Novel Methodologies for the One-Pot Synthesis of Functionalized Pyroglutamates

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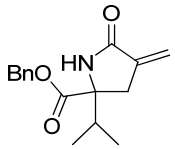
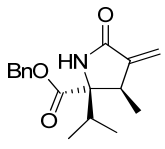
Experimental:

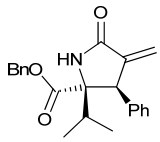


Valine α-methylene-γ-carboxy-γ-lactam 10a: To a solution of imine **7a** (2g, 5.82 mmol) in anhydrous THF was added LiHMDS (8.72 mL, 8.72 mmol, 1.0M in THF) drop wise at 0°C under nitrogen atmosphere and allowed to stir for one hour at 0°C. After 1h, BH bromide **8a** (1.56g, 8.72 mmol) was added drop wise at 0°C and allowed the reaction mixture to stir for 8h. The reaction was quenched with 3N HCl (15 mL) and stirred for additional 30 min. It was extracted with ethyl acetate (3x30 mL), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was refluxed in toluene (20 mL) for 1h, concentrated *in vacuo* and purified by column chromatography (30% EtOAc in hexanes) to yield (67%). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.36 - 7.32 (m, 5H), 6.01 (t, *J* = 2.5 Hz, 1H), 5.36 (d, *J* = 2.5 Hz, 1H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 3.11 (dt, *J* = 3 Hz, *J* = 18 Hz, 1H), 2.83 (dt *J* = 2.5 Hz, *J* = 18 Hz, 1H), 2.17 (septet, *J* = 7 Hz, 1H), 0.87 (d, *J* = 7 Hz, 3H),) 0.85 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.2, 169.9, 138.6, 135.4, 128.8, 128.7, 128.5, 116.8, 67.6, 66.4, 36.0, 33.9, 17.2, 16.3; HRMS (ESI) m/z: calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1398, found 274.1386.

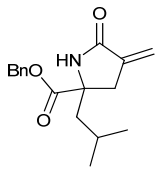


Valine α-methylene-β-methyl-γ-carboxy-γ-lactam 10b: Yield (58%); Viscous liquid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.4 - 7.37 (m, 5H), 6.65 (br s, 1H), 5.98 (d, *J* = 4 Hz, 1H),

5.25 (d, *J* = 4 Hz, 1H), 5.24 (d, *J* = 12 Hz, 1H), 5.19 (d, *J* = 12 Hz, 1H), 3.07 (m, 1H), 2.35 (septet, *J* = 6.5 Hz, 1H), 1.45 (d, *J* = 7Hz, 3H), 0.80(d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 173.1, 169.5, 144.5, 135.3, 129.0, 128.9, 128.6, 114.1, 68.9, 67.5, 42.1, 32.3, 18.4, 17.2, 12.2; HRMS (ESI) m/z: calc'd for $C_{17}H_{21}NO_3$ $[M+H]^+$: 288.1594, found 288.1535.

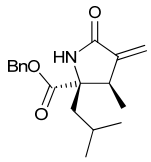


Valine α-methylene-γ-carboxy-γ-lactam 10c: Yield (66%); Yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.52 (br s, 1H), 7.39 -7.30 (m, 10H), 6.24 (d, 1H), 5.31 (d, *J* = 12 Hz, 1H), 5.3 (s, 1H), 5.18 (d, *J* = 12 Hz, 1H), 4.56 (s, 1H), 1.9 (septet, *J* = 6.5 Hz, 1H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.62 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.8, 169.8, 142.4, 137.0, 135.2, 130.7, 129.0, 128.8, 128.6, 128.5, 128.0, 118.9, 70.5, 67.7, 52.6, 32.3, 18.6, 17.7; HRMS (ESI) m/z: calc'd for $C_{22}H_{23}NO_3$ $[M+H]^+$: 350.1751, found 350.1758.

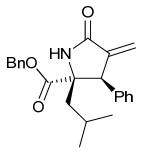


Leucine α-methylene-γ-carboxy-γ-lactam 10d: Yield (60%); ^{1}HNMR (500MHz, $CDCl_3$) δ 7.39 - 7.34 (m, 5H), 6.83(br s, 1H), 6.03 (dd, *J* = 2.5, 2.5 Hz, 1H), 5.38 (m, 1H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 3.22 (ddd, *J* = 2.25, 2.5, 17.5 Hz, 1H), 2.78 (ddd, *J* = 2.25, 2.5, 17.5 Hz, 1H), 1.86 (m, 1H), 1.69 (m, 1H), 1.64 (m, 1H), 0.9 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

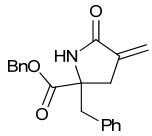
173.5, 169.3, 137.8, 135.2, 128.9, 128.8, 128.7, 117.4, 67.8, 62.7, 48.9, 38.1, 24.9, 24.2, 23.3; HRMS (ESI) m/z: calc'd for $C_{17}H_{21}NO_3$ $[M+H]^+$: 288.1591, found 288.1585.



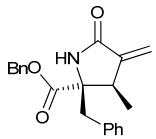
Leucine α-methylene-β-methyl-γ-carboxy-γ-lactam 10e: Yield (53%); Yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.47 (br s, 1H), 7.36 -7.34 (m, 5H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.26 (d, *J* = 3 Hz, 1H), 5.24 (d, *J* = 11.5 Hz, 1H), 5.15 (d, *J* = 11.5 Hz, 1H), 3.00 (m, 1H), 1.78 (dd, *J* = 8.5, 14 Hz, 1H), 1.66 (m, 1H), 1.30 (d, *J* = 4 Hz, 13.5 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.5, 169.2, 143.9, 135.2, 128.9, 128.8, 128.7, 128.6, 115.8, 67.6, 65.5, 43.6, 42.9, 24.6, 24.3, 22.5, 12.4; HRMS (ESI) m/z: calc'd for $C_{18}H_{23}NO_3$ $[M+H]^+$: 302.1751, found 302.1745.



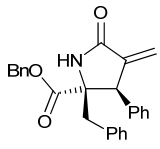
Leucine α-methylene-β-phenyl-γ-carboxy-γ-lactam 10f: Yield (57%); ^{1}H NMR(500MHz, $CDCl_3$): δ 7.6 (br s, 1H), 7.4 - 7.36 (m, 5H), 7.3 -7.29 (m, 3H), 7.19 - 7.17 (m, 2H), 6.26 (d, *J* = 3 Hz, 1H), 5.32 (d, *J* = 12 Hz, 1H), 5.26 (d, *J* = 2 Hz, 1H), 5.16 (d, *J* = 12 Hz, 1H), 4.33 (t, *J* = 3 Hz, 1H), 1.59 (m, 1H), 1.35 (dd, *J* = 7 Hz, 14 Hz, 1H), 1.24 (dd, *J* = 5 Hz, 14 Hz, 1H), 0.81 (d, *J* = 6.5 Hz, 1H), 0.66 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$): δ 173.9, 169.5, 142.1, 137.0, 135.2, 130.8, 129.0, 128.9, 128.8, 128.4, 128.0, 119.7, 67.8, 66.4, 54.4, 45.3, 24.6, 24.4, 22.9; HRMS (ESI) m/z: calc'd for $C_{23}H_{25}NO_3$ $[M+H]^+$: 364.1907, found 364.1887.



Phenylalanine α-methylene-γ-carboxy-γ-lactam 10g: Yield (58%); Viscous liquid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.38 -7.37 (m, 3H), 7.29 -7.25 (m, 5H), 7.07 - 7.05 (m, 2H), 6.56 (br s, 1H), 6.03 (t, *J* = 2.5 Hz, 1H), 5.38 (s, 1H), 5.14 (s, 2H), 3.31 (d, *J* = 13.5 Hz, 1H), 3.22 (dt, *J* = 2.5 Hz, 17.5 Hz, 1H), 2.95 (dt, *J* = 2.5 Hz, 17.5 Hz, 1H), 2.92 (d, *J* = 13.5 Hz, 1H); ^{13}CNMR (125MHz, $CDCl_3$) δ 172.7, 169.1, 135.0, 134.5, 130.1, 129.2, 129.1, 128.9, 128.8, 127.8, 117.8, 67.9, 63.7, 46.1, 37.3; HRMS (ESI) m/z: calc'd for $C_{20}H_{19}NO_3$ $[M+H]^+$: 322.1438, found 322.1434.

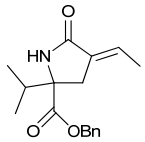


Phenylalanine α-methylidene-β-methyl-γ-carboxy-γ-lactam 10h: Yield (51%); yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.38 - 7.36 (m, 3H), 7.29 - 7.26 (m, 2H), 7.25 - 7.22 (m, 3H), 6.99 - 6.97 (m, 2H), 6.14 (d, *J* = 3.5 Hz, 1H), 6.11 (br s, 1H), 5.39 (d, *J* = 3.5 Hz, 1H), 5.15 (s, 2H), 3.32 (d, *J* = 13, 1H), 3.19 (m, 1H), 2.56 (d, *J* = 13, 1H), 1.48 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.2, 168.4, 143.5, 135.0, 134.6, 129.9, 129.1, 128.9, 128.8, 127.7, 116.7, 67.7, 66.7, 42.7, 40.9, 12.8; HRMS (ESI) m/z: calc'd for $C_{21}H_{21}NO_3$ $[M+H]^+$: 336.1594, found 336.1598.

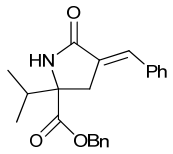


Phenylalanine α-methylene-β-phenyl-γ-carboxy-γ-lactam 10i: Yield (56%); Viscous liquid. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.41 - 7.37 (m, 5H), 7.36 - 7.34 (m, 3H), 7.26 - 7.24

(m, 2H), 7.21 - 7.18 (m, 3H), 6.94 - 6.92 (m, 2H), 6.34 (d, *J* = 3 Hz, 1H), 6.31 (br s, 1H), 5.37 (d, *J* = 3 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 4.51 (t, *J* = 3 Hz, 1H), 2.72 (d, *J* = 13.5, 1H), 2.40 (d, *J* = 13.5 Hz, 1H); ^{13}CNMR (125MHz, $CDCl_3$) δ 172.8, 168.6, 141.9, 137.0, 134.9, 130.8, 129.9, 129.1, 129.0, 128.9, 128.8, 128.3, 127.7, 120.5, 68.0, 67.2, 53.5, 43.4; HRMS (ESI) m/z: calc'd for $C_{26}H_{23}NO_3$ $[M+H]^+$: 398.1751, found 398.1725.

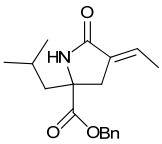


Valine α-ethylidene-γ-carboxy-γ-lactam 11a: Yield (62%); White powder; mp 85-87 ^{o}C. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.39 -7.35 (m, 5H), 6.68 (br s, 1H), 6.39 (m, 1H), 5.21 (d, *J* = 12 Hz, 1H), 5.16 (d, *J* = 12 Hz, 1H), 3.05 (d, *J* = 17.5 Hz, 1H), 2.73 (d, *J* = 17.5 Hz, 1H), 2.17 (septet, *J* = 7 Hz, 1H), 1.78 (d, *J* = 7 Hz, 3H), 0.87 (d, *J* = 7 Hz, 6H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.4, 170.0, 135.4, 130.9, 129.6, 128.9, 128.8, 128.6, 67.6, 66.5, 36.1, 31.7, 17.2, 16.2, 15.1; HRMS (ESI) m/z: calc'd for $C_{17}H_{21}NO_3$ $[M+H]^+$: 288.1594, found 288.1546.

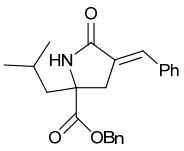


Valine α-benzylidene-γ-carboxy-γ-lactam 11b: Yield (68%); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.51 -7.36 (m, 11H, ten aromatic and one olefinic hydrogen merged), 7.34 (br s, 1H), 5.23 (s, 2H), 3.46 (d, *J* = 16.5 Hz, 1H), 3.12 (d, *J* = 16.5 Hz, 1H), 2.25 septet, *J* = 6.5Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.4, 171.1, 135.5, 135.3, 131.5, 130.0, 129.2, 129.1, 128.9, 128.6, 67.7, 67.0,

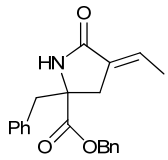
36.2, 34.2, 17.3, 16.3; HRMS (ESI) m/z: calc'd for $C_{22}H_{23}NO_3$ $[M+H]^+$: 350.1751, found 350.1772.



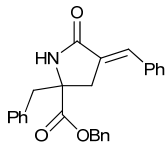
Leucine α-ethylidene-γ-carboxy-γ-lactam 11c: Yield (57%); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.39 - 7.35 (m, 5H), 6.56 (m, 1H), 6.50 (br s, 1H), 5.20 (d, *J* = 12 Hz, 1H), 5.15 (d, *J* = 12 Hz, 1H), 3.14 (d, *J* = 17.5 Hz, 1H), 2.68 (d, *J* = 17.5 Hz, 1H), 1.88 (dd, *J* = 7Hz, 14 Hz, 1H), 1.77 (d, *J* = 7 Hz, 3H), 1.69 (dd, *J* = 7, 14 Hz, 1H), 1.67 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.8, 169.7, 135.2, 130.3, 130.1, 128.9, 128.8, 128.6, 67.7, 62.9, 49.2, 35.9, 24.9, 24.2, 23.4, 15.0; HRMS (ESI) m/z: calc'd for $C_{18}H_{23}NO_3$ $[M+H]^+$: 302.1751, found 302.1743.



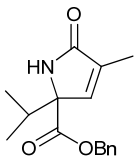
Leucine α-benzylidene-γ-carboxy-γ-lactam 11d: Yield (64%); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.48 - 7.41 (m, 6H, five aromatic and one olefinic proton merged), 7.39 (m, 5H), 7.11 (s, 1H), 5.20 (s, 2H), 3.57 (d, *J* = 19.5 Hz, 1H), 3.08 (d, *J* = 19.5Hz, 1H), 1.95 (dd, *J* = 7.5 Hz, 14 Hz, 1H), 1.75 (dd, *J* = 5.5 Hz, 19.5 Hz, 1H), 1.7 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.7, 170.9, 135.5, 135.2, 132.0, 130.0, 129.2, 129.0, 128.8, 128.7, 128.6, 67.9, 63.3, 49.2, 38.2, 25.0, 24.2, 23.5; HRMS (ESI) m/z: calc'd for $C_{23}H_{25}NO_3$ $[M+H]^+$: 364.1907, found 364.1897.



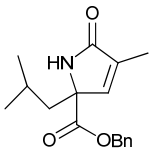
Phenylalanine α-ethylidene-γ-carboxy-γ-lactam 11e: Yield (55%); yellow oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 3H), 7.27 - 7.26 (m, 2H), 7.25 - 7.24 (m, 3H), 7.07 - 7.05 (m, 2H), 6.53 (m, 1H), 6.48 (br s, 1H), 5.13 (s, 2H), 3.31 (d, *J* = 13.5 Hz, 1H), 3.12 (d, *J* = 17.5 Hz, 1H), 2.91 (d, *J* = 13.5 Hz, 1H), 2.84 (d, *J* = 17.5 Hz, 1H), 1.75 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 173.0, 169.6, 135.1, 134.7, 130.3, 130.2, 130.1, 129.1, 129.0, 128.9, 128.8, 128.7, 127.7, 67.8, 64.0, 46.3, 35.0, 15.1; HRMS (ESI) m/z: calc'd for $C_{21}H_{21}NO_3$ $[M+H]^+$: 336.1594, found 336.1630.



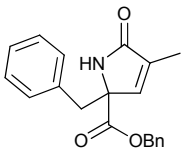
Phenylalanine α-benzylidene-γ-carboxy-γ-lactam 11f: Yield (63%); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 3H), 7.40 - 7.37 (m, 2H), 7.36 - 7.34 (m, 3H), 7.28 - 7.26 (m, 2H), 7.26 - 7.24 (m, 3H), 7.08 -7.06 (m, 2H), 6.2 (br s, 1H), 5.16 (d, *J* = 12 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 3.53 (dd, *J* = 3 Hz, 17.5 Hz, 1H), 3.40 (d, *J* = 13 Hz, 1H), 3.26 (dd, *J* = 2.5 Hz, 17.5 Hz, 13.5 Hz, 1H), 2.92 (d, *J* = 13 Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ 172.8, 170.3, 135.3, 134.9, 134.6, 132.5, 130.1, 129.9, 129.3, 129.0, 128.9, 128.8, 128.1, 127.8, 68.0, 64.3, 46.8, 37.8; HRMS (ESI) m/z: calc'd for $C_{26}H_{23}NO_3$ $[M+H]^+$: 398.1751, found 398.1726.



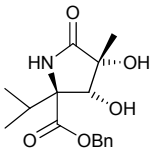
Valine α-methyl-γ-carboxy-γ-lactam 16a: To a stirred solution of lactam **10a** (2.87g, 10.5 mmol) dissolved in THF (20 mL), $RhCl_3.H_2O$ (0.227g, 1 mmol) was added and refluxed for 24 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Diethyl ether was added to the residue and insoluble inorganic impurities are filtered. The filtrate was evaporated in *vacuo* to give the isomer **16a** (2.57g, 90%) as red colored viscous liquid which was used in next step without any further purification. ^{1}H NMR (500MHz, $CDCl_3$): δ 7.40 - 7.35 (m, 5H), 6.71 (br s, 1H), 6.66 (s, 1H), 5.18 (s, 2H), 2.39 (septet, J = 6.5 Hz, 1H), 1.90 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H); 13CNMR (125MHz, CDCl3) δ 174.4, 170.5, 141.4, 135.7, 135.3, 128.9, 128.8, 128.6, 72.5, 67.9, 34.0, 18.2, 16.2, 10.9.



Leucine α-methyl-γ-carboxy-γ-lactam 16b: Yield (90%), viscous dark liquid, ^{1}HNMR (500MHz, $CDCl_3$) δ 7.38 - 7.33 (m, 1H), 6.69 (s, 1H), 6.67 (br s, 1H), 5.17 (d, J = 12 Hz, 1H), 5.15 (d, J = 12 Hz, 1H), 1.98 (m, 1H), 1.88 (s, 3H), 1.65 (m, 2H), 0.91 (d, J = 6.5, 3H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 173.8, 170.7, 142.3, 135.1, 128.9, 128.8, 128.6, 68.5, 68.0, 45.4, 25.2, 24.1, 23.7, 10.9; HRMS (ESI) m/z: calc'd for $C_{17}H_{21}NO_3$ $[M+Na]^+$: 310.1414, found 310.1385.

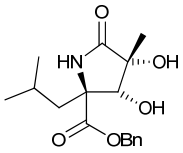


Phenylalanine α-methyl-γ-carboxy-γ-lactam 16c: Yield (87%), viscous dark liquid ^{1}HNMR (500MHz, $CDCl_3$) δ 7.39 - 7.36 (m, 3H), 7.26 - 7.22 (m, 5H), 7.08 - 7.06 (m, 2H), 6.81 (s,1H), 6.40 (br s, 1H), 5.12 (s, 2H), 3.41 (d, J = 13.5 Hz, 1H), 2.88 (d, J = 13.5 Hz, 1H), 1.88 (s, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 173.3, 169.6, 141.4, 135.9, 134.9, 134.7, 129.9, 128.9, 128.8, 127.7, 69.4, 68.0, 43.7, 10.9; HRMS (ESI) m/z: calc'd for $C_{20}H_{19}NO_3$ $[M+Na]^+$: 344.1257, found 344.1241.

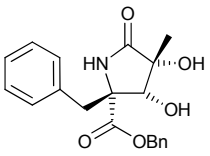


Valine diol lactam 17a: NMO (50% wt in water 1.63 mL, 6.96 mmol) and OsO_4 (17.7 mg, 0.07mmol) were added successively to the olefinic lactam **16a** (1g, 3.66 mmol) dissolved in acetone (20 mL). The reaction mixture was stirred at room temperature for 40h. After completion of the reaction, water was added, extracted with ethyl acetate (3 x 40 mL), washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (70% EtOAc in hexanes) to afford inseparable mixture of diols **17a**. Yield (0.88g, 79%); >98% de (NMR). ^{1}HNMR (500MHz, DMSO-d_6) δ 8.44 (br s, 1H), 7.43 – 7.46 (m, 5H), 5.17 (s, 1H), 5.12 (d, J = 12 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 4.81 (d, J = 8.5 Hz, 1H), 3.76 (d, J = 8.5 Hz, 1H), 2.13 (septet, J = 7Hz, 1H), 1.18 (s, 3H), 0.93 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H); ^{13}CNMR (125MHz, DMSO-d_6) δ 175.6, 172.8, 136.6, 129.0, 128.7, 128.6, 77.4, 72.9,

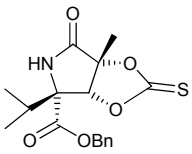
69.9, 66.7, 33.3, 22.1, 18.7, 17.4; HRMS (ESI) m/z: calc'd for $C_{16}H_{21}NO_5$ $[M+Na]^+$: 330.1312, found 330.1312.



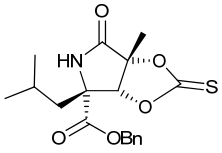
Leucine diol lactam 17b: Yield (75%); (diastereomeric ratio of 9:1). ^{1}H NMR (500MHz, $CDCl_3$) δ (peaks corresponding to major isomer), 7.5 (br s, 1H), 7.40 - 7.35 (m, 5H), 5.24 (m, 2H), 4.61 (s, 1H), 4.18 (d, J = 6.5 Hz, 1H), 3.86 (d, J = 6.5 Hz, 1H), 2.20 (dd, J = 7Hz, 14 Hz, 1H), 1.68 (m, J = 6.5,7 Hz, 1H), 1.60 (dd, J = 7 Hz, 14 Hz, 1H), 1.46 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 177.5, 172.4, 135.2, 128.9, 129.1, 129.0, 128.7, 80.9, 73.6, 68.5, 67.9, 45.6, 25.0, 24.2, 23.5, 22.9; HRMS (ESI) m/z: calc'd for $C_{17}H_{23}NO_5$ $[M+Na]^+$: 344.1468, found 344.1469.



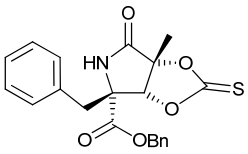
Phenylalanine diol lactam 17c: Yield (80%); diastereomeric ratio of 10:1 by NMR, R_f = (0.4, 60% EtOAc in hexanes). ^{1}HNMR (500MHz, $CDCl_3$) δ 7.35 - 7.24 (m, 8H), 7.07 - 7.05 (m, 2H), 6.89 (br s, 1H), 5.16 (s, 2H), 4.75 (s, 1H), 4.20 (d, J = 6 Hz, 1H), 3.99 (d, J = 6 Hz, 1H), 3.55 (d, J = 13.5 Hz, 1H), 2.92 (d, J = 13.5 Hz, 1H), 1.43 (s, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 176.8, 171.3, 135.2, 134.4, 130.2, 129.1, 129.0, 128.9, 128.8, 128.7, 127.8, 79.3, 73.5, 69.1, 68.0, 42.5, 23.0; HRMS (ESI) m/z: calc'd for $C_{20}H_{21}NO_5$ $[M+Na]^+$: 378.1312, found 378.1295.



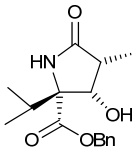
Valine diol thiocarbonate 18a: Leucine diol **17a** (1 g, 3.25 mmol) and thiocarbonyl imidazole (0.834 g, 4.68 mmol) were taken in dry THF (20 mL) refluxed for 8h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to obtain .97g of thiocarbonate **18a** (85% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.5 (br s, 1H), 7.39 - 7.28 (m, 5H), 5.28 (d, J = 12 Hz, 1H), 5.20 (d, J = 12 Hz, 1H), 4.98 (s, 1H), 2.46 (septet, J = 6.5 Hz, 1H), 1.73 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5, 1H); ^{13}C NMR (125MHz, DMSO-d_6) δ 188.0, 169.4, 168.5, 134.8, 129.0, 128.9, 128.8, 88.9, 87.3, 72.5, 68.7, 34.7, 18.5, 18.1, 16.6; HRMS (ESI) m/z: calc'd for $C_{17}H_{19}NO_5S$ $[M+Na]^+$: 372.0876, found 372.0858.



Leucine diol thiocarbonate 18b: Yield (87%). ^{1}H NMR (500MHz, $CDCl_3$) δ 8.9 (br s, 1H), 7.33 - 7.27 (m, 5H), 5.19 (d, J = 12 Hz, 1H), 5.14 (d, J = 12 Hz, 1H), 4.8 (s, 1H), 2.05 (dd, J = 9, 13.5 Hz, 1H), 1.67 (s, 3H), 1.65 (m, 1H), 1.30 (dd, J = 9, 13.5 Hz, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 188.1, 169.1, 168.6, 134.6, 129.0, 128.9, 128.8, 89.3, 88.3, 68.6, 67.2, 46.9, 24.4, 24.3, 21.9, 19.1; HRMS (ESI) m/z: calc'd for $C_{18}H_{21}NO_5S$ $[M+Na]^+$: 386.1033, found 386.1017.

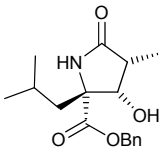


Phenylalanine thiocarbonate 18c: Yield (90%). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.43 - 7.41 (m, 5H), 7.33 - 7.31(m, 3H), 7.26 (br s, 1H), 7.10 - 7.08 (m, 2H), 5.34 (d, J = 10.5 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.03 (s, 1H), 3.36 (d, J = 14 Hz, 1H), 3.10 (d, J = 14 Hz, 1H), 1.14 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 187.7, 169.0, 167.7, 134.5, 132.2, 130.8, 129.6, 129.2, 129.1, 129.0, 128.8, 88.7, 87.2, 69.2, 68.6, 43.4, 17.6; HRMS (ESI) m/z: calc'd for $C_{21}H_{19}NO_5S$ $[M+Na]^+$: 420.0876, found 420.0886.

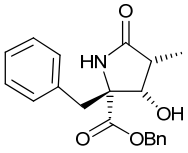


Valine α-methyl-β-hydroxy-γ-carboxy-γ-lactam 19a: Thiocarbonate **18a** (0.48 g, 1.38 mmol) and tributyltin hydride (0.742 mL, 2.75 mmol) in dichloromethane were cooled to -78^{o}C. 20 mol % of triethylboron was added and stirred for 1h. The reaction was quenched with 3 mL dry HCl (1M) at -78^{o}C and was warmed to 25^{o}C. Water was added to the mixture and extracted with ethyl acetate (3x25 mL), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to provide product as a colorless liquid. The crude reaction mixture was purified by column chromatography to get inseparable mixture of β-hydroxy lactams **19a** (353 mg, 88%) colorless oil (dr:10:1 by crude NMR); diastereomers are separable by column. ^{1}H NMR (500MHz, $CDCl_3$) δ (only major isomer) 7.33 - 7.30 (m, 5H), 7.20 (br s, 1H), 5.21 (d, J = 12.5 Hz, 1H), 5.15 (d, J = 12.5 Hz, 1H), 4.28 (d, J = 7 Hz, 1H), 3.99 (dd, J = 7Hz, 8.5 Hz, 1H), 2.44 (m, 1H), 2.33 (septet, J = 7Hz, 1H), 1.22 (d, J = 7.5 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 0.93 (d, J = 7 Hz, 3H); ^{13}C NMR (125MHz,

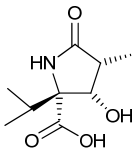
$CDCl_3$) δ 177.9, 172.6, 135.3, 128.8, 128.7, 128.4, 78.3, 71.2, 67.6, 44.1, 32.5, 18.1, 17.1, 13.2; HRMS (ESI) m/z: calc'd for $C_{16}H_{21}NO_4$ $[M+Na]^+$: 314.1363, found 314.1335.



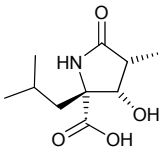
Leucine α-methyl-β-hydroxy-γ-carboxy-γ-lactam 19b: Yield (88%); (dr: 6.7:1 by crude NMR). ^{1}H NMR (500MHz, $CDCl_3$) δ (major isomer) 8.42 (br s, 1H), 7.45 - 7.38 (m, 5H), 5.29 (m, 3H), 4.13 (dd, J = 5 Hz, 12.5 Hz, 1H), 2.73 (m, 1H), 2.06 (dd, J = 8.5 Hz, 13.5 Hz, 1H), 1.77 (m, 1H), 1.54 (dd, J = 8.5 Hz, 13.5 Hz, 1H), 1.24 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 178.3, 173.9, 135.3, 128.9, 128.8, 128.7, 79.1, 72.4, 68.1, 43.5, 40.3, 25.2, 24.1, 22.2, 7.8; HRMS (ESI) m/z: calc'd for $C_{17}H_{23}NO_4$ $[M+Na]^+$: 328.1519, found 328.1497.



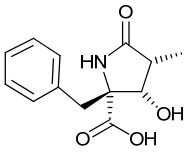
Phenylalanine α-methyl-β-hydroxy-γ-carboxy-γ-lactam 19c: Yield (80%); colorless oil (dr 5:1 by crude NMR); diasteromers are inseparable by column;. ^{1}HNMR (500MHz, $CDCl_3$) δ (major isomer) 7.5 (br s, 1H), 7.28 - 7.24 (m, 5H), 7.15 - 7.10 (m, 3H), 6.89 - 6.88 (m, 2H), 5.08 (d, J = 13 Hz, 1H), 5.05 (d, J = 13 Hz, 1H), 4.85 (d, J = 11 Hz, 1H), 4.19 (dd, J = 5.5, 11.5 Hz, 1H), 3.17 (d, J = 13.5 Hz, 1H), 2.74 (d, J = 13.5 Hz, 1H), 2.33 (m,1H), 1.07 (d, J = 7.5 Hz, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 178.2, 171.1, 135.3, 134.9, 129.9, 129.0, 128.9, 128.8, 128.7, 128.6, 127.5, 73.3, 68.1, 41.6, 40.7, 7.9; HRMS (ESI) m/z: calc'd for $C_{20}H_{21}NO_4$ $[M+Na]^+$: 362.1363, found 362.1327.



Valine β-hydroxy acid 20a: To a solution of β-hydroxyl benzyl ester **19a** (0.29 g, 1.00 mmol) in methanol (8 mL), was added Pd/C (32 mg) and stirred under hydrogen atmosphere for 1h. The reaction mixture was filtered and concentrated *in vacuo* to give hydroxy acid **20a** (0.18 mg, 89% yield) which was used for next step without any further purification. ^{1}H NMR (500MHz, CD_3OD) δ (major isomer) 3.99 (d, J = 9 Hz, 1H), 2.48 (m, 1H), 2.41 (m, 1H), 1.20 (d, J = 7 Hz, 3H), 1.04 (d, J = 7 Hz, 3H), 0.98 (d, J = 7 Hz, 3H); ^{13}CNMR (125MHz, CD_3OD) δ 179.2, 173.7, 90.9, 78.3, 77.4, 72.0, 30.8, 17.7, 15.9, 12.2.

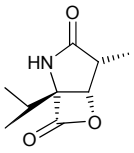


Leucine β-hydroxy acid 20b: Yield (90%). ^{1}HNMR (500MHz, CD_3OD) δ (major isomer) 4.12 (d, J = 5 Hz, 1H), 2.78 (m,1H),1.97 (dd, J = 8.5 Hz, 13.5 Hz, 1H), 1.73 (m, 1H), 1.6 (dd, J = 8.5, 13.5 Hz, 1H), 1.13 (d, J = 7.5 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H); ^{13}CNMR (125MHz, CD_3OD) δ 178.9, 173.8, 76.9, 70.9, 47.4, 40.2, 24.7, 23.6, 21.6, 7.3.

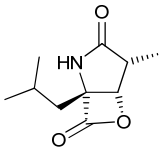


Phenylalanine β-hydroxy acid 20c: Yield (86%). ^{1}H NMR (500MHz, CD_3OD) δ (major isomer) 7.30 - 7.22 (m, 5H), 4.34 (d, J = 5.5, 1H), 3.31 (d, J = 13.5 Hz, 1H), 3.05 (d, J = 13.5 Hz, 1H), 2.36 (m, 1H), 1.07 (d, J = 7.5 Hz, 3H); ^{13}CNMR (125MHz, CD_3OD) δ

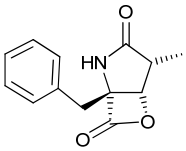
179.0, 172.5, 135.7, 130.8, 128.5, 128.4, 127.0, 75.2, 43.2, 41.5, 7.2; HRMS (ESI) m/z: calc'd for $C_{13}H_{15}NO_4$ $[M+Na]^+$: 272.0893, found 272.0867.



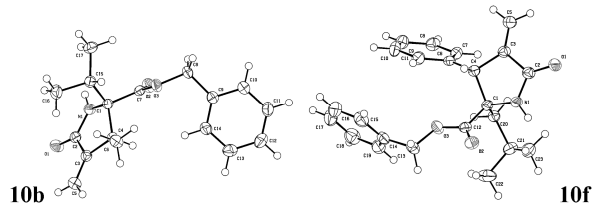
Valine [3.2.0] γ-lactam β-lactone 21a: To a suspension of β-hydroxy acid **20a** (0.1 g, 0.5 mmol) in dichloromethane (20 mL), pyridine (0.12 mL, 3 mmol) and bis (2-oxo-3-oxazolidinyl) phosphonic chloride (191 mg, 1.5 mmol) were added successively. The reaction mixture was stirred at room temperature for 3h. Water was added and extracted with ethyl acetate (3 x10 mL), washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography to afford 32 mg (35 % yield) of **21a**. ^{1}HNMR (500MHz, C_5D_5N) δ 9.34 (br s, 1H), 3.82 (s, 1H), 1.91 (q, J = 8 Hz, 1H), 1.24 (septet, J = Hz, 1H), 0.25 (d, J = 8 Hz, 3H), 0.07 (d, J = 7 Hz, 3H), 0.02 (d, J = 7 Hz, 3H); ^{13}CNMR (500MHz, C_5D_5N) δ 178.8, 171.6, 81.9, 79.9, 42.3, 28.5, 17.3, 17.2, 14.8; HRMS (ESI) m/z: calc'd for $C_9H_{13}NO_3$ $[M+Na]^+$: 206.0788, found 206.0726.



Leucine [3.2.0] γ-lactam β-lactone 21b: (Yield 40%). Pure isomer obtained by column chromatography ^{1}H NMR (500MHz, $CDCl_3$) δ 7.32 (br s, 1H), 4.95 (d, J = 6 Hz, 1H), 2.77 (m, 1H), 2.0 (dd, J = 5 Hz, 14 Hz, 1H), 1.87 (m, 1H), 1.81 (dd, J = 5, 14 Hz, 1H), 1.33 (d, J = 7.5, 3H), 1.04 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}CNMR (125MHz, $CDCl_3$) δ 177.2, 170.0, 78.8, 75.5, 39.0, 37.8, 24.4, 23.7, 23.0, 8.3; HRMS (ESI) m/z: calc'd for $C_{10}H_{15}NO_3$ $[M+Na]^+$: 220.0944, found 220.0929.

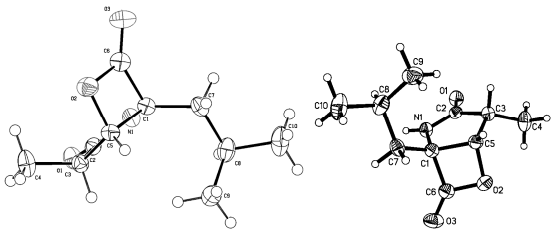


Phenylalanine [3.2.0] γ-lactam β-lactone 21c: Pure isomer obtained by column chromatography (Yield 33%). ^{1}HNMR (500MHz, C_5D_5N) δ 9.23 (br s, 1H), 6.15 - 6.13 (m, 2H),6.04 - 5.97 (m, 3H), 3.97 (d, J = 5.5 Hz, 1H), 2.18 (d, J = 14 Hz, 1H), 2.02 (d, J = 14 Hz, 1H), 1.39 (m, 1H), 0.17 (d, J = 7.5 Hz, 3H); ^{13}CNMR (500MHz, C_5D_5N) δ 175.7, 170.0, 133.5, 129.2, 128.0, 126.6, 77.1, 75.4, 37.9, 34.5, 7.2; HRMS (ESI) m/z: calc'd for $C_{13}H_{13}NO_3$ $[M+Na]^+$: 254.0788, found 254.0751.

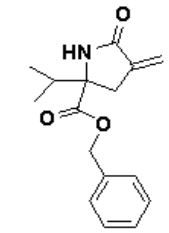


10b **10f**

X-Ray crystal structure for lactams 10b and 10f.



X-Ray crystal structure for fused γ-lactam-β-lactone 21b.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HN
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O
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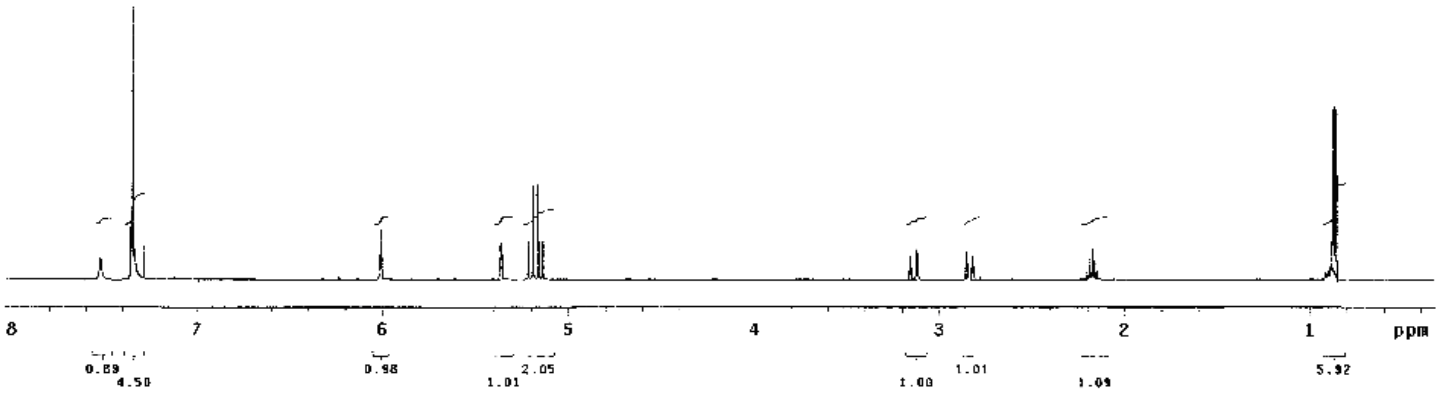
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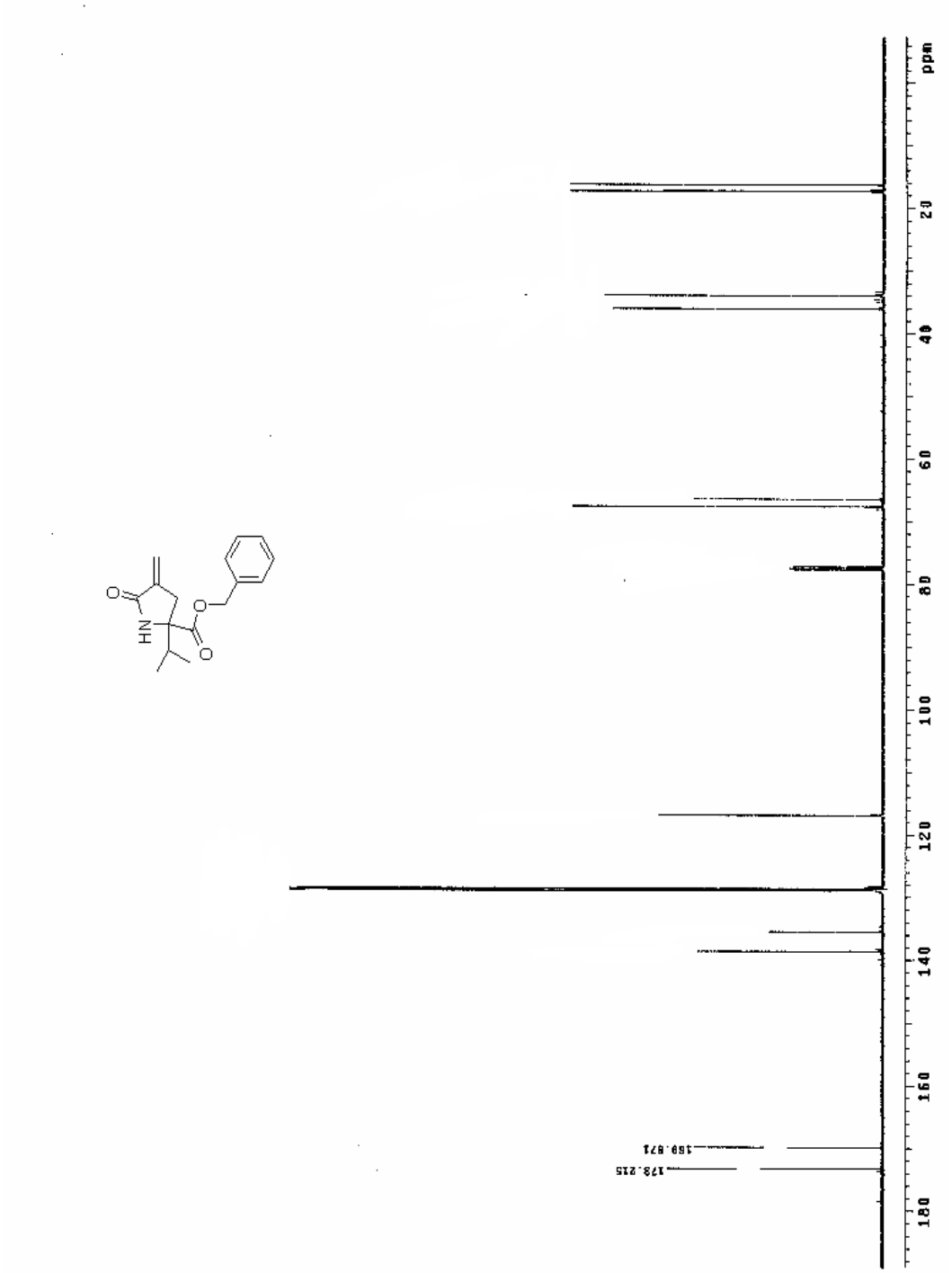
0.98
1.01
2.05
1.00
1.01
1.09
5.92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HN
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O
O
ppm
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60
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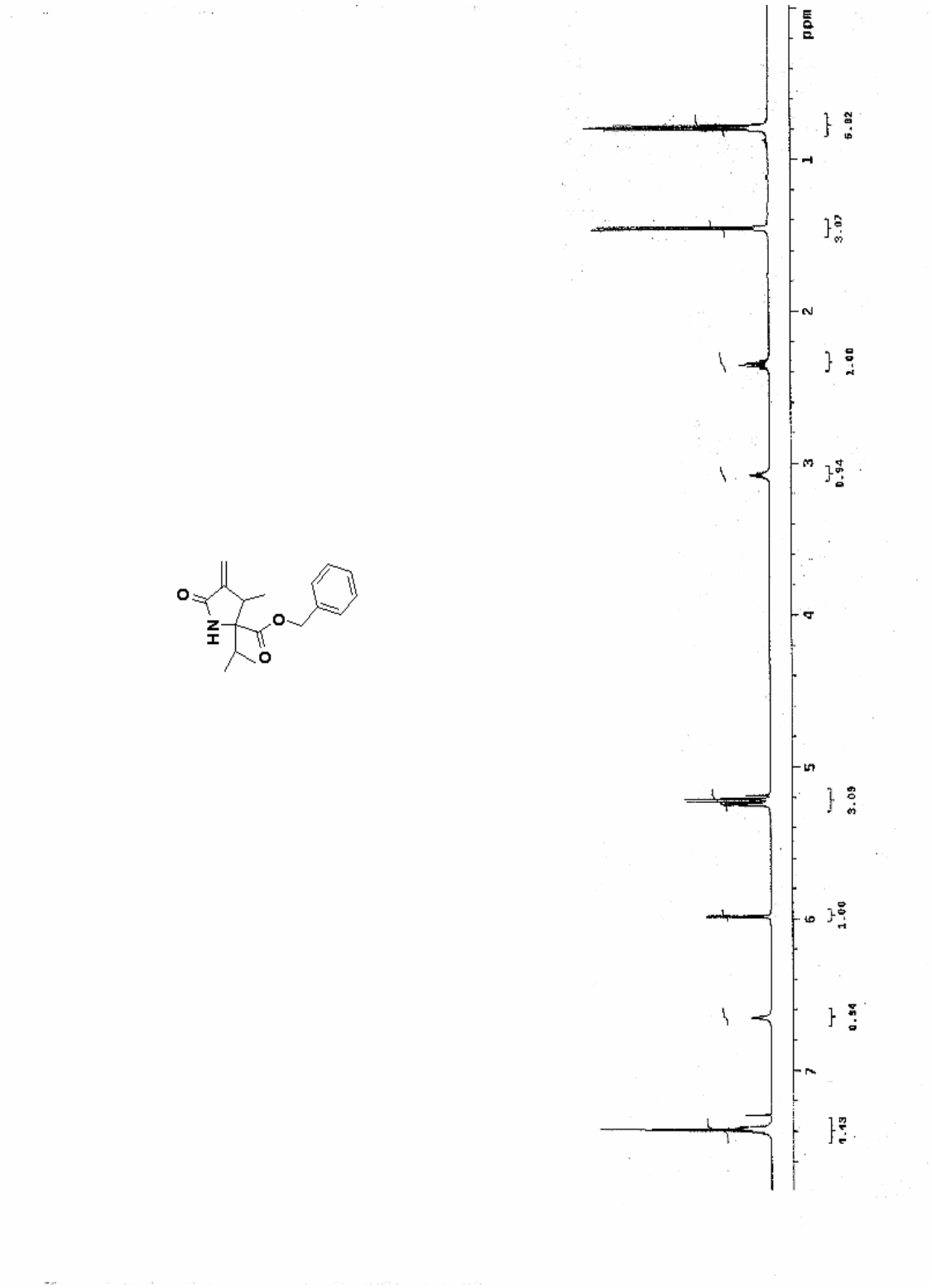
100
120
140
160
180
173.215
169.871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HN
O
O
O
ppm
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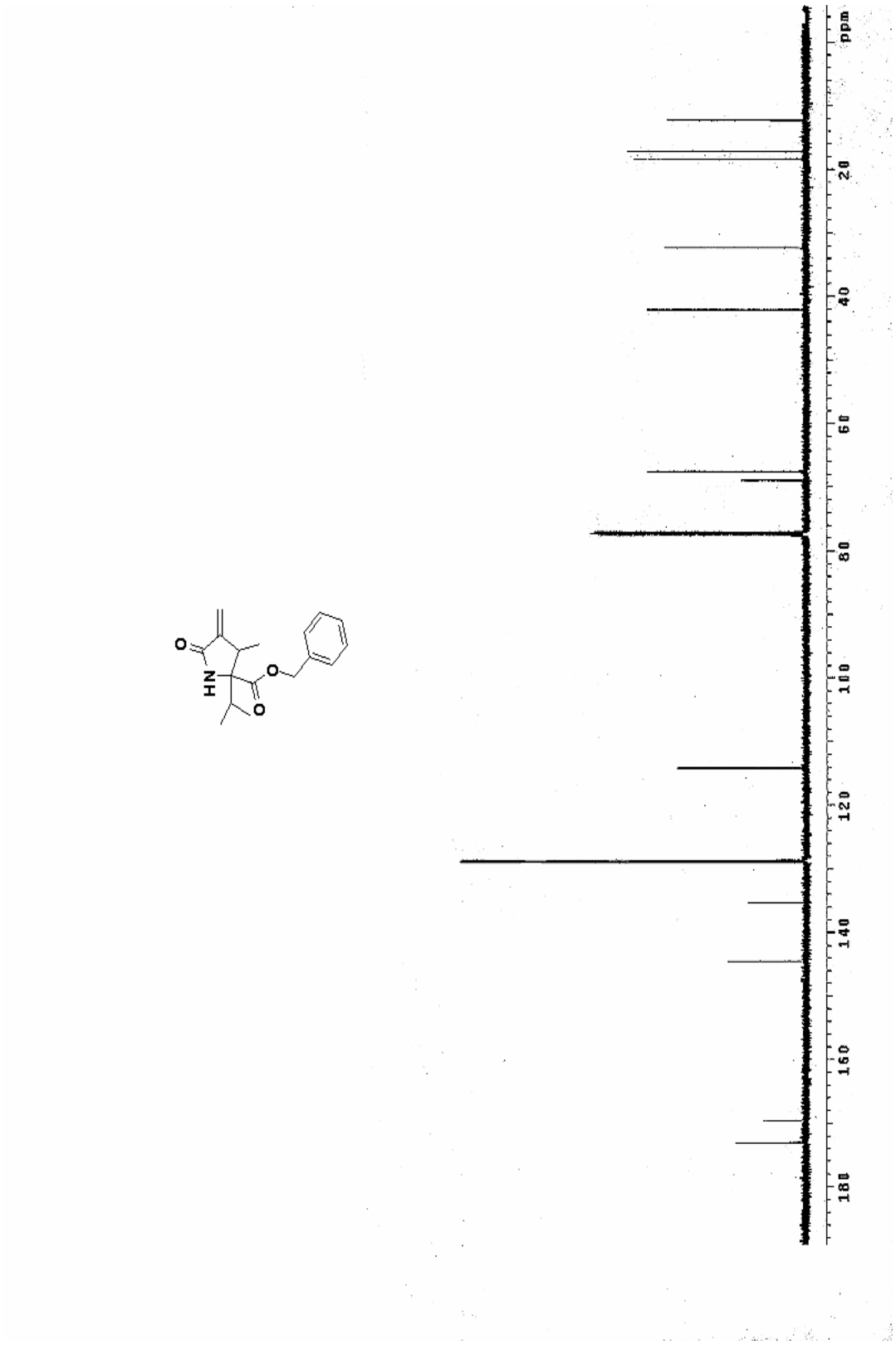
0.94
3.09
1.00
0.94
1.43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160
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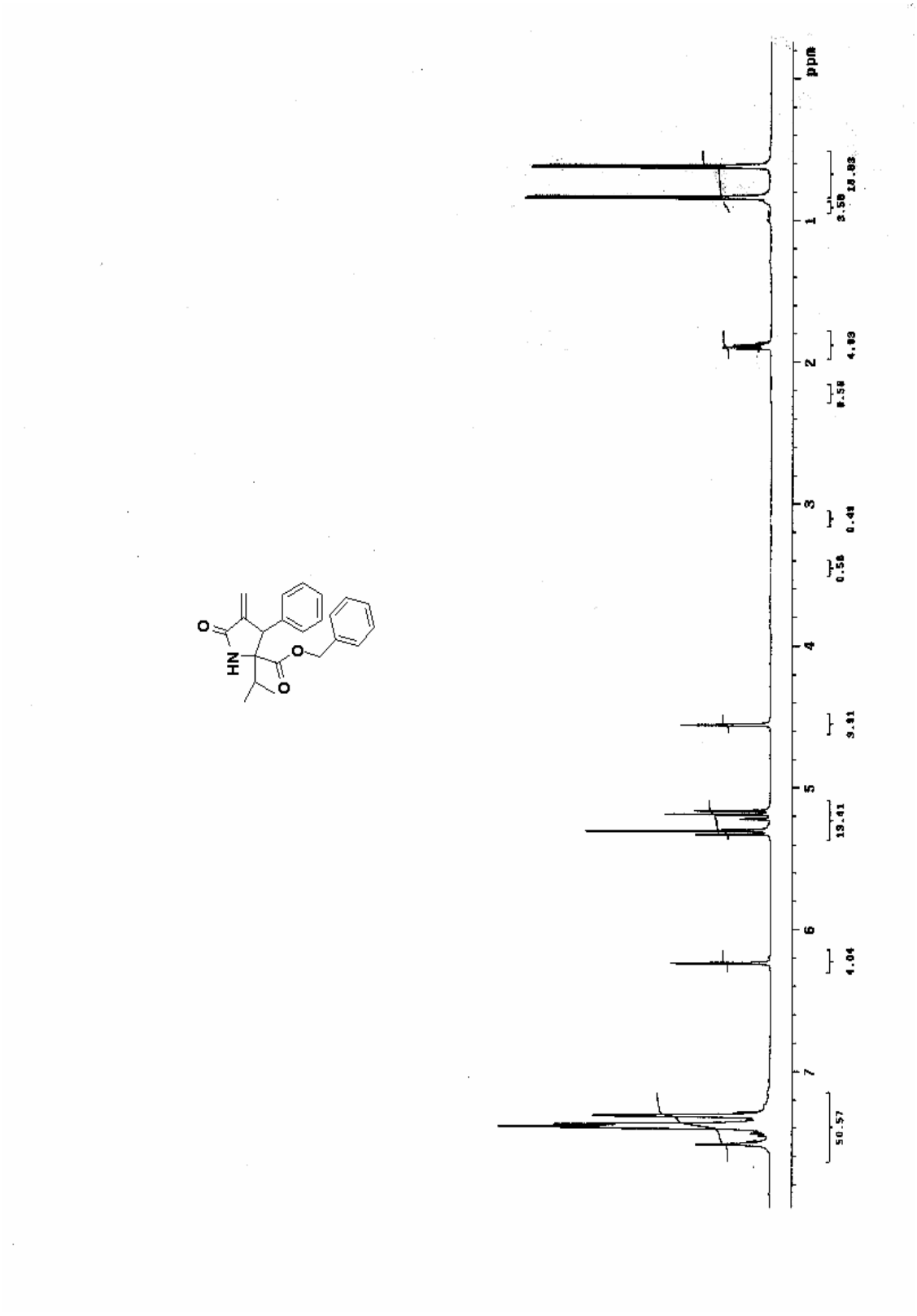
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HN
O
O
O
ppm
1
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3
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0.58
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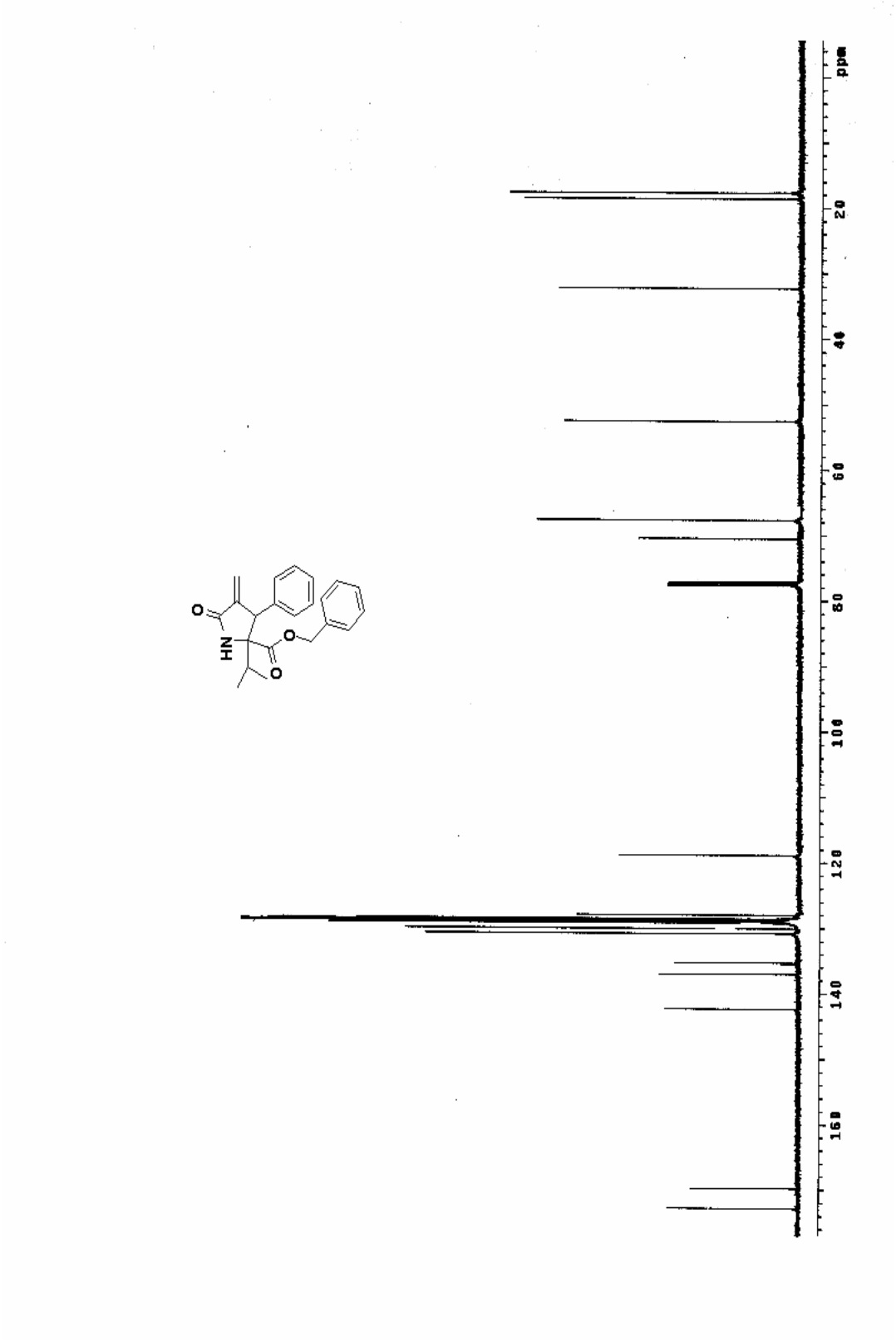
19.41
4.04
50.57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HN
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O
ppm
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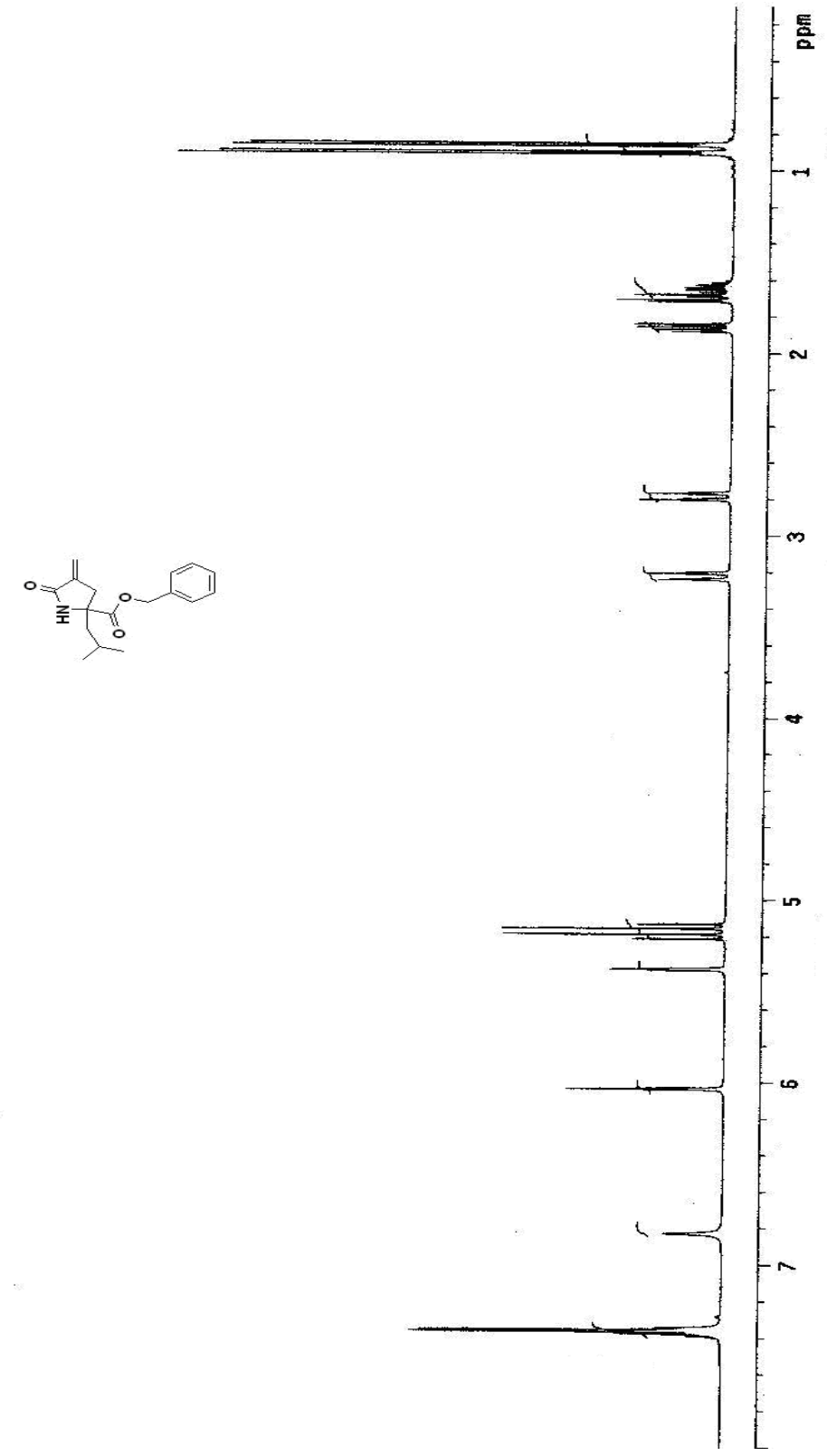
80
100
120
140
160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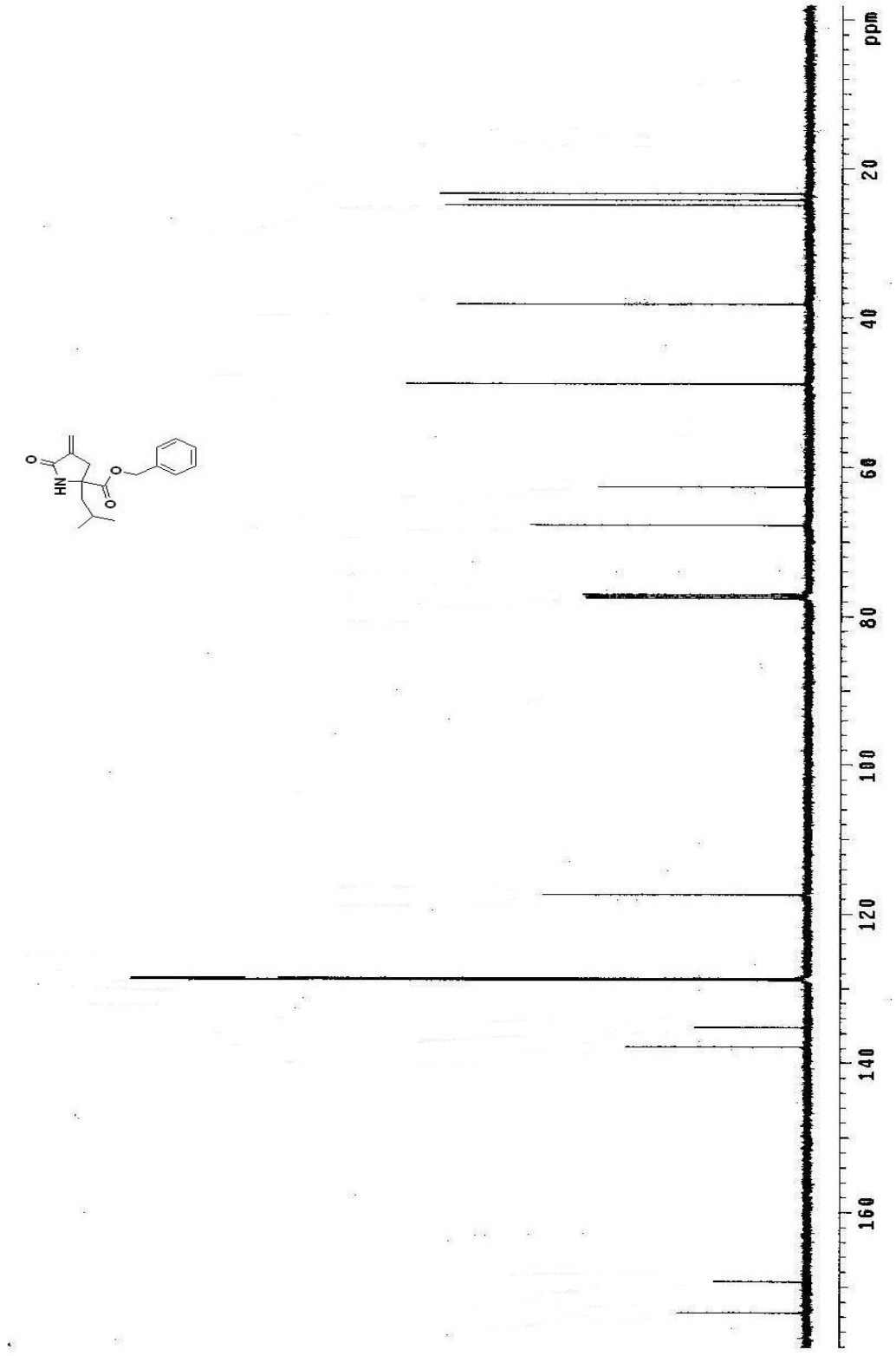
HN
O
O
O
ppm
1
2
3
4
5
6
7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ppm
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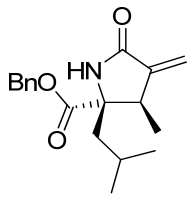
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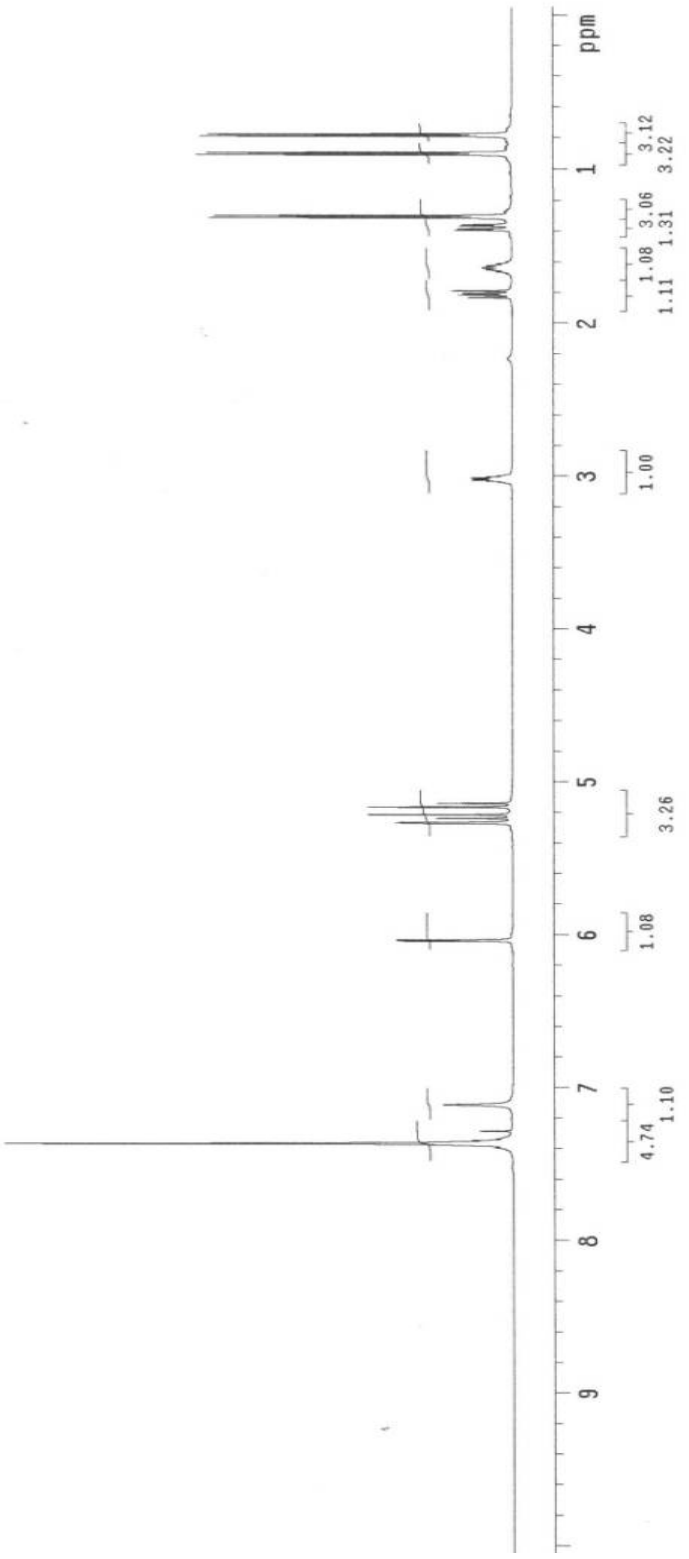
HN
BnO
O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6
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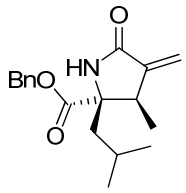
3.06
1.31
1.11
1.00
3.26
1.08
4.74
1.10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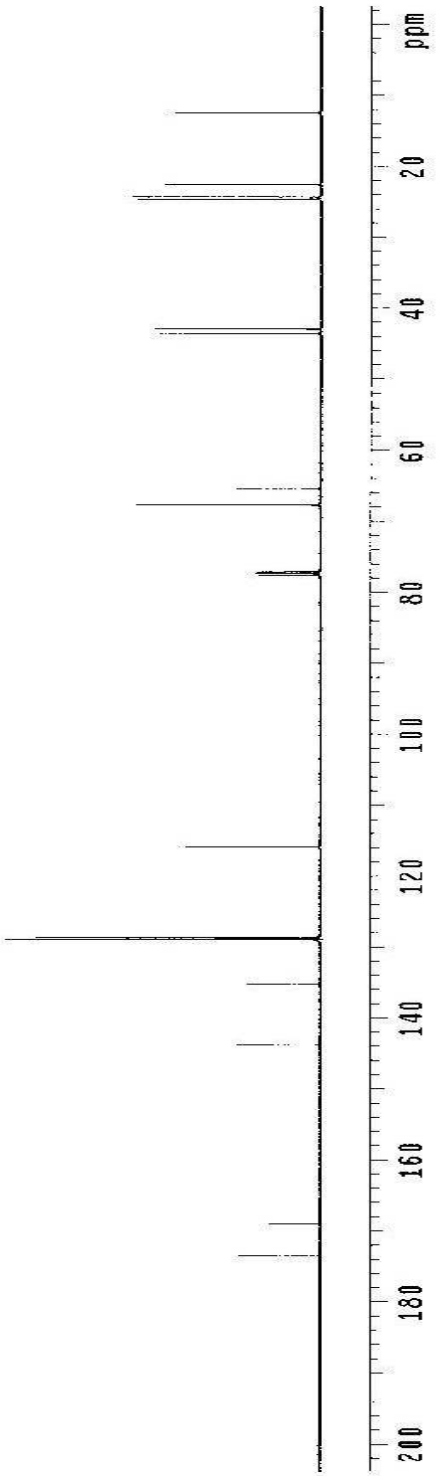
HN
BnO
O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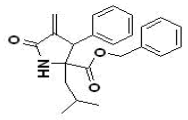
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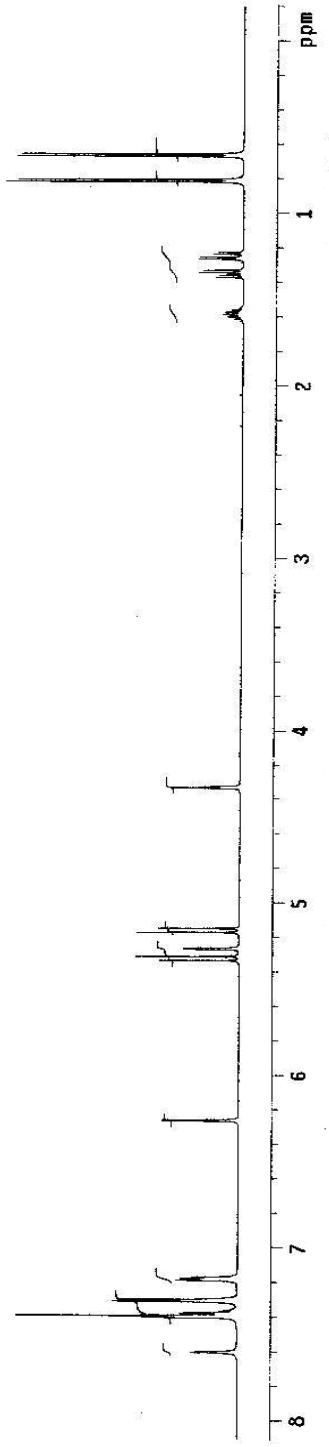
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3
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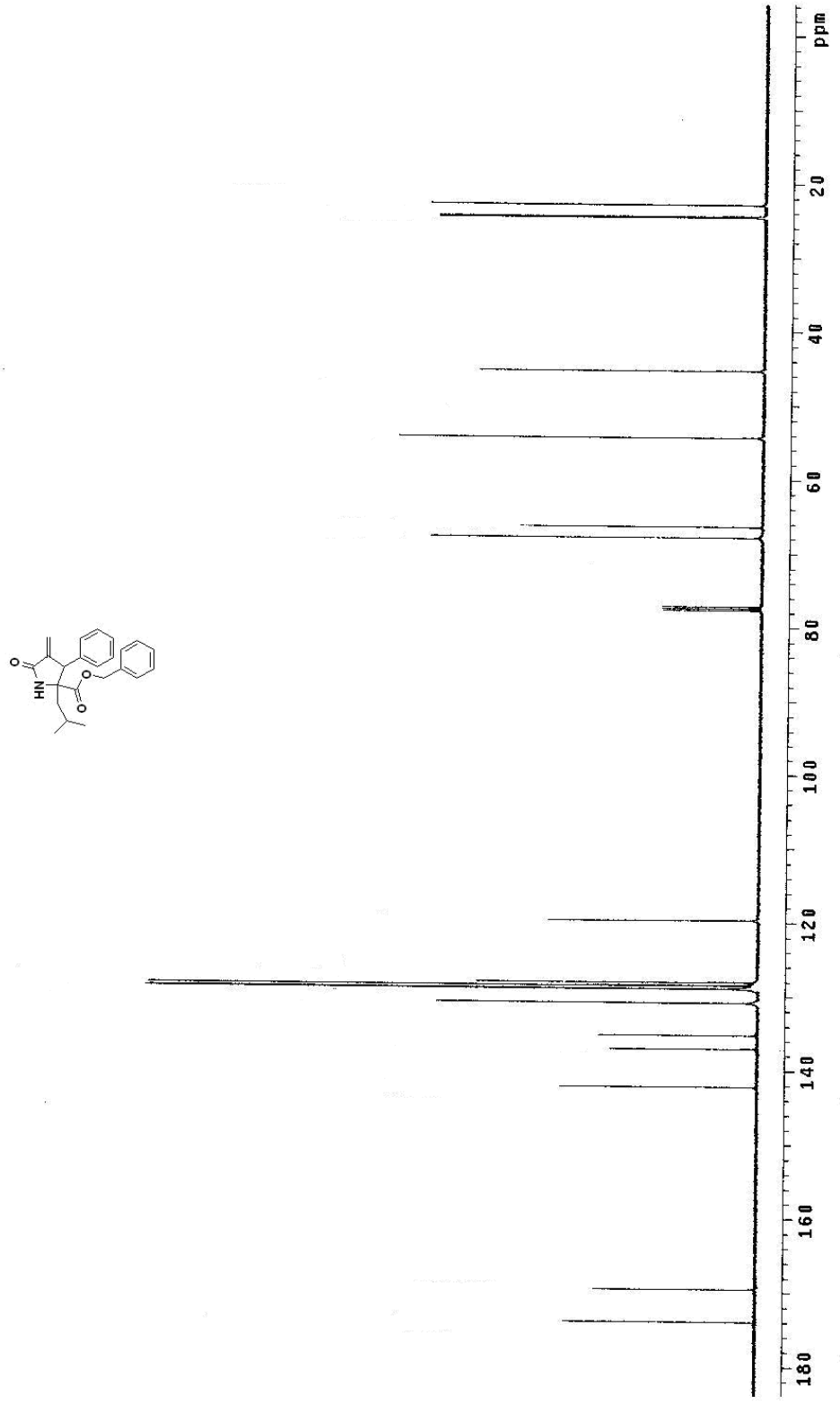
5
6
7
8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HN
O
O
ppm
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160
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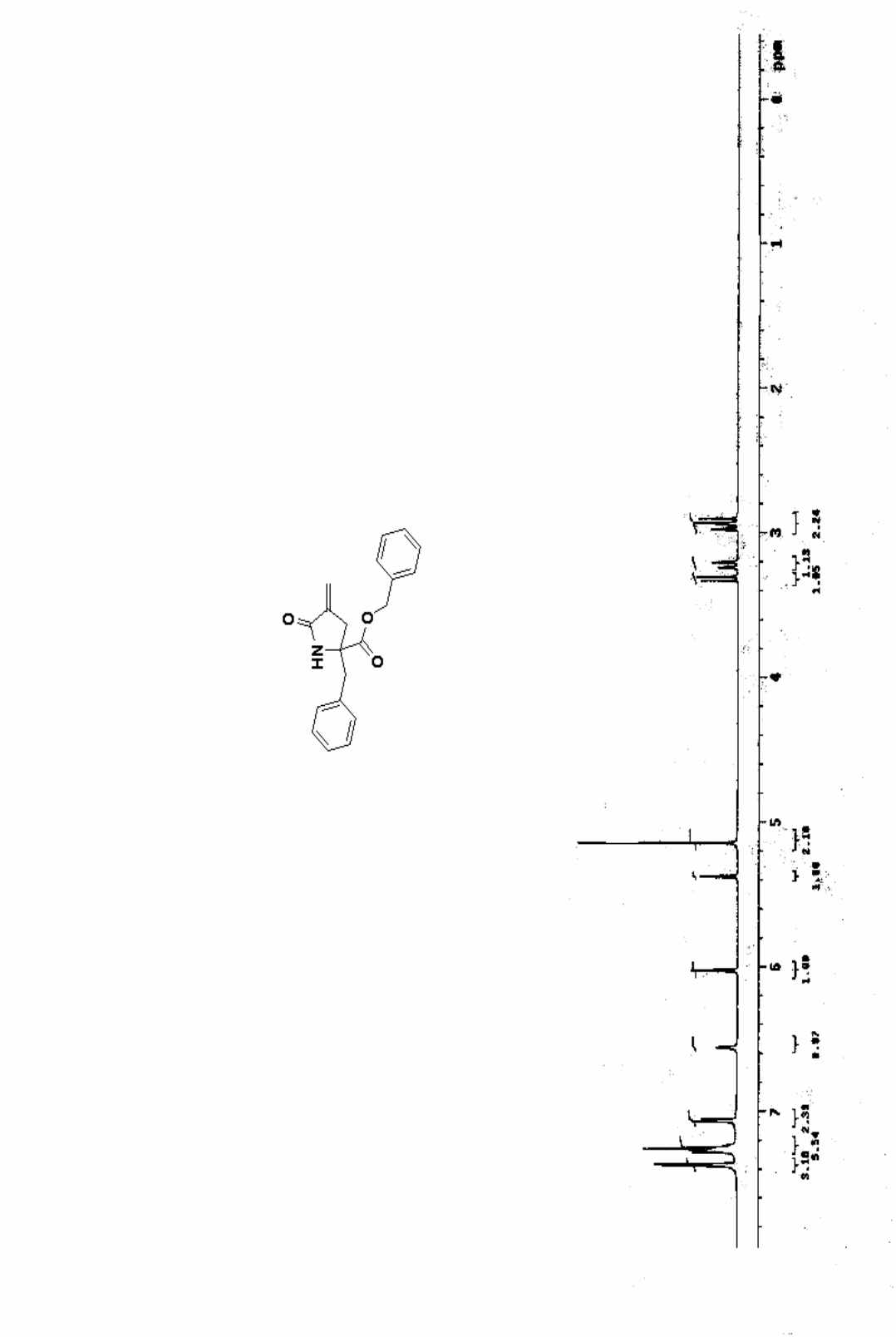
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O
O
ppm
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2
3
4
5
6
7
8
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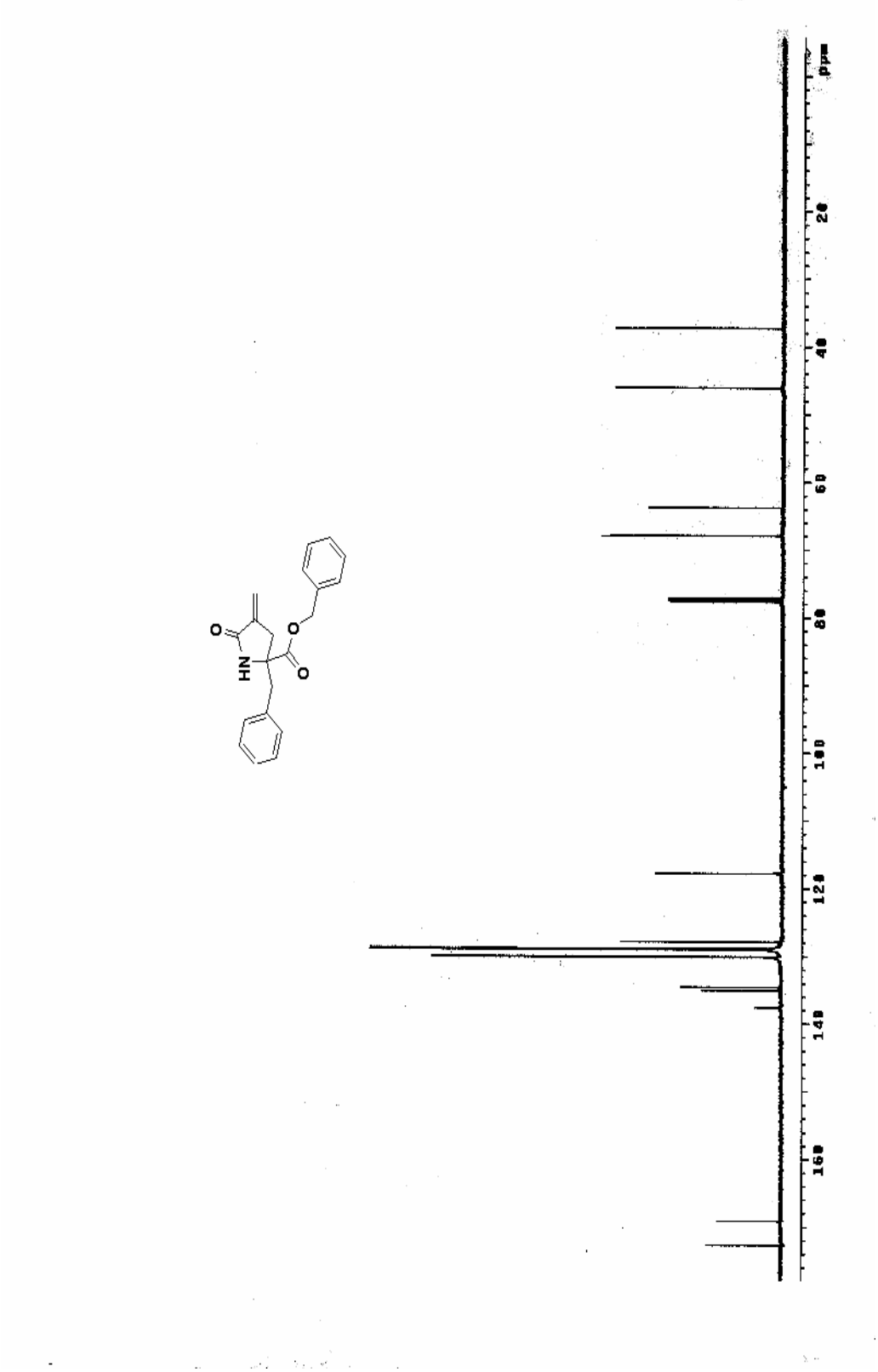
1.85
2.24
3.50
2.19
1.00
8.97
5.18
2.59
5.54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O
ppm
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100
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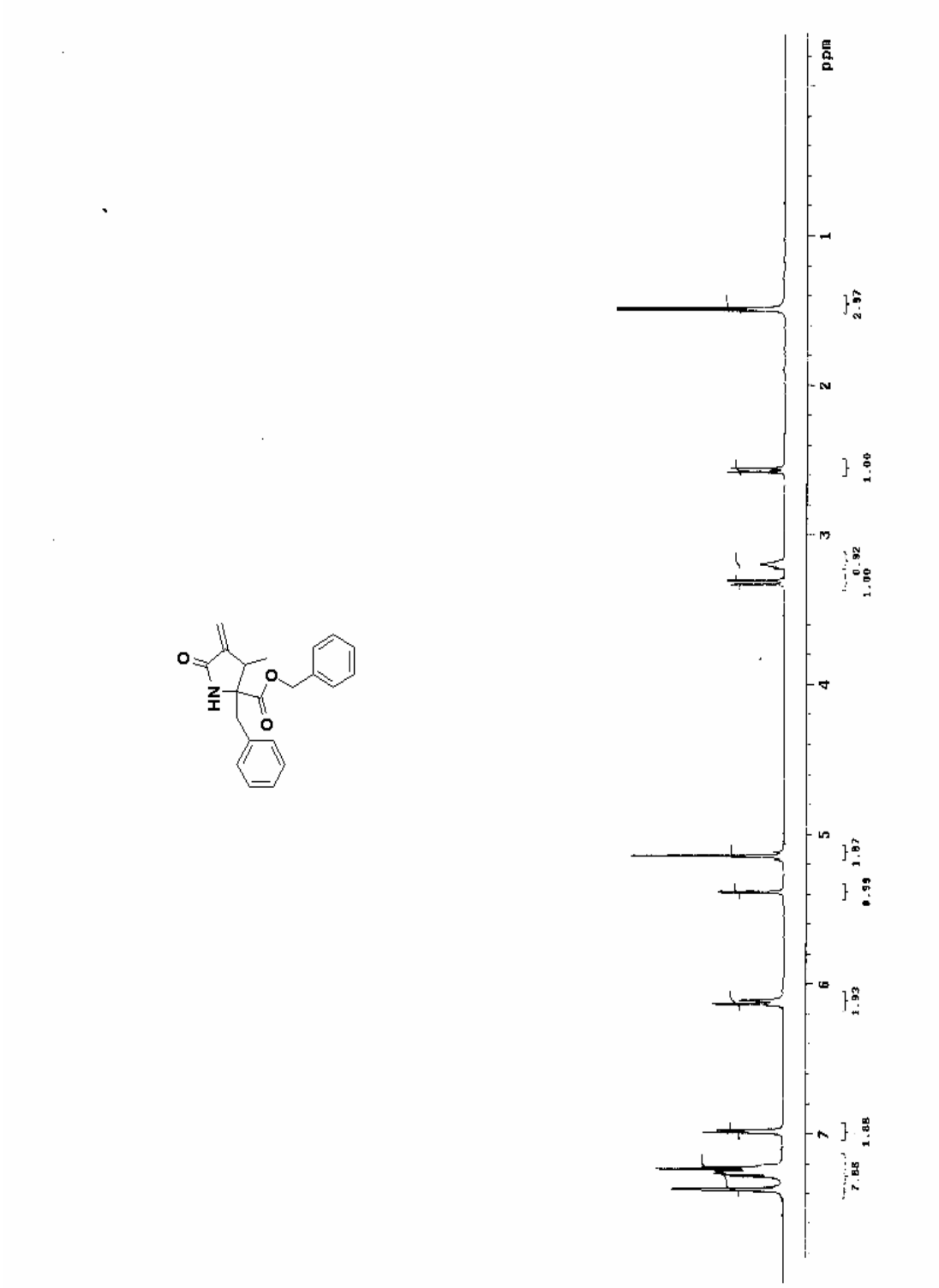
140
160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O
ppm
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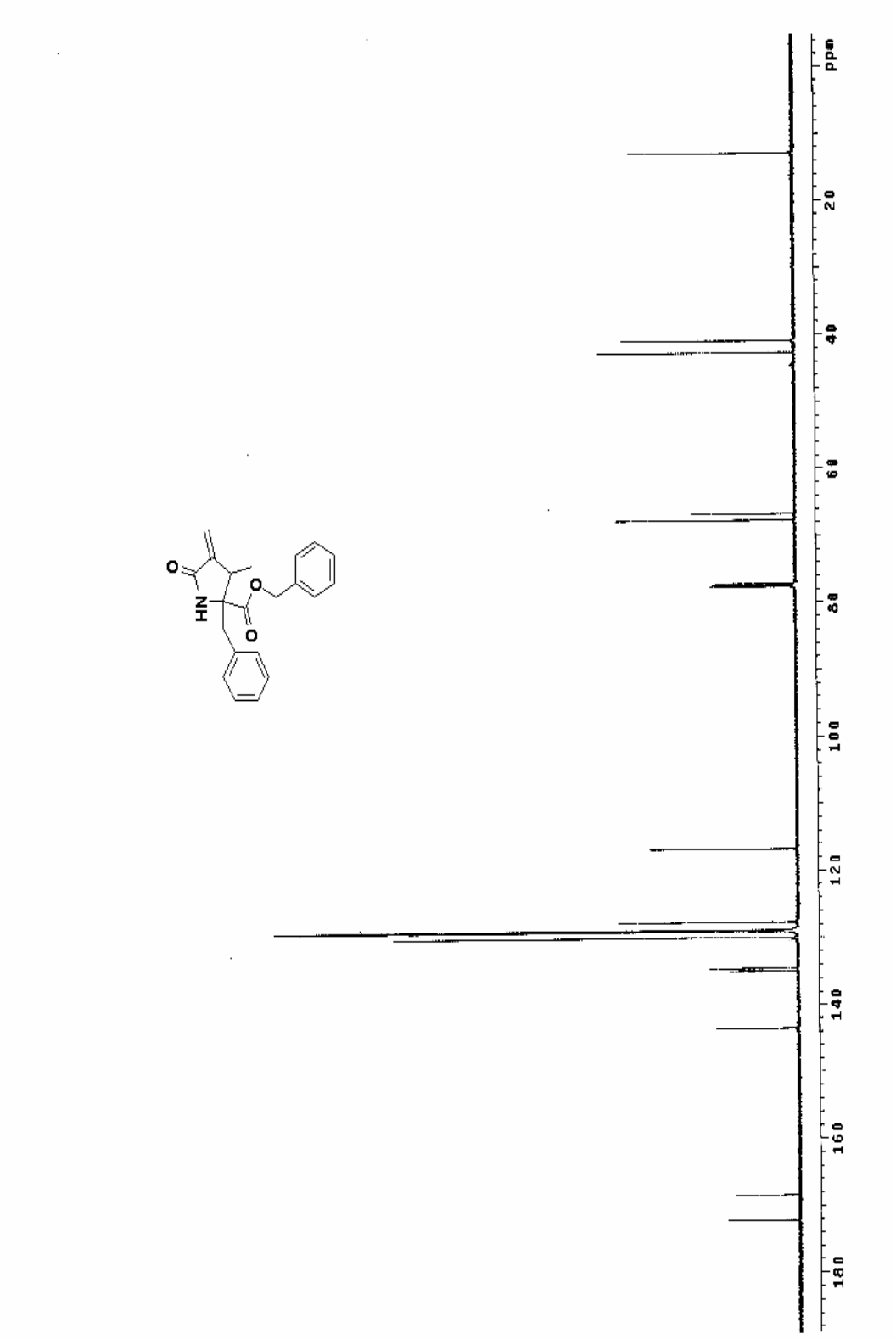
0.99
1.93
7.88
1.88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80
100
120
140
160
180

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6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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2.0
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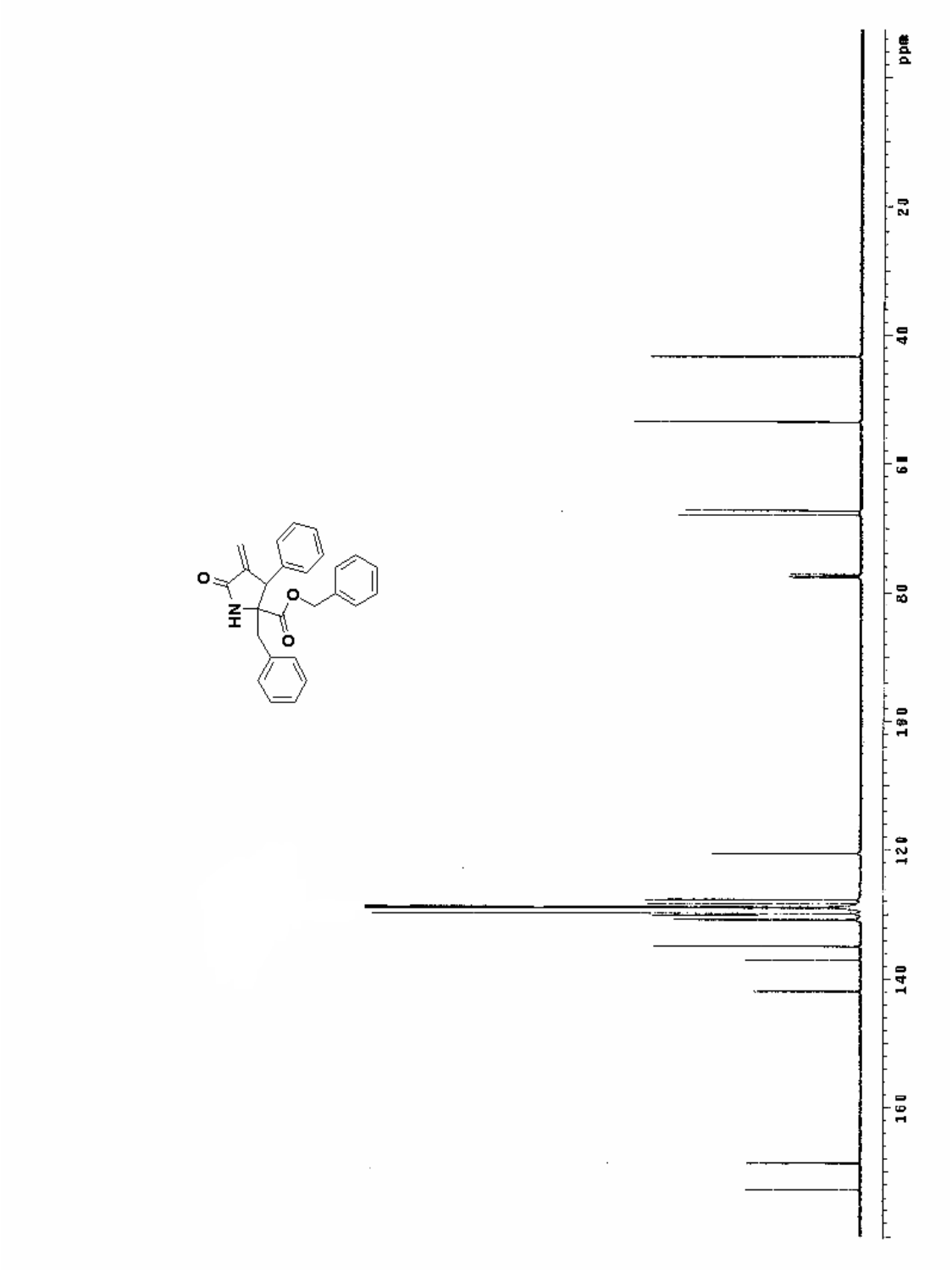
1.08
2.11
1.00
1.05
1.10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100
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140
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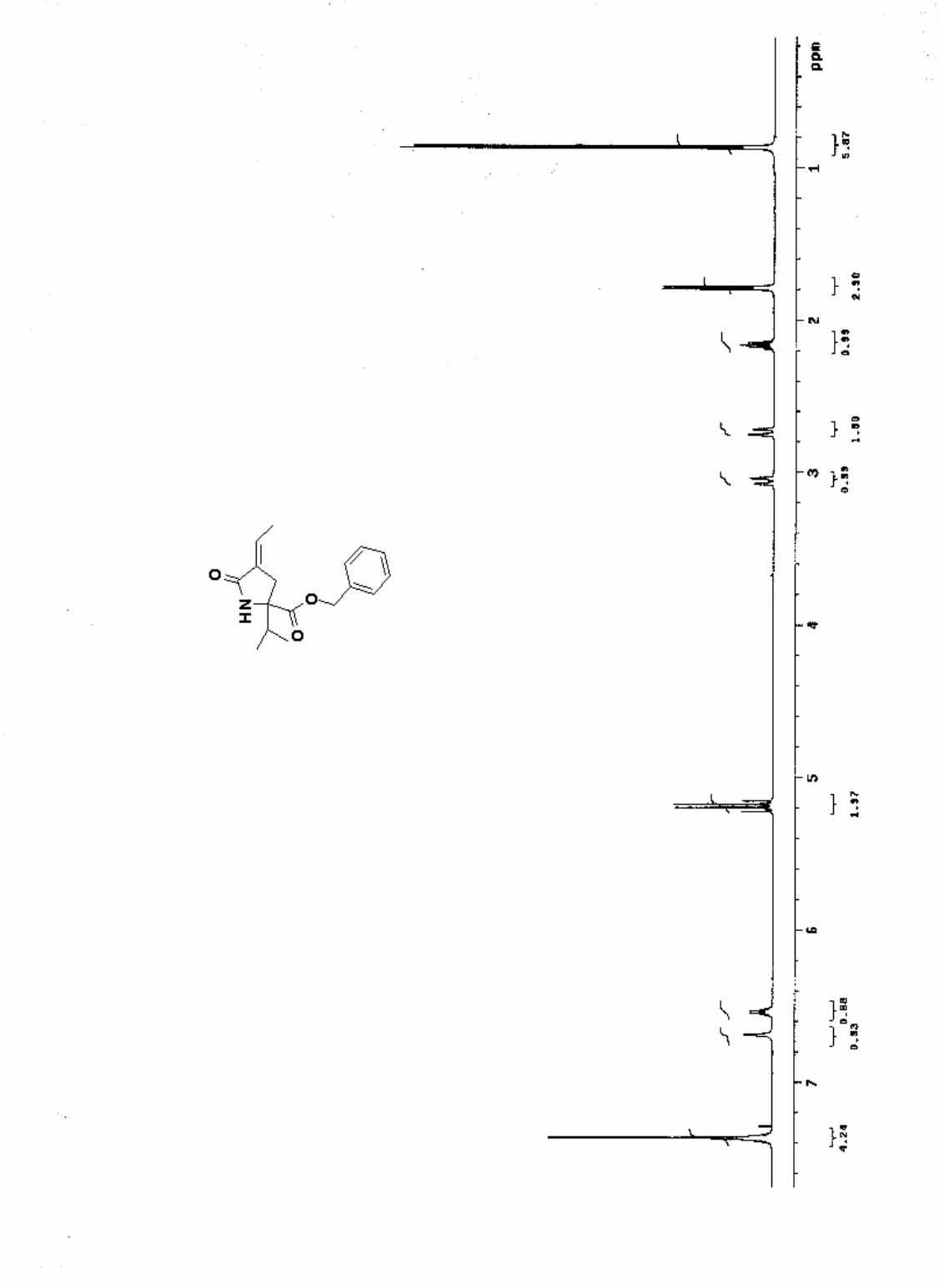
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HN
O
O
O
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7
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1.00
0.39
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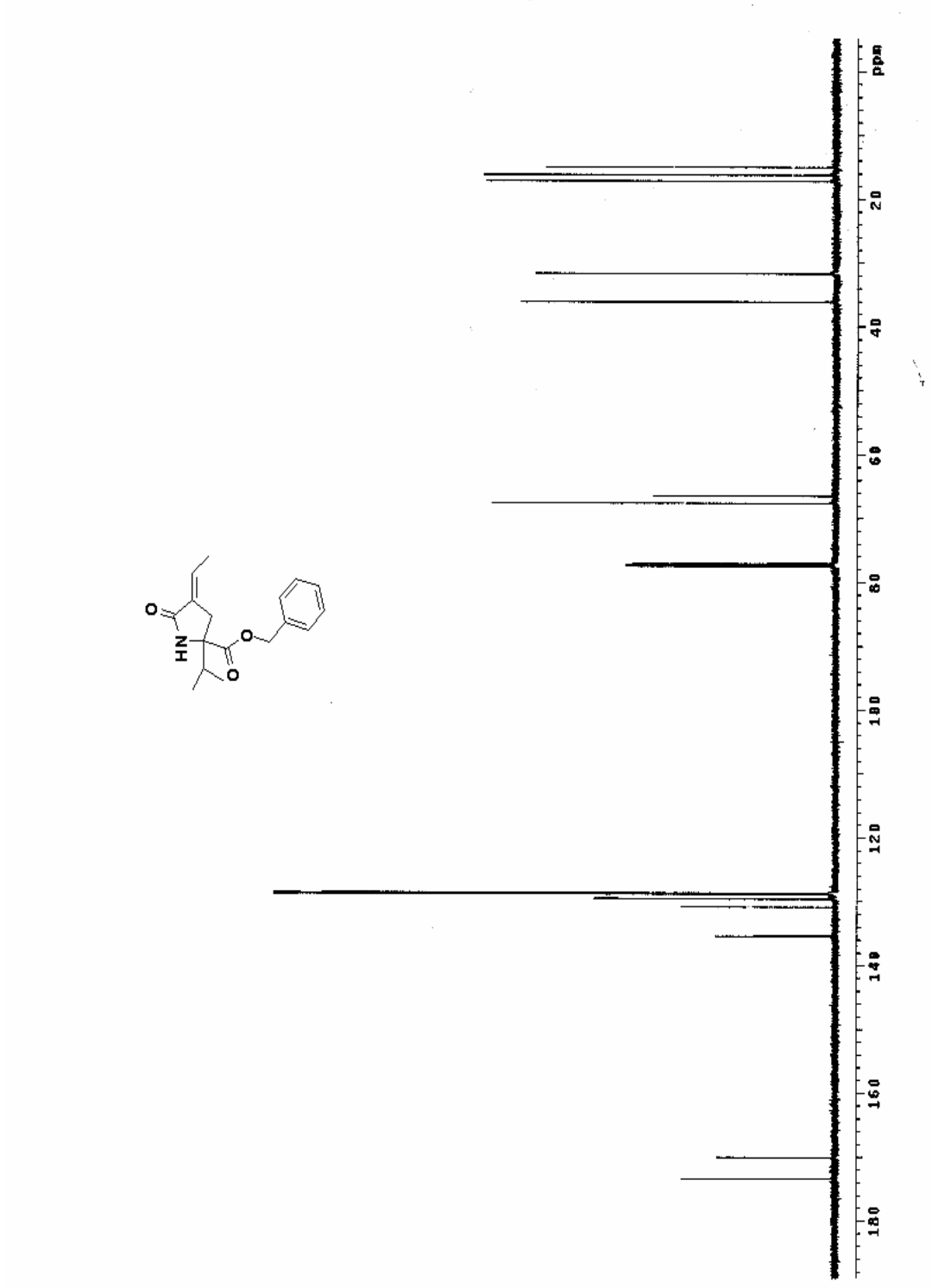
0.83
4.24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O
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ppm
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100
120
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160
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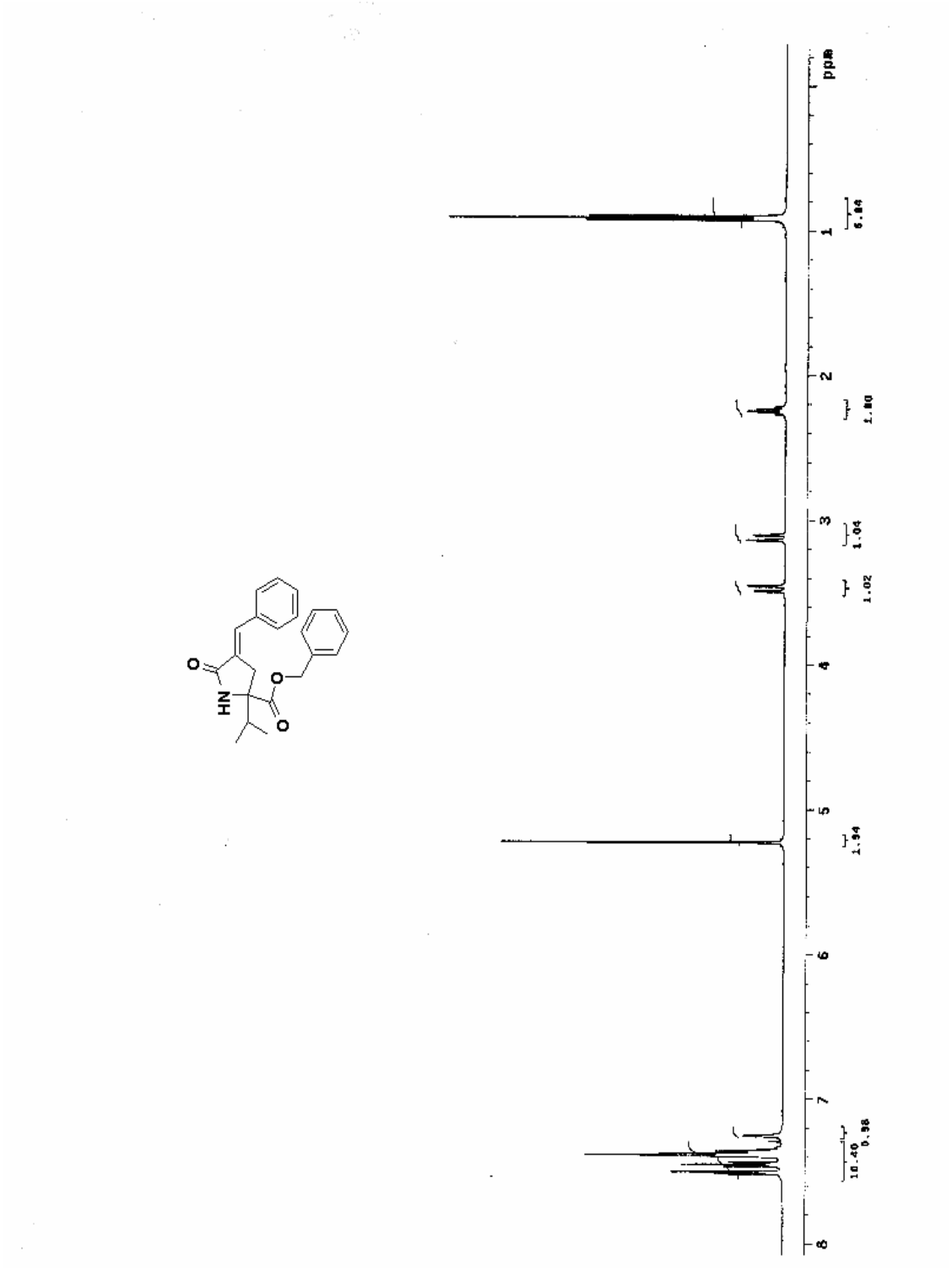
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HN
O
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ppm
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6
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8
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1.04
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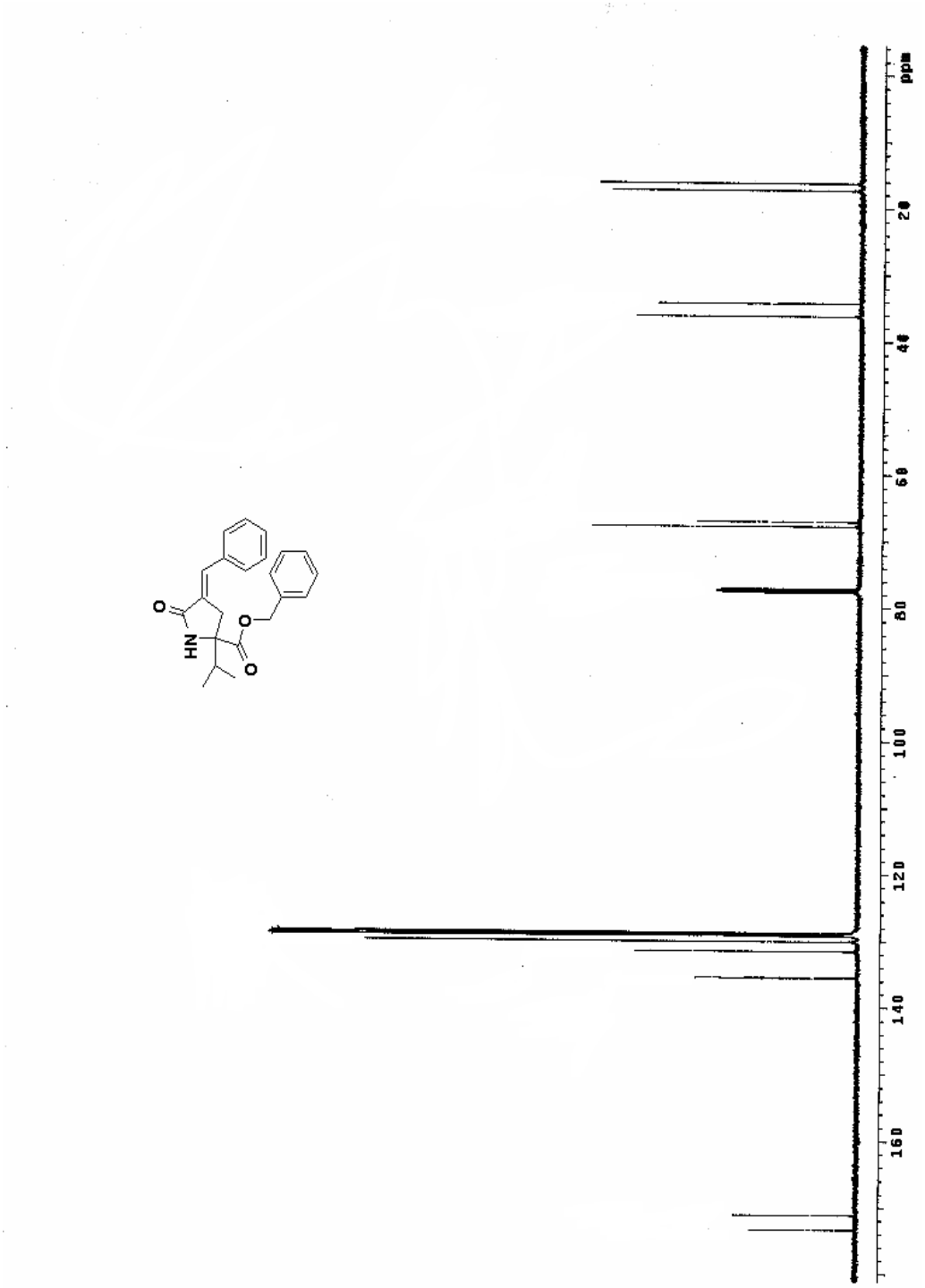
10.40
0.98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100
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140
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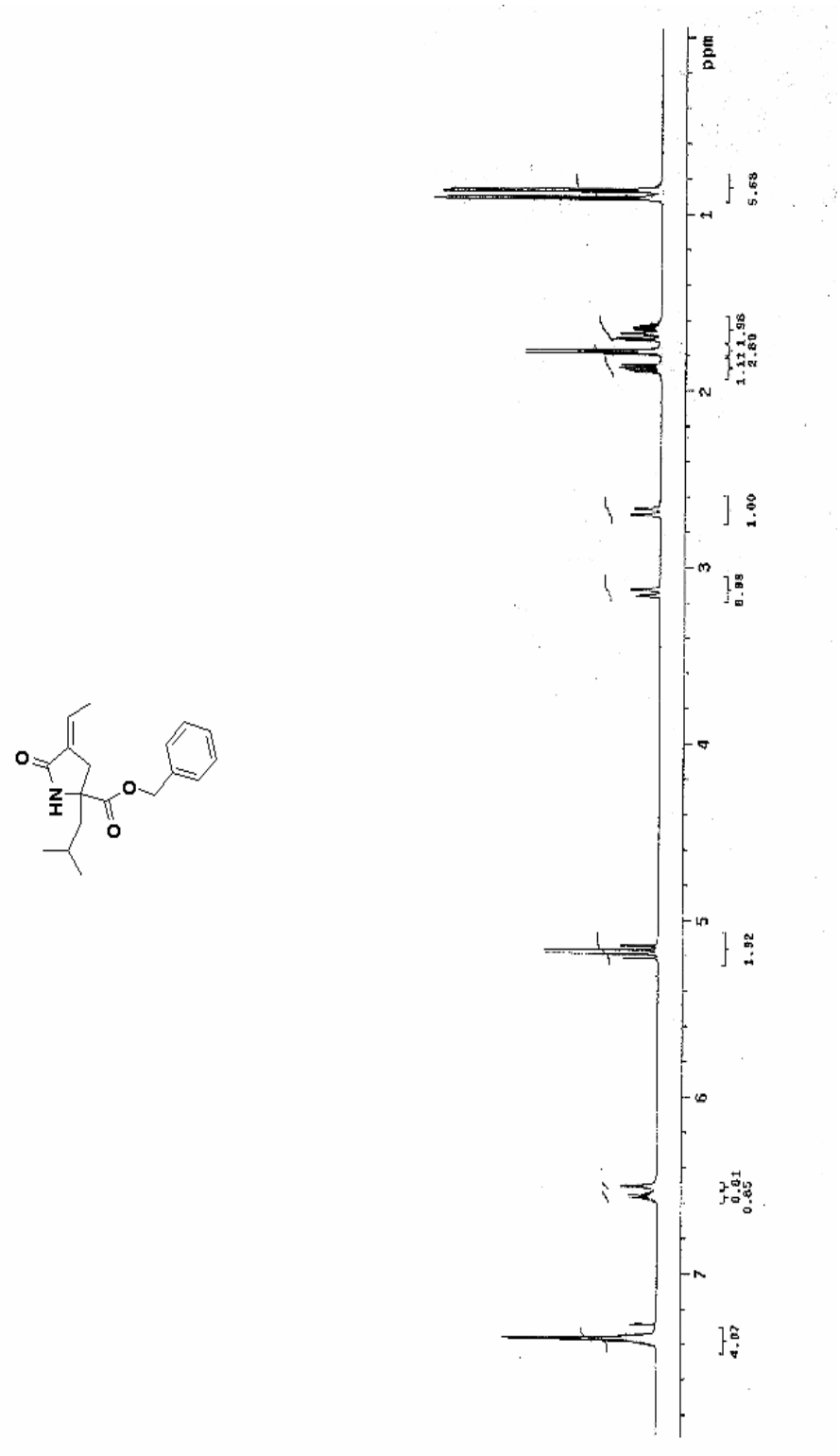
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8.88
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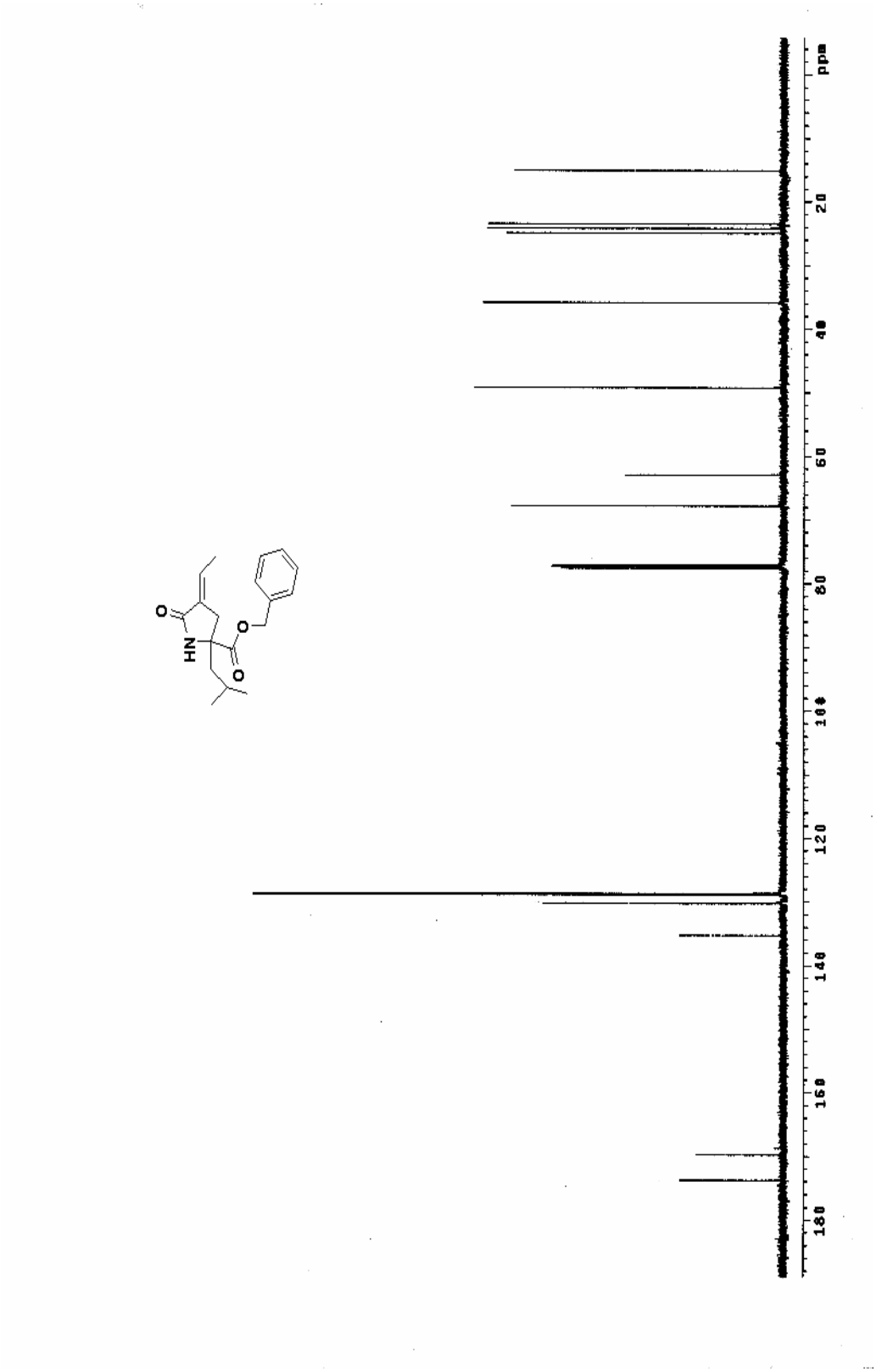
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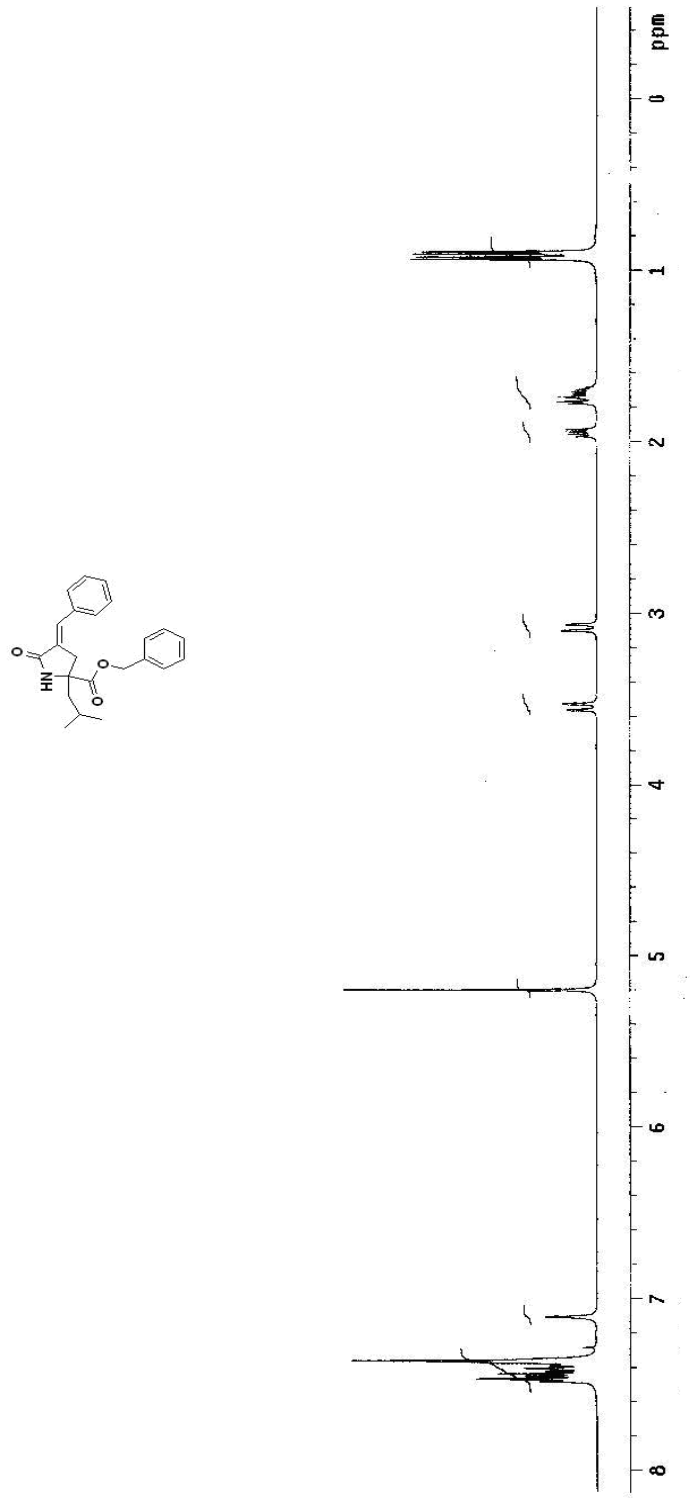
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ppm
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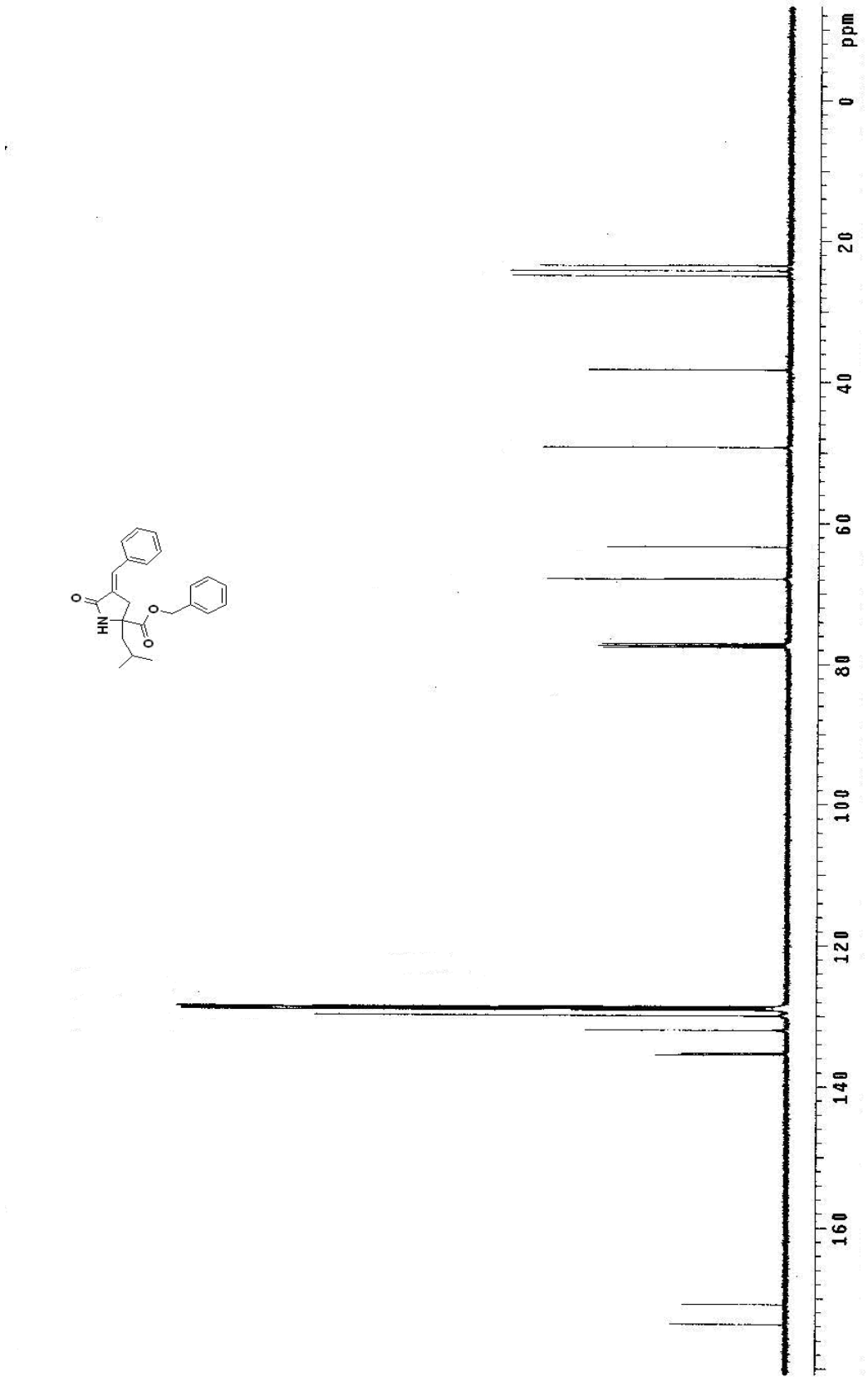
3
4
5
6
7
8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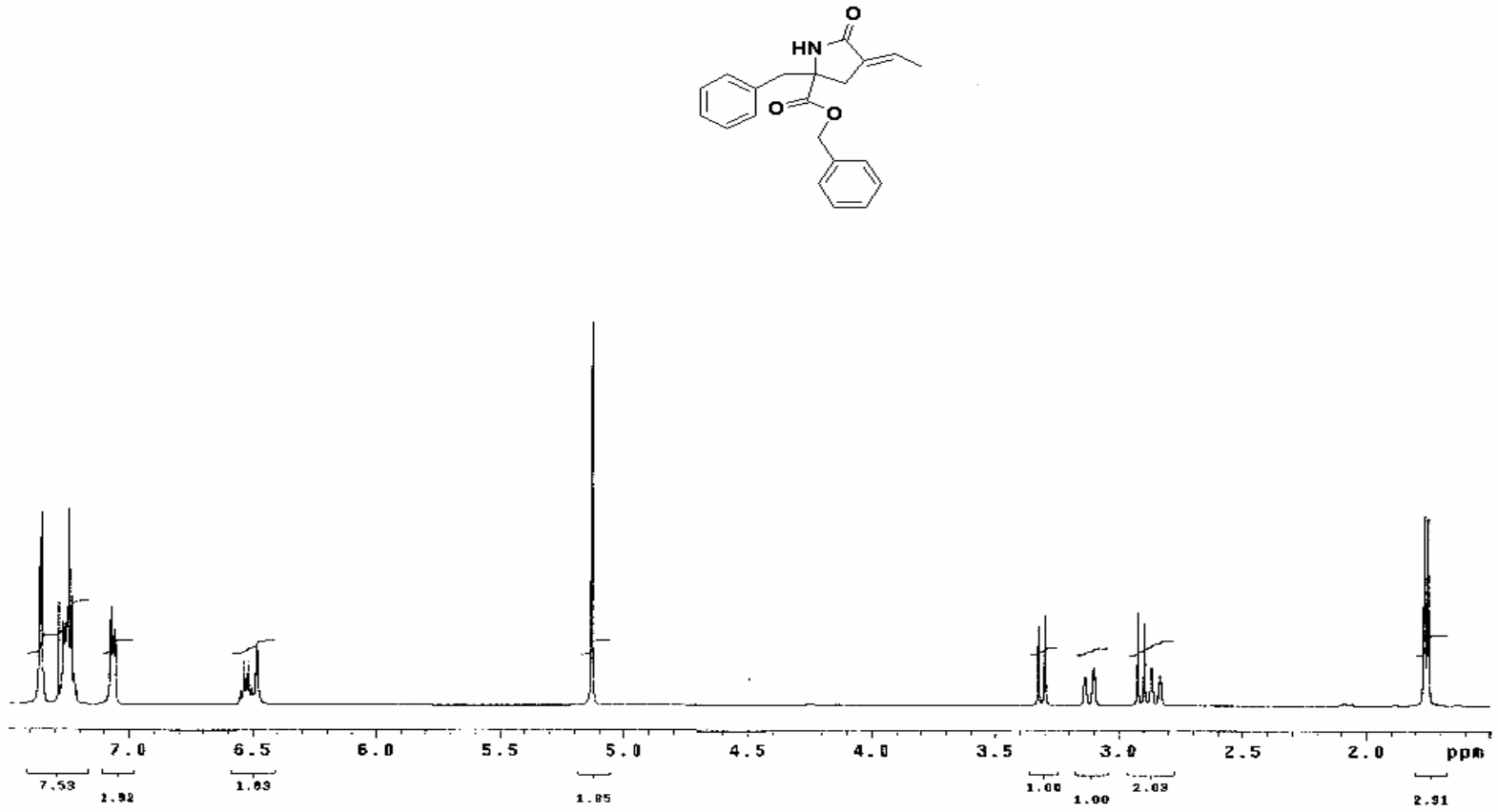
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5.5
5.0
4.5
4.0
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2.0
ppm
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1.03
1.85
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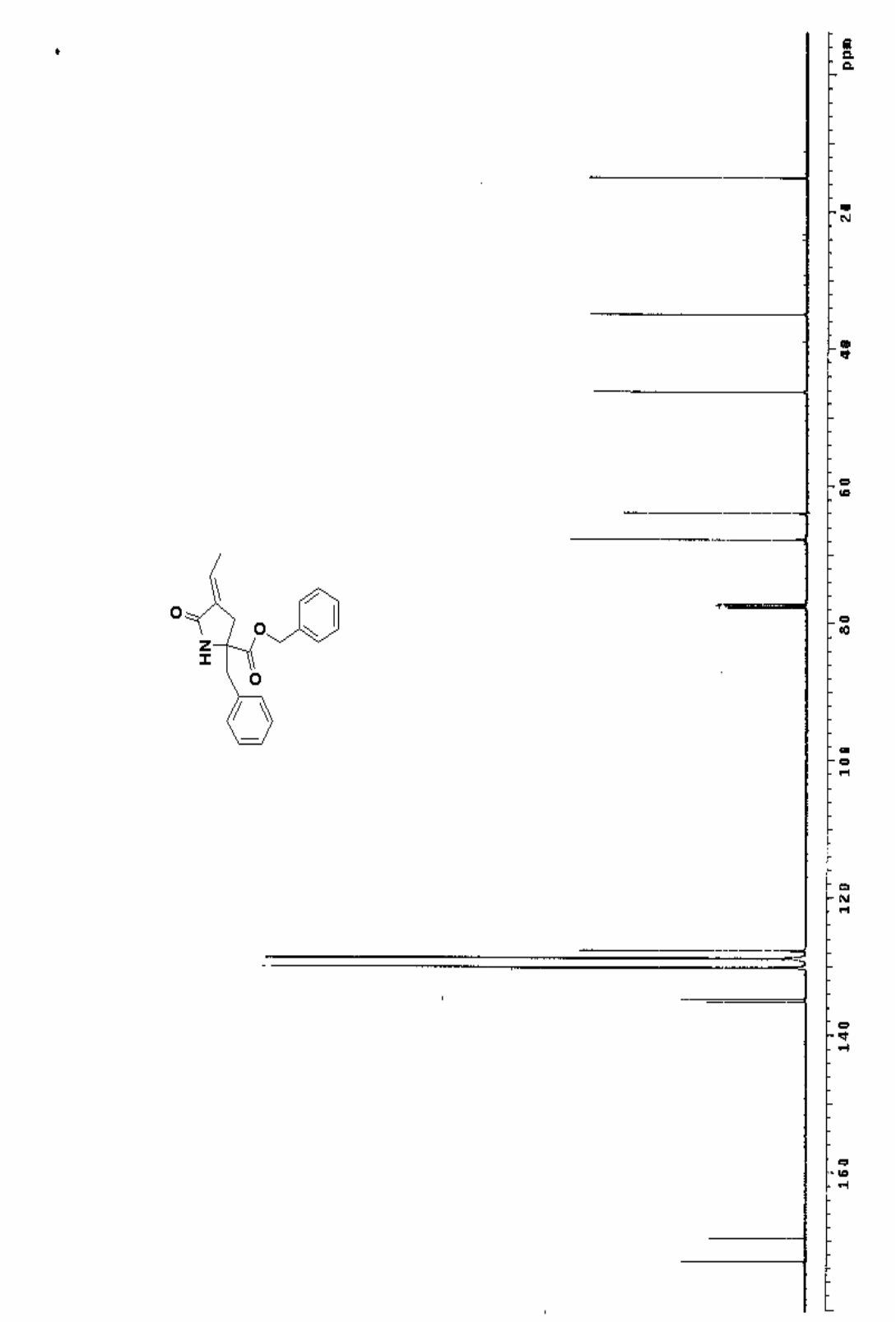
1.00
2.03
2.91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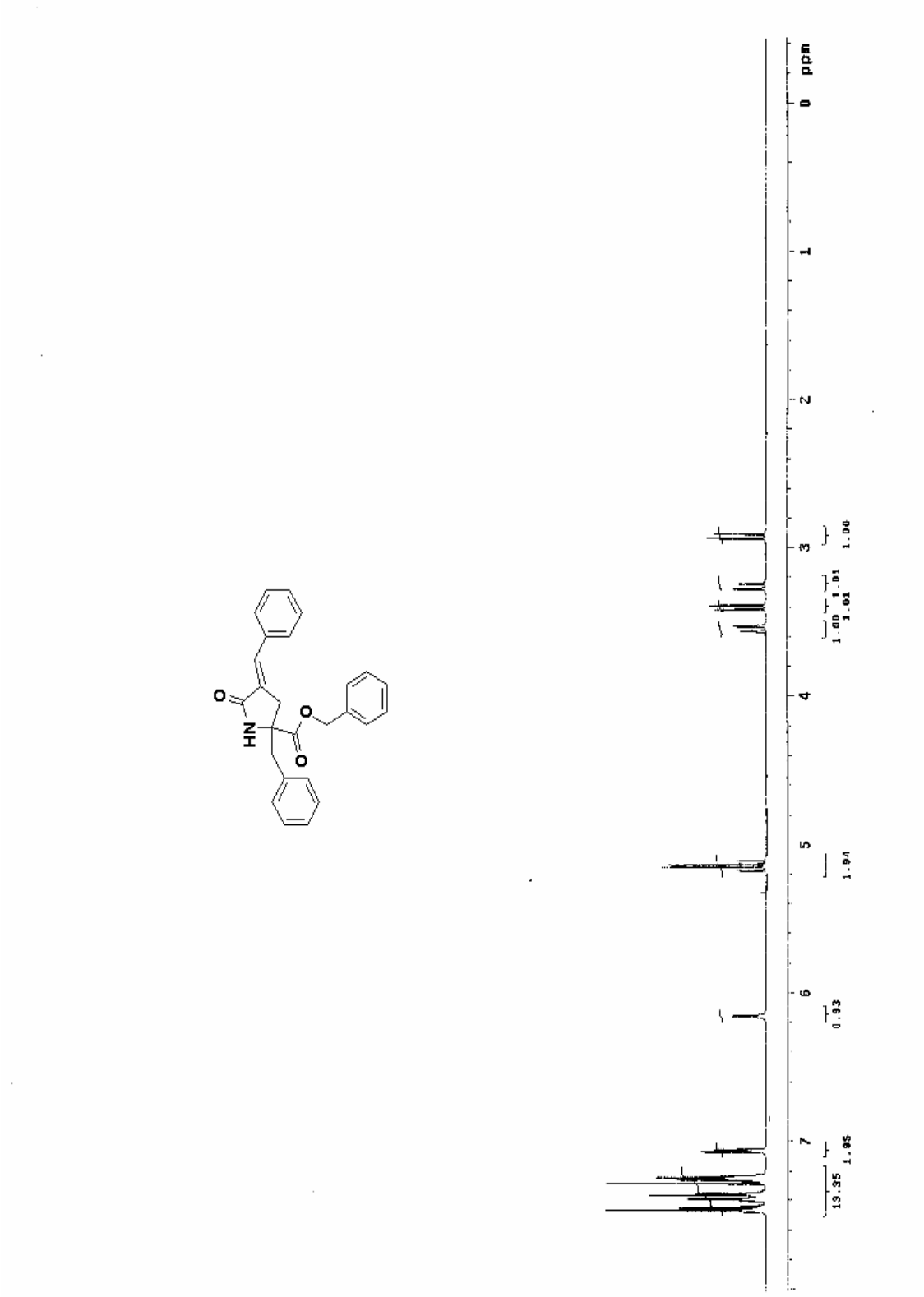
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1.01
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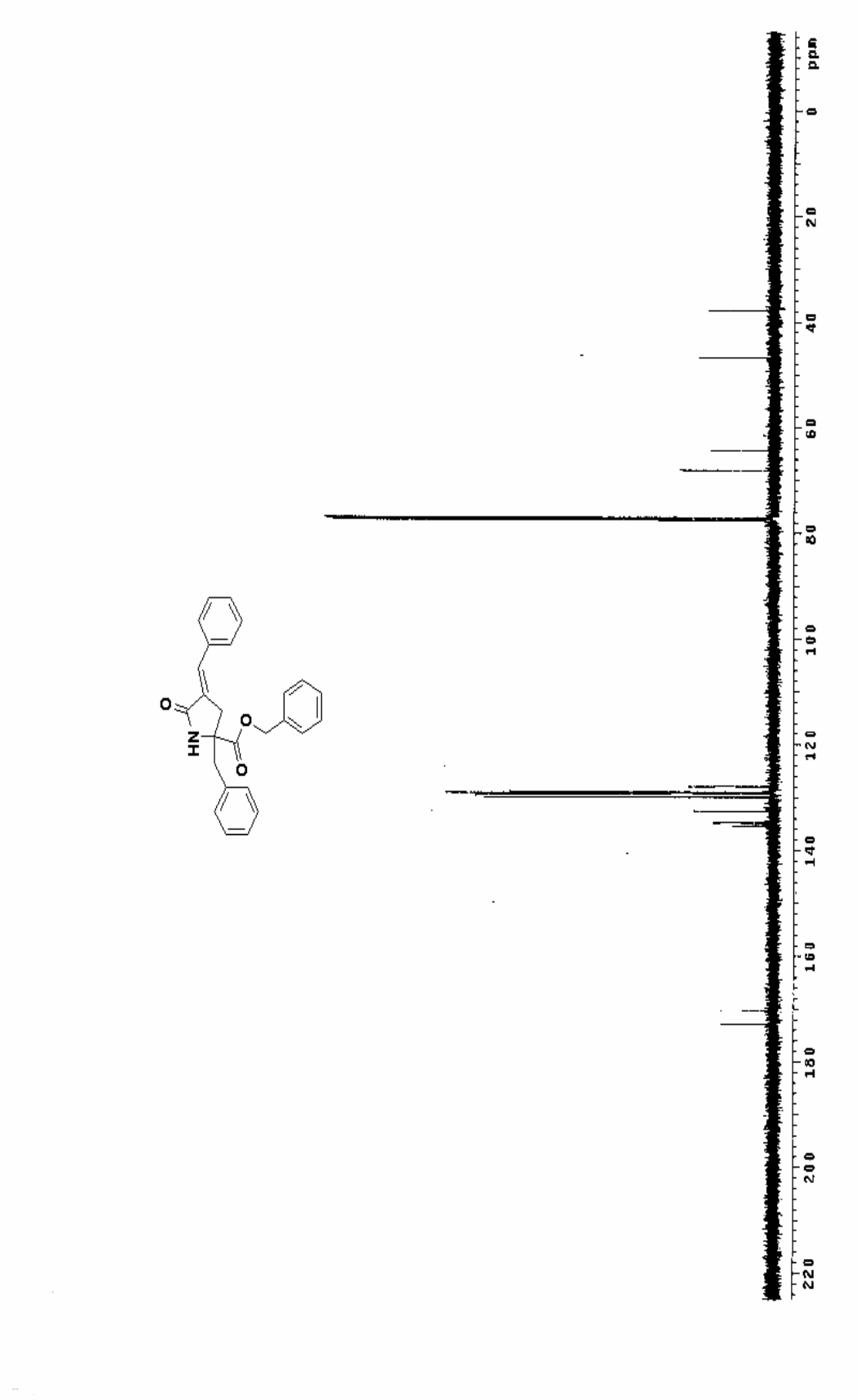
1.95
13.35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ppm
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80
100
120
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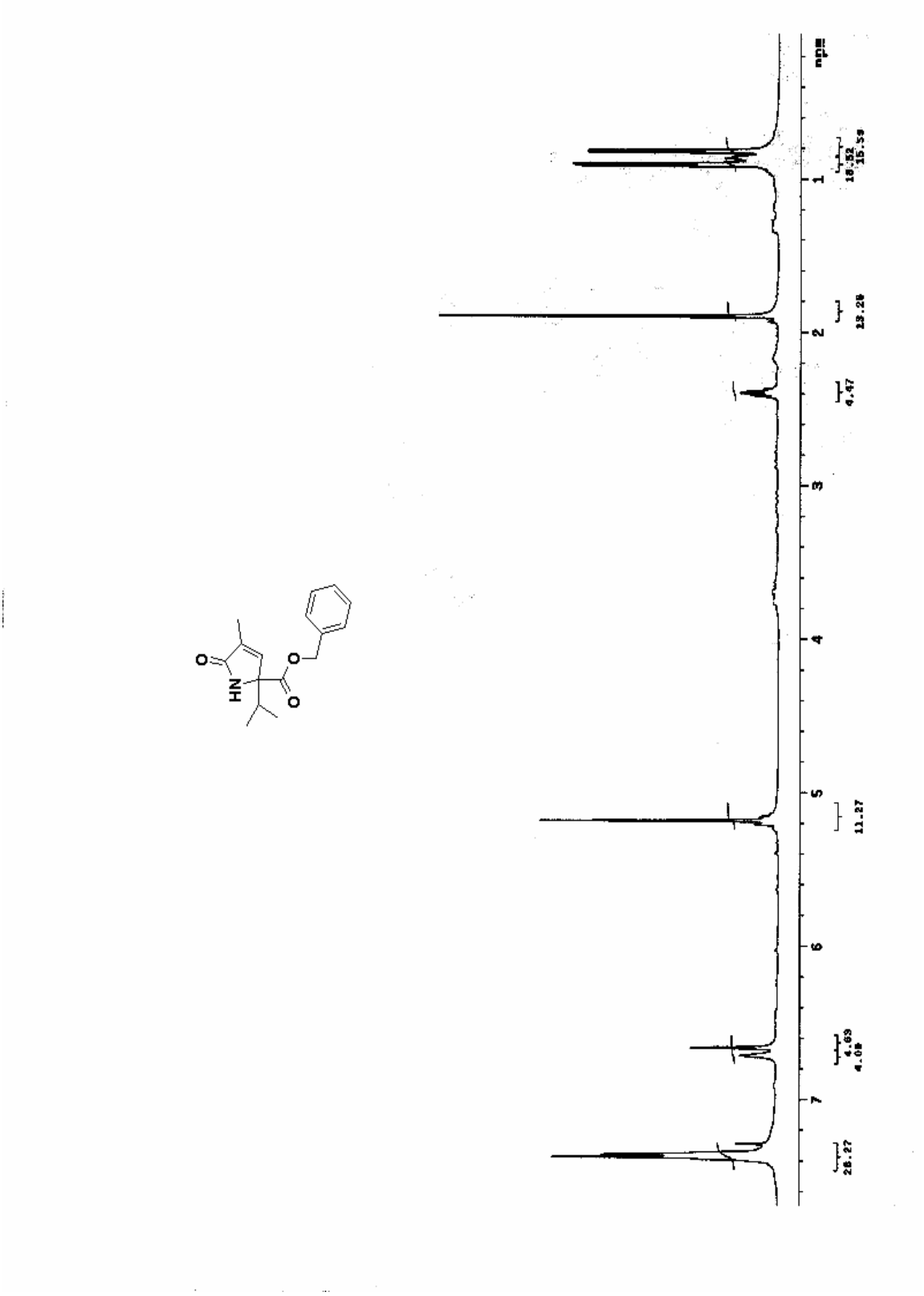
160
180
200
220


O
HN
O
O
O
ppm
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5
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7
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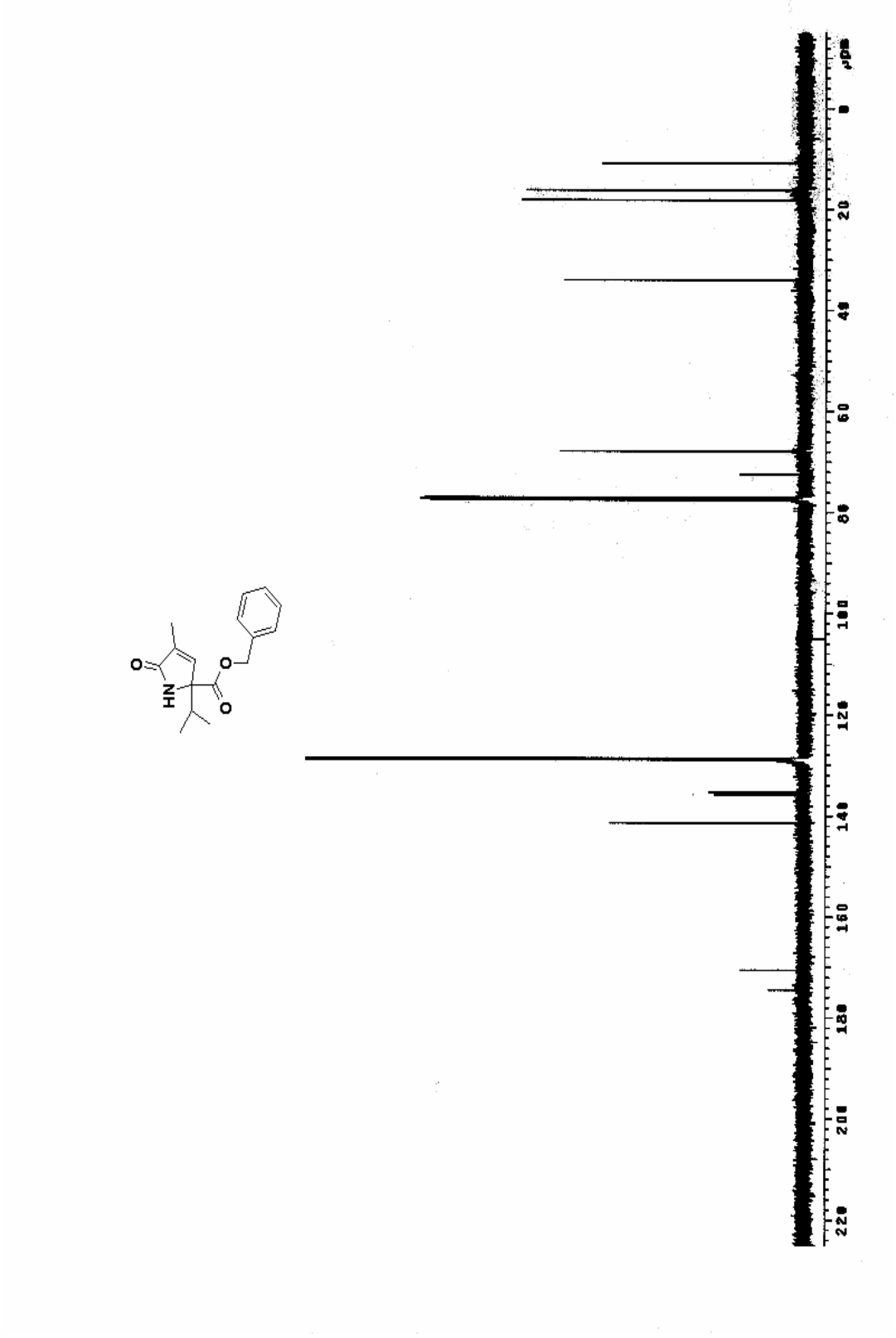
15.59
13.28
4.47
11.27
4.69
4.08
28.27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ppm
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80
100
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200
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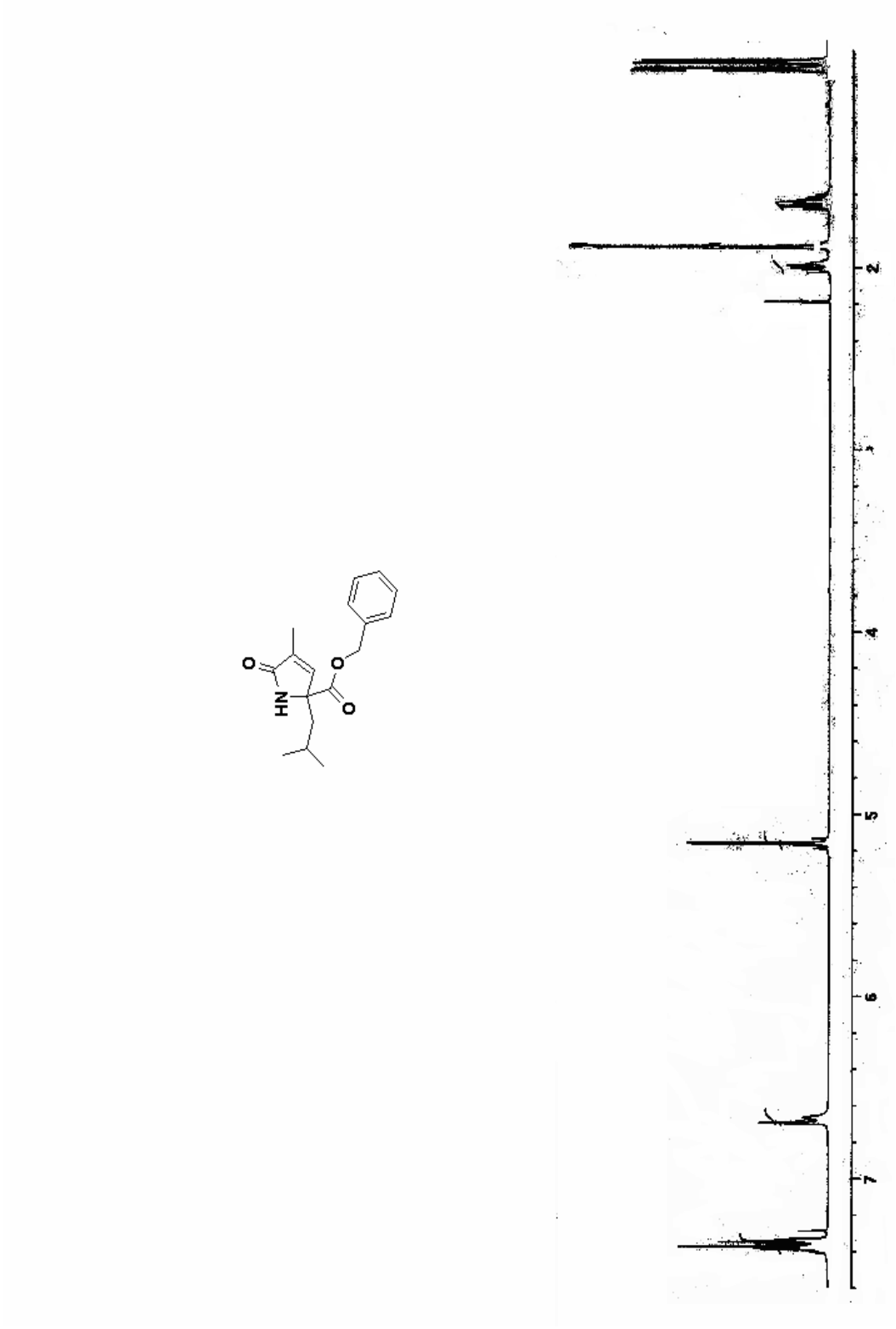
O
HN
O
O
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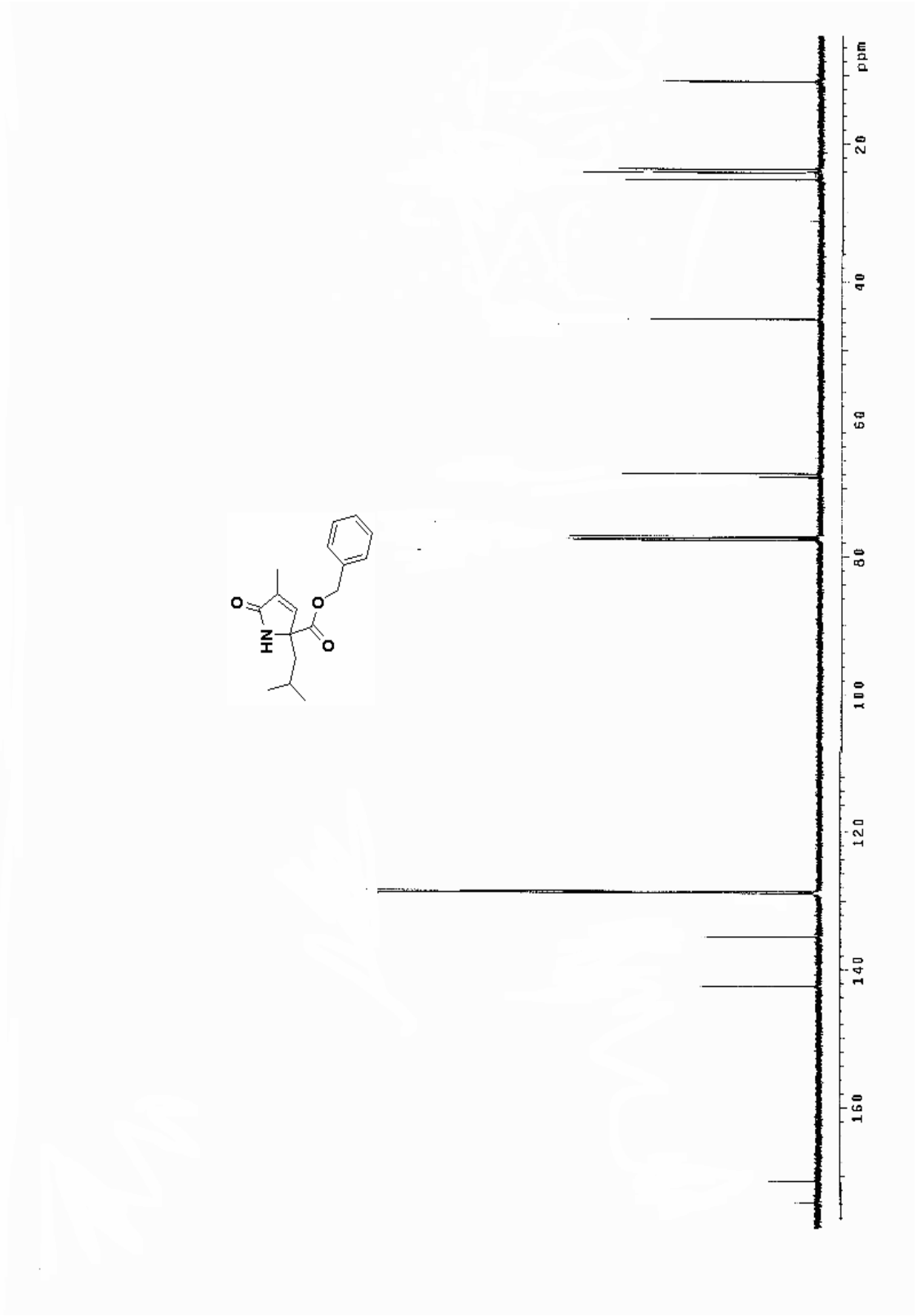
6
5
4
2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HN
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O
ppm
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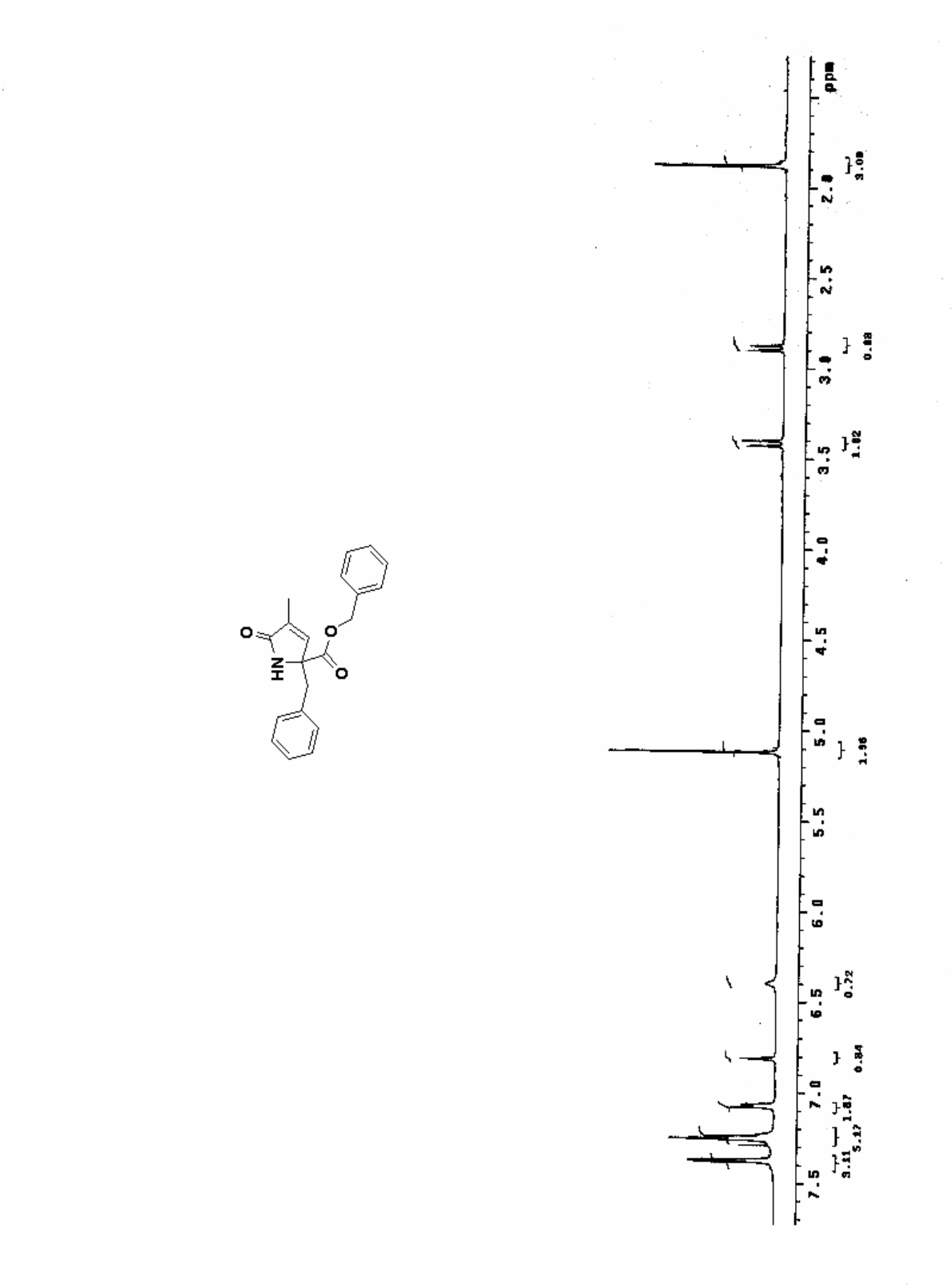
100
120
140
160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HN
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ppm
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6.5
6.0
5.5
5.0
4.5
4.0
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2.0
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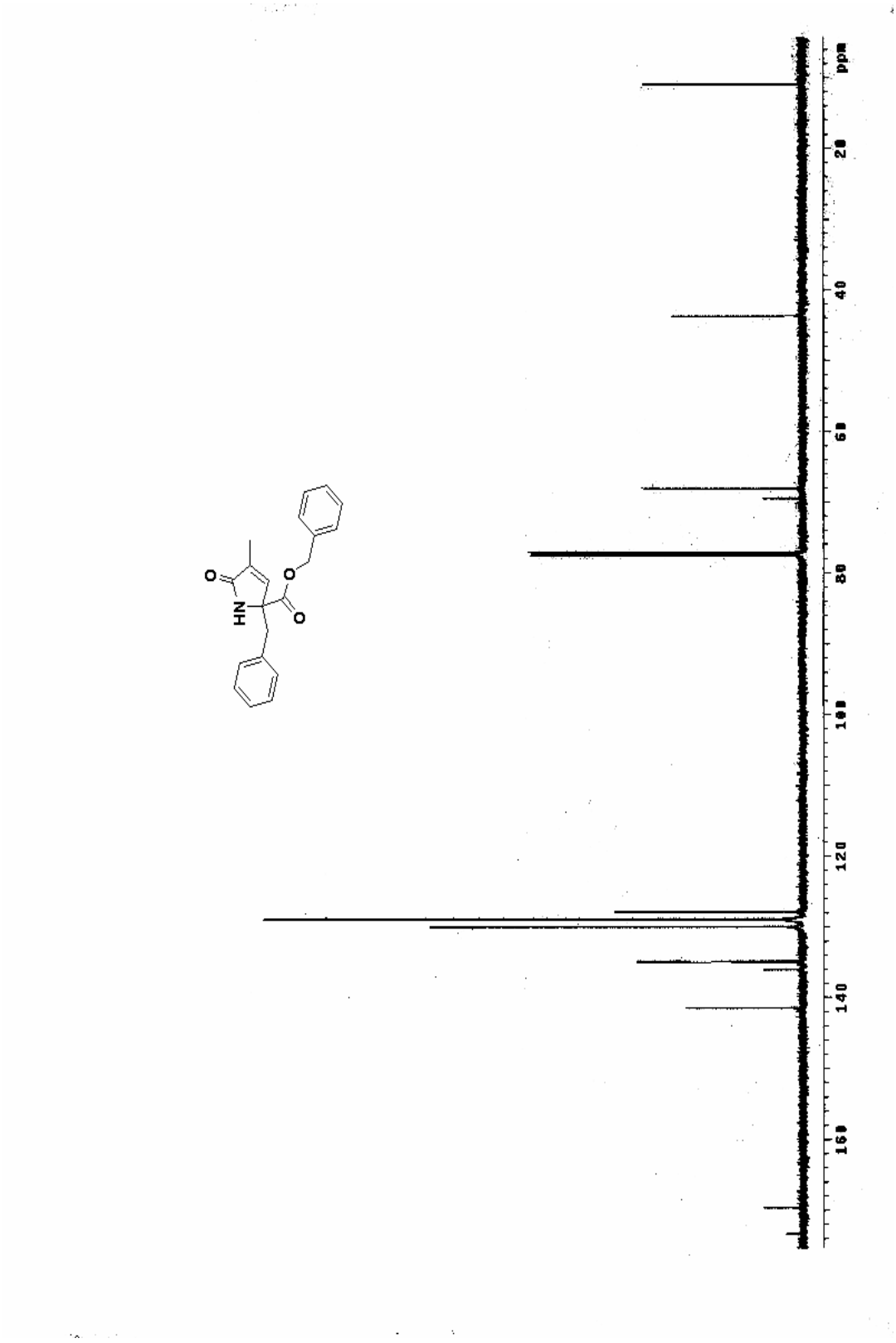
0.84
0.72
1.96
1.82
0.88
3.08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HN
O
O
ppm
20
40
60
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100
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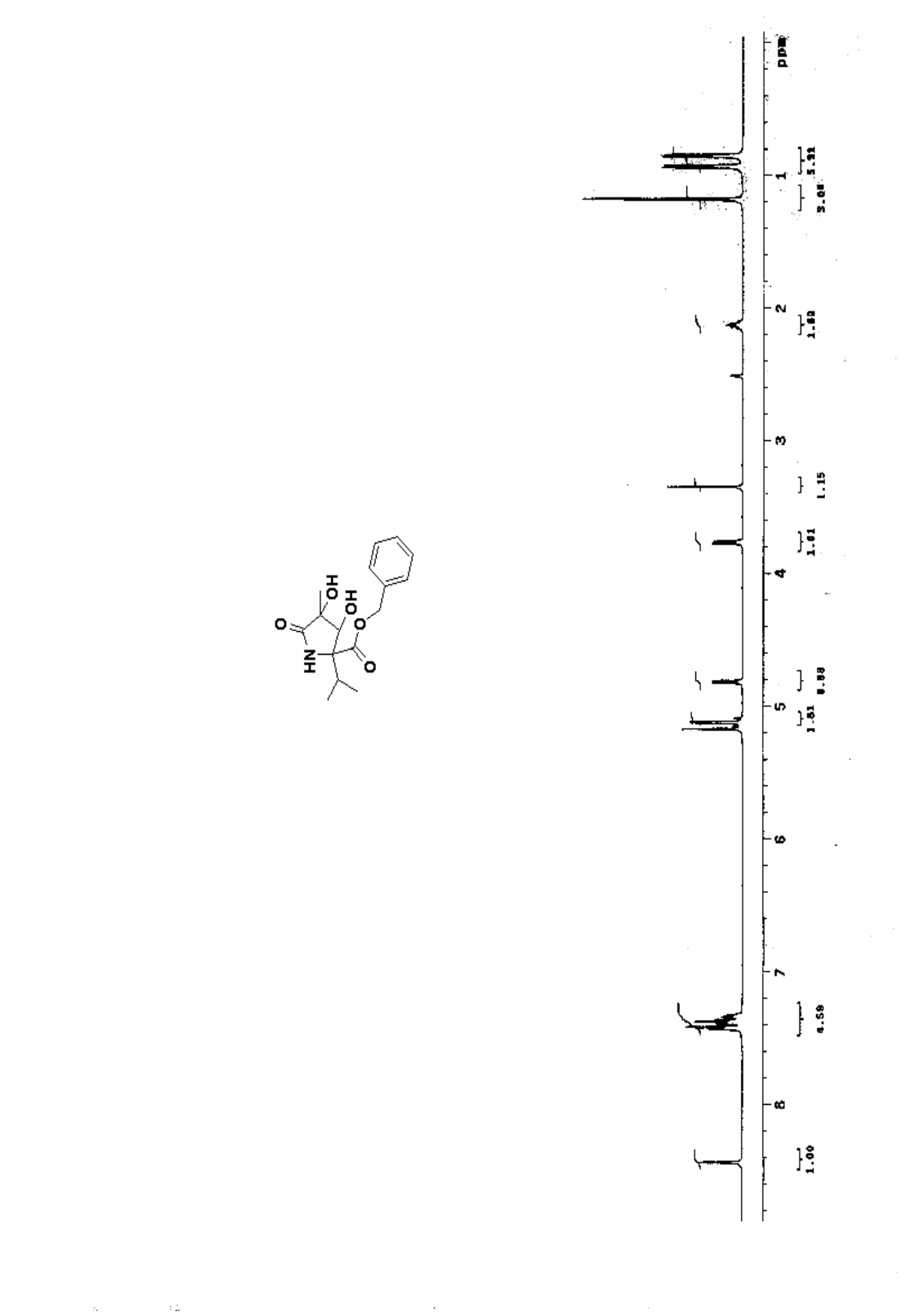
140
160


OH
OH
O
O
HN
O
O
ppm
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2
3
4
5
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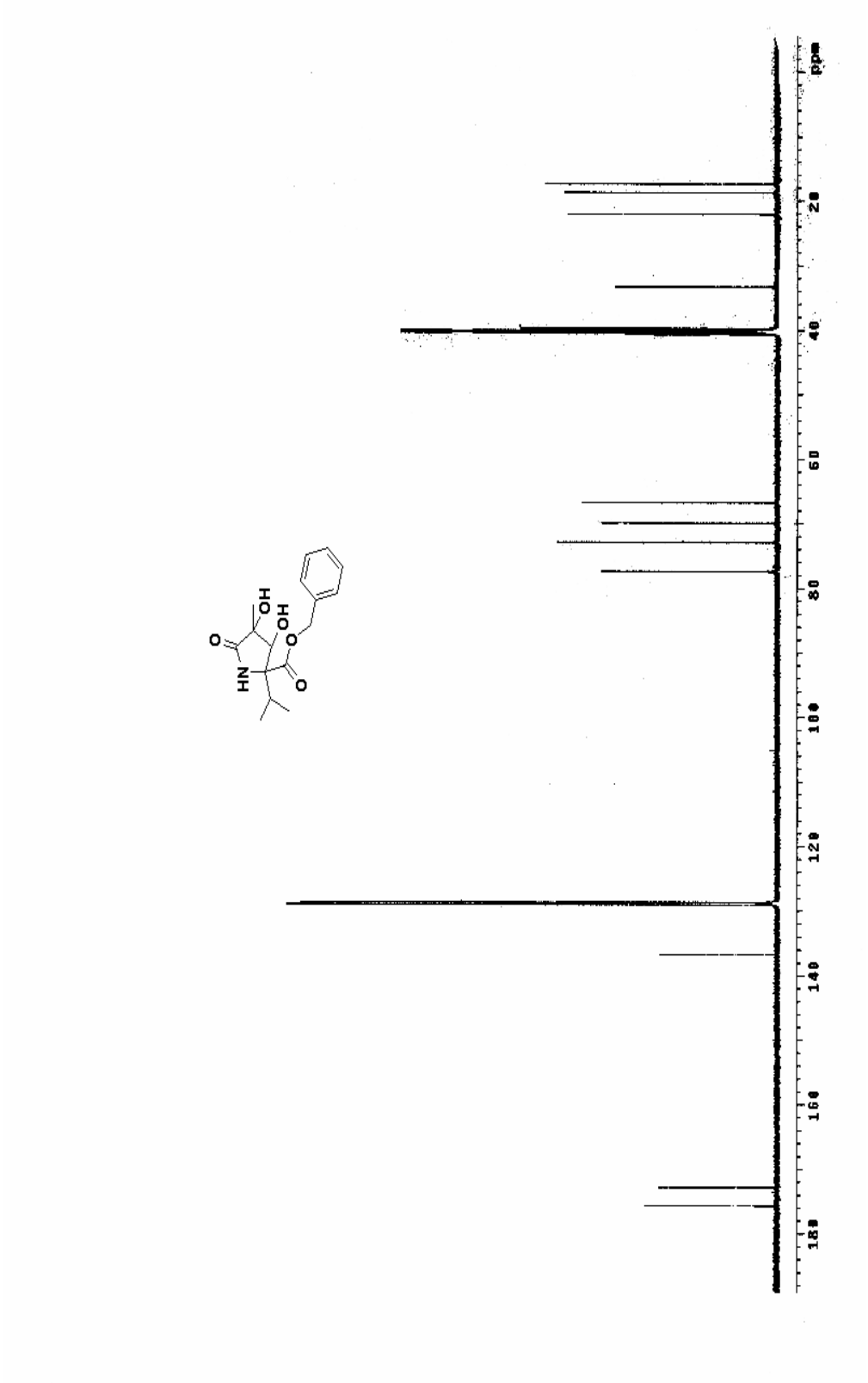
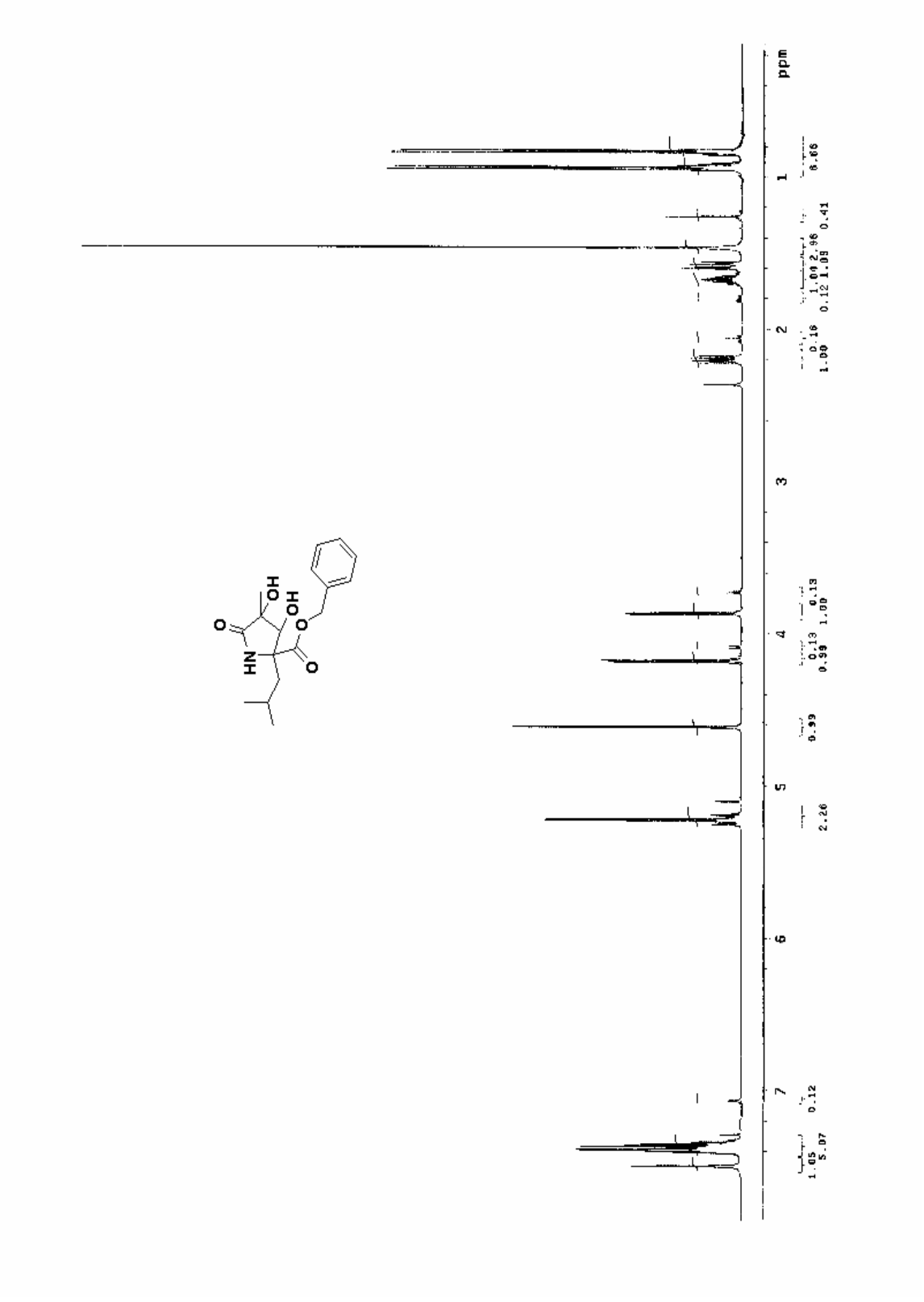
8
5.91
3.08
1.89
1.15
1.01
0.88
1.01
4.59
1.00


OH
OH
O
O
HN
O
O
ppm
20
40
60
80
100
120
140
160
180


OH
OH
O
HN
O
O
ppm
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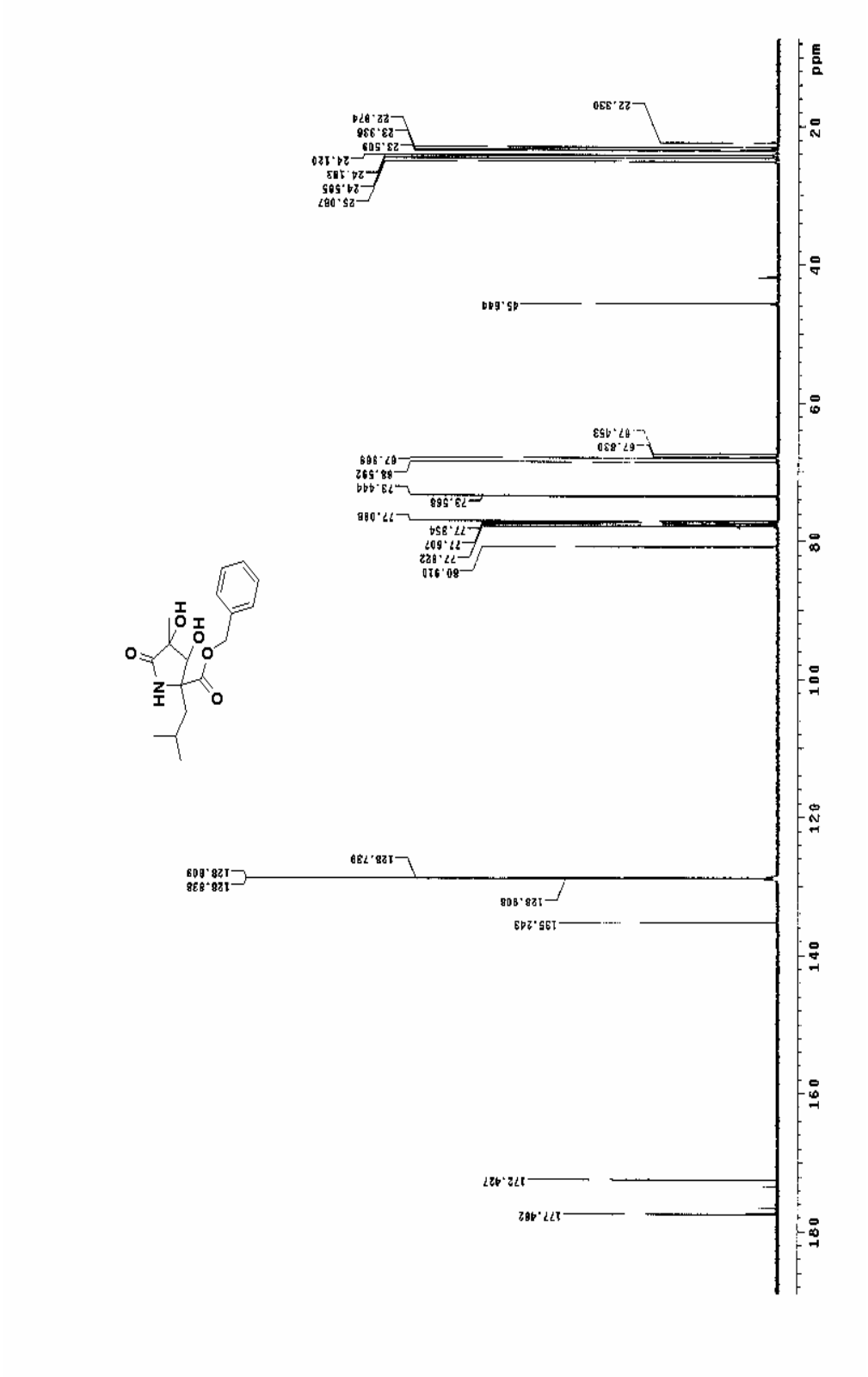
2
3
4
5
6
7
1.05
5.07
0.12
2.26
0.99
0.13
0.99
1.00
0.13
0.12
1.00
0.16
1.00
2.96
1.08
0.41
6.66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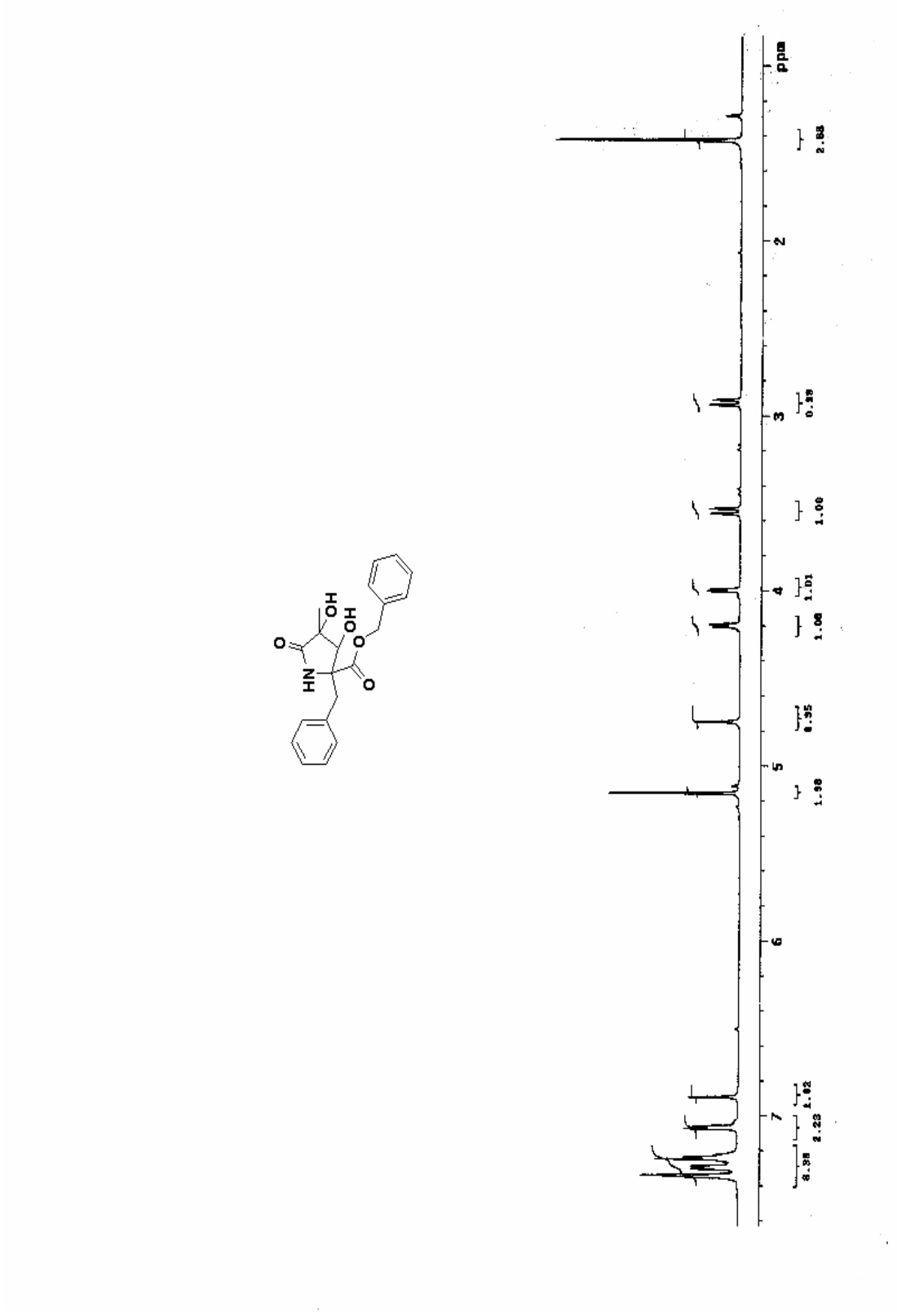
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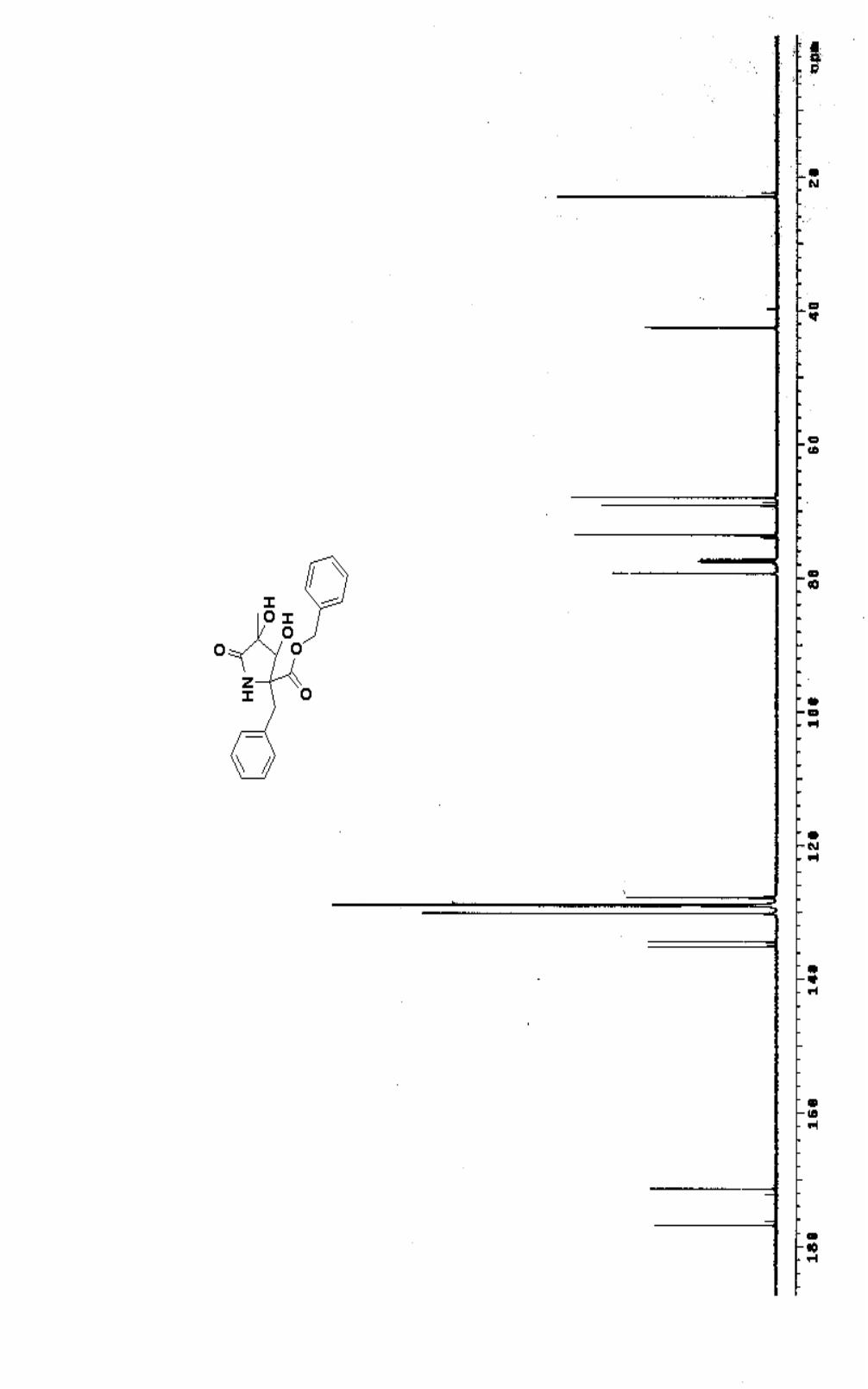
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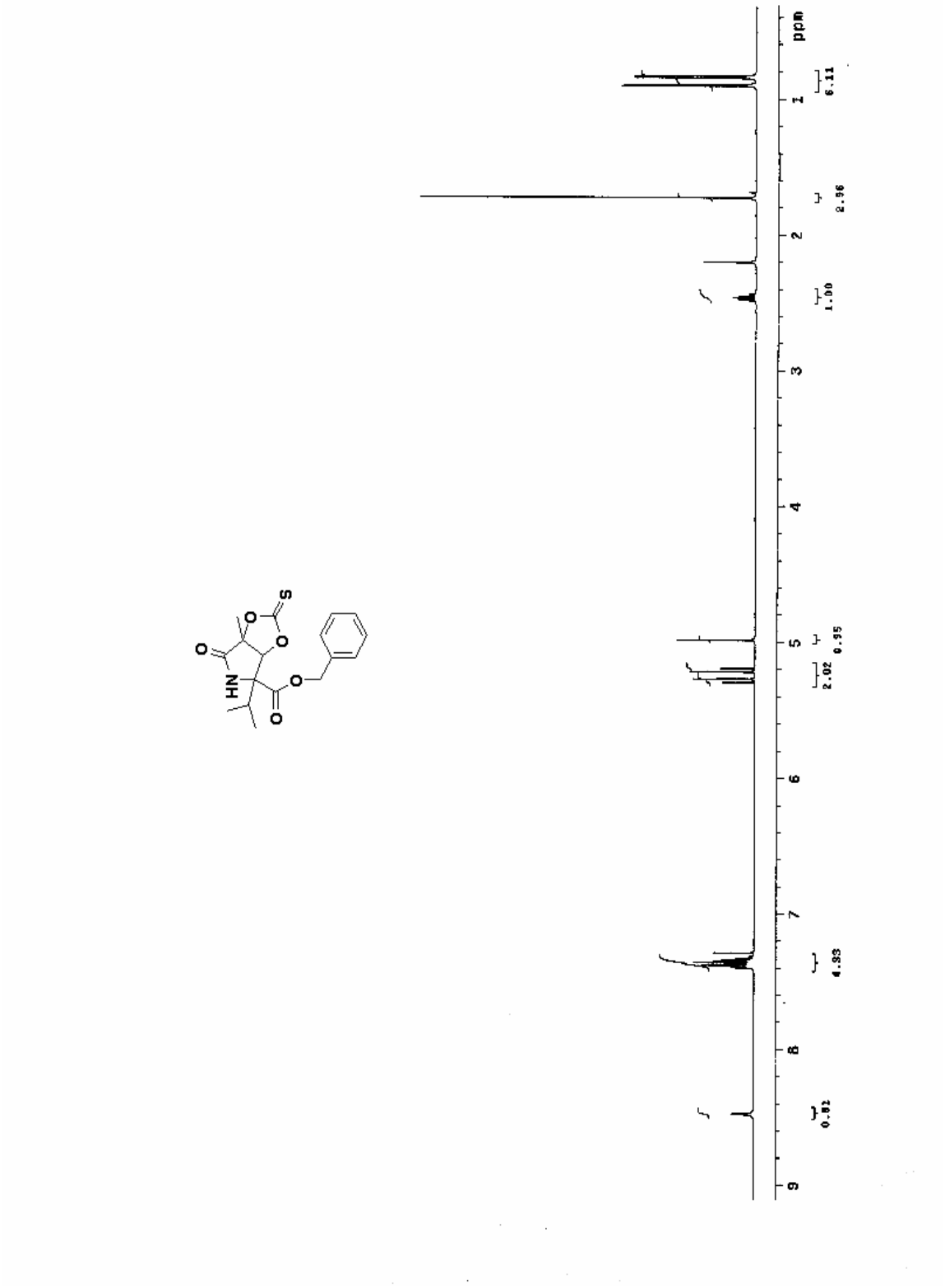
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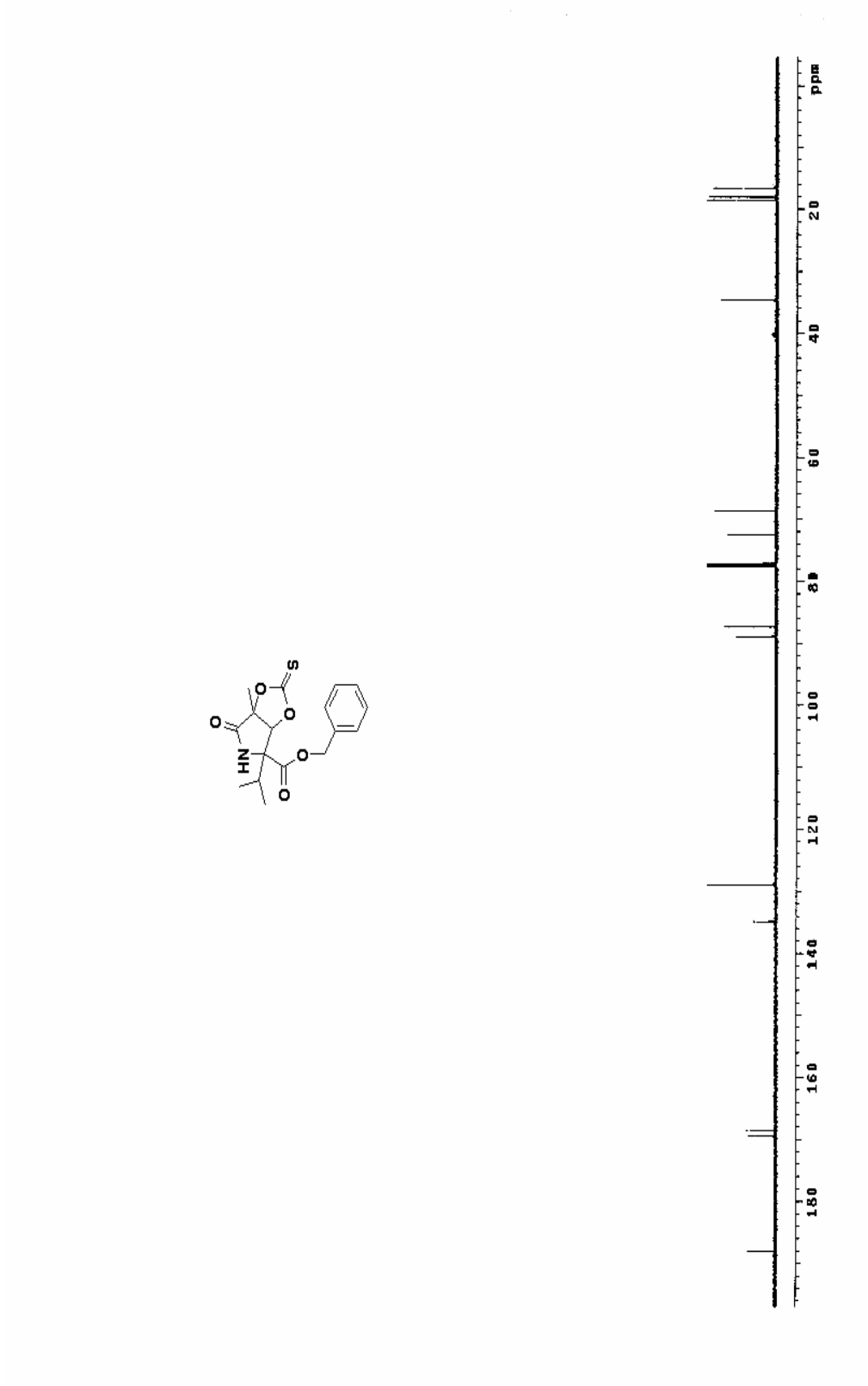
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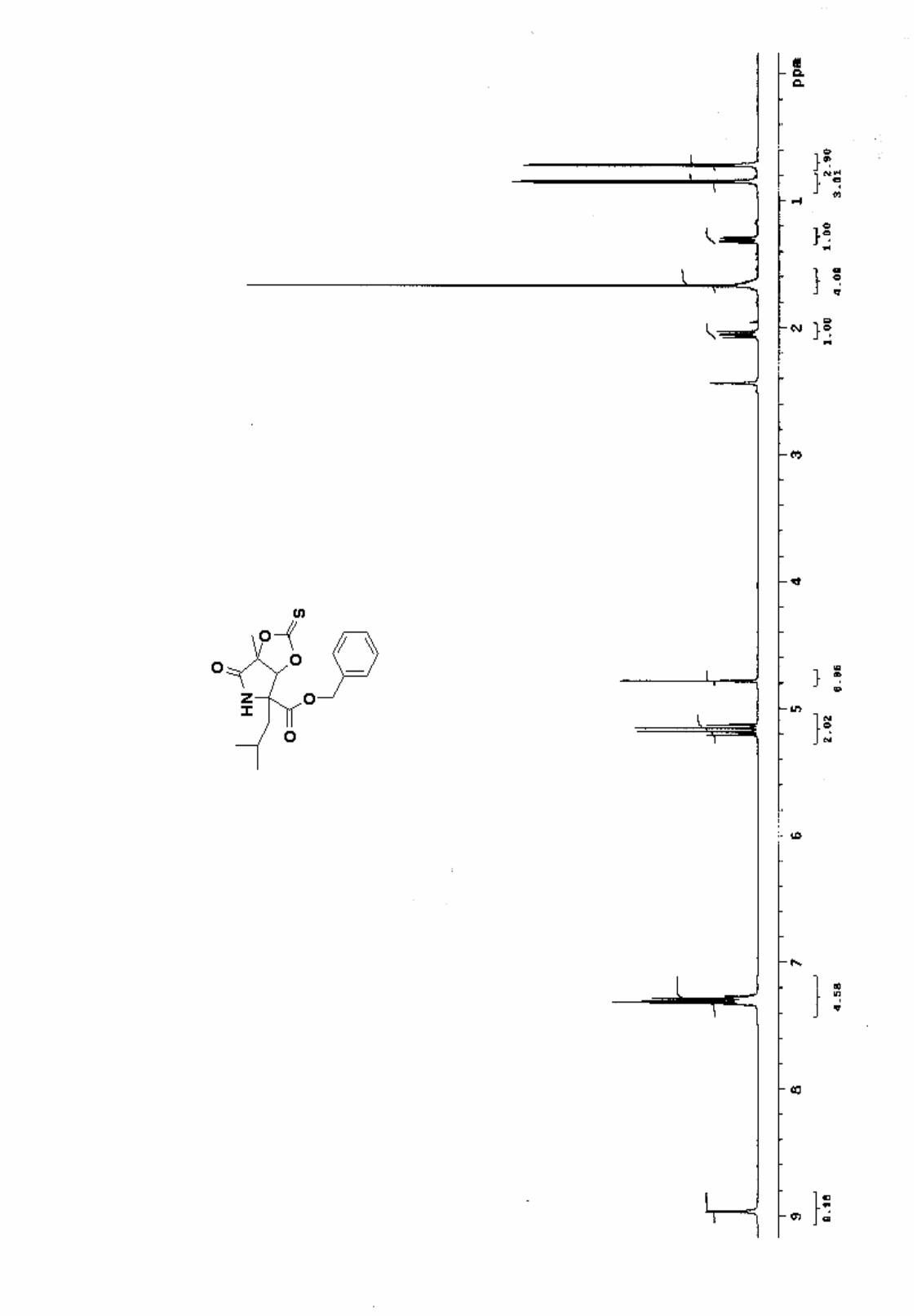
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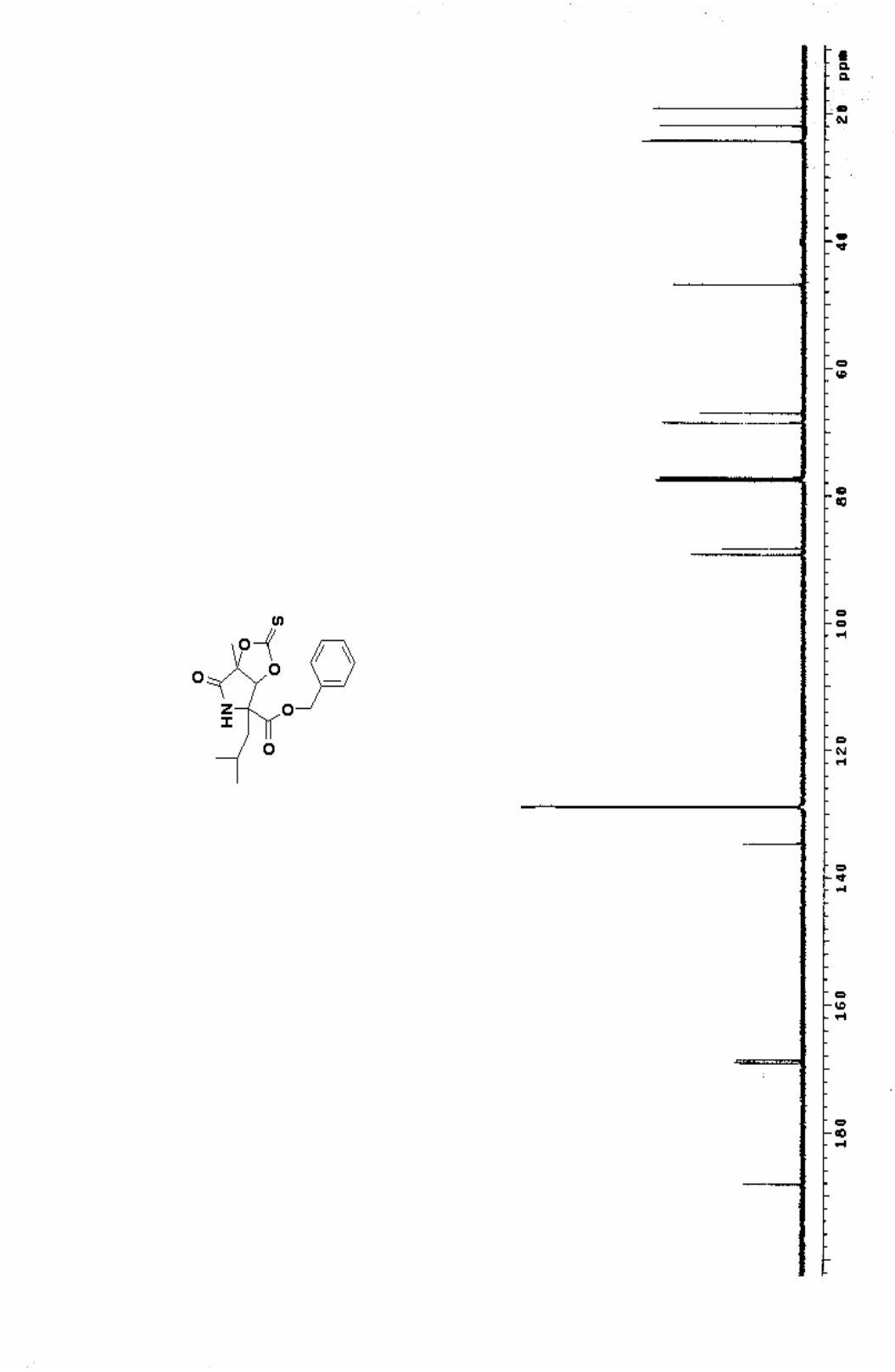
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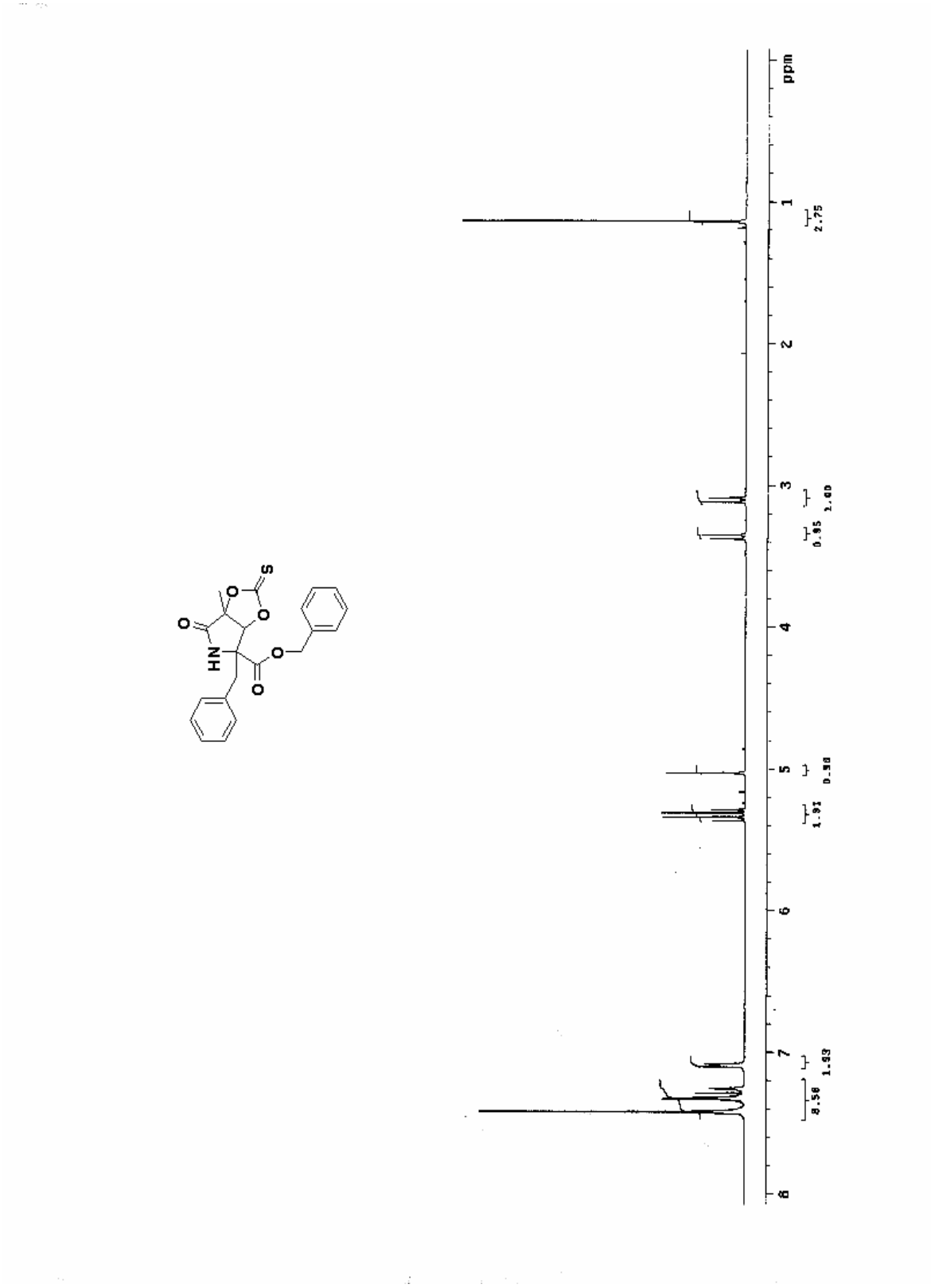
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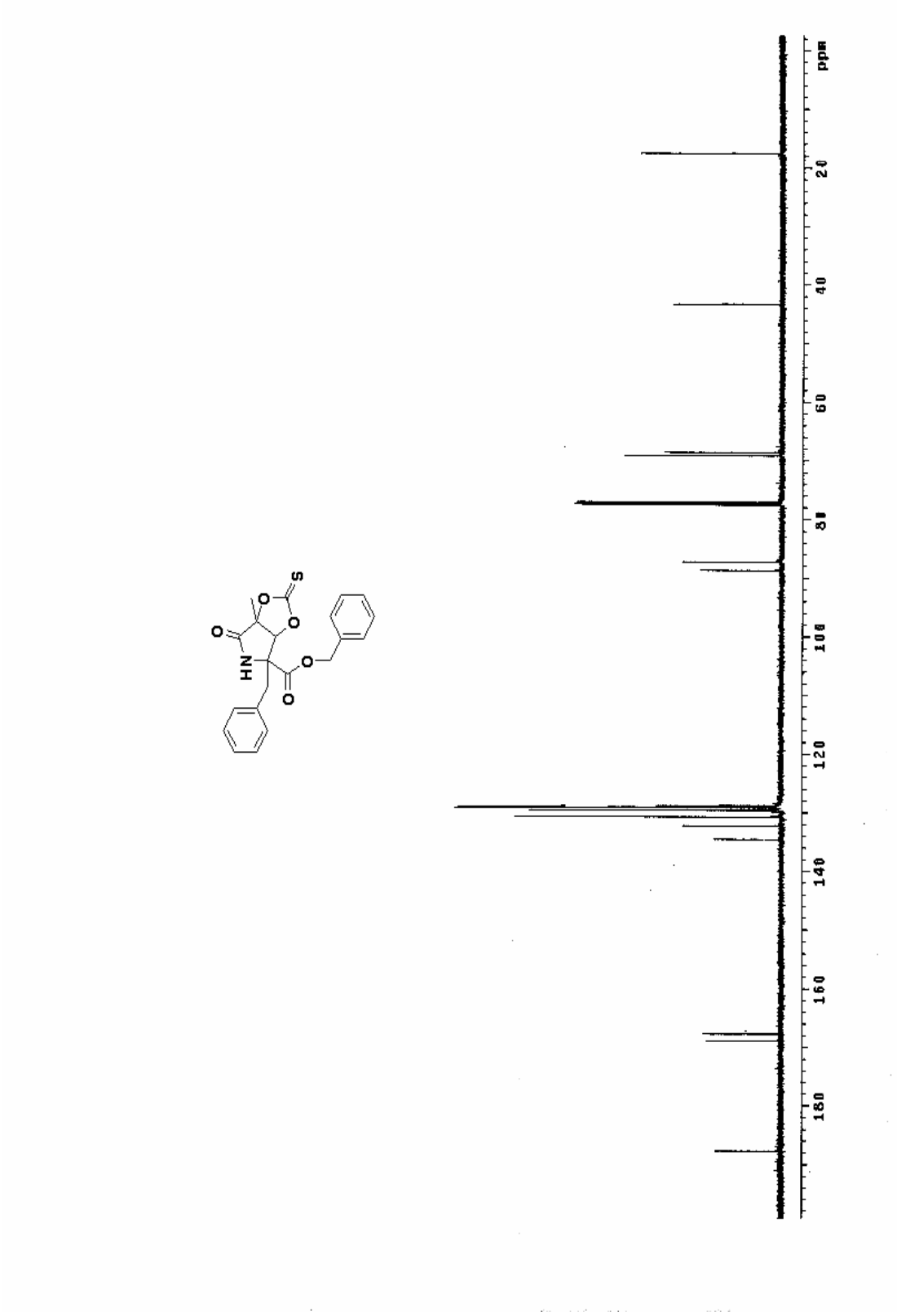
1.93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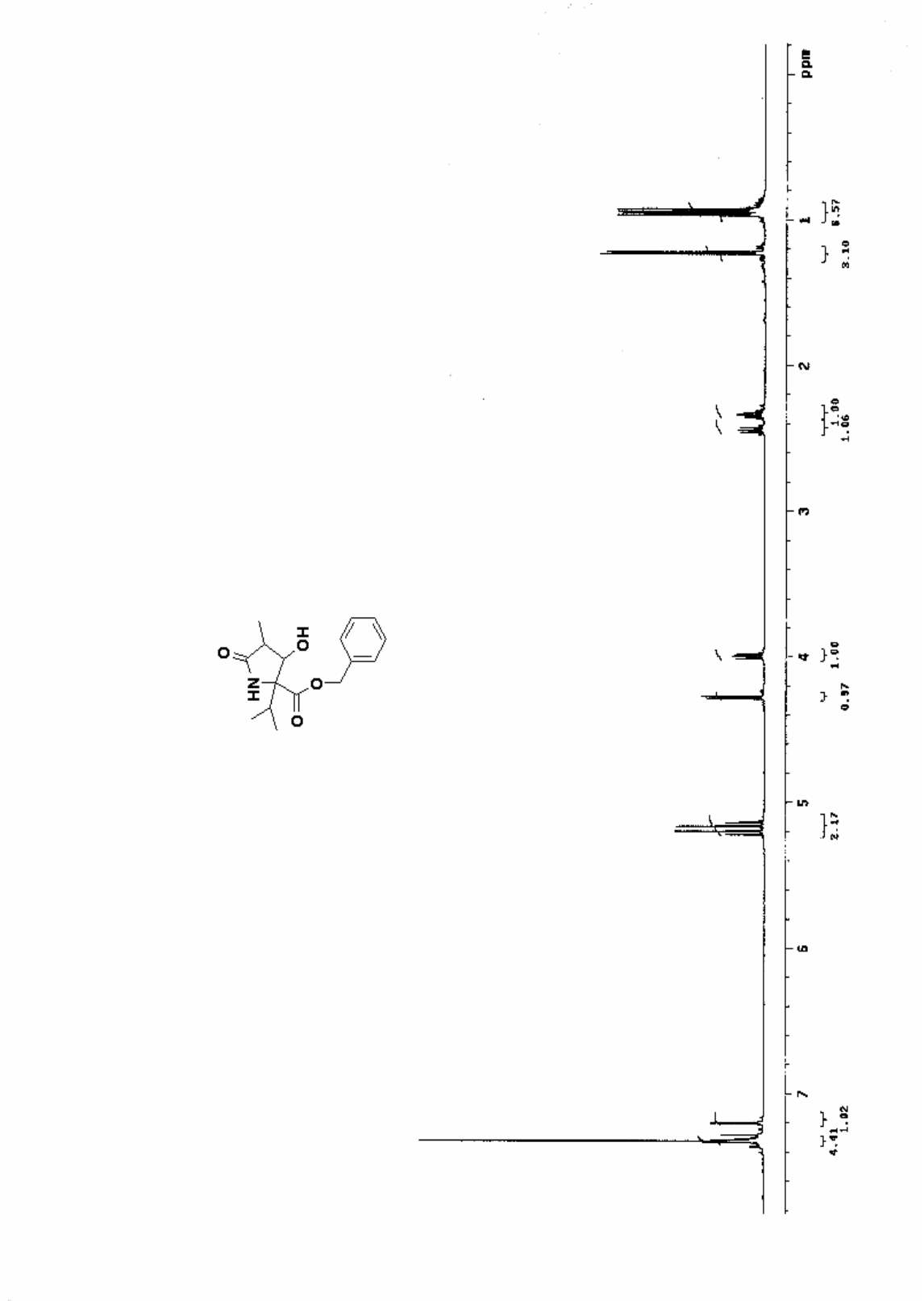
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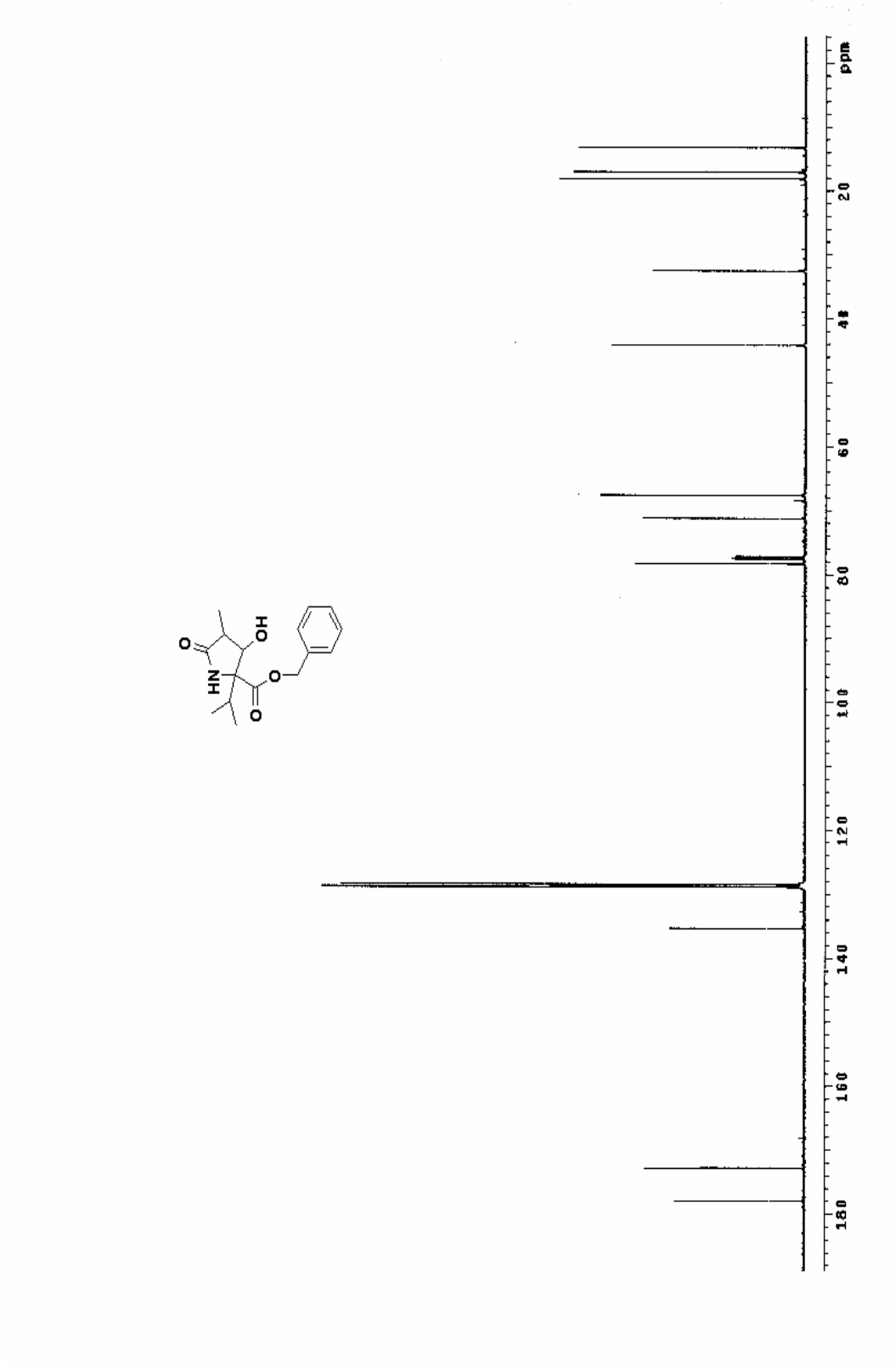
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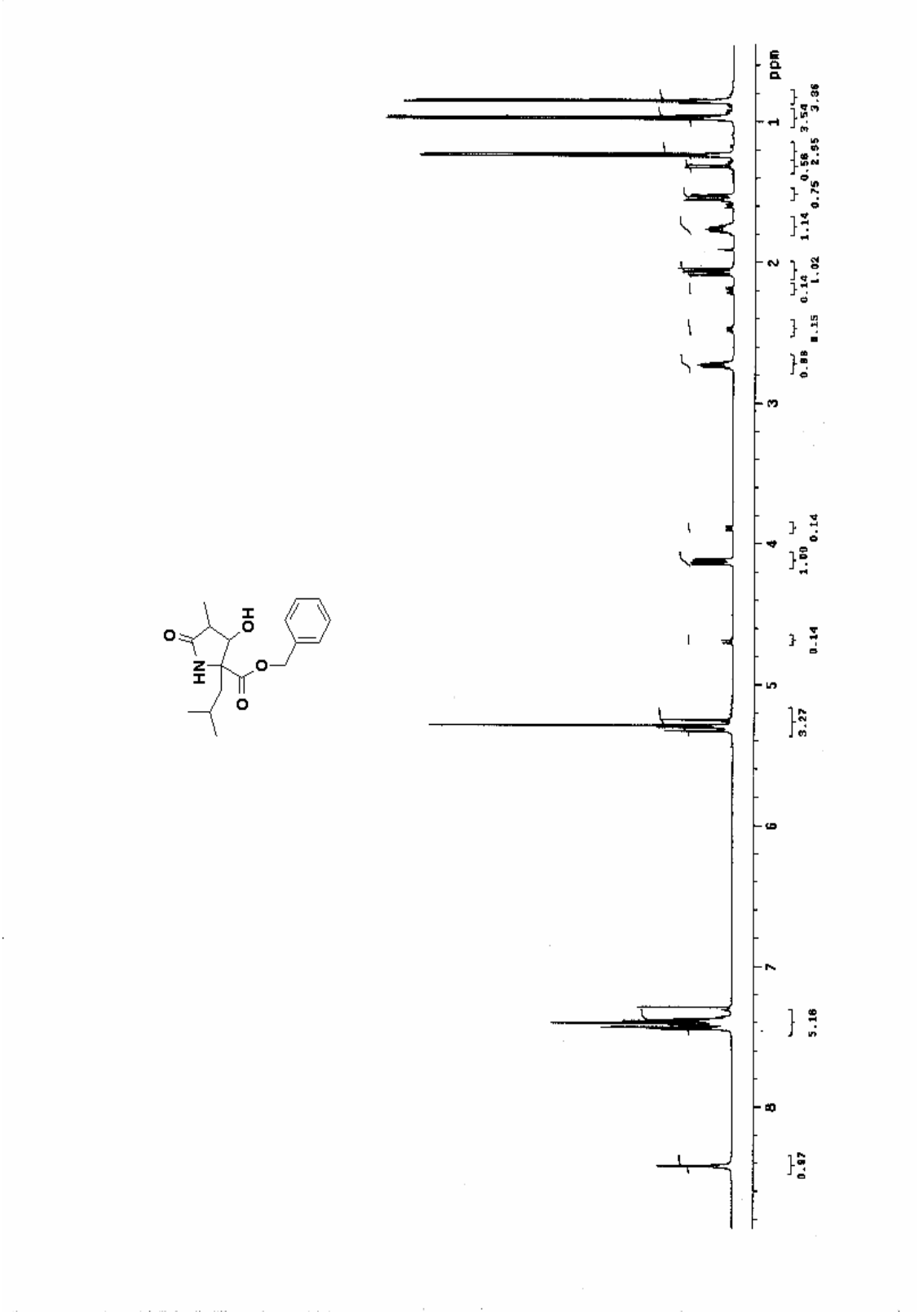
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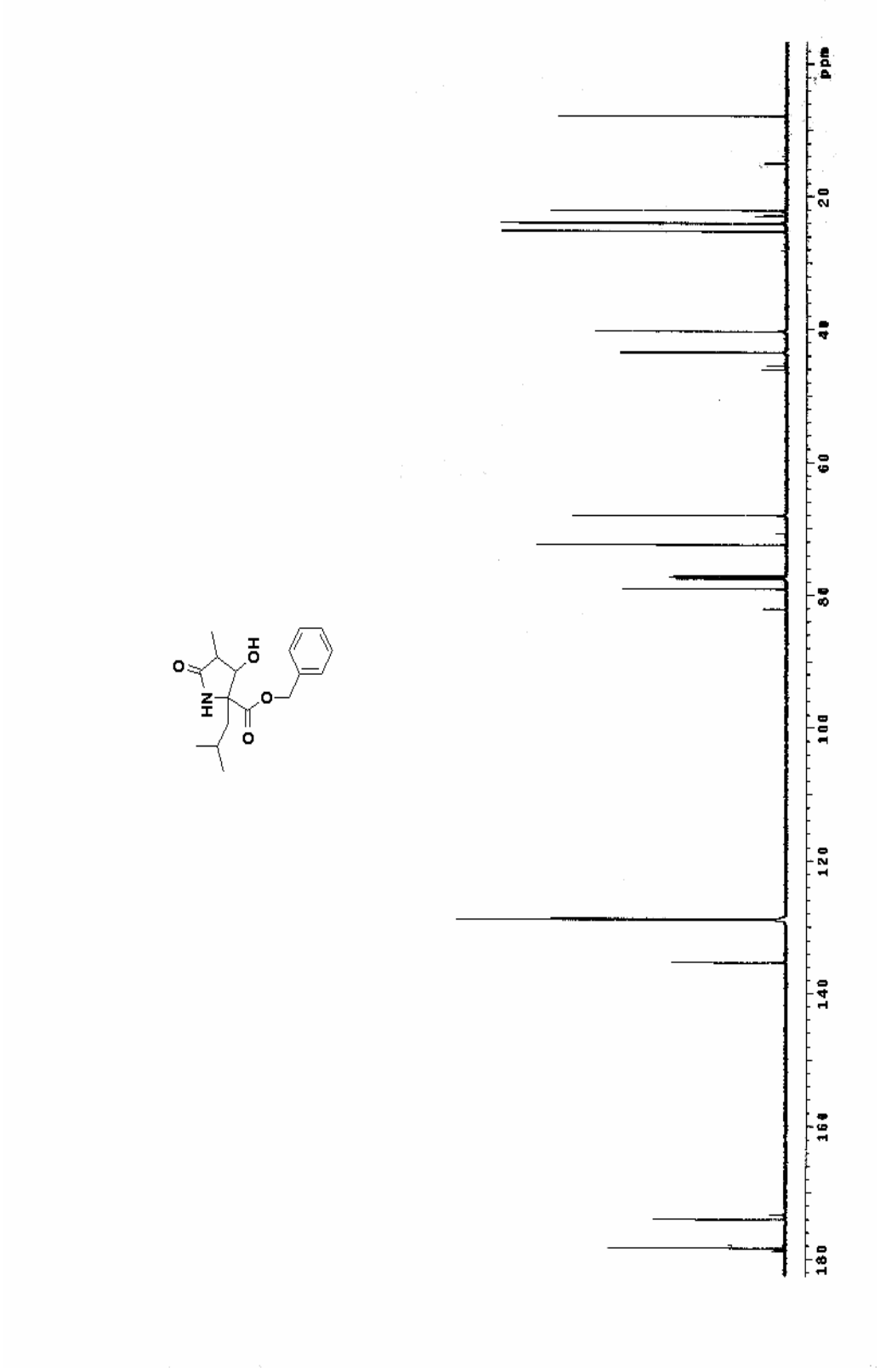
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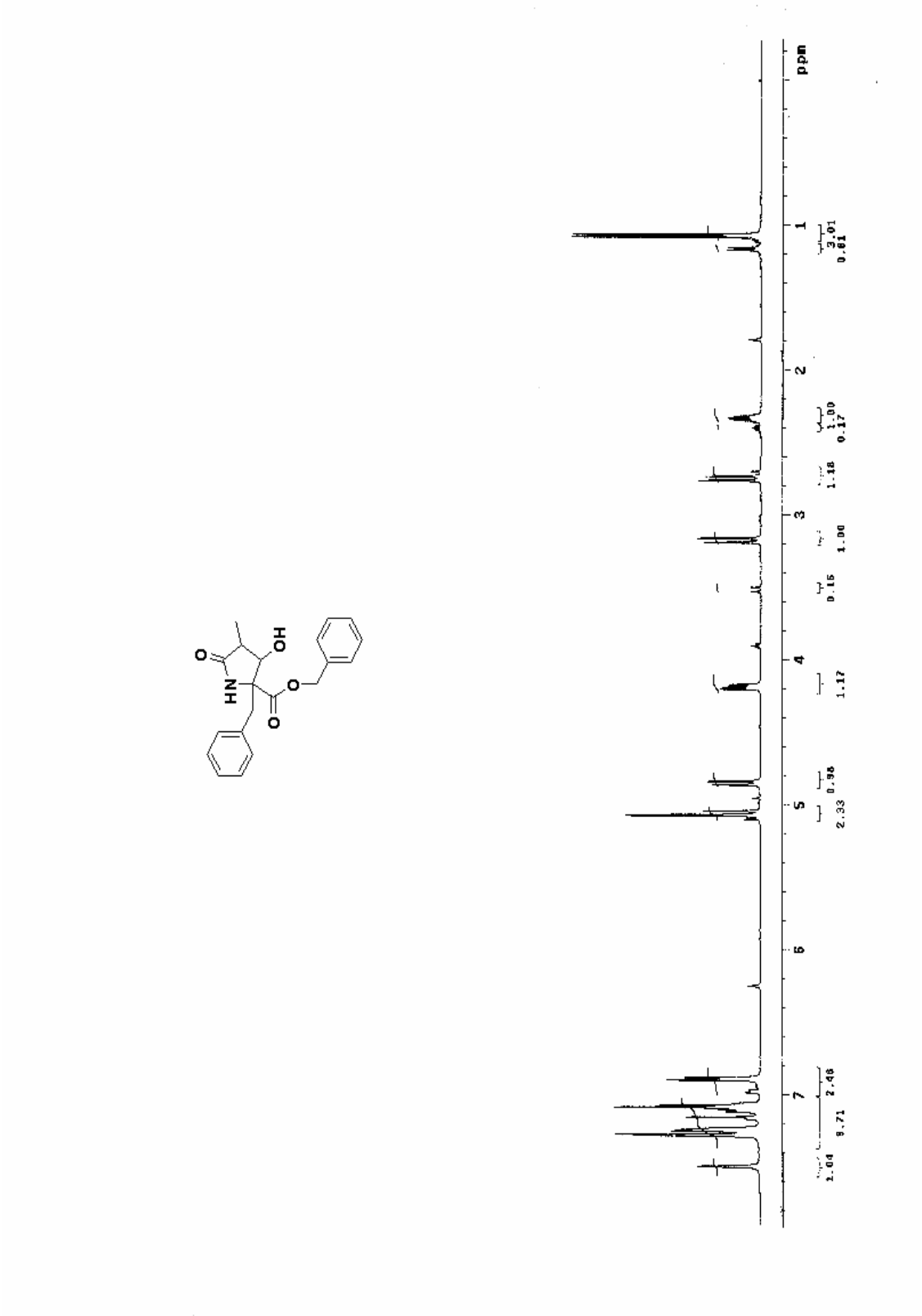
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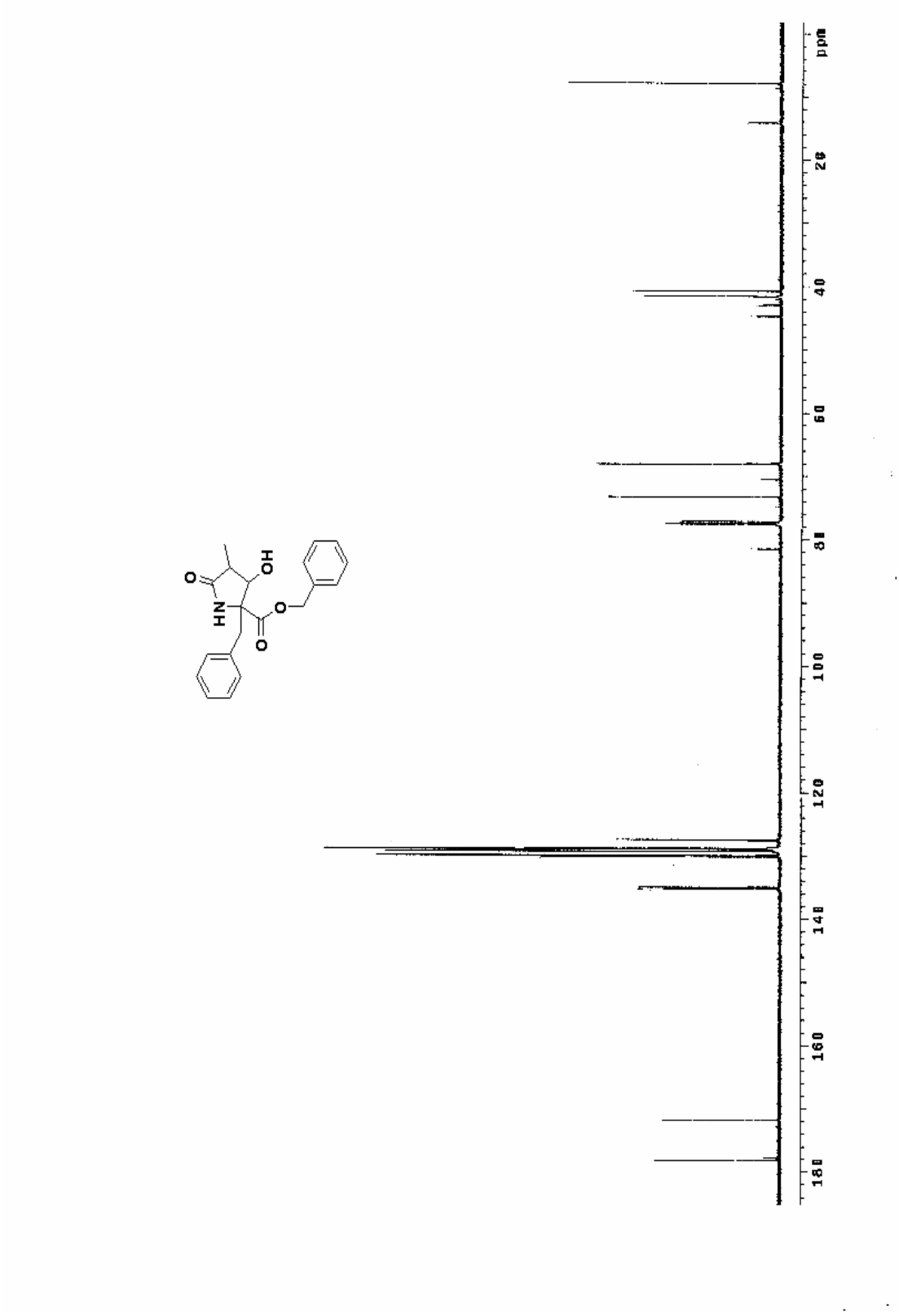
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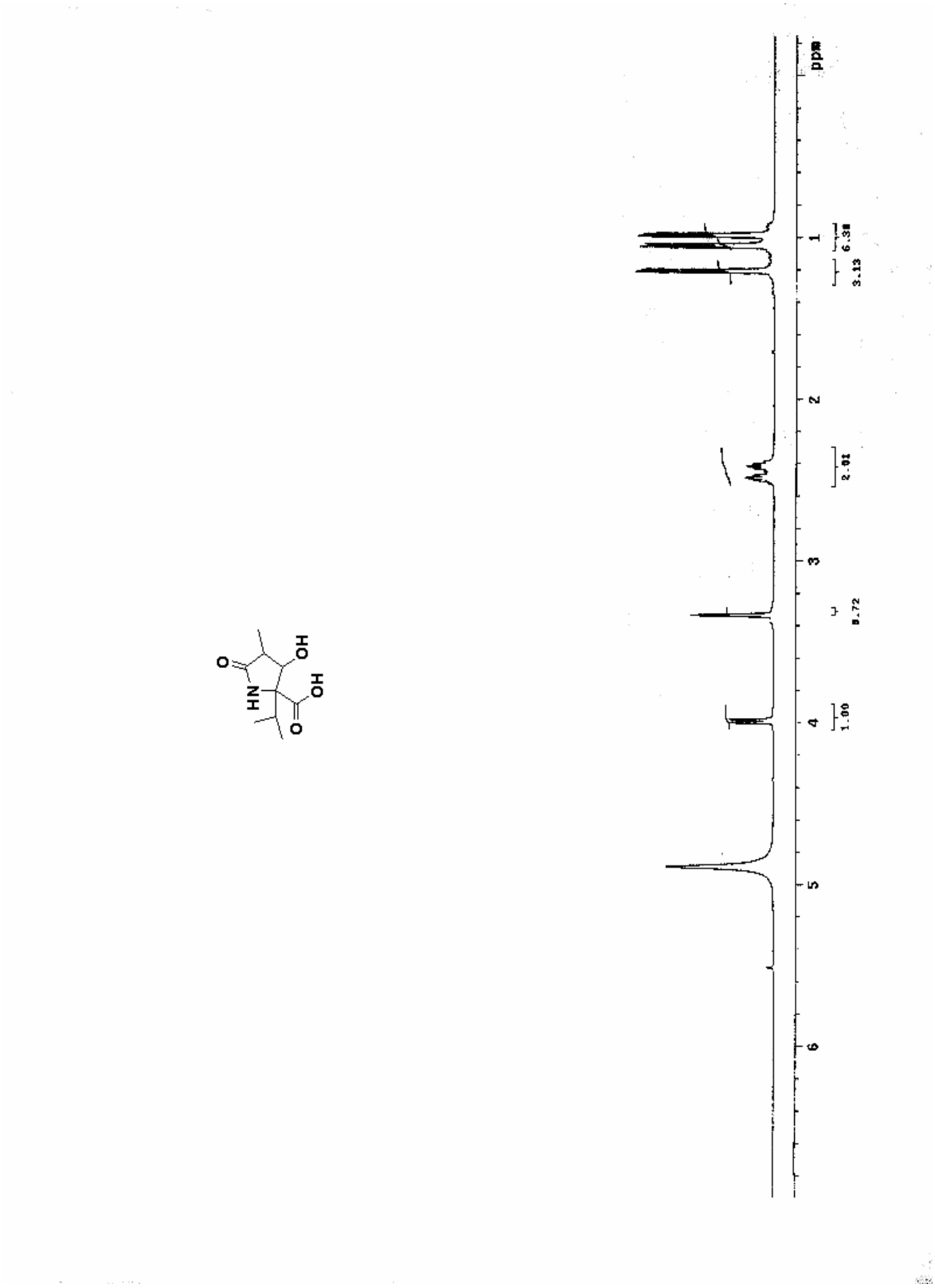
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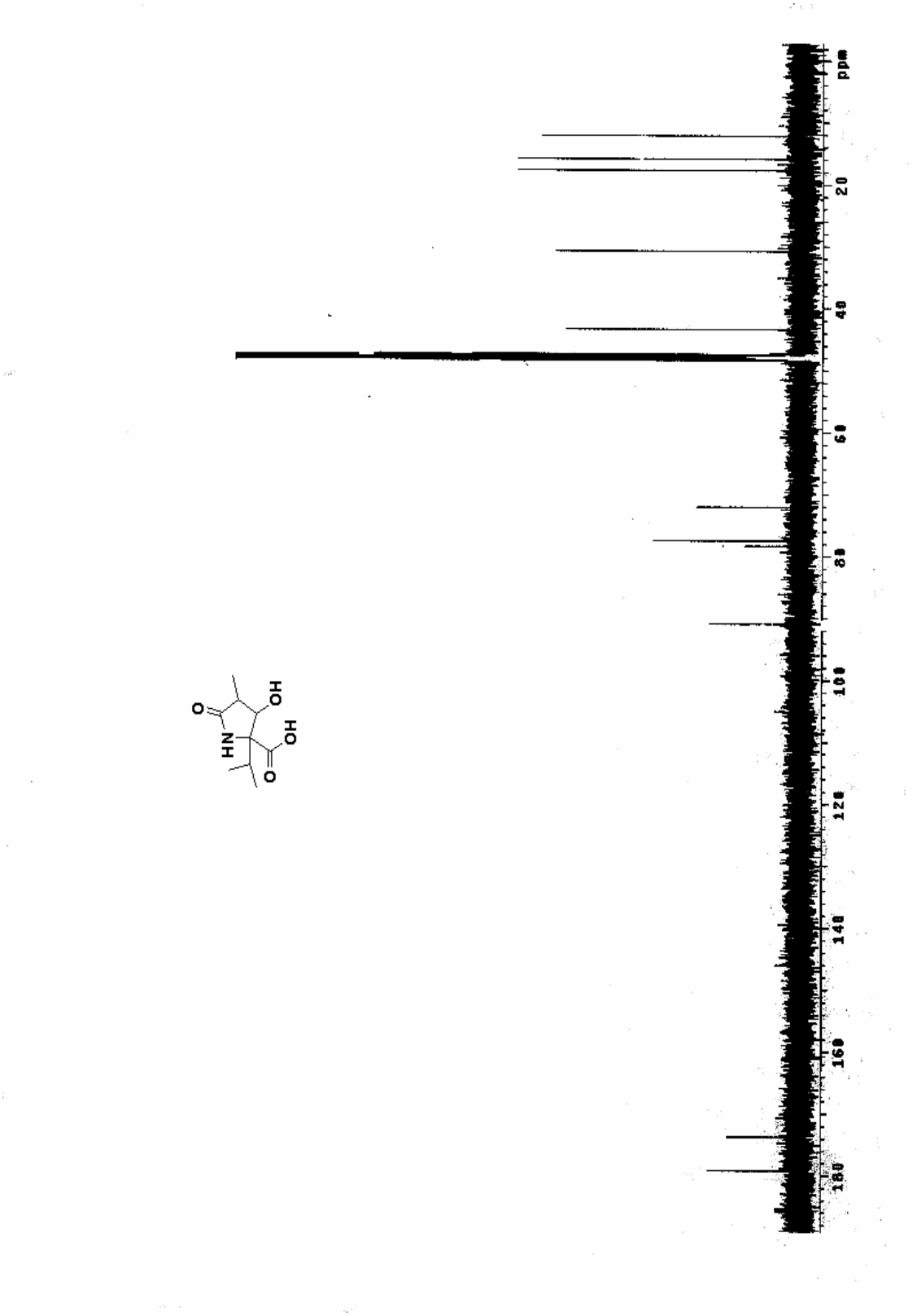
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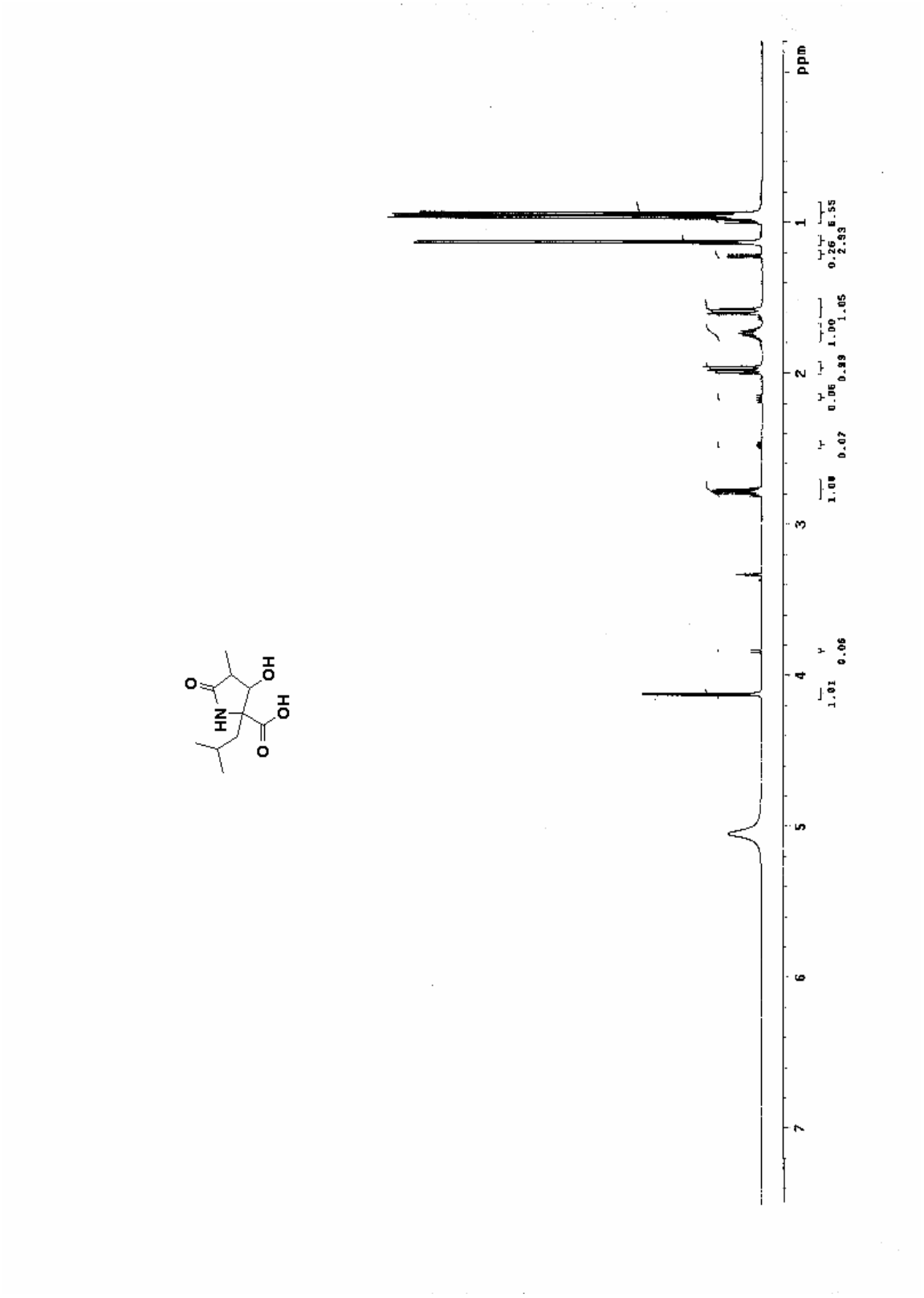
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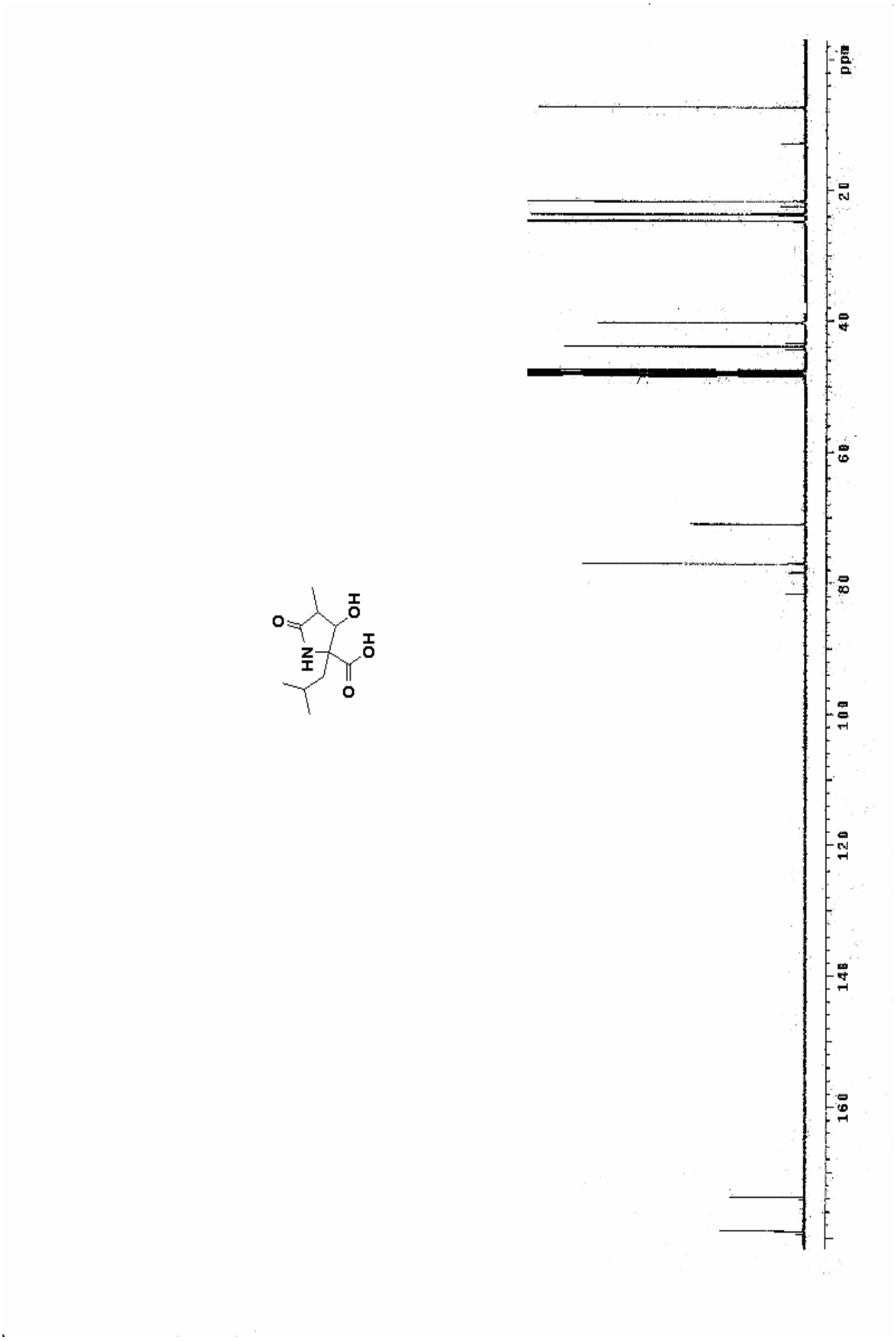
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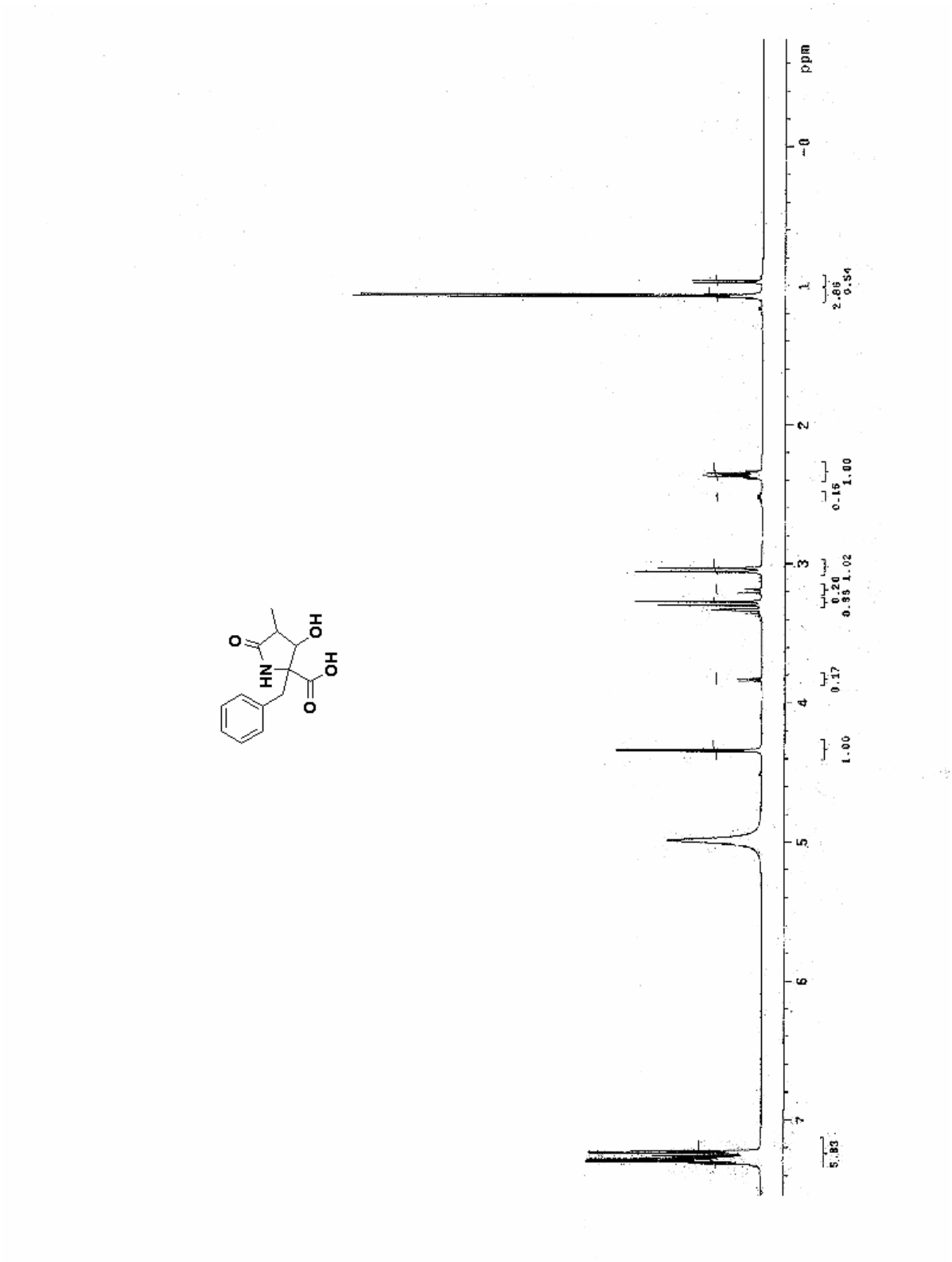
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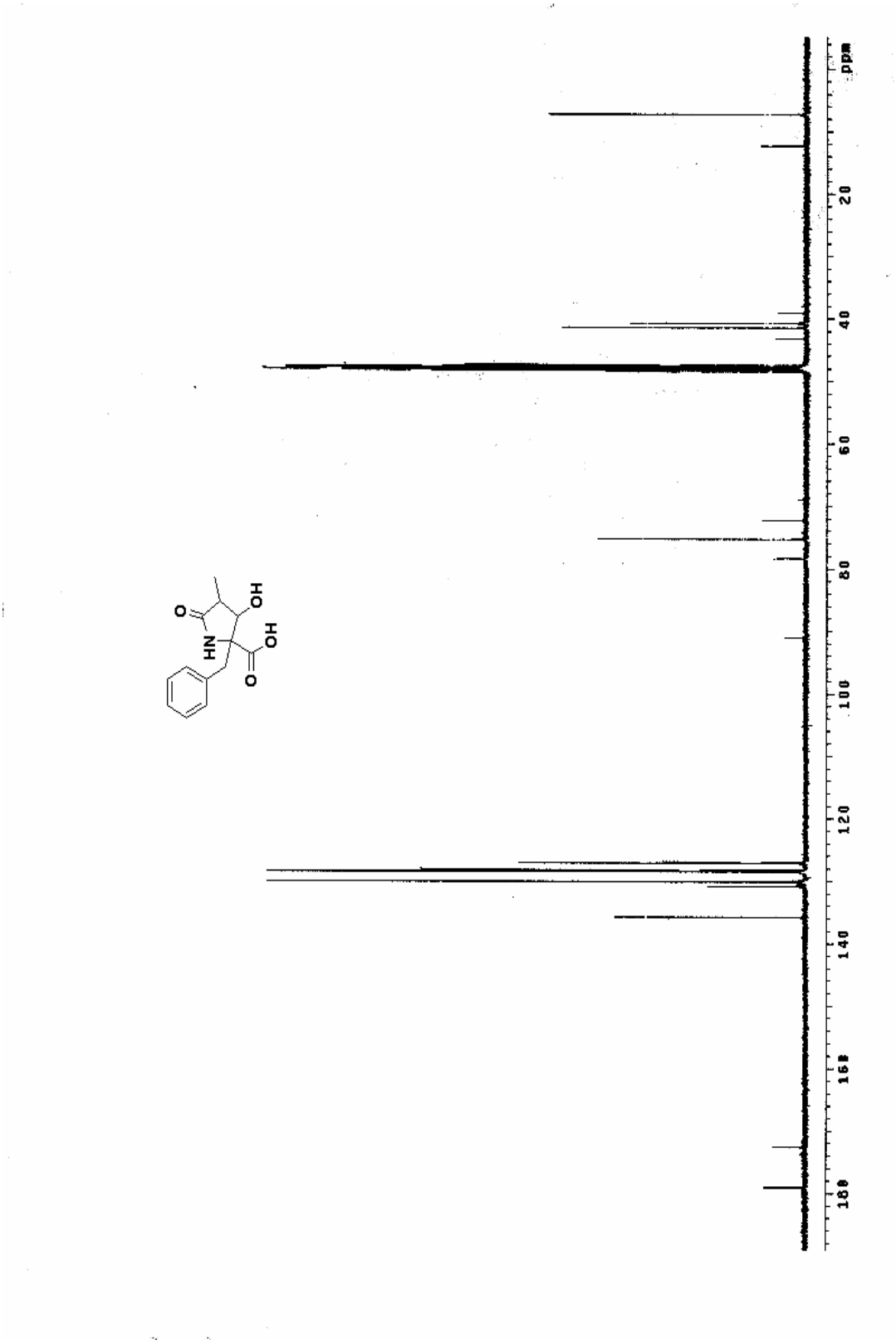
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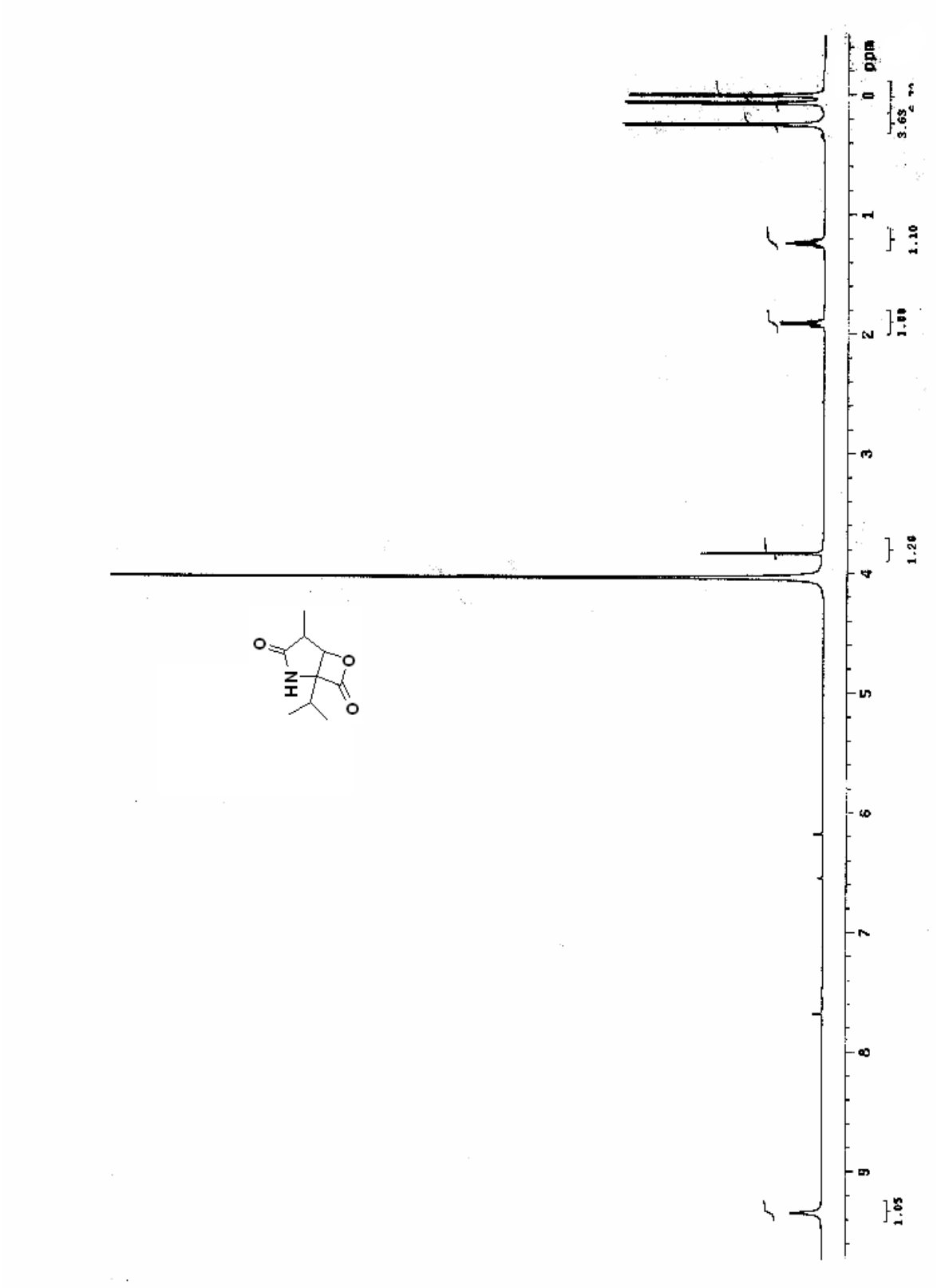
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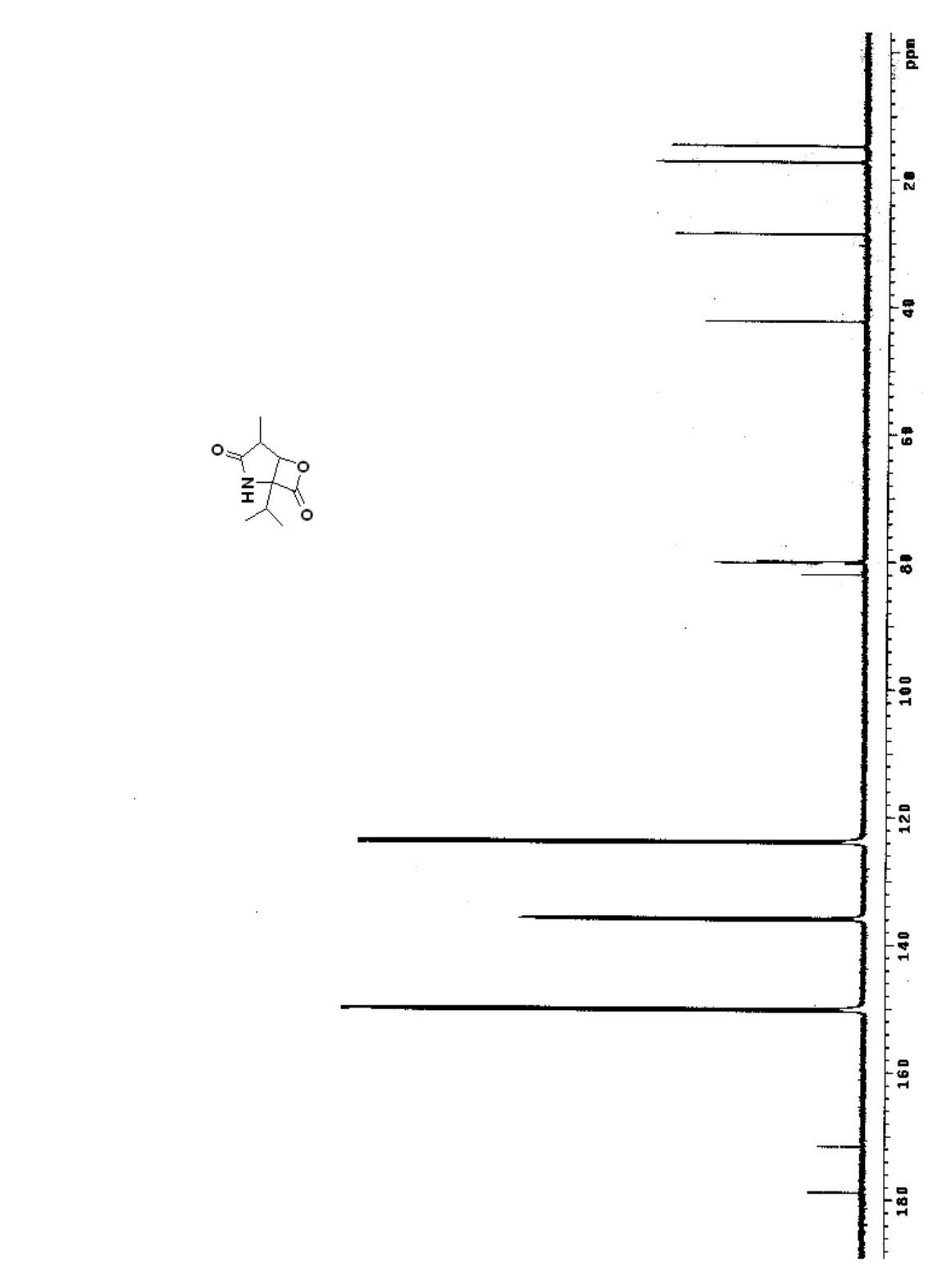
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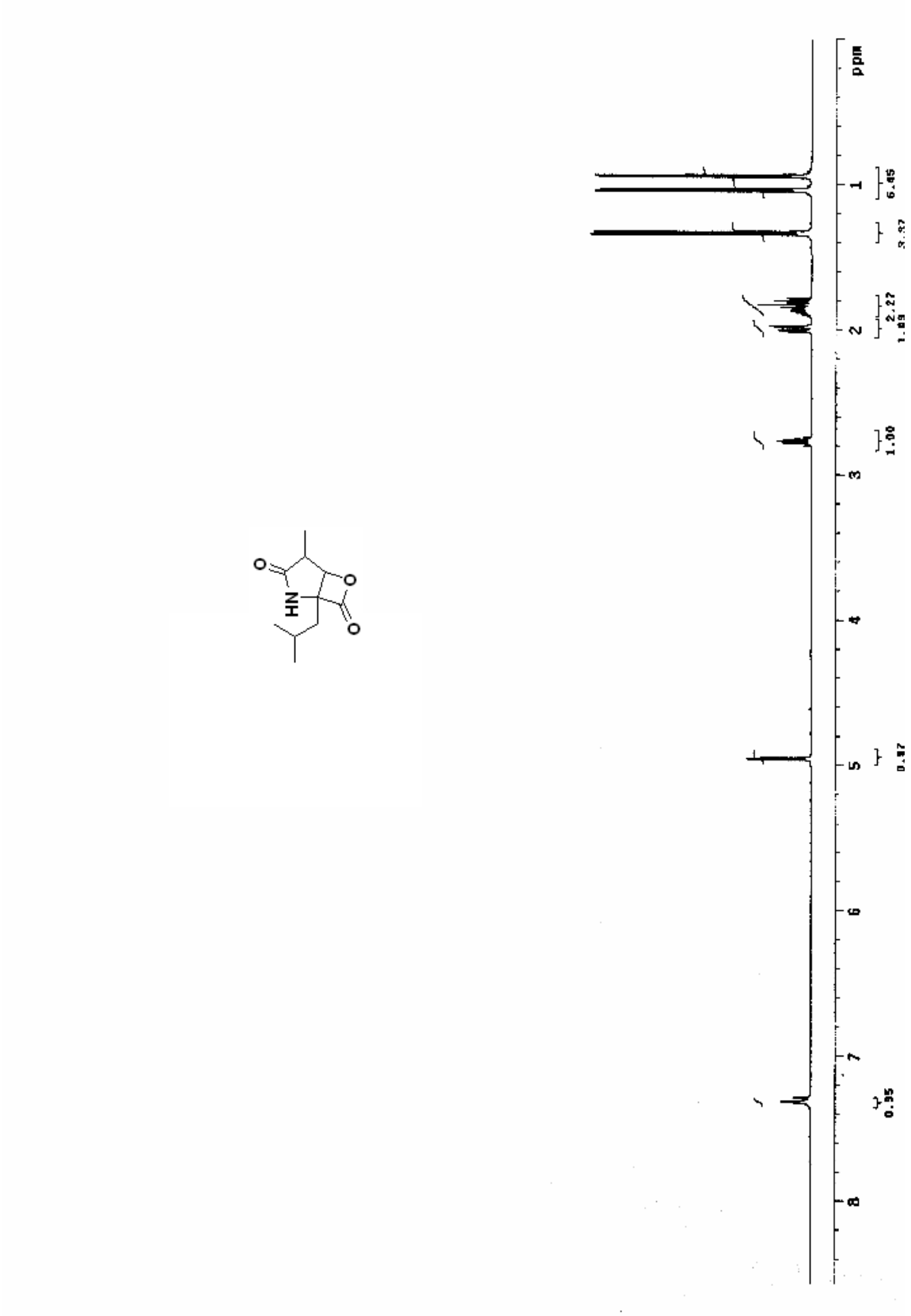
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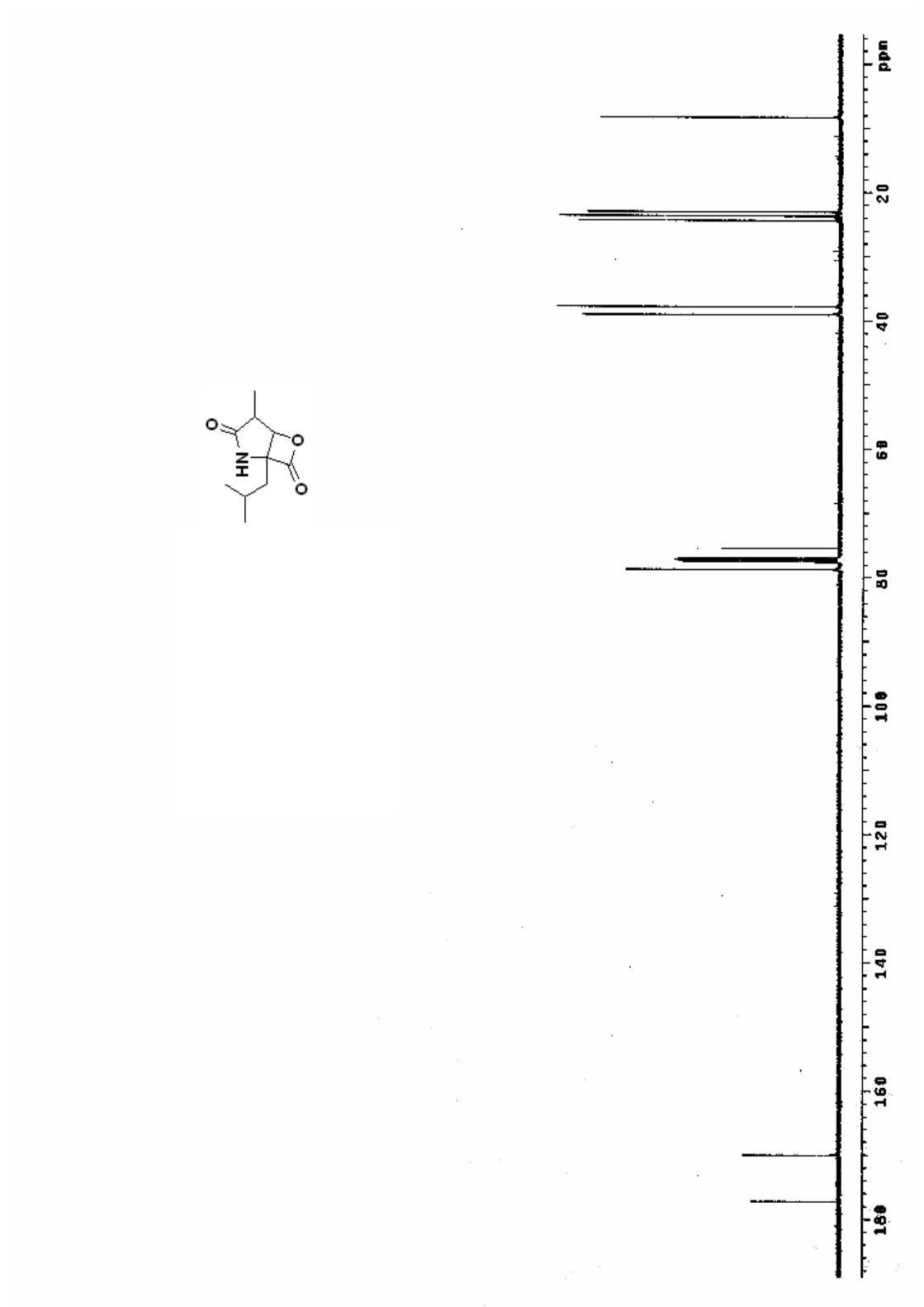
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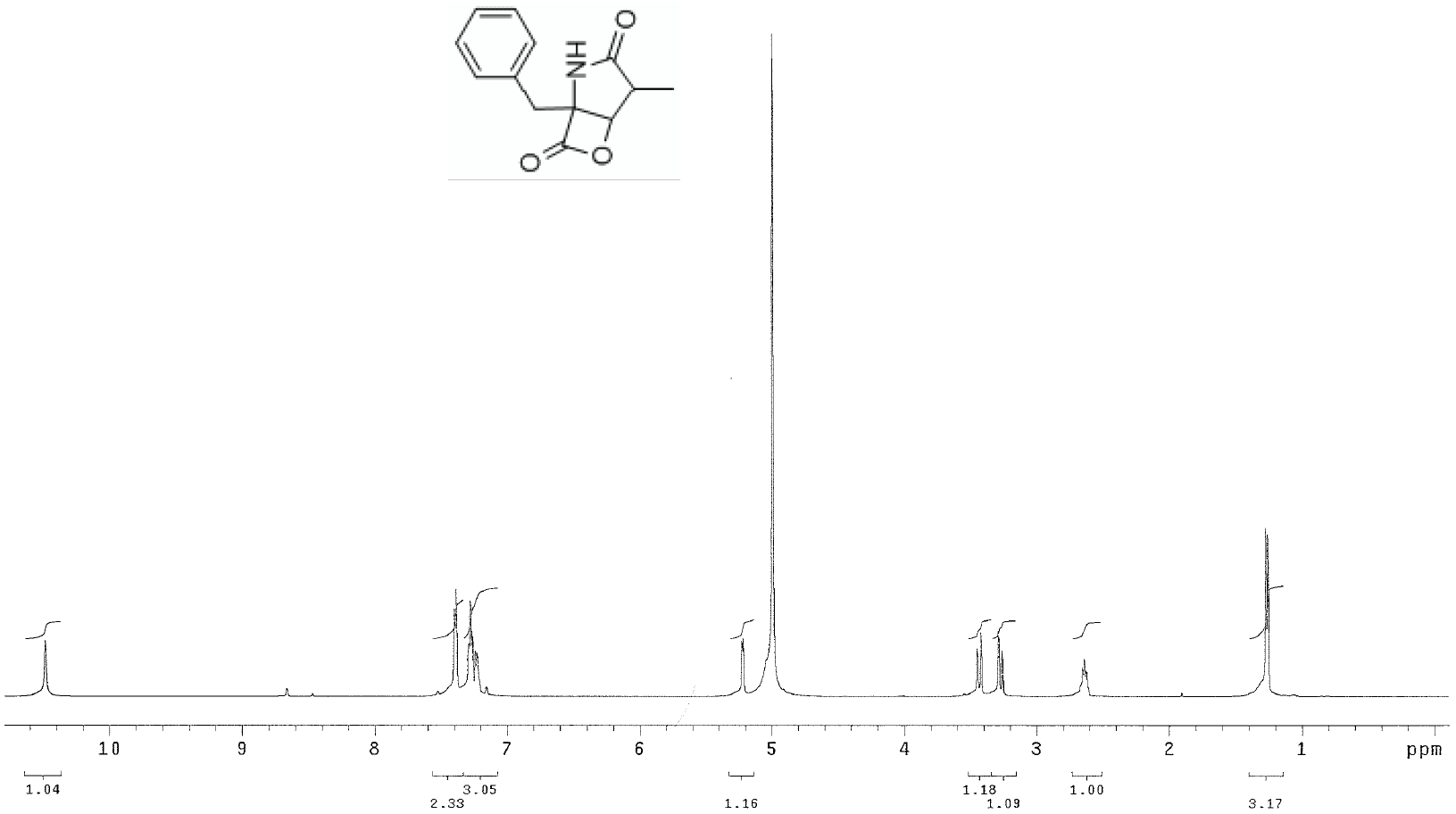
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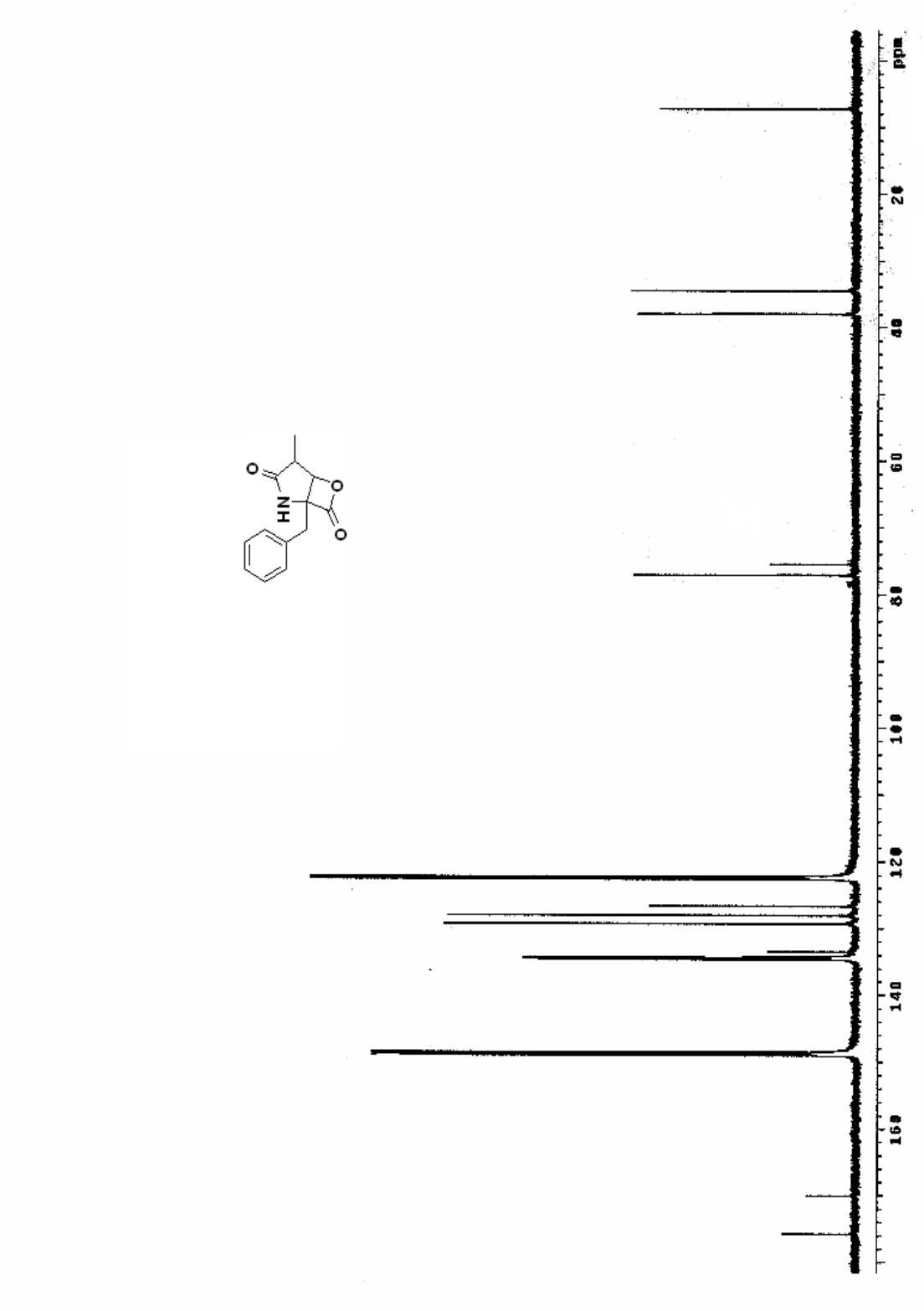
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