Multistep Synthesis of Cationic Lipid-like Compounds Based on a Difluorotetrahydropyridine Scaffold as Amphiphilic Nanocarriers

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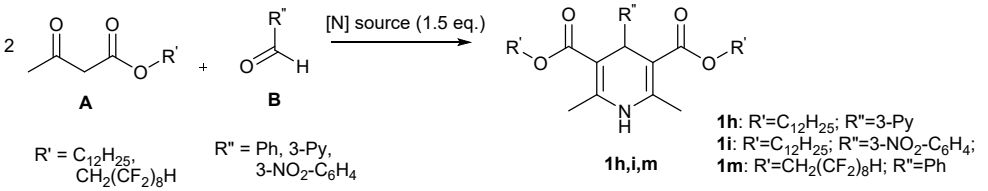
1.1. Synthesis of 1,4-dihydropyridines 1h-j,m.

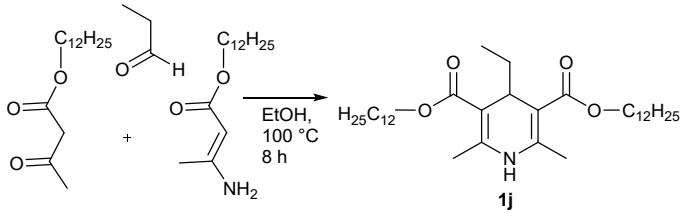


Scheme S1. *Synthesis of 1,4-dihydropyridines **1h,i,m**.*

Didodecyl 2',6'-dimethyl-1',4'-dihydro-[3,4'-bipyridine]-3',5'-dicarboxylate (1h).
A mixture of dodecyl 3-oxobutanoate (2.5 g, 9.5 mmol), 3-pyridinecarboxaldehyde (0.5 g, 439 µL, 4.73 mmol) and ammonium acetate (0.51 g, 7.1 mmol) was stirred at reflux in ethanol (15 mL) for 8 h. After cooling the reaction mixture to 4 °C, the resulting precipitates were filtered, recrystallised from ethanol, and dried under vacuum giving compound **1h** (1.65 g, 58%) as a slightly yellow solid; Mp. 144–145 °C, decomposition. ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.52 (dd, $^{3}J_{H\text{-}H}$ = 2.4 Hz, $^{4}J_{H\text{-}H}$ = 0.8 Hz, 1H, CH, Py), 8.36 (dd, $^{3}J_{H\text{-}H}$ = 4.8 Hz, $^{4}J_{H\text{-}H}$ = 1.7 Hz, 1H, CH, Py), 7.61 – 7.54 (m, 1H, CH, Py), 7.13 (ddd, $^{3}J_{H\text{-}H}$ = 7.8 Hz, $^{3}J_{H\text{-}H}$ = 4.8 Hz, $^{4}J_{H\text{-}H}$ = 0.9 Hz, 1H, CH, Py), 6.06 (s, 1H, NH), 4.98 (s, 1H, CH(4)), 4.09 – 3.95 (m, 4H, 2×$COOC\underline{H_2}(CH_2)_{10}CH_3$), 2.34 (s, 6H, 2×$CH_3$), 1.63 – 1.54 (m, 4H, 2×$COOCH_2(CH_2)_9C\underline{H_2}CH_3$), 1.30 – 1.23 (m, 36H, 2×$COOCH_2(C\underline{H_2})_9CH_2CH_3$), 0.92 – 0.82 (m, 6H, 2×$COOC_{11}H_{22}C\underline{H_3}$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 167.4, 149.7, 147.4, 144.8, 143.4, 135.7, 123.2, 103.5, 64.3, 37.9, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 28.8, 26.2, 22.8, 19.7, 14.3 ppm. HRMS (TOF MS ES+): calculated [$C_{38}H_{63}N_2O_4$ + H] 611.4788; found 611.4796.

Didodecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate (1i).
A mixture of dodecyl 3-oxobutanoate (2.05 g, 7.6 mmol), 3-nitrobenzaldehyde (0.56 g, 3.7 mmol) and ammonium acetate (0.43 g, 5.6 mmol) was stirred at reflux in ethanol (15 mL) for 24 h. After cooling the reaction mixture to 4 °C, the resulting precipitates were filtered, washed with cold methanol, and dried under vacuum giving compound **1i** (1.4 g, 77%) as a yellow solid; Mp. 88–89 °C. ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.15 – 8.09 (m, 1H, CH, Ph), 8.05 – 7.96 (m, 1H, CH, Ph), 7.68 – 7.59 (m, 1H, CH, Ph), 7.40 – 7.31 (m, 1H, CH, Ph), 5.72 (s, 1H, NH), 5.09 (s, 1H, CH(4)), 4.10 – 3.95 (m, 4H, 2×$COOC\underline{H_2}(CH_2)_{10}CH_3$), 2.37 (s, 6H, 2×$CH_3$), 1.63 – 1.53 (m, 4H, 2×$COOCH_2(CH_2)_9C\underline{H_2}CH_3$), 1.30 – 1.21 (m, 36H, 2×$COOCH_2(C\underline{H_2})_9CH_2CH_3$), 0.91 – 0.84 (m, 6H, 2×$COOC_{11}H_{22}C\underline{H_3}$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 167.3, 150.0, 148.3, 144.8, 134.6, 128.7, 123.2, 121.5, 103.6, 64.4, 40.0, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 26.2, 22.8, 19.8, 14.3 ppm. HRMS (TOF MS ES+): calculated [$C_{39}H_{61}N_2O_6$ + H] 653.4530; found 653.4532.

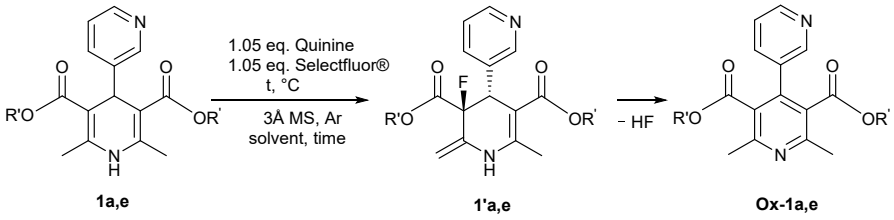
Bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1m).
A mixture of 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluoro 3-oxobutanoate (2.5 g, 4.8 mmol), benzaldehyde (0.51 g, 480µL, 2.4 mmol) and 25% ammonia solution (0.41 g, 456 µL, 3.6 mmol) was stirred at 100 °C in 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononan-1-ol (5 mL) for 24 h and then concentrated in vacuum. The crude product was purified by flash chromatography (eluent: EtOAc/Hexane 1:1) giving compound **1m** as a slightly yellow oil (1.32 g, 25%). ^{1}H-NMR (400 Hz, DMSO-d_6): δ 9.37 (s, 1H, NH), 7.34 – 7.01 (m, 7H, 5×CH, Ph and 2×$COOCH_2(CF_2)_8\underline{H}$), 4.90 – 4.75 (m, 3H, CH(4) and $COOC\underline{H_2}(CF_2)_8H$), 4.59 (q, $^{3}J_{H\text{-}F}$ = 13.6 Hz, 2H, $COOC\underline{H_2}(CF_2)_8H$), 2.31 (s, 6H, 2×$CH_3$) ppm. ^{13}C-NMR (101 Hz, DMSO-d_6): δ 165.3, 148.9, 147.7, 128.5, 127.4, 126.8, 108.4, 101.1, 59.1, 58.9, 58.7 (t, *J* = 26 Hz), 58.6, 38.2, 18.7 ppm. ^{19}F-NMR (376 Hz, DMSO-d_6): δ -118.58 (s, 4F), -122.10 (s, 12F), -122.66 (d, *J* = 15 Hz, 4F), -123.22 (s, 4F), -129.01 (s, 4F), -138.61 (d, *J* = 50 Hz, 4F) ppm. HRMS (TOF MS ES+): calculated [$C_{33}H_{20}NO_4F_{32}$ + H] 1102.0881; found 1102.0897.



Scheme S2. *Synthesis of 1,4-dihydropyridine **1j**.*

Didodecyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1j).
A mixture of propionaldehyde (2.15 g, 2.65 mL, 0.037 mol), dodecyl 3-oxobutanoate (10 g, 0.037 mol) and dodecyl 3-aminobutanoate (10 g, 0.037 mol) was stirred at reflux in ethanol (15 mL) for 8 h. After cooling the reaction mixture to 4 °C, the resulting precipitates were filtered, recrystallised twice from ethanol, and dried under vacuum giving compound **1j** (15.9 g, 76%) as a slightly yellow solid; Mp. 47–49 °C. ^{1}H-NMR (400 Hz, $CDCl_3$): δ 5.48 (s, 1H, NH), 4.18 – 4.02 (m, 4H, 2×$COOC\underline{H_2}(CH_2)_{10}CH_3$), 3.93 (t, $^{3}J_{H\text{-}H}$ = 5.5 Hz, 1H, CH(4)), 2.28 (s, 6H, 2×CH_3), 1.70 – 1.59 (m, 4H, 2×$COOCH_2C\underline{H_2}(CH_2)_8CH_2CH_3$), 1.40 – 1.33 (m, 6H, 2×$COOCH_2(CH_2)_9C\underline{H_2}CH_3$ and $COOC\underline{H_2}CH_3$), 1.30 – 1.23 (m, 32H, 2×$COOCH_2CH_2(C\underline{H_2})_8CH_2CH_3$), 0.91 – 0.84 (m, 6H, 2×$COOC_{11}H_{22}C\underline{H_3}$), 0.75 (t, *J* = 7.5 Hz, 3H, $COOCH_2C\underline{H_3}$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 168.4, 144.9, 103.0, 63.9, 34.2, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 26.3, 22.8, 19.6, 14.3, 9.4 ppm. HRMS (TOF MS ES+): calculated [$C_{35}H_{62}NO_4$ + H – 2H] 660.4679; found 660.4678.

1.2. Monofluorination of 1,4-dihydropyridnes 1a,e



Scheme S3. *Monofluorination of 1,4-dihydropyridines **1a,e**.*

General procedure: To a solution of Quinine (1.05 eq.) and Selectfluor® (1.05 eq.) in dry MeCN (3 mL) under an argon atmosphere 3Å MS were added. The reaction mixture was stirred for 1 hour followed by the addition of 1,4-dihydropyridine (0.05 mmol, 1.0 eq.). After being stirred at RT for additional 24 hours the reaction mixture was concentrated in vacuum, resuspended in diethyl ether, filtered and the filtrate was concentrated in vacuum. The remaining residue was purified via column chromatography (eluent: mixture of EtOAc/PE) giving:

Dimethyl (3',4')-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (1'a). Following the general procedure and using quinine (15 mg, 0.05 mmol), Selectfluor® (17 mg, 0.05 mmol) and 1,4-DHP **1a** (15 mg, 0.05 mmol), after purification with column chromatography (eluent: EtOAc/PE = 1/3), compound **1'a** (11 mg, 66%) was obtained as a pale yellow solid. ^{1}H-NMR (400 Hz, DMSO-d_6): δ 9.40 (br s, 1H, NH), 8.38 (dd, $^{3}J_{H\text{-}H}$ = 4.9 Hz, $^{4}J_{H\text{-}H}$ = 1.5 Hz, 1H, CH, Py), 8.21 (d, $^{4}J_{H\text{-}H}$ = 1.9 Hz, 1H, CH, Py), 7.35 (dt, $^{3}J_{H\text{-}H}$ = 7.8, $^{4}J_{H\text{-}H}$ = 1.9 Hz, 1H, CH, Py), 7.26 (dd, $^{3}J_{H\text{-}H}$ = 7.8 Hz, $^{4}J_{H\text{-}H}$ = 4.9 Hz, 1H, CH, Py), 4.88 – 4.83 (m, 1H, $=CH_A\underline{H_B}$), 4.49 – 4.43 (m, 1H, $=C\underline{H_A}H_B$), 4.26 (d, $^{3}J_{H\text{-}F}$ = 10.7 Hz, 1H, CH(4)), 3.55 (s, 3H, $COOC\underline{H_3}$), 3.46 (s, 3H, $COOC\underline{H_3}$), 2.36 (s, 3H, CH_3) ppm. ^{13}C-NMR (101 Hz, DMSO-d_6): δ 166.8 (d, *J* = 25 Hz), 166.5, 149.4, 148.2, 148.1, 135.8 (d, *J* = 16 Hz), 135.4, 135.0 (d, *J* = 8 Hz), 123.3, 97.4 (d, *J* = 9 Hz), 95.3, 91.1 (d, *J* = 186 Hz), 52.5, 50.5, 45.2 (d, *J* = 29 Hz), 19.1 ppm. ^{19}F-NMR (376 Hz, DMSO-d_6): δ -136.9 (m) ppm.

Diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (1'e). Following the general procedure and using quinine (15 mg, 0.05 mmol), Selectfluor® (17 mg, 0.05 mmol) and 1,4-DHP **1e** (15 mg, 0.05 mmol), after purification with column chromatography (eluent: EtOAc/PE = 1/3), compound **1'e** (11 mg, 72%) was obtained as a pale yellow solid. ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.45 (dd, $^{3}J_{H\text{-}H}$ = 4.9 Hz, $^{4}J_{H\text{-}H}$ = 1.5 Hz, 1H, CH, Py), 8.37 (d, $^{4}J_{H\text{-}H}$ = 1.9 Hz, 1H, CH, Py), 7.42 (dt, $^{3}J_{H\text{-}H}$ = 7.9 Hz, $^{4}J_{H\text{-}H}$ = 1.9 Hz, 1H, CH, Py), 7.18 (dd, $^{3}J_{H\text{-}H}$ = 7.9 Hz, $^{4}J_{H\text{-}H}$ = 4.9 Hz, 1H, CH, Py), 6.73 (br s, 1H, NH), 4.77 – 4.74 (m, 1H, $=CH_A\underline{H_B}$), 4.59 (dd, $^{2}J_{H\text{-}F}$ = 5.7 Hz, $^{4}J_{H\text{-}F}$ = 2.0 Hz, 1H, $=C\underline{H_A}H_B$), 4.40 (d, $^{3}J_{H\text{-}F}$ = 11.8 Hz, 1H, CH(4)), 4.13 – 4.05 (m, 1H, $COOCH_A\underline{H_B}CH_3$), 4.04 – 3.95 (m, 3H, $COOC\underline{H_2}CH_3$ un $COOC\underline{H_A}H_BCH_3$), 2.44 (s, 3H, CH_3), 1.14 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 3H, $COOCH_AH_BC\underline{H_3}$), 1.05 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 3H, $COOCH_AH_BC\underline{H_3}$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 167.0 (d, *J* = 25 Hz), 166.8, 150.0, 148.3, 146.7, 136.2, 136.1 (d, *J* = 18 Hz), 135.6 (d, *J* = 8 Hz), 123.3, 98.1, 97.5 (d, *J* = 9 Hz), 91.1 (d, *J* = 188 Hz), 62.2, 59.7, 46.1 (d, *J* = 28 Hz), 20.4, 14.4, 13.9 ppm. ^{19}F-NMR (376 Hz, $CDCl_3$): δ -138.0 (m) ppm.

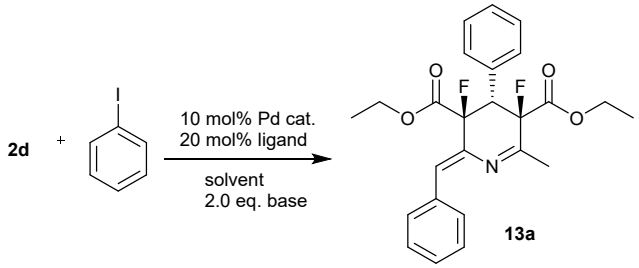
Stability and transformation of 3-fluoro-2-methylene-1,2,3,4-tetrahydropyridine derivatives

The 3-fluoro-2-methylene-1,2,3,4-tetrahydropyridine-3,5-dicarboxylates **1'a,e**, obtained as products from equimolar reactions of 1,4-DHPs **1a,e** with *N*-fluoro quinine were found to be unstable. After one week of storage, these compounds were converted to the corresponding pyridines **Ox-1a,e** through the elimination of hydrogen fluoride. The structure of obtained diethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1e**) was confirmed by NMR spectra (Figure S21), ^{1}H-NMR data were in accordance with the literature.[1] Dimethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1a**) was confirmed by LC-MS data in analogy with compound **Ox-1e**. The synthesis of dimethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1a**) from the corresponding 1,4-DHP derivatives was previously reported.[2]

Dimethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1a**): ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.63 (dd, $^3J_{H\text{-}H}$ = 4.9 Hz, $^4J_{H\text{-}H}$ = 1.7 Hz, 1H, CH, Py), 8.49 (dd, $^4J_{H\text{-}H}$ = 2.3 Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 1H, CH, Py), 7.59 (ddd, $^3J_{H\text{-}H}$ = 7.9 Hz, $^4J_{H\text{-}H}$ = 2.3 Hz, $^4J_{H\text{-}H}$ = 1.7 Hz 1H, CH, Py), 7.33 (ddd, $^3J_{H\text{-}H}$ = 7.9 Hz, $^3J_{H\text{-}H}$ = 4.9, Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 1H, CH, Py), 3.57 (s, 6H, 2×$COOCH_3$), 2.62 (s, 6H, 2×$C\underline{H}_3$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 168.0, 156.3, 149.7, 148.5, 135.6, 132.5, 126.9, 122.9, 77.4, 52.5, 23.3 ppm.
Diethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1e**): ^{1}H-NMR (400 Hz, $CDCl_3$): δ 8.61 (dt, $^3J_{H\text{-}H}$ = 4.9 Hz, $^4J_{H\text{-}H}$ = 1.5 Hz, 1H, CH, Py), 8.50 (dt, $^4J_{H\text{-}H}$ = 2.4 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz, 1H, CH, Py), 7.58 (ddd, $^3J_{H\text{-}H}$ = 7.8 Hz, $^4J_{H\text{-}H}$ = 2.4 Hz, $^4J_{H\text{-}H}$ = 1.5 Hz 1H, CH, Py), 7.30 (ddd, $^3J_{H\text{-}H}$ = 7.8 Hz, $^3J_{H\text{-}H}$ = 4.9, Hz, $^4J_{H\text{-}H}$ = 1.2 Hz, 1H, CH, Py), 4.05 – 3.98 (m, 4H, 2×$COOC\underline{H}_2CH_3$), 2.60 (s, 6H, 2×$C\underline{H}_3$), 0.96 – 0.90 (m, 6H, 2×$COOCH_2C\underline{H}_3$) ppm. ^{13}C-NMR (101 Hz, $CDCl_3$): δ 167.4, 156.1, 149.7, 148.7, 142.7, 135.8, 132.7, 127.0, 122.8, 61.7, 23.2, 13.8 ppm.

1.3. Heck reaction

Table S1. *Studies of Heck reaction of 2-methylenetetrahydropyridine **2d** with iodobenzene*.



Entry	Pd cat.	Solvent	Base	Ligand	T (°C)	Time (h)	Conversion[a] (%)
1	$Pd(OAc)_2$	DMF	TEA	PPh_3	90	18	0
2	$Pd(dppf)Cl_2$	DMF	TEA	PPh_3	90	18	0
3	$Pd(OAc)_2$	MeCN	Ag_2CO_3	PPh_3	RT	18	0
4	$Pd(OAc)_2$	MeCN	Ag_2CO_3	PPh_3	60	18	< 5
5	$Pd(dppf)Cl_2$	MeCN	Ag_2CO_3	-	60	18	0
6	$Pd(PPh3)_2Cl_2$	MeCN	Ag_2CO_3	-	60	18	< 5

[a]By LCMS data

General procedure: To a stirred solution of 2-methylenetetrahydropyridine **2d** (1.0 eq.) in a pressure tube at the selected temperature of the experiment under an argon atmosphere, iodobenzene (1.3 eq.), base (2.0 eq.), Pd catalyst (10 mol%), and ligand (20 mol%, if required) were added. The reaction mixture was stirred at the selected temperature for 18 hours, with progress monitored by LC-MS.

1.4. Bromination of compound 2d

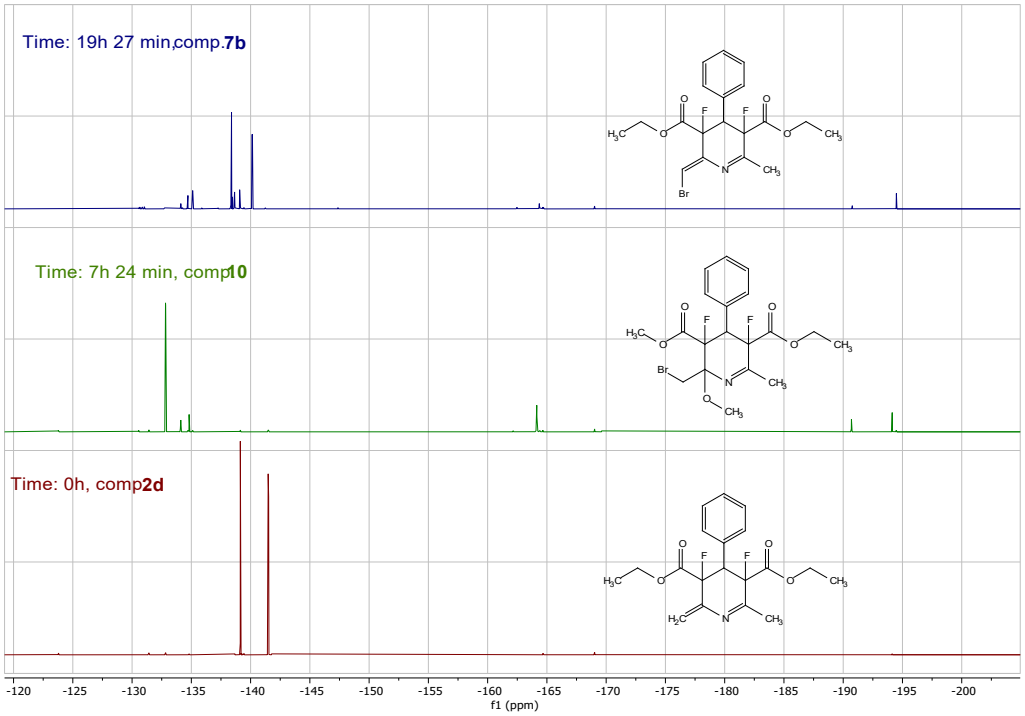
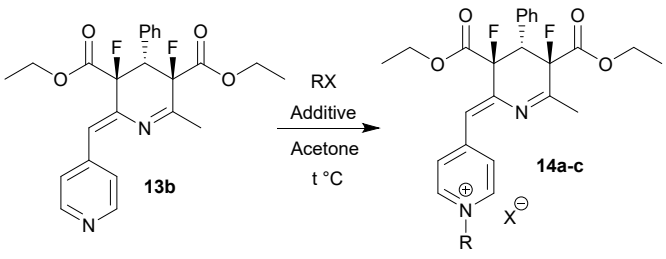


Figure S1. Studies *of bromination reaction the methylene group of 2-methylenetetrahydropyridine* ***2d*** *with NBS monitored via* ^{19}F *NMR spectroscopy to track intermediate formation and product conversion.*

2d: $^{19}F\{^{1}H\}$ NMR (564 MHz, MeOD) δ -139.15 (d, *J* = 22 Hz), -141.50 (d, *J* = 22 Hz).
10: $^{19}F\{^{1}H\}$ NMR (564 MHz, MeOD) δ -132.83 (d, *J* = 7 Hz), -164.14 (br.s).
7b: $^{19}F\{^{1}H\}$ NMR (564 MHz, MeOD) δ -138.37 (d, *J* = 22 Hz), -140.14 (d, *J* = 22 Hz).

1.5. Optimisation of quaternisation reaction

Table S2. *Screening for the optimal conditions of quaternisation of the pyridine moiety in dialkyl 3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylates* ***13b,c.***



Entry	Comp.	R	X	Additive	T (°C)	Time (days)	Conversion[a] (%)
1	**14a**	CH_3	I	-	RT	1	99
2	**14b**	C_6H_{13}	Br	-	50	3	9
3	**14b**	C_6H_{13}	Br	KI	50	3	28
4	**14b**	C_6H_{13}	Br	NaI	50	3	76
5	**14c**	$C_{12}H_{25}$	Br	-	50	3	0
6	**14c**	$C_{12}H_{25}$	Br	KI	50	3	15

[a]By LCMS data

General procedure: To a solution of 2-methylenetetrahydropyridine **13b** (1.0 eq.) in acetone (1 mL), the corresponding alkyl halide: MeI (5.0 eq.), hexyl bromide (3.0 eq.), or dodecyl bromide (3.0 eq.) was added. For

reactions with hexyl bromide or dodecyl bromide, potassium iodide (KI, 3.0 eq.) or sodium iodide (NaI, 3.0 eq.) was also added to the mixture. The reaction mixture was stirred at RT or heated to 50 °C, depending on the conditions, and the conversion was monitored by LC-MS.

1.6. Dynamic light scaterring measurements

Table S3. *DLS measurement results.*

Entry	Comp.	After 1 day storage		After 4 days storage		After 7 days storage		After 32 days storage		Zeta potencial ±SD (mV)
		D_{avg}±SD (nm)	PDI±SD	D_{avg}±SD (nm)	PDI±SD	D_{avg}±SD (nm)	PDI±SD	D_{avg}±SD (nm)	PDI±SD	
1	**14a**	61±2	0.17±0.01	65±2	0.25±0.02	62±1	0.23±0.01	61±1	0.23±0.01	21.2±0.5
2	**14b**	196±11	0.46±0.07	306±4	0.38±0.01	253±5	0.31±0.01	-	-	5.5±0.1
3	**14c**	117±1	0.26±0.01	108±1	0.17±0.01	111±1	0.17±0.01	115±3	0.19±0.01	40.9±1.2
4	**15a**	75±2	0.37±0.01	74±1	0.37±0.02	72±1	0.37±0.01	69±1	0.37±0.01	51.6±1.0
5	**15b**	199±3	0.56±0.01	202±2	0.54±0.01	183±1	0.47±0.01	160±3	0.44±0.01	46.4±1.2
6	**15c**	158±5	0.46±0.03	121±1	0.20±0.01	120±1	0.22±0.01	112±1	0.25±0.01	30.9±0.9

1.7. NMR spectra

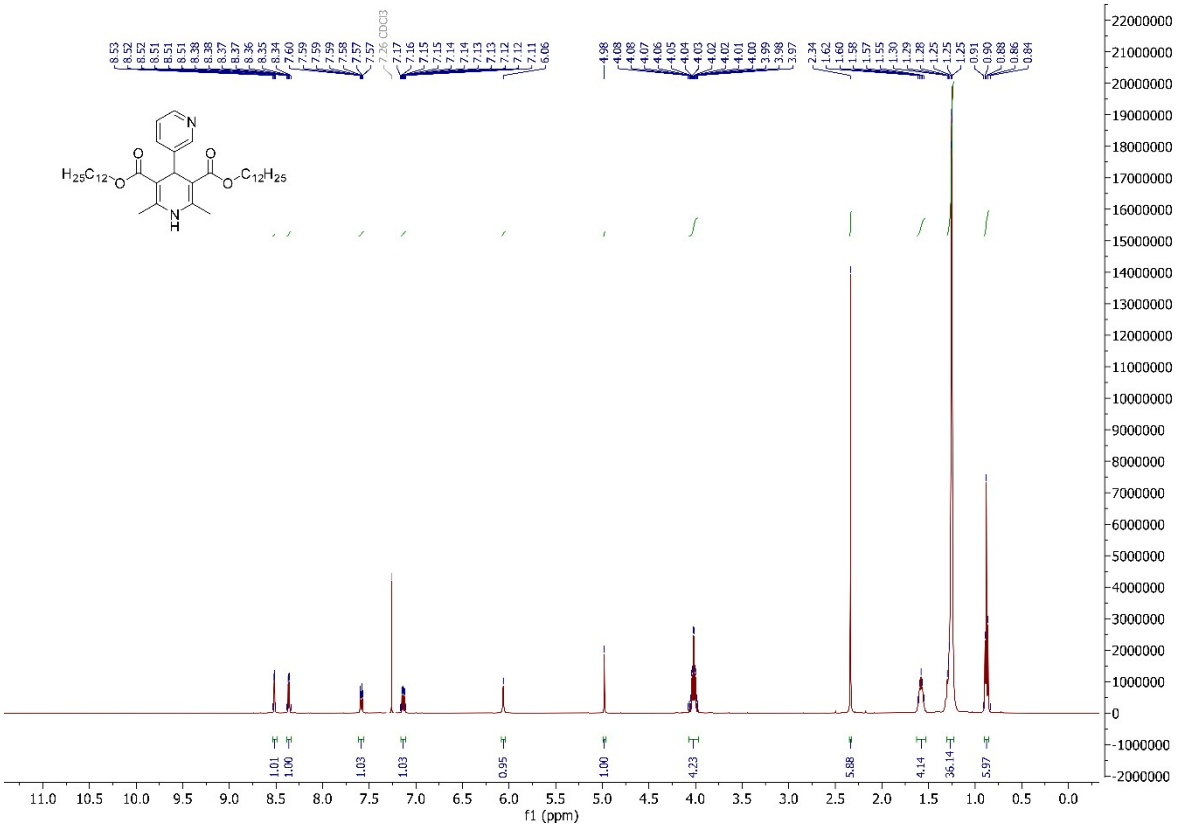


Figure S2. ^{1}H-NMR spectrum of didodecyl 2',6'-dimethyl-1',4'-dihydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1h**).

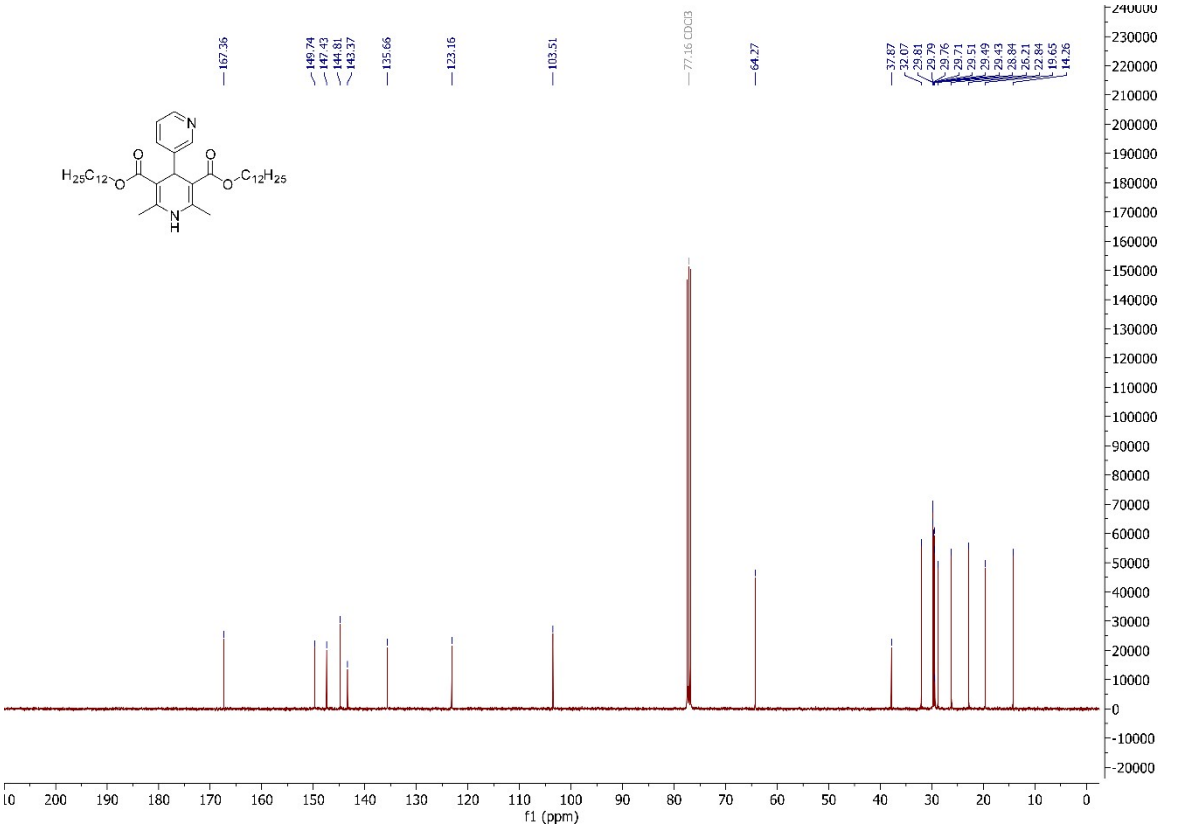


Figure S3. ^{13}C-NMR spectrum of didodecyl 2',6'-dimethyl-1',4'-dihydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1h**).

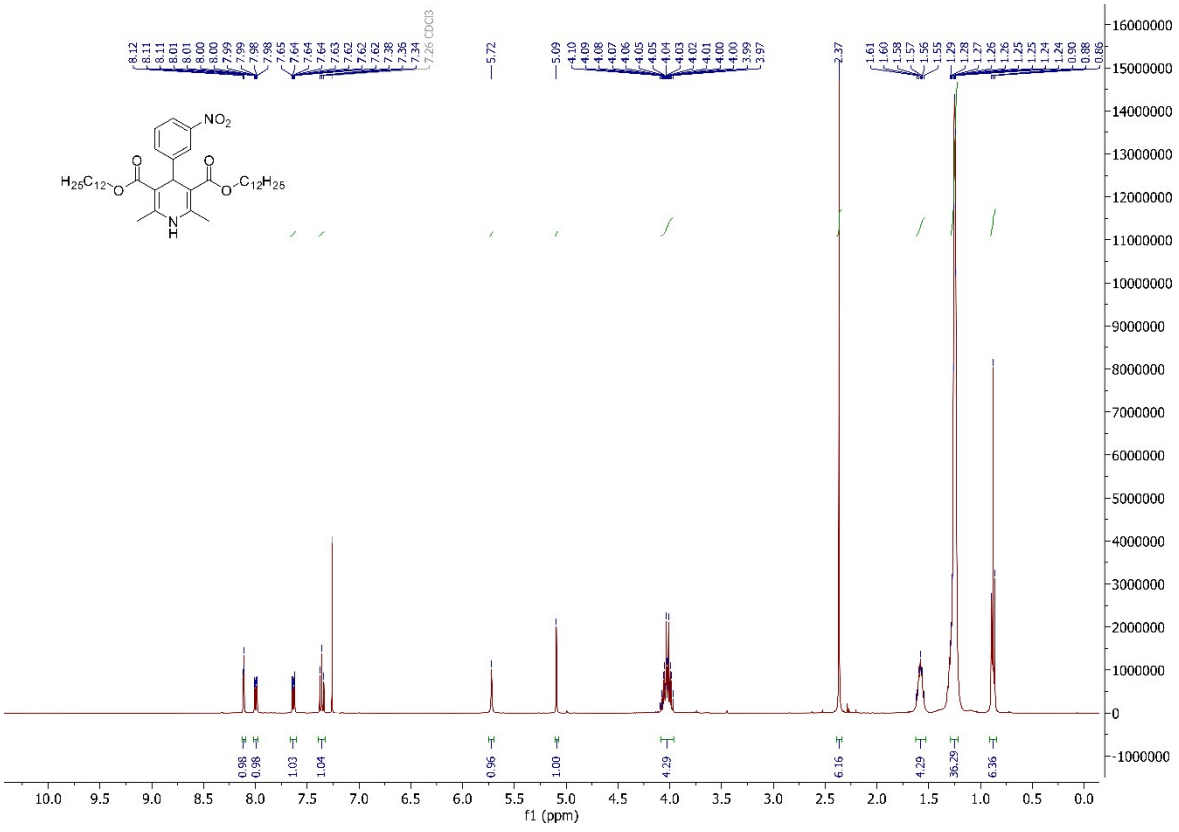


Figure S4. ^{1}H-NMR spectrum of didodecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate (**1i**).

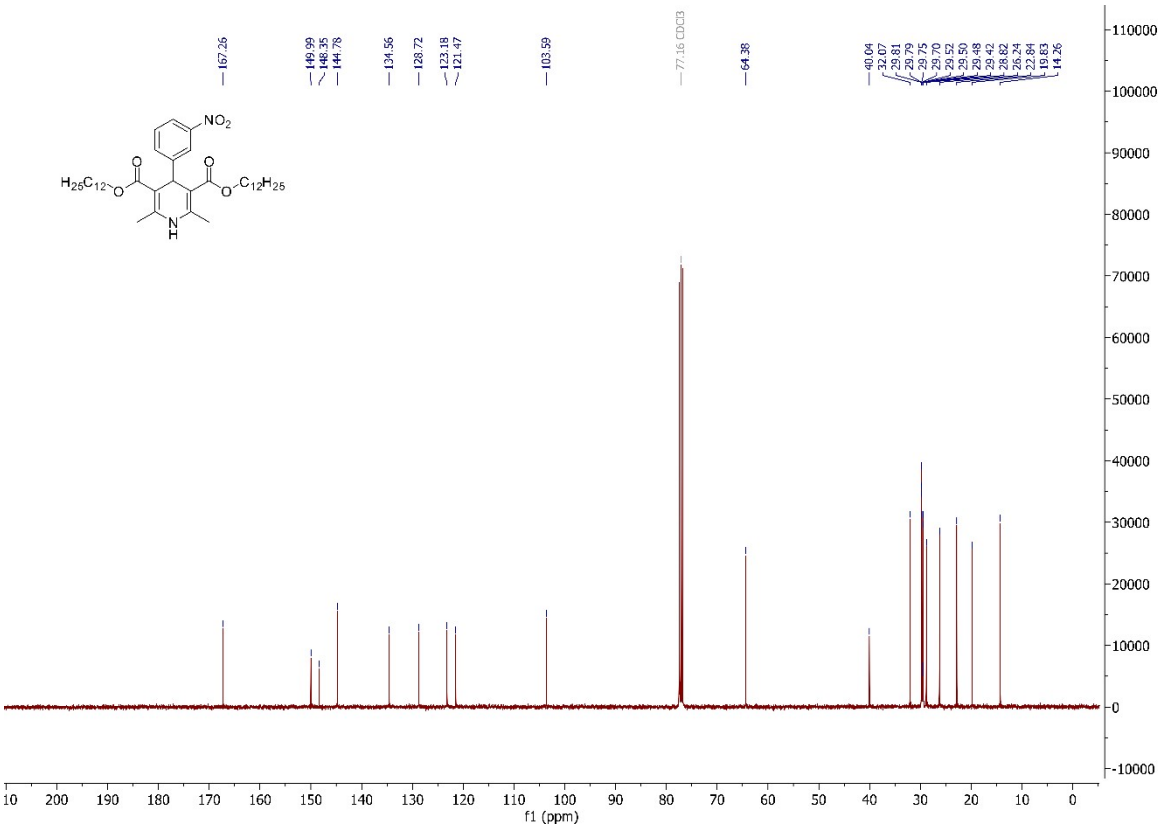


Figure S5. ^{13}C-NMR spectrum of didodecyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate (**1i**).

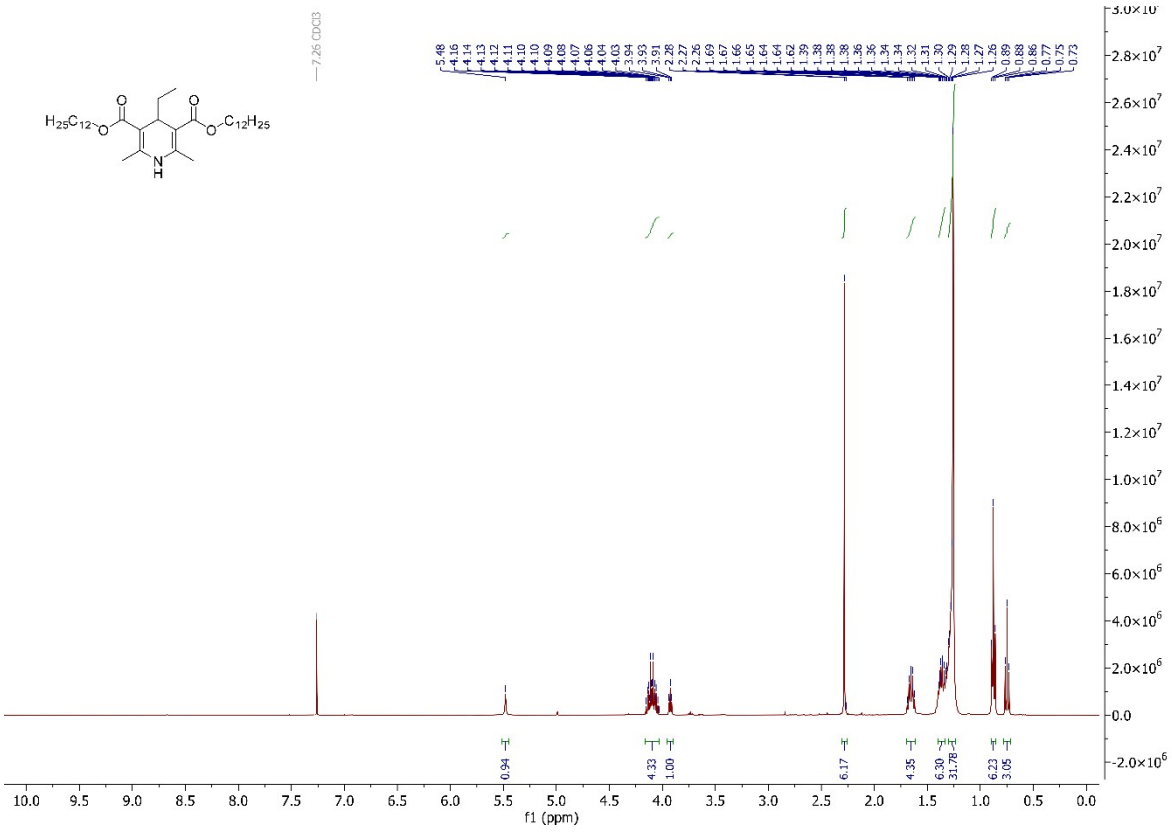


Figure S6. ^{1}H-NMR spectrum of didodecyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1j**).

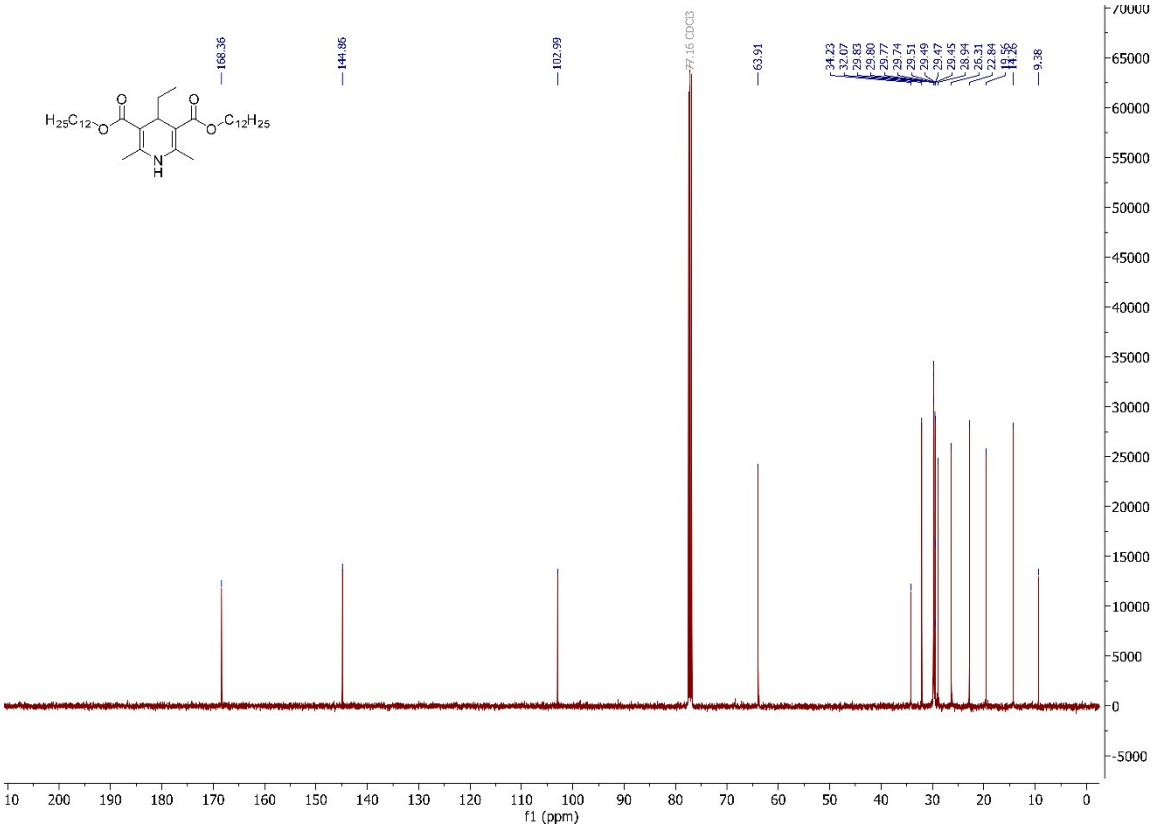


Figure S7. ^{13}C-NMR spectrum of didodecyl 4-ethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**1j**).

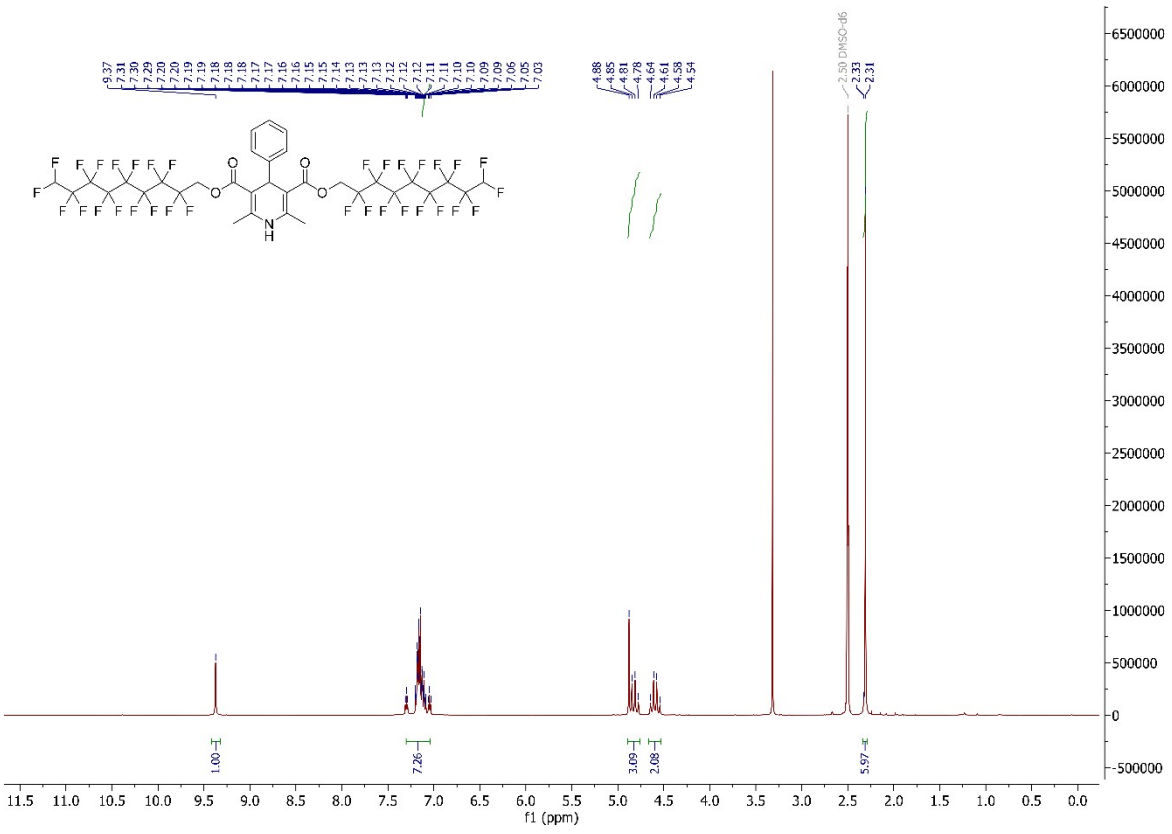


Figure S8. ^{1}H-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1m**).

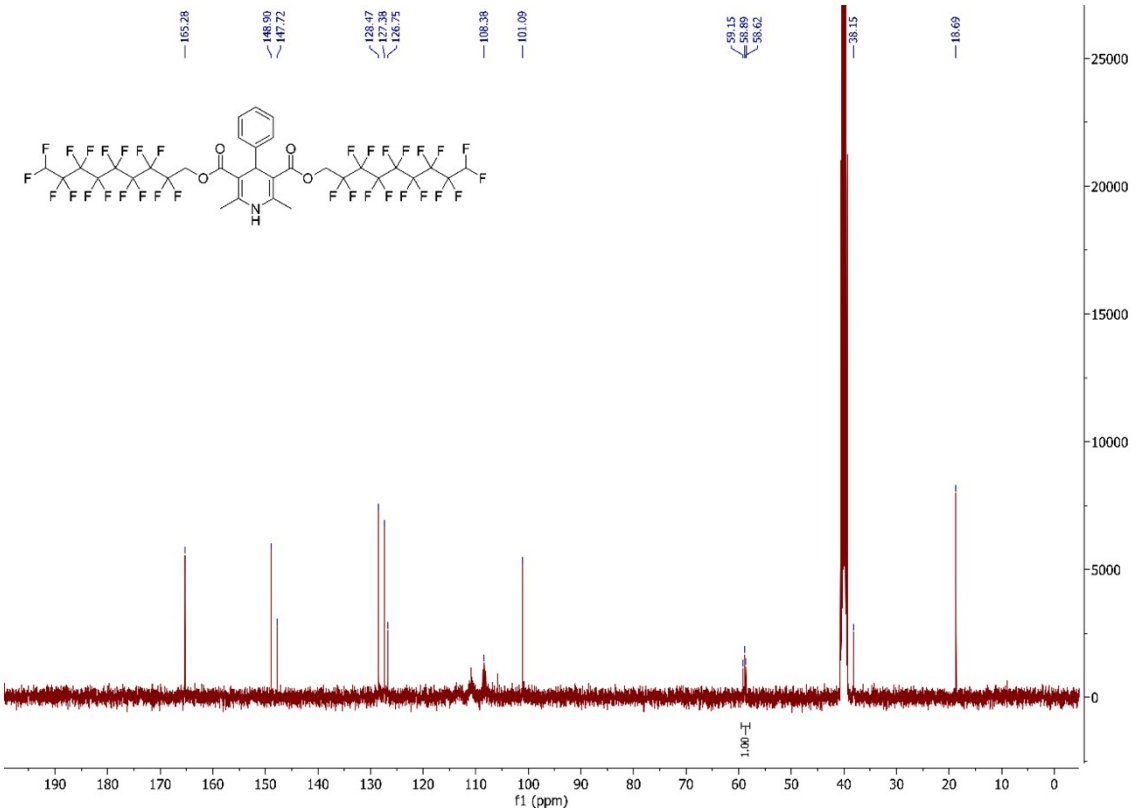


Figure S9. ^{13}C-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1m**).

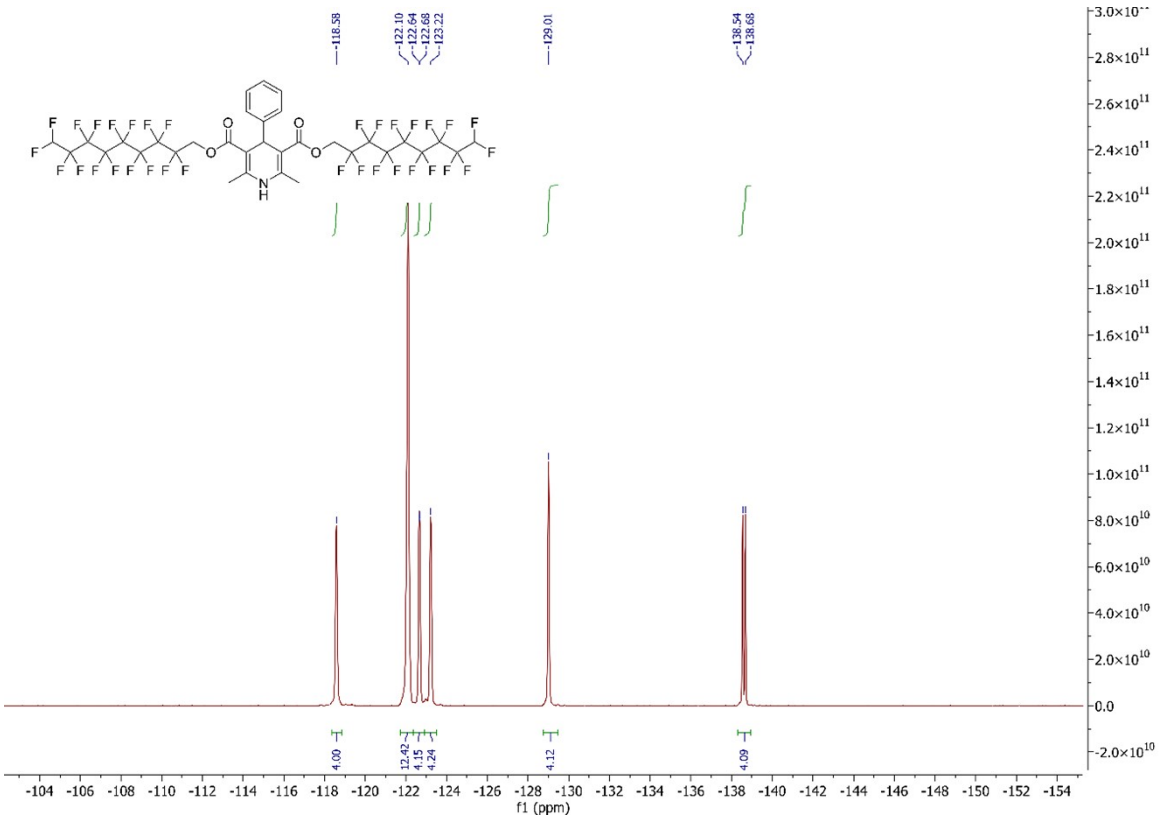


Figure S10. ^{19}F-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1m**).

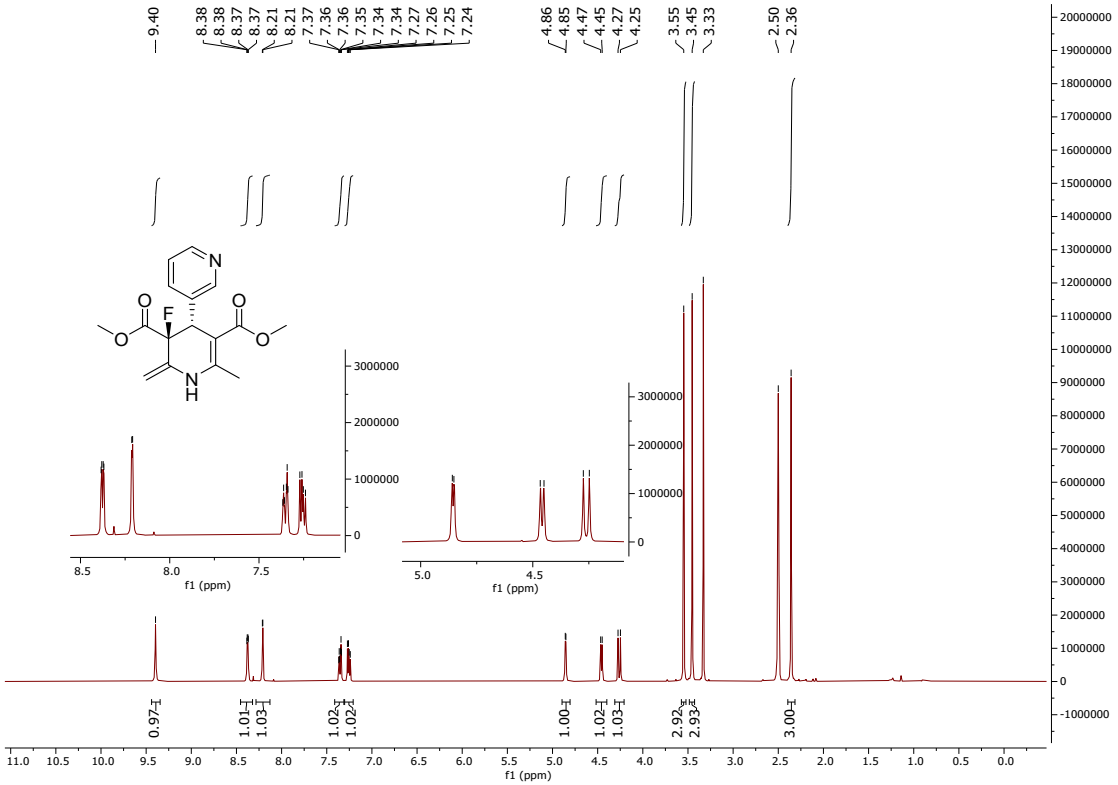


Figure S11. ^{1}H-NMR spectrum of dimethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'a**).

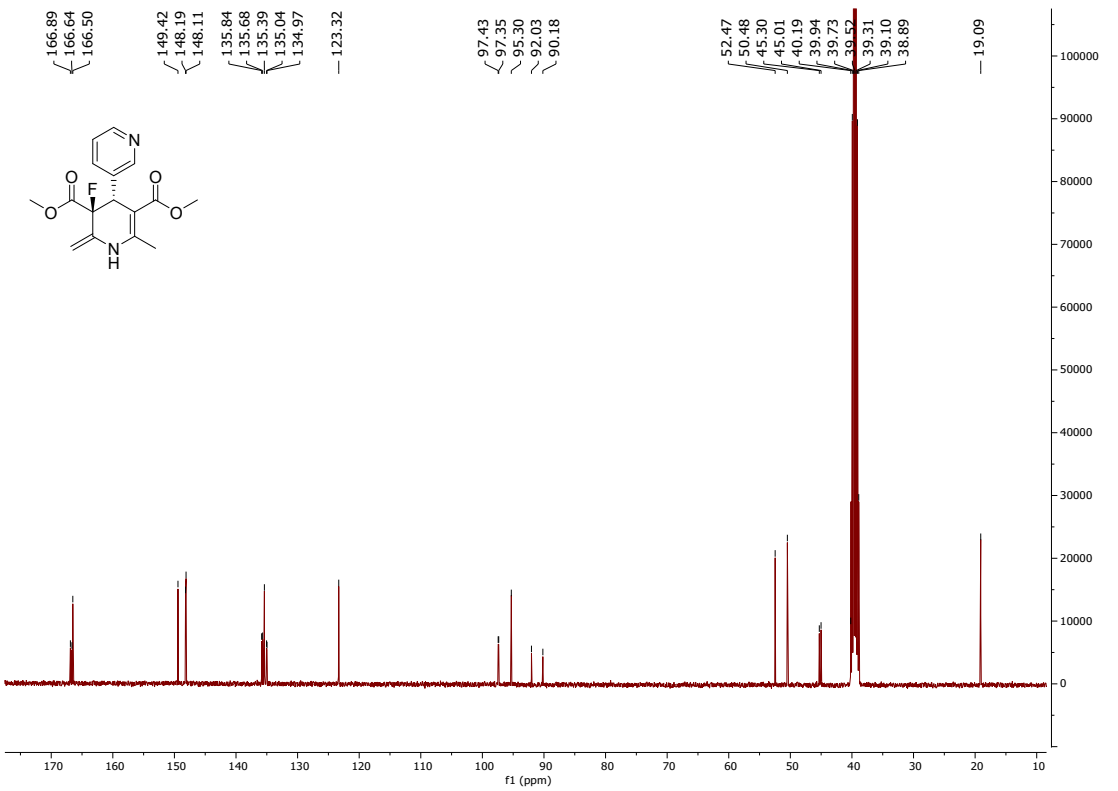


Figure S12. ^{13}C-NMR spectrum of dimethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'a**).

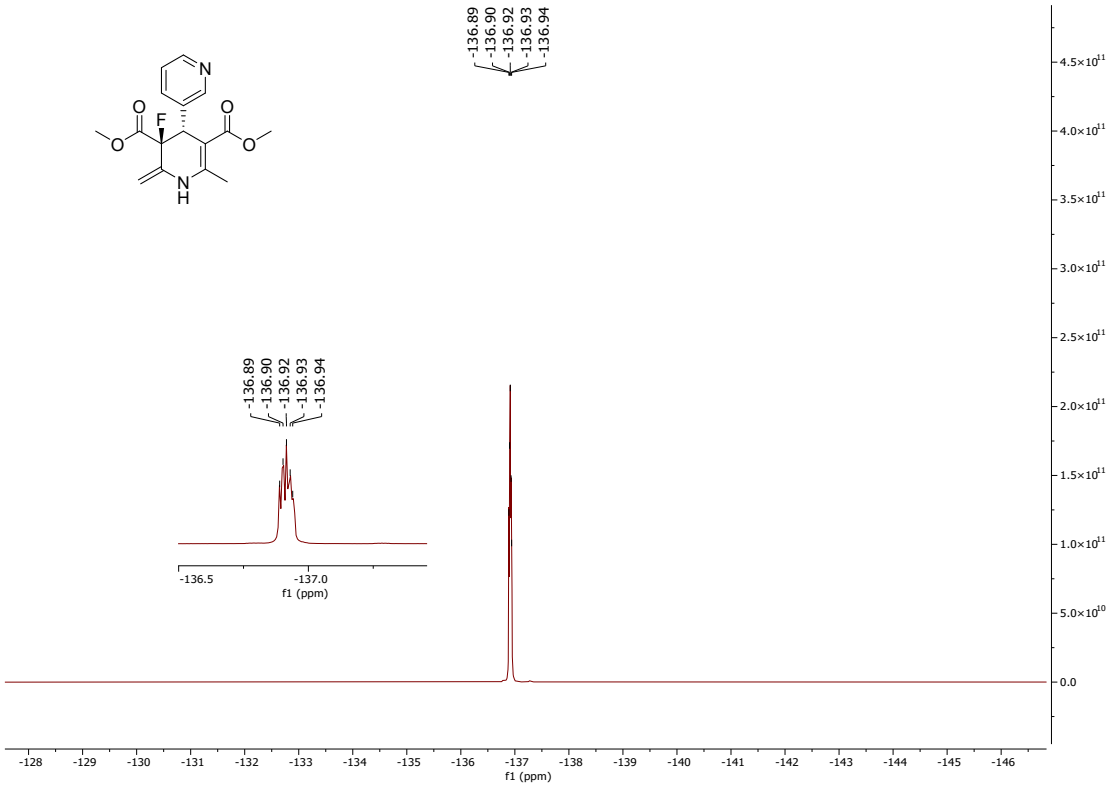


Figure S13. ^{19}F-NMR spectrum of dimethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'a**).

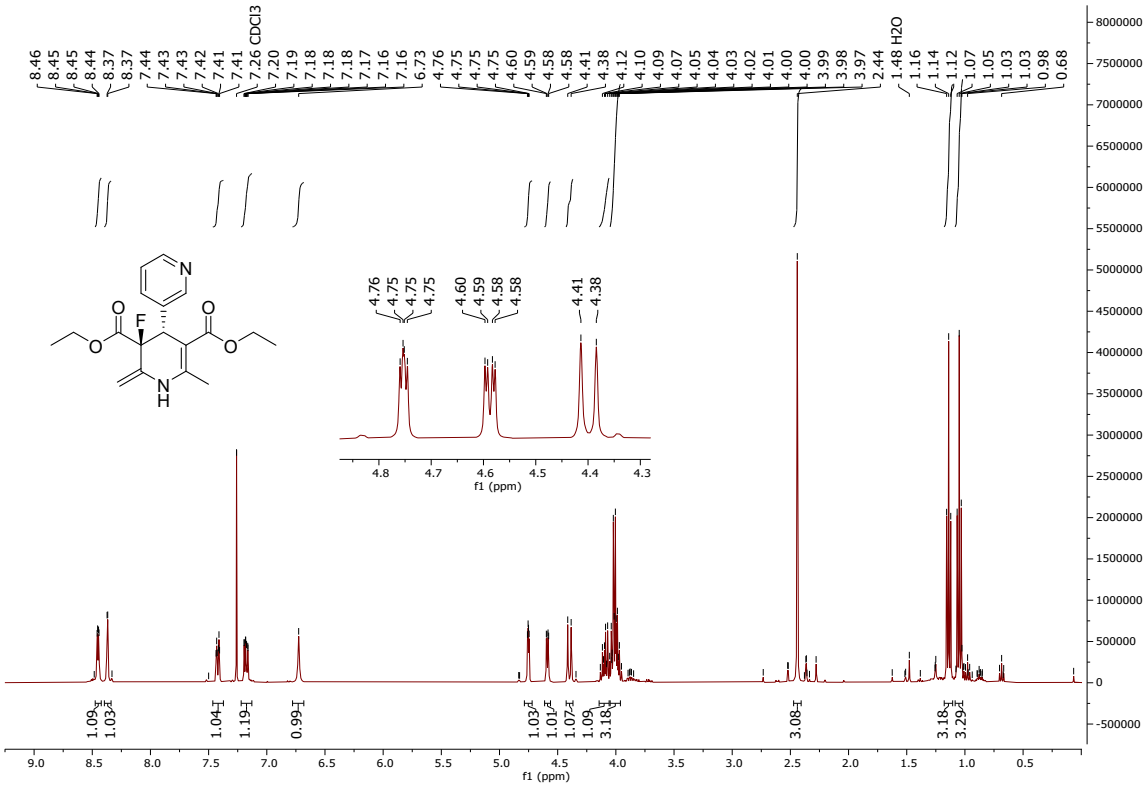


Figure S14. ^{1}H-NMR spectrum of diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'e**).

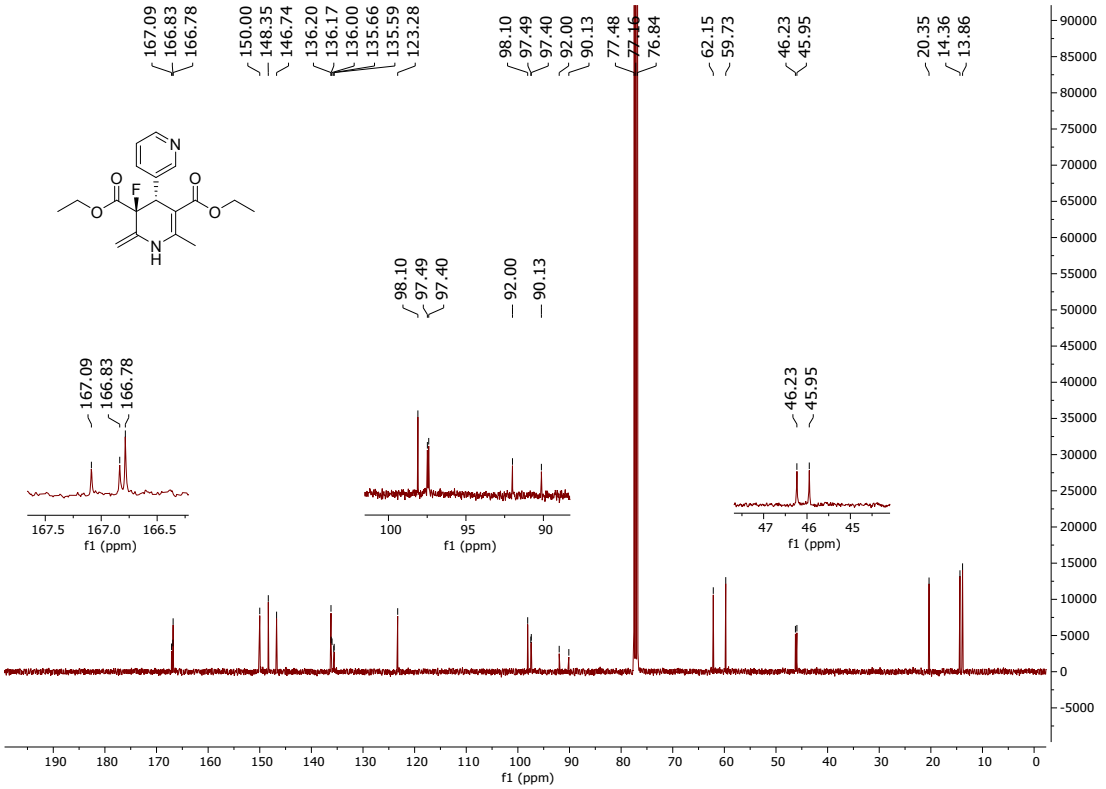


Figure S15. ^{13}C-NMR spectrum of diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'e**).

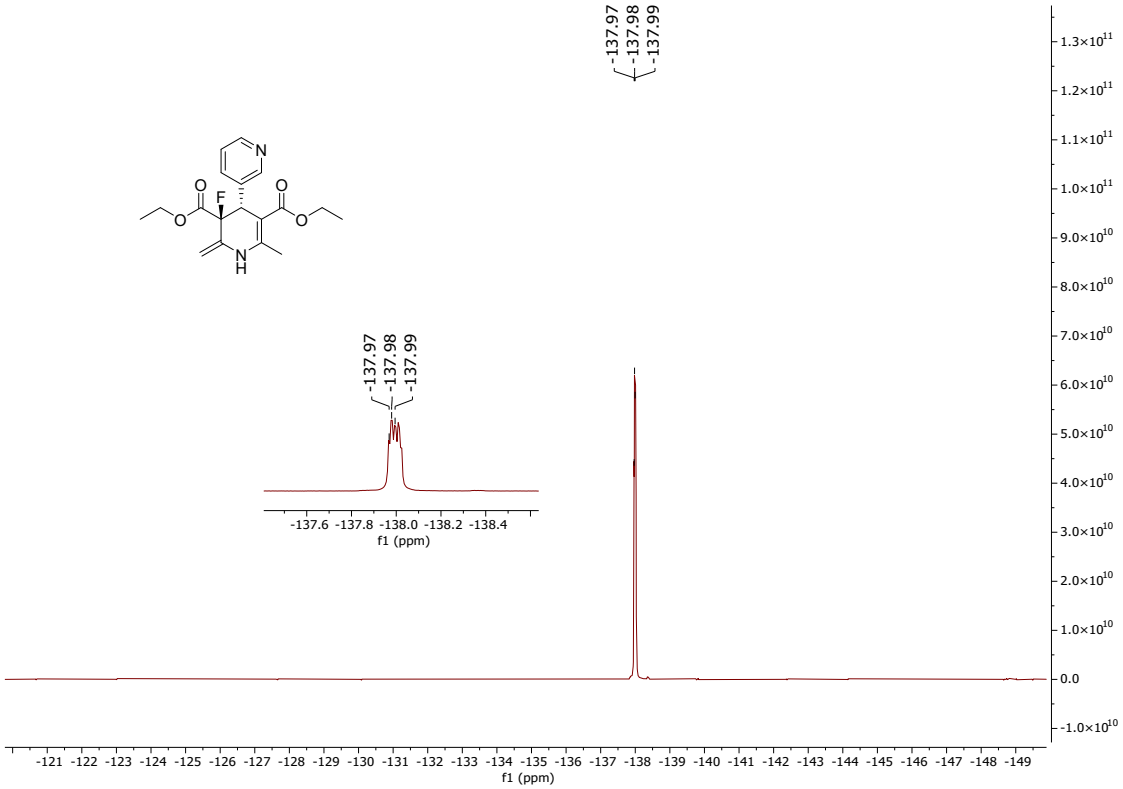


Figure S16. ^{19}F-NMR spectrum of diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'e**).

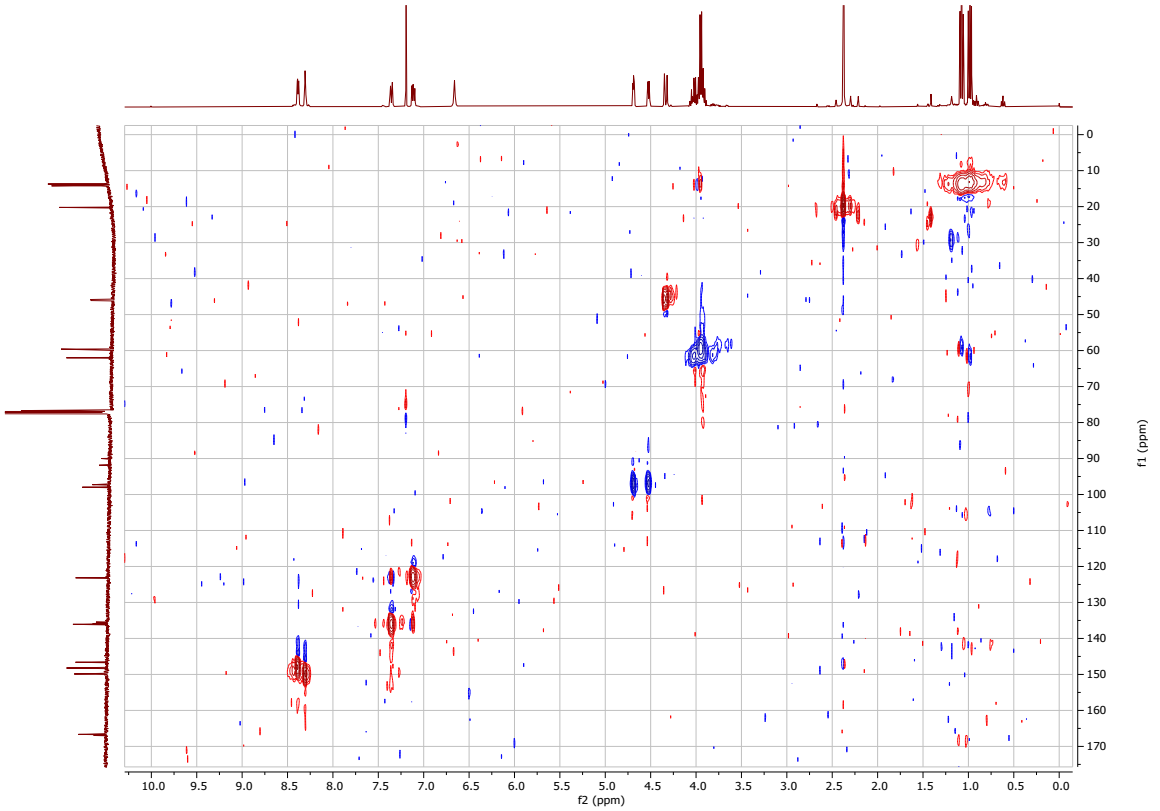


Figure S17. 2D HSQC NMR spectrum of diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'e**).

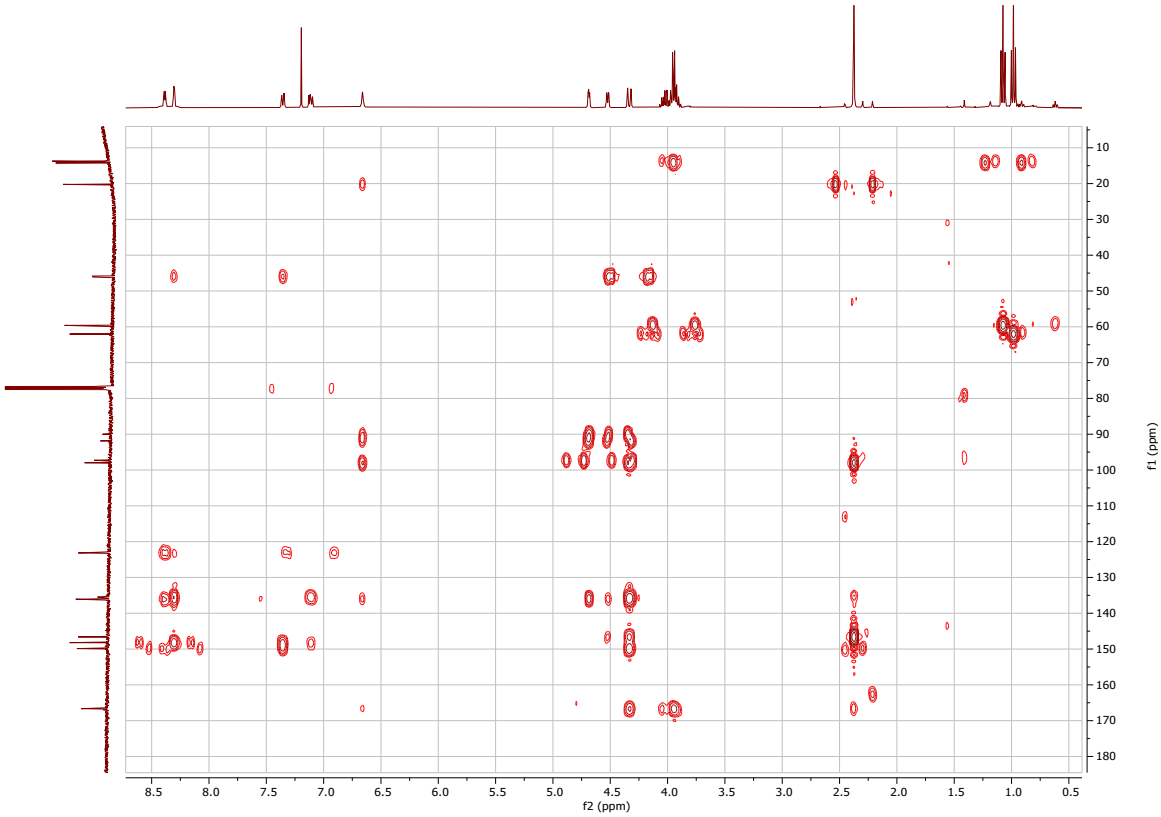


Figure S18. 2D HMBC NMR spectrum of diethyl (3,4)-3'-fluoro-6'-methyl-2'-methylene-1',2',3',4'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**1'e**).

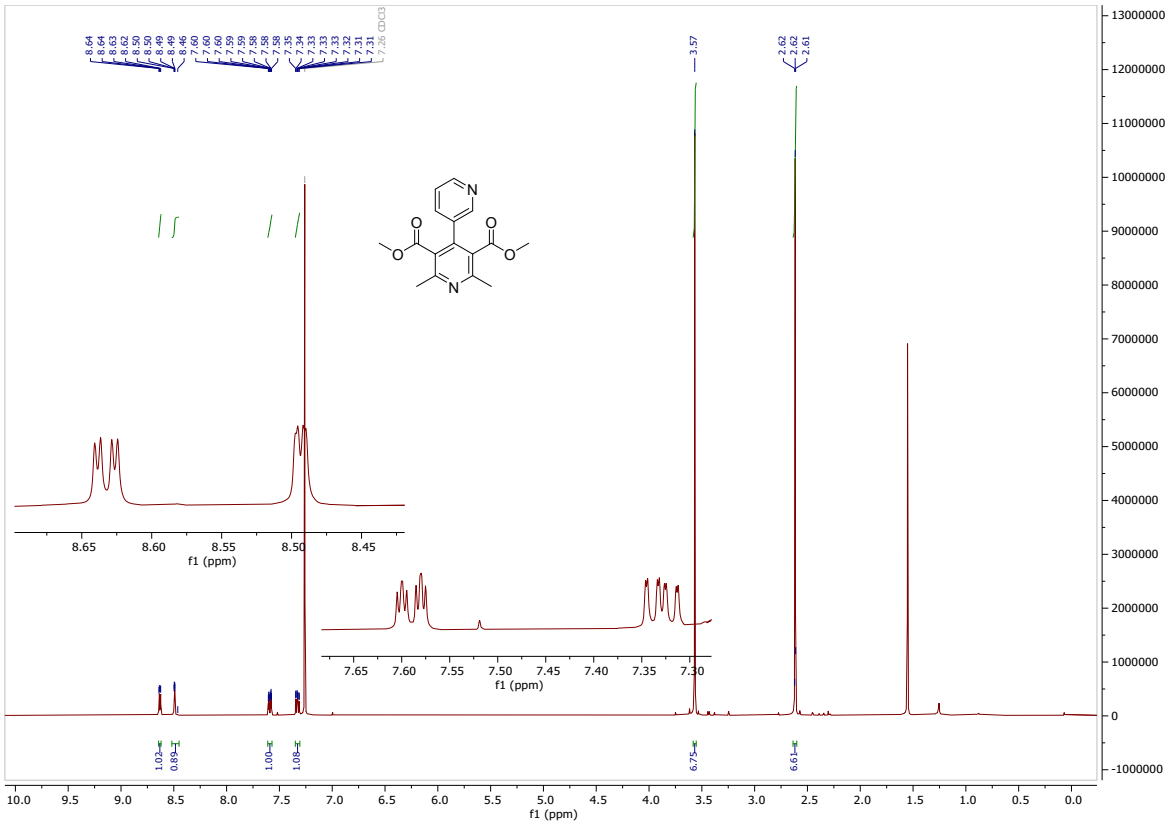


Figure S19. ^{1}H-NMR spectrum of dimethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1a**).

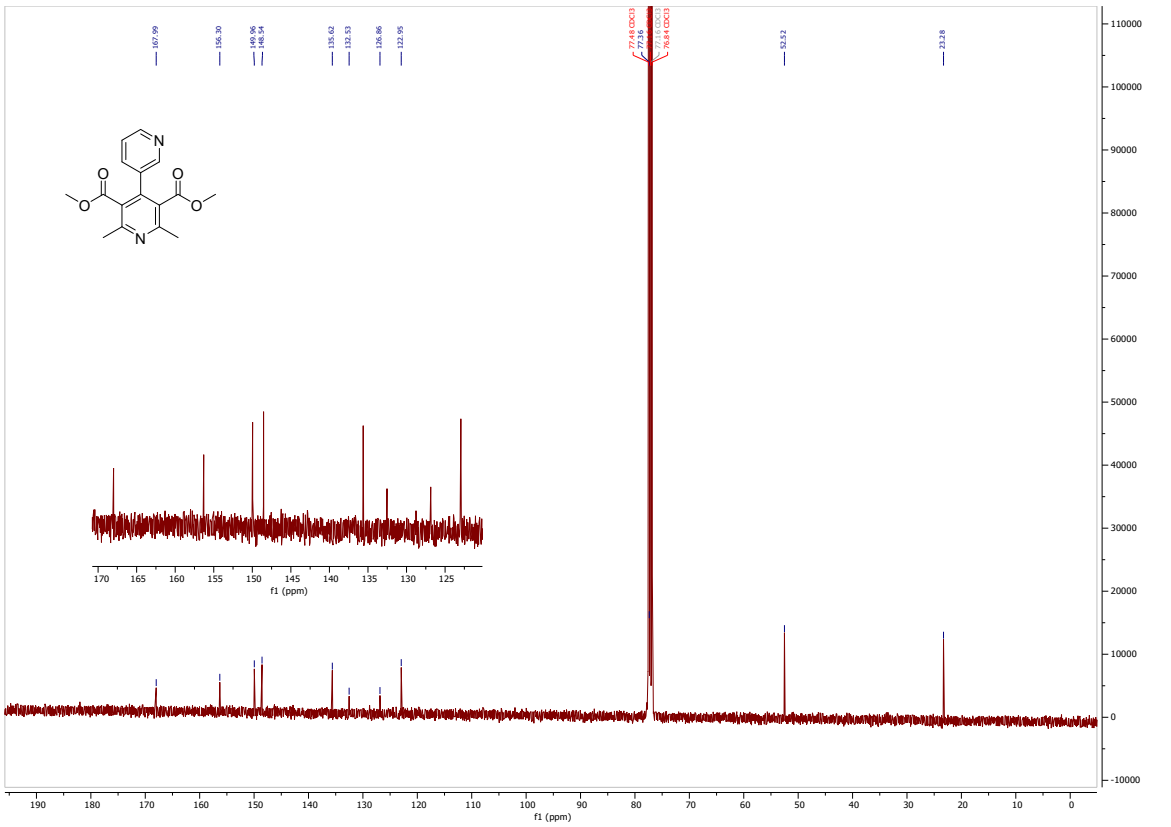


Figure S20. ^{13}C-NMR spectrum of dimethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1a**).

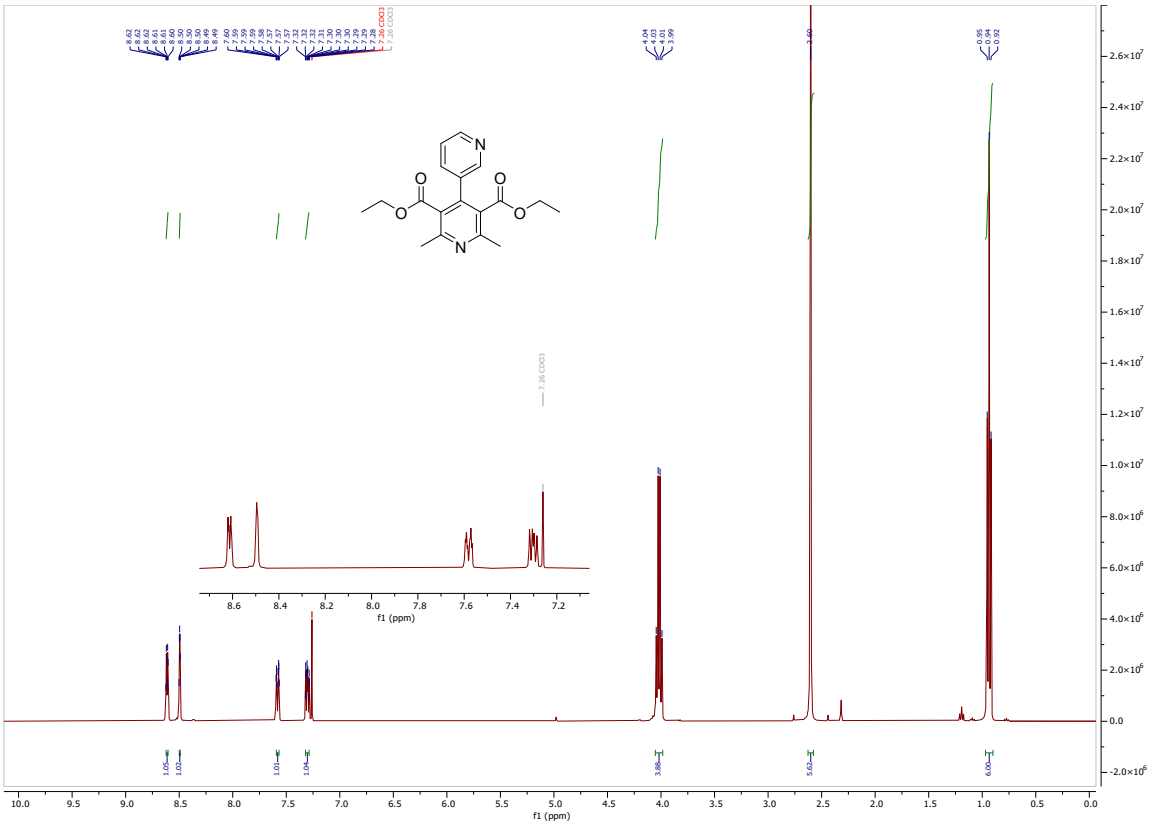


Figure S21. ^{1}H-NMR spectrum of diethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1e**).

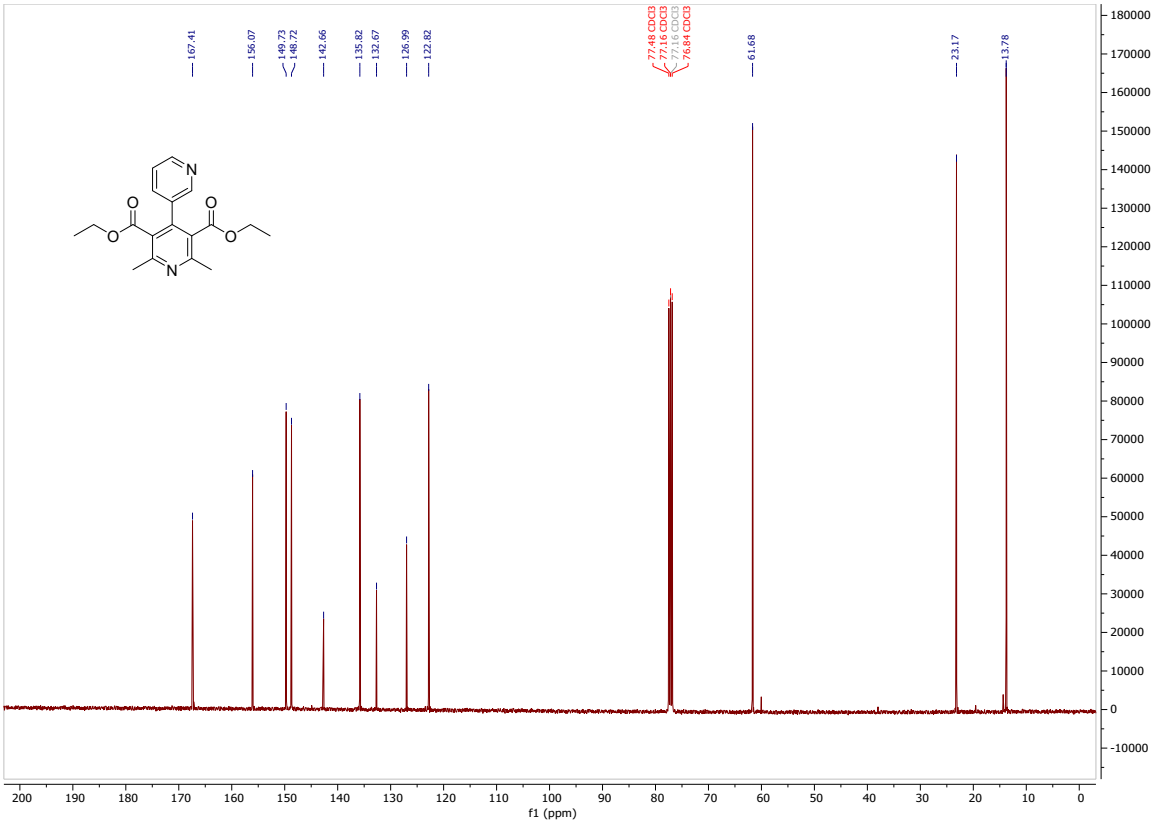


Figure S22. ^{13}C-NMR spectrum of diethyl 2',6'-dimethyl-[3,4'-bipyridine]-3',5'-dicarboxylate (**Ox-1e**).

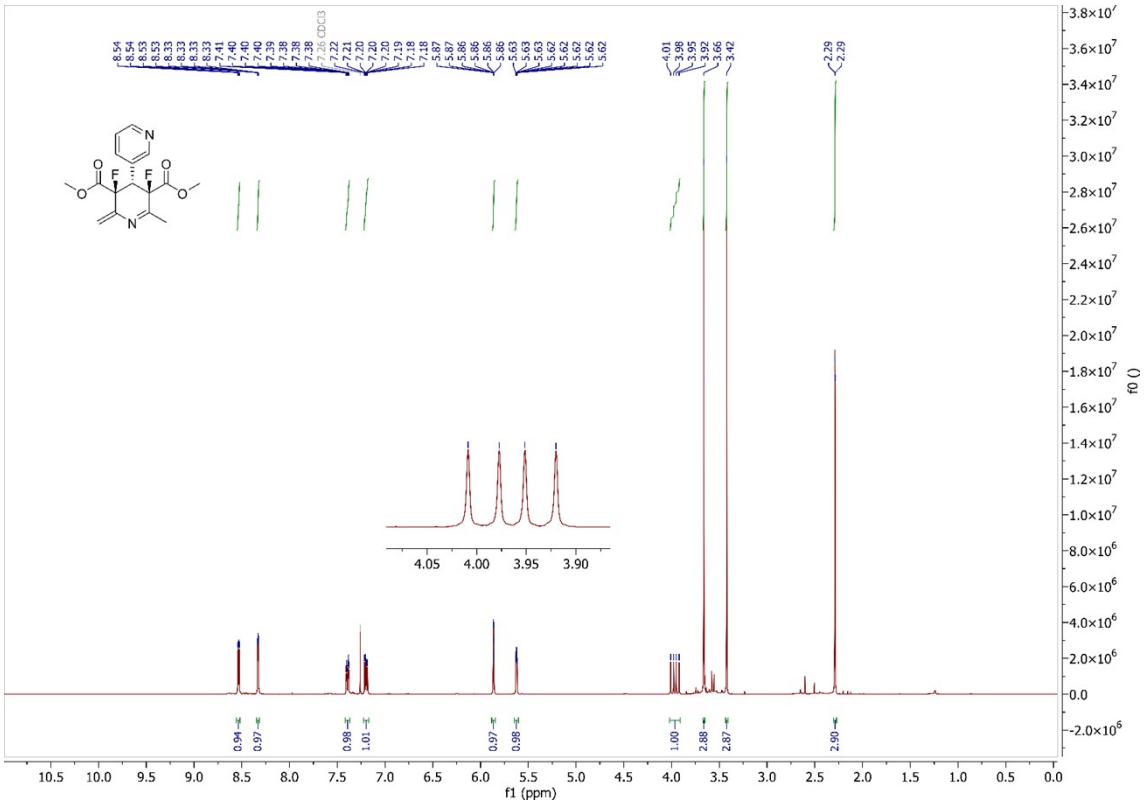


Figure S23. ^{1}H-NMR spectrum of dimethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2a**).

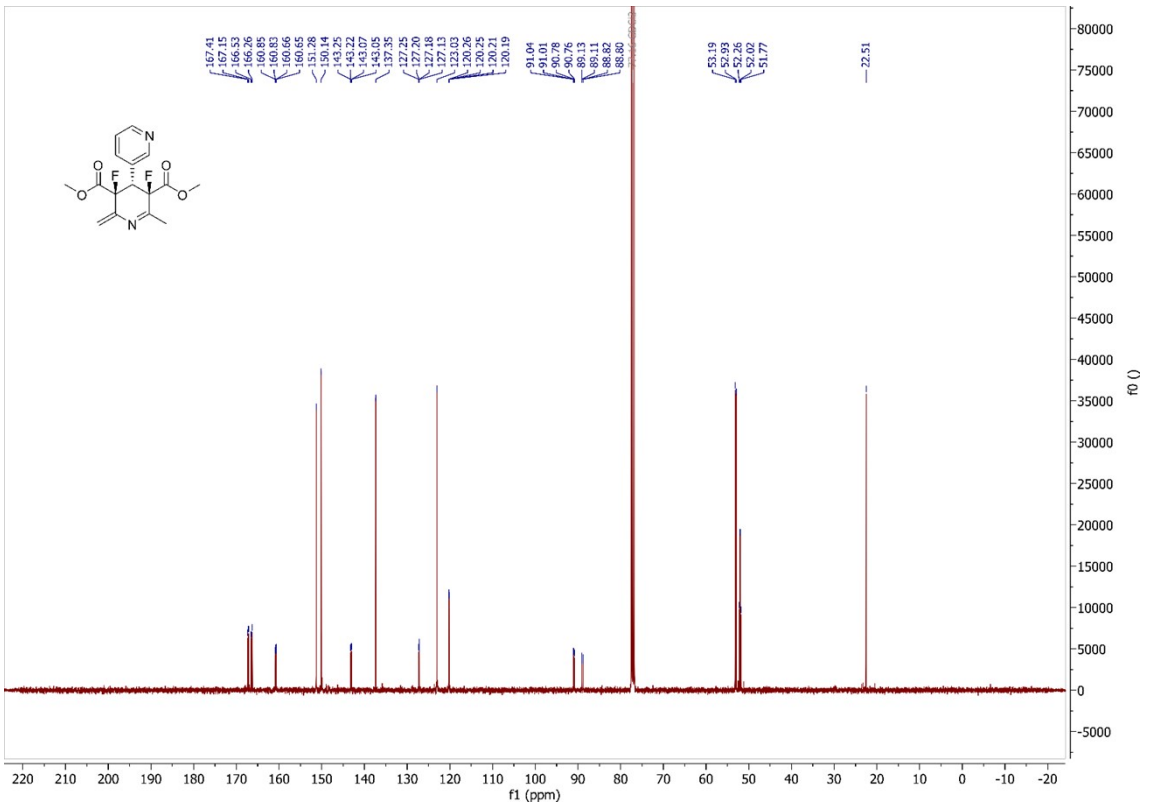


Figure S24. ^{13}C-NMR spectrum of dimethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2a**).

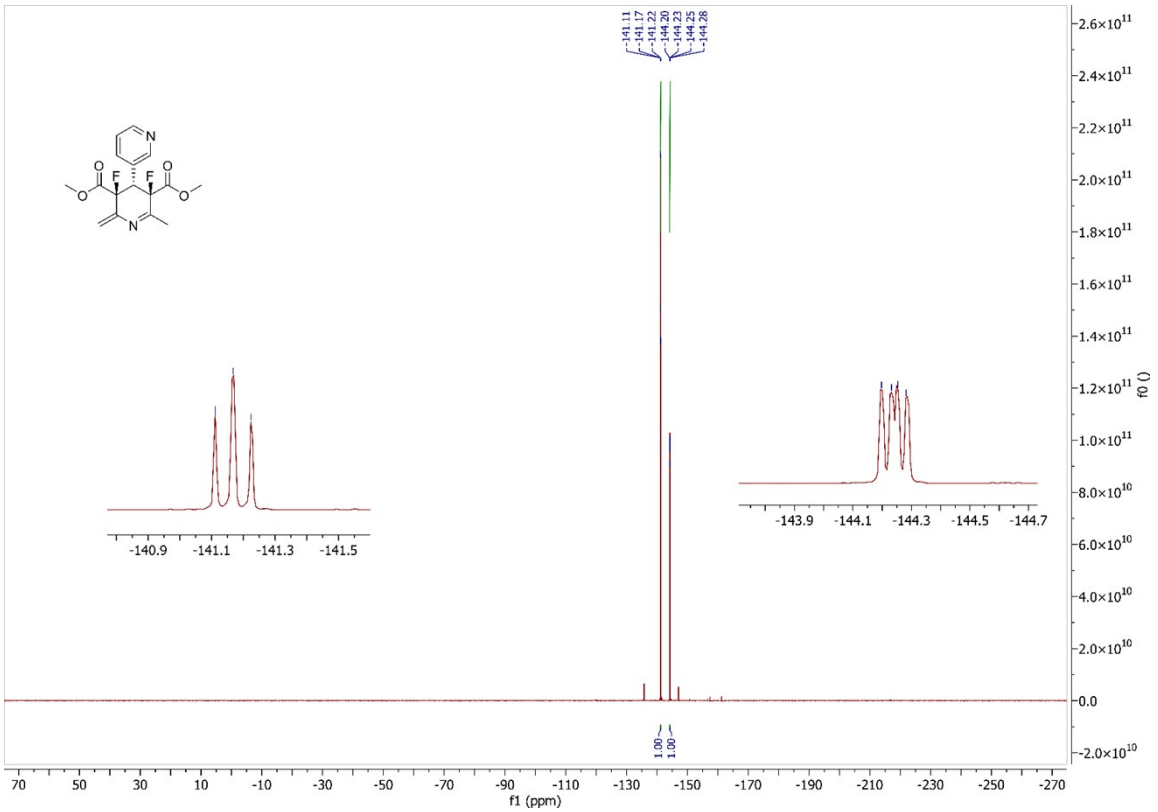


Figure S25. ^{19}F-NMR spectrum of dimethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2a**).

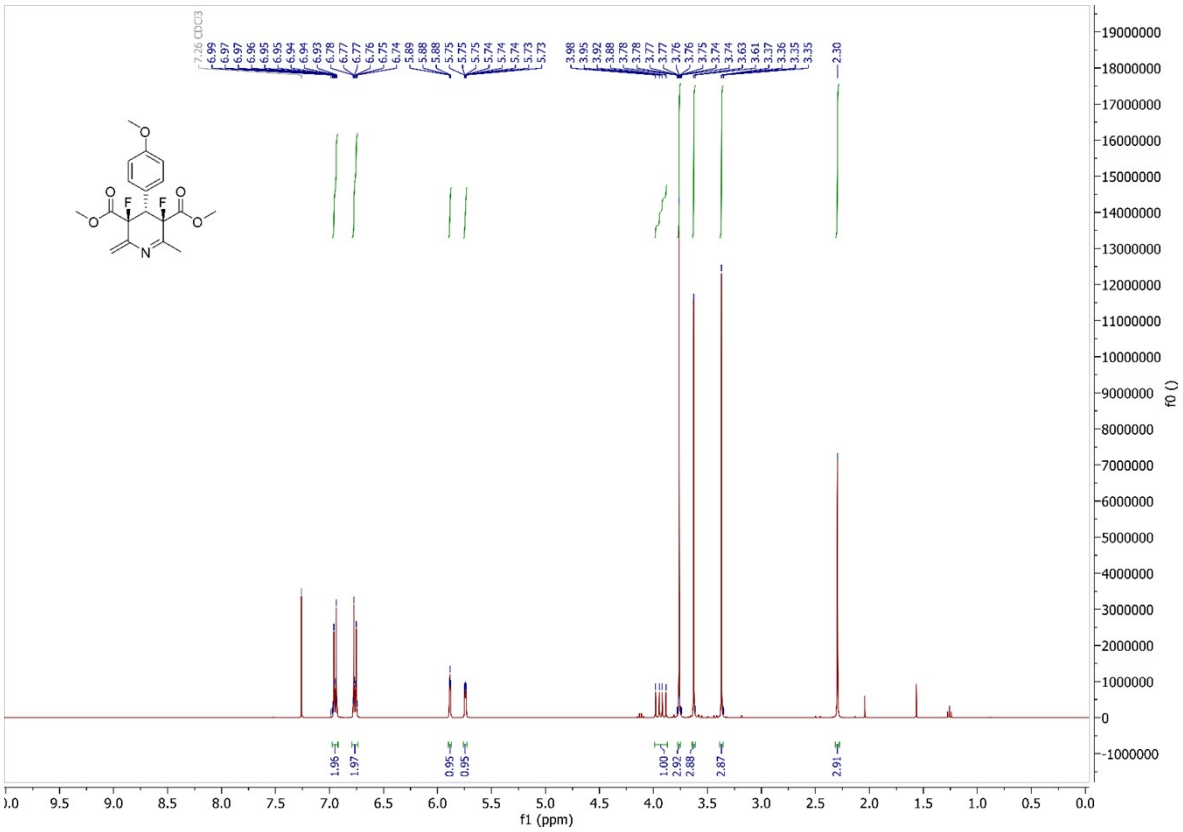


Figure S26. ^{1}H-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-4-(4-methoxyphenyl)-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2b**).

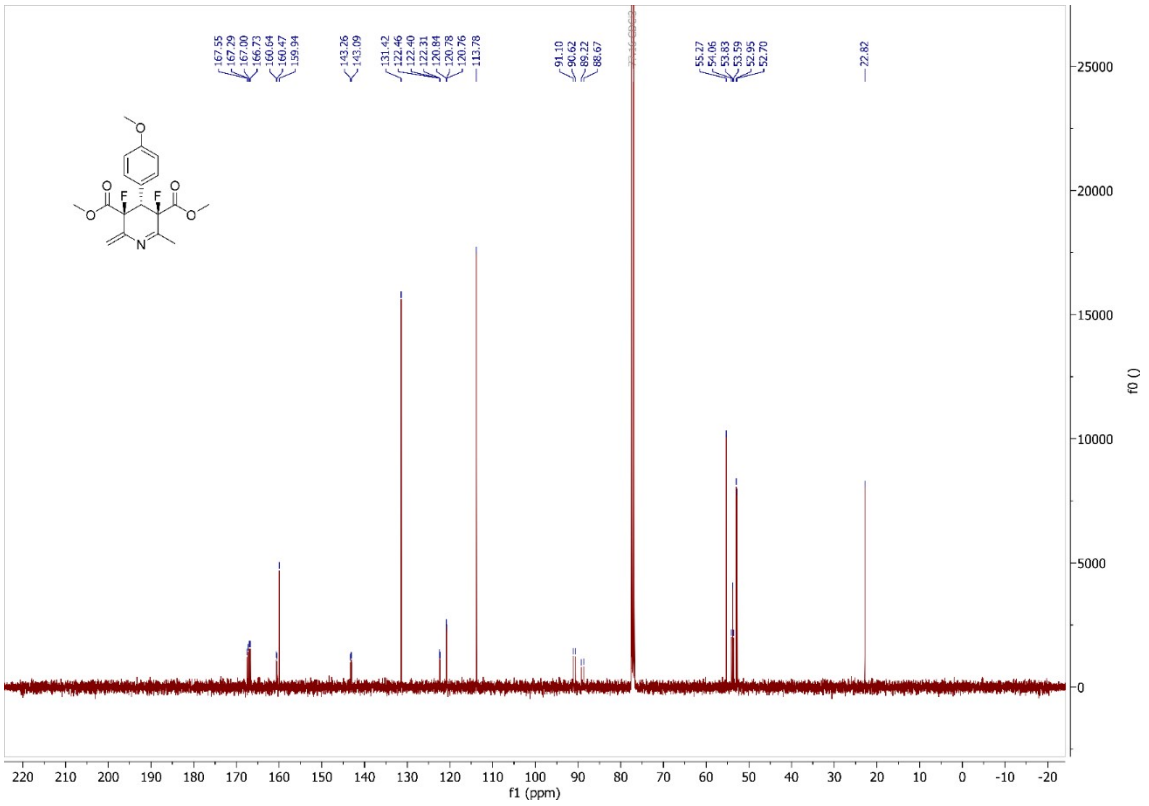


Figure S27. ^{13}C-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-4-(4-methoxyphenyl)-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2b**).

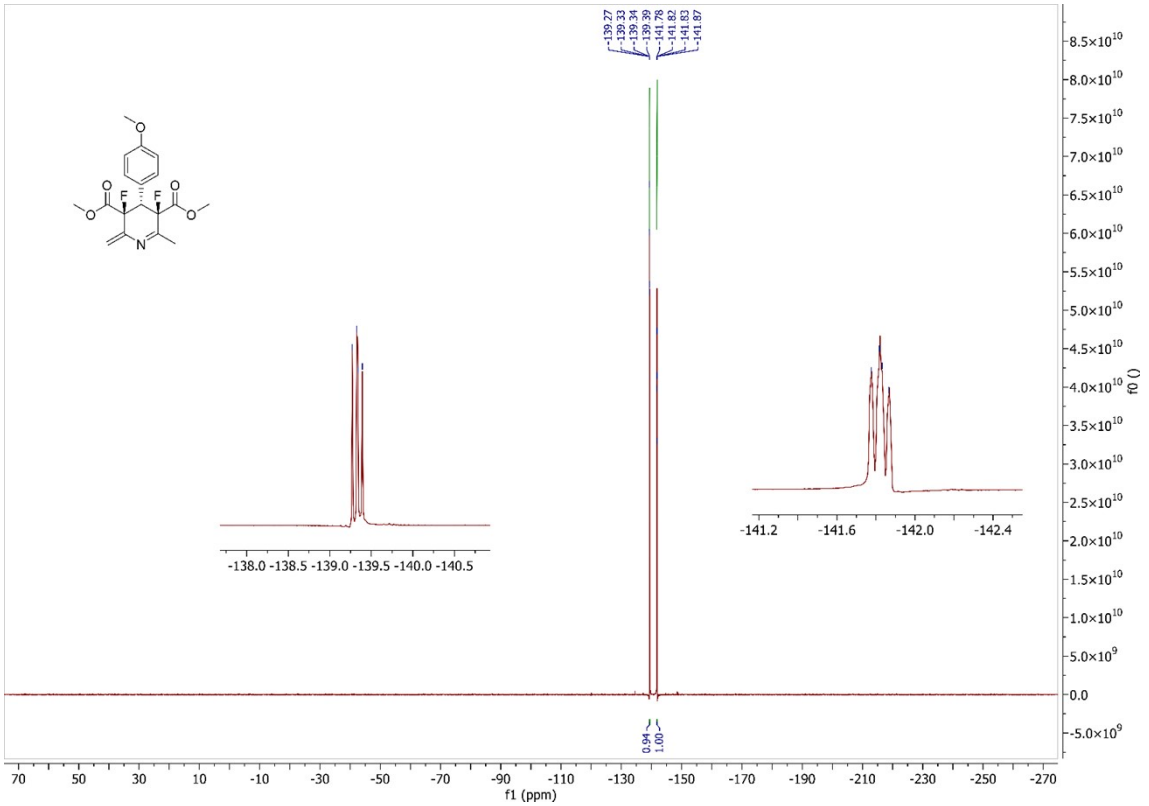


Figure S28. ^{19}F-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-4-(4-methoxyphenyl)-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2b**).

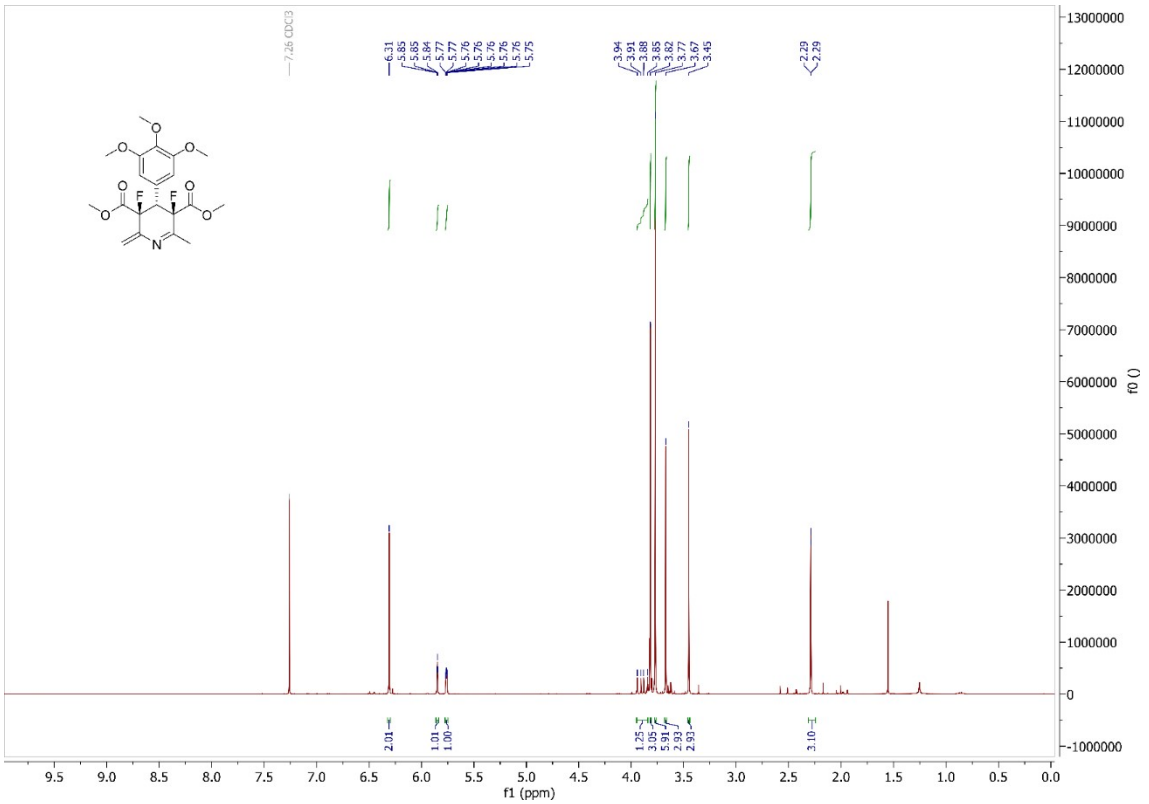


Figure S29. ^{1}H-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3,4,5-trimethoxyphenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2c**)

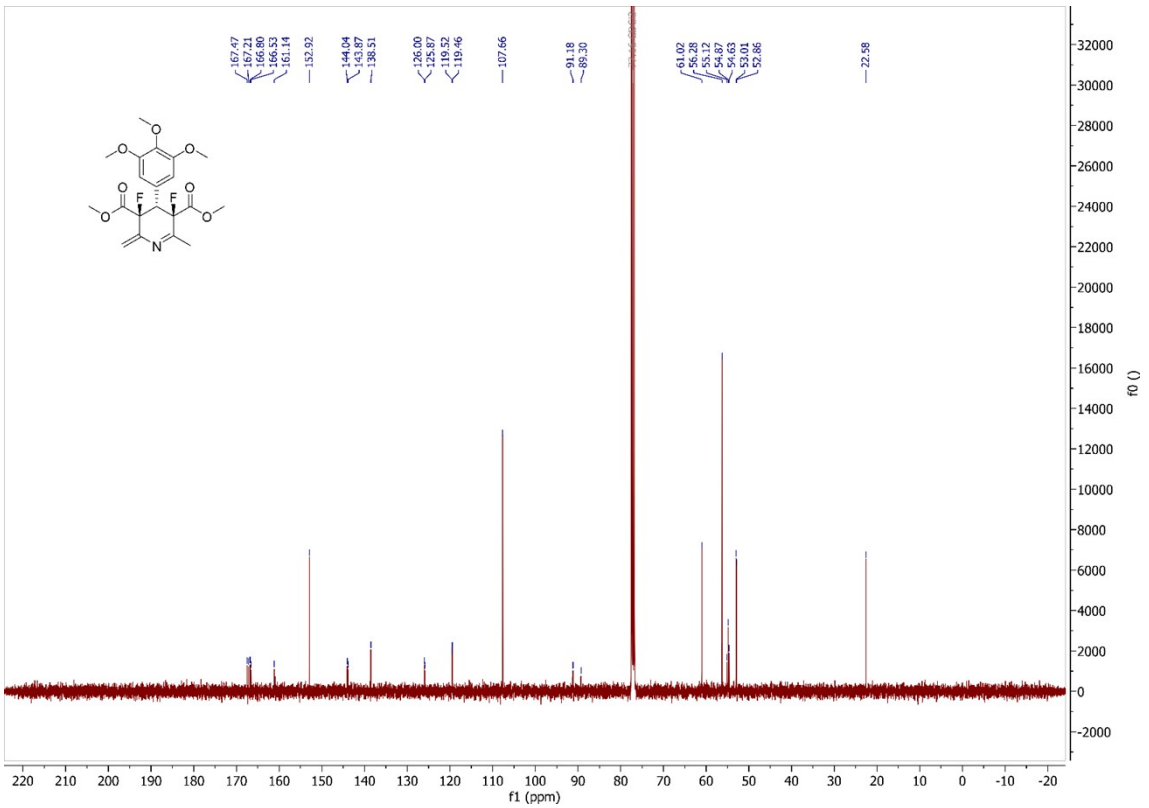


Figure S30. ^{13}C-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3,4,5-trimethoxyphenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2c**).

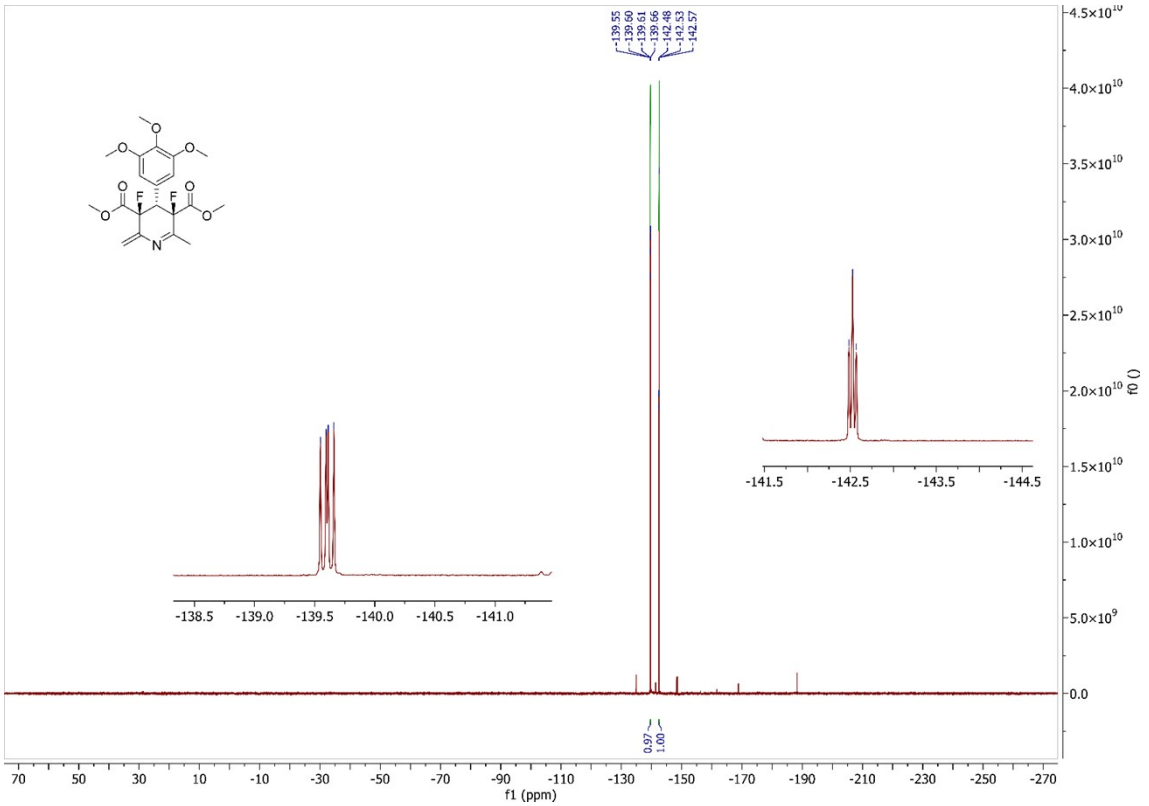


Figure S31. ^{19}F-NMR spectrum of dimethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3,4,5-trimethoxyphenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2c**).

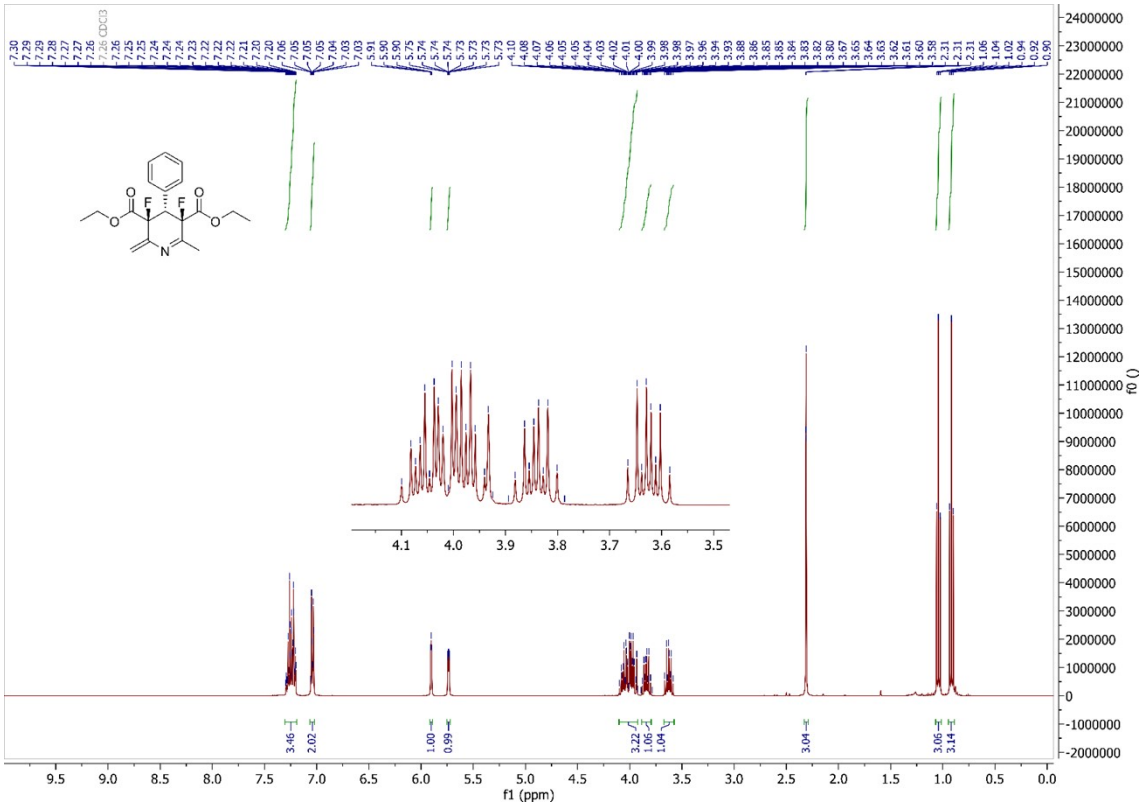


Figure S32. ^{1}H-NMR spectrum of diethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2d**).

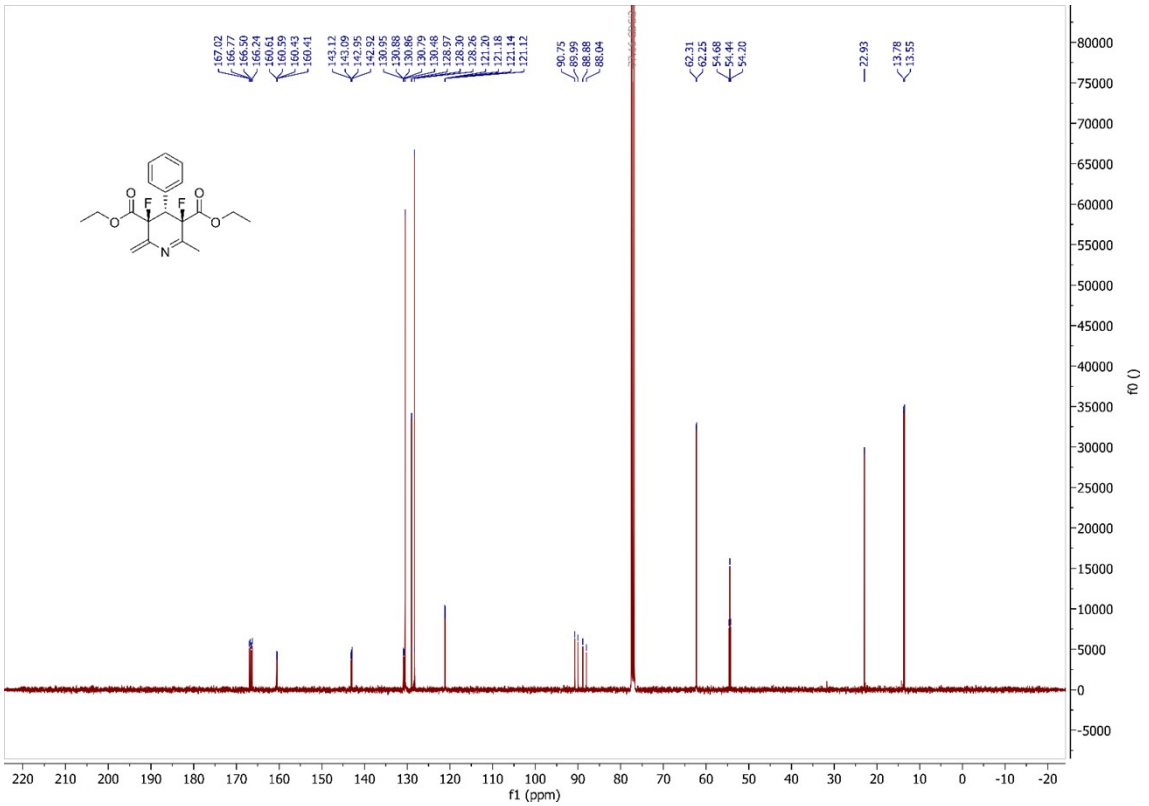


Figure S33. ^{13}C-NMR spectrum of diethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2d**).

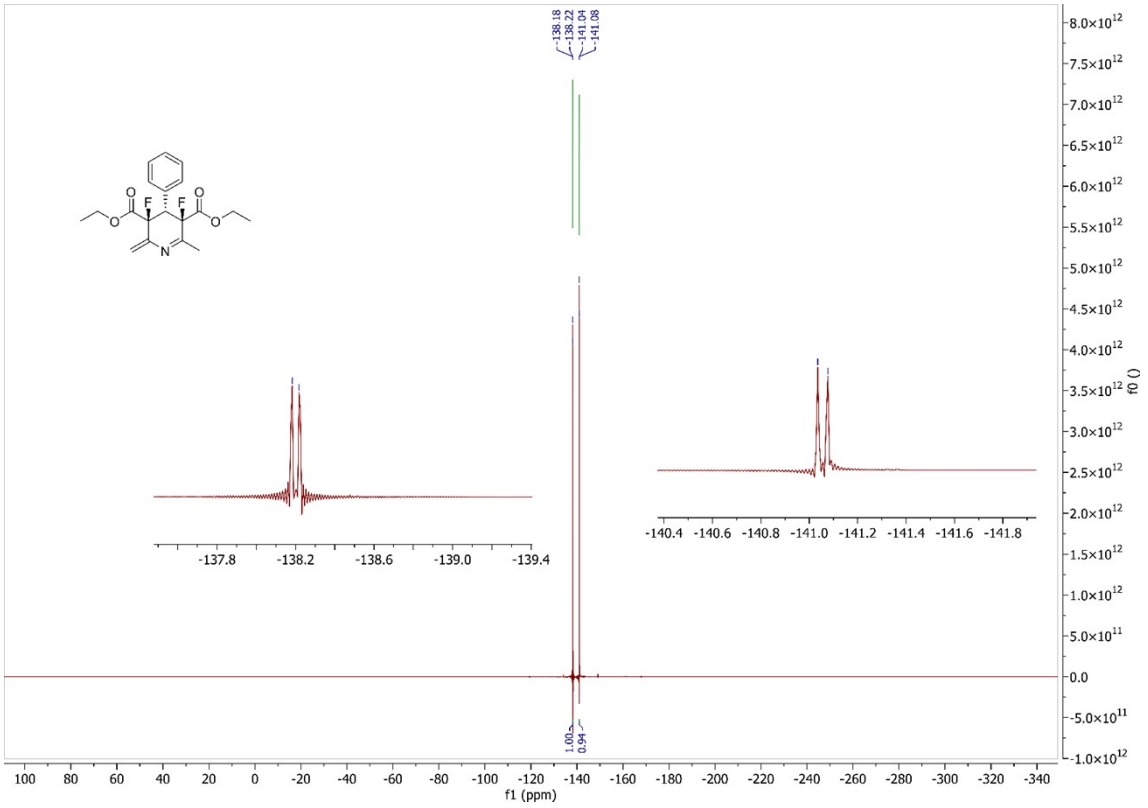


Figure S34. ^{19}F-NMR spectrum of diethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2d**).

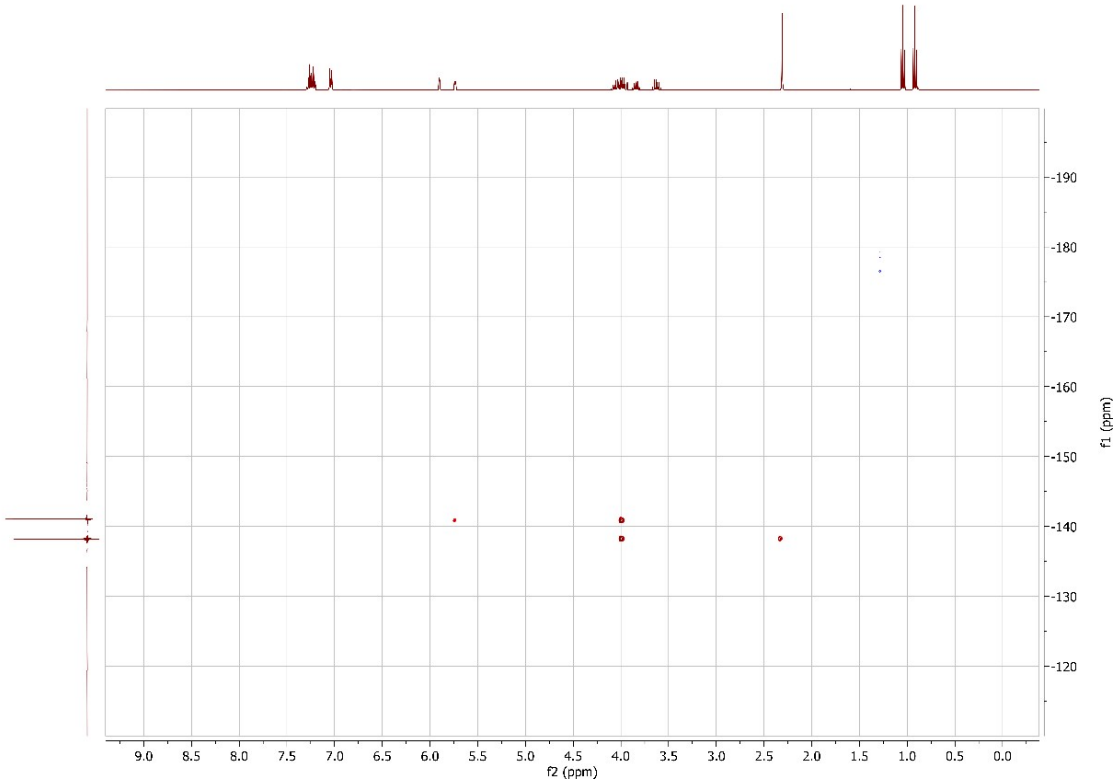


Figure S35. ^{19}F-^{1}H HOESY spectrum of diethyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2d**).

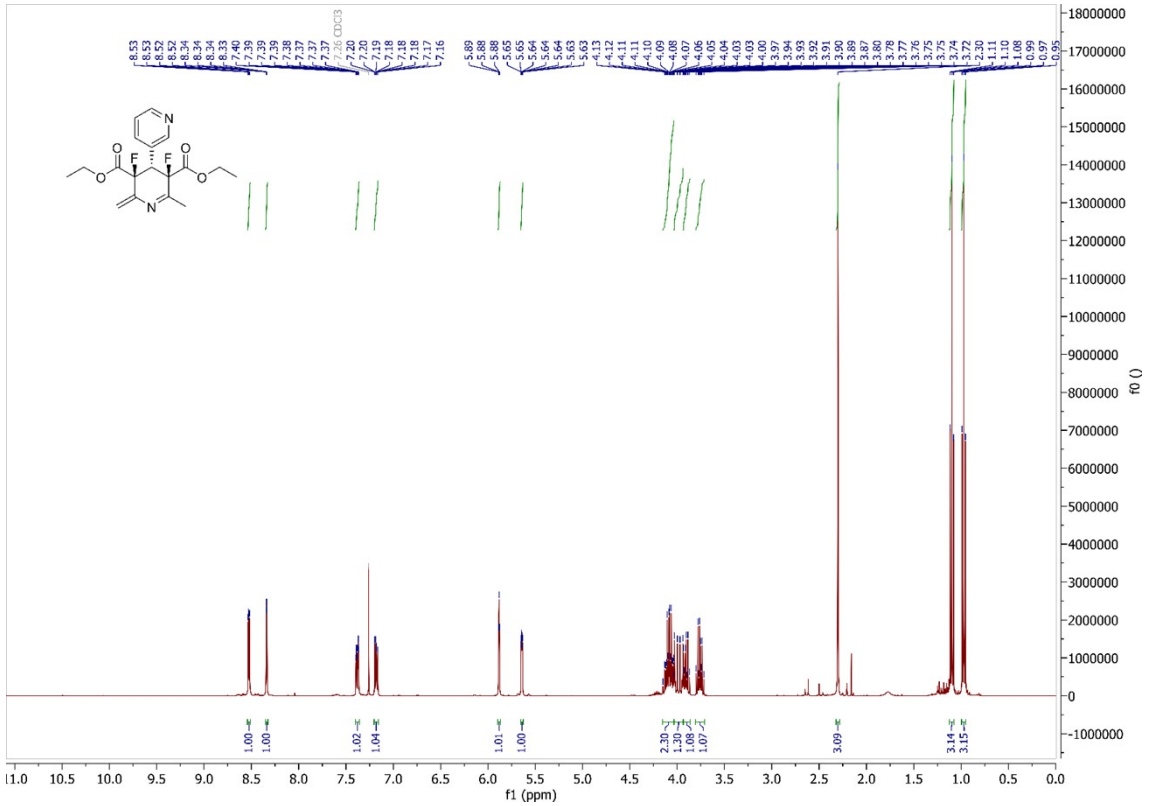


Figure S36. ^{1}H-NMR spectrum of diethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2e**).

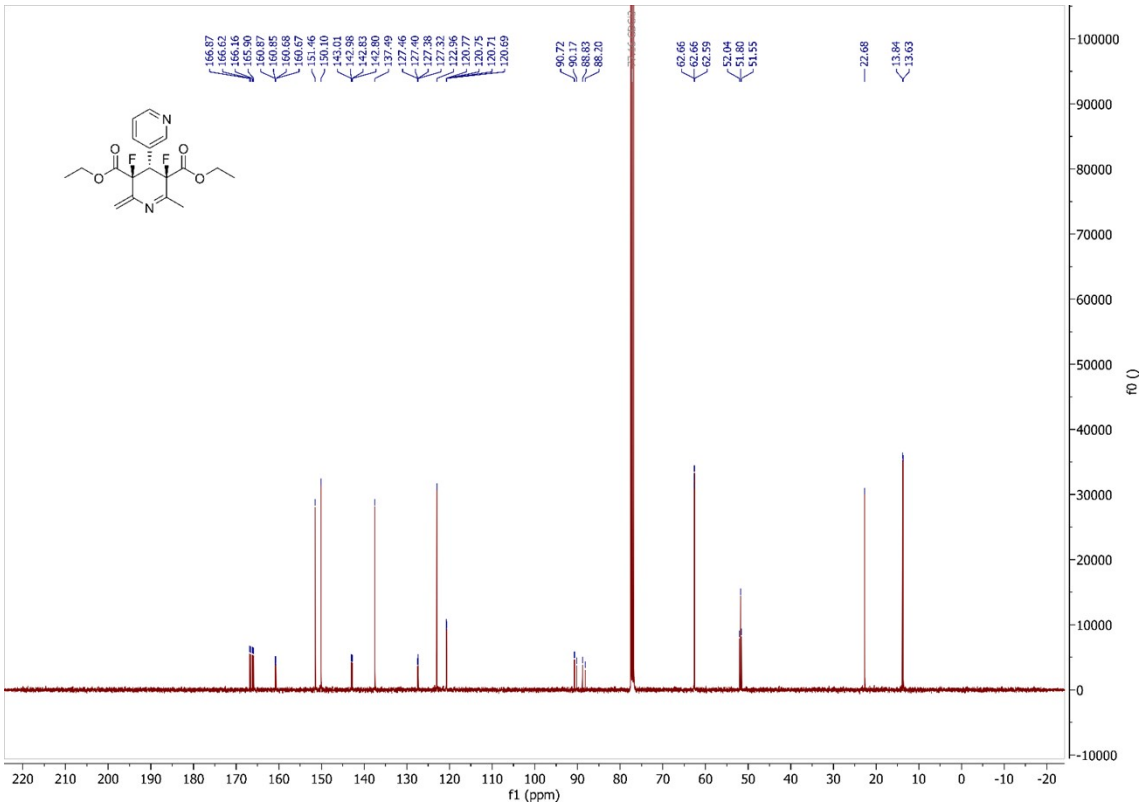


Figure S37. ^{13}C-NMR spectrum of diethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2e**).

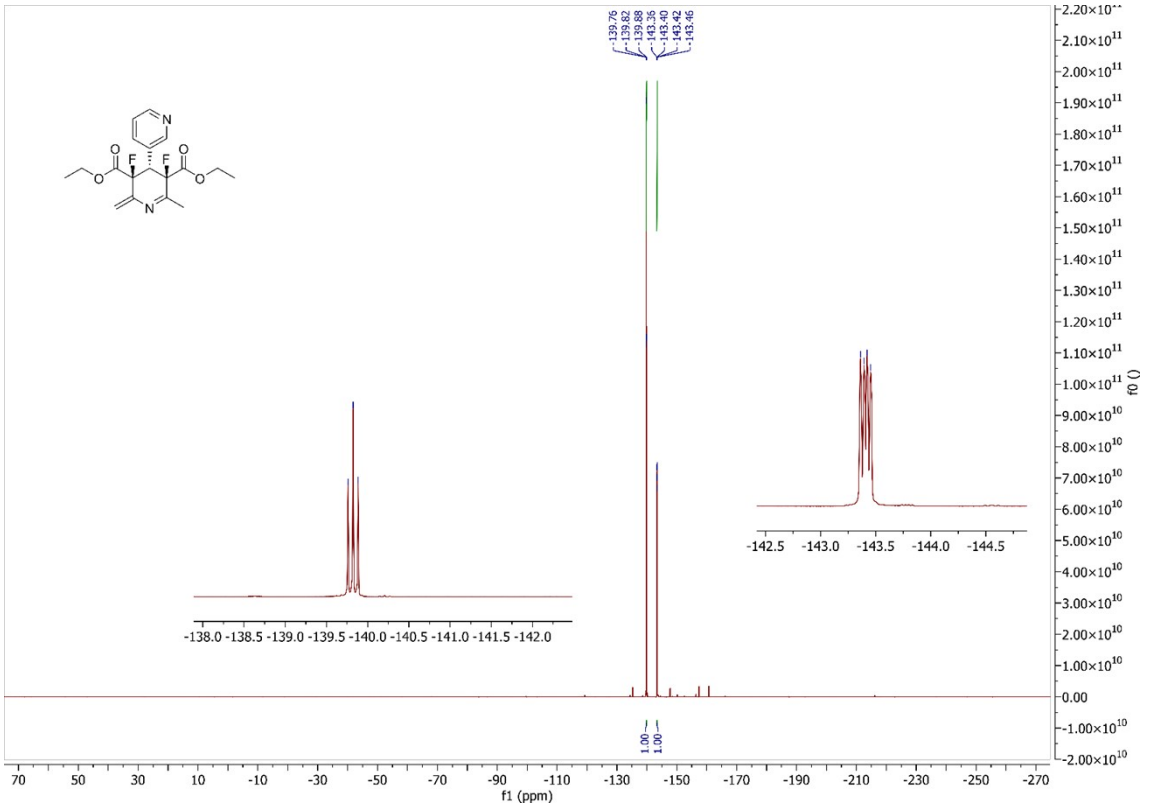


Figure S38. ^{19}F-NMR spectrum of diethyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2e**).

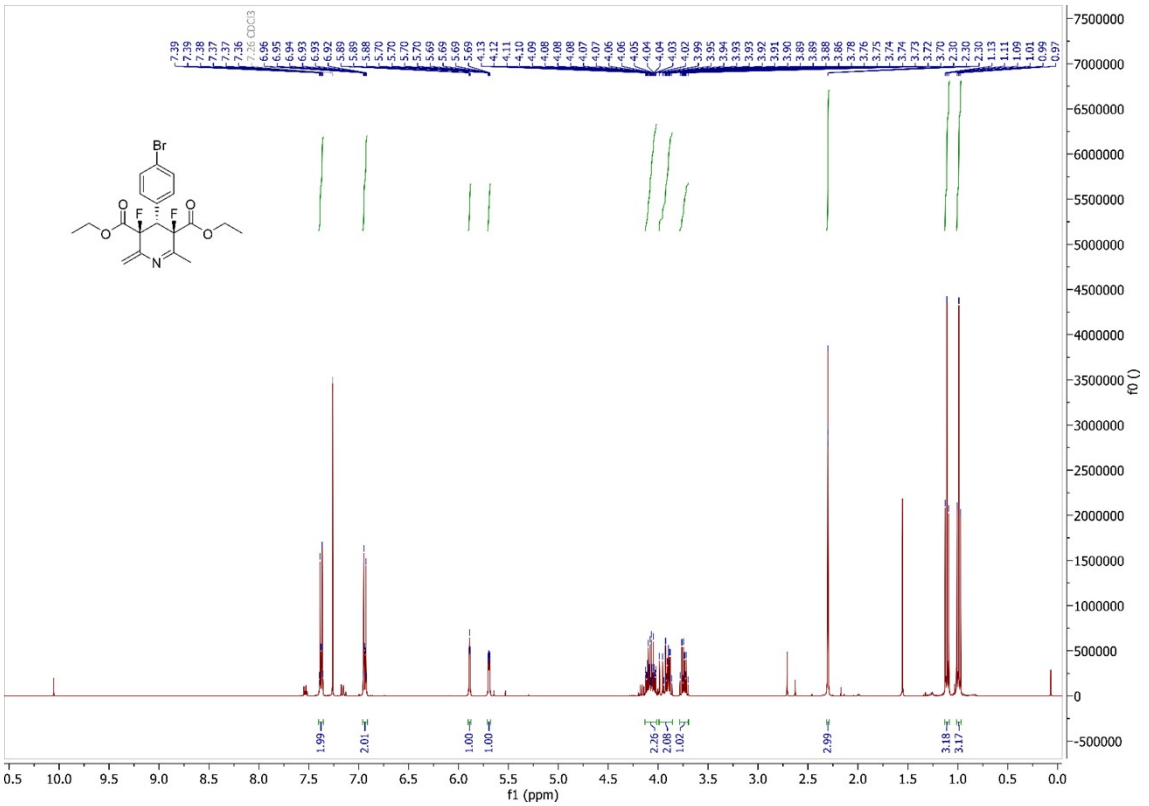


Figure S39. ^{1}H-NMR spectrum of diethyl (3,4,5)-4-(4-bromophenyl)-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2f**).

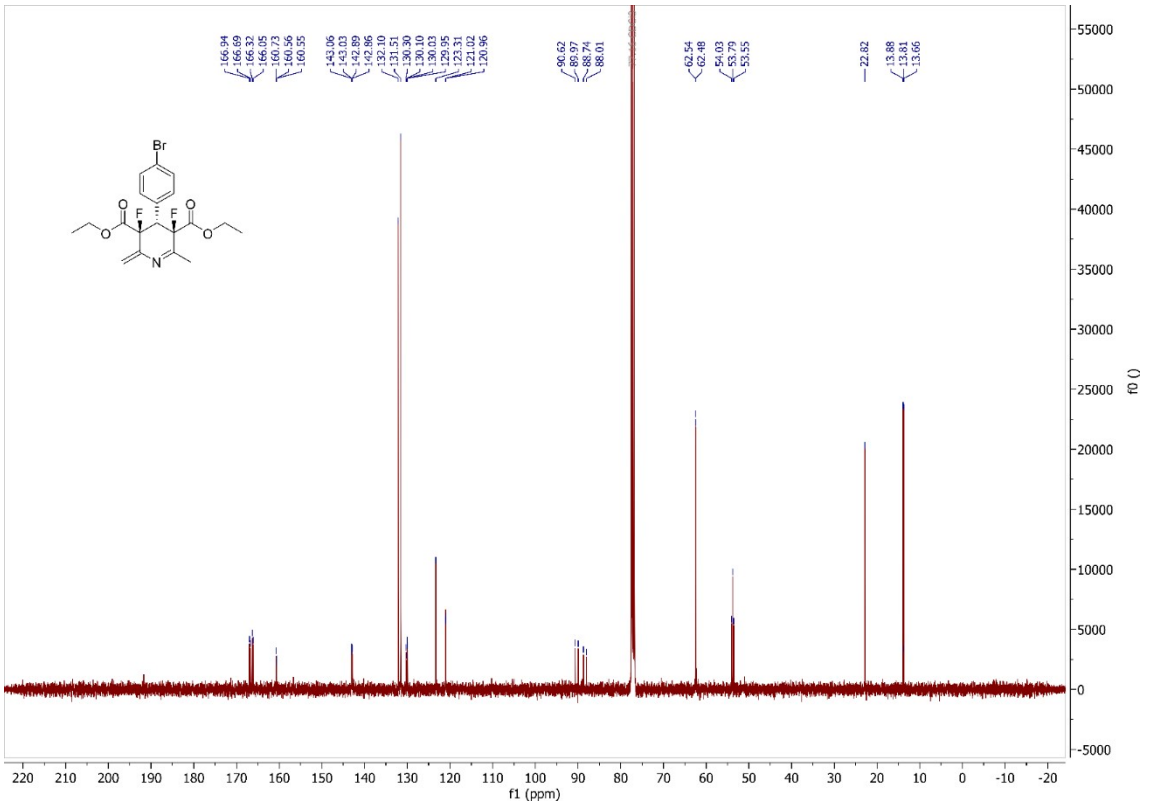


Figure S40. ^{13}C-NMR spectrum of diethyl (3,4,5)-4-(4-bromophenyl)-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2f**).

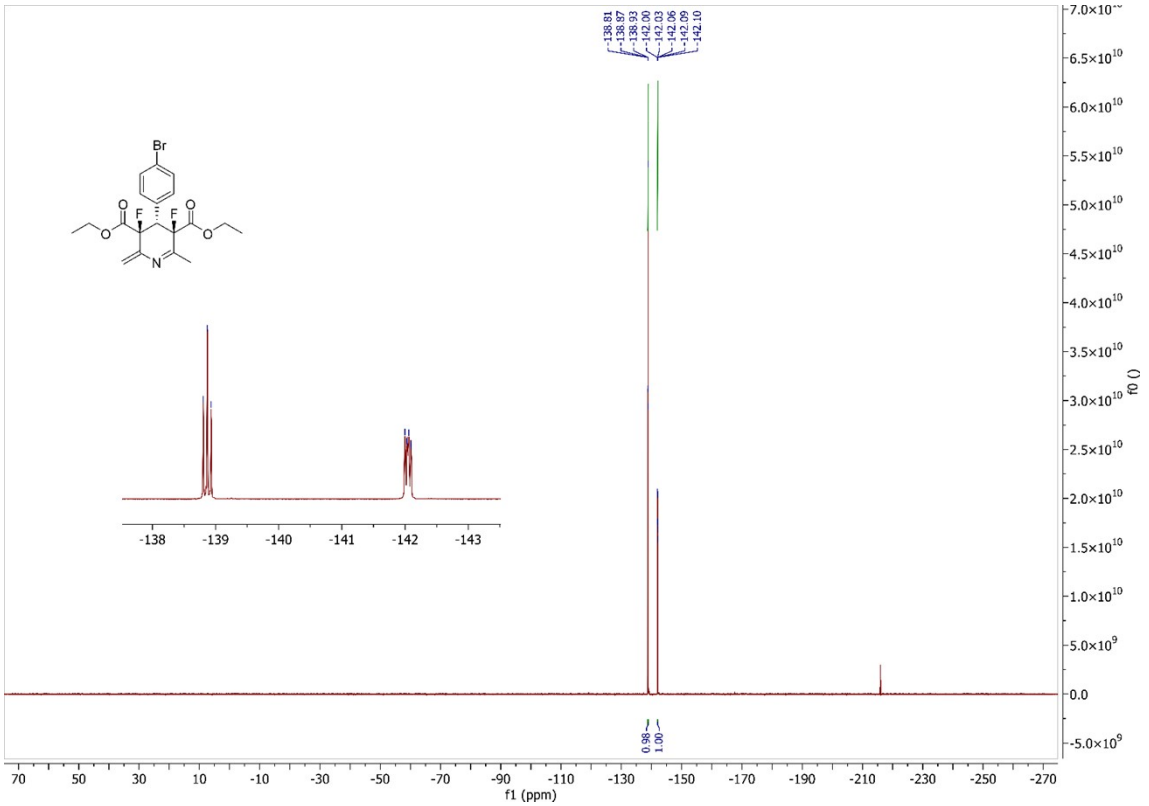


Figure S41. ^{19}F-NMR spectrum of diethyl (3,4,5)-4-(4-bromophenyl)-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2f**).

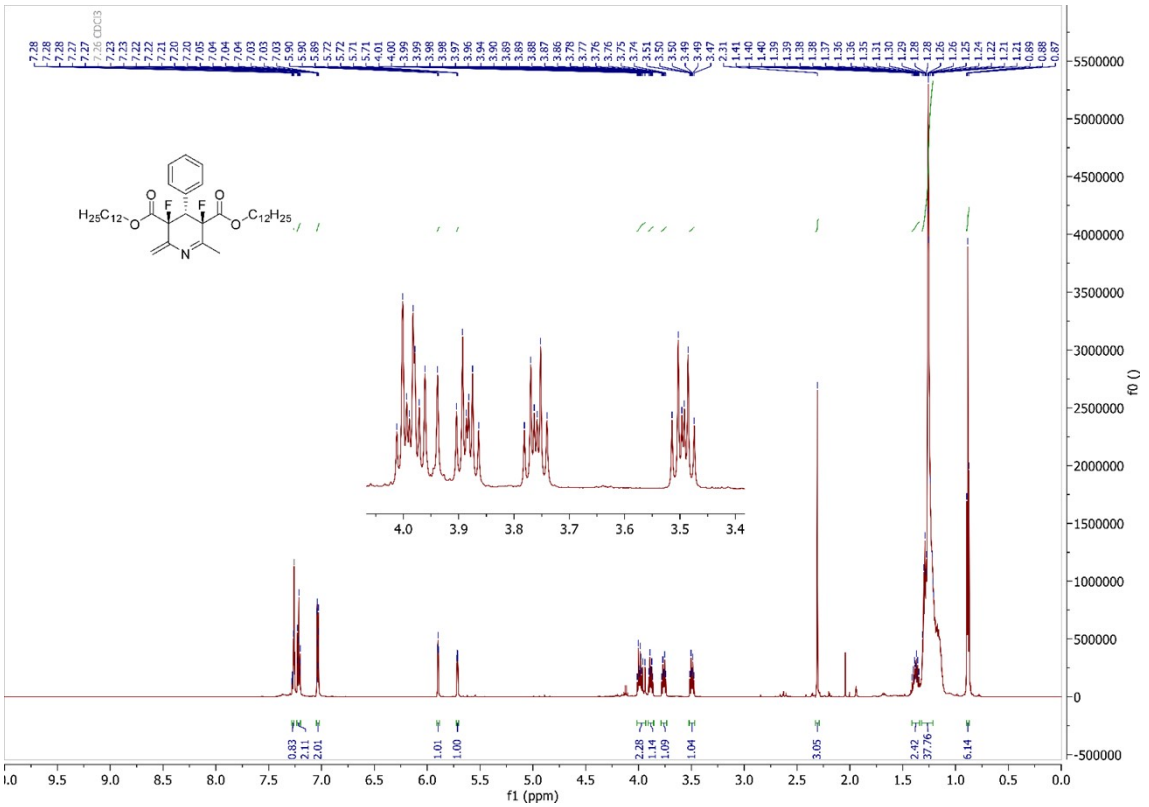


Figure S42. ^{1}H-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2g**).

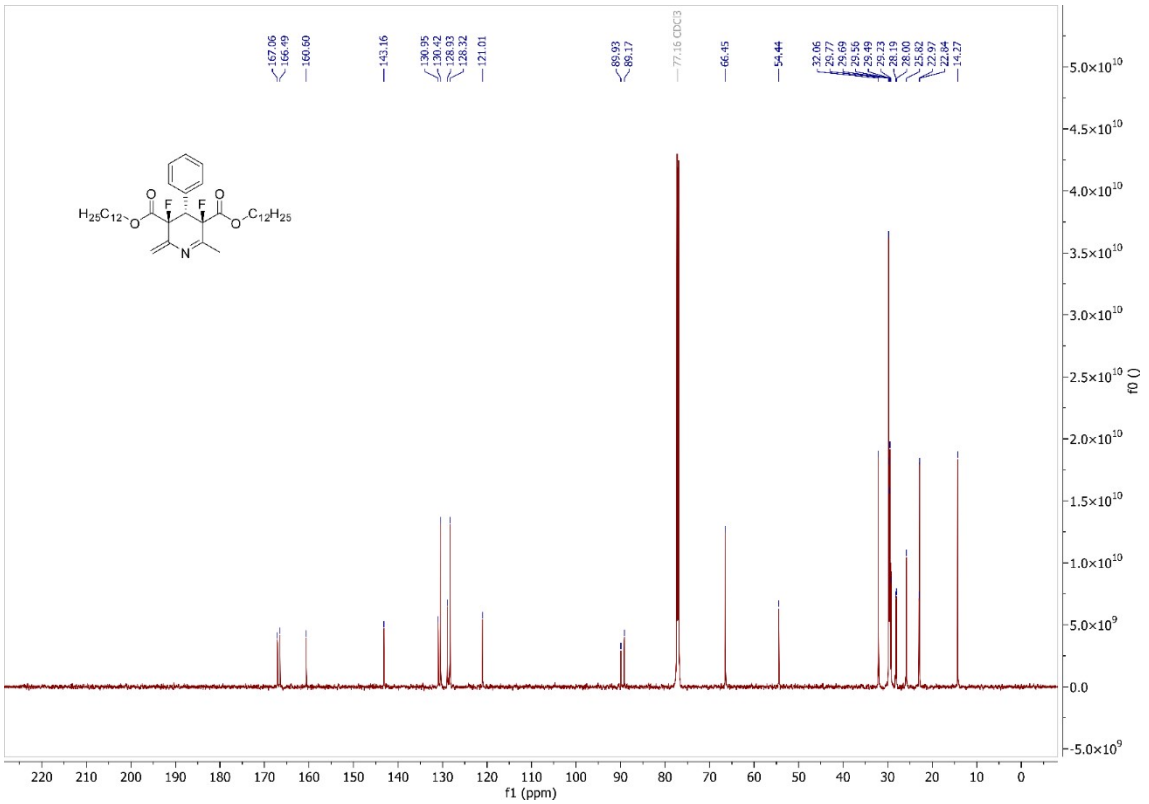


Figure S43. ^{13}C-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2g**).

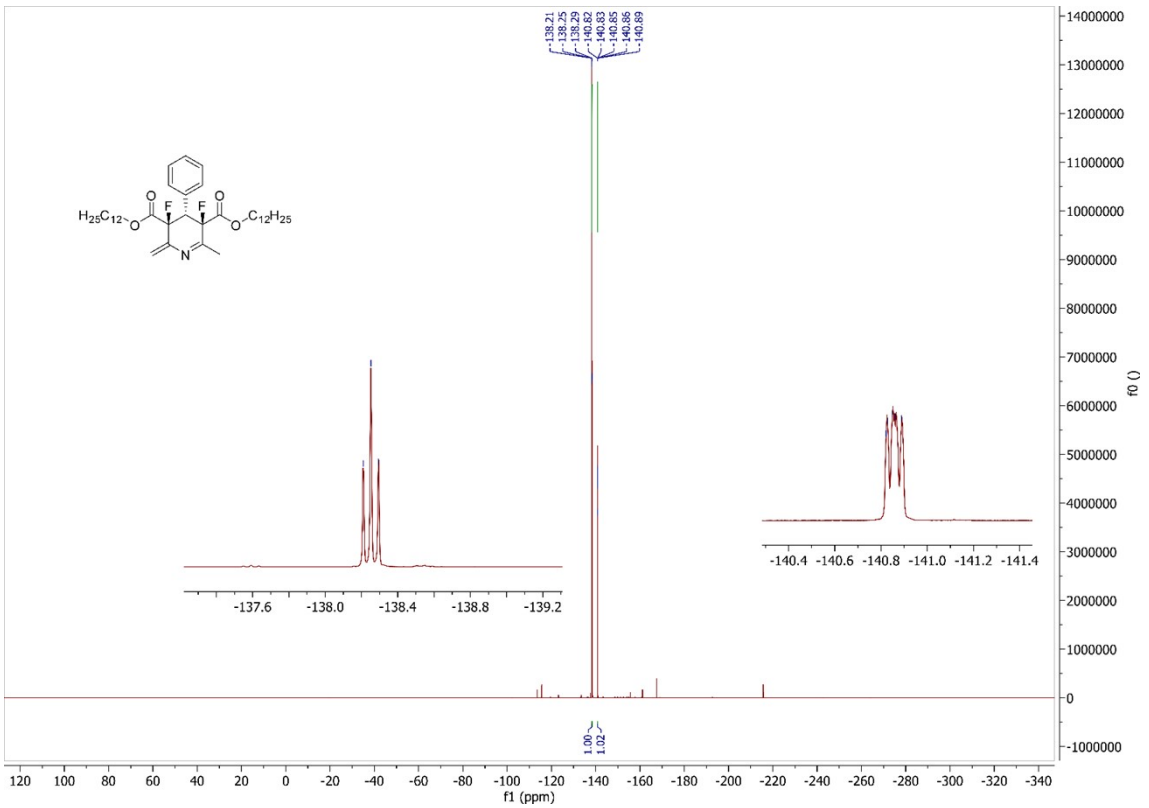


Figure S44. ^{19}F-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2g**).

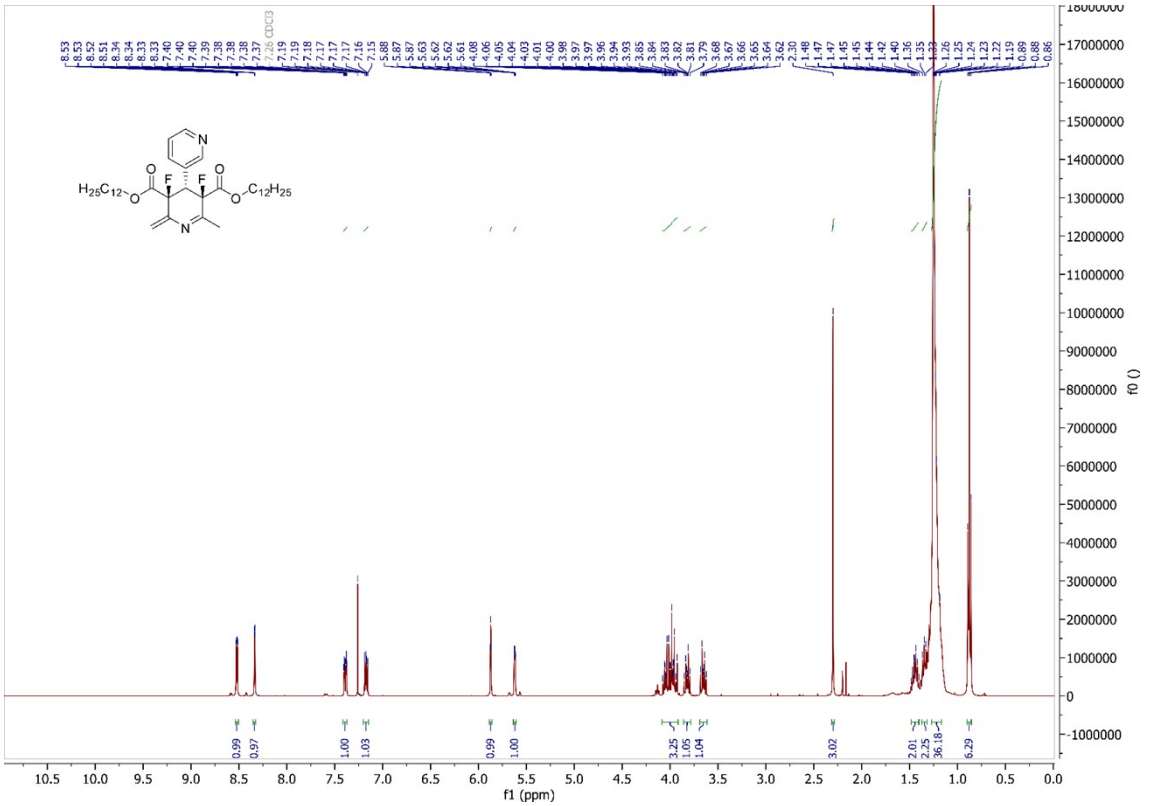


Figure S45. ^{1}H-NMR spectrum of didodecyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2h**).

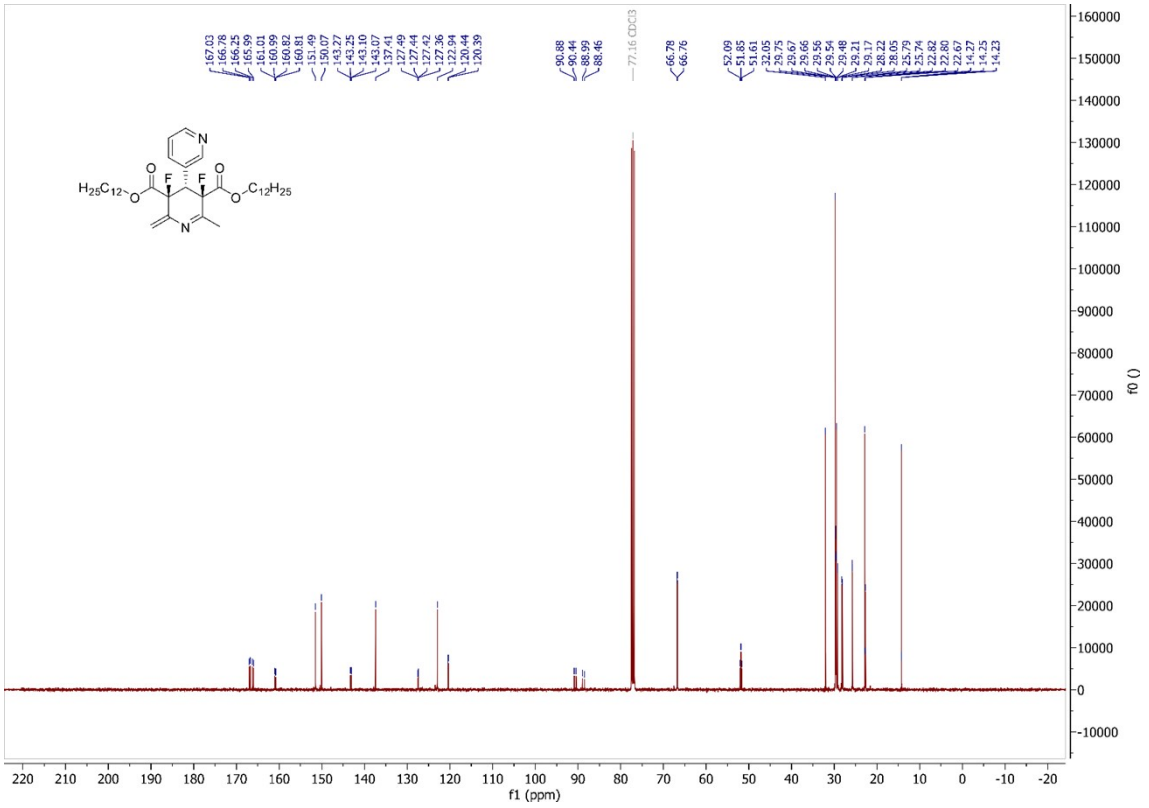


Figure S46. ^{13}C-NMR spectrum of didodecyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2h**).

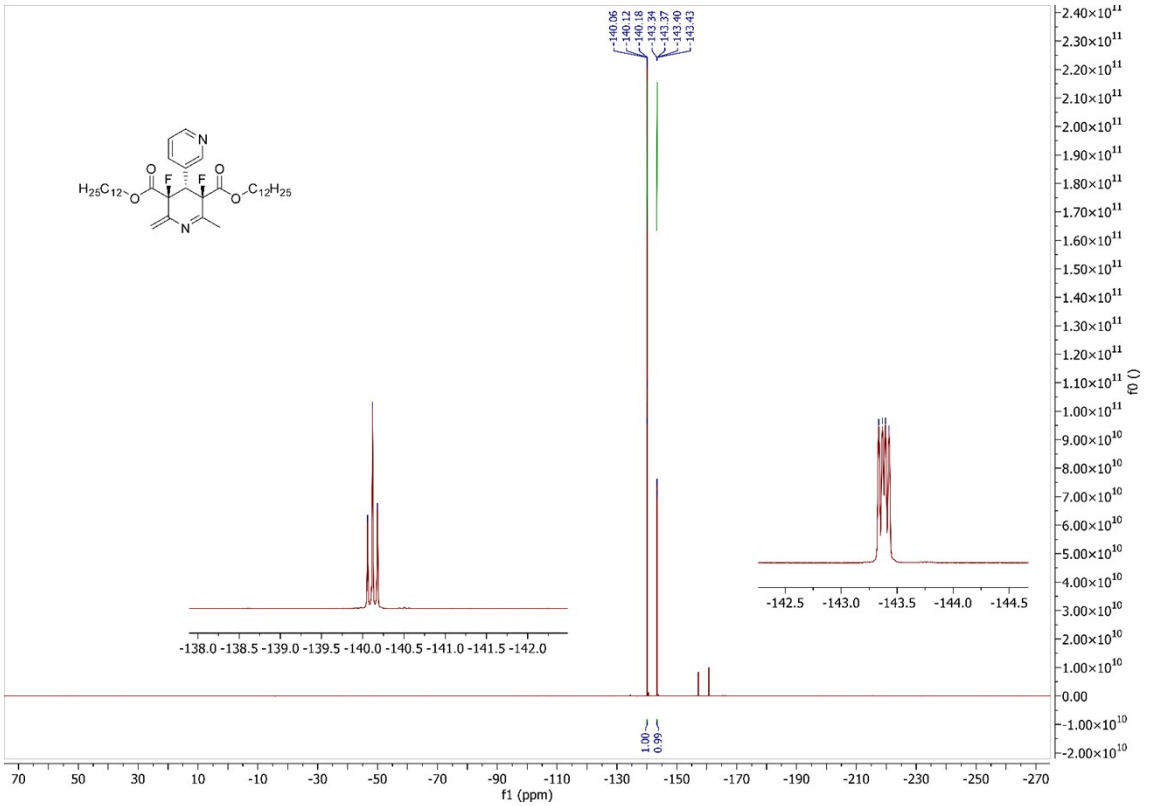


Figure S47. ^{19}F-NMR spectrum of Didodecyl (3',4',5')-3',5'-difluoro-6'-methyl-2'-methylene-2',3',4',5'-tetrahydro-[3,4'-bipyridine]-3',5'-dicarboxylate (**2h**).

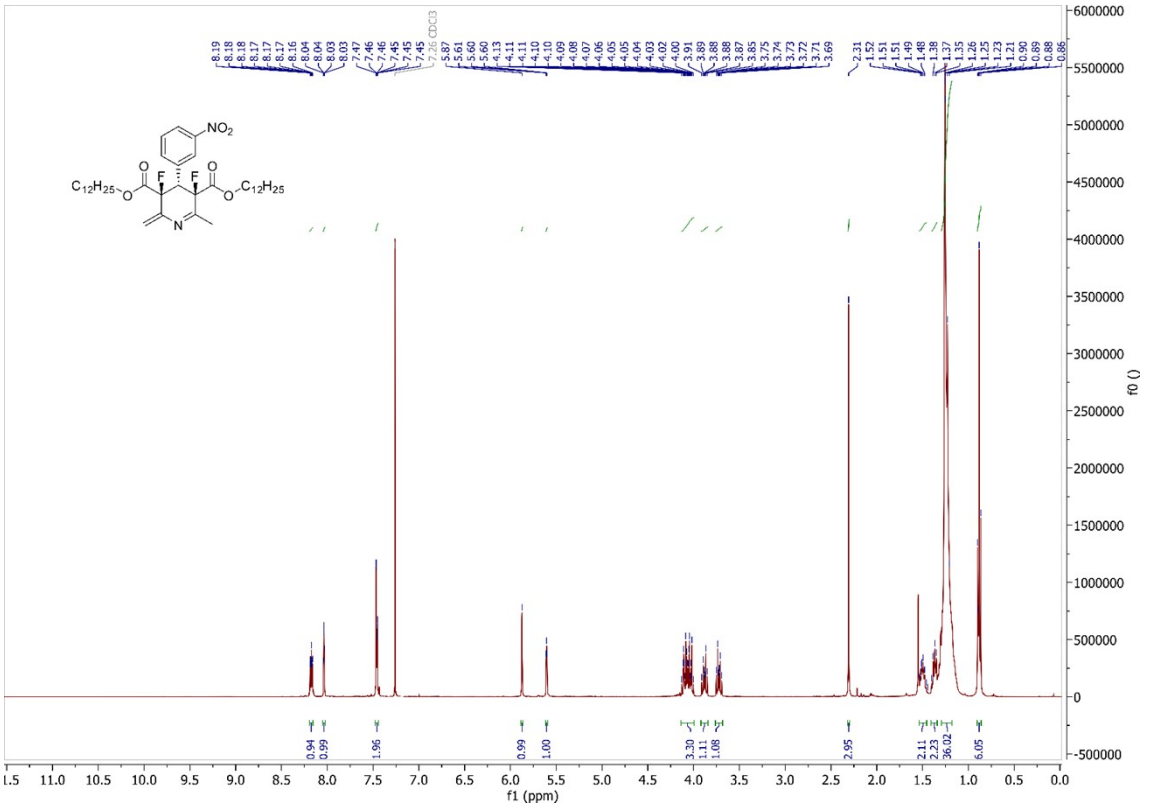


Figure S48. ^{1}H-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3-nitrophenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2i**).

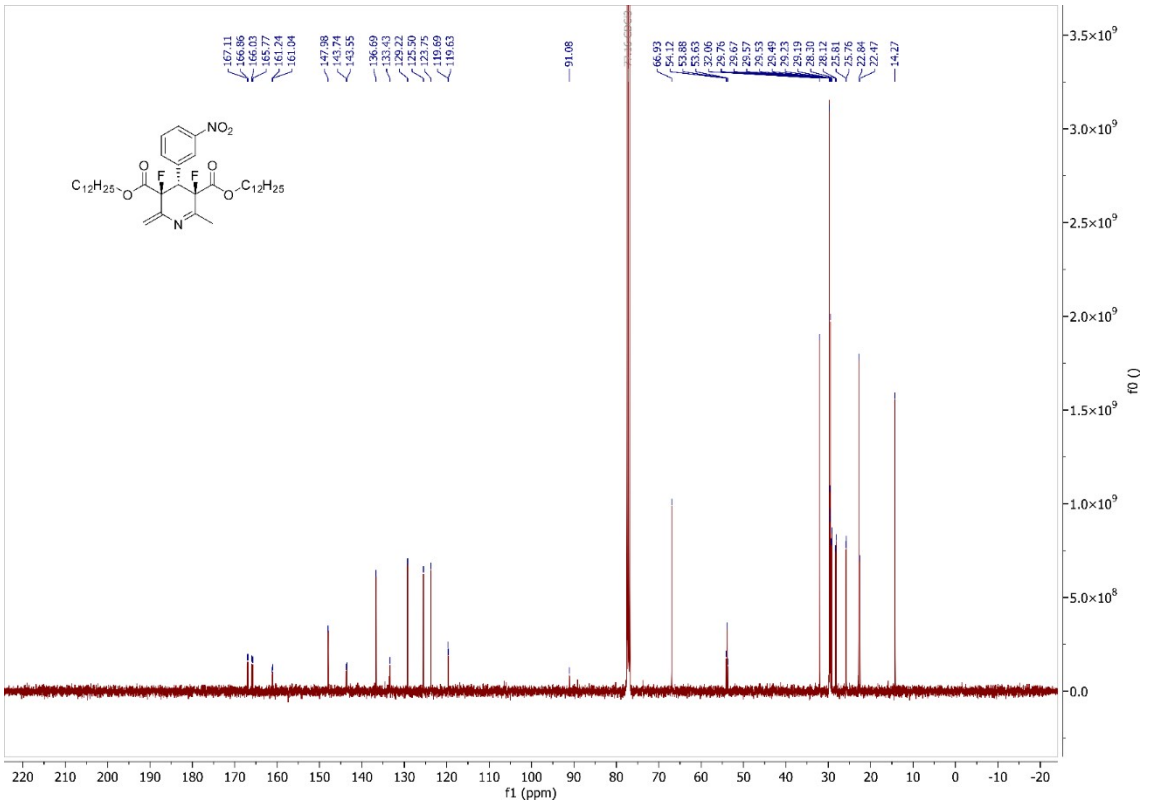


Figure S49. ^{13}C-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3-nitrophenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2i**).

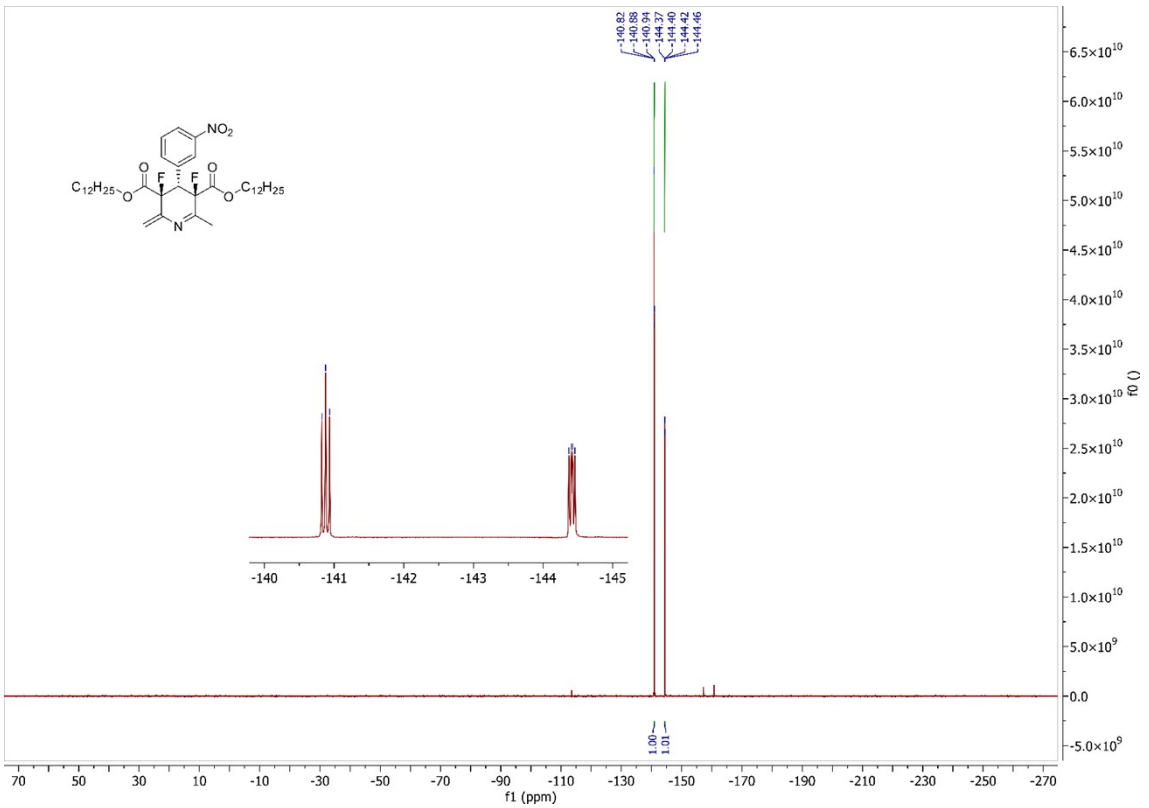


Figure S50. ^{19}F-NMR spectrum of Didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(3-nitrophenyl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2i**).

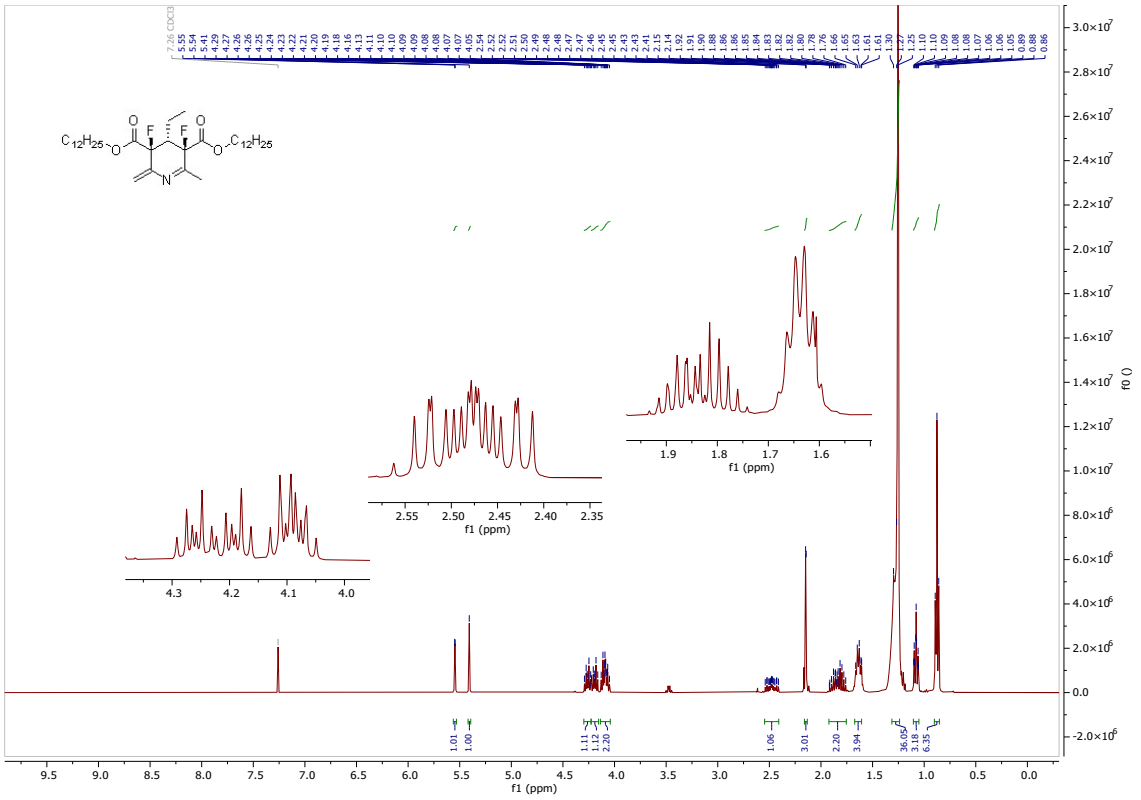


Figure S51. ^{1}H-NMR spectrum of didodecyl (3,4,5)-4-ethyl-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2j**).

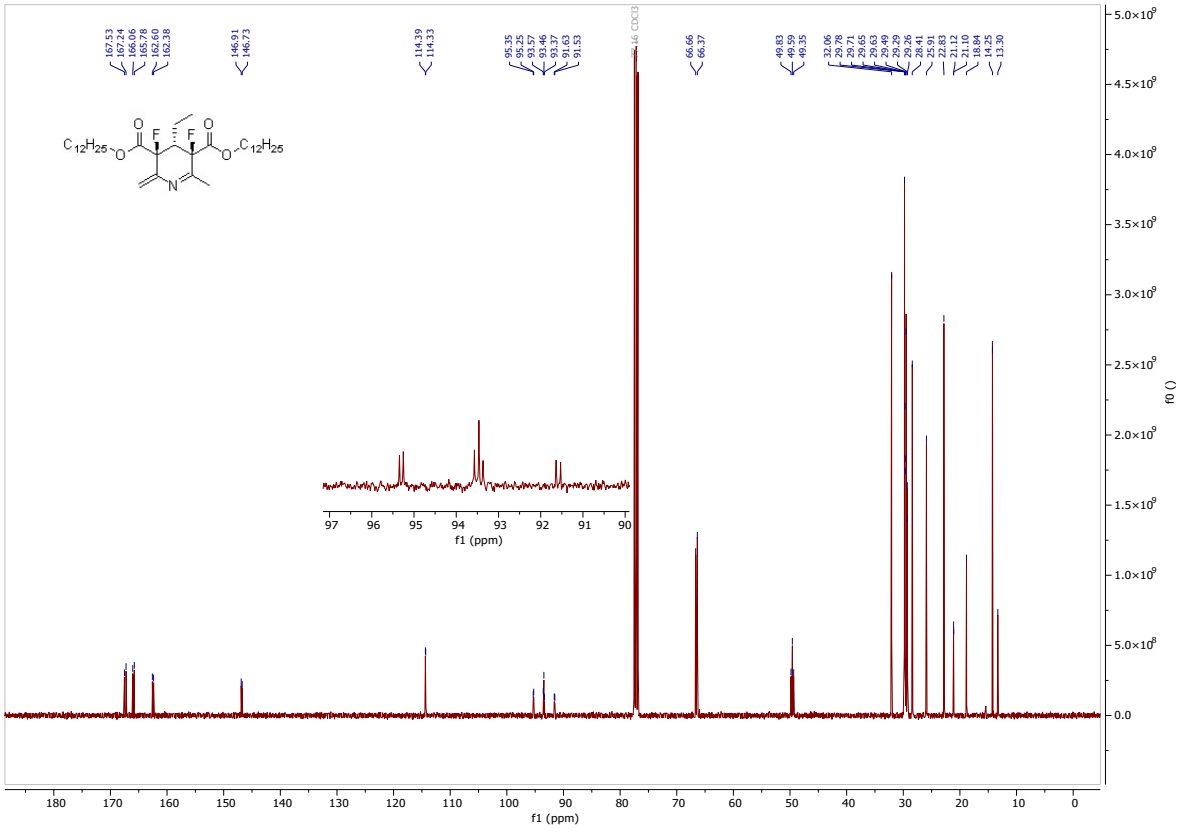


Figure S52. ^{13}C-NMR spectrum of didodecyl (3,4,5)-4-ethyl-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2j**).

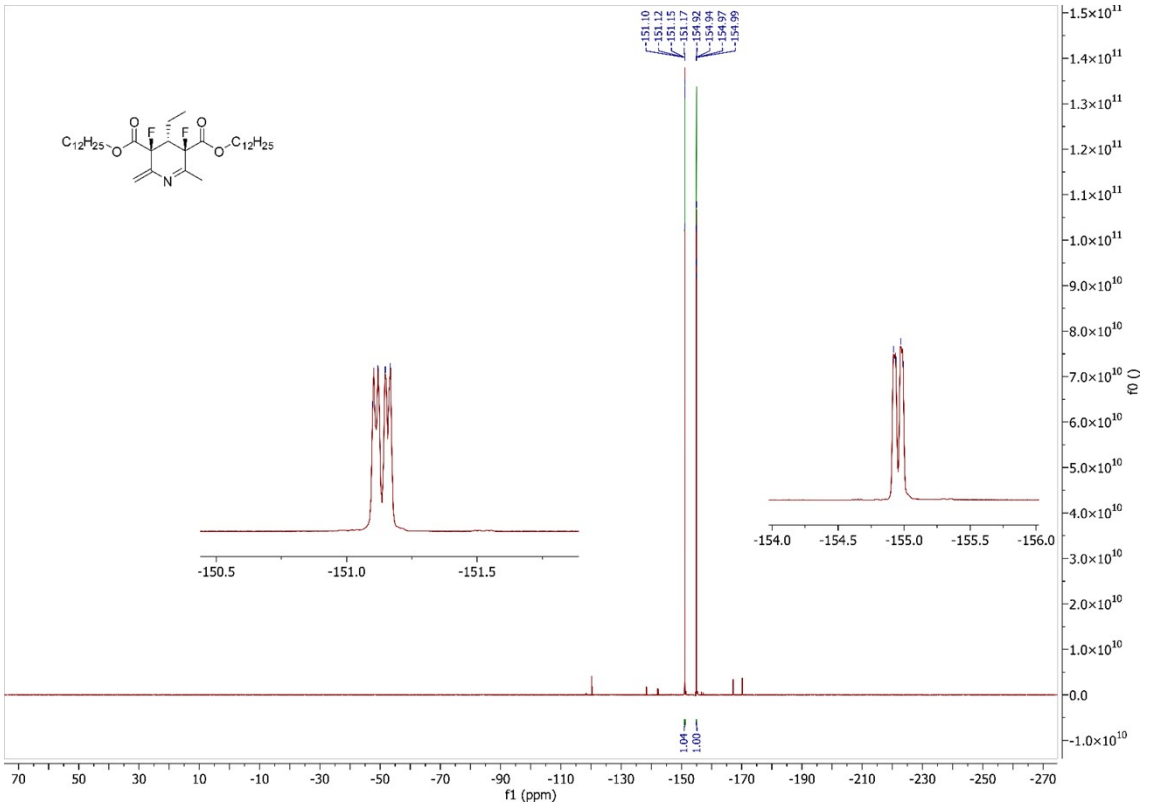


Figure S53. ^{19}F-NMR spectrum of didodecyl (3,4,5)-4-ethyl-3,5-difluoro-6-methyl-2-methylene-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2j**).

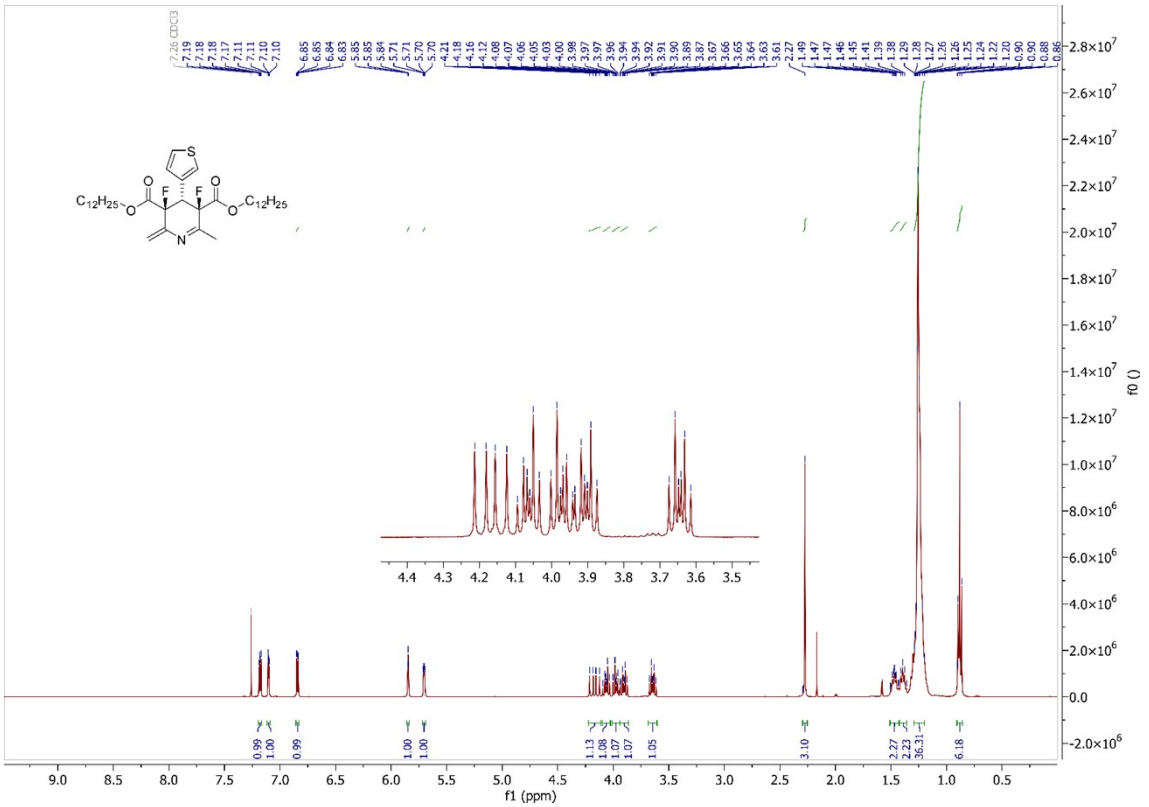


Figure S54. ^{1}H-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(thiophen-3-yl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2k**).

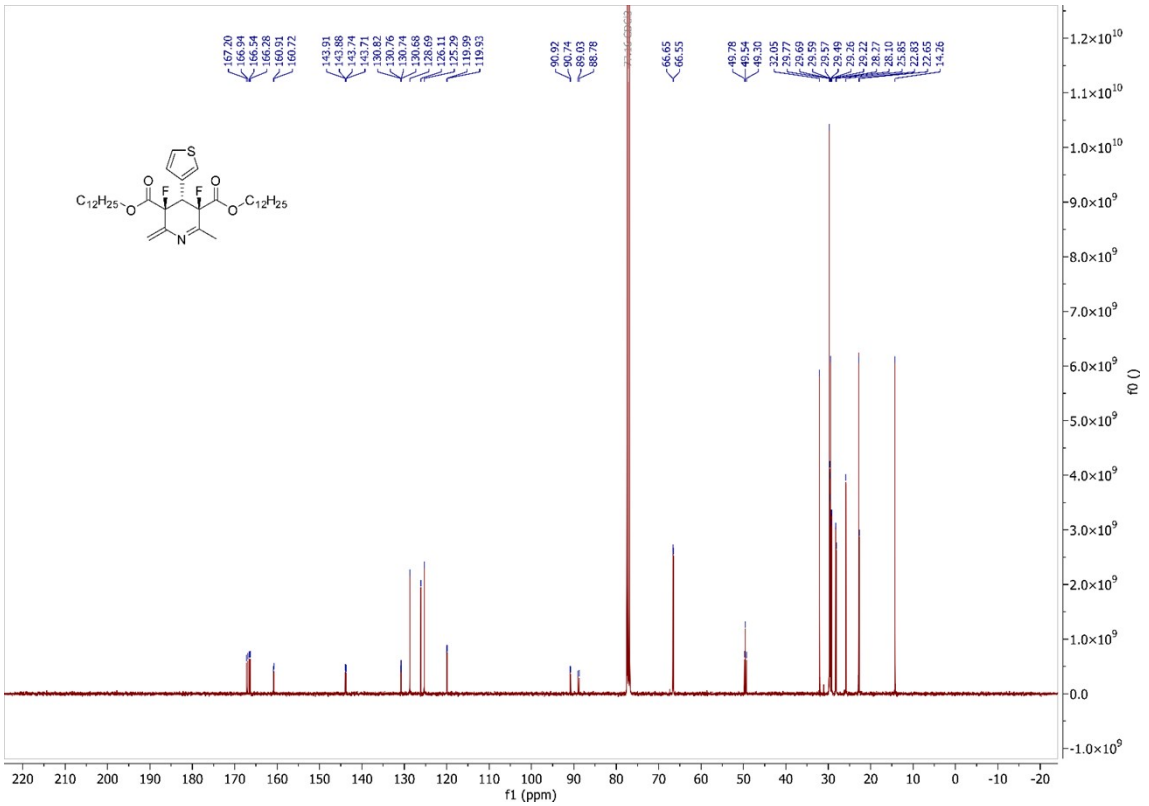


Figure S55. ^{13}C-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(thiophen-3-yl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2k**).

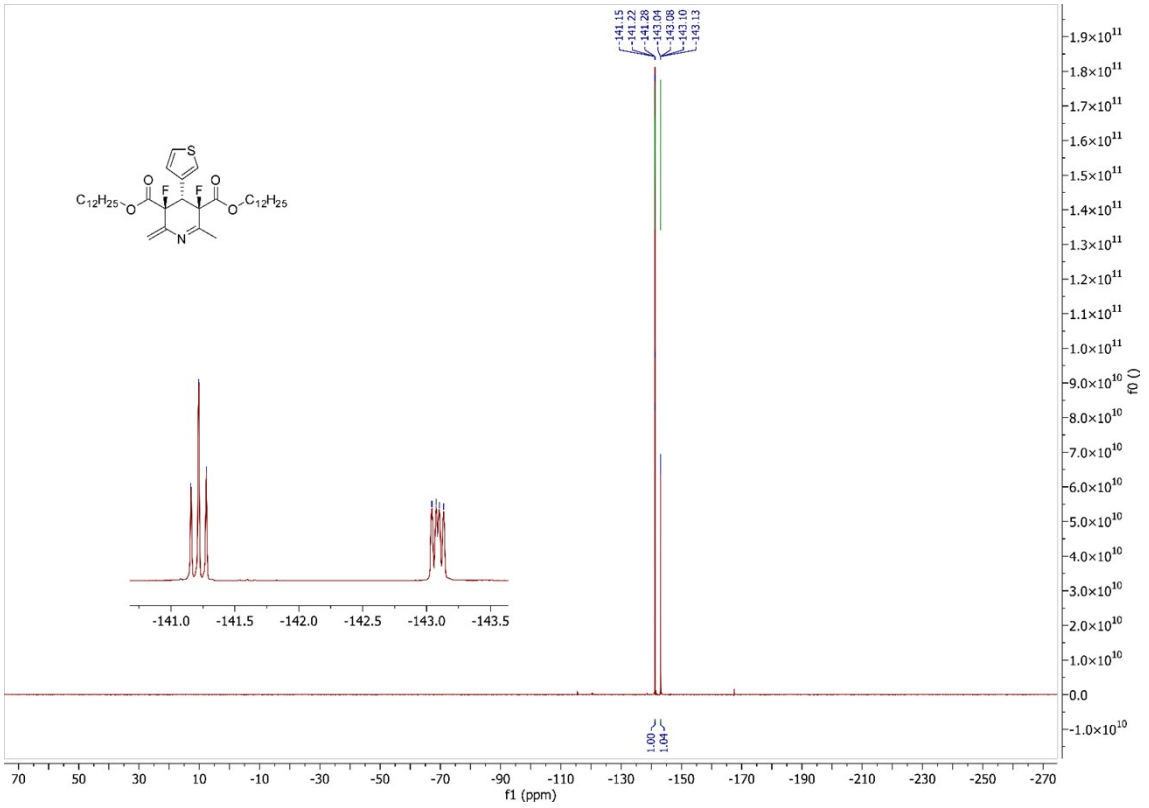


Figure S56. ^{19}F-NMR spectrum of didodecyl (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-(thiophen-3-yl)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2k**).

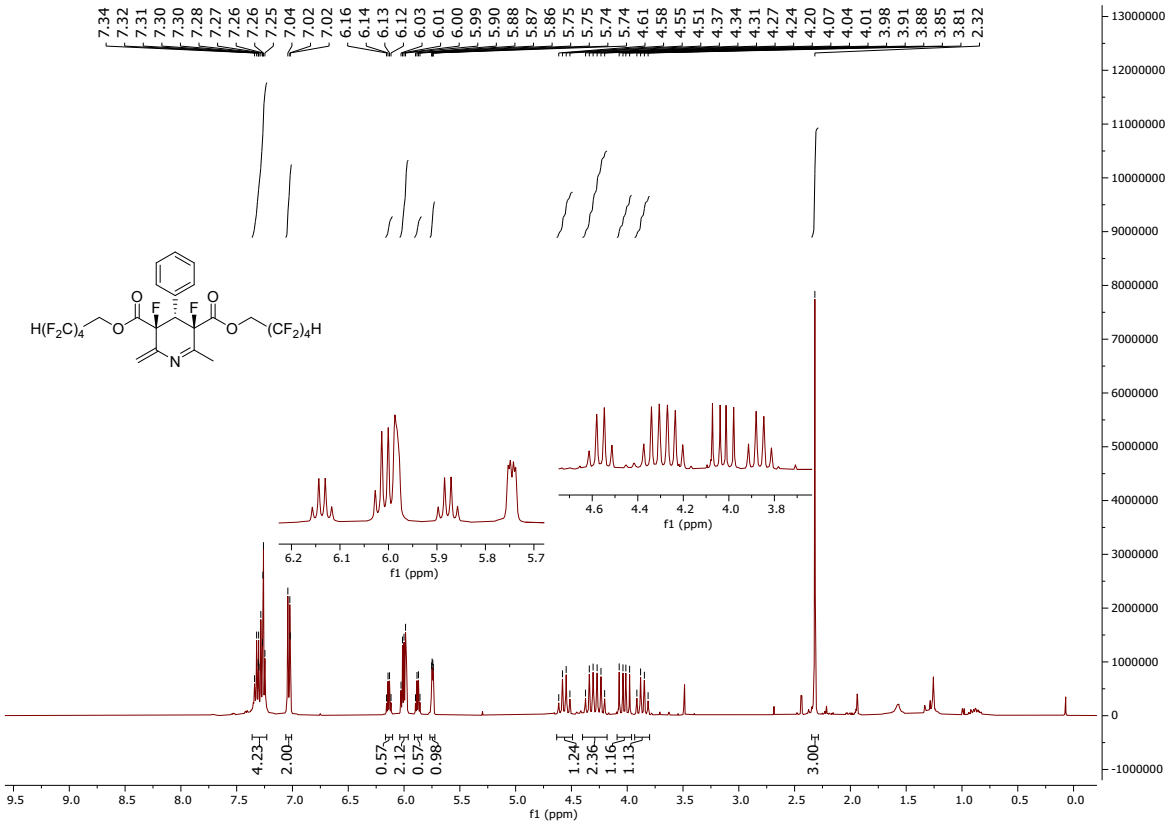


Figure S57. ^{1}H-NMR spectrum of bis(2,2,3,3,4,4,5,5-octafluoropentyl) (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2l**).

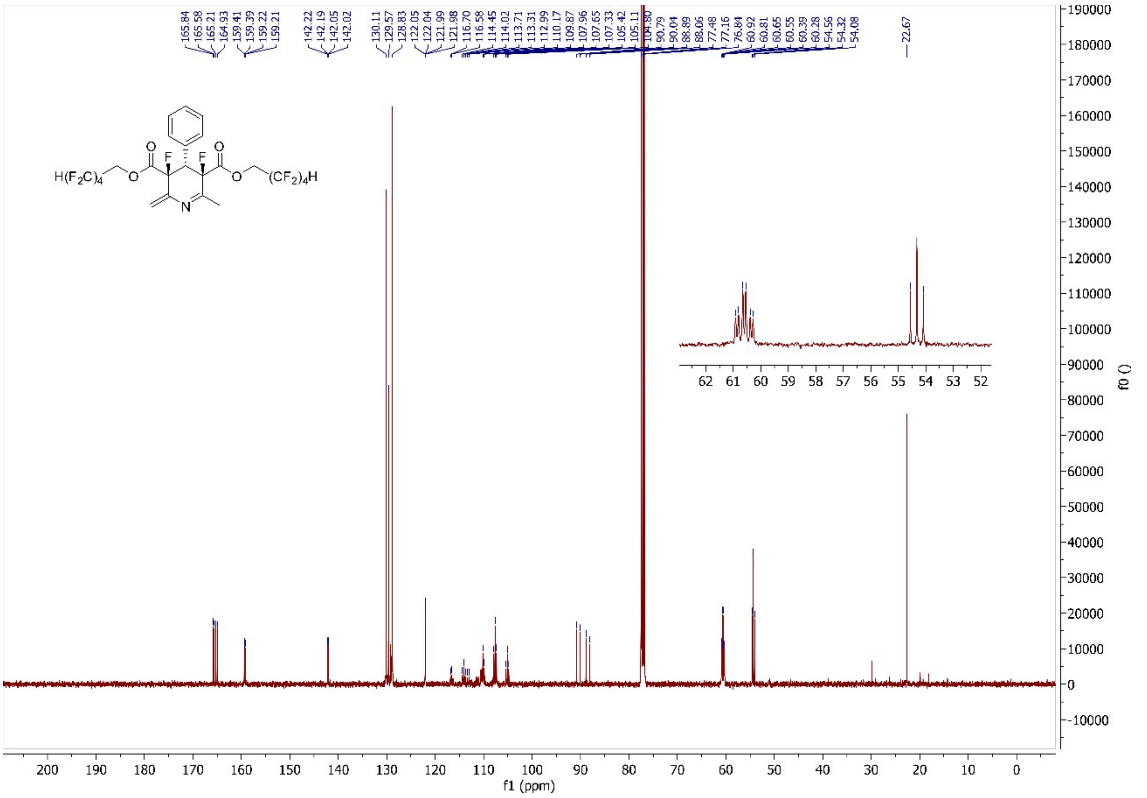


Figure S58. ^{13}C-NMR spectrum of bis(2,2,3,3,4,4,5,5-octafluoropentyl) (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2l**).

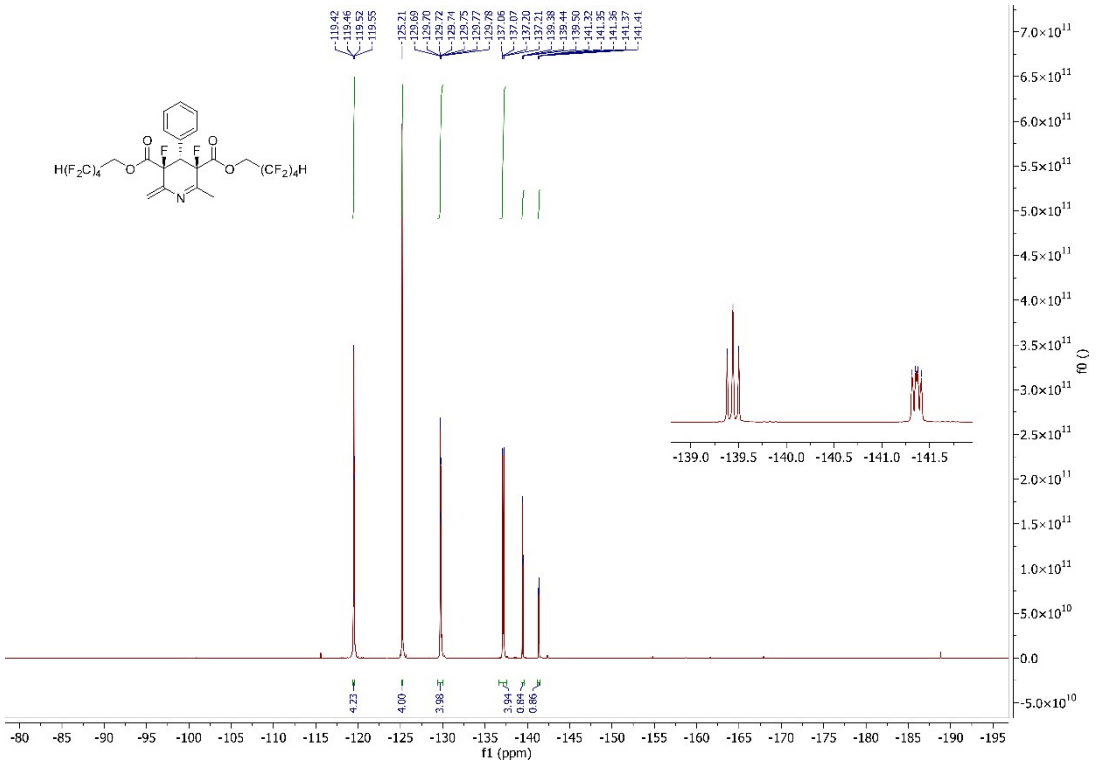


Figure S59. ^{19}F-NMR spectrum of bis(2,2,3,3,4,4,5,5-octafluoropentyl) (3,4,5)-3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2l**).

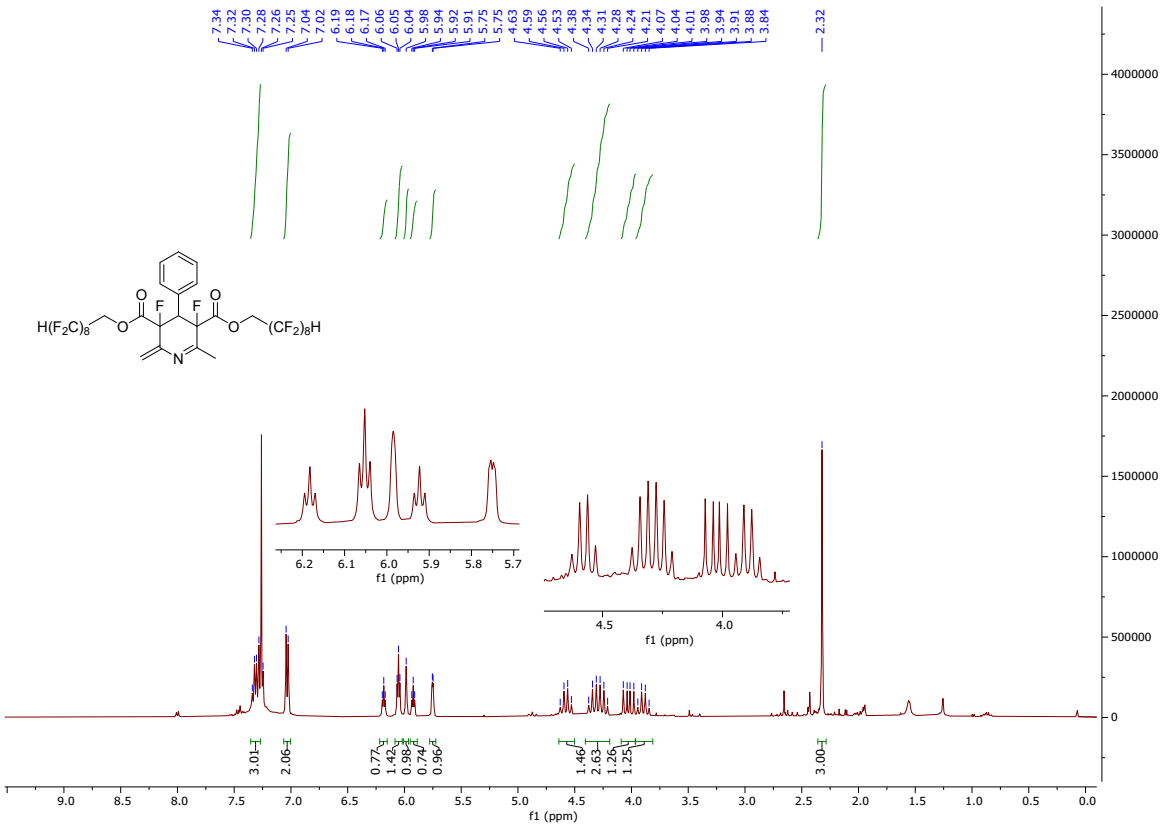


Figure S60. ^{1}H-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) (3,4,5) 3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2m**).

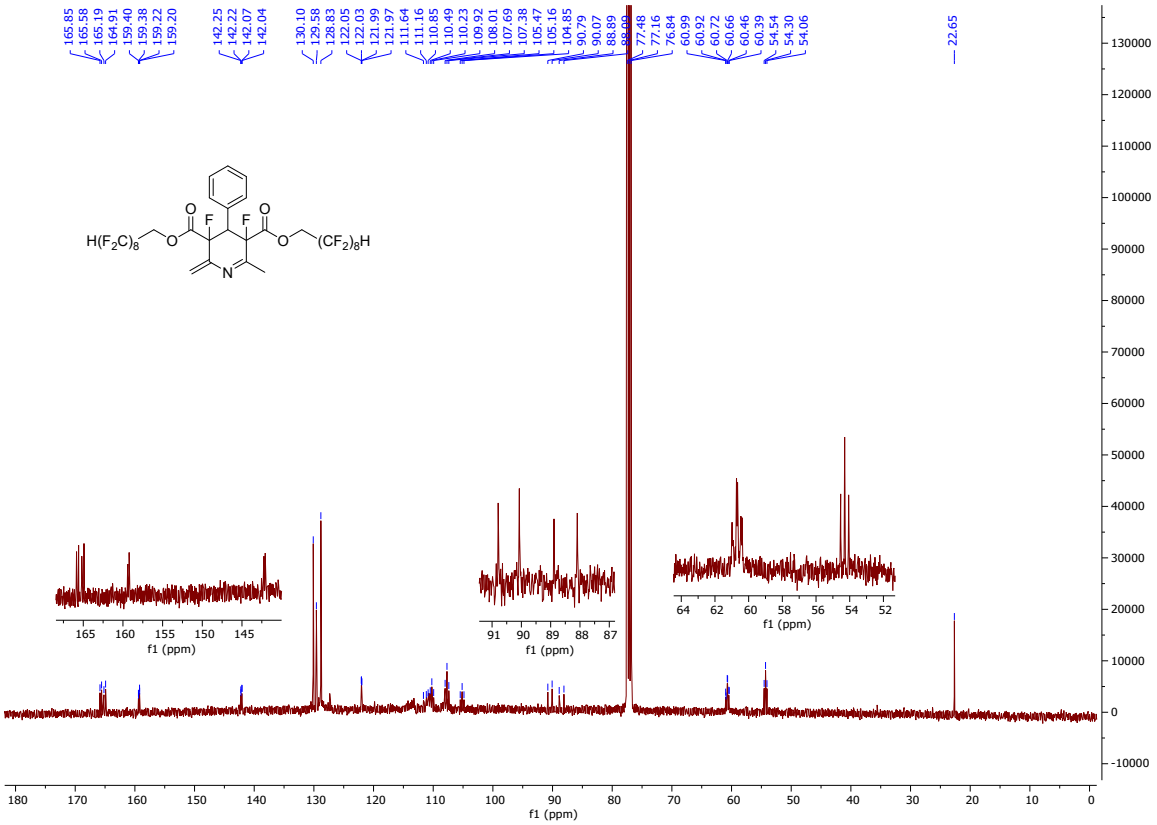


Figure S61. ^{13}C-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) (3,4,5) 3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2m**).

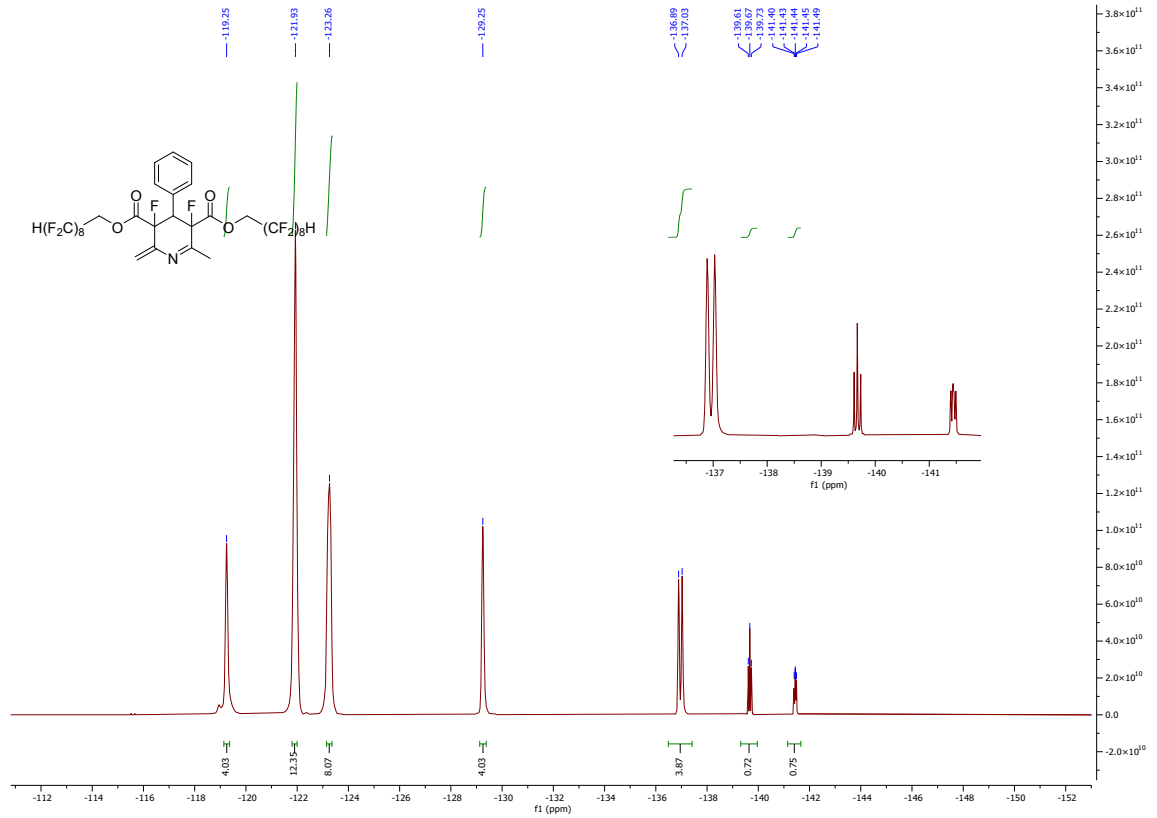


Figure S62. ^{19}F-NMR spectrum of bis(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl) (3,4,5) 3,5-difluoro-6-methyl-2-methylene-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**2m**).

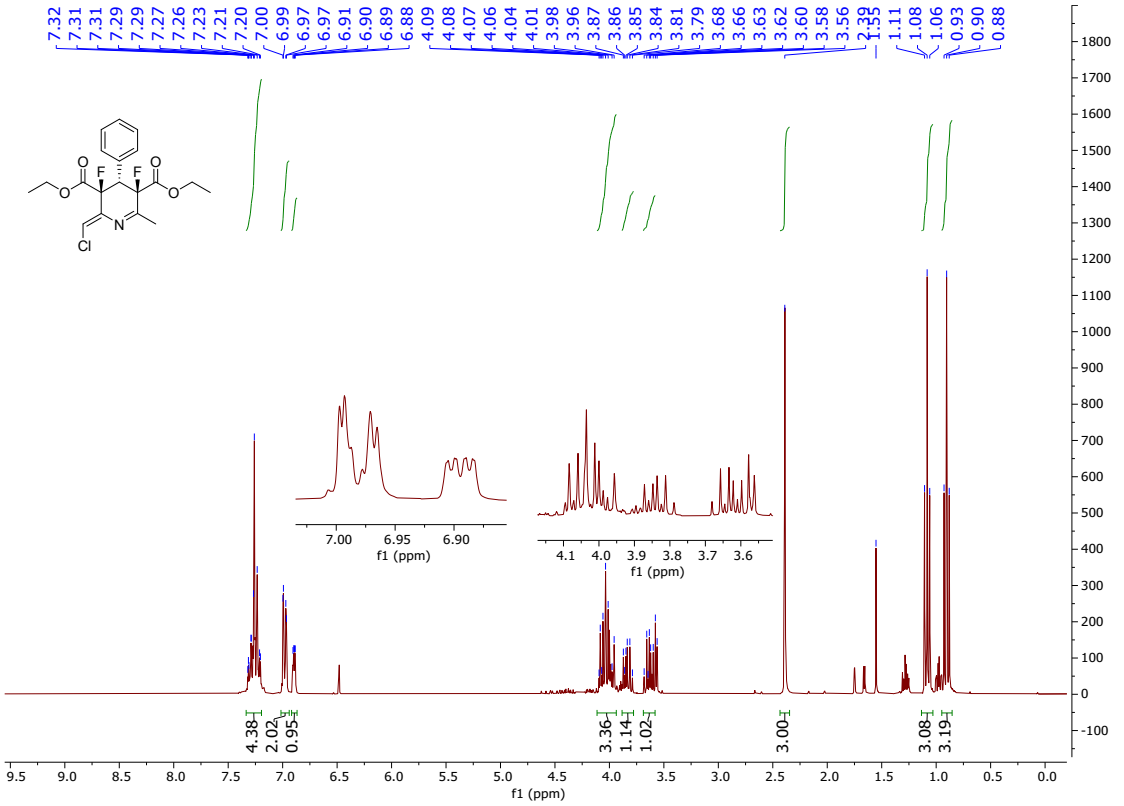


Figure S63. ^{1}H-NMR spectrum of diethyl (3,4,5,Z)-2-(chloromethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7a**).

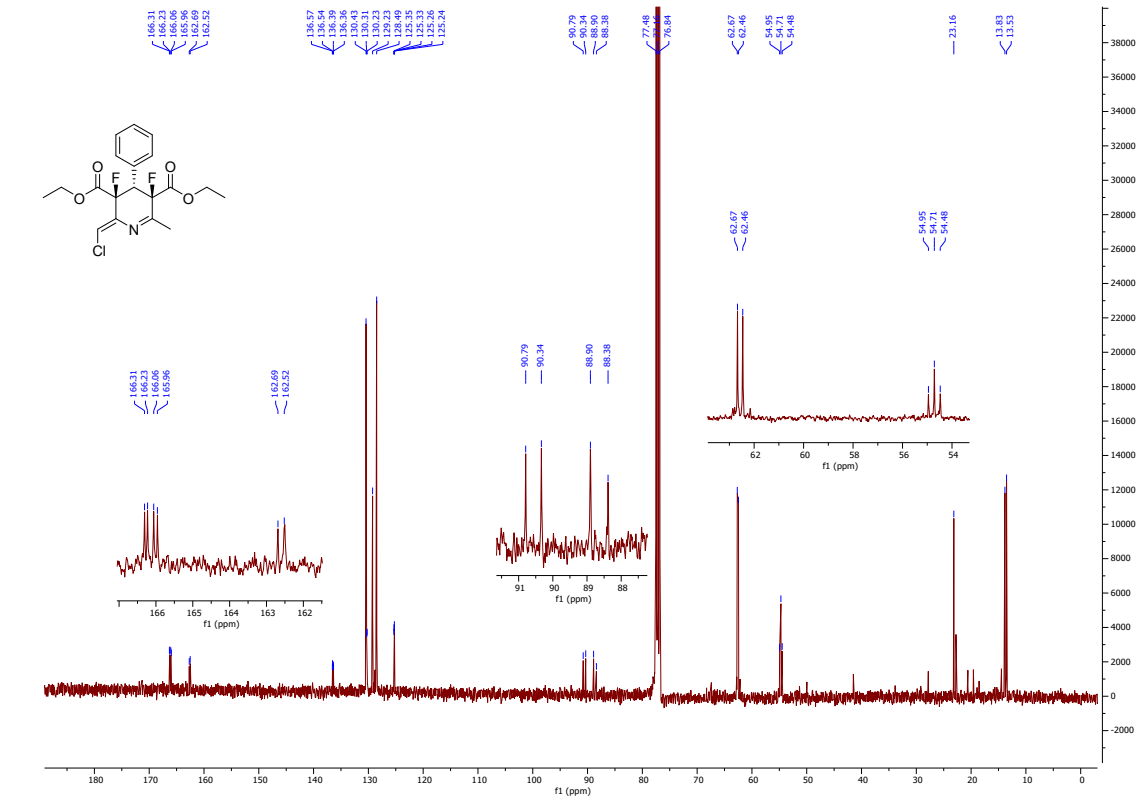


Figure S64. ^{13}C-NMR spectrum of diethyl (3,4,5,Z)-2-(chloromethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7a**).

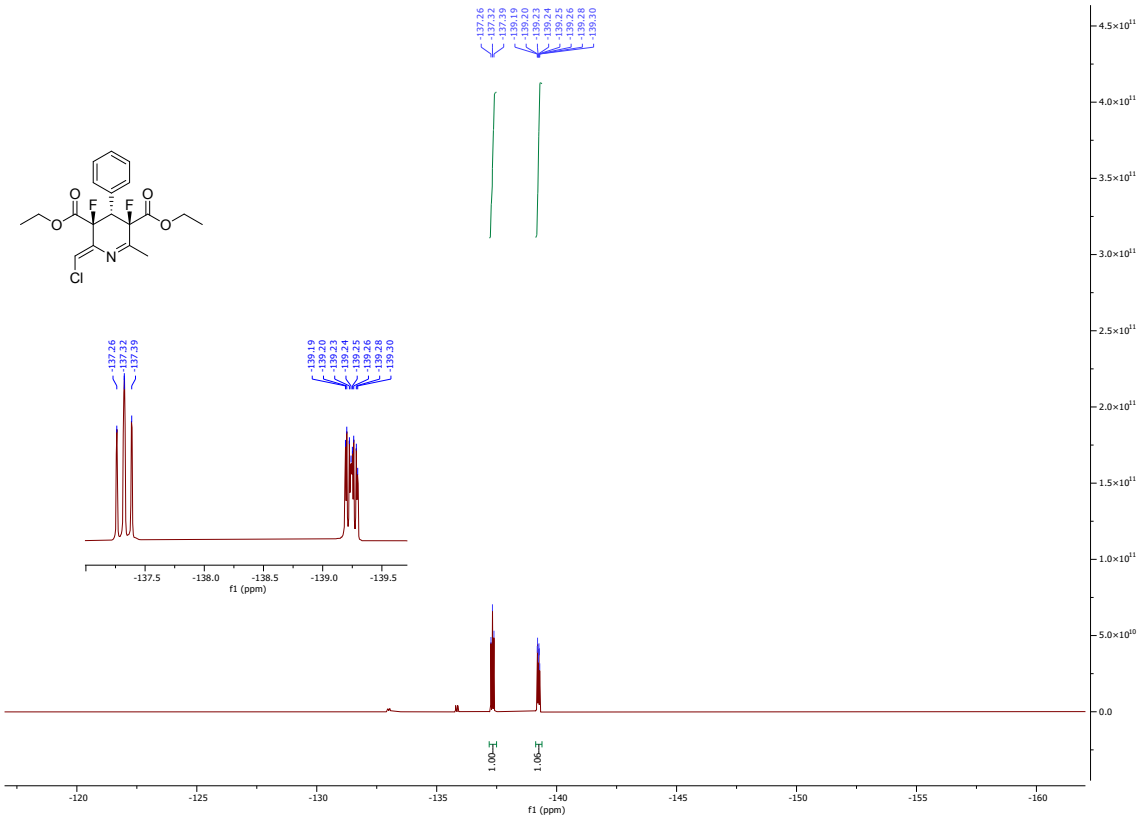


Figure S65. ^{19}F-NMR spectrum of diethyl (3,4,5,Z)-2-(chloromethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7a**).

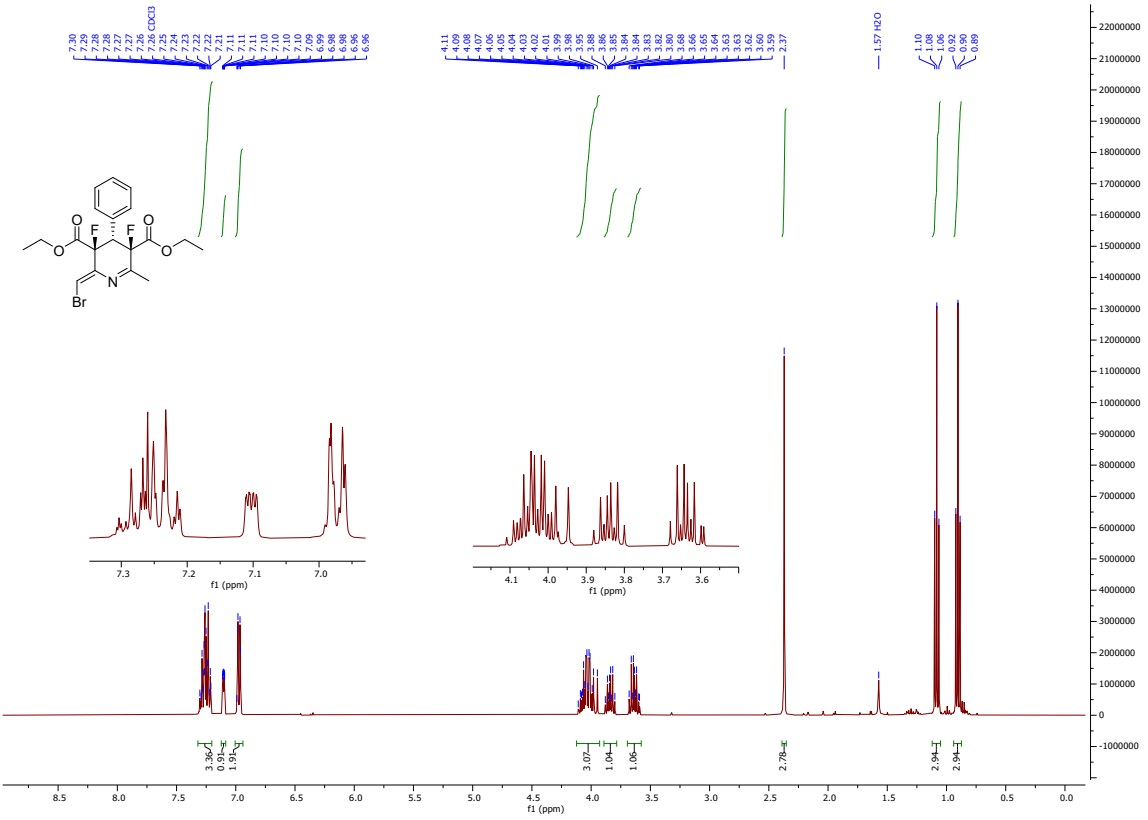


Figure S66. ^{1}H-NMR spectrum of diethyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7b**).

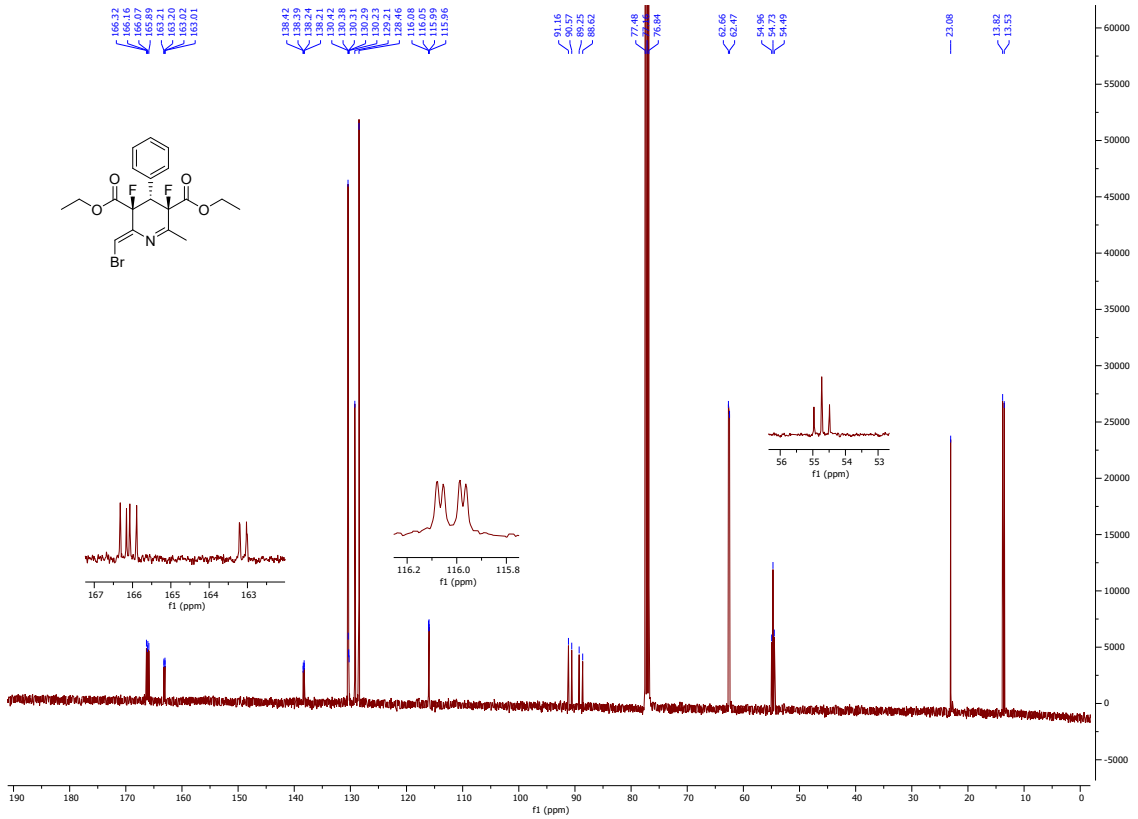


Figure S67. ^{13}C-NMR spectrum of diethyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7b**).

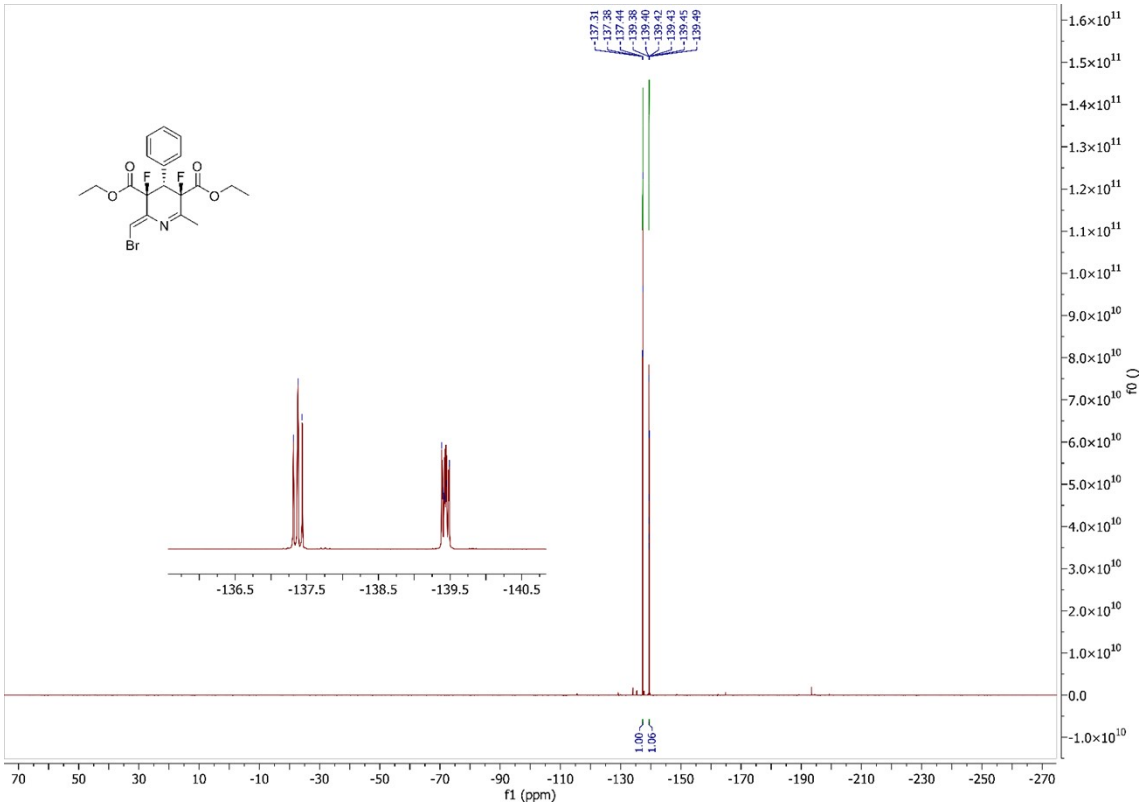


Figure S68. ^{19}F-NMR spectrum of diethyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7b**).

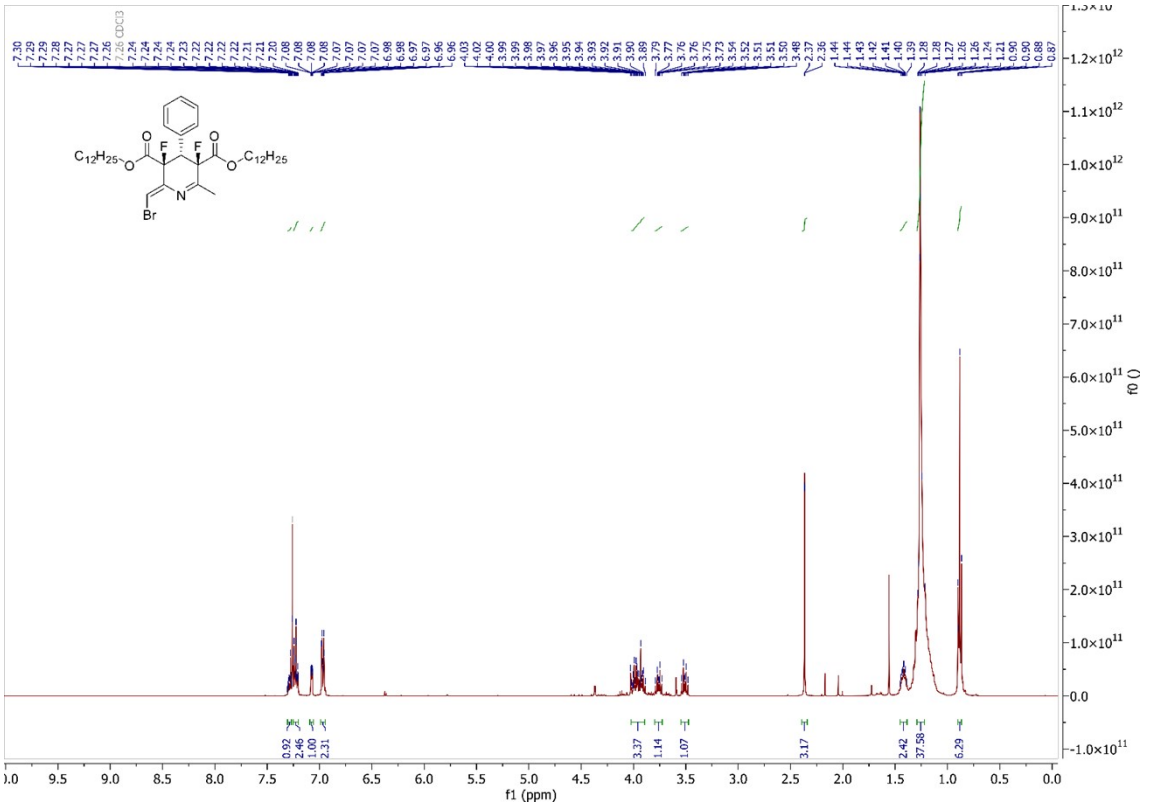


Figure S69. ^{1}H-NMR spectrum of didodecyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7c**).

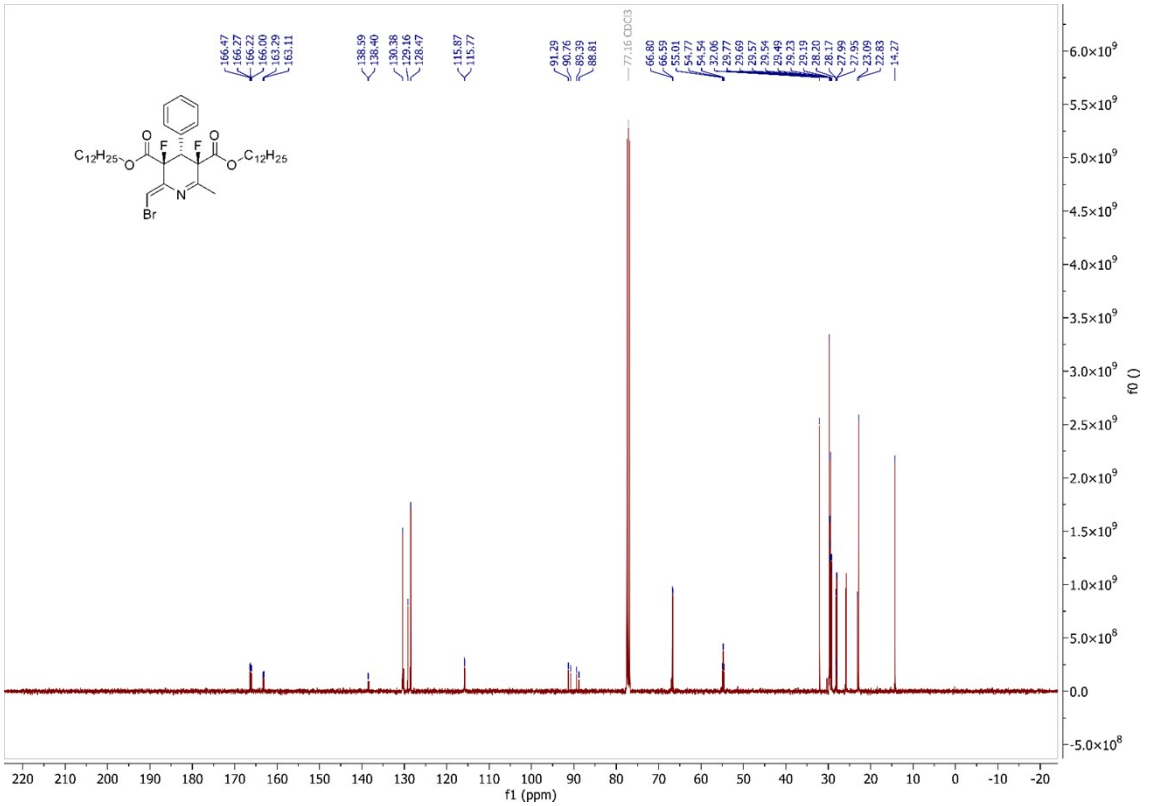


Figure S70. ^{13}C-NMR spectrum of didodecyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7c**).

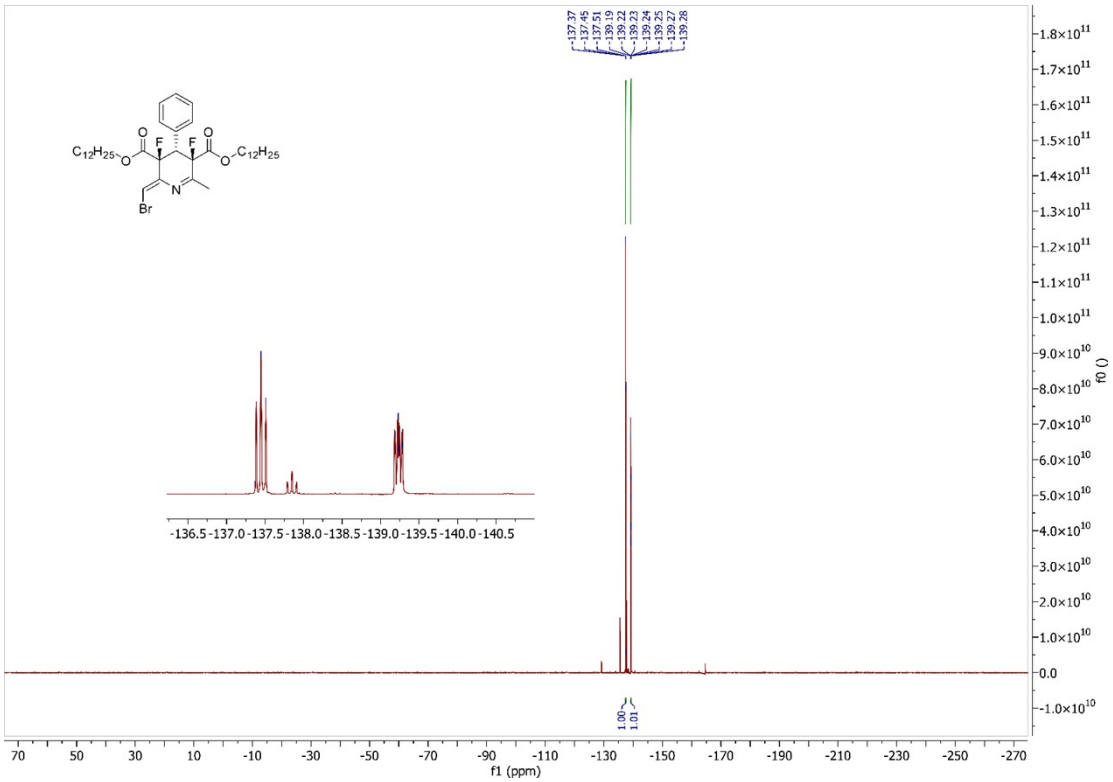


Figure S71. ^{19}F-NMR spectrum of didodecyl (3,4,5,Z)-2-(bromomethylene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**7c**).

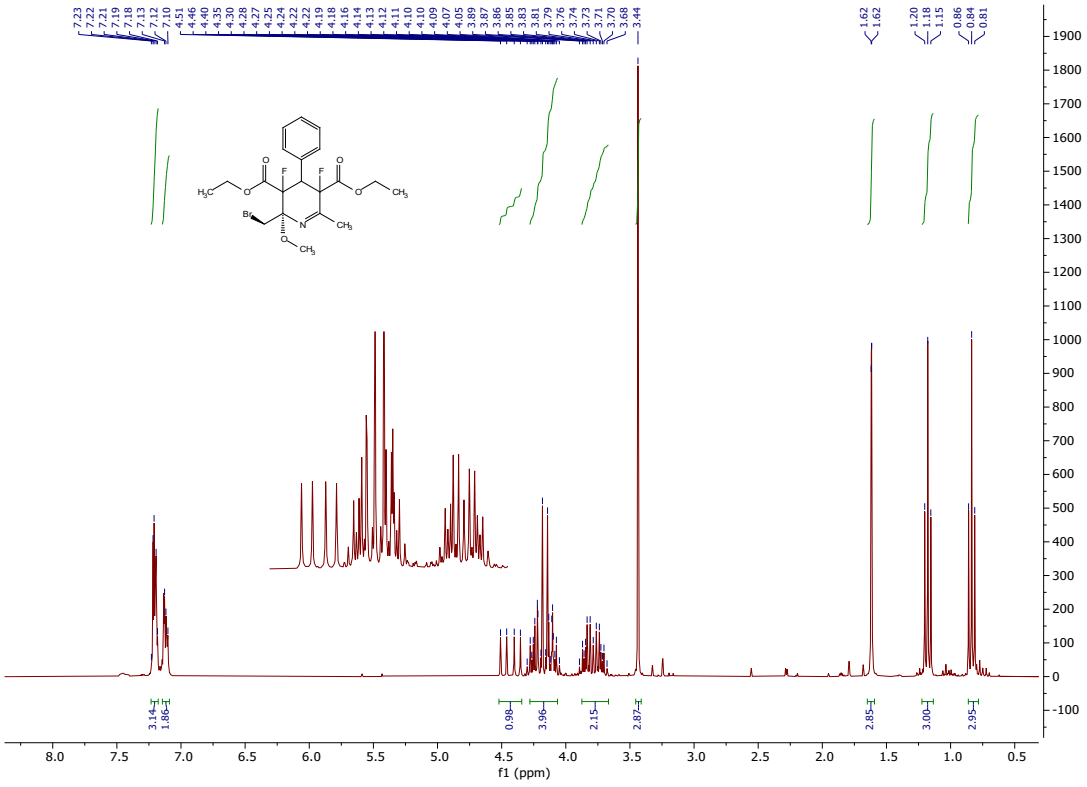


Figure S72. ^{1}H-NMR spectrum of bromination intermediate - diethyl 2-(bromomethyl)-3,5-difluoro-2-methoxy-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**10**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 3H, Ph), 7.15 – 7.09 (m, 2H, Ph), 4.42 (dd, $^{3}J_{H\text{-}F}$ = 32.4 Hz, $^{3}J_{H\text{-}F}$ = 14.5 Hz, 1H, CH(4)), 4.30 – 4.03 (m, 4H, $COOC\underline{H_2}CH_3$ and $C\underline{H_2}Br$), 3.90 – 3.68 (m, 2H, $COOC\underline{H_2}CH_3$), 3.44 (s, 3H, OCH_3), 1.64 – 1.62 (m, 3H, $C\underline{H_3}$), 1.18 (t, *J* = 7.1 Hz, 3H, $COOCH_2C\underline{H_3}$), 0.84 (t, *J* = 7.1 Hz, 3H, $COOCH_2C\underline{H_3}$) ppm.

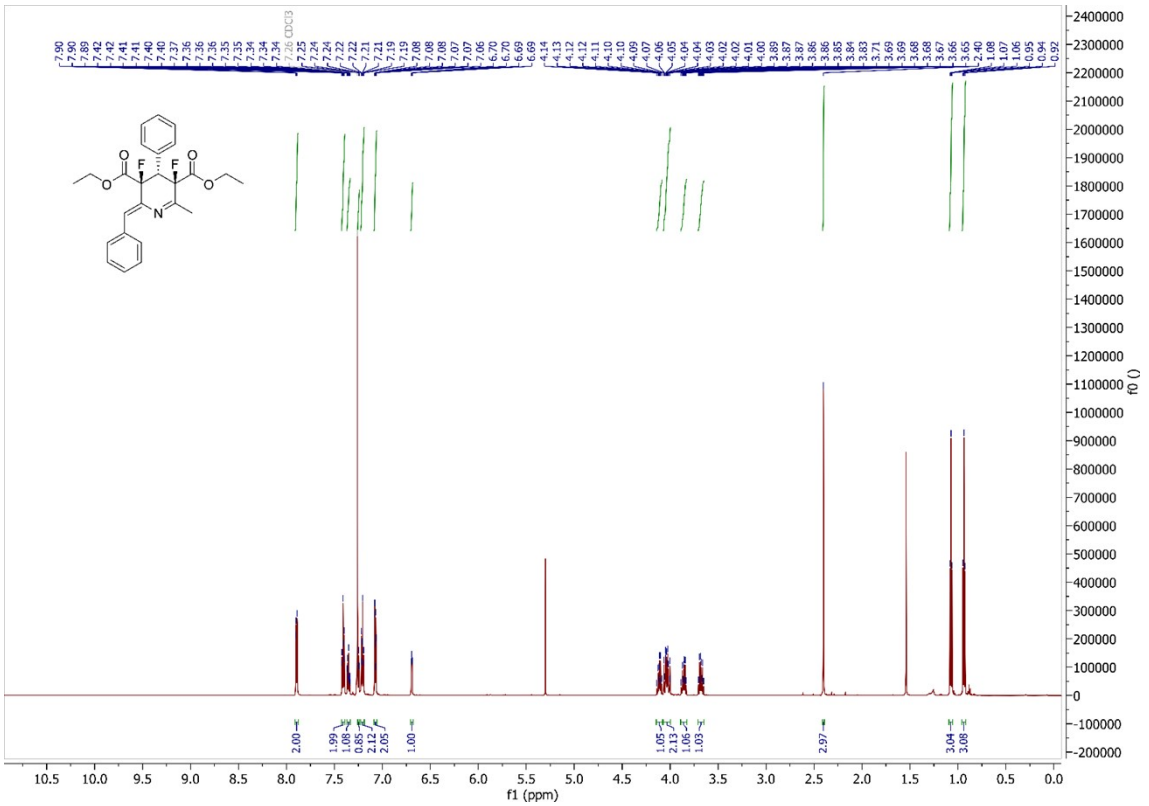


Figure S73. ^{1}H-NMR spectrum of diethyl (3,4,5)-2-((Z)-benzylidene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13a**).

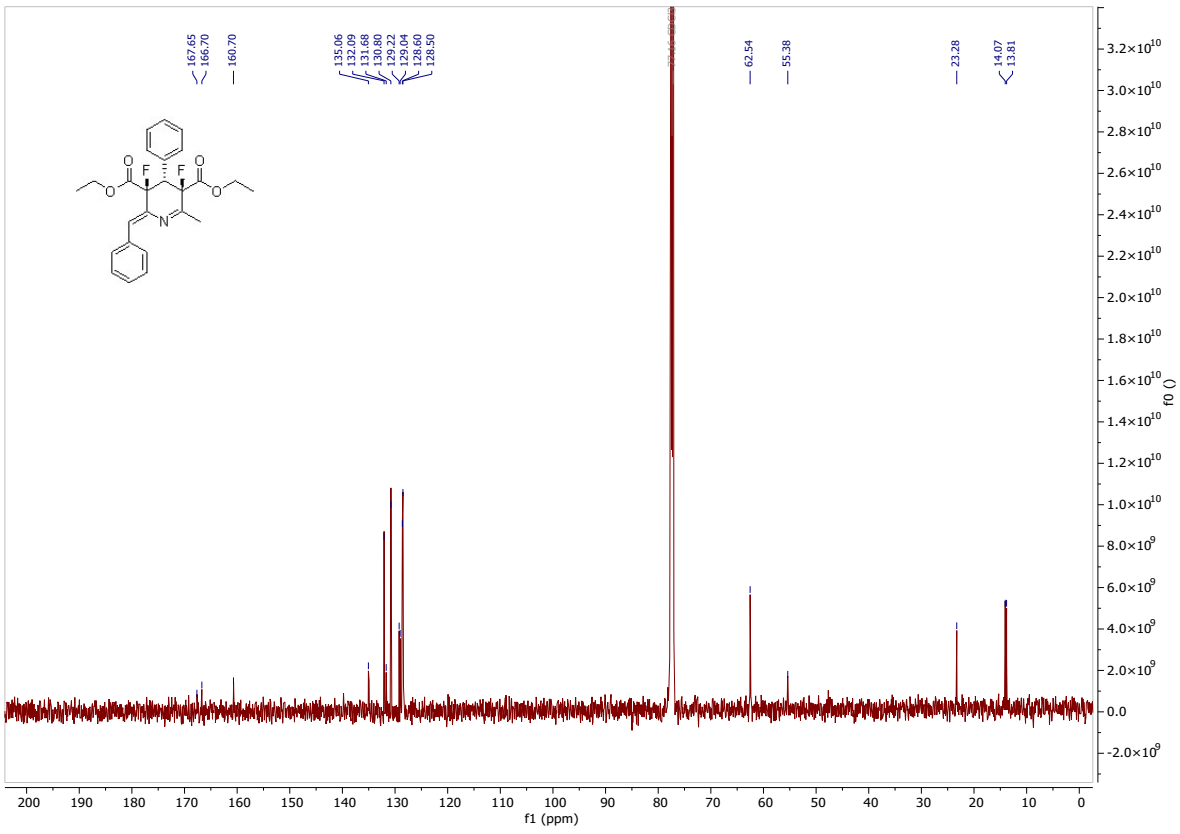


Figure S74. ^{13}C-NMR spectrum of diethyl (3,4,5)-2-((Z)-benzylidene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13a**).

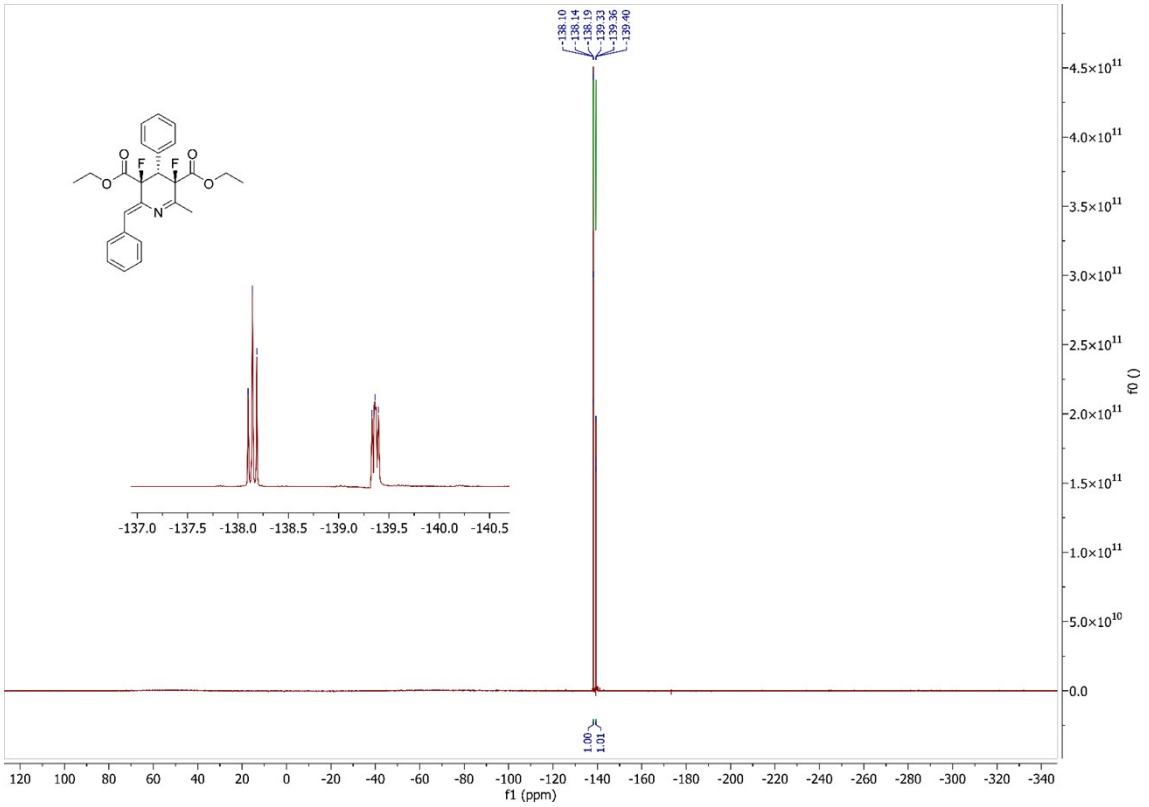


Figure S75. ^{19}F-NMR spectrum of diethyl (3,4,5)-2-((Z)-benzylidene)-3,5-difluoro-6-methyl-4-phenyl-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13a**).

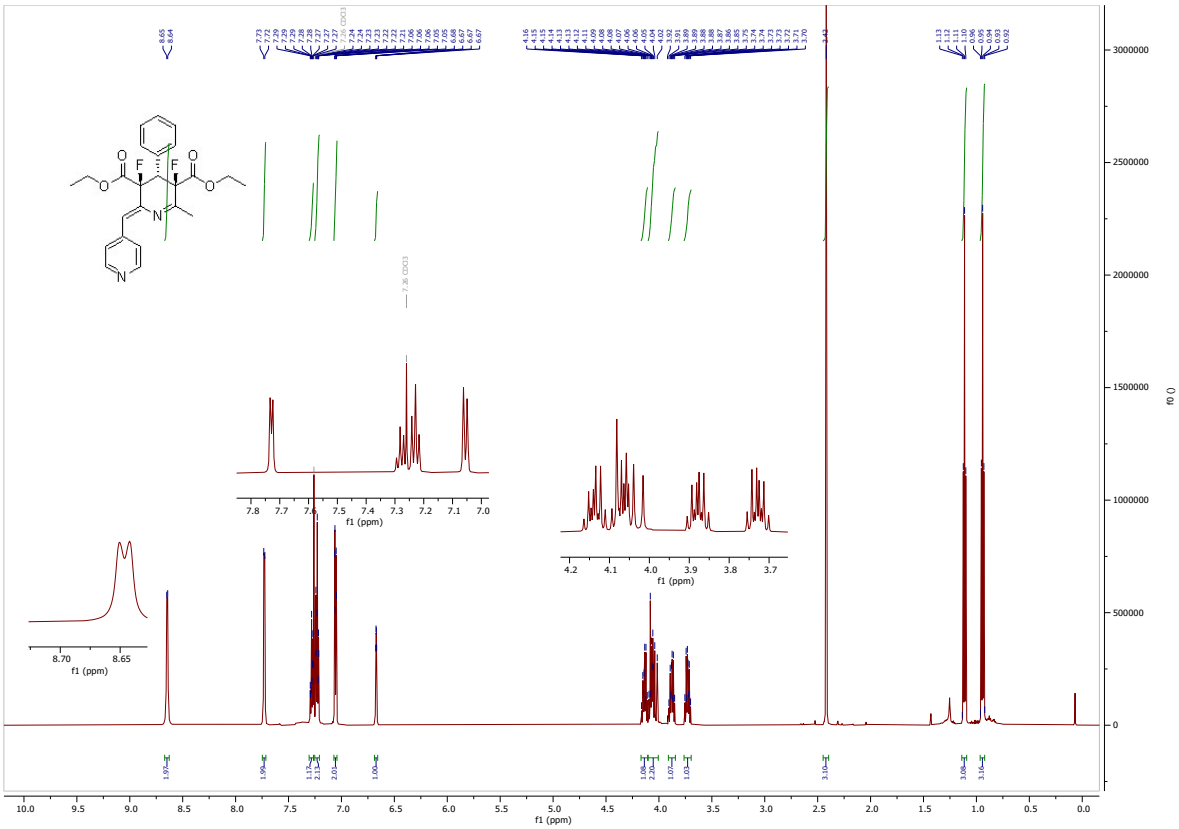


Figure S76. ^{1}H-NMR spectrum of diethyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13b**).

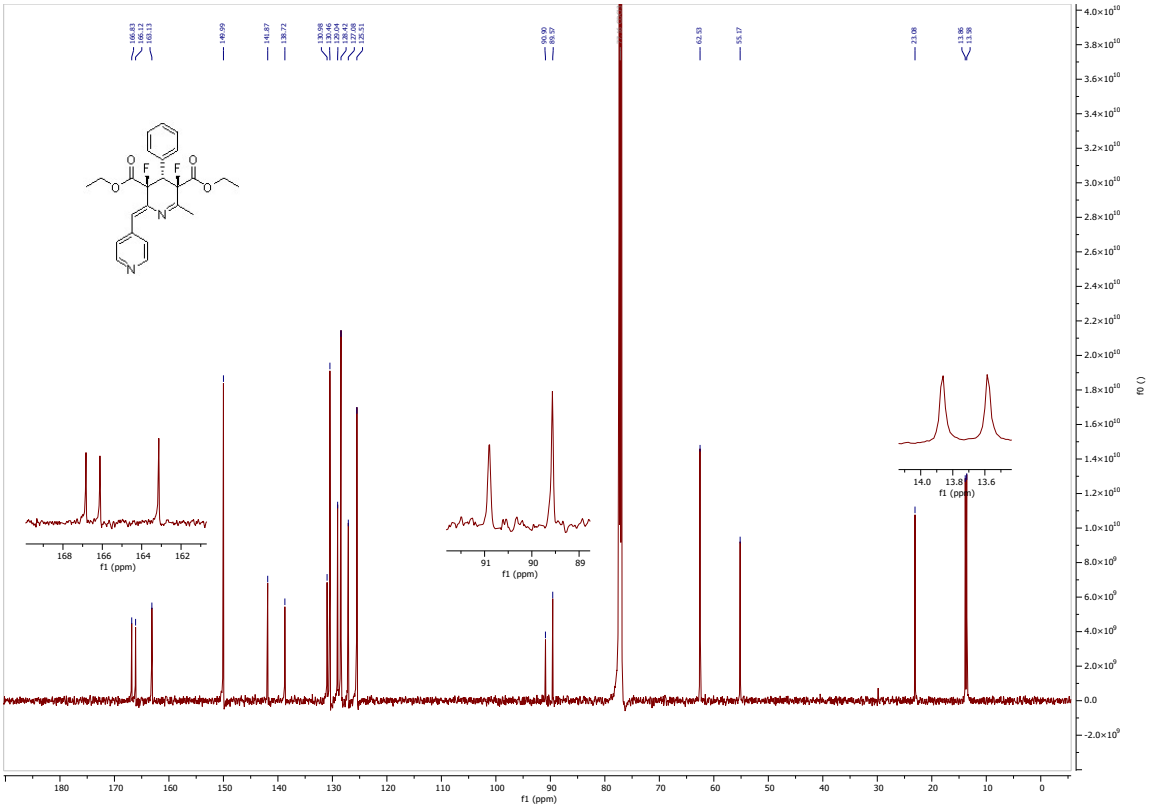


Figure S77. ^{13}C-NMR spectrum of diethyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13b**).

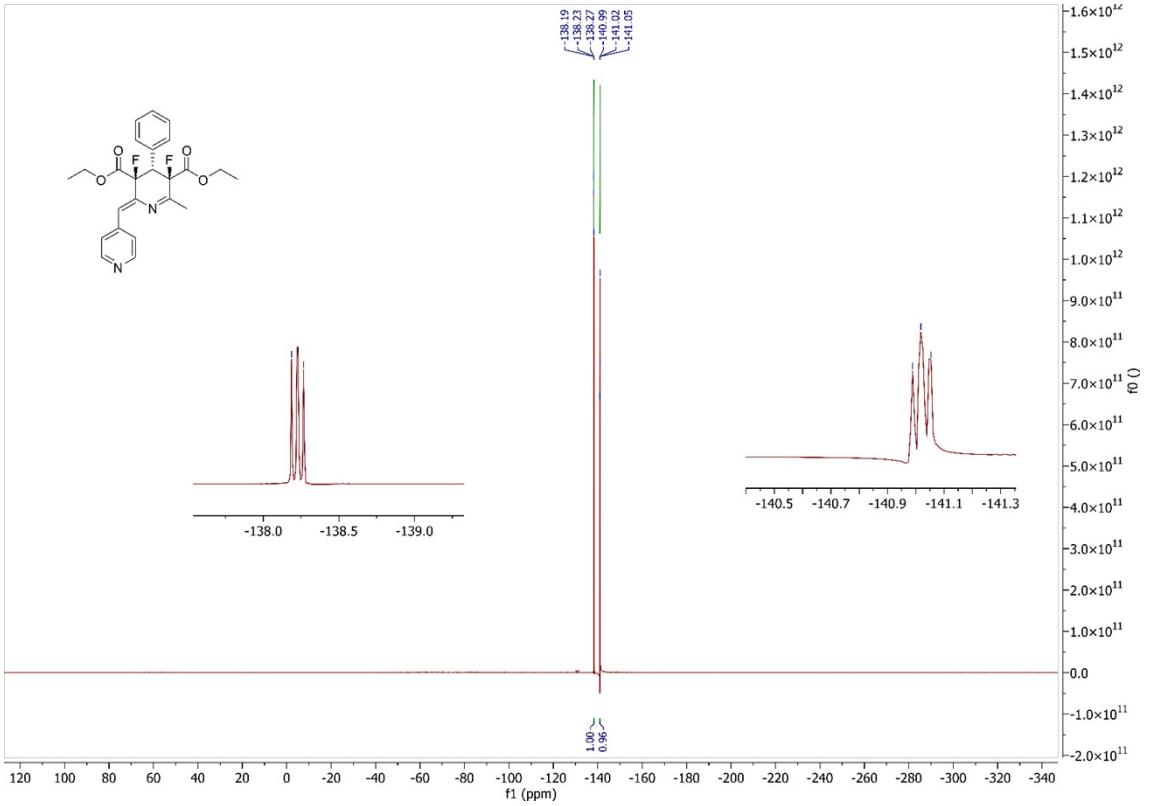


Figure S78. ^{19}F-NMR spectrum of diethyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13b**).

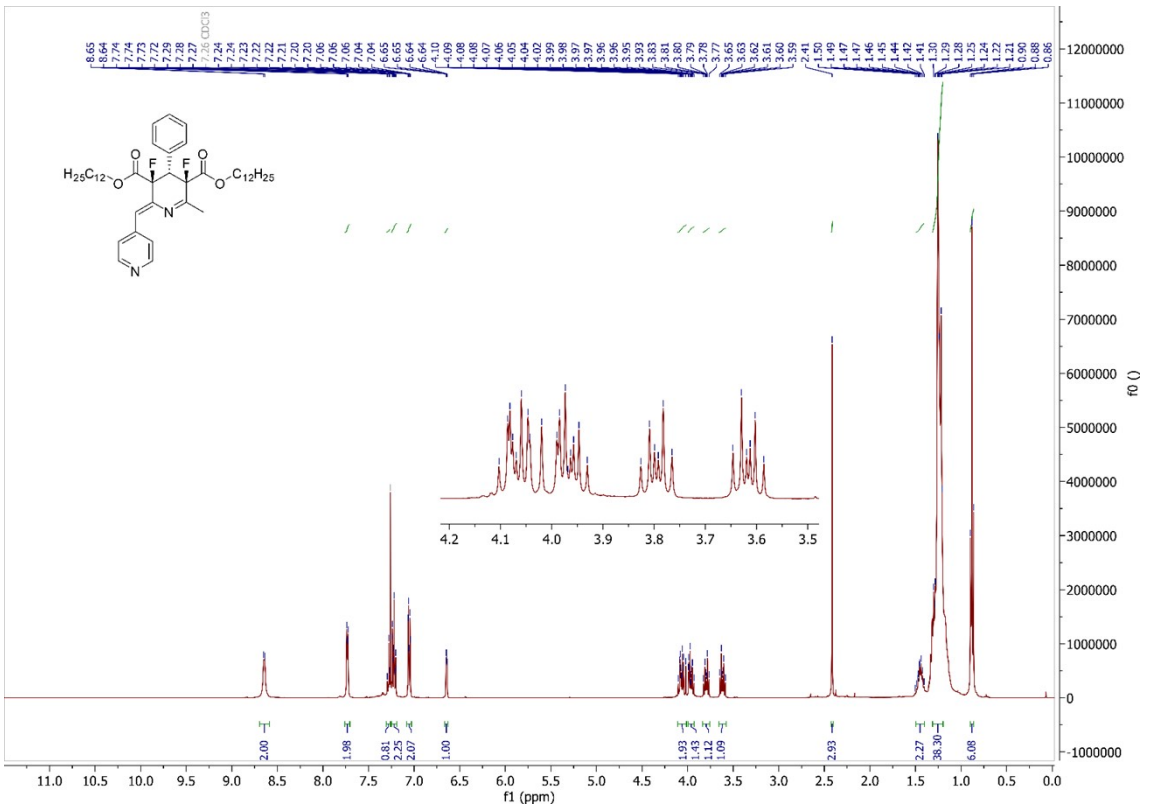


Figure S79. ^{1}H-NMR spectrum of didodecyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13c**).

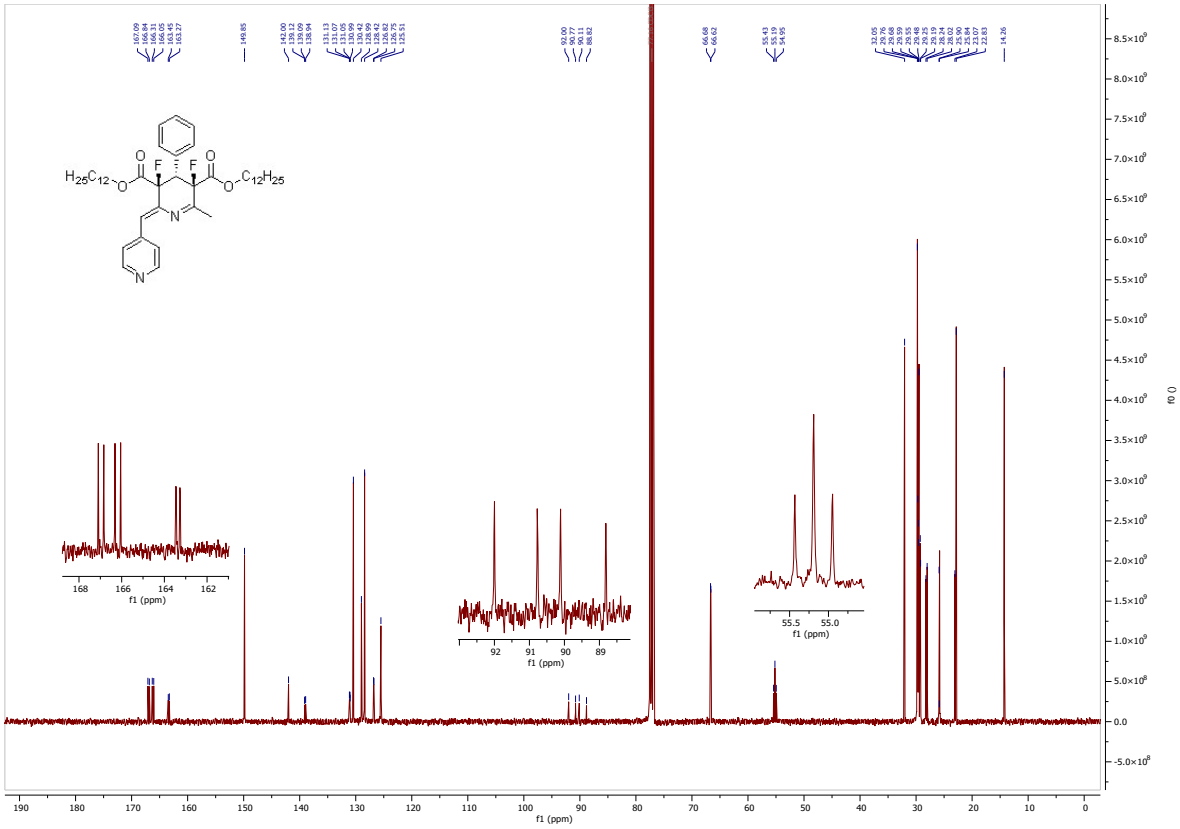


Figure S80. ^{13}C-NMR spectrum of didodecyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13c**).

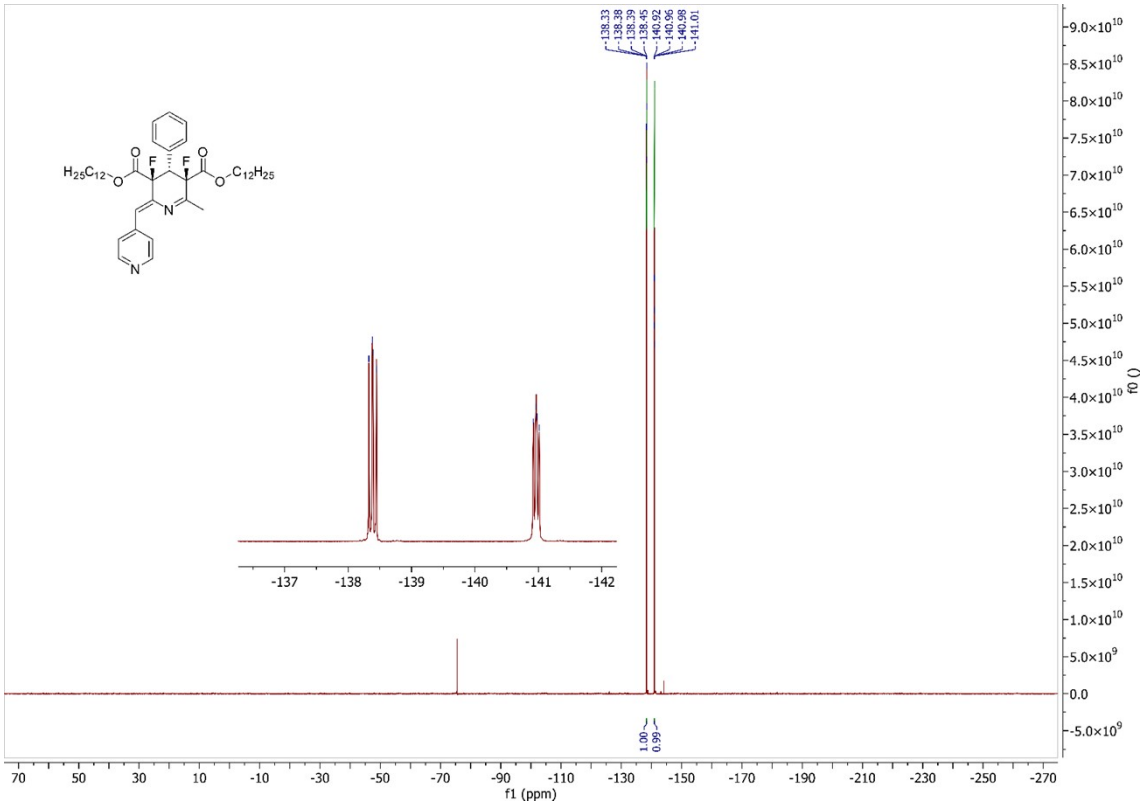


Figure S81. ^{19}F-NMR spectrum of didodecyl (3,4,5,Z)-3,5-difluoro-6-methyl-4-phenyl-2-(pyridin-4-ylmethylene)-2,3,4,5-tetrahydropyridine-3,5-dicarboxylate (**13c**).

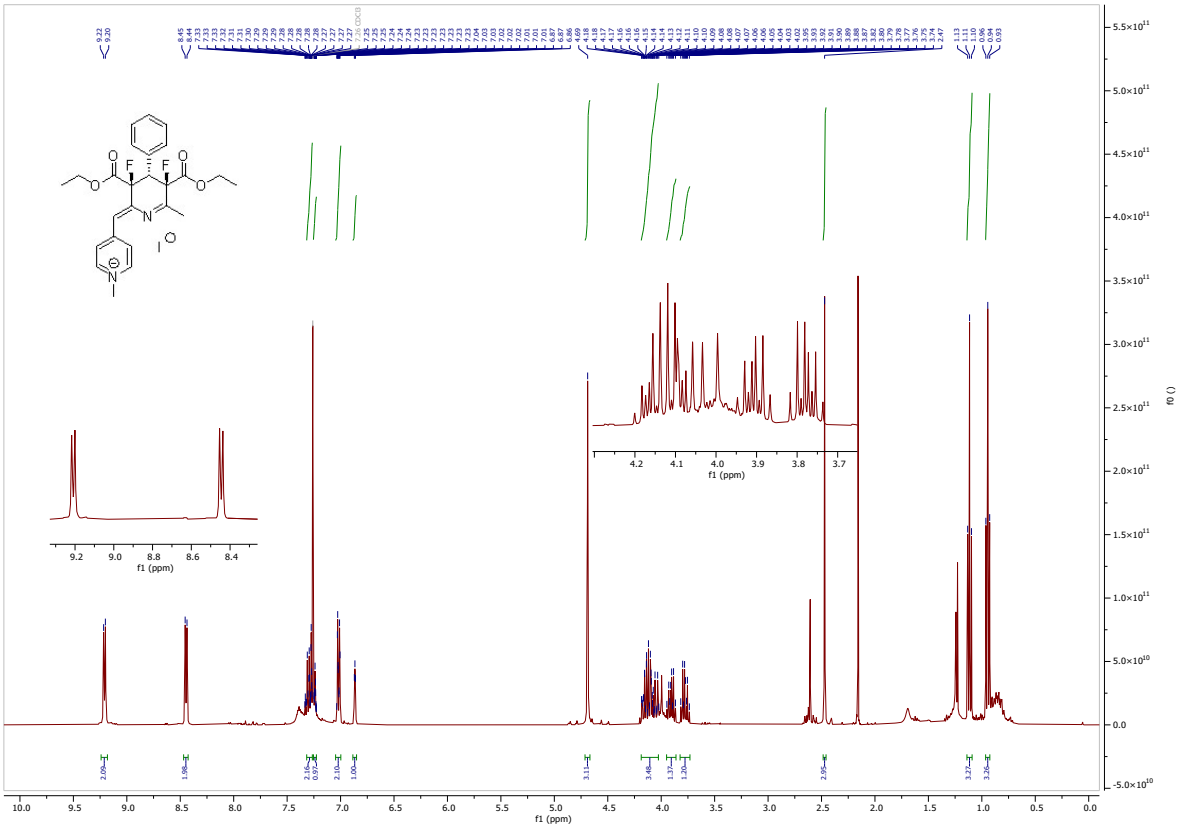


Figure S82. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**14a**).

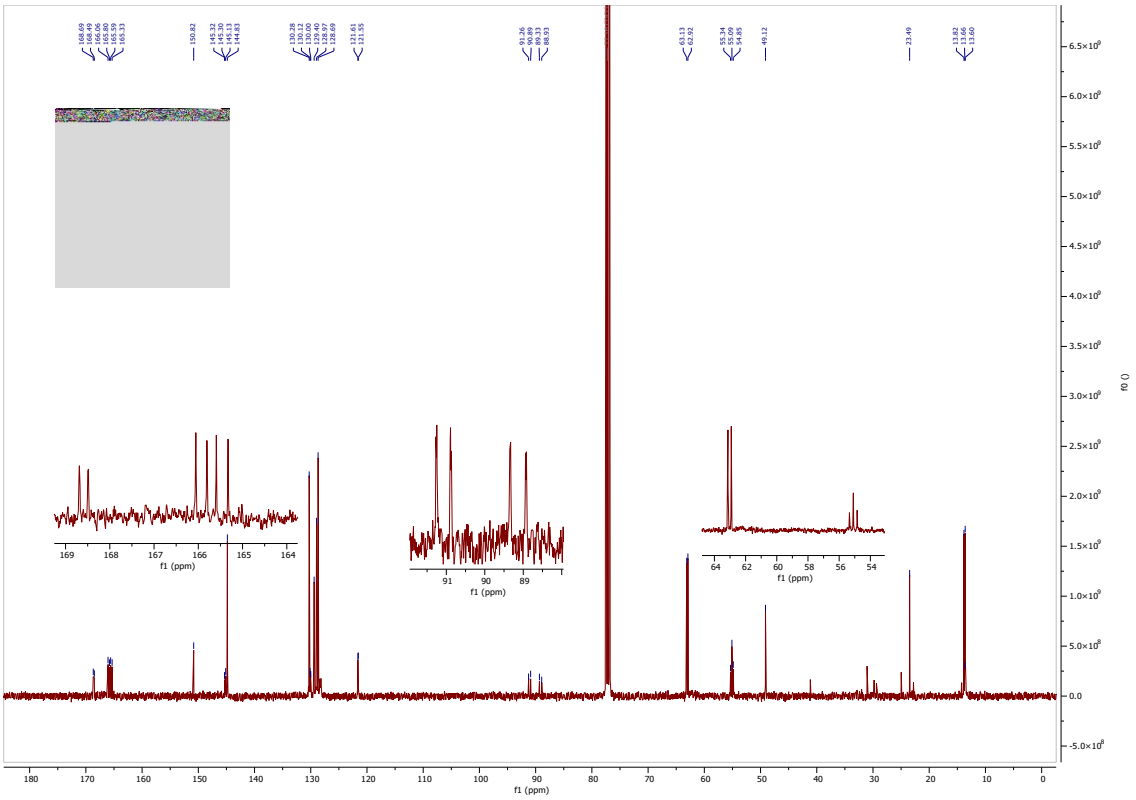


Figure S83. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**14a**).

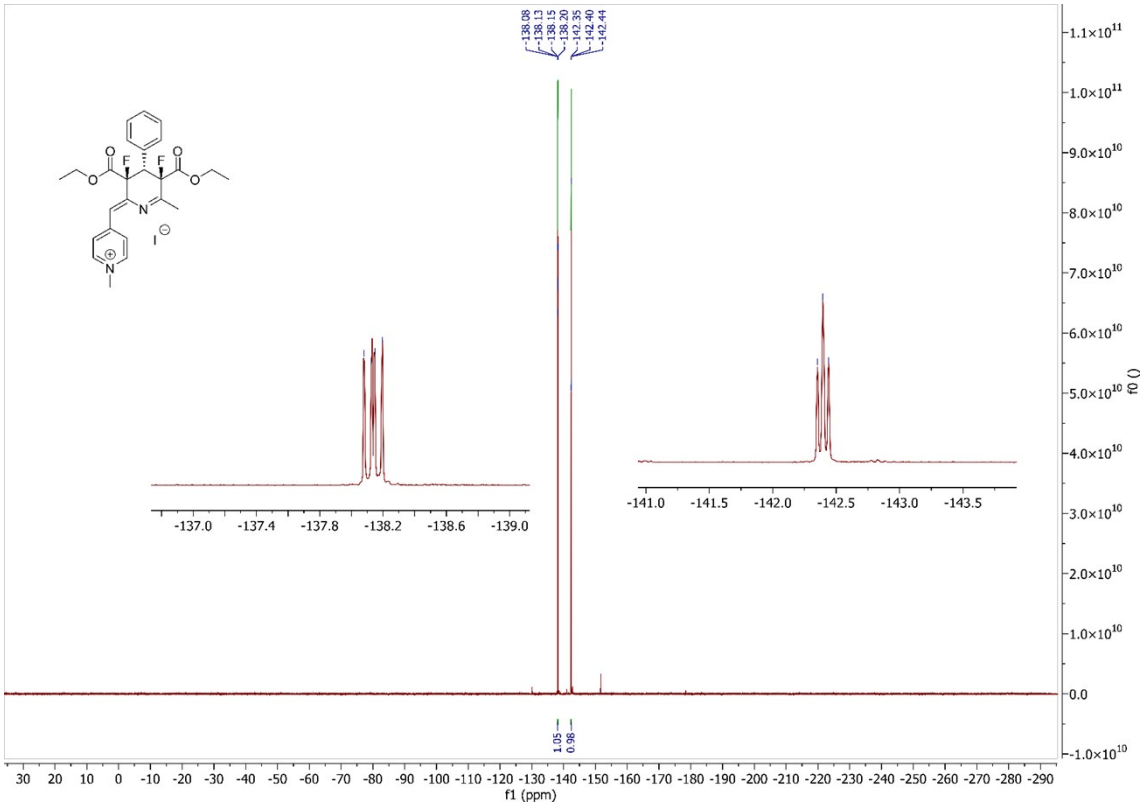


Figure S84. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**14a**).

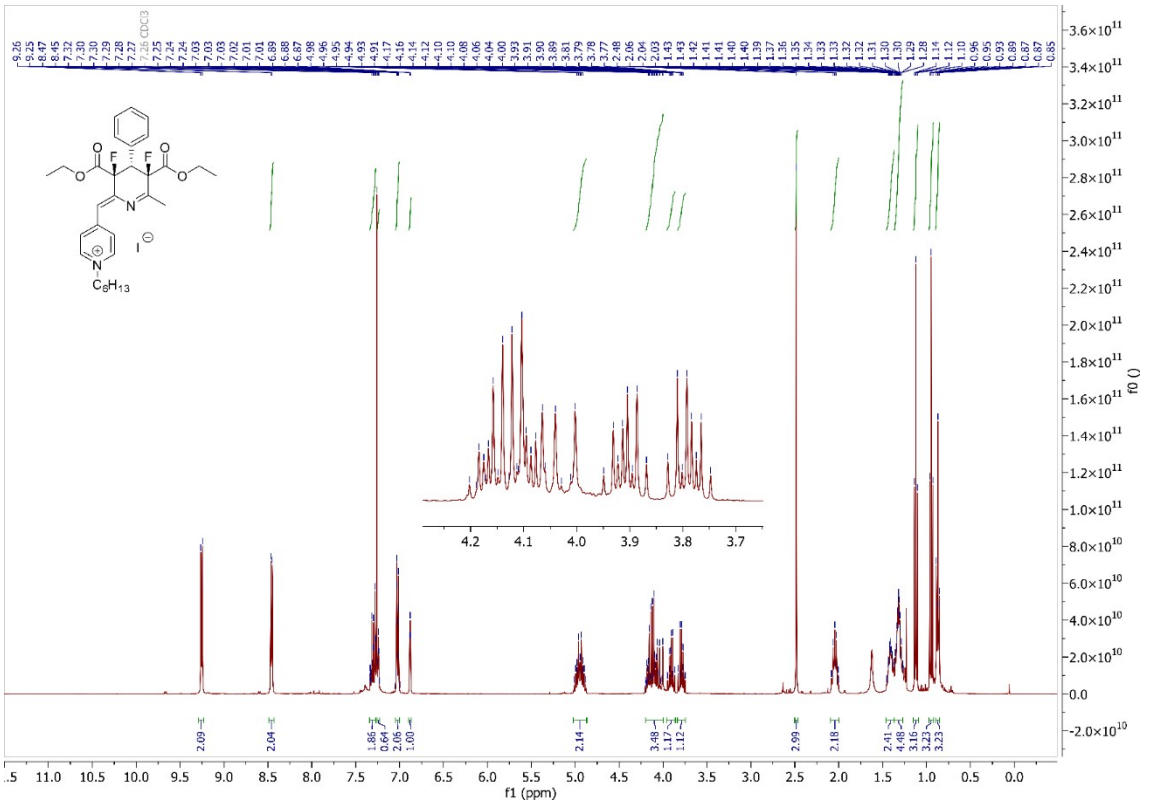


Figure S85. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**14b**).

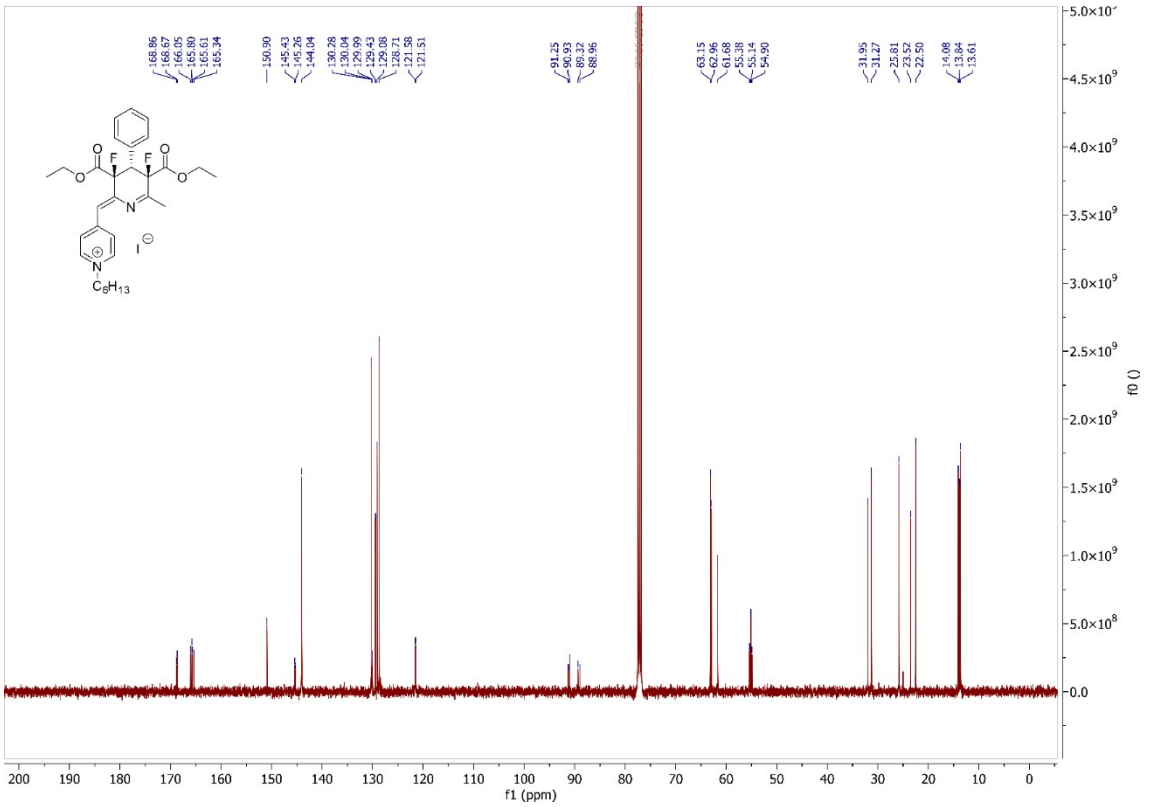


Figure S86. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**14b**).

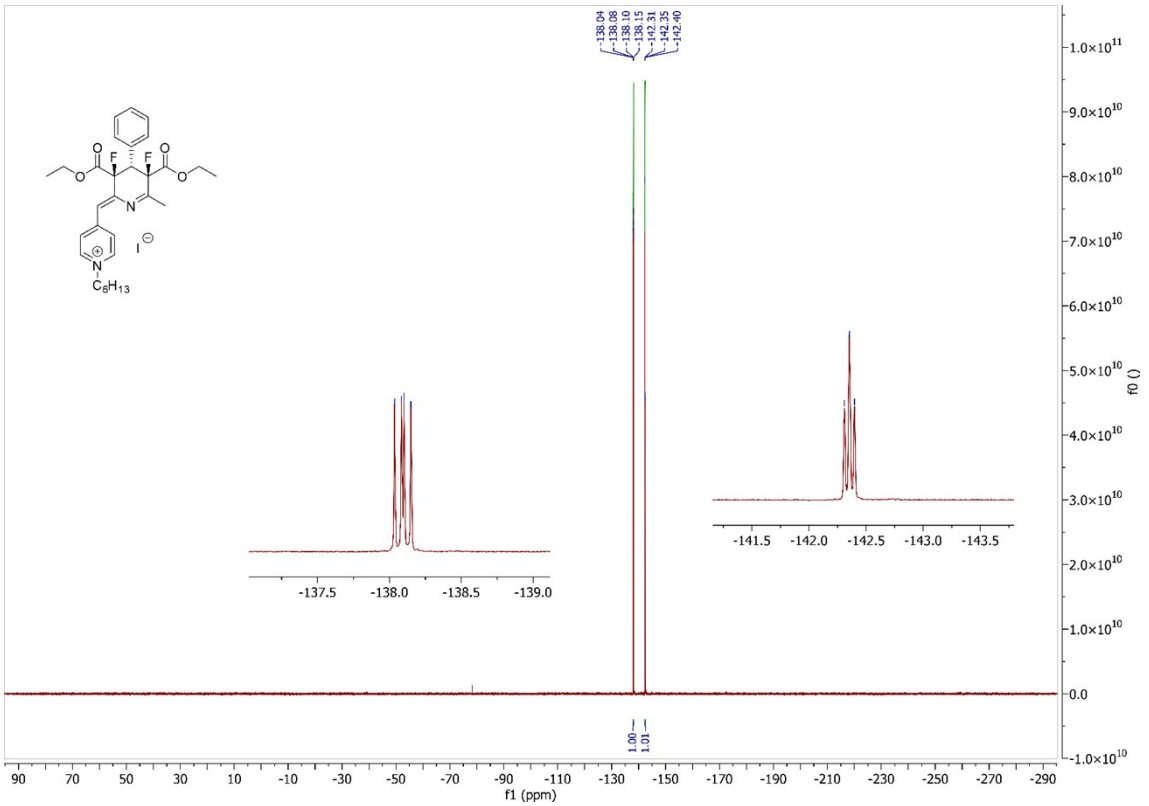


Figure S87. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**14b**).

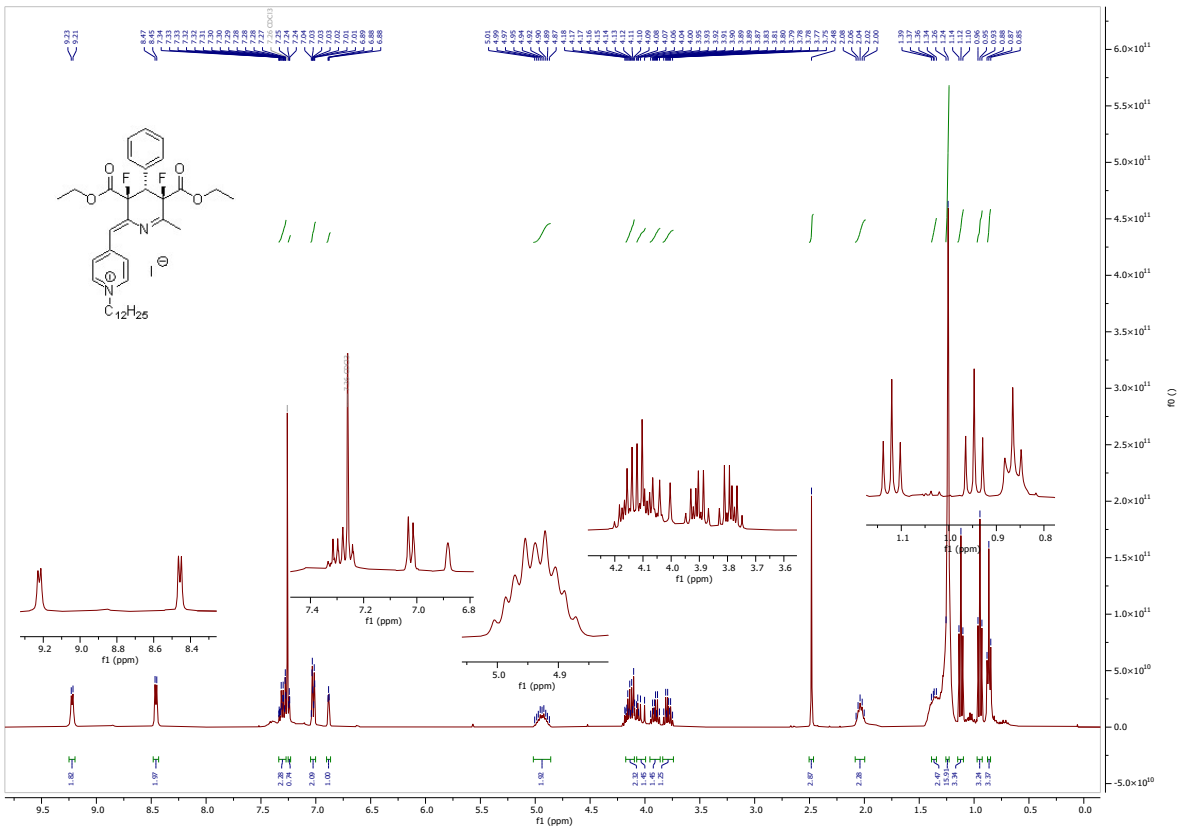


Figure S88. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**14c**).

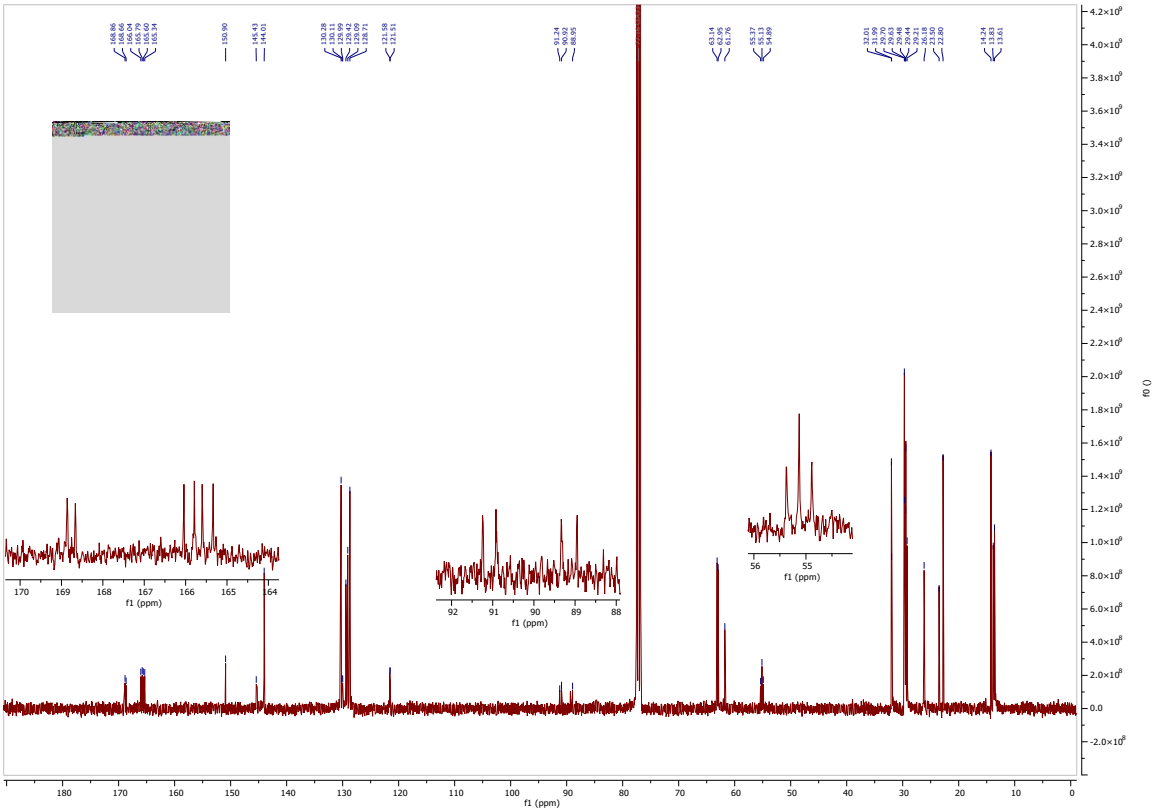


Figure S89. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**14c**).

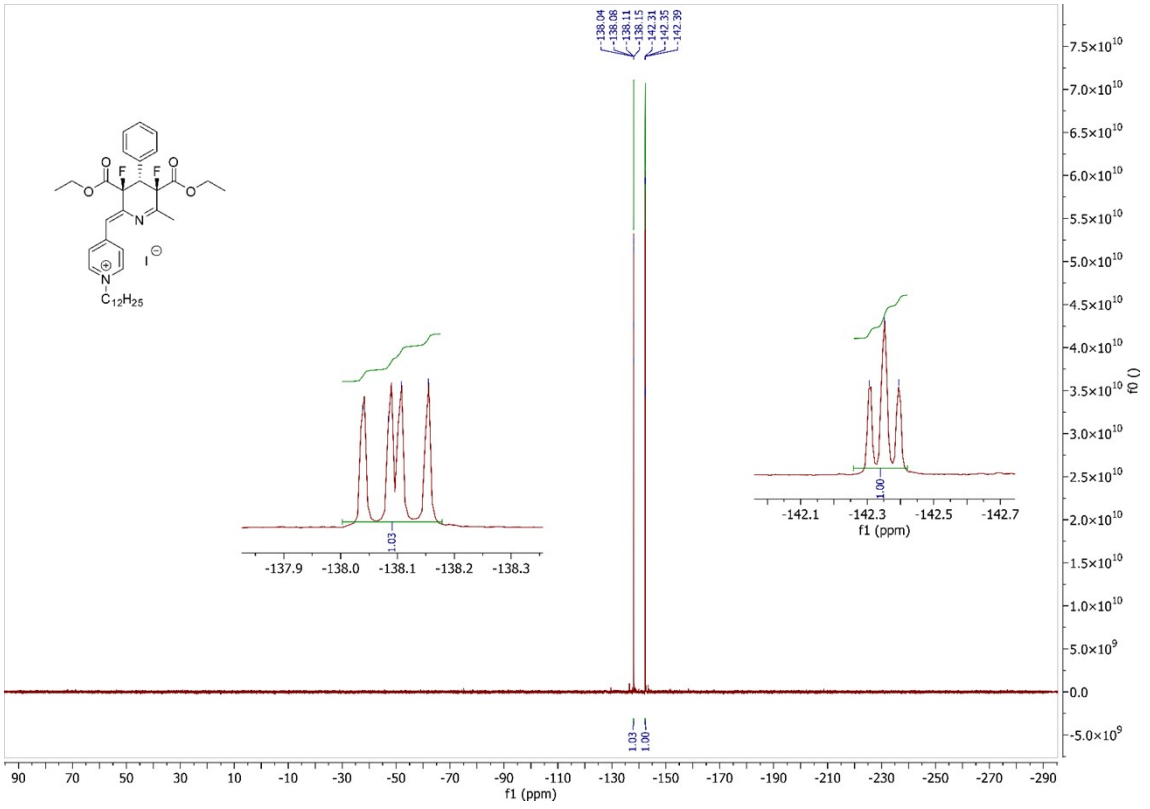


Figure S90. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(ethoxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**14c**).

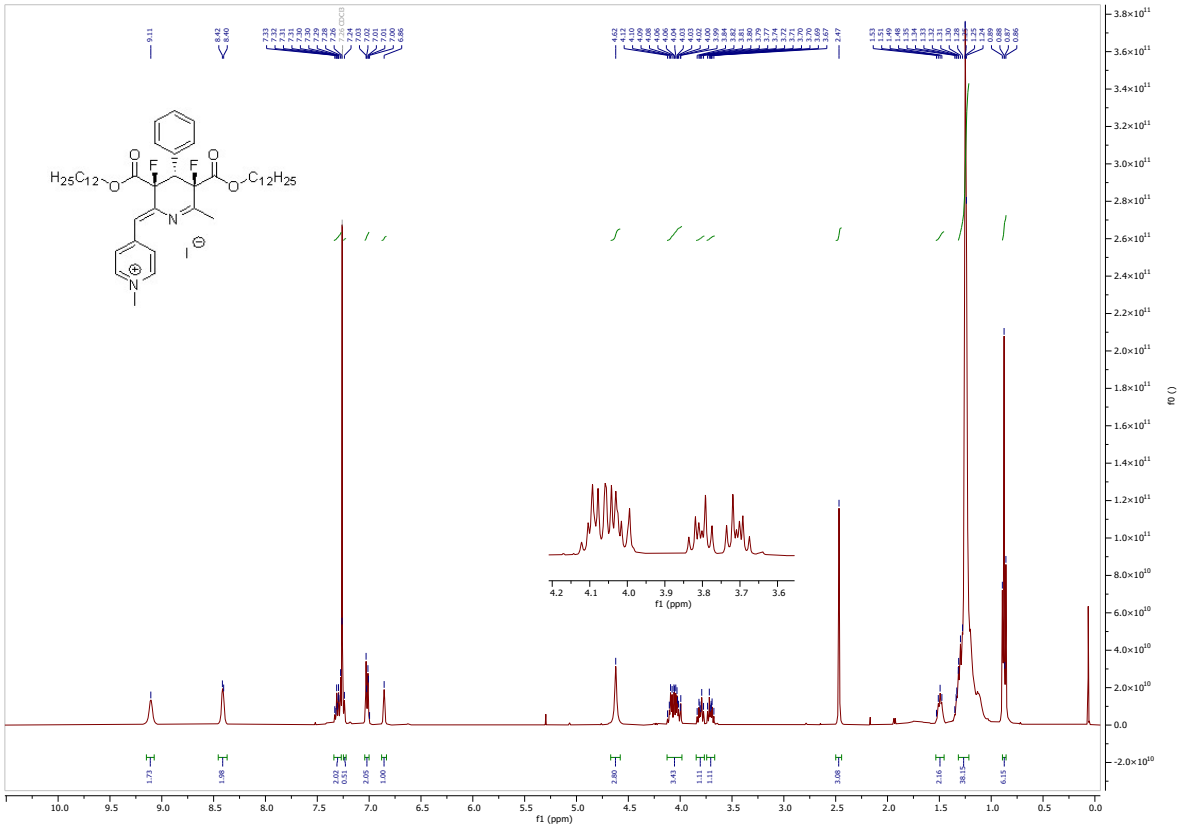


Figure S91. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**15a**).

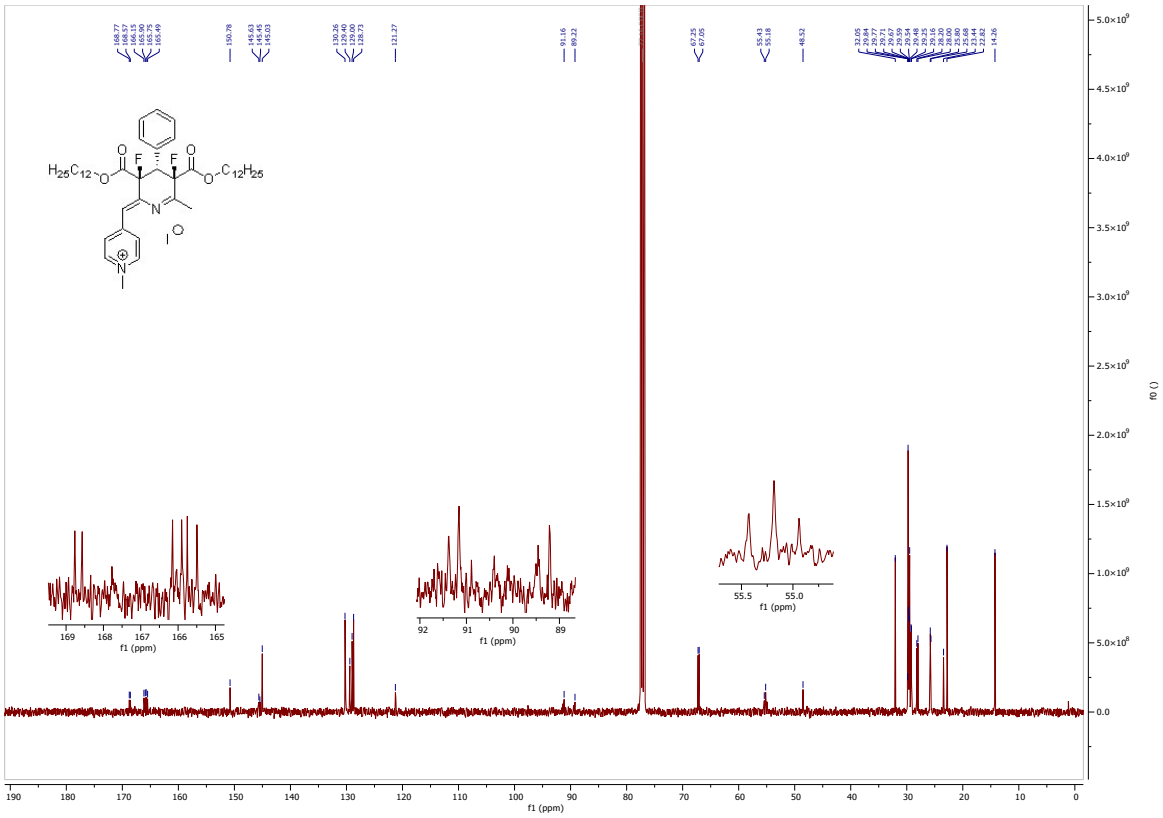


Figure S92. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**15a**).

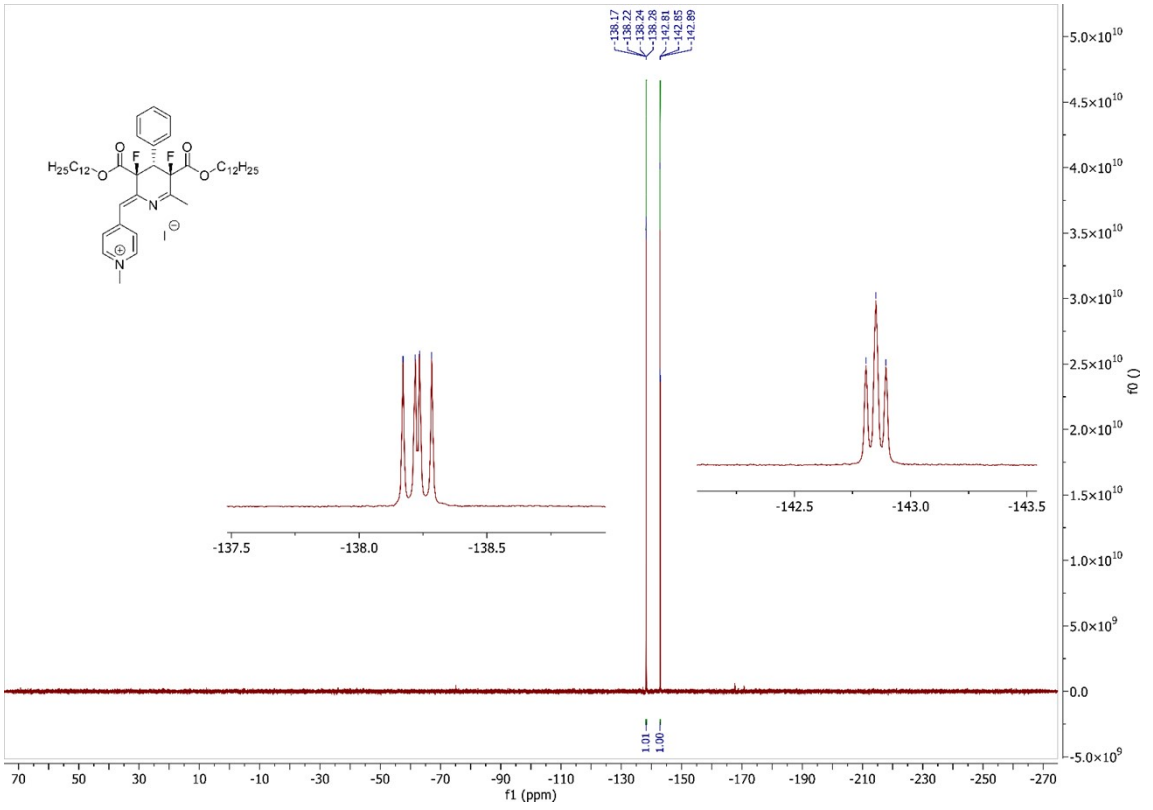


Figure S93. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-methylpyridin-1-ium iodide (**15a**).

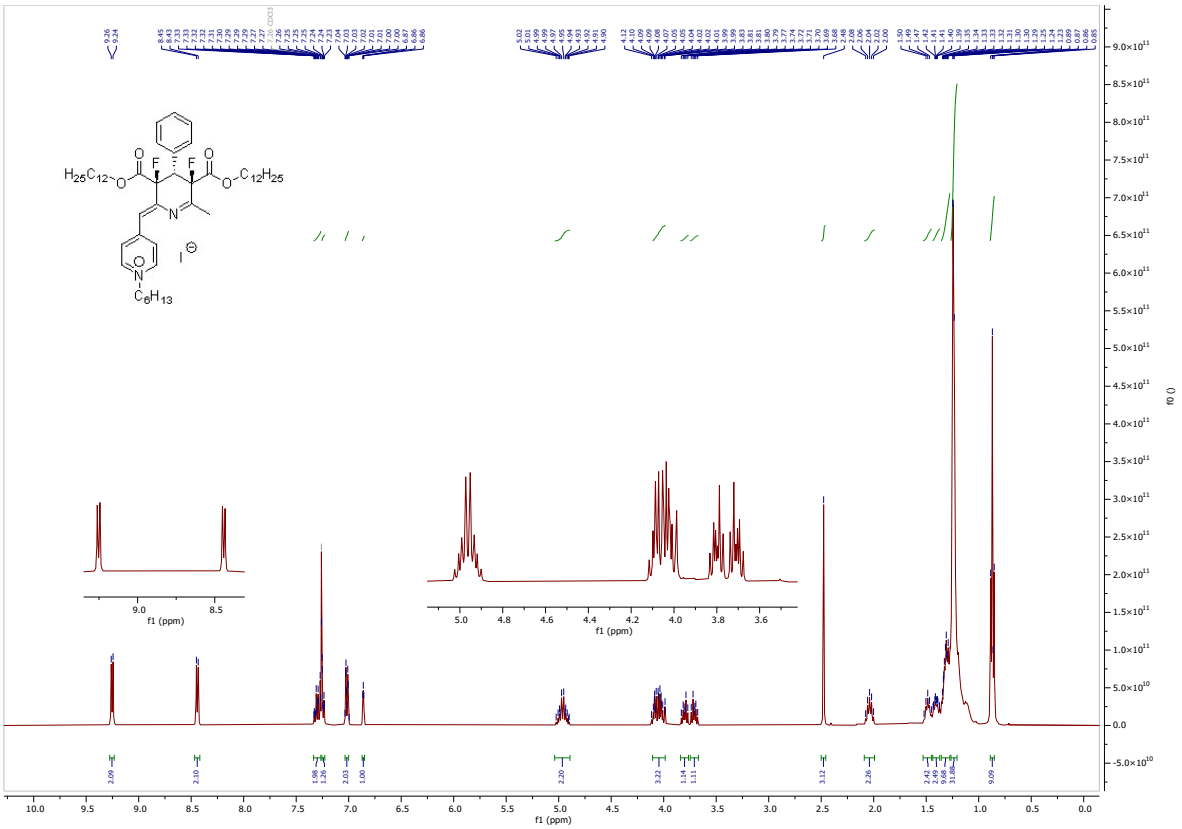


Figure S94. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**15b**).

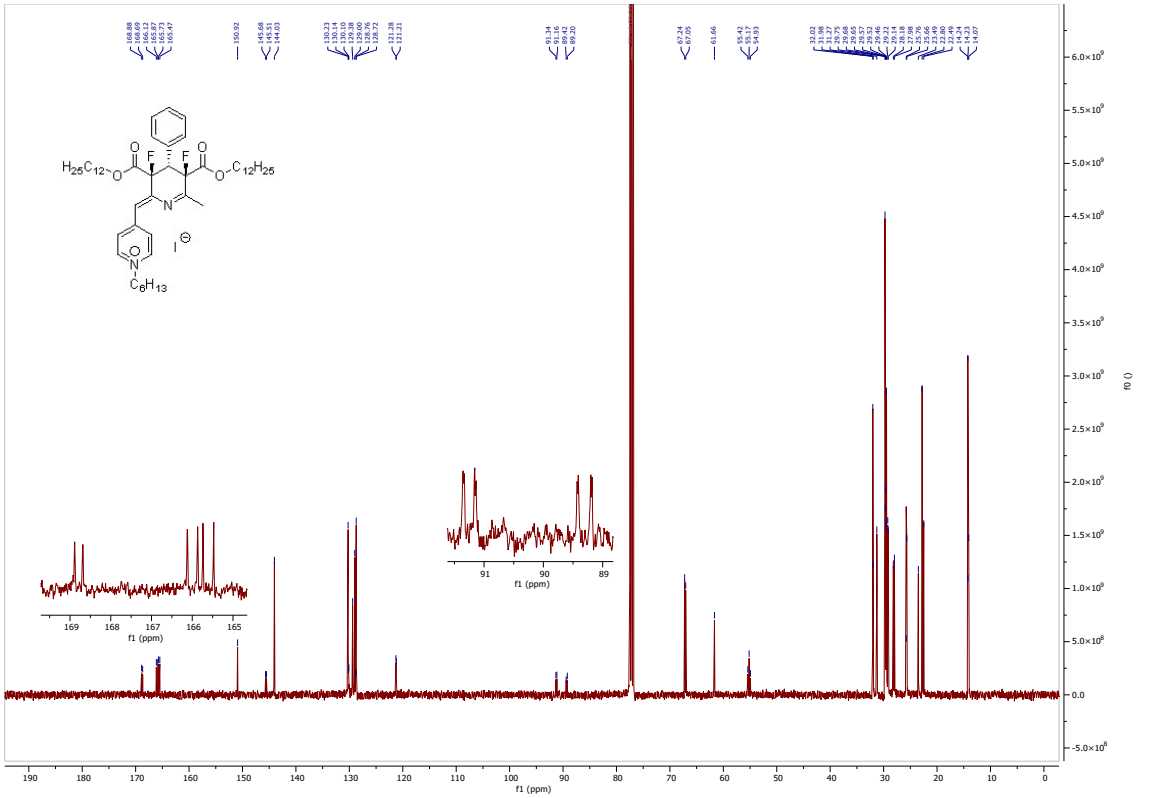


Figure S95. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**15b**).

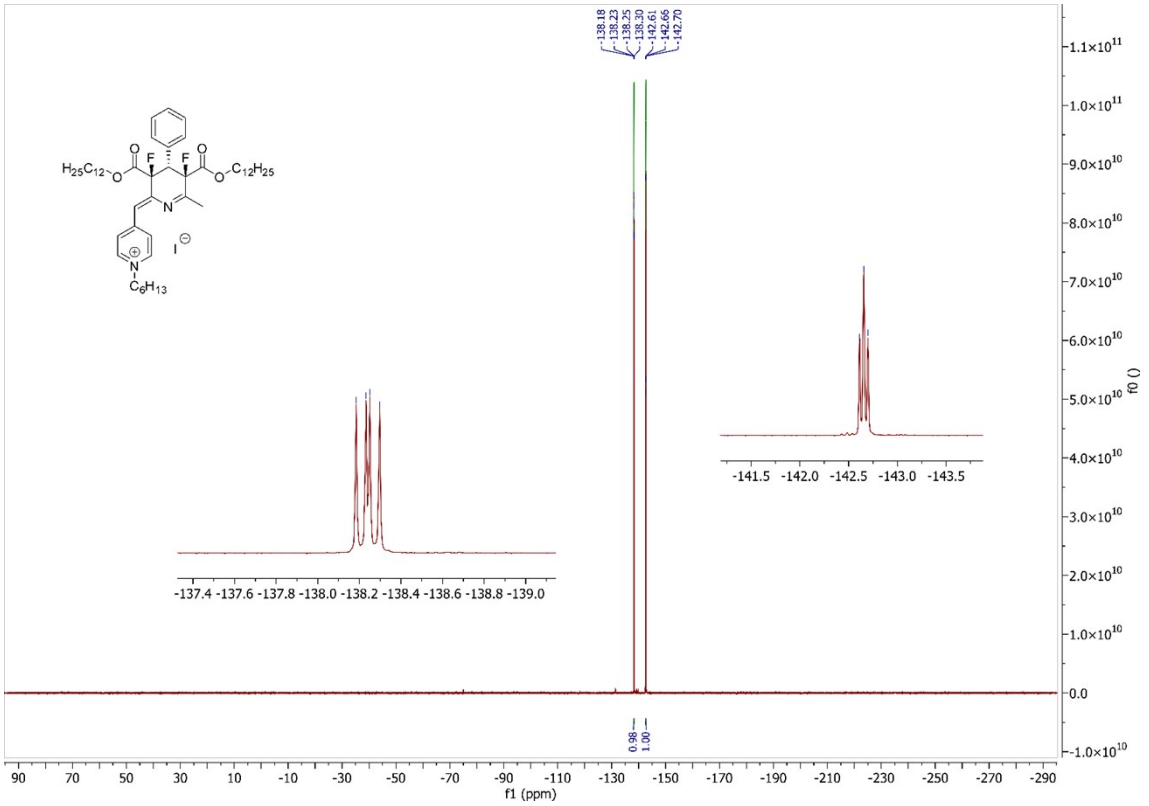


Figure S96. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-hexylpyridin-1-ium iodide (**15b**).

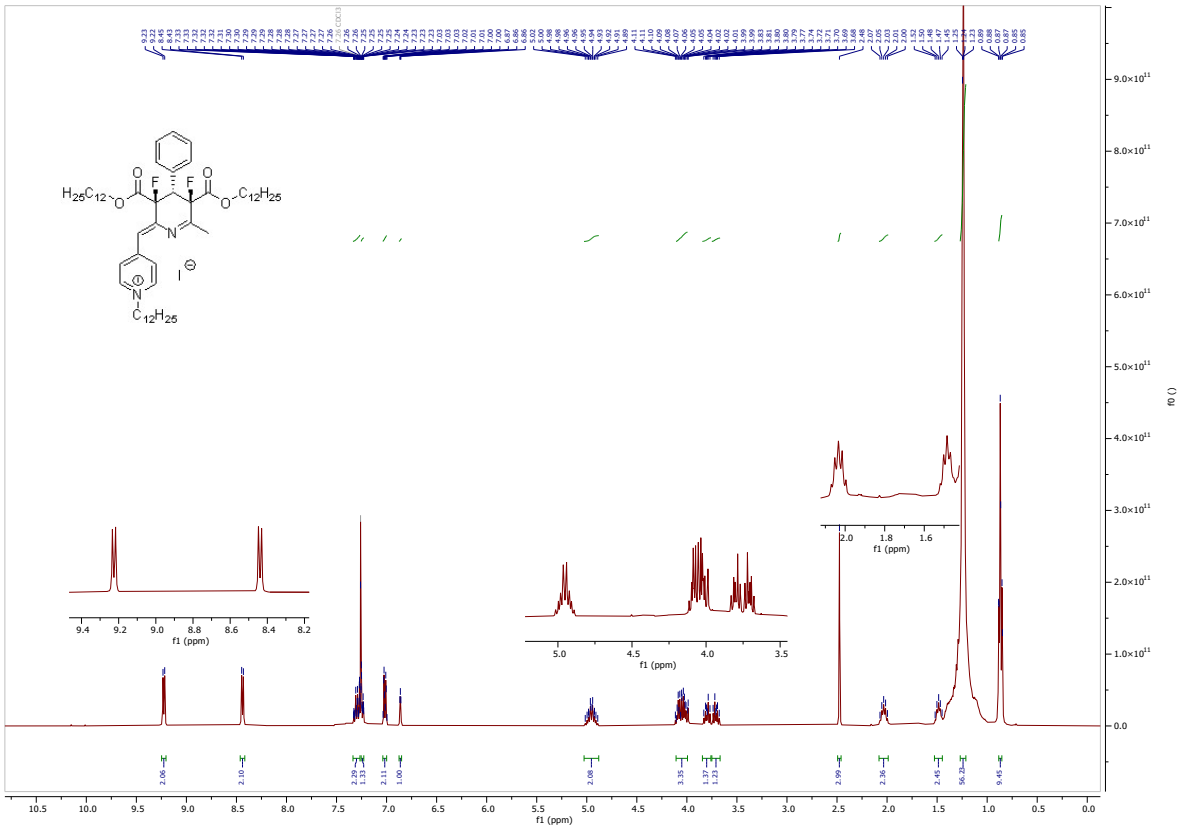


Figure S97. ^{1}H-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**15c**).

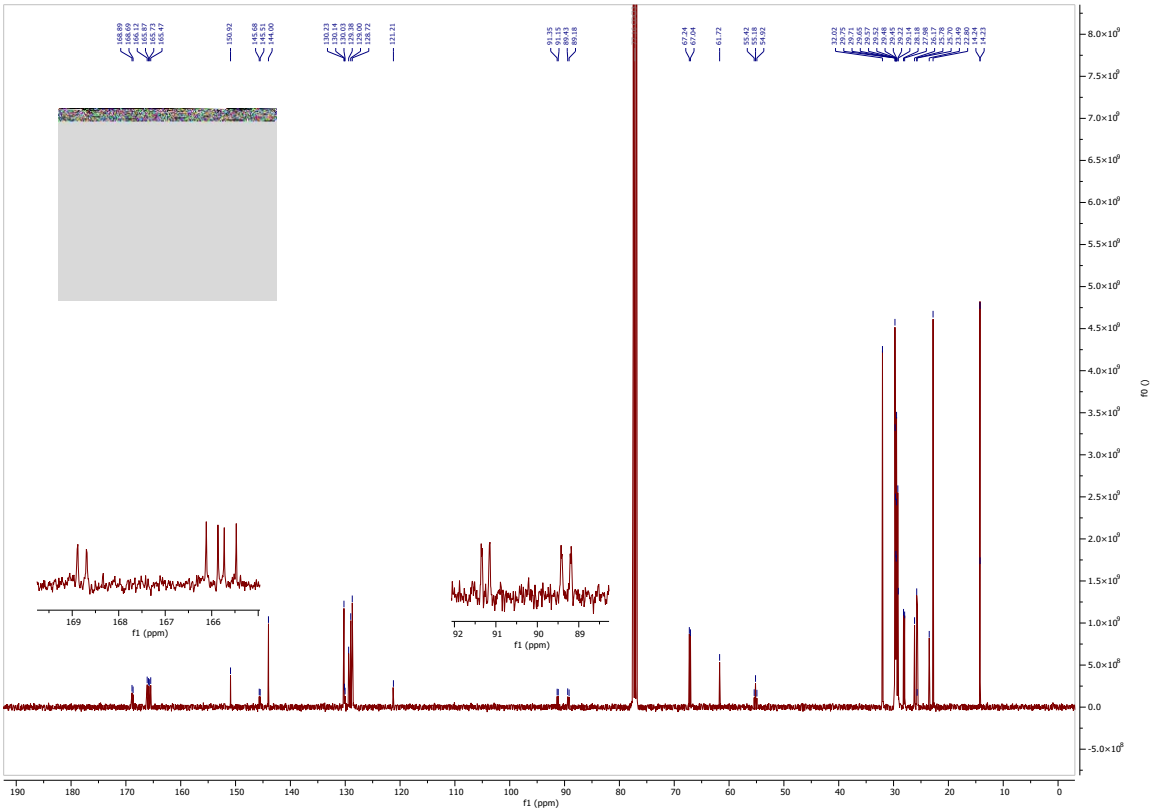


Figure S98. ^{13}C-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**15c**).

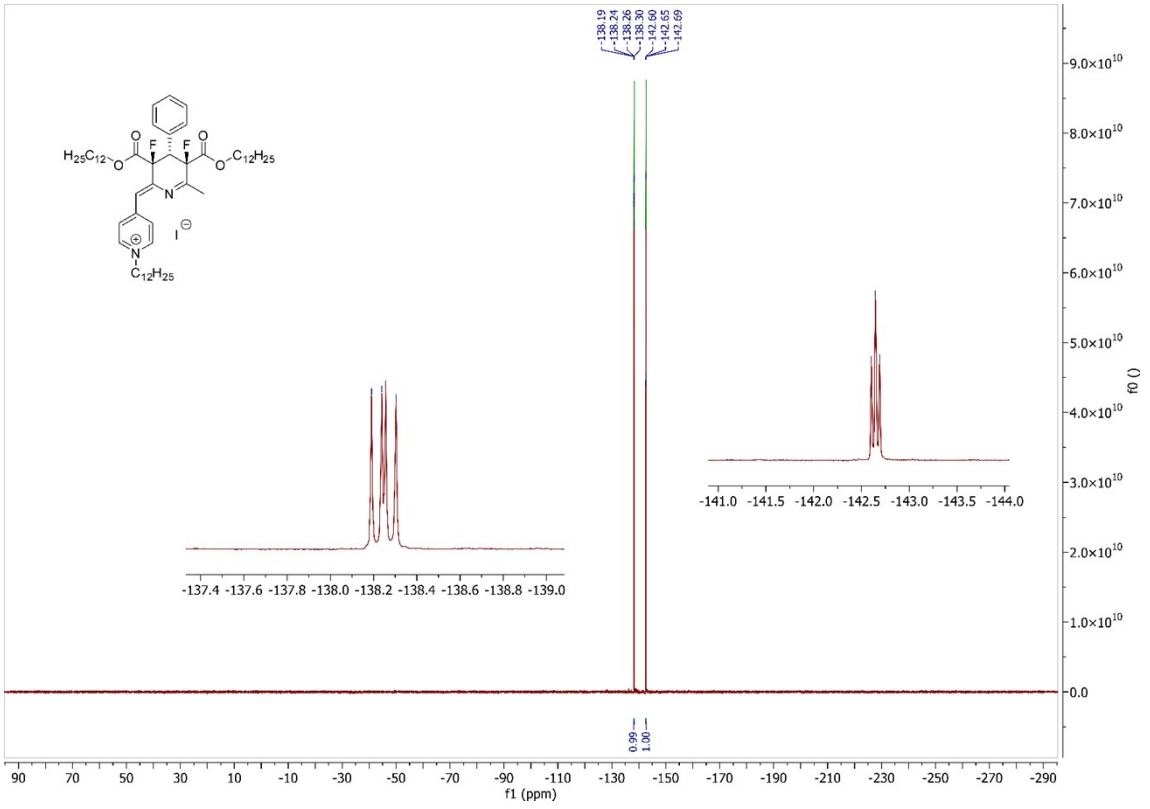


Figure S99. ^{19}F-NMR spectrum of 4-((Z)-((3,4,5)-3,5-bis(dodecyloxycarbonyl)-3,5-difluoro-6-methyl-4-phenyl-4,5-dihydropyridin-2(3H)-ylidene)methyl)-1-dodecylpyridin-1-ium iodide (**15c**).

1.8. Crystallization procedure, crystal data, data collection and structure refinement details

Breafly, compound **2d** or **13a** (4 mg) was dissolved in hexane (4 mL) under reflux in a glass vial. The vial was loosely capped with a septum and pierced by a needle to allow slow solvent evaporation under ambient conditions. After two weeks, colorless single crystals suitable for X-ray diffraction were obtained.

Table S4. *Experimental details for compound **2d**, CCDC Deposition Number: 2395307.*

Crystal data[3]	
Chemical formula	$C_{19}H_{21}F_2NO_4$
M_r	365.37
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	160
a, b, c (Å)	16.7661 (2), 6.89850 (9), 16.2957 (2)
β (°)	102.2959 (14)
V (Å^3)	1841.55 (4)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.89
Crystal size (mm)	0.3 × 0.22 × 0.14
Data collection	
Diffractometer	XtaLAB Synergy, Dualflex, HyPix
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.40.71a (Rigaku Oxford Diffraction, 2020) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.845, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	17724, 3734, 3578
R_{int}	0.022
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.631
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.035, 0.100, 1.06
No. of reflections	3734
No. of parameters	239
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.38, -0.18

Computer programs: *CrysAlis PRO* 1.171.42.93a (Rigaku OD, 2023), SHELXT 2014/4 (Sheldrick, 2014), *SHELXL2018*/3

(Sheldrick, 2018).

Table S5. *Experimental details for compound **13a**, CCDC Deposition Number: 2395308.*

Crystal data[3]	
Chemical formula	$C_{25}H_{25}F_2NO_4$
M_r	441.46
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	150
a, b, c (Å)	12.5465 (5), 8.4111 (4), 20.7394 (3)
β (°)	94.1132 (19)
V (Å^3)	2183.00 (14)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.85
Crystal size (mm)	0.24 × 0.16 × 0.10
Data collection	
Diffractometer	XtaLAB Synergy, Dualflex, HyPix
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.42.93a (Rigaku Oxford Diffraction, 2023) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.787, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	20862, 4331, 3903
R_{int}	0.031
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.630
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.033, 0.089, 1.00
No. of reflections	4331
No. of parameters	292
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.30, -0.19

Computer programs: *CrysAlis PRO* 1.171.42.93a (Rigaku OD, 2023), SHELXT 2014/4 (Sheldrick, 2014), *SHELXL2018*/3 (Sheldrick, 2018).

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