Electronic Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting Information

Fast and efficient microwave-assisted synthesis of functionalized peptoids via Ugi reactions

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General Information

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75.46 MHz for ^{13}C NMR. Column chromatography was perfomed with silica gel (Acros Organic 0,035-0,070 mm) or reversed phase silica (RP-18). Reactions were performed on a CEM Co., Discover microwave reactor using sealed vessels. Melting points were recorded on a Logen Scientific-LS melting point apparatus and are uncorrected. IR spectra were recorded on a Varian 640-IR. Low resolution ESI mass spectra were obtained on a mass spectrometer hybrid triple quadrupole-3200 Qtrap model linear ion trap (Applied Biosystems) using electrospray ionization (TurbolonSpray®) in positive mode and on a Finnigan TSQ 7000 spectrometer, LC-Tech Ultra Plus pumps, Linear UV-VIS 200 detector, Sepserve Ultrasep ES RP-18, 5 μm, 1 × 100 mm column, flow 70 μl min^{-1}. High resolution ESI mass spectra were obtained on Autospec Ultima Mass Spectrometer [Waters Corp (Micromass UK)] equipped with an electrospray ionisation source (ESI) and Micro TOF- Bruker Daltonics instrument. All compounds were analyzed by IR, ^{1}H NMR, ^{13}C NMR and high/low resolution ESI mass spectra giving data consistent with the proposed structures.

Experimental Section

General procedure for the Ugi reaction:

Method A. A 10 mL glass tube containing the amine (1.0 mmol), paraformaldehyde (1.0 mmol), methyl isocyanoacetate (1.0 mmol), *Cbz*-glycine (1 mmol) [Et_3N (1.0 mmol) was also added when the amine hydrochloride **4a** was used], methanol (1 mL) and a small amount of sodium sulfate was sealed and introduced in the microwave reactor (CEM Co., Discover). The flask was irradiated for 0.5 to 3 min (150 W) under medium speed magnetic stirring. The temperature raised to 45 °C. If starting material was still present, additional cycles of 0.5 min heating were applied until no trace of the starting material was present by TLC analysis. After completion, the reaction was filtered, the solution

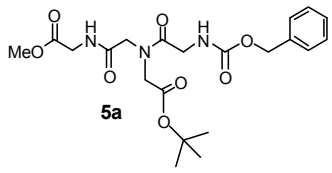
was concentrated in vacuum and the residue was purified by column chromatography to yield the respective peptoid.

Method B. Same procedure as method A, but without the use of solvent (methanol). The flask was introduced in the cavity of a microwave reactor (CEM Co., Discover) and irradiated for 1 - 6 min (150 W).

Method C. To a solution of the amine (1.0 mmol) in methanol (50 mL) was added sodium sulfate (0.20 g), paraformaldehyde (1.0 mmo), *Cbz*-glycine (1 mmol) and methyl isocyanoacetate (1.0 mmol). The reaction was heated to 45 °C for 18 h. The reaction mixture was filtered, the solution was concentrated in vacuum and the residue was purified by column chromatography to yield the respective peptoid.

General procedure for ester hydrolysis: A 10 mL glass tube containing a solution of the ester (0.5 mmol) in THF/H_2O (2:1, 7.5 mL) was added LiOH (1.25 mmol). The tube was sealed and introduced in a microwave reactor (CEM Co., Discover). The flask was irradiated for 3 - 5 min (150 W) under medium magnetic stirring and the temperature raised to 60°C. The solution was acidified with a 2 M solution of $NaHSO_4$ to pH 2 and extracted twice with ethyl acetate (25 mL). The organic phase was dried with sodium sulfate and concentrated to yield the respective acid, which was used without further purification.

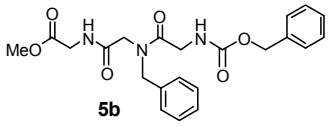
Compound data



5a

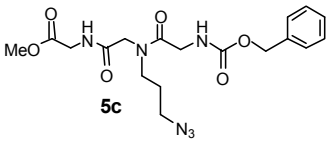
Compound 5a: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol), amine (0.066 g, 0.50 mmol) and Et_3N (0.069 mL, 0.50 mmol) yielding product **5a** (0.180 g, 80%) after column chromatography (CH_2Cl_2/MeOH 99:1) as a viscous pale yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.44. IR (KBr): $\nu_{máx}$/ cm^{-1} 3321, 3069, 2955, 1738, 1732, 1667, 1214, 1156, 1041, 986, 745, 699. ^1H NMR (300 MHz,$CDCl_3$): δ 8.65 (br s, 1H), 7.33 (br s, 5H), 5.62 (2br s, 1H), 5.10 (s,

2H), 4.13-3.97 (m, 8H), 3.70 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 169.9, 169.7, 168.3, 168.1, 156.2, 136.3, 128.4, 128.1, 128.0, 83.5, 67.0, 53.2, 52.3, 50.8, 42.4, 40.9, 27.9. ESI-MS *m/z* 474.4 (100%), 469.3 (26%), 452.2 ($[M+H]^+$, 21%), 428.3 (52%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{21}H_{30}N_3O_8$: 452.2033; found: 452.2020.



5b

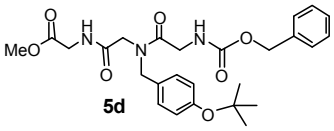
Compound 5b: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and benzylamine (0.054 g, 0.50 mmol) yielding product **5b** (0.186 g, 87%) after column chromatography (CH_2Cl_2/MeOH 99:1) as a light yellow solid. m.p (from CH_2Cl_2): 92-94°C. R_f (CH_2Cl_2/MeOH 3%)= 0.33. IR (KBr): $\nu_{máx}$/ cm^{-1} 3289, 3069, 2949, 1752, 1718, 1675, 1649, 1543, 1228, 1037, 994, 748, 693. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.35-7.15 (m, 10H), 7.07 (br s, 1H), 5.98 (br s, 1H), 5.05 (s, 2H), 4.63 and 4.59 (2 br s, 2H), 4.12-3.88 (m, 6H), 3.66 (s, 3H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.1, 169.8, 168.5, 156.3, 136.2, 134.7, 129.0, 128.7, 128.4, 128.0, 127.9, 126.7, 66.8, 52.2, 51.3, 49.1, 42.5, 40.9. ESI-MS *m/z* 450.1 (100%), 445.6 (25%), 428.0 ($[M+H]^+$, 26%), 339.4 (35%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{22}H_{26}N_3O_6$: 428.1822; found: 428.1816.



5c

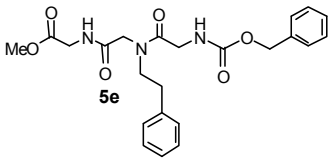
Compound 5c: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and 1-azido-3-amineпropane (0.050 g, 0.5 mmol) yielding product **5c** (0.193 g, 92%) after column chromatography (CH_2Cl_2/MeOH 99:1) as a viscous yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.26. IR (KBr): $\nu_{máx}$/ cm^{-1} 3321, 2098, 1752, 1717, 1684, 1646, 1535, 1266, 1211, 739, 699. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.31 (br s, 5H), 7.16 (br t, *J* = 5.3 Hz, 1H), 5.96-5.93 (m, 1H), 5.07 and 5.05 (2s, 2H), 4.12-3.78 (m, 6H), 3.68 (s, 3H), 3.47-3.26 (m, 4H), 1.88-1.69 (2m, 2H). ^{13}C NMR

(75.46 MHz, $CDCl_3$): δ 170.1, 169.6, 161.7, 156.6, 135.9, 128.3, 128.0, 127.7, 66.8, 52.2, 48.7, 45.5, 44.2, 39.5, 36.6, 28.2. ESI-MS *m/z* 443.6 (100%), 432.3 (35%), 421.3 ($[M+H]^+$, 28%), 332.4 (35%), 313.4 (28%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{18}H_{25}N_6O_6$: 421.1836; found: 421.1843.



5d

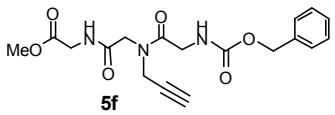
Compound 5d: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and 4-*t*-butoxybenzylamine (0.090 g, 0.50 mmol) yielding product **5d** (0.197 g, 79 %) after column chromatography (CH_2Cl_2/MeOH 99:1) as a viscous yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.29. IR (KBr): $\nu_{máx}$/ cm^{-1} 3321, 2980, 2929, 1724, 1715, 1672, 1664, 1509, 1237, 1160, 899. ^1H NMR (300 MHz,$CDCl_3$): δ 7.40-7.28 (m, 5H), 7.15-7.07 (m, 2H), 6.99-6.90 (m, 2H), 6.68 (br s, 1H), 5.78 (s, 1H), 5.11 (s, 2H), 4.63 and 4.56 (2s, 1H), 4.19-3.89 (m, 6H), 3.74 (s, 3H), 1.34 and 1.33 (2s, 9H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.3, 169.8, 168.7, 156.5, 155.6, 136.5, 129.4, 128.8, 128.4, 128.2, 127.8, 124.9, 79.1, 67.2, 52.7, 51.2, 49.5, 42.9, 41.3, 29.0. ESI-MS *m/z* 523.7 (57%), 522.4 (100%), 500.6 ($[M+H]^+$, 22%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{26}H_{34}N_3O_7$: 500.2397; found: 500.2404.



5e

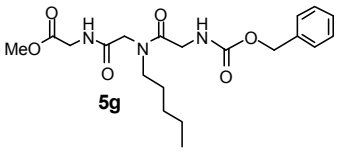
Compound 5e: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and phenylamine (0.060 g, 0.50 mmol) yileding product **5e** (0.192 mg, 87 %) after column chromatography (CH_2Cl_2/MeOH 99:1) as a viscous brown oil. R_f (CH_2Cl_2/MeOH 3%)= 0.27. IR (KBr): $\nu_{máx}$/ cm^{-1} 3318, 2952, 2926, 1718, 1684, 1651, 1260, 1211, 1030, 750, 700. ^1H NMR (300 MHz,$CDCl_3$): δ 7.35-7.15 (m, 10H), 6.81 (br s, 1H), 5.61 (br s, 1H), 5.10 (s, 2H), 4.11-3.95 (m, 4H), 3.86-3.78 (m, 2H), 3.73 (s, 3H), 3.60 (t, *J* = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.0, 169.2, 168.8, 156.3, 137.2, 136.1, 128.6, 128.4, 128.2, 127.8,

127.6, 126.2, 66.6, 52.0, 49.5, 41.8, 40.4, 35.2, 34.2. ESI-MS *m/z* 464.3 (100%), 442.6 ([M+H]$^+$, 34%), 353.3 (30%), 281.5 (20%). HRMS (ESI) *m/z*: calc. for [M+H]$^+$ $C_{23}H_{28}N_3O_6$: 442.1978; found: 442.1984.



5f

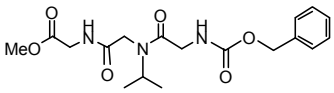
Compound 5f: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and propargylamine (0.028 g, 0.50 mmol) yielding product **5f** (0.144 g, 77 %) after column chromatography (CH_2Cl_2/MeOH 99:1) as a white solid. m.p (from CH_2Cl_2): 100-102°C. R_f (CH_2Cl_2/MeOH 3%)= 0.24. IR (KBr): $\nu_{máx}$/ cm^{-1} 3338, 3292, 2124,1726, 1666, 1222, 1030, 750, 698, 647. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.35 (br s, 5H), 6.91 and 6.76 (2br s, 1H), 5.76 (br s, 1H), 5.12 and 5.10 (2s, 2H), 4.20-4.15 (m, 5H), 4.06-3.99 (m, 3H), 3.74 (s, 3H), 2.38 and 2.30 (2s, 1H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.0, 169.1, 168.4, 156.3, 136.1, 128.3, 128.0, 127.8, 77.7, 74.0, 66.8, 52.2, 48.9, 42.4, 40.8, 37.6. ESI-MS *m/z* 398.2 (100%), 395.3 (46%), 376.3 ([M+H]$^+$, 27%), 287.1 (23%). HRMS (ESI) *m/z*: calc. for [M+H]$^+$ $C_{18}H_{22}N_3O_6Na$: 376.1509; found: 376.1508.



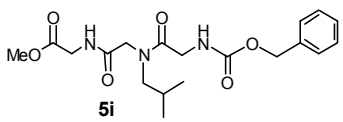
5g

Compound 5g: Prepared following the general procedure A for the Ugi reaction using *Cbz*-glycine (0.105 g, 0.50 mmol), methyl isocyanoacetate (0.050 g, 0.50 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and 1-pentylamine (0.044 g, 0.50 mmol) yielding product **5g** (0.171 g, 84 %) after column chromatography (CH_2Cl_2/MeOH 99:1) as a viscous pale yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.26. IR (KBr): $\nu_{máx}$/ cm^{-1} 3349, 2950, 2932,1729, 1675, 1618, 1540, 1439, 1212. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.37-7.29 (m, 5H), 6.89 (br t, *J* = 5.2 Hz, 1H), 5.82 (br t, *J* = 4.7 Hz, 1H), 5.12 and 5.09 (2s, 2H), 4.10 (d,

J = 4.7 Hz, 2H), 4.05 (s, 2H), 3.98 (d, *J* = 5.3 Hz, 2H), 3.72 (s, 3H), 3.41 and 3.31 (2t, *J* = 7.6 Hz and *J* = 7.9 Hz, 2H), 1.66-1.48 (m, 2H), 1.37-1.22 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.1, 169.3, 168.9, 156.3, 136.2, 128.4, 128.1, 127.9, 66.9, 52.3, 50.1, 48.7, 42.3, 40.9, 28.7, 27.9, 22.3, 13.9. ESI-MS *m/z* 408.1 ($[M+H]^+$, 100%), 319.3 (10%), 281.3 (12%), 118.1 (13%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{20}H_{30}N_3O_6$: 408.2135; found: 408.2127.

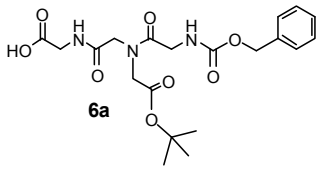

5h

Compound 5h: Prepared following the general procedure B for the Ugi reaction using *Cbz*-glycine (0.063 g, 0.30 mmol), methyl isocyanoacetate (0.030 g, 0.30 mmol), paraformaldehyde (0.009 g, 0.30 mmol) and isopropylamine (0.018 g, 0.30 mmol) yielding product **5h** (0.100 g, 88 %) after column chromatography (CH_2Cl_2/MeOH 99:1) as a white solid. m.p (from CH_2Cl_2): 92-94°C. R_f (CH_2Cl_2/MeOH 3%)= 0.23. IR (KBr): $\nu_{máx}$/ cm^{-1} 3350, 3284, 3090, 2980, 2952, 1764, 1724, 1684, 1641, 1552, 1257, 1208, 742, 702. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.36-7.30 (m, 5H), 7.10 (br t, *J* = 5.0 Hz, 1H), 5.92 (br t, *J* = 4.2 Hz, 1H), 5.12 and 5.09 (2s, 2H), 4.15-3.89 (m, 7H), 3.71 (s, 3H), 1.24 and 1.12 (2d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.1, 169.6, 169.0, 156.3, 136.2, 128.4, 128.0, 127.9, 66.8, 52.2, 48.1, 44.7, 42.7, 40.9, 20.6. ESI-MS *m/z* 380.2 ($[M+H]^+$, 100%), 145.1 (14%), 102.1 (18%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{18}H_{25}N_3O_6$ Na: 402.1641; found: 402.1656.


5i

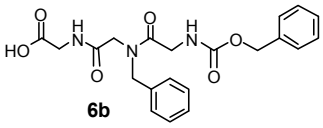
Compound 5i: Prepared following the general procedure A or B for the Ugi reaction using *Cbz*-glycine (0.084 g, 0.40 mmol), methyl isocyanoacetate (0.040 g, 0.40 mmol), paraformaldehyde (0.012 g, 0.40 mmol) and isobutylamine (0.029 g, 0.40 mmol) yielding product **5i** (0.142 g, 90%) after column chromatography (CH_2Cl_2/MeOH 99:1) as a pale yellow solid. m.p (from CH_2Cl_2): 102-104°C. R_f (CH_2Cl_2/MeOH 3%)= 0.24. IR (KBr): $\nu_{máx}$/ cm^{-1} 3339, 3293, 2958, 1755, 1698, 1664, 1532, 1211, 1062. ^{1}H NMR (300 MHz,$CDCl_3$): δ

7.36-7.30 (m, 5H), 7.00 (br t, *J* = 4.5 Hz, 1H), 5.84 (br s, 1H), 5.12 and 5.10 (2s, 2H), 4.10 (s, 2H), 4.05 (s, 2H), 3.98 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H), 3.28 and 3.16 (2d, *J* = 7.6 Hz, 2H), 2.02-1.90 (m, 1H), 0.94 and 0.88 (2d, *J* = 6.4 Hz, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.1, 169.8, 168.8, 156.3, 136.2, 128.4, 128.1, 127.9, 66.9, 55.9, 52.3, 50.6, 42.5, 41.0, 27.3, 19.9. ESI-MS *m/z* 394.2 ([M+H]$^+$, 100%), 215.3 (54%). HRMS (ESI) *m/z*: calc. for [M+Na]$^+$ $C_{19}H_{27}N_3O_6$ Na: 416.1798; found: 416.1799.



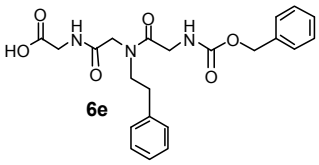
6a

Compound 6a[1]: Prepared following the general procedure for ester hydrolysis using compound **5a** (0.281 g, 0.60 mmol) with LiOH (0.037 g, 1.55 mmol) in THF/ H_2O (2:1, 9 mL) yielding product **6a** (0.255 g, 94%) as a viscous pale yellow oil. IR (KBr): $\nu_{máx}$/ cm^{-1} 3413, 3316, 1735, 1664, 1537, 1216, 1156, 1041, 984, 745, 699. ^{1}H NMR (300 MHz,CD_3OD): δ 7.38-7.25 (m, 5H), 5.10 (s, 2H), 4.21-3.90 (m, 8H), 1.49 and 1.46 (2s, 9H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 173.2, 172.5, 171.0, 170.5, 158.9, 138.1, 129.4, 129.0, 128.8, 83.4, 67.7, 52.5, 51.3, 43.1, 41.9, 28.2. ESI-MS *m/z* 460.5 (100%). HRMS (ESI) *m/z*: calc. for [M+Na]$^+$ $C_{21}H_{29}N_3O_8Na$: 460.1696; found: 460.1698.



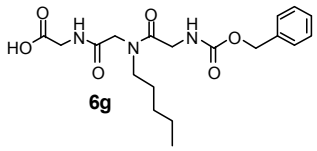
6b

Compound 6b[1]: Prepared following the general procedure for ester hydrolysis using compound **5b** (0.179 g, 0.40 mmol) with LiOH (0.025 g, 1.05 mmol) in THF/ H_2O (2:1, 6 mL) yielding product **6b** (0.161 g, 93%) as a pale yellow solid, which was used without further purification. m.p (from AcOEt): 96-98°C. IR (KBr): $\nu_{máx}$/ cm^{-1} 3279, 1762, 1677, 1656, 1541, 1182. ^{1}H NMR (300 MHz, CD_3OD): δ 7.39-7.22 (m, 10H), 5.10 and 5.07 (2s, 2H), 4.65 and 4.62 (2s, 2H), 4.13-4.03 (m, 4H), 3.90 (s, 2H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 172.8, 172.2, 171.3, 159.0, 138.1, 137.7, 130.0, 129.6, 129.4, 128.9, 128.8, 128.1, 67.7, 51.1, 49.7, 43.5, 41.7. ESI-MS *m/z* 436.4 (100%), 431.5 (31%), 414.2 ([M+H]$^+$, 75%), 370.2 (22%), 339.2 (70%). HRMS (ESI) *m/z*: calc. for [M+H]$^+$ $C_{21}H_{24}N_3O_6Na$: 414.1665; found: 414.1657.



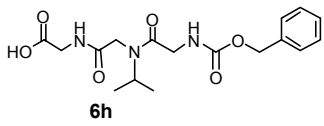
6e

Compound 6e: Prepared following the general procedure for ester hydrolysis using compound **5e** (0.120 g, 0.27 mmol) with LiOH (0.016 g, 0.68 mmol) in THF/ H_2O (2:1, 4 mL) yielding product **6e** (0.107 g, 92%) as a pale yellow foam. IR (KBr): $\nu_{máx}$/ cm^{-1} 3344, 1732, 1678, 1646, 1615, 1543, 1214, 699. ^1H NMR (300 MHz,CD_3OD): δ 7.38-7.14 (m, 10H), 5.08 and 5.06 (2s, 2H), 4.07-3.73 (m, 6H), 3.62-3.54 (m, 1H), 3.40 (t, *J* = 7.1 Hz, 1H), 2.93-2.73 (m, 2H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 172.8, 171.8, 171.4, 158.8, 139.5, 138.0, 130.0, 129.7, 129.4, 128.8, 127.7, 127.3, 67.7, 50.2, 43.0, 41.7, 36.5, 34.5. ESI-MS *m/z* 450.2 (100%), 445.6 (26%), 428.1 ($[M+H]^+$, 71%), 353.2 (64%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{22}H_{26}N_3O_6Na$: 428.1822; found: 428.1842.



6g

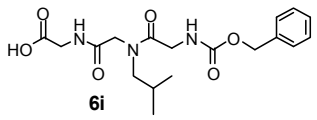
Compound 6g: Prepared following the general procedure for ester hydrolysis using compound **5g** (0.075 g, 0.18 mmol) with LiOH (0.011 g, 0.46 mmol) in THF/ H_2O (2:1, 2.8 mL) yielding product **6g** (0.069 g, 96%) as a viscous yellow oil, which was used without further purification. IR (KBr): $\nu_{máx}$/ cm^{-1} 3331, 2957, 2928, 1715, 1669, 1649, 1537, 1212, 738, 698. ^1H NMR (300 MHz,CD_3OD): δ 7.38-7.26 (m, 5H), 5.09 (s, 2H), 4.12-3.90 (m, 6H), 3.40-3.33 (m, 2H), 1.70-1.48 (m, 2H), 1.39-1.21 (m, 4H), 0.95-0.87 (m, 3H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 172.8, 171.8, 171.6, 159.0, 138.1, 129.4, 128.9, 128.8, 67.8, 50.7, 50.0, 43.3, 41.7, 29.9, 28.9, 23.4, 14.3. ESI-MS *m/z* 394.3 ($[M+H]^+$, 100%), 243.3 (16%), 130.2 (26%), 116.2 (18%), 102.1 (18%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{19}H_{27}N_3O_6Na$: 416.1798; found: 416.1810.



6h

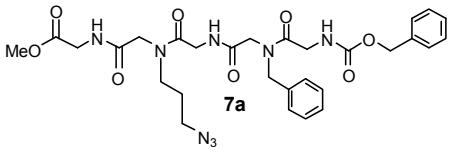
Compound 6h: Prepared following the general procedure for ester hydrolysis using compound **5h** (0.084 g, 0.22 mmol) with LiOH (0.013 g, 0.55 mmol) in THF/ H_2O (2:1, 3.3 mL) gave the product **6d** (0.079 g, 98%) as a white solid.

m.p (from AcOEt): 126-128°C. IR (KBr): $\nu_{máx}$/ cm^{-1} 3355, 1729, 1675, 1540, 1200, 1052, 736, 697. ^{1}H NMR (300 MHz,CD_3OD): δ 7.38-7.26 (m, 5H), 5.09 (s, 2H), 4.17-4.10 (m, 3H), 3.98-3.90 (m, 4H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 172.8, 172.1, 171.3, 159.0, 138.1, 129.4, 129.0, 128.8, 67.7, 47.3, 44.7, 43.6, 41.7, 20.7, 19.8. HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{17}H_{23}N_3O_6Na$: 388.1485; found: 388.1496.



6i

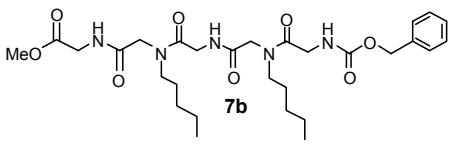
Compound 6i: Prepared following the general procedure for ester hydrolysis using compound **5i** (0.068 g, 0.17 mmol) with LiOH (0.010 g, 0.43 mmol) in THF/ H_2O (2:1, 2.8 mL) yielding product **6i** (0.063 g, 96%) as a pale yellow foam, which was used without further purification. IR (KBr): $\nu_{máx}$/ cm^{-1} 3424, 3275, 1749, 1721, 1615, 1225. ^{1}H NMR (300 MHz,CD_3OD): δ 7.37-7.25 (m, 5H), 5.08 (s, 2H), 4.14-3.90 (m, 6H), 3.22 and 3.20 (2d, *J* = 7.5 Hz, 2H), 2.01-1.86 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75.46 MHz, CD_3OD): δ 172.7, 171.9, 171.3, 158.9, 138.1, 129.4, 128.9, 128.8, 67.7, 56.3, 51.0, 43.3, 41.7, 28.5, 20.4, 20.2. ESI-MS *m/z* 398.4 (31%), 397.4 (100%), 380.3 ($[M+H]^+$, 44%), 342.3 (37%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{18}H_{25}N_3O_6Na$: 402.1641; found: 402.1657.



7a

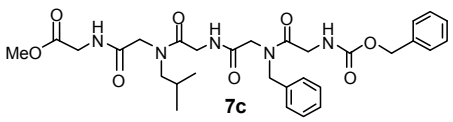
Compound 7a: Prepared following the general procedure (method B) for the Ugi reaction using acid **6b** (0.113 g, 0.27 mmol), methyl isocyanoacetate (0.027 g, 0.27 mmol), paraformaldehyde (0.015 g, 0.50 mmol) and 1-azido-3-aminepropane (0.027 g, 0.27 mmol) yielding product **7a** (0.145 g, 86%) after column chromatography (CH_2Cl_2/MeOH 97:3) as a viscous yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.22. IR (KBr): $\nu_{máx}$/ cm^{-1} 3309, 2101, 1749, 1721, 1660, 1540, 1217, 753, 702. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.37-7.17 (m, 10H), 5.98 (br s, 1H), 5.08 (s, 2H), 4.66 and 4.61 (2br s, 2H), 4.16-3.91 (m, 10H), 3.70 and 3.67 (2s, 3H), 3.49-3.25 (2m, 4H), 1.87-1.73 (2m, 2H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.3, 170.0, 169.4, 168.9, 168.7, 156.4, 136.2, 134.9,

129.0, 128.6, 128.4, 128.0, 127.9, 126.7, 66.9, 52.2, 51.4, 49.9, 48.8, 48.2, 45.6, 42.6, 40.9, 27.3, 26.6. ESI-MS *m/z* 647.6 (100%), 642.3 (24%), 636.4 (49%), 625.5 ($[M+H]^+$, 38%), 518.2 (23%), 507.1 (21%), 339.2 (25%). HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{29}H_{37}N_8O_8$: 625.2734; found: 625.2740.



7b

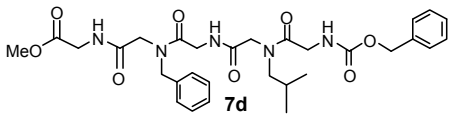
Compound 7b: Prepared following the general procedure (method B) for the Ugi reaction using acid **6g** (0.600 g, 1.52 mmol), methyl isocyanoacetate (0.150 g, 1.52 mmol), paraformaldehyde (0.045 g, 1.52 mmol) and 1-pentylamine (0.132 g, 1.52 mmol) yielding product **7b** (0.728 g, 81%) after column chromatography (CH_2Cl_2/MeOH 97:3) as a viscous yellow oil. R_f (CH_2Cl_2/MeOH 3%)= 0.23. IR (KBr): $\nu_{máx}$/ cm^{-1} 3315, 2958, 2932, 1746, 1722, 1651, 1540, 1209, 736, 698. ^1H NMR (300 MHz,$CDCl_3$): δ 7.34-7.27 (m, 5H), 7.12 (br t, *J* = 5.3 Hz, 1H), 5.91 (br t, *J* = 4.5 Hz, 1H), 5.09 and 5.06 (2s, 2H), 4.10-3.94 (m, 10H), 3.69 (s, 3H), 3.41-3.23 (m, 4H), 1.62-1.44 (m, 4H), 1.35-1.18 (m, 8H), 0.90-0.83 (2t, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.2, 169.1, 168.9, 168.7, 168.3, 156.3, 136.3, 128.4, 128.0, 127.9, 66.8, 52.2, 49.9, 49.8, 49.6, 48.6, 47.8, 42.4, 40.9, 28.9, 28.7, 27.9, 26.9, 26.8, 22.3, 13.9. ESI-MS *m/z* 593.5 (53%), 592.5 ($[M+H]^+$, 100%), 465.4 (18%), 259.4 (34%), 254.4 (16%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{29}H_{45}N_5O_8$: 614.3166; found: 614.3166.



7c

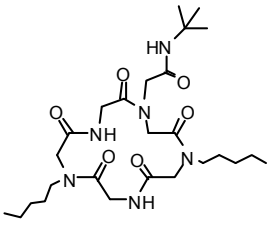
Compound 7c: Prepared following the general procedure (method B) for the Ugi reaction using acid **6b** (0.102 g, 0.25 mmol), methyl isocyanoacetate (0.025 g, 0.25 mmol), paraformaldehyde (0.007 g, 0.25 mmol) and isobutylamine (0.018 g, 0.25 mmol) yielding product **7c** (0.137 g, 92%) after column chromatography (CH_2Cl_2/MeOH 97:3) as a yellow foam. R_f (CH_2Cl_2/MeOH 3%)= 0.21. IR (KBr): $\nu_{máx}$/ cm^{-1} 3289, 2960, 1752, 1695, 1664, 1552, 1214, 739, 702. ^1H NMR (300 MHz,$CDCl_3$): δ 7.38-7.16 (m, 10H), 5.98 (br s, 1H), 5.08 (s, 2H), 4.65 and 4.61 (2br s, 2H), 4.18-3.93 (m, 10H), 3.68 and

3.66 (2s, 3H), 3.24 and 3.15 (2d, *J* = 6.8 Hz and 7.6 Hz, 2H), 2.00-1.87 (m, 1H), 0.97-0.84 (m, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 170.2, 169.7, 169.5, 168.8, 168.4, 156.3, 136.2, 134.8, 129.0, 128.6, 128.4, 127.9, 127.7, 126.6, 66.8, 55.7, 52.2, 51.3, 50.1, 49.0, 42.6, 40.8, 41.0, 27.2, 20.0, 19.8. ESI-MS *m/z* 598.3 ($[M+H]^+$, 100%), 509.3 (24%), 469.4 (25%), 203.3 (17%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{30}H_{39}N_5O_8$: 620.2696; found: 620.2699.



7d

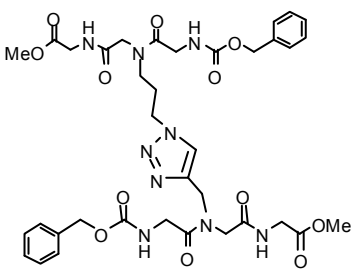
Compound 7d: Prepared following the general procedure (method B) for the Ugi reaction using acid **6i** (0.120 g, 0.32 mmol), methyl isocyanoacetate (0.032 g, 0.32 mmol), paraformaldehyde (0.0100 g, 0.32 mmol) and benzylamine (0.034 g, 0.32 mmol) yielding product **7d** (0.170 g, 89%) after column chromatography (CH_2Cl_2/MeOH 97:3) as a yellow foam. R_f (CH_2Cl_2/MeOH 3%)= 0.21. IR (KBr): $\nu_{máx}$/ cm^{-1} 3318, 3297, 2954, 1758, 1692, 1666, 1542, 1214, 740, 697. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.37-7.27 (m, 7H), 7.22-7.13 (m, 3H), 5.93 (br t, *J* = 4.6 Hz, 1H), 5.07 and 5.04 (2s, 2H), 4.65 and 4.60 (2s, 2H), 4.19-3.91 (m, 10H), 3.68 and 3.67 (2s, 3H), 3.23 and 3.12 (2d, *J* = 7.5 and 7.3 Hz, 2H), 1.97-1.84 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75.46 MHz, $CDCl_3$): 170.4, 169.8, 169.2, 168.7, 168.2, 156.3, 136.2, 134.8, 128.9, 128.6, 128.3, 127.9, 127.6, 126.6, 66.7, 55.6, 52.1, 51.3, 49.8, 49.1, 42.4, 41.2, 40.8, 27.2, 19.9, 19.8. ESI-MS *m/z* 598.4 ($[M+H]^+$, 100%), 338.3 (51%), 279.3 (23%). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{30}H_{39}N_5O_8$: 620.2696; found: 620.2691.



10

Compounds 8, 9, 10: Compound **7b** (0.562 g, 0.95 mmol) was hydrolyzed following the general procedure for hydrolysis, yielding the compound **8** (0.494 g, 0.86 mmol, 90% yield). To compound **8** (0.312 g, 0.54 mmol) in *i*-PrOH (5 mL) was added ammonium formiate (60 mg) and 10% Pd/C (10%

in weight with respect to the substrate, 31 mg). The mixture was heated in a microwave to 120°C for 5 min (150W) under stirring. After filtration through Celite®, the solvent was concentrated to give the acyclic amino acid **9** (0.211 g, 0.48 mmol) which was used without further purification. Compound **9** (0.211 g, 0.48 mmol) was submitted to macrocyclization: A solution of paraformaldehyde (0.014 g, 0.48 mmol) in methanol (100 mL) was added simultaneously, using a syringe pump, a solution of amino acid (0.211 g, 0.48 mmol) in 50 mL of MeOH and a solution of *t*-butyl isocyanide (0.040 g, 0.48 mmol) in 50 mL of MeOH at a rate of 0.6 mL/h at rt. After the addition was complete, the reaction mixture was stirred for 24 h, filtered and the solvent was removed. The resulting residue was purified by reverse phase column chromatography (MeOH/H_2O 95:5), furnishing the cyclic peptoid **10** (0.178 g, 0.33 mmol, 69% yield) as a yellow foam. R_f (CH_2Cl_2/MeOH 6%)= 0.30. IR (KBr): $\nu_{máx}$/ cm^{-1} 3275, 2961, 2929, 1669, 1658, 1652, 1632. ^1H NMR (300 MHz,$CDCl_3$): δ 4.34-4.05 (m, 5H), 4.00 (s, 2H), 3.94 (s, 2H), 3.87-3.51 (m, 3H), 3.42-3.32 (m, 4H), 1.72-1.48 (m, 4H), 1.44-1.24 (m, 17H), 0.96-0.88 (m, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 171.3, 169.4, 167.8, 166.1, 165.8, 163.3, 54.7, 53.1, 51.8, 51.3, 50.3, 49.6, 49.4, 46.2, 45.0, 42.5, 40.1, 29.0, 28.7, 28.6, 28.2, 27.8, 26.2, 22.2, 13.8. ESI-MS *m/z* 561.5 (89 %), 539.4 ($[M+H]^+$, 100 %), 316.4 (43 %), 203.3 (48 %), 185.3 (48 %), 105.1 (63 %). HRMS (ESI) *m/z*: calc. for $[M+Na]^+$ $C_{26}H_{46}N_6O_6$: 561.3377; found: 561.3379.



11

Compound 11: A 10 mL glass tube containing a solution of the compound **5c** (0.084 g, 0.20 mmol) and **5f** (0.075 g, 0.20 mmol) in DCM/H_2O (1:1, 6 mL), sodium ascorbate (6 mg, 0.03 mmol) and copper sulfate pentahydrate (0.050 g, 0.20 mmol) was sealed and introduced in a microwave reactor (CEM Co., Discover). The flask was irradiated for 1 min (150 W) under medium magnetic stirring and the temperature raised to 50°C. The solution was extracted twice with DCM (2 × 25 mL). The organic phase was dried with sodium sulfate and concentrated yielding compound **11** (0.116 g, 73%) after

column chromatography (CH_2Cl_2/MeOH 93:7) as a viscous yellow oil. R_f (CH_2Cl_2/MeOH 6%)= 0.25. IR (KBr): $\nu_{máx}$/ cm^{-1} 3332, 2954, 2931, 1750, 1713, 1660, 1538, 1214, 740, 698. ^1H NMR (300 MHz,$CDCl_3$): δ 7.58 (br s, 1H), 7.31 (br s, 11H), 6.05-5.92 (m, 2H), 5.06 (s, 4H), 4.63 (br s, 2H), 4.42-3.79 (m, 14H), 3.67 (s, 6H), 3.33 (br s, 2H), 2.30-2.05 (m, 2H).^{13}C NMR (75.46 MHz, $CDCl_3$): 170.3, 170.0, 170.1, 169.5, 169.0, 168.5, 156.6, 156.5, 136.3, 136.3, 128.4, 128.1, 128.1, 127.9, 127.9, 127.8, 123.5, 66.8, 52.3, 52.2, 49.9, 47.8, 47.3, 45.6, 42.8, 43.4, 41.1, 42.5, 40.9, 29.6. ESI-MS *m/z* 796.5 ($[M+H]^+$), 818.5. HRMS (ESI) *m/z*: calc. for $[M+H]^+$ $C_{36}H_{46}N_9O_{12}$: 796.3266; found: 796.3246.

References:

[1] O. E. Vercillo, C. K. Z. Andrade and L. A. Wessjohann, *Org. Lett*., 2008, **10**, 205.

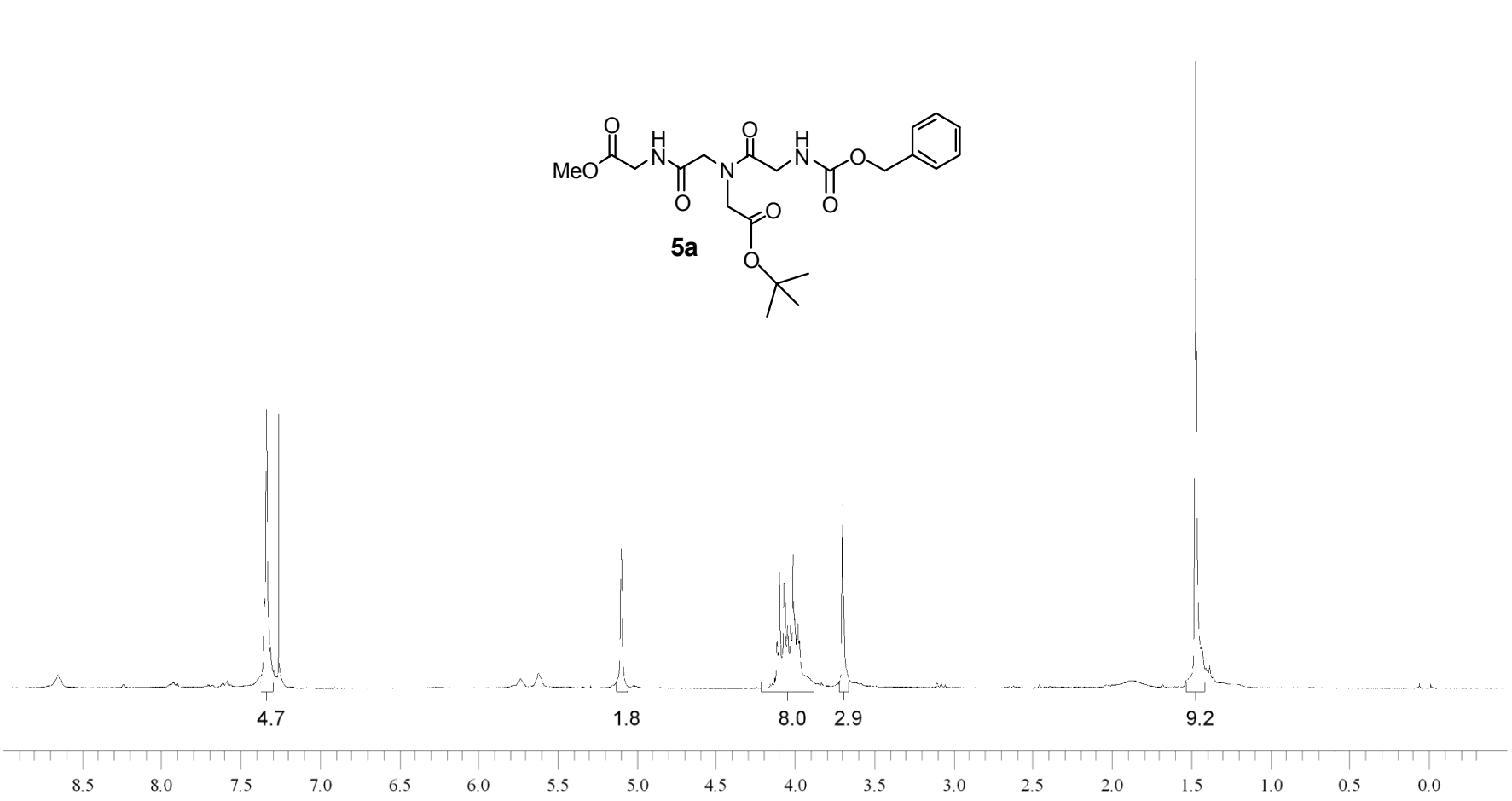


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5a**.

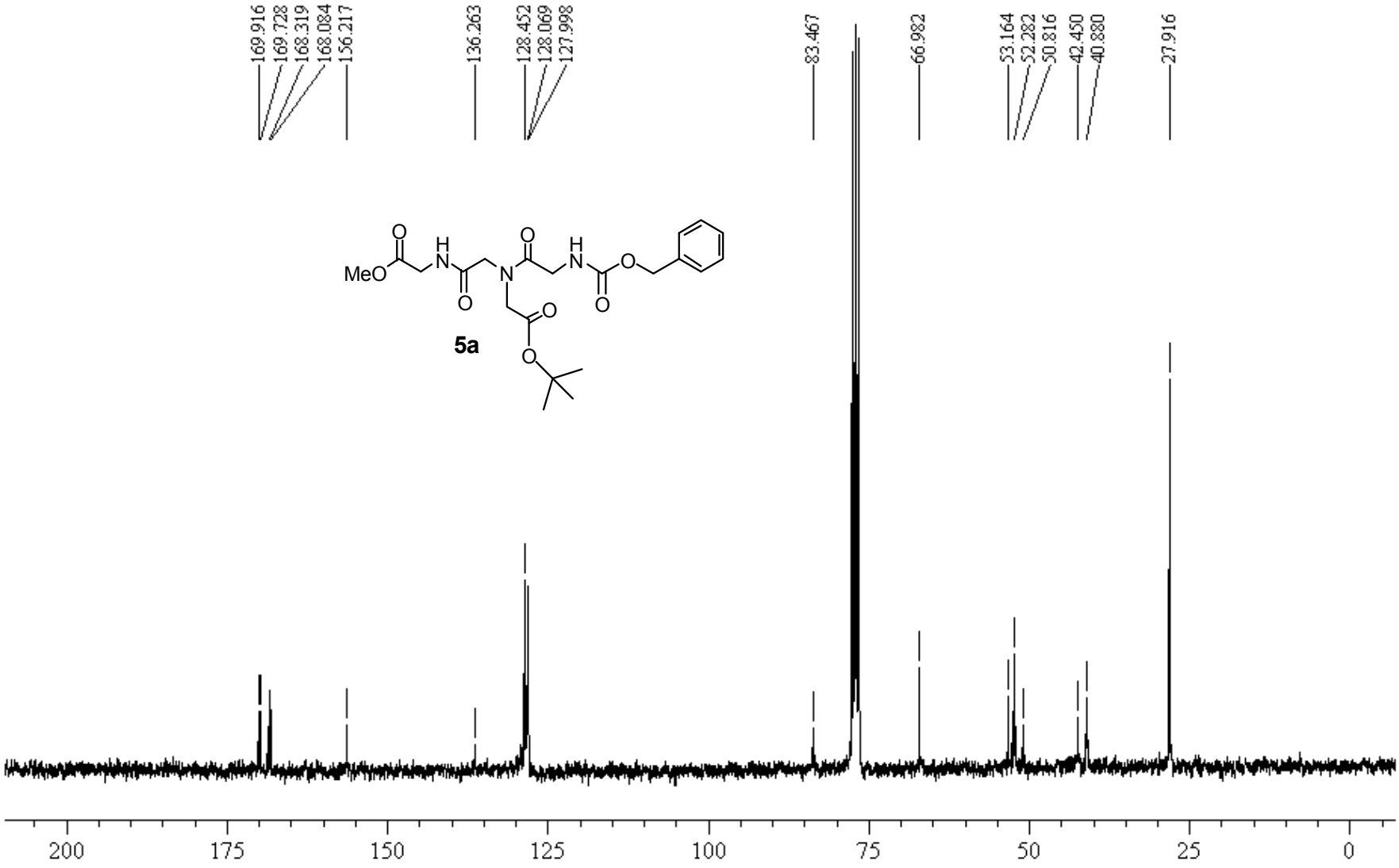


Figure 2. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5a**.

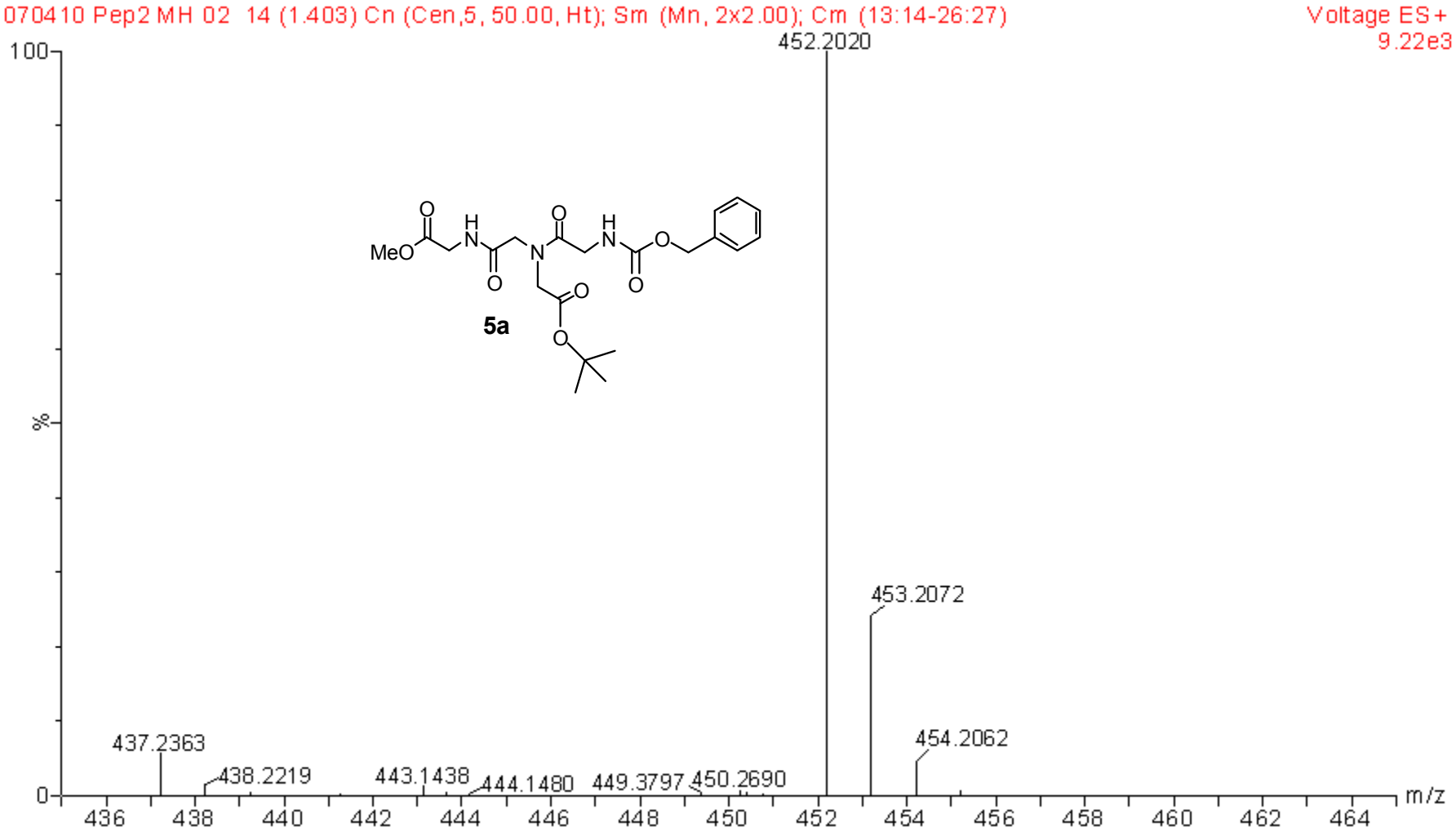


Figure 3. EI-HRMS of compound **5a**.

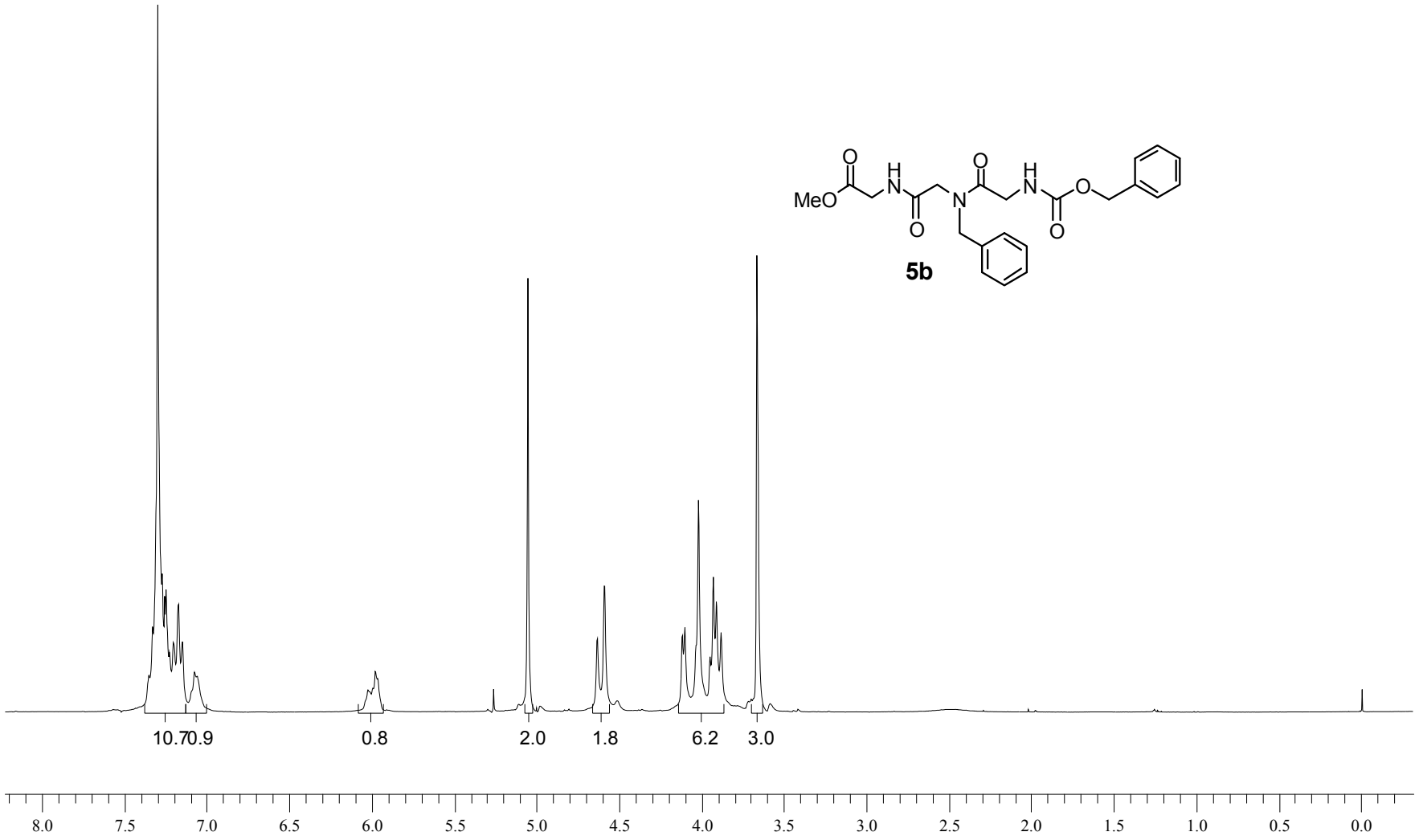


Figure 4. ^{1}H NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5b**.

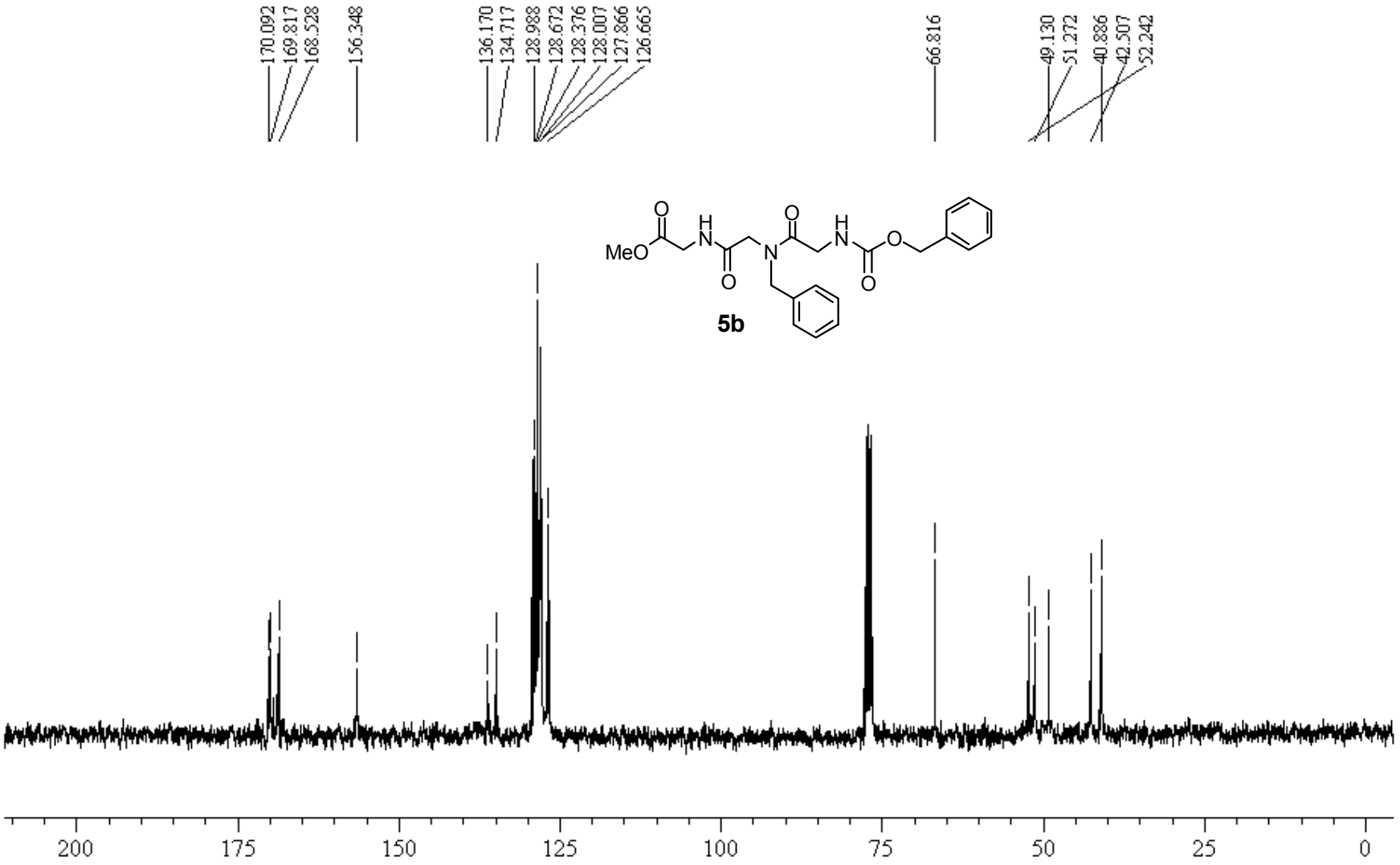
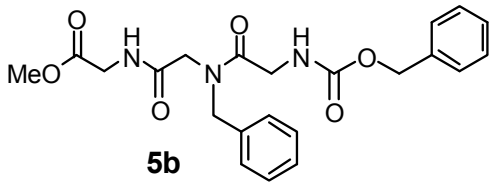


Figure 5. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5b**.



5b

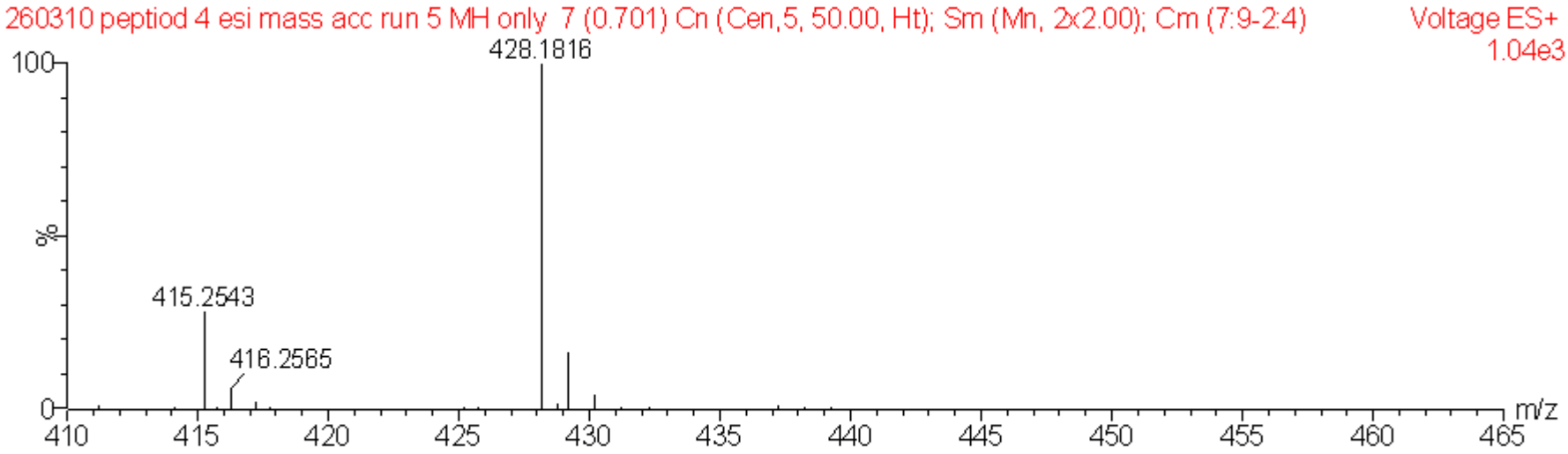


Figure 6. EI-HRMS of compound **5b**.

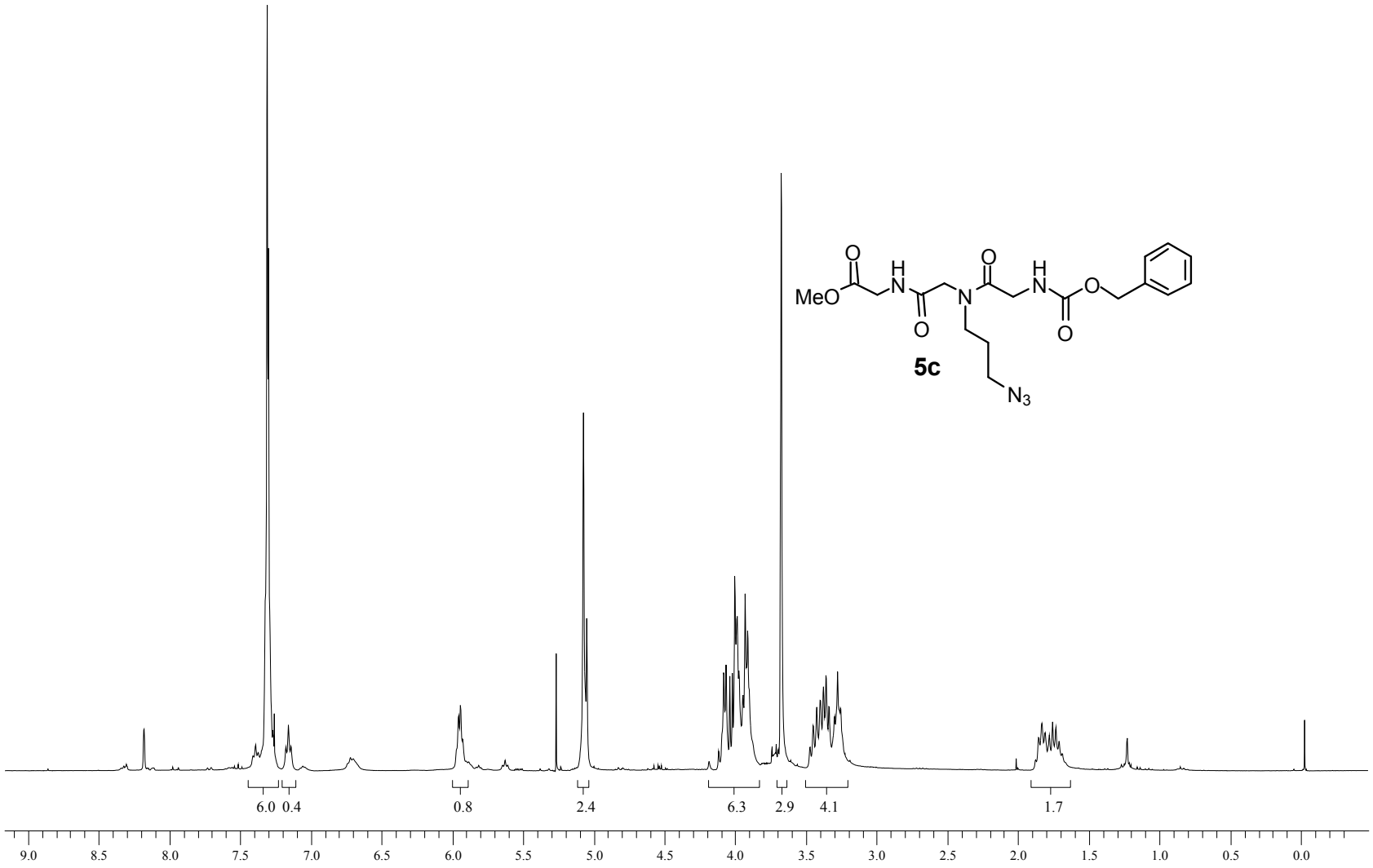


Figure 7. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5c**.

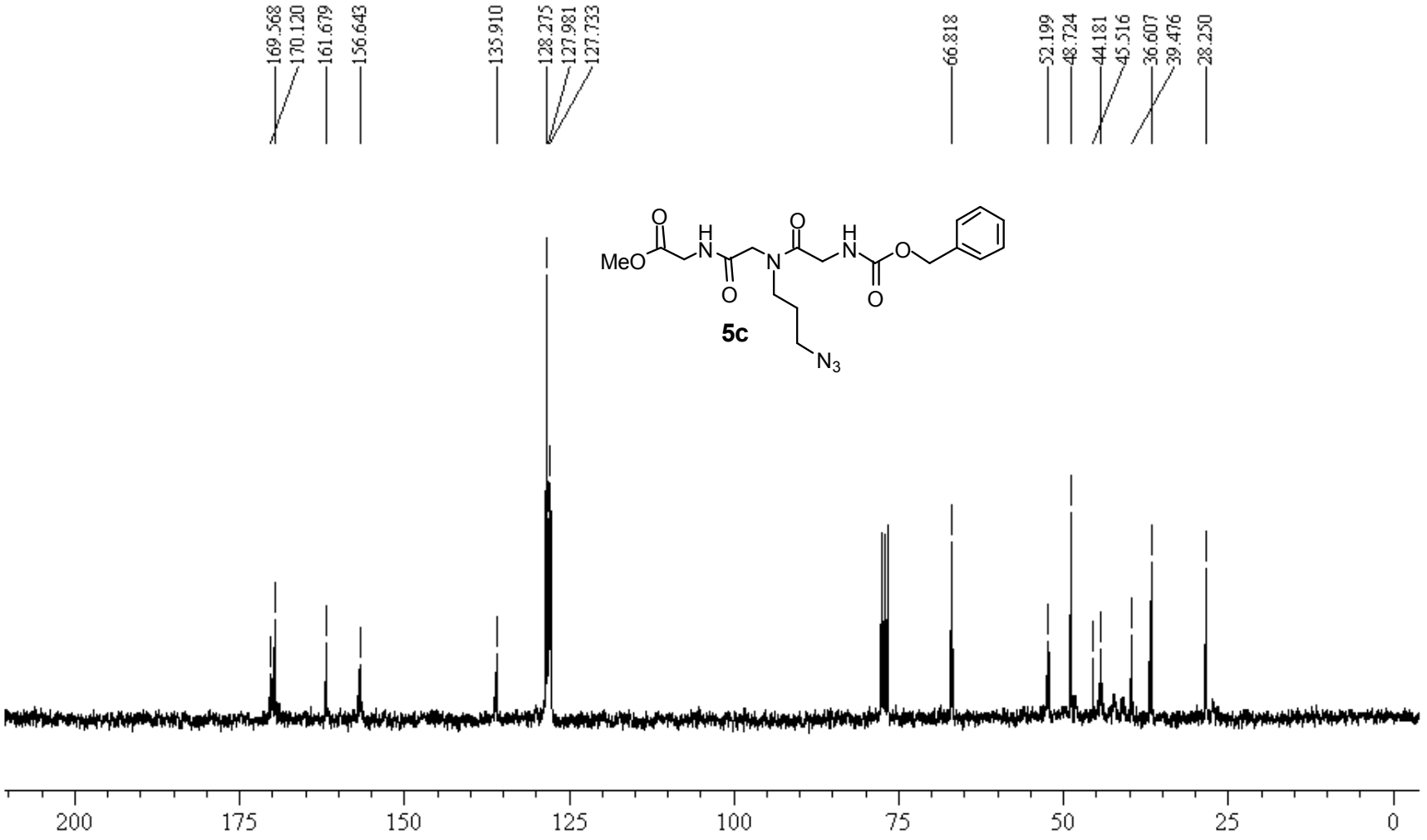


Figure 8. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5c**.

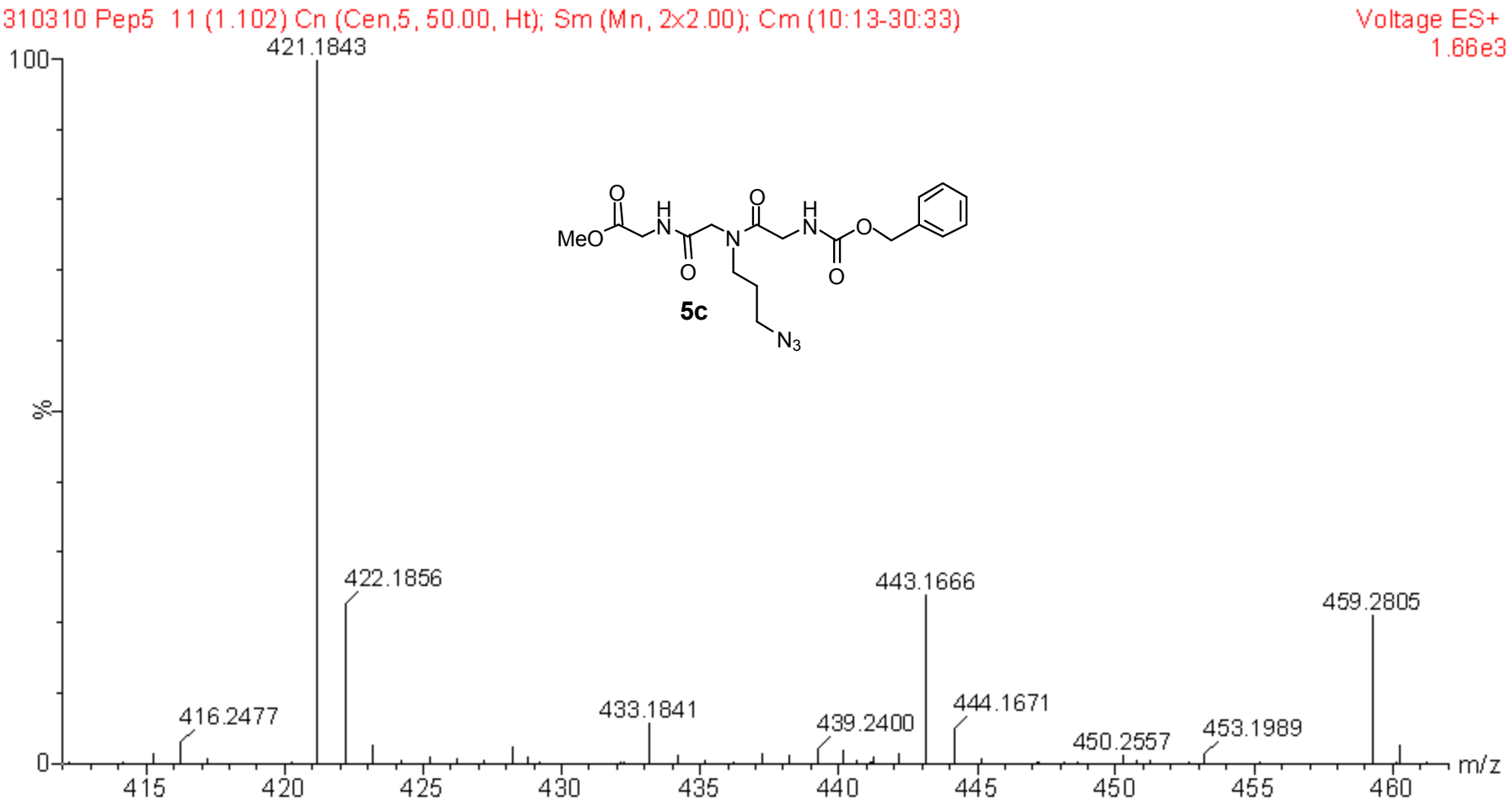


Figure 9. EI-HRMS of compound **5c**.

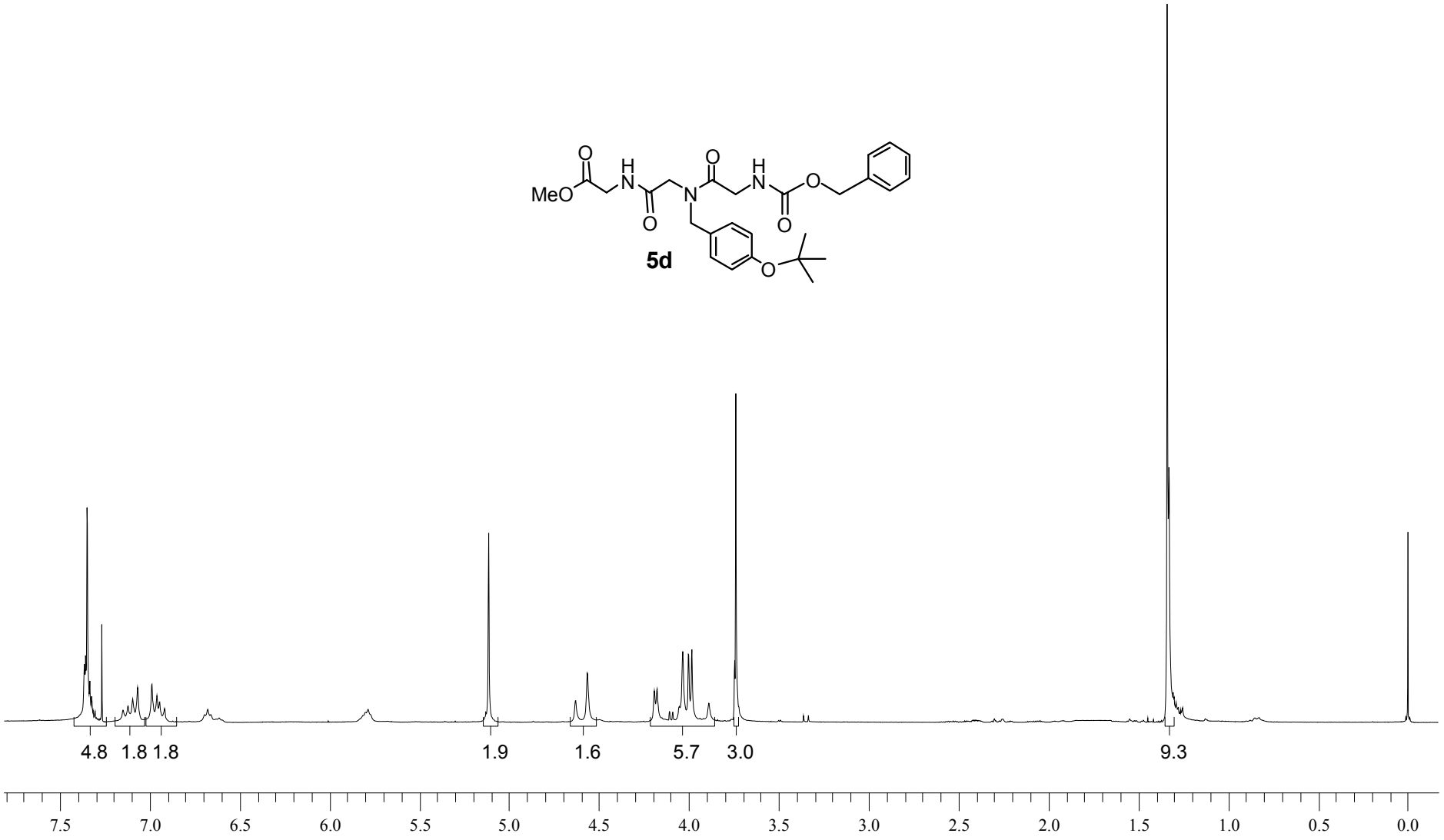


Figure 10. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5d**.

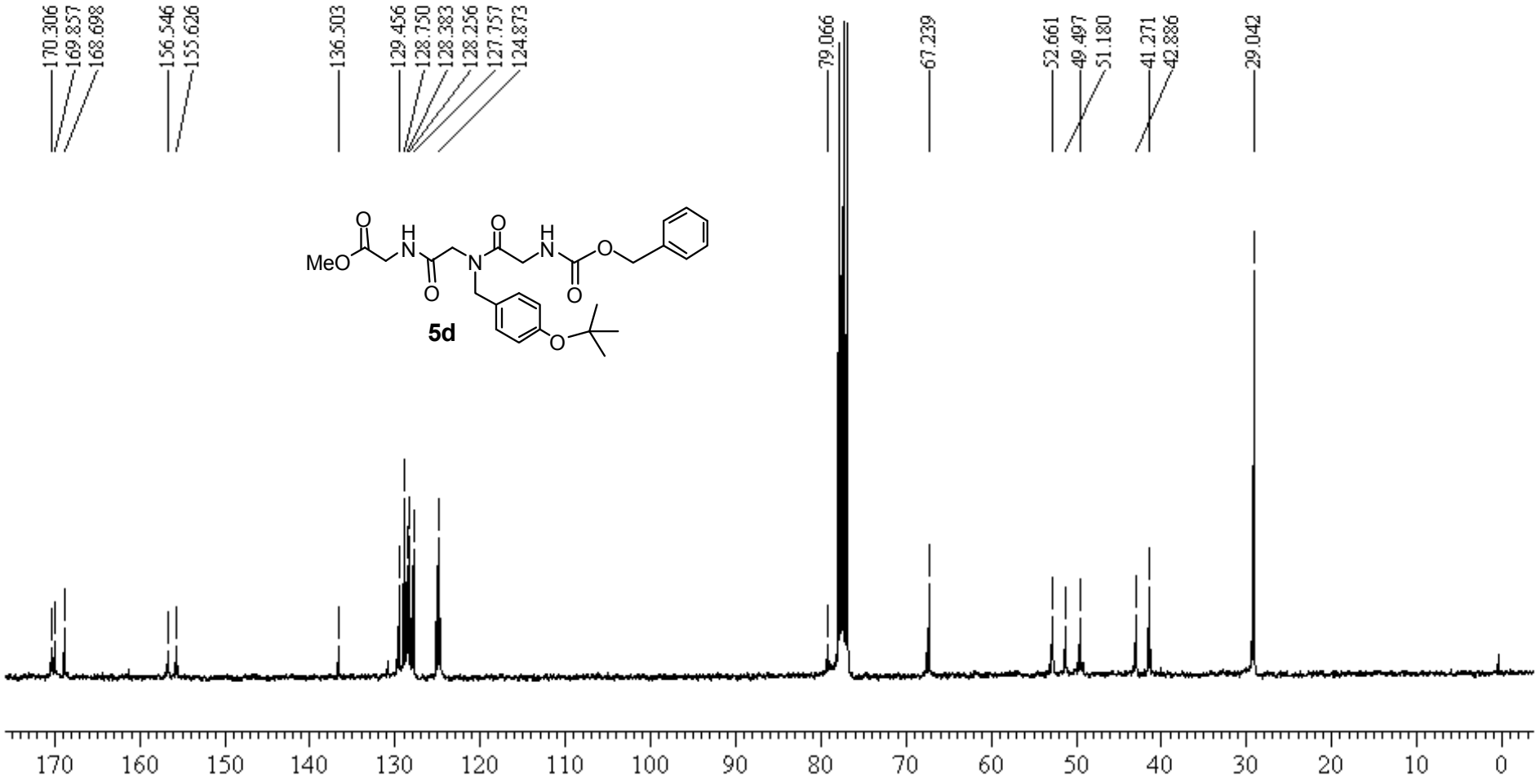


Figure 11. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5d**.

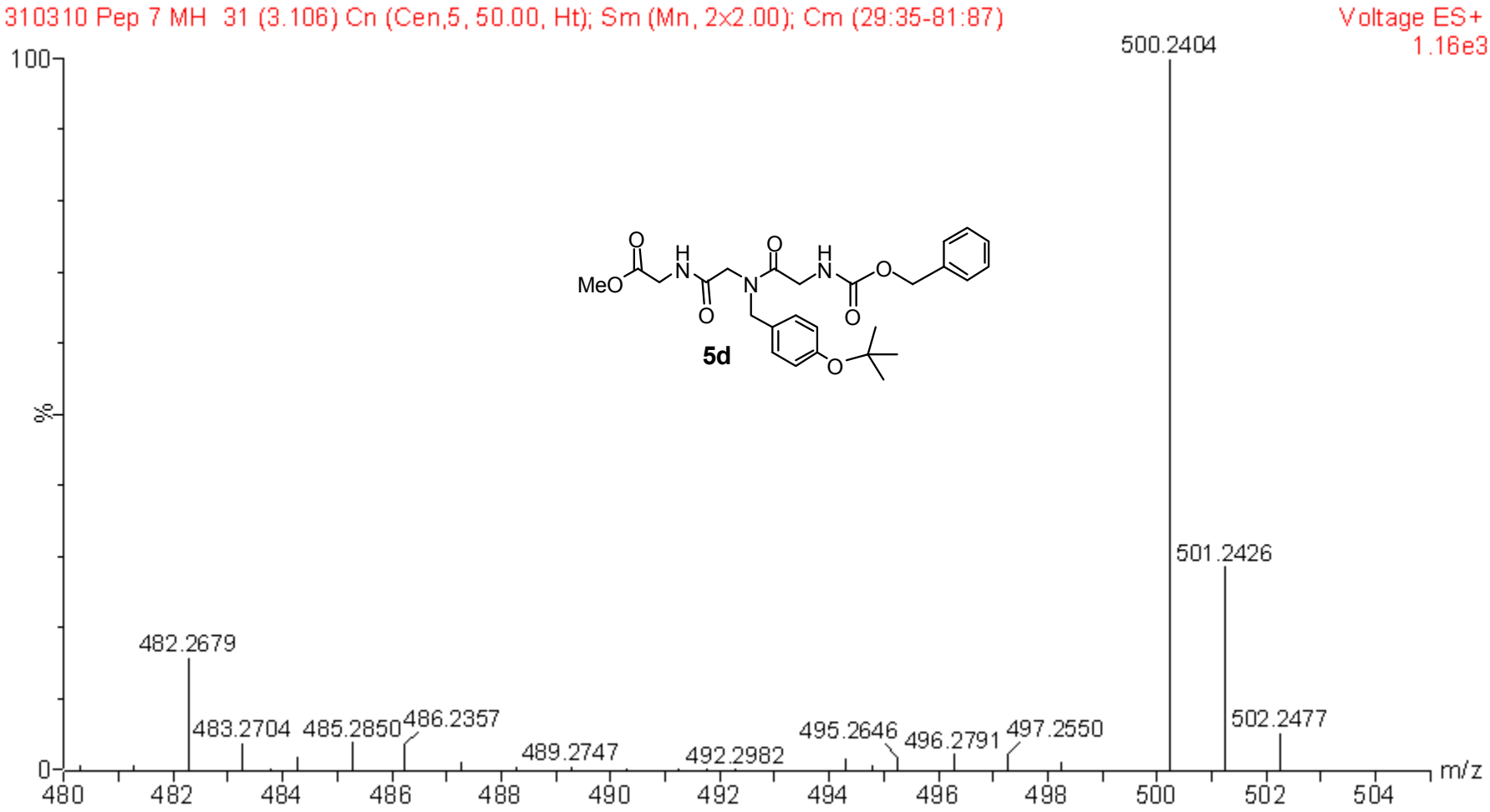


Figure 12. EI-HRMS of compound **5d**.

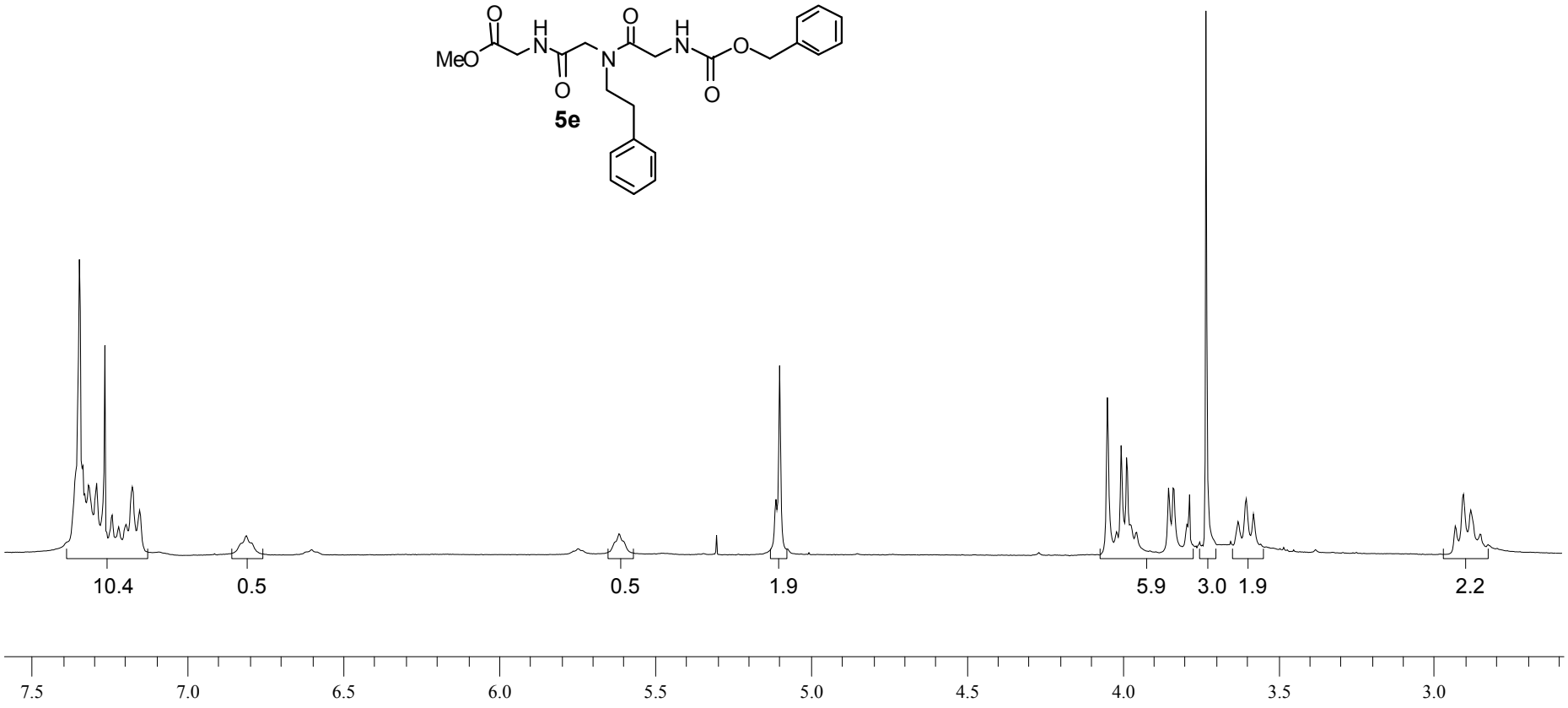


Figure 13. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5e**.

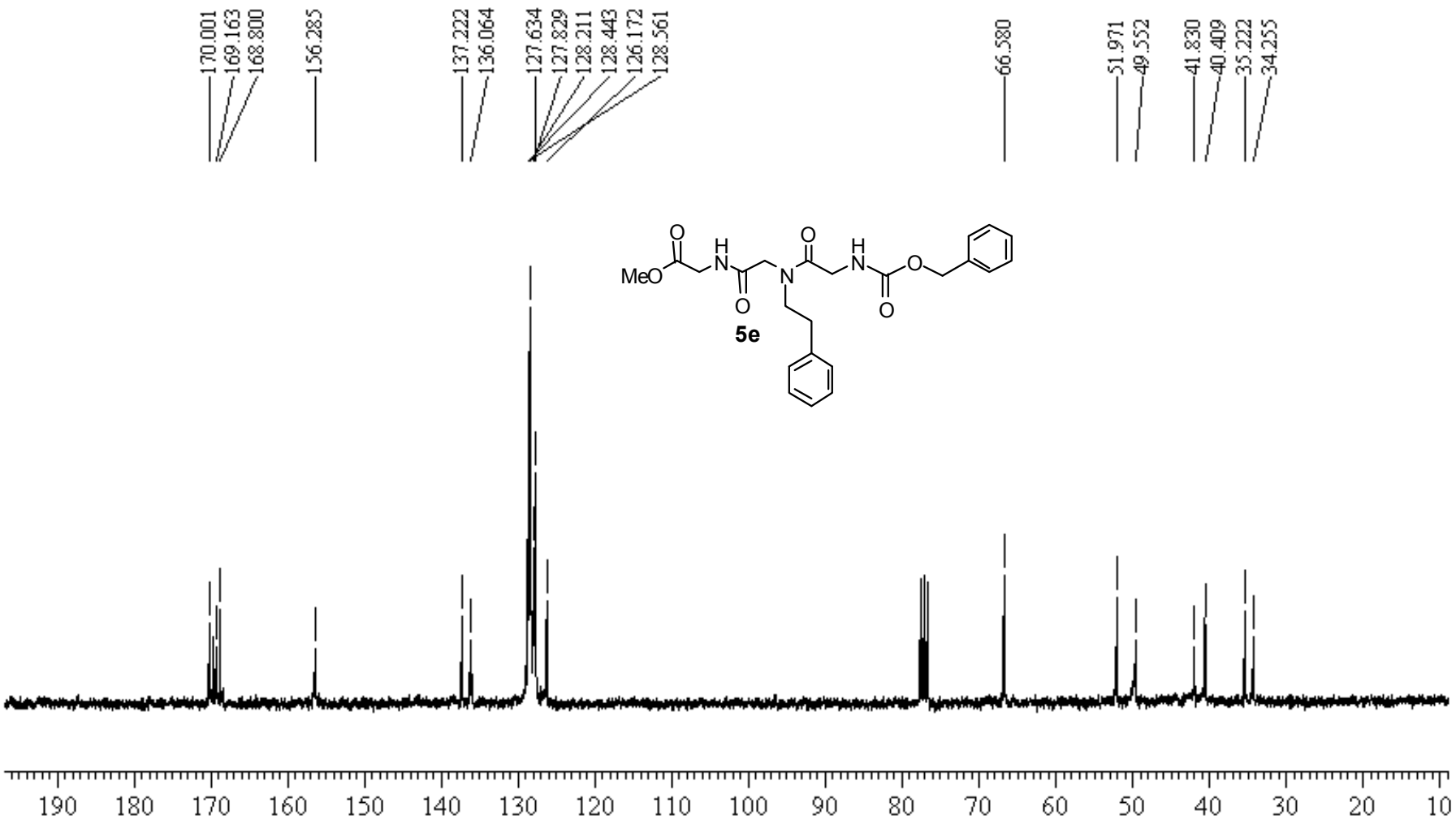


Figure 14. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5e**.

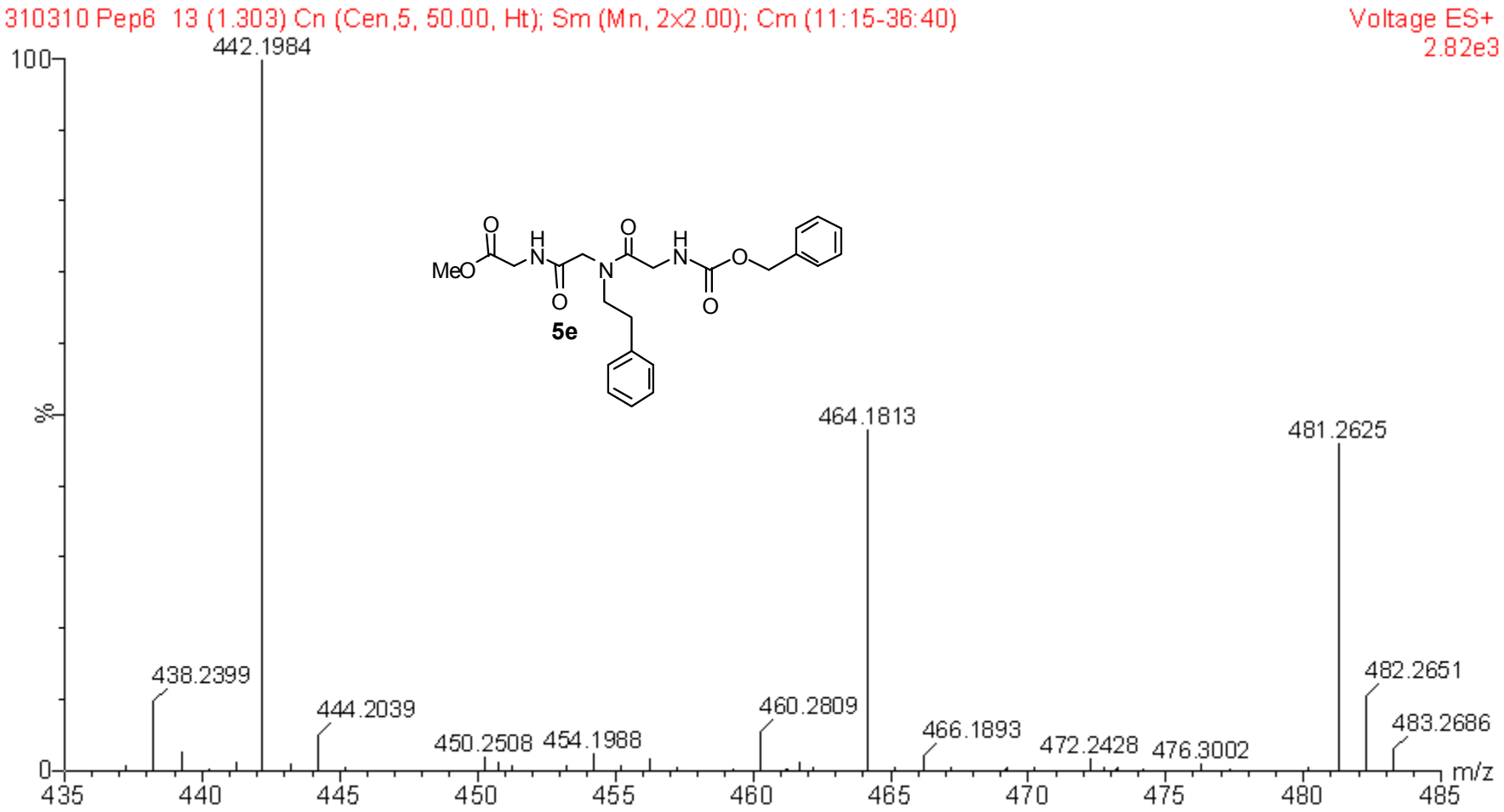


Figure 15. EI-HRMS of compound **5e**.

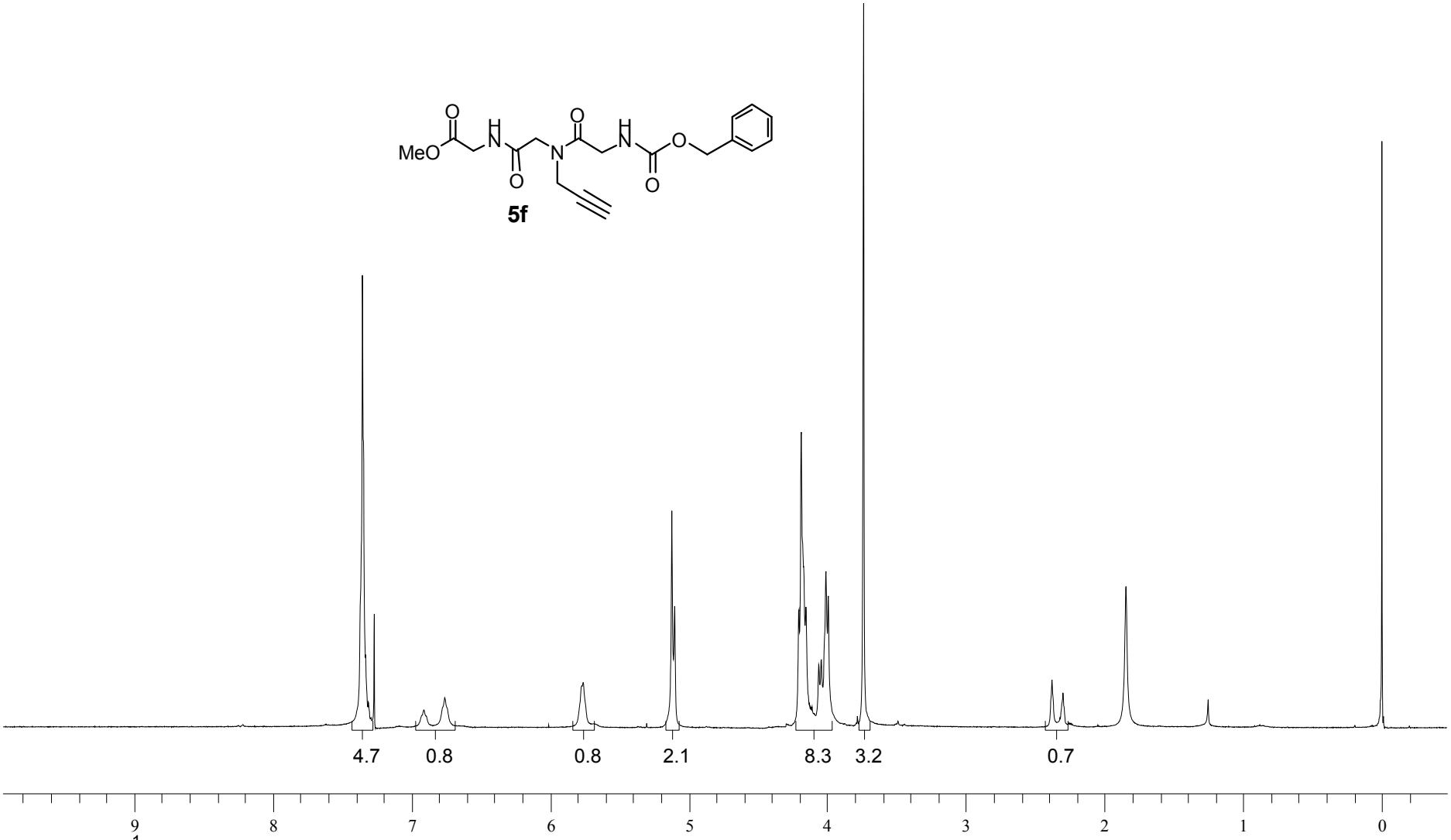


Figure 16. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5f**.

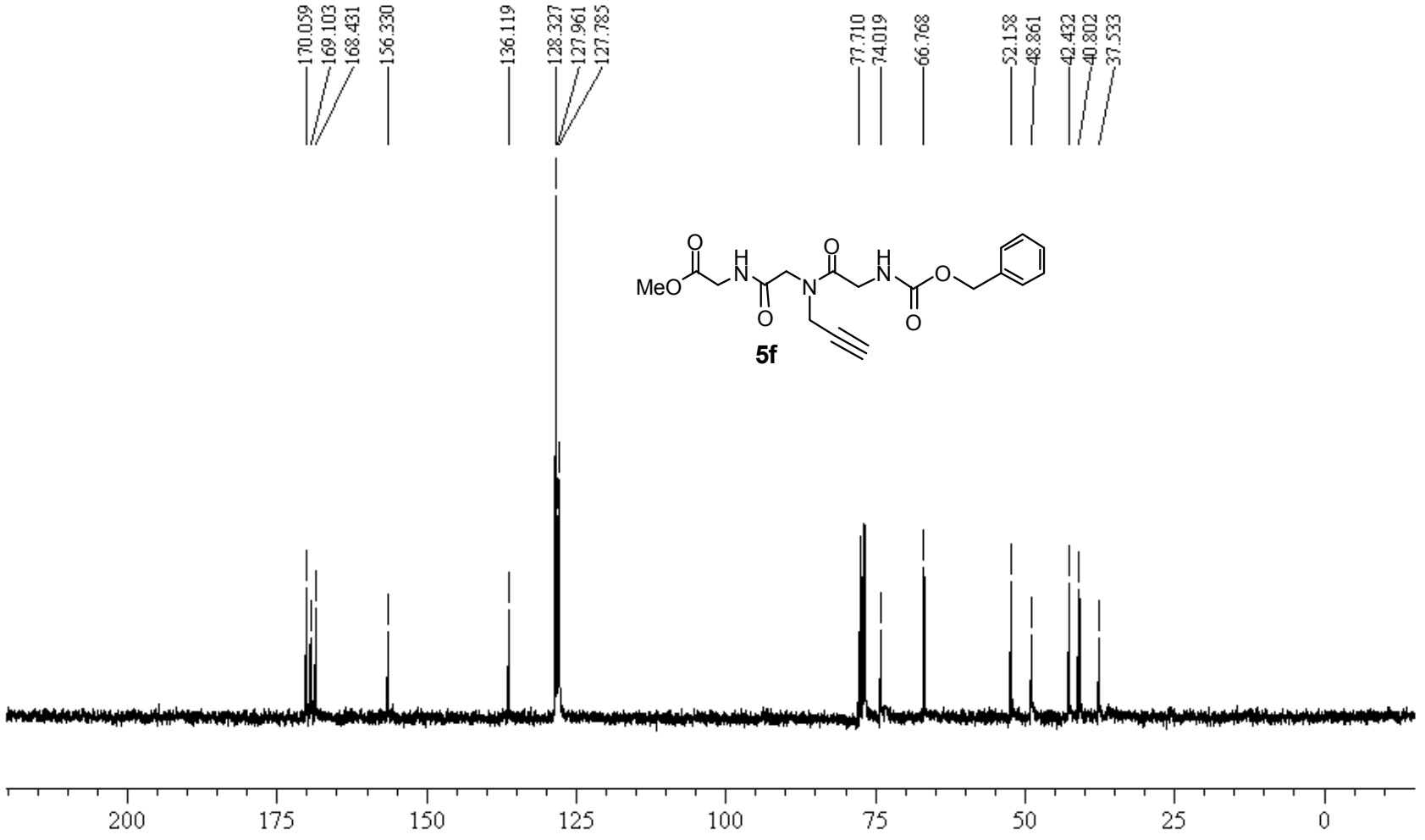


Figure 17. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5f**.

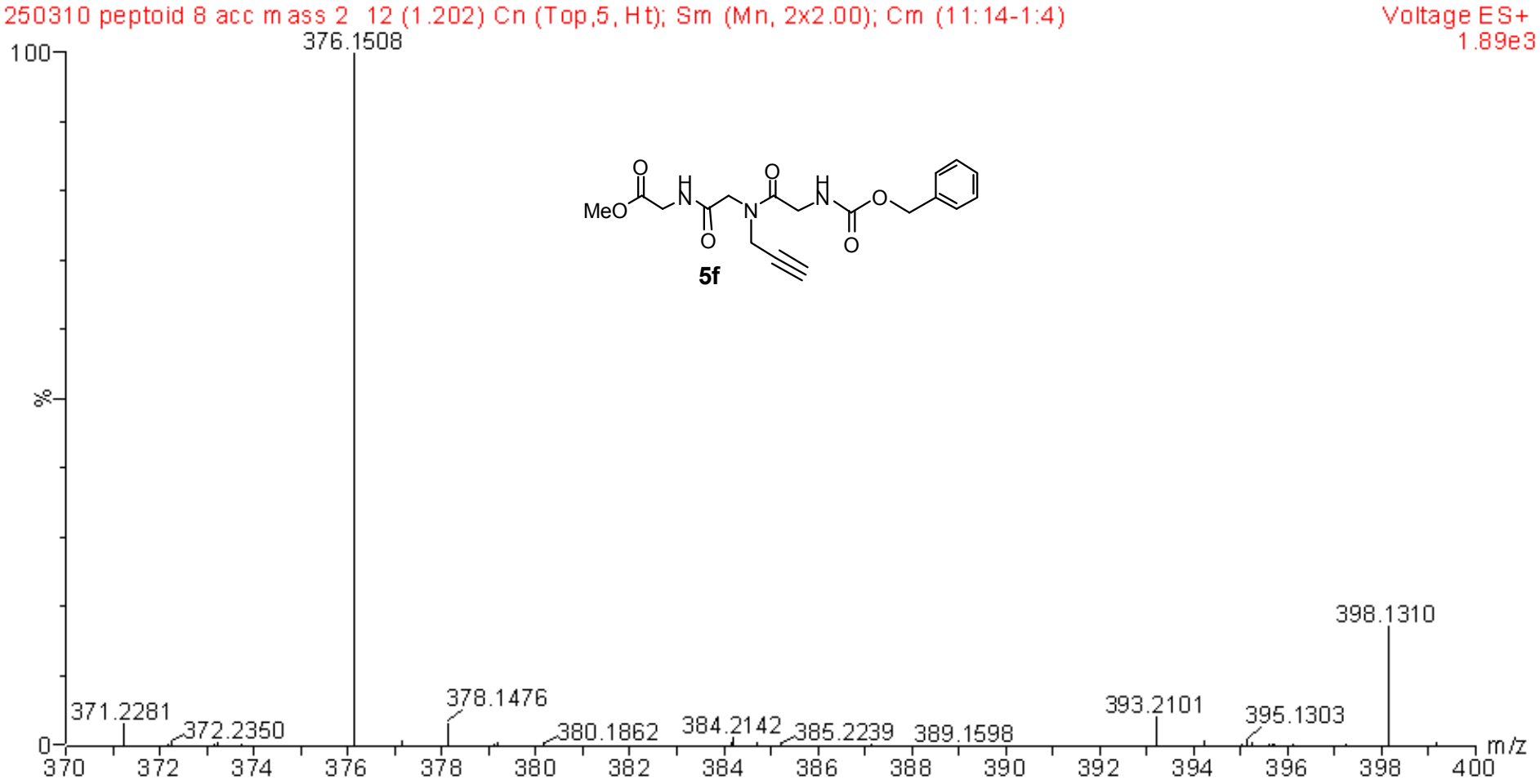


Figure 18. EI-HRMS of compound **5f**.

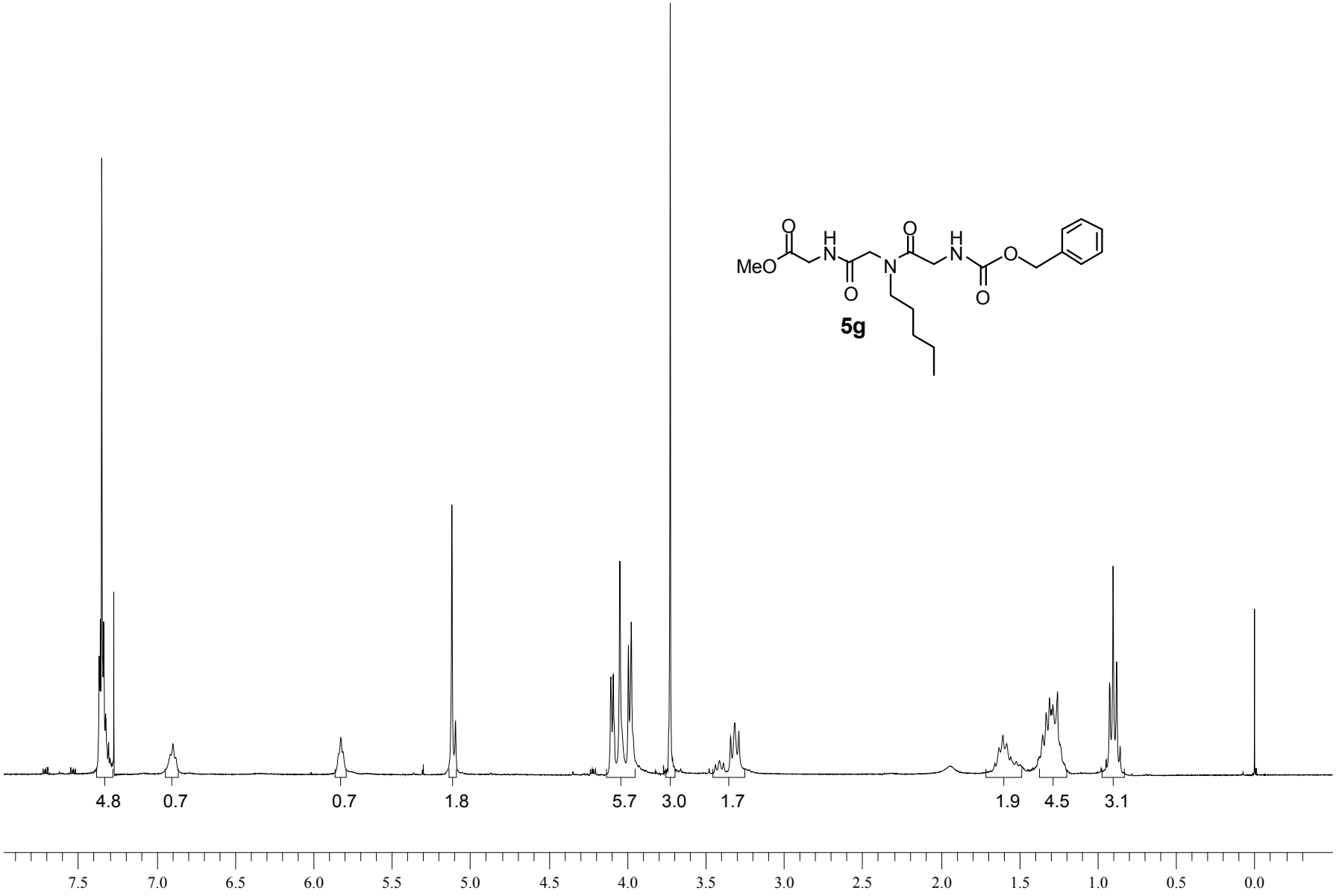


Figure 19. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5g**.

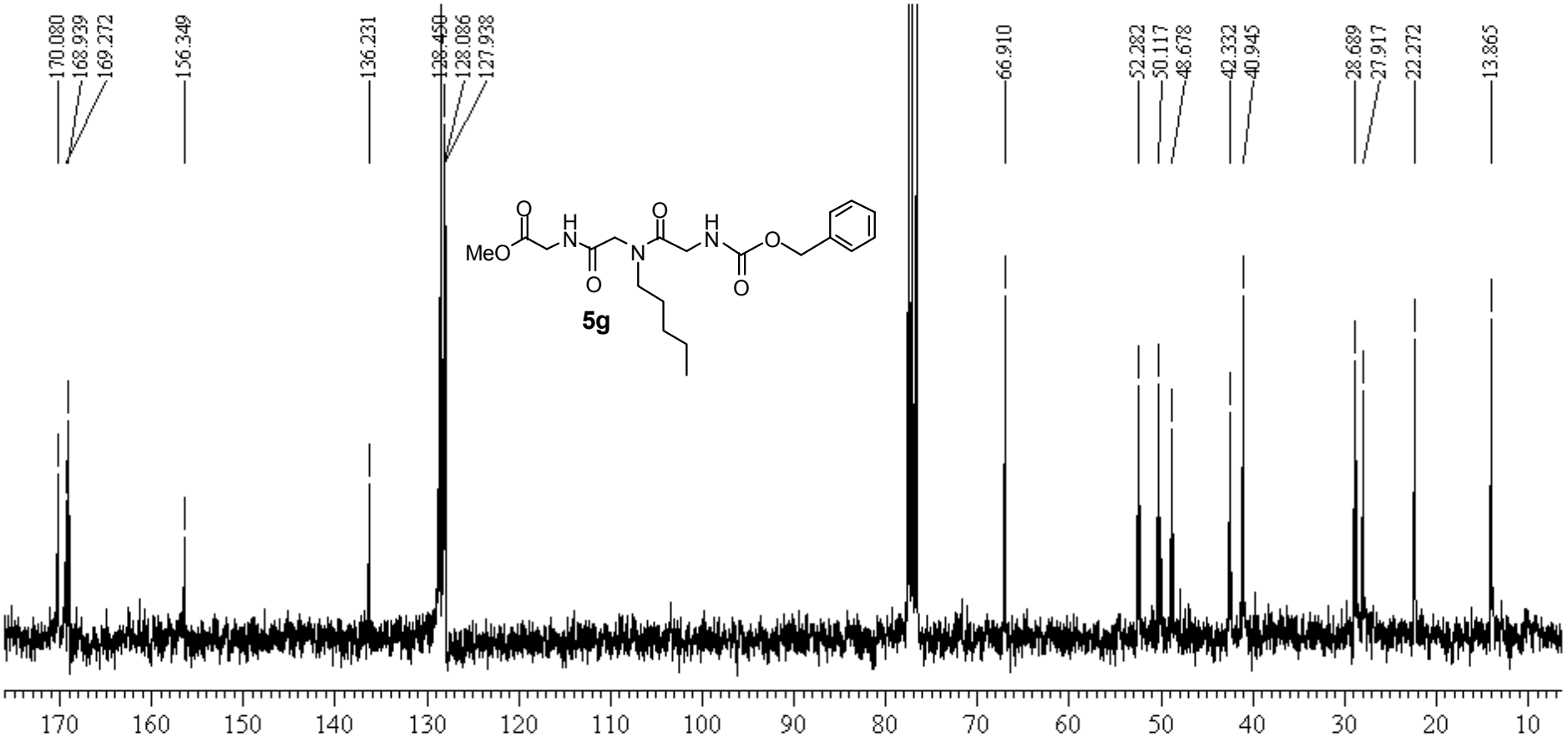


Figure 20. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5g**.

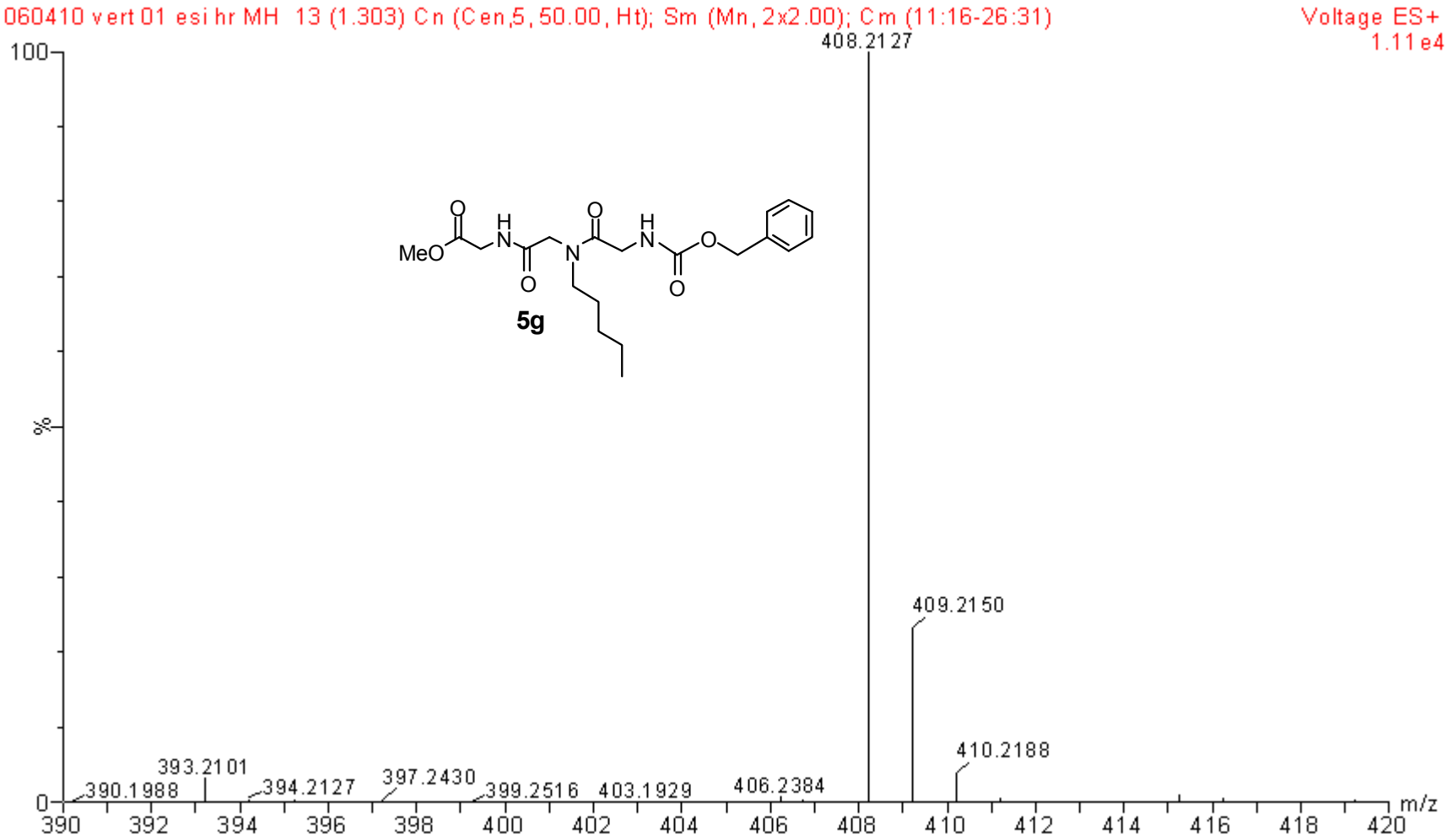


Figure 21. EI-HRMS of compound **5g**.

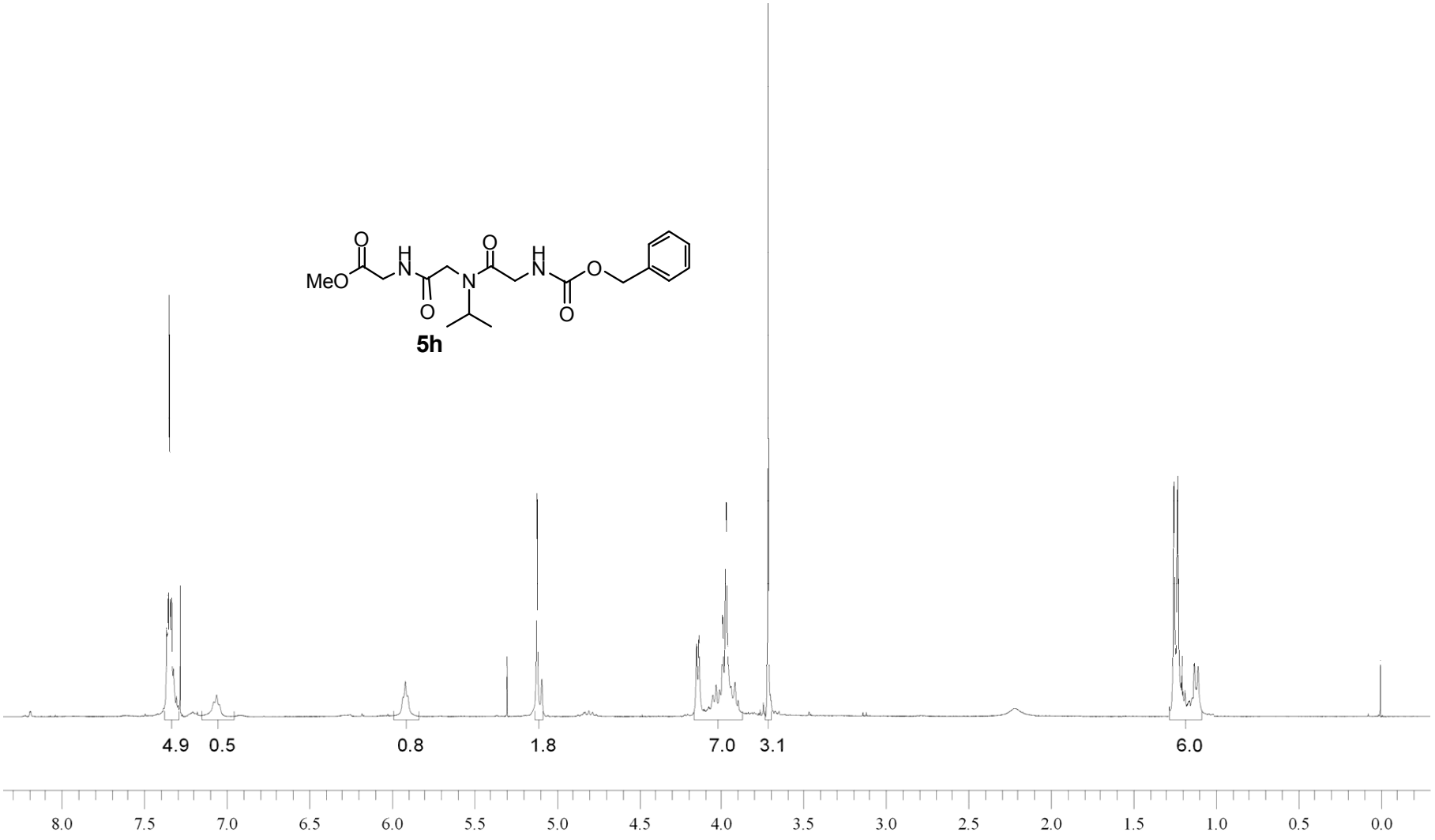


Figure 22. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5h**.

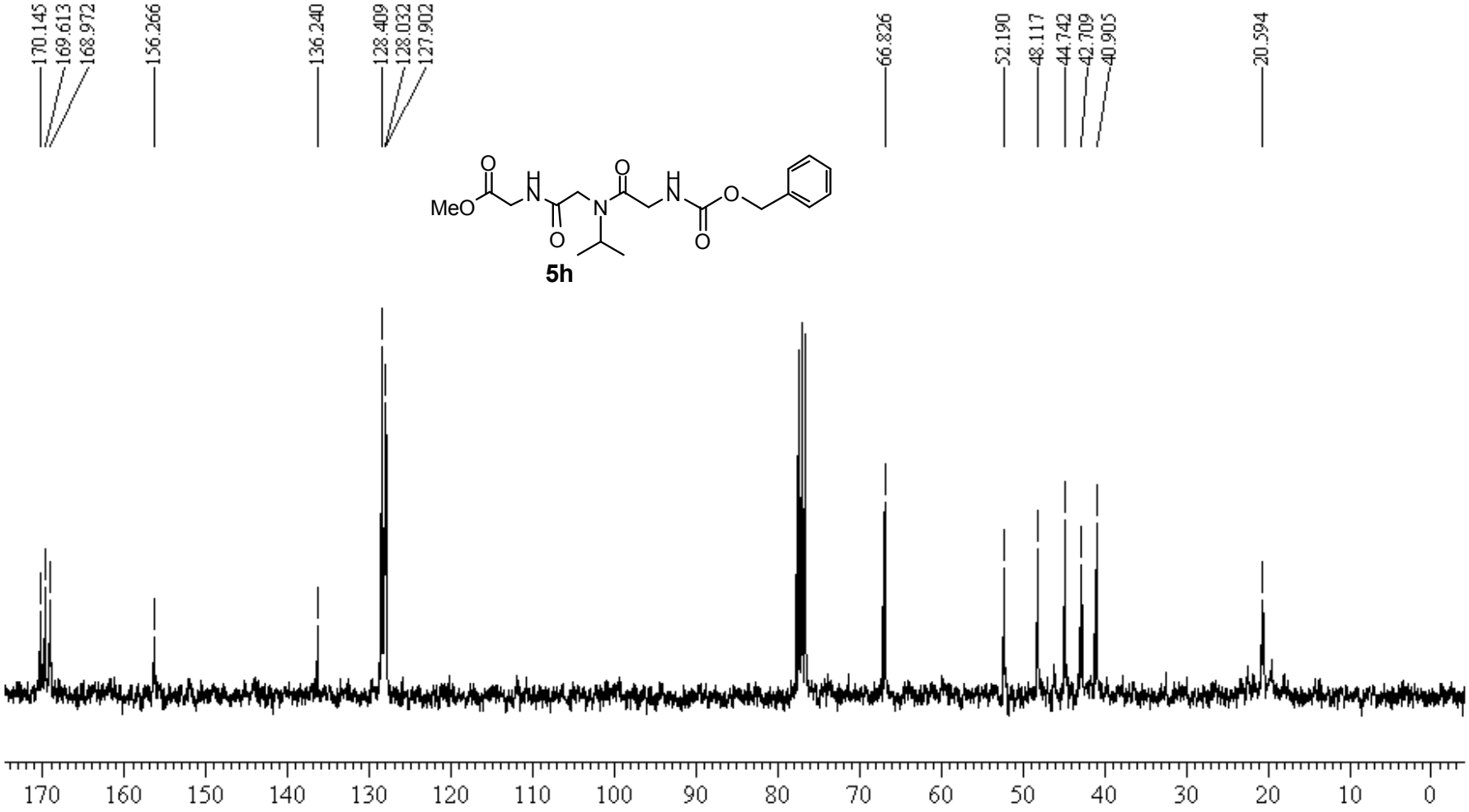


Figure 23. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5h**.

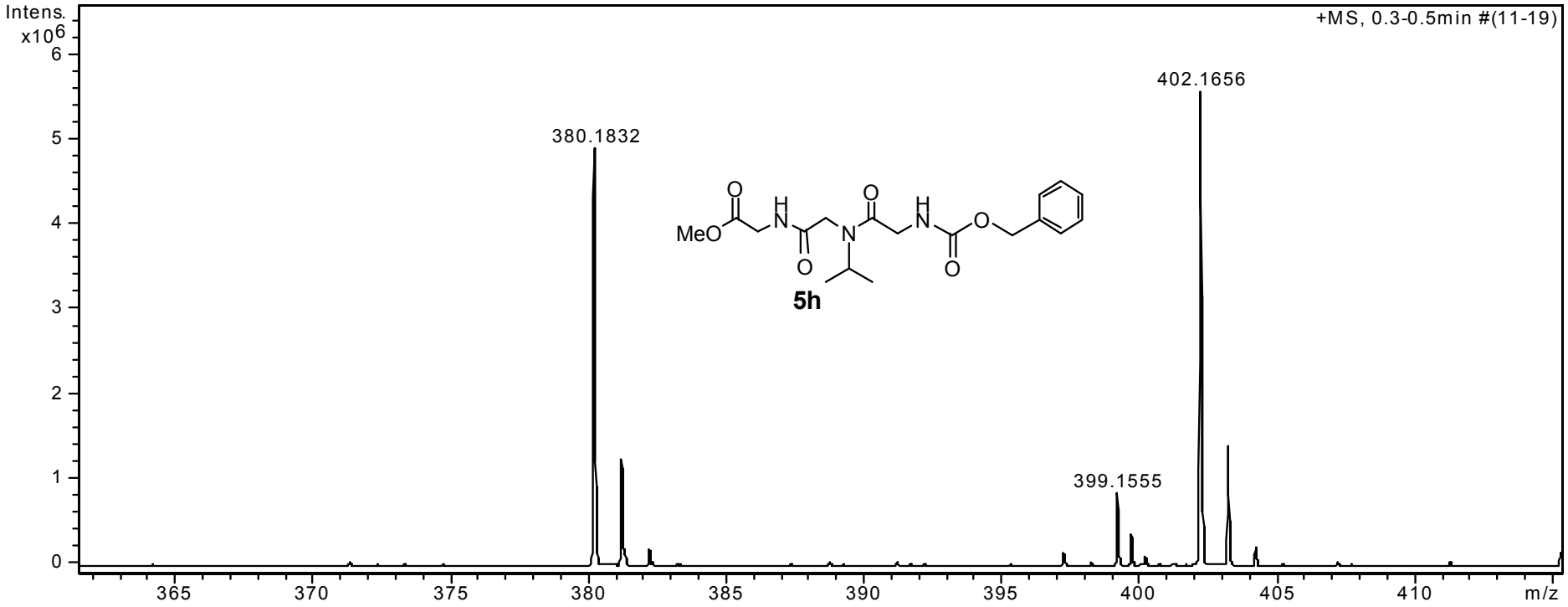


Figure 24. EI-HRMS of compound **5h**.

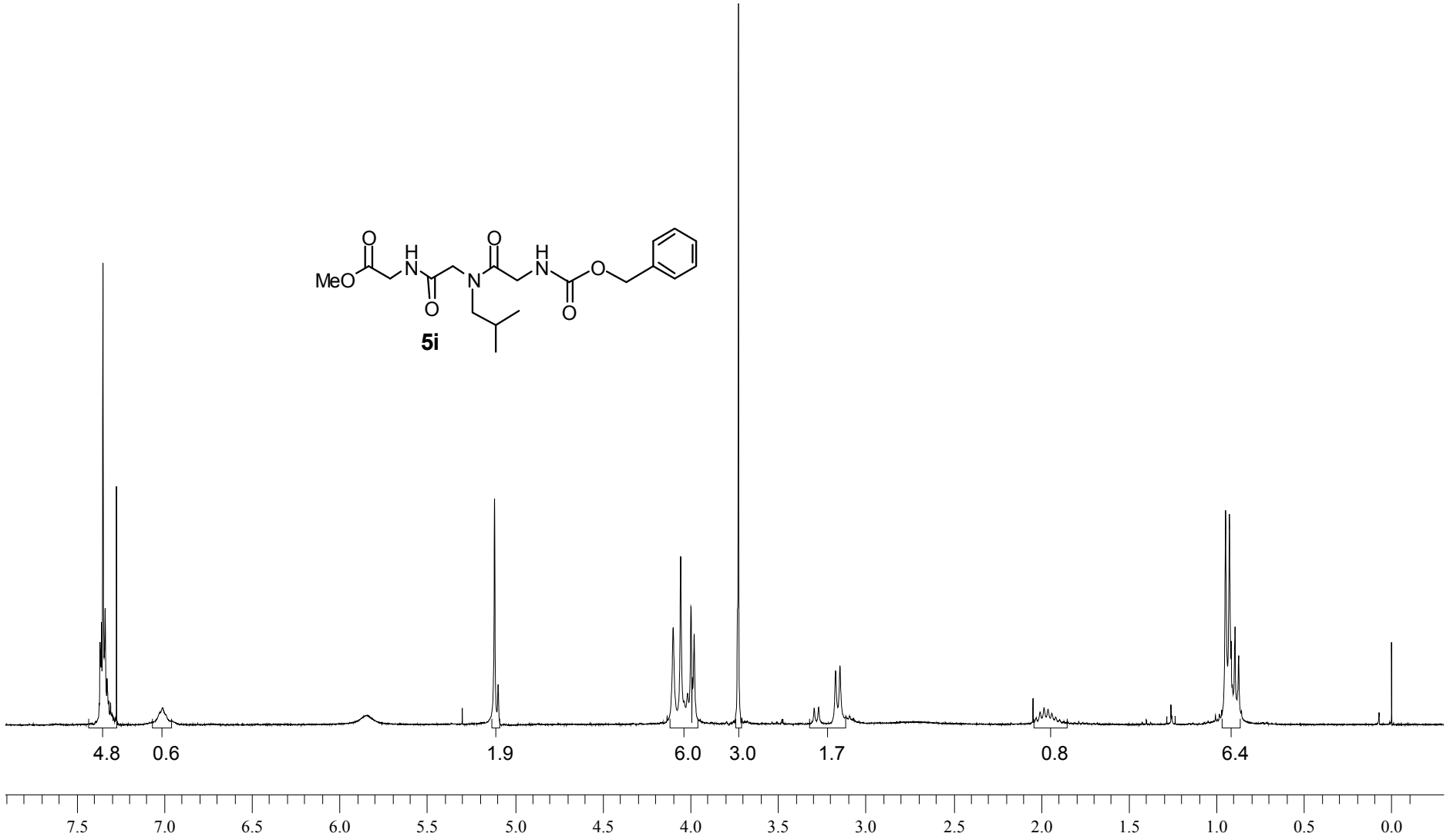


Figure 25. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **5i**.

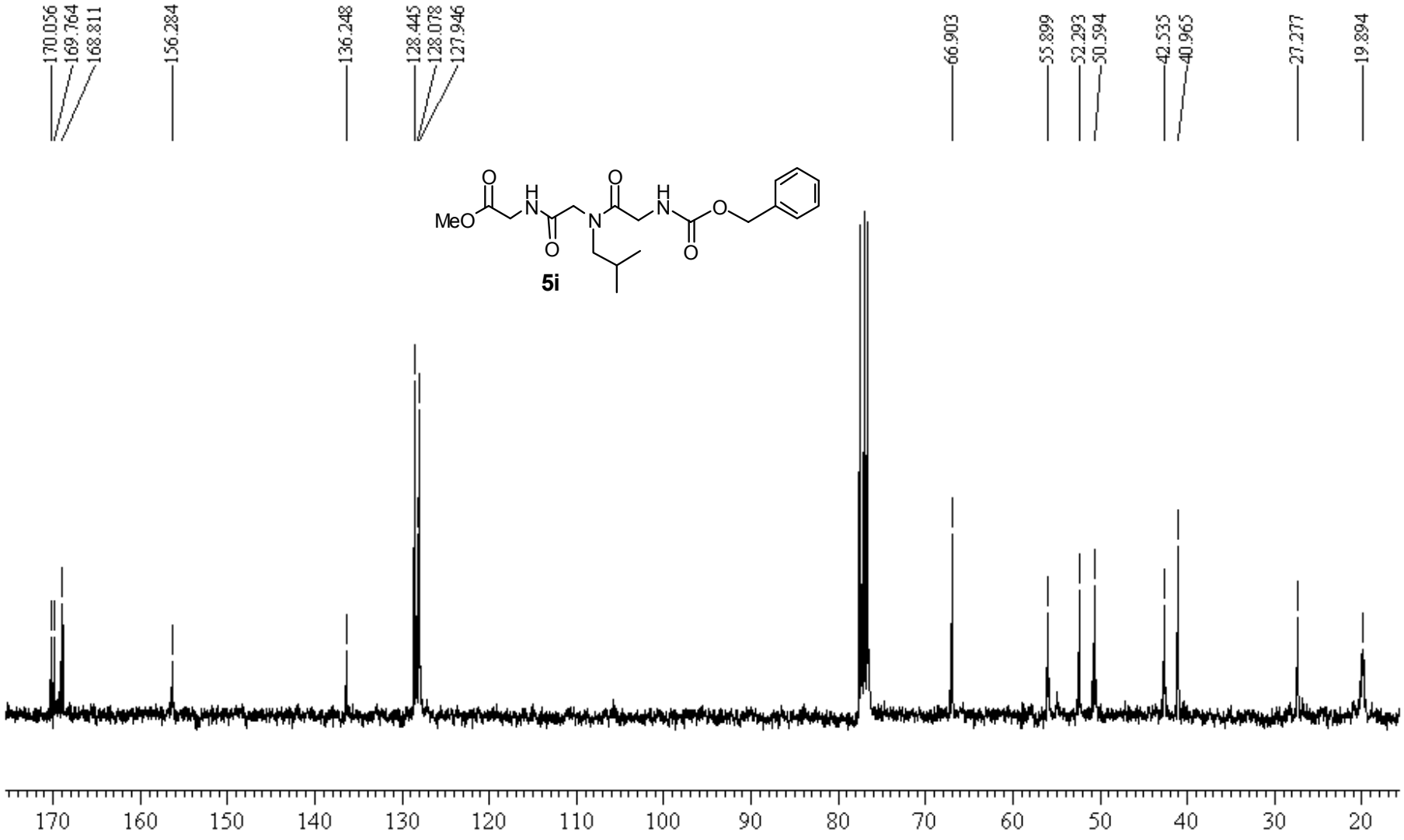


Figure 26. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **5i**.

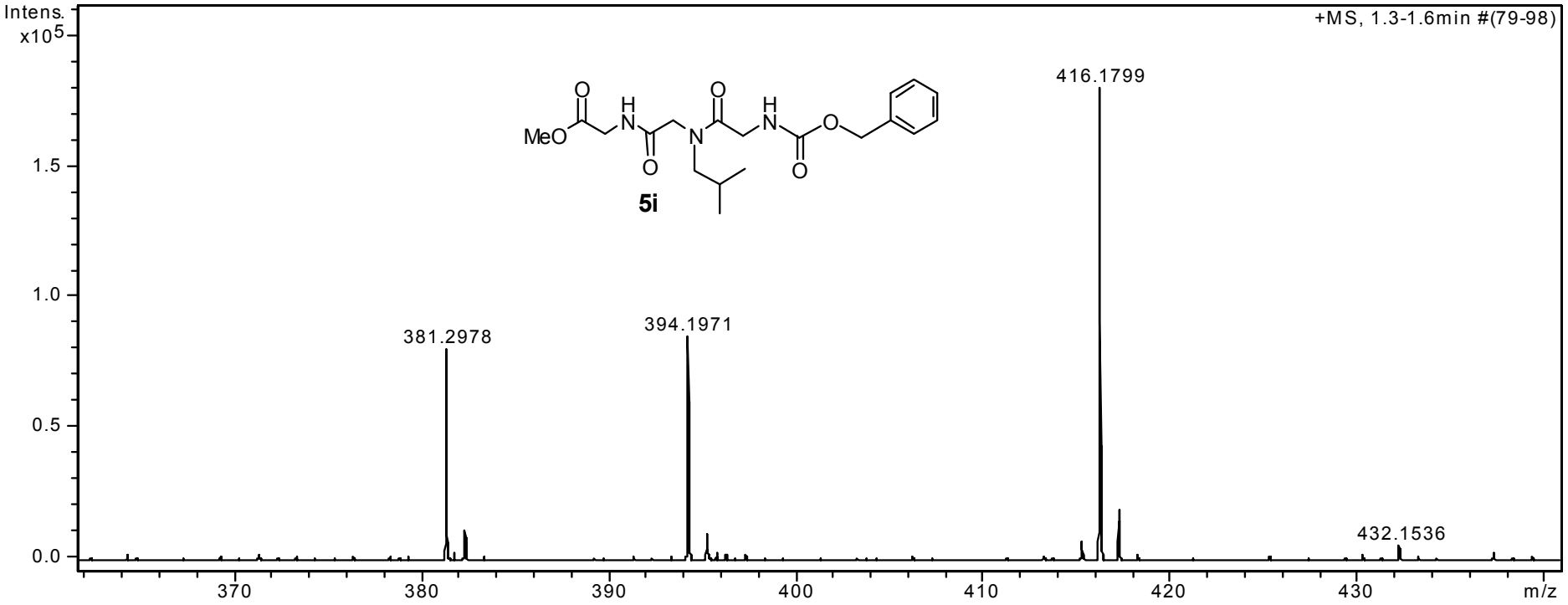


Figure 27. EI-HRMS of compound **5i**.

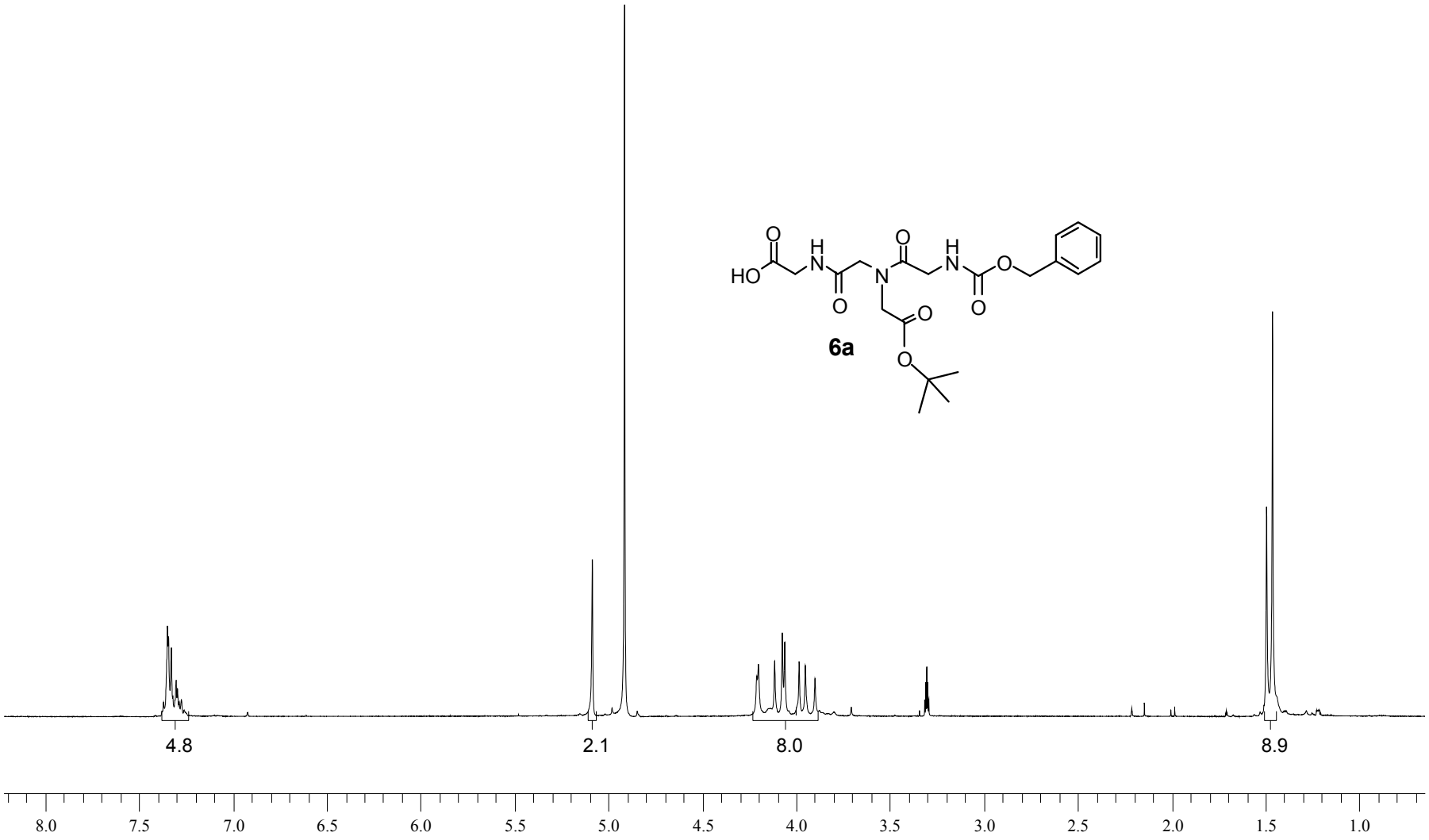


Figure 28. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6a**.

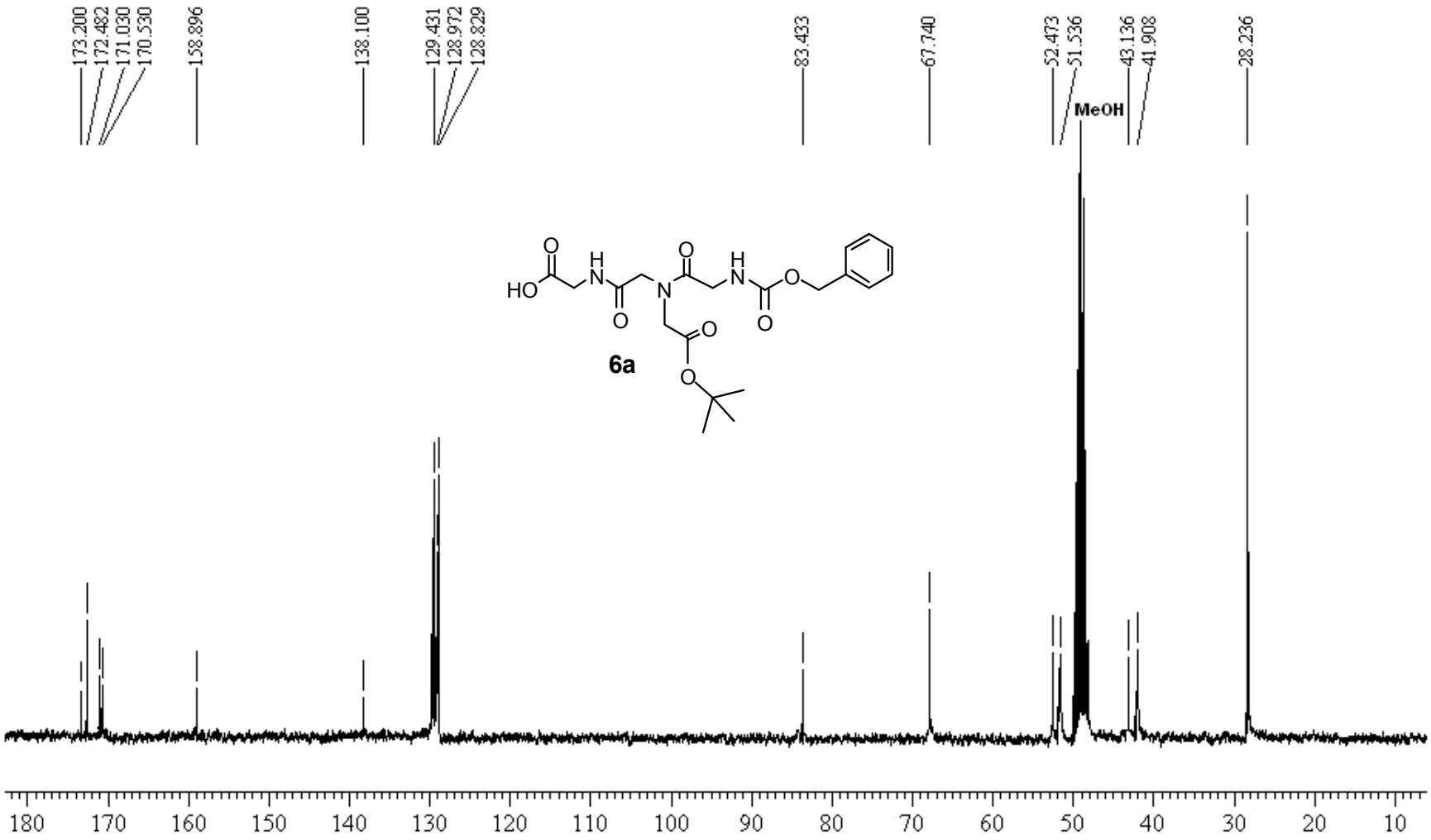


Figure 29. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6a**.

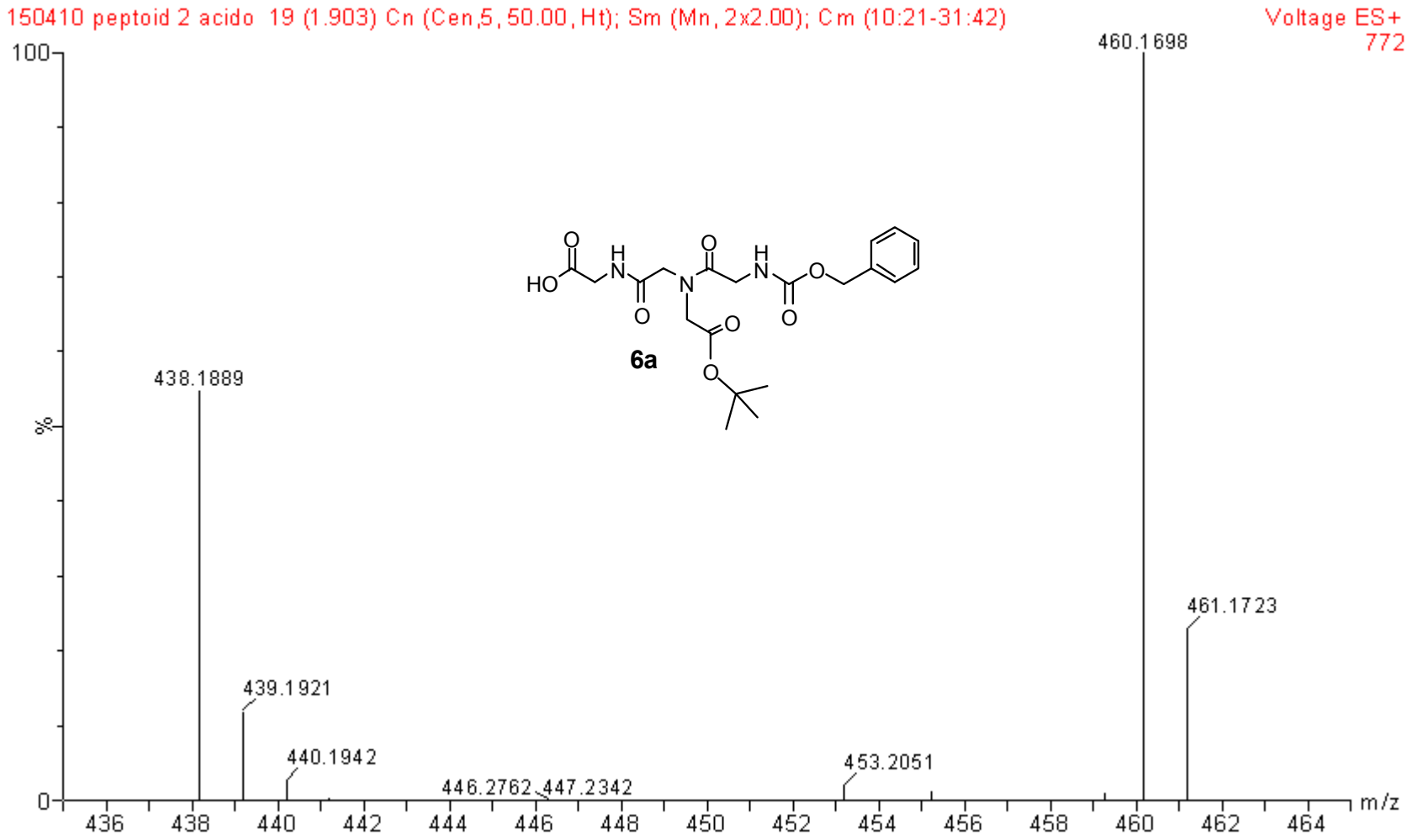


Figure 30. EI-HRMS of compound **6a**.

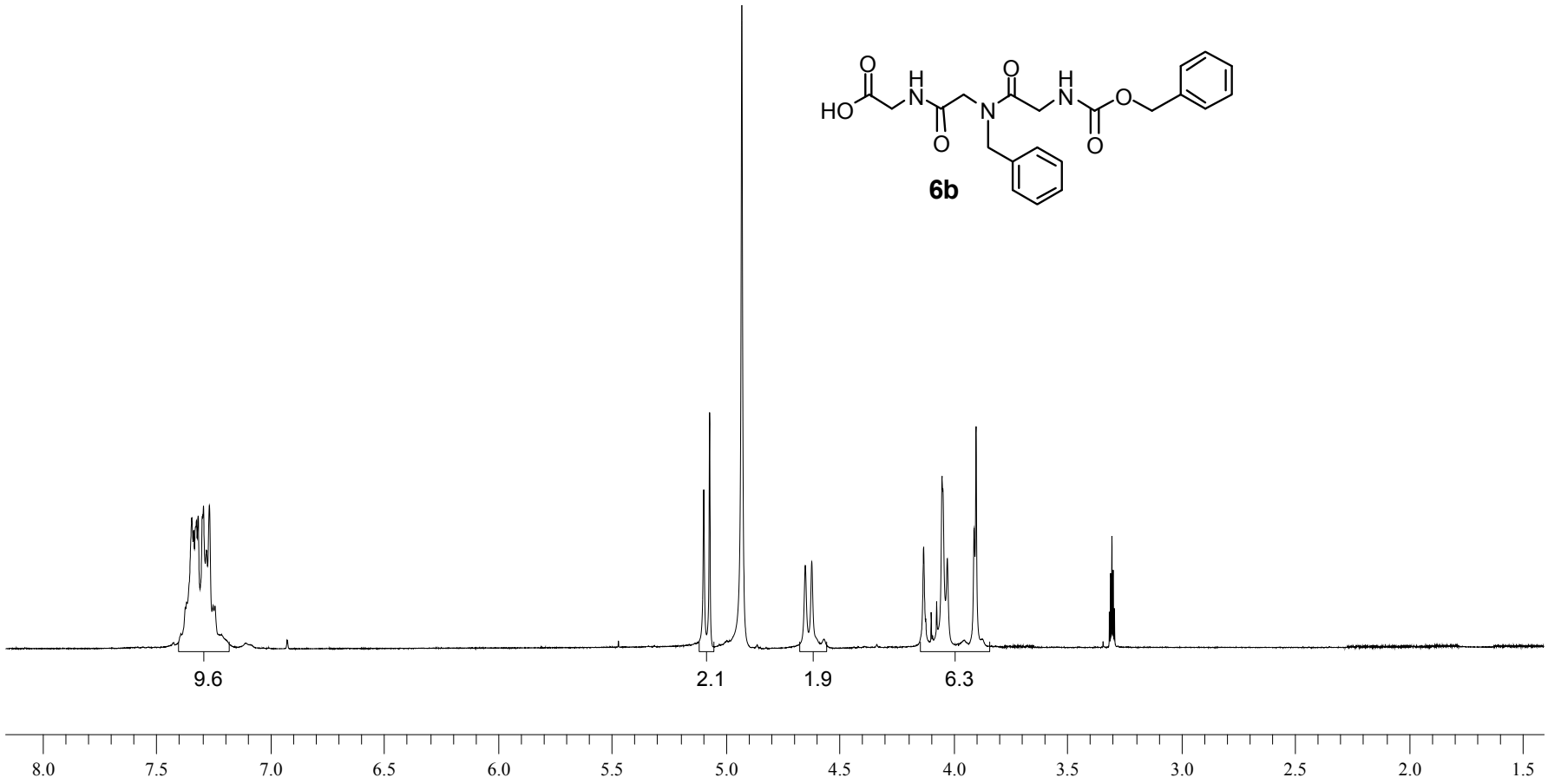


Figure 31. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6b**.

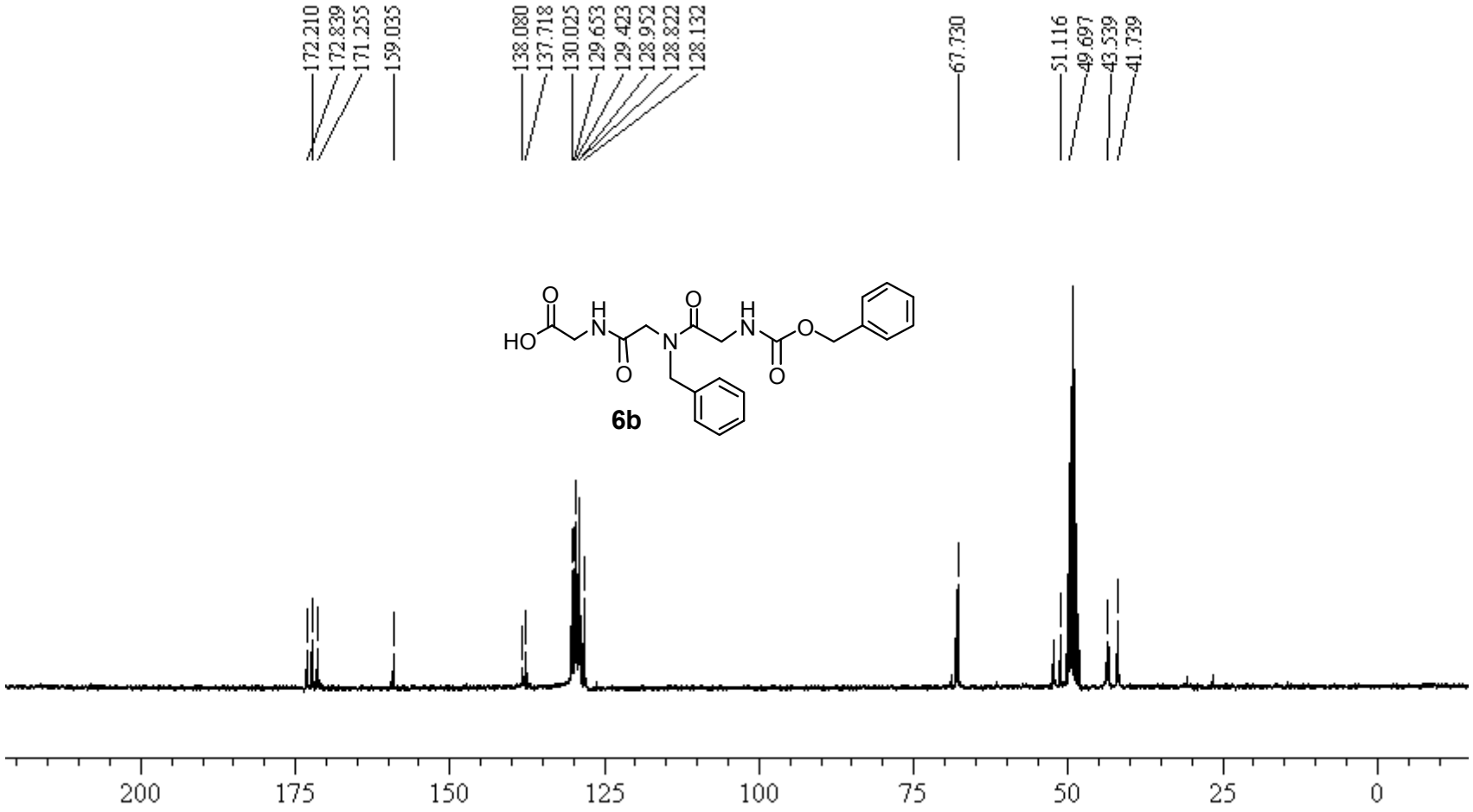


Figure 32. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6b**.

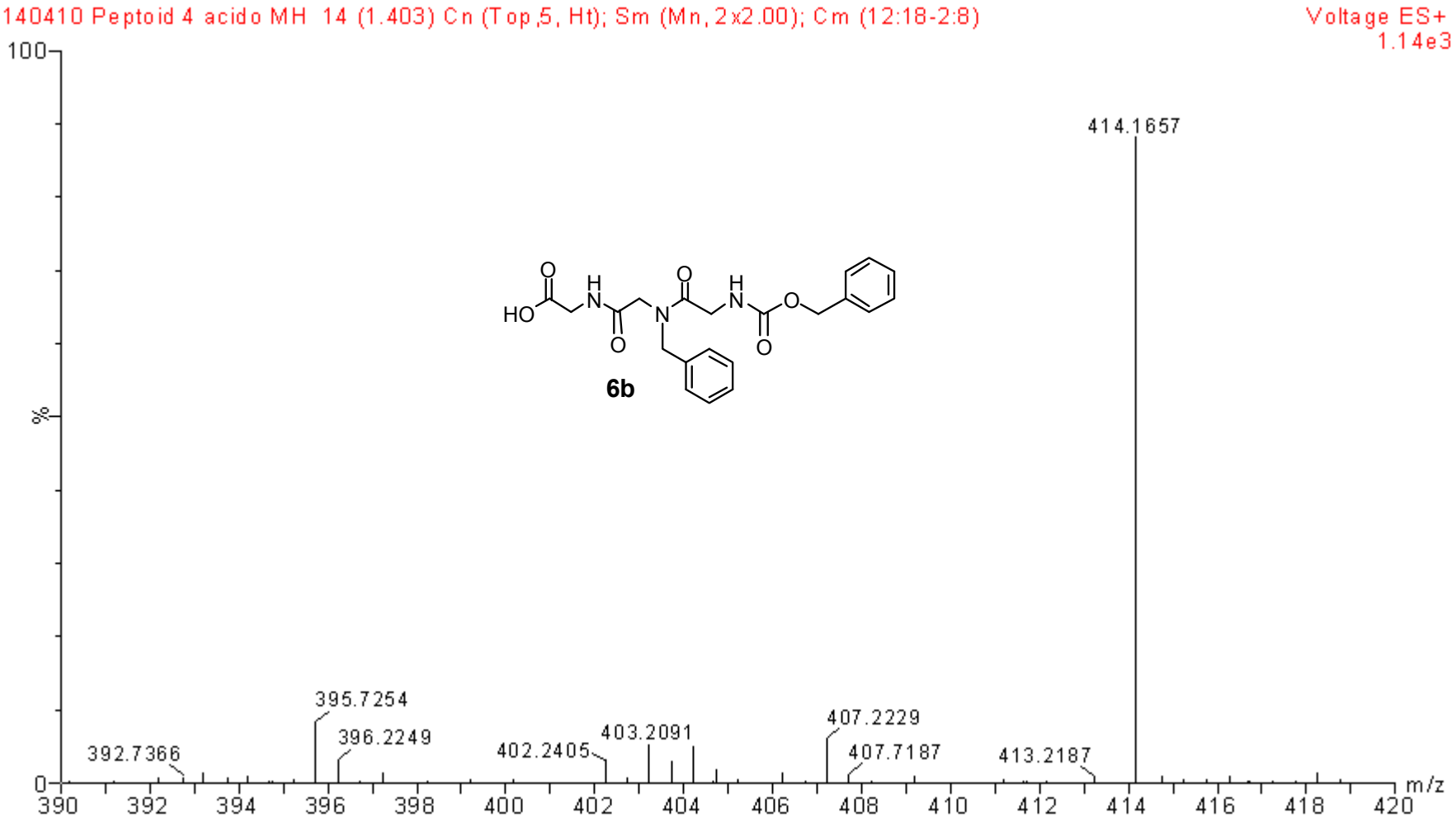


Figure 33. EI-HRMS of compound **6b**.

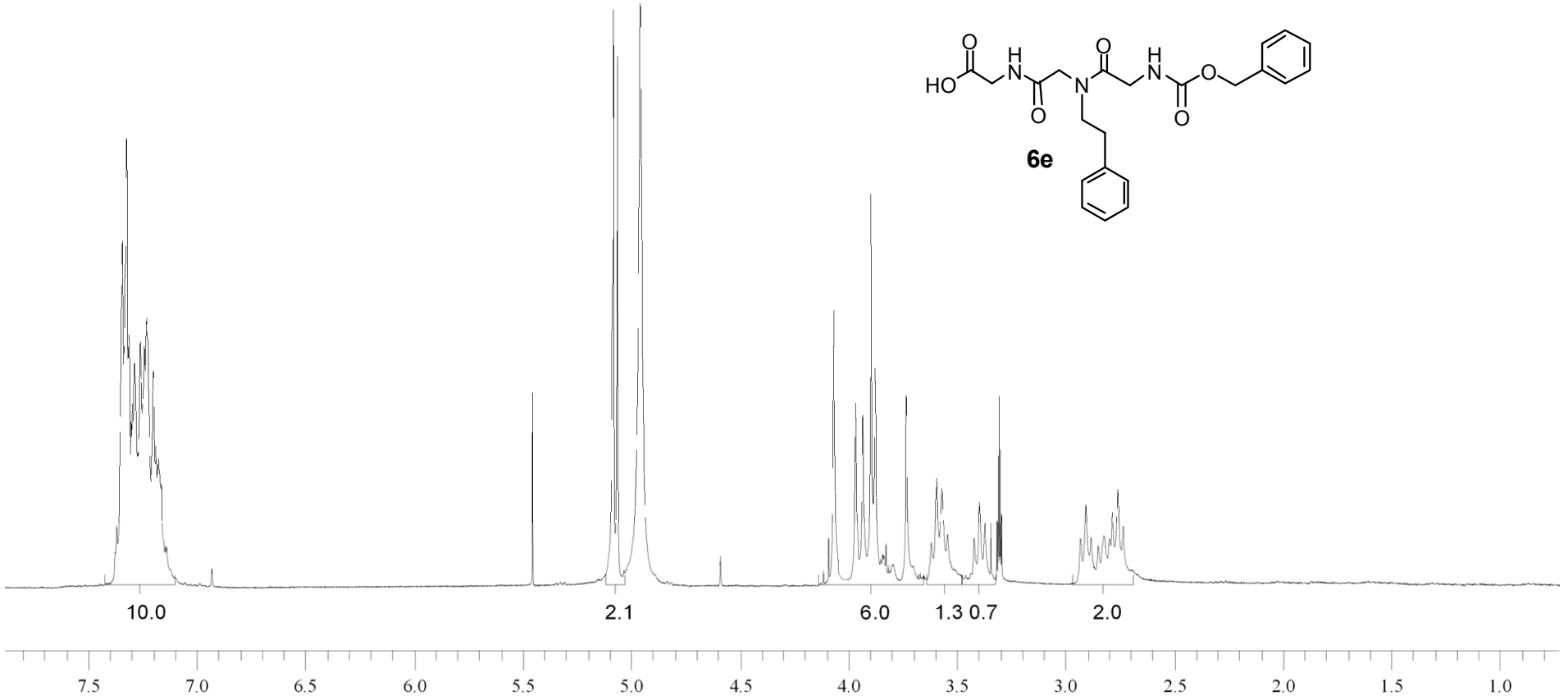


Figure 34. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6e**.

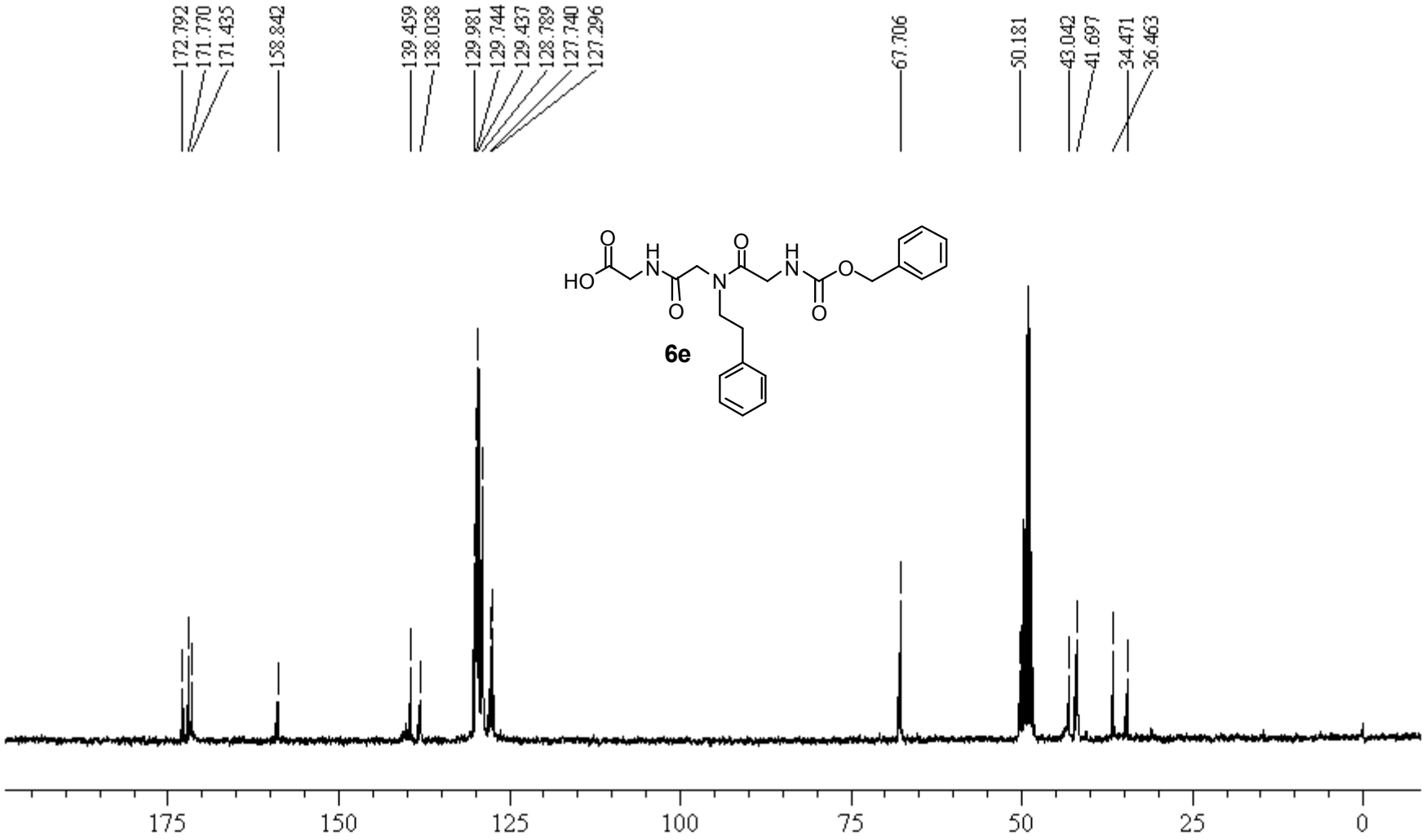


Figure 35. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6e**.

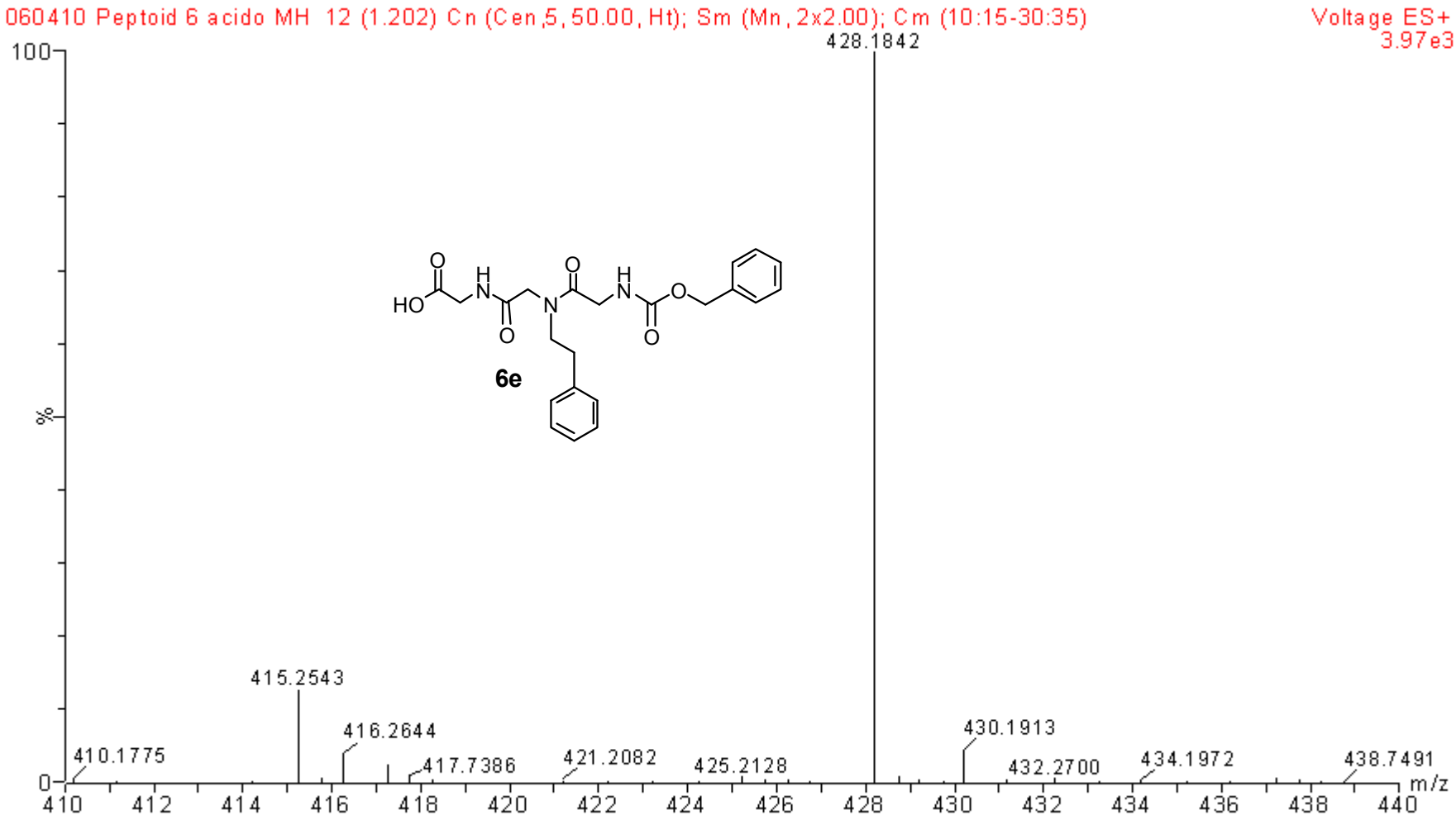


Figure 36. EI-HRMS of compound **6e**.

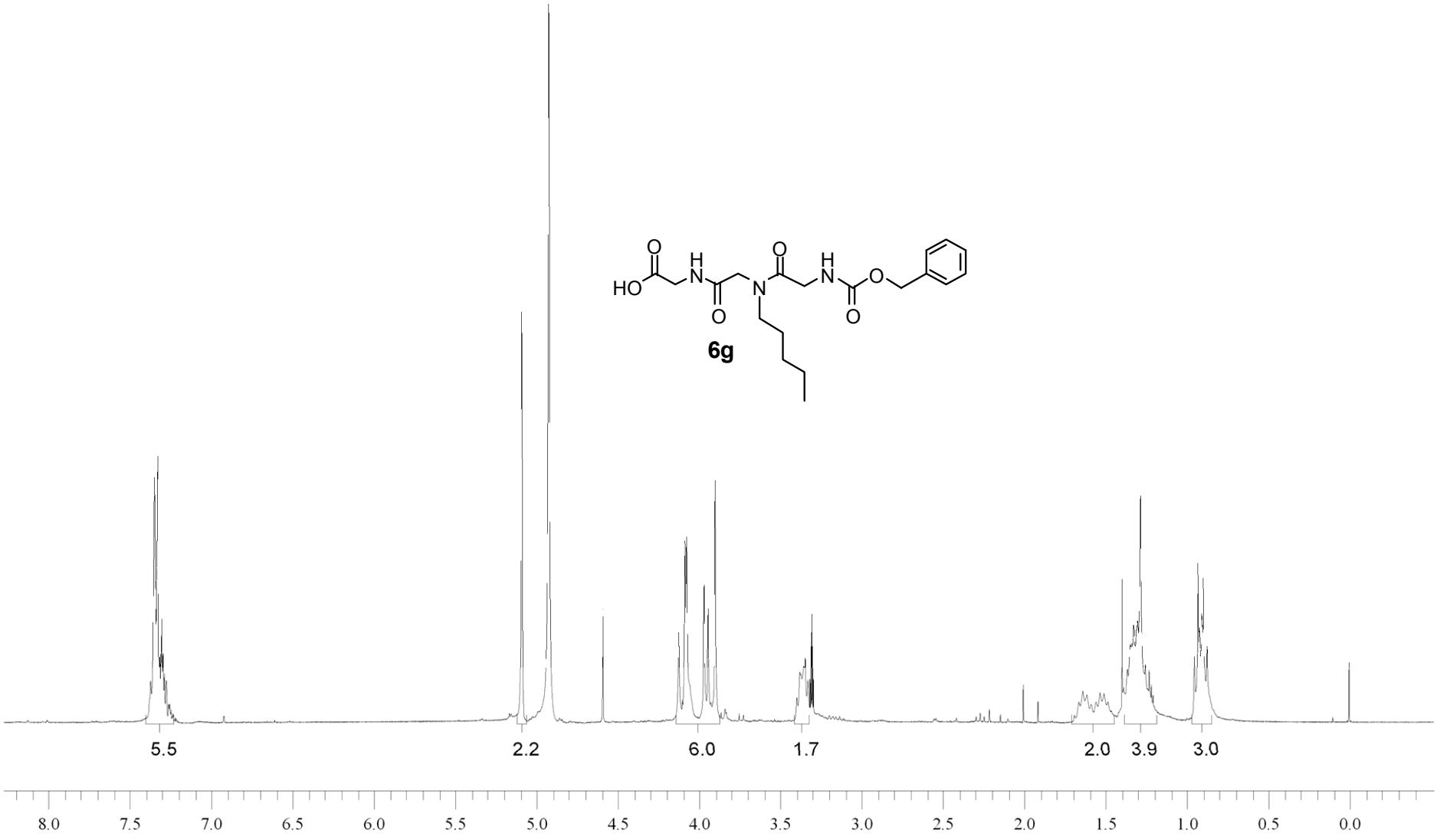


Figure 40. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6g**.

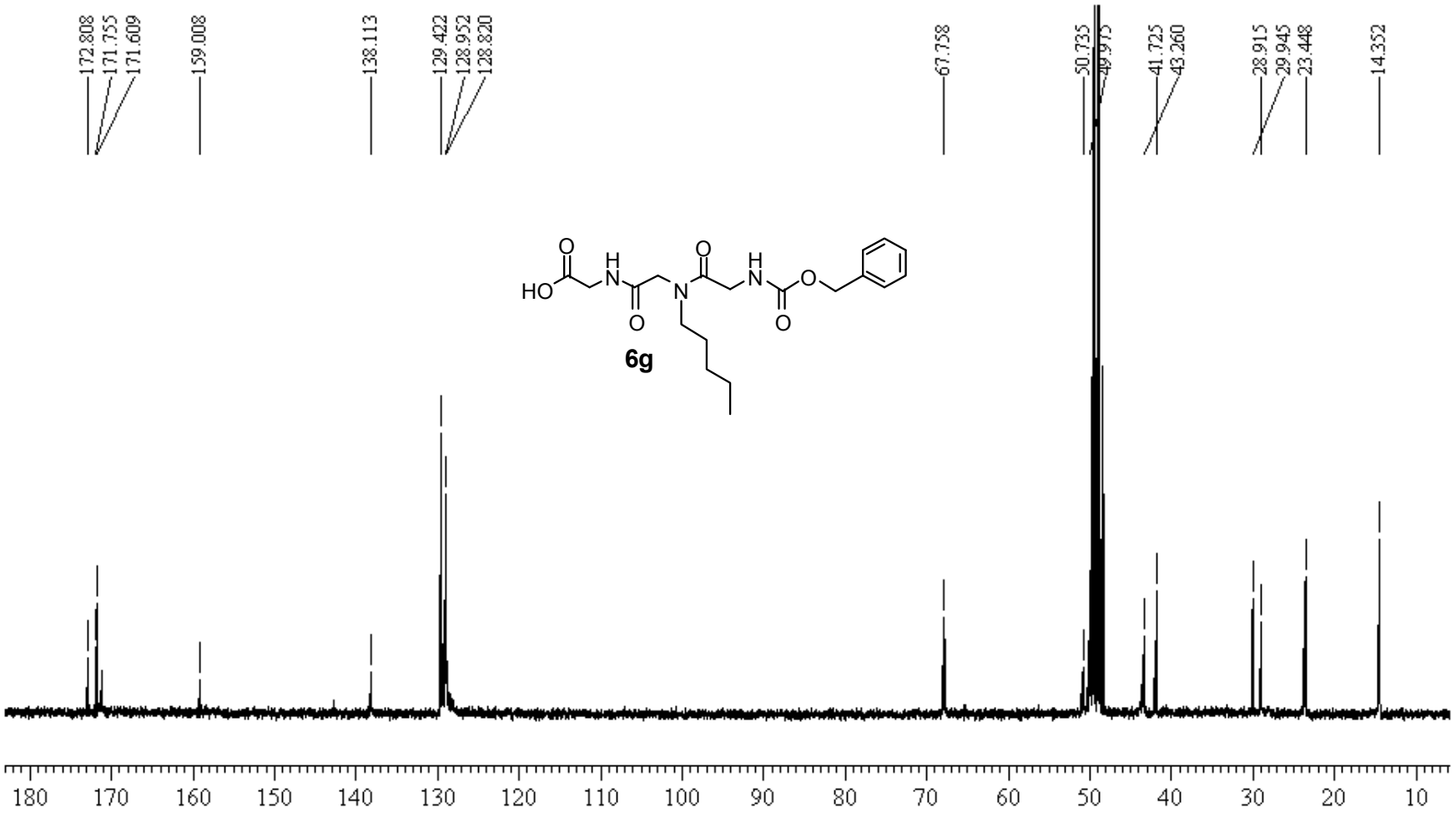


Figure 41. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6g**.

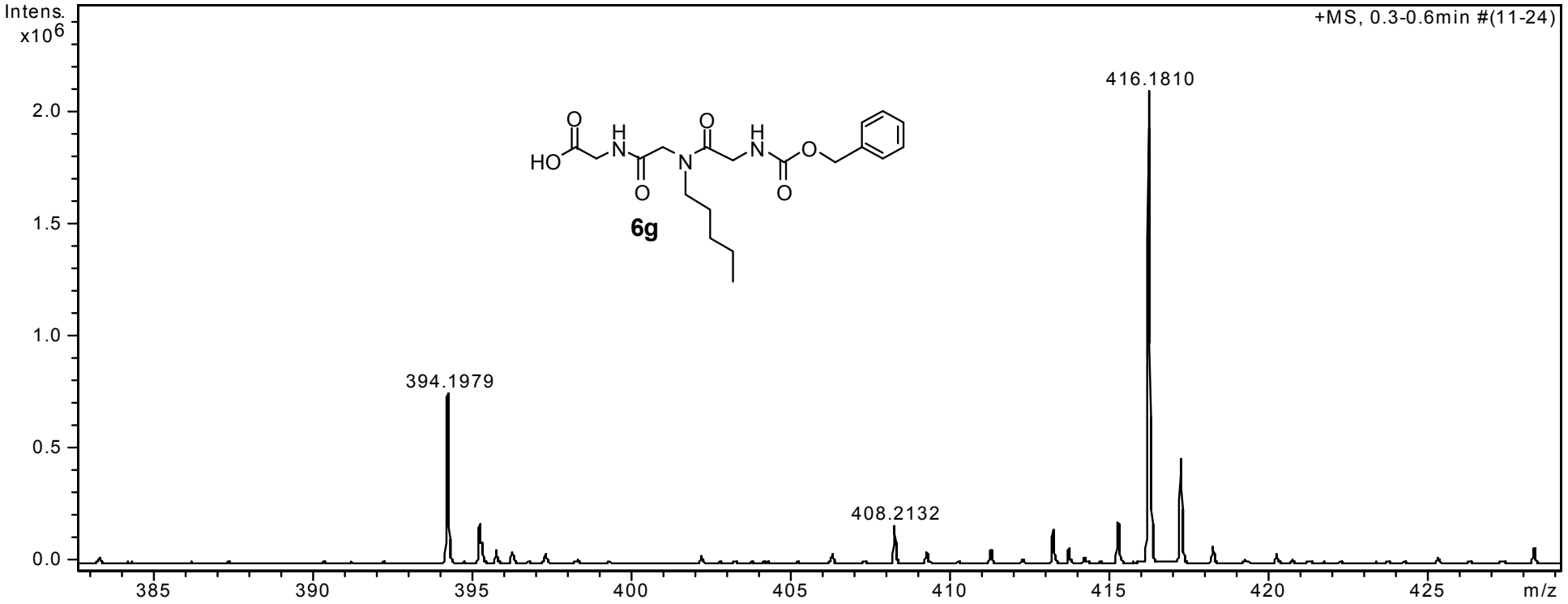


Figure 42. EI-HRMS of compound **6g**.

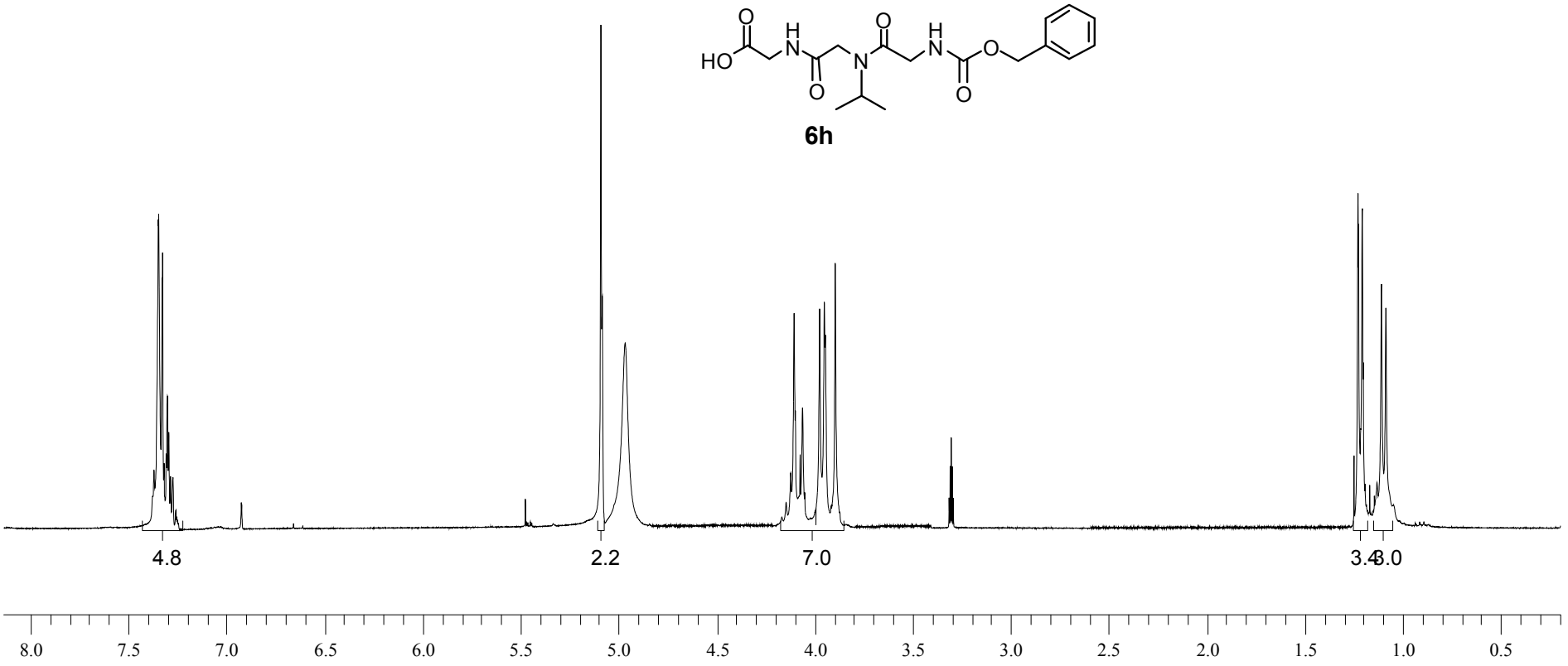


Figure 37. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6h**.

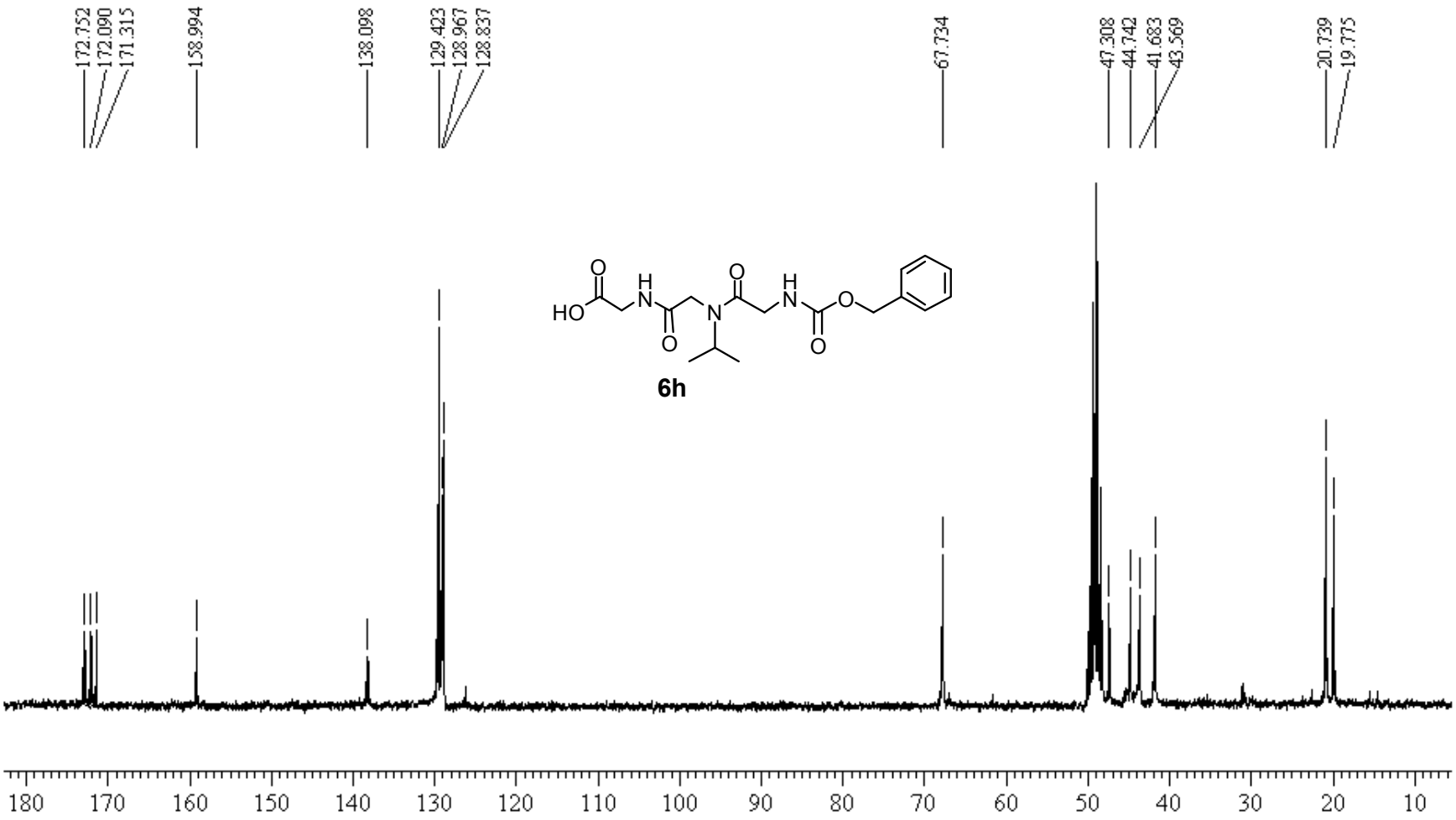


Figure 38. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6h**.

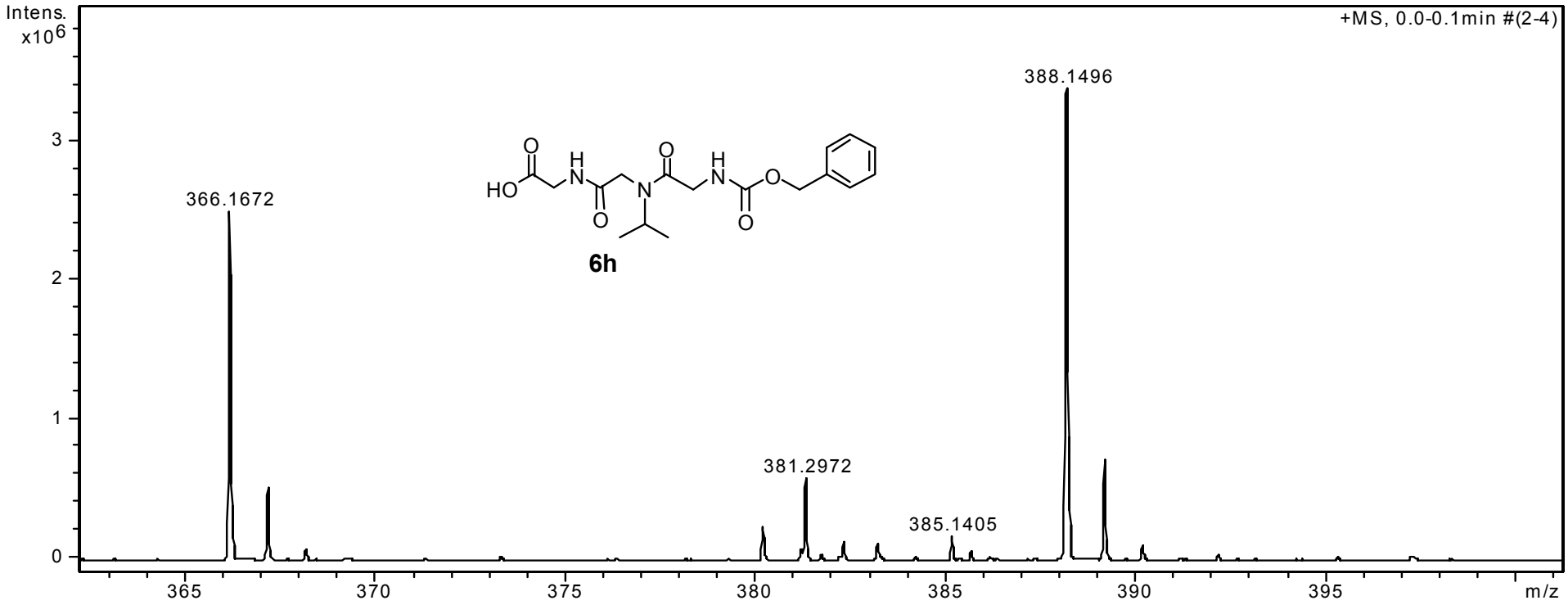


Figure 39. EI-HRMS of compound **6d**.

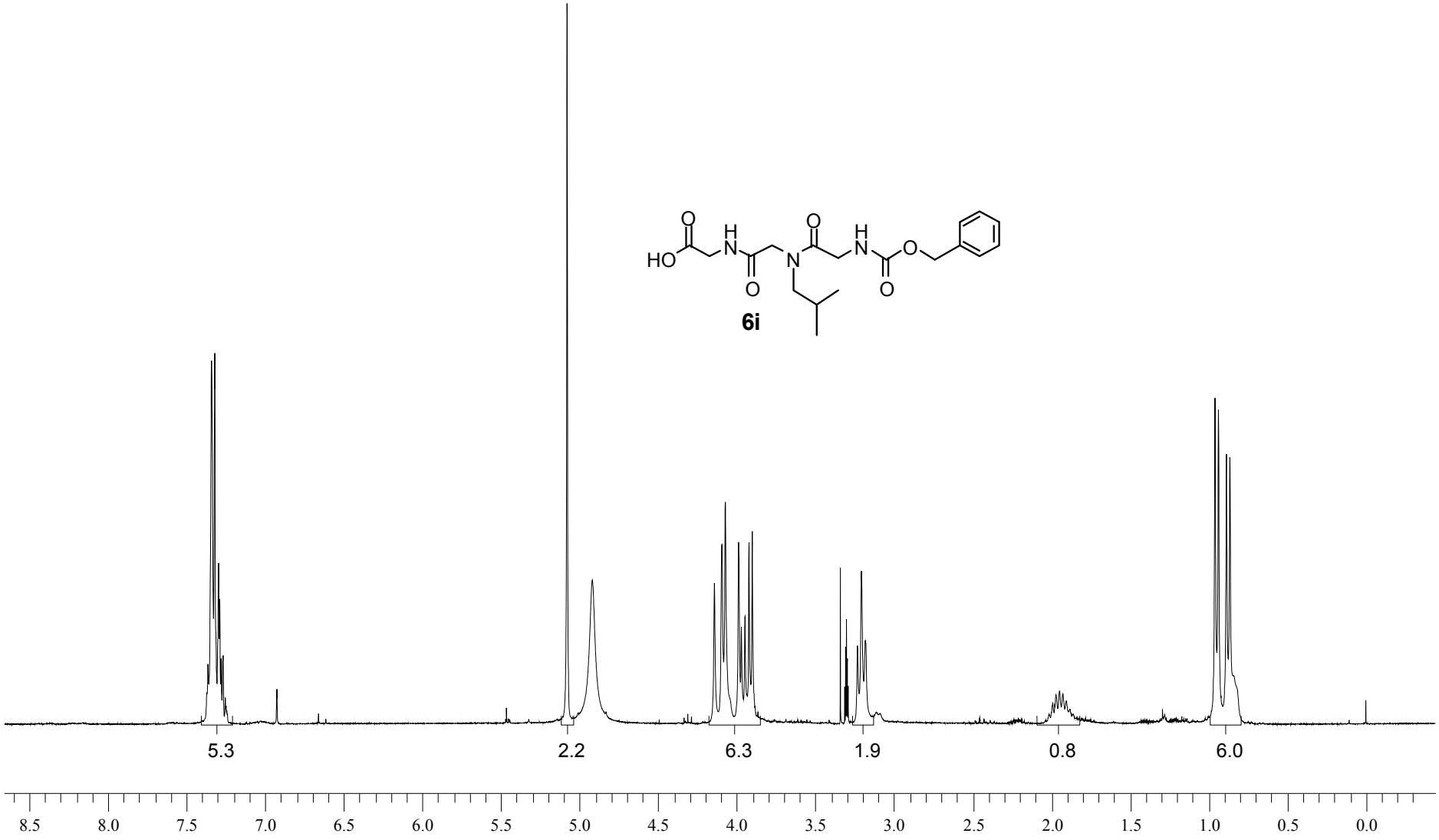


Figure 43. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **6i**.

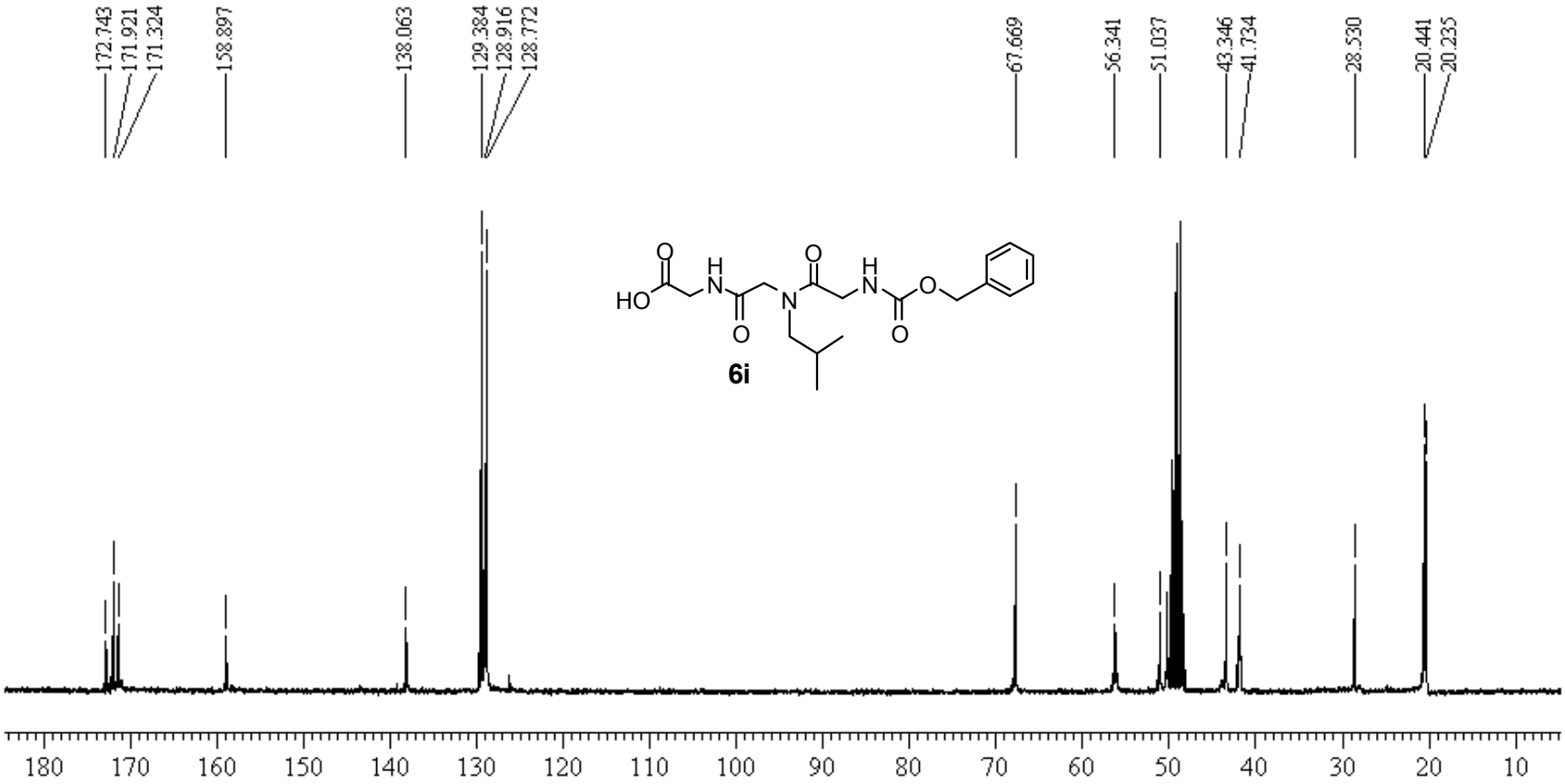


Figure 44. ^{13}C NMR (75.46 MHz, CD_3OD) spectrum of compound **6i**.

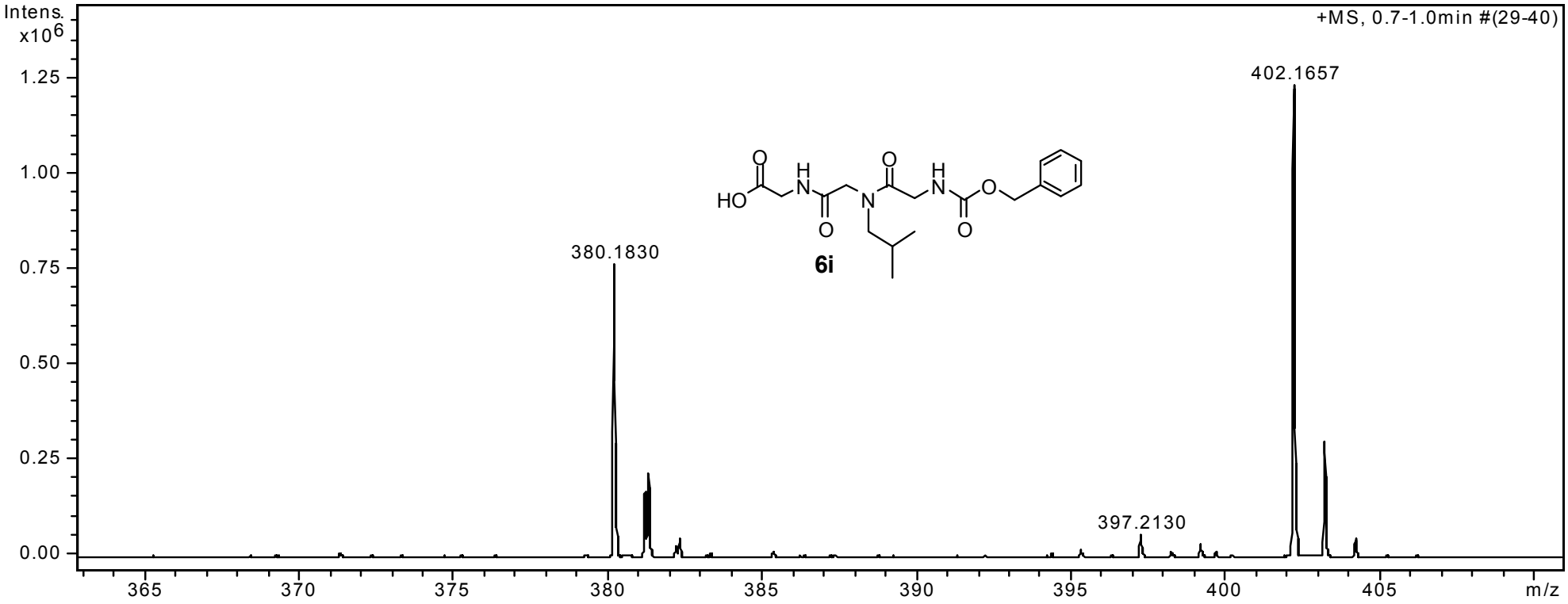


Figure 45. EI-HRMS of compound **6i**.

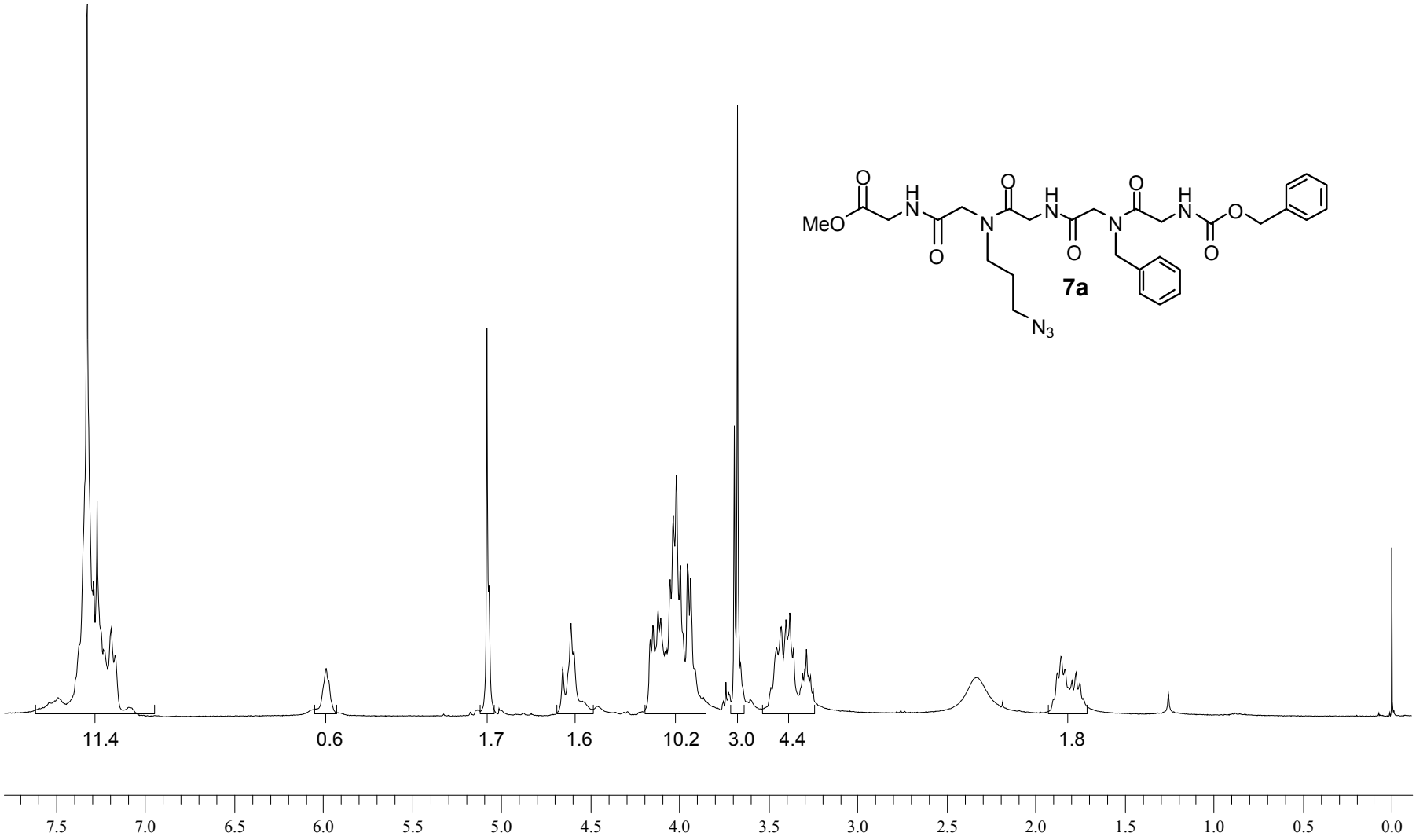


Figure 46. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7a**.

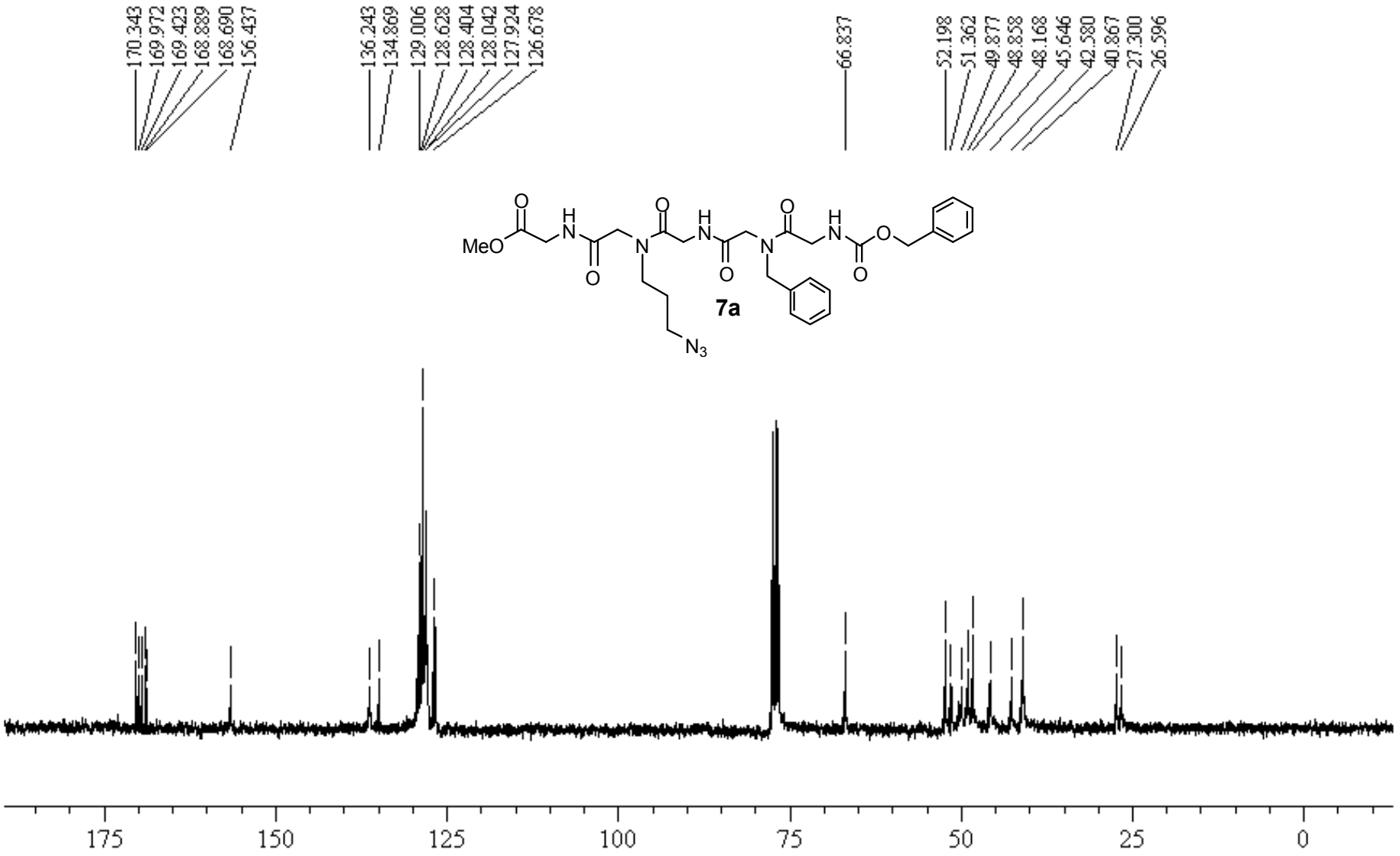


Figure 47. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **7a**.

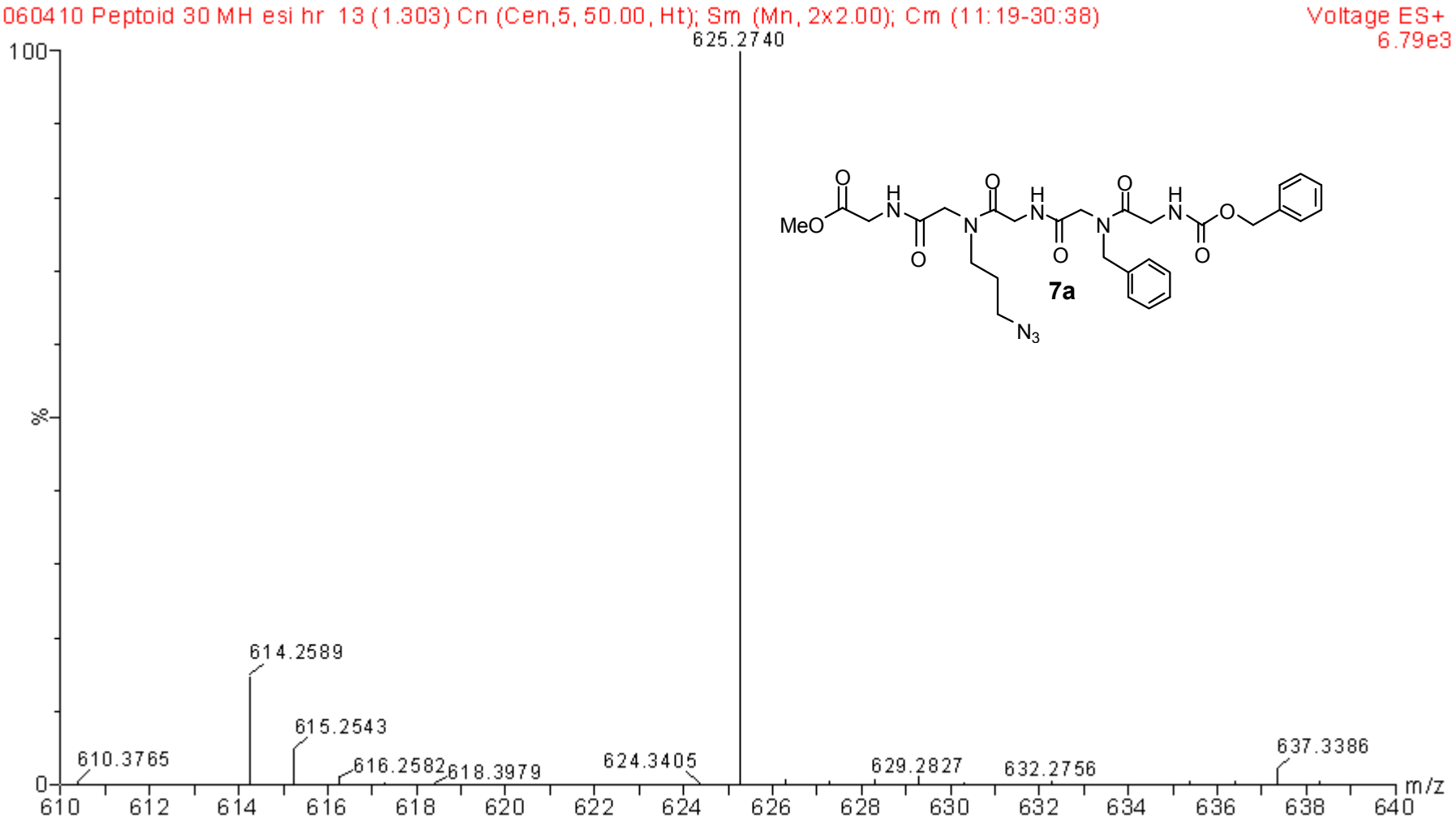


Figure 48. EI-HRMS of compound **8a**.

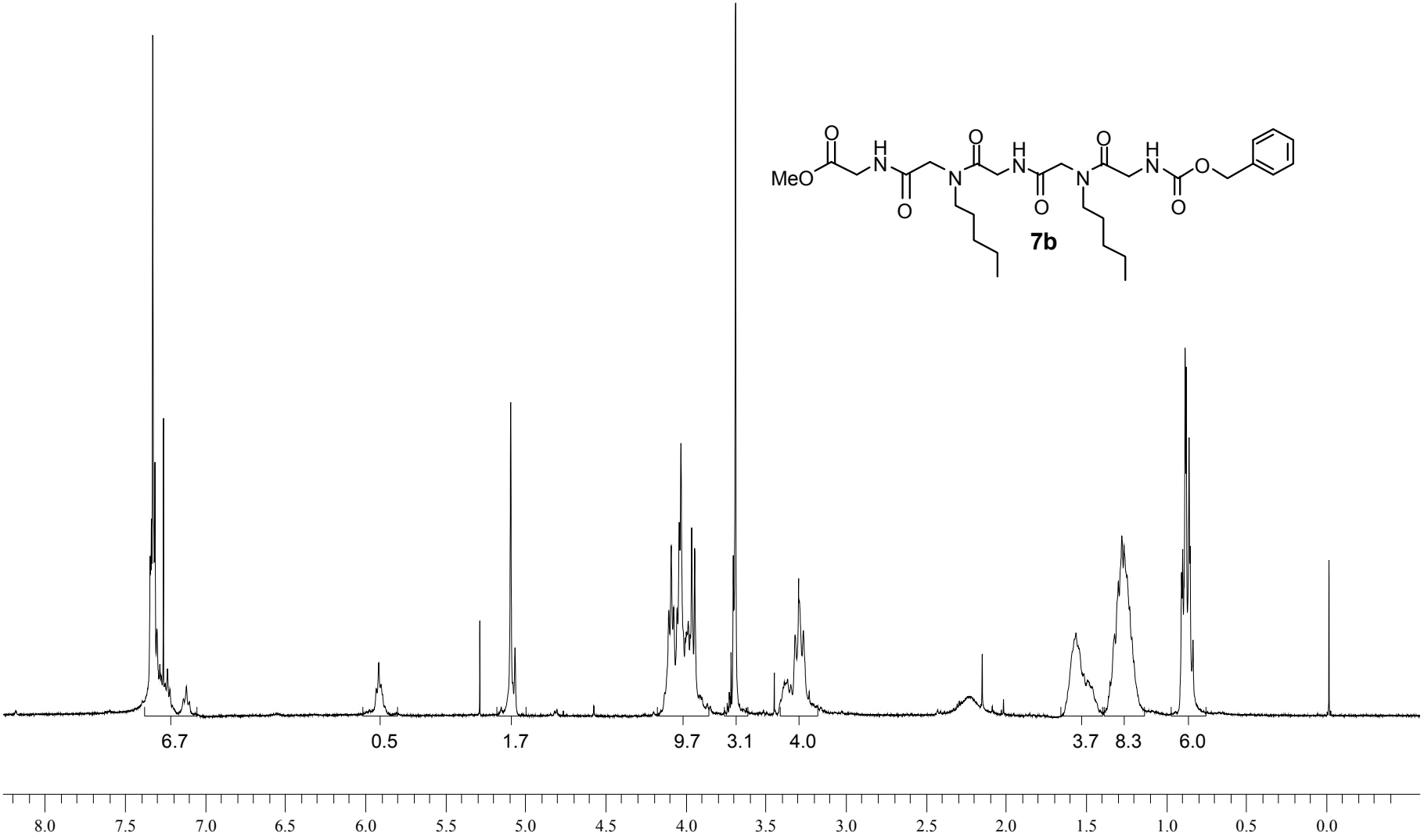


Figure 49. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7b**.

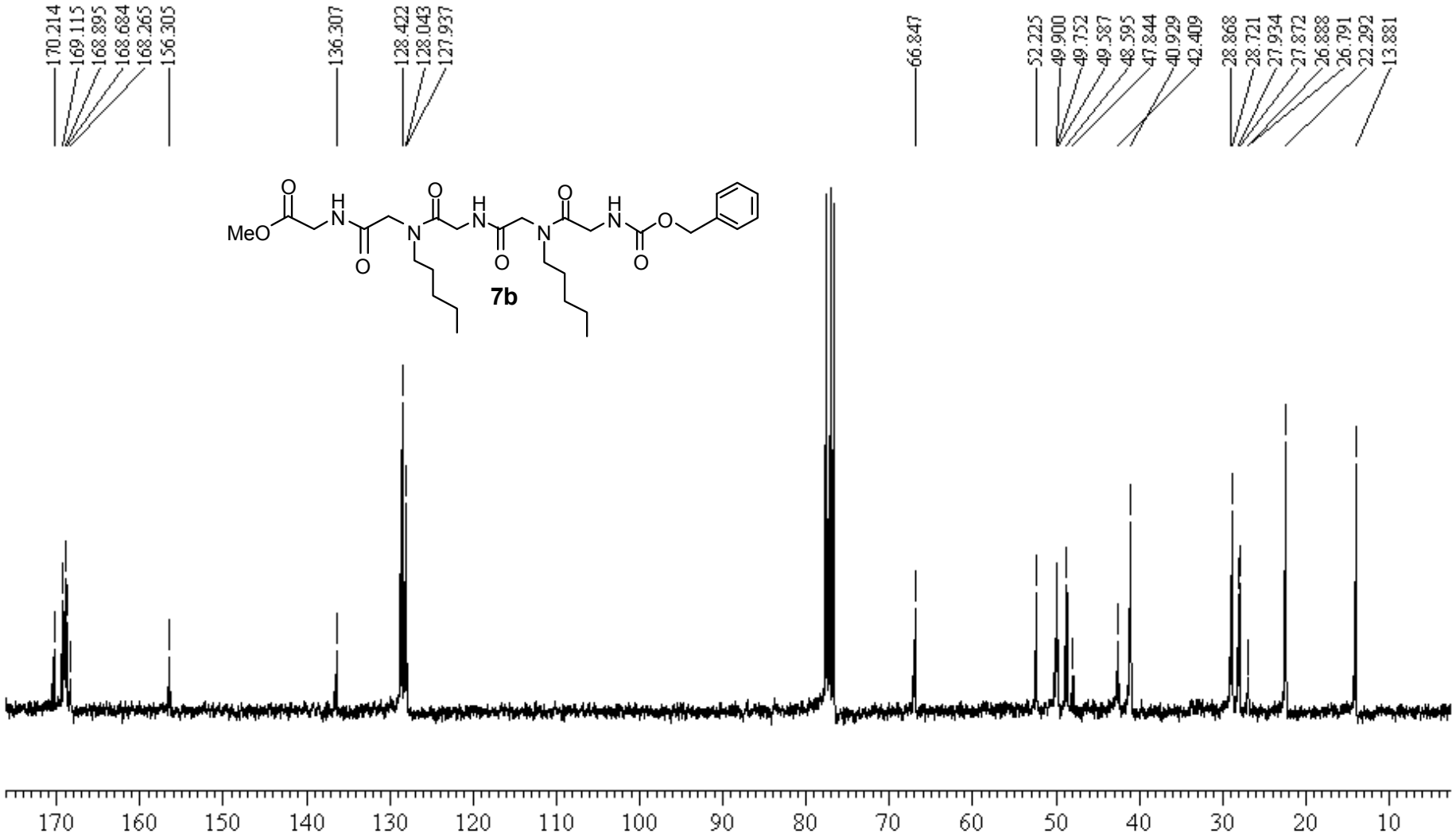


Figure 50. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **7b**.

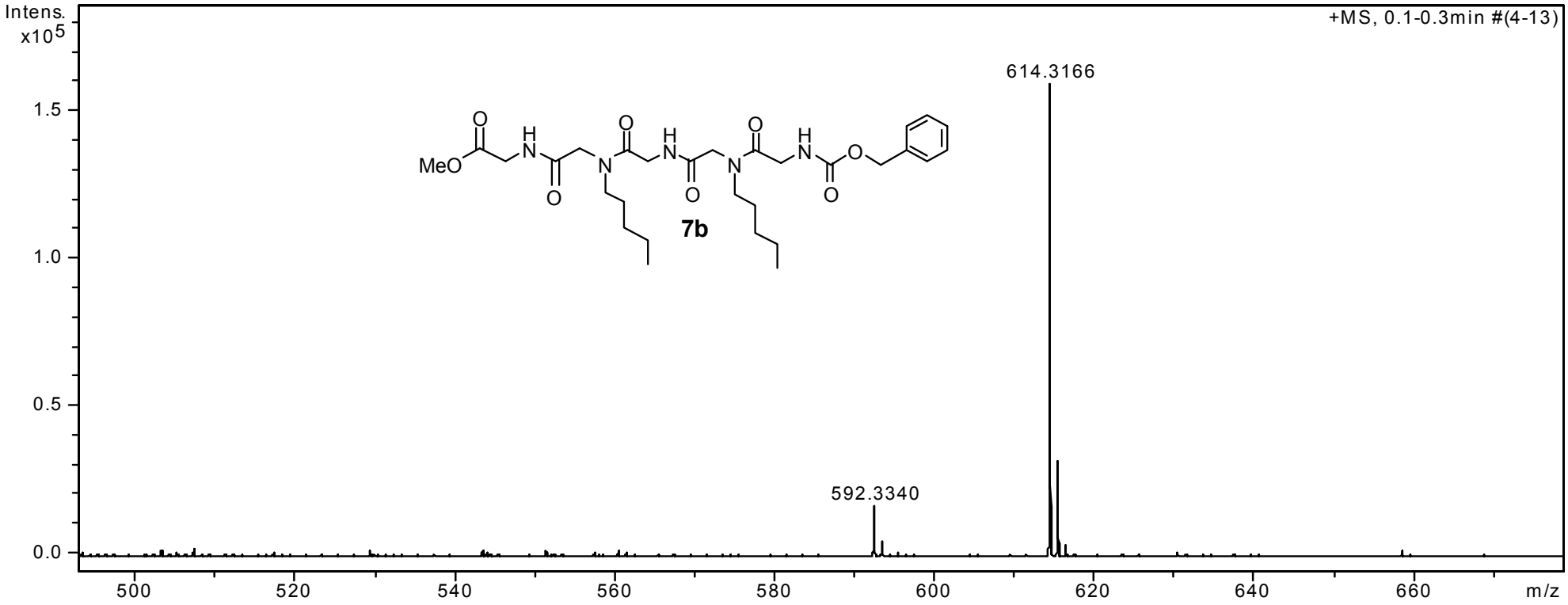


Figure 51. EI-HRMS of compound **7b**.

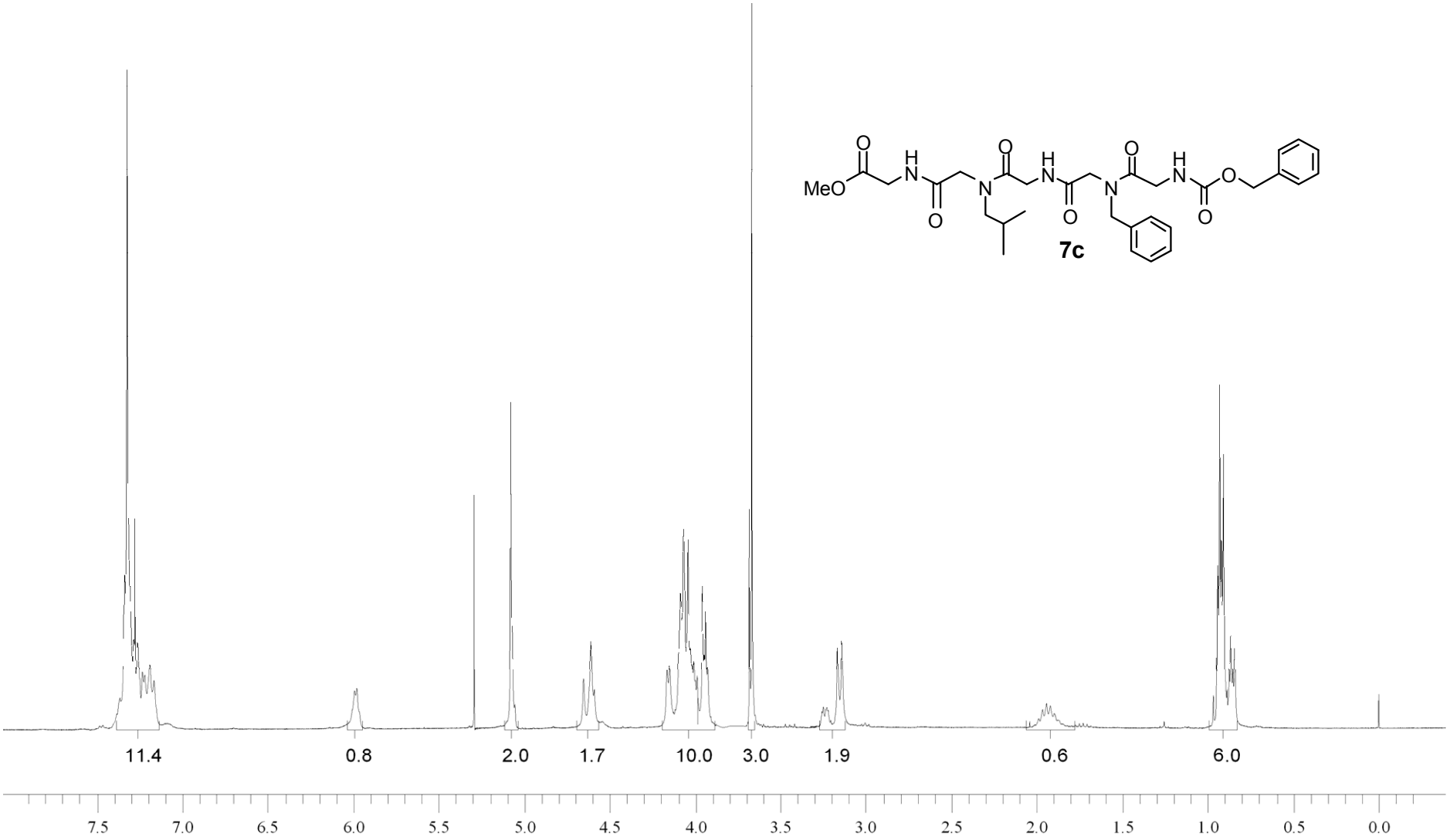


Figure 52. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7c**.

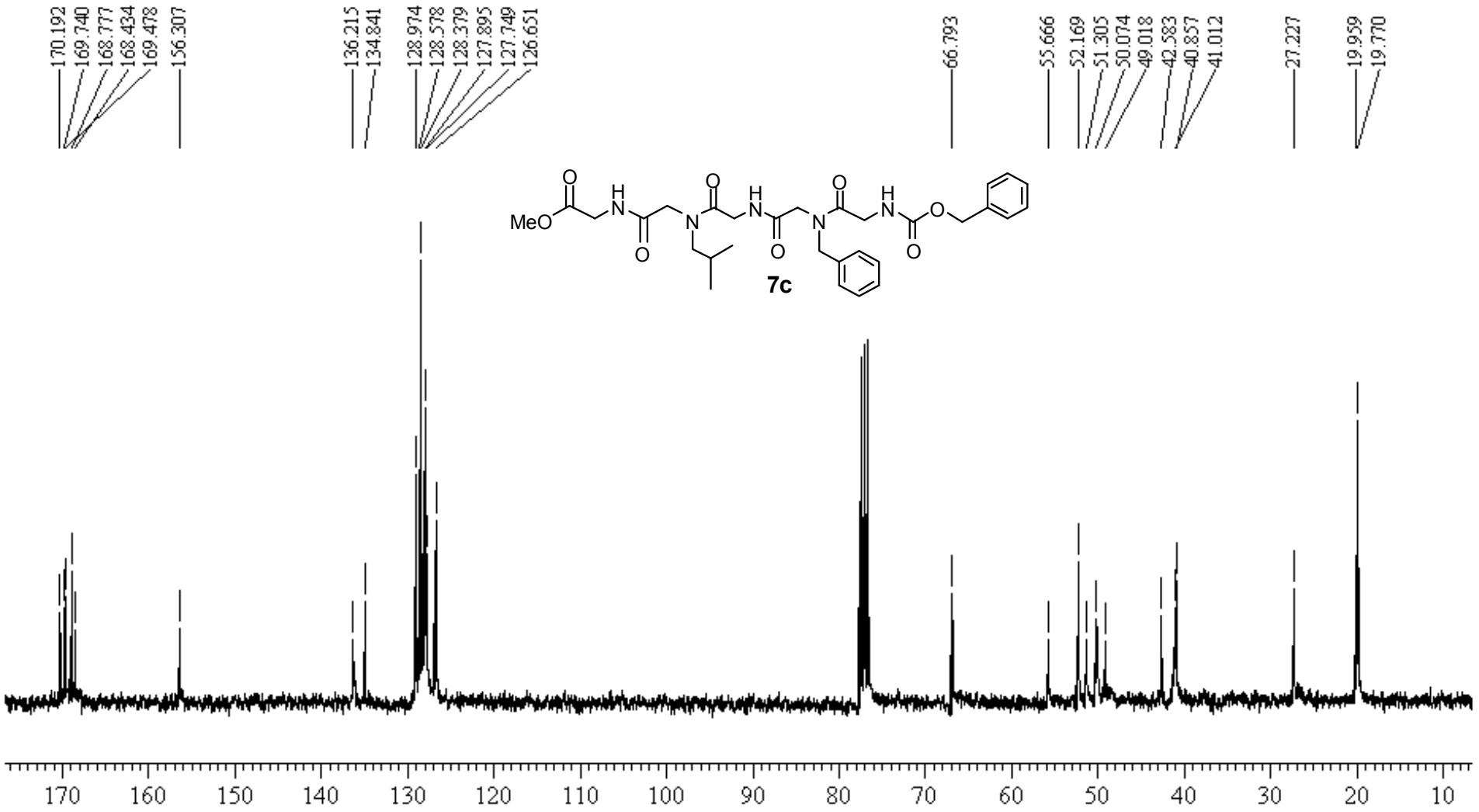


Figure 53. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **7c**.

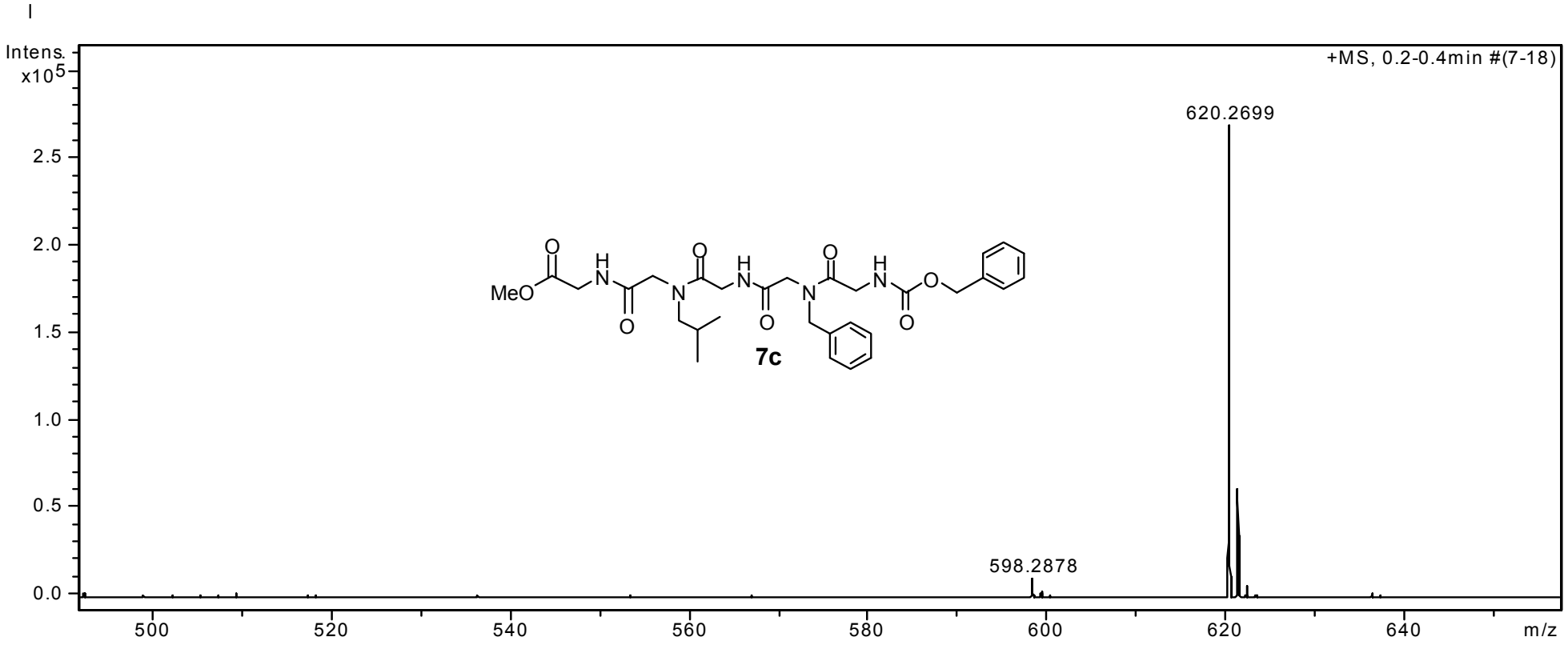


Figure 54. EI-HRMS of compound **7c**.

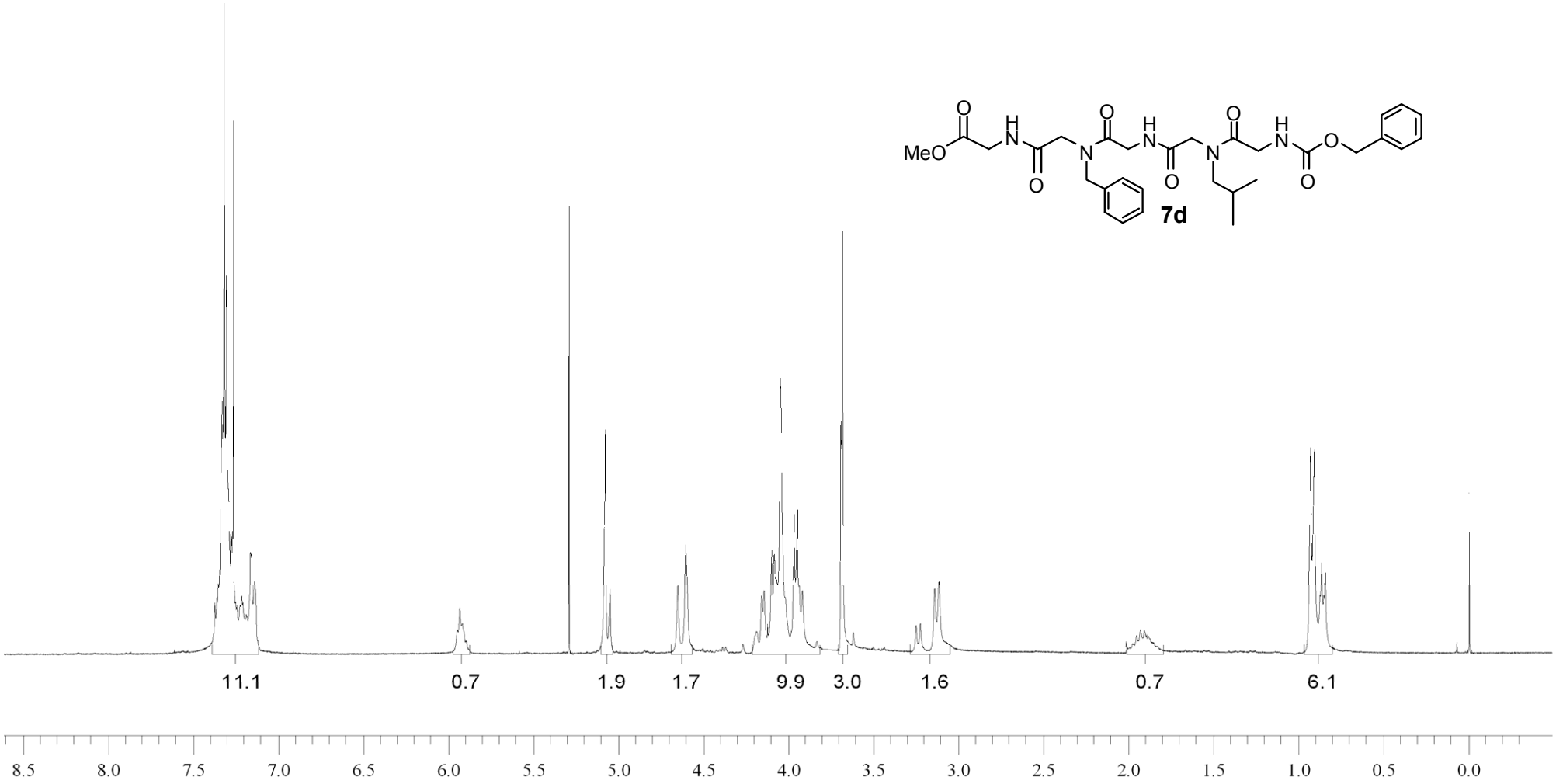


Figure 55. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7d**.

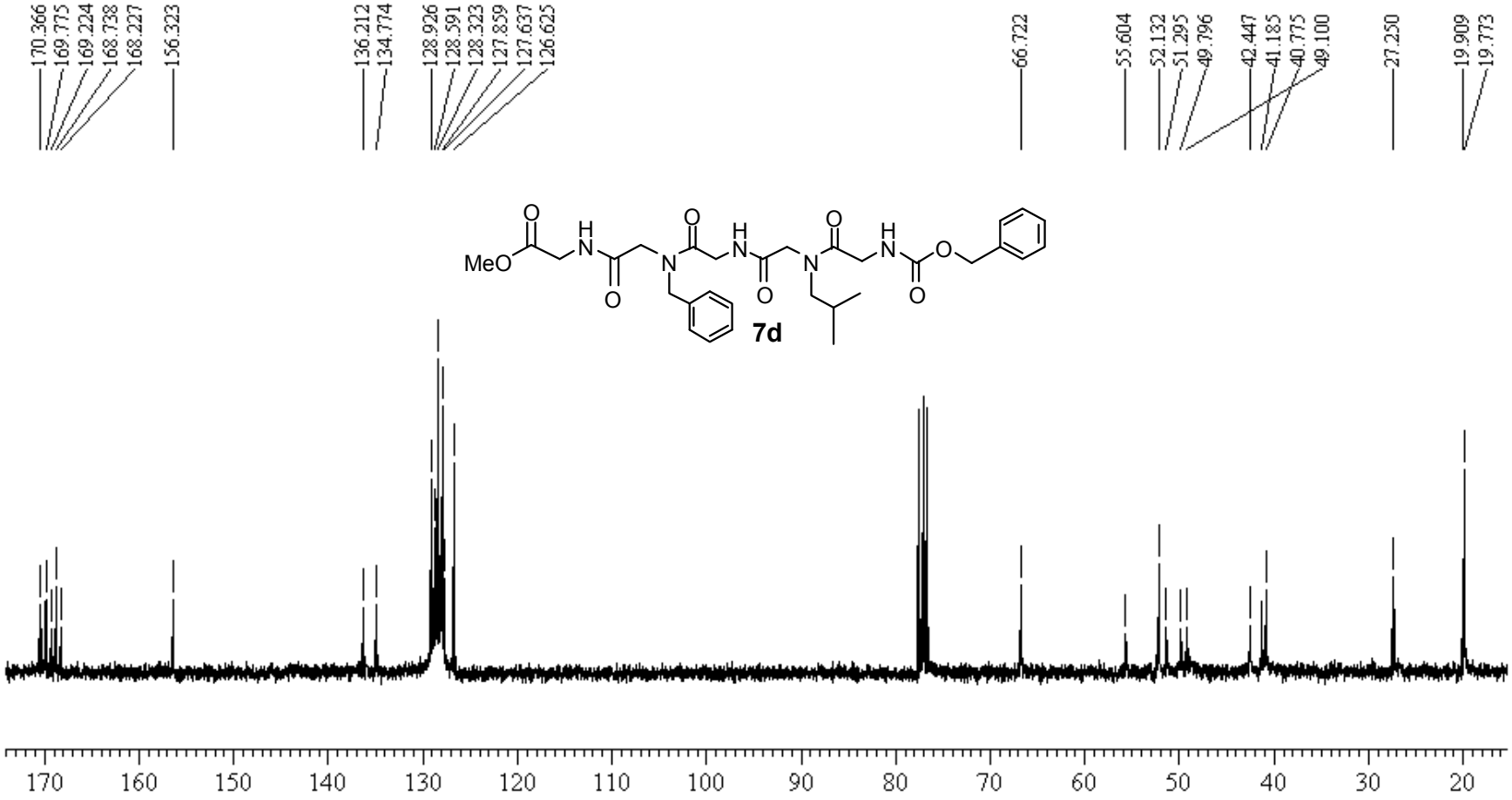


Figure 56. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **7d**.

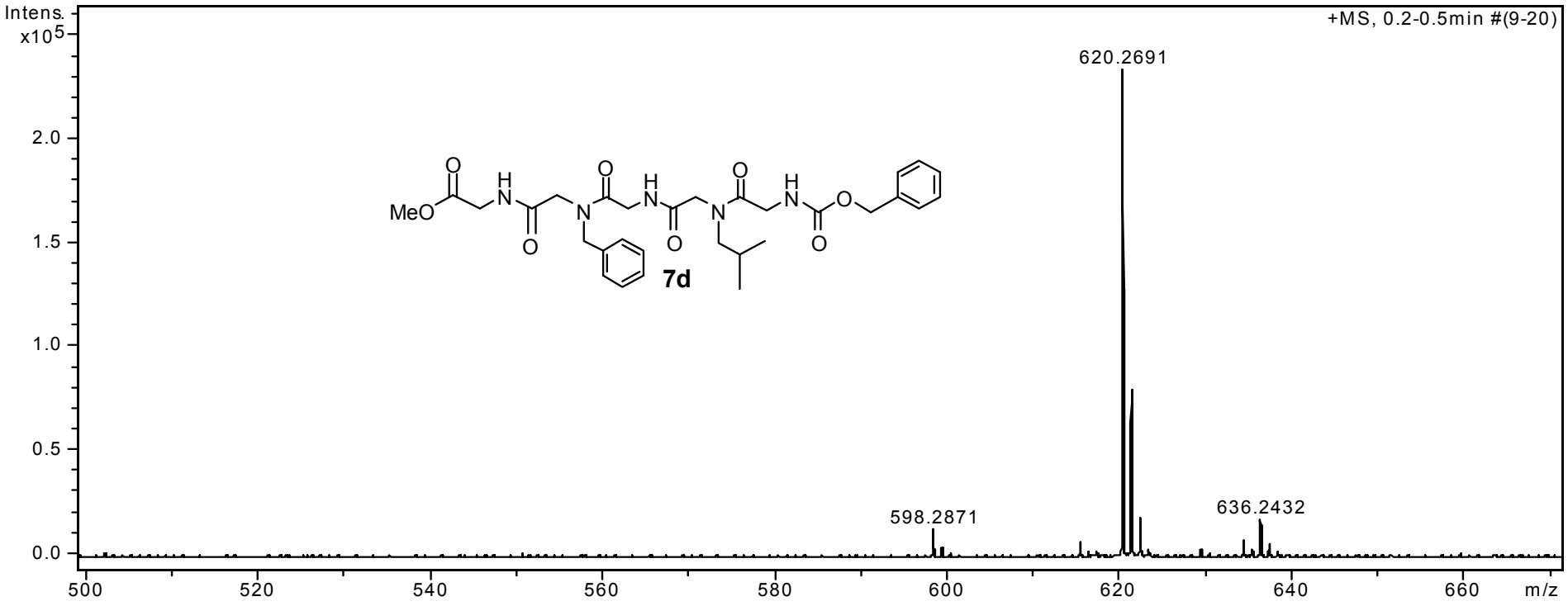


Figure 57. EI-HRMS of compound **7d**.

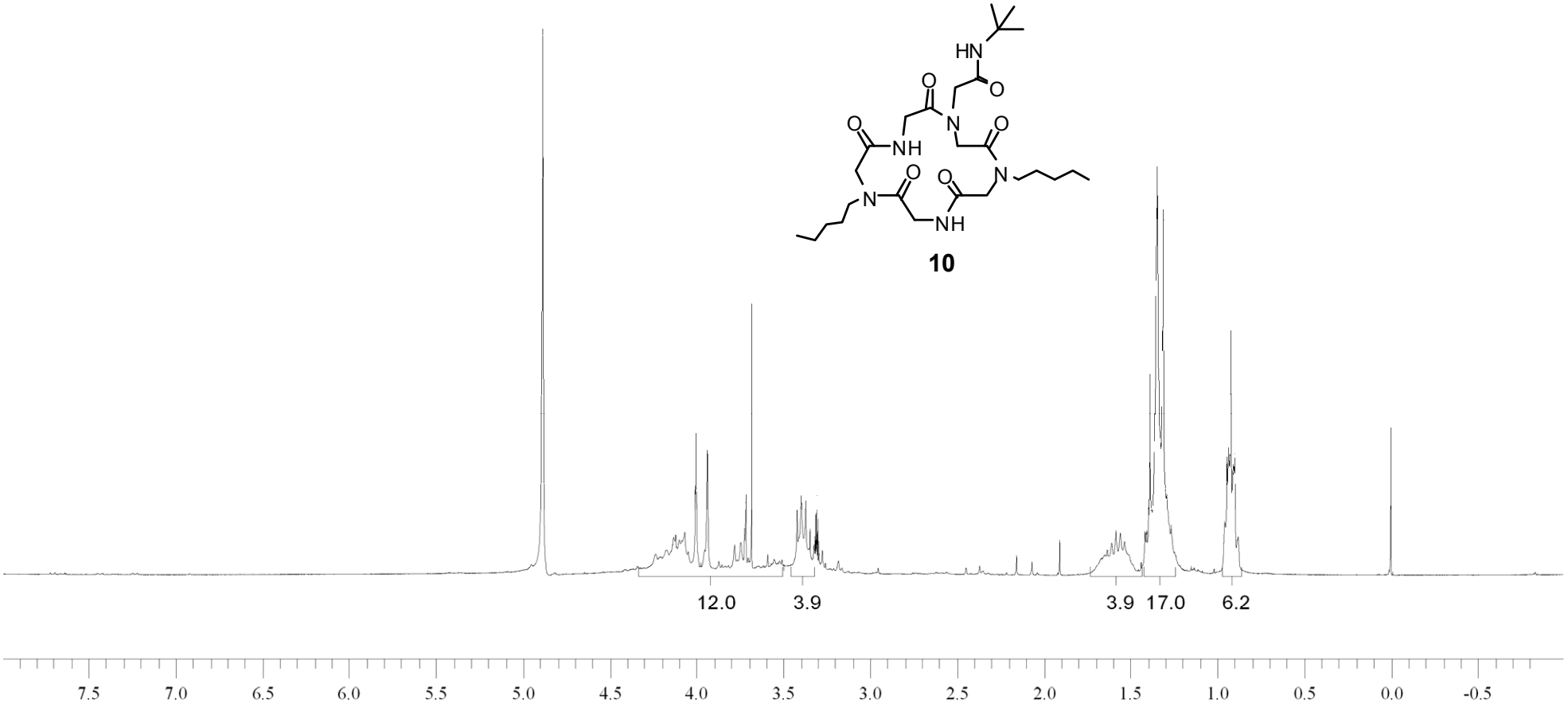


Figure 58. ^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **10**.

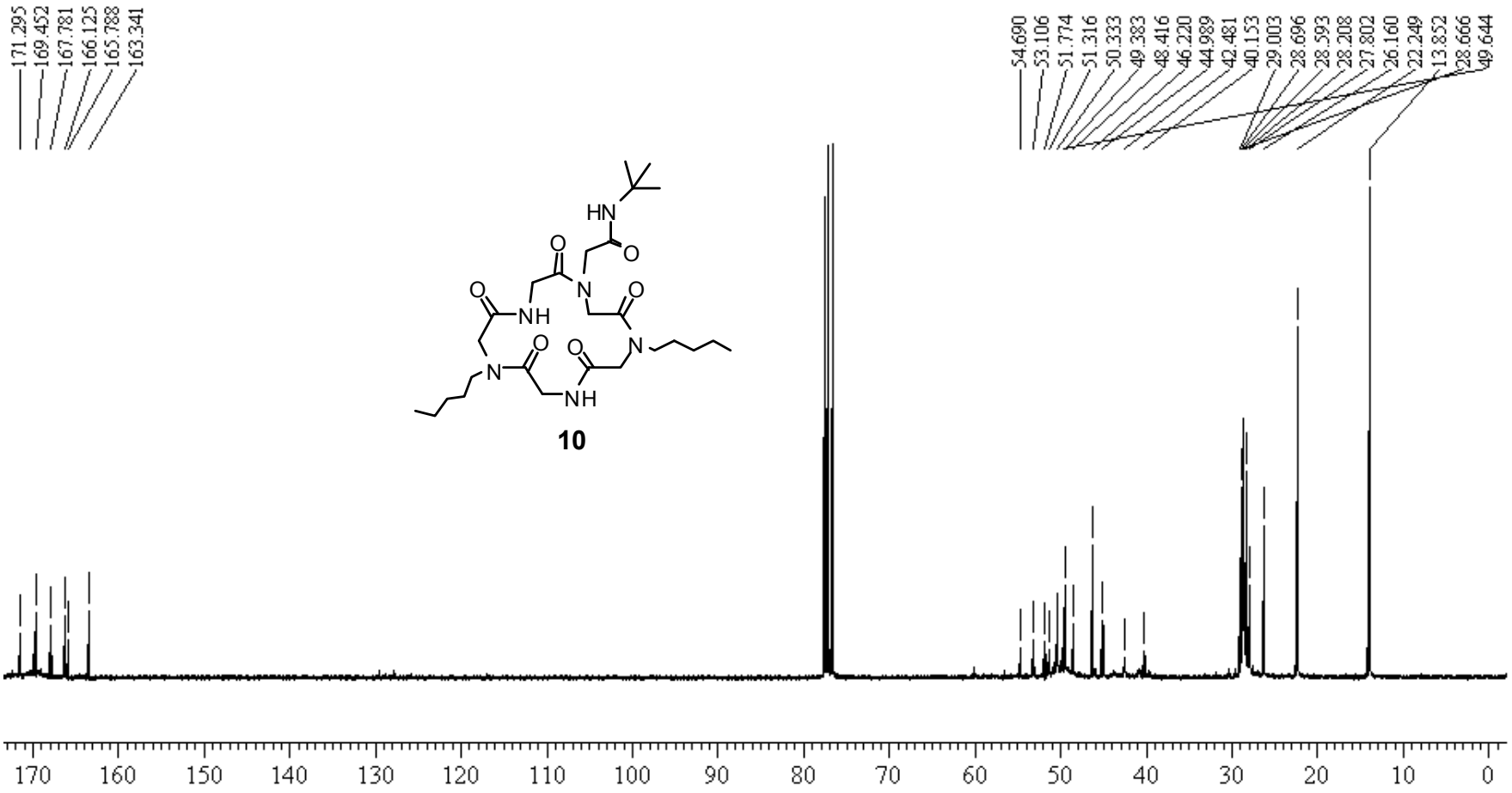


Figure 59. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **10**.

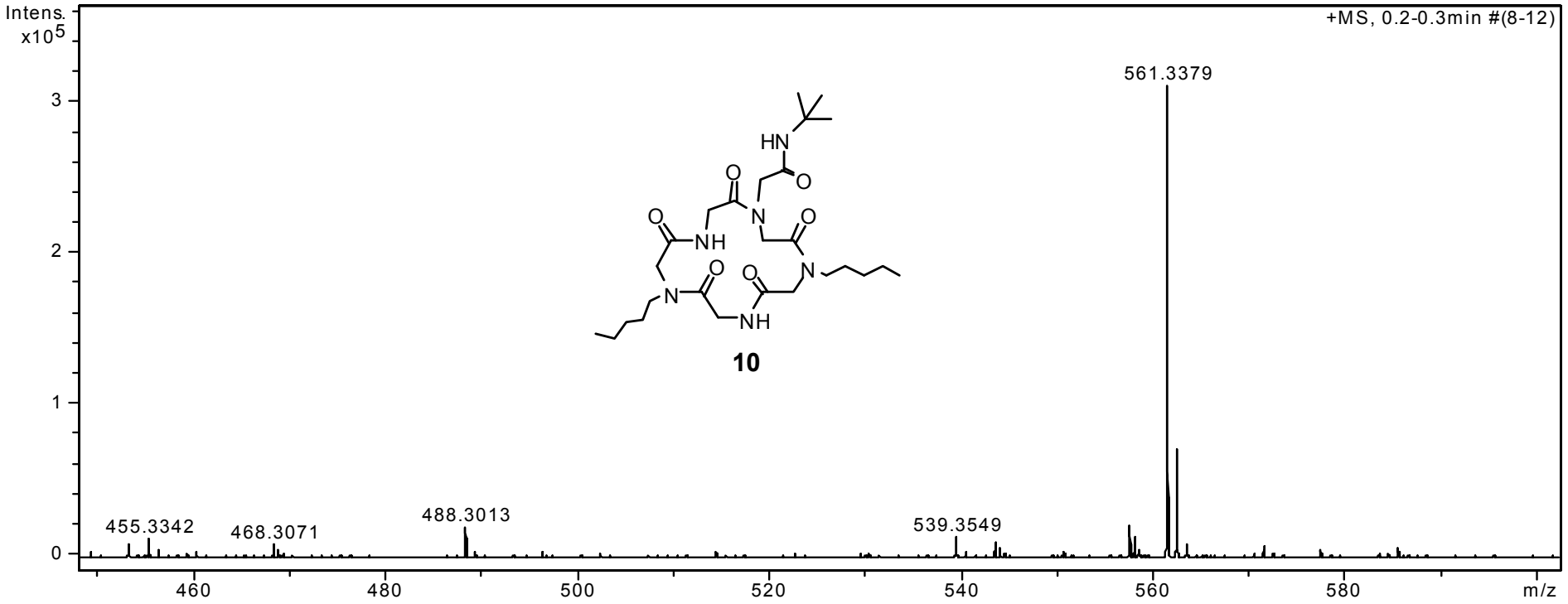


Figure 60. EI-HRMS of compound **10**.

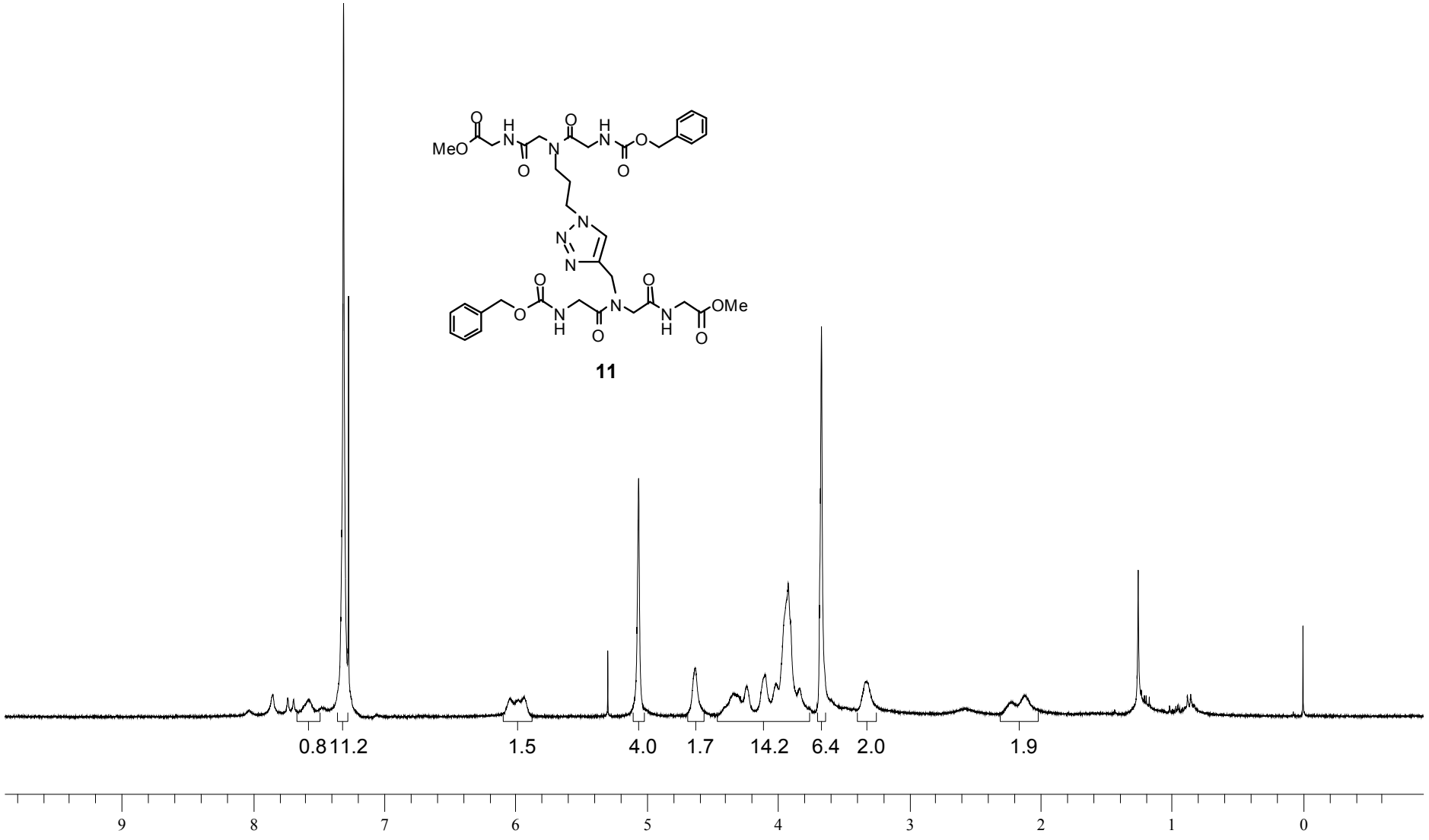


Figure 61. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **11**.

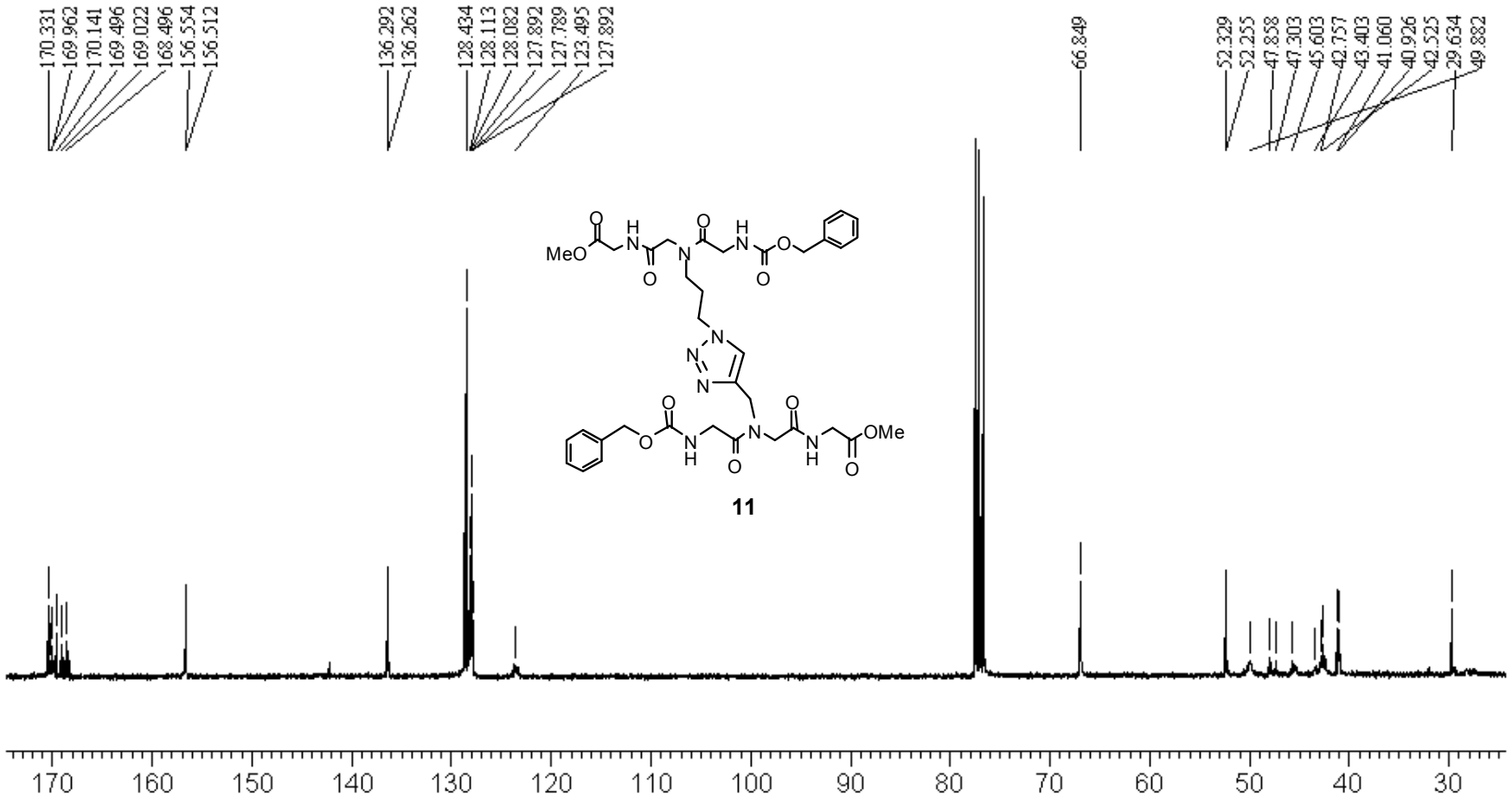
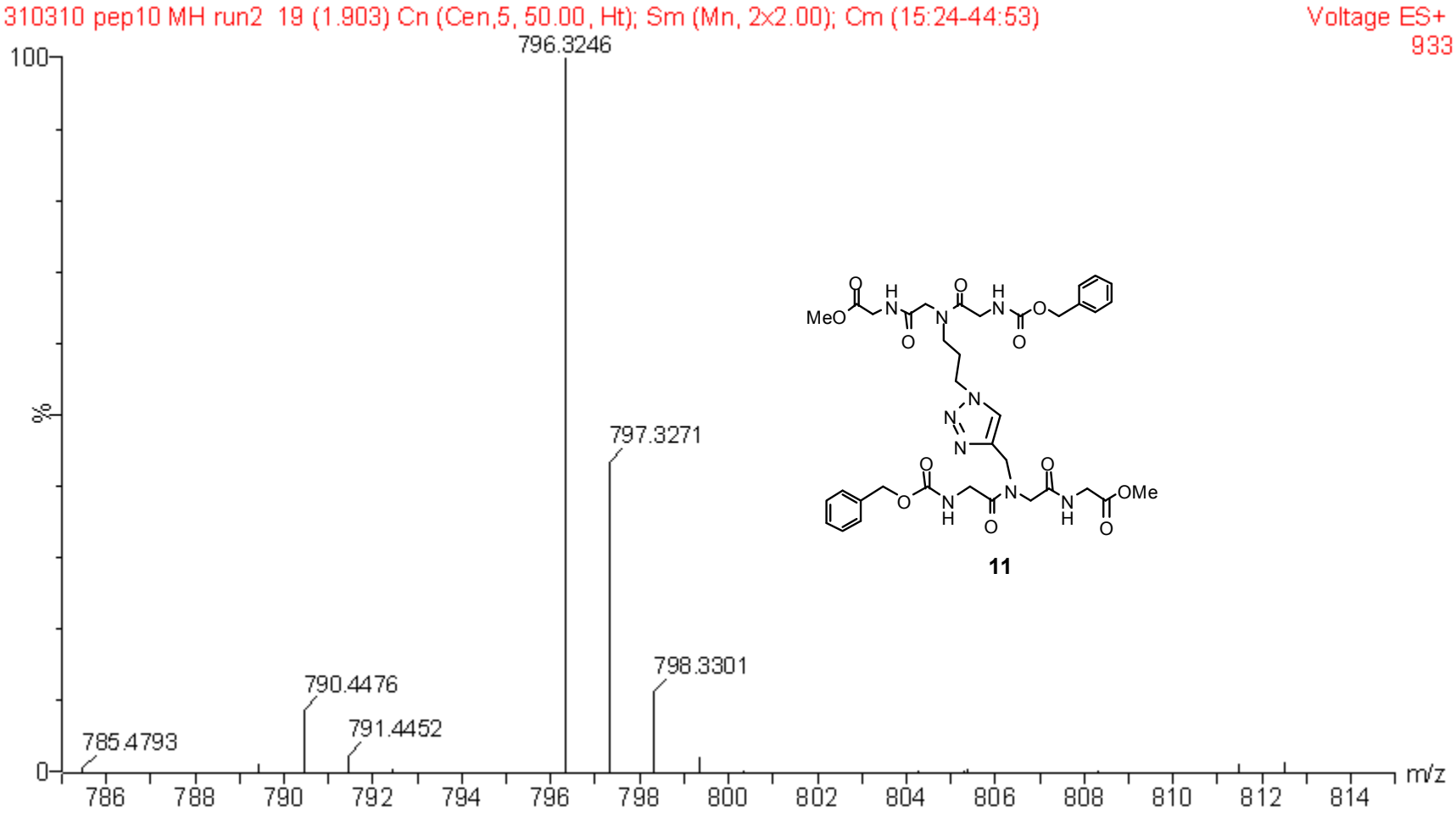


Figure 62. ^{13}C NMR (75.46 MHz, $CDCl_3$) spectrum of compound **11**.



11

Figure 63. EI-HRMS of compound **11**.