

Supporting Information for

Nucleophilic Substitution of Hydrogen Facilitated by Quinone Methide Moieties in Benzo[*cd*]azulen-3-ones

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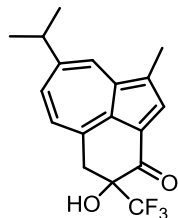
1. General information

All reactions were carried out using commercially available starting materials (Sigma-Aldrich, Schnelldorf, Germany; Fluka, Buchs, Switzerland and Alfa Aesar, Ward Hill, Massachusetts, USA) and solvents without further purification. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled under argon with sodium/benzophenone ketyl and dichloromethane with calcium hydride. Column chromatography was performed with Merck 230–400 mesh silica gel or with an automated Biotage high performance flash chromatography Sp4-system (Uppsala, Sweden) using a 0.1-mm path length flow cell UV-detector/recorder module (fixed wavelength 254 nm). Analytical thin layer chromatography (TLC) was carried out using 0.2-mm silica gel plates (silica gel 60, F₂₅₄, Merck KGaA, Darmstadt, Germany). The melting points were recorded with an Electrothermal capillary tube melting point apparatus (Bibby Scientific Limited, Staffordshire, UK) and are uncorrected. Nuclear magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on a Varian Mercury *Plus* 300 spectrometer (Agilent Technologies, Santa Clara, California, USA) or Bruker Ascent 400 (Bruker corporation, Billerica, Massachusetts, USA). ¹H NMR at 300 or 400 MHz and ¹³C NMR at 75 or 100 MHz. For CDCl₃, CD₂Cl₂, acetone-*d*₆, C₆D₆, and DMSO-*d*₆ the chemical shifts are reported in parts per million (ppm) and on the δ scale using the residual solvent peak of the NMR solvent as an internal reference [acetone-*d*₆: 2.05 (¹H), 29.84 (¹³C); C₆D₆: 7.16 (¹H), 128.1 (¹³C); CDCl₃: 7.24 (¹H), 77.16 (¹³C); CD₂Cl₂: 5.32 (¹H), 54.00 (¹³C); DMSO-*d*₆: 2.50 (¹H), 39.50 (¹³C)]. The coupling constants *J* are quoted in Hertz (Hz). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, integration, coupling constant(s)). The multiplicity was abbreviated as follows: br = broad signal, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, m_c = centered multiplet. High resolution mass spectra (HRMS) were measured on a Waters Synapt G2 (Waters Corporation, Milford, Massachusetts, USA) and reported for the molecular ions [M+H]⁺ or [M–H][–].

2. Experimental procedures and characterization data

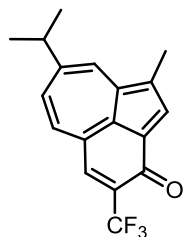
2.1 Synthesis of benzo[*cd*]azulen-3-one

4-Hydroxy-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-4,5-dihydro-3*H*-benzo[*cd*]azulen-3-one (**6**)



Guaiazulene (4.34 g, 21.9 mmol) was dissolved under argon in abs. diethyl ether (35 mL) and cooled to -16°C in a sodium chloride/acetone/ice bath. A solution of LDA in THF/heptane/ethylbenzene (2.0 M, 11.4 mL, 22.8 mmol, 1.05 equiv) was added and the reaction mixture was stirred for 25 min at -16°C . Methyl trifluoropyruvate (2.23 mL, 21.9 mmol, 1 equiv) was added fast via syringe and the reaction mixture was stirred for 45 min at -16°C . Diethyl ether (100 mL) was added and the organic phase was washed three times with water (70 mL). The solvent was removed at the rotary evaporator and the residue was dissolved in a mixture of THF, MeOH and water (2:1:1, 60 mL) and cooled to 0°C in an ice bath. Sodium hydroxide (1.23 g, 30.6 mmol, 1.4 equiv) was added and the reaction mixture was stirred for 2 hours at 0°C and for 6 hours at room temperature. Hexane (100 mL) was added and the organic phase was extracted once with water (100 mL) and twice with water (20 mL). The combined aqueous phases were washed three times with hexane (50 mL) and five times with diethyl ether (50 mL). The solvent of the combined organic phases was removed at the rotary evaporator and automated chromatography on silica gel (100% hexane) gave 496 mg (2.50 mmol) recovered starting material guaiazulene. The aqueous phase was acidified with 1 M hydrochloric acid and extracted with diethyl ether. The organic phase was washed five times with water (100 mL) until the aqueous phase remained neutral. The solvent was removed at the rotary evaporator and three times a small amount of chloroform was added to the residue and removed at the rotary evaporator. The residue was dissolved in chloroform (120 mL). *p*-TsOH (1.25 g, 6.57 mmol, 0.3 equiv) was added and the reaction mixture was stirred for 6 days at room temperature. Chloroform (50 mL) was added and the organic phase was washed three times with a saturated solution of sodium hydrogencarbonate in water (50 mL). The combined aqueous phases were re-extracted once with chloroform (20 mL) and the combined organic phases were washed four times with water (50 mL). The solvent was removed at the rotary evaporator and the residue was filtered with EtOAc through a small amount of silica gel (10 g). The solvent was removed at the rotary evaporator and the residue was dissolved in EtOAc (12 mL). Hexane (25 mL) was added and the product crystallized overnight in the refrigerator to yield **6** (2.66 g, 8.25 mmol, 38%) as dark violet crystals. The solvent of the mother liquor was removed at the rotary evaporator and the residue was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give additional **6** (1.11 g, 3.43 mmol), increasing the yield to 3.77 g (53%). Under consideration of consumed starting material, the total yield was 60%. ^1H NMR (300 MHz, DMSO- d_6): identical with reference.¹

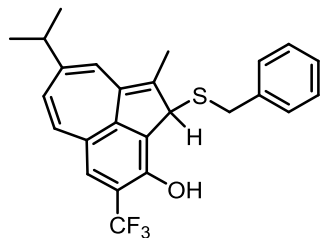
1-Methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (3)



4-Hydroxy-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-4,5-dihydro-3*H*-benzo[*cd*]azulen-3-one **6** (764 mg, 2.37 mmol) was dissolved in abs. pyridine (10 mL) under argon and cooled to 0 °C. Trifluoroacetic anhydride (346 μ L, 2.49 mmol, 1.05 equiv) was added, and the reaction mixture was stirred at 0 °C for 3.5 h. Crushed ice and 15 minutes later EtOAc were added to the reaction mixture. The organic phase was washed five times with water. The solvent was removed at the rotary evaporator. Toluene was added twice to the residue and removed at the rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **3** as brown needles (510 mg, 71%) and recovered starting material **6** (158 mg) increasing the yield to 89% with respect to the consumed starting material. ^1H NMR (300 MHz, C_6D_6): identical with reference.¹

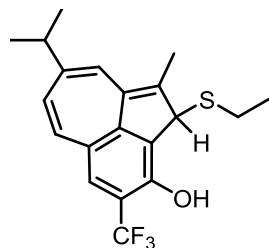
2.2.1 Conjugate addition of thiols towards protonated σ^{H} -adducts

2-(Benzylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-2*H*-benzo[*cd*]azulen-3-ol (7a)



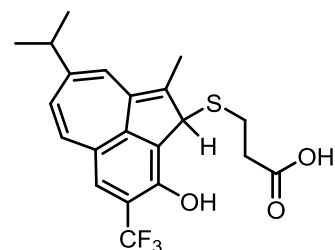
8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.10 g, 0.33 mmol) was dissolved in anhydrous ethanol (4 mL) and benzyl mercaptan (85 μ L, 0.66 mmol, 2 equiv) was added. The reaction mixture was stirred at room temperature under argon atmosphere until TLC analysis indicated the complete consumption of the green starting material (1.5 h) and formation of an orange product. The reaction mixture was evaporated, and the obtained crude product was purified by fast column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:8) to give **7a** as an orange solid (118 mg, 81%). M. p. 114–116 °C (dec.); ^1H NMR (300 MHz, C_6D_6): δ 7.28 (s, 1H), 7.03–6.88 (m, 4H), 6.84 (d, 1H, J = 1.5 Hz), 6.82 (m, 1H), 5.84 (s, 1H), 5.72 (d, 1H, J = 12.3 Hz), 5.33 (dd, 1H, J = 1.5 Hz, 12.3 Hz), 3.44 (s, 1H), 2.89 (d, 1H, J = 12.9 Hz), 2.81 (d, 1H, J = 12.9 Hz), 2.08 (sep, 1H, J = 6.9 Hz), 1.51 (d, 3H, J = 1.2 Hz), 0.98 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2): δ 152.1 (q, J = 2 Hz), 149.6, 144.6, 139.1, 137.7, 134.3, 132.3, 130.3 (m), 129.3, 129.3, 128.7, 128.7, 127.8, 127.6, 125.6, 124.1 (q, J = 271 Hz), 122.1, 122.0, 115.4 (q, J = 31 Hz), 52.9, 38.5, 32.6, 22.0, 22.0, 11.3 ppm; HRMS-APPI/APCI m/z : calc. for $\text{C}_{25}\text{H}_{22}\text{F}_3\text{OS}$ $[\text{M}-\text{H}]^-$: 427.1342, found 427.1371.

2-(Ethylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-2*H*-benzo[*cd*]azulen-3-ol (7b)



8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (53.5 mg, 176 μ mol) was dissolved in ethanol (2 mL) under argon. Ethanethiol (78.1 μ L, 1.05 mmol, 6 equiv) was added, and the reaction mixture was stirred in a sealed tube for 1.5 h at room temperature. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **7b** as a brown solid (51.1 mg, 80%). M. p. 73–75 °C (dec.); ^1H NMR (300 MHz, CD_2Cl_2): δ 7.58 (s, 1H), 7.04 (s, 1H), 6.00 (m, 1H), 5.99 (d, 1H, $J = 12.3$ Hz), 5.51 (dd, 1H, $J = 1.5$ Hz, $J = 12.3$ Hz), 4.32 (s, 1H), 2.28 (sep, 1H, $J = 6.8$ Hz), 2.09 (mc, 2H), 1.93 (s, 3H), 1.08 (t, 3H, $J = 7.5$ Hz), 1.07 (d, 6H, $J = 6.8$ Hz) ppm; ^{13}C NMR (75 MHz, acetone- d_6): δ 152.9 (q, $J = 1.7$ Hz), 150.2, 144.6, 138.5, 136.5, 133.0, 130.5 (q, $J = 5.1$ Hz), 130.1, 127.5, 125.6, 125.0 (q, $J = 270.1$ Hz), 122.5, 115.6 (q, $J = 30.4$ Hz), 52.7, 38.7, 22.1, 22.0, 21.6, 14.9, 11.5 ppm; HRMS-ESI m/z : calc. for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{OS}$ [$\text{M}-\text{H}$] $^-$: 365.1187, found 365.1188.

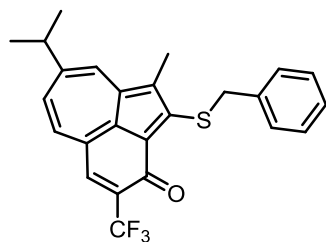
3-[(3-Hydroxy-8-isopropyl-1-methyl-4-(trifluoromethyl)-2*H*-benzo[*cd*]azulen-2-yl)thio]propanoic acid (7c)



8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.20 g, 0.65 mmol) was dissolved in anhydrous ethanol (4 mL) followed by addition of 3-mercaptopropionic acid (68 μ L, 0.80 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature under argon atmosphere until TLC analysis indicated the complete consumption of the green starting material (3 h) and formation of an intensively orange product. The reaction mixture was evaporated and the obtained crude product was purified by fast column chromatography on silica gel (eluent: EtOAc–*n*-hexane–AcOH 10:90:2) followed by recrystallization from acetone–*n*-hexane to give **7c** as an orange, crystalline powder (154 mg, 58%). M. p. 118–119 °C (dec.); ^1H NMR (300 MHz, CDCl_3): δ 7.31 (br s, 1H), 7.05 (s, 1H), 5.99 (d, 1H, $J = 12.3$ Hz), 5.97 (s, 1H), 5.51 (dd, 1H, $J = 1.8$ Hz, 12.3 Hz), 4.29 (s, 1H), 2.49–2.40 (m, 2H), 2.37–2.25 (m, 2H), 2.28 (sep, 1H, $J = 6.9$ Hz, overlapping), 1.92 d, (3H, $J = 0.9$ Hz), 1.08 (d, 6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 176.6, 151.8, 149.1, 144.6, 139.0, 133.3, 132.3, 130.4 (q, $J = 5.0$ Hz), 127.3, 127.3, 125.3, 123.7 (q, $J = 271.1$ Hz), 121.6, 115.7 (q, $J = 31.2$ Hz), 52.3, 38.8, 34.0, 22.1, 21.9, 21.8, 11.3 ppm; HRMS-APPI/APCI m/z : calc. for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{O}_3\text{S}$ [$\text{M}-\text{H}$] $^-$: 409.1085, found 409.1093.

2.2.2 Substitution of **3** with thiols via oxidative nucleophilic aromatic substitution of hydrogen (oxidative S_N^H)

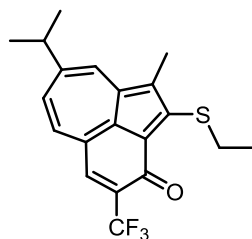
2-(Benzylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**8a**)



Reaction 1: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (40.0 mg, 0.132 mmol) was dissolved in anhydrous THF (3 mL) followed by addition of benzyl mercaptan (26 μ L, 0.20 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature under argon atmosphere until TLC analysis indicated the complete consumption of the green starting material (2 h) and formation of an orange product. The reaction mixture was cooled to 0 $^{\circ}$ C and 1,4-benzoquinone (22 mg, 0.20 mmol, 1.5 equiv) was added, and the reaction mixture stirred for additional 20 h. Then EtOAc (30 mL) was added and the organic phase was washed with aqueous NaOH (1.0 M, 2×10 mL). The phases were separated and the organic phase was washed with water (10 mL) and brine (10 mL). The combined aqueous phases were washed with EtOAc (20 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and evaporated to give the crude product, which was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:4) to give **8a** as a green solid (39 mg, 68%) and recovered starting material **3** (9 mg), increasing the yield to 90% based on recovered starting material.

Reaction 2: 2-(Benzylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-2*H*-benzo[*cd*]azulen-3-ol **7a** (75 mg, 0.17 mmol) was dissolved in anhydrous THF (3 mL) followed by addition of 1,4-benzoquinone (28 mg, 0.26 mmol, 1.5 equiv) and the reaction mixture was stirred for 2 d at room temperature. Then EtOAc (30 mL) was added, and the organic phase was washed with aqueous NaOH (1.0 M, 2×10 mL). The phases were separated and the organic phase was washed with water (10 mL) and brine (10 mL). The combined aqueous phases were washed with EtOAc (20 mL) and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and evaporated to give the crude material, which was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:4) to give **8a** as a green solid (22 mg, 30%) M. p. 114–116 $^{\circ}$ C (dec.); ^1H NMR (300 MHz, acetone- d_6): δ 8.53 (d, 1H, $J = 1.8$ Hz), 8.35 (q, 1H, $J = 1.2$ Hz), 8.26 (d, 1H, $J = 10.5$ Hz), 8.09 (dd, 1H, $J = 10.5$ Hz, 1.8 Hz), 7.35–7.10 (m, 5H), 4.70 (m, 2H), 3.48 (sep, 1H, $J = 6.9$ Hz), 2.57 (s, 3H), 1.46 (d, 6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (75 MHz, acetone- d_6): δ 174.1, 158.4, 150.8, 145.0, 140.9 (q, $J = 6.0$ Hz), 139.5, 137.1, 136.1, 135.5, 134.6, 134.4 (q, $J = 27.3$ Hz), 131.2, 130.8, 129.9, 129.9, 129.2, 129.2, 127.8, 124.8, 124.1 (q, $J = 271.2$ Hz), 40.6, 38.3, 24.6, 24.6, 11.1 ppm; HRMS-ESI m/z : calc. for $\text{C}_{25}\text{H}_{22}\text{F}_3\text{OS}$ $[\text{M}+\text{H}]^+$: 427.1343, found 427.1343.

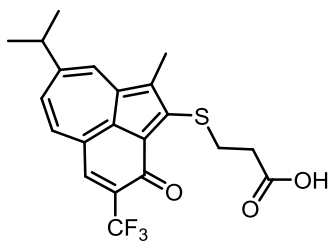
2-(Ethylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**8b**)



Reaction 1: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (63.1 mg, 207 μ mol) was dissolved under argon in THF (3 mL). Ethanethiol (76.8 μ L, 1.04 mmol, 5 equiv) was added, and the reaction mixture was stirred in a sealed tube 1.5 h at room temperature. 1,4-Benzoquinone (44.7 mg, 414 μ mol, 2 equiv) was added, and the resulting mixture was stirred in a sealed tube for 8 h at room temperature. The reaction mixture was diluted with EtOAc and washed once with aqueous NaOH (0.5 M) and three times with water until the aqueous phase remained neutral. The solvent was removed with a the rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **8b** as dark greenish grey needles (43.7 mg, 58%).

Reaction 2: 2-(Ethylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-2*H*-benzo[*cd*]azulen-3-ol **7b** (25.5 mg, 69.6 μ mol) was dissolved under argon in THF (1 mL). 1,4-Benzoquinone (8.3 mg, 77 μ mol, 1.1 equiv) was added and the resulting mixture was stirred for 5 h at room temperature. The reaction mixture was diluted with EtOAc and washed once with a 0.5 M solution of NaOH in water and three times with a mixture of water and brine (3:1) until the aqueous phase remained neutral. The solvent was removed with a the rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **8b** as dark greenish grey needles (11.7 mg, 46%). M. p. 128–129 °C; ^1H NMR (300 MHz, acetone-*d*₆): δ 8.54 (d, 1H, *J* = 1.5 Hz), 8.32 (s, 1H), 8.23 (d, 1H, *J* = 10.5 Hz), 8.07 (dd, 1H, *J* = 10.5 Hz, 1.5 Hz), 3.46 (m, 3H), 2.65 (s, 3H), 1.48 (d, 6H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 7.5 Hz), ppm; ^{13}C NMR (75 MHz, acetone-*d*₆): δ 173.8, 158.1, 152.2, 145.1, 140.9 (q, *J* = 6.1 Hz), 136.8, 136.1, 135.1, 134.2 (q, *J* = 27.2 Hz), 133.8, 130.4, 130.2, 124.1 (q, *J* = 271.0 Hz), 124.5, 40.6, 28.5, 24.6, 24.6, 15.6, 11.3 ppm; HRMS-ESI *m/z*: calc. for C₂₀H₂₀F₃OS [M+H]⁺: 365.1187, found 365.1184

3-[(8-Isopropyl-1-methyl-3-oxo-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-2-yl)thio]propanoic acid (**8c**)



8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.040 g, 0.13 mmol) was dissolved in anhydrous THF (3 mL) followed by addition of 3-mercaptopropionic acid (15 μ L, 0.19 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature under argon atmosphere until TLC analysis indicated the complete consumption of the green starting material (3.5 h) and formation of an orange product. Then reaction mixture was cooled to 0 °C and 1,4-benzoquinone (21 mg, 0.20 mmol, 1.5 equiv) was added and the reaction mixture stirred for additional 20 h. Then EtOAc (40 mL) was added, and the organic phase was washed several times with water (5 \times 10 mL) and brine (10 mL). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated to give the crude product, which was purified by column chromatography on silica gel (eluent: EtOAc-*n*-hexane 1:2 to \rightarrow EtOAc-*n*-hexane-AcOH 10:20:1) to give **8c** as a green solid (33 mg, 62%). M. p. 143–144 °C; ^1H NMR (300 MHz, acetone-*d*₆): δ 10.63 (br s, 1H), 8.60 (d, 1H, *J* = 1.8 Hz), 8.35 (s, 1H), 8.29 (d, 1H, *J* = 10.2 Hz), 8.12 (dd, 1H, *J* = 10.2 Hz, 1.8 Hz), 3.66 (t, 2H, *J* = 7.2 Hz), 3.47 (sep, 1H, *J* = 6.9 Hz), 2.66 (s, 3H), 2.58 (t, 2H, *J* = 7.2 Hz), 1.49 (d, 6H, *J* = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, acetone-*d*₆): δ 173.9, 172.8, 158.4, 150.4, 145.1, 140.9 (q, *J* = 6.1 Hz), 137.1, 136.2, 135.5, 134.6, 134.4 (q, *J* = 25.0 Hz, overlapping), 131.4, 130.9, 125.9, 124.0 (q, *J* = 271.1 Hz), 40.6, 35.4, 24.6, 24.6, 24.6, 11.2 ppm; HRMS-ESI *m/z*: calc. for C₂₁H₁₉F₃OS [M+H]⁺: 409.1085, found 409.1085.

2.3 Substitution of **3** with amines via oxidative nucleophilic aromatic substitution of hydrogen (oxidative S_N^H)

General procedure for the solvent-free amine addition with excess of amine. Method [a]

Unless otherwise noted, 8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (1.0 equiv) is mixed with amine (12.0–14.7 equiv) and shaken for 1.5–2.5 h at room temperature. The crude product is directly purified by column chromatography on silica gel and recrystallized if applicable.

General procedure for the amine addition with excess of amine in alcohol. Method [b]

Unless otherwise noted, 8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (1.0 equiv) and amine (2.0–8.0 equiv) are stirred under argon in ethanol (4–8 mL) at room temperature until TLC shows consumption of starting material. The solvent is evaporated, and the crude product is directly purified by column chromatography on silica gel.

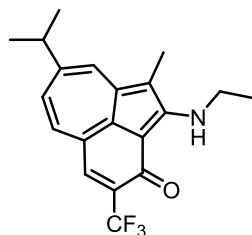
General procedure for the amine addition with 1,4-benzoquinone. Method [c]

Herein, all the oxidative S_N^H procedures using 1,4-benzoquinone (BQ) are regarded as reactions of Method [c]. The actual reaction conditions employed are described in detail in the respective synthesis procedures. The following is a suggested general procedure for the Method [c]. 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (1.0 equiv) is dissolved in THF (approx. 1 mL / 100 μ mol) and cooled to 0 °C. The respective amine (1 equiv) and 1,4-benzoquinone (1.0 equiv) are each dissolved separately in THF (approx. 1 mL / 100 μ mol) and transferred to syringes. The amine and BQ solutions are added to the azulene solution in portions of one fifth of the total volume at a time interval of 3 min. Starting with the amine solution, the first portion of the BQ solution is added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the BQ solution, the reaction mixture is stirred for another 30 min at 0 °C. The reaction is monitored by TLC, an appropriate amount of amine (2.0–3.0 equiv) is added and stirring is continued for 30–60 min at 0 °C. The solvent is evaporated, and the crude product is purified by manual or automated chromatography on silica gel. Unless an eluent mixture is given for manual chromatography, automated chromatography was performed using a gradient of increasing EtOAc starting with 100% *n*-hexane. Before or after column chromatography, the by-product hydroquinone can be removed by partitioning the crude product between EtOAc and aqueous NaOH (0.5–1 M) followed by washing neutral with water.

General procedure for the amine addition with silver(I) oxide. Method [d]

The following general procedure for the oxidative S_N^H with silver(I) oxide was used throughout the work only with minor deviations. 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (1.0 equiv) is dissolved in THF (approx. 2–3 mL / 100 μ mol) and cooled to 0 °C. Silver(I) oxide (5.0 equiv) is added to this solution, and the respective amine (1.0–1.4 equiv) is added directly to the formed suspension. The reaction mixture is stirred for approximately 30 min at 0 °C. According to TLC monitoring, an appropriate amount of amine (up to 0.7 equiv) is added, and stirring is continued for another 30–60 min. The solvent is evaporated, and the crude product is purified by manual or automated chromatography on silica gel. Unless an eluent mixture is given for manual chromatography, automated chromatography was performed using a gradient of increasing EtOAc starting with 100% *n*-hexane.

2-(Ethylamino)-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3H-benzo[*cd*]azulen-3-one (9a)

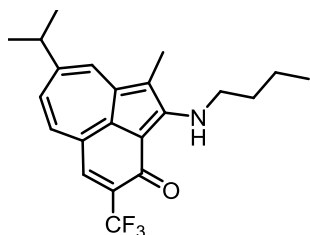


Method [b]: A 2 M solution of ethylamine in methanol (10.0 mL, 20.0 mmol, 12 equiv) was cooled to 0 °C. 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[*cd*]azulen-3-one **3** (0.500 g, 1.64 mmol) was added to this solution, and the reaction mixture was stirred for 30 min at 0 °C and for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel (eluent: hexane/EtOAc 5:2) to give **9a** as a brown solid (255 mg, 45%).

Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[*cd*]azulen-3-one **3** (26.5 mg, 87.1 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. A 2 M solution of ethylamine in methanol (43.6 μL, 87.2 μmol) and 1,4-benzoquinone (BQ, 9.4 mg, 86.9 μmol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 200 μL at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred for another 30 min at 0 °C. A 2 M solution of ethylamine in methanol (131 μL, 261 μmol, 3 equiv) was added to this mixture. After the reaction mixture was stirred for 30 min at 0 °C, a 2 M solution of ethylamine in methanol (43.6 μL, 87.2 μmol) was added, and after another 30 min another portion of the amine solution (43.6 μL, 87.2 μmol) was added. The reaction mixture was stirred for 30 min at 0 °C and diluted with EtOAc. The organic phase was washed once with a 0.5 M solution of NaOH in water and twice with an equimixture of water and brine. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9a** as a brown solid (21.0 mg, 70%).

Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[*cd*]azulen-3-one **3**: 20.6 mg (67.7 μmol), 2 M ethylamine in MeOH: 33.8 μL (67.7 μmol, 1.0 equiv) + 16.9 μL (33.9 μmol, 0.5 equiv) after 30 min, Ag₂O: 78.4 mg (338 μmol, 5 equiv). **9a**: 21.1 mg (90%), a brown solid. M. p. 177 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.90 (br t, 1H, *J* = 5.8 Hz), 8.14 (s, 1H), 7.66 (s, 1H), 7.63 (d, 1H, *J* = 11.2 Hz), 7.13 (d, 1H, *J* = 11.2 Hz), 3.92 (dq_≈quin, 2H, *J* = 7.0 Hz), 3.10 (sep, 1H, *J* = 6.8 Hz), 2.46 (s, 3H), 1.35 (t, 3H, *J* = 7.2 Hz), 1.30 (d, 6H, *J* = 6.8 Hz) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 172.5, 163.4, 154.8, 147.1, 140.4 (q, *J* = 5.6 Hz), 136.5, 134.8, 128.2 (q, *J* = 27.1 Hz), 127.0, 124.4, 123.6 (q, *J* = 271.1 Hz), 120.8, 111.3, 109.5, 39.3, 23.8, 23.8, 23.8, 16.1, 10.9. ppm; HRMS-ESI *m/z*: calc. for C₂₀H₂₁F₃NO [M+H]⁺: 348.1575, found 348.1578.

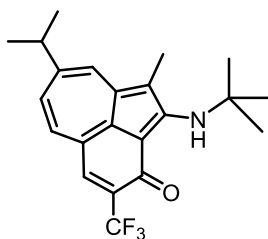
2-(Butylamino)-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3H-benzo[*cd*]azulen-3-one (9b)



Method [a]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.600 g, 1.97 mmol) was mixed with *n*-butylamine (2.00 mL, 20.2 mmol, 14.7 equiv) and shaken for 1.5 h at room temperature. The mixture was diluted with toluene, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (eluent: PhMe/EtOAc: 9:1) and recrystallized from hot MeOH to give **9b** as brown needles (307 mg, 42%).

Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (24.1 mg, 79.2 μ mol) was dissolved in THF (1 mL) in a round-bottomed flask and cooled to 0 °C. *n*-Butylamine (7.9 μ L, 79 μ mol) and BQ (8.6 mg, 79 μ mol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 200 μ L at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution the reaction mixture was stirred for another 15 min at 0 °C. *n*-Butylamine (7.9 μ L, 79 μ mol) was added, and after another 30 min another equivalent of *n*-butylamine (7.9 μ L, 79 μ mol) was added. Stirring of the reaction mixture was continued for 1.5 h. The reaction mixture was diluted with EtOAc, washed once with a 1 M solution of NaOH in water and twice with a mixture of water and brine (4:1). The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9b** as brown needles (22.8 mg, 77%). M. p. 112 °C; ^1H NMR (300 MHz, DMSO-*d*₆): δ 9.98 (t, 1H, *J* = 5.7 Hz), 8.14 (d, 1H, *J* = 1.5 Hz), 7.67 (s, 1H), 7.64 (d, 1H, *J* = 11.2 Hz), 7.14 (d, 1H, *J* = 1.5 Hz, *J* = 11.2 Hz), 3.89 (dt \approx q, 2H, *J* = 6.8 Hz), 3.11 (sep, 1H, *J* = 6.8 Hz), 2.47 (s, 3H), 1.77 – 1.66 (m, 2H), 1.52 – 1.39 (m, 2H), 1.30 (d, 6H, *J* = 6.8 Hz), 0.96 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-*d*₆): δ 172.5, 163.6, 154.8, 147.1, 140.3 (q, *J* = 5.1 Hz), 136.4, 134.7, 128.1 (q, *J* = 27.3 Hz), 127.0, 124.3, 123.5 (q, *J* = 273.4 Hz), 120.7, 111.3, 109.3, 43.8, 32.3, 23.7, 23.7, 23.7, 19.3, 13.5, 10.9 ppm; HRMS-ESI *m/z*: calc. for C₂₂H₂₅F₃NO [M+H]⁺: 376.1888, found 376.1887.

2-(*tert*-Butylamino)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9c**)

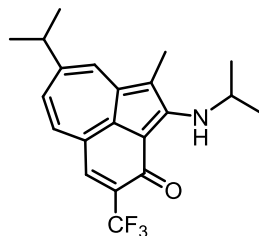


Method [b]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (74 mg, 0.24 mmol) was dissolved in ethanol (4 mL) and *tert*-butylamine (51 μ L, 0.49 mmol, 2 equiv) was added. The reaction mixture was stirred for 24 h at room temperature under argon atmosphere, after which TLC indicated the complete consumption of **3** and formation of less polar dark grey product along with side products. Solvents were evaporated, and the crude product purified by column chromatography on silica gel (eluent: EtOAc-*n*-hexane: 1:8→1:3) to give **9c** as a dark grey solid (7 mg, 8%).

Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.020 g, 0.066 mmol); THF (3 mL); *tert*-butylamine (10 μ L, 1.4 equiv); Ag₂O (77 mg, 0.33 mmol, 5 equiv); the crude product purified by column chromatography on silica gel (eluent: EtOAc-*n*-hexane: 1:8→1:3) to give **9c** (23 mg, 95%). M. p. 185–187 °C; ^1H NMR (300 MHz, CDCl₃): δ 11.18 (br s, 1H), 7.87 (d, 1H, *J* = 0.9 Hz), 7.61 (d, 1H, *J* = 1.5 Hz), 7.42 (d, 1H, *J* = 11.1 Hz), 7.07 (dd, 1H, *J* = 1.8 Hz, 11.1 Hz), 3.08 (sep, 1H, *J* = 6.9 Hz), 2.57 (s, 3H), 1.67 (s, 9H), 1.37 (d, 6H, *J* = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, CDCl₃): δ 174.0, 164.2, 155.8, 150.6, 139.6 (q, *J* = 6.2 Hz), 136.5, 135.5, 130.2 (q, *J* = 28.2 Hz), 127.2, 124.8, 123.7 (q, *J* = 270.1 Hz),

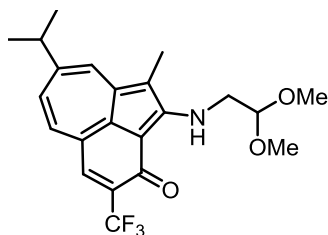
121.5, 113.8, 107.2, 53.5, 40.5, 31.7, 31.7, 31.7, 24.3, 24.3, 13.8 ppm; HRMS-ESI m/z : calc. for $C_{22}H_{25}F_3NO$ $[M+H]^+$: 376.1888, found 376.1898.

2-(Isopropylamino)-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one (9d)



Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one **3** (45.1 mg, 148 μ mol) was dissolved in THF (2 mL) in a round-bottomed flask and cooled to 0 °C. Isopropylamine (12.1 μ L, 148 μ mol) and 1,4-benzoquinone (BQ) (16.0 mg, 148 μ mol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 200 μ L at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred for another 30 min at 0 °C. Isopropylamine (24.1 μ L, 296 μ mol, 2 equiv) was added to the reaction mixture, and stirring was continued for 30 min at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9d** as a dark grey solid (45.3 mg, 85%). M. p. 141.0 °C; 1H NMR (300 MHz, DMSO- d_6): δ 9.97 (d, 1H, J = 9.3 Hz), 8.16 (q \approx d, 1H, J = 1.1 Hz), 7.72 (d, 1H, J = 1.5 Hz), 7.67 (d, 1H, J = 11.2 Hz), 7.17 (dd, 1H, J = 1.5 Hz, J = 11.2 Hz), 4.57 (m $_c$, 1H), 3.13 (sep, 1H, J = 6.8 Hz), 2.49 (s, 3H), 1.41 (d, 6H, J = 6.4 Hz), 1.32 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, DMSO- d_6): δ 172.5, 162.4, 155.0, 147.4, 140.3 (q, J = 5.6 Hz), 136.3, 134.9, 128.2 (q, J = 27.0 Hz), 127.1, 124.5, 123.4 (q, J = 273.0 Hz), 120.9, 111.2, 108.8, 45.8, 39.2, 23.9, 23.9, 23.7, 23.7, 10.8 ppm; HRMS-ESI m/z : calc. for $C_{21}H_{23}F_3NO$ $[M+H]^+$: 362.1732, found 362.1733.

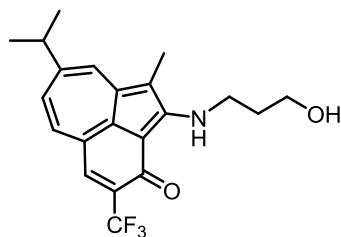
2-[(2,2-Dimethoxyethyl)amino]-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one (9e)



Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one **3** (51.0 mg, 166 μ mol) was dissolved in THF (2 mL) in a round-bottomed flask and cooled to 0 °C. 2,2-Dimethoxyethylamine (18.1 μ L, 166 μ mol) and 1,4-benzoquinone (BQ, 17.9 mg, 166 μ mol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and the BQ solutions were added to the azulene solution in portions of 200 μ L at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred for another 30 min at 0 °C. 2,2-Dimethoxyethylamine (36.2 μ L, 332 μ mol, 2 equiv) was added, and stirring was continued for 30 min at 0 °C. 2,2-Dimethoxyethylamine (18.1 μ L, 166 μ mol) was added, and stirring was continued for 1 h at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane. The solvents of the resulting

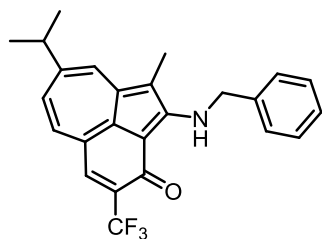
fractions were evaporated and the residue was dissolved in EtOAc. The resulting solution was washed with a 0.5 M solution of NaOH in water and twice with water. The solvent was evaporated to give **9e** as dark greenish grey needles (52.9 mg, 78%). M. p. 168 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.04 (bs, 1H), 7.85 (q≈d, 1H, *J* = 1.2 Hz), 7.61 (d, 1H, *J* = 1.3 Hz), 7.39 (d, 1H, *J* = 11.1 Hz), 7.09 (dd, 1H, *J* = 1.6 Hz, *J* = 11.1 Hz), 4.65 (t, 1H, *J* = 5.4 Hz), 3.99 (dd, 2H, *J* = 5.4 Hz, *J* = 6.6 Hz), 3.48 (s, 6H), 3.07 (sep, 1H, *J* = 6.9 Hz), 2.50 (s, 3H), 1.37 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 174.3, 164.3, 155.1, 148.4, 140.2 (q, *J* = 5.6 Hz), 136.7, 134.8, 130.3 (q, *J* = 27.8 Hz), 127.6, 124.8, 123.5 (q, *J* = 273.2 Hz), 122.0, 112.8, 108.8, 103.2, 55.0, 47.0, 40.4, 24.3, 24.3, 11.6 ppm; HRMS-ESI *m/z*: calc. for C₂₂H₂₅F₃NO₃ [M+H]⁺: 408.1787, found 408.1787.

2-[(3-Hydroxypropyl)amino]-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9f)



Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (102 mg, 0.34 mmol) was dissolved in THF (5 mL) in a round-bottomed flask and cooled to 0 °C. 1,3-Aminopropanol (26 μL, 0.34 mmol) and BQ (36 mg, 0.34 mmol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 200 μL at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred for another 30 min at 0 °C. 1,3-aminopropanol (52 μL, 0.68 mmol, 2 equiv) was added to the mixture, and stirring was continued for 1 h at 0 °C. The solvent was evaporated, and the crude product was purified by column chromatography on silica gel gel (eluent: EtOAc–*n*-heptane: 1:1→3:1) to give **9f** as brown needles (96 mg, 75%). M. p. 227 °C; ¹H NMR (400 MHz, CDCl₃): δ 10.14 (br s, 1H), 7.83 (s, 1H), 7.54 (d, 1H, *J* = 1.2 Hz), 7.35 (d, 1H, *J* = 11.2 Hz), 7.03 (dd, 1H, *J* = 11.2 Hz, 1.2 Hz), 4.04 (q, 2H, *J* = 6.4 Hz), 3.88 (t, 2H, *J* = 6.0 Hz), 3.08 (sep, 1H, *J* = 6.9 Hz), 2.49 (s, 3H), 2.05 (2Hm pentet, *J* = 6.4 Hz), 1.36 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 174.0, 164.7, 155.2, 148.7, 140.1 (q, *J* = 5.5 Hz), 137.0, 134.9, 129.9 (q, *J* = 27.6 Hz), 127.4, 124.5, 123.6 (q, *J* = 271.5 Hz), 121.7, 119.5, 112.7, 109.2, 59.5, 41.9, 40.4, 33.1, 24.2, 24.2, 11.4 ppm; HRMS-ESI *m/z*: calc. for C₂₁H₂₂F₃NO₂ [M+H]⁺: 378.1681, found 378.1682.

2-(Benzylamino)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9g)

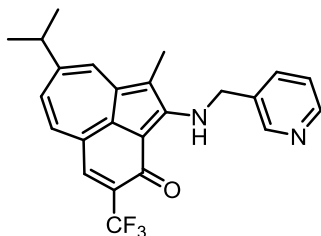


Method [b]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.080 g, 0.26 mmol) was dissolved in ethanol (5 mL) and benzylamine (150 μL, 0.65 mmol, 2.5 equiv) was added. The reaction mixture was stirred for 19 h at room temperature under argon atmosphere, after which TLC indicated the complete consumption of **3** and formation of a less polar dark grey product. Solvents were evaporated and

the resulting crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:4) to give **9g** as a dark grey solid (38 mg, 36%).

Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (20.0 mg, 0.066 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. Benzylamine (7.2 µL, 0.066 mmol) and benzoquinone (7.1 mg, 0.066 mmol) were each dissolved in THF (1 mL) and transferred each to a 1-mL syringe. The amine and the benzoquinone solutions were added to the azulene solution in portions of 200 µL at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later and the second portion of the amine solution another 3 min later. After the last portion of the quinone solution was added, the reaction mixture was stirred for another 30 min at 0 °C. Benzylamine (14.4 µL, 0.132 mmol) was added and stirring was continued for 2 h. The reaction mixture was diluted with EtOAc and washed aqueous NaOH (1.0 M, 2 × 10 mL). The phases were separated and the organic phase was washed with water (10 mL) and brine (10 mL). The combined aqueous phases were washed with EtOAc (20 mL), and the combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated to give the crude product, which was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:4) to give **9g** as a dark grey solid (22 mg, 83%). M. p. 155–157 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.34 (br s, 1H), 7.89 (d, 1H, *J* = 0.9 Hz), 7.62 (d, 1H, *J* = 1.5 Hz), 7.44 (d, 1H, *J* = 11.1 Hz), 7.38–7.28 (m, 5H), 7.12 (dd, 1H, *J* = 1.5 Hz, 11.1 Hz), 5.07 (s, 1H), 5.05 (s, 1H), 3.08 (sep, 1H, *J* = 6.9 Hz), 2.44 (s, 3H), 1.37 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 174.5, 164.3, 155.4, 148.7, 140.3 (q, *J* = 6.0 Hz), 140.0, 137.5, 136.8, 135.0, 129.2, 129.2, 128.1, 127.8, 127.1, 127.1, 124.9, 123.5 (q, *J* = 272 Hz), 122.3, 112.8, 108.7, 48.8, 40.5, 24.3, 24.3, 11.3 ppm; HRMS-ESI *m/z*: calc. for C₂₅H₂₃F₃NO [M+H]⁺: 410.1732, found 410.1747.

8-Isopropyl-1-methyl-2-[(pyridin-3-ylmethyl)amino]-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9h**)**

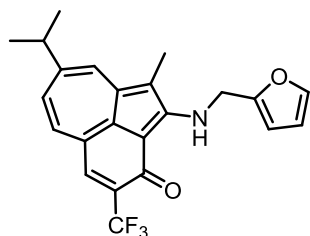


Method [b]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.080 g, 0.26 mmol) was dissolved in ethanol (5 mL) and 3-picolylamine (108 µL, 1.08 mmol, 4 equiv) was added. The reaction mixture was stirred for 3 d at room temperature under argon atmosphere, after which TLC indicated the complete consumption of **3** and formation of polar dark grey product. Solvents were evaporated, and the crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 3:4 → EtOAc 100%) to give **9h** as a dark grey solid (25 mg, 23%).

Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.020 g, 0.066 mmol) was dissolved in THF (1 mL) and cooled to 0 °C. 3-Picolylamine (7.0 µL, 0.066 mmol) and 1,4-benzoquinone (7.1 mg, 0.066 mmol) were each dissolved in THF (1 mL) and transferred each to a 1-mL syringe. The amine and the benzoquinone solutions were added to the azulene solution in portions of 200 µL at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later and the second portion of the amine solution another 3 min later. After the last portion of the quinone solution was added, the reaction mixture was stirred for another 30 min at 0 °C. 3-Picolylamine (14.0 µL, 0.14 mmol) was added and stirring was continued for 2 h. The reaction mixture was diluted with EtOAc and washed with aqueous NaOH (1.0 M, 2 × 10 mL). The phases were separated and the organic phase was washed with water (10 mL) and brine (10 mL). The combined aqueous phases were washed with EtOAc (20 mL) and the combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated to give the crude material, which was purified by column chromatography on silica gel (eluent: EtOAc 100%) to give **9h** as a

dark grey solid (22 mg, 81%). M. p. 177–178 °C; ^1H NMR (300 MHz, CDCl_3): δ 10.27 (br, s, 1H), 8.65 (s, 1H), 8.58 (d, 1H, $J = 4.5$ Hz), 7.92 (s, 1H), 7.73 (d, 1H, $J = 8.1$ Hz), 7.67 (s, 1H), 7.49 (d, 1H, $J = 11.1$ Hz), 7.31 (dd, 1H, $J = 4.8$ Hz, 7.8 Hz), 7.19 (dd, 1H, $J = 1.5$ Hz, 11.1 Hz), 5.11 (s, 1H), 5.07 (s, 1H), 3.10 (sep, 1H, $J = 6.9$ Hz), 2.45 (s, 3H), 1.38 d, (6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 174.6, 163.8, 155.9, 149.6, 148.9, 148.7, 140.4 (q, $J = 5.3$ Hz), 136.5, 135.3, 134.8, 133.3, 130.7 (q, $J = 28.2$ Hz), 128.2, 125.3, 124.1, 123.4 (q, $J = 272.3$ Hz), 122.8, 112.9, 108.1, 46.3, 40.5, 24.3, 24.3, 11.3 ppm; HRMS-ESI m/z : calc. for $\text{C}_{24}\text{H}_{22}\text{F}_3\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 411.1684, found 411.1690.

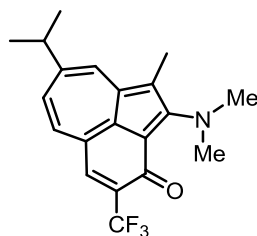
2-[(Furan-2-ylmethyl)amino]-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9i)



Method [b]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (65 mg, 0.21 mmol) was dissolved in ethanol (4 mL) and furfurylamine (0.10 μL , 1.1 mmol, 5.2 equiv) was added. The reaction mixture was stirred for 2 d at room temperature under argon atmosphere, after which TLC indicated the complete consumption of **3** and formation of less polar dark grey product. Solvents were evaporated, and the crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:5) to give **9i** as a dark grey solid (21 mg, 25%).

Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.020 g, 0.066 mmol); THF (3 mL); furfurylamine (15 μL , 2.5 equiv); Ag_2O (77 mg, 0.33 mmol, 5 equiv); crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:5) to give **9i** (17 mg, 65%). M. p. 144–146 °C; ^1H NMR (300 MHz, CDCl_3): δ 10.20 (br s, 1H), 7.87 (d, 1H, $J = 0.9$ Hz), 7.65 (d, 1H, $J = 1.2$ Hz), 7.42 (d, 1H, $J = 11.1$ Hz), 7.40 (m, 1H), 7.13 (dd, 1H, $J = 1.8$ Hz, 11.1 Hz), 6.35 (m, 2H), 5.02 (s, 1H), 5.01 (s, 1H), 3.09 (sep, 1H, $J = 6.9$ Hz), 2.53 (s, 3H), 1.37 (d, 6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 174.4, 163.7, 155.5, 150.0, 148.6, 143.0, 140.2 (q, $J = 5.4$ Hz), 136.7, 135.0, 130.6 (q, $J = 28.1$ Hz), 127.9, 125.0, 123.5 (q, $J = 272.2$ Hz), 122.4, 112.9, 110.8, 108.6, 108.3, 42.1, 40.5, 24.3, 24.3, 11.3 ppm; HRMS-ESI m/z : calc. for $\text{C}_{23}\text{H}_{21}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$: 400.1524, found 400.1527.

2-(Dimethylamino)-1-methyl-8-(propan-2-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9j)

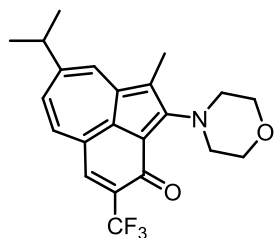


Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (29.0 mg, 95.3 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. A 2 M solution of dimethylamine in THF (52.4 μL , 105 μmol , 1.1 equiv) was added, and the reaction mixture was stirred for 2 min at 0 °C. A solution of 1,4-benzoquinone (BQ, 11.3 mg, 105 μmol , 1.1 equiv) in THF (1 mL) was added dropwise during 2 min via syringe. The reaction mixture was stirred for 15 min at 0 °C, and again a 2 M solution of dimethylamine in

THF (52.4 μ L, 105 μ mol, 1.1 equiv) was added and after 2 min, again a solution of BQ (11.3 mg, 105 μ mol, 1.1 equiv) in THF (1 mL) was added dropwise during 2 min. After 15 min, 20 min, 35 min, 50 min, and 65 min further portions of a 2 M solution of dimethylamine in THF (each 52.4 μ L, each 105 μ mol, each 1.1 equiv) were added. The resulting mixture was stirred for 15 min at 0 $^{\circ}$ C, diluted with EtOAc and washed once with a 1 M solution of NaOH in water and twice with water. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9j** as dark grey crystals (26.2 mg, 79%).

Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3**: 21.9 mg (72.0 μ mol), 2 M dimethylamine in THF: 50.5 μ L (101 μ mol, 1.4 equiv) + 25.2 μ L (50.5 μ mol, 0.7 equiv) after 30 min, Ag₂O: 83.4 mg (360 μ mol, 5 equiv). Yield of **9j**: 18.1 mg (72%), dark grey crystals. M. p. 188 $^{\circ}$ C; ¹H NMR (300 MHz, CDCl₃): δ 7.84 (q_≈d, 1H, *J* = 1.1 Hz), 7.68 (d, 1H, *J* = 1.6 Hz), 7.39 (d, 1H, *J* = 11.1 Hz), 7.14 (d, 1H, *J* = 1.7 Hz, *J* = 11.1 Hz), 3.48 (s, 6H), 3.08 (sep, 1H, *J* = 6.9 Hz), 2.49 (s, 3H), 1.37 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 172.2, 166.2, 154.0, 146.1, 140.1 (q, *J* = 5.7 Hz), 139.0, 134.4, 132.1 (q, *J* = 27.1 Hz), 128.2, 125.3, 123.6 (q, *J* = 273.2 Hz), 123.4, 115.0, 114.5, 45.3, 45.3, 40.0, 24.3, 24.3, 12.7 ppm; HRMS-ESI *m/z*: calc. for C₂₀H₂₁F₃NO [M+H]⁺: 348.1575, found 348.1575.

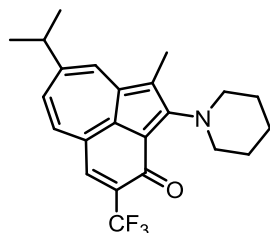
1-Methyl-2-(morpholin-4-yl)-8-(propan-2-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9k**)



Method [a]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (75.0 mg, 246 μ mol) was mixed with morpholine (0.300 mL, 3.47 mmol, 14 equiv) and shaken for 2.5 h at room temperature. The crude product was directly purified by column chromatography on silica gel (eluent: hexane/EtOAc: 5:2) to give **9k** as dark grey needles (11.0 mg, 11%).

Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (24.0 mg, 78.9 μ mol) was dissolved in THF (1 mL) and cooled to 0 $^{\circ}$ C. Morpholine (6.9 μ L, 78.9 μ mol) and 1,4-benzoquinone (BQ, 8.5 mg, 78.9 μ mol) were each dissolved in THF (1 mL) and transferred to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 200 μ L at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution the reaction mixture was stirred for another 30 min at 0 $^{\circ}$ C. Morpholine (13.8 μ L, 158 μ mol, 2 equiv) was added and stirring was continued for 30 min at 0 $^{\circ}$ C. Morpholine (6.9 μ L, 78.9 μ mol) was added three times of 30 min. The reaction mixture was stirred for 30 min at 0 $^{\circ}$ C. The solvent was evaporated, the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane and recrystallized from a mixture of MeOH and water (10+1) to give **9k** as dark grey needles (21.7 mg, 71%). M. p. 158 $^{\circ}$ C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.18 (s, 1H), 7.85 (d, 1H, *J* = 1.6 Hz), 7.75 (d, 1H, *J* = 11.1 Hz), 7.34 (dd, 1H, *J* = 1.6 Hz, *J* = 11.1 Hz), 3.91–3.85 (m, 4H), 3.83–3.77 (m, 4H), 3.17 (sep, 1H, *J* = 6.8 Hz), 2.45 (s, 3H), 1.32 (d, 6H, *J* = 6.8 Hz) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 170.7, 163.4, 154.5, 145.5, 140.3 (q, *J* = 5.7 Hz), 138.0, 134.8, 130.2 (q, *J* = 26.3 Hz), 128.5, 125.9, 123.4 (q, *J* = 273.2 Hz), 123.3, 114.3, 114.0, 67.1, 67.1, 52.3, 52.3, 38.9, 23.8, 23.8, 12.0 ppm. HRMS-ESI *m/z*: calc. for C₂₂H₂₃F₃NO₂ [M+H]⁺: 390.1681, found 390.1681.

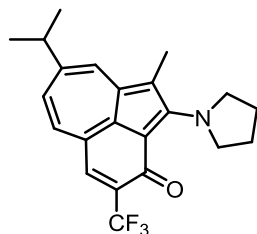
1-Methyl-2-(piperidin-1-yl)-8-(propan-2-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9l)



Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (25.3 mg, 83.1 μmol) was dissolved in THF (1 mL) in a round-bottomed flask and cooled to 0 °C. Piperidine (9.0 μL , 91.5 μmol , 1.1 equiv) was dissolved in THF (550 μL), and BQ (9.0 mg, 83 μmol) was dissolved in THF (500 μL). Both solutions were transferred separately to 1-mL syringes. The amine and BQ solutions were added to the azulene solution in portions of 50 μL at a time interval of 2 min. Starting with the amine solution, the first portion of the quinone solution was added 2 min later, and the second portion of the amine solution another 2 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred for another 45 min at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9l** as a dark grey resin (23.5 mg, 73%).

Method [d]: Deviating from the general procedure for method [d], amine was added only once in the beginning. 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3**: 37.8 mg (124 μmol), piperidine: 16.0 μL (161 μmol , 1.3 equiv), Ag_2O : 144 mg (620 μmol , 5 equiv). Yield of **9l**: 39.0 mg (81%), dark grey resin. ^1H NMR (300 MHz, acetone- d_6): δ 8.03 (q \approx d, 1H, J = 1.0 Hz), 7.86 (d, 1H, J = 1.7 Hz), 7.67 (d, 1H, J = 11.1 Hz), 7.31 (dd, 1H, J = 1.7 Hz, J = 11.1 Hz), 3.80 (mc, 4H), 3.18 (sep, 1H, J = 6.9 Hz), 2.51 (s, 3H), 1.95 – 1.85 (m, 4H), 1.85 – 1.74 (m, 2H), 1.38 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, DMSO- d_6): δ 170.6, 164.1, 154.0, 145.2, 140.1 (q, J = 5.6 Hz), 138.3, 134.5, 130.0 (q, J = 26.2 Hz), 127.9, 125.2, 123.5 (q, J = 273.3 Hz), 122.6, 114.6, 114.0, 53.3, 53.3, 38.8, 26.8, 26.8, 23.8, 23.8, 23.2, 12.0 ppm; HRMS-ESI m/z : calc. for $\text{C}_{23}\text{H}_{26}\text{F}_3\text{NO}$ [$\text{M}+\text{H}$] $^+$: 388.1888, found 388.1888.

1-Methyl-8-(propan-2-yl)-2-(pyrrolidin-1-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (9m)

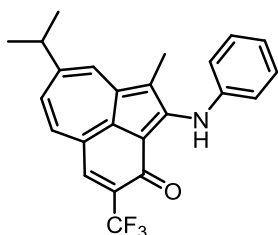


Method [c]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (24.5 mg, 80.5 μmol) was dissolved in THF (1 mL) in a round-bottomed flask and cooled to 0 °C. Pyrrolidine (6.7 μL , 80.5 μmol) and 1,4-benzoquinone (BQ, 8.7 mg, 80.5 μmol) were each dissolved separately in THF (1 mL) and transferred to 1-mL syringes. The amine and the BQ solutions were added to the azulene solution in portions of 200 μL at a time interval of 3 min. Starting with the amine solution, the first portion of the quinone solution was added 3 min later, and the second portion of the amine solution another 3 min later. After the addition of the last portion of the quinone solution, the reaction mixture was stirred at 0 °C. After 30 and 60 min pyrrolidine (6.7 μL , 81 μmol) batches were added and stirring was continued for another 30 min at 0 °C. The

solvent was evaporated, and the residue was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9m** as a dark greenish grey resin (26.3 mg, 87%).

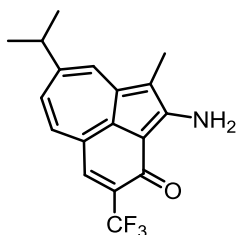
Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3**: 20.8 mg (68.4 μ mol), pyrrolidine: 6.8 μ L (82.0 μ mol, 1.2 equiv) + 3.4 μ L (41.0 μ mol, 0.6 equiv) after 25 min, Ag₂O: 63.4 mg (274 μ mol, 4 equiv). Yield of **9m**: 17.4 mg (68%), dark greenish grey resin. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.09 (q \approx d, 1H, *J* = 1.0 Hz), 7.63 (d, 1H, *J* = 1.6 Hz), 7.55 (d, 1H, *J* = 11.3 Hz), 7.08 (dd, 1H, *J* = 1.6 Hz, *J* = 11.2 Hz), 4.00 (m_c, 4H), 3.09 (sep, 1H, *J* = 6.9 Hz), 2.58 (s, 3H), 2.01 (m_c, 4H), 1.30 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 172.2, 162.9, 152.9, 145.1, 139.9 (q, *J* = 5.7 Hz), 139.4, 134.0, 131.3 (q, *J* = 27.2 Hz), 127.2, 124.1, 123.8 (q, *J* = 273.0 Hz), 122.0, 114.6, 114.0, 54.2, 54.2, 40.0, 25.9, 25.9, 24.2, 24.2, 13.2 ppm; HRMS-ESI *m/z*: calc. for C₂₂H₂₃F₃NO [M+H]⁺: 374.1732, found 374.1734.

8-Isopropyl-1-methyl-2-(phenylamino)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9n**)



Method [d]: Deviating from the general procedure for the method [d], aniline was added only once in the beginning, and the reaction time was 8 h at room temperature. 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3**: 50.0 mg (164 μ mol), aniline: 45.0 μ L (493 μ mol, 3 equiv), Ag₂O: 190 mg (820 μ mol, 5 equiv), THF: 2 mL, reaction time 8 h room temperature; yield of **9n**: 53.8 mg (83%), dark grey solid. M. p. 168 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.02 (s, 1H), 8.31 (q \approx d, 1H, *J* = 1.1 Hz), 7.88 (d, 1H, *J* = 11.0 Hz), 7.87 (d, 1H, *J* = 1.7 Hz), 7.53 – 7.29 (m, 6H), 3.20 (sep, 1H, *J* = 6.8 Hz), 1.90 (s, 3H), 1.33 (d, 6H, *J* = 6.8 Hz) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 173.1, 159.0, 156.0, 147.7, 141.0 (q, *J* = 5.6 Hz), 137.8, 135.6, 135.5, 129.2 (q, *J* = 27.1 Hz), 129.0, 129.0, 128.9, 126.7, 126.5, 124.9, 124.9, 123.3 (q, *J* = 273.3 Hz), 123.0, 112.5, 109.1, 39.3, 23.8, 11.4 ppm; HRMS-ESI *m/z*: calc. for C₂₄H₂₁F₃NO [M+H]⁺: 396.1575, found 396.1580.

2-Amino-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9o**)

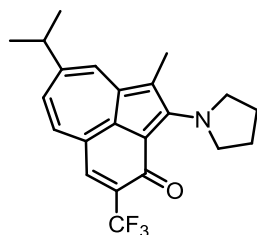


Method [d]: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3**: (20.0 mg, 65.7 μ mol), silver(I) oxide (45.7 mg, 197 μ mol, 3 equiv) and ammonium chloride (10.5 mg, 197 μ mol) were dissolved in THF (1 mL) and cooled to 0 °C. Triethylamine (45.8 μ L, 329 μ mol, 5 equiv) was added, and the reaction mixture was stirred for 9 h at 0 °C. The solvent was evaporated and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to

give **9o** as a dark brown solid (7.4 mg, 35%). Starting material **3** (5.6 mg) was recovered, increasing the yield to 49% based on recovered starting material. M. p. 237 °C; ^1H NMR (300 MHz, DMSO- d_6): δ 9.03 (br s, 1H), 8.77 (br s, 1H), 8.13 (s, 1H), 7.63 (s, 1H), 7.61 (dd, 1H, J = 1.5 Hz, 11.7 Hz), 7.16 (dd, 1H, J = 1.5 Hz, 11.7 Hz), 3.10 (sep, 1H, J = 6.9 Hz), 2.25 (s, 3H), 1.30 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, CDCl $_3$): δ 174.9, 163.9, 155.1, 146.5, 141.0 (q, J = 5.2 Hz), 137.3, 134.4, 130.9 (q, J = 28.2 Hz), 128.5, 125.7, 123.4, 123.3 (q, J = 272.1 Hz), 112.3, 109.1, 40.3, 24.4, 24.4, 7.8 ppm; HRMS-ESI m/z : calc. for C $_{18}$ H $_{17}$ F $_3$ NO [M+H] $^+$: 320.1262, found 320.1262.

2.4 Reversible Michael reaction of benzo[*cd*]azulen-3-ones bearing a nucleofugal leaving group (NLG).

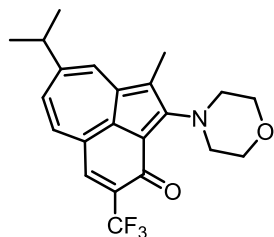
8-Isopropyl-1-methyl-2-(pyrrolidin-1-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9m**)



Reaction 1: 3-[(8-Isopropyl-1-methyl-3-oxo-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-2-yl)thio]propanoic acid **8c** (8.5 mg, 21 μmol) was dissolved in THF (500 μL) and cooled to 0 °C. A solution of pyrrolidine (3.9 μL , 46 μmol , 2.2 equiv) in THF (100 μL) was added, and the reaction mixture was stirred for 10 min at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9m** as dark greenish grey needles (5.0 mg, 64%).

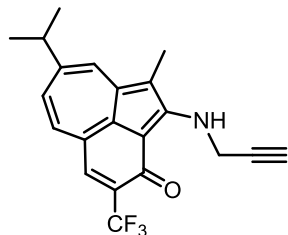
Reaction 2: 2-(Ethylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **8b** (21.0 mg, 57.6 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. Pyrrolidine (9.6 μL , 115 μmol , 2 equiv) was added, and the reaction mixture was stirred for 6 min at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9m** as a dark greenish grey resin (17.5 mg, 81%).

8-Isopropyl-1-methyl-2-(morpholin-1-yl)-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**9k**)



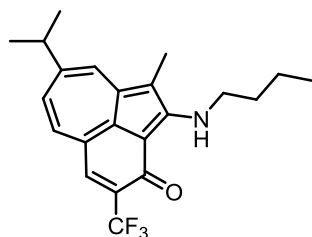
2-(Ethylthio)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **8b** (19.9 mg, 54.6 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. Morpholine (9.5 μL , 0.11 mmol, 2 equiv) was added, and the reaction mixture was stirred for 15 min at 0 °C. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9k** as dark grey needles (14.9 mg, 70%).

8-Isopropyl-1-methyl-2-(prop-2-yn-1-ylamino)-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one (9p)



8-Isopropyl-1-methyl-2-(pyrrolidin-1-yl)-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one **9m** (20.0 mg, 53.6 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. Propargylamine (17.2 μL , 268 μmol , 5 equiv) was added, and the reaction mixture was stirred for 1.5 h at 0 °C. The reaction mixture was diluted with EtOAc and washed twice with water. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9p** as a dark grey resin (14.9 mg, 78%). ^1H NMR (300 MHz, DMSO- d_6): δ 10.00 (br t \approx s, 1H), 7.89 (q \approx d, 1H, J = 0.9 Hz), 7.71 (d, 1H, J = 1.6 Hz), 7.48 (d, 1H, J = 11.1 Hz), 7.20 (dd, 1H, J = 1.6 Hz, J = 11.1 Hz), 4.57 (m $_c$, 2H), 3.12 (sep, 1H, 3J = 6.9 Hz), 2.58 (s, 3H), 2.42 (dd \approx t, 1H, J = 2.5 Hz), 1.39 (d, 6H, J = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, DMSO- d_6): δ 174.5, 163.1, 155.8, 148.7, 140.4 (q, J = 5.6 Hz), 136.4, 135.1, 130.8 (q, J = 27.9 Hz), 128.3, 125.5, 123.4 (q, J = 273.1 Hz), 122.9, 113.0, 108.3, 79.2, 73.9, 40.5, 34.5, 24.4, 24.4, 10.9 ppm; HRMS-ESI m/z : calc. for $\text{C}_{21}\text{H}_{19}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]^+$: 358.1419, found 358.1428.

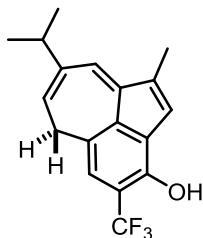
2-(Butylamino)-8-isopropyl-1-methyl-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one (9b)



Reaction 1: 8-Isopropyl-1-methyl-2-(pyrrolidin-1-yl)-4-(trifluoromethyl)-3H-benzo[cd]azulen-3-one **9m** (30.9 mg, 82.7 μmol) was dissolved in THF (1 mL) and cooled to 0 °C. *n*-Butylamine (41.1 μL , 414 μmol , 5 equiv) was added, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with EtOAc and washed three times with water. The solvent was evaporated, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing EtOAc starting with 100% hexane to give **9b** as brown needles (28.3 mg, 91%).

2.5 Reaction of **3** with hydrides

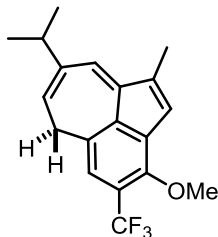
8-Isopropyl-1-methyl-4-(trifluoromethyl)-6*H*-benzo[*cd*]azulen-3-ol (**12**)



Reaction 1: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.20 g, 0.66 mmol) was dissolved in anhydrous ethanol (8 mL) and cooled to -15 °C under argon atmosphere. Sodium borohydride (0.010 g, 0.26 mmol) was added, and the resulting mixture was stirred at -15 to -0 °C for 2 h, after which TLC indicated the complete consumption of **3** and formation of a reaction product. During this period, the color of the reaction mixture changed from bright green to orange-yellow. EtOAc (20 mL) and a saturated aqueous solution of ammonium chloride (10 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:8→1:4) to give **12** as a bright orange solid (97 mg, 48%). A sample of **12** for single crystal X-ray analysis was recrystallized from *n*-hexane.

Reaction 2: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (0.20 g, 0.66 mmol) was dissolved in anhydrous diethyl ether (8 mL) and cooled to -65 °C under argon atmosphere. K-Selectride (1.0 M in THF; 720 µL, 0.72 mmol, 1.2 equiv) was added, and the color of the reaction mixture changed from green to bright orange-red immediately. The resulting mixture was let to warm up to -15 °C over a period of 2 h, after which TLC indicated the complete consumption of **3** and formation a single reaction product. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL) followed by addition of EtOAc (20 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (eluent: EtOAc/*n*-hexane 1:4) to give phenol **12** as a bright orange crystalline solid (140 mg, 70%). M. p. 71–72 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.02 (s, 1H,), 6.71(s, 1H), 6.62 (d, 1H, *J* = 1.5 Hz), 5.58 (t, 1H, *J* = 6.6 Hz), 5.23 (br s, 1H), 3.31 (d, 2H, *J* = 6.6 Hz) 2.52 (sep, 1H, *J* = 6.9 Hz), 2.22 (d, 3H, *J* = 1.5 Hz), 1.10 (d, 6H, *J* = 6.9 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 144.4, 139.2, 139.1, 130.9, 128.4, 124.9 (q, *J* = 271.1 Hz), 123.3, 123.3, 123.1, 123.1, 122.8, 120.6, 117.9 (q, *J* = 29.0 Hz), 36.3, 32.1, 22.8, 22.8, 12.7 ppm; HRMS-APPI/APCI *m/z*: calc. for C₁₈H₁₆F₃O [M–H][–]: 305.1153, found: 305.1153.

8-Isopropyl-3-methoxy-1-methyl-4-(trifluoromethyl)-6*H*-benzo[*cd*]azulene (**13**)

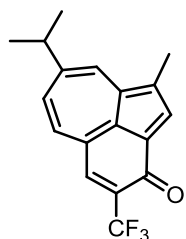


Reaction 1: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-6*H*-benzo[*cd*]azulen-3-ol **12** (0.020 g, 0.070 mmol) in THF (2 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 9.0 mg, 0.38 mmol, 5.4 equiv) in anhydrous THF (3 mL), at room temperature under argon atmosphere. After 10–15 min

dimethyl sulfate (67 μ L, 0.70 mmol, 10 equiv) was added, and the reaction mixture was stirred at room temperature for 18 h, after which TLC indicated the complete consumption of **12**. EtOAc (10 mL) and a saturated aqueous solution of ammonium chloride (10 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (2×10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:15) to give **13** (15 mg, 67%) as a yellow waxy solid.

Reaction 2: 8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one **3** (120 mg, 0.40 mmol) was dissolved in anhydrous diethyl ether (5 mL) and cooled to -65°C under argon atmosphere. K-Selectride (1.0 M in THF; 0.43 mmol, 430 μ L, 1.1 equiv) was added and the color of the reaction mixture changed from green to bright red immediately. The resulting mixture was let to warm up to -15°C over a period of 1.5 h, after which time TLC indicated complete consumption of **3** and formation of intermediate **12**. Then, dimethyl sulfate (188 μ L, 1.97 mmol, 5 equiv) was added, and the reaction mixture was let to warm up to room temperature over period of for 18 h, after which TLC indicated the complete consumption of **12**. EtOAc (10 mL) and water (10 mL) were added, and the phases were separated. The aqueous phase was extracted with EtOAc (2×10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:20) to give **13** as a yellow oil which solidified under prolonged time *in vacuo* (89 mg, 70%). M. p. $54\text{--}55^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3): δ 7.09 (s, 1H), 6.71 (s, 1H), 6.68 (d, 1H, $J = 1.5$ Hz), 5.58 (t, 1H, $J = 6.6$ Hz), 5.23 (br s, 1H), 3.97 (s, 3H), 3.31 (d, 2H, $J = 6.6$ Hz) 2.53 (sep, 1H, $J = 6.9$ Hz), 2.23 (d, 3H, $J = 1.5$ Hz), 1.11 (d, 6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 149.4 (q, $J = 2.0$ Hz), 144.5, 143.8, 139.9, 139.8, 131.7, 130.4, 125.3, 124.3, 124.2 (q, $J = 271.2$ Hz), 123.9, (q, $J = 30.1$ Hz), 123.5 (q, $J = 5.0$ Hz), 120.3, 62.4, 36.2, 32.3, 22.8, 22.8, 12.7 ppm; HRMS-APPI/APCI m/z : calc. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{O}$ $[\text{M}-\text{H}]^-$: 319.1310, found: 319.1310.

8-Isopropyl-1-methyl-4-(trifluoromethyl)-3*H*-benzo[*cd*]azulen-3-one (**3**)^[1]



8-Isopropyl-1-methyl-4-(trifluoromethyl)-6*H*-benzo[*cd*]azulen-3-ol **12** (11 mg, 0.036 mmol) and 1,4-benzoquinone (8.0 mg, 0.072 mmol, 2.0 equiv) were dissolved in anhydrous THF (2 mL), and the resulting mixture was stirred at room temperature for 5 d, after which TLC indicated the complete consumption of **12**. During this period, the color of the reaction mixture changed from orange-yellow to bright green. The reaction mixture was diluted with EtOAc (15 mL) and washed with aqueous NaOH (1.0 M, 2×10 mL) and water. The aqueous phase was extracted with EtOAc (2×10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered, and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (eluent: EtOAc–*n*-hexane 1:4) to give **3**^[1] as a green solid (10 mg, 91%). ^1H NMR (300 MHz, C_6D_6): identical spectra with the reference.^[1]

3. X-ray data for compound 12

Crystals of **12**, suitable for a single crystal X-ray diffraction study, were grown by recrystallization from hot *n*-hexane. All data were collected on an Oxford Gemini S diffractometer. For data collection, cell refinement and data reduction the software CrysAlisPro was used.² The structure was solved by direct methods using SHELXS-2013 and refined by full-matrix least-squares procedures on F^2 using SHELXL-2013.³ The atoms C36–C38 of an *i*-Pr group were refined disordered with split occupancies of 0.4/0.6. Table S1 summarizes on selected crystal and structural refinement data of **12**. For further values as well as for bond lengths and bond and torsion angles *cf.* CCDC 1424751.

Table S1. Crystal data and structure refinement for compound **12**.

Empirical formula	C ₁₈ H ₁₇ F ₃ O	
Formula weight	306.32	
Temperature	110 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, P 2 ₁ /c	
Unit cell dimensions	a = 18.8665(4) Å b = 17.8365(4) Å c = 18.9721(4) Å	alpha = 90 deg. beta = 107.034(2) deg. gamma = 90 deg.
Volume	6104.3(2) Å ³	
Z, Calculated density	16, 1.333 Mg/m ³	
Absorption coefficient	0.106 mm ⁻¹	
F(000)	2560	
Crystal size	0.4 × 0.3 × 0.3 mm	
Theta range for data collection	3.018 to 24.999 deg.	
Limiting indices	-22 ≤ h ≤ 22, -21 ≤ k ≤ 20, -22 ≤ l ≤ 22	
Reflections collected / unique	32039 / 10712 [R(int) = 0.0274]	
Completeness to theta = 25.000	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.79968	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10712 / 768 / 845	
Goodness-of-fit on F^2	1.056	
Final R indices [I > 2σ(I)]	R1 = 0.0435, wR2 = 0.1063	
R indices (all data)	R1 = 0.0584, wR2 = 0.1130	
Largest diff. peak and hole	0.781 and -0.559 e.Å ⁻³	

The asymmetric unit of **12** comprises four crystallographically independent, but otherwise identical molecules. One of them is displayed below in Figure S1.

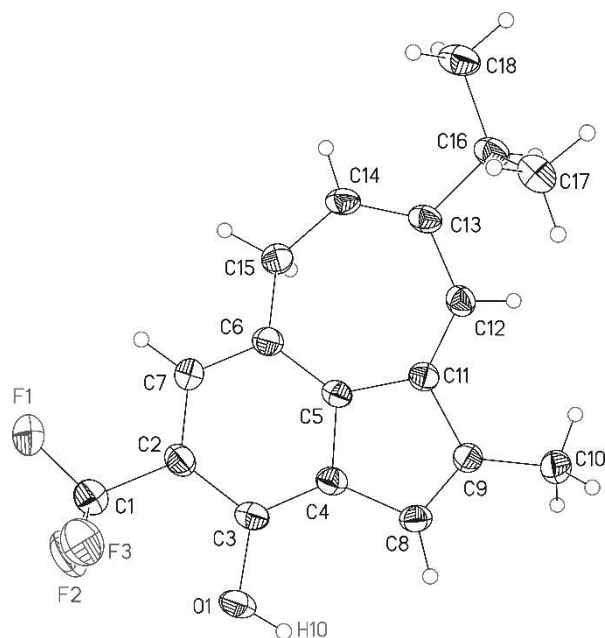


Figure S1. ORTEP diagram (50 % ellipsoid probability) of the molecular structure of one crystallographically independent molecule of **12**.

In the solid state, the four crystallographically independent molecules of **9** form a tetramer due to formation of intermolecular hydrogen bonds. A graphical illustration of a tetramer is given in Figure S2, Table S2 summarizes selected geometrical features of the hydrogen bonds.

Table S2. Selected geometrical details (bond lengths in Å, bond angles in °) of the intermolecular hydrogen bonds of **9** in the solid state.

D–H···A	D···A	D–H···A
O1–H1O···O3	2.791(2)	159(3)
O2–H2O···O1	2.796(2)	148(3)
O3–H3O···O4	2.857(2)	151(2)
O4–H4O···O2	2.705(2)	156(3)

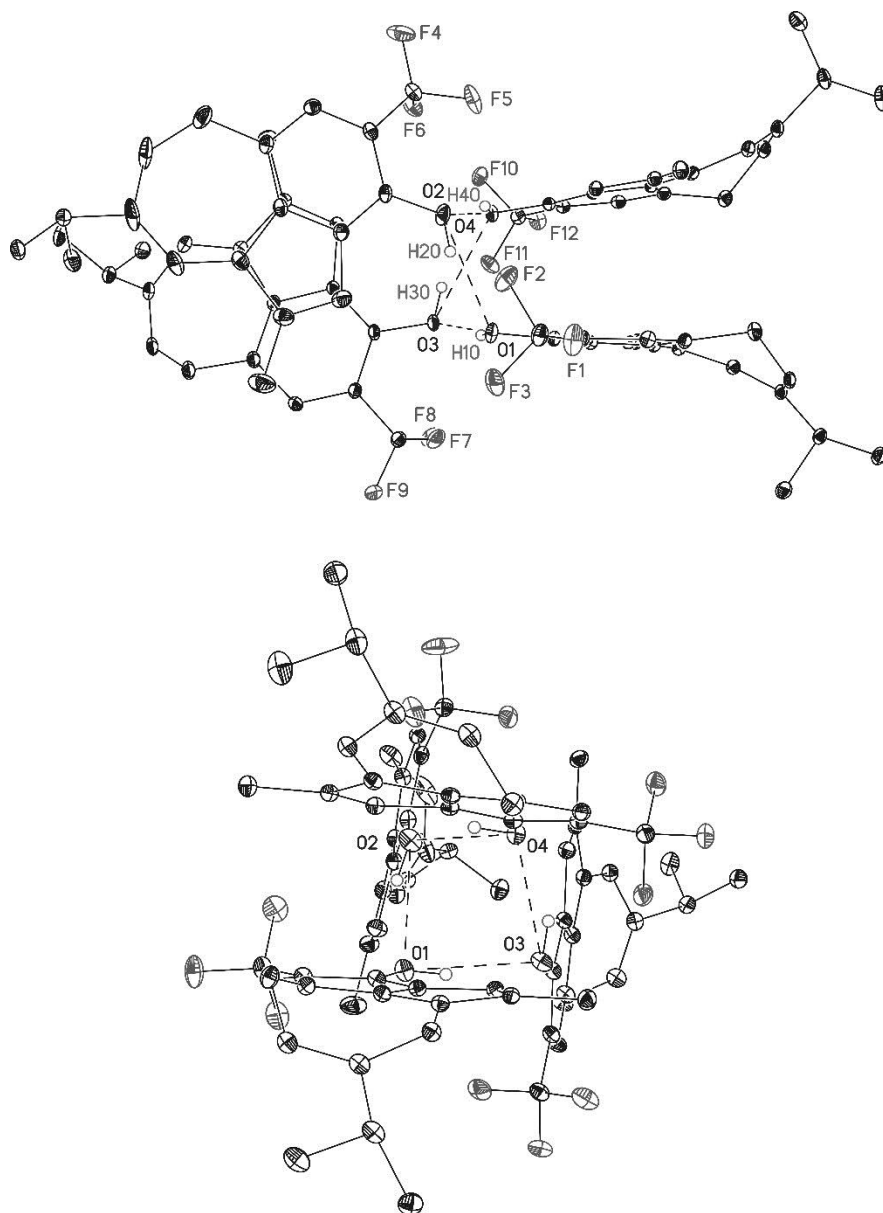
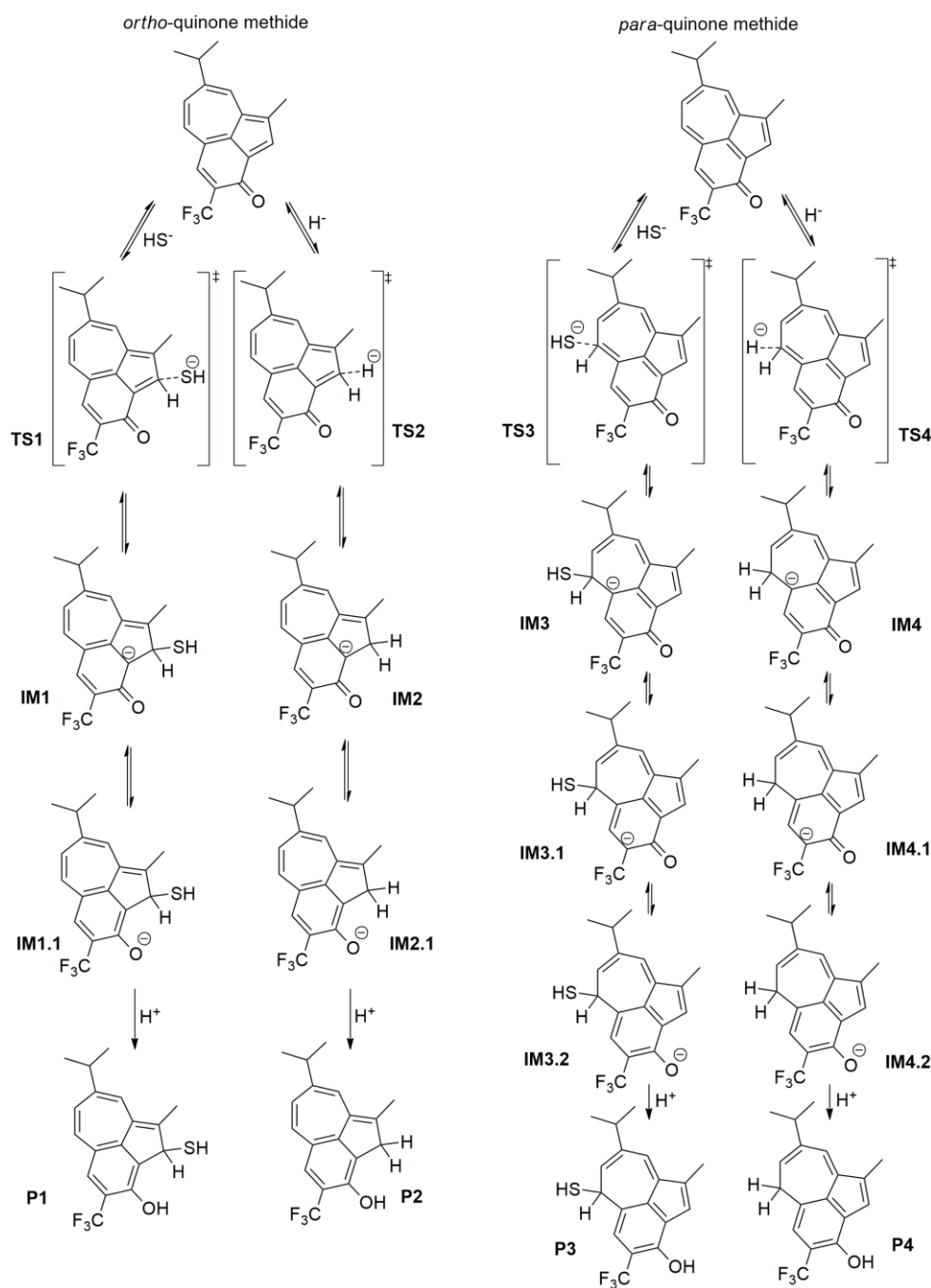


Figure S2. Graphical illustration of the interaction of the four crystallographically independent molecules of **12** in the solid state by means of formation of intermolecular hydrogen bonds.

4. Computational study

Thermochemical calculations. All models were drawn in ChemDraw Pro (v 12.0) and saved as PDB file. Density functional theoretical calculations are carried out using the Gaussian 09 package software.⁴ Optimizations of the stationary point geometries (reactants (R), transition states (TS), intermediates (IM) and products) are conducted at the DFT/B3LYP/6-311++G(d,p) level of theory.⁵ Energies are summarized in Table S3.



Scheme S1. Structures of the considered transition-states, intermediates and products of the competing nucleophilic addition reactions studied by *ab initio* computational studies at the B3LYP/6-311++G(d,p) level.

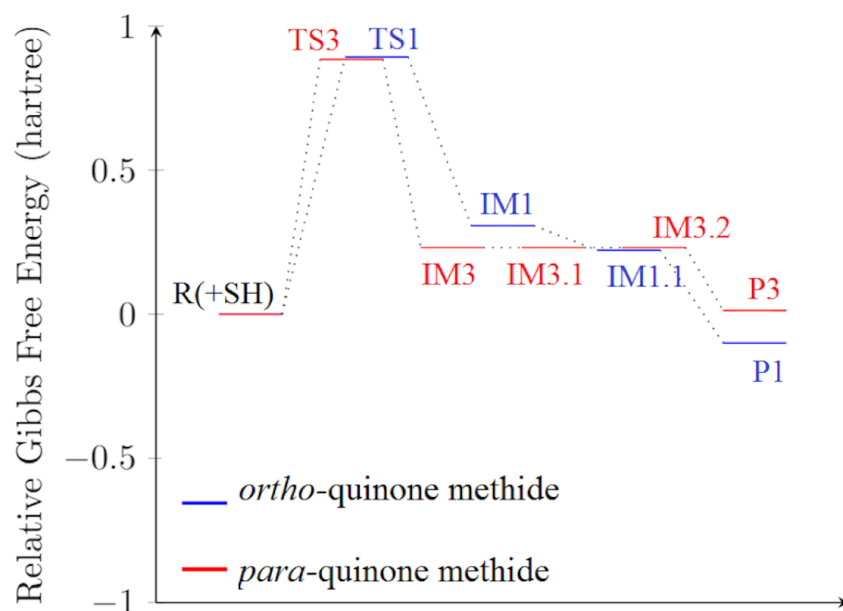


Figure S3. Relative free energy profile for nucleophilic addition of **thiols** (H_2S) giving the possible products **P1** and **P3**, computed at the DFT/B3LYP/6-311++G(d,p) level of theory.

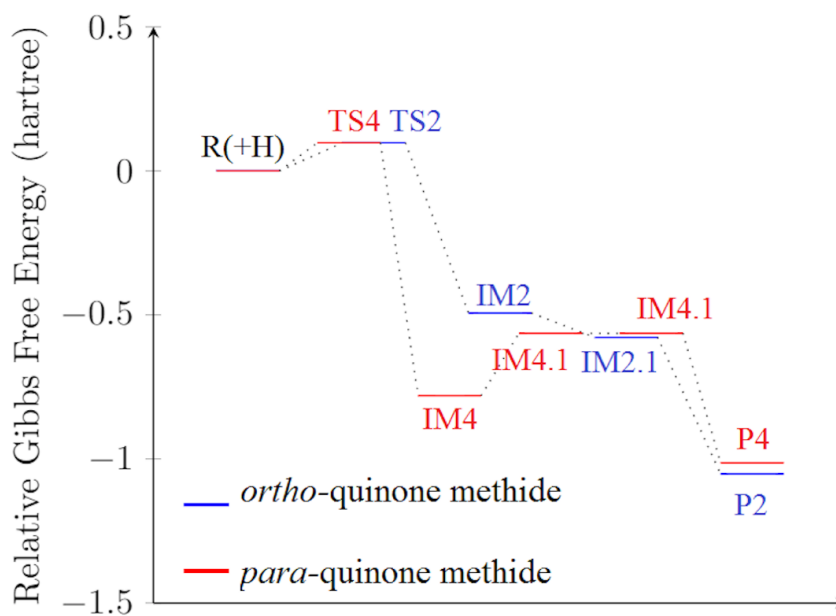


Figure S4. Relative free energy profile for **hydride** addition giving the possible products **P2** and **P4**, computed at the DFT/B3LYP/6-311++G(d,p) level of theory.

Table S3. Total Energies, Zero-point Energies, Gibbs Free Energies and Relative Gibbs Free Energies at 298 K (in Hartree).

Compound	E(UB3LYP)	ZPE	ΔG	$E_R(\Delta G)$
R (+SH)	-912.6775359	0.172334937	-912.545699	0.000
R (+H)	-1331.394902	0.172292727	-1311.557579	0.000
TS1	-1310.792069	0.169347015	-1310.665620	0.891959
TS2	-912.5783126	0.169838009	-912.449121	0.096578
TS3	-1310.799477	0.169545405	-1310.673170	0.884409
TS4	-912.5783124	0.169835491	-912.449120	0.096579
IM1	-1311.384423	0.179097455	-1311.250274	0.307305
IM1.1	-1311.473244	0.181377762	-1311.336031	0.221548
IM2	-913.1778444	0.179861817	-913.039751	-0.494052
IM2.1	-913.2639823	0.181853840	-913.123571	-0.577872
IM3	-1311.402752	0.181376217	-1311.325603	0.231976
IM3.1	-1311.462394	0.181380822	-1311.325582	0.231997
IM3.2	-1311.462394	0.181376217	-1311.325603	0.231976
IM4	-913.4623943	0.181376217	-913.325603	-0.779904
IM4.1	-913.2497058	0.182114827	-913.109569	-0.563870
IM4.2	-913.2497058	0.182114842	-913.109570	-0.563871
P1	-1309.79207	0.166162951	-1311.656469	-0.0988896
P2	-911.5783459	0.166814916	-913.5984486	-1.05274963
P3	-1309.799479	0.166288050	-1311.544164	0.01341469
P4	-911.5783184	0.166655426	-913.5605423	-1.01484331

Table S4. Cartesian coordinates of geometries optimized at the DFT/B3LYP/6-311++G(d,p) level.

Standard orientation of R(+SH)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	0.709604	4.050652	-0.088507
2	6	0	-0.351910	3.234741	-0.126460
3	6	0	-0.440194	1.779515	-0.046950
4	6	0	0.635039	0.971308	0.013884
5	6	0	2.055780	1.284885	0.048423
6	6	0	2.715081	2.558048	0.108928
7	6	0	2.113740	3.753038	0.058919
8	6	0	-1.760621	1.117924	-0.050635
9	6	0	-1.963104	-0.215858	-0.008508
10	6	0	-0.807866	-1.142455	0.031874
11	6	0	0.500565	-0.472529	0.040536
12	6	0	1.733037	-1.000122	0.066781
13	6	0	2.696662	0.093481	0.076396
14	8	0	-0.922200	-2.359228	0.056846
15	6	0	-3.287647	-0.881988	0.006584

16	9	0	-3.492188	-1.619546	1.126503
17	9	0	-3.484115	-1.690334	-1.064471
18	9	0	-4.302161	0.029504	-0.026152
19	1	0	0.507406	5.119514	-0.175829
20	1	0	-1.316975	3.729532	-0.245747
21	1	0	3.797661	2.536122	0.220246
22	1	0	2.751010	4.634953	0.128458
23	1	0	-2.625450	1.780400	-0.080490
24	1	0	3.764058	-0.063347	0.124173
25	1	0	1.983481	-2.049601	0.089053
26	16	0	4.229177	-3.364711	-0.134258
27	1	0	5.066770	-4.238834	0.522997

Standard orientation of R(+H)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.084594	-2.284772	-0.057567
2	6	0	-1.747395	-2.217072	-0.093326
3	6	0	-0.848299	-1.068065	-0.036686
4	6	0	-1.274251	0.208885	-0.005215
5	6	0	-2.621720	0.758435	0.013470
6	6	0	-3.887716	0.086591	0.085327
7	6	0	-4.071514	-1.239260	0.064078
8	6	0	0.614222	-1.273616	-0.031788
9	6	0	1.538417	-0.290211	-0.008813
10	6	0	1.113932	1.129133	-0.000939
11	6	0	-0.343466	1.321123	-0.000546
12	6	0	-1.058133	2.455707	-0.001327
13	6	0	-2.472439	2.103303	0.012162
14	8	0	1.899160	2.065940	0.005521
15	6	0	3.006852	-0.493951	0.014843
16	9	0	3.591069	0.021498	1.125271
17	9	0	3.630693	0.035954	-1.066455
18	9	0	3.324084	-1.820784	0.012278
19	1	0	-3.525128	-3.281003	-0.124128
20	1	0	-1.233907	-3.174866	-0.190071
21	1	0	-4.766511	0.721861	0.180213
22	1	0	-5.097151	-1.601489	0.138797
23	1	0	0.949714	-2.310488	-0.037824
24	1	0	-3.261929	2.839547	0.041509
25	1	0	-0.668136	3.461950	-0.000193
26	1	0	-1.686219	7.509574	-0.414360

Standard orientation of TS1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-2.585471	-2.875782	-0.182098
2	6	0	-1.251240	-2.705930	-0.271587
3	6	0	-0.553074	-1.575175	-0.050607
4	6	0	-1.141318	-0.374356	0.031367
5	6	0	-2.445461	-0.056800	0.001770
6	6	0	-3.490753	-0.899876	0.045051
7	6	0	-3.528072	-2.178372	0.505877
8	6	0	0.793202	-1.571736	-0.059031
9	6	0	1.544189	-0.454572	0.018127
10	6	0	0.927007	0.765320	0.063619
11	6	0	-0.430661	0.762274	0.042157
12	6	0	-1.291570	1.791828	-0.016359
13	6	0	-2.530481	1.281171	-0.080418
14	8	0	1.594332	1.777159	0.102847
15	16	0	-0.974934	3.576245	-0.058601
16	6	0	3.068361	-0.547820	0.020339
17	9	0	3.569377	-0.010950	1.123139
18	9	0	3.581390	0.089728	-1.021703
19	9	0	3.513443	-1.793575	-0.035621
20	1	0	-2.992807	-3.807091	-0.622325
21	1	0	-0.686788	-3.583869	-0.638624
22	1	0	-4.487468	-0.491420	-0.205926
23	1	0	-2.750145	-1.913322	1.249973
24	1	0	1.310844	-2.541974	-0.140574
25	1	0	-3.459305	1.864808	-0.140042
26	1	0	-2.125483	4.231476	-0.296368
27	1	0	-0.450411	2.076338	-0.092842

Standard orientation of TS2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.020582	-2.027216	-0.156394
2	6	0	-1.675071	-2.051757	-0.239368
3	6	0	-0.826619	-1.025569	-0.036045
4	6	0	-1.251172	0.242993	0.020021
5	6	0	-2.492733	0.751415	-0.020279
6	6	0	-3.645595	0.063629	0.031045
7	6	0	-3.859142	-1.190553	0.511356
8	6	0	0.509708	-1.197998	-0.038903
9	6	0	1.403430	-0.188311	0.017485
10	6	0	0.952421	1.102271	0.035849
11	6	0	-0.391696	1.267677	0.012169

12	6	0	-1.076922	2.416776	-0.067811
13	6	0	-2.376799	2.086909	-0.127573
14	8	0	1.718598	2.042480	0.053293
15	6	0	2.901539	-0.475958	0.025033
16	9	0	3.465962	0.018166	1.117009
17	9	0	3.490229	0.071607	-1.027930
18	9	0	3.184711	-1.769032	-0.003936
19	1	0	-3.553733	-2.899371	-0.583131
20	1	0	-1.236776	-3.006217	-0.586988
21	1	0	-4.574487	0.603095	-0.231751
22	1	0	-3.056664	-1.023774	1.257683
23	1	0	0.894707	-2.229516	-0.100007
24	1	0	-0.668724	3.434579	-0.109188
25	1	0	-3.205015	2.804328	-0.203172
26	1	0	-0.520803	2.444531	-0.435583

Standard orientation of TS3

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.137607	1.089656	0.491547
2	6	0	-1.860602	1.271873	0.052777
3	6	0	-0.809338	0.417815	0.014588
4	6	0	-0.956682	-0.915991	0.050212
5	6	0	-2.056729	-1.682289	-0.037922
6	6	0	-3.306318	-1.250974	-0.248061
7	6	0	-3.691990	0.033341	-0.158861
8	6	0	0.474505	0.832668	-0.043249
9	6	0	1.555210	0.025271	-0.002627
10	6	0	1.374936	-1.326180	0.068984
11	6	0	0.090021	-1.751548	0.068535
12	6	0	-0.336425	-3.021802	0.052222
13	6	0	-1.672918	-2.970709	-0.038454
14	8	0	2.313437	-2.093985	0.103989
15	16	0	-1.629919	3.086991	-0.114611
16	6	0	2.968152	0.603100	-0.035271
17	9	0	3.634601	0.147044	-1.085668
18	9	0	3.636259	0.261718	1.056652
19	9	0	2.996546	1.924899	-0.106013
20	1	0	-2.750776	0.388081	1.254218
21	1	0	-4.049728	-1.990122	-0.597290
22	1	0	-4.685225	0.273903	-0.585197
23	1	0	0.689101	1.909837	-0.088917
24	1	0	0.274794	-3.933172	0.046287
25	1	0	-2.330856	-3.844654	-0.138234
26	1	0	-2.560784	3.753886	0.595070
27	1	0	-1.227256	1.673925	0.324676

Standard orientation of TS4

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.112438	-2.127595	-0.177194
2	6	0	1.741807	-2.142757	-0.247304
3	6	0	0.824123	-1.035796	-0.016653
4	6	0	1.282738	0.282410	0.035300
5	6	0	2.624732	0.840418	-0.054938
6	6	0	3.792857	0.178457	0.022556
7	6	0	3.841101	-1.150480	0.558814
8	6	0	-0.587746	-1.223331	-0.008807
9	6	0	-1.463782	-0.189650	0.024463
10	6	0	-1.044511	1.201016	0.029543
11	6	0	0.372499	1.373630	0.011926
12	6	0	1.106969	2.591298	-0.098644
13	6	0	2.473848	2.267091	-0.153695
14	8	0	-1.839053	2.167393	0.032593
15	1	0	1.277403	-3.170205	-0.620245
16	6	0	-2.939772	-0.466811	0.025142
17	9	0	-3.535589	0.046994	1.141638
18	9	0	-3.226785	-1.803740	0.004933
19	9	0	-3.547968	0.080059	-1.069360
20	1	0	3.648951	-2.972971	-0.588949
21	1	0	4.709884	0.699545	-0.225490
22	1	0	3.179551	-1.029842	1.490383
23	1	0	-0.959877	-2.255094	-0.068356
24	1	0	0.661909	3.565085	-0.139745
25	1	0	3.292468	2.942692	-0.233030
26	1	0	0.871398	-2.415569	-0.273259

Standard orientation of IM1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.703057	-2.618578	0.459754
2	6	0	1.372144	-2.429092	0.570661
3	6	0	0.644446	-1.403417	0.082896
4	6	0	1.241520	-0.284063	-0.346447
5	6	0	2.531913	0.077340	-0.339425
6	6	0	3.580812	-0.752947	-0.214161
7	6	0	3.613678	-2.098507	-0.405948
8	6	0	-0.703723	-1.401168	0.179731
9	6	0	-1.571916	-0.408494	-0.120164
10	6	0	-1.115836	0.787609	-0.587523
11	6	0	0.405826	0.929965	-0.779405
12	6	0	1.247611	2.133709	-0.524780

13	6	0	2.581678	1.422456	-0.392182
14	8	0	-1.831002	1.718013	-0.889318
15	1	0	1.232933	2.829927	-1.391309
16	16	0	0.835083	2.904322	1.068220
17	6	0	-3.069410	-0.599457	0.061295
18	9	0	-3.719403	-0.460755	-1.085379
19	9	0	-3.574556	0.276689	0.918024
20	9	0	-3.394813	-1.796797	0.524504
21	1	0	3.139841	-3.407586	1.103147
22	1	0	0.843752	-3.181780	1.185963
23	1	0	4.566623	-0.302352	0.003898
24	1	0	2.808748	-2.001558	-1.163840
25	1	0	-1.156941	-2.326810	0.574878
26	1	0	3.519825	1.997198	-0.356894
27	1	0	1.760067	3.875338	0.987037

Standard orientation of IM1.1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-2.630704	-2.818993	-0.275079
2	6	0	-1.304910	-2.616938	-0.299302
3	6	0	-0.600974	-1.486930	-0.101556
4	6	0	-1.135472	-0.283330	0.162974
5	6	0	-2.416096	0.094719	0.313076
6	6	0	-3.531846	-0.640599	0.228252
7	6	0	-3.622069	-1.949278	-0.040097
8	6	0	0.747233	-1.550058	-0.164740
9	6	0	1.546214	-0.485381	0.034943
10	6	0	0.991992	0.703750	0.296306
11	6	0	-0.343283	0.788833	0.341713
12	6	0	-1.095336	2.061352	0.610870
13	6	0	-2.449534	1.409634	0.594740
14	8	0	1.785788	1.774468	0.504070
15	1	0	-0.857900	2.503540	1.602429
16	16	0	-1.028970	3.221246	-0.785935
17	6	0	3.050705	-0.548710	-0.019059
18	9	0	3.461601	-1.773857	-0.291786
19	9	0	3.636827	-0.239294	1.130371
20	9	0	3.582708	0.209892	-0.968947
21	1	0	-2.958785	-3.859197	-0.472274
22	1	0	-0.727324	-3.537592	-0.513767
23	1	0	-4.492554	-0.117169	0.393653
24	1	0	-4.648213	-2.365115	-0.069166
25	1	0	1.234185	-2.516061	-0.378626
26	1	0	-3.364836	1.990352	0.784787
27	1	0	-1.373117	2.326476	-1.729621

Standard orientation of IM2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	1	0	-0.864147	3.242677	-0.858218
2	1	0	-0.956418	3.196603	0.927148
3	8	0	1.876751	2.086824	0.089969
4	6	0	-2.559582	2.158612	-0.078753
5	6	0	-1.119085	2.625237	0.008390
6	6	0	-0.343849	1.353929	0.015533
7	6	0	1.094722	1.150936	0.037564
8	6	0	1.509173	-0.271683	-0.013733
9	6	0	0.577796	-1.248123	-0.082181
10	6	0	-3.865292	-1.071116	0.573421
11	6	0	-3.860165	0.026290	-0.213585
12	6	0	-2.647240	0.815725	-0.109973
13	6	0	-1.289224	0.266775	-0.064186
14	6	0	-0.879812	-1.024391	-0.099570
15	6	0	-1.804262	-2.173691	-0.217484
16	6	0	-3.120794	-2.223199	0.073692
17	6	0	2.976132	-0.487270	0.014309
18	9	0	3.284383	-1.815328	-0.032096
19	9	0	3.555809	-0.013625	1.145371
20	9	0	3.610855	0.075450	-1.044097
21	1	0	-3.399746	2.838491	-0.110642
22	1	0	0.901604	-2.287543	-0.120450
23	1	0	-3.647602	-0.936383	1.637903
24	1	0	-4.096388	-0.108550	-1.273485
25	1	0	-1.343387	-3.097725	-0.566411
26	1	0	-3.678452	-3.148819	-0.038862

Standard orientation of IM2.1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-2.993287	-2.151186	-0.000103
2	6	0	-1.653417	-2.089600	0.000243
3	6	0	-0.839318	-1.017691	0.000411
4	6	0	-1.249771	0.260717	0.000143
5	6	0	-2.486997	0.785893	-0.000168
6	6	0	-3.671809	0.161975	-0.000569
7	6	0	-3.892866	-1.158586	-0.000475
8	6	0	0.495983	-1.222314	0.000623
9	6	0	1.403659	-0.227099	0.001365
10	6	0	0.972766	1.042447	0.000570
11	6	0	-0.349730	1.259944	0.000299
12	6	0	-0.975546	2.627215	-0.000126

13	6	0	-2.389893	2.127434	-0.000261
14	8	0	1.854422	2.067891	0.000817
15	1	0	-0.741433	3.202250	0.923385
16	1	0	-0.741239	3.201688	-0.924002
17	6	0	2.891708	-0.483238	-0.000477
18	9	0	3.511258	0.009013	-1.065339
19	9	0	3.157744	-1.779725	-0.015240
20	9	0	3.505078	-0.016437	1.079105
21	1	0	-3.424369	-3.172355	-0.000056
22	1	0	-1.171185	-3.086901	0.000546
23	1	0	-4.575947	0.799870	-0.001055
24	1	0	-4.956173	-1.468805	-0.000927
25	1	0	0.878553	-2.256565	0.000489
26	1	0	-3.239192	2.826563	-0.000505

Standard orientation of IM3

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.174211	-1.153915	-0.285467
2	6	0	-1.765029	-1.719822	-0.372707
3	6	0	-0.775615	-0.643541	-0.695571
4	6	0	-1.097317	0.797898	-0.275201
5	6	0	-2.278622	1.419957	-0.157085
6	6	0	-3.482727	0.931431	-0.503237
7	6	0	-3.724391	-0.247556	-1.130759
8	6	0	0.736927	-0.926962	-0.709637
9	6	0	1.608036	-0.017020	-0.237203
10	6	0	1.190721	1.205180	0.224995
11	6	0	-0.117209	1.567279	0.194420
12	6	0	-0.681470	2.708859	0.617953
13	6	0	-2.007324	2.603646	0.420477
14	8	0	2.011519	1.984113	0.659722
15	16	0	-1.305855	-2.441142	1.242085
16	1	0	-1.744044	-2.509541	-1.159689
17	6	0	3.088963	-0.368002	-0.220679
18	9	0	3.372038	-1.570689	-0.698856
19	9	0	3.579045	-0.333508	1.010428
20	9	0	3.787437	0.491511	-0.949020
21	1	0	-3.826239	-1.518447	0.529705
22	1	0	-4.375720	1.498922	-0.185188
23	1	0	-2.837678	-0.253427	-1.804853
24	1	0	1.070407	-1.905031	-1.087865
25	1	0	-0.172965	3.570363	1.070062
26	1	0	-2.745562	3.372494	0.685892
27	1	0	-2.337748	-3.300372	1.316048

Standard orientation of IM3.1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.136327	-1.150325	-0.955293
2	6	0	-1.825697	-1.563865	-0.356678
3	6	0	-0.696174	-0.582747	-0.147042
4	6	0	-0.844357	0.750159	-0.028117
5	6	0	-1.938641	1.521598	-0.185386
6	6	0	-3.182421	1.233957	-0.594493
7	6	0	-3.698629	0.063079	-0.986607
8	6	0	0.528324	-1.124336	0.010149
9	6	0	1.773000	-0.248092	0.247301
10	6	0	1.431855	1.227317	0.552010
11	6	0	0.150593	1.593649	0.313940
12	6	0	-0.301755	2.849587	0.406739
13	6	0	-1.600077	2.795290	0.093637
14	8	0	2.315594	1.964662	0.932552
15	16	0	-2.239930	-2.241069	1.287685
16	1	0	-1.443039	-2.377603	-1.021940
17	6	0	3.091029	-0.648379	-0.337220
18	9	0	4.042999	-0.651214	0.582357
19	9	0	3.445995	0.189444	-1.298587
20	9	0	3.058021	-1.859771	-0.869693
21	1	0	-3.758600	-1.988080	-1.326697
22	1	0	-3.876832	2.091621	-0.688231
23	1	0	-4.729823	0.099271	-1.389111
24	1	0	0.663352	-2.217435	-0.020277
25	1	0	0.263038	3.752966	0.669769
26	1	0	-2.258699	3.674450	0.055127
27	1	0	-0.972742	-2.302874	1.733653

Standard orientation of IM3.2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.241620	-1.124725	-0.772340
2	6	0	-1.819021	-1.526318	-0.504434
3	6	0	-0.730436	-0.500430	-0.310595
4	6	0	-0.934043	0.802565	-0.066243
5	6	0	-2.048890	1.548221	0.005347
6	6	0	-3.331251	1.228915	-0.210600
7	6	0	-3.849860	0.054708	-0.591889
8	6	0	0.554038	-0.914598	-0.341890
9	6	0	1.604757	-0.099174	-0.133218
10	6	0	1.384323	1.194645	0.130658
11	6	0	0.113343	1.613824	0.159197

12	6	0	-0.334149	2.852015	0.400959
13	6	0	-1.668946	2.803976	0.308356
14	8	0	2.435311	2.013840	0.349456
15	16	0	-1.898780	-2.523563	1.027544
16	1	0	-1.517575	-2.169493	-1.368195
17	6	0	3.036683	-0.565996	-0.161424
18	9	0	3.101036	-1.862145	-0.406706
19	9	0	3.678017	-0.402945	0.988587
20	9	0	3.759168	0.000098	-1.119542
21	1	0	-3.892307	-1.958873	-1.102092
22	1	0	-4.061873	2.055815	-0.119815
23	1	0	-4.938989	0.059289	-0.794838
24	1	0	0.746477	-1.981706	-0.538918
25	1	0	0.268042	3.743118	0.619432
26	1	0	-2.329009	3.673302	0.436618
27	1	0	-0.630317	-2.976020	0.999084

Standard orientation of IM4

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.241620	-1.124725	-0.772340
2	6	0	-1.819021	-1.526318	-0.504434
3	6	0	-0.730436	-0.500430	-0.310595
4	6	0	-0.934043	0.802565	-0.066243
5	6	0	-2.048890	1.548221	0.005347
6	6	0	-3.331251	1.228915	-0.210600
7	6	0	-3.849860	0.054708	-0.591889
8	6	0	0.554038	-0.914598	-0.341890
9	6	0	1.604757	-0.099174	-0.133218
10	6	0	1.384323	1.194645	0.130658
11	6	0	0.113343	1.613824	0.159197
12	6	0	-0.334149	2.852015	0.400959
13	6	0	-1.668946	2.803976	0.308356
14	8	0	2.435311	2.013840	0.349456
15	16	0	-1.898780	-2.523563	1.027544
16	1	0	-1.517575	-2.169493	-1.368195
17	6	0	3.036683	-0.565996	-0.161424
18	9	0	3.101036	-1.862145	-0.406706
19	9	0	3.678017	-0.402945	0.988587
20	9	0	3.759168	0.000098	-1.119542
21	1	0	-3.892307	-1.958873	-1.102092
22	1	0	-4.061873	2.055815	-0.119815
23	1	0	-4.938989	0.059289	-0.794838
24	1	0	0.746477	-1.981706	-0.538918
25	1	0	0.268042	3.743118	0.619432
26	1	0	-2.329009	3.673302	0.436618
27	1	0	-0.630317	-2.976020	0.999084

Standard orientation of IM4.1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.230194	-2.054371	-0.001230
2	6	0	-1.751957	-2.162757	-0.213163
3	6	0	-0.821999	-0.973228	-0.199459
4	6	0	-1.188724	0.315609	-0.072323
5	6	0	-2.409423	0.862721	0.094229
6	6	0	-3.628483	0.316494	0.202493
7	6	0	-3.993875	-0.970041	0.168291
8	6	0	0.483752	-1.275342	-0.344670
9	6	0	1.576673	-0.189540	-0.314999
10	6	0	1.013457	1.247953	-0.267950
11	6	0	-0.327061	1.352828	-0.109012
12	6	0	-0.975708	2.515508	0.025789
13	6	0	-2.268119	2.201011	0.154804
14	8	0	1.783060	2.180940	-0.349909
15	1	0	-1.390929	-2.867566	0.576323
16	1	0	-1.621122	-2.671201	-1.199978
17	6	0	2.966365	-0.520988	0.128644
18	9	0	3.228142	0.043267	1.297172
19	9	0	3.863387	-0.095481	-0.746741
20	9	0	3.154199	-1.822838	0.275730
21	1	0	-3.756418	-3.029162	-0.002670
22	1	0	-4.469754	1.022568	0.346294
23	1	0	-5.076698	-1.167776	0.292563
24	1	0	0.792969	-2.324676	-0.477319
25	1	0	-0.553268	3.528255	0.033493
26	1	0	-3.069037	2.942373	0.286463

Standard orientation of IM4.2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.234534	-2.027030	-0.000274
2	6	0	1.740128	-2.158483	0.000616
3	6	0	0.827448	-0.959693	0.000529
4	6	0	1.220565	0.321596	0.000238
5	6	0	2.433745	0.897327	-0.000188
6	6	0	3.659069	0.357614	-0.000600
7	6	0	4.009254	-0.934854	-0.000755
8	6	0	-0.503061	-1.182725	0.000661
9	6	0	-1.428198	-0.203596	0.001078
10	6	0	-1.020000	1.074459	0.000468
11	6	0	0.300347	1.300701	0.000342
12	6	0	0.925218	2.484824	0.000044

13	6	0	2.239565	2.229648	-0.000135
14	8	0	-1.921032	2.083429	0.000595
15	1	0	1.481263	-2.768035	-0.899457
16	1	0	1.482185	-2.766984	0.901719
17	6	0	-2.910099	-0.490466	-0.000490
18	9	0	-3.539134	-0.015173	-1.067337
19	9	0	-3.534297	-0.034023	1.077353
20	9	0	-3.146148	-1.792776	-0.011534
21	1	0	3.764196	-3.000118	-0.000374
22	1	0	4.505475	1.071365	-0.001010
23	1	0	5.099465	-1.131822	-0.001275
24	1	0	-0.839590	-2.232462	0.000568
25	1	0	0.460466	3.479020	-0.000004
26	1	0	3.019927	3.003431	-0.000477

Standard orientation of P1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-2.597924	-2.852798	-0.181757
2	6	0	-1.263143	-2.687323	-0.271241
3	6	0	-0.561315	-1.558756	-0.050671
4	6	0	-1.145656	-0.355998	0.030794
5	6	0	-2.448757	-0.034215	0.000999
6	6	0	-3.496788	-0.873869	0.044558
7	6	0	-3.538289	-2.152054	0.505890
8	6	0	0.784965	-1.559698	-0.059023
9	6	0	1.539577	-0.444952	0.017732
10	6	0	0.926363	0.776959	0.062706
11	6	0	-0.431306	0.778319	0.041171
12	6	0	-1.288860	1.810644	-0.017801
13	6	0	-2.529421	1.303993	-0.081725
14	8	0	1.596973	1.786637	0.101568
15	16	0	-0.966419	3.594005	-0.060734
16	6	0	3.063438	-0.543156	0.020064
17	9	0	3.566138	-0.007480	1.122678
18	9	0	3.578593	0.092307	-1.022203
19	9	0	3.504469	-1.790374	-0.035377
20	1	0	-3.008264	-3.782953	-0.621636
21	1	0	-0.701530	-3.567238	-0.637898
22	1	0	-4.492155	-0.462274	-0.206635
23	1	0	-2.759544	-1.889239	1.249923
24	1	0	1.299454	-2.531647	-0.140152
25	1	0	-3.456339	1.890625	-0.141631
26	1	0	-2.114819	4.252880	-0.298825

Standard orientation of P2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.029525	-2.001188	-0.151659
2	6	0	-1.684053	-2.029365	-0.234108
3	6	0	-0.833177	-1.004322	-0.035188
4	6	0	-1.254671	0.265507	0.014988
5	6	0	-2.494984	0.776746	-0.028000
6	6	0	-3.649524	0.091994	0.026093
7	6	0	-3.866252	-1.159473	0.512029
8	6	0	0.502729	-1.179998	-0.036853
9	6	0	1.398879	-0.172234	0.015224
10	6	0	0.950994	1.119508	0.027589
11	6	0	-0.392711	1.288059	0.002746
12	6	0	-1.075127	2.438439	-0.082660
13	6	0	-2.375782	2.111454	-0.141321
14	8	0	1.719442	2.057927	0.040999
15	6	0	2.896284	-0.463471	0.024536
16	9	0	3.461581	0.034239	1.114430
17	9	0	3.486610	0.077879	-1.030723
18	9	0	3.176330	-1.757345	0.001525
19	1	0	-3.564662	-2.873978	-0.574594
20	1	0	-1.247970	-2.986452	-0.577257
21	1	0	-4.577029	0.632510	-0.239434
22	1	0	-3.063592	-0.991250	1.257836
23	1	0	0.885246	-2.212713	-0.093155
24	1	0	-0.664451	3.455053	-0.128533
25	1	0	-3.202234	2.830526	-0.220431

Standard orientation of P3

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.139547	1.119092	0.496801
2	6	0	-1.861724	1.294433	0.057609
3	6	0	-0.815462	0.434328	0.017824
4	6	0	-0.970537	-0.898642	0.051862
5	6	0	-2.075063	-1.658423	-0.036668
6	6	0	-3.322229	-1.219593	-0.245636
7	6	0	-3.700386	0.066830	-0.154642
8	6	0	0.470742	0.841785	-0.040147
9	6	0	1.546756	0.028071	-0.001079
10	6	0	1.358666	-1.322398	0.068941
11	6	0	0.071300	-1.740290	0.068614
12	6	0	-0.362529	-3.008023	0.050935
13	6	0	-1.698748	-2.949051	-0.038999

14	8	0	2.292707	-2.095687	0.102513
15	16	0	-1.620580	3.108387	-0.107635
16	6	0	2.963016	0.597719	-0.033720
17	9	0	3.626278	0.139109	-1.085022
18	9	0	3.629674	0.251098	1.057438
19	9	0	2.999057	1.919418	-0.102830
20	1	0	-2.756420	0.414330	1.258401
21	1	0	-4.070097	-1.953971	-0.595408
22	1	0	-4.692419	0.313692	-0.580174
23	1	0	0.691573	1.917745	-0.084583
24	1	0	0.243380	-3.922922	0.043555
25	1	0	-2.361804	-3.819032	-0.139534
26	1	0	-2.547197	3.779794	0.603348

Standard orientation of P4

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.029696	-2.001146	-0.151594
2	6	0	1.684190	-2.029367	-0.233752
3	6	0	0.833188	-1.004443	-0.034786
4	6	0	1.254814	0.265471	0.015302
5	6	0	2.494926	0.776800	-0.028035
6	6	0	3.649700	0.092215	0.025551
7	6	0	3.866693	-1.159159	0.511594
8	6	0	-0.502634	-1.180087	-0.036418
9	6	0	-1.398884	-0.172463	0.015535
10	6	0	-0.950994	1.119239	0.027875
11	6	0	0.392702	1.287906	0.002931
12	6	0	1.074975	2.438351	-0.082515
13	6	0	2.375530	2.111569	-0.141452
14	8	0	-1.719495	2.057666	0.041103
15	1	0	1.248249	-2.986594	-0.576716
16	6	0	-2.896441	-0.463430	0.024415
17	9	0	-3.461823	0.033615	1.114502
18	9	0	-3.176621	-1.757245	0.000357
19	9	0	-3.486456	0.078733	-1.030527
20	1	0	3.564761	-2.874103	-0.574423
21	1	0	4.577005	0.632705	-0.240268
22	1	0	3.064333	-0.990843	1.257692
23	1	0	-0.885236	-2.212864	-0.092804
24	1	0	0.664162	3.454937	-0.128340
25	1	0	3.202014	2.830778	-0.220862

5. Biological assays of benzo[*cd*]azulenes

Kinase activity assays

To evaluate the Pim-inhibitory properties of the compounds, *in vitro* kinase assays were performed as previously described.⁶ Prior to the kinase reactions with radioactive [γ -³²P]-ATP, the compounds were dissolved in DMSO at 10 μ M concentration and pre-incubated for 10 min with 1 μ g aliquots of bacterially produced GST-fused human Pim-1 (hPim-1) or murine Pim-3 (mPim-3) proteins. Phosphorylated samples were resolved by SDS-PAGE and autoradiography images of them were analyzed by the Bio-Rad ChemiDoc™ MP System with Image Lab™ Software (Bio-Rad, USA). Residual kinase activities were calculated as the percentage of kinase activity in the presence of the test compound as compared to the DMSO-treated control samples.

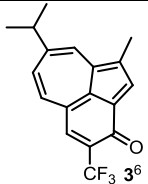
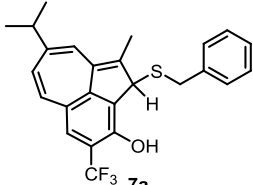
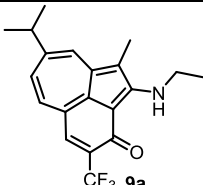
Cell viability assays

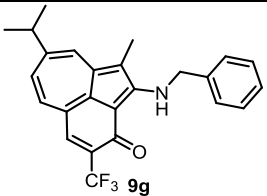
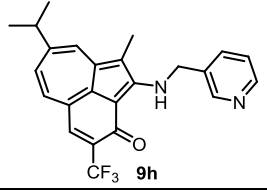
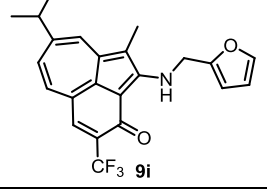
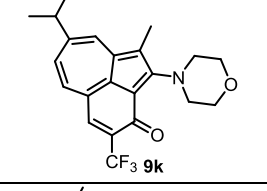
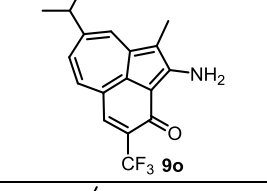
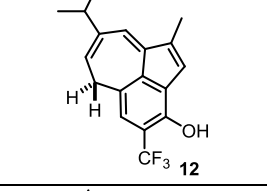
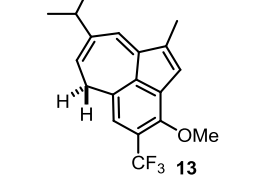
The murine myeloid FDCP1 cell lines expressing only neomycin (FD/Neo) or also human Pim-1 (FD/Pim44)⁷ were cultured in the RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine and antibiotics. WEHI-conditioned medium was used as the source of IL-3 during cell maintenance. To evaluate the effects of the compounds on cell viability, cells were plated on 96-well plates at the concentration of 4×10^4 cells/well. Cells were treated with 0.1% DMSO (control samples) or with DMSO-dissolved compounds at 5 μ M concentration (test samples). Three parallel samples were used for each treatment. After 24-h incubation in medium lacking IL-3, the viability of the cells was determined by the MTT assay, as previously described.⁸

Statistical analysis

Microsoft Excel was used for calculation of the residual kinase activities and cell viability percentages. For determination of EC₅₀ values in FDCP-1 cell lines, non-linear regression fitting of Log[dose] vs. response values were measured by GraphPad Prism6.

Table S5. *In vitro* and cell-based assays for the Pim-inhibitory effects of benzo[*cd*]azulene derivatives

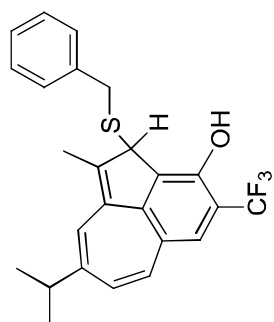
Compound and structure	Residual hPim-1 activity 10 μ M	Residual mPim-3 activity 10 μ M	Cell viability FD/Neo 5 μ M	Cell viability FD/Pim44 5 μ M
 3⁶	51% ⁴	24% ⁴	6% ⁴	3% ⁴
 7a	40%	-	74%	75%
 9a	98%	112%	102%	95%

 <p>9g</p>	72%	88%	118%	116%
 <p>9h</p>	78%	62%	106%	108%
 <p>9i</p>	49%	-	194%	159%
 <p>9k</p>	98%	95%	52%	50%
 <p>9o</p>	53%	-	81%	62%
 <p>12</p>	28%	-	49%	33%
 <p>13</p>	35%	-	67%	77%

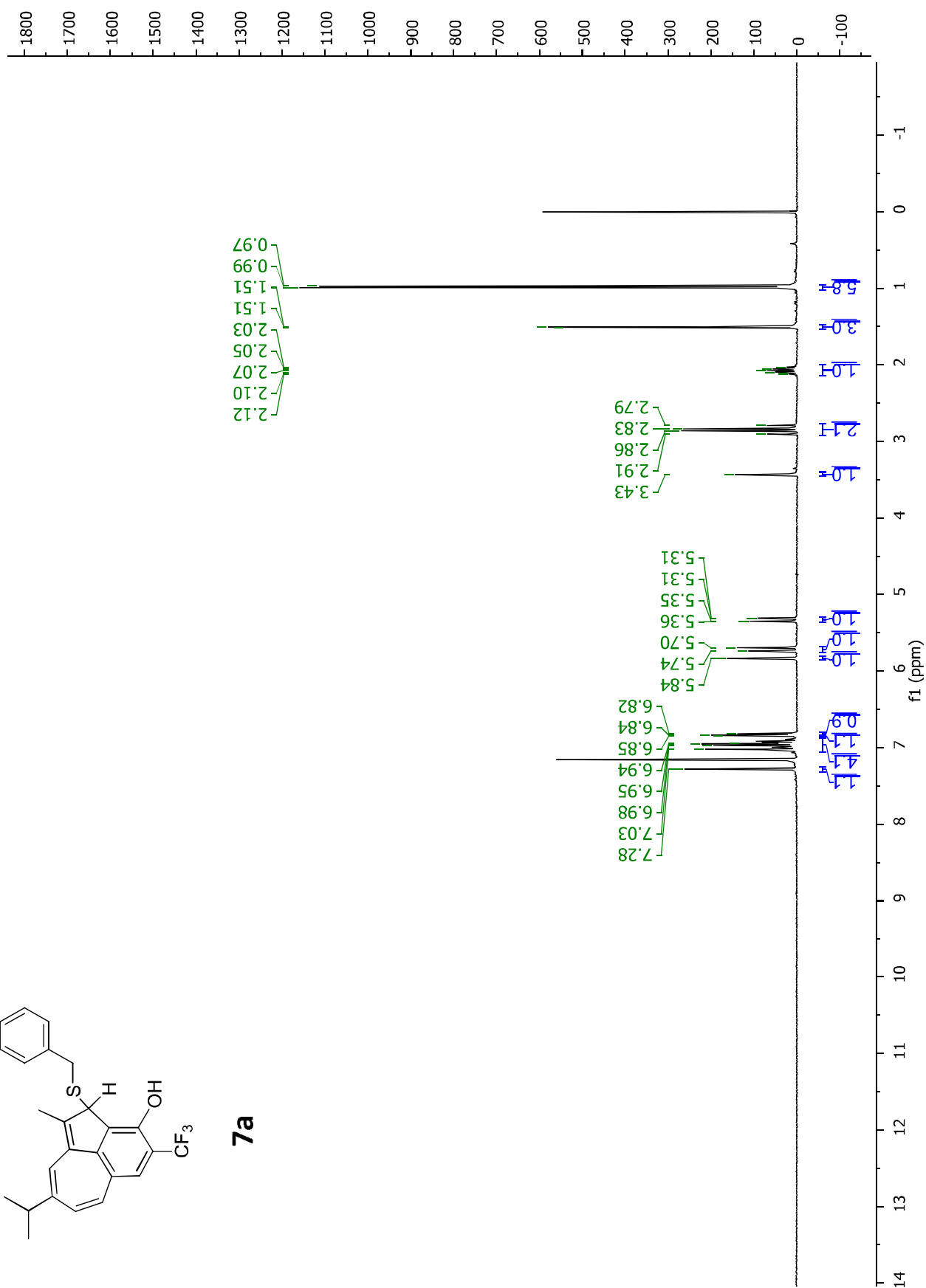
6. References

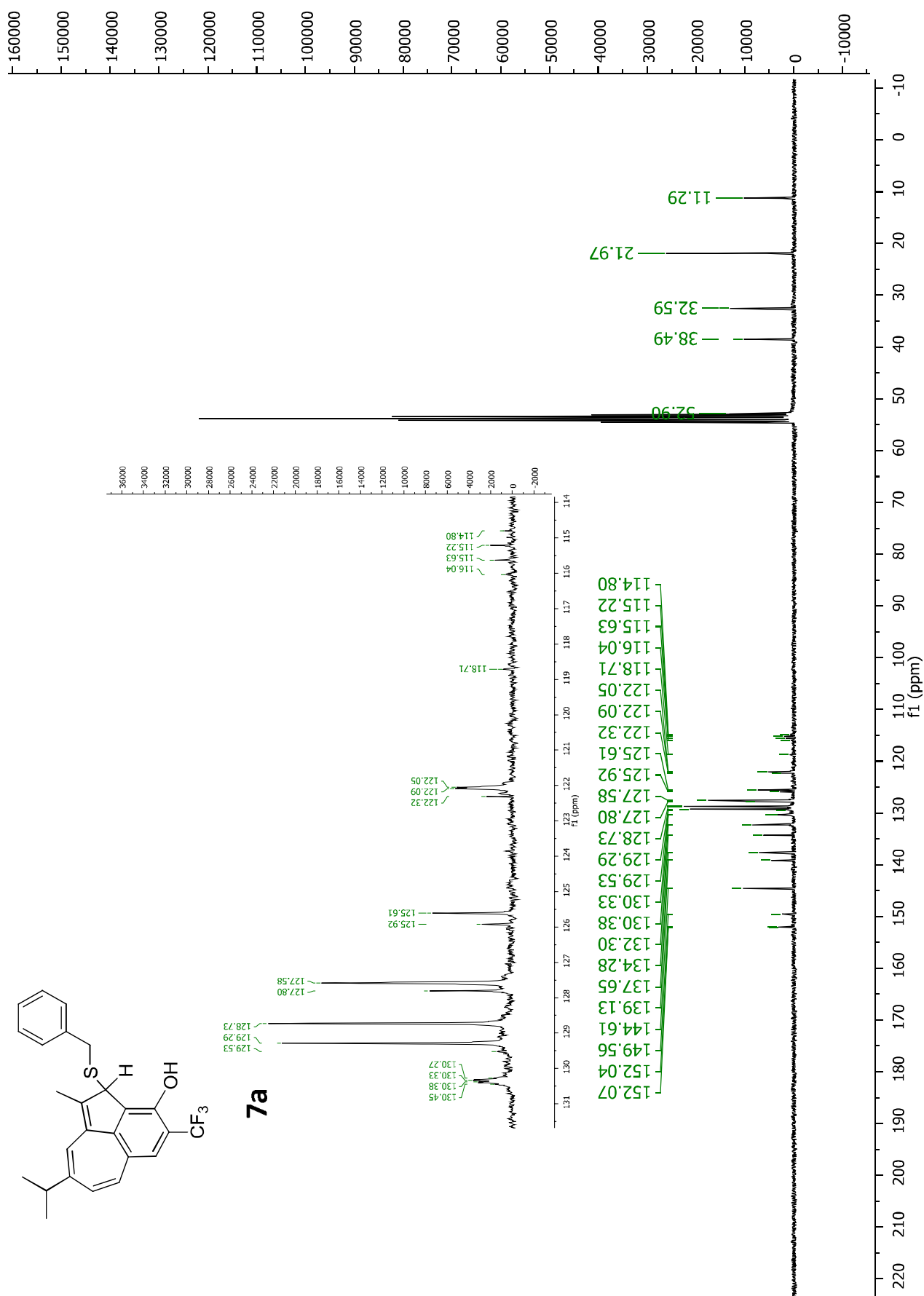
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- (2) CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.34.44 (release 25-10-2010 CrysAlis171 .NET) (compiled Oct 25 2010,18:11:34)
- (3) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, **2008**, *64*, 112.
- (4) Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.
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- (8) N. M. Santio, R. L. Vahakoski, E. M. Rainio, J. A. Sandholm, S. S. Virtanen, M. Prudhomme, F. Anizon, P. Moreau, P. J. Koskinen, *Mol. Cancer* **2010**, *9*, 279–291.

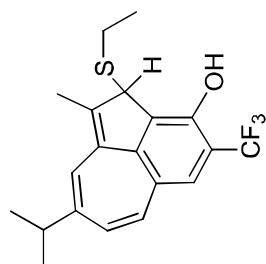
7. ^1H NMR and ^{13}C NMR Spectra



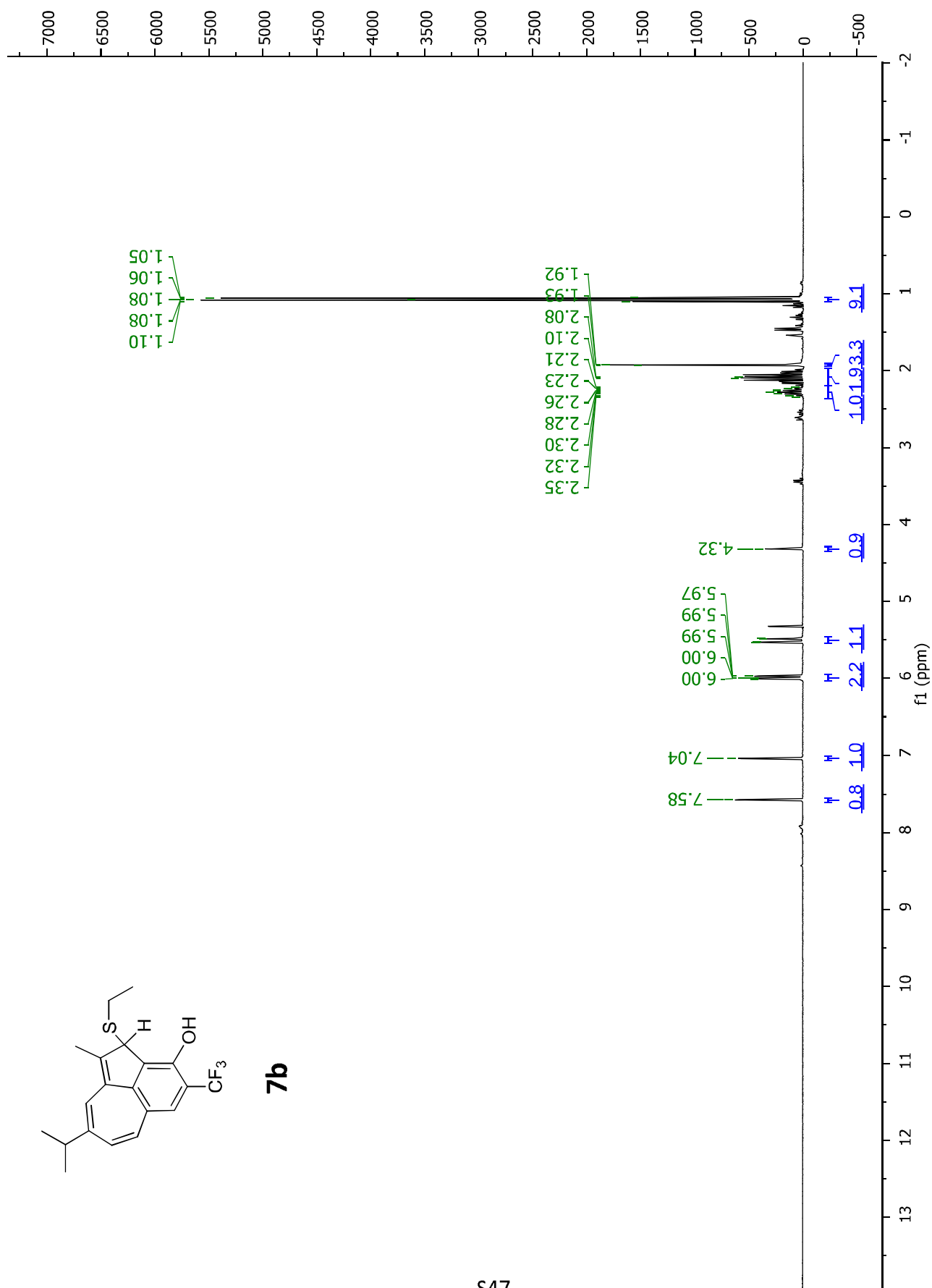
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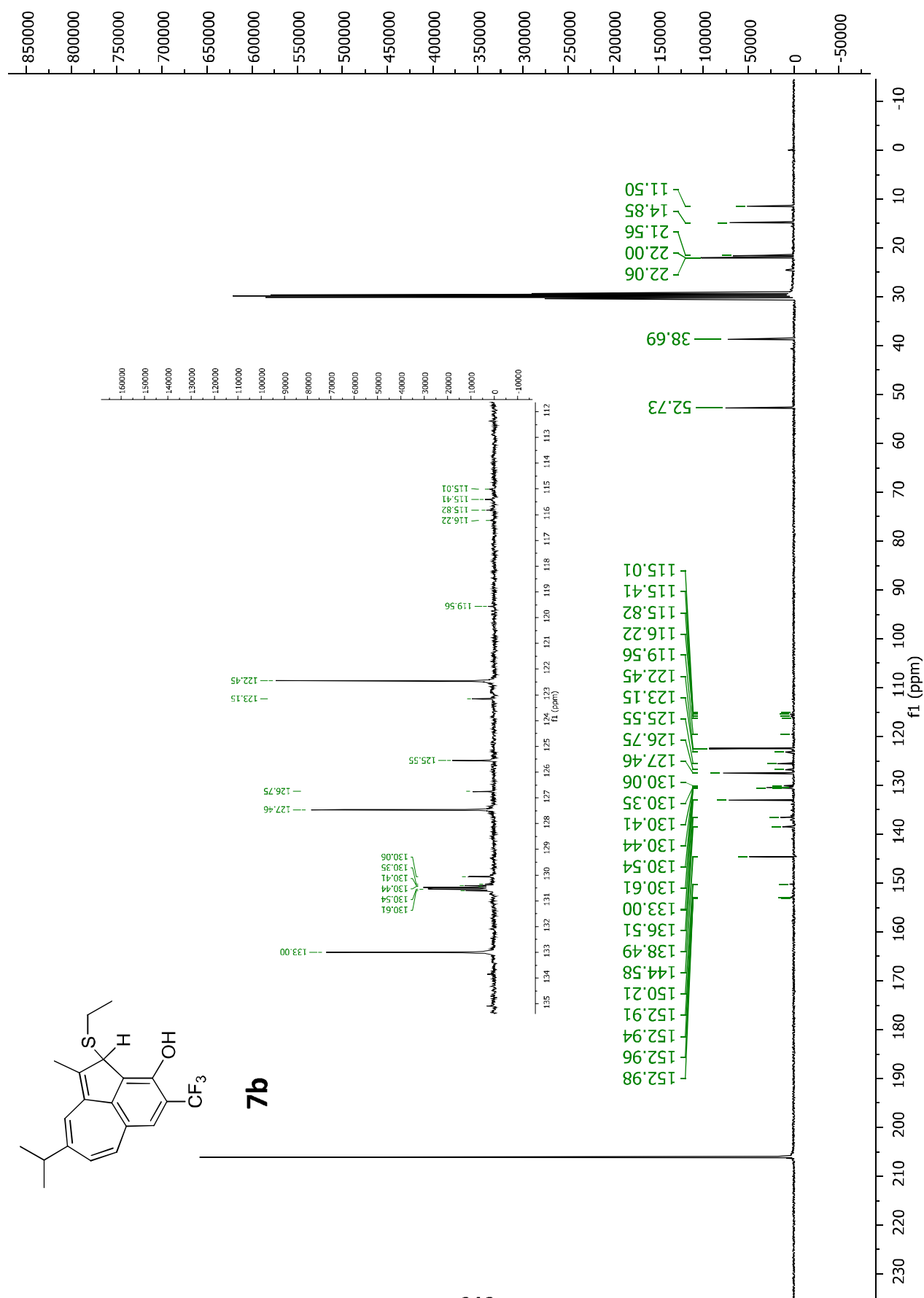


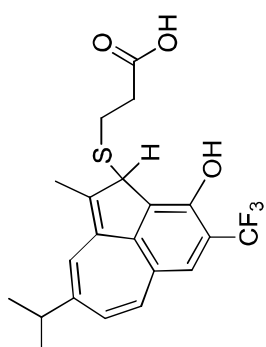




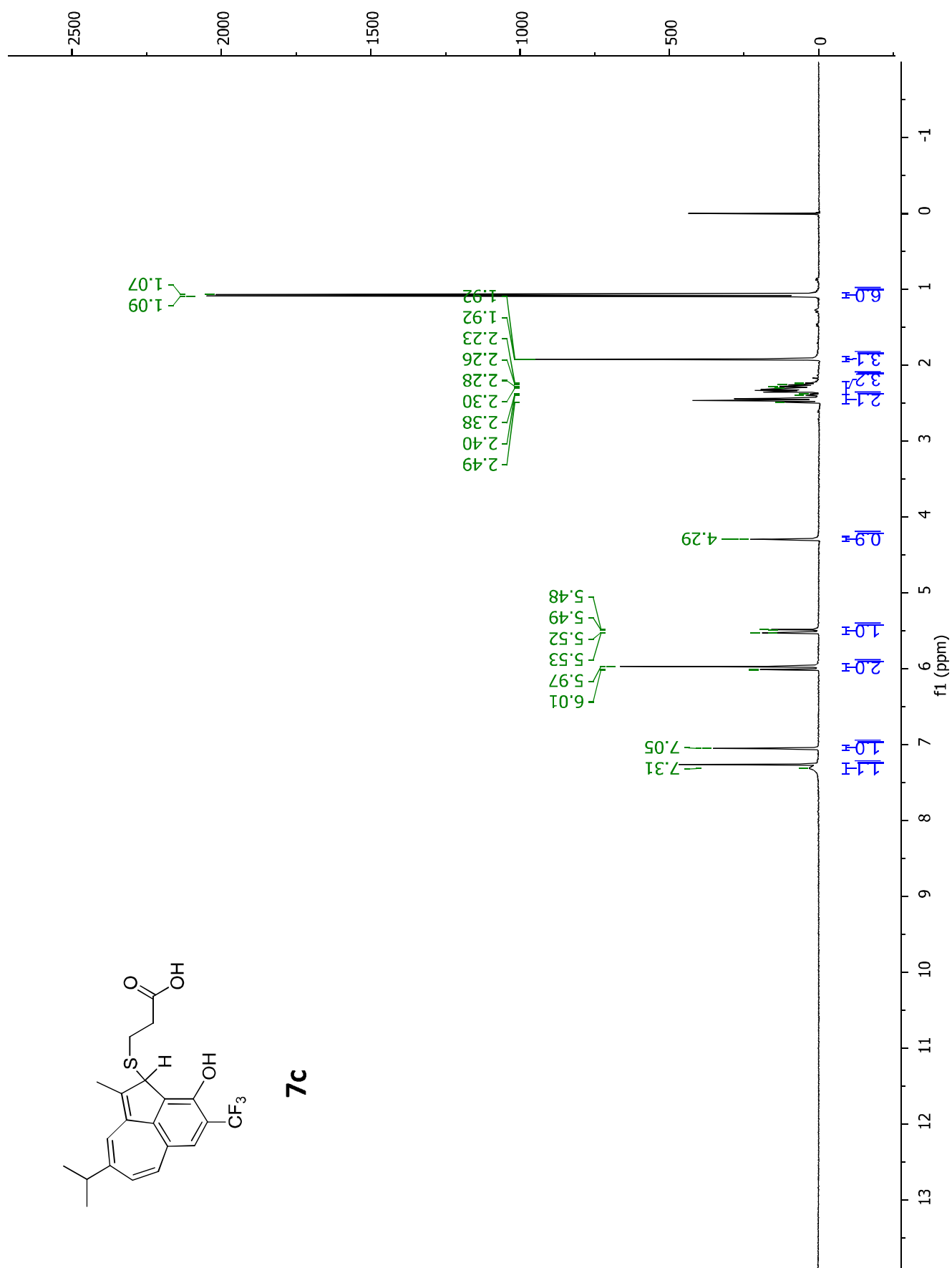
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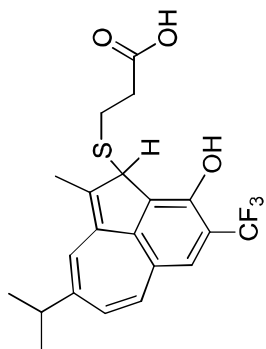




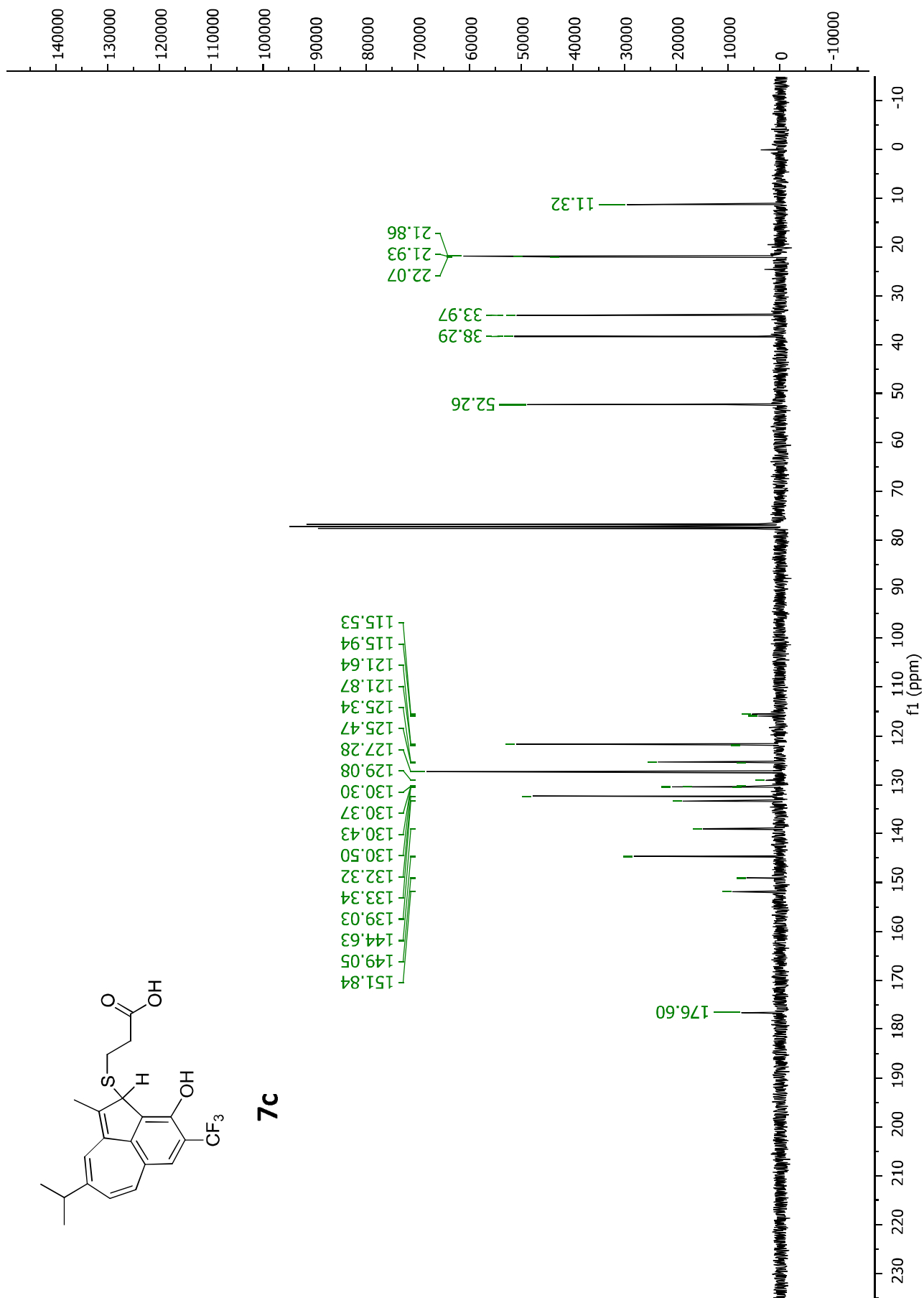


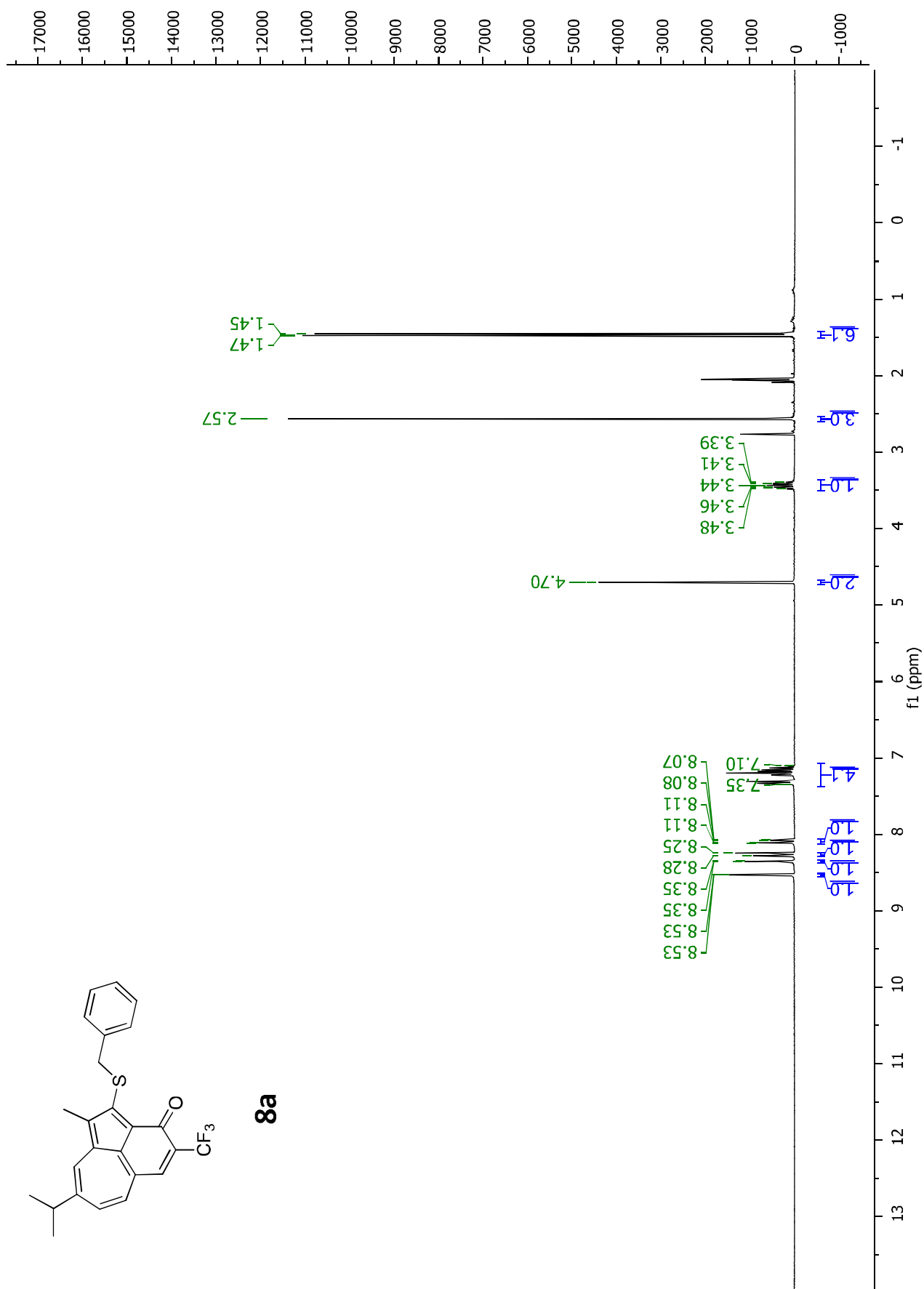
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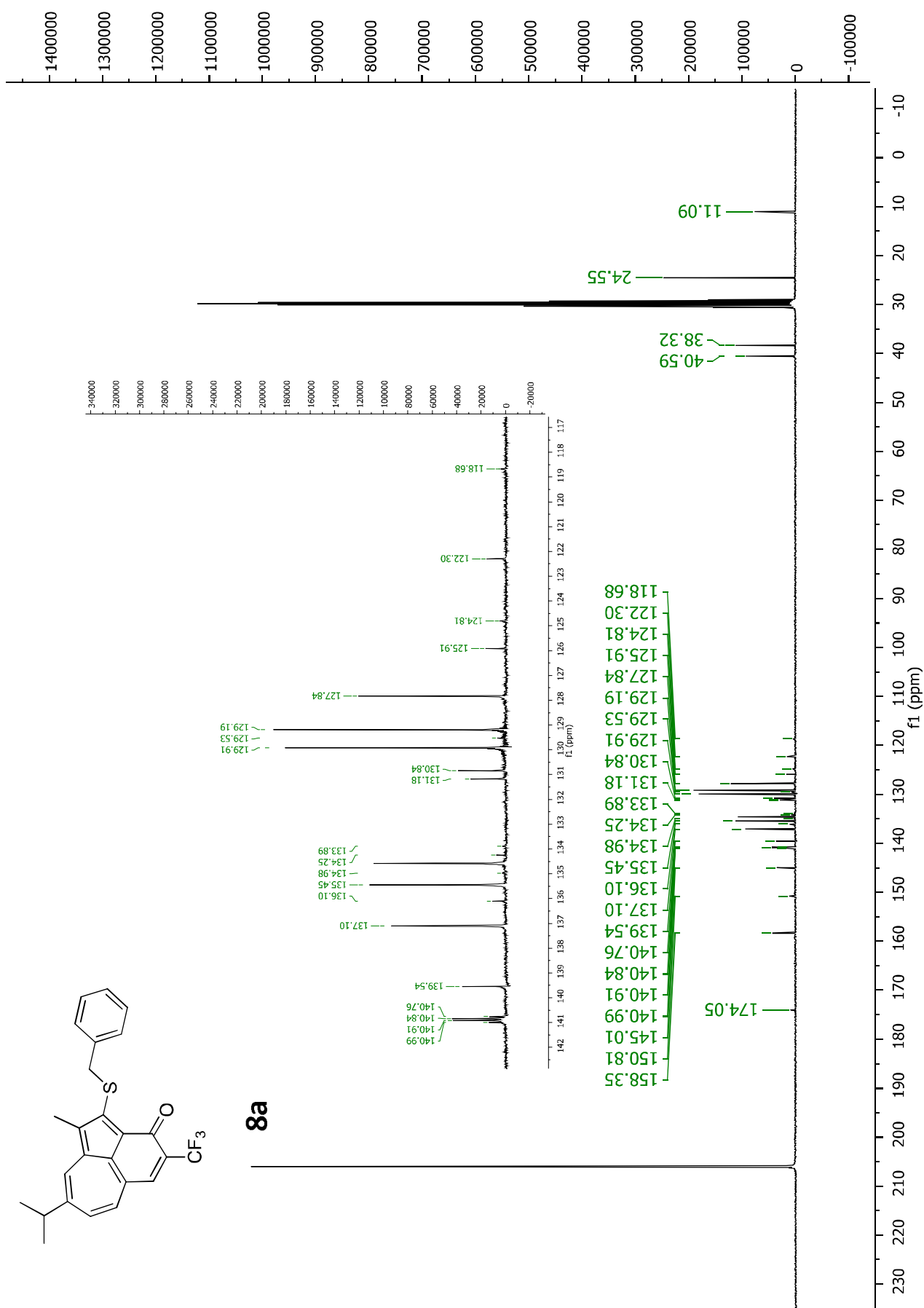


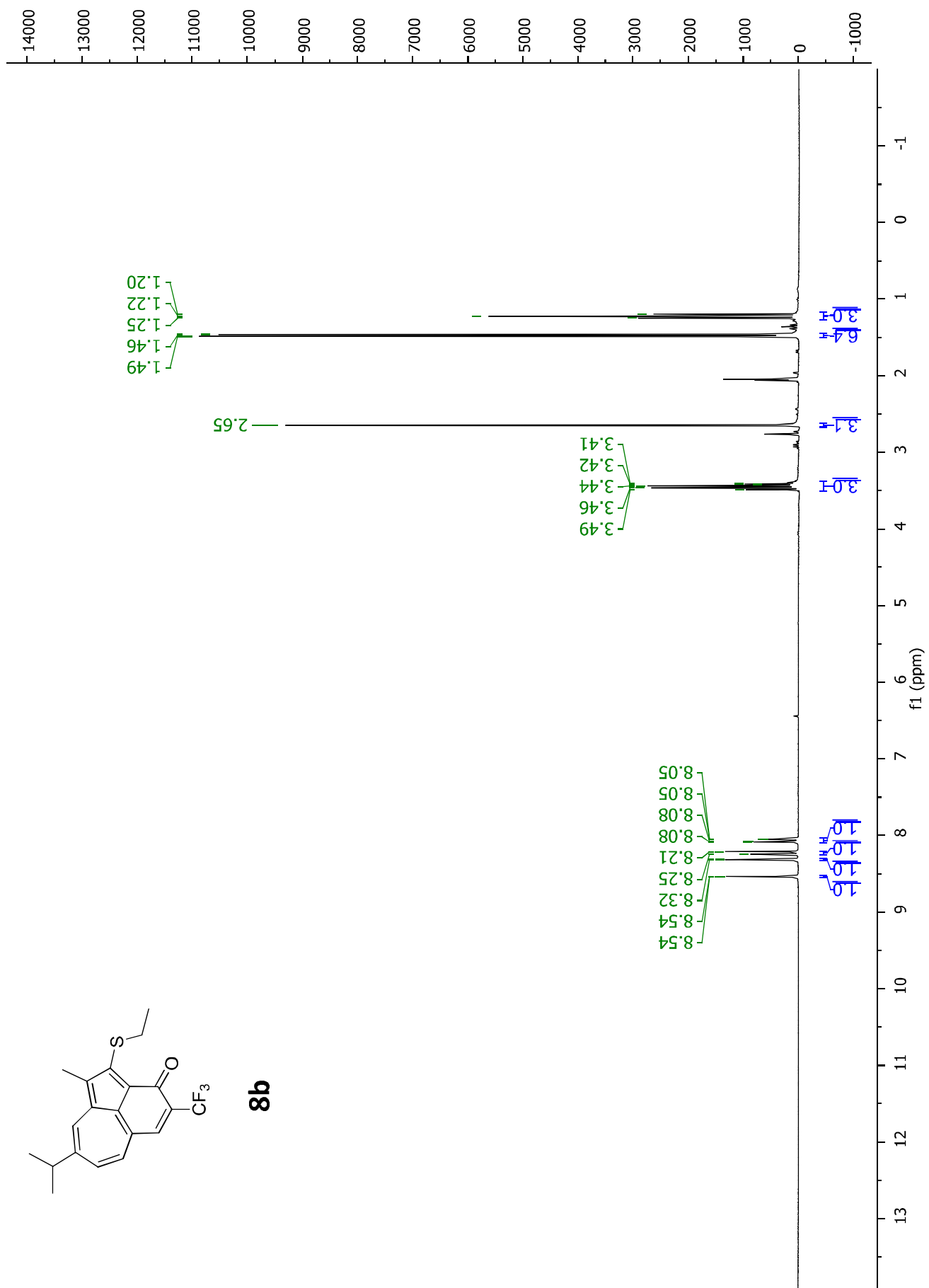


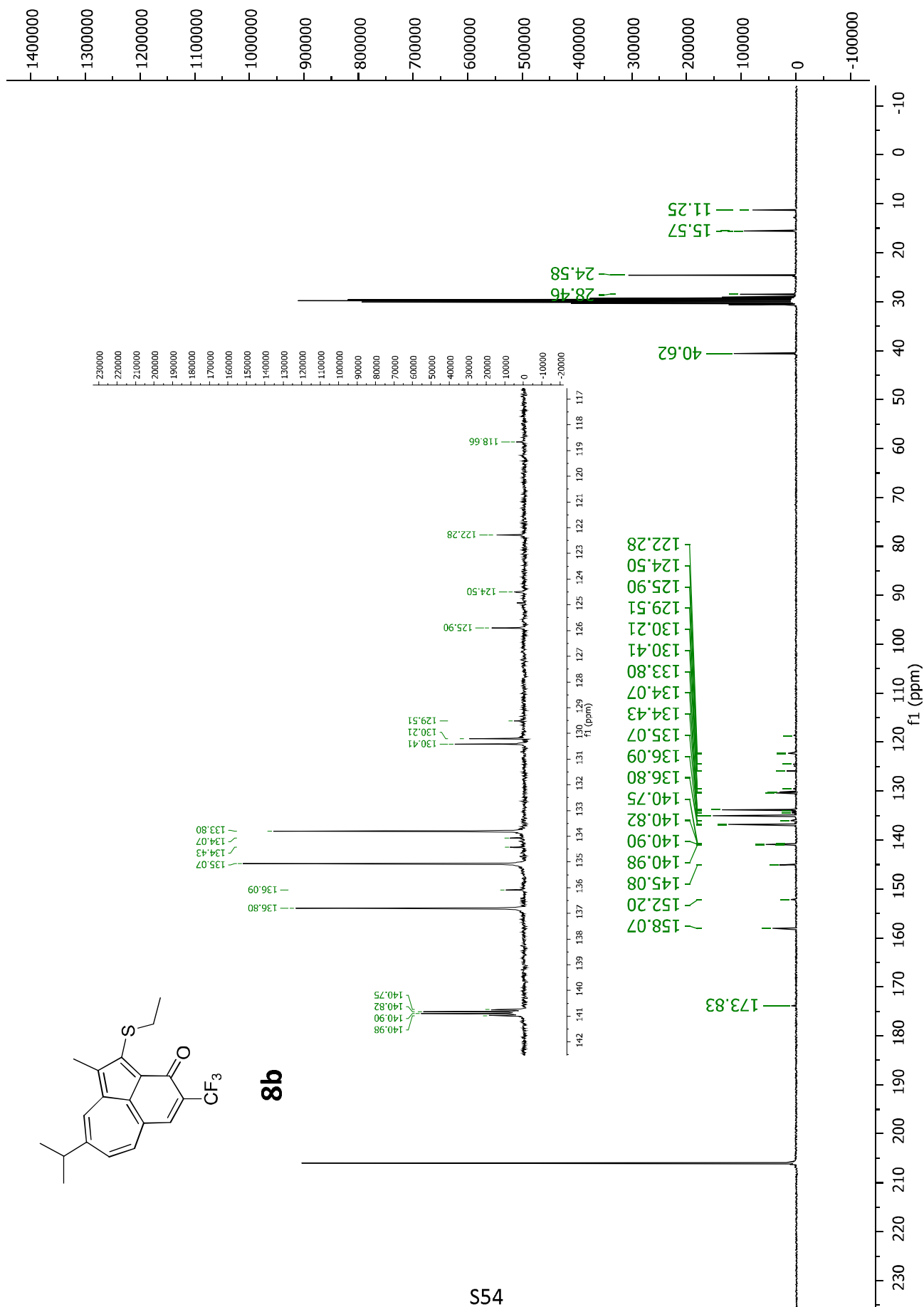
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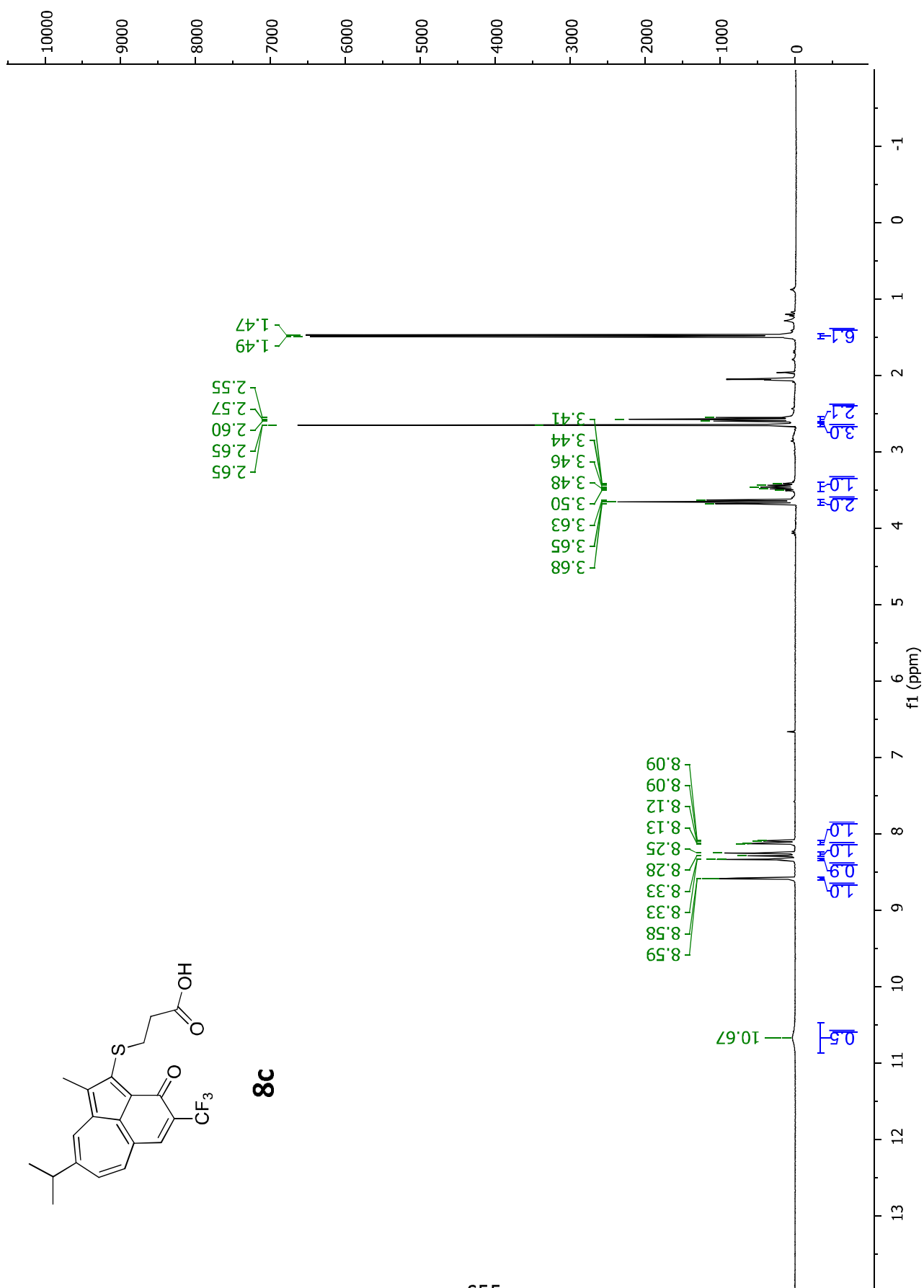


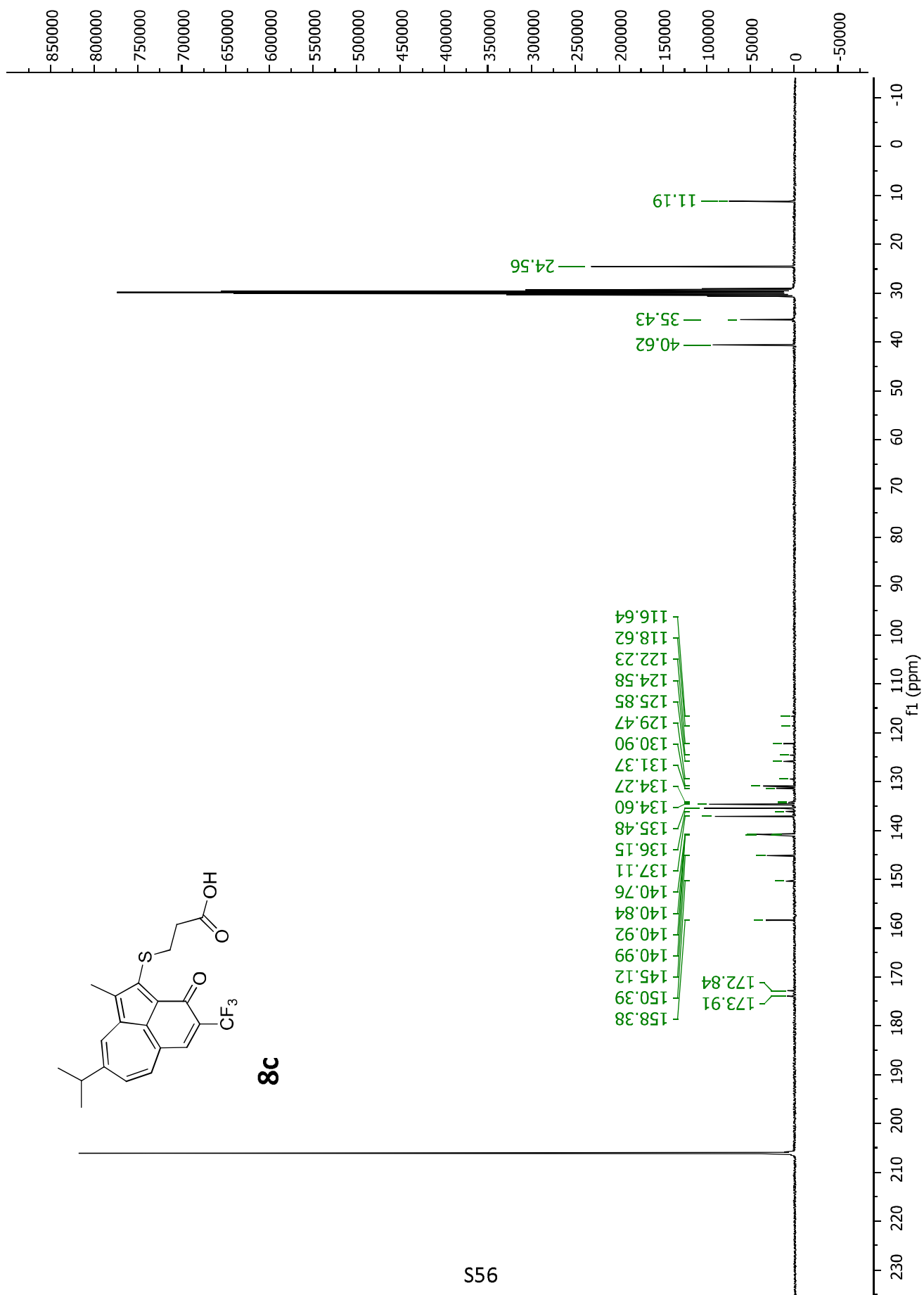


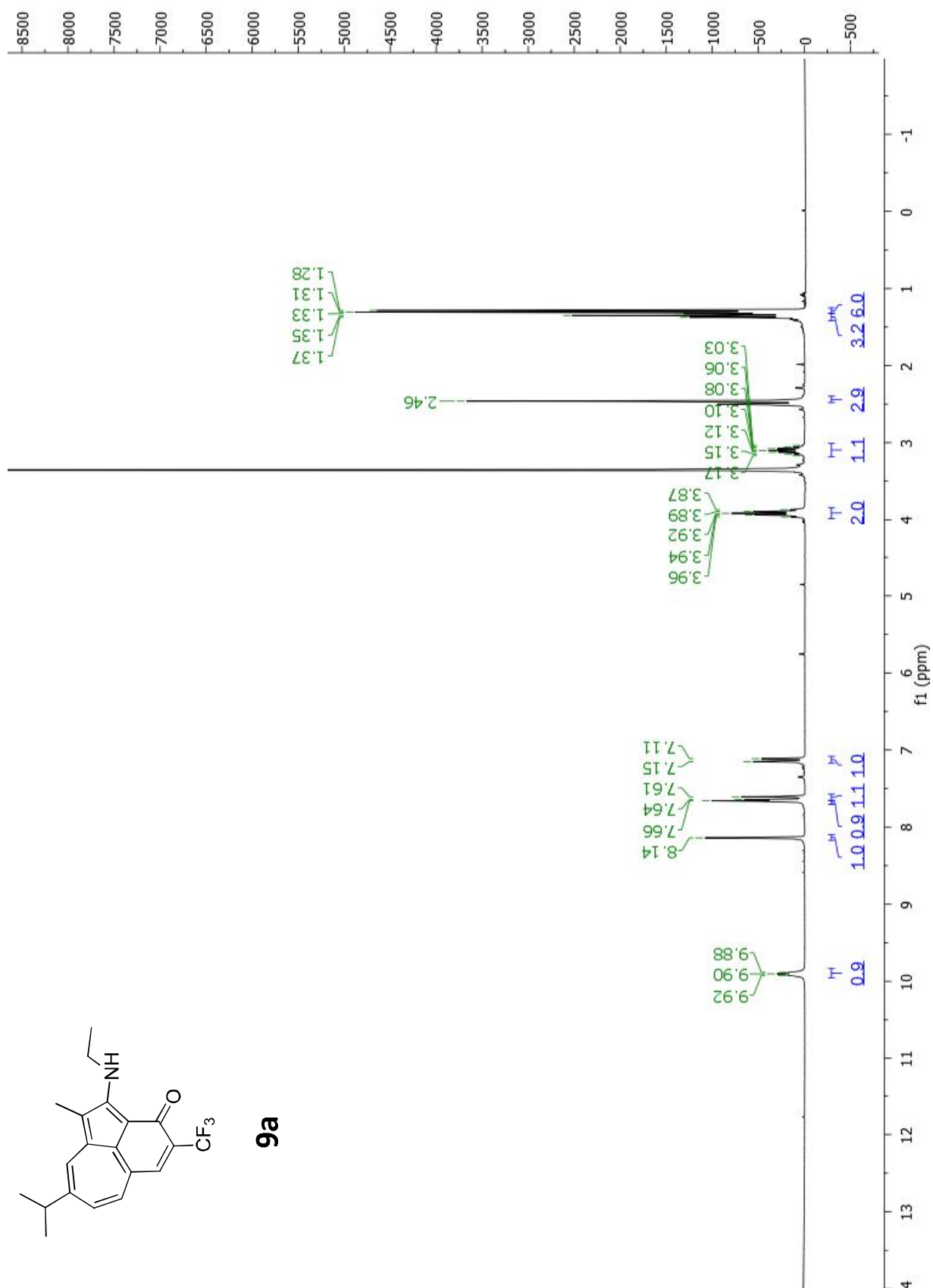


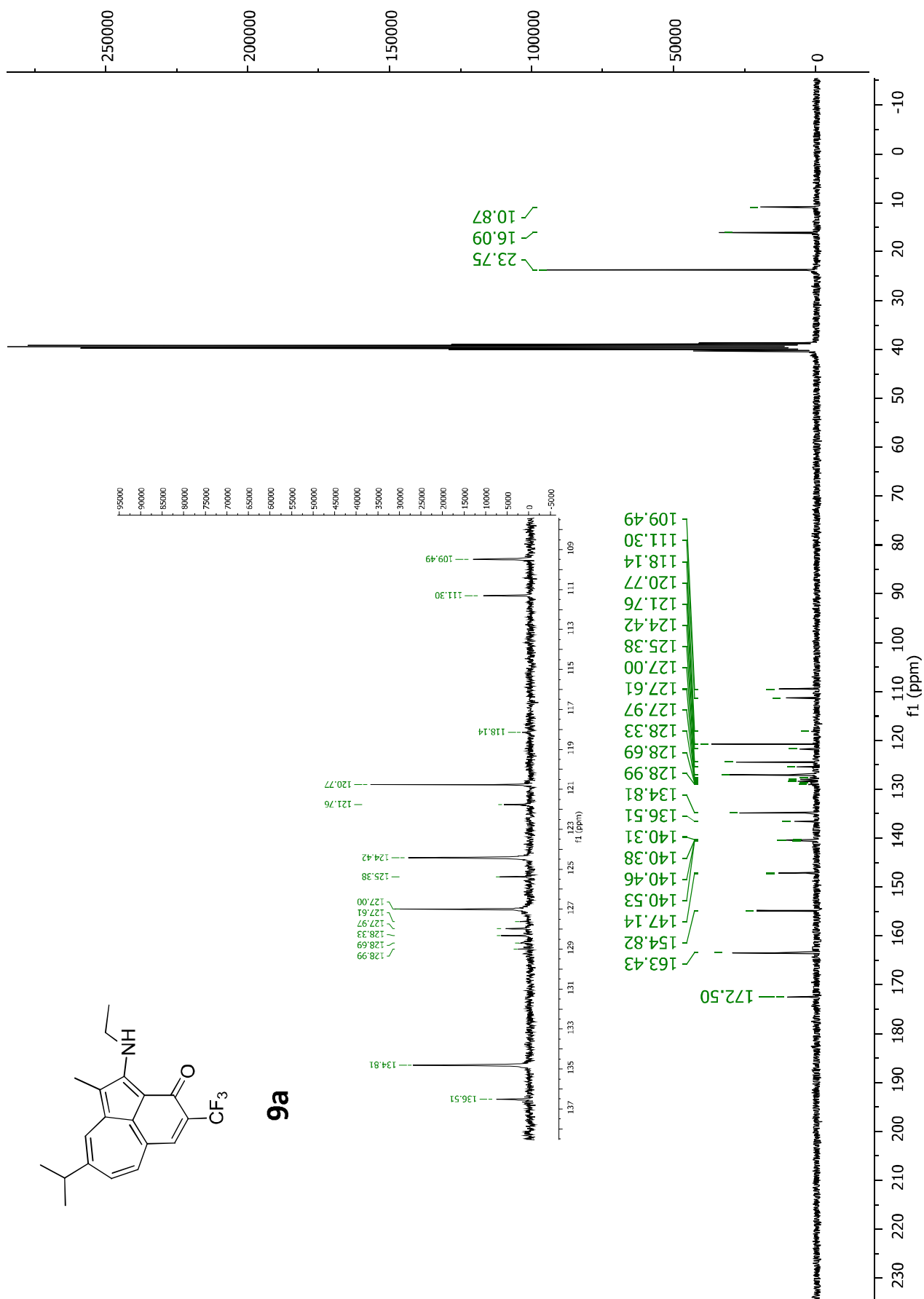


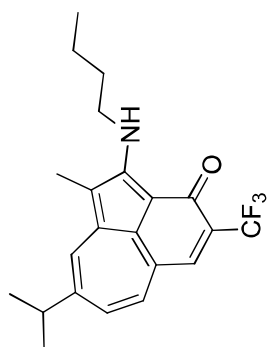




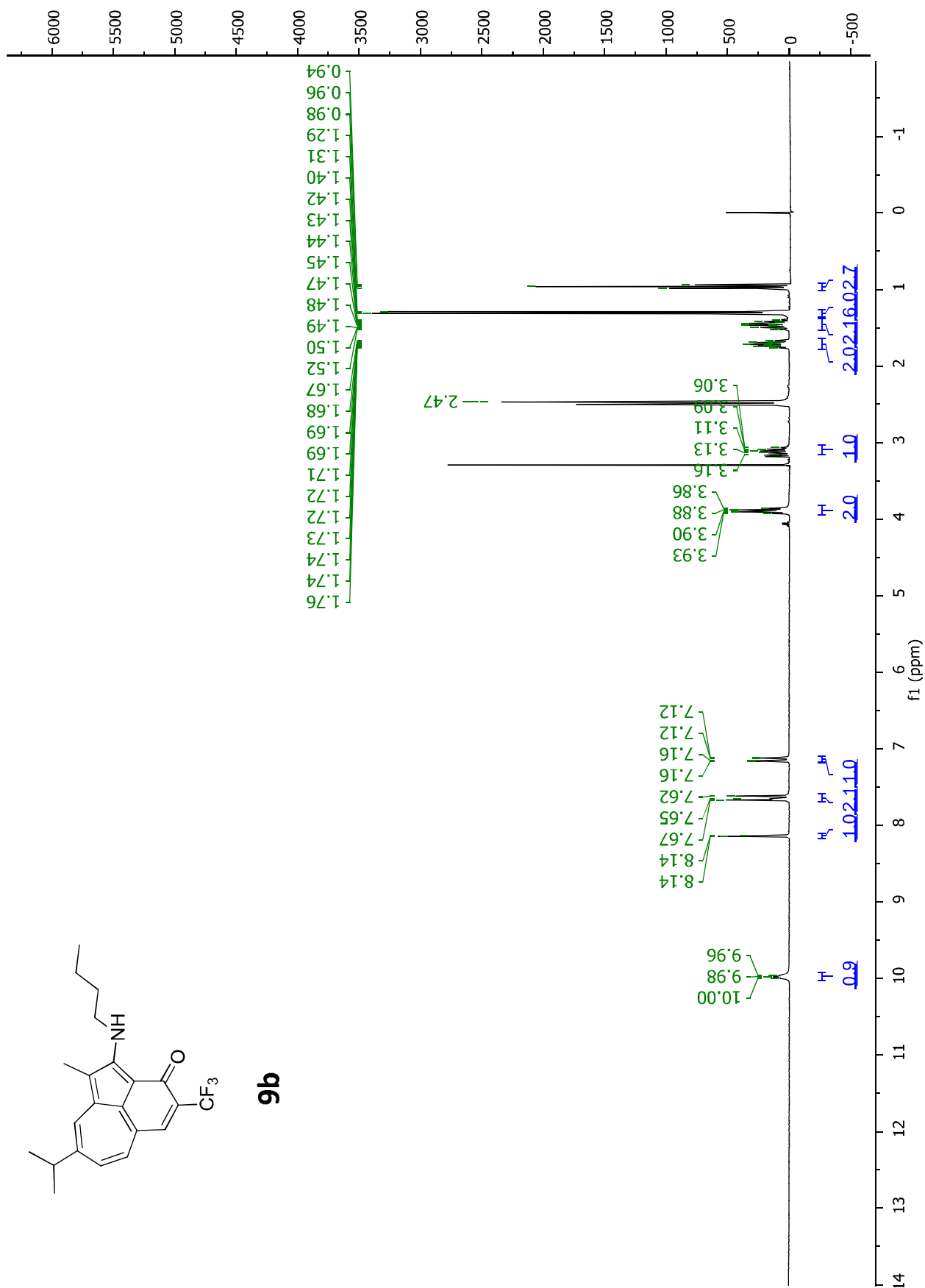


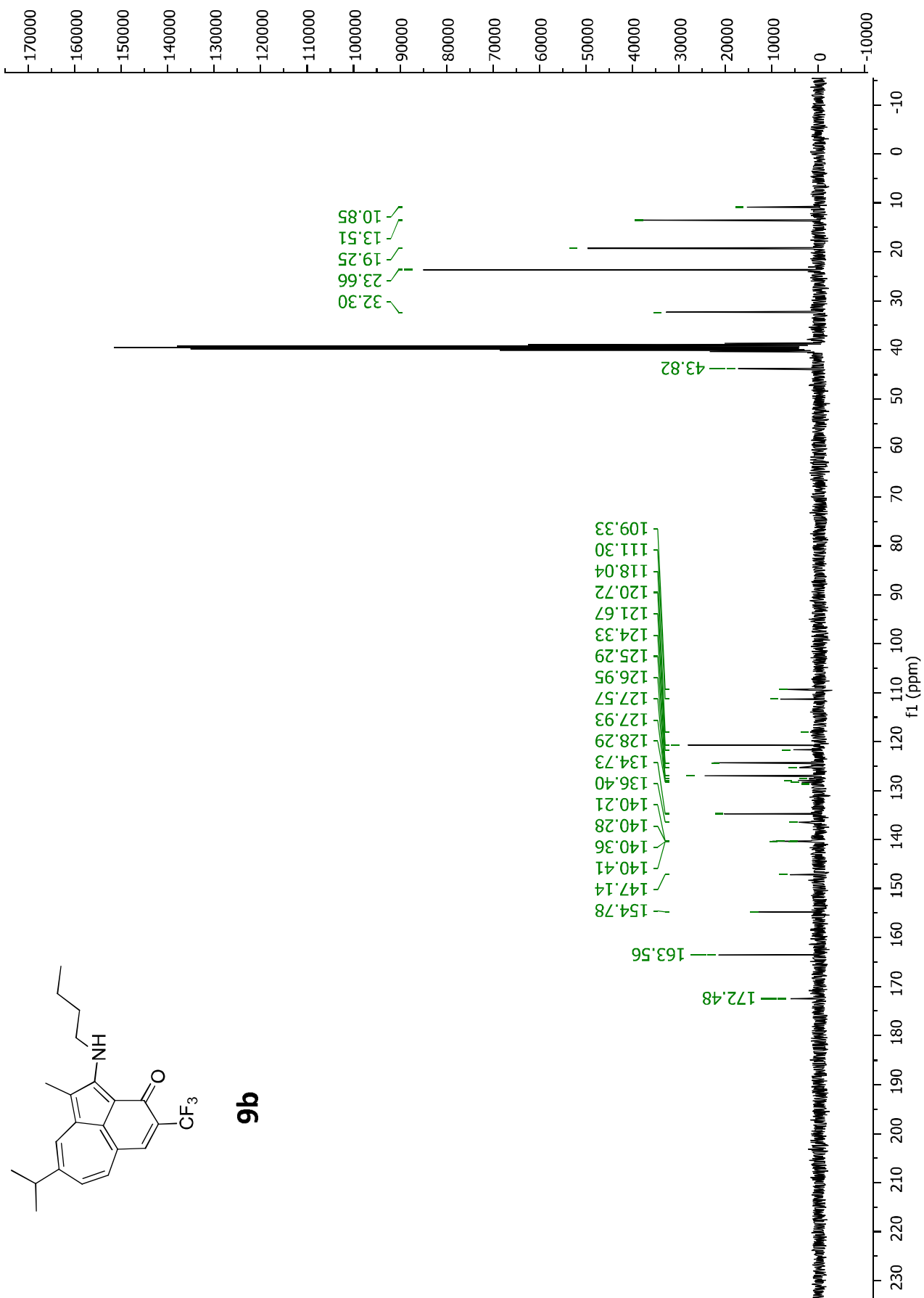


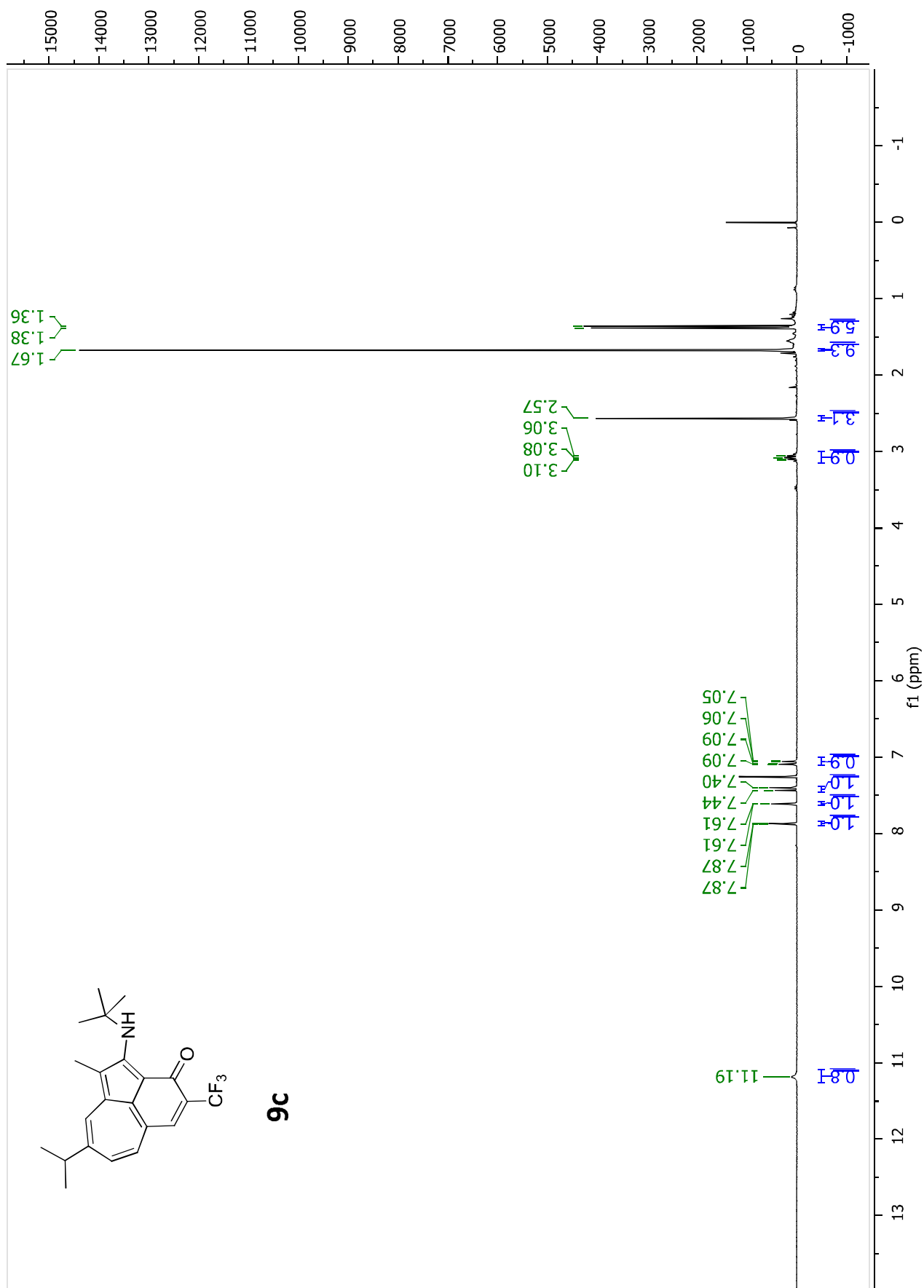


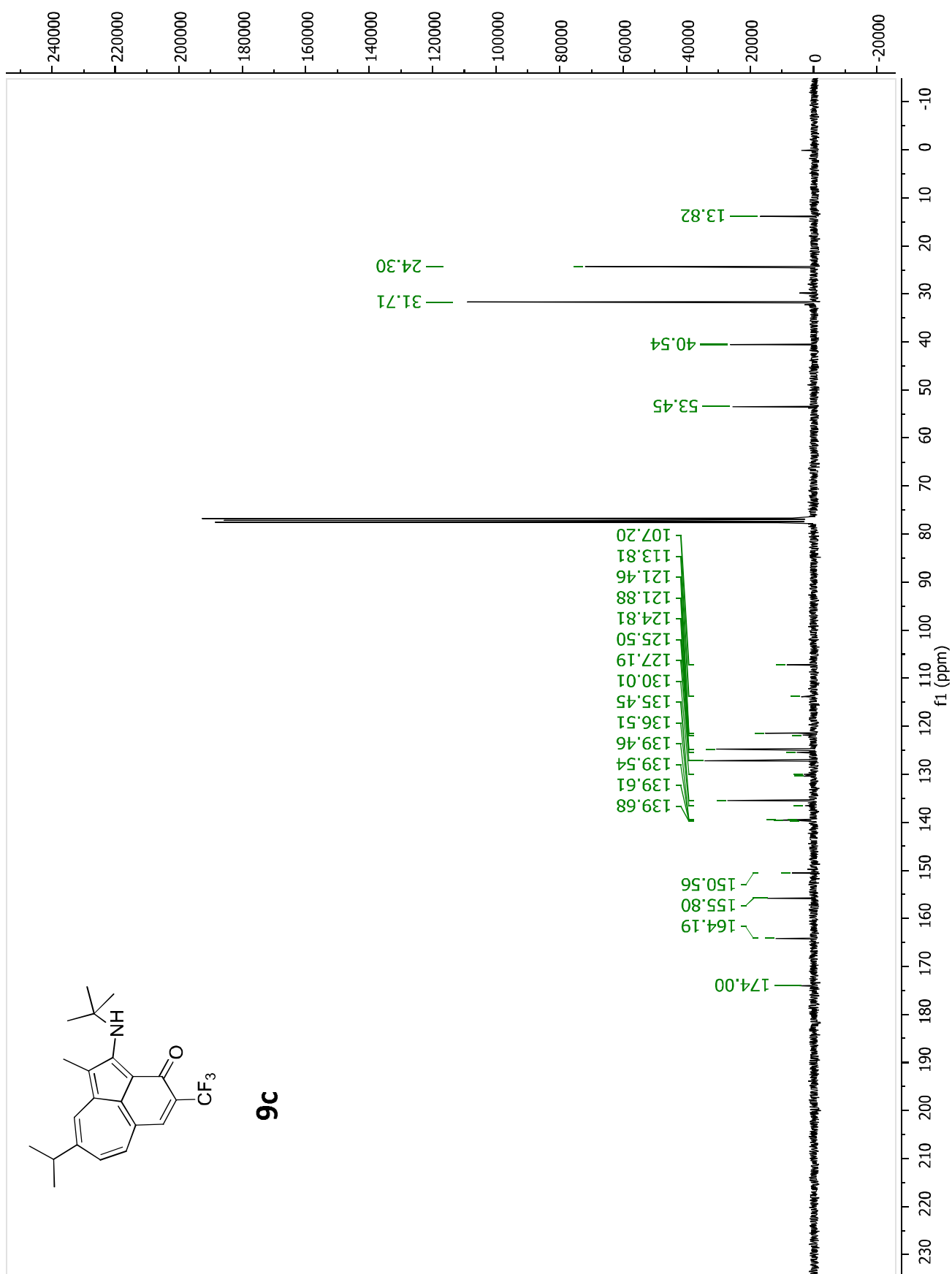


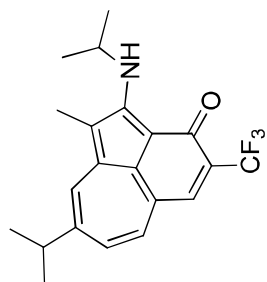
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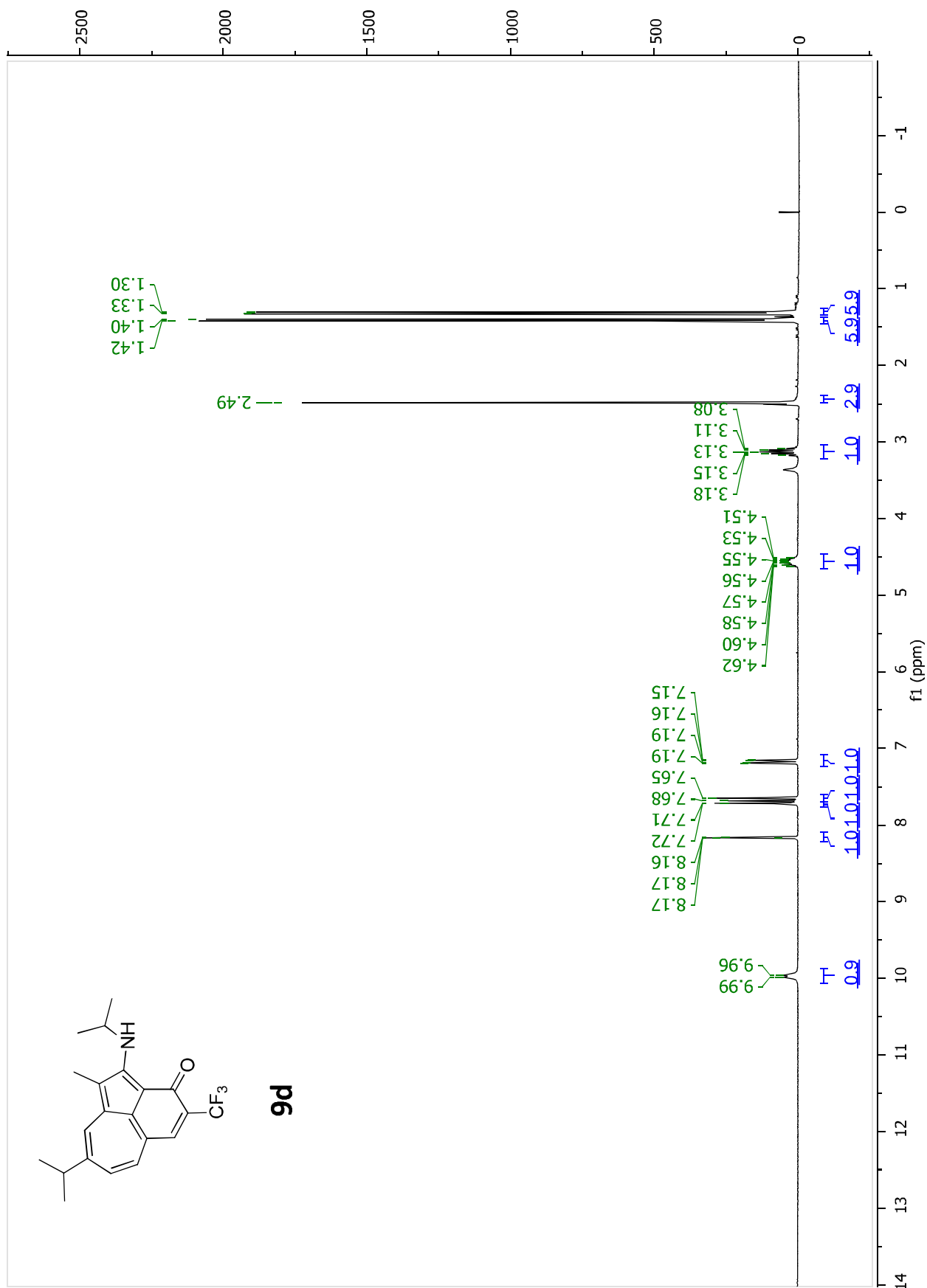


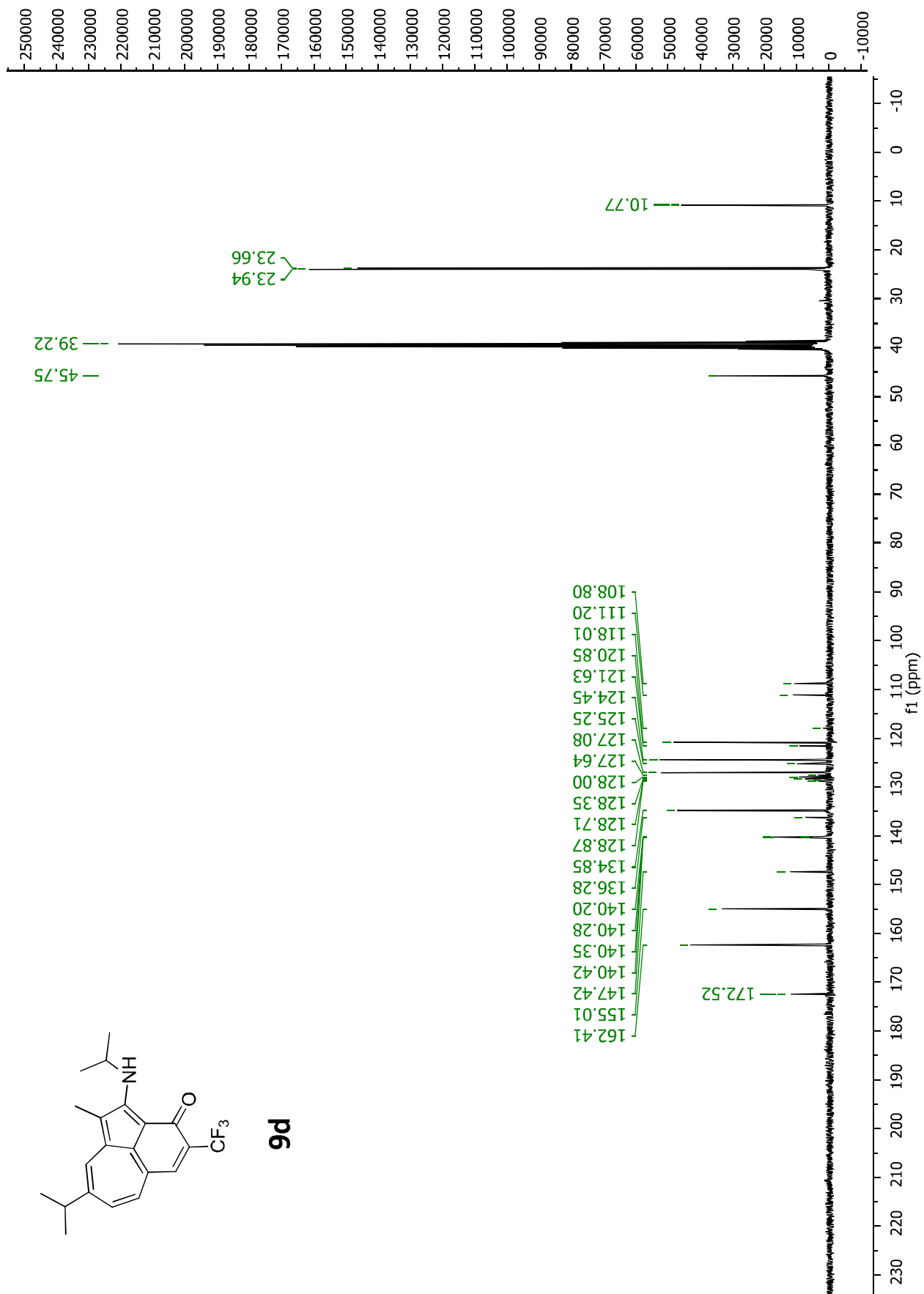


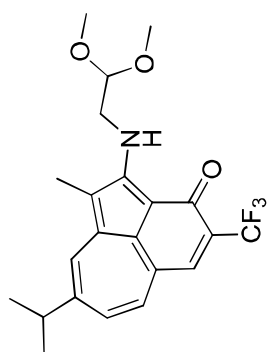




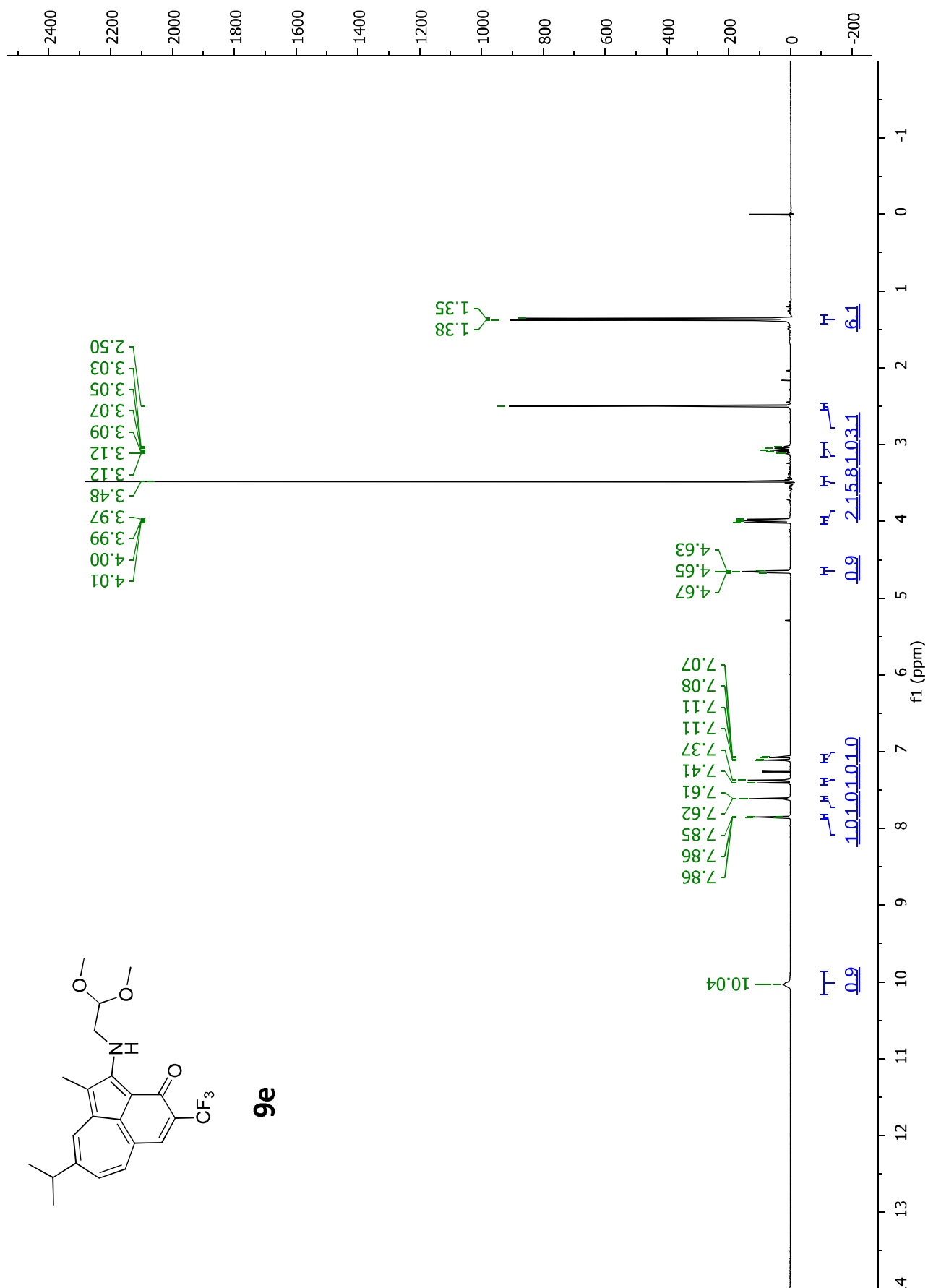
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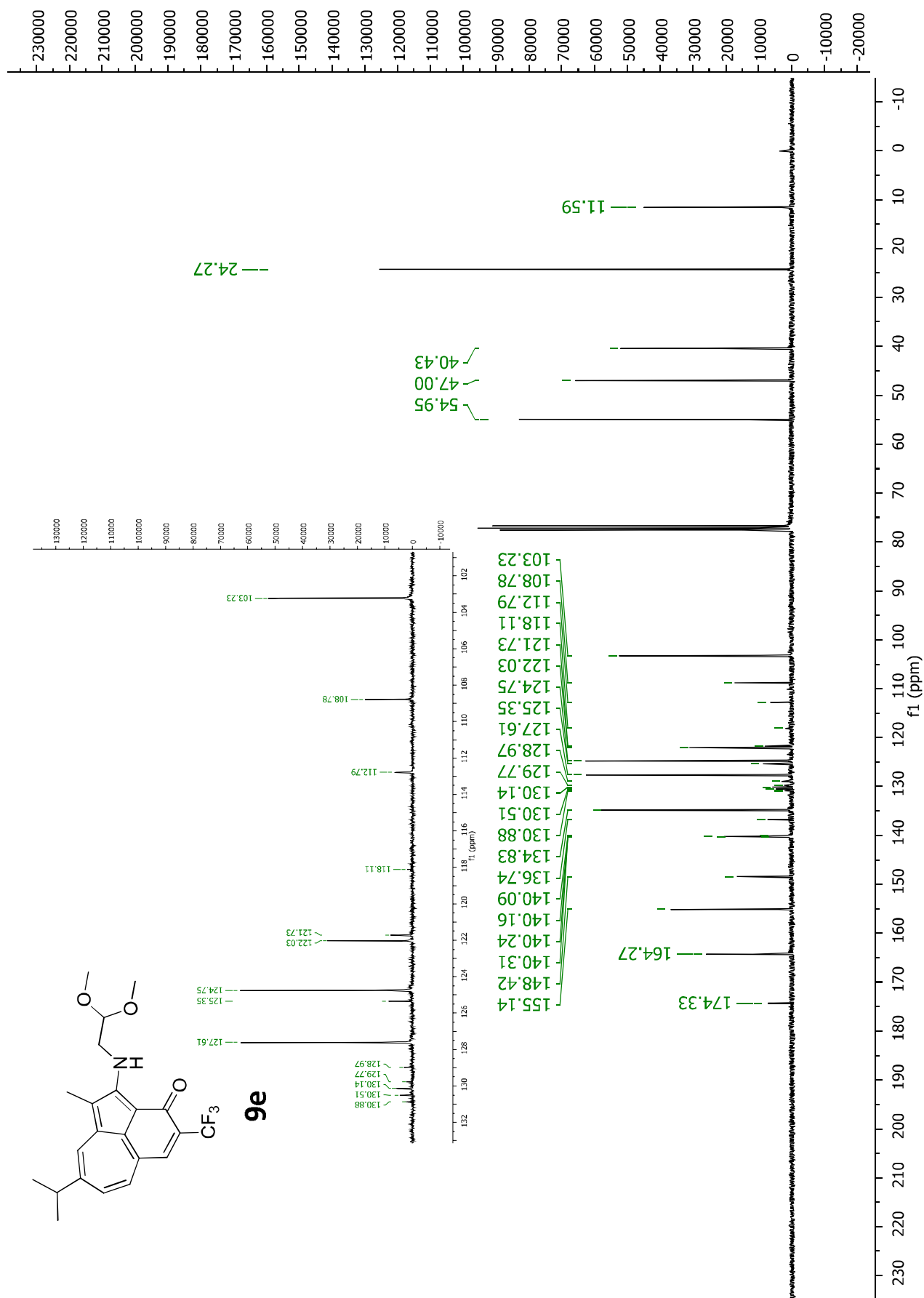


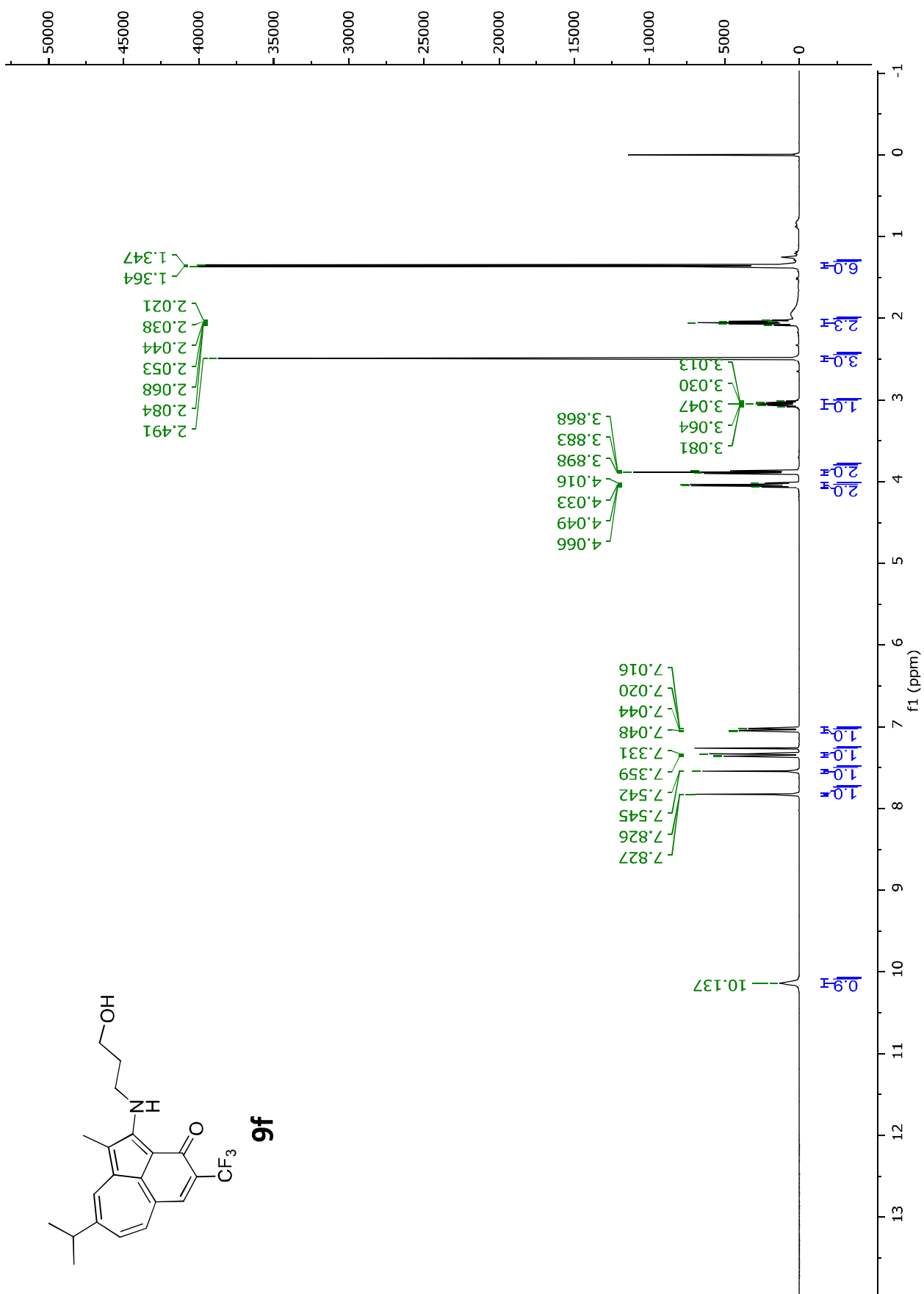


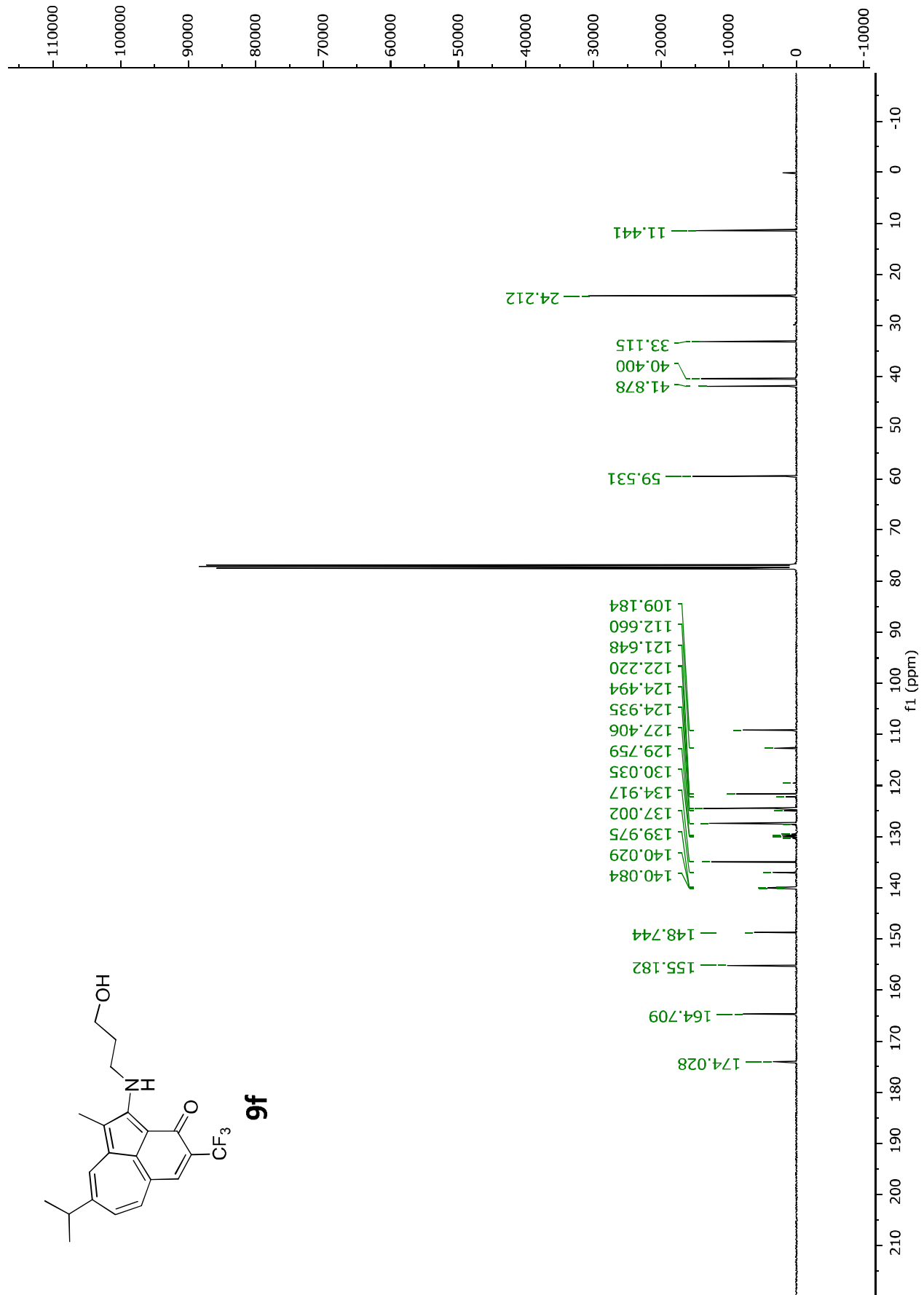


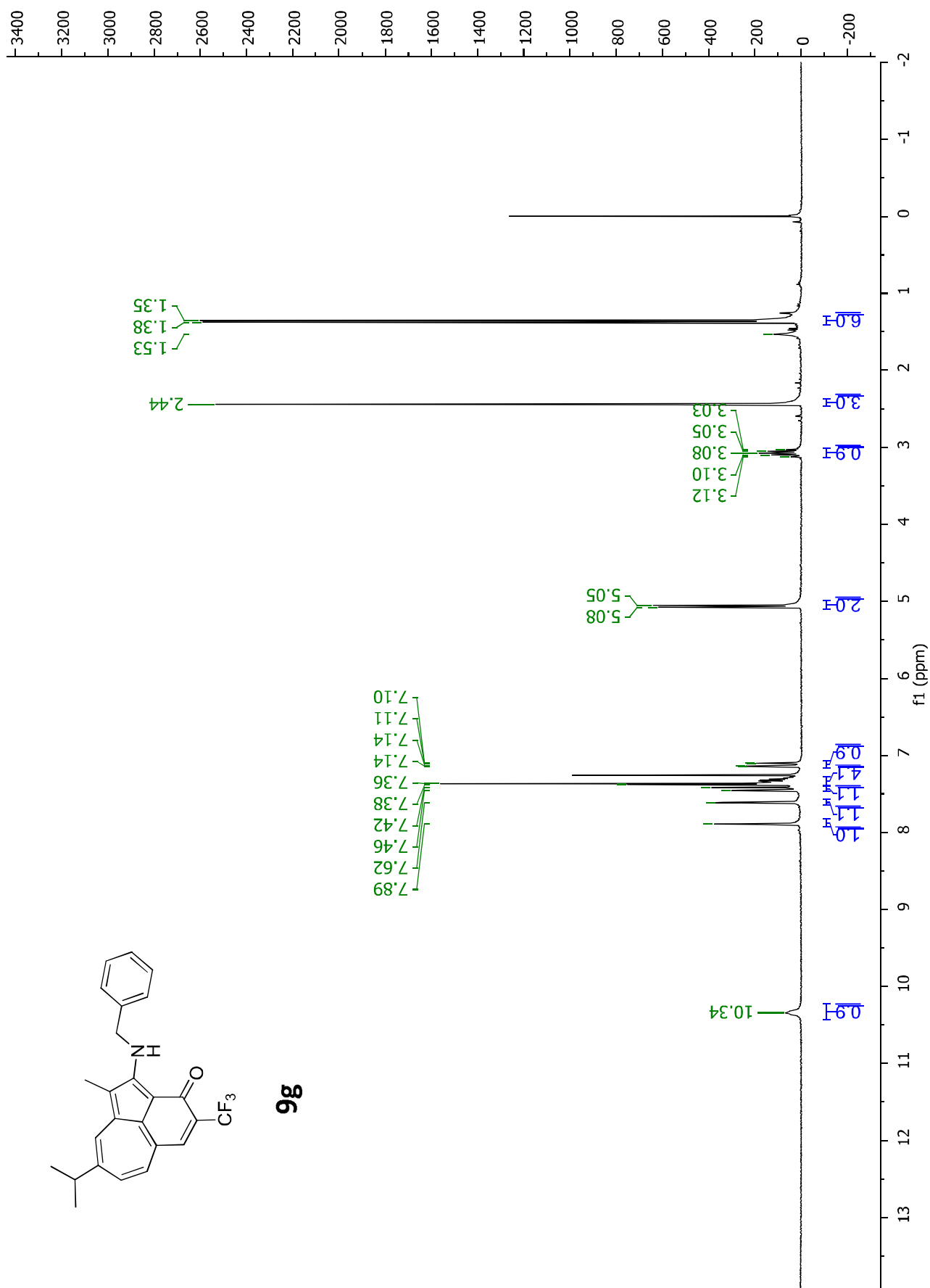
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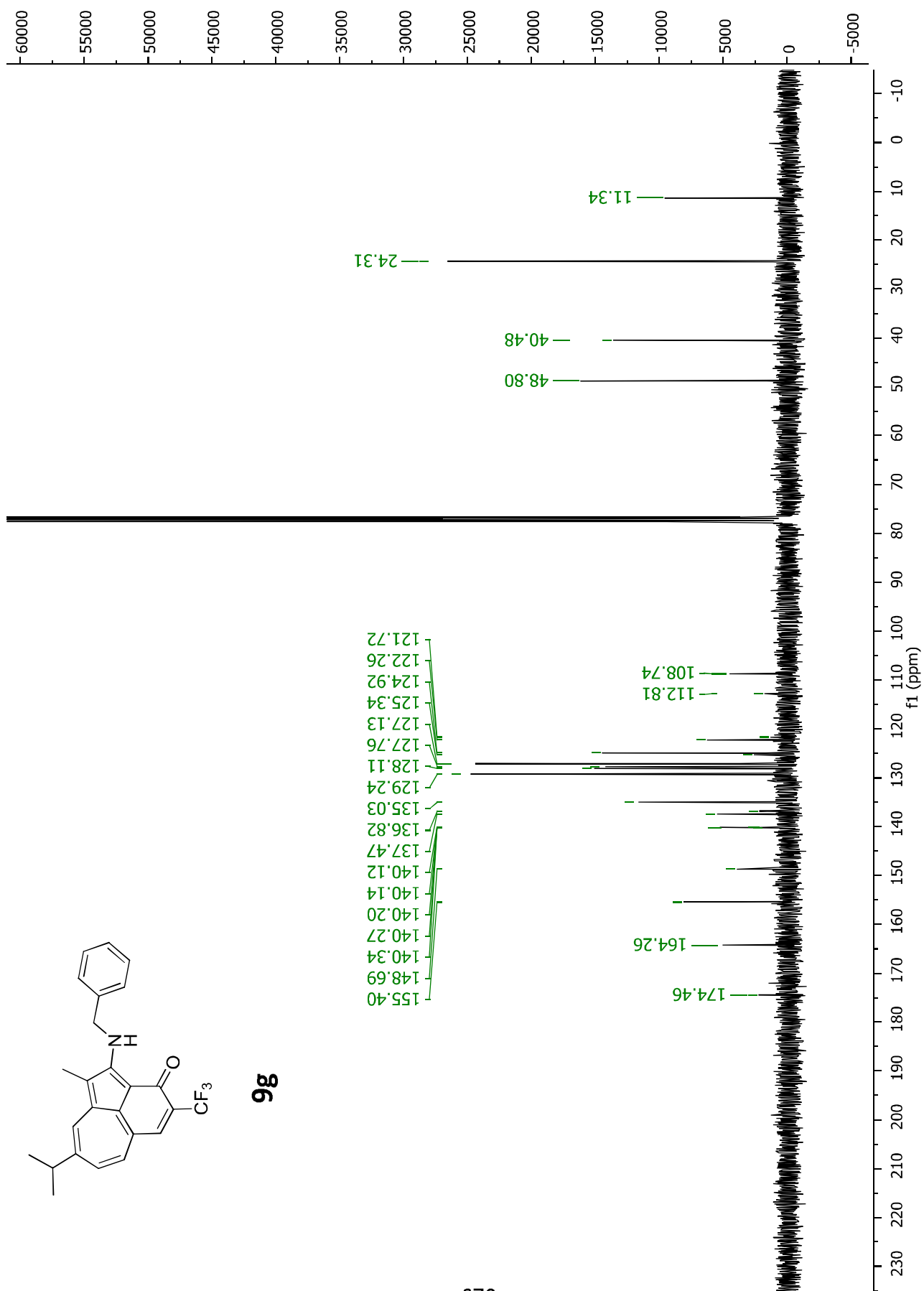


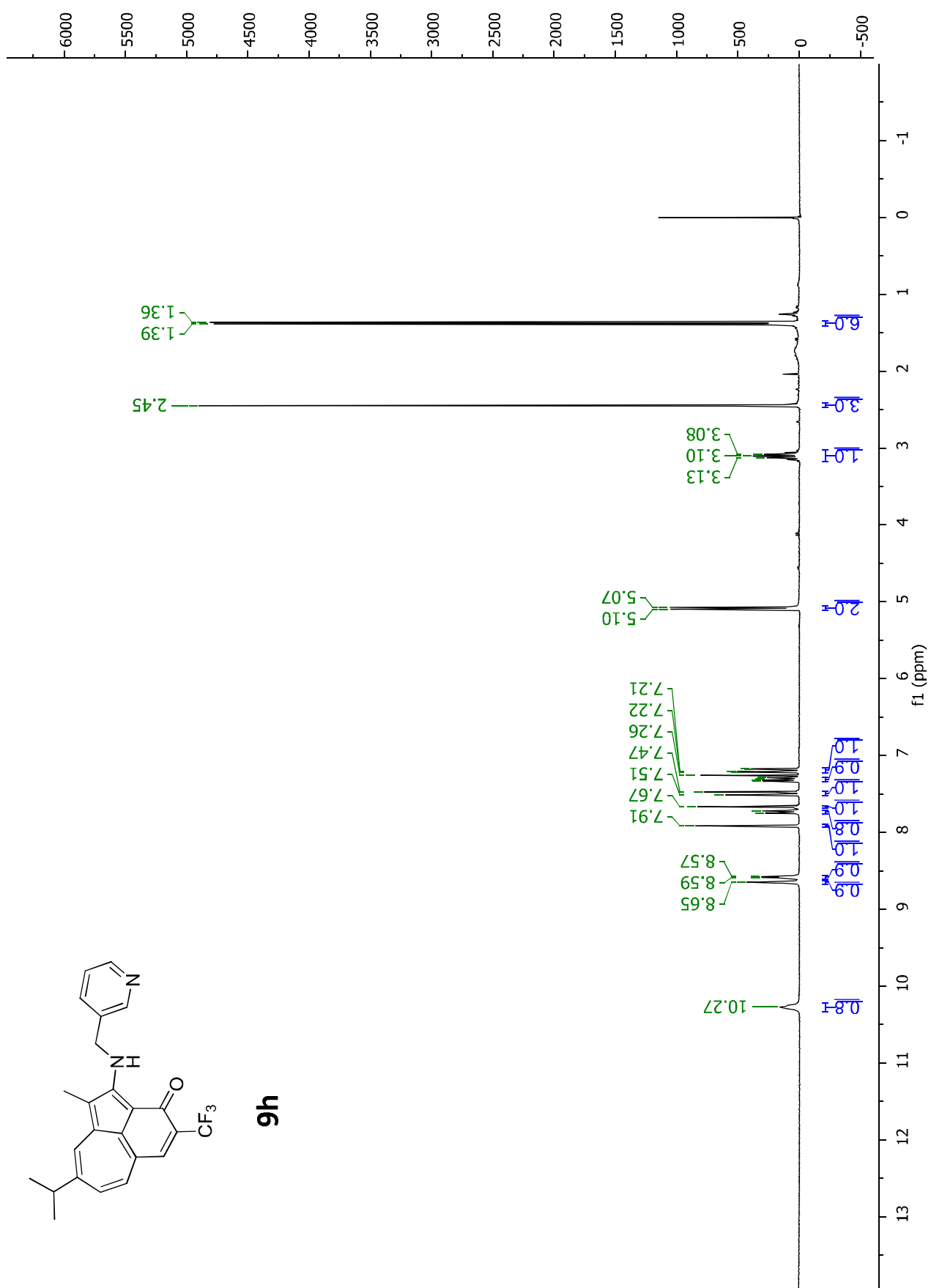


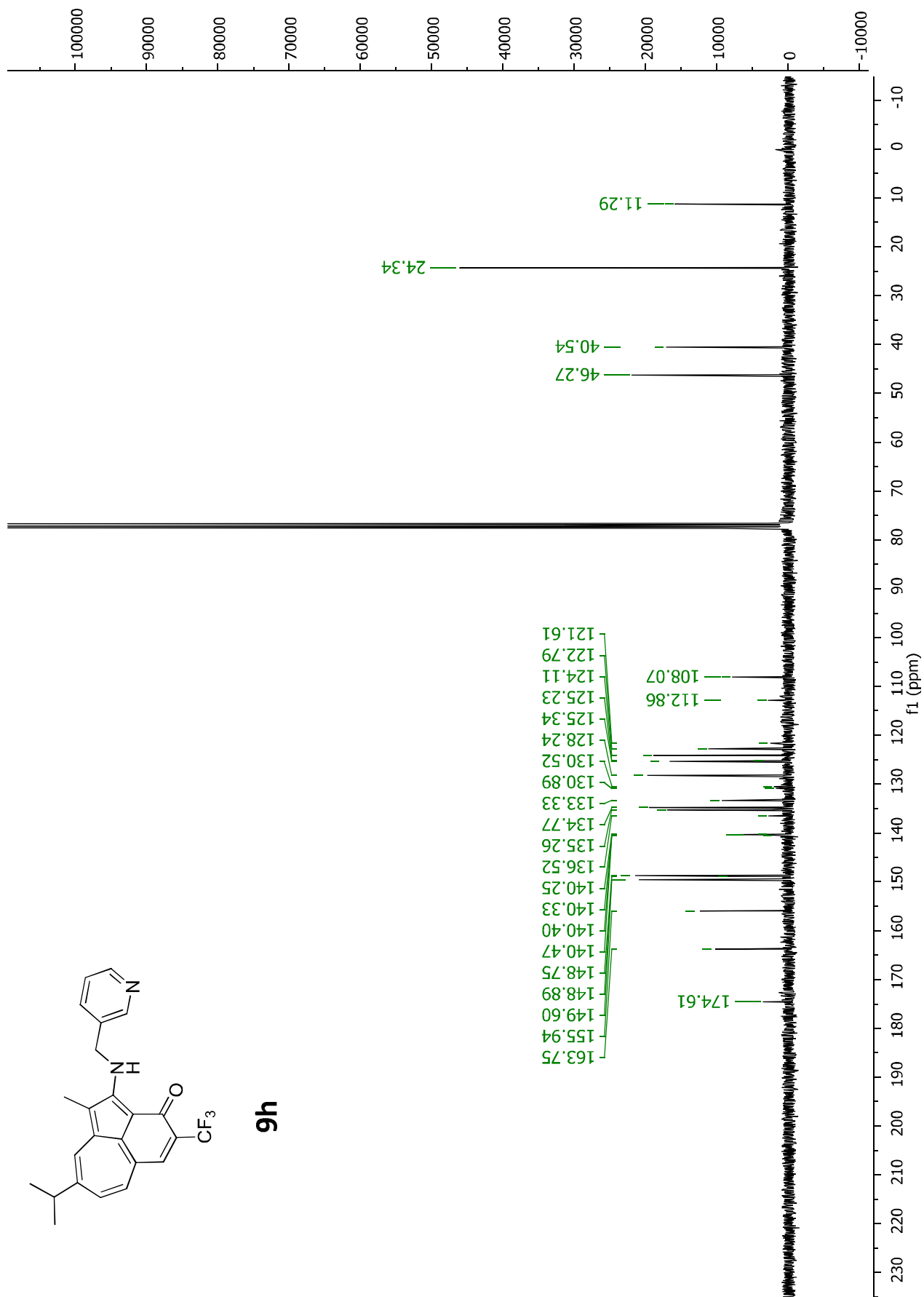


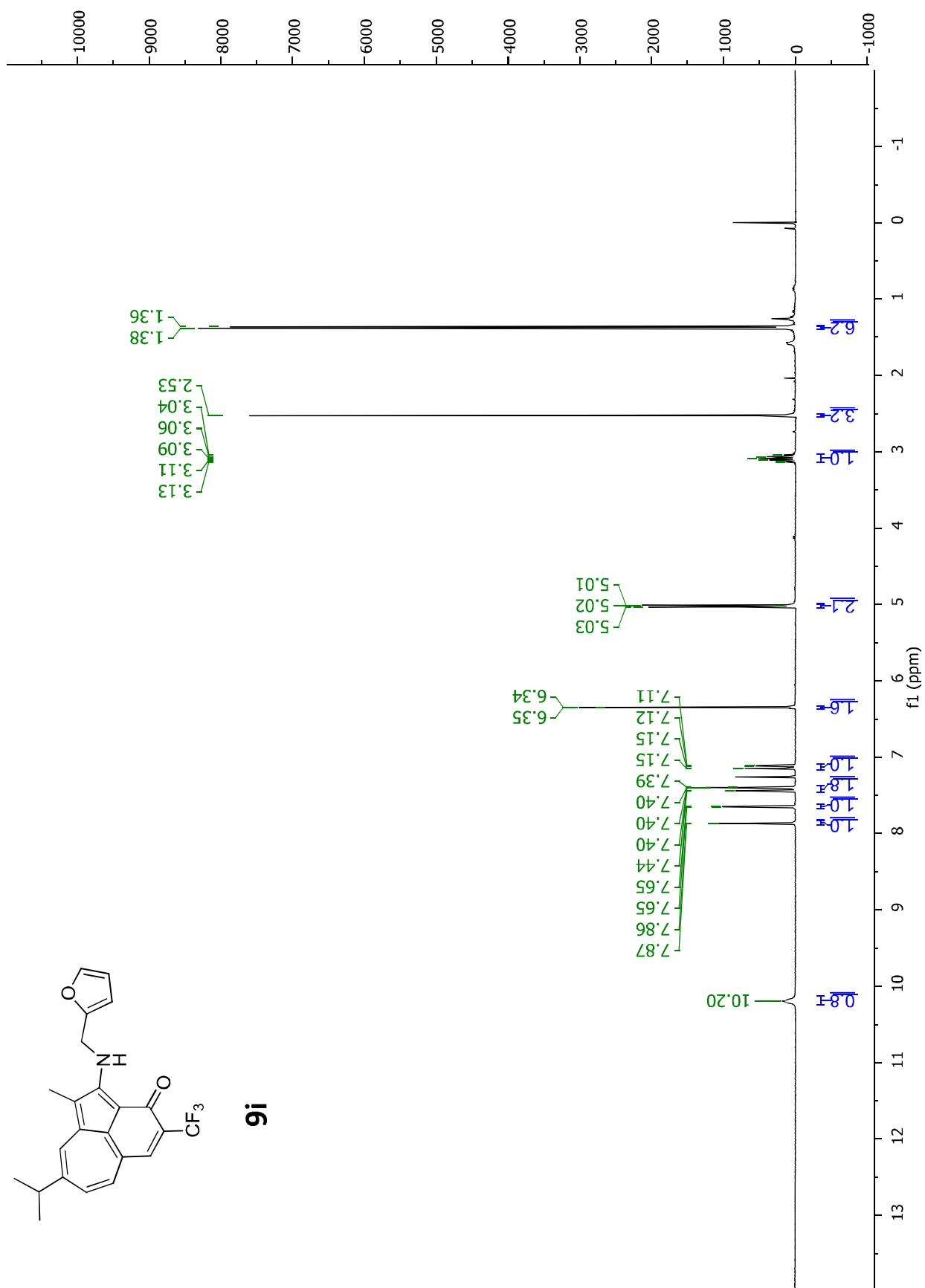


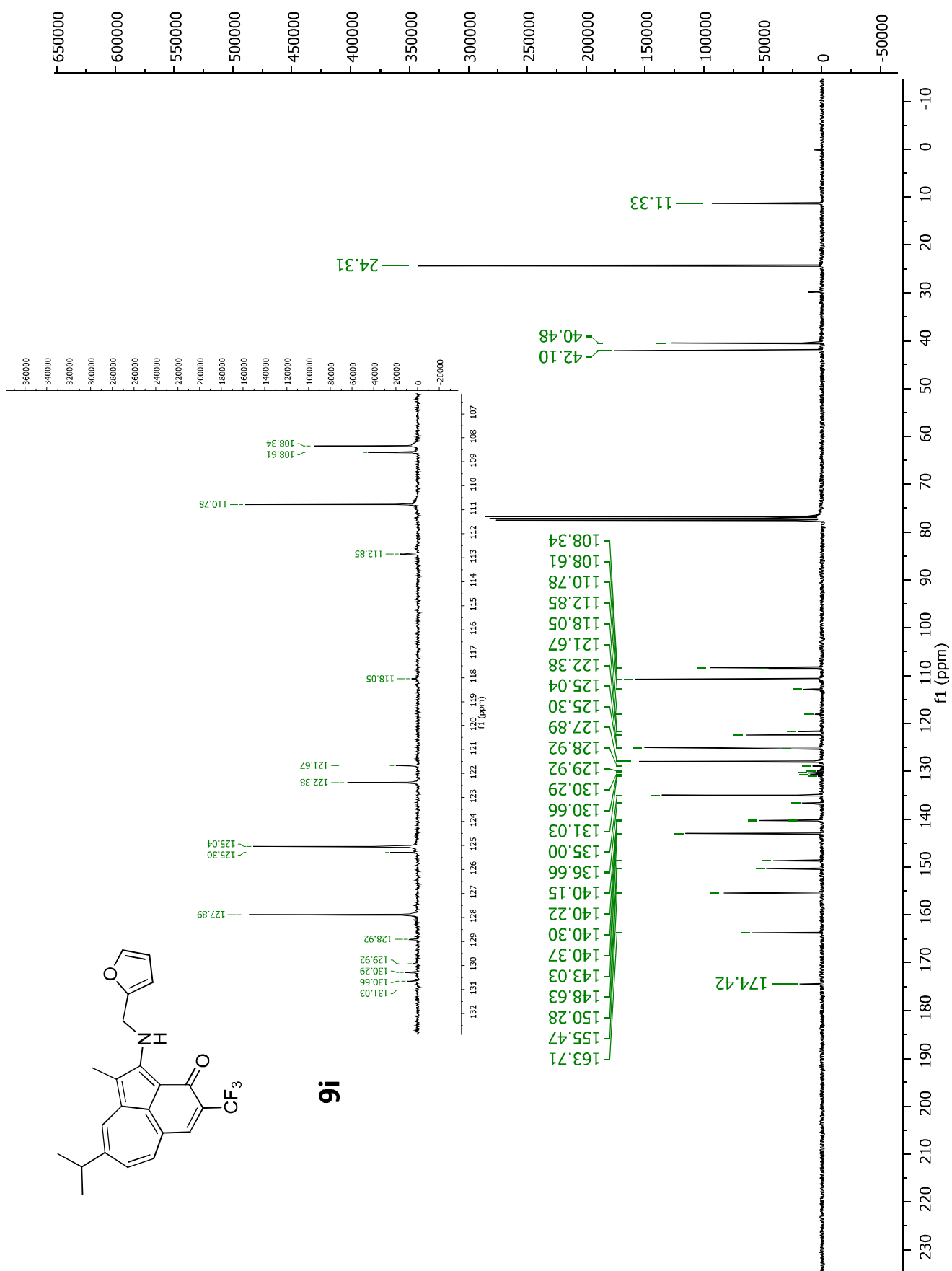


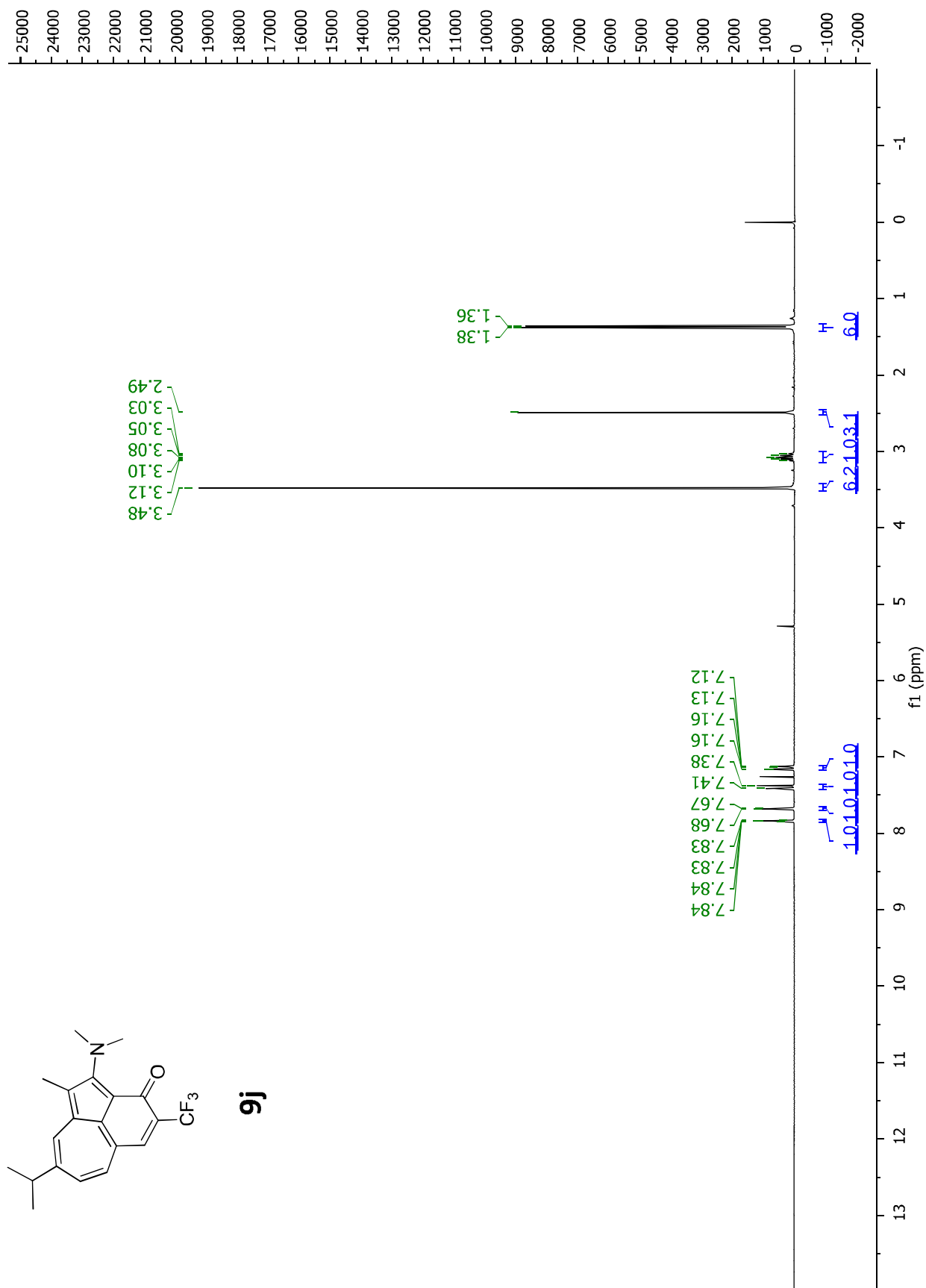


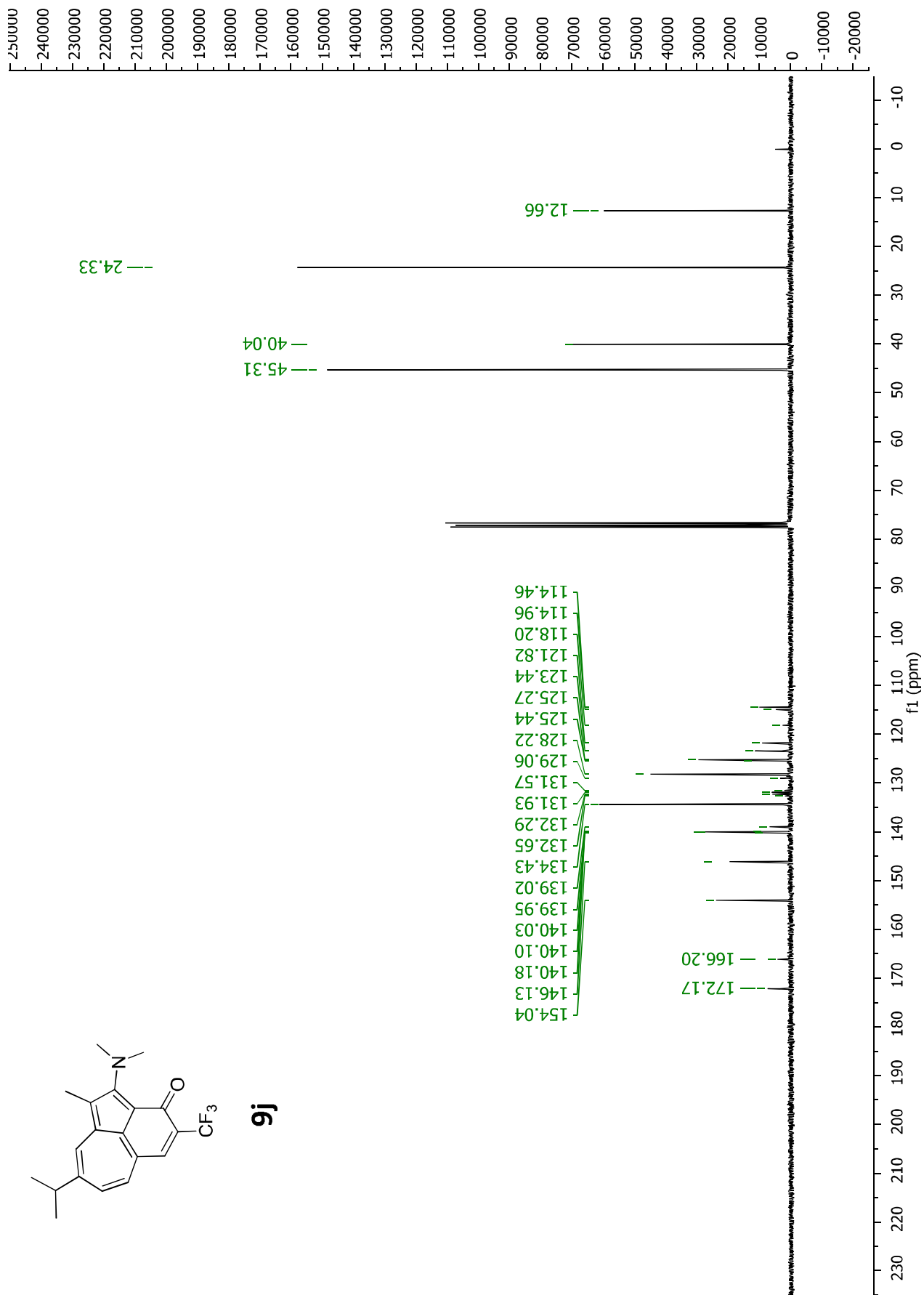


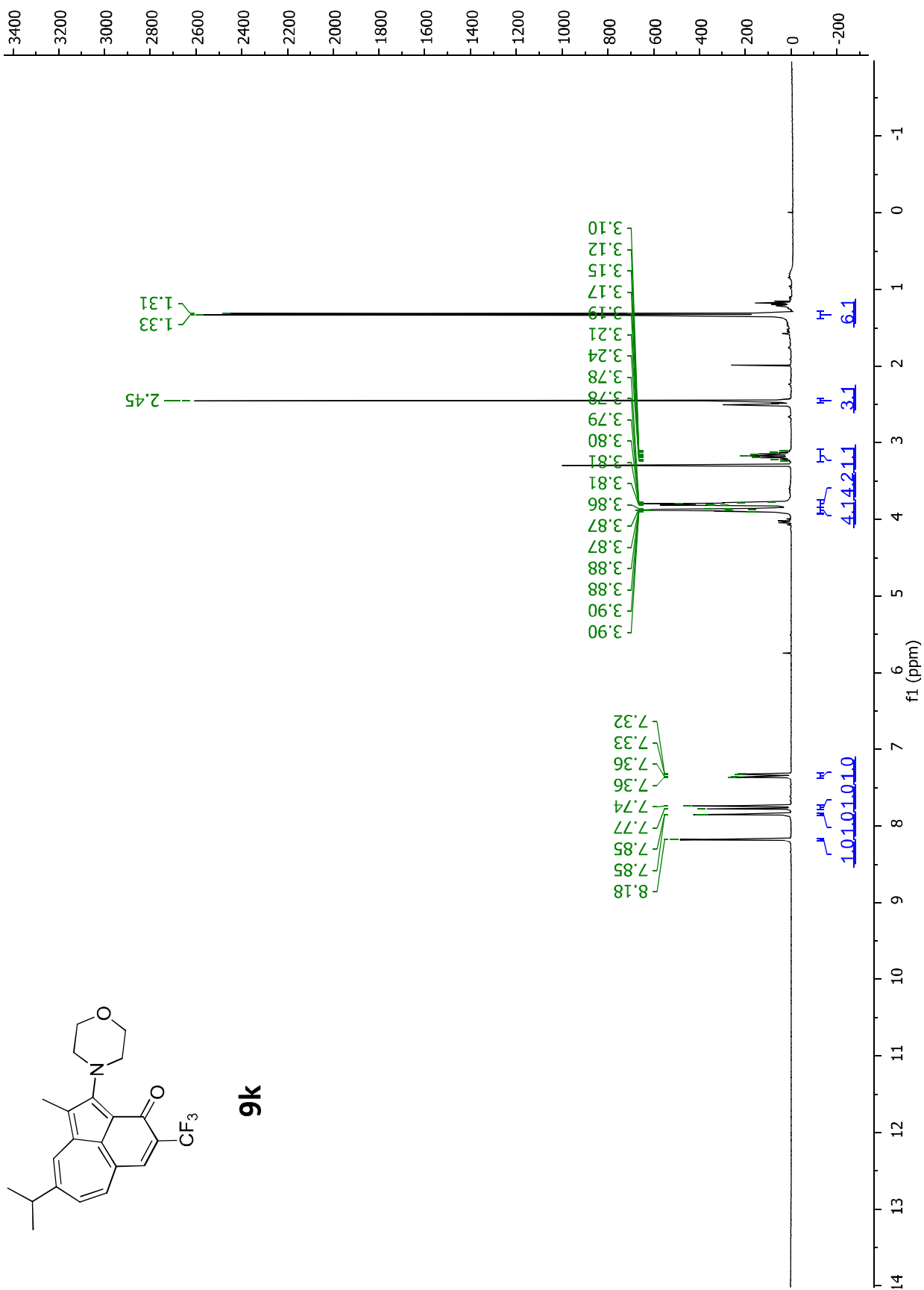


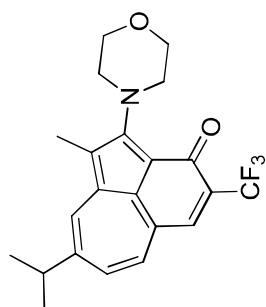




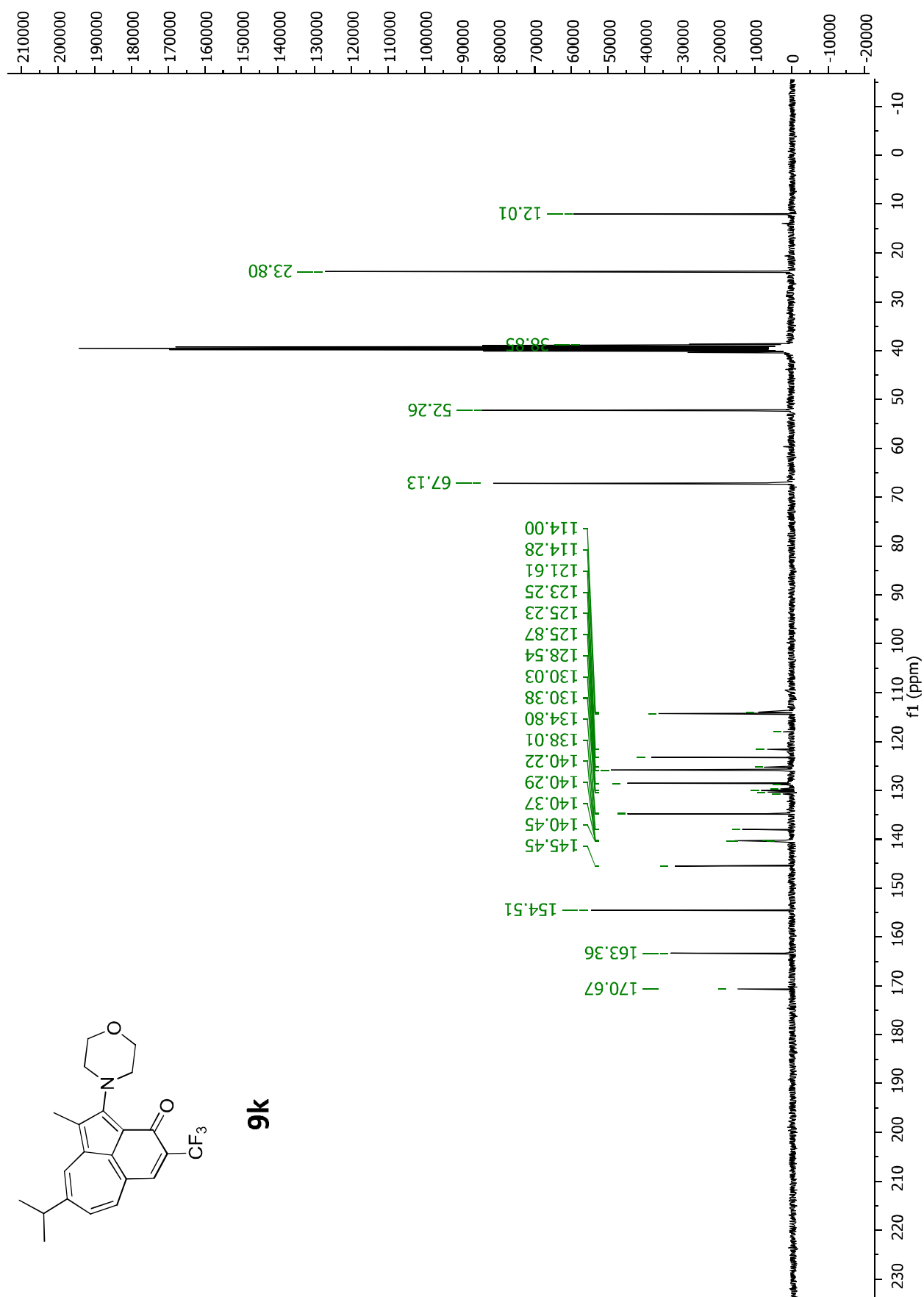


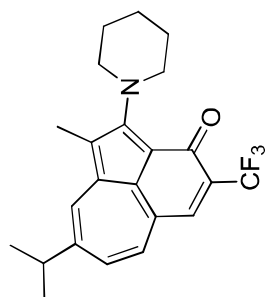




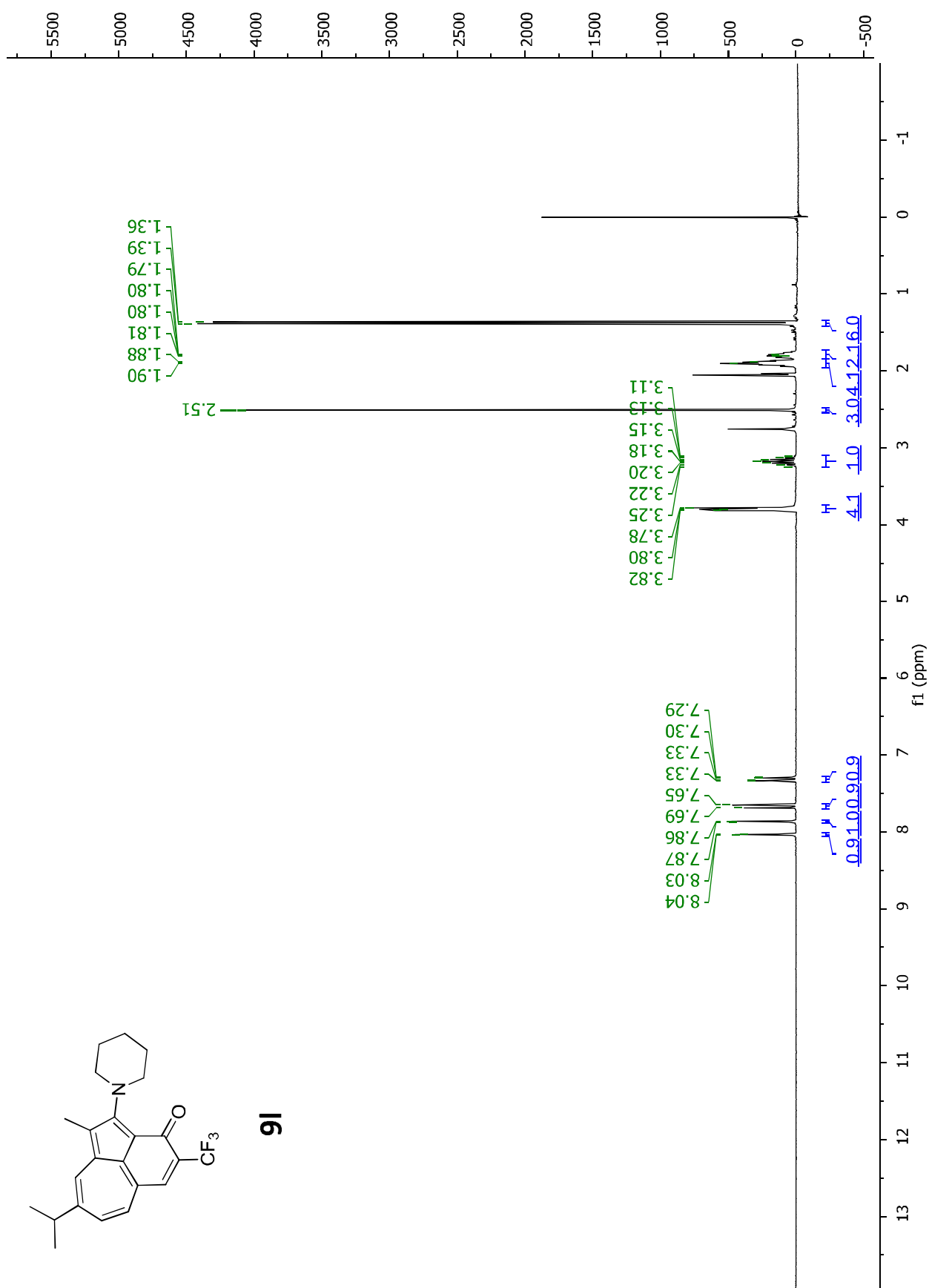


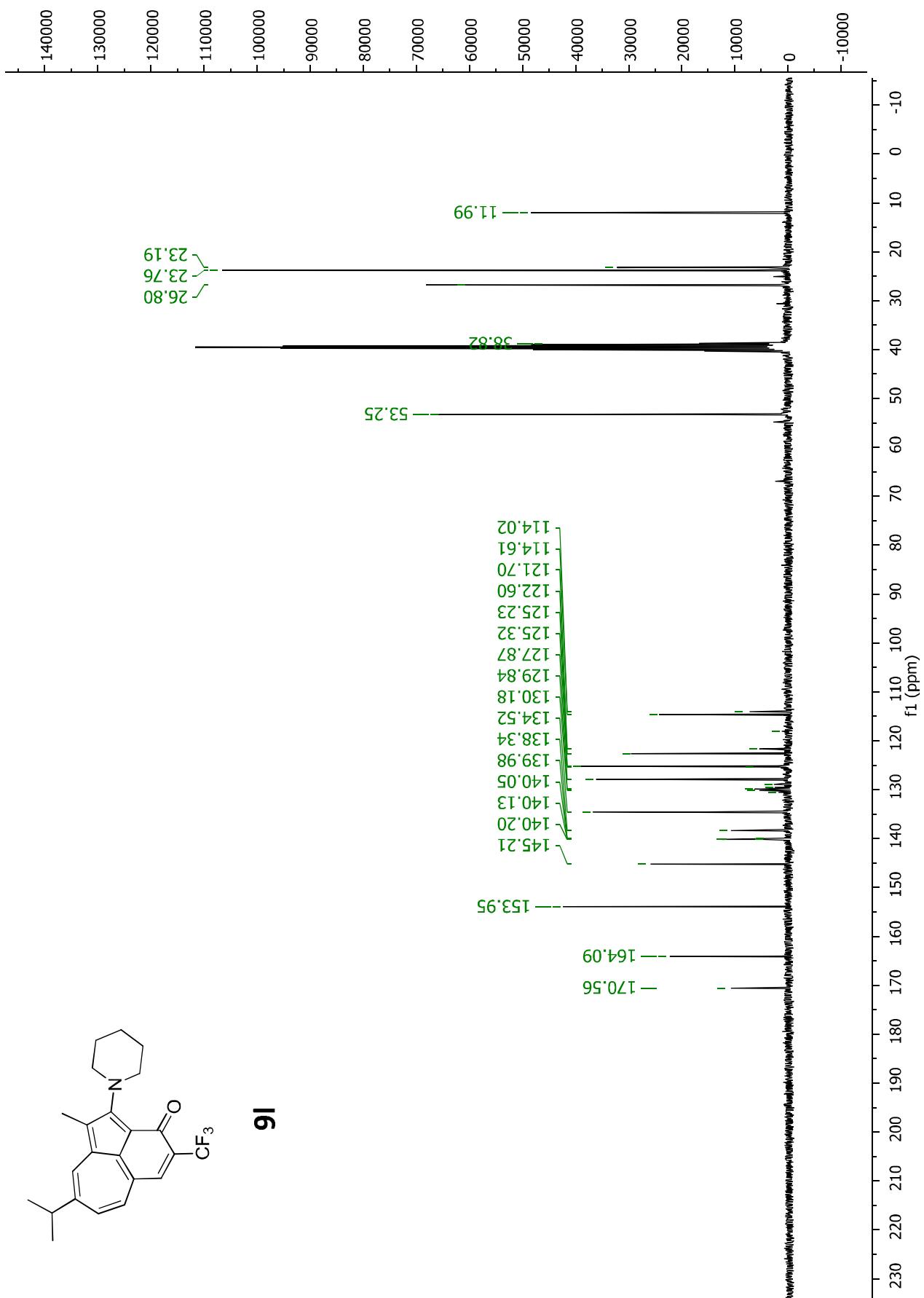
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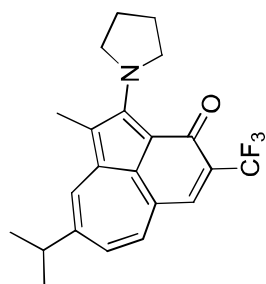




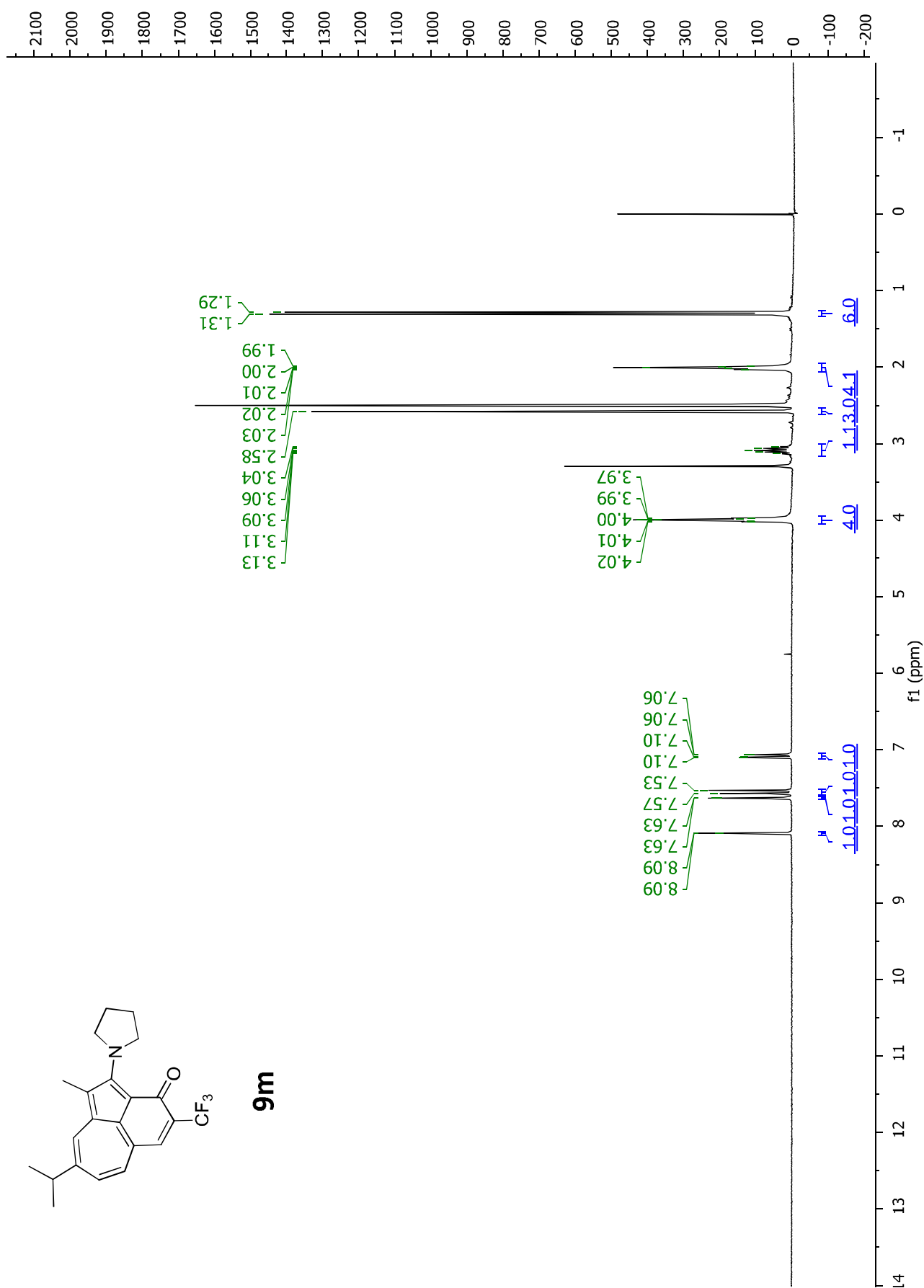
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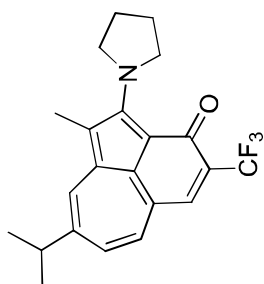




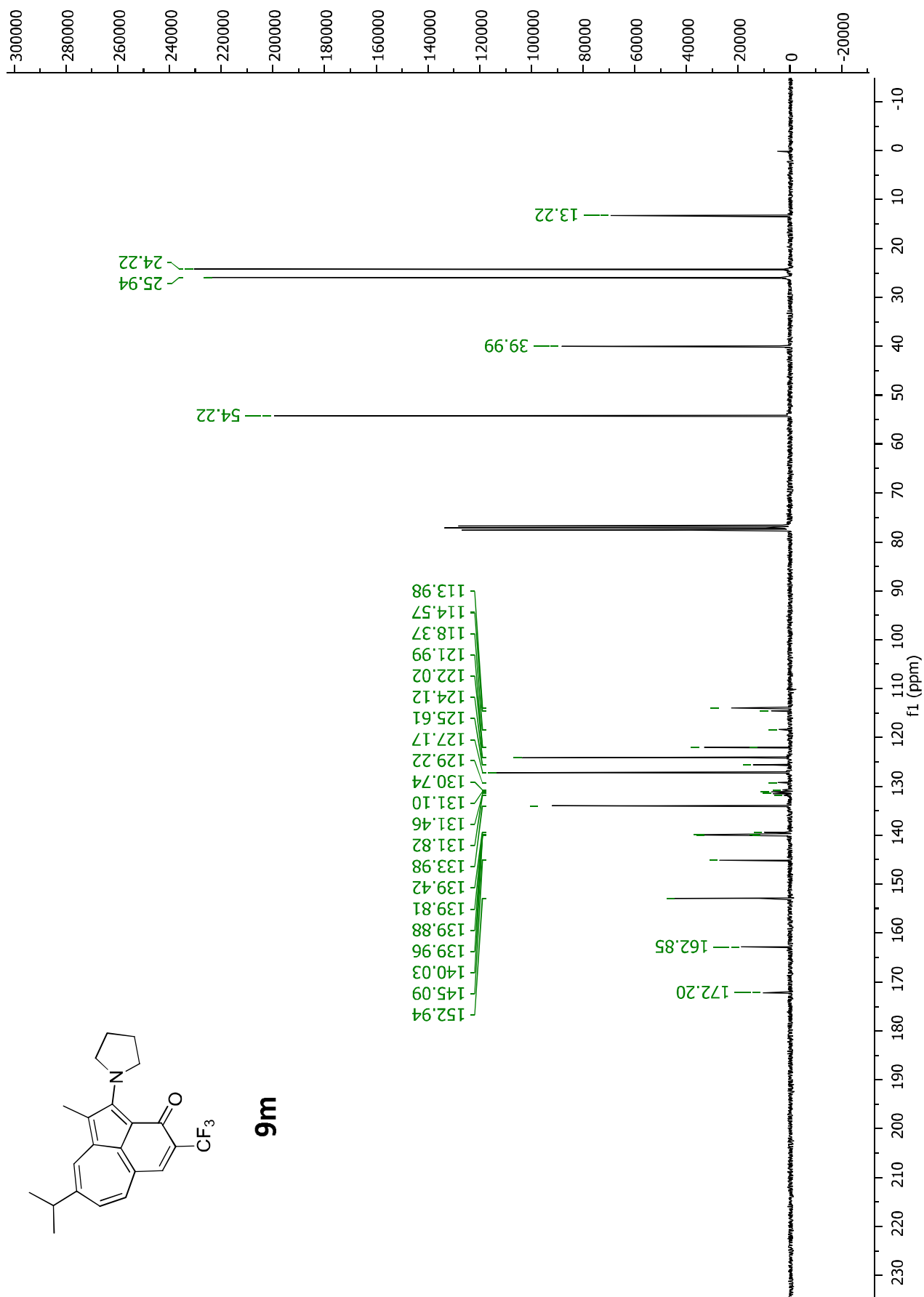


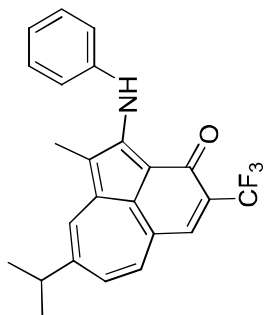
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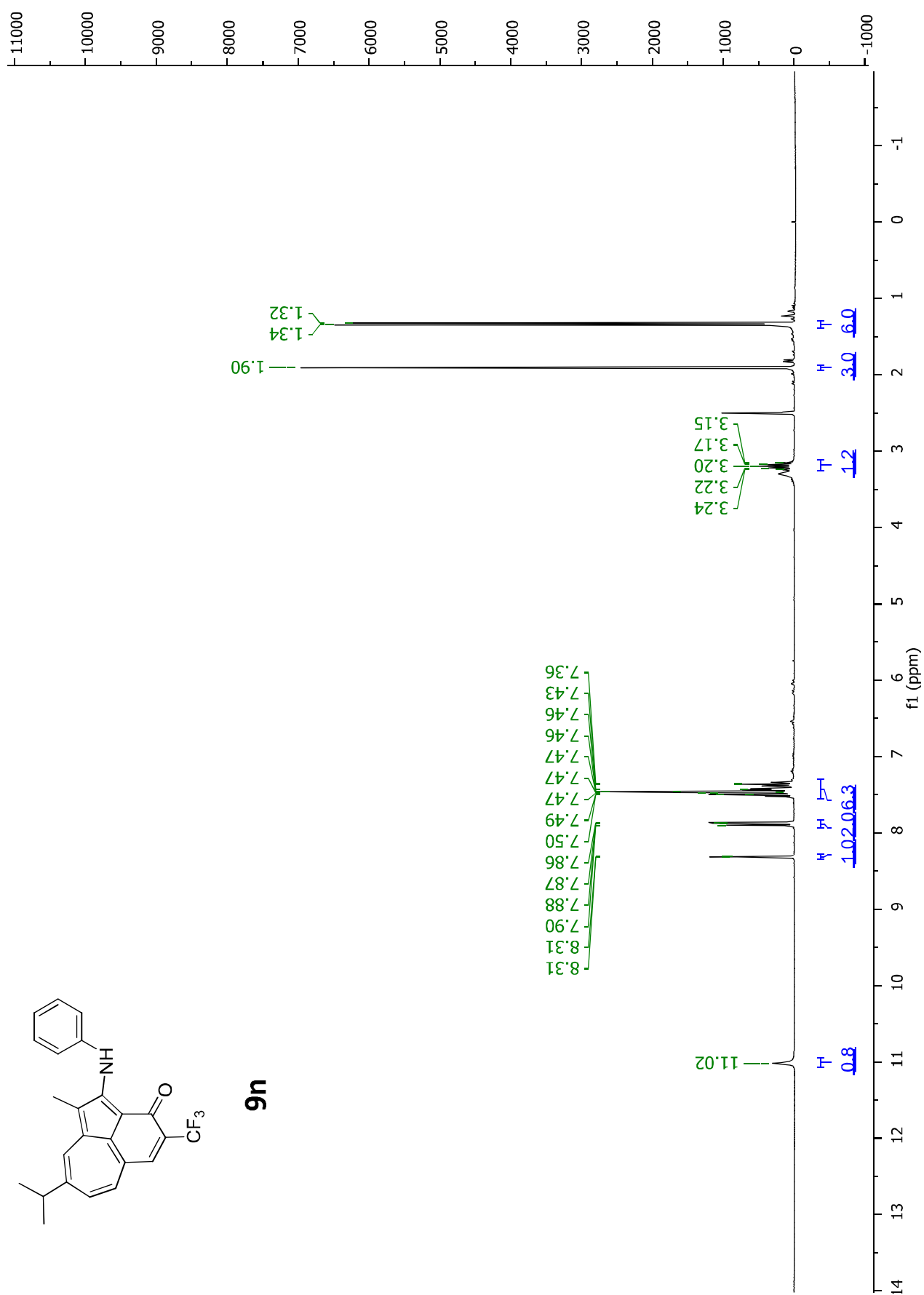


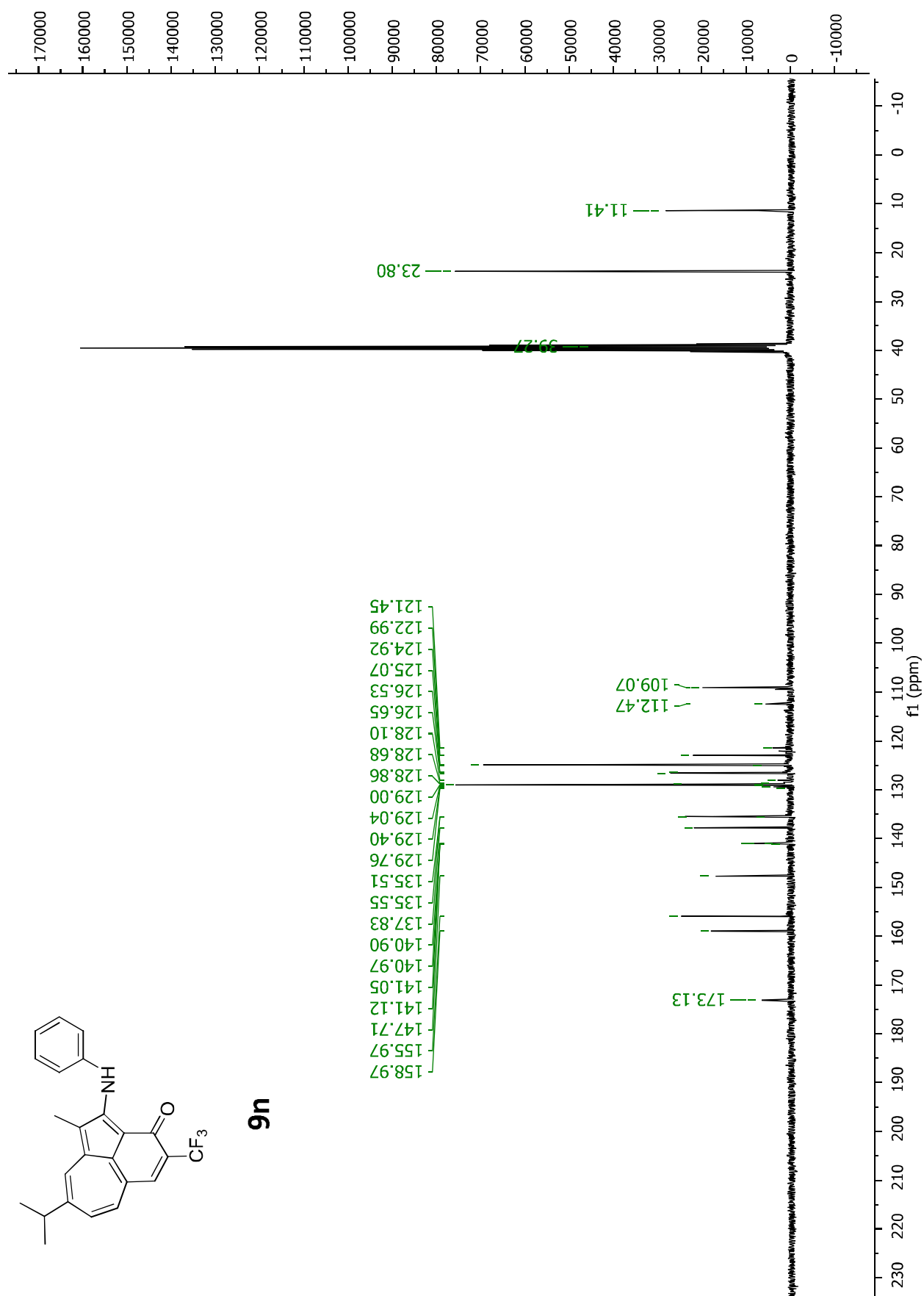
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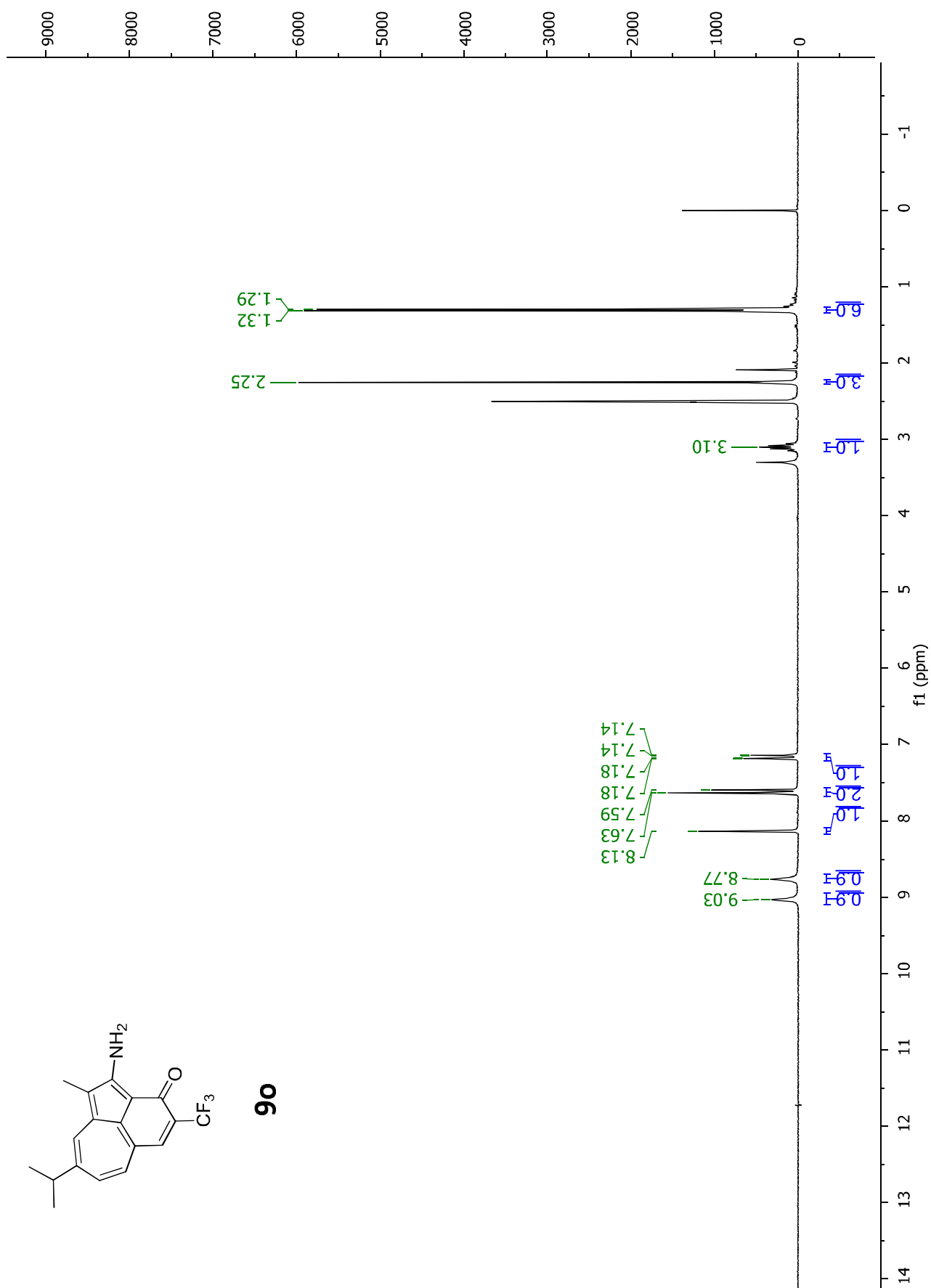


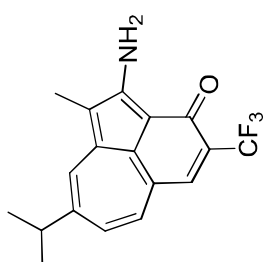


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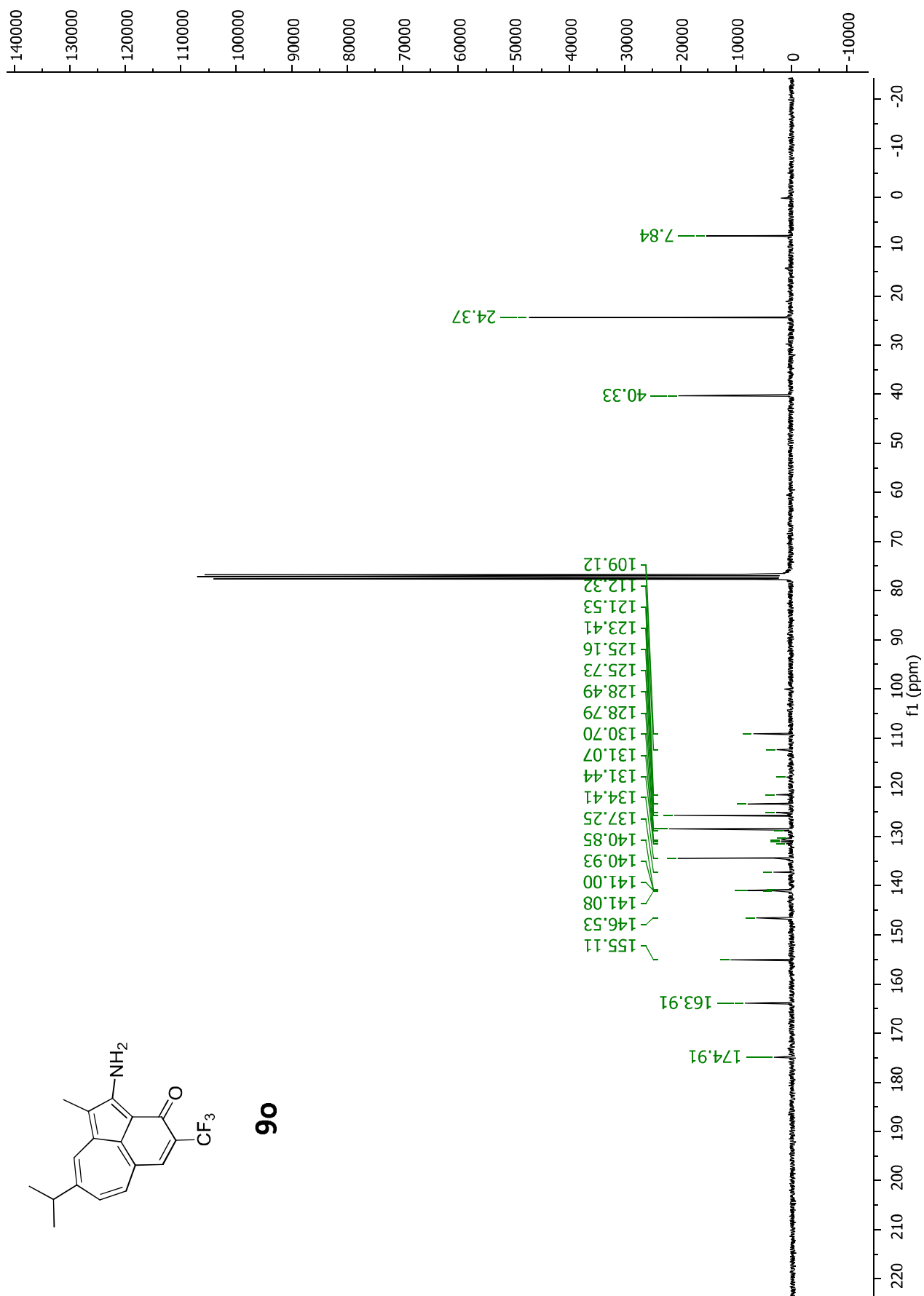


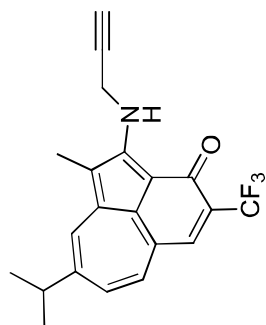




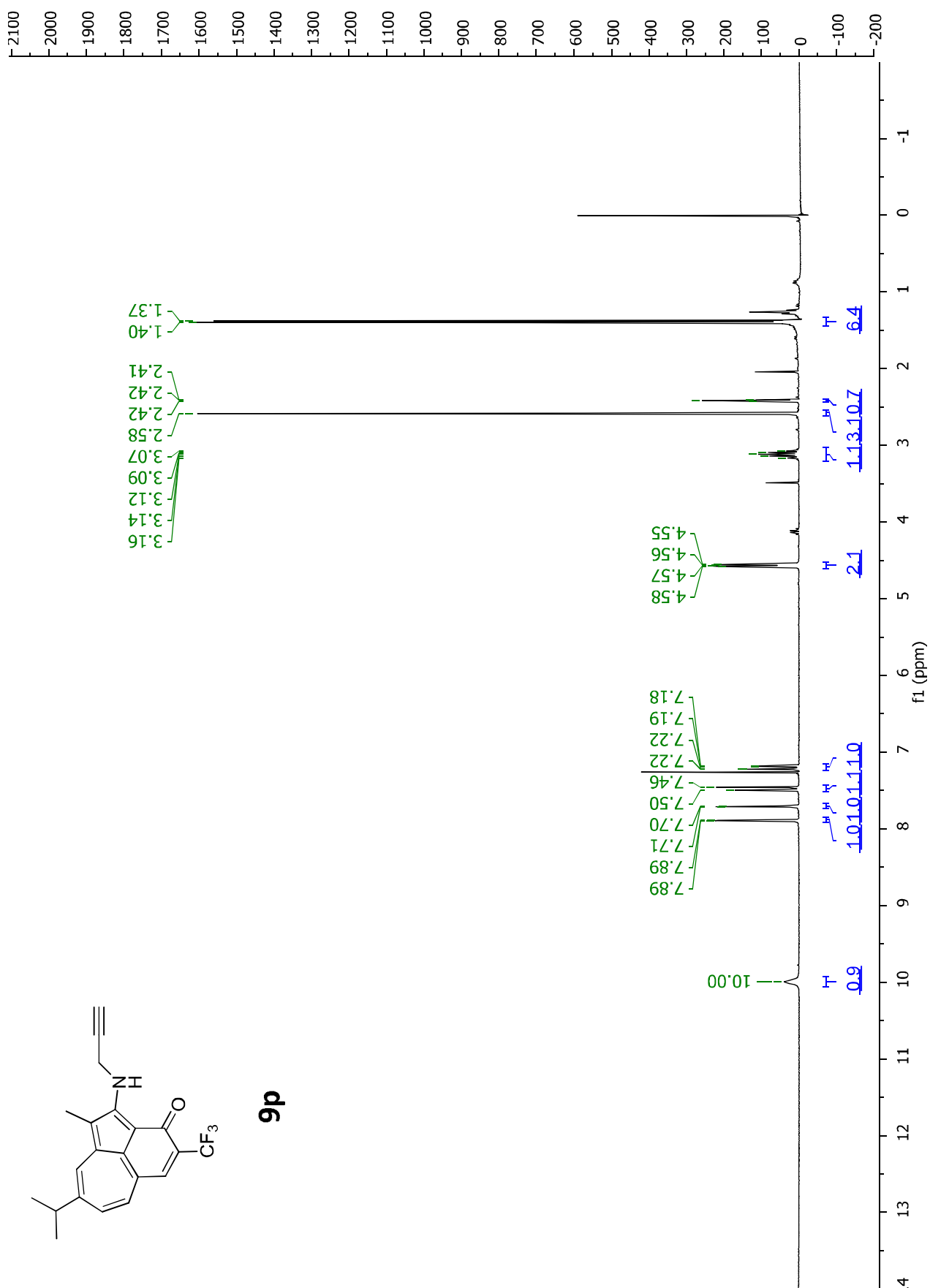


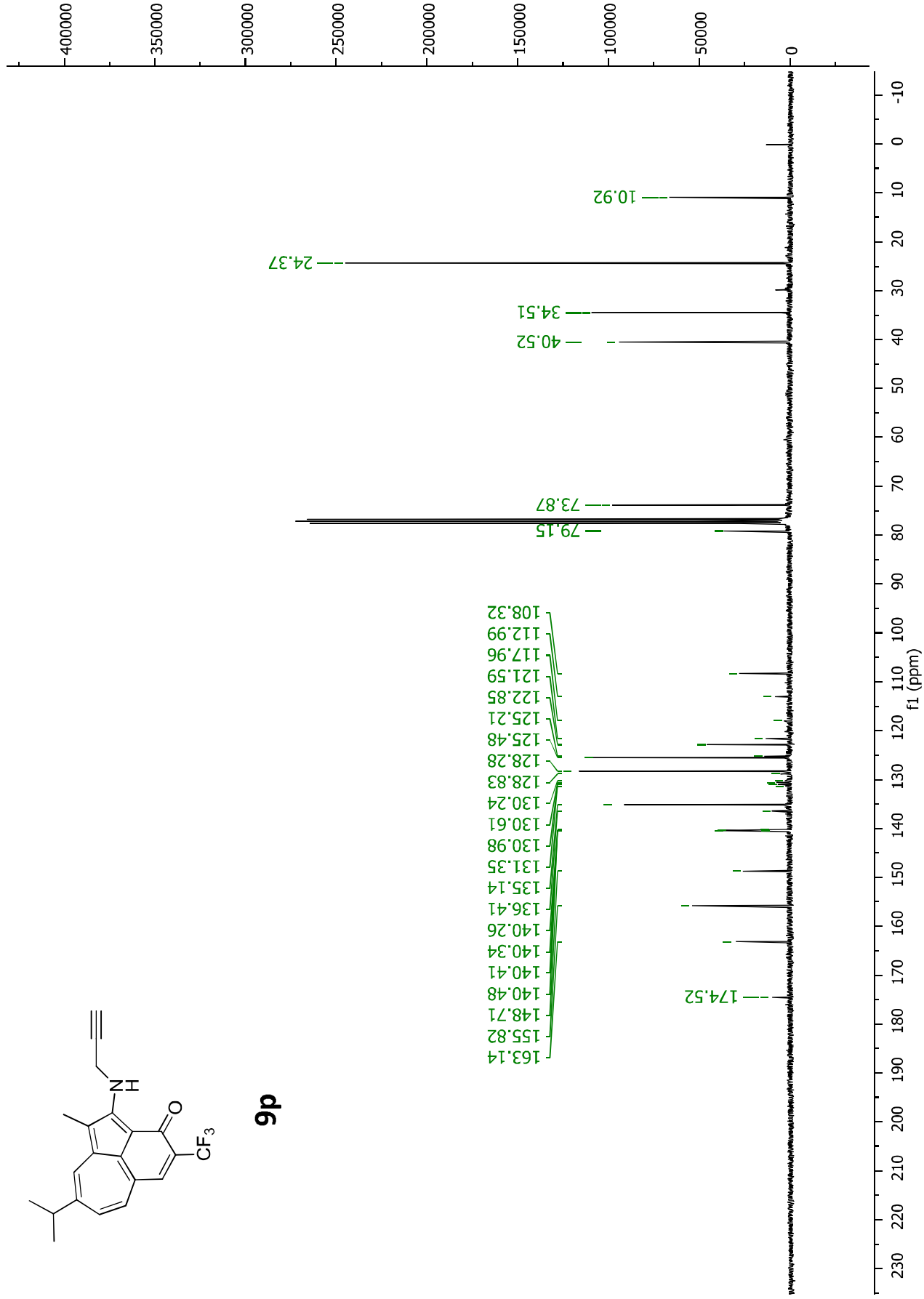
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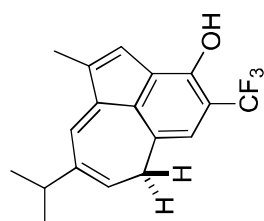




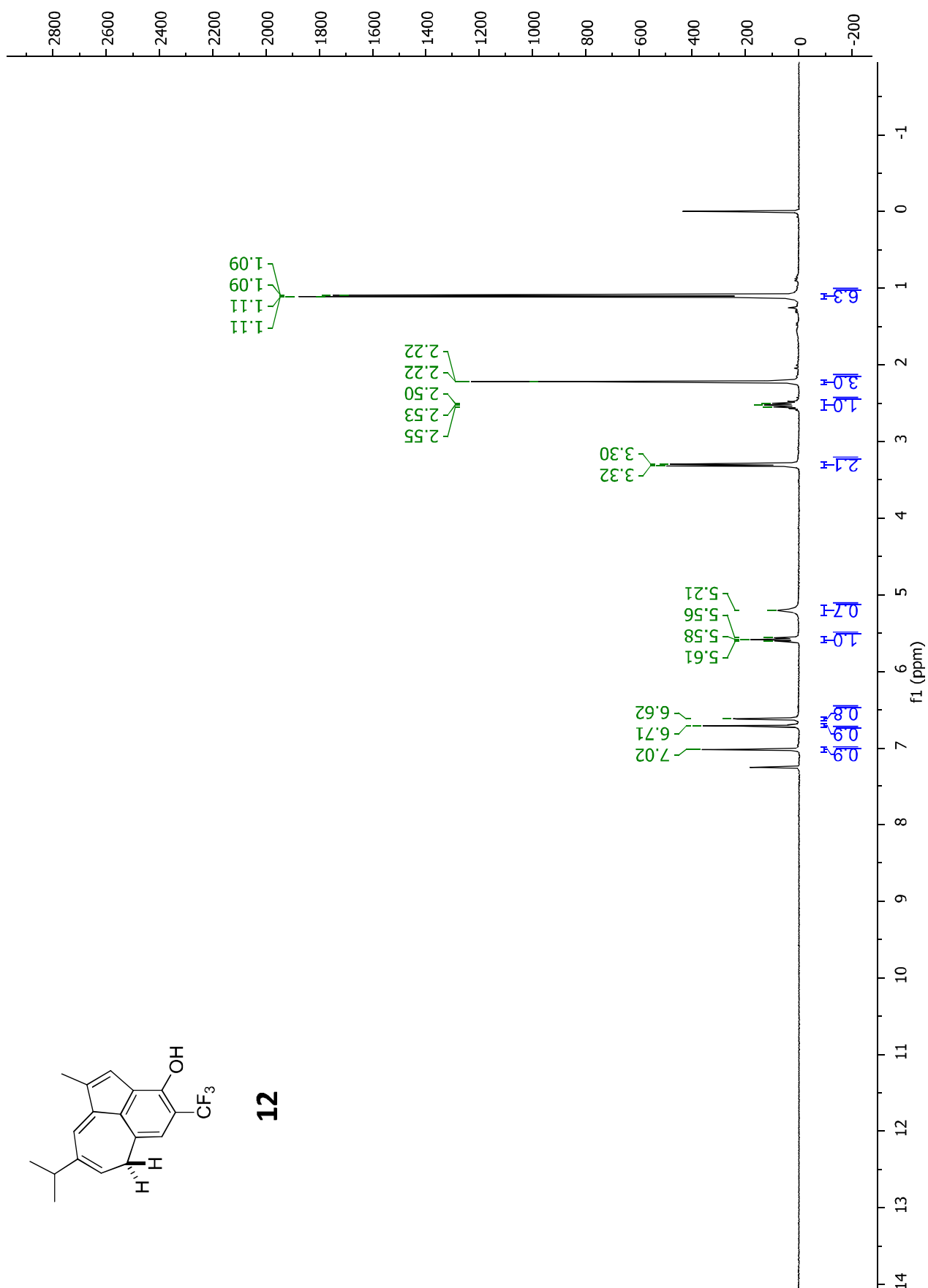
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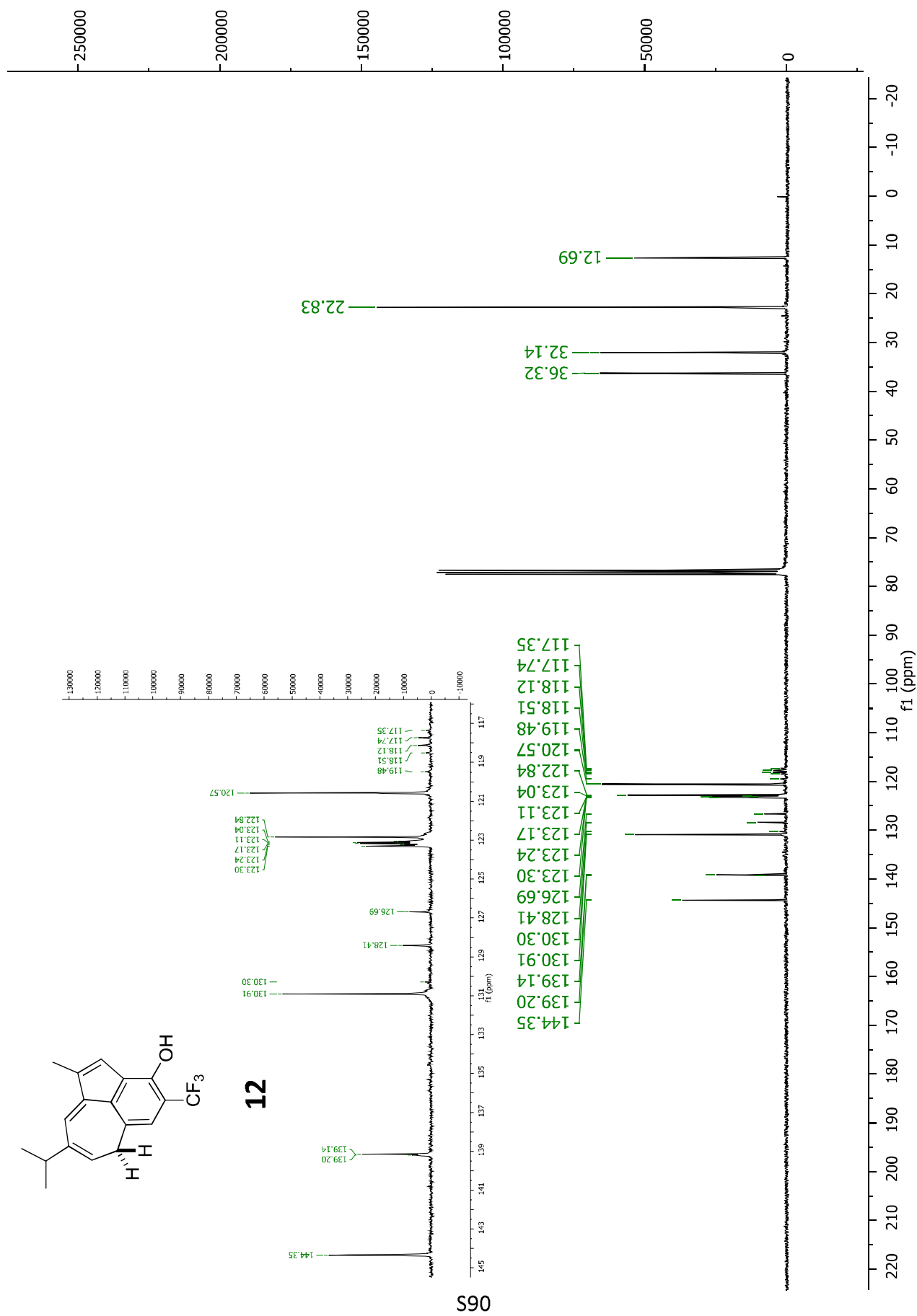


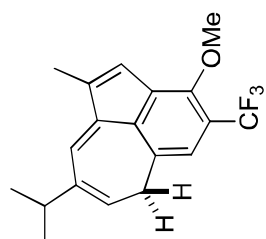




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