Using PE:DCM as eluent (Rf = 0.67, PE:DCM = 1:2). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.48 (d, J = 1.8 Hz, 1H), 8.05−8.04 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -83.4 (t, J = 10.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 149.6, 146.2 (CH), 138.6, 135.3 (CH), 124.7 (d, J = 9.7 Hz), 114.78 (tt, $J_{C\text{-}D}$ = 35.0 Hz, $J_{C\text{-}F}$ = 267.6 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_6H_2DBrF_2N_2O_3$ $[M]^+$：268.93579; Found: 268.93527.



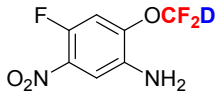
2u

2-(Difluoromethoxy-d$_1$)-1-(2-(difluoromethoxy-d$_1$)naphthalen-1-yl)naphthalene. Using PE:DCM = 20:1 as eluent (Rf = 0.67, PE:DCM = 1:2). White foam; (**2u**, 116.5 mg, yield 30 %, 99.0 atom % D) ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 8.02 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 8.2 Hz 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.48−7.44 (m, 2H), 7.32−7.28 (m, 2H), 7.13 (d, J = 8.5 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -79.2 (dt, J = 11.3 Hz, 165.7 Hz), -81.2 (dt, J = 11.0 Hz, 165.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 146.9, 133.5, 131.4, 130.6 (CH), 128.2 (CH), 127.3 (CH), 125.8 (CH), 123.0, 119.3 (CH), 116.1 (tt, $J_{C\text{-}D}$ = 34.2 Hz, $J_{C\text{-}F}$ = 257.1 Hz). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{22}H_{12}D_2F_4O_2$ $[M]^+$：388.10555; Found: 388.10496. GC−MS (EI, *m/z*): $[M]^+$ 388.1.



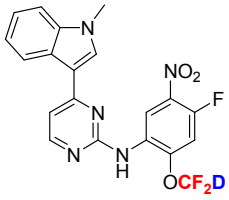
2v

((8R,9S,13S,14S)-16,16-D,D-3-(difluoromethoxy-d_1)-7,8,9,11,12,13,15,16-octahydro-13-methyl-6H-cyclopenta[a]phenanthren-17(14H)-one. (**2v**, 193.9 mg, yield 60%, 99.0 atom % D): Using PE:DCM = 5:1 as eluent (Rf = 0.28, PE:DCM = 1:2). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 7.26 (d, J = 8.5 Hz, 1H), 6.90 (dd, J = 2.4 Hz, 8.5 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 2.93−2.90 (m, 2H), 2.48−2.24 (m, 2H), 2.07−1.95 (m, 3H), 1.70−1.42 (m, 6H), 0.91 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ = -81.1 (t, J = 11.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 220.7, 149.2 (t, $J_{C\text{-}F}$ = 2.7 Hz), 138.5, 137.0, 126.7 (CH), 119.7 (CH), 116.8 (CH), 115.8 (tt, $J_{C\text{-}D}$ = 33.6 Hz, $J_{C\text{-}F}$ = 256.2 Hz), 50.4 (CH), 47.9, 44.0 (CH), 38.1 (CH), 35.4−35.0 (CD_2) (m), 31.5 (CH_2), 29.4 (CH_2), 26.3 (CH_2), 25.8(CH_2), 21.4 (CH_2), 13.8 (CH_3). HRMS (EI-Orbitrap) *m/z*: Calcd for $C_{19}H_{19}D_3F_2O_2$ $[M]^+$: 323.17762; Found: 323.17694. GC−MS (EI, *m/z*): $[M]^+$ 323.2.



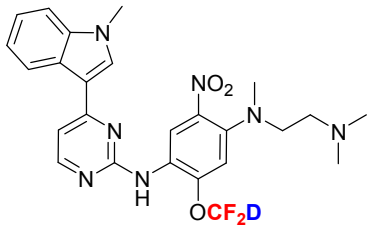
3l

2-(Difluoromethoxy-d_1)-4-fluoro-5-nitrobenzenamine (3l). Using PE:DCM = 4:1 as eluent (Rf = 0.31, PE:DCM = 2:1). Mp. 59−61 °C. Orange solid; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 7.49 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 5.59 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ = 145.8 (d, J = 250.6 Hz), 141.1−141.0 (m), 136.8 (d, J = 1.9 Hz), 133.2 (d, J = 7.4 Hz), 115.6 (tt, $J_{C\text{-}D}$ = 34.9 Hz, $J_{C\text{-}F}$ = 257.9 Hz), 109.7, 107.7 (d, J = 25.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6, ppm): δ = -80.1 (t, J = 10.9 Hz), -132.2 (s). HRMS (ESI−TOF), *m/z*: calcd for $C_7H_5DF_3N_2O_3$ $[M + H]^+$, 224.0393; found, 224.0388.



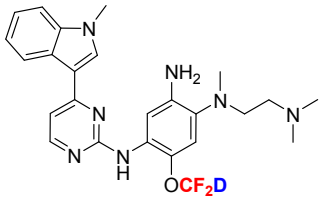
DFA-1

N-(2-(difluoromethoxy-d_1)-4-fluoro-5-nitrophenyl)-4-(1-methyl-1H-indol-3-yl)pyrimidin-2-amine (DFA-1). (Rf = 0.71, MeOH:DCM = 1:10). Mp. 181−183 °C. Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 9.07 (d, J = 8.3 Hz, 1H), 8.7 (s, 1H), 8.36−8.29 (m, 3H), 7.54 (dd, J = 26.3 Hz, 11.9 Hz, 2H), 7.30−7.23 (m, 2H), 7.14 (t, 6.85 (d, J = *7.4* Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ = 162.1, 159.3, 157.1, 150.2 (J = 258.6 Hz), 144.3−146.2 (m), 137.6, 133.2, 132.5 (d, J = 7.2 Hz), 127.8 (d, J = 3.0 Hz), 125.3, 122.2, 121.7, 120.9, 119.1, 112.1, 110.4, 108.4, 107.5 (d, J = 25.4 Hz), 33.0 (d, J = 5.3 Hz). HRMS (ESI−TOF), *m/z*: calcd for $C_{20}H_{14}DF_3N_5O_3$ $[M + H]^+$, 431.1190; found, 431.1193.



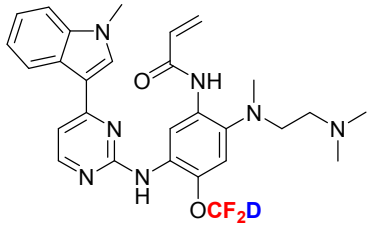
DFA-2

2-(difluoromethoxy-d_1)-N^4-(2-(dimethylamino)ethyl)-N^4-methyl-N^1-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)-5-nitrobenzene-1,4-diamine (DFA-2). (Rf = 0.42, MeOH:DCM = 1:10). Mp. 133−135°C. Orange solid; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 8.56 (s,1H), 8.40 (s,1H), 8.33−8.29 (m, 3H), 7.51 (d, J = 8.2 Hz, 1H), 7.26−7.21 (m, 2H), 7.11−7.07(m, 1H), 3.87 (s, 1H), 3.26 (t, J = 6.9 Hz, 2H), 2.84 (s, 1H), 2.46 (t, J = 6.8 Hz, 2H), 2.15 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ = 162.2, 160.3, 157.1, 147.4, 142.4, 137.6, 136.1, 133.0, 125.5, 122.8, 122.3, 122.2, 122.0, 120.7, 112.2, 110.3, 109.4, 107.4, 56.2, 52.5, 45.4 (d, J = 17.6 Hz), 33.0 (d, J = 5.4 Hz). HRMS (ESI−TOF), *m/z*: calcd for $C_{25}H_{27}DF_2N_7O_3$ [M + H]$^+$, 513.2284; found, 513.2287.



DFA-3

5-(difluoromethoxy-d_1)-N^1-(2-(dimethylamino)ethyl)-N^1-methyl-N^4-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-yl)benzene-1,2,4-triamine (DFA-3). (Rf = 0.35, MeOH:DCM = 1:10). Mp. 68−70 °C. Brown solid; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 8.33 (d, J = 7.9 Hz, 1H), 8.27−8.20 (m, 3H), 7.51 (d, J = 8.2 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.13−7.08 (m, 3H), 6.85 (s, 1H), 3.86 (s, 3H), 2.89 (t, J = 6.3 Hz, 2H), 2.63 (s, 1H), 2.44 (t, J = 6.2 Hz, 2H), 2.22 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ = 162.1, 160.9, 156.9, 141.2, 137.5, 134.7, 134.2, 132.7, 127.8, 125.5, 122.3, 122.1, 120.7, 113.0, 112.3, 110.8, 110.2, 106.7, 57.0, 53.4, 45.5, 41.0, 33.0 (d, J = 3.0 Hz). HRMS (ESI−TOF), *m/z*: calcd for $C_{25}H_{29}DF_2N_7O$ [M+H]$^+$, 483.2543; found, 483.2544.



DFA

N-(5-(4-(1-methyl-1H-indol-3-yl)pyrimidin-2-ylamino)-2-(N-(2-(dimethylamino)ethyl)-N-methylamino)-4-(difluoromethoxy-d_1)phenyl)acrylamide (DFA). (Rf = 0.48, MeOH:DCM = 1:10). Mp. 82−84 °C. Offwhite solid; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 10.3 (s，1H), 8.95 (s, 1H), 8.49 (s, 1H), 8.36−8.23 (m, 3H), 7.51 (d, J = 7.6 Hz, 1H), 7.22−7.09 (m, 4H), 6.49−6.42 (m, 1H), 6.28 (d, J = 16.5 Hz, 1H), 5.80 (d, J = 9.5 Hz, 1H), 3.88 (s, 1H), 2.88 (brs, 2H), 2.71 (s, 1H), 2.36 (s, 2H), 2.22 (s, 6H). ^{13}C NMR (100 MHz, DMSO-

d_6, ppm): δ = 162.9, 161.9, 160.2, 157.4, 138.9 (d, J = 8.34 Hz), 137.6, 133.4, 131.9, 128.0, 126.9 (d, J = 2.6 Hz), 125.4, 122.0, 121.7, 120.7, 116.5, 113.6, 112.3, 110.4, 107.2, 56.7, 55.7, 45.2, 42.0, 33.0 (d, J = 3.0 Hz). HRMS (ESI−TOF), *m/z*: calcd for $C_{28}H_{31}DF_2N_7O_2$ $[M+H]^+$, 537.2648; found, 537.2650.

4. ^{1}H, ^{13}C and ^{19}F NMR spectra for difluorodeuteromethyl aryl ethers

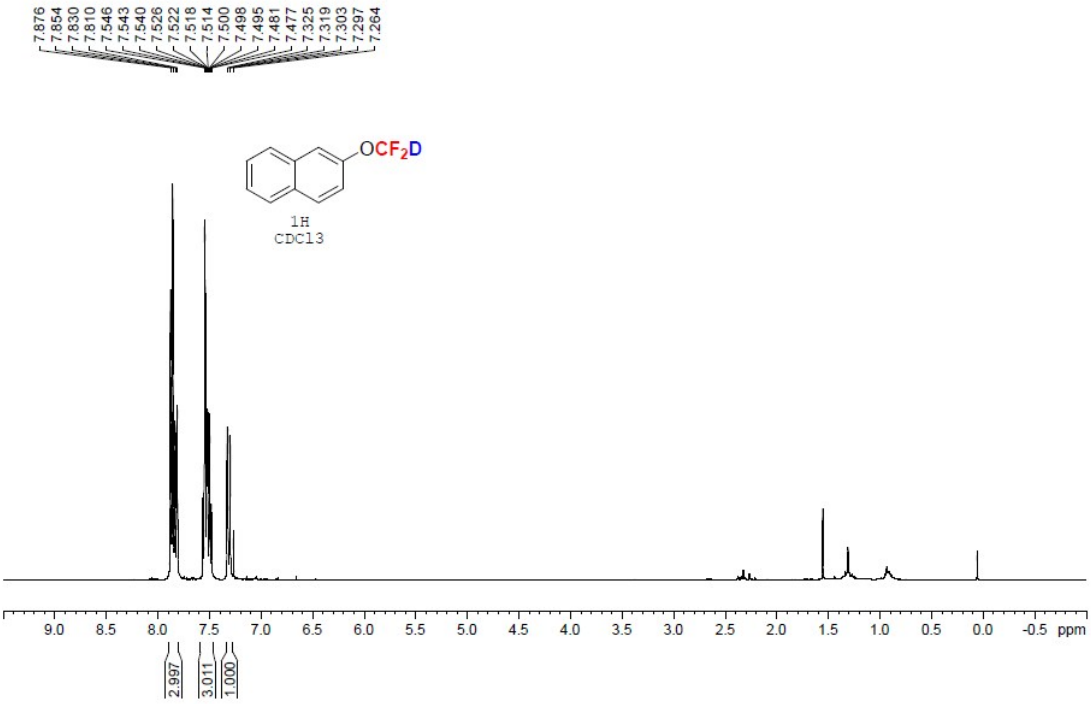


Figure S1 ^{1}H NMR of compound **2a** ($CDCl_3$)

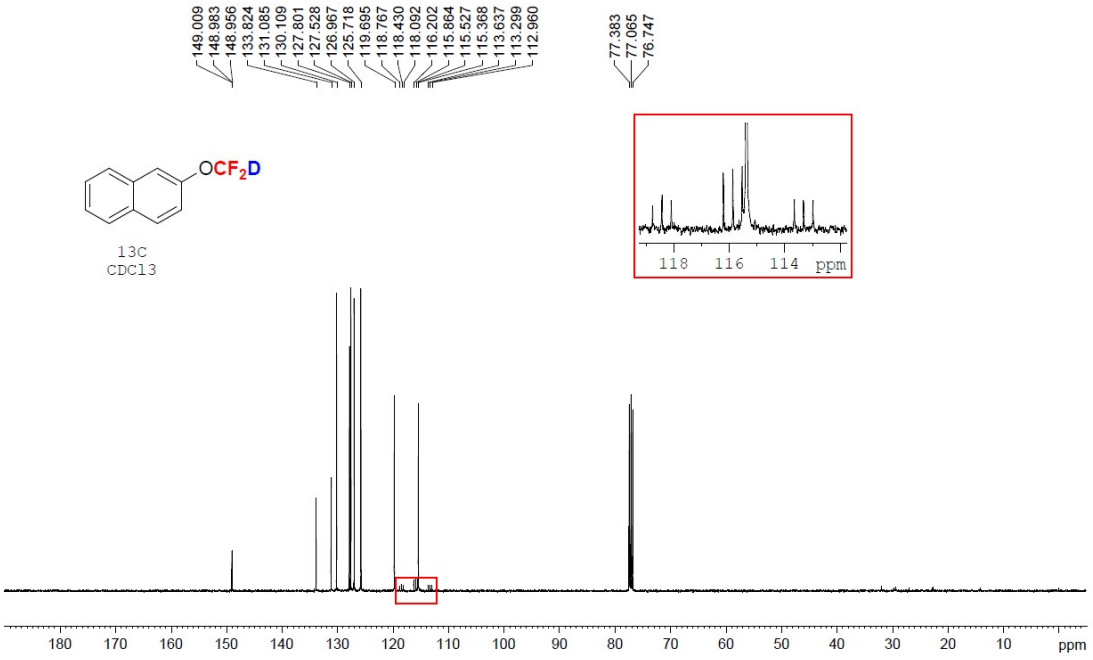


Figure S2 ^{13}C NMR of compound **2a** ($CDCl_3$)

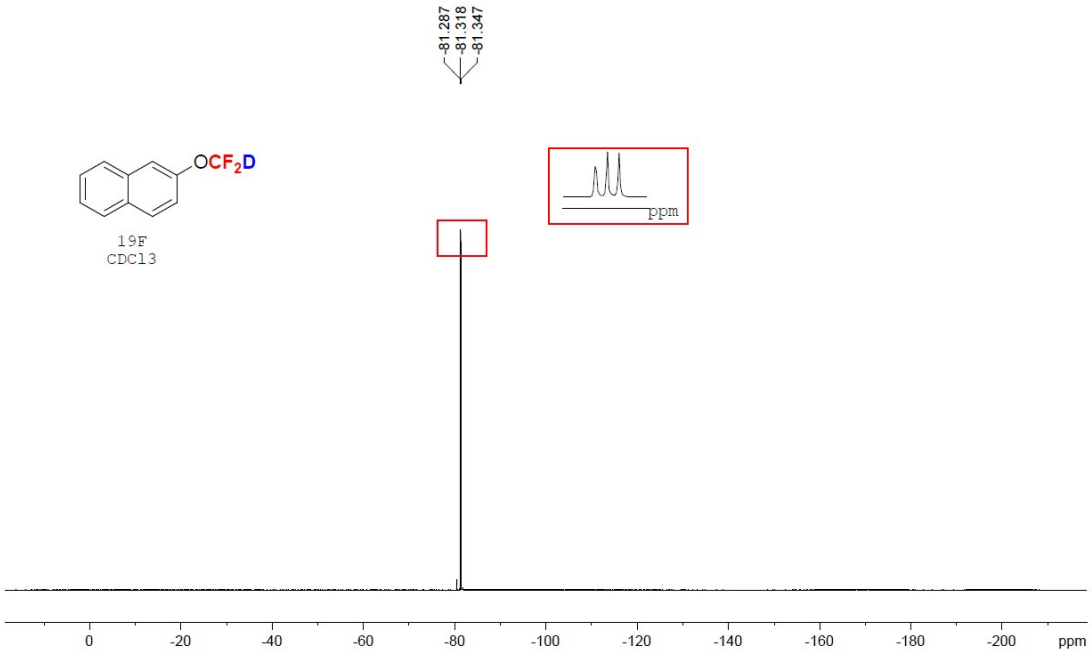


Figure S3 ^{19}F NMR of compound **2a** ($CDCl_3$)

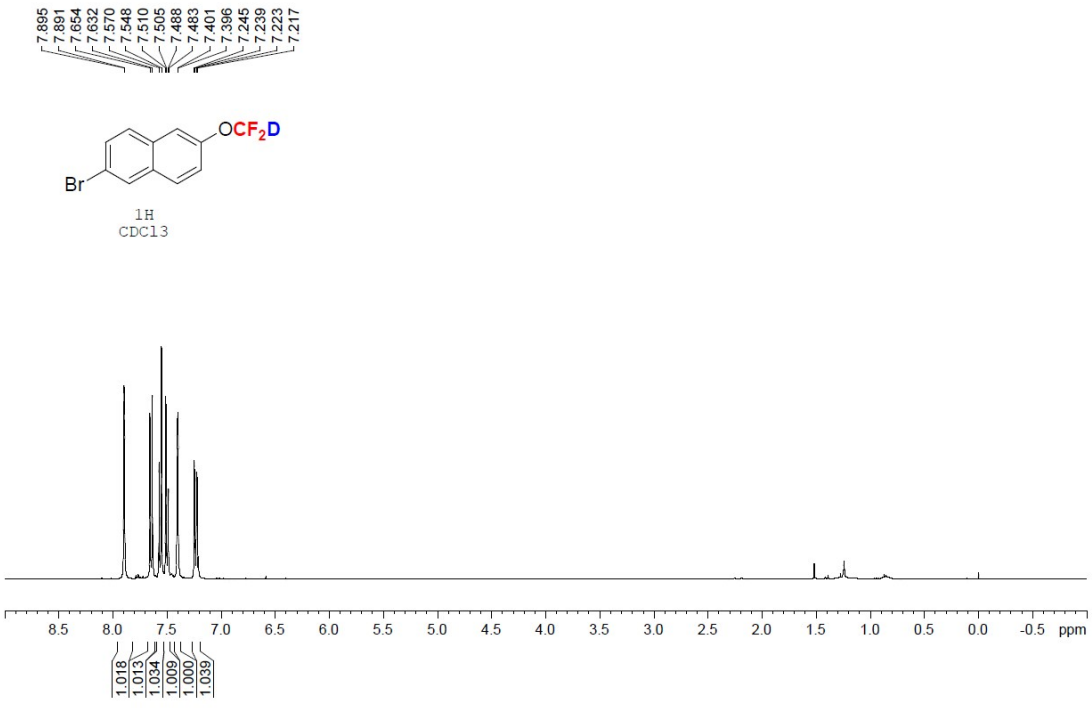


Figure S4 ^{1}H NMR of compound **2b** ($CDCl_3$)

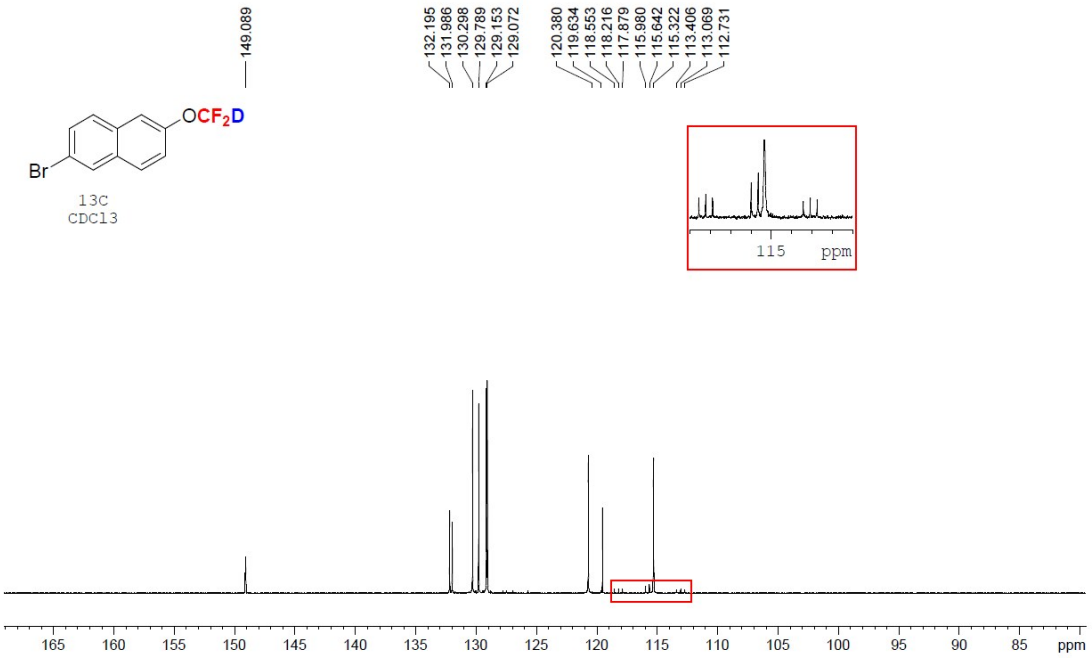


Figure S5 ^{13}C NMR of compound **2b** ($CDCl_3$)

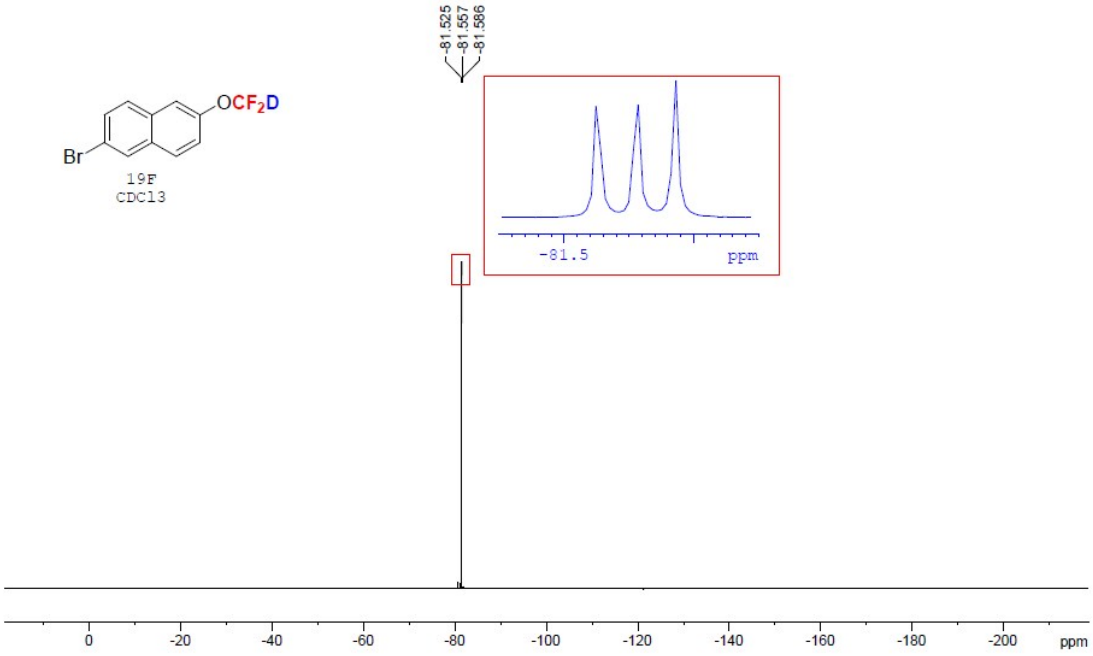


Figure S6 ^{19}F NMR of compound **2b** ($CDCl_3$)

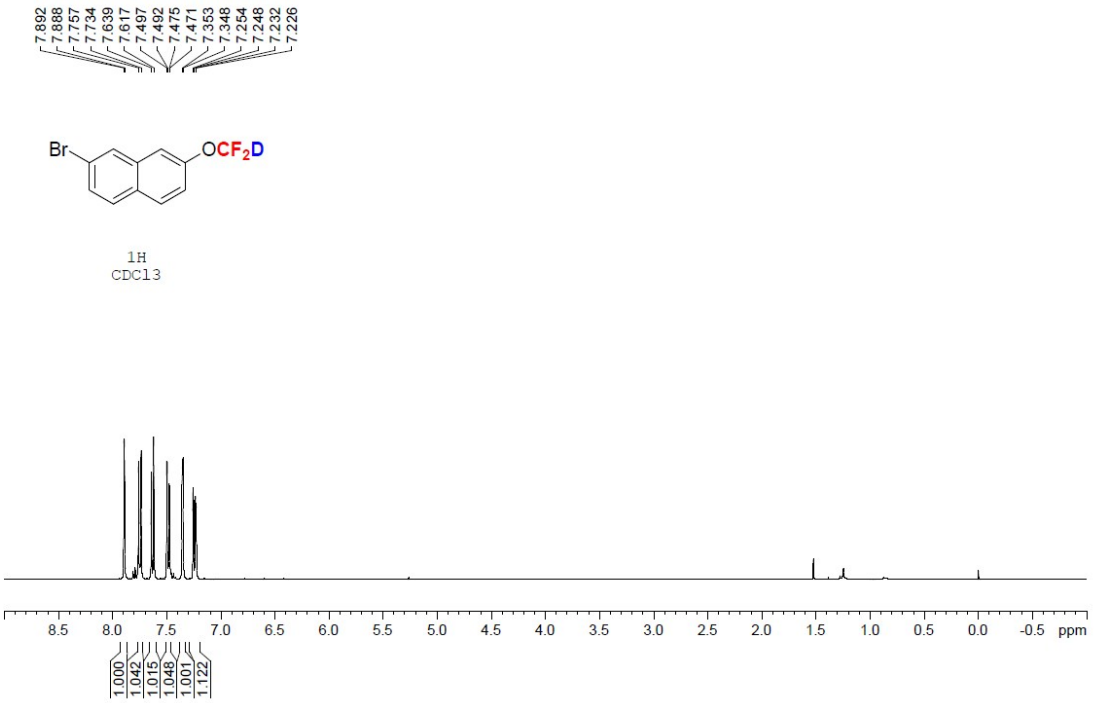


Figure S7 ^{1}H NMR of compound **2c** ($CDCl_3$)

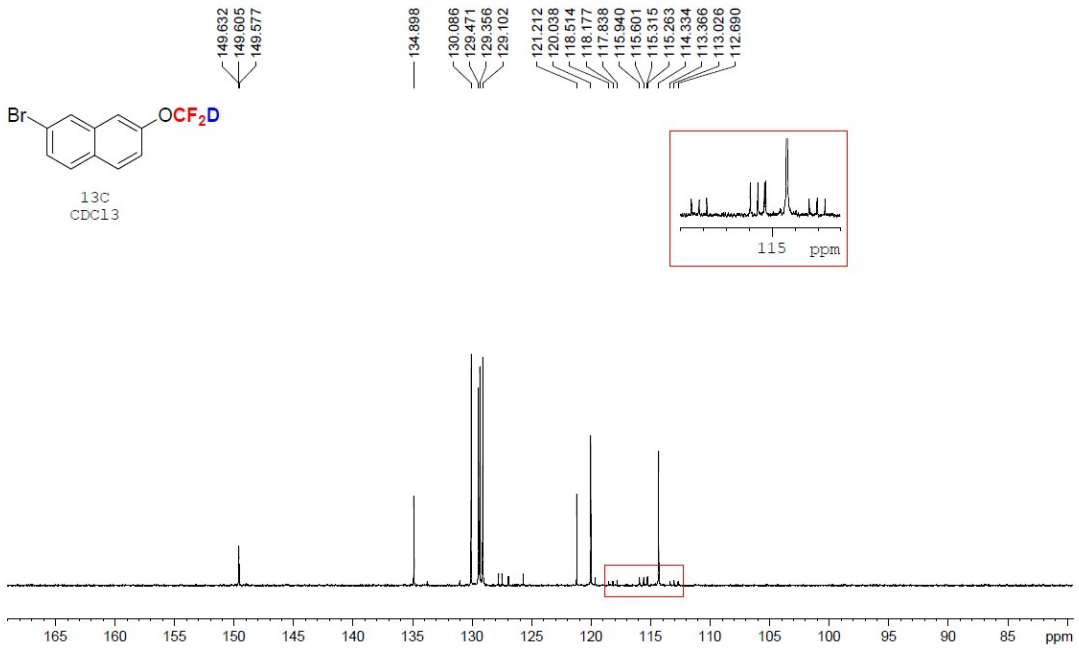


Figure S8 ^{13}C NMR of compound **2c** ($CDCl_3$)

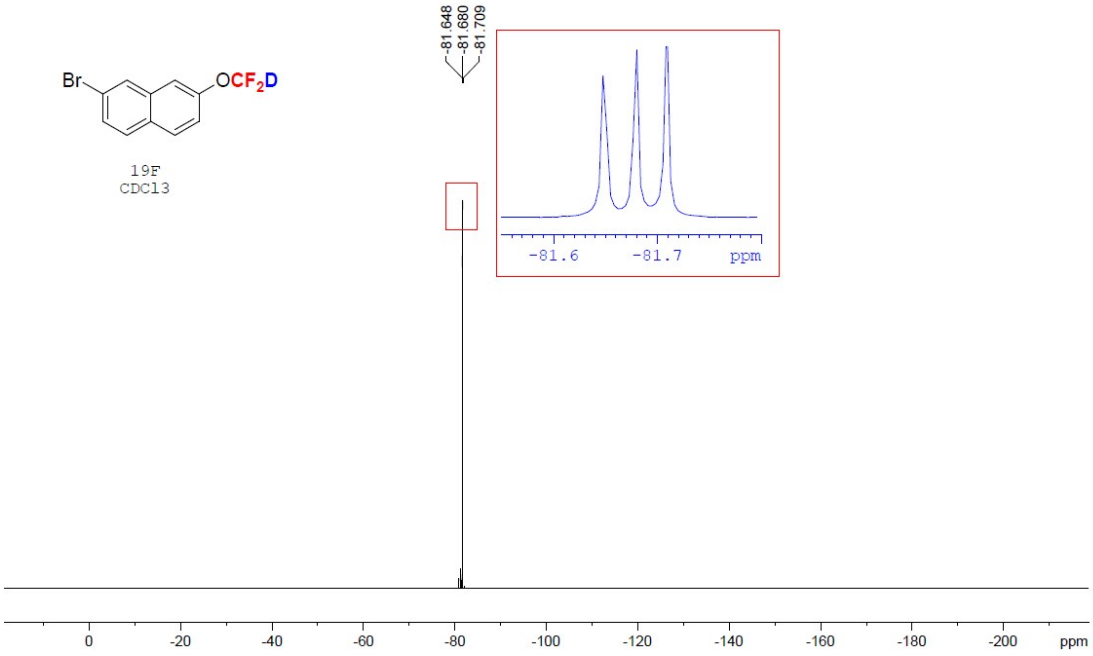


Figure S9 ^{19}F NMR of compound **2c** ($CDCl_3$)

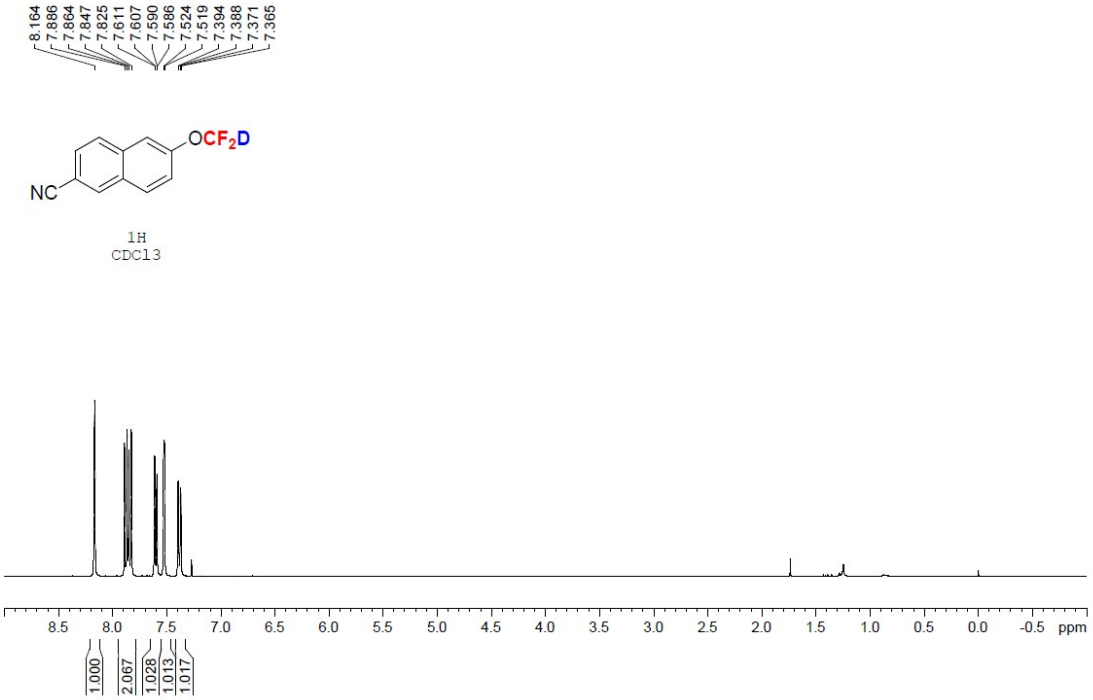


Figure S10 ^{1}H NMR of compound **2d** ($CDCl_3$)

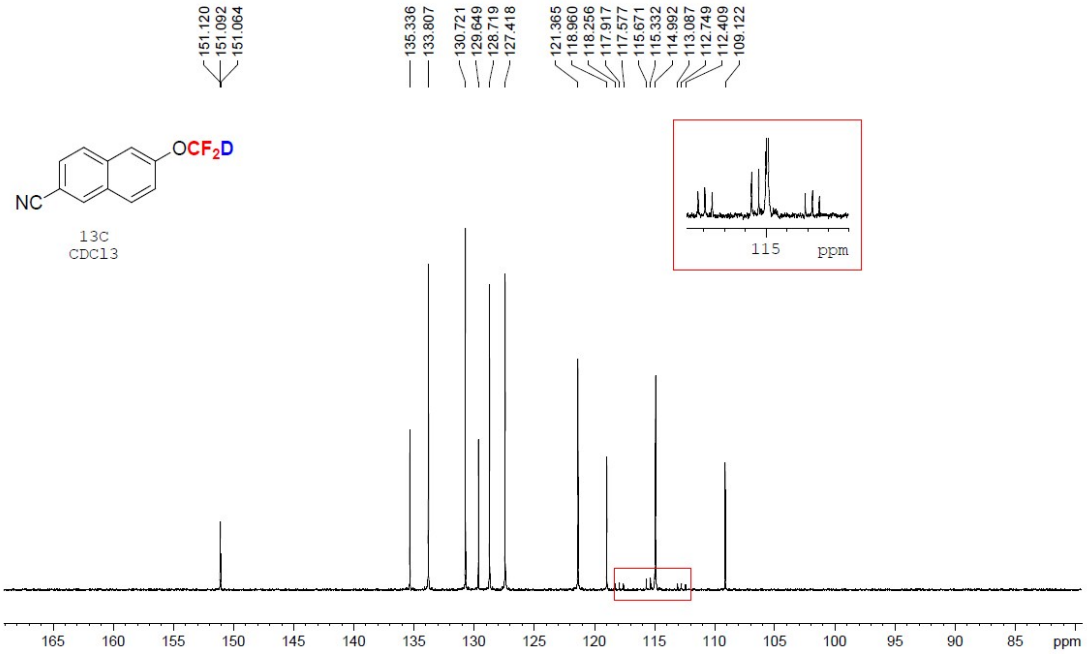


Figure S11 ^{13}C NMR of compound **2d** ($CDCl_3$)

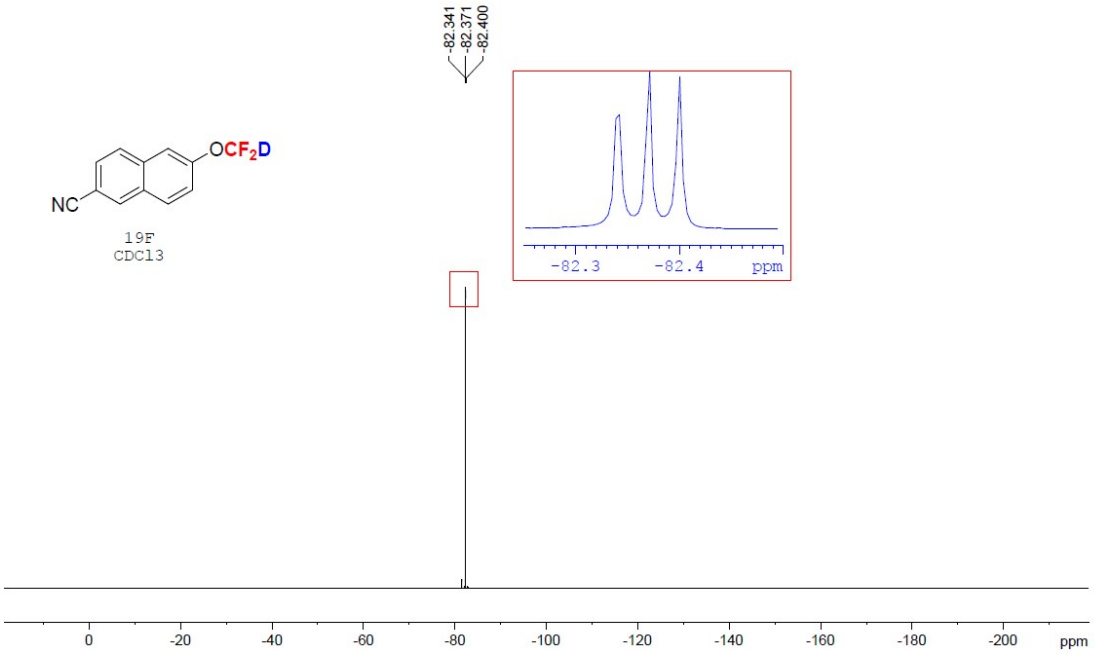


Figure S12 ^{19}F NMR of compound **2d** ($CDCl_3$)

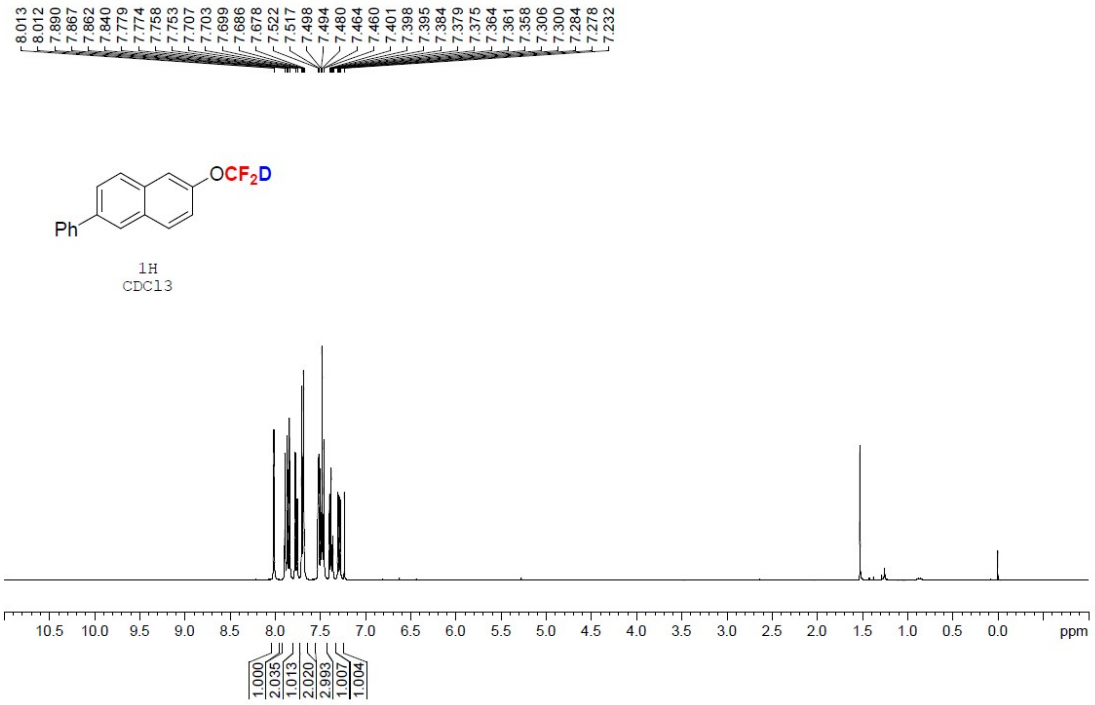


Figure S13 ^{1}H NMR of compound **2e** ($CDCl_3$)

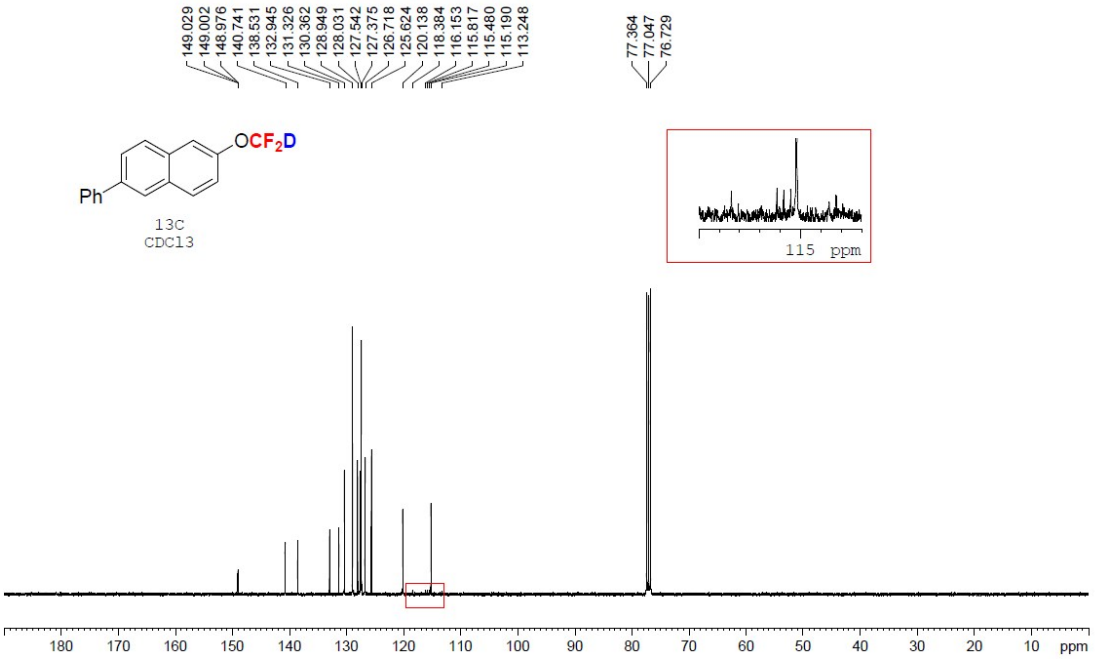


Figure S14 ^{13}C NMR of compound **2e** ($CDCl_3$)

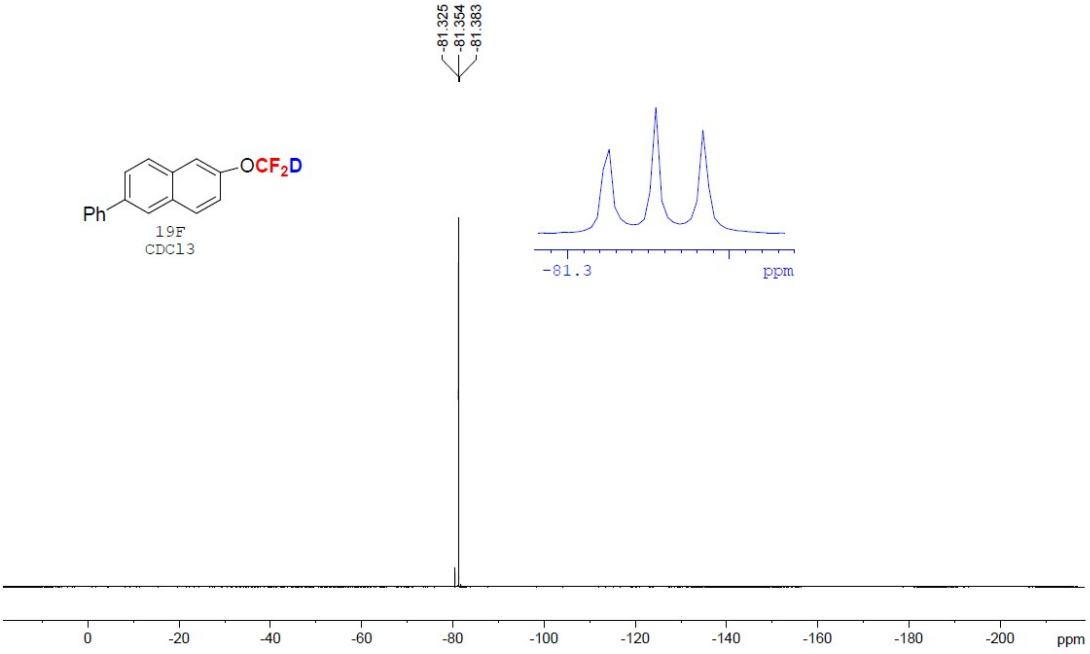


Figure S15 ^{19}F NMR of compound **2e** ($CDCl_3$)

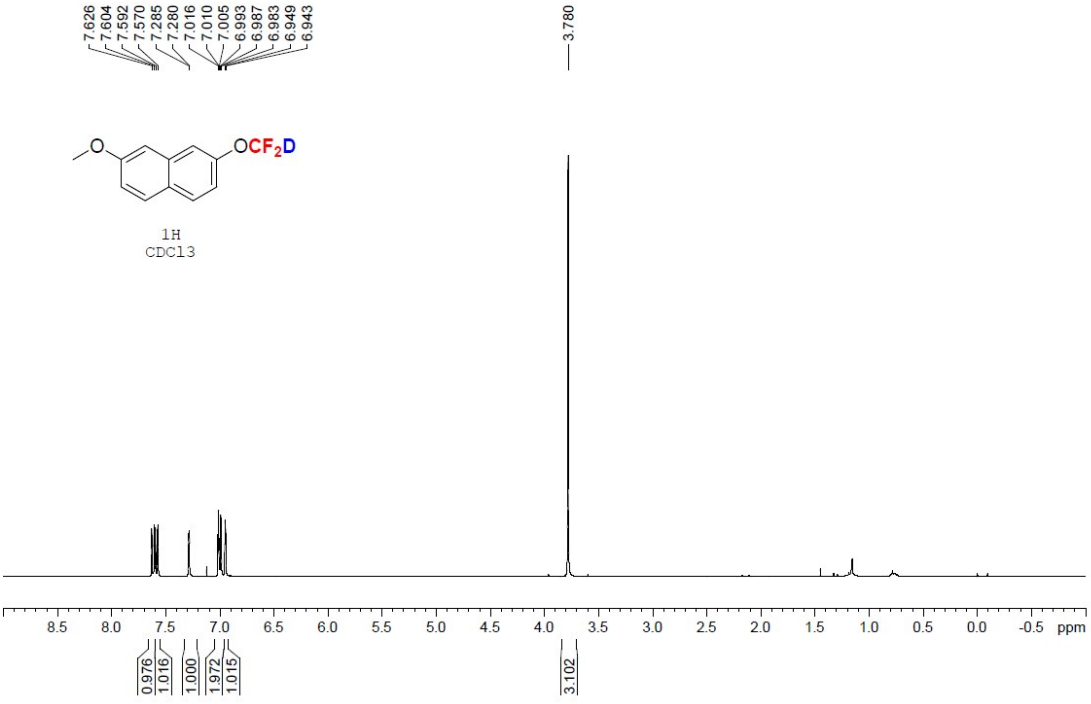


Figure S16 ^{1}H NMR of compound **2f** ($CDCl_3$)

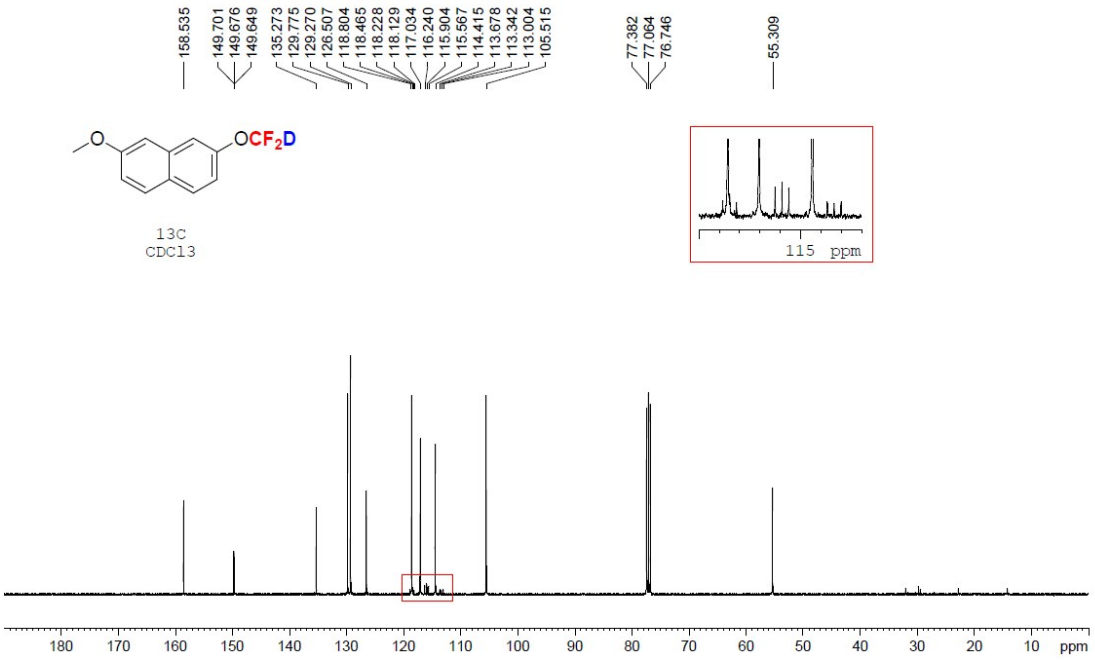


Figure S17 ^{13}C NMR of compound **2f** ($CDCl_3$)

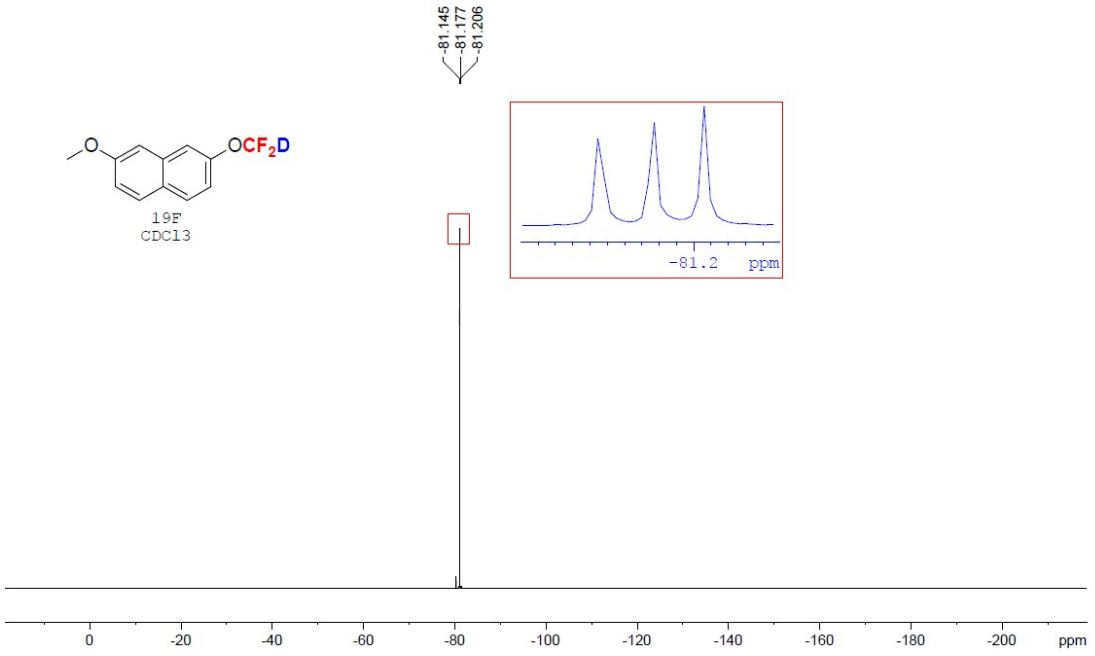


Figure S18 ^{19}F NMR of compound **2f** ($CDCl_3$)

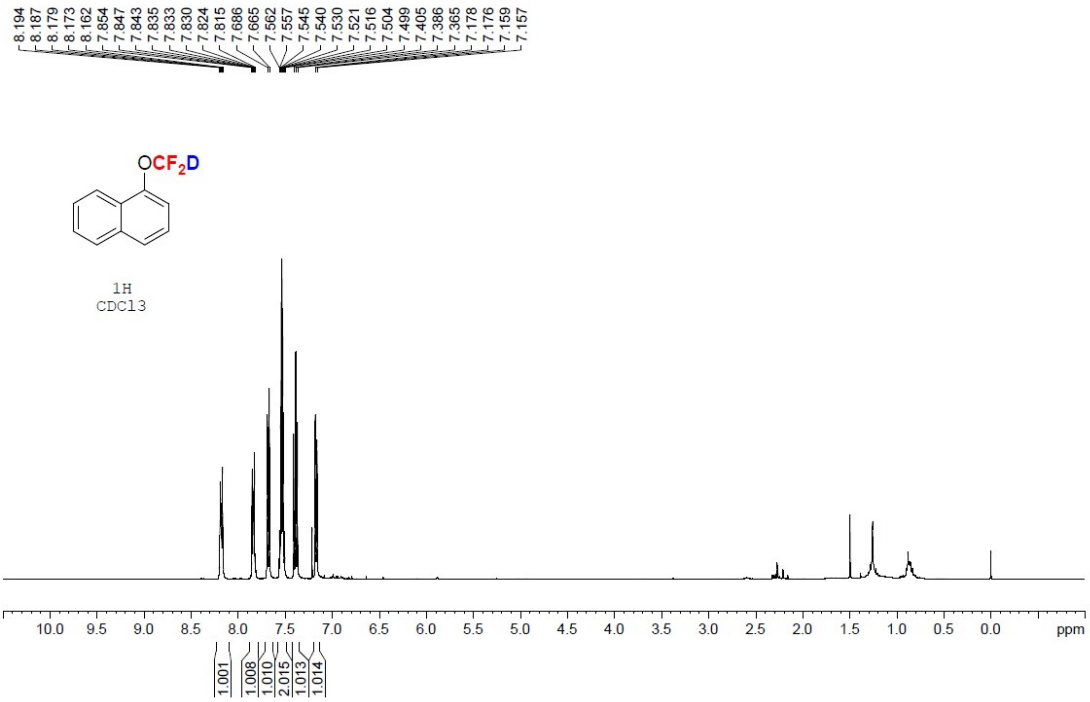


Figure 19 ^{1}H NMR of compound **2g** ($CDCl_3$)

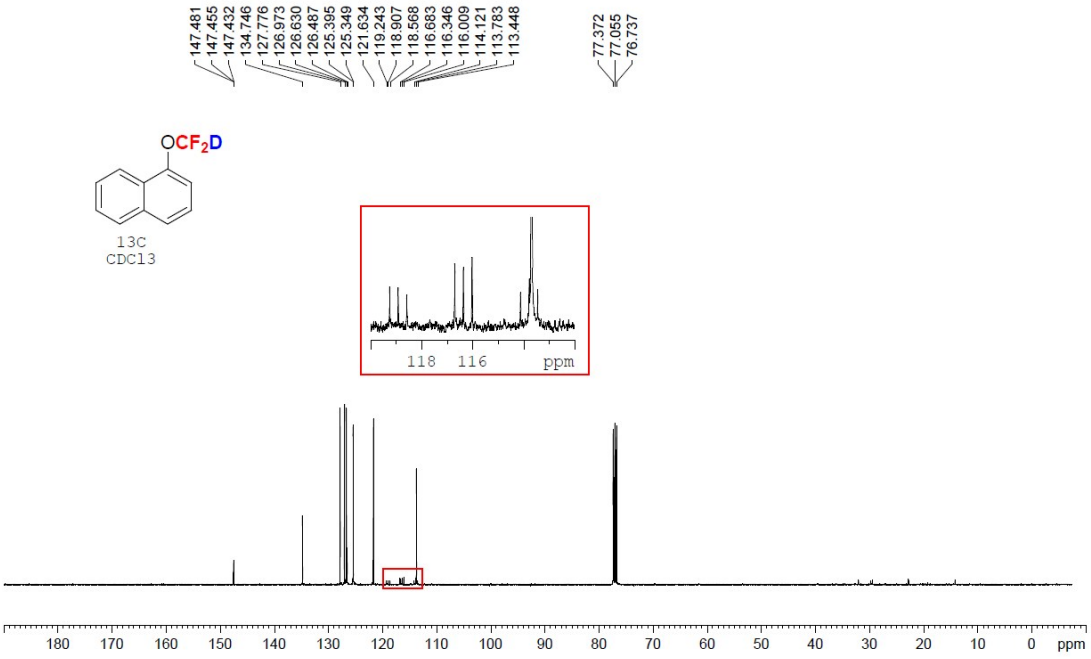


Figure 20 ^{13}C NMR of compound **2g** ($CDCl_3$)

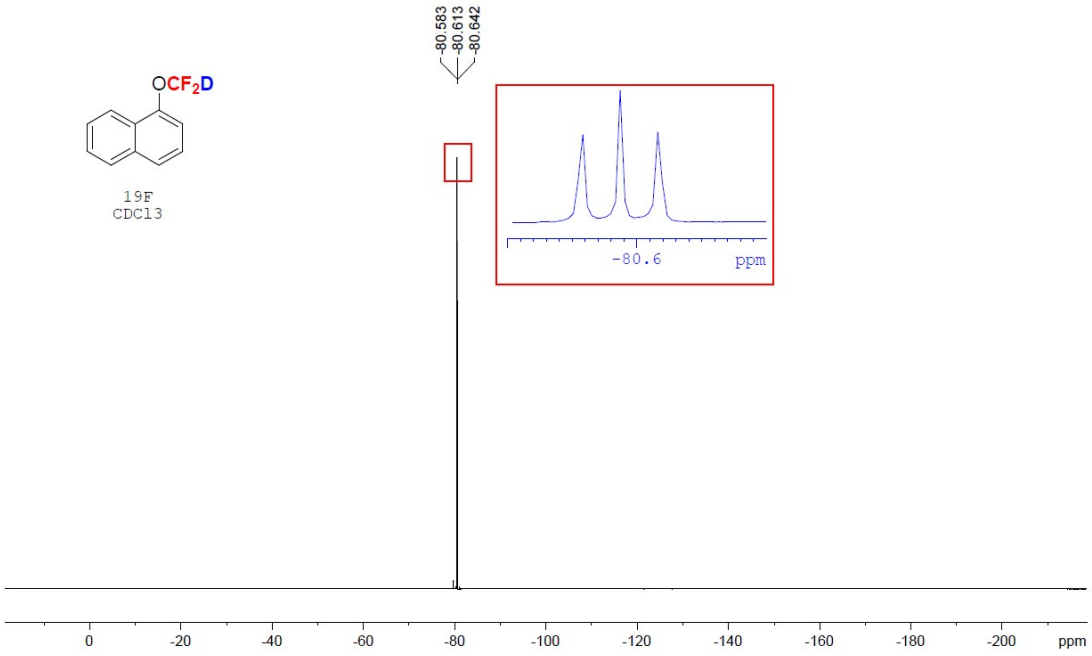


Figure 21 ^{19}F NMR of compound **2g** ($CDCl_3$)

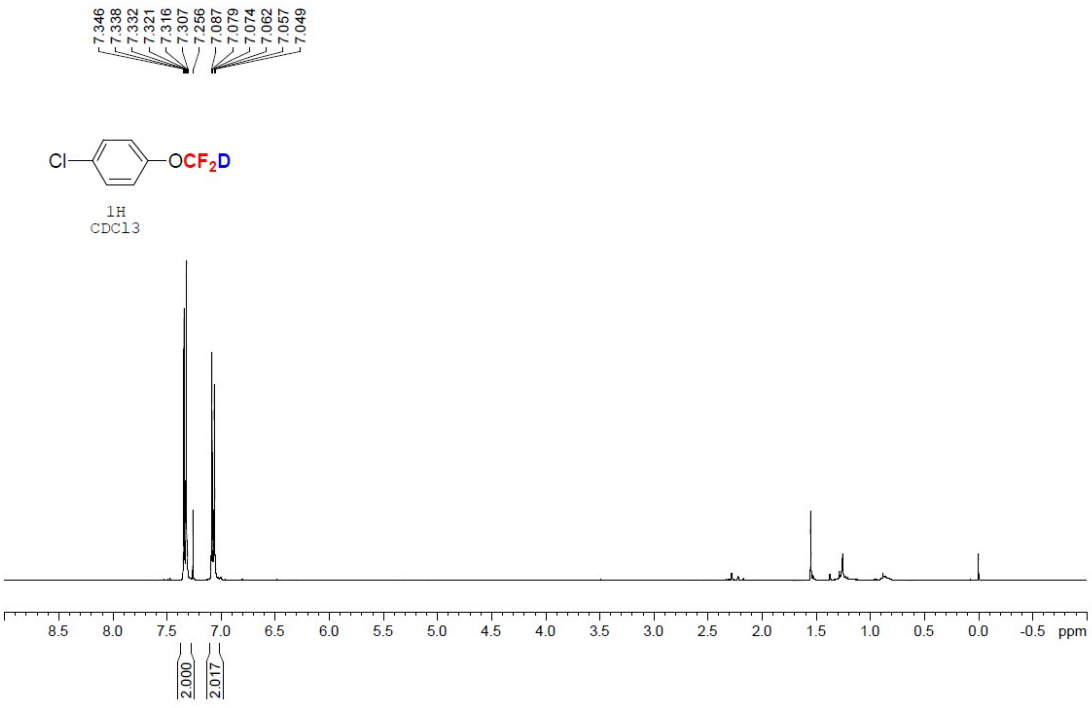


Figure S22 ^{1}H NMR of compound **2h** ($CDCl_3$)

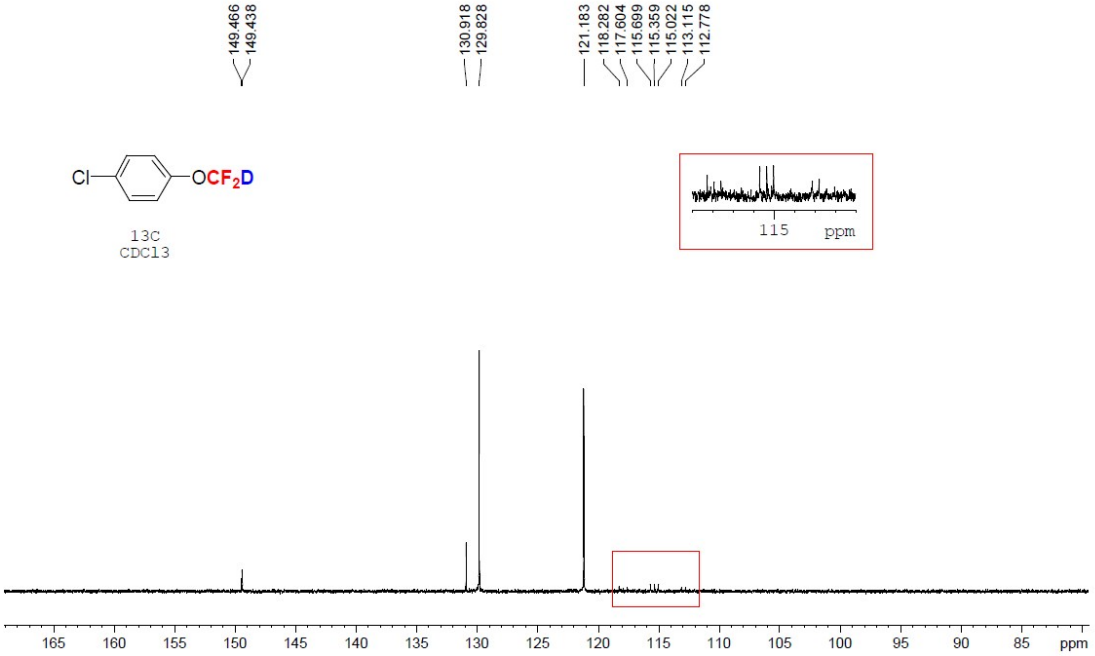


Figure S23 ^{13}C NMR of compound **2h** ($CDCl_3$)

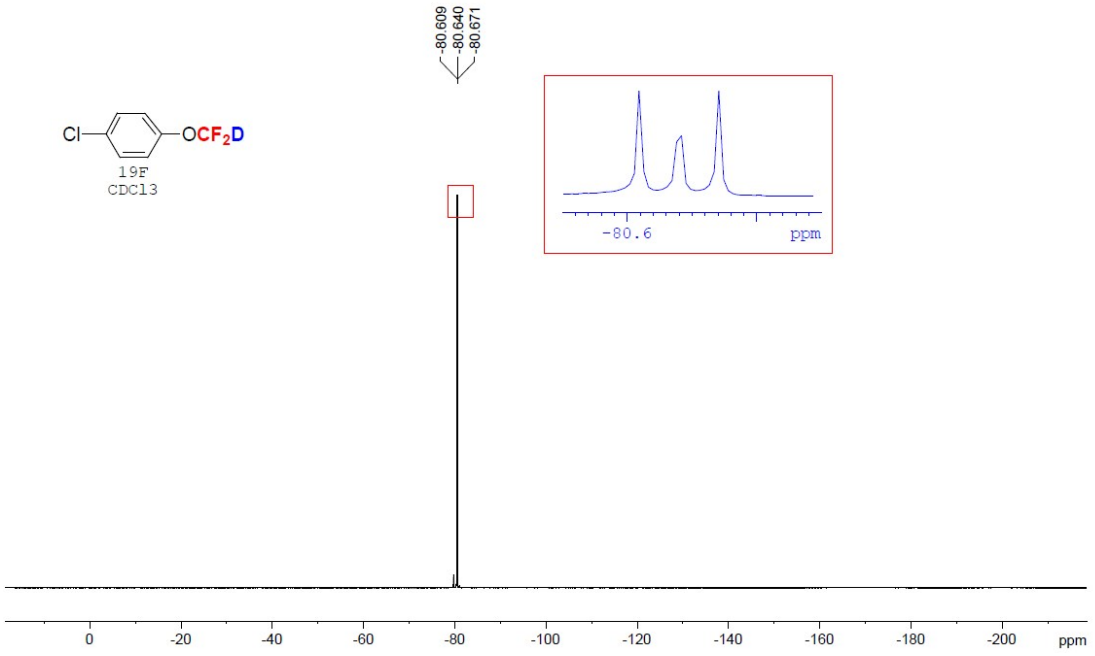


Figure S24 ^{19}F NMR of compound **2h** ($CDCl_3$)

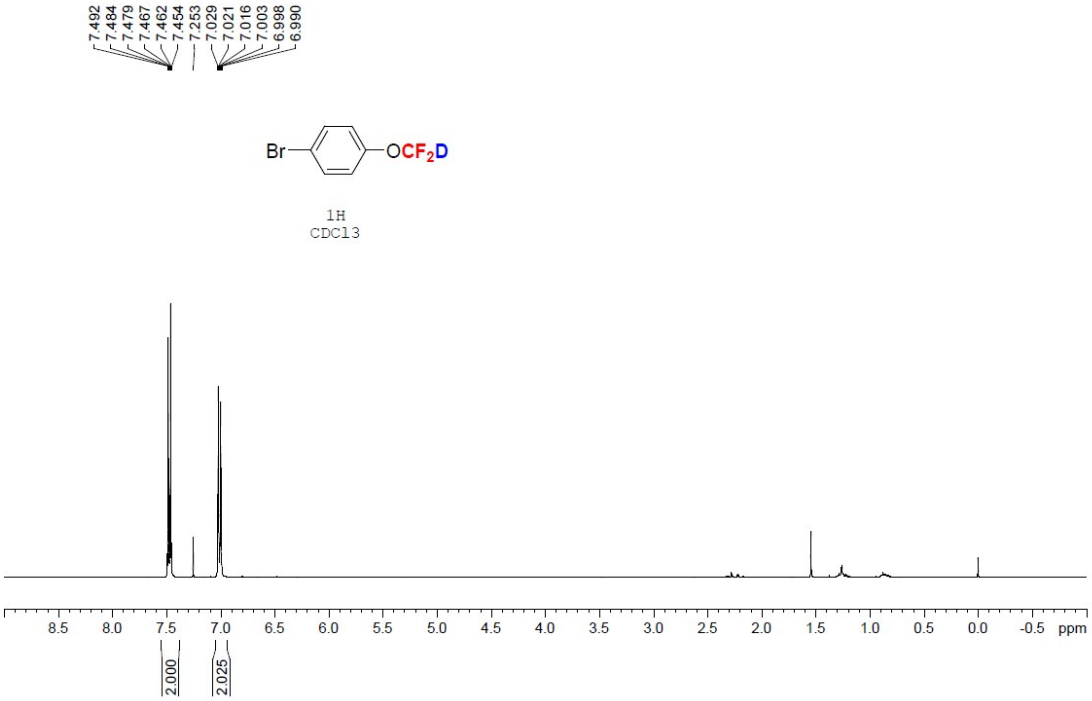


Figure S25 ^{1}H NMR of compound **2i** ($CDCl_3$)

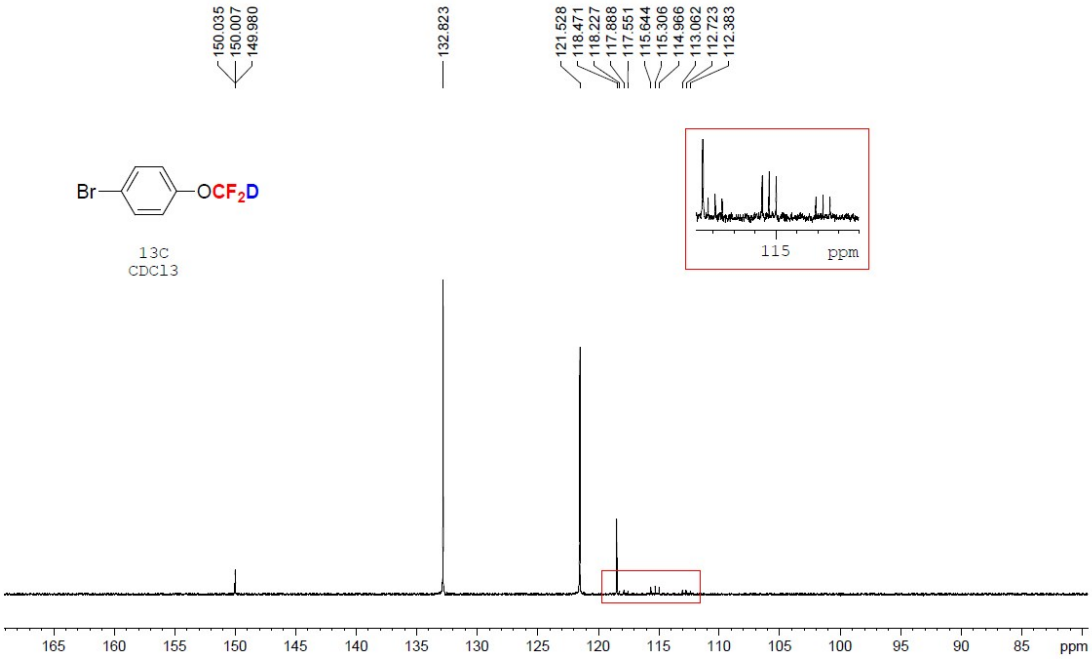


Figure S26 ^{13}C NMR of compound **2i** ($CDCl_3$)

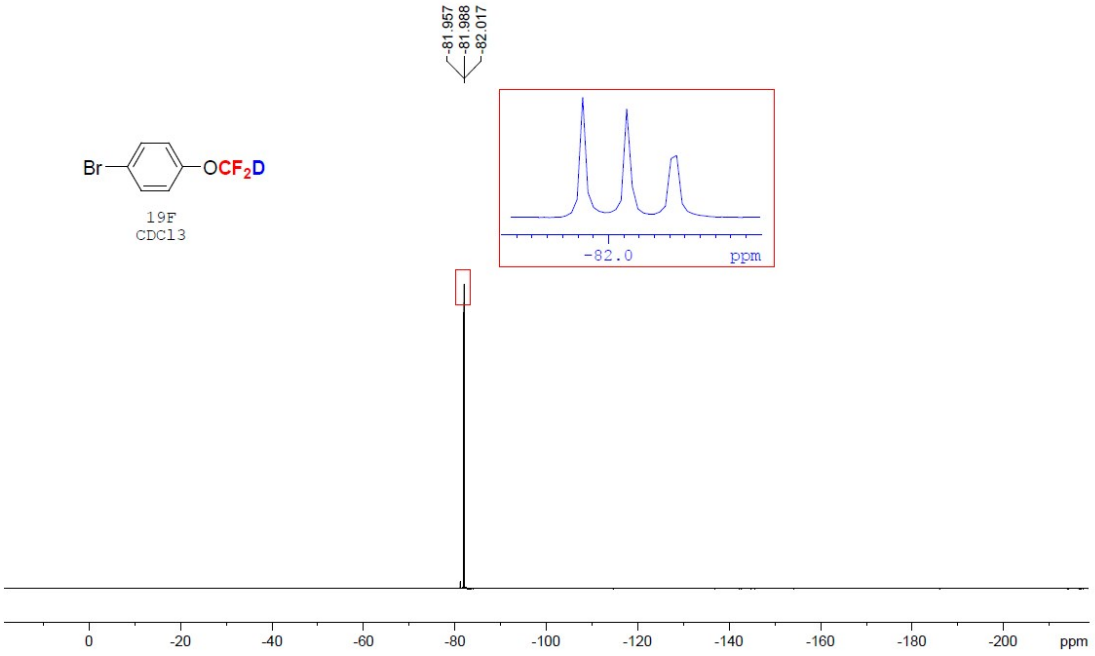


Figure S27 ^{19}F NMR of compound **2i** ($CDCl_3$).

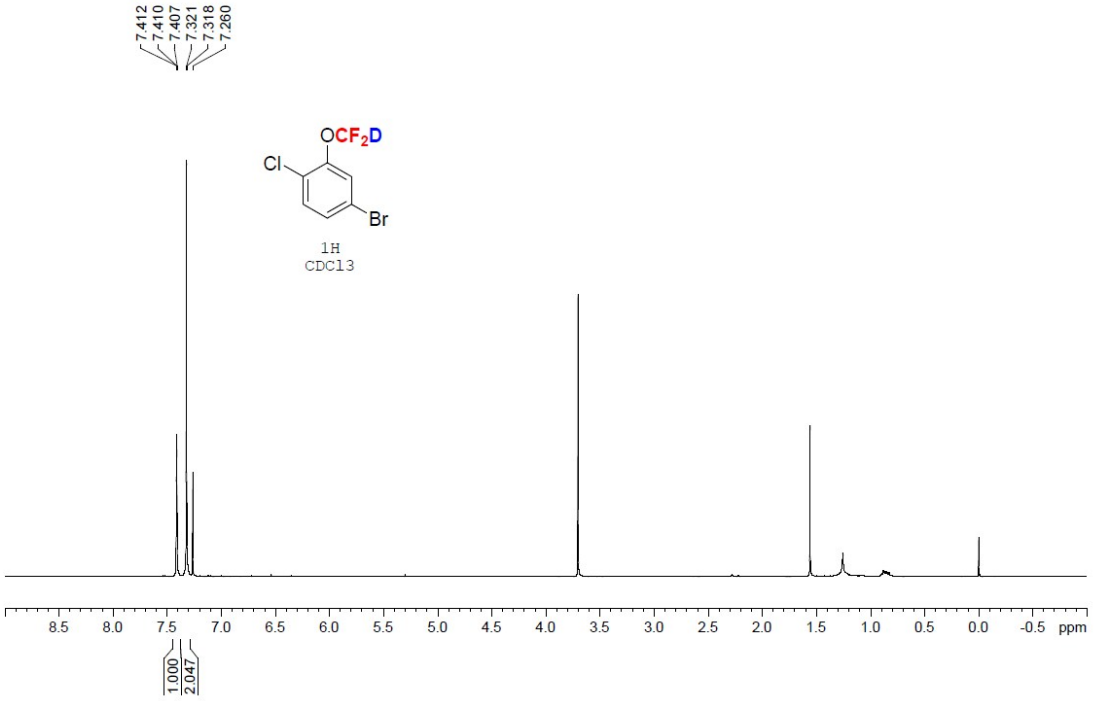


Figure S28 ^{1}H NMR of compound **2j** ($CDCl_3$)

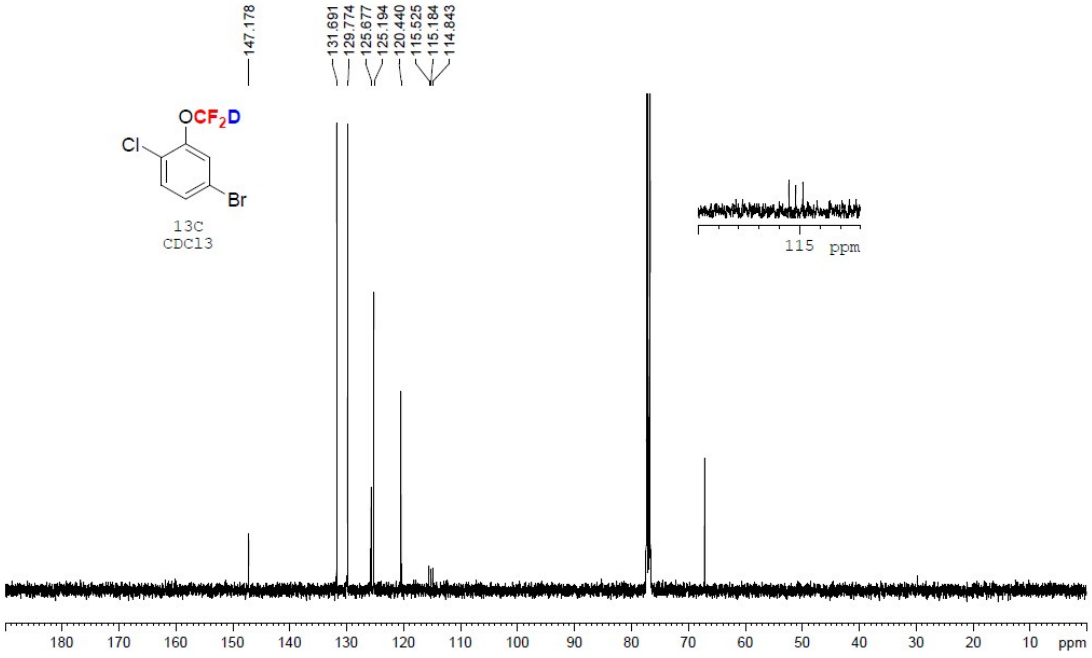


Figure S29 ^{13}C NMR of compound **2j** ($CDCl_3$)

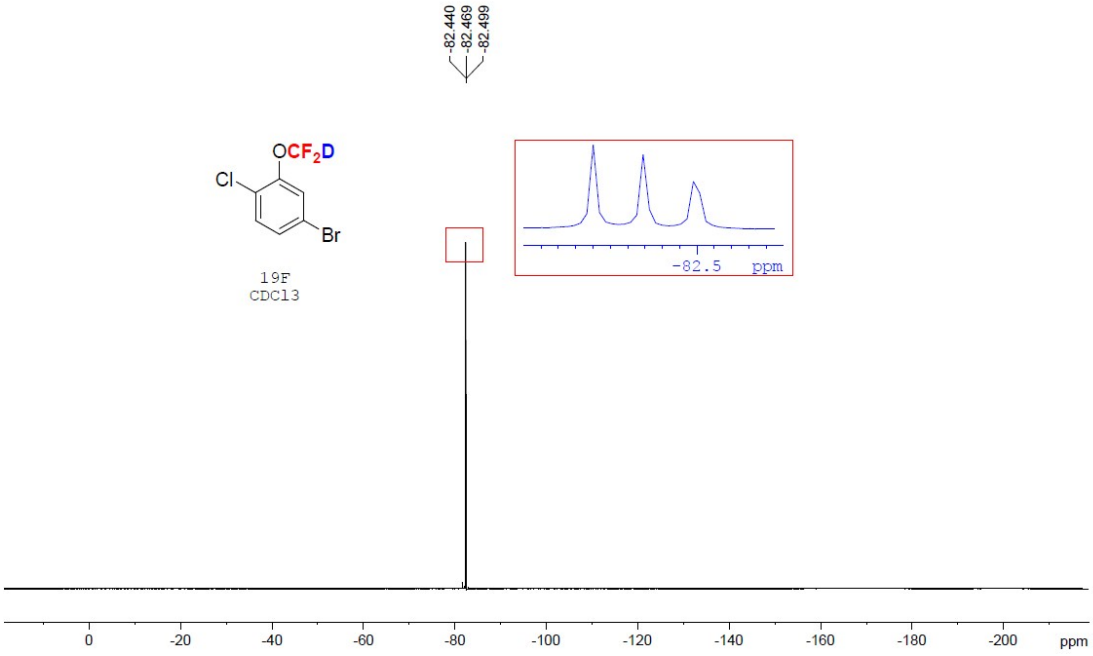


Figure S30 ^{19}F NMR of compound **2j** ($CDCl_3$)

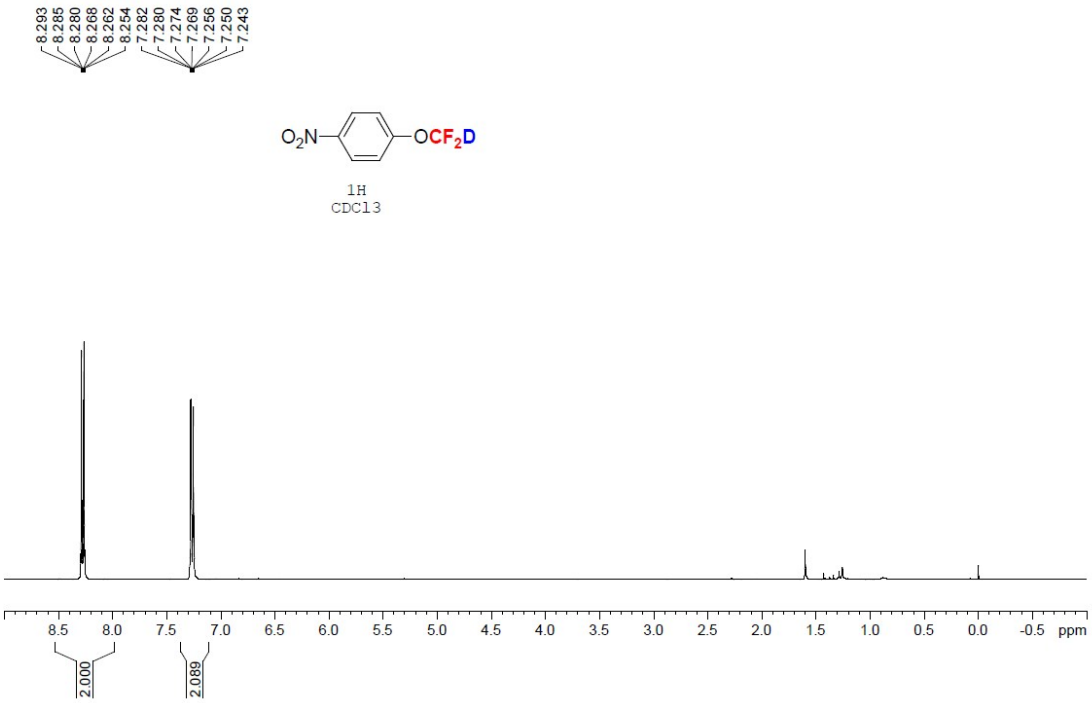


Figure S31 ^{1}H NMR of compound **2k** ($CDCl_3$)

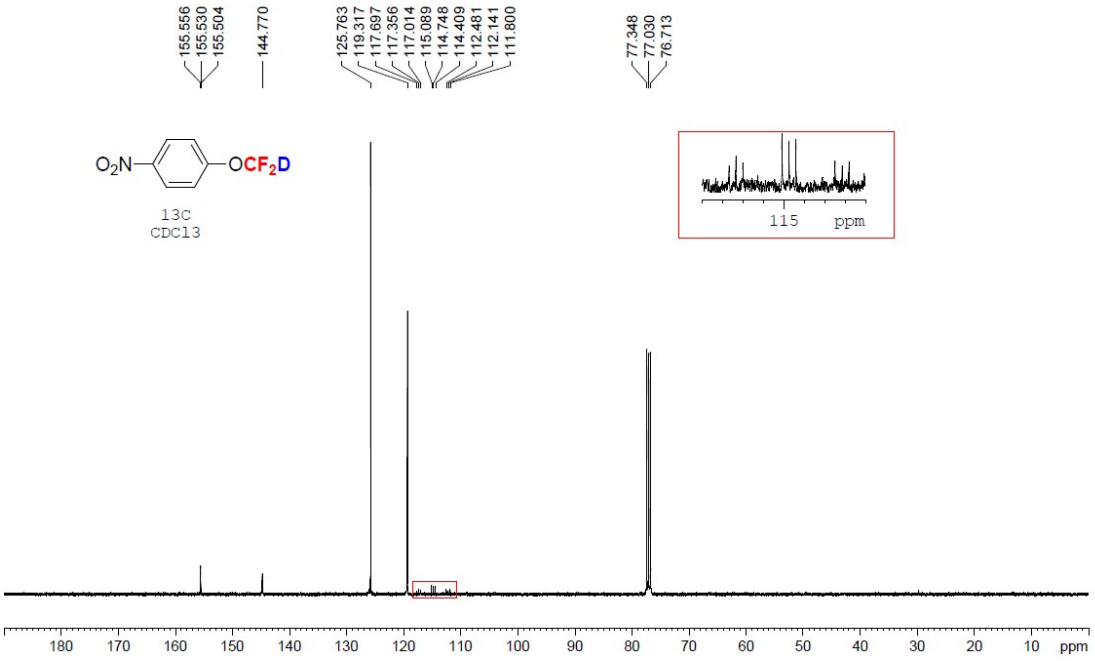


Figure S32 ^{13}C NMR of compound **2k** ($CDCl_3$)

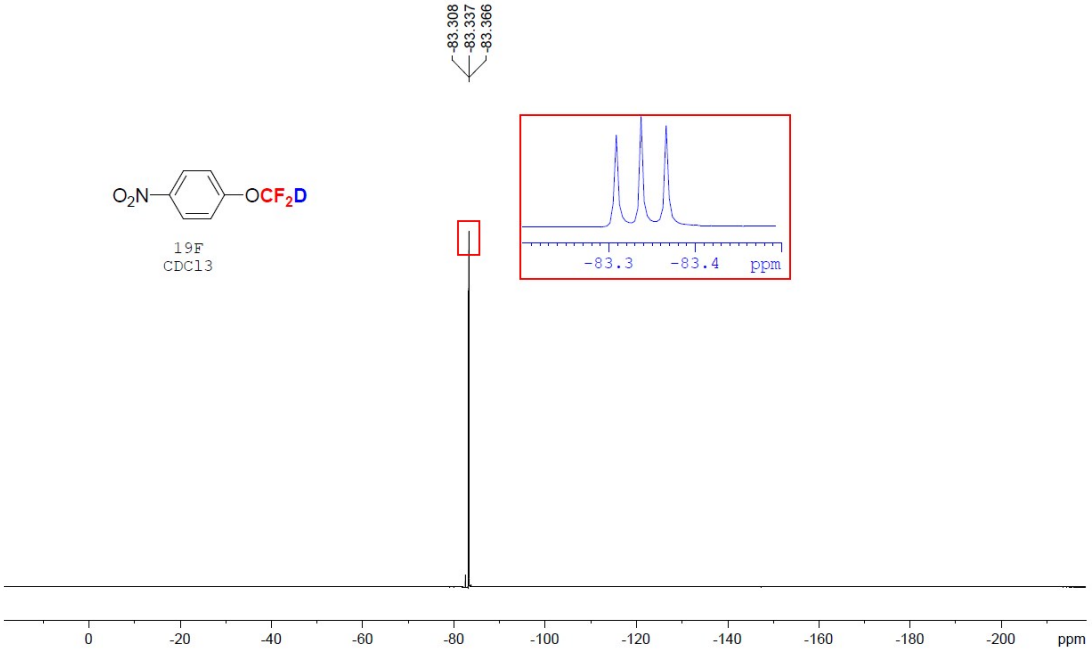


Figure S33 ^{19}F NMR of compound **2k** ($CDCl_3$)

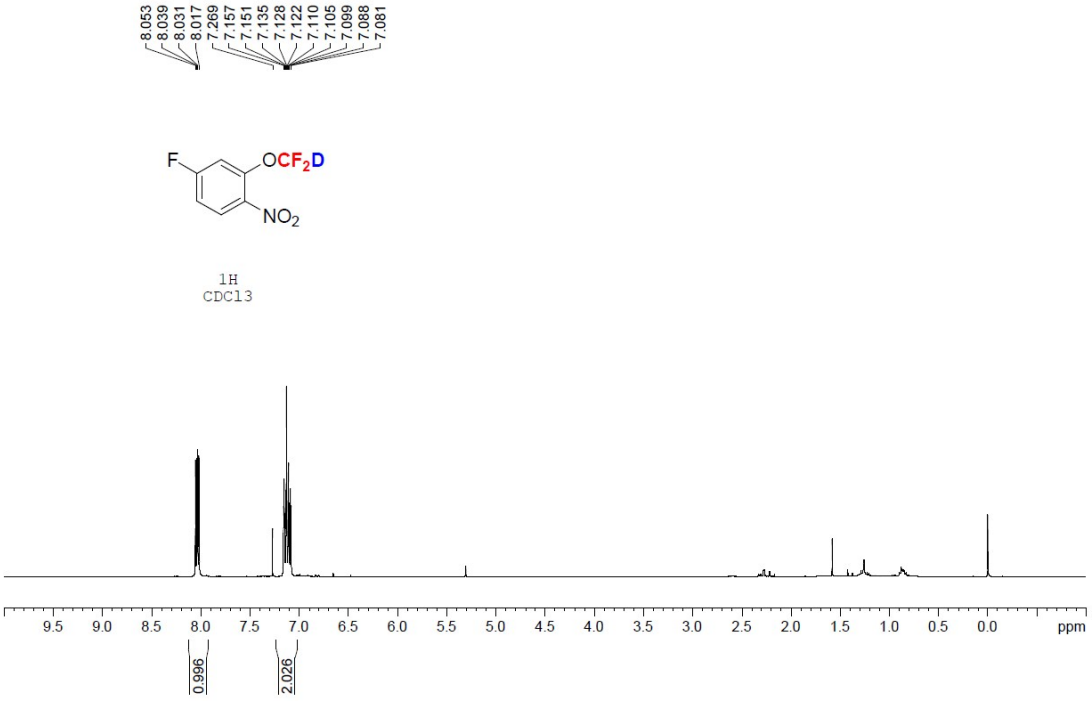


Figure S34 ^{1}H NMR of compound **2l** ($CDCl_3$)

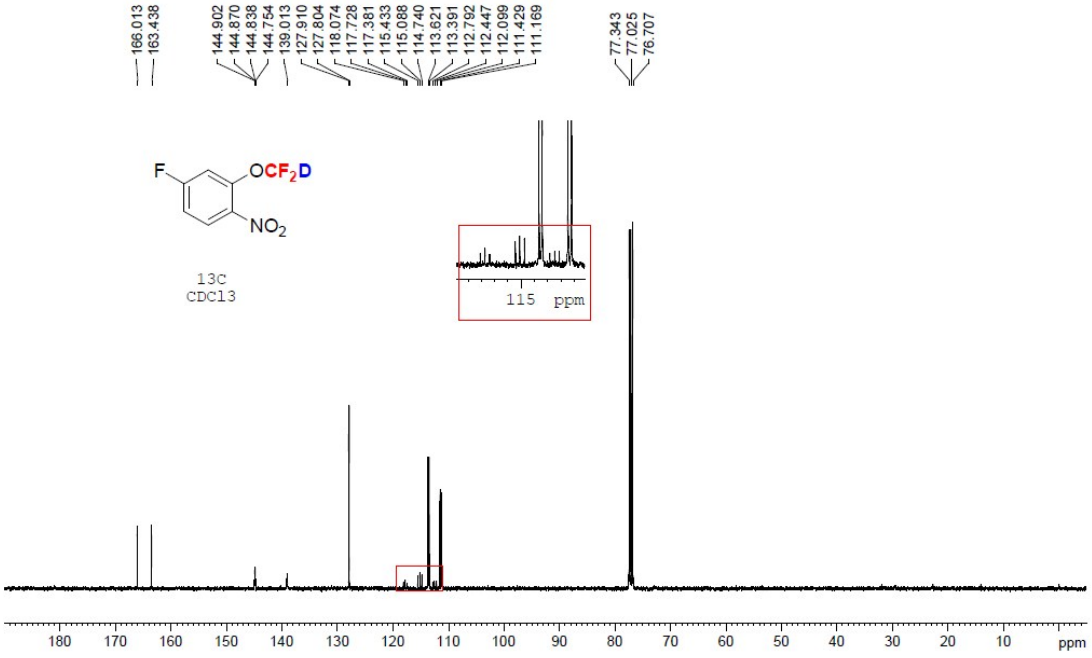


Figure S35 ^{13}C NMR of compound **2l** ($CDCl_3$)

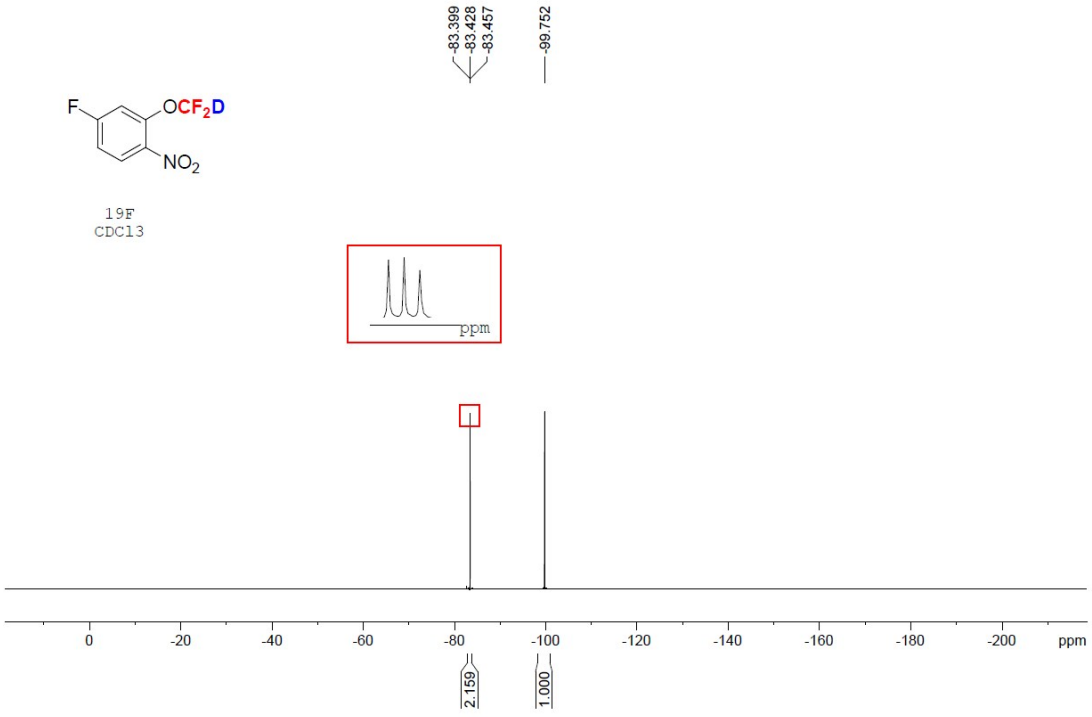


Figure S36 ^{19}F NMR of compound **2l** ($CDCl_3$)

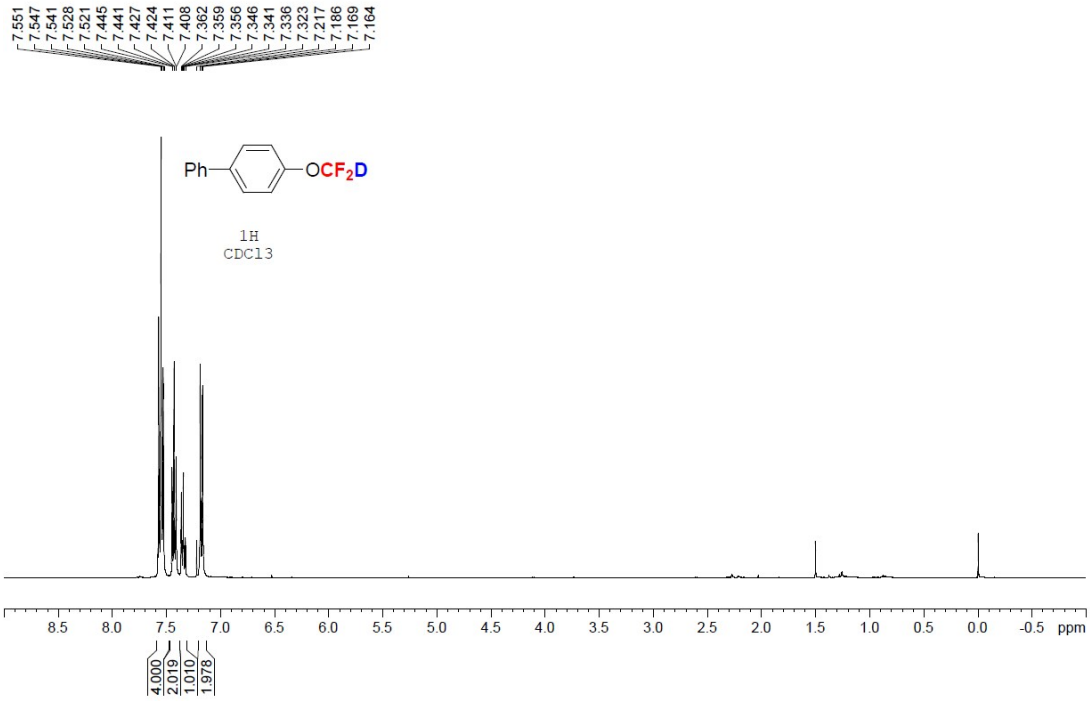


Figure S37 ^{1}H NMR of compound **2m** ($CDCl_3$)

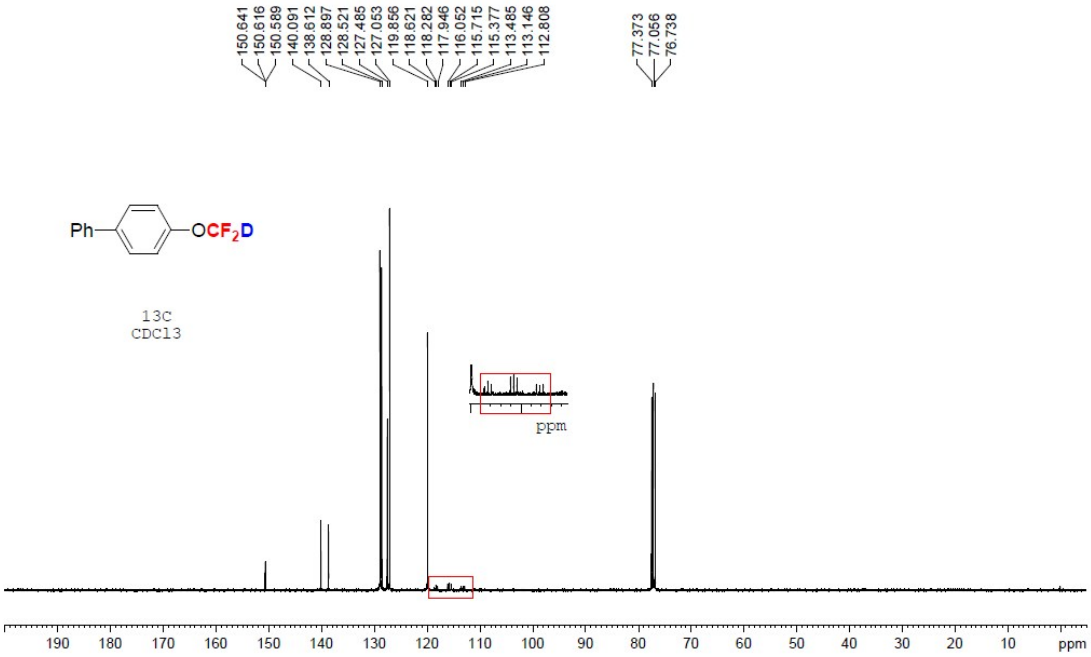


Figure S38 ^{13}C NMR of compound **2m** ($CDCl_3$)

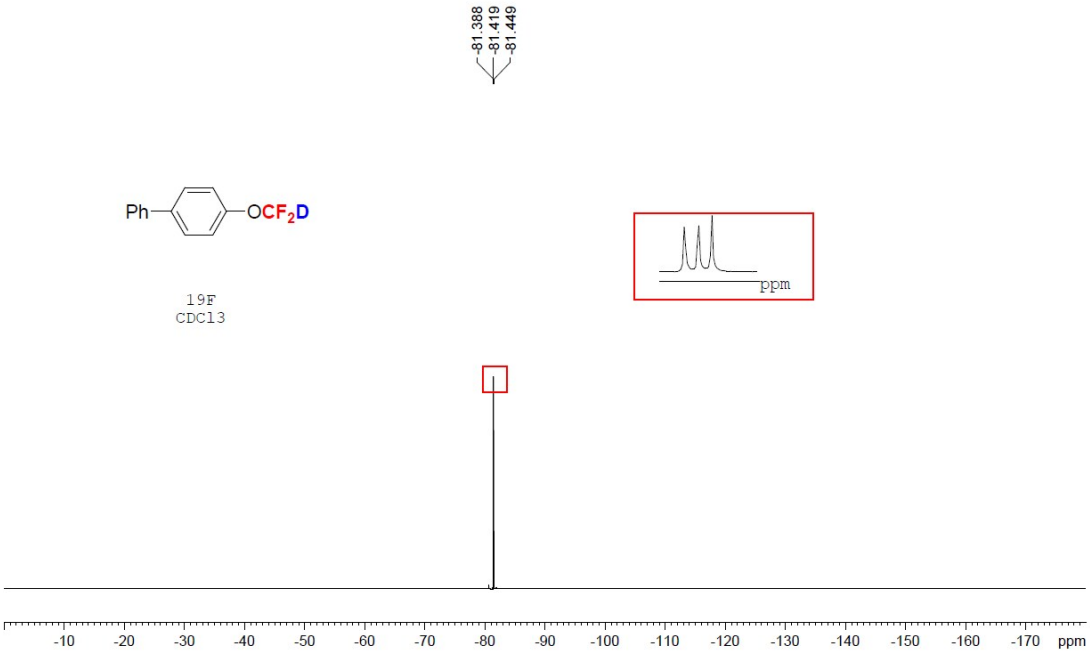


Figure S39 ^{19}F NMR of compound **2m** ($CDCl_3$)

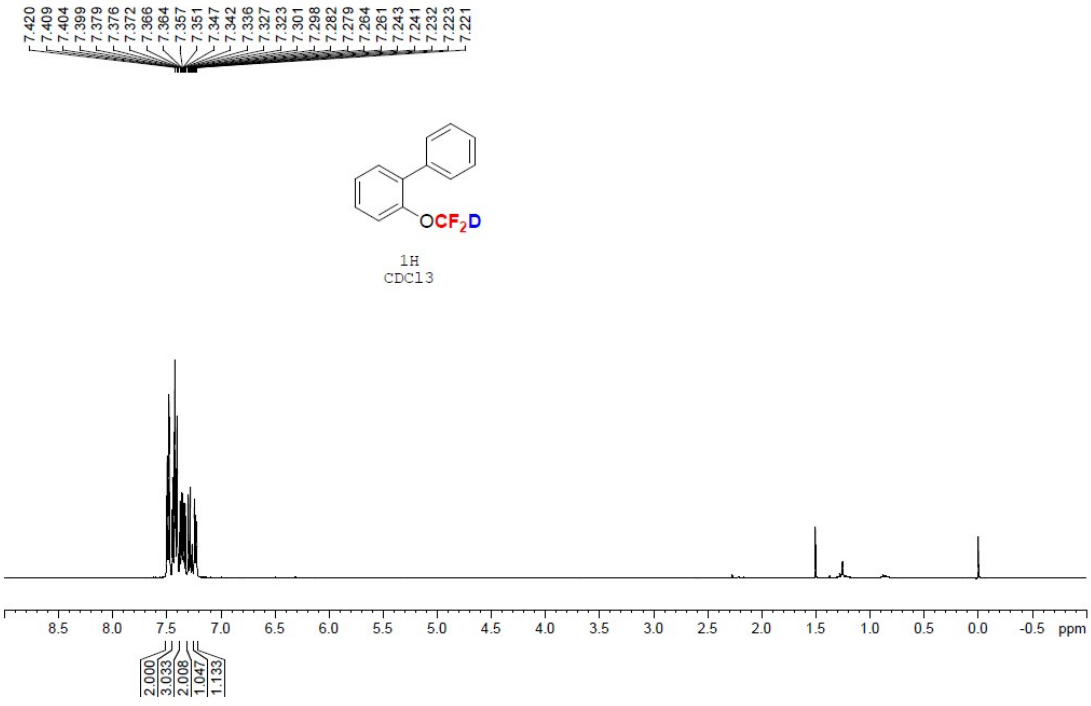


Figure S40 ^{1}H NMR of compound **2n** ($CDCl_3$)

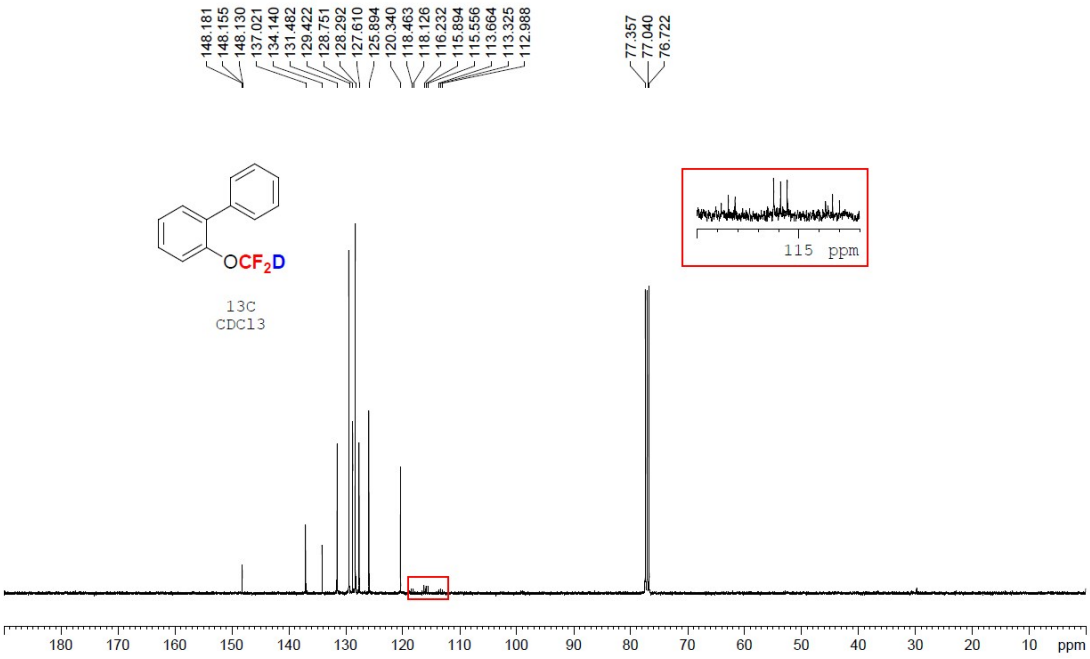


Figure S41 ^{13}C NMR of compound **2n** ($CDCl_3$)

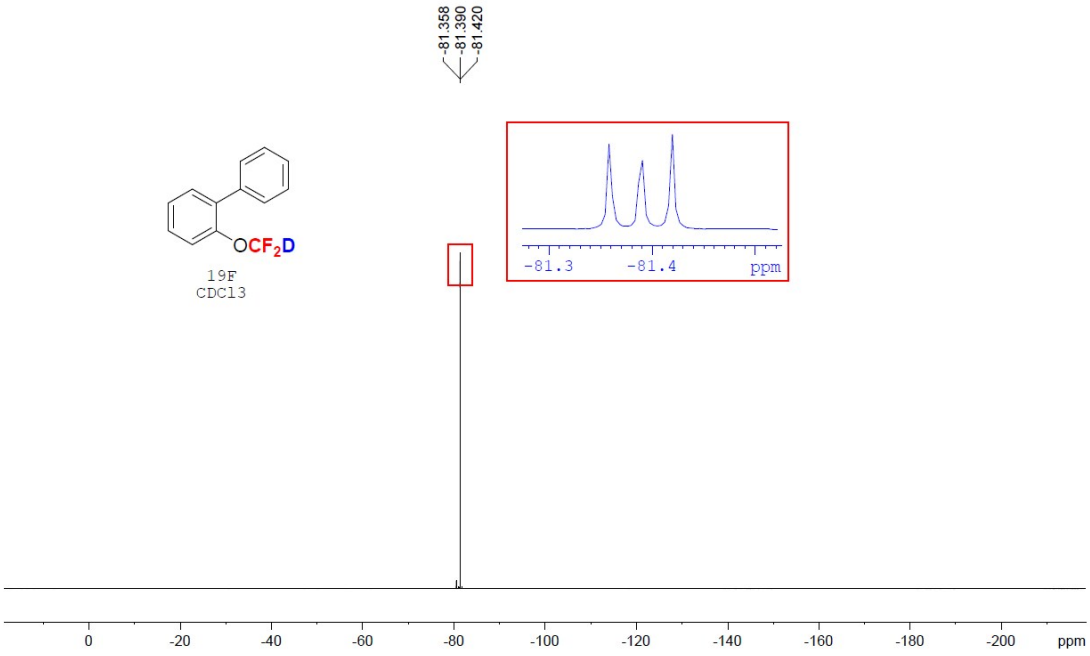


Figure S42 ^{19}F NMR of compound **2n** ($CDCl_3$)

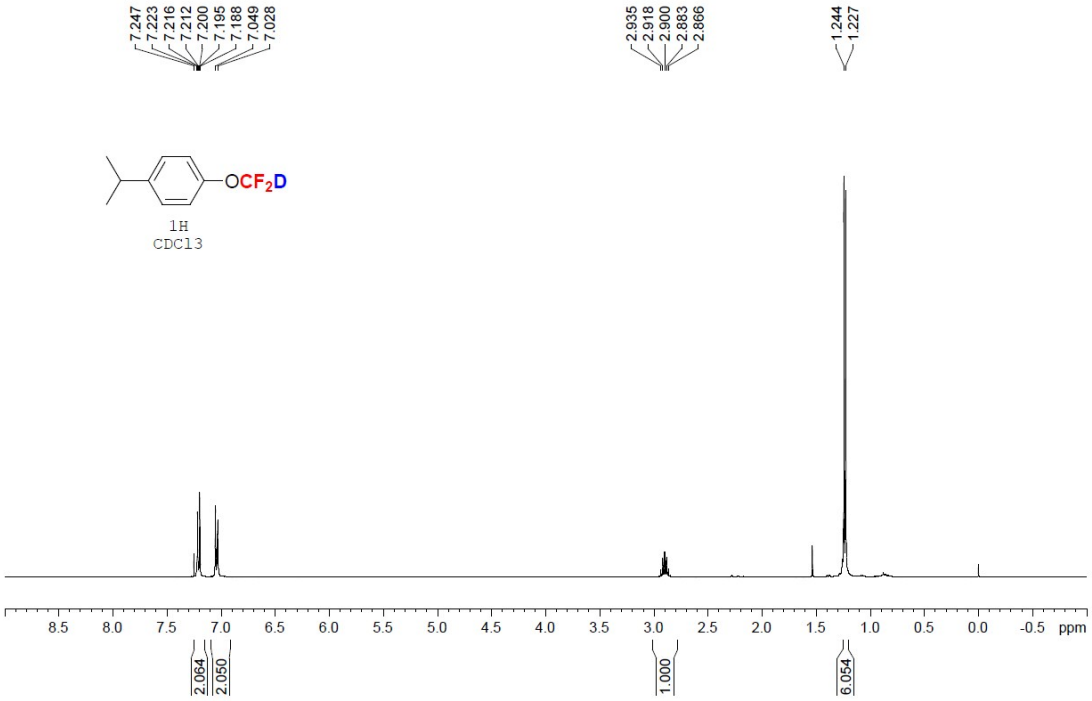


Figure S43 ^{1}H NMR of compound **2o** ($CDCl_3$)

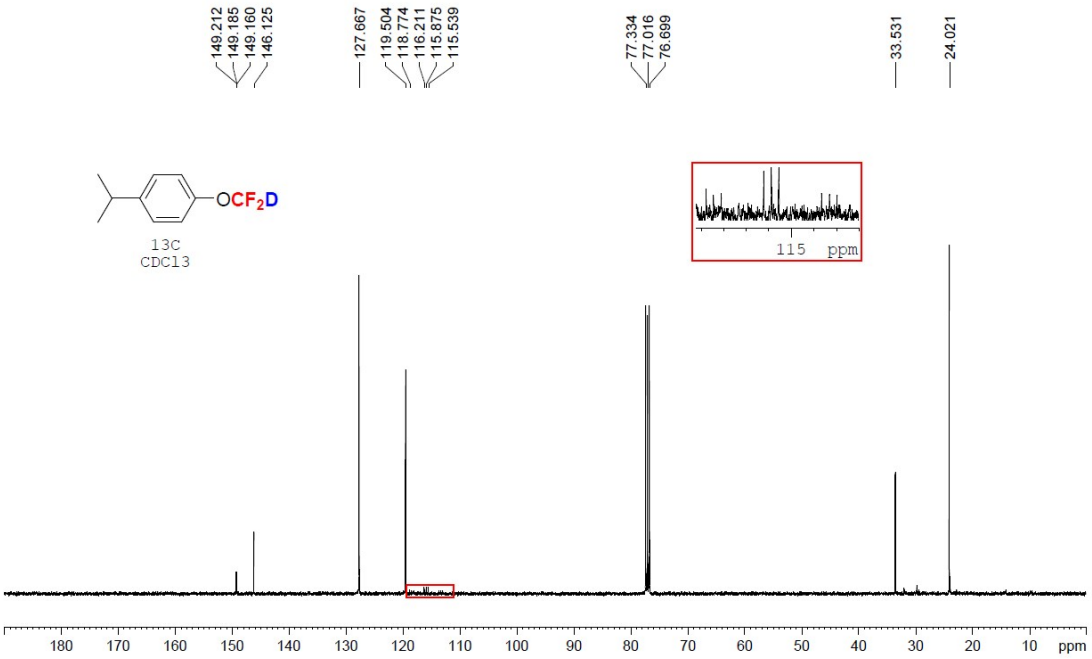


Figure S44 ^{13}C NMR of compound **2o** ($CDCl_3$)

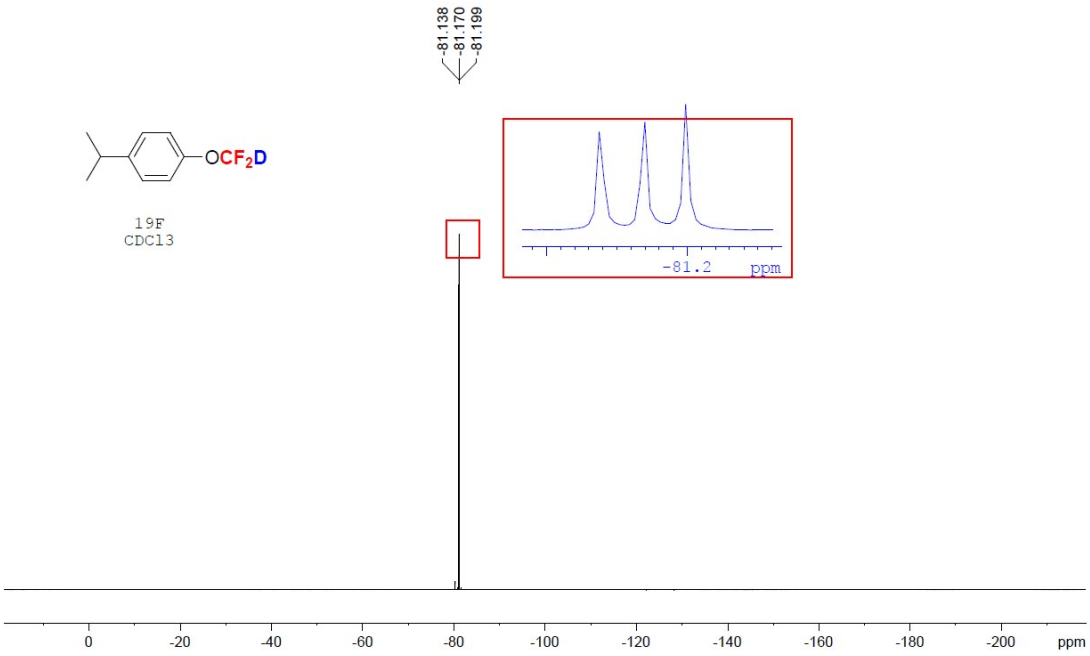


Figure S45 ^{19}F NMR of compound **2o** ($CDCl_3$)

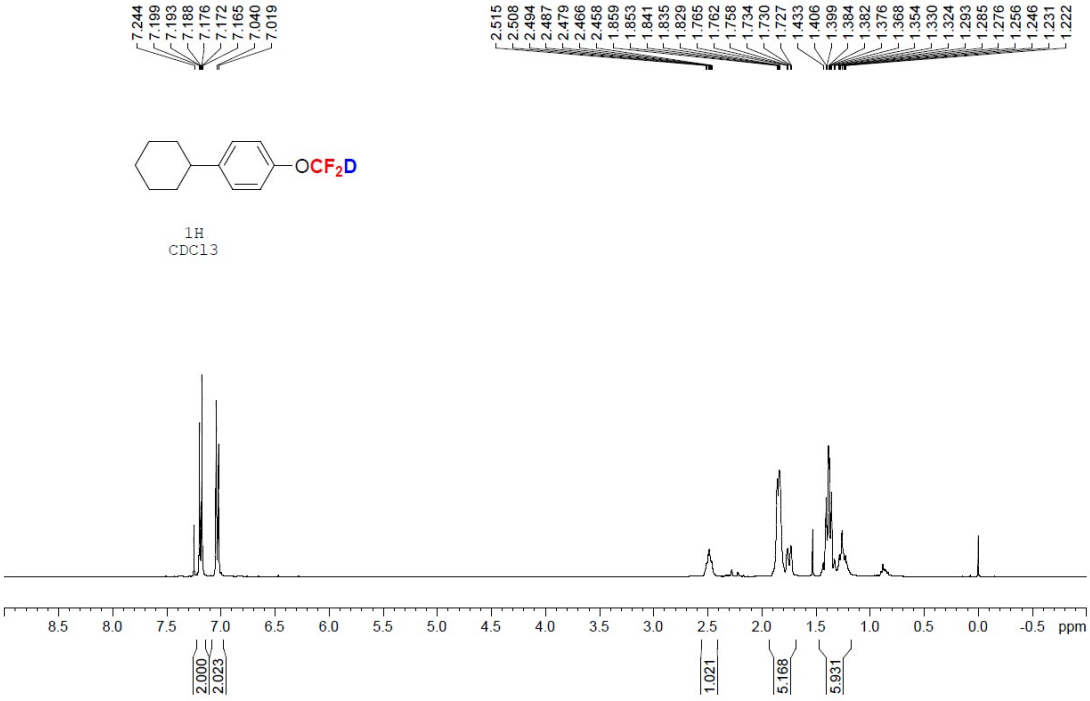


Figure S46 ^{1}H NMR of compound **2p** ($CDCl_3$)

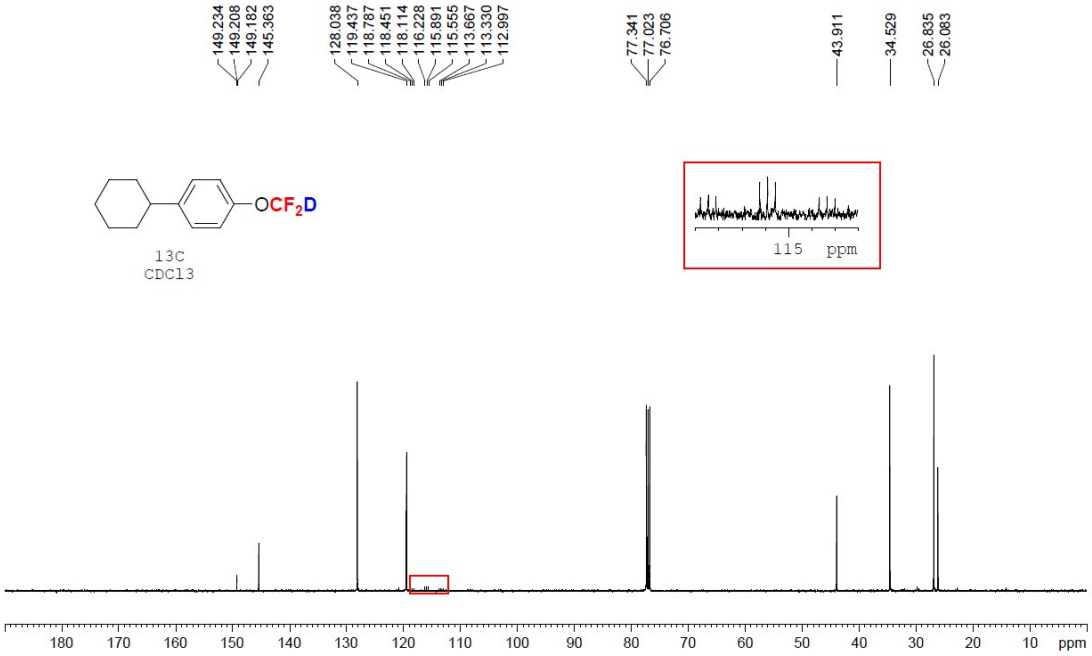


Figure S47 ^{13}C NMR of compound **2p** ($CDCl_3$)

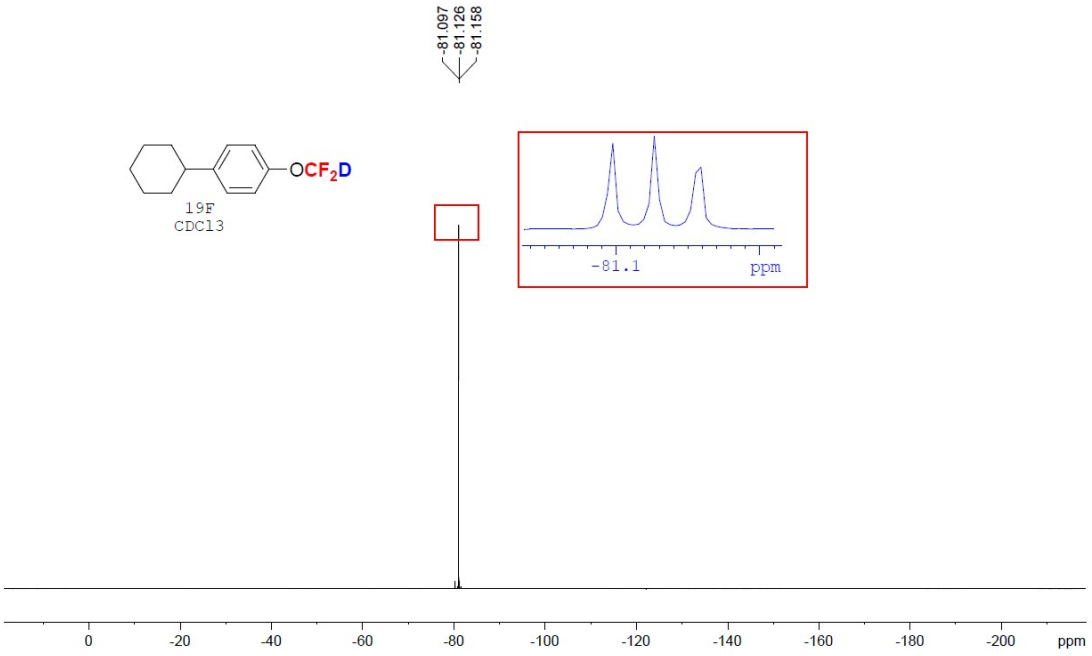


Figure S48 ^{19}F NMR of compound **2p** ($CDCl_3$)

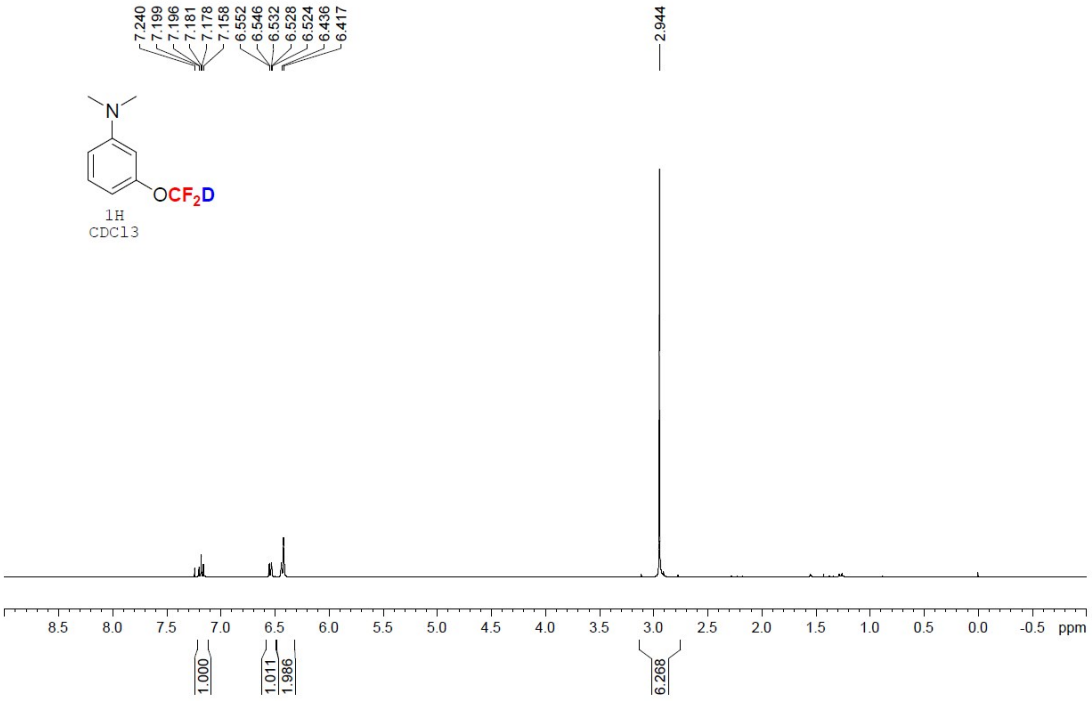


Figure S49 ^{1}H NMR of compound **2q** ($CDCl_3$)

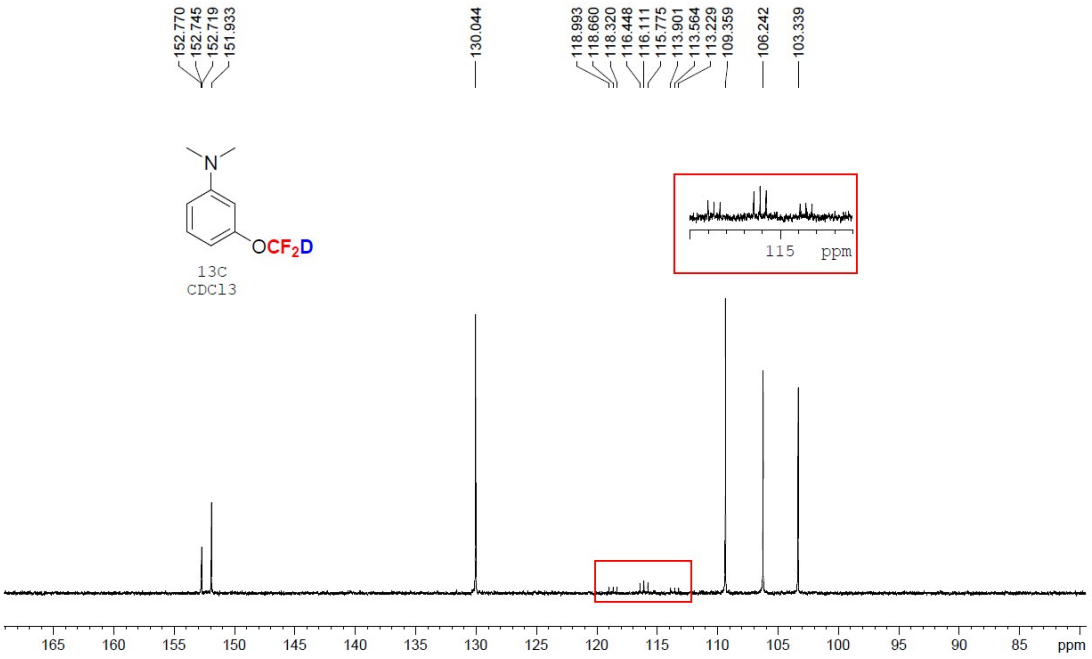


Figure S50 ^{13}C NMR of compound **2q** ($CDCl_3$)

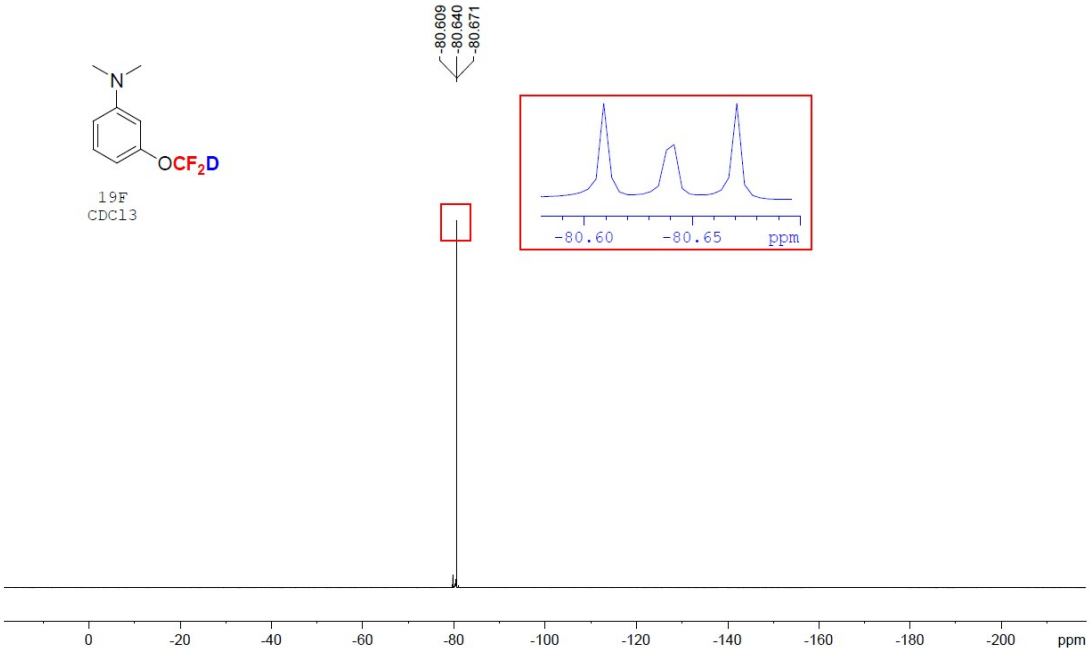


Figure S51 ^{19}F NMR of compound **2q** ($CDCl_3$)

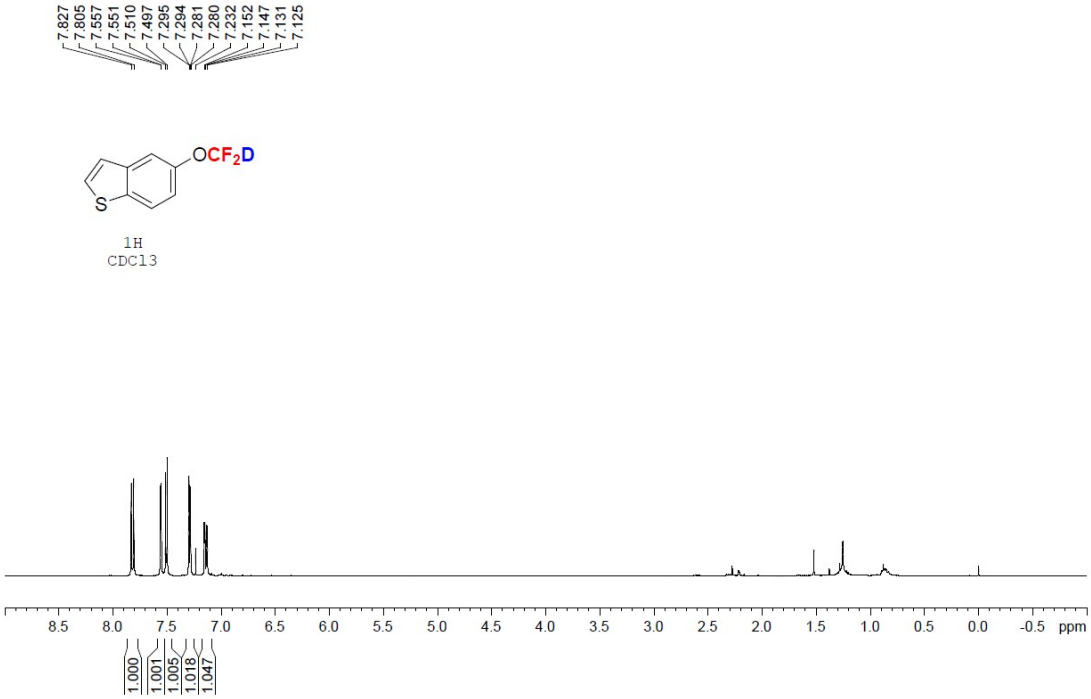


Figure S52 ^{1}H NMR of compound **2r** ($CDCl_3$)

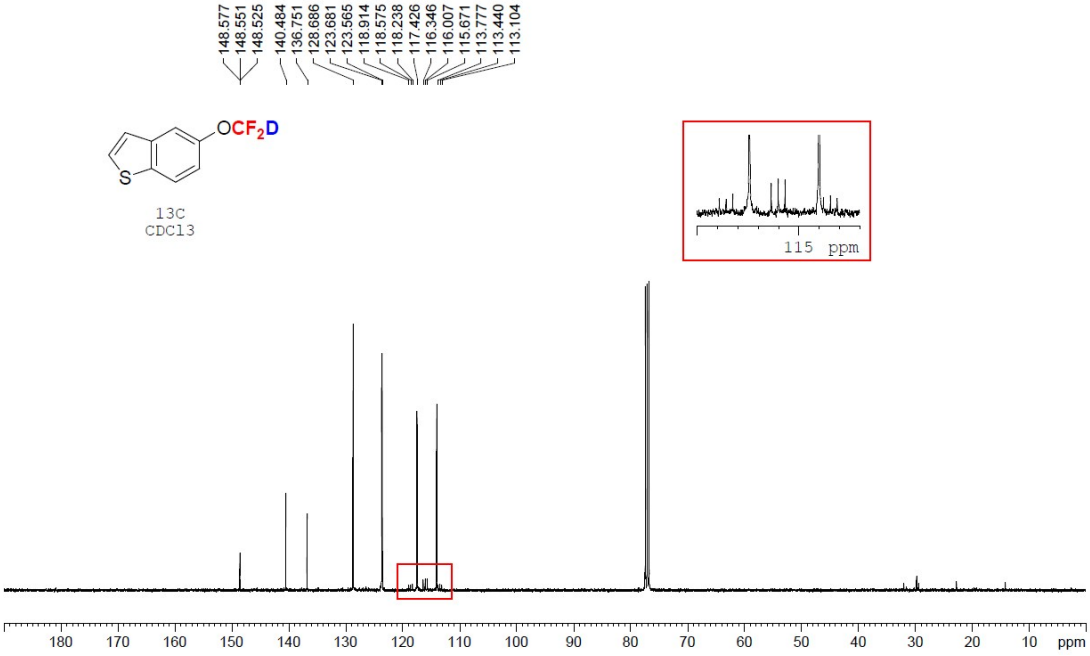


Figure S53 ^{13}C NMR of compound **2r** ($CDCl_3$)

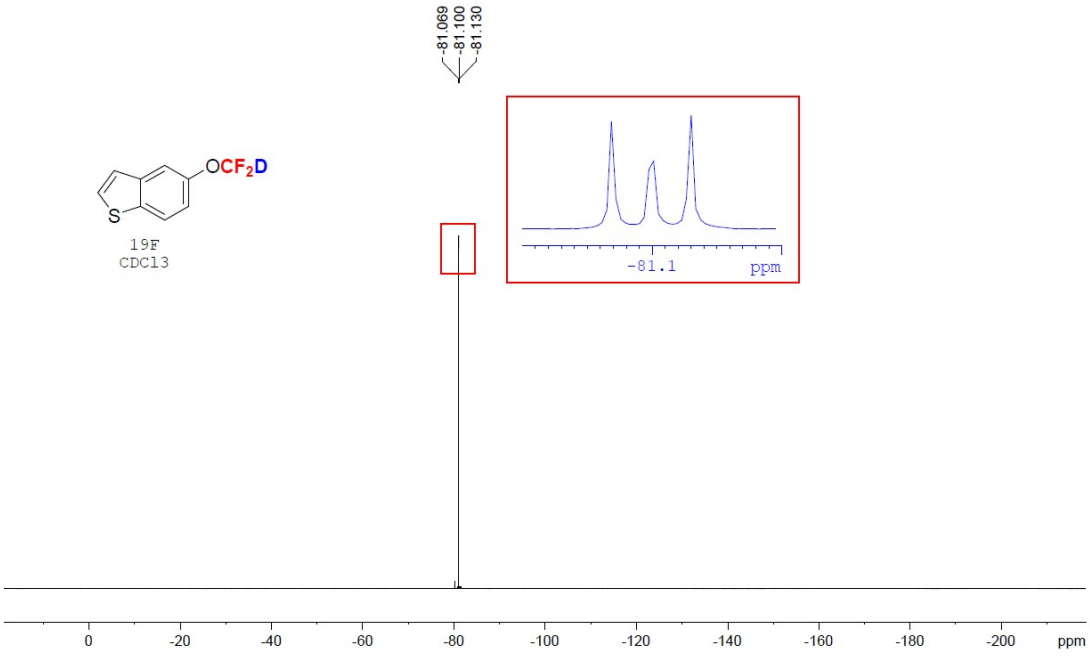


Figure S54 ^{19}F NMR of compound **2r** ($CDCl_3$)

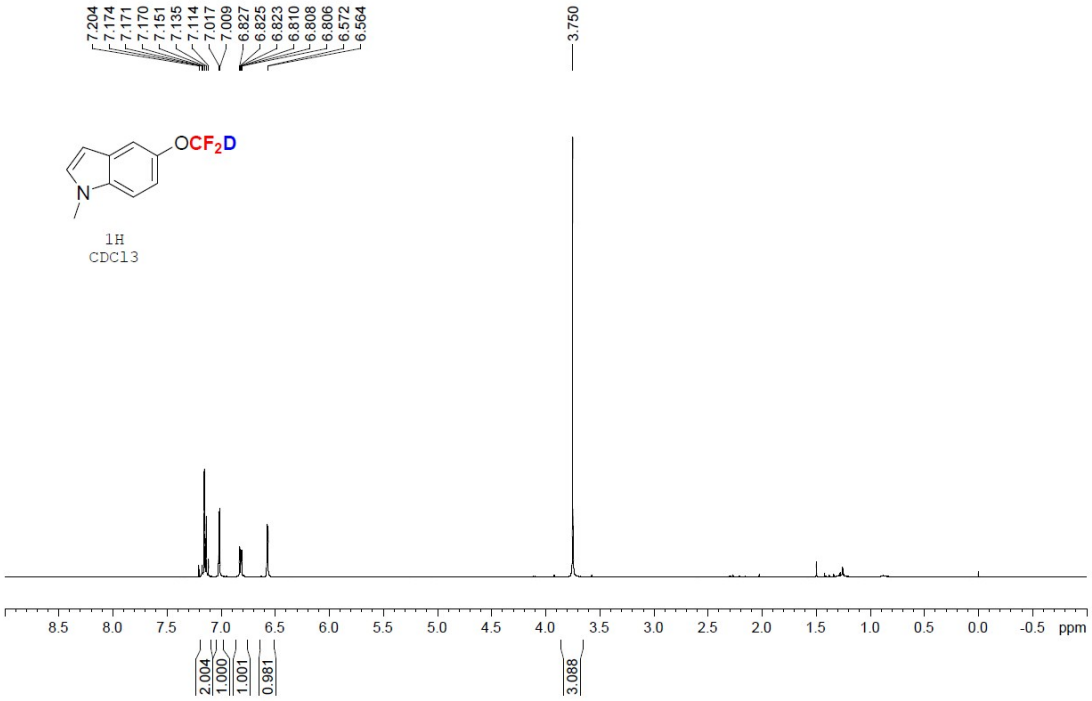


Figure S55 ^{1}H NMR of compound **2s** ($CDCl_3$)

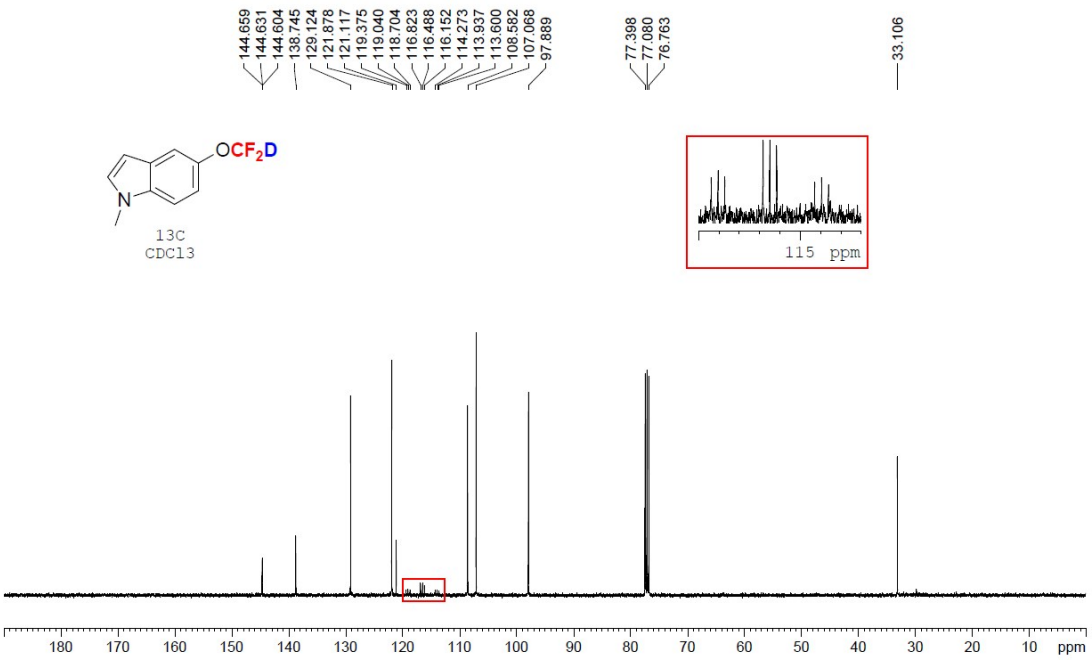


Figure S56 ^{13}C NMR of compound **2s** ($CDCl_3$)

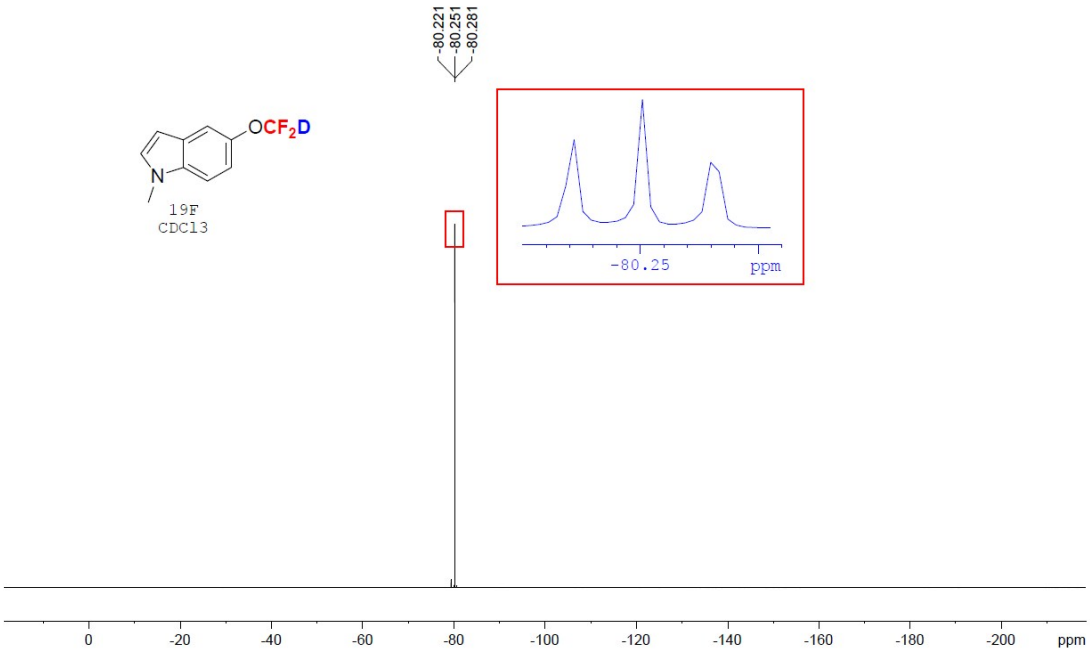


Figure S57 ^{19}F NMR of compound **2s** ($CDCl_3$)

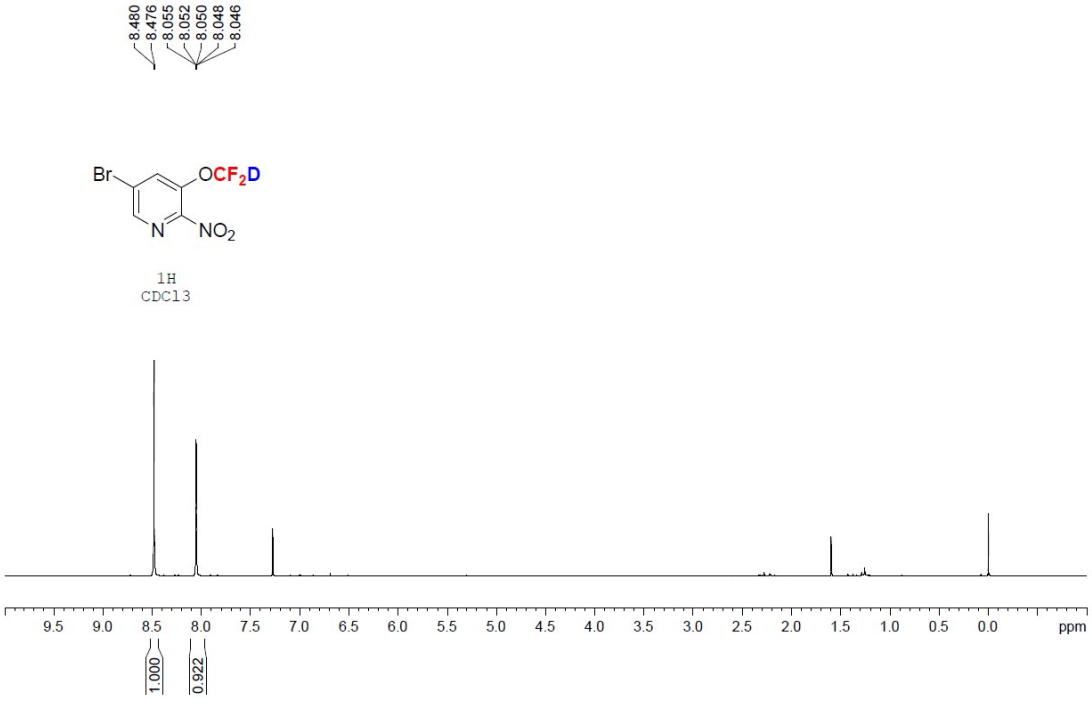


Figure S58 ^{1}H NMR of compound **2t** ($CDCl_3$)

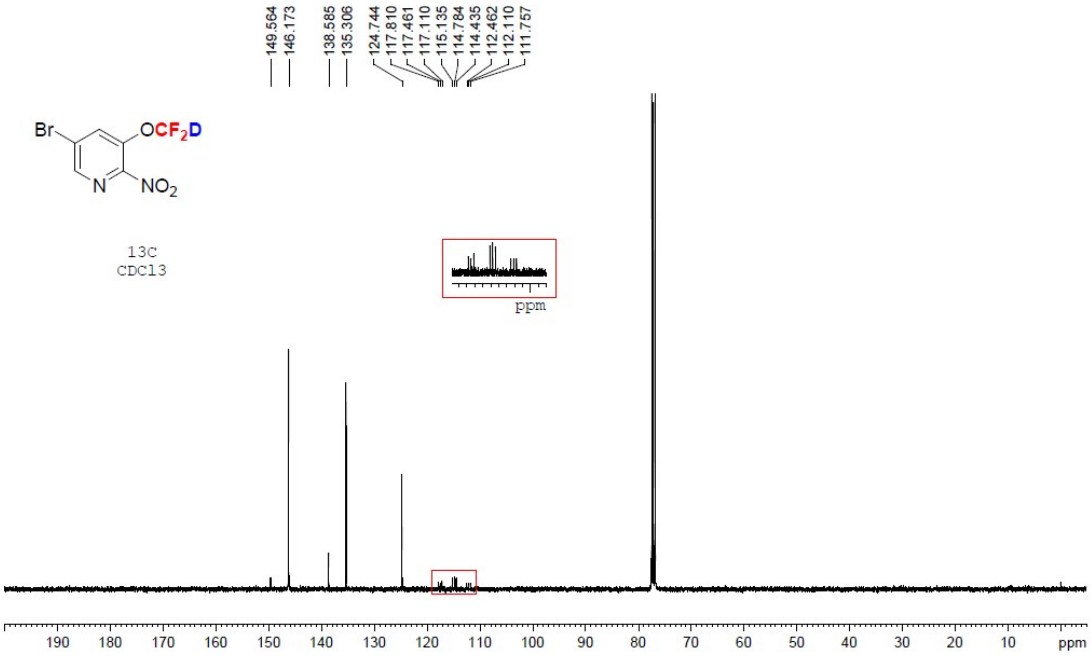


Figure S59 ^{13}C NMR of compound **2t** ($CDCl_3$)

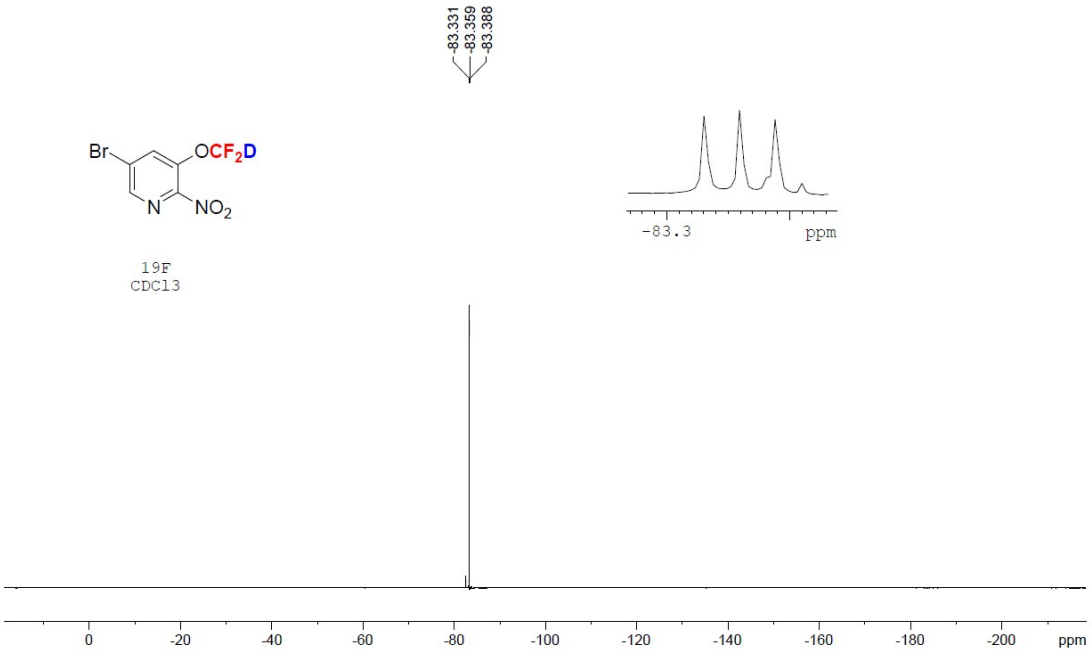


Figure S60 ^{19}F NMR of compound **2t** ($CDCl_3$)

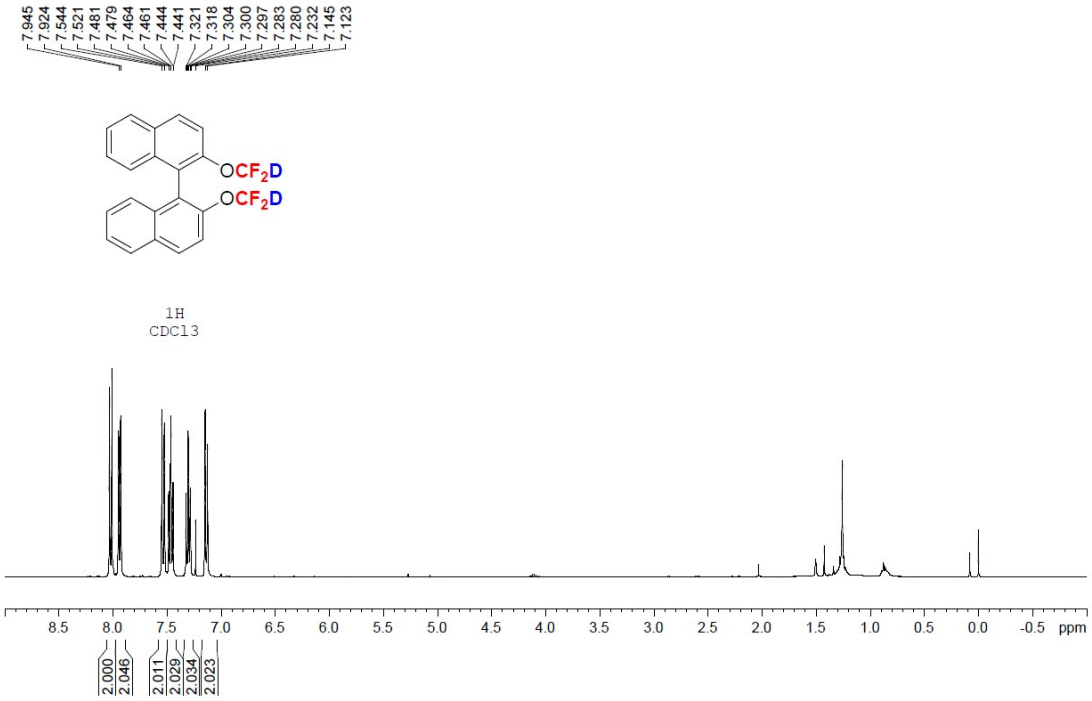


Figure S61 ^{1}H NMR of compound **2u** ($CDCl_3$)

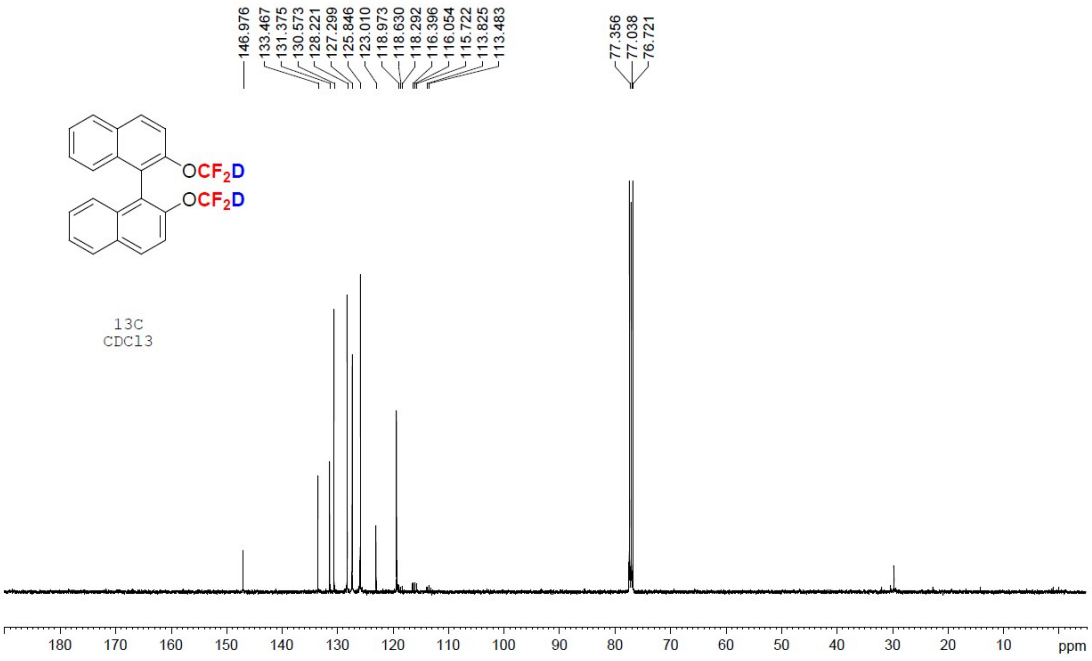


Figure S62 ^{13}C NMR of compound **2u** ($CDCl_3$)

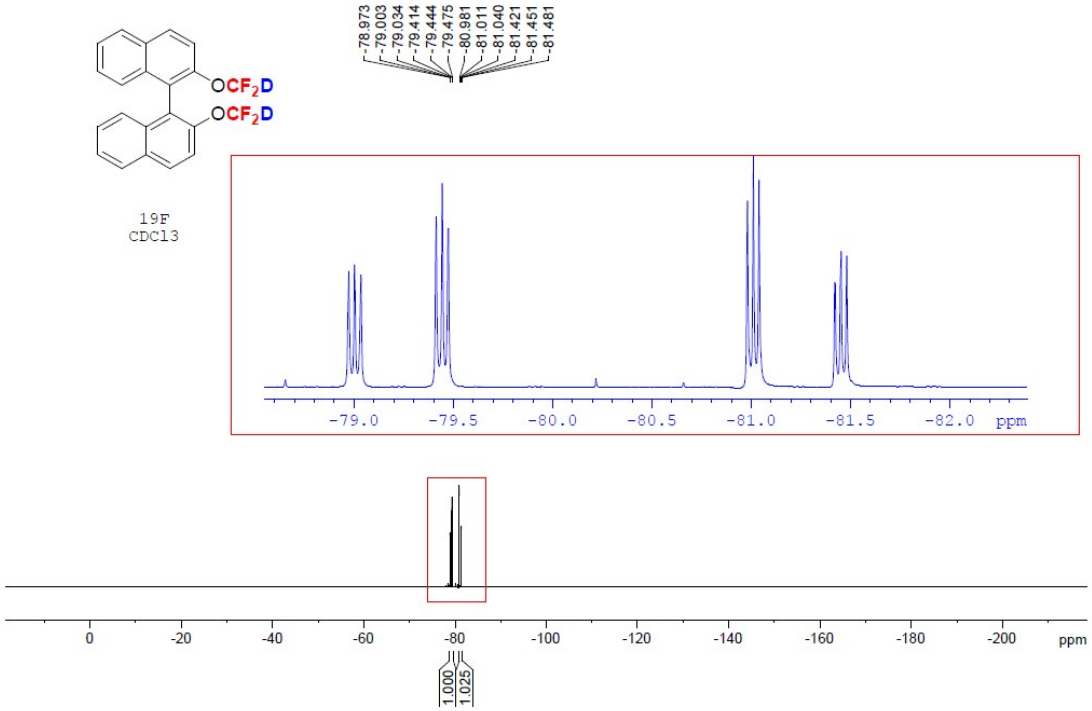


Figure S63 ^{19}F NMR of compound **2u** ($CDCl_3$)

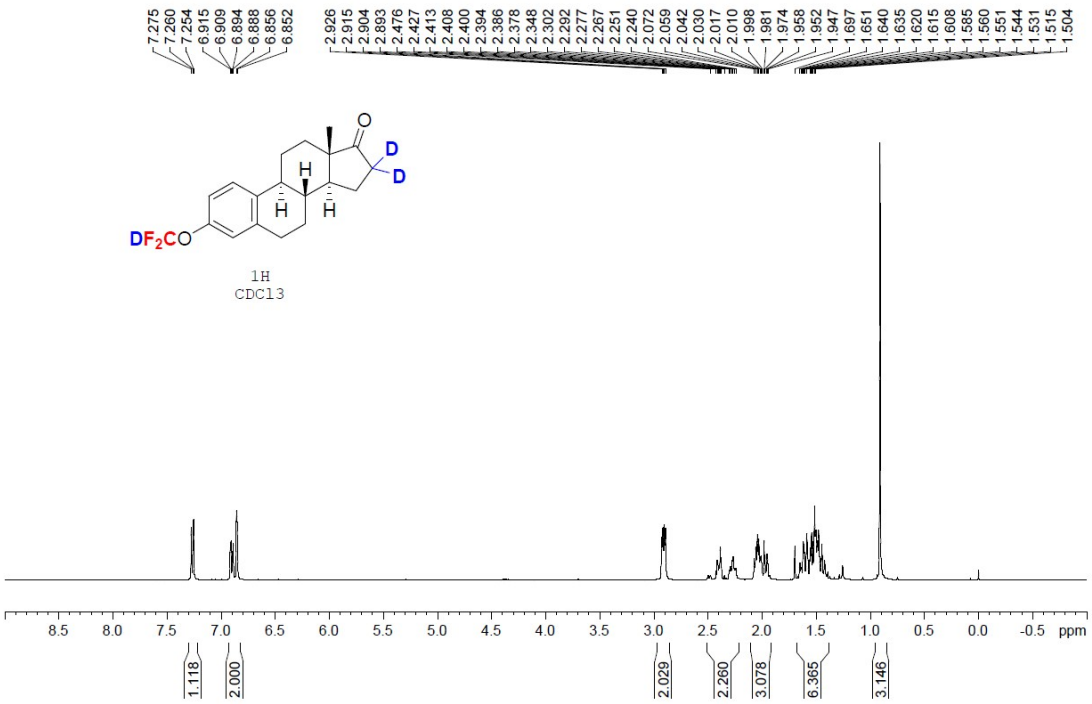


Figure S64 ^{1}H NMR of compound **2v** ($CDCl_3$)

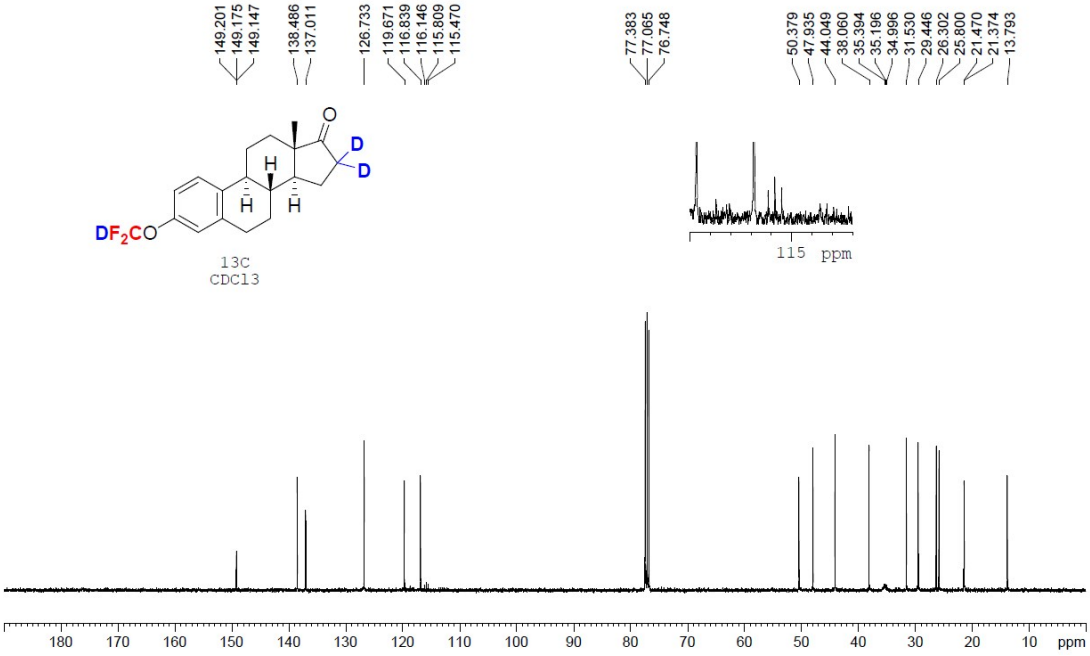


Figure S65 ^{13}C NMR of compound **2v** ($CDCl_3$)

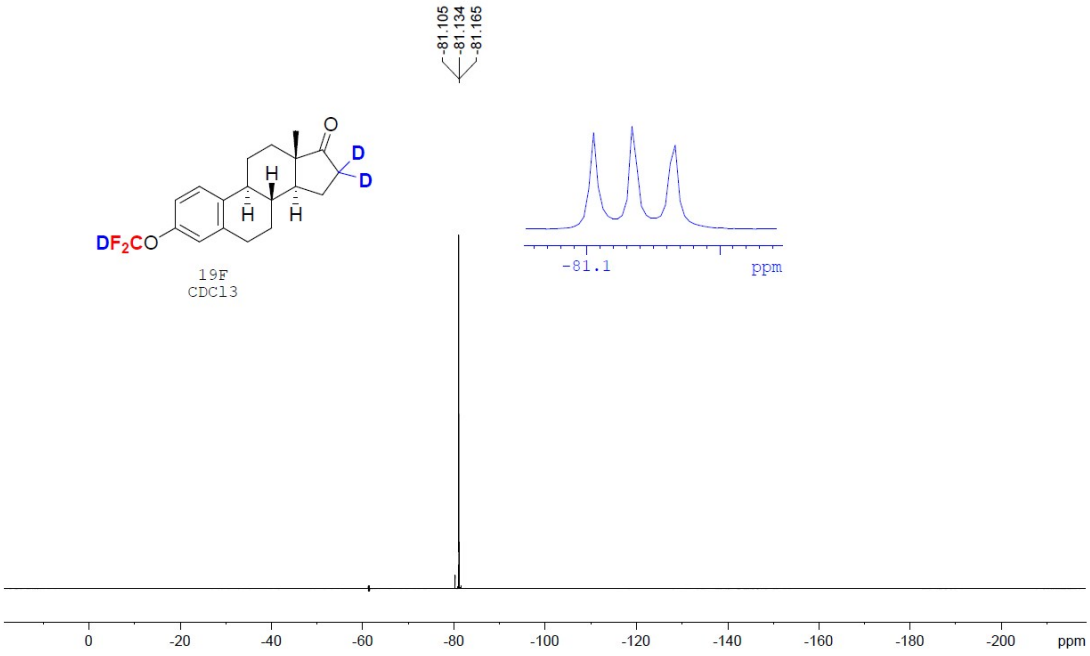


Figure S66 ^{19}F NMR of compound **2v** ($CDCl_3$)

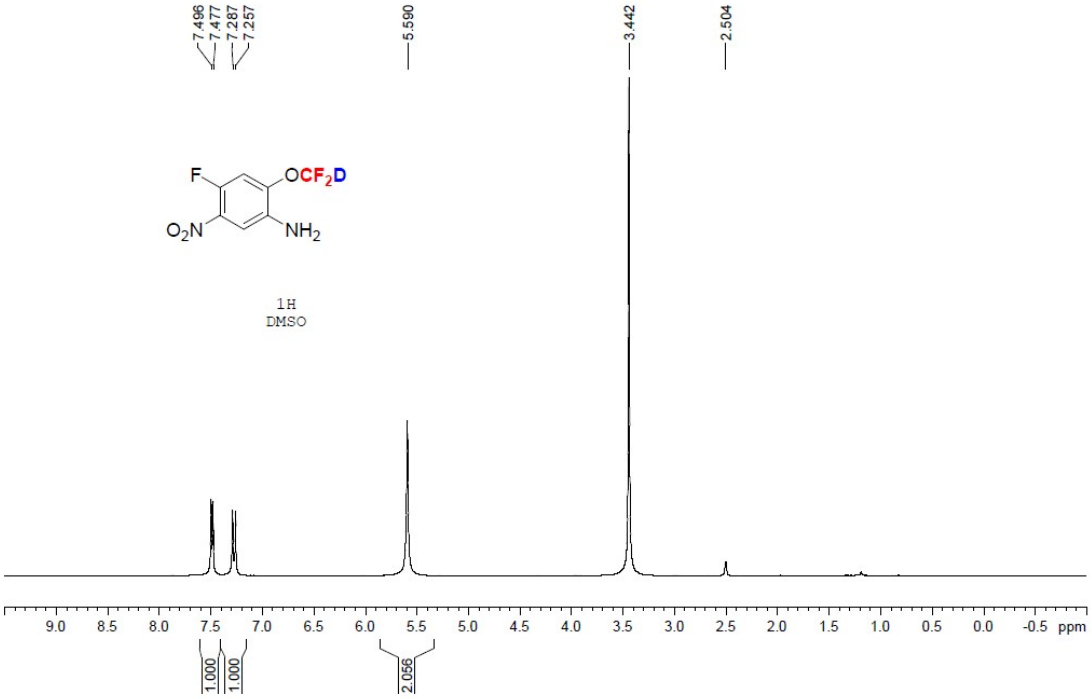


Figure S67 1H NMR of compound **3l** (d_6-DMSO)

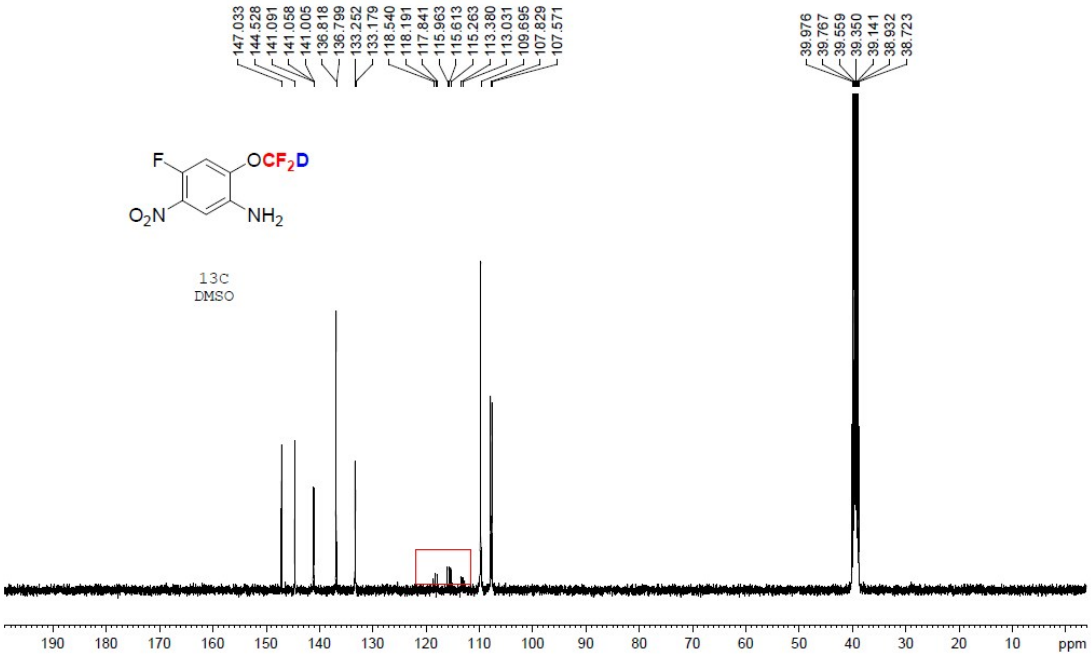


Figure S68 ^{13}C NMR of compound **3l** (d_6-DMSO)

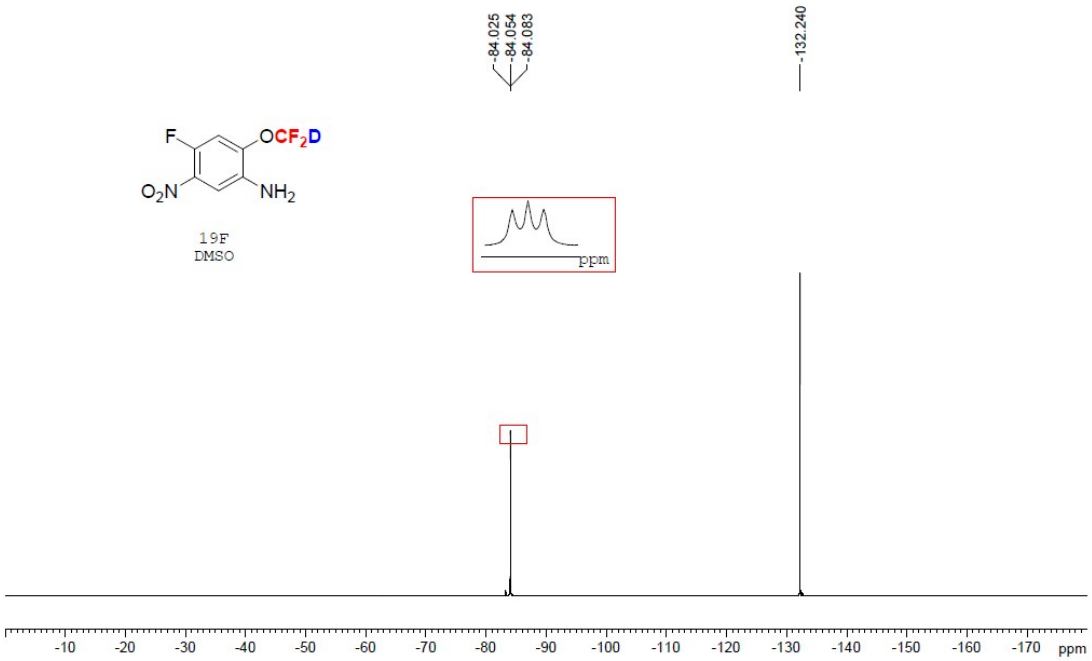


Figure S69 ^{19}F NMR of compound **3l** (d**6**-DMSO)

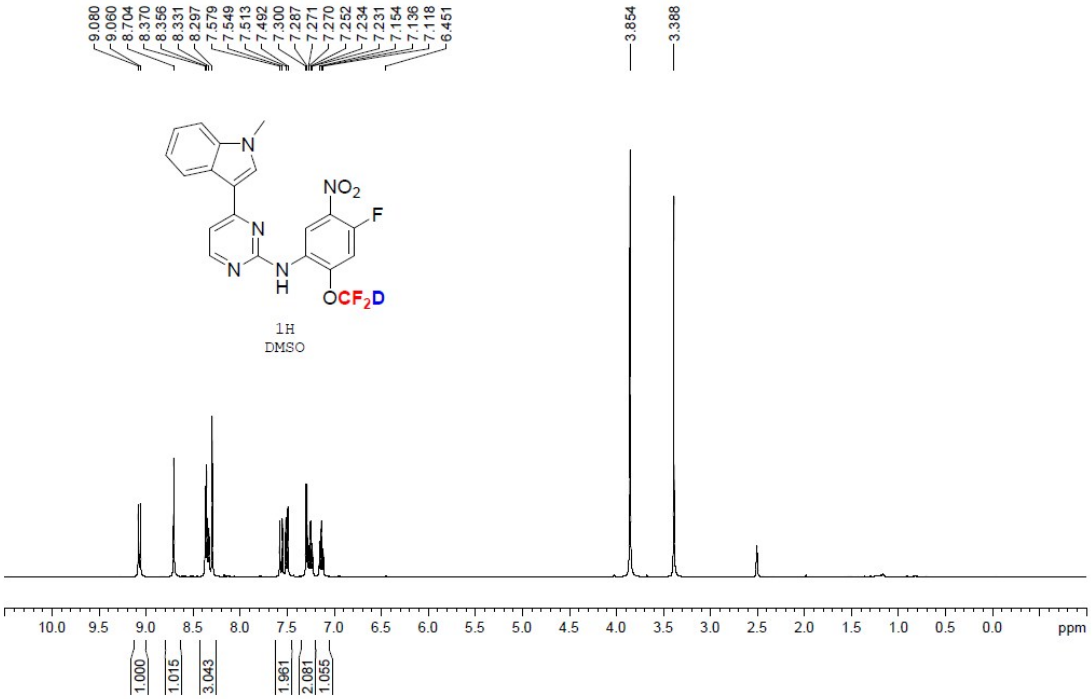


Figure S70 ^{1}H NMR of compound **DFA-1** (d_6-DMSO)

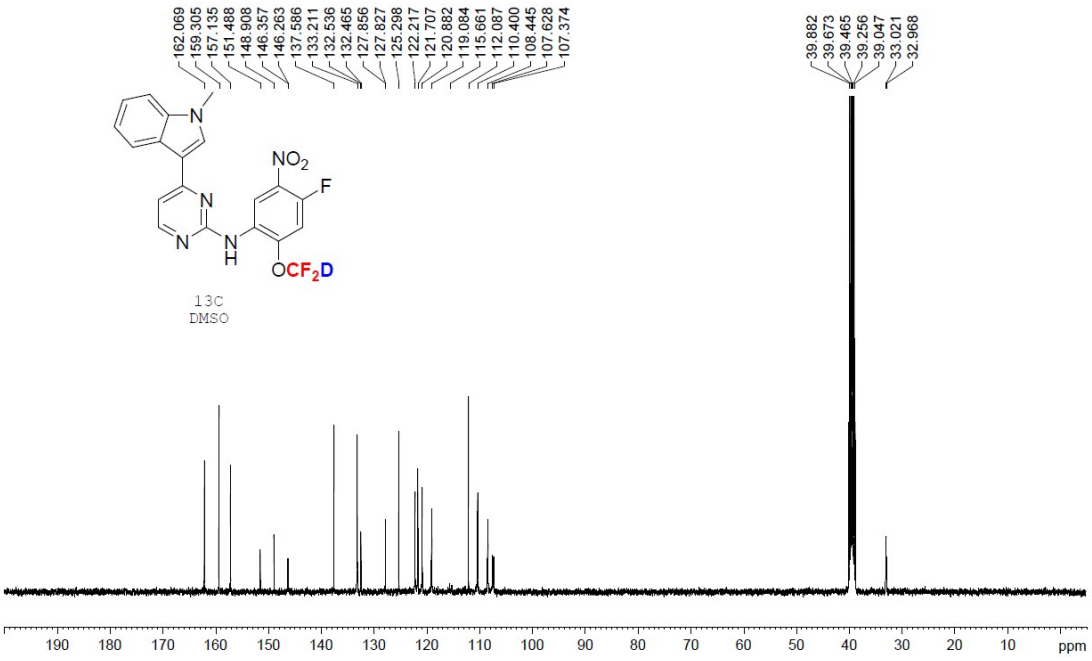


Figure S71 ^{13}C NMR of compound **DFA-1** (d_6-DMSO)

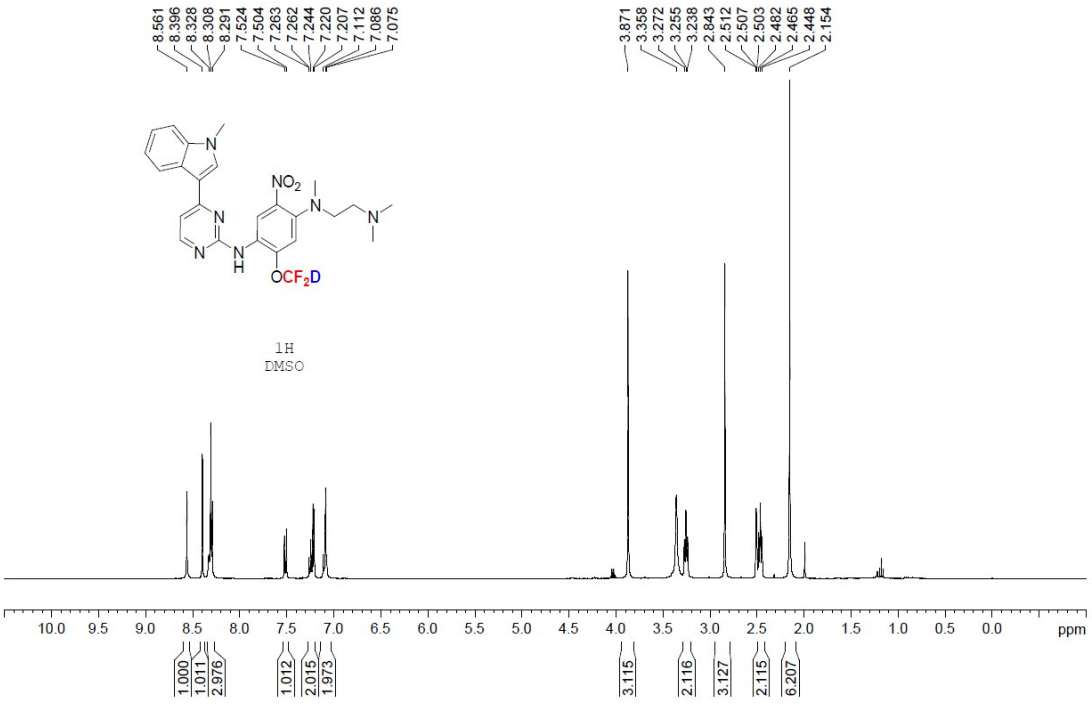


Figure S72 ^{1}H NMR of compound **DFA-2** (d_6-DMSO)

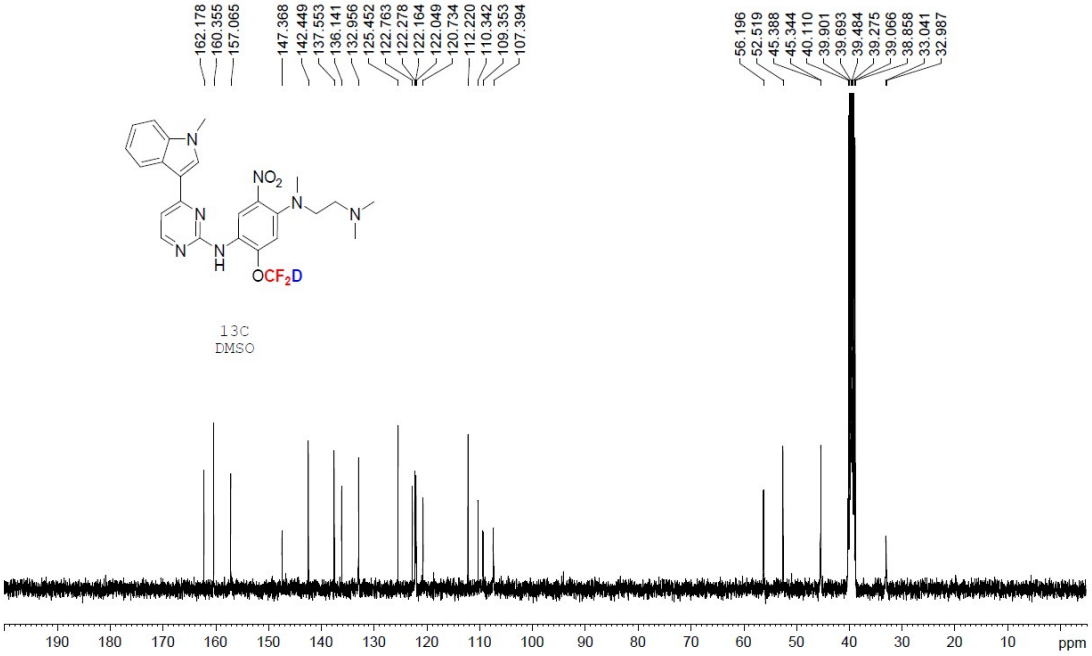


Figure S73 ^{1}H NMR of compound **DFA-2** (d_6-DMSO)

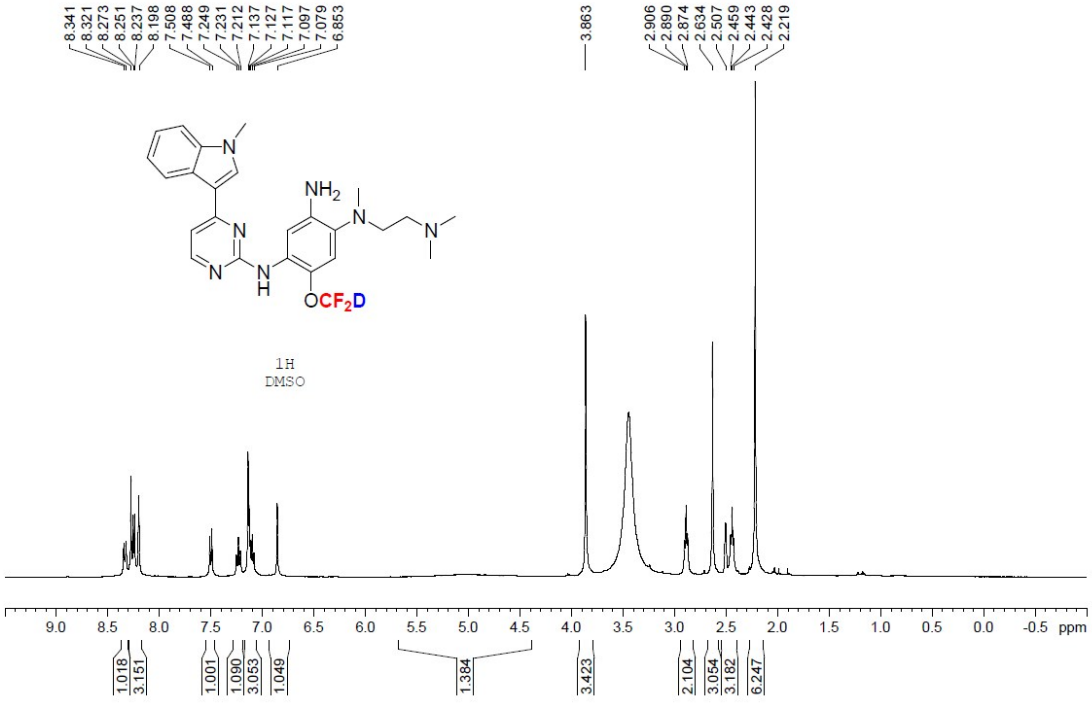


Figure S74 ^{1}H NMR of compound **DFA-3** (d_6-DMSO)

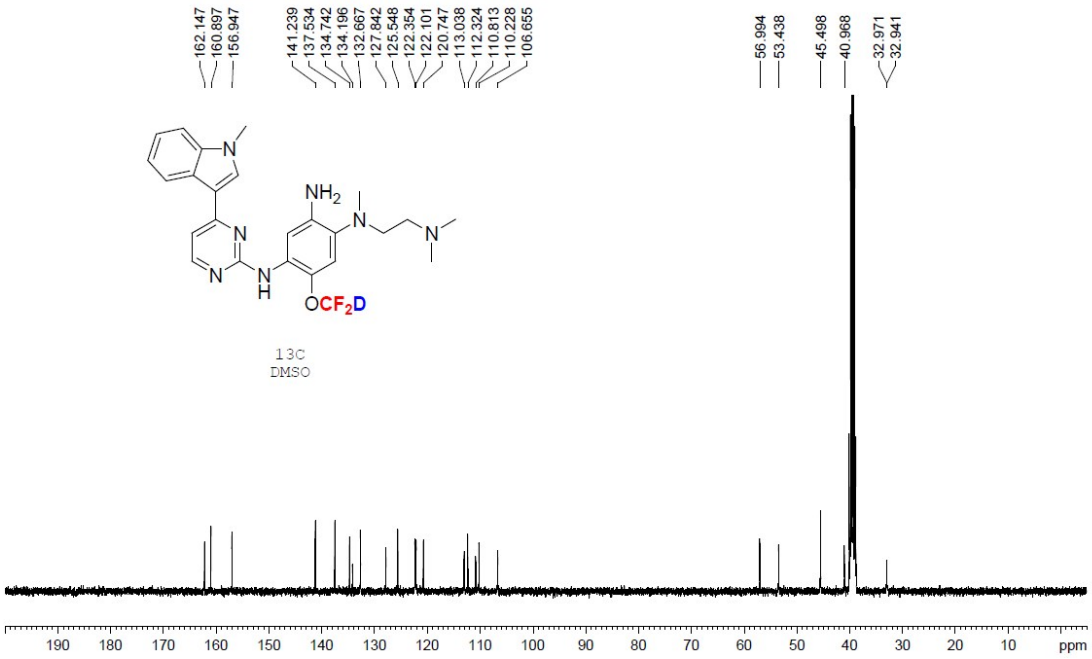


Figure S75 ^{13}C NMR of compound **DFA-3** (d_6-DMSO)

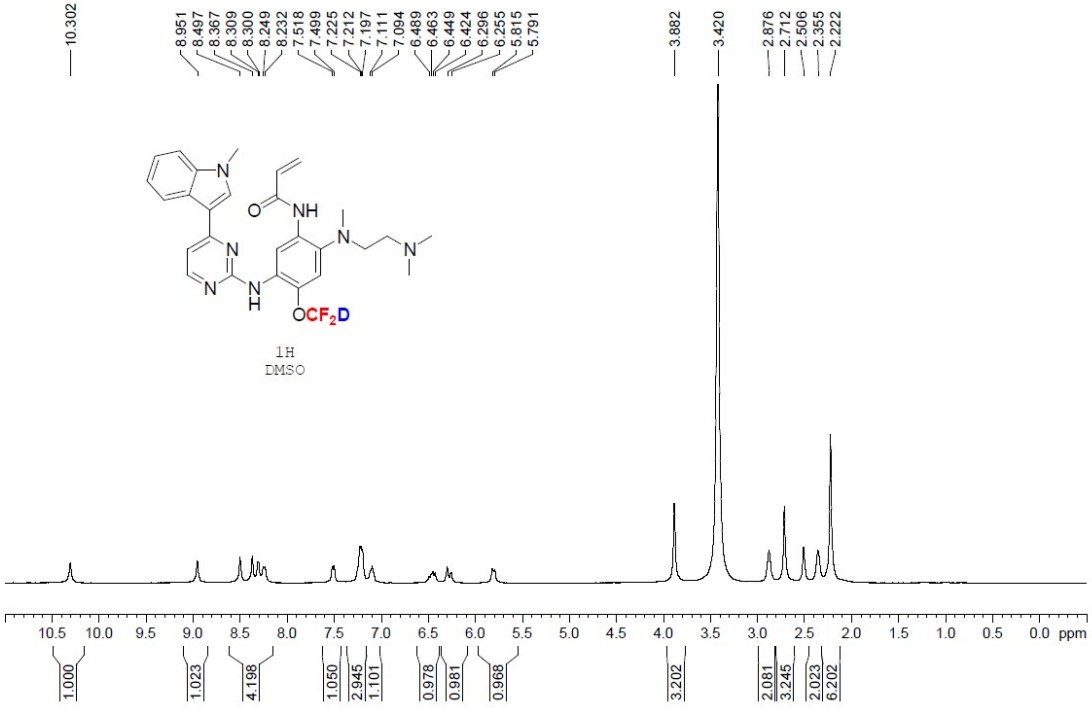


Figure S76 ^{1}H NMR of compound **DFA-3** (d_6-DMSO)

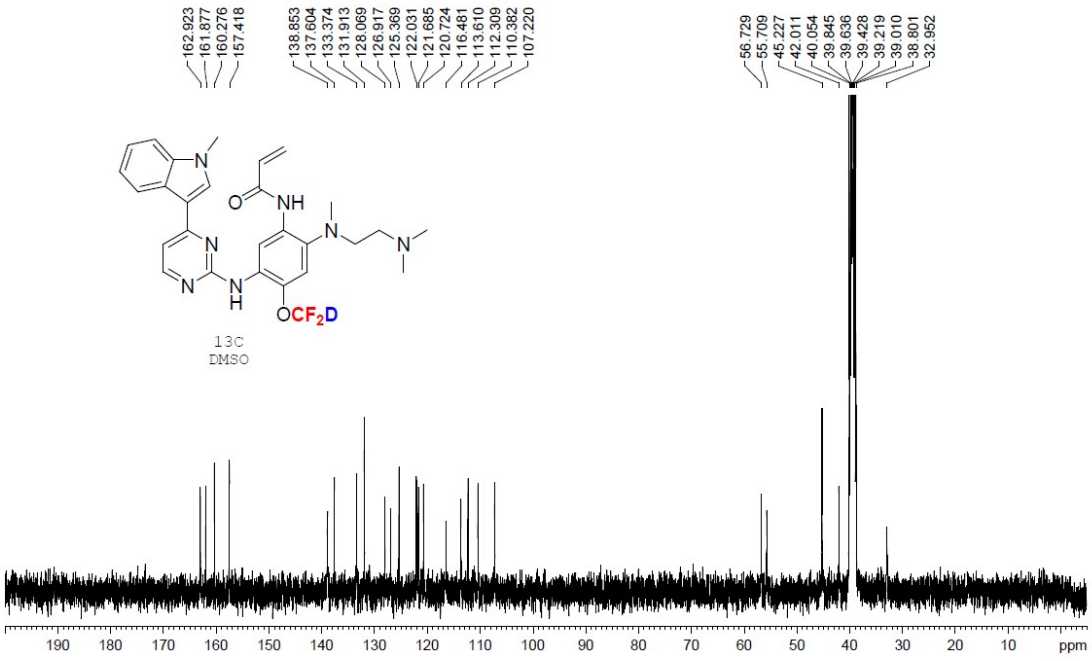


Figure S77 ^{13}C NMR of compound **DFA-3** (d_6-DMSO)

5. References:

(1) Y. S. Wu, C. S. Niu, Y. Geng, A. P. Liang, Z. W. Guo, J. T. Liu, J. L. Yang, Y. F. Huo, X. W. Han, Q. G. Meng, Patent, *CN* 106083736 A 2016.

(2) Hu, S., Liu, X., Bai, J., Long, W. Patent, *WO* 2015003658 A1, 2015.

(3) R. A. Ward, M. J. Anderton, S. Ashton, P. A. Bethel, M. Box, S. Butterworth, N. Colclough, C. G. Chorley, C. Chuaqui, D. A. E. Cross, L. A. Dakin, J. É. Debreczeni, C. Eberlein, M. R. V. Finlay, G. B. Hill, M. Grist, T. C. M. Klinowska, C. Lane, S. Martin, J. P. Orme, P. Smith, F. Wang, M. J. Waring, *J. Med. Chem.* 2013, **56**, 7025.

(4) Y. S. Wu; Y. Geng, D. Zou, J. Y. Li, C. S. Niu, M. L. Zheng, A. P. Liang, Patent, *CN* 107226769 A, 2017.