Various Cyclization Scaffolds by a truly Ugi 4-CR

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Supporting Information

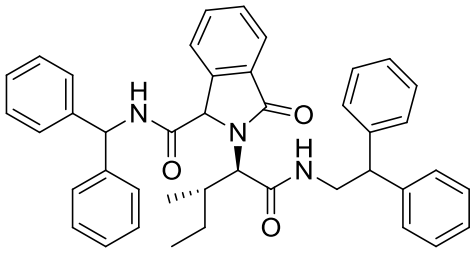
1. Generalities:

Dry solvents were purchased from Aldrich, Fisher Scientific, Acros Organics or Alfa Aesar and used as received. Starting materials were purchased from Aldrich, Fisher Scientific, Acros Organics or Alfa Aesar. Isocyanides were prepared according to the two step Ugi or one-step Hoffmann methods. ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker Ultrashield Plus 600. Chemical shift values are in ppm relative either to $CDCl_3$ or DMSO-d_6. Abbreviations used are s = singlet, brs = broad singlet d = doublet, dd = double doublet, t = triplet, td = triple doublet, dt = double triplet q=quartet, m=multiplet; data in parenthesis are given in the following order: multiplicity, number of protons, and coupling constants in Hz. MS spectra were recorded on a Waters Super Critical Fluid Chromatograph with a 3100 MS Detector using solvent system of Methanol and CO_2 on an ethyl pyridine. Purifications were done on either the Waters Super Critical Fluid Chromatograph Prep 100 system using CO2 and Methanol or the Teledyne ISCO Combiflash RF System using Hexane/Ethyl Acetate/Dichloromethane/Methanol or silica gel prep TLC plate.

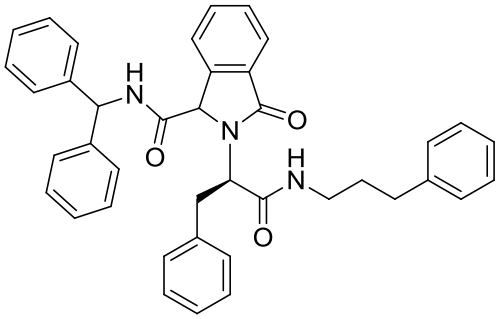
2. General procedure of Ugi-Cyclization reaction yielding oxoisoindolines:

A mixture of L-amino acid (0.5 mmol), aldehyde (0.5 mmol), isocyanide (0.5 mmol) and primary or secondary amine (0.5 mmol), in TFE (5 mL) were stirred at 85 ºC for 24 – 72 hours. SFC-MS trace showed both the Ugi product as well as the desired cyclized product. TFE was evaporated under reduced pressure and residue was dissolved in DCM. Unreacted amino acid was filtered off and filtrate was evaporated and dissolved in 1 mL EtOH and let sit in an oil bath at 60˚C for 24 hours to allow for the remainder of the Ugi product to cyclize. Precipitate was filtered off and confirmed to be the desired cyclized product by SFC-MS and NMR.

N-benzhydryl-2-(1-((2,2-diphenylethyl)amino)-3-methyl-1-oxopentan-2-yl)-3-oxoisoindoline-1-carboxamide [7a]: 35% yield as a white solid ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.52 (d, *J* = 6.6 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H), 1.13 – 1.18 (m, 2H), 1.57 (s, 2H), 1.92 – 1.96 (m, 1H), 3.34 – 3.38 (m, 2H), 3.87 – 3.94 (m, 2H), 4.04 (t, *J* = 8.1 Hz, 1H), 5.04 (s, 1H), 6.13 (d, *J* = 8.1 Hz, 1H), 6.95 – 6.97 (m, 2H), 7.04 – 7.13 (m, 10H), 7.16 – 7.21 (m, 9H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 8.46 – 8.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.0, 15.4, 27.1, 29.7, 34.1, 43.9, 50.5, 57.3, 64.0, 123.3, 123.8, 126.8, 126.9, 126.9, 127.1, 127.5, 128.0, 128.1, 128.3, 128.5, 128.6, 128.7, 129.0, 130.0, 132.6, 140.7, 141.5, 141.7, 142.2, 167.2, 170.8, 170.9 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.:636.31; found: 636.33.

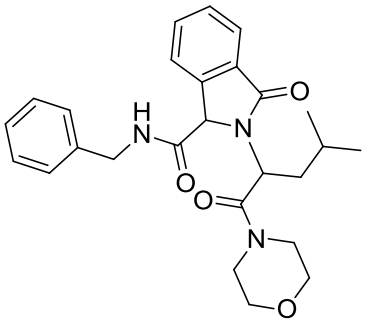


N-benzhydryl-3-oxo-2-(1-oxo-3-phenyl-1-((3-phenylpropyl)amino)propan-2-yl)isoindoline-1-carboxamide [7b]:



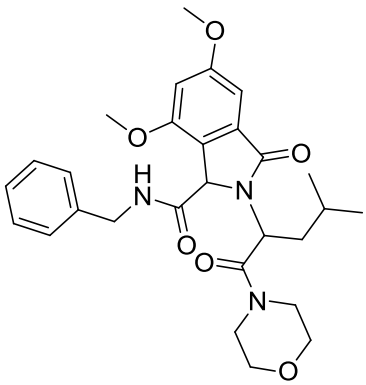
50% yield as a yellow oil ^{1}H NMR (600 MHz, Chloroform-d) δ 1.52 – 1.61 (m,2H), 2.41 – 2.48 (m, 2H), 2.90 – 2.94 (m,1H), 2.99 – 3.04 (m, 1H), 3.14 – 3.20 (m, 2H), 4.58 (dd, *J* = 10.7, 6.3 Hz, 1H), 5.30 (s, 1H), 5.47 – 5.50 (m, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 7.11 – 7.13 (m, 1H), 7.19 – 7.33 (m, 12H), 7.47 – 7.48 (m, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.84 (t, *J* = 8.2 Hz, 1H), 10.29 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.6, 32.9, 35.1, 39.3, 57.1, 60.2, 63.4, 123.5, 123.5, 126.0, 127.0, 127.1, 127.3, 128.4, 128.4, 128.5, 128.5, 128.8, 128.9, 129.0, 129.7, 132.6, 135.7, 140.6, 141.3, 142.2, 142.3, 167.8, 170.7, 171.4 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 608.28; found: 608.36

N-benzyl-2-(4-methyl-1-morpholino-1-oxopentan-2-yl)-3-oxoisoindoline-1-carboxamide [7c]:



42% yield as a yellow solid ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.79-0.86 (m, 12H), 1.42-1.46 (m, 2H), 1.57-1.61 (m, 1H), 1.64-1.68 (m, 2H), 1.74-1.78 (m, 1H), 3.35-3.47 (m, 4H), 3.51-3.61 (m, 5H), 3.62-3.70 (m, 5H), 3.77-3.88 (m, 2H), 4.16-4.25 (m, 2H), 4.37 (dd, J=14.6, 6.4Hz, 1H), 4.46 (dd, J=14.6, 6.3Hz, 1H), 4.94 (t, J=7.4Hz, 1H), 5.12 (s, 1H), 5.29 (t, J=7.5Hz, 1H), 5.41 (s, 1H), 7.01-7.02 (m, 1H), 7.10-7.13 (m, 3H), 7.14-7.18 (m, 4H), 7.19-7.24 (m, 4H), 7.38-7.44 (m, 3H), 7.48 (q, J=7.7 2H), 7.67 (d, 6.1Hz, 1H), 7.70-7.71 (m, 2H), 9.39-9.40 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.3, 22.7, 22.8, 23.0, 25.0, 25.4, 38.3, 38.7, 43.0, 43.5, 43.8, 46.7, 49.6, 51.3, 62.8, 63.7, 66.4, 66.6, 122.4, 123.1, 123.5, 124.0, 127.2, 127.7, 127.9, 128.0, 128.4, 128.7, 129.0, 129.0, 129.9, 130.6, 132.5, 132.6, 137.6, 138.1, 142.5, 142.6, 168.4, 168.5, 169.6, 170.1, 170.4, 171.2 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 450.23; found: 450.21.

N-benzyl-5,7-dimethoxy-2-(4-methyl-1-morpholino-1-oxopentan-2-yl)-3-oxoisoindoline-1-carboxamide [7d]: 40% yield as a yellow solid **Diastereomer A**: ^{1}H NMR (600 MHz, Chloroform-d) δ

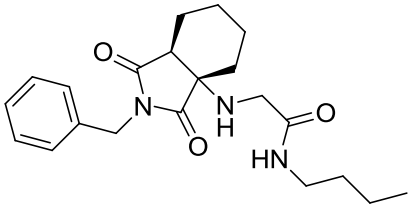


0.93 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.57 – 1.63 (m, 1H), 1.77 – 1.80 (m,2H), 3.46 – 3.59 (m, 4H), 3.64 – 3.68 (m, 4H), 3.71 (s, 3H), 3.86 (s, 3H), 4.32 (dd, *J* = 14.8, 4.8 Hz, 1H), 4.72 (dd, *J* = 14.8, 7.0 Hz, 3H), 5.13 (s, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 6.87 – 6.89 (m, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 7.29 – 7.31 (m, 1H), 7.35 – 7.36 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.6, 22.7, 22.8, 24.9, 38.8, 42.5, 43.9, 46.5, 49.0, 55.9, 60.9, 66.8, 67.0, 98.3, 103.1, 122.9, 127.5, 128.0, 128.6, 133.6, 137.9, 154.8, 162.3, 167.7, 169.1, 169.4 ppm **Diastereomer B:**^{1}H NMR (600 MHz, Chloroform-d) δ 0.92 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.34 – 1.39 (m, 1H), 1.78 (t, *J* = 7.2 Hz, 2H), 3.48 – 3.61 (m, 4H), 3.66 (s, 3H), 3.69 – 3.82 (m, 4H), 3.86 (s, 3H), 4.22 (dd, *J* = 14.8, 4.5 Hz, 1H), 4.63 (dd, *J* = 14.8, 7.2 Hz, 1H), 4.97 (s, 1H), 5.38 (t, *J* = 7.5 Hz, 1H), 6.53 – 6.58 (m, 2H), 6.96 (d, *J* = 2.1 Hz, 1H), 7.25 – 7.37 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.52, 23.00, 24.54, 39.23, 42.46, 43.87, 45.96, 48.43, 55.36, 55.91, 59.38, 66.23, 76.84, 77.05, 77.27, 98.64, 103.12, 127.43, 127.93, 128.55, 133.58, 138.06, 154.70, 162.38, 166.37, 167.87, 168.71 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 510.25; found: 510.28.

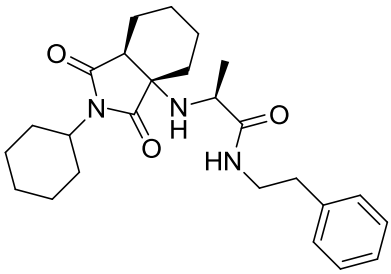
General procedure of Ugi-Cyclization reaction yielding dioxopyrrolidines:

A mixture of L-amino acid (0.5 mmol), ketone (0.5 mmol), isocyanide (0.5 mmol) and primary or secondary amine (0.5 mmol), in TFE (5 mL) were stirred at 85 ºC for 24 – 72 hours. Solvents were concentrated under nitrogen to 0.5-1.0 mL and then Cs_2CO_3 was added to mixture. Resultant mixture was heated at 85 ºC for overnight. Reaction mixture was diluted with DCM and water, extracted with DCM, dried over $MgSO_4$, filtered and solvents were evaporated to get crude product, which was purified by SFC or flash chromatography to yield title compound.

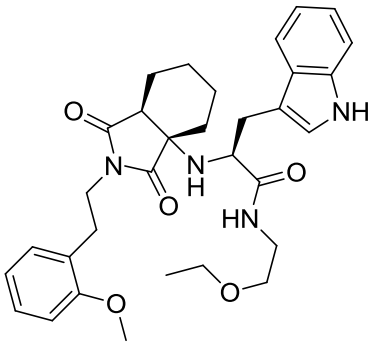
2-((2-benzyl-1,3-dioxooctahydro-1*H*-isoindol-3a-yl)amino)-*N*-butylacetamide [9a]: 40% yield as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.8 Hz, 3H), 1.13-1.20 (m, 1H), 1.31-1.41 (m, 3H), 1.45-1.57 (m, 5H), 1.63-1.66 (m, 1H), 1.71-1.74 (m, 1H), 2.21-2.25 (m, 1H), 2.66 (d, *J* = 5.4 Hz, 1H), 3.03 (d, *J* = 17.4 Hz, 1H), 3.26 (q, *J* = 13.8, 7.2 Hz, 2H), 3.45 (d, *J* = 17.4 Hz, 1H), 4.63 (dd, *J* = 31.4, 14.4 Hz, 2H), 7.09 (s, 1H), 7.27-7.33 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 19.7, 20.1, 20.1, 21.5, 31.7, 33.5, 38.8, 42.4, 42.6, 47.4, 62.8, 128.0, 128.5, 128.7, 135.6, 170.6, 175.9, 180.1 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc 372.47; found: 372.29.



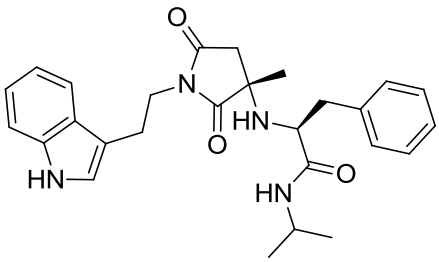
(2*S*)-2-((2-cyclohexyl-1,3-dioxooctahydro-1*H*-isoindol-3a-yl)amino)-*N*-phenethylpropan-amide [9b]: 49% yield as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97-1.05 (m, 2H), 1.10-1.30 (m, 5H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.40-1.42 (m, 1H), 1.44-1.47 (m, 1H), 1.51-1.58 (m, 3H), 1.61-1.64 (m, 1H), 1.77-1.81 (m, 2H), 1.99-2.08 (m, 3H), 2.40 (d, *J* = 3.6 Hz, 1H), 2.76-2.81 (m, 1H), 2.84-2.91 (m, 2H), 3.37-3.43 (m, 1H), 3.66-3.71 (m, 1H), 3.85-3.91 (m, 1H), 7.21-7.25 (m, 3H), 7.30-7.34 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.4, 19.7, 21.0, 21.8, 24.9, 25.6, 25.7, 28.4, 29.2, 35.0, 35.3, 39.8, 41.7, 51.5, 55.1, 62.9, 126.7, 128.6, 128.7, 138.5, 174.9, 175.8, 181.4 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 426.56; found: 426.34.



(2*S*)-*N*-(2-ethoxyethyl)-3-(1*H*-indol-3-yl)-2-((2-(2-methoxyphenethyl)-1,3dioxooctahydro-1*H*-isoindol-3a-yl)amino)propanamide [9c]: 45% yield as a light brownish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00-1.03 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.12-1.17 (m, 1H), 1.21-1.28 (m, 1H), 1.32-1.35 (m, 1H), 1.39-1.45 (m, 2H), 1.52-1.55 (m, 1H), 1.97 (brs, 1H), 2.15 (d, *J* = 13.8 Hz, 1H), 2.47 (d, *J* = 6.6 Hz, 1H), 2.93-2.98 (m, 3H), 3.10 (dd, *J* = 14.4, 6.0 Hz, 1H), 3.12-3.16 (m, 1H), 3.21-3.25 (m, 1H), 3.25-3.29 (m, 1H), 3.30-3.36 (m, 2H), 3.41 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.47-3.54 (m, 1H), 3.82 (t, *J* = 6.6 Hz, 2H), 3.86 (s, 3H), 6.86-6.91 (m, 2H), 7.04-7.06 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.23 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 5.4 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.9, 19.4, 20.0, 22.1, 28.3, 28.5, 35.1, 38.0, 38.9, 42.6, 55.4, 57.9, 62.8, 66.2, 68.9, 110.1, 110.6, 111.0, 119.2, 119.6, 120.4, 122.1, 123.5, 126.0, 128.1, 128.3, 130.7, 136.2, 157.9, 174.1, 176.1, 181.2 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 561.68; found: 561.42.



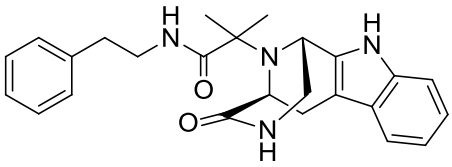
(2*S*)-2-((1-(2-(1*H*-indol-3-yl)ethyl)-3-methyl-2,5-dioxopyrrolidin-3-yl)amino)-*N*-isopropyl-3-phenylpropanamide [9d]: 34% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (dd, *J* = 14.4, 6.6 Hz, 6H), 1.12 (s, 3H), 1.75 (brs, 1H), 2.36-2.45 (m, 2H), 2.63 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.67 (brs, 1H), 2.94 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.06-3.17 (m, 2H), 3.75-3.80 (m, 1H), 3.89-3.94 (m, 1H), 3.99-4.05 (m, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.03-7.05 (m, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.22-7.25 (m, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5, 22.6, 22.8, 25.5, 38.7, 39.3, 40.2, 41.0, 58.1, 60.2, 111.4, 111.6, 118.7, 119.5, 122.2, 122.6, 127.1, 127.3, 128.6, 129.7, 135.9, 136.4, 172.3, 174.0, 180.1 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 461.57; found: 461.31.

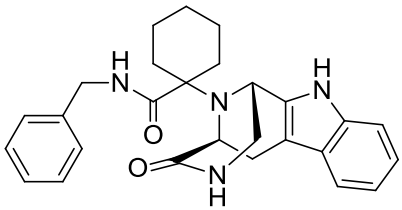


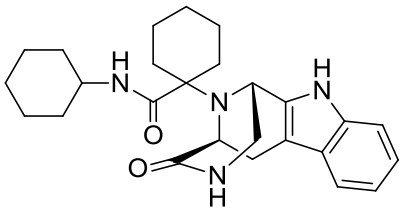
General procedure of Ugi-Pictet-Spengler type reaction:

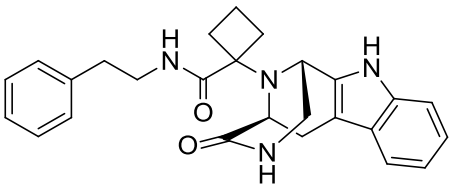
A mixture of L-amino acid (0.5 mmol), ketone (0.5 mmol), isocyanide (0.5 mmol) and aminoacetaldehyde dimethyl acetal (0.5 mmol), in 0.1 M of MeOH/H_2O (4:1) were stirred for 24 – 72 hours at room temperature. Solvents were evaporated under reduced pressure and residue was dissolved in DCM. Unreacted amino acid was filtered off and filtrate was evaporated to get crude product. The crude Ugi product was dissolved in formic acid (2 mL) and stirred for 16 h at room temperature. Reaction mixture was quenched with aq. $NaHCO_3$, extracted with DCM, dried over

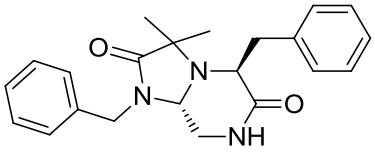
Na_2SO_4, filtered and solvents were evaporated to get crude product, which was purified by SFC or Isco to yield title compound.

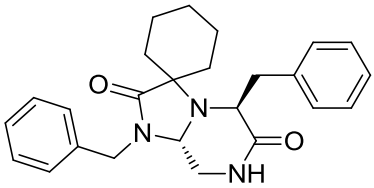
2-methyl-2-((5*S*)-4-oxo-2,3,4,5,6,11-hexahydro-1*H*-1,5-epiminoazocino[4,5-*b*]indol-12-yl)-*N*-phenethylpropanamide [11a]:  44% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.35 (s, 3H), 2.81-2.76 (m, 1H), 2.90-2.86 (m, 2H), 3.00-2.95 (m, 2H), 3.11 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.50-3.46 (m, 1H), 3.56-3.52 (m, 1H), 3.76 (d, *J* = 3.6 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 1H), 6.40 (s, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.31-7.27 (m, 3H), 7.43-7.39 (m, 2H), 8.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3, 24.8, 25.2, 35.3, 40.5, 47.1, 47.4, 55.1, 63.6, 108.0, 111.1, 118.2, 119.6, 122.1, 126.5, 126.7, 128.6, 128.7, 131.8, 135.7, 138.6, 173.1, 176.9 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 417.52; found: 417.30.

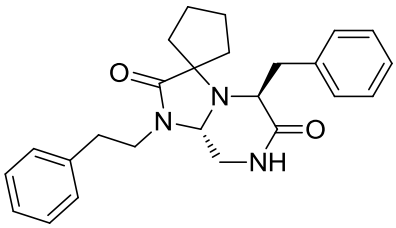
***N*-benzyl-1-((5*S*)-4-oxo-2,3,4,5,6,11-hexahydro-1*H*-1,5-epiminoazocino[4,5-*b*]indol-12-yl)cyclohexanecarboxamide [11b]:**  40% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.86-1.47 (m, 7H), 1.31-1.12 (m, 3H), 3.04-2.91 (m, 3H), 3.32-3.30 (m, 1H), 4.27-4.15 (m, 4H), 6.24 (s, 1H), 6.97-6.94 (m, 1H), 7.08-7.03 (m, 2H), 7.17-7.14 (m, 2H), 7.26-7.22 (m, 3H), 7.39 (d, *J* = 7.2 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.9, 23.3, 24.9, 25.4, 31.0, 33.6, 43.5, 45.8, 47.9, 54.6, 65.0, 107.7, 111.2, 118.0, 119.3, 121.8, 126.7, 127.5, 127.7, 128.7, 132.9, 135.7, 138.3, 173.4, 175.1 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 443.55; found: 443.31.

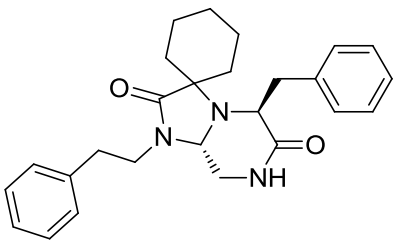
***N*-cyclohexyl-1-((5*S*)-4-oxo-2,3,4,5,6,11-hexahydro-1*H*-1,5-epiminoazocino[4,5-*b*]indol-12-yl)cyclohexanecarboxamide [11c]:**  48% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32-0.98 (m, 9H), 1.87-1.51 (m, 11H), 2.99 (d, *J* = 16.2 Hz, 1H), 3.08 (dd, *J* = 16.2, 6.0 Hz, 1H), 3.21 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.56-3.51 (m, 2H), 4.30-4.27 (m, 2H), 6.35 (d, *J* = 7.8 Hz, 1H), 6.43 (s, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.8, 23.4, 24.7, 24.8, 24.9, 25.3, 25.4, 30.9, 32.7, 33.0, 34.0, 45.9, 48.2, 48.3, 54.7, 64.8, 107.6, 111.3, 117.9, 119.2, 121.6, 126.8, 132.9, 135.6, 173.4, 174.1 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 435.57; found: 435.37.

1-((5*S*)-4-oxo-2,3,4,5,6,11-hexahydro-1*H*-1,5-epiminoazocino[4,5-*b*]indol-12-yl)-*N*-phenethylcyclobutanecarboxamide [11d]:  30% yield as a white solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.46-1.55 (m, 2H), 2.13-2.22 (m, 4H), 2.62-2.72 (m, 2H), 2.74 (d, *J* = 15.6 Hz, 1H), 2.93 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.05 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.23-3.32 (m, 2H), 3.56 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.83 (d, *J* = 5.4 Hz, 1H), 4.20 (d, *J* = 4.2 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H),7.17 (t, *J* = 6.6 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 5.4 Hz, 1H), 10.74 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 13.7, 24.6, 28.4, 28.9, 34.9, 40.5, 46.0, 46.8, 54.9, 66.5, 107.0, 111.2, 117.6, 118.5, 120.8, 126.0, 126.4, 128.3, 128.5, 133.7, 135.6, 139.4, 171.35, 173.9 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 429.53; found: 429.31.

(5*S*)-1,5-dibenzyl-3,3-dimethyltetrahydroimidazo[1,2-*a*]pyrazine-2,6(3*H*,5*H*)-dione [13a]:  63% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.22 (s, 3H), 2.90 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.05-3.13 (m, 2H), 3.20-3.24 (m, 1H), 3.67 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.05 (d, *J* = 15.6 Hz, 1H), 4.10 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 7.08-7.11 (m, 3H), 7.12-7.15 (m, 5H), 7.31-7.36 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.3, 25.5, 39.3, 44.1, 46.2, 56.0, 61.1, 64.4, 126.5, 127.5, 127.9, 128.0, 128.8, 129.7, 135.5, 137.7 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 364.45; found: 364.30.

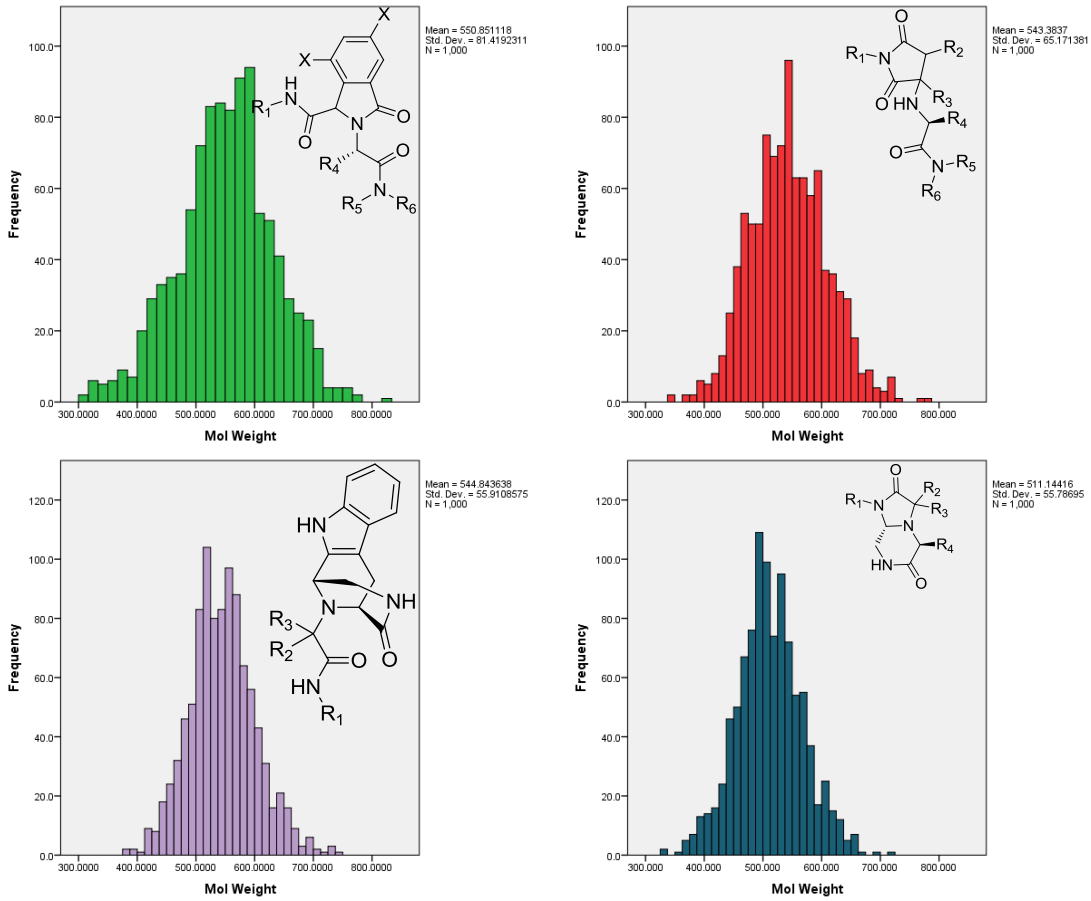
(5'*S*)-1',5'-dibenzyldihydro-1'*H*-spiro[cyclohexane-1,3'-imidazo[1,2-*a*]pyrazine]-2',6'(5'*H*,7'*H*)-dione 13b]: 
87% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83-0.88 (m, 1H), 0.99-1.05 (m, 1H), 1.23-1.29 (m, 1H), 1.36-1.42 (m, 2H), 1.48-1.67 (m, 3H), 1.78-1.85 (m, 1H), 2.04-2.10 (m, 1H), 2.86 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.04 (dd, *J* = 13.2, 7.8 Hz, 1H), 3.10 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.22 (dt, *J* = 12.0, 4.2 Hz, 1H), 3.68 (dd, *J* = 6.6, 4.8 Hz, 1H), 3.90 (d, *J* = 15.6 Hz, 1H), 4.08-4.11 (m, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 7.07-7.09 (m, 2H), 7.11-715 (m, 5H), 7.30-7.36 (m, 3H), 7.38 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 22.0, 24.9, 32.9, 34.4, 40.0, 43.8, 46.4, 55.5, 61.7, 63.9, 126.5, 127.6, 127.9, 128.0, 128.8, 129.7, 135.7, 137.6, 172.8, 175.0 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 404.52; found: 404.32.

(5'*S*)-5'-benzyl-1'-phenethyldihydro-1'*H*-spiro[cyclopentane-1,3'-imidazo[1,2-*a*]pyrazine]-2',6'(5'*H*,7'*H*)-dione [13c]: 
40% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93-0.98 (m, 1H), 1.41-1.46 (m, 1H), 1.55-1.66 (m, 3H), 1.70-1.78 (m, 3H), 2.78-2.81 (m, 2H), 2.95 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.00-3.11 (m, 3H), 3.31 (dt, *J* = 11.4, 4.2 Hz, 1H), 3.55 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.75-3.80 (m, 1H), 4.07 (dd, *J* = 9.0, 4.2 Hz, 1H), 6.80 (brs, 1H), 7.16-7.19 (m, 4H), 7.22-7.27 (m, 4H), 7.30-7.33 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.1, 26.2, 33.9, 34.2, 36.3, 40.1, 42.0, 45.9, 57.0, 65.1, 70.5, 126.6, 126.7, 128.1, 128.6, 129.7, 138.0, 138.2, 172.2, 176.7 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 404.23; found: 404.32.

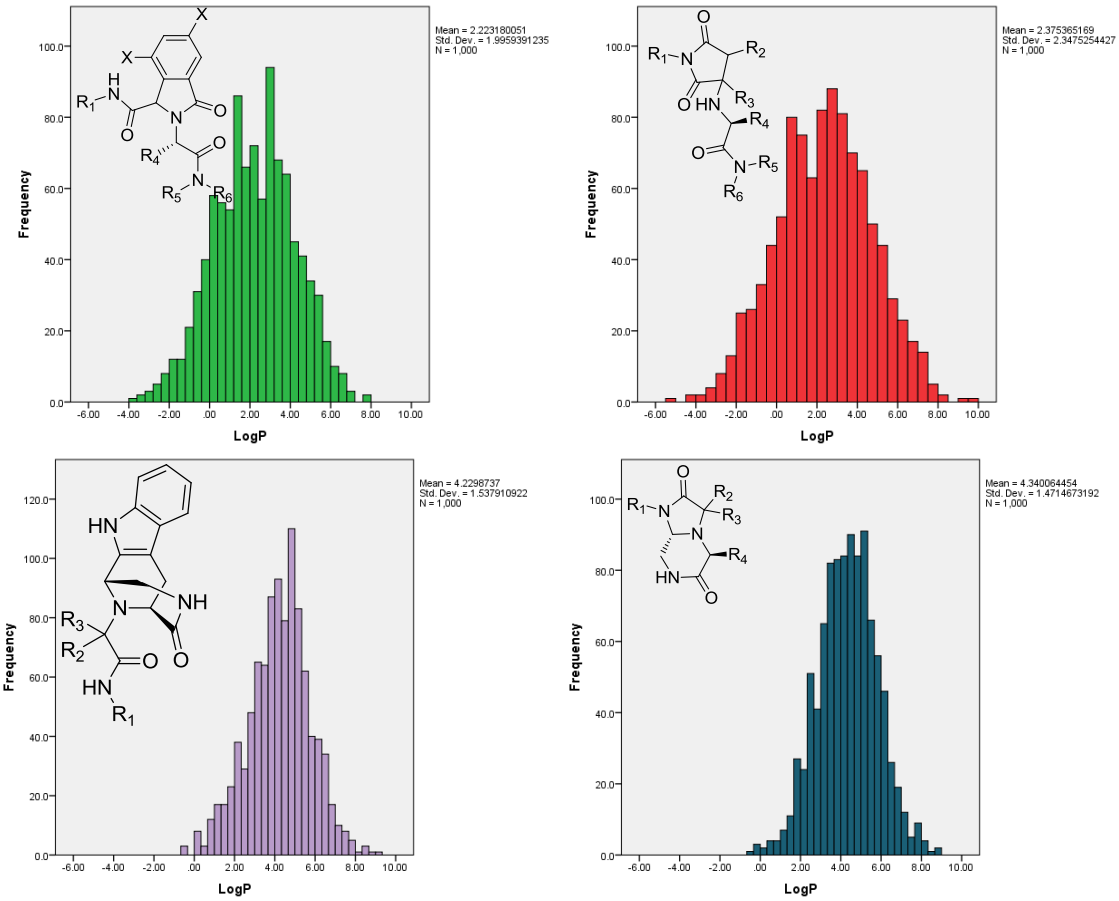
(5'*S*)-5'-benzyl-1'-phenethyldihydro-1'*H*-spiro[cyclohexane-1,3'-imidazo[1,2-*a*]pyrazine]-2',6'(5'*H*,7'*H*)-dione [13d]: 
54% yield as a light yellowish solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (td, *J* = 13.2, 4.8 Hz, 1H), 0.96-1.04 (m, 1H), 1.30-1.38 (m, 2H), 1.44 (td, *J* = 9.0, 3.6 Hz, 1H), 1.49-1.53 (m, 1H), 1.57-1.59 (m, 2H), 1.73-1.80 (m, 1H), 1.94-2.04 (m, 1H), 2.75-2.83 (m, 2H), 2.88 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.04-3.11 (m, 3H), 3.33 (dt, *J* = 12.0, 4.2 Hz, 1H), 3.65 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.72-3.77 (m, 1H), 4.16 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.78 (brs, 1H), 7.16-7.21 (m, 4H), 7.21-7.26 (m, 4H), 7.30-7.32 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 22.0, 24.9, 32.9, 33.8, 34.4, 40.0, 41.7, 46.4, 55.9, 61.7, 64.8, 126.6, 126.7, 128.1, 128.6, 128.7, 129.9, 137.9, 138.3, 172.4, 175.1 ppm. SFCMS (APCI, *m/z*): $[M]^+$ calc.: 418.24; found: 418.35.

3. Chemical Descriptor/Drug Property analysis

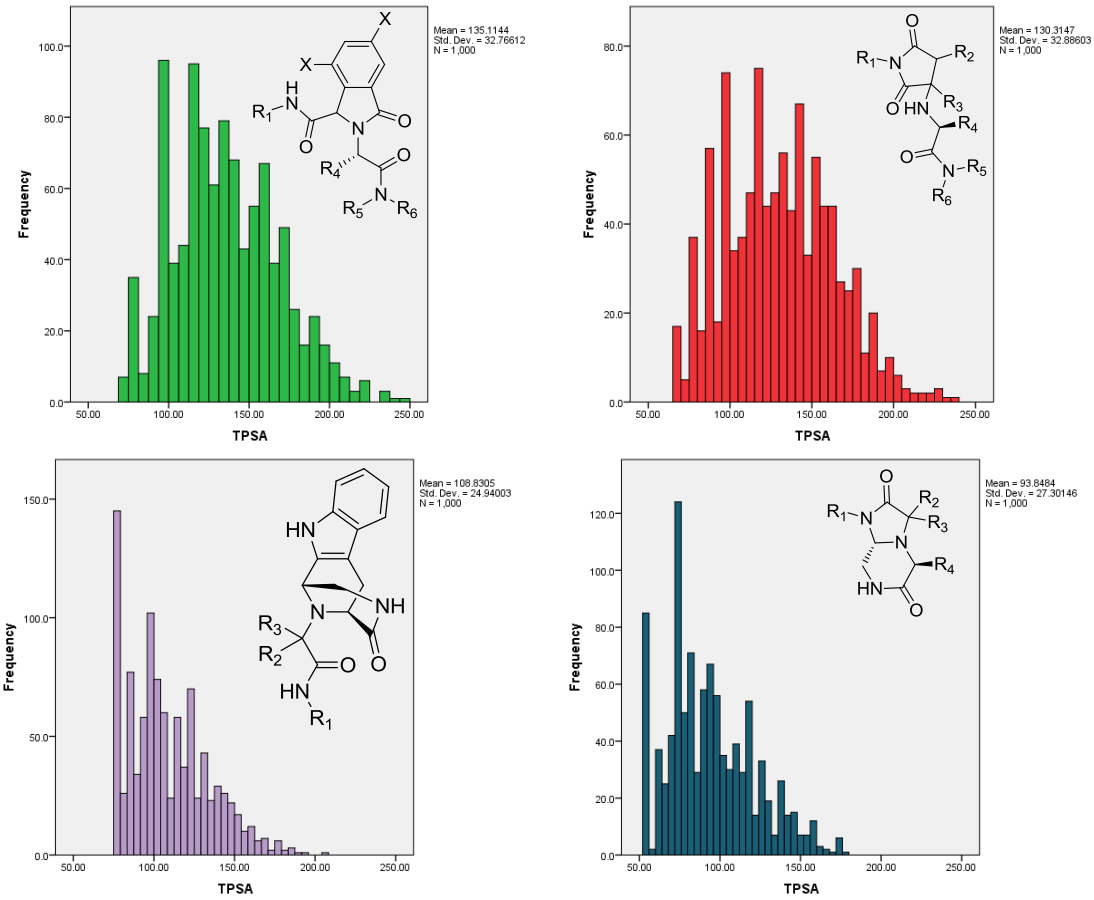
A virtual library of 500,000 randomly generated compounds were made for each of the four reactions using previously described methods (Koes, D. et al. *PLoS One* **2012**, *7*, e32839.). 1000 compounds of each reaction were randomly selected and physiochemical properties relating to drug likeness were analyzed via ChemAxon's Instant JChem Software (Instant JChem 5.9.2, 2012, ChemAxon http://www.chemaxon.com). 3D compounds for PMI calculation were made using Moloc (http://www.moloc.ch). Principal moment of inertia was calculated using Schrodinger's Maestro V 9.3(**Suite 2012**: Maestro, version 9.3, Schrödinger, LLC, New York, NY, 2012.)



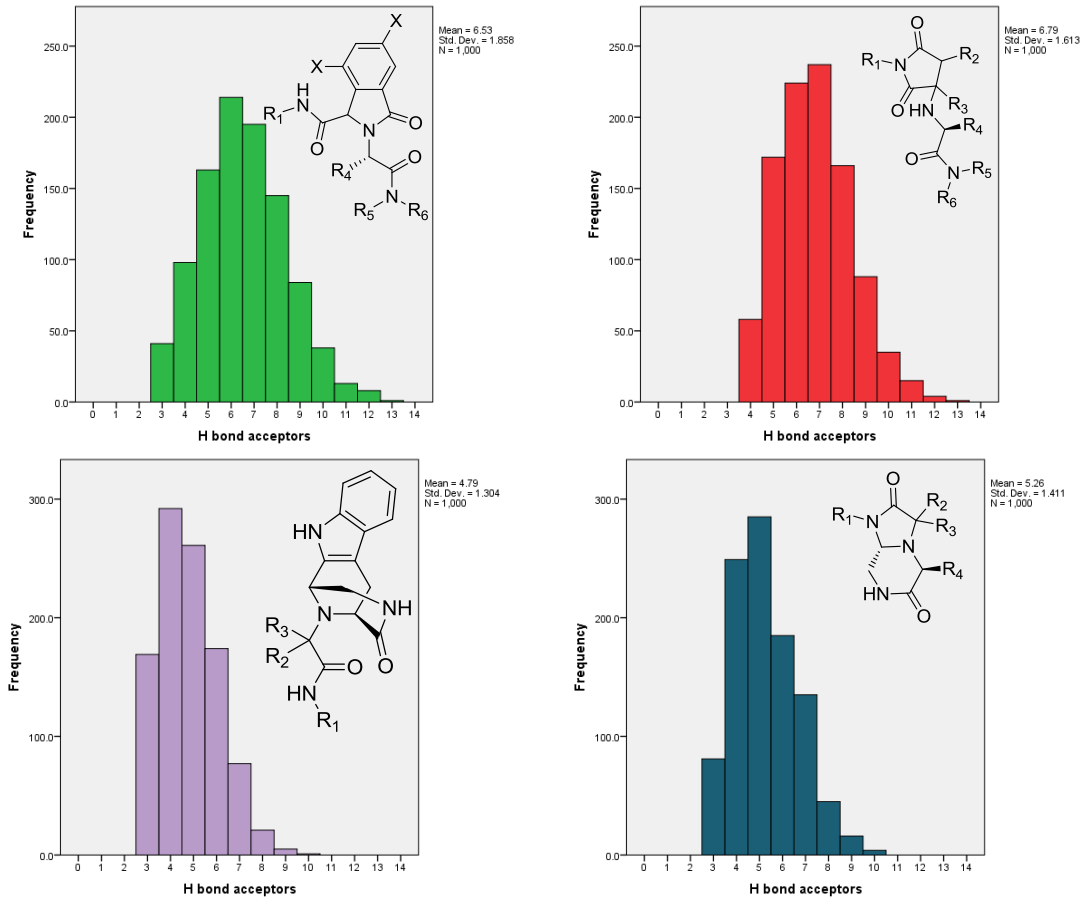
SI-Fig 1: Distribution of molecular weight of 1000 randomly generated compounds of all four scaffold classes.



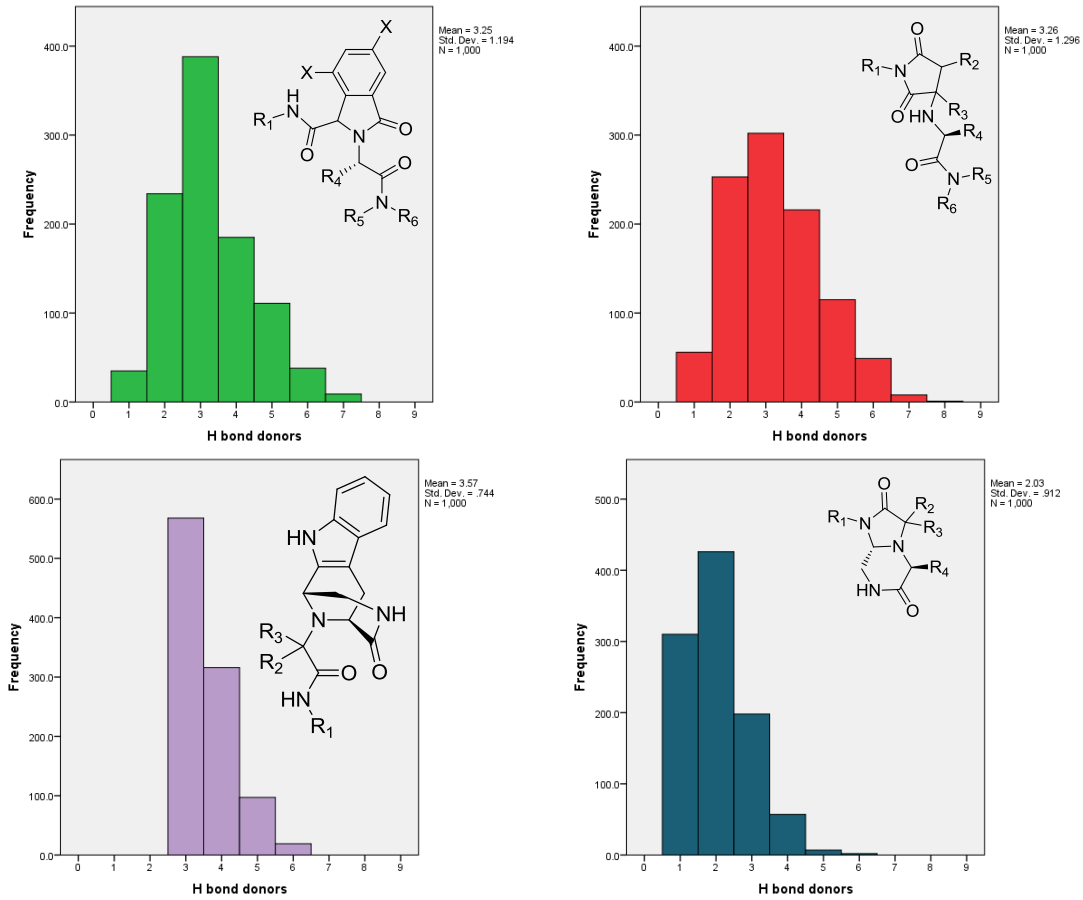
SI-Fig 2: Distribution of LogP of 1000 randomly generated compounds of all four scaffold classes.



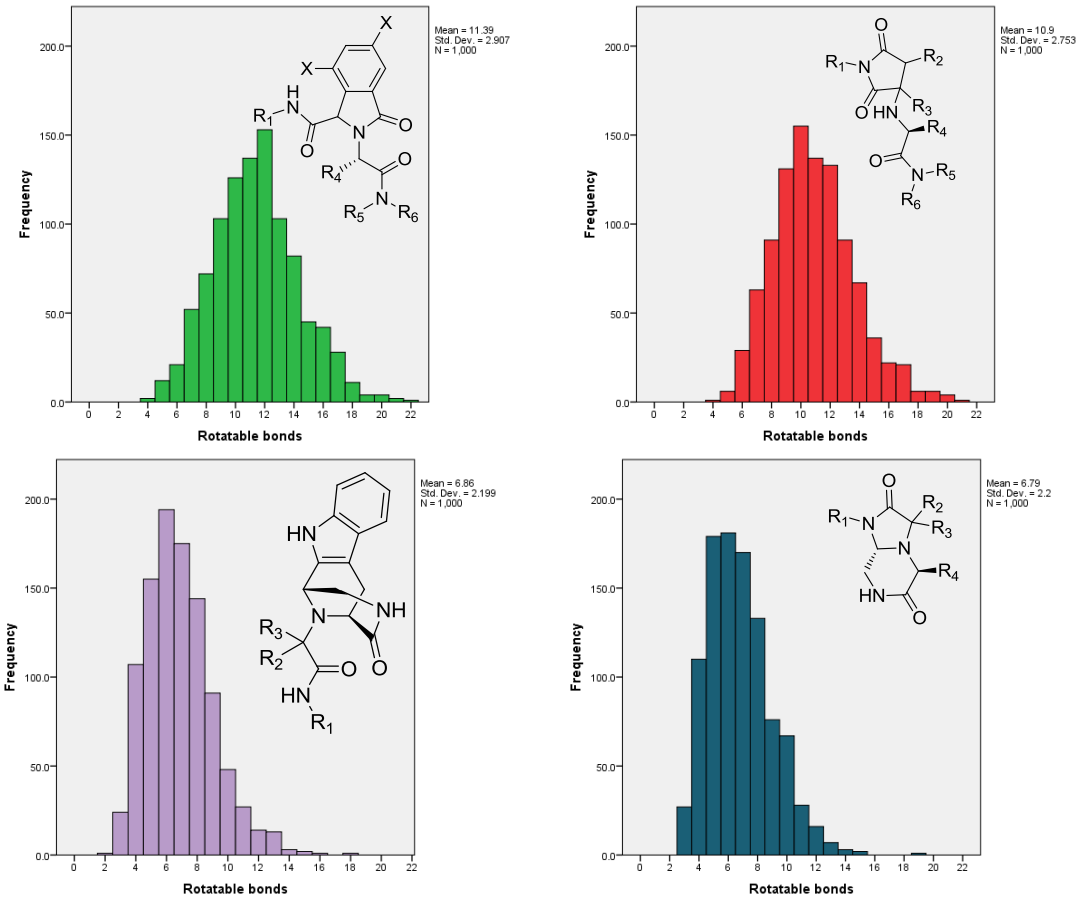
SI-Fig 3: Distribution of Total Polar Surface Area (TPSA) of 1000 randomly generated compounds of all four scaffold classes



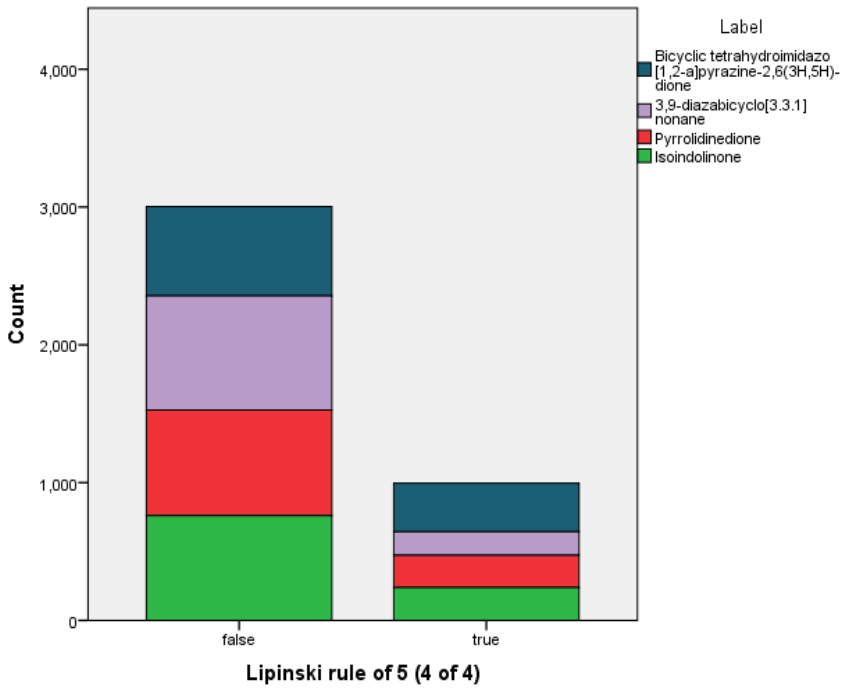
SI-Fig 4: Distribution of hydrogen bond acceptors of 1000 randomly generated compounds of all four scaffold classes



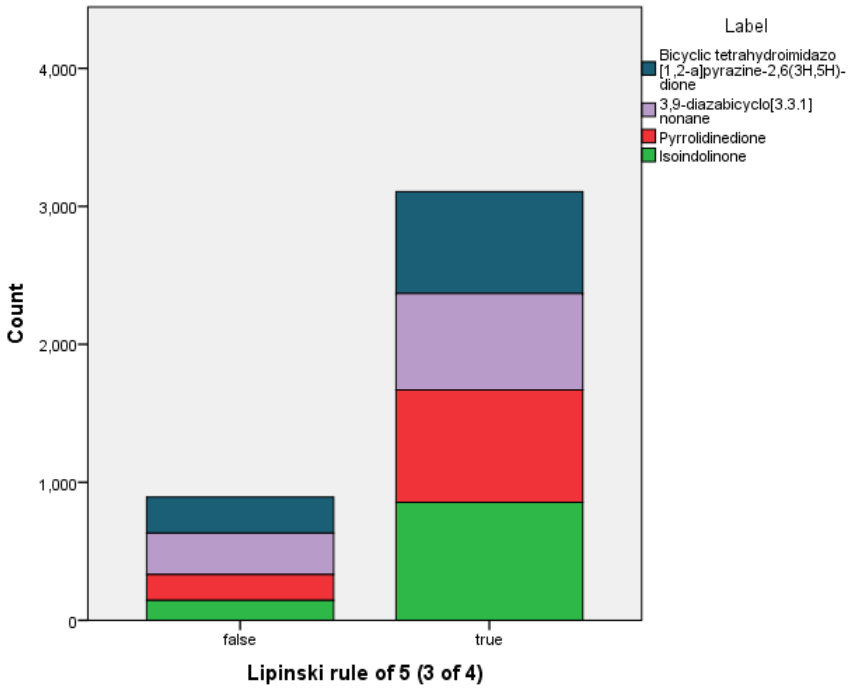
SI-Fig 5: Distribution of hydrogen bond donors of 1000 randomly generated compounds of all four scaffold classes



SI-Fig 6: Distribution of rotatable bonds of 1000 randomly generated compounds of all four scaffold classes



SI-Fig 7: Count of compounds which pass all 4 of Lipinski's rule of 5 1000 randomly generated compounds of all four scaffold classes



SI-Fig 8: Count of compounds which pass 3 of 4 of Lipinski's rule of 5 1000 randomly generated compounds of all four scaffold classes

5. Single crystal X-Ray structure determination of Products 9a, 11d and 13c

General:

The data was collected on a X-ray single crystal diffractometer equipped with a CCD detector (Bruker, APEX II, κ–CCD), a rotating anode (Bruker AXS, FR591) with MoK$_\alpha$ radiation (λ = 0.71073 Å), and a graphite monochromator by using the SMART software package.[1] The measurements were performed on single crystals coated with perfluorinated ether. The crystals were fixed on the top of a glass fiber, transferred to the diffractometer and frozen under a stream of cold nitrogen. A matrix scan, using three short runs, was used to determine the initial lattice parameters. Reflections were merged and corrected for Lorenz and polarization effects, scan speed, and background using SAINT.[2] Absorption corrections, including odd and even ordered spherical harmonics were performed using SADABS.[2] Space group assignments were based upon systematic absences, *E* statistics, and successful refinement of the structures. Structures were solved by direct methods with the aid of successive difference Fourier maps, and were refined against all data using WinGX[7] based on SIR-92.[3] Hydrogen atoms could be located in the difference Fourier maps and were allowed to refine freely. If not mentioned otherwise, non-hydrogen atoms were refined with anisotropic displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$ with SHELXL-97[5] weighting scheme. Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from *International Tables for Crystallography*.[4] Images of the crystal structures were generated by PLATON[6]. CCDC 922313 (**9a**), CCDC 922314 (**11d**) and 92315 (**13c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Single Crystal X-Ray Structure Determination of Product 9a

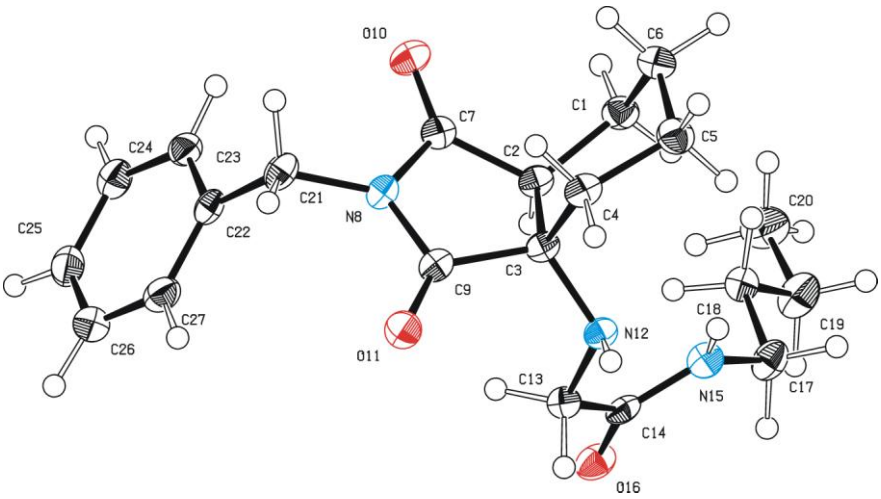


Figure 1 – Ortep drawing of product **9a** with 50% ellipsoids.[6]

Operator: *** Herdtweck ***
Molecular Formula: $C_{21}H_{29}N_3O_3$
Crystal Color / Shape Colorless plate
Crystal Size Approximate size of crystal fragment used for data collection:
0.05 × 0.13 × 0.41 mm
Molecular Weight: 371.47 a.m.u.
F_{000}: 800
Systematic Absences: 0kl: l≠2n; h0l: h≠2n; 00l: l≠2n
Space Group: Orthorhombic *P ca*2_1 (I.T.-No.: 29)
Cell Constants: Least-squares refinement of 9924 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 1.97° < θ < 25.40°; Mo($K\overline{\alpha}$); λ = 71.073 pm

a = 1035.28(4) pm
b = 1033.25(3) pm
c = 1878.03(7) pm
V = 2008.94(12)·10^6 pm^3; *Z* = 4; D_{calc} = 1.228 gcm^{-3}; Mos. = 0.72

Diffractometer: Kappa APEX II (Area Diffraction System; Bruker AXS); rotating anode; graphite monochromator; 50 kV; 40 mA; λ = 71.073 pm; Mo($K\overline{\alpha}$)
Temperature: (-150±1) °C; (123±1) K
Measurement Range: 1.97° < θ < 25.40°; h: -12/12, k: -12/12, l: -22/22
Measurement Time: 2 × 15 s per film
Measurement Mode: measured: 9 runs; 4510 films / scaled: 9 runs; 4510 films
φ– and ω–movement; Increment: $\Delta\varphi/\Delta\omega$ = 0.50°; dx = 40.0 mm
LP - Correction: Yes[2]
Intensity Correction No/Yes; during scaling[2]
Absorption Correction: Multi-scan; during scaling; μ = 0.083 mm^{-1} [2]
Correction Factors: T_{min} = 0.6816 T_{max} = 0.7452
Reflection Data: 68063 reflections were integrated and scaled
4735 reflections systematic absent and rejected
63328 reflections to be merged
3686 independent reflections
0.027 R_{int}: (basis F_o^2)
3686 independent reflections (all) were used in refinements
3564 independent reflections with $I_o > 2\sigma(I_o)$
99.5 % completeness of the data set
360 parameter full-matrix refinement
10.2 reflections per parameter
Solution: Direct Methods[3]; Difference Fourier syntheses
Refinement Parameters: In the asymmetric unit:
27 Non-hydrogen atoms with anisotropic displacement parameters
29 Hydrogen atoms with isotropic displacement parameters
Hydrogen Atoms: All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.
Atomic Form Factors: For neutral atoms and anomalous dispersion[4]
Extinction Correction: no
Weighting Scheme: $w^{-1} = \sigma^2(F_o^2)+(a*P)^2+b*P$
with a: 0.0354; b: 0.3238; P: [Maximum(0 or F_o^2)+2*F_c^2]/3
Shift/Err: Less than 0.001 in the last cycle of refinement:
Resid. Electron Density: +0.15 $e_{0;-}/Å^3$; -0.16 $e_{0;-}/Å^3$
R1: $\Sigma(||F_o|-|F_c||)/\Sigma|F_o|$
[$F_o > 4\sigma(F_o)$; N=3564]: = 0.0242
[all reflctns; N=3686]: = 0.0259
wR2: $[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
[$F_o > 4\sigma(F_o)$; N=3564]: = 0.0609
[all reflctns; N=3686]: = 0.0624
Goodness of fit: $[\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2}$ = 1.064
Flack's Parameter : x = 0.1(7)
Remarks: Refinement expression $\Sigma w(F_o^2-F_c^2)^2$
The correct enantiomere could **not** be proved by Flack's Parameter.

Single Crystal X-Ray Structure Determination of Product 11d

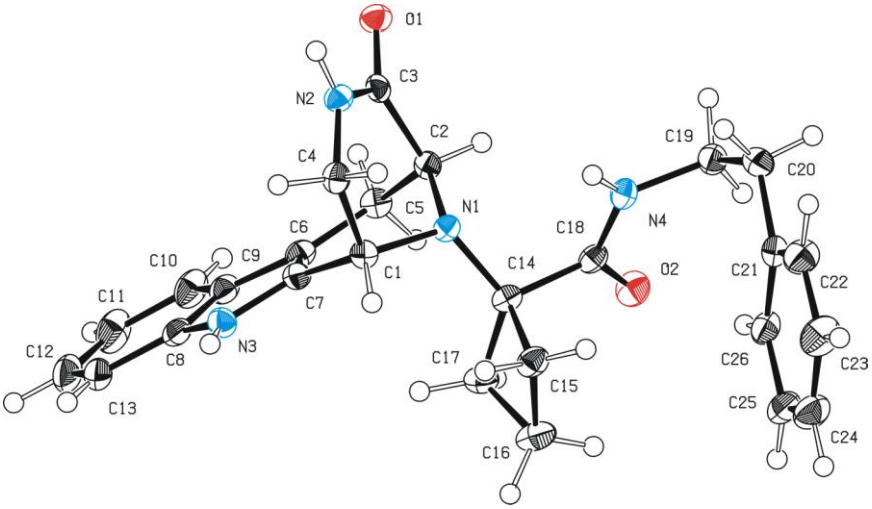


Figure 2 – Ortep drawing of product **11d** with 50% ellipsoids.[6]

Operator: *** Herdtweck ***
Molecular Formula: $C_{26}H_{28}N_4O_2$
Crystal Color / Shape Colourless fragment
Crystal Size Approximate size of crystal fragment used for data collection:
0.33 × 0.38 × 0.51 mm
Molecular Weight: 428.52 a.m.u.
F_{000}: 456
Systematic Absences: 0k0: k≠2n
Space Group: Monoclinic $P\,2_1$ (I.T.-No.: 4)
Cell Constants: Least-squares refinement of 9155 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 2.14° < θ < 25.52°; Mo(K$\overline{\alpha}$); λ = 71.073 pm
a = 682.29(1) pm
b = 1900.16(3) pm β = 92.3910(7)°
c = 843.35(1) pm
V = 1092.42(3)·10^6 pm^3; Z = 2; D_{calc} = 1.303 gcm^{-3}; Mos. = 0.40
Diffractometer: Kappa APEX II (Area Diffraction System; Bruker AXS); sealed tube; graphite monochromator; 50 kV; 30 mA; λ = 71.073 pm; Mo(K$\overline{\alpha}$)
Temperature: (-150±1) °C; (123±1) K
Measurement Range: 2.14° < θ < 25.52°; h: -8/8, k: -22/22, l: -10/10
Measurement Time: 2 × 5 s per film
Measurement Mode: measured: 6 runs; 3183 films / scaled: 6 runs; 3183 films
φ– and ω–movement; Increment: $\Delta\varphi/\Delta\omega$ = 0.50°; dx = 50.0 mm
LP - Correction: Yes[2]
Intensity Correction No/Yes; during scaling[2]
Absorption Correction: Multi-scan; during scaling; μ = 0.084 mm^{-1} [2]
Correction Factors: T_{min} = 0.6898 T_{max} = 0.7452
Reflection Data: 22029 reflections were integrated and scaled
90 reflections systematic absent and rejected
21939 reflections to be merged
4057 independent reflections
0.016 R_{int}: (basis F_o^2)
4057 independent reflections (all) were used in refinements
4015 independent reflections with $I_o > 2\sigma(I_o)$
99.5 % completeness of the data set
401 parameter full-matrix refinement
10.1 reflections per parameter

Solution: Direct Methods [3, 7]; Difference Fourier syntheses
Refinement Parameters: In the asymmetric unit:
32 Non-hydrogen atoms with anisotropic displacement parameters
28 Hydrogen atoms with isotropic displacement parameters
Hydrogen Atoms: All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.
Atomic Form Factors: For neutral atoms and anomalous dispersion[4, 5, 7]
Extinction Correction: no
Weighting Scheme: $w^{-1} = \sigma^2(F_o^2)+(a*P)^2+b*P$
with a: 0.0390; b: 0.1287; P: [Maximum(0 or F_o^2)+2*F_c^2]/3
Shift/Err: Less than 0.001 in the last cycle of refinement:
Resid. Electron Density: +0.17 $e_{0;-}/Å^3$; -0.16 $e_{0;-}/Å^3$
R1: $\Sigma(||F_o|-|F_c||)/\Sigma|F_o|$
[$F_o > 4\sigma(F_o)$; N=4015]: = 0.0236
[all reflctns; N=4057]: = 0.0239
wR2: $[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
[$F_o > 4\sigma(F_o)$; N=4015]: = 0.0604
[all reflctns; N=4057]: = 0.0606
Goodness of fit: $[\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2}$ = 1.043
Flack's Parameter : x = -0.2(7)
Remarks: Refinement expression $\Sigma w(F_o^2-F_c^2)^2$
The correct enantiomere is proved by synthesis

Single Crystal X-Ray Structure Determination of Product 13c

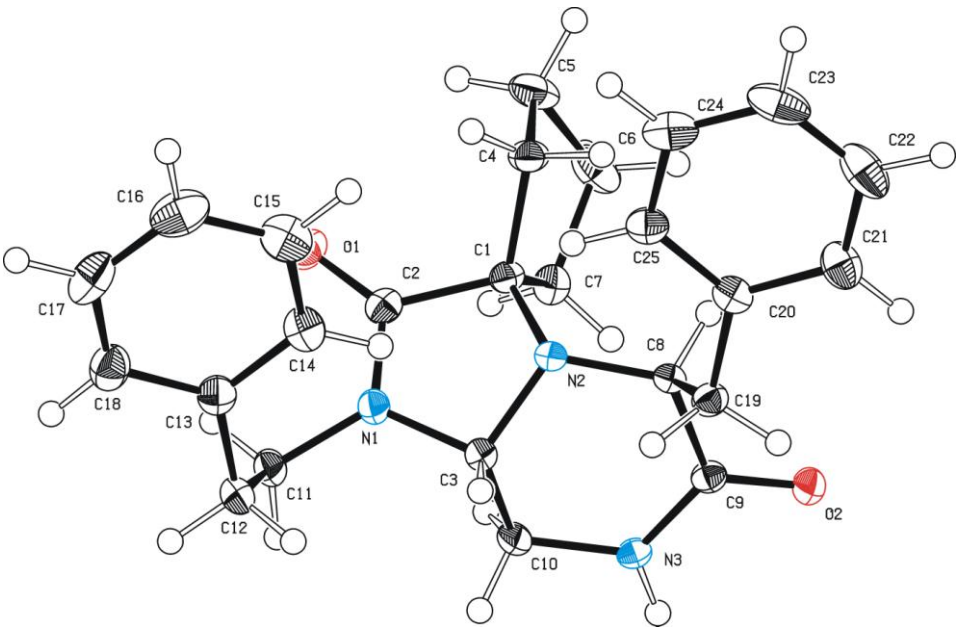


Figure 3 – Ortep drawing of product **13c** with 50% ellipsoids.[6]

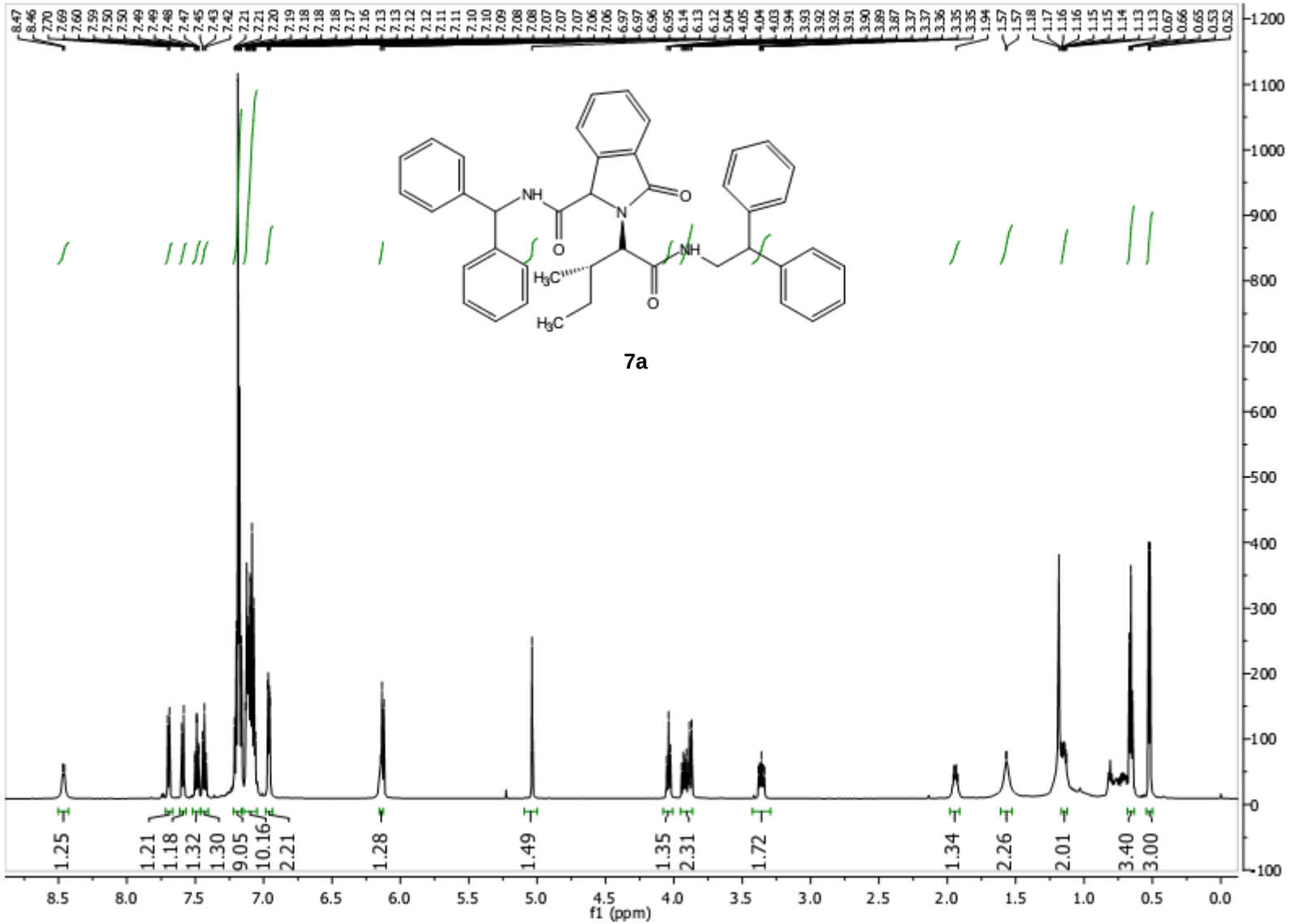
Operator: *** Herdtweck ***
Molecular Formula: $C_{25}H_{29}N_3O_2$
Crystal Color / Shape Colorless fragment
Crystal Size Approximate size of crystal fragment used for data collection:
0.36 × 0.61 × 0.64 mm
Molecular Weight: 403.51 a.m.u.
F_{000}: 864
Systematic Absences: h00: h≠2n; 0k0: k≠2n, 00l: l≠2n
Space Group: Orthorhombic $P\,2_12_12_1$ (I.T.-No.: 19)
Cell Constants: Least-squares refinement of 9827 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 1.88° < θ < 25.42°; Mo($K\overline{\alpha}$); λ = 71.073 pm

a = 799.93(2) pm
b = 1214.97(2) pm
c = 2171.98(4) pm
V = 2110.93(7)·10^6 pm^3; Z = 4; D_{calc} = 1.270 gcm^{-3}; Mos. = 0.67
Diffractometer: Kappa APEX II (Area Diffraction System; Bruker AXS); sealed tube; graphite monochromator; 50 kV; 30 mA; λ = 71.073 pm; Mo($K\overline{\alpha}$)
Temperature: (-150±1) °C; (123±1) K
Measurement Range: 1.88° < θ < 25.42°; h: -9/9, k: -14/14, l: -26/26
Measurement Time: 2 × 5 s per film
Measurement Mode: measured: 7 runs; 3519 films / scaled: 7 runs; 3519 films
φ– and ω–movement; Increment: $\Delta\varphi/\Delta\omega$ = 0.50°; dx = 50.0 mm
LP - Correction: Yes[2]
Intensity Correction No/Yes; during scaling[2]
Absorption Correction: Multi-scan; during scaling; μ = 0.081 mm^{-1} [2]
Correction Factors: T_{min} = 0.7029 T_{max} = 0.7452
Reflection Data: 47946 reflections were integrated and scaled
231 reflections systematic absent and rejected
47715 reflections to be merged
3904 independent reflections
0.017 R_{int}: (basis F_o^2)
3904 independent reflections (all) were used in refinements
3859 independent reflections with $I_o > 2\sigma(I_o)$
100 % completeness of the data set
388 parameter full-matrix refinement
10.1 reflections per parameter
Solution: Direct Methods [3, 7]; Difference Fourier syntheses
Refinement Parameters: In the asymmetric unit:
30 Non-hydrogen atoms with anisotropic displacement parameters
29 Hydrogen atoms with isotropic displacement parameters
Hydrogen Atoms: All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.
Atomic Form Factors: For neutral atoms and anomalous dispersion [4, 5, 7]
Extinction Correction: F_c (korr) = kF_c[1+ 0.001 ·ε·F_c^2·λ^3/sin(2Θ)]-1/4 SHELXL-97[5, 7]; ε refined to ε = 0.0069(5)
Weighting Scheme: $w^{-1} = \sigma^2(F_o^2)+(a*P)^2+b*P$
with a: 0.0256; b: 0.4759; P: [Maximum(0 or F_o^2)+2*F_c^2]/3
Shift/Err: Less than 0.001 in the last cycle of refinement:
Resid. Electron Density: +0.17 $e_{0;-}/Å^3$; -0.14 $e_{0;-}/Å^3$
R1: $\Sigma(||F_o|-|F_c||)/\Sigma|F_o|$
[$F_o > 4\sigma(F_o)$; N=3859]: = 0.0235
[all reflctns; N=3904]: = 0.0238
wR2: $[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
[$F_o > 4\sigma(F_o)$; N=3859]: = 0.0577
[all reflctns; N=3904]: = 0.0581
Goodness of fit: $[\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2}$ = 1.064
Flack's Parameter : x = -0.1(8)
Remarks: Refinement expression $\Sigma w(F_o^2-F_c^2)^2$
The correct enantiomere is proved by synthesis

References:

[1] APEX suite of crystallographic software. APEX 2 Version 2008.4. Bruker AXS Inc., Madison, Wisconsin, USA (2008).
[2] SAINT, Version 7.56a and SADABS Version 2008/1. Bruker AXS Inc., Madison, Wisconsin, USA (2008).
[3] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli M. "**SIR92**", *J. Appl. Cryst.* **1994**, *27*, 435-436.

[4] International Tables for Crystallography, Vol. C, Tables 6.1.1.4 (pp. 500-502), 4.2.6.8 (pp. 219-222), and 4.2.4.2 (pp. 193-199), Wilson, A. J. C., Ed., Kluwer Academic Publishers, Dordrecht, The Netherlands, 1992.
[5] Sheldrick, G. M. "**SHELXL-97**", University of Göttingen, Göttingen, Germany, (1998).
[6] Spek, A. L. "**PLATON**", A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, (2010).
[7] L. J. Farrugia, "**WinGX** (Version 1.70.01 January 2005) ", *J. Appl. Cryst.* **1999**, *32*, 837-838.



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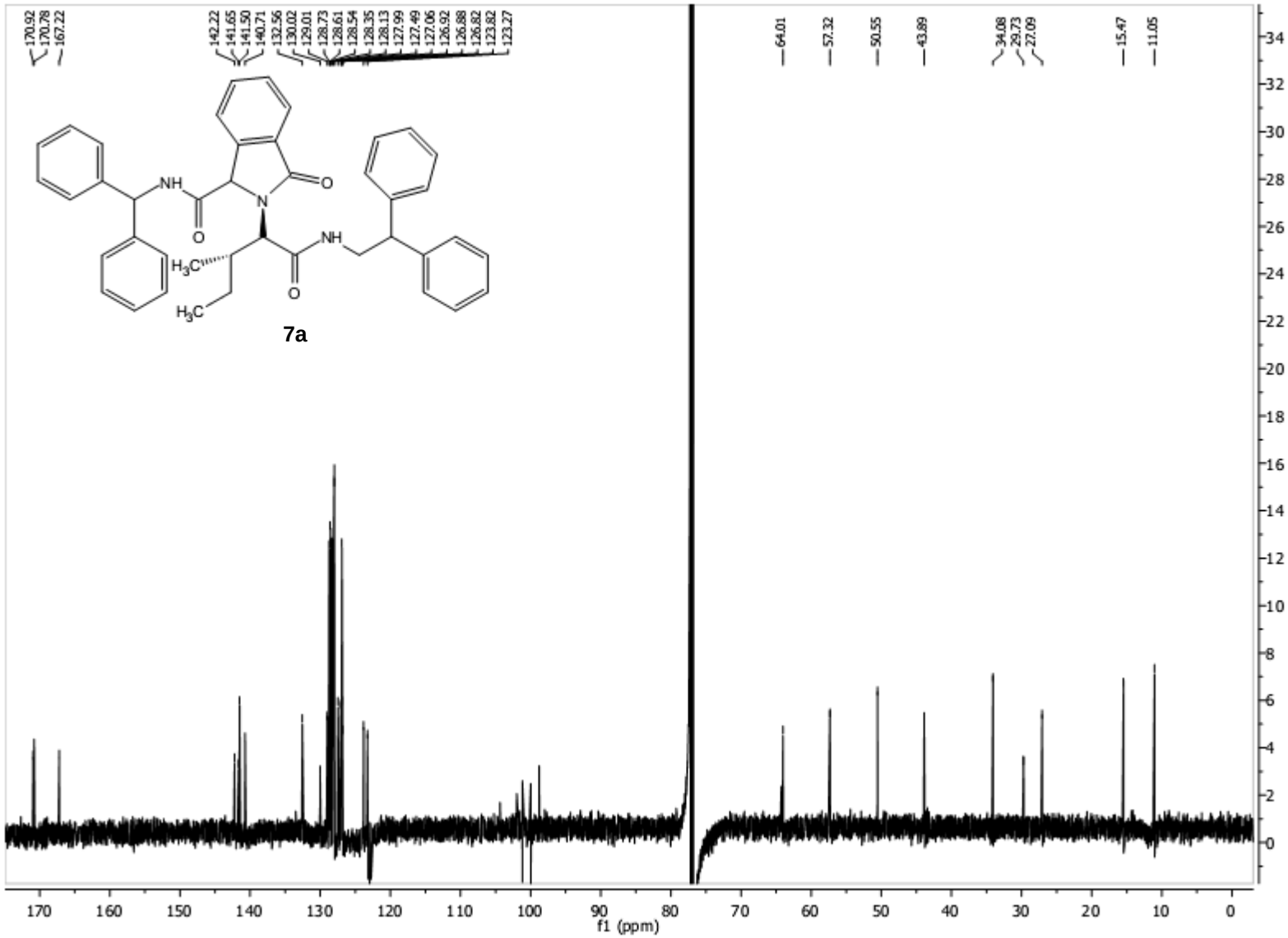

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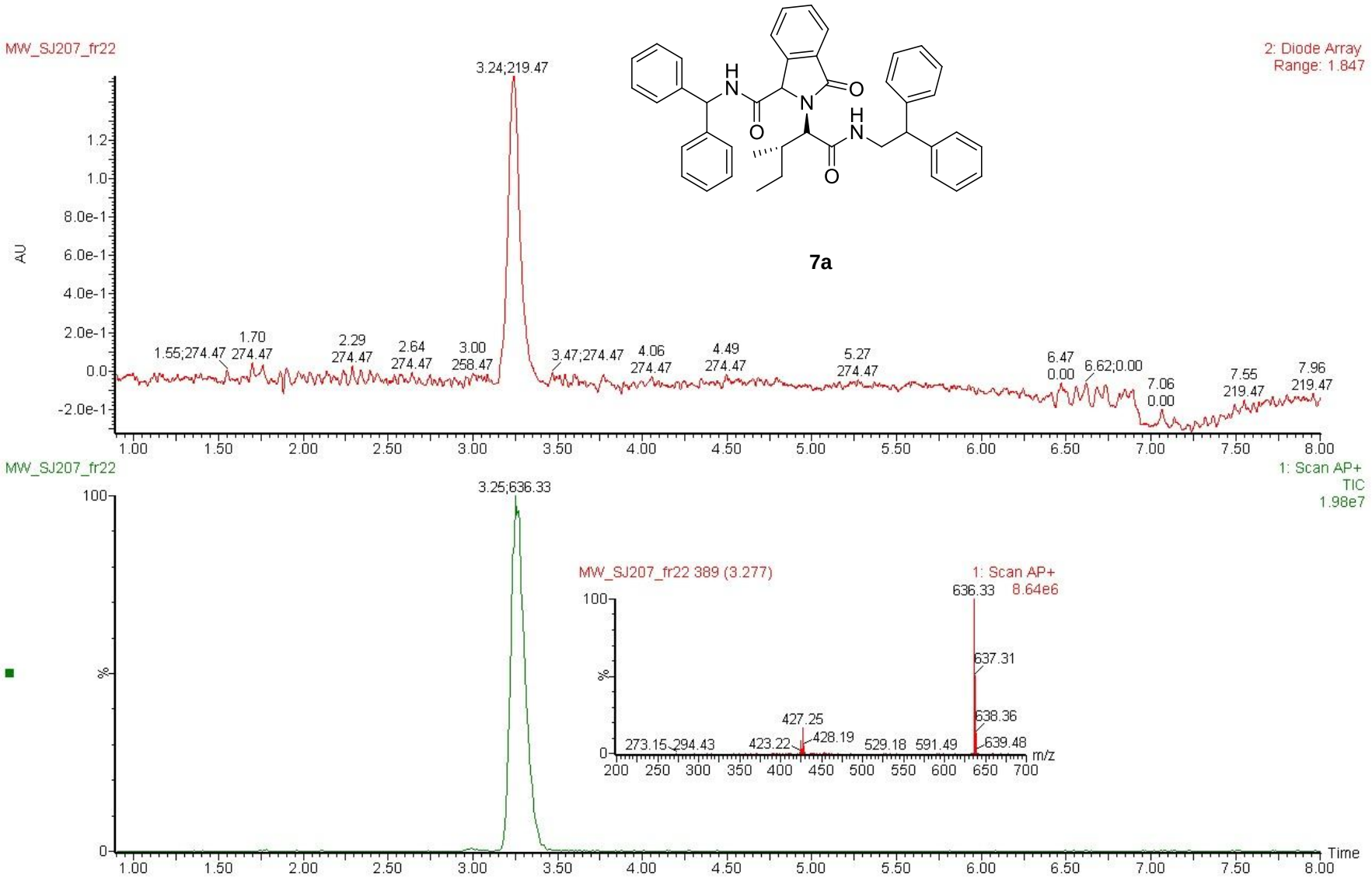

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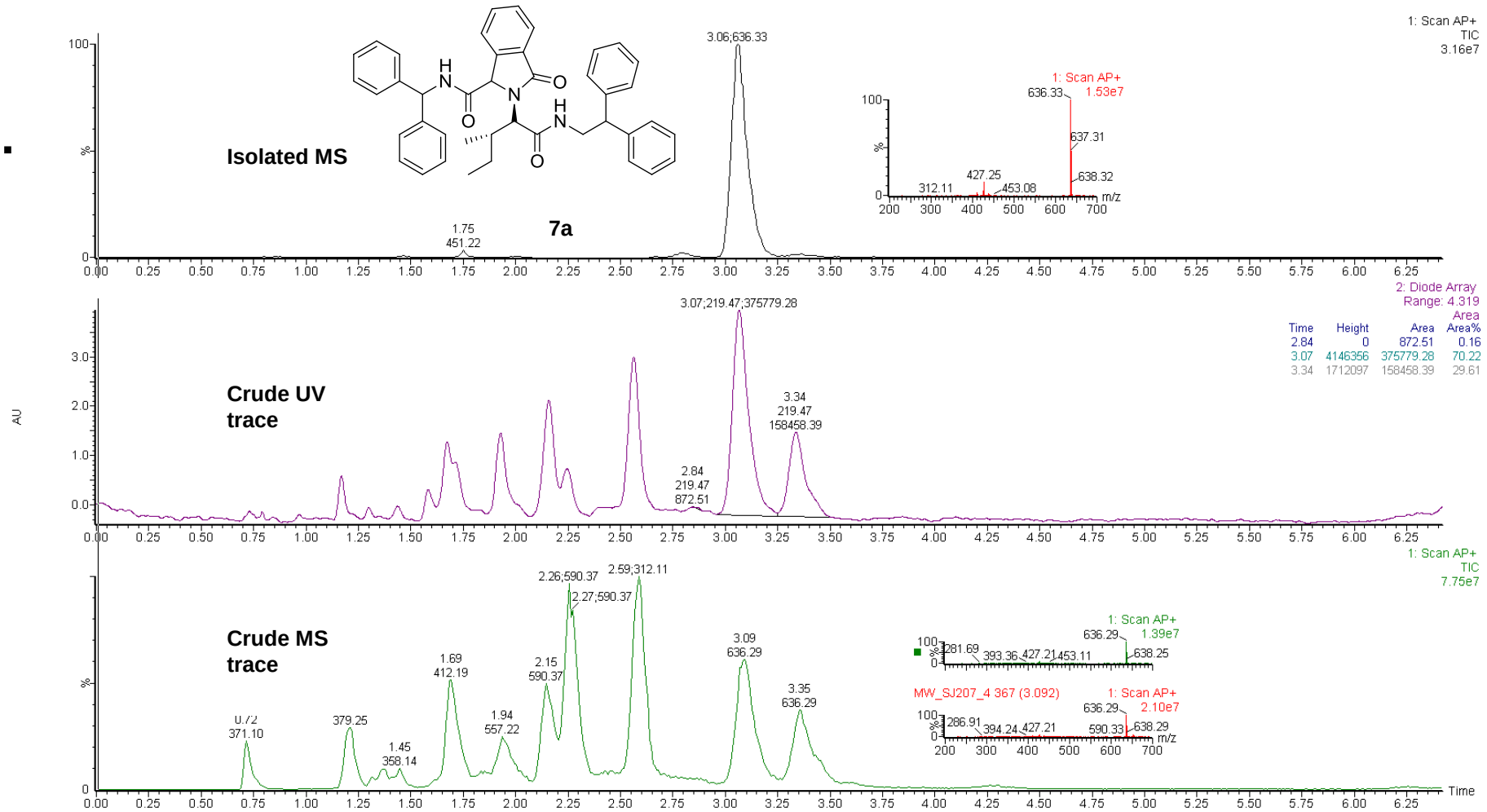

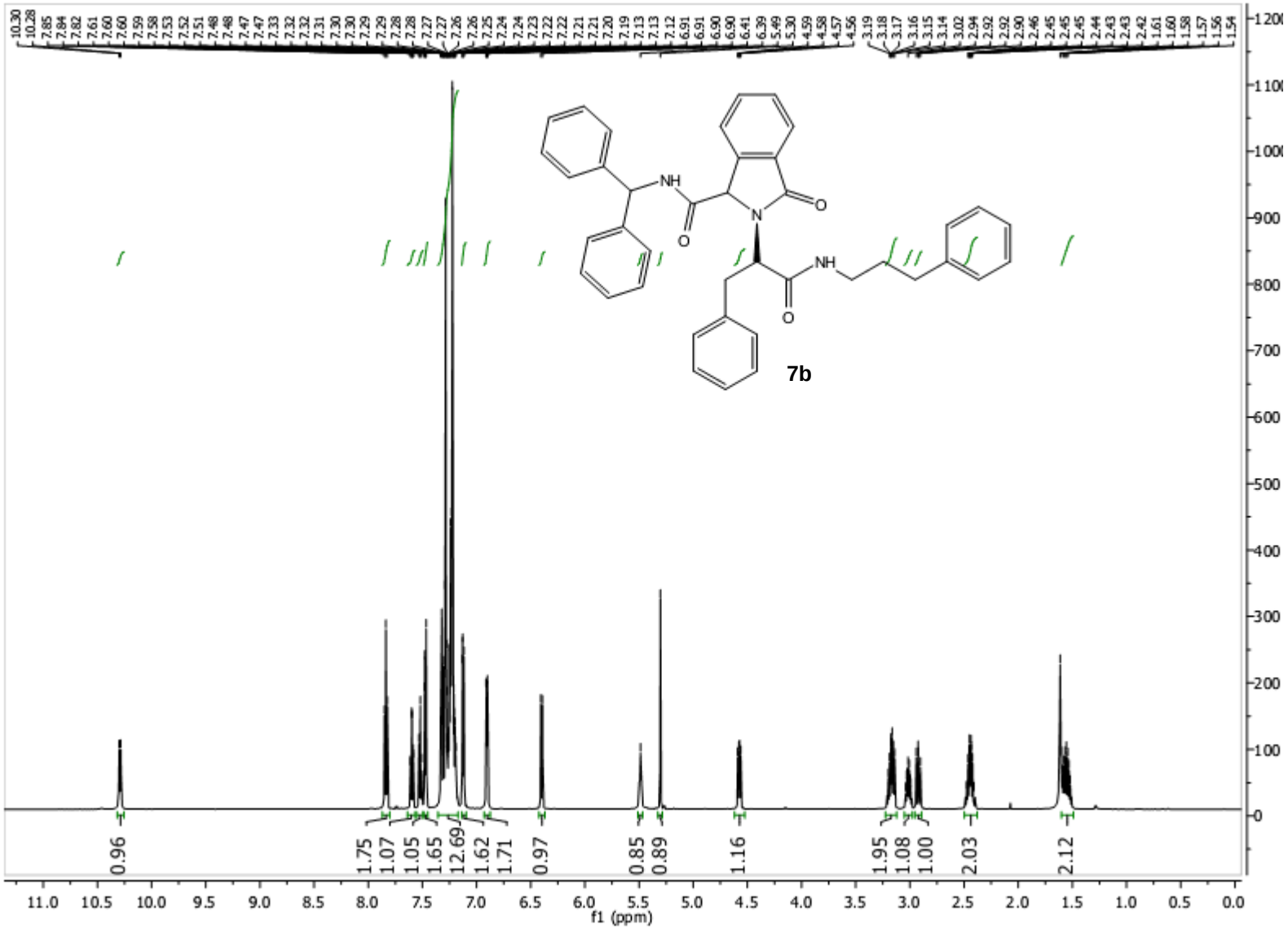

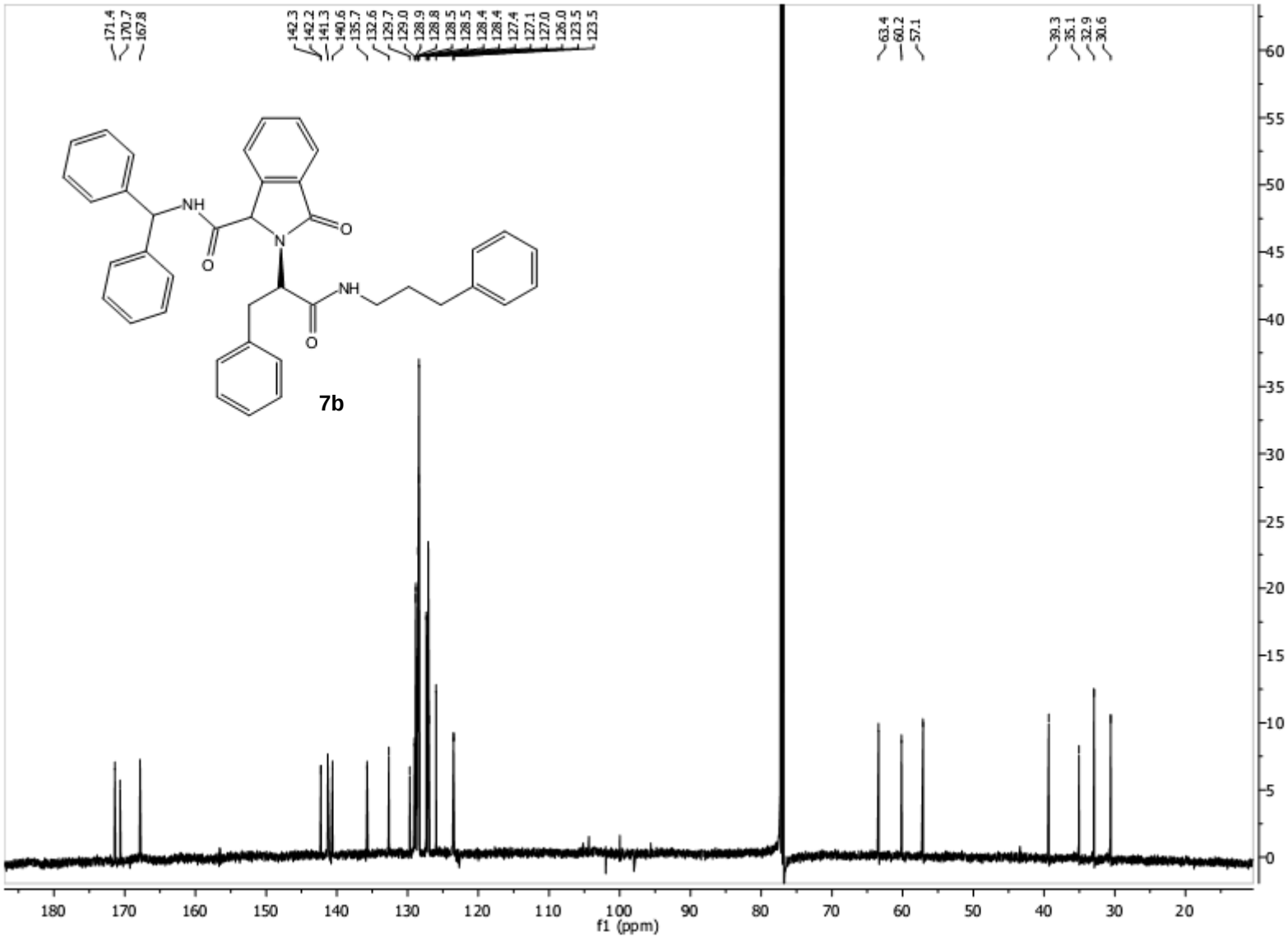

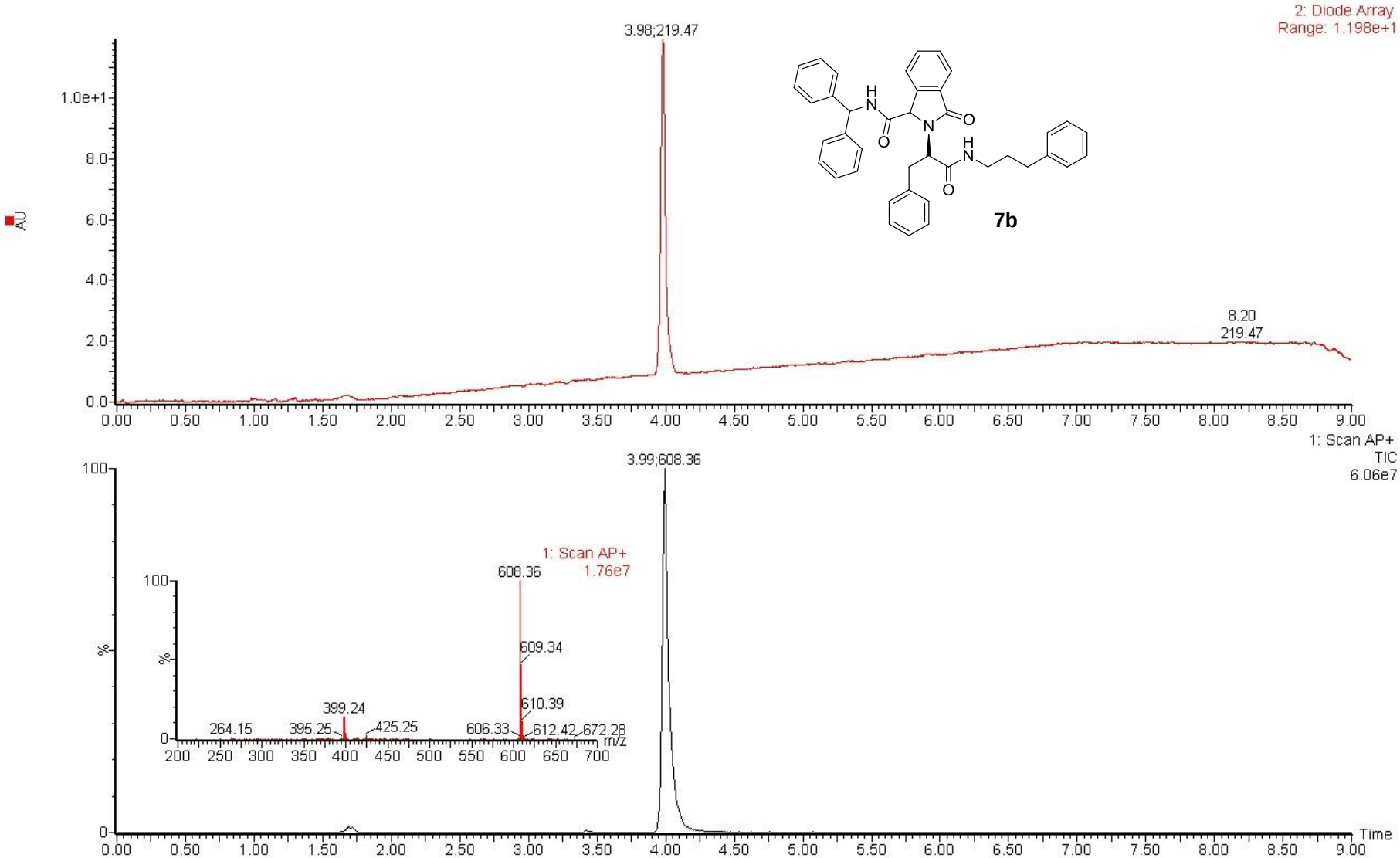

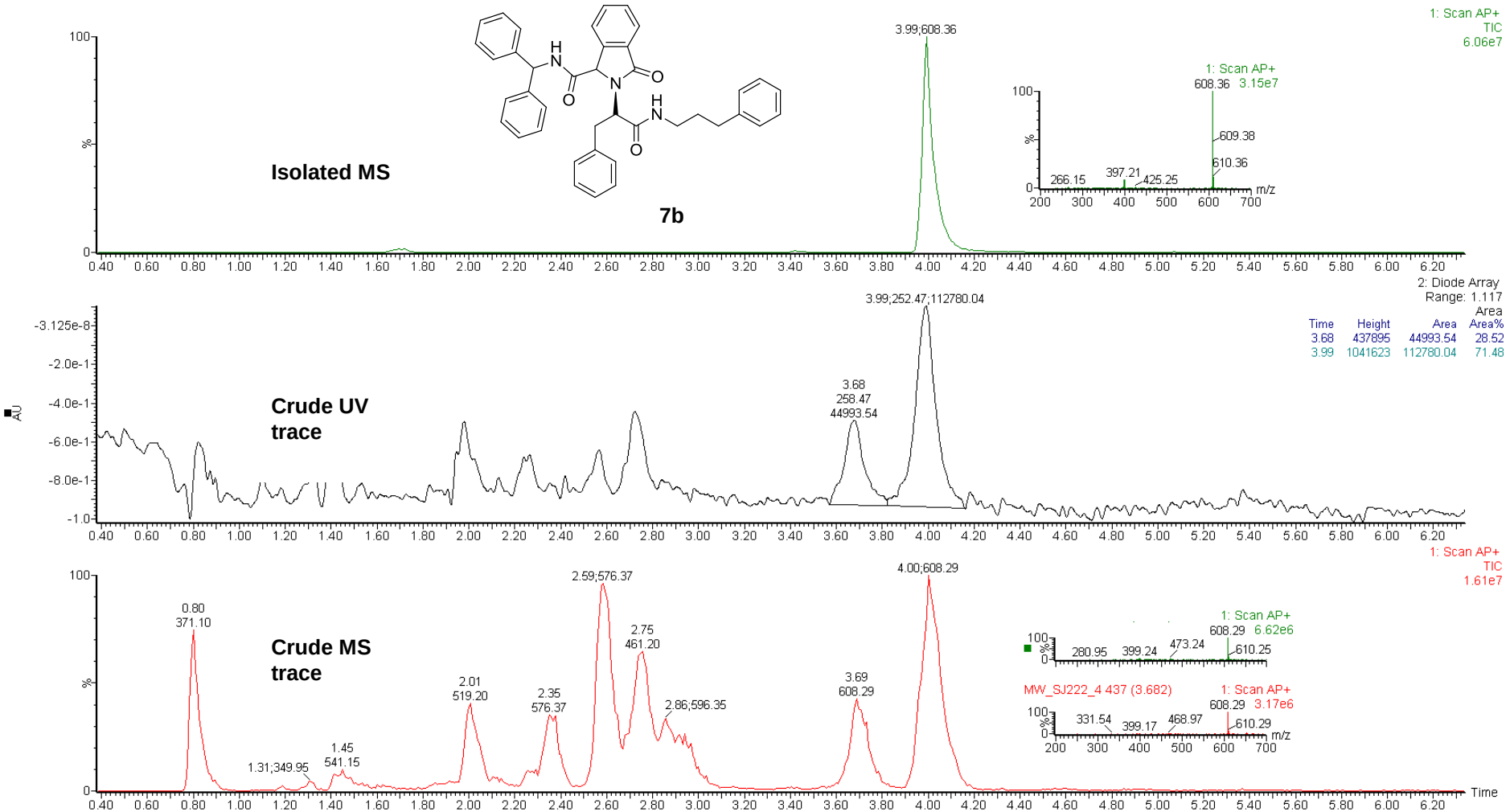

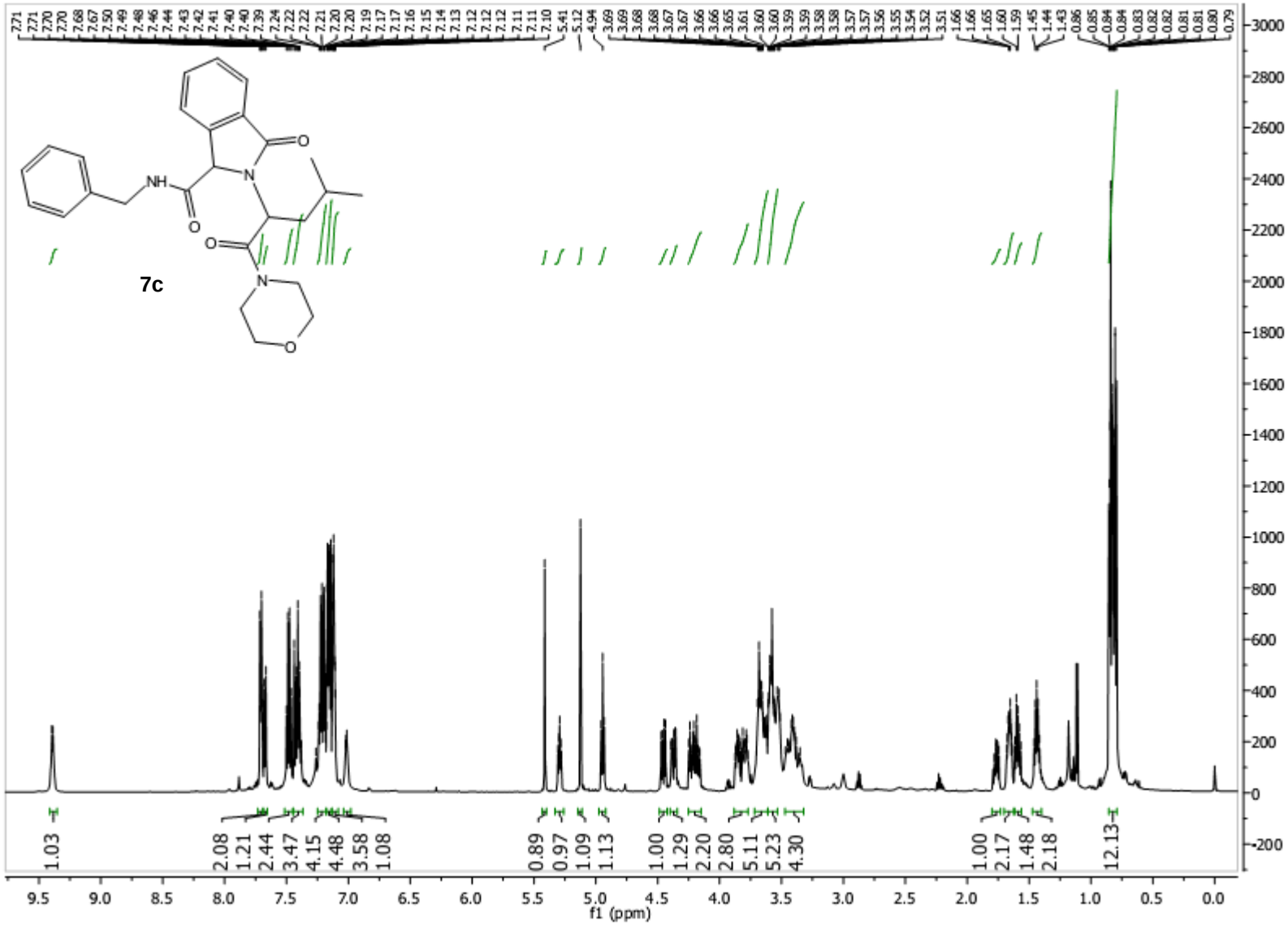

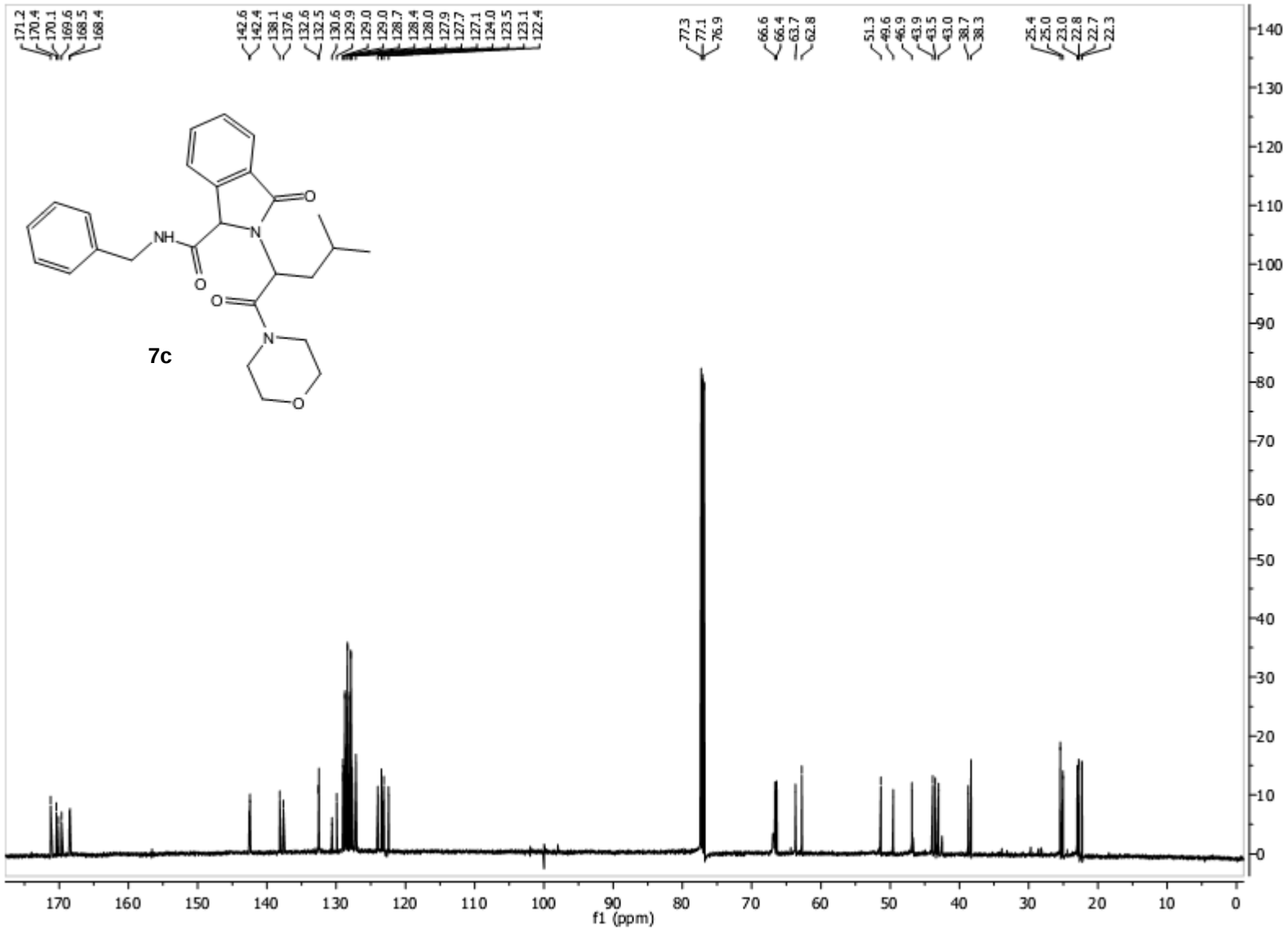

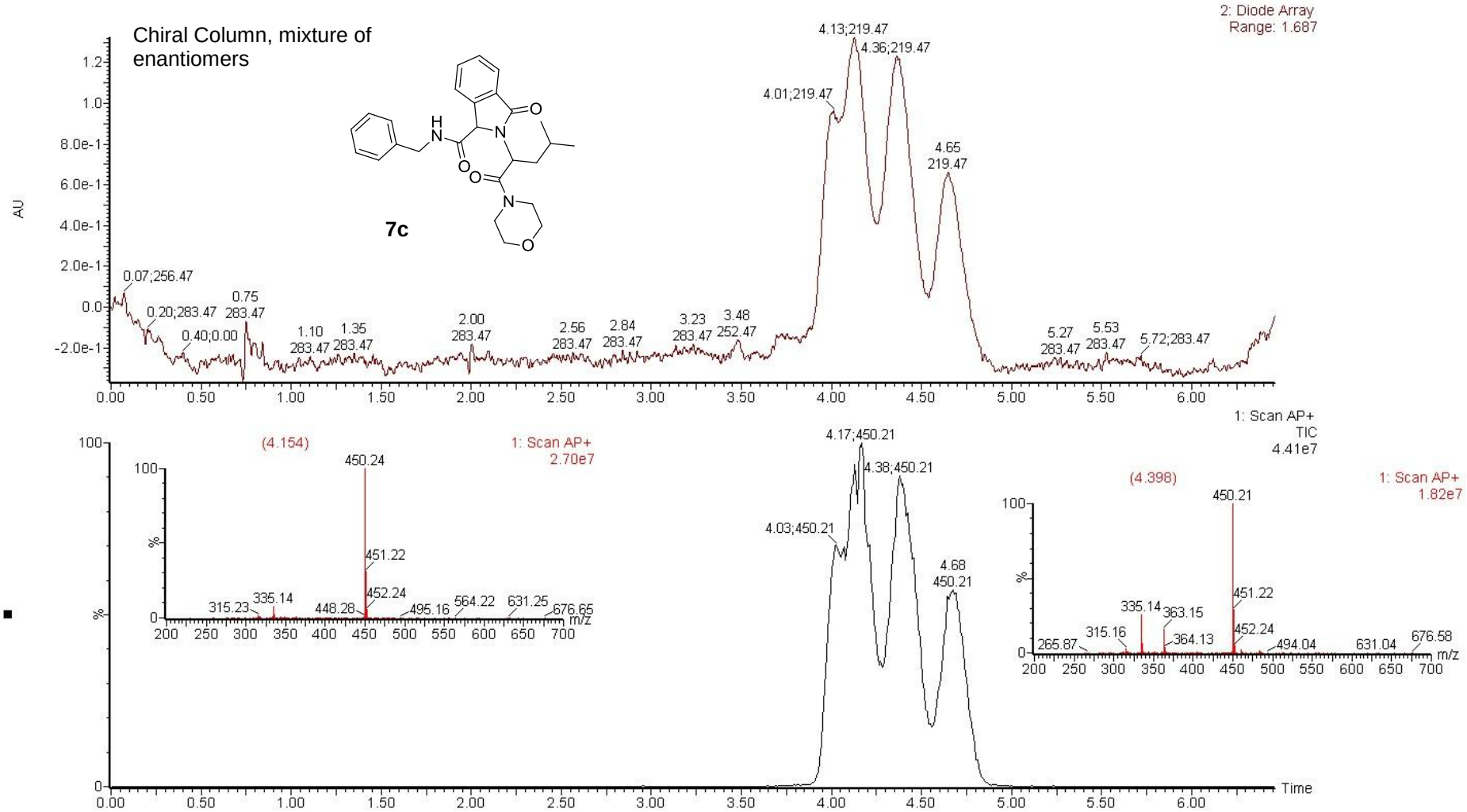

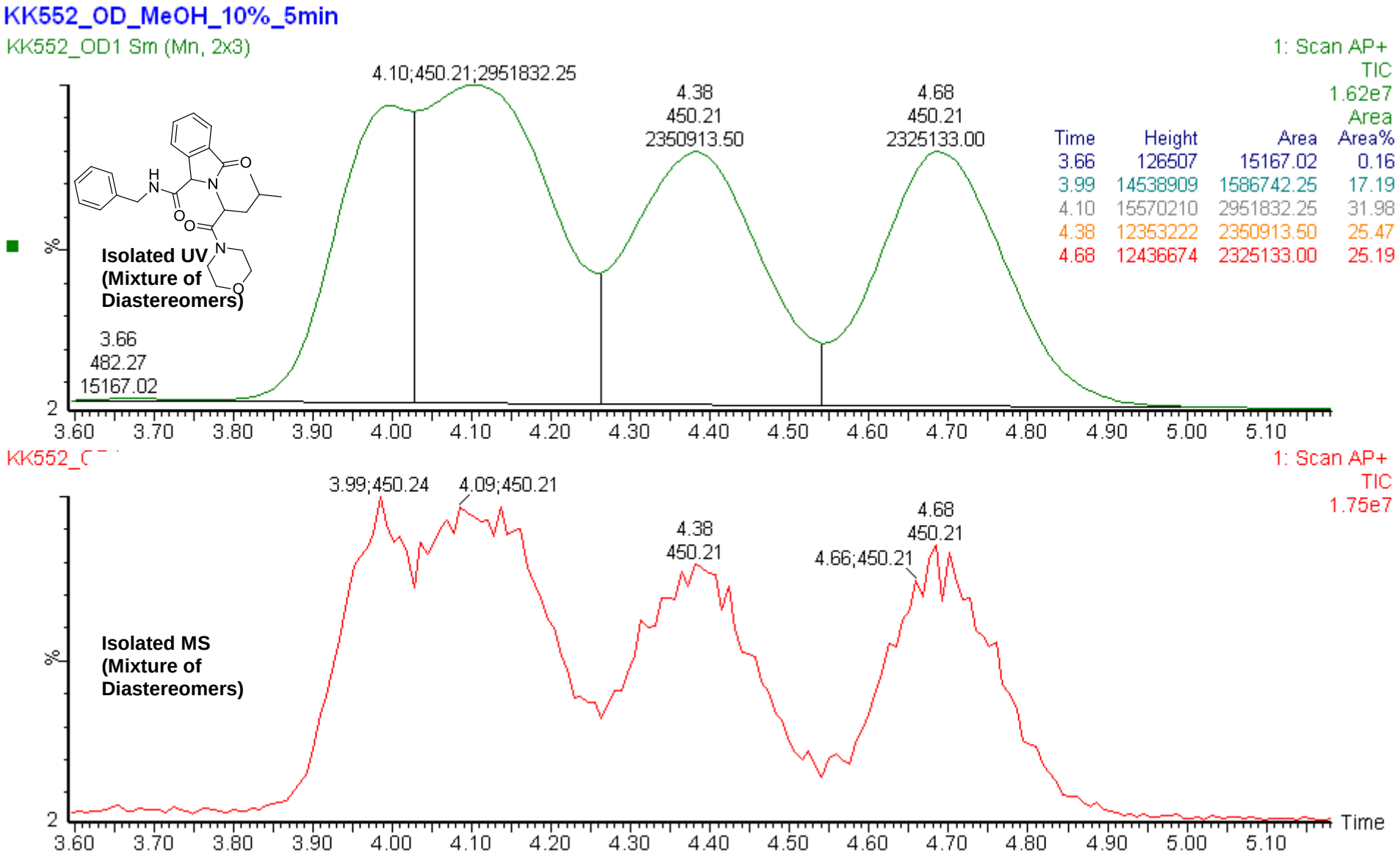

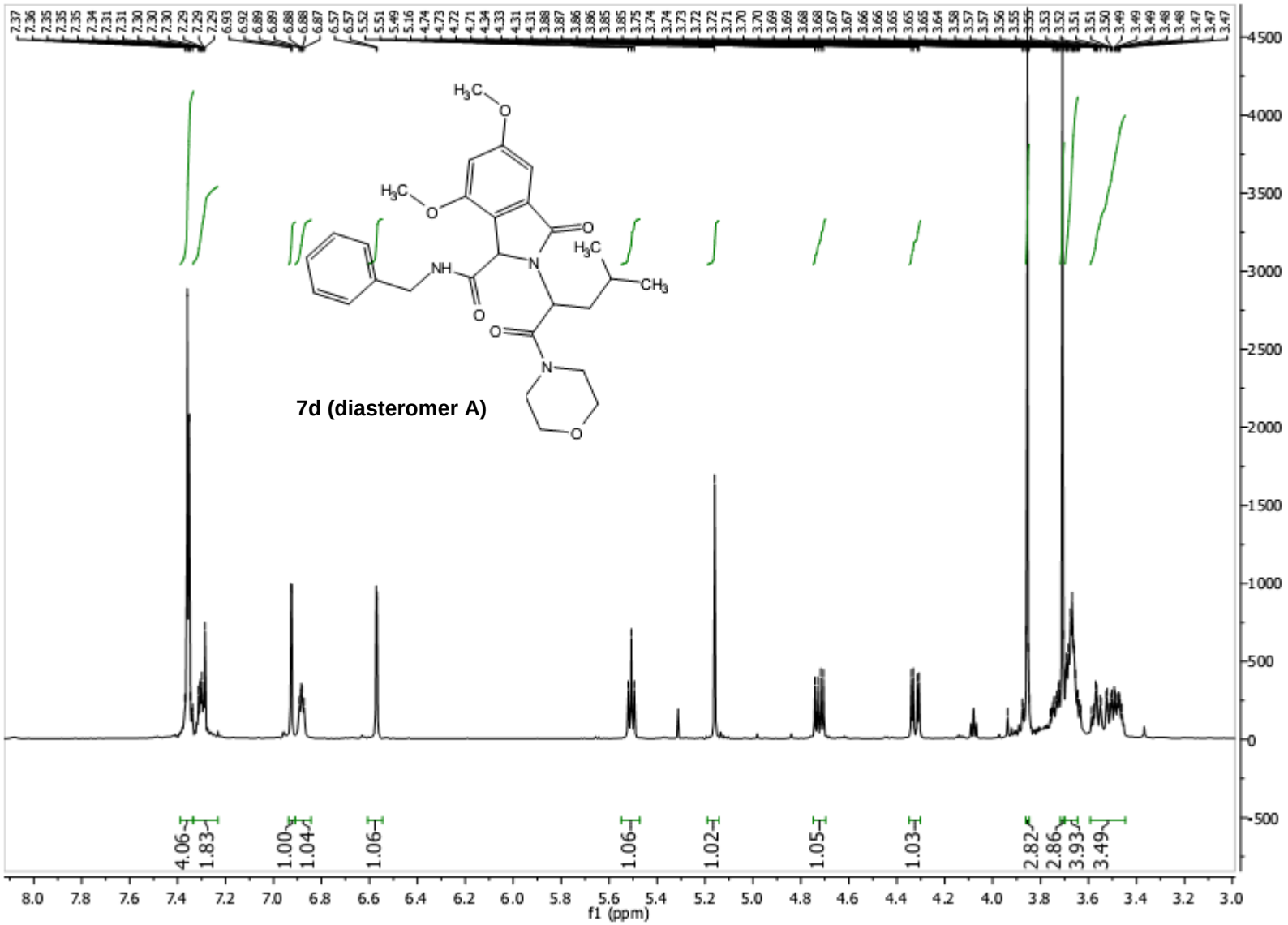

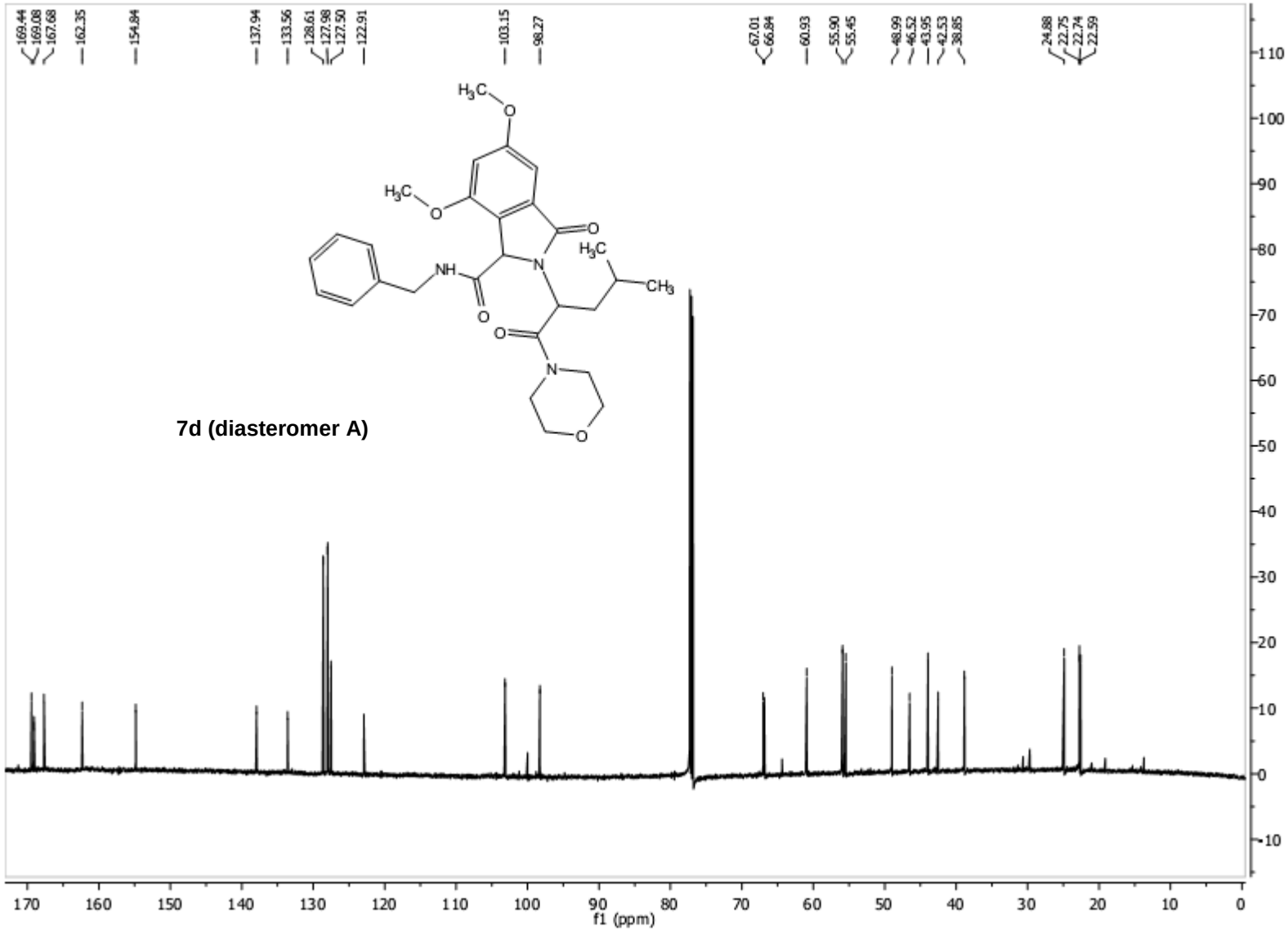

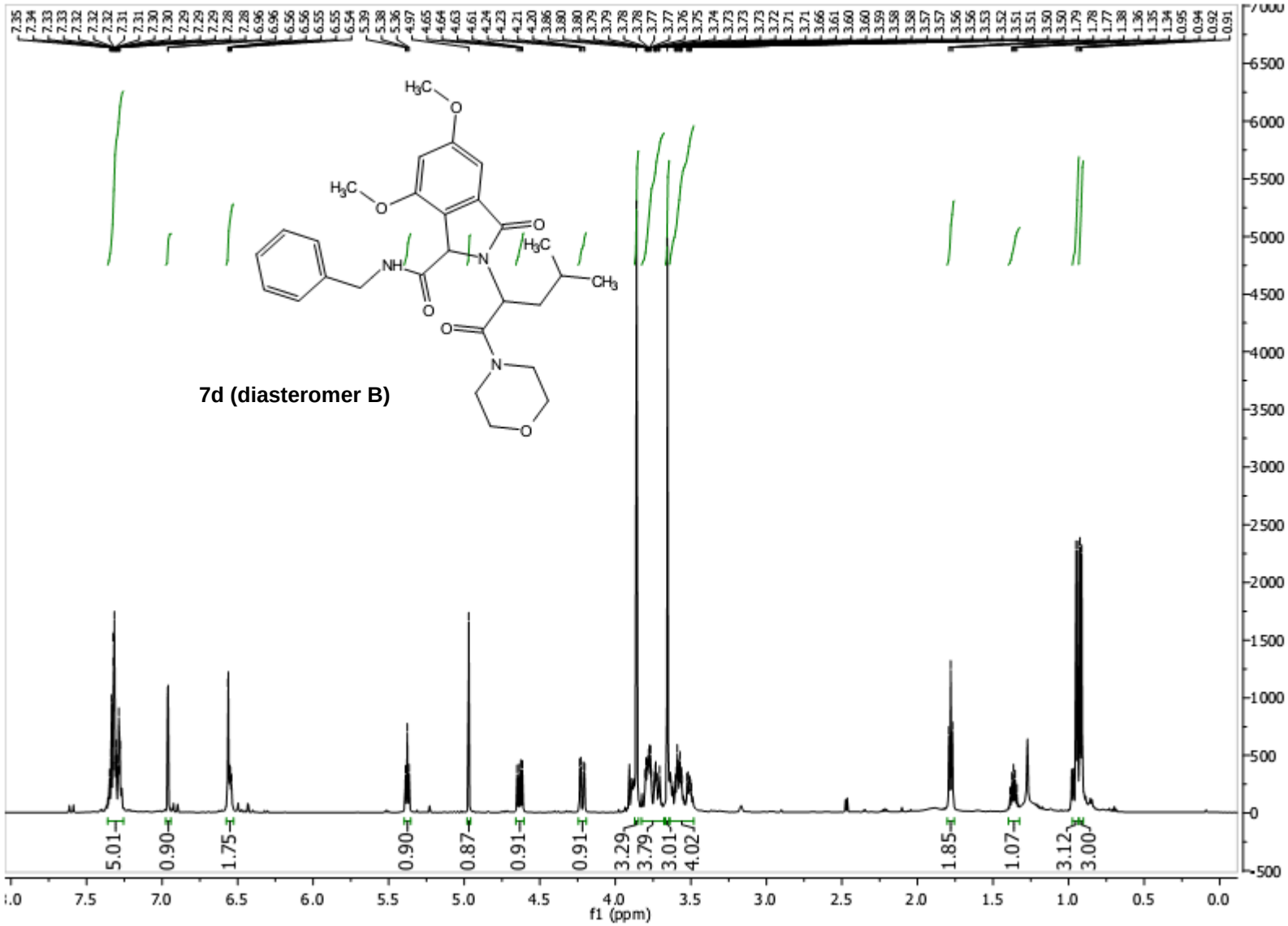

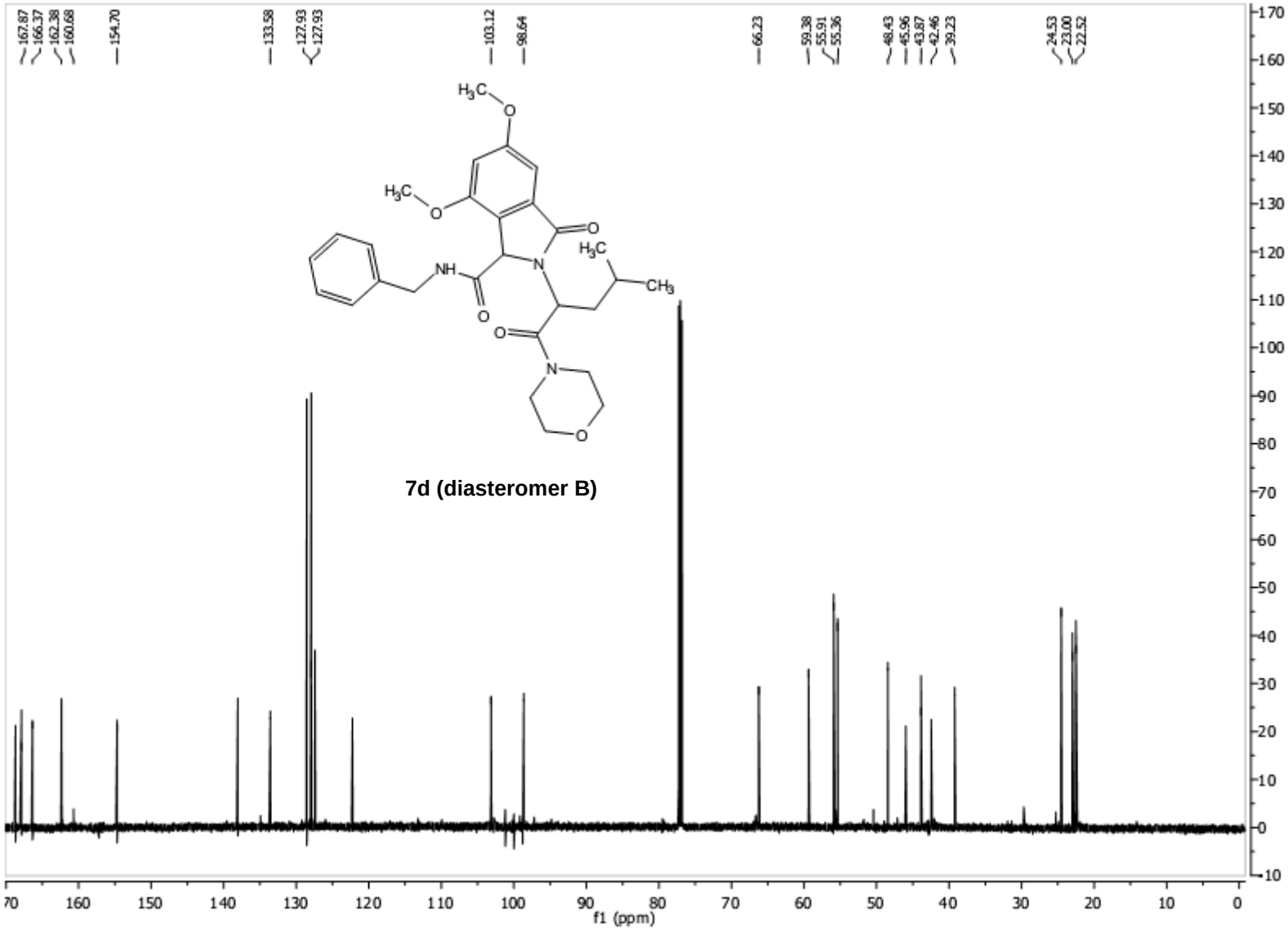

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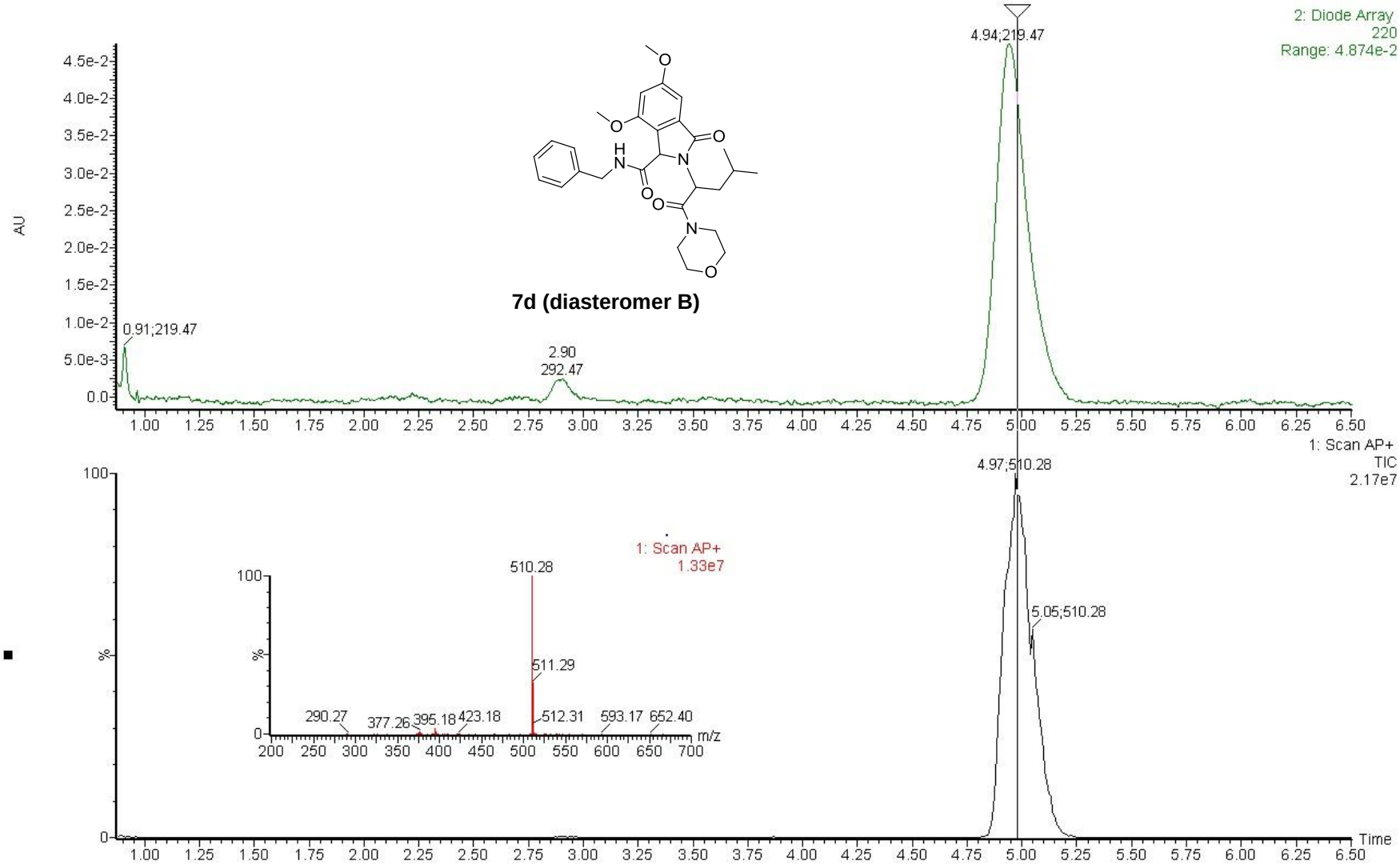

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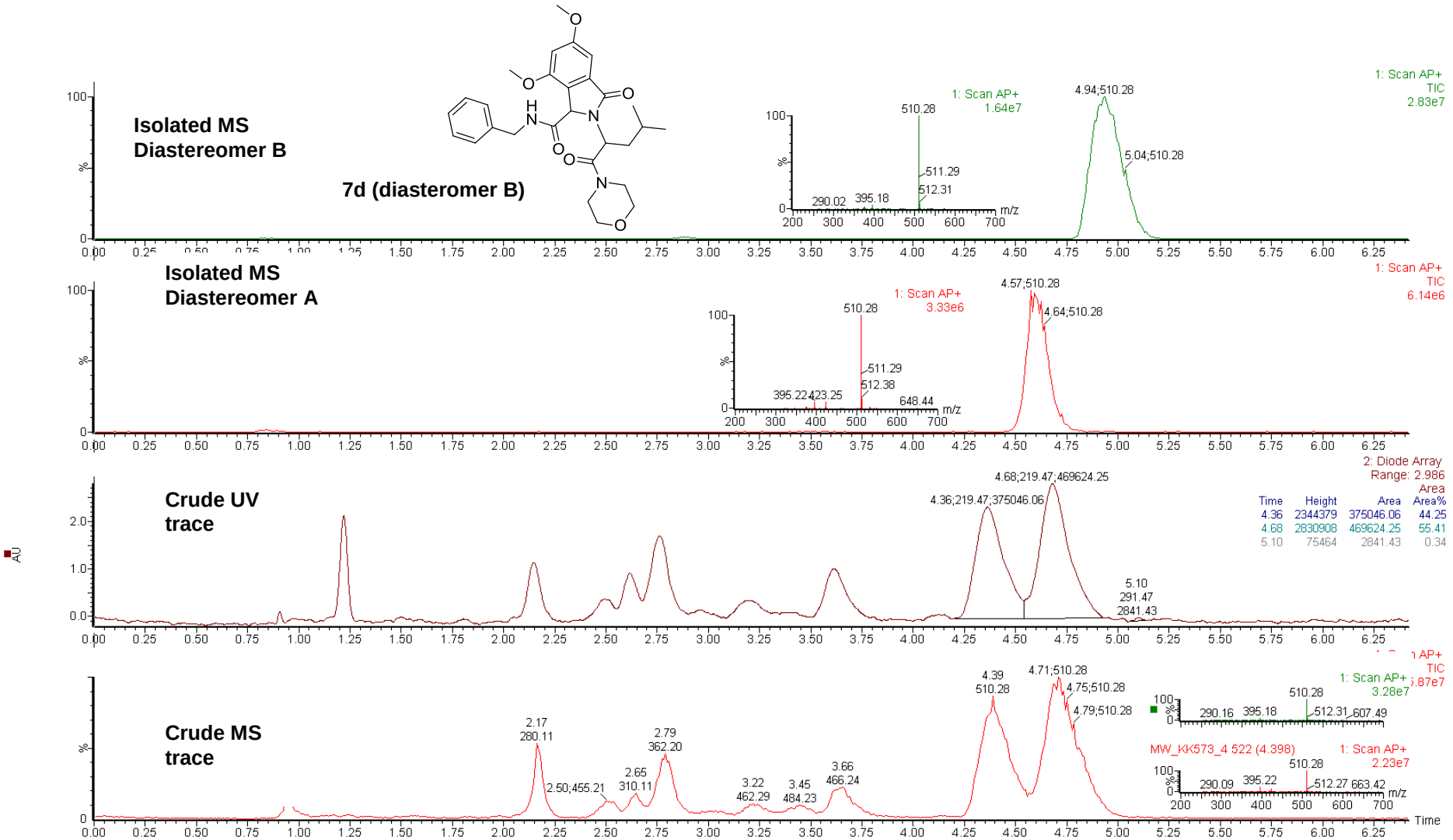

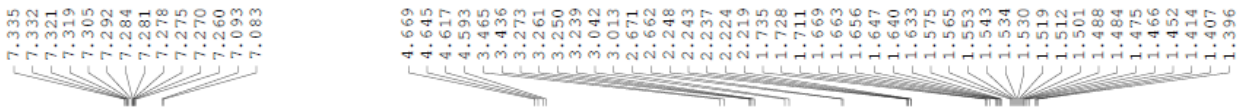

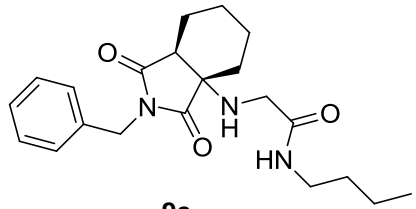

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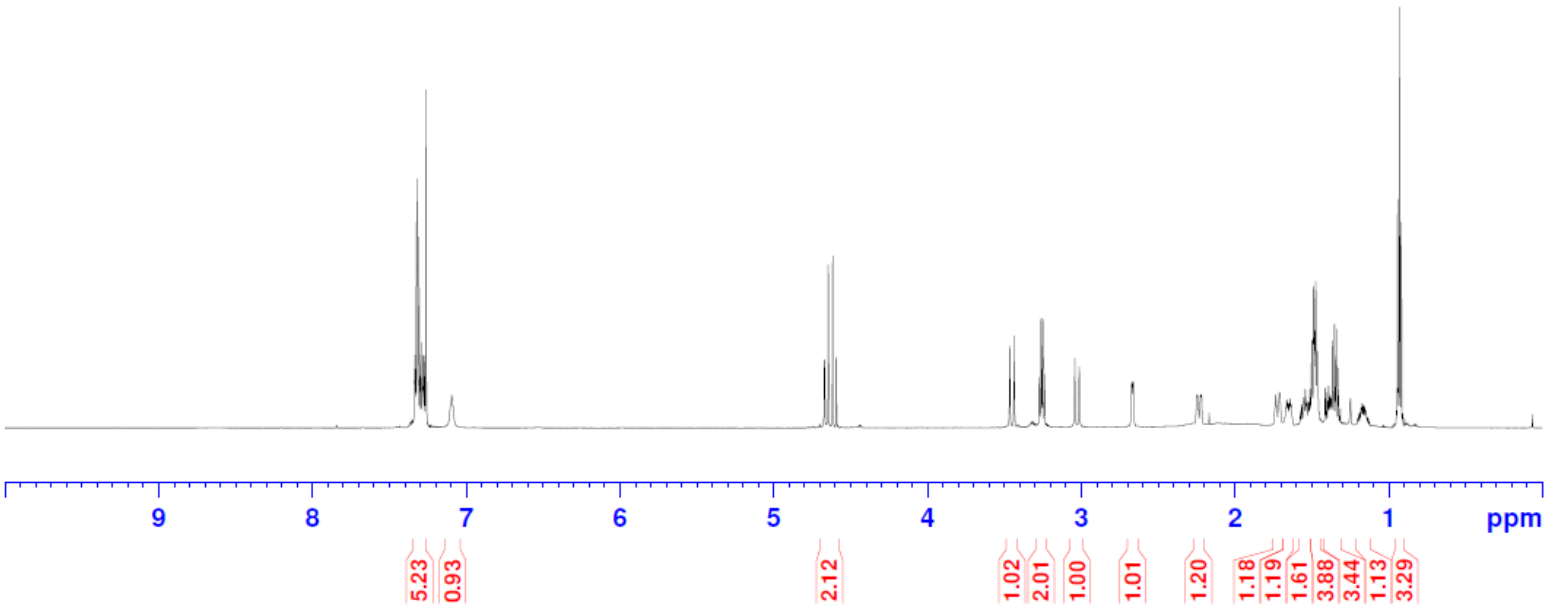

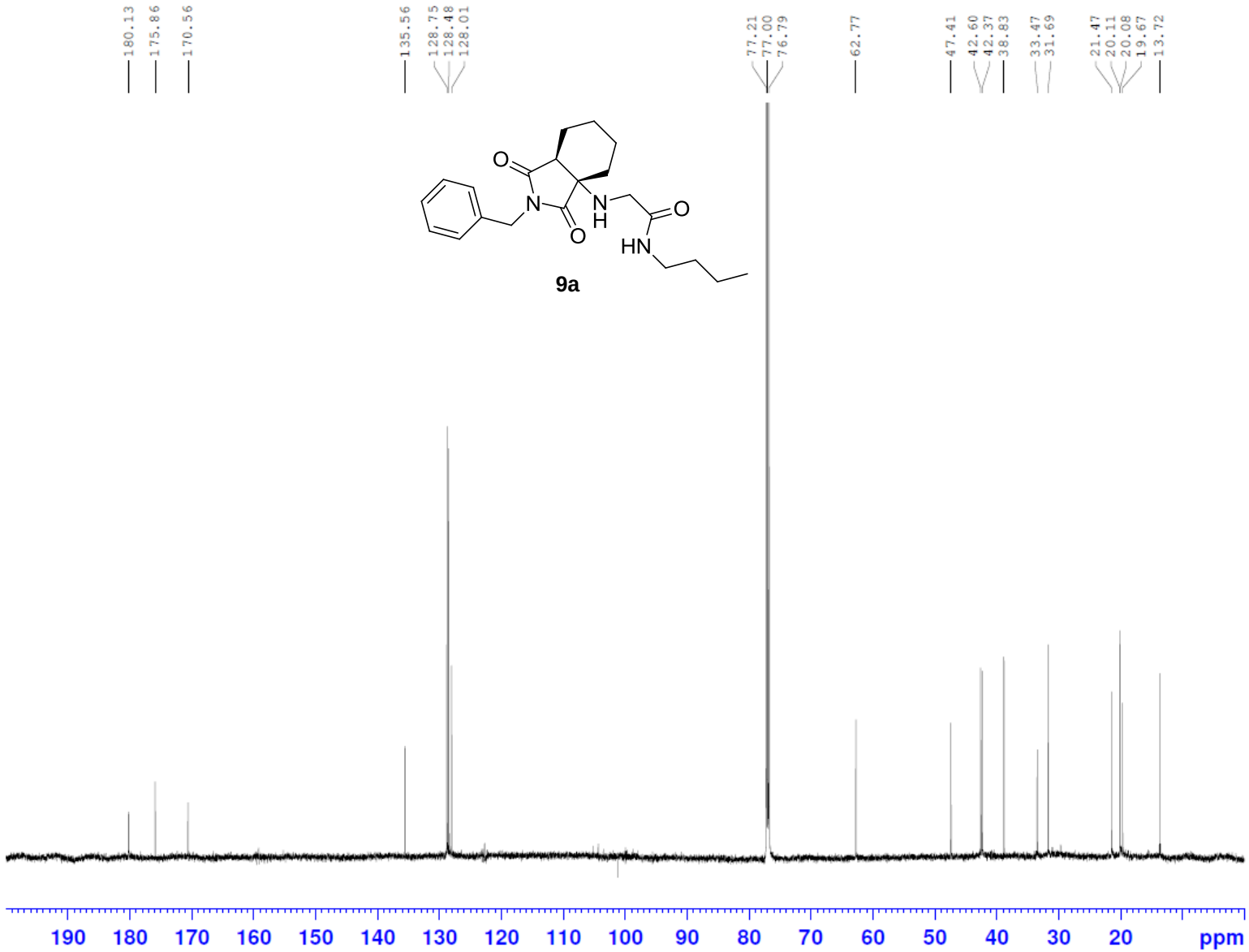

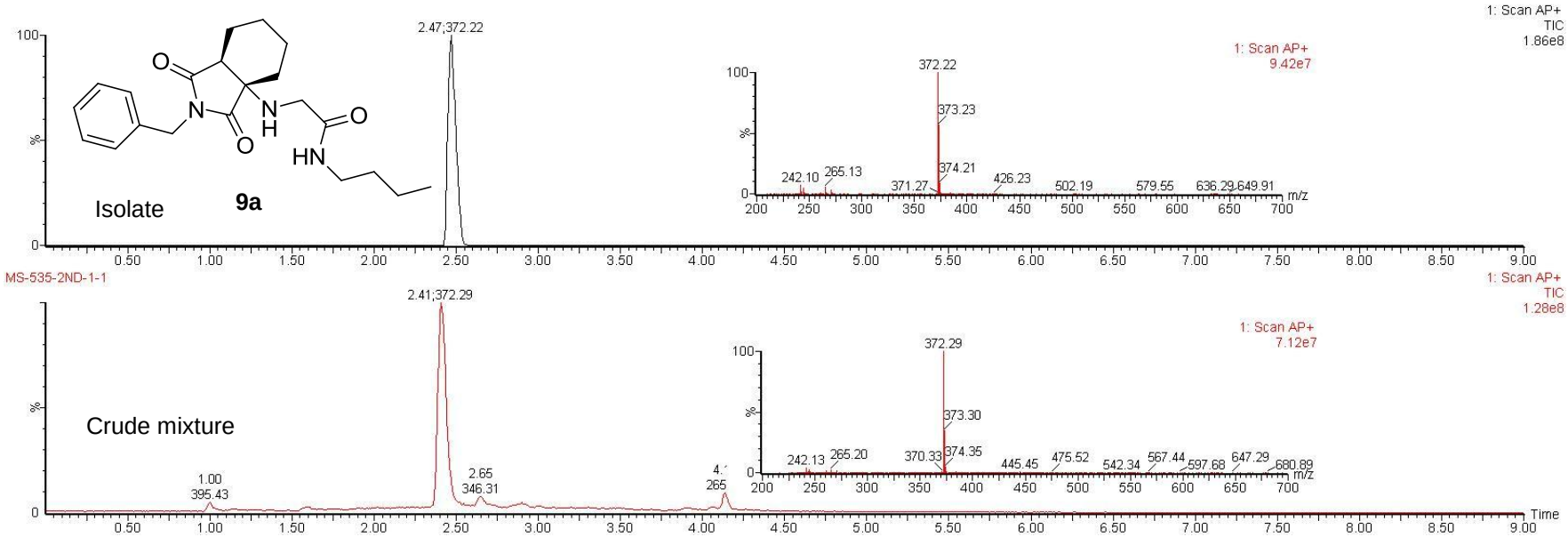

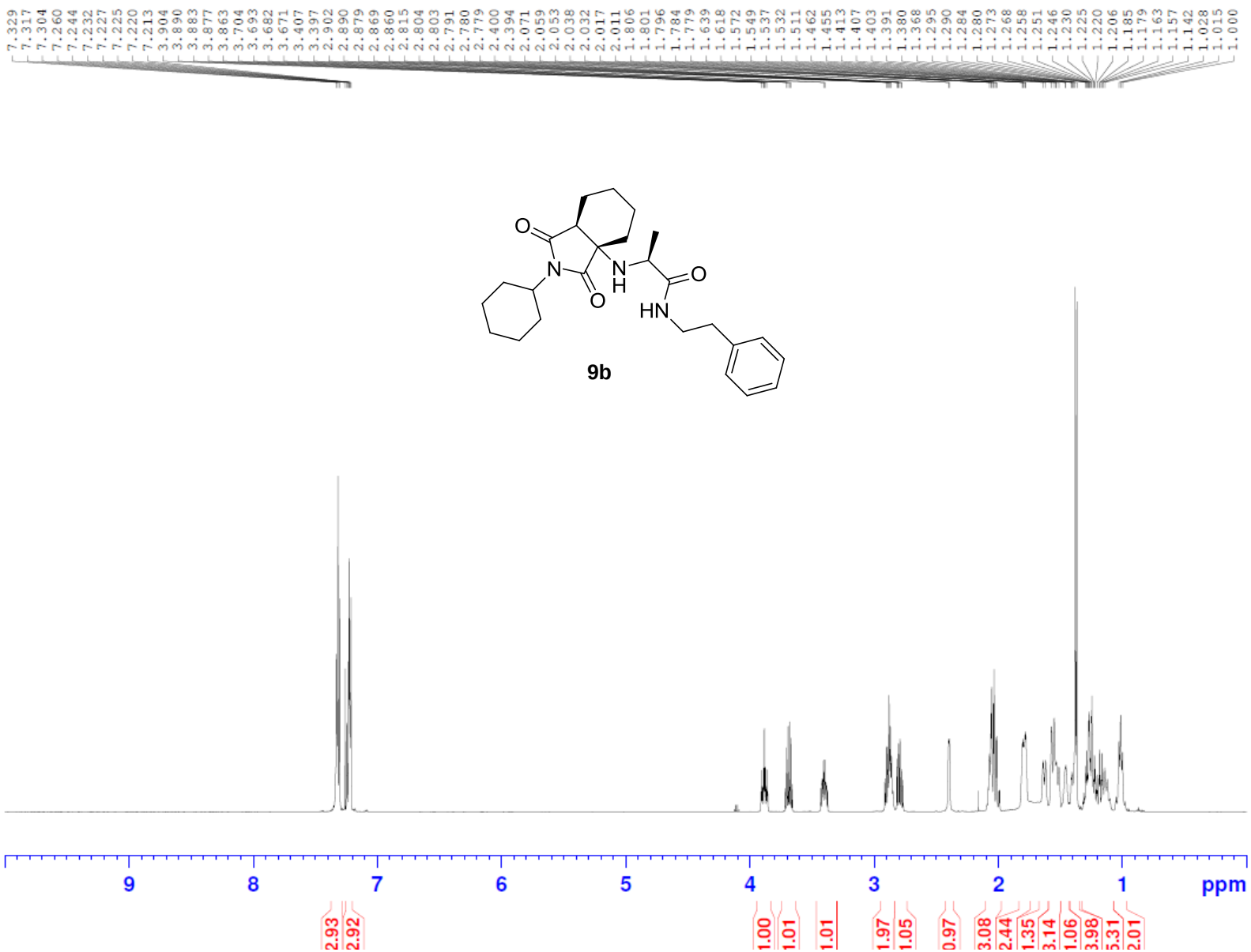

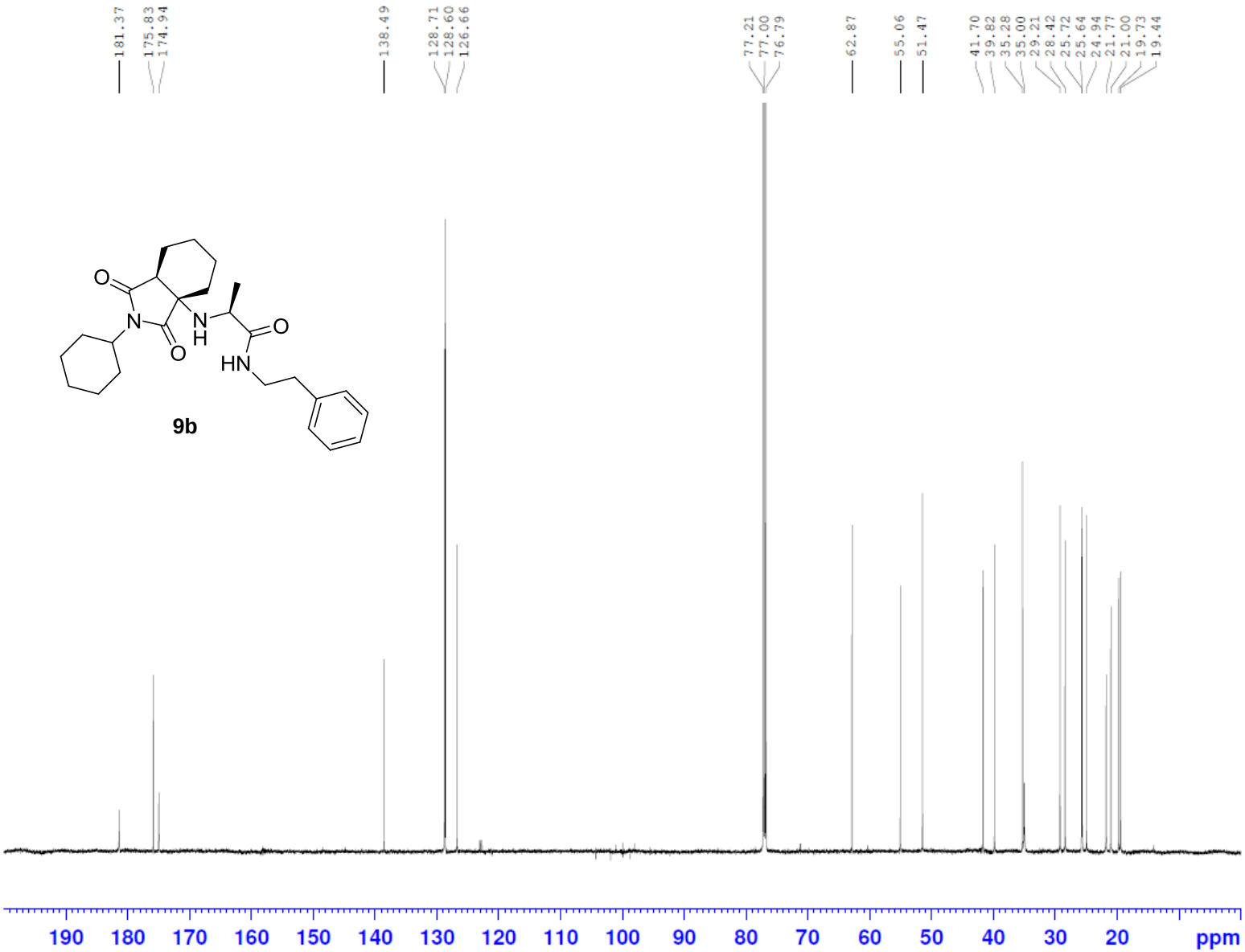

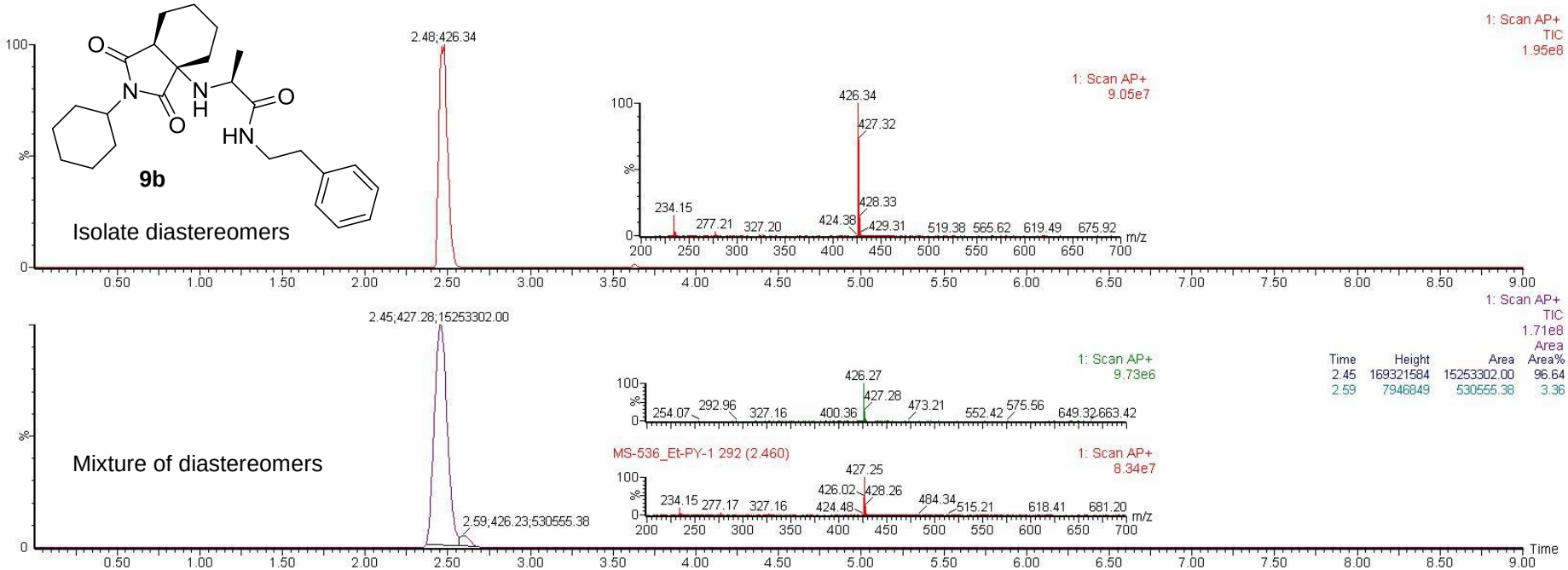

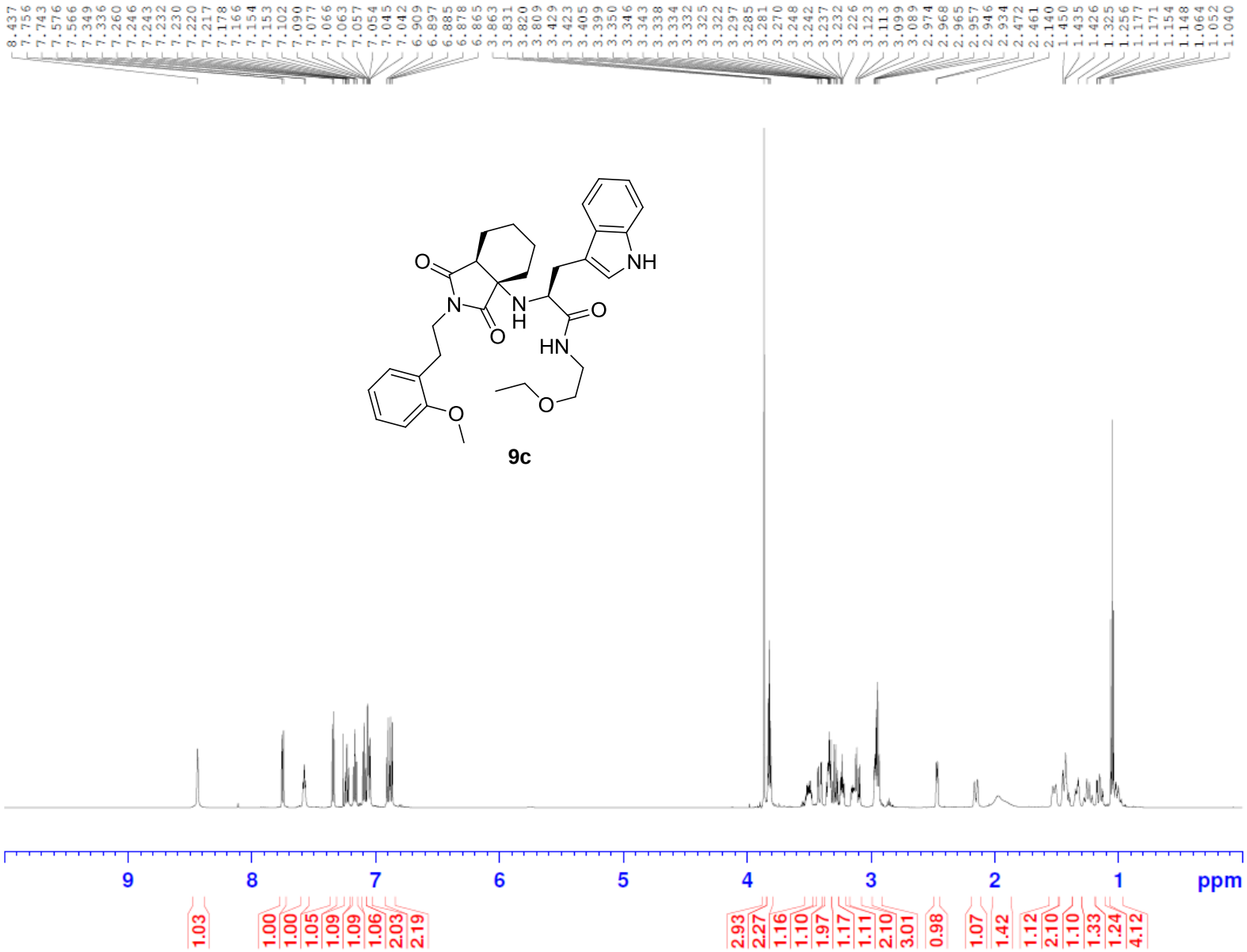

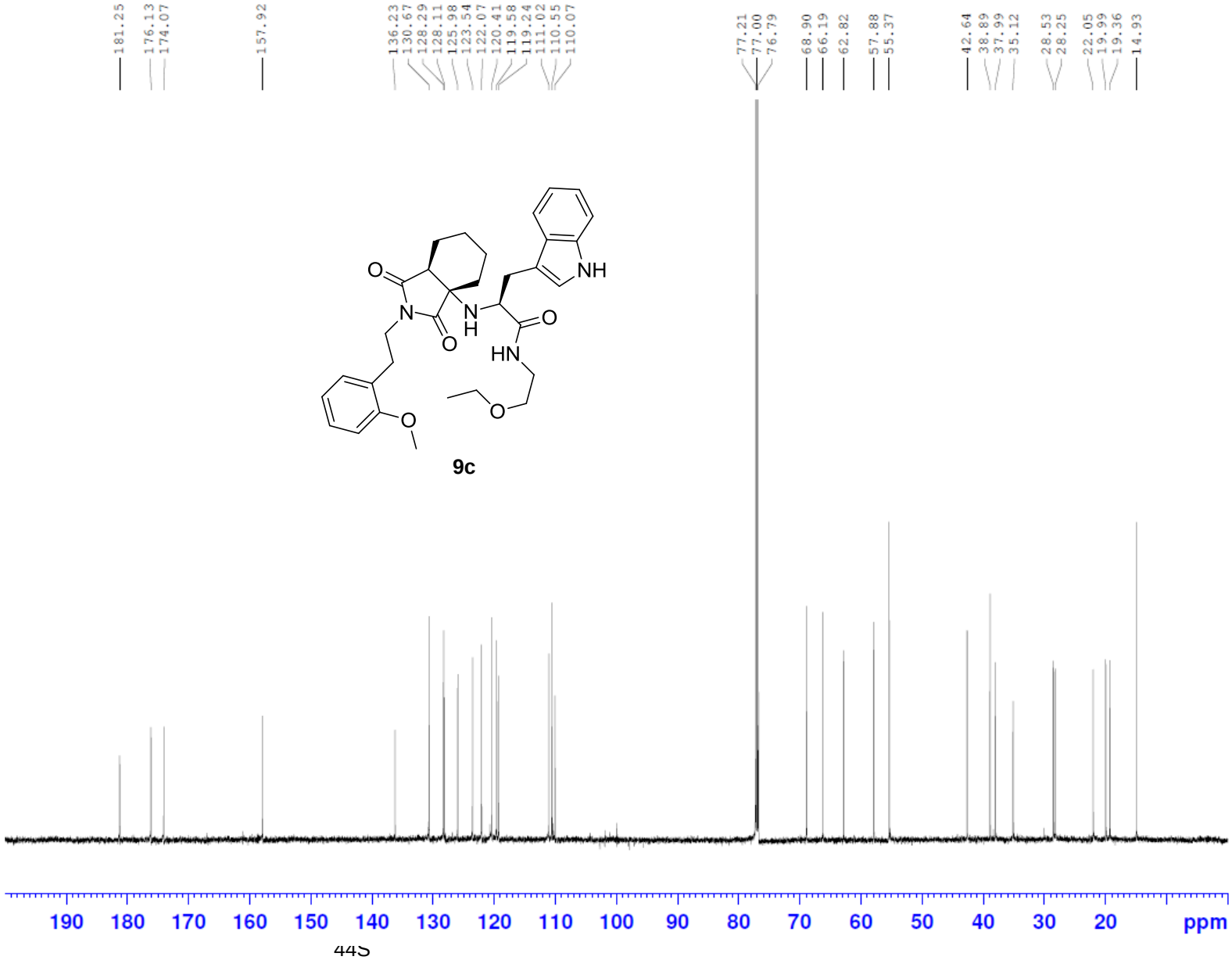

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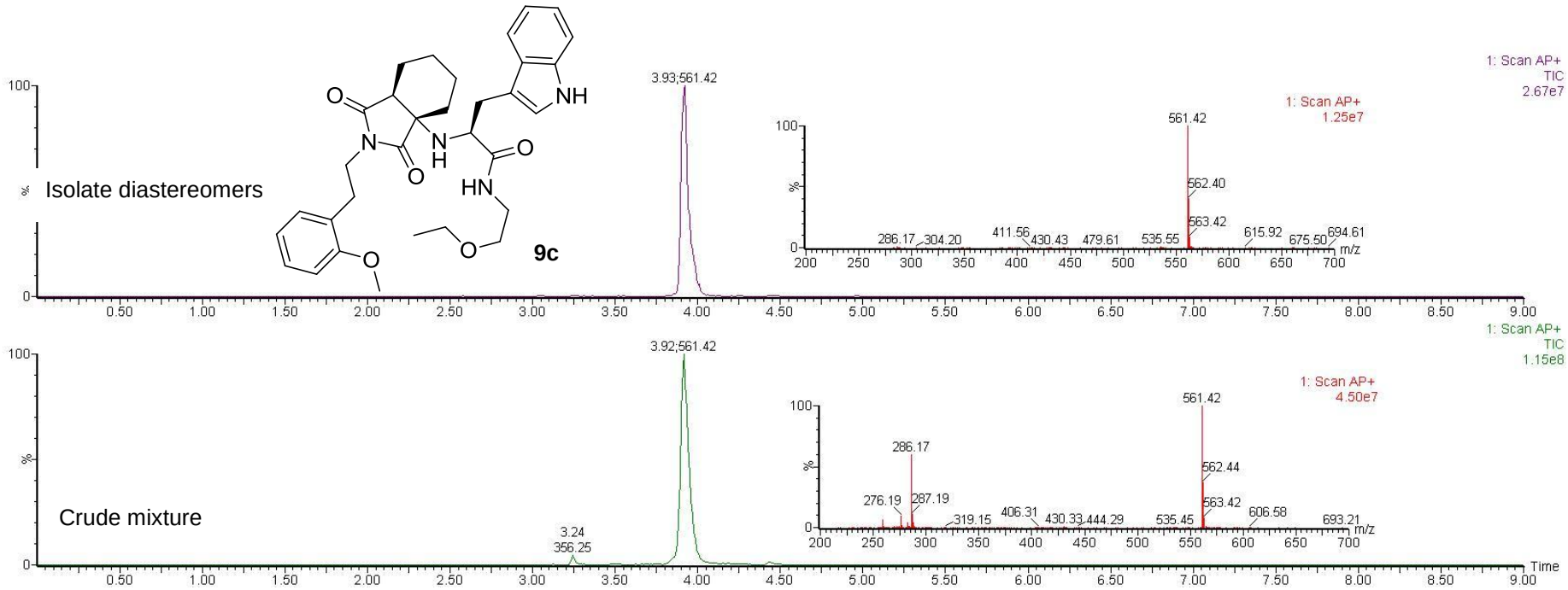

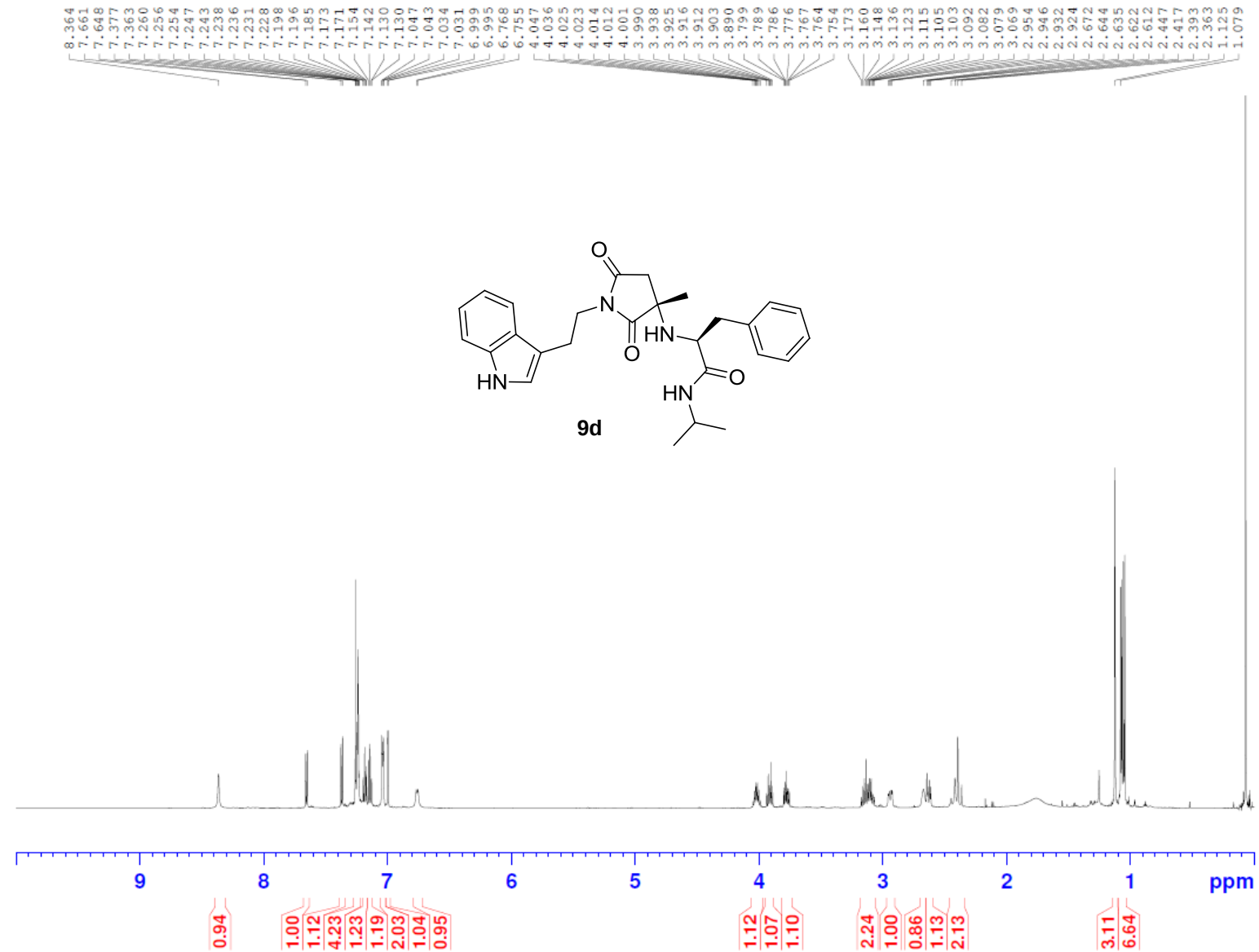

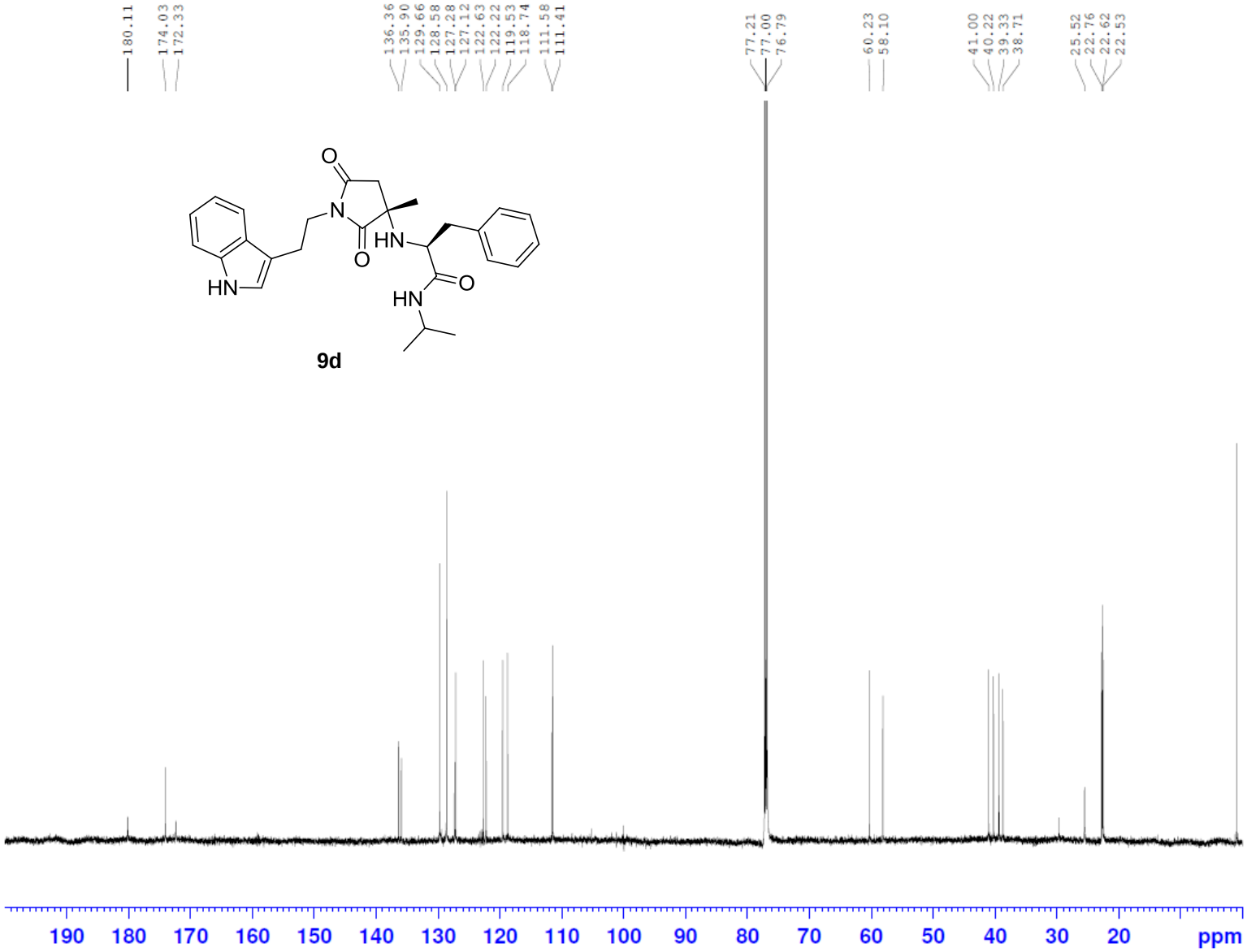

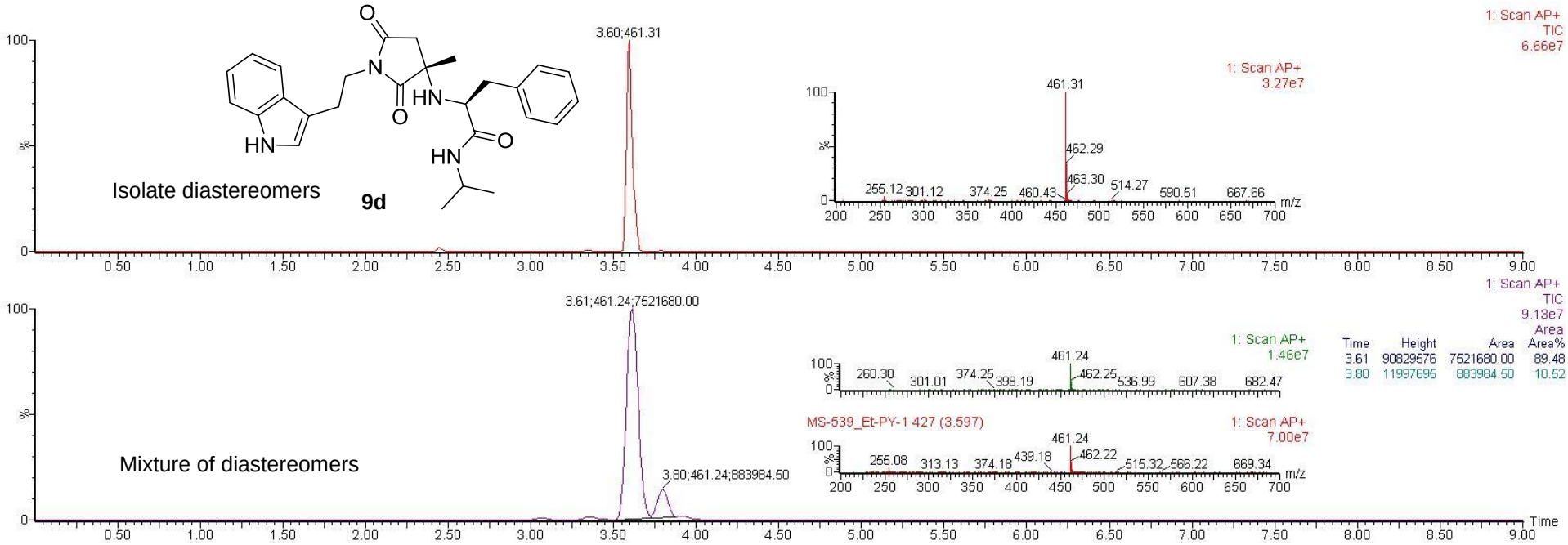

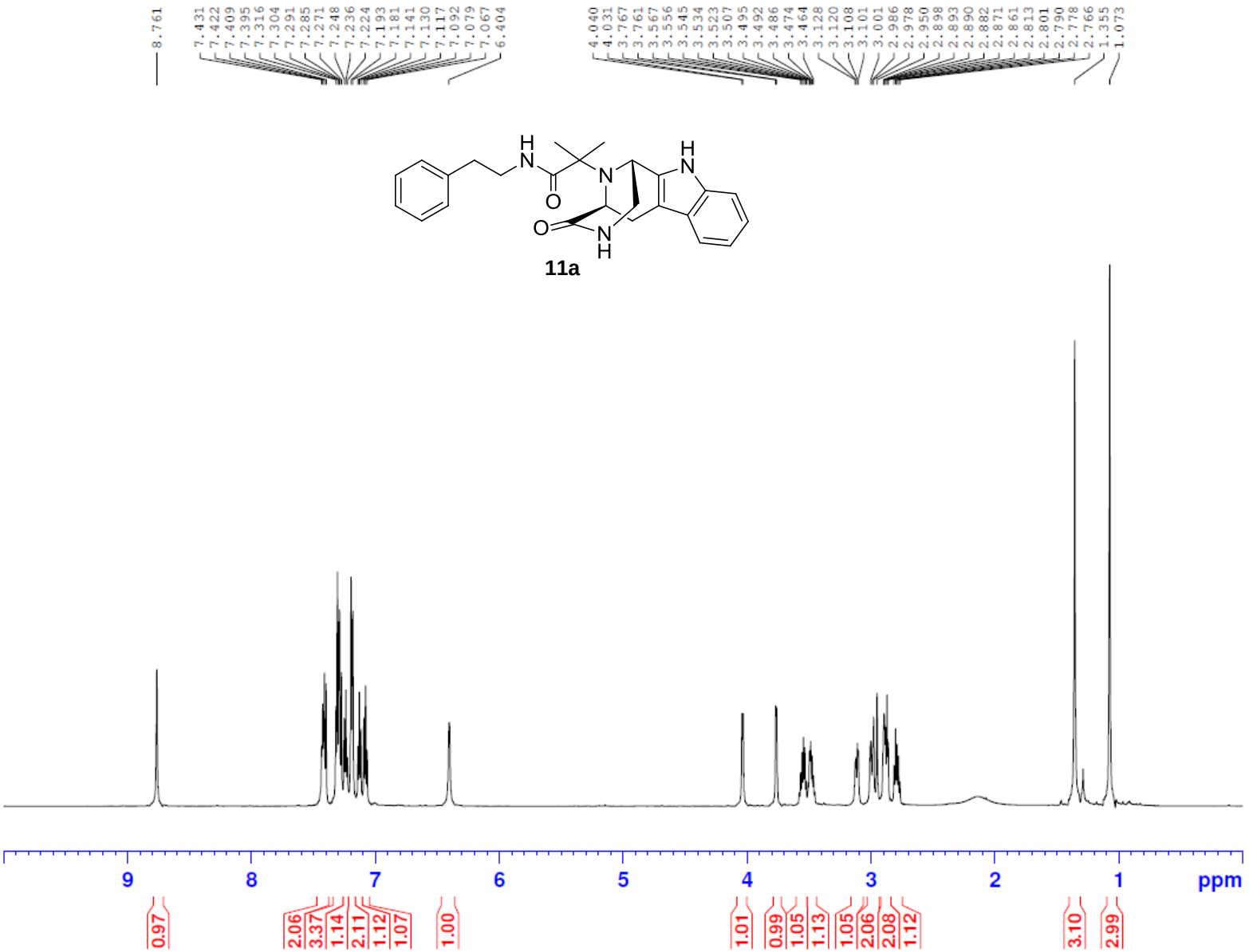

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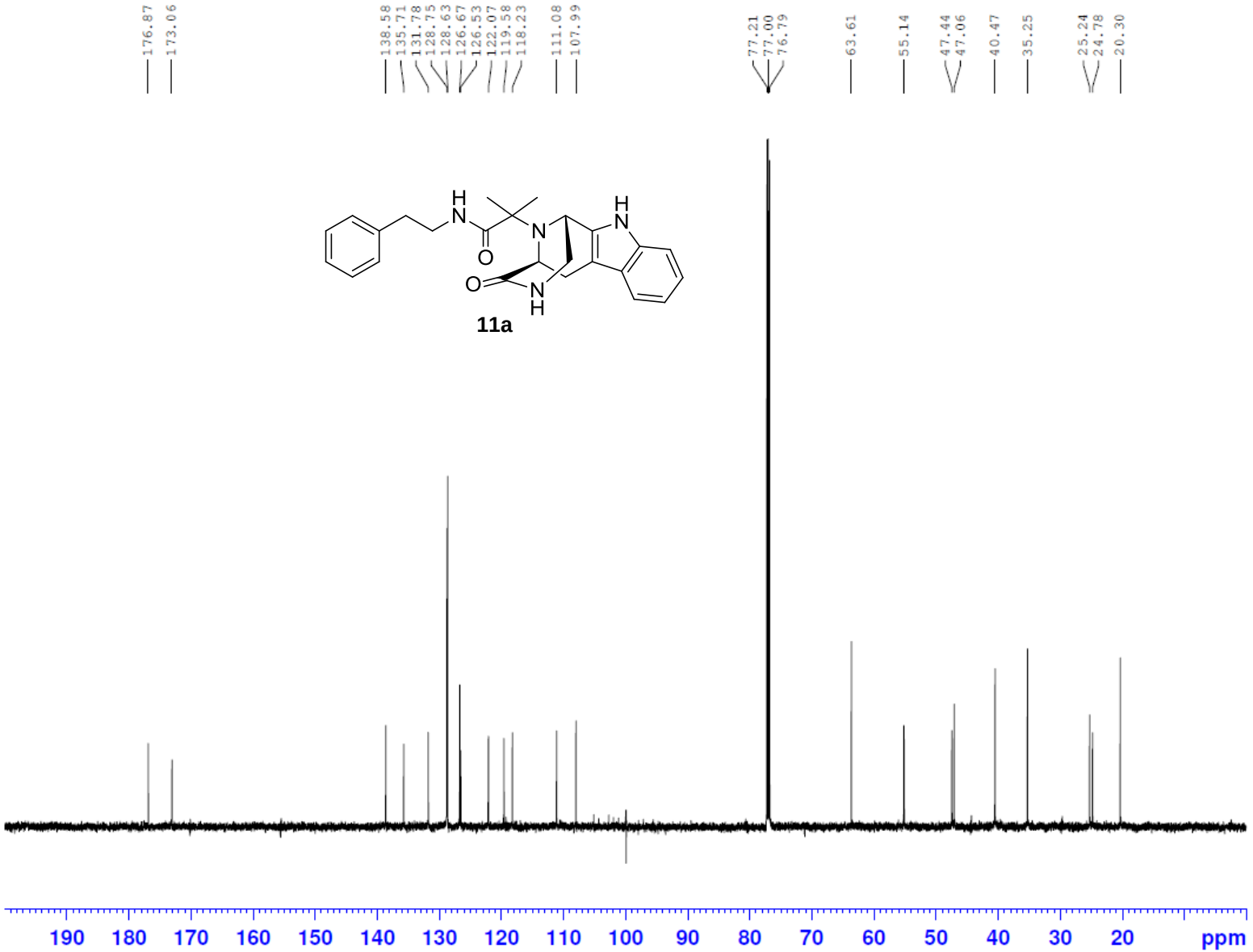

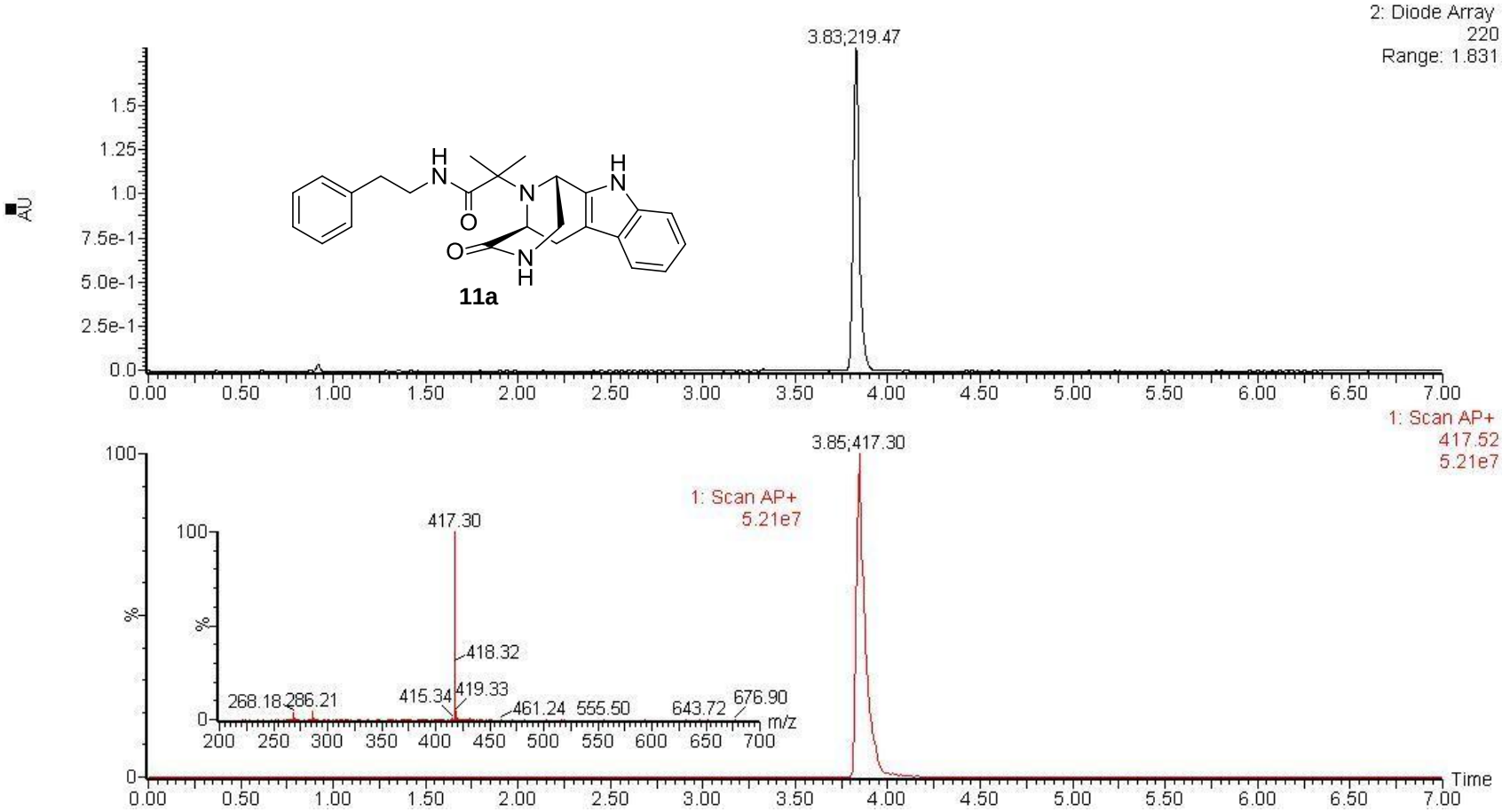

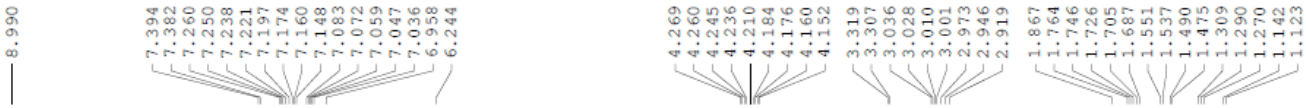

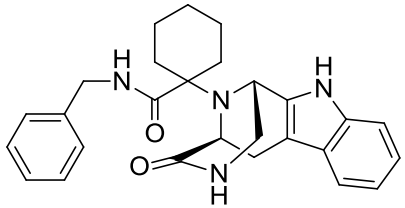

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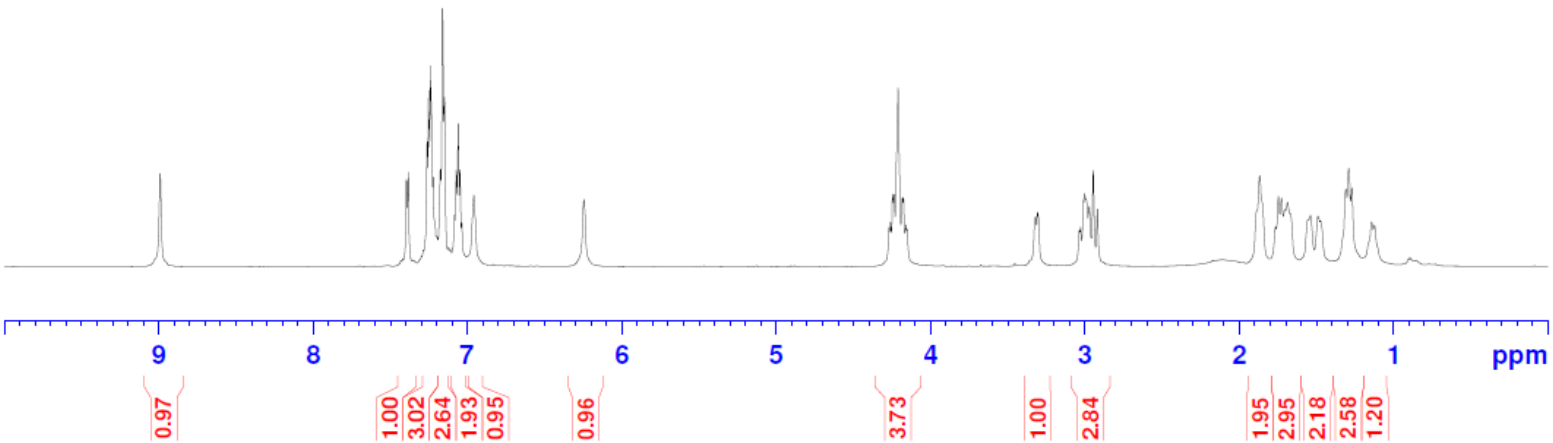

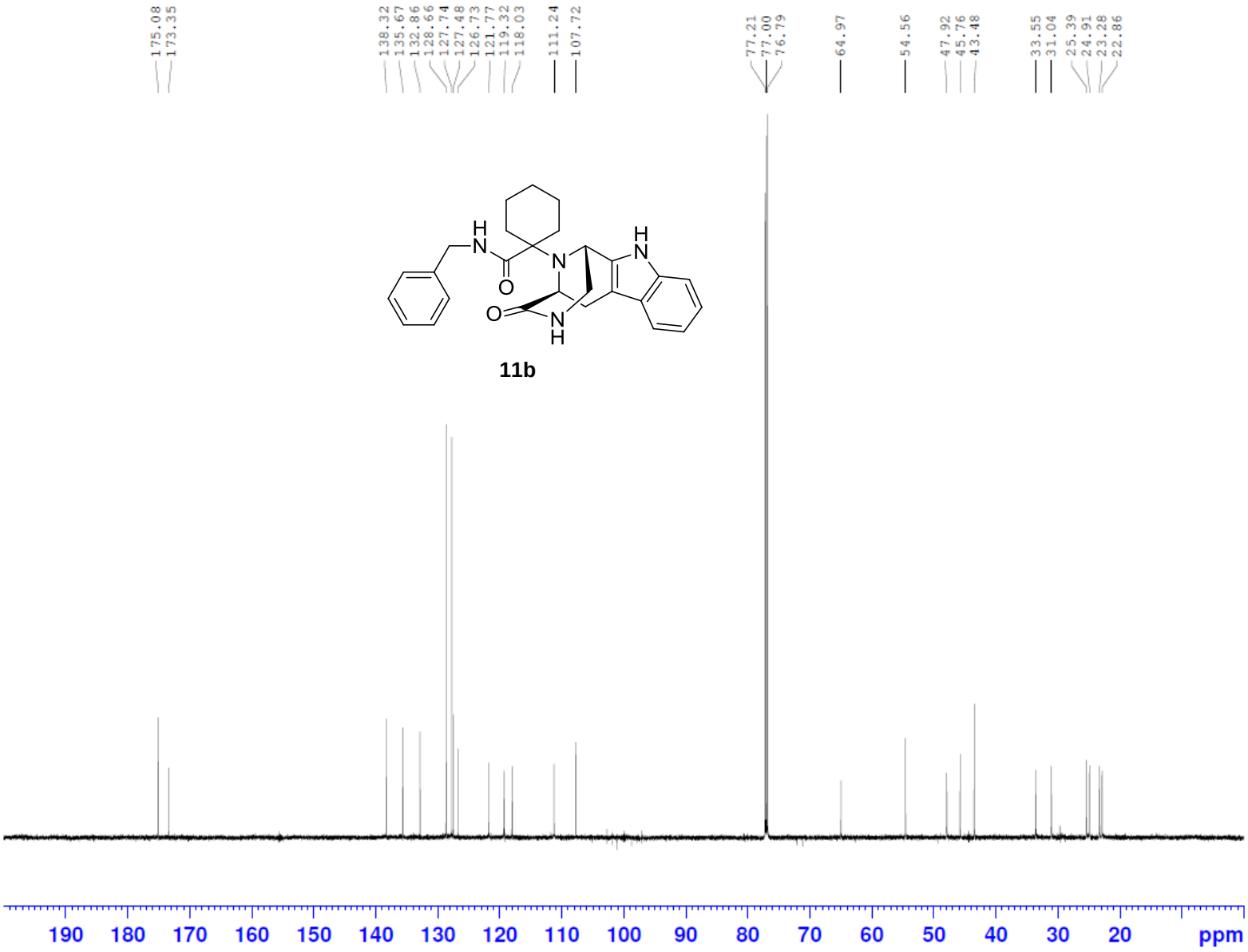

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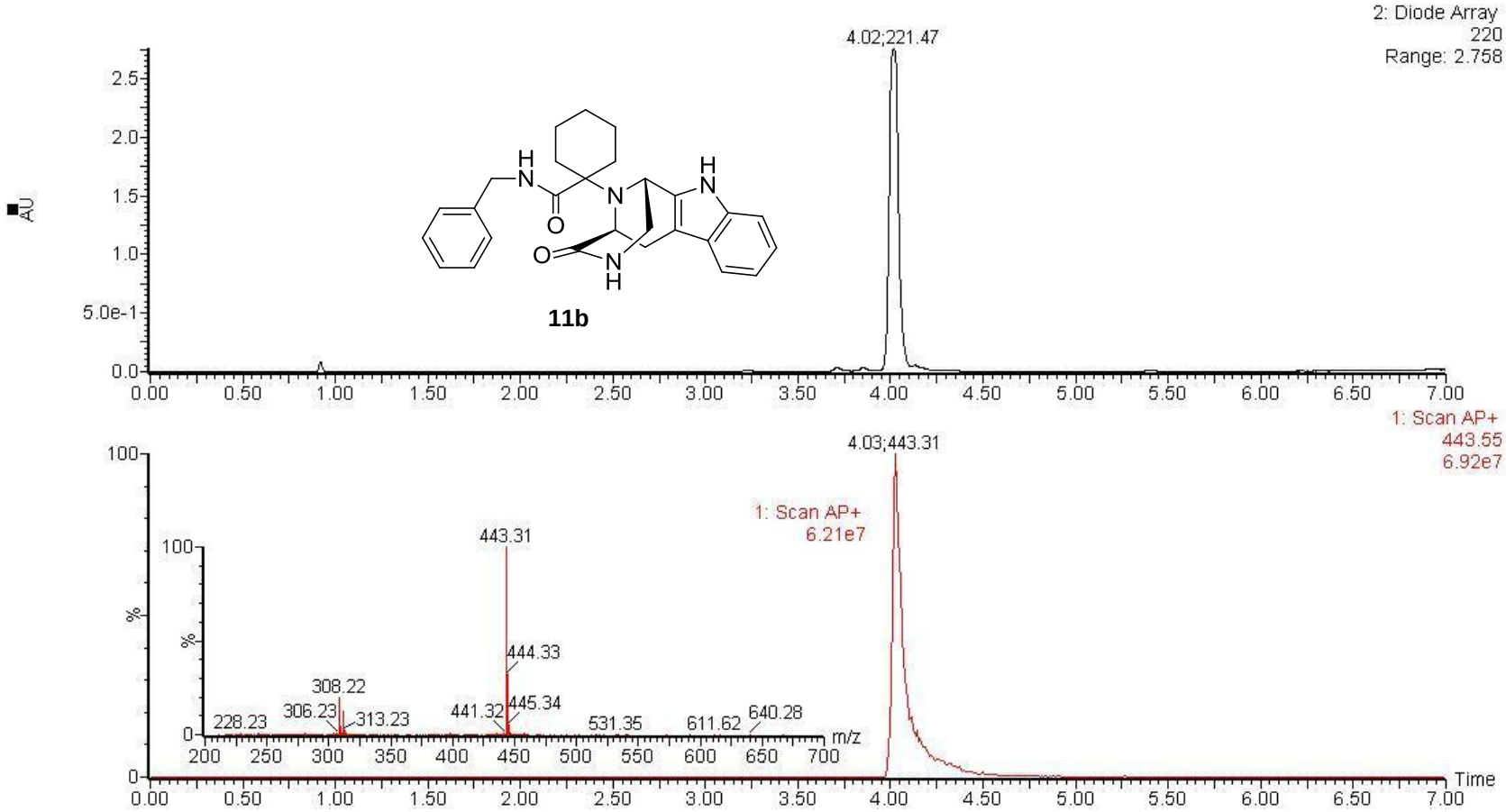

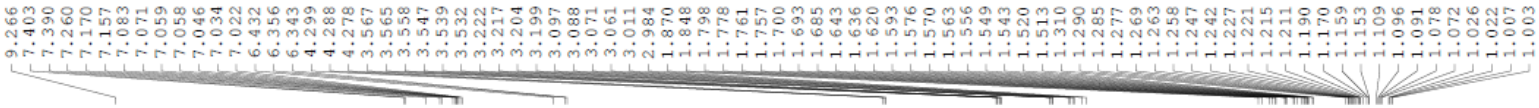

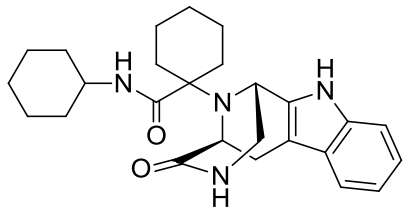

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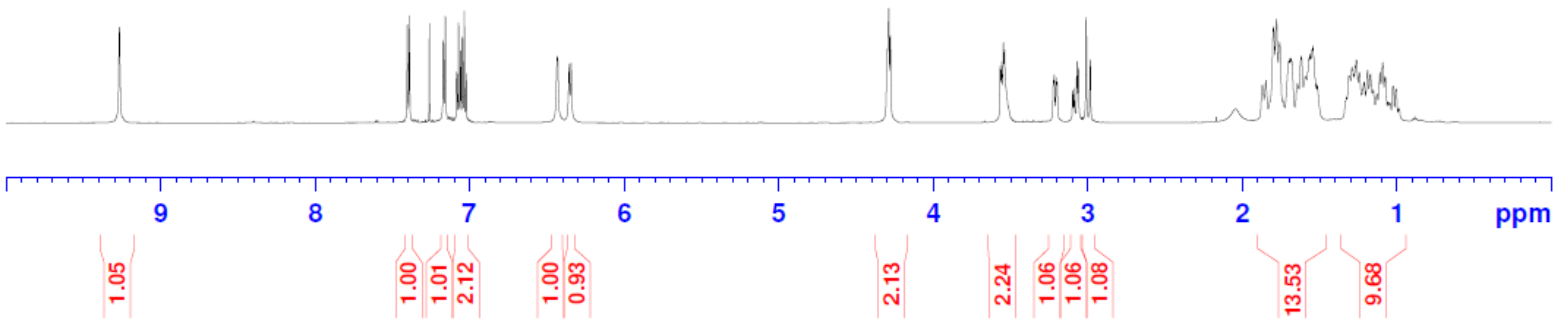

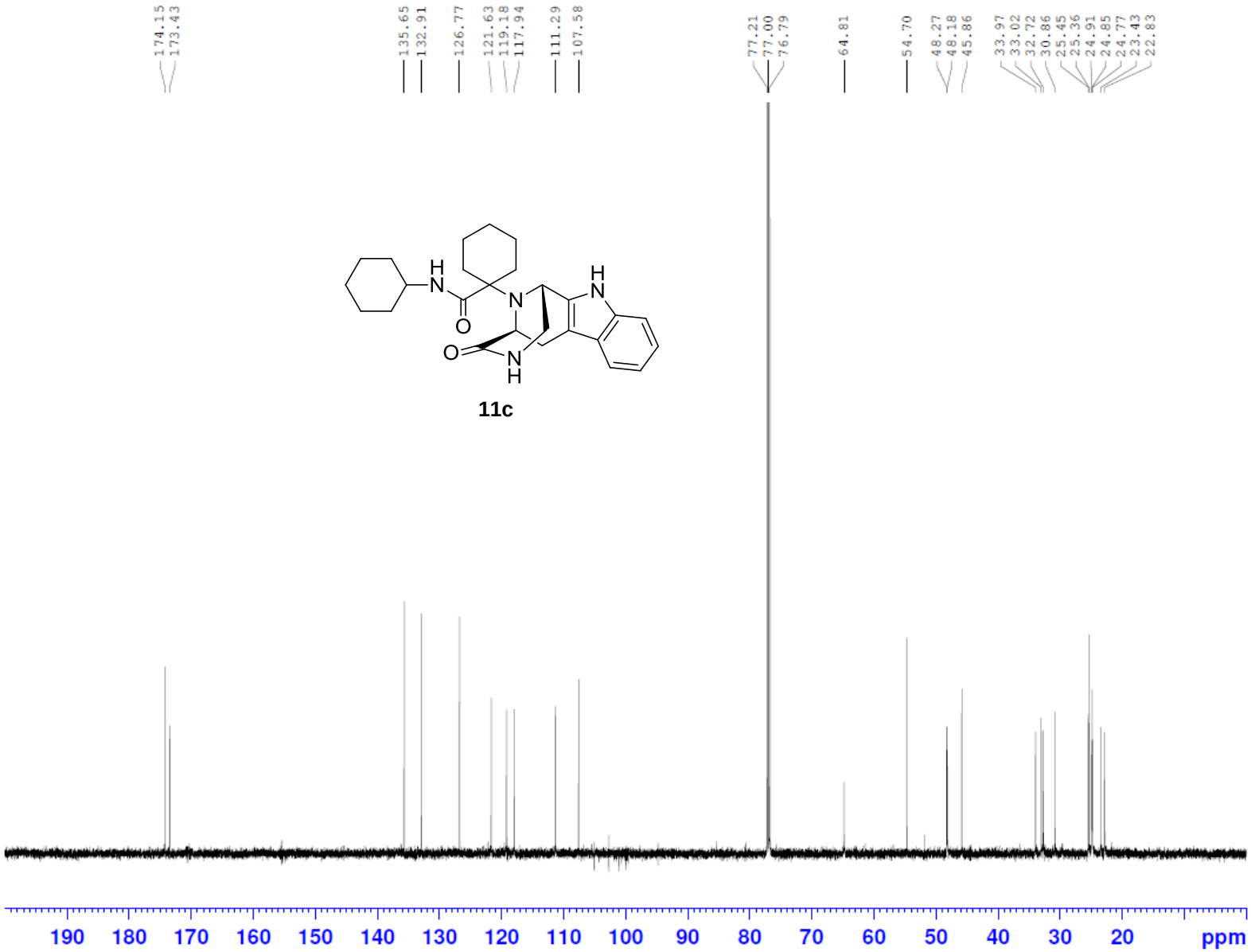

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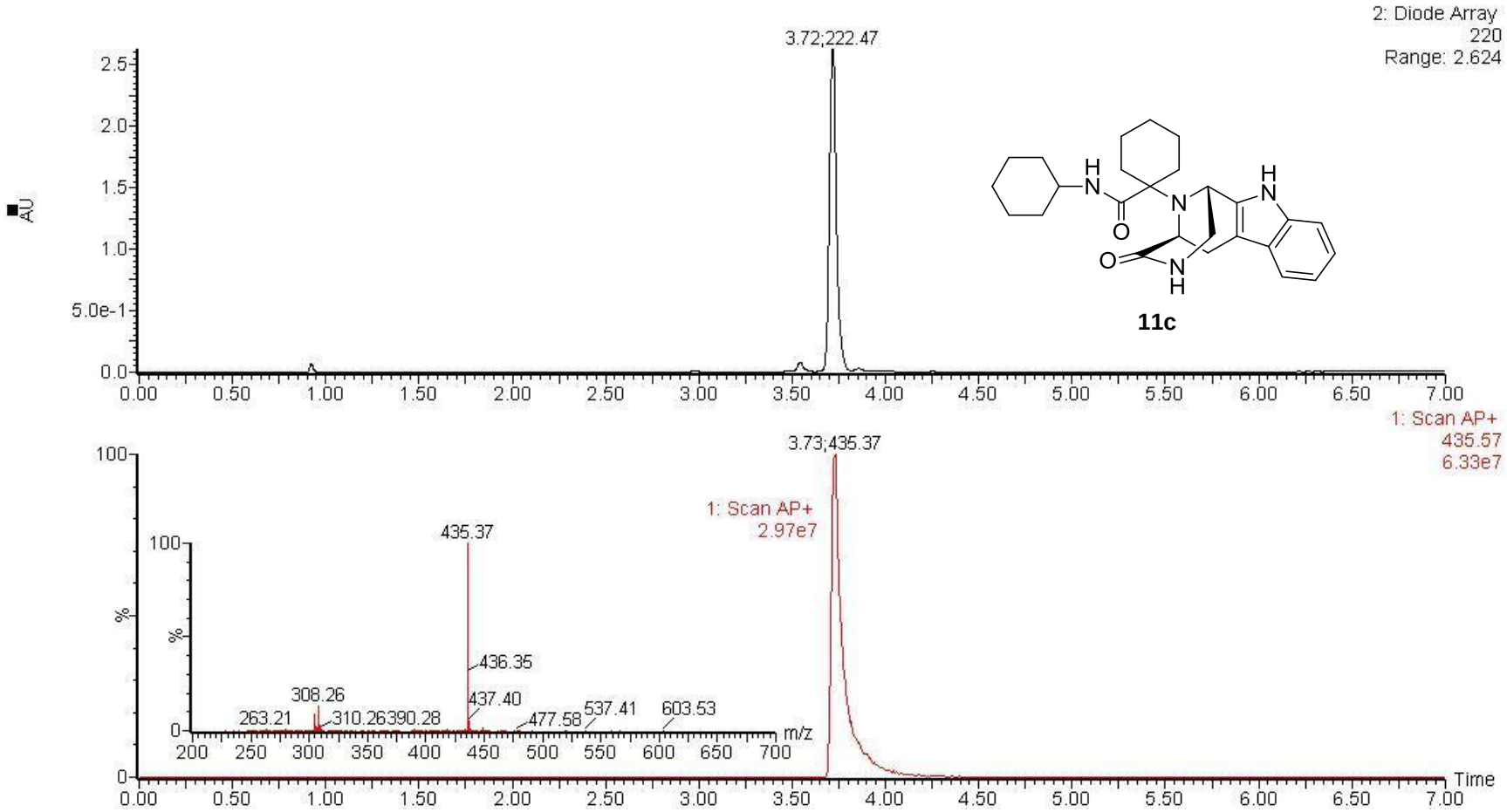

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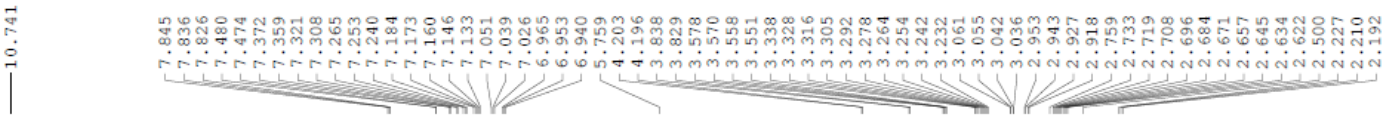

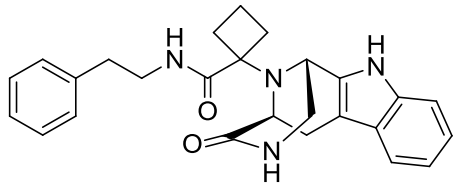

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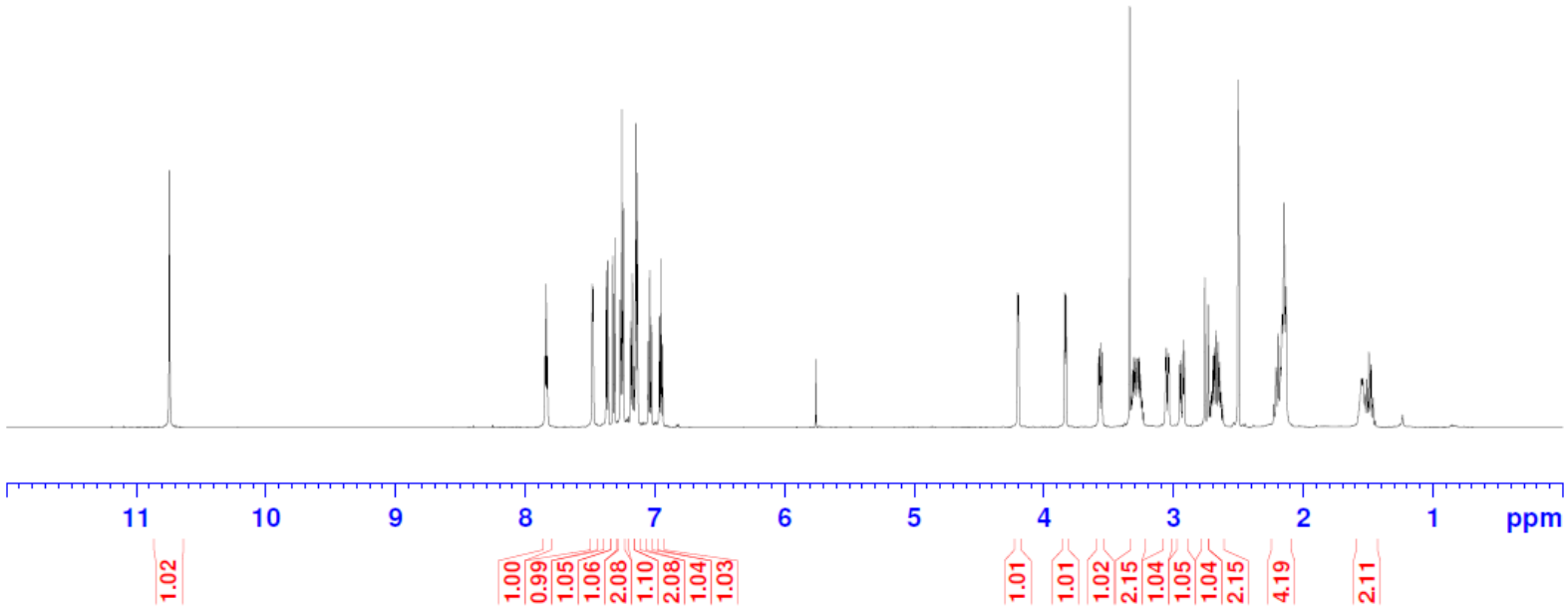

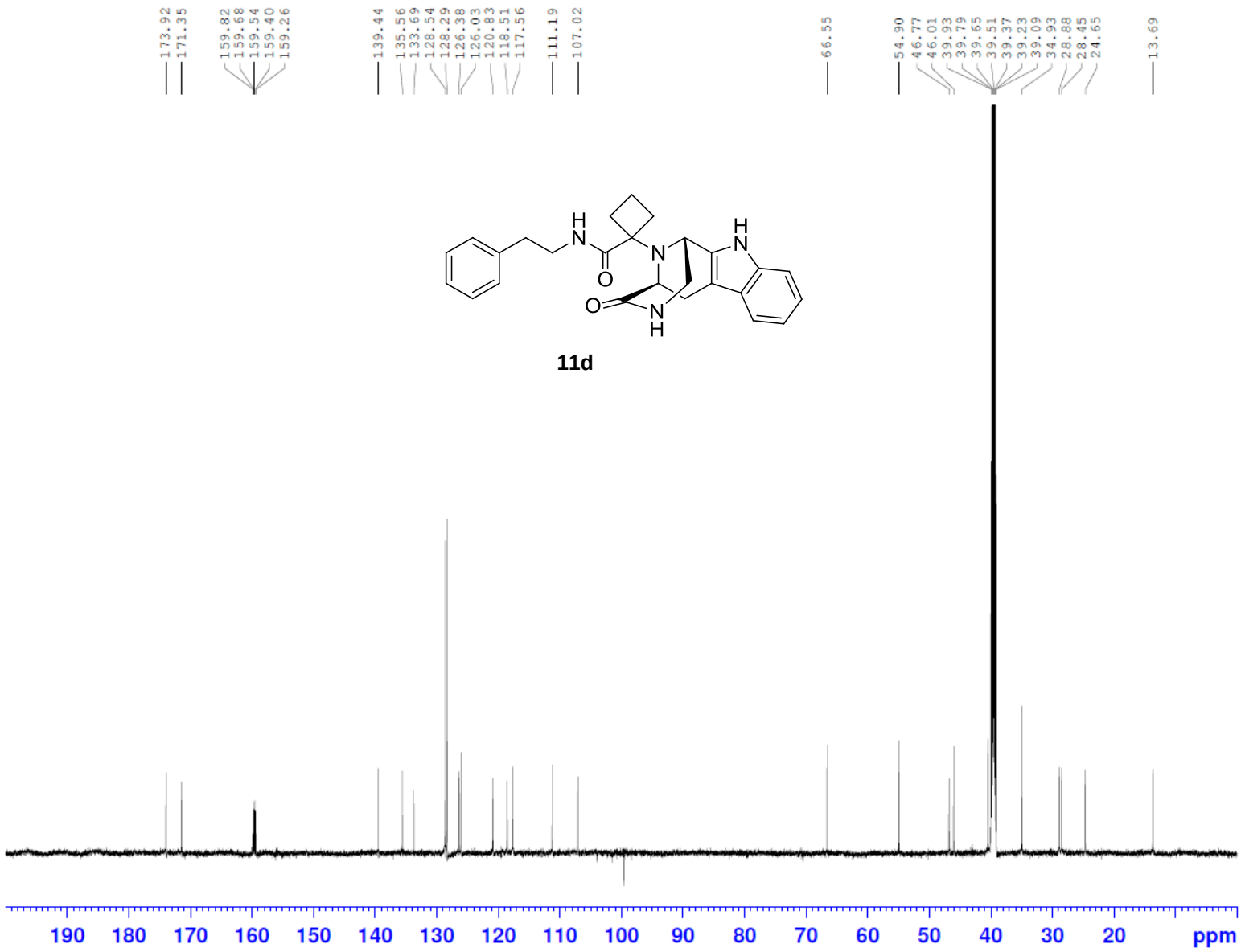

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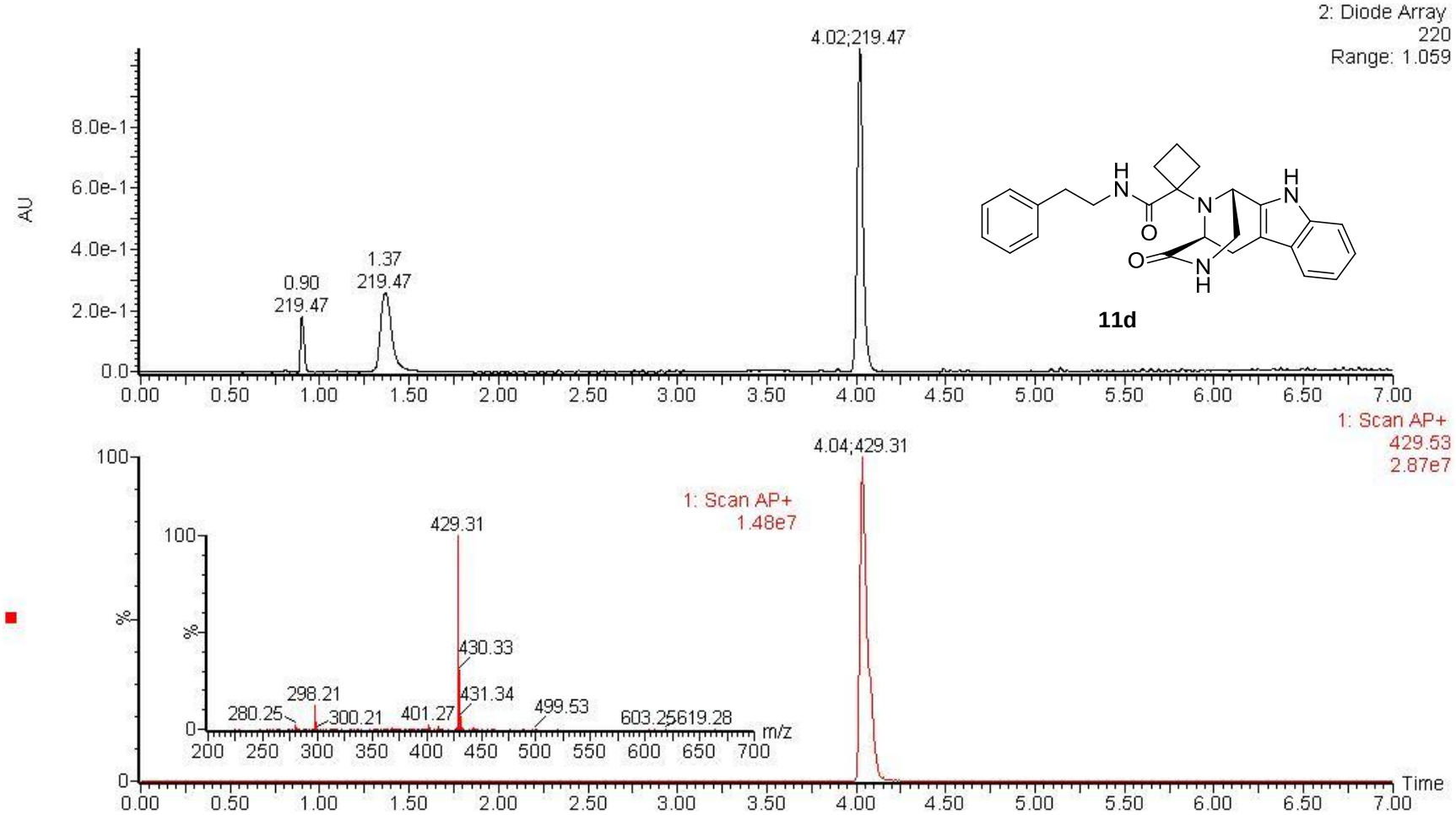

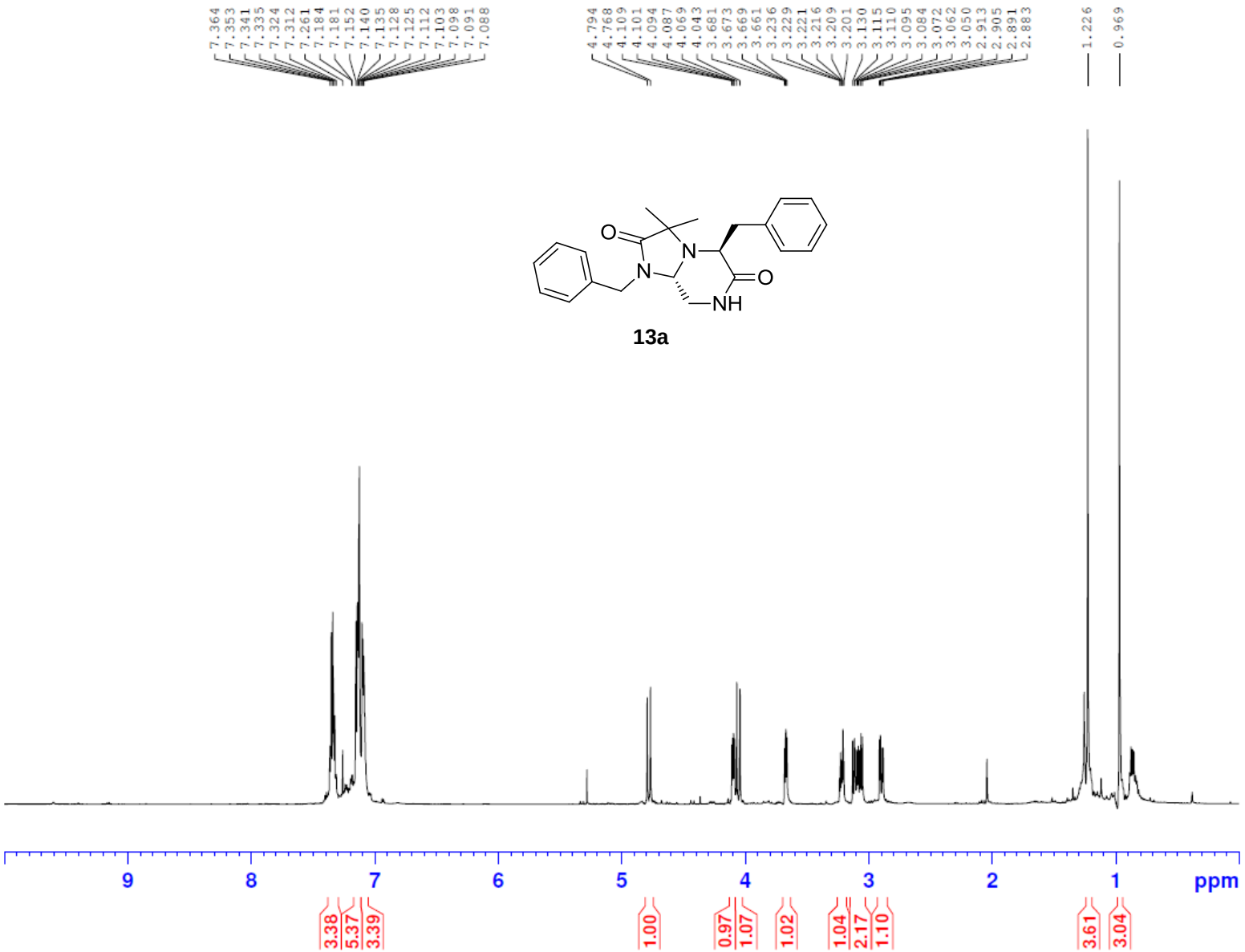

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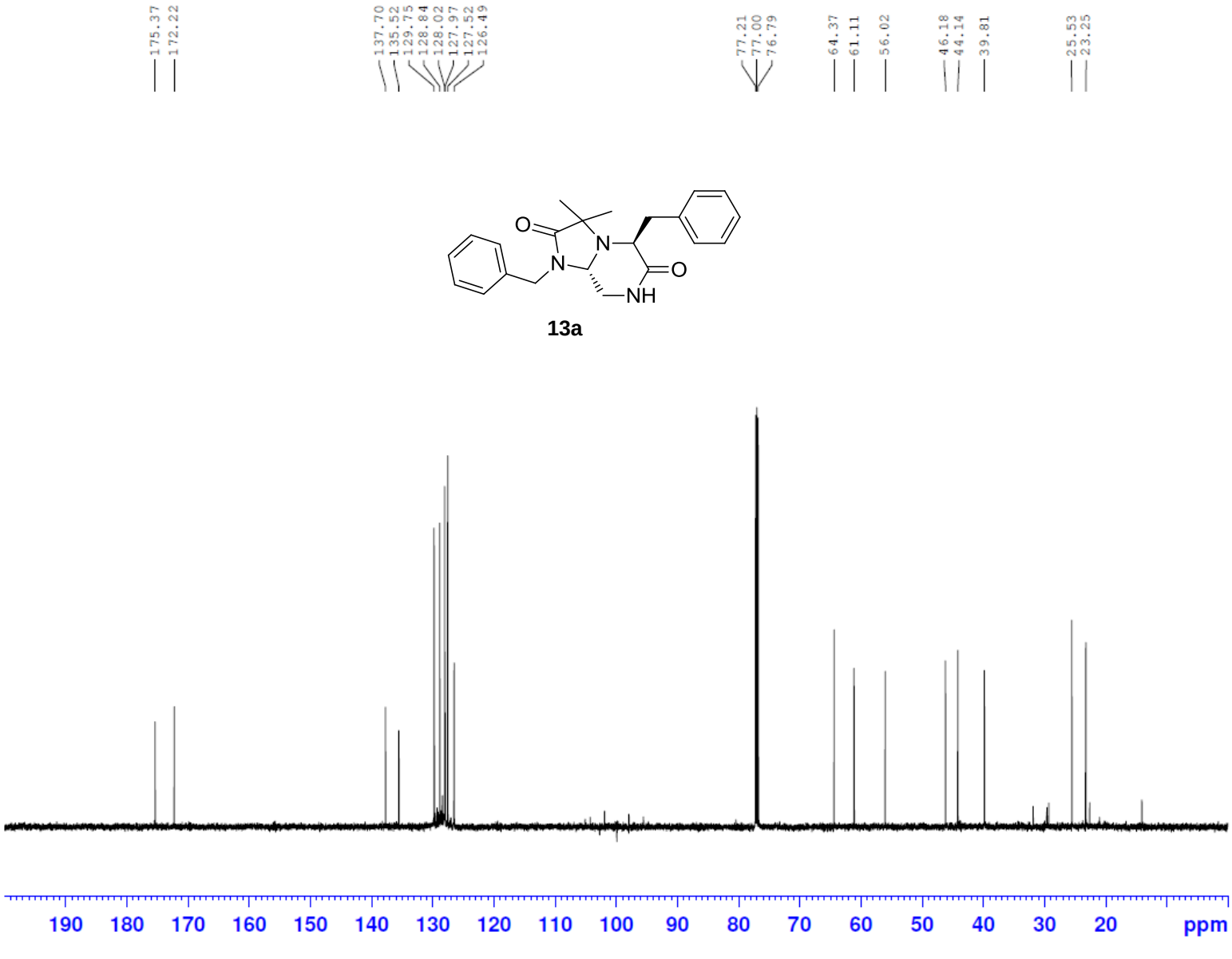

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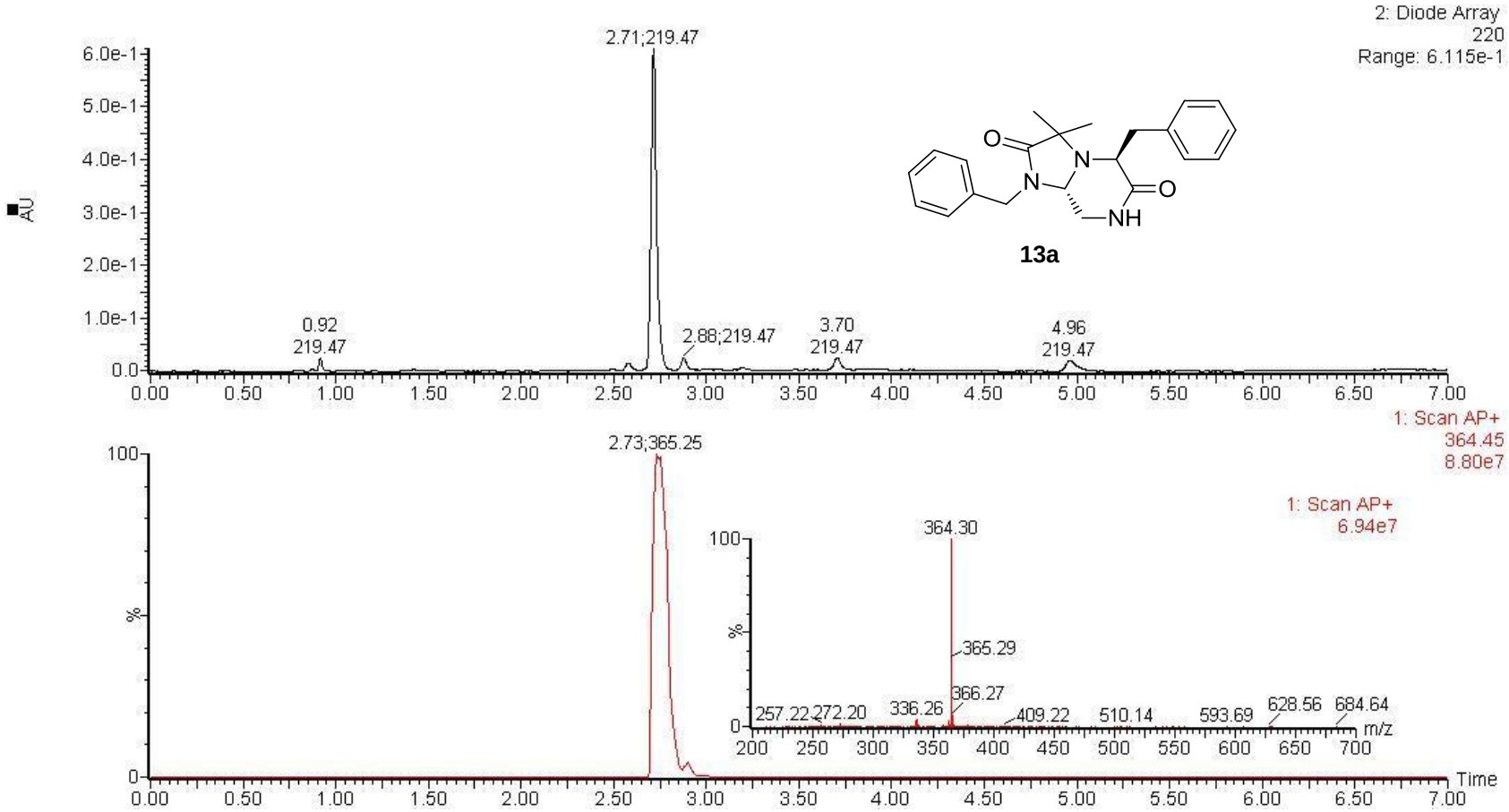

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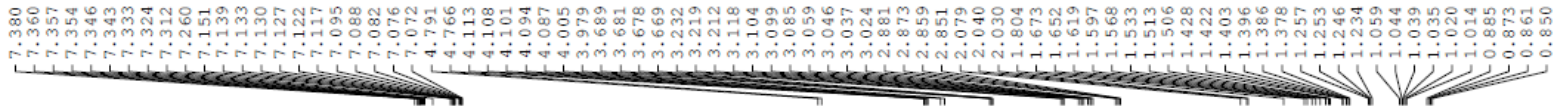

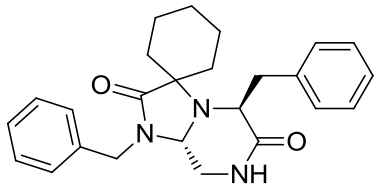

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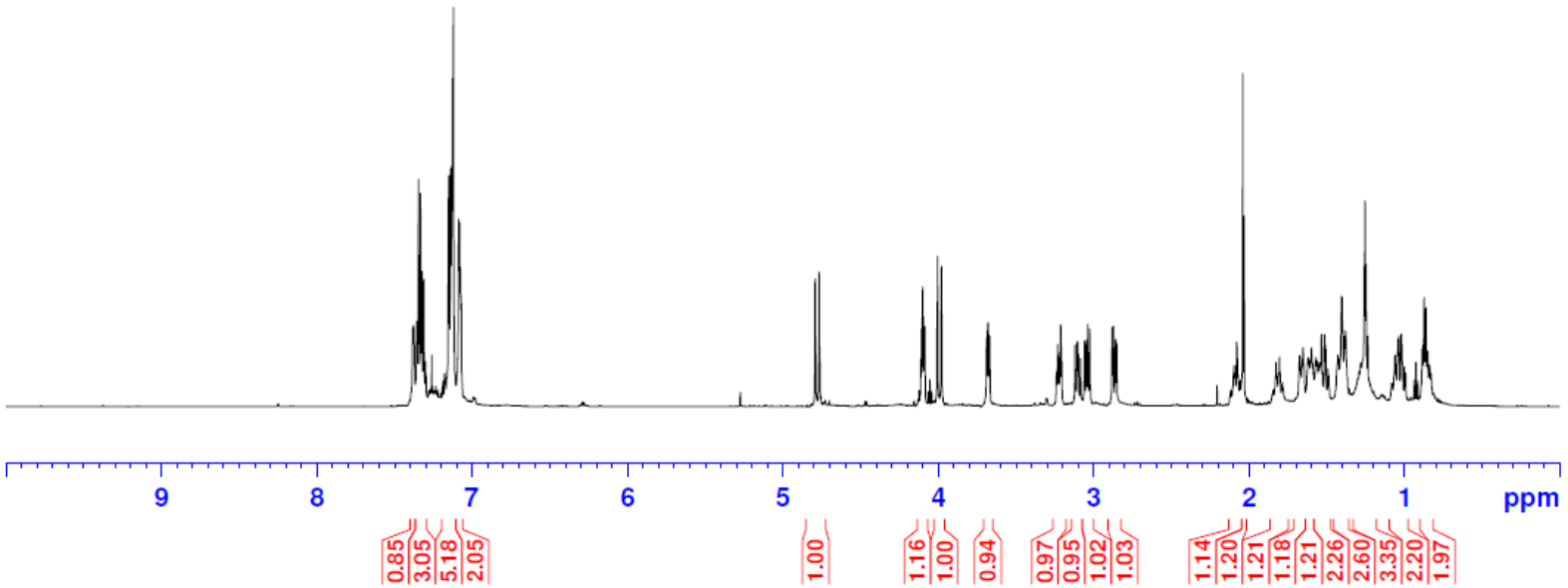

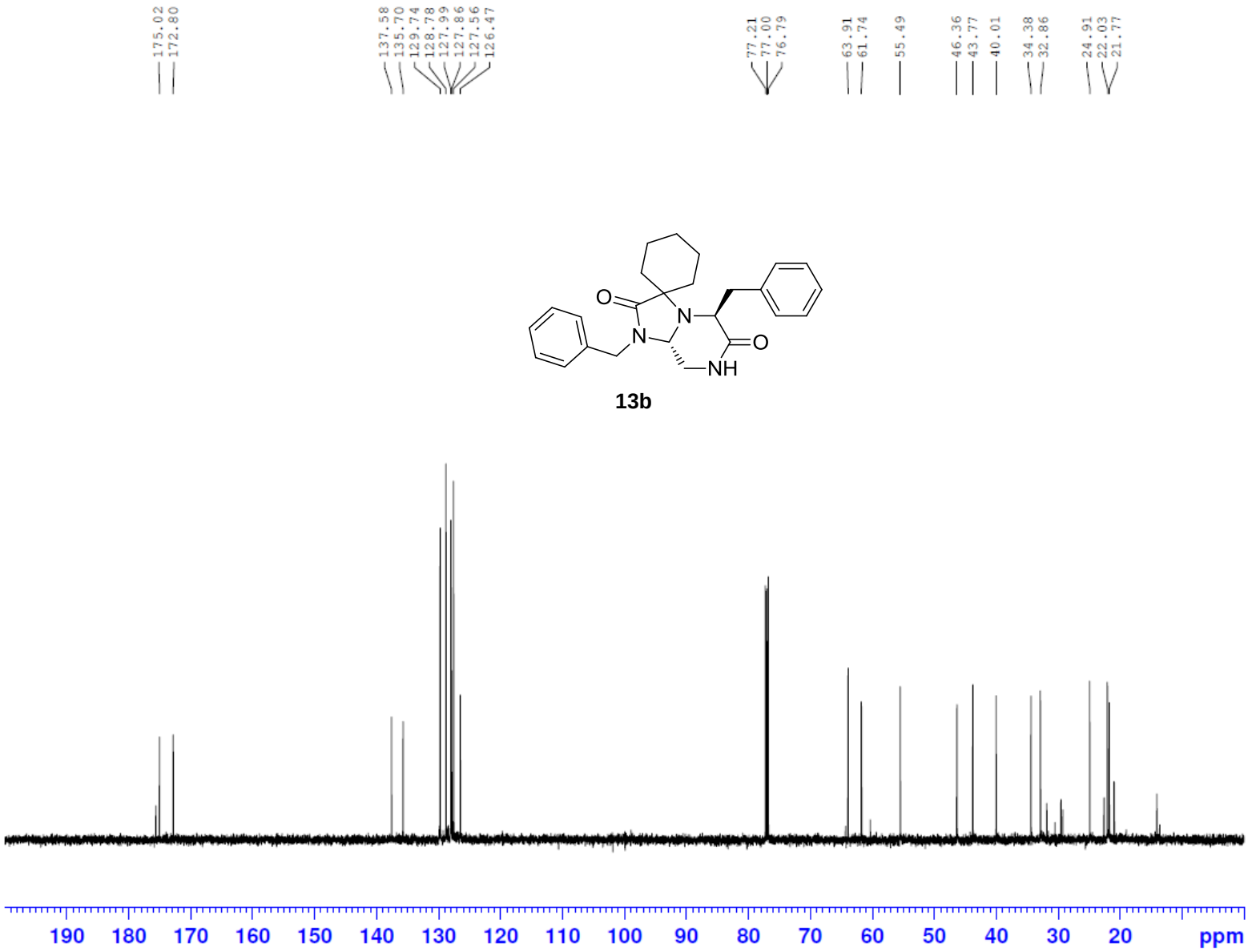

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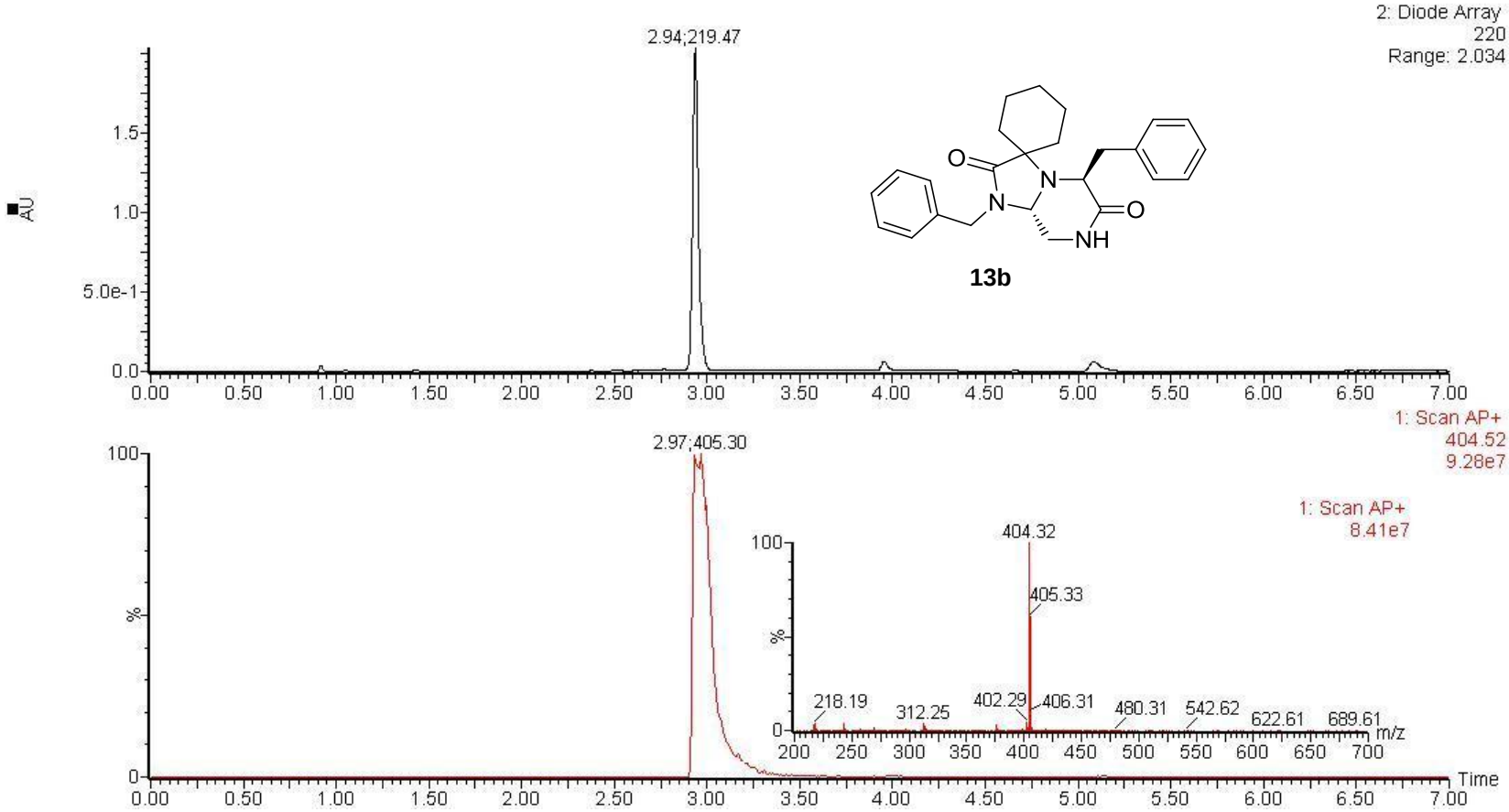

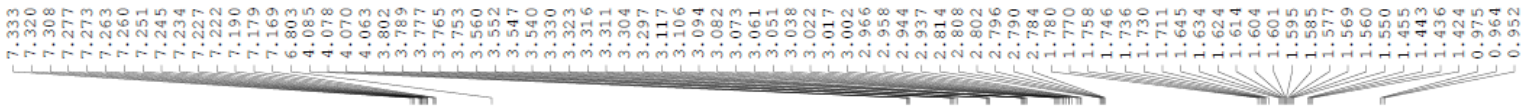

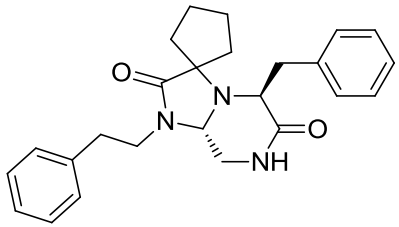

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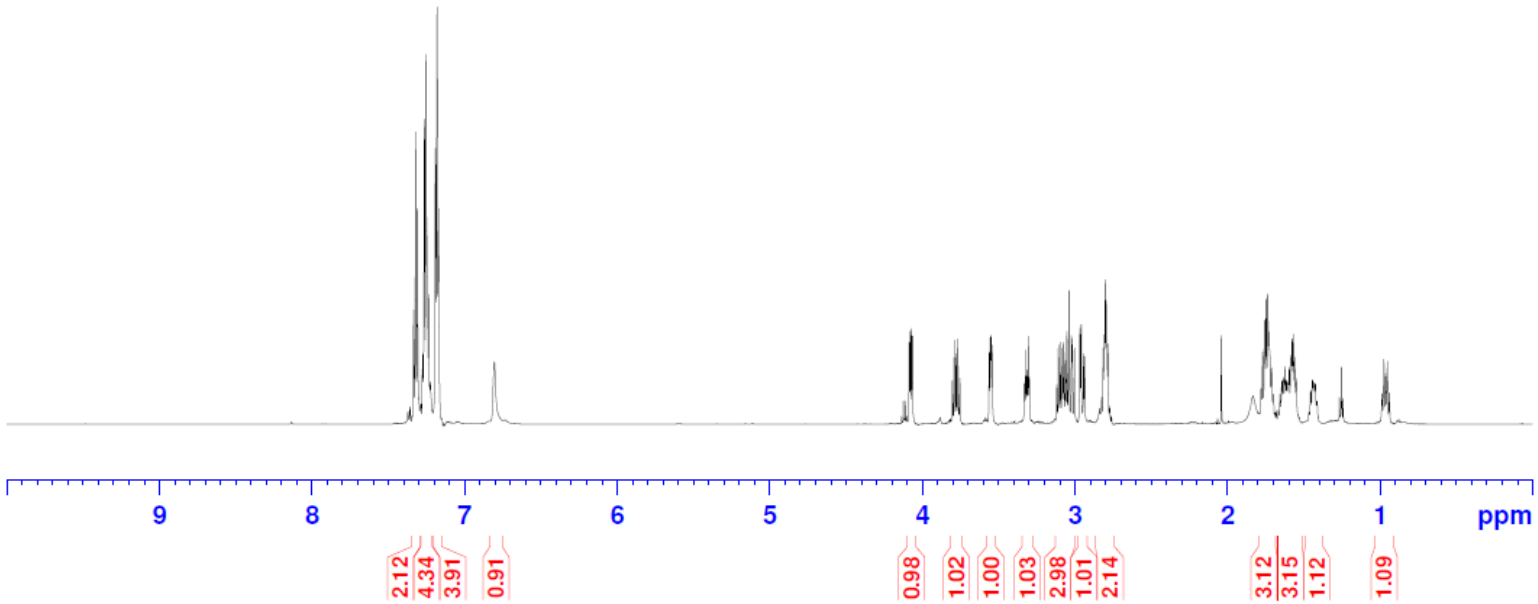

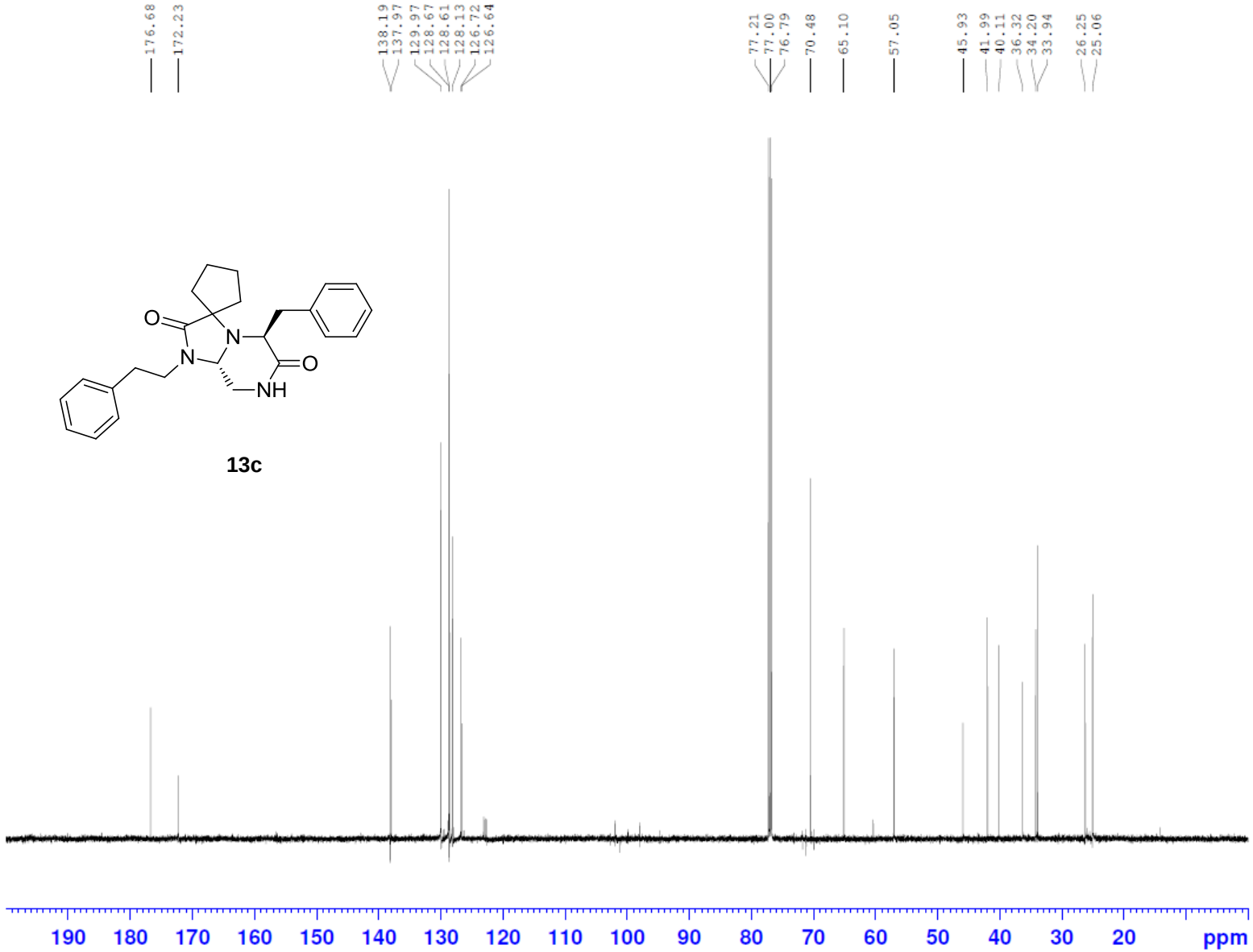

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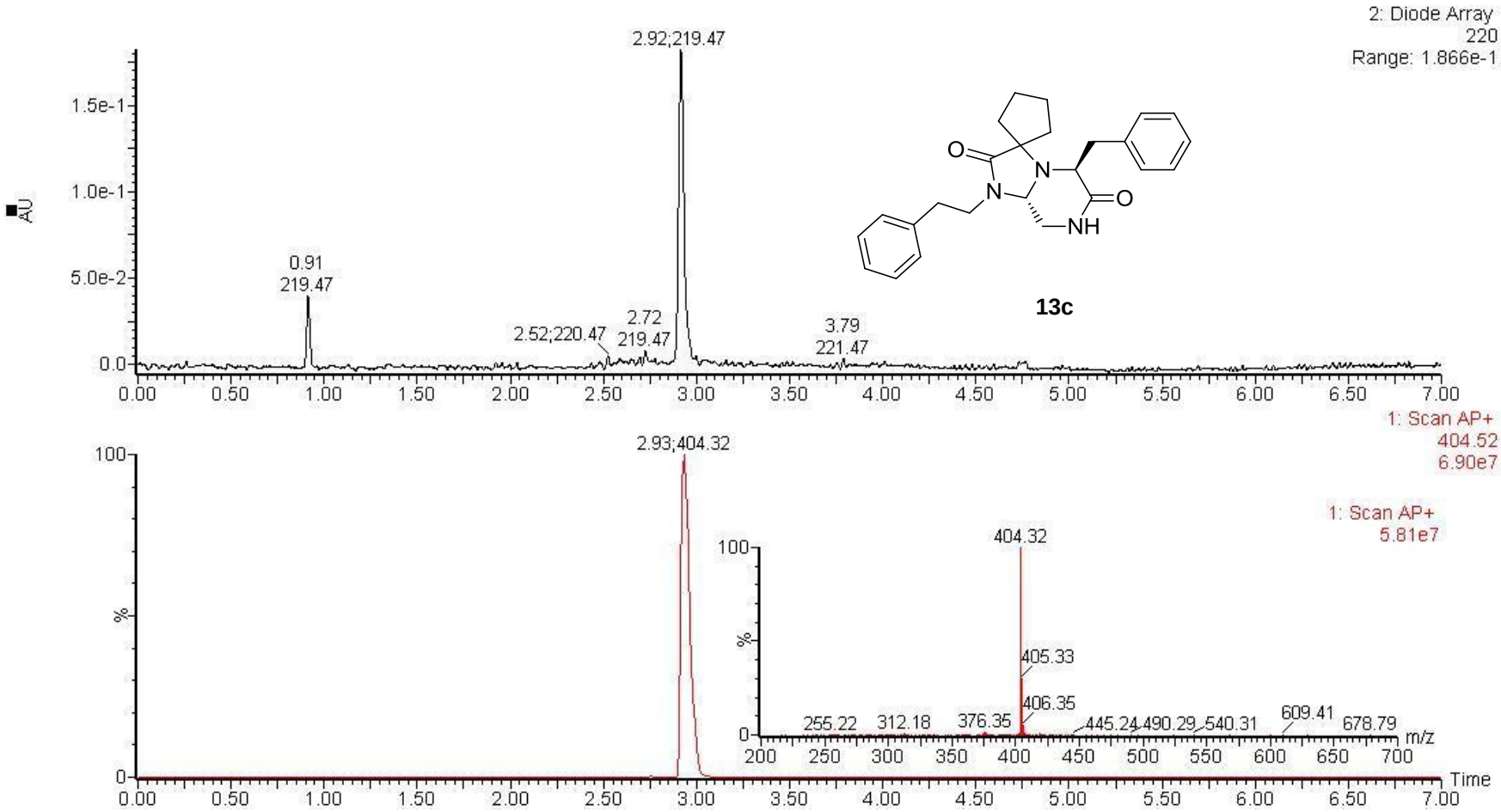

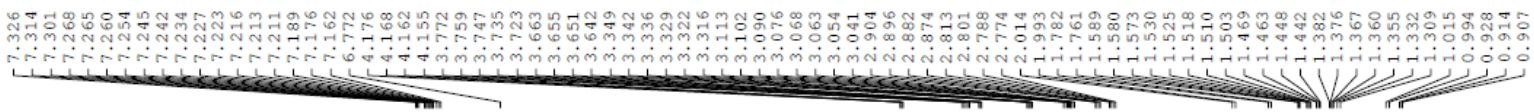

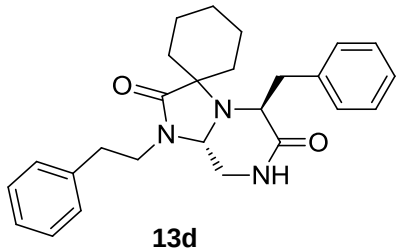

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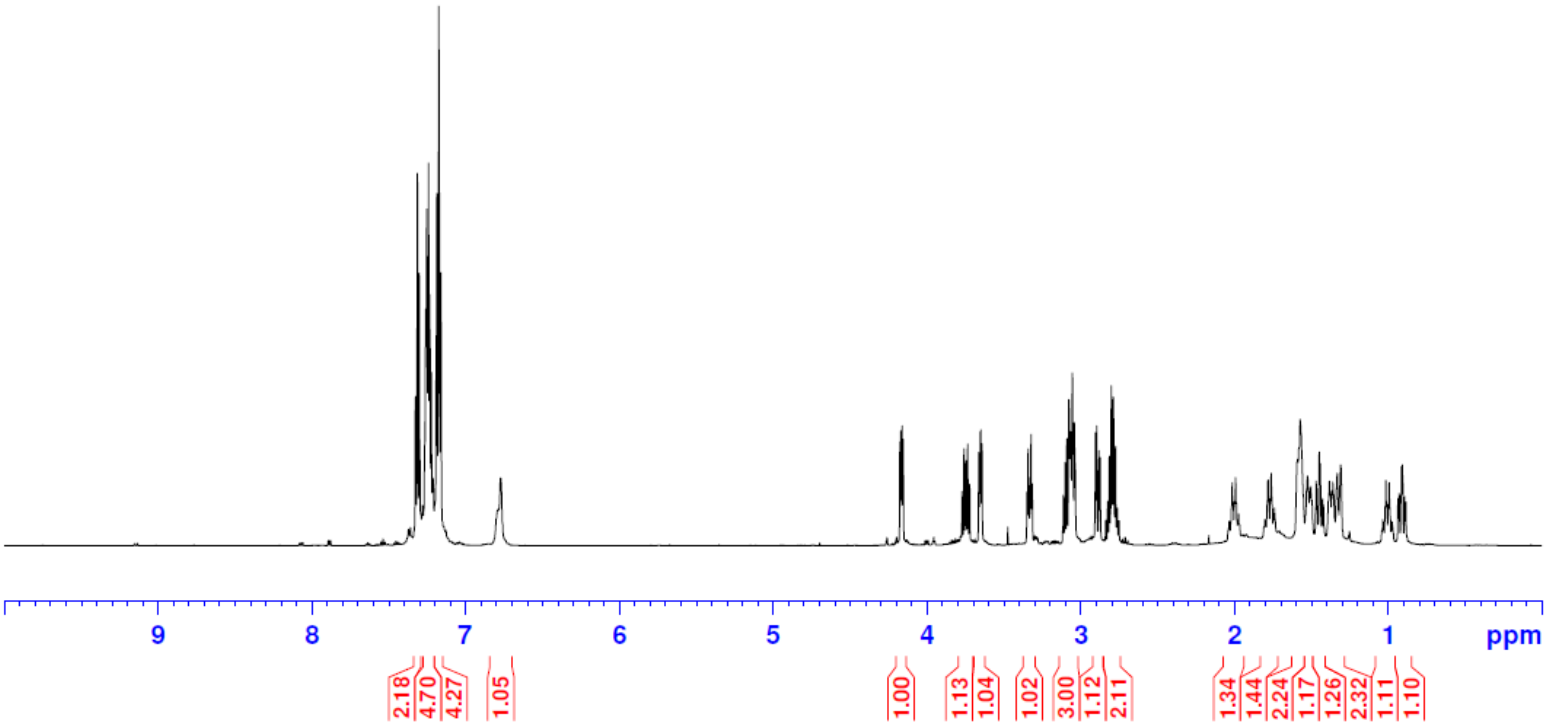

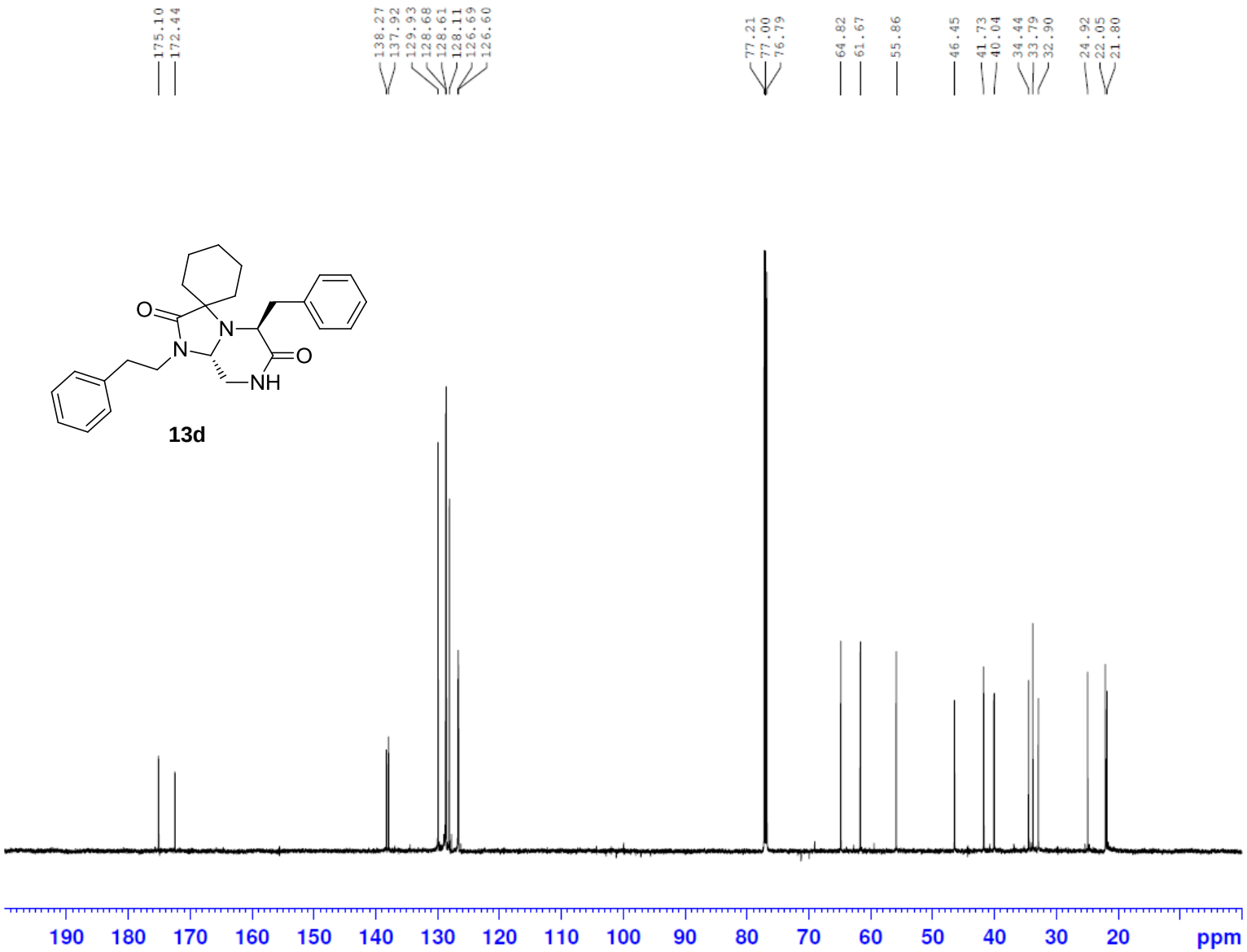

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