Supporting Information

Organocatalytic Decarboxylative Cyanomethylation of Difluoromethyl and Trifluoromethyl Ketones

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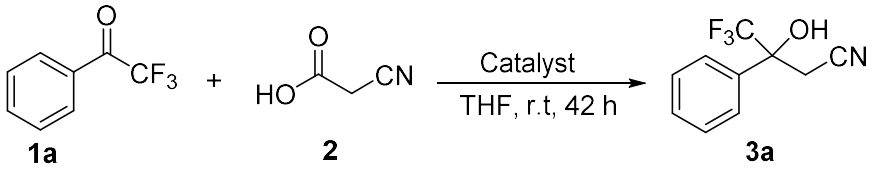
1. General Information

Commercially available trifluoromethyl ketones (**1a-1n**), difluoromethyl ketone (**4a**), chlorodifluoromethyl ketone (**6**), cyanoacetic acid (**2**), reagents, catalysts and solvents were used as purchased without further purification. Difluoromethyl ketones (**4b-4h**)[1] and *tert*-butylsulfinyl imide **8** were synthesized by following literature procedures.[2] The reaction between **1a** and ethyl malonic acid gave compound **11** which is reported in the literature.[3] NMR spectra were obtained at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) in deuterated solvents. Reaction products were purified by column chromatography on silica gel (particle size 40-63 μm) as described below.

2. Cyanomethylation optimization

2.1. Catalyst screening[a]

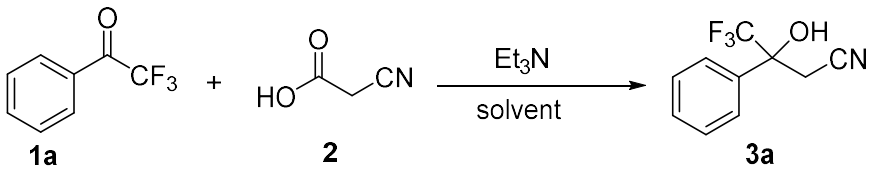


1a **2** **3a**

entry	catalyst	catalyst mol%	solvent	time (h)	temp (°C)	yield (%)[b]
1	DBU	50	THF	42	25	49
2	No base	--	THF	42	25	nr
3	Et_3N	50	THF	42	25	45
4	DIPEA	50	THF	42	25	29
5	DABCO	50	THF	42	25	13
6	TMEDA	50	THF	42	25	23
7	DMAP	50	THF	42	25	36
8	Barton's base	50	THF	42	25	42
9	K_2CO_3	50	THF	42	25	<5
10	Cs_2CO_3	50	THF	42	25	9
11	$Cu(OTf)_2$	20	THF	42	25	nr
12	$Zn(OTf)_2$	20	THF	42	25	<5

[a]Conditions: 0.3 mmol of **1a**, 0.9 mmol of **2**, 1 mL of THF at 25 °C. [b]By NMR analysis. nr=no reaction.

2.2. Solvent and temperature optimization[a]



1a **2** **3a**

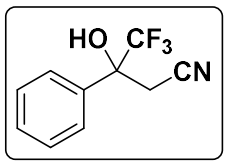
entry	Et_3N (mol%)	solvent	time (h)	temp (^oC)	yield (%)[b]
1	50	CH_2Cl_2	48	25	<5
2	50	1,4-Dioxane	48	25	27
3	50	Toluene	48	25	<5
4	50	CH_3CN	48	25	8
5	50	CH_3OH	48	25	<5
6	50	H_2O	48	25	nr
7	10	Neat, MW	0.75	100	89
8	10	Neat, MW	0.5	125	90
9	10	Neat, MW	1	90	35
10	50	THF	16	60	99
11	20	THF	21	60	98[d]
12[c]	20	THF	24	60	98[d]
13[c]	10	THF	36	60	91

[a]Conditions: 0.3 mmol of **1a**, 0.9 mmol of **2**, 1 mL of solvent. [b]By NMR analysis. [c]Two equivalents of **2** were used. [d]Isolated yields. nr=no reaction.

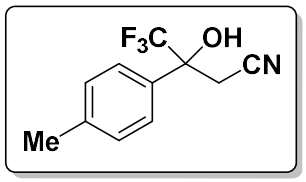
3. Synthetic methods and compound characterization

3.1. General procedure for the cyanomethylation of trifluoromethyl ketones

To a solution of a trifluoromethyl ketone (0.3 mmol) and cyanoacetic acid (0.6 mmol) in THF (1.0 mL) was added triethylamine (20 mol%). The resulting mixture was stirred at 60 ºC for 24 to 30 hours and the reaction was monitored by ^{19}F NMR for the disappearance of the trifluoromethyl ketone. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate as mobile phase as described below.

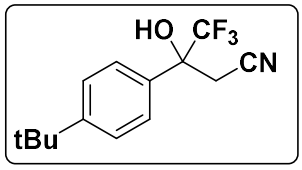


4,4,4-Trifluoro-3-hydroxy-3-phenylbutanenitrile (3a). Compound **3a** was obtained as a colorless solid in 98% yield (63 mg, 0.294 mmol) from 2,2,2-trifluoro-1-phenylethan-1-one (52 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 75.1-75.9 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.61 – 7.52 (m, 2H), 7.52 – 7.42 (m, 3H), 3.25 – 3.12 (m, 2H), 3.12 (s, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 134.3, 129.8, 128.9, 125.9 (q, J_{C-F} = 1.3 Hz), 124.1 (q, J_{C-F} = 286.0 Hz), 114.8, 75.2 (q, J_{C-F} = 29.7 Hz), 26.9 (q, J_{C-F} = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.5; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8F_3NO$ 215.0558, found 215.0553.

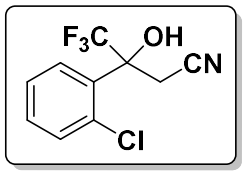


4,4,4-Trifluoro-3-hydroxy-3-(*p*-tolyl)butanenitrile (3b). Compound **3b** was obtained as a colorless solid in 97% yield (67 mg, 0.291 mmol) from 2,2,2-trifluoro-1-(*p*-tolyl)ethan-1-one (56 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 116.3-117.1 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.42 (d,

J = 7.9 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 3.38 (s, 1H), 3.23 – 3.08 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 140.0, 131.4, 129.6, 125.8 (q, $J_{C\text{-}F}$ = 1.5 Hz), 124.2 (q, $J_{C\text{-}F}$ = 286.0 Hz), 114.8, 75.2 (q, $J_{C\text{-}F}$ = 29.8 Hz), 26.9 (q, $J_{C\text{-}F}$ = 1.7 Hz), 21.1; ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.8; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{11}H_{10}F_3NO$ 229.0714, found 229.0707.

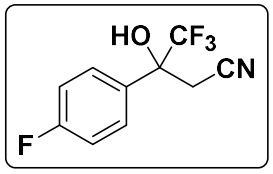


3-(4-(*tert*-Butyl)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3c). Compound **3c** was obtained as a colorless solid in 98% yield (80 mg, 0.294 mmol) from 1-(4-(*tert*-butyl)phenyl)-2,2,2-trifluoroethan-1-one (69 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 127.6-128.6 °C; R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.52 – 7.44 (m, 4H), 3.24 – 3.16 (m, 2H), 3.00 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 152.9, 131.3, 125.8, 125.6 (q, $J_{C\text{-}F}$ = 1.4 Hz), 124.2 (q, $J_{C\text{-}F}$ = 286.1 Hz), 115.0, 75.1 (q, $J_{C\text{-}F}$ = 29.7 Hz), 34.6, 31.1, 26.8 (q, $J_{C\text{-}F}$ = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.6; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{16}F_3NO$ 271.1184, found 271.1175.

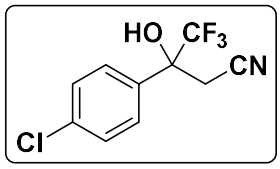


3-(2-Chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3d). Compound **3d** was obtained as a colorless solid in 93% yield (69 mg, 0.279 mmol) from 1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-one (62 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 87.5-88.3 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.67 (m, 1H), 7.47 (m, 1H), 7.43 – 7.36 (m, 2H), 4.52 (s, 1H), 3.73 (d, J = 17.1 Hz, 1H), 3.31 (d, J = 17.1 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 132.4, 132.0,

131.4, 130.7, 130.3 (q, J_{C-F} = 1.3 Hz), 127.6, 124.2 (q, J_{C-F} = 287.5 Hz), 114.9, 76.6 (q, J_{C-F} = 30.7 Hz), 26.4 (q, J_{C-F} = 1.9 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -78.8; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_7ClF_3NO$ 249.0168, found 249.0166.

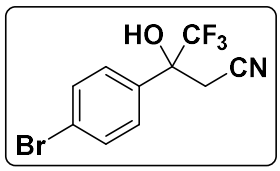


4,4,4-Trifluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (3e). Compound **3e** was obtained as a colorless solid in 99% yield (69 mg, 0.297 mmol) from 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-one (57 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 111.5-112.7 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.55 (dd, *J* = 8.7, 5.0 Hz, 2H), 7.20 – 7.09 (m, 2H), 3.55 (s, 1H), 3.22 – 3.13 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 163.5 (d, J_{C-F} = 250.3 Hz), 130.1 (d, J_{C-F} = 3.4 Hz), 128.1 (dq, J_{C-F} = 8.7, 1.5 Hz), 124.1 (q, J_{C-F} = 285.8 Hz), 116.0 (d, J_{C-F} = 21.9 Hz), 114.5, 75.0 (q, J_{C-F} = 30.0 Hz), 27.1 (q, J_{C-F} = 1.8 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.7 (s, 3F), -111.0 (m, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_7F_4NO$ 233.0464, found 233.0459.

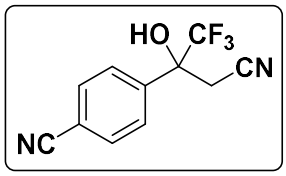


3-(4-Chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3f). Compound **3f** was obtained as a colorless solid in 99% yield (74 mg, 0.297 mmol) from 1-(4-chlorophenyl)-2,2,2-trifluoroethan-1-one (62 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 123.0-124.3 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.53 – 7.50 (m, 2H), 7.49 – 7.43 (m, 2H), 3.19 (s, 2H), 3.00 (s, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 136.2, 132.8, 129.2, 127.5 (q, J_{C-F} = 1.5 Hz), 124.0 (q, J_{C-F} = 286.1 Hz), 114.4, 75.0 (q, J_{C-F} = 29.9 Hz), 27.1 (q, J_{C-F} = 1.7 Hz); ^{19}F NMR (376 MHz,

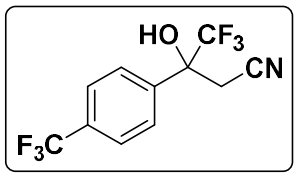
Chloroform-*d*) δ = -79.6; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_7ClF_3NO$ 249.0168, found 249.0166.



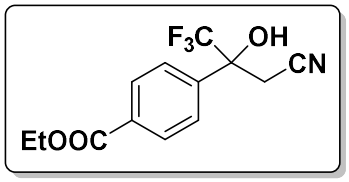
3-(4-Bromophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3g). Compound **3g** was obtained as a colorless solid in 96% yield (84 mg, 0.288 mmol) from 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (76 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 121.3-122.6 °C; R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.60 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 3.63 (s, 1H), 3.17 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 133.3, 132.1, 127.7 (q, $J_{C\text{-}F}$ = 1.4 Hz), 124.5, 123.9 (q, $J_{C\text{-}F}$ = 286.1 Hz), 114.5, 75.0 (q, $J_{C\text{-}F}$ = 29.9 Hz), 27.0 (q, $J_{C\text{-}F}$ = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.7; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_7BrF_3NO$ 292.9663, found 292.9658.



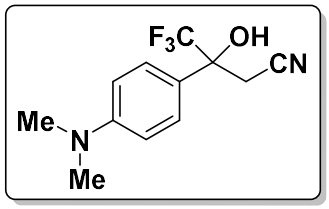
4-(3-Cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (3h). Compound **3h** was obtained as a colorless solid in 97% yield (70 mg, 0.291 mmol) from 4-(2,2,2-trifluoroacetyl)benzonitrile (60 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 123.7-124.8 °C; R_f = 0.4 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.01 – 7.95 (m, 2H), 7.91 – 7.84 (m, 3H), 3.85 (d, *J* = 17.1 Hz, 1H), 3.43 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 141.1, 132.3, 127.8, 124.4 (q, $J_{C\text{-}F}$ = 287.7 Hz), 118.3, 116.2, 112.2, 74.2 (q, $J_{C\text{-}F}$ = 28.8 Hz), 25.5; ^{19}F NMR ((376 MHz, DMSO-d_6) δ = -78.5; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{11}H_7F_3N_2O$ 240.051, found 240.0508.



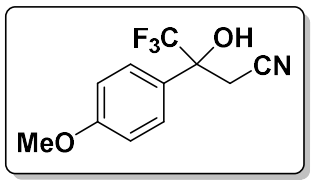
4,4,4-Trifluoro-3-hydroxy-3-(4-(trifluoromethyl)phenyl)butanenitrile (3i). Compound **3i** was obtained as a colorless solid in 99% yield (84 mg, 0.297 mmol) from 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one (73 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 71.6-72.4 °C; R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.75 – 7.70 (m, 4H), 3.53 (s, 1H), 3.23 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 138.1, 132.1 (q, $J_{C\text{-}F}$ = 33.0 Hz), 126.7 (q, $J_{C\text{-}F}$ = 1.4 Hz), 125.9 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.9 (q, $J_{C\text{-}F}$ = 285.1 Hz), 123.6 (q, $J_{C\text{-}F}$ = 271.3 Hz), 114.4, 75.1 (q, $J_{C\text{-}F}$ = 30.1 Hz), 27.0 (q, $J_{C\text{-}F}$ = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -63.1 (s, 3F), -79.5 (s, 3F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{11}H_7F_6NO$ 283.0432, found 283.0427.



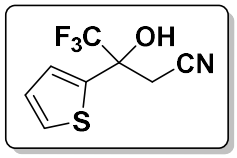
Ethyl 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (3j). Compound **3j** was obtained as a colorless oil in 96% yield (83 mg, 0.288 mmol) from ethyl 4-(2,2,2-trifluoroacetyl)benzoate (74 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 30 hours at 60 ºC by following the general procedure described above. R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.09 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 4.49 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.22 (s, 2H), 1.39 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 166.2, 139.2, 131.6, 129.9, 126.3 (q, $J_{C\text{-}F}$ = 1.6 Hz), 124.1 (q, $J_{C\text{-}F}$ = 286.4 Hz), 114.5, 75.1 (q, $J_{C\text{-}F}$ = 29.8 Hz), 61.5, 26.9 (q, $J_{C\text{-}F}$ = 1.8 Hz), 14.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.4; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{13}H_{12}F_3NO_3$ 287.0769, found 287.0763.



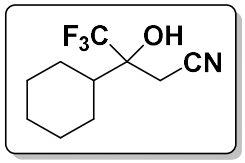
3-(4-(Dimethylamino)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3k). Compound **3k** was obtained as a colorless solid in 93% yield (58 mg, 0.279 mmol) from 1-(4-(dimethylamino)phenyl)-2,2,2-trifluoroethan-1-one (72 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 30 hours at 60 ºC by following the general procedure described above. Mp. 110.3-111.2 °C; R_f = 0.4 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.37 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.73 (dd, *J* = 7.2, 2.0 Hz, 2H), 3.44 (s, 1H), 3.19 – 3.07 (m, 2H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 151.0, 126.8 (q, $J_{C\text{-}F}$ = 1.6 Hz), 124.4 (q, $J_{C\text{-}F}$ = 286.0 Hz), 121.2, 115.2, 112.0, 75.1 (q, $J_{C\text{-}F}$ = 29.6 Hz), 40.1, 26.7 (q, $J_{C\text{-}F}$ = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.9; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{12}H_{13}F_3N_2O$ 258.098, found 258.097.



4,4,4-Trifluoro-3-hydroxy-3-(4-methoxyphenyl)butanenitrile (3l). Compound **3l** was obtained as a colorless solid in 96% yield (70 mg, 0.288 mmol) from 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one (61 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 30 hours at 60 ºC by following the general procedure described above. Mp. 89.1-90.4 °C; R_f = 0.5 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.46 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.61 (s, 1H), 3.25 – 3.05 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 160.5, 127.4 (q, $J_{C\text{-}F}$ = 1.6 Hz), 126.2, 124.2 (q, $J_{C\text{-}F}$ = 286.0 Hz), 115.0, 114.2, 75.0 (q, $J_{C\text{-}F}$ = 29.8 Hz), 55.3, 26.9 (q, $J_{C\text{-}F}$ = 1.7 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -79.9; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{11}H_{10}F_3NO_2$ 245.0664, found 245.0658.

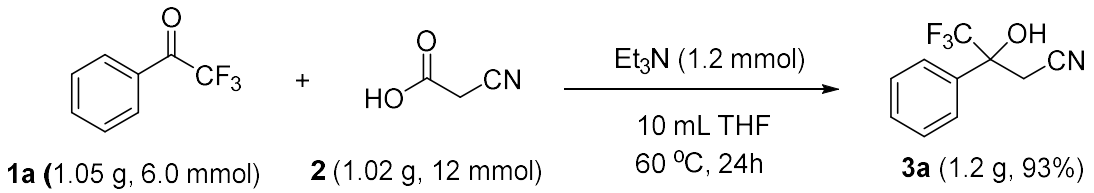


4,4,4-Trifluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (3m). Compound **3m** was obtained as a colorless solid in 94% yield (62 mg, 0.282 mmol) from 2,2,2-trifluoro-1-(thiophen-2-yl)ethan-1-one (54 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 24 hours at 60 ºC by following the general procedure described above. Mp. 64.0-65.2 °C; R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.43 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.23 (d, *J* = 5.2 Hz, 1H), 7.08 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.82 (s, 1H), 3.21 – 3.12 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 137.7, 127.6, 127.5, 126.9 (q, $J_{C\text{-}F}$ = 1.6 Hz), 123.7 (d, $J_{C\text{-}F}$ = 286.0 Hz), 114.3, 74.5 (q, $J_{C\text{-}F}$ = 31.2 Hz), 27.9 (q, $J_{C\text{-}F}$ = 1.6 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -80.5; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_8H_6F_3NOS$ 221.0122, found 221.0119.



3-Cyclohexyl-4,4,4-trifluoro-3-hydroxybutanenitrile (3n). Compound **3n** was obtained as a colorless solid in 92% yield (61 mg, 0.276 mmol) from 1-cyclohexyl-2,2,2-trifluoroethan-1-one (54 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 30 hours at 60 ºC by following the general procedure described above. Mp. 50.2-51.4 °C; R_f = 0.3 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 2.87 (s, 1H), 2.79 (s, 2H), 1.98 – 1.79 (m, 5H), 1.71 (m, 1H), 1.38 – 1.04 (m, 5H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 125.3 (q, $J_{C\text{-}F}$ = 288.1 Hz), 115.3, 75.8 (q, $J_{C\text{-}F}$ = 27.2 Hz), 43.1, 26.8 (q, $J_{C\text{-}F}$ = 1.8 Hz), 26.3, 25.8, 22.5 (q, $J_{C\text{-}F}$ = 2.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -75.9; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_{14}F_3NO$ 221.1027, found 221.1024.

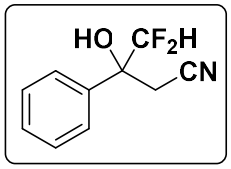
3.2. Gram scale synthesis of 4,4,4-trifluoro-3-hydroxy-3-phenylbutanenitrile (3a)



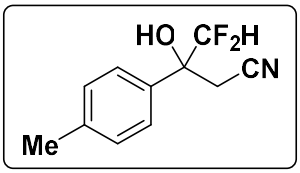
1a (1.05 g, 6.0 mmol) **2** (1.02 g, 12 mmol) **3a** (1.2 g, 93%)

3.3. General procedure for the cyanomethylation of difluoromethyl ketones

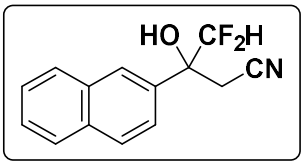
To a solution of a difluoromethyl ketone (0.3 mmol) and cyanoacetic acid (0.6 mmol) in THF (1.0 mL) was added triethylamine (20 mol%). The resulting mixture was stirred at 70 ºC for 48 hours and the reaction was monitored by ^{19}F NMR for the disappearance of the difluoromethyl ketone. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate as mobile phase as described below.



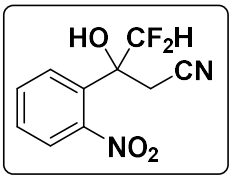
4,4-Difluoro-3-hydroxy-3-phenylbutanenitrile (5a). Compound **5a** was obtained as a colorless oil in 99% yield (58 mg, 0.297 mmol) from 2,2-difluoro-1-phenylethan-1-one (47 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. R_f = 0.16 (hexanes/EtOAc, 8:2); ^1H NMR (400 MHz, Chloroform-*d*) δ = 7.51 (dd, *J* = 7.7, 2.0 Hz, 2H), 7.48 – 7.40 (m, 3H), 5.83 (t, *J* = 55.6 Hz, 1H), 3.30 (s, 1H), 3.07 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 136.3 (t, J_{C-F} = 1.4 Hz), 129.5, 129.1, 125.8 (t, J_{C-F} = 1.5 Hz), 115.8, 115.6 (t, J_{C-F} = 251.0 Hz), 74.6 (t, J_{C-F} = 22.1 Hz), 25.7 (t, J_{C-F} = 3.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -129.0 (dd, *J* = 282.0, 56.4 Hz, 1F), -130.0 (dd, *J* = 282.0, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_9F_2NO$ 197.0652, found 197.0648.



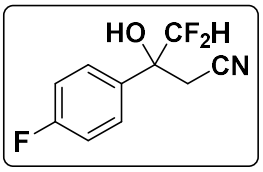
4,4-Difluoro-3-hydroxy-3-(*p*-tolyl)butanenitrile (5b). Compound **5b** was obtained as a colorless oil in 92% yield (58 mg, 0.276 mmol) from 2,2-difluoro-1-(*p*-tolyl)ethan-1-one (51 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. R_f = 0.13 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.42 – 7.36 (m, 2H), 7.28 – 7.23 (m, 2H), 5.83 (t, *J* = 55.6 Hz, 1H), 3.07 (s, 2H), 2.93 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 139.6, 133.3, 129.9, 125.7 (t, $J_{C\text{-}F}$ = 1.5 Hz), 115.7, 115.6 (t, $J_{C\text{-}F}$ = 250.1 Hz), 74.6 (t, $J_{C\text{-}F}$ = 22.2 Hz), 25.7 (t, $J_{C\text{-}F}$ = 3.3 Hz), 21.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -129.1 (dd, *J* = 280.9, 56.4 Hz, 1F), -130.2 (dd, *J* = 281.0, 56.3 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{11}H_{11}F_2NO$ 211.0809, found 211.0800.



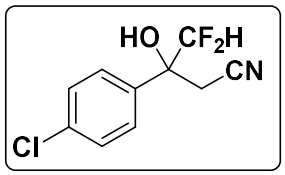
4,4-Difluoro-3-hydroxy-3-(naphthalen-2-yl)butanenitrile (5c). Compound **5c** was obtained as a colorless solid in 93% yield (69 mg, 0.279 mmol) from 2,2-difluoro-1-(naphthalen-2-yl)ethan-1-one (62 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. Mp. 80.0-82.9 °C; R_f = 0.13 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.03 (s, 1H), 7.95 – 7.80 (m, 3H), 7.62 – 7.48 (m, 3H), 5.92 (t, *J* = 55.5 Hz, 1H), 3.30 (s, 1H), 3.16 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 133.6 (t, $J_{C\text{-}F}$ = 1.5 Hz), 133.5, 133.0, 129.1, 128.6, 127.8, 127.3, 127.0, 125.8 (t, $J_{C\text{-}F}$ = 1.5 Hz), 122.7 (t, $J_{C\text{-}F}$ = 1.6 Hz), 115.7, 115.6 (t, $J_{C\text{-}F}$ = 250.5 Hz), 74.8 (t, $J_{C\text{-}F}$ = 22.1 Hz), 25.8 (t, $J_{C\text{-}F}$ = 3.2 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -128.7 (dd, *J* = 281.6, 56.4 Hz, 1F), -129.6 (dd, *J* = 282.4, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{11}F_2NO$ 247.0809, found 247.0803.



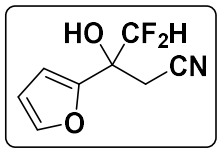
4,4-Difluoro-3-hydroxy-3-(2-nitrophenyl)butanenitrile (5d). Compound **5d** was obtained as a colorless oil in 99% yield (72 mg, 0.297 mmol) from 2,2-difluoro-1-(2-nitrophenyl)ethan-1-one (60 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. R_f = 0.1 (hexanes/EtOAc, 1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.68 – 7.61 (m, 2H), 7.60 – 7.52 (m, 2H), 6.36 (t, *J* = 56.0 Hz, 1H), 3.44 (s, 1H), 3.34 (d, *J* = 17.2 Hz, 1H), 3.21 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 150.5, 132.0, 130.9, 128.9 (t, $J_{C\text{-}F}$ = 1.9 Hz), 128.8 (t, $J_{C\text{-}F}$ = 1.6 Hz), 125.3, 115.1, 114.3 (t, $J_{C\text{-}F}$ = 250.5 Hz), 75.6 (t, $J_{C\text{-}F}$ = 22.1 Hz), 25.3 (t, $J_{C\text{-}F}$ = 3.8 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -129.0 (dd, *J* = 286.1, 55.3 Hz, 1F), -130.4 (dd, *J* = 286.1, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8F_2N_2O_3$ 242.0503, found 242.05.



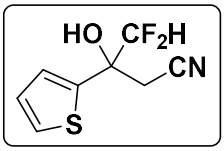
4,4-Difluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (5e). Compound **5e** was obtained as a colorless solid in 92% yield (59 mg, 0.276 mmol) from 2,2-difluoro-1-(4-fluorophenyl)ethan-1-one (52 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. Mp. 71.2-72.6 °C; R_f = 0.18 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.50 – 7.46 (m, 2H), 7.12 (dd, *J* = 8.6, 7.8 Hz, 2H), 5.77 (t, *J* = 55.6 Hz, 1H), 3.49 (s, 1H), 3.05 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 163.3 (d, $J_{C\text{-}F}$ = 249.1 Hz), 132.1 (t, $J_{C\text{-}F}$ = 2.6 Hz), 128.0 (dt, $J_{C\text{-}F}$ = 8.6, 1.6 Hz), 116.0 (d, $J_{C\text{-}F}$ = 21.7 Hz), 115.7, 115.4 (t, $J_{C\text{-}F}$ = 251.3 Hz), 74.3 (t, $J_{C\text{-}F}$ = 22.2 Hz), 25.7 (t, $J_{C\text{-}F}$ = 3.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -112.1 (m, 1F), -129.1 (dd, *J* = 282.0, 56.4 Hz, 1F), -129.8 (dd, *J* = 282.0, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8F_3NO$ 215.0558, found 215.0554.



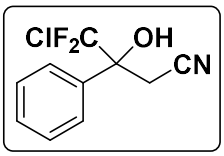
3-(4-Chlorophenyl)-4,4-difluoro-3-hydroxybutanenitrile (5f). Compound **5f** was obtained as a colorless solid in 99% yield (68 mg, 0.297 mmol) from 1-(4-chlorophenyl)-2,2-difluoroethan-1-one (57 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. Mp. 64.2-64.8 °C; R_f = 0.13 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.56 – 7.33 (m, 4H), 5.79 (t, *J* = 55.5 Hz, 1H), 3.30 (s, 1H), 3.05 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 135.8, 134.7, 129.3, 127.4 (t, $J_{C\text{-}F}$ = 1.5 Hz), 115.5, 115.3 (t, $J_{C\text{-}F}$ = 250.5 Hz), 74.4 (t, $J_{C\text{-}F}$ = 22.3 Hz), 25.8 (t, $J_{C\text{-}F}$ = 3.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -128.9 (dd, *J* = 282.4, 56.4 Hz, 1F), -129.8 (dd, *J* = 282.4, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8ClF_2NO$ 231.0262, found 231.0256.



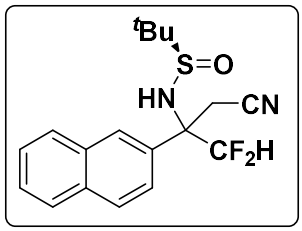
4,4-Difluoro-3-(furan-2-yl)-3-hydroxybutanenitrile (5g). Compound **5g** was obtained as a colorless oil in 90% yield (51 mg, 0.27 mmol) from 2,2-difluoro-1-(furan-2-yl)ethan-1-one (44 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. R_f = 0.12 (hexanes/EtOAc, 7:3); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.49 (m, 1H), 6.58 (d, *J* = 3.4 Hz, 1H), 6.45 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.95 (t, *J* = 55.3 Hz, 1H), 3.32 (s, 1H), 3.14 – 3.02 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 148.9 (t, $J_{C\text{-}F}$ = 1.5 Hz), 144.0, 115.3, 114.3 (t, $J_{C\text{-}F}$ = 251.1 Hz), 111.2, 109.8 (t, $J_{C\text{-}F}$ = 1.3 Hz), 72.0 (t, $J_{C\text{-}F}$ = 23.6 Hz), 23.8 (t, $J_{C\text{-}F}$ = 3.2 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -130.0 (dd, *J* = 282.7, 56.4 Hz, 1F), -131.0 (dd, *J* = 282.5, 56.4 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_8H_7F_2NO_2$ 187.0445, found 187.044.



4,4-Difluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (5h). Compound **5h** was obtained as a colorless oil in 94% yield (57 mg, 0.282 mmol) from 2,2-difluoro-1-(thiophen-2-yl)ethan-1-one (49 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in the presence of 20 mol% Et_3N in 1 mL of THF after 48 hours at 70 ºC by following the general procedure described above. R_f = 0.17 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.41 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.07 (dd, *J* = 4.9, 3.9 Hz, 1H), 5.87 (t, *J* = 55.6 Hz, 1H), 3.49 (s, 1H), 3.12 – 3.03 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 139.8 (t, $J_{C\text{-}F}$ = 1.6 Hz), 127.7, 127.2, 126.2 (t, $J_{C\text{-}F}$ = 1.6 Hz), 115.4, 114.9 (t, $J_{C\text{-}F}$ = 251.9 Hz), 74.0 (t, $J_{C\text{-}F}$ = 23.4 Hz), 26.6 (t, $J_{C\text{-}F}$ = 3.0 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -128.9 (dd, *J* = 281.2, 56.0 Hz, 1F), -129.7 (dd, *J* = 281.2, 55.6 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_8H_7F_2NOS$ 203.0216, found 203.021.



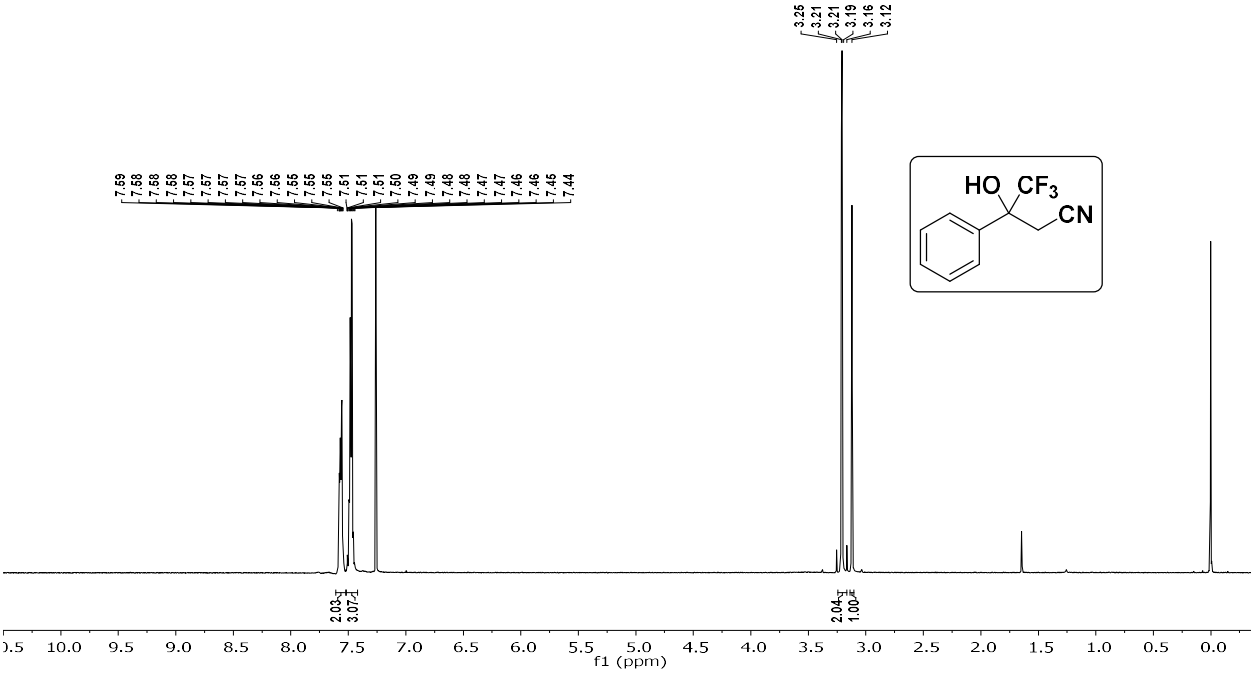
4-Chloro-4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (7). To a solution of 2-chloro-2,2-difluoro-1-phenylethan-1-one (**6**) (57 mg, 0.3 mmol) and cyanoacetic acid (51 mg, 0.6 mmol) in THF (1.0 mL) was added triethylamine (20 mol%). The resulting mixture was stirred at 70 ºC for 48 hours and the reaction was monitored by ^{19}F NMR for the disappearance of chlorodifluoromethyl ketone **6**. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate (9:1) as mobile phase. Compound **7** was obtained as a colorless solid in 96% yield (66 mg, 0.288 mmol). mp: 102.9-103.5 °C; R_f = 0.2 (hexanes/EtOAc, 8:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.57 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.48 – 7.44 (m, 3H), 3.45 (s, 1H), 3.34 – 3.18 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 135.0, 130.0, 129.9 (t, $J_{C\text{-}F}$ = 300.0 Hz), 128.9, 126.4 (t, $J_{C\text{-}F}$ = 1.8 Hz), 115.1, 78.8 (t, $J_{C\text{-}F}$ = 25.3 Hz), 27.4 (t, $J_{C\text{-}F}$ = 2.2 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ = -64.2; HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{10}H_8ClF_2NO$ 231.0262, found 231.0255.



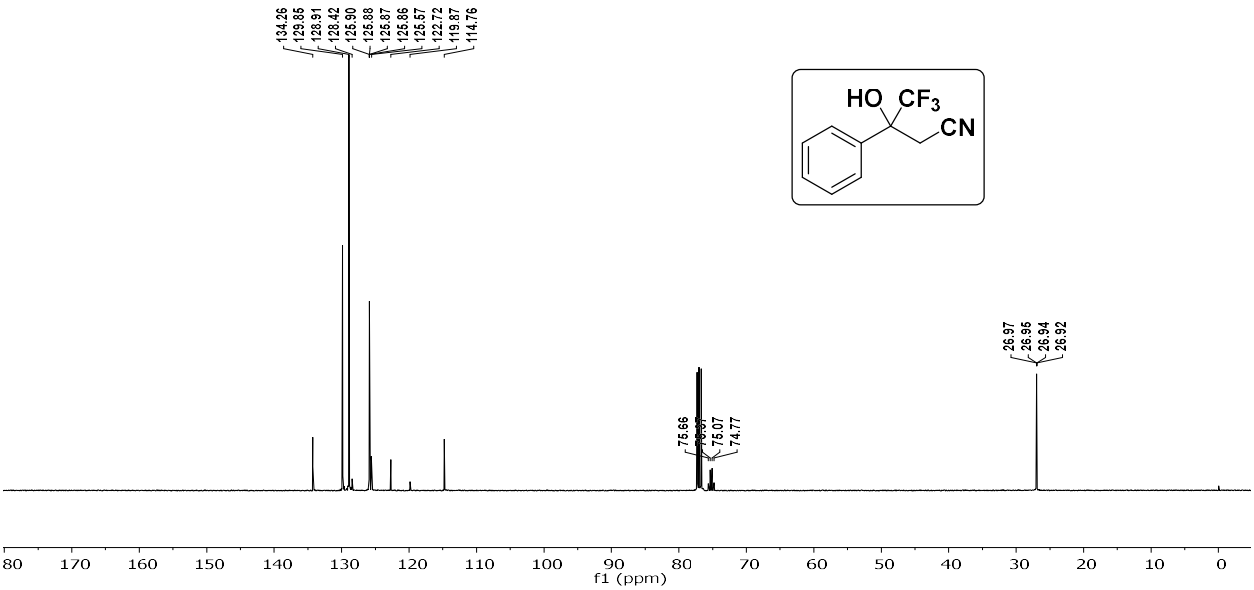
(*R*)-*N*-(3-cyano-1,1-difluoro-2-(naphthalen-2-yl)propan-2-yl)-2-methylpropane-2-sulfinamide (9). To a solution of 2-chloro-2,2-difluoro-1-phenylethan-1-one (**4c**) (250 mg, 1.21 mmol) and (*R*)-2-methylpropane-2-sulfinamide (161mg, 1.33 mmol) in THF (5.0 mL) was added $Ti(OEt)_4$ (552 mg, 2.42 mmol) and the reaction was refluxed for 48 hours. Cyanoacetic acid (308 mg, 3.63 mmol) and triethylamine (20 mol%) were added to the reaction mixture and stirred at 70 ºC for another 48 hours. The crude product was purified by flash chromatography on silica gel using hexanes-ethyl acetate (8:2) as mobile phase. Compound **9** was obtained as a pale yellow solid in 82% yield (347 mg, 0.992 mmol). mp: 109.2-110.1 °C; R_f = 0.21 (hexanes/EtOAc, 7:3); ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.01 (s, 1H), 7.97 – 7.81 (m, 3H), 7.64 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 6.64 (t, *J* = 54.5 Hz, 1H), 4.41 (s, 1H), 3.34 – 3.13 (m, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ = 133.3, 132.7, 131.6, 129.1, 128.7, 127.5, 127.5, 127.1, 126.9, 124.0, 115.7, 115.6 (t, $J_{C\text{-}F}$ = 243.8 Hz), 63.1 (t, $J_{C\text{-}F}$ = 20.6 Hz), 57.3 , 25.1 (t, $J_{C\text{-}F}$ = 3.4 Hz), 22.6; ^{19}F NMR (376 MHz, Chloroform-*d*) δ = Major diastereomer: -122.5 (dd, *J* = 282.0, 54.7 Hz, 1F), -129.5 (dd, *J* = 282.0, 54.3 Hz, 1F); Minor diastereomer: -125.3 (dd, *J* = 279.1, 55.6 Hz, 1F), -127.3 (dd, *J* = 279.1, 54.5 Hz, 1F); HRMS (ESI-TOF) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{20}F_2N_2OS$ 350.1264, found 350.1265.

4. NMR spectra

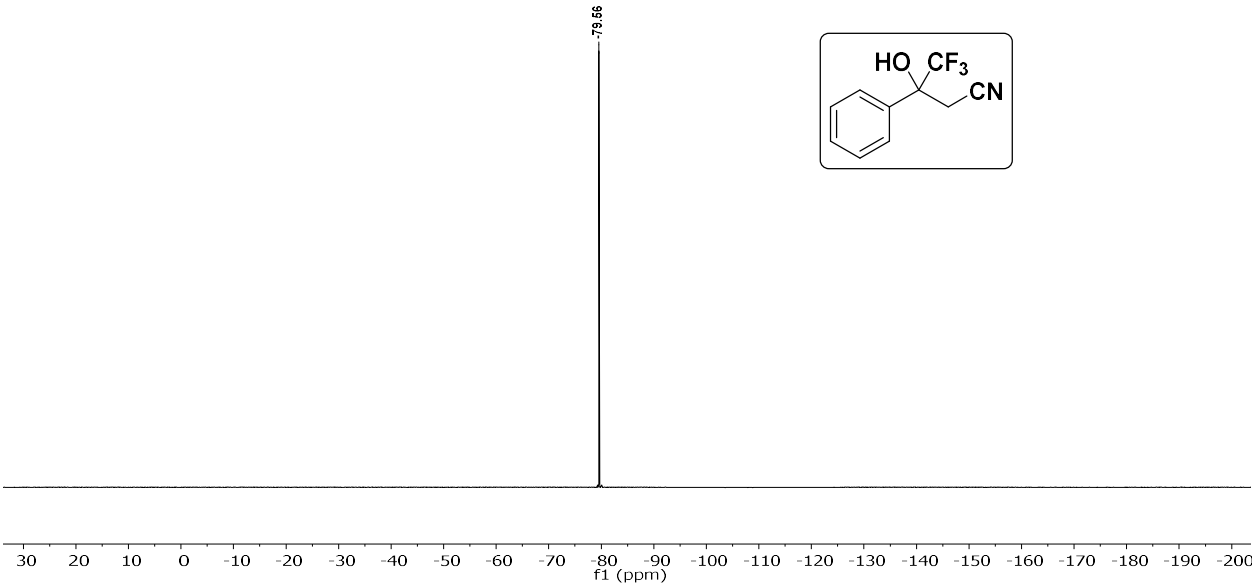
^{1}H NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-phenylbutanenitrile (3a).



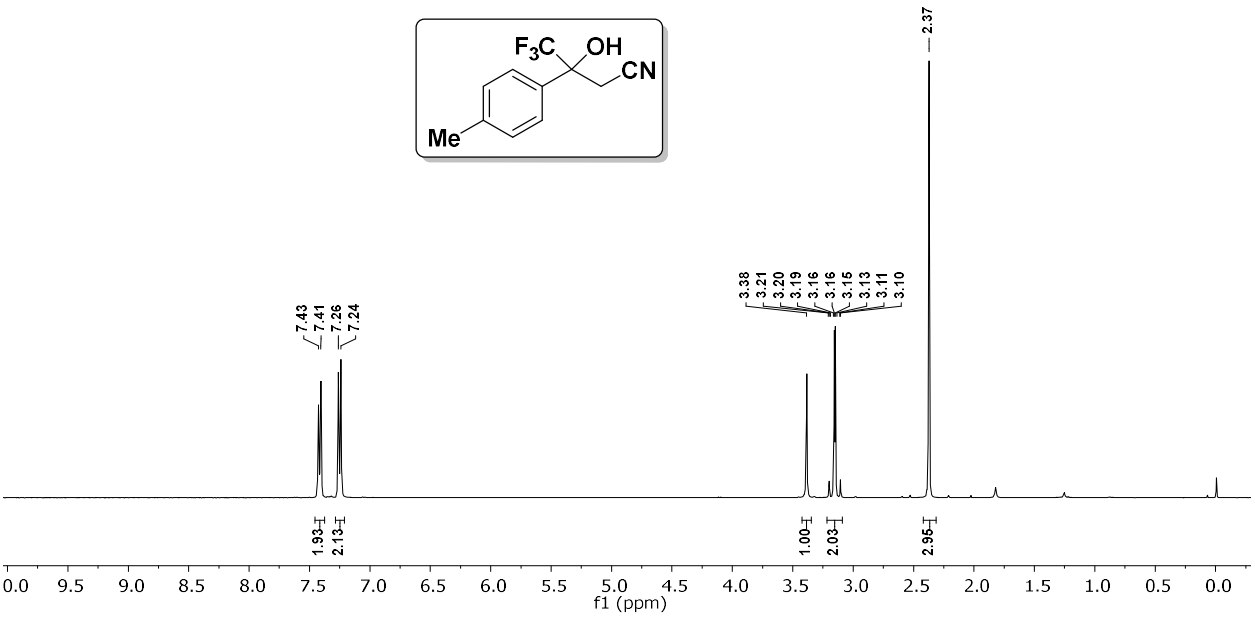
^{13}C NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-phenylbutanenitrile (3a).



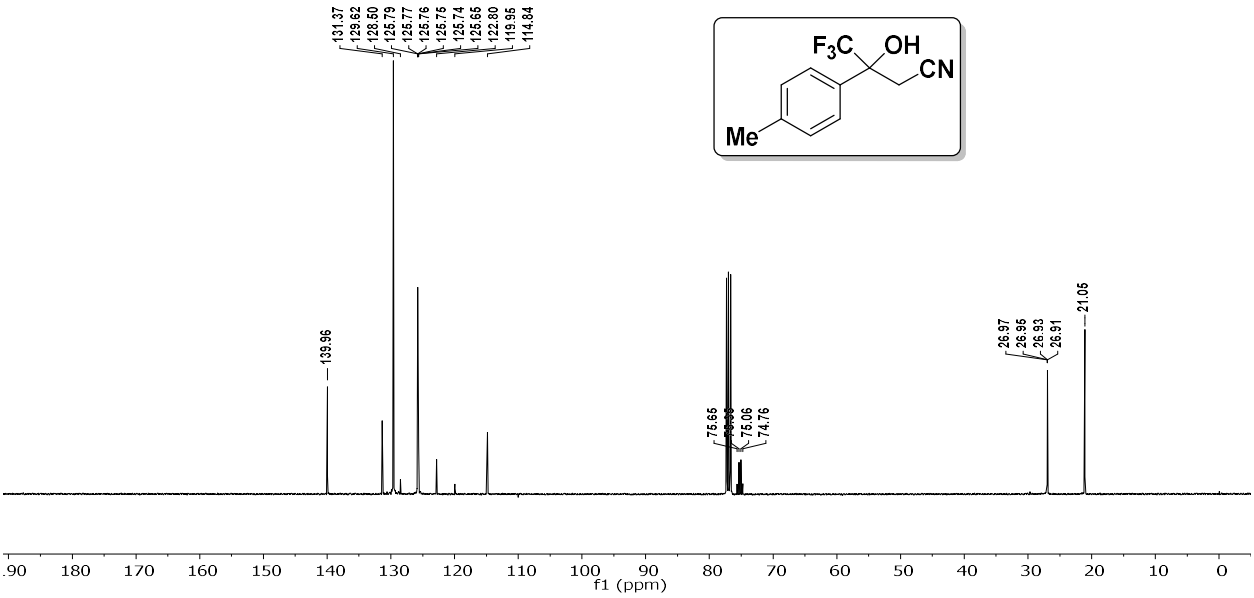
^{19}F NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-phenylbutanenitrile (3a).



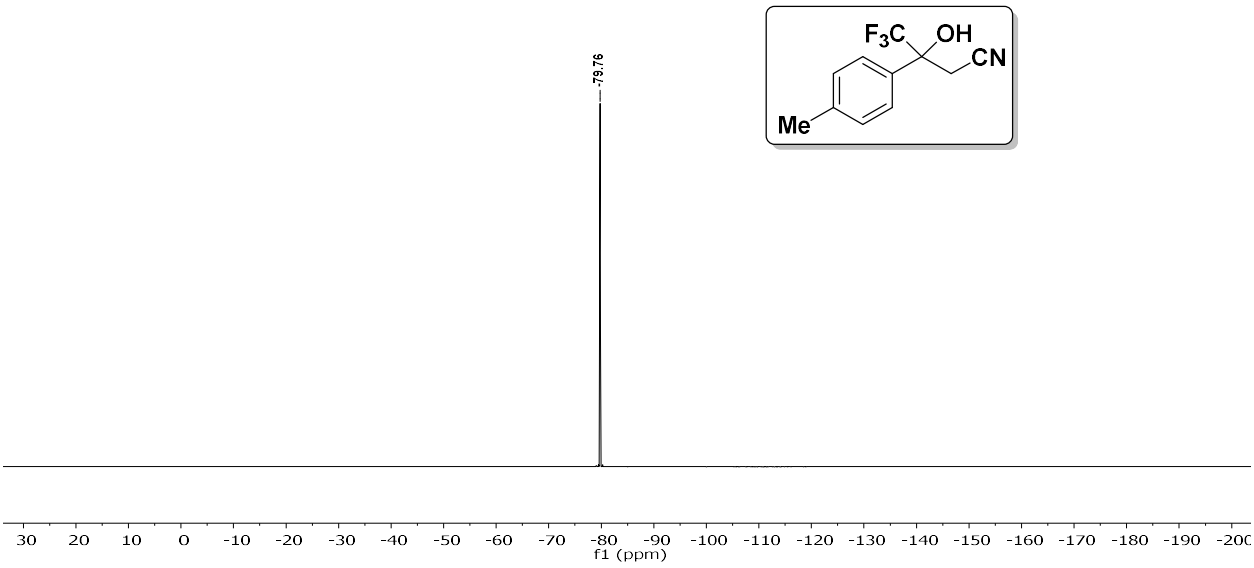
^{1}H NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(*p*-tolyl)butanenitrile (3b).



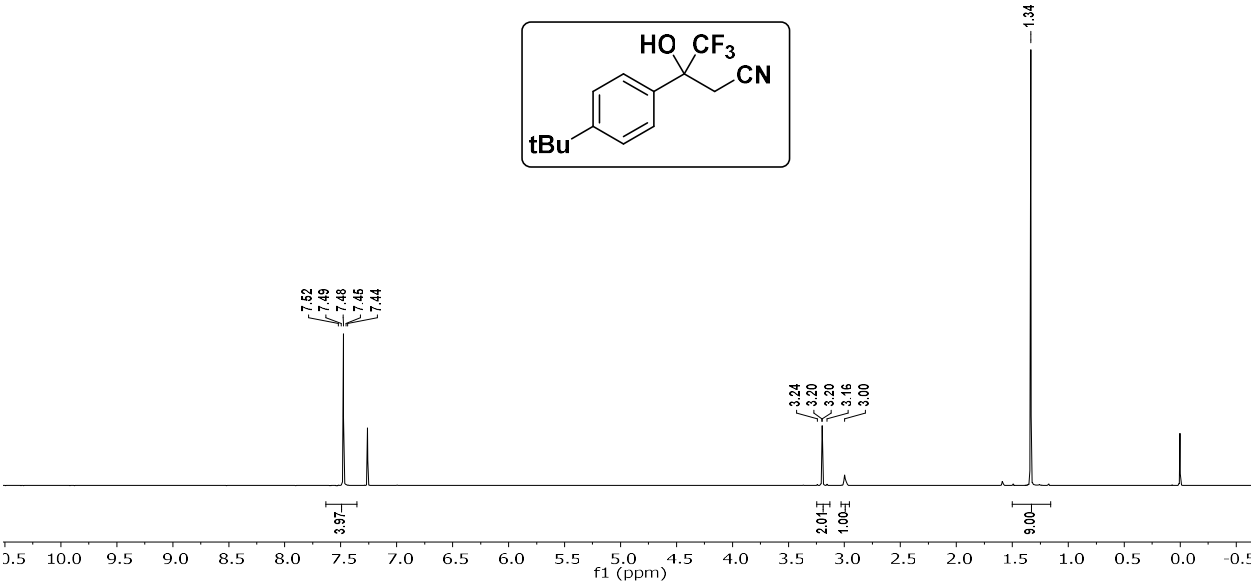
^{13}C NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(*p*-tolyl)butanenitrile (3b).



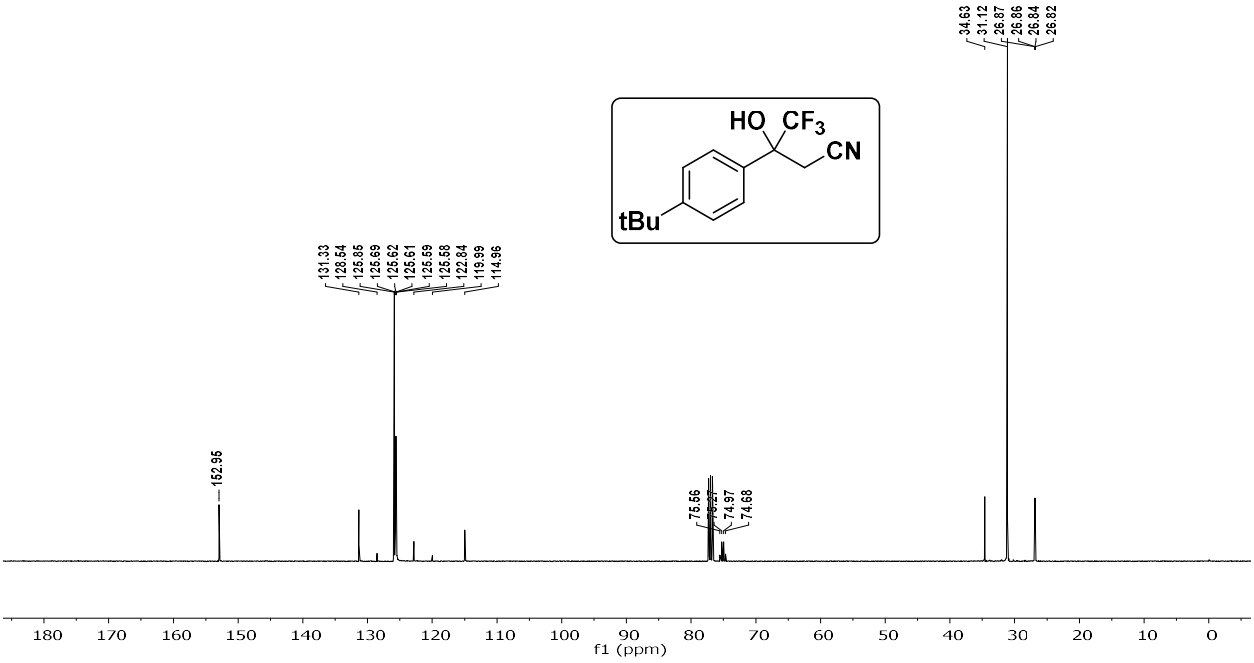
^{19}F NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(*p*-tolyl)butanenitrile (3b).



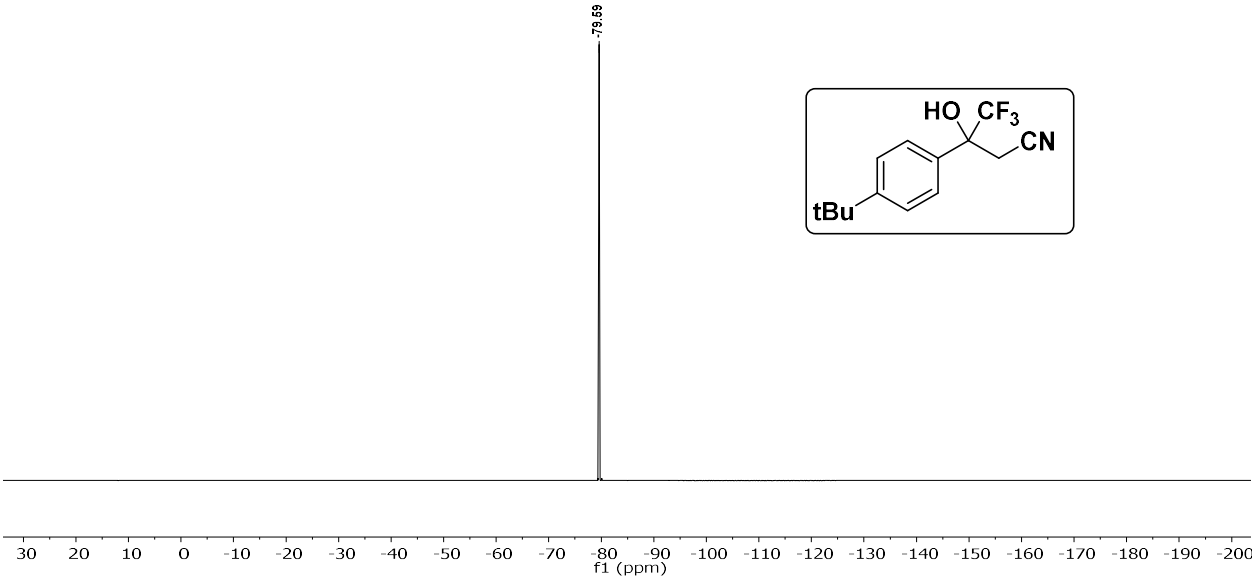
^{1}H NMR spectrum of 3-(4-(*tert*-butyl)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3c).



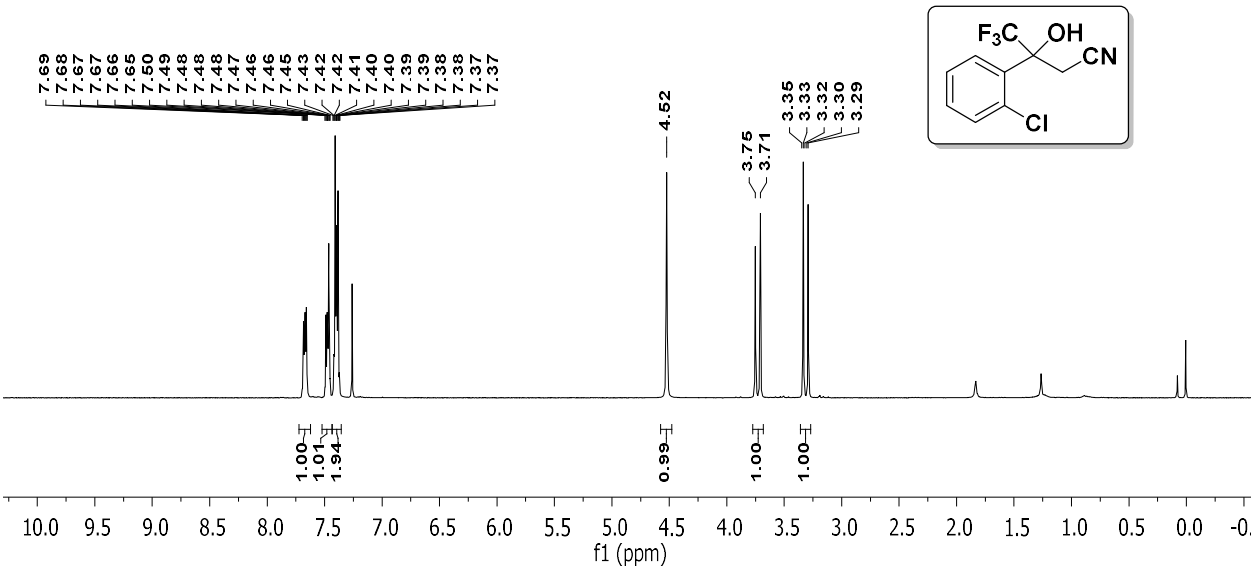
^{13}C NMR spectrum of 3-(4-(*tert*-butyl)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3c).



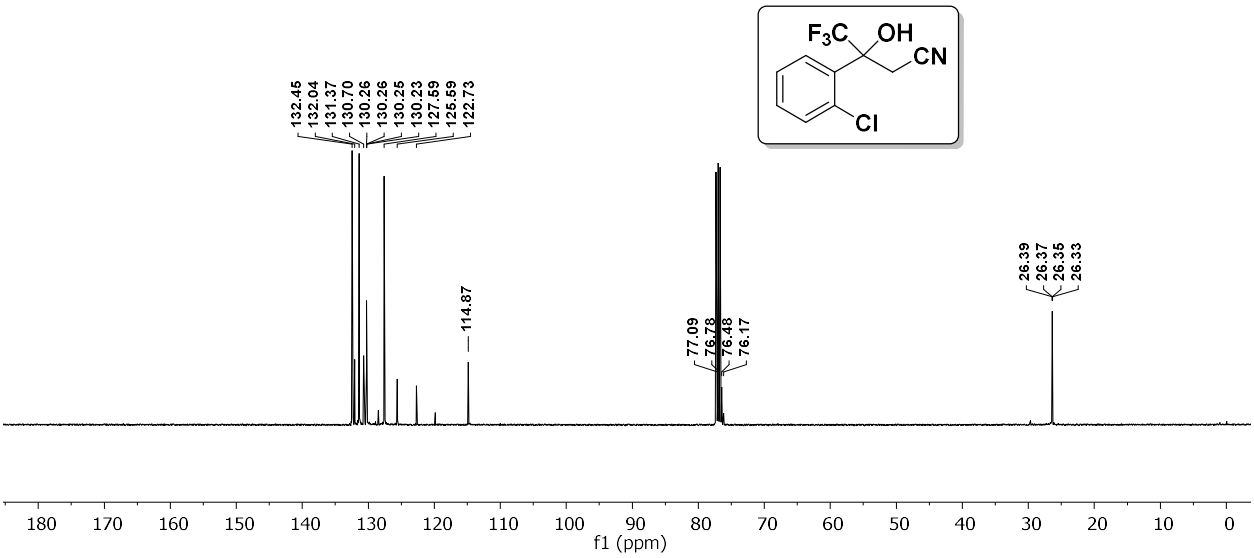
^{19}F NMR spectrum of 3-(4-(*tert*-butyl)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3c).



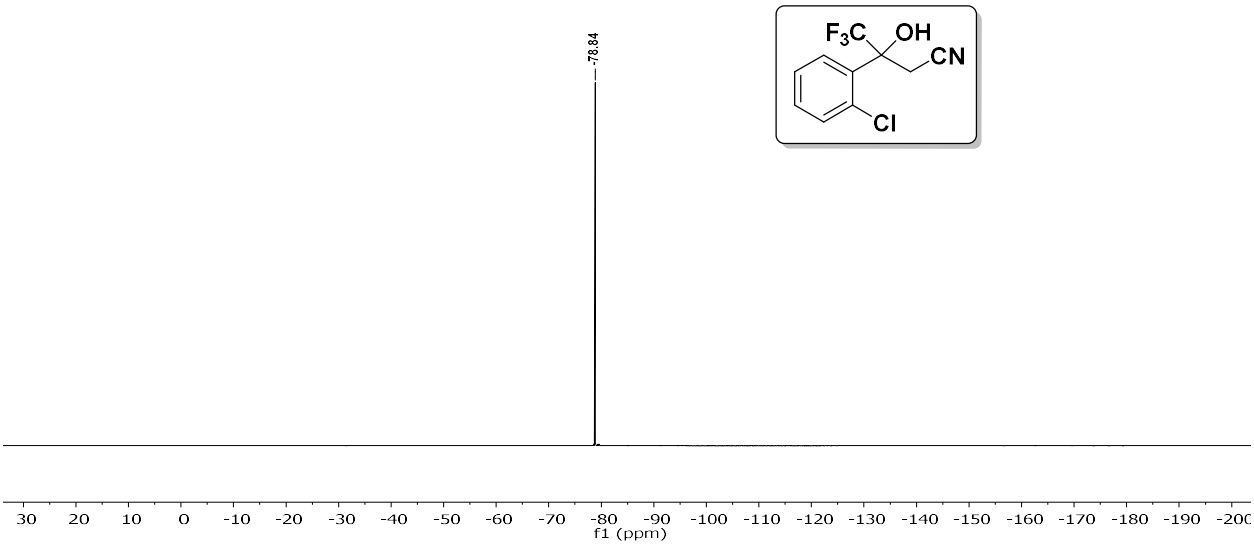
^{1}H NMR spectrum of 3-(2-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3d).



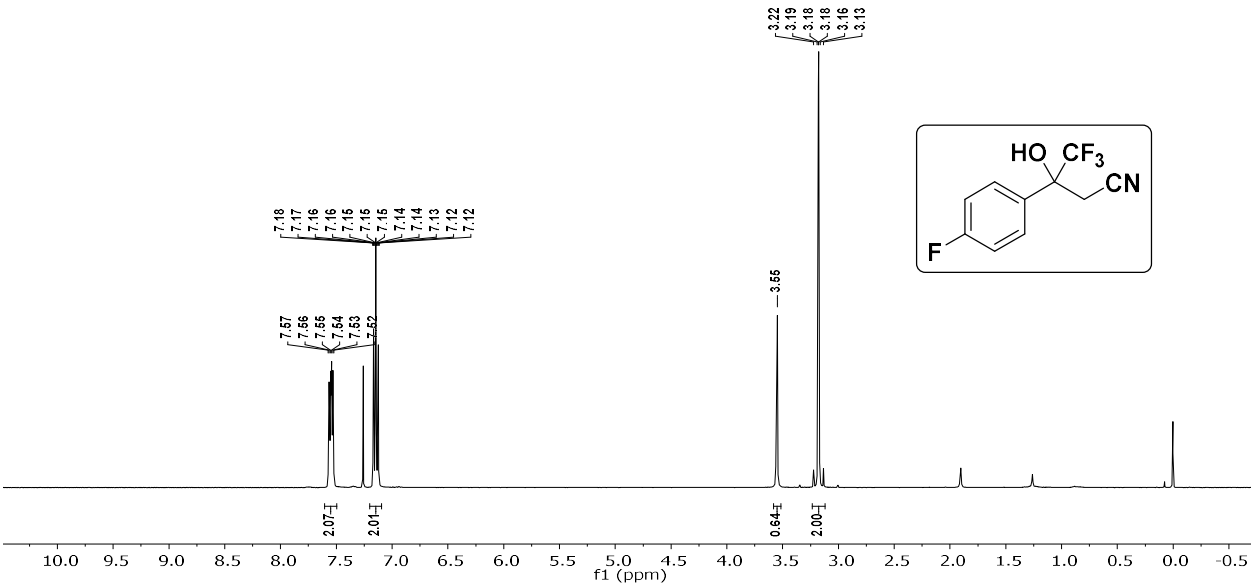
^{13}C NMR spectrum of 3-(2-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3d).



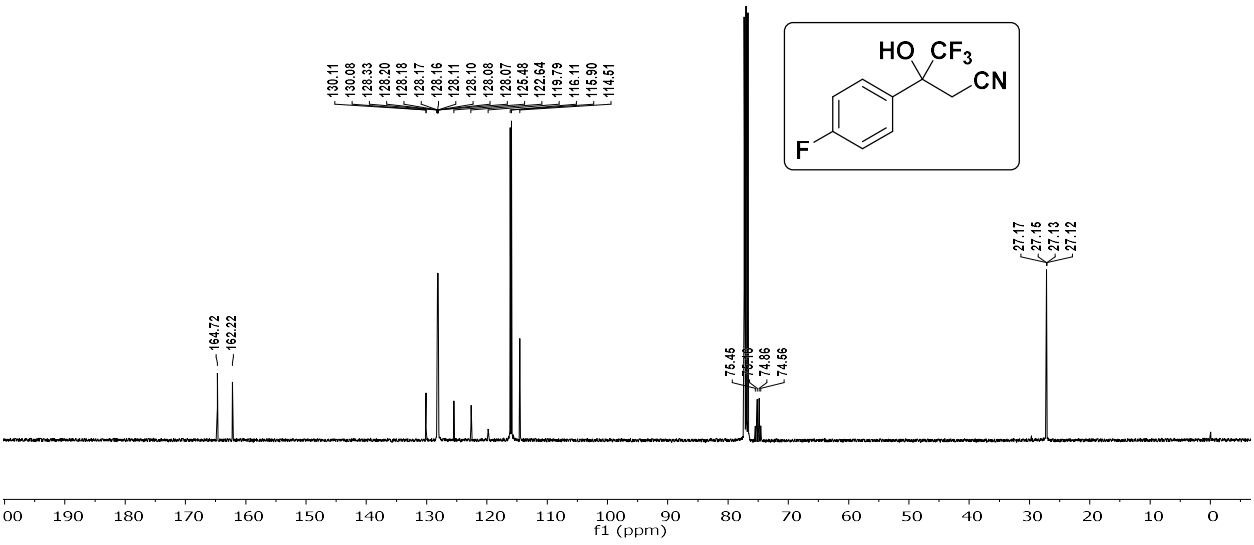
^{19}F NMR spectrum of 3-(2-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3d).



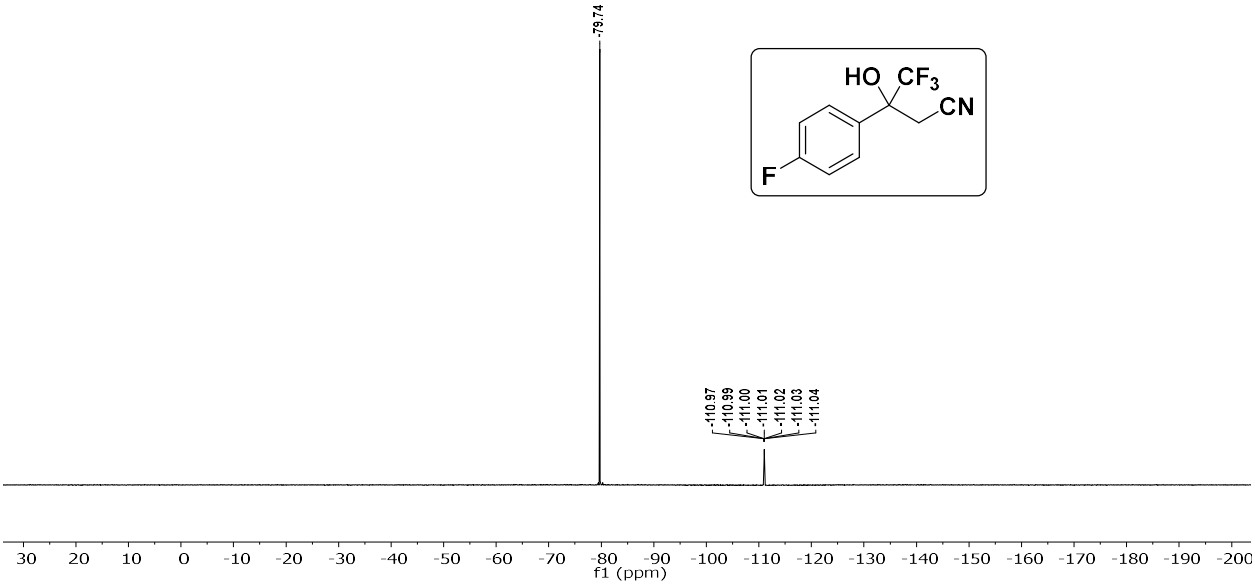
^{1}H NMR spectrum of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (3e).



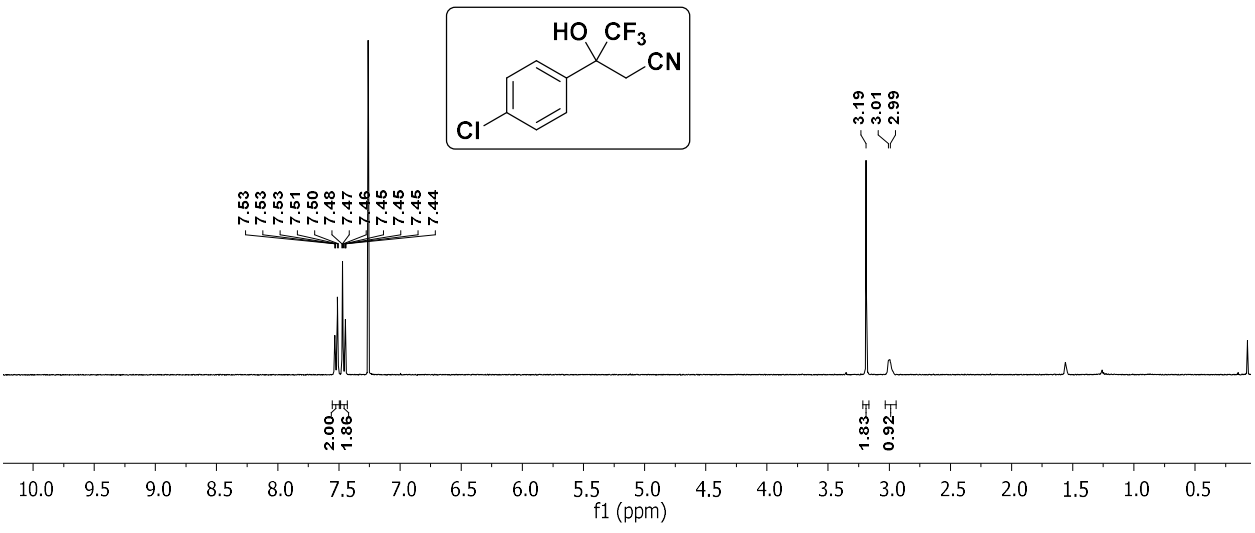
^{13}C NMR spectrum of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (3e).



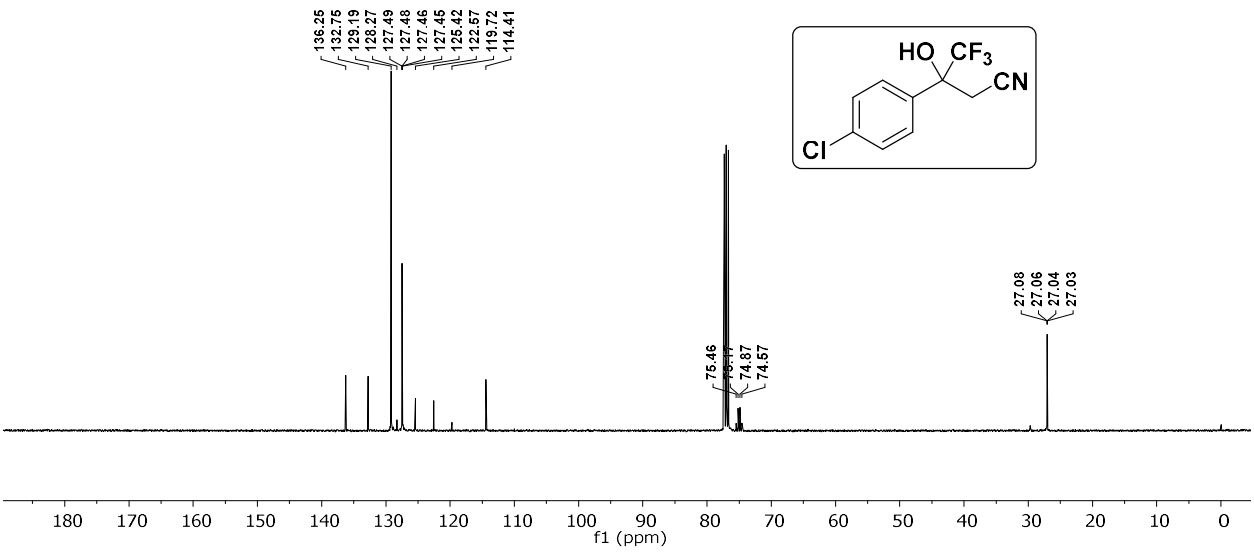
^{19}F NMR spectrum of 4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (3e).



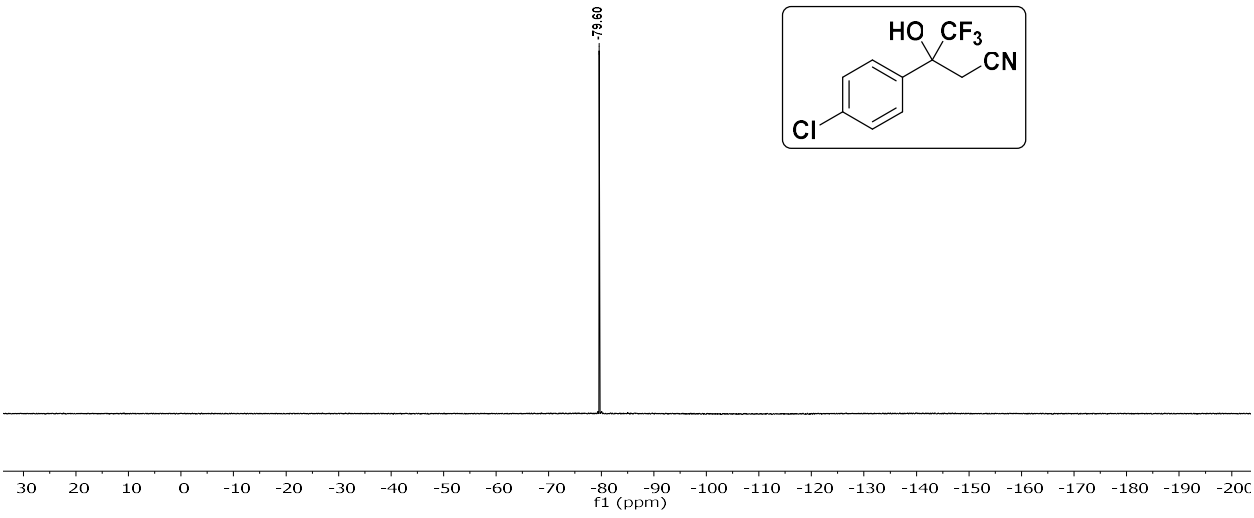
^{1}H NMR spectrum of 3-(4-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3f).



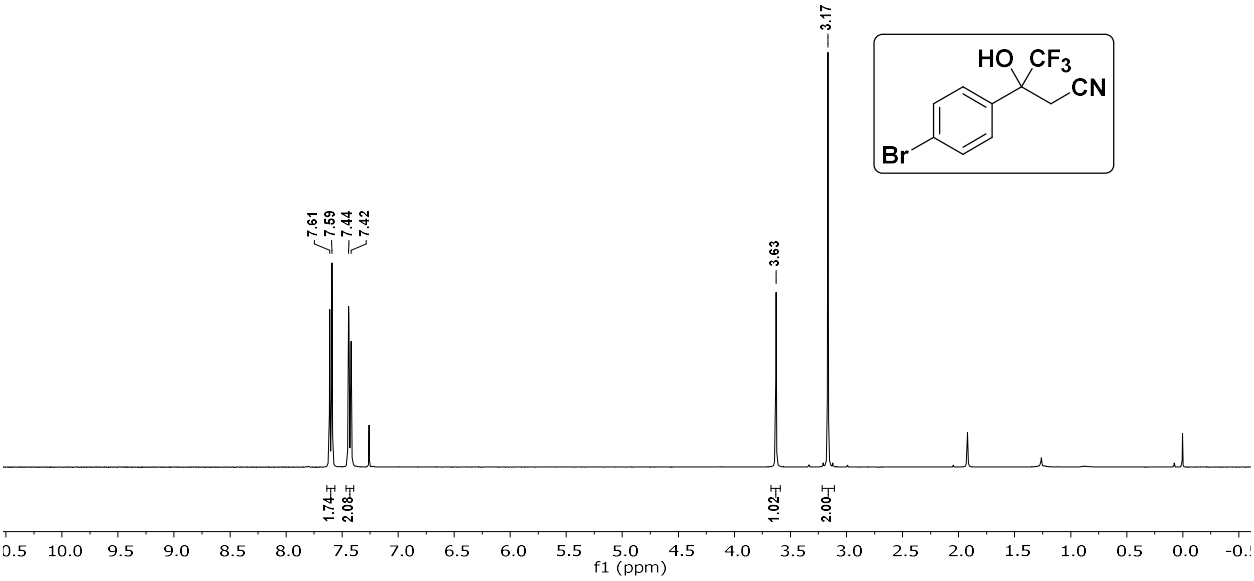
^{13}C NMR spectrum of 3-(4-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3f).



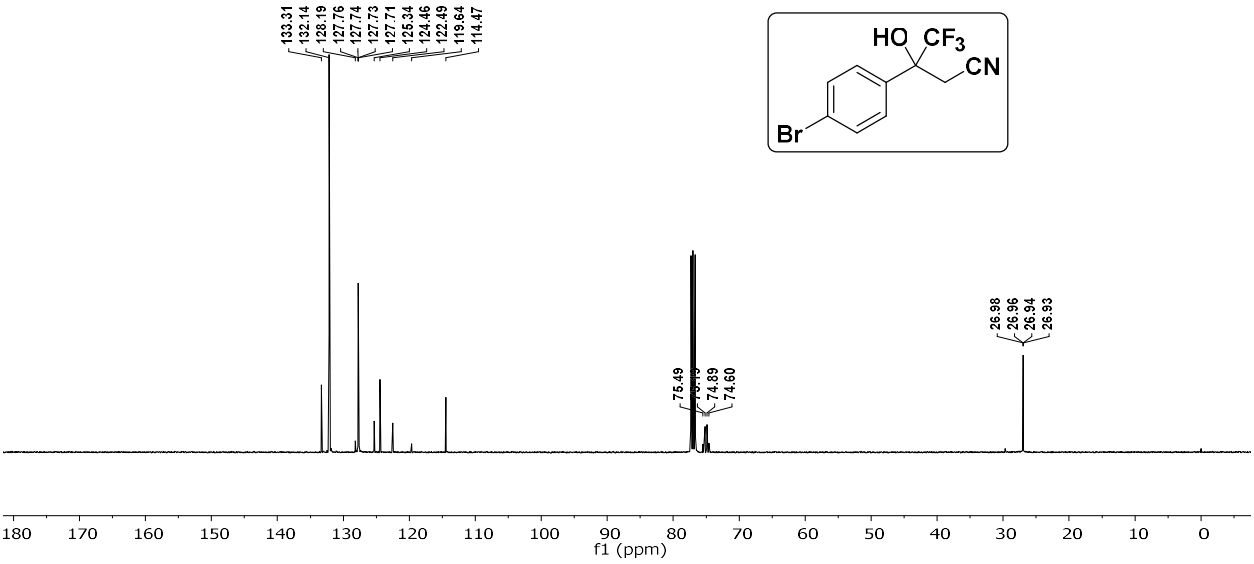
^{19}F NMR spectrum of 3-(4-chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3f).



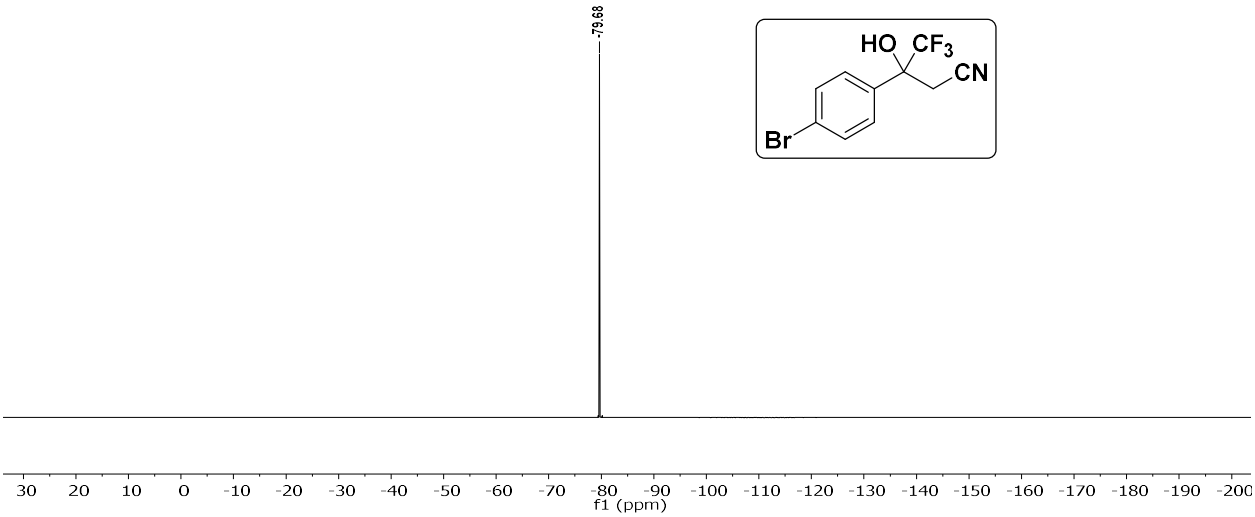
^{1}H NMR spectrum of 3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3g).



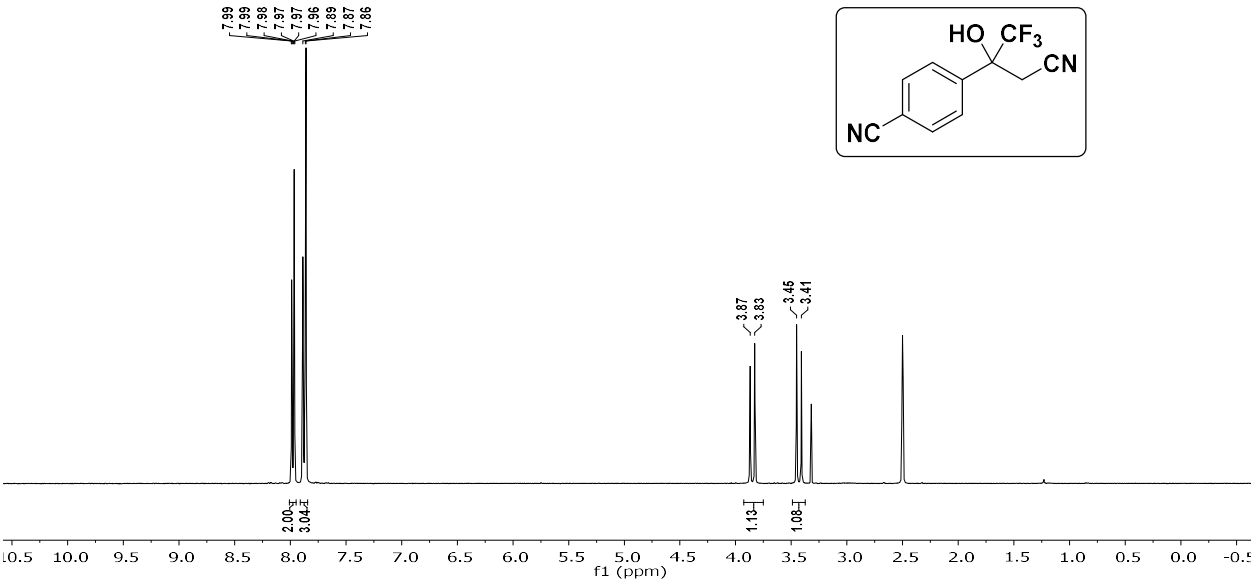
^{13}C NMR spectrum of 3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3g).



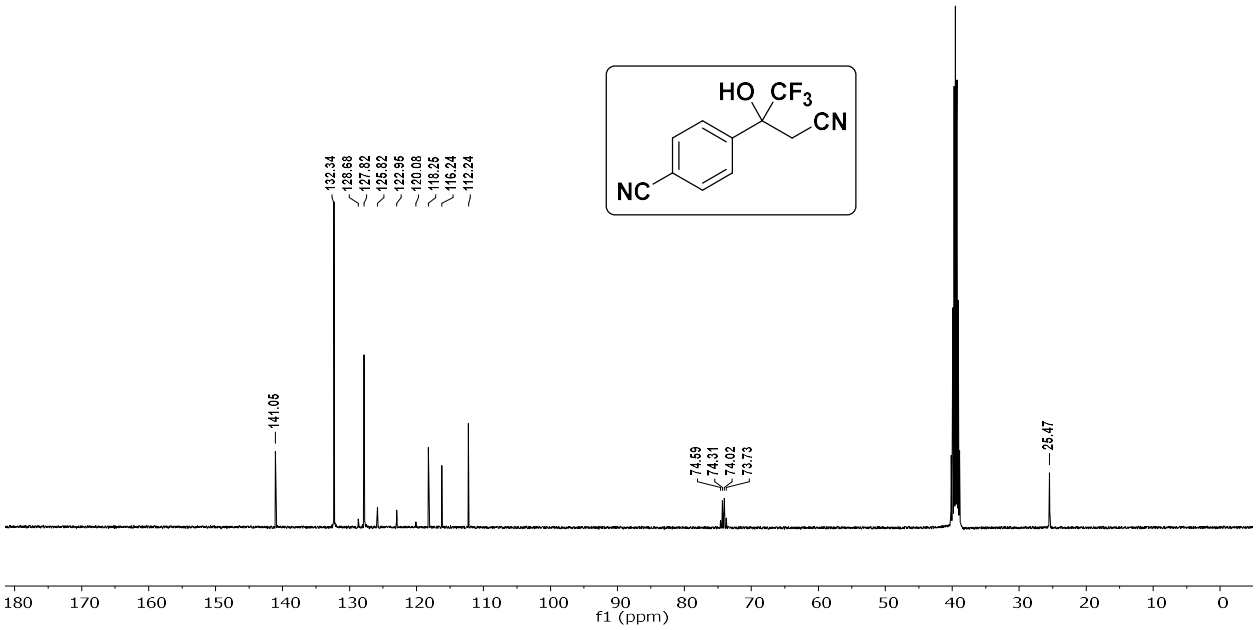
^{19}F NMR spectrum of 3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3g).



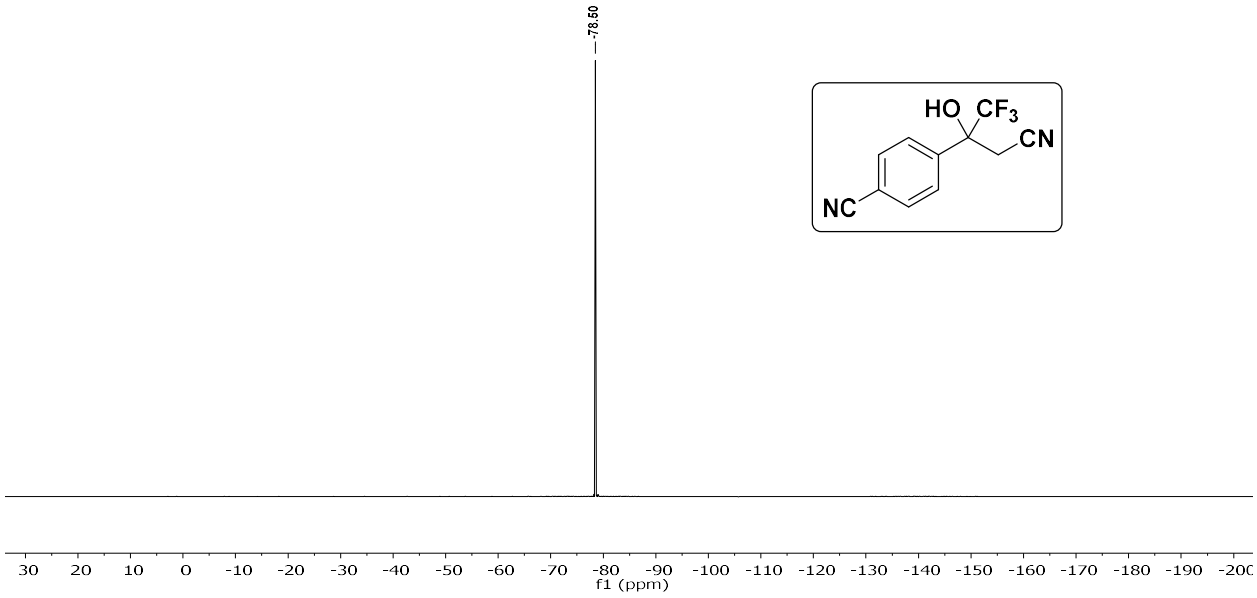
^{1}H NMR spectrum of 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (3h).



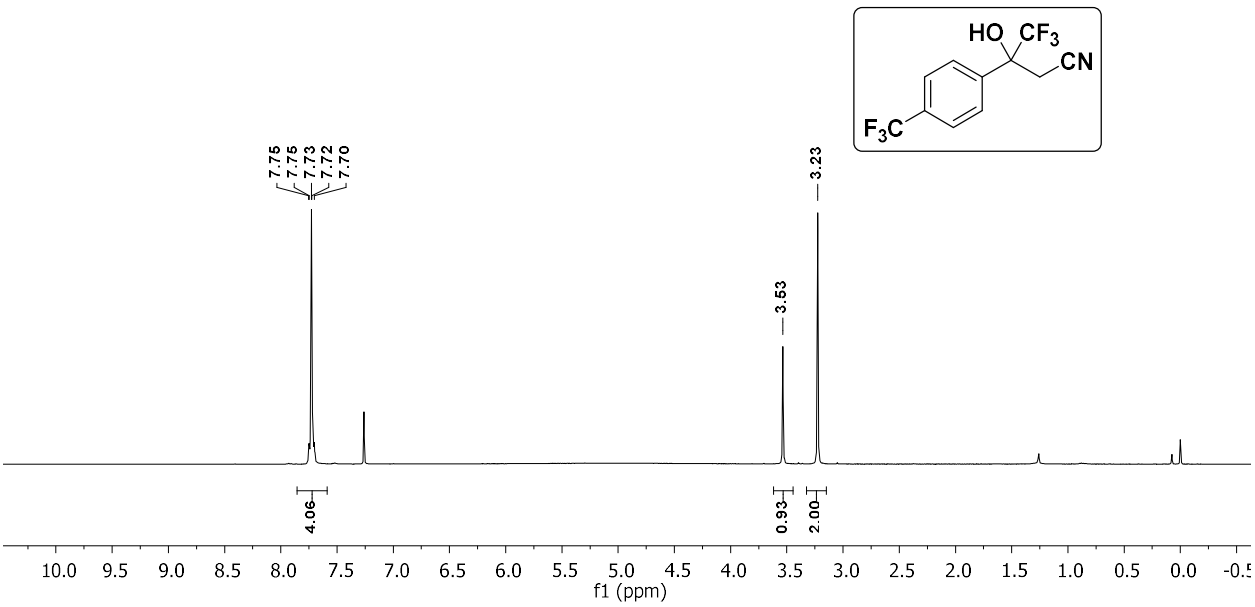
^{13}C NMR spectrum of 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (3h).



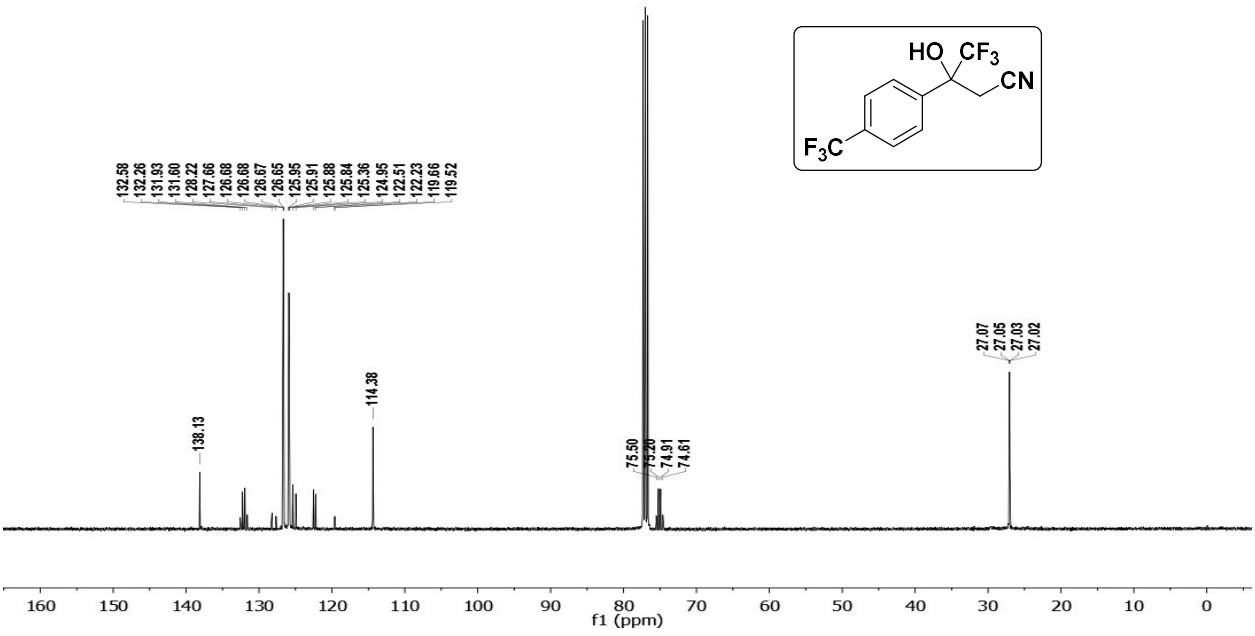
^{19}F NMR spectrum of 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (3h).



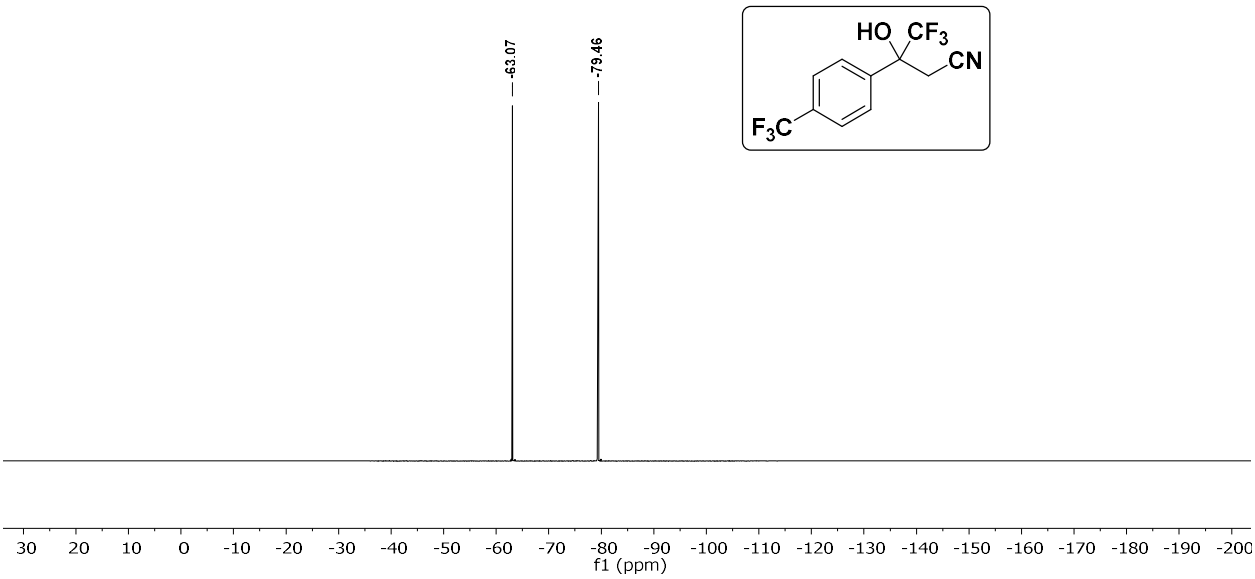
^{1}H NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-(trifluoromethyl)phenyl)butanenitrile (3i).



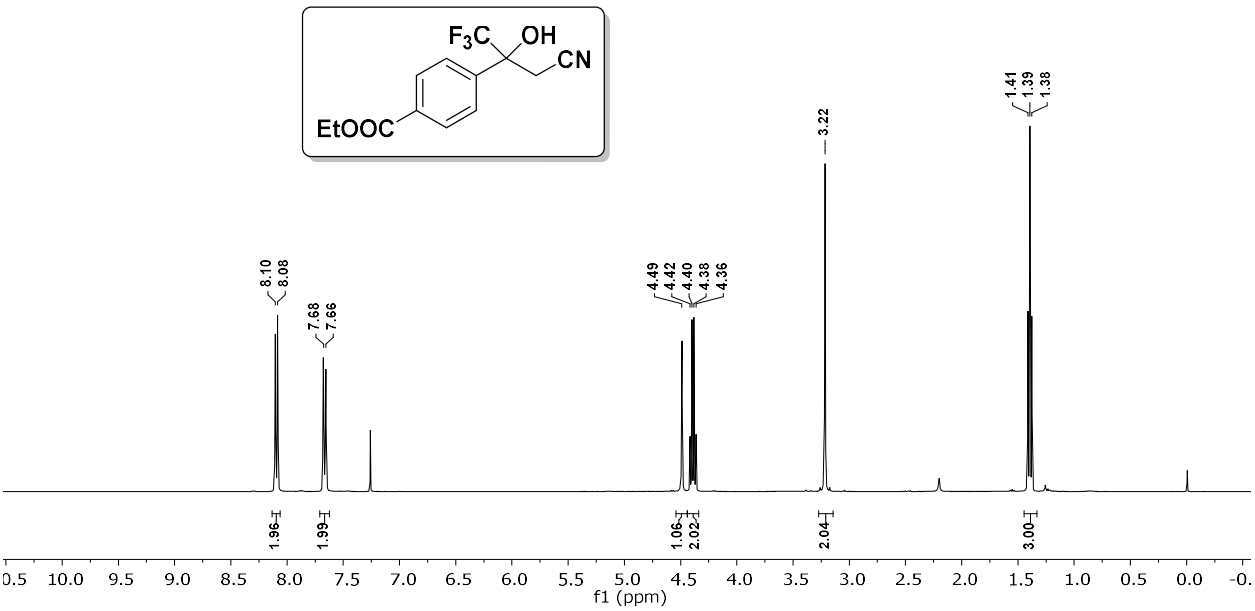
^{13}C NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-(trifluoromethyl)phenyl)butanenitrile (3i).



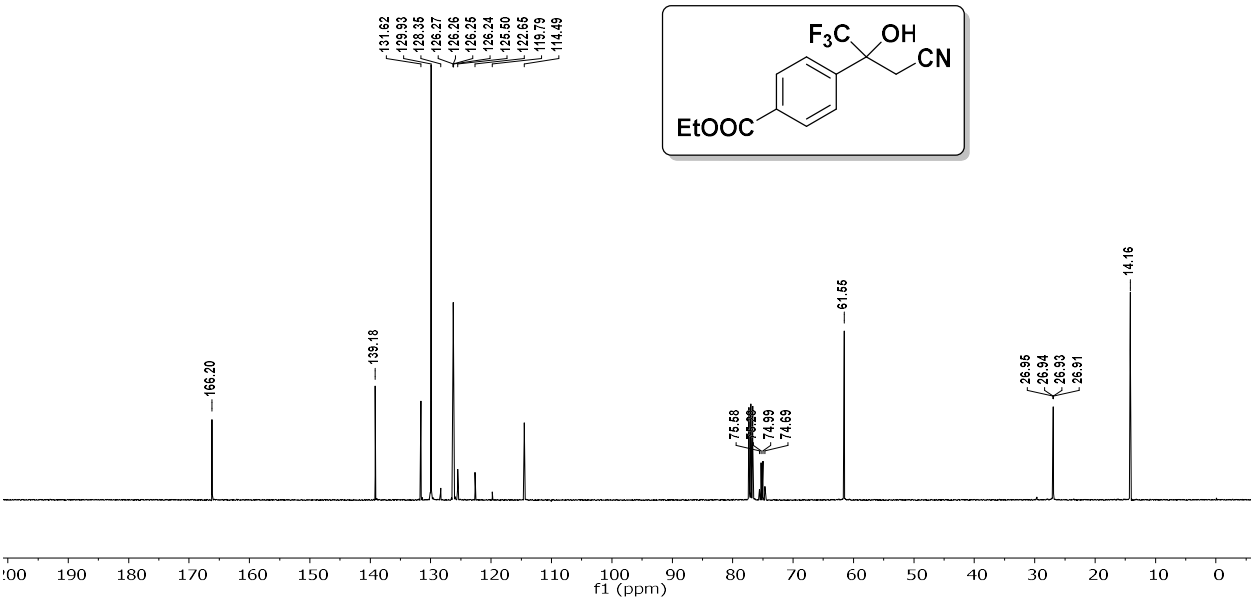
^{19}F NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-(trifluoromethyl)phenyl)butanenitrile (3i).



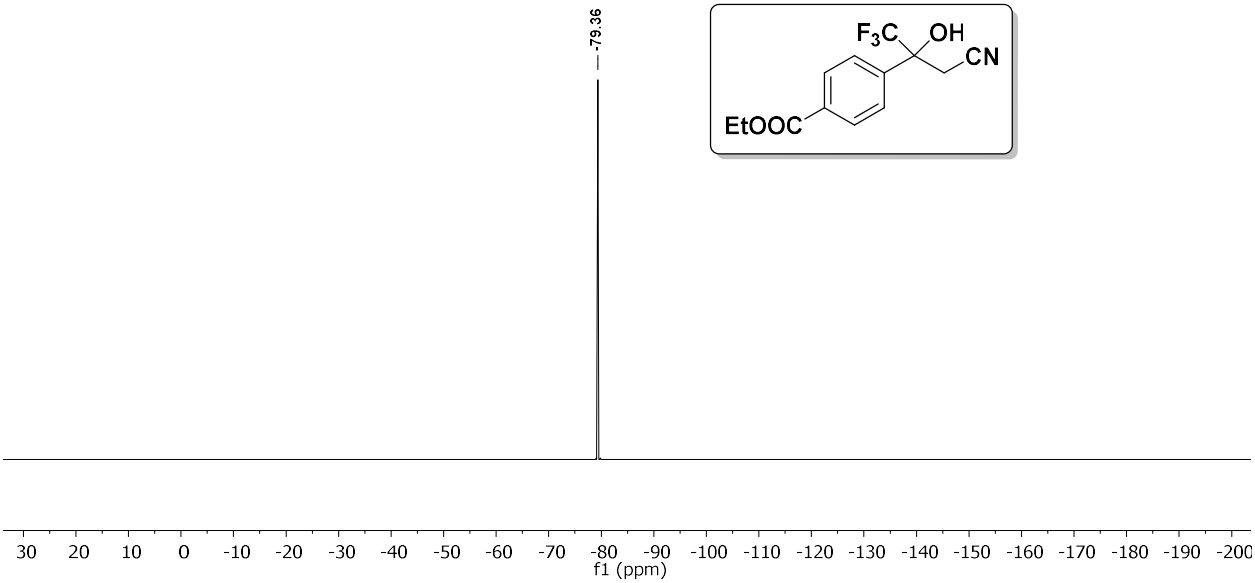
^{1}H NMR spectrum of ethyl 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (3j).



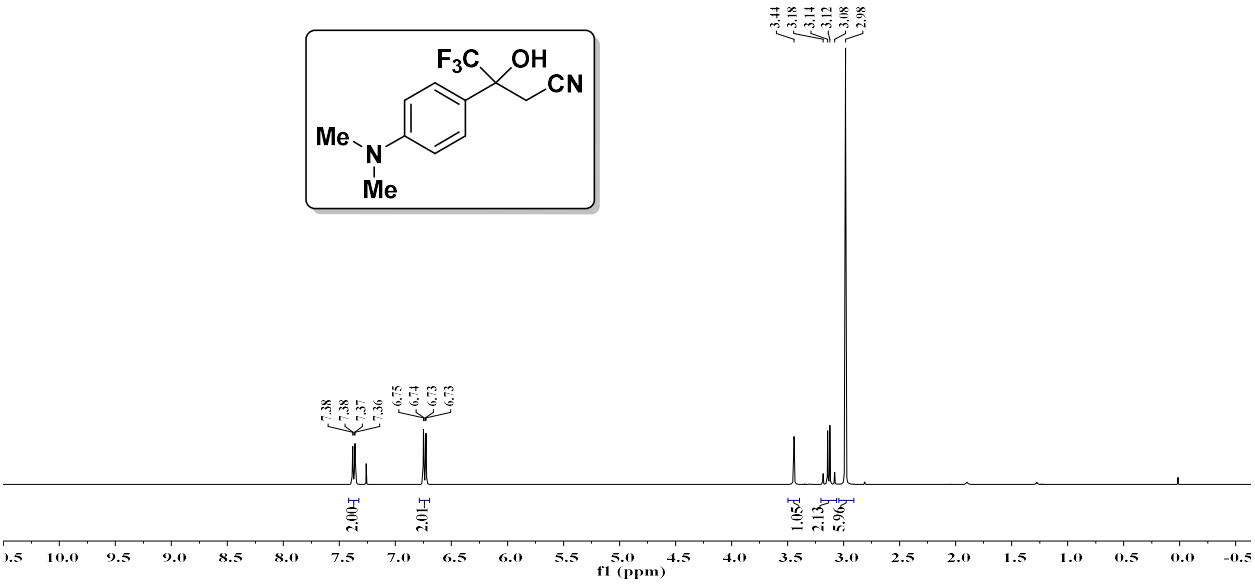
^{13}C NMR spectrum of ethyl 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (3j).



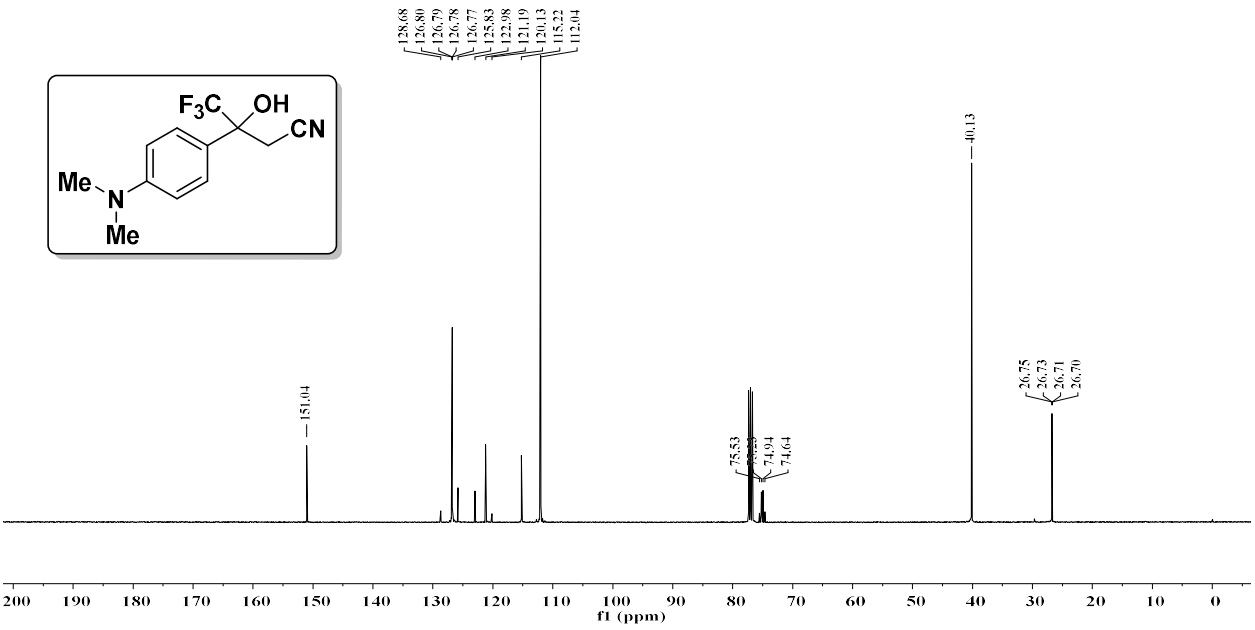
^{19}F NMR spectrum of ethyl 4-(3-cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoate (3j).



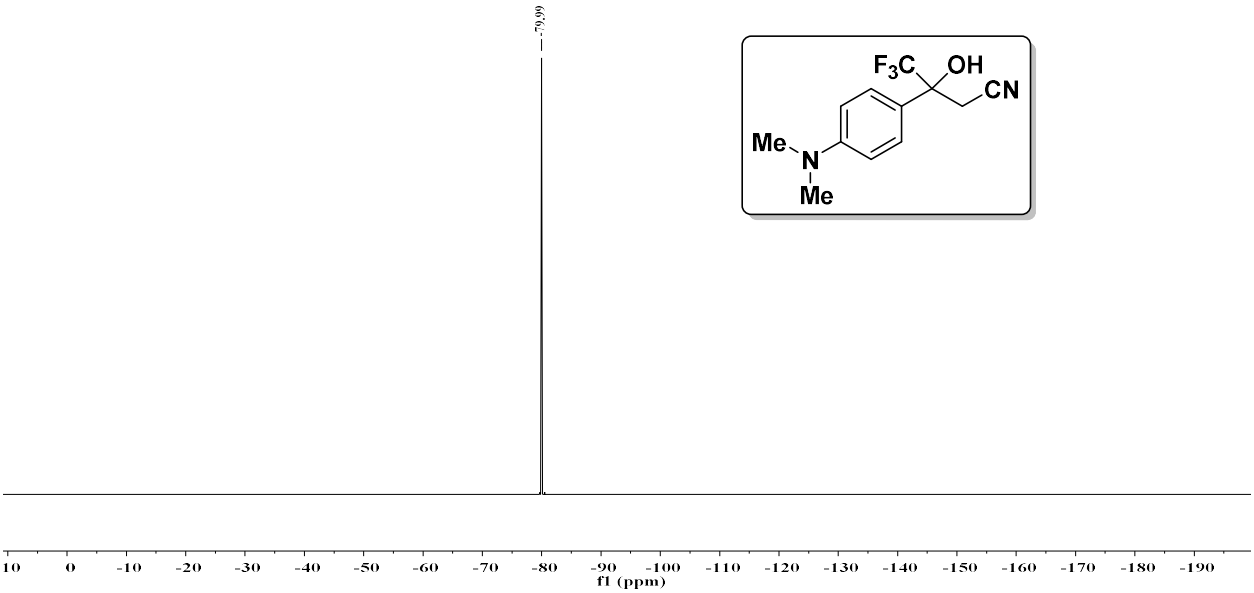
^{1}H NMR spectrum of 3-(4-(dimethylamino)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3k).



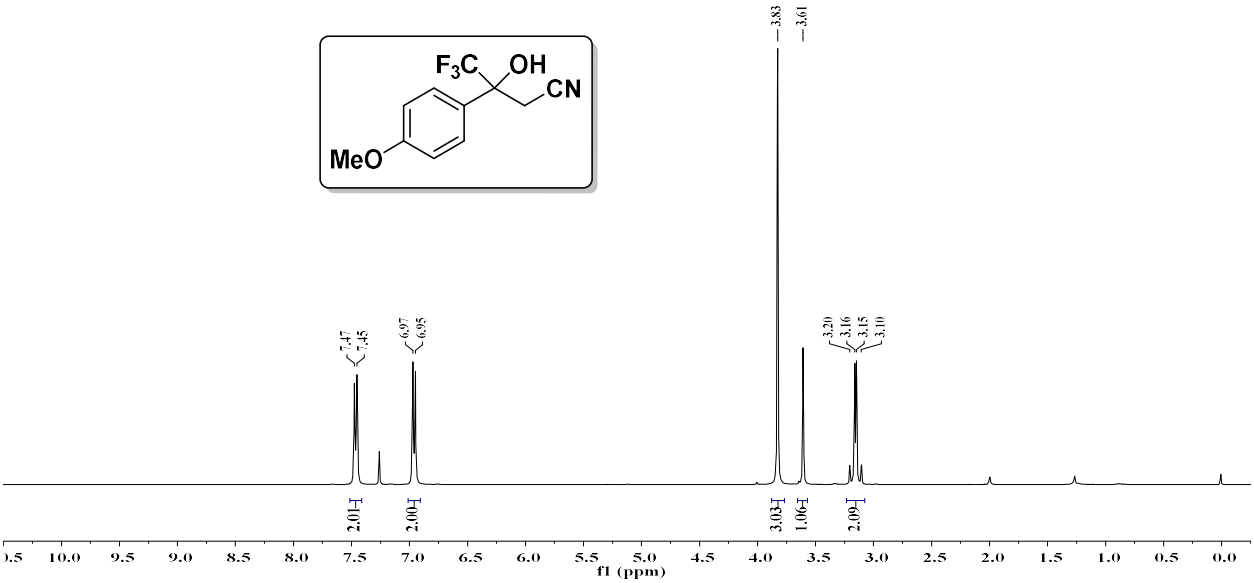
^{13}C NMR spectrum of 3-(4-(dimethylamino)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3k).



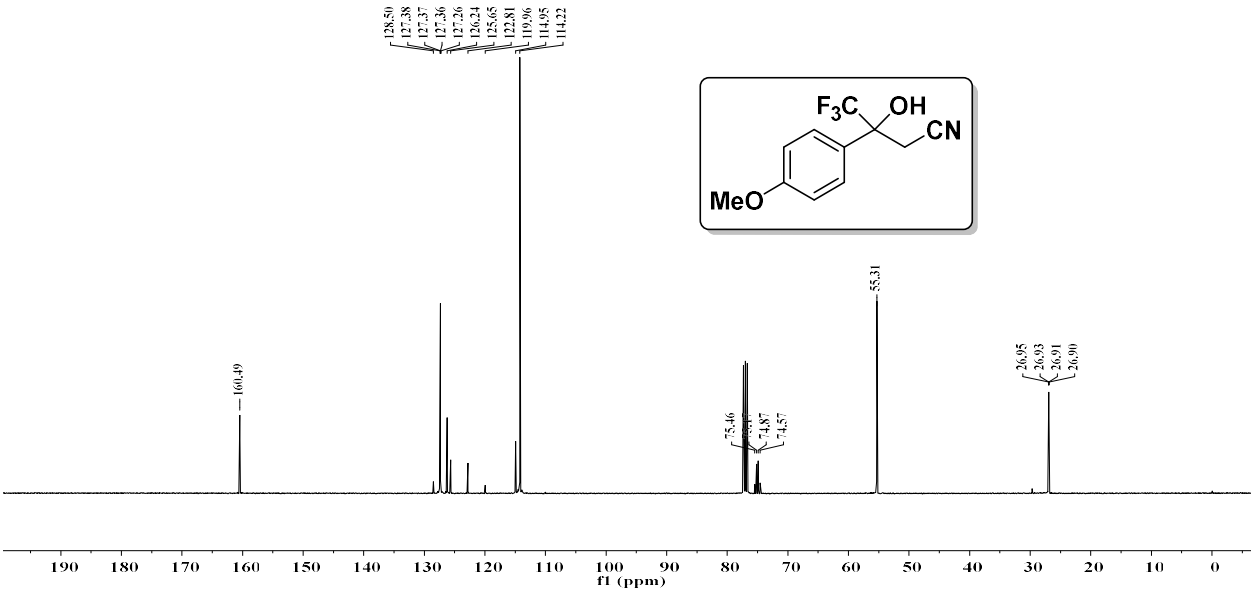
^{19}F NMR spectrum of 3-(4-(dimethylamino)phenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3k).



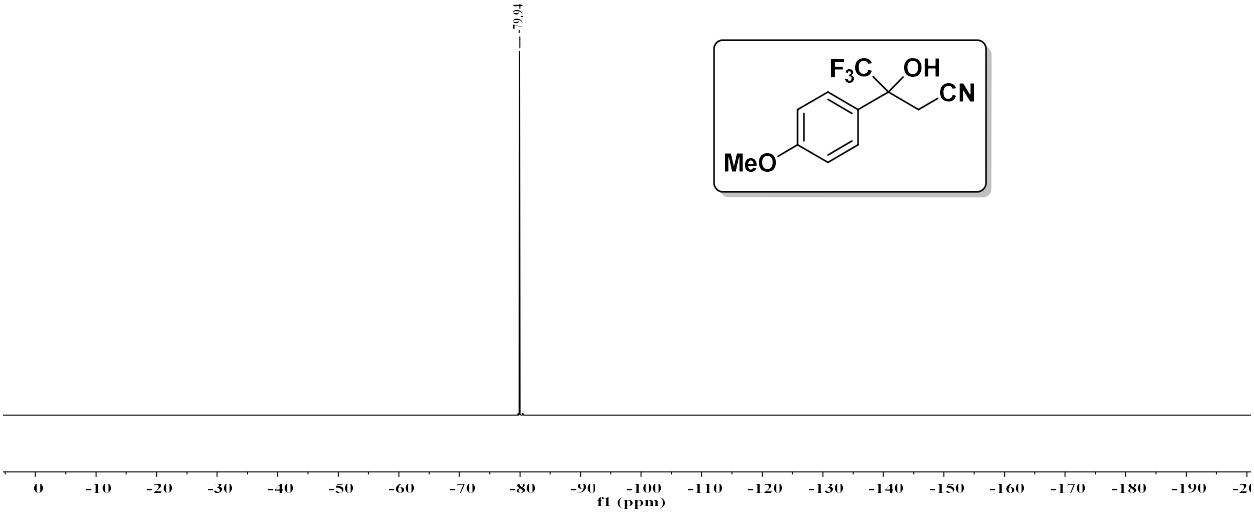
^{1}H NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-methoxyphenyl)butanenitrile (3l).



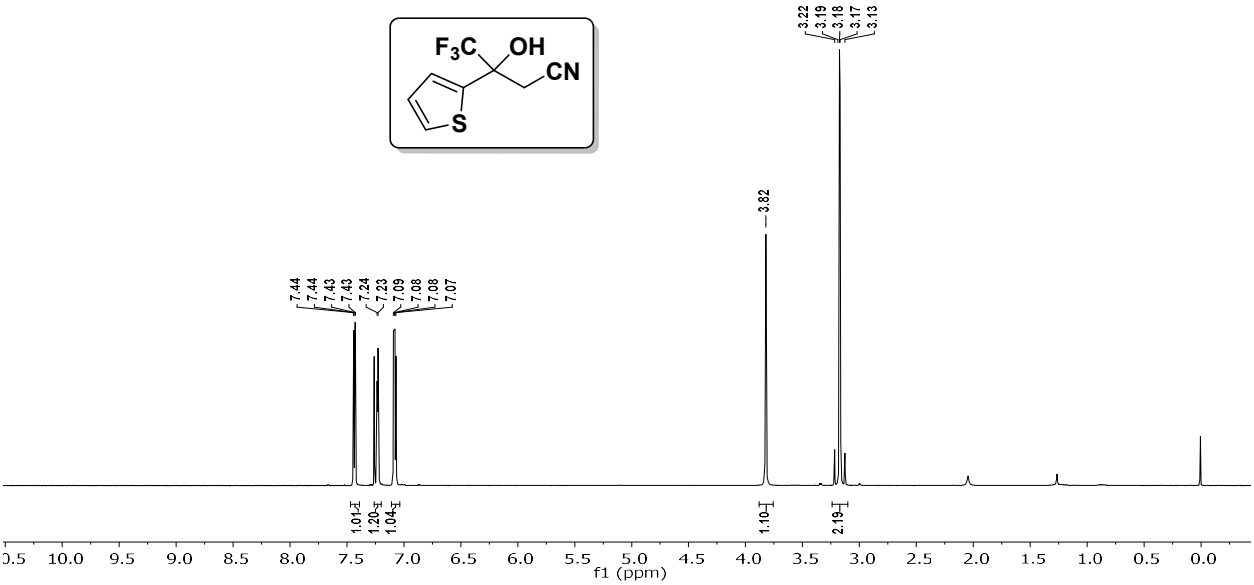
^{13}C NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-methoxyphenyl)butanenitrile (3l).



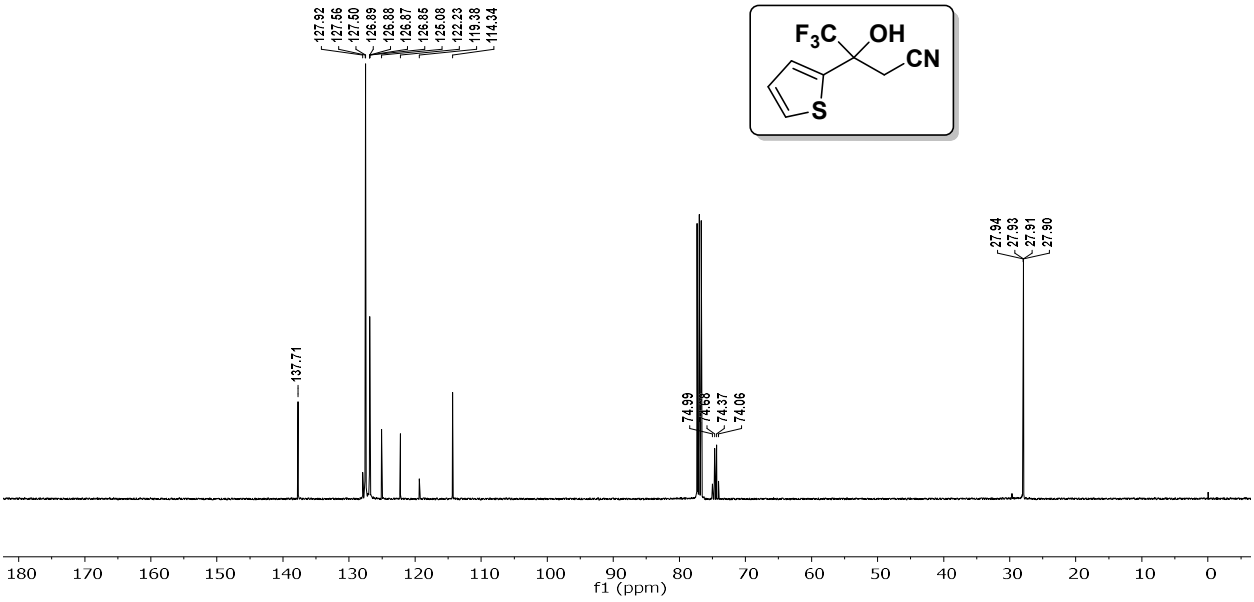
^{19}F NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(4-methoxyphenyl)butanenitrile (3l).



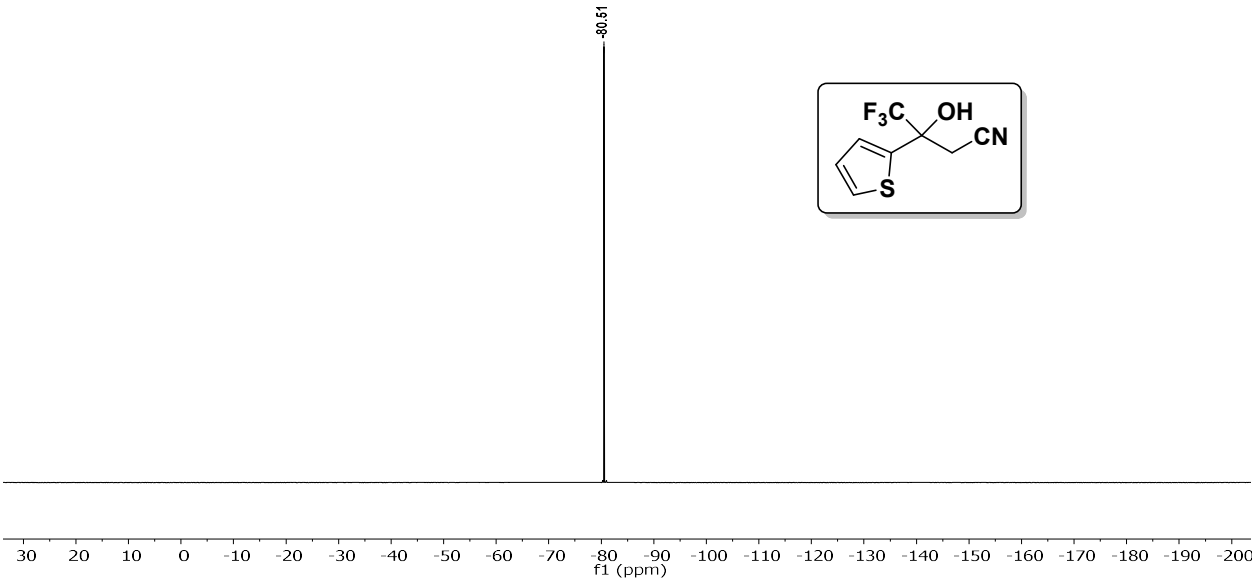
^{1}H NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (3m).



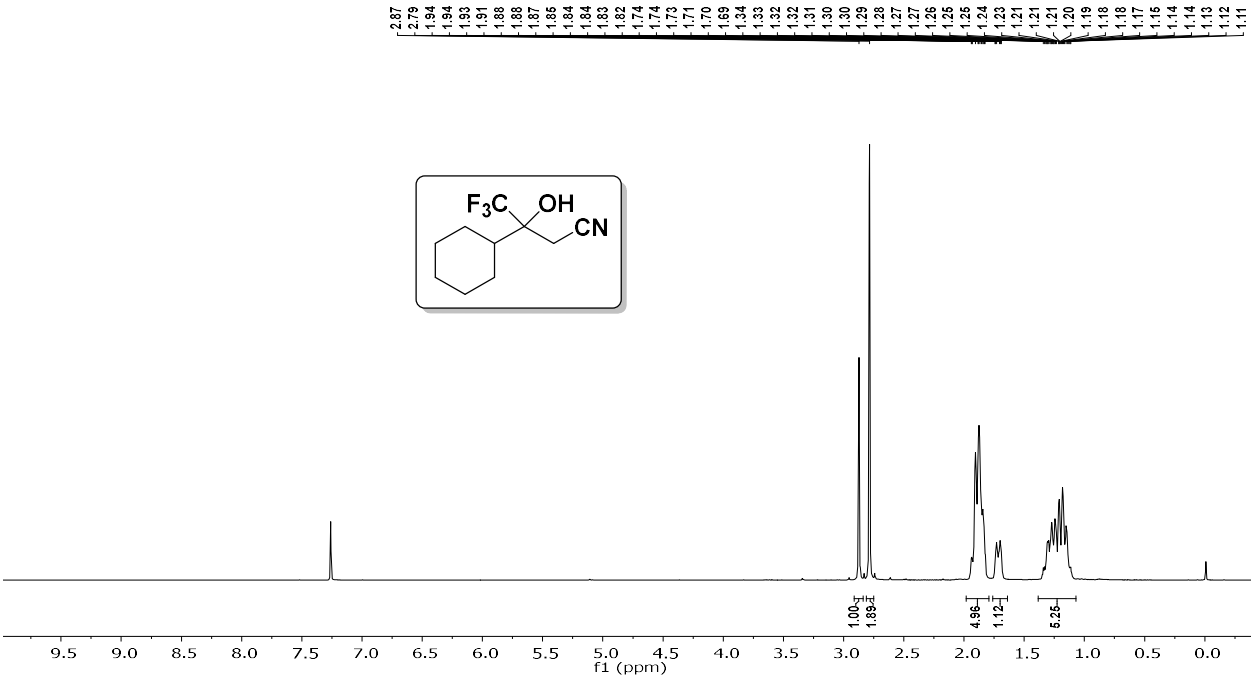
^{13}C NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (3m).



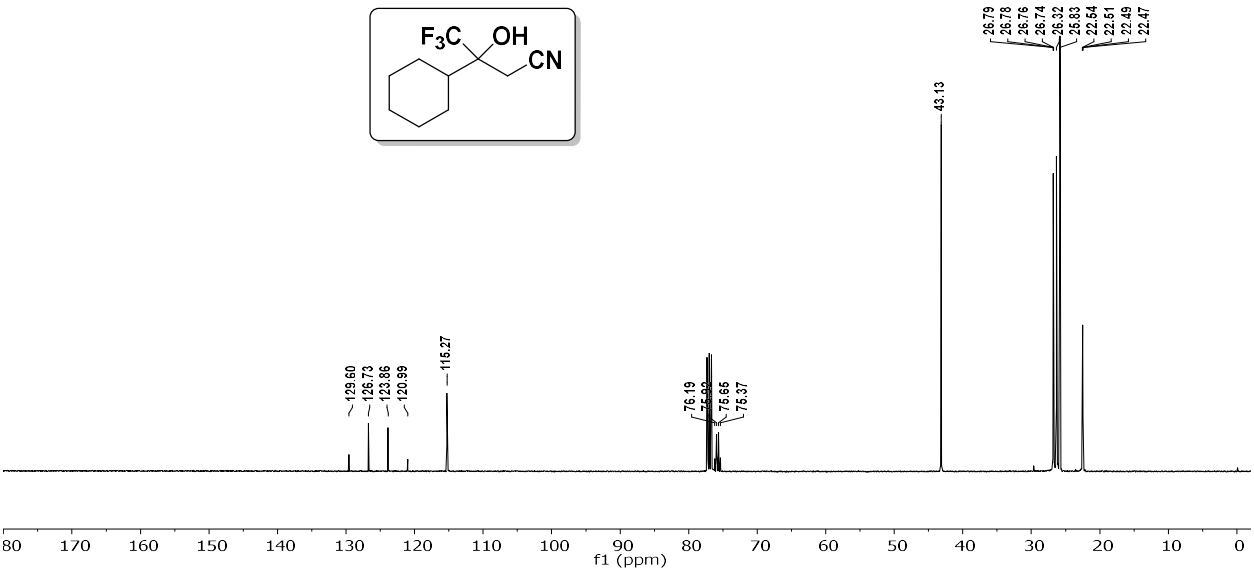
^{19}F NMR spectrum of 4,4,4-trifluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (3m).



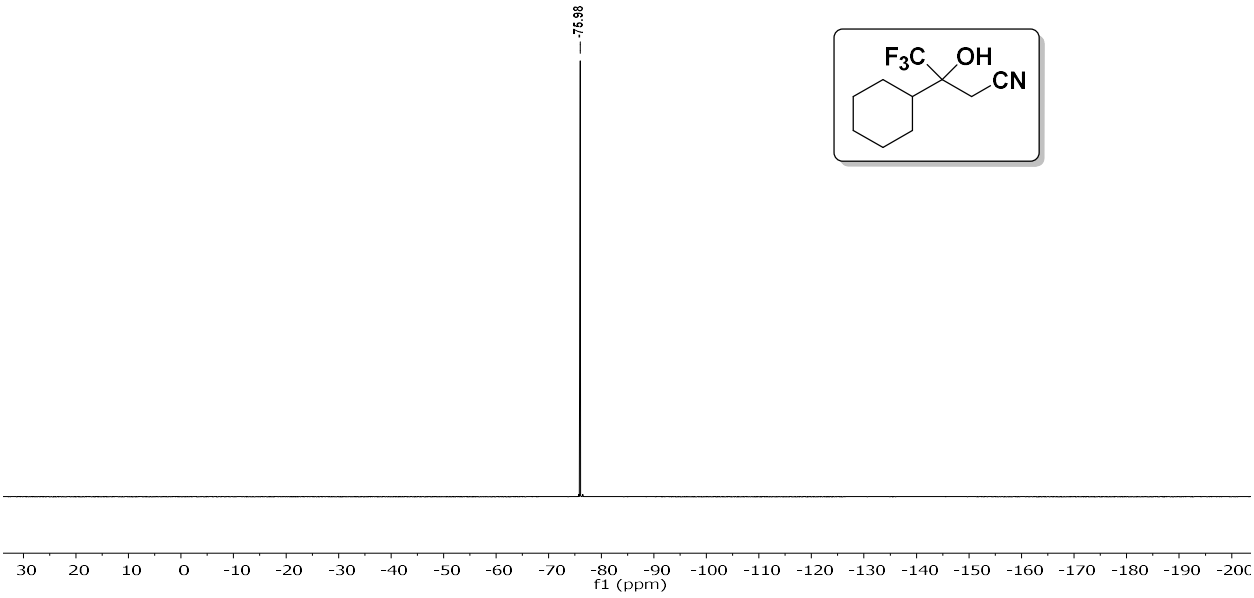
^{1}H NMR spectrum of 3-cyclohexyl-4,4,4-trifluoro-3-hydroxybutanenitrile (3n).



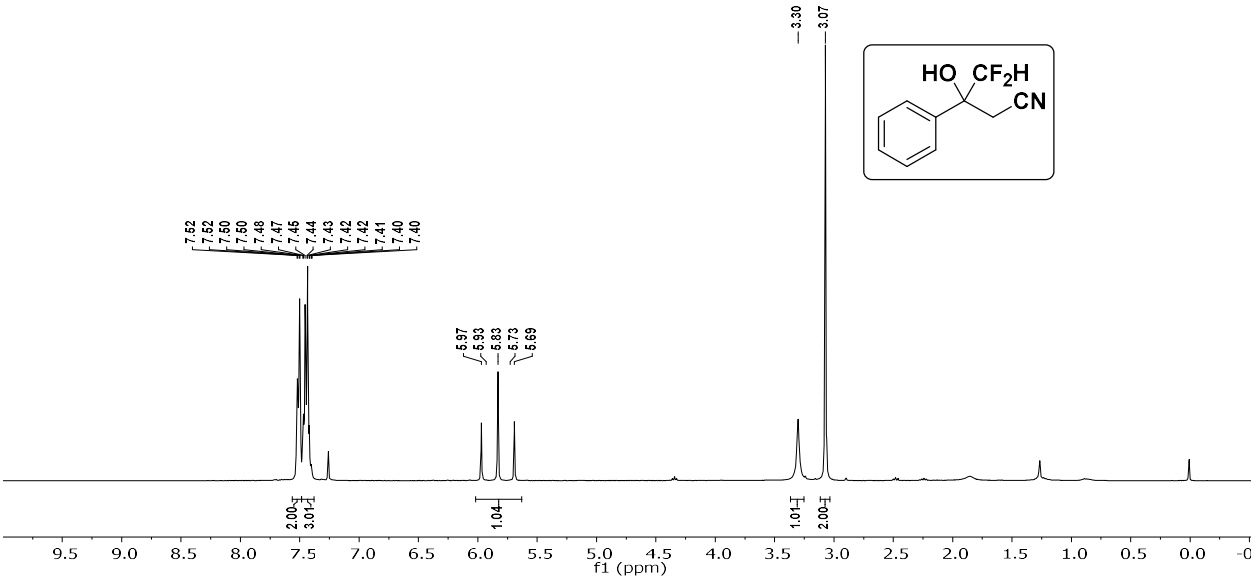
^{13}C NMR spectrum of 3-cyclohexyl-4,4,4-trifluoro-3-hydroxybutanenitrile (3n).



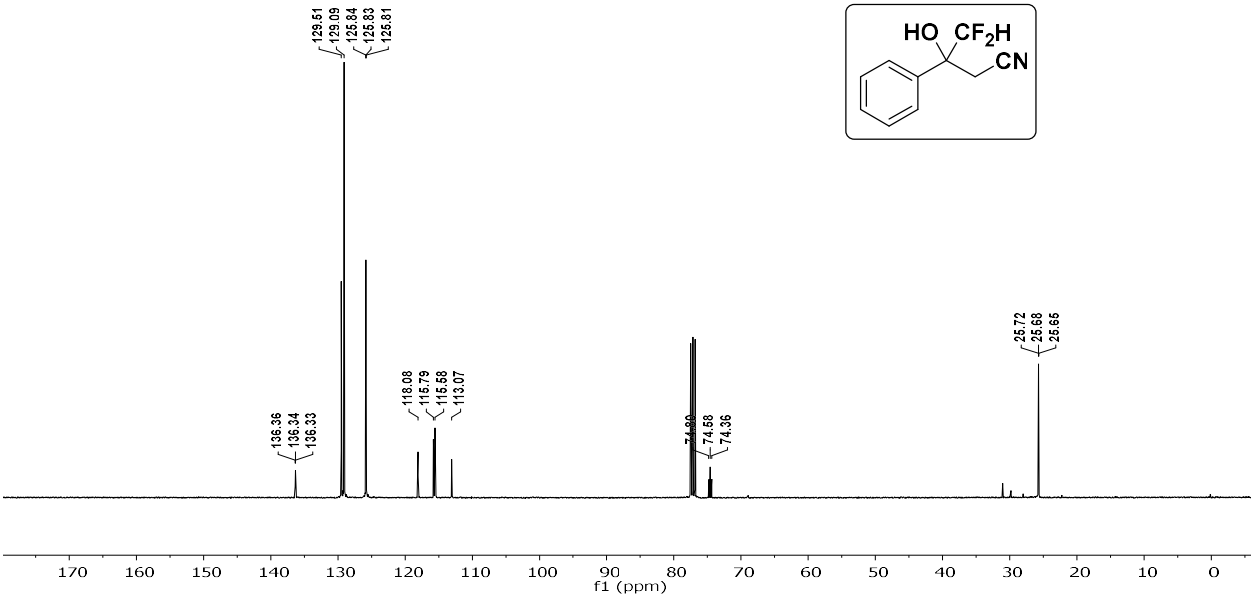
^{19}F NMR spectrum of 3-cyclohexyl-4,4,4-trifluoro-3-hydroxybutanenitrile (3n).



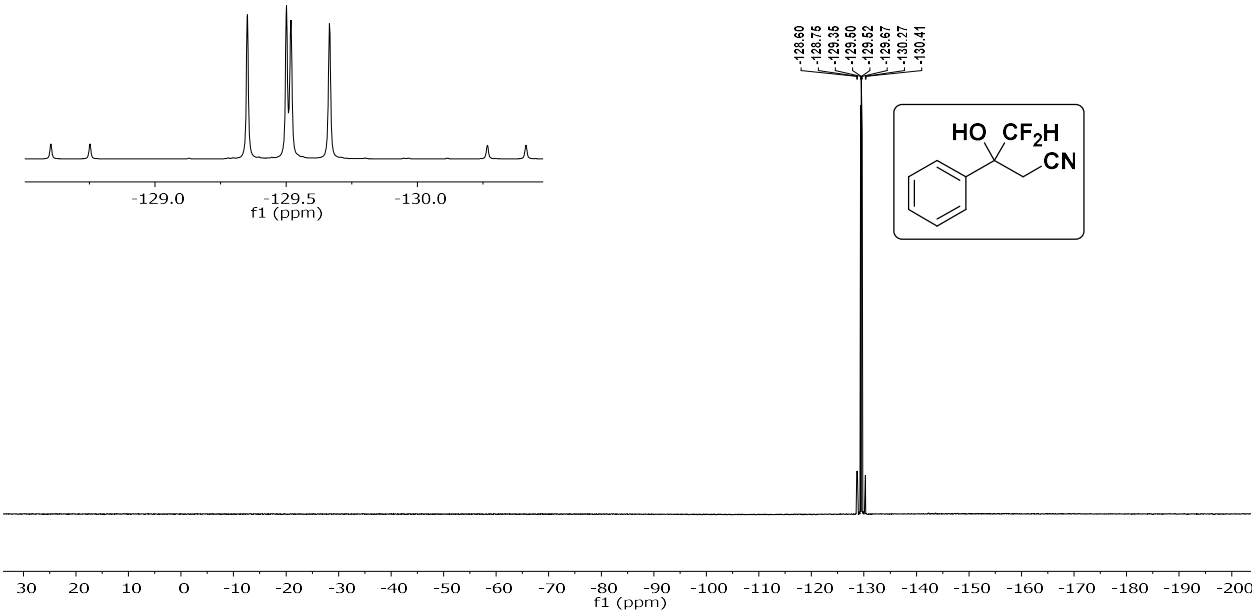
^{1}H NMR spectrum of 4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (5a).



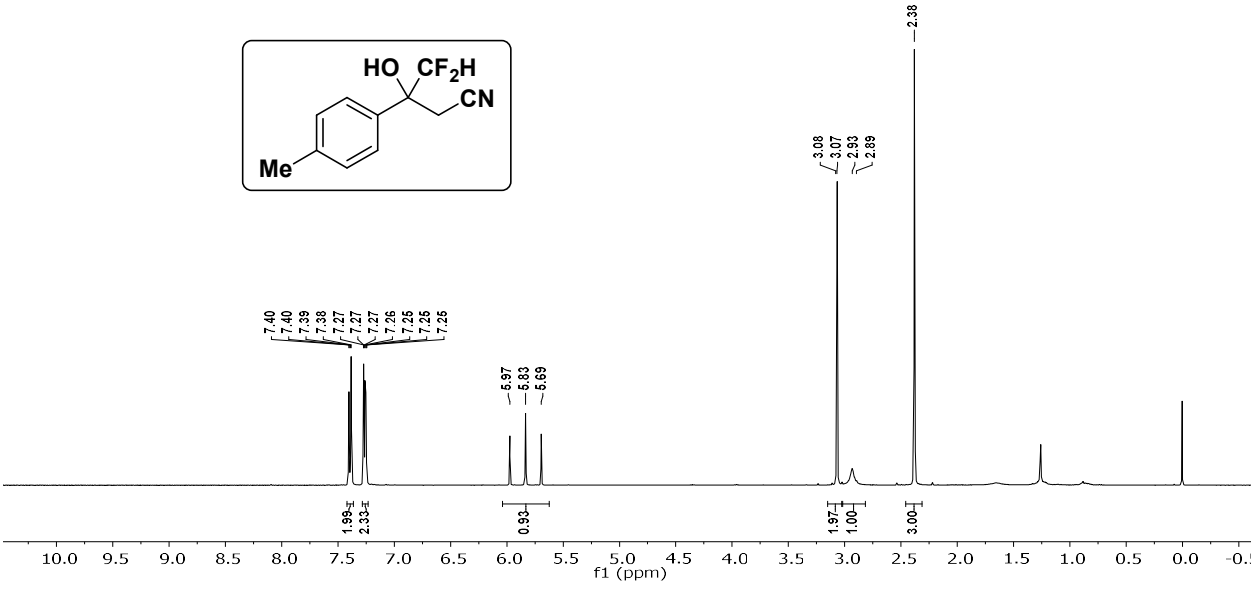
^{13}C NMR spectrum of 4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (5a).



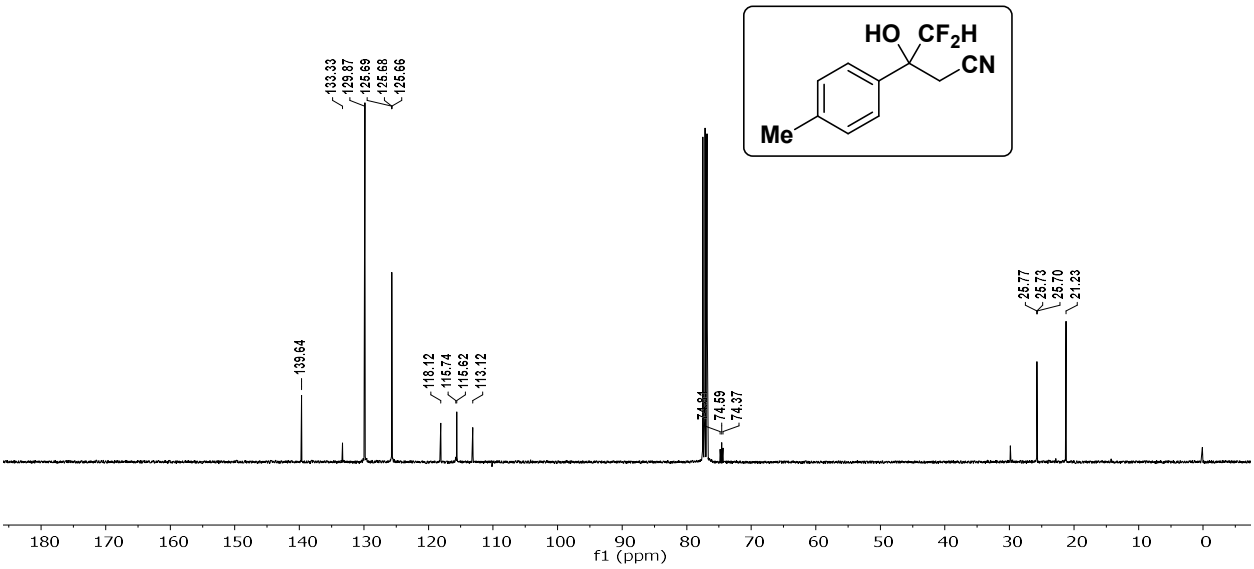
^{19}F NMR spectrum of 4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (5a).



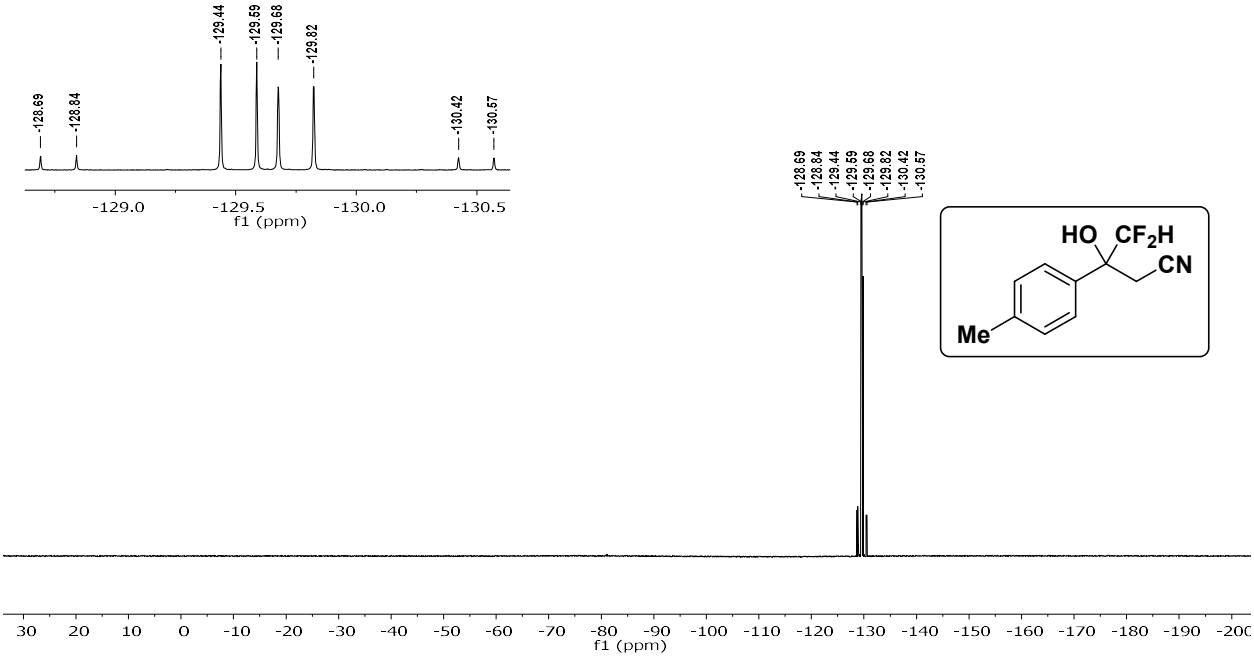
^{1}H NMR spectrum of 4,4-difluoro-3-hydroxy-3-(p-tolyl)butanenitrile (5b).



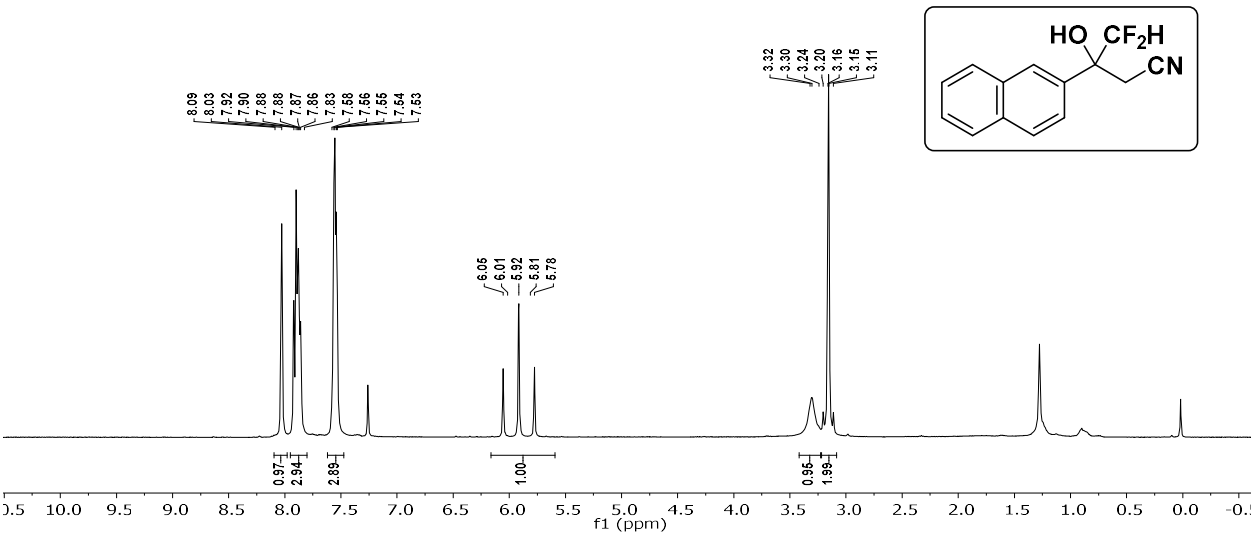
^{13}C NMR spectrum of 4,4-difluoro-3-hydroxy-3-(p-tolyl)butanenitrile (5b).



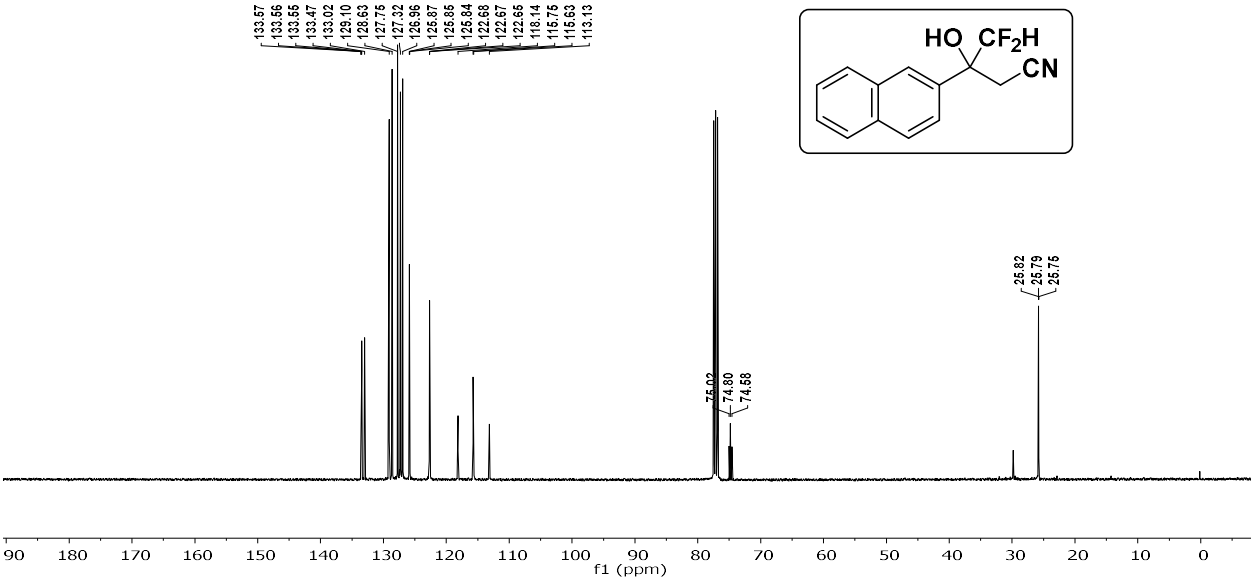
^{19}F NMR spectrum of 4,4-difluoro-3-hydroxy-3-(p-tolyl)butanenitrile (5b).



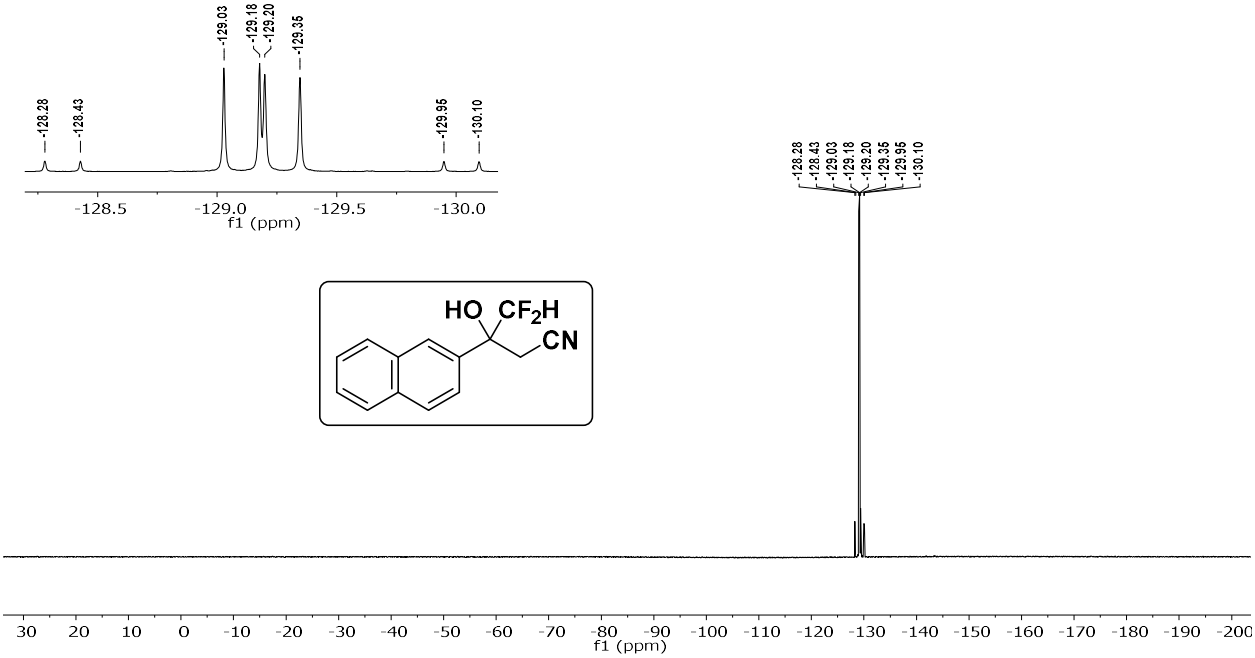
^{1}H NMR spectrum of 4,4-difluoro-3-hydroxy-3-(naphthalen-2-yl)butanenitrile (5c).



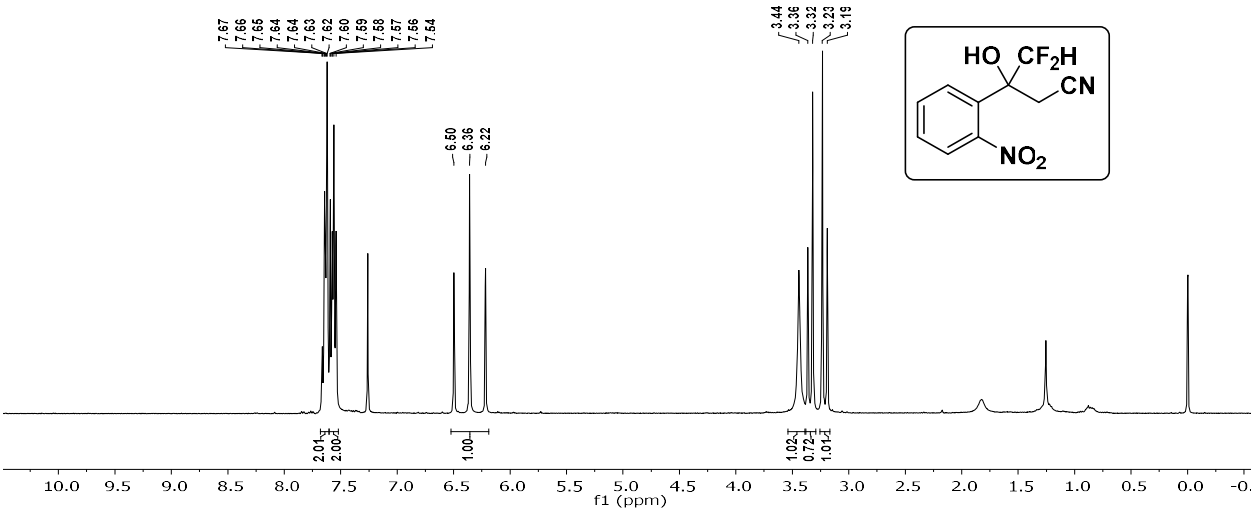
^{13}C NMR spectrum of 4,4-difluoro-3-hydroxy-3-(naphthalen-2-yl)butanenitrile (5c).



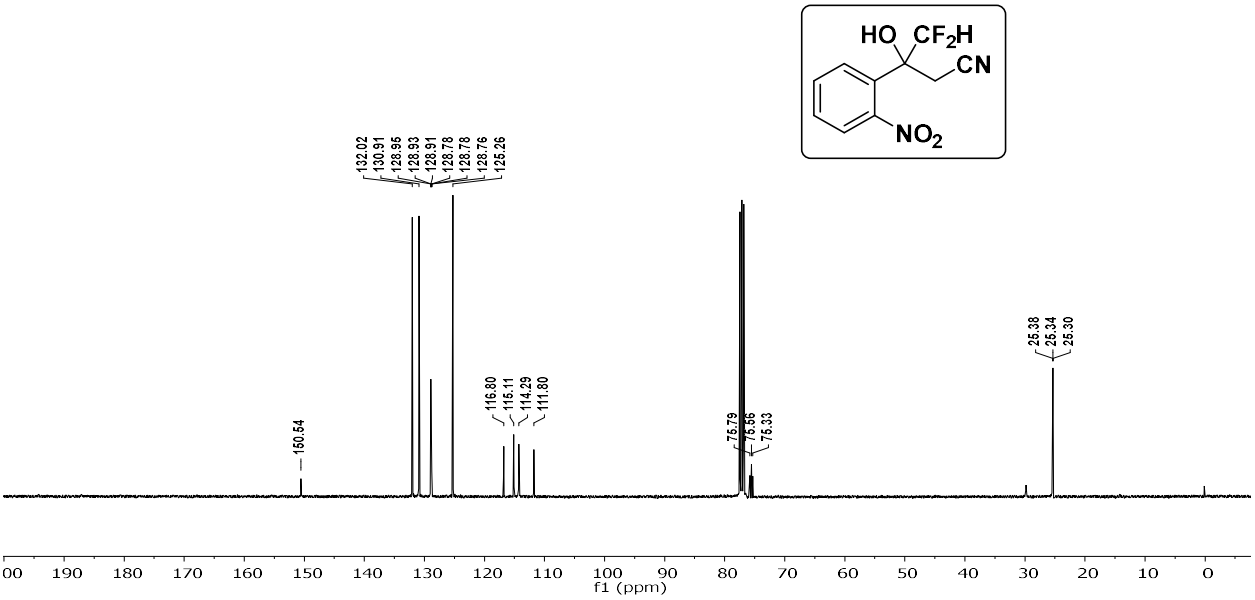
^{19}F NMR spectrum of 4,4-difluoro-3-hydroxy-3-(naphthalen-2-yl)butanenitrile (5c).



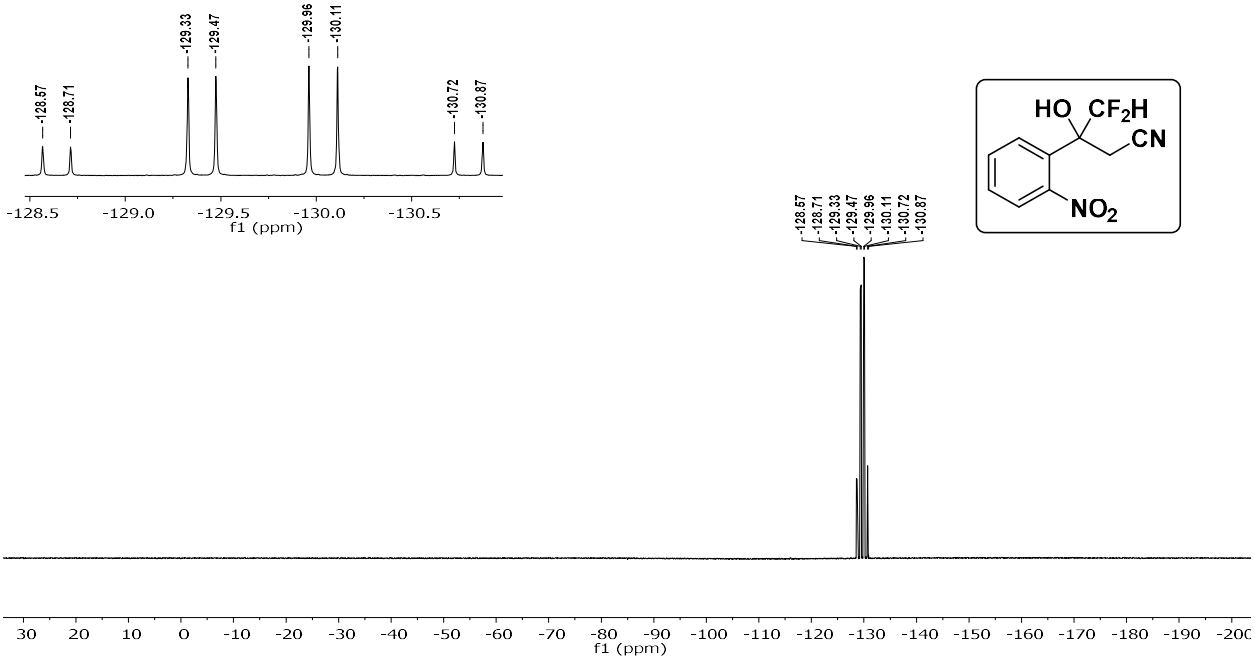
^{1}H NMR spectrum of 4,4-difluoro-3-hydroxy-3-(2-nitrophenyl)butanenitrile (5d).



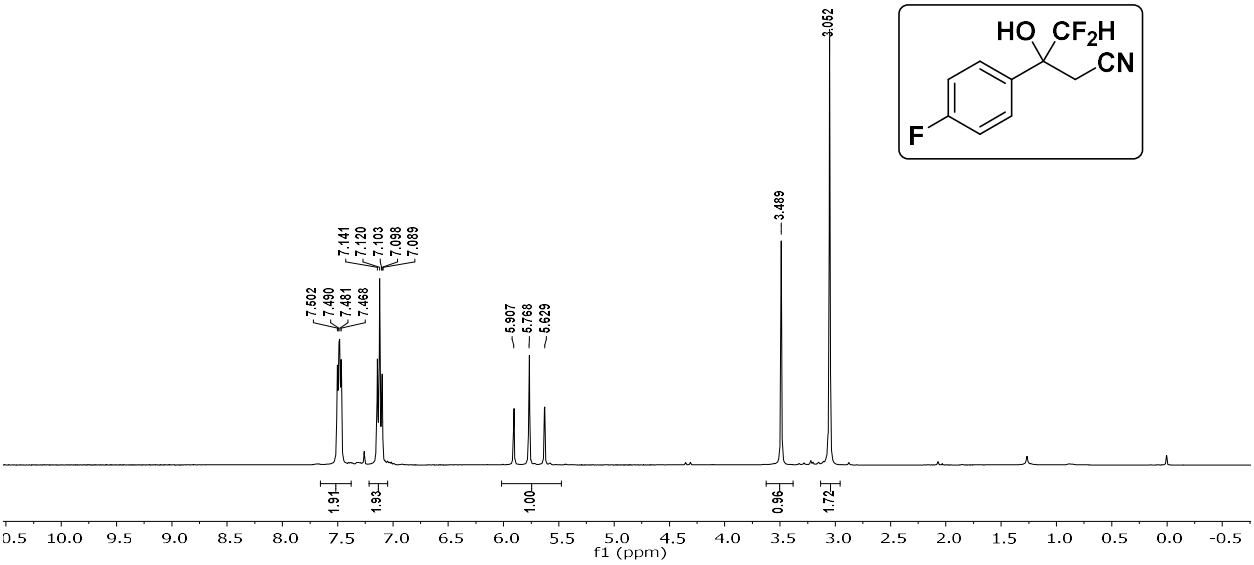
^{13}C NMR spectrum of 4,4-difluoro-3-hydroxy-3-(2-nitrophenyl)butanenitrile (5d).



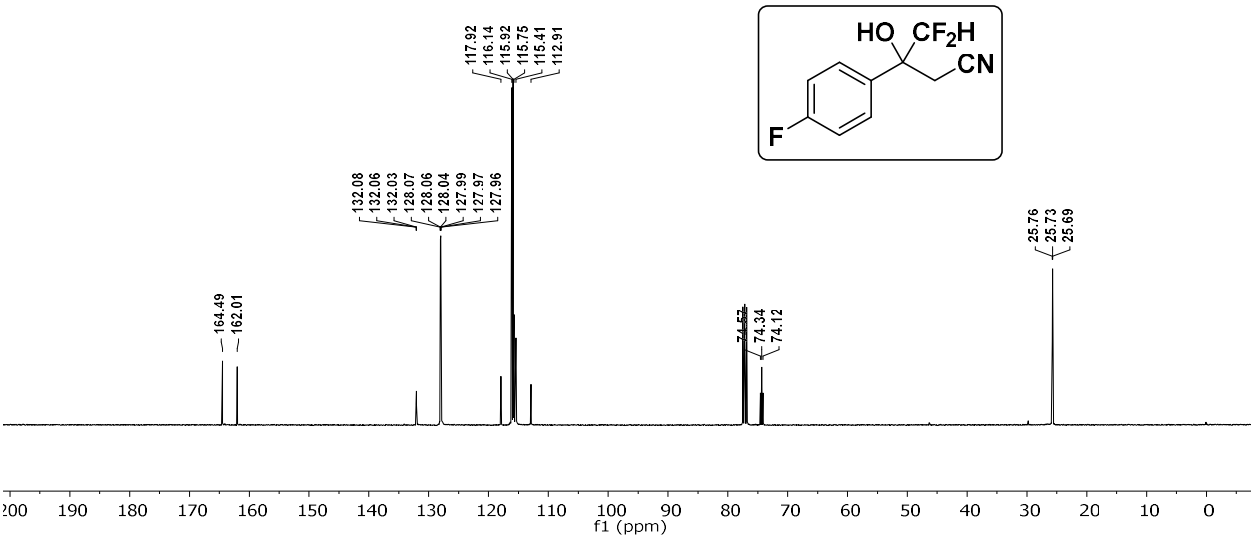
^{19}F NMR spectrum of 4,4-difluoro-3-hydroxy-3-(2-nitrophenyl)butanenitrile (5d).



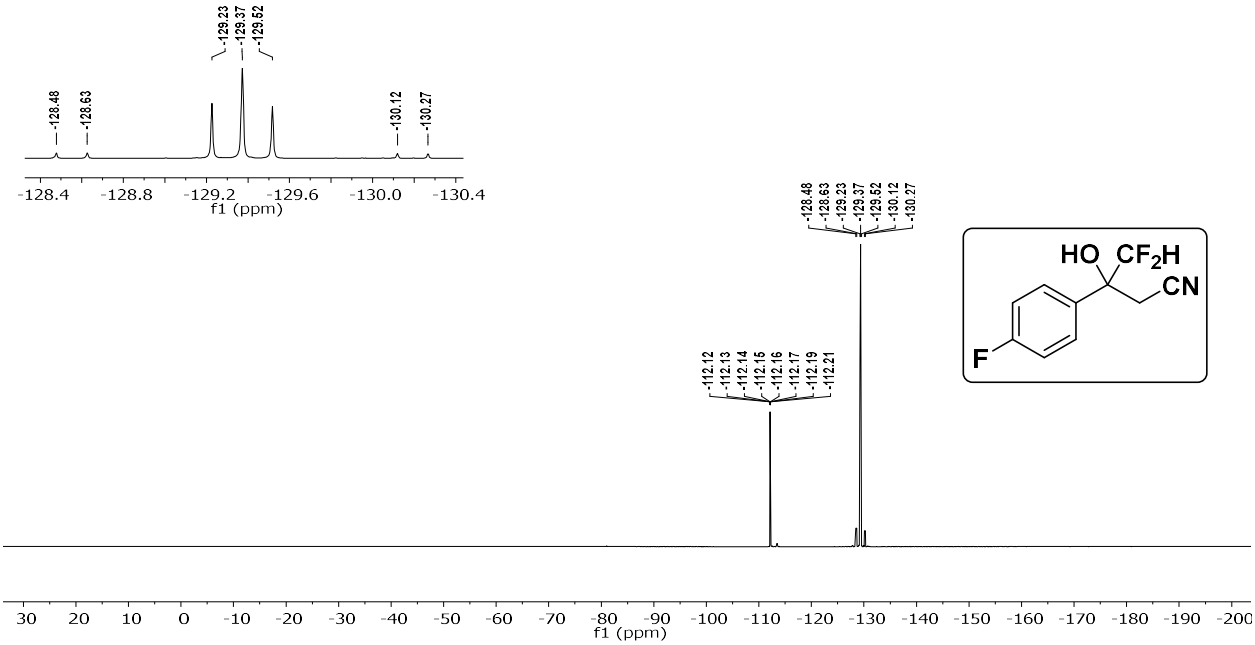
^{1}H NMR spectrum of 4,4-difluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (5e).



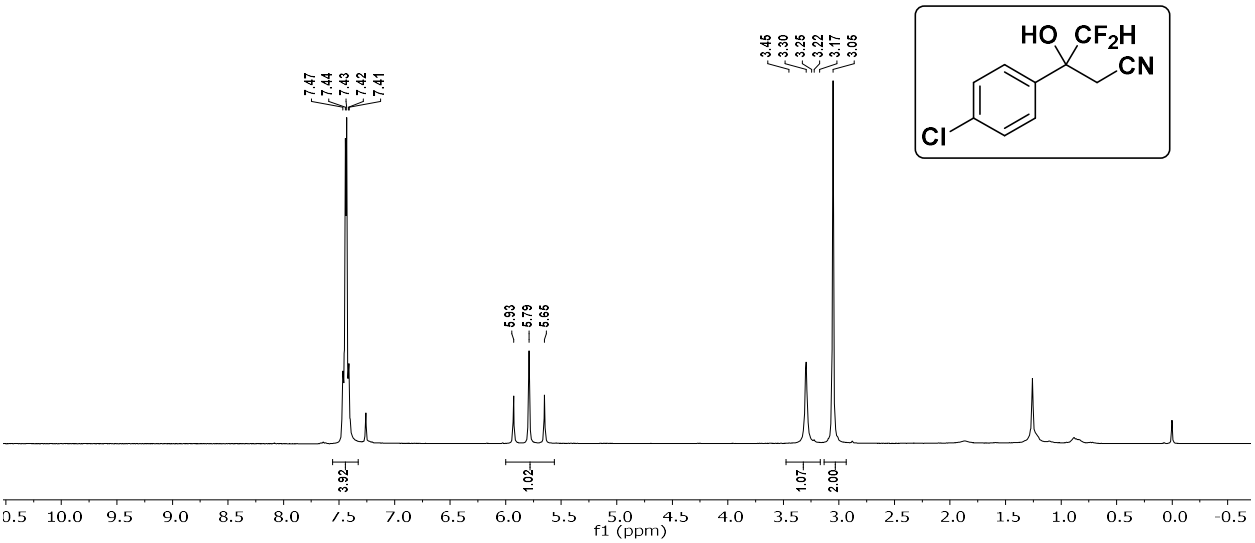
^{13}C NMR spectrum of 4,4-difluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (5e).



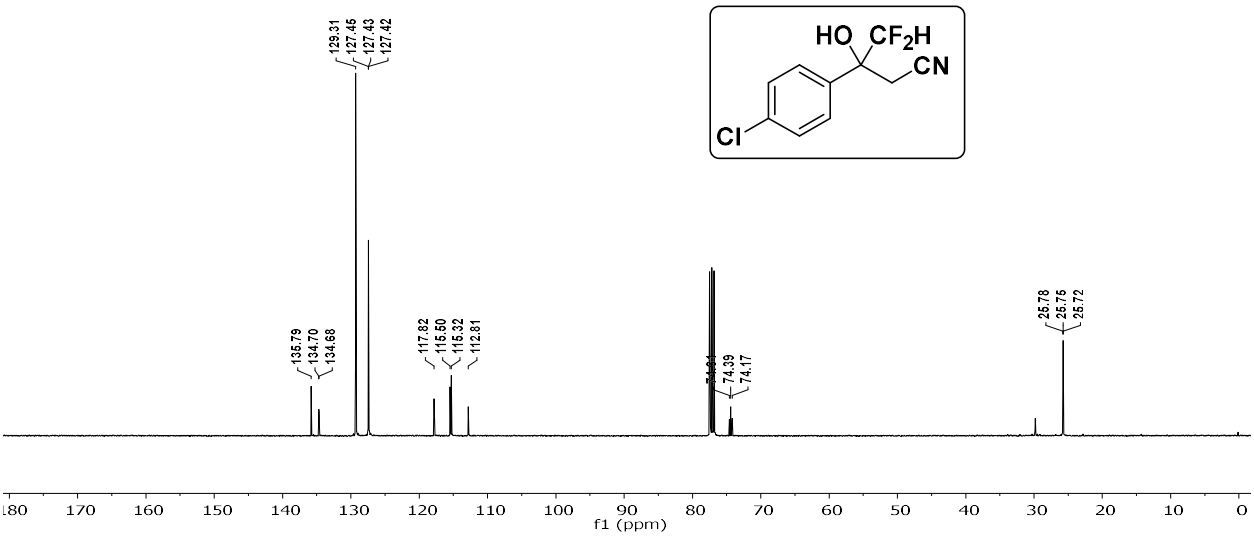
^{19}F NMR spectrum of 4,4-difluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (5e).



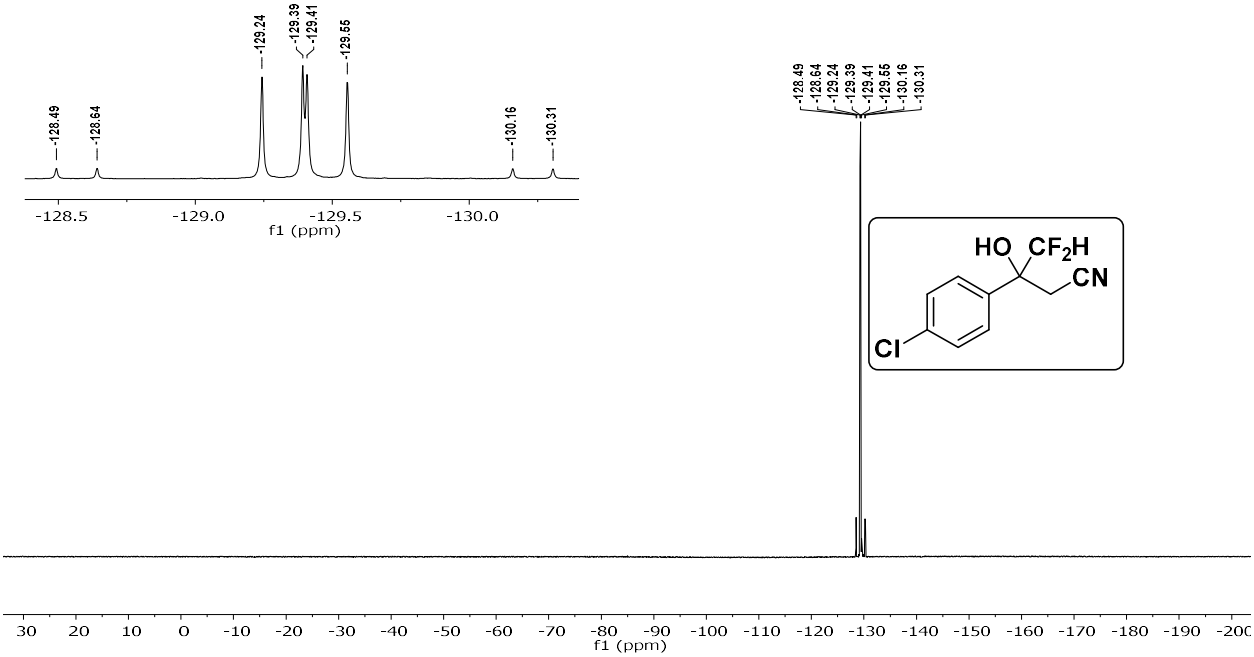
^{1}H NMR spectrum of 3-(4-chlorophenyl)-4,4-difluoro-3-hydroxybutanenitrile (5f).



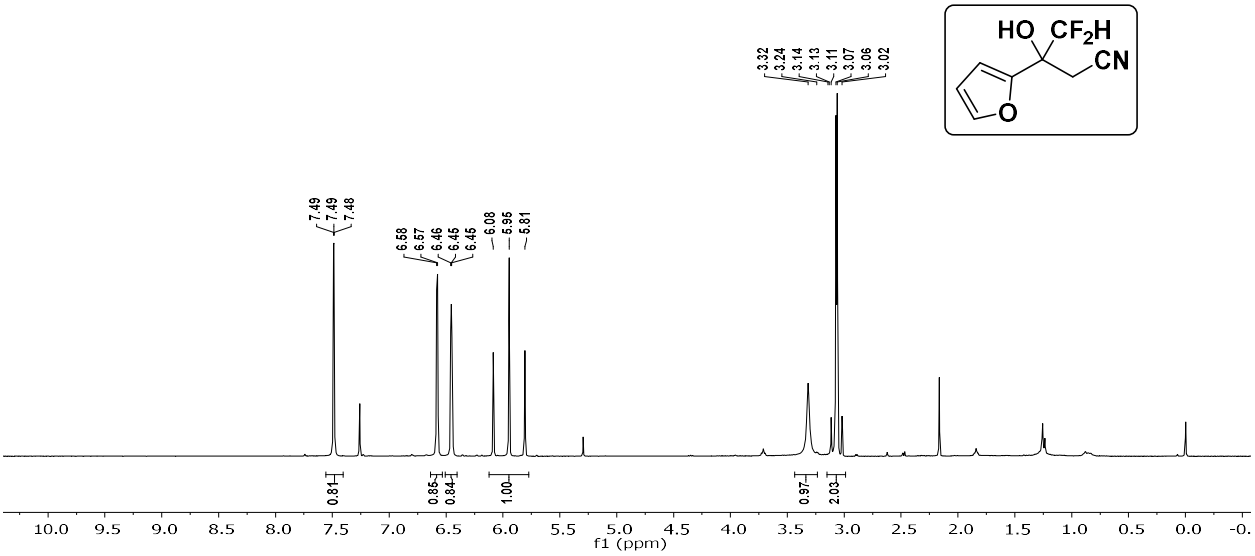
^{13}C NMR spectrum of 3-(4-chlorophenyl)-4,4-difluoro-3-hydroxybutanenitrile (5f).



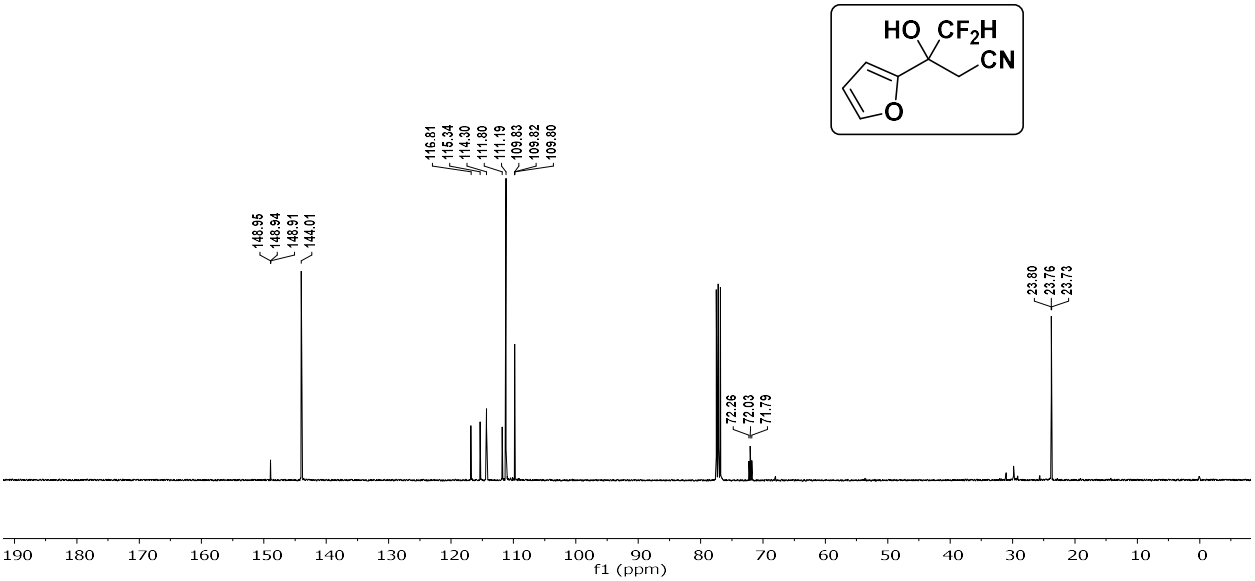
^{19}F NMR spectrum of 3-(4-chlorophenyl)-4,4-difluoro-3-hydroxybutanenitrile (5f).



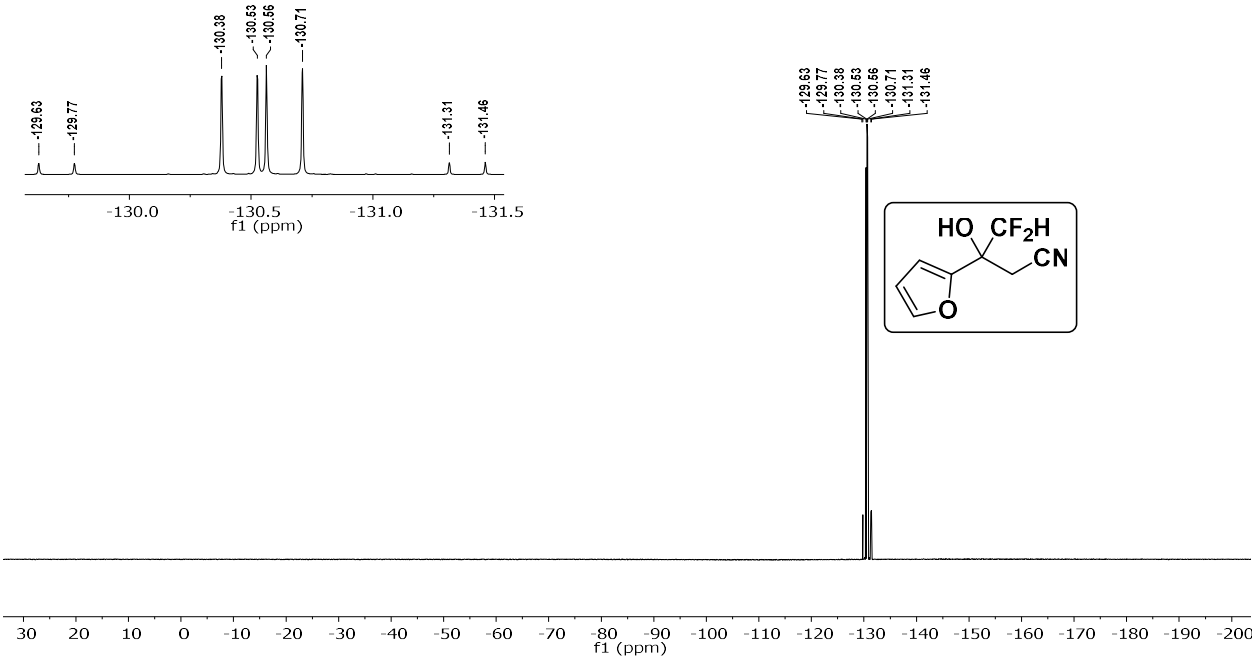
^{1}H NMR spectrum of 4,4-difluoro-3-(furan-2-yl)-3-hydroxybutanenitrile (5g).



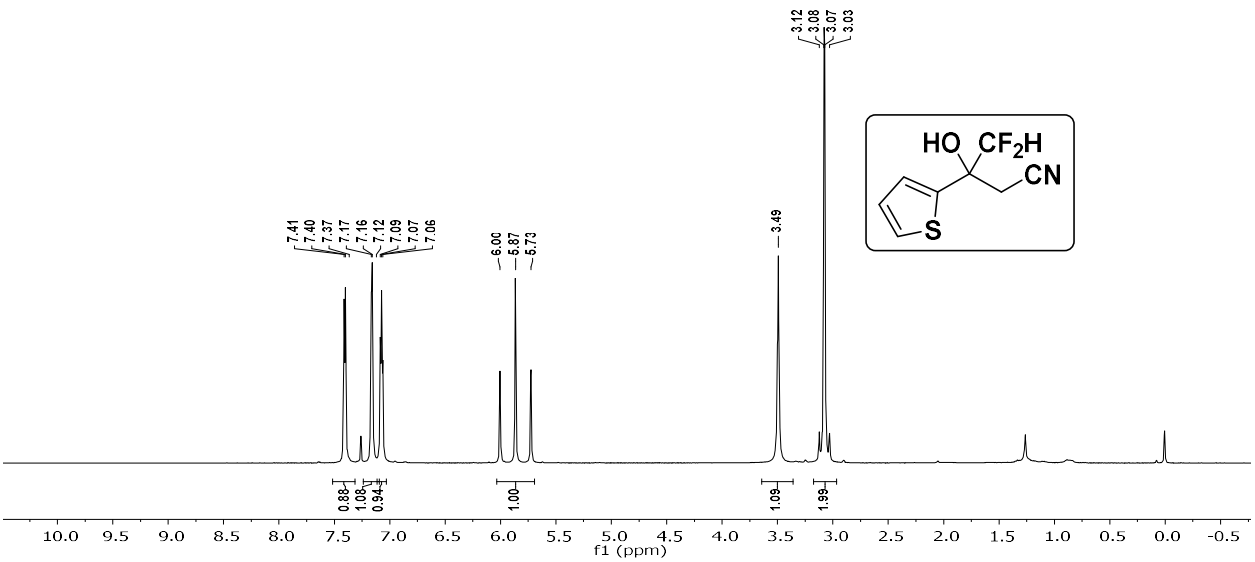
^{13}C NMR spectrum of 4,4-difluoro-3-(furan-2-yl)-3-hydroxybutanenitrile (5g).



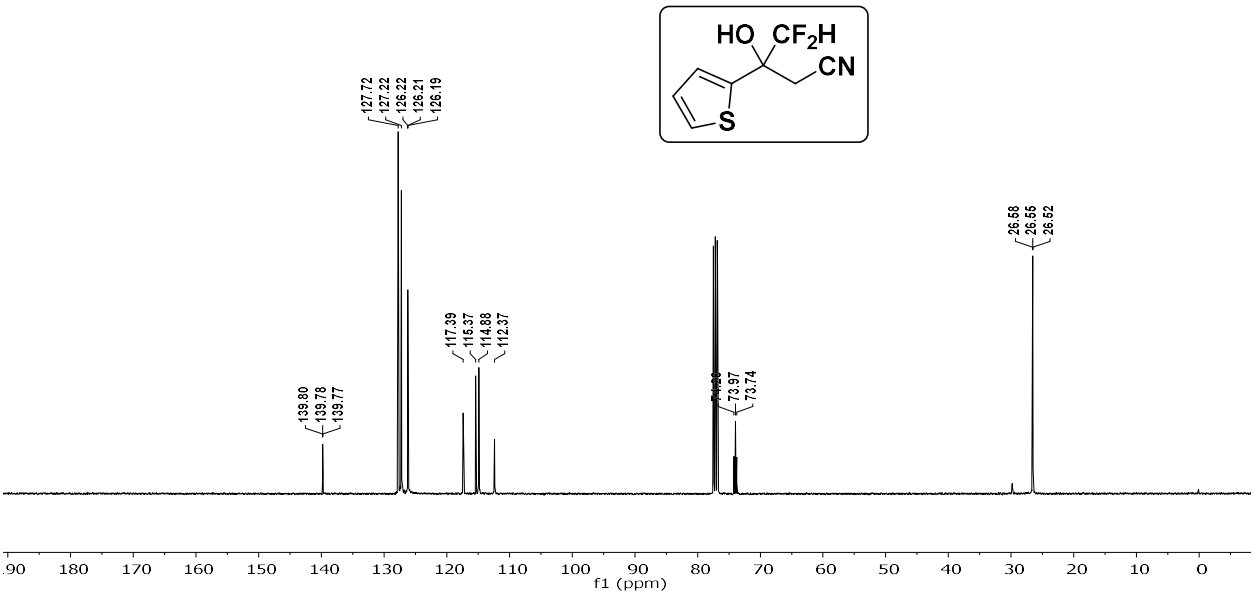
^{19}F NMR spectrum of 4,4-difluoro-3-(furan-2-yl)-3-hydroxybutanenitrile (5g).



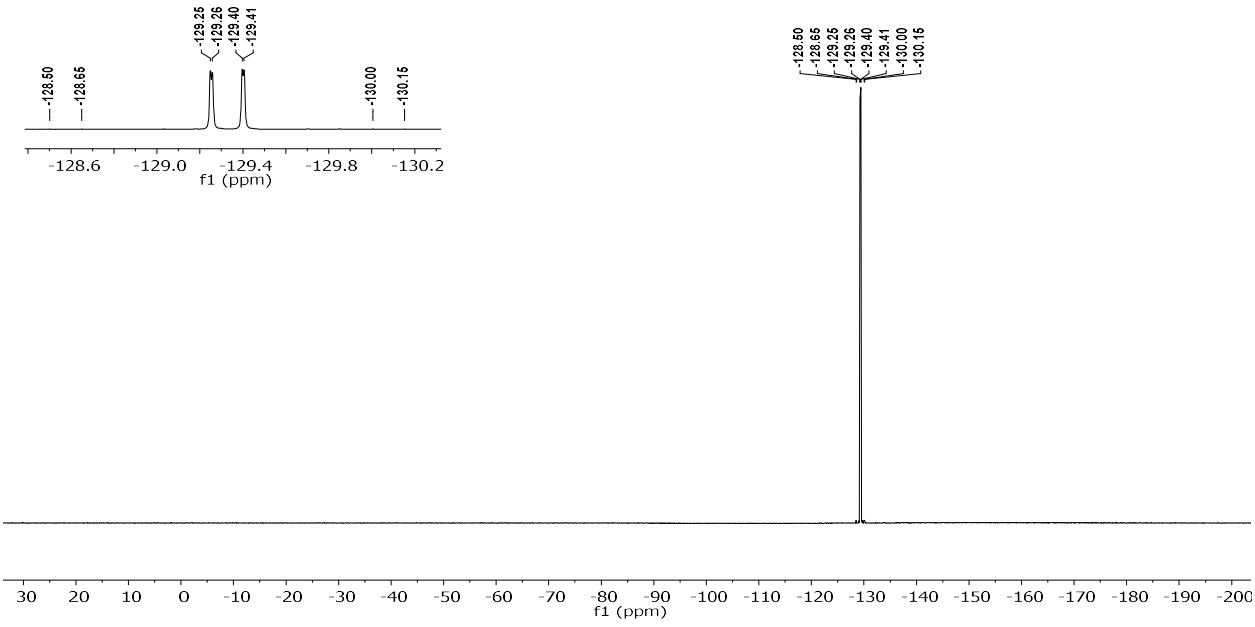
^{1}H NMR spectrum of 4,4-difluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (5h).



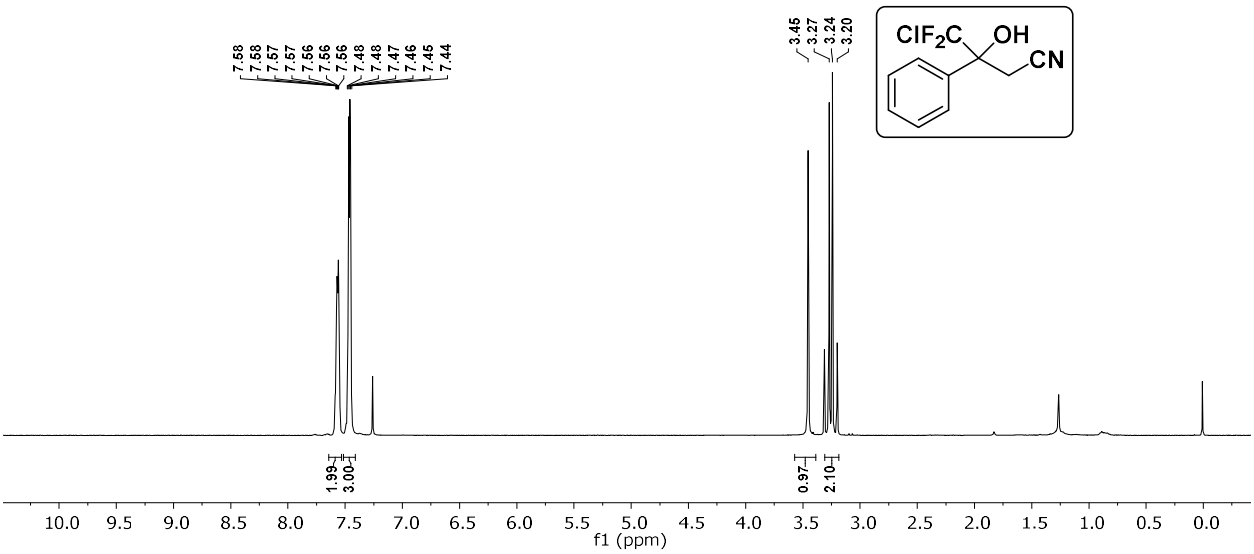
^{13}C NMR spectrum of 4,4-difluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (5h).



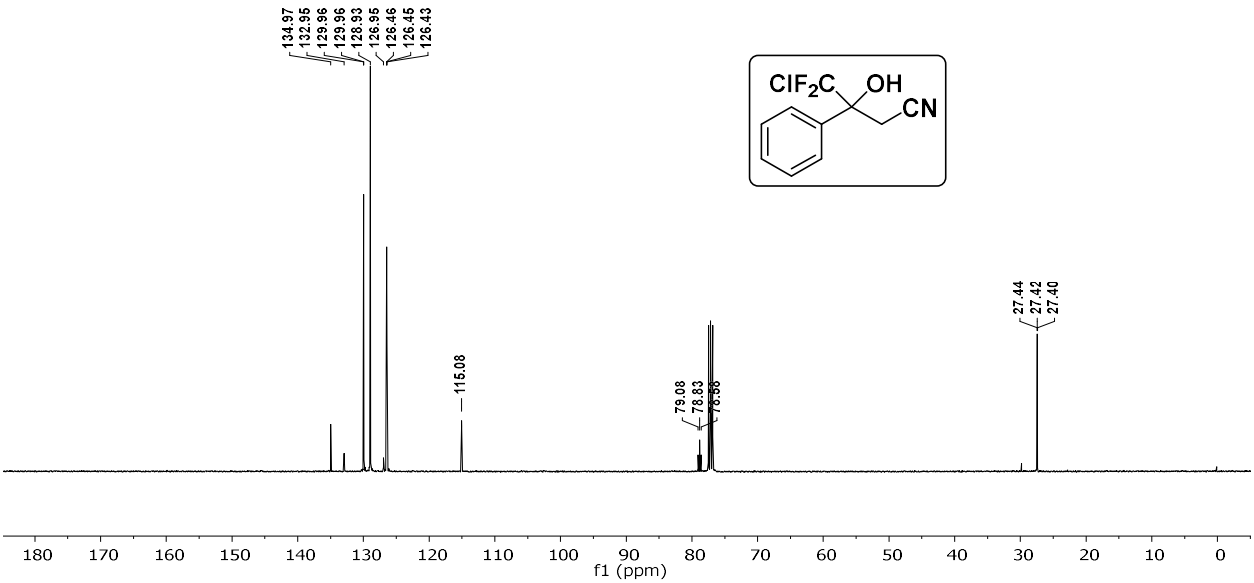
^{19}F NMR spectrum of 4,4-difluoro-3-hydroxy-3-(thiophen-2-yl)butanenitrile (5h).



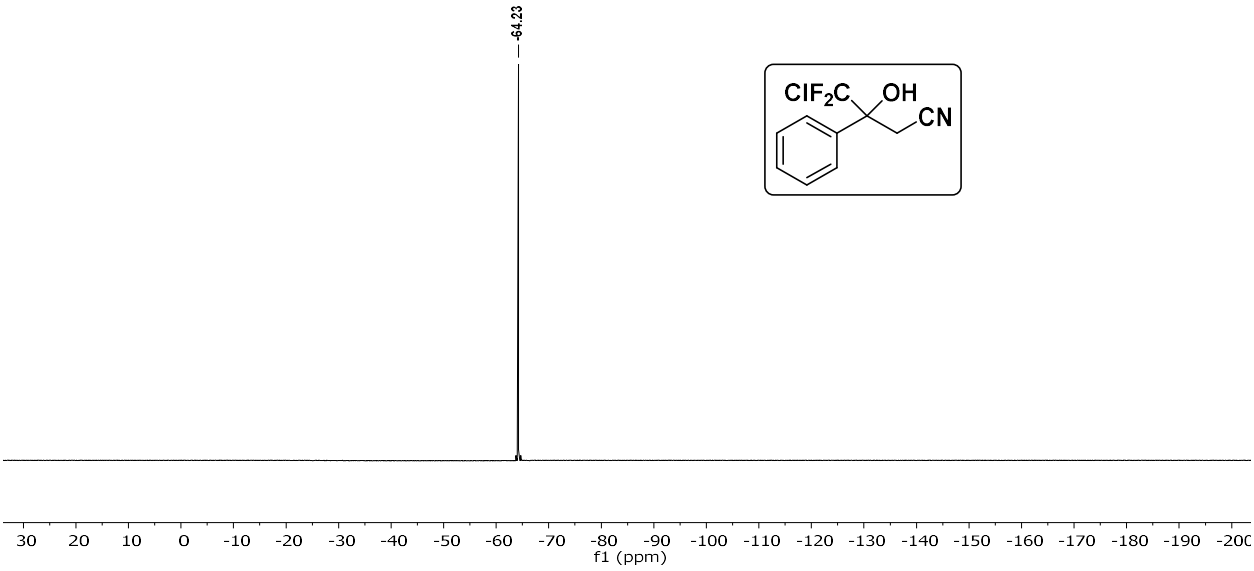
^{1}H NMR spectrum of 4-chloro-4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (7).



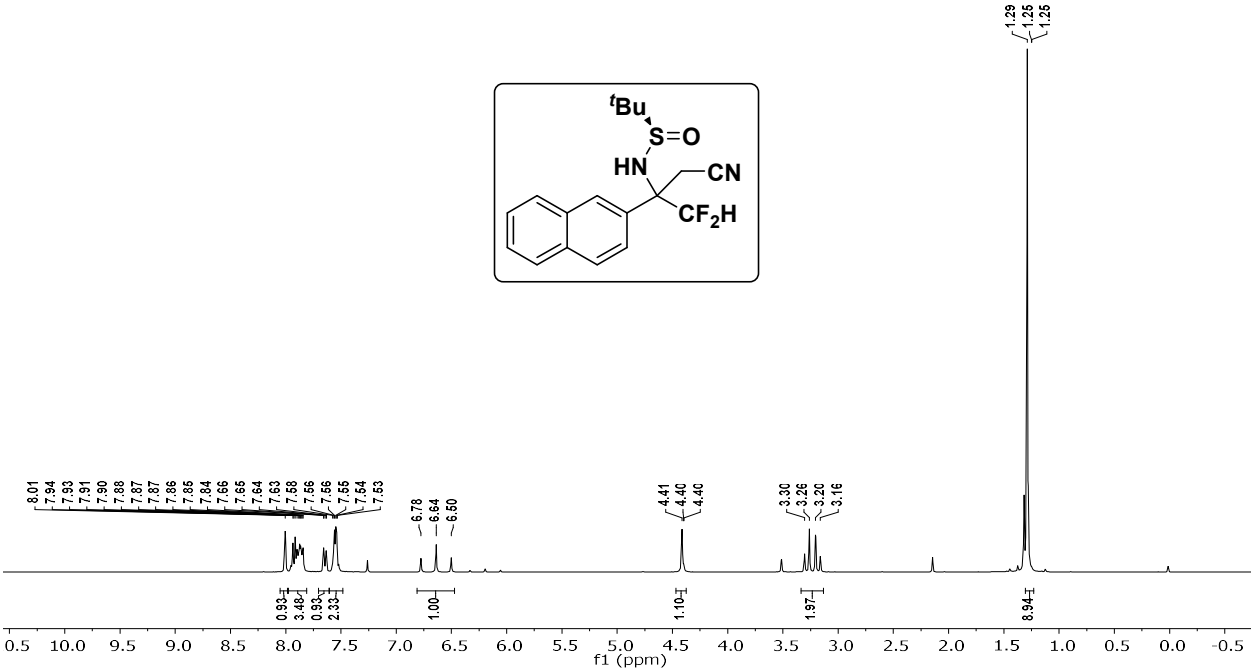
^{13}C NMR spectrum of 4-chloro-4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (7).



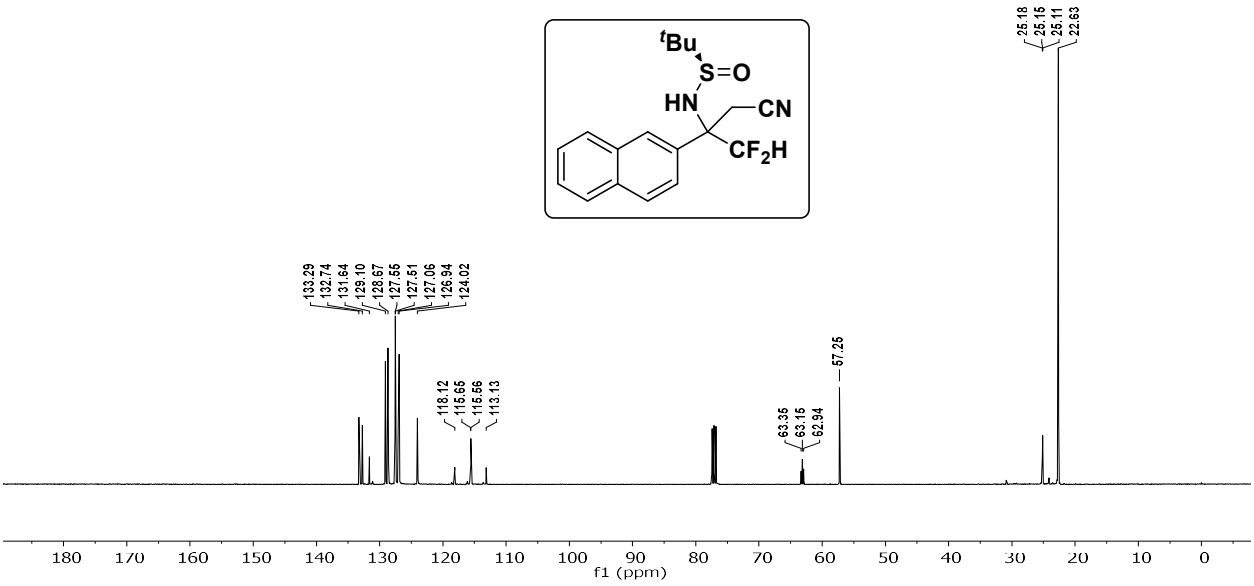
^{19}F NMR spectrum of 4-chloro-4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (7).



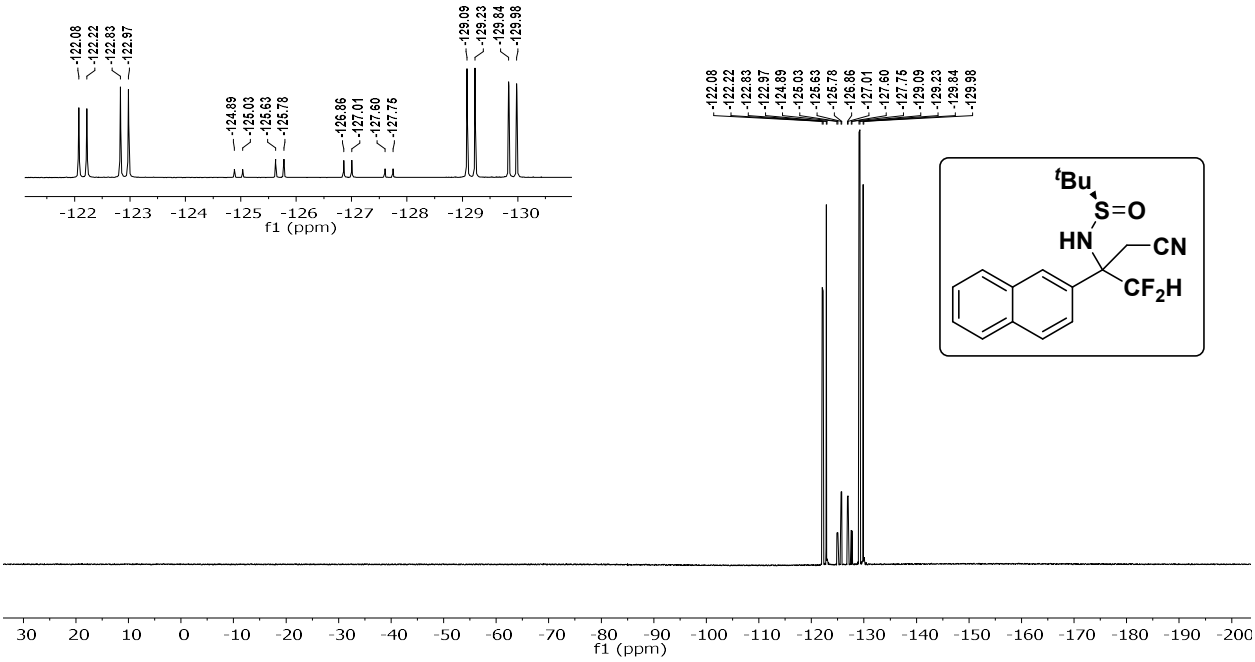
^{1}H NMR spectrum of (*R*)-*N*-(3-cyano-1,1-difluoro-2-(naphthalen-2-yl)propan-2-yl)-2-methylpropane-2-sulfinamide (9).



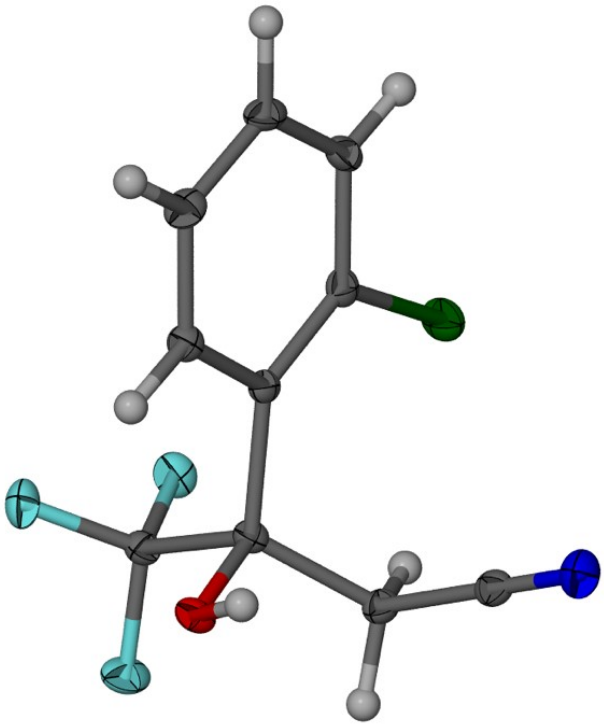
^{13}C NMR spectrum of (*R*)-*N*-(3-cyano-1,1-difluoro-2-(naphthalen-2-yl)propan-2-yl)-2-methylpropane-2-sulfinamide (9).



^{19}F NMR spectrum of (*R*)-*N*-(3-cyano-1,1-difluoro-2-(naphthalen-2-yl)propan-2-yl)-2-methylpropane-2-sulfinamide (9).

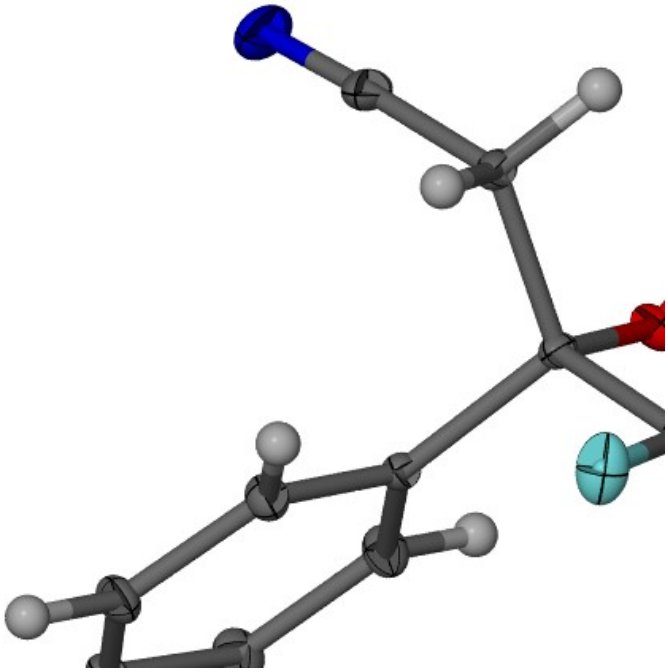

-122.08
-122.22
-122.83
-122.97
-124.89
-125.03
-125.63
-125.78
-126.86
-127.01
-127.60
-127.76
-129.09
-129.23
-129.84
-129.98
f1 (ppm)
tBu
S=O
HN
CN
CF2H

5. Crystallographic data



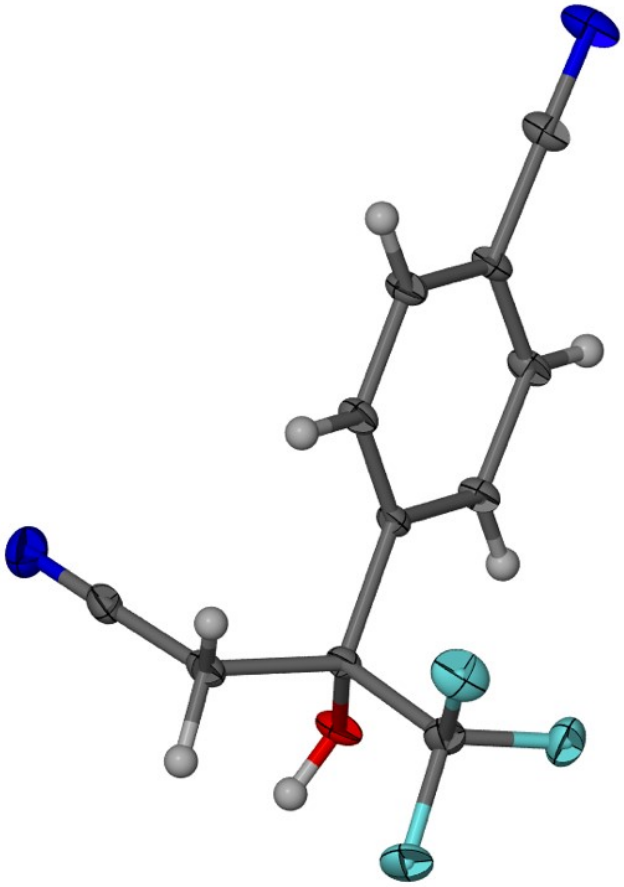
3-(2-Chlorophenyl)-4,4,4-trifluoro-3-hydroxybutanenitrile (3d)

A single crystal was obtained by slow evaporation of a solution containing the chiral alcohol in a mixture of hexanes and ethyl acetate (4:1). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 3 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{10}H_7ClF_3NO$, M = 249.02, colorless block, 0.63 x 0.44 x 0.38 mm^3, orthorhombic, space group *Pccn* = 12.2156(19), b = 23.4862(12), c = 7.1398(4) Å, V = 2048.40(19) $Å^3$, Z = 8.



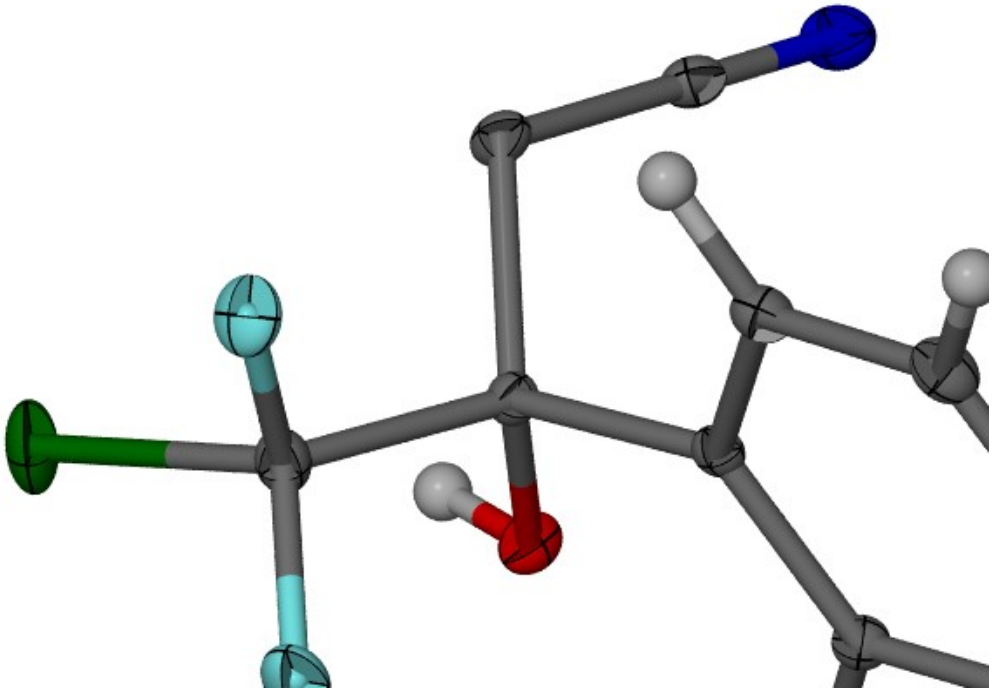
4,4,4-Trifluoro-3-(4-fluorophenyl)-3-hydroxybutanenitrile (3e)

A single crystal was obtained by slow evaporation of a solution containing the chiral alcohol in a mixture of hexanes and ethyl acetate (4:1). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 3 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{10}H_7F_4NO$, M = 233.05, colorless needle, 0.49 x 0.12 x 0.12 mm^3, triclinic, space group *P-1* a = 9.0187(9), b = 10.7542(11), c = 21.489(2) Å, V = 1973.9(3) $Å^3$, Z = 8.



4-(3-Cyano-1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (3h)

A single crystal was obtained by slow evaporation of a solution containing the chiral alcohol in a mixture of hexanes and ethyl acetate (1:1). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 3 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{11}H_7F_3N_2O$, M = 240.05, colorless prism, 0.35 x 0.25 x 0.18 mm^3, monoclinic, space group $P2_1/c$, a = 10.8248(11), b = 9.7905(10), c = 10.1948(10) Å, V = 1071.91(19) $Å^3$, Z = 4.



4-Chloro-4,4-difluoro-3-hydroxy-3-phenylbutanenitrile (7)

A single crystal was obtained by slow evaporation of a solution containing the chiral alcohol in a mixture of hexanes and ethyl acetate (4:1). Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 3 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{10}H_8ClF_2NO$, M = 231.03, colorless prism, 0.89 x 0.73 x 0.52 mm^3, triclinic, space group *P-1,* a = 6.2345(3), b = 12.8524(6), c = 13.8297(6) Å, V = 99.7.34(8) $Å^3$, Z = 4.

6. References

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