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New Organofluorine Building Blocks: Inhibition of the Malarial Aspartic Proteases Plasmepsin II and IV by Alicyclic *α,α*-Difluoroketone Hydrates

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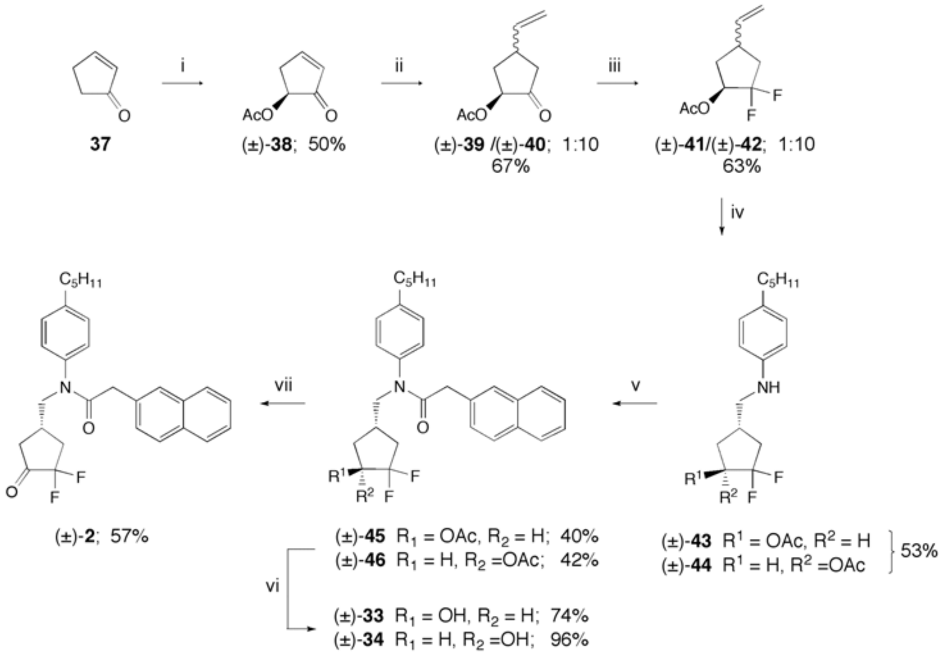
Contents

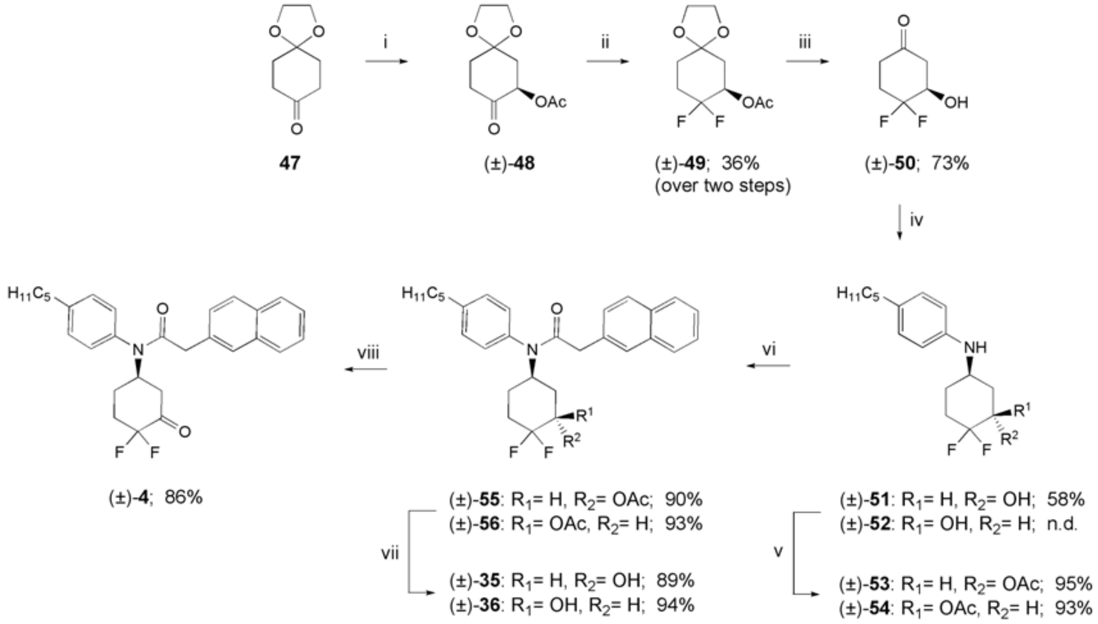
1. Synthesis of difluoroketones (±)-2, (±)-4 and piperidinium salts 5 and 6

Cyclopentenone (**37**) was oxidised with $Pb(OAc)_4$ to give (±)-**38**, which was alkylated to provide the diastereoisomeric pairs of enantiomers (±)-**39** and (±)-**40**. The obtained product mixture (±)-**39**/(±)-**40** decomposed rapidly at r.t. and, due to an epimerization in the reductive amination step later in the synthesis, the diastereoisomers were not separated. Chemoselective fluorination to the difluorinated acetates (±)-**41**/(±)-**42,** followed by oxidation to the corresponding aldehydes and reductive amination with 4-pentylaniline **(19)**, yielded amines (±)-**43** and (±)-**44**. Even a sequential series of column chromatographic runs did not lead to their successful separation. Therefore, the mixture (±)-**43**/(±)-**44** was coupled with 2-naphthylacetic acid chloride (**20**) to give the diastereoisomeric amides (±)-**45** and (±)-**46**, respectively, which were separated and their constitution and relative configuration assigned with the help of $^{1}H,^{1}H$-COSY and 1D-NOE spectra. Saponification to (±)-**33** and (±)-**34** and subsequent oxidation with *Dess-Martin* periodinane yielded ketone (±)-**2** (Scheme S1).



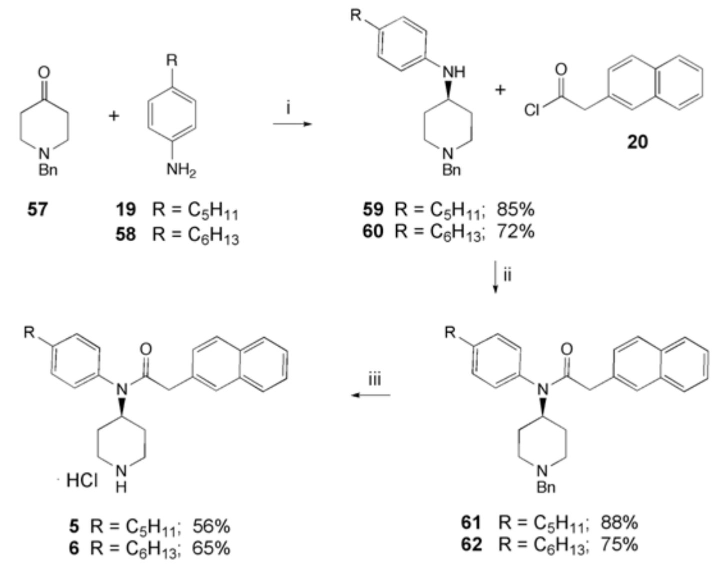
Scheme S1 (i) $Pb(OAc)_4$, benzene, reflux, 50 h; (ii) vinylmagnesium bromide, CuI, TMEDA, TMSCl, CH_2Cl_2, –78 °C, 1 h; (iii) DAST, CH_2Cl_2, reflux, 18 h; (iv) 1. OsO_4, $NaIO_4$, 1,4-dioxane, H_2O, r.t., 12 h. 2. $NaBH(OAc)_3$, 4-pentylaniline (**19**), 1,2-dichloroethane, r.t., 16 h; (v) 2-naphthylacetic acid chloride (**20**), DIPEA, CH_2Cl_2, r.t., 5 h; (vi) K_2CO_3, H_2O, MeOH, CH_2Cl_2, r.t., 3 h; (vii) *Dess-Martin* periodinane, CH_2Cl_2, 0° C, 7 h; 4 Å mol. sieves, CH_2Cl_2, 3 h.

For the synthesis of (±)-**4**, 1,4-dioxaspiro[4.5]decan-8-one (**47**) was oxidised with $Pb(OAc)_4$ to (±)-**48** and subsequently fluorinated to the difluorinated acetate (±)-**49**. The acetal protecting group was removed to give ketone (±)-**50** which was transformed into amines (±)-**51** and (±)-**52** by reductive amination with 4-pentylaniline (**19**). The hydroxy functionality of (±)-**51** and (±)-**52** had to be protected, yielding (±)-**53** and (±)-**54**, respectively. The constitution and relative configuration of the two compounds could be identified by ^1H, ^1H COSY and 1D-NOE spectra. Coupling of the sterically hindered amines (±)-**53** and (±)-**54** with 2-naphthylacetic acid chloride (**20**) to the amides (±)-**55** and (±)-**56**, respectively, had to be performed in a sealed tube. Saponification to (±)-**35** and (±)-**36** and subsequent oxidation with *Dess-Martin* periodinane afforded ketone (±)-**4** (Scheme S2).



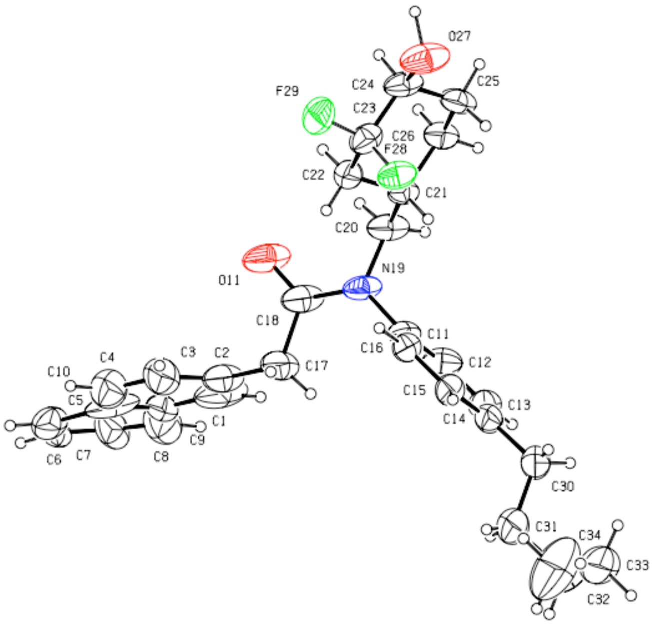
Scheme S2 (i) $Pb(OAc)_4$, cyclohexane, r.t., 24 h; (ii) DAST, CH_2Cl_2, r.t., 16 h; (iii) 10% HCl(aq), THF, r.t., 16 h; (iv) 4-pentylaniline (**19**), $NaBH(OAc)_4$, AcOH, CH_2Cl_2, r.t., 16 h; (v) Ac_2O, pyridine, r.t., 18 h; (vi) 2-naphthylacetic acid chloride (**20**), DIPEA, CH_2Cl_2, sealed tube, 50 °C, 16 h; (vii) K_2CO_3, H_2O, MeOH, CH_2Cl_2, r.t., 3 h; (viii) *Dess-Martin* periodinane, CH_2Cl_2, 0° C, 7 h, then 4 Å mol. sieves, CH_2Cl_2, 3 h.

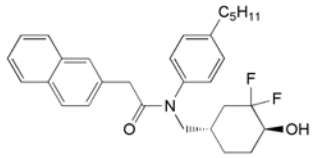
The synthesis of the piperidinium-based inhibitors **5** and **6** was carried out in three steps. *N*-Benzyl-4-piperidone (**57**) was transformed with 4-pentylaniline (**19**) or 4-hexylaniline (**58**) into amines **59** and **60**, respectively, which were subsequently coupled in a sealed tube with 2-naphthylacetic acid chloride (**20**) to give amides **61** and **62**, respectively. Deprotection using conditions developed by *Yang*[1] *et al.* yielded the piperidinium salts **5** and **6** (Scheme S3).



Scheme S3 (i) NaBH(OAc)$_3$, AcOH, 1,2-dichloroethane, r.t., 18 h; (ii) DIPEA, CH_2Cl_2, sealed tube, 50 °C, 16 h; (iii) 1. 1-chloroethyl chloroformate, CH_2Cl_2, 0 °C, 1 h; 2. MeOH, reflux, 3 h.

2. X-Ray crystal structure of (±)-11





(±)-**11**

Fig. S1 ORTEP plot of (±)-**11** showing the 1,4-trans geometry. Numbering is arbitrarily. Atomic displacement parameters obtained are drawn at the 50% probability level. The more populated (60%) position of the F atoms is shown. Selected torsional angles (°): F29-C23-C24-O27 = 67, F28-C23-C24-O27 = 49.

Crystal data at 223 K for $C_{30}H_{35}F_2NO_2$: M_r 479.61, monoclinic, space group $P2_1/n$, D_x = 1.220 Mg m^{-3}, Z = 4, a = 9.4492(4) Å, b = 16.4318(8) Å, c = 16.9333(7) Å, α = 90.00°, β = 96.750(3)°, γ = 90.00°, V = 2611.0(2) Å^3. Bruker–Nonius KappaCCD diffractometer, Mo$K\alpha$ radiation, λ = 0.71073, μ = 0.085 mm^{-1}. Crystal dimensions *ca.* 0.5 x 0.32 x 0.06 mm. The numbers of measured and independent reflections were 7607 and 4432, respectively. The structure was solved by direct methods (SIR-97).[2] The CF_2 group is disordered over the two α-positions to the COH moiety with occupancy 0.6:0.4. All non

H-atoms were refined anisotropically by full-matrix least-squares analysis, H-positions are based on stereochemical considerations and were included in the structure factor calculation (SHELXL-97).[3] No sign of twinning could be found, relatively high R-values due to the disorder. Final R(gt) = 0.1624, wR(gt) = 0.4312 for 334 parameters and 4432 reflections with $I > 2\sigma(I)$ and θ_{max} = 25.01°.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre: CCDC reference number 729040. For crystallographic data in CIF or other electronic format see xxx.

3. Experimental

General procedure J for the oxidation of an olefin to an aldehyde

The olefin (1.0 eq.) was dissolved in dioxane/H_2O 10:1 under Ar at 0° C, and OsO_4 (0.1 eq.) was added. The mixture was stirred at r.t. for 1 h, $NaIO_4$ (3.0 eq.) was added, and stirring was continued. The mixture was filtrated over Celite and the organic phase concentrated *in vacuo*. The resulting aldehyde was used without further purification.

General procedure K for the reductive amination of an aldehyde with an amine

The aldehyde (1.0 eq.) was dissolved in CH_2Cl_2 under Ar at r.t., and amine (1.0 eq.) and $NaBH(OAc)_3$ (1.2 eq.) were added. The mixture was stirred at r.t., then treated with a saturated aqueous NaCl solution. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by CC (SiO_2; EtOAc/pentane) afforded the product.

General Procedure L for the reductive amination of a ketone with an amine

The ketone (1.0 eq.) was dissolved in CH_2Cl_2 under Ar at r.t., and amine (1.0 eq.) was added. $NaBH(OAc)_3$ (1.4 eq.) and AcOH (1.0 eq.) were added to the mixture. After stirring at r.t., the solution was treated with saturated aqueous NaCl solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over

$MgSO_4$, filtrated and concentrated *in vacuo*. Purification by CC (SiO_2; EtOAc/pentane 1:4) afforded the product.

General procedure M for the acetalization of an alcohol

An alcohol (1.0 eq.) was dissolved in pyridine under Ar at r.t., and Ac_2O (2.0 eq.) was added. The solution was cooled to 0 °C, DMAP (0.2 eq.) was added and the mixture stirred at r.t. The mixture was treated with saturated aqueous NaCl solution and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by CC (SiO_2; EtOAc/pentane) afforded the product.

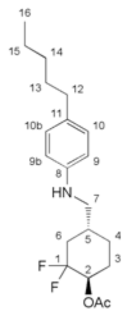
General procedure N for the coupling of acyl halides with sterically hindered amines

In a sealed tube, the acyl chloride (1.2 eq.) was dissolved in CH_2Cl_2 under Ar at r.t. and amine (1.0 eq.), dissolved in CH_2Cl_2, was added. DIPEA (1.2 eq.) was added, the tube was sealed and the mixture stirred at 50 °C. The mixture was then treated with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and the crude product purified by CC (SiO_2; EtOAc/pentane) affording the product.

General procedure O for the removal of an *N*-benzyl protecting group

The amide (1.0 eq.) was dissolved in CH_2Cl_2 under Ar at 0 °C and 1-chloroethyl chloroformate (1.3 eq.) was added. The mixture was stirred at 0 °C and the solvent evaporated *in vacuo*. The resulting solid was dissolved in MeOH, the solution stirred under reflux, and the solvent was removed *in vacuo*. The resulting solid was dissolved in EtOAc and washed with saturated aqueous Na_2CO_3 solution. The organic phase was dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by CC (SiO_2; $MeOH/CH_2Cl_2$) afforded the product.

(1*RS*,4*RS*)-2,2-Difluoro-4-{[(4-pentylphenyl)amino]methyl}cyclohexyl acetate ((±)-28)



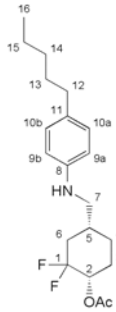
(±)-**28**

Using general procedure C, ketone (±)-**9** (300 mg, 1.65 mmol) and DAST (880 mm^3, 1.062 g, 6.58 mmol) in CH_2Cl_2 (8 cm^3) for 22 h, followed by CC purification (SiO_2; EtOAc/pentane 1:9), afforded olefin (±)-**12**.

Using general procedure J, reaction of olefin (±)-**12** (143 mg, 0.70 mmol), OsO_4 (0.025 M solution in *t*-BuOH, 838 mm^3, 712 mg, 0.07 mmol) and $NaIO_4$ (449 mg, 2.10 mmol) in dioxane/H_2O 10:1 (9.0 cm^3) for 12 h resulted, after concentration, in the crude aldehyde (±)-**16**.

Using general procedure K, reaction of aldehyde (±)-**16** (144 mg, 0.70 mmol), 4-pentylaniline (124 mm^3, 114 mg, 0.70 mmol) and $NaBH(OAc)_3$ (207 mg, 0.98 mmol) in CH_2Cl_2 (3.0 cm^3) for 3.5 h, followed by CC purification (SiO_2; EtOAc/pentane 1:8), afforded (±)-**28** (110 mg, 18%) as a white solid. mp. 79-81 °C. Found: C, 67.81; H, 8.18; N, 3.95. $C_{20}H_{29}F_2NO_2$ requires C, 67.96; H, 8.27; N, 3.96%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3400, 2951, 2924, 2852, 1729 (CO), 1615, 1520, 1474, 1372, 1325, 1235, 1179, 1125, 1058, 1033, 850, 821; δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.8, H_3–C(16)), 1.14–1.27 (1 H, m, H–C(4)), 1.26–1.39 (4 H, m, H_2–C(14), H_2–C(15)), 1.42–1.54 (2 H, m, H_2–C(13)), 1.52–1.63 (2 H, m, H–C(3), H–C(4)), 1.92–2.02 (2 H, m, H–C(3), H–C(6)), 2.02–2.13 (1 H, m, H–C(6)), 2.14 (3 H, s, O=C–CH_3), 2.30–2.42 (1 H, m, H–C(5)), 2.50 (2 H, t, *J* 7.7, H_2–C(12)), 3.05 (2 H, d, *J* 6.2, H_2–C(7)), 3.57 (1 H, br s, NH), 4.90–5.04 (1 H, m, H–C(2)), 6.53, 7.00 (4 H, AA'BB', *J* 8.7, H–C(9a,b), H–C(10a,b)); δ_C(75 MHz, $CDCl_3$) 14.2, 21.1, 22.7, 27.6 (d, *J* 6.1), 31.6, 31.7, 34.5, 34.7, 35.1, 37.9 (dd, *J* 20.4, 24.1), 49.1, 71.8 (t, *J* 20.1), 112.7, 120.4 (t, *J* 245.7), 129.1, 132.1, 145.7, 170.0; δ_F(282 MHz, $CDCl_3$) (–116.6) - (–115.6) (1 F, m), –103.53 (1 F, d, *J* 235.8); *m/z* (MALDI-HRMS) 353.2161 (100%, [*M*]$^+$. $C_{20}H_{29}F_2NO_2^+$ requires 353.2161).

(1*SR*,4*RS*)-2,2-Difluoro-4-{[(4-pentylphenyl)amino]methyl}-cyclohexyl acetate ((±)-29)



(±)–29

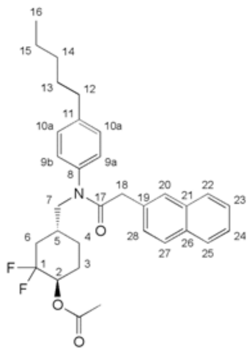
Using general procedure C, ketone (±)-**10** (1.000 g, 5.49 mmol) and DAST (1.450 cm^3, 1770 g, 10.98 mmol) in CH_2Cl_2 (30 cm^3) for 22 h, followed by CC purification (SiO_2; EtOAc/pentane 2:95), afforded olefin (±)-**13**.

Using general procedure J, reaction of olefin (±)-**13** (400 mg, 1.96 mmol), OsO_4 (0.025 M solution in *t*-BuOH, 2.343 cm^3, 1.992 g, 7.84 mmol) and $NaIO_4$ (1.257 g, 5.88 mmol) in dioxane/H_2O (10:1) (18 cm^3) for 12 h, followed by CC purification (SiO_2; EtOAc/pentane 1:9) afforded aldehyde (±)-**17** as a brown oil.

Using general procedure K, aldehyde (±)-**17**, 4-pentylaniline (348 mm^3, 320 mg, 1.96 mmol), and $NaBH(OAc)_3$ (581 mg, 2.74 mmol) in CH_2Cl_2 (3.0 cm^3) for 3.5 h, followed by CC purification (SiO_2; EtOAc/pentane 1:9), afforded (±)-**29** (233 mg, 21%) as a colourless oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3413, 2927, 2856, 1739 (CO), 1616, 1519, 1438, 1370, 1228, 1178, 1132, 1030, 820; δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.9, H_3–C(16)), 1.24–1.34 (5 H, m, H–C(4), H_2–C(14), H_2–C(15)), 1.52–1.62 (2 H, m, H_2–C(13)), 1.65–1.91 (1 H, m, H–C(3)), 1.69–1.82 (2 H, m, H–C(3), H–C(4)), 1.95–2.09 (2 H, m, H_2–C(6)), 2.12

(3 H, s, O=C–CH_3), 2.14–2.18 (1 H, m, H–C(5)), 2.50 (2 H, t, *J* 7.8, H_2–C(12)), 3.08 (2 H, d, *J* 7.6, H_2–C(7)), 3.58 (1 H, br s, NH), 5.14 (1 H, br s, H–C(2)), 6.55, 7.01 (4 H, AA'BB', *J* 8.4 Hz, H–C(9a,b), H–C(10a,b)); δ_C(75 MHz, $CDCl_3$) 14.2, 21.2, 22.8, 23.7, 27.1 (d, *J* 4.9), 31.7, 34.4, 34.5, 34.8 (d, *J* 22.6), 35.2, 49.6, 69.3 (m), 112.9, 121.1 (t, *J* 245.2), 129.4, 132.3, 146.1, 169.6; δ_F(282 MHz, $CDCl_3$) (–106.6) - (–105.5) (1 F, m), –103.4 (1 F, d, *J* 250.8); *m/z* (MALDI-HRMS) 354.2239 (100%, $[M+H]^+$. $C_{20}H_{30}F_2NO_2^+$ requires 354.2239).

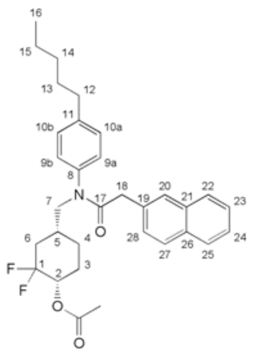
(1*RS*,4*RS*)-2,2-Difluoro-4-{[(2-naphthylacetyl)(4-pentylphenyl)amino]-methyl}cyclohexyl acetate ((±)-30)



(±)–30

Using general procedure E, reaction of secondary amine (±)-**28** (60 mg, 0.17 mmol), 2-naphthylacetic acid chloride (**20**) (38 mg, 0.19 mmol), and DIPEA (33 mm^3, 24 mg, 0.19 mmol) in CH_2Cl_2 (5.0 cm^3) for 24 h, followed by CC purification (SiO_2; EtOAc/pentane 1:5), afforded (±)-**30** (89 mg, 75%) as a colourless oil. Found: C, 73.43; H, 7.44; N, 2.68; F, 7.37. $C_{32}H_{37}F_2NO_3$ requires C, 73.68; H, 7.15; N, 2.69; F, 7.28%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3054, 2930, 2857, 1745 (CO), 1656 (CO), 1510, 1369, 1233, 1124, 1061, 952, 852; δ_H(300 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 6.7, H_3–C(16)), 1.21–1.31 (1 H, m, H–C(4)), 1.34–1.41 (4 H, m, H_2–C(14), H_2–C(15)), 1.42–1.64 (2 H, m, H_2–C(13)), 1.64–1.72 (1 H, m, H–C(3)), 1.65–1.78 (2 H, m, H–C(3), H–C(4)), 1.89–2.05 (2 H, m, H–C(5), H–C(6)), 2.11 (3 H, s, (O=C–CH_3)), 2.12–2.24 (1 H, m, H–C(6)), 2.65 (2 H, t, *J* 7.8, H_2–C(12)), 3.56–3.75 (2 H, m, H_2–C(7)), 3.60 (2 H, s, H_2–C(18)), 4.86–4.98 (1 H, m, H–C(2)), 6.96, 7.19 (4 H, AA'BB', *J* 8.4, H–C(9a,b), H–C(10a,b)), 7.20 (1 H, m, H–C(28)), 7.38 (1 H, s, H–C(20)), 7.40–7.46 (2 H, m, H–C(23), H–C(24)), 7.67–7.80 (3 H, m, H–C(22), H–C(25), H–C(27)); δ_C(75 MHz, $CDCl_3$) 14.2, 21.0, 22.7, 27.3 (m), 31.2, 31.6, 33.3 (d, *J* = 8.5), 35.6, 37.6 (t, *J* 22.3), 41.7, 53.6, 71.7 (t, *J* 20.2), 76.6, 120.3 (t, *J* 246.0), 125.5, 125.8, 127.2, 127.5, 127.8, 128.1, 129.6, 132.2, 132.7, 133.3, 139.7, 143.3, 169.9, 171.3; δ_F(282 MHz, $CDCl_3$) –116.6 (1 F, dt, *J* 21.4, 238.0), –103.80 (1 F, d, *J* 238.0); *m/z* (MALDI-HRMS) 522.2797 (100%, $[M+H]^+$. $C_{32}H_{38}F_2NO_3^+$ requires 522.2814), 544.2545 (12, $[M+Na]^+$. $C_{32}H_{37}F_2NO_3Na^+$ requires 544.2634).

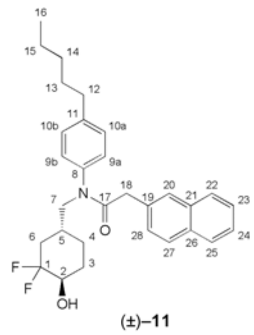
(1*SR*,4*RS*)-2,2-Difluoro-4-{[(2-naphthylacetyl)(4-pentylphenyl)amino]-methyl}cyclohexyl acetate ((±)-31)



(±)–31

Using general procedure E, reaction of secondary amine (±)-**29** (205 mg, 0.58 mmol), 2-naphthylacetic acid chloride (**20**) (178 mg, 0.87 mmol) and DIPEA (50 mm^3, 37 mg, 0.29 mmol) in CH_2Cl_2 (7.0 cm^3) for 24 h, followed by CC purification (SiO_2; EtOAc/pentane 1:5), afforded (±)-**31** (239 mg, 79%) as a colourless oil. Found: C, 73.91; H, 7.40; N, 2.66. $C_{32}H_{37}F_2NO_3$ requires C, 73.68; H, 7.15; N, 2.69%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3054, 2929, 2857, 1755 (CO), 1740, 1656 (CO), 1510, 1386, 1370, 1230, 1124, 1035, 973, 853; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.8, H_3–C(16)), 1.33–1.53 (5 H, m, H–C(4), H_2–C(14), H_2–C(15)), 1.55–1.59 (1 H, m, H–C(3)), 1.61–1.71 (4 H, m, H–C(3), H–C(4), H_2–C(13)), 1.75–1.91 (1 H, m, H–C(6)), 1.86–2.03 (2 H, m, H–C(5), H–C(6)), 2.05 (3 H, s, (O=C–CH_3)), 2.65 (2 H, t, *J* 7.8, H_2–C(12)), 3.60 (2 H, s, H_2–C(18)), 3.64–3.76 (2 H, m, H_2–C(7)), 5.07 (1 H, s, H–C(2)), 6.96, 7.19 (4 H, AA’BB’, *J* 8.2, H–C(9a,b), H–C(10a,b)), 7.17–7.20 (1 H, m, H–C(28)), 7.38–7.46 (3 H, m, H–C(20), H–C(23), H–C(24)), 7.67–7.80 (3 H, m, H–C(22), H–C(25), H–C(27)); δ_C(75 MHz, $CDCl_3$) 14.0, 20.9, 22.7 (d, *J* 36.0), 26.8 (d, *J* 4.9), 29.6, 31.0, 31.4, 32.7 (d, *J* 8.5), 33.9 (t, *J* 22.6), 35.4, 41.5, 53.6, 68.7 (dd, *J* 22.3, 38.8), 120.7 (t, *J* 245.4), 125.4, 125.8, 127.2, 127.5, 127.5, 127.8, 128.1, 129.3, 129.6, 132.2, 132.7, 133.3, 139.6, 143.3, 169.4, 171.4; δ_F(282 MHz, $CDCl_3$) –105.7 (1 F, dd, *J* 30.4, 250.2), –102.6 (1 F, d, *J* 248.6); *m/z* (MALDI-HRMS) 522.2811 (100%, [*M*+H]$^+$. $C_{32}H_{38}F_2NO_3^+$ requires 522.2814), 544.2645 (38, [*M*+Na]$^+$. $C_{32}H_{37}F_2NO_3Na^+$ requires 544.2634), 560.2388 (18, [*M*+K]$^+$. $C_{32}H_{37}F_2NO_3K^+$ requires 560.2373).

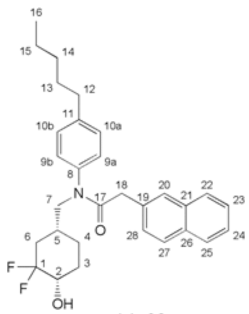
N-{[(1RS,4RS)-3,3-Difluoro-4-hydroxycyclohexyl]methyl}-2-(2-naphthyl)-N-(4-pentylphenyl)acetamide ((±)-11)



(±)–11

Using general procedure G, reaction of acetate (±)-**30** (169 mg, 0.32 mmol) and aqueous K_2CO_3/MeOH (4.0 cm^3) solution in CH_2Cl_2 (1.0 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**11** (86 mg, 55%) as a colourless wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3423, 3054, 2927, 2856, 2359, 1734, 1652 (CO), 1509, 1399, 1304, 1273, 1245, 1070, 1036, 853; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.8, H_3–C(16)), 1.34–1.39 (4 H, m, H_2–C(14), H_2–C(15)), 1.36–1.43 (2 H, m, H_2–(4)), 1.56–1.68 (3 H, m, H–C(3), H_2–C(13)), 1.80–1.97 (2 H, m, H_2–C(6)), 1.85–1.94 (2 H, m, H–C(3), OH), 2.13 (1 H, s, H–C(5)), 2.64 (2 H, t, *J* 7.8, H_2–C(12)), 3.53–3.58 (1 H, m, H–C(7)), 3.60 (2 H, s, H_2–C(18)), 3.77 (1 H, dd, *J* 7.3, 13.5, H–C(7)), 3.86 (1 H, s, H–C(2)), 6.96, 7.18 (4 H, AA'BB', *J* 8.3, H–C(9a,b), H–C(10a,b)), 7.17–7.22 (1 H, m, H–C(28)), 7.38 (1 H, s, H–C(20)), 7.40–7.46 (2 H, m, H–C(23), H–C(24)), 7.67–7.80 (3 H, m, H–C(22), H–C(25), H–C(27)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.6, 22.7, 28.5, 31.2, 31.6, 32.9, 33.3 (d, *J* 9.2), 35.6, 41.7, 54.1, 68.0, 119.2 (t, *J* 285.3), 125.4, 125.8, 126.2, 127.2, 127.5, 127.8, 128.1, 129.5, 132.2, 132.8, 133.3, 139.8, 143.1, 171.2 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) (–107.2) - (–106.2) (1 F, m), –103.03 (1 F, d, *J* 245.4); *m/z* (MALDI-HRMS) 480.2707 (100%, $[M+H]^+$. $C_{30}H_{36}F_2NO_2^+$ requires 480.2709), 502.2540 (16, $[M+Na]^+$. $C_{30}H_{35}F_2NO_2Na^+$ requires 502.2528), 518.2282 (5, $[M+K]^+$. $C_{30}H_{35}F_2NO_2K^+$ requires 518.2267).

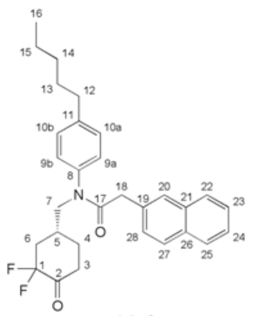
N-{[(1*RS*,4*SR*)-3,3-Difluoro-4-hydroxycyclohexyl]methyl}-2-(2-naphthyl)-*N*-(4-pentylphenyl)acetamide ((±)-32)



(±)–32

Using general procedure G, reaction of acetate (±)-**31** (75 mg, 0.14 mmol) and aqueous K_2CO_3/MeOH (2.0 cm^3) solution in CH_2Cl_2 (0.5 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**32** (73 mg, quant.) as a colourless wax. Found: C, 74.92; H, 7.52; N, 2.93; F, 7.88. $C_{30}H_{35}F_2NO_2$ requires C, 75.13; H, 7.36; N, 2.92; F, 7.92%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3411, 3053, 2927, 2856, 2361, 1648 (CO), 1510, 1446, 1307, 1173, 1099, 979, 849, 742; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 6.9, H_3–C(16)), 1.13–1.29 (1 H, m, H–C(4)), 1.34–1.40 (4 H, m, H_2–C(14), H_2–C(15)), 1.37–1.56 (2 H, m, H–C(3), H–C(4)), 1.60–1.72 (3 H, m, H–C(3), H_2–C(13)), 1.83–1.89 (1 H, m, H–C(6)), 1.97–2.05 (1 H, m, H–C(6)), 2.17–2.20 (1 H, m, H–C(5)), 2.26 (1 H, br s, OH), 2.65 (2 H, t, *J* 7.8, H_2–C(12)), 3.55–3.74 (3 H, m, H–C(2), H_2–C(7)), 3.59 (2 H, s, H_2–C(18)), 6.96, 7.19 (4 H, AA'BB', *J* 8.2, H–C(9a,b), H–C(10a,b)), 7.19 (1 H, d, *J* 8.1, H–C(28)), 7.38 (1 H, s, H–C(20)), 7.40–7.46 (2 H, m, H–C(23), H–C(24)), 7.67–7.80 (3 H, m, H–C(22), H–C(25), H–C(27)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 27.2, 30.0 (d, *J* 6.7), 31.2, 31.6, 33.4 (d, *J* 8.6), 35.6, 37.0 (t, *J* 22.9), 41.6, 53.6, 71.5 (t, *J* 21.7), 121.8 (t, *J* 243.8), 125.5, 125.8, 127.2, 127.5, 127.6, 127.8, 128.1, 129.6, 132.2, 132.7, 133.3, 139.6, 143.3, 171.3 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) (–120.8) - (–120.0) (1 F, m), –104.71 (1 F, d, *J* 233.7); *m/z* (MALDI-HRMS) 480.2706 (100%, $[M+H]^+$. $C_{30}H_{36}F_2NO_2^+$ requires 480.2709), 502.2530 (33, $[M+Na]^+$. $C_{30}H_{35}F_2NO_2Na^+$ requires 502.2528), 518.2272 (12, $[M+K]^+$. $C_{30}H_{35}F_2NO_2K^+$ requires 518.2267).

***N*-{[(1*RS*)-3,3-Difluoro-4-oxocyclohexyl]methyl}-2-(2-naphthyl)-*N*-(4-pentyl-phenyl)acetamide ((±)-3)**

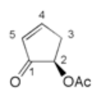


(±)–3

Using general procedure H, reaction of alcohol (±)-**32** (31 mg, 0.07 mmol) and 15% *Dess-Martin* periodinane solution in CH_2Cl_2 (201 mm^3, 274 mg, 0.13 mmol) in CH_2Cl_2

(0.5 cm^3) for 7 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**3** (21 mg, 68%) as a colourless wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3393, 2924, 2854, 1755 (CO), 1654 (CO), 1510, 1457, 1350, 1304, 1108, 1037, 850; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 6.7, H_3–C(16)), 1.24–1.52 (5 H, m, H–C(4), H_2–C(14), H_2–C(15)), 1.55–1.64 (1 H, m, H–C(3)), 1.63–1.84 (4 H, m, H–C(3), H–C(4), H_2–C(13)), 1.96–2.08 (1 H, m, H–C(5)), 2.20–2.37 (1 H, m, H–C(6)), 2.43–2.53 (1 H, m, H–C(6)), 2.65 (2 H, t, *J* 7.8, H_2–C(12)), 3.55–3.60 (1 H, m, H–C(7)), 3.60 (2 H, s, H_2–C(18)), 3.70–3.76 (1 H, m, H–C(7)), 6.96, 7.19 (4 H, AA'BB', *J* 8.4, H–C(9a,b), H–C(10a,b)), 7.17–7.23 (1 H, m, H–C(28)), 7.37 (1 H, s, H–C(20)), 7.40–7.45 (2 H, m, H–C(23), H–C(24)), 7.67–7.80 (3 H, m, H–C(22), H–C(25), H–C(27)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 29.5, 29.7, 31.2, 31.6 32.0, 35.6, 41.6, 53.3, 70.8 (m), 121.7 (t, *J* 274.3), 125.5, 125.9, 126.3, 127.1, 127.5, 127.9, 128.0, 129.8, 132.2, 132.5, 133.3, 139.5, 143.5, 171.4, 190.5 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) –113.3 (1 F, d, *J* = 252.9), (–104.5) - (–103.4) (1 F, m); *m/z* (MALDI-HRMS) 478.2556 (100%, $[M+H]^+$. $C_{30}H_{34}F_2NO_2^+$ requires 478.2552), 500.2380 (83, $[M+Na]^+$. $C_{30}H_{33}F_2NO_2Na^+$ requires 500.2372), 516.2121 (48, $[M+K]^+$. $C_{30}H_{33}F_2NO_2K^+$ requires 516.2111).

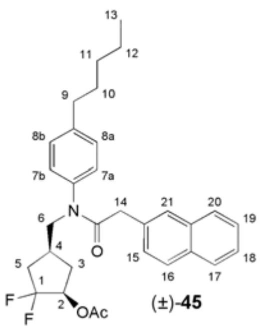
(1*SR*)-2-Oxocyclopent-3-en-1-yl acetate ((±)-38)[4]



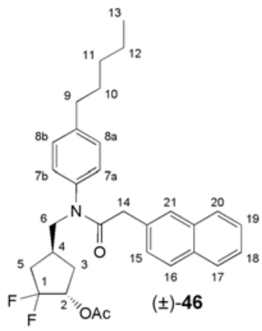
(±)-**38**

Using general procedure A, reaction of 2-cyclopentenone (**37**) (15.31 cm^3, 15.00 g, 182 mmol) and $Pb(OAc)_4$ (121.56 g, 274 mmol) in benzene (300 cm^3) for 50 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4 then 1:3), afforded (±)-**38** (12.75 g, 50%) as a yellow oil. δ_H(300 MHz; $CDCl_3$) 2.15 (3 H, s, CO_2CH_3), 2.61 (1 H, ddd, *J* 2.4, 5.4, 18.8, H–C(3)), 3.17 (1 H, m, H–C(3)), 5.12 (1 H, dd, *J* 3.1, 6.9, H–C(2)), 6.27 (1 H, m, H–C(5)), 7.67 (1 H, m, H–C(4)).

(1*RS*,4*SR*)-2,2-Difluoro-4-{[(2-naphthylacetyl)(4-pentylphenyl)amino]-methyl}cyclopentyl acetate ((±)-45) and **(1*SR*,4*SR*)-2,2-Difluoro-4-{[(2-naphthylacetyl)(4-pentylphenyl)amino]-methyl}cyclopentyl acetate ((±)-46)**



(±)-**45**



(±)-**46**

Using general procedure B, copper iodide (1.04 g, 5.40 mmol), TMEDA (16.47 cm^3, 12.69 g, 109.2 mmol), vinylmagnesium bromide (1 M solution in THF, 131.4 cm^3, 100.1 mmol), TMSCl (13.95 cm^3, 11.86 g, 109.2 mmol), and ketone (±)-**38** (12.75 g, 90.98 mmol), dissolved in THF (50 cm^3), in THF (250 cm^3) for 1 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**39** and (±)-**40** (10.24 g, 67%) as a yellow oil in a 1:10 mixture. Following general procedure C, reaction of ketones ((±)-

39/(±)-**40** (1.000 g, 5.49 mmol) and DAST (1.572 cm^3, 1.917 g, 11.9 mmol) in CH_2Cl_2 (30.0 cm^3) for 18 h, followed by CC purification (SiO_2; EtOAc/pentane 1:20) afforded (±)-**41** and (±)-**42** (703 mg, 63%) as a yellow oil in a 1:10 mixture.

Following general procedure J, reaction of (±)-**41**/(±)-**42** (1.00 g, 4.20 mmol), OsO_4 (0.025 M solution in *t*-BuOH, 5.02 cm^3, 4.27 g, 16.80 mmol) and $NaIO_4$ (2.69 g, 12.60 mmol) in a dioxane/water mixture (10:1) (50 cm^3) for 12 h gave crude aldehyde (0.96 g), which was used without further purification.

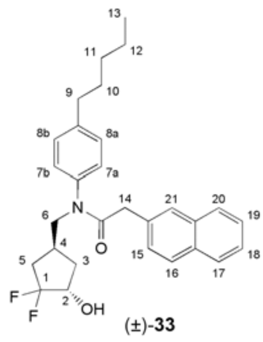
Using general procedure K, reaction of the crude aldehyde (960 mg, 4.99 mmol), 4-pentylaniline (887 mm^3, 815 mg, 4.99 mmol) and $NaBH(OAc)_3$ (1.481 g, 6.99 mmol) in 1,2-dichloroethane (40 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 3:97), afforded a 1:1 mixture of (±)-**43** and (±)-**44** (895 mg, 53%) as a colourless oil.

Using general procedure E, reaction of the 1:1 mixture of (±)-**43** and (±)-**44** (200 mg, 0.59 mmol), 2-naphthylacetic acid chloride (**20**) (132 mg, 0.65 mmol) and DIPEA (113 mm^3, 84 mg, 0.65 mmol) in CH_2Cl_2 (5 cm^3) for 5 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded amides (±)-**45** (120 mg, 40%) and (±)-**46** (124 mg, 42 %), each as a colourless wax in the given elution order.

(±)-**45**: $\tilde{\nu}_{max}$(solid)/cm^{-1} 2926, 2855, 2358, 2341, 1753, 1656, 1510, 1435, 1397, 1365, 1231, 1112, 851, 668, 632; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.9, H_3–C(13)), 1.31–1.42 (4 H, m, H_2–C(11), H_2–C(12)), 1.52–1.71 (3 H, m, H–C(5), H_2–C(10)), 1.85–2.04 (1 H, m, H–C(5)), 2.11 (3 H, s, O=C–CH_3), 2.17–2.35 (3 H, m, H–C(3), H_2–C(4)), 2.65 (2 H, t, *J* 7.8, H_2–C(9)), 3.59 (2 H, s, H_2–C(14)), 3.79 (2 H, d, *J* 6.0, H_2–C(6)), 5.04 (1 H, ddd, *J* 5.7, 12.3, 17.8, H–C(2)), 6.94, 7.18 (4 H, AA'BB', *J* 8.3, H–C(7a, b), H–C(8a, b), 7.15–7.22 (1 H, m, H–C(15)), 7.37 (1 H, s, H–C(21)), 7.41–7.45 (2 H, m, H–C(18), H–

C(19)), 7.67–7.80 (3 H, m, H–C(16), H–C(17), H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.0, 20.8, 22.5, 30.9 (dd, *J* 1.8, 6.0), 31.1, 31.5, 32.9 (d, *J* = 2.3), 35.5, 37.1 (t, *J* 3.1), 41.6, 53.7, 73.9 (dd, *J* 19.2, 34.9), 125.6, 125.9 (t, *J* 125.2), 125.9, 127.3, 127.6, 127.6, 127.9, 128.2, 129.7, 132.3, 132.8, 133.4, 139.5, 143.5, 169.8, 171.4 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) (–109.92) - (–109.02) (1 F, m), (–101.37) - (–100.37) (1 F, m); *m/z* (MALDI-HRMS) 508.2658 (100%, $[M+H]^+$. $C_{31}H_{36}F_2NO_3^+$ requires 508.2663), 530.2469 (58, $[M+Na]^+$. $C_{31}H_{35}F_2NO_3Na^+$ requires 530.2477), 546.2211 (31, $[M+K]^+$. $C_{31}H_{35}F_2NO_3K^+$ requires 546.2217). (±)-**46**: $\tilde{\nu}_{max}$(solid)/cm^{-1} 2927, 2856, 1753, 1652, 1509, 1435, 1395, 1364, 1228, 1120, 1014, 918, 851; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.9, H_3–C(13)), 1.31–1.44 (4 H, m, H_2–C(11), H_2–C(12)), 1.62–1.71 (2 H, m, H_2–C(10)), 1.83–1.97 (1 H, m, H–C(3)), 1.84–1.89 (2 H, m, H_2–C(5)), 2.07 (3 H, s, O=C–CH_3), 2.13–2.34 (1 H, m, H–C(3)), 2.54–2.68 (1 H, m, H–C(4)), 2.65 (2 H, t, *J* 7.8, H–C(9)), 3.59 (2 H, s, H_2–C(14)), 3.75 (2 H, dd, *J* 2.5, 7.6, H_2–C(6)), 5.12–5.19 (1 H, m, H–C(2)), 6.94, 7.18 (4 H, AA'BB', *J* 8.3, H_2–C(7a,b), H_2–C(8a,b), 7.15–7.22 (1 H, m, H–C(15)), 7.38 (1 H, s, H–C(21)), 7.40–7.47 (2 H, m, H–C(18), H–(19)), 7.66–7.80 (3 H, m, H–C(16), H–C(17), H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.0, 20.8, 22.5, 31.1, 31.5, 32.3–33.0 (m), 33.0, 35.5, 36.9 (t, *J* 23.5), 41.6, 53.9, 74.1 (q, *J* 18.1), 125.6, 125.9, 126.7 (dd, *J* 45.3, 180.5), 127.3, 127.6, 127.6, 127.9, 128.2, 129.7, 132.3, 132.8, 133.4, 139.8, 143.4, 169.6, 171.4 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) –112.30 (1 F, d, *J* 237.8), –99.16 (1 F, d, *J* = 237.8); *m/z* (MALDI-HRMS) 508.2660 (100%, $[M+H]^+$. $C_{31}H_{36}F_2NO_3^+$ requires 508.2663), 530.2470 (73, $[M+Na]^+$. $C_{31}H_{35}F_2NO_3Na^+$ requires 530.2477), 546.2211 (40, $[M+K]^+$. $C_{31}H_{35}F_2NO_3K^+$ requires 546.2217).

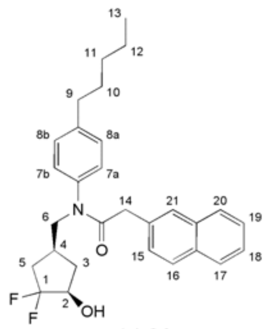
_N_-{[(1_SR_,4_SR_)-3,3-Difluoro-4-hydroxycyclopentyl]methyl}-2-(2-naphthyl)-_N_-(4-pentylphenyl)acetamide ((±)-33)



(±)-**33**

Using general procedure G, reaction of acetate (±)-**45** (48 mg, 0.10 mmol) and aqueous K_2CO_3/MeOH (1.0 cm^3) solution in CH_2Cl_2 (0.5 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**33** (33 mg, 74%) as a colourless oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3396, 2922, 2854, 2358, 1636, 1509, 1436, 1399, 1363, 1245, 1141, 1119, 1020, 1001, 853, 797, 740; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.9, H_3–C(13)), 1.33–1.40 (4 H, m, H_2–C(11), H_2–C(12)), 1.60–1.70 (2 H, m, H_2–C(10)), 1.77–1.92 (1 H, m, H–C(3)), 1.77–1.86 (2 H, m, H_2–C(5)), 1.97 (1 H, d, *J* 2.9, OH), 2.17–2.36 (1 H, m, H–C(3)), 2.50–2.63 (1 H, m, H–C(4)), 2.64 (2 H, t, *J* 7.8, H–C(9)), 3.58 (2 H, s, H_2–C(14)), 3.75 (2 H, dd, *J* 2.5, 7.8, H_2–C(6)), 4.09–4.15 (1 H, m, H–C(2)), 6.94, 7.18 (4 H, AA'BB', *J* 8.4, H_2–C(7a, b), H_2–C(8a, b)), 7.18–7.26 (1 H, m, H–C(17)), 7.41 (1 H, s, H–C(15)), 7.42–7.46 (2 H, m, H–C(18), H–C(19)), 7.67–7.80 (3 H, m, H–C(16), H–C(17), H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 31.2, 31.6, 31.9, 34.6, 36.0 (t, *J* 27.1), 41.7, 53.6, 73.8 (t, *J* 26.9), 77.2, 125.4, 125.8, 127.2, 127.5, 127.8, 128.1, 129.6, 130.8, 132.2, 132.7, 133.3, 139.3, 143.3, 171.2 (one signal in the aromatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) –115.4 (1 F, d, *J* 235.2), (–101.4) - (–100.2) (1 F, m); *m/z* (MALDI-HRMS) 466.2546 (100%, [*M*+H]$^+$. $C_{29}H_{34}F_2NO_2^+$ requires 466.2558), 488.2370 (10, [*M*+Na]$^+$. $C_{29}H_{33}F_2NO_2Na^+$ requires 488.5639), 504.2108 (7, [*M*+K]$^+$. $C_{29}H_{33}F_2NO_2K^+$ requires 504.2111).

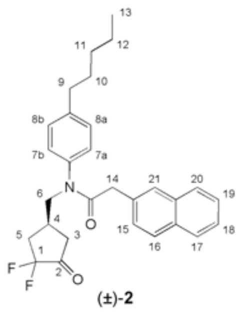
N-{[(1*SR*,4*RS*)-3,3-Difluoro-4-hydroxycyclopentyl]methyl}-2-(2-naphthyl)-*N*-(4-pentylphenyl)acetamide ((±)-34)



(±)-**34**

Using general procedure G, reaction of acetate (±)-**46** (92 mg, 0.18 mmol) and aqueous K_2CO_3/MeOH (2.0 cm^3) solution in CH_2Cl_2 (0.5 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**34** (84 mg, 96%) as a colourless oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3387, 2926, 2855, 1638, 1509, 1399, 1303, 1159, 1114, 1019, 960, 936, 851, 794, 738; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.6, H_3–C(13)), 1.32–1.42 (4 H, m, H_2–C(12), H_2–(11)), 1.51–1.67 (1 H, m, H–C(5)), 1.59–1.71 (2 H, m, H_2–C(10)), 1.86–2.03 (1 H, m, H–C(5)), 2.06–2.19 (2 H, m, H_2–C(3)), 2.21–2.35 (1 H, m, H–C(4)), 2.65 (2 H, t, *J* 7.8, H_2–C(9)), 2.72 (1 H, dd, *J* 1.5, 4.5, OH), 3.60 (2 H, s, H_2–C(14)), 3.79 (2 H, ddd, *J* 8.0, 13.7, 79.4, H_2–C(6)), 3.94–4.04 (1 H, m, H–C(2)), 6.94, 7.18 (4 H, AA'BB', *J* 8.2, H_2–C(7a, b), H_2–C(8a, b)), 7.18–7.22 (1 H, m, H–C(16)), 7.38 (1 H, s, H–C(15)), 7.40–7.46 (2 H, m, H–C(18), H–C(19)), 7.66–7.81 (3 H, m, H–C(16), H–C(17), H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 30.1 (d, *J* 55.8), 31.9, 31.6, 34.5, 35.6, 36.3 (t, *J* 23.8), 41.6, 54.5, 73.7 (dd, *J* 21.3, 32.4), 125.5, 125.9, 127.2, 127.5, 127.6, 127.9, 128.0, 128.8 (d, *J* 7.9), 129.6, 132.2, 132.6, 133.3, 139.4, 143.3, 171.6 ; δ_F(282 MHz, $CDCl_3$) (–112.8) - (–111.7) (1 F, m), (–102.6) - (101.5) (1 F, m); *m/z* (MALDI-HRMS) 466.2554 (100%, $[M+H]^+$. $C_{29}H_{34}F_2NO_2^+$ requires 466.2558), 488.2381 (26, $[M+Na]^+$. $C_{29}H_{33}F_2NO_2Na^+$ requires 488.5639), 504.1249 (8, $[M+K]^+$. $C_{29}H_{33}F_2NO_2K^+$ requires 504.2111).

***N*-{[(1*SR*)-3,3-Difluoro-4-oxocyclopentyl]methyl}-2-(2-naphthyl)-*N*-(4-pentyl-phenyl)acetamide ((±)-2)**

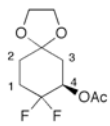


(±)-**2**

Using general procedure H, reaction of alcohol (±)-**33** (62 mg, 0.13 mmol) and 15% *Dess-Martin* periodinane solution in CH_2Cl_2 (1.776 cm^3, 85 mg, 0.266 mmol) in CH_2Cl_2 (0.5 cm^3) for 7 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**2** (35 mg, 57%) as a colourless solid. m.p. 165 °C; $\tilde{\nu}_{max}$(solid)/cm^{-1} 2953, 2855, 2360, 1776 (CO), 1652, 1508, 1396, 1330, 1263, 1192, 1166, 1112, 1037, 1018, 853, 794, 739, 639; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.9, H_3–C(13)), 1.37–1.42 (4 H, m, H_2–C(11),

H_2–C(12)), 1.61–1.71 (2 H, m, H_2–C(10)), 1.90–2.12 (1 H, m, H–C(3)), 2.19–2.33 (1 H, m, H–C(3)), 2.42–2.57 (2 H, m, H_2–C(5)), 2.50–2.64 (1 H, m, H–C(4)), 2.65 (2 H, t, *J* 7.8, H_2–C(9)), 3.61 (2 H, s, H_2–C(14)), 3.79–3.94 (2 H, m, H_2–C(6)), 6.96, 7.20 (4 H, AA'BB', *J* 8.2, H_2–C(7a, b), H_2–C(8a, b)), 7.12–7.21 (1 H, m, H–C(15)), 7.36 (1 H, s, H–C(21)), 7.41–7.47 (2 H, m, H–C(18), H–C(19)), 7.66–7.82 (3 H, m, H–(16), H–C(17), H–C(20)); δ_C(75 MHz, $CDCl_3$) = 14.04, 22.53, 29.10 (d, *J* 6.6), 31.03, 31.50, 35.50, 36.80 (dd, *J* 19.7, 22.6), 39.02 (d, *J* 2.6), 41.53, 53.39, 117.07 (dd, *J* 252.3, 255.6), 125.65, 126.03, 127.18, 127.58, 127.62, 127.67, 128.01, 128.05, 129.89, 132.35, 132.57, 133.39, 139.50, 143.70, 171.65, 202.51 (t, *J* 25.4); δ_F(282 MHz, $CDCl_3$)δ = –113.52 (1 F, dd, *J* = 11.0, 277.0), (–109.15) - (–108.02) (1 F, m); *m/z* (MALDI-HRMS) 464.2393 (76%, [*M*+H]$^+$. $C_{29}H_{32}F_2NO_2^+$ requires 464.2401), 486.2214 (100, [*M*+Na]$^+$. $C_{29}H_{31}F_2NO_2Na^+$ requires 486.2215), 502.1959 (40, [*M*+K]$^+$. $C_{29}H_{31}F_2NO_2K^+$ requires 502.1954).

(7*RS*)-8,8-Difluoro-1,4-dioxaspiro[4.5]dec-7-yl acetate ((±)-49)

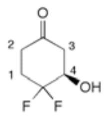


(±)-**49**

Using general procedure F, reaction of ketone **47** (19.5 g, 0.125 mol) and $Pb(OAc)_4$ (100.0 g, 0.224 mol) in cyclohexane (250 cm^3) for 24 h, followed by filtration through a plug (SiO_2; EtOAc), afforded (±)-**48**, contaminated with starting material **47**.

Using general procedure G, reaction of acetate (±)-**48** (140 mg, 0.65 mmol) and DAST (0.17 cm^3, 211 mg, 1.31 mmol) in CH_2Cl_2 (1.0 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**49** (69 mg, 36%) as a colourless oil. Found: C, 51.01; H, 6.08; F, 16.20. $C_{10}H_{14}F_2O_4$ requires C, 50.85; H, 5.97; F, 16.09%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 2968, 1747 (CO), 1370, 1224, 1163, 1125, 1036, 1054, 1005, 962; δ_H(300 MHz; $CDCl_3$) 1.74–1.81 (1 H, m, H–C(1)), 1.84–1.92 (1 H, m, H–C(1)), 1.93–2.00 (1 H, m, H–C(2)), 2.04–2.12 (2 H, m, H–C(2), H–C(3)), 2.13 (3 H, s, H_3C–COO), 2.14–2.20 (1 H, m, H–C(3)), 3.92–4.03 (4 H, m, H_2–(OCH_2CH_2O), H_2–(OCH_2CH_2O)), 5.13–5.27 (1 H, m, H–C(4)); δ_C(75 MHz, $CDCl_3$) 21.0, 29.5 (t, *J* 23.5), 31.1 (d, *J* 7.9), 36.9 (d, *J* 6.1), 64.6, 64.8, 69.4 (t, *J* 22.3), 107.1, 121.8 (d, *J* 245.4), 169.6; δ_F(282 MHz, $CDCl_3$) –108.4, –109.3 (1 F, 2 x m), –119.3 (1 F, d, *J* 241.2); *m/z* (EI) 236.0886 (1%, $[M]^+$. $C_{10}H_{14}F_2O_4^+$ requires 236.0855), 216.0790 (13), 115.0388 (100).

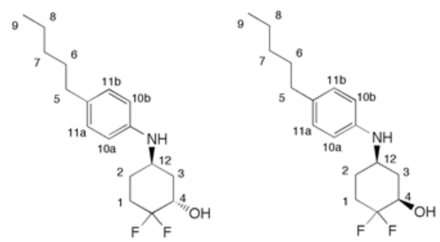
(3*RS*)-4,4-Difluoro-3-hydroxycyclohexanone ((±)-50)



(±)-**50**

Acetate (±)-**49** (2.085 g, 8.47 mmol, 1.0 eq.) was dissolved in THF (20 cm^3), and 10% aqueous HCl solution (80 cm^3) was added dropwise. The solution was stirred at r.t. for 16 h and subsequently neutralized with saturated aqueous Na_2CO_3 solution (5 cm^3). Saturated aqueous $NaHCO_3$ solution (100 cm^3) and saturated aqueous NH_4Cl solution (50 cm^3) were added, and the aqueous phase was extracted with CH_2Cl_2 (3 x 300 cm^3). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by CC (SiO_2; EtOAc/pentane 1:4) afforded (±)-**50** (927 mg, 73%) as a white solid. mp 63 °C; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3324, 1710 (CO), 1429, 1374, 1286, 1211, 1168, 1102, 1049, 991, 933; δ_H(300 MHz; $CDCl_3$) 2.17–2.30 (1 H, m, H–C(1)), 2.44–2.59 (3 H, m, H–C(2), H–C(1), H–C(3)), 2.62–2.64 (1 H, m, H–C(2)), 2.77–2.84 (1 H, m, H–C(3)), 4.23–4.29 (1 H, m, H–C(4)); δ_C(75 MHz, $CDCl_3$) 27.7 (t, *J* 24.4), 36.3 (m), 44.6 (d, *J* 4.3), 70.0 (dd, *J* 25.3, 154.2), 121.1 (dd, *J* 242.9, 246.6), 206.0; δ_F(282 MHz, $CDCl_3$) –110.3, –111.2 (1 F, 2 x m), –112.7, –113.1 (1 F, 2 x m); *m/z* (EI) 150.0487 (44%, $[M]^+$. $C_6H_8F_2O_2^+$ requires 150.0492), 71.0124 (100).

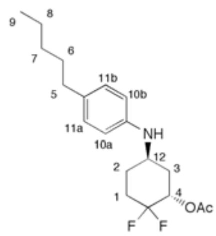
(1*SR*, 5*RS*)-2,2-Difluoro-5-[(4-pentylphenyl)amino]cyclohexanol ((±)-51) and **(1*RS*, 5*RS*)-2,2-Difluoro-5-[(4-pentylphenyl)amino]cyclohexanol ((±)-52)**



(±)-**51** (±)-**52**

Using general procedure L, reaction of ketone (±)-**50** (1.028 g, 6.85 mmol), 4-pentylaniline (**19**) (1.217 cm^3, 1.118 g, 6.85 mmol), $NaBH(OAc)_3$ (2.032 g, 9.59 mmol) and AcOH (390 mm^3, 411 mg, 6.85 mmol) in CH_2Cl_2 (4.0 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**51** (1.181 g, 58%) as a yellow oil and (±)-**52** (1.501 g) contaminated with 4-pentylaniline. (±)-**51**: $\tilde{\nu}_{max}$(solid)/cm^{-1} 3394, 2927, 2855, 2358, 1616, 1516, 1263, 1116, 1053, 821. δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 6.9, H_3–C(9)), 1.26–1.36 (4 H, m, H_2–C(7), H_2–C(8)), 1.44–1.53 (1 H, m, H–C(1)), 1.56 (2 H, t, *J* 7.7, H_2–C(6)), 1.61–1.67 (1 H, m, H–C(1)), 2.00–2.18 (2 H, m, H–C(2), H–C(3)), 2.21–2.31 (2 H, m, H–C(2), H–C(3)), 2.49 (2 H, t, *J* 7.7, H_2–C(5)), 3.26 (1 H, br s, OH), 3.73–3.81 (1 H, m, H–C(12)), 3.98–4.08 (1 H, m, H–C(4)), 6.57, 7.00 (4 H, AA´BB´, *J* 8.5, H_2–C(10a, b), H_2–C(11a, b)); δ_C(75 MHz, $CDCl_3$) 14.0, 22.5, 27.9 (t, *J* 23.5), 28.4 (t, *J* 5.2), 31.4, 34.9, 35.8, 45.5, 69.0 (t, *J* 28.7), 113.4, 122,2 (t, *J* 244.8), 129.1, 132.2, 144.5 (one signal in the aliphatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) –108.4 (1 F, dd, *J* 28.3, 59.6), –109.66, –110.55 (1 F, 2 x m); *m/z* (MALDI-HRMS) 298.1973 (100%, $[M+H]^+$. $C_{17}H_{26}F_2NO^+$ requires 298.1977).

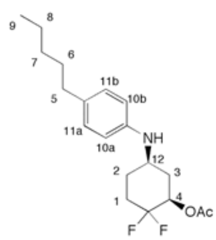
(1*SR*,5*RS*)-2,2-Difluoro-5-[(4-pentylphenyl)amino]cyclohexyl acetate ((±)-53)



(±)-**53**

Using general procedure M, reaction of alcohol (±)-**51** (500 mg, 1.68 mmol), Ac_2O (0.18 cm^3, 197 mg, 1.93 mmol) and DMAP (21 mg, 0.17 mmol) in pyridine (4.0 cm^3) for 18 h, followed by CC purification (SiO_2; EtOAc/pentane 1:7), afforded (±)-**53** (542 mg, 95%) as a red oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3338, 2930, 2860, 1750 (CO), 1613, 1515, 1369, 1227, 1133, 1045, 832; δ_H(300 MHz; CD_3OD) 0.89 (3 H, t, *J* 7.0, H_3–C(9)), 1.25–1.38 (4 H, m, H_2–C(7), H_2–C(8)), 1.49–1.59 (3 H, m, H_2–C(6), H–C(1)), 1.73–1.82 (1 H, m, H–C(1)), 2.03–2.22 (4 H, m, H_2–C(2), H_2–C(3)), 2.13 (3 H, s, H_3C–COO), 2.46 (2 H, t, *J* 7.6, H_2–C(5)), 3.61–3.69 (1 H, m, H–C(12)), 5.17–5.24 (1 H, m, H–C(4)), 6.58, 6.93 (4 H, AA´BB´, *J* 8.7, H_2–C(10a, b), H_2–C(11a, b)); δ_C(75 MHz, $CDCl_3$) 14.0, 20.9, 22.5, 28.8 (t, *J* 23.8), 28.8 (t, *J* 36.9), 31.4, 34.3, 34.9, 46.3, 69.0 (t, *J* 29.9), 113.3, 120.0 (t, *J* 245.68), 129.2, 132.5, 144.3, 169.3 (one signal in the aliphatic region not visible due to overlap); δ_F(282 MHz, $CDCl_3$) –107.0 (1 F, dd, *J* 36.8, 246.0), –109.48, –110.39 (1 F, 2 x m); *m/z* (MALDI-HRMS) 340.2077 (100%, $[M+H]^+$. $C_{19}H_{28}F_2NO_2^+$ requires 340.2083).

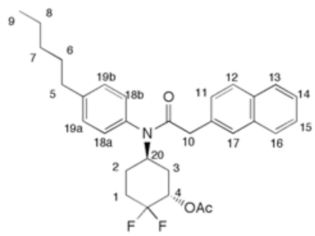
(1*SR*, 5*SR*)-2,2-Difluoro-5-[(4-pentylphenyl)amino]cyclohexyl acetate ((±)-54)



(±)-**54**

Using general procedure M, reaction of alcohol (±)-**52** (816 mg, 2.74 mmol), Ac_2O (0.52 cm^3, 560 mg, 5.49 mmol) and DMAP (67 mg, 0.55 mmol) in pyridine (9.0 cm^3) for 18 h, followed by CC purification (SiO_2; EtOAc/pentane 1:9), afforded (±)-**54** (867 mg, 93%) as a red oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3396, 2927, 2856, 1748, 1616, 1518, 1369, 1229, 1182, 1129, 1086, 1040, 969, 821; δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.0, H_3–C(9)), 1.21–1.39 (4 H, m, H_2–C(7), H_2–C(8)), 1.40–1.63 (3 H, m, H_2–C(6), H–C(1)), 1.82–1.90 (1 H, m, H–C(1)), 1.91–1.97 (1 H, m, H–C(2)), 1.97–2.08 (1 H, m, H–C(3)), 2.07 (3 H, s, H_3C–COO), 2.09–2.20 (1 H, m, H–C(3)), 2.23–2.31 (1 H, m, H–C(2)), 2.46 (2 H, t, *J* 7.6, H_2–C(5)), 3.53–3.61 (1 H, m, H–C(12)), 5.07–5.20 (1 H, m, H–C(4)), 6.61, 6.94 (4 H, AA′BB′, *J* 8.4, H_2–C(10a, b), H_2–C(11a, b)); δ_C(75 MHz, CD_3OD) 14.2, 20.4, 23.4, 29.0 (d, *J* 9.2), 31.4 (t, *J* 22.9), 32.3, 32.5, 35.1 (t, *J* 6.1), 35.2, 50.0, 70.9 (t, *J* 21.4), 114.9, 121.5 (t, *J* 244.8), 129.6, 132.9, 145.9, 170.8; δ_F(282 MHz, $CDCl_3$) –107.8, –108.6 (1 F, 2 x m), –116.35, –117.22 (1 F, 2 x bs); *m/z* (MALDI-HRMS) 339.2007 (100%, $[M]^+$. $C_{19}H_{27}F_2NO_2^+$ requires 339.2004).

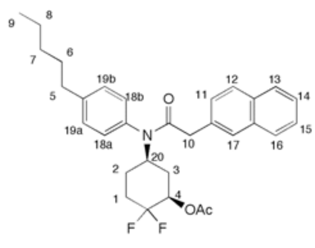
(1*RS*,5*SR*)-2,2-Difluoro-5-[(2-naphthylacetyl)-(4-pentyl-phenyl)amino]cyclohexyl acetate ((±)-55)



(±)-**55**

Using general procedure N, reaction of acyl chloride **20** (282 mg, 1.38 mmol) (±)-**53** (390 mg, 1.15 mmol) and DIPEA (0.26 cm^3, 193 mg, 1.49 mmol) in CH_2Cl_2 (1.0 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**55** (523 mg, 90%) as a yellow wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3054, 2931, 2858, 1752, 1652 (CO), 1510, 1370, 1223, 1122, 1049, 738; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* = 6.9, H_3–C(9)), 1.35–1.43 (4 H, m, H_2–C(7), H_2–C(8)), 1.44–1.50 (1 H, m, H–C(1)), 1.54–1.59 (1 H, m, H–C(1)), 1.67 (2 H, m, H_2–C(6)), 1.89–1.94 (1 H, m, H–C(2)), 1.98–2.08 (2 H, m, H–C(2), H–C(3)), 2.14 (3 H, s, H_3C–COO), 2.19–2.36 (1 H, m, H–C(3)), 2.66 (2 H, t, *J* 7.8, H_2–C(5)), 3.48 (2 H, s, H_2–C(10)), 4.98–5.08 (1 H, m, H–C(20)), 5.09–5.30 (1 H, m, H–C(4)), 6.87 (2 H, t, *J* 7.1, H_2–C(18a, b), H_2–C(19a, b)), 7.16–7.21 (1 H, m, H–C(11)), 7.19 (2 H, t, *J* 7.1, H–C(18a), H–C(18b)), 7.37 (1 H, s, H–C(17)), 7.40–7.46 (2 H, m, H–C(14), H–C(15)), 7.67–7.73 (2 H, m, H–C(13), H–C(16)), 7.76–7.80 (1 H, m, H–C(12)); δ_C(75 MHz, $CDCl_3$) 13.9, 20.9, 22.4, 26.1, 28.6 (t, *J* 23.2), 30.9, 31.4, 32.1 (d, *J* 4.9), 35.4, 42.0, 47.2, 69.2 (dd, *J* 25.3, 38.2), 119.5 (t, *J* 245.7), 125.5, 125.8, 127.3, 127.5, 127.6, 127.8, 129,3, 129.4, 130.1, 132.2, 132.6, 133.2, 135.2, 143.9, 169.3, 170.9; δ_F(282 MHz, $CDCl_3$) –107.1 (1 F, d, *J* 250.8), –108.5 (1 F, dd, *J* 32.0, 252.4); *m/z* (MALDI-HRMS) 508.2666 (100%, [*M*+H]$^+$. $C_{31}H_{36}F_2NO_3^+$ requires 508.2658), 530.2501 (34, [*M*+Na]$^+$. $C_{31}H_{35}F_2NO_3Na^+$ requires 530.2477), 546.2243 (12, [*M*+K]$^+$. $C_{31}H_{35}F_2NO_3K^+$ requires 546.2217,

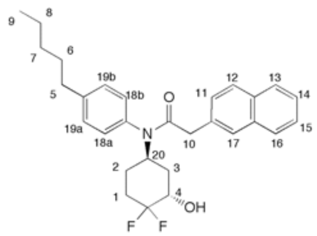
(1*SR*,5*SR*)-2,2-Difluoro-5-[(2-naphthylacetyl)-(4-pentylphenyl)amino]cyclohexyl acetate ((±)-56)



(±)-**56**

Using general procedure N, reaction of acetate (±)-**54** (300 mg, 0.88 mmol), acyl chloride **20** (362 mg, 1.77 mmol) in CH_2Cl_2 (2.0 cm^3) and DIPEA (0.31 cm^3, 229 mg, 1.77 mmol) in CH_2Cl_2 (1.0 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded (±)-**56** (418 mg, 93%) as a yellow wax. Found: C, 73.08; H, 7.03; N, 2.70. $C_{31}H_{35}F_2NO_3$ requires C, 73.35; H, 6.95; N, 2.76%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 2931, 2858, 2361, 1748, 1652, 1510, 1370, 1327, 1228, 1094, 966, 740; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 6.9, H_3–C(9)), 1.32–1.41 (4 H, m, H_2–C(7), H_2–C(8)), 1.43–1.52 (2 H, m, H_2–C(1)), 1.62–1.72 (2 H, m, H_2–C(6)), 1.76–1.97 (2 H, m, H–C(2), H–C(3)), 2.03–2.26 (2 H, m, H–C(2), H–C(3)), 2.08 (3 H, s, H_3C–COO), 2.65 (2 H, t, *J* 7.8, H_2–C(5)), 3.48 (2 H, s, H_2–C(10)), 4.84–4.93 (1 H, m, H–C(20)), 5.04–5.29 (1 H, m, H–C(4)), 6.85, 7.16 (4 H, AA´BB´, *J* 8.1, H_2–C(18a, b), H_2–C(19a, b)), 7.14–7.18 (1 H, m, H–C(11)), 7.34 (1 H, s, H–C(17)), 7.40–7.46 (2 H, m, H–C(14), H–C(15)), 7.66–7.72 (2 H, m, H–C(13), H–C(16)), 7.75–7.80 (1 H, m, H–C(12)); δ_C(75 MHz, $CDCl_3$) 14.2, 20.9, 22.7, 26.5 (d, *J* 9.8), 31.1, 31.3 (t, *J* 24.4), 31.6, 32.9 (d, *J* 6.1), 35.6, 42.1, 50.1, 70.1 (t, *J* 20.5), 119.7 (t, *J* 246.0), 125.5, 125.8, 127.2, 127.5, 127.8, 129.3, 129.3, 130.0, 130.1, 132.6, 133.2, 134.5, 135.1, 143.9, 169.4, 170.6; δ_F(282 MHz, $CDCl_3$) –107.4 (1 F, d, *J* 233.7), –118.15, –118.90 (1 F, 2 x m); *m/z* (MALDI-HRMS) 508.2655 (100%, $[M+H]^+$. $C_{31}H_{36}F_2NO_3^+$ requires 508.2658), 530.2500 (18, $[M+Na]^+$. $C_{31}H_{35}F_2NO_3Na^+$ requires 530.2477), 546.2235 (9, $[M+K]^+$. $C_{31}H_{35}F_2NO_3K^+$ requires 546.2217).

_N_-[(1_SR_,3_RS_)-4,4-Difluoro-3-hydroxycyclohexyl]-2-(2-naphthyl)-_N_-(4-pentyl-phenyl)acetamide ((±)-35)

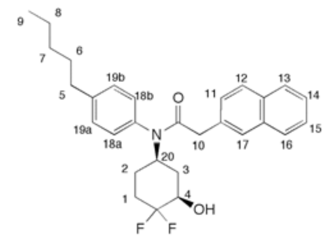


(±)-**35**

Using general procedure G, reaction of acetate (±)-**55** (521 mg, 1.06 mmol) and aqueous K_2CO_3/MeOH (16 cm^3) solution in CH_2Cl_2 (3.0 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**35** (455 mg, 89%) as a yellow oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3397, 2930, 2857, 1634, 1510, 1400, 1329, 1178, 1128, 1088, 964, 741; δ_H(400 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7.0, H_3–C(9)), 1.24–1.35 (5 H, m, H–C(2), H_2–C(7), H_3–C(8)), 1.40–1.48 (1 H, m, H–C(2)), 1.54–1.62 (2 H, m, H_2–C(6)), 1.73–1.79 (1 H, m, H–C(1)), 1.80–1.86 (1 H, m, H–C(3)), 1.90–1.96 (1 H, m, H–C(3)), 2.11–2.28 (1 H, m, H–C(6)), 2.56 (2 H, t, *J* 7.8, H_2–C(5)), 2.77 (1 H, s, OH)), 3.39 (2 H, s, H–C(10)), 3.82–3.88 (1 H, m, H–C(20)), 5.01 (1 H, dt, *J* 3.5, 12.5, H–C(4)), 6.76, 7.06 (4 H, AA'BB', *J* 7.6, H_2–C(18a, b), H_2–C(19a, b)), 7.10 (1 H, dd, *J* 1.8, 8.4, H–C(11)), 7.28 (1 H, s, H–C(17)), 7.32–7.36 (2 H, m, H–C(14), H–C(15)), 7.59–7.63 (2 H, m, H–C(13), H–C(16)), 7.68–7.71 (1 H, m, H–C(12)); δ_C(100 MHz, $CDCl_3$) 13.0, 21.5, 25.4 (d, *J* 9.8), 27.0 (t, *J* 23.5), 30.0, 30.5, 33.0 (d, *J* 4.0), 34.5, 41.2, 46.5, 67.8 (dd, *J* 24.1, 34.6), 120.7 (dd, *J* 241.8, 247.8), 124.5, 124.9, 126.3, 126.4, 126.6, 126.6, 126.7, 128.2, 129.1, 131.3, 131.9, 132.4, 134.8, 142.7, 170.0 (one signal in the aromatic region not visible due to overlap);

δ_F(282 MHz, $CDCl_3$) –108.8 (1 F, d, *J* 247.8), –107.3 (1 F, d, *J* 248.3); *m/z* (MALDI-HRMS) 466.2549 (100%, $[M+H]^+$. $C_{29}H_{34}F_2NO_2^+$ requires 466.2552), 488.2368 (25, $[M+Na]^+$. $C_{29}H_{33}F_2NO_2Na^+$ requires 488.2372), 504.2118 (9, $[M+K]^+$. $C_{29}H_{33}F_2NO_2K^+$ requires 504.2111).

N-[(1SR,3SR)-4,4-Difluoro-3-hydroxycyclohexyl]-2-(2-naphthyl)-N-(4-pentyl-phenyl)acetamide ((±)-36)

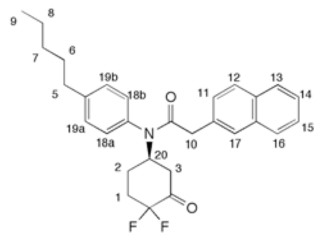


(±)-**36**

Using general procedure G, reaction of acetate (±)-**56** (380 mg, 0.75 mmol) and aqueous K_2CO_3/MeOH (115 cm^3) solution in CH_2Cl_2 (0.5 cm^3) for 3 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**36** (327 mg, 94%) as a yellow oil. Found: C, 74.54; H, 7.27; N, 3.00. $C_{29}H_{33}F_2NO_2$ requires C, 74.81; H, 7.14; N, 3.01%; $\tilde{\nu}_{max}$(solid)/cm^{-1} 3397, 2930, 2857, 1634, 1510, 1400, 1329, 1178, 1128, 1088, 964, 741; δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 6.9, H_3–C(9)), 1.31–1.43 (5 H, m, H–C(1), H_2–C(7), H_2–C(8)), 1.61–1.78 (2 H, m, H_2–C(6)), 1.71–1.89 (2 H, m, H–C(1), H–C(2)), 2.07–2.19 (2 H, m, H–C(2), H–C(3)), 2.25 (1 H, d, *J* 6.2, H–C(3)), 2.64 (2 H, t, *J* 7.8, H_2–C(5)), 3.49 (2 H, s, H_2–C(10)), 3.79–3.95 (1 H, m, H–C(20)), 4.81 (1 H, tt, *J* 3.1, 12.3, H–C(4)), 6.83–6.89 (2 H, m, H–C(19a), H–C(19b)), 7.15–7.19 (3 H, m, H–C(11), H–C(18a), H–

C(18b)), 7.36 (1 H, s, H–C(17)), 7.40–7.46 (2 H, m, H–C(14), H–C(15)), 7.66–7.73 (2 H, m, H–C(13), H–C(16)), 7.76–7.80 (1 H, m, H–C(12)); δ_C(100 MHz, $CDCl_3$) 14.0, 22.4, 26.5 (d, *J* 9.9), 30.6 (t, *J* 23.2), 30.9, 31.4, 35.4 (d, *J* 7.3), 35.4, 41.9, 50.0, 70.1 (t, *J* 22.0), 121.1 (t, *J* 244.8), 125.4, 125.8, 127.2, 127.5, 127.8, 129.2, 129.3, 130.0, 130.1, 132.2, 132.6, 133.2, 135.1, 143.9, 170.8; δ_F(282 MHz, $CDCl_3$) –108.6 (1 F, d, *J* 233.7), –122.32, –123.10 (1 F, 2 x m); *m/z* (MALDI-HRMS) 466.2552 (100%, $[M+H]^+$. $C_{29}H_{34}F_2NO_2^+$ requires 466.2552), 488.2372 (14, $[M+Na]^+$. $C_{29}H_{33}F_2NO_2Na^+$ requires 488.2372), 504.2115 (10, $[M+K]^+$. $C_{29}H_{33}F_2NO_2K^+$ requires 504.2111).

_N_-[(1*SR*)-4,4-Difluoro-3-oxocyclohexyl]-2-(2-naphthyl)-*N*-(4-pentylphenyl)-acetamide ((±)-4)

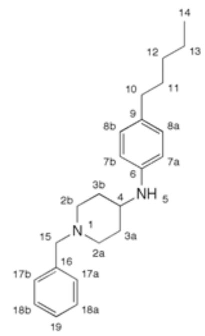


(±)-**4**

Using general procedure H, reaction of alcohol (±)-**36** (330 mg, 0.71 mmol) and 15% *Dess-Martin* periodinane solution in CH_2Cl_2 (2.900 cm^3, 4.008 g, 9.45 mmol) in CH_2Cl_2 (3.0 cm^3) for 7 h, followed by CC purification (SiO_2; EtOAc/pentane 1:1), afforded (±)-**4** (283 mg, 86%) as a colourless wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3342, 3054, 2930, 2858, 1753 (CO) (ketone), 1649, 1510, 1398, 1325, 1262, 1178, 1128, 1073, 908, 732; δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.0, H_3–C(9)), 1.25–1.36 (4 H, m, H_2–C(7), H_2–C(8)), 1.56–1.64

(2 H, m, H_2–C(6)), 1.71–1.80 (1 H, m, H–C(2)), 1.82–1.95 (1 H, m, H–C(1)), 1.98–2.03 (1 H, m, H–C(2)), 2.25–2.32 (1 H, m, H–C(1)), 2.48–2.58 (1 H, m, H–C(3)), 2.60 (2 H, t, *J* 7.8, H_3–C(5)), 2.64–2.70 (1 H, m, H–C(3)), 3.43 (2 H, s, H_2–C(10)), 4.88–4.95 (1 H, m, H–C(20)), 6.80 (2 H, dd, *J* 6.9, 21.4, H_2–C(18a, b)), 7.08 (2 H, dd, *J* 1.7, 8.4, H_2–C(19a, b)), 7.13 (1 H, d, *J* 8.5, H–C(11)), 7.27 (1 H, s, H–C(17)), 7.34–7.39 (2 H, m, H–C(14), H–C(15)), 7.60–7.65 (2 H, m, H–C(13), H–C(16)), 7.70–7.73 (1 H, m, H–C(12)); δ_C(100 MHz, $CDCl_3$) 14.0, 22.5, 26.3 (d, *J* 8.7), 31.0, 31.5 (d, *J* 22.0), 35.5, 42.2, 44.0, 52.4, 115.2 (dd, *J* 244.9, 258.6), 125.7, 126.0, 127.2, 127.6, 127.6, 127.6, 128.0, 129.7, 130.1, 132.4, 133.4, 135.0, 144.5, 170.9, 195.0 (dd, *J* 24.2, 28.2); δ_F(282 MHz, $CDCl_3$) –117.14 (1 F, d, *J* 255.0), –106.44 (1 F, d, *J* 255.8); *m/z* (MALDI-HRMS) 464.2388 (100%, $[M+H]^+$. $C_{29}H_{32}F_2NO_2^+$ requires 464.2396), 486.2207 (30, $[M+Na]^+$. $C_{29}H_{31}F_2NO_2^+$ requires 486.2215), 502.1954 (27, $[M+K]^+$. $C_{29}H_{31}F_2NO_2^+$ requires 502.1954).

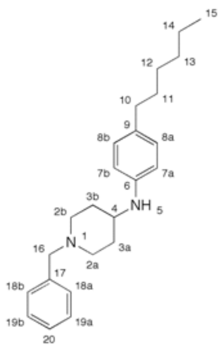
1-Benzyl-*N*-(4-pentylphenyl)piperidin-4-amine (59)



59

Using general procedure L, reaction of ketone **57** (472 cm^3, 500 mg, 2.64 mmol), 4-pentylaniline (**19**) (469 cm^3, 431 mg, 2.64 mmol), $NaBH(OAc)_3$ (784 mg, 3.70 mmol) and AcOH (151 cm^3, 159 mg, 2.64 mmol) in CH_2Cl_2 (10 cm^3) for 18 h, followed by CC purification (SiO_2; EtOAc/pentane 1:4), afforded **59** (756 mg, 85%) as a colourless oil. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3026, 2925, 2854, 2800, 1616, 1527, 1454, 1313, 1267, 1120, 1092, 819, 736, 697; δ_H(300 MHz; $CDCl_3$) 0.83 (3 H, t, *J* 6.9, H_2–C(14)), 1.21–1.29 (4 H, m, H_2–C(12), H_2–C(13)), 1.39–1.53 (4 H, m, H_2–C(11), H_2–C(3a, b), 1.98 (2 H, d, *J* 11.9, H_2–C(3a, b)), 2.09 (2 H, dt, *J* 2.2, 9.2, H_2–C(2a, b)), 2.42 (2 H, t, *J* 7.7, H_2–C(10)), 2.76–2.82 (2 H, m, H_2–C(2a, b)), 3.16–3.26 (1 H, m, H–C(4)), 3.33 (1 H, br s, NH), 3.47 (2 H, s, H_2–C(15), 6.47, 6.92 (4 H, AA'BB', *J* 7.8, H_2–C(7a, b) H_2–C(8a, b)), 6.94–7.24 (1 H, m, H–C(19)), 7.27 (4 H, d, *J* 4.4, H_2–C(17a, b), H_2–C(18a, b)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 31.7, 32.8, 35.1, 50.3, 52.5, 63.3, 113.3, 126.9, 128.1, 128.3, 129.1, 131.6, 138.4, 144.9 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 337.2640 (100%, $[M+H]^+$. $C_{23}H_{33}N_2^+$ requires 337.2638).

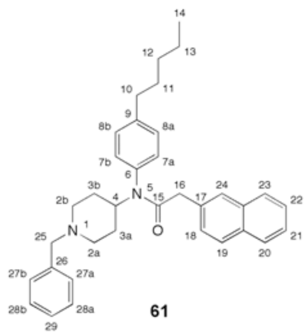
1-Benzyl-*N*-(4-hexylphenyl)piperidin-4-amine (60)



60

Using general procedure L, reaction of ketone **57** (472 cm^3, 500 mg, 2.64 mmol), 4-hexylaniline **58** (515 cm^3, 468 mg, 2.64 mmol), $NaBH(OAc)_3$ (784 mg, 3.70 mmol) and AcOH (151 cm^3, 159 mg, 2.64 mmol) in CH_2Cl_2 (10 cm^3) for 18 h, followed by CC purification (SiO_2; EtOAc/pentane 1:2), afforded **60** (926 mg, 72%) as a colourless oil. $\tilde{\nu}_{max}$(solid)/ cm^{-1} 3029, 2923, 2852, 2802, 2760, 1616, 1527, 1454, 1312, 1267, 1121, 1093, 909, 820, 735, 698; δ_H(300 MHz; $CDCl_3$) 0.88 (3 H, d, *J* 6.7, H_3–C(15)), 1.26–1.33 (6 H, m, H_2–C(12), H_2–C(13), H_2–C(14)), 1.40–1.57 (4 H, m, H_2–C(11), H_2–C(3a, b)), 2.03 (2 H, d, *J* 4.1, H_2–C(3a, b)), 2.15 (2 H, dt, *J* 2.3, 11.3, H_2–C(2a, b)), 2.48 (2 H, t, *J* 7.7, H_2–C(10)), 2.82–2.88 (2 H, m, H_2–C(2a, b)), 3.22–3.31 (1 H, m, H–C(4)), 3.39 (1 H, br s, NH), 3.53 (2 H, s, H_2–C(16)), 6.53, 6.97 (4 H, AA'BB', *J* 8.5, H_2–C(7a, b), H_2–C(8a, b)), 7.25–7.36 (1 H, m, H–C(20)), 7.32 (4 H, d, *J* 4.5, H_2–C(18a, b), H_2–C(19a, b)); δ_C(75 MHz, $CDCl_3$) 14.3, 22.8, 29.1, 31.9, 31.9, 32.8, 35.1, 50.3, 52.5, 63.2, 113.3, 126.9, 128.1, 128.3, 128.8, 129.1, 131.6, 138.3, 144.9 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 351.2792 (100%, $[M+H]^+$. $C_{24}H_{34}N_2^+$ requires 351.2795).

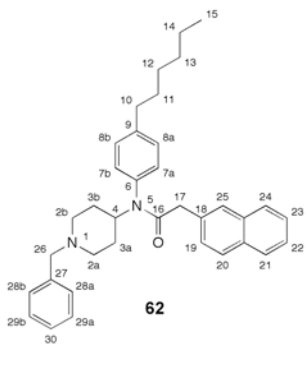
N-(1-Benzylpiperidin-4-yl)-2-(2-naphthyl)-*N*-(4-pentylphenyl)acetamide (61)



61

Using general procedure N, reaction of aniline **59** (673 mg, 2.00 mmol), acyl chloride **20** (614 mg, 3.00 mmol) and DIPEA (0.52 cm^3, 388 mg, 1.5 mmol) in CH_2Cl_2 (7.0 cm^3) for 16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:2), afforded **61** (418 mg, 88%) as a white wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3028, 2927, 2856, 2359, 1648, 1508, 1365, 1327, 1241, 1122, 1065, 973, 856, 789, 735, 698, 633; δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 6.9, H_3–C(14)), 1.32–1.46 (6 H, m, H_2–C(3a, b), H_2–C(12), H_2–C(13)), 1.60–1.68 (4 H, m, H_2–C(3a, b), H_2–C(11)), 2.09 (2 H, dt, *J* 2.1, 11.8, H_2–C(2a, b)), 2.64 (2 H, t, *J* 7.8, H_2–C(10)), 2.86 (2 H, d, *J* 11.7, H_2–C(2a, b)), 3.43 (2 H, s, H_2–C(25)), 3.48 (2 H, s, H_2–C(16)), 4.60–4.71 (1 H, m, H–C(4)), 6.87, 7.14 (4 H, AA'BB', *J* 8.3, H_2–C(7a, b), H_2–C(8a, b)), 7.18–7.29 (6 H, m, H–C(18), H_2–C(27a, b), H_2–C(28a, b), H–C(29)), 7.38–7.45 (3 H, m, H–C(21), H–C(22), H–C(24)), 7.66–7.72 (2 H, m, H–C(20), H–C(23)), 7.75–7.80 (1 H, m, H–C(19)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 30.6, 31.2, 31.7, 35.6, 42.3, 52.8, 53.1, 63.1, 125.3, 125.7, 126.9, 127.4, 127.5, 127.5, 127.6, 128.1, 129.0, 129.1, 130.4, 132.2, 133.1, 133.3, 135.9, 138.1, 143.3, 170.5 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 505.3211 (100%, [*M*+H]$^+$. $C_{35}H_{41}N_2O^+$ requires 505.3213).

N-(1-Benzylpiperidin-4-yl)-N-(4-hexylphenyl)-2-(2-naphthyl)acetamide (62)

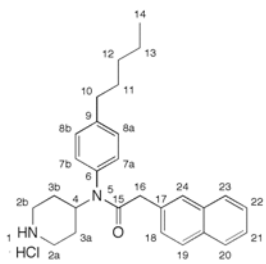


62

Using general procedure N, reaction of aniline **60** (501 mg, 1.42 mmol), acyl chloride **20** (439 mg, 2.14 mmol) and DIPEA (0.37 cm^3, 277 mg, 1.5 mmol) in CH_2Cl_2 (5.0 cm^3) for

16 h, followed by CC purification (SiO_2; EtOAc/pentane 1:2), afforded **62** (555 mg, 75%) as a white wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3028, 2926, 2855, 2801, 1648, 1508, 1387, 1366, 1327, 1241, 1123, 1065, 1022, 988, 856, 788, 736, 698; δ_H(300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 6.7, H_3–C(15)), 1.25–1.45 (8 H, m, H_2–C(3a, b), H_2–C(12), H_2–C(13), H_2–C(14)), 1.59–1.76 (4 H, m, H_2–C(3a, b), H_2–C(11)), 2.08 (2 H, dt, *J* 2.0, 11.8, H_2–C(2a, b)), 2.64 (2 H, t, *J* 7.7, H_2–C(10)), 2.86 (2 H, d, *J* 11.8, H_2–C(2a, b)), 3.42 (2 H, s, H_2–C(26)), 3.48 (2 H, s, H_2–C(17)), 4.60–4.71 (1 H, m, H–C(4)), 6.87, 7.14 (4 H, AA'BB', *J* 8.1, H_2–C(7a, b), H_2–C(8a, b)), 7.18–7.29 (6 H, m, H–C(19), H_2–C(28a, b), H_2–C(29a, b), H–C(30)), 7.38–7.45 (3 H, m, H–C(22), H–C(23), H–C(25)), 7.66–7.69 (2 H, m, H–C(21), H–C(24)), 7.70–7.80 (1 H, m, H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.3, 22.7, 29.1, 30.6, 31.5, 31.8, 35.6, 42.2, 52.7, 53.1, 63.1, 125.3, 125.7, 126.8, 127.4, 127.4, 127.5, 127.6, 128.0, 128.9, 129.0, 130.3, 132.1, 133.1, 133.2, 135.8, 138.1, 143.3, 170.5 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 519.3383 (100%, $[M+H]^+$. $C_{36}H_{43}N_2O^+$ requires 519.3370).

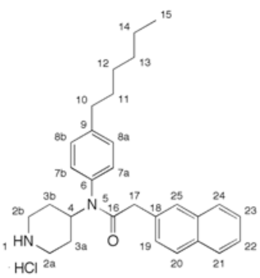
2-(2-Naphthyl)-*N*-(4-pentylphenyl)-*N*-piperidin-4-ylacetamide hydrochloride (5)



5

Using general procedure O, reaction of amide **61** (100 mg, 0.20 mmol) and 1-chloroethyl chloroformate (28 mm^3, 37 mg, 0.26 mmol) in CH_2Cl_2 (2.0 cm^3) for 1 h and MeOH (3.0 cm^3) for 3 h, followed by CC purification (SiO_2; MeOH/CH_2Cl_2 1:20), afforded **5** (82 mg, 56%) as a white wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 3377, 2927, 2856, 2720, 2361, 1648, 1602, 1509, 1374, 1340, 1276, 1115, 1078, 1039, 959, 856, 812, 788, 737; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, t, *J* 6.8 H_3–C(14)), 1.31–1.48 (6 H, m, H_2–C(3a, b), H_2–C(12), H_2–C(13)), 1.60–1.70 (2 H, m, H_2–C(11)), 1.84 (2 H, d, *J* 11.9, H_2–C(3a, b)), 2.63 (2 H, t, *J* 7.7, H_2–C(10)), 2.77 (2 H, dt, *J* 2.1, 12.5, H_2–C(2a, b)), 3.17 (2 H, d, *J* 12.1, H_2–C(2a, b)), 3.48 (2 H, s, H_2–C(16)), 4.67–4.81 (3 H, m, H–C(3), NH_2^+)), 6.85, 7.15 (4 H, AA'BB', *J* 8.2, H_2–C(7a, b), H_2–C(8a, b)), 7.19 (1 H, d, *J* 1.7, H–C(18)), 7.36 (1 H, s, H–C(24)), 7.40–7.43 (2 H, m, H–C(21), H–C(22)), 7.66–7.72 (2 H, m, H–C(20), H–C(23)), 7.74–7.79 (1 H, m, H–C(19)); δ_C(75 MHz, $CDCl_3$) 14.2, 22.7, 30.0, 31.1, 31.6, 35.6, 42.2, 45.0, 51.7, 125.4, 125.8, 127.3, 127.5, 127.5, 127.7, 129.2, 130.1, 132.2, 132.8, 133.2, 135.4, 143.7, 170.7 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 415.2747 (100%, [*M*–Cl]$^+$. $C_{28}H_{35}N_2O^+$ requires 415.2744).

_N_-(4-Hexylphenyl)-2-(2-naphthyl)-_N_-piperidin-4-ylacetamide hydrochloride (6)



6

Using general procedure O, reaction of amide **62** (50 mg, 0.10 mmol) and 1-chloroethyl chloroformate (18 mg, 0.13 mmol) in CH_2Cl_2 (1.0 cm^3) for 1 h and MeOH (2.0 cm^3) for 3 h, followed by CC purification (SiO_2; MeOH/CH_2Cl_2 1:20), afforded **6** (41 mg, 65%) as a white wax. $\tilde{\nu}_{max}$(solid)/cm^{-1} 2923, 2853, 2705, 2490, 1652, 1602, 1508, 1455, 1366, 1327, 1259, 1241, 1141, 1077, 1021, 901, 862, 811, 797, 782, 765, 737, 667; δ_H(400 MHz; $CDCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ = 0.84 (3 H, t, *J* 7.0, H_3–C(15)), 1.23–1.34 (6 H, m, H_2–C(12), H_2–C(13), H_2–C(14)), 1.42 (2 H, dt, *J* 3.9, 12.7, H_2–C(3a, b)), 1.53–1.62 (2 H, m, H_2–C(11)), 1.81 (2 H, d, *J* 12.1, H_2–C(2a, b)), 2.56 (2 H, t, *J* 7.8, H_2–C(10)), 2.74 (2 H, dt, *J* 2.0, 12.6, H_2–C(3a, b)), 3.17 (2 H, d, *J* 12.6, H_2–C(2a, b)), 3.41 (2 H, s, H_2–C(17)), 4.62–4.70 (1 H, m, H–C(4)), 6.77, 7.08 (4 H, AA'BB', *J* 8.3, H_2–C(7a, b), H_2–C(8a, b)), 7.08–7.11 (1 H, m, H–C(19)), 7.28 (1 H, s, H–C(25)), 7.33–7.37 (2 H, m, H–C(22), H–C(23)), 7.59–7.64 (2 H, m, H–C(21), H–C(24)), 7.69–7.71 (1 H, m, H–C(20)); δ_C(75 MHz, $CDCl_3$) 14.0, 22.5, 28.9, 30.2, 31.2, 31.4, 31.6, 35.4, 42.0, 45.1, 51.8, 125.4, 125.7, 127.3, 127.4, 127.5, 127.7, 129.1, 130.1, 132.1, 132.8, 133.2, 135.4, 143.6, 170.7 (one signal in the aromatic region not visible due to overlap); *m/z* (MALDI-HRMS) 429.2899 (100%, [*M*–Cl]$^+$. $C_{29}H_{37}N_2O^+$ requires 429.2900), 451.2720 (11, [*M*–HCl+Na]$^+$. $C_{29}H_{36}N_2ONa^+$ requires 451.2720).

4. Literature

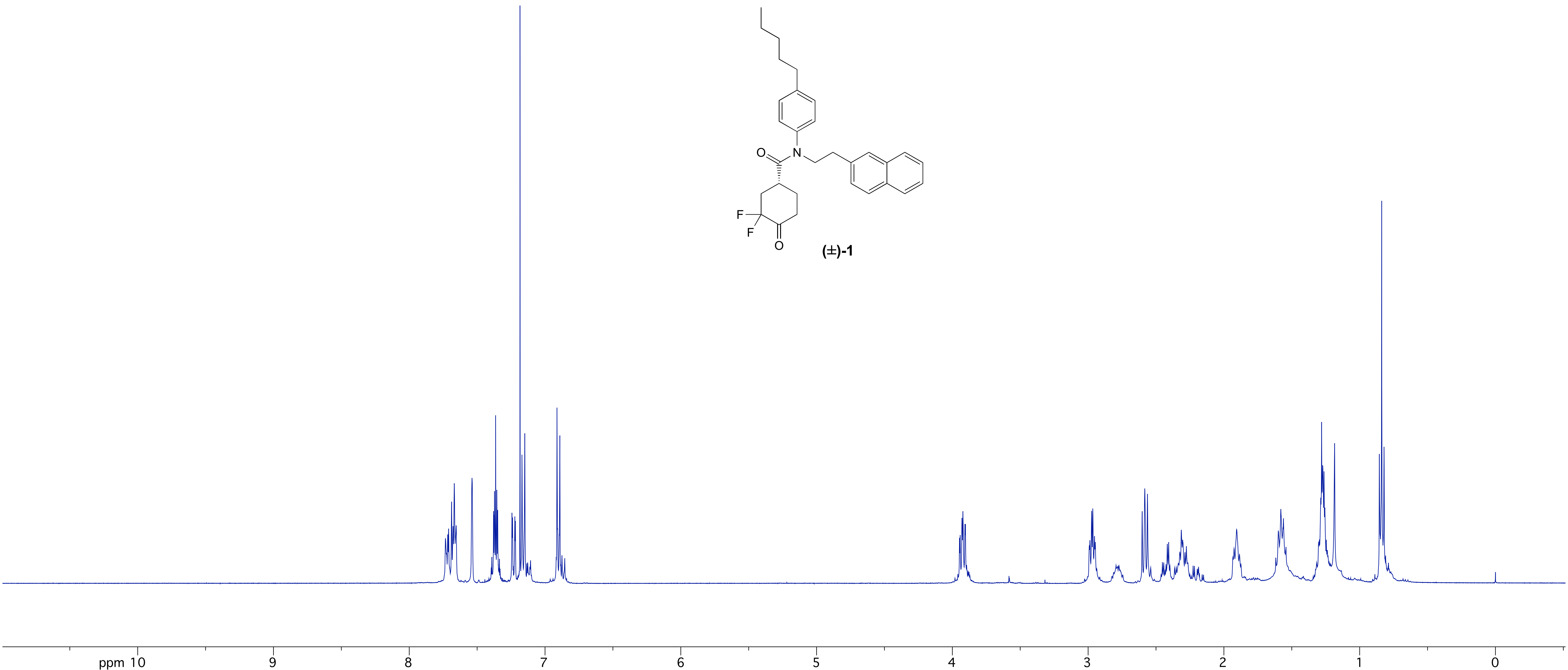
1 B. V. Yang, D. Orourke and J. C. Li, *Synlett*, 1993, 195–196.

2 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115–119.

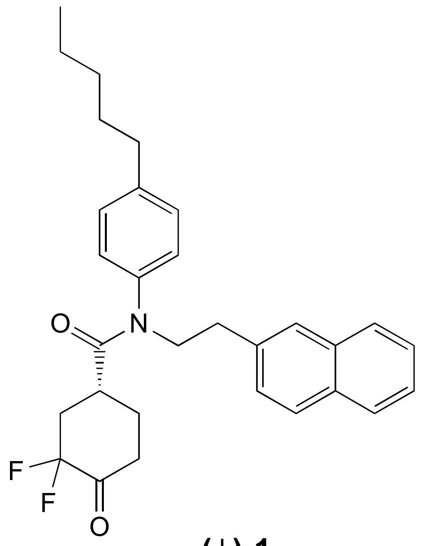
3 G. M. Sheldrick, *SHELXL*-97, *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.

4 C. Tanyeli, E. Turkut and M. Akhmedov, *Tetrahedron Asymmetry*, 2004, **15**, 1729–1733.

^{1}H NMR, 400 MHz, $CDCl_3$



^{19}F NMR, 282 MHz, $CDCl_3$



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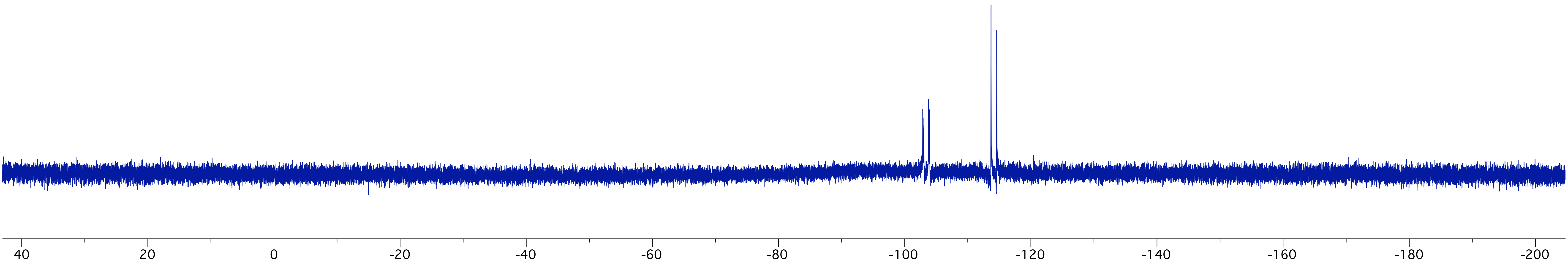
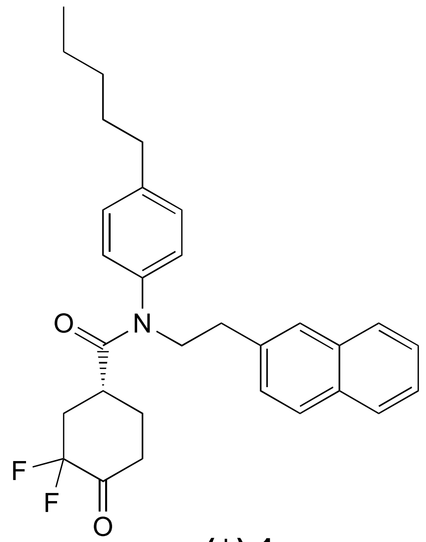


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$



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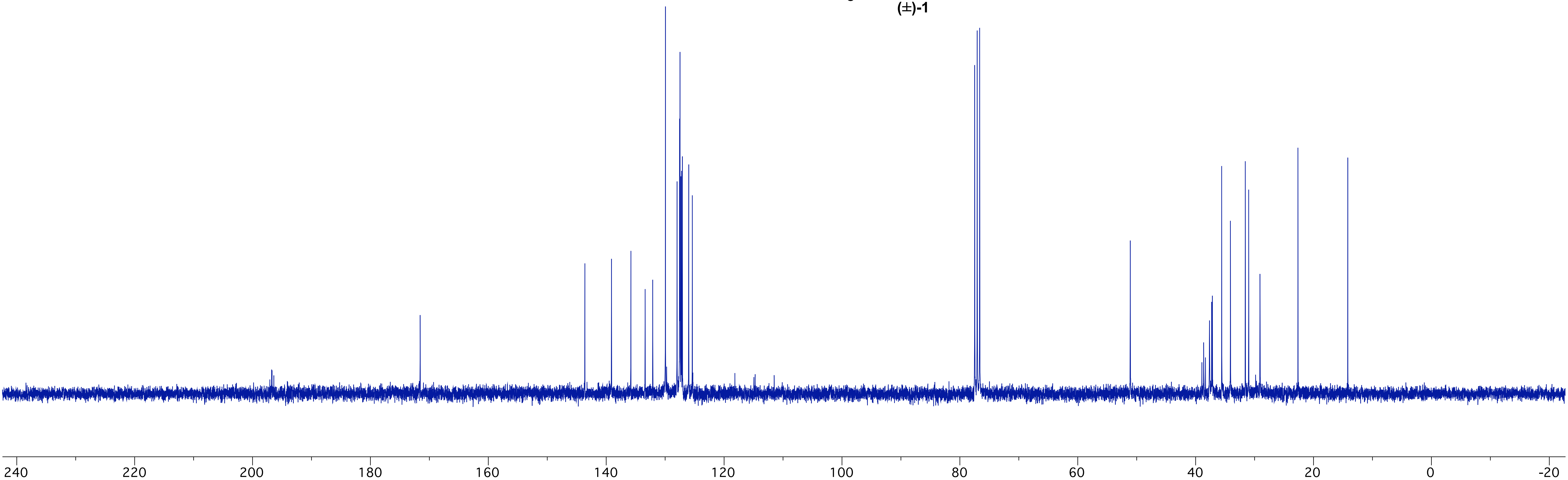
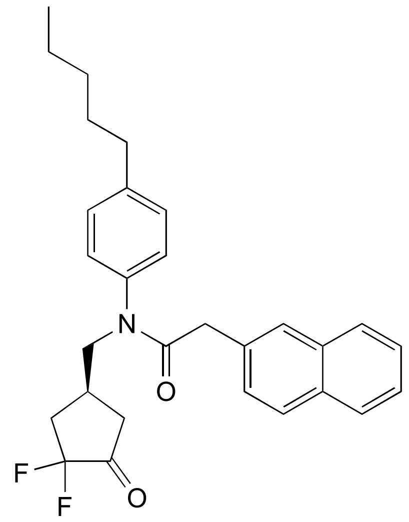


^{1}H NMR, 300 MHz, $CDCl_3$



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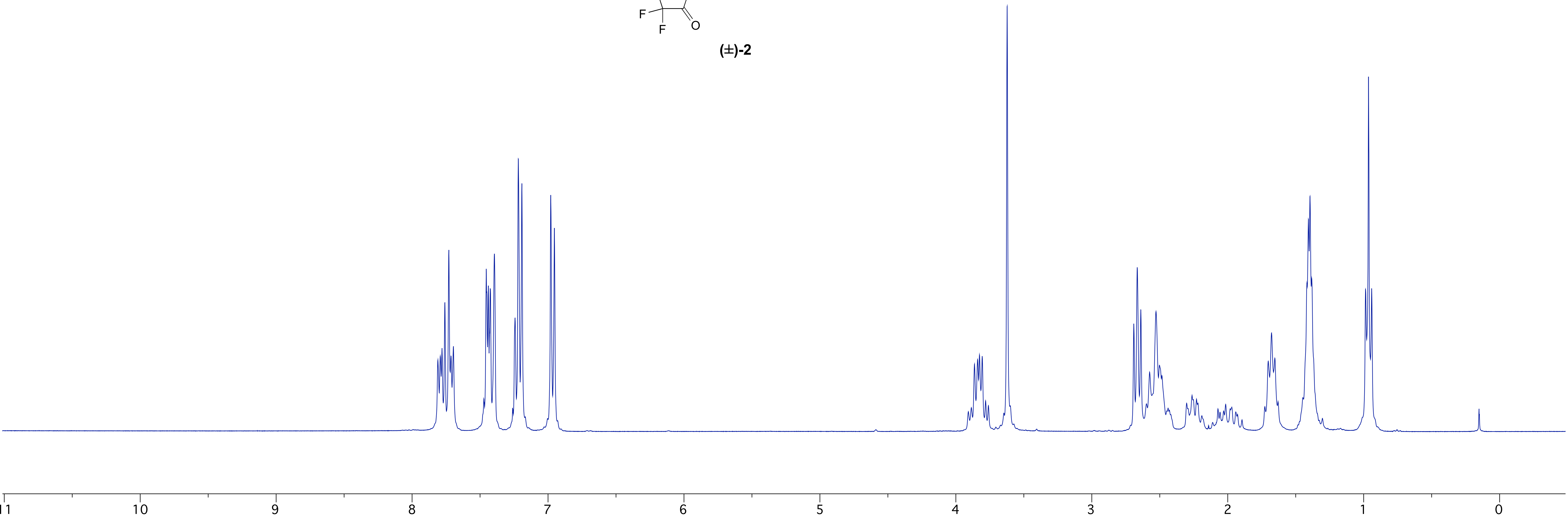
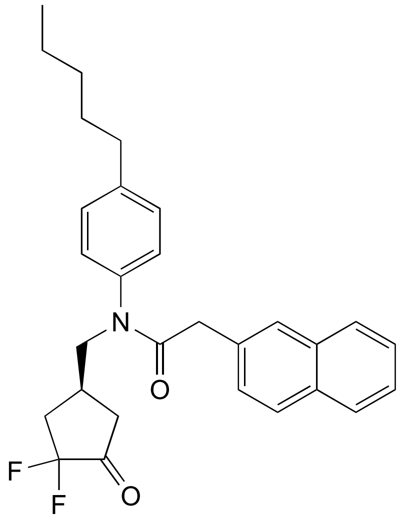


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{19}F NMR, 282 MHz, $CDCl_3$



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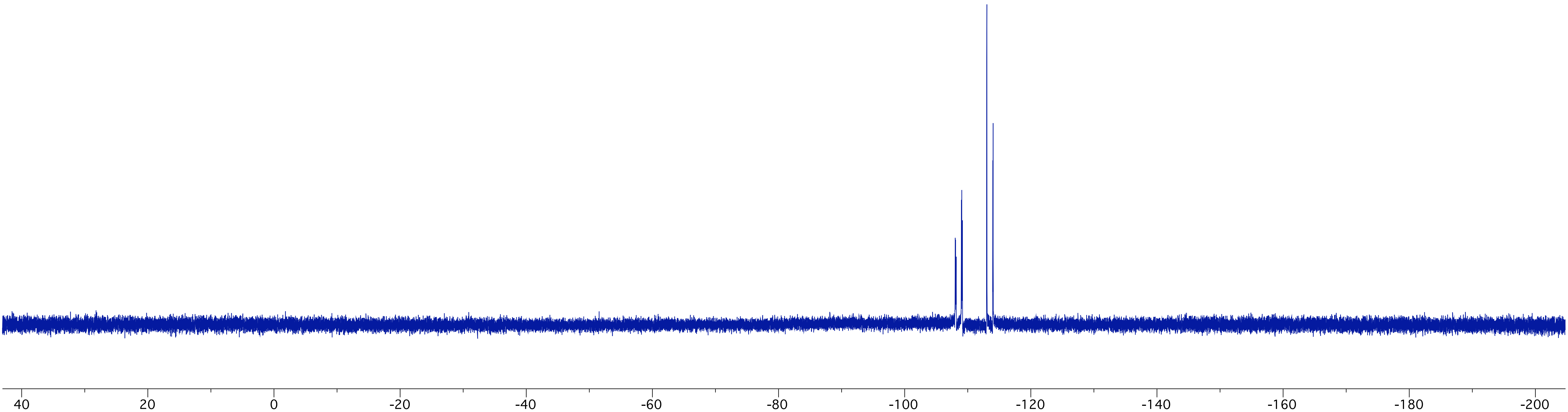
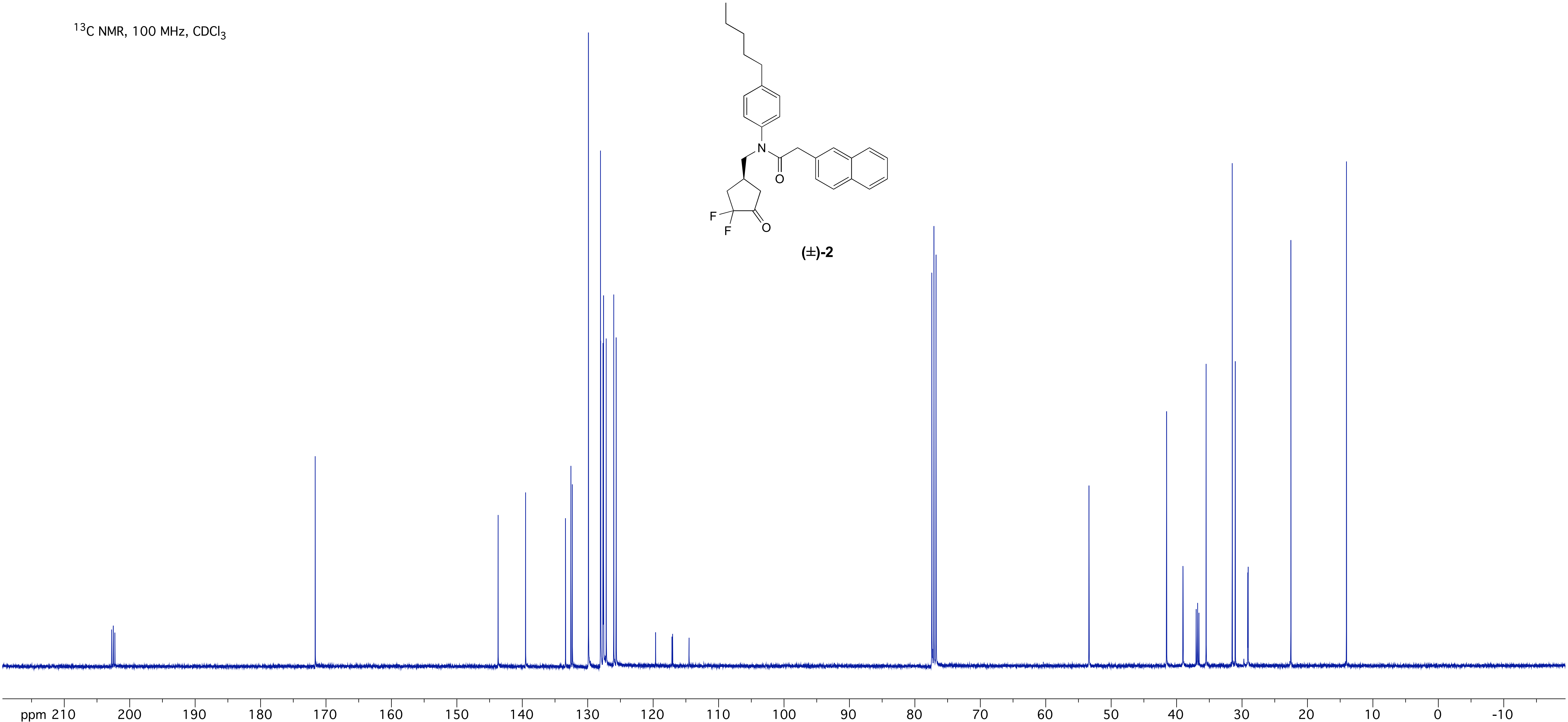
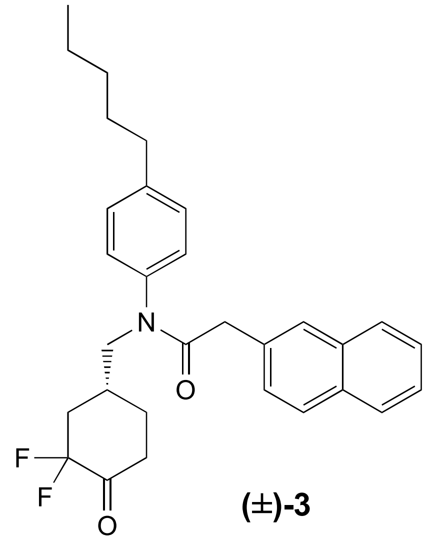


Supplementary Material (ESI) for Organic & Biomolecular Chemistry



^{1}H NMR, 300 MHz, $CDCl_3$



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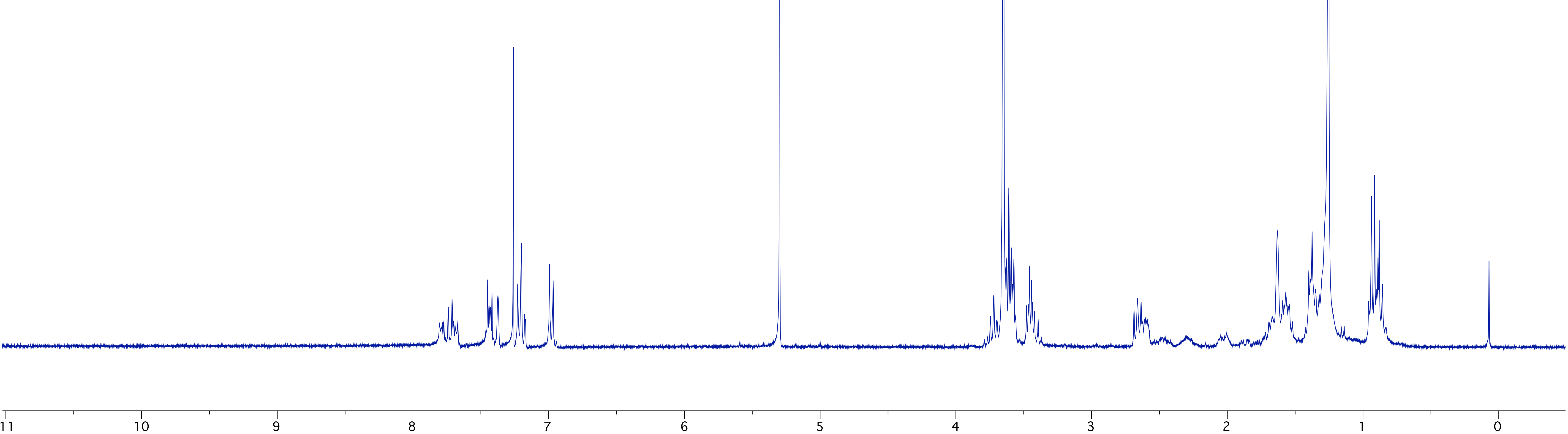
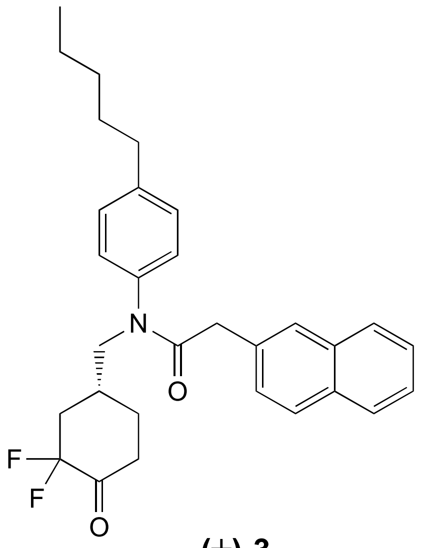


^{19}F NMR, 282 MHz, $CDCl_3$



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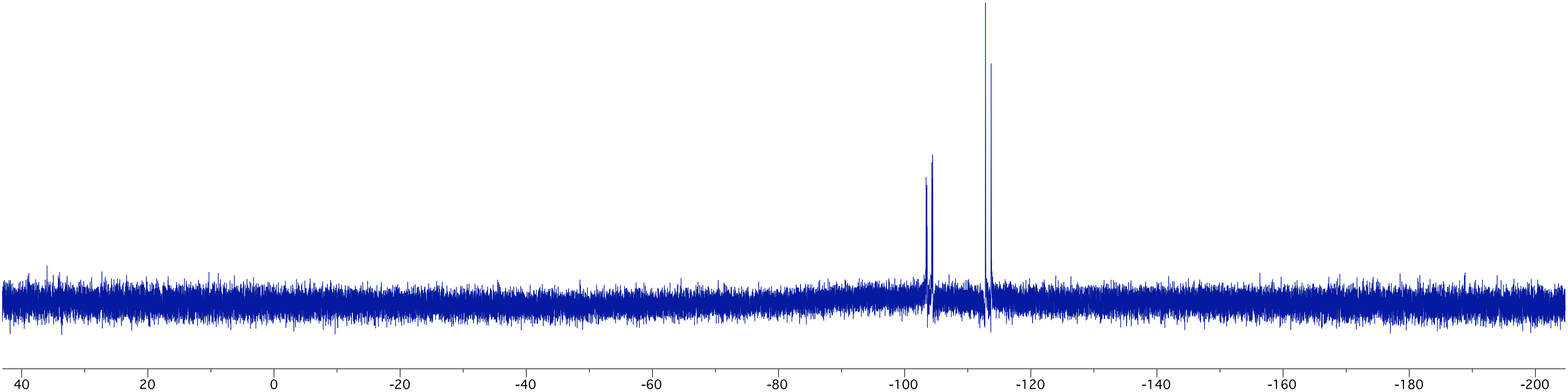
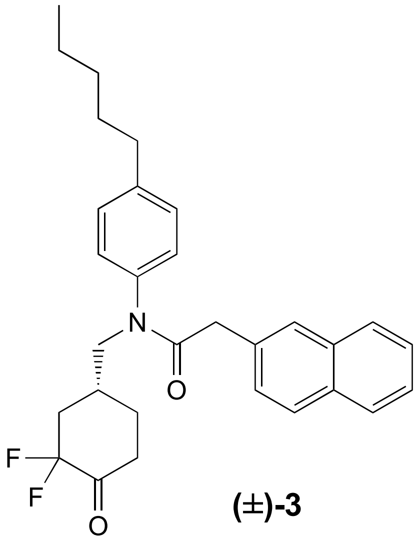


^{13}C NMR, 75 MHz, $CDCl_3$



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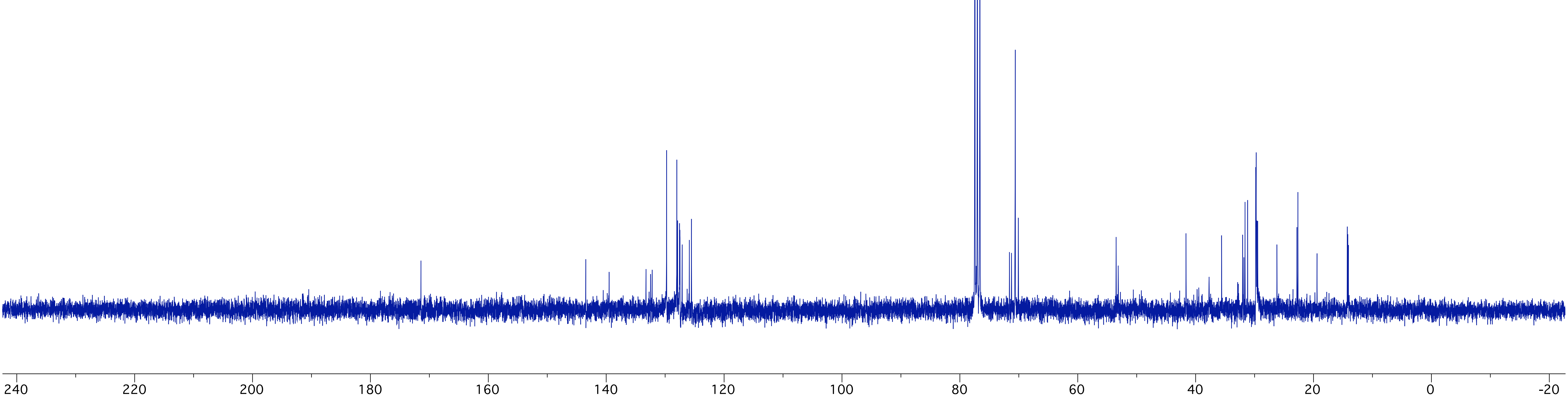
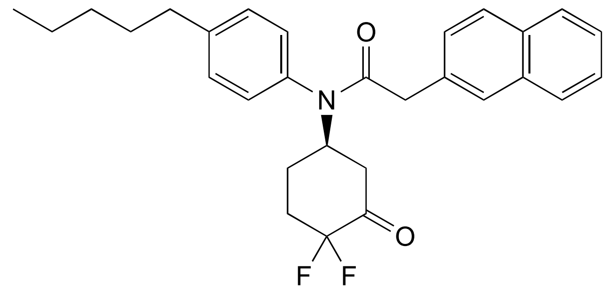


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 400 MHz, $CDCl_3$



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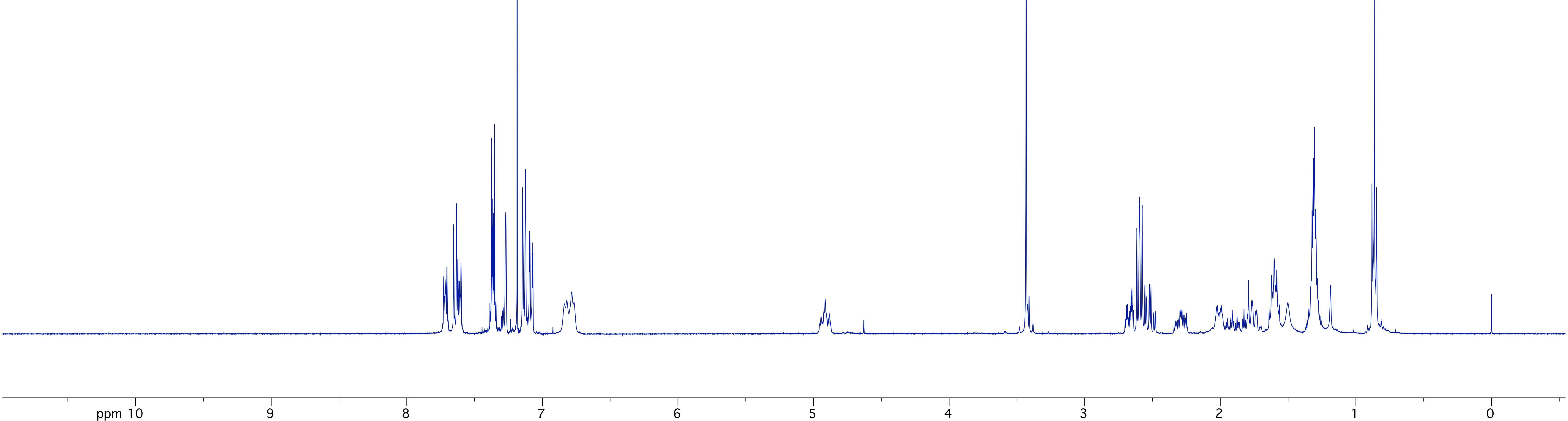
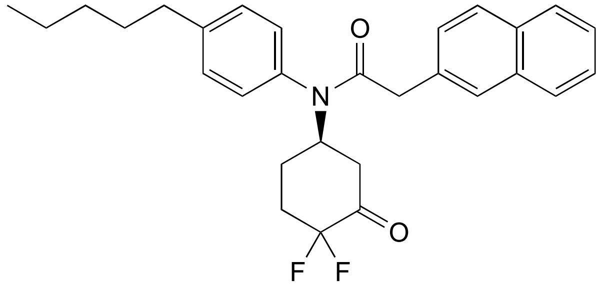


^{19}F NMR, 376 MHz, $CDCl_3$



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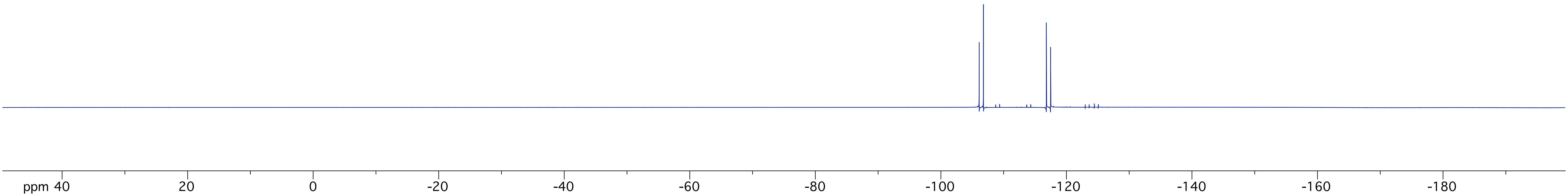
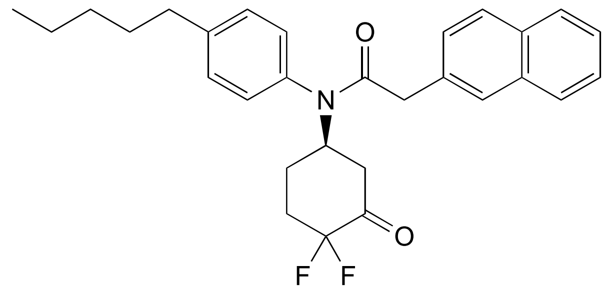


^{13}C NMR, 100 MHz, $CDCl_3$



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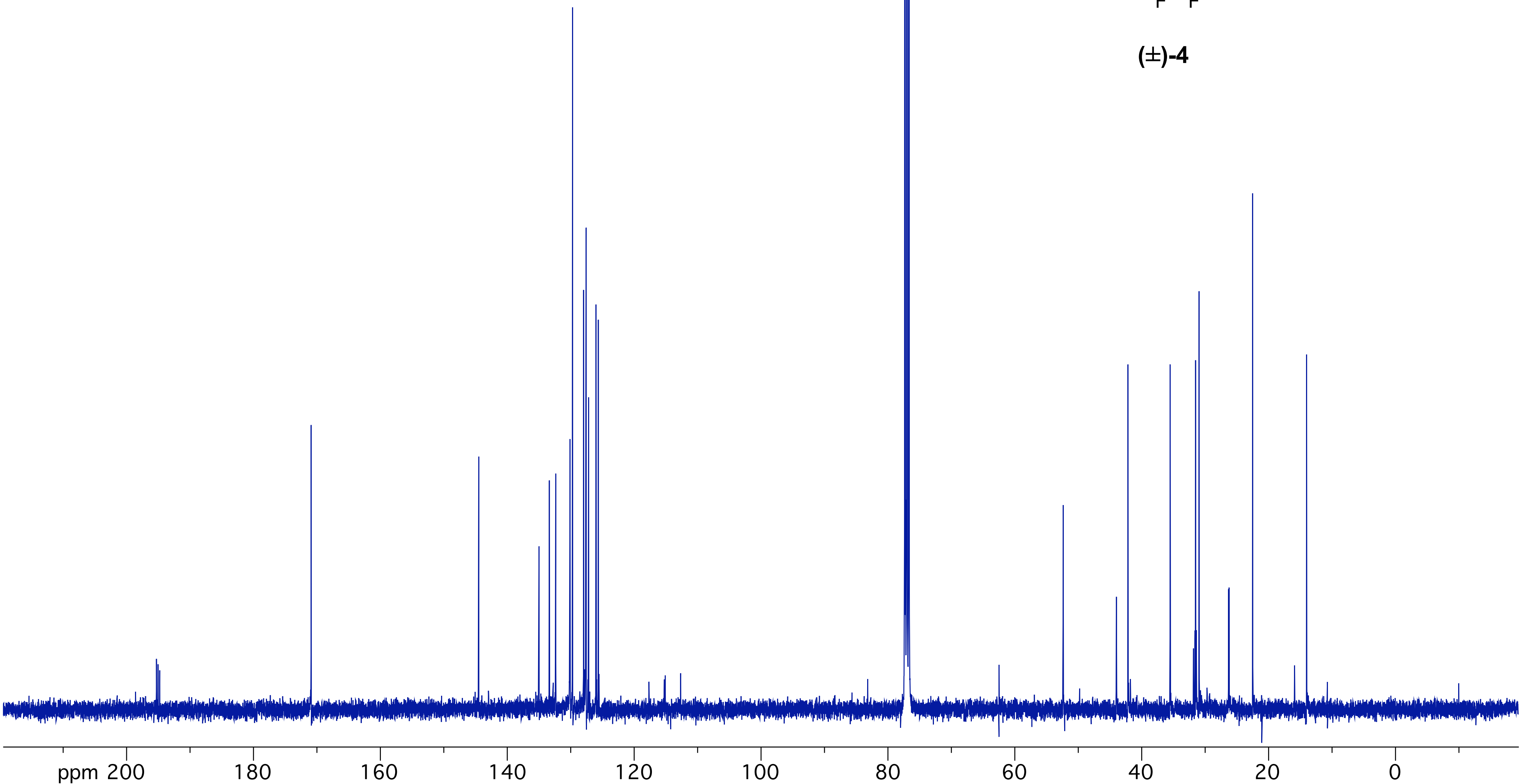
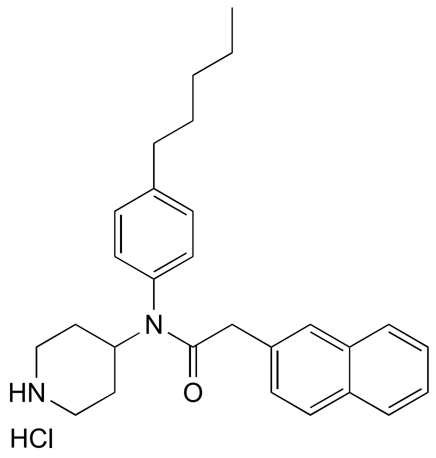


^{1}H NMR, 300 MHz, $CDCl_3$



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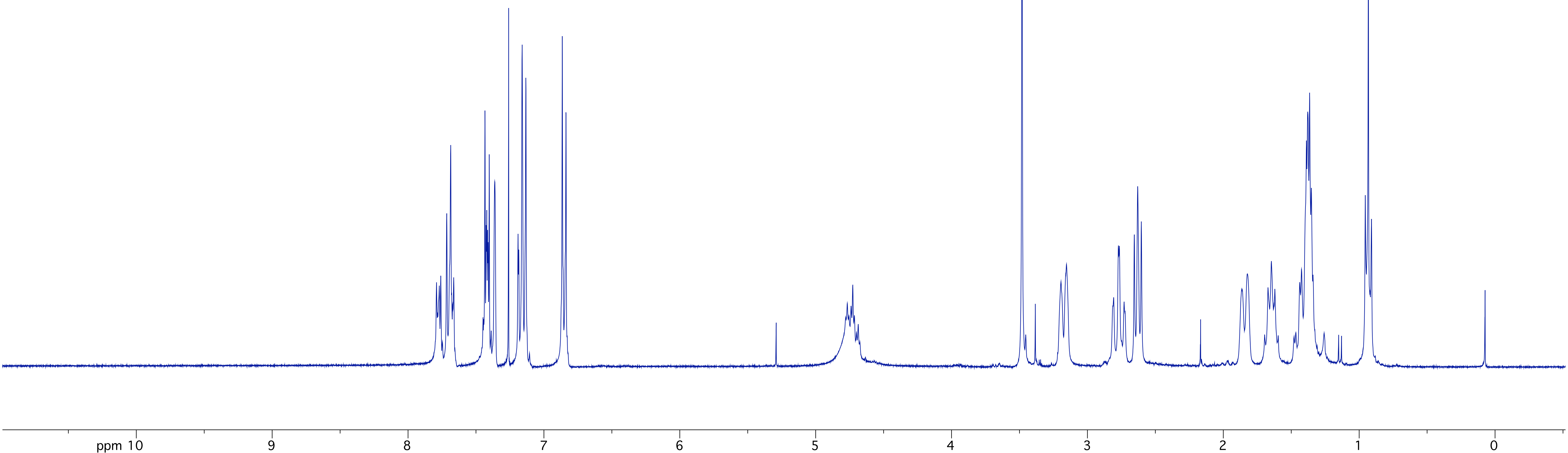
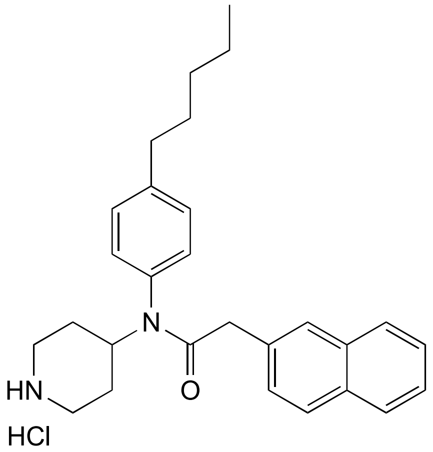


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$



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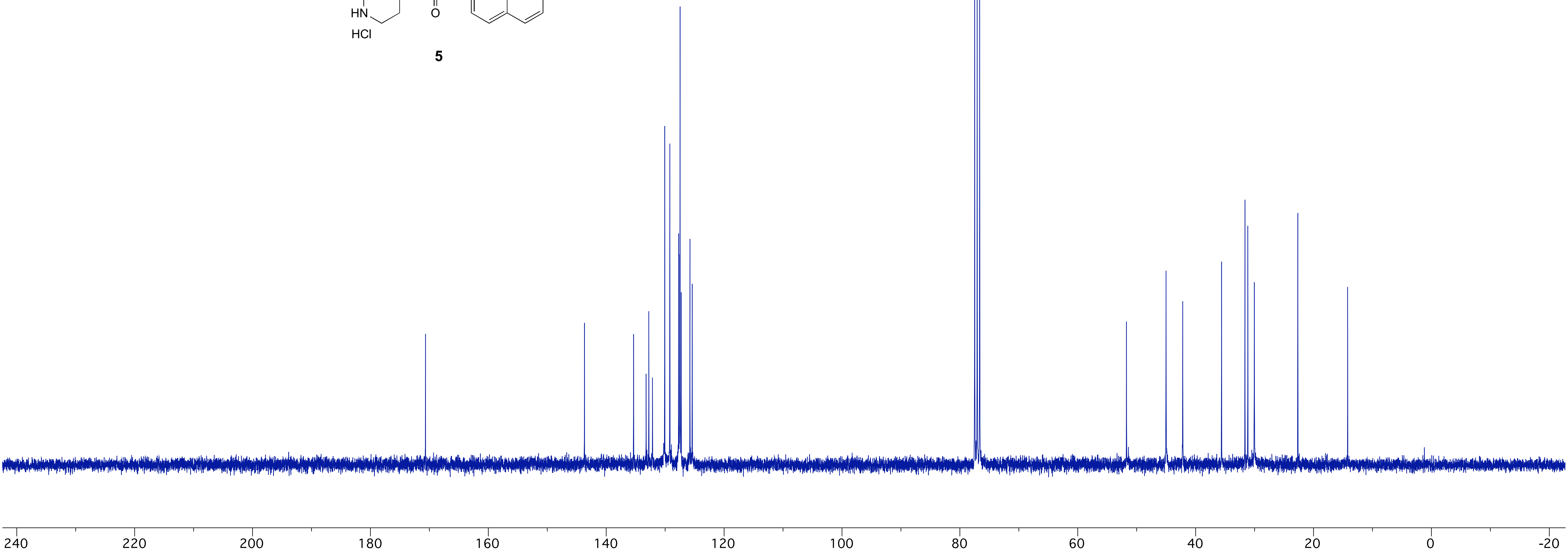
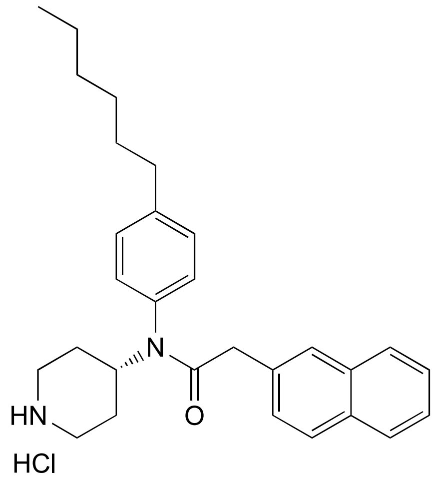


^{1}H NMR, 400 MHz, $CDCl_3$



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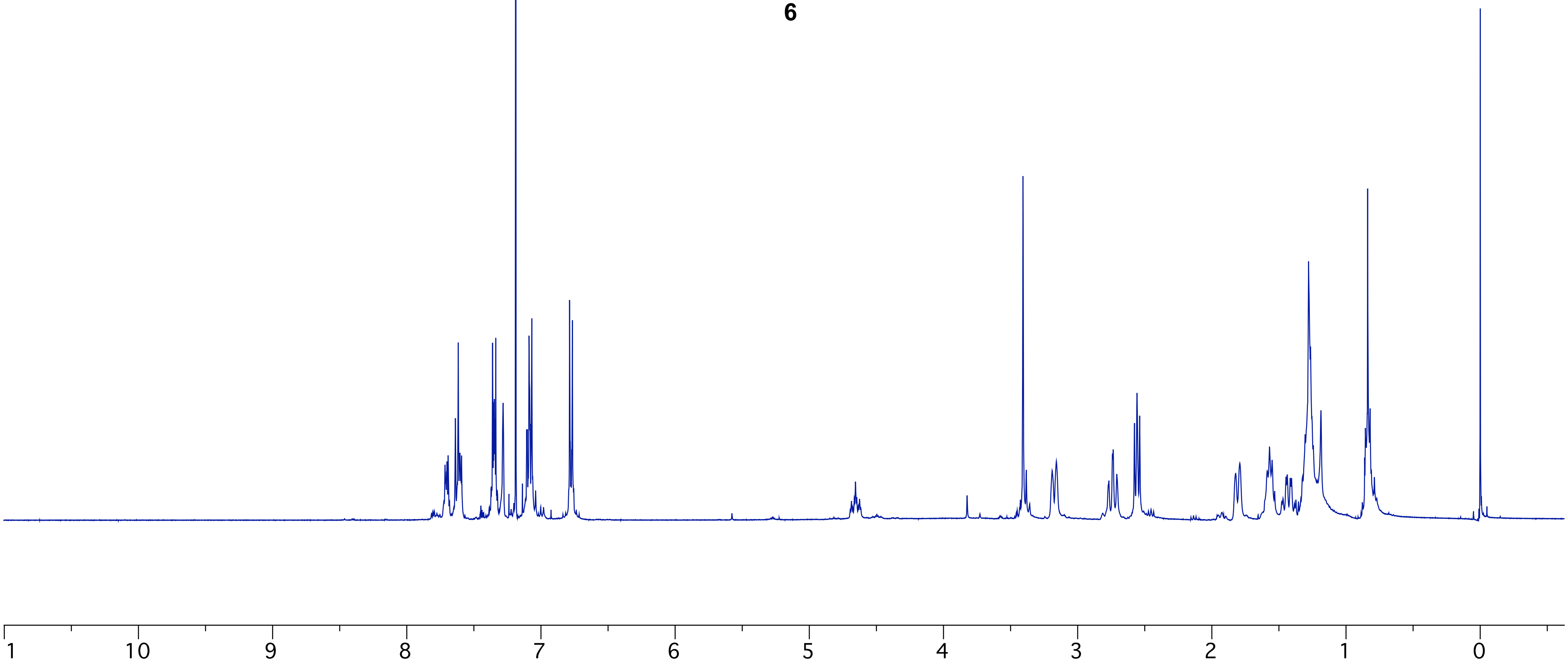
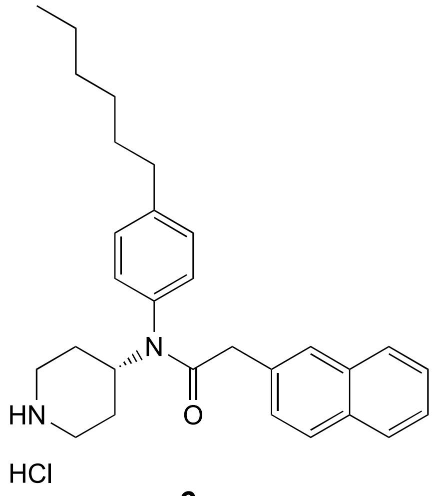
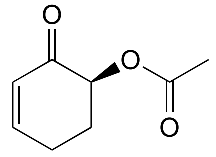


^{13}C NMR, 75 MHz, $CDCl_3$



6

^{1}H NMR, 300 MHz, $CDCl_3$



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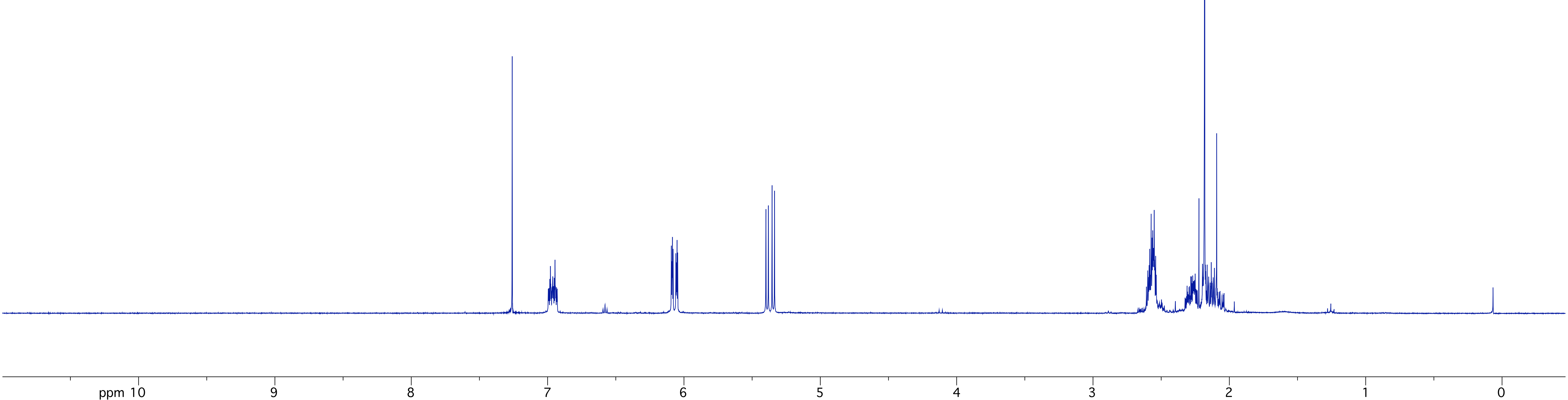
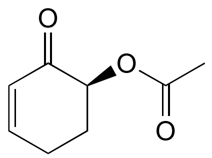


^{13}C NMR, 75 MHz, $CDCl_3$



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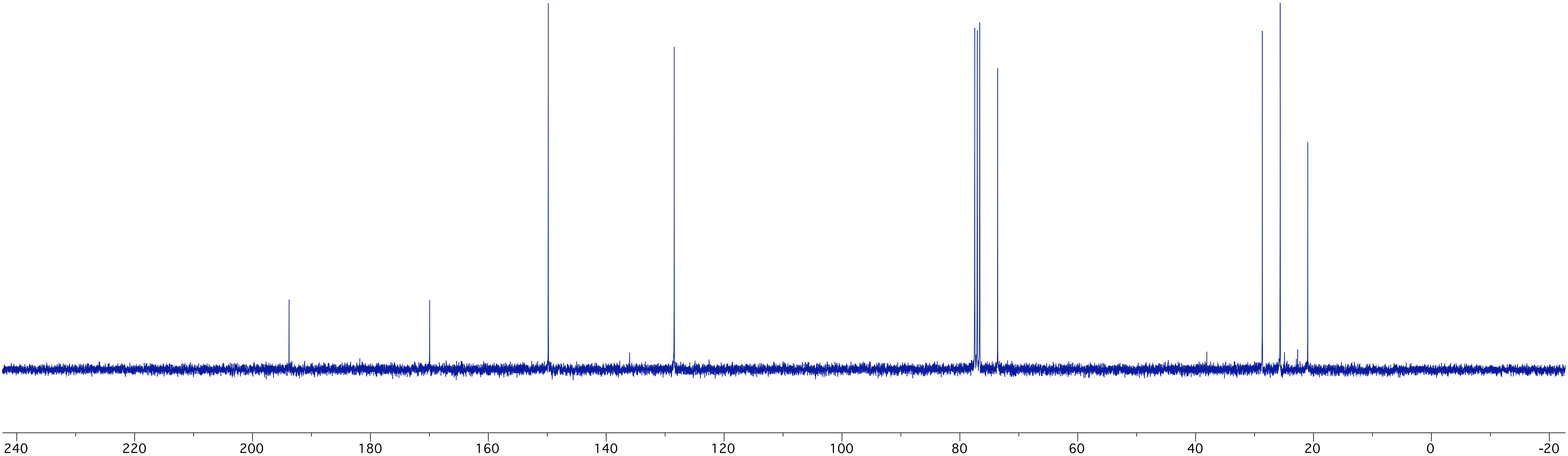
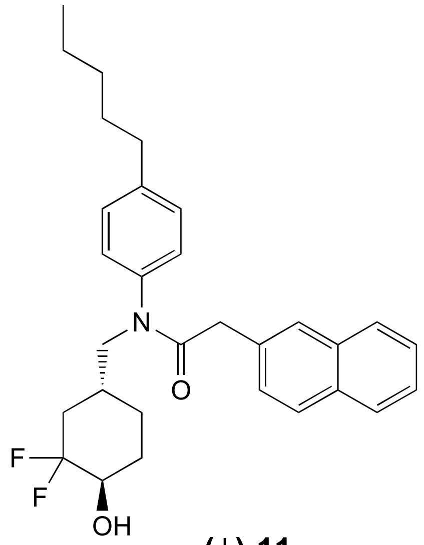


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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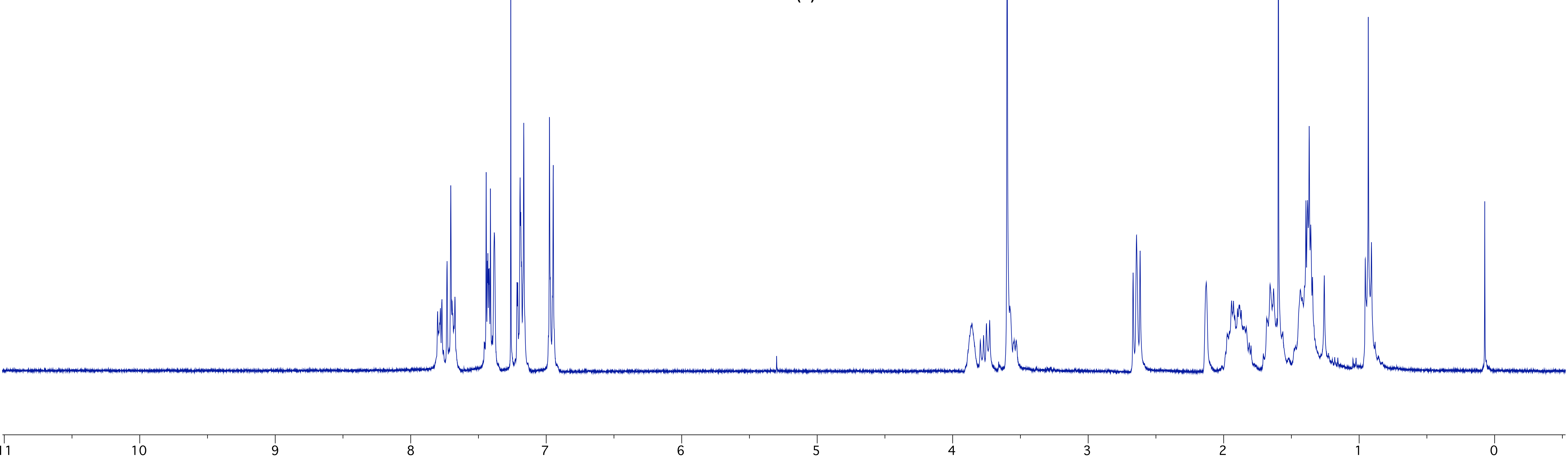
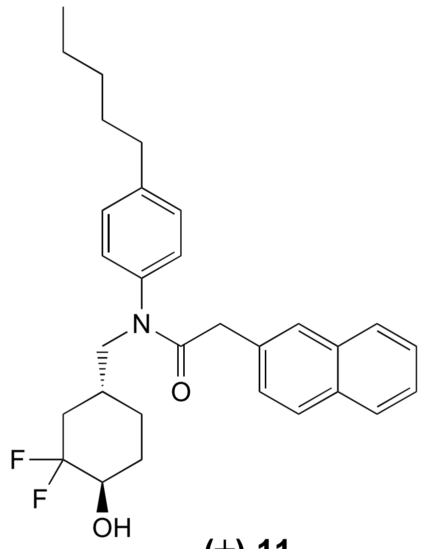


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{19}F NMR, 282 MHz, $CDCl_3$



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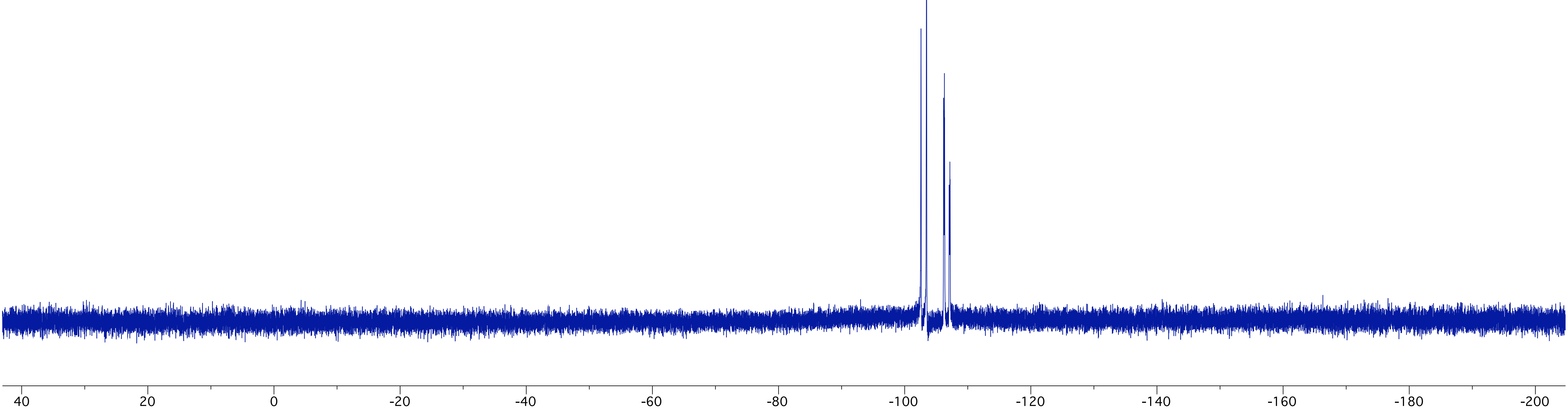
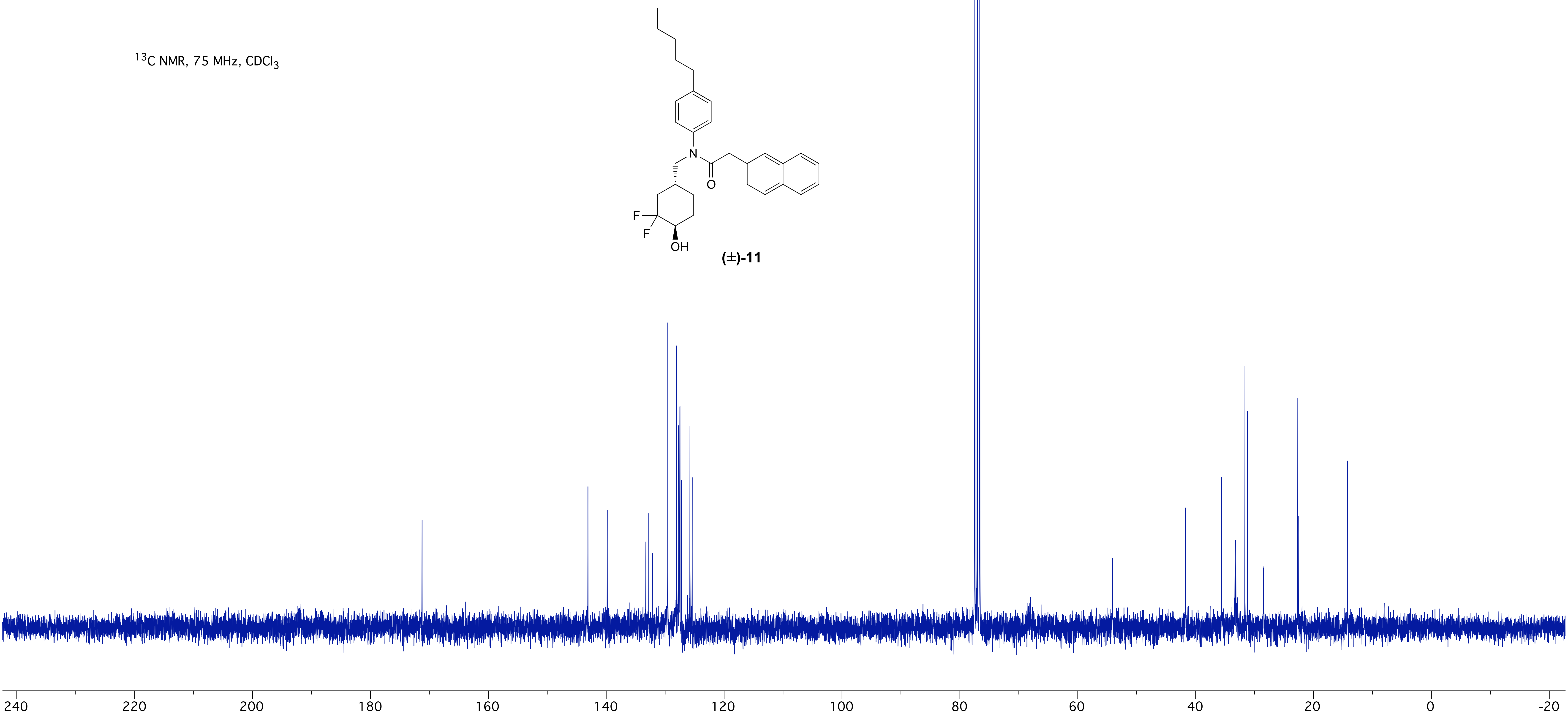
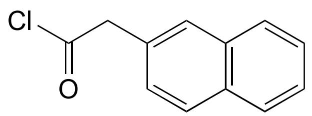



^{13}C NMR, 75 MHz, $CDCl_3$
F
F
N
O
OH
(±)-11
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

^{1}H NMR, 300 MHz, $CDCl_3$



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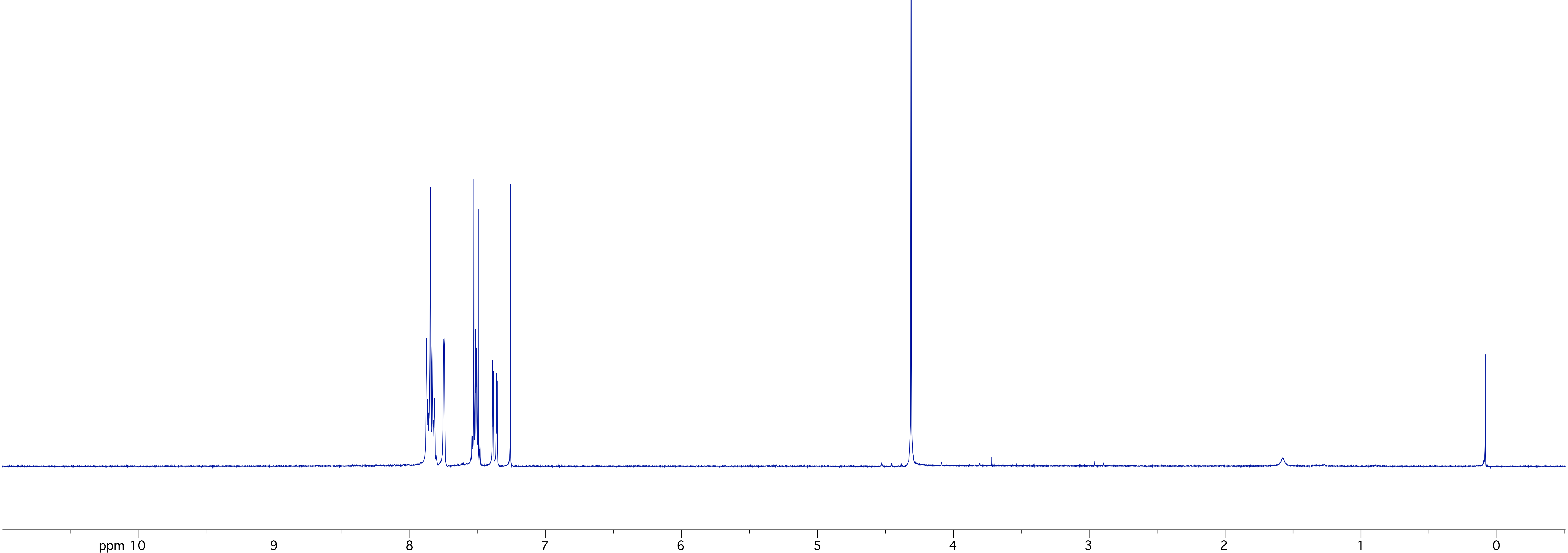
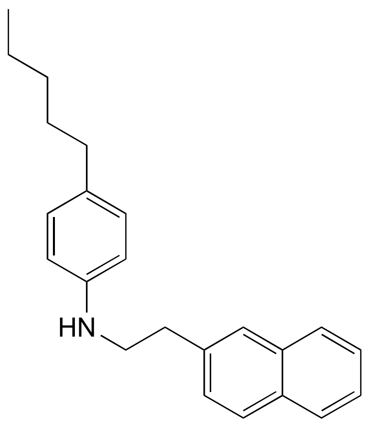


^{1}H NMR, 300 MHz, $CDCl_3$



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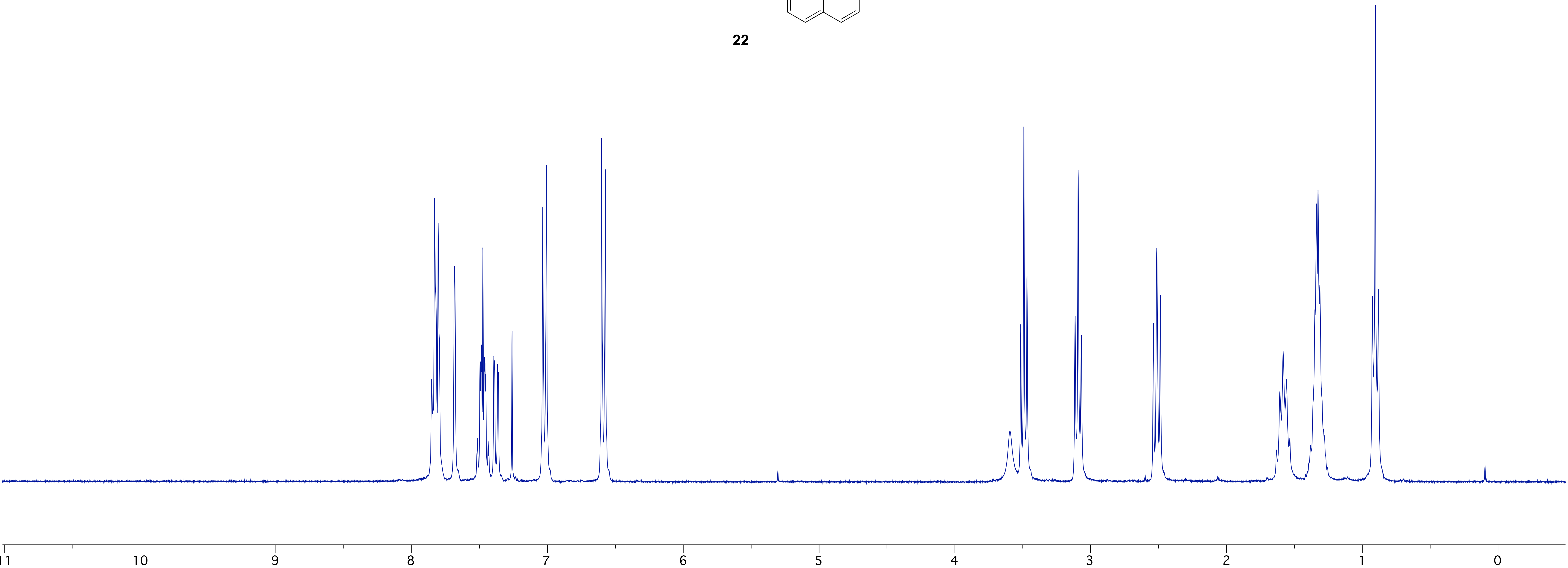
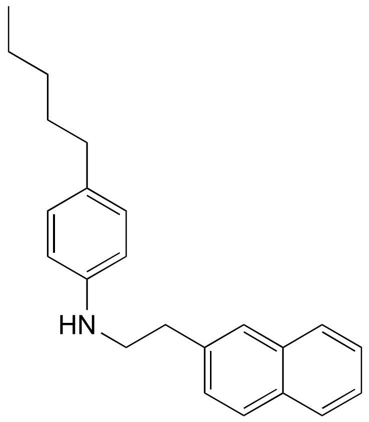


^{13}C NMR, 75 MHz, $CDCl_3$



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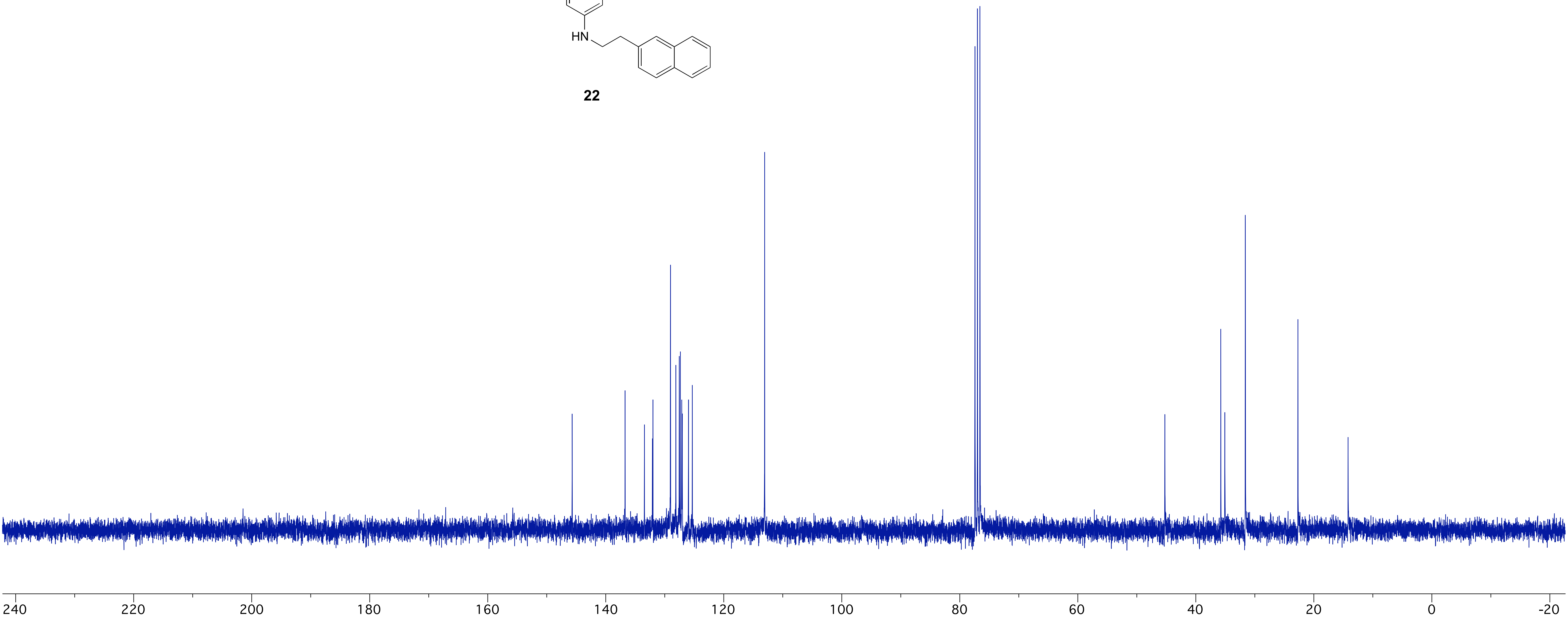
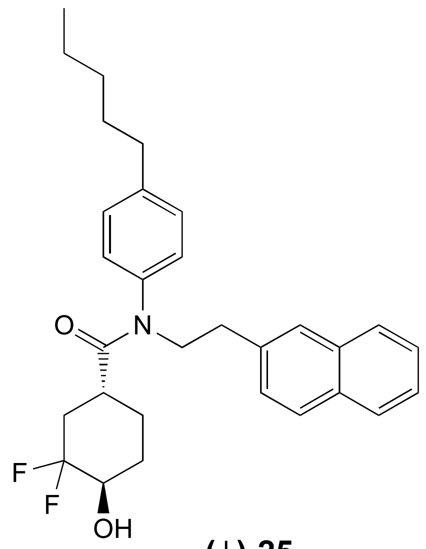


^1H NMR, 300 MHz, $CDCl_3$



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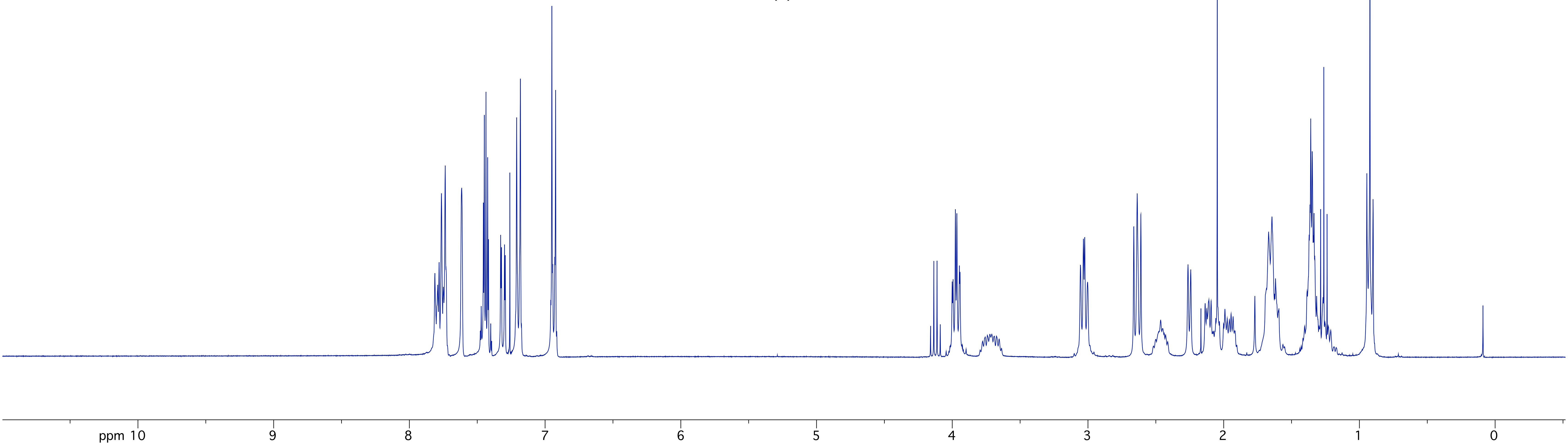
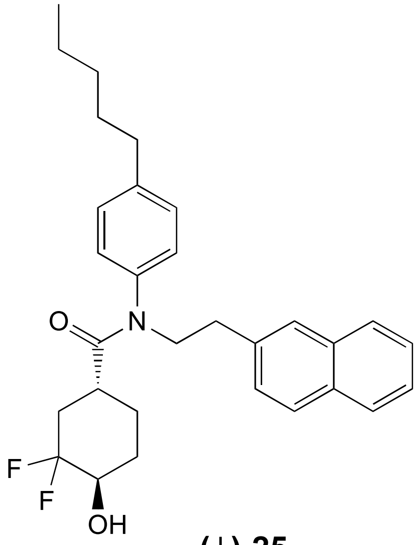


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{19}F NMR, 282 MHz, $CDCl_3$



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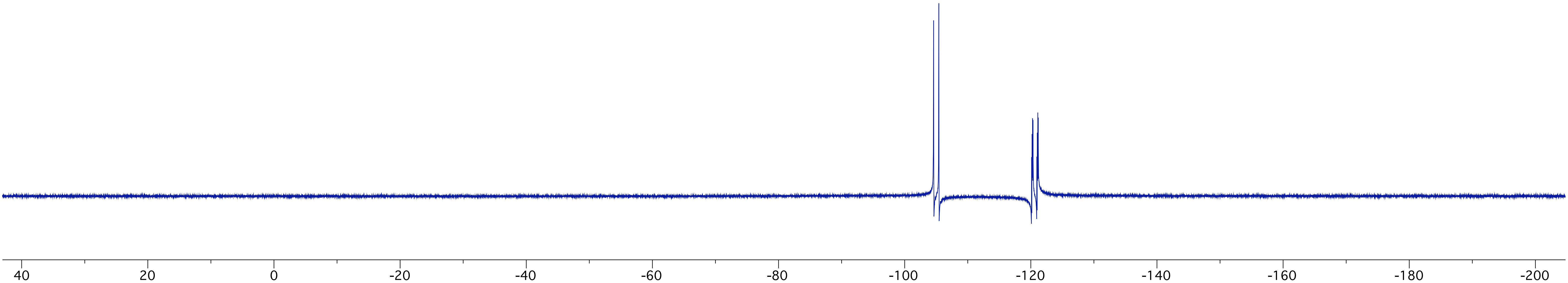
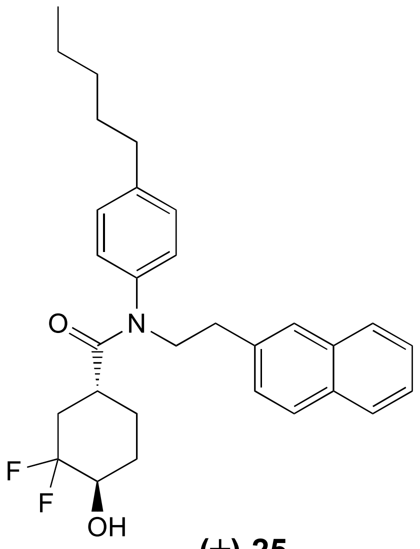


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$



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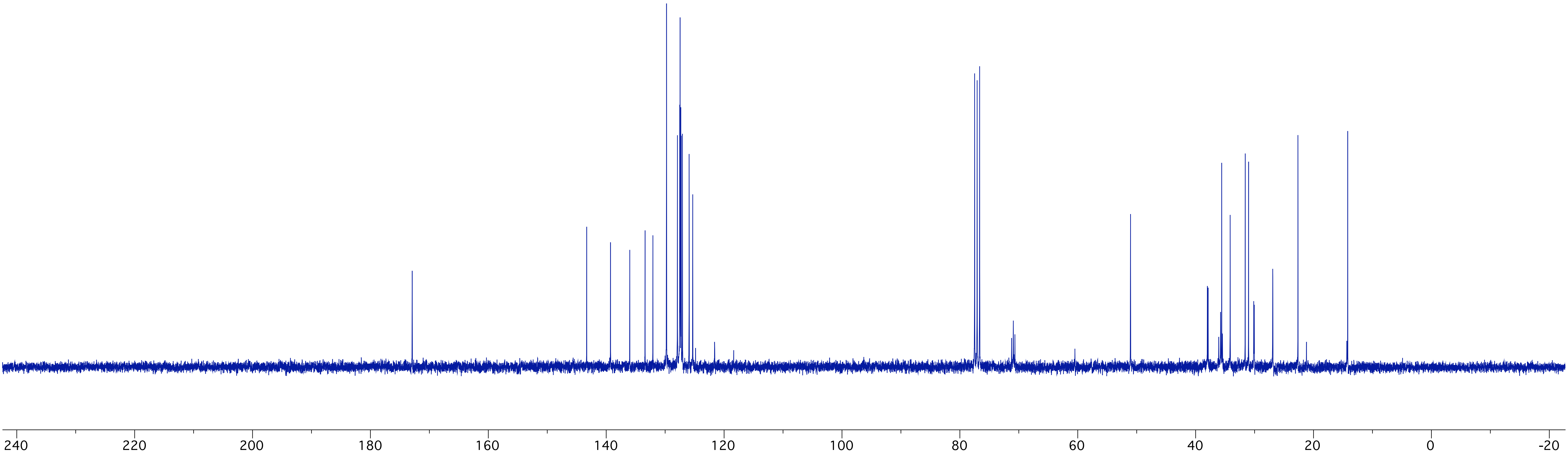
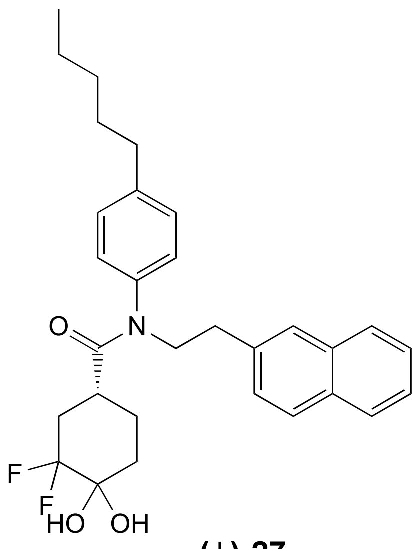


^{1}H NMR, 300 MHz, $CDCl_3$



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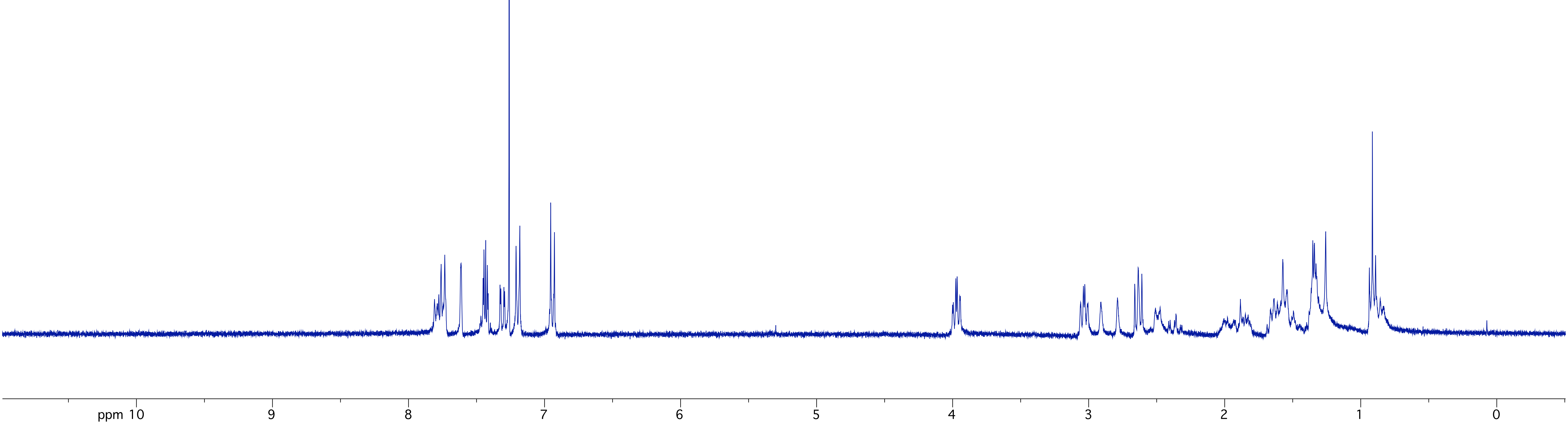
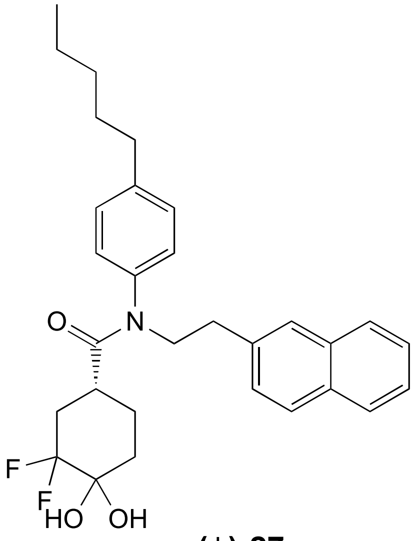
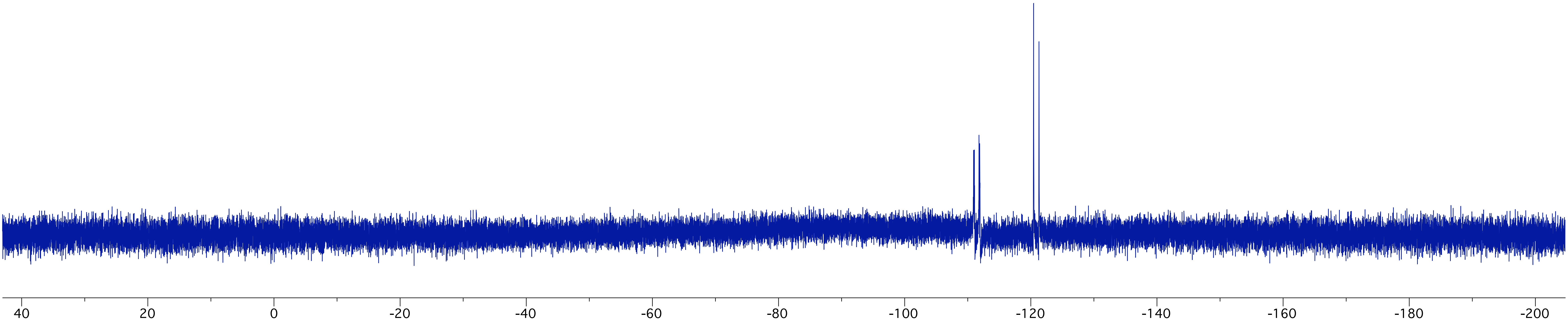


^{19}F NMR, 282 MHz, $CDCl_3$

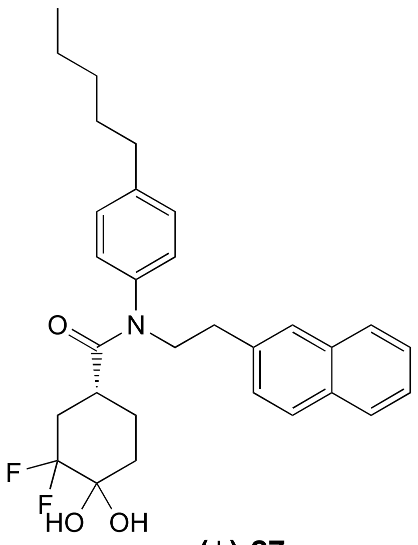


(±)-27



Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$



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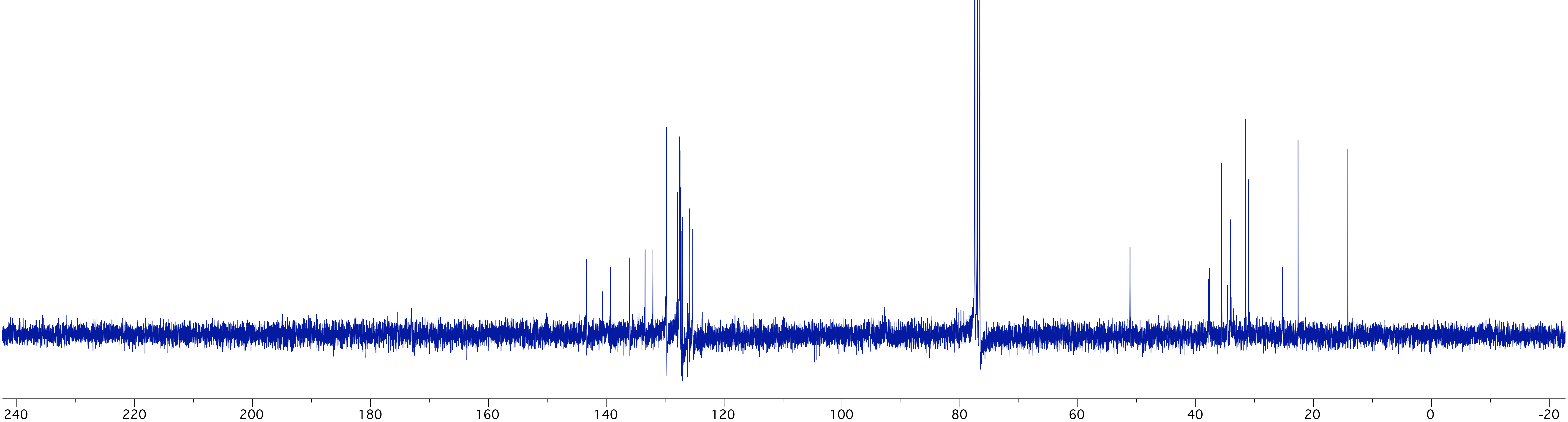
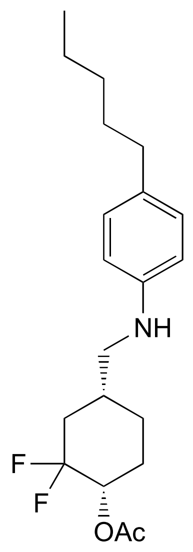


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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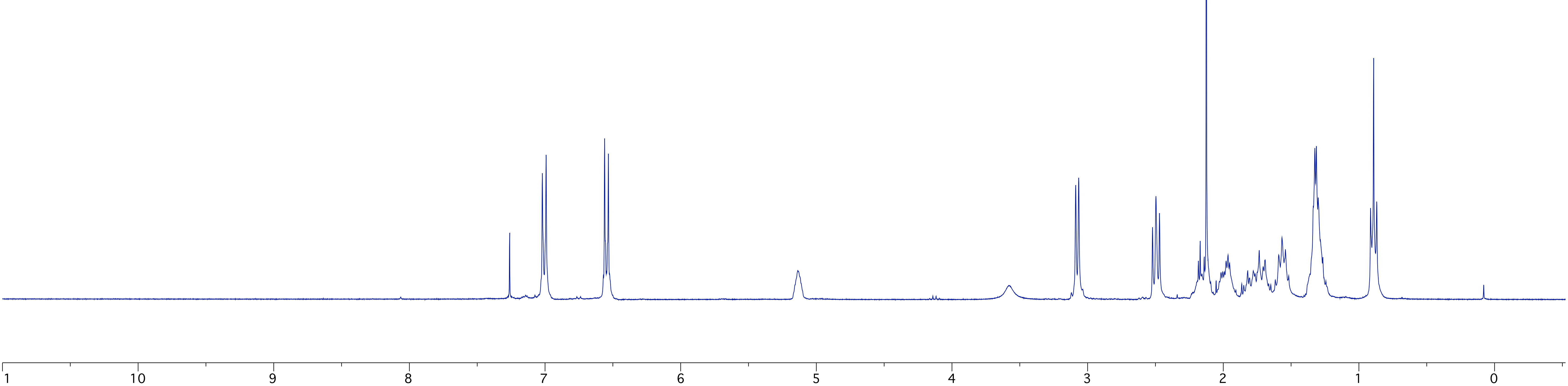
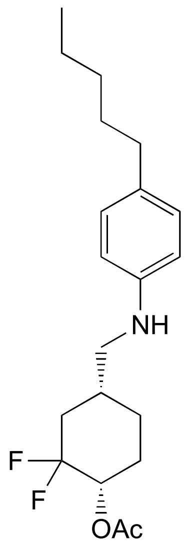
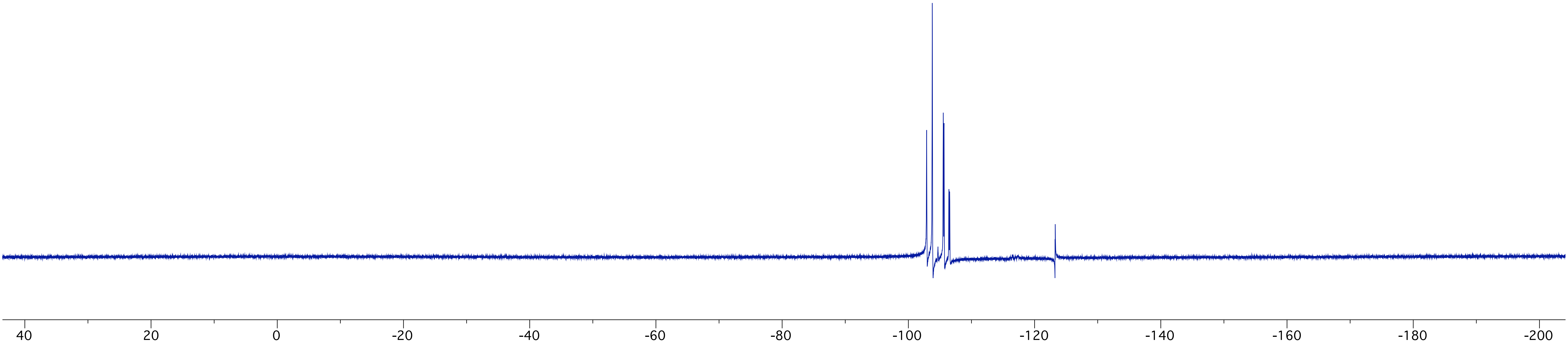


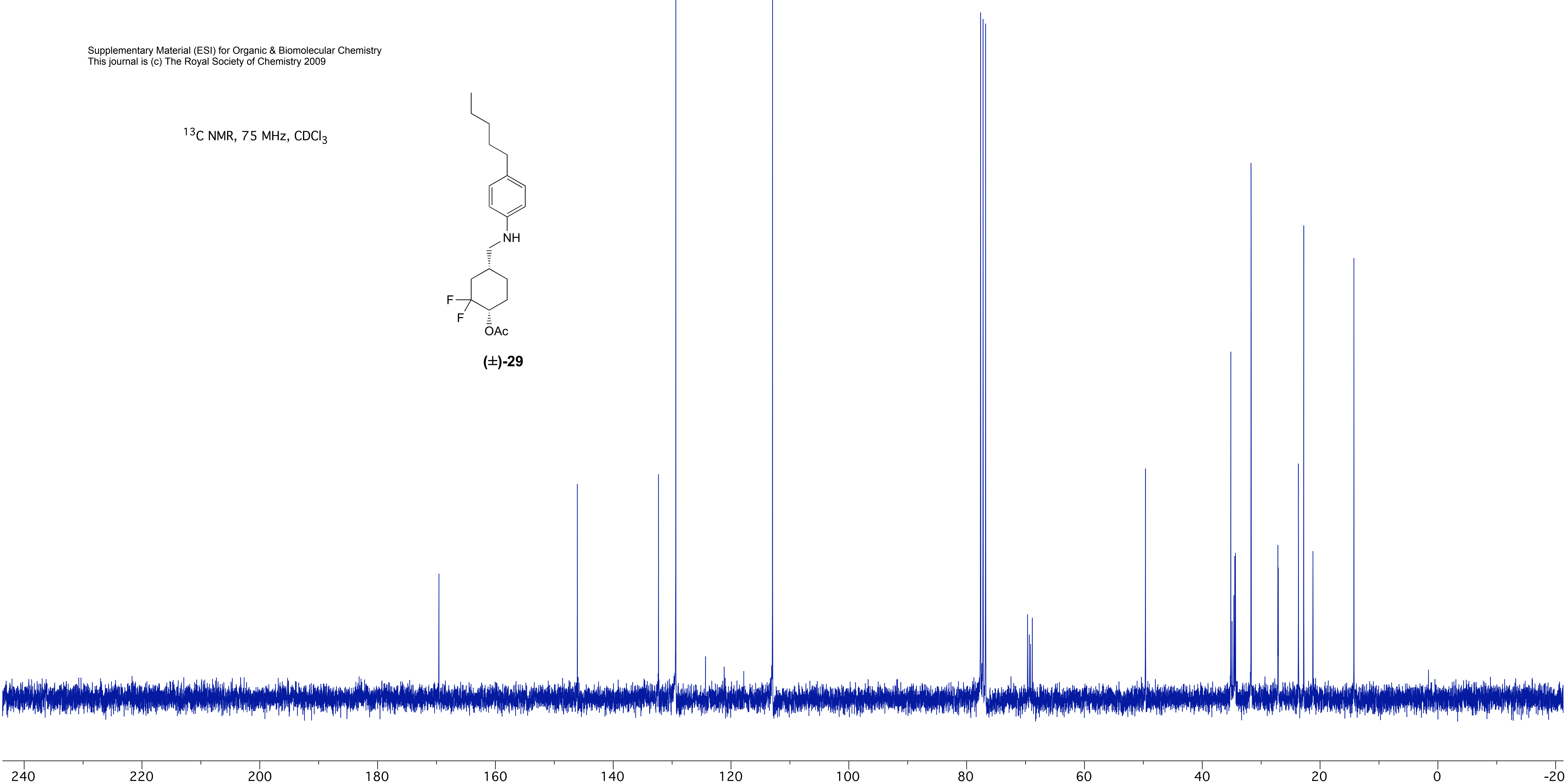
^{19}F NMR, 282 MHz, $CDCl_3$



(±)-29



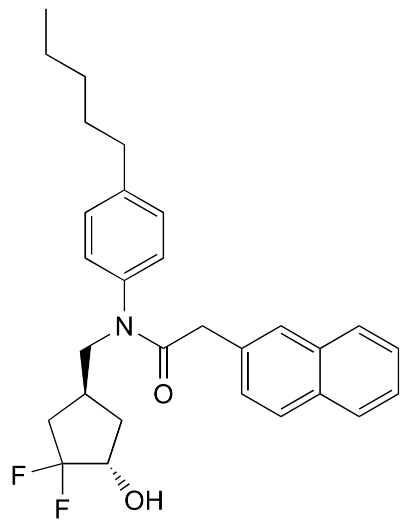
^{13}C NMR, 75 MHz, $CDCl_3$



(±)-29

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^1H NMR, 300 MHz, $CDCl_3$



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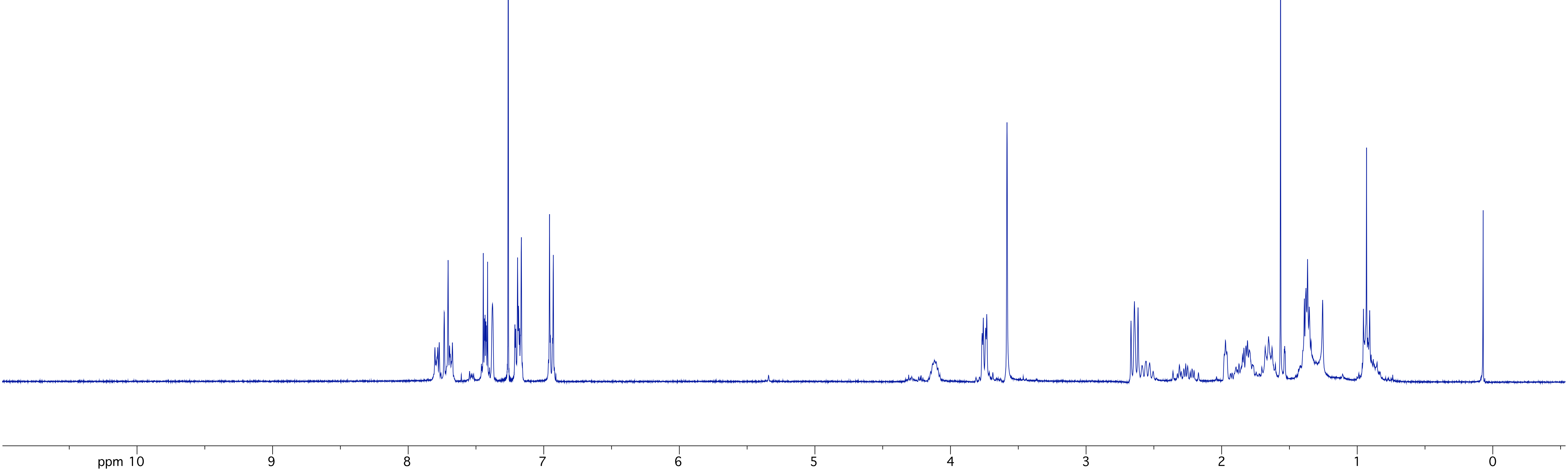
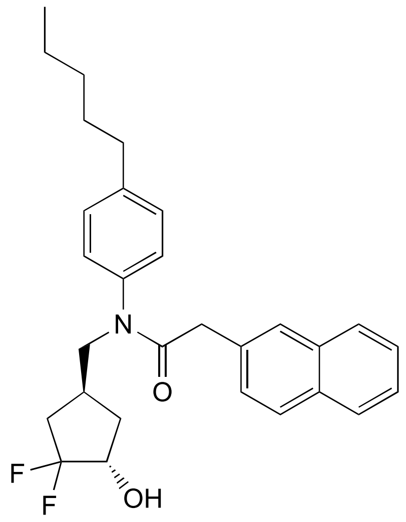
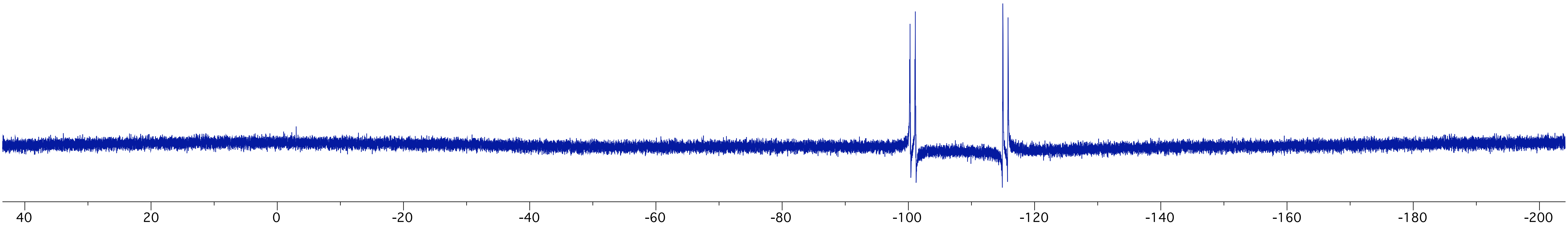


^{19}F NMR, 282 MHz, $CDCl_3$

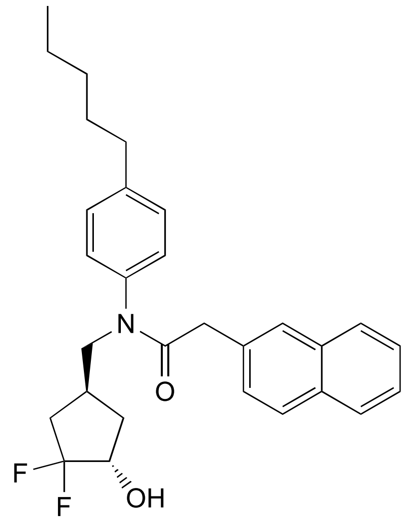


(±)-33



Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$



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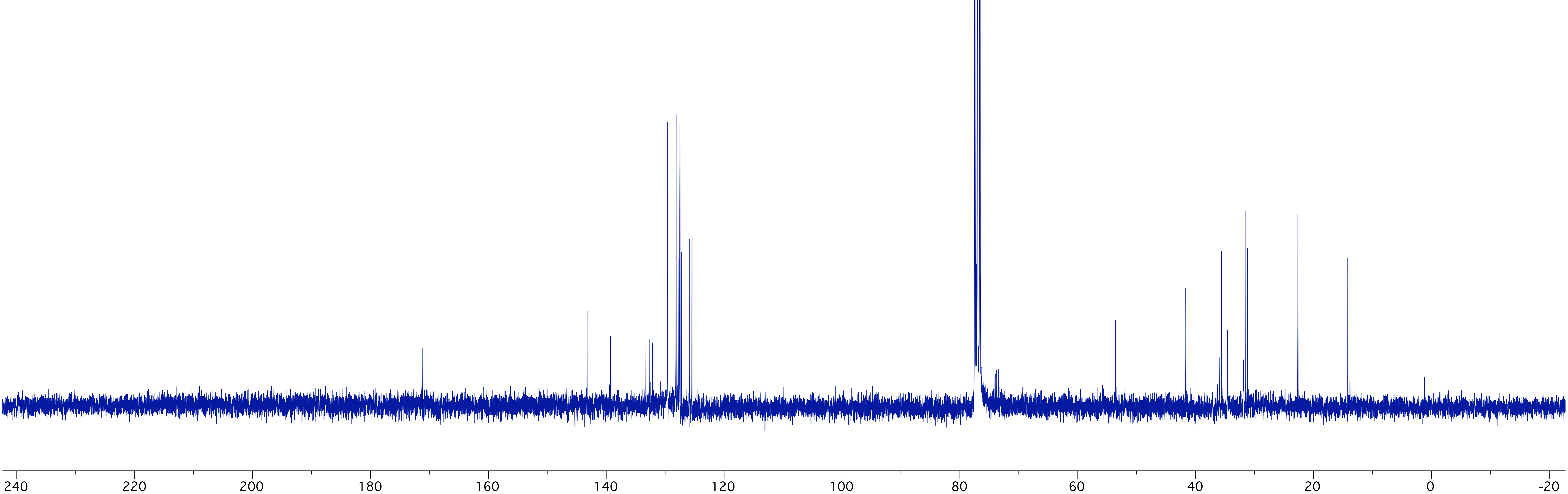
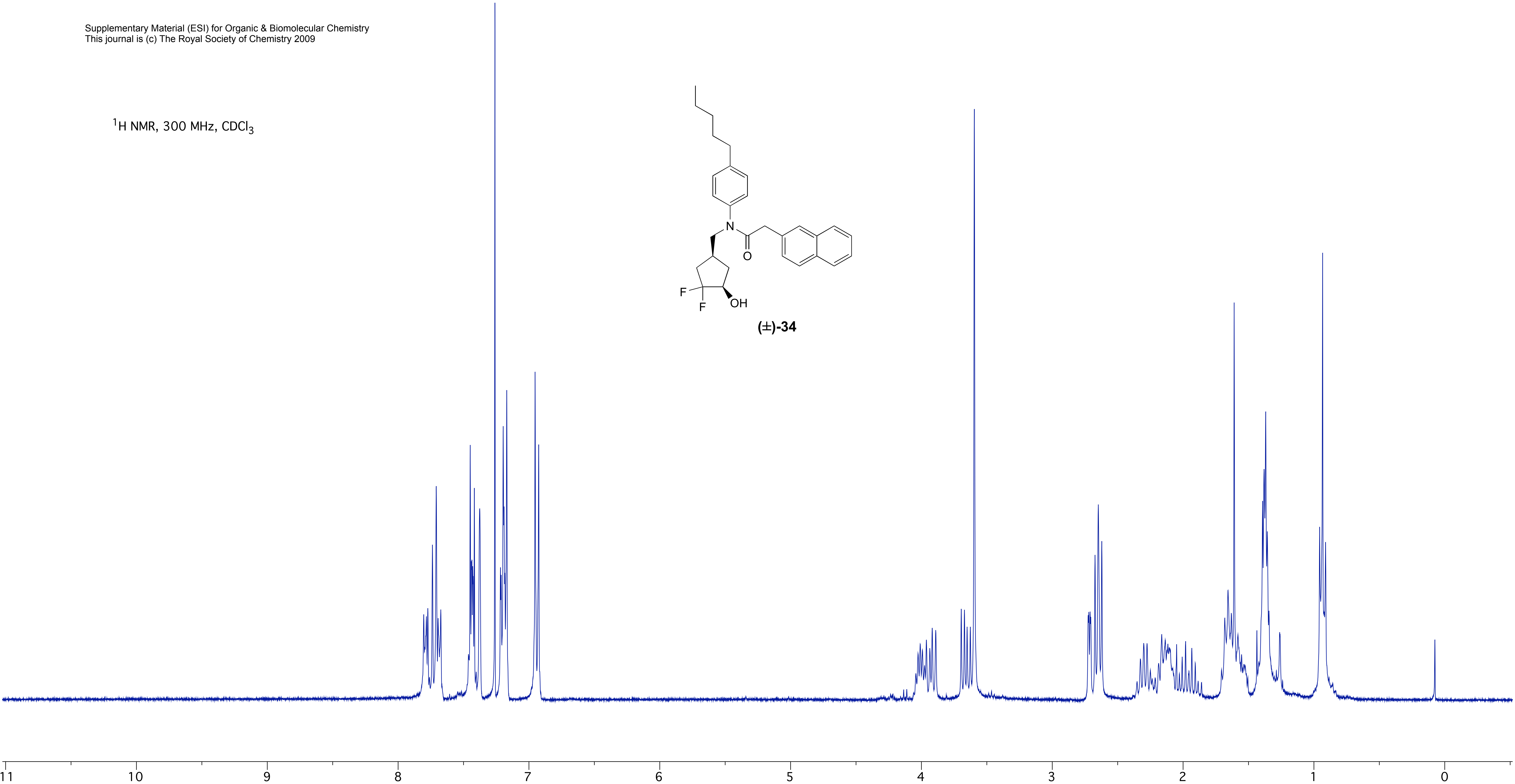


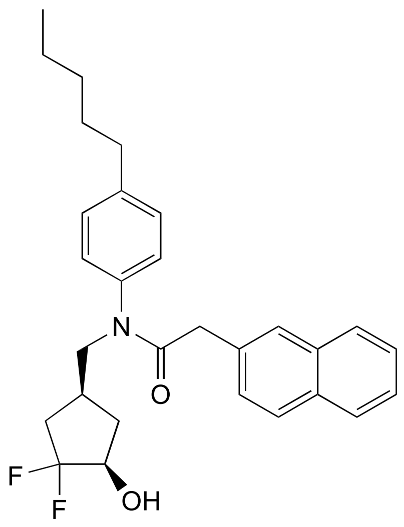
^{1}H NMR, 300 MHz, $CDCl_3$



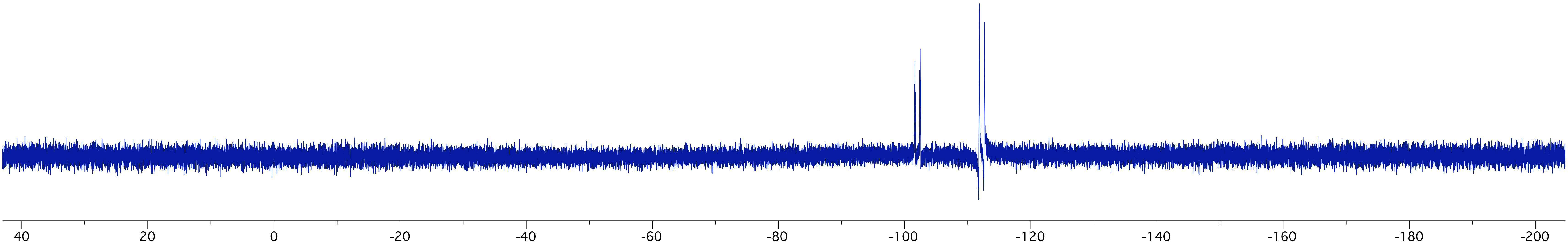
(±)-34

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

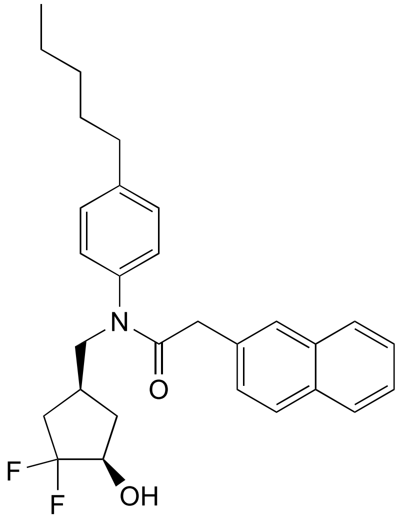
^{19}F NMR, 282 MHz, $CDCl_3$



(±)-34



^{13}C NMR, 75 MHz, $CDCl_3$



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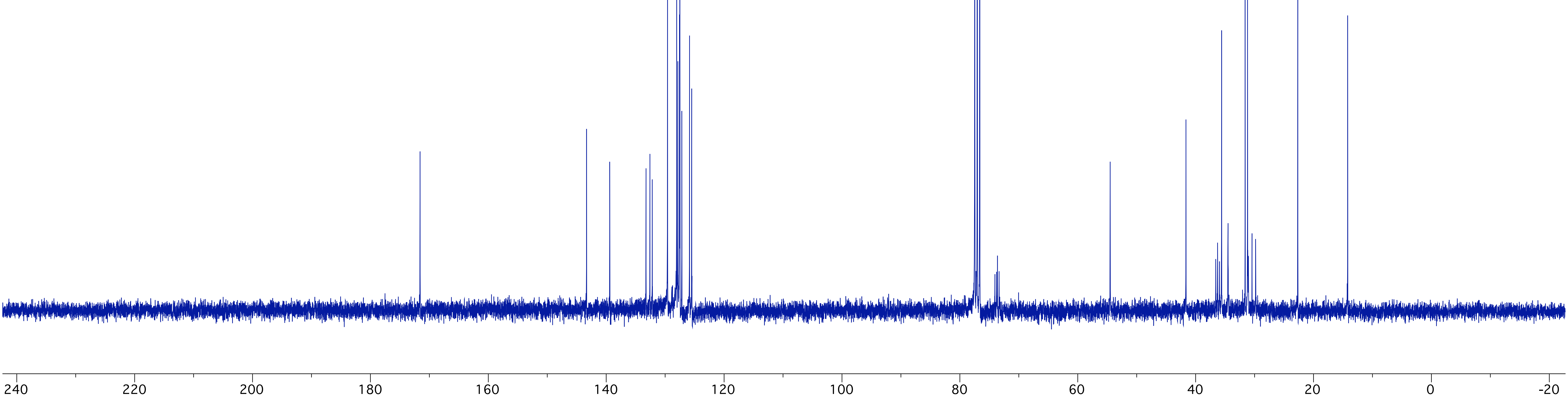
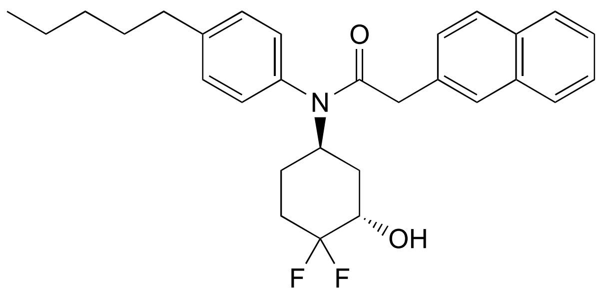


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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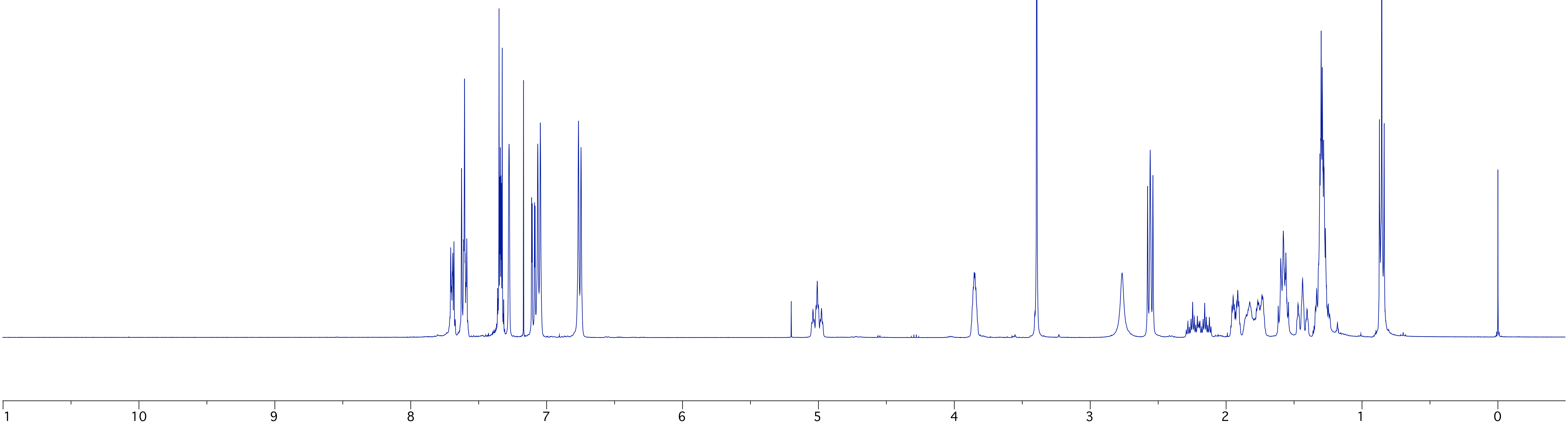
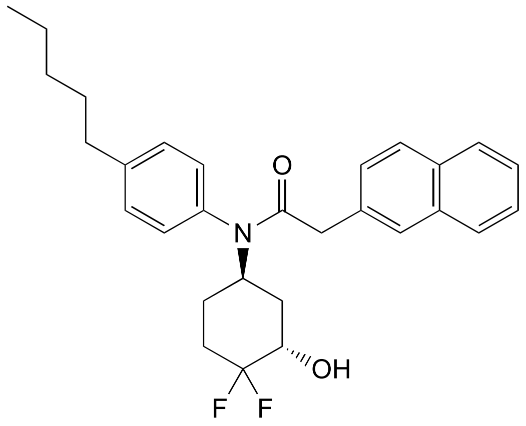
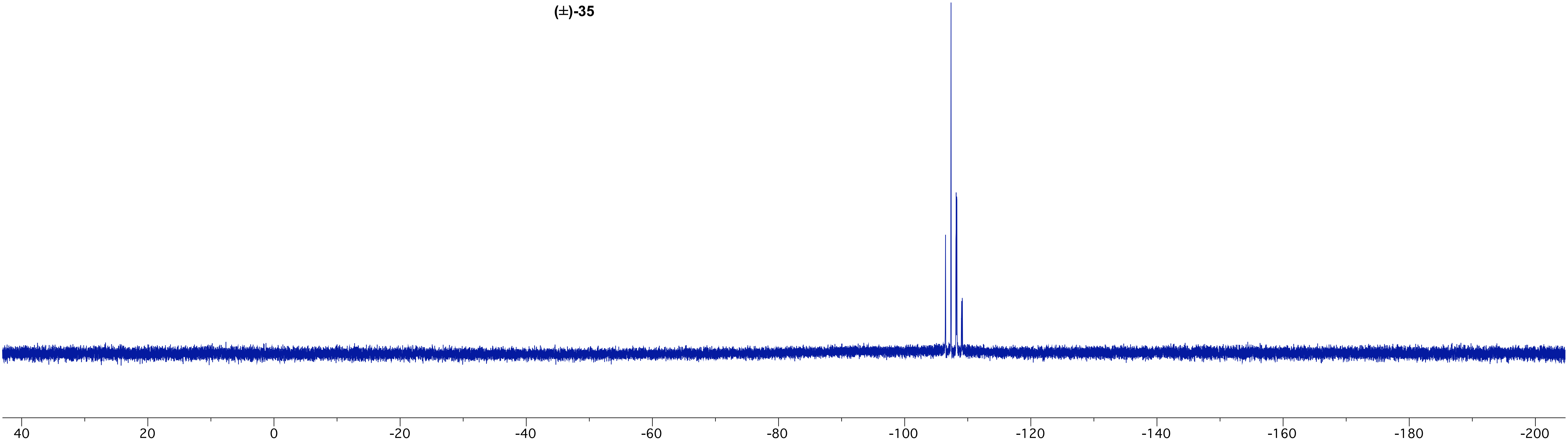


^{19}F NMR, 282 MHz, $CDCl_3$

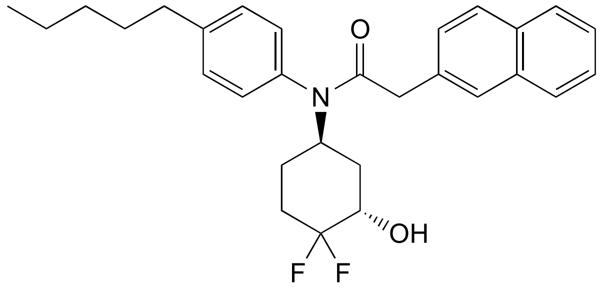


(±)-35



Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 100 MHz, $CDCl_3$



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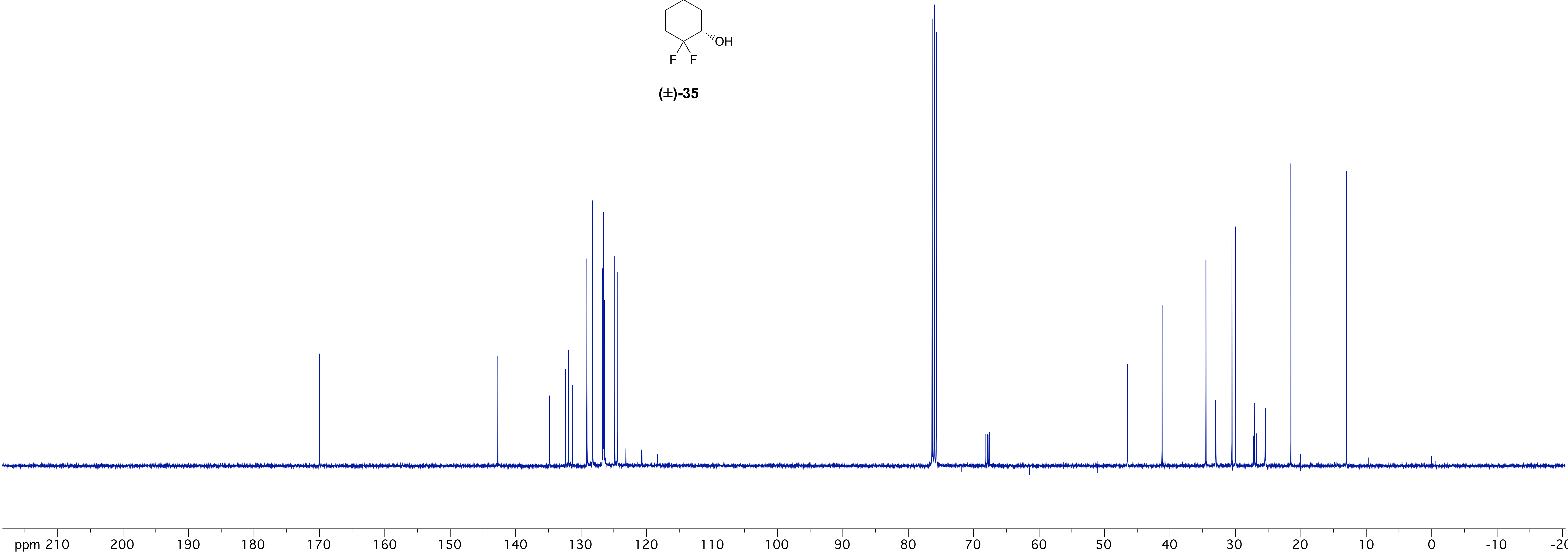
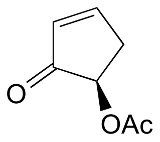


^{1}H NMR, 300 MHz, $CDCl_3$



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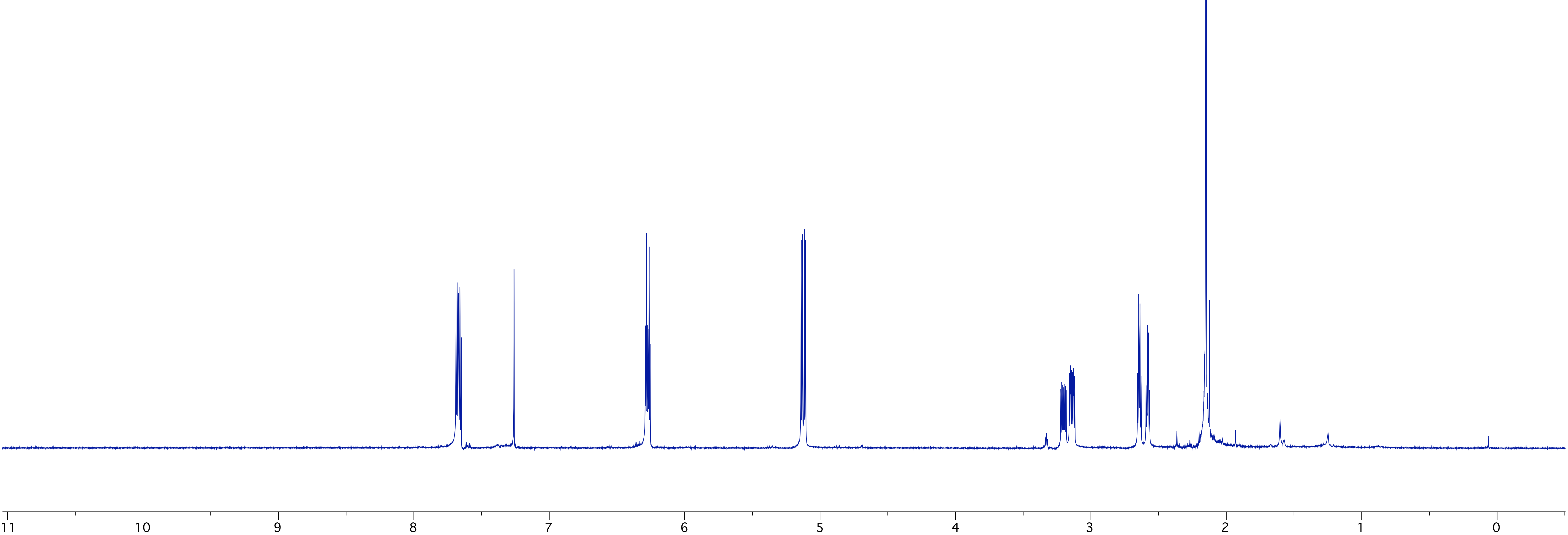
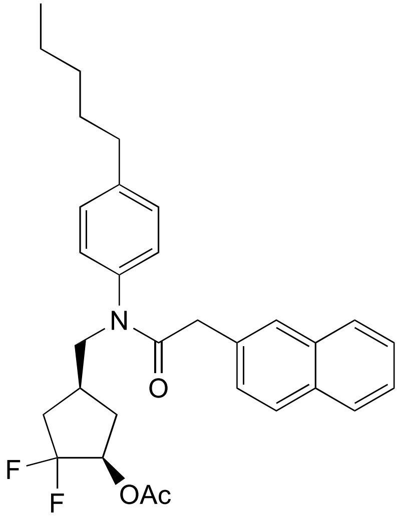


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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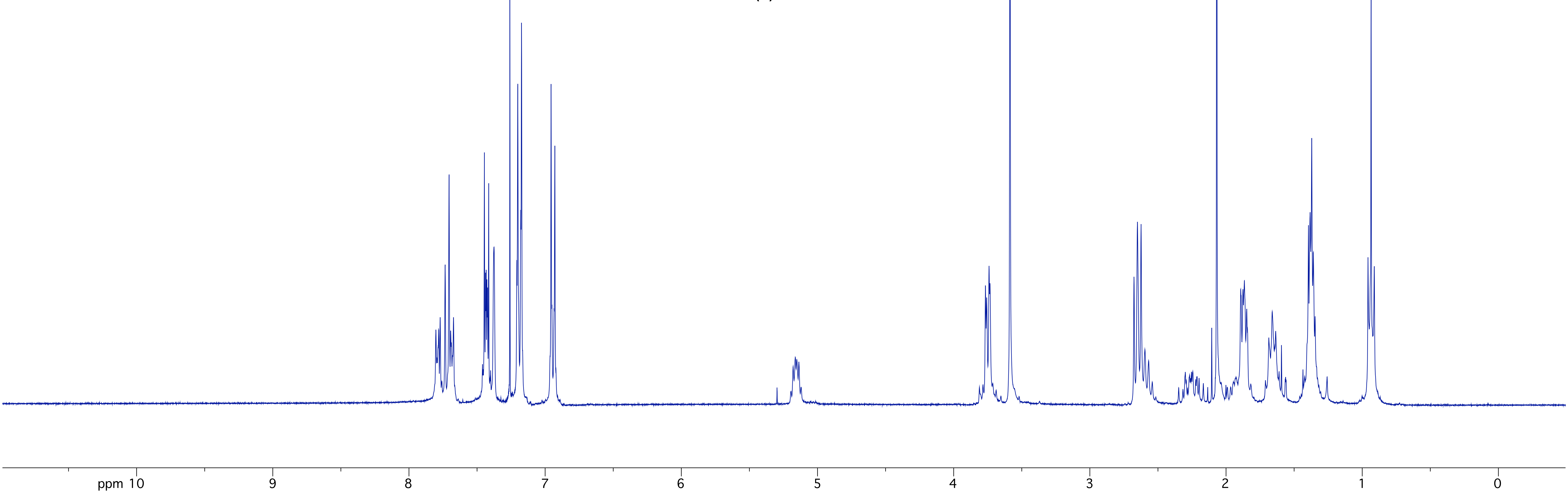
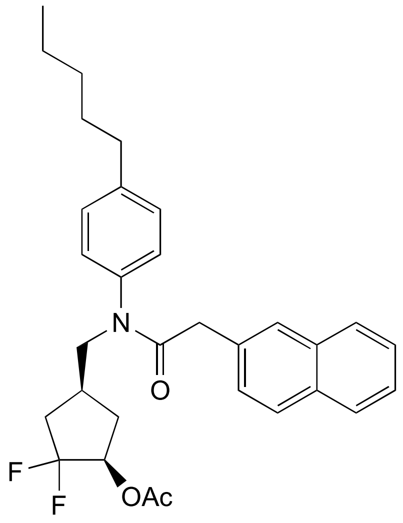


^{19}F NMR, 376 MHz, $CDCl_3$



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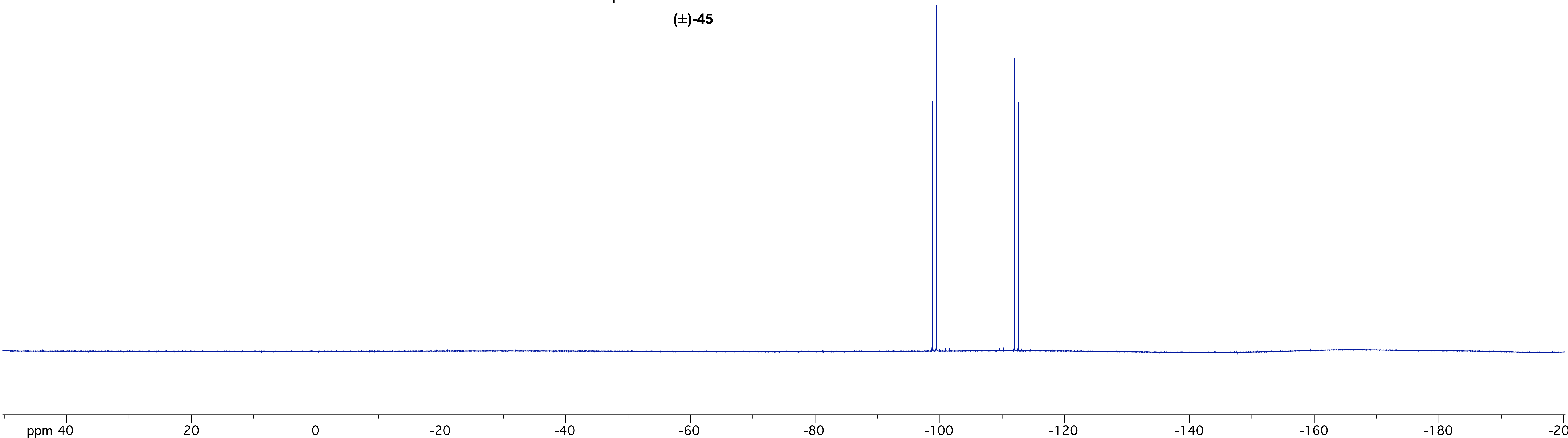
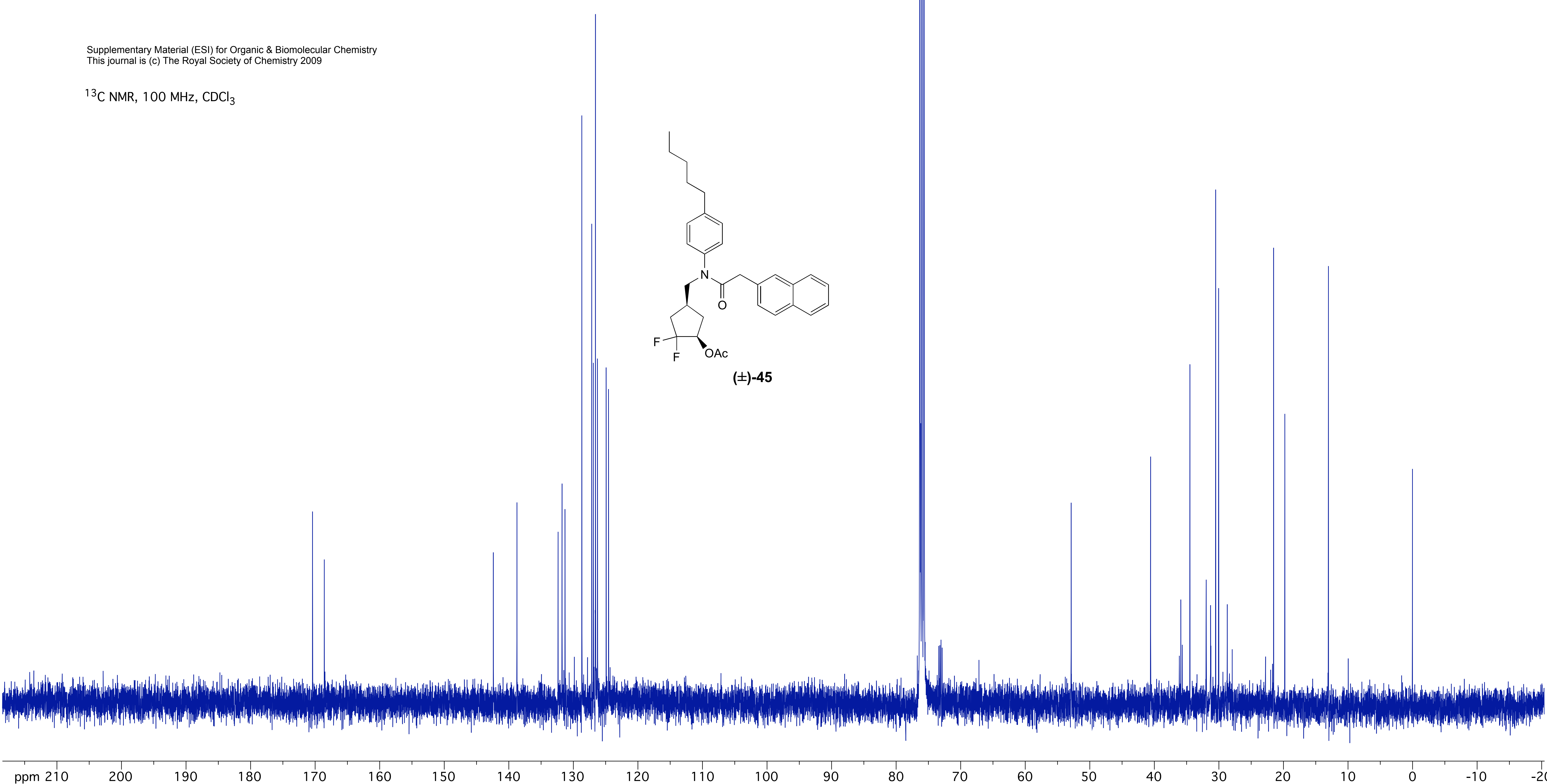


^{13}C NMR, 100 MHz, $CDCl_3$



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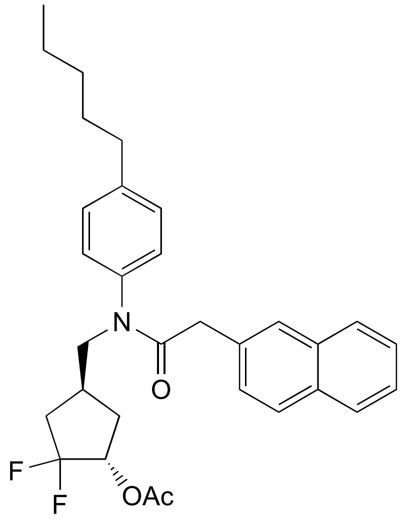
Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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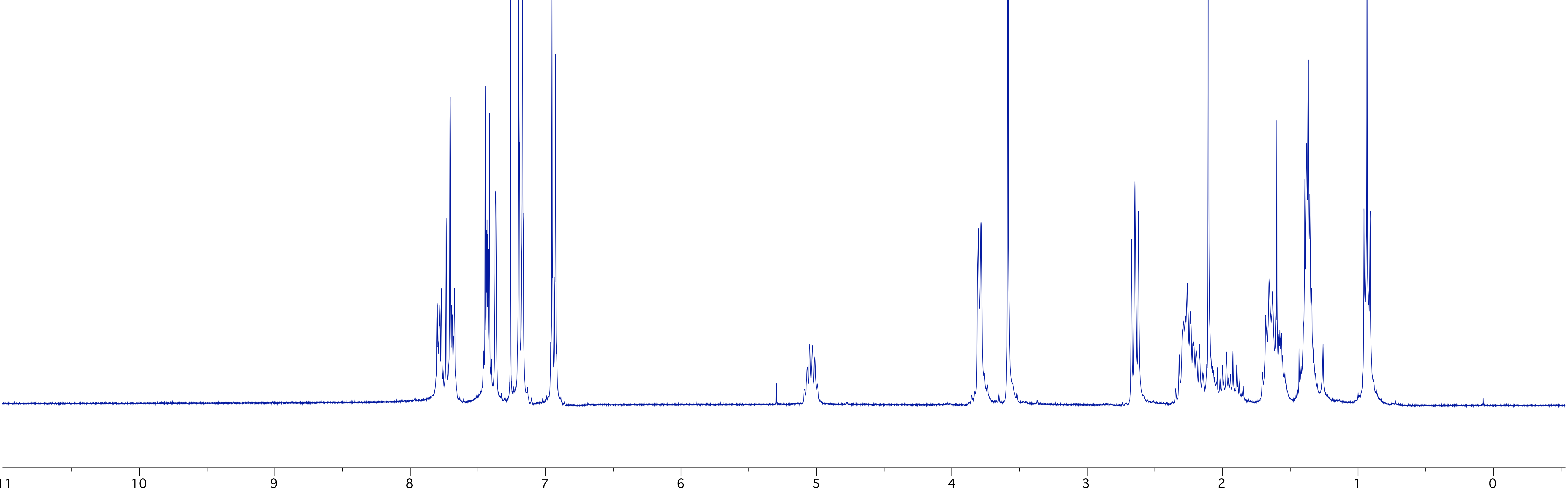
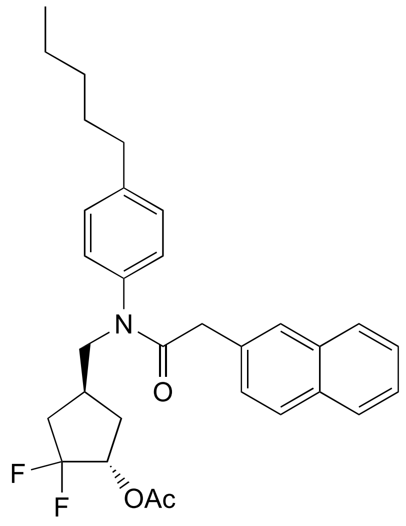
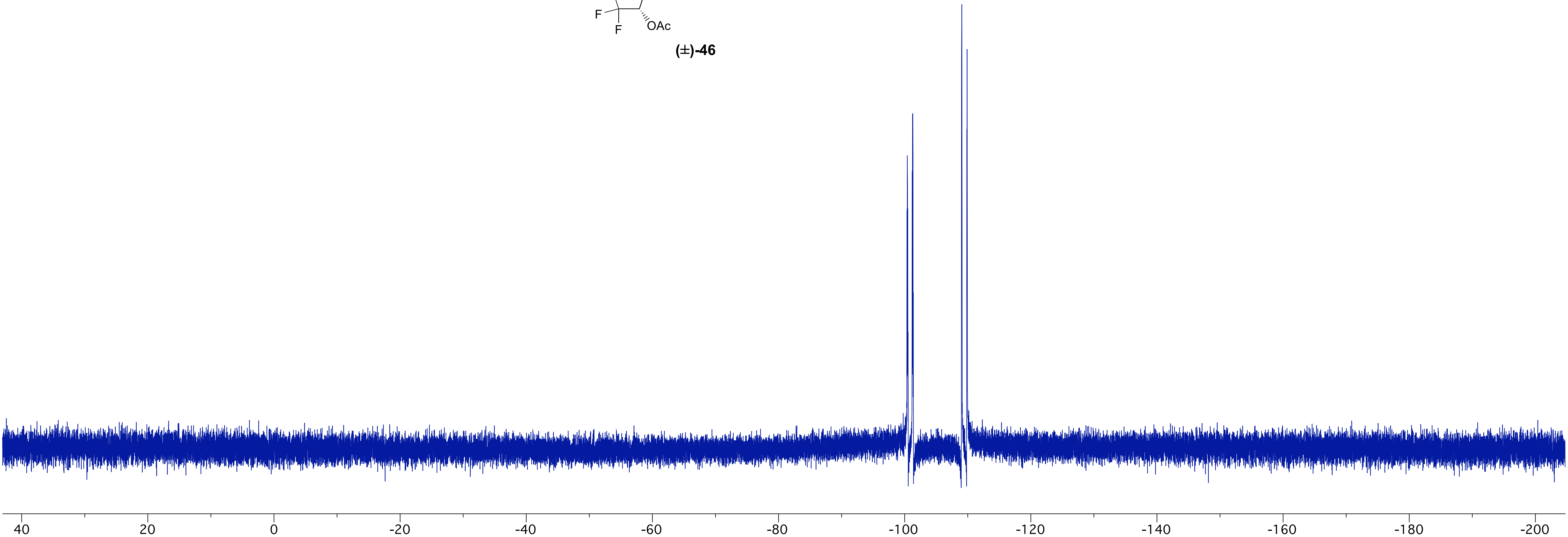


^{19}F NMR, 282 MHz, $CDCl_3$

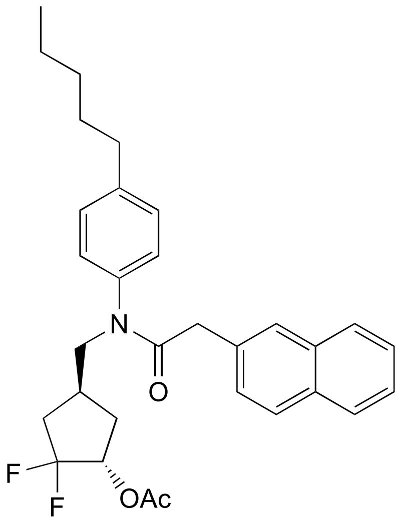


(±)-46



Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 100 MHz, $CDCl_3$



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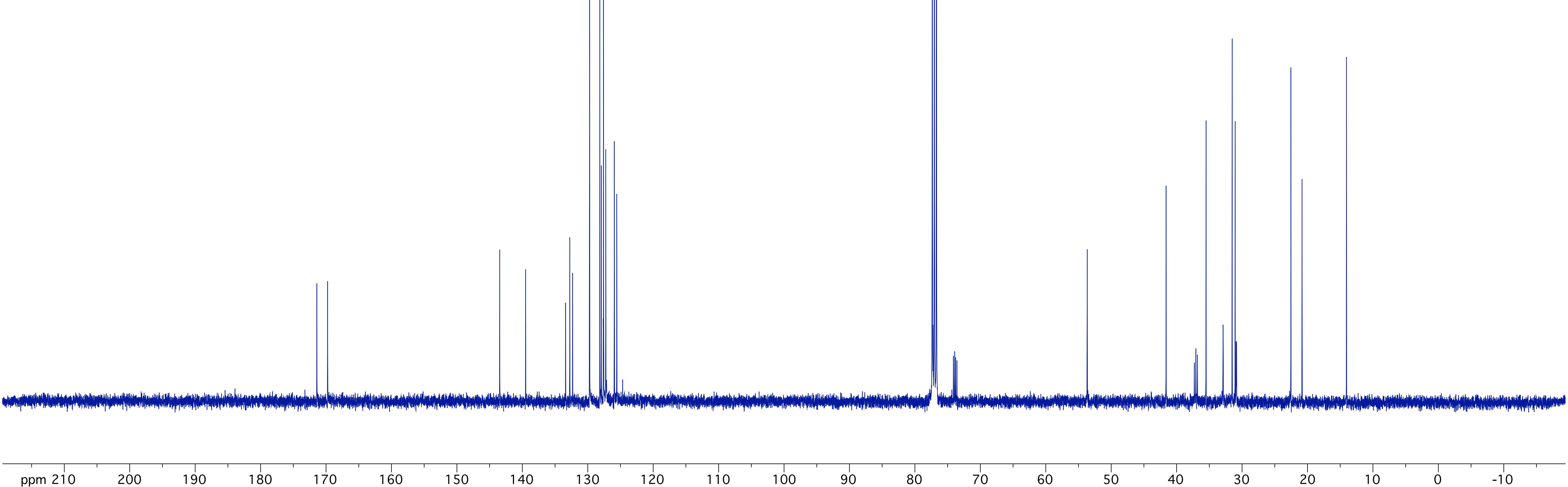
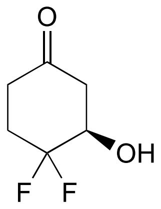


^1H NMR, 300 MHz, $CDCl_3$



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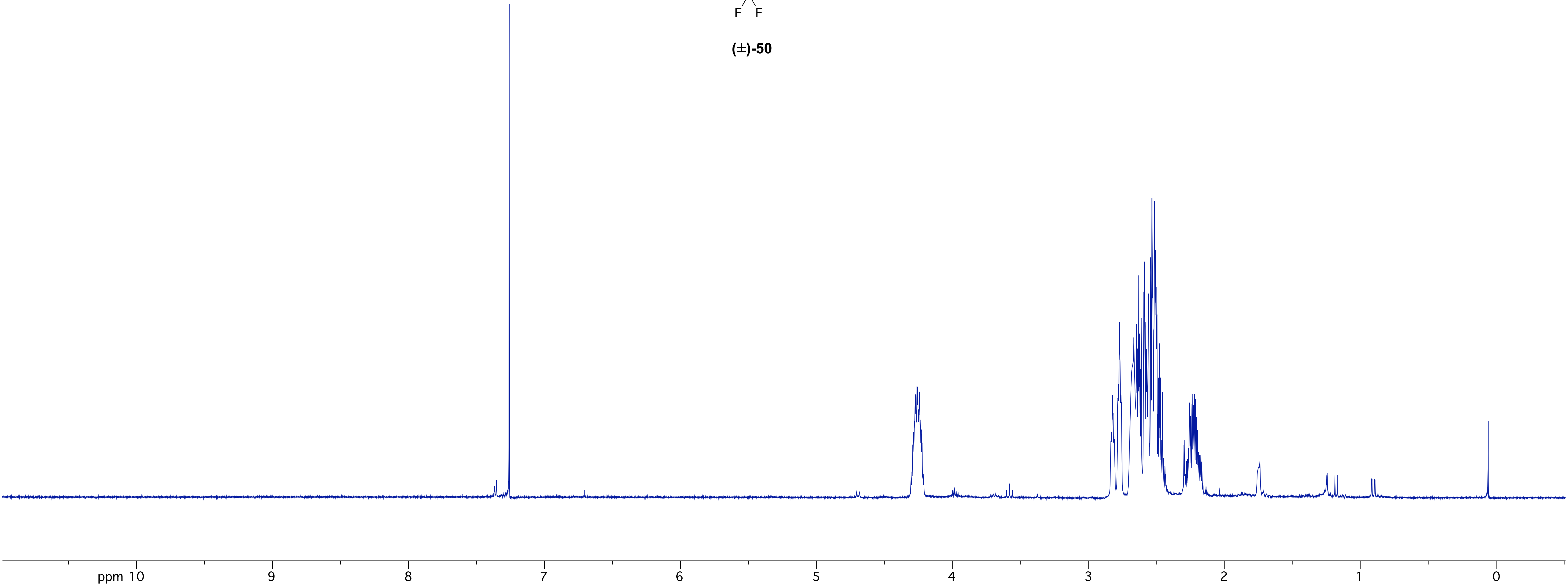
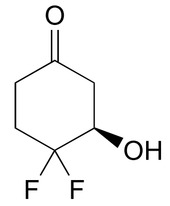


^{19}F NMR, 282 MHz, $CDCl_3$



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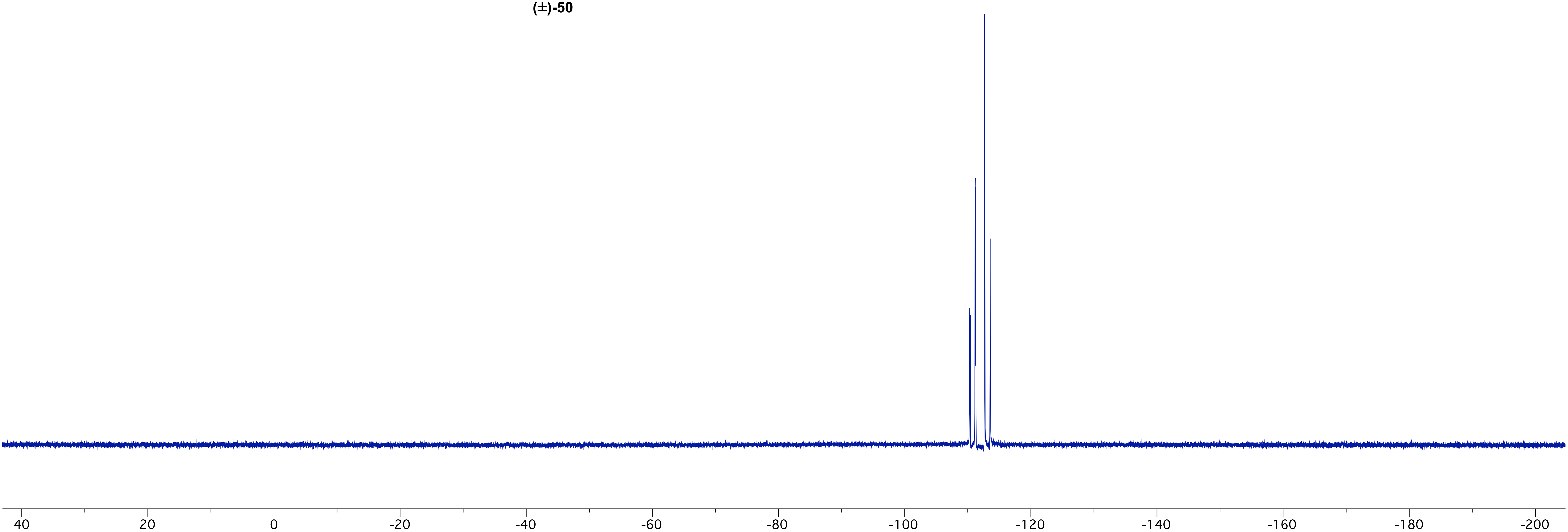
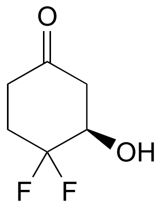


^{13}C NMR, 75 MHz, $CDCl_3$



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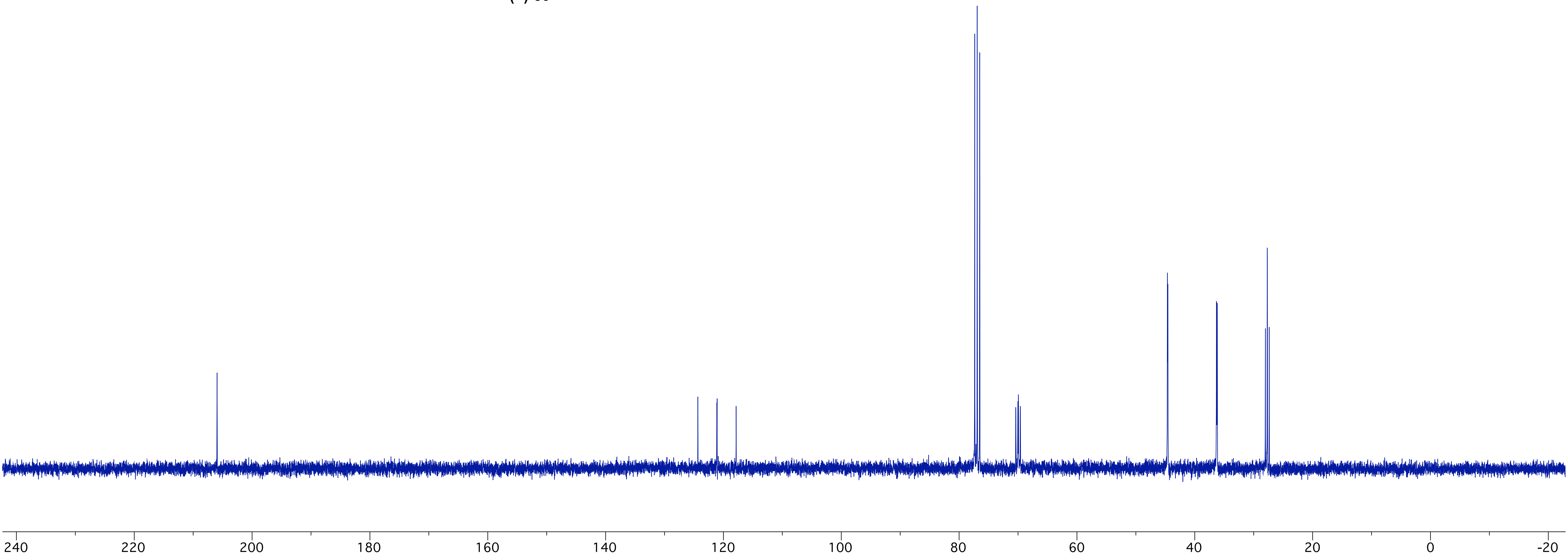
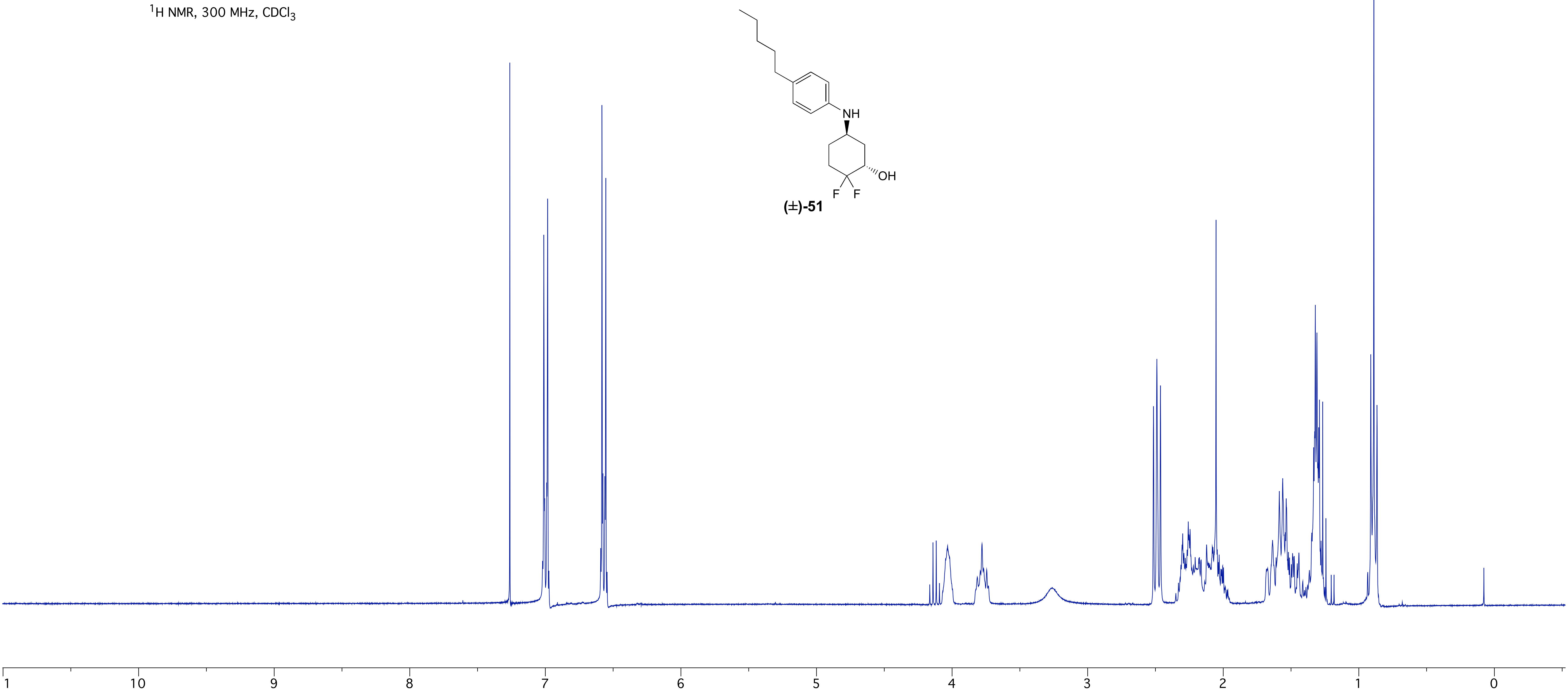
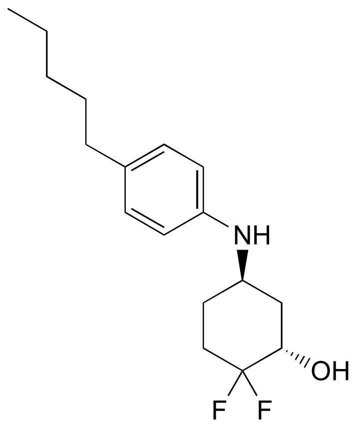


^{1}H NMR, 300 MHz, $CDCl_3$



^{19}F NMR, 282 MHz, $CDCl_3$



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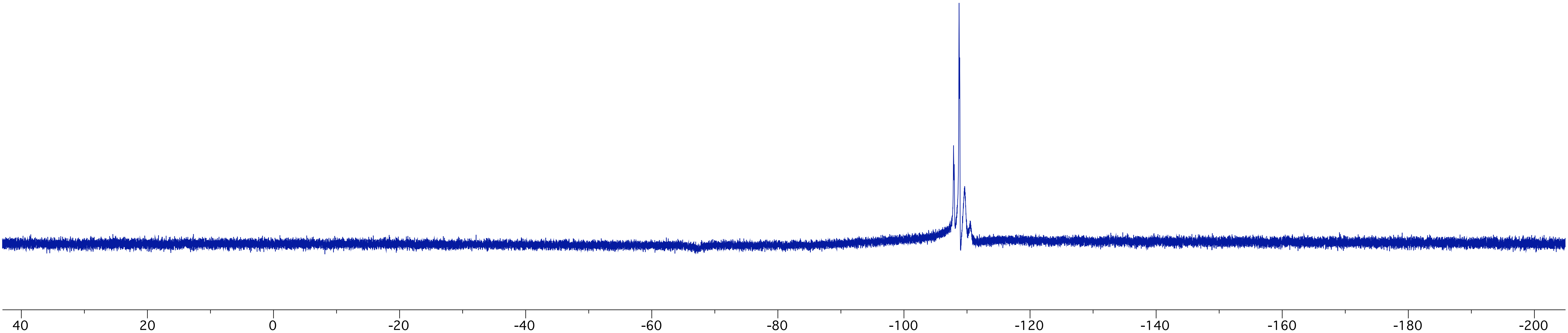
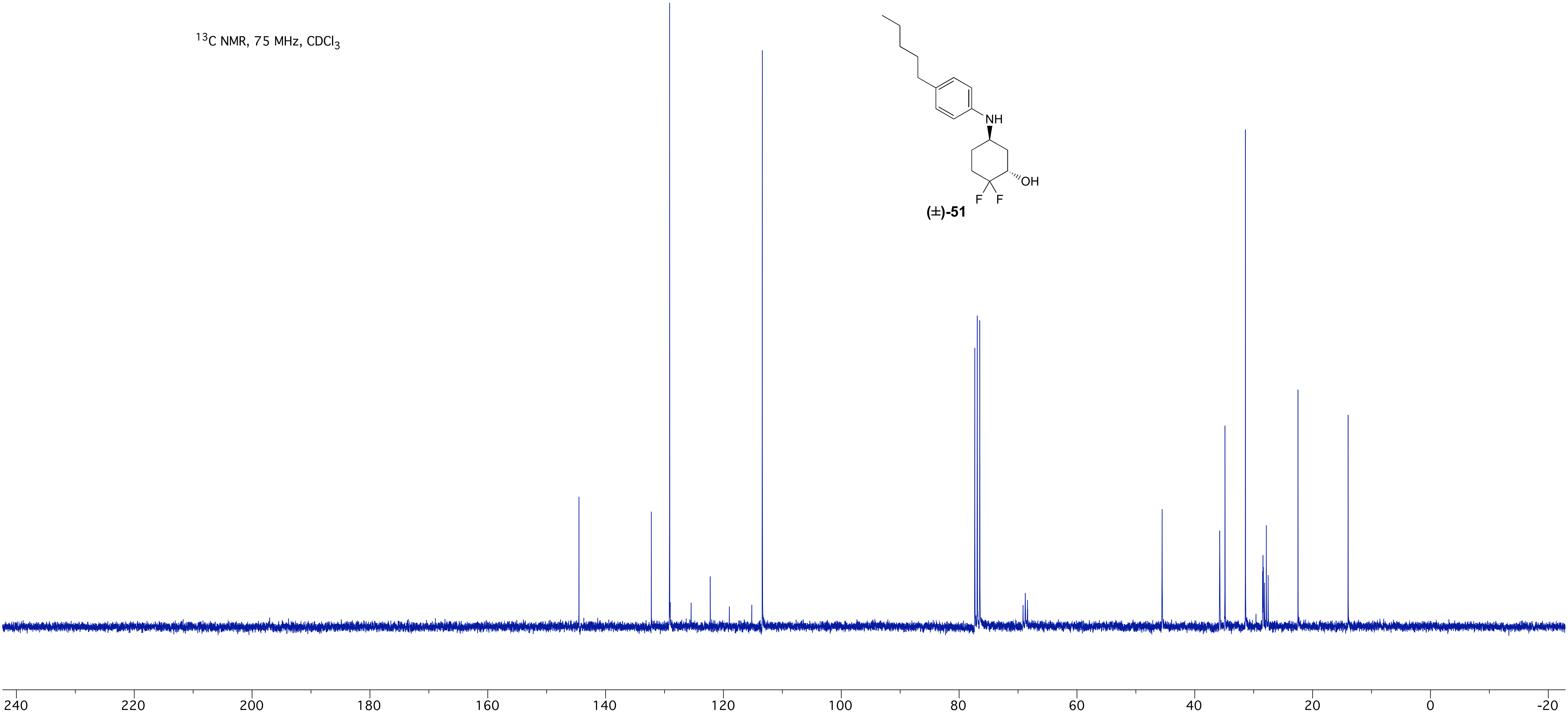
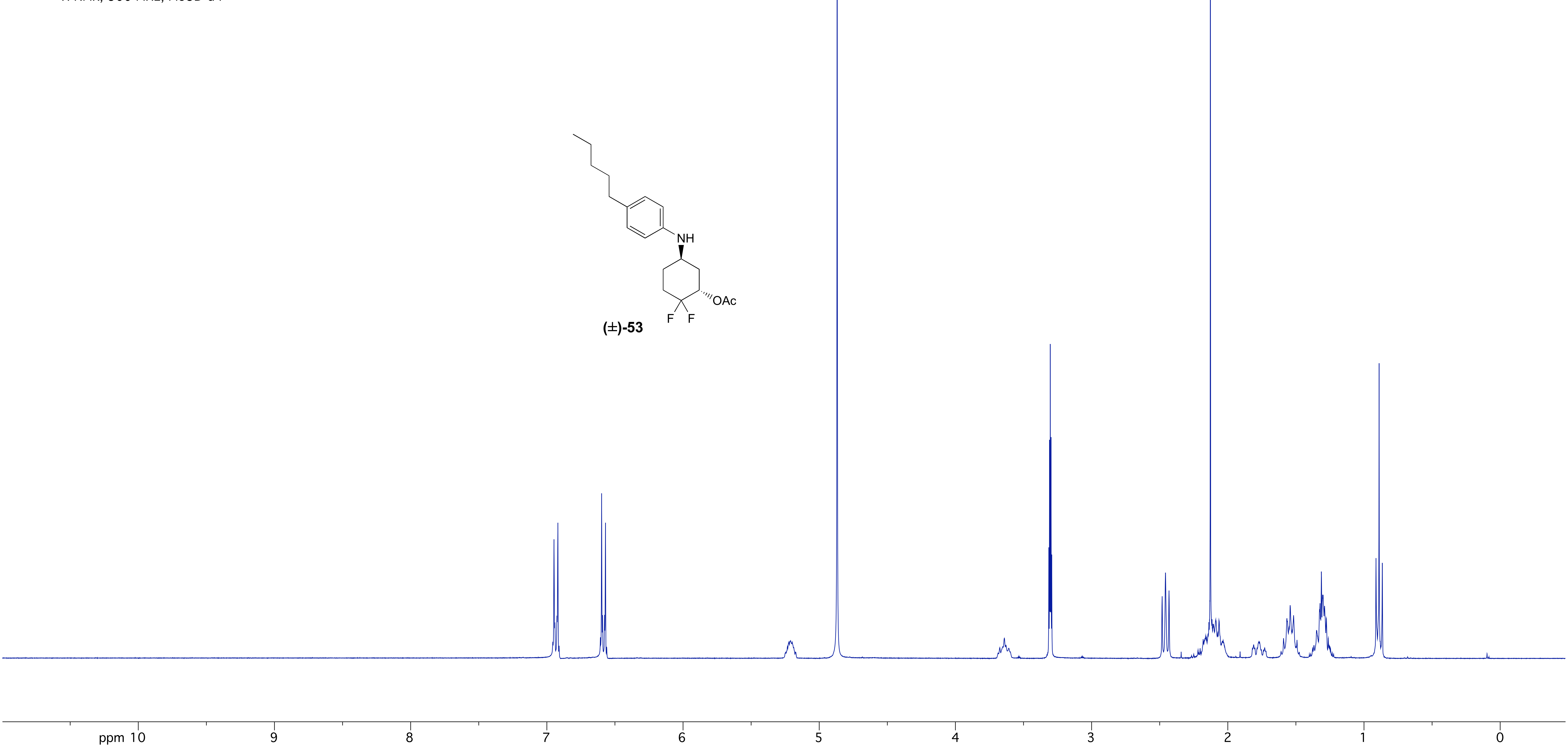


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

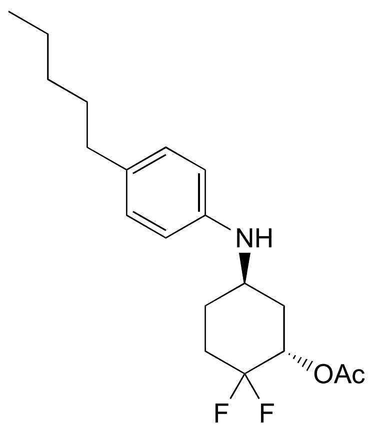


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, MeOD-d4



^{19}F NMR, 282 MHz, $CDCl_3$



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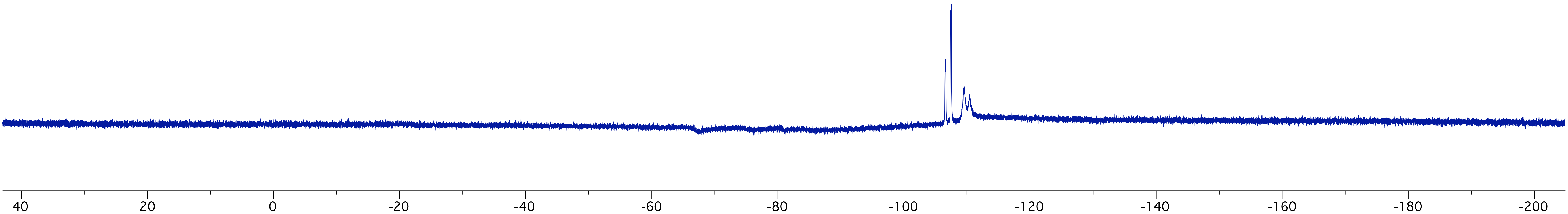
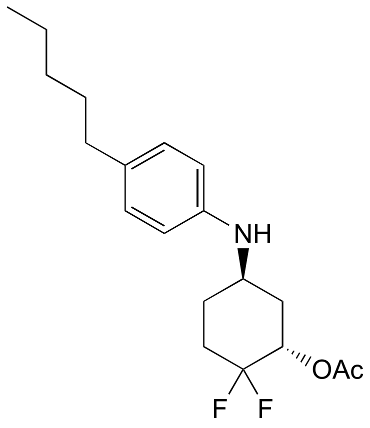


^{13}C NMR, 75 MHz, $CDCl_3$



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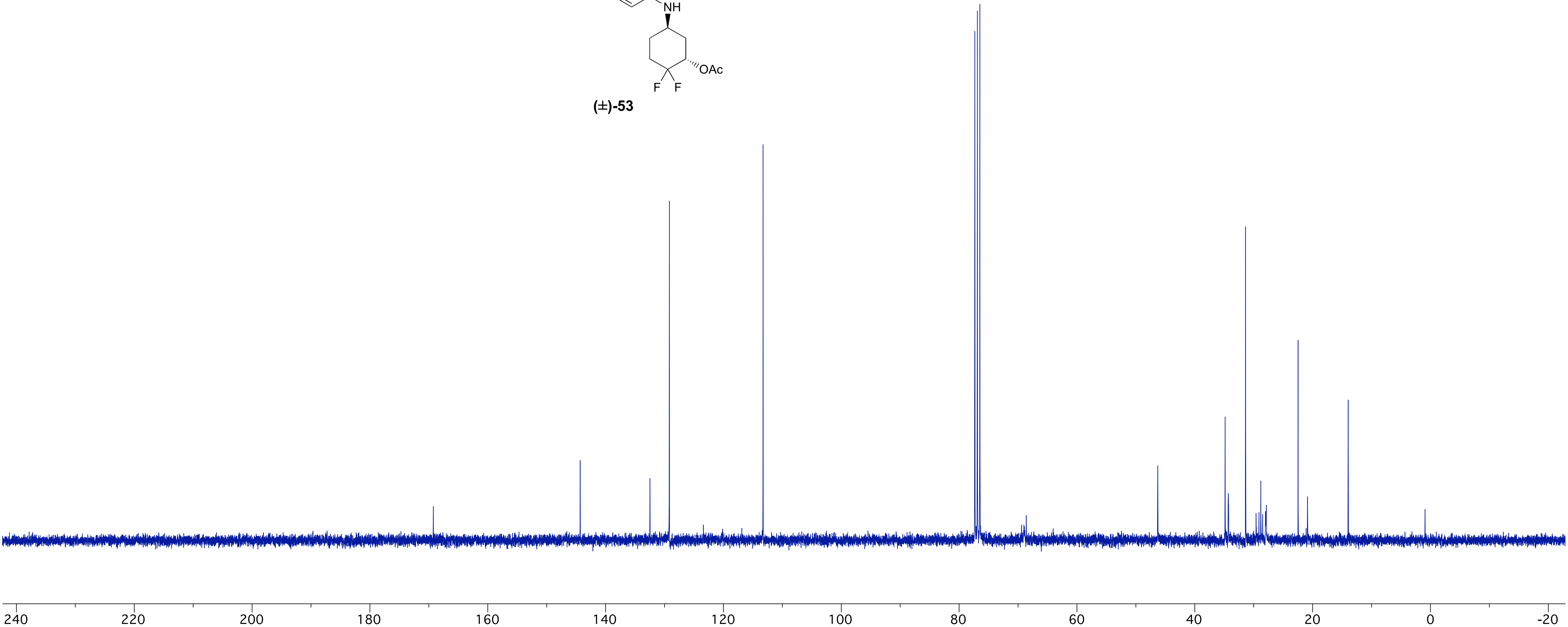
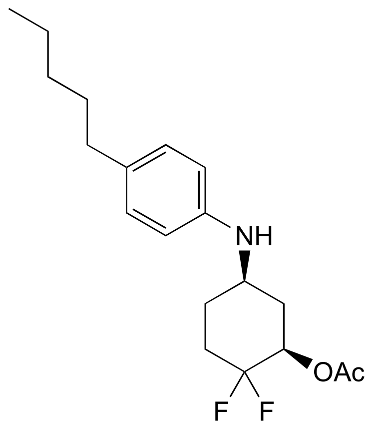
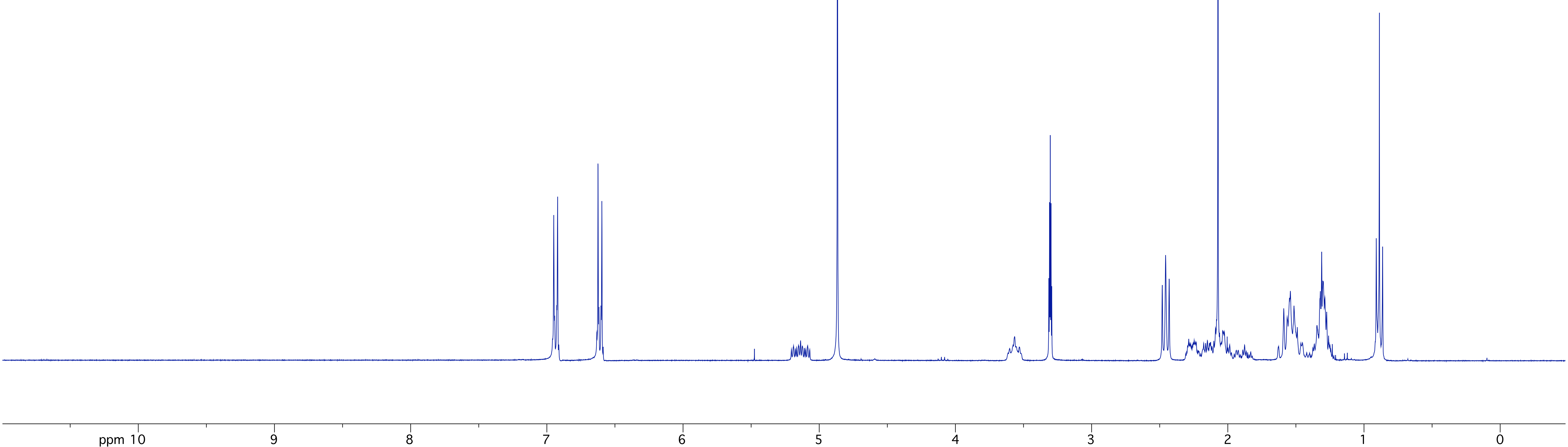


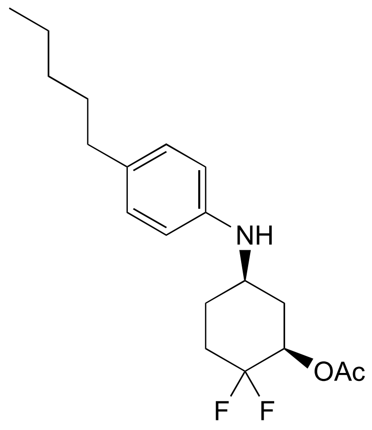
^{1}H NMR, 300 MHz, MeOD-d4



(±)-54



^{19}F NMR, 282 MHz, $CDCl_3$



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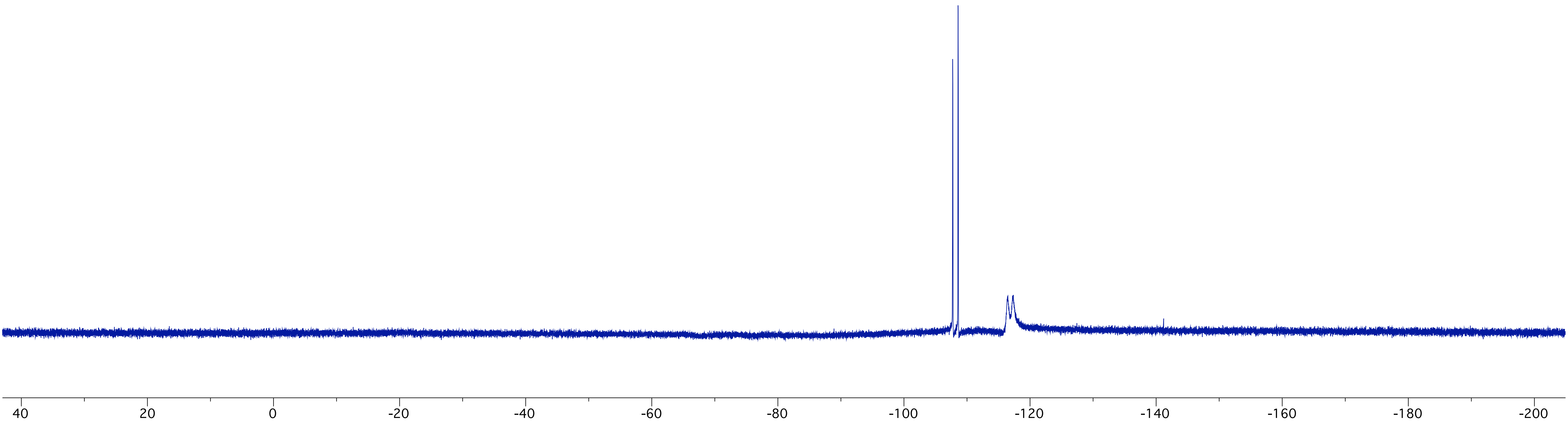
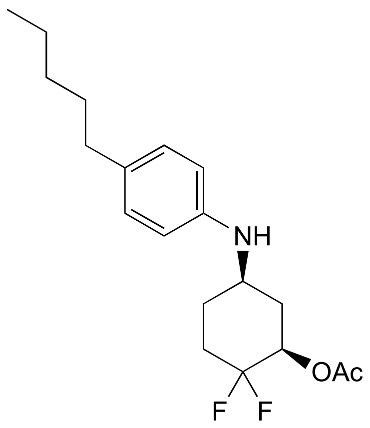


^{13}C NMR, 75 MHz, MeOD-d4



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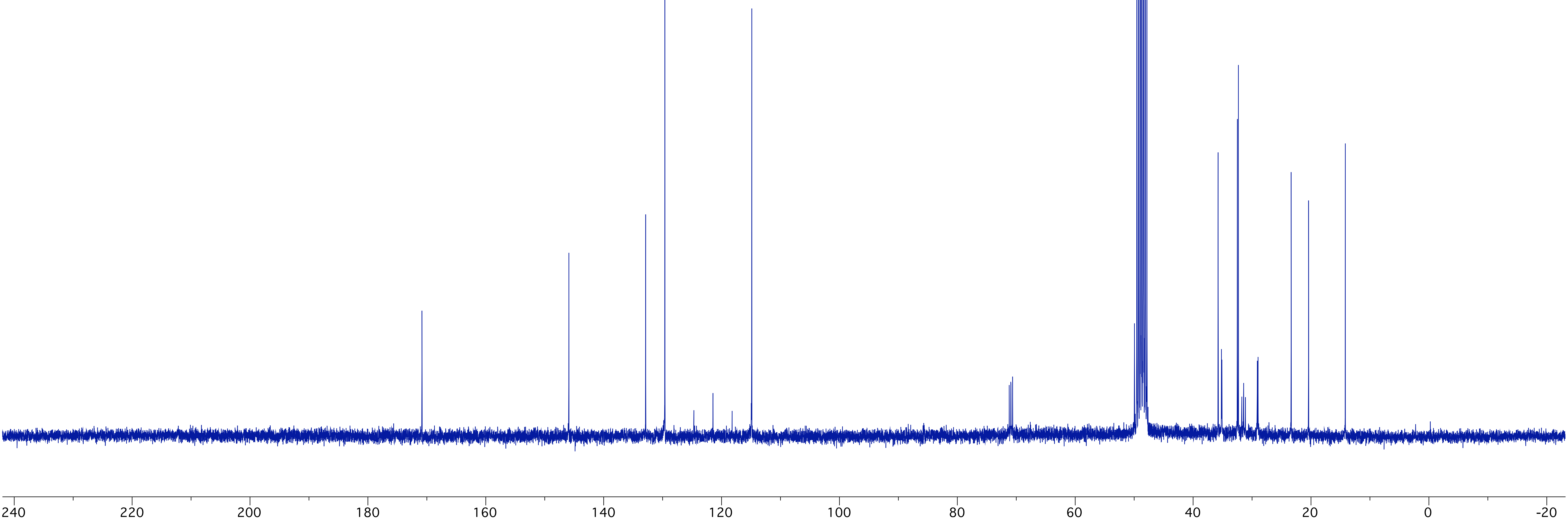
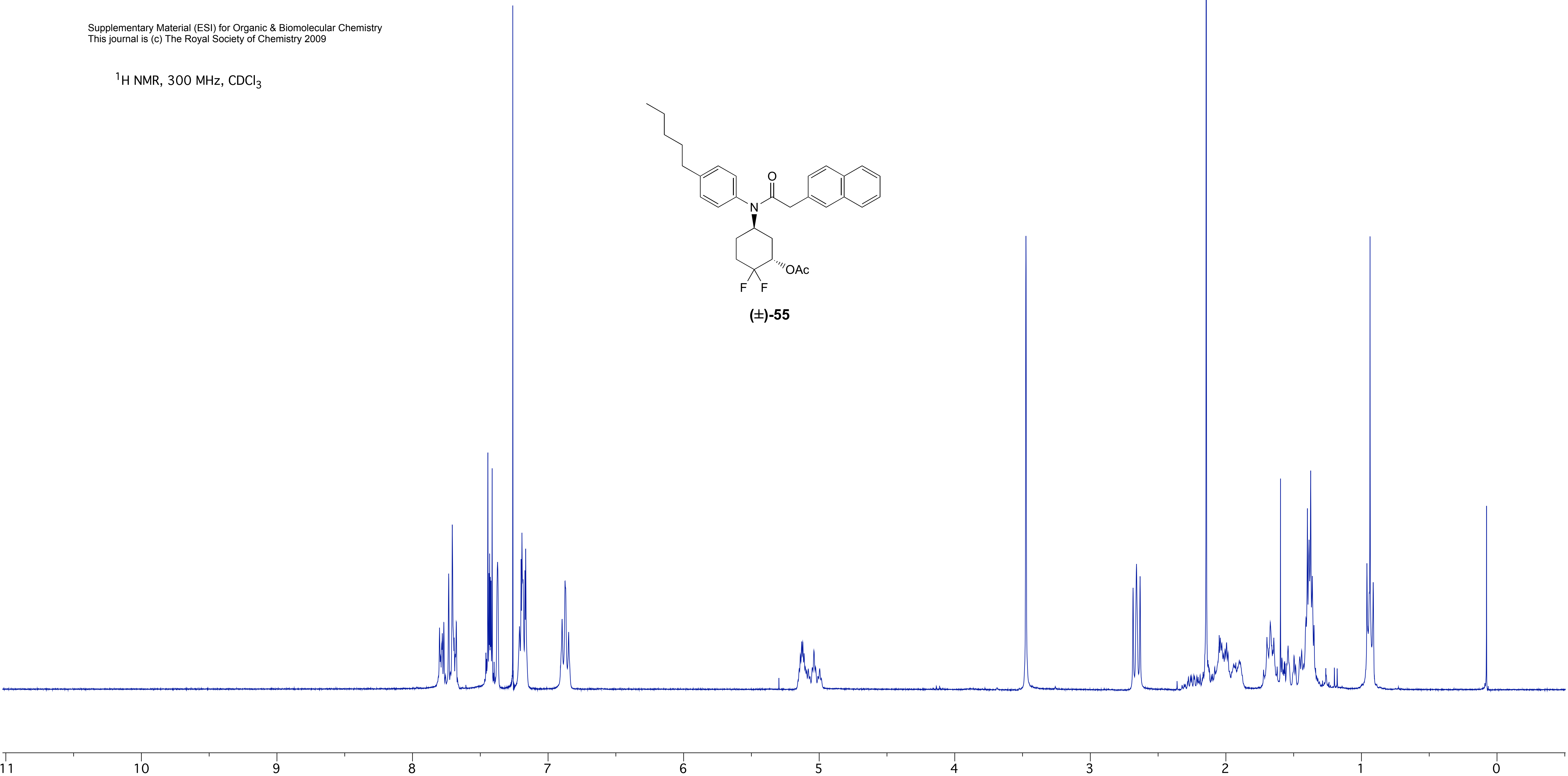
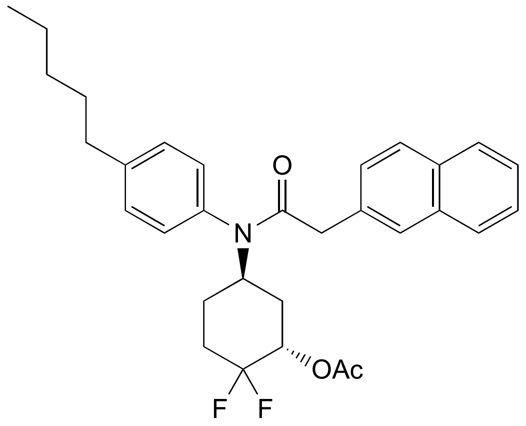


^{1}H NMR, 300 MHz, $CDCl_3$



^{19}F NMR, 282 MHz, $CDCl_3$



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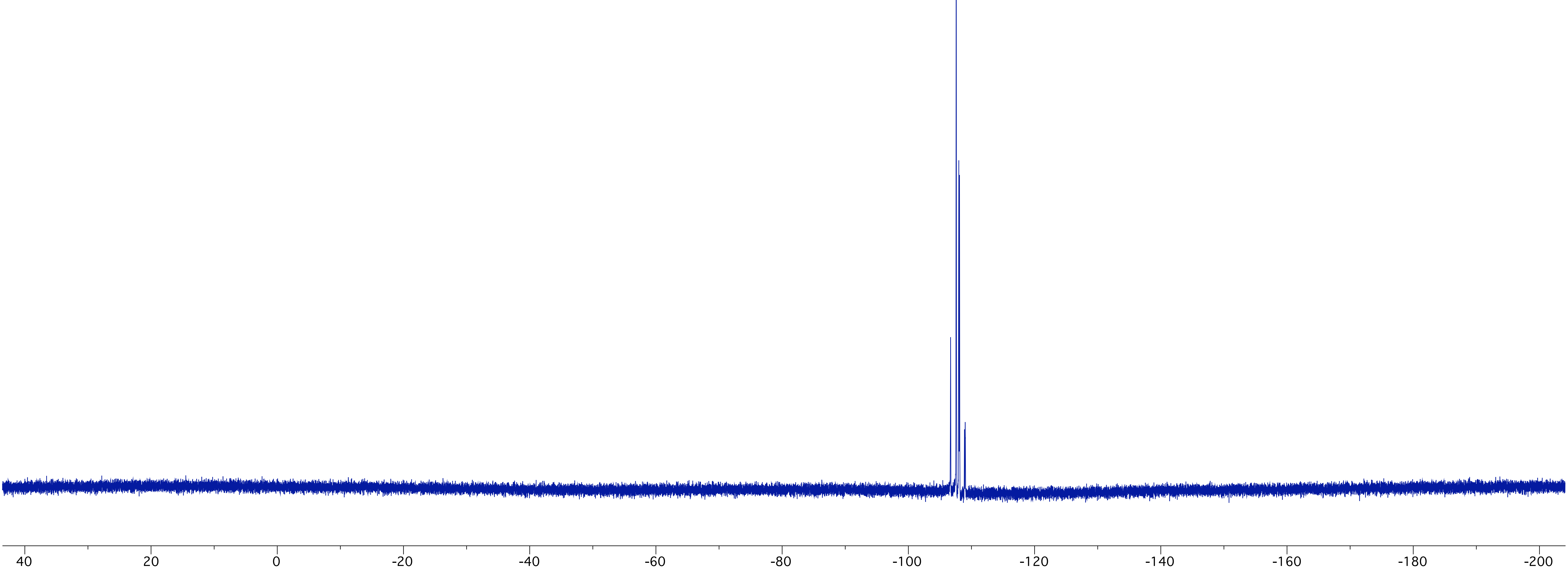
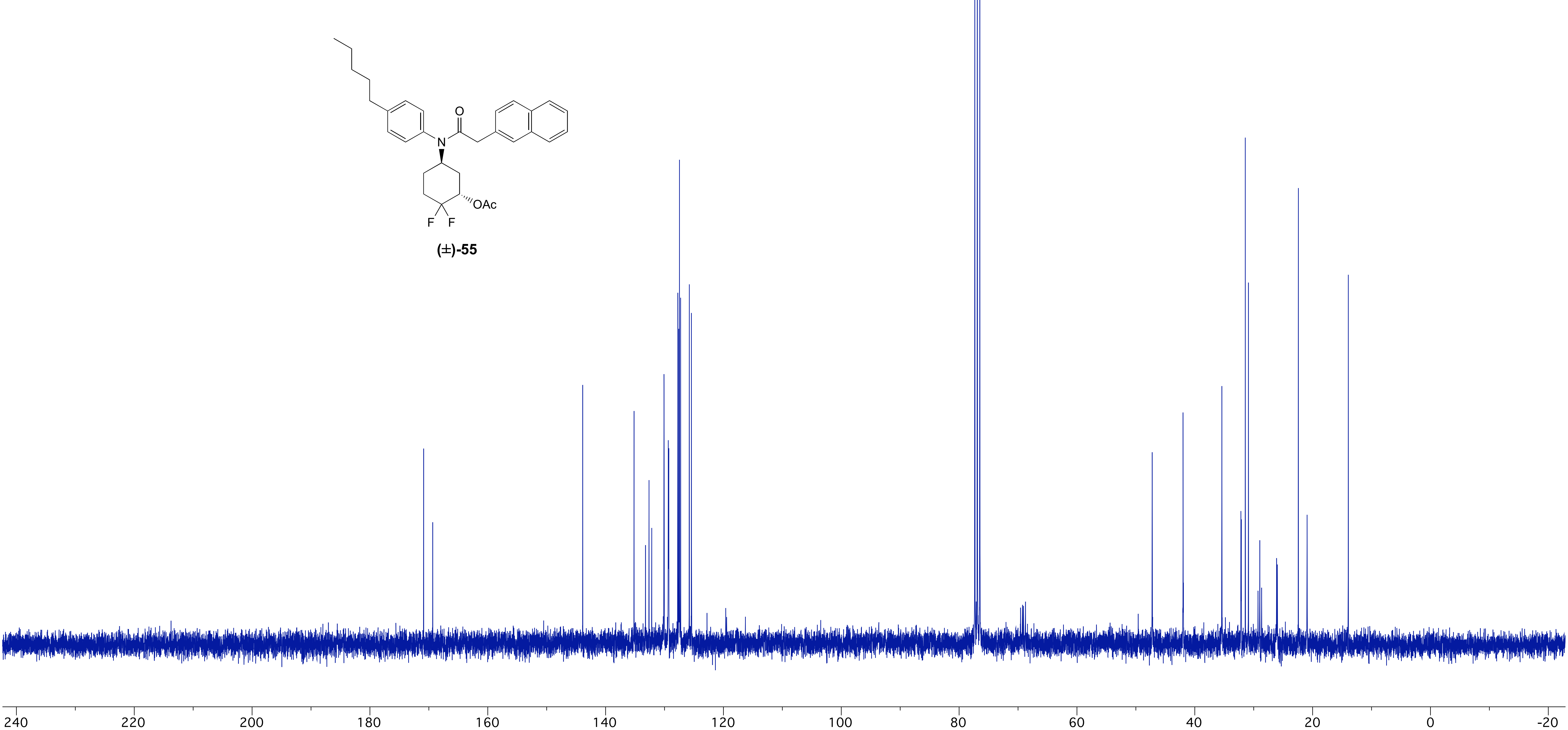


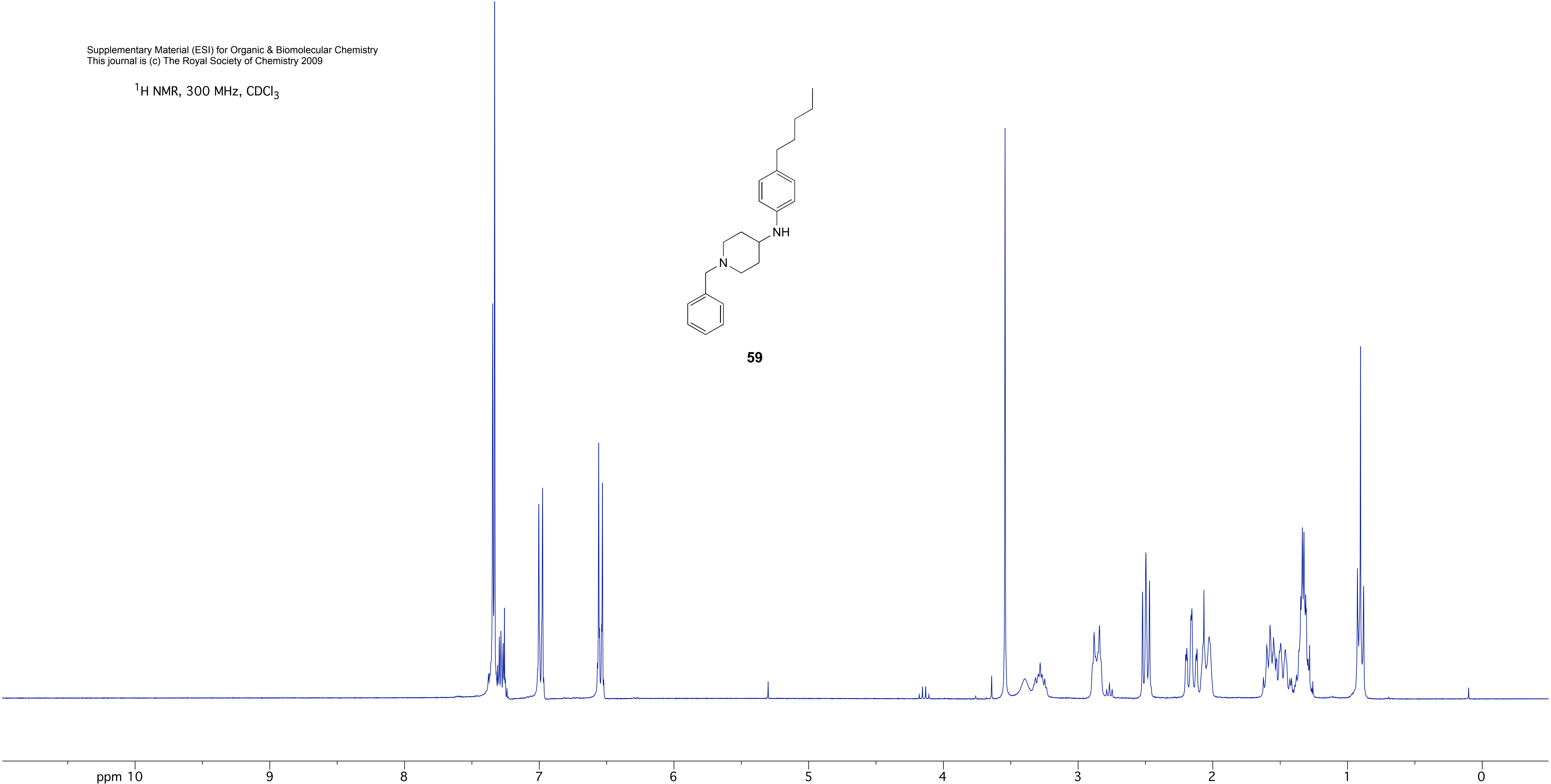
Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{13}C NMR, 75 MHz, $CDCl_3$

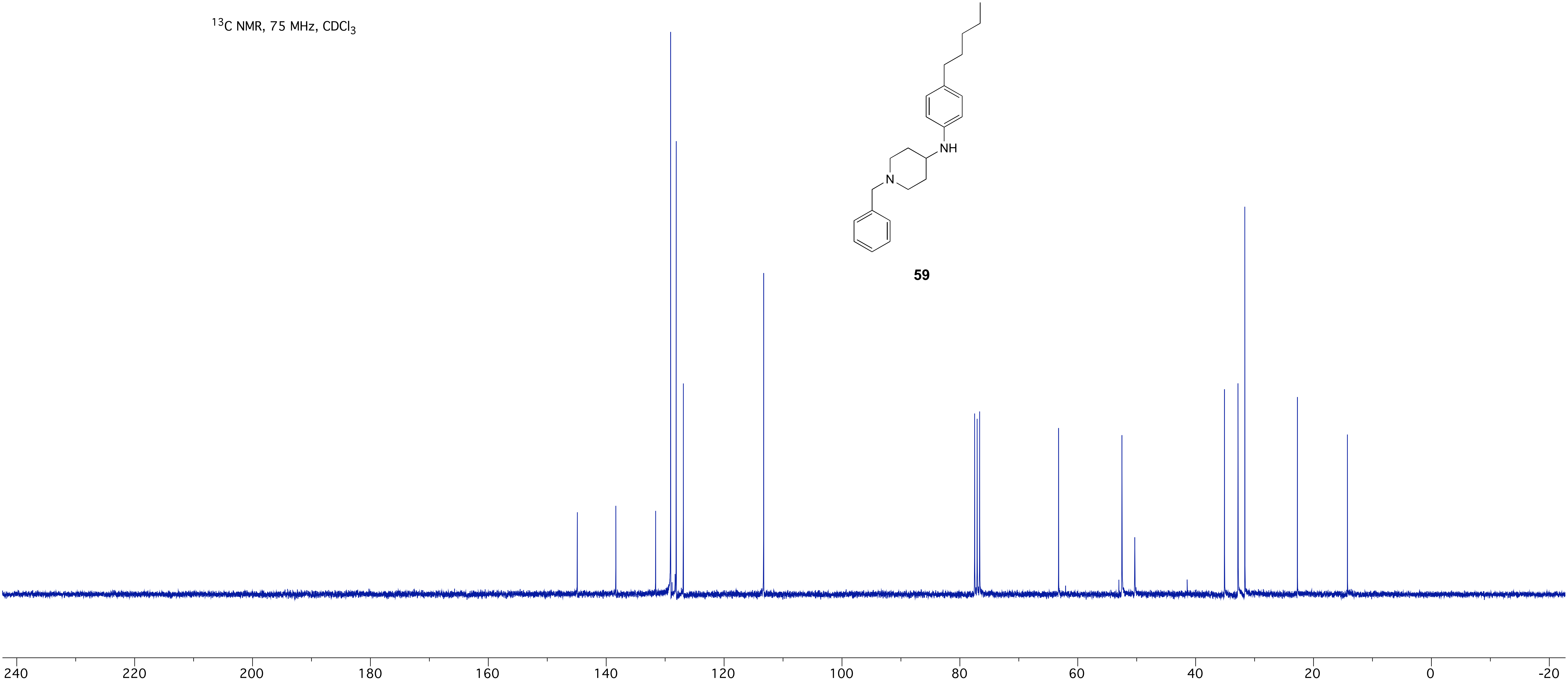


Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$

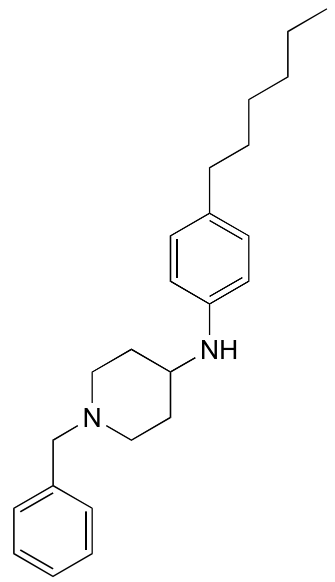


59


^{13}C NMR, 75 MHz, $CDCl_3$
NH
N
59
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

^{1}H NMR, 300 MHz, $CDCl_3$



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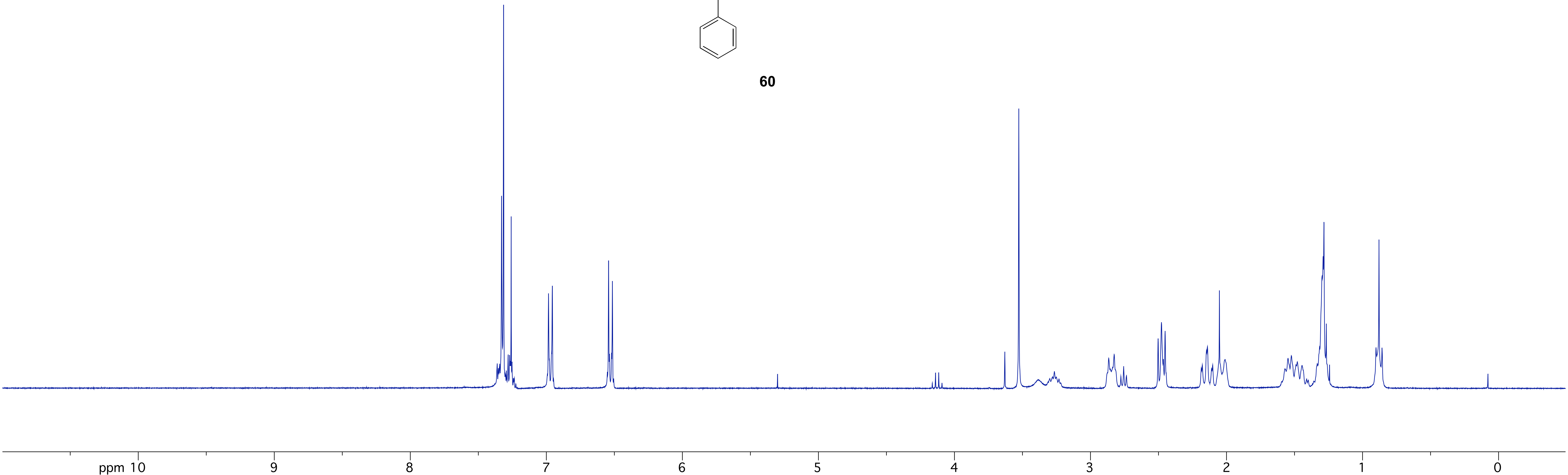
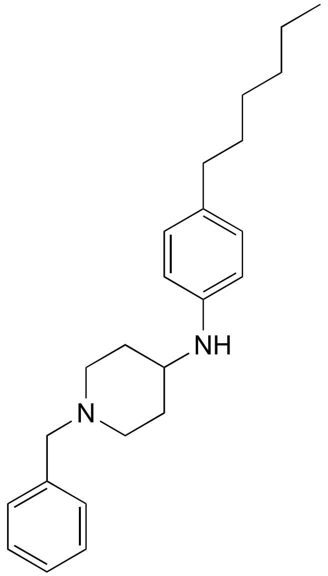


^{13}C NMR, 75 MHz, $CDCl_3$



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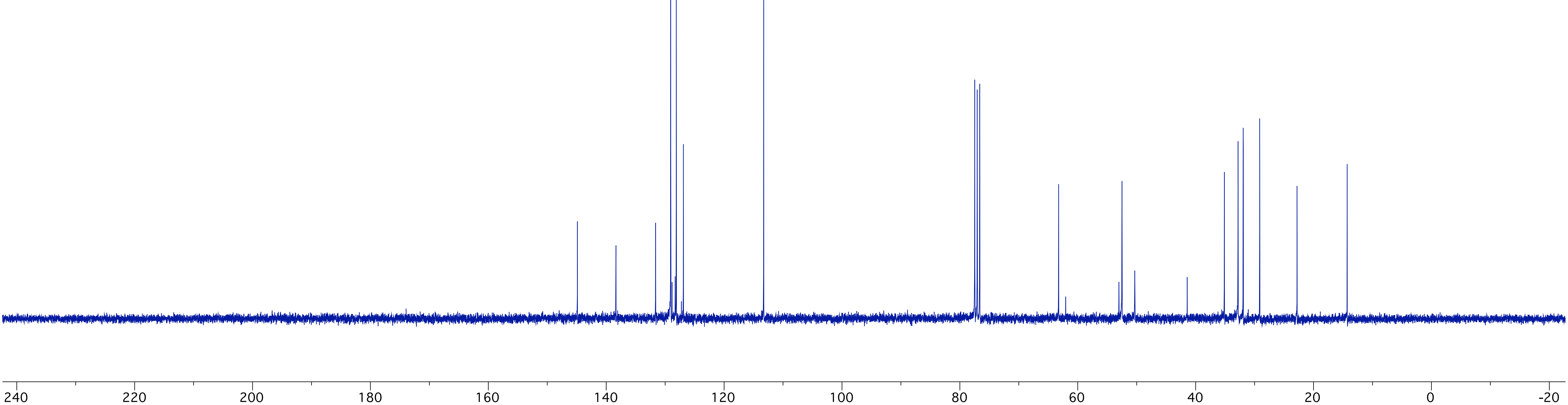
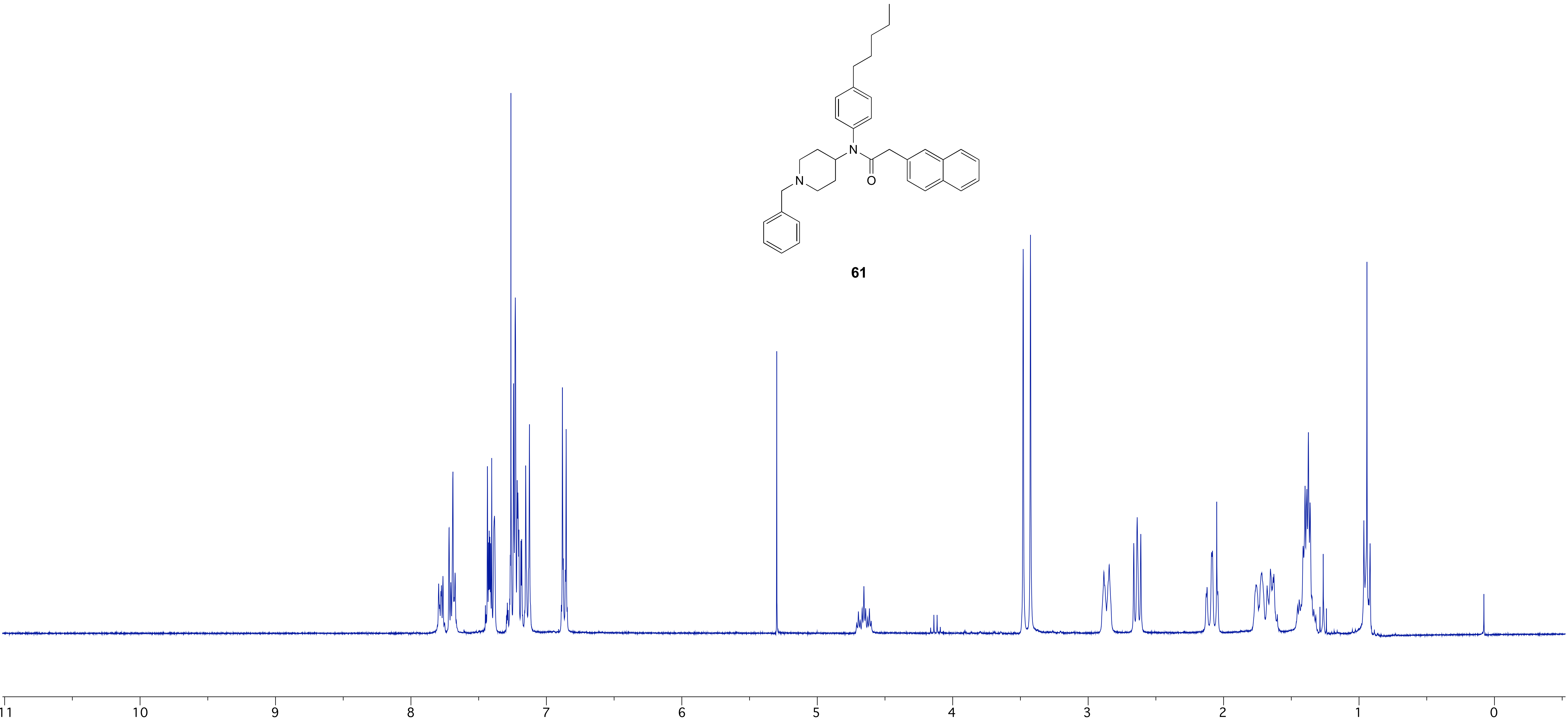
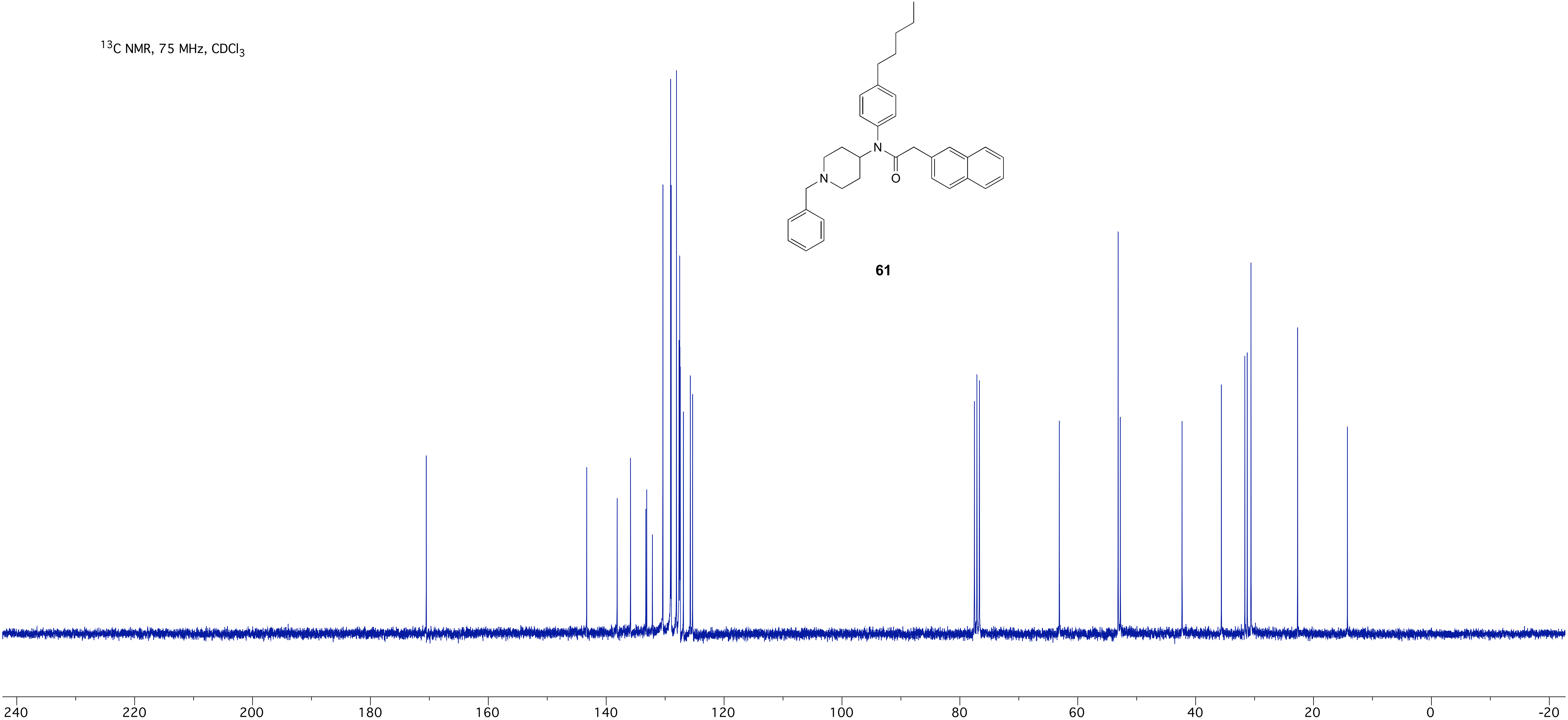
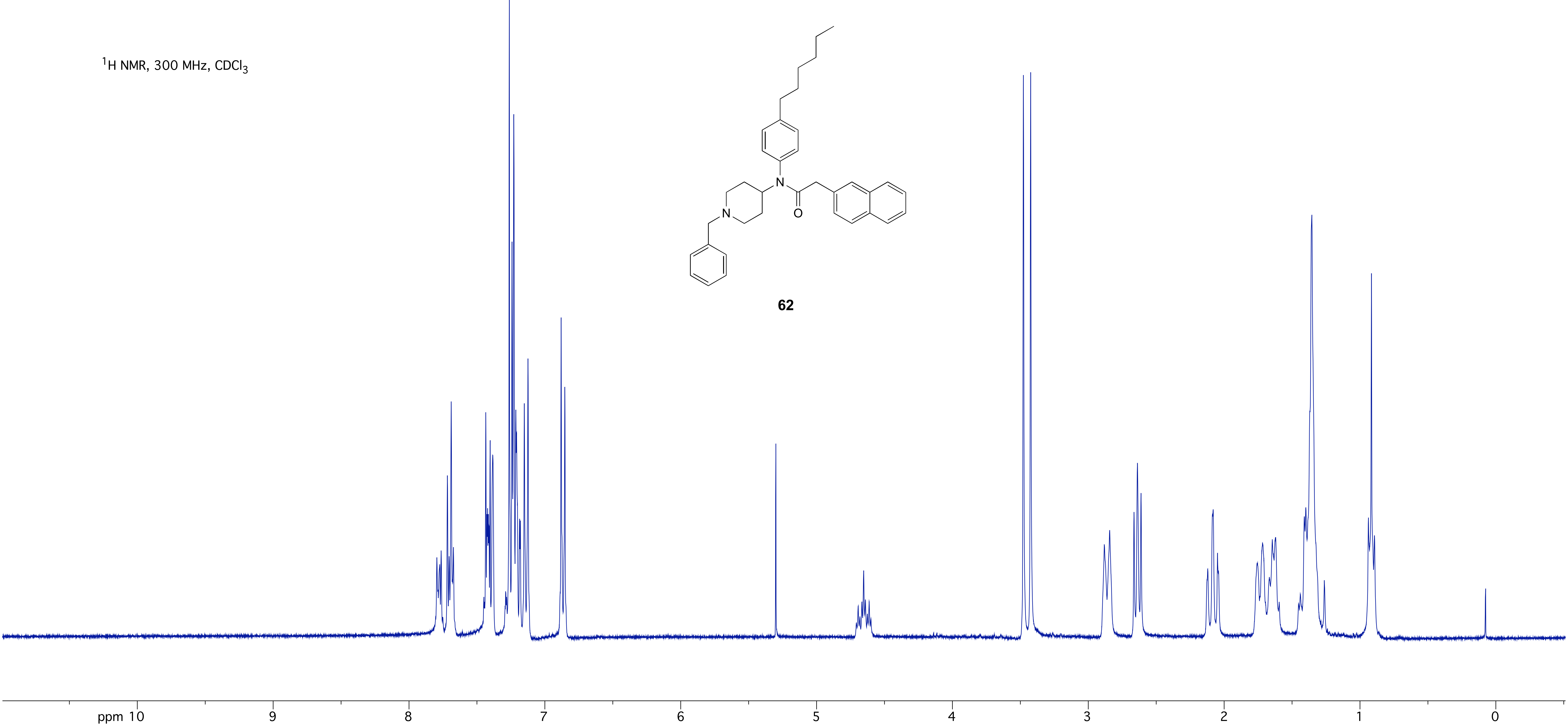


^1H NMR, 300 MHz, $CDCl_3$



^{13}C NMR, 75 MHz, $CDCl_3$




^{1}H NMR, 300 MHz, $CDCl_3$
N
N
O
62
ppm 10
9
8
7
6
5
4
3
2
1
0

^{13}C NMR, 75 MHz, $CDCl_3$