Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

A Brønsted acid catalyzed tandem reaction for the diastereoselective synthesis of cyclobuta-fused tetrahydroquinoline carboxylic esters

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Contents

General Methods

^{1}H NMR spectra were recorded on a 600 MHz spectrometer at ambient temperature with $CDCl_3$ as solvent. Data are reported as follows: chemical shifts (δ), multiplicity, coupling constants and integration. ^{13}C NMR spectra were recorded on the same instrument at 151 MHz with $CDCl_3$ as solvent. Infrared spectra were recorded on an FT-IR spectrophotometer in ATP mode. High resolution mass spectrometry (HRMS) was performed using an electrospray ionization (ESI) and Q-TOF mass analyzer. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60–F plates. Flash chromatography was performed using columns of 230–400 mesh silica gel 60 (0.040–0.063 mm).

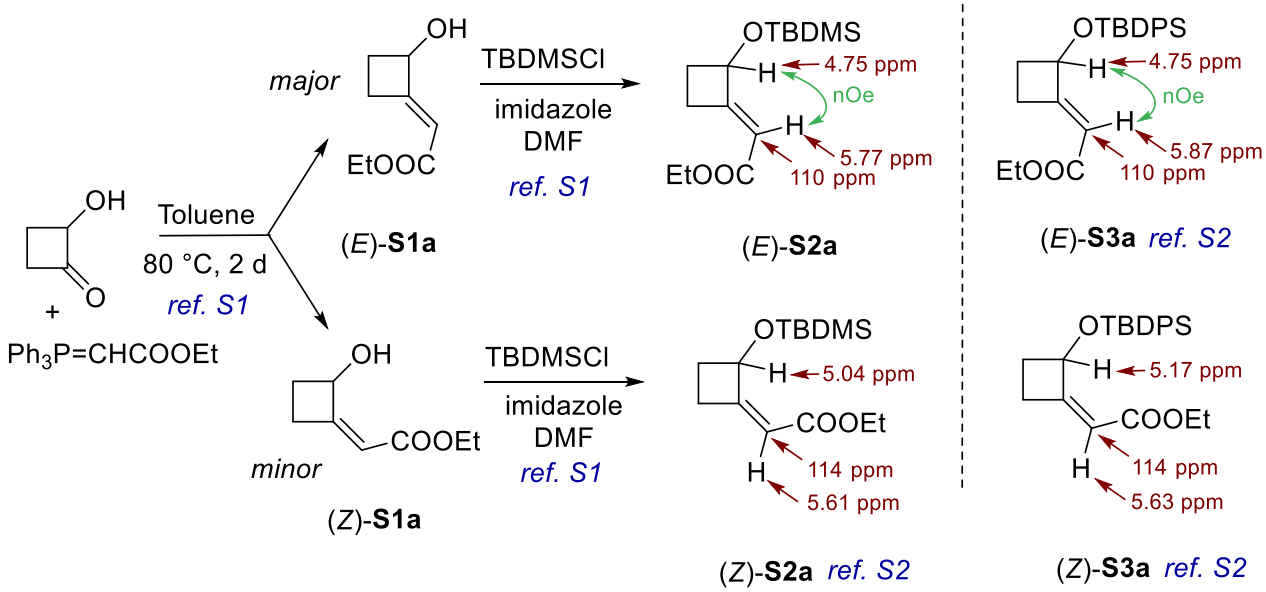
Preparation and diastereoisomeric assignment of starting materials S1a-d.

The synthesis of the 2-(carboxymethylidene)cyclobutanones used in this work (**1a-d**) is described in the next section. We used as precursors of these compounds the corresponding alcohols, **S1a-d**, which were available from a recent literature procedure involving treatment of 2-hydroxycyclobutanone with an alkyl (triphenylphosphoranylidene)acetate.[S1] Two separable diastereoisomers were obtained using this procedure and the configuration of the major one was assigned as *E* on the following basis, illustrated for **S1a**. As previously described,[S1] each isomer was transformed into its *tert*-butyldimethylsilyl ether **S2a** and the NMR data were compared with those published for (*Z*)-**S2a** the *Z* and *E* isomers of a known silyl ether with a very similar structure **S3a**, these three compounds having been made by an alternative route.[S2] Salient diagnostic observations are illustrated in the scheme below and are summarized as follows:

a) ^{1}H and ^{13}C NMR data for our minor **S2a** isomer were identical with those previously described for (*Z*)-**S2a**;

b) ^{1}H and ^{13}C NMR data for our major and minor **S2a** isomers were very similar to those previously described for the *E* and *Z* isomers of **S3a**, respectively;

c) ^{1}H NOESY correlation was found between the alkene CH and the cyclobutane CH for the major isomer of **S2a**, but not for the minor isomer, in complete analogy with the previously described behavior of the *E* and *Z* isomers of **S3a**, respectively.

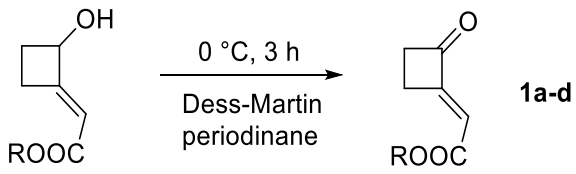


It is also of note that reactions of alkyl (triphenylphosphoranylidene)acetates with other cyclic or acyclic α-hydroxyketones gave unsaturated esters predominantly with an *E* configuration.[S3]

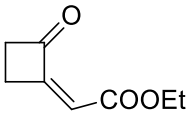
On the basis of the above observations, and given that the behavior of the other starting materials in the series was analogous, we are confident of the stereochemical assignments of the compounds **S1a-d**, as indicated previously.[S1] Since the synthesis of compounds **1a-d** by Dess-Martin oxidation (described in the next section) is assumed to proceed without isomerization, we are equally confident regarding their stereochemical assignments.

In a previous work, the preparation of (*Z*)-**1a** and (*Z*)-**1c** was described via a ruthenium catalyzed ring expansion of alkynylcyclopropanols.[S4] The NMR spectral data presented for those compounds in that work were identical to our spectra for (*E*)-**1a** and (*E*)-**1c**, leading us to suggest that revision of the structural assignment in that previous work may be appropriate.

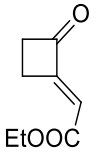
Procedure for the preparation of cyclobutanones 1.



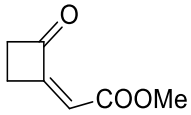
To a stirred solution of hydroxycyclobutylidene **S1a-d** (838 µmol) in CH_2Cl_2 (4 mL) at 0 °C was added Dess-Martin periodinane (838 µmol, 0.356 g) and the reaction mixture was stirred at 0 °C for 3 h. The precipitate was filtered then the mixture was quenched with sat. aq. $NaHCO_3$ solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (eluent: petroleum ether/ether = 5:1→1:1) to give compound **1**. Yields refer to chromatographically purified materials.



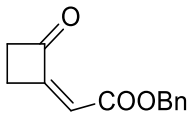
(*Z*)-**1a**: Yield 79% (102 mg); colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.21 (t, *J* = 3.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.16 – 3.12 (m, 2H), 3.08 – 3.04 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.9, 165.4, 162.1, 114.6, 61.2, 46.1, 24.4, 14.3. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_{11}O_3$: 155.0703; found: 155.0710.



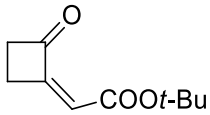
(*E*)-**1a**: Yield 82% (106 mg); colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (t, *J* = 2.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.06 – 3.03 (m, 2H), 2.76 – 2.73 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.0, 163.2, 160.4, 118.7, 61.2, 44.6, 22.3, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_{11}O_3$: 155.0703; found: 155.0710.



(*Z*)-**1b**: Yield 75% (88 mg); colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.22 (t, *J* = 3.0 Hz, 1H), 3.78 (s, 3H), 3.15 – 3.12 (m, 2H), 3.07 – 3.03 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.8, 165.8, 162.3, 114.1, 52.1, 46.1, 24.4. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_7H_9O_3$: 141.0546; found: 141.0550.

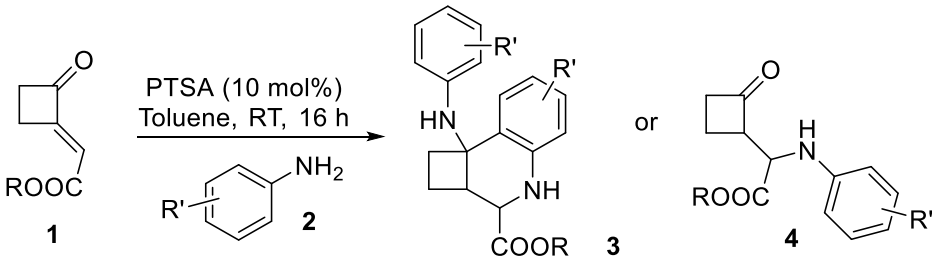


(*Z*)-**1c**: Yield 85% (154 mg); colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 5H), 6.26 (t, *J* = 3.0 Hz, 1H), 5.23 (s, 2H), 3.15 – 3.12 (m, 2H), 3.08 – 3.04 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.7, 165.2, 162.6, 135.5, 128.8, 128.6, 128.4, 114.2, 67.0, 46.1, 24.5. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{12}O_3Na$: 239.0679; found: 239.0680.

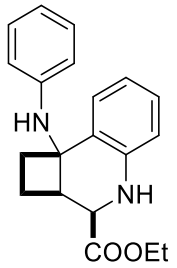


(*Z*)-**1d**: Yield 73% (124 mg); white semi-solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.10 (t, *J* = 3.0 Hz, 1H), 3.10 – 3.07 (m, 2H), 3.02 – 2.98 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.1, 164.6, 160.9, 116.4, 81.8, 45.9, 28.1, 24.2. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{10}H_{14}O_3Na$: 205.0835; found: 205.0830.

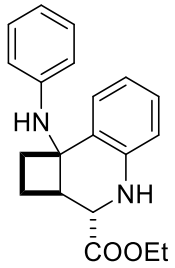
Procedure for the preparation of cyclobuta-fused tetrahydroquinolines 3 (and/or cyclobutanones 4).



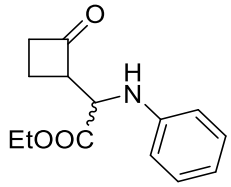
A mixture of **1** (0.26 mmol), **2** (0.52 mmol) and PTSA (0.026 mmol) in toluene (0.5 mL) was stirred in a sealed tube reactor for 16 h at room temperature (unless otherwise stated). The crude product mixture, without aqueous work-up, was purified directly by flash column chromatography (eluent: petroleum ether/ether = 10:1→1:1) to give the corresponding cyclobuta-fused tetrahydroquinoline **3** (or the cyclobutanone **4p**). Yields refer to chromatographically pure materials.



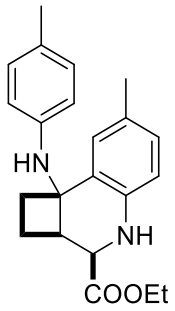
3a (from (*E*)-**1a** and **2a**): Yield 83% (70 mg); yellow oil. IR (ATR): 3396, 3383, 3084, 3053, 3014, 2980, 2944, 2872, 2849, 1729, 1600, 1500, 1484, 1371, 1298, 1249, 1213, 1159, 1040 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 1H), 7.12 – 7.08 (m, 1H), 7.07 – 7.04 (m, 2H), 6.80 – 6.78 (m, 1H), 6.77 – 6.74 (m, 1H), 6.67 – 6.65 (m, 1H), 6.55 – 6.53 (m, 2H), 4.53 (br s, 1H), 4.26 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (d, *J* = 3.8 Hz, 1H), 3.31 (td, *J* = 8.5, 3.8 Hz, 1H), 2.32 – 2.28 (m, 1H), 2.22 – 2.18 (m, 1H), 1.98 – 1.95 (m, 1H), 1.82 – 1.77 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 145.6, 143.3, 129.1, 127.7, 127.5, 126.8, 119.7, 117.8, 115.7, 115.0, 61.3, 56.0, 55.0, 45.0, 38.3, 14.3, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_2$: 323.1754; found: 323.1765.



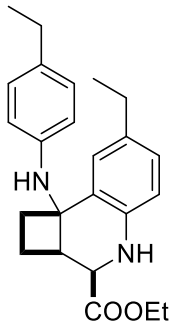
3a' (minor diastereoisomer isolated from the above-described reaction between (*E*)-**1a** and **2a**): yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 1H), 7.09 – 7.03 (m, 3H), 6.76 – 6.74 (m, 2H), 6.66 – 6.63 (m, 1H), 6.49 – 6.47 (m, 2H), 4.37 (br s, 2H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.95 (d, *J* = 4.5 Hz, 1H), 3.88 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.33 – 3.32 (m, 1H), 2.45 – 2.37 (m, 2H), 2.33 – 2.27 (m, 1H), 1.98 – 1.92 (m, 1H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 145.6, 143.4, 129.0, 128.0, 127.9, 126.9, 119.9, 117.9, 115.8, 115.2, 61.3, 56.9, 56.0, 41.7, 37.5, 19.6, 14.0. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{22}N_2O_2Na$: 343.1573; found: 343.1570.



4a/**4a'** (from (*E*)-**1a** and **2a** in solvent-free, catalyst-free conditions; see Table 1, entry 2): Yield 64% (58 mg), d.r: 52:48; yellow oil. IR (ATR): 2981, 1785, 1735, 1720, 1685, 1647, 1605, 1558, 1372, 1188, 754 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 4H), 6.79 – 6.76 (m, 2H), 6.73 – 6.72 (m, 2H), 6.65 – 6.64 (m, 2H), 4.47 (br s, 1H), 4.38 (d, *J* = 4.8 Hz, 1H), 4.31 (d, *J* = 5.2 Hz, 1H), 4.28 – 4.22 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.90 – 3.86 (m, 1H), 3.78 – 3.76 (m, 1H), 3.11 – 3.05 (m, 2H), 3.04 – 2.92 (m, 2H), 2.20 – 2.14 (m, 2H), 2.08 – 2.01 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.0, 207.6, 171.9, 171.4, 146.7, 146.6, 129.4, 129.3, 119.2, 118.9, 114.5, 113.9, 61.8, 61.7, 61.4, 61.3, 56.7, 56.2, 45.66, 45.60, 14.2, 14.1, 13.2 (2 C). HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{18}NO_3$: 348.1281; found: 348.1282.

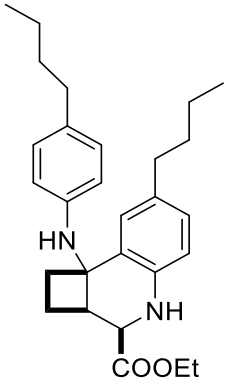


3b (from (*E*)-**1a** and **2b**): Yield 81% (82 mg); orange oil. IR (ATR): 3400, 3387, 3018, 2980, 2939, 2915, 2866, 1731, 1615, 1587, 1517, 1466, 1450, 1391, 1311, 1288, 1213, 1032 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.5 Hz, 1H), 6.92 – 6.89 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.47 – 6.45 (m, 2H), 4.39 (br s, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.98 (d, *J* = 3.8 Hz, 1H), 3.25 (td, *J* = 8.5, 3.7 Hz, 1H), 2.30 – 2.25 (m, 1H), 2.20 (s, 6H), 2.19 – 2.15 (m, 1H), 1.94 – 1.89 (m, 1H), 1.80 – 1.73 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 143.3, 140.9, 129.6, 128.9, 128.4, 127.7, 127.1, 127.0, 115.7, 115.5, 61.2, 56.2, 55.1, 44.8, 38.4, 20.8, 20.4, 14.3, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$: 351.2067; found: 351.2085.

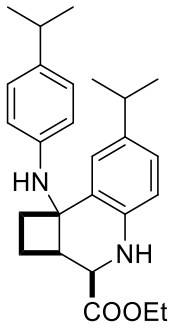


3c (from (*E*)-**1a** and **2c**): Yield 90% (88 mg); orange oil. IR (ATR): 3398, 3388, 3040, 3024, 2980, 2960, 2929, 2869, 1732, 1616, 1587, 1512, 1466, 1451, 1391, 1371, 1316, 1288, 1110, 1030 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 – 7.21 (m, 1H), 6.95 – 6.93 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 2H), 4.40 (br s, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.97 (d, *J* = 3.8 Hz, 1H), 3.27 (td, *J* = 8.6, 3.7 Hz, 1H), 2.50 (q, *J* = 7.6 Hz, 4H), 2.32 – 2.27 (m, 1H), 2.19 – 2.15 (m, 1H), 1.94 – 1.88 (m, 1H), 1.79 – 1.74 (m, 1H), 1.26 (t, *J* = 7.1

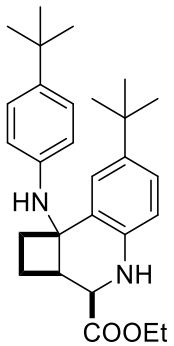
Hz, 3H), 1.17 – 1.14 (m, 3H), 1.13 – 1.12 (m, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 143.6, 141.1, 135.5, 133.7, 128.4, 127.7, 127.1, 126.0, 115.7, 115.5, 61.2, 56.4, 55.1, 44.8, 38.4, 28.3, 27.9, 15.9, 15.8, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{31}N_2O_2$: 379.2380; found: 379.2388.



3d (from (*E*)-**1a** and **2d**): Yield 66% (75 mg); orange oil. IR (ATR): 3396, 3377, 3041, 3013, 2956, 2929, 2871, 2852, 1730, 1615, 1582, 1514, 1506, 1465, 1402, 1369, 1315, 1293, 1249, 1213, 1178, 1115, 1033 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 1.9 Hz, 1H), 6.91 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.47 – 6.45 (m, 2H), 4.38 (br s, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.96 (d, *J* = 3.7 Hz, 1H), 3.26 (td, *J* = 8.6, 3.7 Hz, 1H), 2.47 – 2.43 (m, 4H), 2.32 – 2.27 (m, 1H), 2.18 – 2.14 (m, 1H), 1.94 – 1.88 (m, 1H), 1.78 – 1.73 (m, 1H), 1.53 – 1.44 (m, 4H), 1.33 – 1.29 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.20 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 143.5, 141.1, 134.1, 132.4, 128.9, 127.6, 126.6, 115.6, 115.5 (2 C), 61.2, 56.4, 55.1, 44.8, 38.3, 35.1, 34.8, 33.9 (2 C), 22.4, 22.3, 14.4, 14.1, 14.0 (2 C). HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{39}N_2O_2$: 435.3006; found: 435.3008.

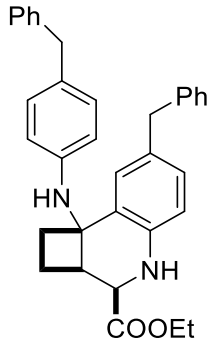


3e (from (*E*)-**1a** and **2e**): Yield 89% (94 mg); yellow oil. IR (ATR): 3398, 3383, 3099, 3040, 3014, 2965, 2926, 2867, 1727, 1611, 1518, 1500, 1463, 1402, 1371, 1314, 1283, 1249, 1211, 1048 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 2.0 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.50 – 6.47 (m, 2H), 4.39 (br s, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.95 (d, *J* = 3.7 Hz, 1H), 3.28 (td, *J* = 8.6, 3.7 Hz, 1H), 2.77 – 2.73 (m, 2H), 2.35 – 2.30 (m, 1H), 2.19 – 2.14 (m, 1H), 1.93 – 1.86 (m, 1H), 1.79 – 1.73 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.14 (d, *J* = 2.8 Hz, 3H), 1.13 (d, *J* = 2.8 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 143.7, 141.1, 140.2, 138.4, 127.6, 126.9, 125.4, 125.0, 115.6, 61.3, 56.6, 54.9, 44.8, 38.2, 33.5, 33.2, 24.4, 24.3, 24.24, 24.20, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_2$: 407.2693; found: 407.2684.

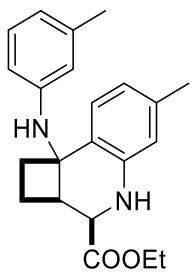


3f (from (*E*)-**1a** and **2f**): Yield 61% (69 mg); yellow oil. IR (ATR): 3395, 3377, 3055, 3016, 2957, 2902, 2864, 1729, 1613, 1517, 1463, 1393, 1362, 1313, 1275, 1251, 1218, 1117, 1030 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.3 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.09 – 7.06 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.51 – 6.49 (m, 2H), 4.25 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.96 (d, *J* = 3.7 Hz,

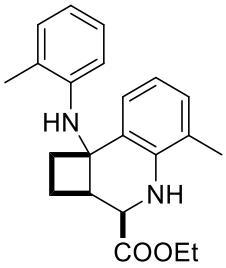
1H), 3.32 (td, *J* = 8.6, 3.7 Hz, 1H), 2.40 – 2.38 (m, 1H), 2.19 – 2.15 (m, 1H), 1.92 – 1.87 (m, 1H), 1.79 – 1.72 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 9H), 1.20 (s, 9H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 143.3, 142.3, 140.8, 140.7, 127.0, 125.7, 124.5, 123.9, 115.3, 115.2, 61.2, 56.7, 54.7, 44.8, 38.0, 34.2, 33.9, 31.6 (2 C), 14.4, 13.9. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{39}N_2O_2$: 435.3006; found: 435.3000.



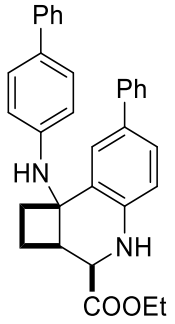
3g (from (*E*)-**1a** and **2g**): Yield 84% (109 mg); orange oil. IR (ATR): 3408, 3382, 3080, 3060, 3026, 2980, 2840, 1731, 1615, 1517, 1504, 1450, 1318, 1290, 1215, 1179, 1073, 1030 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 2H), 7.13 – 7.12 (m, 1H), 7.11 – 7.06 (m, 5H), 7.04 – 7.02 (m, 1H), 6.96 – 6.95 (m, 2H), 6.80 – 6.77 (m, 3H), 6.61 – 6.60 (m, 1H), 6.37 – 6.36 (m, 2H), 4.33 (br s, 1H), 4.17 – 4.15 (m, 1H), 4.10 – 4.07 (m, 1H), 3.89 (d, *J* = 3.8 Hz, 1H), 3.75 (s, 2H), 3.73 (s, 2H), 3.18 (td, *J* = 8.6, 3.7 Hz, 1H), 2.22 – 2.17 (m, 1H), 2.11 – 2.06 (m, 1H), 1.85 – 1.82 (m, 1H), 1.72 – 1.65 (m, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 143.8, 142.0, 141.9, 141.5, 132.1, 130.5, 129.4, 129.0, 128.8, 128.4, 128.36, 128.35, 127.5, 127.3, 125.9, 125.8, 116.0, 115.4, 61.3, 56.2, 55.0, 45.0, 41.3, 41.1, 38.3, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{34}H_{35}N_2O_2$: 503.2693; found: 503.2690.



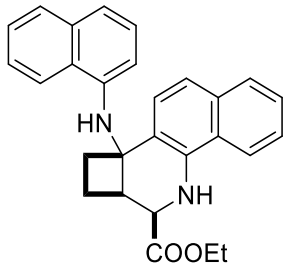
3h (from (*E*)-**1a** and **2h**): Yield 90% (82 mg); orange oil. IR (ATR): 3410, 3374, 3049, 2972, 2956, 2918, 2866, 1727, 1653, 1615, 1593, 1517, 1470, 1445, 1366, 1312, 1219, 1118, 1030 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.60 (s, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.48 (d, *J* = 7.4 Hz, 1H), 6.40 (s, 1H), 6.31 – 6.29 (m, 1H), 4.44 (br s, 1H), 4.26 – 4.23 (m, 1H), 4.18 – 4.16 (m, 1H), 4.02 (d, *J* = 3.8 Hz, 1H), 3.28 (td, *J* = 8.6, 3.7 Hz, 1H), 2.31 – 2.26 (m, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.19 – 2.15 (m, 1H), 1.93 – 1.90 (m, 1H), 1.79 – 1.72 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 145.7, 143.1, 138.9, 137.4, 128.9, 126.7, 124.8, 120.9, 118.7, 116.2, 116.1, 111.8, 61.3, 55.9, 55.0, 45.0, 38.4, 21.7, 21.3, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$: 351.2067; found: 351.2045.



3i (from (*E*)-**1a** and **2i**): Yield 88% (80 mg); yellow oil. IR (ATR): 3437, 3418, 3041, 2981, 2948, 2915, 2858, 2732, 1732, 1601, 1511, 1500, 1470, 1446, 1369, 1309, 1252, 1213, 1170, 1091, 1033 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.88 – 6.86 (m, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.39 – 6.38 (m, 1H), 4.53 (br s, 1H), 4.30 – 4.27 (m, 1H), 4.25 – 4.19 (m, 1H), 4.18 (br s, 1H), 4.12 (d, *J* = 3.9 Hz, 1H), 3.34 – 3.30 (m, 1H), 2.36 – 2.33 (m, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.25 – 2.20 (m, 1H), 2.02 – 2.00 (m, 1H), 1.99 – 1.78 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 143.4, 141.6, 130.5, 128.8, 127.5, 126.6, 124.1, 122.7, 122.5, 118.9, 117.1, 112.9, 61.4, 56.1, 55.2, 45.0, 38.4, 18.0, 17.5, 14.3 (2 C). HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$: 351.2067; found: 351.2057.

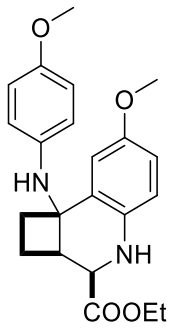


3j (from (*E*)-**1a** and **2j**): Yield 75% (92 mg); yellow oil. IR (ATR): 3407, 3382, 3057, 3035, 2978, 2934, 2869, 2844, 1740, 1648, 1612, 1587, 1514, 1489, 1462, 1410, 1372, 1320, 1262, 1164, 1071 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.1 Hz, 1H), 7.41 – 7.38 (m, 4H), 7.30 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.29 – 7.23 (m, 6H), 7.16 – 7.12 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 2H), 4.57 (br s, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.11 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.03 (d, *J* = 3.8 Hz, 1H), 3.27 (td, *J* = 8.6, 3.8 Hz, 1H), 2.30 – 2.26 (m, 1H), 2.20 – 2.16 (m, 1H), 1.90 – 1.86 (m, 1H), 1.75 – 1.72 (dq, *J* = 11.8, 8.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 145.0, 142.7, 141.2, 141.1, 132.6, 130.8, 128.73, 128.70, 127.80, 127.5, 126.6, 126.5, 126.36, 126.35, 126.2, 125.5, 116.1, 115.4, 61.4, 56.2, 54.9, 45.0, 38.5, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{32}H_{30}N_2O_2Na$: 497.2199; found: 497.2200.

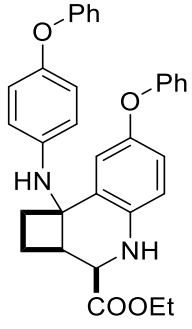


3k (from (*E*)-**1a** and **2k**): Yield 85% (94 mg); violet oil. IR (ATR): 3437, 3418, 3060, 2983, 2937, 2869, 1738, 1659, 1623, 1585, 1574, 1530, 1514, 1476, 1462, 1407, 1369, 1320, 1290, 1246, 1162, 1130, 1033 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.68 (m, 2H), 7.47 – 7.42 (m, 3H), 7.41 – 7.37 (m, 2H), 7.18 – 7.15 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.94 (t, *J* = 7.9 Hz, 1H), 6.47 (d, *J* = 7.7 Hz, 1H), 5.32 (br s, 1H), 4.27 (d, *J* = 3.6 Hz, 1H), 4.22 (dq, *J* = 10.8,

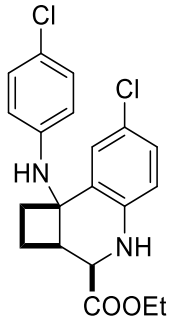
7.1 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.36 (td, *J* = 8.8, 3.7 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.25 – 2.21 (m, 1H), 1.91 – 1.86 (m, 1H), 1.75 – 1.69 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 140.4, 137.8, 134.6, 133.6, 129.0, 128.7, 126.2, 125.85, 125.82, 125.3, 125.0, 124.7, 124.2, 123.6, 121.0, 120.4, 119.9, 119.6, 117.8, 108.3, 61.5, 56.4, 55.0, 45.6, 38.6, 14.4, 13.8. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_2$: 423.2067; found: 423.2054.



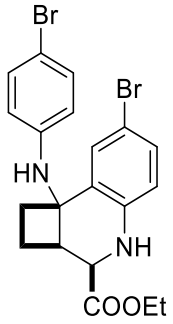
3l (from (*E*)-**1a** and **2l**): Yield 76% (75 mg); orange oil. IR (ATR): 3393, 3380, 3052, 2985, 2941, 2830, 1739, 1610, 1597, 1515, 1496, 1468, 1440, 1404, 1367, 1277, 1238, 1174, 1153, 1040 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 2.4 Hz, 1H), 6.73 – 6.70 (m, 2H), 6.67 – 6.64 (m, 2H), 6.51 – 6.48 (m, 2H), 4.27 – 4.13 (m, 3H), 3.85 (d, *J* = 3.7 Hz, 1H), 3.694 (s, 3H), 3.694 (s, 3H), 3.19 (td, *J* = 8.5, 3.7 Hz, 1H), 2.27 – 2.22 (m, 1H), 2.19 – 2.15 (m, 1H), 1.91 – 1.88 (m, 1H), 1.78 – 1.72 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.3, 153.7, 152.8, 139.4, 137.3, 129.1, 117.4, 116.8, 114.6, 114.3, 111.4, 61.3, 57.0, 55.8, 55.7, 55.2, 44.5, 38.3, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_4$: 383.1965; found: 383.1988.



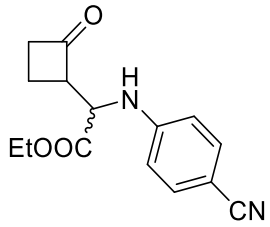
3m (from (*E*)-**1a** and **2m**): Yield 62% (82 mg); orange oil. IR (ATR): 3418, 3382, 3057, 3027, 2983, 2934, 2871, 2852, 1727, 1648, 1612, 1525, 1496, 1465, 1399, 1372, 1323, 1271, 1221, 1156, 1074, 1028 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 2H), 7.22 – 7.19 (m, 2H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.92 – 6.90 (m, 2H), 6.83 – 6.80 (m, 3H), 6.77 – 6.76 (m, 3H), 6.47 – 6.46 (m, 2H), 4.46 (br s, 1H), 4.28 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.00 (d, *J* = 3.8 Hz, 1H), 3.27 (td, *J* = 8.5, 3.7 Hz, 1H), 2.27 – 2.21 (m, 2H), 1.99 – 1.95 (m, 1H), 1.83 – 1.79 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), one N*H* signal is not visible in the ^1H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 158.9, 158.8, 149.2, 148.4, 141.7, 140.0, 129.64, 129.61, 128.8, 122.2, 122.0, 120.7, 120.0, 118.5, 117.5, 117.1, 116.9, 116.4, 61.4, 56.4, 55.2, 44.9, 38.2, 14.4, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{32}H_{31}N_2O_4$: 507.2278; found: 507.2275.



3n (from (*E*)-**1a** and **2n**): Yield 75% (76 mg); orange oil. IR (ATR): 3408, 3031, 2988, 2954, 2926, 2866, 1731, 1602, 1509, 1489, 1453, 1401, 1370, 1316, 1280, 1251, 1177, 1086 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.44 – 6.40 (m, 2H), 4.56 (br s, 1H), 4.33 – 4.23 (m, 2H), 4.21 – 4.16 (m, 1H), 3.96 (d, *J* = 3.8 Hz, 1H), 3.22 (td, *J* = 8.7, 3.9 Hz, 1H), 2.28 – 2.22 (m, 1H), 2.19 – 2.15 (m, 1H), 1.96 – 1.93 (m, 1H), 1.77 – 1.70 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 143.8, 141.9, 129.1, 128.7, 128.0, 126.4, 124.4, 123.0, 117.0, 116.2, 61.6, 56.0, 55.0, 44.7, 38.3, 14.4, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{21}Cl_2N_2O_2$: 391.0974; found: 391.0970.

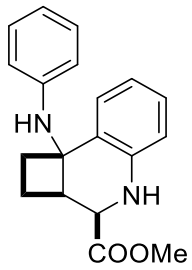


3o (from (*E*)-**1a** and **2o**): Yield 67% (83 mg); orange oil. IR (ATR): 3404, 3390, 3087, 3054, 2980, 2948, 2907, 2871, 2852, 1732, 1650, 1596, 1511, 1497, 1481, 1437, 1394, 1369, 1314, 1252, 1183, 1115, 1077 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.3 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.14 – 7.12 (m, 2H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.39 – 6.36 (m, 2H), 4.58 (br s, 1H), 4.34 – 4.23 (m, 2H), 4.20 – 4.16 (m, 1H), 3.97 (d, *J* = 3.8 Hz, 1H), 3.22 (td, *J* = 8.6, 3.8 Hz, 1H), 2.28 – 2.23 (m, 1H), 2.20 – 2.15 (m, 1H), 1.97 – 1.91 (m, 1H), 1.75 – 1.70 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 144.2, 142.3, 131.9, 130.8, 129.3, 129.0, 117.4, 116.6, 111.6, 110.0, 61.6, 55.9, 54.9, 44.7, 38.3, 14.3, 14.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{21}Br_2N_2O_2$: 478.9964; found: 478.9917.

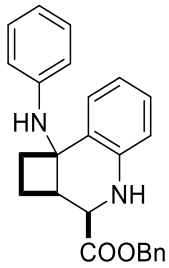


4p/**4p'** (from (*E*)-**1a** and **2p**): Yield 23% (16 mg), d.r. 55:45; orange oil. IR (ATR): 3368, 3082, 2983, 2929, 2871, 2855, 2213, 1779, 1732, 1628, 1607, 1516, 1465, 1391, 1372, 1336, 1260, 1208, 1172, 1085, 1019 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 4H), 6.70 – 6.69 (m, 2H), 6.62 – 6.60 (m, 2H), 5.05 (d, *J* = 8.4 Hz, 1H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.42 (dd, *J* = 8.5, 4.7 Hz, 1H), 4.34 (dd, *J* = 7.2, 5.6 Hz, 1H), 4.31 – 4.25 (m, 2H), 4.24 – 4.21 (m, 2H), 3.89 – 3.85 (m, 1H), 3.80 – 3.76 (m, 1H), 3.14 – 3.09 (m, 2H), 2.99 – 2.95 (m, 2H), 2.25 – 2.18 (m, 2H), 2.07 – 2.02 (m, 1H), 1.97 – 1.92 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.4, 206.6, 170.8, 170.4, 149.85, 149.80, 133.8 (2 C), 120.0 (2 C), 113.7,

113.2, 101.1, 100.9, 62.4, 62.3, 60.8, 60.7, 55.4, 55.1, 45.8, 45.7, 14.3, 14.2, 13.2 (2 C). HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_3$: 273.1234; found: 273.1238.

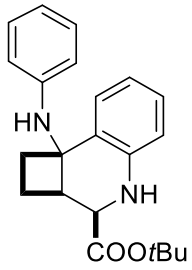


3r (from (*E*)-**1b** and **2a**): Yield 91% (83 mg); orange oil. IR (ATR): 3410, 3393, 3082, 3052, 3019, 2989, 2953, 2852, 1730, 1601, 1566, 1500, 1435, 1366, 1317, 1298, 1249, 1222, 1162, 1110, 1030 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.06 – 7.02 (m, 2H), 6.79 – 6.74 (m, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.53 – 6.51 (m, 2H), 4.51 (br s, 1H), 4.05 (d, *J* = 3.8 Hz, 1H), 3.75 (s, 3H), 3.30 (td, *J* = 8.6, 3.7 Hz, 1H), 2.34 – 2.28 (m, 1H), 2.22 – 2.16 (m, 1H), 1.96 – 1.94 (m, 1H), 1.80 – 1.76 (m, 1H), one N*H* signal is not visible in the ^1H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 145.6, 143.2, 129.1, 127.74, 127.71, 126.8, 119.9, 117.9, 115.7, 115.1, 56.1, 55.0, 52.3, 45.0, 38.3, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1582.



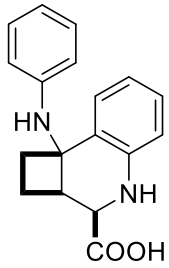
3s (from (*E*)-**1c** and **2a**, reaction carried out at 70 °C): Yield 50% (50 mg); orange oil. IR (ATR): 3398, 3390, 3084, 3054, 3021, 2980, 2956, 2929, 2852, 1738, 1612, 1596, 1511, 1500, 1484, 1462, 1432, 1380, 1298, 1175, 1082 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 6H), 7.10 – 7.07 (m, 1H), 7.05 – 7.02 (m, 2H), 6.78 – 6.74 (m, 2H), 6.66 – 6.63 (m, 1H), 6.51 – 6.49 (m, 2H), 5.27 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 4.52 (br s, 1H), 4.09 (d, *J* = 3.6 Hz, 1H), 3.30 (td, *J* = 8.6, 3.7 Hz, 1H), 2.29 – 2.26 (m, 1H), 2.20 – 2.16 (m, 1H), 1.89 – 1.85 (m, 1H), 1.79 – 1.72 (m,

1H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.1, 145.4, 143.2, 135.5, 129.1, 128.7, 128.6, 128.5, 127.7, 126.8, 119.8, 117.9, 115.7, 115.0, 67.1, 56.0, 55.0, 45.0, 38.3, 14.2. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_2$: 385.1911; found: 385.1944.



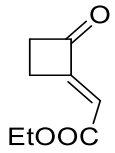
3t (from (*E*)-**1d** and **2a**, reaction carried out at 70 °C): Yield 48% (44 mg); white solid; m.p. = 150–153 °C. IR (ATR): 3404, 3379, 3046, 3003, 2953, 2923, 2855, 1716, 1604, 1584, 1495, 1458, 1372, 1312, 1252, 1175, 1162, 1053 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 1H), 7.10 – 7.05 (m, 3H), 6.78 – 6.77 (m, 1H), 6.76 – 6.73 (m, 1H), 6.68 – 6.65 (m, 1H), 6.54 – 6.52 (m, 2H), 4.52 (br s, 1H), 3.97 (d, *J* = 3.9 Hz, 1H), 3.26 (td, *J* = 8.6, 3.9 Hz, 1H), 2.31 – 2.27 (m, 1H), 2.23 – 2.18 (m, 1H), 1.99 – 1.96 (m, 1H), 1.82 – 1.76 (m, 1H), 1.48 (s, 9H), one N*H* signal is not visible in the ^{1}H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 145.6, 143.5, 129.1, 127.6, 127.2, 126.7, 119.5, 117.6, 115.6, 114.8, 82.0, 55.9, 55.2, 45.2, 38.2, 28.2, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_2$: 351,2067; found: 351,2076.

Procedure for the preparation of tetrahydroquinoline carboxylic acid 5.

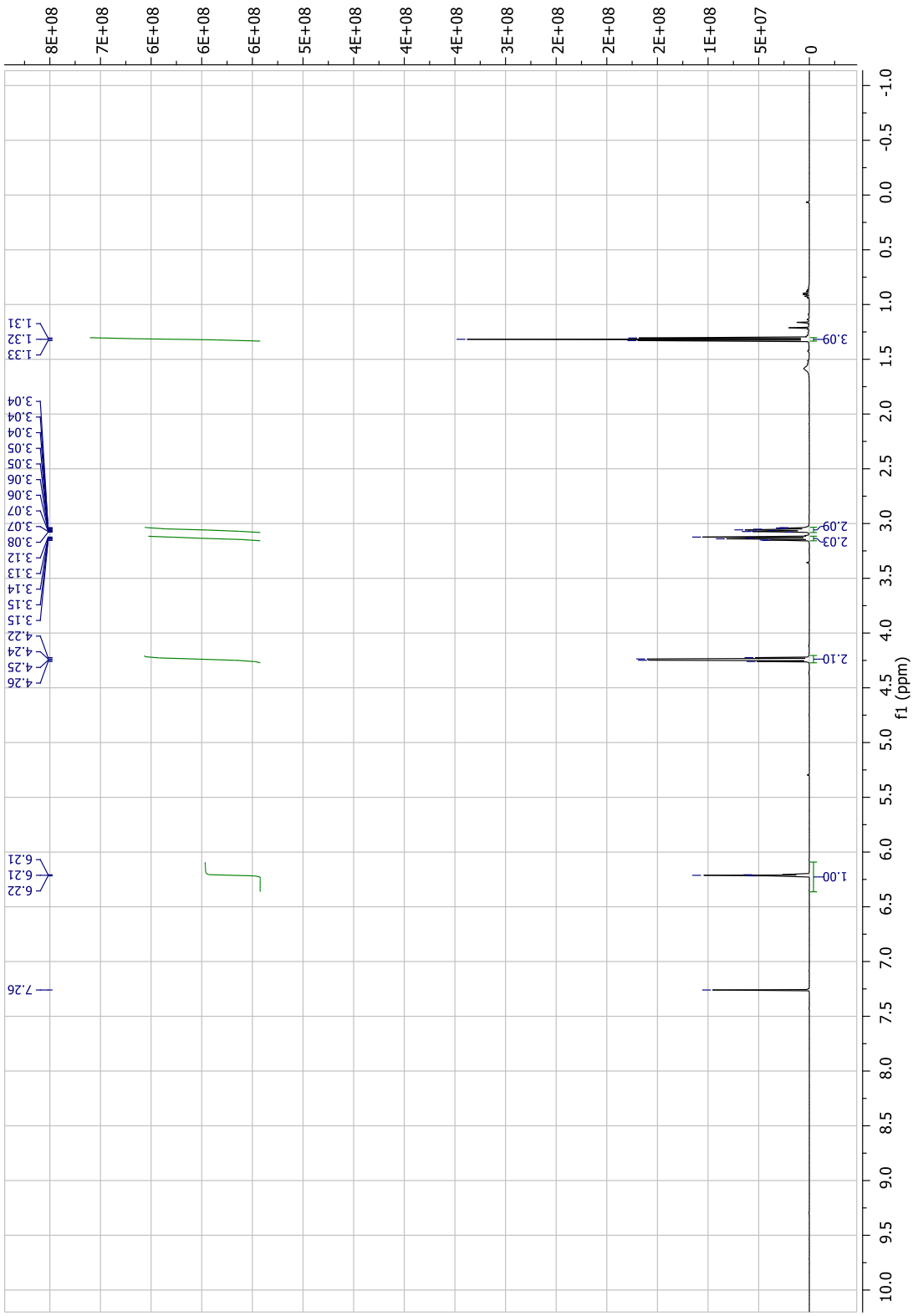


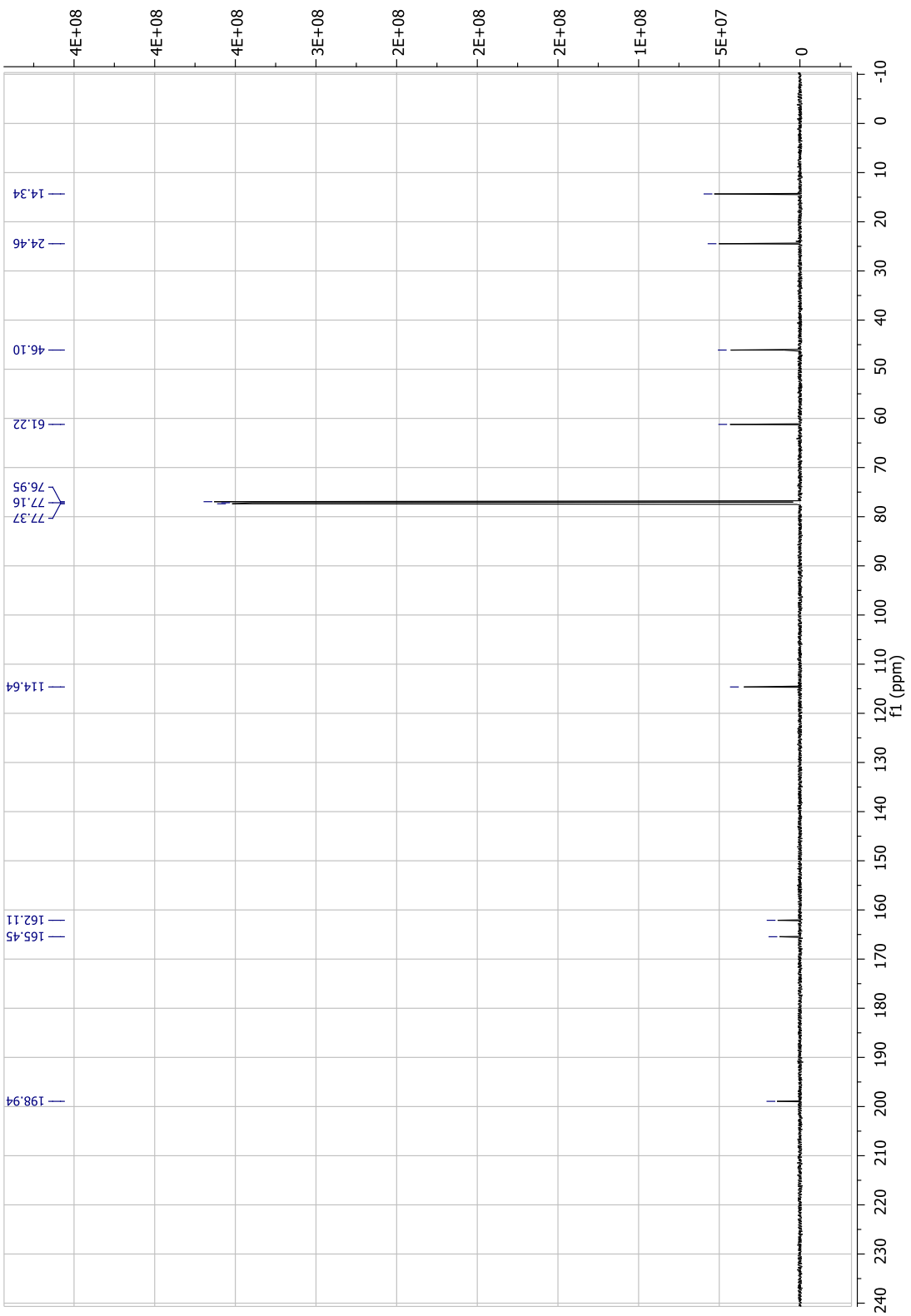
To a solution of **3a** (0.311 mmol, 100 mg) in a mixture of dioxane (2.4 mL) and water (1.1 mL) was added sodium hydroxide (1.244 mmol, 50 mg) and the mixture was stirred at reflux for 10 h. After the mixture was cooled to room temperature, water was added, and the mixture was washed with ethyl acetate. The aqueous phase was acidified with 1 M aqueous HCl to pH 1. The aqueous layer was then extracted with ethyl acetate and the combined organic phases were washed with water, then brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate 1/1 → ethyl acetate) gave the tetrahydroquinoline carboxylic acid **5**: Yield 74% (67 mg); orange solid; m.p. = 105–108 °C. IR (ATR): 3450, 2953, 2923, 2874, 1732, 1691, 1661, 1596, 1563, 1503, 1481, 1440, 1421, 1263, 1399, 1263, 1208, 1173, 1097 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.06 – 7.03 (m, 2H), 6.79 – 6.77 (m, 2H), 6.67 – 6.65 (m, 1H), 6.51 (d, *J* = 8.2 Hz, 2H), 4.11 (d, *J* = 3.7 Hz, 1H), 3.32 (td, *J* = 8.6, 3.7 Hz, 1H), 2.37 – 2.32 (m, 1H), 2.23 – 2.17 (m, 1H), 2.02 – 1.97 (m, 1H), 1.85 – 1.80 (m, 1H), the COO*H* signal is not visible in the ^1H NMR spectrum. ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.3, 145.5, 142.9, 129.1, 127.8, 127.0, 120.1, 118.1, 115.8, 115.2, 56.1, 54.5, 44.8, 38.3, 14.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_2$: 295.1441; found: 295.1434.

Copies of NMR spectra of new compounds.



(*E*)-**1a**

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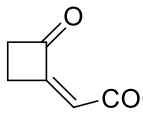
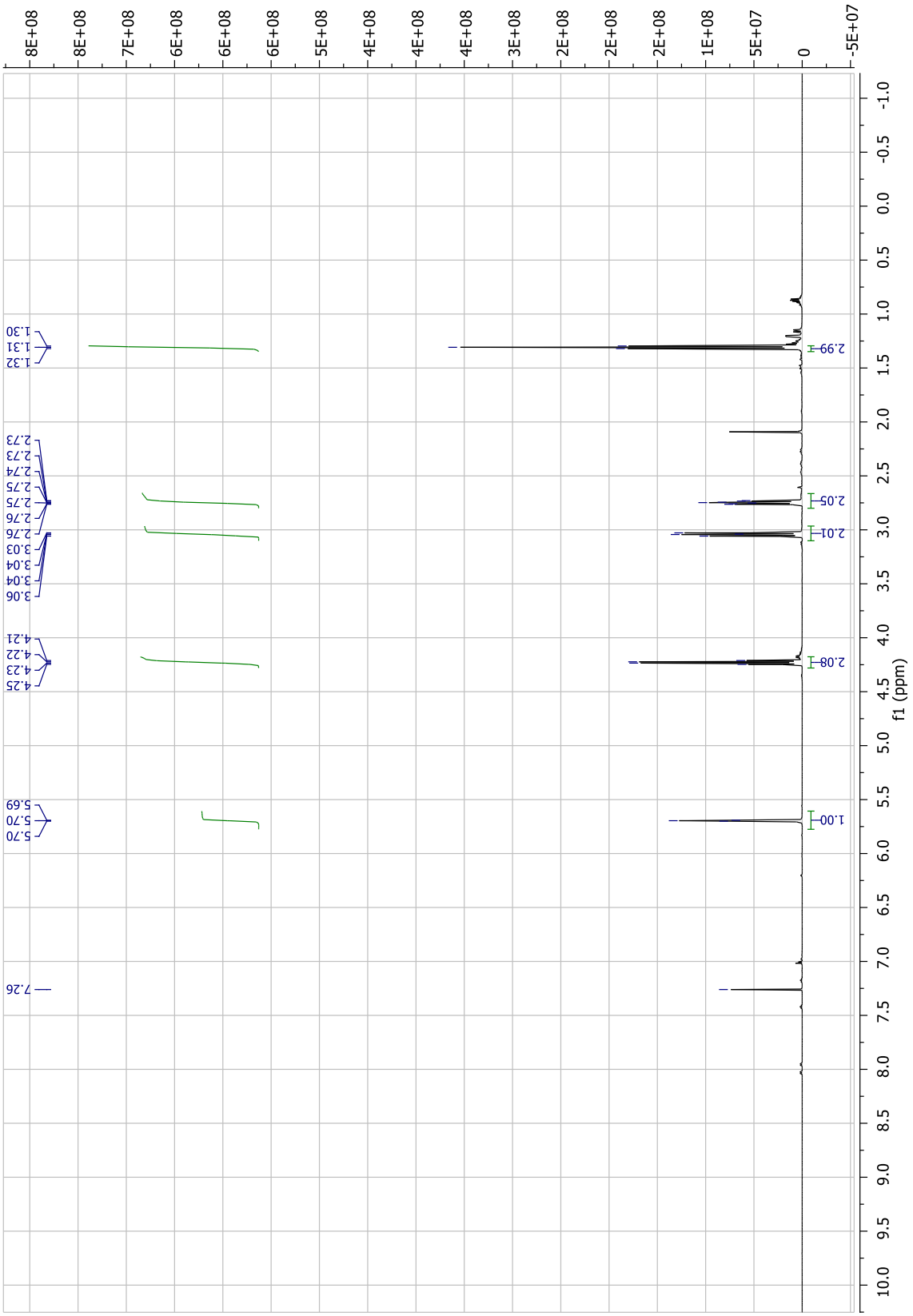
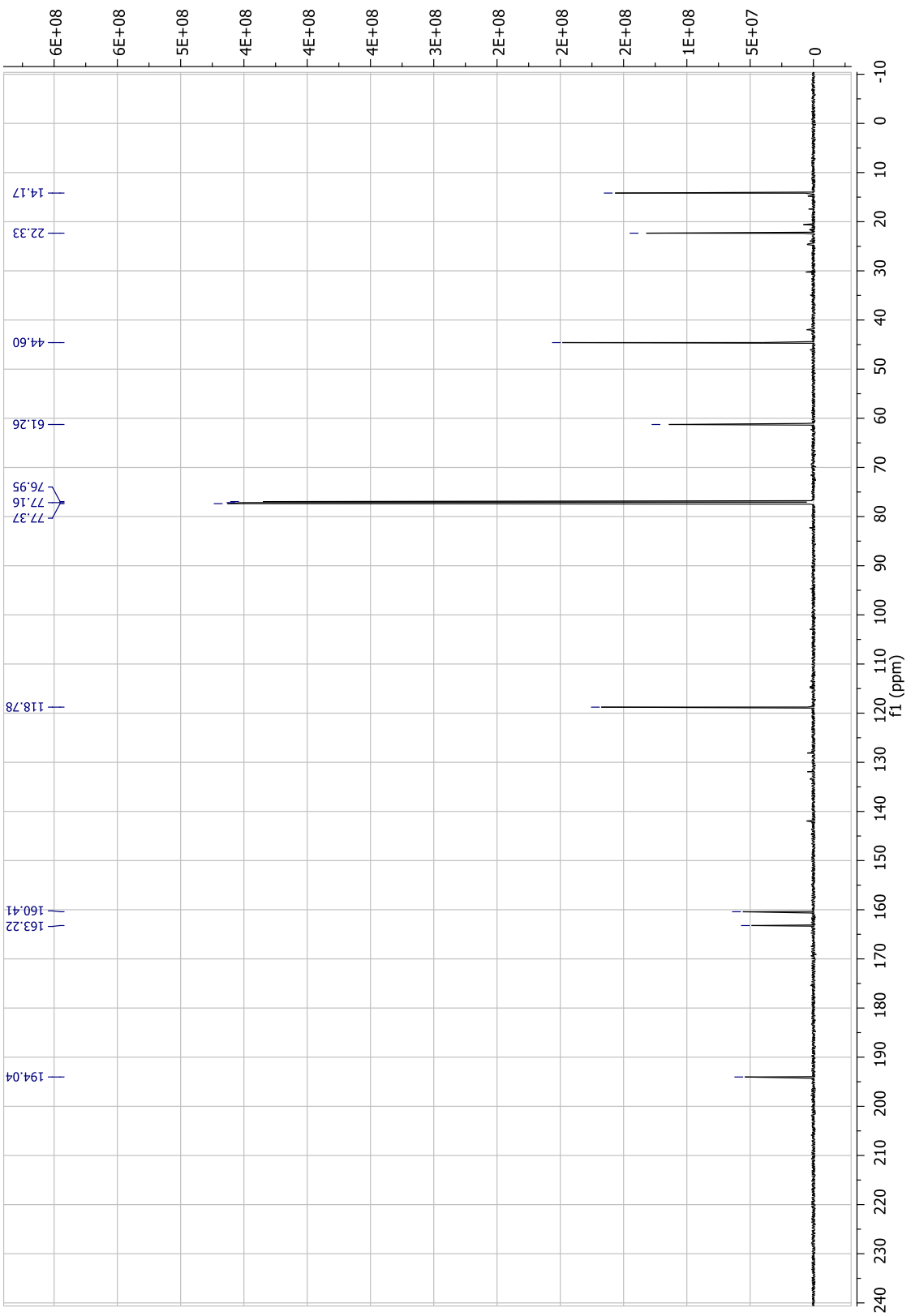
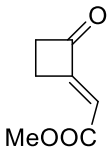
61.22
77.37
77.16
76.95
114.64
162.11
165.45
198.94
f1 (ppm)


O
COOEt

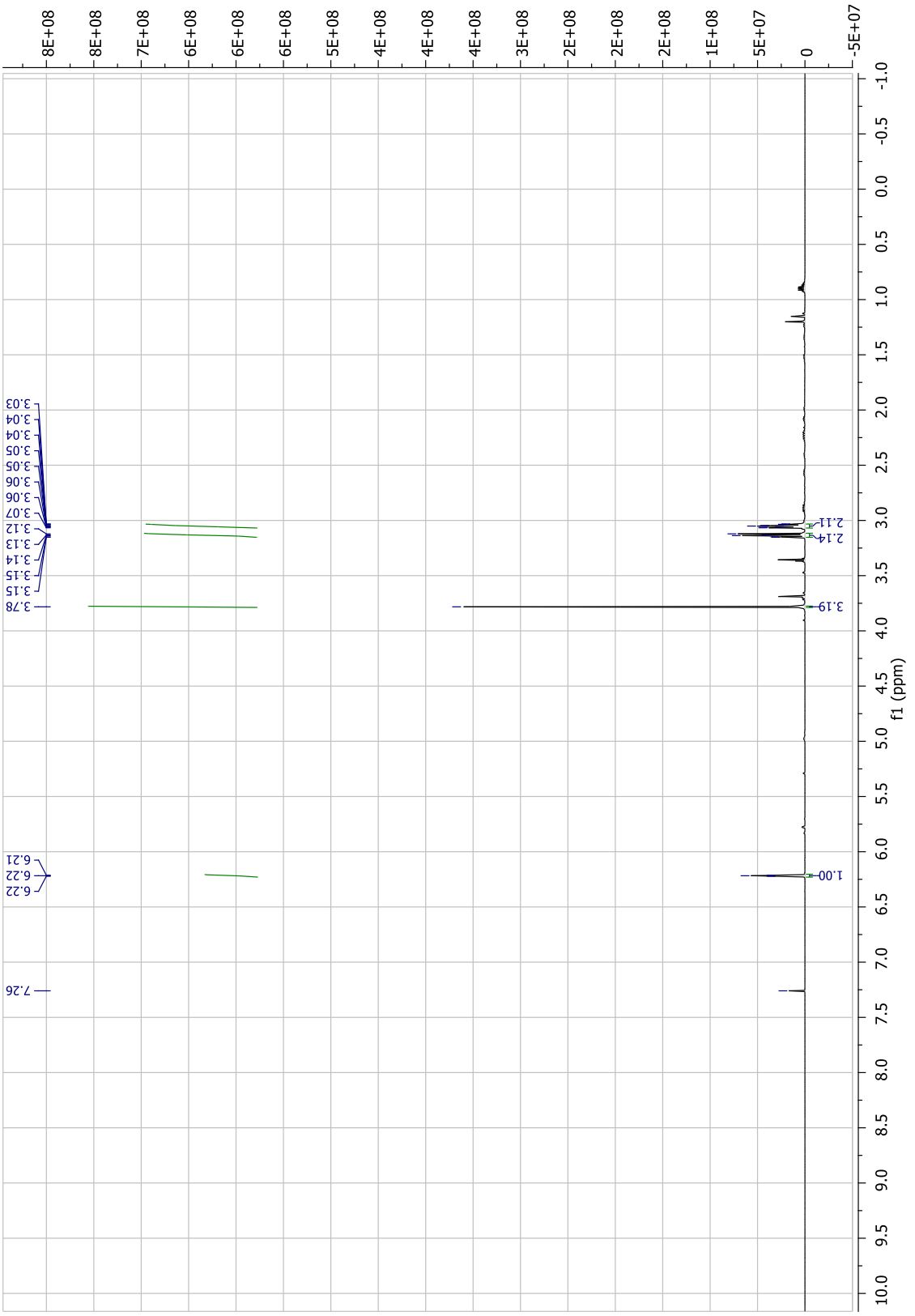
(*Z*)-1a


1.30
1.31
1.32
2.73
2.73
2.74
2.75
2.75
2.76
2.76
3.03
3.04
3.04
3.06
4.21
4.22
4.23
4.25
5.69
5.70
5.70
7.26
2.99
2.05
2.01
2.08
1.00
f1 (ppm)


14.17
22.33
44.60
61.26
76.95
77.16
77.37
118.78
160.41
163.22
194.04
f1 (ppm)


O
MeOOC

(*E*)-**1b**


f1 (ppm)
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3.15
3.15
3.14
3.13
3.12
3.07
3.06
3.06
3.05
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3.03
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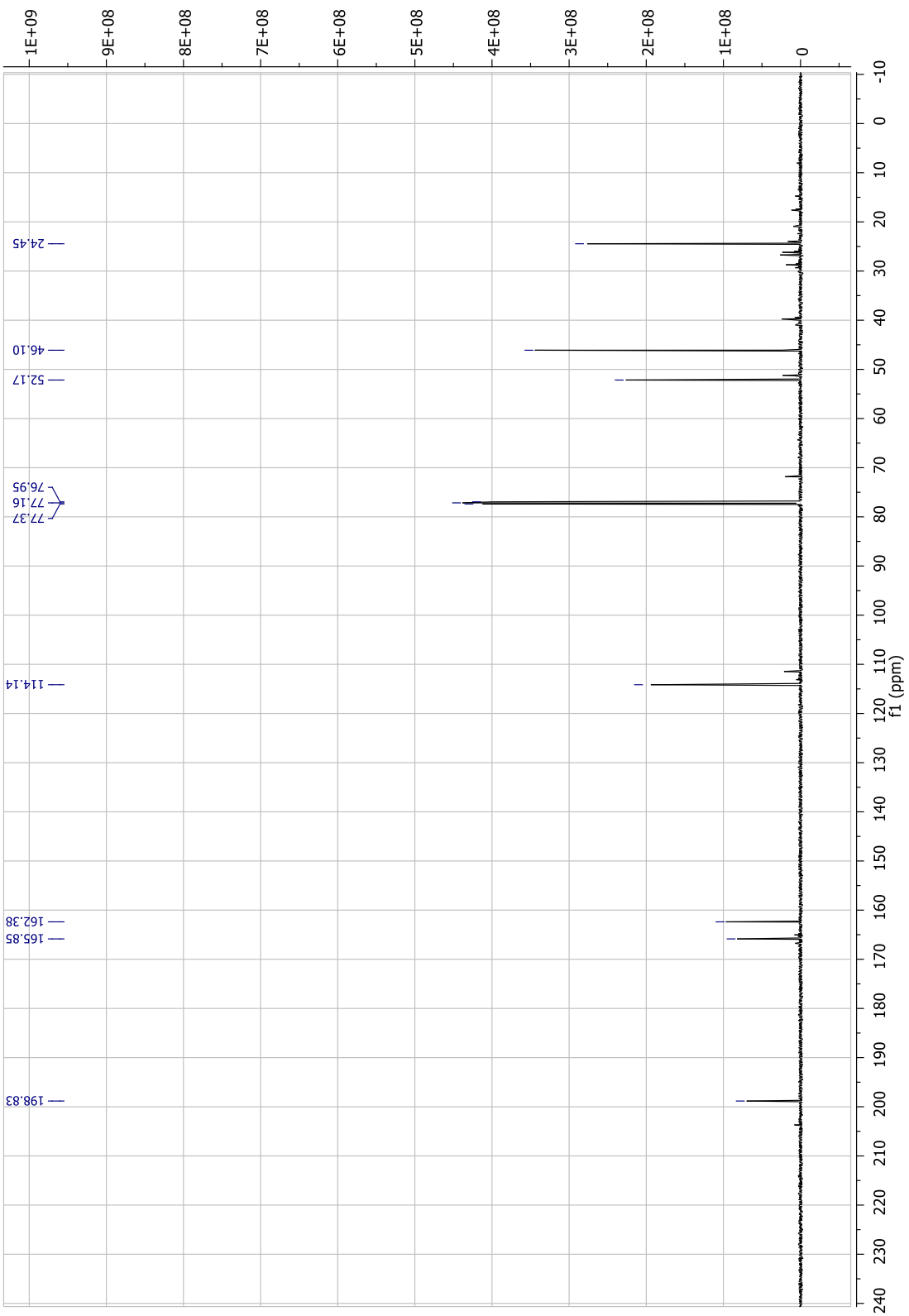
6.21
7.26
1.00
3.19
2.14
2.11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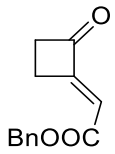
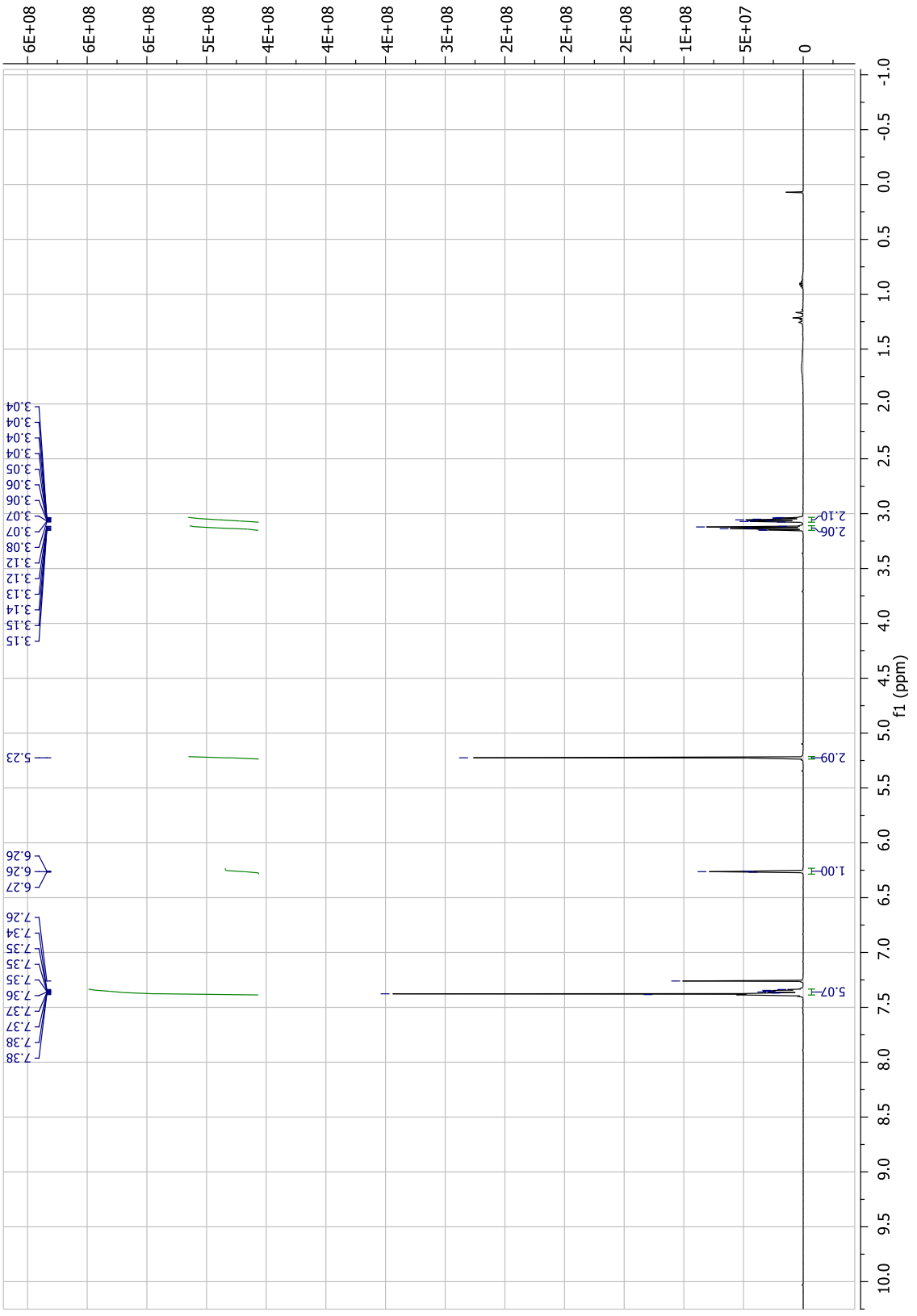
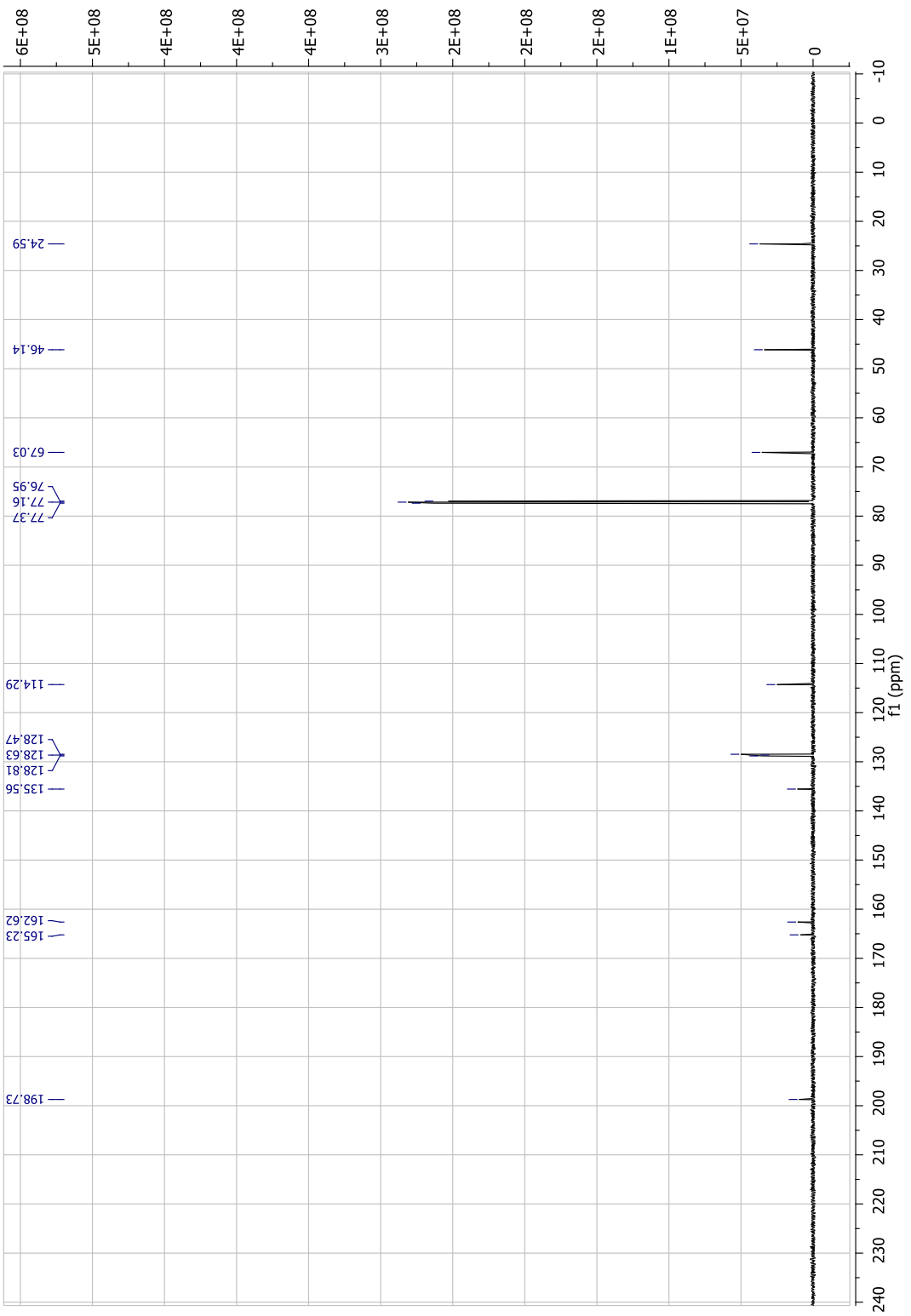
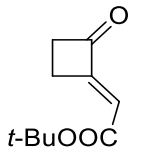
165.85
162.38
114.14
77.37
77.16
76.95
52.17
46.10
24.45
f1 (ppm)



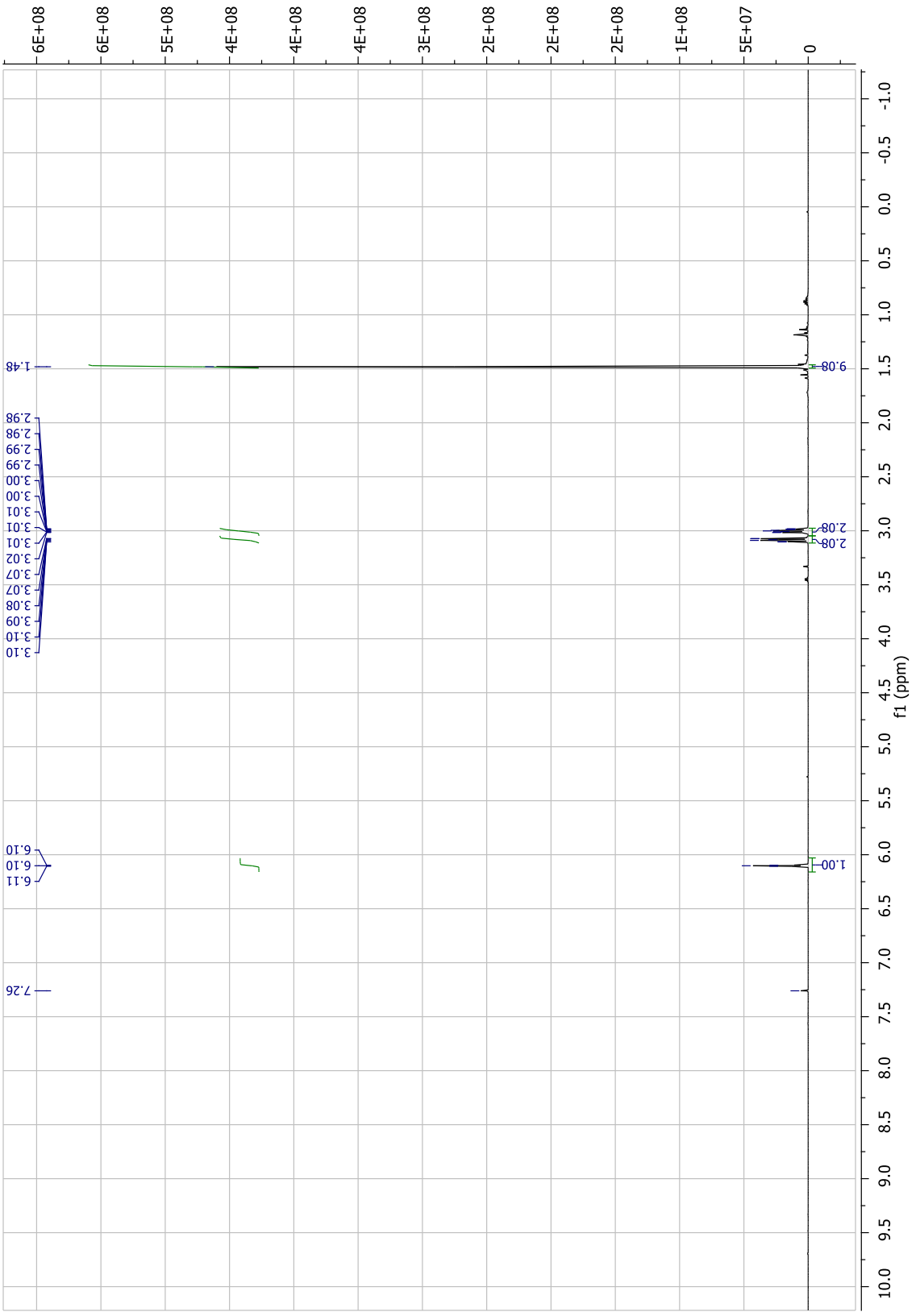
(*E*)-1c




198.73
165.23
162.62
135.56
128.81
128.63
128.47
114.29
77.37
77.16
76.95
67.03
46.14
24.59
f1 (ppm)


O
t-BuOOC

(*E*)-1d


6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
1.48
2.98
2.98
2.99
2.99
3.00
3.00
3.01
3.01
3.01
3.02
3.07
3.07
3.08
3.09
3.10
3.10
6.10
6.10
6.11
7.26
9.08
2.08
2.08
1.00
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
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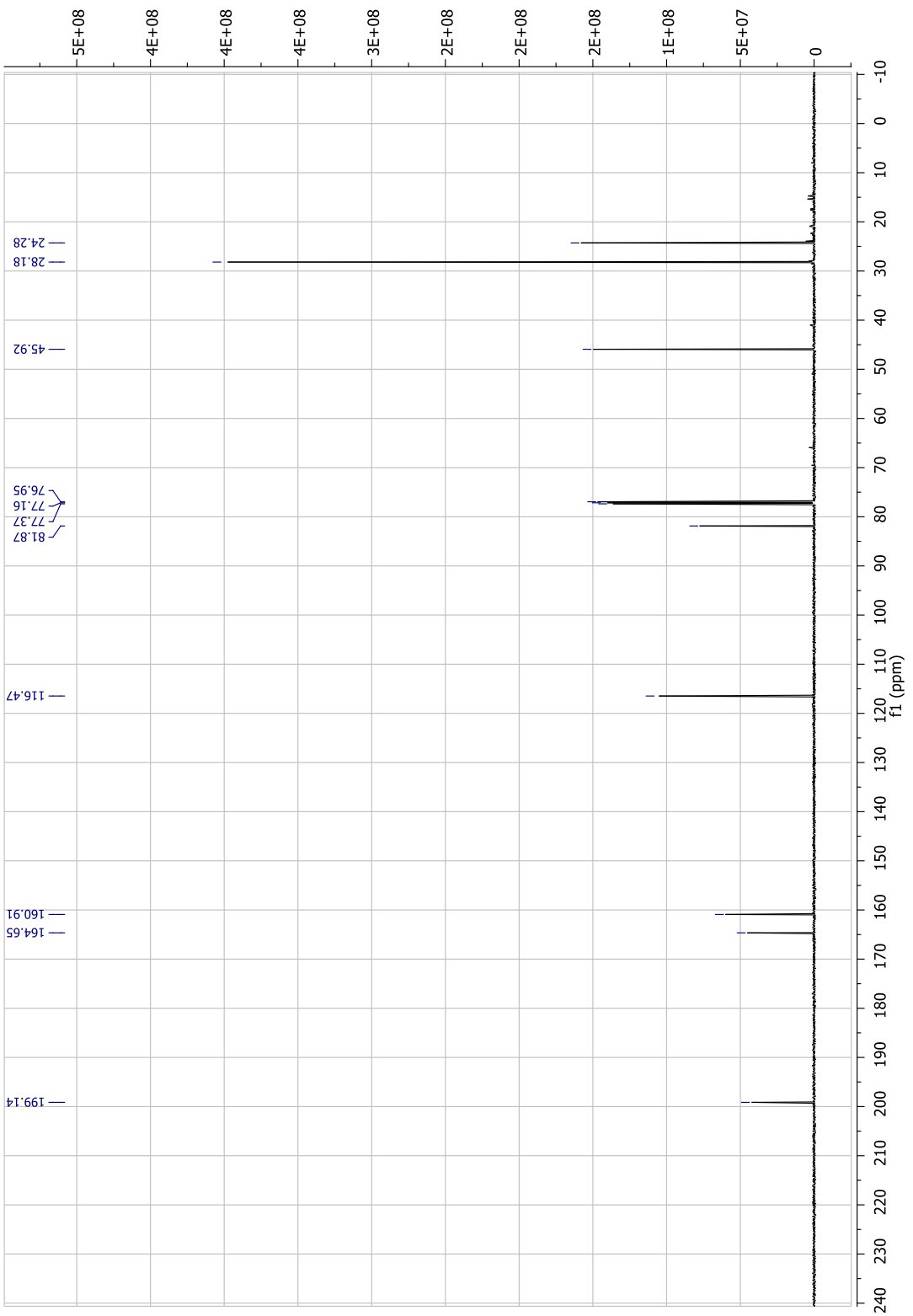
8.5
9.0
9.5
10.0
f1 (ppm)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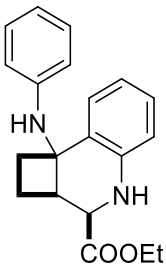
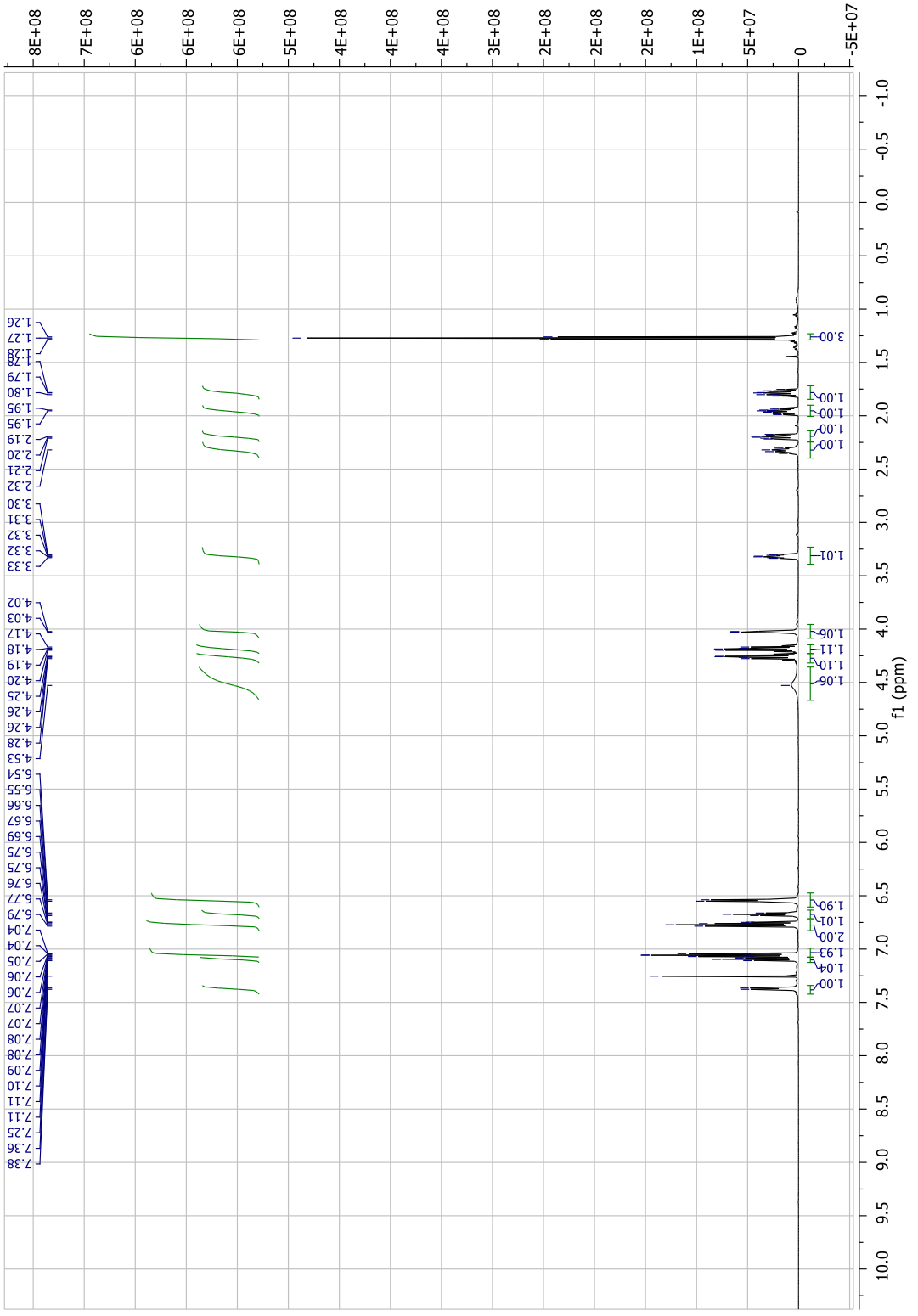
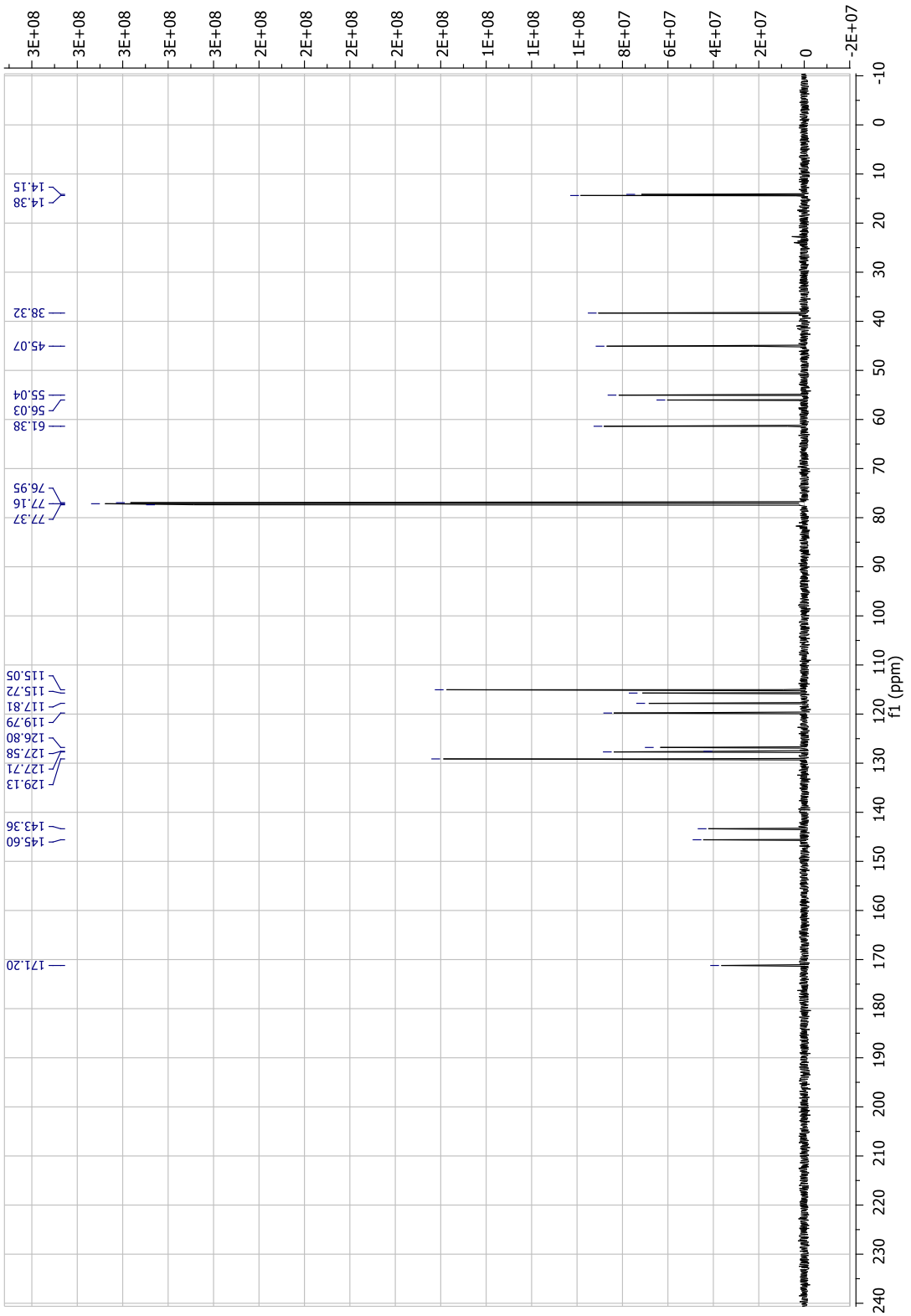
77.16
76.95
45.92
28.18
24.28
f1 (ppm)



3a




14.15
14.38
38.32
45.07
55.04
56.03
61.38
76.95
77.16
77.37
115.05
115.72
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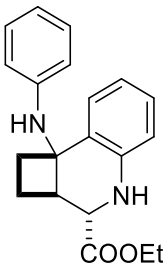
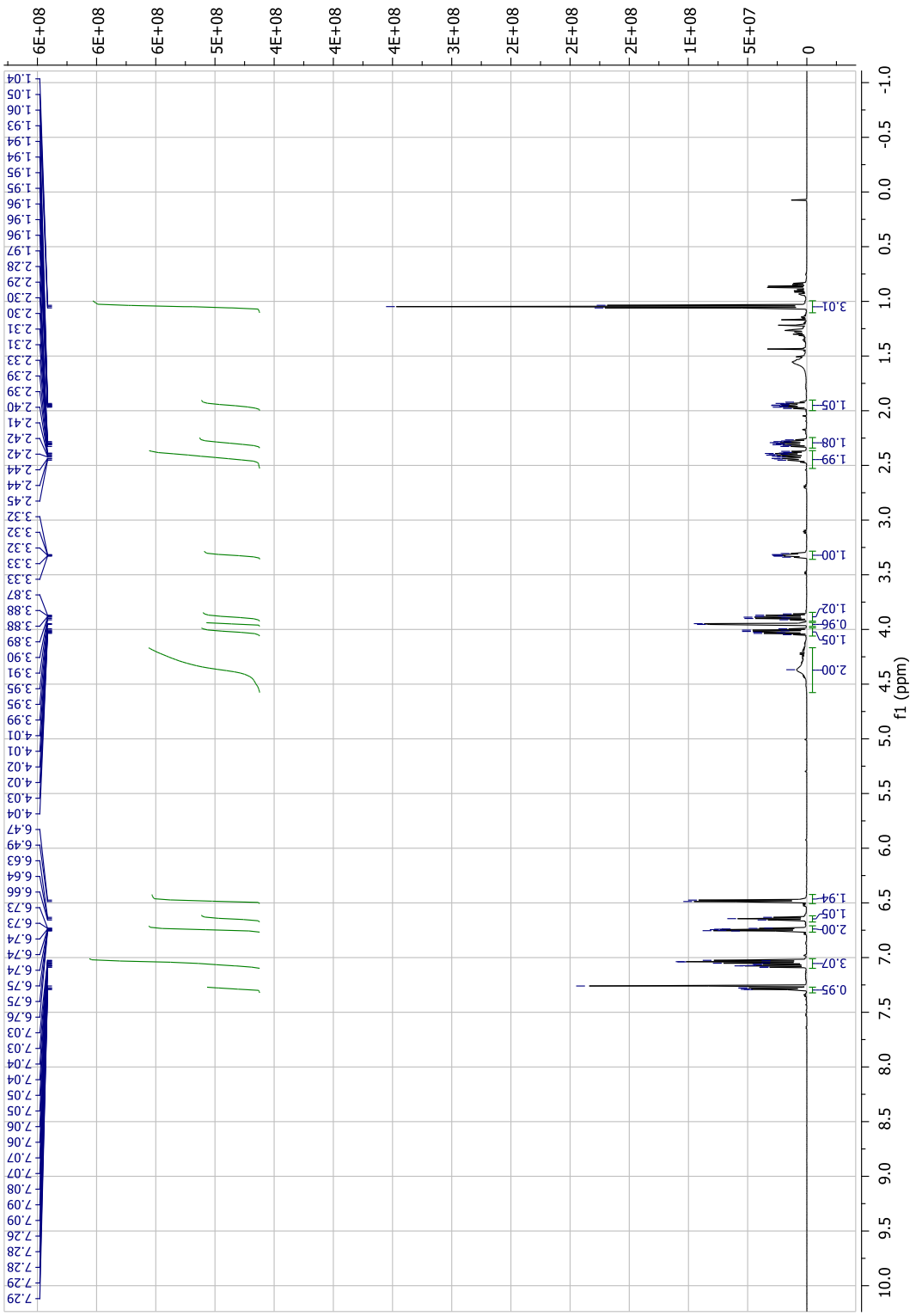
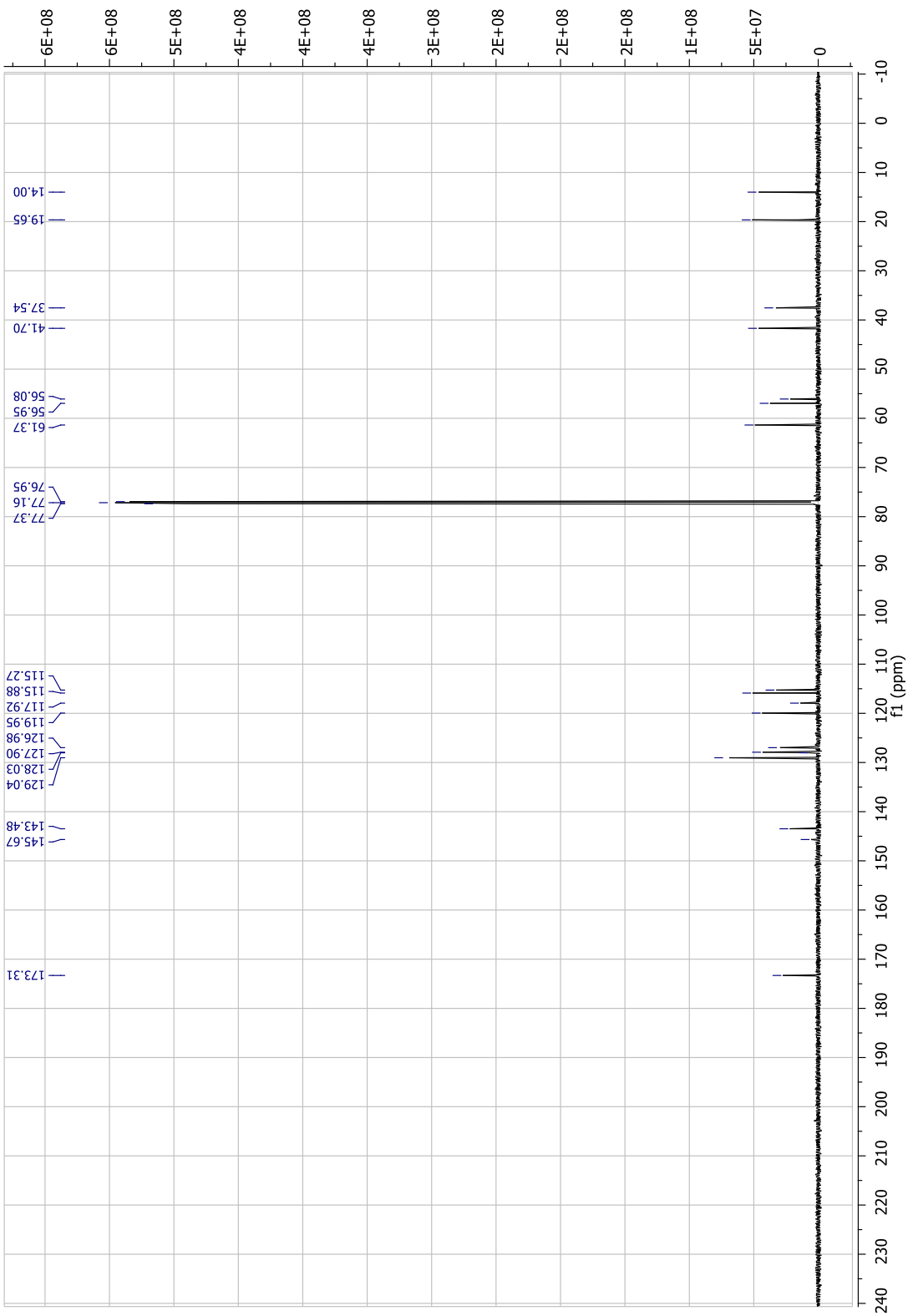
129.13
143.36
145.60
171.20
f1 (ppm)



3a'




14.00
19.65
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41.70
56.08
56.95
61.37
76.95
77.16
77.37
115.27
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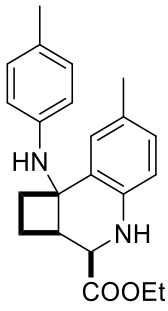
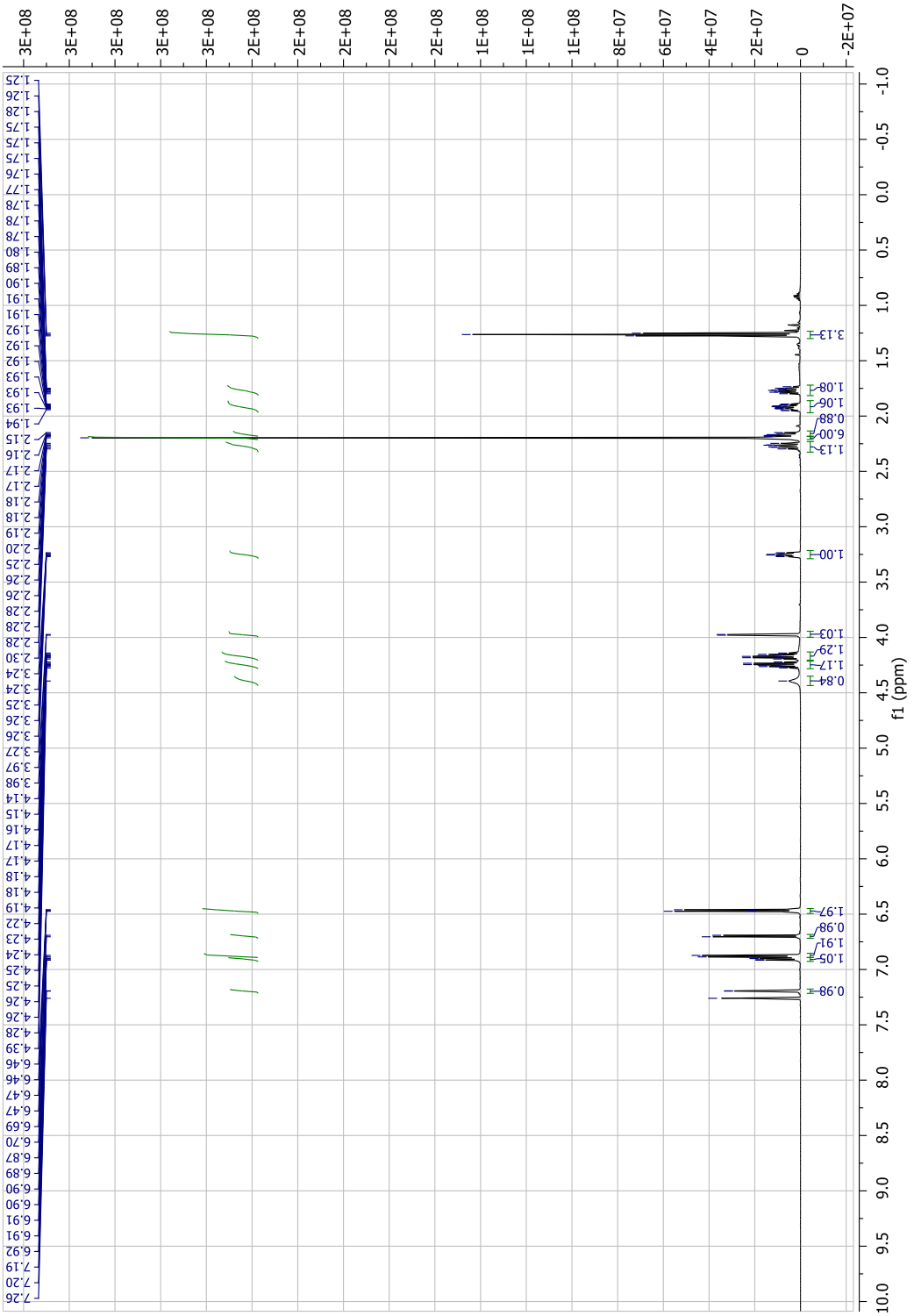
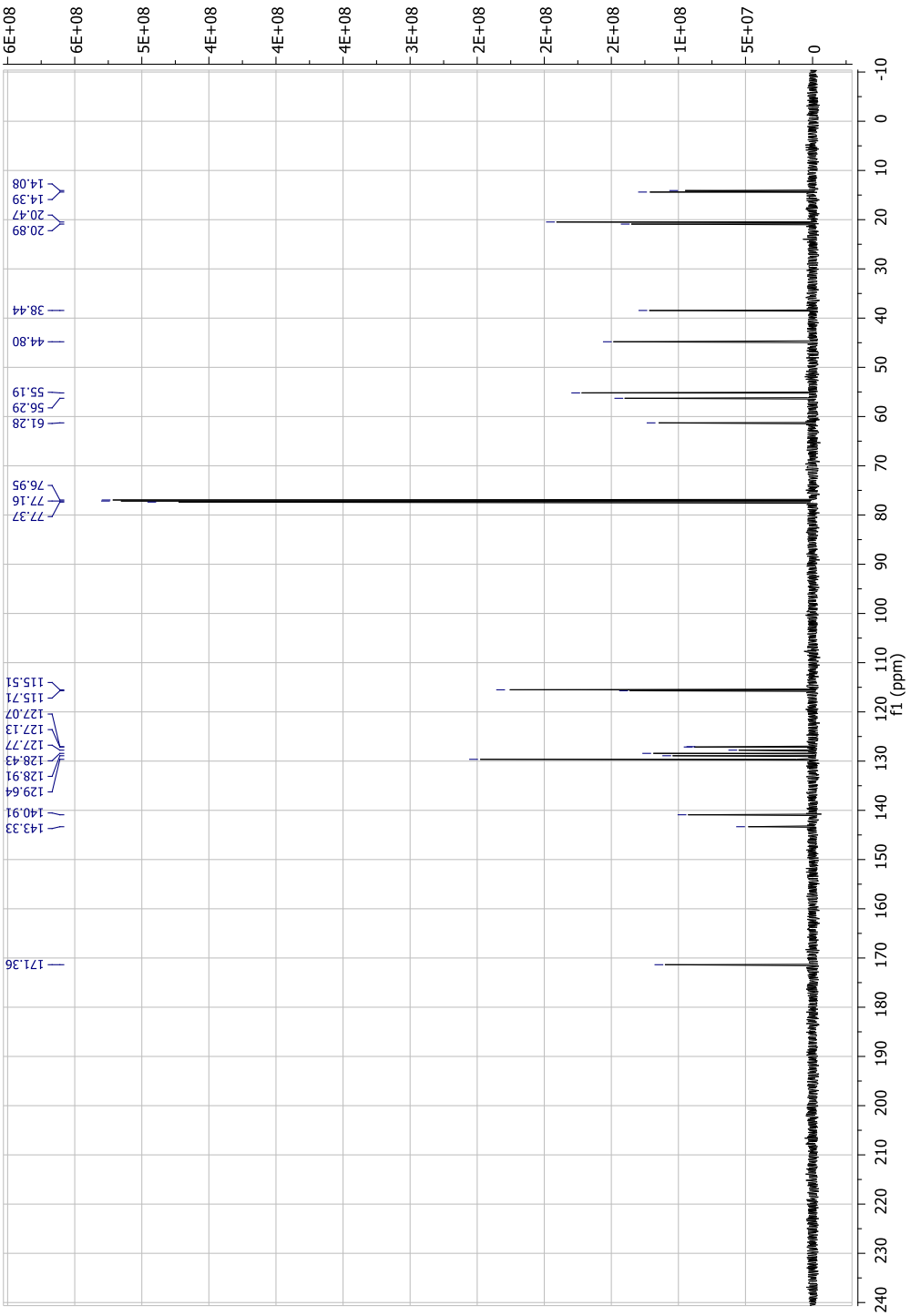
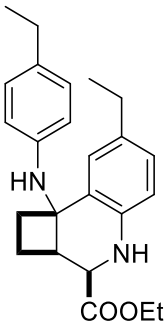
129.04
143.48
145.67
173.31
f1 (ppm)



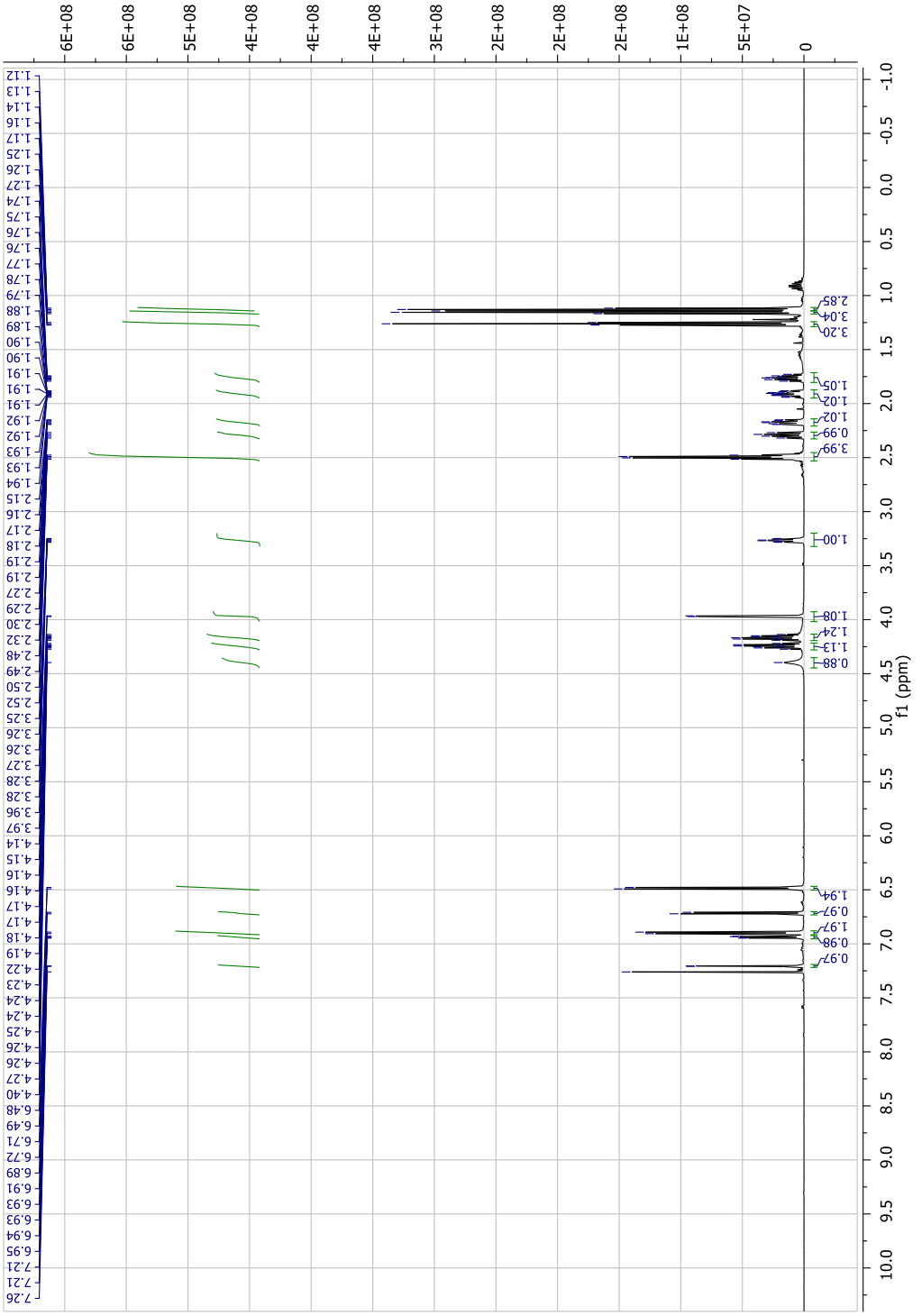
3b

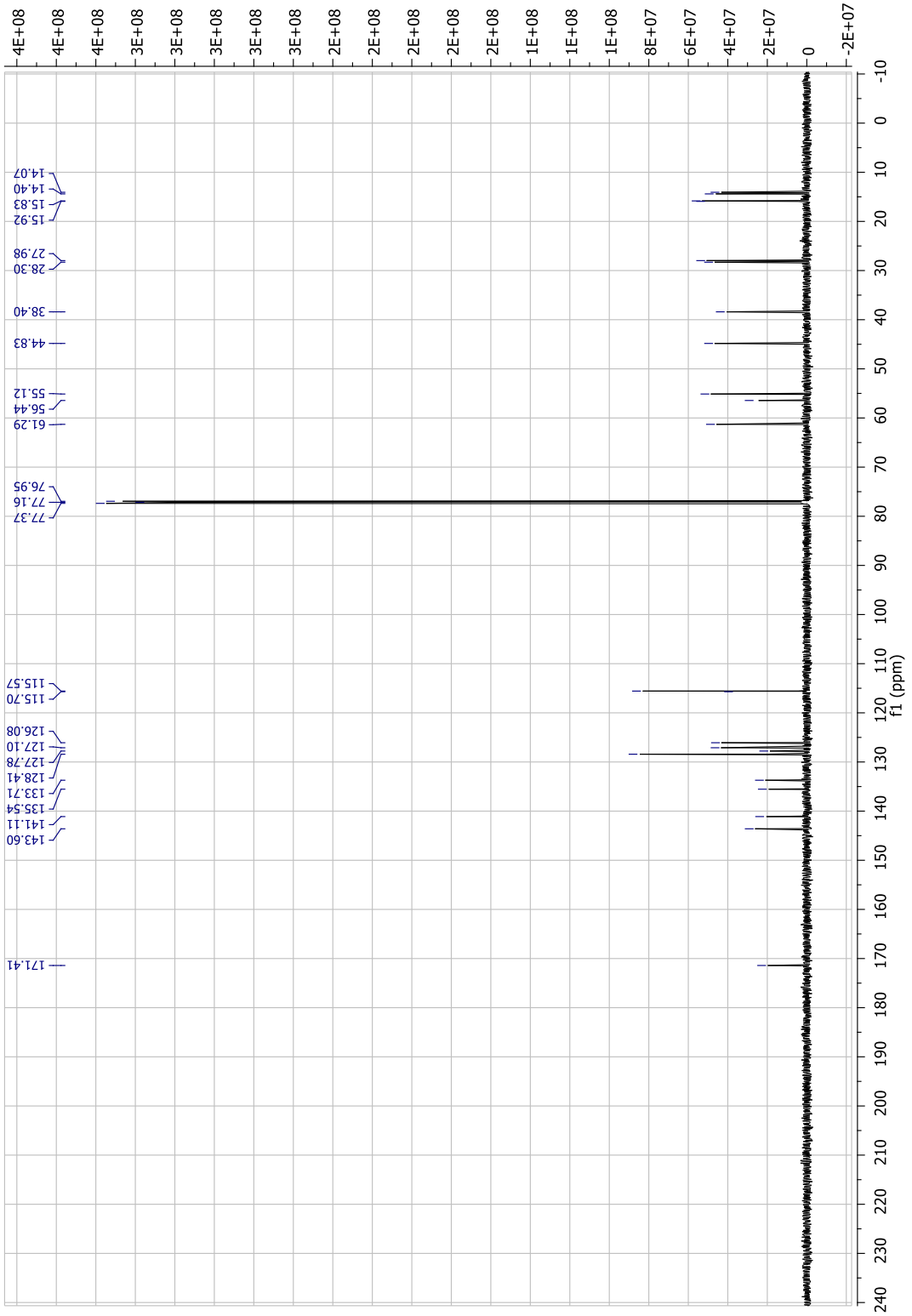



14.08
14.39
20.47
20.89
38.44
44.80
55.19
56.29
61.28
76.95
77.16
77.37
115.51
115.71
127.07
127.13
127.77
128.43
128.91
129.64
140.91
143.33
171.36
f1 (ppm)



3c

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14.40
15.83
15.92
27.98
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38.40
44.83
55.12
56.44
61.29
76.95
77.16
77.37
115.57
115.70
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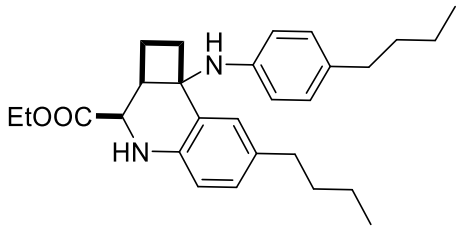
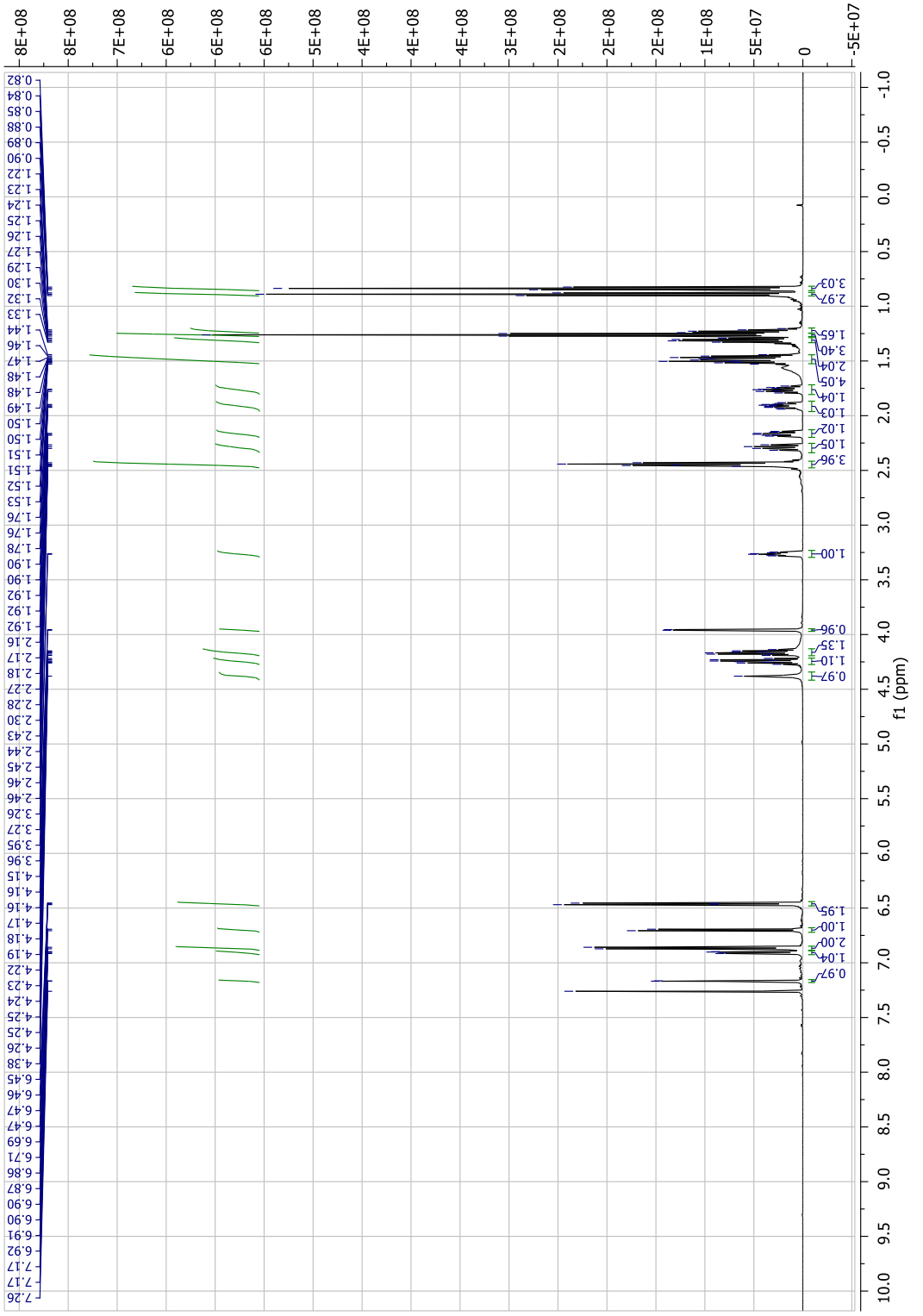
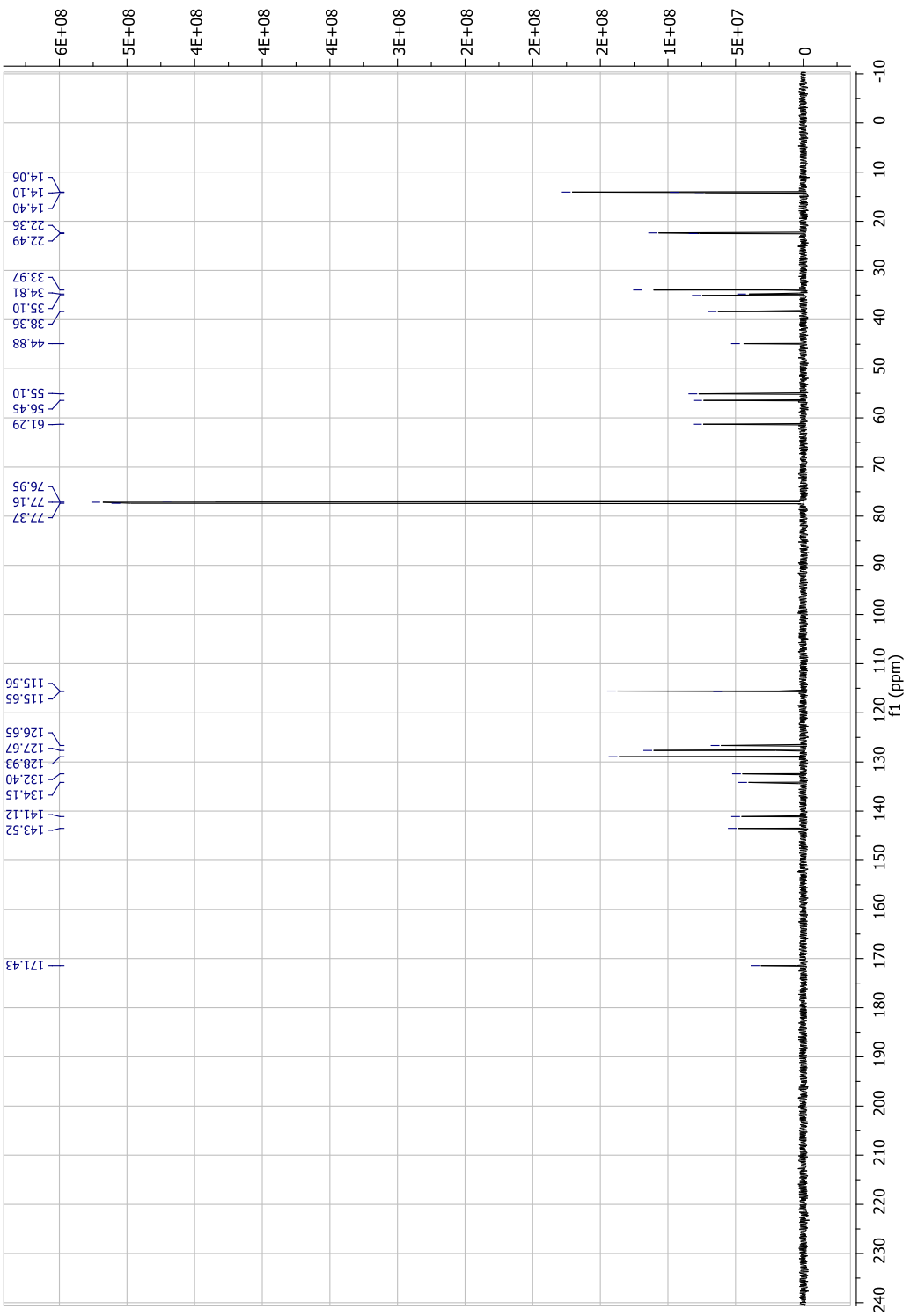
127.10
127.78
128.41
133.71
135.54
141.11
143.60
171.41
f1 (ppm)



3d

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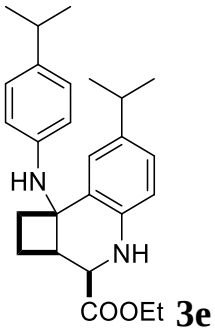
14.10
14.40
22.36
22.49
33.97
34.81
35.10
38.36
44.88
55.10
56.45
61.29
76.95
77.16
77.37
115.56
115.65
126.65
127.67
128.93
132.40
134.15
141.12
143.52
171.43
f1 (ppm)



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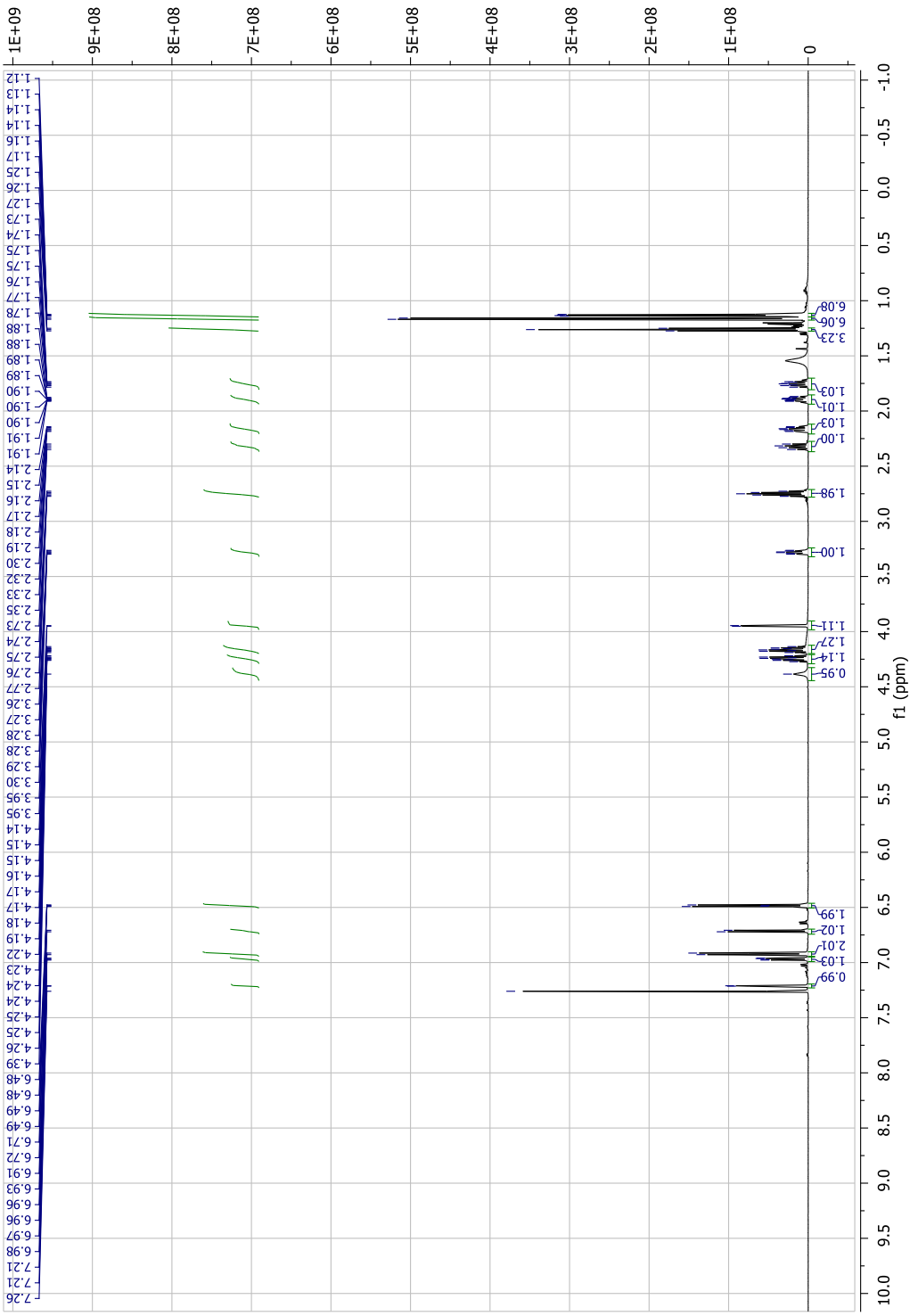

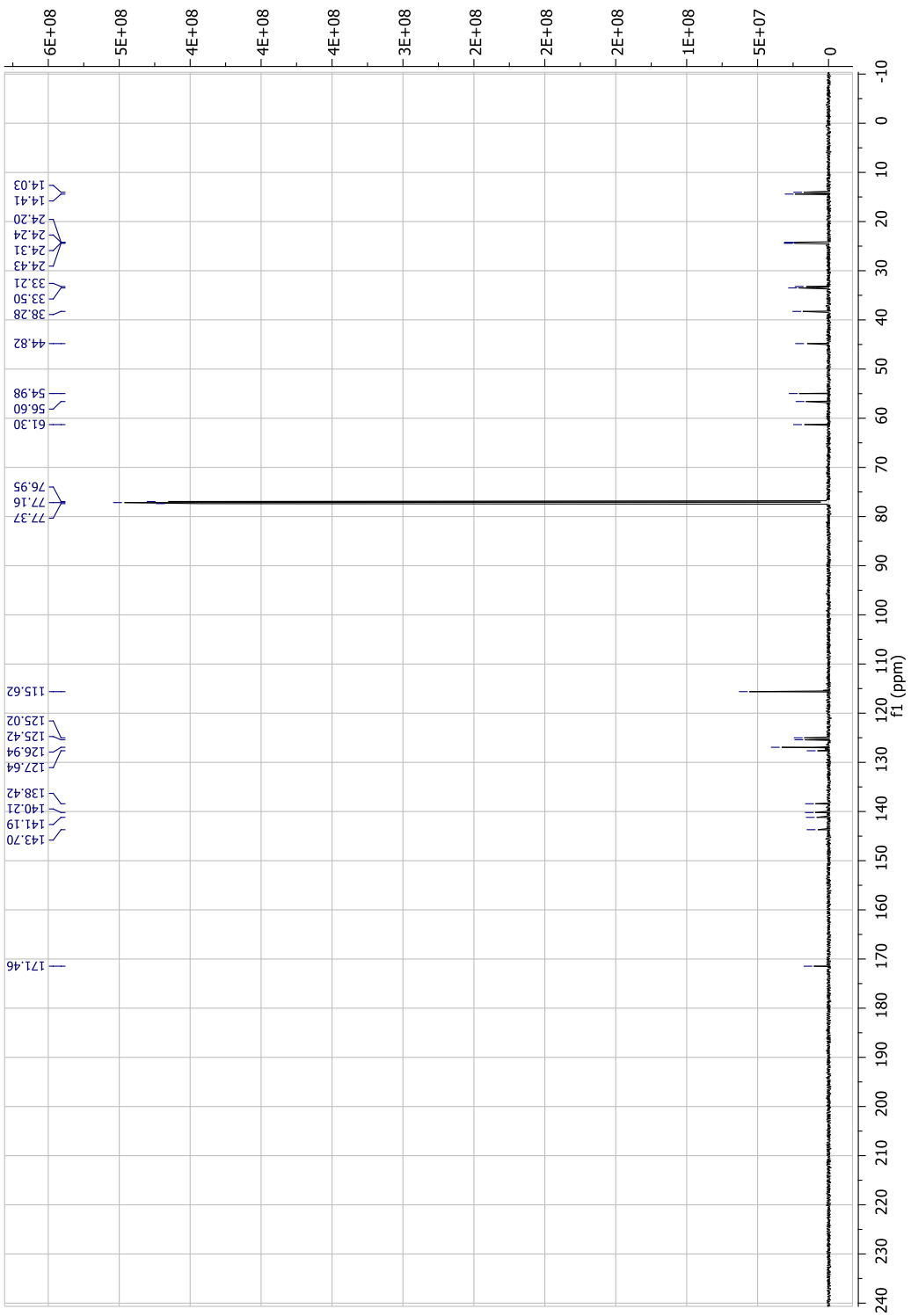
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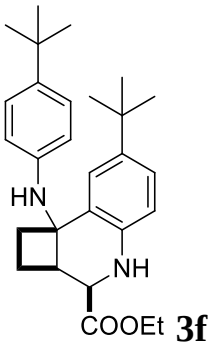
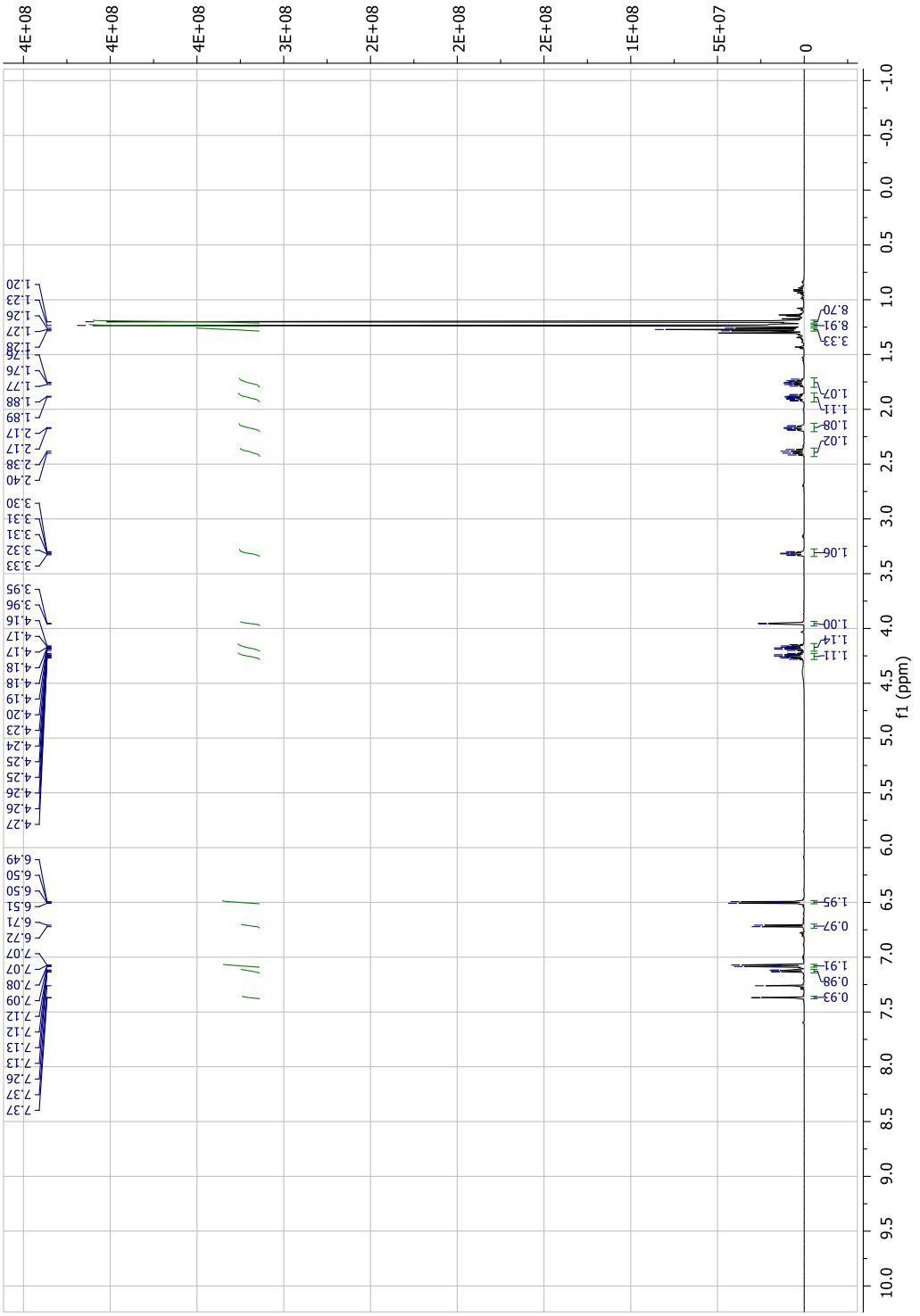
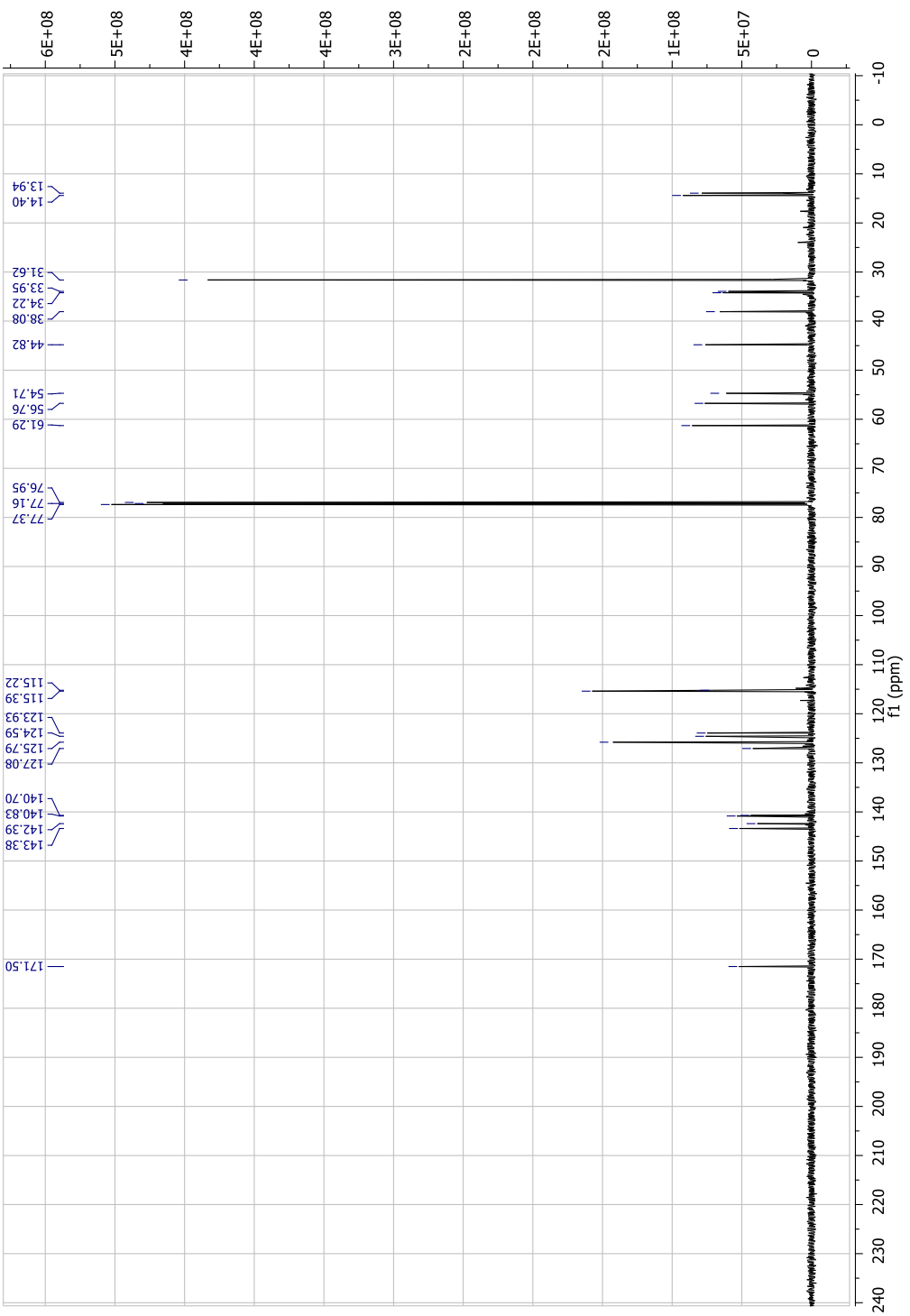
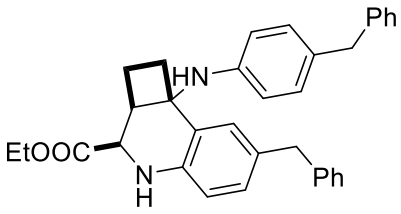
14.41
24.20
24.24
24.31
24.43
33.21
33.50
38.28
44.82
54.98
56.60
61.30
76.95
77.16
77.37
115.62
125.02
125.42
126.94
127.64
138.42
140.21
141.19
143.70
171.46
f1 (ppm)



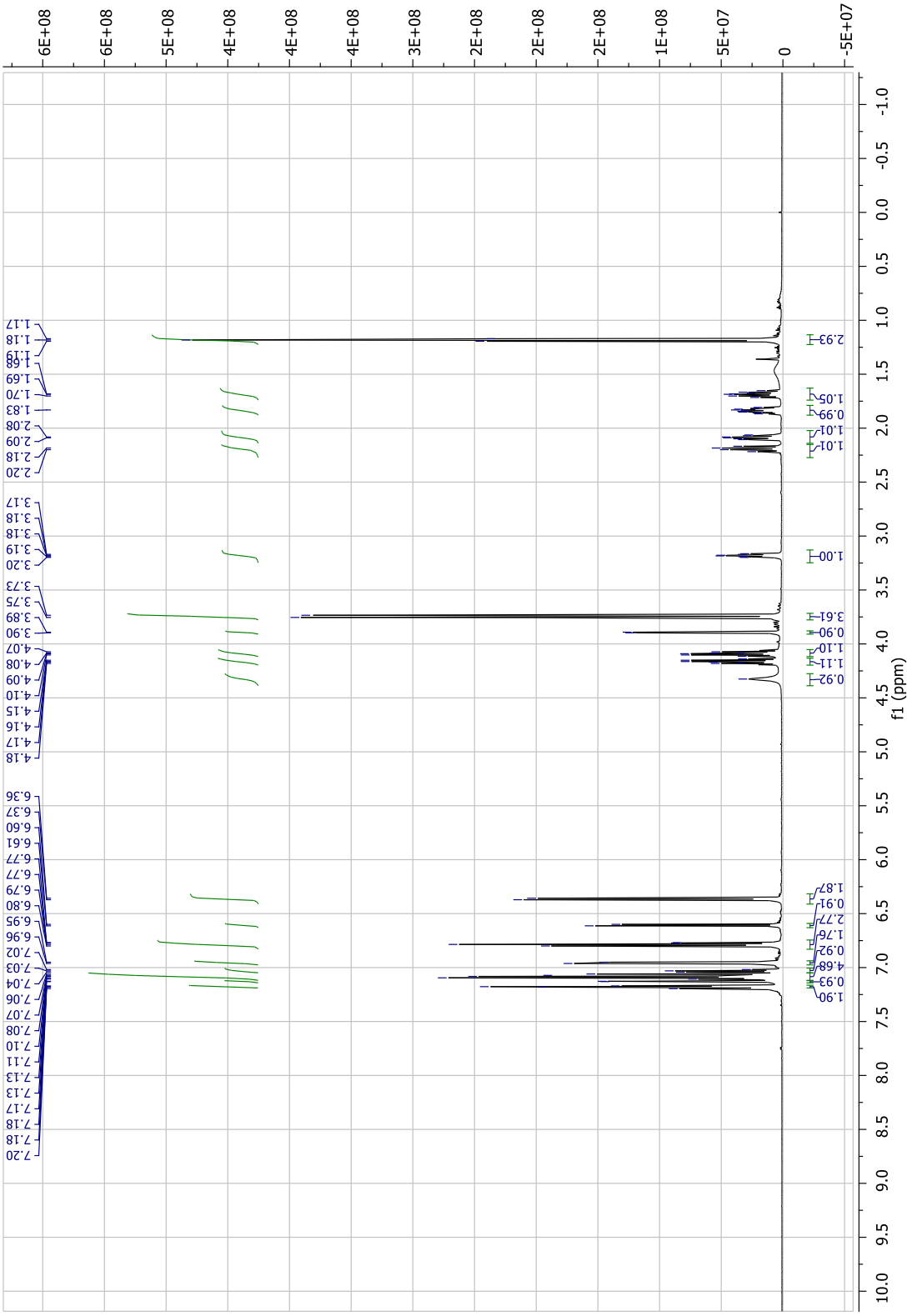
3f

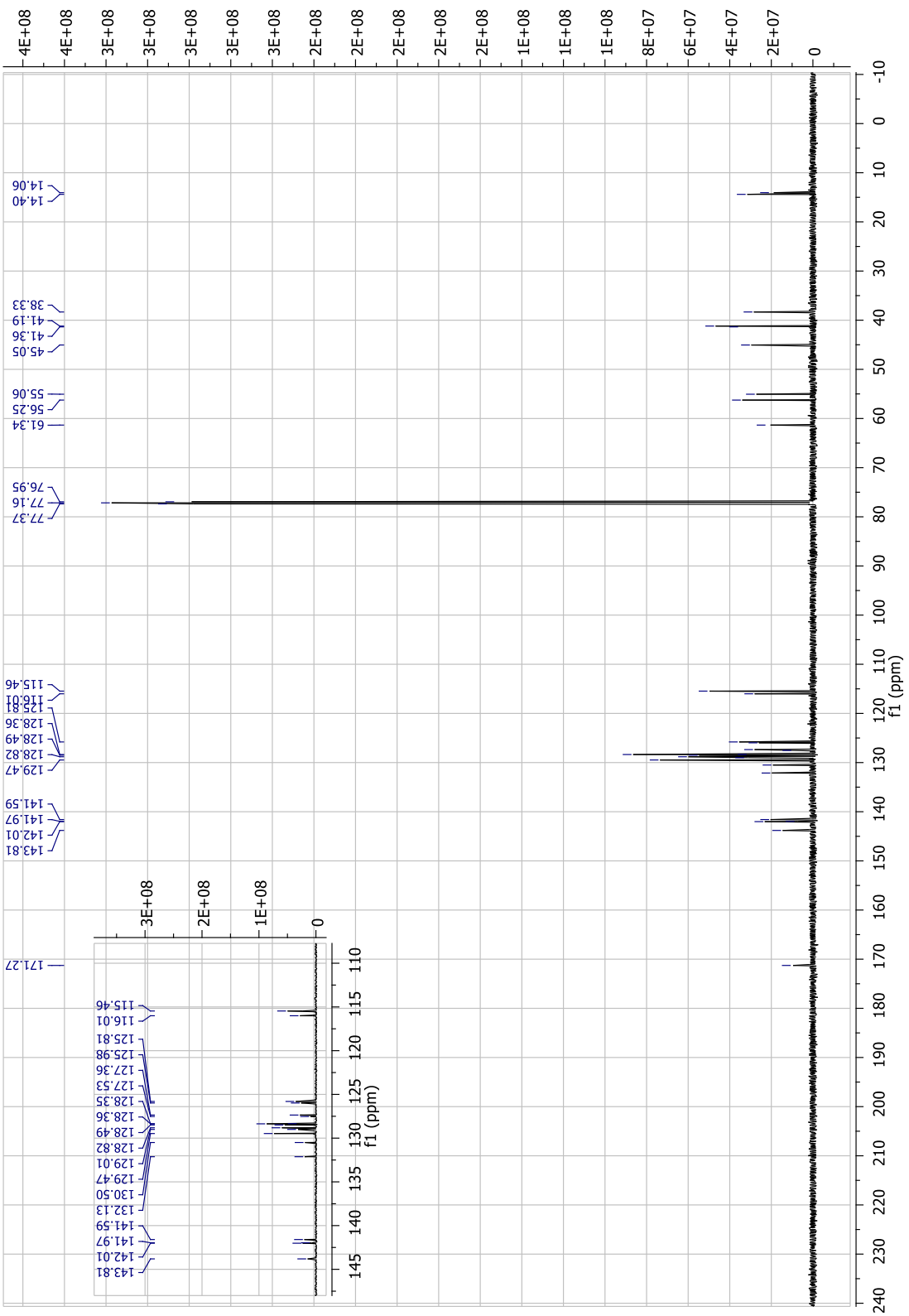


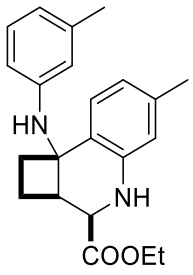

13.94
14.40
31.62
33.95
34.22
38.08
44.82
54.71
56.76
61.29
76.95
77.16
77.37
115.22
115.39
123.93
124.59
125.79
127.08
140.70
140.83
142.39
143.38
171.50
f1 (ppm)



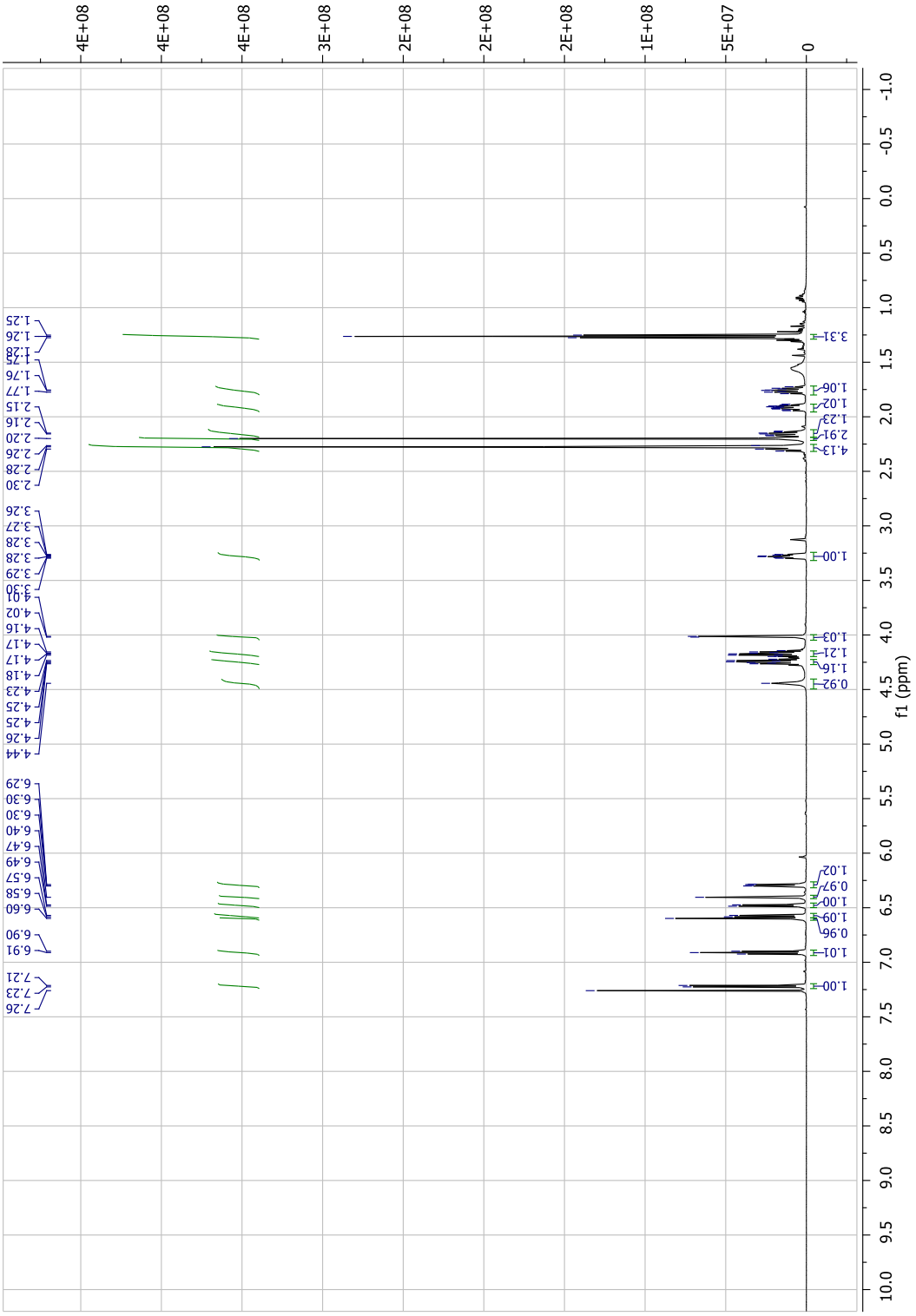
3g

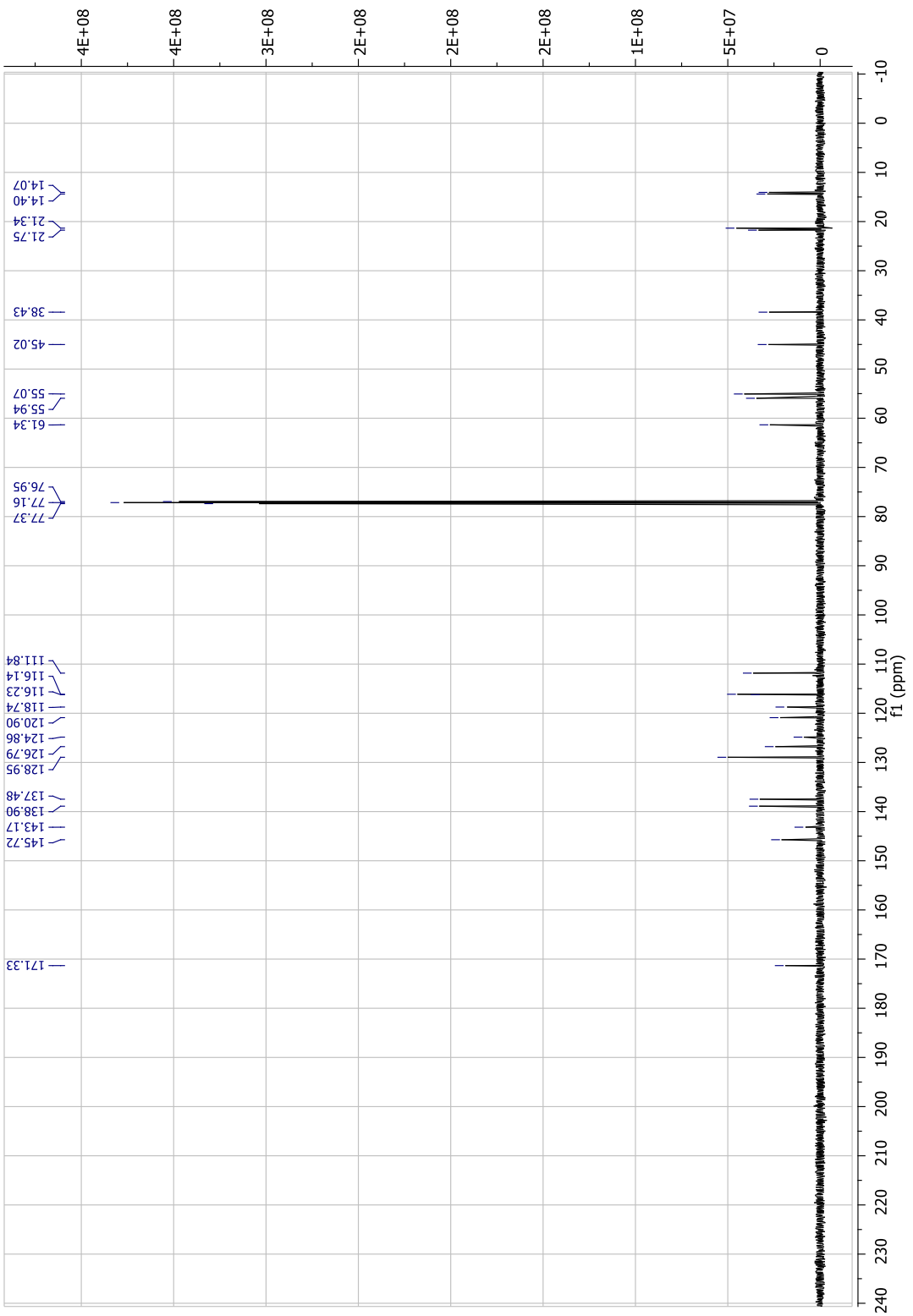



14.06
14.40
38.33
41.19
41.36
45.05
55.06
56.25
61.34
76.95
77.16
77.37
115.46
116.01
125.81
128.36
128.49
128.82
129.47
141.59
141.97
142.01
143.81
171.27
f1 (ppm)



3h




14.07
14.40
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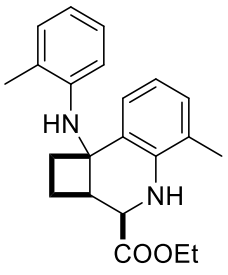
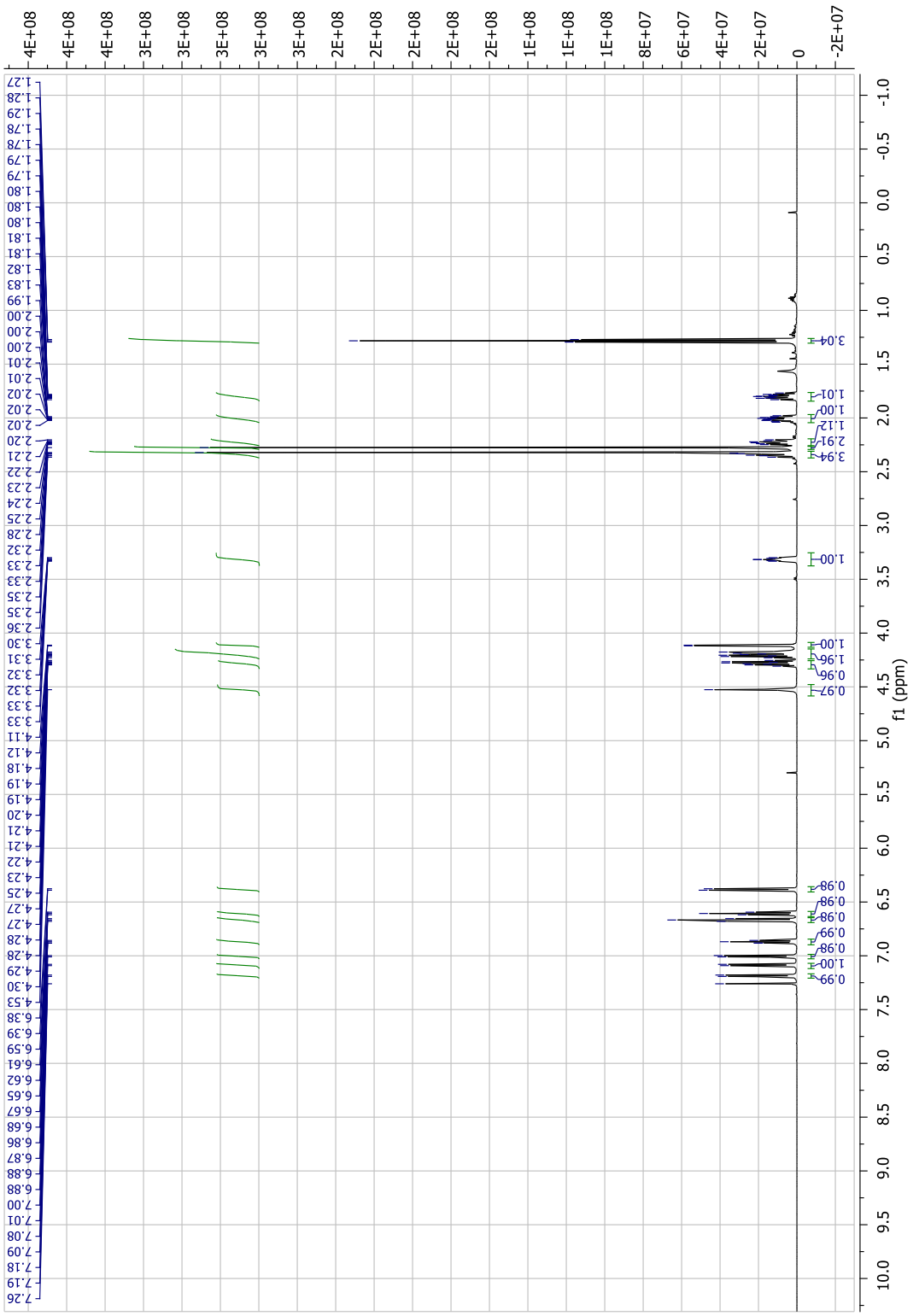
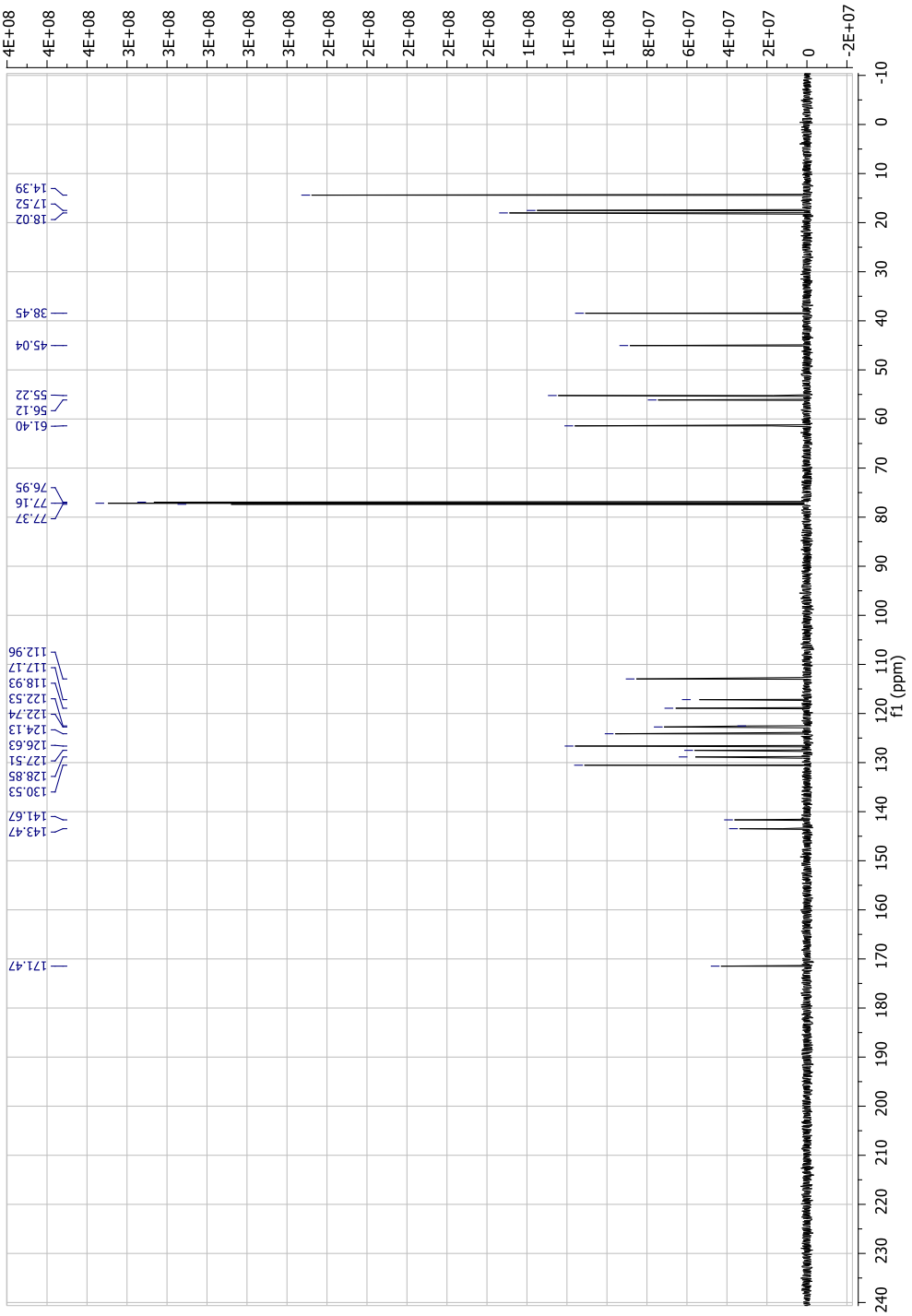
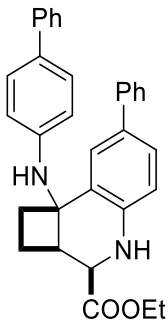
21.75
38.43
45.02
55.07
55.94
61.34
76.95
77.16
77.37
111.84
116.14
116.23
118.74
120.90
124.86
126.79
128.95
137.48
138.90
143.17
145.72
171.33
f1 (ppm)



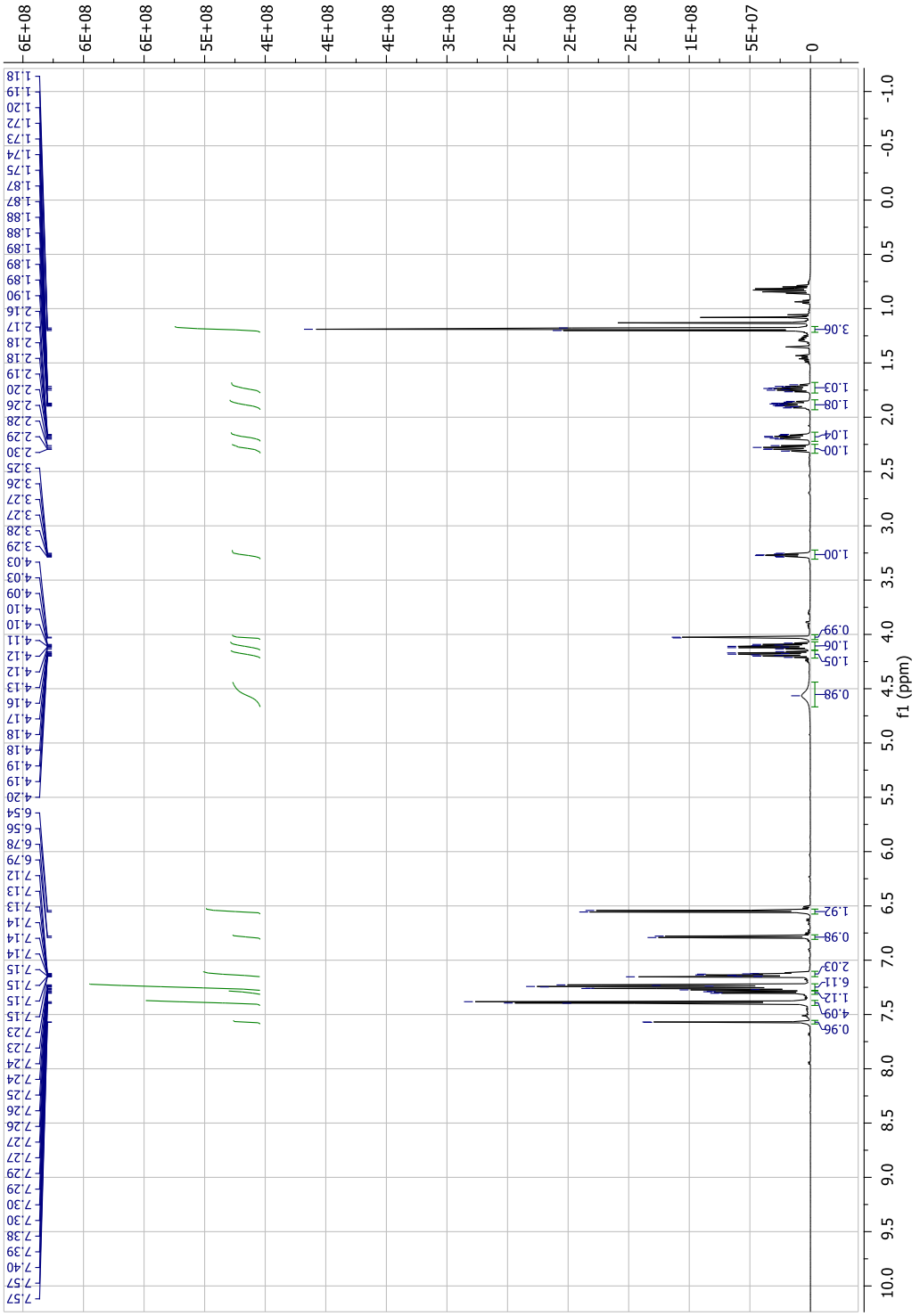
3i

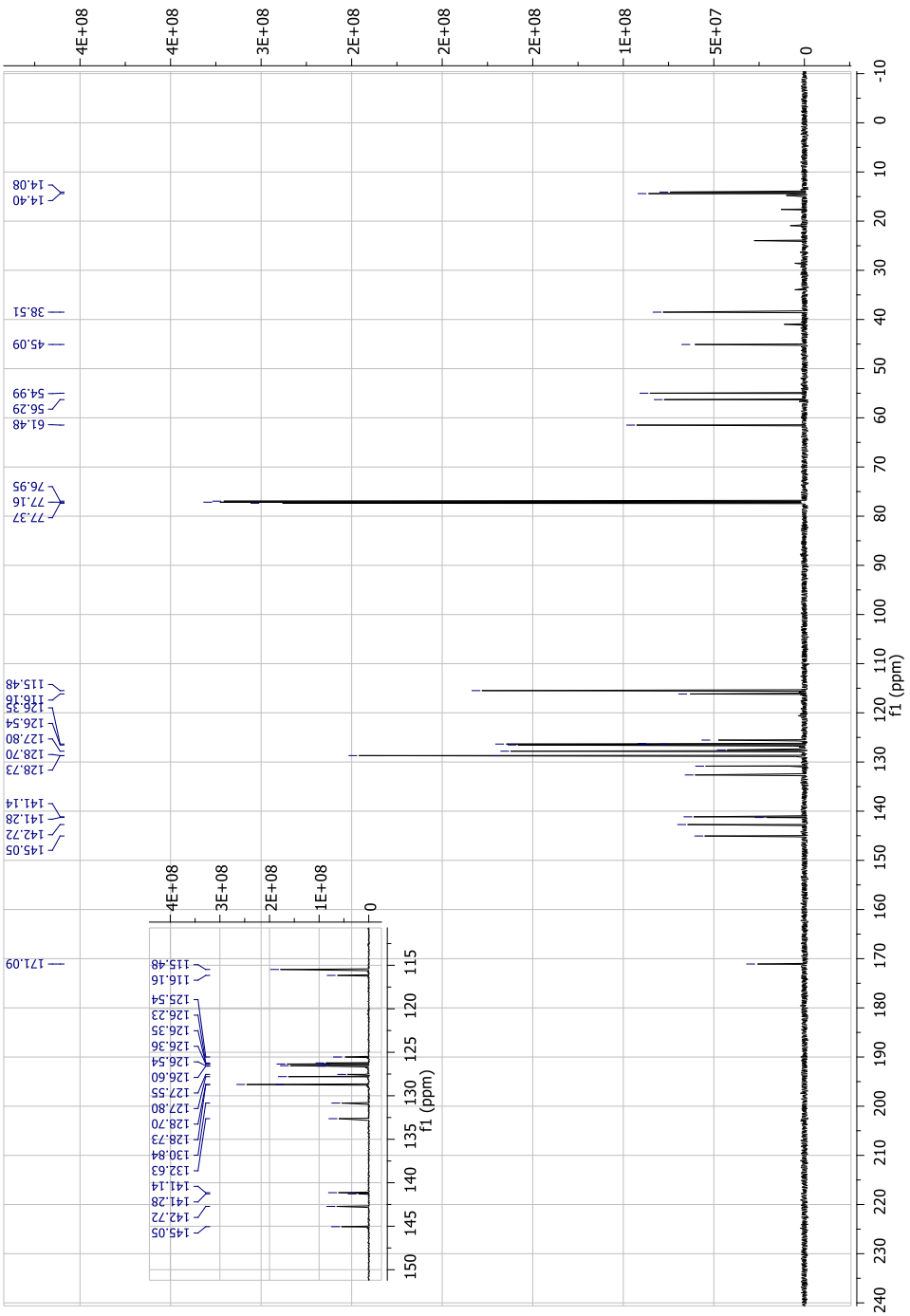


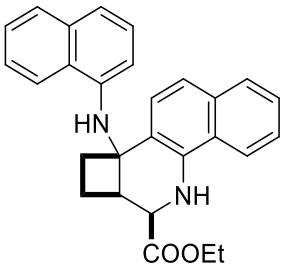

14.39
17.52
18.02
38.45
45.04
55.22
56.12
61.40
76.95
77.16
77.37
112.96
117.17
118.93
122.53
122.74
124.13
126.63
127.51
128.85
130.53
141.67
143.47
171.47
f1 (ppm)



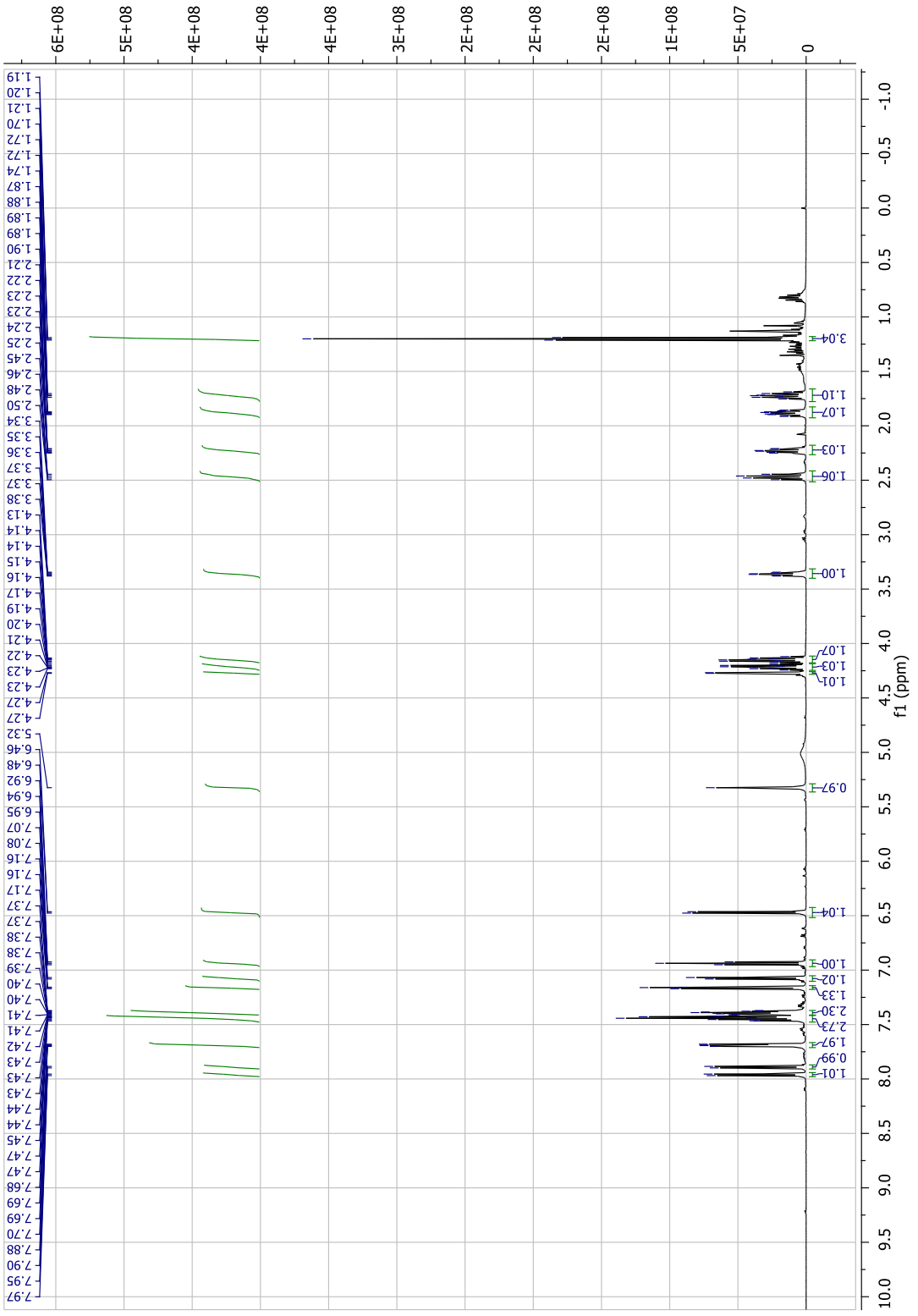
3j

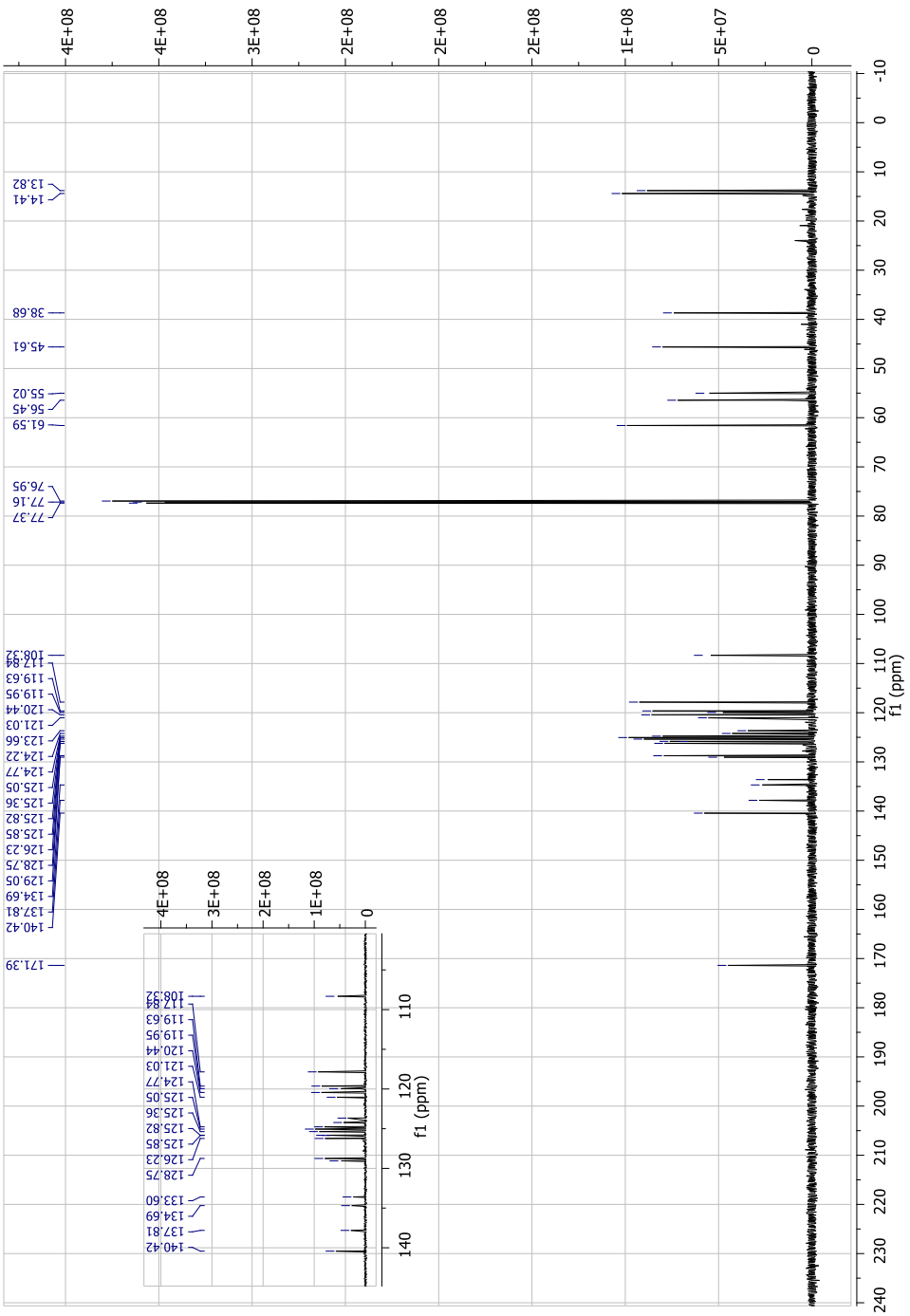


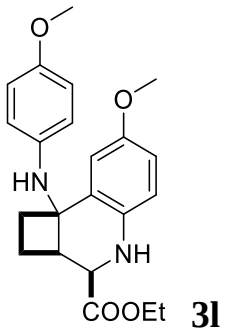

f1 (ppm)
14.08
14.40
38.51
45.09
54.99
56.29
61.48
76.95
77.16
77.37
115.48
116.16
126.35
126.54
127.80
128.70
128.73
141.14
141.28
142.72
145.05
171.09



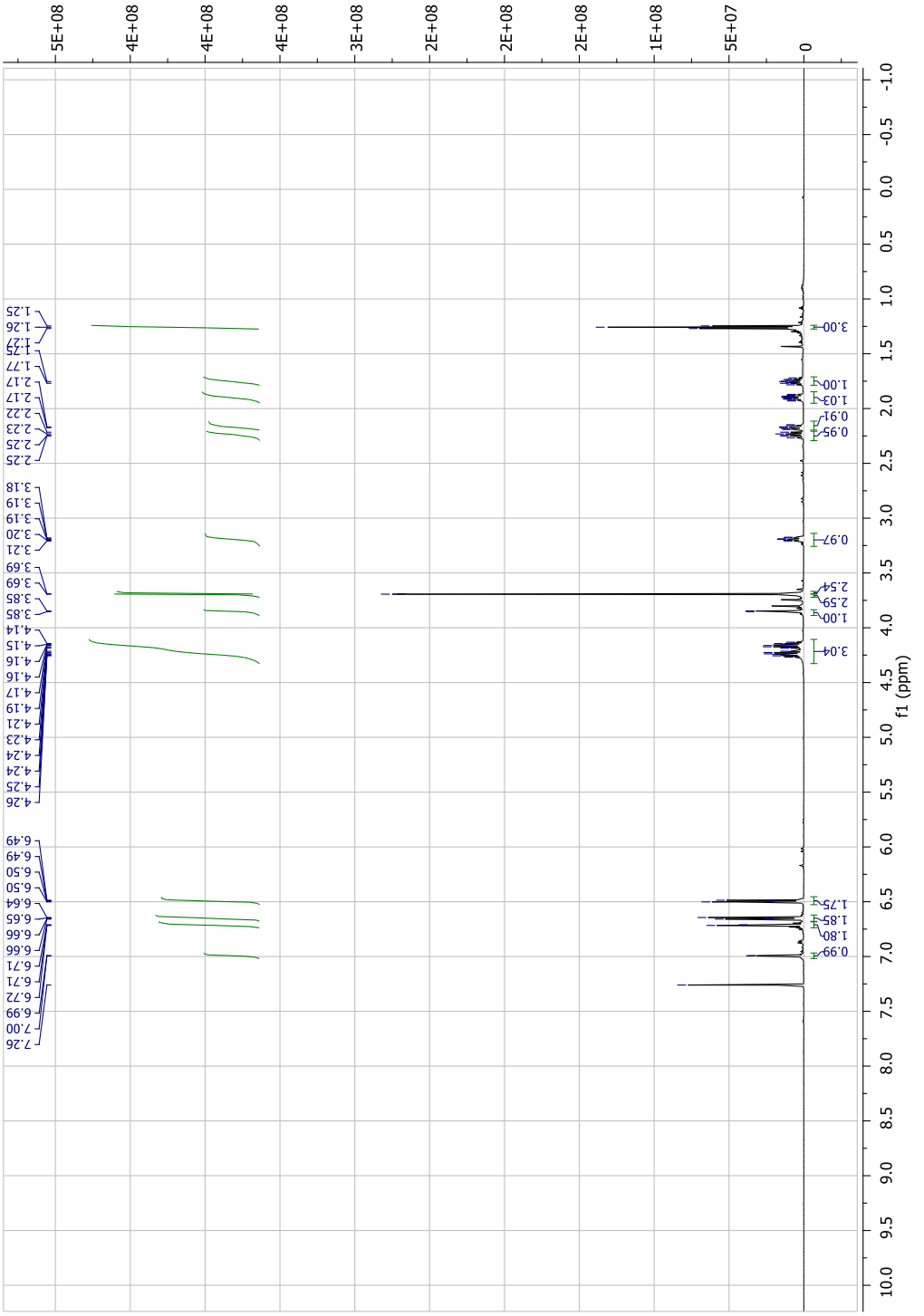
3k

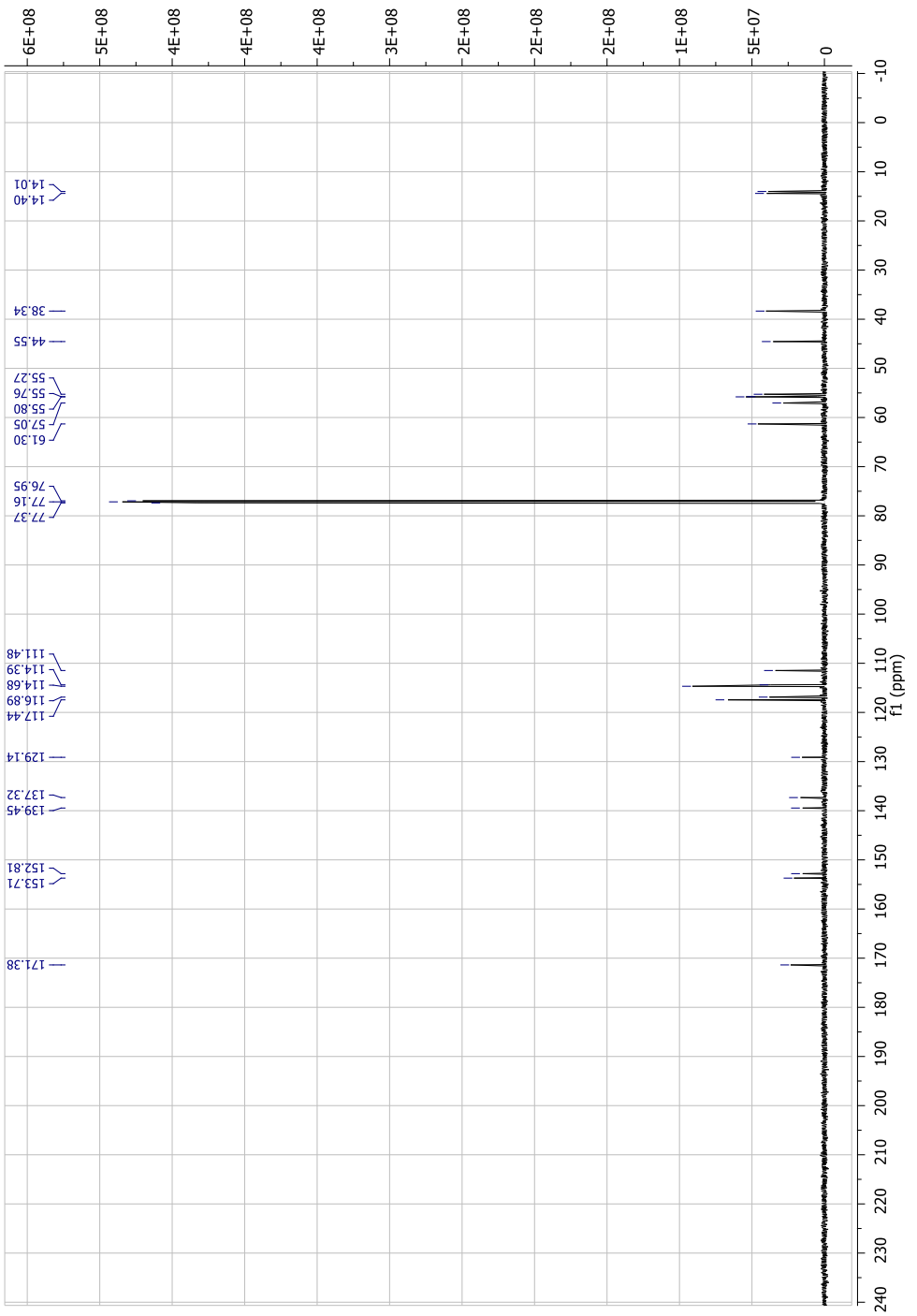



f1 (ppm)
13.82
14.41
38.68
45.61
55.02
56.45
61.59
76.95
77.16
77.37
106.32
117.84
119.63
119.95
120.44
121.03
123.66
124.22
124.77
125.05
125.36
125.82
125.85
126.23
128.75
129.05
134.69
137.81
140.42
171.39



3l

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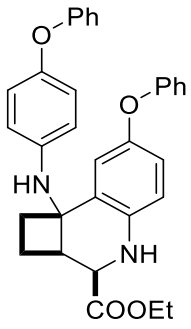
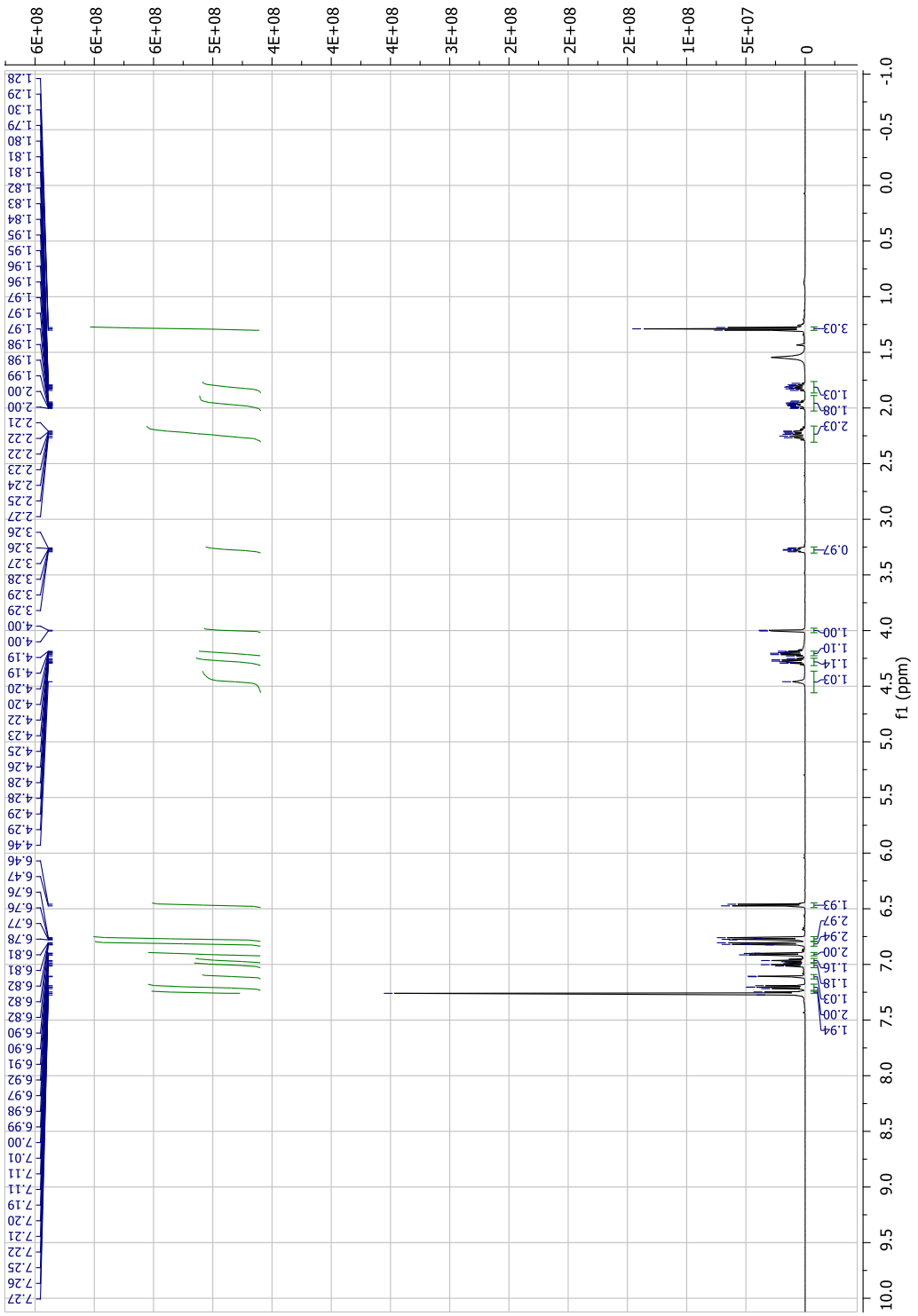
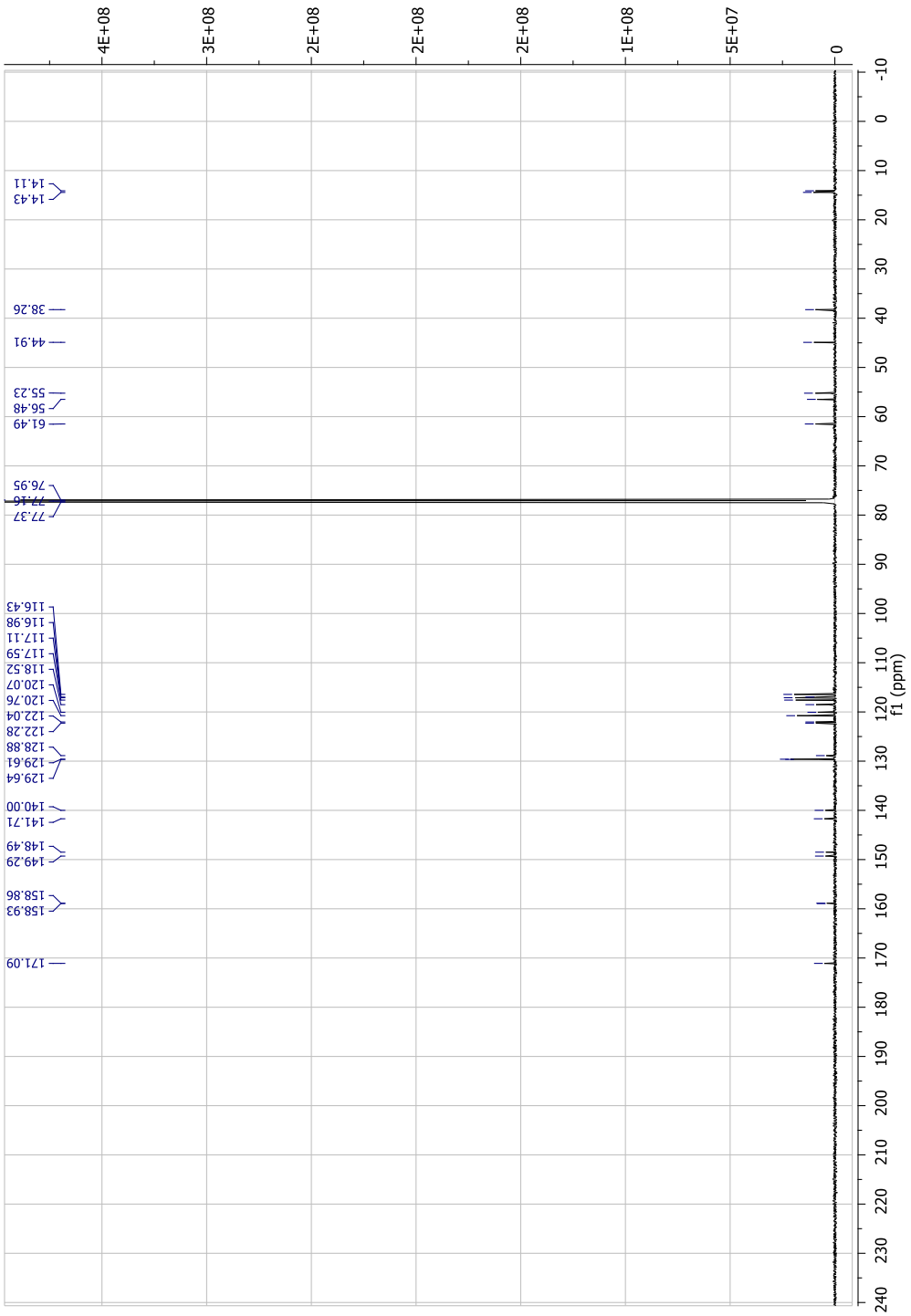
38.34
44.55
55.27
55.76
55.80
57.05
61.30
76.95
77.16
77.37
111.48
114.39
114.68
116.89
117.44
129.14
137.32
139.45
152.81
153.71
171.38
f1 (ppm)



3m

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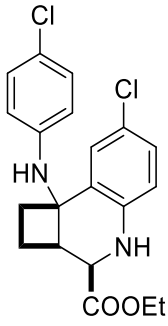
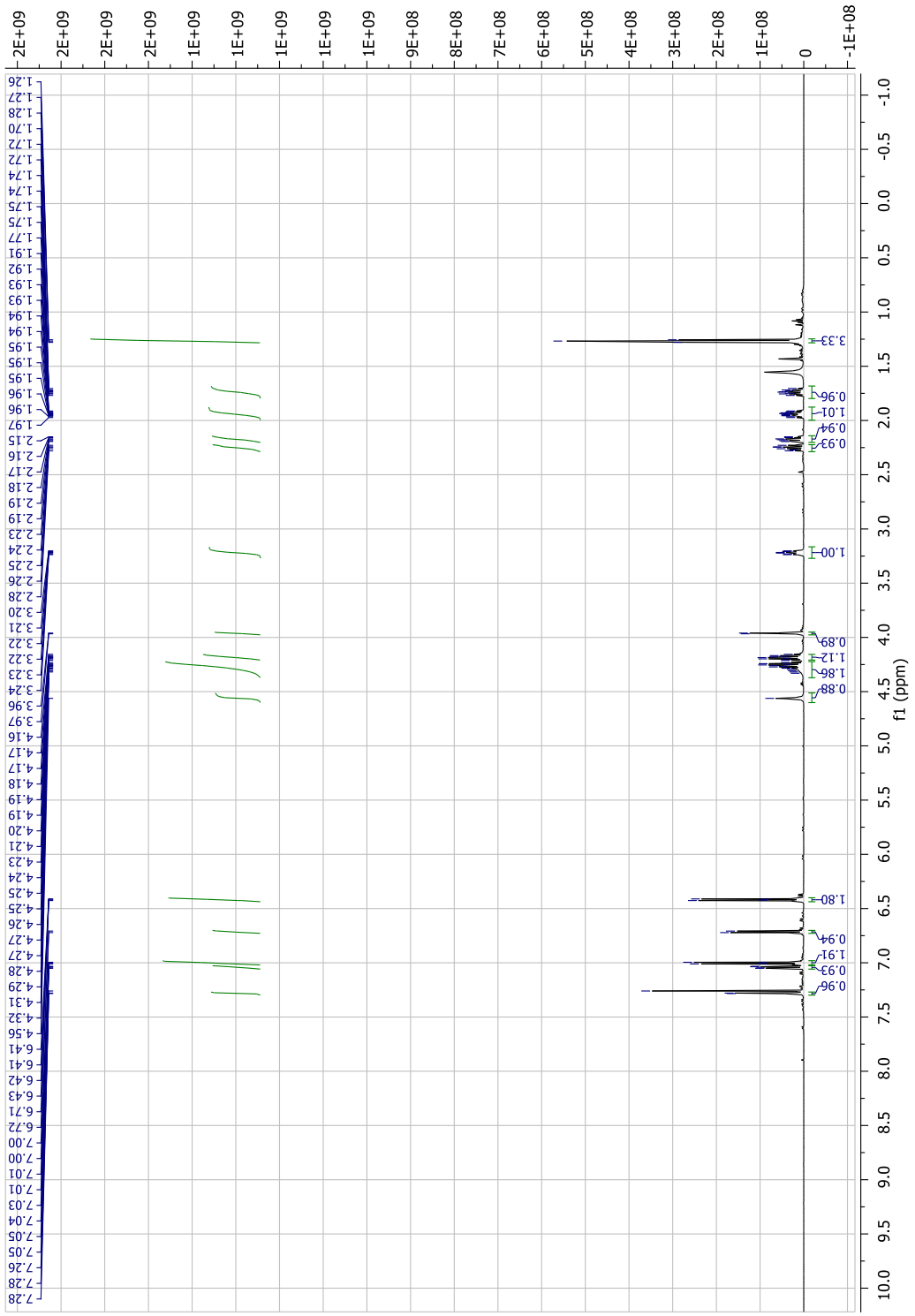
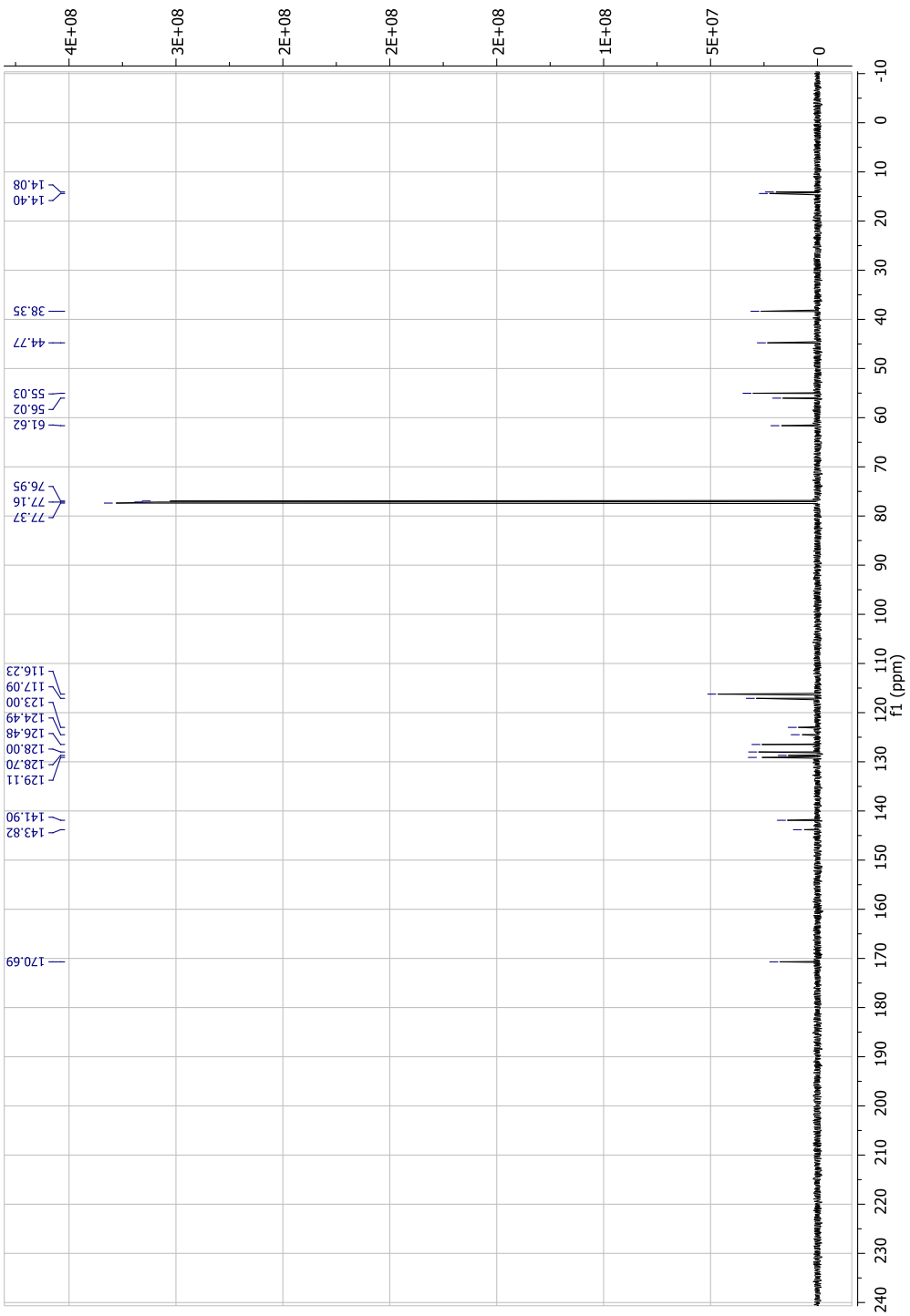
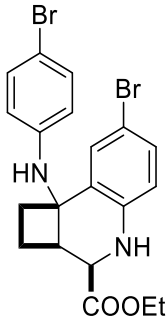
61.49
76.95
77.46
77.37
116.43
116.98
117.11
117.59
118.52
120.07
120.76
122.04
122.28
128.88
129.61
129.64
140.00
141.71
148.49
149.29
158.86
158.93
171.09
f1 (ppm)


Cl
Cl
HN
NH
COOEt

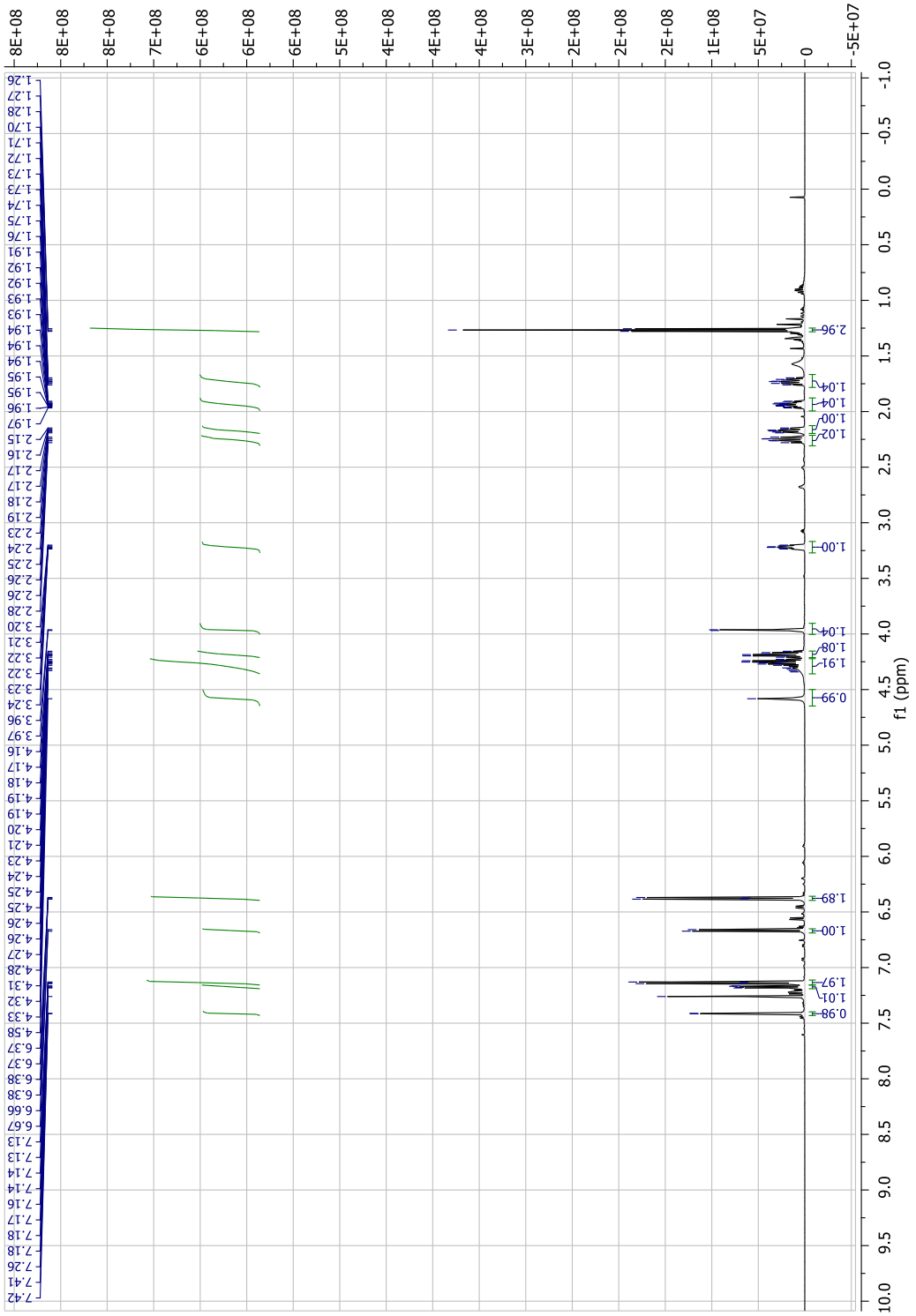
3n

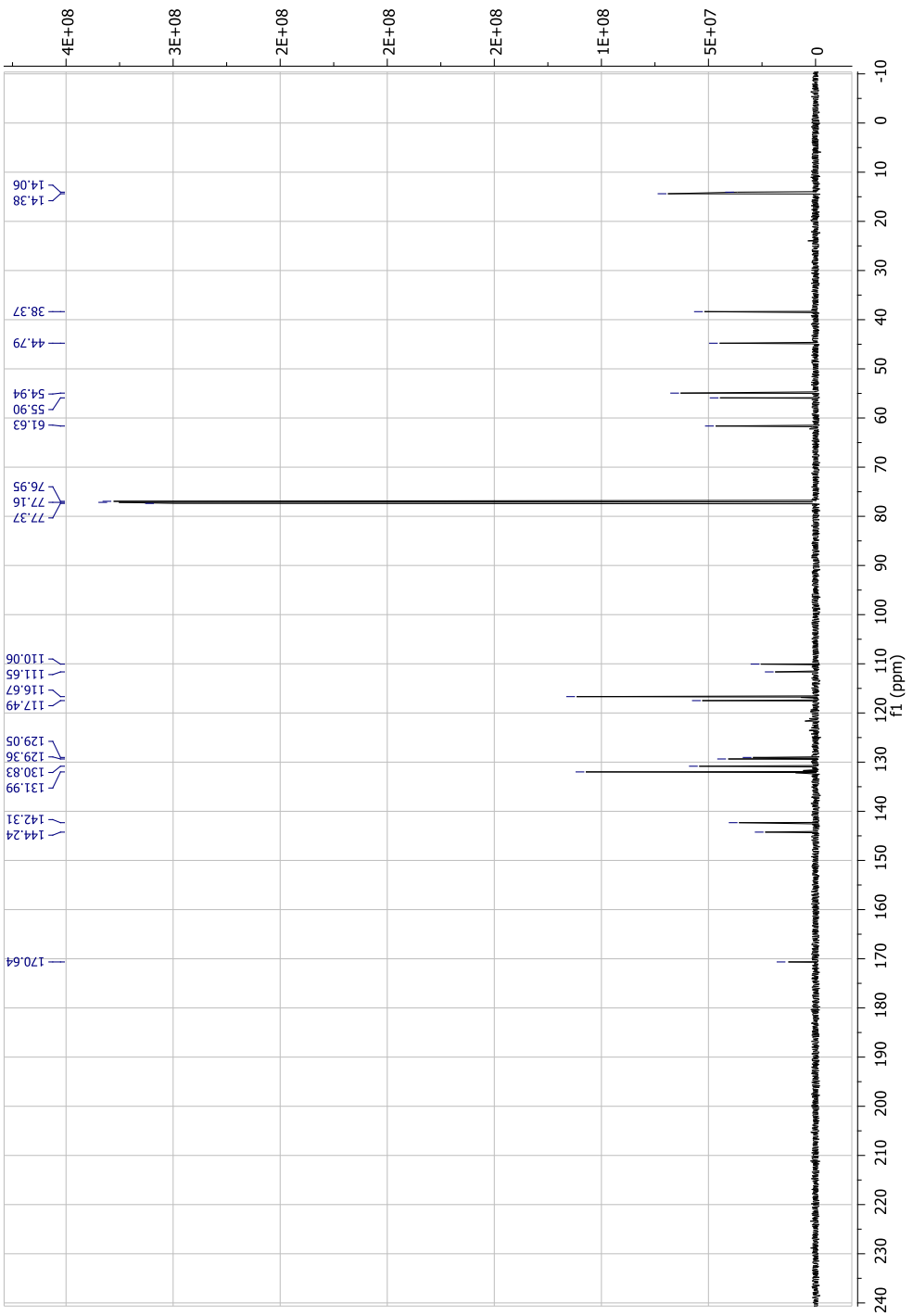

3.33
0.96
1.01
0.94
0.93
1.00
0.89
1.12
1.86
0.88
1.80
0.94
1.91
0.93
0.96
f1 (ppm)


14.08
14.40
38.35
44.77
55.03
56.02
61.62
76.95
77.16
77.37
116.23
117.09
123.00
124.49
126.48
128.00
128.70
129.11
141.90
143.82
170.69
f1 (ppm)



3o




14.06
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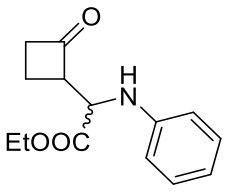
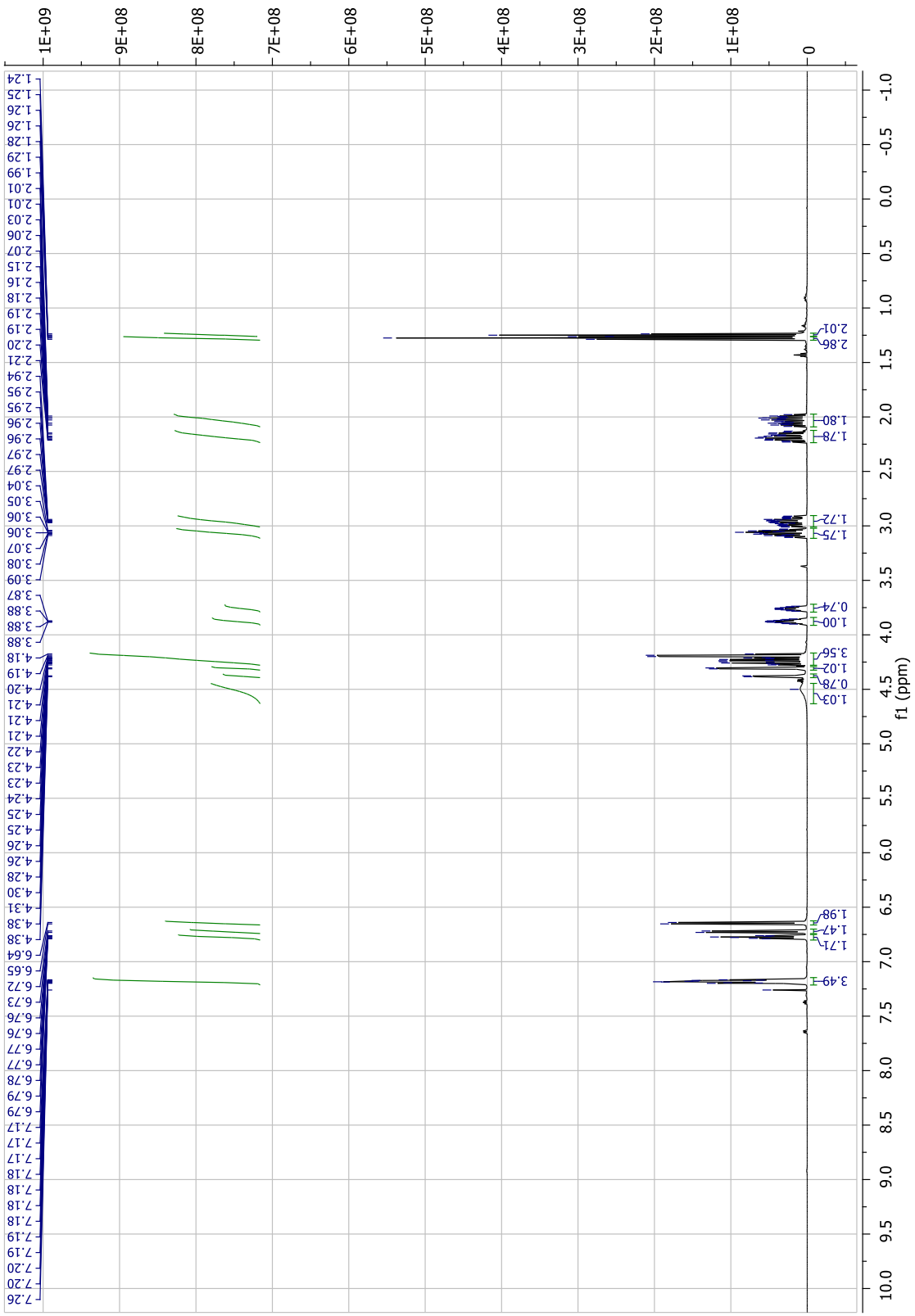
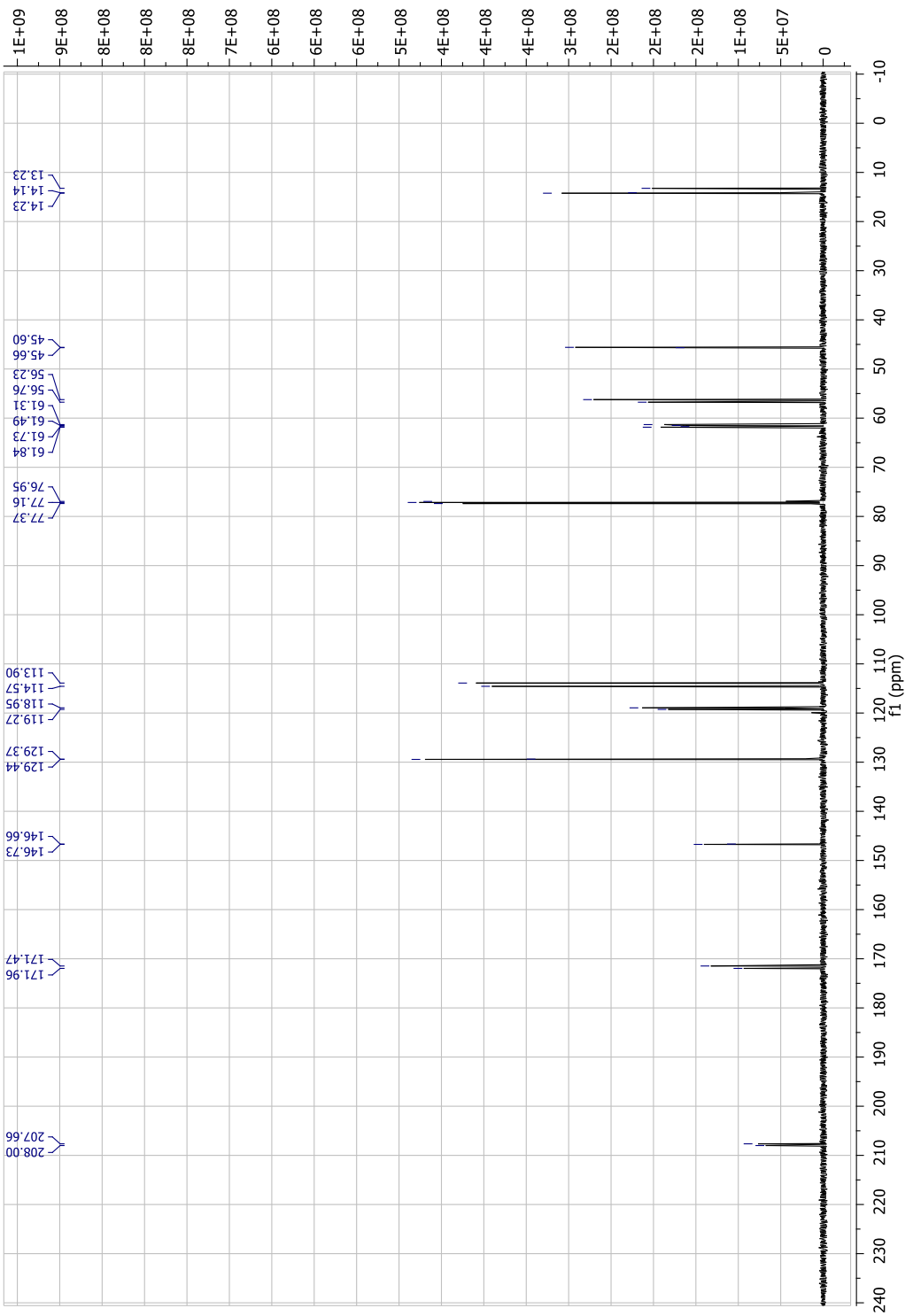
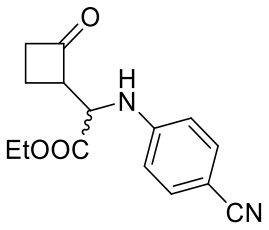
54.94
55.90
61.63
76.95
77.16
77.37
110.06
111.65
116.67
117.49
129.05
129.36
130.83
131.99
142.31
144.24
170.64
f1 (ppm)


O
H
N
EtOOC

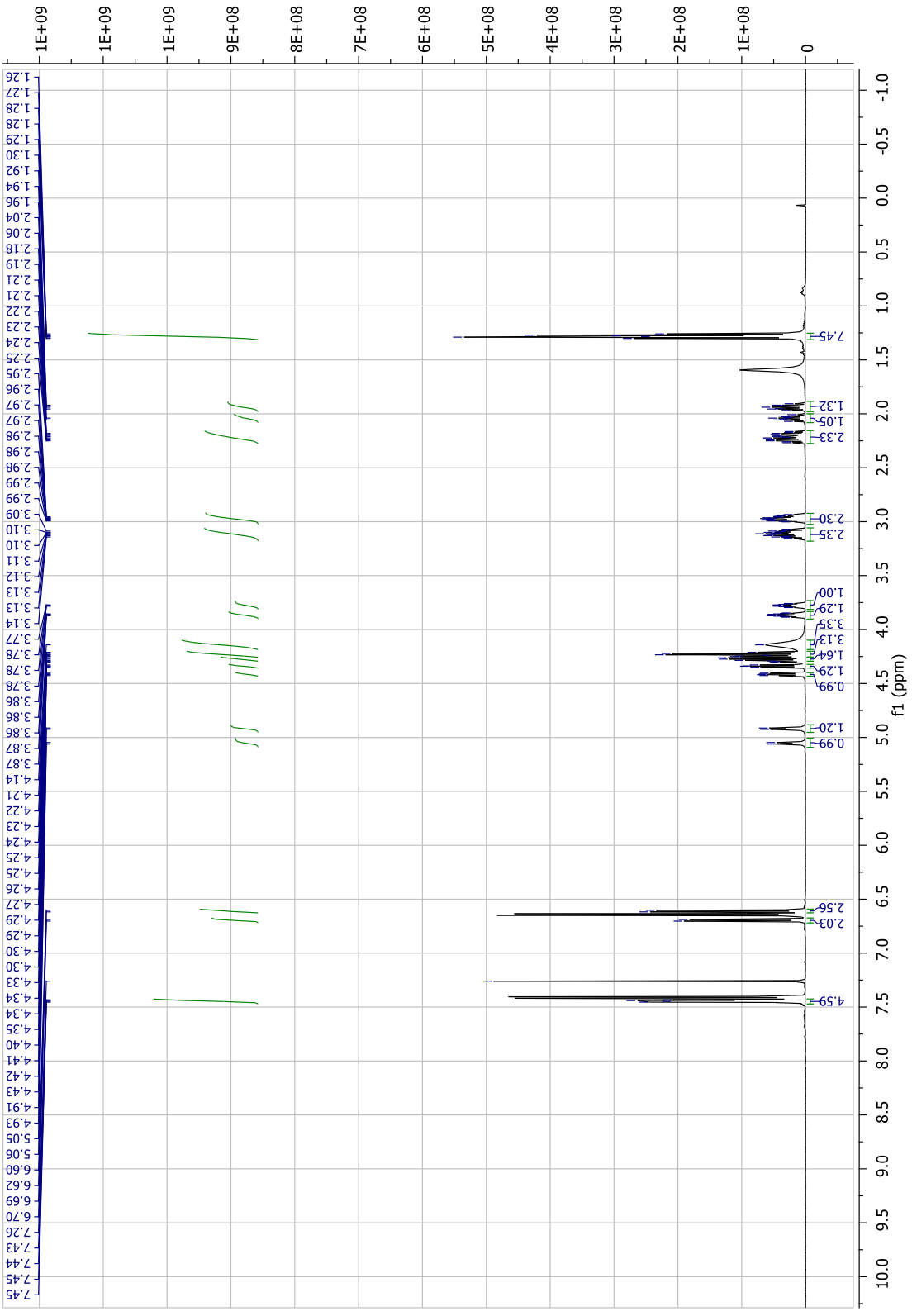
4a/4a'

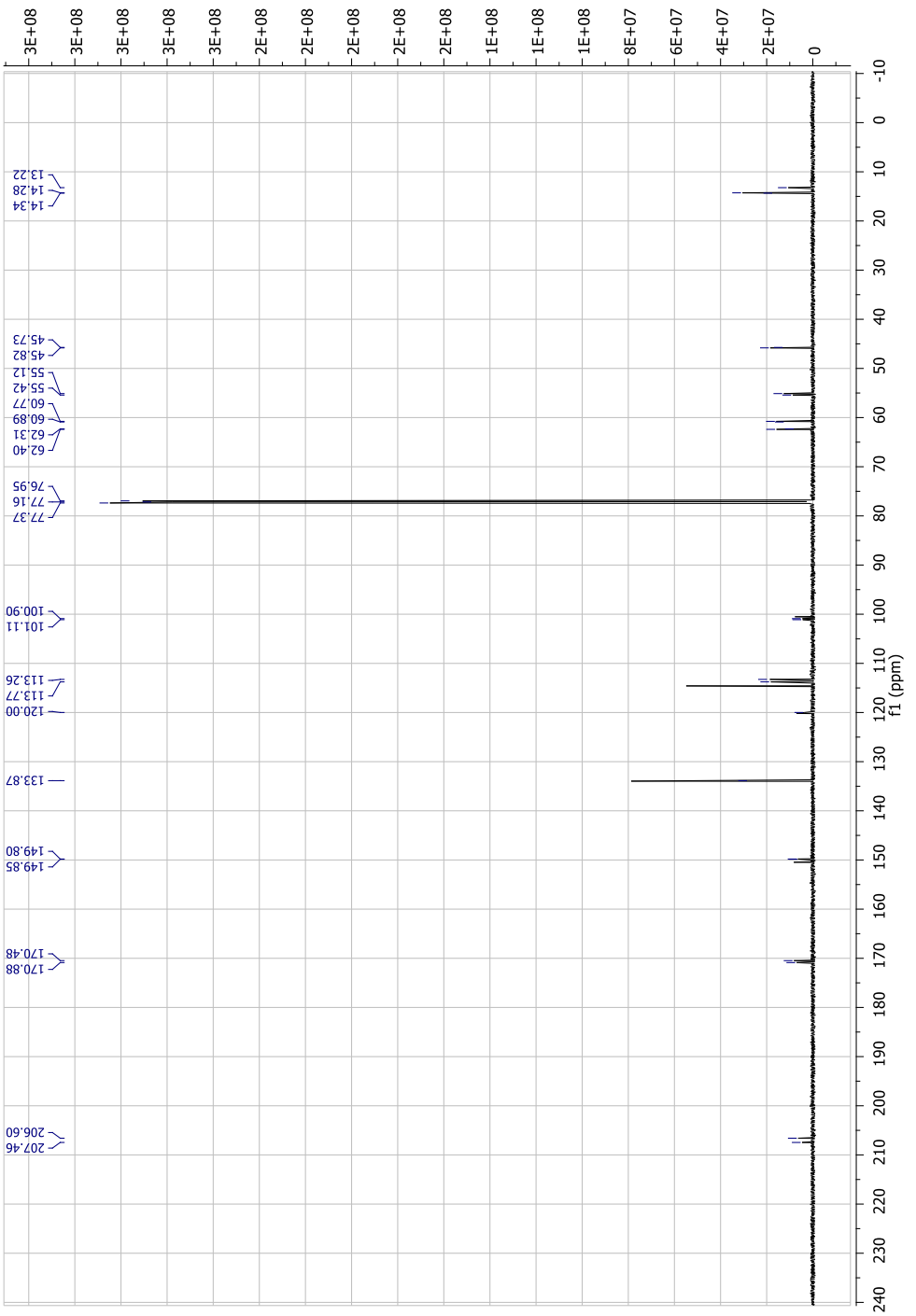

f1 (ppm)
2.01
2.86
1.80
1.78
1.72
1.75
0.74
1.00
3.56
1.02
0.78
1.03
1.98
1.47
1.71
3.49

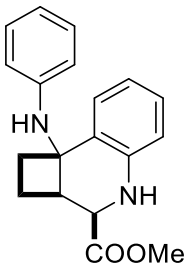

13.23
14.14
14.23
45.60
45.66
56.23
56.76
61.31
61.49
61.73
61.84
76.95
77.16
77.37
113.90
114.57
118.95
119.27
129.37
129.44
146.66
146.73
171.47
171.96
208.00
207.66
f1 (ppm)



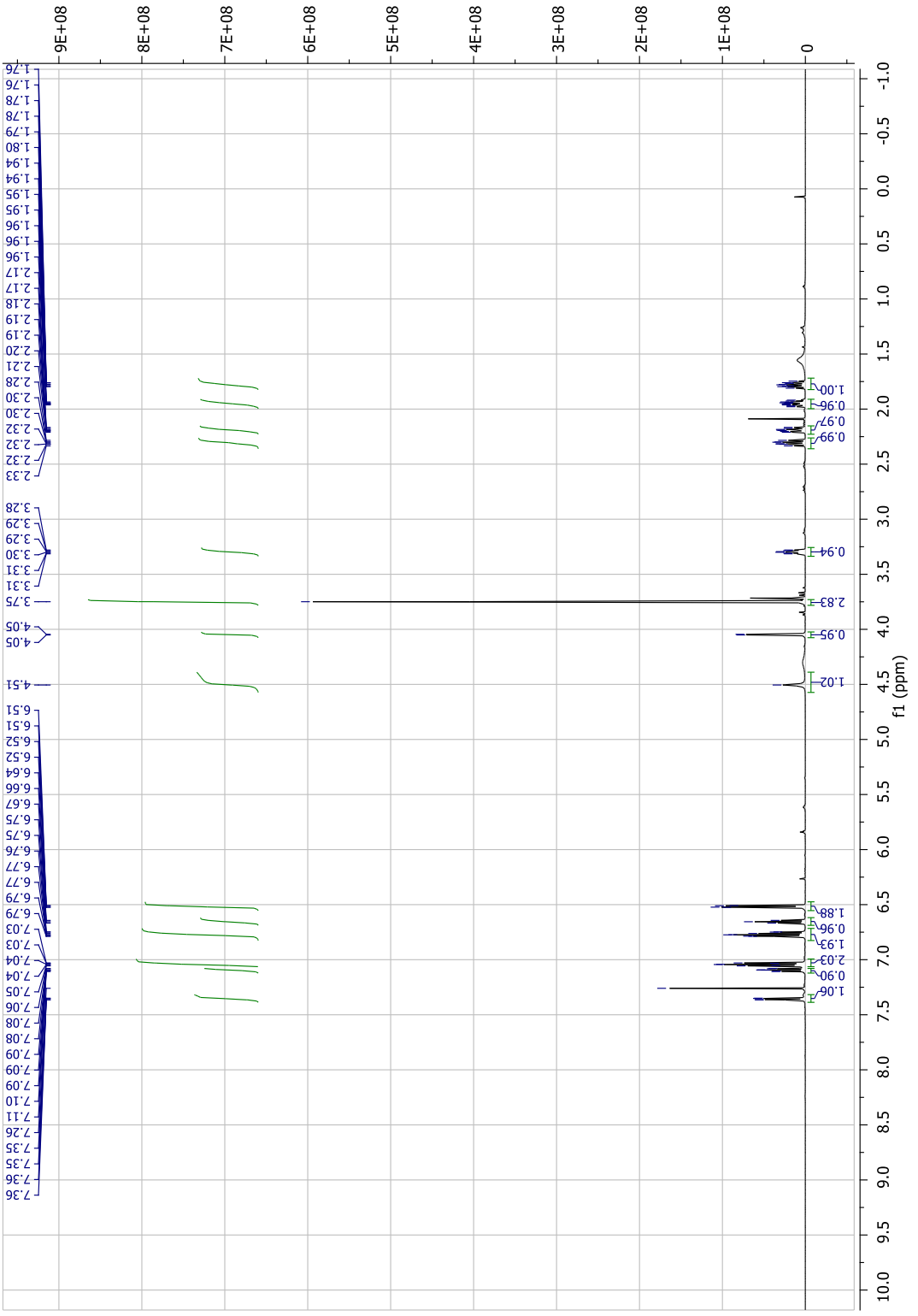
4p/4p' (contaminated by *p*-cyanoaniline **2p**)

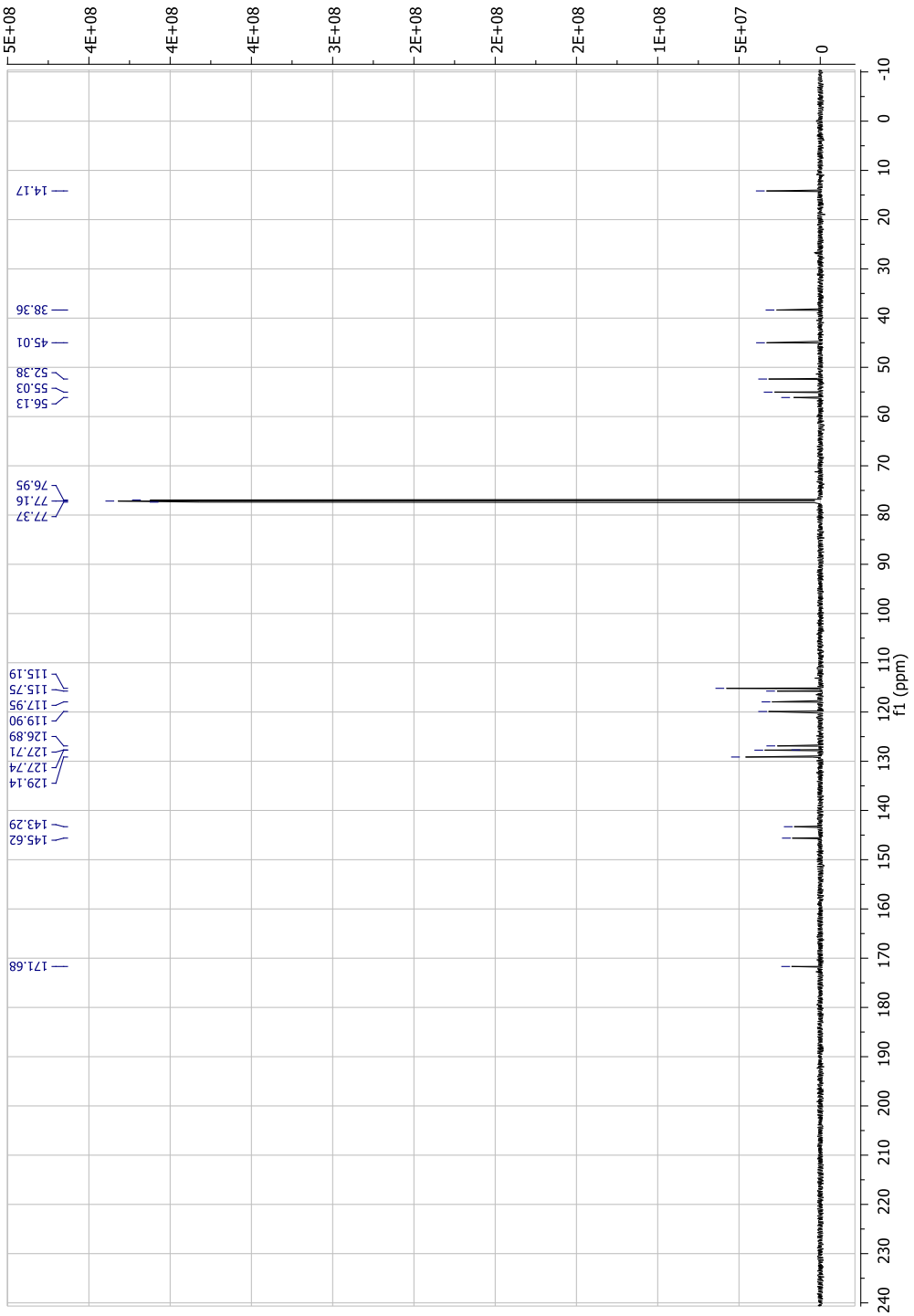


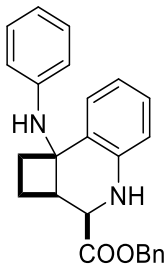

13.22
14.28
14.34
45.73
45.82
55.12
55.42
60.77
60.89
62.31
62.40
76.95
77.16
77.37
100.90
101.11
113.26
113.77
120.00
133.87
149.80
149.85
170.48
170.88
206.60
207.46
f1 (ppm)



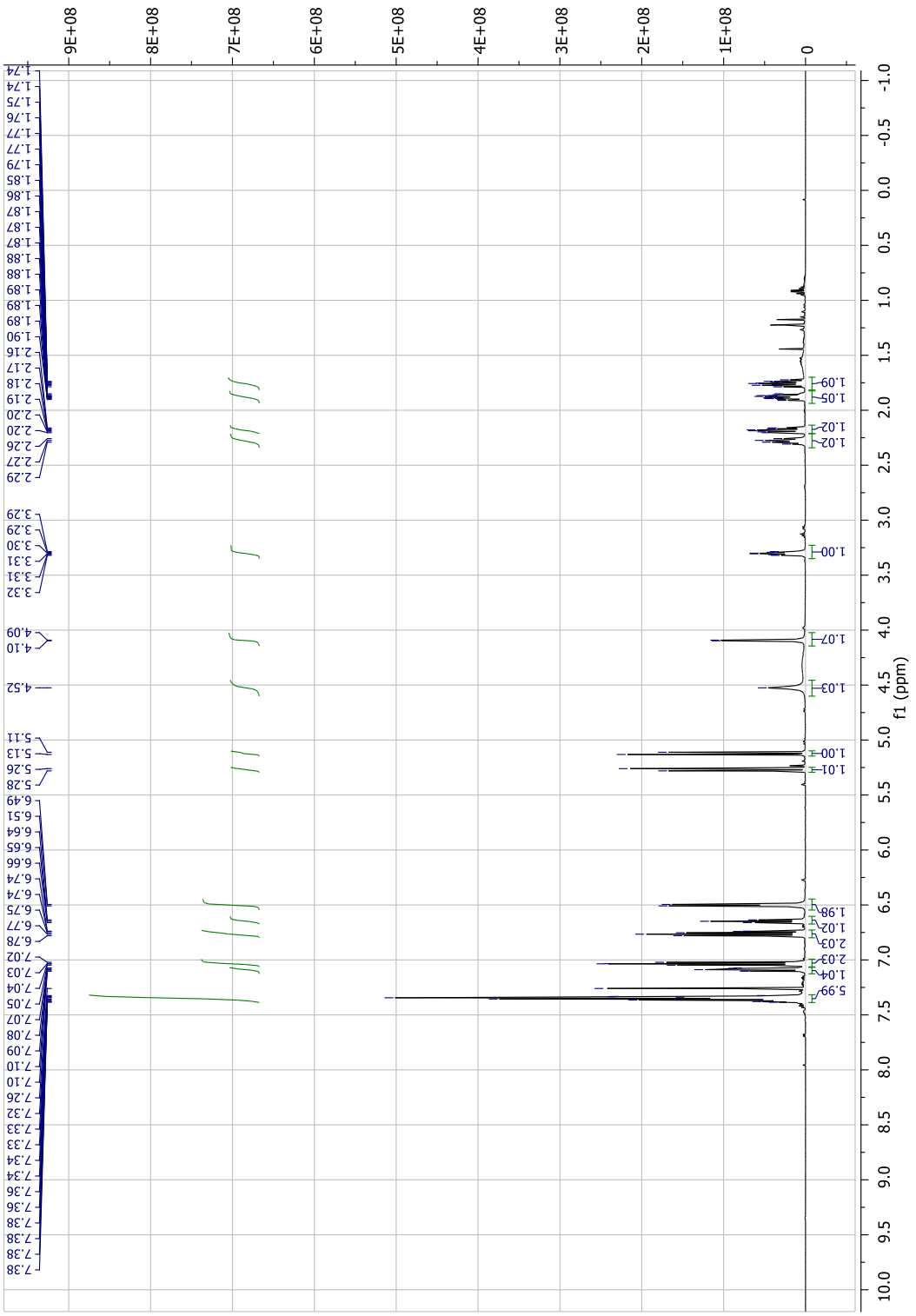
3r

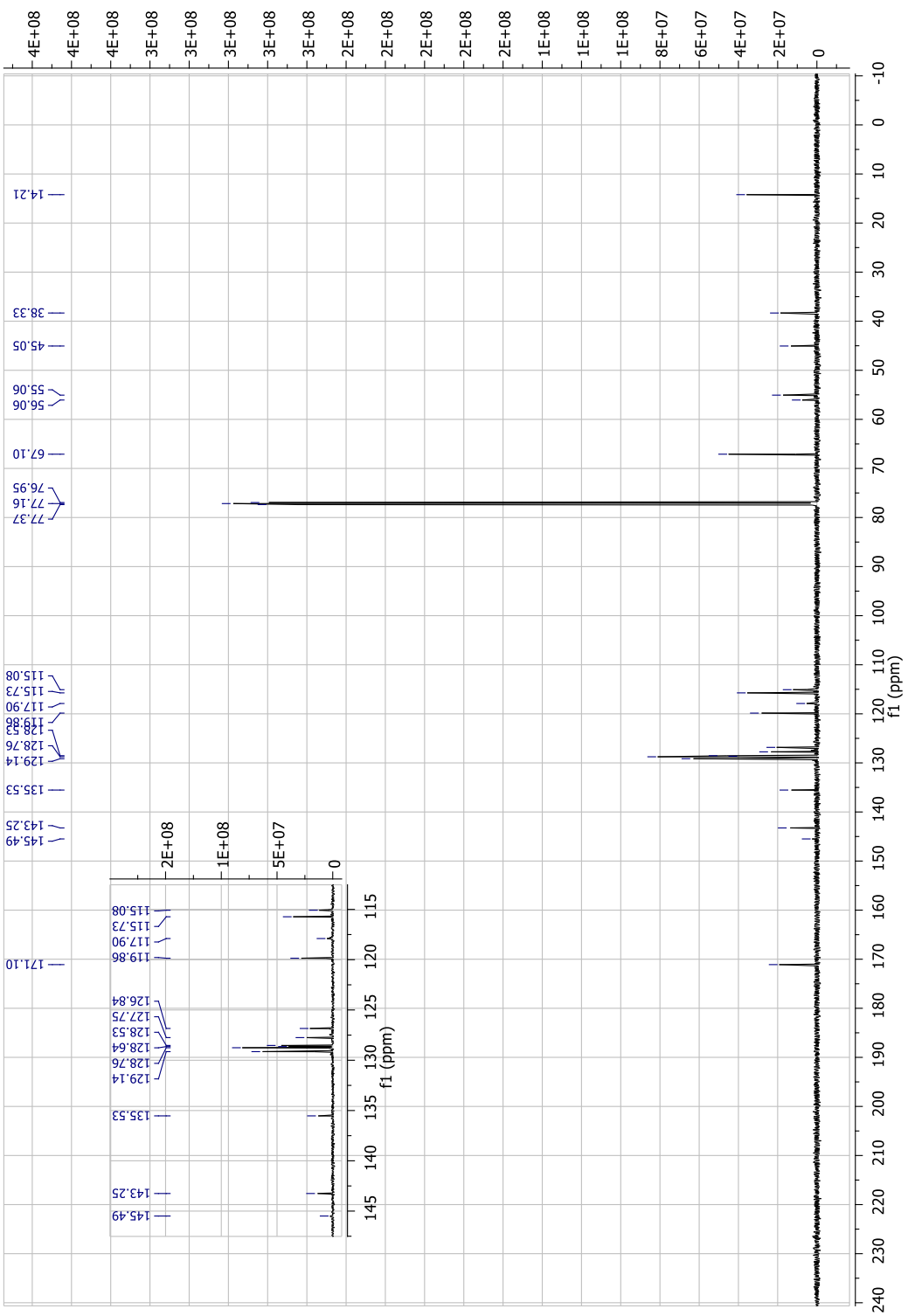


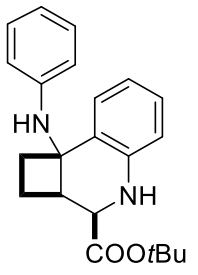

5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
f1 (ppm)
14.17
38.36
45.01
52.38
55.03
56.13
76.95
77.16
77.37
115.19
115.75
117.95
119.90
126.89
127.71
127.74
129.14
143.29
145.62
171.68



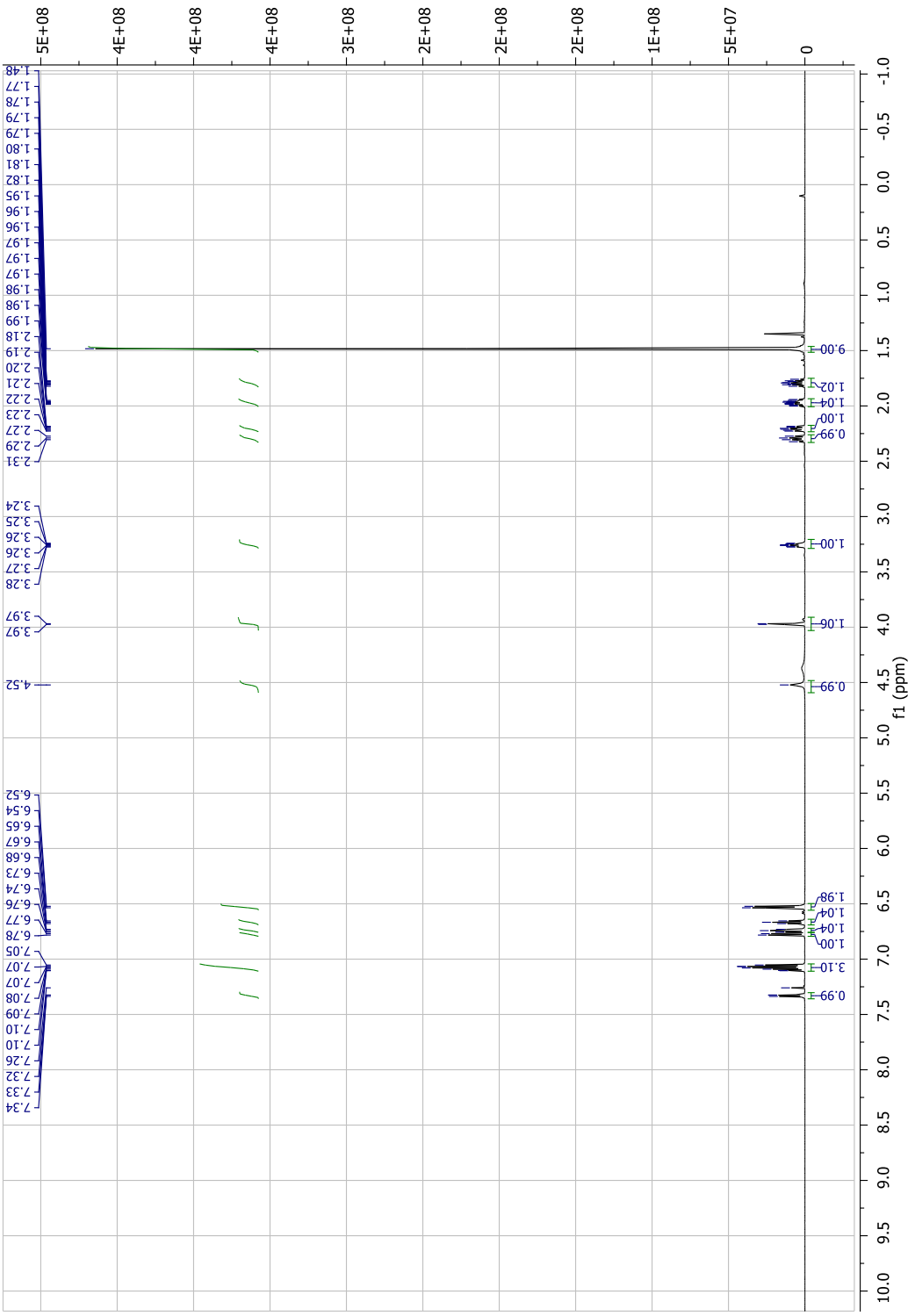
3s

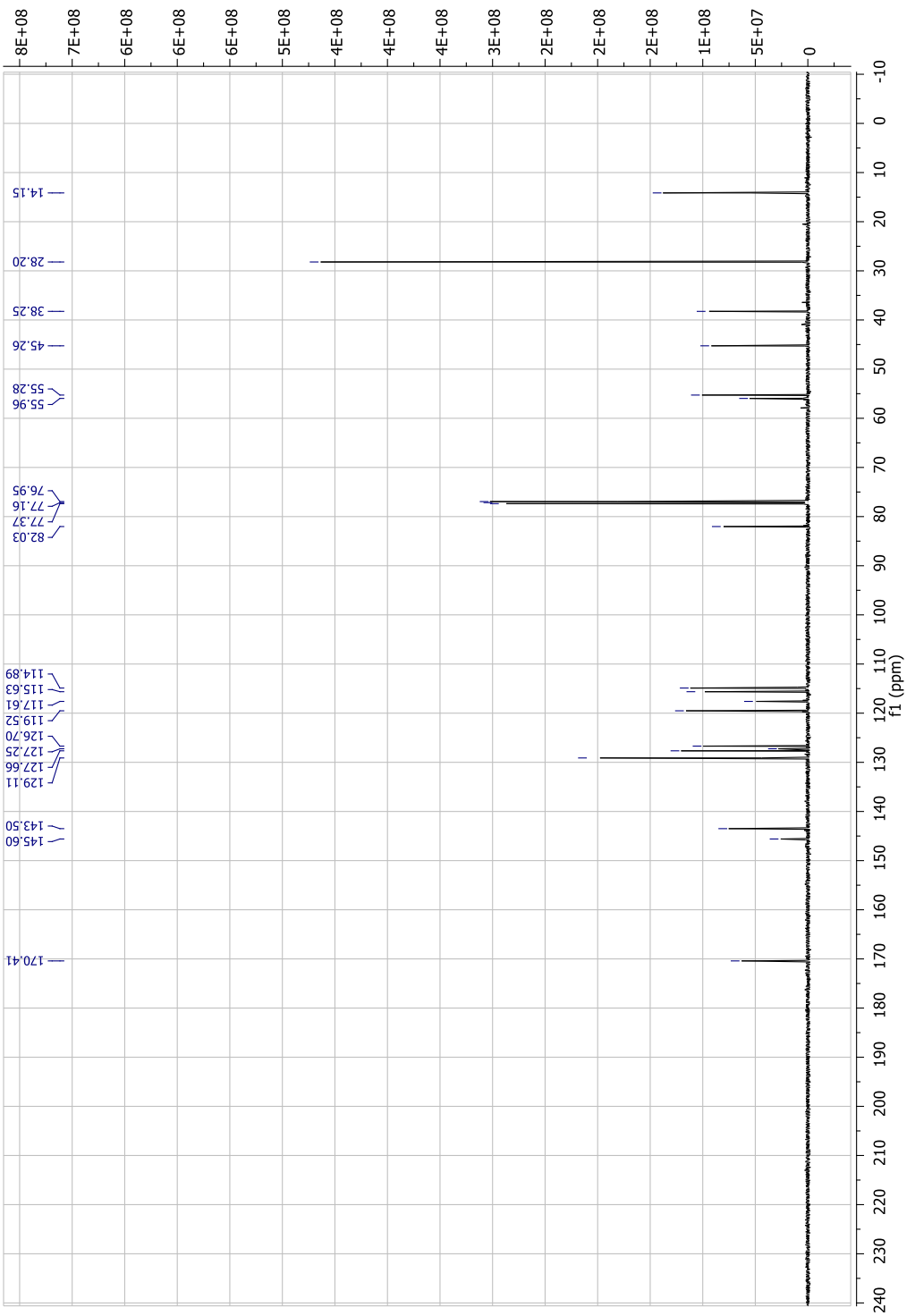


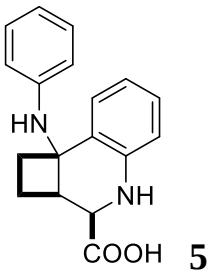

14.21
38.33
45.05
55.06
56.06
67.10
76.95
77.16
77.37
115.08
115.73
117.90
119.86
128.53
128.76
129.14
135.53
143.25
145.49
171.10
f1 (ppm)



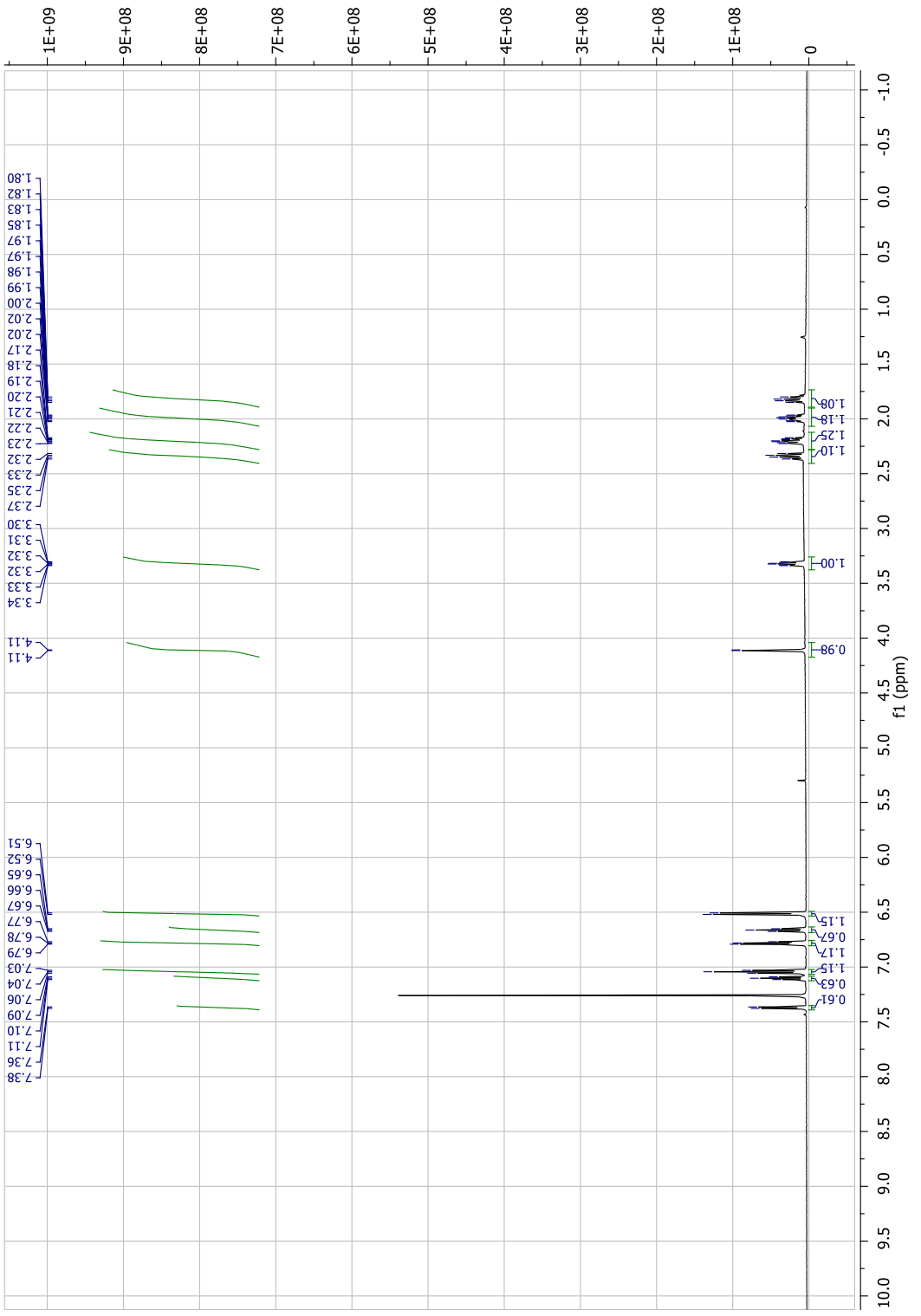
3t

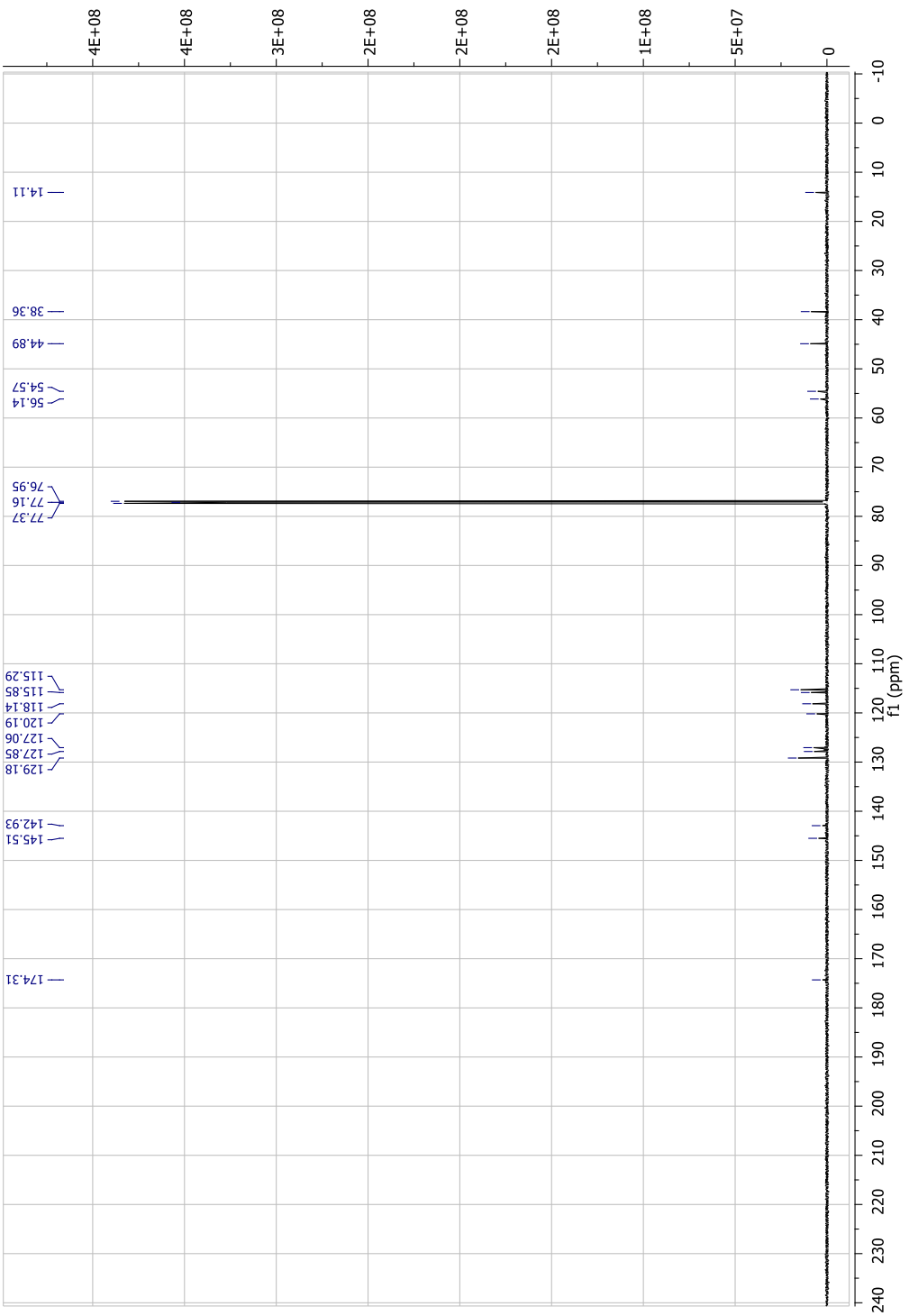



14.15
28.20
38.25
45.26
55.96
55.28
76.95
77.16
77.37
82.03
114.89
115.63
117.61
119.52
126.70
127.25
127.66
129.11
143.50
145.60
170.41
f1 (ppm)



5




14.11
38.36
44.89
54.57
56.14
76.95
77.16
77.37
115.29
115.85
118.14
120.19
127.06
127.85
129.18
142.93
145.51
174.31
f1 (ppm)

X-Ray diffraction studies

Crystals of **3s** and **5** suitable for X-ray diffraction were obtained by slow evaporation of ethyl acetate solutions at ambient temperature.

X-ray diffraction data were collected using a VENTURE PHOTON100 CMOS Bruker diffractometer with Micro-focus IuS source Cu Kα radiation. Crystals were mounted on a CryoLoop (Hampton Research) with Paratone-N (Hampton Research) as cryoprotectant and then flash frozen in a nitrogen gas stream at 100 K. The temperature of the crystals was maintained at the selected value by means of a 700 series Cryostream cooling device to within an accuracy of ±1 K. The data were corrected for Lorentz polarization and absorption effects.

The structures were solved by direct methods using SHELXS-97[S5] and refined against *F*2 by full matrix least-squares techniques using SHELXL-2018[S6] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[S7]

The crystal data collection and refinement parameters are given in Table S1. ORTEP drawings of the molecules are shown in Figures S1 and S2. CCDC 2087041 & 2087042 contain the crystallographic data for these compounds. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/Community/Requestastructure.

Table S1. Crystallographic data and structure refinement details.

Compound	**3s**	**5**
CCDC	2087042	2087041
Empirical Formula	C_{22} H_{26} N_2 O_2	C_{18} H_{18} N_2 O_2
M_r	350.45	294.34
Crystal size, mm^3	0.18 × 0.16 × 0.11	0.07 × 0.05 × 0.04
Crystal system	monoclinic	monoclinic
Space group	*P* 2_1	*P* 2_1/c
a, Å	11.1401(3)	6.56070(10)
b, Å	28.7617(7)	7.5167(2)
c, Å	11.7457(3)	28.7149(6)
α, °	90	90
β, °	90.5210(10)	95.4260(10)
γ, °	90	90
Cell volume, $Å^3$	3763.26(17)	1409.72(5)
Z ; Z’	8 ; 4	4 ; 1
T, K	100 (1)	100 (1)
Radiation type ; wavelength Å	CuKα ; 1.54178	CuKα ; 1.54178
F_{000}	1504	624
μ, mm^{-1}	0.627	0.733
range, °	3.073 - 65.200	3.092 - 66.758
Reflection collected	50 526	25 459
Reflections unique	12 738	2 486
R_{int}	0.0348	0.0492
GOF	1.025	1.118
Refl. obs. (*I*>2(*I*))	12 154	2 237
Parameters	945	195
wR_2 (all data)	0.0817	0.1019
R value (*I*>2(*I*))	0.0324	0.0457
Largest diff. peak and hole (e-.$Å^{-3}$)	0.220 ; -0.204	0.201 ; -0.245

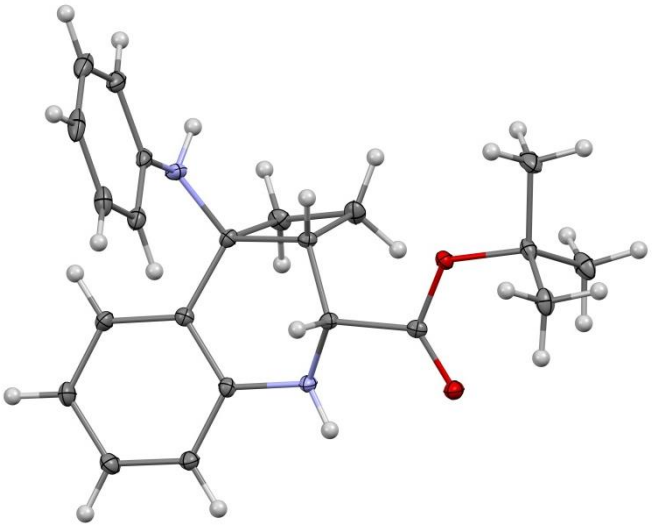


Figure S1. An ORTEP drawing of compound **3s** compound**.** Thermal ellipsoids are shown at the 30% level. For the sake of clarity, only one molecule of the asymmetric unit is shown.

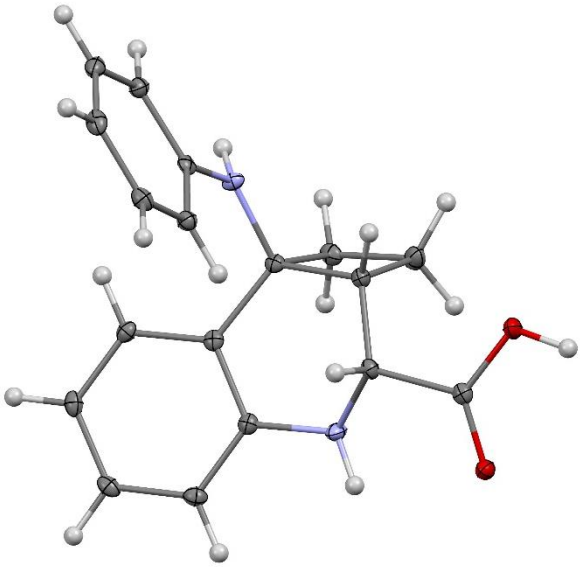
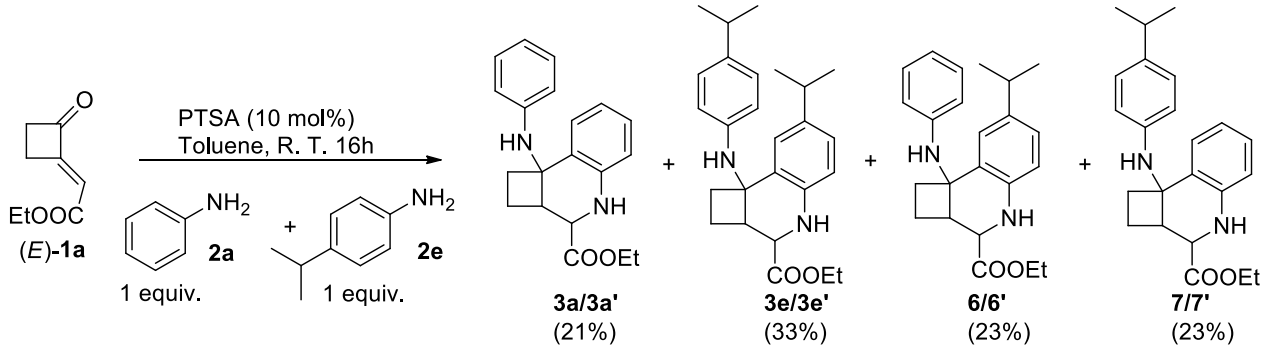


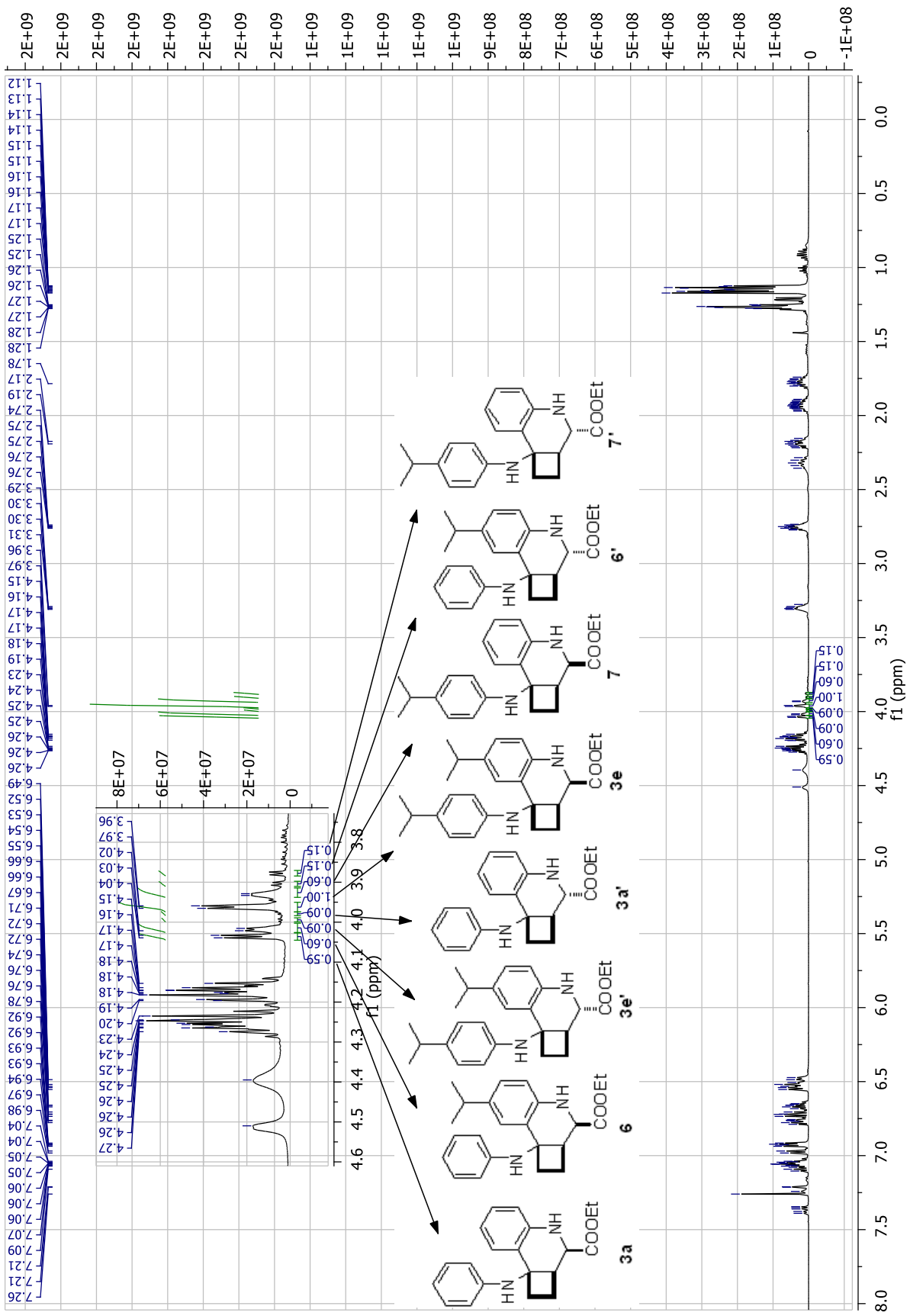
Figure S2. An ORTEP drawing of compound **5** compound. Thermal ellipsoids are shown at the 30% level.

Control reaction of (*E*)-1a with two different anilines



A mixture of (*E*)-**1a** (0.26 mmol), **2a** (0.26 mmol), **2e** (0.26 mmol) and PTSA (0.026 mmol) in toluene (0.5 mL) was stirred in a sealed tube reactor for 16 h at room temperature. The reaction mixture was passed through a short flash column column (eluent: petroleum ether/ether = 10:1→1:1) and evaporated to give a crude product mixture which was analyzed directly by ^{1}H NMR spectroscopy.

^{1}H NMR of the crude reaction mixture



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S3. P. Garner, S. Ramakanth, *J. Org. Chem.* 1987, **52**, 2631-2634.

S4. B. M. Trost, J. Xie, N. Maulide, *J. Am. Chem. Soc.* 2008, **130**, 17258-17259.

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S6. G. M. Sheldrick, *Acta Crystallogr., Sect. A* 2008, **64**, 112-122.

S7. Farrugia, L. J. *J. Appl. Cryst.* 1999, **32**, 837.