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Decarboxylative Reissert Type Trifluoro- and Trichloro-Methylation of Quinoline Derivatives in Batch and Continuous Flow

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General Considerations. All chemicals were used as received without further purification. Starting materials were made according to literature procedures. Flash chromatography was carried out on activated aluminum oxide, neutral, Brockmann activity I. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400, 100 and 378 MHz respectively. Chemical shifts are reported in ppm downfield from TSM (δ = 0) and referenced to the residual solvent peak, using peak pattern abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; sext, sextet; m, multiplet; dd, doublet of doublets; td, triplet of doublets. HRMS was recorded on an LC TOF (ES).

General Method A:

Stock solution A: substrate (1.2 M) in DMF. Stock solution B: alkylating agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.88 M) in MeCN. Stock solution D: triethylamine (3.6 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 1.309 ml/min. Stock solutions C and D were pumped at 1.309 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d 2.0 mm, length 5 m, reactor volume 15.7 mL) placed in an oil bath heated at 120 ^{o}C or 140 ^{o}C, providing a retention time of 6 min. in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d 2.0 mm, length 5 m, reactor volume 15.7 mL) heated at 40 ^{o}C, providing a retention time of 3 min. in the second reactor for an overall retention time of 9 min. The flow reactors were allowed to run for 13.5 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 3 h, corresponding to a turnover of 282.7 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous $NaHCO_3$ 10 % (250 mL). The crude reaction mixture was extracted with Et_2O (3 × 250 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10 (3 × 250 mL) and brine (250 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration.

General Method B:

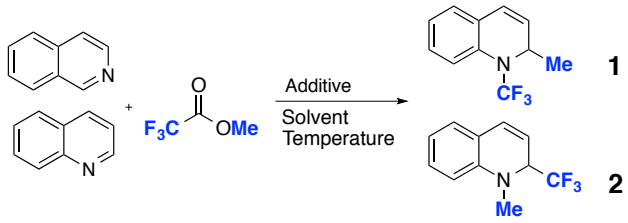
Stock solution A: substrate (1.2 M) in DMF. Stock solution B: alkylating agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.4 M) in MeCN. Stock solution D: triethylamine (3 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.055 ml/min. Stock solutions C and D were pumped at 0.066 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 ^{o}C, providing a retention time of 20 min. in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d 0.75 mm, length 5.5 m, reactor volume 2.43 mL) heated at 40 ^{o}C, providing a retention time of 10 min. in the second reactor for an overall retention time of 30 min. The flow reactors were allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 1 h, corresponding to a turnover of 3.96 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous $NaHCO_3$ 10 % (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10 % (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration.

Generel procedure C:

Substrate (5 mmol) was dissolved in 20 mL NMP in a 100 mL reaction flask. Methyl trifluoroacetate (1005.8 µL, 10 mmol) was added. The flask was then sealed (caution – use blast shield) and stirred at 150 °C for 19 h. The reaction mixture was extracted with Et_2O (3 x 75 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10 % (3 x 50 mL) and brine (50 mL). The organic phase was dried over $NaSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using alumina as the solid phase, the mobile phase is specified for each individual entry as stated below.

Optimization of the decarboxylative trifluoromethylation of (iso)qiunoline.

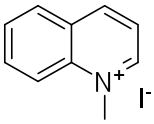


Starting material	MTFA	CuI	Additive	Solvent/temp	Conv./% (yield)[a]
Isoquinoline	1.2 eq.	0.3 eq.	LiCl 0.5 eq.	NMP/150 °C	70
Isoquinoline	1.2 eq.	0 eq.	LiCl 0.5 eq.	NMP/150 °C	71
Isoquinoline	1.2 eq.	0.3 eq.		NMP/150 °C	75
Isoquinoline	2 eq.	1 eq.		NMP/150 °C	100
Isoquinoline	2 eq.	0 eq.		NMP/150 °C	100
Quinoline	2 eq.	1 eq.		NMP/150 °C	100
Quinoline	2 eq.	0 eq.		NMP/150 °C	100 (59)[b]
Quinoline	2 eq.			NMP/150 °C	100 (53)
Quinoline	2 eq.			Chlorobenzene/150 °C	89 (40)
Quinoline	2 eq.			Diglyme/150 °C	90 (23)
Quinoline	2 eq.			O-Xylene/150 °C	69 (26)
Quinoline	2 eq.			Sulfolane/150 °C	100 (50)
Quinoline	2 eq.			NMP/150 °C	100 (65)
Quinoline	4 eq.			NMP/150 °C	100 (64)
Quinoline	2 eq.			NMP/180 °C	100 (35)
Quinoline	2 eq.			NMP/125 °C	100 (55)
Quinoline	2 eq.			DMF/150 °C	100 (56)

[a] NMR yield. [b]Isolated yield.

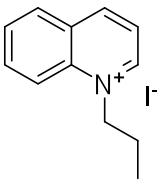
Experimental Details

1-Methylquinolin-1-ium iodide[1].



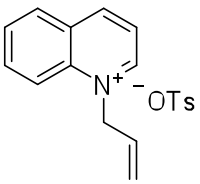
Stock solution A: quinoline (1.2 M) in 20% DMF/MeCN. Stock solution B: MeI (2.4 M) in 20% DMF/MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.184 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 °C, providing a retention time of 6 min. The flow reactor was allowed to run for 9 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 1 h, corresponding to 13.25 mmol of starting quinoline. Excess MeI and solvents were removed by freeze-drying to give the title compound as a yellow solid. (3.43 g, 97%); mp 133.1-135.9 ^{o}C. ^{1}H NMR (400MHz, CD_3CN) δ 9.23 (d, *J* = 6.0 Hz, 1H) 9.13 (d, *J* = 8.4 Hz, 1H) 8.39 (dd, *J* = 8.4, 1.6 Hz, 2H) 8.25 (td, *J* = 8.4, 1.2 Hz, 1H) 8.03 (t, *J* = 7.2 Hz, 2H) 4.6 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 150.6, 148.3, 139.6, 136.6, 131,3, 131.0, 130.4, 122.6, 119.6, 46.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{10}H_{10}N$: 144.0808; found: 144.0807. Obtained melting point and NMR-data fits with literature values.

1-Propylquinolin-1-ium iodide[2].



Stock solution A: quinoline (1.2 M) in 10% DMF/MeCN. Stock solution B: propyl iodide (2.4 M) in 10% DMF/MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.074 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 150 ^{O}C, providing a retention time of 15 min. The flow reactor was allowed to run for 22.5 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 42.29 min, corresponding to 3.76 mmol of starting quinoline. Excess propyl iodide and solvents were removed by freeze-drying to give a yellow solid. This was tritruated using toluene to give the title compound as a yellow solid. (0.87 g, 77%); mp 128.5-130 ^{o}C. ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 9.60 (d, *J* = 4.4 Hz, 1H), 9.32 (d, *J* = 8.0 Hz, 1H), 8.67 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 7.8 Hz, 1H), 8.28 (t, 7.2 Hz, 1H), 8.21 (t, 6.4 Hz, 1H), 8.06 (t, *J* = 7.6 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 2H), 2.00 (m, 2H), 0.97 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 149.6, 147.3, 137.4, 135.6, 130.7, 129.9, 129.7, 122.1, 119.0, 58.5, 22.9, 10.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{12}H_{14}N$: 172.1121; found: 172.1122. Obtained melting point is within 10 degrees of literature value.

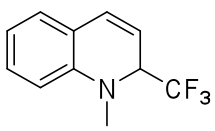
1-Allylquinolin-1-ium 4-methylbenzenesulfonate.



Stock solution A: quinoline (1.2 M) in DMF. Stock solution B: allyl tosylate (2.4 M) in DMF. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.055 ml/min and combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to a plug-flow reactor (stainless steel tubing, o.d. 1/16 in, i.d 0.75 mm, length 5 m, reactor volume 2.21 mL) placed in an oil bath heated at 120 ^{O}C, providing a retention time of 20 min. The flow reactor was allowed to run for 30 minutes (1.5 times the retention time) before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 60 min, corresponding to 3.96 mmol of

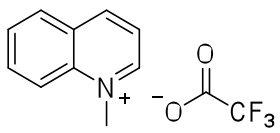
starting quinoline. Excess solvents were removed by freeze-drying to give an orange solid. This was triturated using toluene to give the title compound as an orange solid. (0.92 g, 69%, average of 2 runs); mp 88.1-90.0 °C. ^{1}H NMR (400MHz, CD_3SOCD_3) δ 9.58 (d, *J* = 4.8 Hz, 1H), 9.33 (d, *J* = 8.0 Hz, 1H), 8.57-8.46 (m, 2H), 8.30-8.15 (m, 2H), 8.04 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.30-6.13 (m, 1H), 5.75 (d, *J* = 3.6 Hz, 2H), 5.39 (d, *J* = 10.4 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 150.2, 148.1, 145.9, 137.9, 137.7, 135.8, 131.6, 130.9, 130.1, 129.9, 128.3, 125.7, 122.6, 120.7, 119.5, 59.3, 21.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{12}H_{12}N$: 170.0964; found: 170.0964. Unidentified impurity at 2.55 ppm (triplet) with a corresponding carbon signal at 34.6 ppm.

1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (**2**).



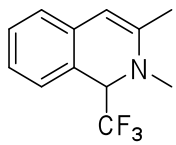
The compound was obtained using general procedure C with quinoline (591.0 µL, 5.0 mmol) as substrate. The crude product was purified by flash chromatography eluting with 50 % toluene in pentane to give the title compound as a green oil (539.4 mg, 51 %). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.18 (td, *J* = 8.0, 1.5 Hz, 1H), 7.02 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.74 (d, *J* = 9.7 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.67 (dd, *J* = 9.7, 5.9 Hz, 1H), 4.68 (pent, *J* = 6.8 Hz, 1H), 3.06 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 144.8, 131.3, 130.8, 128.3, 126.4 (q, *J* =290 Hz), 121.7, 118.5, 115.6, 112.1, 61.6 (q, *J* = 29 Hz), 39.3. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -77.8. HRMS (ESI-TOF) m/z: $[M + H^+]$ calculated for $C_{11}H_{11}F_3N$: 214.0838; found: 214.0834.

1-methylquinolin-1-ium 2,2,2-trifluoroacetate (**3**).



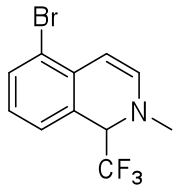
Quinoline (4 mmol, 1 equiv) and methyl trifluoroacetate (16 mmol, 4 equiv) were dissolved in 10 mL methanol in a 100 mL sealed reaction flask (caution – use blast shield). The reaction mixture was stirred at 85 °C for 2 days. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and a brown solid was isolated. The solid was washed 3 times with diethyl ether (20 mL) and dried under reduced pressure to give the title compound as brown needles (0.87 g, 85%);. mp 100.8-103.1 °C. ^{1}H NMR (400MHz, CD_3CN) δ 9.40 (d, *J* = 5.6 Hz, 1H), 9.12 (d, *J* = 8.4 Hz, 1H), 8.38 (t, *J* = 8.8 Hz, 2H), 8.28 (t, *J* = 7.6 Hz, 1H), 8.01 (dd, *J* = 6.0 Hz, 2H), 4.62 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 160.0 (q, *J* = 93 Hz), 151.2, 148.6, 139.9, 136.8, 131.5, 131.1, 130.7, 122.9, 120.3, 118.8 (q, *J* = 297 Hz), 46.4. ^{19}F NMR (378 MHz, CD_3CN) δ -75.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{10}H_{10}N$: 144.0808; found: 144.0807.

2,3-Dimethyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (**5**).



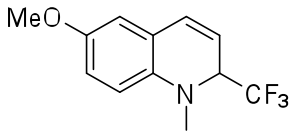
The compound was obtained using general procedure C with 3-methylisoquinoline (999.8 mg, 4.9 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a pale red solid (646.1 mg, 58 %); mp 85.7 - 87.2 °C. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.21 (td, *J* = 7.5, 1.5 Hz, 1H), 7.10-7.03 (m, 2H), 6.91 (d, *J* = 7.6 Hz, 1 H), 5.32 (s, 1 H), 5.02 (q, *J* = 8.0 Hz, 1H), 3.11 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 144.0, 136.1, 129.9, 128.7, 127.3 (q, *J* = 290 Hz), 124.9, 123.1, 120.6, 98.2, 65.3 (q, *J* = 29 Hz), 39.4, 20.0. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -76.9. HRMS (ESI-TOF) m/z: $[M + H^+]$ calculated for $C_{12}H_{13}F_3N$: 228.0995; found: 228.0987.

5-Bromo-2-methyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (**6**).



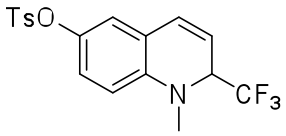
The compound was obtained using general procedure C with 5-bromoisoquinoline (1040.3 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a red oil (938.1 mg, 64 %). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.43 (dd, *J* = 7.5, 1.1 Hz, 1H), 5.59 (d, *J* = 7.5 Hz, 1H), 5.09 (q, *J* = 7.7 Hz, 1H), 3.10 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 139.50, 134.25, 133.97, 128.92, 126.83 (q, *J* = 290 Hz), 126.67, 121.88, 118.78, 96.04, 63.03 (q, *J* = 29 Hz), 42.50. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -76.80. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{11}H_{10}BrF_3N$: 291.9943; found: 291.9971.

6-Methoxy-1-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (**7**).



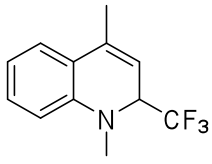
The compound was obtained using general procedure C with 6-methoxyquinoline (689.8 µL, 5.0 mmol) as substrate. In this reaction 3 equivalents of methyl trifluoroacetate (1.50 mL, 14.9 mmol) were used. The crude product was purified by flash chromatography with 10% DCM in toluene to give the title compound as a green solid (750.3 mg, 62 %); mp 47.0 – 48.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.65 (d, *J* = 9.7 Hz, 1H), 6.62 (d, *J* = 2.9 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 5.67 (dd, *J* = 9.7, 5.8 Hz, 1H), 4.44 (pent, *J* = 6.7 Hz, 1H), 3.76 (s, 3H), 3.05 (s, 3H) ^{13}C NMR (100 MHz, CD_3CN) δ 152.9, 139.0, 131.1, 126.5 (q, *J* = 290 Hz), 122.6, 116.8, 115.9, 114.0, 112.9, 61.5 (q, *J* = 29 Hz), 56.2, 39.3. ^{19}F NMR (378 MHz, CD_3CN) δ -76.9. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{12}H_{13}F_3NO$: 244.0944; found: 244.0943.

1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinolin-6-yl 4-methylbenzenesulfonate (**8**).



The compound was obtained using general procedure C with quinolin-6-yl 4-methylbenzenesulfonate (1393.8 mg, 4.7 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a brownish red solid (400.1 mg, 22 %); mp 120.0 – 125.8 °C. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.69 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 6.59 (d, *J* = 9.8 Hz, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 5.70 (dd, *J* = 9.8, 5.8 Hz, 1H), 4.68 (pent, *J* = 6.7 Hz, 1H), 3.01 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 147.0, 143.6, 141.7, 133.1, 130.9, 130.3, 129.3, 126.0 (q, *J* = 259 Hz), 124.0, 122.2, 121.8, 117.3, 112.5, 61.6, (q, *J* = 29 Hz), 39.5, 21.7. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -77.8 HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{18}H_{17}F_3SO_3N$: 384.0876; found: 384.0879.

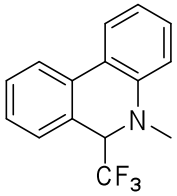
1,4-Dimethyl-2-(trifluoromethyl)-1,2-dihydroquinoline (**9**).



The compound was obtained using general procedure C with lepidine (661.0 µL, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 2% DCM in pentane to give the title compound as a green oil (723.0 mg, 64 %). ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.22-7.17 (m, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 5.54 (d, *J* = 6.0 Hz, 1H), 4.58 (pent, *J* = 6.9 Hz, 1H), 3.05 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 144.8, 136.7, 126.6 (q, *J* = 290 Hz), 125.1, 122.9, 118.2, 113.0, 112.1, 61.5

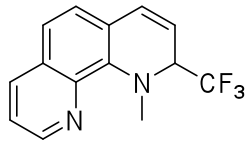
(q, *J* = 29 Hz), 39.4, 18.9. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -77.4. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{12}H_{13}F_3N$: 228.0995; found: 228.0991.

5-Methyl-6-(trifluoromethyl)-5,6-dihydrophenanthridine (**10**).



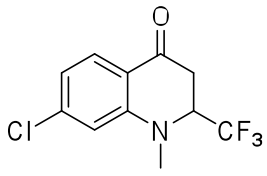
The compound was obtained using general procedure C with phenanthridine (896.1 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with pentane to give the title compound as a white solid (856.1 mg, 65 %); mp 58.2 -59.5 °C. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.91 (d, *J* = 7.9, 1H), 7.83 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.49 (td, *J* = 7.8, 2.1 Hz, 1H), 7.39-7.28 (m, 3H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.07 (q, *J* = 7.7 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 144.4, 133.0, 130.7, 130.5, 129.4, 128.2, 127.2 (q, *J* = 290 Hz), 127.0, 124.1, 123.6, 122.3, 119.4, 113.7, 64.1 (q, *J* = 29 Hz), 39.6. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -74.2. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{15}H_{13}F_3N$: 264.0995; found: 264.0994.

1-Methyl-2-(trifluoromethyl)-1,2-dihydro-1,10-phenanthroline (**11**).



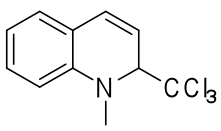
The compound was obtained using general procedure C with phenanthroline (901.1 mg, 5.0 mmol) as substrate. The crude product was purified by flash chromatography with 10% DCM in toluene to give the title compound as a yellow solid (475.1 mg, 36 %); mp 81.2 – 85.1 °C. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 8.87 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.36 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 9.5 Hz, 1H), 5.77 (dd, *J* = 9.5, 6.1 Hz, 1H), 4.67 (pent, *J* = 8.1 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 148.7, 142.1, 141.9, 137.2, 131.0, 130.8, 127.1, 126.3 (q, *J* = 285 Hz), 123.3, 122.1, 120.5, 115.9, 63.7 (q, *J* = 30 Hz), 47.3. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -74.9. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{14}H_{12}F_3N_2$: 265.0947; found: 265.0952.

7-Chloro-1-methyl-2-(trifluoromethyl)-2,3-dihydroquinolin-4-one (**13**).



The compound was obtained using general procedure C with 7-chloro-4-(N,N-dimethylamino)quinoline (1040.9 mg, 5.0 mmol) as substrate. The product was purified by flash chromatography with 0-50 % EtOAc in toluene to give the title compound as a brown solid (637.0 mg, 56 %); mp 76.3 – 79.9 °C. ^{1}H NMR (400 MHz, CD_3CN) δ (ppm): 7.70 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 1.7 Hz, 1H), 6.76 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.41-4.30 (m, 1H), 3.25 (dd, *J* = 17.5, 7.7 Hz, 1H), 3.14 (s, 3H), 2.76 (dd, *J* = 17.5, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ (ppm): 190.3, 151.1, 142.6, 129.2, 127.6 (q, *J* = 288 Hz), 118.5, 118.4, 113.8, 61.7 (q, *J* = 29 Hz), 40.1, 35.0. ^{19}F NMR (378 MHz, CD_3CN) δ (ppm): -74.1. HRMS (ESI-TOF) m/z: [M + H^+] calculated for $C_{11}H_{10}ClF_3NO$: 264.0398; found: 264.0399.

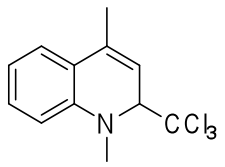
1-Methyl-2-(trichloromethyl)-1,2-dihydroquinoline (**14**)[3].



The compound was obtained using general method B and purified using plug filtration with 10% DCM in toluene to give the title compound as a brown solid (0.86 g, 83%, average of 2 runs); mp 67.9-69.7 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.28-7.21 (m, 1H), 7.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.88 (d, *J* = 10.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.73 (td, *J* = 7.6, 1.2 Hz, 1H), 6.02 (dd, *J* = 9.6, 5.6 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR (100 MHz,

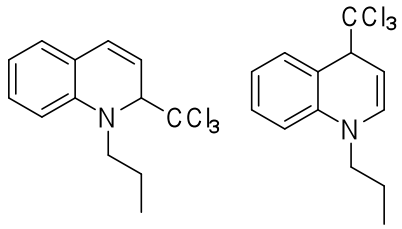
CD_3CN) δ 145.4, 131.1, 130.5, 128.0, 122.6, 118.7, 118.0, 113.6, 106.7, 76.4, 44.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{11}Cl_3N$: 261.9952; found: 261.9945. Obtained melting point and NMR-data fits with reported values.

1,4-Dimethyl-2-(trichloromethyl)-1,2-dihydroquinoline (**15**)[3].



The compound was obtained using general method B and purified using plug filtration with 10% DCM in toluene to give the title compound as a brown oil (0.94 g, 86%, average of 2 runs). ^{1}H NMR (400MHz, CD_3SOCD_3) δ 7.24-7.17 (m, 2H), 6.80 – 6.70 (m, 2H), 5.84 (dd, *J* = 6.0, 1.2 Hz, 1H), 5.03 (d, *J* = 6.0 Hz, 1H), 3.33 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 144.0, 135.0, 129.2, 123.6, 122.3, 117.2, 114.7, 112.5, 106.3, 74.4, 43.2, 18.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{12}H_{13}Cl_3N$: 276.0108; found: 276.0101. Obtained NMR-data fits with reported values.

1-Propyl-2-(trichloromethyl)-1,2-dihydroquinoline and 1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (**16 + 17**).



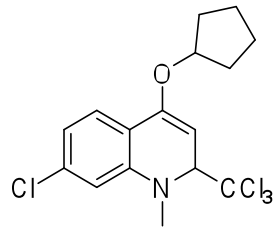
The compounds was obtained using general method B and purified using plug filtration 10% toluene in pentane to give **16** and **17** as an inseparable mixture (0.96 g. 84%, average of 2 runs) brown oil.

1-propyl-2-(trichloromethyl)-1,2-dihydroquinoline(16): ^{1}HNMR (400MHz, CD_3CN) δ *inter alia* 7.19-7.15 (m, 1H) 7.08 (dd, *J* = 7.2, 1.2 Hz, 1H) 6.93 (d, *J* = 8.4 Hz, 1H) 6.87 (d, *J* = 9.6 Hz, 1H) 6.03 (dd, *J* = 9.6, 6.0 Hz, 1H) 4.19-4.10 (m, 1H) 0.79 (t, *J* = 7.2, 3H)

1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (17): ^{1}HNMR (400MHz, CD_3CN) δ *inter alia* 7.49 (dd, *J* = 7.6, 1.6 Hz, 1H) 7.35-7.30 (m, 1H) 6.61 (d, *J* = 7.6 Hz, 1H) 4.53 (d, *J* = 5.6 Hz, 1H) 3.77-3.68 (m, 1H) 0.94 (t, *J* = 7.2 Hz, 3H).

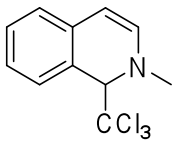
Both isomers: ^{13}C NMR (100 MHz, CD_3CN) δ 143.6, 137.1, 133.9, 131.4, 130.1, 129.7, 128.4, 124.3, 121.2, 118.9, 118.1, 115.9, 113.2, 106.8, 93.6, 75.1, 59.4, 57.3, 52.7, 22.2, 21.0, 11.6, 11.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{15}Cl_3N$: 290.0265; found: 290.0263.

7-Chloro-4-(cyclopentyloxy)-1-methyl-2-(trichloromethyl)-1,2-dihydroquinoline (**18**).



The compound was obtained using general method B (run at half concentration) and purified using plug filtration with 10% DCM in toluene to give the title compound as a white solid (0.28 g, 37%, average of 2 runs); mp 145.2-147.6 °C. ^{1}H NMR (400MHz, CD_3Cl_3) δ 7.41 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 6.4 Hz, 1H), 4.74 – 4.69 (m, 1H), 3.37 (s, 3H), 2.00 – 1.85 (m, 4H), 1.84 – 1.72 (m, 2H), 1.70 – 1.50 (m, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 152.3, 147.1, 135.8, 124.2, 118.9, 117.8, 113.1, 108.0, 91.0, 79.9, 77.0, 43.9, 33.4, 33.2, 24.81, 24.78; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{16}H_{18}Cl_4NO$: 380.0137; found: 380.0134.

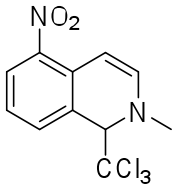
2-Methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**19**)[3].



The compound was obtained using general method B and purified using plug filtration with 10% toluene in pentane to give the title compound as a white solid. (0.91 g, 88%); mp 76.8-80.4 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.37 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.61 (d, *J* = 7.2 Hz, 1H), 5.27 (s, 1H), 3.27 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 136.7, 135.5, 131.7, 129.8, 125.4, 124.2, 121.6, 107.8, 101.4, 77.7, 45.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{11}Cl_3N$: 261.9949; found: 261.9956.

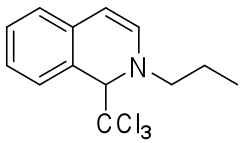
2-Methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**19**) - scaleup. The compound was obtained using general method A. The oil bath for the first reactor was heated to 140 °C. Product was collected for 3 hours. The product was purified using plug filtration with toluene to give the title compound as a white solid (65.4 g, 88%); mp 76.9-81.4 °C; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{11}Cl_3N$: 261.9952; found: 261.9952. Obtained melting point and NMR-data fits with reported values.

2-Methyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (**20**).



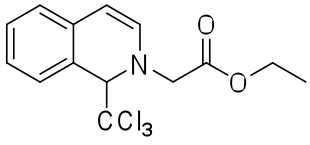
The compound was obtained using general method B and purified using plug filtration with 50% DCM in toluene to give the title compound as a dark red solid (1.06 g, 87%, average of 2 runs); mp 128.2-129.8 °C. ^{1}H NMR (400MHz, CD_3CN) δ 8.02 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.0, 1H), 6.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 1H), 3.37 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 143.6, 142.1, 137.7, 130.6, 126.9, 124.4, 123.3, 105.8, 95.3, 77.1, 45.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{10}Cl_3N_2O_2$: 306.9802; found: 306.9801.

2-Propyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**21**).



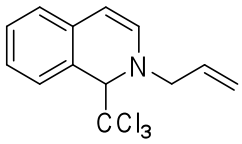
The compound was obtained using general method B and purified using plug filtration with 10% Toluene in pentane to give the title compound as a purple solid (0.84 g, 73%, average of 2 runs); mp 59.4-61.6 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.40 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.64 (d, *J* = 7.2 Hz, 1H), 5.32 (s, 1H), 3.50 (t, *J* = 7.2 Hz, 2H), 1.47 (sext, *J* = 7.2 Hz, 2H), 0.73 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 135.9, 135.7, 131.5, 129.8, 125.5, 124.3, 122.1, 107.3, 102.3, 76.4, 59.9, 24.2, 11.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{14}Cl_3N$: 290.0265; found: 290.0267.

Ethyl 2-(1-(trichloromethyl)isoquinolin-2(1H)-yl)acetate (**22**).



The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a light brown solid (0.67 g, 50%); mp 94.6-96.9 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.33 (td, *J* = 7.6, 1.2 Hz, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.28 (d, *J* = 7.2 Hz, 1H), 5.70 (d, *J* = 7.2 Hz, 1H), 5.35 (s, 1H), 4.38 (d, *J* = 18.0 Hz, 1H), 4.18 (d, *J* = 18.0 Hz, 1H), 4.11 – 3.92 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 171.1, 135.7, 135.3, 131.6, 129.8, 125.8, 124.6, 123.0, 106.8, 103.6, 76.2, 61.7, 59.0, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{14}H_{15}Cl_3NO_2$: 334.0163; found: 334.0165.

2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**23**).[5]

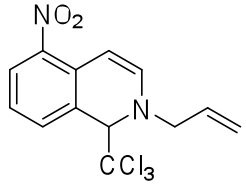


The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a purple solid (1.06 g, 93%, average of 2 runs); mp 32.7-35.8 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 7.19 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.41 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.84 – 5.70 (m, 1H), 5.68 (d, *J* = 7.2 Hz, 1H), 5.28 (s, 1H), 5.08 – 4.95 (m, 2H), 4.26-4.09 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ 135.1, 134.53, 134.48, 130.8, 129.5, 129.2, 125.1, 124.1, 121.6, 116.8, 102.8, 75.8, 60.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{13}Cl_3N$: 288.0108; found: 288.0108.

2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**23**) – Scaleup.

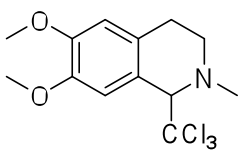
The compound was obtained using general method A. Product was collected for three hours and purified using plug filtration with toluene to give the title compound as a purple solid (72.7 g, 89%); mp 33.8-36.3 °C; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{13}Cl_3N$: 288.0108; found: 288.0109. Obtained NMR-data fits with reported values.

2-Allyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (**24**).



The compound was obtained using general method B and purified using plug filtration with 25% DCM in toluene to give the title compound as an orange solid (0.92 g, 76%, average of 2 runs); mp 101-102.9 °C. ^{1}H NMR (400MHz, CD_3CN) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.34 (d, *J* = 7.6 Hz, 1H), 5.87 – 5.71 (m, 1H), 5.44 (s, 1H), 5.14 – 5.00 (m, 2H), 4.36 – 4.15 (m, 2H). ^{13}C NMR (100 MHz, CD_3CN) δ 143.9, 140.9, 137.5, 135.1, 130.7, 126.9, 124.9, 123.8, 118.1, 106.7, 96.7, 75.2, 60.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{12}Cl_3N_2O_2$: 332.9959; found: 332.9960.

6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (**25**).



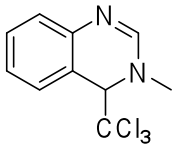
The compound was obtained using general method B and purified using plug filtration with 50% DCM in pentane to give the title compound as a white solid (0.98 g, 76%, average of 2 runs); mp 107.8-110.2 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.08 (s, 1H), 6.78 (s, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.31-3.26 (m, 1H), 3.20 – 3.09 (m, 1H), 2.76 (s, 3H), 2.65 – 2.53 (m, 1H), 2.46 – 2.33 (m, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 150.3, 147.4, 133.0, 122.9, 117.1, 112.0, 108.5, 79.8, 56.6, 56.3, 53.4, 48.1, 29.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{17}Cl_3NO_2$: 324.0319; found: 324.0325.

6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (**25**). Stock solution A: isoquinoline (1.2 M) in DMF. Stock solution B: alkylating agent (2.4 M) in DMF. Stock solution C: trichloroacetic acid (2.88 M) in MeCN. Stock solution D: triethylamine (3.6 M) in MeCN. The stock solutions were connected to separate HPLC pumps. Stock solutions A and B were pumped at 0.393 ml/min. Stock solutions C and D were pumped at 0.393 ml/min. Stock solutions A and B were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d 2.0 mm, length 5 m, reactor volume 15.7 mL) placed in an oil bath heated at 120 °C, providing a retention time of 20 min. in the first reactor. Stock solutions C and D were combined in a T-connector (o.d. 1/16 in, i.d. 0.75 mm) attached to another T-connector combining all 4 stock solutions

attached by a 1/16 – 1/8 in. adaptor to a plug-flow reactor (stainless steel tubing, o.d. 1/8 in, i.d 2.0 mm, length 5 m, reactor volume 15.7 mL) heated to 40 °C providing a retention time of 10 min. in the second reactor for an overall retention time of 30 min. The flow reactor was allowed to run for 45 min. (1.5 times the retention time), before collection was initiated. The crude reaction mixture coming off the reactor was collected in a round-bottom flask. Collection was continued for 5 h, corresponding to the turnover of 141.56 mmol of starting isoquinoline.

To the crude reaction mixture was added aqueous $NaHCO_3$ 10 % (250 mL). The crude reaction mixture was extracted with diethyl ether (3 × 250 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10% (3 × 250 mL) and brine (250 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 50% DCM in toluene to give the title compound as a white solid (38.83 g, 85%), mp 109.6-111.7 °C; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{13}H_{17}Cl_3NO_2$: 324.0319; found: 324.0323.

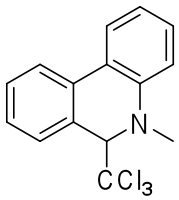
3-methyl-4-(trichloromethyl)-3,4-dihydroquinazoline (**26**).



The compound was obtained using general method B and purified using plug filtration with ethyl acetate to give title compound as a white solid (0.23 g, 22%); mp 118.4-120.3 °C. ^{1}H NMR (400MHz, CD_3SOCD_3)δ 7.47 (s, 1H), 7.42 – 7.30 (m, 2H), 7.18 (td, *J* = 7.2, 1.2 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 5.64 (s, 1H), 3.42 (s, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 149.9, 143.3, 130.1, 129.6, 124.2, 124.0, 117.3, 104.7, 72.1, 41.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{10}H_{10}Cl_3N_2$: 262.9904; found: 262.9907.

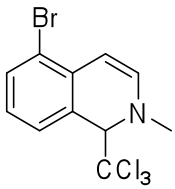
TOCSY confirmed the structure given.

5-Methyl-6-(trichloromethyl)-5,6-dihydrophenanthridine (**27**)[3].



The compound was obtained using general method B and purified using plug filtration with toluene to give the title compound as a white solid (1.06 g, 86%, average of 2 runs); mp 73.1-75.9 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.86 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.51 (td, *J* = 7.6, 1.2 Hz, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36-7.31 (m, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.90 (td, *J* = 7.6, 1.2 Hz, 1H) 5.35 (s, 1H), 3.46 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 144.1, 133.6, 131.7, 130.4, 130.2, 127.8, 127.4, 123.7, 123.5, 123.4, 119.5, 115.1, 106.6, 78.3, 44.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{15}H_{13}Cl_3N$: 312.0108; found: 312.0110. Obtained melting point and NMR-data fits with reported values.

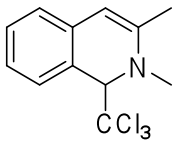
5-Bromo-2-methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**28**).



5-Bromoisoquinoline (1.06 g., 5.1 mmol) and MeI (0.623 μL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (1.63 g., 10 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous $NaHCO_3$ 10% (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10% (3 × 50 mL) and brine (50 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 10% DCM in toluene to give the title compound as a dark purple oil (1.61 g, 94%); ^{1}H NMR (400MHz, CD_3CN) δ 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H),

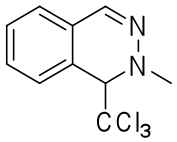
7.07 (t, *J* = 7.6 Hz, 1H), 6.53 (dd, *J* = 7.2, 1.2 Hz, 1H), 5.85 (d, *J* = 7.2 Hz, 1H), 5.31 (s, 1H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 139.0, 134.8, 133.7, 131.5, 126.2, 123.0, 118.8, 106.6, 99.6, 77.4, 45.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{11}H_{10}BrCl_3N$: 339.9057; found: 339.9052.

2,3-Dimethyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (**29**).



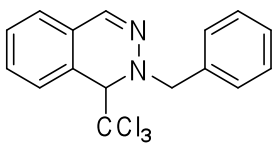
3-Methylisoquinoline (366.5 mg., 2.56 mmol) and MeI (311 µL, 5 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (0.87 mL, 6.25 mmol) and trichloroacetic acid (817 mg, 5 mmol) were added. The reaction mixture was heated at 40 °C for 2 h. To the crude reaction mixture was added aqueous $NaHCO_3$ 10% (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with toluene to give the title compound as a brown solid (0.97 g, 72%); mp 46.5-49.0 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.37 (d, *J* = 7.6 Hz, 1H), 7.27 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.54 (s, 1H), 5.20 (s, 1H), 3.28 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 143.4, 136.5, 131.2, 129.7, 124.5, 123.5, 122.0, 107.4, 101.9, 79.7, 43.1, 20.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{12}H_{13}Cl_3N$: 276.0108; found: 276.0107.

2-Methyl-1-(trichloromethyl)-1,2-dihydrophthalazine (**30**).



Phthalazine (664 mg, 5 mmol) and MeI (623 µL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (2.45 g, 15 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous $NaHCO_3$ (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ 10% (3 × 50 mL) and brine (50 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 50% DCM in toluene to give the title compound as a colorless solid (1.25 g, 95%); mp 101.1-103.4 °C. ^{1}H NMR (400MHz, CD_3CN) δ 7.56 – 7.46 (m, 3H), 7.43 (s, 1H), 7.37 – 7.28 (m, 1H), 5.52 (s, 1H), 3.54 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 134.9, 131.2, 130.6, 130.3, 128.0, 124.8, 122.4, 105.8, 74.7, 47.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{10}H_{10}Cl_3N_2$: 262.9904; found: 262.9902.

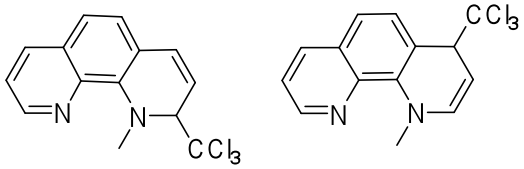
2-Benzyl-1-(trichloromethyl)-1,2-dihydrophthalazine (**31**).



Phthalazine (665 mg, 5.1 mmol) and benzyl bromide (1.2 mL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 mL, 12.5 mmol) and trichloroacetic acid (1.63 g., 10 mmol) were added. The reaction mixture was heated at 40 °C for 1 h. To the crude reaction mixture was added aqueous $NaHCO_3$ 10% (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with DCM to give the title compound as a brown solid (1.48 g, 87%); mp 98.2-

100.2 °C; ^{1}H NMR (400MHz, CD_3CN) δ 7.61 – 7.39 (m, 4H), 7.39 – 7.28 (m, 1H), 7.26 – 7.14 (m, 3H), 7.14 – 7.03 (m, 2H), 5.67 (s, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 139.9, 136.5, 131.0, 130.69, 130.65, 129.4, 128.4, 128.2, 127.9, 125.0, 122.8, 105.9, 73.5, 63.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{16}H_{14}Cl_3N_2$: 339.0217; found: 339.0219.

1-Methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline and 1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10- phenanthroline (**32 + 33**).



Phenanthridine (901 mg, 5 mmol) and MeI (623 µL, 10 mmol) were dissolved in 20 mL of DMF in a sealed 100 mL flask (caution – use blast shield). The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and triethyl amine (1.74 ml, 12.5 mmol) and trichloroacetic acid (2.45 g., 15 mmol) was added. The reaction mixture was heated at 40 °C for 2 h. To the crude reaction mixture was added aqueous $NaHCO_3$ 10% (25 mL). The crude reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried using Na_2SO_4, filtered, and solvent was removed under reduced pressure. The crude product was purified using plug filtration with 10% DCM in toluene pentane to give **32** and **33** as an inseparable mixture (1.22 g, 77%) green solid; mp 114-116 °C.

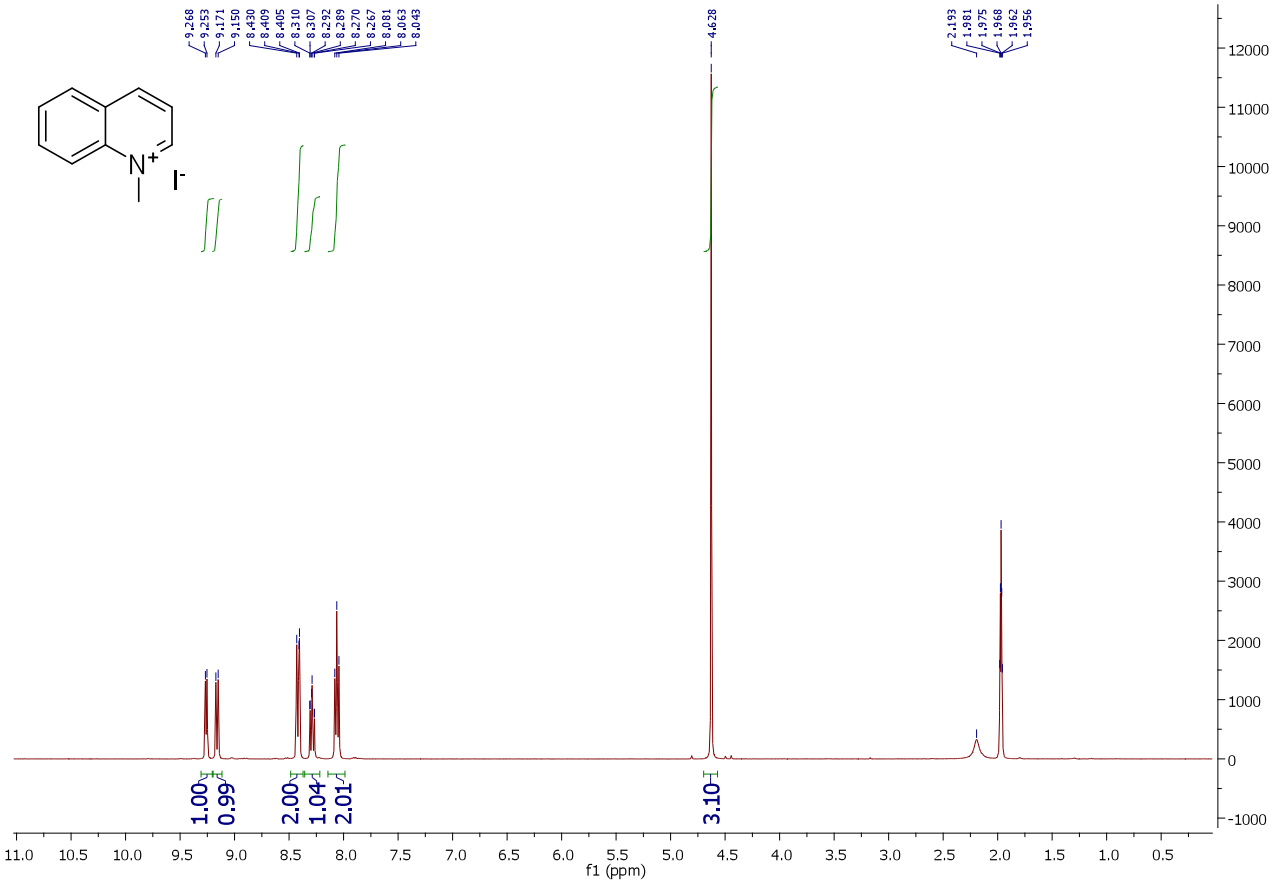
1-methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline (32): ^{1}HNMR (400MHz, CD_3CN) δ *inter alia* 8.13 (dd, *J* = 8.4, 1.6 Hz, 1H) 7.39 (dd, *J* = 8.4, 4.4 Hz, 1H) 7.36-7.28 (m, 2H), 7.03 (d, *J* = 9.2 Hz, 1H), 6.15 (dd, *J* = 9.6, 6.0 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 3.77 (s, 3H)

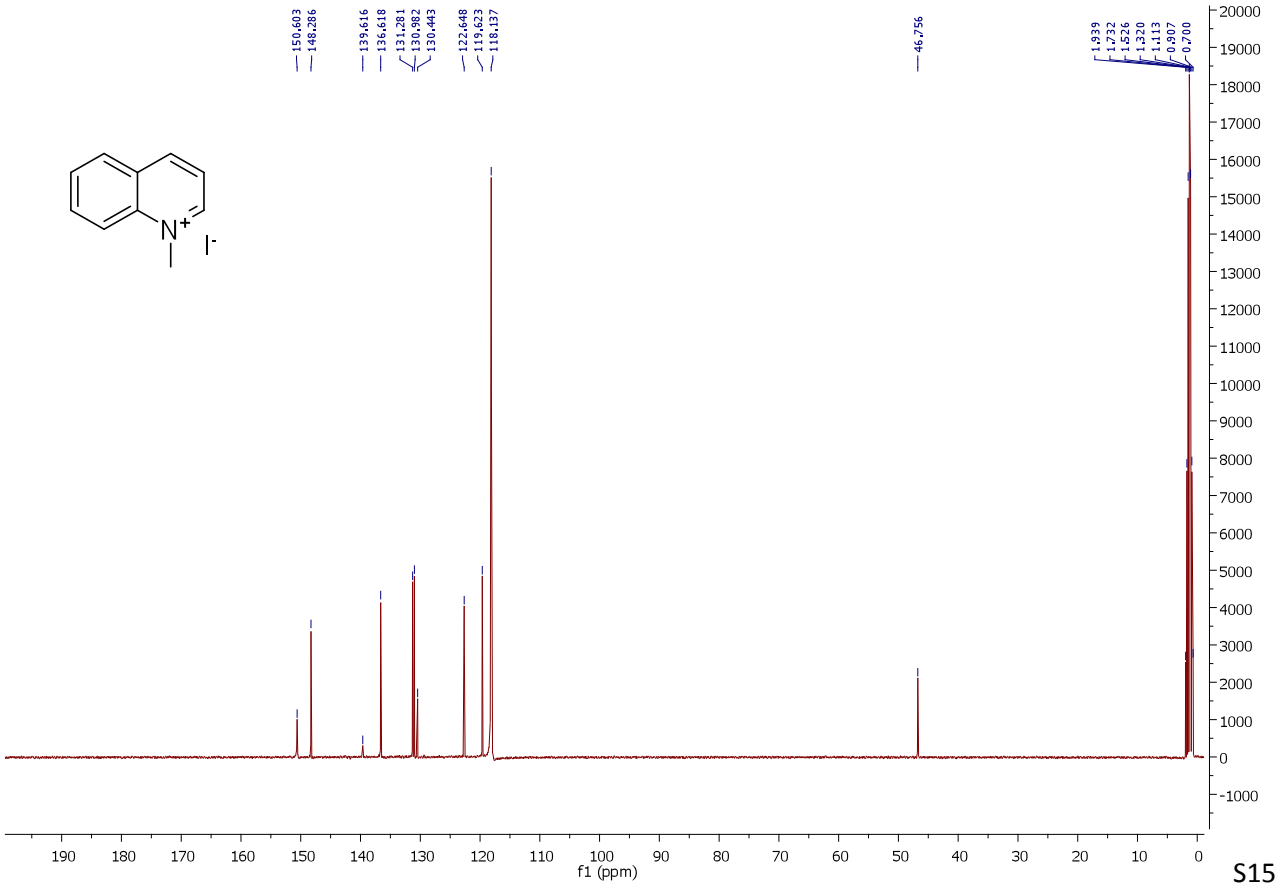
1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10-phenanthroline (33): ^{1}HNMR (400MHz, CD_3CN) δ *inter alia* 8.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.57-7.47 (m, 3H), 6.68 (d, *J* = 6.8 Hz, 1H), 5.16 (dd, *J* = 7.2, 6.0 Hz ,1H), 4.66 (d, *J* = 1.6 Hz. 1H), 3.98 (s, 3H)

Both isomers: ^{13}C NMR (100 MHz, CD_3CN) δ 148.5, 147.9, 142.4, 141.9, 140.1, 137.5, 137.0, 132.2, 131.0, 130.8, 127.0, 123.8, 122.3, 122.1, 121.1, 120.4, 119.0, 106.2, 97.4, 78.1, 60.2, 50.0, 43.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{14}H_{12}Cl_3N_2$: 313.0061; found: 313.0062.

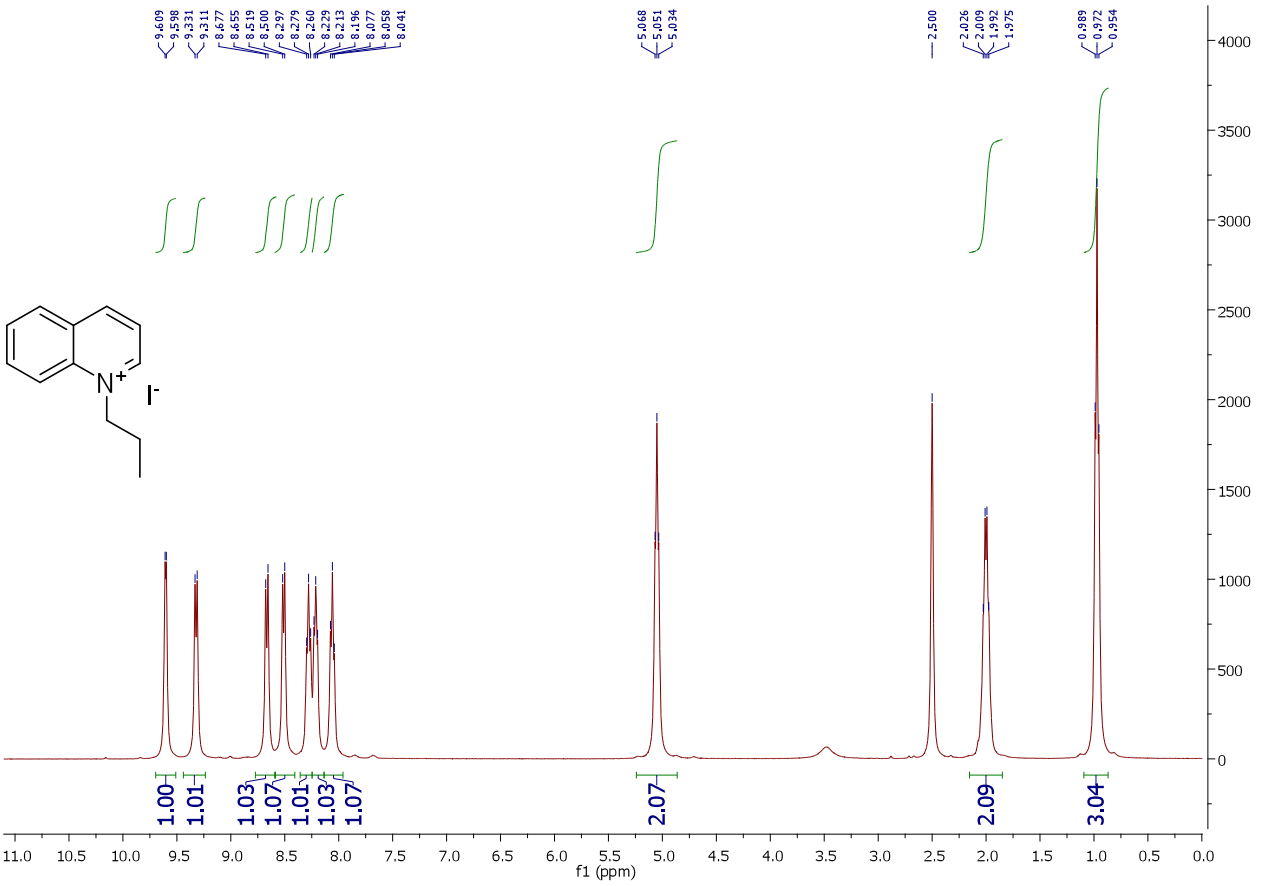
NMR-spectra

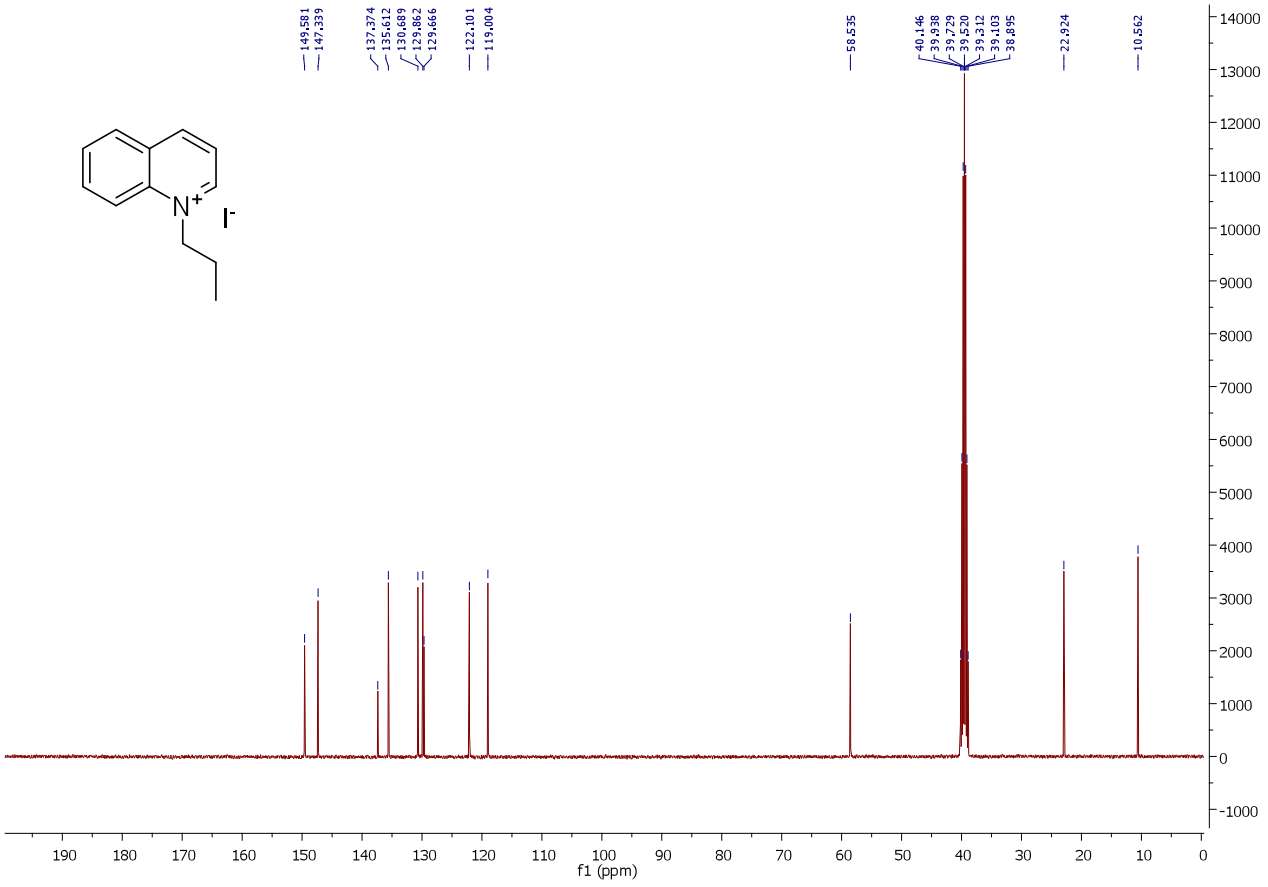
1-Methylquinolin-1-ium iodide



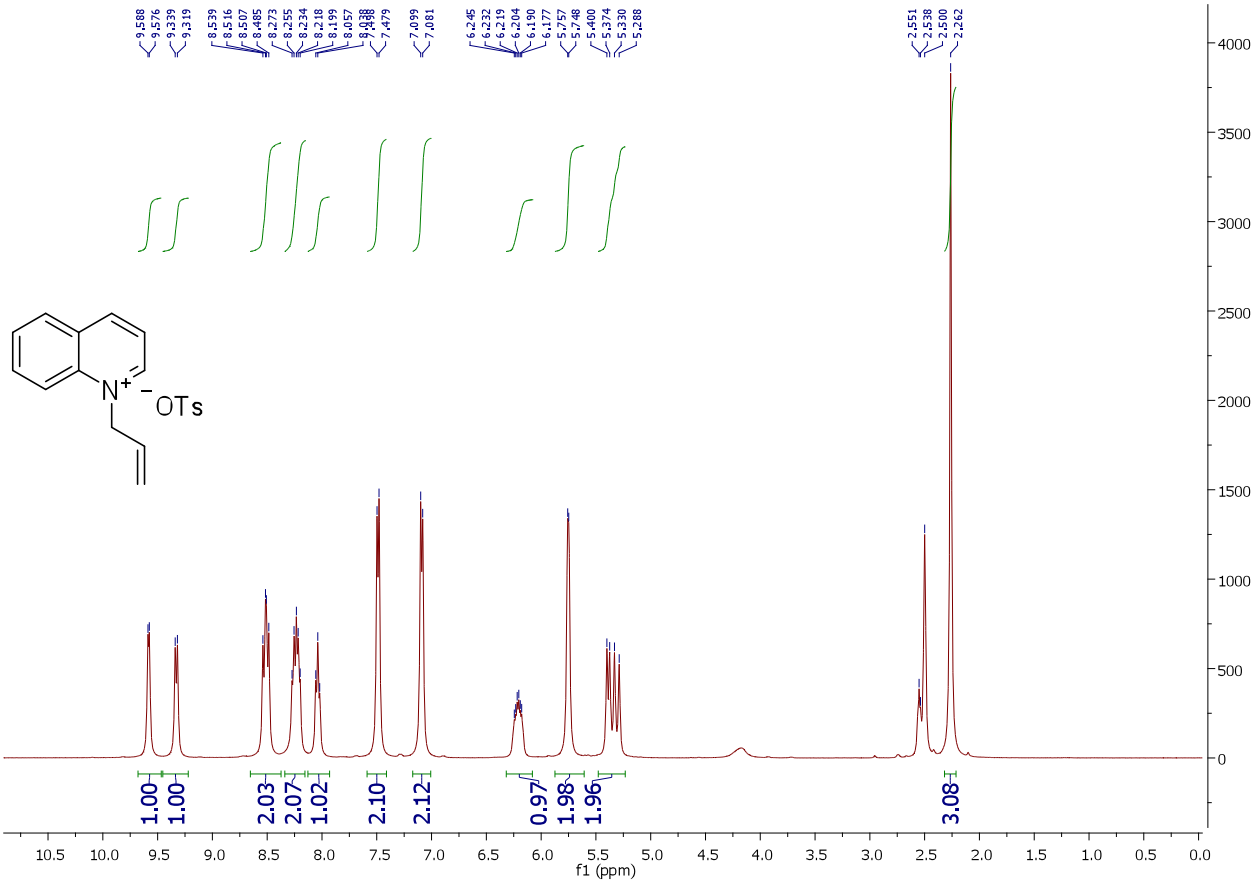


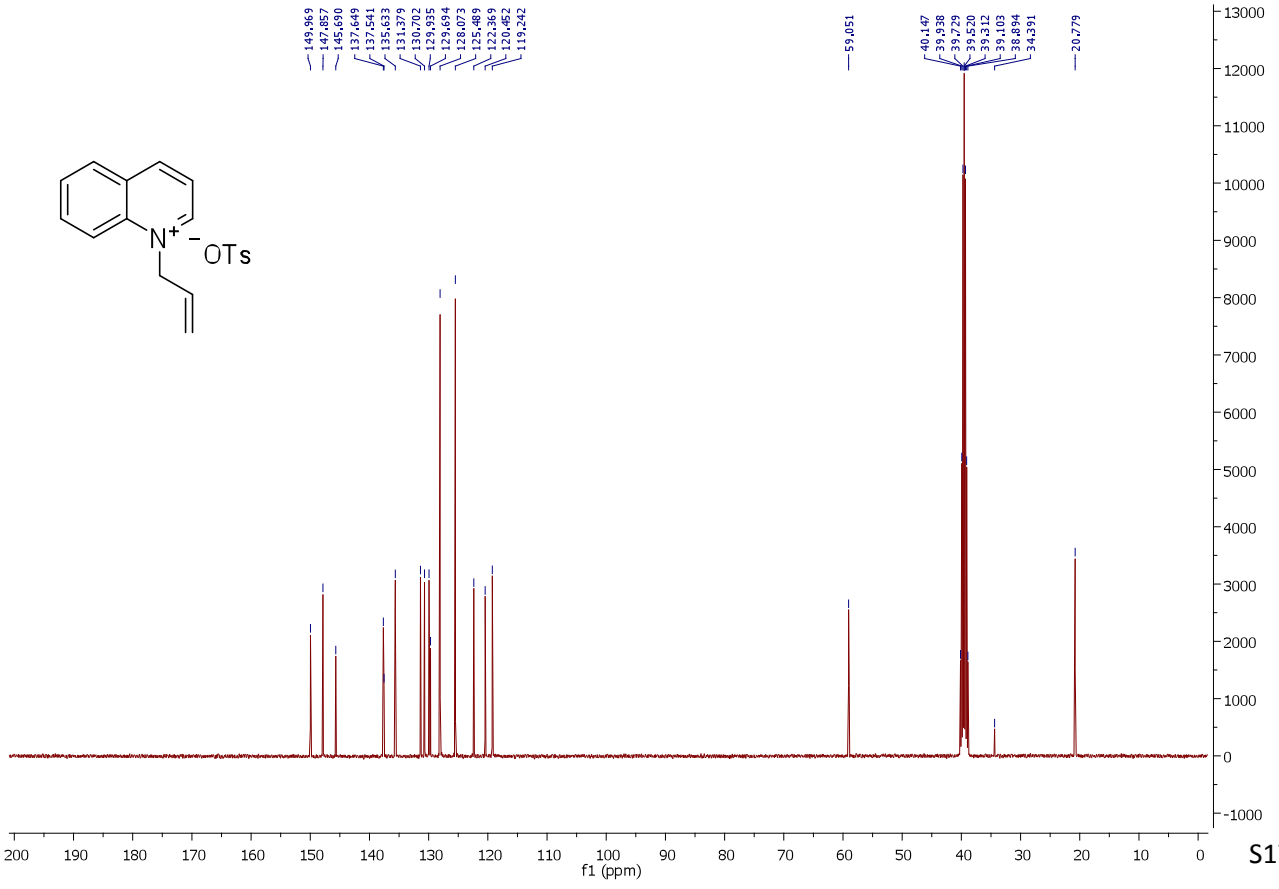
1-Propylquinolin-1-ium iodide



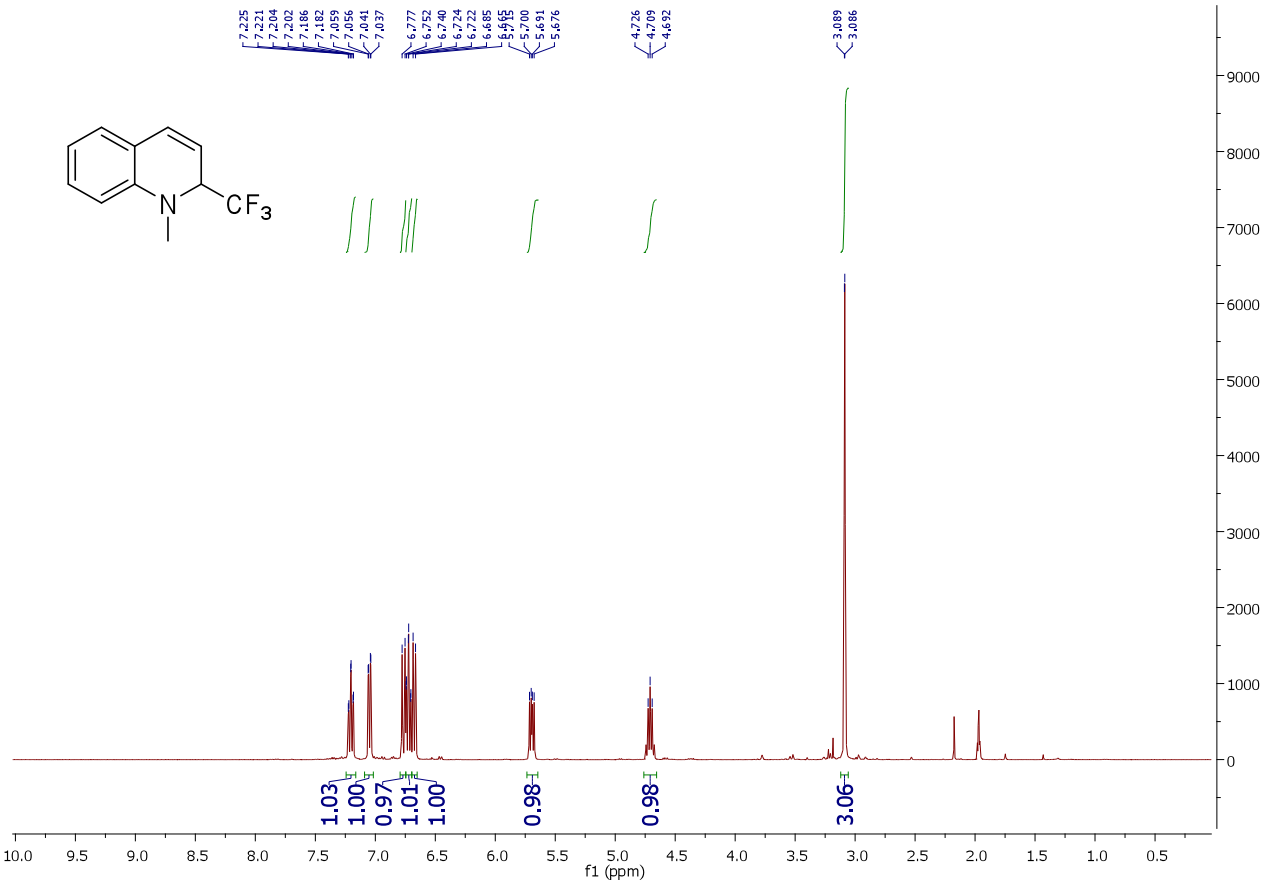


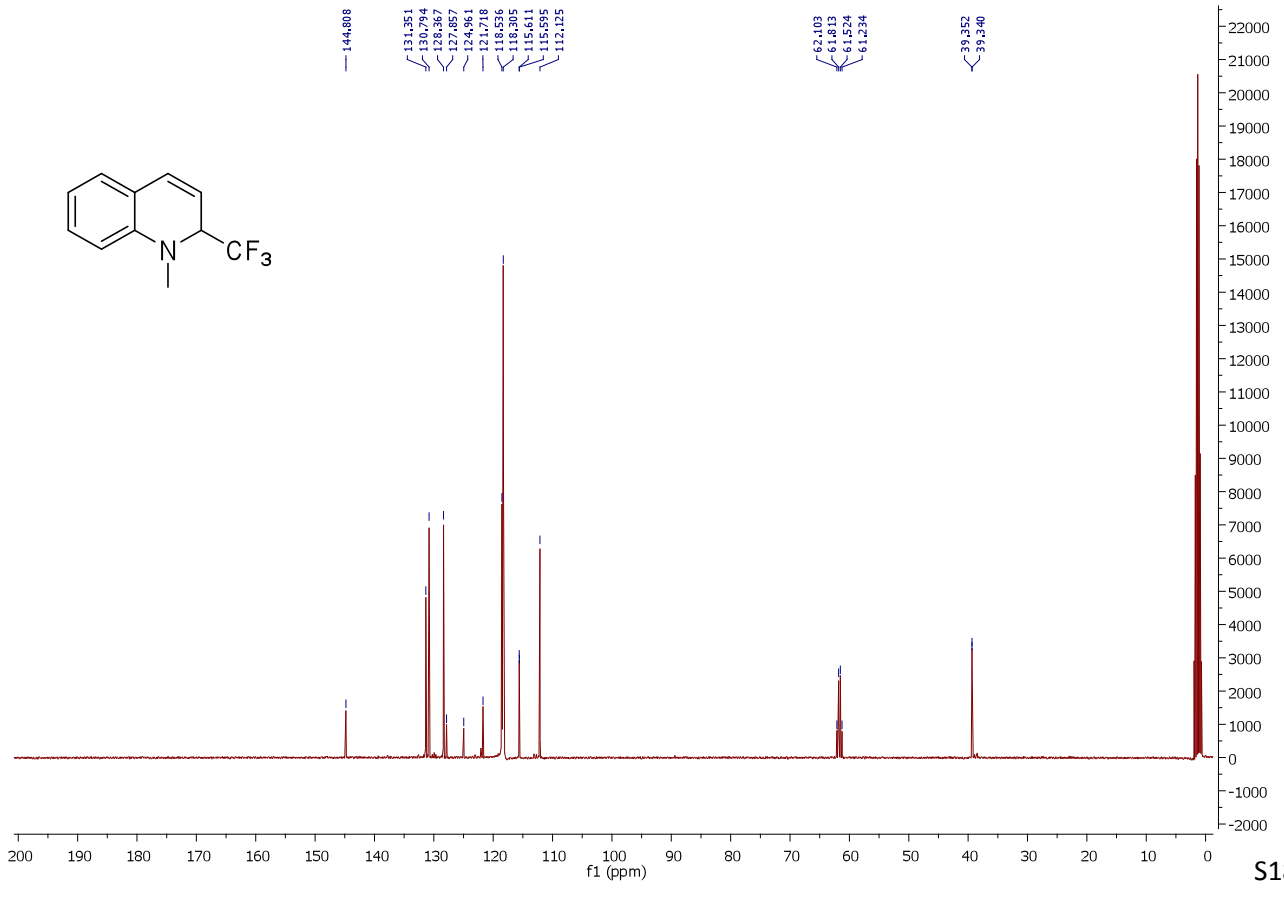
1-Allylquinolin-1-ium 4-methylbenzenesulfonate

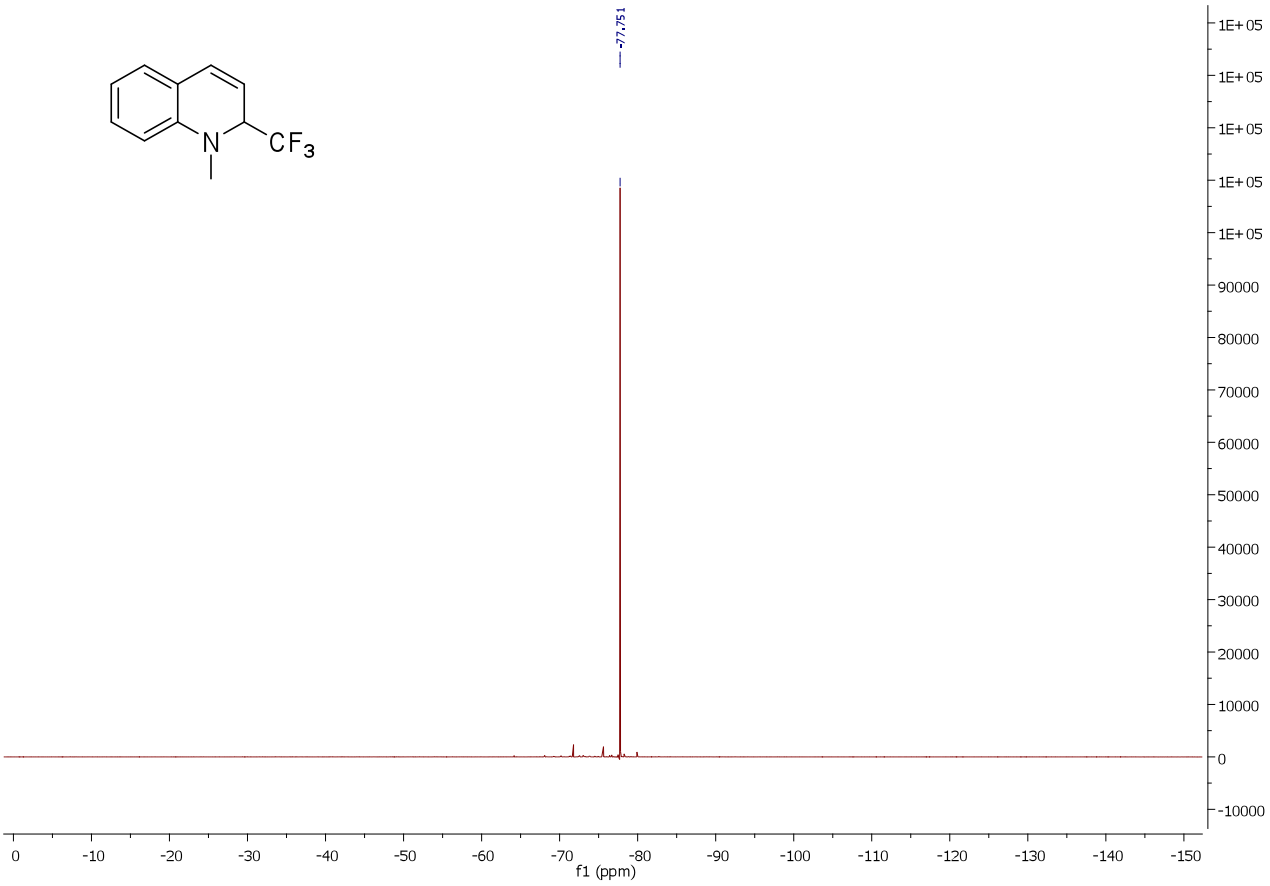




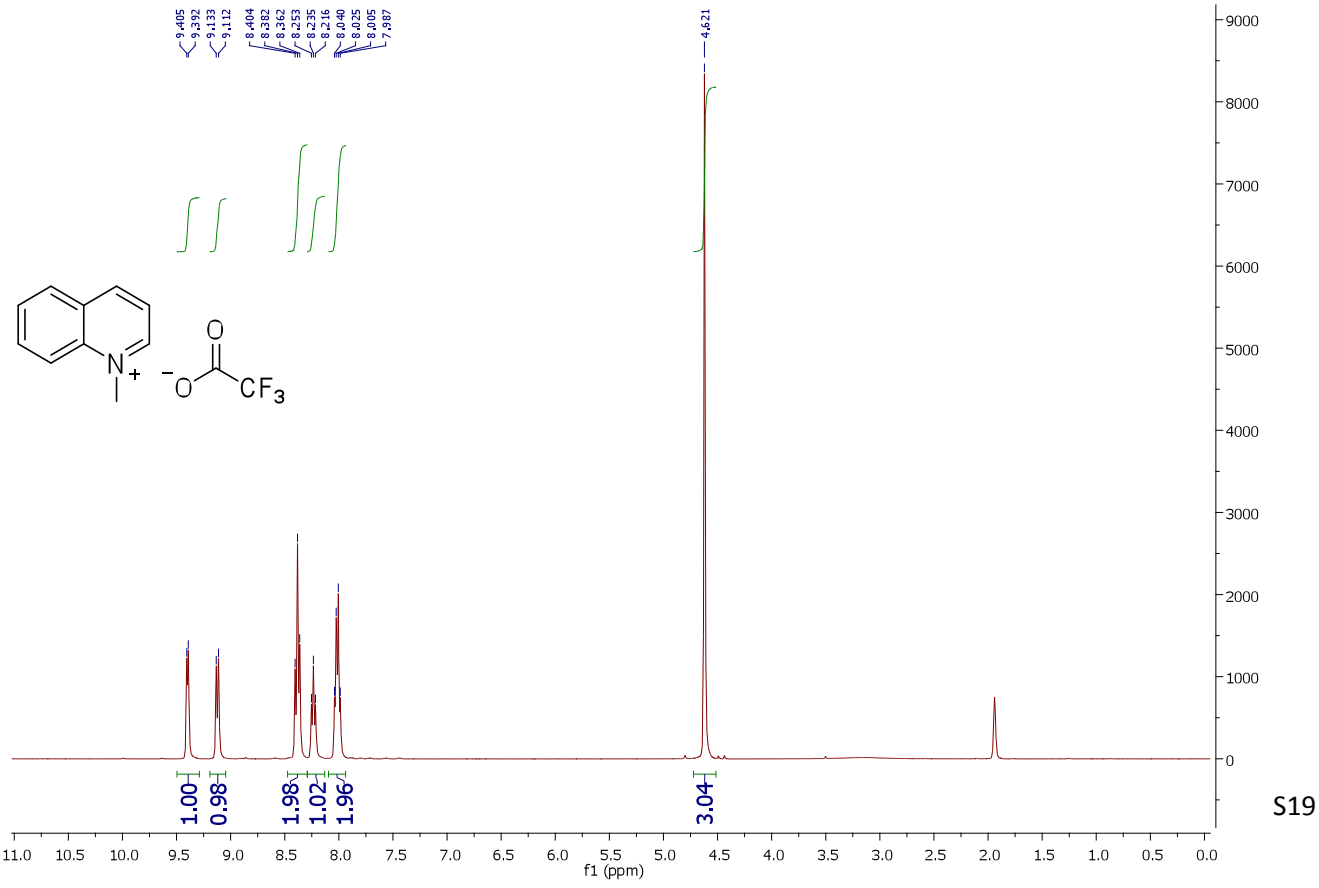
1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (2)

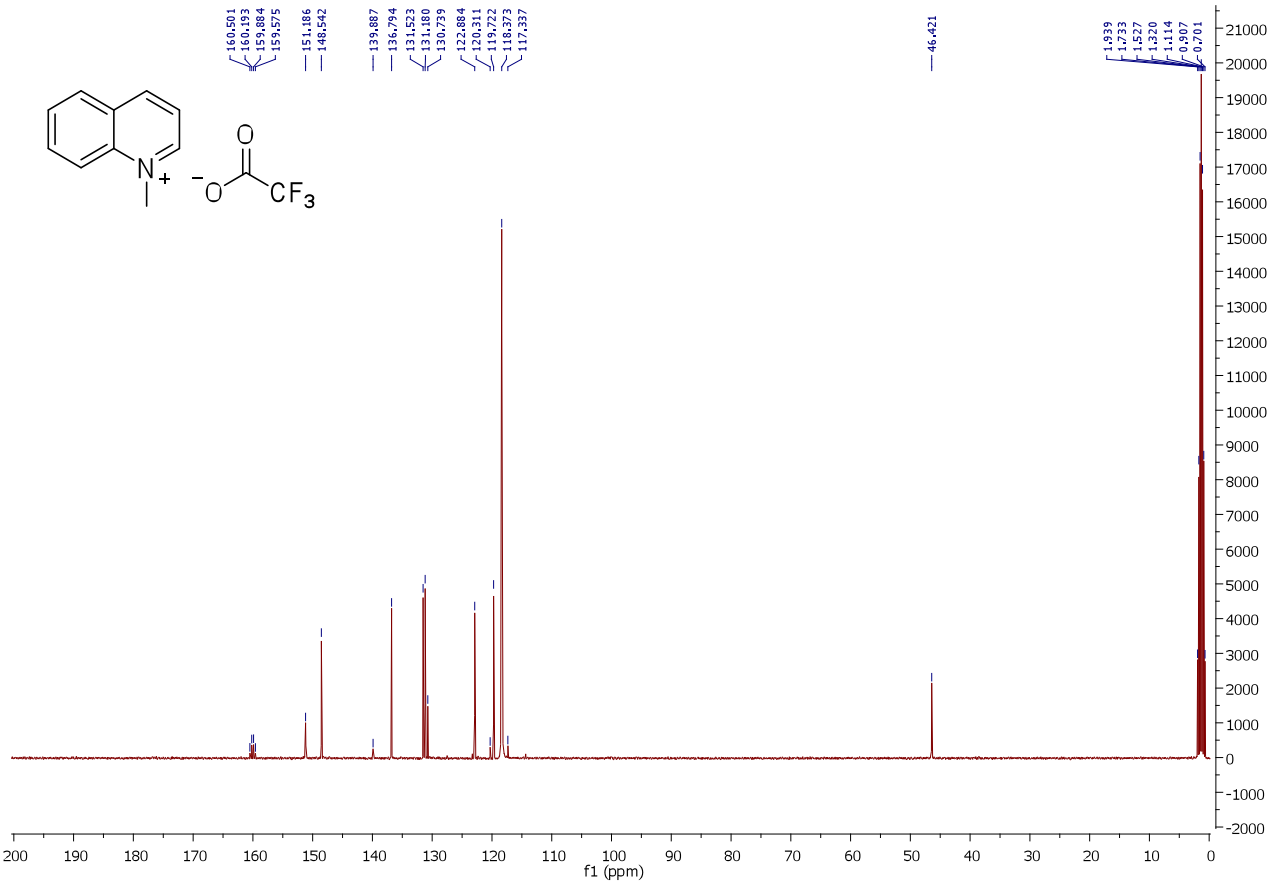


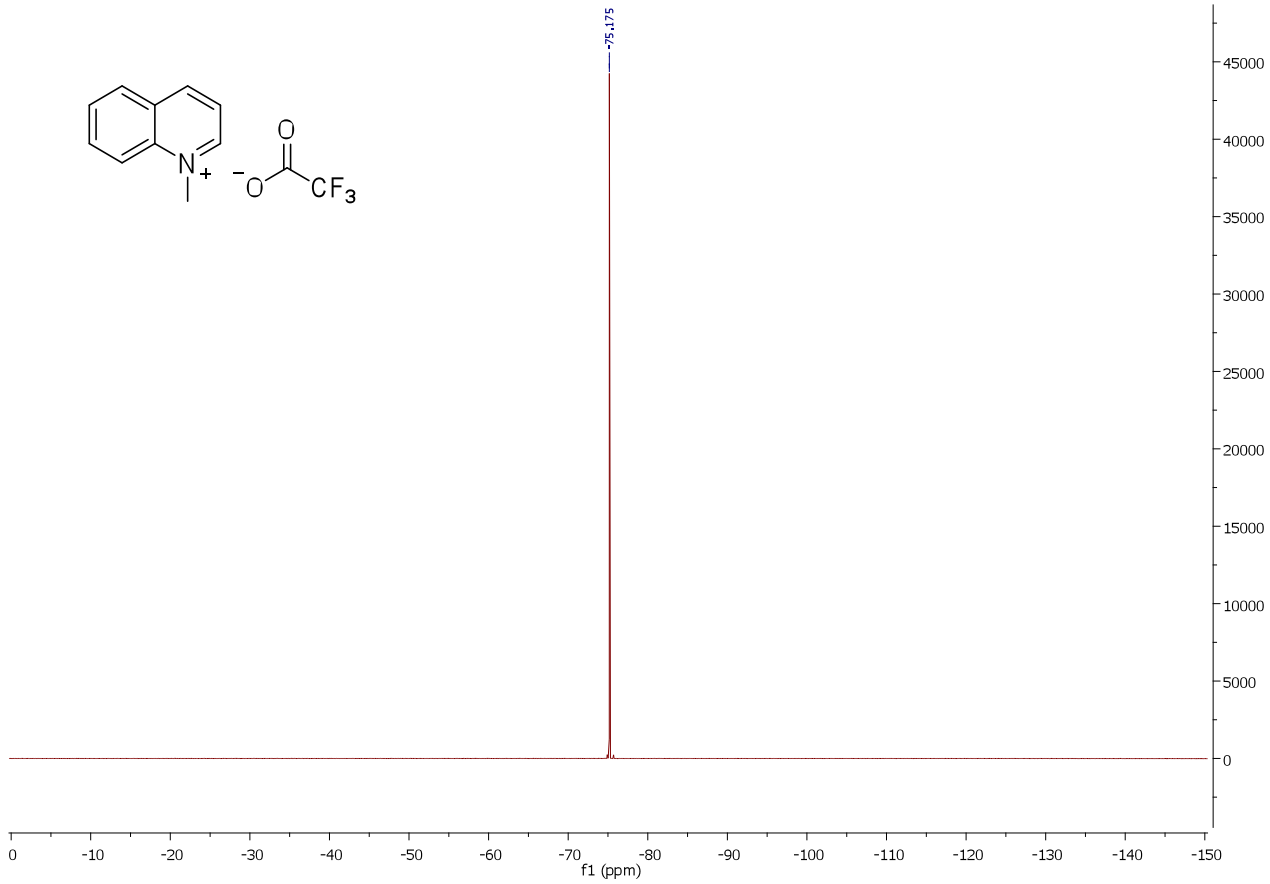




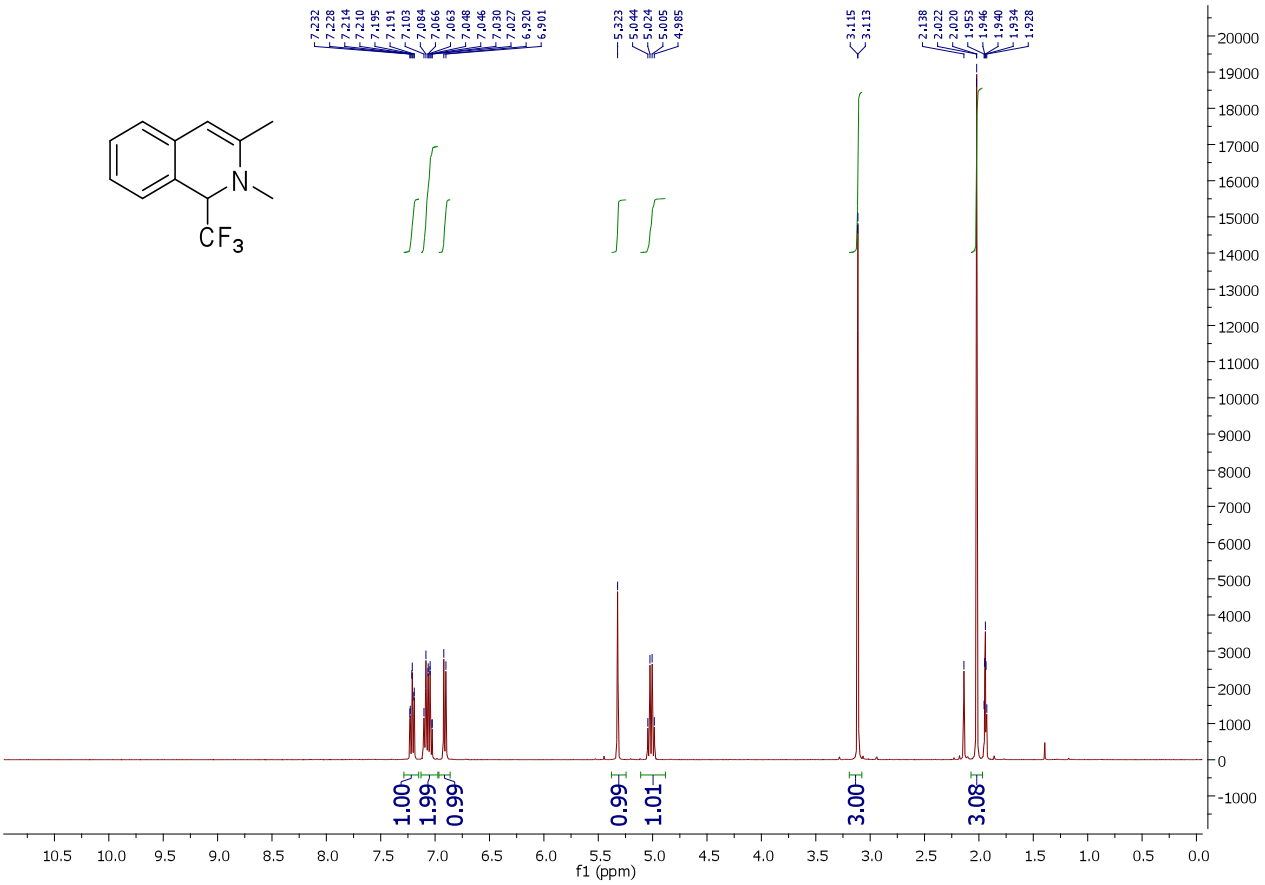
1-methylquinolin-1-ium 2,2,2-trifluoroacetate (3)

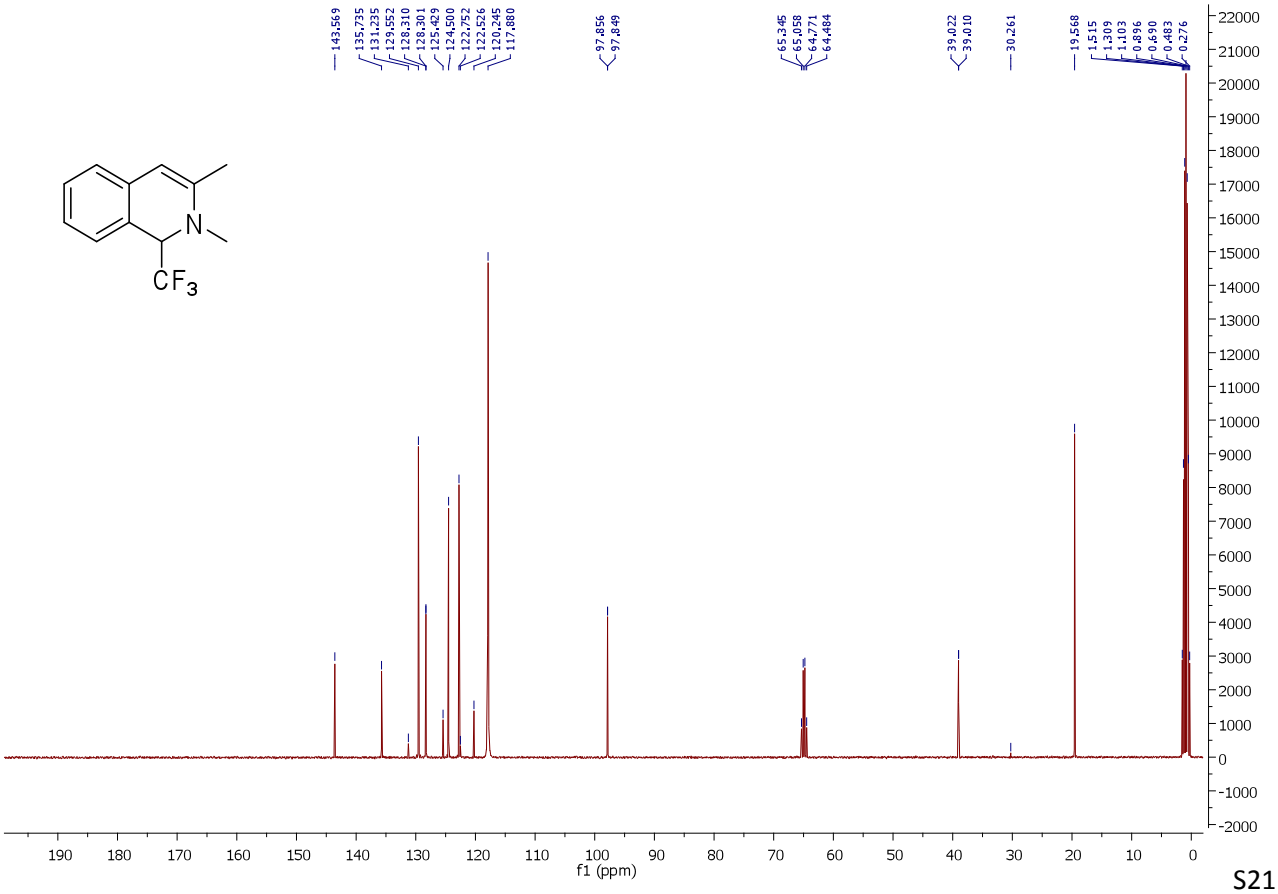


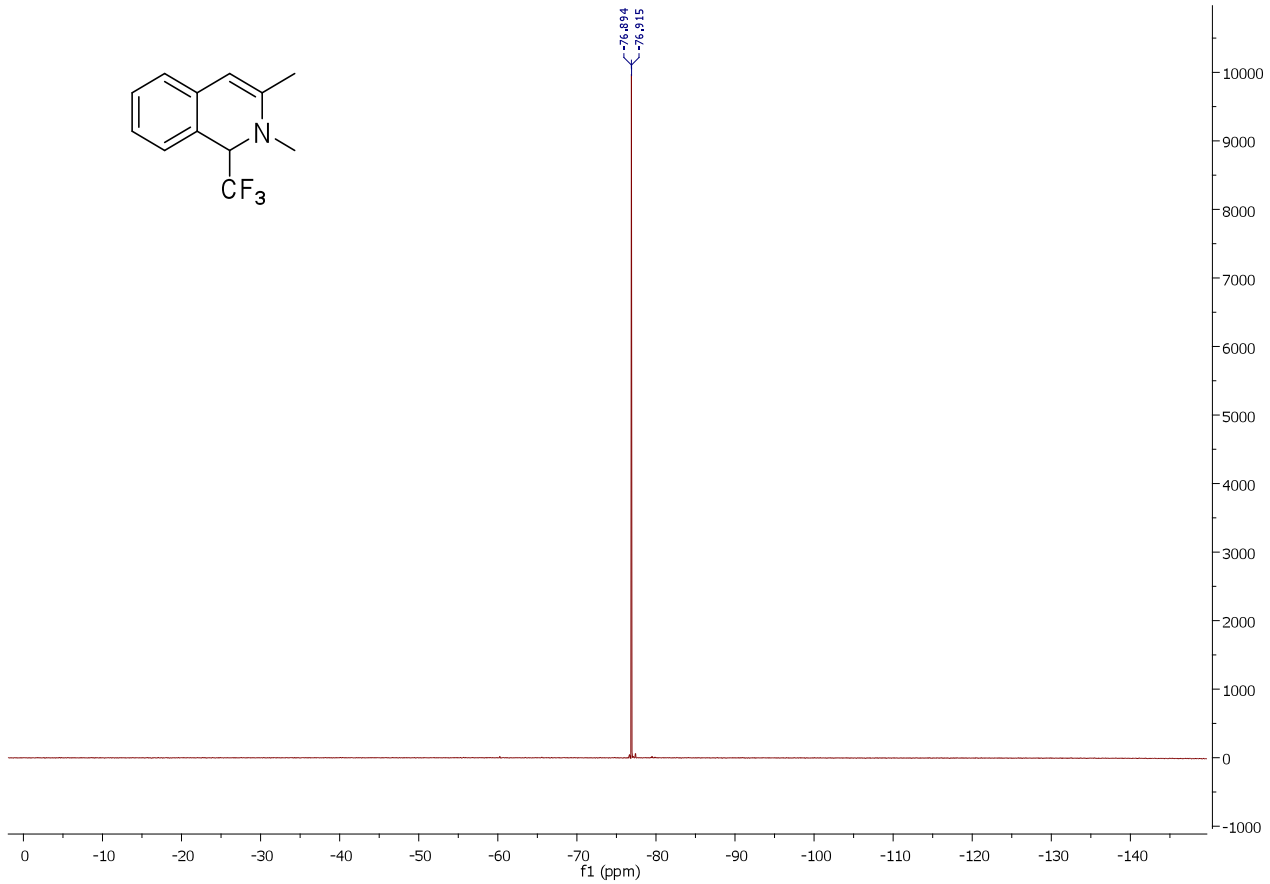

160.501
160.193
159.884
159.575
151.186
148.542
139.887
136.794
131.523
131.180
130.739
122.884
120.311
119.722
118.373
117.337
46.421
1.939
1.733
1.527
1.320
1.114
0.907
0.701
f1 (ppm)


-75.175
f1 (ppm)

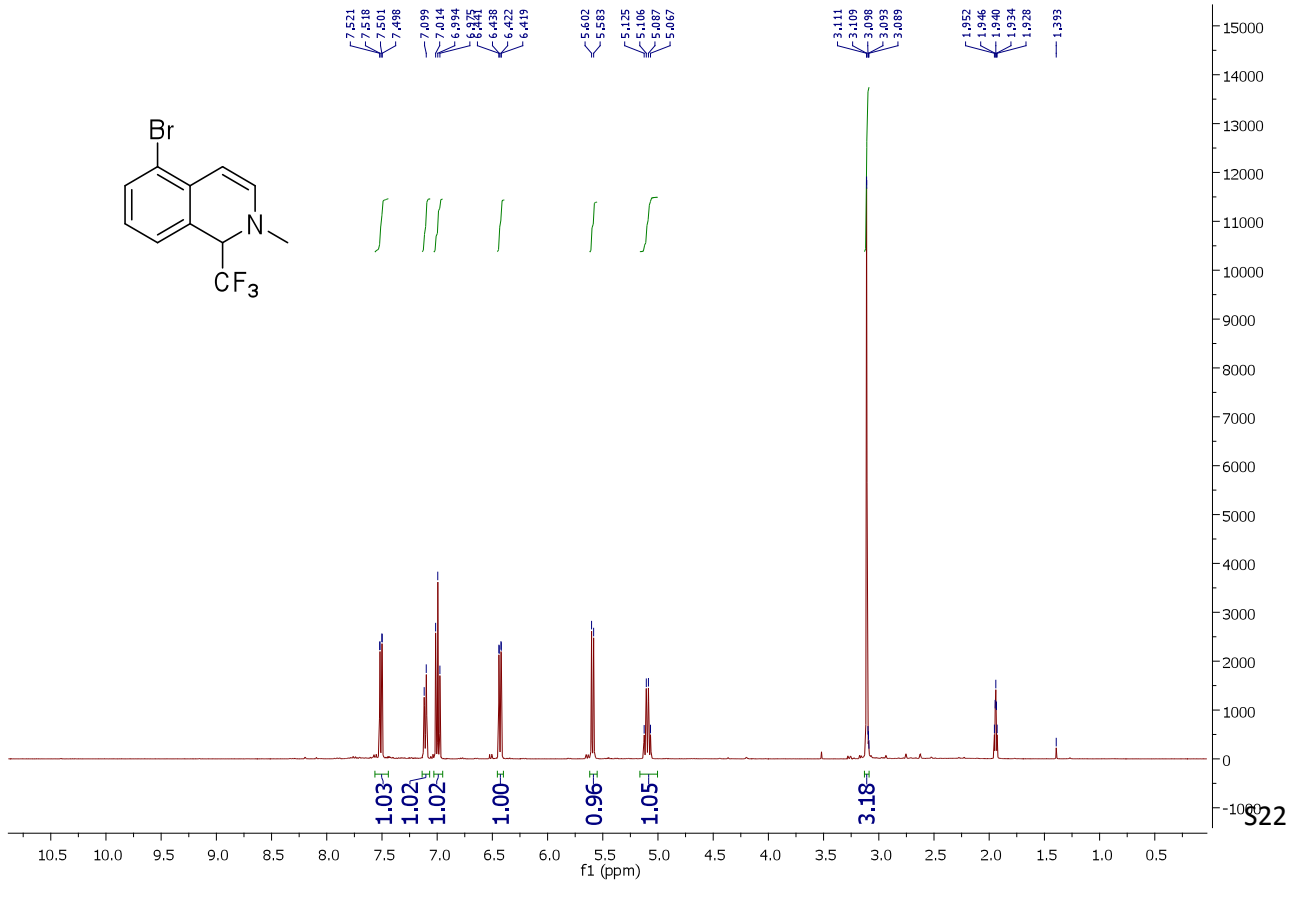
2,3-Dimethyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (5)

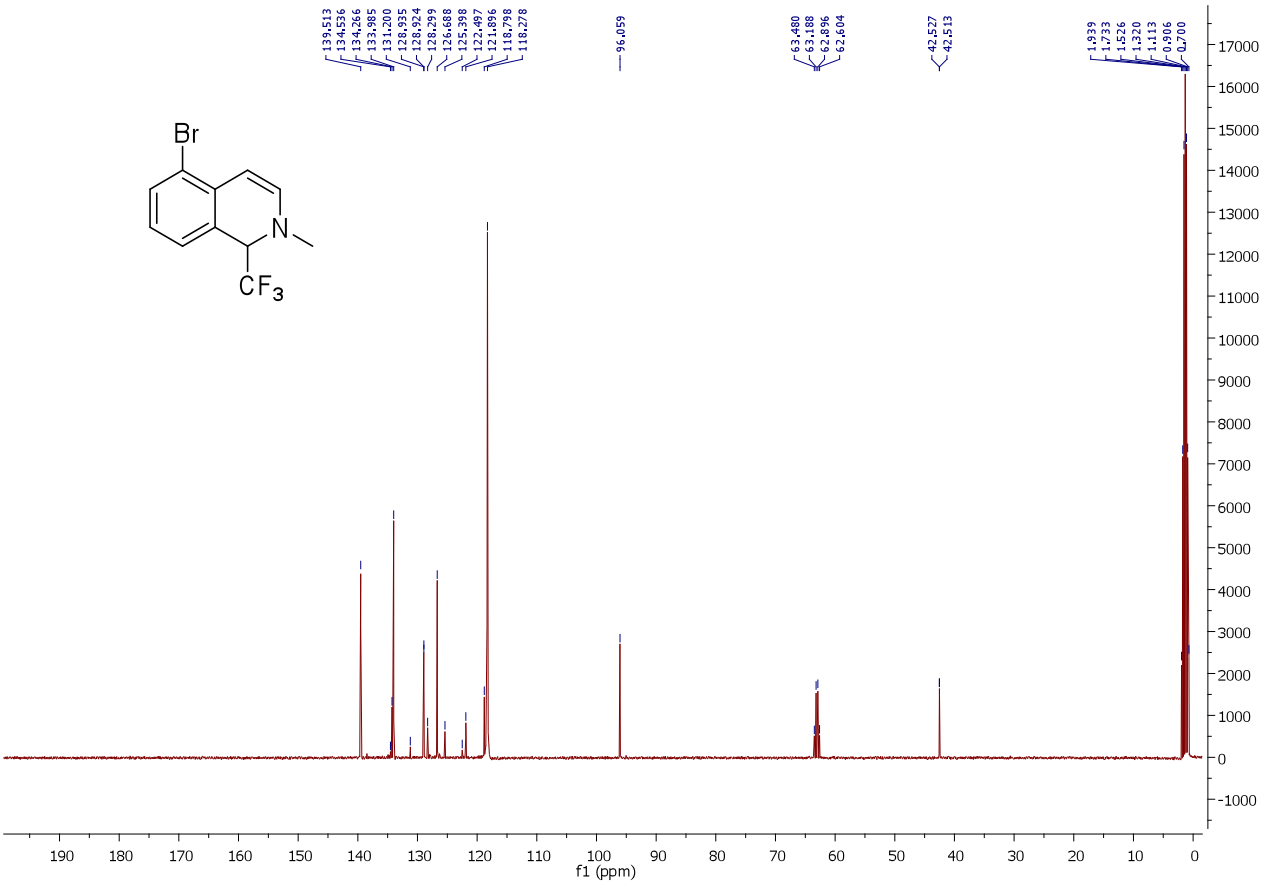


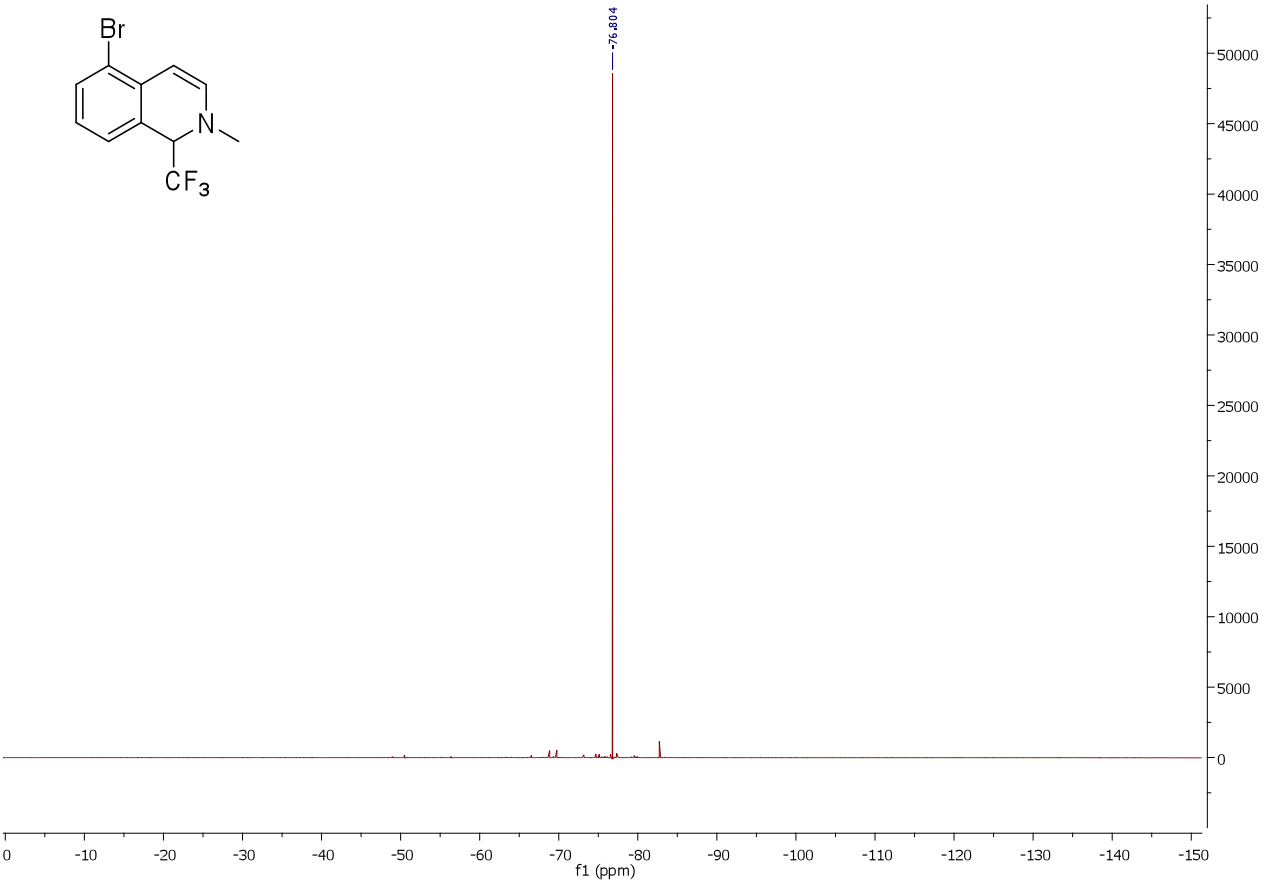




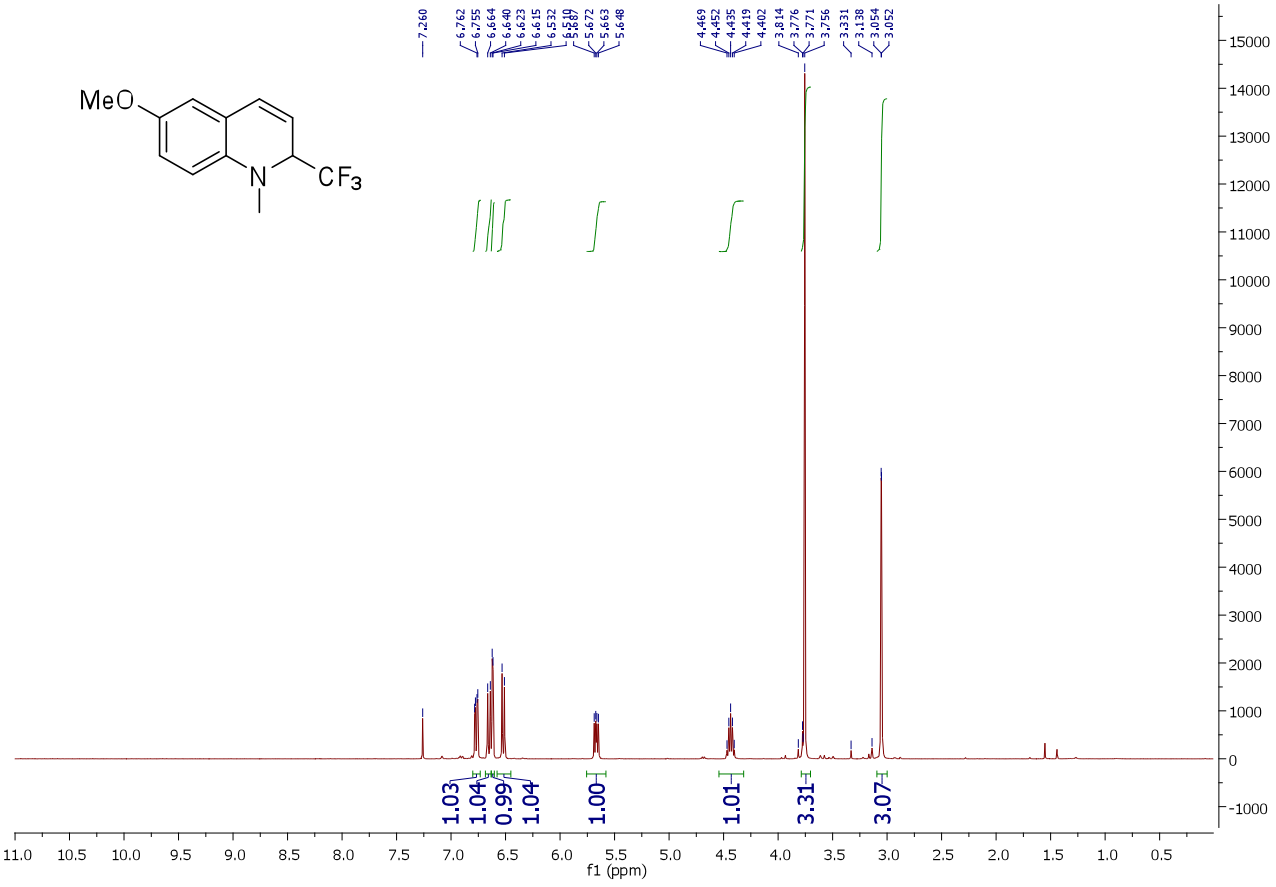
5-Bromo-2-methyl-1-(trifluoromethyl)-1,2-dihydroisoquinoline (6)

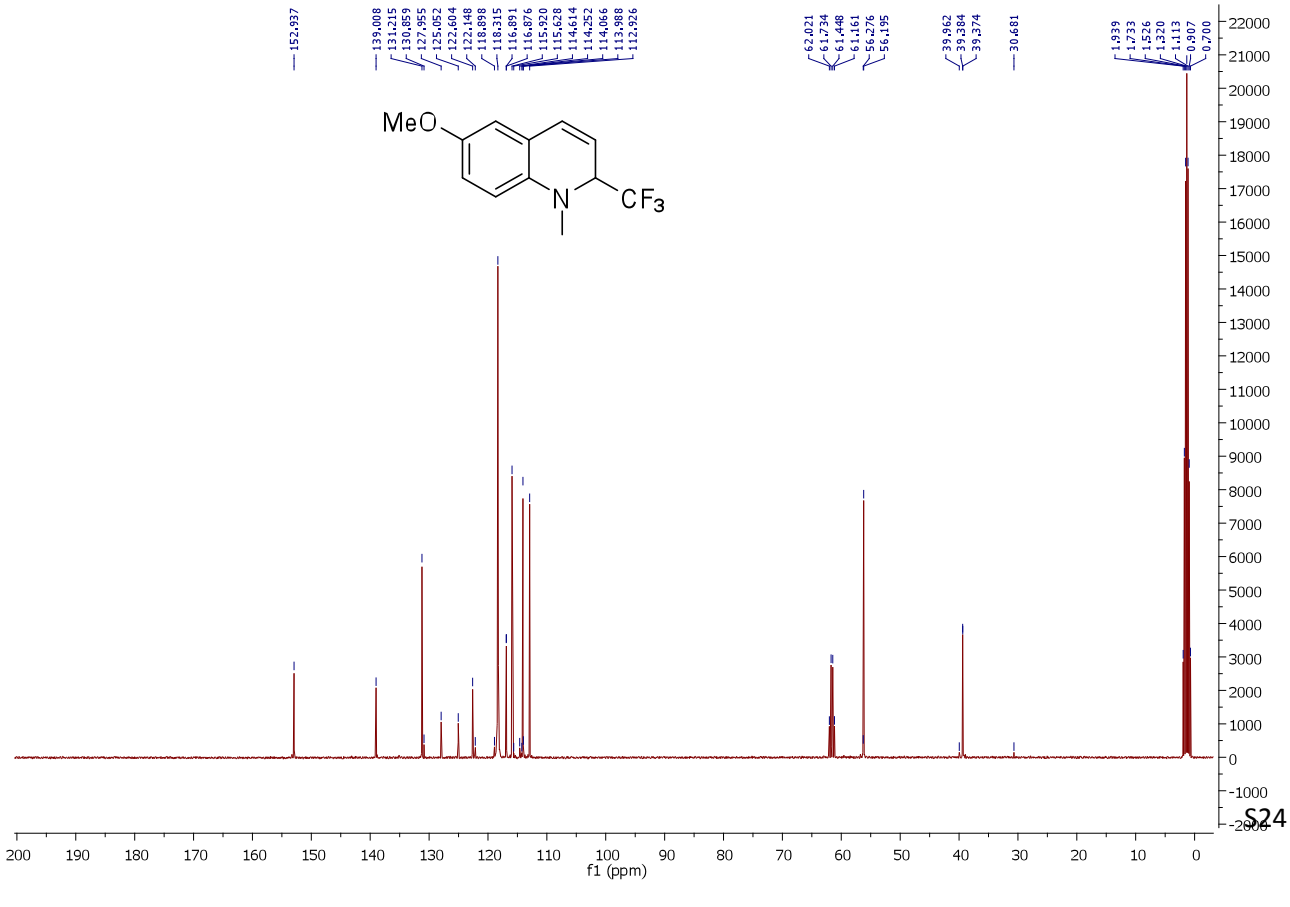


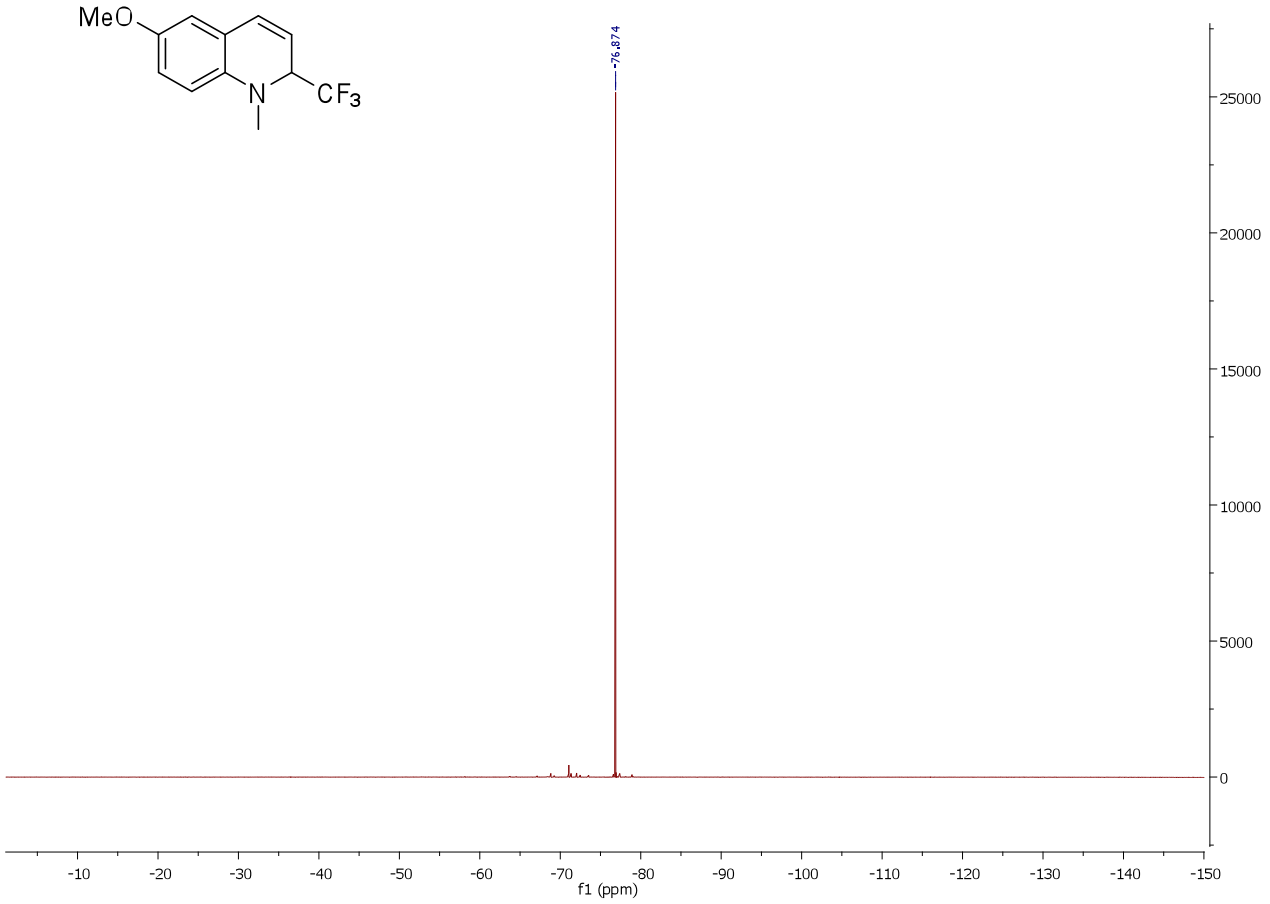

Br
N
CF3
139.513
134.536
134.266
133.985
131.200
128.935
128.924
128.299
126.688
125.398
122.497
121.896
118.798
118.278
96.059
63.480
63.188
62.896
62.604
42.527
42.513
1.939
1.733
1.526
1.320
1.113
0.906
0.700
f1 (ppm)


Br
N
CF3
-76.804
f1 (ppm)

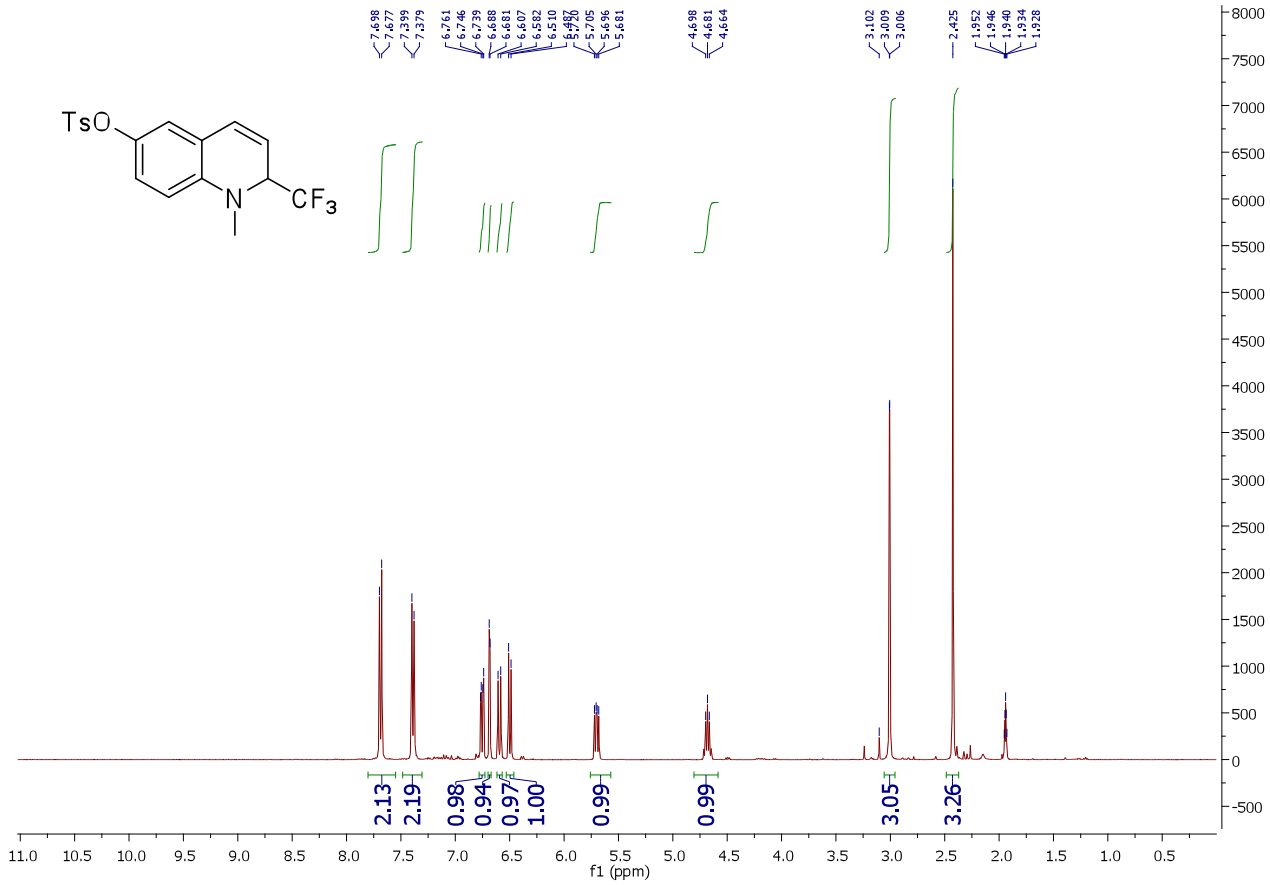
6-Methoxy-1-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (7)

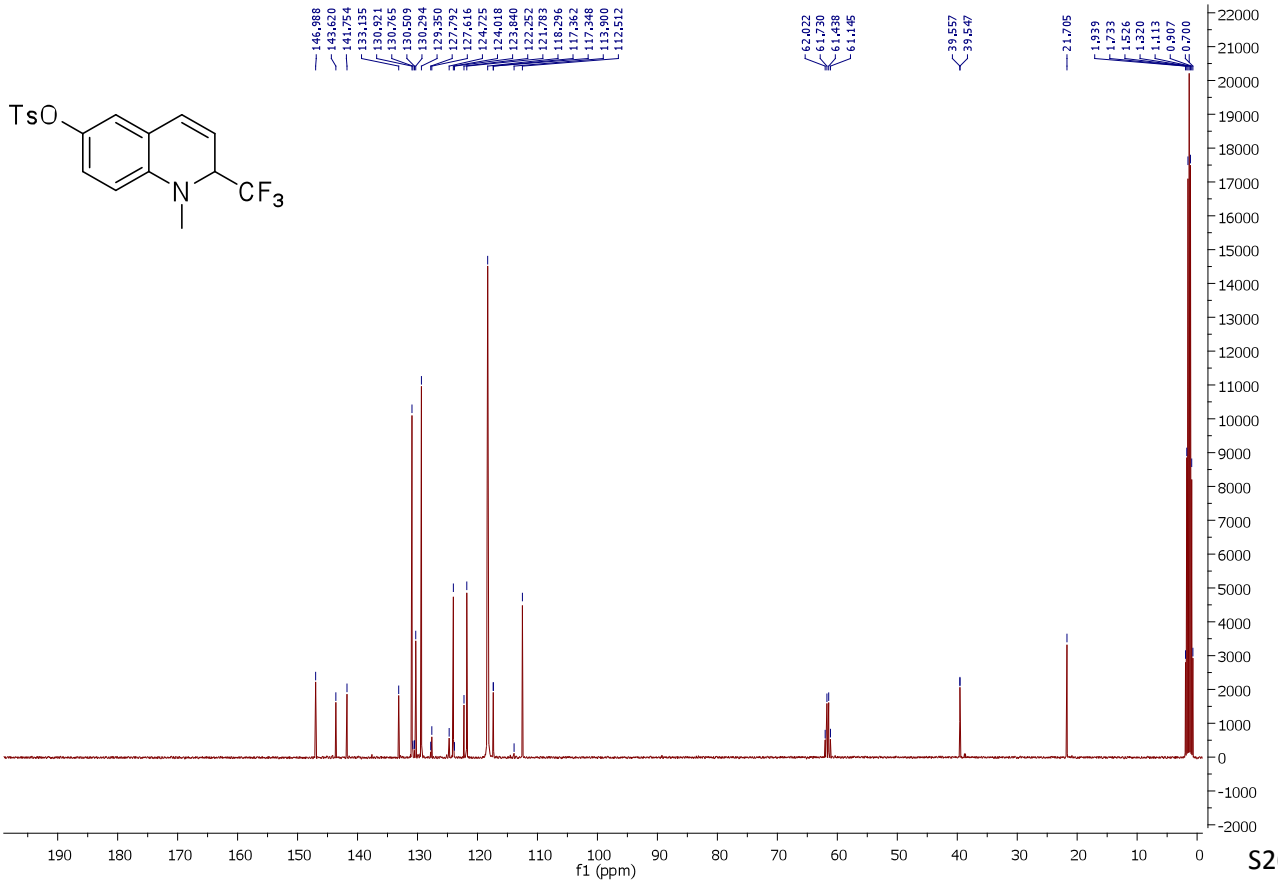


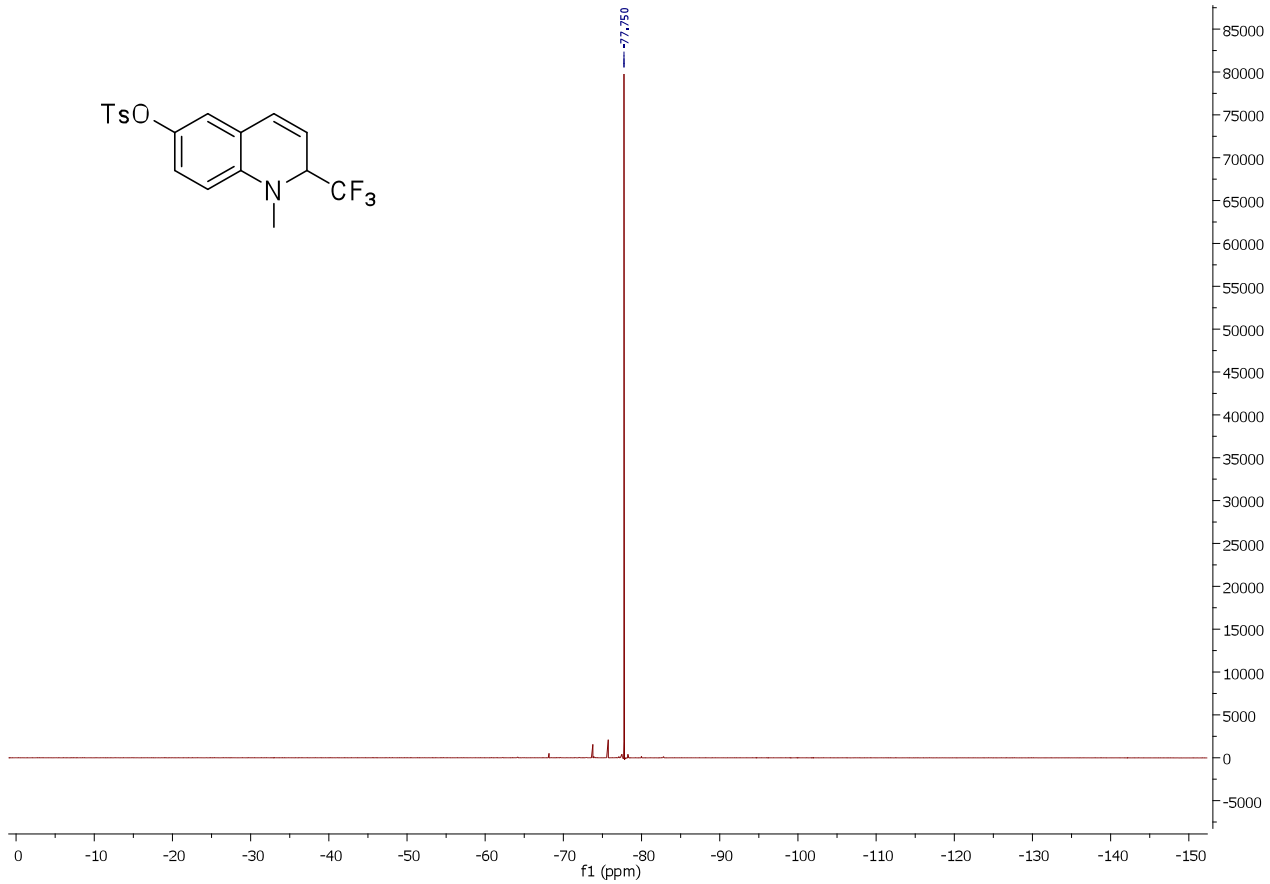



MeO
N
CF3
-76.874
25000
20000
15000
10000
5000
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
f1 (ppm)

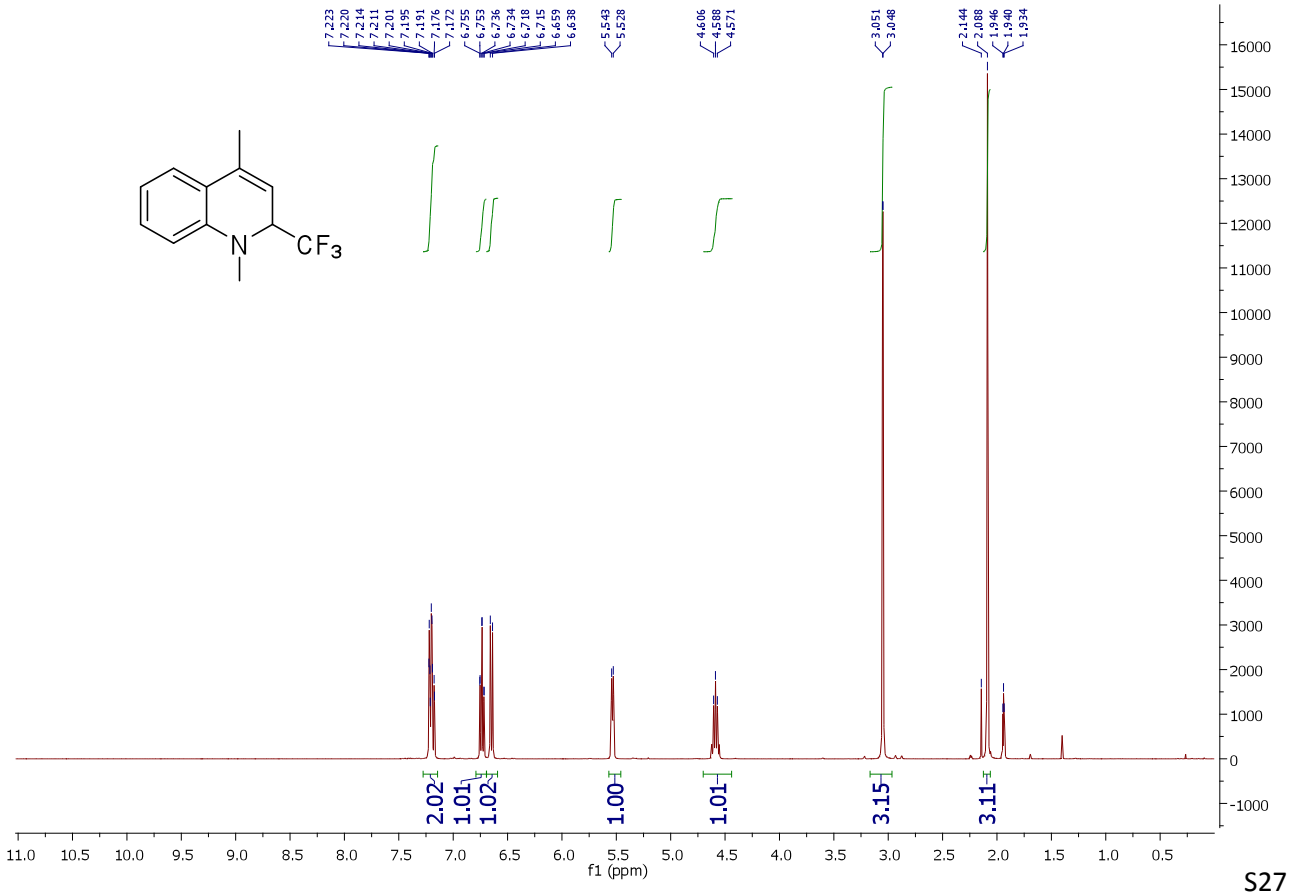
1-Methyl-2-(trifluoromethyl)-1,2-dihydroquinolin-6-yl 4-methylbenzenesulfonate (8)

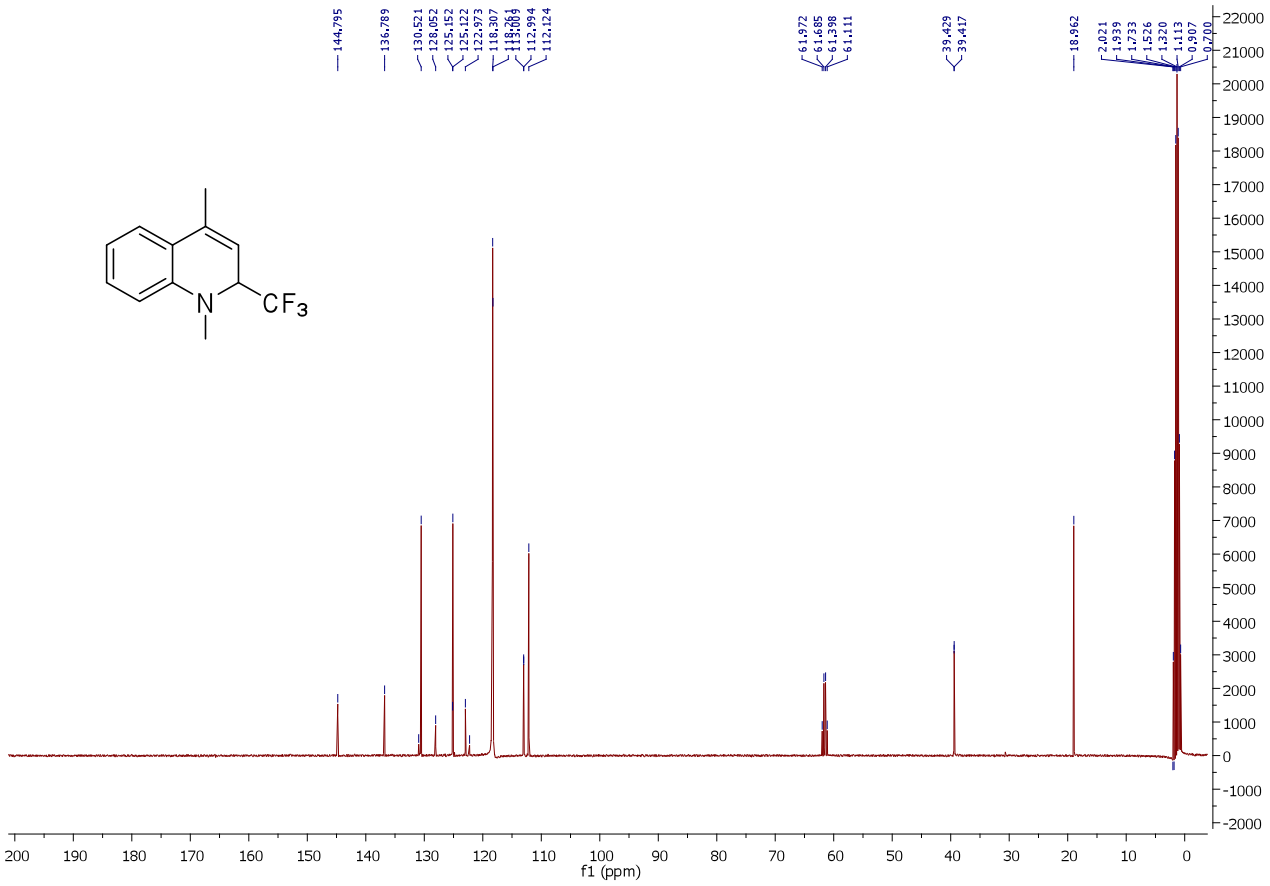






1,4-Dimethyl-2-(trifluoromethyl)-1,2-dihydroquinoline (9)

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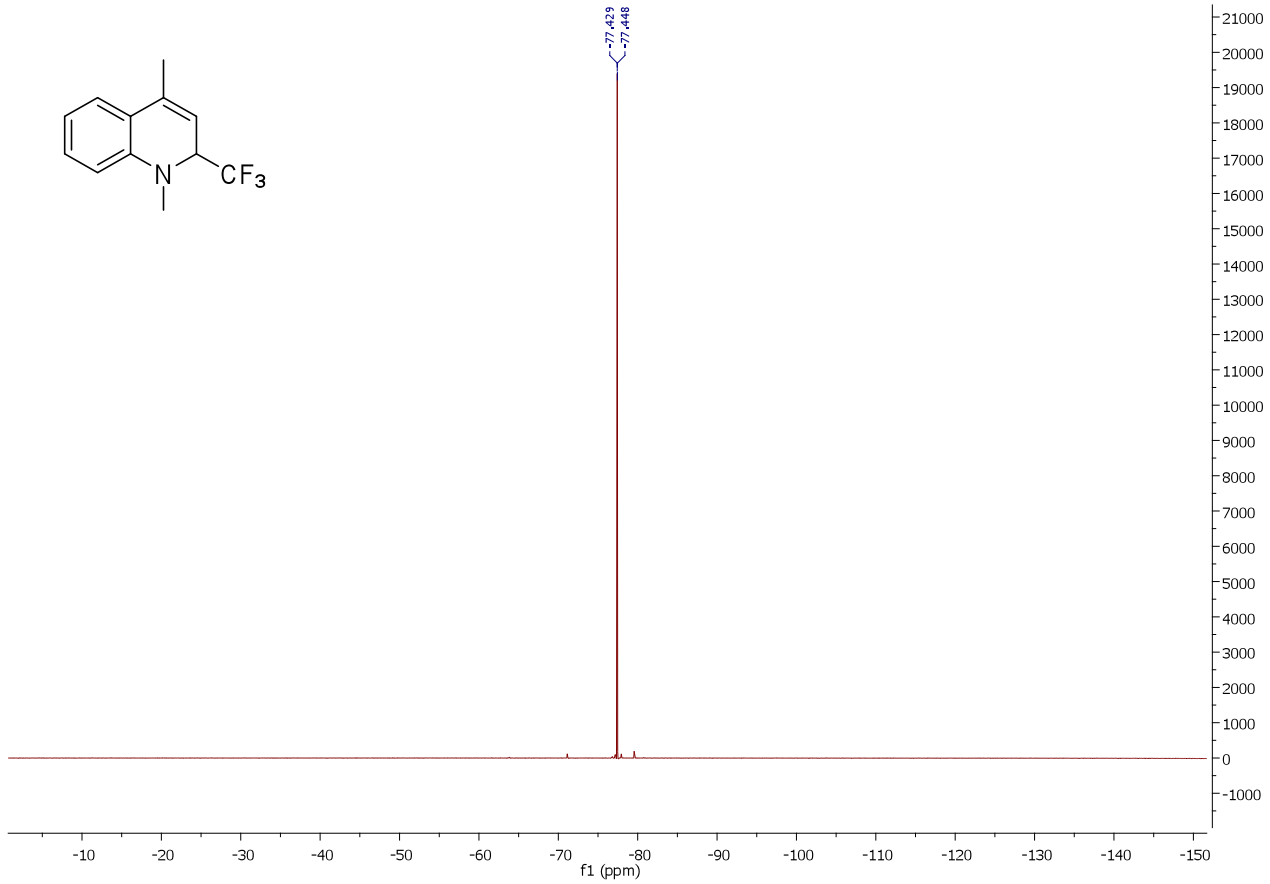
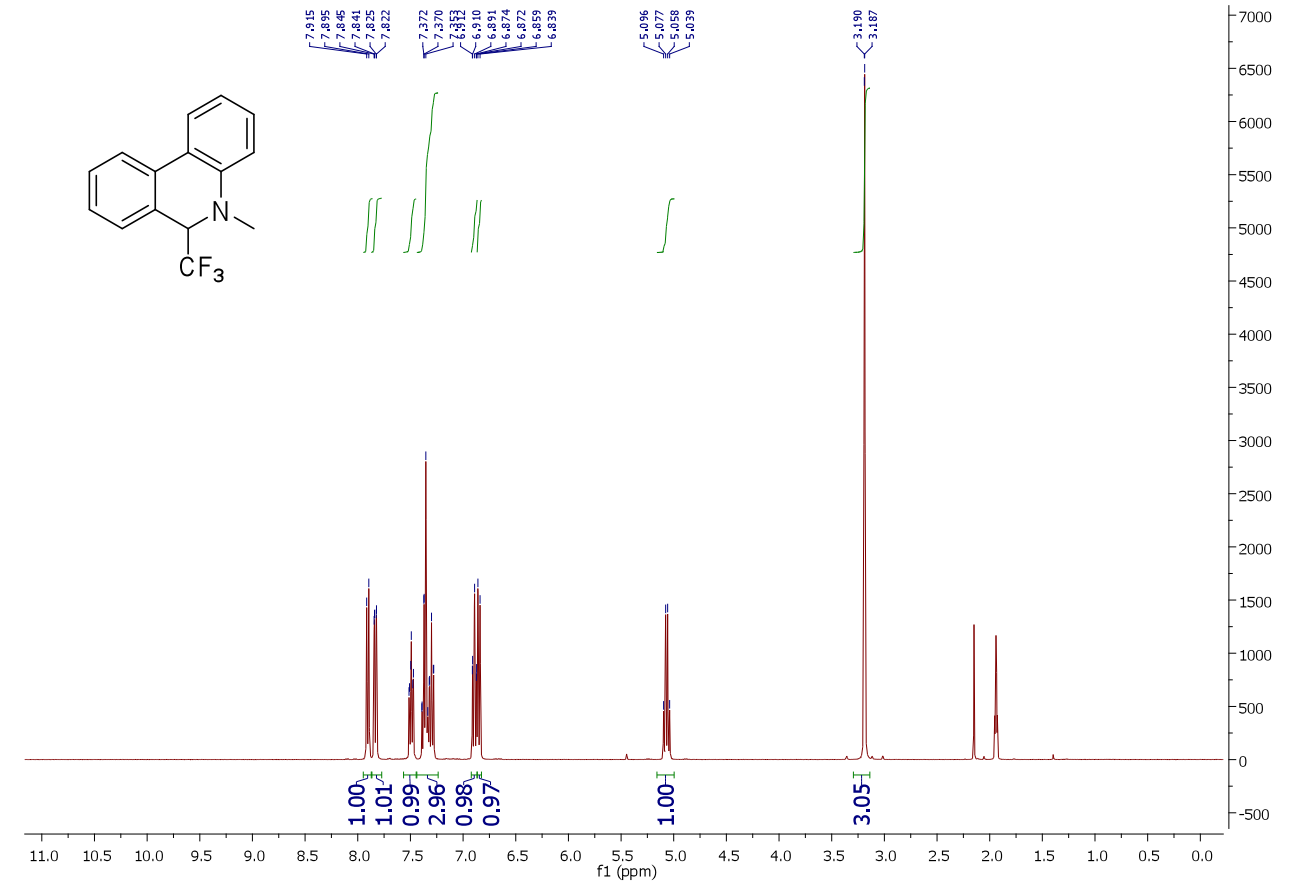
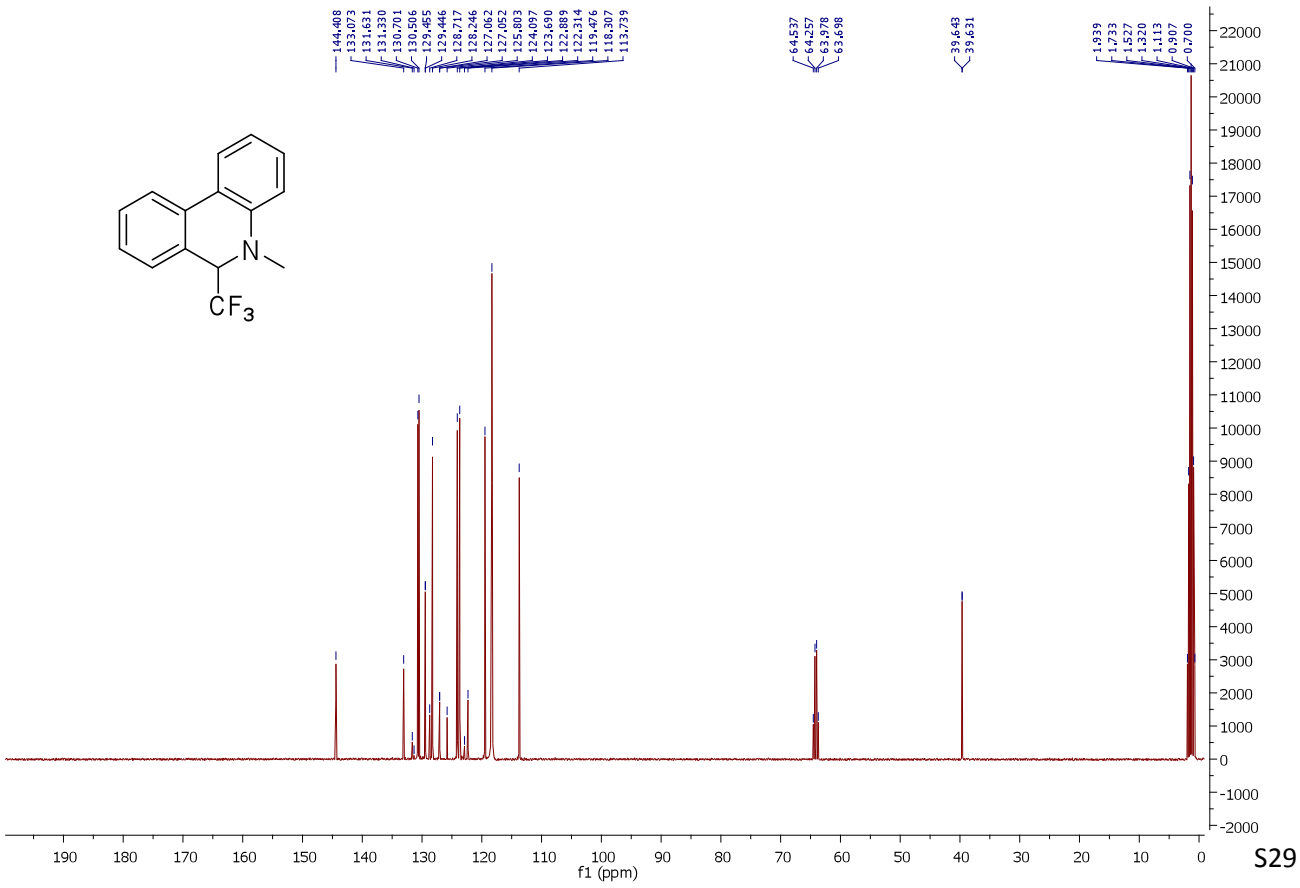
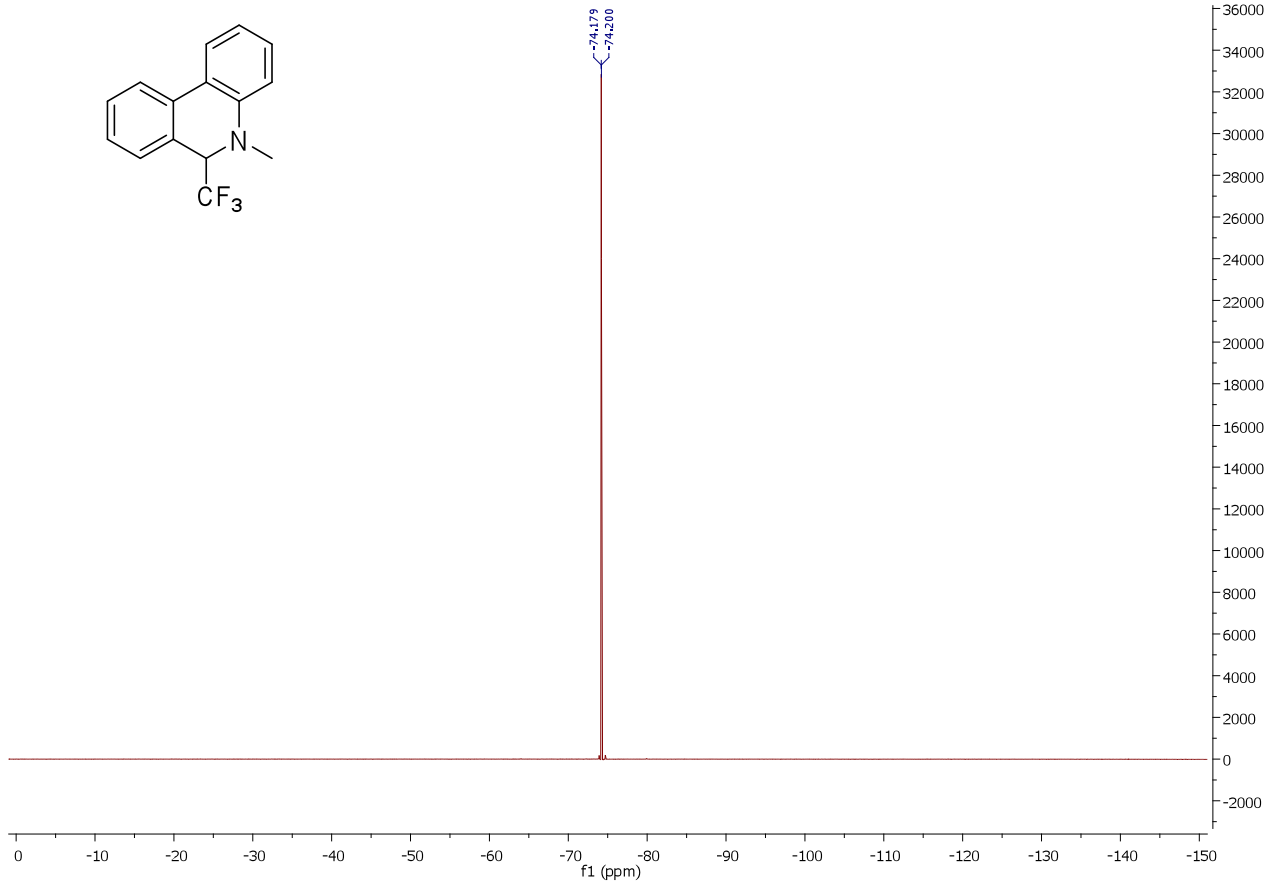
136.789
130.521
128.052
125.152
125.122
122.973
118.307
112.994
112.124
61.972
61.685
61.398
61.111
39.429
39.417
18.962
2.021
1.939
1.733
1.526
1.320
1.113
0.907
0.700
N
CF3
f1 (ppm)


77.429
77.448
N
CF3
f1 (ppm)

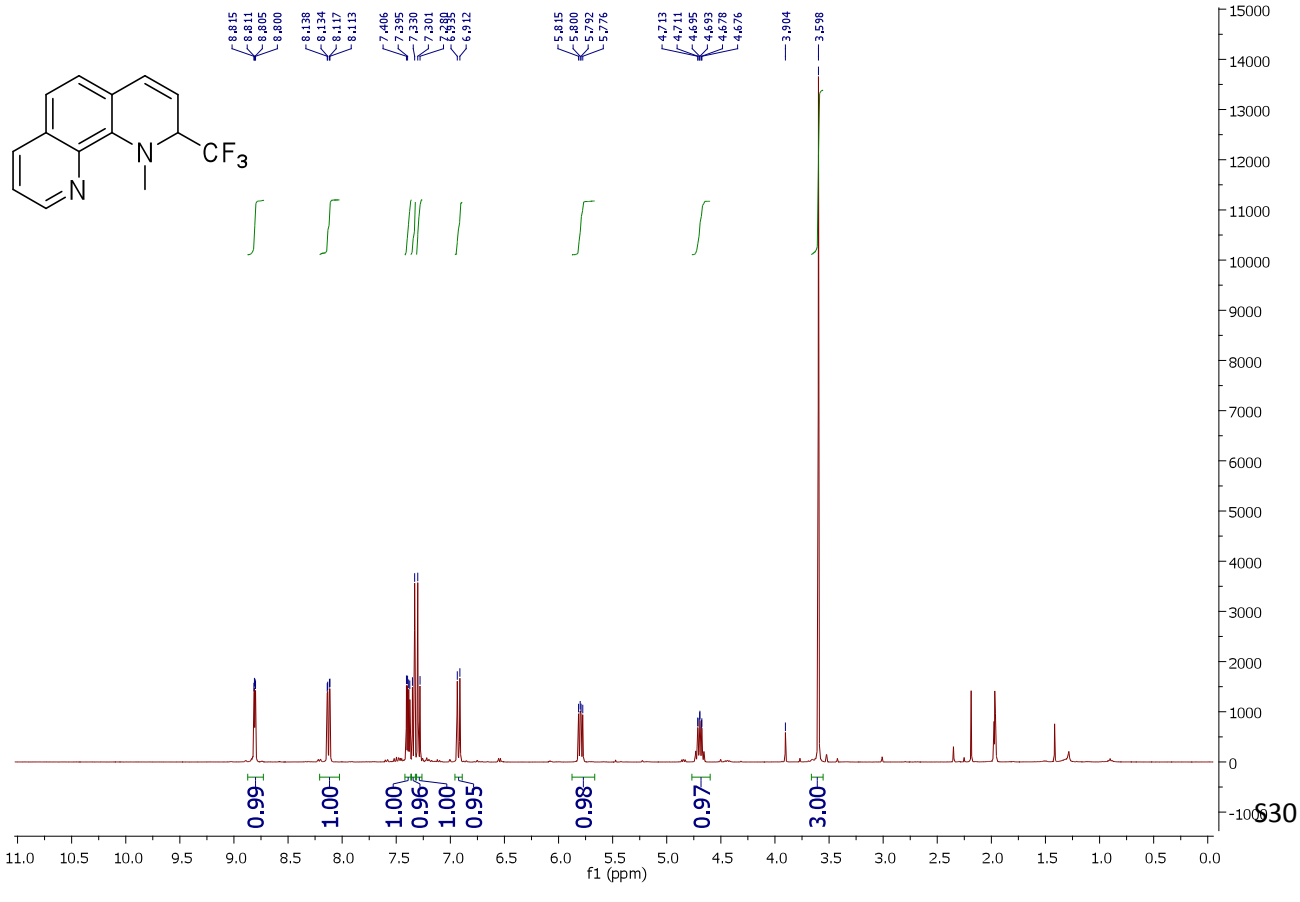
5-Methyl-6-(trifluoromethyl)-5,6-dihydrophenanthridine (10)

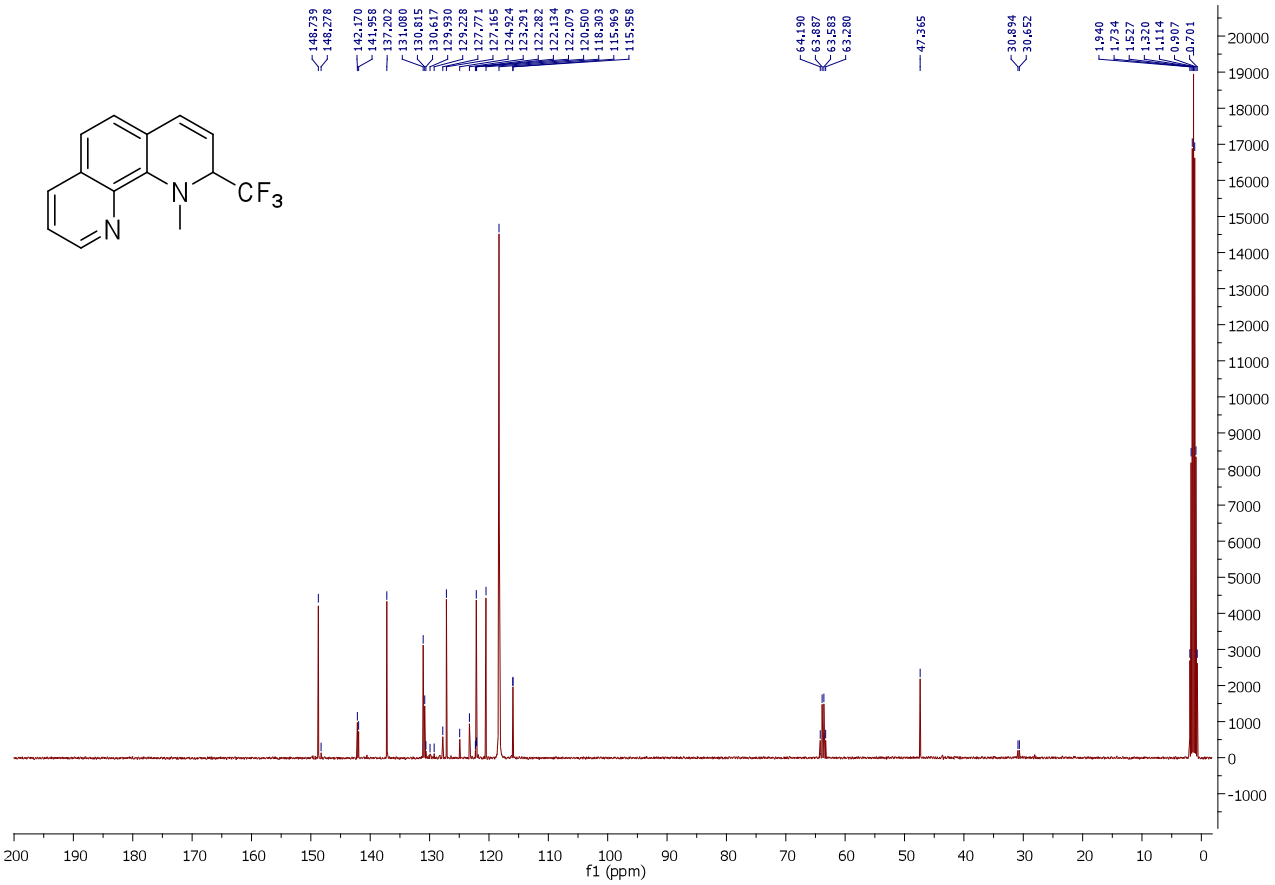






1-Methyl-2-(trifluoromethyl)-1,2-dihydro-1,10-phenanthroline (11)

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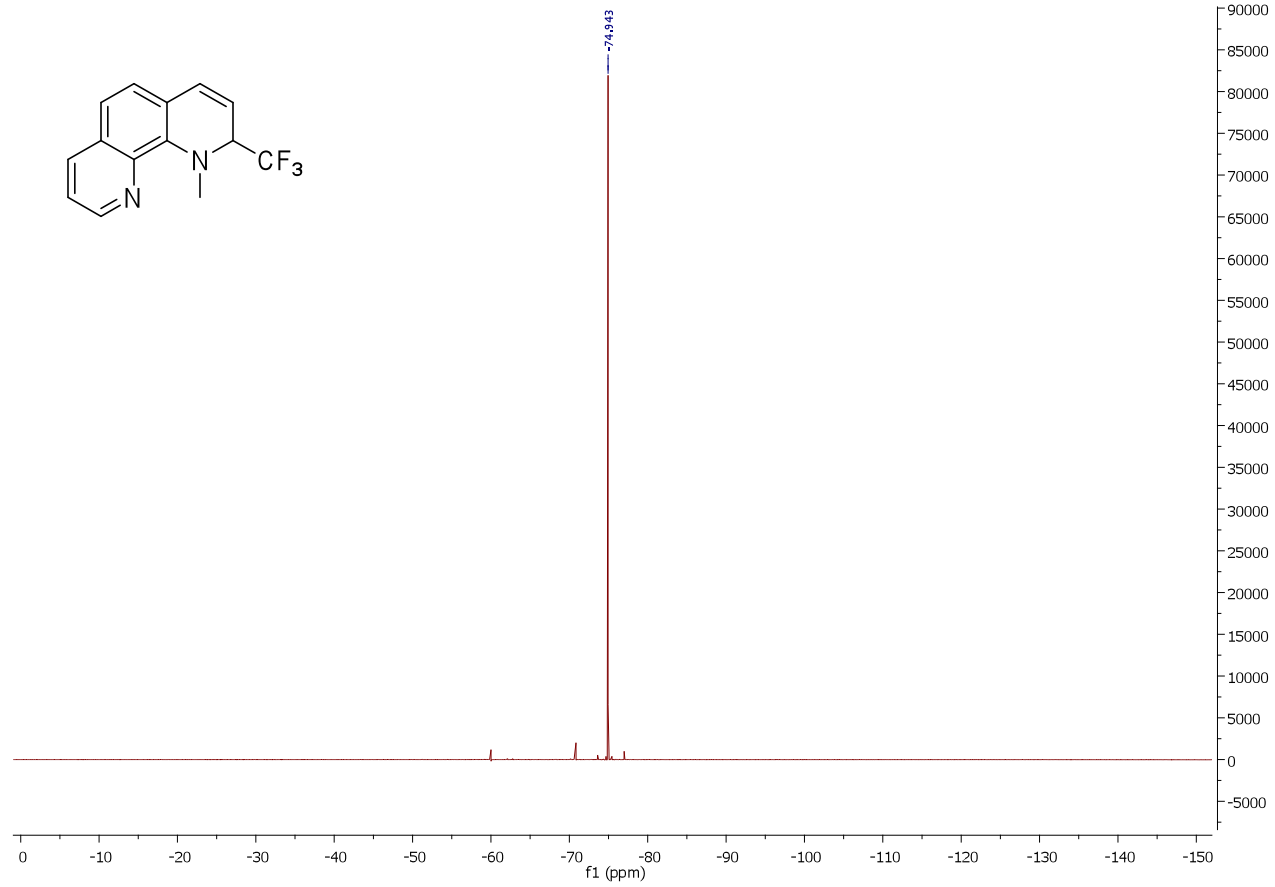
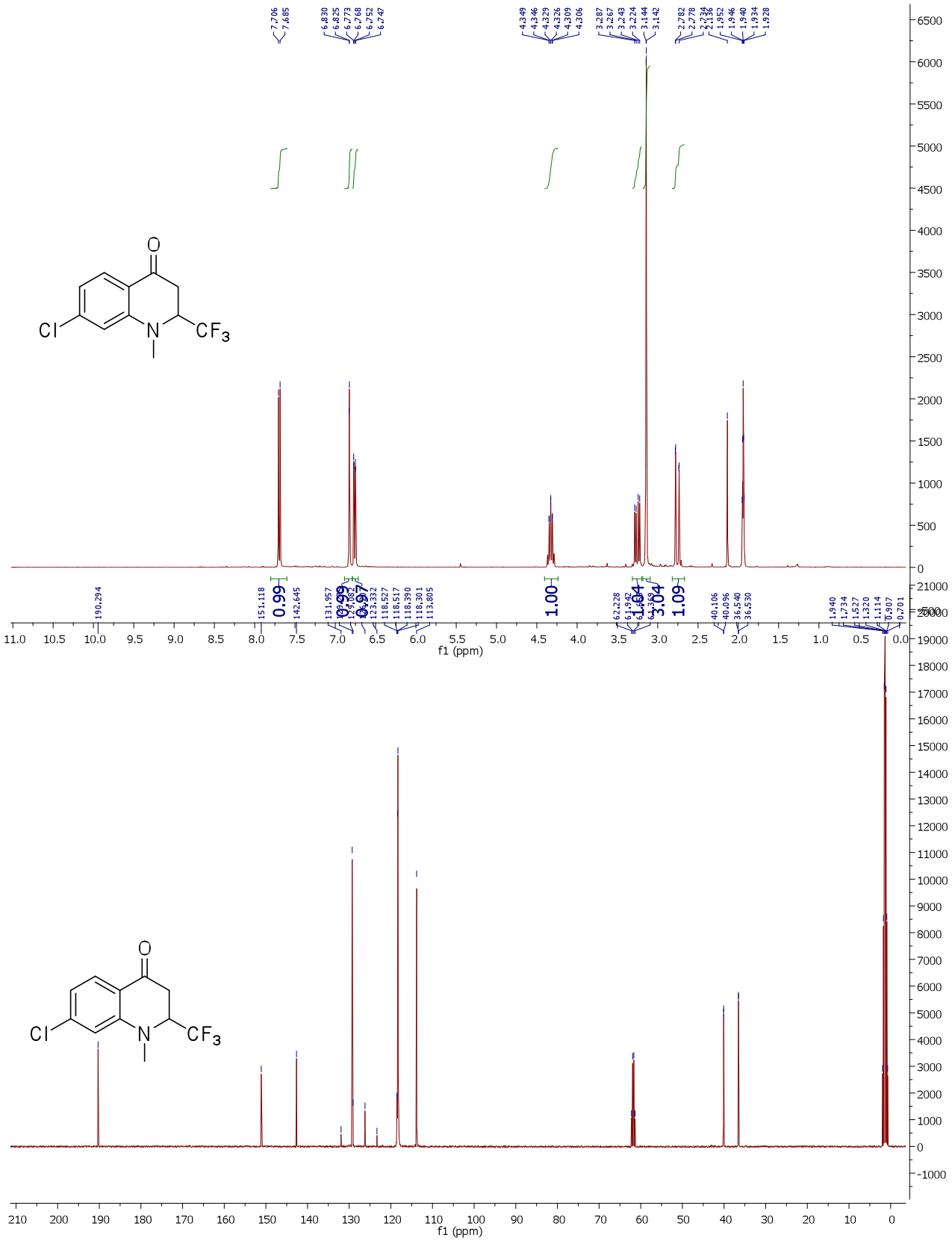
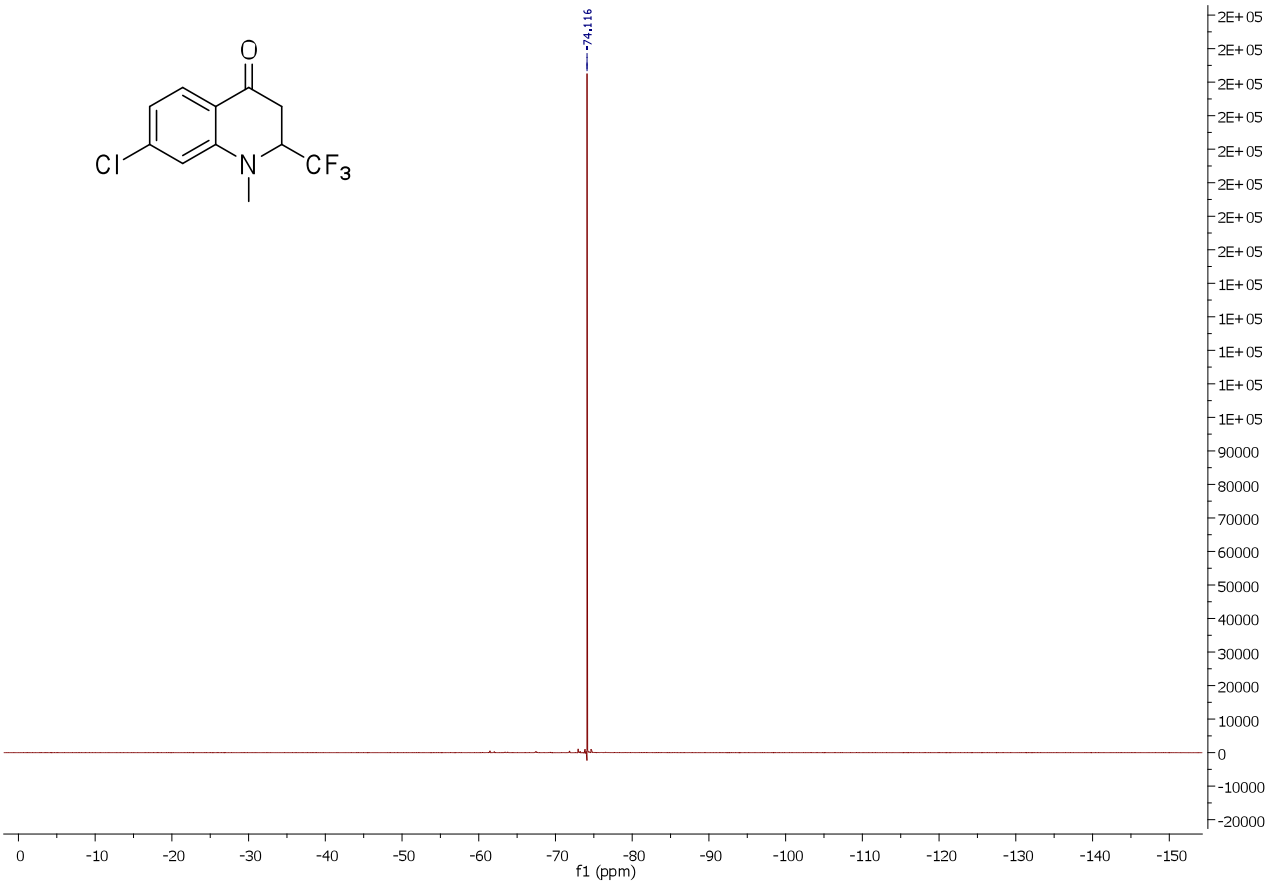
127.165
124.924
123.291
122.282
122.134
122.079
120.500
118.303
115.969
115.958
64.190
63.887
63.583
63.280
47.365
30.894
30.652
1.940
1.734
1.527
1.320
1.114
0.907
0.701
N
CF3
f1 (ppm)

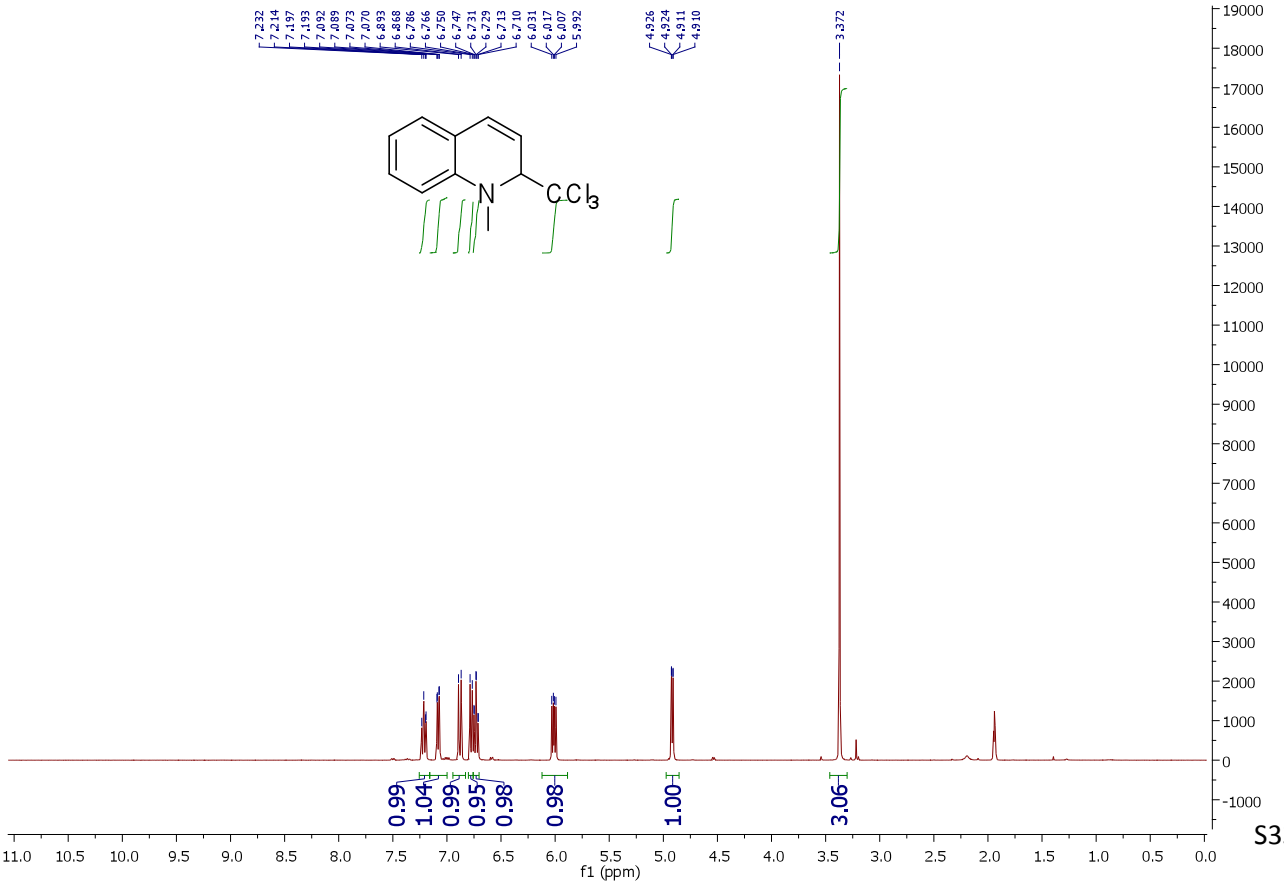

-74.943
N
CF3
f1 (ppm)

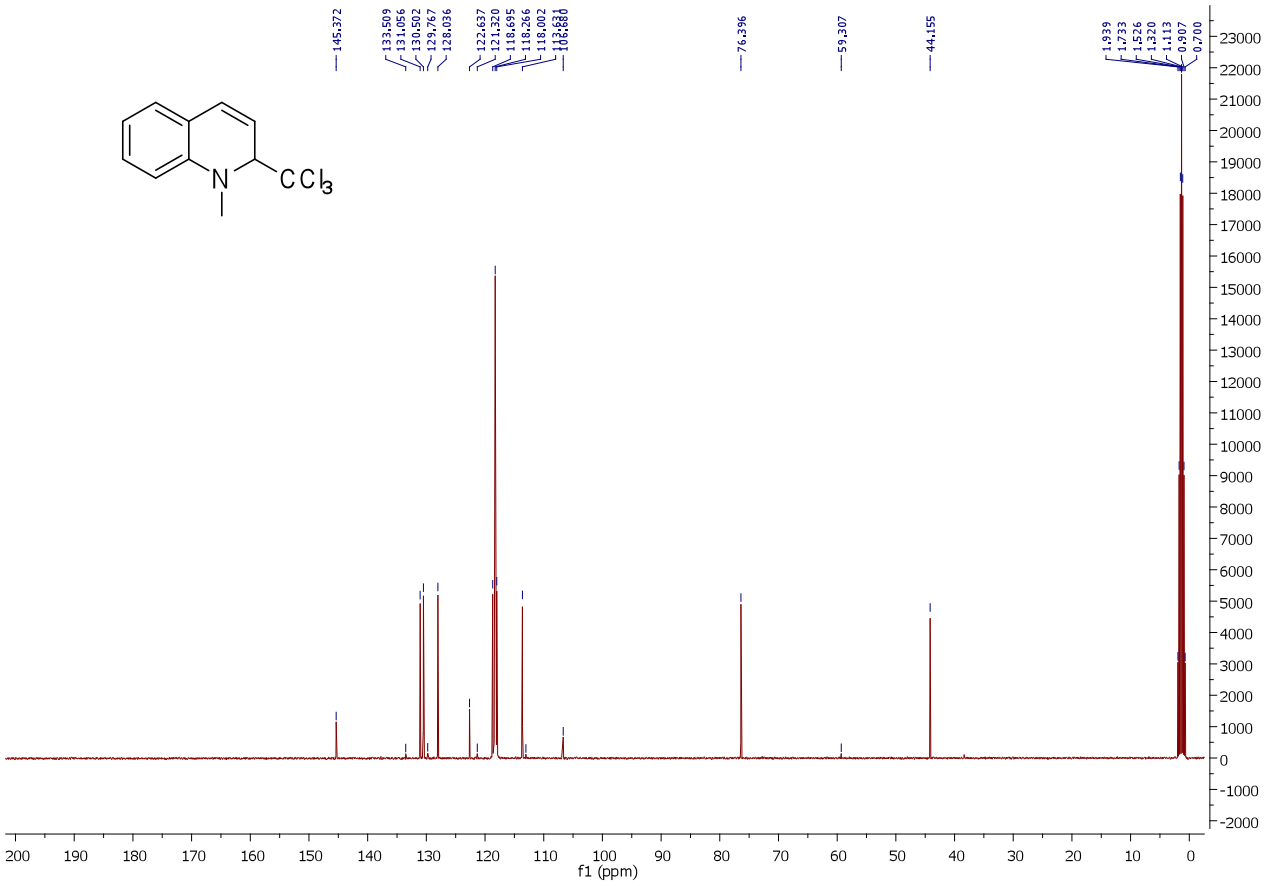
7-Chloro-1-methyl-2-(trifluoromethyl)-2,3-dihydroquinolin-4-one (13)



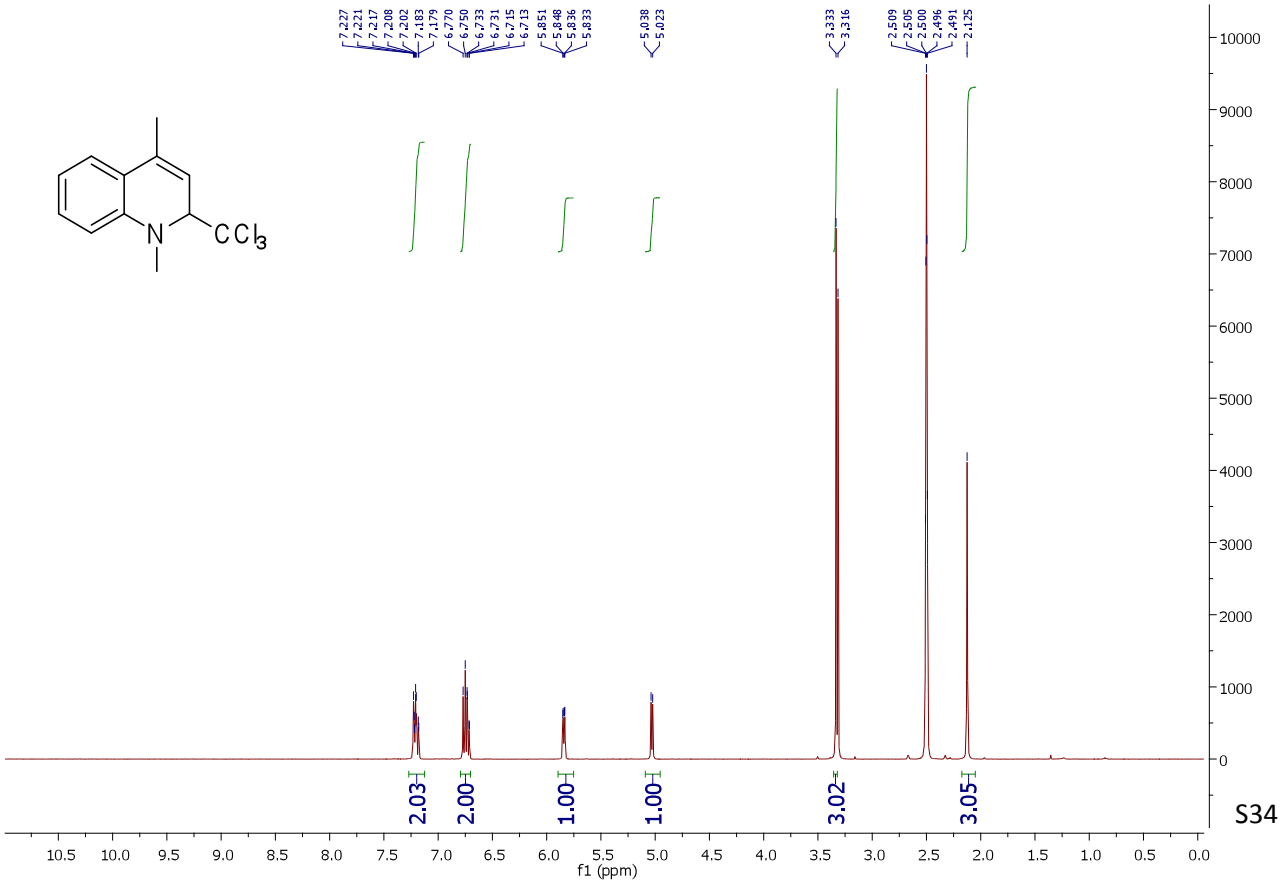


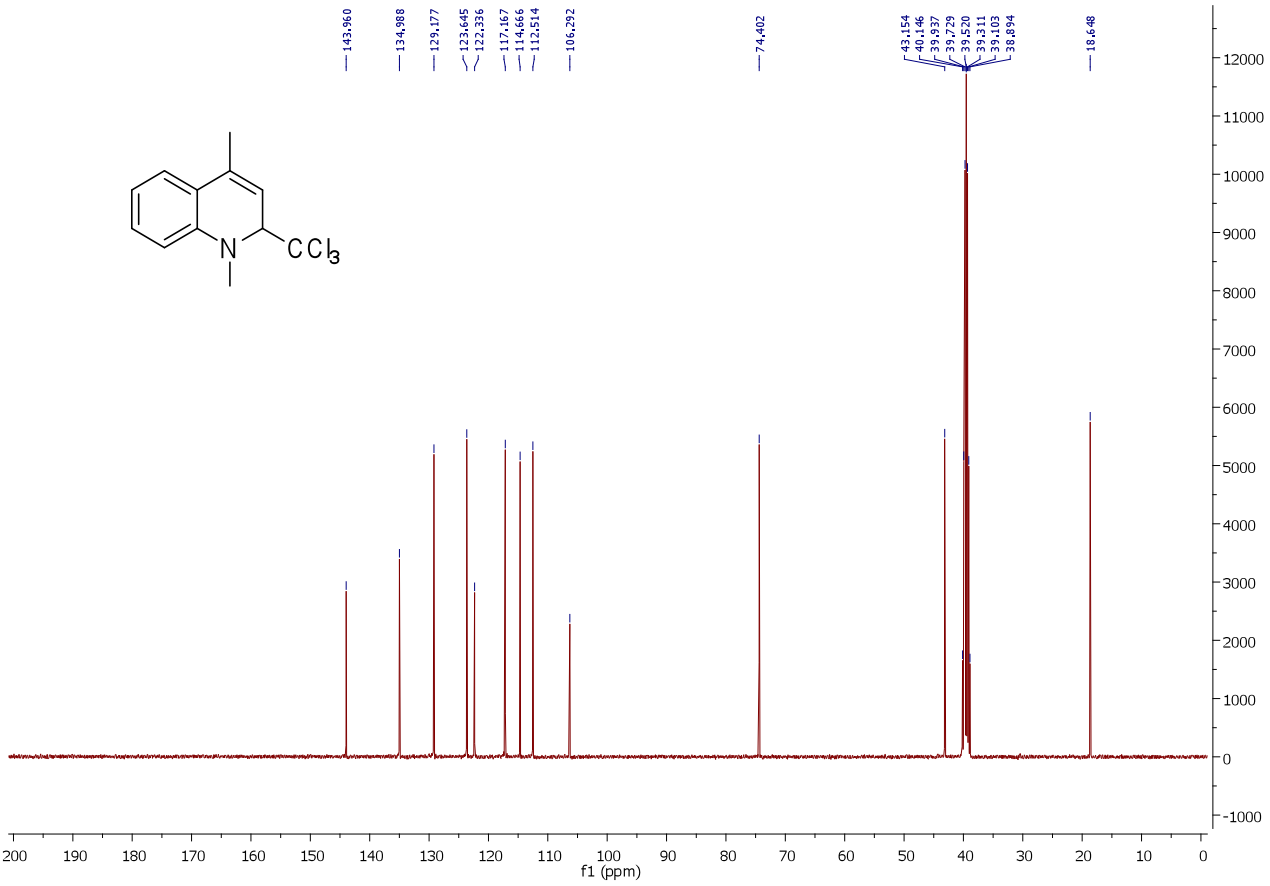
1-Methyl-2-(trichloromethyl)-1,2-dihydroquinoline (14)



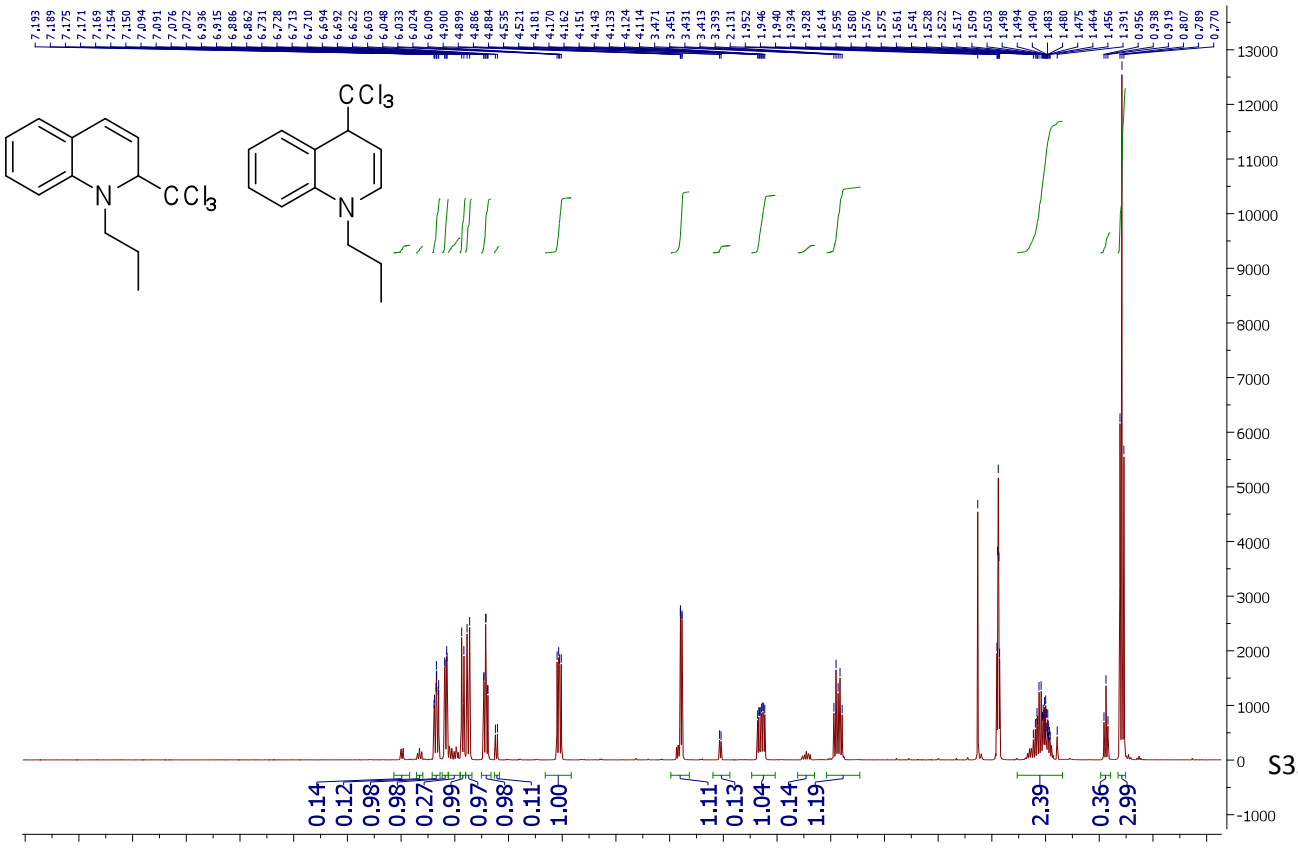


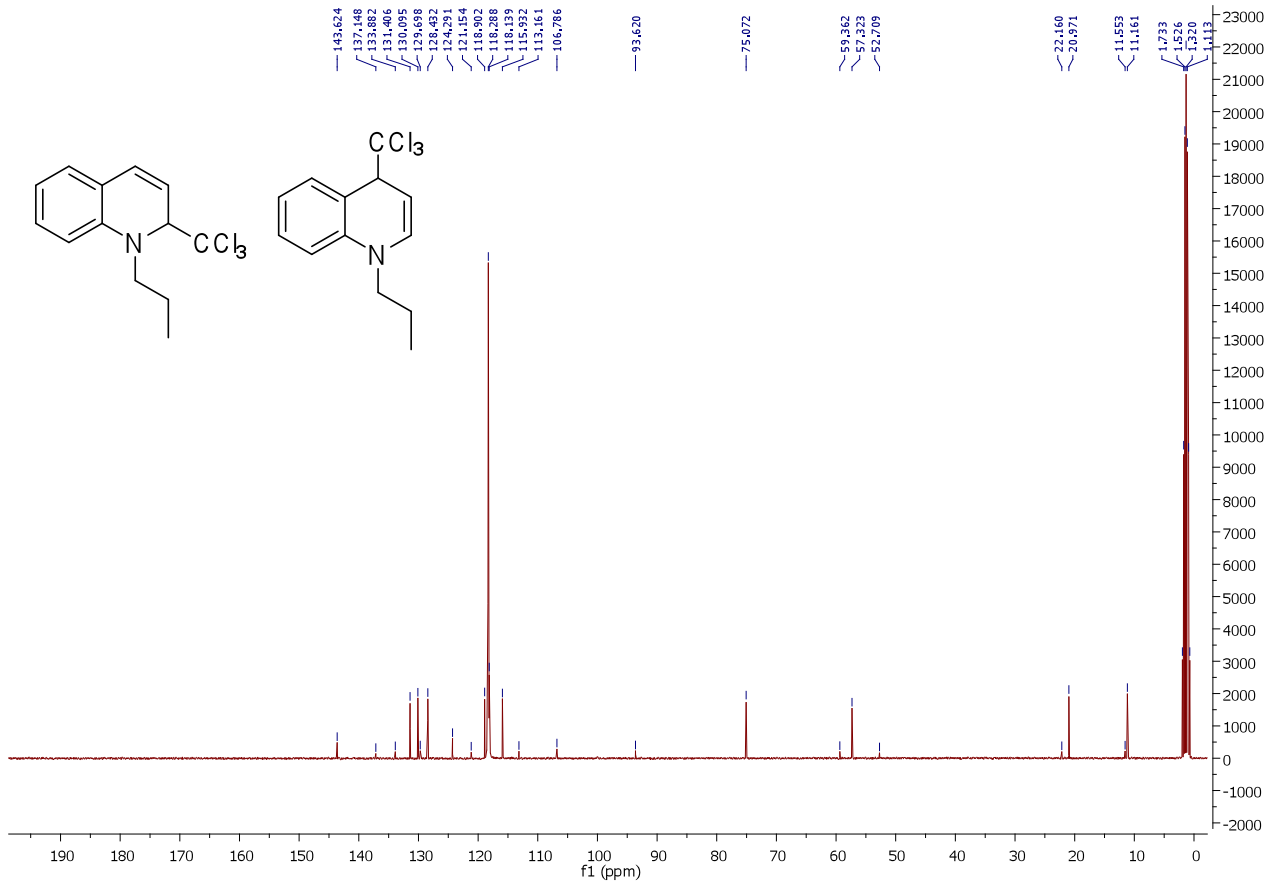
1,4-Dimethyl-2-(trichloromethyl)-1,2-dihydroquinoline (15)



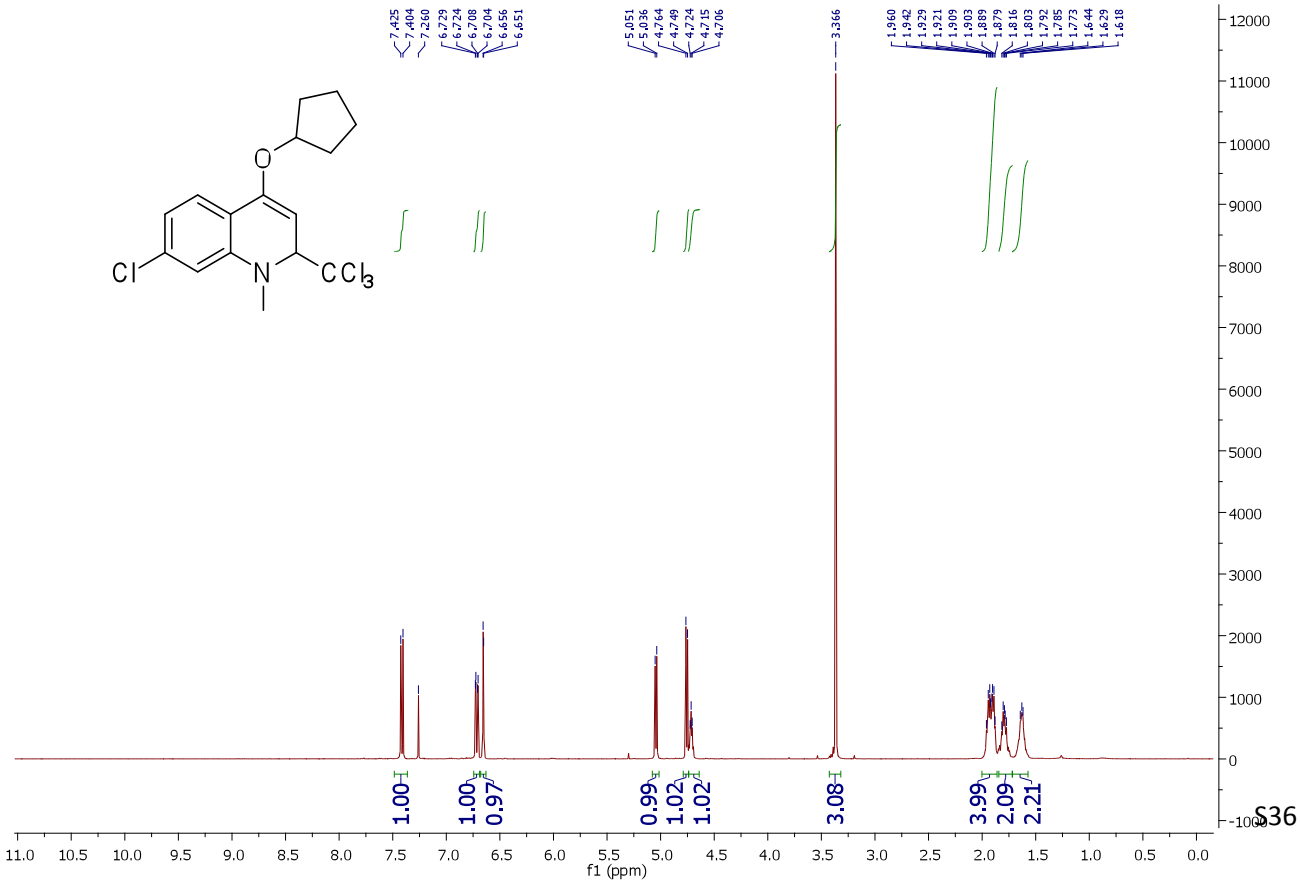


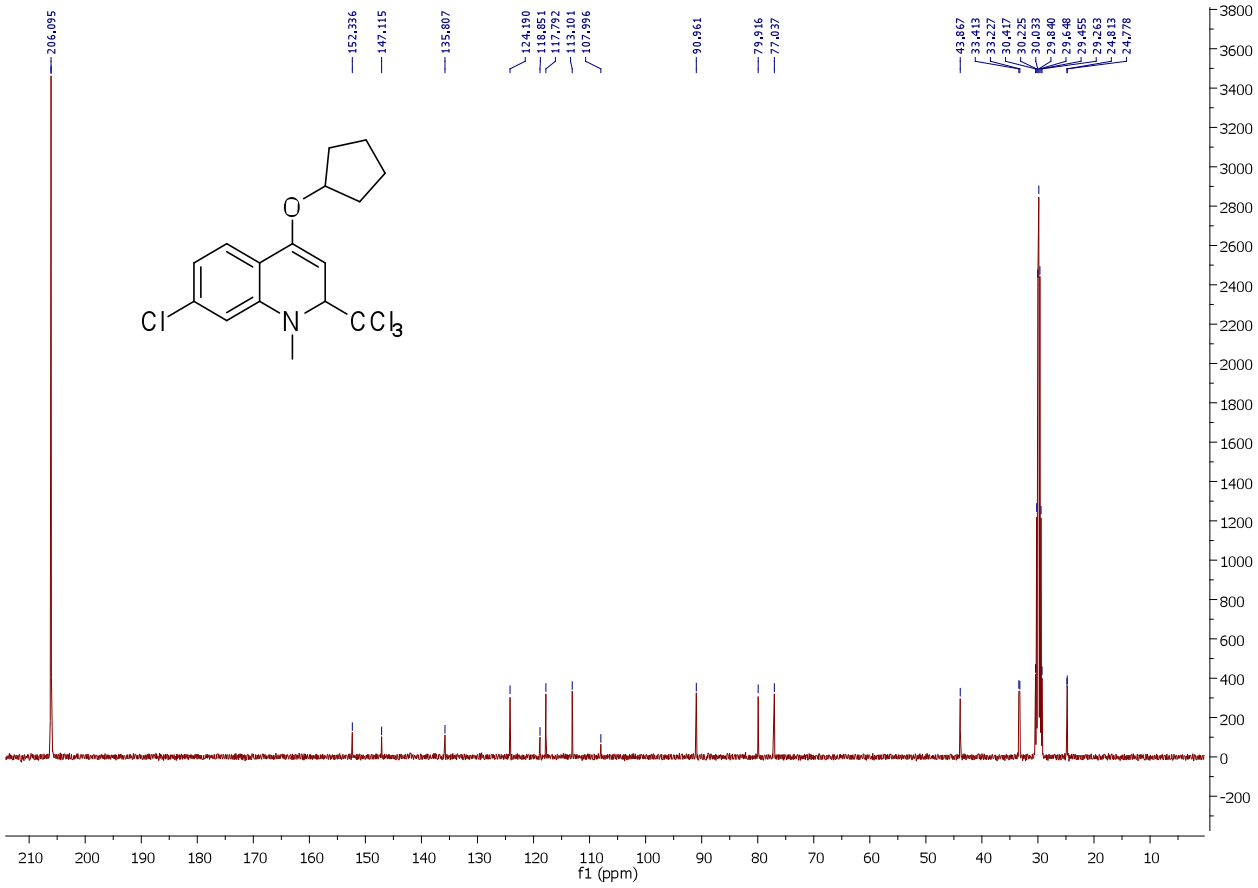
1-Propyl-2-(trichloromethyl)-1,2-dihydroquinoline and 1-propyl-4-(trichloromethyl)-1,4-dihydroquinoline (16 + 17)



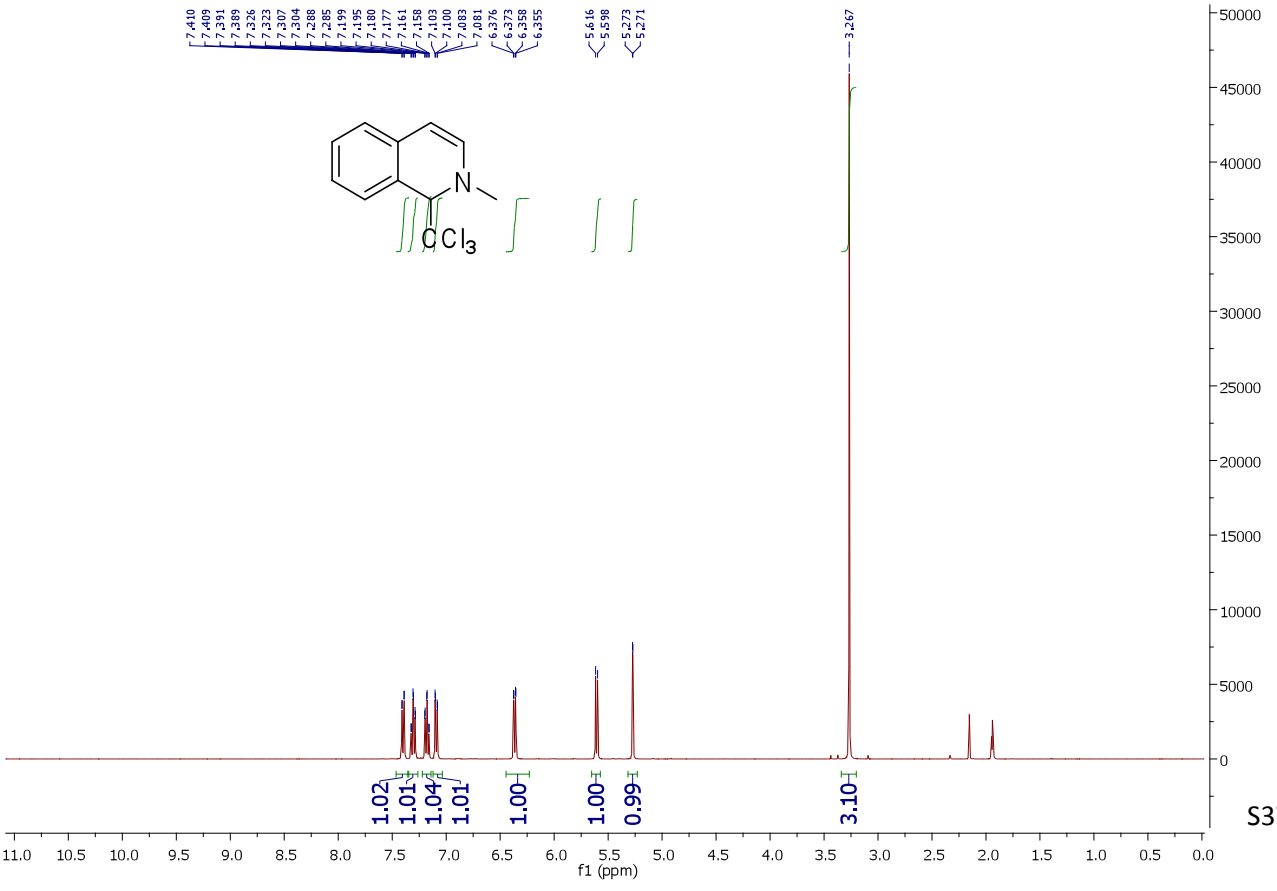


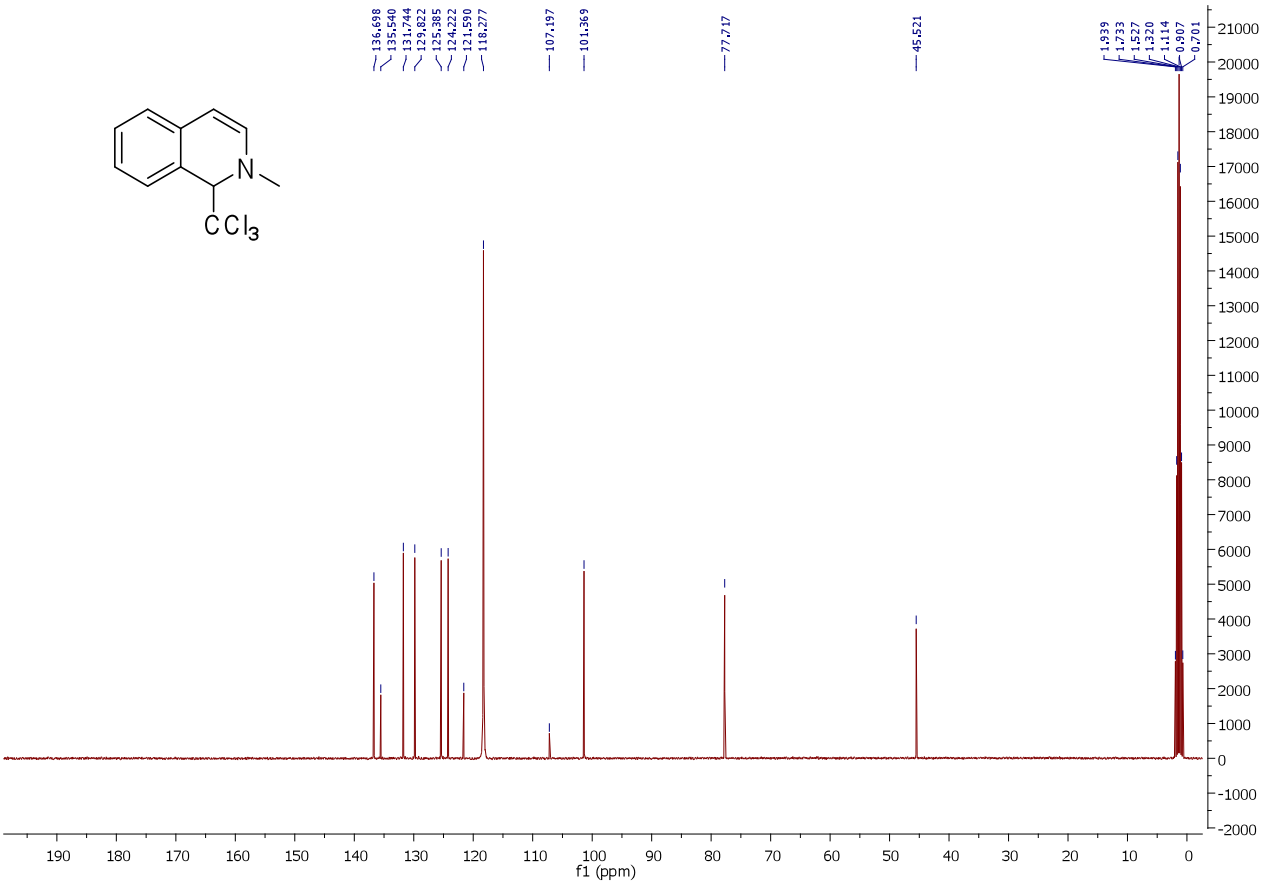
7-Chloro-4-(cyclopentyloxy)-1-methyl-2-(trichloromethyl)-1,2-dihydroquinoline (18)



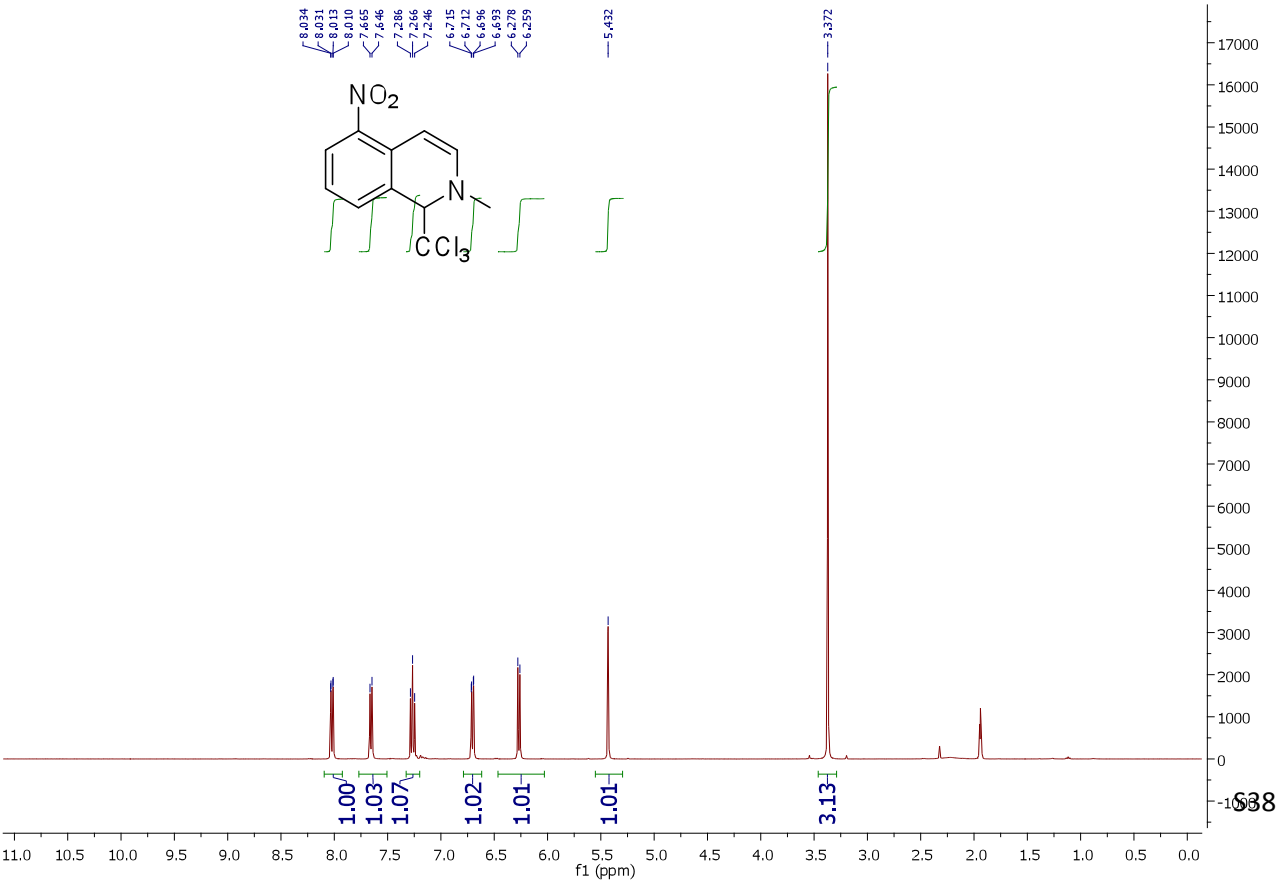


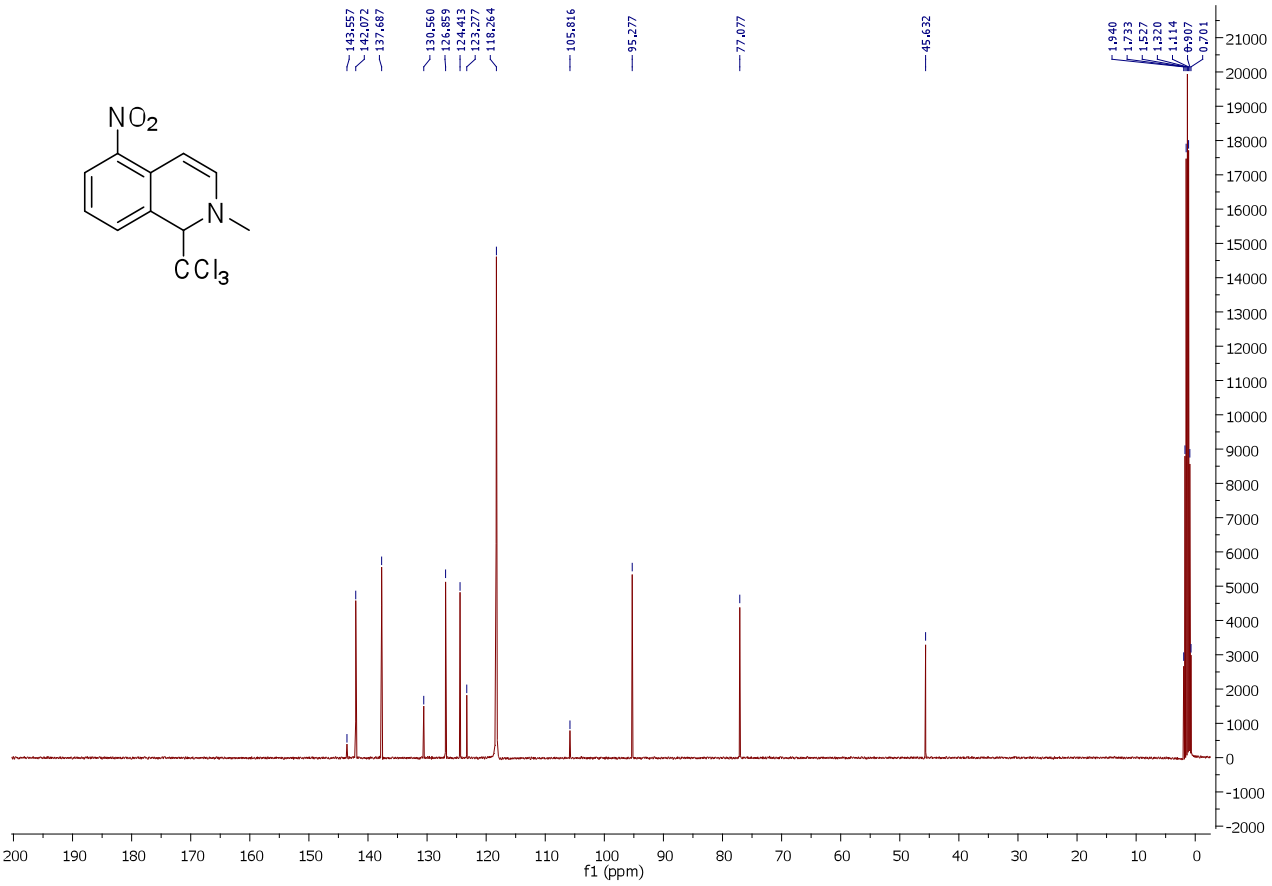
2-Methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (19)



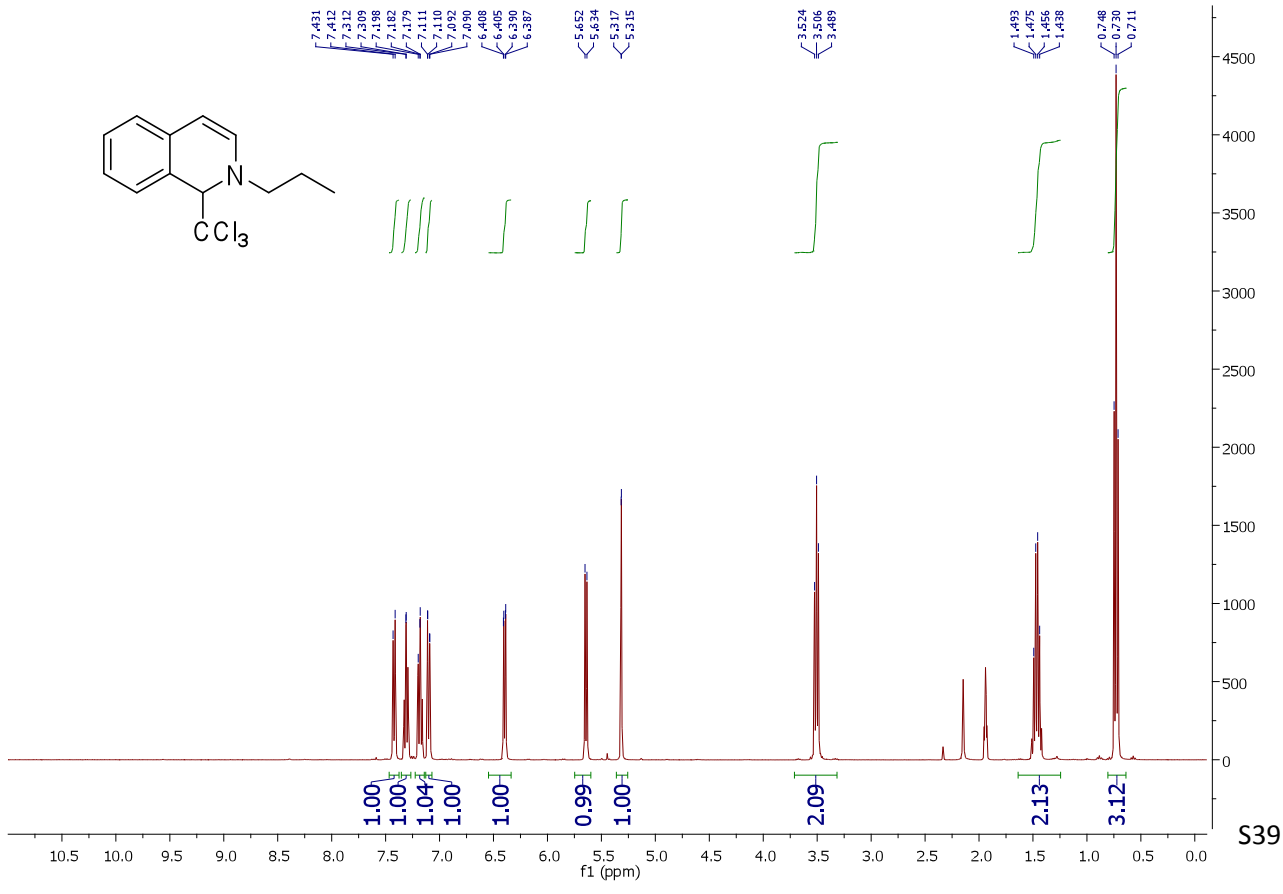


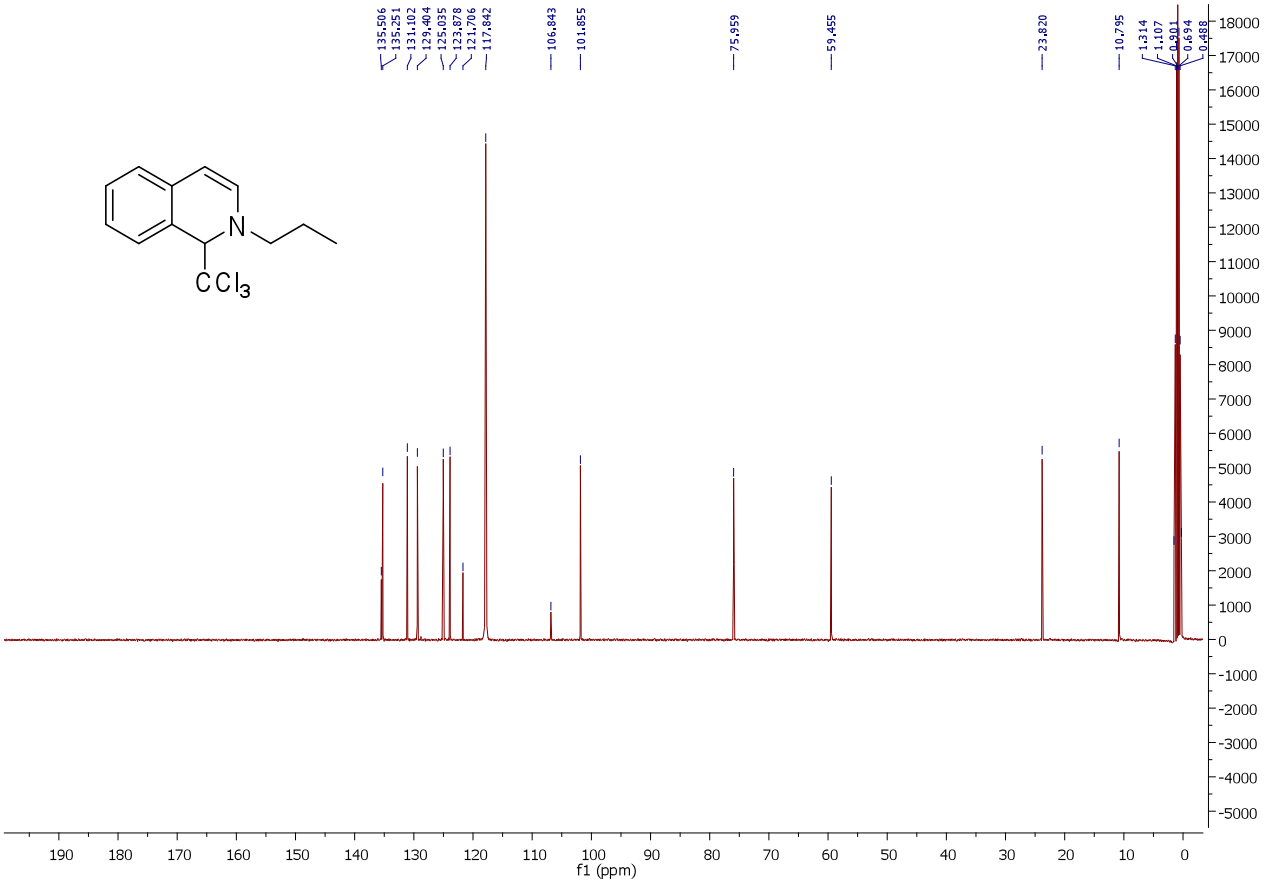
2-Methyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (20)



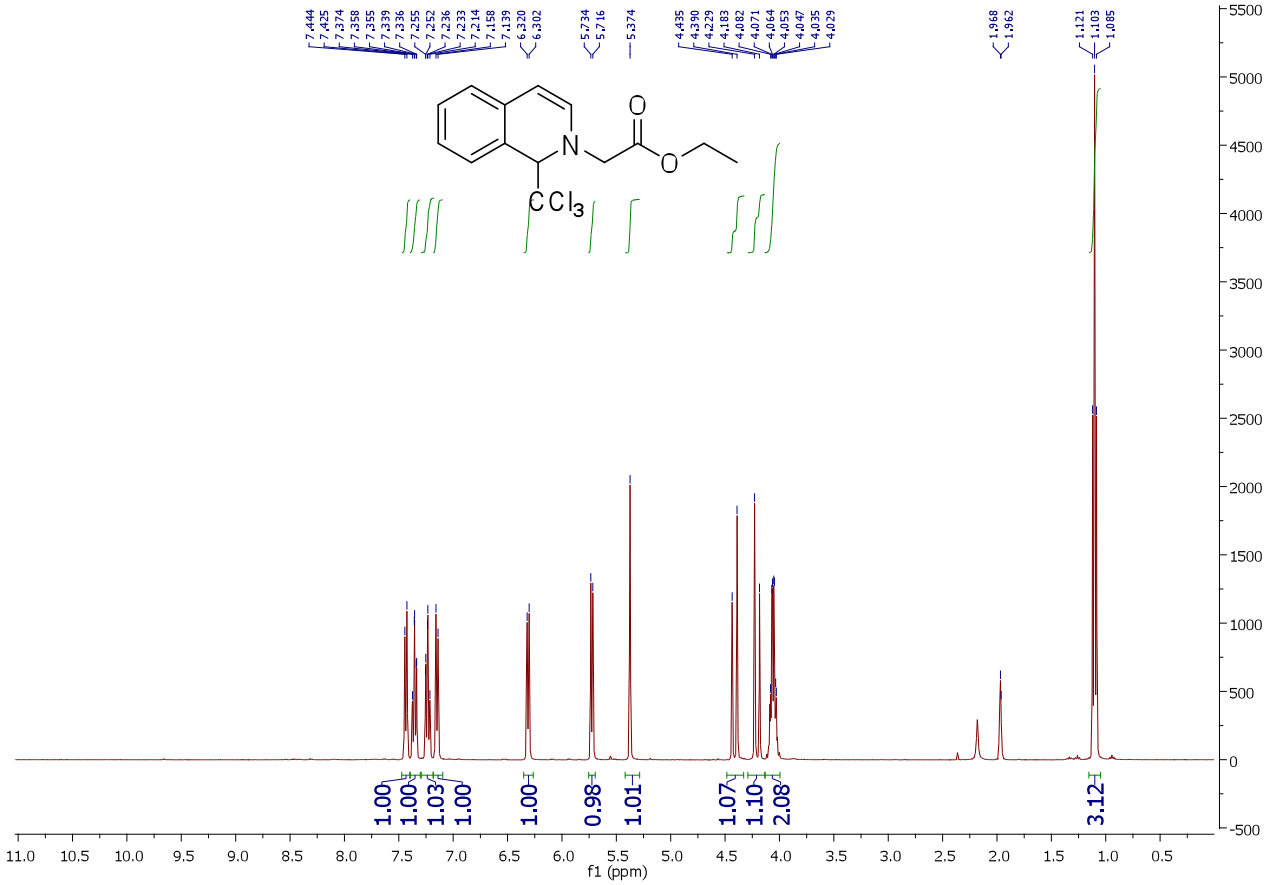


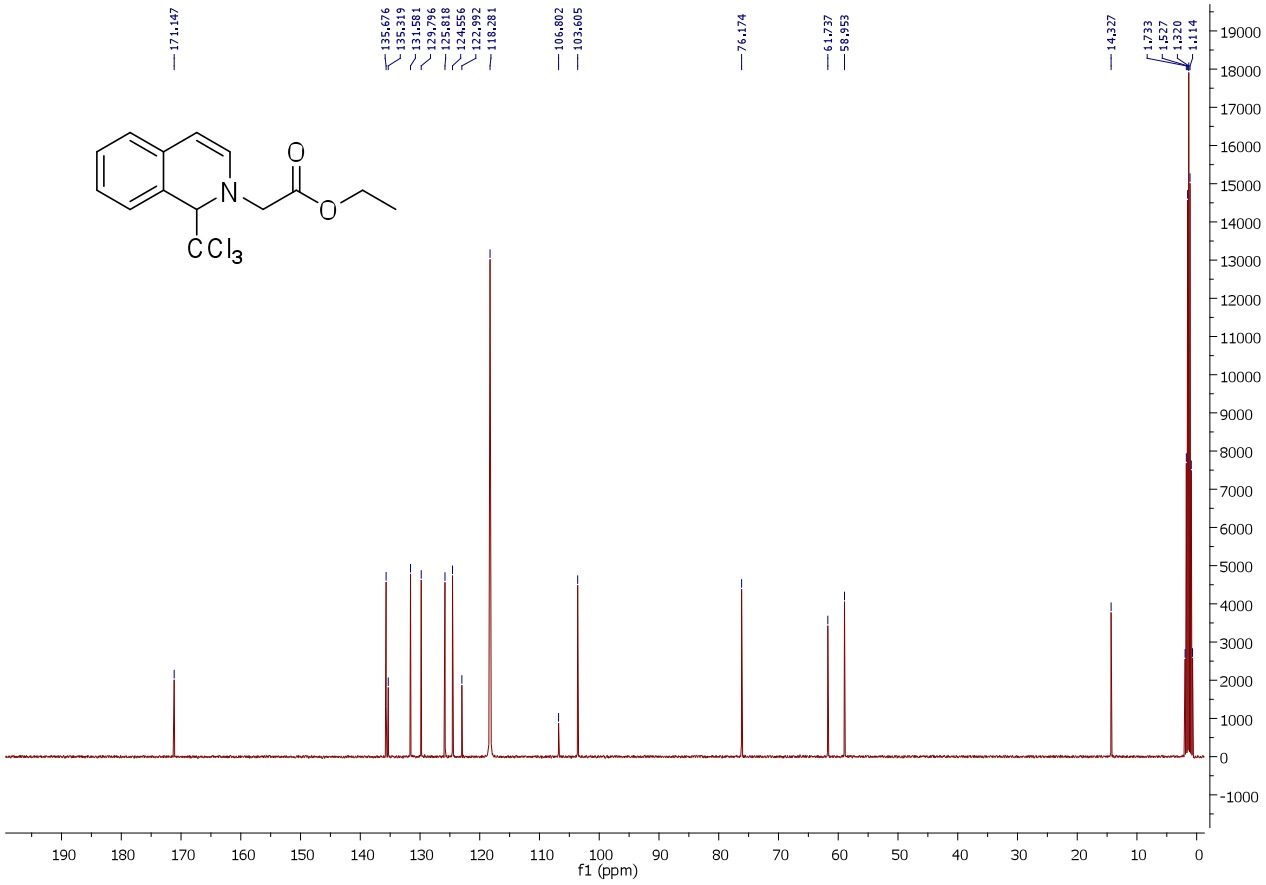
2-Propyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (21)



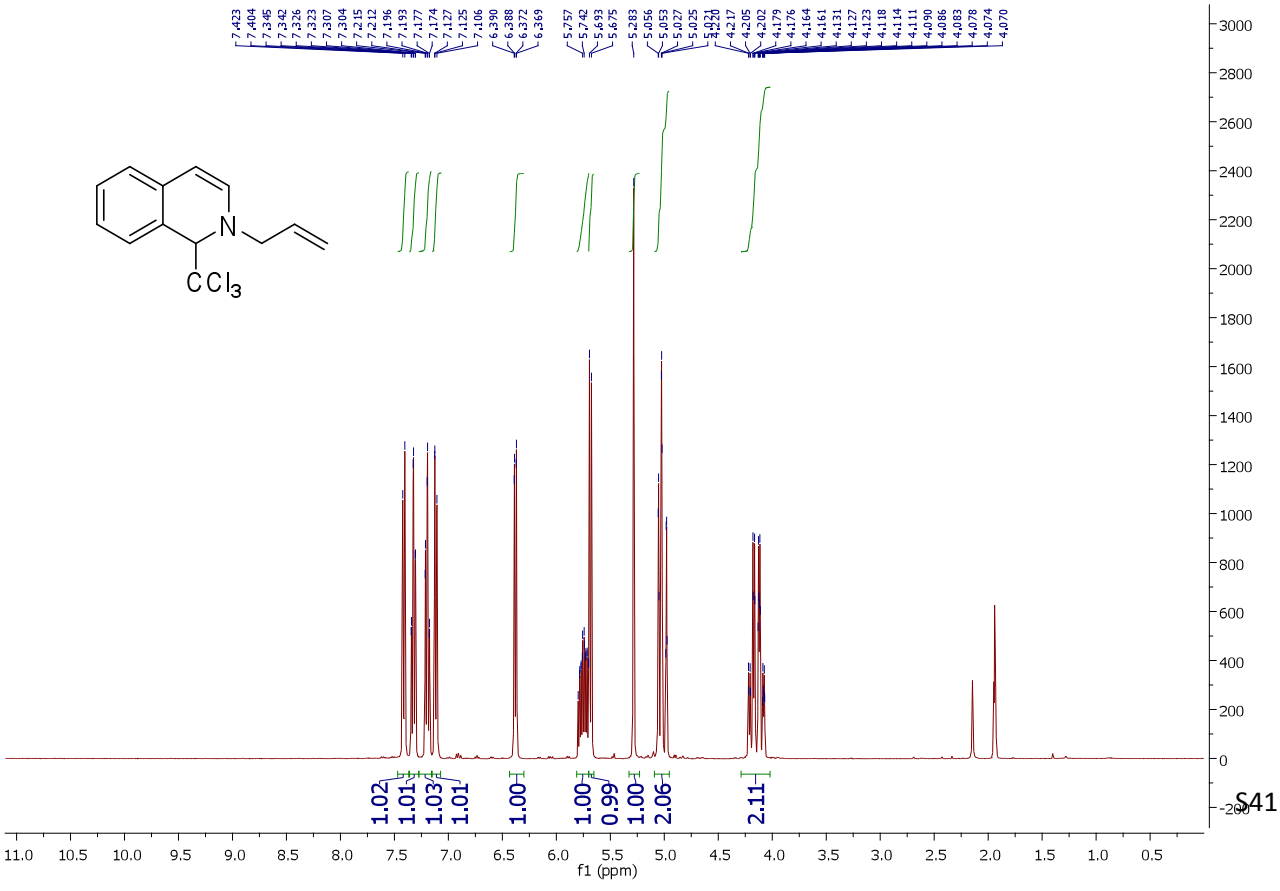


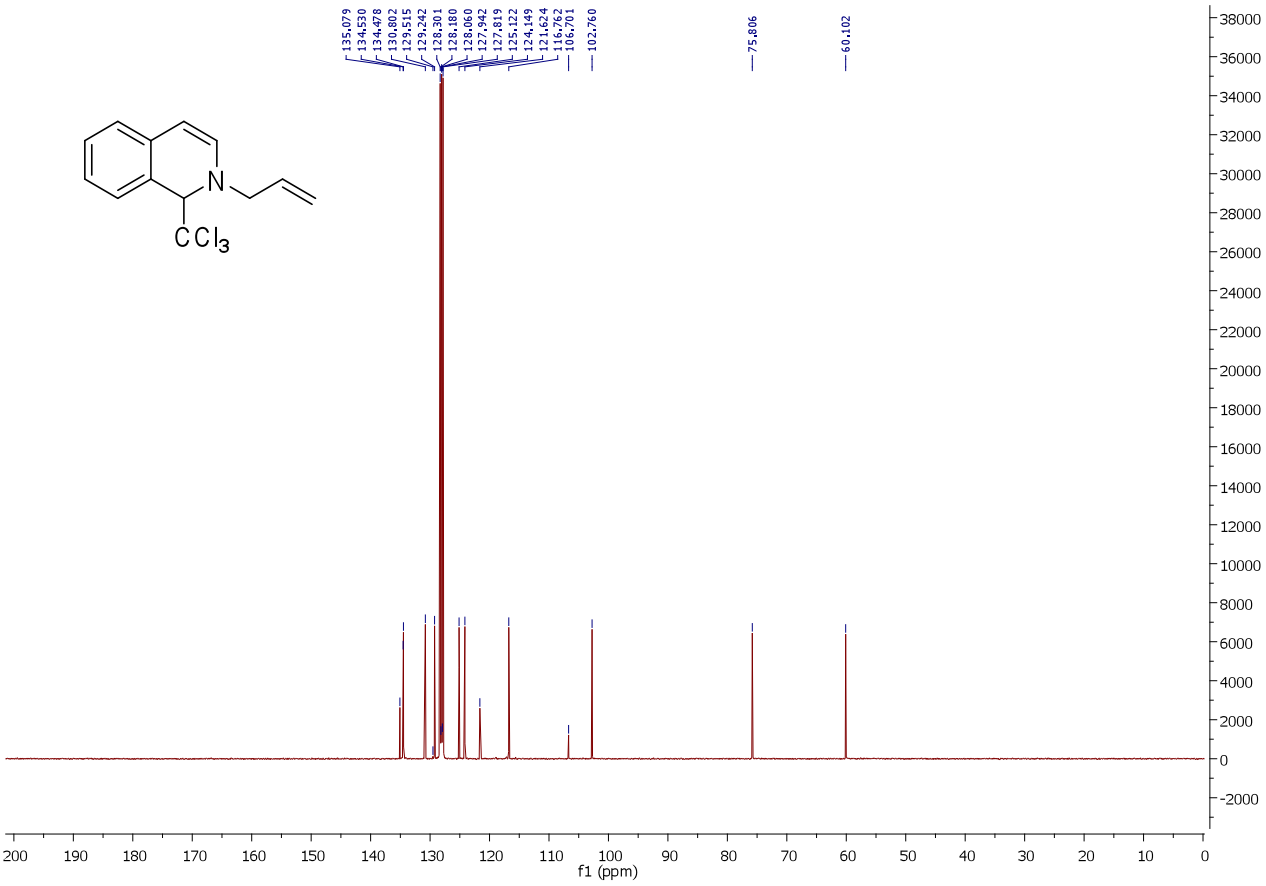
Ethyl 2-(1-(trichloromethyl)isoquinolin-2(1H)-yl)acetate (22)



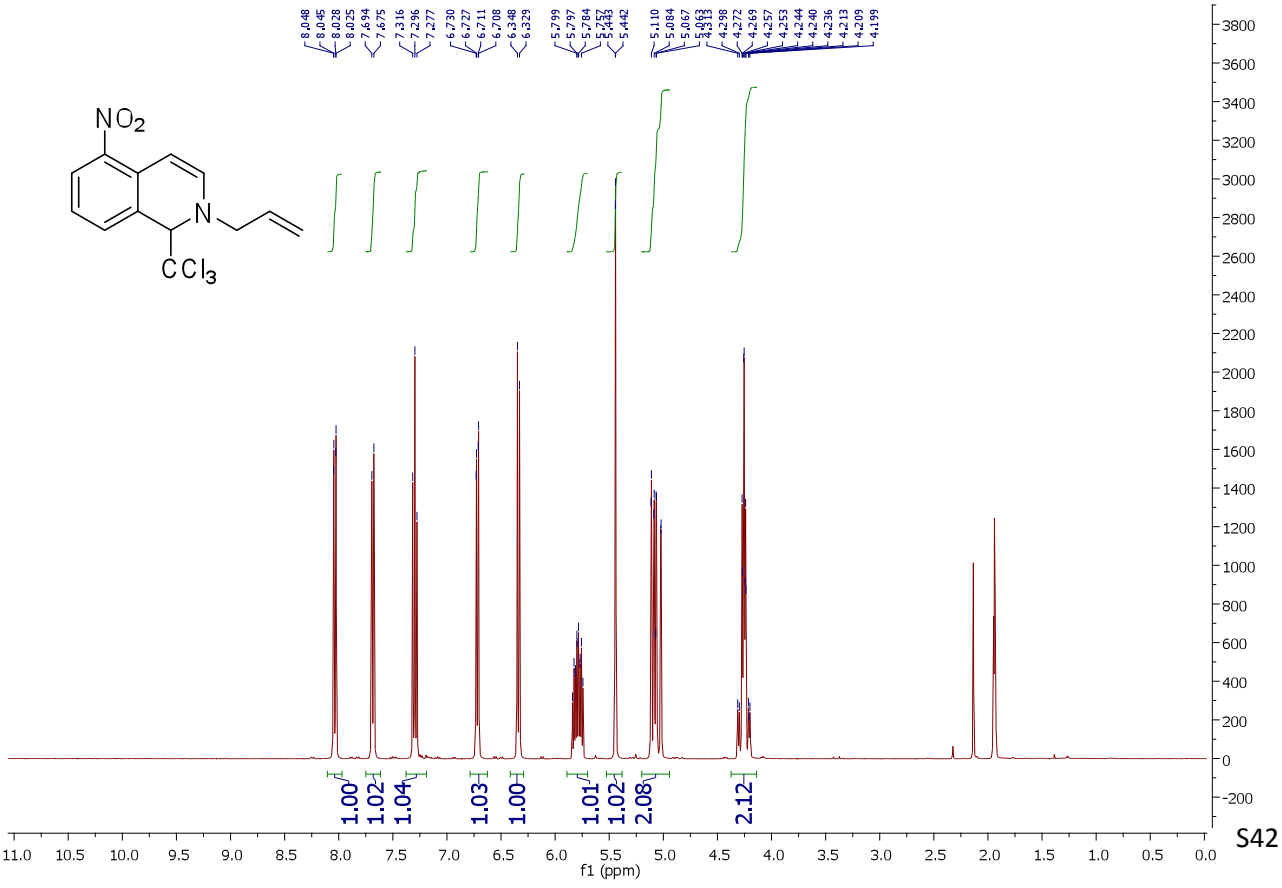


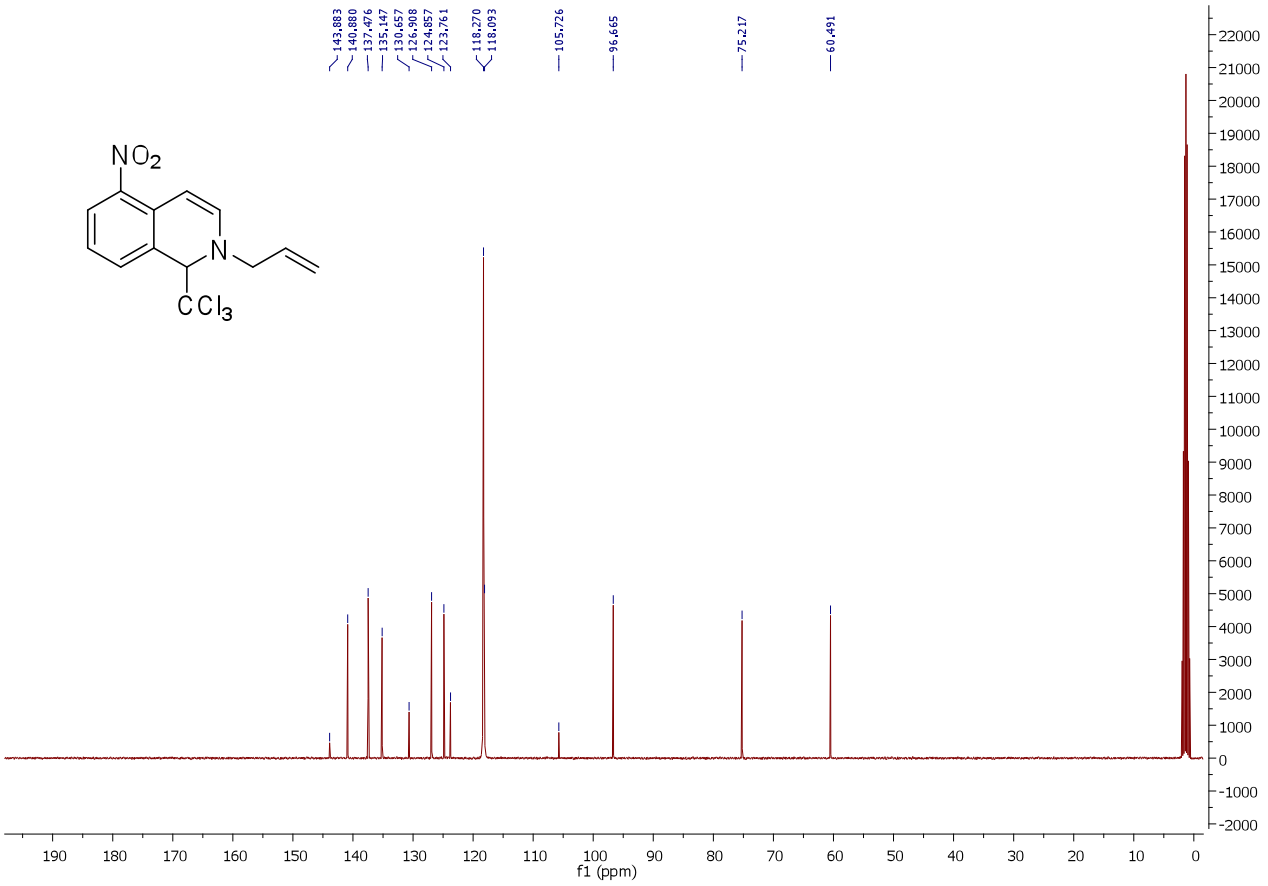
2-Allyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (23)



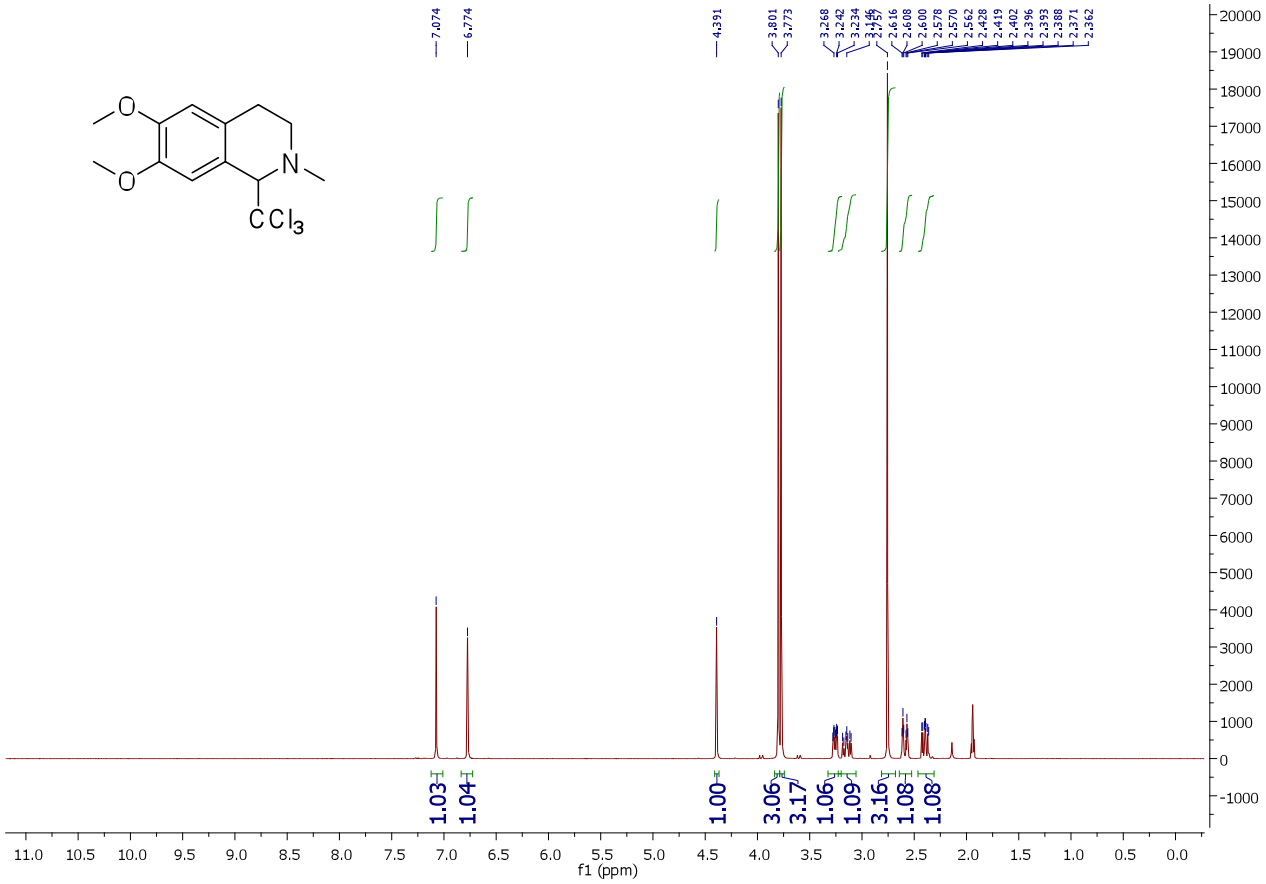


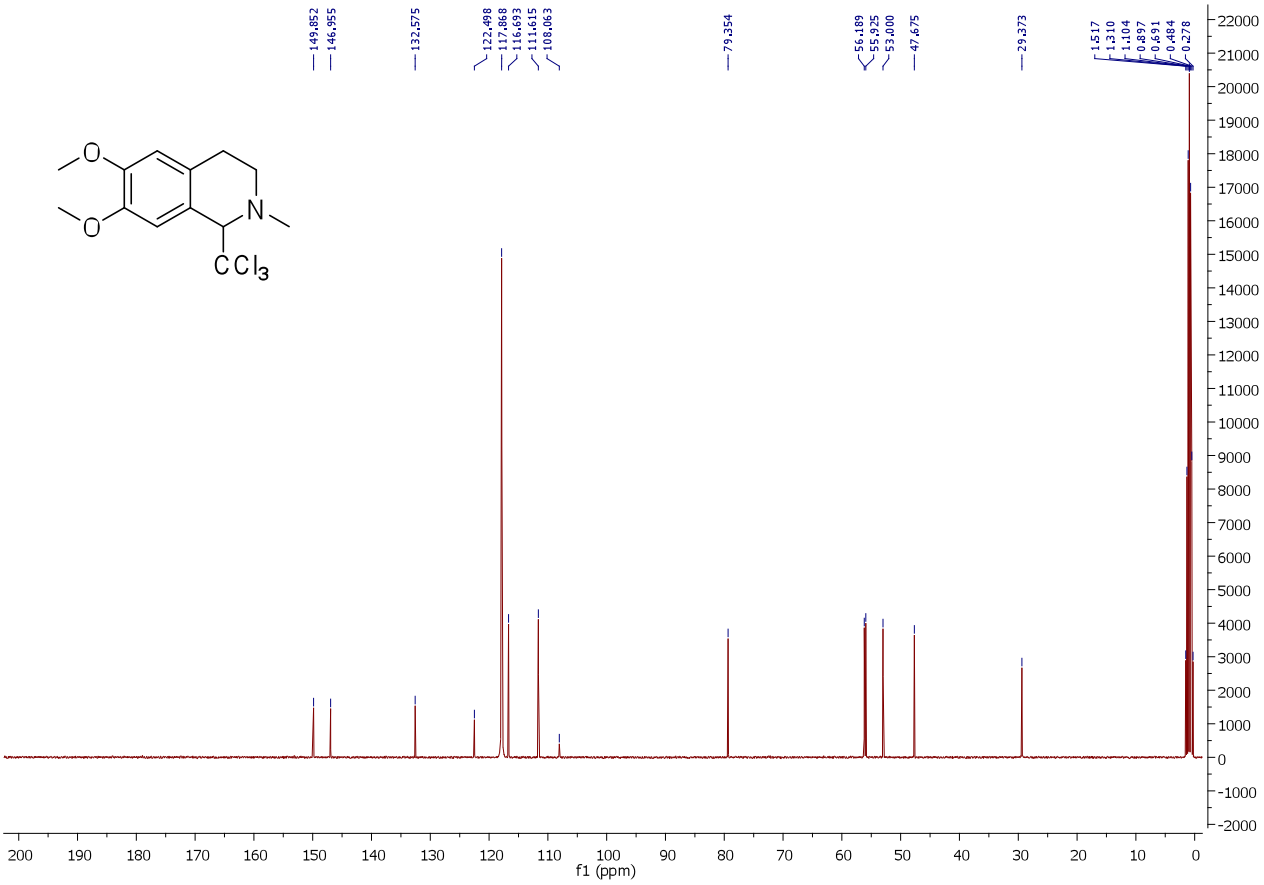
2-Allyl-5-nitro-1-(trichloromethyl)-1,2-dihydroisoquinoline (24)



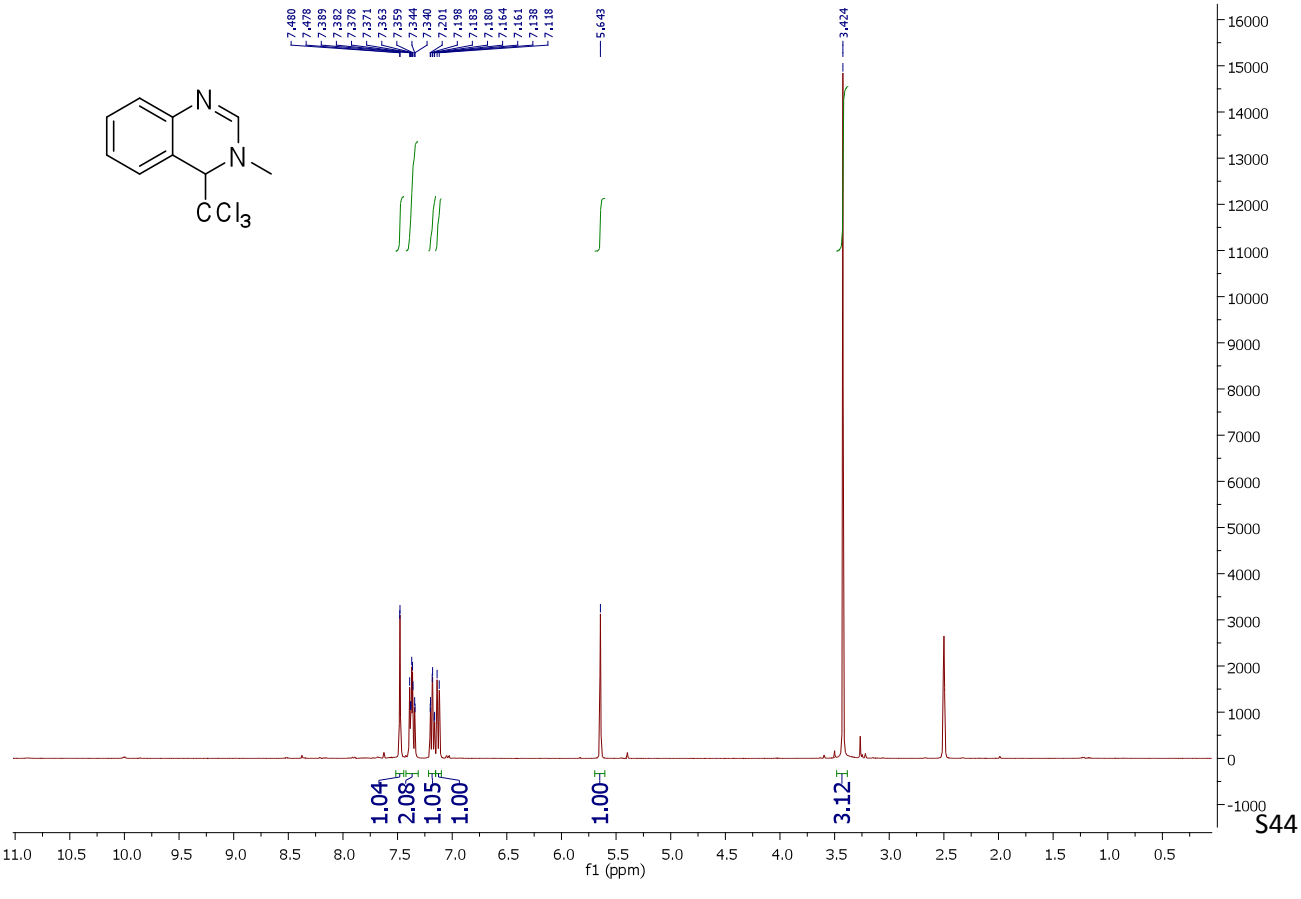


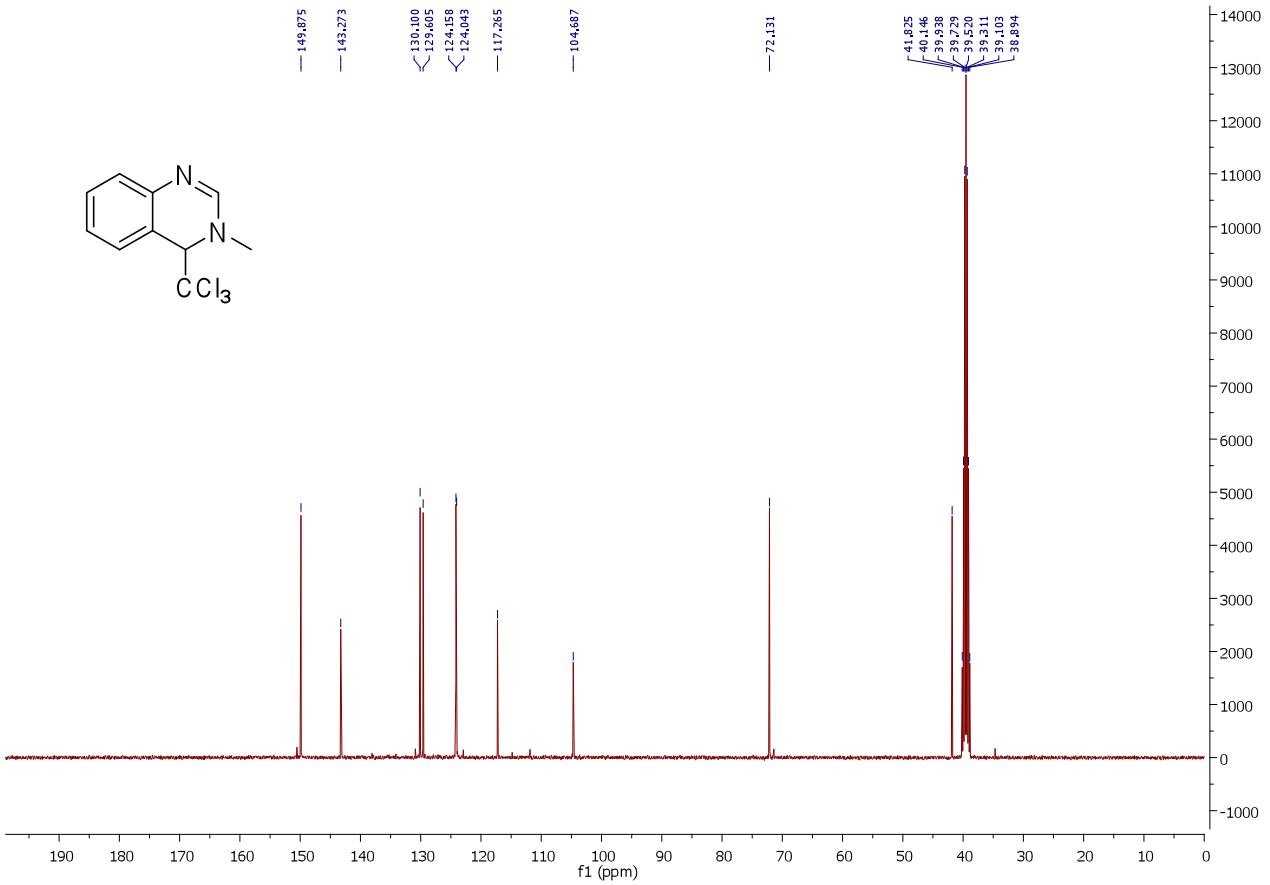
6,7-Dimethoxy-2-methyl-1-(trichloromethyl)-1,2,3,4-tetrahydroisoquinoline (25)

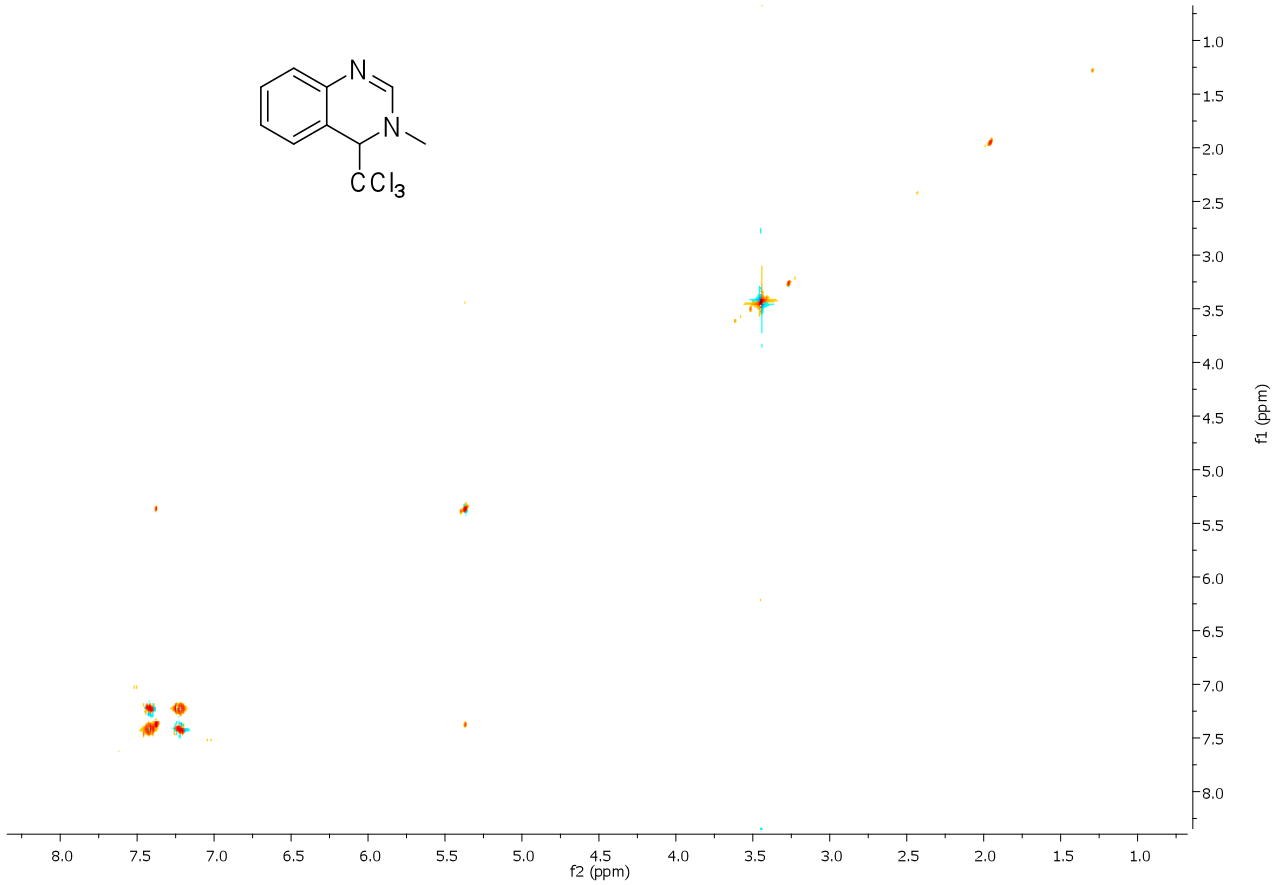




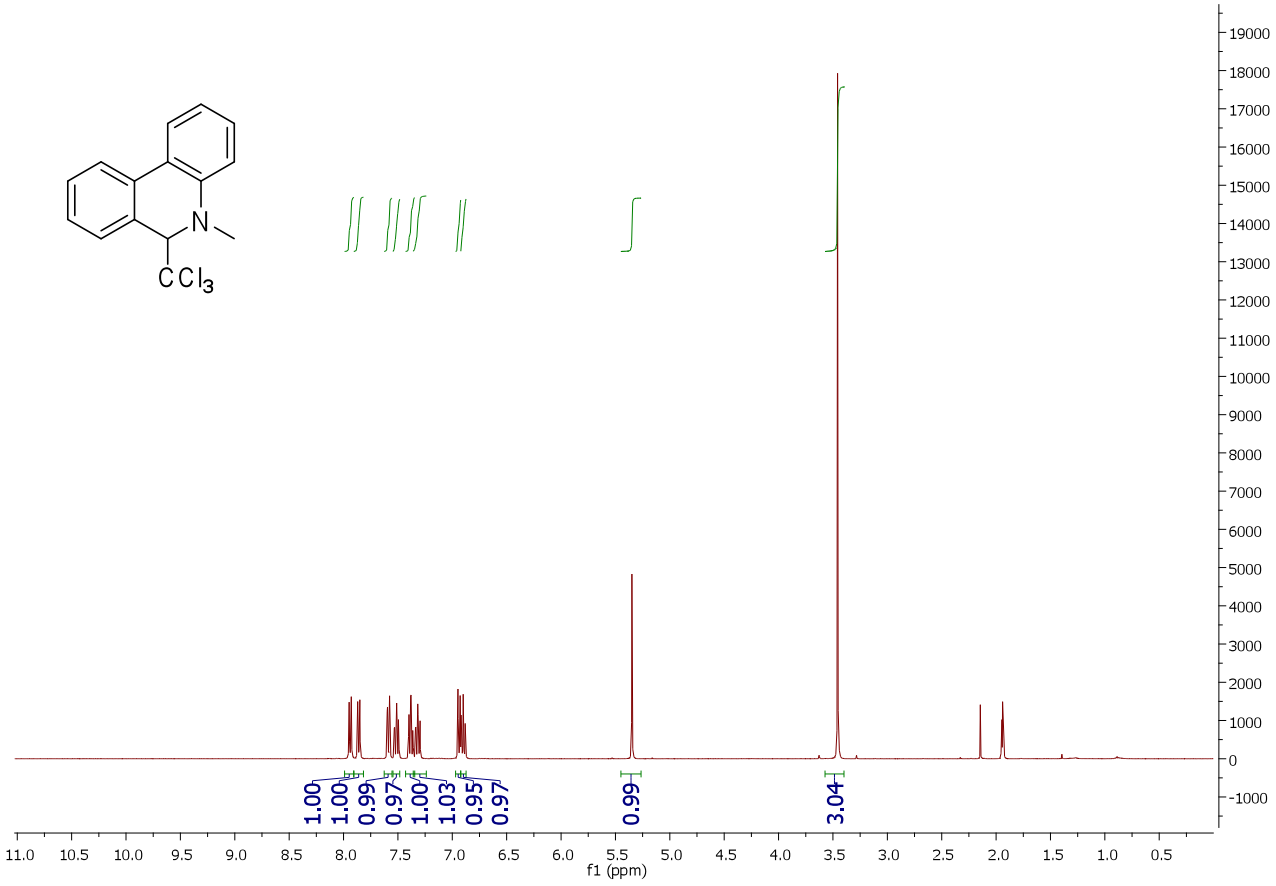
3-methyl-4-(trichloromethyl)-3,4-dihydroquinazoline (26)

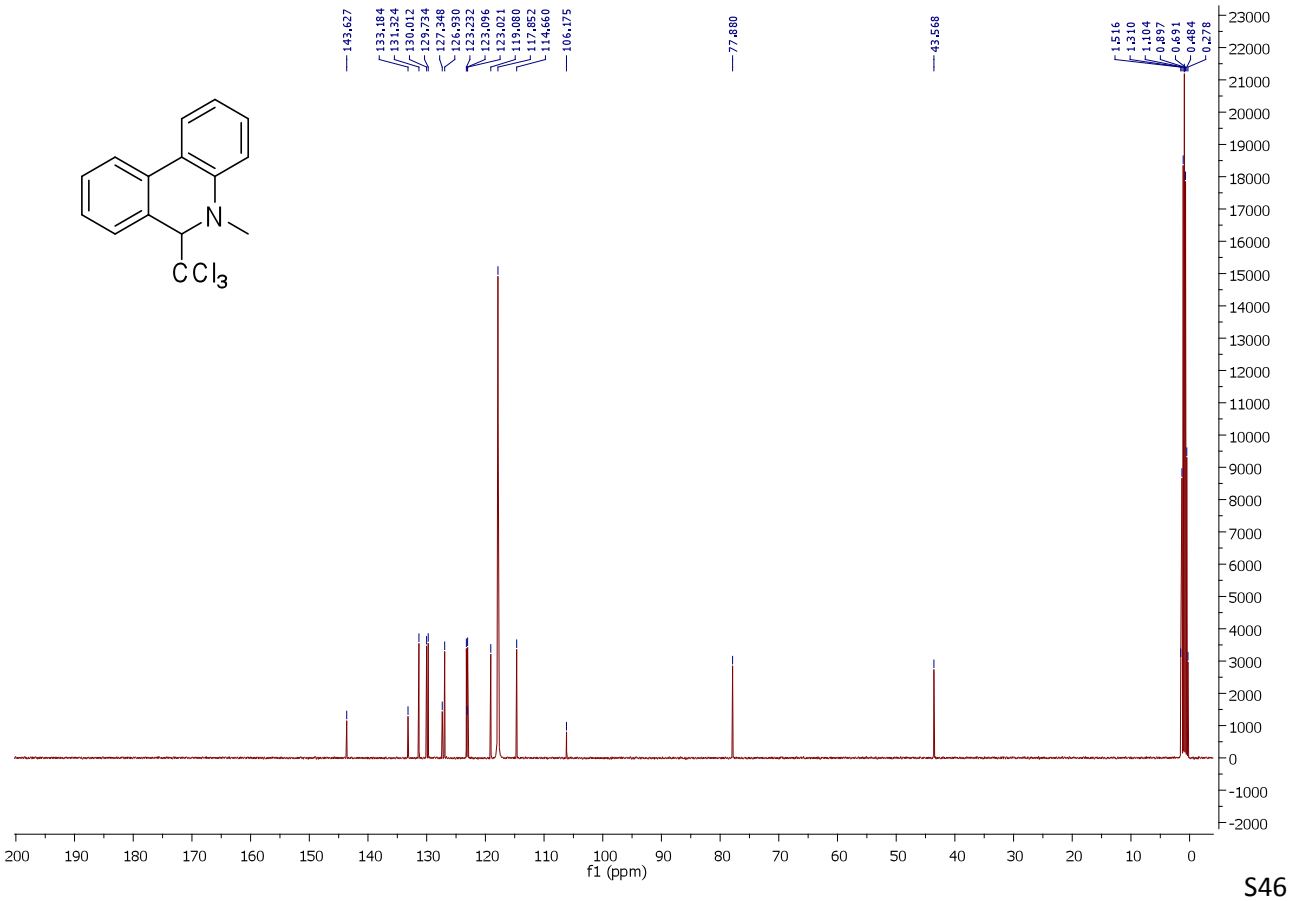



149.875
143.273
130.100
129.605
124.158
124.043
117.265
104.687
72.131
41.825
40.146
39.938
39.729
39.520
39.311
39.103
38.894
N
N
CCl3
f1 (ppm)

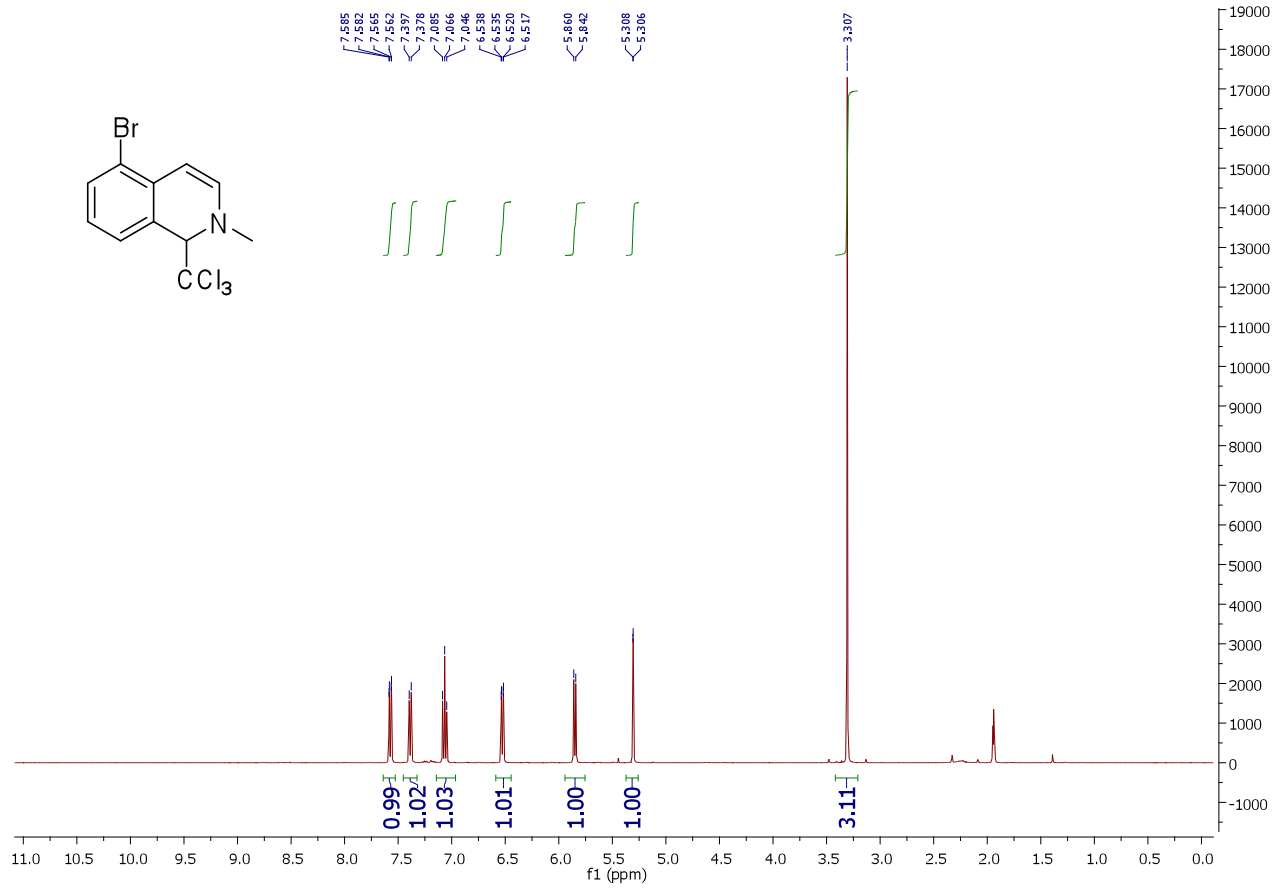

N
N
CCl3
f2 (ppm)
f1 (ppm)

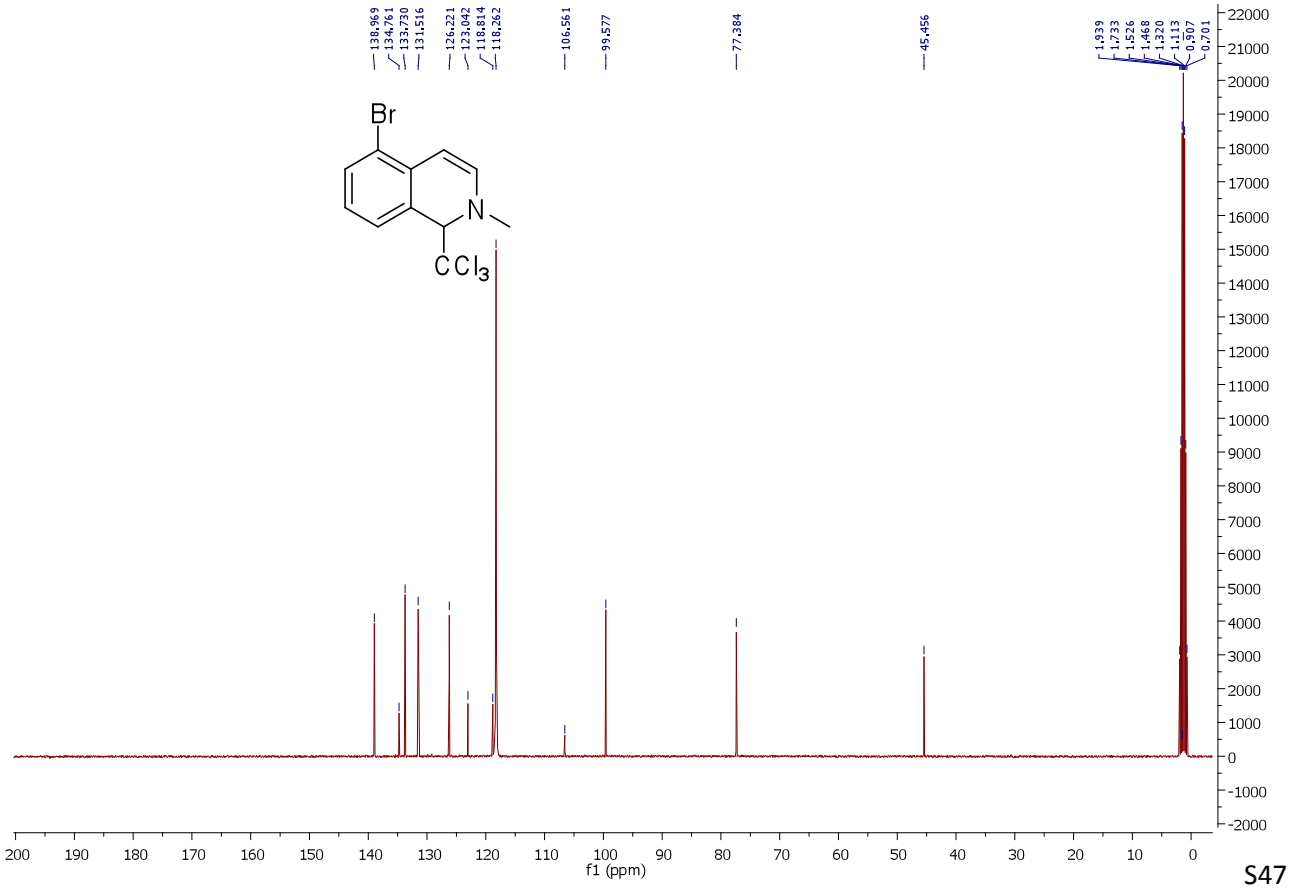
5-Methyl-6-(trichloromethyl)-5,6-dihydrophenanthridine (27)



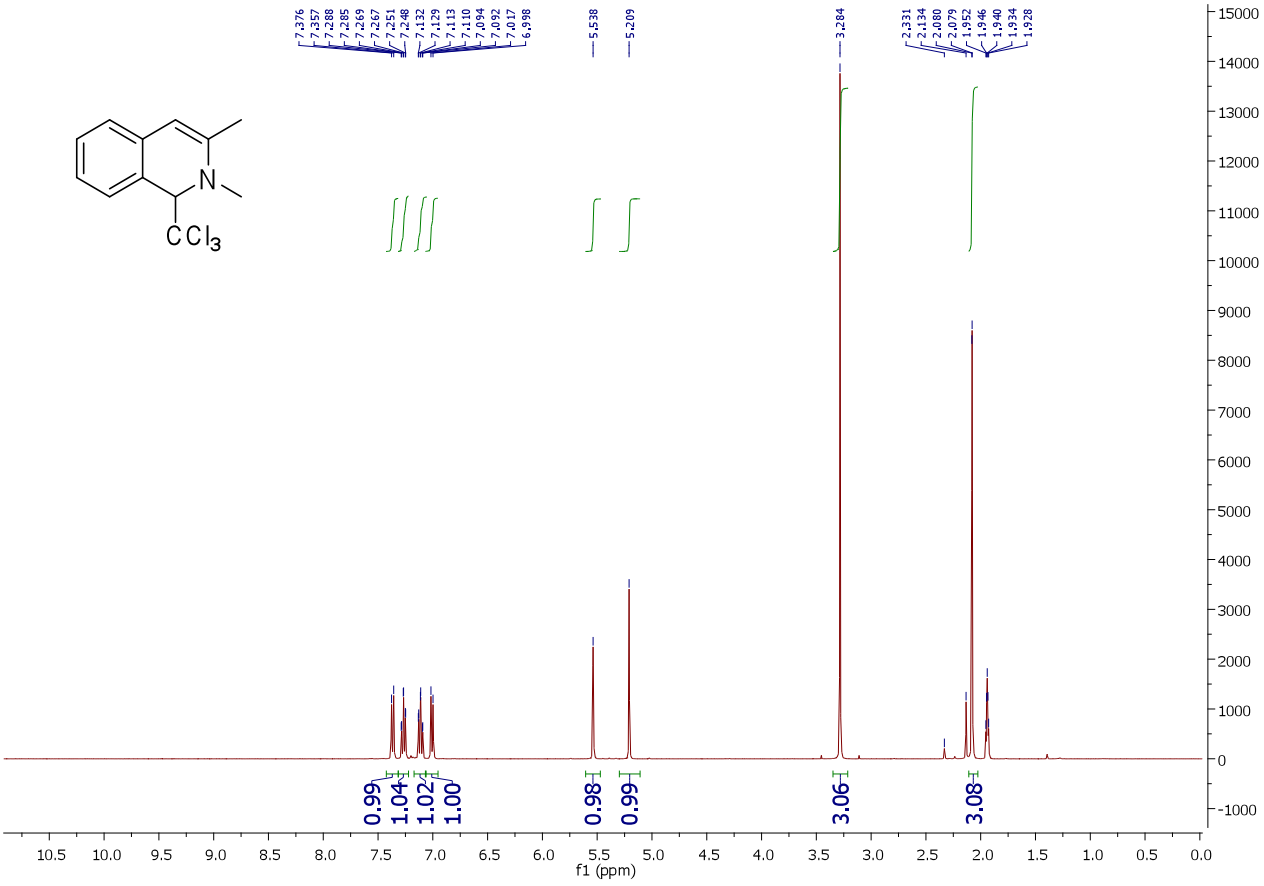


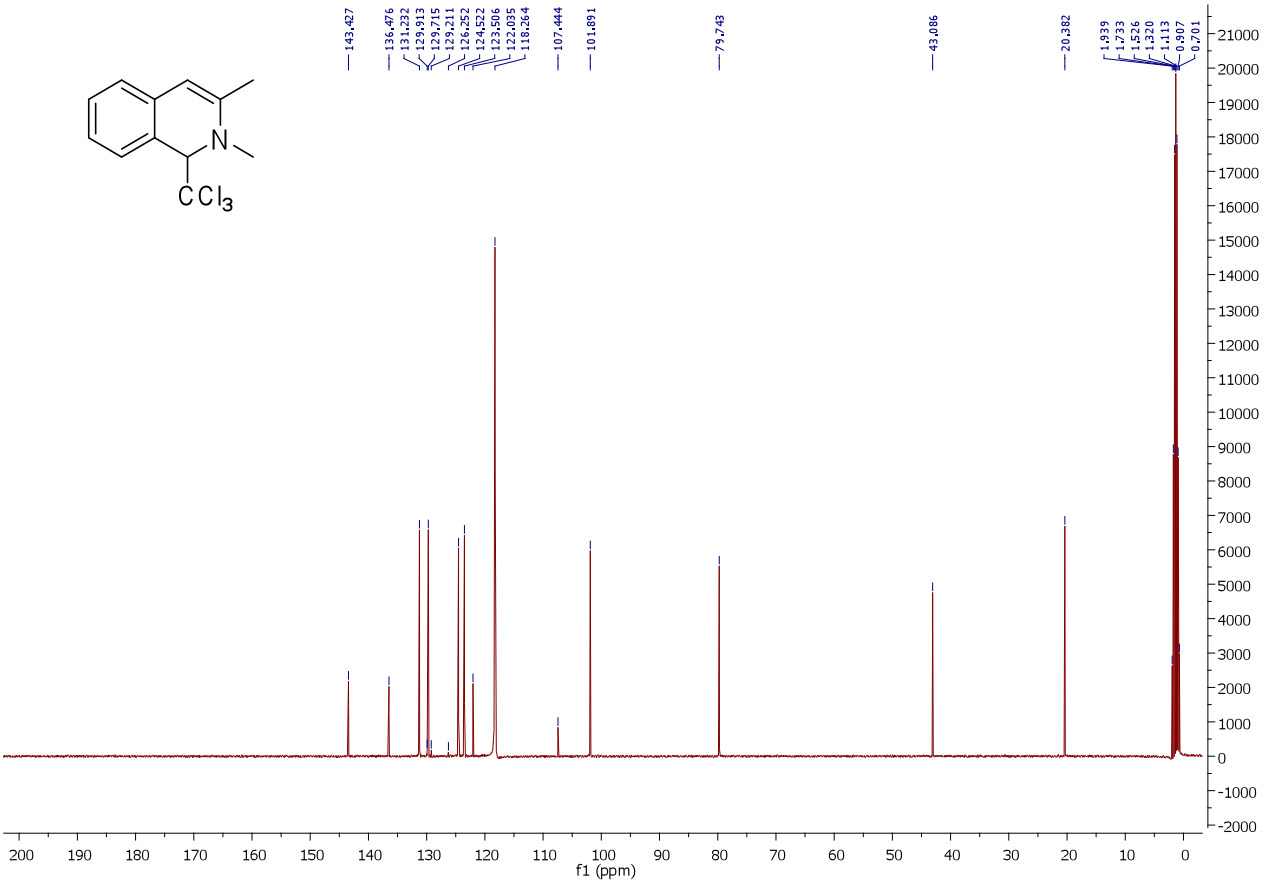
5-Bromo-2-methyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (28)



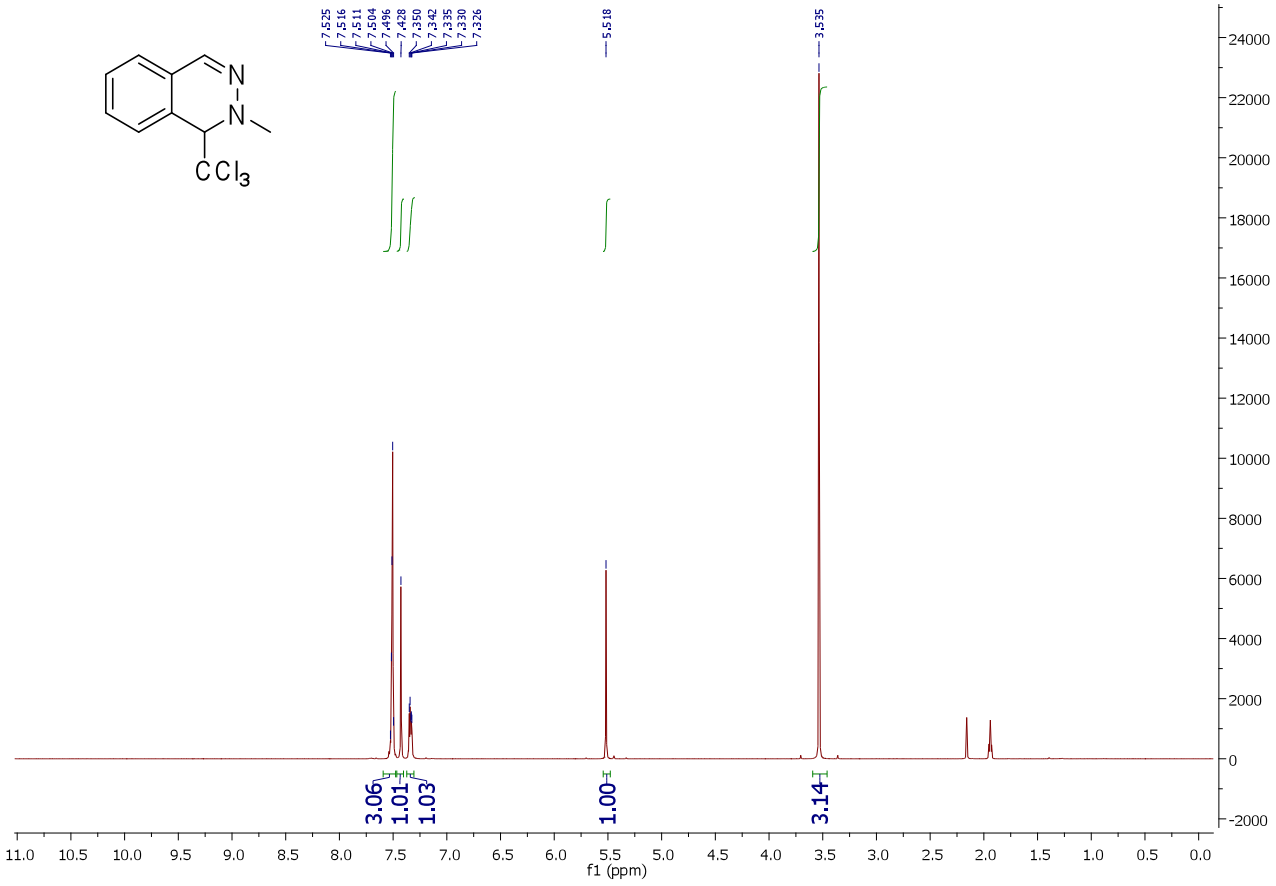


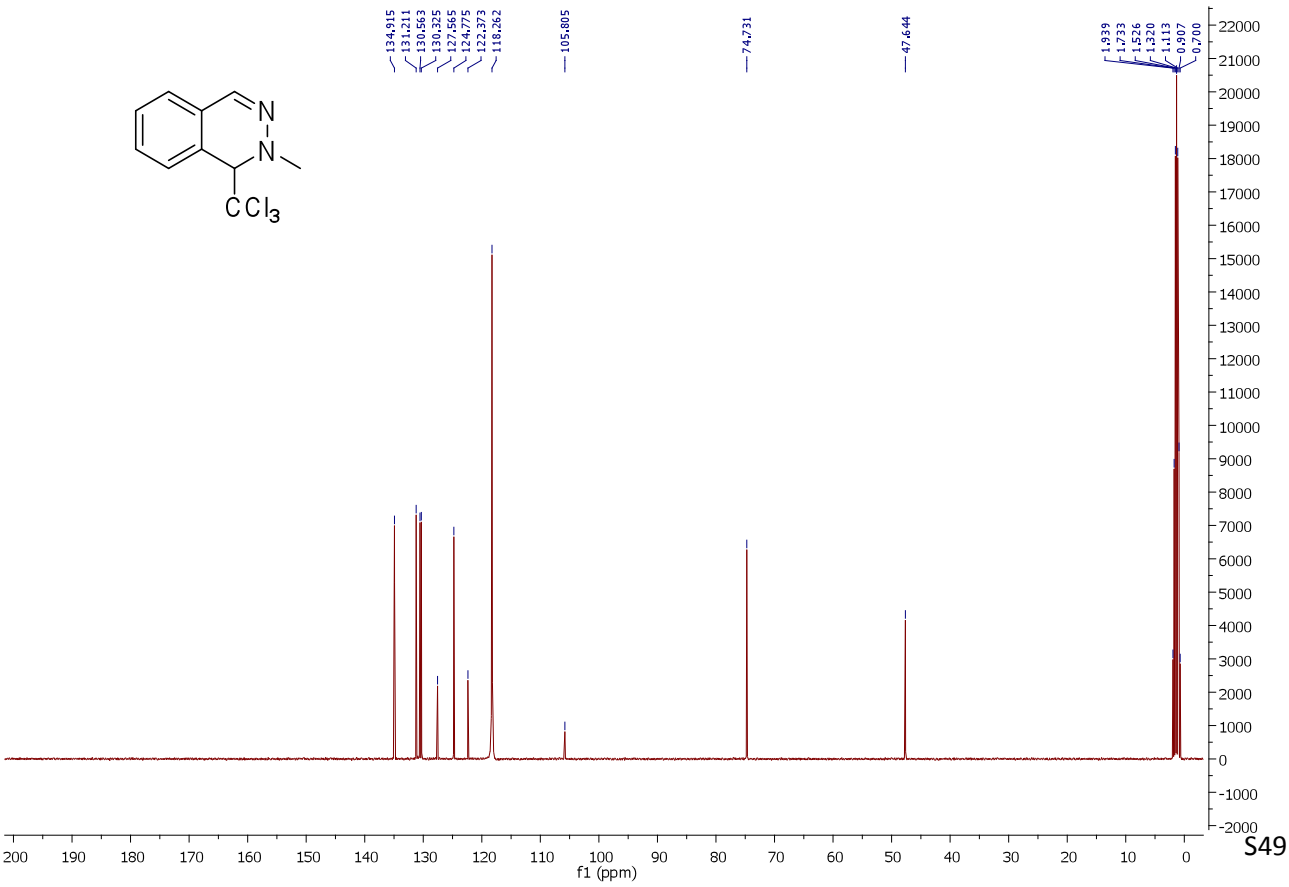
2,3-Dimethyl-1-(trichloromethyl)-1,2-dihydroisoquinoline (29)



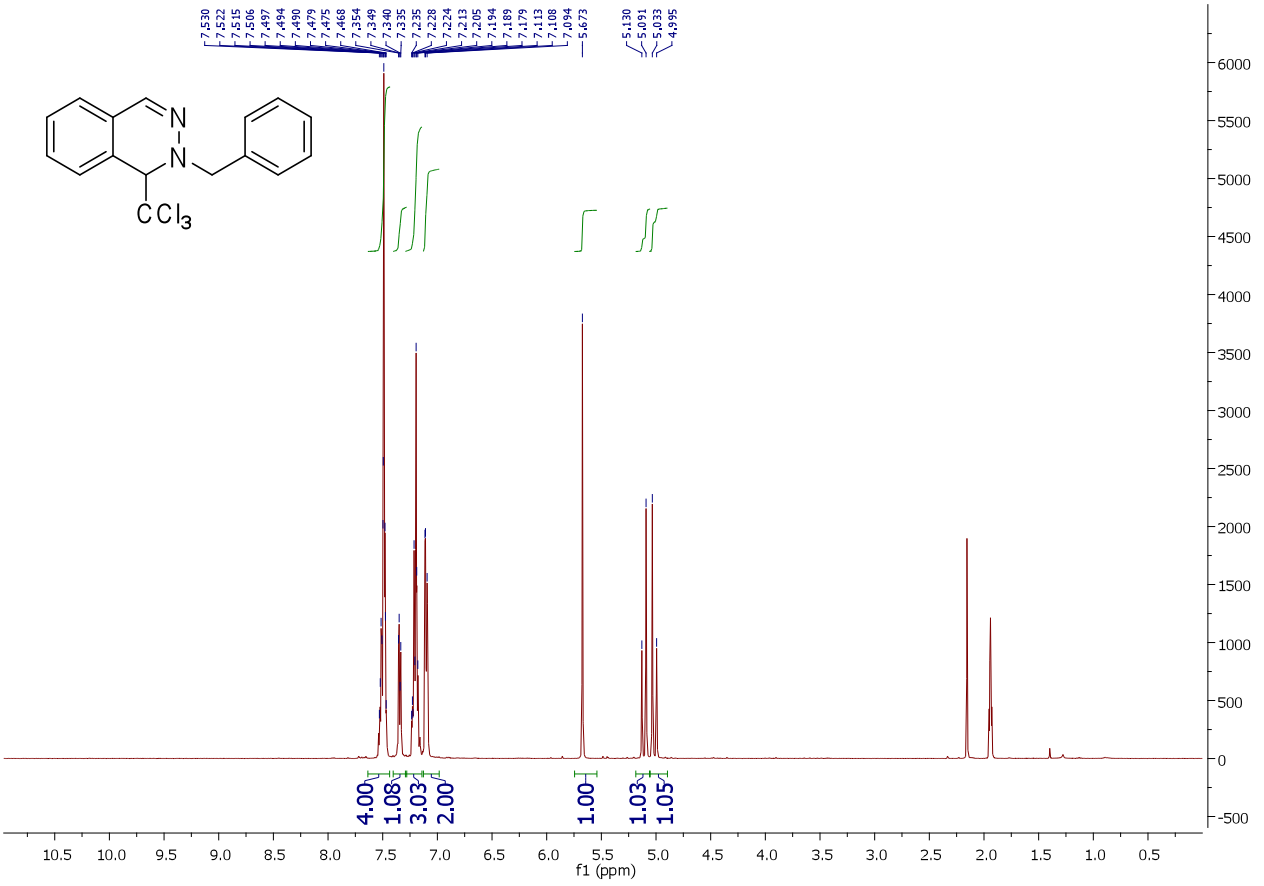


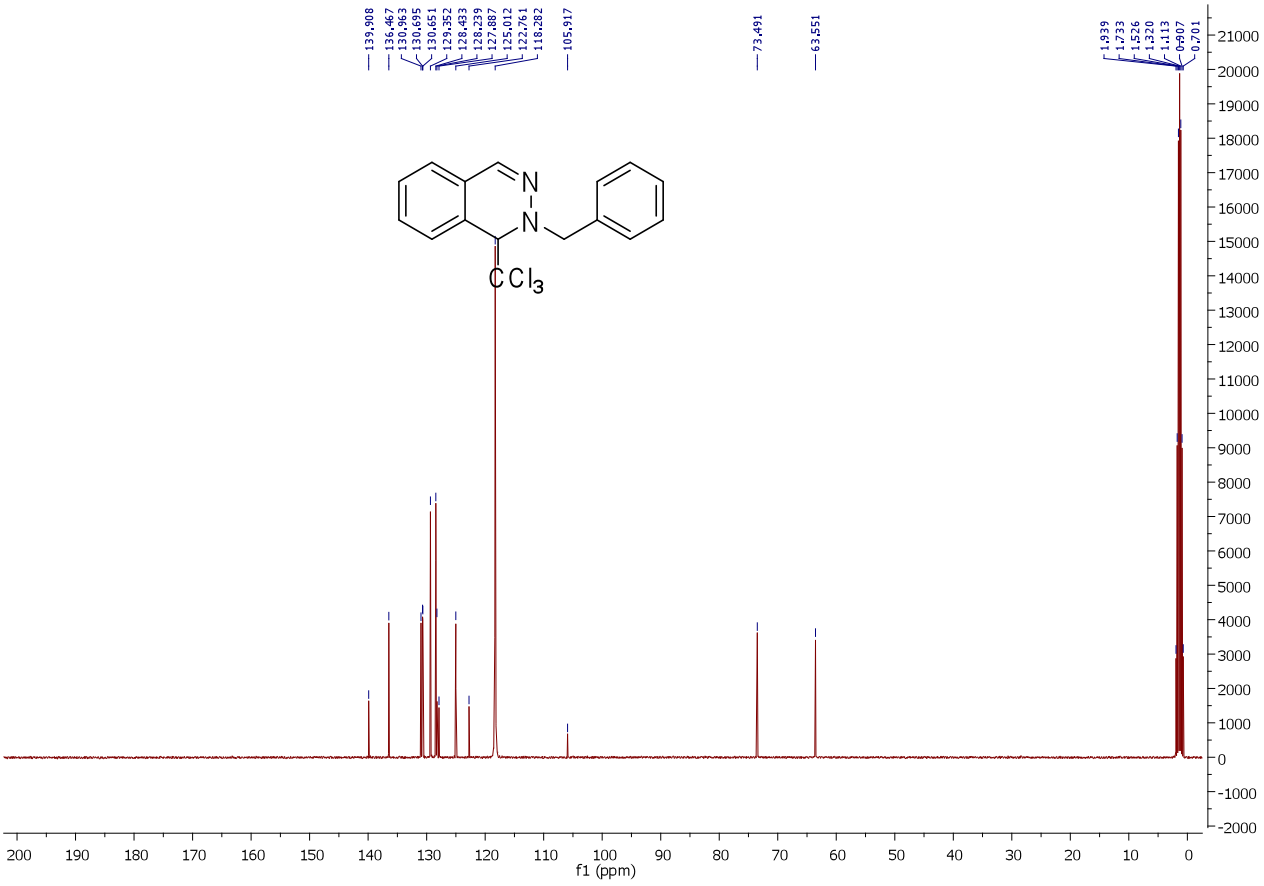
2-Methyl-1-(trichloromethyl)-1,2-dihydrophthalazine (30)



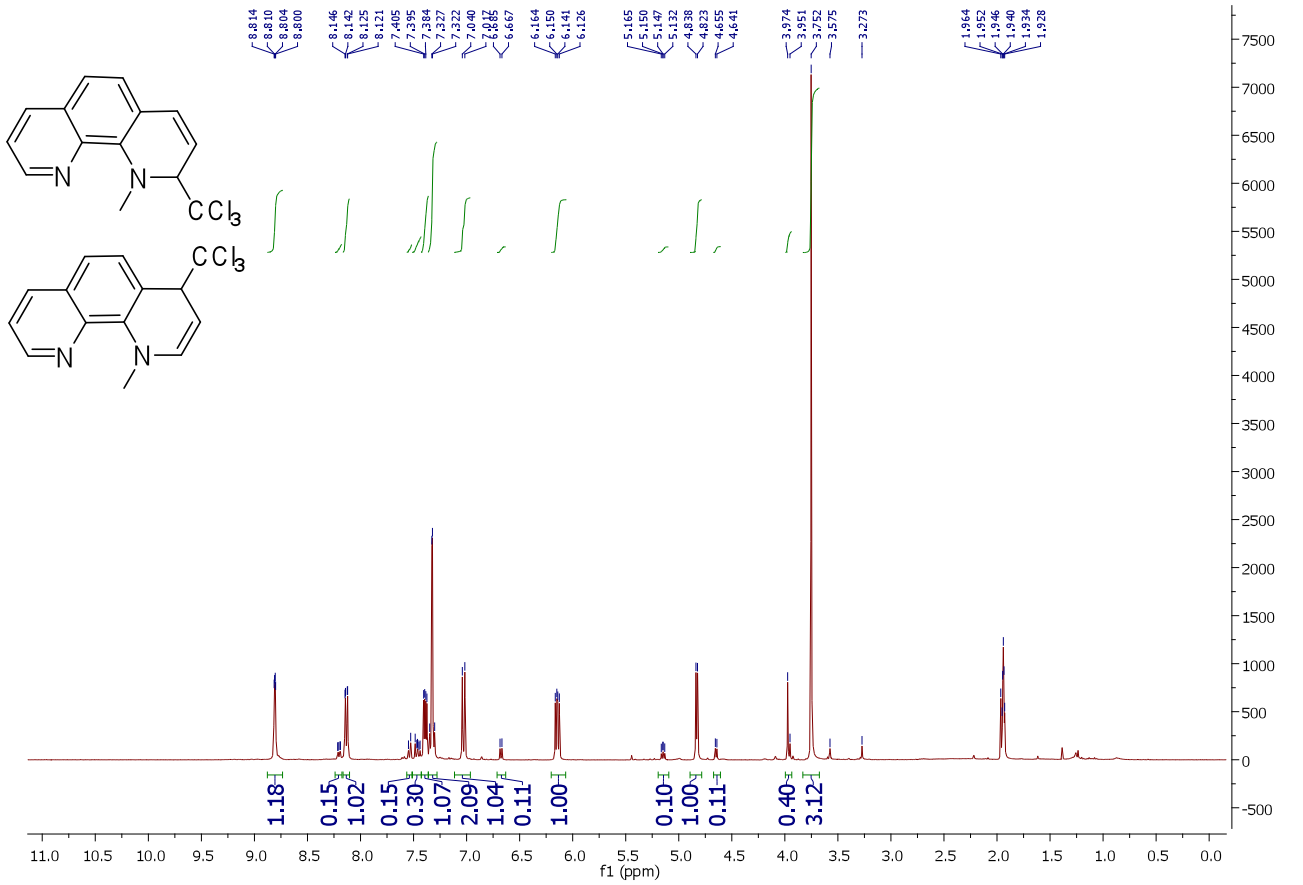


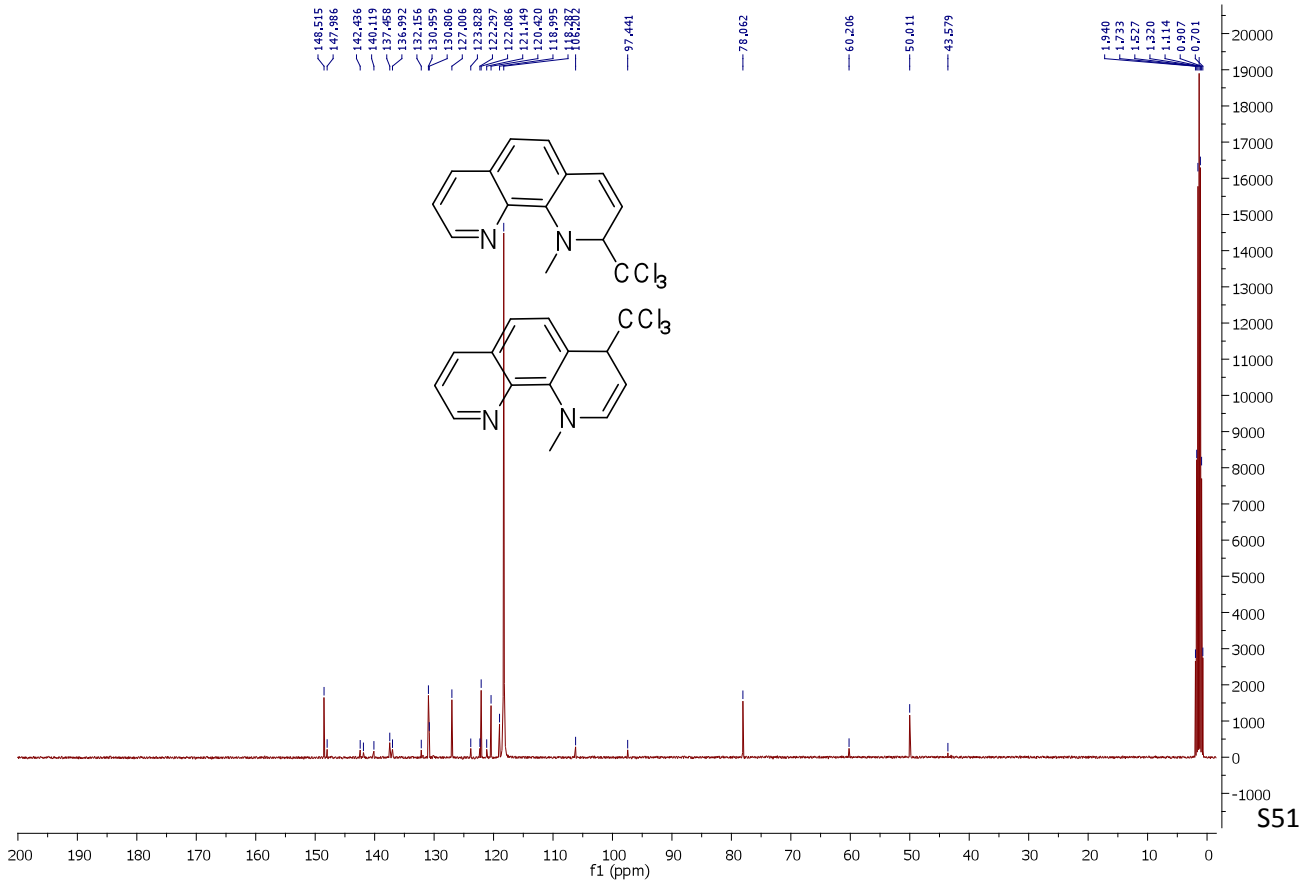
2-Benzyl-1-(trichloromethyl)-1,2-dihydrophthalazine (31)





1-Methyl-2-(trichloromethyl)-1,2-dihydro-1,10-phenanthroline and 1-methyl-4-(trichloromethyl)-1,4-dihydro-1,10- phenanthroline (32 + 33)





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[1] Carreon, J.R; Mahon, K.P; Kelley S.O; *Org. Lett.*, **2004**, 4, 517.

[2] Collischonn, C; Chemische Berichte, **1886**, 19, 2507.

[3] Dubois, M.G; Diaba F; Grellier-Marly, M.C, *Synthesis*, **1994**, 8, 800.

[4] Berenbold, G, *Justus liebigs Annalen der chemie*, **1978**, 1536.

[5] Asao, A.; Iso, K.; Yudha S. S. *Org. Lett.* **2006**, *8*, 4149.