Synthesis of 6-Substituted-4-Hydroxy-2-Pyridinones via Intramolecular Ketene Trapping of Functionalized Enamine-Dioxinones

Supporting Information

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General Methods. All reactions were carried out in oven-dried glassware under N_2, using commercially supplied solvents and reagents unless otherwise stated. THF and PhMe were redistilled from Na-Ph_2CO and Na respectively. Hexanes refers petroleum spirit b.p. 40–60 °C. Column chromatography was carried out on silica gel, using flash techniques (eluants are given in parenthesis). Analytical thin layer chromatography was performed on pre-coated silica gel F_{254} aluminium plates with visualization under UV light or by staining using acidic vanillin spray reagent. Melting points were obtained using a melting point apparatus and are uncorrected. Infrared spectra were recorded neat unless otherwise stated. Indicative features of each spectrum are given with adsorptions reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 400 or 500 MHz with chemical shifts (δ) quoted in parts per million (ppm) and coupling constants (J) recorded in Hertz (Hz). ^{13}C NMR spectra were recorded at 101 or 126 MHz with chemical shifts (δ) quoted in ppm.

Experimental

General Procedure for the Synthesis of Acyl Imidazolides 7b–g. Carboxylic acid **6b**–**g** (4.0 mmol) in THF (8 mL) was cooled to 0 °C and carbonyl diimidazole (90%; 0.79 g, 4.4 mmol) was added portionwise over 5 min. After 1.5–2 h, the mixture was diluted with Et_2O (60 mL), H_2O (20 mL) added carefully and the layers separated. The organic layer was washed with H_2O (2 x 20 mL) and brine (25 mL), dried ($MgSO_4$) and rotary evaporated to give the acyl imidazolides **7b**–**g**, which was used in the next step without further purification.

1-Acetylimidazole (7a): commercially available.[1]

1-(3-Methylbutanoyl)-imidazole (7b): 90%; colorless oil; R_f 0.15 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.30 (s, 1H), 7.64 (br m, 1H), 7.03 (br m, 1H), 2.94 (d, J = 6.8 Hz, 2H), 2.26 (m, 1H), 1.03 (d, J = 6.4 Hz, 6H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 171.3, 138.4, 132.3, 118.0, 45.0, 26.9, 23.5 (2C).[2]

1-(2-Benzyloxyethanoyl)-imidazole (7c): 84%; white solid; R_f 0.12 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.31 (s, 1H), 7.64 (br m, 1H), 7.43–7.41 (m, 2H), 7.39–7.29 (m, 3H), 7.05 (br m, 1H), 4.89 (s, 2H), 4.73 (s, 2H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 169.2, 139.5, 138.3, 132.2, 130.2 (2C), 129.8 (2C), 129.7, 117.7, 75.0, 70.9; HRMS (ESI) calcd $C_{12}H_{12}N_2O_2$: $[M + H]^+$ 217.0977; found $[M + H]^+$ 217.0967.[3]

2-(*tert*-Butyl 2-oxoethyl(methyl)carbamoyl)-imidazole (7d): 90%; white solid; R_f 0.10 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.34 (s, 1H, rotamer 1 and 2), 7.67 (br m, 1H, rotamer 1 and 2), 7.07 (br m, 1H, rotamer 1 and 2), 4.79 (s, 1.5H, rotamer 1), 4.76 (s, 1.5H, rotamer 2), 3.01 (s, 1.5H, rotamer 1), 2.98 (s, 1.5H, rotamer 2), 1.47 (s, 4.5H, rotamer 1), 1.35 (s, 4.5H, rotamer 2); ^{13}C NMR (acetone-d_6, 101 MHz) δ 168.9 (rotamer 1), 168.7 (rotamer 2), 157.6 (rotamer

1), 156.8 (rotamer 2), 138.2, 132.5, 117.8, 81.4 (rotamer 1), 81.3 (rotamer 2), 53.8 (rotamer 1), 53.3 (rotamer 2), 36.9 (rotamer 1), 36.8 (rotamer 2), 29.4 (3C, rotamer 1), 29.2 (3C, rotamer 2).[4]

3-(*tert*-Butyl (1-carbonyl)piperidine-1-carboxylate)-imidazole (7e): 96%; colorless gum; R_f 0.06 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.37 (s, 1H), 7.68 (br m, 1H), 7.06 (br m, 1H), 4.35–4.04 (br m, 1H), 4.03–3.72 (br m, 1H), 3.51–2.87 (br m, 3H), 2.19–2.05 (br m, 1H), 1.95–1.77 (br m, 2H), 1.63–1.54 (br m, 1H), 1.41 (br s, 9H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 172.7, 138.4, 132.5, 118.0, 80.7, 48.3, 47.6, 46.5, 45.2, 43.1, 29.4 (3C), 25.7, 25.1 (contains rotamers); HRMS (ESI) calcd $C_{14}H_{21}N_3O_3$: $[M + H]^+$ 280.1661; found $[M + H]^+$ 280.1652.[5]

1-(4-Methoxybenzoyl)-imidazole (7f): 76%; off-white solid; R_f 0.10 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.12 (s, 1H), 7.87 (m, 2H), 7.61 (br m, 1H), 7.15 (m, 2H), 7.12 (br m, 1H), 3.94 (s, 3H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 167.2, 165.9, 139.9, 134.5, 134.3, 132.1, 125.9, 120.1, 116.2, 116.1, 57.1.[6]

1-(2-Furoyl)-imidazole (7g): 77%; off-white solid; R_f 0.07 (hexanes : EtOAc 1 : 1); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.53 (s, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.86 (br m, 1H), 7.66 (d, J = 4.0 Hz, 1H), 7.12 (br m, 1H), 6.85 (dd, J = 3.6, 1.6 Hz, 1H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 155.8, 150.6, 147.4, 139.5, 132.2, 124.4, 119.4, 114.9; HRMS (ESI) calcd $C_8H_6N_2O_2$: $[M + H]^+$ 163.0508; found $[M + H]^+$ 163.0501.[7]

General Procedure for the Synthesis of Functionalized Keto-dioxinones 4a–4g. *n*-BuLi in hexanes (2.5 M; 1.40 mL, 3.50 mmol) was added dropwise with stirring to hexamethyldisilazane (0.74 mL, 3.50 mmol) in THF (7 mL) at –78 °C. After 20 min, dioxinone **5** (0.36 g, 2.50 mmol) in THF (1 mL) was added dropwise. After 1 h, Et_2Zn in hexanes (1.0 M; 3.50 mL, 3.50 mmol) was added slowly, and after a further 20 min, the mixture was allowed to warm up to –20 °C. Imidazole **7a–g** (3.00 mmol) in THF (1.5 mL) was added and the reaction mixture immediately warmed to –10 °C. After 2.5–3 h, the reaction was quenched with 1 M aqueous HCl (20 mL), and the aqueous layer acidified to pH 1–2 using 1 M aqueous HCl. The product was extracted twice with EtOAc (2 x 50 mL) and the combined organic extracts dried ($MgSO_4$), rotary evaporated and chromatographed (hexanes : Et_2O 3 : 1 to 2 : 1 to 1 : 2) to give keto-dioxinones **4a–g**.

2,2-Dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one (4a): pale yellow solid; R_f 0.20 (hexanes : Et_2O 1 : 1); mp 48–51 °C (hexanes : Et_2O 2 : 1); IR 1726, 1636, 1374, 1275, 1206, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.29 (s, 1H), 3.31 (s, 2H), 2.19 (s, 3H), 1.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.8, 164.3, 160.5, 107.0, 96.5, 47.7, 30.0, 24.8 (2C); HRMS (CI) calcd $C_9H_{12}O_4$: $[M + H]^+$ 185.0814; found: $[M + H]^+$ 185.0812. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; Found: C, 58.75; H, 6.62.[8]

2,2-Dimethyl-6-(4-methyl-2-oxopentyl)-4*H*-1,3-dioxin-4-one (4b): 73%; yellow oil; R_f 0.55 (hexanes : Et_2O 1 : 1); IR 2959, 1719, 1635, 1372, 1271, 1201, 1013, 810 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 5.39 (s, 1H), 3.54 (s, 2H), 2.48 (d, J = 6.8 Hz, 2H), 2.14 (m, 1H), 1.69 (s, 6H), 0.93 (d, J = 6.8 Hz, 6H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 204.8, 167.3, 161.6, 108.4, 98.1, 53.1, 48.7, 26.1 (2C), 25.9, 23.6 (2C); HRMS (ESI) calcd $C_{12}H_{18}O_4$: $[M + H]^+$ 227.1283; found $[M + H]^+$ 227.1276.[9]

6-(3-(Benzyloxy)-2-oxopropyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4c): 63%; yellow oil; R_f 0.30 (hexanes : Et_2O 1 : 1); IR 1725, 1636, 1376, 1272, 1203, 1098, 1016 cm^{-1}; ^1H NMR (acetone-d_6, 400

MHz) δ 7.42–7.29 (m, 5H), 5.39 (s, 1H), 4.62 (s, 2H), 4.25 (s, 2H), 3.62 (s, 2H), 1.66 (s, 6H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 203.7, 166.9, 161.5, 139.8, 130.2 (2C), 129.6 (2C), 129.6, 108.5, 98.4, 76.7, 74.8, 45.0, 26.1 (2C); HRMS (ESI) calcd $C_{16}H_{18}O_5$: $[M + H]^+$ 291.1232; found $[M + H]^+$ 291.1230.[10]

***tert*-Butyl 3-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-oxopropyl(methyl)carbamate (4d)**: 58%; white solid; R_f 0.36 (hexanes : Et_2O 1 : 1); mp 58–60 °C (hexanes : Et_2O 1 : 1); IR 1726, 1694, 1637, 1453, 1373, 1270, 1245, 1201, 1156, 1014, 895 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 5.41 (s, 0.45H, rotamer 1), 5.39 (s, 0.55H, rotamer 2), 4.19 (br s, 2H, rotamer 1 and 2), 3.55 (2s, 2H, rotamer 1 and 2), 2.87 (s, 1.65H, rotamer 2), 2.84 (s, 1.35H, rotamer 1), 1.68 (2s, 6H, rotamer 1 and 2), 1.44 (s, 4.05H, rotamer 1), 1.39 (s, 4.95H, rotamer 2); ^{13}C NMR (acetone-d_6, 101 MHz) δ 201.8, 166.7, 108.5, 98.3, 98.2, 81.0, 80.9, 60.2, 59.6, 45.5, 45.4, 36.8, 36.7, 29.4 (3C, rotamer 1), 29.4 (3C, rotamer 2), 26.2 (2C) (contains rotamers); HRMS (ESI) calcd $C_{15}H_{23}NO_6$: $[M + Na]^+$ 336.1423; found $[M + H]^+$ 336.1423. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47; Found: C, 57.39; H, 7.30; N, 4.39.

***tert*-Butyl 3-(2-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetyl)piperidine-1-carboxylate (4e)**: 73%; pale yellow gum; R_f 0.34 (hexanes : Et_2O 1 : 1); IR 1727, 1689, 1637, 1420, 1370, 1268, 1148, 1014 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 5.38 (s, 1H), 4.01 (br dd, J = 13.6, 4.0 Hz, 1H), 3.79 (br d, J = 12.8 Hz, 1H), 3.67 (br s, 2H), 3.06 (br t, J = 10.2 Hz, 1H), 2.89–2.82 (br m, 1H), 2.72–2.65 (br m, 1H), 2.05–2.02 (br m, 1H), 1.75–1.69 (br m, 1H), 1.67 (s, 6H), 1.63–1.54 (br m, 1H), 1.48–1.40 (br m, 1H), 1.43 (br s, 9H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 206.4, 167.3, 161.5, 108.5, 98.3, 80.7, 50.1, 46.8, 46.7, 29.5 (3C), 28.2, 26.2 (2C), 26.1 (2C), 25.9; HRMS (ESI) calcd $C_{18}H_{27}NO_6$: $[M + Na]^+$ 376.1736; found $[M + Na]^+$ 376.1731.

6-(2-(4-Methoxyphenyl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4f): 67%; pale yellow solid; R_f 0.26 (hexanes : Et_2O 1 : 1); mp 77–78 °C (hexanes : Et_2O 1 : 1); IR 1721, 1680, 1634, 1597, 1375, 1256, 1205, 1170, 1016, 836, 810 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 8.03–7.99 (m, 2H), 7.08–7.05 (m, 2H), 5.47 (s, 1H), 4.08 (s, 2H), 3.91 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 193.6, 168.2, 166.0, 161.6, 132.5 (2C), 131.2, 115.8 (2C), 108.5, 98.4, 57.0, 44.6, 26.1 (2C); HRMS (ESI) calcd $C_{15}H_{16}O_5$: $[M + H]^+$ 277.1076; found $[M + H]^+$ 277.1074. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84; Found: C, 65.21; H, 5.91.

6-(2-(Furan-2-yl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4g): 65%; pale orange solid; R_f 0.28 (hexanes : Et_2O 1 : 1); mp 64–65 °C (hexanes : Et_2O 1 : 1); IR 1720, 1677, 1634, 1464, 1376, 1271, 1250, 1200, 1014, 903, 769 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 7.90 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 4.0 Hz, 1H), 6.72 (dd, J = 3.6, 1.6 Hz, 1H), 5.49 (s, 1H), 3.95 (s, 2H), 1.65 (s, 6H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 183.3, 167.0, 161.5, 153.7, 149.7, 120.5, 114.5, 108.6, 98.6, 44.5, 26.1 (2C); HRMS (ESI) calcd $C_{12}H_{12}O_5$: $[M + H]^+$ 237.0763; found $[M + H]^+$ 237.0755. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12; Found: C, 61.10; H, 5.22.[9]

***tert*-Butyl 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (4h)**: off-white solid; R_f 0.20 (hexanes : Et_2O 1 : 1); mp 43–45 °C (hexanes : Et_2O 1 : 1); IR 1732, 1717, 1635, 1373, 1336, 1267, 1204, 1165, 1130, 1054, 1013, 850 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 5.40 (s, 1H), 3.68 (s, 2H), 3.55 (s, 2H), 1.68 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (acetone-d_6, 101 MHz) δ 198.8, 167.7, 166.5, 161.5, 108.5, 98.5, 83.1, 51.9, 48.4, 29.1 (3C), 26.1 (2C); HRMS (ESI) calcd $C_{14}H_{20}O_6$: $[M - {}^tBu + H]^+$ 229.0712; found $[M - {}^tBu + H]^+$ 229.0705. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09; Found: C, 59.11; H, 7.14.[11,12]

General Procedure for the Synthesis of 6-Substituted-4-Hydroxy-2-Pyridinones 1a–h. Keto-dioxinone **4a–h** (0.60 mmol) and NH_4OAc (0.23 g, 3.00 mmol) were stirred in absolute EtOH (2.5 mL). After 2–3 h, the solvent was evaporated and EtOAc (10 mL) added. The resultant solid was filtered and the solvent evaporated to provide crude enamine-dioxinone **3a–h**, which in PhMe (5 mL), was added using a syringe pump to PhMe (50 mL) at reflux, over 30 min. After 4 h, the solvent was evaporated and the residue triturated with Et_2O (25 mL) to provide the desired pyridinone product **1a–h**.

4-Hydroxy-6-methylpyridin-2(1*H*)-one (1a): 91%: yellow/orange solid; mp 260 °C (dec.) (MeOH : acetone 1 : 1); IR 1596, 1531, 1443, 1349, 1255, 1230, 1170, 828 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.90 (s, 1H), 10.30 (s, 1H), 5.58 (d, J = 1.2 Hz, 1H), 5.32 (d, J = 2.4 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 167.4, 164.5, 145.8, 97.9, 95.6, 18.3; HRMS (ESI) calcd $C_6H_7NO_2$: $[M + H]^+$ 126.0555; found $[M + H]^+$ 126.0535.[13]

4-Hydroxy-6-iso-butylpyridin-2(1*H*)-one (1b): 92%: yellow/orange solid; mp 252 °C (dec.) (MeOH : acetone 1 : 1); IR 1593, 1535, 1431, 1392, 1359, 1258, 1229, 1166, 837 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.90 (s, 1H), 10.39 (s, 1H), 5.57 (d, J = 2.4 Hz, 1H), 5.35 (d, J = 2.0 Hz, 1H), 2.21 (d, J = 7.2 Hz, 2H), 1.88 (m, 1H), 0.84 (d, J = 6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.4, 164.7, 148.9, 98.2, 96.0, 41.0, 27.5, 21.8 (2C); HRMS (ESI) calcd $C_9H_{13}NO_2$: $[M + H]^+$ 168.1025; found $[M + H]^+$ 168.1021.

6-(Benzyloxymethyl)-4-hydroxypyridin-2(1*H*)-one (1c): 89%: pale brown solid; mp 155–157 °C (MeOH : acetone 1 : 1); IR 1631, 1603, 1449, 1359, 1246, 1161, 1101, 832 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.03 (s, 1H), 10.54 (s, 1H), 7.39-7.30 (m, 5H), 5.87 (d, J = 2.4 Hz, 1H), 5.44 (d, J = 2.0 Hz, 1H), 4.53 (s, 2H), 4.27 (s, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.2, 164.4, 146.1, 137.8, 128.2 (2C), 127.5 (3C), 97.4, 97.2, 71.8, 67.4; HRMS (ESI) calcd $C_{13}H_{13}NO_3$: $[M + H]^+$

232.0974; found $[M + H]^+$ 232.0963. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; Found: C, 67.36; H, 5.56; N, 5.95.

***tert*-Butyl (4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)methyl(methyl)carbamate (1d)**: 93%: off-white solid; mp 159–161 °C (MeOH : acetone 1 : 1); IR 1603, 1442, 1389, 1365, 1236, 1144, 832 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 10.22 (br s, 2H), 5.62 (d, J = 2.0 Hz, 1H), 5.44 (d, J = 2.0 Hz, 1H), 4.14 (s, 2H), 2.85 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 166.9, 163.8, 154.5, 146.1, 96.2, 96.0, 78.8, 48.7, 34.1, 27.5 (3C); HRMS (ESI) calcd $C_{12}H_{18}N_2O_4$: $[M + H]^+$ 255.1345; found $[M + H]^+$ 255.1337. Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02; Found: C, 56.59; H, 7.07; N, 10.94.

***tert*-Butyl 3-(4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate (1e)**: 92%: off-white solid; mp 190–192 °C (MeOH : acetone 1 : 1); IR 1701, 1658, 1623, 1583, 1418, 1364, 1164, 1136, 834 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 10.20 (br s, 2H), 5.66 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 2.0 Hz, 1H), 3.97–3.90 (m, 1H), 3.89–3.83 (m, 1H), 2.97–2.93 (br m, 2H), 2.86–2.80 (br m, 1H), 2.55–2.50 (br m, 1H), 1.93–1.90 (br m, 1H), 1.70–1.66 (br m, 1H), 1.64–1.60 (br m, 1H), 1.43 (br s, 9H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 166.8, 164.0, 153.4, 150.7, 96.1, 95.9, 78.2, 46.9, 43.0, 38.7, 28.6, 27.5 (3C), 23.6; HRMS (ESI) calcd $C_{15}H_{22}N_2O_4$: $[M + H]^+$ 295.1658; found $[M + H]^+$ 295.1655. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52; Found: C, 61.13; H, 7.62; N, 9.58.

4-Hydroxy-6-(4-methoxyphenyl)pyridin-2(1*H*)-one (1f): 90%: pale yellow solid; mp 275 °C (dec.) (MeOH : acetone 1 : 1); IR 1607, 1574, 1510, 1369, 1327, 1246, 1210, 1177, 1028, 820 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.14 (br s, 1H), 10.55 (br s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.05 (d, J = 2.0 Hz, 1H), 5.51 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.3, 164.8, 160.4, 146.9, 128.0 (2C), 125.7, 114.1 (2C), 96.9, 96.5, 55.2; HRMS (ESI)

calcd $C_{12}H_{11}NO_3$: $[M + H]^+$ 218.0817; found $[M + H]^+$ 218.0813. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45; Found: C, 66.24; H, 5.03; N, 6.48.[14]

6-(Furan-2-yl)-4-hydroxypyridin-2(1*H*)-one (1g): 90%: pale brown solid; mp 240 °C (dec.) (MeOH : acetone 1 : 1); IR 1597, 1571, 1485, 1446, 1370, 1288, 1217, 1019, 834, 737 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.24 (br s, 1H), 10.70 (br s, 1H), 7.83 (br m, 1H), 7.33 (br d, J = 3.2 Hz, 1H), 6.64 (br d, J = 1.6 Hz, 1H), 6.20 (br d, J = 1.6 Hz, 1H), 5.50 (br d, J = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.1, 164.4, 146.7, 144.7, 137.6, 112.2, 110.1, 97.3, 94.8; HRMS (ESI) calcd $C_9H_7NO_3$: $[M + H]^+$ 178.0504; found $[M + H]^+$ 178.0501. Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91; Found: C, 61.12; H, 4.02; N, 7.85.

***tert*-Butyl 2-(4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)acetate (1h)**: 84%: off-white solid; mp 278 °C (dec.) (MeOH : acetone 1 : 1); IR 1730, 1634, 1602, 1441, 1365, 1332, 1267, 1218, 1148, 850 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.98 (br s, 1H), 10.46 (br s, 1H), 5.71 (d, J = 2.4 Hz, 1H), 5.40 (d, J = 2.4 Hz, 1H), 3.41 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 168.0, 167.2, 164.4, 142.5, 99.6, 96.8, 80.7, 38.5, 27.6 (3C); HRMS (ESI) calcd $C_{11}H_{15}NO_4$: $[M + H]^+$ 226.1079; found $[M + H]^+$ 226.1069.

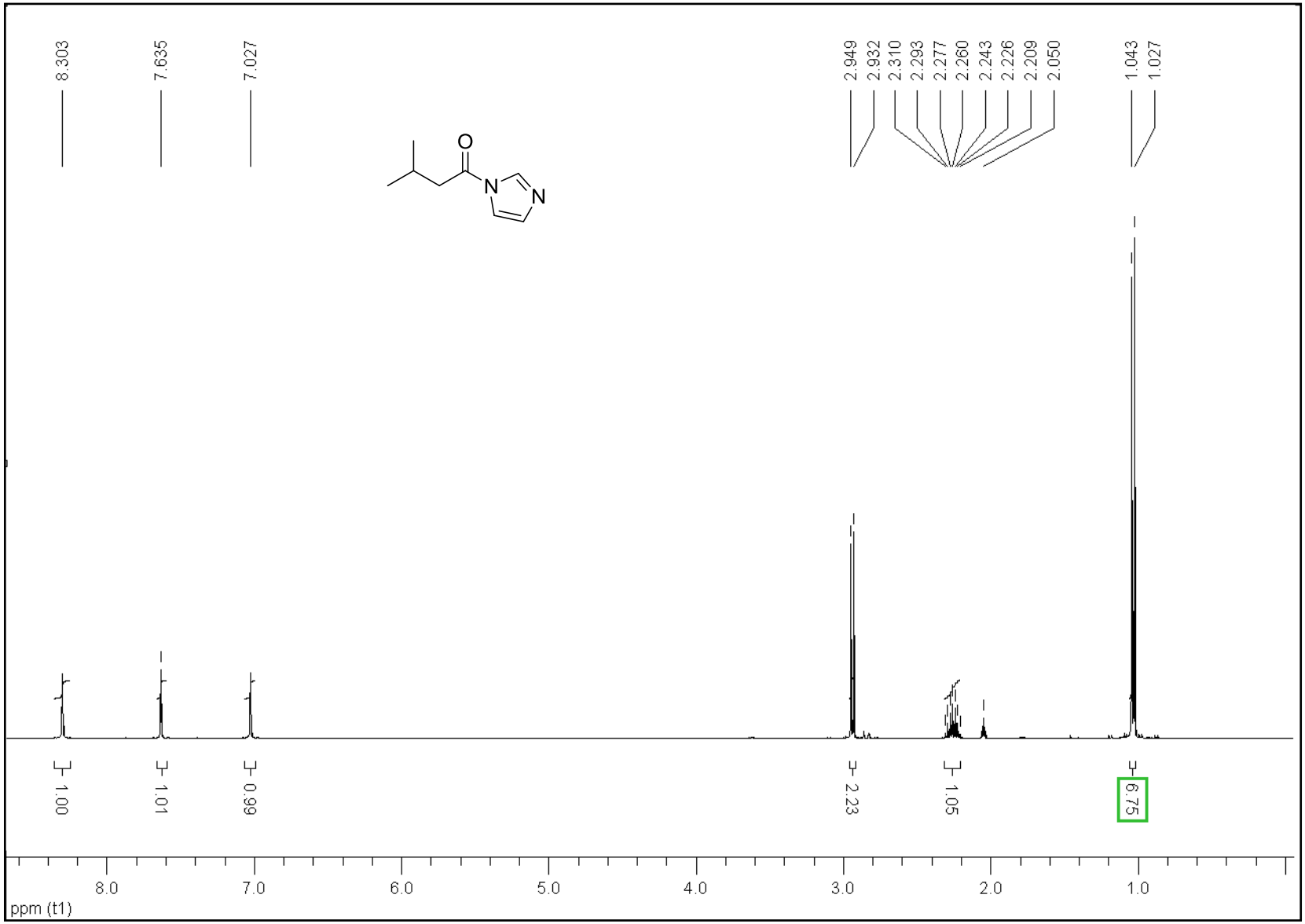
1-Benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (8). Keto-dioxinone **4a** (129 mg, 0.70 mmol), benzylamine (0.076 mL, 0.70 mmol) and molecular sieves 4Å (70 mg) were stirred in CH_2Cl_2 (2.5 mL). After 3 h, the solid was filtered and the solvent evaporated to provide the crude enamine-dioxinone (verified by ^1H NMR spectroscopy), which in PhMe (5 mL) and EtOAc (5 mL), was added using a syringe pump to PhMe (45 mL) at reflux, over 30 min. After 4 h, the solvent was evaporated and the residue triturated with Et_2O (25 mL) to provide the desired pyridinone product **8** (112 mg, 75%) as a pale yellow solid: mp 205–208 °C (MeOH : acetone 1 : 1); IR 1614, 1524, 1510, 1494, 1452, 1426, 1316, 1291, 1231, 1210, 1156, 832 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.53

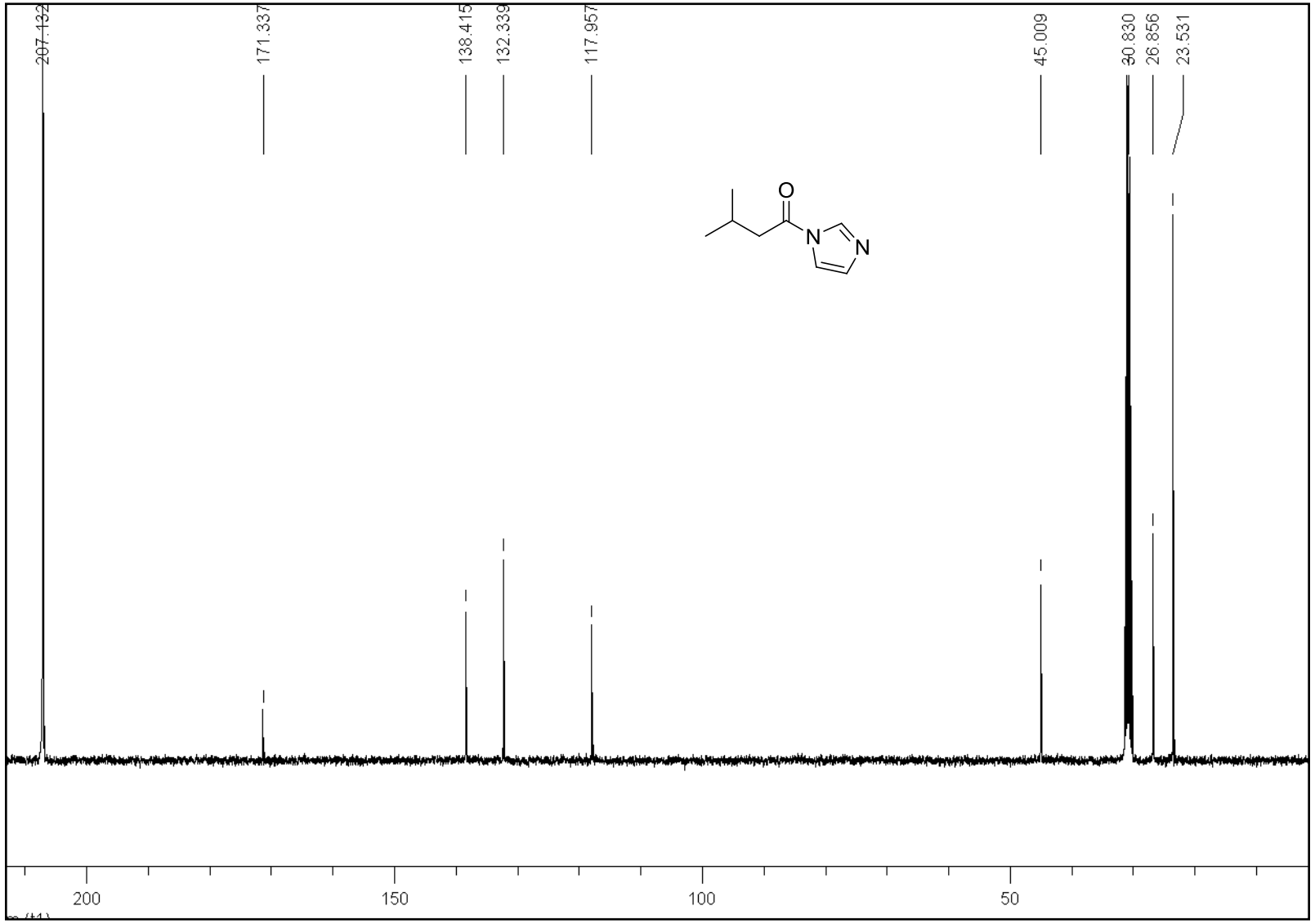
(br s, 1H), 7.32 (m ,2H), 7.23 (m, 1H), 7.08 (m, 2H), 5.80 (d, *J* = 2.0 Hz, 1H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.19 (s, 2H), 2.16 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 165.8, 164.0, 147.5, 137.7, 128.5 (2C), 126.8, 126.0 (2C), 100.4, 95.8, 45.2, 19.8; HRMS (ESI) calcd $C_{13}H_{13}NO_2$: $[M + H]^+$ 216.1025; found $[M + H]^+$ 216.1030.[15]

***N*-Benzyl-5-(benzylamino)3-oxohex-4-enamide (9)**: pale yellow solid; mp 106–108 °C (MeOH : acetone 1 : 1); IR 3306, 1639, 1604, 1567, 1536, 1515, 1495, 1450, 1314, 1249, 1067, 1028, 950, 805 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.93 (br t, *J* = 6.0 Hz, 1H), 8.44 (br t, *J* = 5.6 Hz, 1H), 7.41–7.23 (m, 5H), 5.07 (s, 1H), 4.53 (d, *J* = 6.0 Hz, 2H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.11 (s, 2H), 1.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 189.4, 167.4, 163.9, 139.4, 138.3, 128.6 (2C), 128.1 (2C), 127.2, 127.1 (2C), 127.0 (2C), 126.6, 94.6, 49.4, 45.9, 42.0, 18.6; HRMS (ESI) calcd $C_{20}H_{22}N_2O_2$: $[M + H]^+$ 323.1760; found $[M + H]^+$ 323.1763.

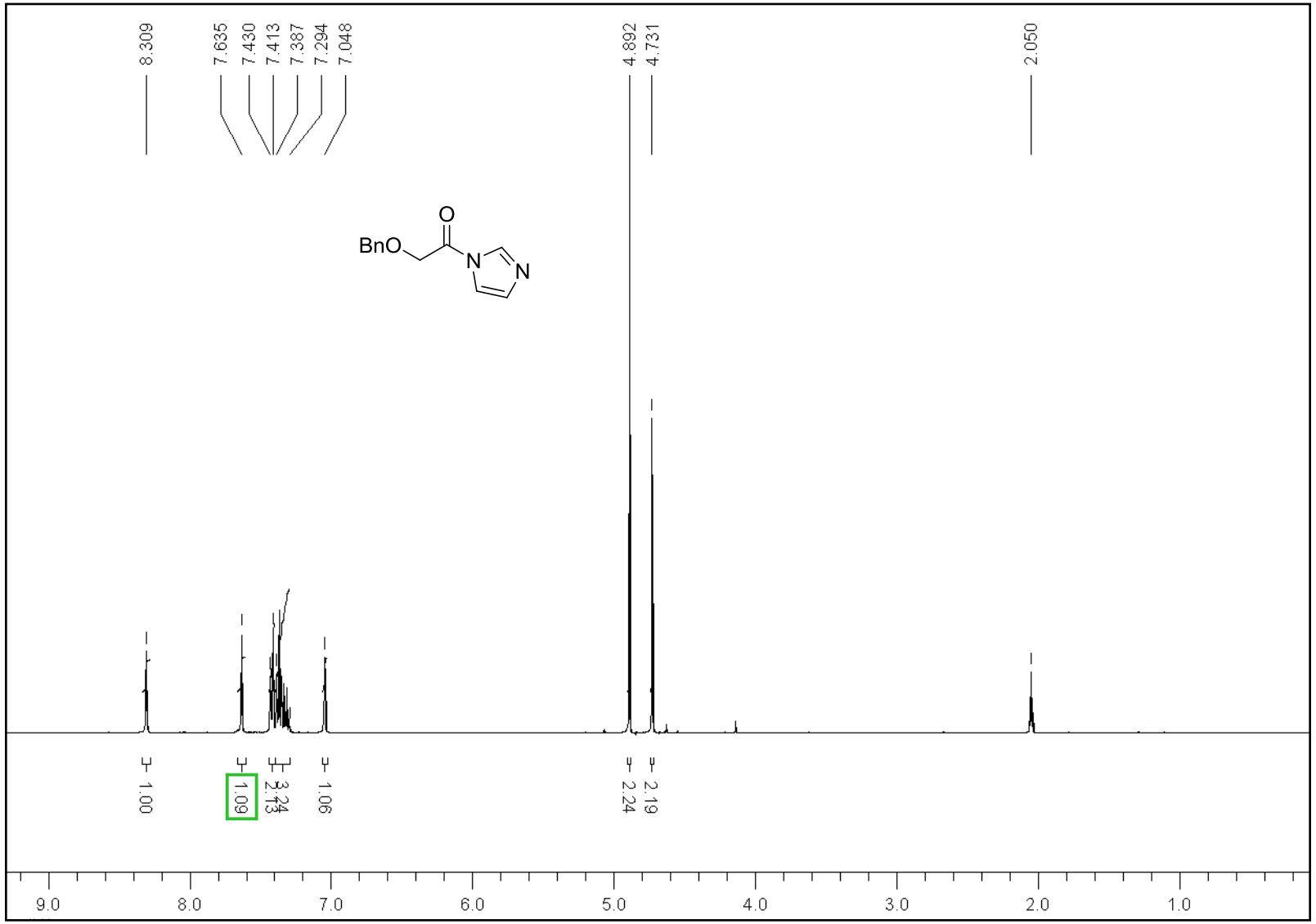
^{1}H and ^{13}C spectra

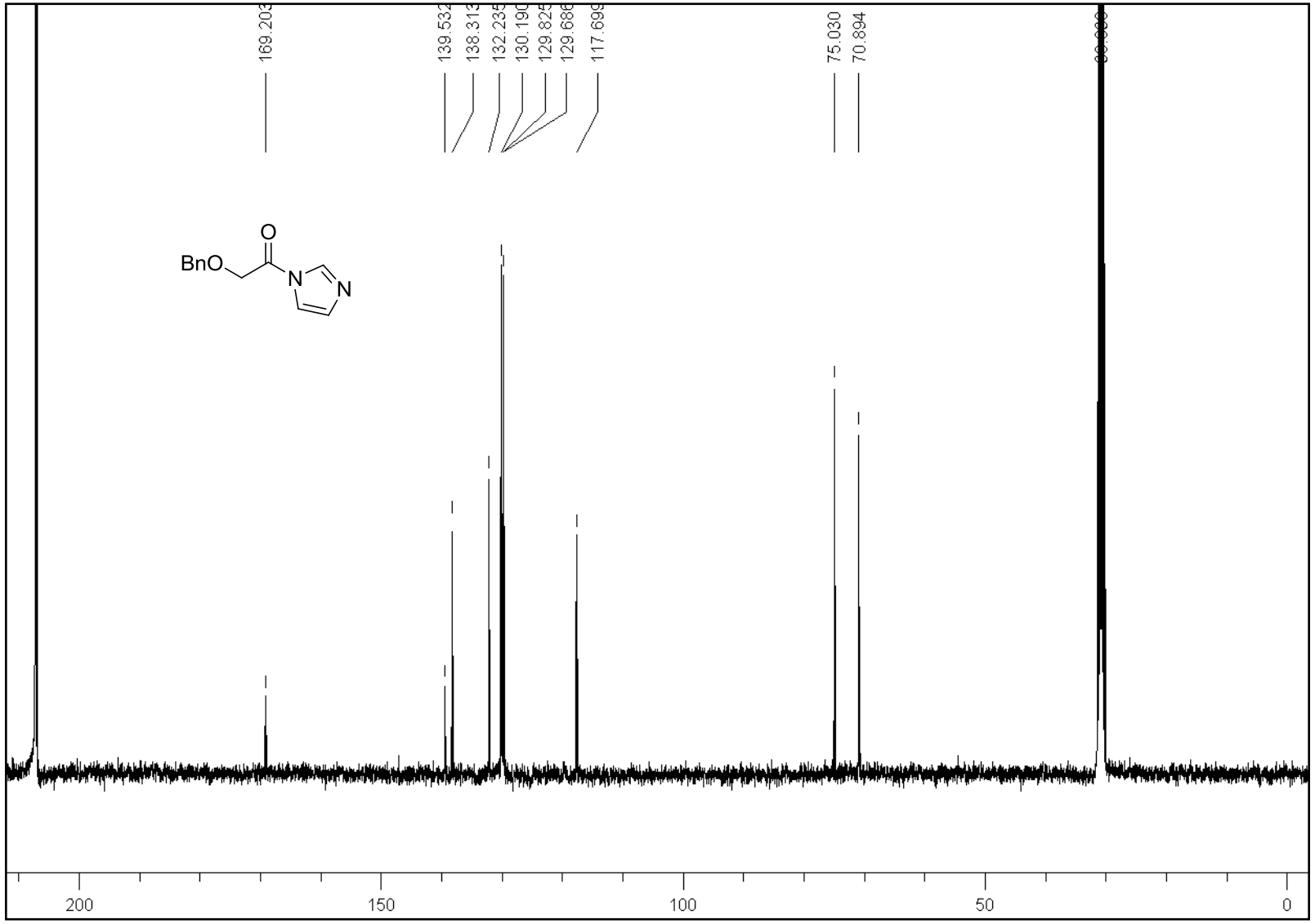
1-(3-Methylbutanoyl)-imidazole (7b)



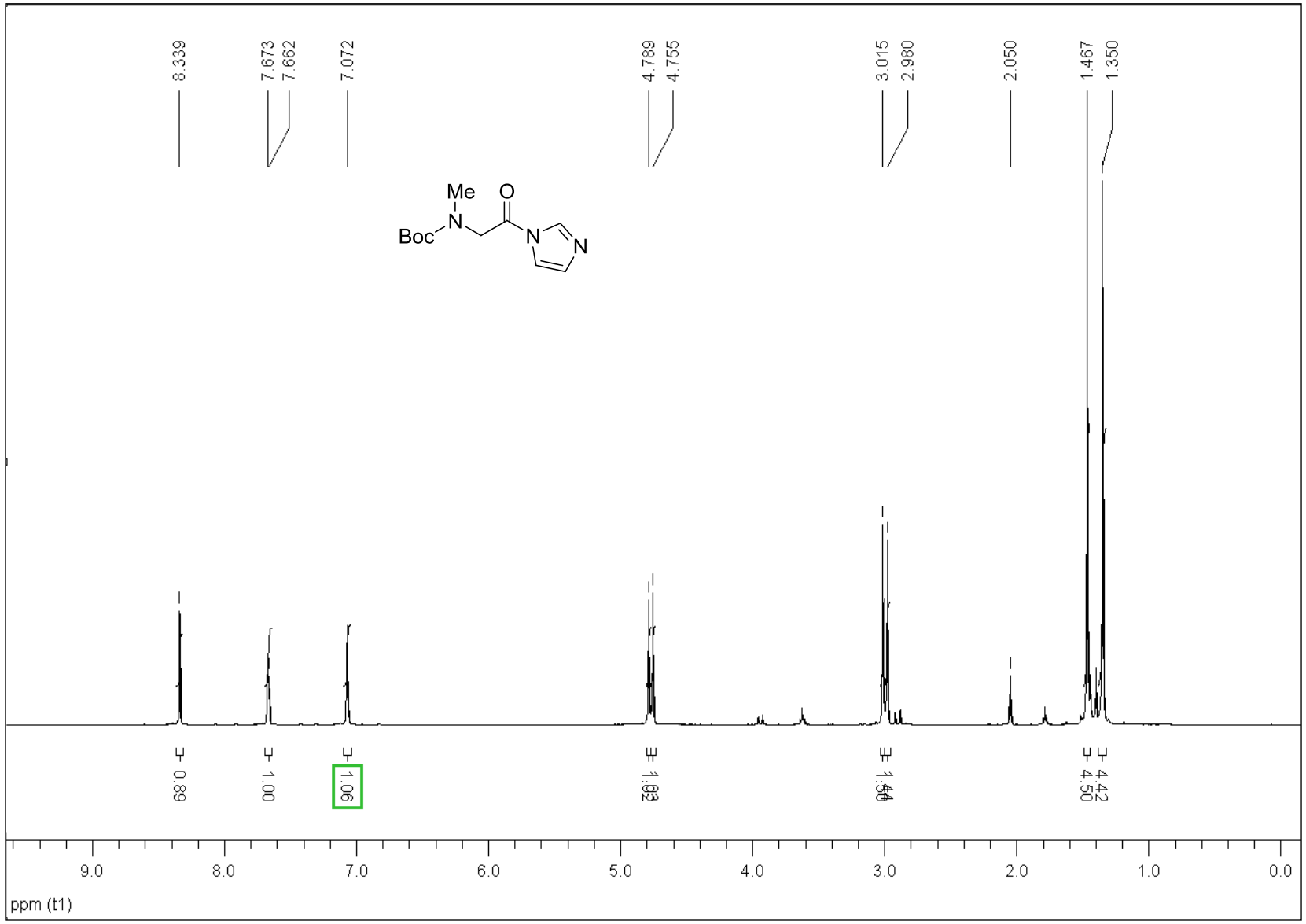

207.132
171.337
138.415
132.339
117.957
45.009
30.830
26.856
23.531
O
N
N
200
150
100
50

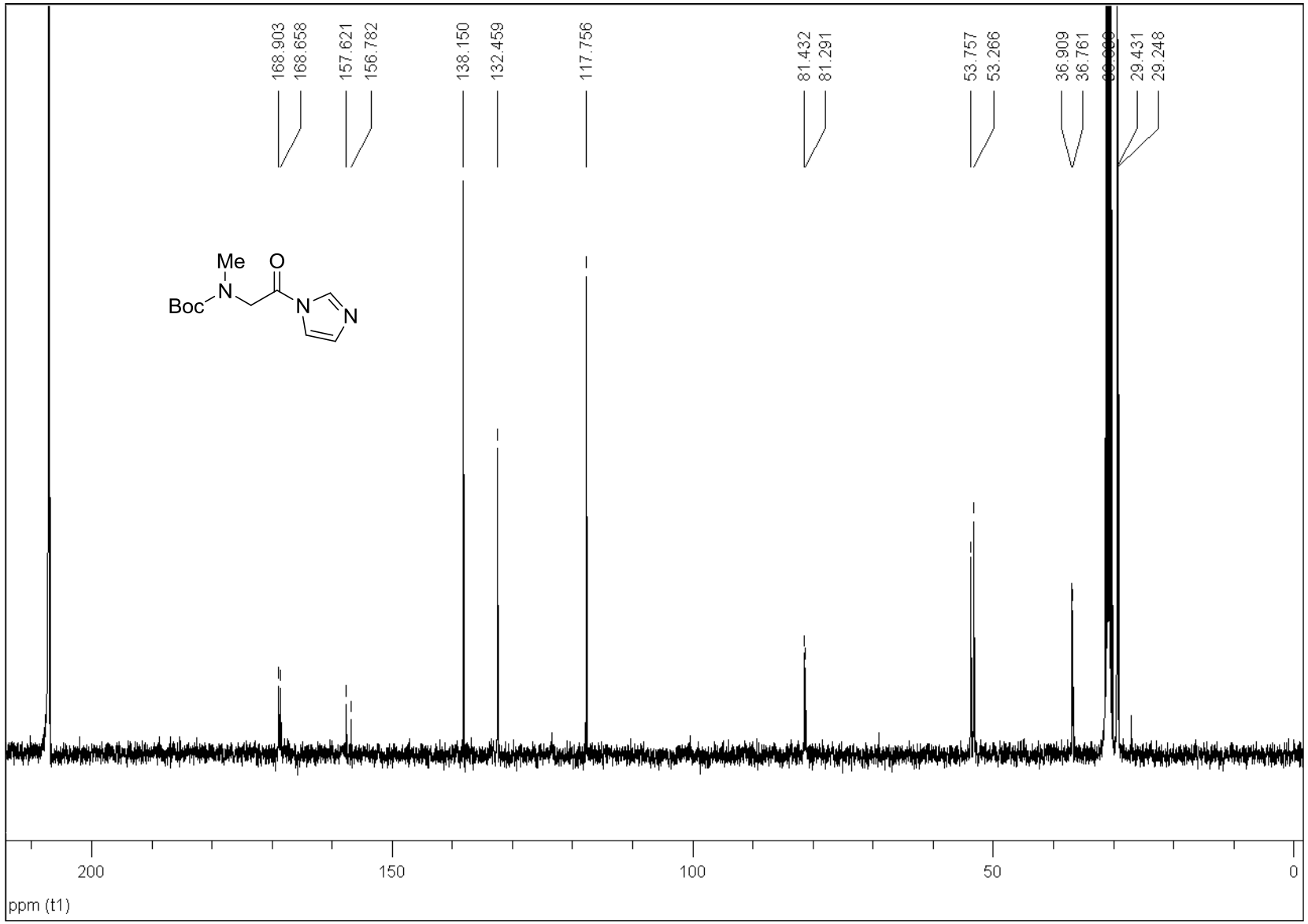
1-(2-Benzyloxyethanoyl)-imidazole (7c)



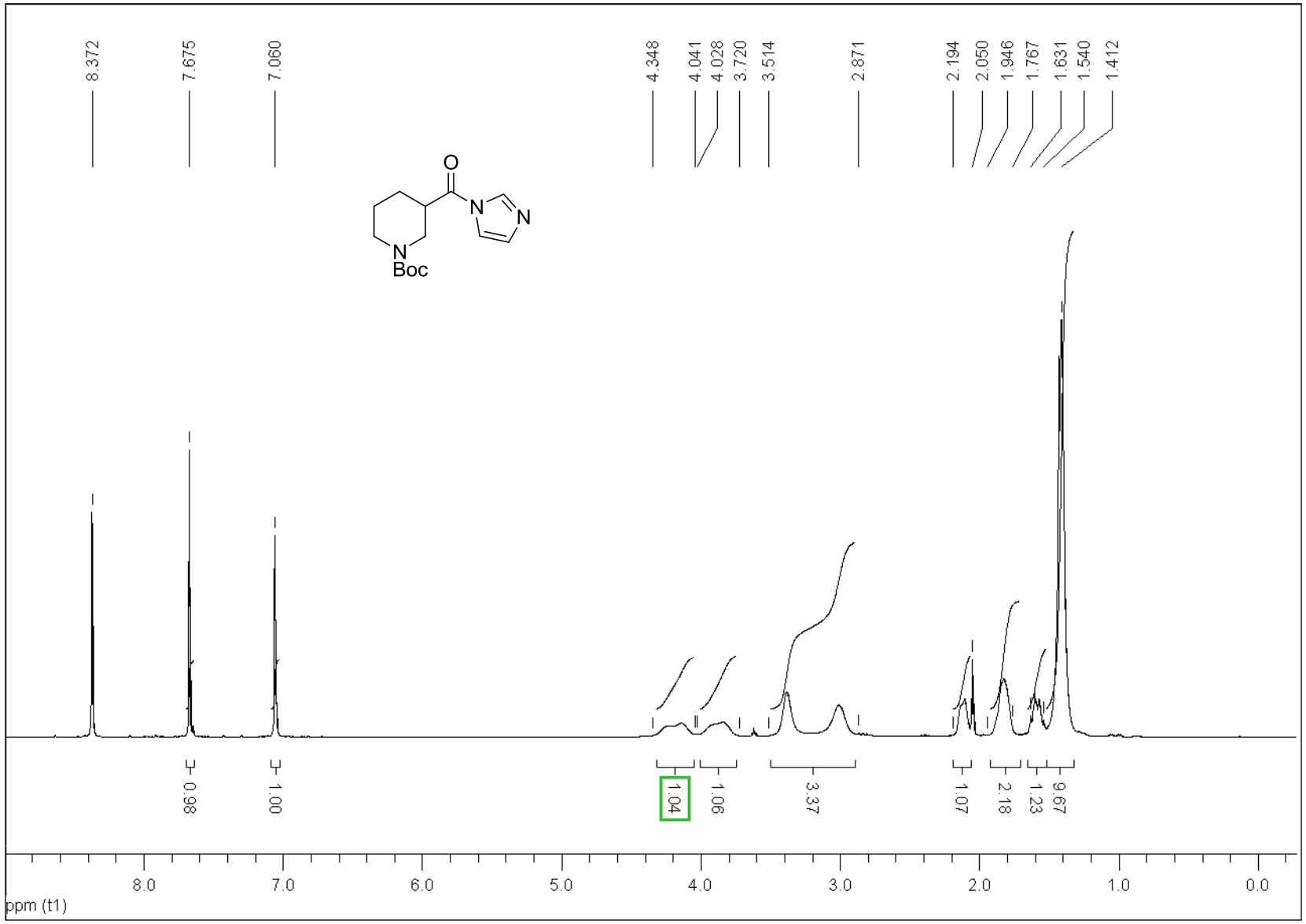

169.203
139.532
138.313
132.235
130.190
129.825
129.686
117.699
75.030
70.894
O
BnO
N
N
200
150
100
50
0

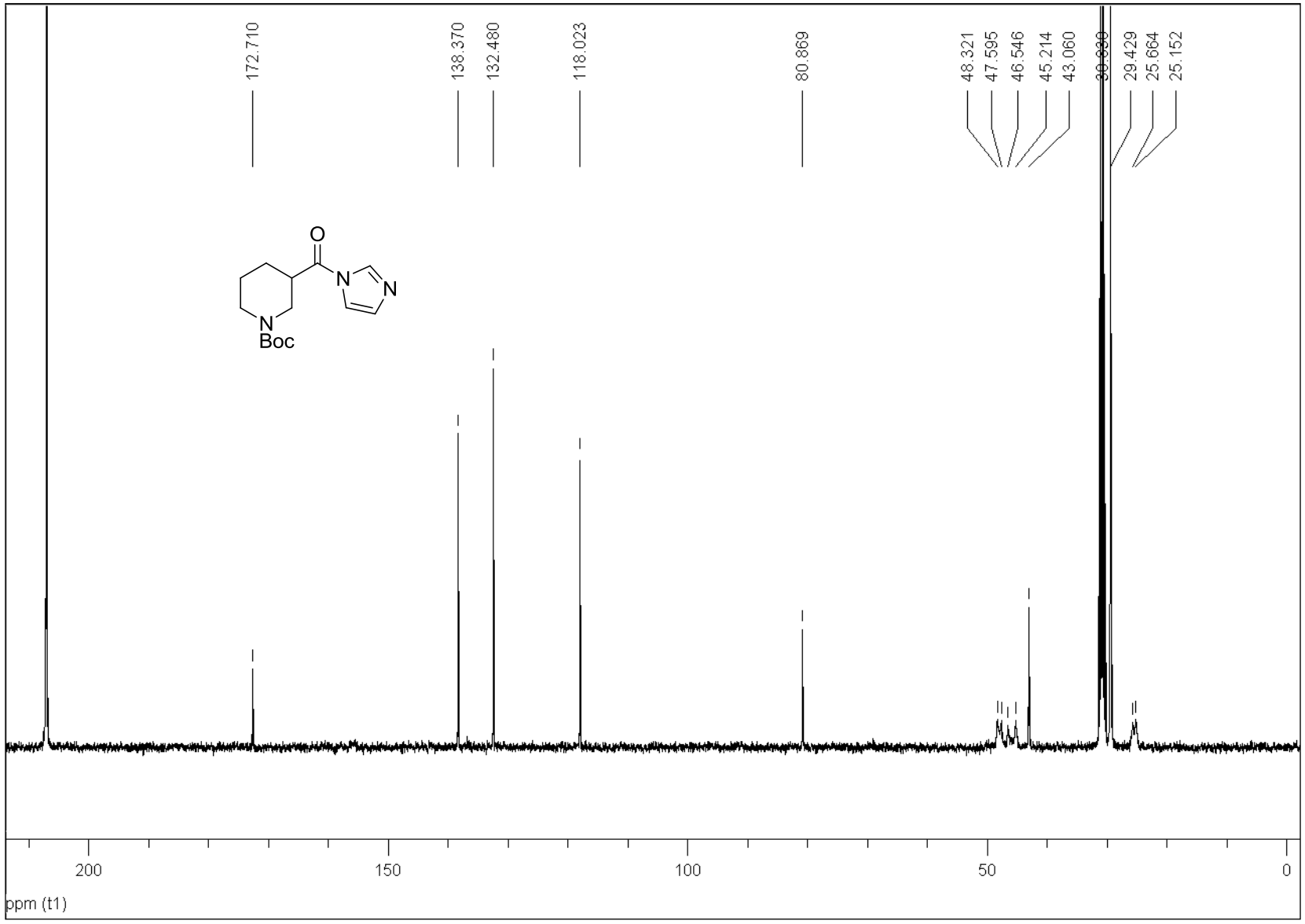
2-(*tert*-Butyl 2-oxoethyl(methyl)carbamoyl)-imidazole (7d)



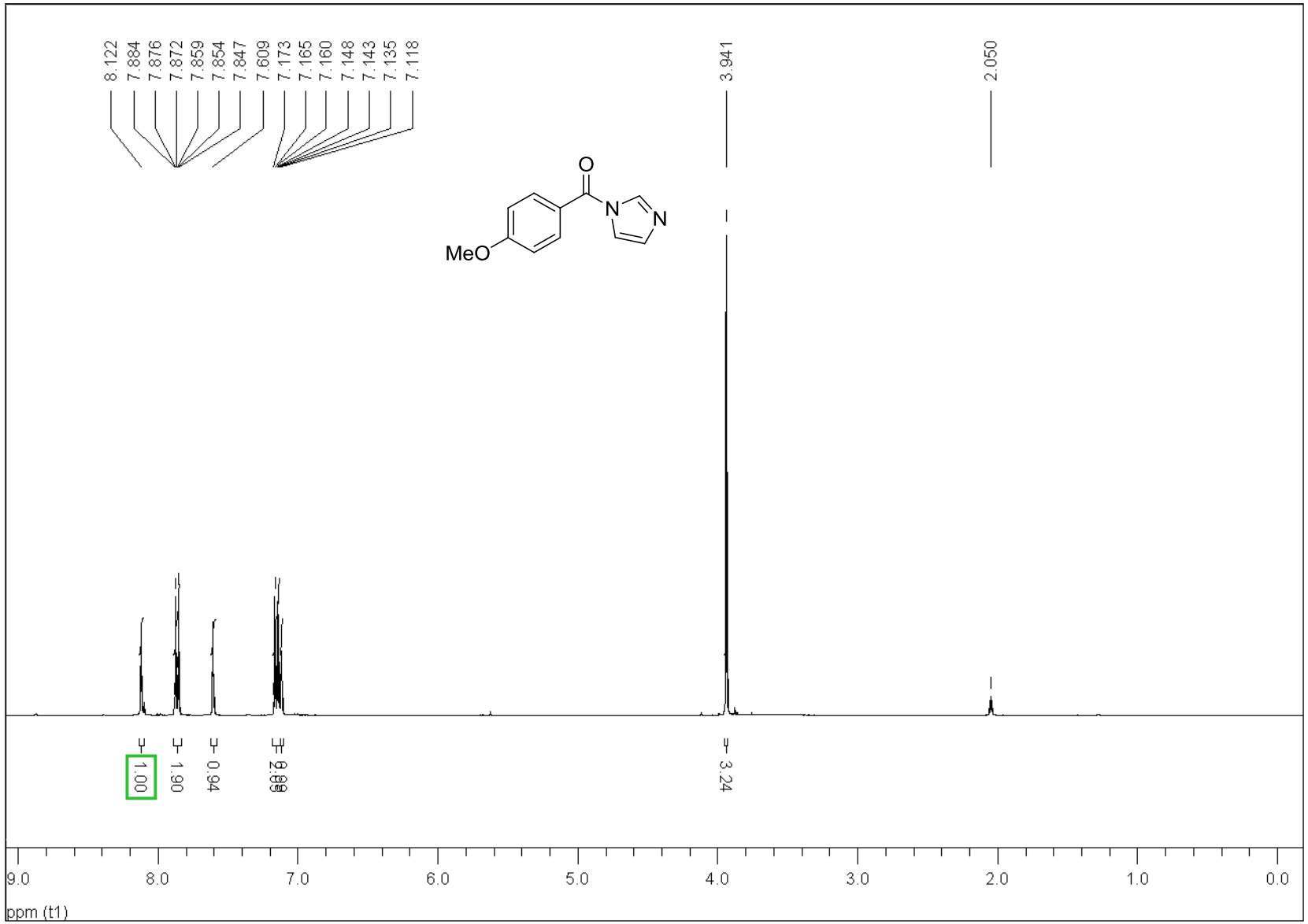

168.903
168.658
157.621
156.782
138.150
132.459
117.756
81.432
81.291
53.757
53.266
36.909
36.761
29.431
29.248
Me
O
Boc
N
N
N
200
150
100
50
0
ppm (t1)

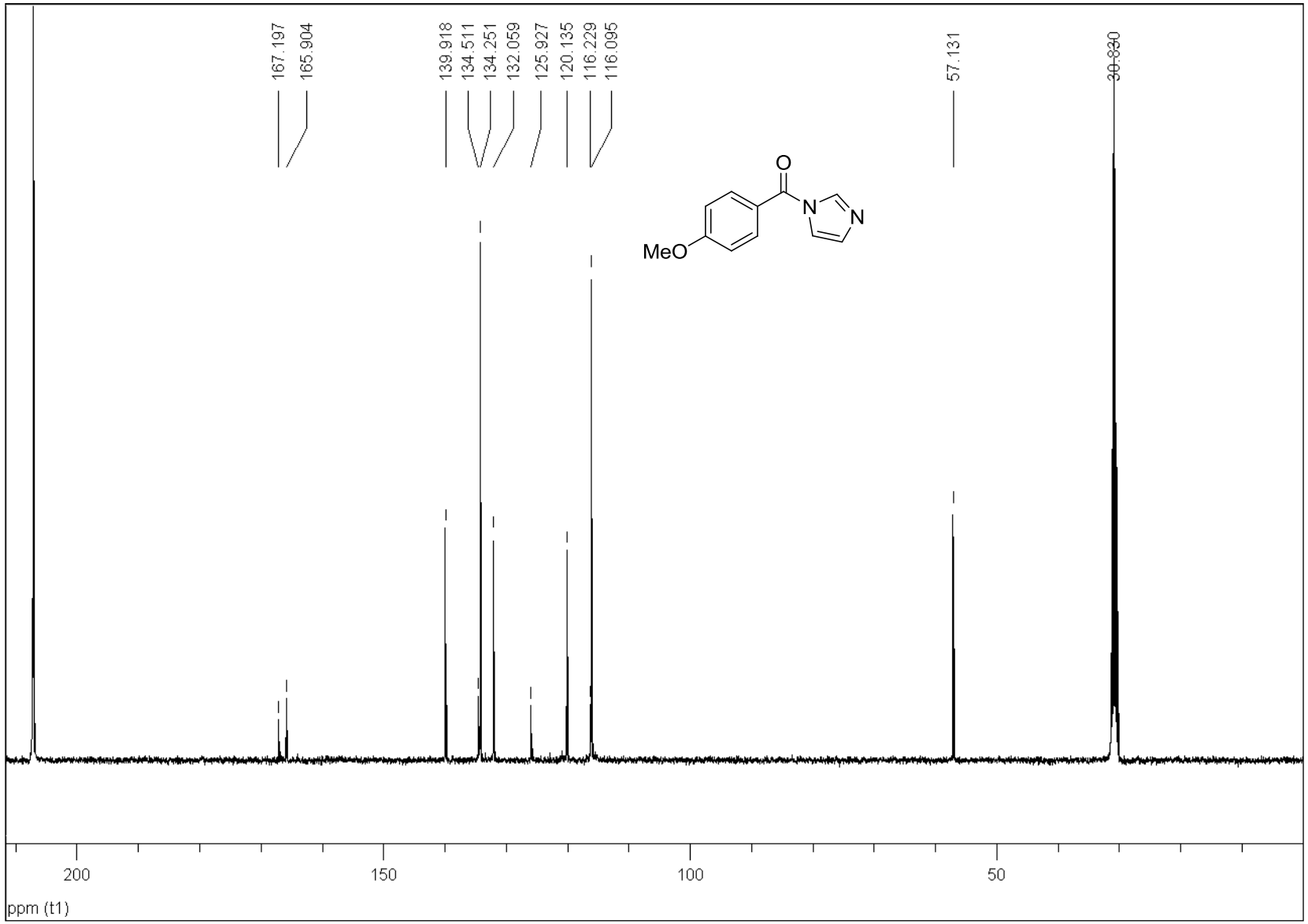
3-(*tert*-Butyl (1-carbonyl)piperidine-1-carboxylate)-imidazole (7e)



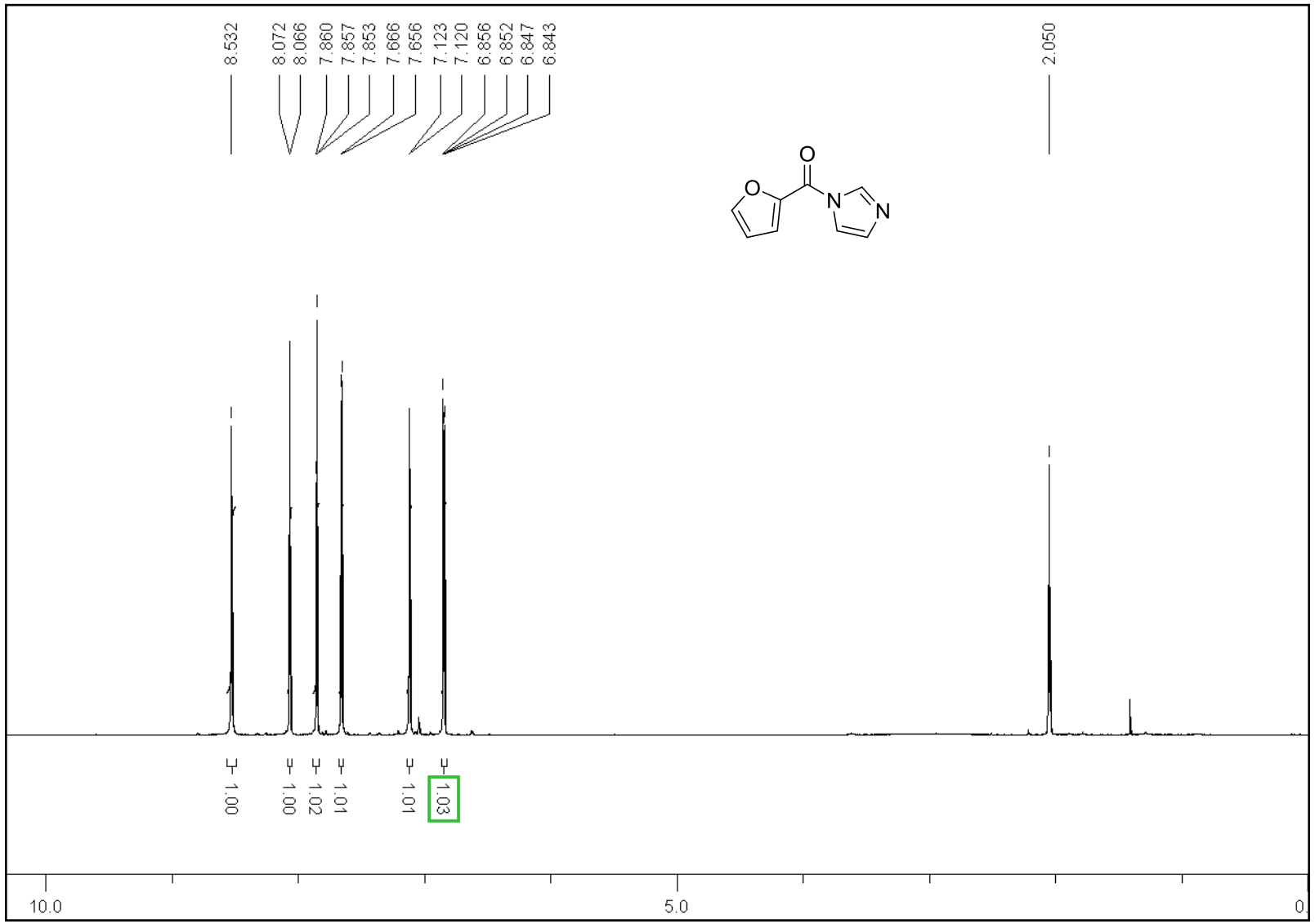

172.710
138.370
132.480
118.023
80.869
48.321
47.595
46.546
45.214
43.060
30.030
29.429
25.664
25.152
O
N
N
N
Boc
200
150
100
50
0
ppm (t1)

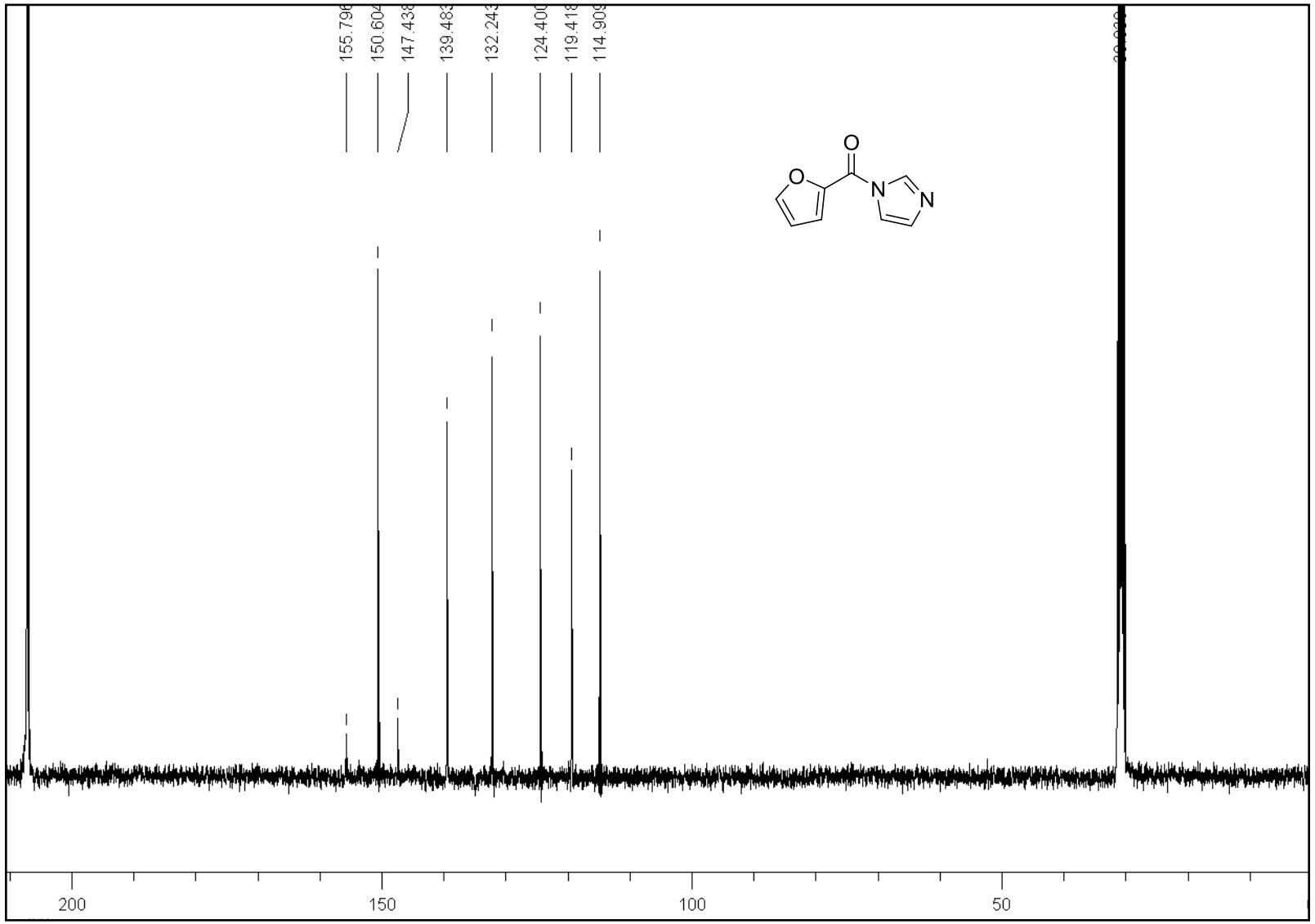
1-(4-Methoxybenzoyl)-imidazole (7f)



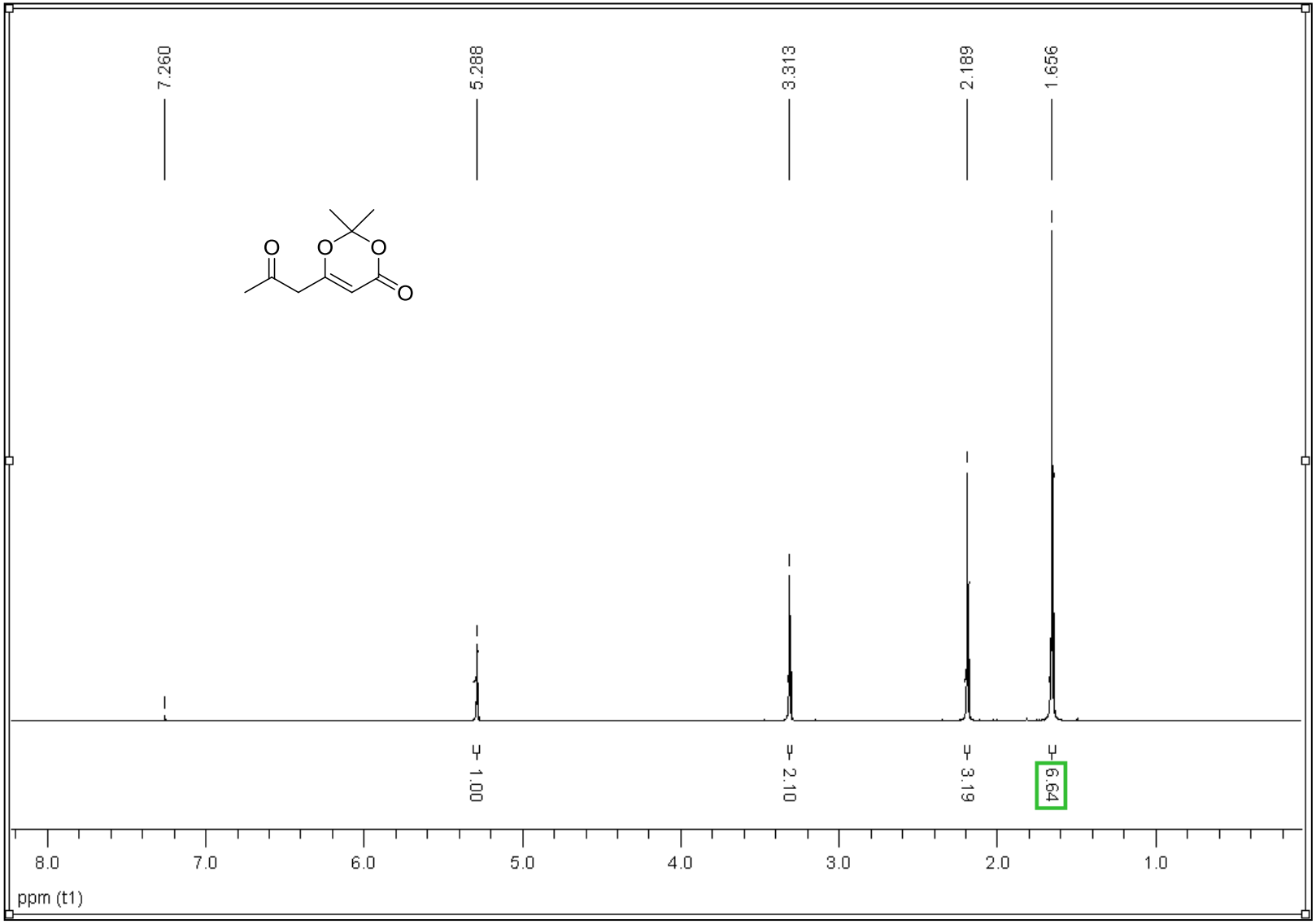

167.197
165.904
139.918
134.511
134.251
132.059
125.927
120.135
116.229
116.095
57.131
30.830
O
N
N
MeO
200
150
100
50
ppm (t1)

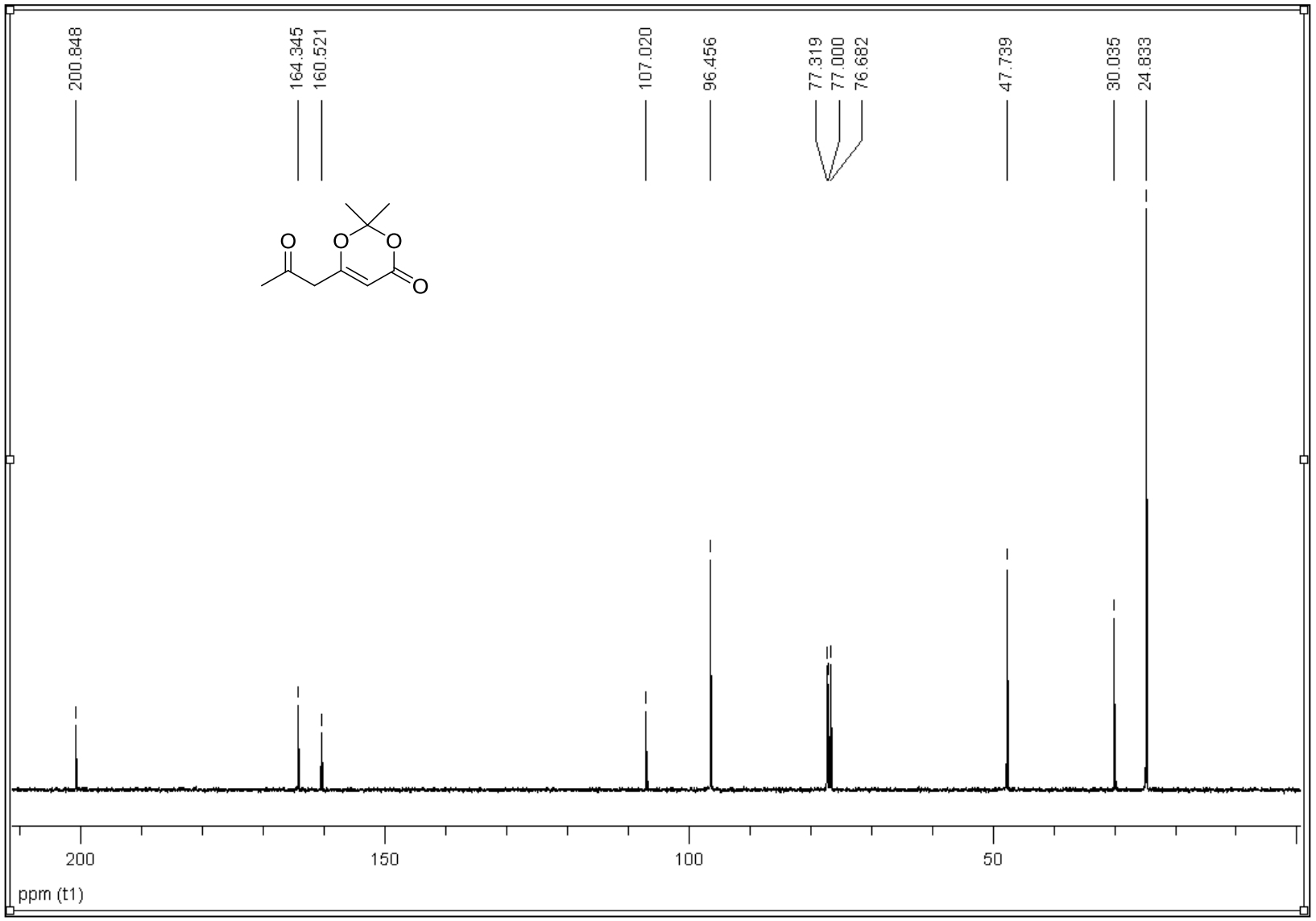
1-(2-Furoyl)-imidazole (7g)



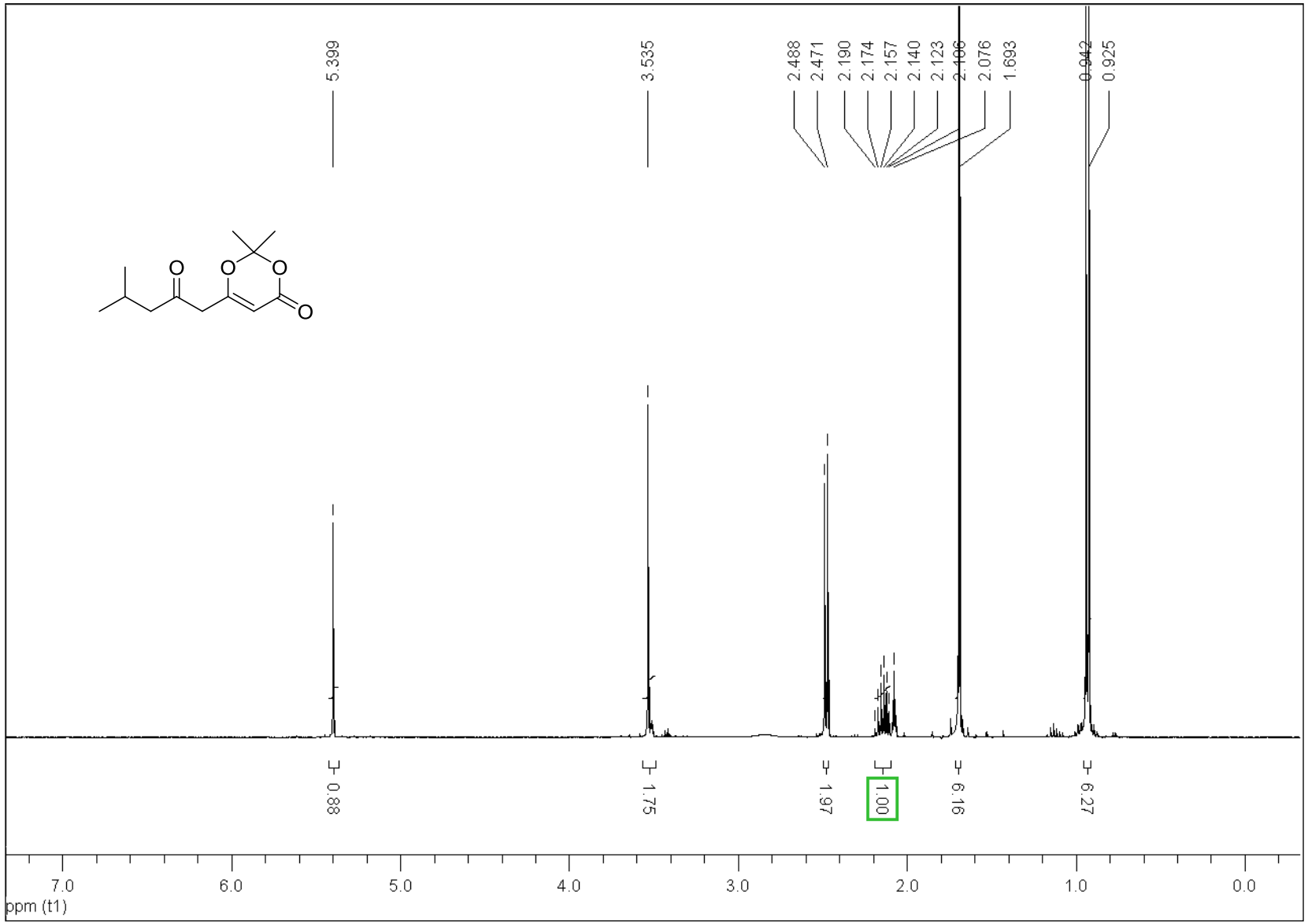

155.796
150.604
147.438
139.483
132.243
124.400
119.418
114.909
O
O
N
N
200
150
100
50

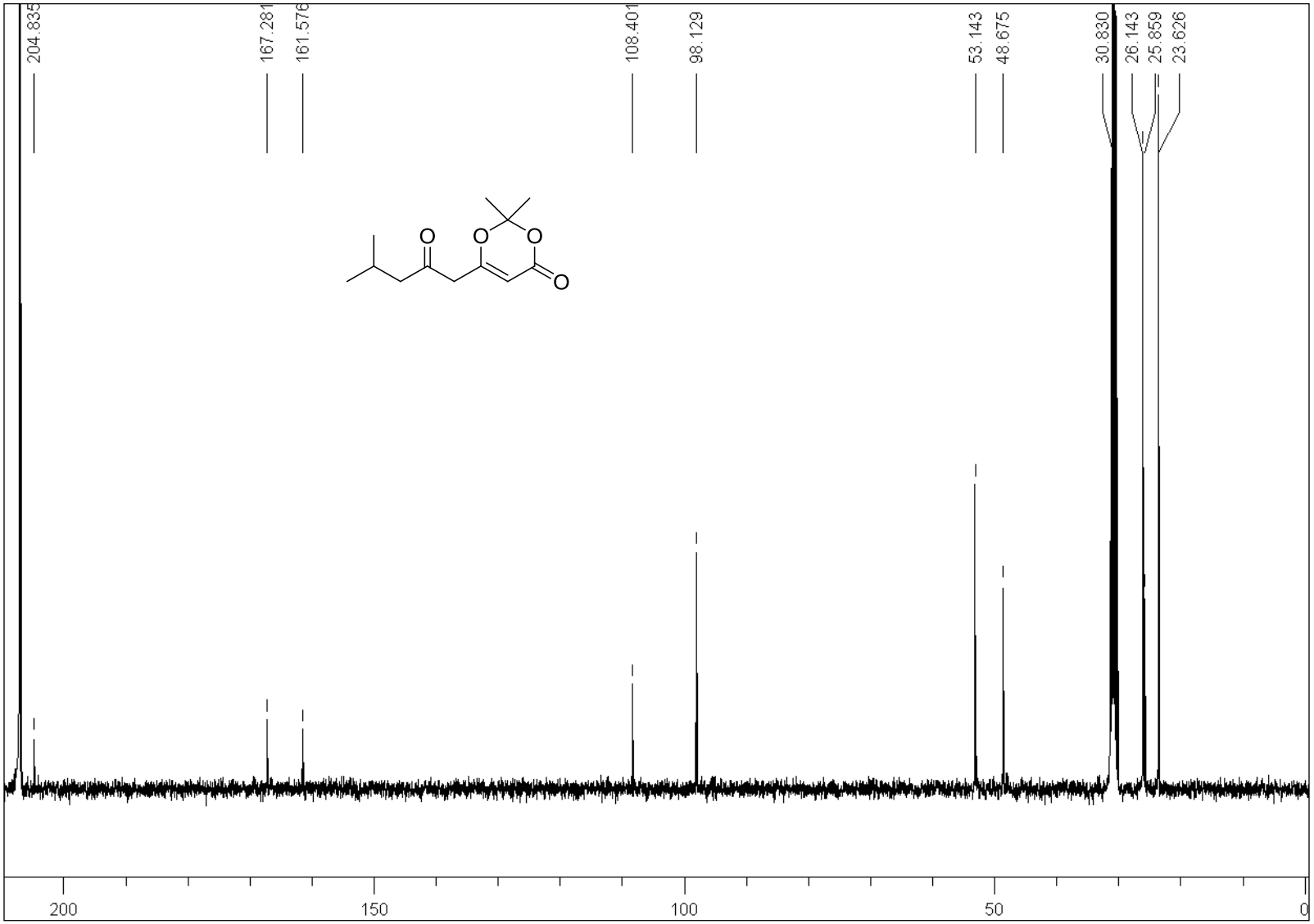
2,2-Dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one (4a)



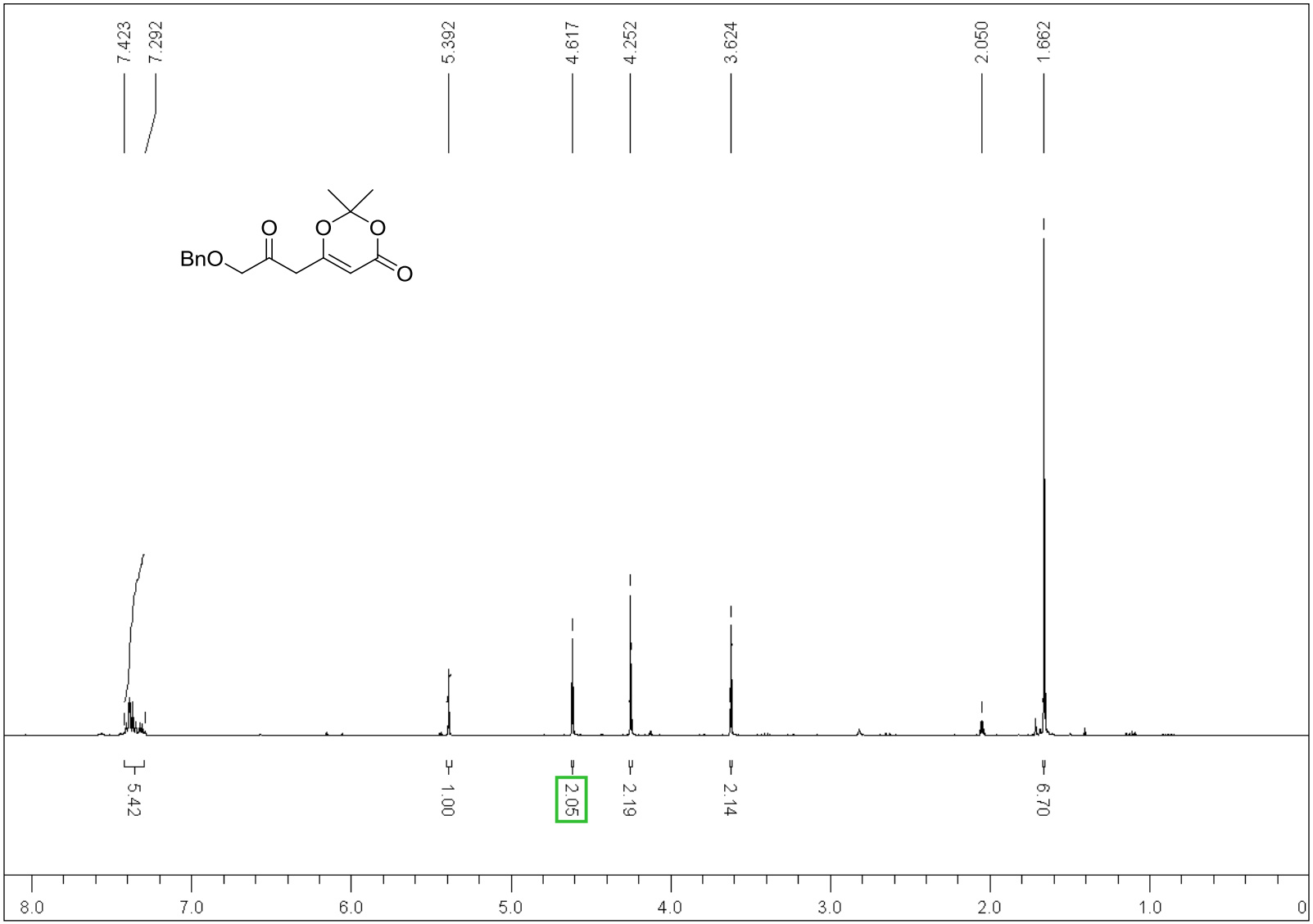

200.848
164.345
160.521
107.020
96.456
77.319
77.000
76.682
47.739
30.035
24.833
O
O
O
O
200
150
100
50
ppm (t1)

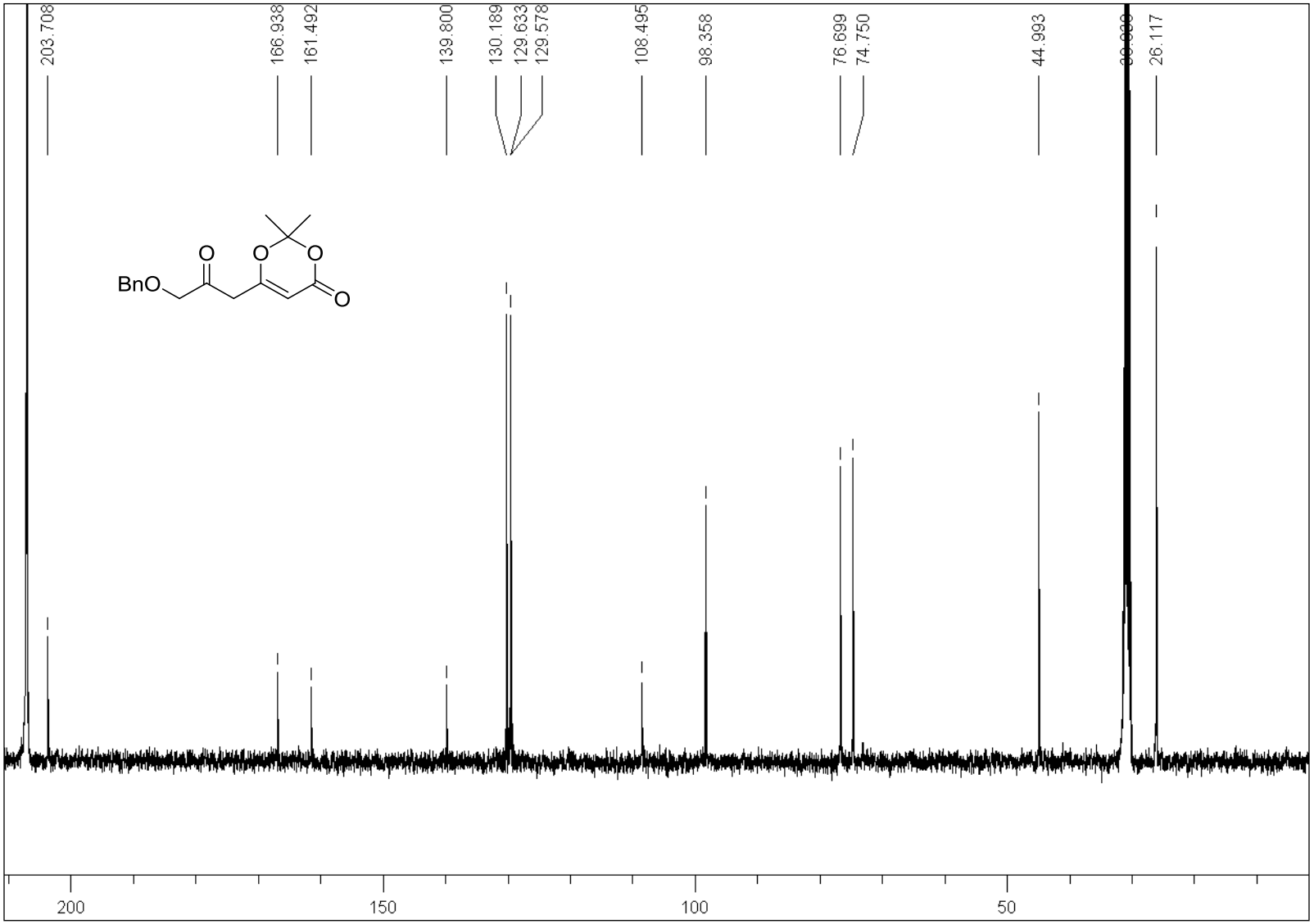
2,2-Dimethyl-6-(4-methyl-2-oxopentyl)-4*H*-1,3-dioxin-4-one (4b)



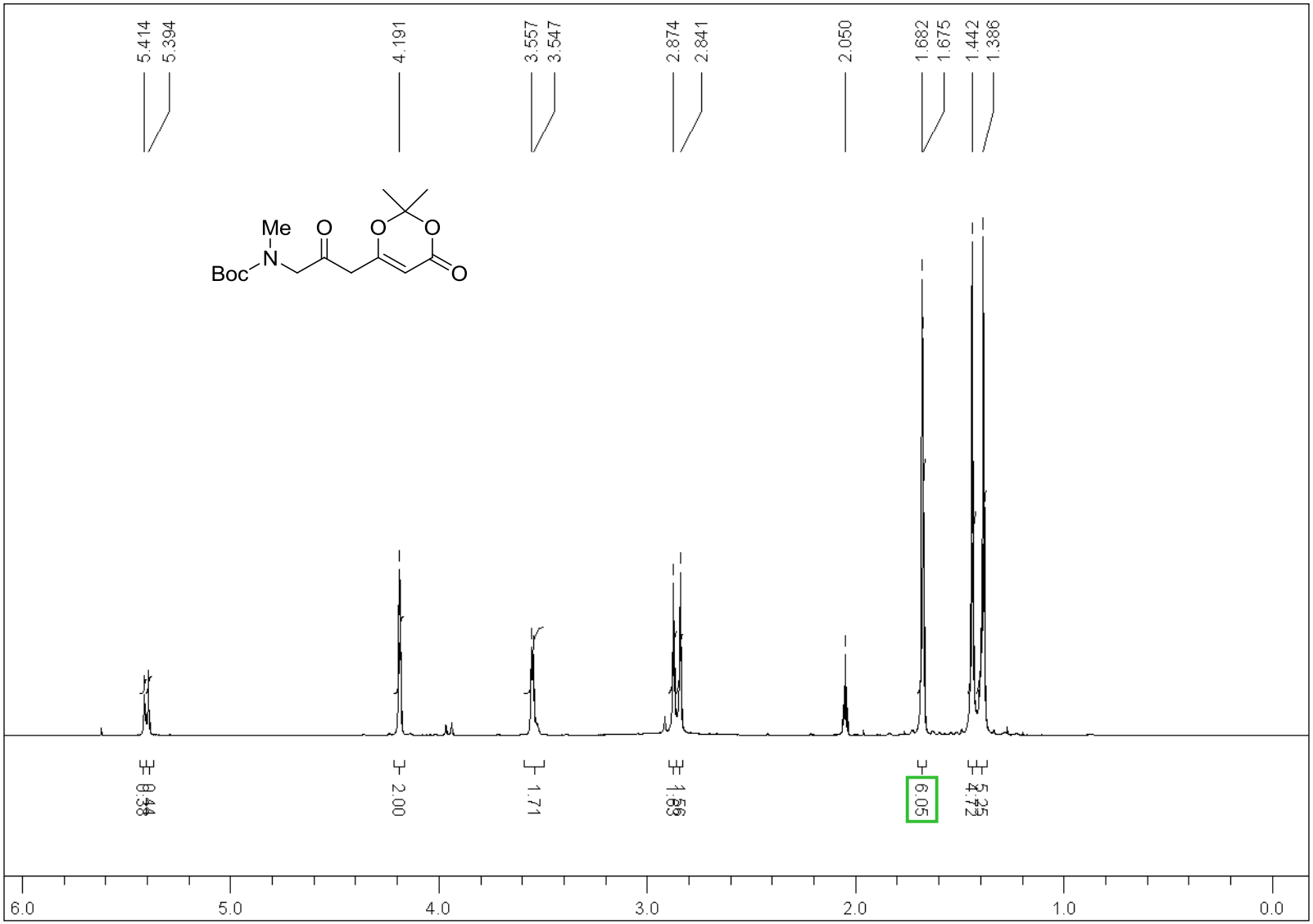

204.835
167.281
161.576
108.401
98.129
53.143
48.675
30.830
26.143
25.859
23.626
O
O
O
O
200
150
100
50
0

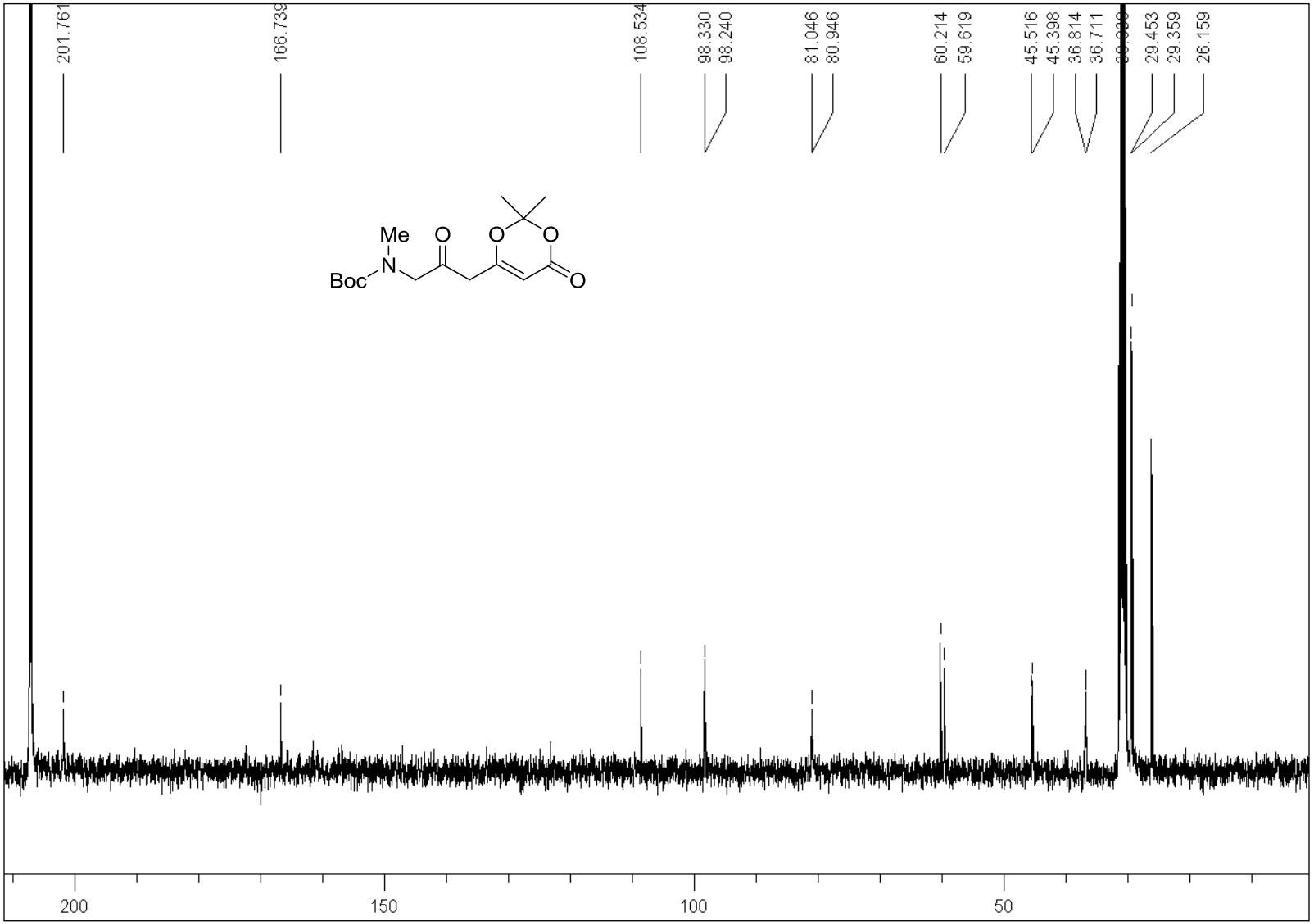
6-(3-(Benzyloxy)-2-oxopropyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4c)



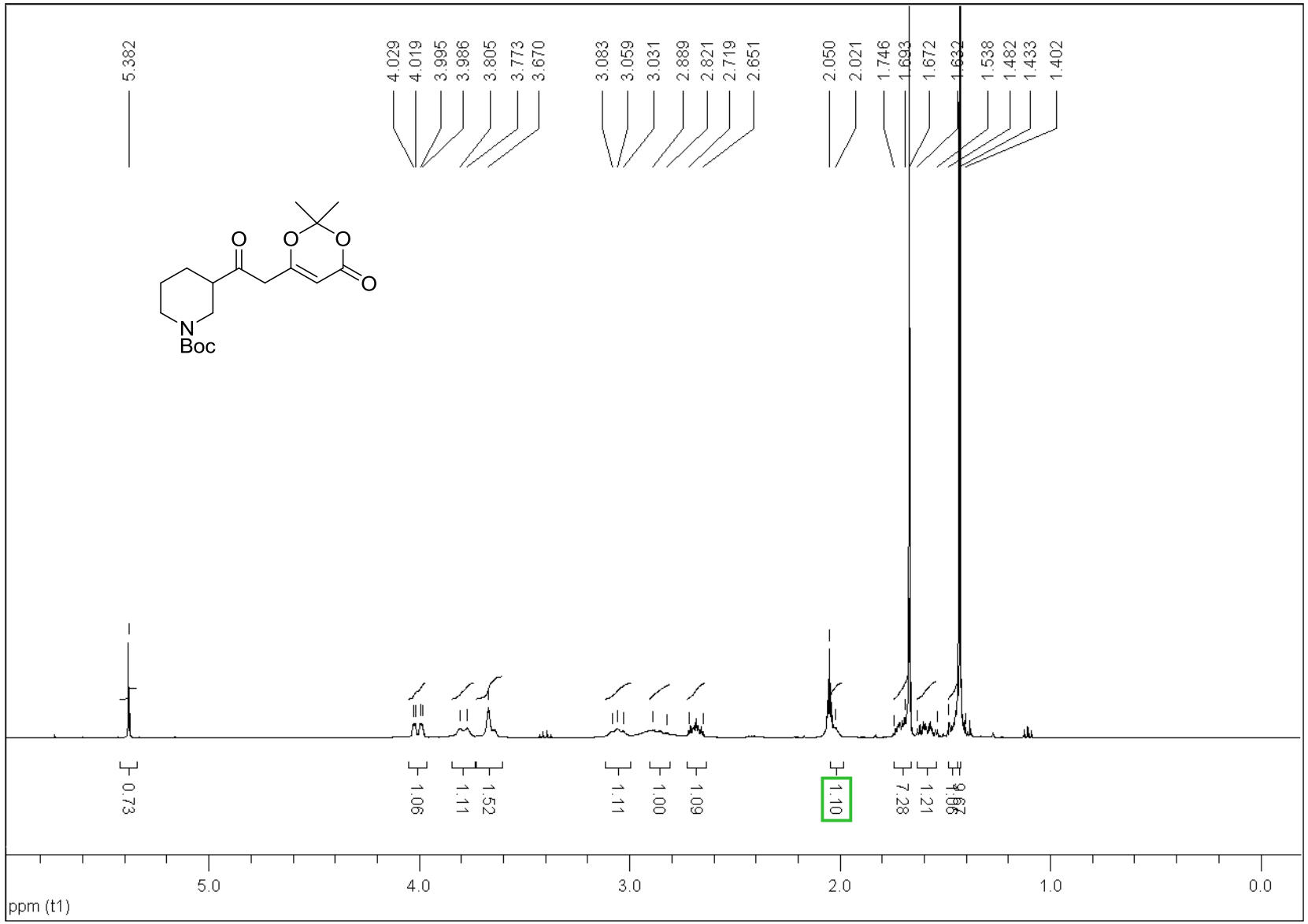

203.708
166.938
161.492
139.800
130.189
129.633
129.578
108.495
98.358
76.699
74.750
44.993
26.117
BnO
O
O
O
O
200
150
100
50

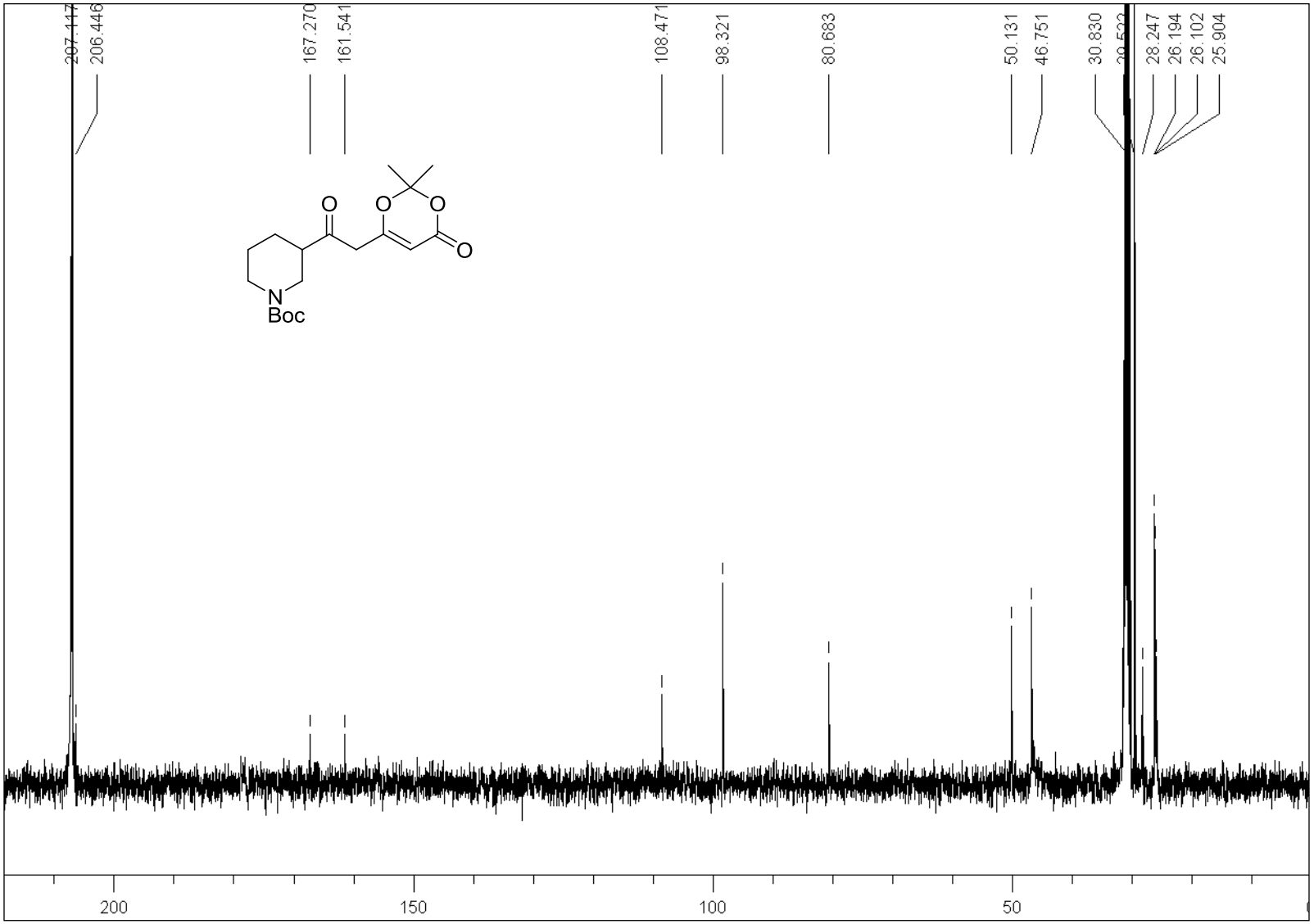
***tert*-Butyl 3-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-oxopropyl(methyl)carbamate (4d)**



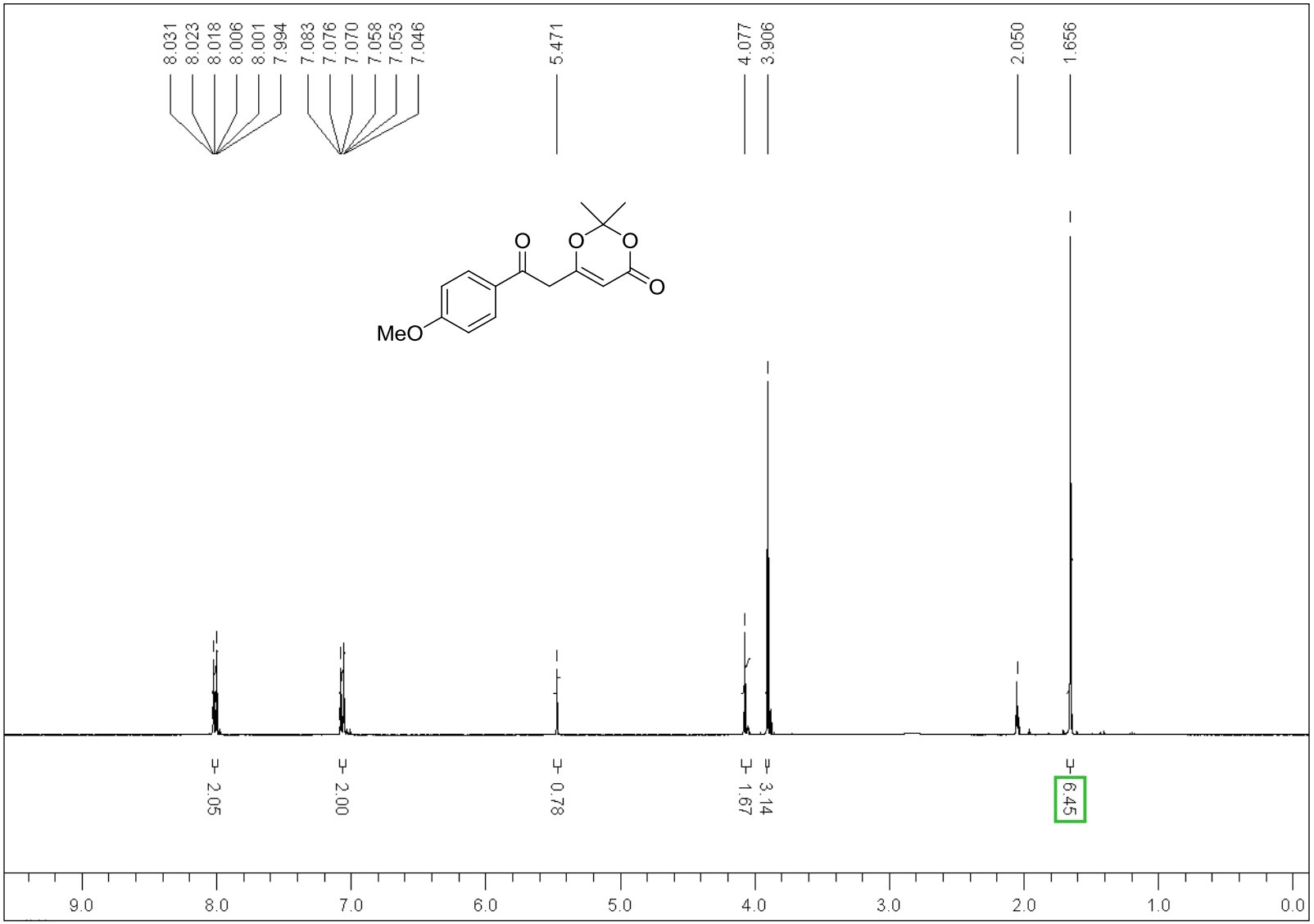

201.761
166.739
108.534
98.330
98.240
81.046
80.946
60.214
59.619
45.516
45.398
36.814
36.711
29.453
29.359
26.159
Me
N
Boc
O
O
O
O
200
150
100
50

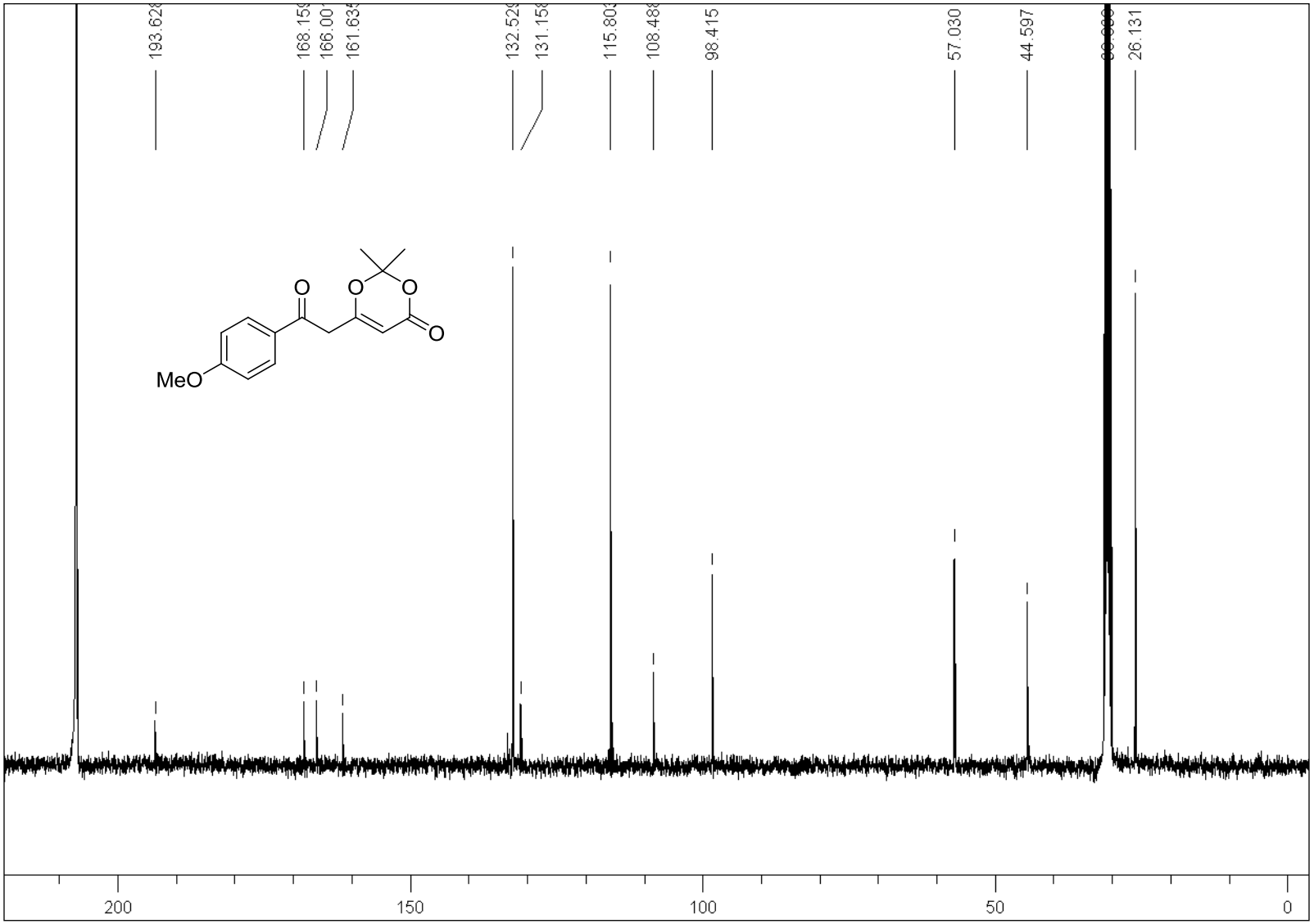
***tert*-Butyl 3-(2-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetyl)piperidine-1-carboxylate (4e)**



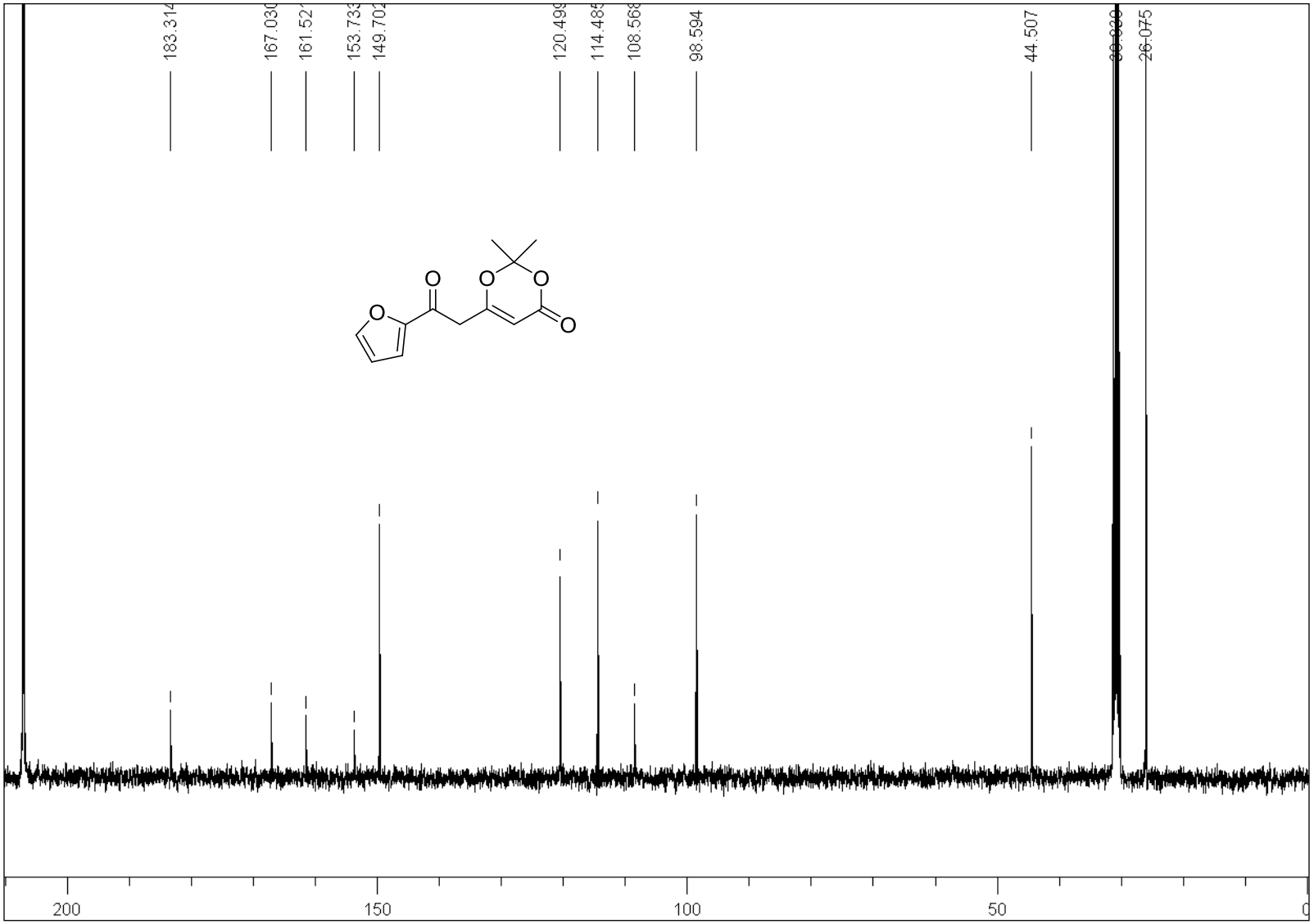

207.417
206.446
167.270
161.541
108.471
98.321
80.683
50.131
46.751
30.830
28.247
26.194
26.102
25.904
O
O
O
O
N
Boc
200
150
100
50

6-(2-(4-Methoxyphenyl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4f)

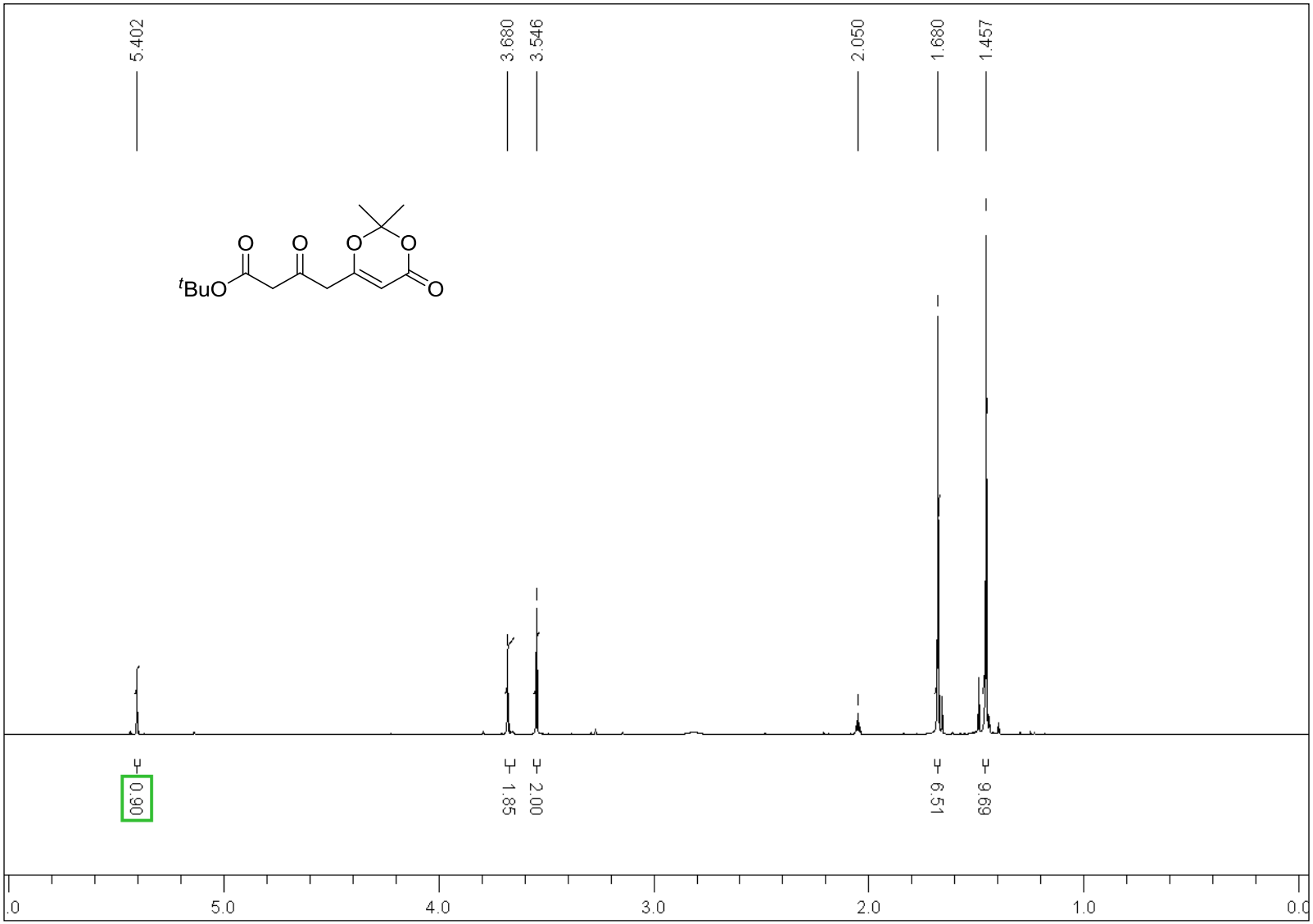


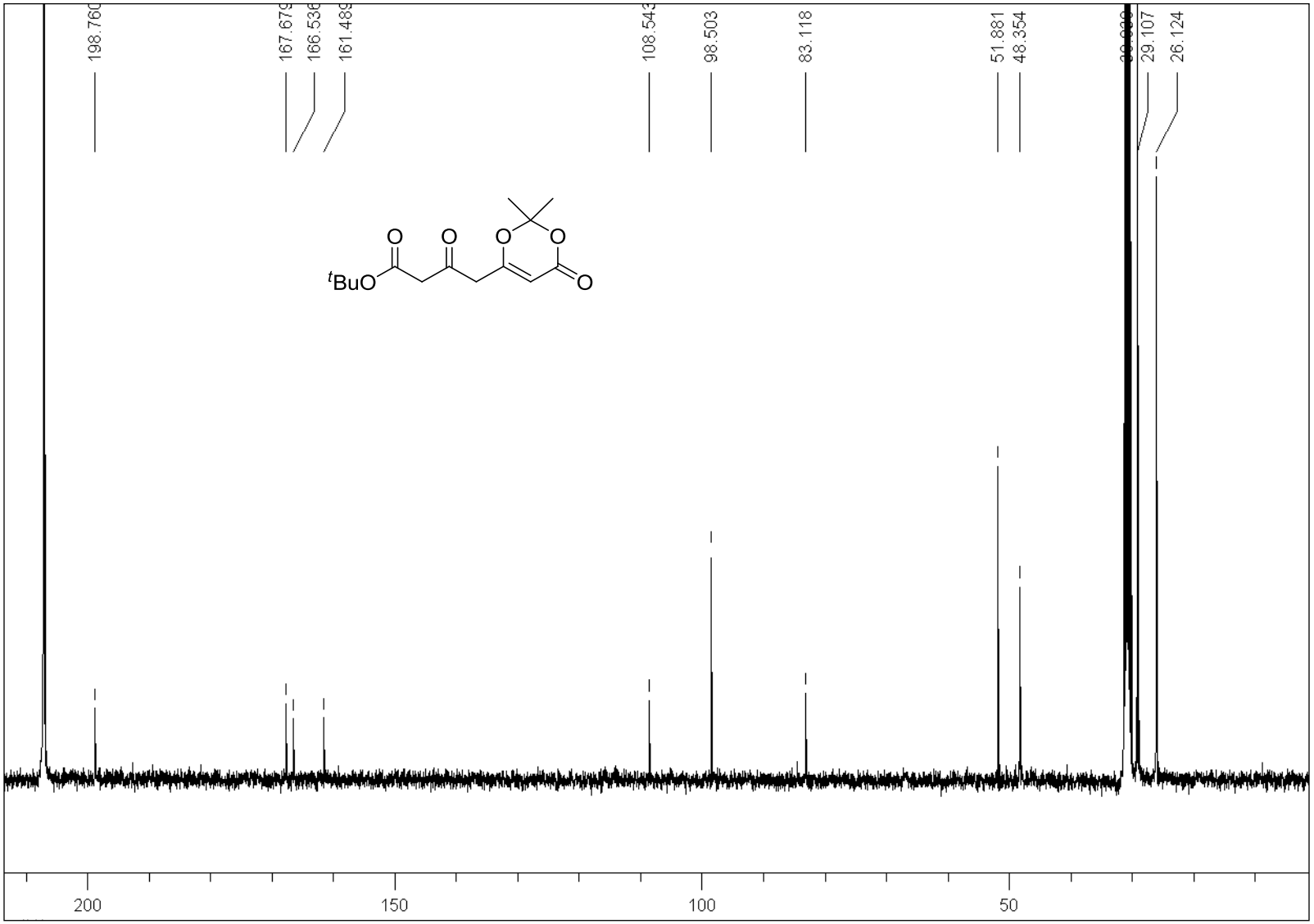

193.628
168.159
166.001
161.635
132.529
131.158
115.803
108.488
98.415
57.030
44.597
26.131
O
O
O
O
MeO
200
150
100
50
0

6-(2-(Furan-2-yl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (4g)

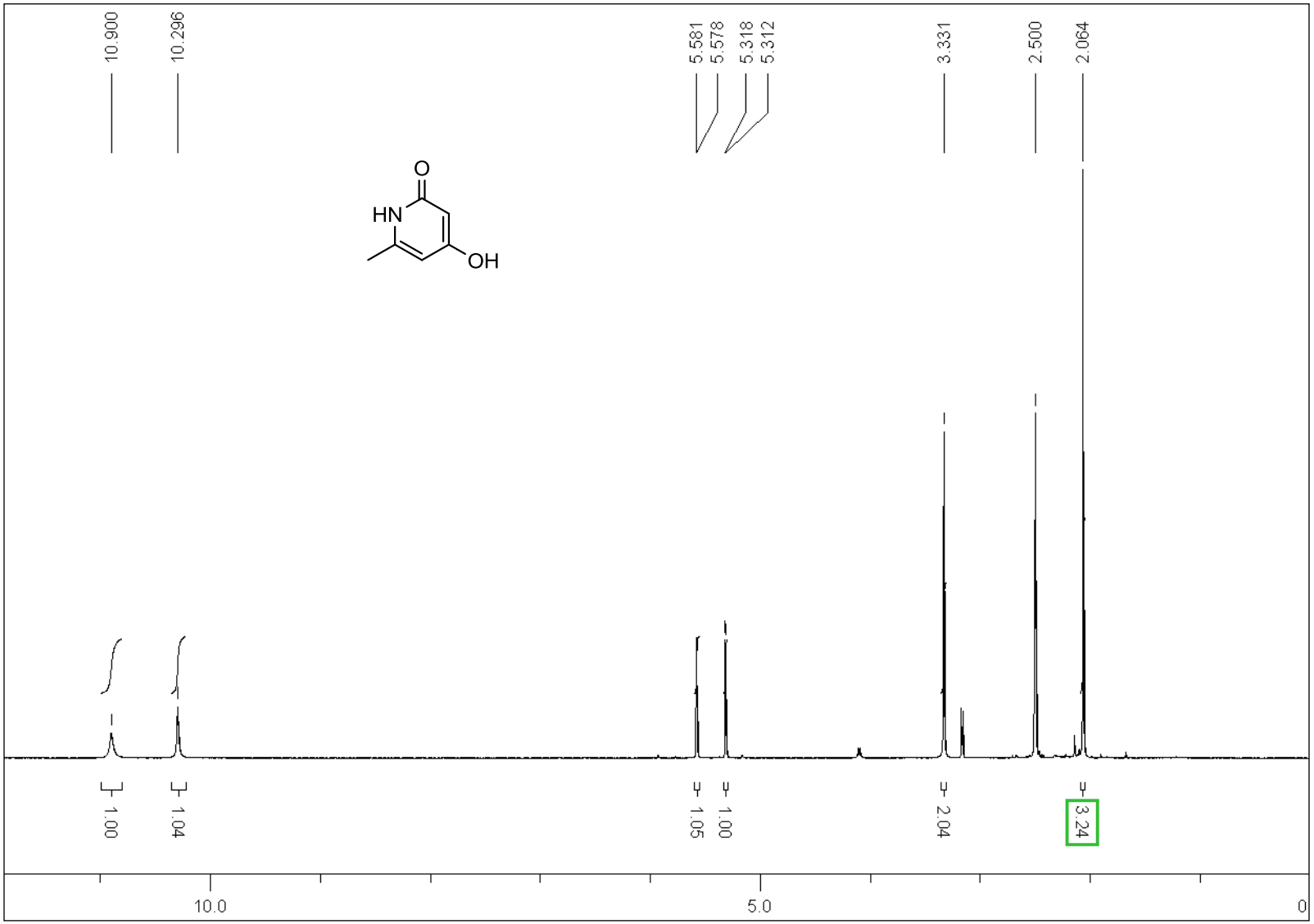

183.314
167.030
161.521
153.733
149.702
120.499
114.485
108.568
98.594
44.507
30.030
26.075
O
O
O
O
O
200
150
100
50
0

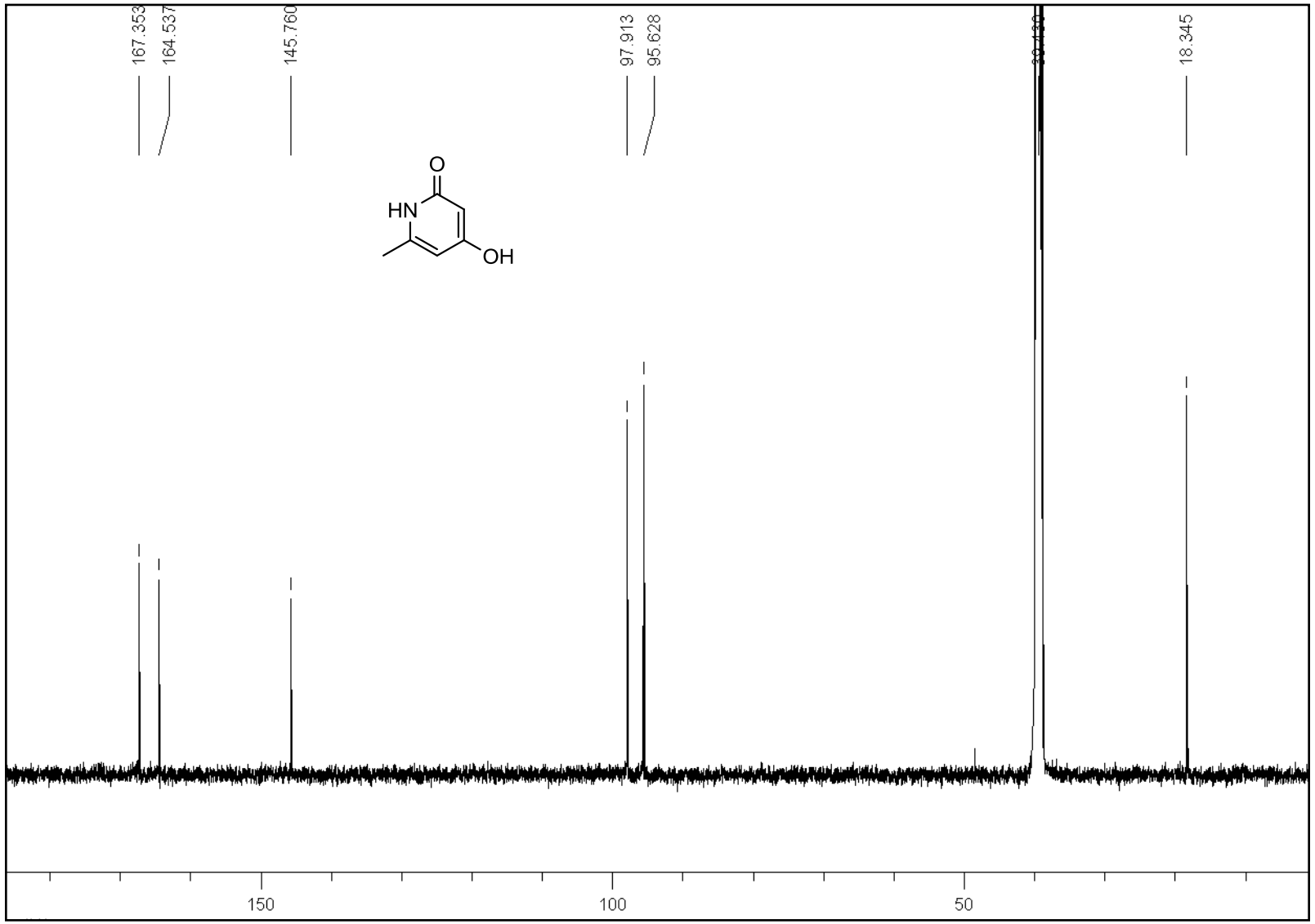
***tert*-Butyl 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (4h)**



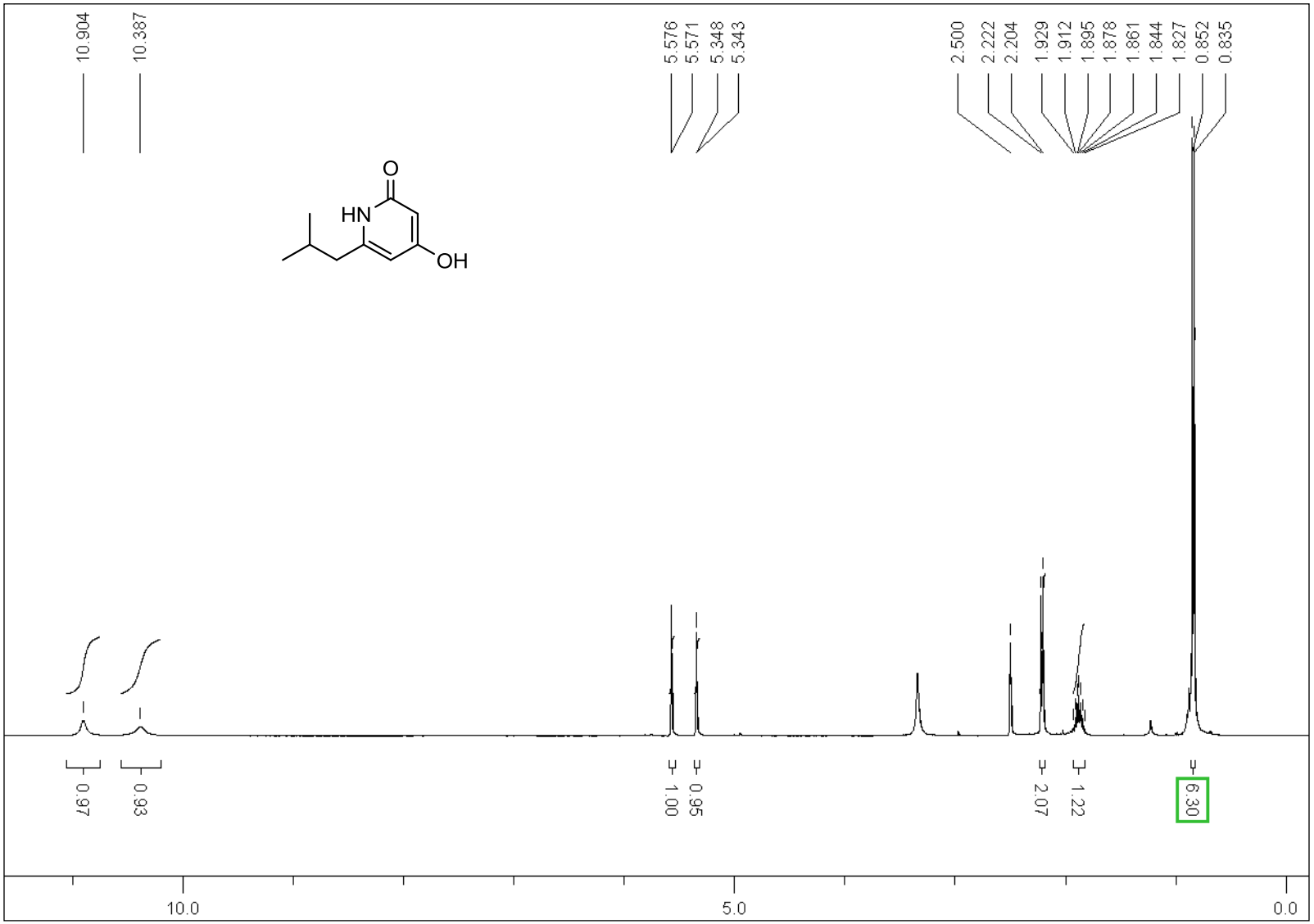

198.760
167.679
166.536
161.489
108.543
98.503
83.118
51.881
48.354
29.107
26.124
O
O
O
O
O
tBuO
200
150
100
50

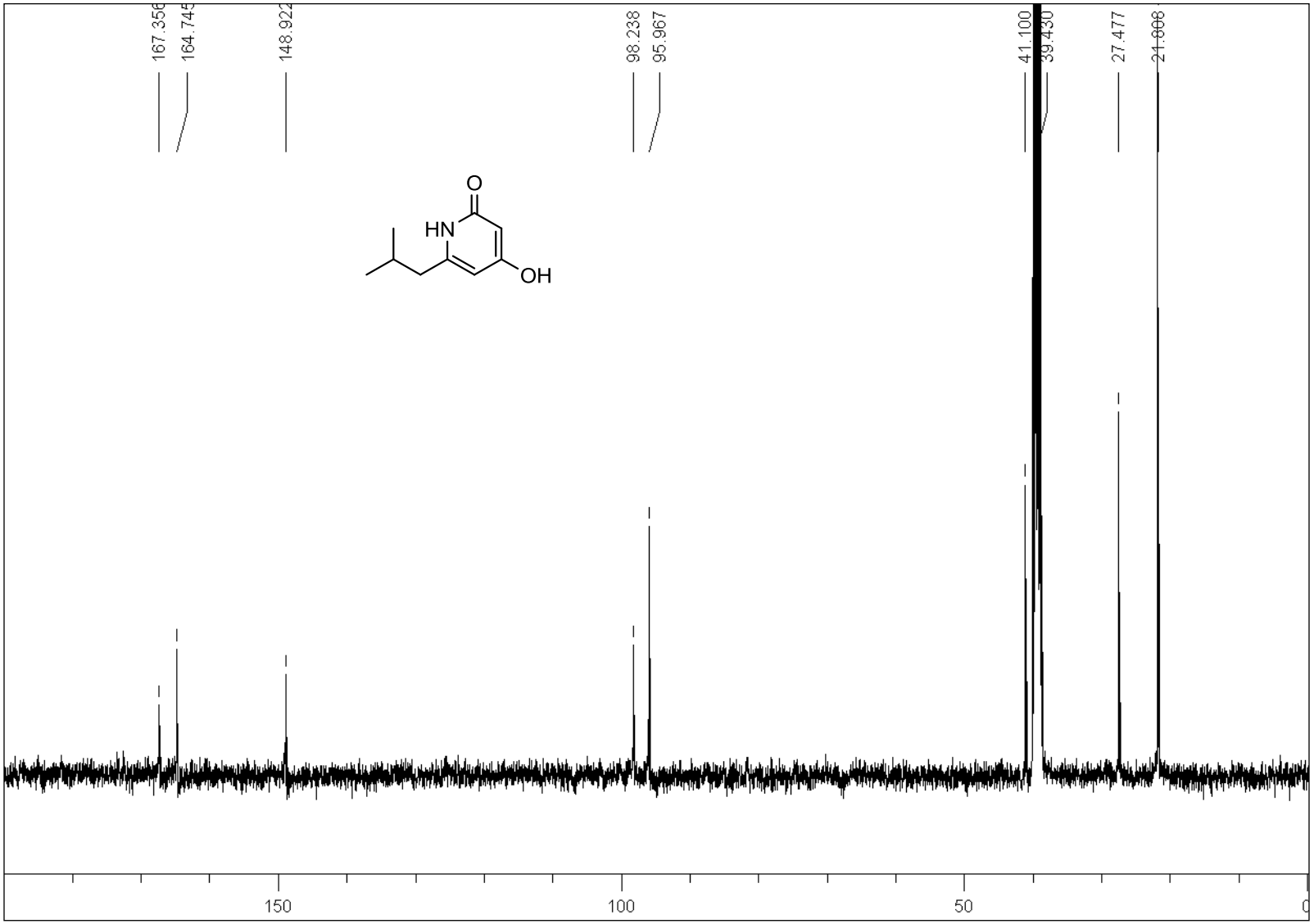
4-Hydroxy-6-methylpyridin-2(1*H*)-one (1a)



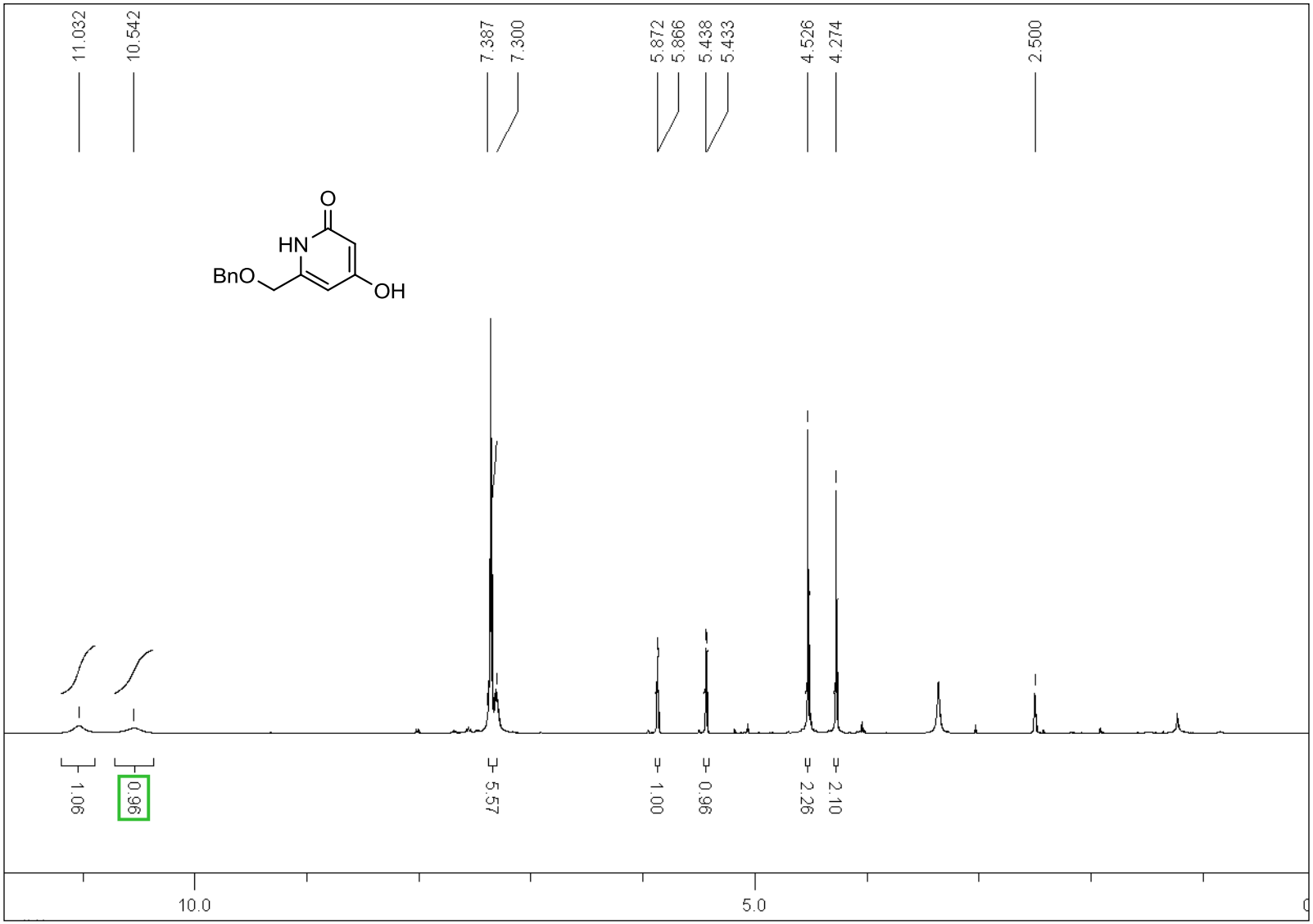

167.353
164.537
145.760
97.913
95.628
39.430
18.345
O
HN
OH
150
100
50

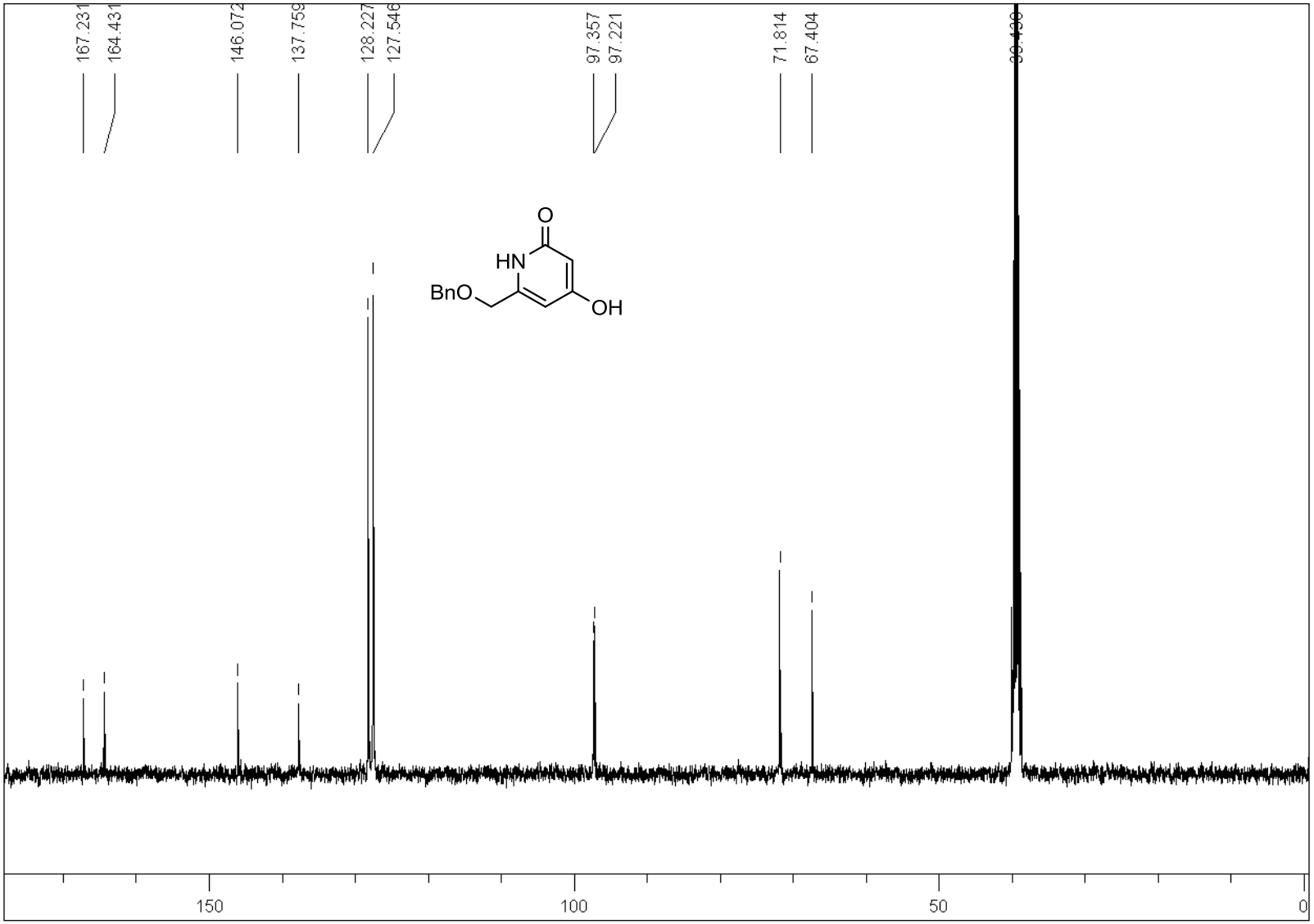
4-Hydroxy-6-isobutylpyridin-2(1*H*)-one (1b)



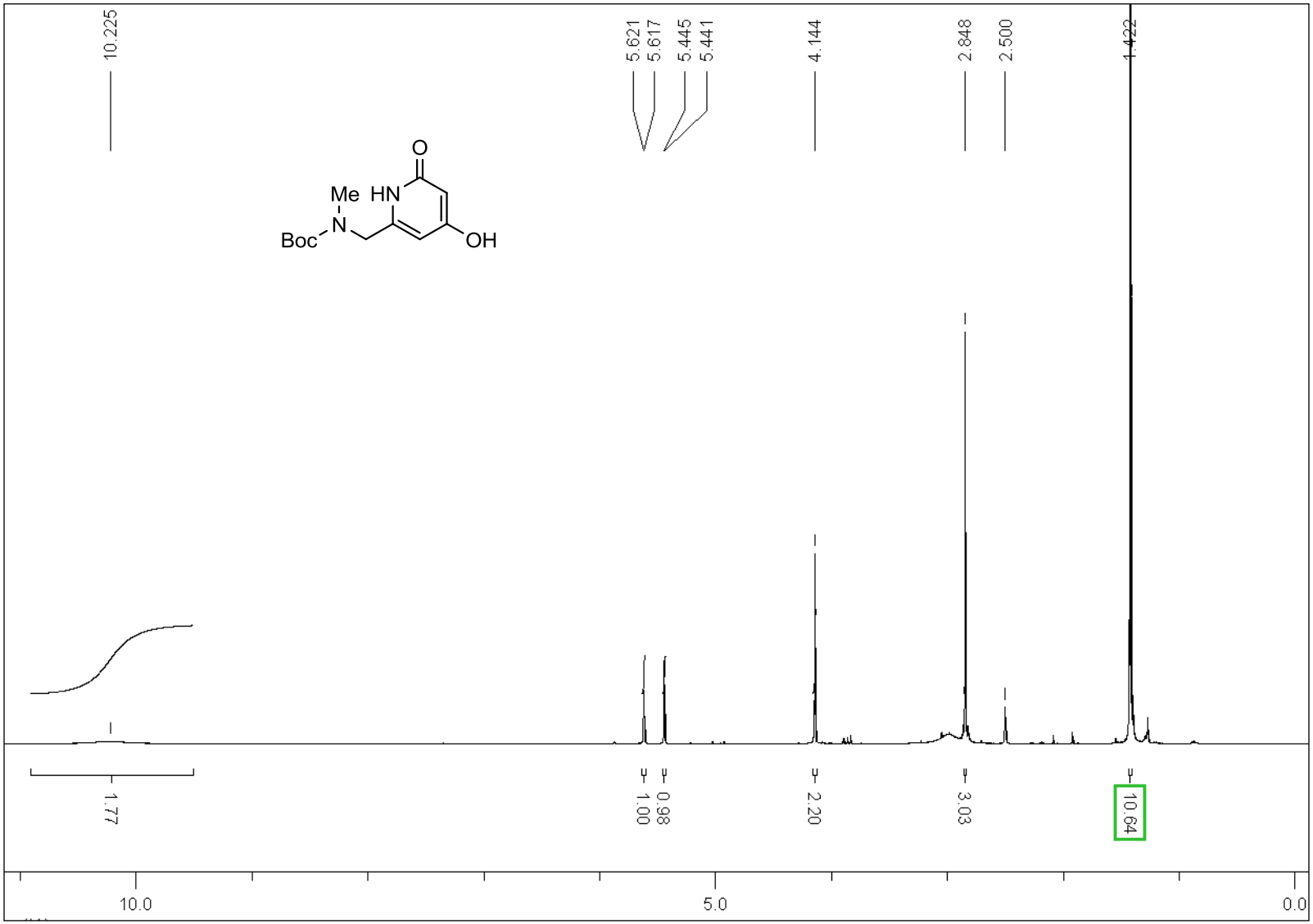

167.356
164.745
148.922
98.238
95.967
41.100
39.430
27.477
21.008
O
HN
OH
150
100
50
0

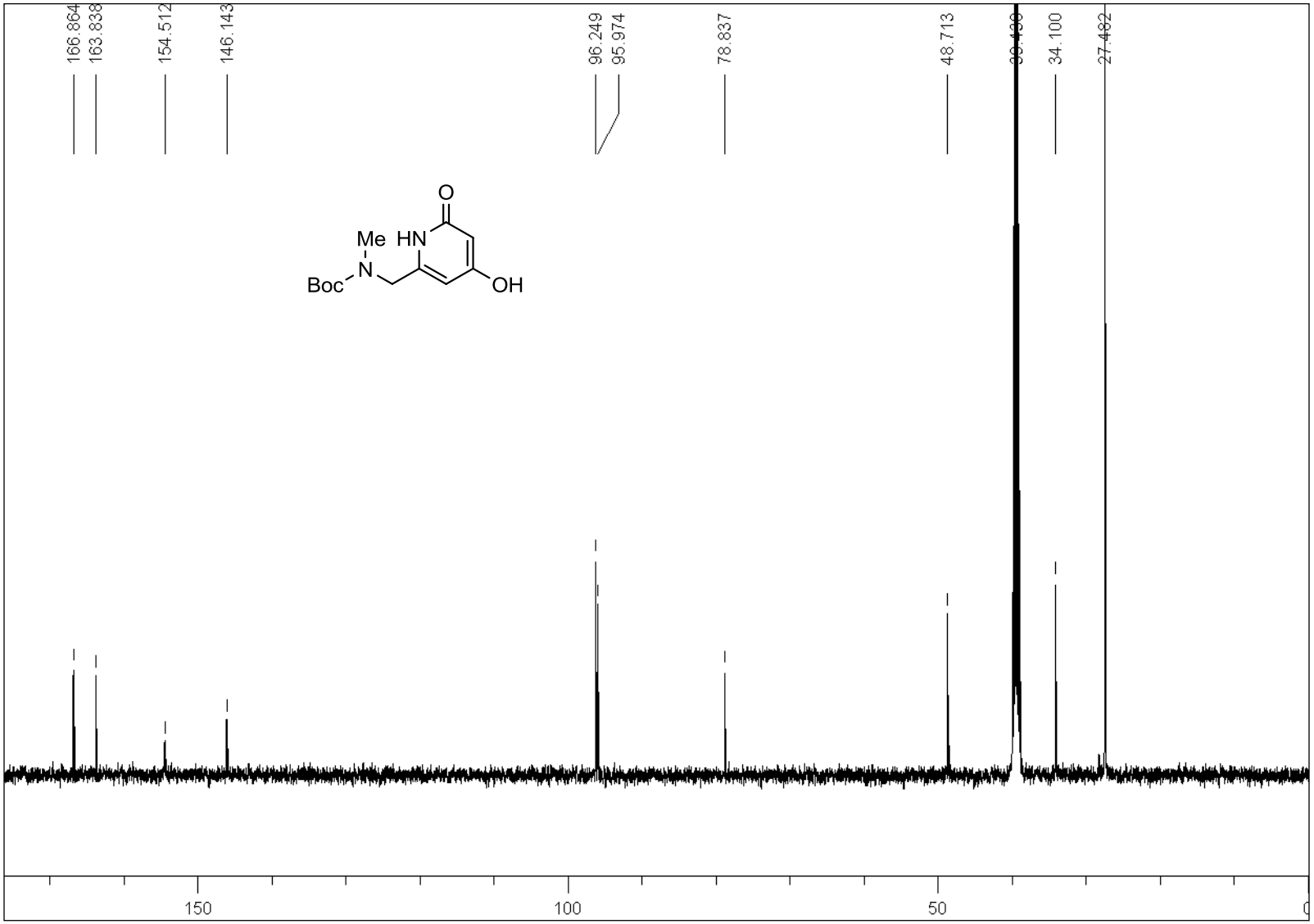
6-(Benzyloxymethyl)-4-hydroxypyridin-2(1*H*)-one (1c)



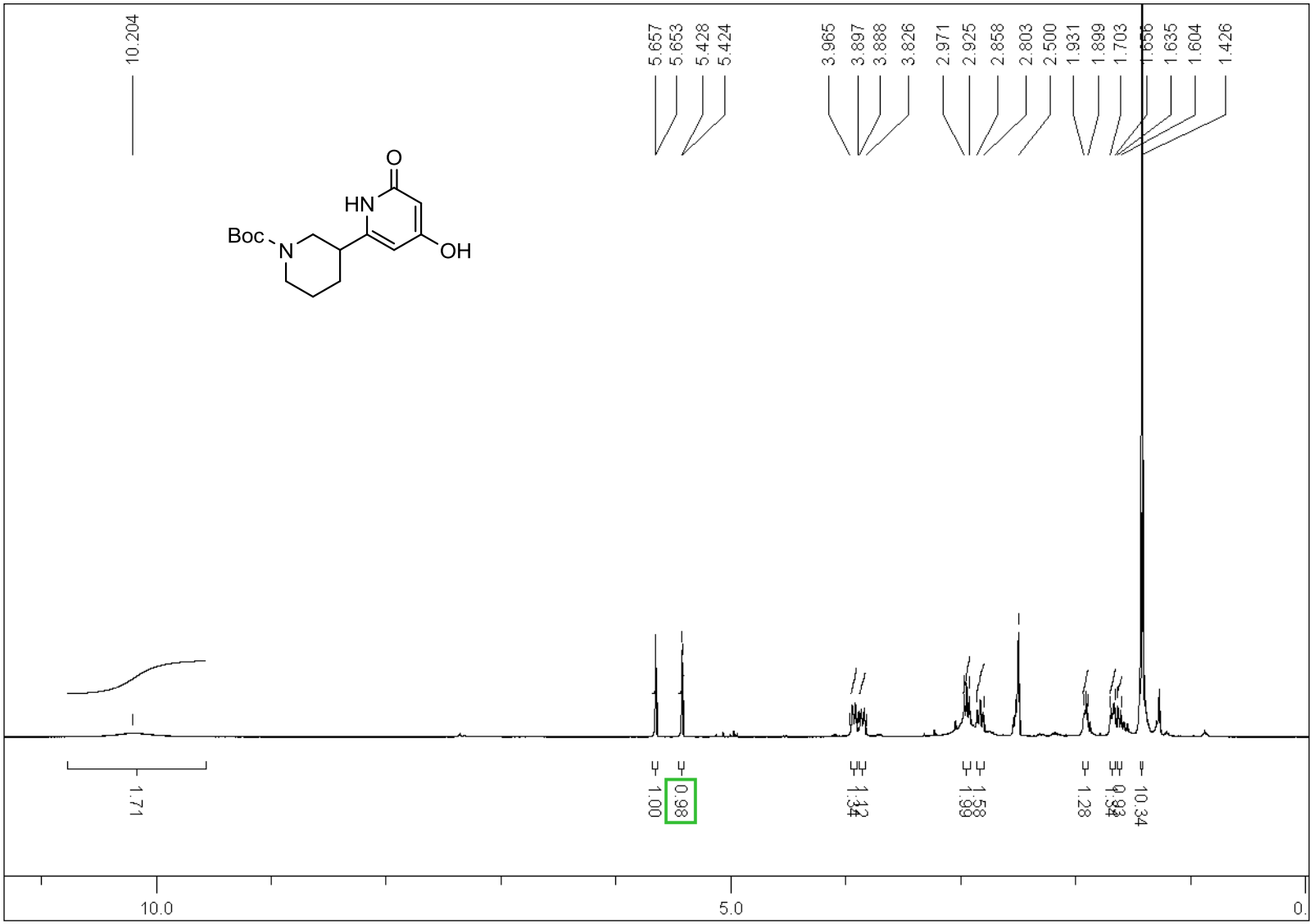

167.231
164.431
146.072
137.759
128.227
127.546
97.357
97.221
71.814
67.404
39.430
O
HN
BnO
OH
150
100
50
0

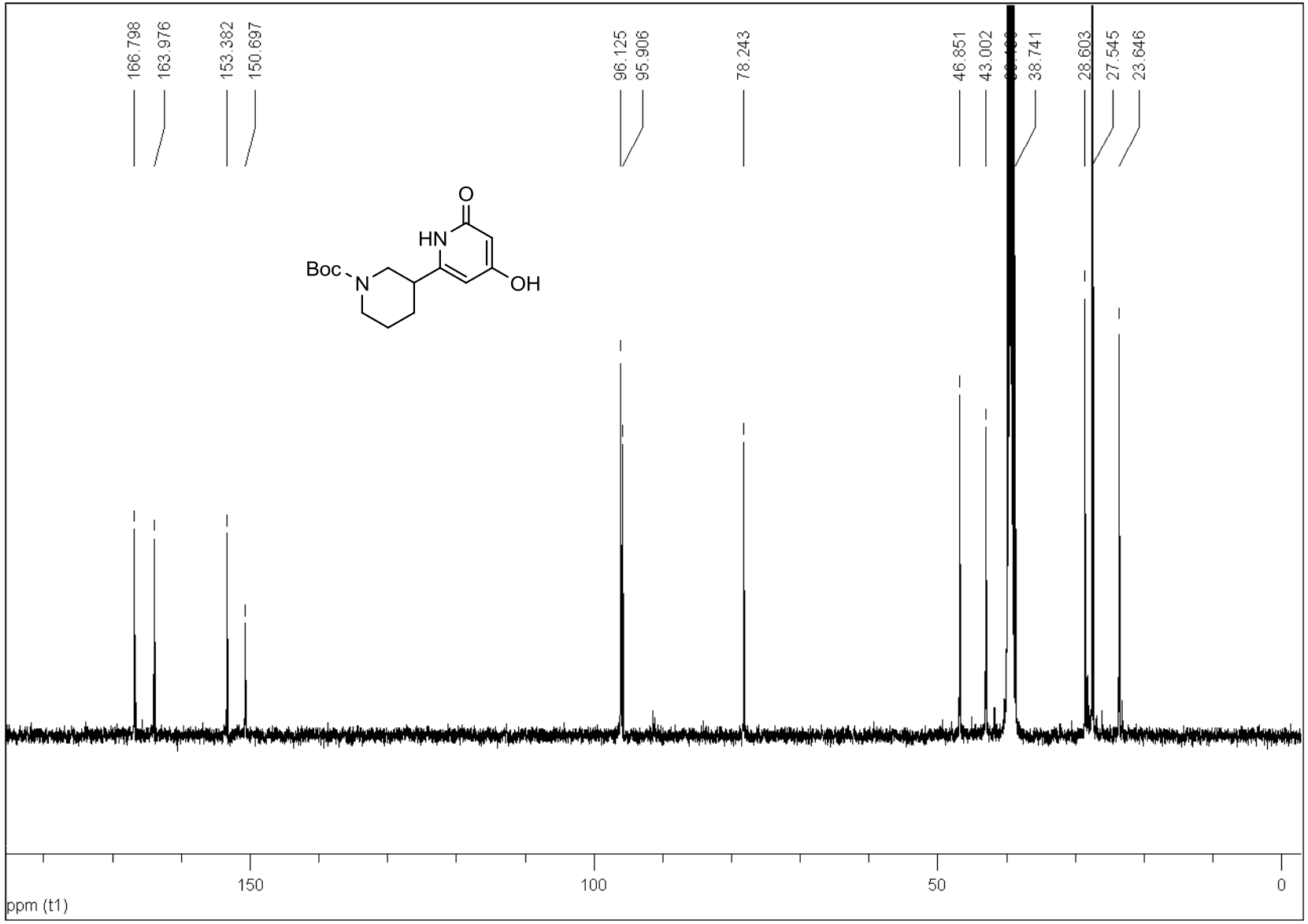
***tert*-Butyl (4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)methyl(methyl)carbamate (1d)**



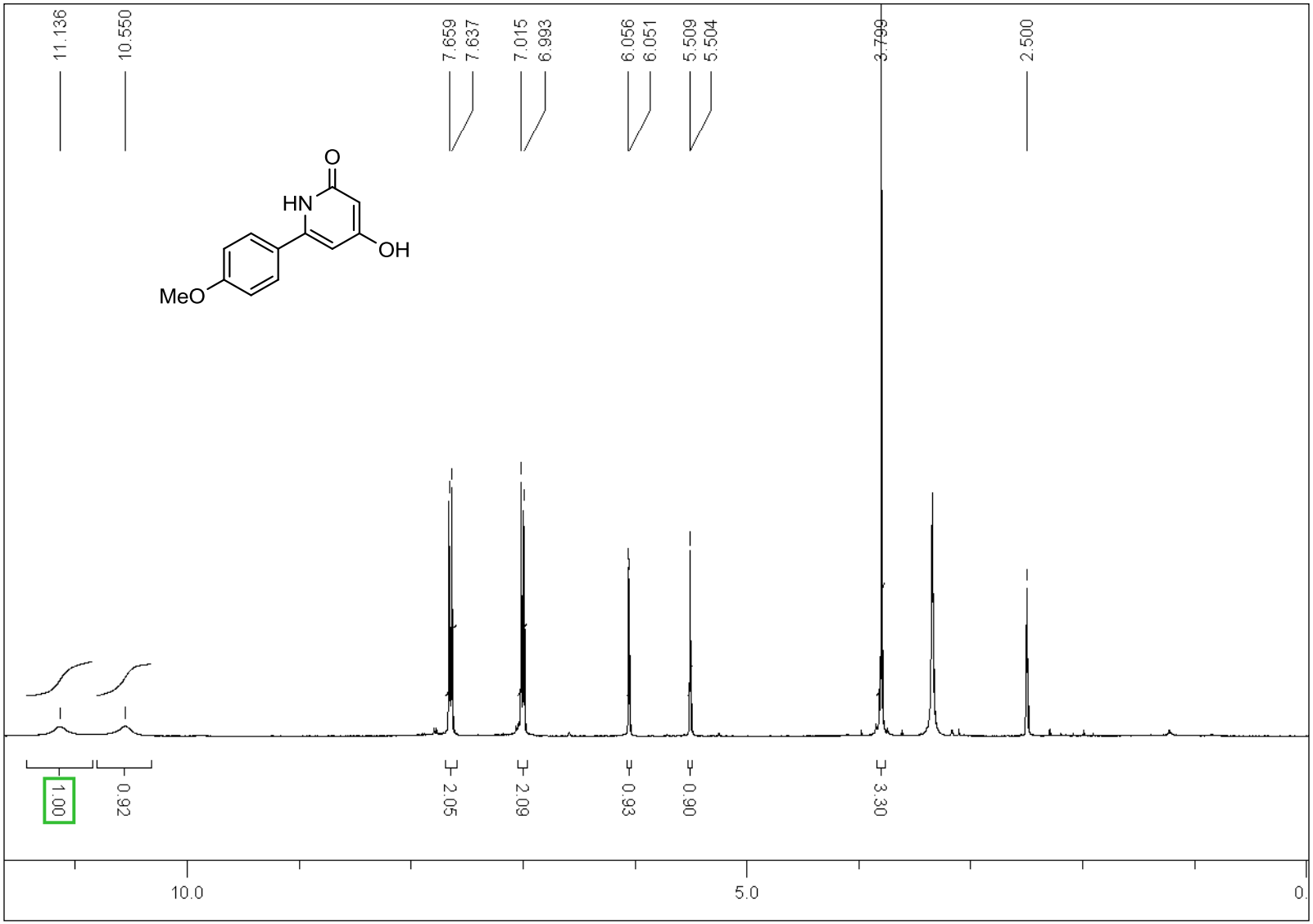

166.864
163.838
154.512
146.143
96.249
95.974
78.837
48.713
30.430
34.100
27.482
O
HN
Me
N
Boc
OH
150
100
50

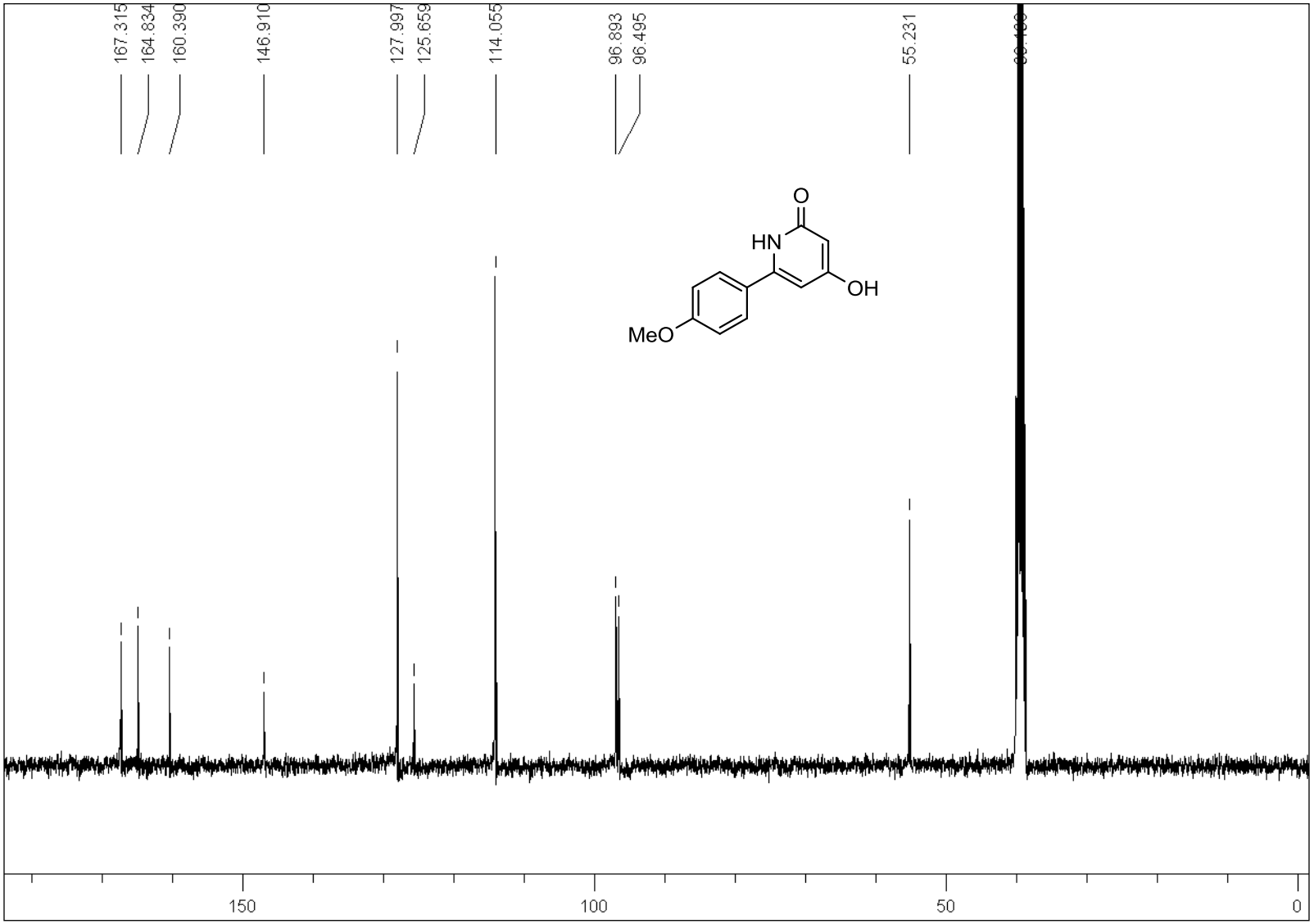
***tert*-Butyl 3-(4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)piperidine-1-carboxylate (1e)**



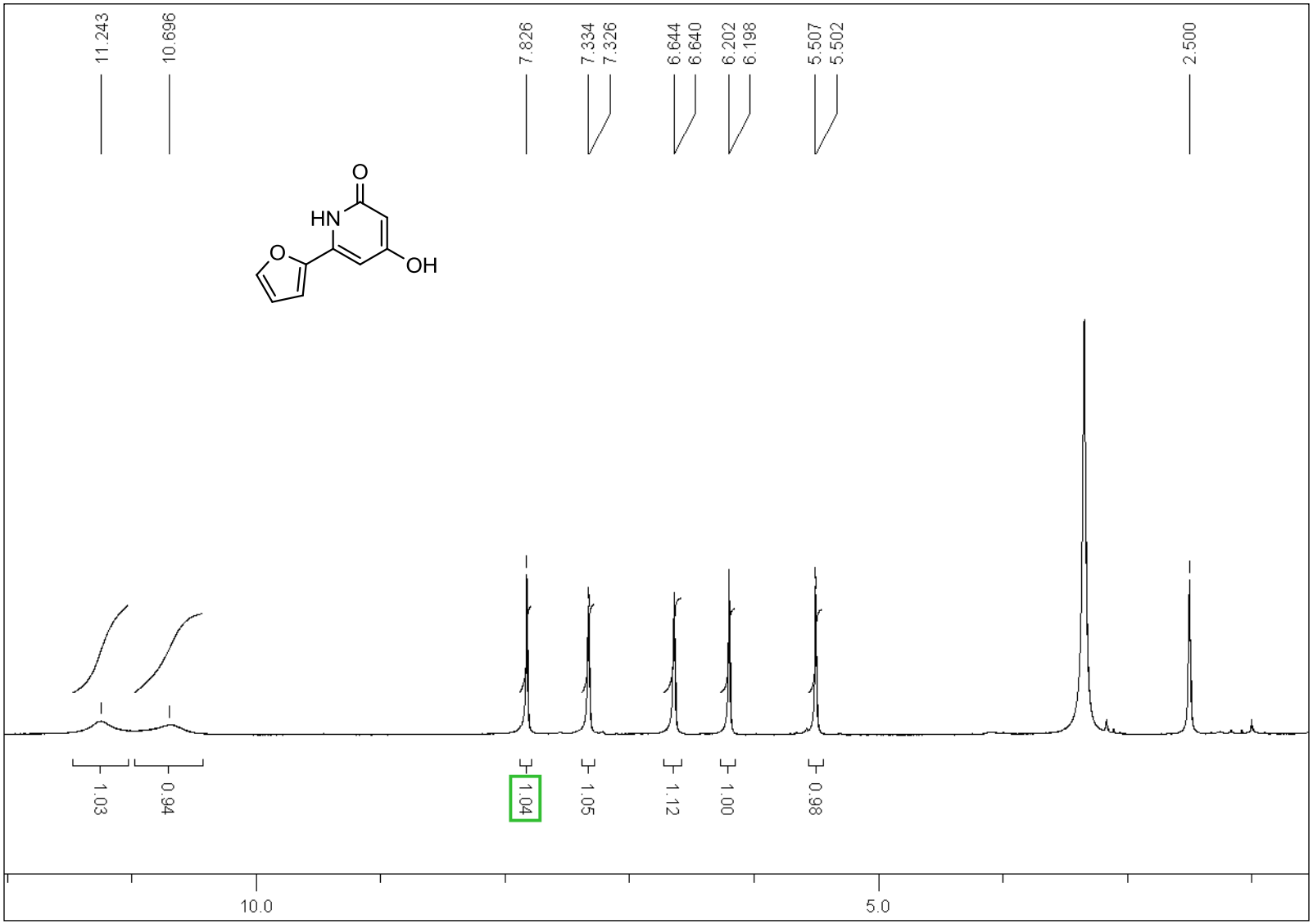

166.798
163.976
153.382
150.697
96.125
95.906
78.243
46.851
43.002
38.741
28.603
27.545
23.646
O
HN
Boc
N
OH
150
100
50
0
ppm (t1)

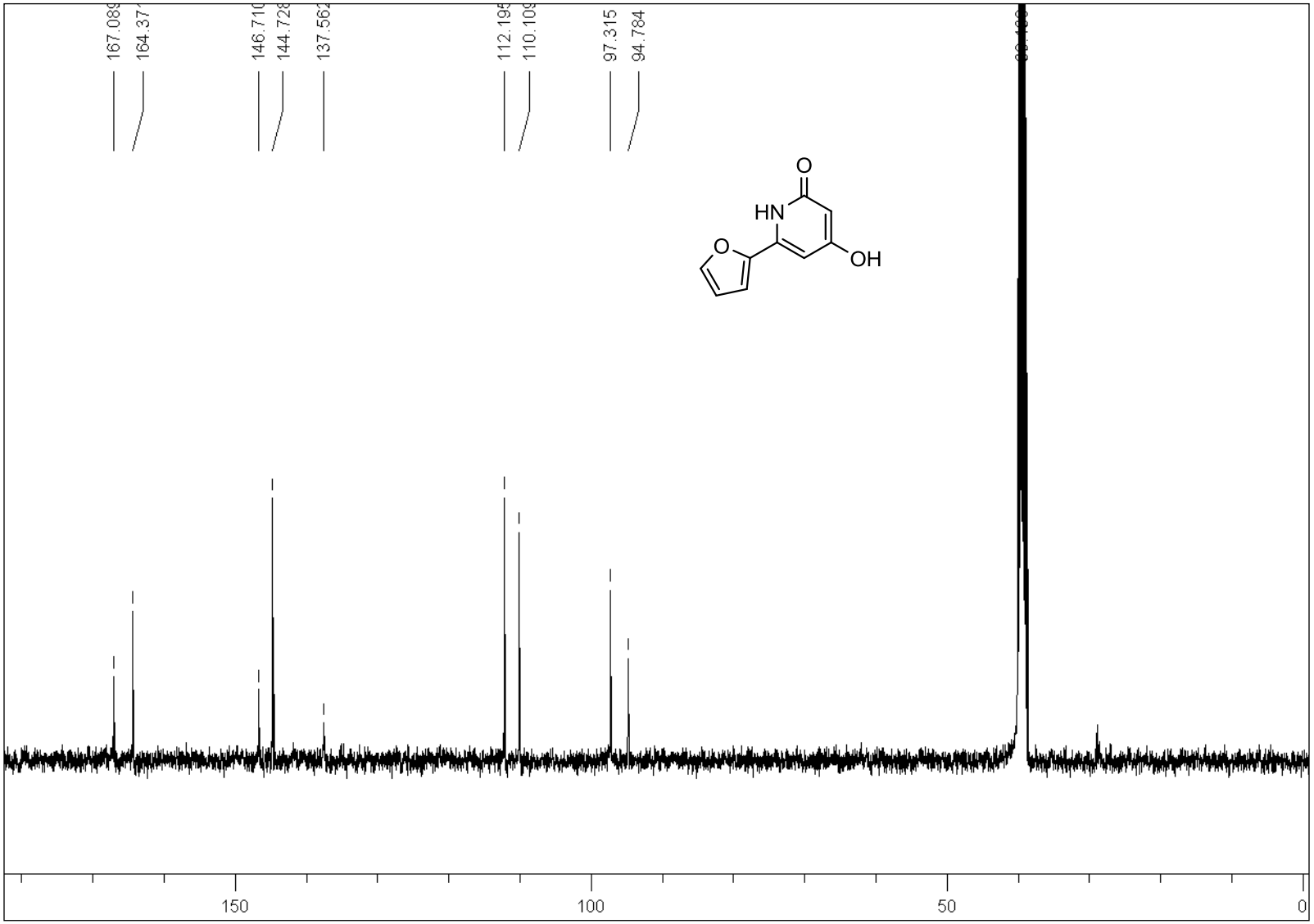
4-Hydroxy-6-(4-methoxyphenyl)pyridin-2(1*H*)-one (1f)



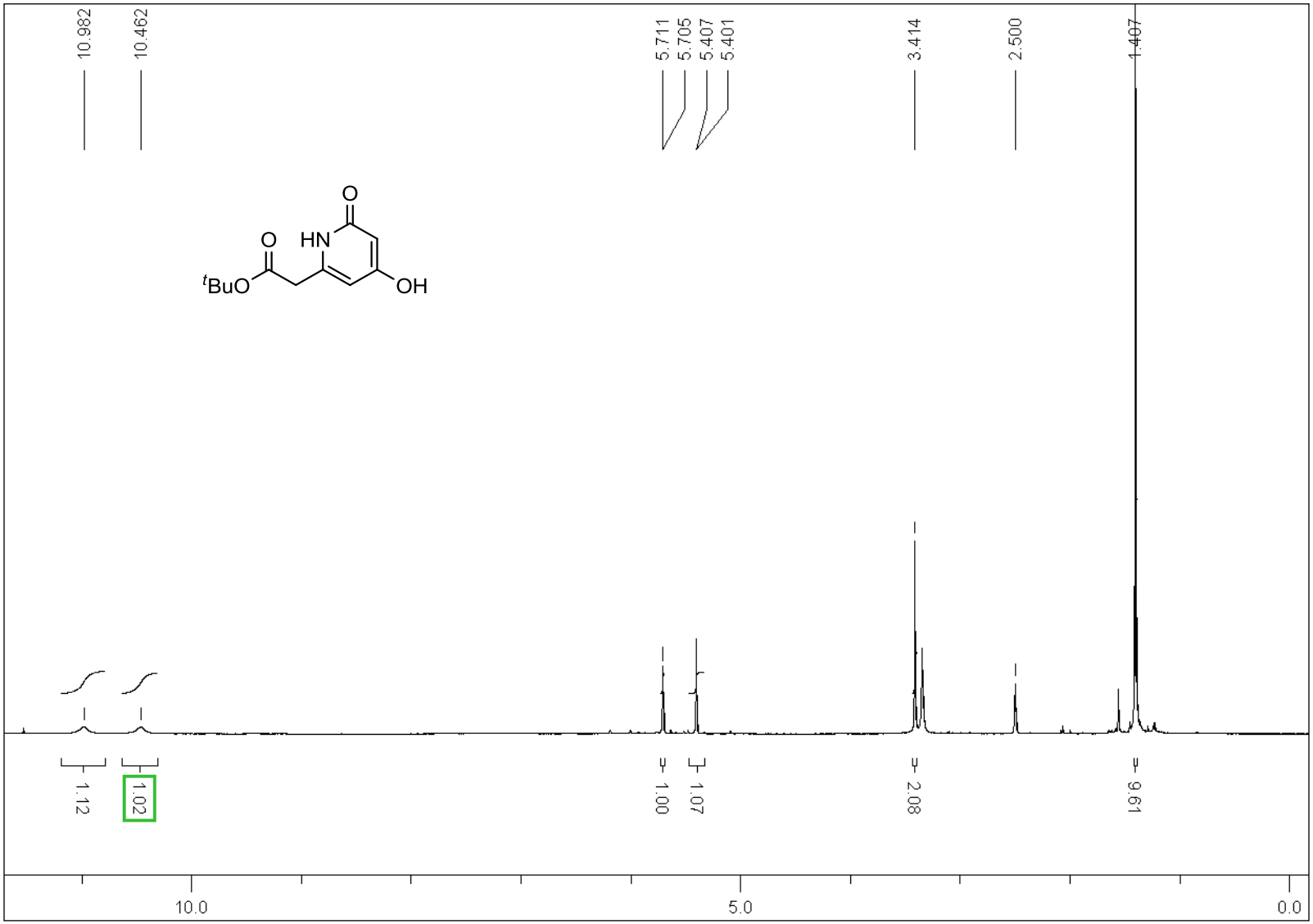

167.315
164.834
160.390
146.910
127.997
125.659
114.055
96.893
96.495
55.231
O
HN
OH
MeO
150
100
50
0

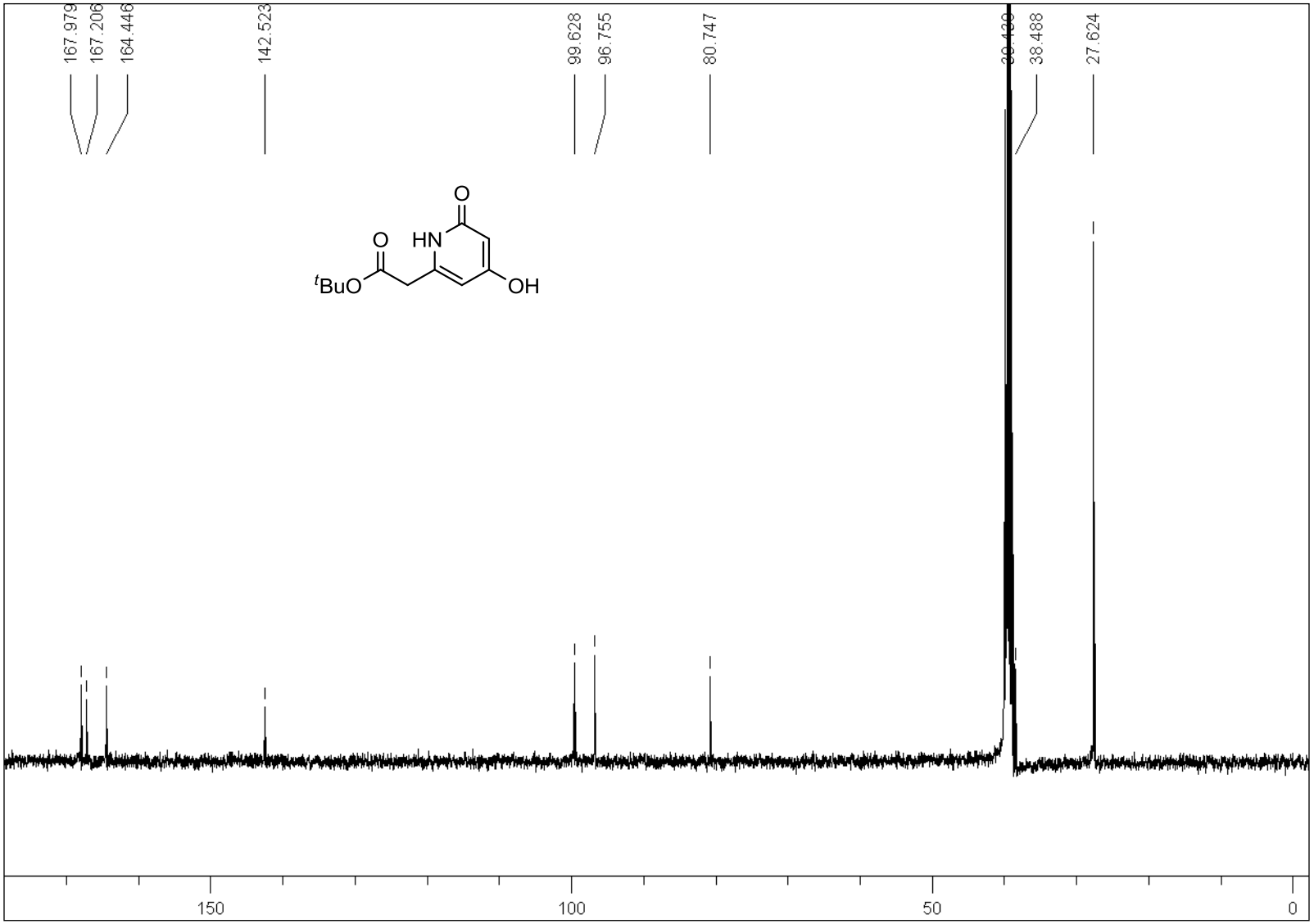
6-(Furan-2-yl)-4-hydroxypyridin-2(1*H*)-one (1g)



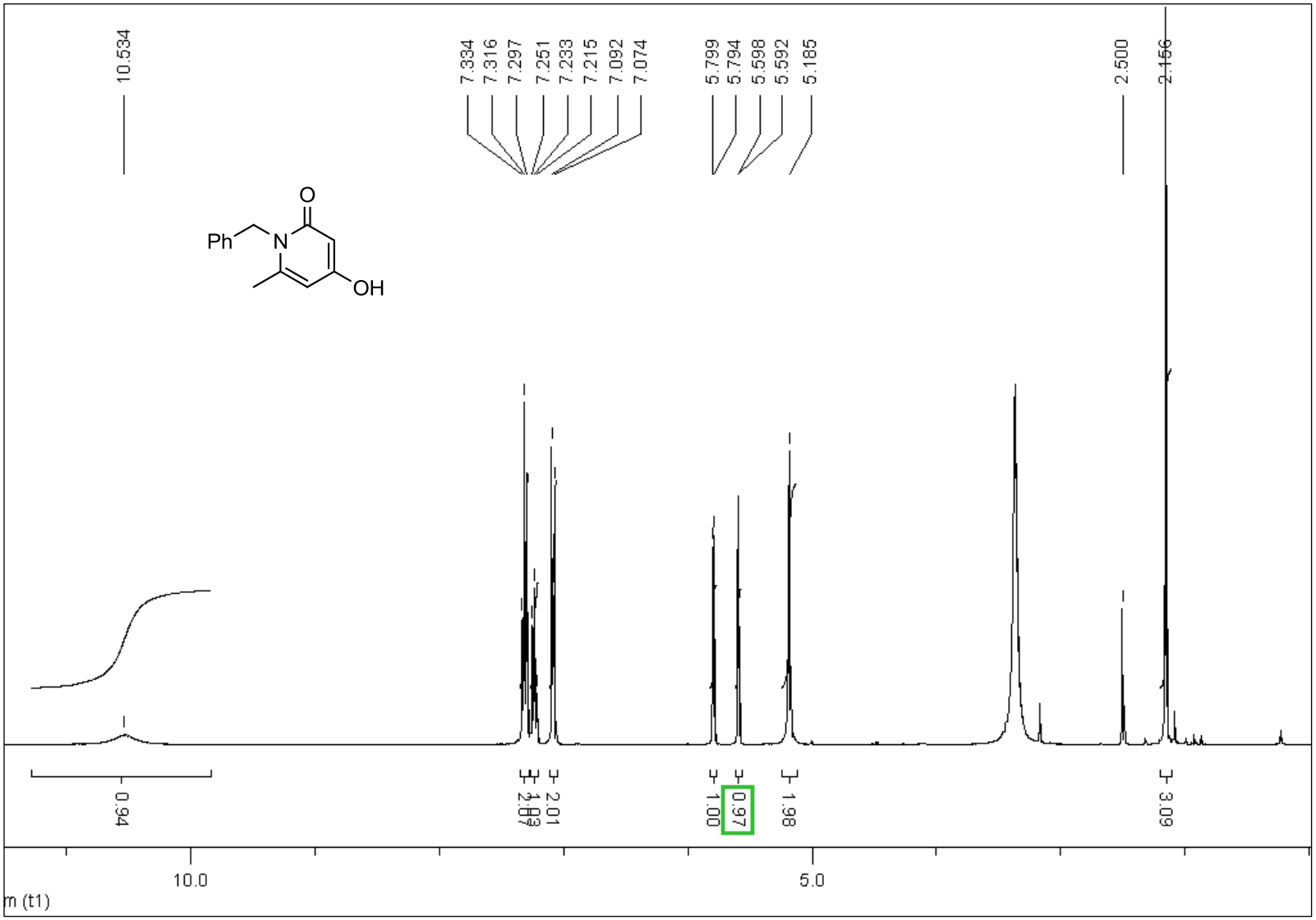

167.089
164.37
146.710
144.728
137.562
112.195
110.109
97.315
94.784
O
HN
O
OH
150
100
50
0

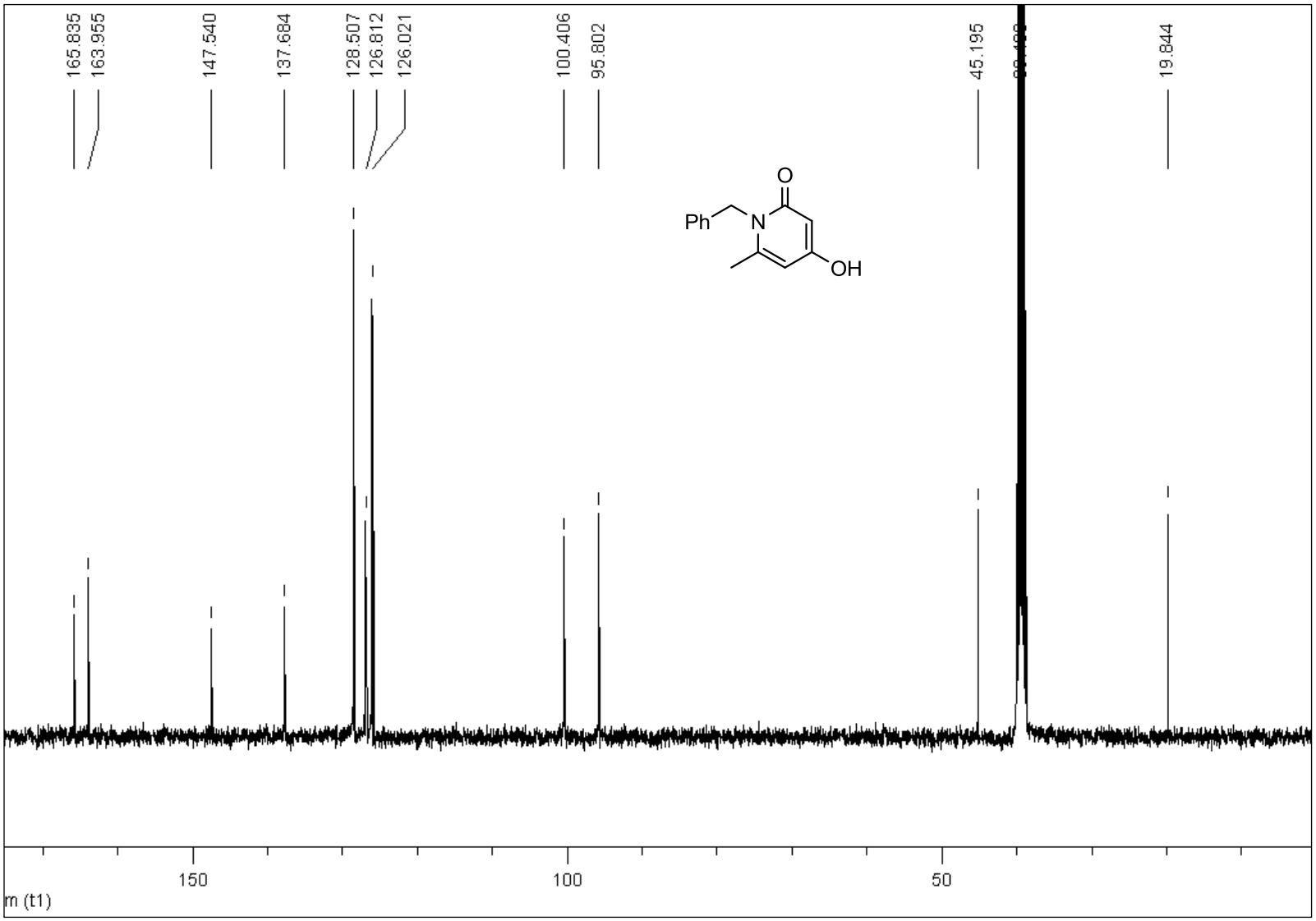
***tert*-Butyl 2-(4-Hydroxy-6-oxo-1,6-dihydropyridin-2-yl)acetate (1h)**



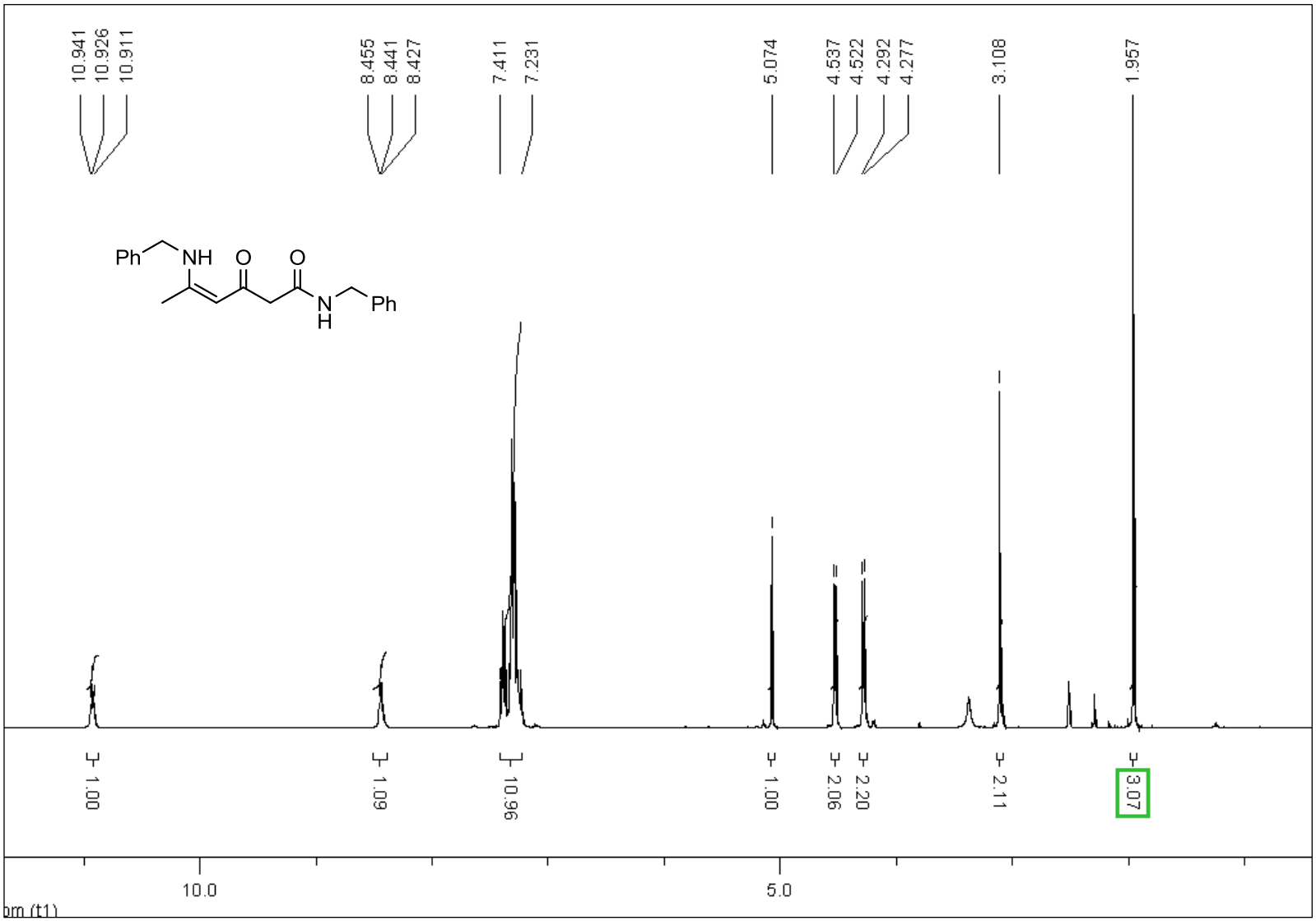

167.979
167.206
164.446
142.523
99.628
96.755
80.747
38.488
27.624
O
HN
O
OH
150
100
50
0

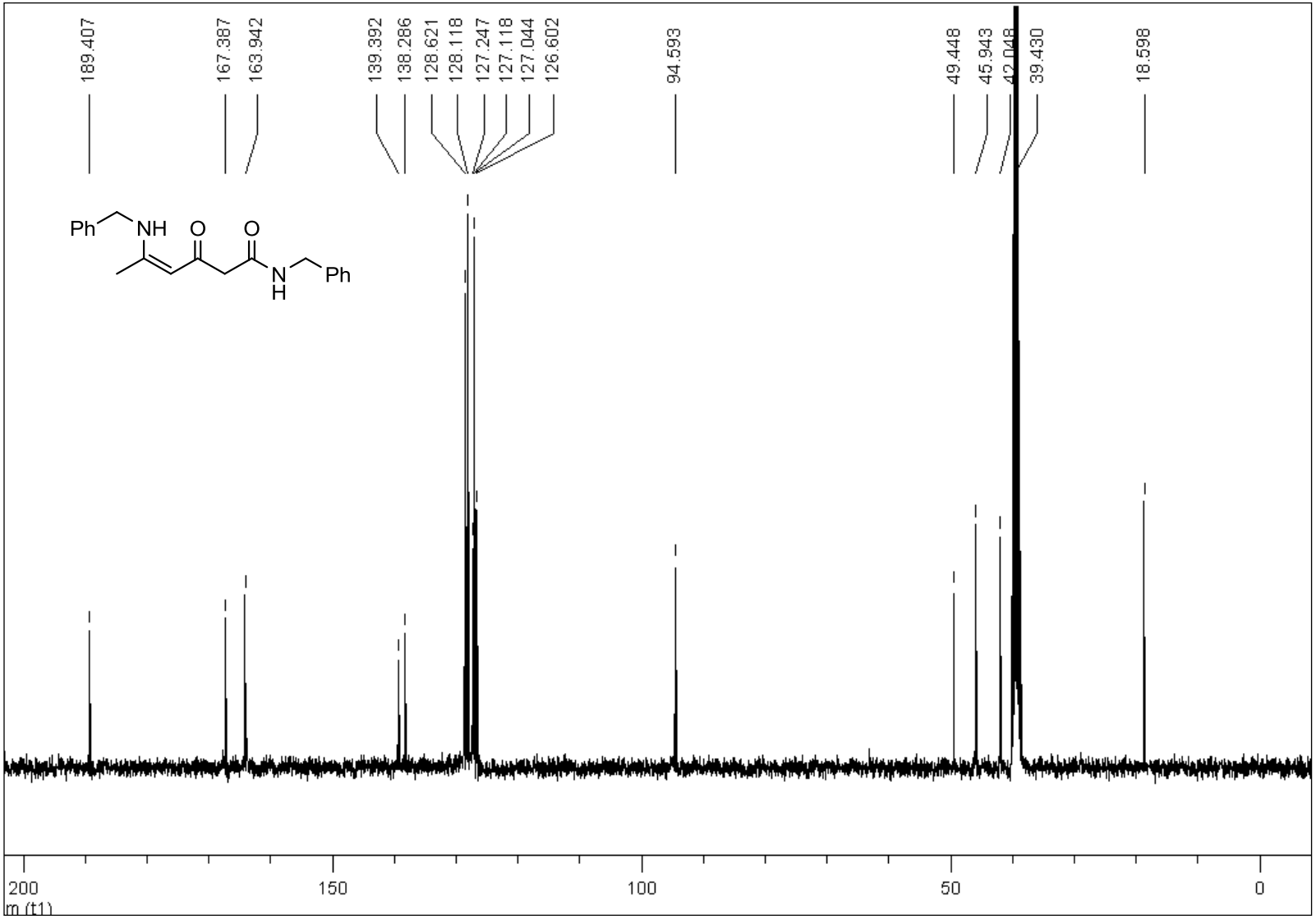
1-Benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (8)




165.835
163.955
147.540
137.684
128.507
126.812
126.021
100.406
95.802
45.195
19.844
O
Ph
N
OH
150
100
50
m (t1)

***N*-Benzyl-5-(benzylamino)3-oxohex-4-enamide (9)**




189.407
167.387
163.942
139.392
138.286
128.621
128.118
127.247
127.118
127.044
126.602
94.593
49.448
45.943
42.048
39.430
18.598
Ph
NH
O
O
N
H
Ph
200
150
100
50
0
m (t1)

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