

SUPPORTING INFORMATION

On-water pyrrolidine-mediated domino synthesis of 2-iminoisatins.

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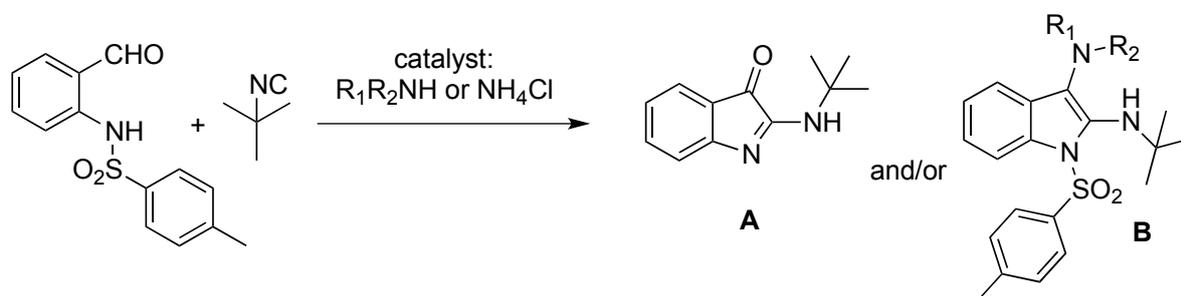
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Optimization of Reaction Conditions.



ENTRY ^a	SOLVENT	CATALYST	EQUIVALENTS	YIELD of A	YIELD of B
1	DCM	Pyrrolidine	1	44%	N.D. ^b
2	DCM	NH_4Cl	1	traces	N.D. ^b
3	DCM	Diethylamine	1	traces	85%
4	DCM	Morpholine	1	traces	92%
5	DCM	Piperidine	1	11%	66%
6	DCM	L-Pro	1	N.D. ^b	N.D. ^b
7	H_2O	Piperidine	1	8%	18%

Table S1. Screening of different secondary amines and ammonium chloride [**a**] Reaction conditions: rt, 20h; **b**) N.D.: Not Detected].

Experimental procedures and spectral data.

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P₂O₅ and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ¹H and ¹³C APT NMR were recorded on a 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with KMnO₄. The HPLC analysis was conducted on a HP1050 HPLC system equipped with an autosampler, a quaternary pump and a Diode-Array Detector. A Zorbax SB C-18 2.1 x 100 mm (particle size 3.5 micron) column was employed. The flow rate was 0.3 mL/min and the eluents were monitored at wavelengths between 210-280 nm. A linear gradient of mobile phase B (acetonitrile containing 0.1% TFA) over mobile phase A (0.1% TFA in water) from 0-90% B in 20 minutes was adopted. Data were collected and analyzed using ChemStation software. Samples were prepared by diluting 1 microliter of the reaction mixture in 1 mL of methanol followed by 10 microliter injection.

The UHPLC-HRMS analysis was conducted on a Dionex Ultimate 3000 UHPLC coupled to a Thermo Q-Exactive Orbitrap Mass Spectrometer. A Waters UPLC BEH-C18 column (2.1 x 50 mm, 1.7 micron) was used at a flow rate of 0.3 mL/min using linear gradients of acetonitrile/0.3% FA in water/0.3% FA. The Orbitrap MS was operated in both positive and negative ESI modes scanning a range between 50-500 m/z at a set resolution of 70000. The AGC target and the Maximum IT were set at 1 e⁶ and 50 ms, respectively. Samples were prepared by diluting the HPLC samples as above by a factor of 1000 in methanol followed by 10 microliter injection.

General preparation of *N*-(2-formylphenyl)arylsulfonamides 1. The *N*-(2-formylphenyl)arylsulfonamides were readily synthesized in two or three steps as previously reported.^[1]

General one-pot preparation of 2-iminoisatins (13, 14-31). The *N*-(2-formylphenyl)arylsulfonamide (1 mmol, 1 eq.), pyrrolidine (1 mmol, 1 eq.) and the isocyanide (1 mmol, 1 eq.) were one-pot mixed in water (HPLC grade) (0.5 M, 1 mL) and sonicated at room temperature for 1-3 hours. The formation of the 2-iminoisatin and the disappearance of the starting *N*-(2-formylphenyl)arylsulfonamide were monitored by TLC (typically *n*-hexane/ethyl acetate 7:3), and after evaporation of the solvent the crude material was purified by column chromatography.

2-(*tert*-butylamino)-3*H*-indol-3-one (13). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 95:5) to give the product as a purple solid (109 mg, 54% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (m, 2H), 6.99 (d, *J*= 8.0 Hz, 1H), 6.82 (t, *J*= 7.6 Hz, 1H), 5.47 (br s, -*NH*), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 191.6, 167.8, 155.4, 138.5, 125.2, 122.6, 121.3, 119.0, 52.4, 28.5. IR (KBr) 3341, 3049, 2968, 2854, 1960, 1727 $\nu_{\max}/\text{cm}^{-1}$; Mp 124-125°C; MS (ESI) *m/z* Calcd for C₁₂H₁₅N₂O⁺: 203.1179; Found: 203.1177 [M+H]⁺.

2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-3*H*-indol-3-one (14). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (98 mg, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (m, 2H), 6.98 (d, *J*= 8.0 Hz, 1H), 6.82 (t, *J*= 7.2 Hz, 1H), 5.38 (br s, -*NH*), 2.14-2.08 (m, 8H), 1.76-1.68 (m, 7H); ¹³C NMR (100 MHz, CDCl₃) δ 191.8, 168.1, 155.1, 138.5, 125.2, 122.4, 121.2, 119.0, 52.8, 41.4, 36.1, 29.4. IR (KBr) 2920, 2852, 2660, 2345, 2081, 1730 $\nu_{\max}/\text{cm}^{-1}$; Mp 166-167°C; MS (ESI) *m/z* Calcd for C₁₈H₂₁N₂O⁺: 281.1649; Found: 281.1643 [M+H]⁺.

2-(*tert*-butylamino)-6-chloro-3*H*-indol-3-one (15). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (182 mg, 77% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J*= 8.0 Hz, 1H), 6.99 (d, *J_m*= 1.6 Hz, 1H), 6.80 (d, *J*= 7.6 Hz, 1H), 5.55 (br s, -*NH*), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 190.0, 169.3, 156.1, 144.7, 125.8, 122.5, 119.7, 119.6, 52.7, 28.5. IR (KBr) 3333, 3041, 2966, 2604, 2378, 1875, 1736 $\nu_{\max}/\text{cm}^{-1}$; Mp 147-148°C; MS (ESI) *m/z* Calcd for C₁₂H₁₄ClN₂O⁺: 237.0790; Found: 237.0786 [M+H]⁺.

6-chloro-2-((2,4,4-trimethylpentan-2-yl)amino)-3*H*-indol-3-one (16). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 97:3) to give the product as a purple solid (249 mg, 85% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J*= 8.0 Hz, 1H), 7.00 (d, *J_m*= 1.6 Hz, 1H), 6.79 (dd, *J_a*= 8.0 Hz, *J_b*= 1.6 Hz, 1H), 5.60 (br s, -*NH*), 1.84 (s, 2H), 1.54 (s, 6H), 1.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 190.0, 169.6, 155.9, 144.7, 125.8, 122.3, 119.7, 119.5, 110.0, 56.5, 51.6, 31.7, 31.3, 28.7. IR (KBr) 3340, 3042, 2957, 2384, 1734, 1415 $\nu_{\max}/\text{cm}^{-1}$; Mp 145-146°C; MS (ESI) *m/z* Calcd for C₁₆H₂₂ClN₂O⁺: 293.1416; Found: 293.1410 [M+H]⁺.

2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-5-methyl-3*H*-indol-3-one (17). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 97:3) to give the product as a purple solid (79 mg, 27% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.17-7.14 (m, 2H), 6.88 (d, *J*= 8.0 Hz, 1H), 5.31 (br s, -*NH*), 2.22 (s, 3H), 2.14-2.11 (m, 9H), 1.75-1.68 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 192.1, 165.7, 154.9, 138.8, 131.9, 125.7, 121.2, 118.6, 52.7, 41.4, 36.1, 29.4, 20.5. IR (KBr) 3339, 2908, 2848, 2678, 2381, 1905, 1723 $\nu_{\max}/\text{cm}^{-1}$; Mp 186-187°C; MS (ESI) *m/z* Calcd for C₁₉H₂₃N₂O⁺: 295.1805; Found: 295.1800 [M+H]⁺.

2-(*tert*-butylamino)-5-methyl-3*H*-indol-3-one (18). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 97:3) to give the product as a purple solid (91 mg, 42% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.16-7.14 (m, 2H), 6.89 (d, *J*= 8.0 Hz, 1H), 5.40 (br s, -NH), 2.22 (s, 3H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 191.8, 165.3, 155.2, 138.9, 132.1, 125.7, 121.3, 118.6, 52.3, 28.6, 20.5. IR (KBr) 3343, 2956, 2731, 2364, 1726, 1478 $\nu_{\max}/\text{cm}^{-1}$; Mp 127-128°C; MS (ESI) *m/z* Calcd for C₁₃H₁₇N₂O⁺: 217.1336; Found: 217.1332 [M+H]⁺.

5-methyl-2-((2,4,4-trimethylpentan-2-yl)amino)-3*H*-indol-3-one (19). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (155 mg, 57% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.17-7.15 (m, 2H), 6.90 (d, *J*= 7.6 Hz, 1H), 5.43 (br s, -NH), 2.23 (s, 3H), 1.84 (s, 2H), 1.54 (s, 6H), 1.01 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 191.9, 165.8, 154.9, 138.9, 131.9, 125.7, 121.2, 118.7, 56.1, 51.7, 31.7, 31.4, 28.8, 20.5. IR (KBr) 3359, 2951, 2727, 2377, 1718, 1476 $\nu_{\max}/\text{cm}^{-1}$; Mp 152-153°C; MS (ESI) *m/z* Calcd for C₁₇H₂₅N₂O⁺: 273.1962; Found: 273.1956 [M+H]⁺.

2-(cyclohexylamino)-3*H*-benzo[*f*]indol-3-one (20). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 95:5) to give the product as a purple solid (200 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.73 (d, *J*= 8.4 Hz, 1H), 7.62 (d, *J*= 8.0 Hz, 1H), 7.46 (t, *J*= 6.8 Hz, 1H), 7.29-7.26 (m, 1H), 7.19 (s, 1H), 5.41 (br d, -NH), 3.92-3.85 (m, 1H), 2.13-2.09 (m, 2H), 1.80-1.64 (m, 3H), 1.50-1.21 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 189.3, 158.1, 157.4, 139.6, 131.3, 130.3, 130.1, 128.1, 127.9, 125.0, 123.7, 114.4, 50.9, 32.9, 25.4, 24.6. IR (KBr) 3348, 3034, 2925, 2855, 1728, 1608 $\nu_{\max}/\text{cm}^{-1}$; Mp 190-191°C; MS (ESI) *m/z* Calcd for C₁₈H₁₉N₂O⁺: 279.1492; Found: 279.1488 [M+H]⁺.

2-(pentylamino)-3*H*-benzo[*f*]indol-3-one (21). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a purple solid (146.5 mg, 55% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.72 (d, *J*= 8.0 Hz, 1H), 7.61 (d, *J*= 8.0 Hz, 1H), 7.45 (t, *J*= 7.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.18 (s, 1H), 5.51 (br s, -NH), 3.53-3.48 (m, 2H), 1.72-1.65 (m, 2H), 1.39-1.36 (m, 4H), 0.91 (t, *J*= 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 188.9, 159.2, 157.1, 139.6, 131.3, 130.4, 130.1, 128.2, 127.9, 125.0, 123.7, 114.5, 42.2, 29.0, 28.9, 22.3, 13.9. IR (KBr) 3343, 3053, 2952, 2868, 1723, 1585 $\nu_{\max}/\text{cm}^{-1}$; Mp 203-204°C; MS (ESI) *m/z* Calcd for C₁₇H₁₉N₂O⁺: 267.1492; Found: 267.1488 [M+H]⁺.

2-(*tert*-butylamino)-3*H*-benzo[*f*]indol-3-one (22). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 98:2) to give the product as a purple solid (182 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.72 (d, *J*= 8.0 Hz, 1H), 7.61 (d, *J*= 8.0 Hz, 1H), 7.45 (t, *J*= 7.2 Hz, 1H), 7.29-7.24 (m, 1H), 7.20 (s, 1H), 5.42 (br s, -NH), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 190.2, 157.8, 157.4, 139.7, 131.3, 130.3, 130.0, 128.1, 127.7, 124.9, 122.9, 114.6, 52.3, 28.6. IR (KBr) 3344, 3047, 2960, 2565, 2390, 1726, 1533 $\nu_{\max}/\text{cm}^{-1}$; Mp 151-152°C; MS (ESI) *m/z* Calcd for C₁₆H₁₇N₂O⁺: 253.1336; Found: 253.1356 [M+H]⁺.

2-(*tert*-butylamino)-6-methoxy-3*H*-indol-3-one (23). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a purple solid (151 mg, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J*= 8.4 Hz, 1H), 6.59 (d, *J*_m= 2.0 Hz, 1H), 6.31 (dd, *J*_a= 8.0 Hz, *J*_b= 2.0 Hz, 1H), 5.57 (br s, -NH), 3.85 (s, 3H), 1.49 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 188.5, 171.3, 169.0, 157.2, 127.3, 114.0, 108.2, 104.8, 55.7, 52.4, 28.6. IR (KBr) 3323, 2970, 2838, 2523, 2408, 1719 *v*_{max}/cm⁻¹; Mp 128-129°C; MS (ESI) *m/z* Calcd for C₁₃H₁₇N₂O₂⁺: 233.1285; Found: 233.1282 [M+H]⁺.

6-methoxy-2-((2,4,4-trimethylpentan-2-yl)amino)-3*H*-indol-3-one (24). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 97:3) to give the product as a purple solid (173 mg, 60% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32 (d, *J*= 8.4 Hz, 1H), 6.59 (d, *J*_m= 1.6 Hz, 1H), 6.31 (dd, *J*_a= 8.0 Hz, *J*_b= 1.6 Hz, 1H), 5.61 (br s, -NH), 3.85 (s, 3H), 1.85 (s, 2H), 1.55 (s, 6H), 1.01 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 188.5, 171.7, 169.0, 157.0, 127.3, 114.0, 108.2, 104.8, 56.3, 55.7, 51.7, 31.7, 31.4, 28.8. IR (KBr) 3341, 3045, 2961, 2853, 2512, 1708, 1433 *v*_{max}/cm⁻¹; Mp 91-92°C; MS (ESI) *m/z* Calcd for C₁₇H₂₅N₂O₂⁺: 289.1911; Found: 289.1905 [M+H]⁺.

2-((3*s*,5*s*,7*s*)-adamantan-1-ylamino)-6-methoxy-3*H*-indol-3-one (25). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 97:3) to give the product as a purple solid (65 mg, 21% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.30 (d, *J*= 8.0 Hz, 1H), 6.55 (d, *J*_m= 2.0 Hz, 1H), 6.29 (dd, *J*_a= 8.4 Hz, *J*_b= 2.4 Hz, 1H), 5.48 (br s, -NH), 3.84 (s, 3H), 2.13-2.11 (m, 9H), 1.75-1.67 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 188.8, 171.7, 169.0, 157.0, 127.2, 114.0, 108.2, 104.8, 55.7, 52.9, 41.4, 36.1, 29.4. IR (KBr) 3306, 3000, 2913, 2853, 2654, 2388, 1719 *v*_{max}/cm⁻¹; Mp 238-239°C; MS (ESI) *m/z* Calcd for C₁₉H₂₃N₂O₂⁺: 311.1755; Found: 311.1747 [M+H]⁺.

2-(*tert*-butylamino)-5-phenyl-3*H*-indol-3-one (26). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 98:2) to give the product as a purple solid (164 mg, 59% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J*= 7.2 Hz, 2H), 7.46-7.39 (m, 4H), 7.28 (s, 1H), 7.08 (d, *J*= 7.6 Hz, 1H), 5.51 (br s, -NH), 1.52 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 190.9, 168.5, 156.1, 151.5, 140.3, 128.8, 128.6, 127.1, 125.6, 121.4, 120.1, 117.8, 52.5, 28.6. IR (KBr) 3381, 2951, 2817, 1711, 1586, 1436, 1112, 1021 *v*_{max}/cm⁻¹; Mp 159-161°C; MS (ESI) *m/z* Calcd for C₁₈H₁₉N₂O⁺: 279.1492; Found: 279.1490 [M+H]⁺.

5-phenyl-2-((2,4,4-trimethylpentan-2-yl)amino)-3*H*-indol-3-one (27). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (217 mg, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J*= 7.2 Hz, 2H), 7.46-7.37 (m, 4H), 7.28 (s, 1H), 7.07 (d, *J*= 7.6 Hz, 1H), 5.56 (br s, -NH), 1.88 (s, 2H), 1.57 (s, 6H), 1.03 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 190.9, 168.9, 155.8, 151.5, 140.3, 128.8, 128.6, 127.1, 125.6, 121.3, 120.0, 117.9, 56.3, 51.6, 31.8, 31.4, 28.8. IR (KBr)

3355, 3036, 2945, 1718, 1582, 1414, 1168, 759 $\nu_{\max}/\text{cm}^{-1}$; Mp 98-100°C; MS (ESI) m/z Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}^+$: 335.2118; Found: 335.2113 $[\text{M}+\text{H}]^+$.

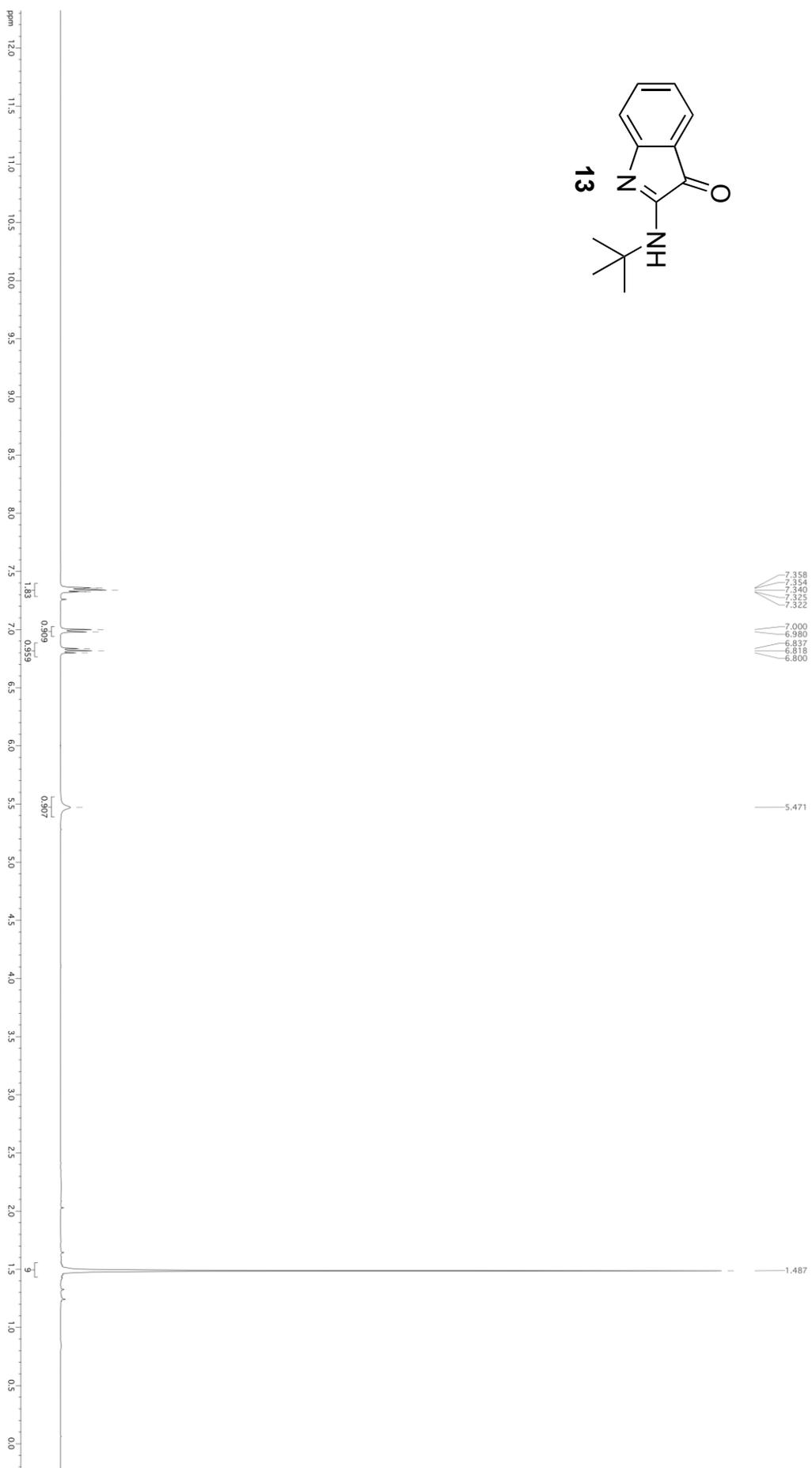
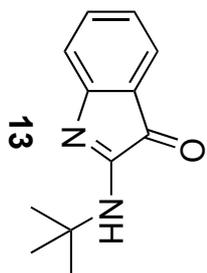
6-bromo-2-((2,4,4-trimethylpentan-2-yl)amino)-3H-indol-3-one (28). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (265 mg, 78.5% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.19 (m, 2H), 6.98 (dd, $J_a=8.0$ Hz, $J_b=1.6$ Hz, 1H), 5.58 (br s, -NH), 1.85 (s, 2H), 1.54 (s, 6H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.2, 169.4, 155.7, 133.7, 125.9, 125.3, 122.7, 119.9, 56.5, 51.6, 31.7, 31.3, 28.7. IR (KBr) 3340, 2970, 1731, 1566, 1411, 1290, 1044, 779 $\nu_{\max}/\text{cm}^{-1}$; Mp 85-87°C; MS (ESI) m/z Calcd for $\text{C}_{16}\text{H}_{22}\text{BrN}_2\text{O}^+$: 337.0911; Found: 337.0907 $[\text{M}+\text{H}]^+$.

2-((3s,5s,7s)-adamantan-1-ylamino)-6-bromo-3H-indol-3-one (29). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 99:1) to give the product as a purple solid (233.5 mg, 65% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.17 (m, 2H), 6.97 (dd, $J_a=7.6$ Hz, $J_b=1.2$ Hz, 1H), 5.46 (br s, -NH), 2.15 (s, 3H), 2.11 (s, 6H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 190.4, 169.2, 155.5, 133.7, 125.9, 125.4, 122.5, 119.8, 53.2, 41.2, 36.0, 29.3. IR (KBr) 3327, 2906, 2849, 2463, 1731, 1564, 897 $\nu_{\max}/\text{cm}^{-1}$; Mp 226-228°C; MS (ESI) m/z Calcd for $\text{C}_{18}\text{H}_{20}\text{BrN}_2\text{O}^+$: 359.0754; Found: 359.0748 $[\text{M}+\text{H}]^+$.

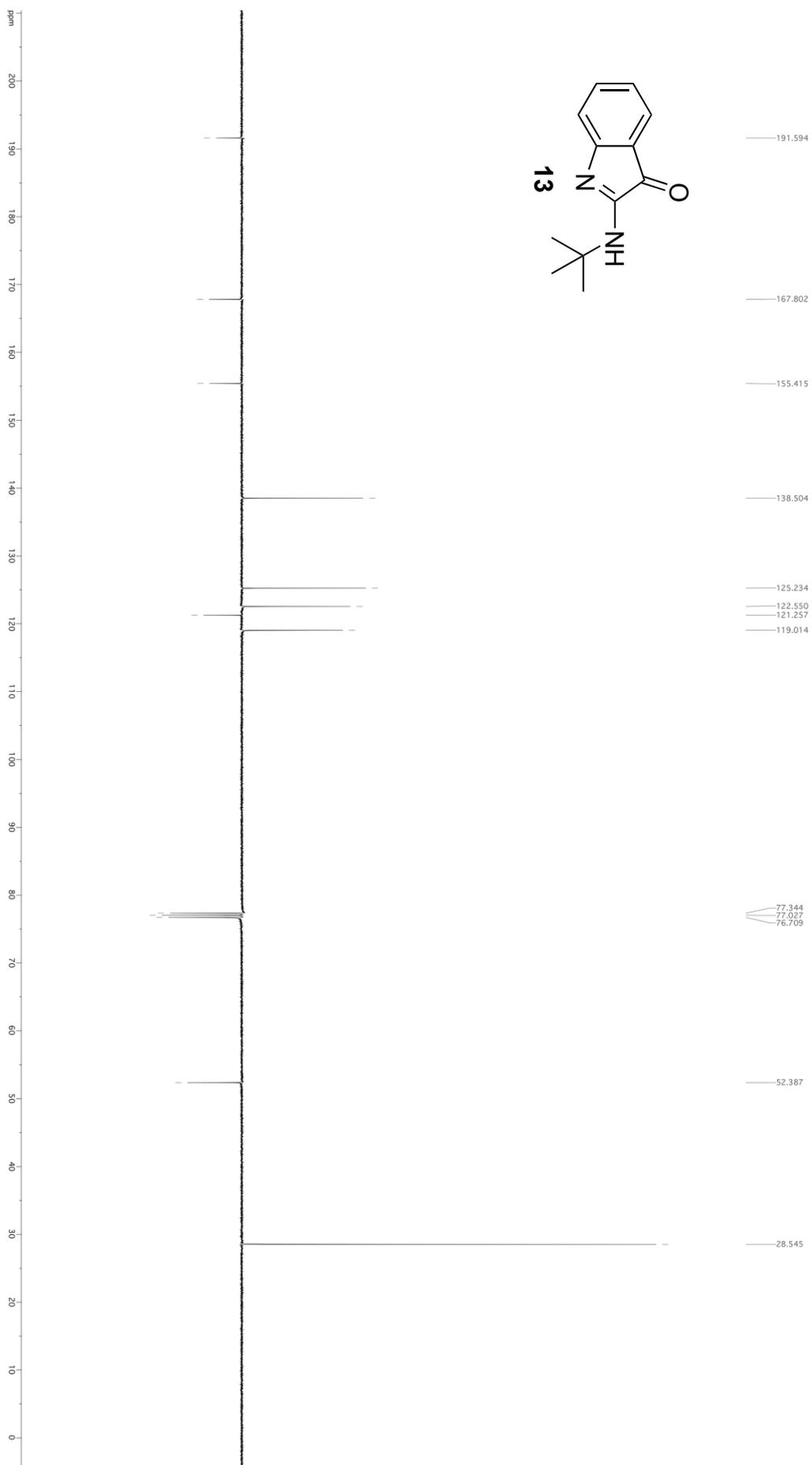
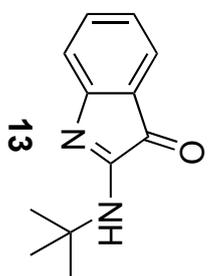
2-(tert-butylamino)-6-fluoro-3H-indol-3-one (30). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 98:2) to give the product as a purple solid (121 mg, 55% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.34 (m, 1H), 6.70 (dd, $J_a=9.6$ Hz, $J_b=2.0$ Hz, 1H), 6.52-6.47 (m, 1H), 5.56 (br s, -NH), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.3, 171.2, 170.0 (d, $J=256.4$ Hz), 156.5, 127.1 (d, $J=12.0$ Hz), 117.4 (d, $J=2.2$ Hz), 109.1 (d, $J=23.8$ Hz), 107.3 (d, $J=24.9$ Hz), 52.7, 28.5. IR (KBr) 3356, 2968, 2920, 1720, 1209, 1123, 1086 $\nu_{\max}/\text{cm}^{-1}$; Mp 126-128°C; MS (ESI) m/z Calcd for $\text{C}_{12}\text{H}_{14}\text{FN}_2\text{O}^+$: 221.1085; Found: 221.1082 $[\text{M}+\text{H}]^+$.

5,6-dimethoxy-2-((2,4,4-trimethylpentan-2-yl)amino)-3H-indol-3-one (31). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 85:15) to give the product as an amorphous purple solid (132 mg, 41.5% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.90 (s, 1H), 6.65 (s, 1H), 5.56 (br s, -NH), 3.94 (s, 3H), 3.80 (s, 3H), 1.84 (s, 2H), 1.54 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.5, 166.8, 158.4, 156.2, 144.8, 111.5, 108.0, 103.0, 56.4 (2C), 56.2, 51.7, 31.7, 31.3, 28.8. IR (KBr) 3381, 2951, 2871, 1711, 1586, 1479, 1216, 1112 $\nu_{\max}/\text{cm}^{-1}$; MS (ESI) m/z Calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_3^+$: 319.2017; Found: 319.2011 $[\text{M}+\text{H}]^+$.

¹H NMR
400 MHz, CDCl₃

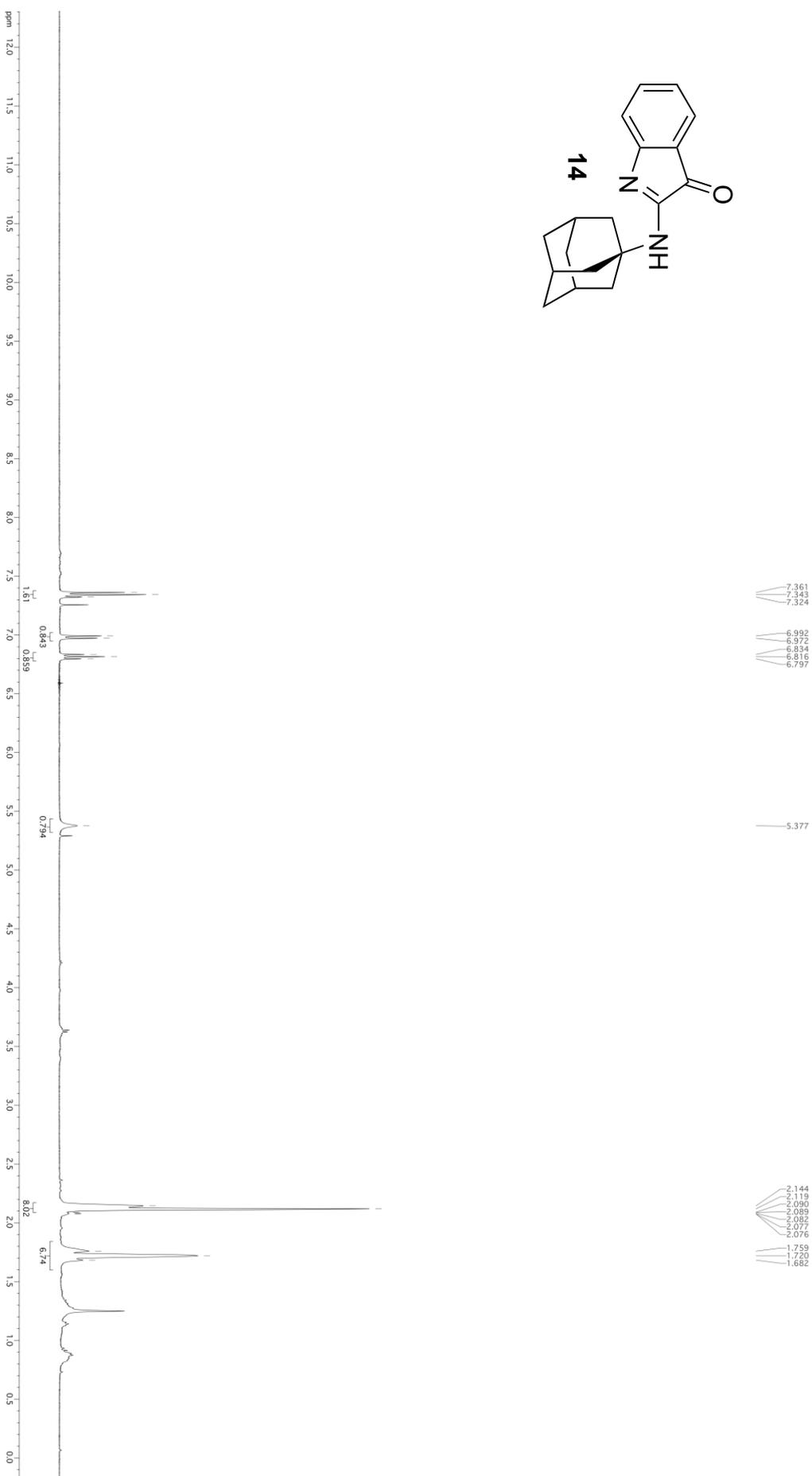
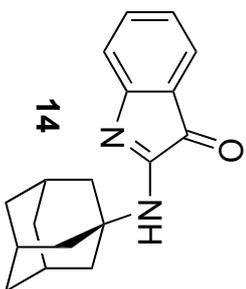


¹³C NMR
100 MHz, CDCl₃

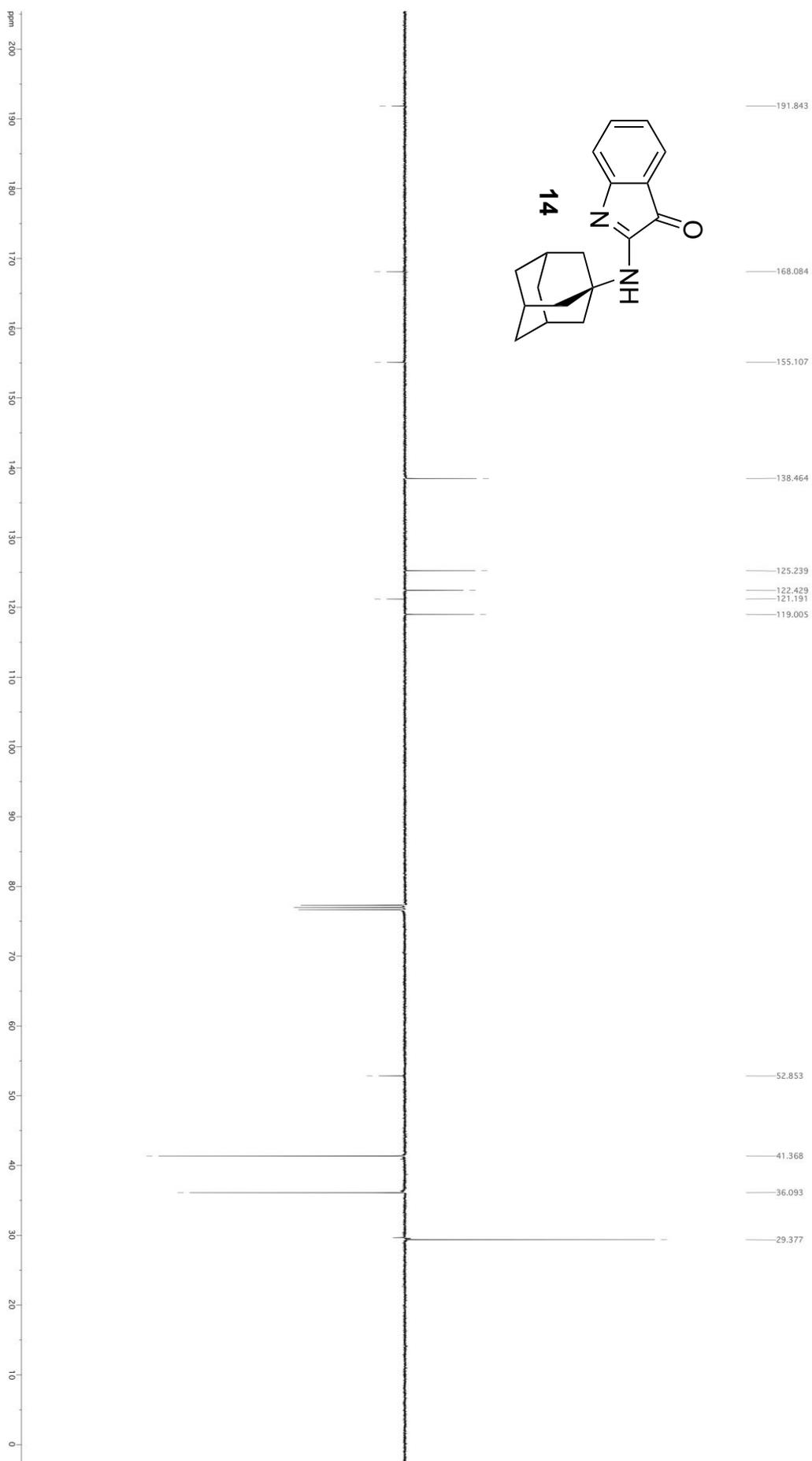
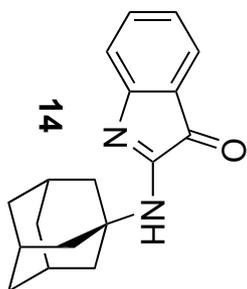


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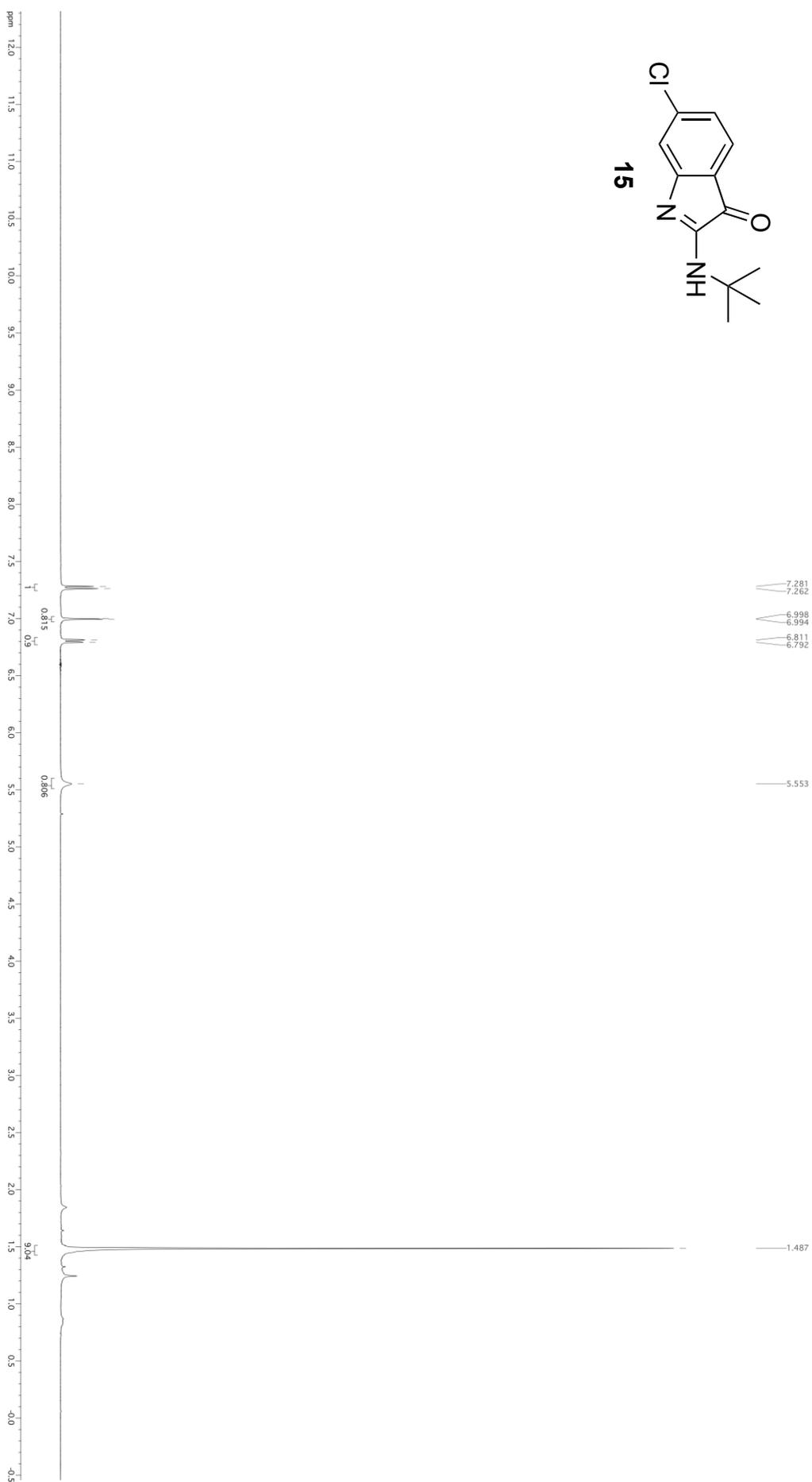
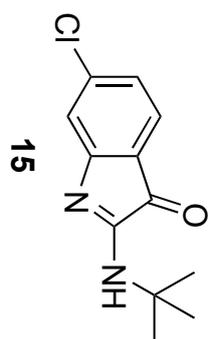
¹H NMR
400 MHz, CDCl₃



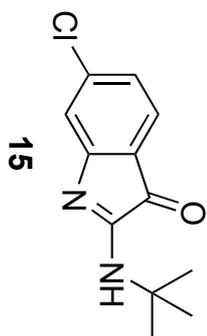
¹³C NMR
100 MHz, CDCl₃



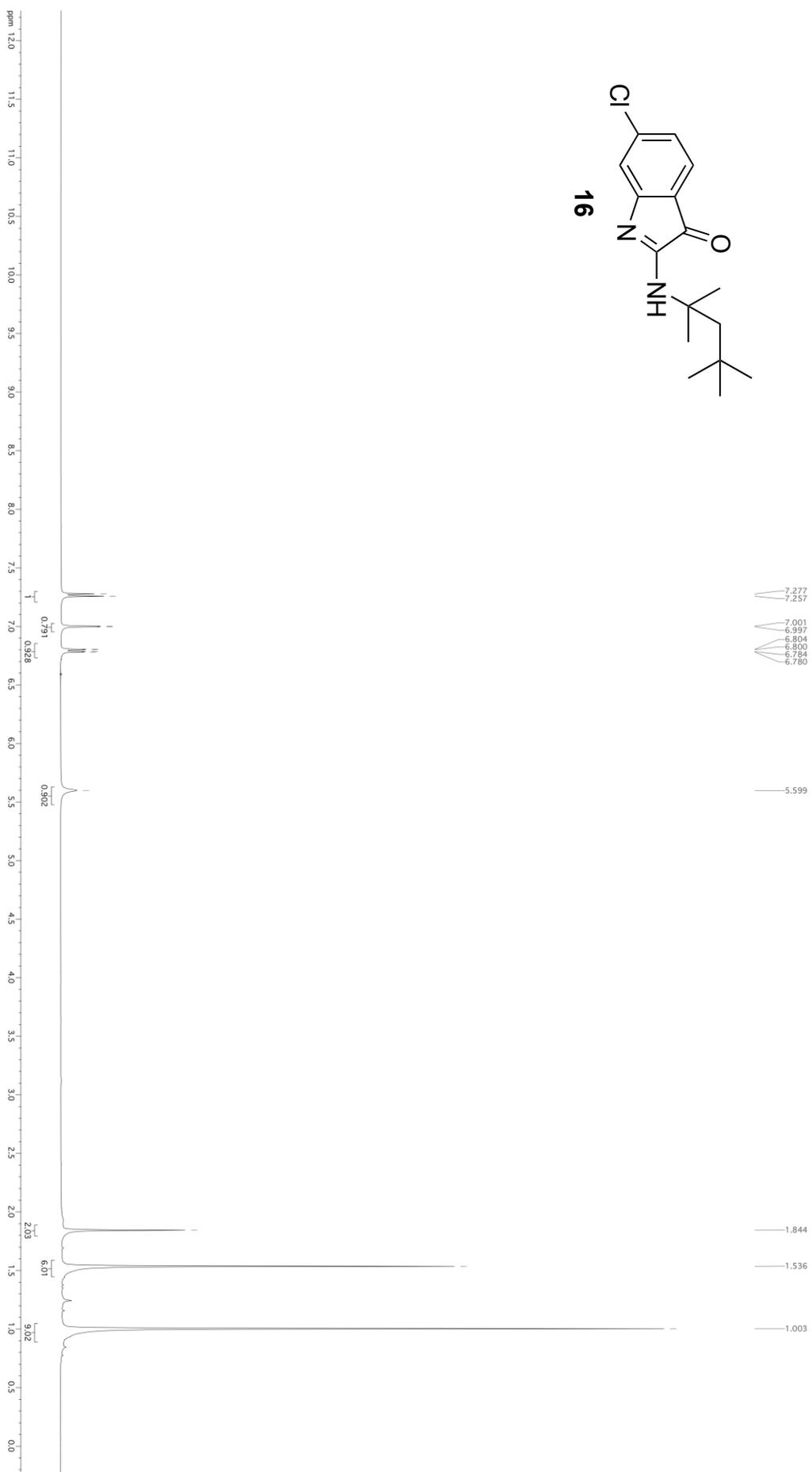
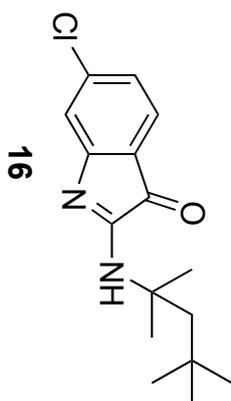
¹H NMR
400 MHz, CDCl₃



¹³C NMR
100 MHz, CDCl₃

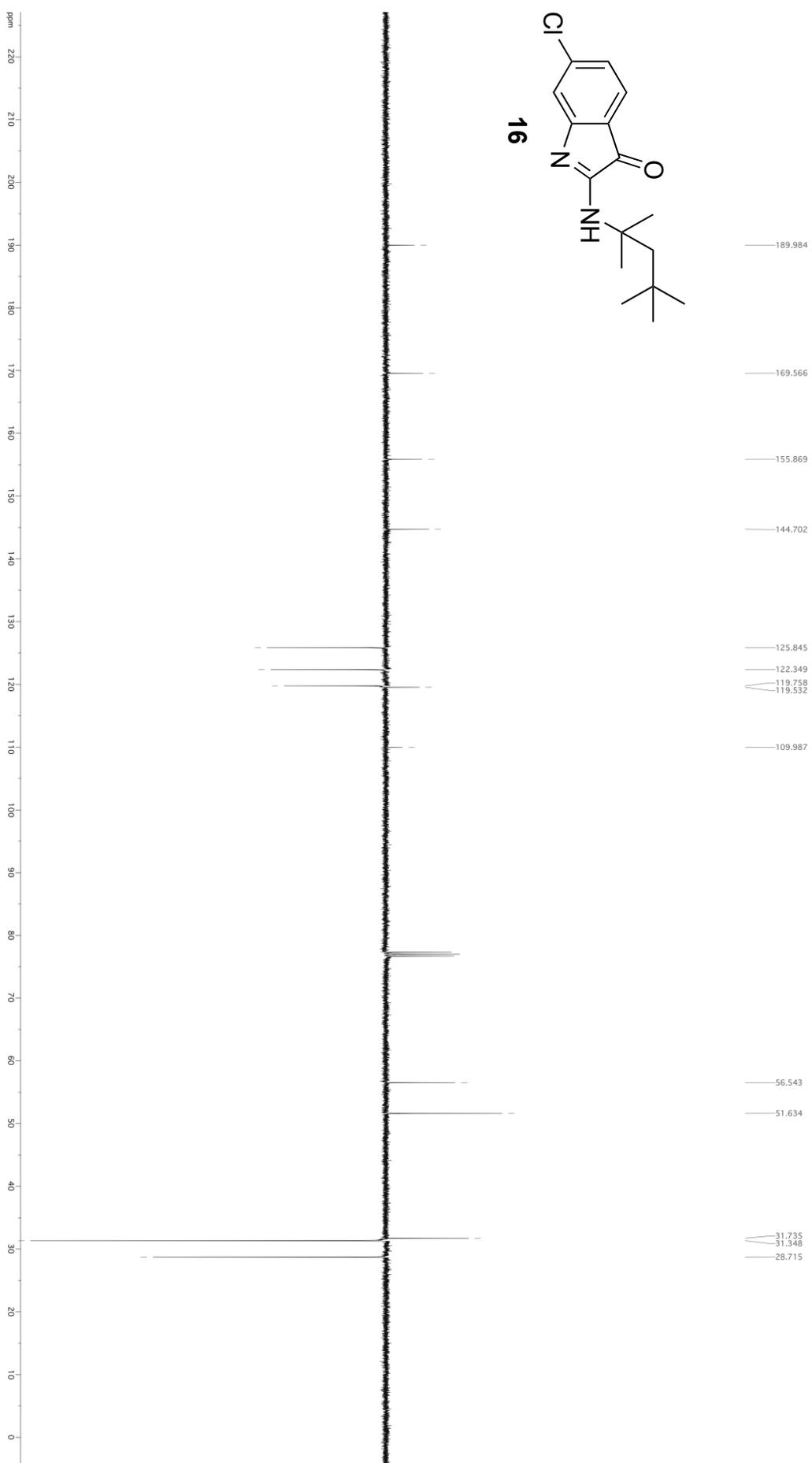
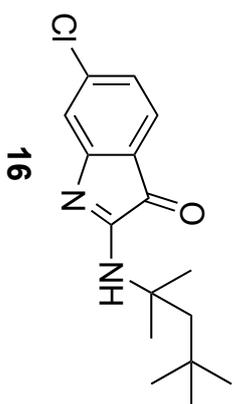


¹H NMR
400 MHz, CDCl₃

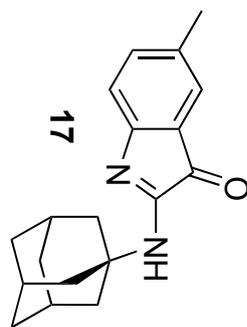


S15

¹³C NMR
100 MHz, CDCl₃



¹H NMR
400 MHz, CDCl₃

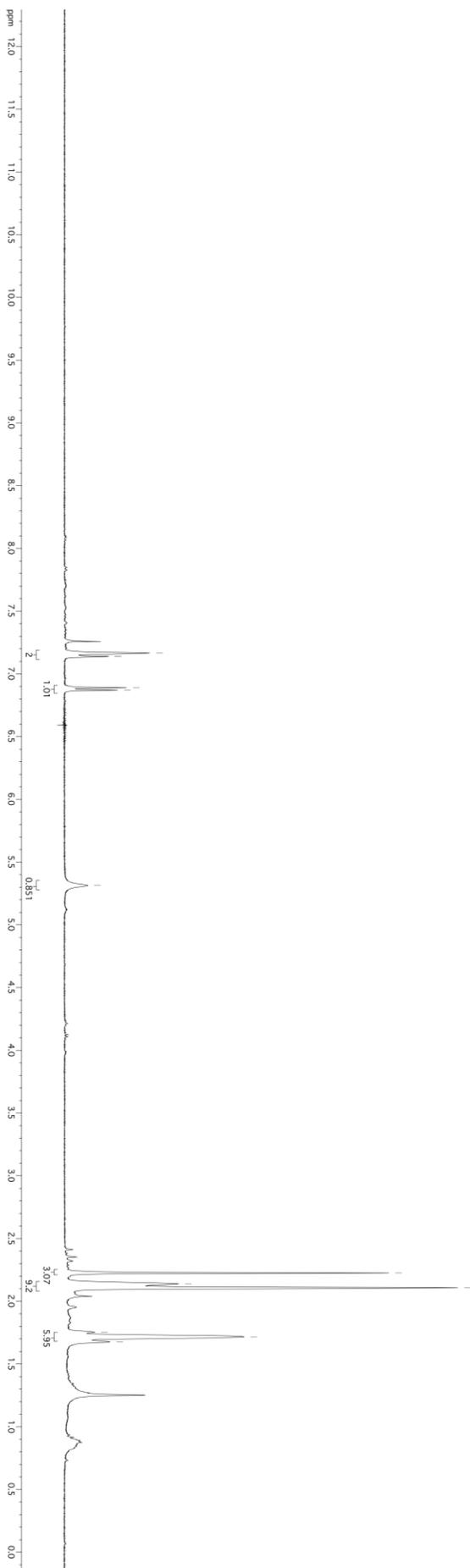


7.166
7.140
7.139
6.890
6.870

5.315

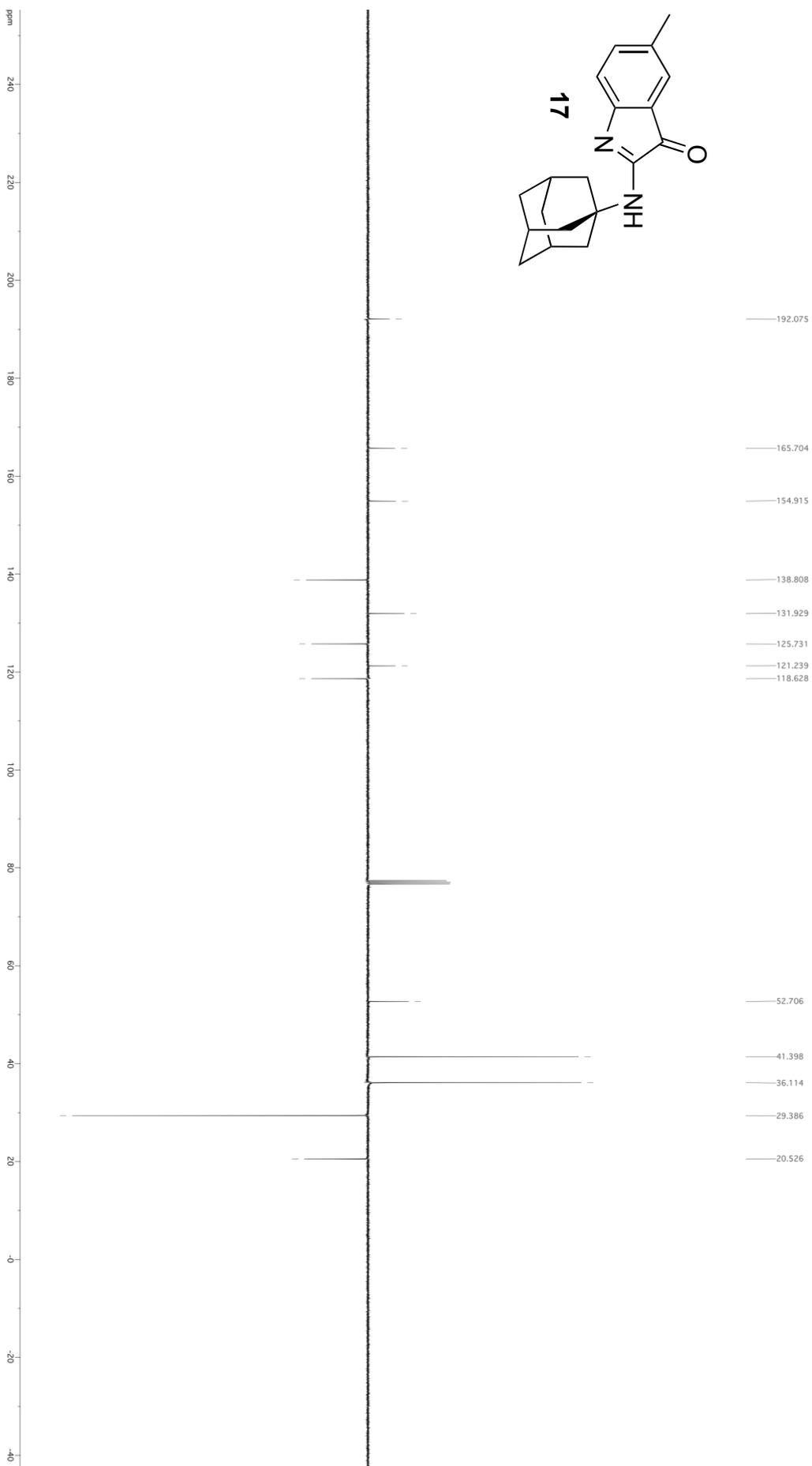
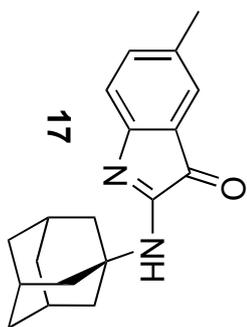
2.225
2.138
2.109

1.754
1.717
1.677

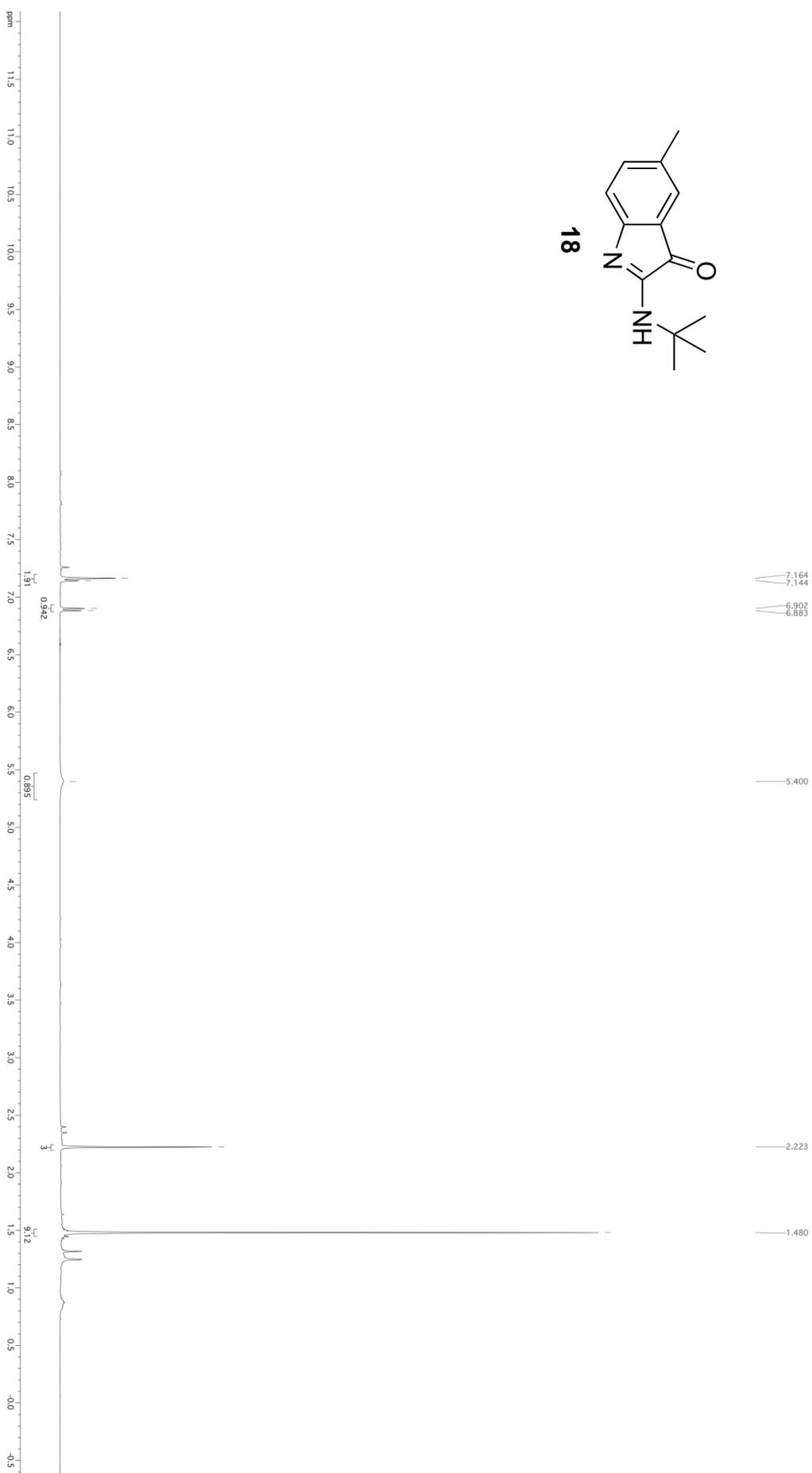
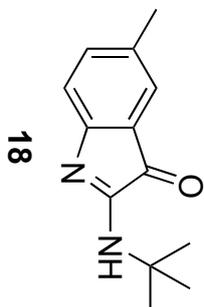


S17

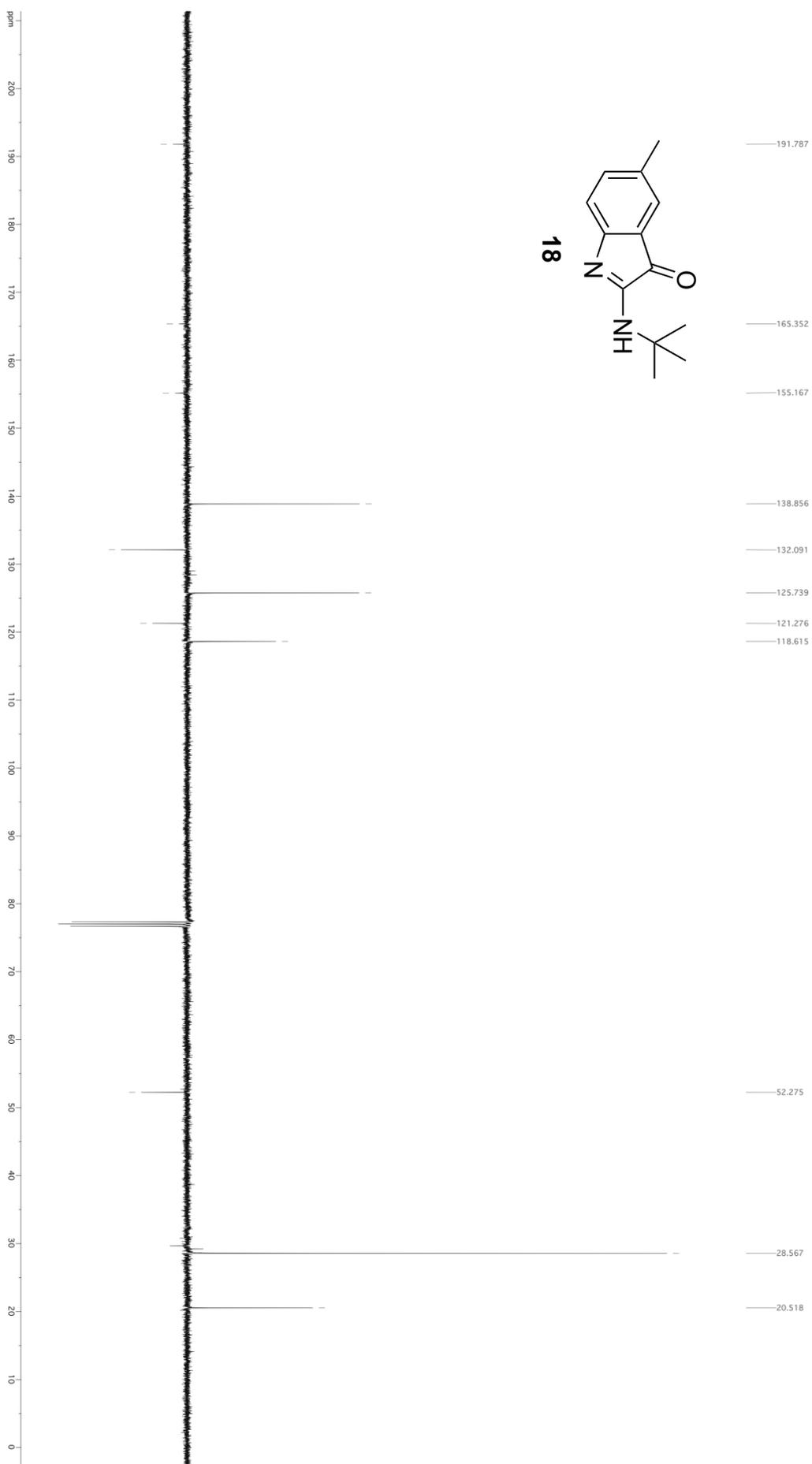
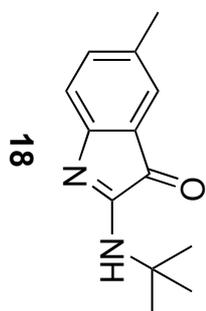
¹³C NMR
100 MHz, CDCl₃



¹H NMR
400 MHz, CDCl₃

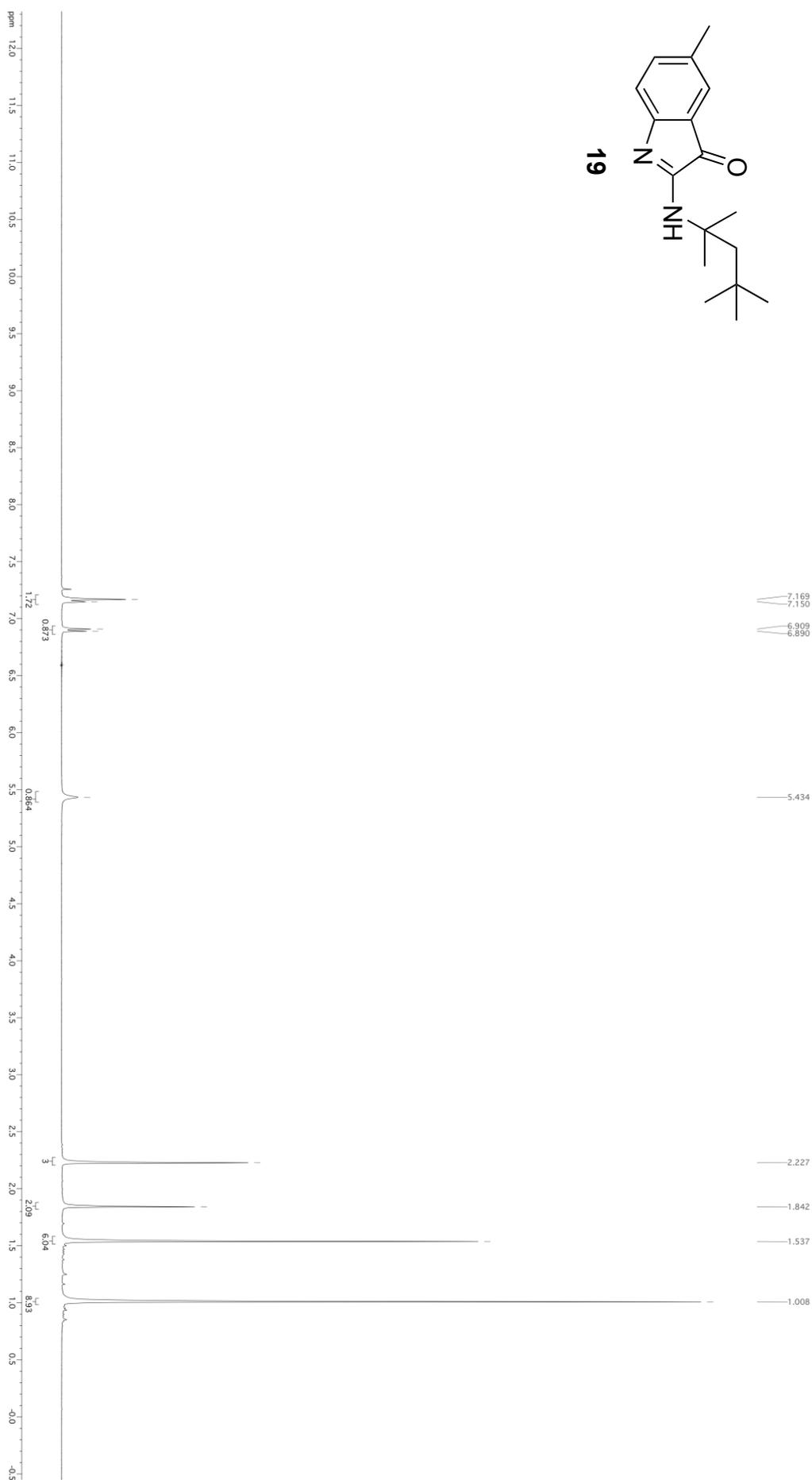
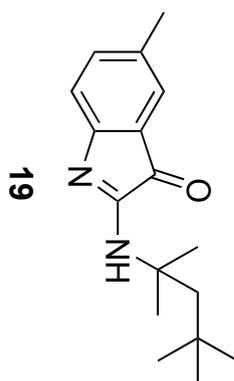


¹³C NMR
100 MHz, CDCl₃

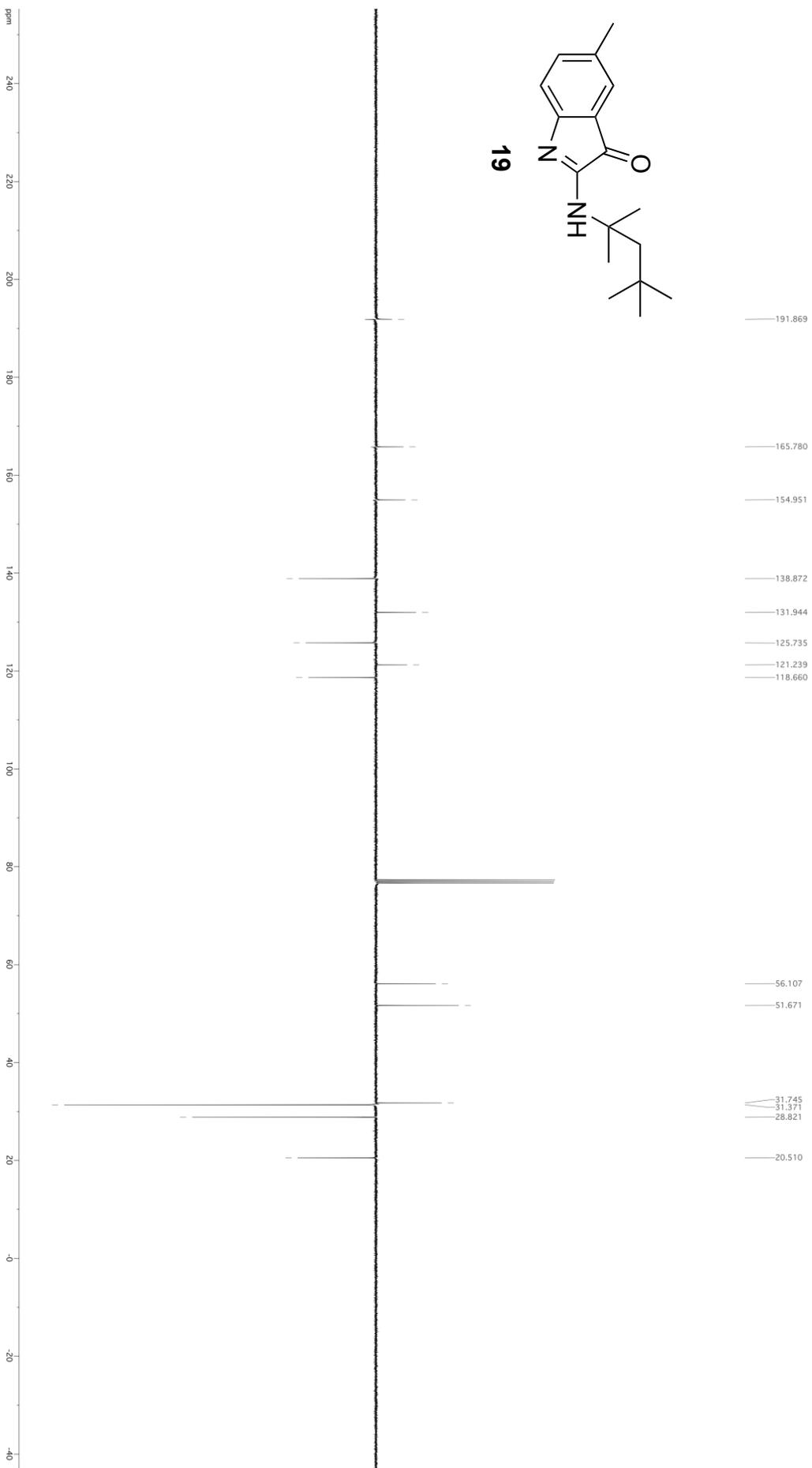
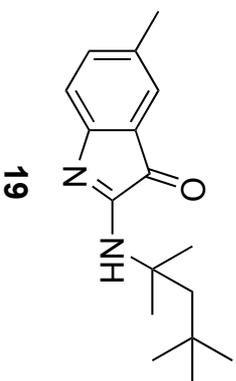


S20

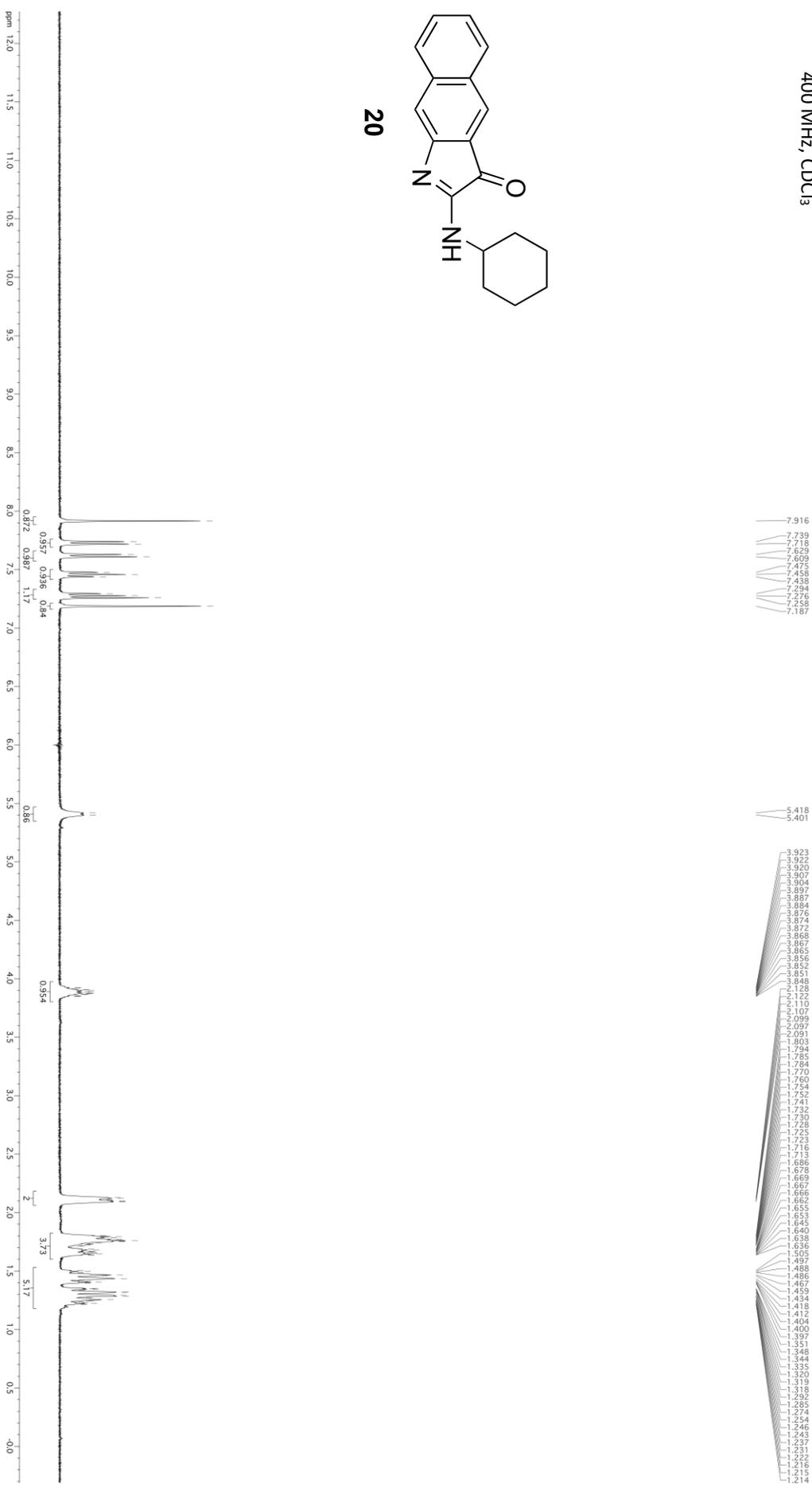
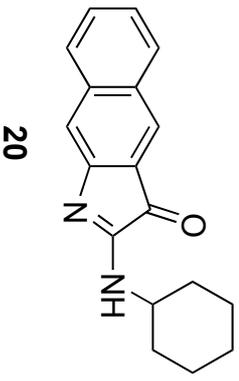
¹H NMR
400 MHz, CDCl₃



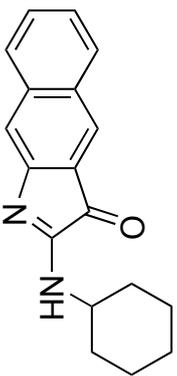
¹³C NMR
100 MHz, CDCl₃



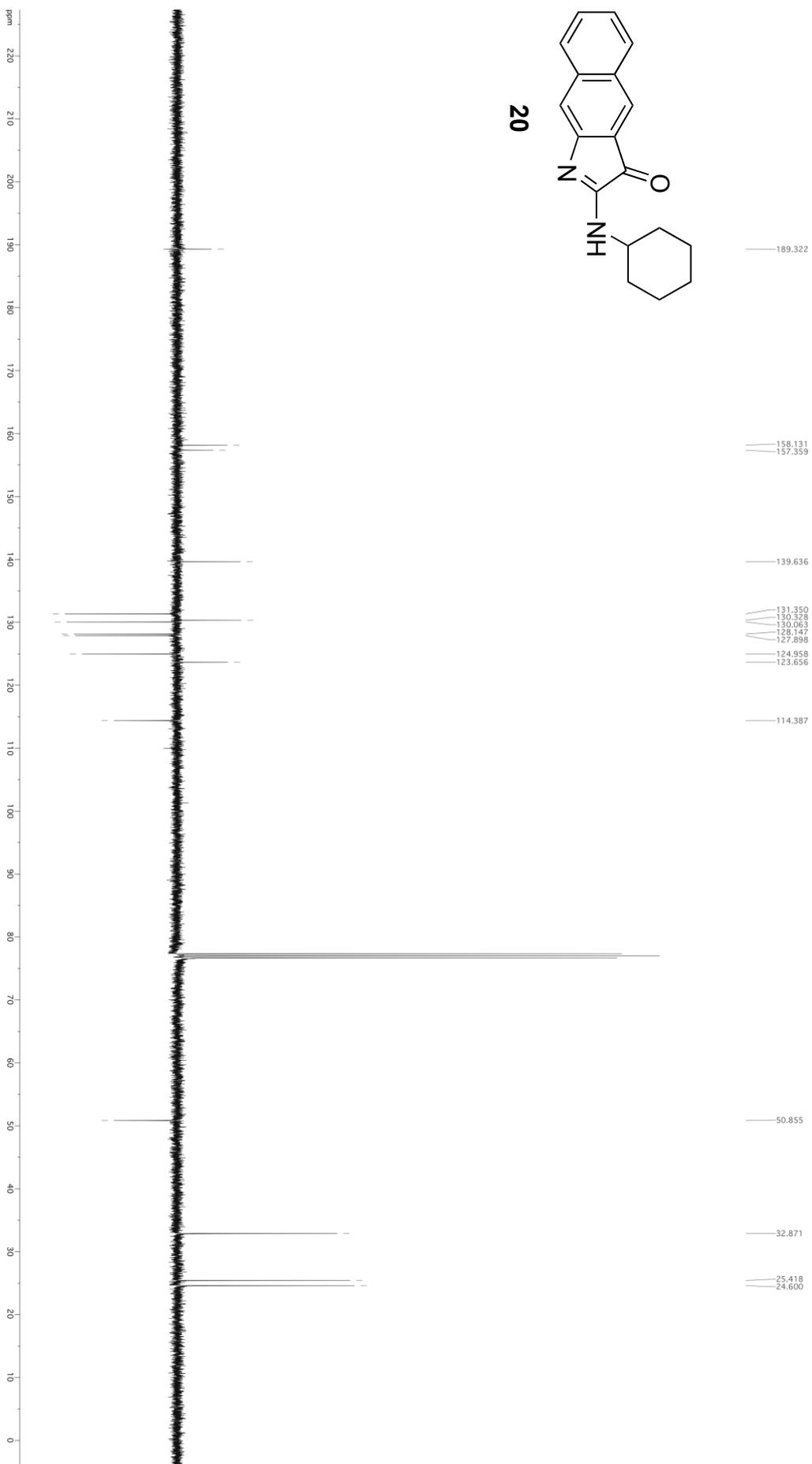
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¹³C NMR
100 MHz, CDCl₃

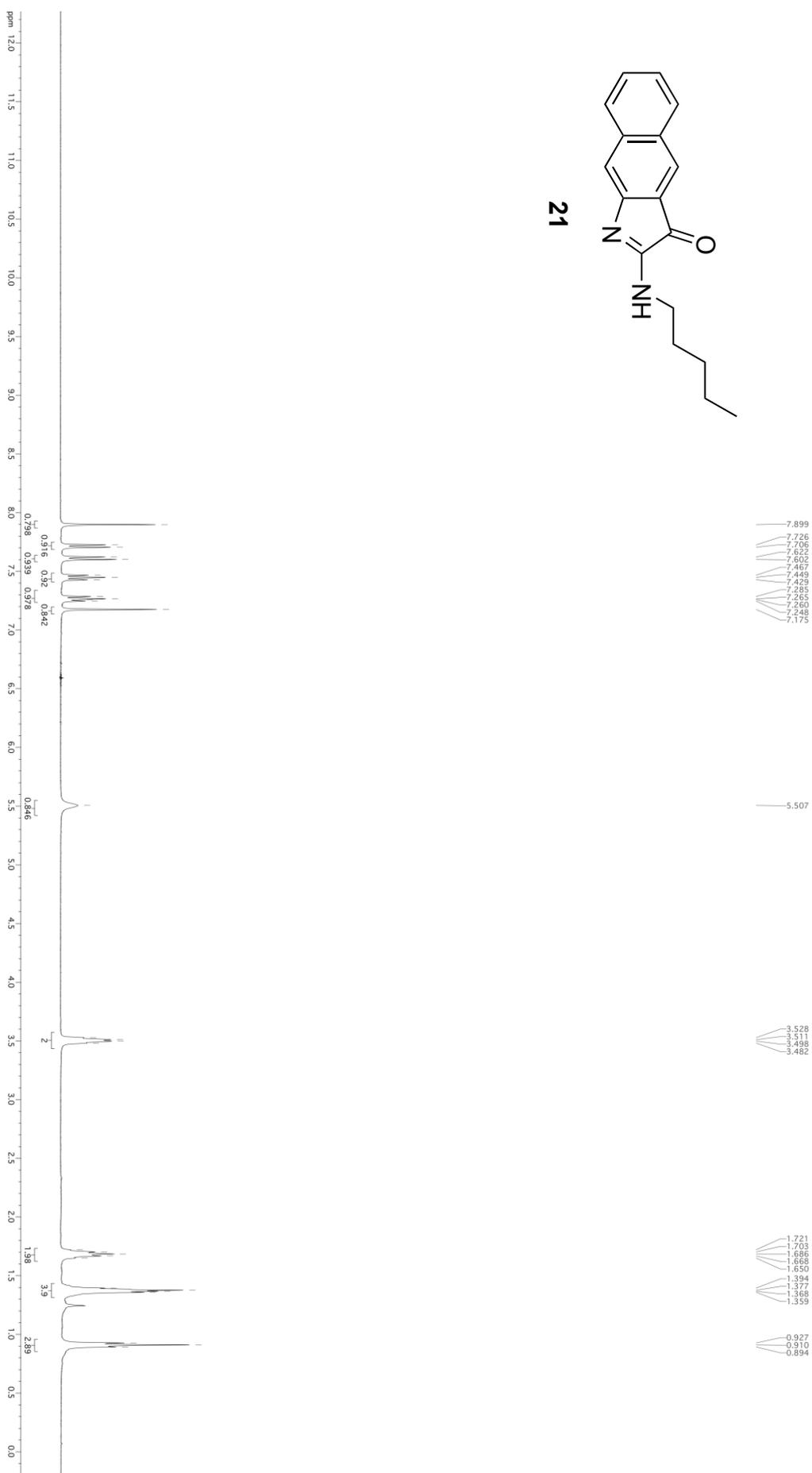
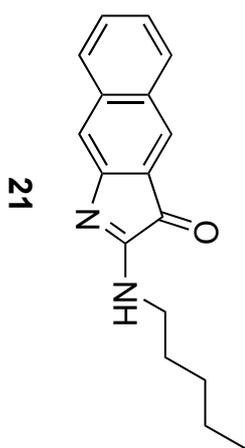


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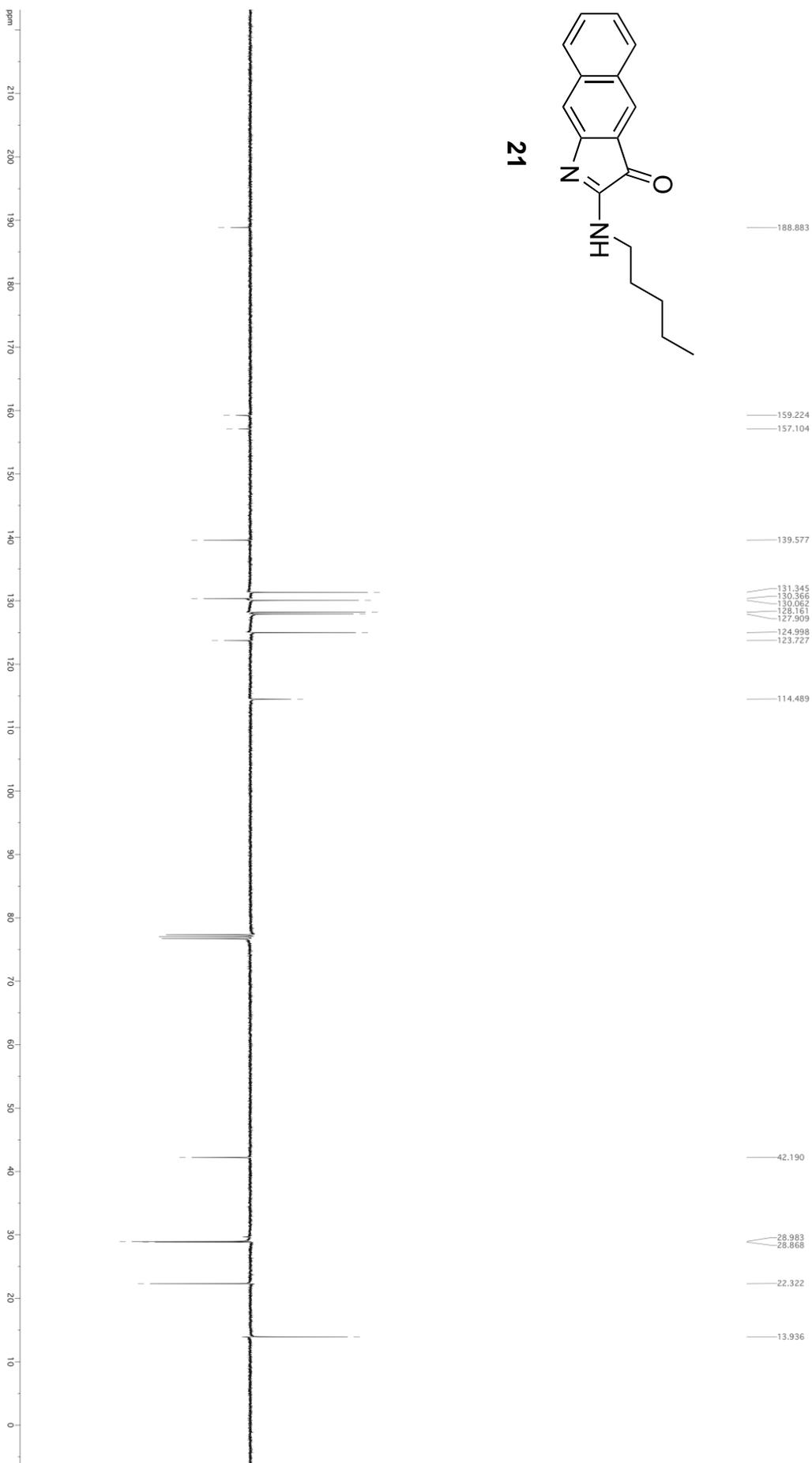
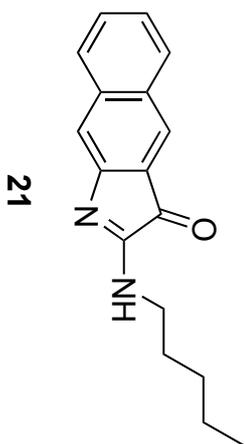


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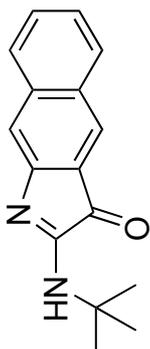
¹H NMR
400 MHz, CDCl₃



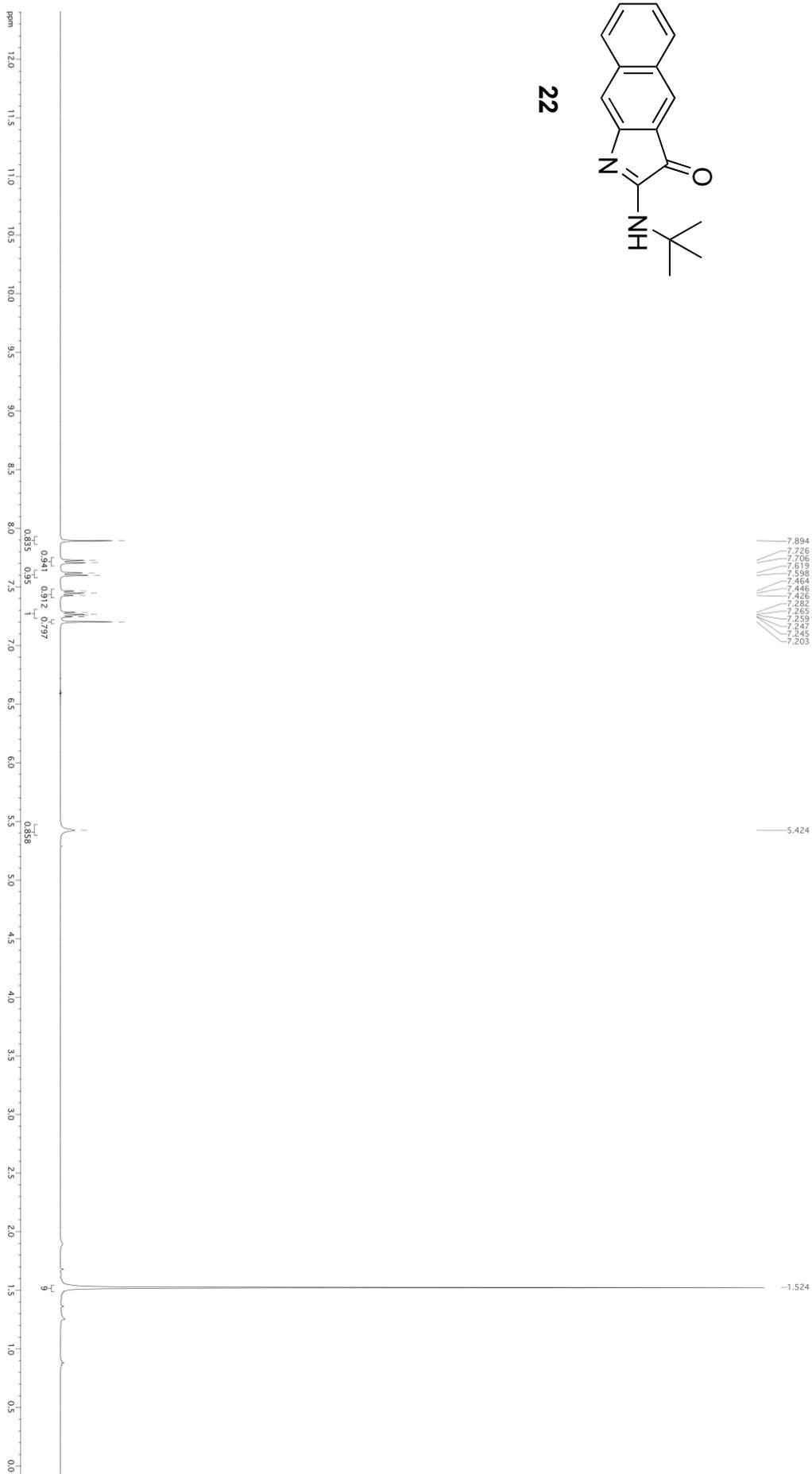
¹³C NMR
100 MHz, CDCl₃



¹H NMR
400 MHz, CDCl₃

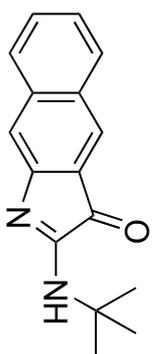


22

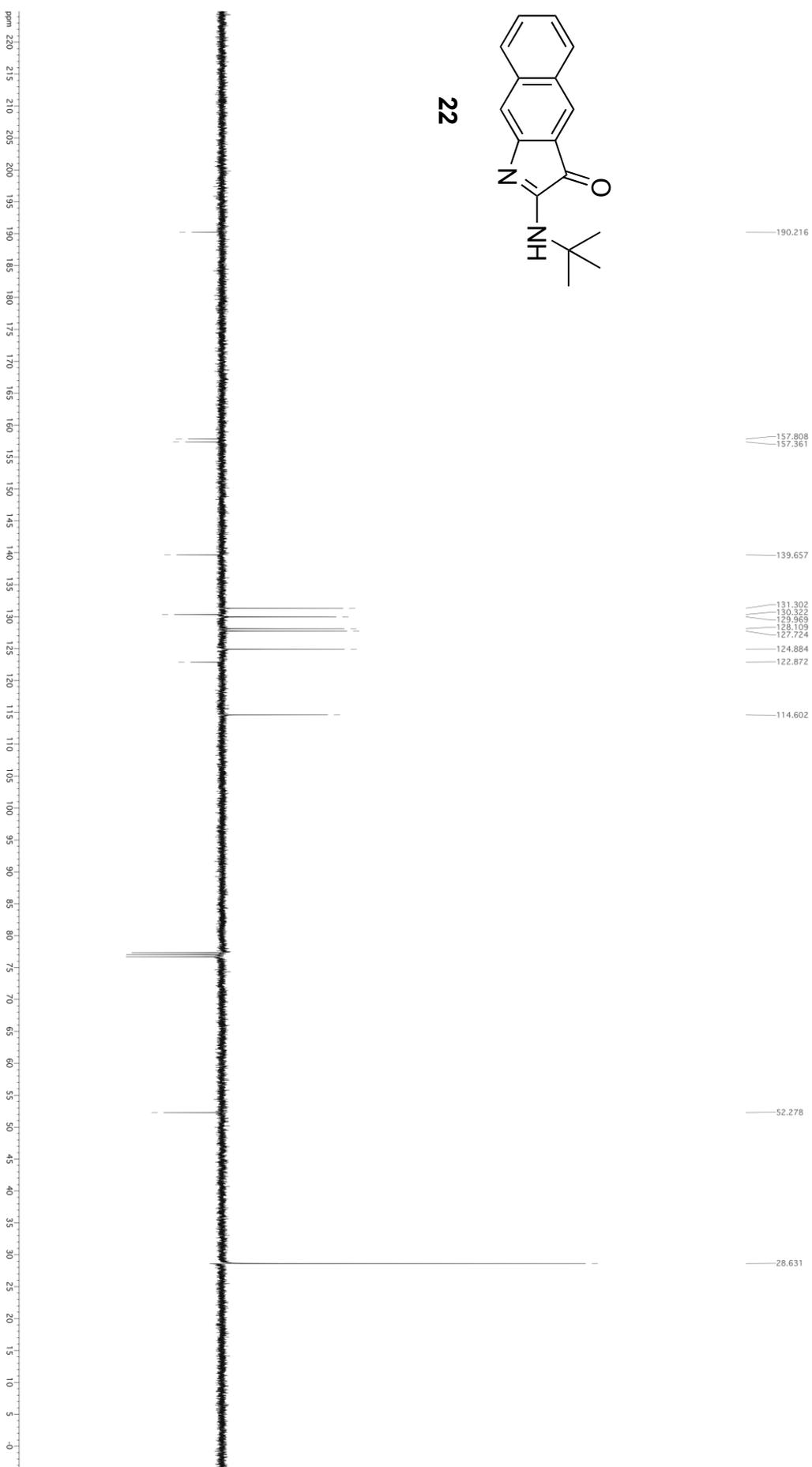


S27

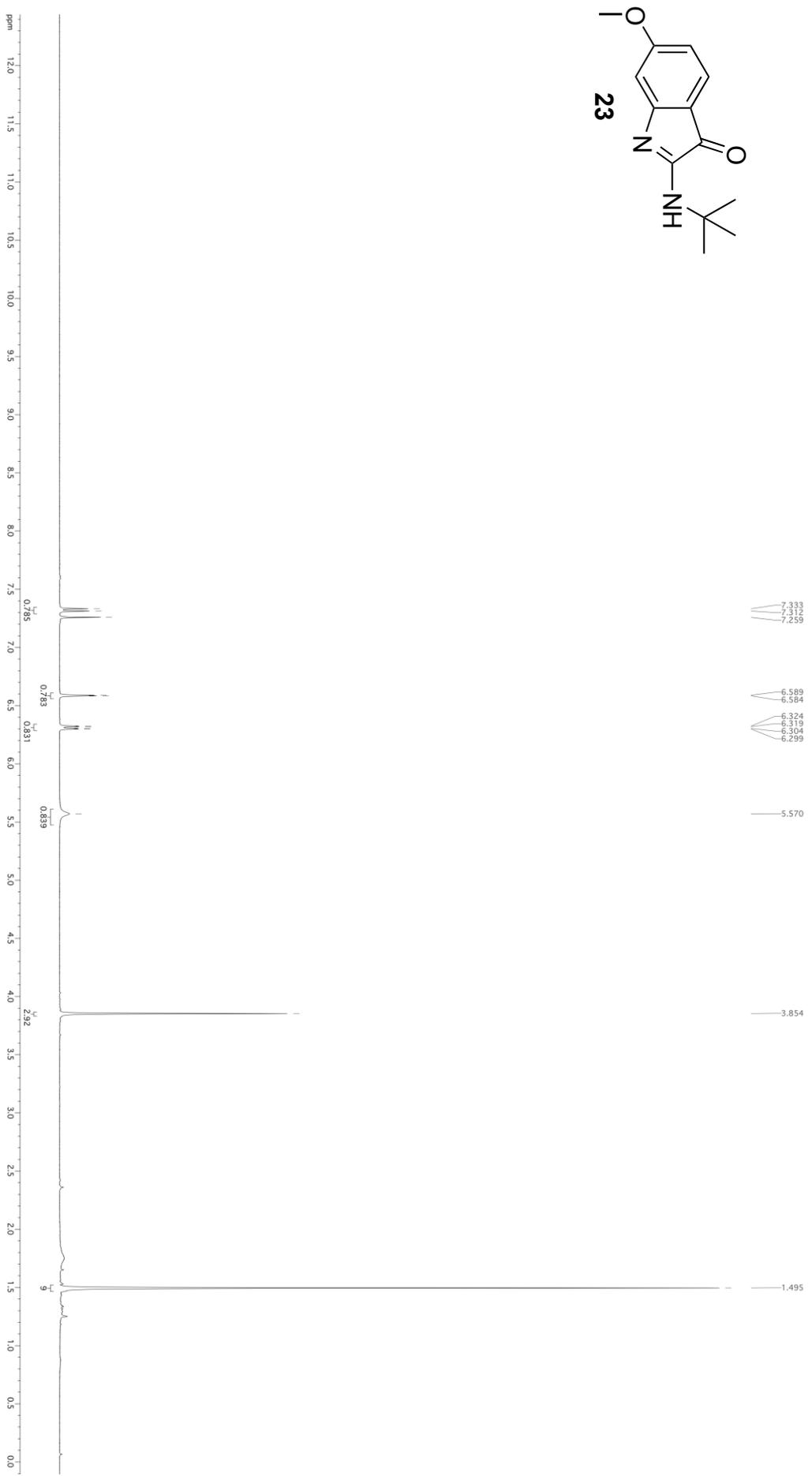
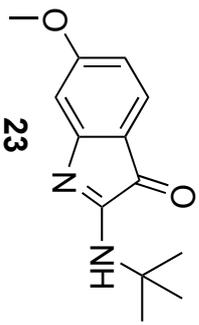
¹³C NMR
100 MHz, CDCl₃



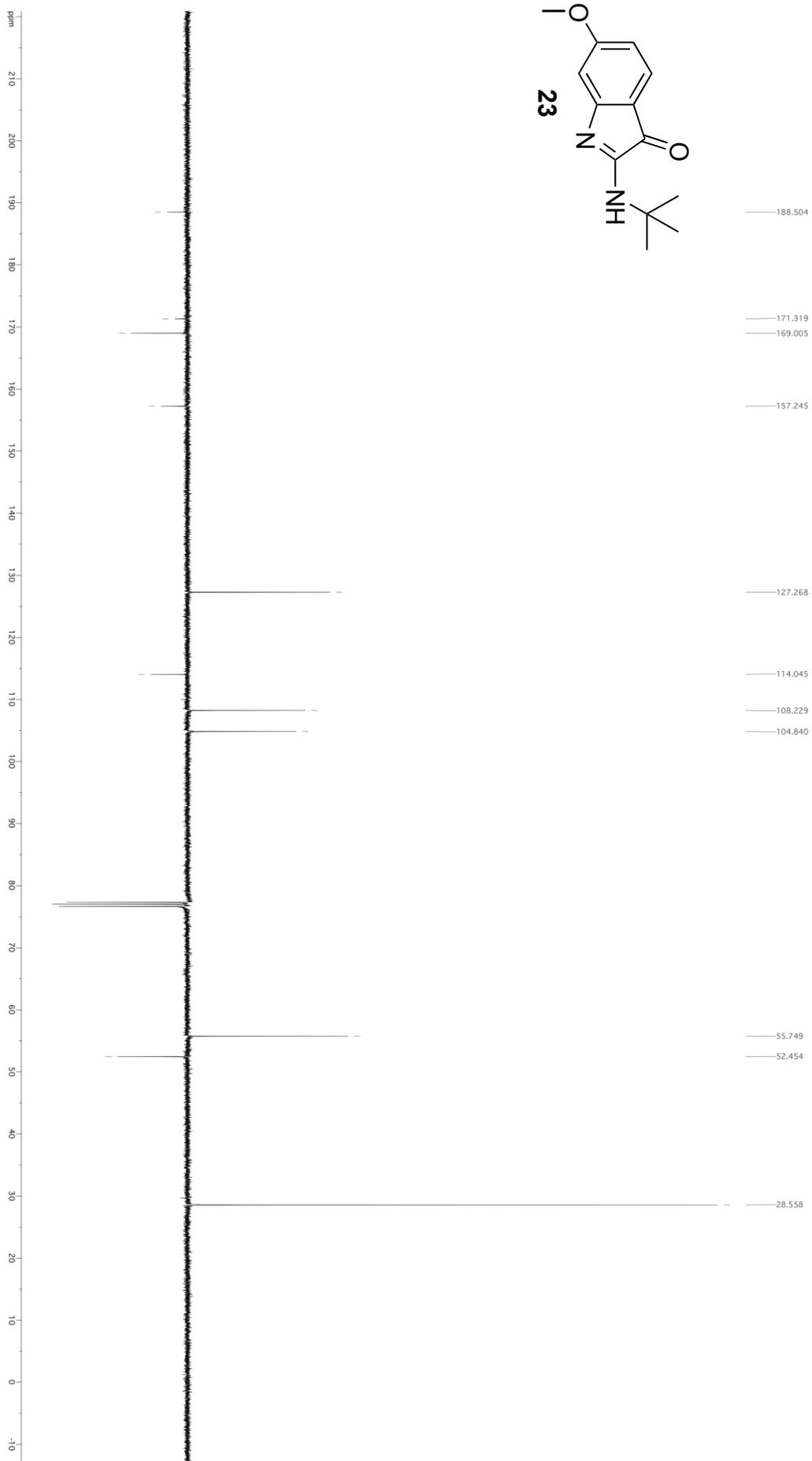
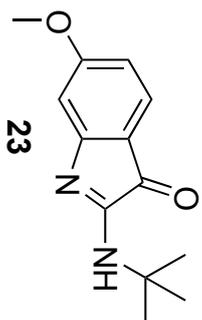
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¹H NMR
400 MHz, CDCl₃

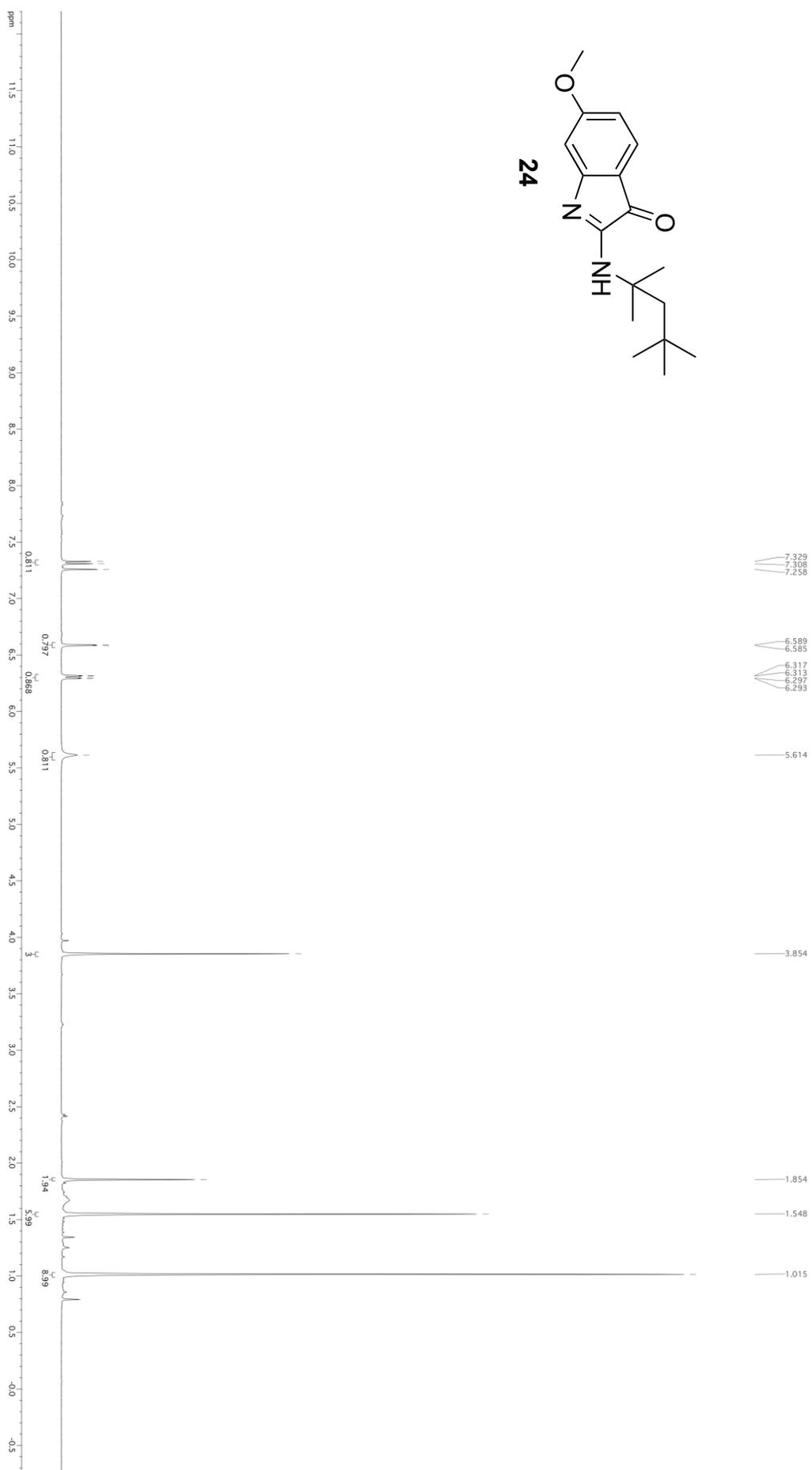
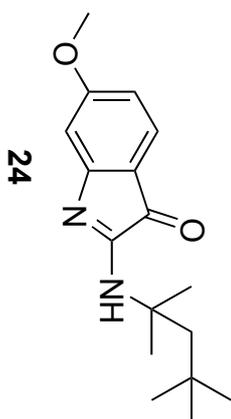


¹³C NMR
100 MHz, CDCl₃



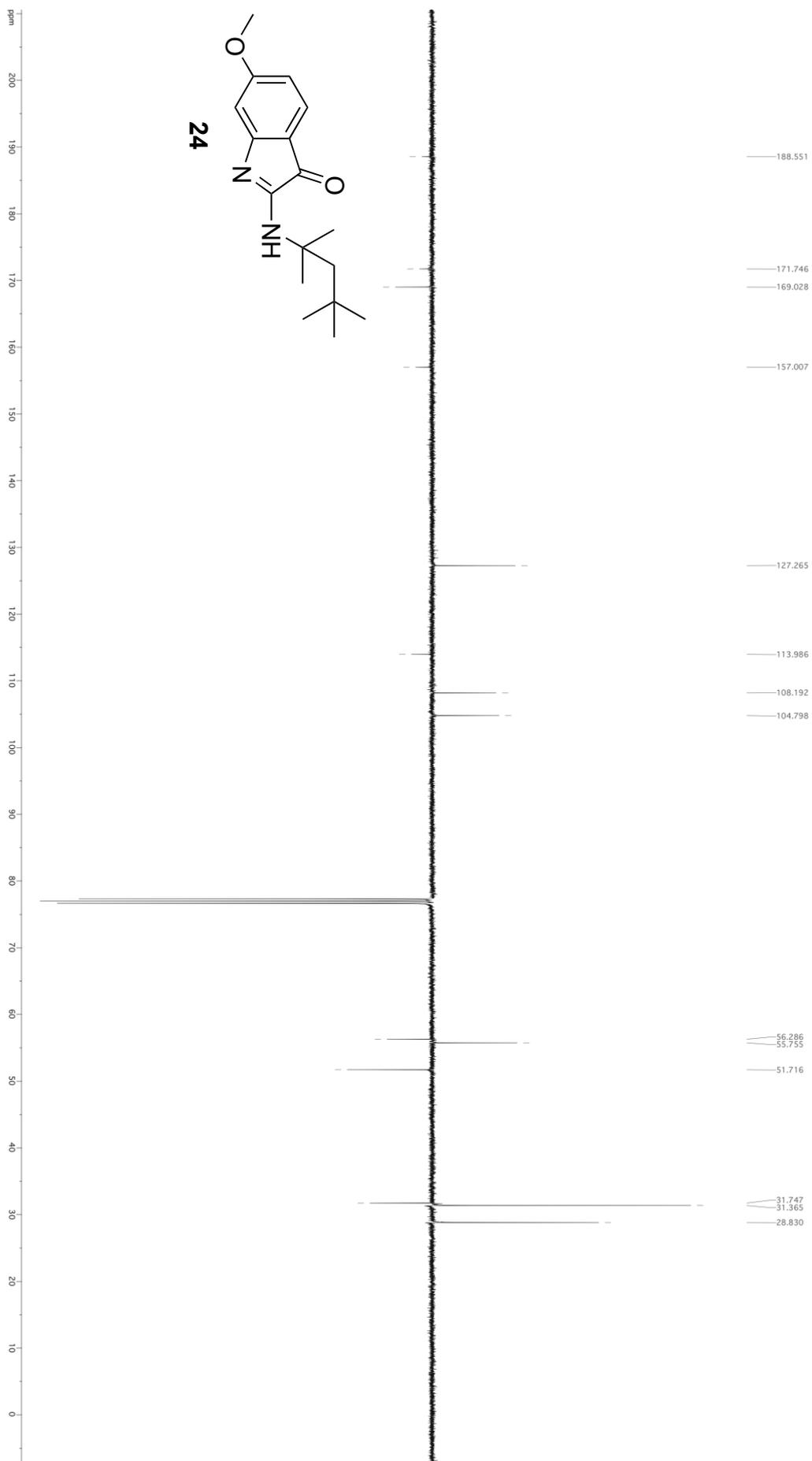
S30

¹H NMR
400 MHz, CDCl₃

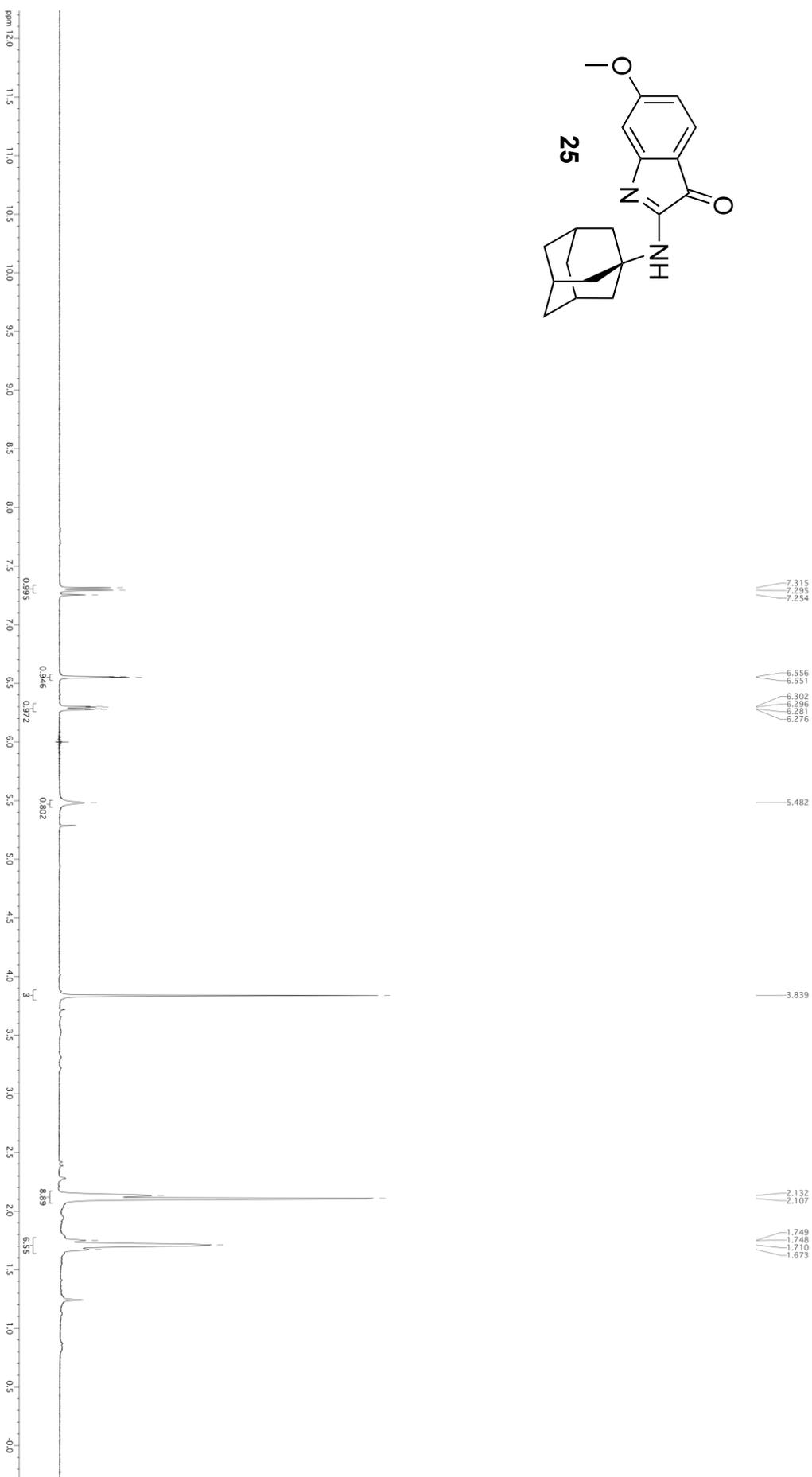
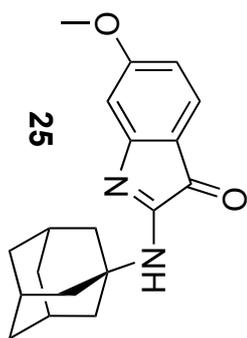


S31

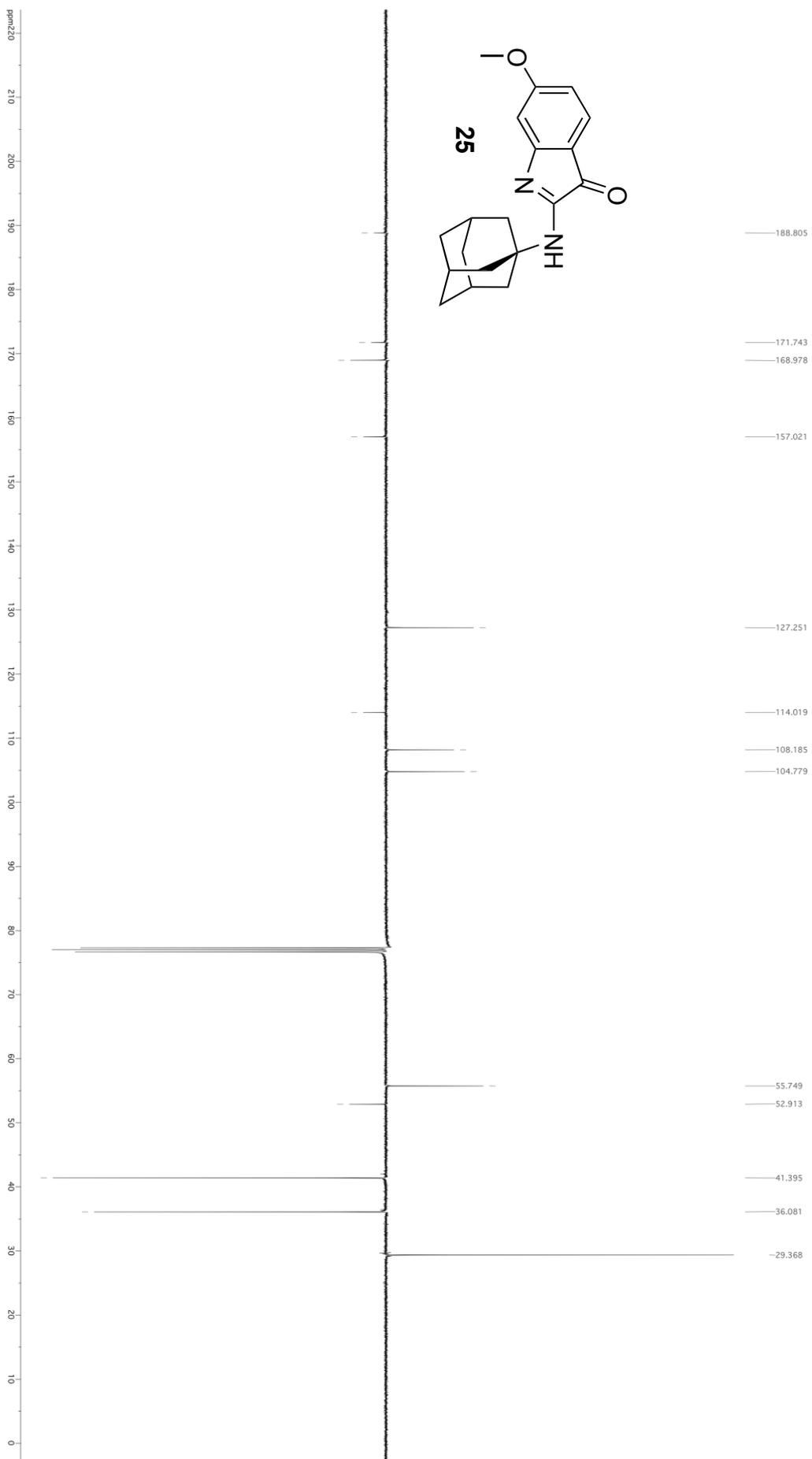
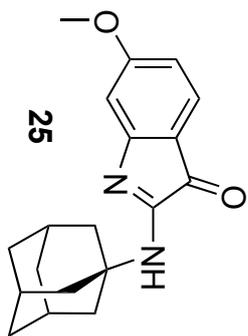
¹³C NMR
100 MHz, CDCl₃



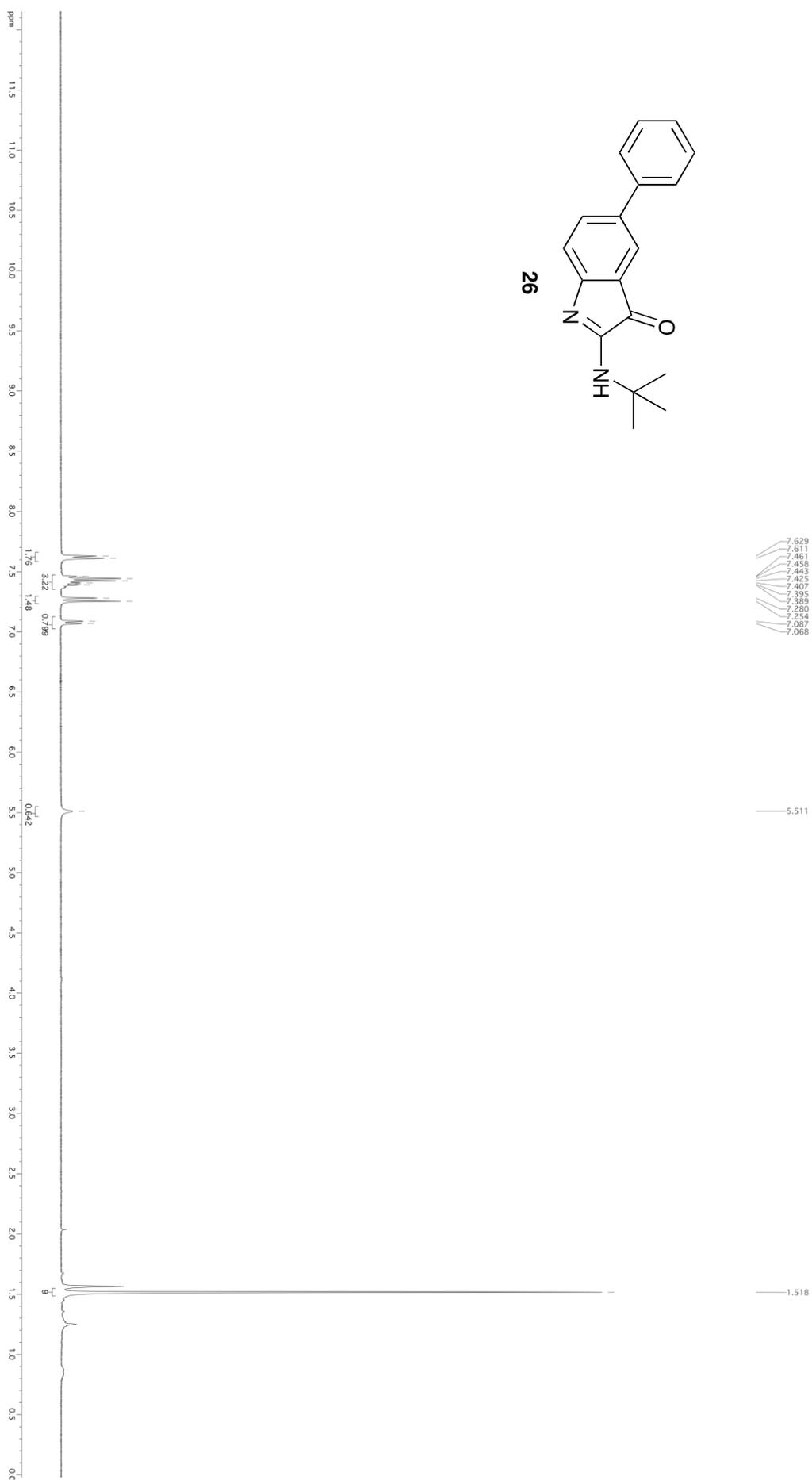
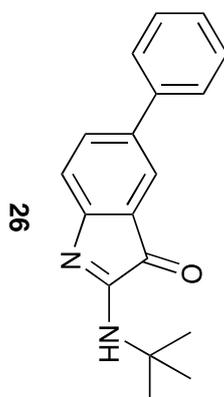
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400 MHz, CDCl₃



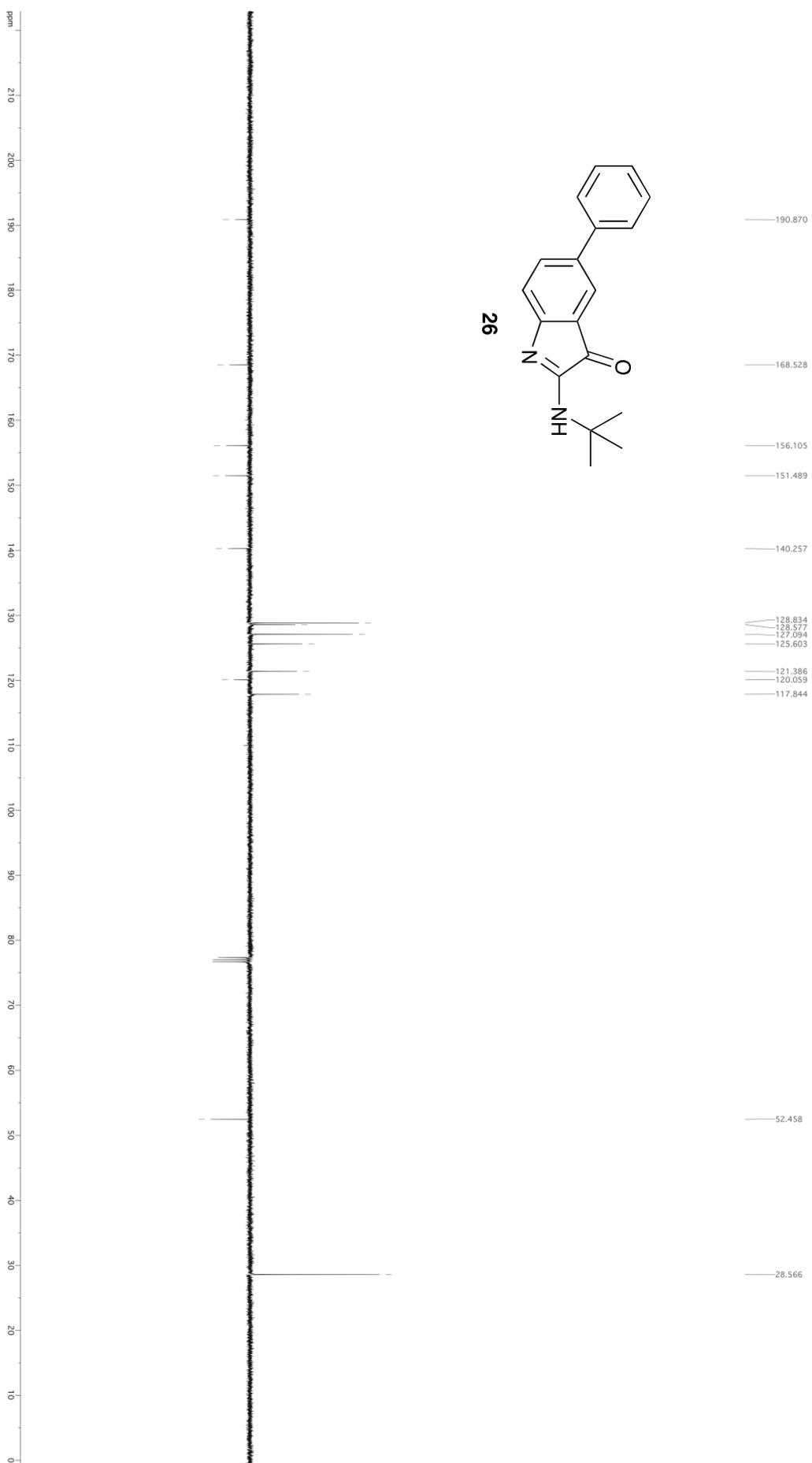
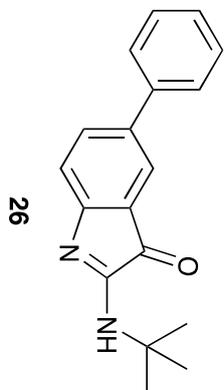
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100 MHz, CDCl₃



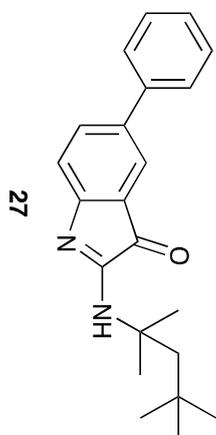
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400 MHz, CDCl₃



¹³C NMR
100 MHz, CDCl₃



¹H NMR
400 MHz, CDCl₃



7.633
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7.445
7.424
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7.266
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7.061

5.557

1.882

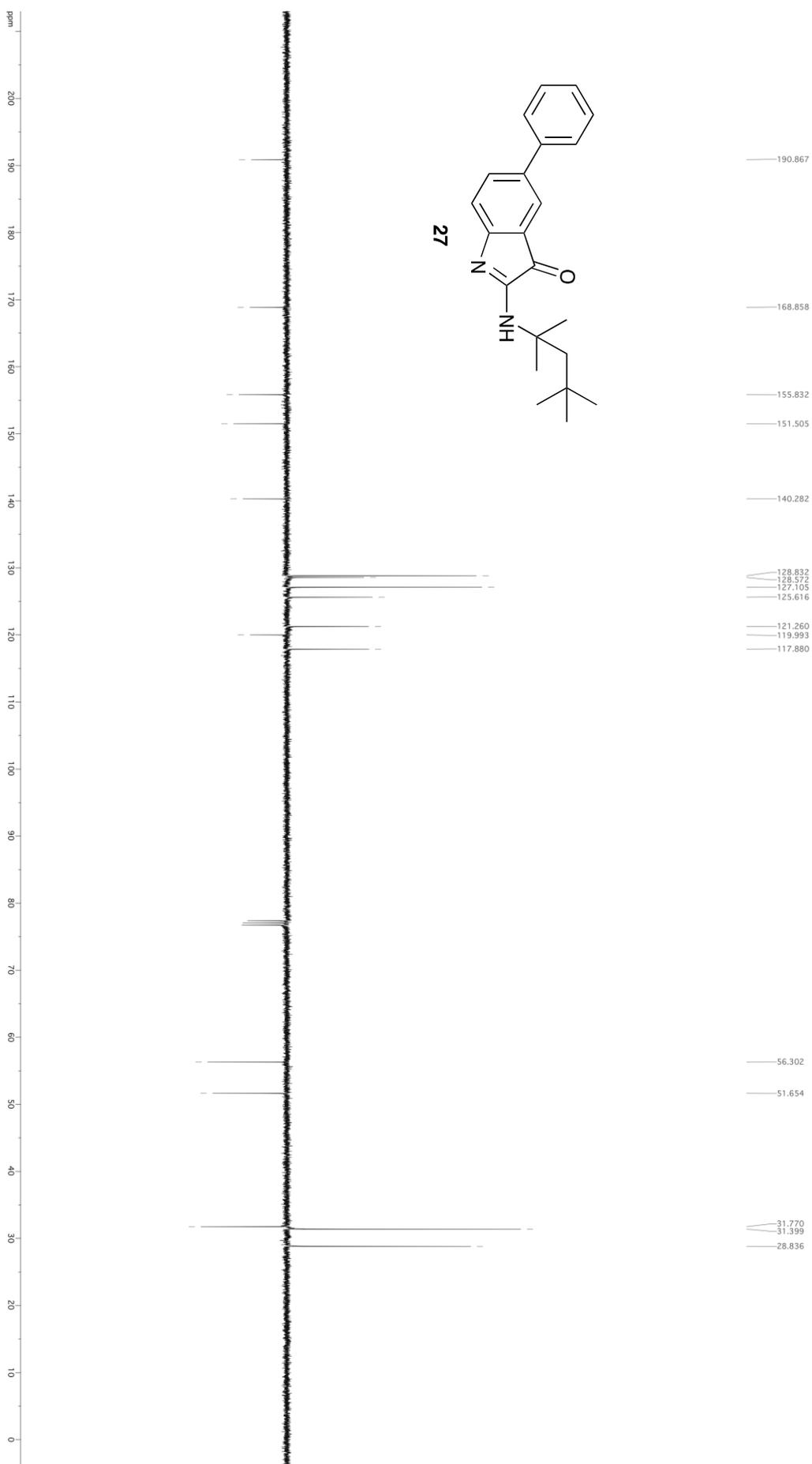
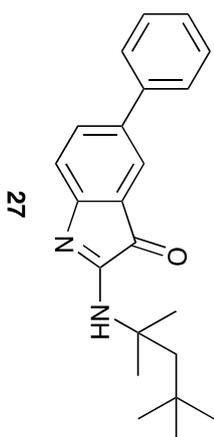
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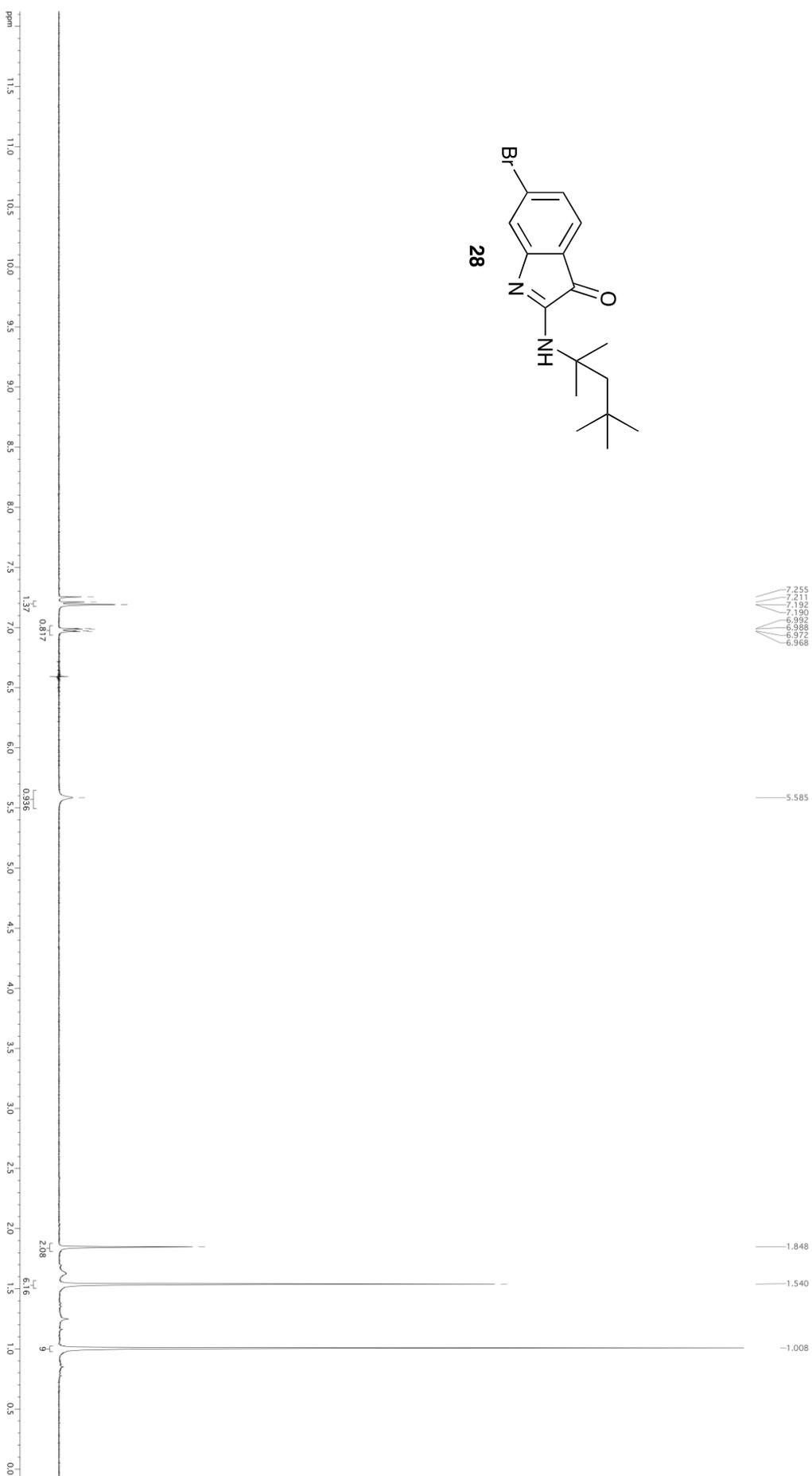
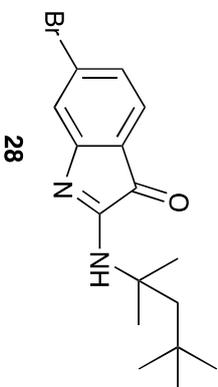


S37

¹³C NMR
100 MHz, CDCl₃

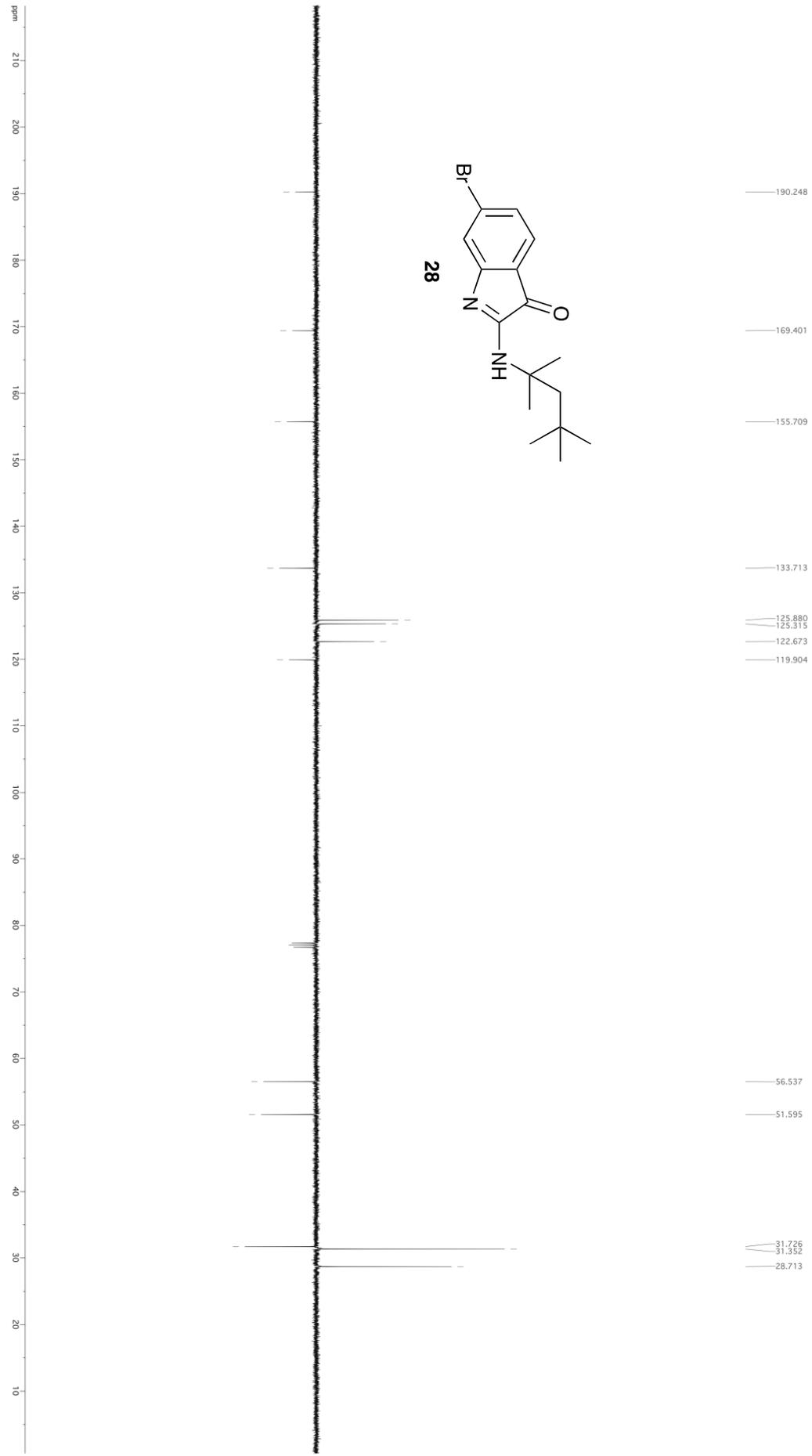
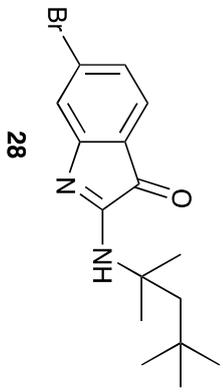


¹H NMR
400 MHz, CDCl₃

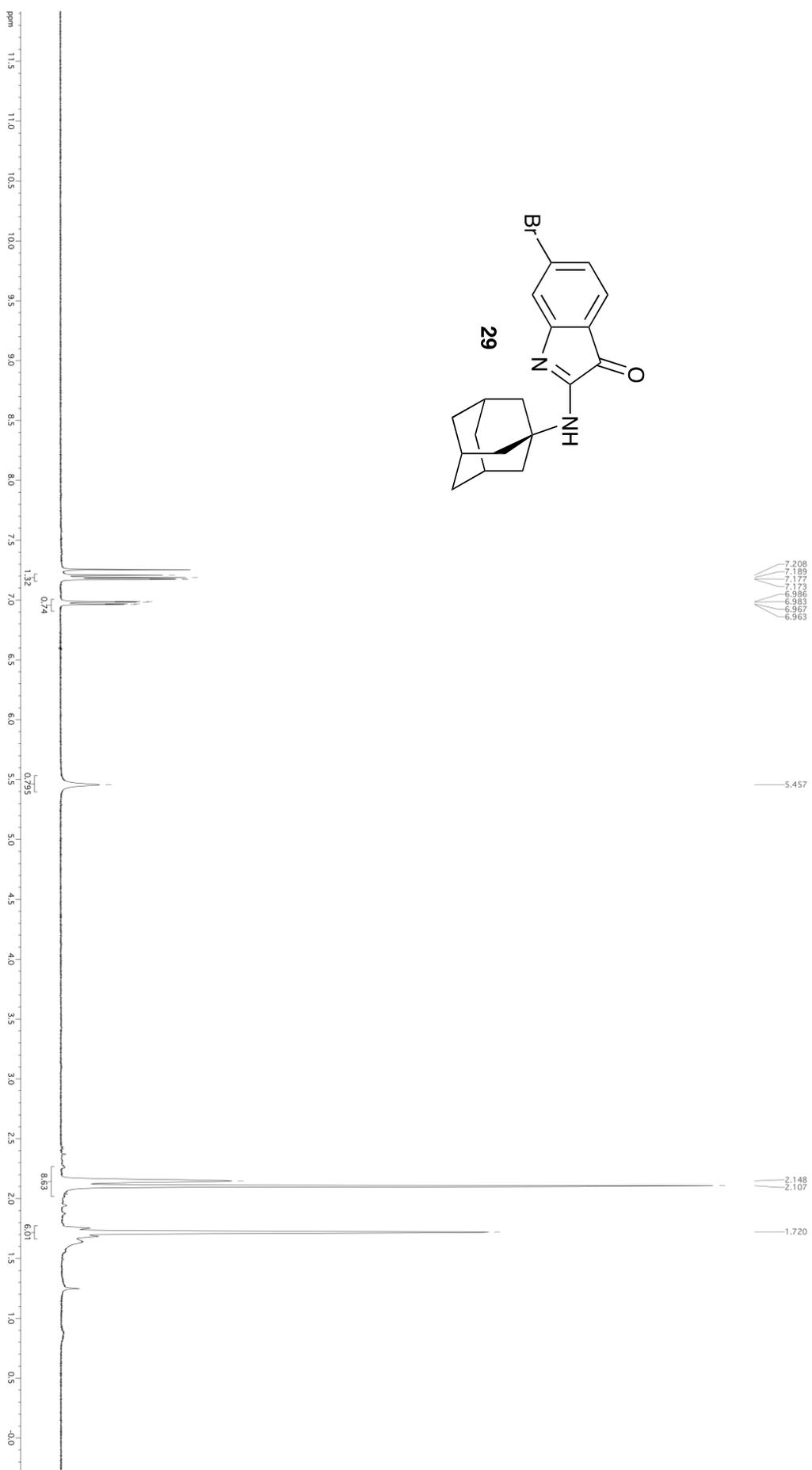
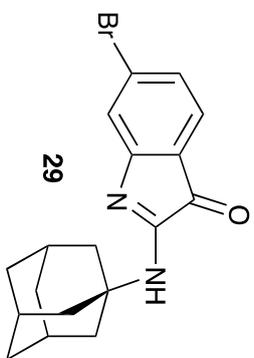


S39

¹³C NMR
100 MHz, CDCl₃

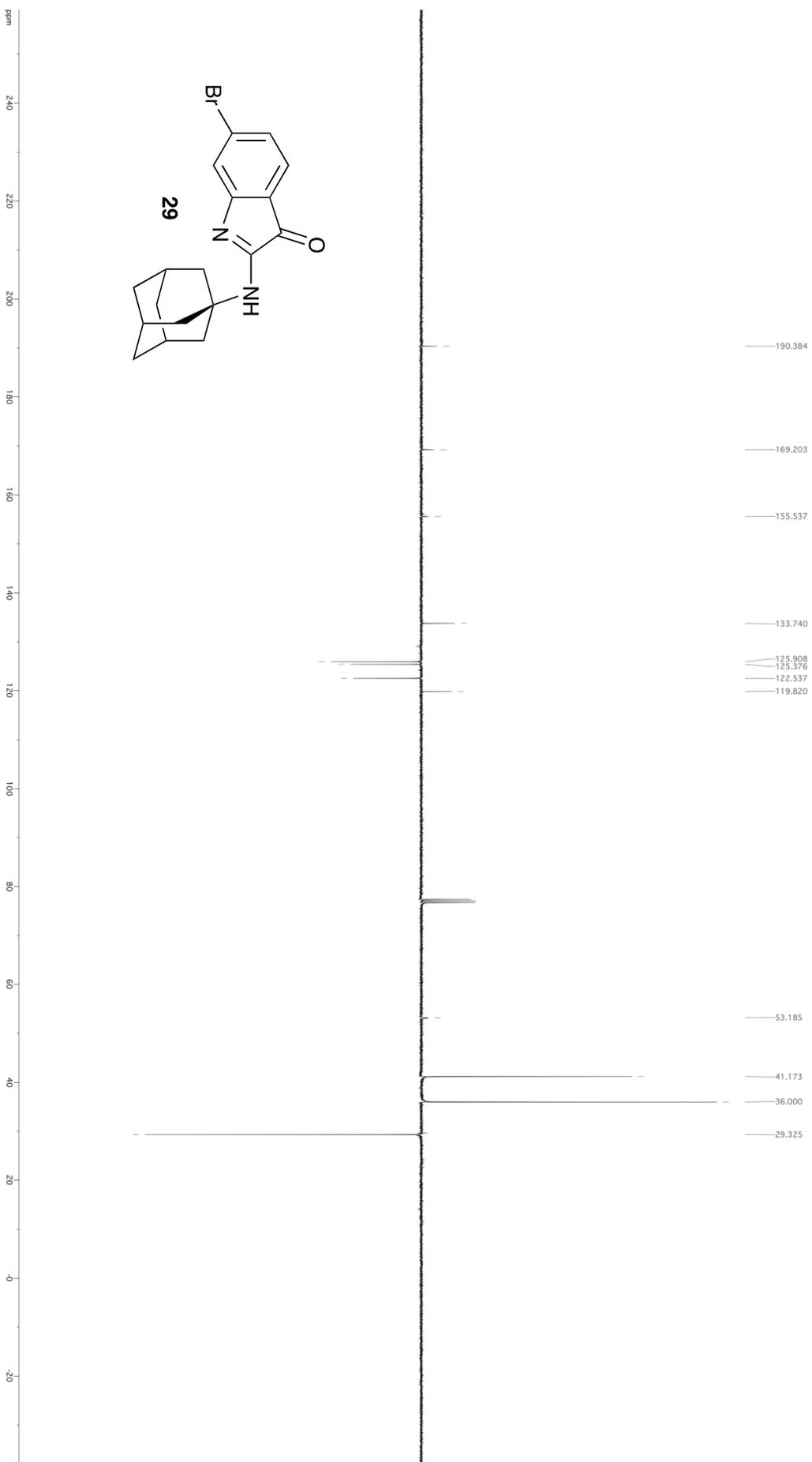
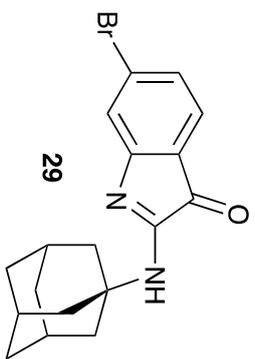


¹H NMR
400 MHz, CDCl₃

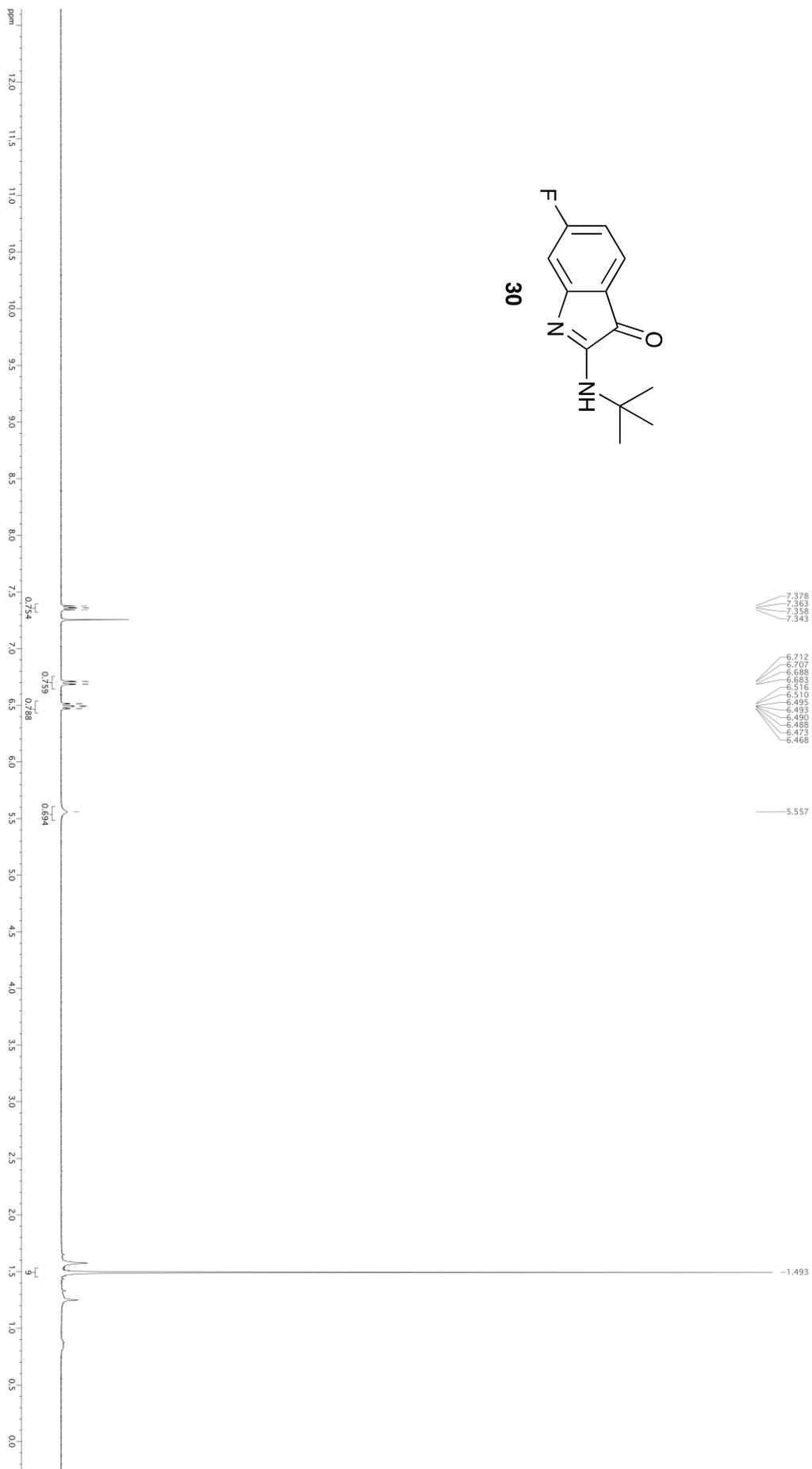
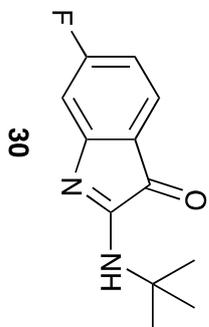


S41

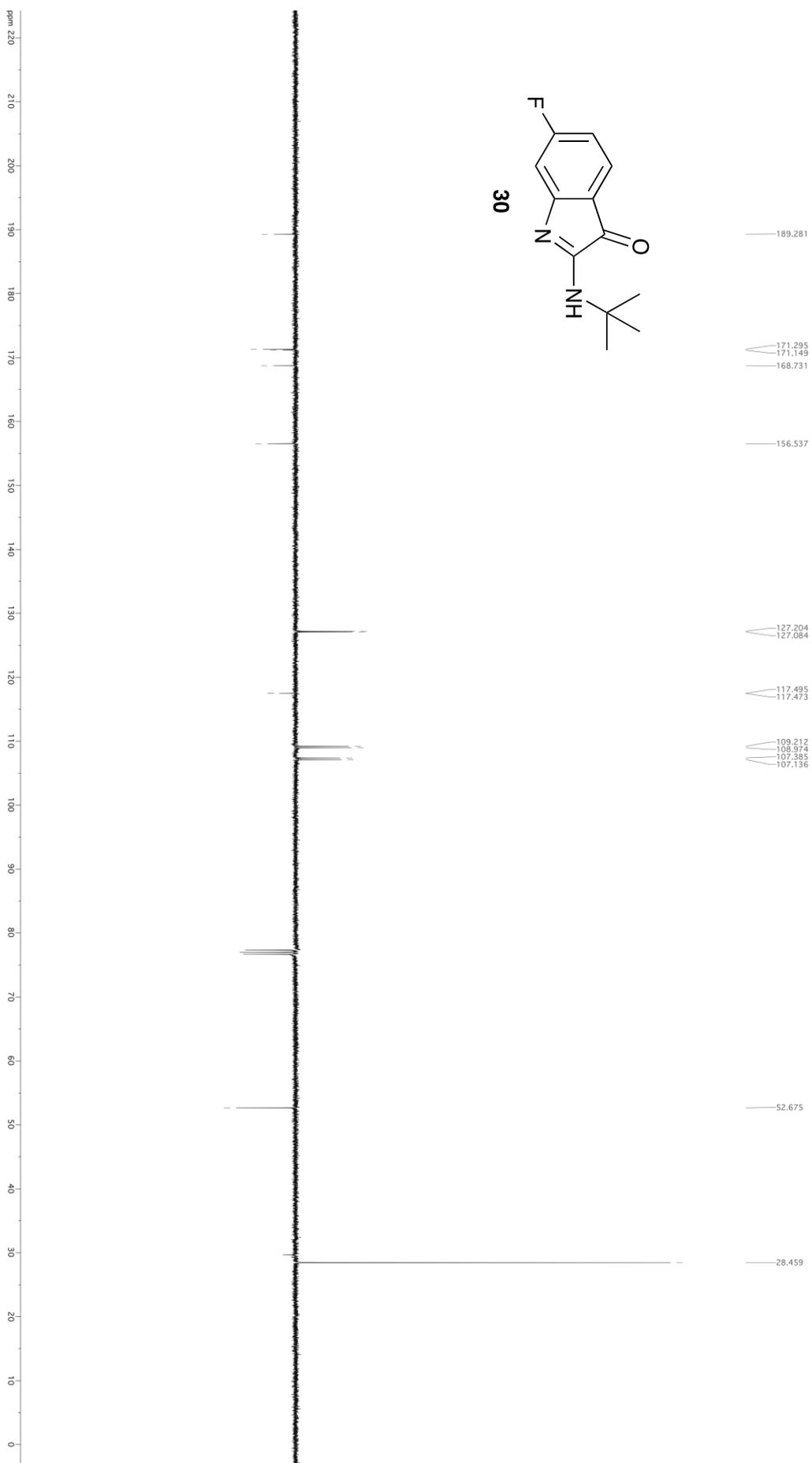
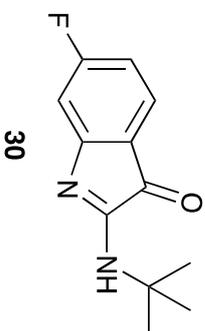
¹³C NMR
100 MHz, CDCl₃



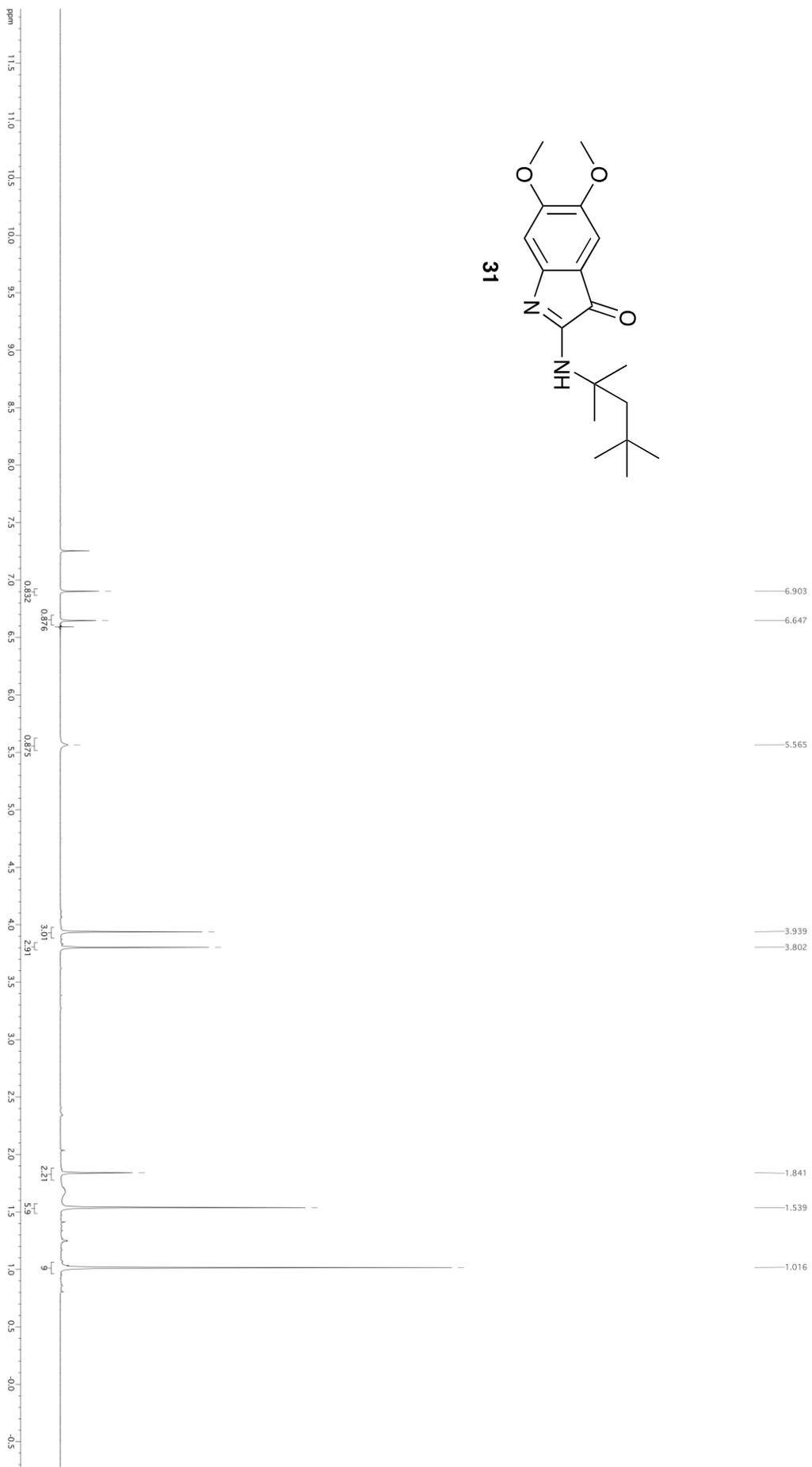
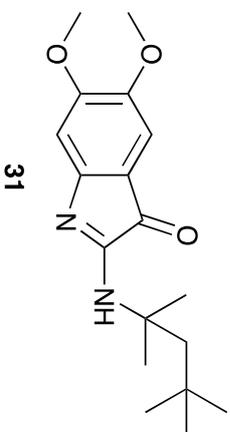
¹H NMR
400 MHz, CDCl₃



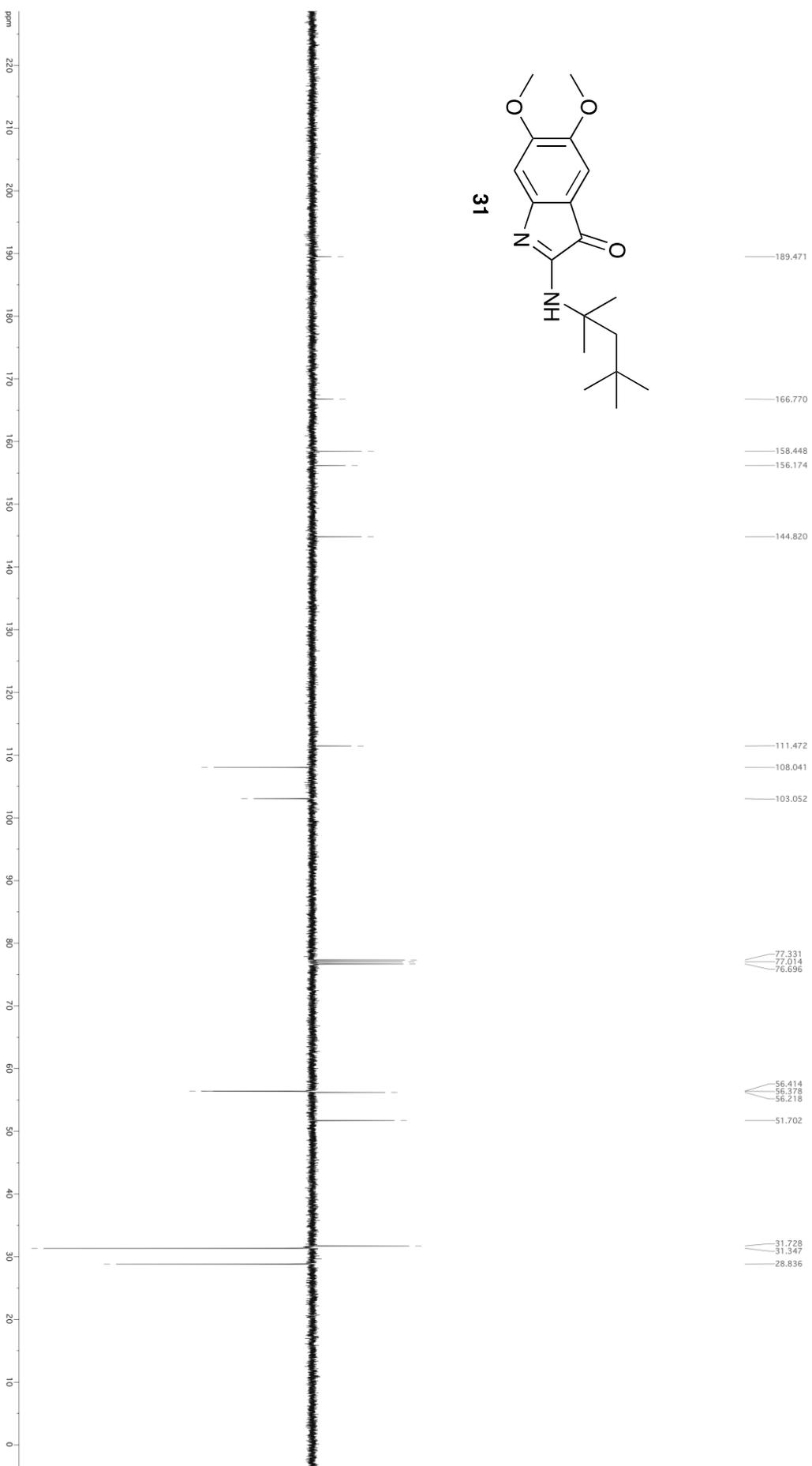
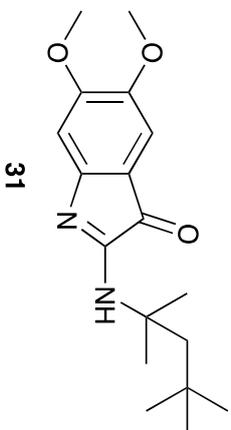
¹³C NMR
100 MHz, CDCl₃



¹H NMR
400 MHz, CDCl₃



¹³C NMR
100 MHz, CDCl₃



X-Ray Diffraction Analysis.

The crystallographic structure of **13** is shown in Fig. S1. The non-H atoms of the bicyclic core are nearly coplanar, with a maximum deviation of 0.040(1) Å for C7. The atom O1 is essentially coplanar with the fused ring system. Atoms C9 and N2 deviated by 0.159(1) Å and 0.283(1) Å, respectively. In the five-membered ring, the C1-N1 (1.428(1) Å) and C6-C7 (1.463(1) Å) bonds have a partial double-bond feature, indicating the conjugation with the π -electrons of the benzene ring and the C=O group, respectively.

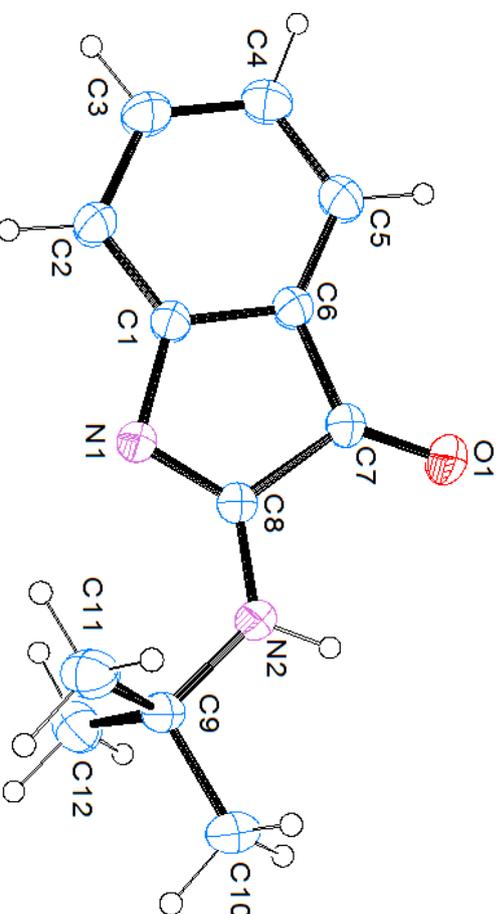


Figure S1. ORTEP^[2] drawing of **13** with the arbitrary atom numbering (ellipsoids are at 40% probability and H atoms are as spheres of arbitrary radii).

In the crystals, the molecules form centrosymmetric dimers connected by hydrogen bonds between N2-H...O1, distance 2.270(1) Å, angle 162.3(1)° and by contacts involving C2-H...N1, distance 2.686(1) Å, angle 172.2(1)°. These latter are arranged into a zigzag chain parallel to the face diagonal of the *ac* plane (Fig. S2).

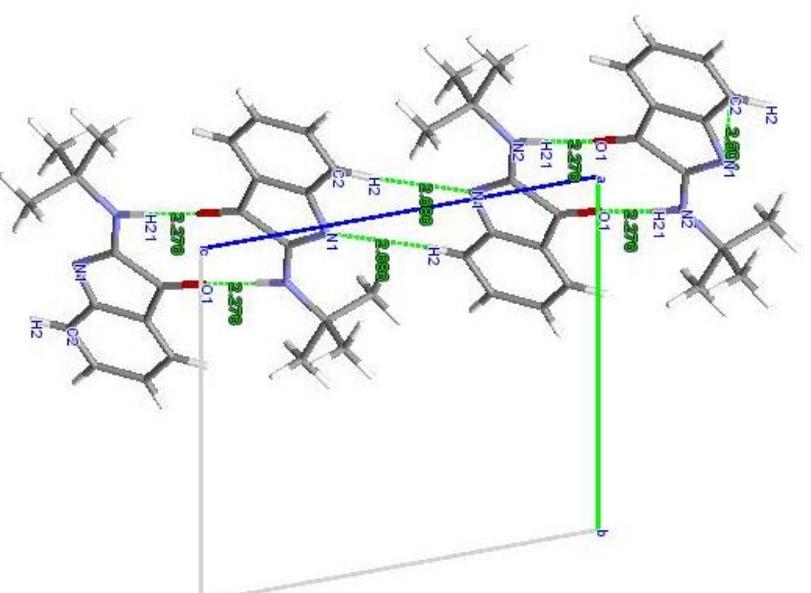


Figure S2. Intermolecular interactions viewed along the *a* axis.

Experimental

Diffraction data for the crystal **13** have been collected by means of a Bruker-Axs CCD-based three circle diffractometer, working at ambient temperature with graphite-monochromatized Mo-K α X-radiation ($\lambda = 0.71073$ Å).

X-ray diffraction data in the θ range 2-30° were collected acquiring 5 sets of 600 bidimensional CCD frames with the following operative conditions: omega rotation axis, scan width 0.3°, acquisition time 20 s, sample-to-detector distance 50 mm, phi angle fixed at five different values (20°, 50°, 120°, 150°, 240°) for each of the five different sets.

Omega-rotation frames were processed with the SAINT software^[3] for data reduction (including intensity integration, background, Lorentz and polarization corrections) and for determination of accurate unit-cell dimensions, obtained by least-squares refinement of the positions of 5161 independent reflections with $I > 10\sigma(I)$ in the θ range 2-27°. Absorption effects were empirically evaluated by the SADABS software^[4] and absorption correction was applied to the data (0.875 and 0.991 min and max transmission factor).

UV-HPLC and HRMS Monitoring of Reaction.

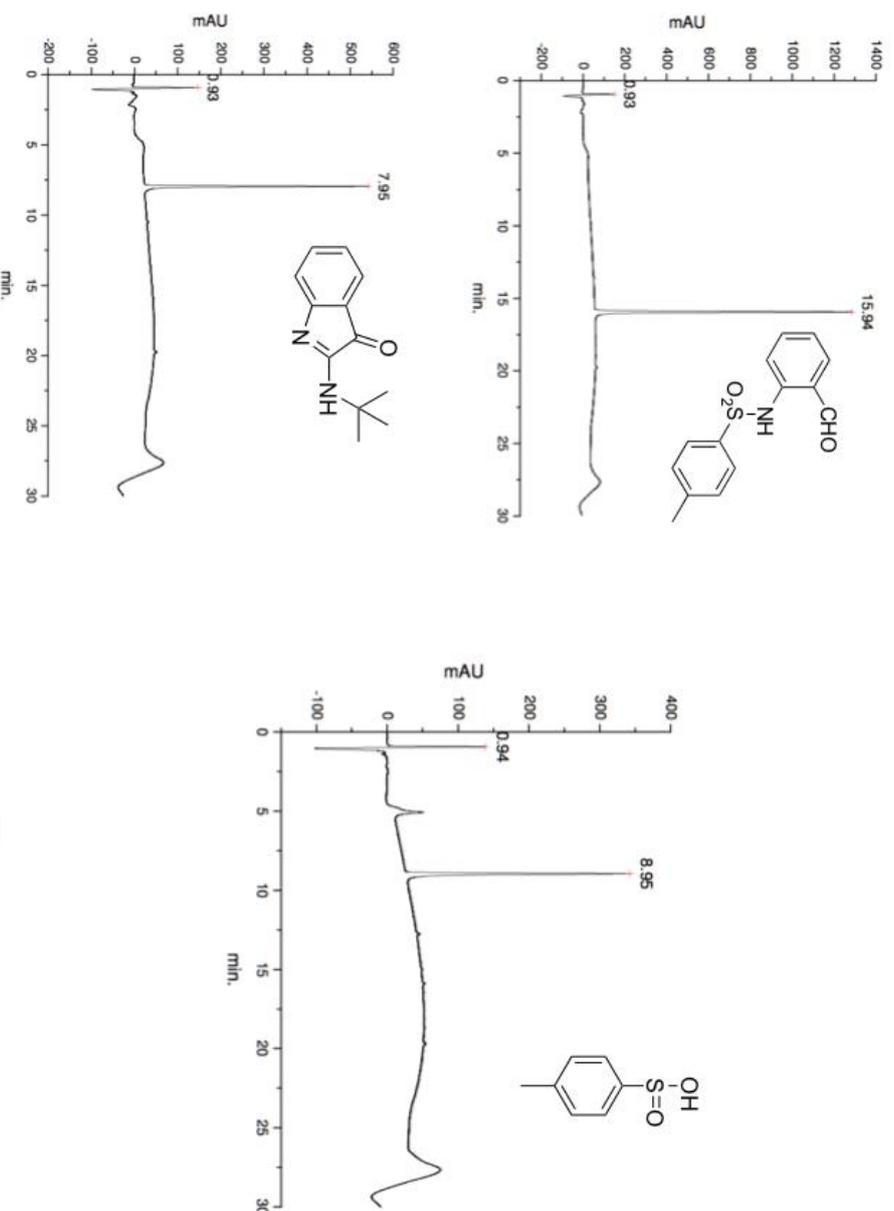


Figure S3: HPLC-DAD analysis of pure standards 2-benzensulfonamide **11**, 2-(*tert*-butylamino)-3*H*-indol-3-one **13**, and *p*-toluenesulfonic acid **37** following 10 microliter injection of pure standards at 100 micrograms/mL in water:acetonitrile 1:1 containing 0/1% TFA.

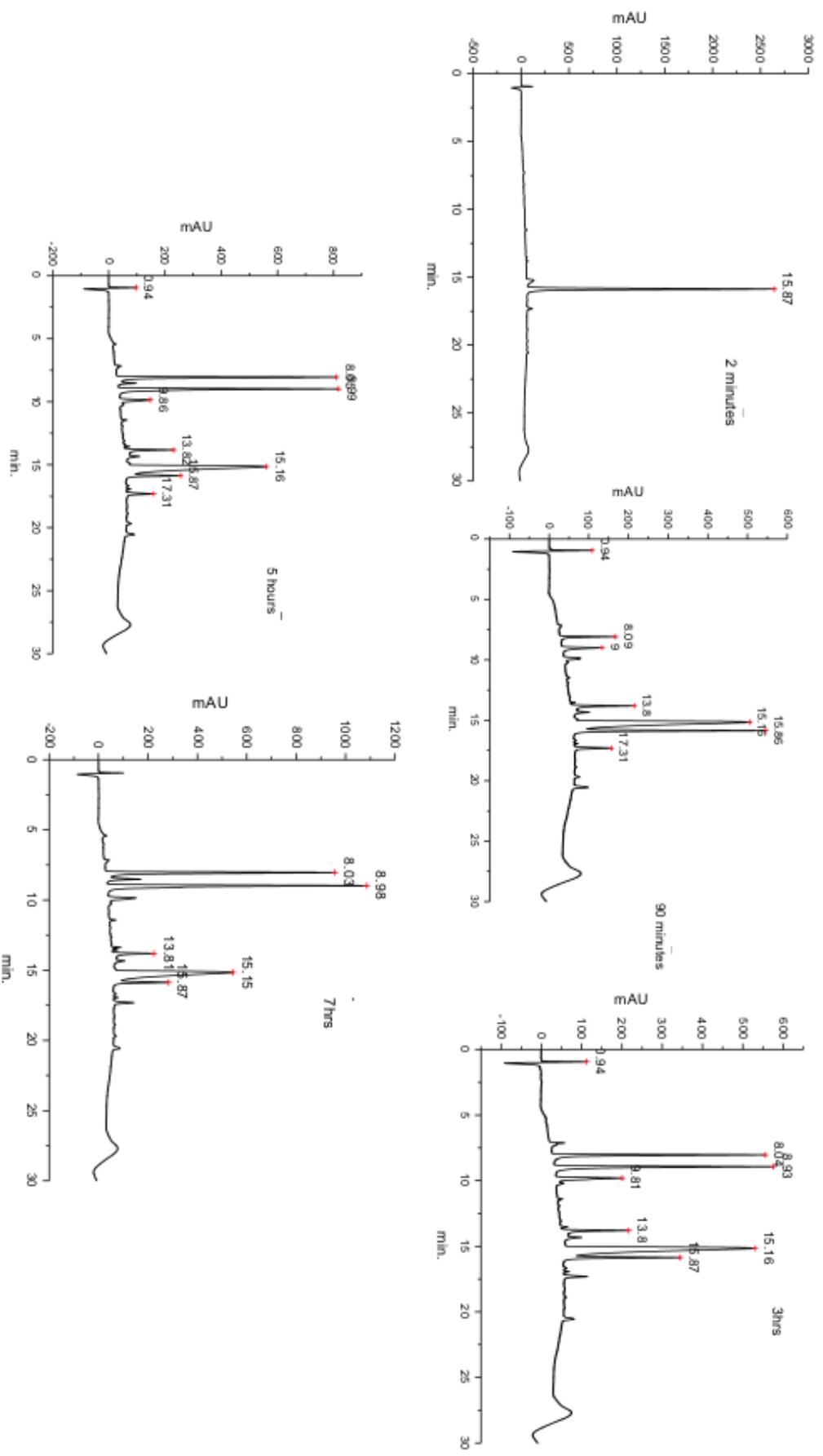


Figure S4: HPLC-DAD analysis of various reaction time points following 10 microliter injection of a 1:1000 dilution of reaction mixture in methanol.

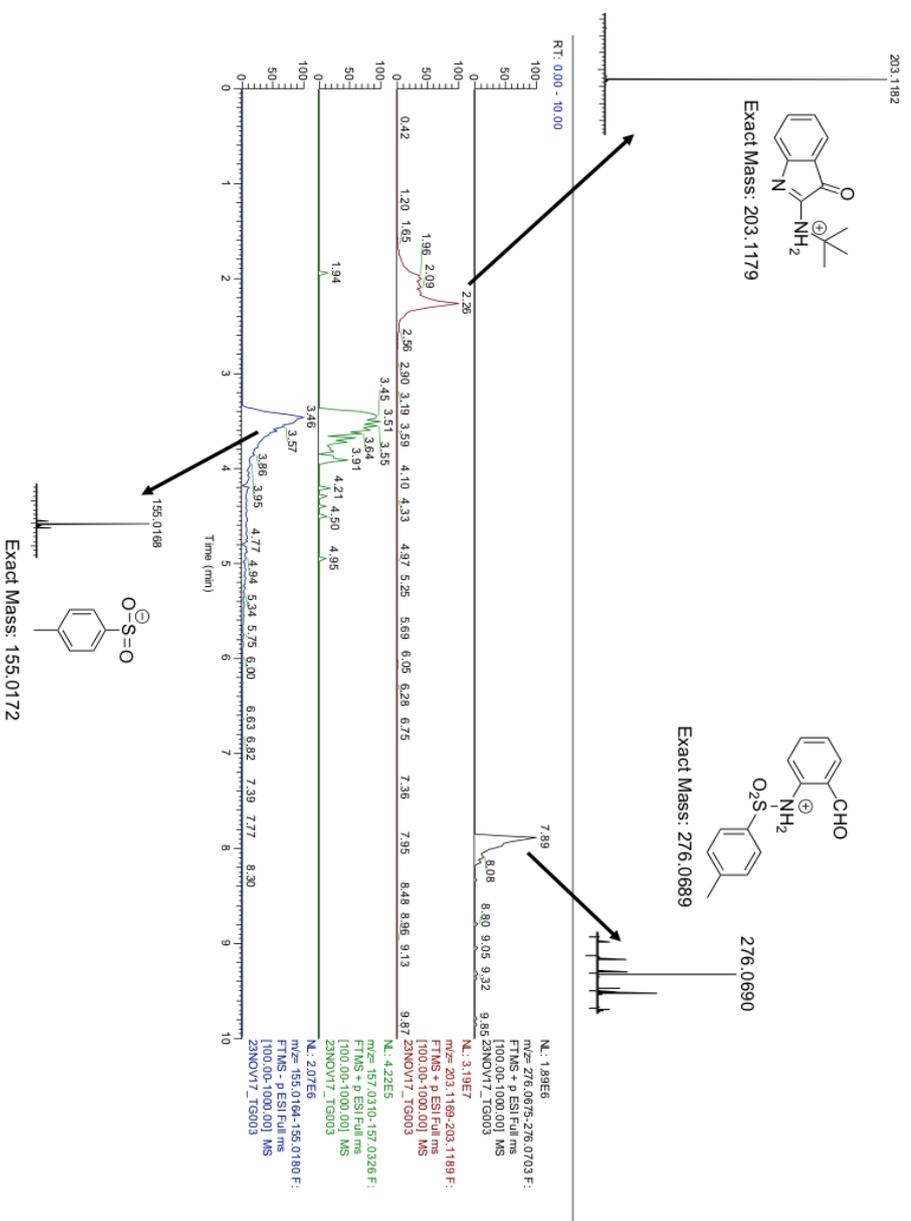


Figure S5: UHPPLC-HMRS analysis of compounds 2-benzensulfonamide **11**, 2-(*tert*-butylamino)-3*H*-indol-3-one **13**, and *p*-toluensulfonic acid **37** following an injection of the mixture of the 3 pure standards at 500 ng/mL in water:acetonitrile 95:5 containing 0.3% TFA. Extracted ion chromatograms for compound **11** (black trace, ESI positive mode); compound **13** (red trace, ESI positive mode); *p*-toluensulfonic acid **37** (blue trace, ESI negative mode) and their HRMS spectra. Green trace represents the extracted ion chromatogram for *p*-toluensulfonic acid **37** in ESI positive mode.

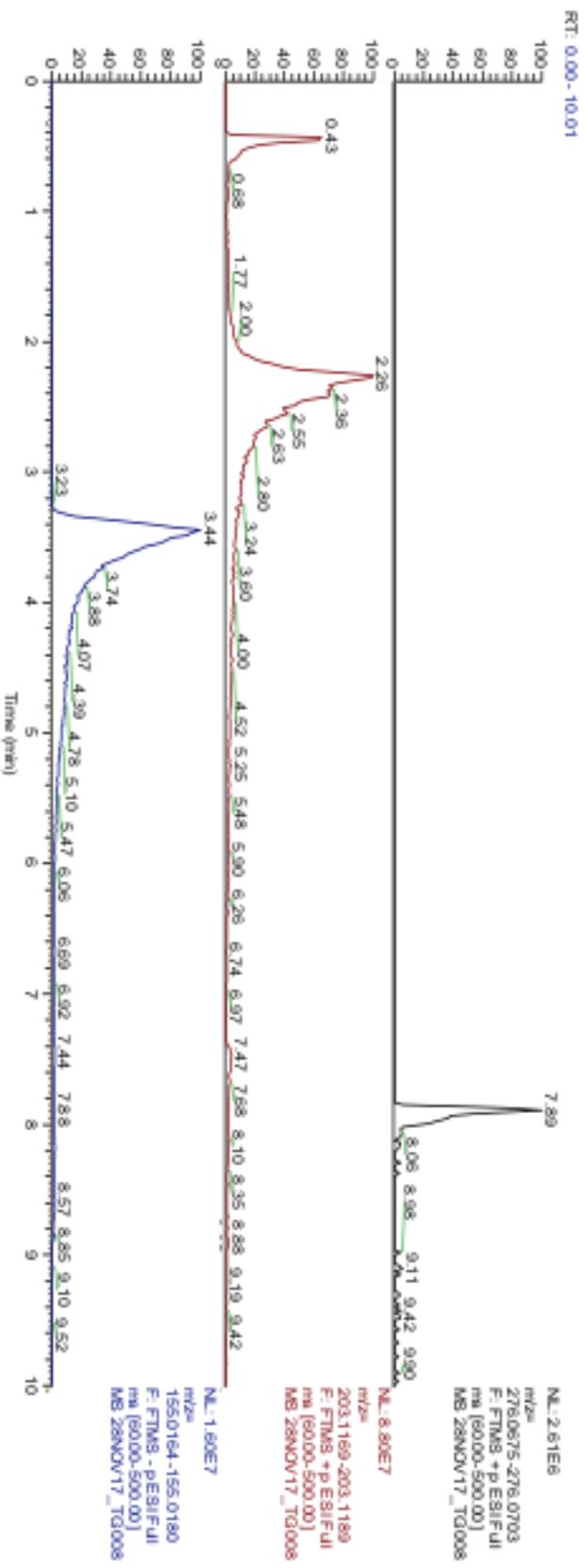


Figure S6: UHPLC-HMRS analysis of a reaction time point 3 hours. Extracted ion chromatograms for compound **11** (black trace, ESI positive mode); compound **13** (red trace, ESI positive mode); *p*-toluensulfonic acid **37** (blue trace, ESI negative mode).

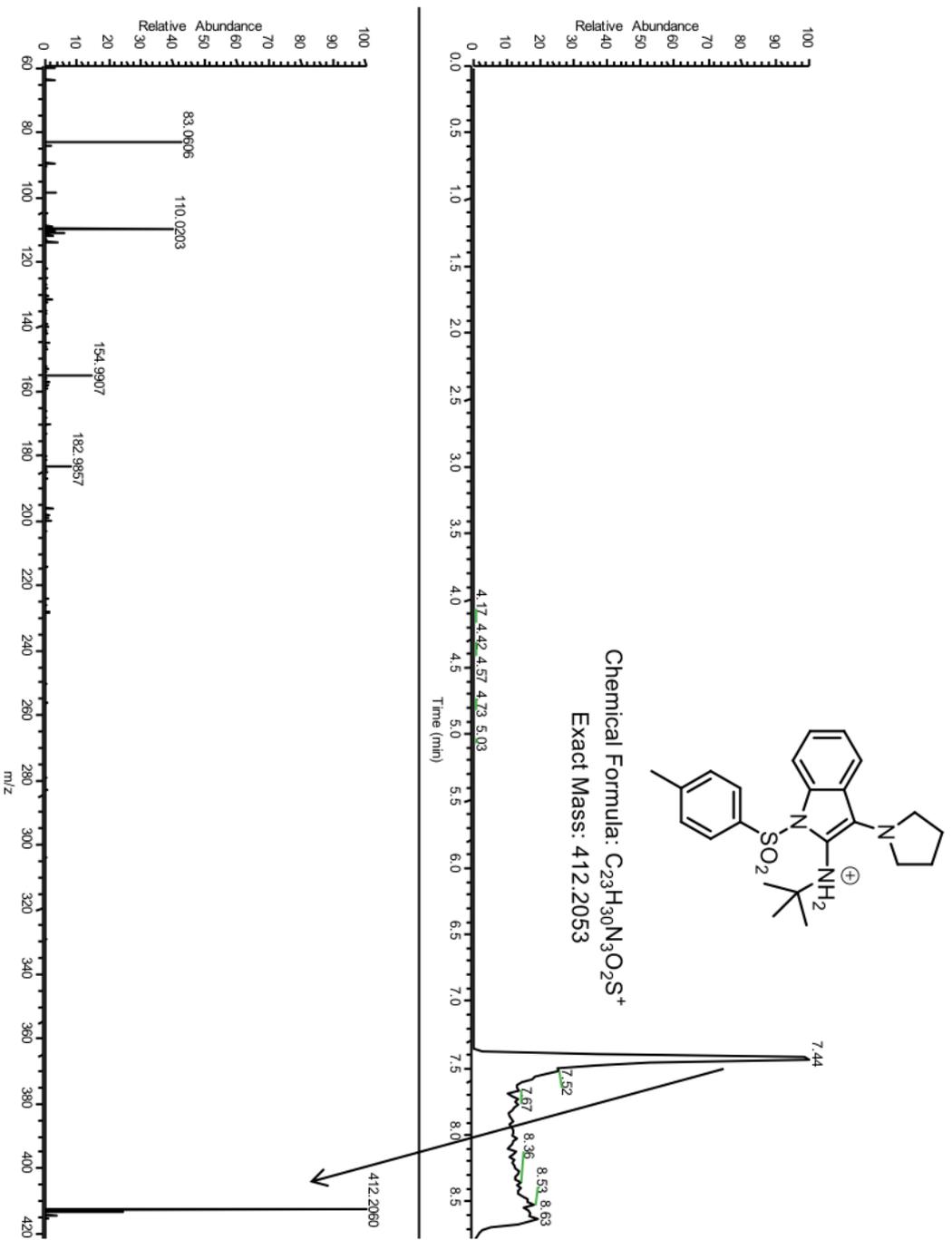


Figure S7: UHP LC-HMRS analysis of a reaction time point 3 hours. Extracted ion chromatogram (top) and HRMS (bottom) of intermediate **40**.

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