Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
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Experimental

S1

Total Synthesis of Azolemycin A and Related Compounds.

1) Experimental details.

General:

Room temperature refers to ambient temperature (20-22 °C) and 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica 60 (F254) plates, visualised using UV254 nm and potassium permanganate as appropriate. Silica column chromatography was carried out routinely using 40-60 Å silica gel.

All the reagents and solvents used were purchased from the Sigma-Aldrich, Alfa-Aesar, TCI, Bachem or Fluorochem Chemical Company and were used as received unless stated otherwise. Dry THF, dry toluene and dry CH_2Cl_2 were prepared by storing over 3 Å molecular sieves as described by Williams and Lawton,[1] and degassed with N_2 before use. Dry DMSO was distilled off CaH_2 onto 3 Å molecular sieves. pH2 buffer was made by dissolving 0.75 M of Na_2SO_4 and 0.25 M H_2SO_4.

^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVII-700 MHz, AVIII-600 MHz, DRX-500 MHz or DPX-400 MHz Fourier transform spectrometer at room temperature unless stated otherwise. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane. Solvents were used as an internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, d_6 -DMSO-D6 2.50 ppm, D_2O 4.79 ppm; δ_C: $CDCl_3$ 77.1 ppm, CD_3OD 49.0 ppm, d_6 -DMSO-D6 39.5 ppm). Coupling constants (*J*) are quoted in Hertz (Hz). Coupling constants are rounded to the nearest 0.5 Hz for spectra recorded on the AVIII-600 MHz, DRX-500 MHz or DPX-400 MHz machines. Coupling constants recorded on the AVII-700 MHz machine are rounded to the nearest 0.1 Hz. Abbreviations used in the descriptions of spectra are as follows; s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, sept. = septet, oct. = octet, m = multiplet, br = broad, i = ipso, o = ortho, m = meta, p = para, ax. = axial and eq. = equatorial. ^{13} C-NMR spectra were recorded with broadband proton decoupling and spectra were assigned on the basis of COSY, PENDANT, HMQC and HMBC spectra. In aromatic characterisations, the ipso carbon is taken to be the carbon bonded to the group with the highest molecular weight

Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer using EZ OMNIC software package 1, Bruker ALPHA Platinum ATR spectrophotometer or Perkin ELMER Spectrum 100 FT-IR spectrophotometer using OPUS software and are quoted in wavenumber (cm^{-1}).

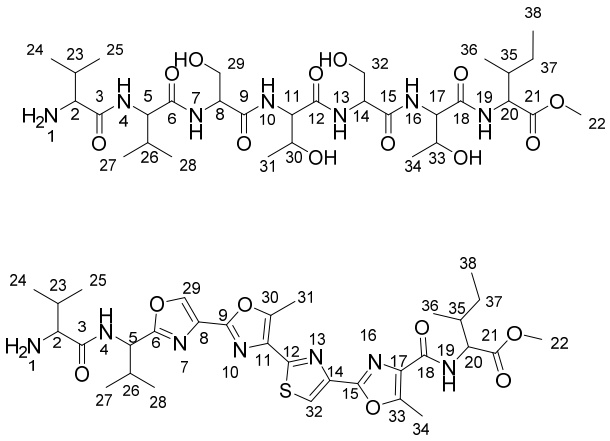
Optical rotations were recorded on an Optical Activity Ltd. AA-1000 millidegree auto-ranging polarimeter (using the sodium D line; 589 nm) and $[\alpha]_{D}$s are given in units of 10^{-1}deg cm^2 g^{-1}. The samples were made using spectroscopic grade MeOH, $CHCl_3$ or H_2O.

ESI mass spectra were obtained on a Bruker Esquire 2000 mass spectrometer or an Agilent 6130B single Quad (ESI)**.** HR ESI spectra were obtained by Dr Lijiang Song, Mr Philip Aston or Dr Rebecca Wills using a Bruker micro-TOF ESI attached to a time of flight (TOF) analyser.

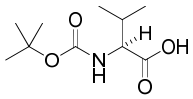
Melting points for solid crystalline products were determined on a Stuart Scientific SMP10 Digital Melting Point Apparatus, with three runs of each compound, and a range given in ˚C rounded to the nearest degree. They are uncorrected. CHN elemental analyses were carried out by Warwick Analytical Services.

Thin Layer Chromatography (TLC) was performed using silica (0.25 mm) coated alumina plates.

Numbering system

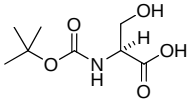


***N-tert*-Butyloxycarbonyl-L-valine 7**



Method modified from literature procedure by Garner *et al*.[2] A solution of di-tert-butyl dicarbonate (112 g, 512 mmol) in dioxane (300 mL) was added dropwise to a stirred and cooled solution of L-valine (50.0 g, 427 mmol) in aqueous NaOH solution (1 M, 875 mL) at 0 °C. The pH of the solution was adjusted to 9 using aqueous NaOH solution and the reaction mixture was allowed to reach room temperature overnight. The pH was adjusted to between 9 and 10, and the reaction mixture extracted with diethyl ether (3 x 250 mL). The aqueous phase was acidified to pH 2 with concentrated H_2SO_4 and extracted with EtOAc (5 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the protected amino-acid as bright white crystals (87.5 g, 403 mmol, 94 %); m.p. 76 - 78 °C, (lit.[3] 77 - 78 °C); $[\alpha]_D^{25}$ +6.6 (c = 1.1, $CHCl_3$), (lit. [4] $[\alpha]_D^{23}$ +11.7 (c = 2.35, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3320 (NH), 2967 (OH), 1711 (acid C=O), 1640 (amide C=O), 1509 (NH); δ_H (400 MHz, $CDCl_3$) 9.15 (1H, br.s., major and minor rotamer CO_2H), 6.21 (1H, d, *J* 6.5 Hz, minor rotamer N*H*CH), 5.08 (1H, d, *J* 9.0 Hz, major rotamer N*H*CH), 4.25 (1H, dd, *J* 9.0, 4.5 Hz, major rotamer NHC*H*), 4.13 - 3.93 (1H, m, minor rotamer NHC*H*), 2.29 – 2.13 (1H, m, major and minor rotamer C*H*$(CH_3)_2$), 1.47-1.40 (9H, m, major and minor rotamer C$(CH_3)_3$), 0.99 (1H, d, *J* 7.0 Hz, major and minor rotamer CH$(CH_3)_2$), 0.93 (1H, d, *J* 7.0 Hz, major and minor rotamer CH$(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 176.8 (CO_2H), 155.8 (*C*ONH), 80.0 ($C(CH_3)_3$), 58.4 (*C*HNH), 30.9 ($CH(CH_3)_2$), 28.3 ($C(CH_3)_3$), 19.0, 17.4 ($CH(CH_3)_2$); *m/z* (ESI+) 240.1 ([M+Na]+, 100.0%); HR ESI, *m/z* = 240.1208 ($C_{10}H_{19}NO_4Na$ requires M+Na = 240.1206). The data are consistent with that previously reported.[5]

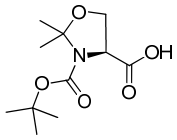
***N-tert*-Butoxy-L-serine 9**



A solution of di-tert-butyl dicarbonate (25.0 g, 115 mmol) in dioxane (75 mL) was added dropwise to a solution of L-serine (10.0 g, 95.2 mmol) in aqueous NaOH solution (1M, 195 mL, 195 mmol) at 0 °C. Following complete addition, the pH of the reaction mixture was adjusted to pH 9 - 10 and it was stirred at room temperature overnight to give a white suspension with a pH of 7 - 8. The pH was adjusted to 9 - 10 to give a clear, colourless solution. This was washed with Et_2O (2 x 50 mL), and the organic phases discarded. The

aqueous phase was acidified to pH 2 buffer and extracted with EtOAc (4 x 100 mL). The organic extracts were combined, washed with saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give protected amino acid **9** as a colourless oil (18.7 g, 91.1 mmol, 80 %); $[\alpha]_D^{27}$ -4.5 (c = 1.3, H_2O), (lit.[6] $[\alpha]_D^{25}$ -7.6 (c = 2.6, H_2O)); υ_{max}/cm^{-1} (neat) 3333.7 (O-H), 1686 (C=O), 1512 (N-H); δ_H (400 MHz, $CDCl_3$) 6.67 (1H, br.s., major and minor rotamer, CO_2H), 5.89 (1H, d, *J* 7.0 Hz, major and minor rotamer, N*H*), 4.40 - 4.30 (1H, m, NHC*H*, major rotamer), 4.28 - 4.17 (1H, m, NHC*H*, minor rotamer), 4.05 (1H, dd, *J* 11.0, 3.0 Hz, major and minor rotamer, CHCH_2), 3.85 (1H, dd, *J* 11.5, 3.0 Hz, major and minor rotamer, CHCH_2), 1.44 (9H, s, major and minor rotamer, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 154.1 (*C*O_2H), 156.2 (*C*O_2^{t}Bu), 80.5 (*C*$(CH_3)_3$), 63.0 (NH*C*H), 55.6 (*C*H_2OH), 28.3 (C(*C*H_3)$_3$; *m/z* (ESI+) 228.0 ([M+Na] 100%); HR ESI, *m/z* = 228.0841, ($C_8H_{15}NO_5Na$ requires M+Na = 228.0842). The data are consistent with that previously reported.[7]

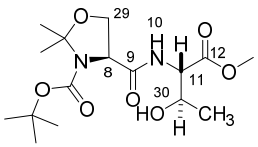
(*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic acid 10



Method modified from literature procedure of Trajkovic *et al.*[8] A solution of *N*-tert-butyloxycarbonyl-L-serine **9** (13.3 g, 64.8 mmol), dimethoxypropane (64.0 g, 520 mmol) and toluene sulphonic acid monohydrate (1.11 g, 6.47 mmol) in CH_2Cl_2 (75 mL) was heated to reflux for 2 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (150 mL) and EtOAc (100 mL). The separated organic phase was washed with water (50 mL) and saturated aqueous NaCl solution (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The protected amino-acid **10** was obtained, after drying under high vacuum, as a low melting point yellow solid (12.7 g, 51.8 mmol, 80 %); m.p. <30°C; $[\alpha]_D^{25}$ -58.2 (c = 1.20, $CHCl_3$), (lit.[9] for opposite enantiomer $[\alpha]_D^{24}$ + 63.1 (c = 1.10, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3307 (O-H), 1687 (C=O), 1646 (C=O); δ_H (400 MHz, $CDCl_3$) 8.59 (1H, br. s., major and minor rotamer CO_2H), 4.49 (1H, dd, *J* 6.5, 2.0 Hz, minor rotamer C*H*CH_2), 4.37 (1H, dd, *J* 7.0 Hz, 3.0 Hz, major rotamer C*H*CH_2), 4.20 - 4.13 (1H, m, major and minor rotamer CHCH_2), 4.09 (1H, td, *J* 9.0, 2.5 Hz, CHCH_2), 1.64 (3H, s, major rotamer C(CH_3)$_2$), 1.59 (3H, s, 3H, s, minor rotamer C(CH_3)$_2$), 1.51 (3H, s, 3H, s, major rotamer C(CH_3)$_2$), 1.47 (12H, s, 3H, s, major rotamer C(CH_3)$_2$, major rotamer C(CH_3)$_3$), 1.40 (9H, s, major rotamer C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 176.3, 175.1 (major and minor rotamer *C*O_2H), 152.7, 151.3 (major amd minor rotamer *C*O_2^{t}Bu), 95.2 (major and minor rotamer *C*$(CH_3)_2$), 82.9, 81.6 (major and minor rotamer *C*$(CH_3)_3$), 66.2, 65.8 (major and minor rotamer CH*C*H_2), 59.1 (major and minor rotamer *C*HCH_2), 28.3 (major and minor rotamer C(*C*H_3)$_3$), 24.9, 24.3 (major and minor rotamer C(*C*H_3)$_2$); *m/z* (ESI+) 268.1 ([M+Na]

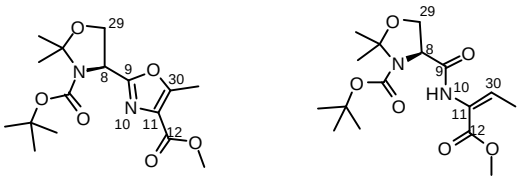
100%); HR ESI, *m/z* = 268.1147, ($C_{11}H_{19}NO_5Na$ requires M+Na = 268.1155). Spectroscopic data are consistent with that previously reported.[10]

Dipeptide 11



A solution of the acid **10** (15.5 g, 62.9 mmol) and HOBt (88%, 1.45 g, 9.44 mmol) in EtOH (300 mL) was stirred at room temperature for 15 minutes. To this was added a solution of L-threonine methyl ester hydrochloride (11.7 g, 69.2 mmol) in EtOH (100 mL) and the mixture was cooled to 0-5 °C. *N*-Methylmorpholine (22.0 mL, 202 mmol) was added over 5 minutes, and the reaction was stirred at 0-5 °C for 15 minutes. EDCI (14.4 g, 75.5 mmol) was added in one portion, and the reaction mixture was allowed to reach room temperature overnight. The reaction was acidified with pH 2 buffer and was reduced *in vacuo*. EtOAc (250 mL) was added, the mixture was vigorously agitated and the phases were separated. The organic phase was washed with pH 2 buffer (100 mL), water (100 mL), saturated aqueous $NaHCO_3$ solution, and saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give dipeptide **10** as an orange crystalline solid (19.1 g, 53.0 mmol, 84 %); m.p. 77 - 80 °C; $[\alpha]_D^{25}$ -61.0 (c = 1.10, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3437 (O-H), 1735 (ester C=O), 1655 (amide C=O), 1524 (N-H); δ_H (500 MHz, $CDCl_3$) 7.27 (1H, s, major and minor rotamer N10-*H*), 4.55 (1H, dd, *J* 9.0, 2.0 Hz, major and minor rotamer C8-*H*), 4.49 - 4.00 (4H, m, major and minor rotamer C11-*H*, C29-H_2, C30-*H*), 3.73 (3H, s, OCH_3), 2.74 (1H, br. s., C30-O*H*), 1.85 – 1.36 (17H, m, major and minor rotamer $C(CH_3)_3$, $C(CH_3)_2$), 1.17 (3H, d, *J* 6.5 Hz, major and minor rotamer C30-CH_3); δ_C (125 MHz, $CDCl_3$) 173.4, 171.0 (major and minor rotamer *C9*, *C12*), 153.1, 151.8 (major and minor rotamer $CO_2{}^tBu$), 95.12, 94.6 (major NS minor rotamer $C(CH_3)_2$), 81.4 (major and minor rotamer $C(CH_3)_3$), 68.2, 67.7 (major and minor rotamer *C*8-H), 67.1, 65.5 (major and minor rotamer *C29*-H_2), 60.8, 60.2 (major and minor rotamer *C30*-H), 57.4 (major and minor rotamer *C11*-H), 52.5 (major and minor rotamer OCH_3), 28.2, 26.6 (major and minor rotamer $C(CH_3)_3$, $C(CH_3)_2$), 19.9 (major and minor rotamer C30-CH_3); *m/z* (ESI+) 383.1 ([M+Na] 100%), 361.1 ([M+H] 60%); HR ESI, *m/z* = 383.1785, ($C_{16}H_{28}N_2O_7Na$ requires M+Na = 383.1789).

Oxazole Methyl Ester 5 and Alkene 13



Method modified from literature procedure of Doi *et al.*[11] A solution of the dipeptide **11** (15.9 g, 44.2 mmol) in dry CH_2Cl_2 (220 mL) was cooled to 0 – 5 °C under a nitrogen atmosphere. Diisopropylethylamine (30.0 mL, 176 mmol) and dry DMSO (16.0 mL, 225 mmol) were added sequentially, followed by the addition of SO_3.pyr (21.1g, 133 mmol) over 5 minutes. The reaction mixture was stirred at 0 – 5 °C for 3 hours, then poured into ice cold pH 2 buffer (200 mL) and stirred for 5 minutes. The phases were separated and the aqueous phase was further extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and ketone **12** obtained by silica chromatography (50% EtOAc: pet ether) as a yellow oil (10.7 g, 29.8 mmol, 68 %). This was used immediately.

Oxazole **5** prepared according to the method of Bagley *et al*.[12] Iodine (14.9 g, 58.6 mmol) and triethylamine (16.8 mL, 120 mmol) were added sequentially to an ice cold solution of triphenylphosphine (15.4 g, 58.6 mmol) in CH_2Cl_2 (150 mL) under a nitrogen atmosphere. A solution of the ketone (10.5 g, 29.3 mmol) in CH_2Cl_2 was added dropwise and the reaction mixture was allowed to reach room temperature overnight. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (150 mL) and pH 2 buffer (100 mL). The phases were separated and the organic phase was washed with pH 2 buffer (100 mL), water (100 mL) and saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Oxazole **5** was obtained by silica chromatography (25% to 50% EtOAc: pet. ether) as a pale yellow solid (4.15 g, 12.2 mmol, 28 % over 2 steps); m.p. 60 - 63 °C; $[\alpha]_D^{25}$ -87.1 (c = 1.10, $CHCl_3$); υ_{max}/cm^{-1} (neat) 1698 (C=O), 1609 (C=N); δ_H (400 MHz, $CDCl_3$) 5.15 - 5.07 (1H, m, minor rotamer C8-*H*), 4.99 (1H, dd, *J* 6.0 Hz, 3.0 Hz, major rotamer C8-*H*), 4.25 - 4.04 (2H, m, major and minor rotamer C29-H_2), 3.88 (3H, s, major rotamer OCH_3), 3.85 (3H, br. s., minor rotamer OCH_3), 2.60 (3H, s, major rotamer C30-CH_3), 2.57 (3H, br. s., minor rotamer C30-CH_3), 1.71 (3H, s, major rotamer C(CH_3)$_2$), 1.67 (3H, br. s., minor rotamer C(CH_3)$_2$), 1.58 - 1.52 (3H, m, minor rotamer C(CH_3)$_2$), 1.46 (9H, br. s., minor rotamer C(CH_3)$_3$), 1.28 (9H, s, major rotamer C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 162.6 (major and minor rotamer *C10*), 161.1 (major and minor rotamer *C9*), 156.2 (major and minor rotamer *C30*), 151.2 (major and minor rotamer *C*O$_2$^{t}Bu), 127.5 (major and minor rotamer *C11*), 65.1 (major and minor rotamer *C*(CH$_3$)$_2$), 81.1, 80.5 (major and minor rotamer *C*(CH$_3$)$_3$), 67.5, 67.4 (major and minor rotamer *C29*-H$_2$), 55.1 (major and minor rotamer *C8*-H), 52.3, 51.9 (major and minor rotamer O*C*H$_3$), 28.3 (major and minor rotamer C(*C*H$_3$)$_3$), 24.9, 24.1 (major and minor rotamer C(*C*H$_3$)$_2$), 11.9 (major and minor rotamer C30-*C*H$_3$);

m/z (ESI+) 363.1 ([M+Na] 100%), 341.1 ([M+H] 60%); HR ESI, *m/z* = 363.1526, ($C_{16}H_{24}N_2O_6Na$ requires M+Na = 363.1527). In some cases this method led to the formation of a significant amount of elimination product **20** (~20 % of isolated product, inseparable from desired oxazole **5**), identifiable by ^1H spectroscopy; δ_H (400 MHz, $CDCl_3$) 6.83 (1H, q, *J* 7.0 Hz, C30-*H*), 1.79 (3H, d, *J* 7.0 Hz, C30-CH_3).

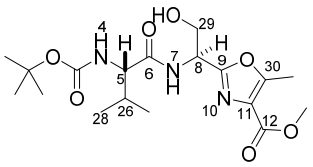
Asymmetric Dihydroxylation of Alkene 13

Both methods of production of oxazole **5** occasionally provided an inseparable mixture of the oxazole **5** and alkene **13**. The alkene was removed using a method modified from literature procedure of a Sharpless *et al*.[13] $K_3[Fe(CN)_6]$ (2.01 g, 6.13 mmol), K_2CO_3 (0.85 g, 6.1 mmol), $(DHQD)_2PHAL$ (0.02 g, 0.02 mmol) and methane sulphonamide (0.19 g, 2.0 mmol) were added to a solution of the mixture of oxazole **5** and alkene **13** (2.10 g; approximately 0.70 g, 2.0 mmol alkene **13**) in ^tBuOH:H_2O (1: 1, 50 mL) at room temperature. After 5 minutes, $K_2OsO_4 \cdot 2H_2O$ (0.008 g, 0.02 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. Sodium sulfite (~0.1 g) was added and the mixture was stirred for a further 30 minutes. The phases were separated and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with pH 2 buffer (10 mL), water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Silica chromatography (50 % EtOAc: pet. ether) gave only the desired oxazole (0.67 g, 1.98 mmol)**.** All characterisation data was consistent to that previously obtained.

Preparation of activated MnO_2

Prepared according to the method set out by Fatiadi.[14] A solution of $KMnO_4$ (26.3 g, 167 mmol) in water (500 mL) was added slowly to a solution of manganese sulfate monohydrate (42.3 g, 250 mmol) in water (720 mL) at 60 ˚C in a 2L beaker. The solution was stirred at 60 °C for 1 hour. After cooling to room temperature, the suspension was filtered. The filtercake was washed with water (~2L) until the pH of the aqueous washes was neutral. The filtercake was dried under vacuum over silica for to give a dense black solid (86.1 g), to give the unactivated MnO_2 with ~68% associated water. This was activated immediately before use according to the method of Goldman.[15]

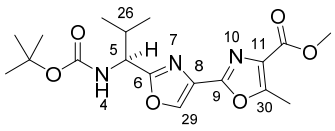
Tripeptide Oxazole 14



Oxazole methyl ester **5** (3.05 g, 8.96 mmol) was dissolved in a solution of methanolic hydrochloric acid (4 M, 21.5 mL) and stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* to give the crude deprotected amine as hydrochloride salt **8**, which was used without further purification assuming quantitative yield.

A solution of Boc-Val-OH (2.83 g, 13.4 mmol) and HOBt (88 %, 0.32g, 2.1 mmol) in EtOH (50 mL) were stirred at room temperature for 15 minutes. To this was added a solution of the crude amine (8.96 mmol) in EtOH (40 mL) and the reaction mixture was cooled to 0-5 °C. *N*-Methylmorpholine (4.70 mL, 43.0 mmol) was added and the reaction was stirred at 0-5 °C for 15 minutes. EDCI (3.08 g, 16.1 mmol) was added, and the reaction mixture allowed to reach room temperature overnight. The reaction mixture was acidified with pH 2 buffer, filtered, and the filtrate was concentrated *in vacuo*. The residue was partitioned between pH 2 buffer (50 mL) and EtOAc (100 mL) and the phases were separated. The organic phase was washed with pH 2 buffer (25 mL), water (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The pure tripeptide, **14**, was obtained by silica chromatography (EtOAc) as a bright white crystalline solid (2.05 g, 5.13 mmol, 57 %; also performed with 1.68 g, 88 %); m.p. 99 – 100 ˚C; $[\alpha]_D^{25}$ -47 (c = 0.52, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3326 (NH), 3306 (OH), 1721 (ester C=O), 1687 (amide C=O), 1519 (NH);^{1}H NMR (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* 8.0 Hz, N7-*H*), 5.43 (1H, d, *J* 8.5 Hz, N4-*H*), 5.22 (1H, dt, *J* 8.0, 4.0 Hz, C8-*H*), 4.23 - 4.16 (1H, m, CH_2OH), 4.02 – 3.96 (2H, m, C5-*H*, CH_2OH), 3.95 – 3.86 (1H, m, CH_2OH), 3.80 (3H, s, OCH_3), 2.51 (3H, s, oxazole CH_3), 2.11 - 2.00 (1H, m, $CHCH_3$), 1.35 (9H, s, $C(CH_3)_3$), 0.90 (3H, d, *J* 7.0 Hz, $CH(CH_3)_2$), 0.86 (3H, d, *J* 6.5 Hz, $CH(CH_3)_2$); δ_C (175 MHz, $CDCl_3$) 172.1 (*C6*), 162.4 (*C12*), 159.8 (*C9*), 156.9 (*C30*), 156.2 ($CO_2{}^tBu$), 127.3 (*C11*), 80.2 ($C(CH_3)_3$), 63.1 (*C29*-H_2), 60.2 (*C5*-H), 52.0 (OCH_3), 49.3 (*C8*-H), 30.8 (*C26*-H), 28.3 ($C(CH_3)_3$), 19.2 (*C*28-H_3), 17.8 (*C*28-H_3), 12.0 (C30-*C*H_3); *m/z* (ESI+) 422.1 ([M+Na] 100%); HR ESI, *m/z* = 400.2087, ($C_{18}H_{30}N_3O_7$ requires M+H = 400.2078).

Bisoxazole 4

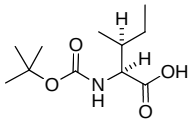


(Diethylamino)sulfur trifluoride (1.22 mL, 9.24 mmol) was added dropwise to a solution of the tripeptide **14** (2.05 g, 5.13 mmol) in dry CH_2Cl_2 (55 mL) at – 78 °C under a nitrogen atmosphere. The recation mixture was stirred at -78 °C for 2 hours, then at room temperature for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (55 mL) and stirred for 15 minutes. The phases were separated and the organic phase was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude oxazoline was used immediately without further purification

A suspension of MnO_2 (prepared by the method of Fatiadi,[14] 17.8 g, 103 mmol) in toluene (100 mL) was heated to reflux with azeotropic water removal using Dean-Stark apparatus until no more water could be removed. A solution of the oxazoline (5.13 mmol) in toluene (10 mL) was added and the reaction heated to reflux with azeotropic water removal for 6 hours. After cooling to room temperature, an acidic solution of sodium sulphite (1.5 g Na_2SO_3/1 g MnO_2 in 5 volumes of water, acidified to pH 5 with concentrated H_2SO_4) was added to the reaction mixture and the pH of the aqueous phase was adjusted to 5 and stirred until dissolution of the suspension. The phases were separated and the aqueous phase was acidified to pH 2 and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), and saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Bisoxazole **4** was obtained by silica chromatography (50 % EtOAc: pet. ether) as a bright white solid (0.53 g, 1.4 mmol, 27% over 2 steps); m.p. 128 - 130 °C; $[\alpha]_D^{24}$ -47 (c = 0.53, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3349 (NH), 2964 (aromatic C-H), 1712 (ester C=O), 1683 (amide C=O), 1519 (NH); δ_H (400 MHz, $CDCl_3$) 8.25 (1H, s, C29-*H*), 5.30 (1H, d, *J* 9.0 Hz, N4-*H*), 4.82 (1H, dd, *J* 9.0, 6.5 Hz, C5-*H*), 3.93 (3H, s, OC*H*$_3$), 2.70 (3H, s, C30-C*H*$_3$), 2.22 (1H, m, C26-*H*), 1.46 - 1.39 (9H, m, C(C*H*$_3$)$_3$), 0.95 (3H, d, *J* 7.5 Hz, C26(C*H*$_3$)$_2$), 0.93 (3H, d, *J* 7.5 Hz, C26(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 165.4 (*C6*), 164.5 (*C*O_2Me), 156.5 (*C30*), 155.3 (*C*ONH), 153.0 (*C9*), 138.8 (*C29*-H), 129.8 (*C8*), 128.3 (*C11*), 80.0 (*C*$(CH_3)_3$), 54.3 (*C5*), 52.0 (O*C*H_3), 33.0 (*C26*), 28.3 (C(*C*H_3)$_3$), 18.7, 18.0 (C26(*C*H_3)$_2$), 12.0 (C30-*C*H_3); *m/z* (ESI+) 402.0 ([M+Na] 100%); HR ESI, *m/z* =402.1640, ($C_{18}H_{25}N_3O_6Na$ requires M+Na =402.1636).

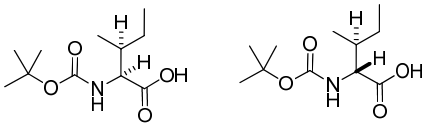
Preparation of Model Isoleucine Oxazoles

***N-tert*Butoxycarbonyl-L-isoleucine**



Prepared as for Boc-Val-OH, **7**, but using L-isoleucine (10.0 g, 76.2 mmol). The Boc-protected product was obtained as a clear, colourless oil (14.5 g, 62.5 mmol, 82 %); $[\alpha]_D^{25}$ + 3.80 (c =1.01, MeOH); (lit.[16] $[\alpha]_D^{20}$+3.9 (c = 2.00, MeOH); υ_{max}/cm^{-1} (neat) 3321 (NH), 2967 (OH), 1708 (acid C=O), 1503 (NH); δ_H (400 MHz, $CDCl_3$) 10.36 (1H, br. s., major and minor rotamer CO_2H), 6.16 (1H, br. s, minor rotamer CHN*H*), 5.13 (1H, d, *J* 8.5 Hz, major rotamer CHN*H*), 4.25 (1H, dd, *J* 8.5, 4.5 Hz, major rotamer C*H*NH), 4.12 – 4.06 (1H, m, major rotamer C*H*NH), 1.99 - 1.81 (1H, m, C*H*CH_3), 1.53 - 1.42 (10H, m, C(CH_3)$_3$, CH_2CH_3), 1.28 – 1.08 (1H, m, CH_2CH_3), 0.96 (3H, d, *J* 6.5 Hz, CHCH_3), 0.92 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 177.2 (*C*O_2H), 155.8 (*C*O_2^{t}Bu), 80.0 (*C*(CH_3)$_3$), 58.1 (*C*HNH), 37.7 (*C*HCH_3), 28.3 (C(*C*H_3)$_3$), 24.9 (*C*H_2CH_3), 15.5 (CH*C*H_3), 11.6 (CH_2*C*H_3); *m/z* (ESI+) 230.1 ([M-H] 100%); HR ESI, *m/z* = 254.1350, ($C_{11}H_{21}NO_4Na$ requires M+Na =254.1363). The data are consistent with that previously reported.[16]

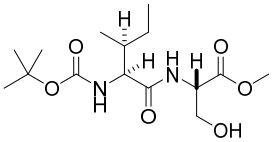
***N-tert*Butoxycarbonyl-L-isoleucine and *N-tert*Butoxycarbonyl-D-*allo*-isoleucine**



Prepared as for Boc-Val-OH, **10**, but using a mixture of l-isoleucine and d-*allo*-isoleucine (0.50 g, 3.8 mmol). The Boc-protected product was obtained as a clear, colourless oil (0.77 g, 3.3 mmol, 88 %, 73: 27 mix of (2*S*, 3*S*) and (2*R*, 3*S*), calculated by ^{1}H NMR); υ_{max}/cm^{-1} (neat) 3314 (NH), 2966 (OH), 1711 (acid C=O), 1506 (NH); δ_H (400 MHz, $CDCl_3$) 8.71 ((2*S*, 3*S*), 1H, br. s., major and minor rotamer CO_2H; (2*R*, 3*S*), 1H, br. s., major and minor rotamer CO_2H), 6.17 ((2*S*, 3*S*), 1H, d, *J* 7.0 Hz, minor rotamer CHN*H*), 6.08 ((2*R*, 3*S*), 1H, d, *J* 7.0 Hz, minor rotamer CHN*H*), 5.06 ((2*S*, 3*S*), 1H, d, *J* 8.5 Hz, major rotamer CHN*H*), 5.00 ((2*R*, 3*S*), 1H, d, *J* 9.0 Hz, major rotamer CHN*H*), 4.41 ((2*R*, 3*S*), 1H, dd, *J* 9.5, 4.0 Hz, major rotamer C*H*NH), 4.30 ((2*S*, 3*S*), 1H, dd, *J* 9.0, 4.5 Hz, major rotamer C*H*NH), 4.24 - 4.17 ((2*R*, 3*S*), 1H, m, minor rotamer C*H*NH), 4.13 - 4.05 ((2*S*, 3*S*), 1H, m, minor rotamer C*H*NH), 2.03 - 1.83 ((2*S*, 3*S*), 1H, m, major and minor rotamer C*H*CH_3; (2*R*, 3*S*), 1H, m, major and minor rotamer C*H*CH_3), 1.45 ((2*S*, 3*S*), 10H, m, major and minor rotamer CH_2CH_3, C(CH_3)$_3$; (2*R*, 3*S*), 10H, m, major and minor rotamer CH_2CH_3, C(CH_3)$_3$), 1.31 - 1.14 ((2*S*, 3*S*), 1H, m, major and minor rotamer CH_2CH_3; (2*R*, 3*S*), 1H, m, major and minor

rotamer C*H*$_2$CH$_3$), 0.99 - 0.87 ((2*S*, 3*S*), 6H, m, major and minor rotamer CH$_2$C*H*$_3$, CHC*H*$_3$; (2*R*, 3*S*), 1H, m, major and minor rotamer CH$_2$C*H*$_3$, CHC*H*$_3$); δ_C (100 MHz, CDCl$_3$) 177.8, 177.3 ((2*S*, 3*S*), *C*O$_2$H; (2*R*, 3*S*), *C*O$_2$H), 155.8 ((2*S*, 3*S*), *C*O$_2$ ^{t}Bu; (2*R*, 3*S*), *C*O$_2$^{t}Bu), 80.1 ((2*S*, 3*S*), *C*(CH$_3$)$_3$; (2*R*, 3*S*), *C*(CH$_3$)$_3$), 59.1, 57.8 ((2*S*, 3*S*), *C*HNH; (2*R*, 3*S*), *C*HNH), 37.7, 37.4 ((2*S*, 3*S*), *C*HCH$_3$; (2*R*, 3*S*), *C*HCH$_3$), 28.3 ((2*S*, 3*S*), C(*C*H$_3$)$_3$; (2*R*, 3*S*), C(*C*H$_3$)$_3$), 26.3, 24.9 ((2*S*, 3*S*), *C*H$_2$CH$_3$; (2*R*, 3*S*), *C*H$_2$CH$_3$), 15.5 ((2*S*, 3*S*), CH*C*H$_3$; (2*R*, 3*S*), CH*C*H$_3$), 11.7 ((2*S*, 3*S*), CH$_2$*C*H$_3$; (2*R*, 3*S*), CH$_2$*C*H$_3$); *m/z* (ESI+) 230.1 ([M+H] 100%); HR ESI, *m/z* = 230.1385, (C$_{11}$H$_{20}$NO$_4$ requires M+H = 230.1398).

***N-tert*Butoxycarbonyl-L-isoleucyl-L-serine methyl ester**

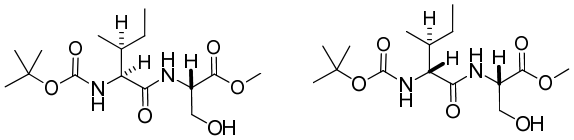


Acetyl chloride (5.20 mL, 73.2 mmol) was added dropwise with stirring to MeOH (30 mL) at 0 °C. The mixture was allowed to reach room temperature and L-serine (1.30 g, 12.2 mmol) was added and the mixture was heated to reflux for 18 hours. The reaction mixture was concentrated *in vacuo* to give the crude methyl ester as the hydrochloride salt, which was used without further purification assuming quantitative yield.

A solution of Boc-L-isoleucine (0.93 g, 4.0 mmol) and HOBt (88 %, 90mg, 0.60 mmol) in EtOH (13 mL) was stirred at room temperature for 15 minutes, then cooled to 0-5°C. To this was added a solution of the crude serine methyl ester (4.42 mmol) and *N*-methyl morpholine (1.40 mL, 12.9 mmol) in EtOH (9 mL) and the resulting colourless solution stirred at 0-5°C for 15 minutes. EDCI (0.92 g, 4.8 mmol) was added and the reaction mixture was allowed to reach room temperature overnight to give a pale yellow solution. This was acidified using pH 2 buffer and *N*-methyl morpholine hydrosulfate was removed by filtration. The filtrate was concentrated *in vacuo*, and extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with pH 2 buffer (10 mL), water (10 mL), saturated aqueous NaHCO$_3$ solution (10 mL) and saturated aqueous NaCl solution (10 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo* to give dipeptide as a white powdery solid (0.79 g, 2.4 mmol, 60 %); m.p. 83 – 85 $^{\circ}$C; $[\alpha]_D^{25}$ -19 (c = 0.26, MeOH); υ_{max}/cm^{-1} (neat) 3323 (NH), 1748 (ester C=O), 1688 (amide C=O), 1520 (NH); δ_H (400 MHz, CDCl$_3$) 7.20 (1H, d, *J* 7.5 Hz, Ser N*H*CH), 5.38 (1H, d, *J* 8.0 Hz, Ile N*H*CH), 4.67 (1H, ddd, *J* 8.0, 4.0, 3.0 Hz, Ser NHC*H*), 4.01 - 3.85 (3H, m, Ile NHC*H*, C*H*$_2$OH), 3.76 (3H, s, OC*H*$_3$), 1.88 - 1.74 (1H, m, C*H*CH$_3$), 1.61 - 1.50 (1H, m, C*H*$_2$CH$_3$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.21 - 1.08 (1H, m, C*H*$_2$CH$_3$), 0.95 (3H, d, *J* 6.5 Hz, C*H*CH$_3$), 0.89 (3H, t, *J* 7.5 Hz, CH$_2$C*H*$_3$); δ_C (100 MHz, CDCl$_3$) 172.3 (*C*O$_2$CH$_3$), 170.8 (*C*ONH), 156.3 (*C*O$_2$^{t}Bu), 80.2 (*C*(CH$_3$)$_3$), 62.7 (*C*H$_2$OH), 59.4 (Ile *C*HNH), 57.9 (Ser

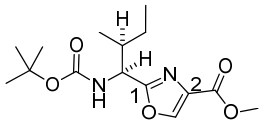
*C*HNH), 52.6 (O*C*H$_3$), 37.2 (*C*HCH$_3$), 28.3 (C(*C*H$_3$)$_3$), 24.8 (*C*H$_2$CH$_3$), 15.4 (CH*C*H$_3$), 11.3 (CH$_2$*C*H$_3$); *m/z* (ESI+) 355.1 ([M+Na] 100%); HR ESI, *m/z* = 355.1823, ($C_{15}H_{28}N_2O_6Na$ requires M+Na = 355.18400). The ^{1}H and ^{13}C data are consistent to that previously reported.[17]

_N-tert_Butoxycarbonyl-L-isoleucyl- and _N-tert_Butoxycarbonyl-D-_allo_-isoleucyl-L-serine methyl ester



Prepared as for the single diastereoisomer using L-serine methyl ester hydrochloride (3.44 mmol) and a mixture of Boc-L-isoleucine and Boc-D-*allo*-isoleucine (0.72 g, 3.1 mmol), *N*-methyl morpholine (1.0 mL, 10 mmol), HOBt (88 %, 0.07 g, 0.5 mmol), EDCI (0.72 g, 3.8 mmol) and EtOH (17 mL) to give the dipeptide as a bright white solid (0.79 g, 2.4 mmol, 76 %; 78: 22 mix of (2*S*, 3*S*) and (2*R*, 3*S*) diastereomers by ^{1}H NMR); υ_{max}/cm^{-1} (neat) 3322 (NH), 1748 (ester C=O), 1689 (amide C=O), 1522 (NH); δ_H (400 MHz, $CDCl_3$) 7.26 (1H, d, *J* 8.0 Hz, (2*S*, 3*S*), Ser CHN*H*; 1H, d, *J* 8.0 Hz, (2*R*, 3*S*), Ser CHN*H*), 5.41 (1H, d, *J* 9.0 Hz, (2*S*, 3*S*), Ile CHN*H*), 5.20 (1H, d, *J* 7.5 Hz, (2*R*, 3*S*), Ile CHN*H*), 4.66 (1H, dt, *J* 7.5, 3.5 Hz, (2*S*, 3*S*), Ser C*H*NH; 1H, dt, *J* 7.5, 3.5 Hz, (2*R*, 3*S*), Ser C*H*NH), 4.19 - 4.11 (1H, m, (2*R*, 3*S*), Ile C*H*NH), 3.98 (1H, dd, *J* 8.5, 7.5 Hz, (2*S*, 3*S*), Ile C*H*NH), 3.98 – 3.83 (2H, m, (2*S*, 3*S*), C*H*$_2$OH; 2H, m, (2*R*, 3*S* C*H*$_2$OH), 3.75 (3H, m, (2*S*, 3*S*), OC*H*$_3$; 3H, m, (2*R*, 3*S*), OC*H*$_3$), 2.06 - 1.94 (1H, m, (2*R*, 3*S*), C*H*CH$_3$), 1.86 – 1.74 (1H, m, (2*S*, 3*S*), C*H*CH$_3$), 1.65 - 1.48 (1H, m, (2*S*, 3*S*), C*H*$_2$CH$_3$; 1H, m, (2*R*, 3*S*), C*H*$_2$CH$_3$), 1.42 (9H, s, (2*R*, 3*S*), C(C*H*$_3$)$_3$), 1.40 (9H, s, (2*S*, 3*S*), C(C*H*$_3$)$_3$), 1.29 – 1.07 (1H, m, (2*S*, 3*S*), C*H*$_2$CH$_3$; 1H, m, (2*S*, 3*S*), C*H*$_2$CH$_3$), 0.97 - 0.85 (1H, m, (2*S*, 3*S*), CHC*H*$_3$,CH$_2$C*H*$_3$; 1H, m, (2*S*, 3*S*), CHC*H*$_3$, CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 172.3 ((2*S*, 3*S*), *C*O$_2$H; (2*R*, 3*S*), *C*O$_2$H), 171.0, 170.8 ((2*S*, 3*S*), *C*ONH; (2*R*, 3*S*), *C*ONH), 156.3 ((2*S*, 3*S*), *C*O$_2$^{t}Bu; (2*R*, 3*S*), *C*O$_2$^{t}Bu), 80.4, 80.2 ((2*S*, 3*S*), *C*(CH$_3$)$_3$; (2*R*, 3*S*), *C*(CH$_3$)$_3$), 62.6 ((2*S*, 3*S*), *C*H$_2$OH; (2*R*, 3*S*), *C*H$_2$OH), 59.4, 58.4 ((2*S*, 3*S*), Ile NH*C*H; (2*R*, 3*S*), Ile NH*C*H), 54.7 ((2*S*, 3*S*), Ser NH*C*H; (2*R*, 3*S*), Ser NH*C*H), 52.7, 52.6 ((2*S*, 3*S*), OCH$_3$; (2*R*, 3*S*), O*C*H$_3$), 37.3, 37.0 ((2*S*, 3*S*), *C*HCH$_3$; (2*R*, 3*S*), *C*HCH$_3$), 28.3 ((2*S*, 3*S*), C(*C*H$_3$)$_3$; (2*R*, 3*S*), C(*C*H$_3$)$_3$), 24.8 ((2*S*, 3*S*), *C*H$_2$CH$_3$; (2*R*, 3*S*), *C*H$_2$CH$_3$), 15.4, 14.2 ((2*S*, 3*S*), CH*C*H$_3$; (2*R*, 3*S*), CH*C*H$_3$), 11.7, 11.2 ((2*S*, 3*S*), CH$_2$*C*H$_3$; (2*R*, 3*S*), CH$_2$*C*H$_3$); *m/z* (ESI+) 355.1 ([M+Na] 100%); HR ESI, *m/z* = 355.1839, ($C_{15}H_{28}N_2O_6Na$ requires M+Na = 355.1840).

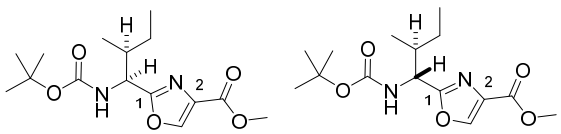
(2*S*, 3*S*) Isoleucine Oxazole



(Diethylamino)sulfur trifluoride (0.17 mL, 1.3 mmol) was added to solution of the *N-tert*Butoxycarbonyl-L-isoleucyl-L-serine methyl ester (0.31 g, 0.92 mmol) in dry CH_2Cl_2 (8.5 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 1.5 hours, and at room temperature for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and stirred for 15 minutes. The phases were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude oxazoline as a yellow oil that was used immediately assuming quantitative yield.

MnO_2 (prepared by the method of Carpino,[18] 5 x mass oxazoline, 1.25 g) was added to a solution of the oxazoline (0.25 g, 0.92 mmol) in dry toluene (12 mL) under a nitrogen atmosphere. The reaction was heated to reflux with azeotropic removal of water over 3Å molecular sieves for 20 hours. After cooling to room temperature, the mixture was filtered through celite. The celite was washed with EtOAc (5 x 5 mL) and the filtrate was concentrated *in vacuo*. (2*S*, 3*S*) Isoleucine oxazole was obtained by silica chromatography (50% EtOAc: pet. ether) as a white solid (7 mg, 0.02 mmol, 2 %); $[\alpha]_D^{25}$ -19 (c = 0.64, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3326 (NH), 2972 (aromatic C-H), 1727 (ester C=O), 1698 (amide C=O), 1529 (NH); δ_H (400 MHz, $CDCl_3$) 8.18 (1H, s, oxazole C-*H*), 5.33 (1H, d, *J* 9.0 Hz, N*H*CH), 4.86 (1H, dd, *J* 9.0, 6.0 Hz, NHC*H*), 3.91 (3H, s, OCH_3), 2.01 - 1.88 (1H, m, C*H*CH_3), 1.51 – 1.39 (10H, m, CH_2CH_3, C(CH_3)$_3$), 1.24 – 1.10 (1H, m, CH_2CH_3), 0.90 (3H, t, *J* 7.0 Hz, CH_2CH_3), 0.86 (3H, d, *J* 7.0 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 164.1 (*C1*), 160.6 (CO_2Me), 154.2 ($CO_2{}^t$Bu), 142.8 (oxazole C-*H*), 132.1 (*C2*), 79.0 (*C*$(CH_3)_3$), 52.3 (*C*HNH), 51.2 (O*C*H_3), 38.5 (*C*HCH_3), 28.7 (C(*C*H_3)$_3$), 24.0 (*C*H_2CH_3), 14.3 (CH*C*H_3),10.4 (CH_2*C*H_3); *m/z* (ESI+) 335.1 ([M+Na] 100%); HR ESI, *m/z* = 335.1572, ($C_{15}H_{24}N_2O_5Na$ requires M+Na = 335.1577). This compound is known, but no characterisation data has been reported.[19]

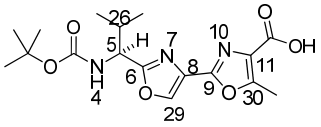
(2*S*, 3*S*) and (2*R*, 3*S*) Oxazole



Prepared as for the (2*S*, 3*S*) Oxazole using a diastereomeric mix of *N-tert*butoxycarbonyl-L-isoleucyl- and *N-tert*butoxycarbonyl-L-*allo*-isoleucyl-L-serine methyl ester (0.39 g, 1.2 mmol), (diethylamino)sulfur trifluoride (0.22 mL, 1.6 mmol) and CH_2Cl_2 (11 mL) to give the

oxazoline. The oxazole was prepared as for the single diastereomer with MnO_2 (2.2 g) and dry toluene (10 mL). Additional MnO_2 (0.85 g) and dry toluene (5 mL) were added after 2 hours at reflux, and the reaction mixture was heated to reflux for a further 7 hours. The cooled reaction mixture was filtered over celite, and the celite washed with EtOAc (5 x 10 mL). The filtrate was concentrated *in vacuo* and the oxazole was obtained by silica chromatography (50% EtOAc: pet. ether) as a white solid (3 mg, 0.09 mmol, 1 %; 72: 28 mix of (2*S*, 3*S*) and (2*R*, 3*S*) diastereomers by ^{1}H NMR): δ_H (400 MHz, $CDCl_3$) 8.18 (1H, s, (2*S*, 3*S* CC-*H*; 1H, s, (2*R*, 3*S*), CC-*H*), 5.32 (1H, d, *J* 9.0 Hz, (2*S*, 3*S*), N*H*CH), 5.27 (1H, d, *J* 9.5 Hz, (2*S*, 3*S*), N*H*CH), 4.95 (1H, dd, *J* 9.5 Hz, 5.0 Hz, (2*R*, 3*S*), NHC*H*), 4.86 (1H, dd, *J* 9.0 Hz, 6.5 Hz, (2*S*, 3*S*), NHC*H*), 3.91 (3H, s, (2*S*, 3*S*), OCH_3; 3H, s, (2*R*, 3*S*), OCH_3), 2.02 – 1.88 (1H, m, (2*S*, 3*S*), C*H*CH$_3$; 1H, m, (2*R*, 3*S*), C*H*CH$_3$), 1.50 – 1.39 (10H, m, (2*S*, 3*S*), CH_2CH$_3$, C(CH_3)$_3$; 10H, m, (2*R*, 3*S*), CH_2CH$_3$, C(CH_3)$_3$), 1.23 – 1.10 (1H, d, *J* 7.0 Hz, (2*S*, 3*S*), CH_2CH$_3$; 1H, d, *J* 7.0 Hz, (2*R*, 3*S*), CH_2CH$_3$), 0.96 - 0.83 (6H, m, (2*S*, 3*S*), CHCH_3, CH$_2$CH_3; 6H, m, (2*R*, 3*S*), CHCH_3, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 165.2 ((2*S*, 3*S*), *C1*; (2*R*, 3*S*), *C1*), 161.6 ((2*S*, 3*S*), *C*O$_2$Me; (2*R*, 3*S*), *C*O$_2$Me), 155.3 ((2*S*, 3*S*), *C*O$_2$^{t}Bu; (2*R*, 3*S*), *C*O$_2$^{t}Bu), 143.8 ((2*S*, 3*S*), C*C*-H; (2*R*, 3*S*), C*C*-H), 133.2 ((2*S*, 3*S*), *C2*; (2*R*, 3*S*), *C2*), 80.1 ((2*S*, 3*S*), *C*(CH$_3$)$_3$; (2*R*, 3*S*), *C*(CH$_3$)$_3$), 53.4, 52.7 ((2*S*, 3*S*), *C*HNH; (2*R*, 3*S*), *C*HNH), 51.6 ((2*S*, 3*S*), O*C*H$_3$; (2*R*, 3*S*), O*C*H$_3$), 39.5, 39.3 ((2*S*, 3*S*), *C*HCH$_3$; (2*R*, 3*S*), *C*HCH$_3$), 28.3 ((2*S*, 3*S*), C(*C*H$_3$)$_3$; (2*R*, 3*S*), C(*C*H$_3$)$_3$), 25.9, 25.1 ((2*S*, 3*S*), *C*H$_2$CH$_3$); (2*R*, 3*S*), *C*H$_2$CH$_3$), 15.2, 14.5 (2*S*, 3*S*), CH*C*H$_3$; (2*R*, 3*S*), CH*C*H$_3$), 11.6, 11.4 ((2*S*, 3*S*), CH$_2$*C*H$_3$; (2*R*, 3*S*), CH$_2$*C*H$_3$); *m/z* (ESI+) 335.1 ([M+Na] 100%); HR ESI, *m/z* = 335.1582, ($C_{15}H_{24}N_2O_5Na$ requires M+Na = 335.1577).

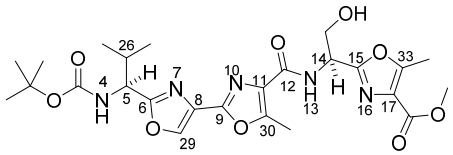
Bisoxazole Acid



Lithium hydroxide (0.13 g, 5.3 mmol) and water (3 mL) were added to a solution of the bioxazole methyl ester **4** (0.50 g, 1.3 mmol) in THF (3 mL) at room temperature. The reaction was stirred for 4 hours and then acidified using pH 2 buffer. The organic solvents were removed *in vacuo* and the residue was partitioned between EtOAc (15 mL) and pH 2 buffer. The separated aqueous phase was further extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a mix of rotamers of acid as a white crystalline solid (0.46 g, 1.3 mmol, 95 %); m.p. 93 - 94 °C; $[\alpha]_D^{26}$ -45.0 (c = 1.05, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3295 (NH), 2117 (OH), 1696 (acid C=O), 1509 (NH); δ_H (400 MHz, $CDCl_3$) 8.29 (1H, s, C29-*H*), 7.68 (1H, br.s., major and minor rotamer, CO$_2$*H*), 6.38 (1H, d, *J* 6.0 Hz, minor rotamer N4-*H*), 5.46 (1H, d, *J* 9.5 Hz, major

rotamer N4-*H*), 4.83 (1H, dd, *J* 9.5, 6.5 Hz, major rotamer C5-*H*), 4.71 - 4.59 (1H, m, minor rotamer C5-*H*), 2.72 (3H, s, major and minor rotamer, C30-CH_3), 2.21 (1H, oct., *J* 6.5 Hz, major and minor rotamer, C26-*H*), 1.48 - 1.37 (9H, m, major and minor rotamer, C(CH_3)$_3$), 0.96 (3H, d, *J* 7.0 Hz, major and minor rotamer, C26(CH_3)$_2$), 0.92 (3H, d, *J* 7.0 Hz, major and minor rotamer, C26(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 165.6, 165.4 (*C6*, *C*O_2H), 157.3 (*C30*), 155.4 (*C*ONH), 153.0 (*C9*), 139.1 (*C29*-H), 129.5 (*C8*), 128.1 (*C9*), 80.1 (*C*(CH_3)$_3$), 54.3 (*C5*), 32.8 (*C26*), 28.2 (*C*(CH_3)$_3$), 18.7, 18.0. (C26(*C*H_3)$_2$), 12.2 (C30-*C*H_3): *m/z* (ESI+) 388.1 ([M+Na] 100%); HR ESI, *m/z* =388.1474, ($C_{17}H_{23}N_3O_6Na$ requires M+Na =388.1479).

Pentapeptide 15

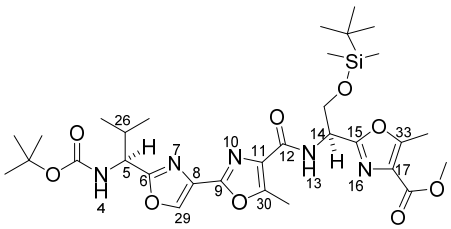


Oxazole methyl ester **5** (0.67 g, 2.0 mmol) was added to methanolic hydrochloric acid solution (4 M, 3 mL) and the reaction mixture was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* to give the crude deprotected amine as hydrochloride salt **8**, which was used without further purification.

HOBt (88 %, 0.03 g, 0.2 mmol) was added to a solution of the bisoxazole (0.46 g, 1.3 mmol) in EtOH (4 mL) and the mixture stirred at room temperature for 15 minutes. A solution of the crude amine (2.0 mmol) in EtOH (3 mL) was added and the mixture cooled to 0 °C. *N*-Methylmorpholine (0.58 mL, 5.3 mmol) was added and the solution was stirred at 0-5 °C for 15 minutes. EDCI (0.29 g, 1.5 mmol) was added and the reaction was stirred to room temperature overnight. The reaction was acidified with pH 2 buffer and concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and pH 2 buffer (10 mL) and the phases were separated. The aqueous phase was further extracted with EtOAc (3 x 2 mL) and the combined organic phases were washed with saturated aqueous NaCl solution (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Pentapeptide **15** was obtained by silica chromatography (EtOAc) as yellow solid (0.50 g, 0.77 mmol, 64 %); m.p. 104 - 105 °C; $[\alpha]_D^{25}$ -29 (c = 0.54, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3320 (NH), 2972 (OH), 1726 (acid C=O), 1683 (amide C=O), 1531 (NH); δ_H (400 MHz, $CDCl_3$) 8.15 (1H, s, C29-*H*), 7.82 (1H, d, *J* 8.5 Hz, N13-*H*), 5.46 (1H, dt, *J* 9.0, 4.5 Hz, C14-*H*), 5.41 (1H, d, *J* 9.0 Hz, N4-*H*), 4.86 – 4.79 (1H, m, C5-*H*), 4.23 (1H, dd, *J* 11.5, 4.5 Hz, CH_2OH), 4.05 (1H, dd, *J* 11.5, 4.5 Hz, CH_2OH), 3.90 (3H, s, OCH_3), 3.32 - 3.36 (1H, m, CH_2O*H*), 2.71 (3H, s, C30-CH_3), 2.61 (3H, s, C33-CH_3), 2.26 - 2.17 (1H, m, C26-*H*), 1.43 (9H, s, C(CH_3)$_3$), 0.97 (2H, d, *J* 7.0 Hz, C26(CH_3)$_2$), 0.94 (3H, d, *J* 6.5 Hz, C26(CH_3)$_2$); δ_C (150 MHz, $CDCl_3$) 165.8 (*C6*), 162.4 (*C*O_2Me), 161.5 (*C12*), 159.8 (*C15*), 157.0 (*C33*), 155.4 (*C*O_2^{t}Bu), 154.0 (*C30*), 152.2 (*C9*), 138.6 (*C29*-H),

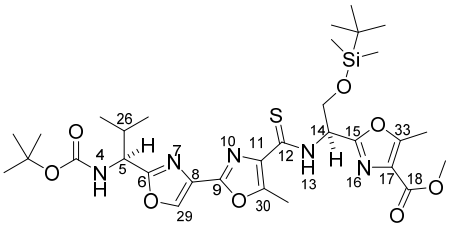
129.8 (*C8*), 159.6 (*C11*), 127.4 (*C17*), 80.0 (*C*(CH_3)$_3$), 63.3 (*C*H_2OH), 54.4 (*C5*), 52.0 (O*C*H_3), 48.5 (*C14*), 33.0 (*C26*), 28.3 (C(*C*H_3)$_3$), 18.8, 18.1 (C26(*C*H_3)$_2$), 12.1 (C33-*C*H_3), 11.8 (C30-*C*H_3); *m/z* (ESI+) 570.2 ([M+Na] 100%); HR ESI, *m/z* =570.2172, ($C_{25}H_{33}N_5O_9Na$ requires M+Na =570.1270).

Pentapeptide Silyl Ether 16



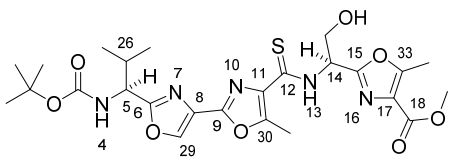
Method modified from literature procedure of McKeever *et al*.[20] Imidazole (0.19 g, 2.8 mmol) was added in one portion to a solution of alcohol **15** (0.75 g, 1.4 mmol) in dry DMF (6.5 mL) under an atmosphere of nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for 5 minutes and ^{t}BuMe$_2$SiCl (0.32 g, 2.10 mmol) was added in one portion. The ice bath was removed and the reaction stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (40 mL), and the phases were separated. The aqueous phase was further extracted with EtOAc (5 x 10mL). The combined organic extracts were washed with water (5 x 10 mL) and saturated aqueous NaCl solution (10 mL), dried over $NaSO_4$ and concentrated *in vacuo*. Protected alcohol **16** was obtained by silica chromatography (1:1 EtOAc: pet. ether) as a bright white crystalline solid (0.57 g, 0.86 mmol, 62 %); m.p. 57 - 58 °C; $[\alpha]_D^{25}$ -1.1 (c = 0.37, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3319 (NH), 1716 (ester C=O), 1672 (amide C=O), 1506 (NH), 836 (Si-C); δ_H (400 MHz, $CDCl_3$) 8.16 (1H, s, *C29*-H), 7.74 (1H, d, *J* 8.5 Hz, N13-*H*), 5.42 (1H, dt, *J* 8.5, 5.0 Hz, C14-*H*), 5.29 (1H, d, *J* 9.0 Hz, N4-*H*), 4.85 (1H, dd, *J* 8.5, 6.0 Hz, C5-*H*), 4.12 (1H, dd, *J* 10.0, 4.5 Hz, C*H*$_2$OH), 4.00 (1H, dd, *J* 10.0, 5.5 Hz, C*H*$_2$OH), 3.90 (3H, s, OC*H*$_3$), 2.71 (3H, s, C30-C*H*$_3$), 2.61 (3H, s, C33-C*H*$_3$), 2.28 - 2.20 (1H, m, C26-*H*), 1.45 (9H, s, OC(C*H*$_3$)$_3$), 0.98 - 0.94 (6H, m, C26(C*H*$_3$)$_2$), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.02 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.6 (*C6*), 162.7 (*C*O_2Me), 161.3 (*C12*), 160.2 (*C15*), 156.6 (*C33*), 155.3 (*CO*^{t}Bu), 153.8 (*C30*), 152.0 (*C9*), 138.5 (*C29*-H), 130.1 (*C8*), 129.7 (*C11*), 127.6 (*C17*), 80.1 (*C*(CH_3)$_3$), 64.3 (C14-*C*H_2), 54.3 (C*5*), 51.9 (CO_2*C*H_3), 48.9 (C*13*), 33.0 (*C26*), 28.3 (C(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.7, 18.0 (C26(*C*H_3)$_2$), 17.9 (Si*C*(CH_3)$_3$), 12.0, 11.8 (C30-*C*H_3, C33-*C*H_3), -5.4 (Si(*C*H_3)$_2$); *m/z* (ESI+) 684.3 ([M+Na] 100%); HR ESI, *m/z* = 684.3023, ($C_{31}H_{47}N_5O_9SiNa$ requires M+Na = 684.3035).

Thioamide Silyl Ether 17



Method modified from literature procedure of McKeever *et al.*[20] Silyl ether **16** (0.50 g, 0.76 mmol) was dissolved in dry THF (10 mL) and dry toluene (6.5 mL) under nitrogen and Lawesson's reagent (0.34 g, 0.83 mmol) was added. The reaction was heated to reflux under a nitrogen atmosphere for 44 hours, during which Lawesson's reagent (1.08 g, 2.67 mmol) and dry THF (15 mL) was added in 3 equal portions after 18, 24 and 40 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between EtOAc (20 mL) and aqueous $NaHCO_3$ solution (1: 1 saturated $NaHCO_3$: water, 20 mL). The separated aqueous phase was further extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The protected thioamide **17** was obtained by silica chromatography (5 % acetone: toluene) as a bright yellow oil (0.39 g, 0.58 mmol, 76 %); $[\alpha]_D^{22}$ +13 (c = 1.2, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3320 (N-H), 1685 (ester C=O), 1504 (N-H), 1252 (C=S), 833 (Si-C); δ_H (400 MHz, $CDCl_3$) 9.52 (1H, d, *J* 8.5 Hz, N13-*H*), 8.15 (1H, s, C29-*H*), 6.01 (1H, dt, *J* 8.5, 4.5 Hz, C14-*H*), 5.30 (1H, d, *J* 9.0 Hz, N4-*H*), 4.83 (1H, dd, *J* 9.0, 6.5 Hz, C5-*H*), 4.22 (1H, dd, *J* 10.5, 4.0 Hz, C14-CH_2), 4.07 (1H, dd, *J* 10.5, 5.5 Hz, C14-CH_2), 3.88 (3H, s, OCH_3), 2.88 (3H, s, C30-CH_3), 2.59 (3H, s, C33-CH_3), 2.28 - 21 (1H, m, C26-*H*), 1.43 (9H, s, C(CH_3)$_3$), 0.96 (2H, d, *J* 7.0 Hz, C26(CH_3)$_2$), 0.94 (3H, d, *J* 6.5 Hz, C26(CH_3)$_2$), 0.84 - 0.87 (9H, m, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), -0.01 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 186.4 (*C12*), 165.6 (*C6*), 162.6 (*C*O_2Me), 159.5 (*C15*), 156.7 (*C33*), 155.4 (*C*O^{t}Bu, *C30*), 150.6 (*C9*), 138.7 (*C29*-H), 134.2 (*C11*), 129.9 (*C8*), 127.6 (*C17*), 80.1 (*C*(CH_3)$_3$), 63.6 (C14-*C*H_2), 54.3 (*C5*), 53.4 (*C14*), 51.9 (CO_2*C*H_3), 32.9 (*C26*), 28.3 (OC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.7, 18.1 (C26(*C*H_3)$_2$), 18.0 (Si*C*(CH_3)$_3$), 13.8 (C30-*C*H_3), 12.0 (C33-*C*H_3), -5.6 (Si(*C*H_3)$_2$); *m/z* (ESI+) 700.3 ([M+Na] 100%); HR ESI, *m/z* =700.2790, ($C_{31}H_{47}N_5O_8SSiNa$ requires M+Na = 700.2807).

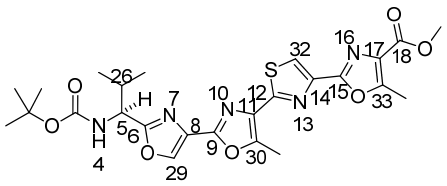
Thioamide 18



Bu_4NF (1M solution in THF, 1.0 mL, 1.0 mmol) was added to the thioamide silyl ether **17** (0.34 g, 0.50 mmol) under a nitrogen atmosphere at 0 °C. The mixture was stirred at 0 °C for 1 hour to give a brown solution. The reaction mixture was concentrated *in vacuo* and the

residue was partitioned between EtOAc (5 mL) and water (2 mL). The phases were separated, and the organic phase was washed with water (2 x 2 mL), saturated aqueous NaCl solution (2 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. Thioamide **18** was obtained by silica chromatography (50 % EtOAc: petrol) as a yellow glassy solid (0.24 g, 0.45 mmol, 90 %); m.p. 127 - 129 °C; $[\alpha]_D^{27}$ -18 (c = 0.36, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3340 (NH), 2972 (OH), 1708 (ester C=O), 1519 (NH), 1249 (C=S); δ_H (400 MHz, $CDCl_3$) 9.56 (1H, d, *J* 8.0 Hz, N13-*H*), 8.17 (1H, s, C29-*H*), 6.15 (1H, dt, *J* 8.5, 4.5 Hz, C14-*H*), 5.53 (1H, d, *J* 9.0 Hz, N4-*H*), 4.81 (1H, dd, *J* 8.5, 6.5 Hz, C5-*H*), 4.31 (1H, dd, *J* 11.5, 4.5 Hz, CH_2OH), 4.16 (1H, dd, *J* 11.5, 4.0 Hz, CH_2OH), 3.86 (3H, s, OCH_3), 2.85 (3H, s, C30-CH_3), 2.57 (3H, s, C33-CH_3), 2.27 – 2.14 (1H, m, C26-*H*), 1.40 (9H, s, C(CH_3)$_3$), 0.96 (3H, d, *J* 7.0 Hz, C26(CH_3)$_2$), 0.92 (3H, d, *J* 6.5 Hz, C26(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 186.5 (*C12*), 165.6 (*C6*), 162.3 (*C18*), 159.2 (*C15*), 157.0 (*C33*), 155.6, 155.5 (*C30*, *C*O_2^{t}Bu), 150.8 (*C9*), 138.9 (*C29*-H), 134.1 (*C11*), 129.6 (*C8*), 127.4 (*C17*), 80.0 (*C*(CH$_3$)$_3$), 62.5 (*C*H$_2$OH), 54.5 (*C5*), 53.2 (*C14*), 51.9 (O*C*H$_3$), 32.9 (*C*26), 29.3 (C(*C*H$_3$)$_3$), 18.8, 18.1 (C26(*C*H$_3$)$_2$), 13.9 (C30-CH_3), 12.0 (C33-*C*H$_3$); *m/z* (ESI+) 586.2 ([M+Na] 100%); HR ESI, *m/z* = 586.1950, ($C_{25}H_{33}N_5O_8SNa$ requires M+Na = 586.1942).

Thiazole 19

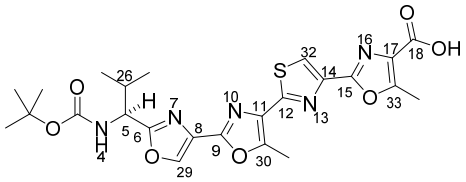


A solution of the thioamide **18** (0.24 g, 0.46 mmol) in dry CH_2Cl_2 (5 mL) was cooled to -78 °C under a nitrogen atmosphere. (Diethylamino)sulfur trifluoride (0.11 mL, 0.80 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 hour, then to room temperature over 30 minutes. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and stirred for 15 minutes. The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude thiazoline as a bright orange oil. This was used without further purification.

The thiazole was prepared using a method modified from the literature procedure of Videnov *et al.*[21] The solution of the crude thiazoline (0.46 mmol) in acetonitrile (1.5 mL), CCl_4 (1.1 mL), pyridine (1.5 mL) was cooled to 0 °C under a nitrogen atmosphere and 1, 8-Diazabicyclo[5.4.0]undec-7-ene (0.30 mL, 2.0 mmol) was added dropwise. The reaction was allowed to reach room temperature overnight. The resulting brown suspension was partitioned between pH 2 buffer (5 mL) and CH_2Cl_2 (5 mL) and the phases separated. The

aqueous phase was further extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude thiazole. This was purified by silica chromatography (50 % EtOAc: pet. ether) to give thiazole **19** as a bright white solid (0.11 g, 0.20 mmol, 45 %); m.p. 206 - 209 °C; $[\alpha]_D^{26}$ -3.6 (c = 0.49, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3349 (NH), 1708 (ester C=O), 1686 (amide C=O), 1523 (NH); δ_H (400 MHz, $CDCl_3$) 8.22 (1H, s, C29-*H*), 8.09 (1H, s, C32-*H*), 5.32 (1H, d, *J* 9.0 Hz, N4-*H*), 4.85 (1H, dd, *J* 8.5, 6.5 Hz, C5-*H*), 3.97 - 3.92 (3H, m, OCH_3), 2.88 (3H, s, C30-CH_3), 2.74 (3H, s, C33-CH_3), 2.22 (1H, s, C26-H), 1.44 (9H, s, C(CH_3)$_3$), 0.96 (3H, d, *J* 7.0 Hz, C26(CH_3)$_2$), 0.94 (8H, d, *J* 7.0 Hz, *M11*); δ_C (150 MHz, $CDCl_3$) 165.6 (*C6*), 162.7 (*C18*), 162.0 (*C12*), 156.5 (*C33*), 155.4, 155.3 (*C*O_2^{t}Bu, *C15*), 153.3 (*C9*), 148.2 (*C30*), 143.6 (*C14*), 138.6 (*C29*-H), 130.8 (*C11*), 130.0 (*C8*), 128.4 (*C17*), 120.5 (*C32*-H), 80.1 (*C*(CH_3)$_3$), 54.4 (*C5*-H), 52.1 (CO_2*C*H_3), 32.4 (*C26*-H), 28.3 (C(*C*H_3)$_3$), 18.8, 18.1 (C26(*C*H_3)$_2$), 12.2, 12.1 (C30-CH_3, C33-CH_3); *m/z* (ESI+) 566.2 ([M+Na] 100%); HR ESI, *m/z* = 566.1679, ($C_{25}H_{29}N_5O_7SNa$ requires M+Na = 566.1680).

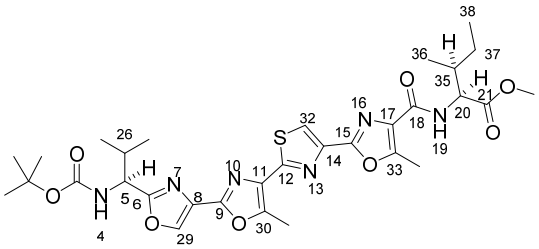
Tetrazole Carboxylic Acid 20



LiOH (80 mg, 3.5 mmol) was added to a stirred suspension of methyl ester **19** (0.19 g, 0.35 mmol) in MeOH (15 mL), THF (15 mL) and water (2.7 mL). After 18 hours at room temperature, THF (5 mL), MeOH (5 mL) and CH_2Cl_2 (3 mL) were added to the suspension, and the mixture stirred for a further 8 hours, until complete by TLC (EtOAc). The mixture was acidified with pH 2 buffer, and the organics removed *in vacuo*. The mixture was extracted with CH_2Cl_2 (5 x 3 mL), and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give acid **20** as a bright white solid (0.17 g, 0.32 mmol, 92%); m.p. 208 - 210 °C; $[\alpha]_D^{24}$ -54 (c = 0.25, MeOH); υ_{max}/cm^{-1} (neat) 3332 (NH), 3120 (OH), 1685 (acid C=O), 1620 (amide C=O), 1518 (NH); δ_H (600 MHz, $CDCl_3$) 8.23 (1H, s, C29-*H*), 8.11 (1H, s, C32-*H*), 5.86 (1H, br.s, minor rotamer N4-*H*), 5.40 (1H, d, *J* 9.5 Hz, major rotamer N4-*H*), 4.86 (1H, dd, J 9.0, 6.5 Hz, major rotamer C5-*H*), 4.70 (1H, br. s., minor rotamer C5-*H*), 2.88 (3H, s, C30-CH_3), 2.77 (3H, s, C33-CH_3), 2.35 - 2.18 (1H, m, C26-*H*), 1.54 - 1.37 (9H, m, C(CH_3)$_3$), 0.98 (3H, d, *J* 7.0 Hz, C26(CH_3)$_2$), 0.95 (3H, d, *J* 7.0 Hz, C26(CH_3)$_2$); δ_C (150 MHz, $CDCl_3$) 165.7 (*C6*), 165.2 (*C*O_2H), 162.2 (*C12*), 157.3 (*C33*), 155.4, 155.3 (*C*O_2^{t}Bu, *C15*), 153.3 (*C30*), 143.4 (*C14*), 140.23 (*C29*-H), 130.8 (*C11*), 129.9 (*C8*), 128.2 (*C17*), 120.8 (*C32*-H), 80.1 (*C*(CH_3)$_3$), 54.4 (*C5*-H), 33.0 (*C26*), 28.3 (C(*C*H_3)$_3$), 18.8, 18.1

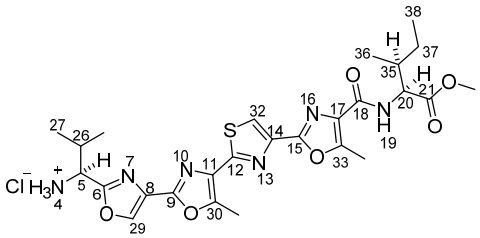
(C26(CH_3)$_2$), 12.3, 12.2 (C30-CH_3, C33-CH_3); *m/z* (ESI-) 528.0 ([M-H] 100%); HR ESI, *m/z* = 552.1540, ($C_{24}H_{27}N_5O_7SNa$ requires M+Na = 552.1523).

Hexapeptide 21



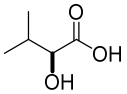
HOBt (88 %, 5 mg, 0.03 mmol) was added to a solution of carboxylic acid **20** (86 mg, 0.16 mmol) in EtOH (2 mL), and the reaction mixture was stirred for 15 minutes at room temperature. To this was added a solution of L-isoleucine methyl ester hydrochloride (70 mg, 0.40 mmol) in EtOH (2 mL) and the mixture was cooled to 0-5 °C. *N*-Methyl morpholine (0.11 mL, 1.05 mmol) was added and the mixture was stirred at 0-5 °C for 15 minutes. EDCI (46 mg, 0.24 mmol) was added and the reaction mixture allowed to reach room temperature overnight. The resulting dense white suspension was acidified with pH 2 buffer, and extracted with EtOAc (5 x 5 mL). The combined organics were washed with saturated aqueous NaCl solution (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude hexapeptide. Hexapeptide **21** was obtained by silica chromatography (2% MeOH: CH_2Cl_2) as a pale yellow crystalline solid (89 mg, 0.14 mmol, 84 %); m.p. 127 - 129 ˚C; $[\alpha]_D^{24}$-18 (c = 0.51, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3305 (NH), 1742 (ester C=O), 1680, 1630 (amide C=O), 1510 (NH); δ_H (500 MHz, $CDCl_3$) 8.23 (1H, s, C29-*H*), 8.00 (1H, s, C32-*H*), 7.51 (1H, d, *J* 9.0 Hz, N19-*H*), 5.33 (1H, d, *J* 10 Hz, N4-*H*), 4.87 (1H, dd, *J* 9.0, 7.0 Hz, C5-*H*), 4.75 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 3.78 (3H, s, OCH_3), 2.91 (3H, s, C30-CH_3), 2.75 (3H, s, C33-CH_3), 2.26 (1H, s, C35-*H*), 2.02 (1H, br. s., C26-*H*), 1.61-.1.56 (1H, m, C37-*H*)1.46 (9H, s, C(CH_3)$_3$), 1.34 - 1.25 (1H, m, C37-*H*), 1.03 - 0.95 (9H, m, C26(CH_3)$_2$, C36-H_3, C38-H_3)**;** δ_C (125 MHz, $CDCl_3$) 172.3 (*C21*), 165.6 (*C6*), 162.3 (*C12*), 161.6 (*C18*), 154.3 (*C15*), 153.6 (*C33*), 153.3 (*C9*), 148.2 (*C30*), 143.8 (*C14*), 139.0 (*C29*-H), 130.8 (*C11*), 130.0, 129.9 (*C8*, *C17*), 120.1 (*C32*-H), 80.1 (*C*(CH_3)$_3$), 56.2 (*C20*), 54.4 (*C5*), 52.1 (O*C*H_3), 38.0 (*C35*), 33.1 (*C26*), 28.3 (C(*C*H_3)$_3$), 25.3 (*C*37), 18.8, 18.1 (C26(*C*H_3)$_2$), 15.6 (*C*36), 12.2, 11.9, 11.5 (C30-*C*H_3, C33-*C*H_3, *C*38). Missing one quaternary carbon; *m/z* (ESI+) 679.1 ([M+Na] 100%); HR ESI, *m/z* = 679.2522, ($C_{31}H_{40}N_6O_8SNa$ requires M+Na = 679.2521).

Hexapeptide hydrochloride



A solution of the Boc-protected hexapeptide **21** (89 mg, 0.14 mmol) in methanolic hydrochloride (2M, 2.1 mL) was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* to give the deprotected amine hydrochloride salt as an amorphous cream solid (80 mg, 0.14 mmol, 99 %); $[\alpha]_D^{28}$ +3.50 (c = 0.495, MeOH); υ_{max}/cm^{-1} (neat) 2966 (NH), 1738 (ester C=O), 1663, 1627 (amide C=O), 1512 (NH); δ_H (700 MHz, MeOD) 8.73 (1H, s, C29-*H*), 8.27 (1H, s, C32-*H*), 4.56 - 4.61 (2H, m, C5-*H*, C20-*H*), 3.80 - 3.76 (3H, m, OCH_3), 2.89 - 2.86 (3H, m, C30-CH_3), 2.67 (3H, s, C33-CH_3), 2.45 (1H, oct. *J* 6.5 Hz, C26-*H*), 2.07 – 2.00 (1H, m, C35-*H*), 1.58 (1H, dqd, *J* 14.5, 7.5, 4.8 Hz, C37-*H*), 1.37 - 1.30 (1H, m, C37-*H*), 1.16 (3H, d, *J* 6.5 Hz, C26-CH_3), 1.05 (3H, d, *J* 6.5 Hz, C26-CH_3), 1.00 (3H, d, *J* 6.5 Hz, C36-H_3), 0.98 (3H, t, *J* 7.5 Hz, C38-H_3); δ_C (175 MHz, MeOD) 172.0 (*C21*), 162.0, 161.9 (*C6*, *C12*), 160.7 (*C18*), 154.7, 154.1, 153.1 (*C15*, *C33*, *C9*), 148.6 (*C30*), 143.8 (*C14*), 140.8 (*C29*-H), 130.4, 130.0, 129.9 (*C8*, *C17*, *C11*), 120.9 (*C32*-H), 56.4 (*C20*), 53.9 (*C5*), 51.2 (O*C*H$_3$), 37.3 (*C35*), 33.1 (*C26*), 25.3 (*C*37), 17.4, 16.7 (C26(*C*H$_3$)$_2$), 14.6 (*C*36), 10.5, 10.4, 10.3 (C30-*C*H$_3$, C33-*C*H$_3$, *C*38); *m/z* (ESI+) 579.1 ([M+Na] 100%); HR ESI, *m/z* = 557.2189, ($C_{26}H_{33}N_6O_6S$ requires M-Cl = 557.217.

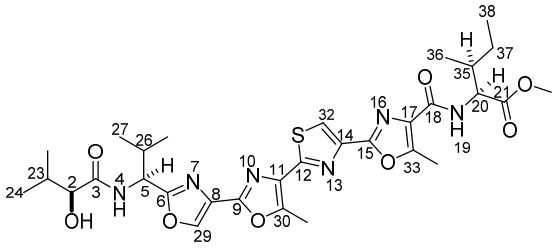
(*S*)-2-Hydroxy-3-methylbutanoic acid 22



Prepared according to the method of Bauer *et al*.[22] A solution of L-valine (1.00 g, 8.54 mmol) in dilute aqueous sulphuric acid (0.5M, 34.0 mL, 17.0 mmol) was cooled to 0 °C. A solution of sodium nitrate (3.53 g, 51.2 mmol) in water (11.5 mL) was added dropwise, and the reaction mixture was stirred at 0-5 °C for a further 30 minutes and at room temperature overnight. The reaction mixture was extracted with Et_2O (5 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give yellow crystals. These were recrystallised from pet. ether to give hydroxyacid **22** as bright white crystals (0.31 g, 2.6 mmol, 31 %); m.p. 65 - 66 °C (lit.[23] 65 - 66 °C); $[\alpha]_D^{26}$ +14.0 (c = 1.01, $CHCl_3$) (lit.[22] $[\alpha]_D^{26}$ +17.3 (c = 1.06, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3414 (OH), 1703 (acid C=O); δ_H (400 MHz, $CDCl_3$) 6.05 (1H, br.s, CO_2H), 4.16 (1H, d, *J* 3.5 Hz, C*HOH*), 2.17 (1H, septd, *J* 6.5, 3.5 Hz, C*H*(CH$_3$)$_2$), 1.07 (3H, d, *J* 6.5 Hz, CH(CH_3)$_2$), 0.93 (3H, d, *J* 7.0 Hz, CH(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 179.4 (*C*O$_2$H), 74.8

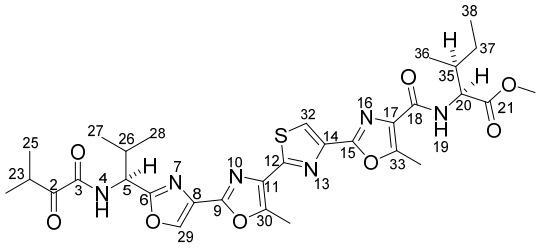
(C*H*OH), 32.0 (*C*H(CH$_3$)$_2$), 18.8 (CH(*C*H$_3$)$_2$), 15.9 (CH(*C*H$_3$)$_2$); *m/z* (ESI-) 117.1 ([M-H] 100%); HR ESI, *m/z* = 117.0554, ($C_5H_9O_3$ requires M-H = 117.0557); This data is consistent with that previously reported.[24]

Heptapeptide 23



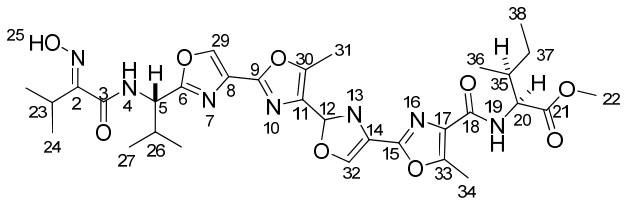
A solution of the (2*S*)-2-hydroxy-3-methylbutanoic acid, **22**, (80 mg, 0.68 mmol) and HOBt (88 %, 21 mg, 0.14 mmol) in EtOH (3 mL) was stirred at room temperature for 15 minutes before being added to a solution of the hexapeptide hydrochloride salt (80 mg, 0.14 mmol) in EtOH (2 mL). The reaction mixture was cooled to 0-5 °C and *N*-methylmorpholine (0.12 mL, 1.1 mmol) was added. After 15 minutes at 0-5 °C, EDCI (0.16 g, 0.68 mmol) was added and the reaction mixture allowed to reach room temperature overnight. The mixture was acidified with pH 2 buffer and EtOH removed *in vacuo*. The mixture was extracted with EtOAc (4 x 5 mL), and the combined organic extracts were washed with water (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude heptapeptide. The alcohol **23** was obtained by silica chromatography (98:2:0.2 EtOAc:MeOH:AcOH) as an amorphous solid (72 mg, 0.11 mmol, 81 %); $[\alpha]_D^{26}$ -50 (c = 0.53, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3432 (NH), 3265 (OH), 1740 (ester C=O), 1648 (amide C=O), 1507 (NH); δ_H (500 MHz, $CDCl_3$) 8.20 (1H, s, C29-*H*), 7.97 (1H, s, C32-*H*), 7.61 (1H, d, *J* 9.5 Hz, N4-*H*), 7.49 (1H, d, *J* 9.0 Hz, N19-*H*), 5.22 (1H, dd, *J* 9.5, 7.0 Hz, C5-*H*), 4.73 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 4.29 – 4.26 (1H, m, C2-*H*), 3.77 (3H, s, OC*H*$_3$), 2.88 (3H, s, C30-C*H*$_3$), 2.74 - 2.71 (3H, m, C30-C*H*$_3$), 2.39 - 2.24 (2H, m, C23-*H*, C26-*H*), 2.05 - 1.96 (1H, m, 1H, m, C35-*H*), 1.62 - 1.51 (1H, m, C37-*H*), 1.34 - 1.23 (1H, m, C37-*H*), 1.06 - 0.90 (18H, m, C24-C*H*$_3$, C25-C*H*$_3$, C27-C*H*$_3$, C28-C*H*$_3$, C36-C*H*$_3$, C38-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 173.4 (*C3*), 172.2 (*C21*), 165.6 (*C6*), 162.1 (*C12*), 161.6 (*C18*), 165.2 (*C15*), 153.6 (*C22*), 153.0 (*C9*), 148.3 (*C30*), 143.8 (*C14*), 138.5 (*C29*-H), 130.8 (*C11*), 129.9, 129.8 (*C8*, *C17*), 120.2 (*C32*-H), 76.4 (*C2*-H), 56.2 (*C20*), 52.3, 52.1 (*C5*, O*C*H$_3$), 38.0 (*C35*), 32.9, 31.7 (*C23*, *C26*), 25.3 (*C37*), 19.2, 19.0, 18.5, 15.6, 15.5 (*C24*, *C25*, *C27*, *C28*, *C36*) 12.1, 11.9, 11.5 (C30-*C*H$_3$, C33-*C*H$_3$, *C38*); *m/z* (ESI+) 679.1 ([M+Na] 100%); HR ESI, *m/z* = 679.2528, ($C_{31}H_{40}N_6O_8SNa$ requires M+Na = 679.2521).

Ketone 24



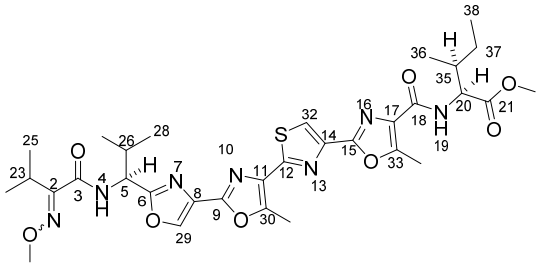
A solution of alcohol **23** (57 mg, 0.087 mmol) in dry CH_2Cl_2 (3 mL) and dry DMSO (0.06 mL) was cooled to 0-5°C under a nitrogen atomosphere. $^{i}Pr_2NEt$ (0.12 mL, 0.69 mmol) and SO_3.pyr (83 mg, 0.52 mmol) were added sequentially, and the reaction stirred at 0-5°C for 3 hours. The mixture was acidified with pH 2 buffer and the phases were separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow gum. This was purified by silica chromatography (50% EtOAc: pet. ether) to give ketone **24** as a bright white solid (37 mg, 0.57 mmol, 65%); m.p. 145-146 °C; $[\alpha]_D^{27}$-31 (c = 0.52, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3406 (NH), 1739 (ester C=O), 1670 (ketone C=O), 1628 (amide C=O), 1511 (NH); δ_H (400 MHz, $CDCl_3$) 8.25 (1H, s, C29-*H*), 8.00 (1H, s, C32-*H*), 7.59 (1H, d, *J* 9.5 Hz, N4-*H*), 7.50 (1H, d, *J* 9.0 Hz, N19-*H*), 5.13 (1H, dd, *J* 9.5, 6.5 Hz, C5-*H*), 4.74 (1H, dd, *J* 9.0, 6.0 Hz, C20-*H*), 3.75 - 3.82 (3H, m, OC*H*$_3$), 3.59 (1H, spt, *J* 7.0 Hz, C23-*H*), 2.91 (3H, s, C30-C*H*$_3$), 2.73 - 2.79 (3H, m, C30-C*H*$_3$), 2.31 - 2.45 (1H, m, C26-*H*), 1.93 - 2.09 (1H, m, C35-*H*), 1.51 - 1.63 (1H, m, C37-*H*), 1.25 - 1.36 (1H, m, C37-*H*), 1.18 (3H, d, *J* 6.5 Hz, C25-*H*$_3$), 1.15 (3H, d, *J* 7.0 Hz, C25-*H*$_3$), 0.94 - 1.03 (12H, m, C27-*H*$_3$, C28-*H*$_3$, C36-*H*$_3$, C38-*H*$_3$); δ_C (125 MHz, $CDCl_3$) 201.5 (*C2*), 172.3 (*C21*), 164.0 (*C6*), 162.3 (*C12*), 161.6 (*C3*), 159.5 (*C18*), 154.3 (*C15*), 153.6 (*C33*), 153.1 (*C9*), 148.3 (*C30*), 143.8 (*C14*), 138.7 (*C29*-H), 130.9 (*C11*), 130.2 (*C8*), 130.0 (*C17*), 120.2 (*C32*-*H*), 56.1 (*C20*-H), 53.0 (*C5*-H), 52.1 (CO_2CH_3), 38.0 (*C35*-H), 34.3 (*C23*-H), 32.9 (*C26*-H), 25.3 (*C37*-H_2), 18.9, 18.2, 17.8, 17.7 (*C24*, *C25*, *C27*, *C28*, *C36*), 12.2, 11.9, 11.5 (C30-*C*H_3, C33-*C*H_3, *C38*); *m/z* (ESI+) 677.1 ([M+Na] 100%); HR ESI, *m/z* = 677.2352, ($C_{31}H_{38}N_6O_8SNa$ requires M+Na = 677.2364).

Azolemycin A 1a and Azolemycin B 1b



Hydroxylamine hydrochloride (3.0 mg, 0.04 mmol) and pyridine (3.3 μL, 0.04 mmol) were added to a stirred solution of the ketone **24** (9 mg, 0.01 mmol) in MeOH (0.6 mL) and $CHCl_3$ (0.6 mL) under a nitrogen atmosphere. After 6 hours at room temperature, additional hydroxylamine hydrochloride (3.0 mg, 0.04 mmol) and pyridine (3.3 μL, 0.040 mmol) were added and the reaction was stirred at room temperature overnight. The reaction mixture was reduced *in vacuo* and the residue partitioned between pH 4 buffer (5 mL) and CH_2Cl_2, and the phases were separated. The aqueous phase was further extracted with CH_2Cl_2 (3 x 2 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude oxime. This was purified by silica chromatography (50% EtOAc: pet ether) to give azolemycins A and B, **1**, as a mixture of *E/Z* geometric isomers (major isomer azolemycin A, minor isomer azolemycin B; 8 mg, 0.012 mmol, 85 %); $[\alpha]_D^{25}$ +6.1 (c = 0.17, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3402 (NH), 3316-3274 (broad, O-H), 1741 (ester C=O), 1668 (C=N), 1629 (amide C=O), 1513 (NH); δ_H (700 MHz, $CDCl_3$) 9.37 (1H, br. s., NO*H*), 8.26 (1H, m, C29-*H*), 8.00 (1H, m, C32-*H*), 7.60 (1H, d, *J* 10.0 Hz, N4-*H*), 7.51 (1H, d, *J* 9.0 Hz, N19-*H*), 5.25 (1H, dd, *J* 10.0, 6.0 Hz, C5-*H*), 4.75 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 3.78 (3H, s, OCH_3), 3.50 (1H, sept, *J* 7.0 Hz, C23-*H*), 2.90 (3H, s, C30-CH_3), 2.75 (3H, s, C33-CH_3), 2.36 - 2.30 (1H, m, C26-*H*), 2.05 – 1.99 (1H, m, C35-*H*), 1.57 (1H, dqd, *J* 15.0, 7.5 Hz, 5.0 Hz, C37-H_2), 1.31 (1H, d, *J* 7.5 Hz, C25-CH_3), 1.30 – 1.23 (4H, m, C25-H_3, C37-H_2), 1.02 (3H, d, *J* 7.0 Hz, C28-CH_3), 1.00 (3H, d, *J* 7.0 Hz, C28-CH_3), 0.98 (3H, d, *J* 7.0 Hz, C36-CH_3), 0.97 (3H, t, *J* 7.5 Hz, C38-CH_3); Minor stereoisomer peaks at 5.34 (1H, dd, *J* 9.0, 6.0 Hz, C5-*H*), 2.97 - 3.02 (1H, m, C23-*H*), 2.43 - 2.37 (1H, m, C26-*H*), 1.19 - 1.17 (3H, m, C25-CH_3), 1.15 - 1.17 (1H, m, C25-CH_3); δ_C (175 MHz, $CDCl_3$) 172.3 (*C21*), 165.6 (*C6*), 163.8 (*C3*), 162.3 (*C12*), 161.6 (*C18*), 158.8 (*C2*), 154.3 (*C15*), 153.7 (*C33*), 152.9 (*C9*), 148.3 (*C30*), 143.8 (*C14*), 138.6 (*C29*-H), 130.9 (*C11*), 129.9, 129.8 (*C17*, *C8*), 120.2 (*C32-H*), 56.2 (*C20*-H), 52.6 (*C5*-H), 52.1 (CO_2CH_3), 38.0 (*C35*-H), 32.9 (*C26*-H), 25.8 (*C23*-H), 25.3 (*C37*-H_2), 18.9, 18.7, 18.5, 18.3, 15.6 (*C24*, *C25*, *C27*, *C28, C36*), 12.1, 11.8, 11.5 (C30-*C*H_3, C33-*C*H_3, *C38*); *m/z* (ESI-) 668.2 ([M-H] 100%); HR ESI, *m/z* = 668.2470, ($C_{31}H_{38}N_7O_8S$ requires M-H = 668.2508), *m/z* = 692.2479, ($C_{31}H_{39}N_7O_8SNa$ requires M+Na = 692.2473). The data are consistent with the natural product.

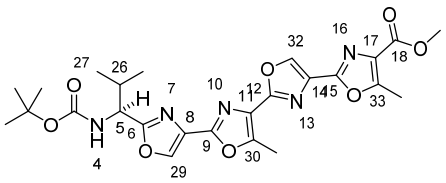
Azolemycin C 2a and Azolemycin D 2b



Methoxyamine hydrochloride (3.8 mg, 0.046 mmol) and pyridine (3.7 μL, 0.046 mmol) were added to a stirred solution of ketone **24** (10 mg, 0.015 mmol) in MeOH (0.5 mL) and $CHCl_3$ (0.2 mL) under a nitrogen atmosphere. After 4 hours, the reaction mixture was reduced *in vacuo* and the residue partitioned between pH 4 buffer (3 mL) and CH_2Cl_2 (2 mL). The phases were separated and the aqueous phase further extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Azolemycins C **2a** (minor isomer) and D **2b** (major isomer) were obtained, as a mixture, by silica chromatography (50% EtOAc: pet. ether) as a white solid (9 mg, 0.013 mmol, 87 %); $[\alpha]_D^{21}$ +27.6 (c = 0.12, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3414 (NH), 1741 (ester C=O), 1672 (C=N), 1630 (amide C=O), 1509 (NH); δ_H (400 MHz, $CDCl_3$), **2b**: 8.24 (1H, s, C29-*H*), 8.00 (1H, s, C32-*H*), 7.51 (1H, d, *J* 9.0 Hz, N19-*H*), 7.36 (1H, d, *J* 8.5 Hz, N4-*H*), 5.29 (1H, dd, *J* 8.5, 6.5 Hz, C5-*H*), 4.75 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 3.95 (3H, s, NOCH_3), 3.78 (3H, s, CO_2CH_3), 2.98 (1H, sept, *J* 7.0 Hz, C23-*H*), 2.91 (3H, s, C30-CH_3), 2.75 (3H, s, C33-CH_3), 2.42 - 2.32 (1H, m, C26-*H*), 2.00 – 1.89 (1H, m, C35-*H*), 1.52 – 1.45 (1H, m, C37-H_2), 1.36 - 1.25 (3H, m, C37-H_2), 1.16 (3H, d, *J* 7.0 Hz, C25-H_3), 1.14 (3H, d, *J* 7.0 Hz, C25-H_3), 1.05 - 0.94 (12H, m, C36-CH_3,C38-CH_3, C28-CH_3, C28-CH_3); Minor stereoisomer peaks at 5.18 (1H, dd, *J* 9.5, 7.0 Hz, C5-*H*), 4.00 (3H, s, NOCH_3), 3.45 - 3.35 (1H, m, C23-*H*), 1.23 (3H, d, *J* 7.0 Hz, C25-CH_3), 1.22 (3H, d, *J* 7.0 Hz, C25-CH_3); During the time taken to resubmit the compound for further NMR experiments, the sample isomerized to give predominately the *E*-geometric isomer, azolemycin C **2a**. δ_H (700 MHz, $CDCl_3$) 8.24 (1H, s, C29-*H*), 8.00 (1H, s, C32-*H*), 7.51 (1H, d, *J* 9.0 Hz, N19-*H*), 7.27 – 7.27 (1H, m, N4-*H*), 5.18 (1H, dd, *J* 9.0, 7.0 Hz, C5-*H*), 4.75 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 4.00 (3H, s, NOCH_3), 3.78 (1H, s, CO_2CH_3), 3.40 (1H, sept, *J* 7.0 Hz, C23-*H*), 2.91 (3H, s, C30-CH_3), 2.75 (3H, s, C33-CH_3), 2.35 (1H, oct, *J* 7.0 Hz, C26-*H*), 2.05 - 1.99 (1H, m, C35-*H*), 1.60 - 1.53 (1H, m, C37-H_2), 1.33 - 1.26 (1H, m, C37-H_2), 1.23 (3H, d, *J* 7.0 Hz, C25-H_3), 1.22 (3H, d, *J* 7.0 Hz, C25-H_3), 1.03 (3H, d, *J* 7.0 Hz, C28-CH_3), 1.00 (3H, d, *J* 6.5 Hz, C28-CH_3), 0.97 (3H, t, *J* 7.5 Hz, C38-H_3), 0.96 (3H, d, *J* 6.5 Hz, C35-H_3); δ_C (175 MHz, $CDCl_3$) 172.3 (*C21*), 165.1 (*C6*), 162.7 (*C3*), 162.3 (*C12*), 161.6 (*C18*), 157.1 (*C2*), 154.3 (*C15*), 153.6 (*C33*), 153.3 (*C9*), 148.3 (*C30*), 143.8 (*C14*), 138.6 (*C29*-H), 130.8 (*C11*), 130.0, 129.9 (*C17, C8*), 120.1 (*C32*-*H*), 63.0 (NO*C*H_3), 56.1 (*C20*-H), 52.6 (*C5*-H), 52.1 ($CO_2C$$H_3$), 38.0 (*C35*-H), 33.0 (*C26*-H), 25.9 (*C23*-H), 25.3

(*C37*-H_2), 19.0, 18.6, 18.5, 15.6 (*C24*, *C25*, *C27*, *C28*, *C36*), 12.2, 11.9, 11.5 (C30-*C*H_3, C33-*C*H_3, *C38*); *m/z* (ESI+) 706.2 ([M+H] 100%); HR ESI, *m/z* = 706.2625, ($C_{32}H_{41}N_7O_8SNa$ requires M+Na = 706.2630). The data are consistent with that obtained for the natural product.

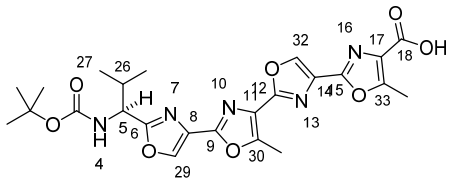
Tetraoxazole Methyl Ester 25



A solution of pentapeptide alcohol **15** (0.10 g, 0.19 mmol) in dry CH_2Cl_2 (20 mL) was cooled to -78 ˚C under nitrogen. (Diethylamino)sulfur trifluoride (0.05 mL, 0.4 mmol) was added and the reaction mixture was stirred at -78 ˚C for 2 hours, then at room temperature for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and was stirred for a further 15 minutes. The phases were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude oxazoline as a bright yellow oil (0.10 g), which was used immediately without further purification.

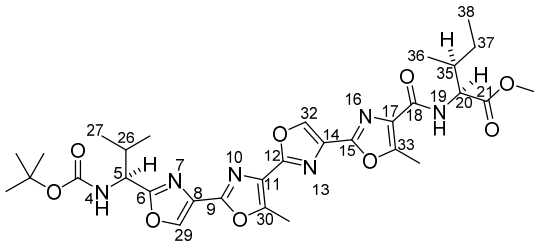
A solution of the oxazoline (0.10 g, 0.19 mmol) in CCl_4 (0.5 mL), MeCN (0.7 mL) and pyridine (0.7 mL) was cooled to 0 ˚C under nitrogen. 1, 8-Diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 0.81 mmol) was added and the reaction mixture was allowed to reach room temperature over 72 hours. The reaction mixture was quenched with pH 2 buffer (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude oxazole. Purification by silica chromatography (5 % MeOH: CH_2Cl_2) gave oxazole **25** as a sticky colourless oil (90 mg, 0.17 mmol, 89 %); $[\alpha]_D^{25}$-38 (c = 0.87, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3330 (NH), 1712 (ester C=O), 1682 (amide C=O), 1523 (NH); δ_H (400 MHz, $CDCl_3$) 8.39 (1H, s, C32-*H*), 8.28 (1H, s, C29-*H*), 5.32 (1H, d, *J* 9.0 Hz, N4-*H*), 4.84 (1H, dd, *J* 9.0, 6.0 Hz, C5-*H*), 3.94 (3H, s, OC*H*$_3$), 2.83 (3H, s, C30-C*H*$_3$), 2.72 (3H, s, C30-C*H*$_3$), 2.29 - 2.18 (1H, m, C36-*H*), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.02 - 0.91 (6H, m, 2 x C27-*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.5 (*C6*), 162.5 (*C18*), 156.7, 156.6 (*C12*, *C33*), 166.4, 154.0, 152.9, 151.3 (*C*O_2^{t}Bu, *C9*, *C15*, *C30*), 138.8, 138.6 (*C29*-H, *C32*-H), 131.0 (*C8*), 129.8 (*C14*), 128.4 (*C17*), 125.7 (*C11*), 80.1 (*C*(CH_3)$_3$), 54.3 (*C5*-H), 52.1 (O*C*H_3), 33.0 (*C26*-H), 28.3 (C(*C*H_3)$_3$), 18.7, 18.0 (2 x *C27*-H_3), 12.1, 11.9 (C30-*C*H_3, C33-*C*H_3); *m/z* (ESI+) 550.1 ([M+Na] 100%); HR ESI, *m/z* = 550.1909, ($C_{25}H_{29}N_5O_8Na$ requires M+Na = 550.1908).

Tetraoxazole Carboxylic Acid 26



A solution of LiOH (40 mg, 1.7 mmol) in water (1.3 mL) was added to a solution of tetraoxazole methyl ester **25** (90 mg, 0.17 mmol) in THF (7.5 mL), CH_2Cl_2, (1.0 mL) and MeOH (7.5 mL). After 6 hours at room temperature, the reaction mixture was acidified with pH 2 buffer and the organic solvents removed *in vacuo*. EtOAc (10 mL) was added and the phases were separated. The aqueous phase was further extracted with EtOAc (3 x 5 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give acid **26** as a sticky colourless oil (60 mg, 0.11 mmol, 67 %); $[\alpha]_D^{23}$ -16 (c = 0.15, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3338 (NH), 3317 (O-H), 1701 (ester C=O), 1655 (amide C=O), 1524 (NH); δ_H (400 MHz, $CDCl_3$) 8.40 (1H, s, C32-*H*), 8.30 (1H, s, C29-*H*), 5.39 (1H, d, *J* 9.5 Hz, N4-*H*), 4.86 (1H, dd, *J* 9.0, 6.0 Hz, C5-*H*), 2.84 (3H, s, C30-CH_3), 2.76 (3H, s, C33-CH_3), 2.29 - 2.19 (1H, m, C26-*H*), 1.49 - 1.44 (9H, m, C(CH_3)$_3$), 0.99 - 0.93 ppm (6H, m, 2 x C27-CH_3); δ_C (100 MHz, $CDCl_3$) 164.6 (*C6*), 164.1 (*C*O_2H), 156.5 (*C33*), 155.8 (*C12*), 154.4, 152.9, 152.0, 150.4 (*C9, C11, C15, C30*), 137.8, 137.8 (*C29*-H, *C32*-H), 129.8 (*C14*), 128.7 (*C8*), 127.1 (*C17*), 124.6 (*C11*), 79.1 (*C*$(CH_3)_3$), 53.3 (*C5*-H), 32.0 (*C26*-H), 27.3 (C(*C*H_3)$_3$), 17.7, 17.0 (2 x C27-*C*H_3), 11.2, 10.9 (C30-*C*H_3, C33-*C*H_3); *m/z* (ESI+) 536.1 ([M+Na] 100%); HR ESI, *m/z* = 536.1751, ($C_{24}H_{27}N_5O_8Na$ requires M+Na = 536.1752).

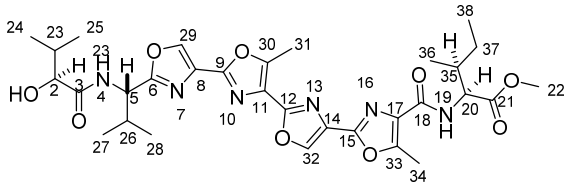
Tetraoxazole Hexapeptide 27



A solution of tetraoxazole carboxylic acid **26** (59 mg, 0.11 mmol) and HOBt (88 %, 4 mg, 0.02 mmol) in EtOH (3 mL) was stirred at room temperature for 15 minutes. L-Isoleucine methyl ester hydrochloride (52 mg, 0.29 mmol) was added and the solution was cooled to 0 ˚C. *N*-Methyl morpholine (0.08 mL, 0.8 mmol) was added followed, after 15 minutes, by EDCI (33 mg, 0.17 mmol), and the mixture was allowed to reach room temperature overnight. pH 2 buffer (5 mL) was added and mixture was extracted with EtOAc (5 x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (5

mL), water (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica chromatography (2% MeOH: CH_2Cl_2) gave the hexapeptide **28** as a clear pale yellow oil (38 mg, 0.060 mmol, 54 %); $[\alpha]_D^{28}$-18 (c = 0.56, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3346 (NH), 3317 (O-H), 1739 (ester C=O), 1667 (amide C=O), 1511 (NH); δ_H (600 MHz, $CDCl_3$) 8.30, 8.29 (1H, s, C29-*H*; 1H, s, C32-*H*), 7.47 (1H, d, *J* 9.0 Hz, N19-*H*), 5.32 (1H, d, *J* 9.0 Hz, N4-*H*), 4.85 (1H, dd, *J* 9.0, 6.0 Hz, C5-*H*), 4.73 (1H, dd, *J* 9.0, 5.3 Hz, C20-*H*), 3.77 (3H, s, OC*H*$_3$), 2.86 (3H, s, C30-C*H*$_3$), 2.72 (3H, s, C33-C*H*$_3$), 2.28 - 2.21 (1H, m, C26-*H*), 2.04 - 1.96 (1H, m, C35-*H*), 1.55 (1H, dqd, *J* 13.0, 8.0, 4.5 Hz, C37-*H*$_2$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.33 - 1.25 (1H, m, C37-*H*$_2$), 1.02 - 0.93 (12H, m, 2 x C27-*H*$_3$, C36-*H*$_3$, C38-*H*$_3$); δ_C (150 MHz, $CDCl_3$) 172.2 (*C21*), 165.5 (*C6*), 161.4 (*C18*), 156.9 (*C12*), 155.4 (*C*O$_2$^{t}Bu), 154.0, 153.7 (*C9*, *C30*), 151.9, 151.4 (*C15*, *C33*), 138.8, 138.3 (*C29*-H, *C32*-H), 131.1, 129.9, 129.7 (*C8*, *C14*, *C17*), 125.7 (*C11*), 80.1 (*C*(CH$_3$)$_3$), 56.1 (*C20*-H), 54.3 (*C5*-H), 52.1 (O*C*H$_3$), 38.0 (*C35*-H), 33.0 (*C26*-H), 28.3 (C(*C*H$_3$)$_3$), 25.3 (*C37*-H$_2$), 18.7, 18.0 (2 x *C27*-H$_3$), 15.6 (*C36*-H$_3$), 12.0, 11.8 (C30-*C*H$_3$, C33-*C*H$_3$), 11.5 (*C38*-H$_3$); *m/z* (ESI+) 663.2 ([M+Na] 100%); HR ESI, *m/z* = 658.3196, ($C_{31}H_{44}N_7O_9$ requires M+NH_3 = 658.3195).

Tetraoxazole Alcohol 28

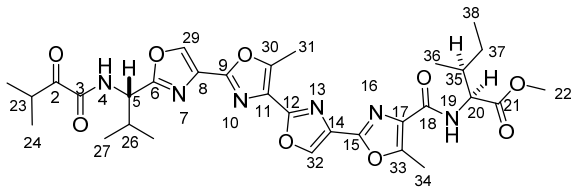


Tetraoxazole **27** (38 mg, 0.060 mmol) was dissolved in a solution of acetyl chloride (0.12 mL, 1.8 mmol) and MeOH (0.8 mL), and the reaction mixture stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to give the deprotected amine as the hydrochloride salt. *m/z* (ESI+) 563.1 ([M+Na] 100%); HR ESI, *m/z* = 563.2237, ($C_{26}H_{32}N_6O_7Na$ requires M+Na = 563.2225).

A solution of the alcohol **22** (14 mg, 0.12 mmol) and HOBt (88 %, 3 mg, 0.02 mmol) in EtOH (3 mL) was stirred at room temperature for 10 minutes and added to the deprotected amine (0.06 mmol). The mixture was cooled to 0 ˚C, and *N*-methyl morpholine (0.04 mL, 0.38 mmol) was added. After 15 minutes, EDCI (30 mg, 0.14 mmol) was added and the reaction mixture was stirred for 18 hours. pH 2 buffer (3 mL) and EtOAc (3 mL) were added and the phases were separated. The aqueous phase was further extracted with EtOAc (3 x 3 mL), and the combined organic extracts were washed with brine (3 mL) and dried over Na_2SO_4. The alcohol **28** was obtained by silica chromatography (2 % MeOH: EtOAc) as a clear oil (24 mg, 0.037 mmol, 62 %); $[\alpha]_D^{28}$-39.4 (c = 0.34, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3408 (NH), 2966 (O-H), 1740 (ester C=O), 1665 (amide C=O), 1515 (NH); δ_H (700 MHz, $CDCl_3$)

8.30 (1H, s, C32-*H*), 8.27 (1H, s, C29-*H*), 7.48 (1H, d, *J* 9.0 Hz, N19-*H*), 7.37 (1H, d, *J* 9.0 Hz, N4-*H*), 5.21 (1H, dd, *J* 9.0, 6.0 Hz, C5-*H*), 4.73 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 4.10 - 4.15 (1H, m, C2-*H*), 3.77 (3H, s, OCH_3), 3.30 (1H, br. s., O*H*), 2.85 (3H, s, C30-CH_3), 2.72 (3H, s, C33-CH_3), 2.34 (1H, oct, *J* 7.0 Hz, C26-*H*), 2.28 - 2.21 (1H, m, C23-*H*), 2.03 – 1.97 (1H, m, C35-*H*), 1.59 - 1.53 (1H, m, C37-H_2), 1.33 - 1.27 (1H, m, C37-H_2), 1.07 – 0.90 (18H, m, 2 x C24-H_3, 2 x C27-H_3, C36-H_3, C38-H_3); δ_C (150 MHz, $CDCl_3$) 173.5 (*C3*), 172.2 (*C21*), 165.3 (*C6*), 161.4 (*C18*), 156.8 (*C12*), 153.9, 153.7 (*C15*, *C33*), 151.8, 151.4 (*C9*, *C30*), 138.9 (*C29*-H), 138.4 (*C32*-H), 131.1 (*C14*), 130.0, 129.7 (*C8*, *C17*), 125.6 (*C11*), 76.5 (*C2*-H), 56.2 (*C20*-H), 52.3, 52.1 (*C5*-H, OCH_3), 37.9 (*C35*-H), 32.6 (*C26*-H), 31.7 (*C23*-H), 25.3 (*C37*-H_2), 19.2, 18.7, 18.2, 15.9, 15.6 (2 x *C27*-H_3, 2 x *C24*-H_3, *C36*-H_3), 12.0, 11.8 (C30-*C*H_3, C33-*C*H_3), 11.5 (*C38*-H_3); *m/z* (ESI+) 663.2 ([M+Na] 100%); HR ESI, *m/z* = 663.2754, ($C_{31}H_{40}N_6O_9Na$ requires M+Na = 663.2749).

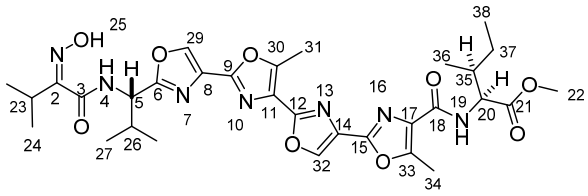
Tetraoxazole Ketone 29



A solution of alcohol **28** (24 mg, 0.037 mmol) in dry CH_2Cl_2 (1.5 mL) and dry DMSO (0.03 mL, 0.4 mmol) was stirred at 0 ˚C under N_2. Diisopropylethylamine (0.05 mL, 0.30 mmol) was added, followed by SO_3. pyridine complex (35 mg, 0.22 mmol) and the reaction mixture was held at 0 ˚C for 6 hours. The reaction mixture was quenched with pH 2 buffer and the phases were separated. The aqueous phase was further extracted with CH_2Cl_2 (5 x 3 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Ketone **29** was obtained by silica chromatography as a clear, colourless oil (17 mg, 0.027 mmol, 72 %); $[\alpha]_D^{25}$-28 (c = 0.87, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3401 (NH), 1740 (ester C=O), 1675 (ketone C=O), 1662 (amide C=O), 1513 (NH); δ_H (400 MHz, $CDCl_3$) 8.30 (1H, s, C29-*H*), 8.291H, s, (1H, s, C32-*H*), 7.57 (1H, d, *J* 9.0 Hz, N4-*H*), 7.46 (1H, d, *J* 9.0 Hz, N19-*H*), 5.11 (1H, dd, *J* 9.5, 7.0 Hz, C5-*H*), 4.72 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 3.79 (3H, s, O (CH_3), 3.58 (1H, spt, *J* 7.0 Hz, C23-*H*), 2.85 (3H, s, C30-CH_3), 2.74 - 2.70 (3H, m, C33-CH_3), 2.35 (1H, oct, *J* 7.0 Hz, C26-*H*), 2.06 - 1.94 (1H, m, C35-*H*), 1.62 - 1.49 (1H, m, C37-H_2), 1.34 - 1.22 (1H, m, C37-H_2), 1.17 (3H, d, *J* 6.5 Hz, C24-H_3), 1.14 (6 H, d, *J* 7.0 Hz, C24-H_3), 1.02 - 0.93 (12H, m, 2 x C27-H_3, C36-H_3, C38-H_3); δ_C (100 MHz, $CDCl_3$) 201.5 (*C2*), 172.2 (*C*O_2Me), 163.9 (*C6*), 161.4 (*C18*), 159.5 (*C3*), 156.9 (*C12*), 153.7, 151.9, 151.5 (*C9*, *C15*, *C30*, *C33*), 139.0 (*C32*-H), 138.3 (*C29*-H), 131.1, 130.1, 129.9 (*C8*, *C14*, *C17*), 125.7 (*C11*), 56.2, (*C20*-H), 53.0 (*C5*-H), 52.1 (OCH_3), 38.0 (*C35*-H), 34.3 (*C23*-H), 32.8 (*C26*-H), 25.3 (*C37*-H_2), 18.2, 17.7, 17.6, 15.6 (2 x *C27*-H_3, 2 x *C24*-H_3, *C36*-H_3), 12.0, 11.8 (C30-*C*H_3, C33-*C*H_3), 11.5

(*C38*-H_3); *m/z* (ESI+) 661.1 ([M+Na] 100%); HR ESI, *m/z* = 661.2606, ($C_{31}H_{38}N_6O_9Na$ requires M+Na = 661.2592).

Tetraoxazole Analogue 30



Pyridine (13 µL, 0.017 mmol) and hydroxylamine hydrochloride (12 mg, 0.017 mmol) were added to a solution of the ketone **29** (17 mg, 0.027 mmol) in MeOH (0.6 mL) and $CHCl_3$ (0.6 mL). The reaction mixture was stirred under nitrogen for 18 hours, and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and pH 4 buffer (5 mL). The phases were separated and the aqueous phase was further extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The tetraoxazole analogue of azolemycin B, **30**, was obtained as a mix of *E/Z* geometric isomers by silica chromatography (50 % EtOAc: pet. ether) as a clear colourless oil (Major isomer assumed to be *Z* by comparison with azolemycins A and B; 6 mg, 0.009 mmol, 33 % of both isomers); $[\alpha]_D^{28}$ +1.6 (c = 0.19, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3394 (NH), 3304 (OH), 1740 (ester C=O), 1665 (C=N), 1513 (NH); Major geometric *Z*-isomer peaks δ_H (700MHz, $CDCl_3$) 8.31 (1H, s, C29-*H*), 8.30 (1H, s, C32-*H*), 7.51 (1H, d, *J* 8.4 Hz, N4-*H*), 7.48 (1H, d, *J* 9.2 Hz, N19-*H*), 5.32 (1H, dd, *J* 8.8, 6.2 Hz, C5-*H*), 4.74 (1H, dd, *J* 9.0, 5.5 Hz, C20-*H*), 3.77 (1H, s, OC*H*$_3$), 3.01 (1H, sept, *J* 6.9 Hz, C23-*H*), 2.86 (1H, s, C30-C*H*$_3$), 2.73 (1H, s, C33-C*H*$_3$), 2.38 (1H, oct, *J* 6.2 Hz, C26-*H*), 2.05 - 1.98 (1H, m, C35-*H*), 1.60 - 1.52 (1H, m, C37-*H*$_2$), 1.35 - 1.21 (1H, m, C37-*H*$_2$), 1.17 (3H, d, *J* 6.6 Hz, C24-*H*$_3$), 1.15 (3H, d, *J* 7.0 Hz, C24-*H*$_3$), 1.03 – 0.99 (9H, m, 2 x C27-*H*$_3$, C33-*H*$_3$), 0.97 (3H, t, *J* 7.3 Hz, C38-*H*$_3$); Minor geometric *E*-isomer peaks at 5.20 (1H, dd, *J* 9.2, 6.6 Hz, C5-*H*), 3.51 - 3.46 (1H, m, C23-*H*), 2.34 – 2.29 (1H, m, C26-*H*); δ_C (175MHz, $CDCl_3$) 172.2 (*C21*), 164.6 (*C6*), 161.8 (*C18*), 161.5 (*C3*), 157.6 (*C2*), 156.9 (*C9*), 153.8, 153.7 (*C12*, *C33*), 151.9, 151.5 (*C15*, *C30*), 139.0 (*C29*-H), 138.3 (*C32*-H), 131.1 (*C17*), 129.9, 129.8 (*C8*, *C14*), 125.7 (*C11*), 56.1 (*C20*-H), 52.9 (*C5*-H), 52.1 (O*C*H$_3$), 38.0 (*C35*-H), 32.8 (*C26*-H), 30.9 (*C23*-H), 25.3 (*C37*-H_2), 20.0, 19.8 (2 x *C24*-H_3), 18.9, 18.4 (2 x *C27*-H_3), 15.6 (C36-*H*$_3$), 12.0, 11.8 (C30-*C*H$_3$, C33-*C*H$_3$), 11.5 (C38-*H*$_3$); *m/z* (ESI+) 675.9 ([M+Na] 100%); HR ESI, *m/z* = 767.2697, ($C_{31}H_{39}N_7O_9Na$ requires M+Na = 676.2701).

2) References

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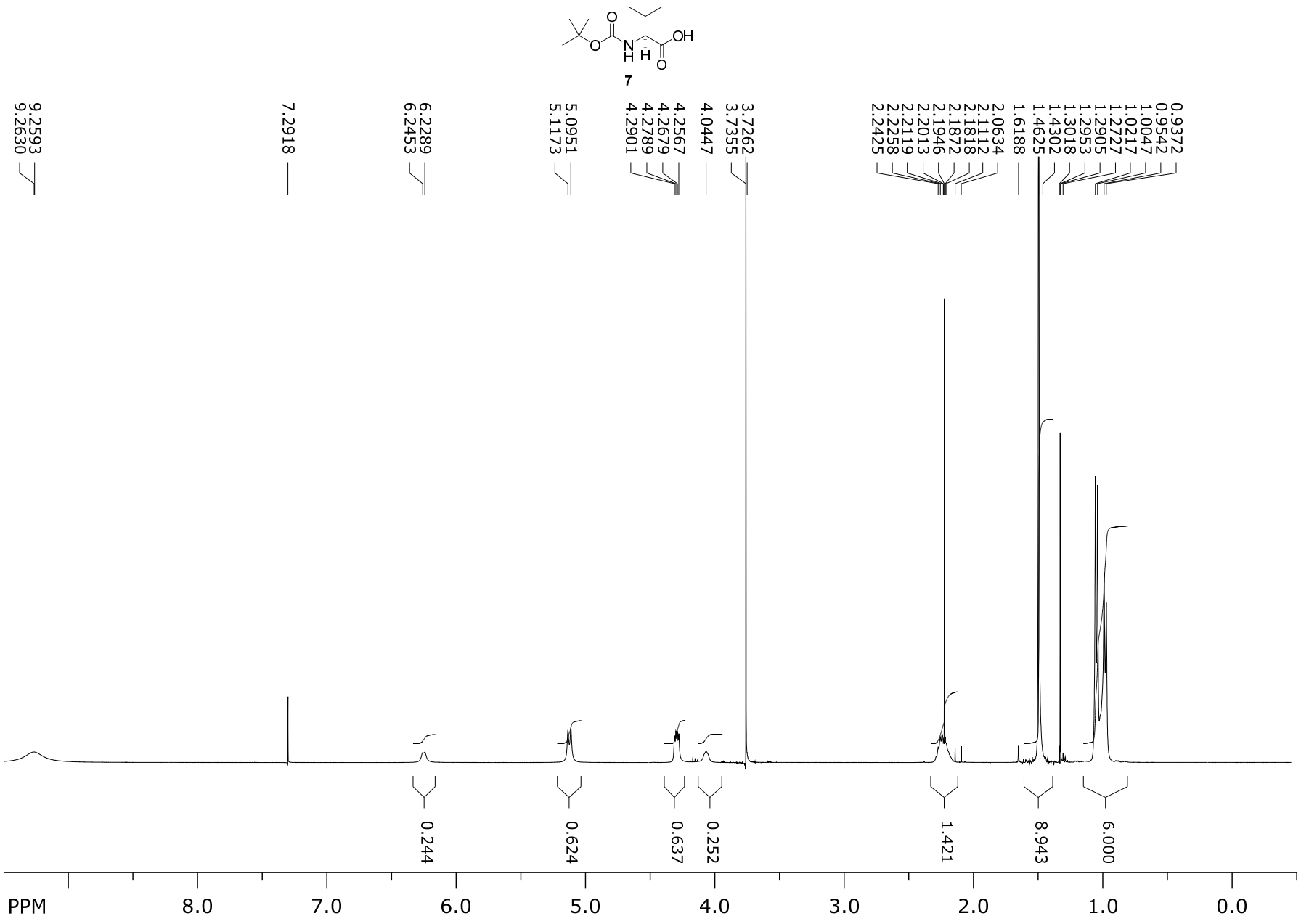
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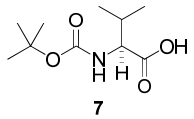
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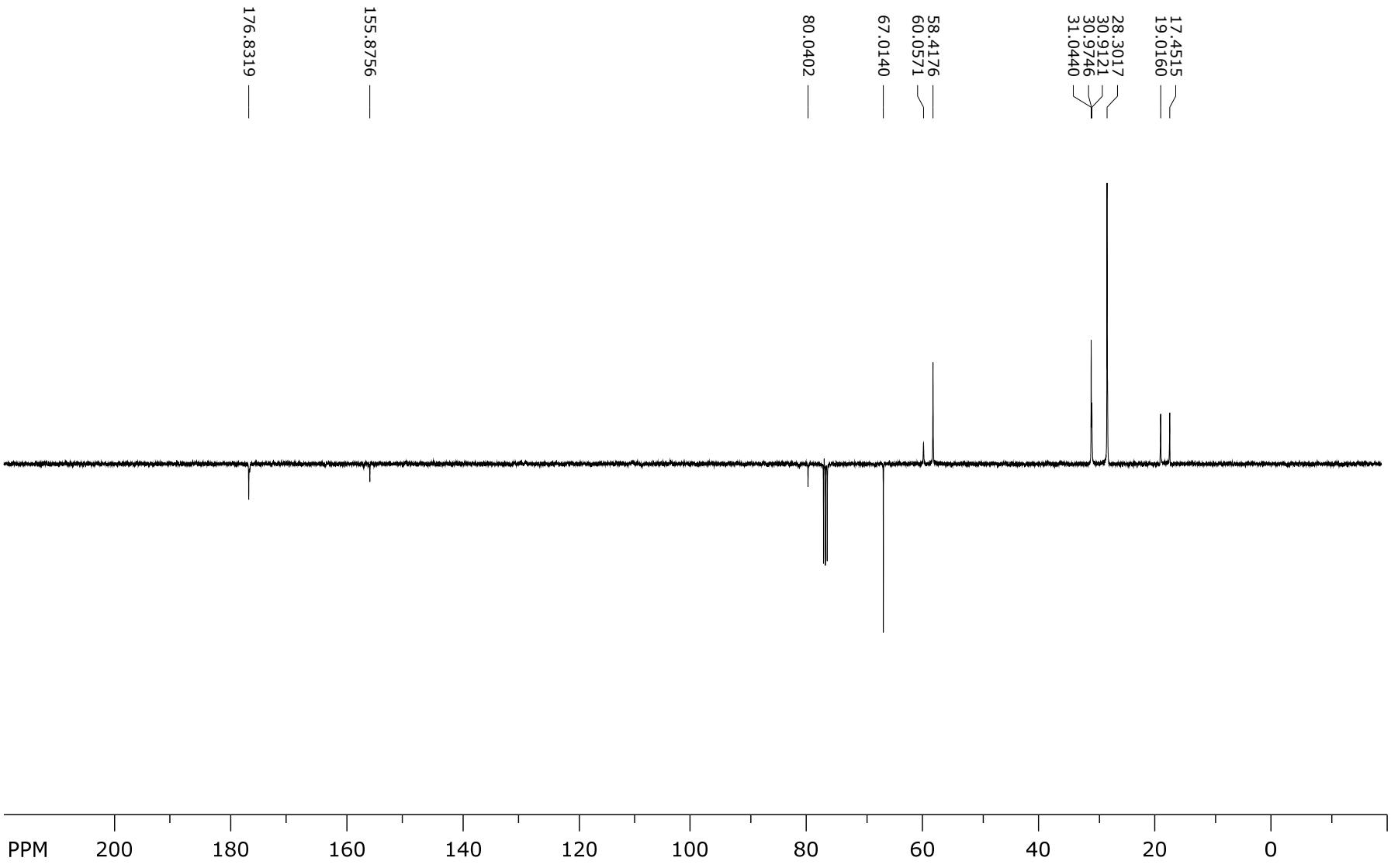
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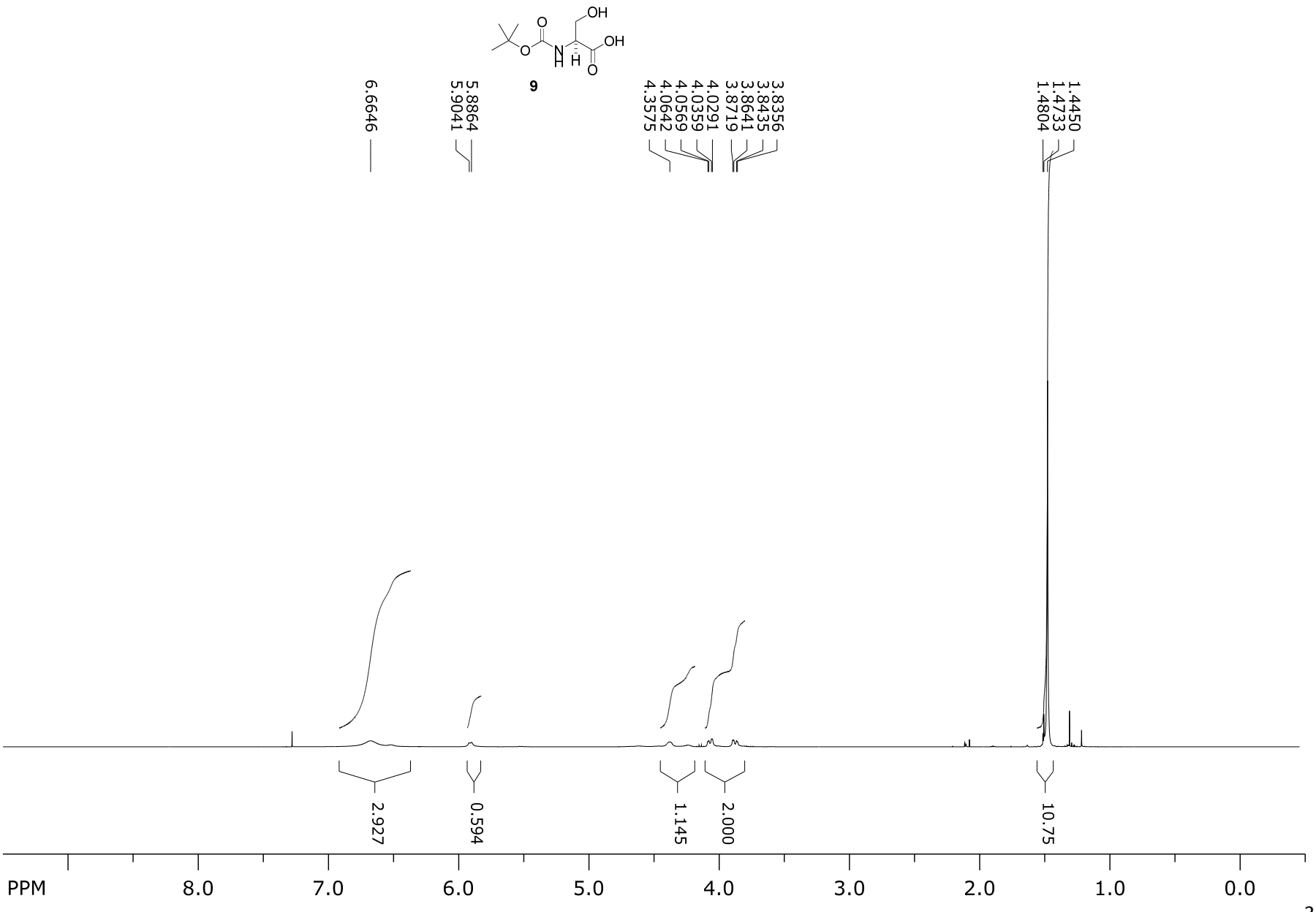
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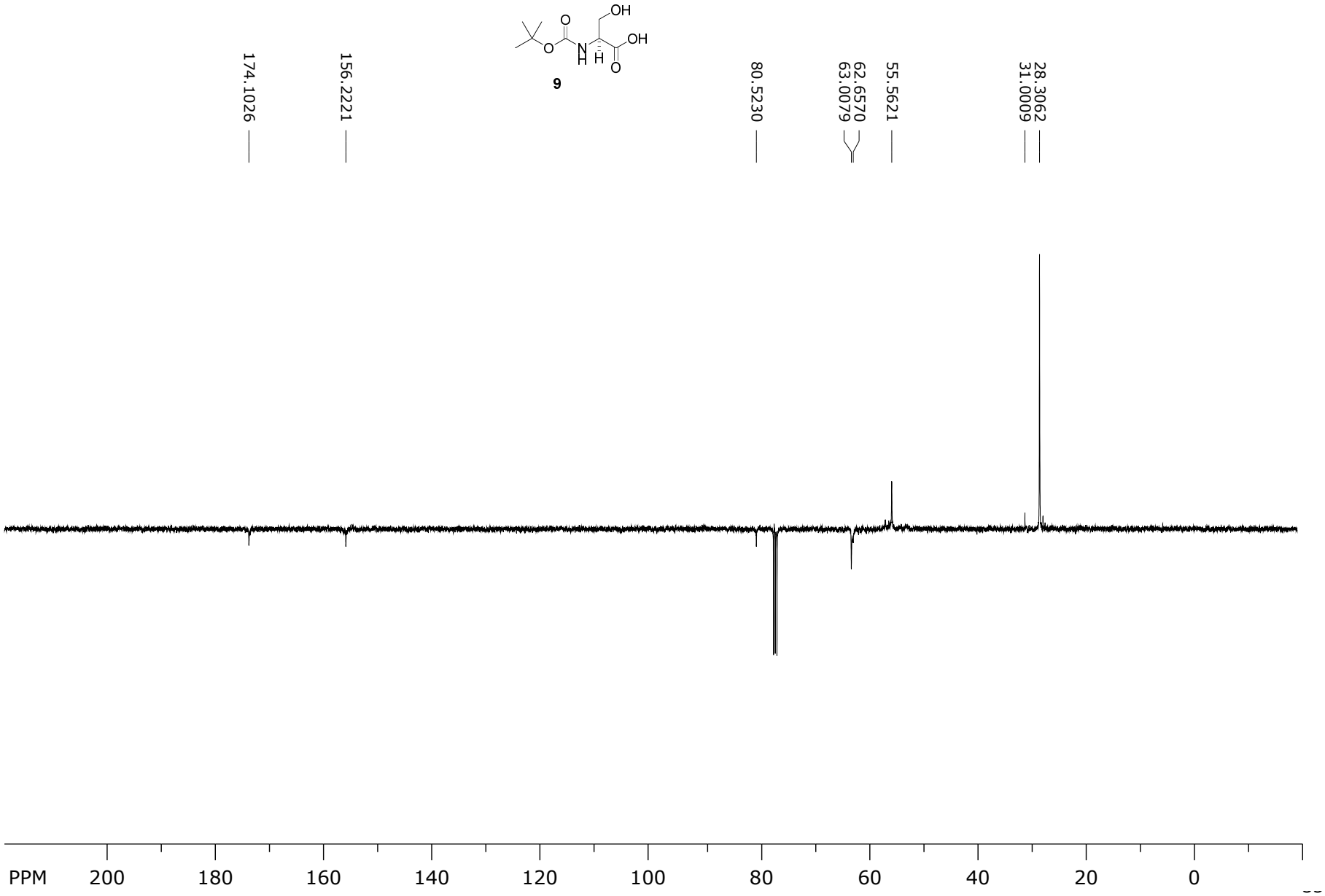
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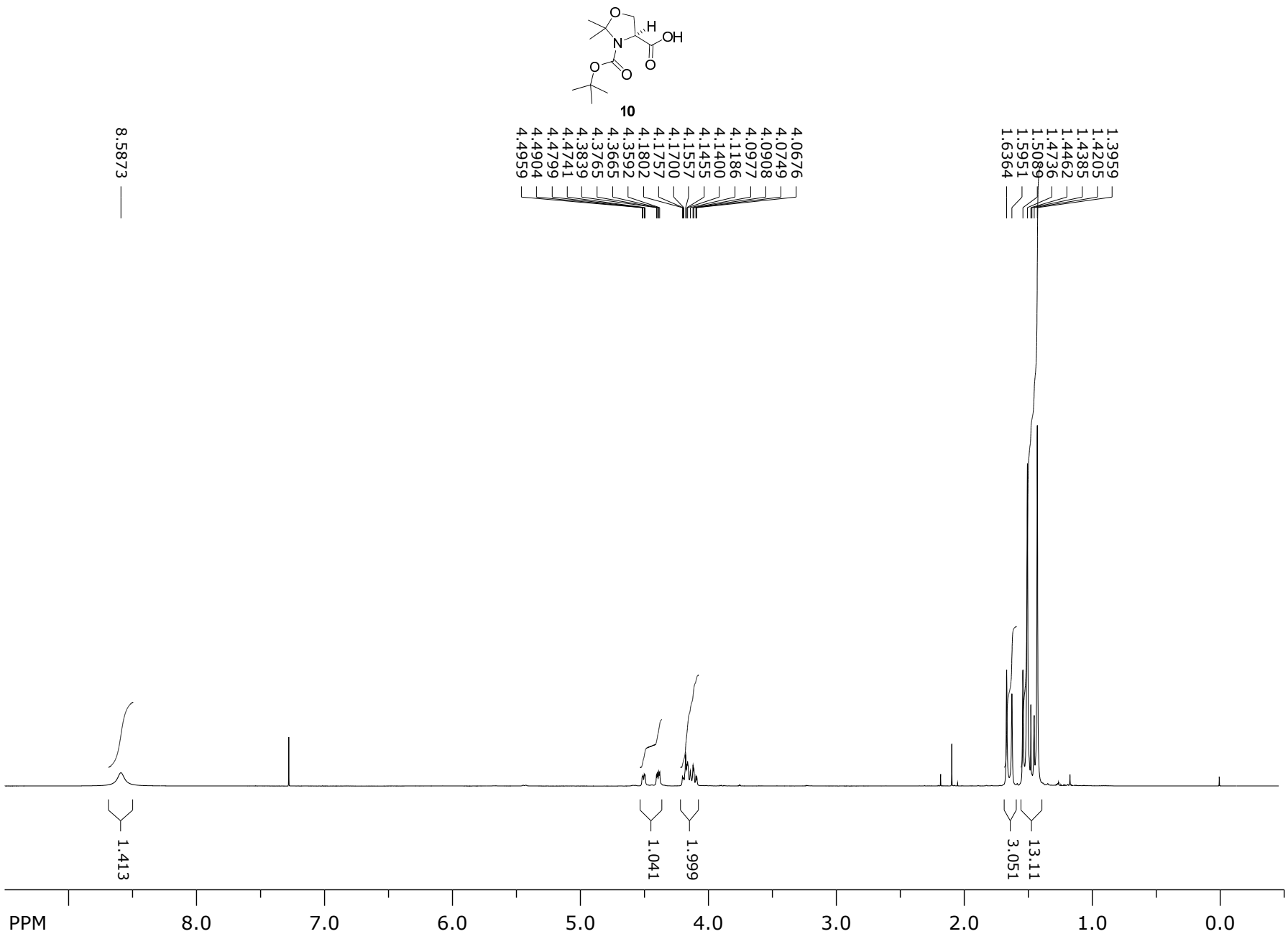
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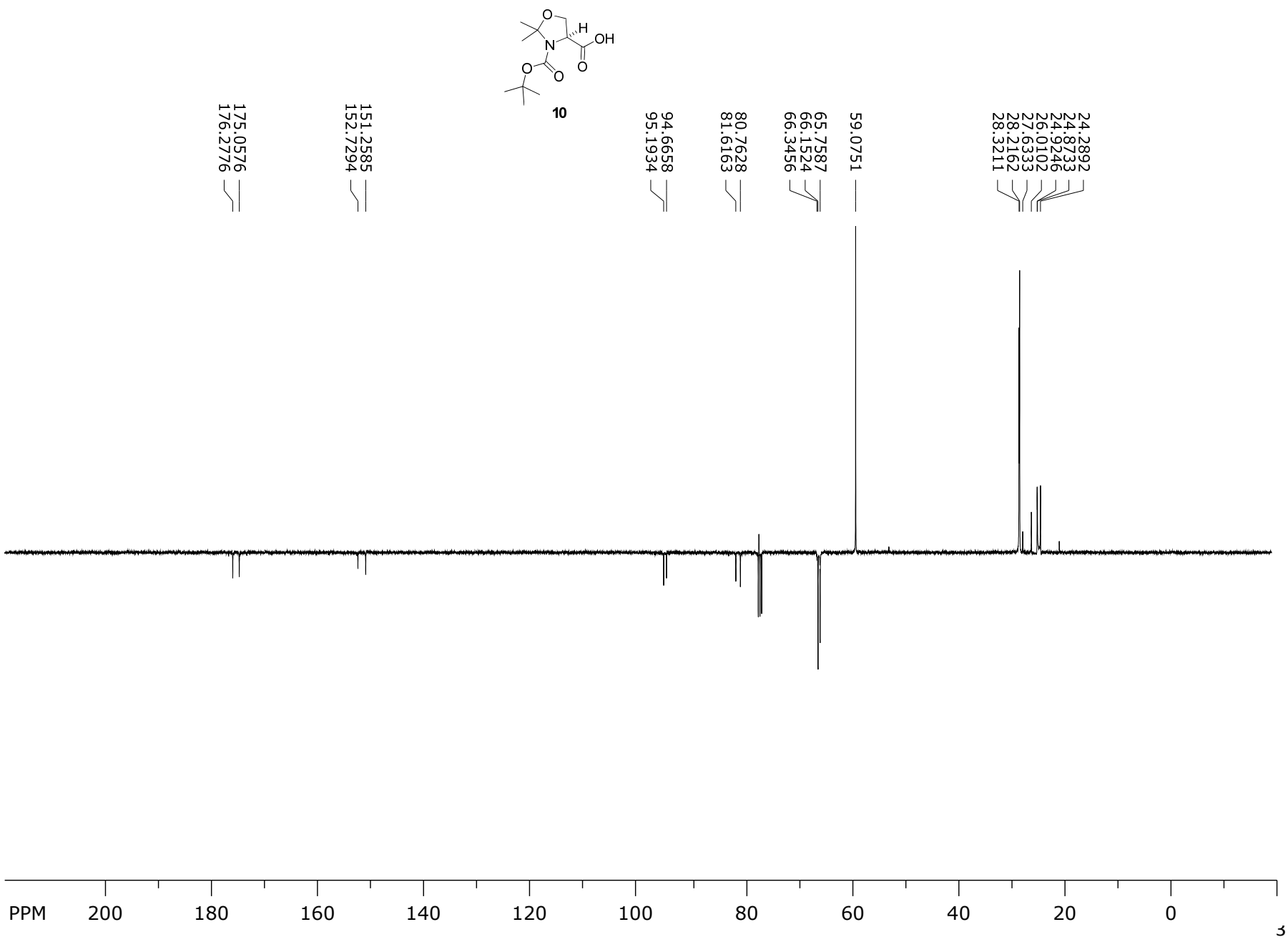
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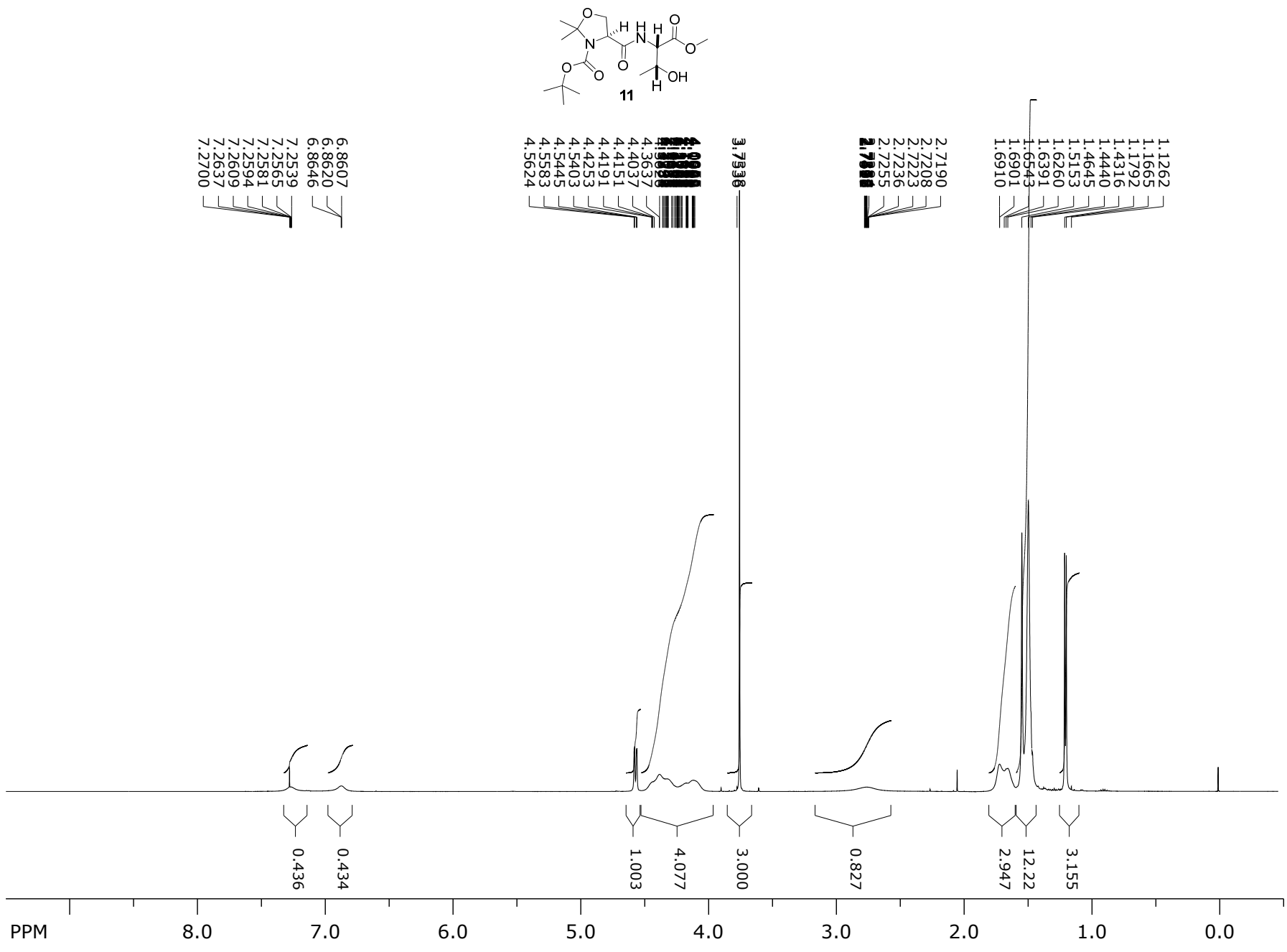
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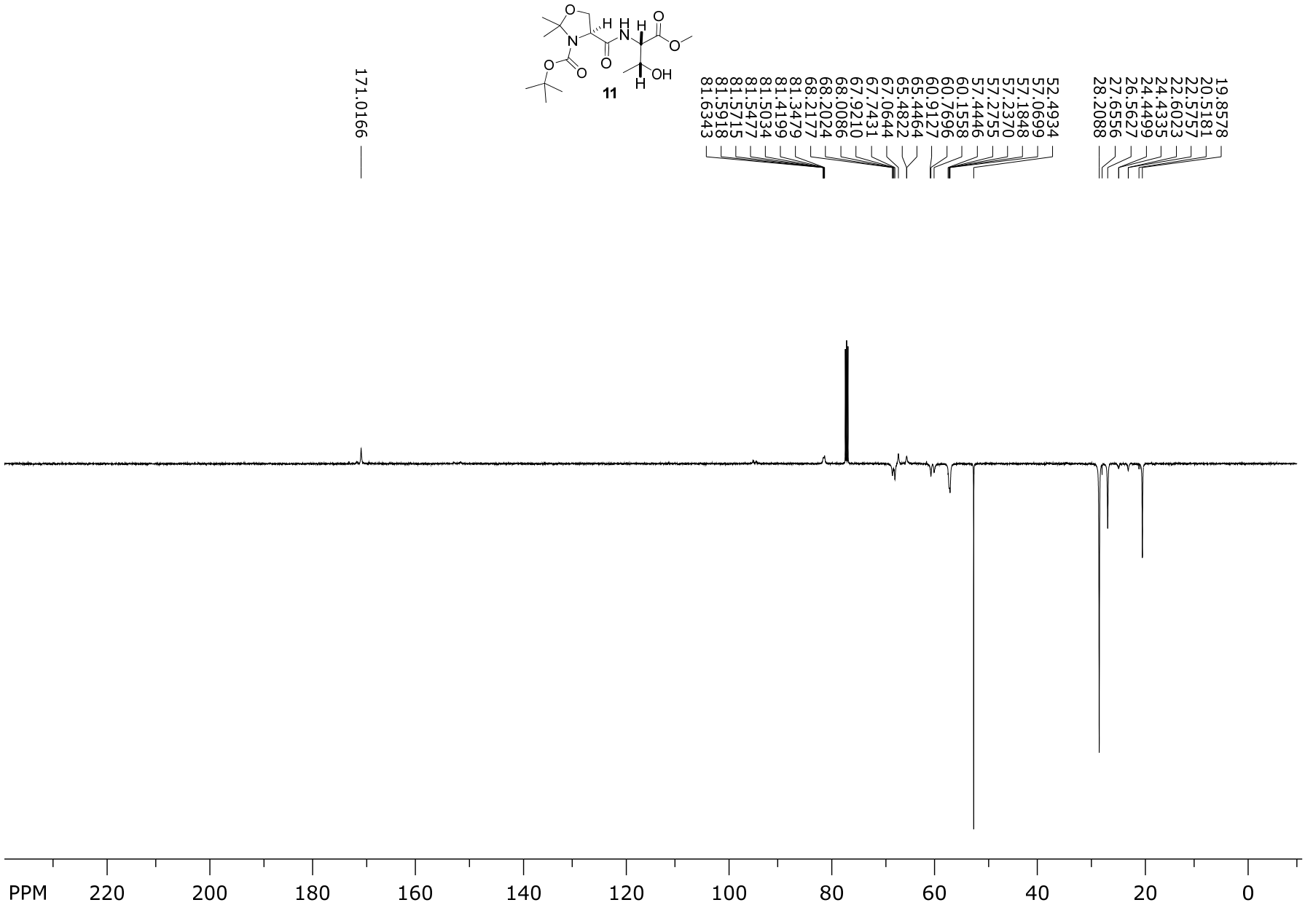
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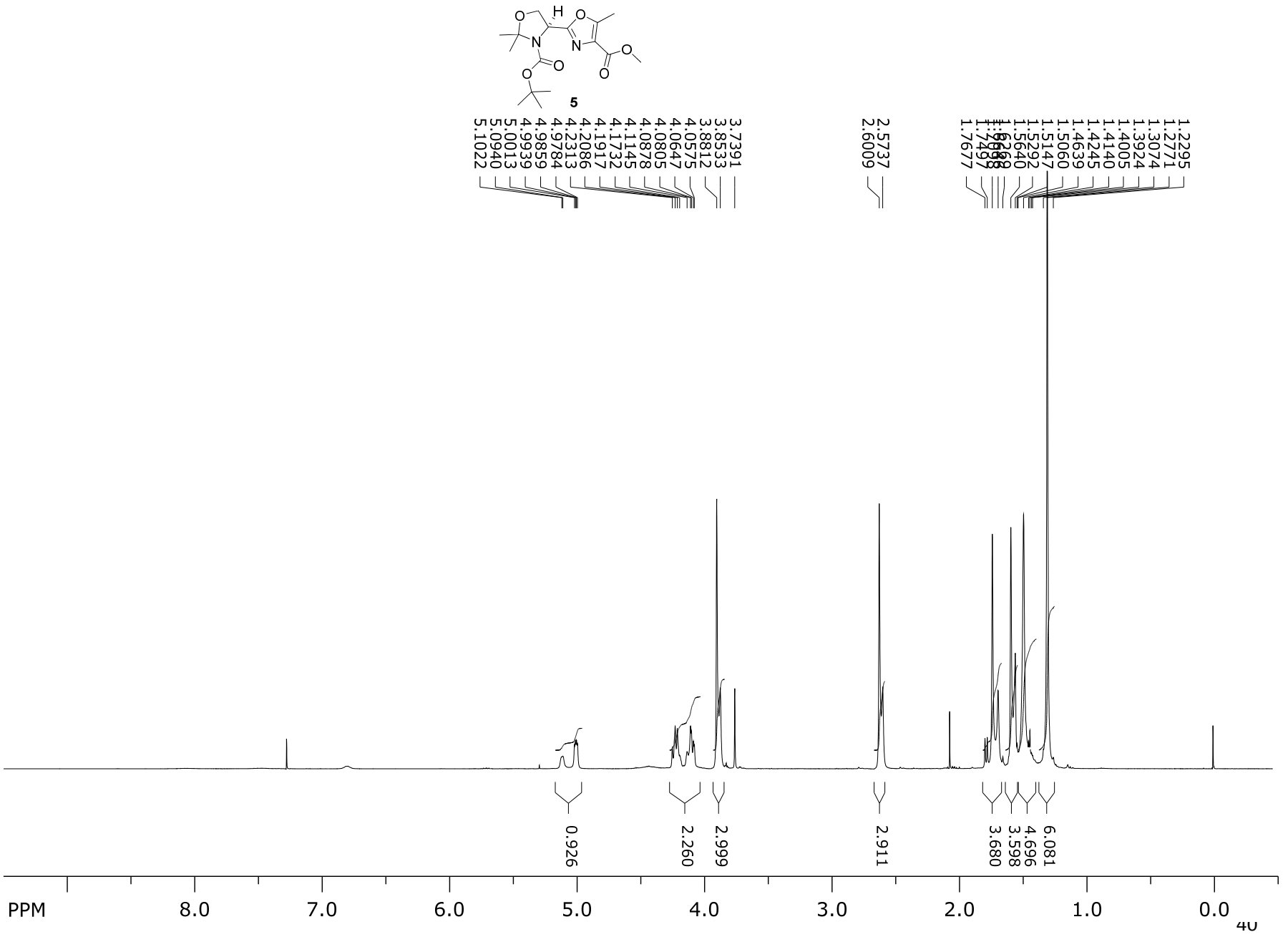
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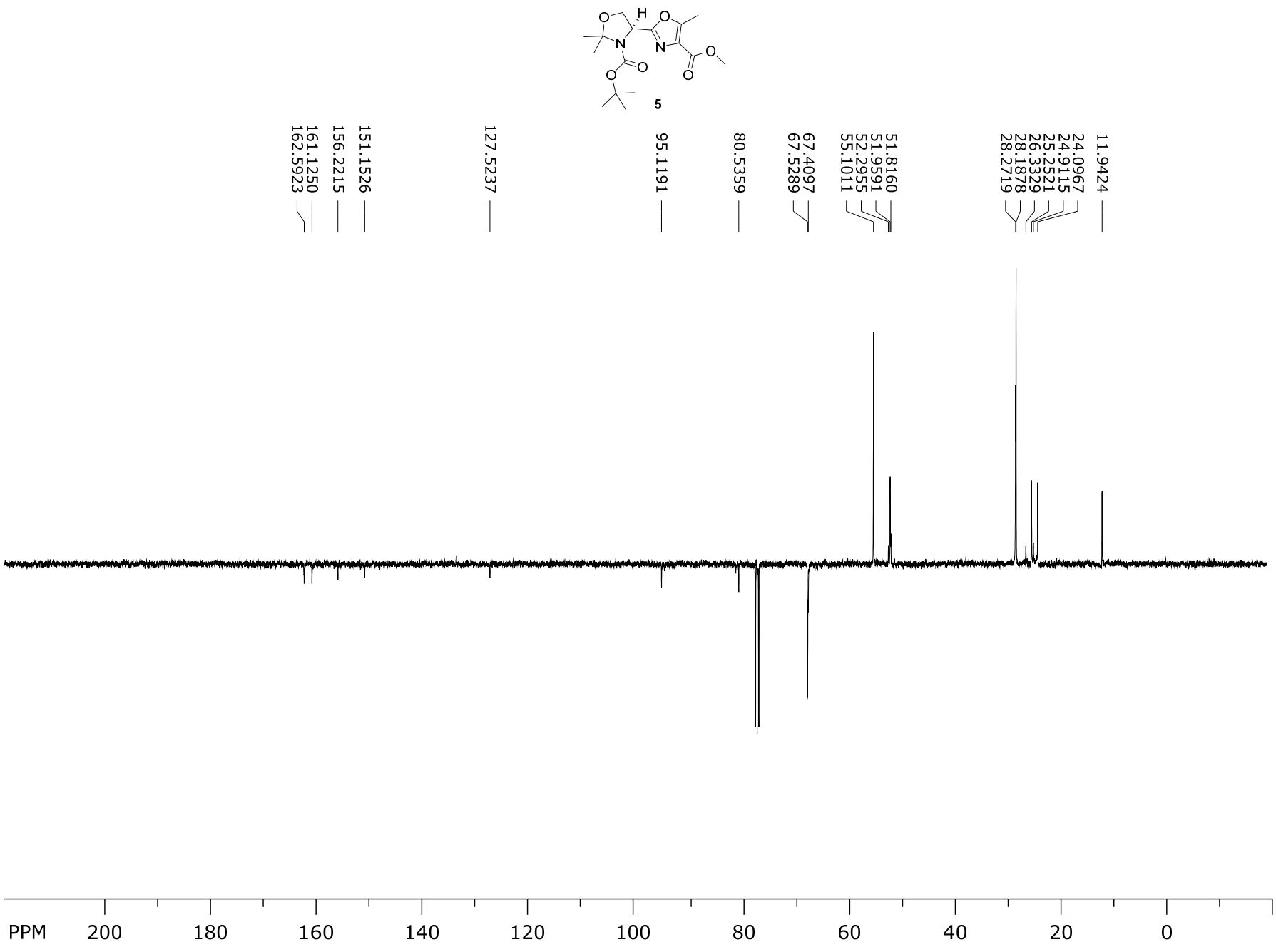
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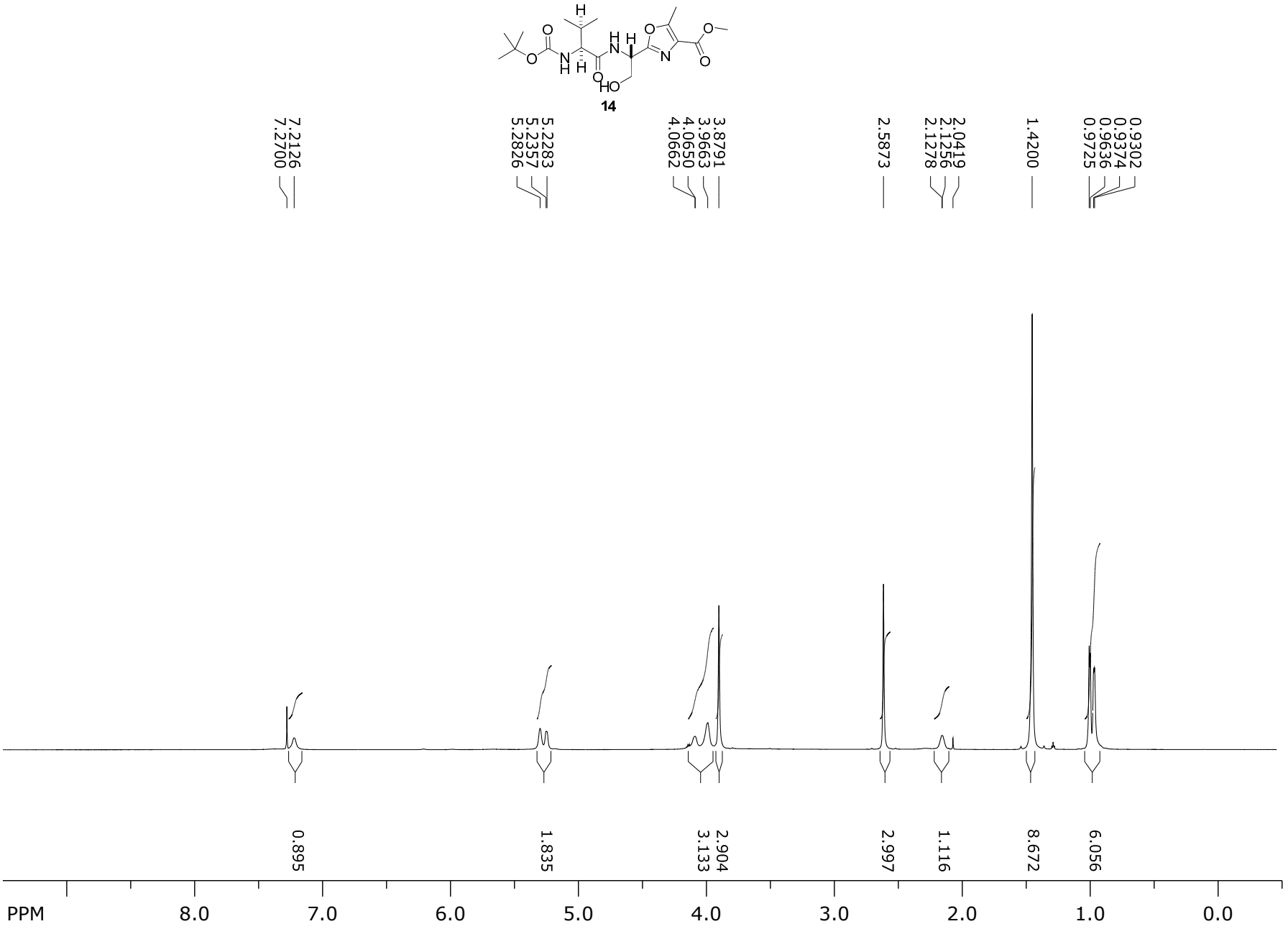
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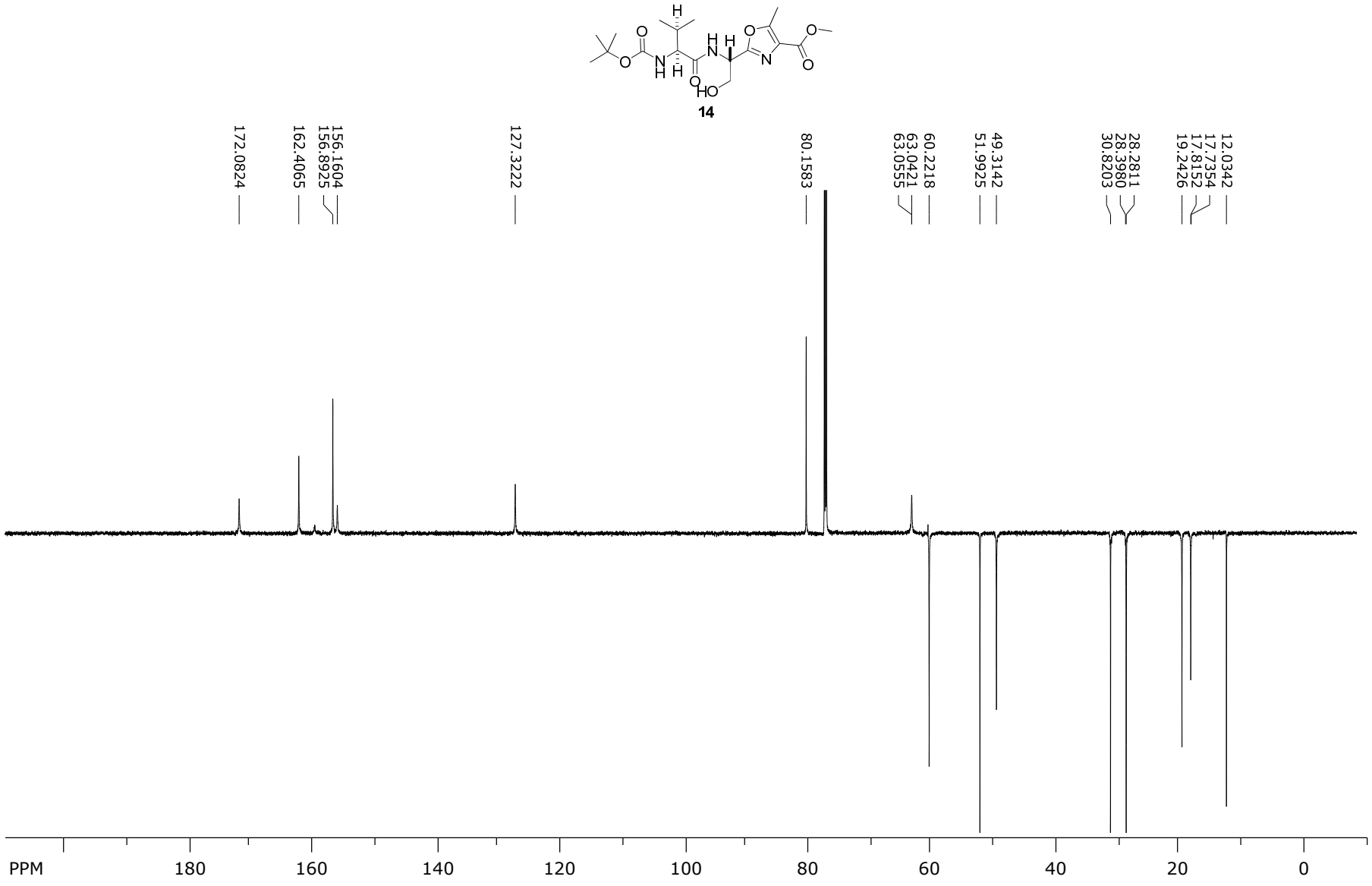
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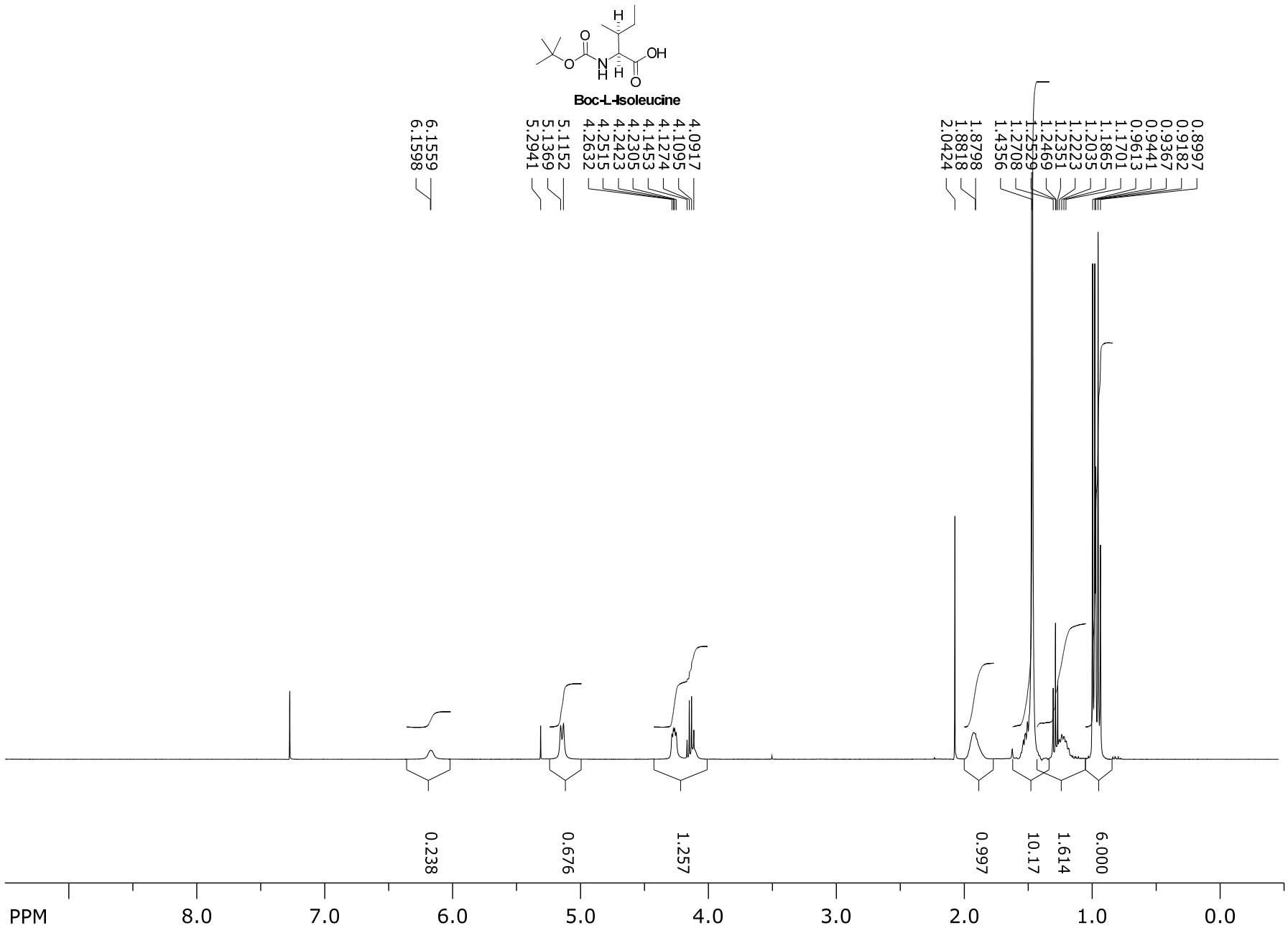
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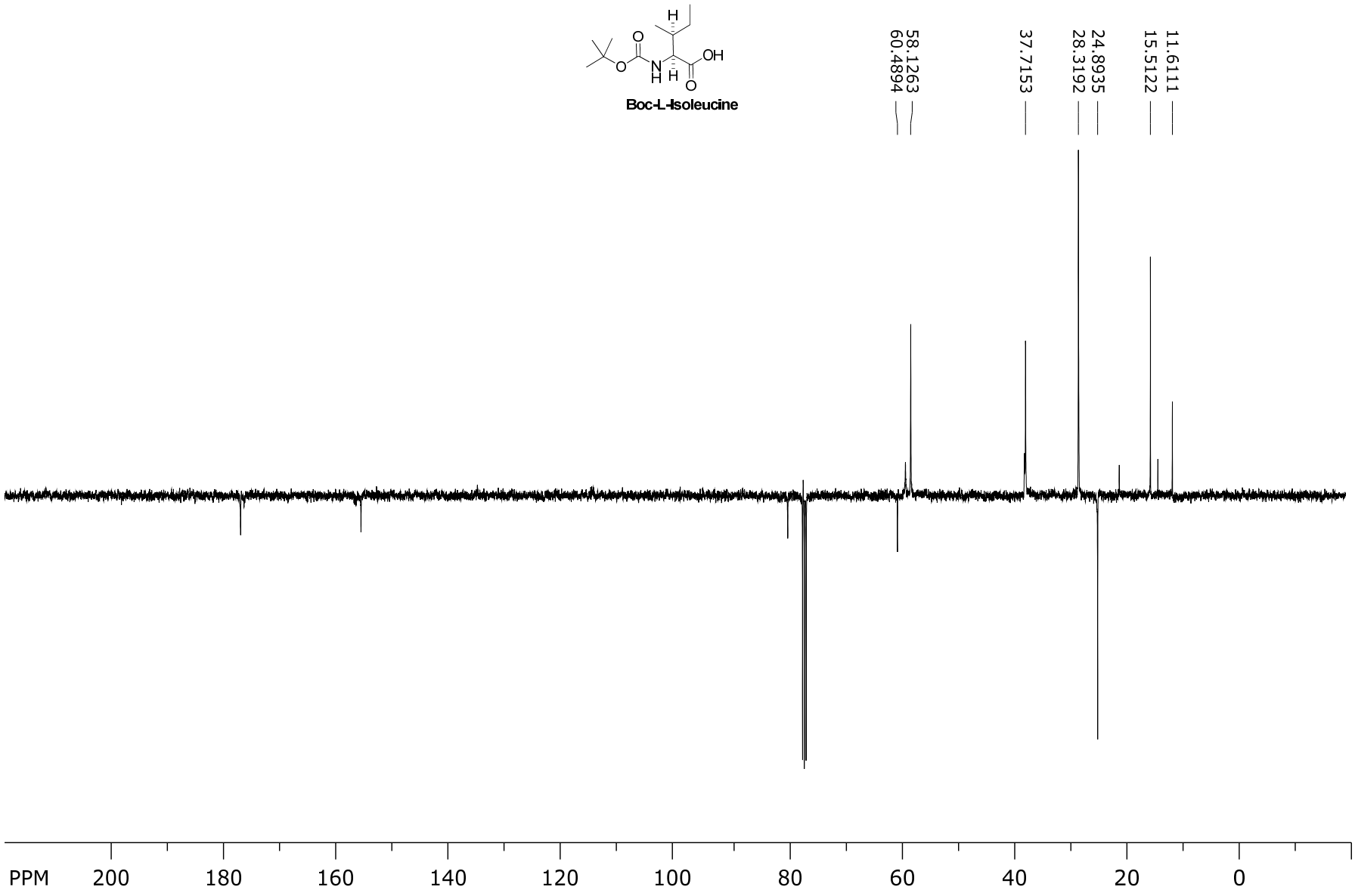
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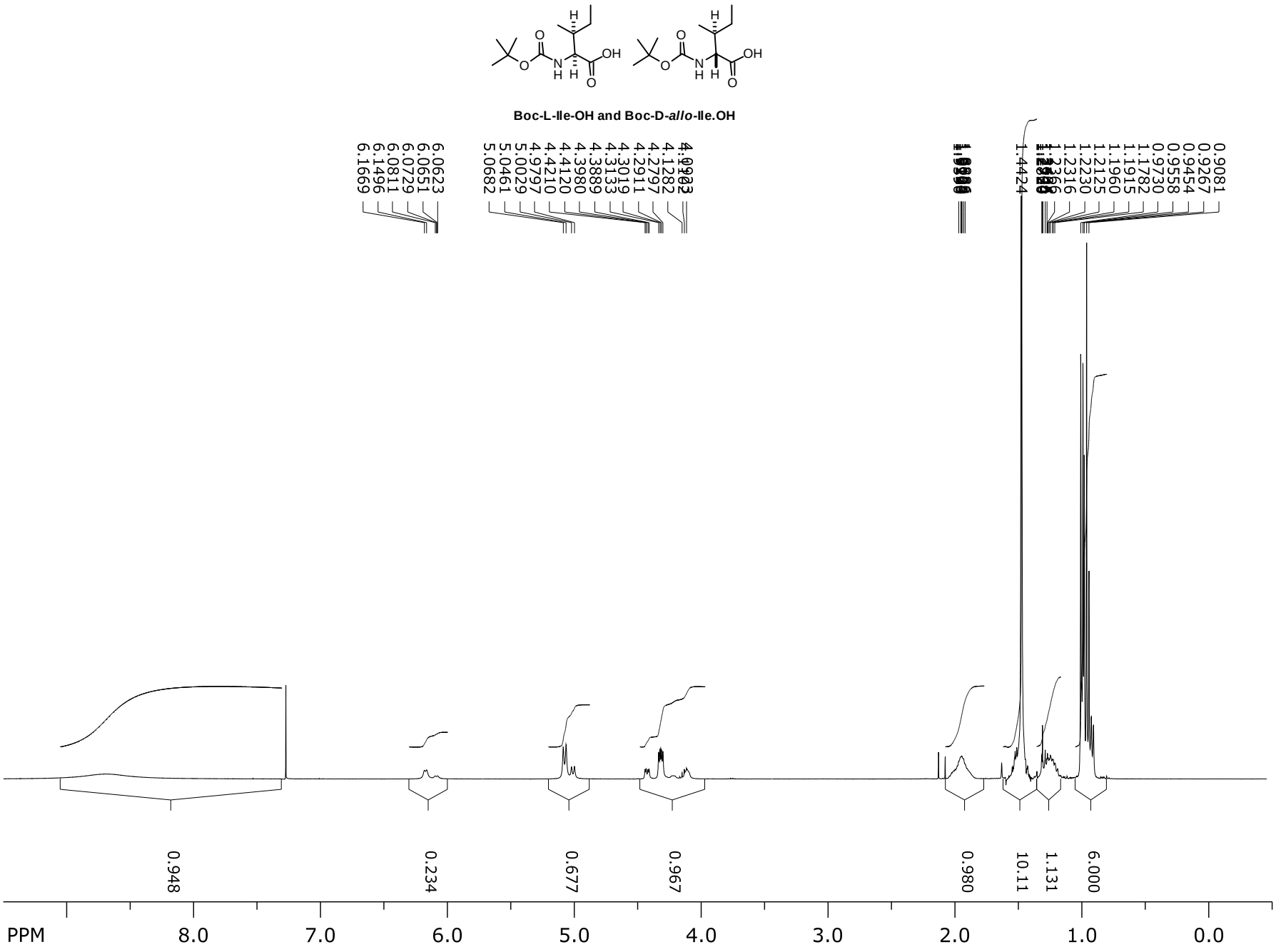
Boc-L-Ile-OH and Boc-D-allo-Ile.OH
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5.0461
5.0029
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4.2911
4.2797
4.1282
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1.2125
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1.1782
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0.980
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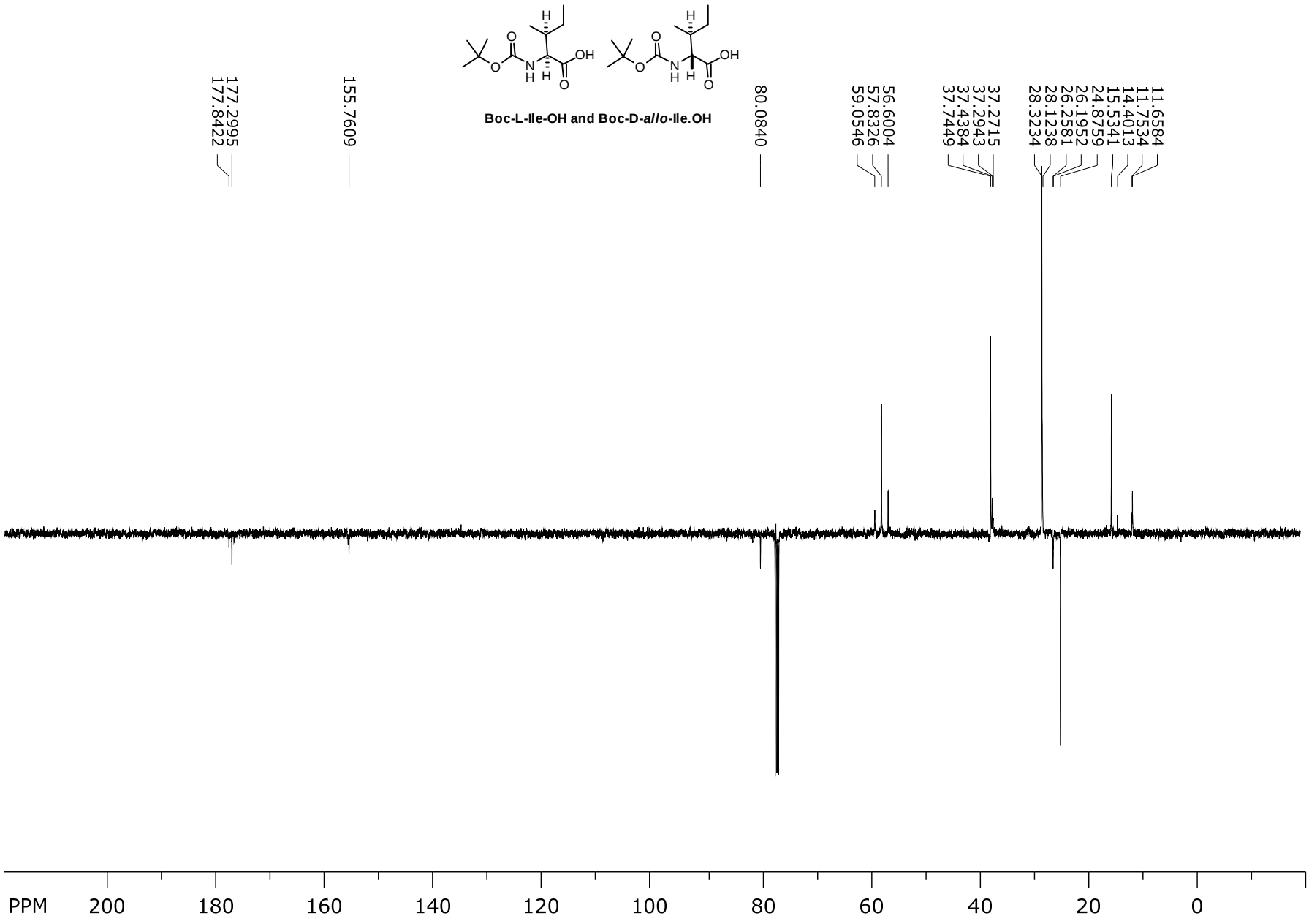
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56.6004
37.7449
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37.2943
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28.1238
26.2581
26.1952
24.8759
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PPM
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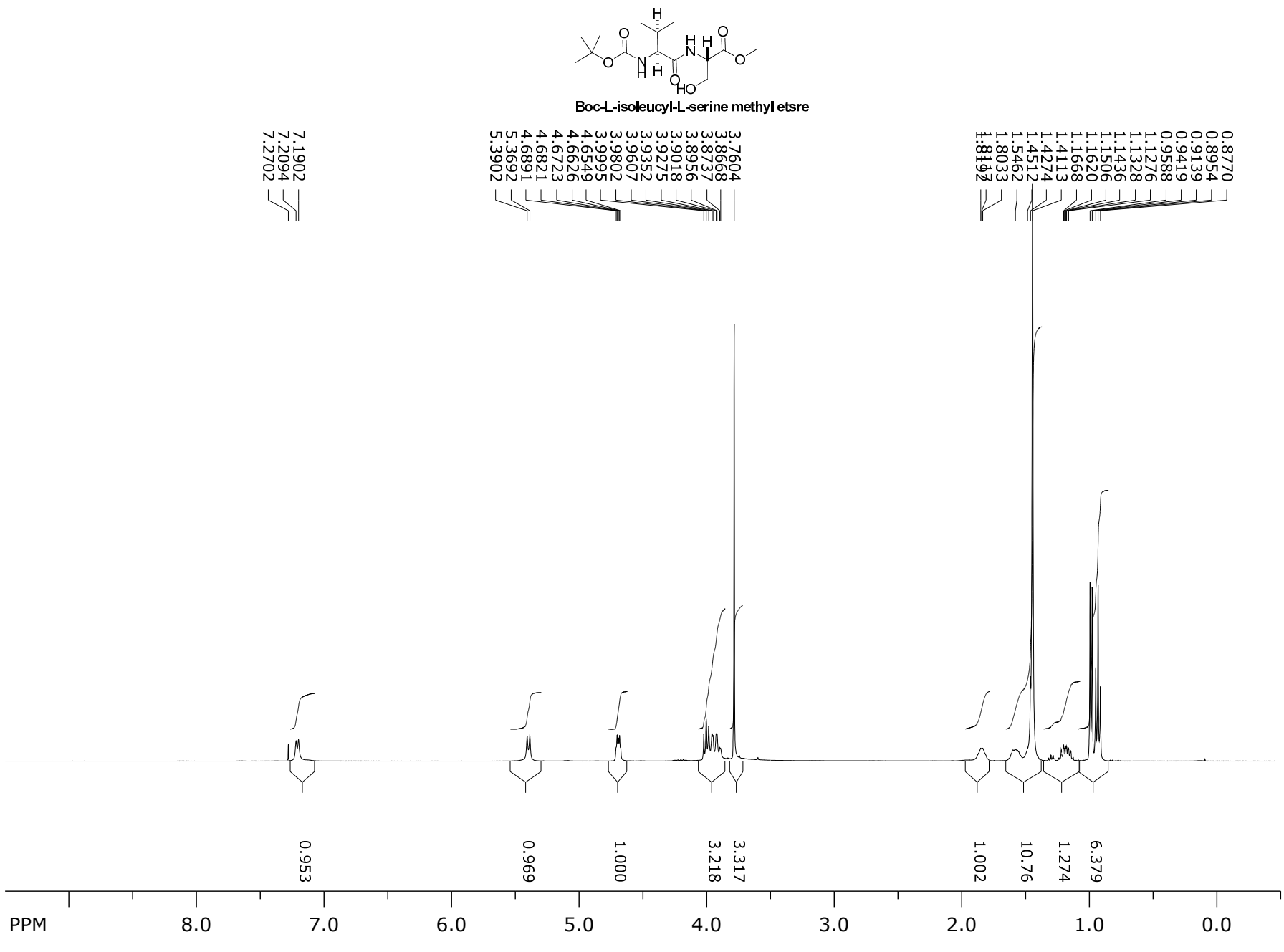
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4.6549
3.9995
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3.9275
3.9018
3.8956
3.8737
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3.7604
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1.5462
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1.4274
1.4113
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1.1506
1.1436
1.1328
1.1276
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0.8954
0.8770
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10.76
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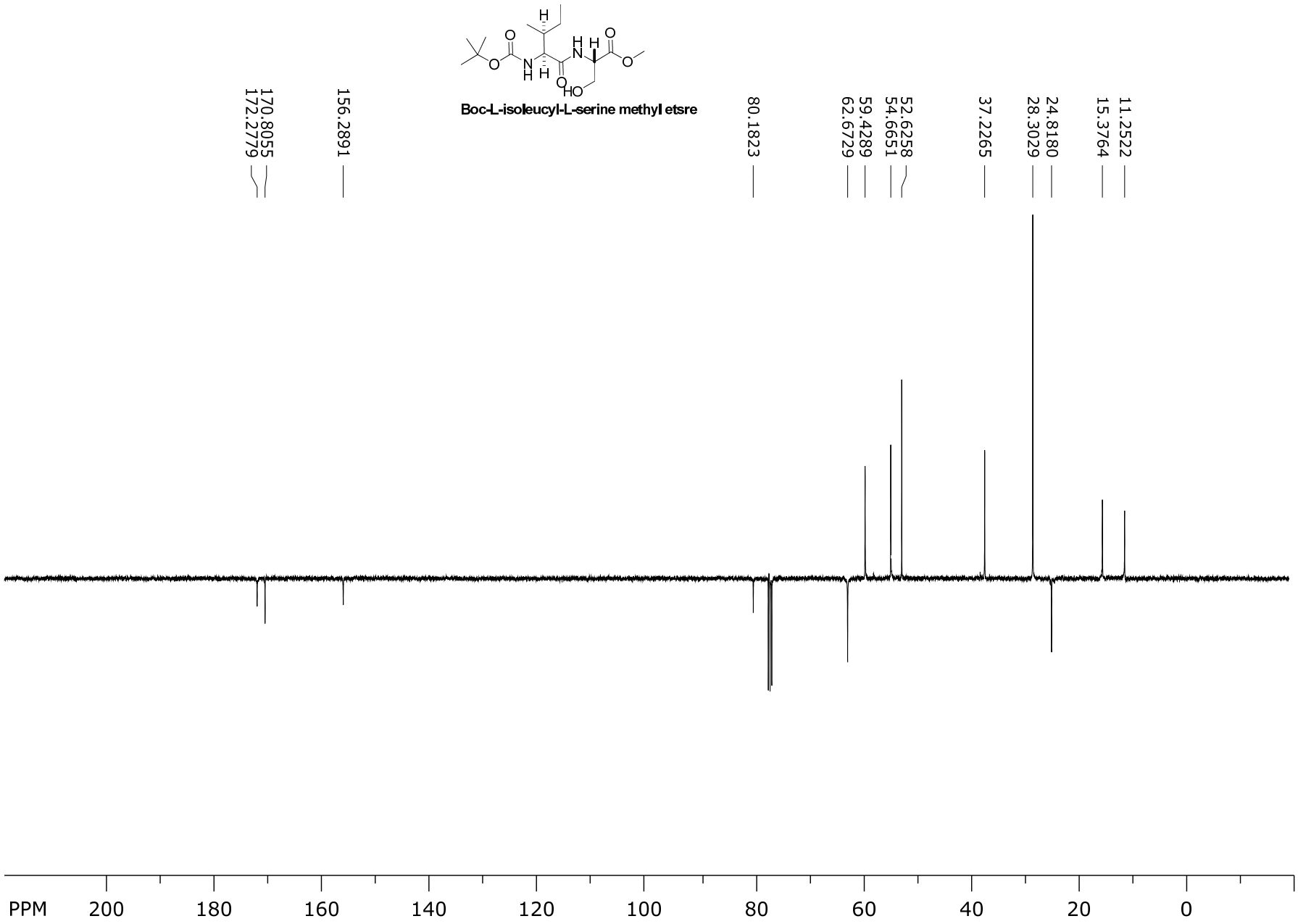
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37.2265
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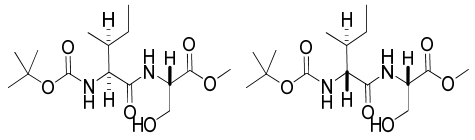

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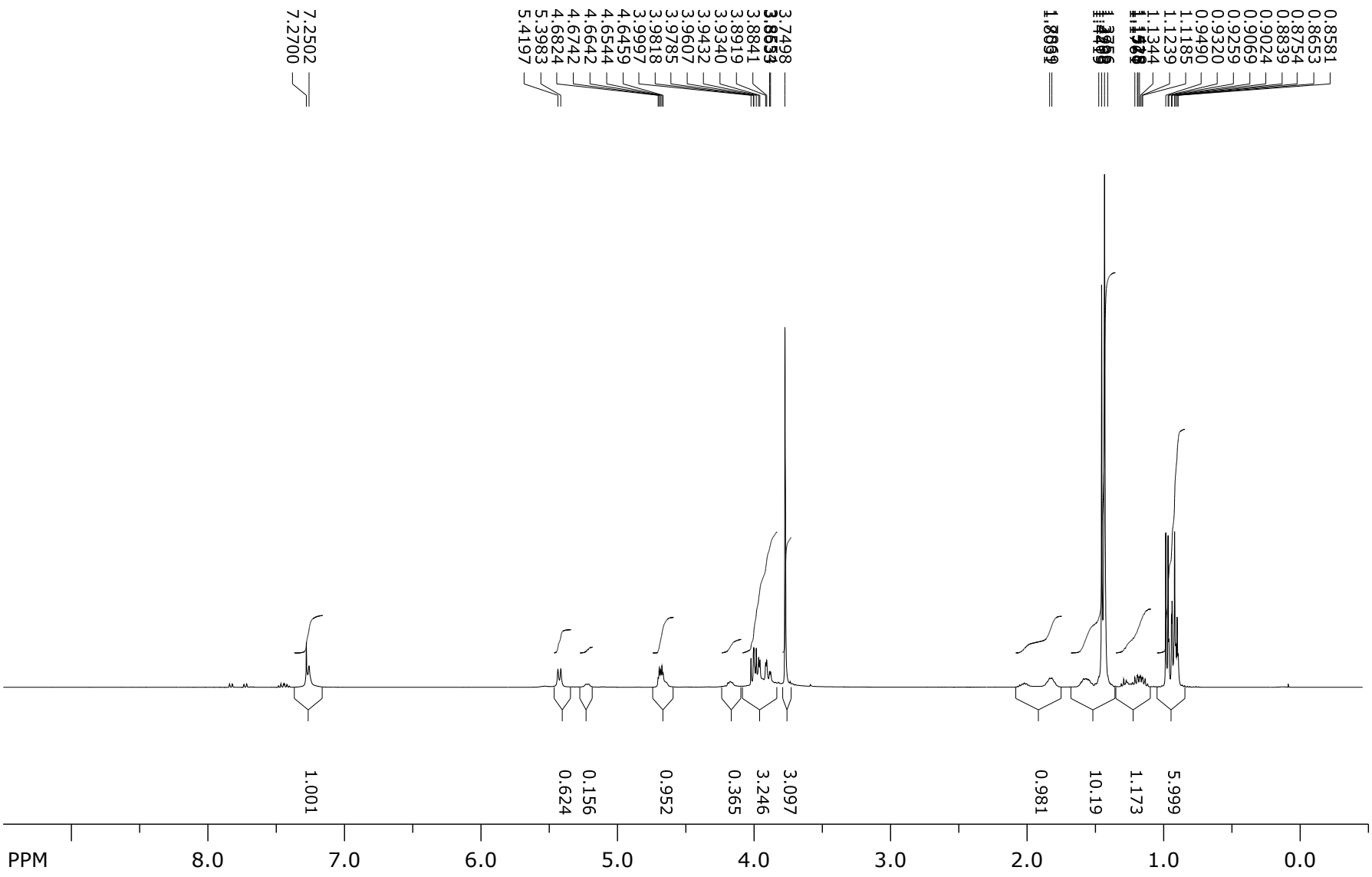

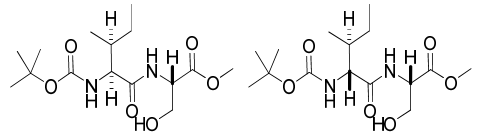

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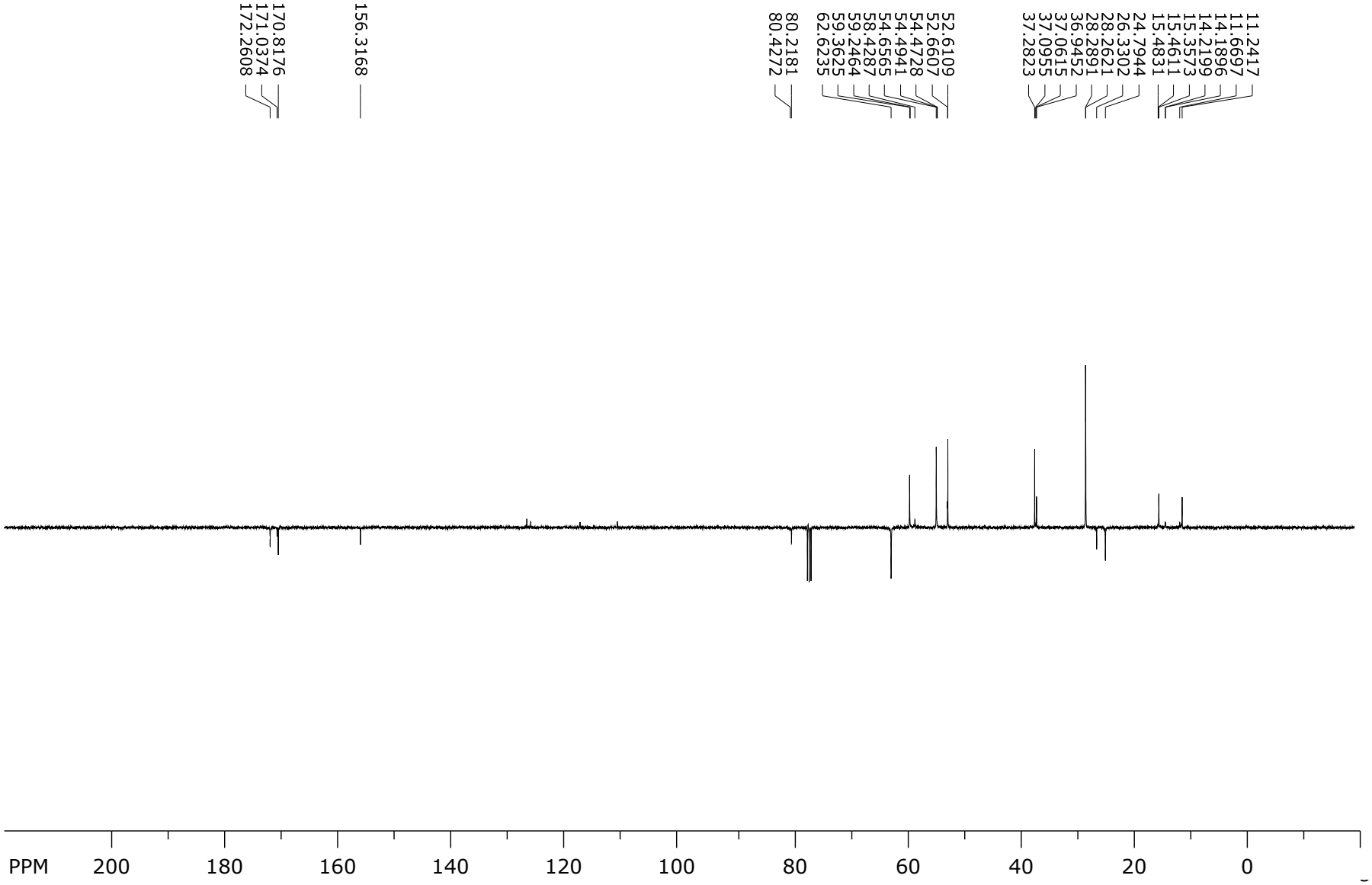

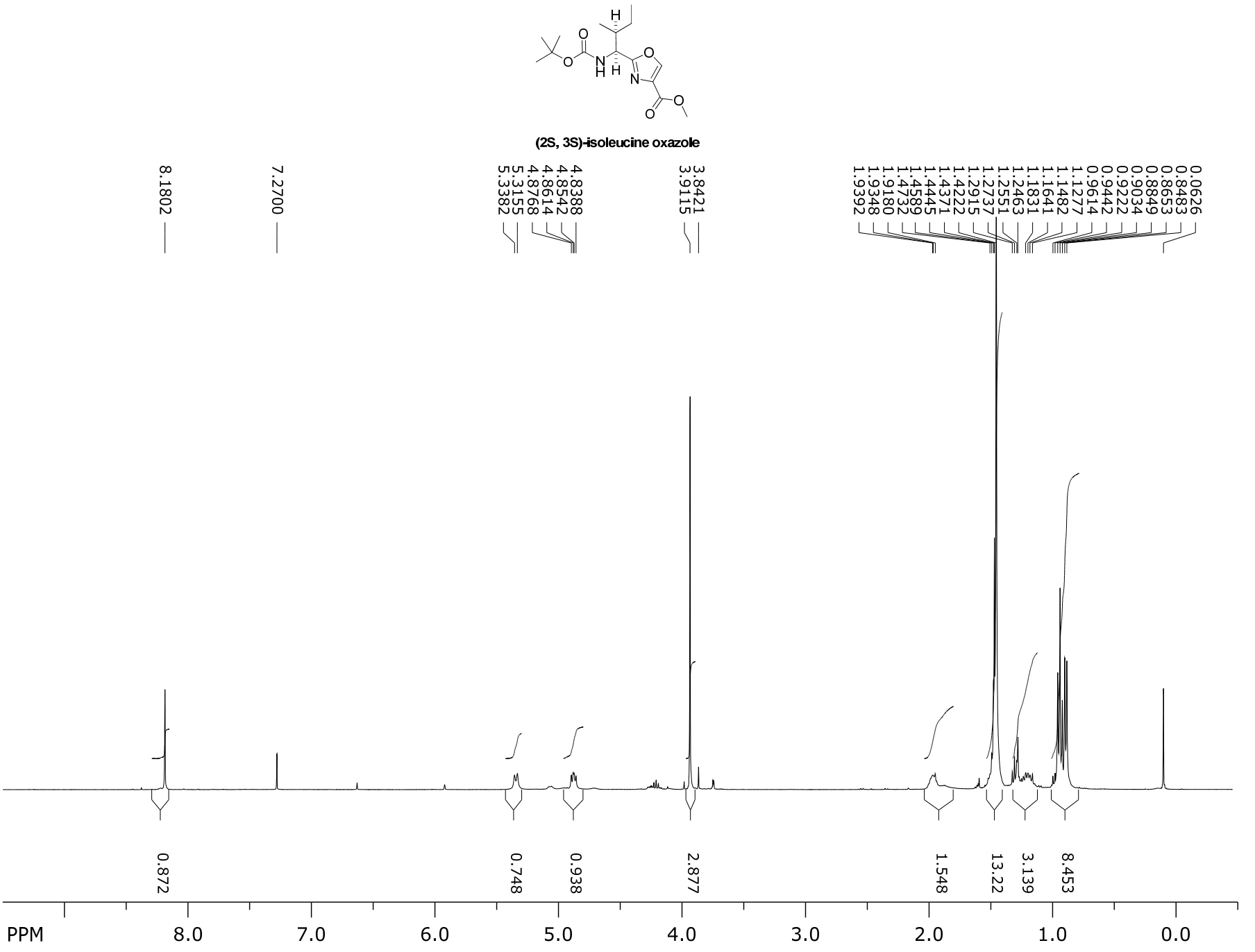
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5.3155
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4.8614
4.8542
4.8388
3.9115
3.8421
1.9392
1.9348
1.9180
1.4732
1.4589
1.4445
1.4371
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1.2737
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1.1831
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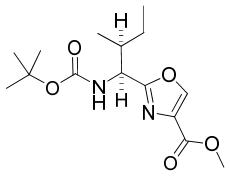
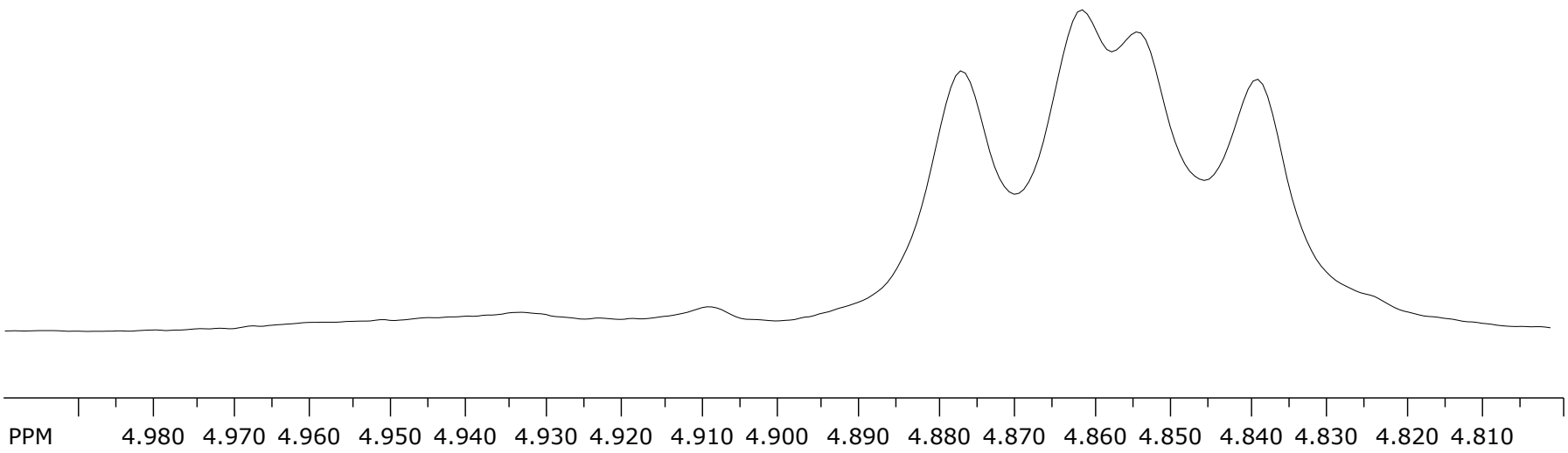
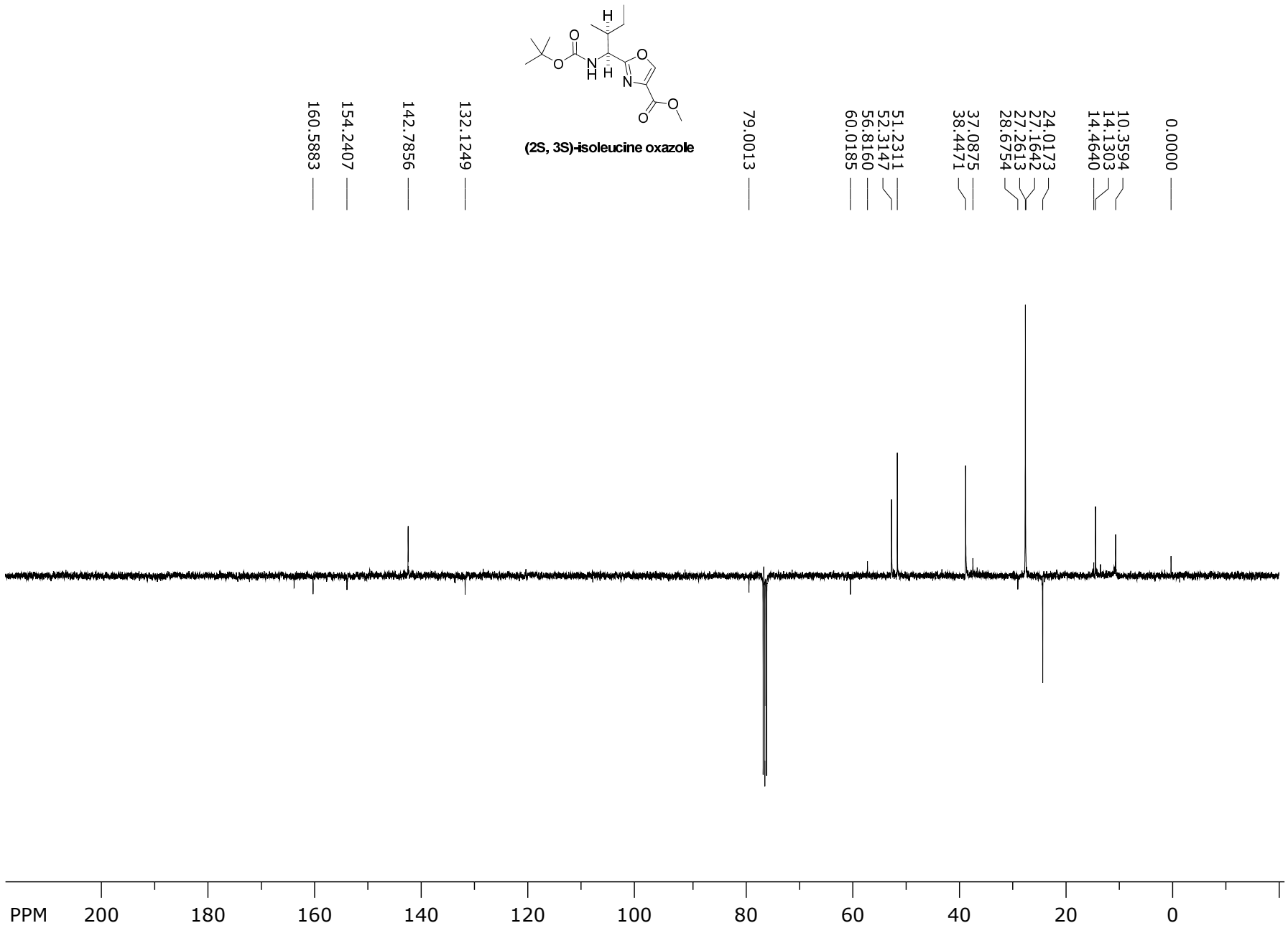


(2S, 3S)-isoleucine oxazole

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51.2311
38.4471
37.0875
28.6754
27.2613
27.1642
24.0173
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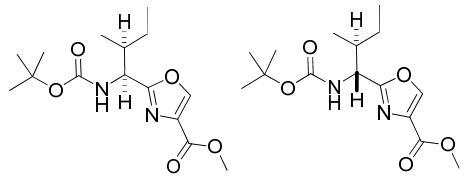
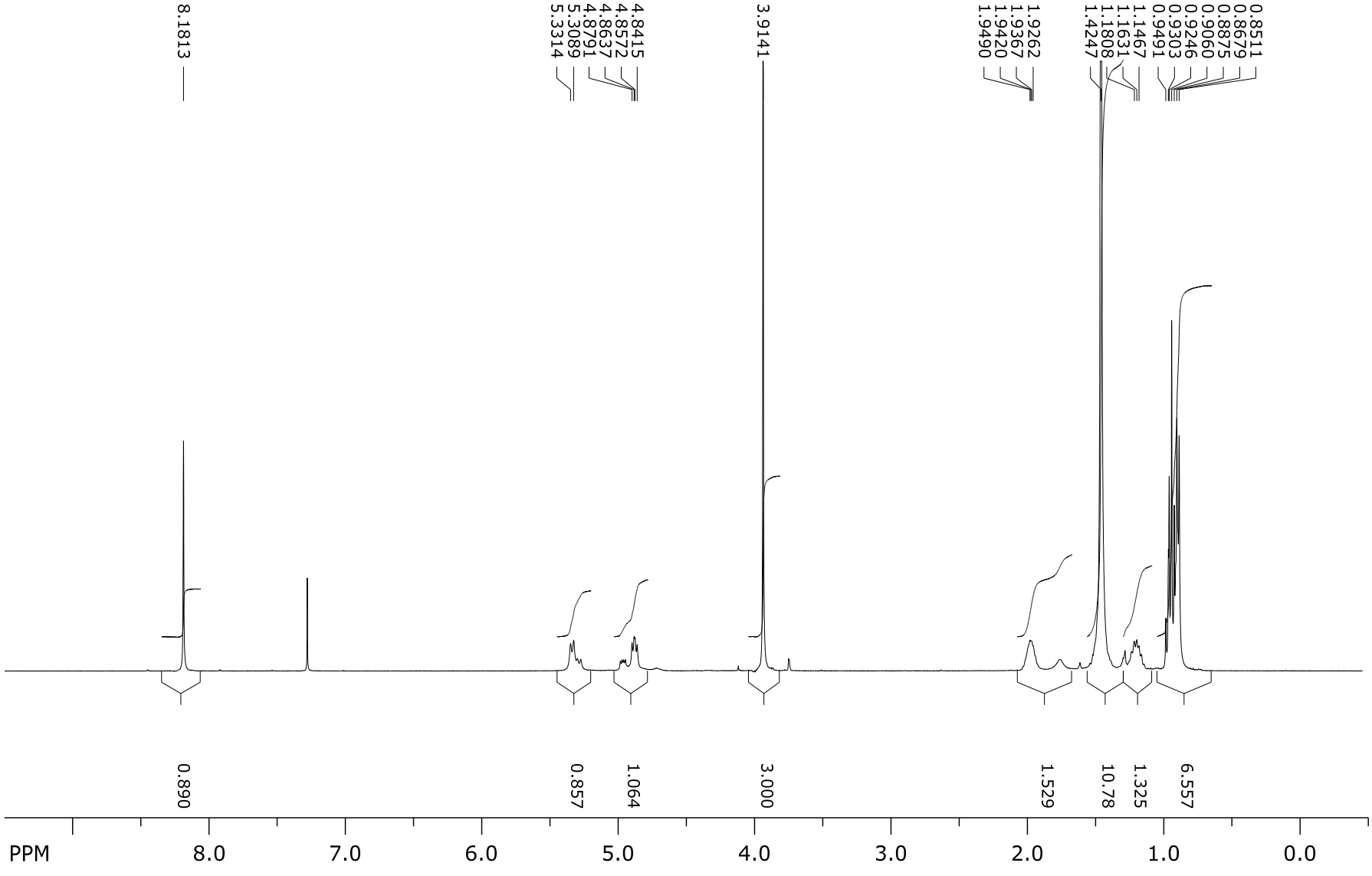
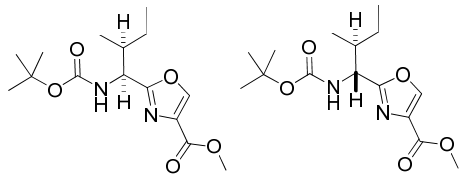
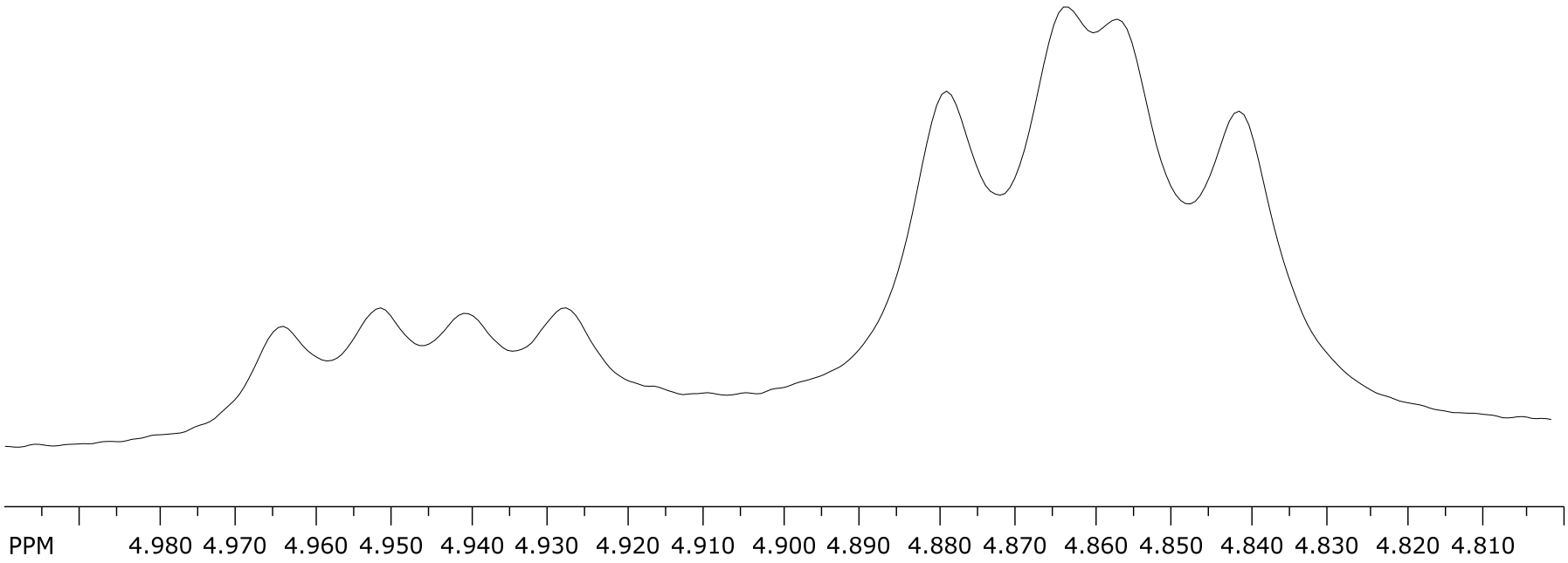


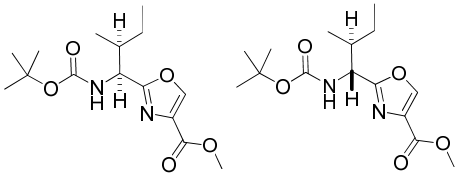
(2S, 3S)-isoleucine oxazole and (2R, 3S)-isoleucine oxazole



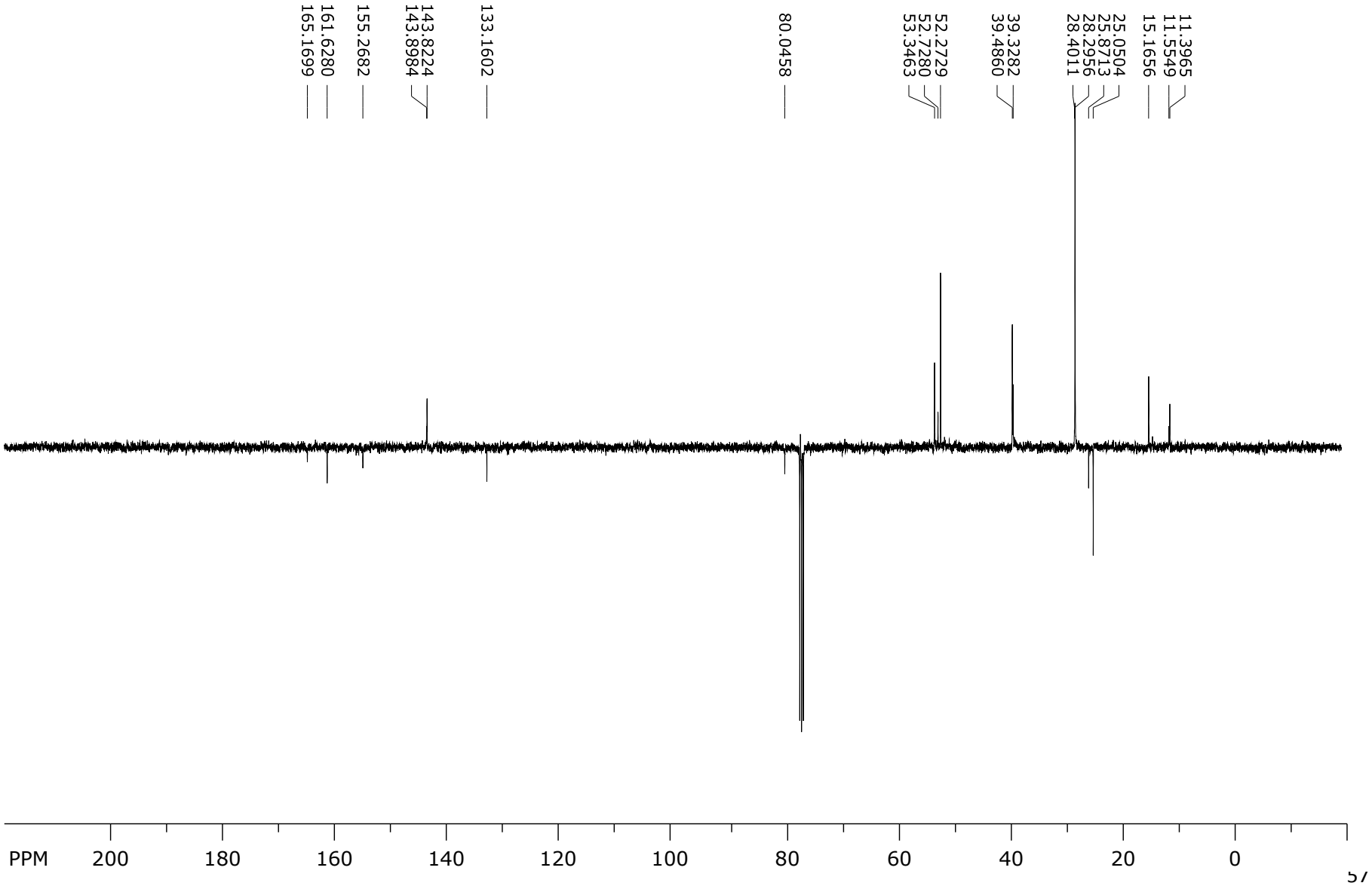


(2S, 3S)-isoleucine oxazole and (2R, 3S)-isoleucine oxazole





(2S, 3S)-isoleucine oxazole and (2R, 3S)-isoleucine oxazole



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0.9174
0.9030
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1.003
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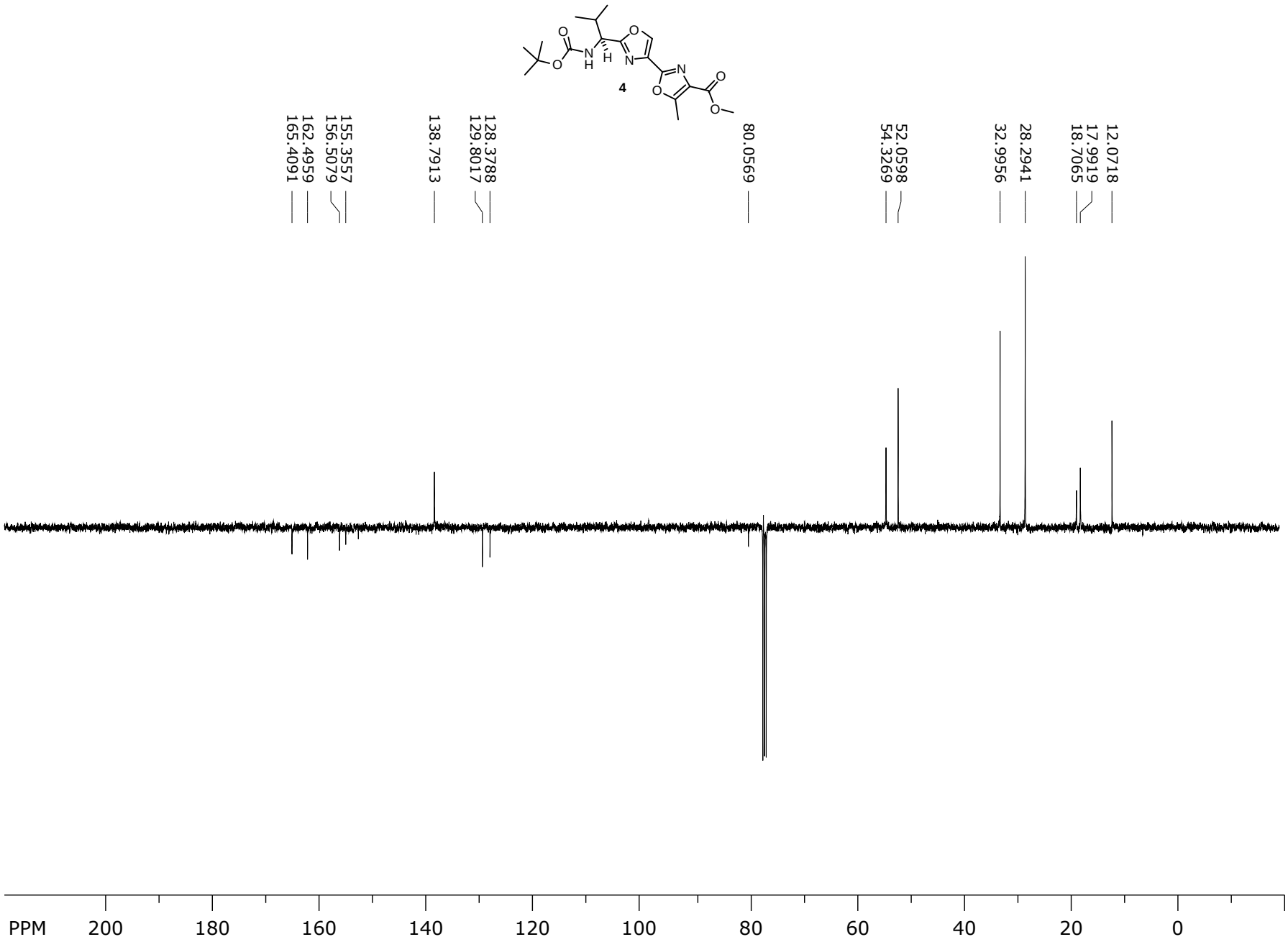
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32.9956
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PPM
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140
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20
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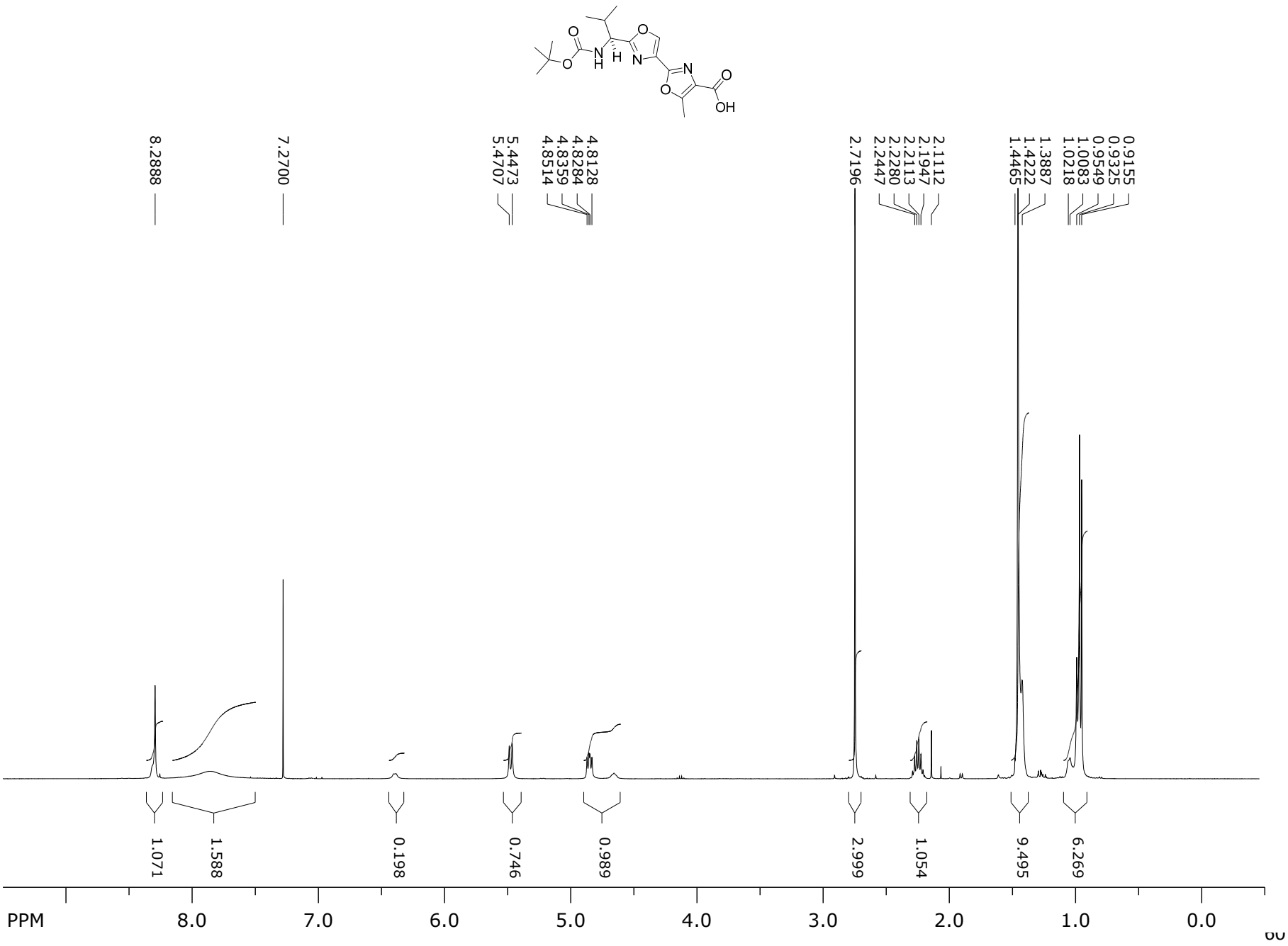
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2.1112
1.4465
1.4222
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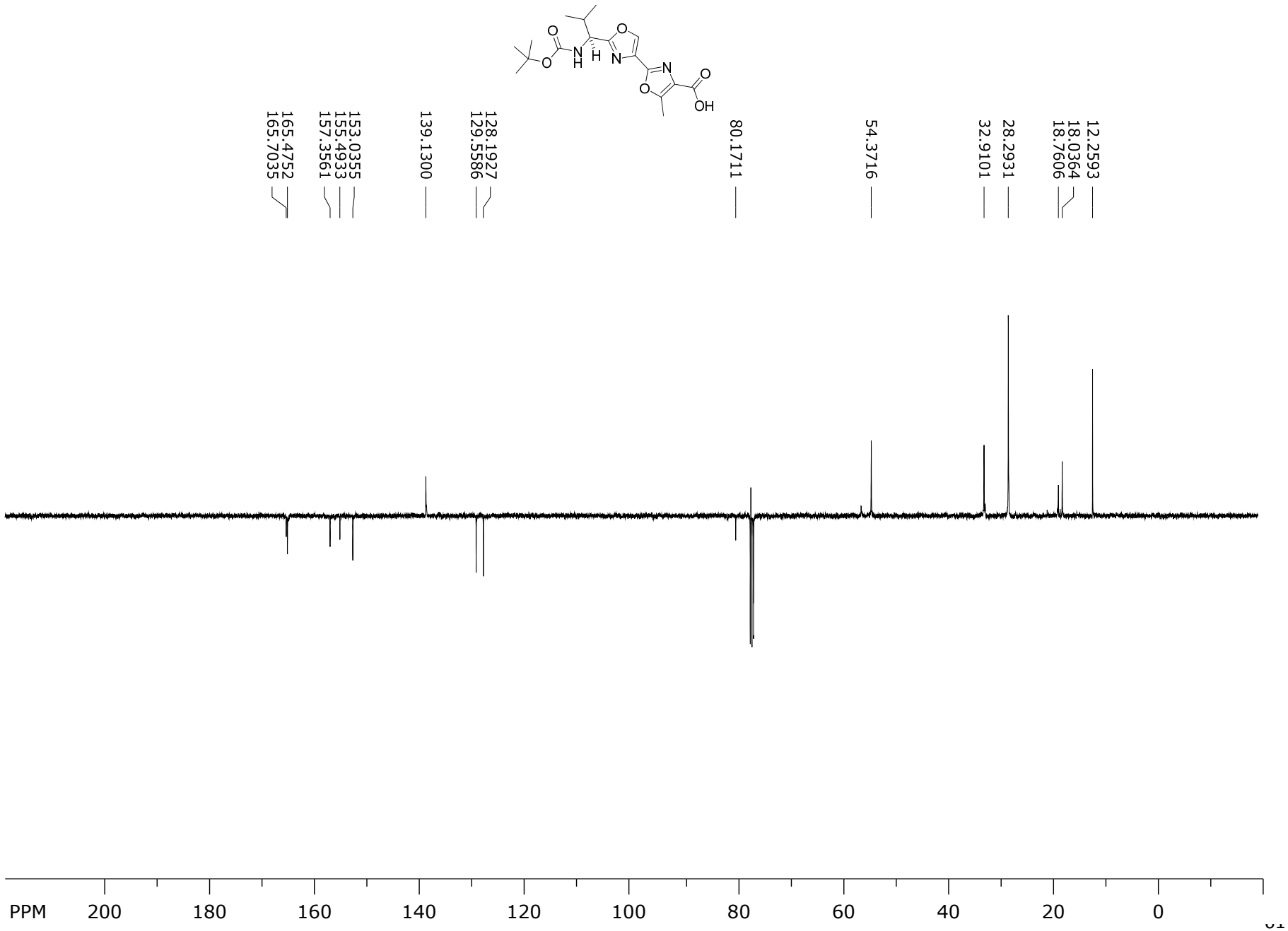
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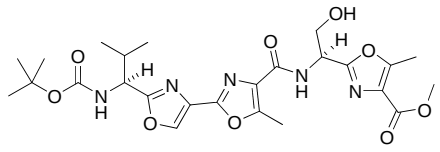

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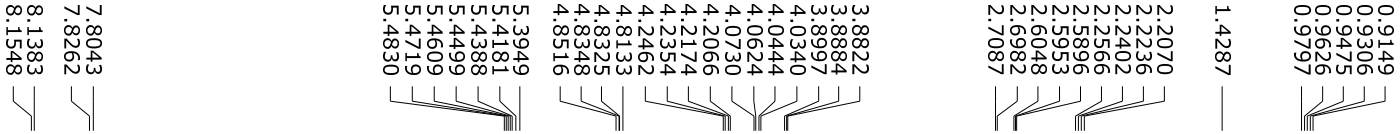
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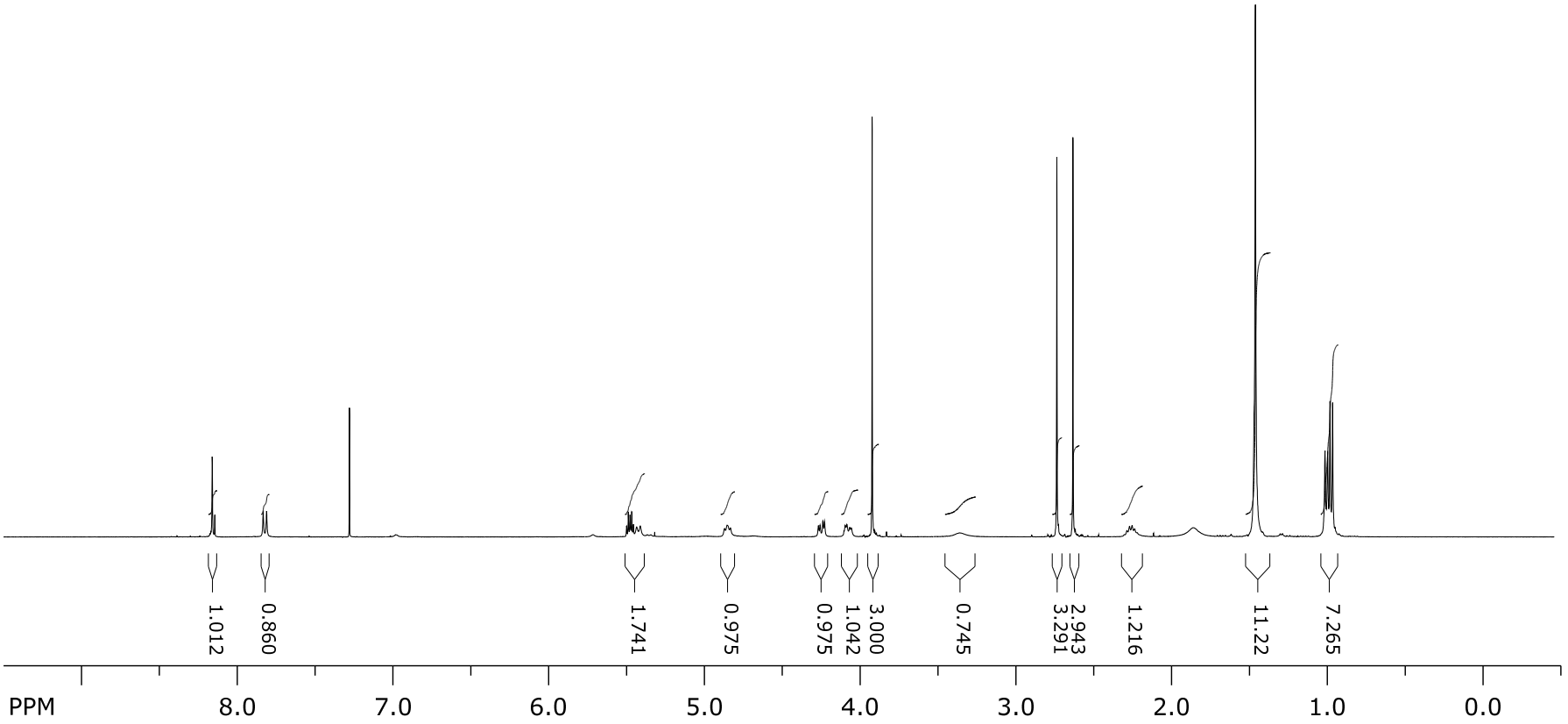
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PPM
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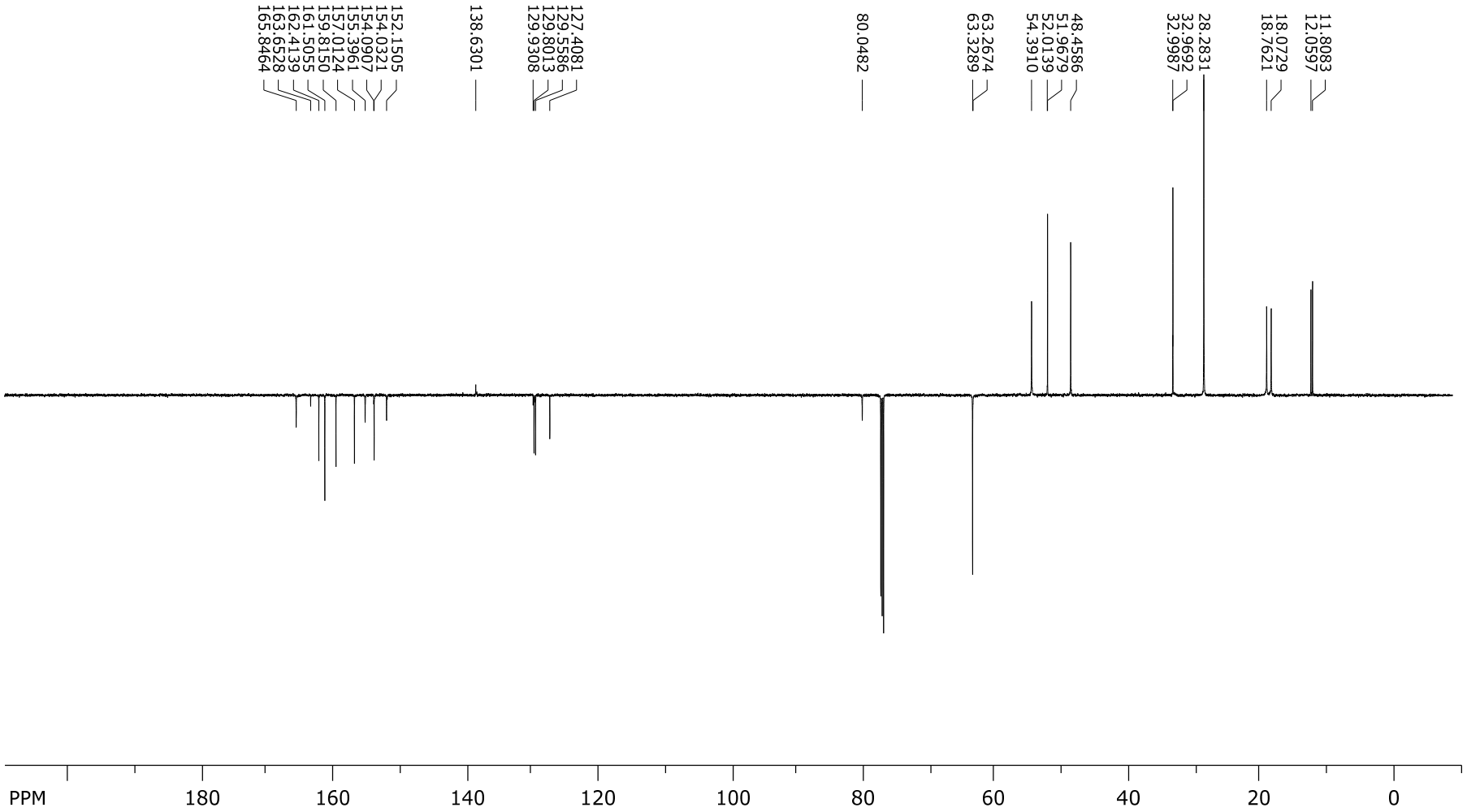
O

15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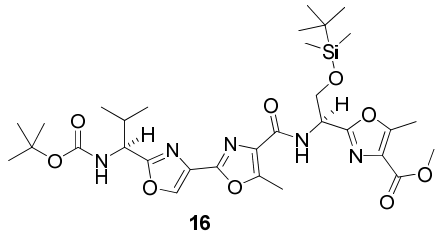

16

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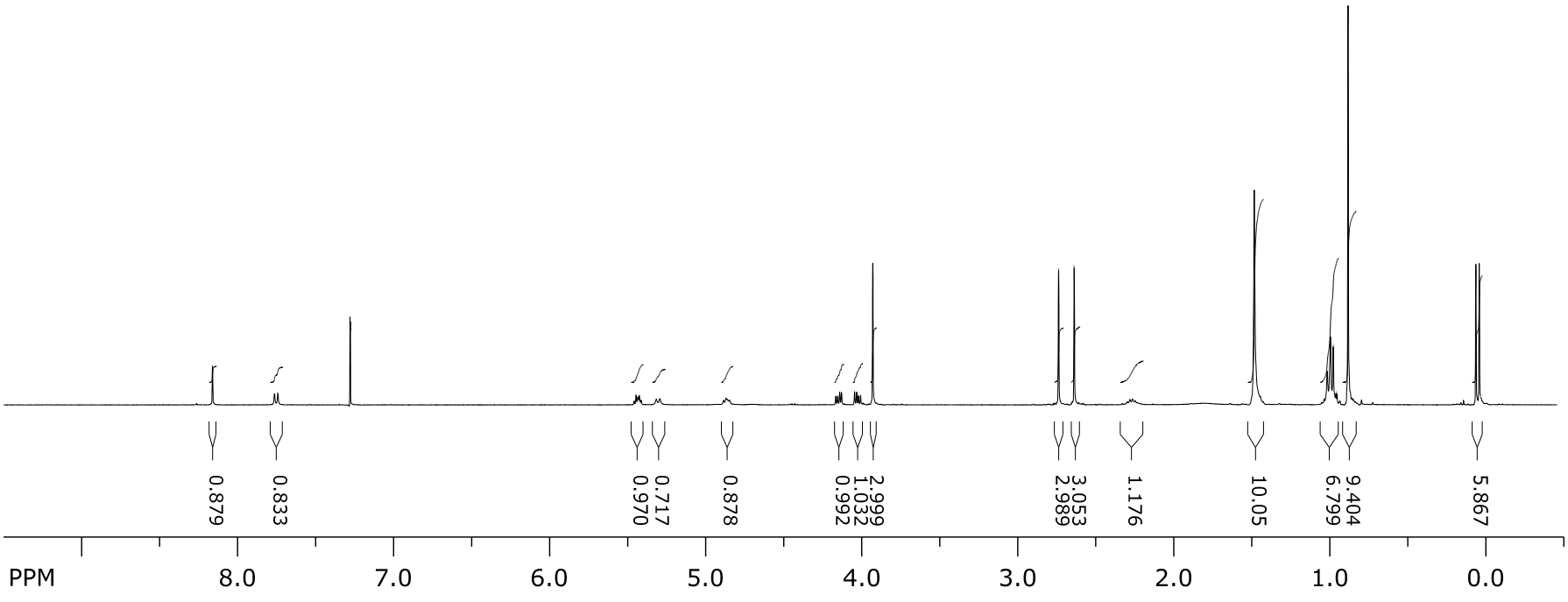

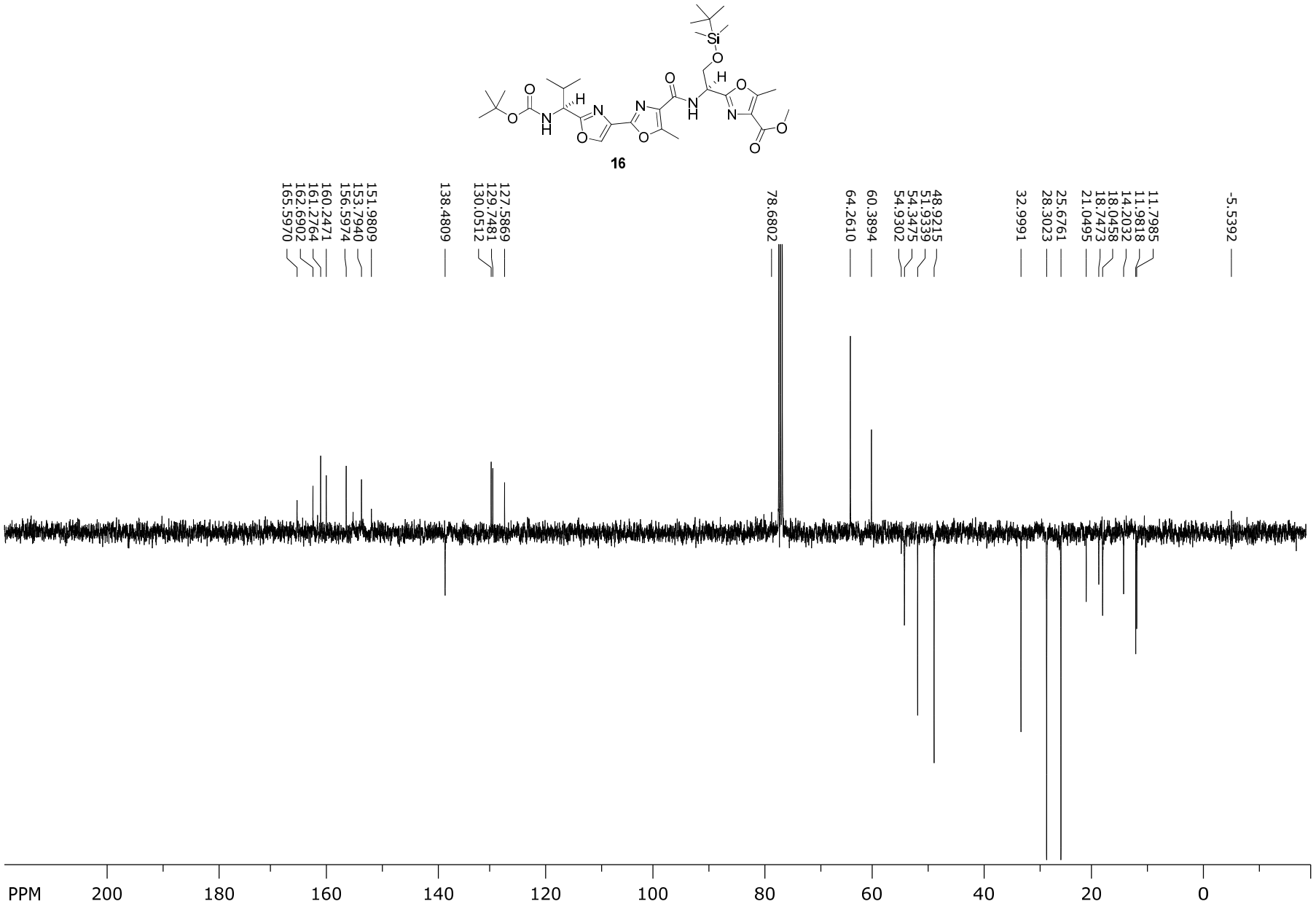
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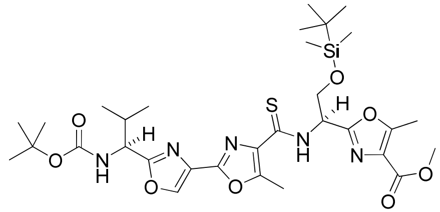

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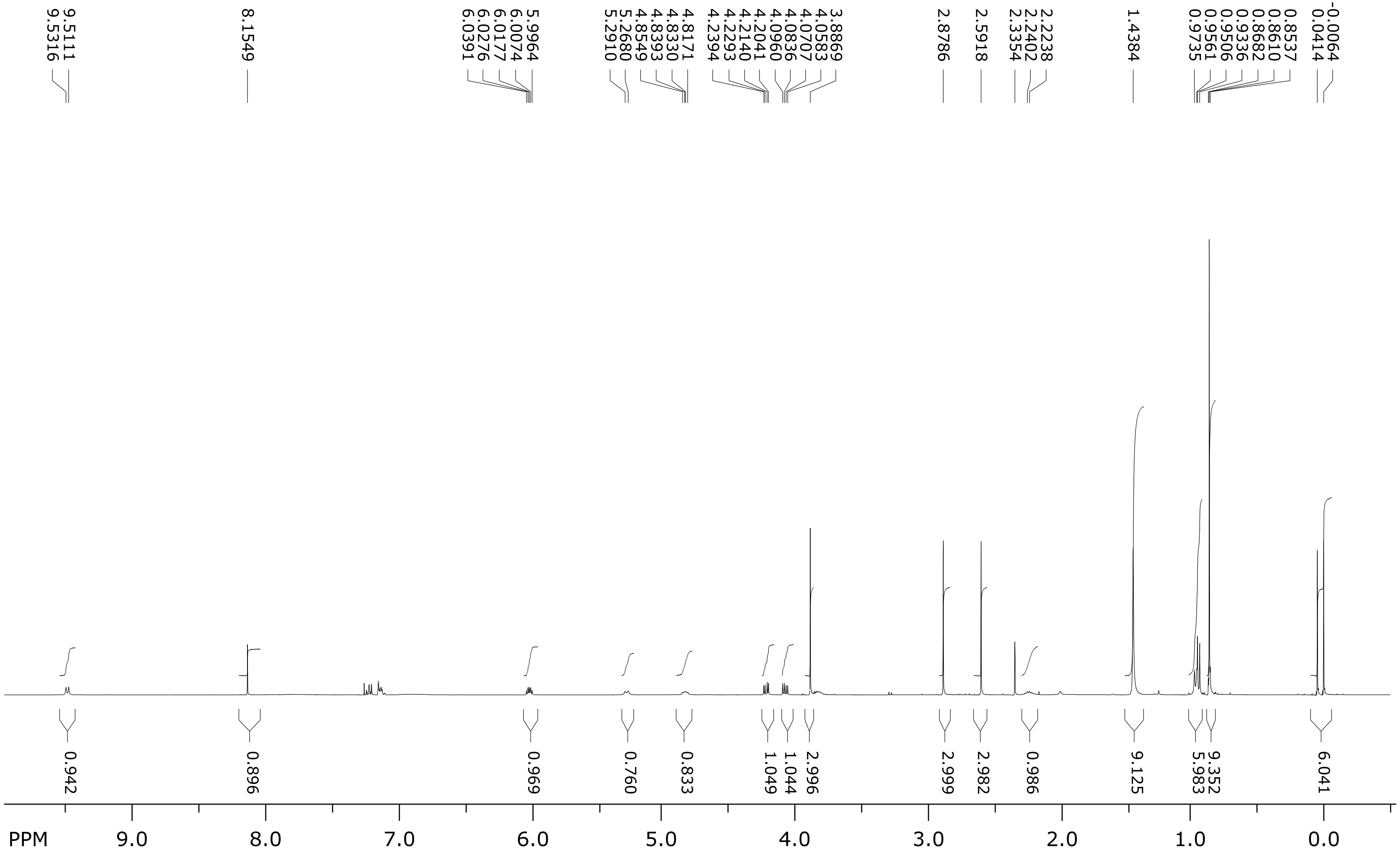

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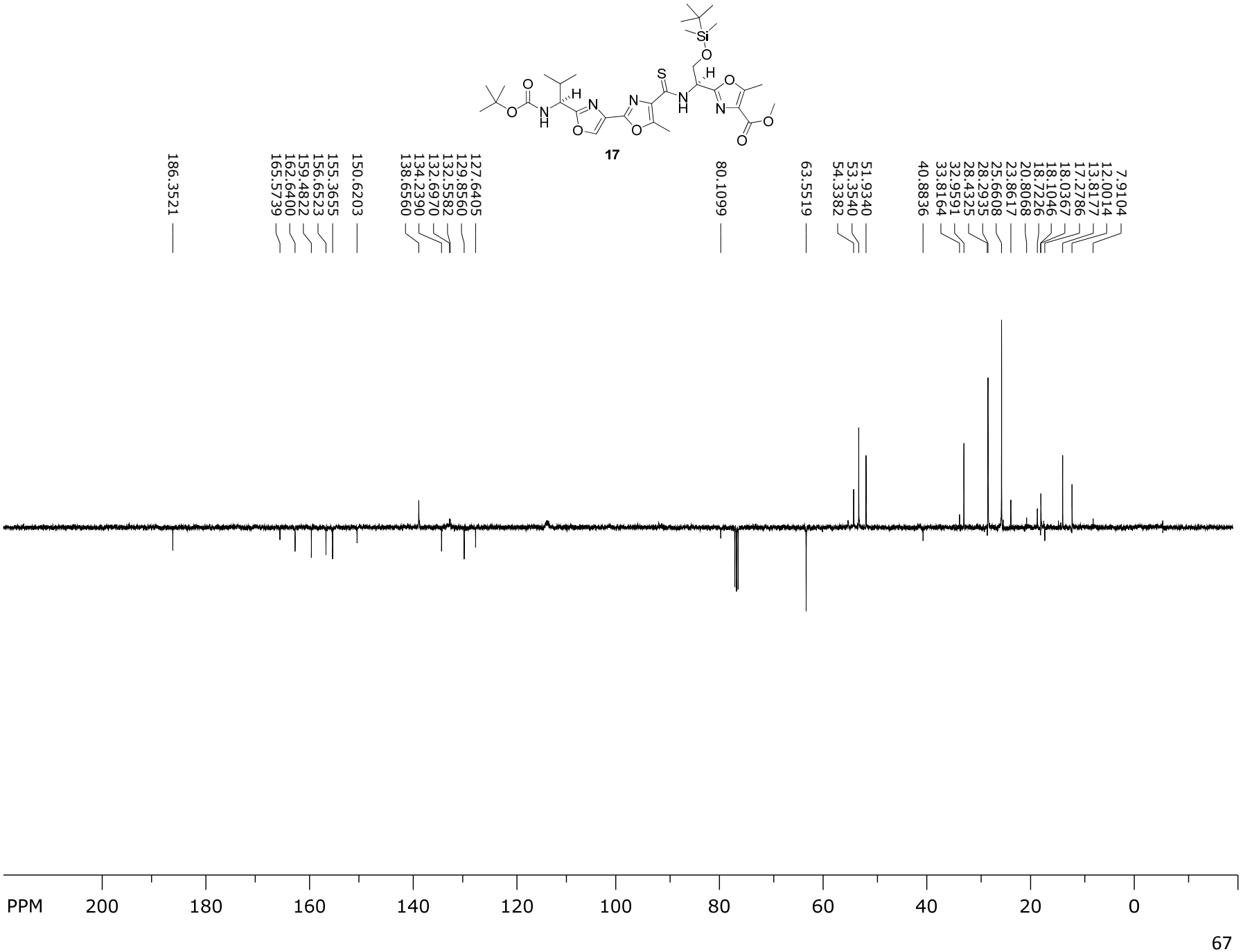
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2.6235
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2.2493
2.2331
2.2270
2.2171
2.2026
2.1995
2.1053
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1.200
1.140
1.245
3.950
3.019
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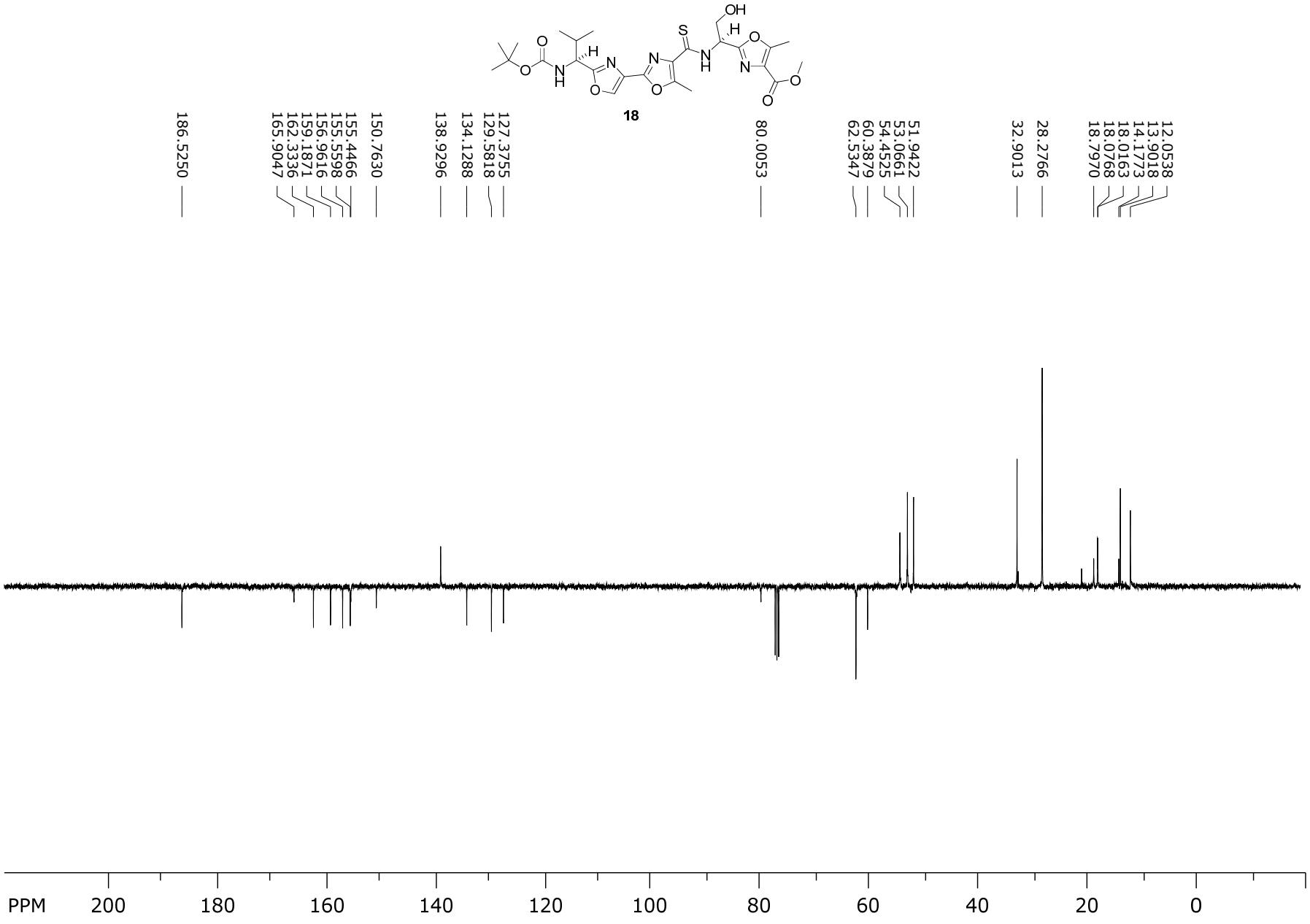
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54.4525
53.0661
51.9422
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28.2766
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18.0768
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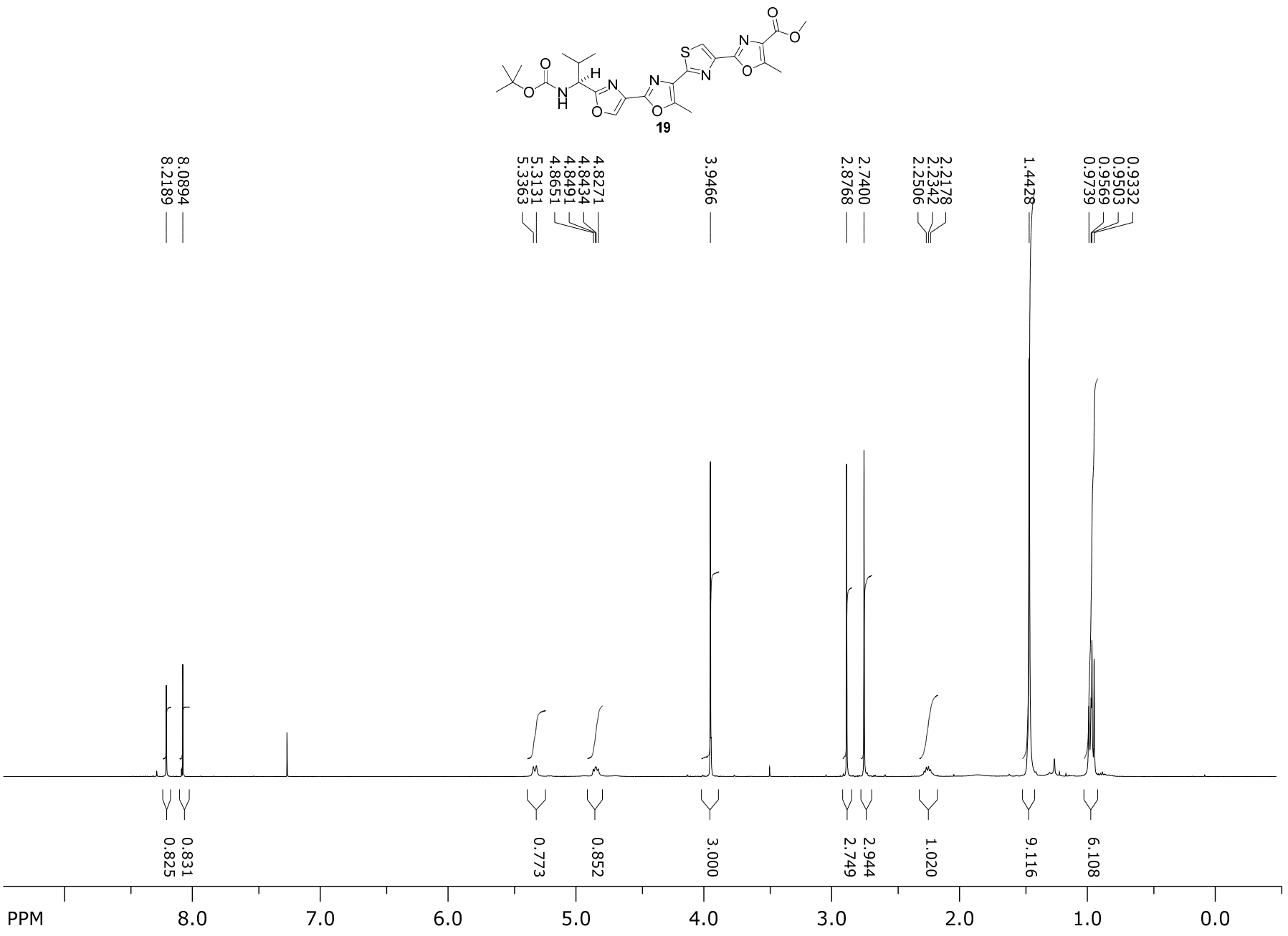
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2.2506
2.2342
2.2178
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0.9569
0.9503
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2.944
1.020
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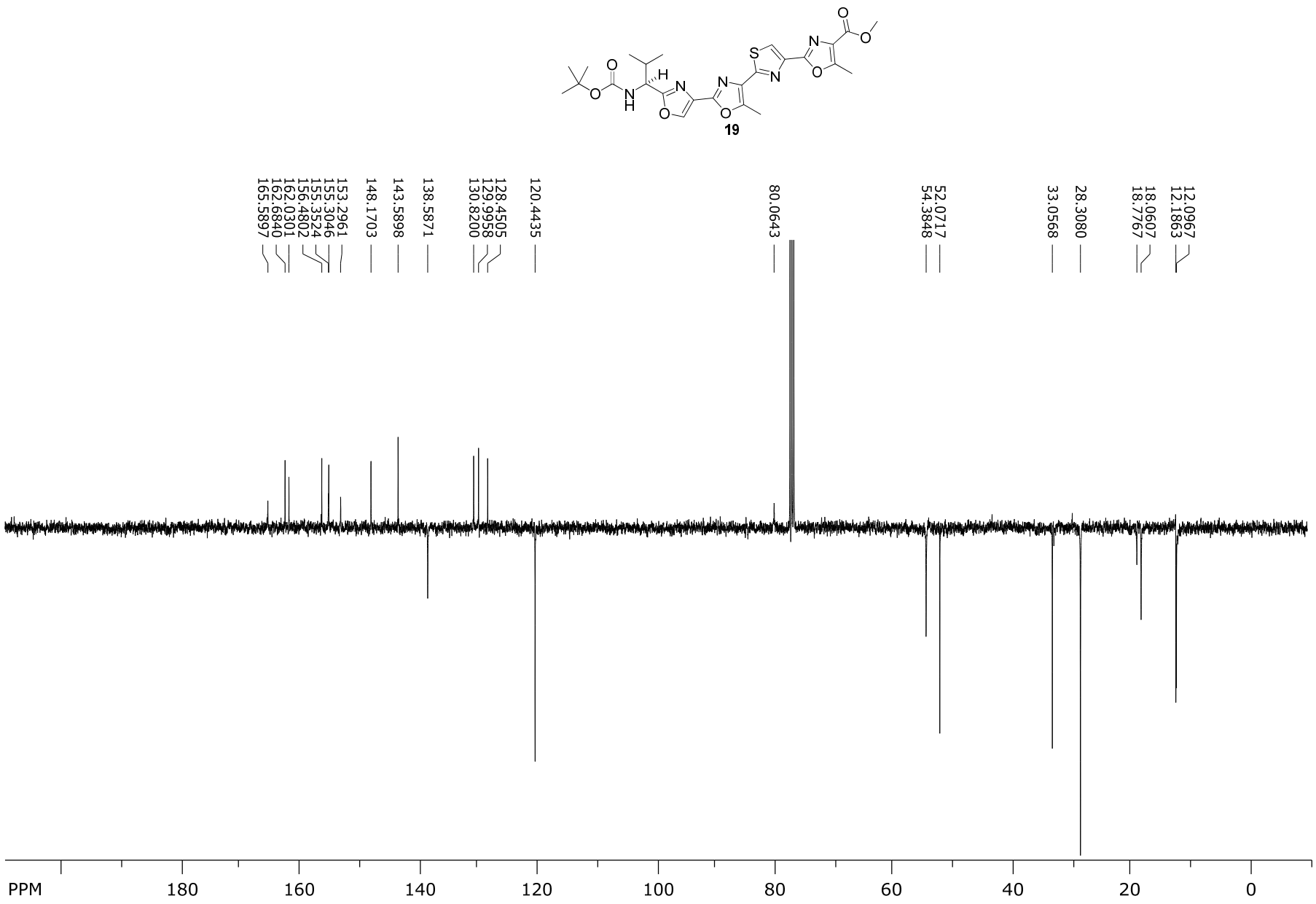
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130.8200
129.9958
128.4505
120.4435
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52.0717
33.0568
28.3080
18.7767
18.0607
12.1863
12.0967
PPM
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160
140
120
100
80
60
40
20
0

20
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8.1130
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5.4196
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4.8687
4.8621
2.8863
2.7757
2.7498
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2.2470
1.4519
1.4298
1.3744
1.2582
1.2529
1.2268
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0.9835
0.9616
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1.031
0.998
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1.230
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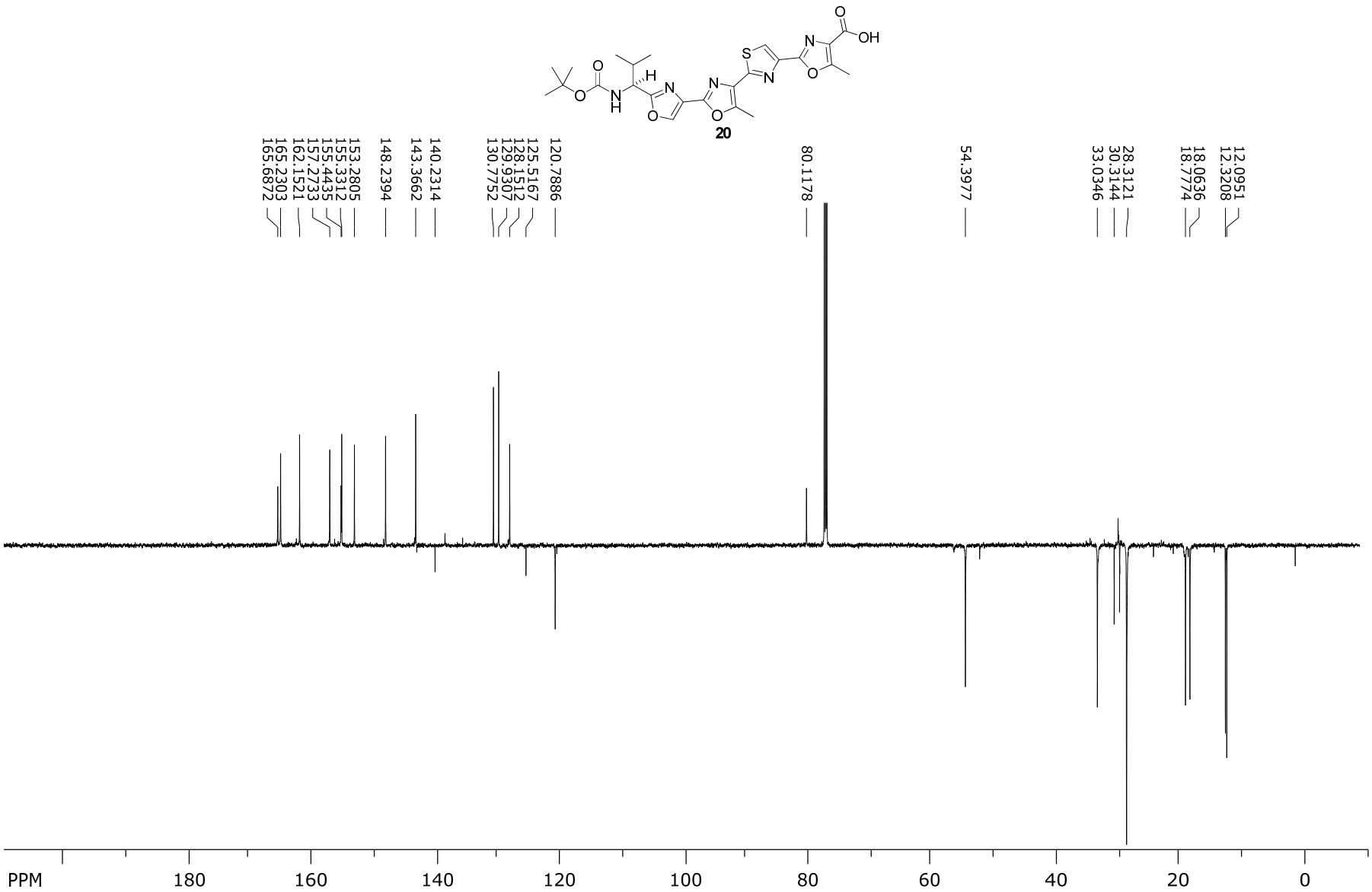
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120.7886
80.1178
54.3977
33.0346
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20
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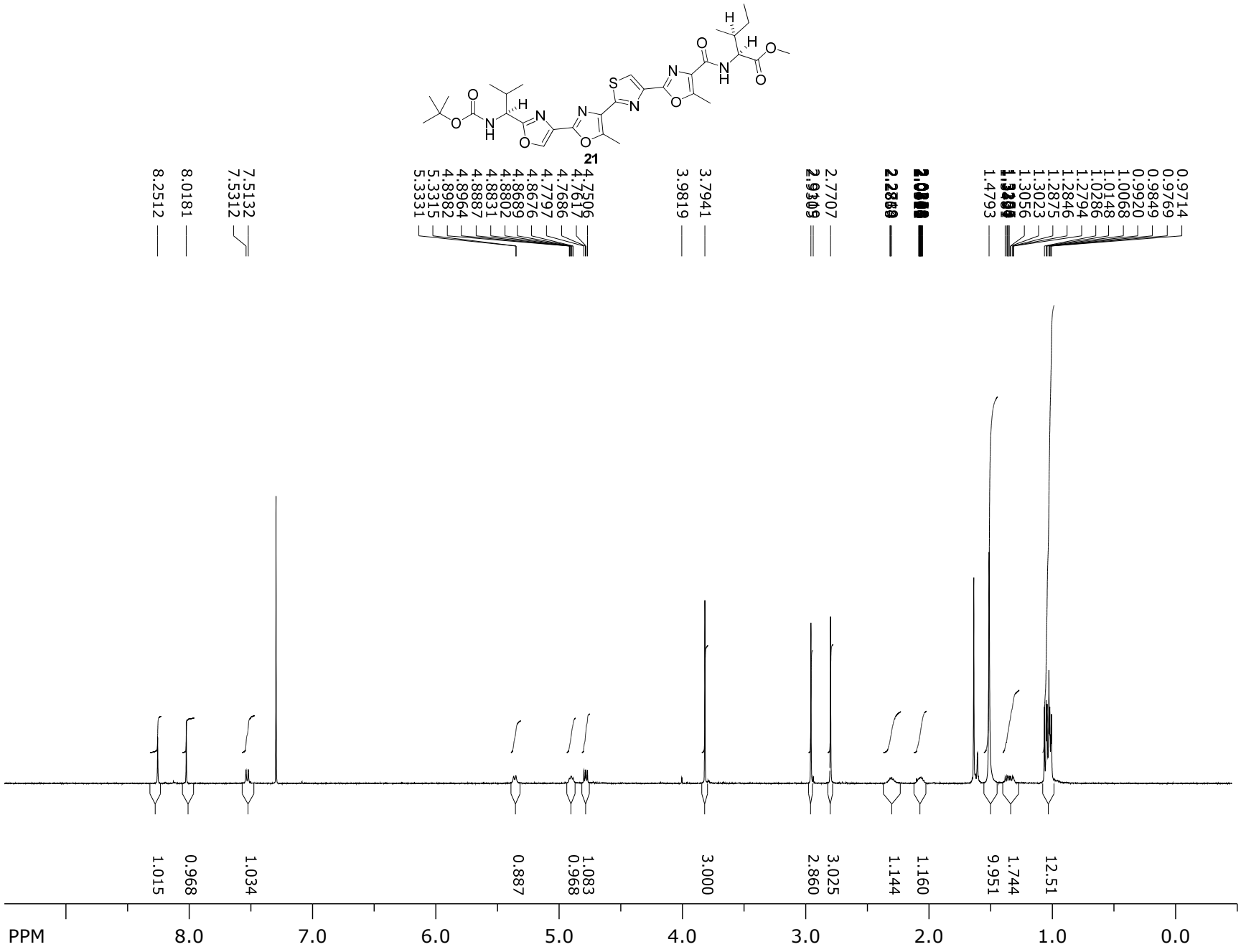
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4.8676
4.7797
4.7686
4.7617
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3.9819
3.7941
2.7707
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1.2875
1.2846
1.2794
1.0286
1.0148
1.0068
0.9920
0.9849
0.9769
0.9714
1.015
0.968
1.034
0.887
1.083
0.968
3.000
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3.025
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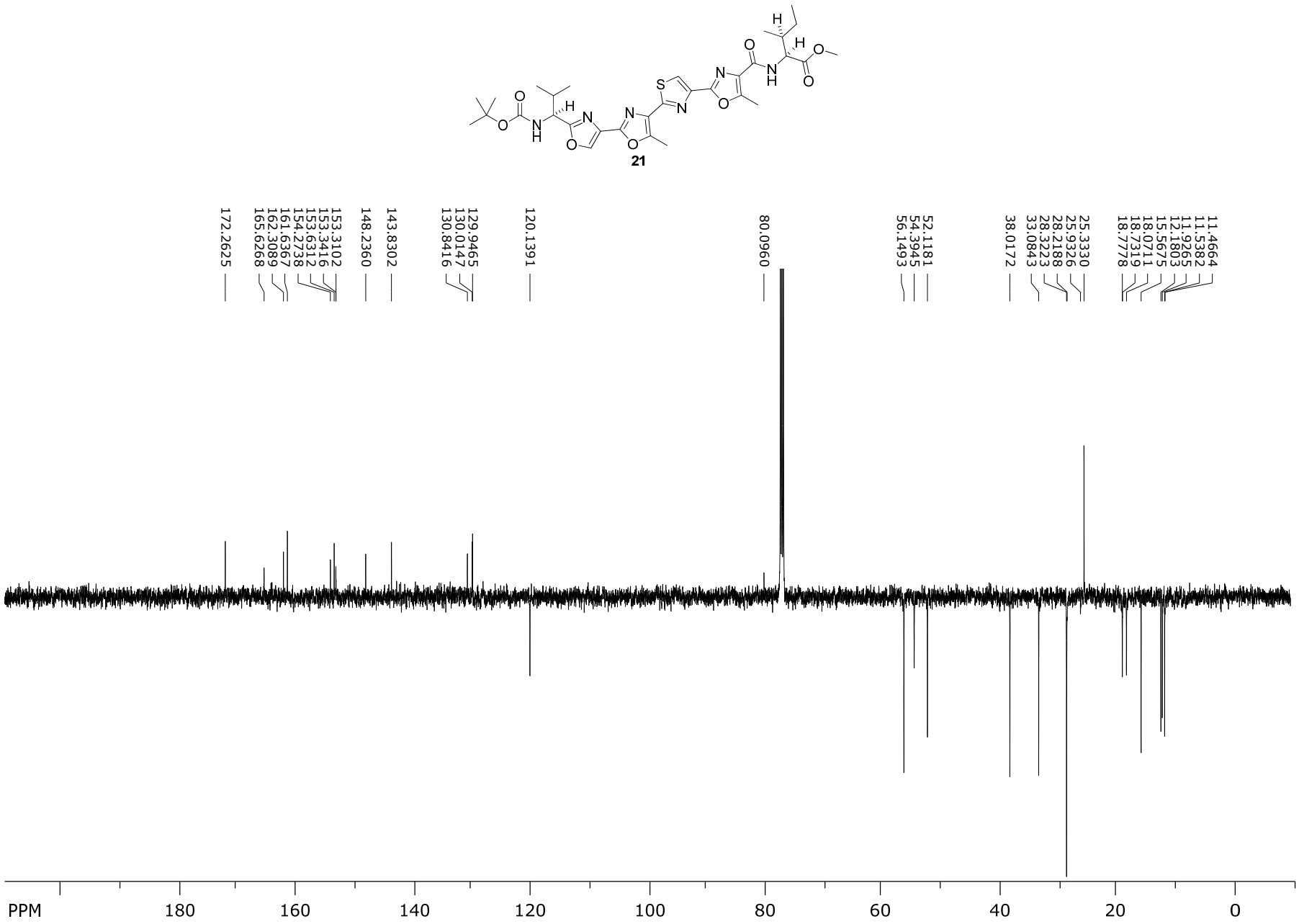
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130.0147
129.9465
120.1391
80.0960
56.1493
54.3945
52.1181
38.0172
33.0843
28.2188
28.3223
25.9326
25.3330
18.7778
18.7319
18.0711
15.5675
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11.4664
PPM
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120
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60
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20
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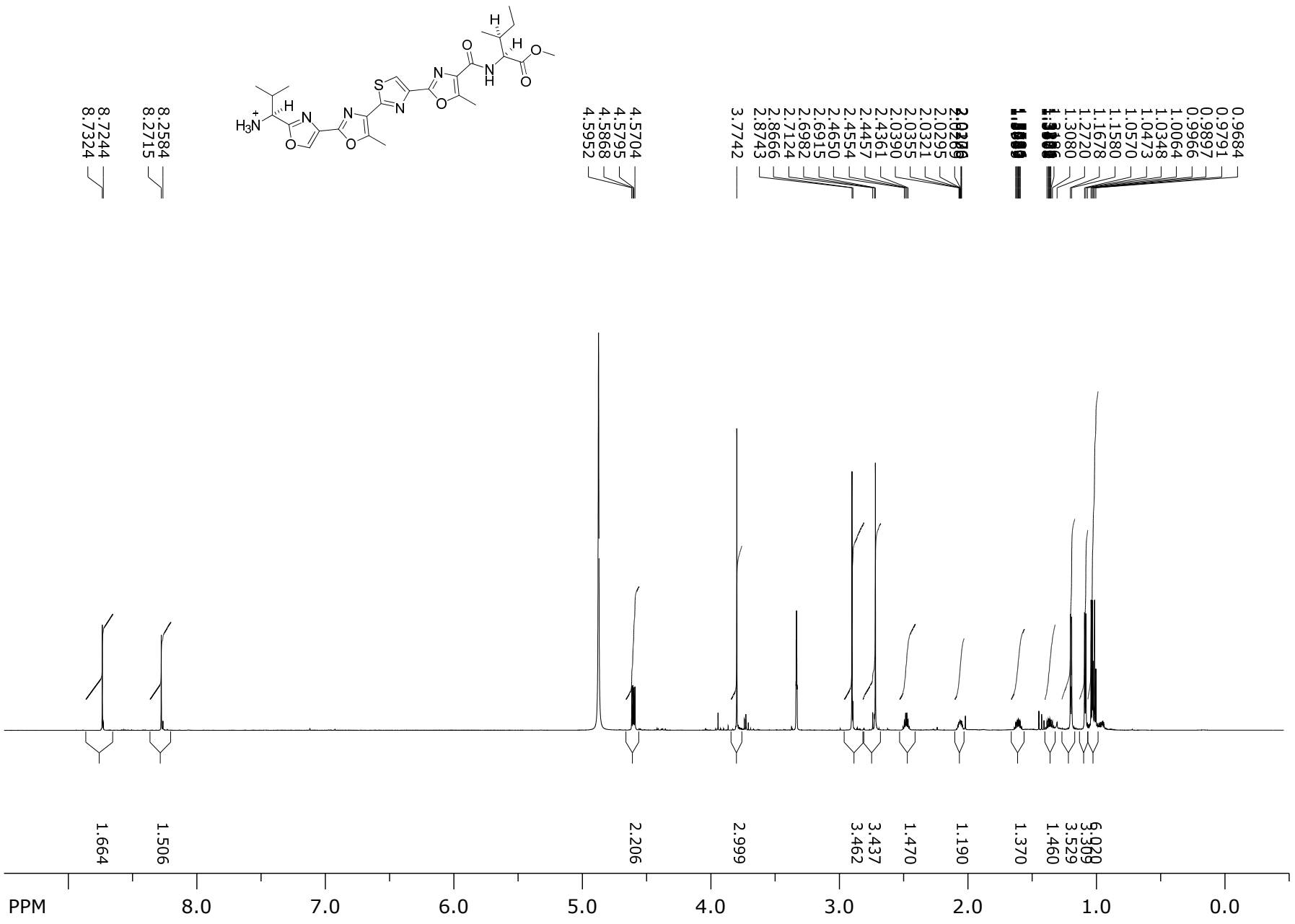
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4.5868
4.5952
3.7742
2.8743
2.8866
2.6915
2.6982
2.7124
2.4457
2.4554
2.4650
2.4361
2.0390
2.0355
2.0321
2.0295
0.9684
0.9791
0.9897
0.9966
1.0064
1.0348
1.0473
1.0570
1.1580
1.1678
1.2720
1.3080
1.664
1.506
2.206
2.999
3.462
3.437
1.470
1.190
1.370
1.460
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PPM
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4.0
3.0
2.0
1.0
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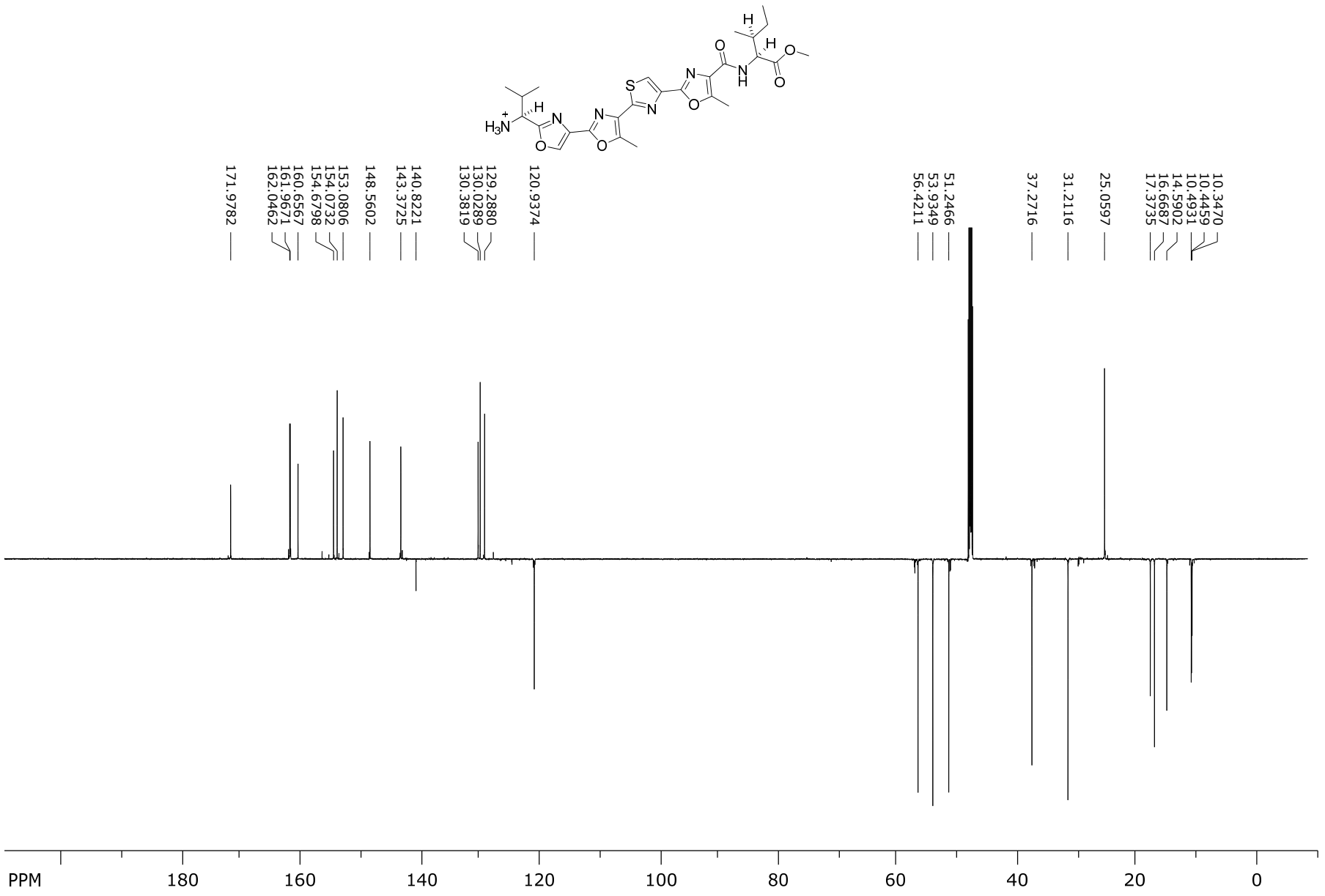
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153.0806
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143.3725
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130.3819
130.0289
129.2880
120.9374
56.4211
53.9349
51.2466
37.2716
31.2116
25.0597
17.3735
16.6687
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10.4459
10.3470
PPM
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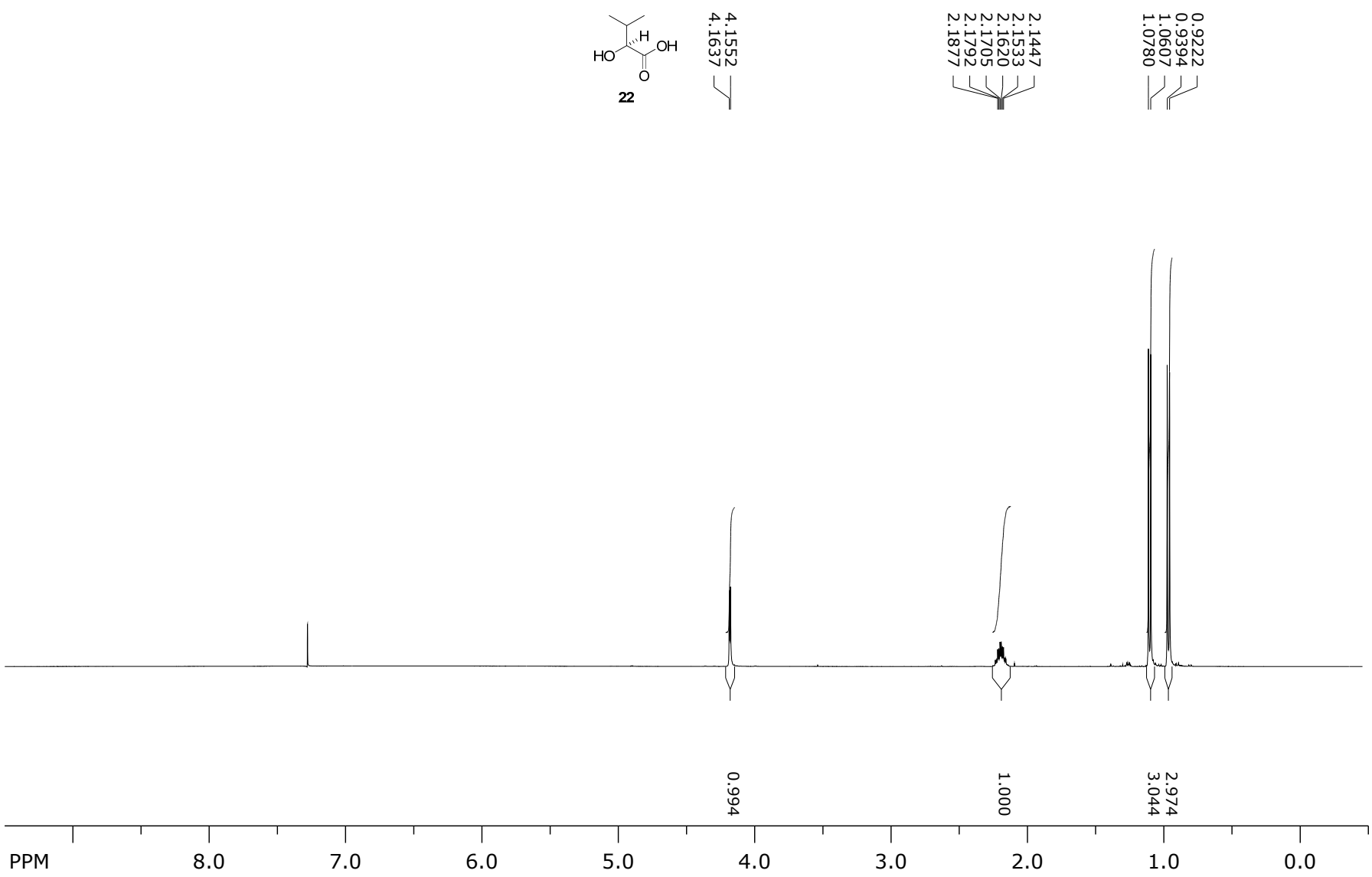
140
120
100
80
60
40
20
0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OH
O
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2.1877
2.1792
2.1705
2.1620
2.1533
2.1447
1.0780
1.0607
0.9394
0.9222
0.994
1.000
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PPM
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6.0
5.0
4.0
3.0
2.0
1.0
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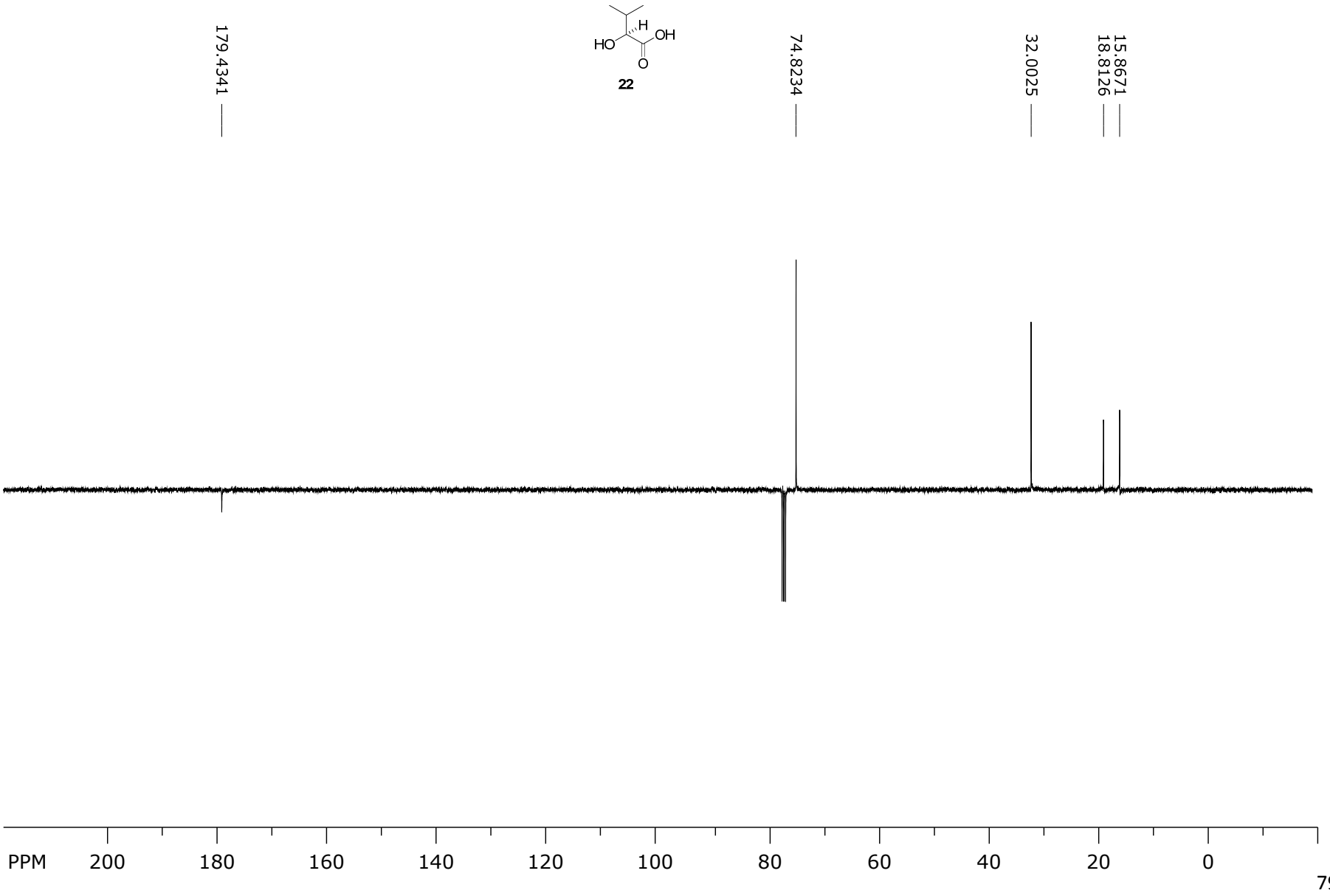
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OH
O
22
PPM
200
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140
120
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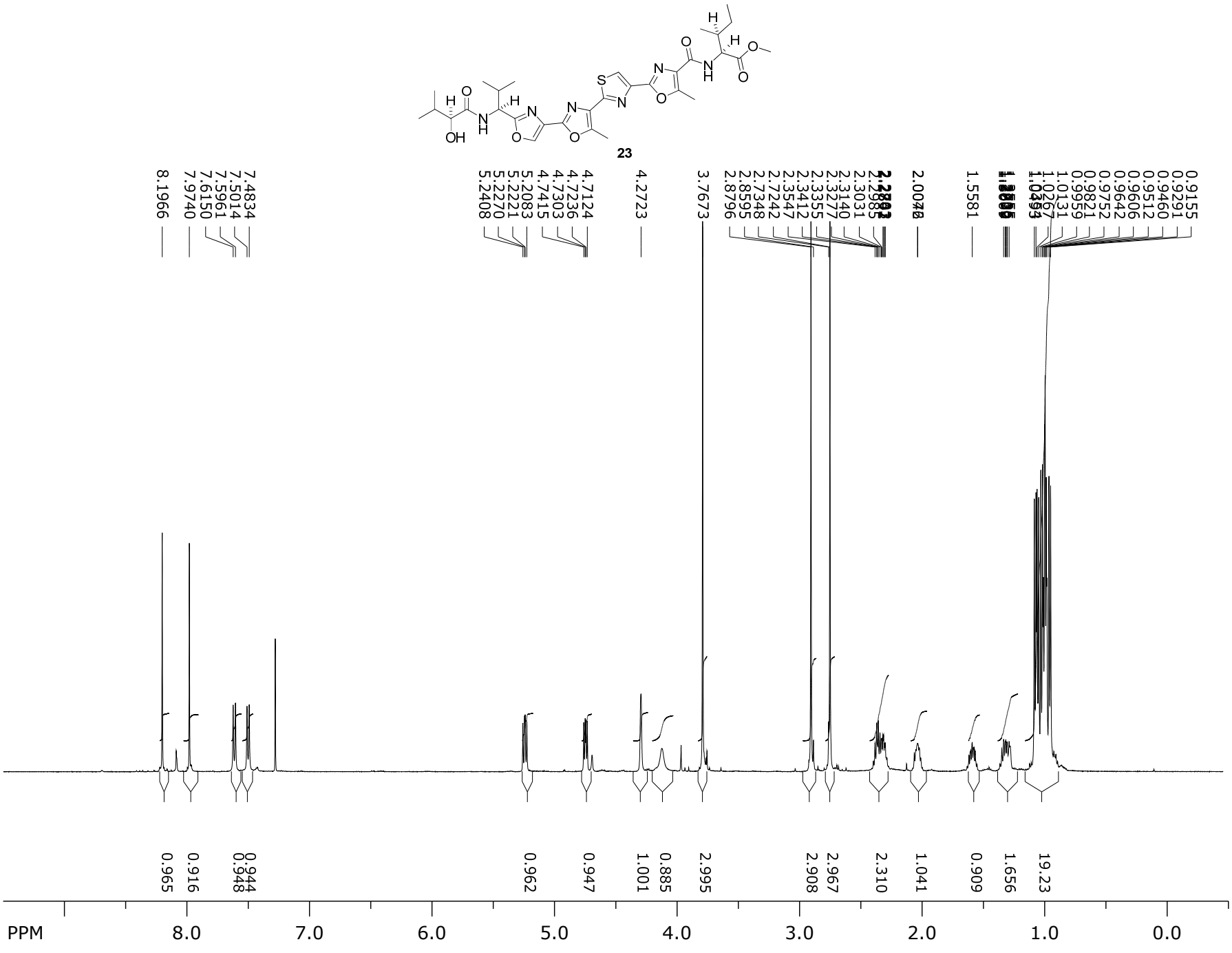
80
60
40
20
0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5.2408
5.2270
5.2221
5.2083
4.7415
4.7303
4.7236
4.7124
4.2723
3.7673
2.8796
2.8595
2.7348
2.7242
2.3547
2.3412
2.3355
2.3277
2.3140
2.3031
2.0078
1.5581
1.0267
1.0131
0.9959
0.9821
0.9752
0.9642
0.9606
0.9512
0.9460
0.9291
0.9155
0.965
0.916
0.944
0.948
0.962
0.947
1.001
0.885
2.995
2.908
2.967
2.310
1.041
0.909
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PPM
8.0
7.0
6.0
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4.0
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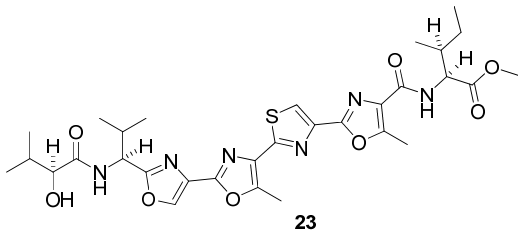
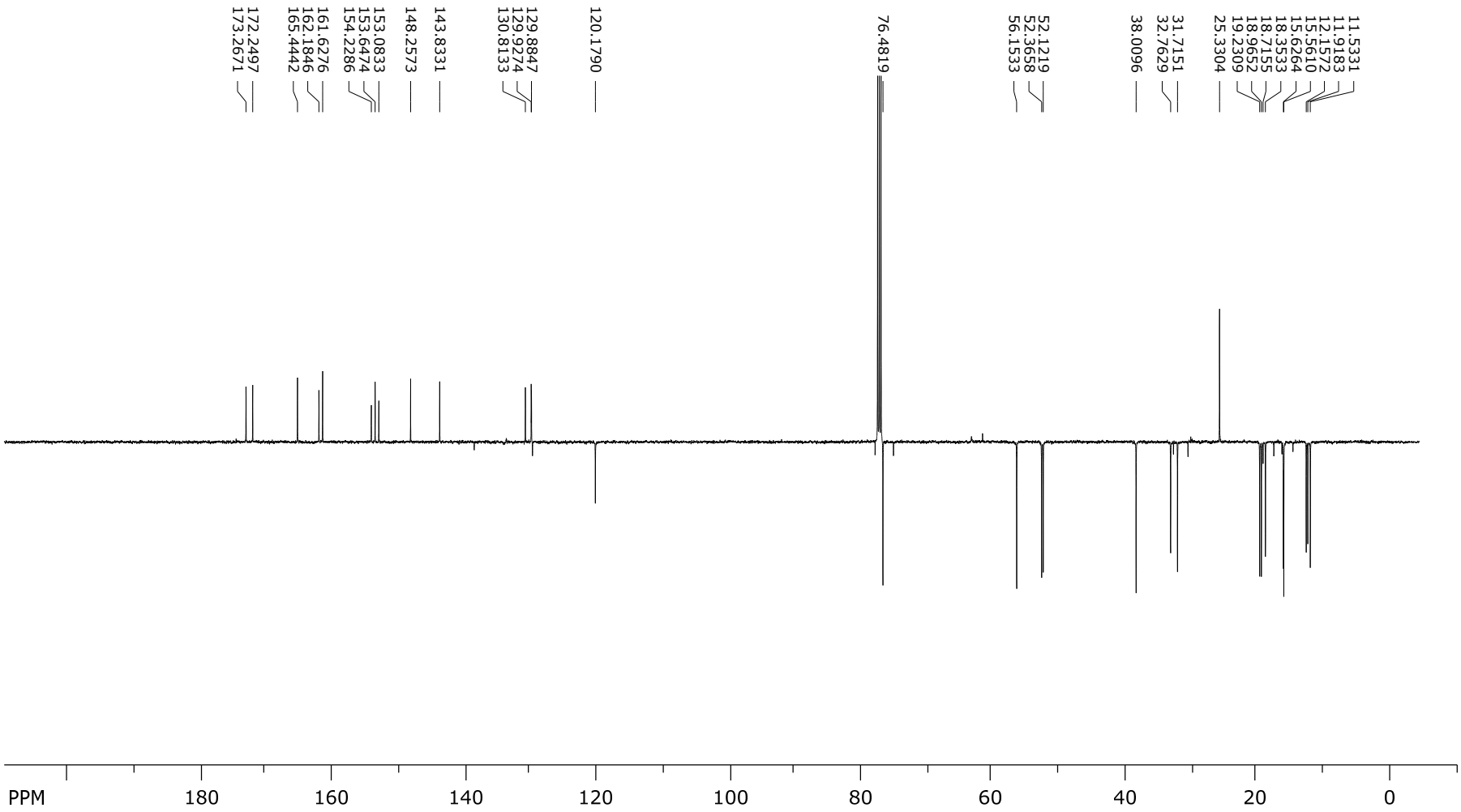
2.0
1.0
0.0



23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148.2573
143.8331
130.8133
129.9274
129.8847
120.1790
76.4819
56.1533
52.3658
52.1219
38.0096
32.7629
31.7151
25.3304
19.2309
18.9652
18.7155
18.3533
15.6264
15.5610
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11.9183
11.5331
PPM
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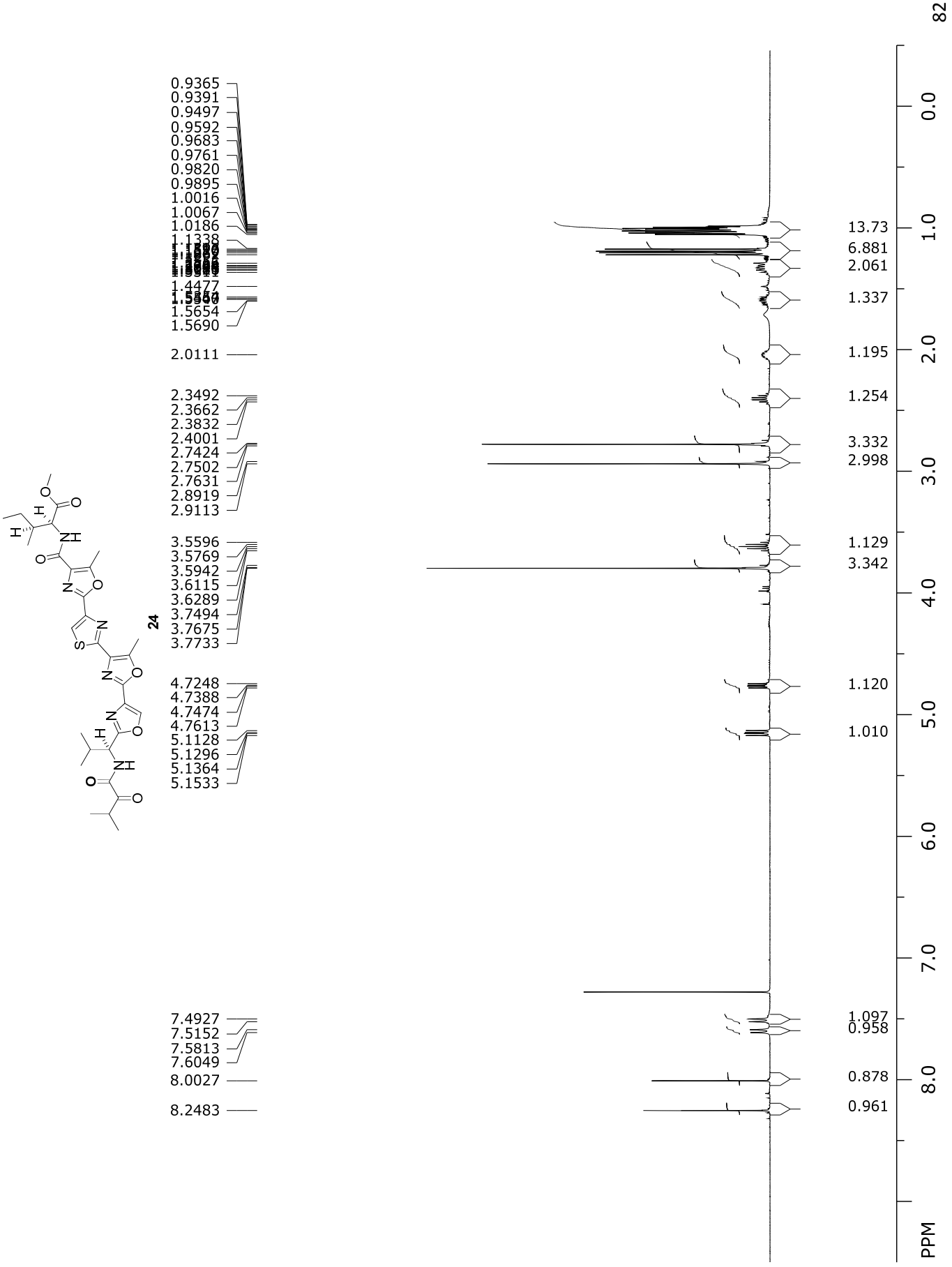
160
140
120
100
80
60
40
20
0


82
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1.4477
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1.5690
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2.3492
2.3662
2.3832
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2.7502
2.7631
2.8919
2.9113
3.5596
3.5769
3.5942
3.6115
3.6289
3.7494
3.7675
3.7733
4.7248
4.7388
4.7474
4.7613
5.1128
5.1296
5.1364
5.1533
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7.5152
7.5813
7.6049
8.0027
8.2483
24
13.73
6.881
2.061
1.337
1.195
1.254
3.332
2.998
1.129
3.342
1.120
1.010
1.097
0.958
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5.0
6.0
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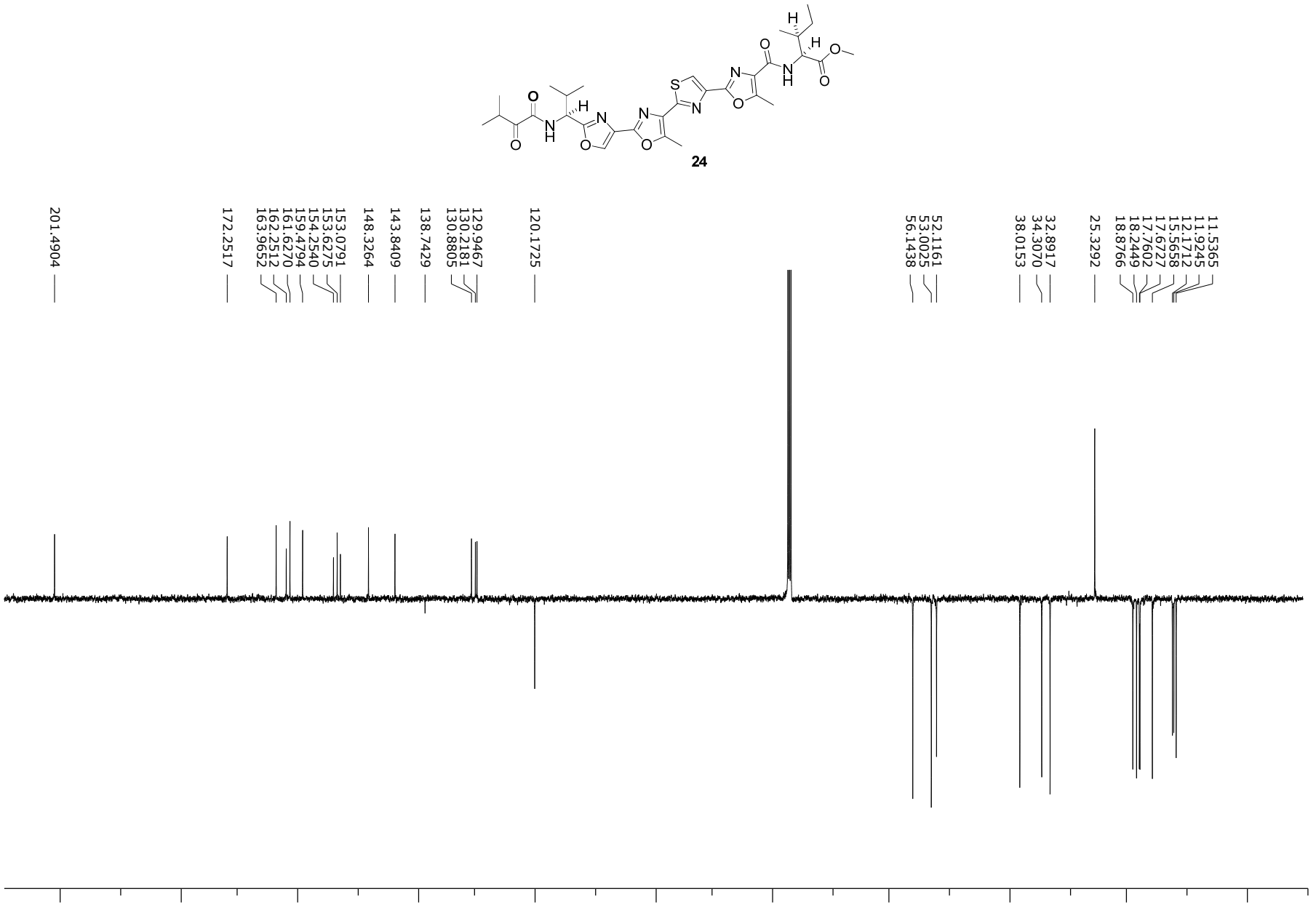
PPM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138.7429
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130.2181
129.9467
120.1725
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32.8917
25.3292
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18.2449
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17.6727
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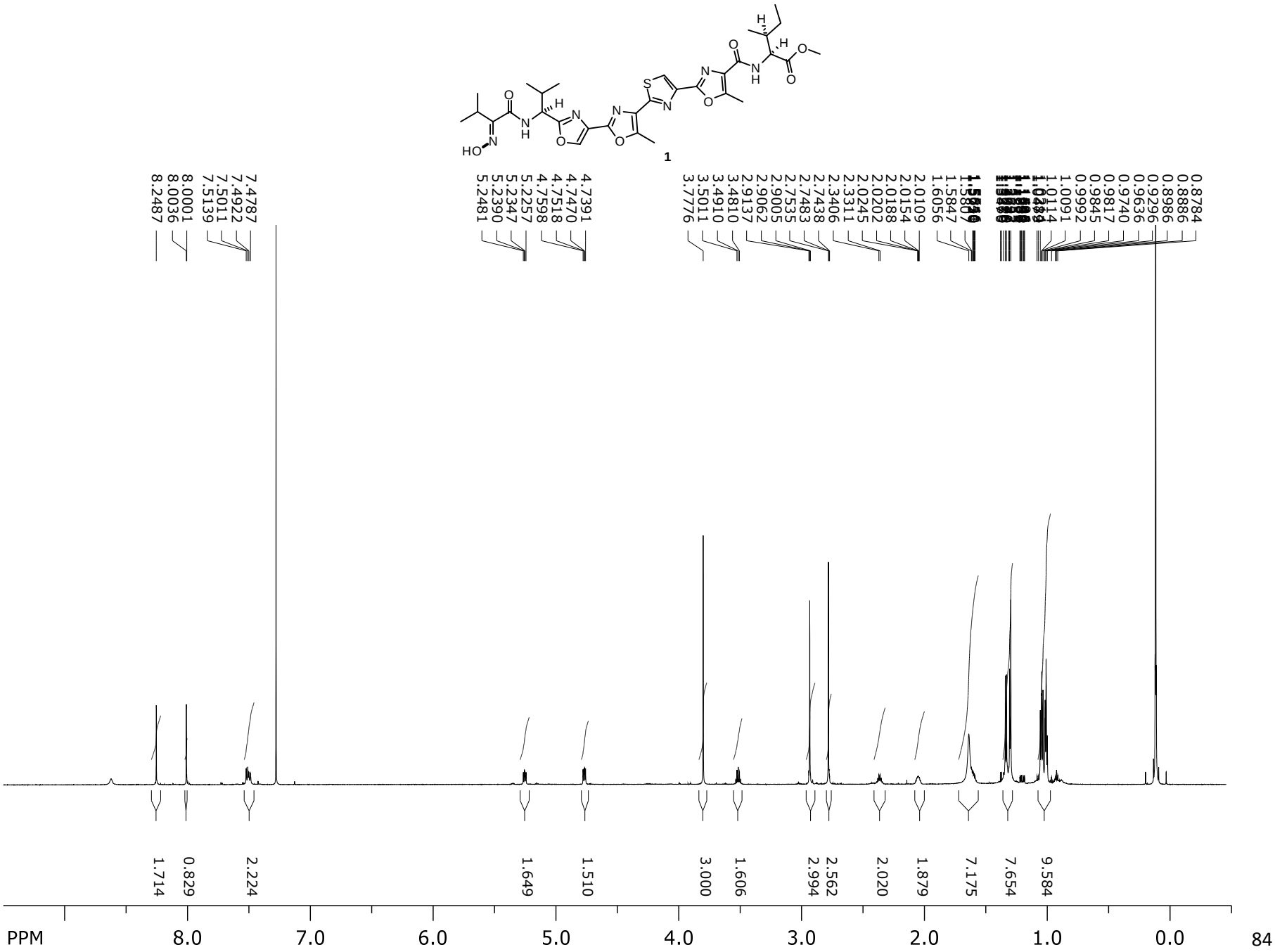
140
120
100
80
60
40
20
0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5.2347
5.2257
4.7598
4.7518
4.7470
4.7391
3.7776
3.5011
3.4910
3.4810
2.9137
2.9062
2.9005
2.7535
2.7483
2.7438
2.3406
2.3311
2.0245
2.0202
2.0188
2.0154
2.0109
1.6056
1.5847
0.9296
0.8986
0.8886
0.8784
1.714
0.829
2.224
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1.510
3.000
1.606
2.994
2.562
2.020
1.879
7.175
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4.0
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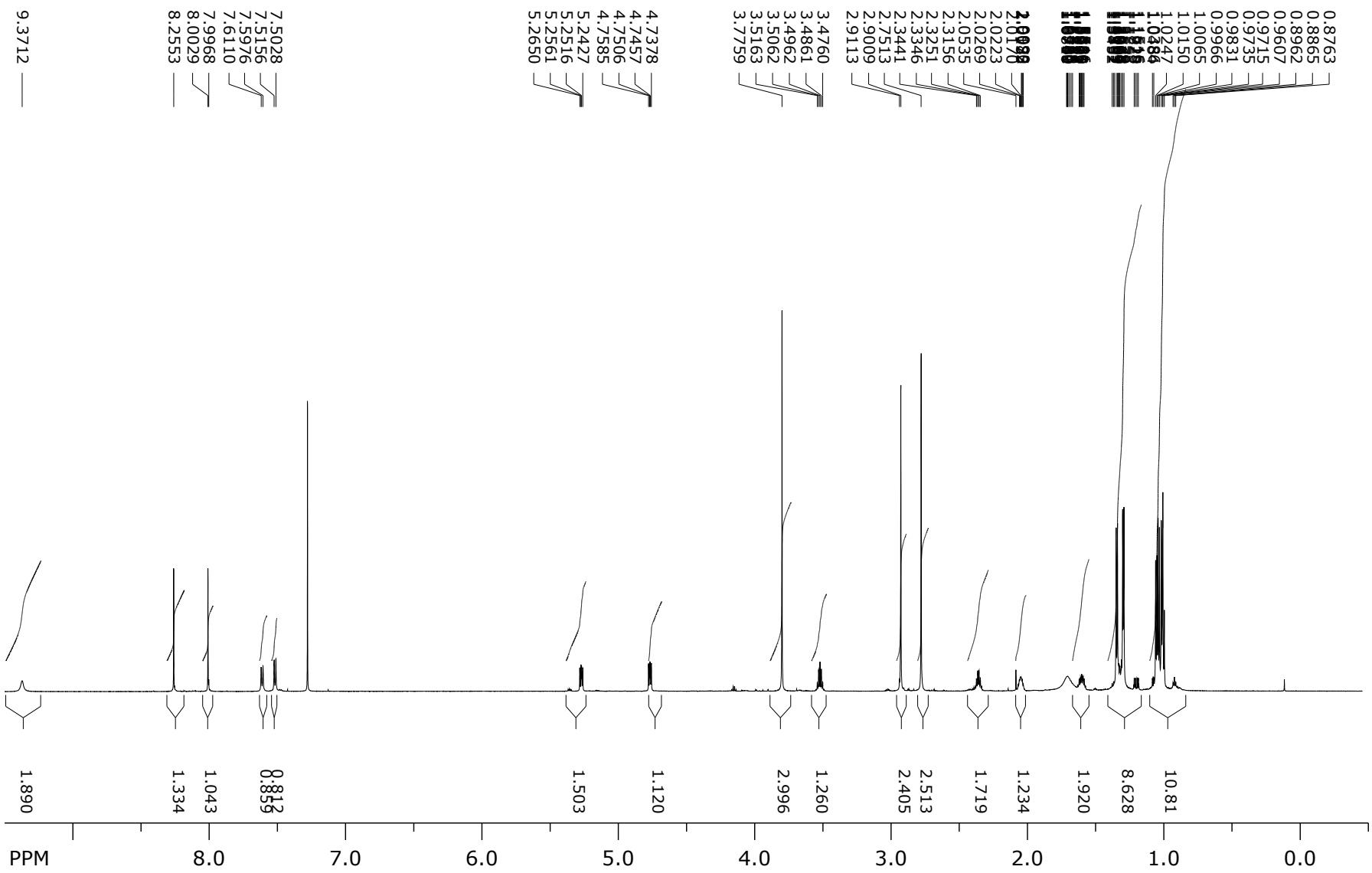
2.0
1.0
0.0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5.2427
4.7585
4.7506
4.7457
4.7378
3.7759
3.5163
3.5062
3.4962
3.4861
3.4760
2.9113
2.9009
2.7513
2.3441
2.3346
2.3251
2.3156
2.0535
2.0269
2.0223
1.0247
1.0150
1.0065
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0.9831
0.9735
0.9715
0.9607
0.8962
0.8865
0.8763
1.890
1.334
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1.503
1.120
2.996
1.260
2.405
2.513
1.719
1.234
1.920
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PPM
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4.0
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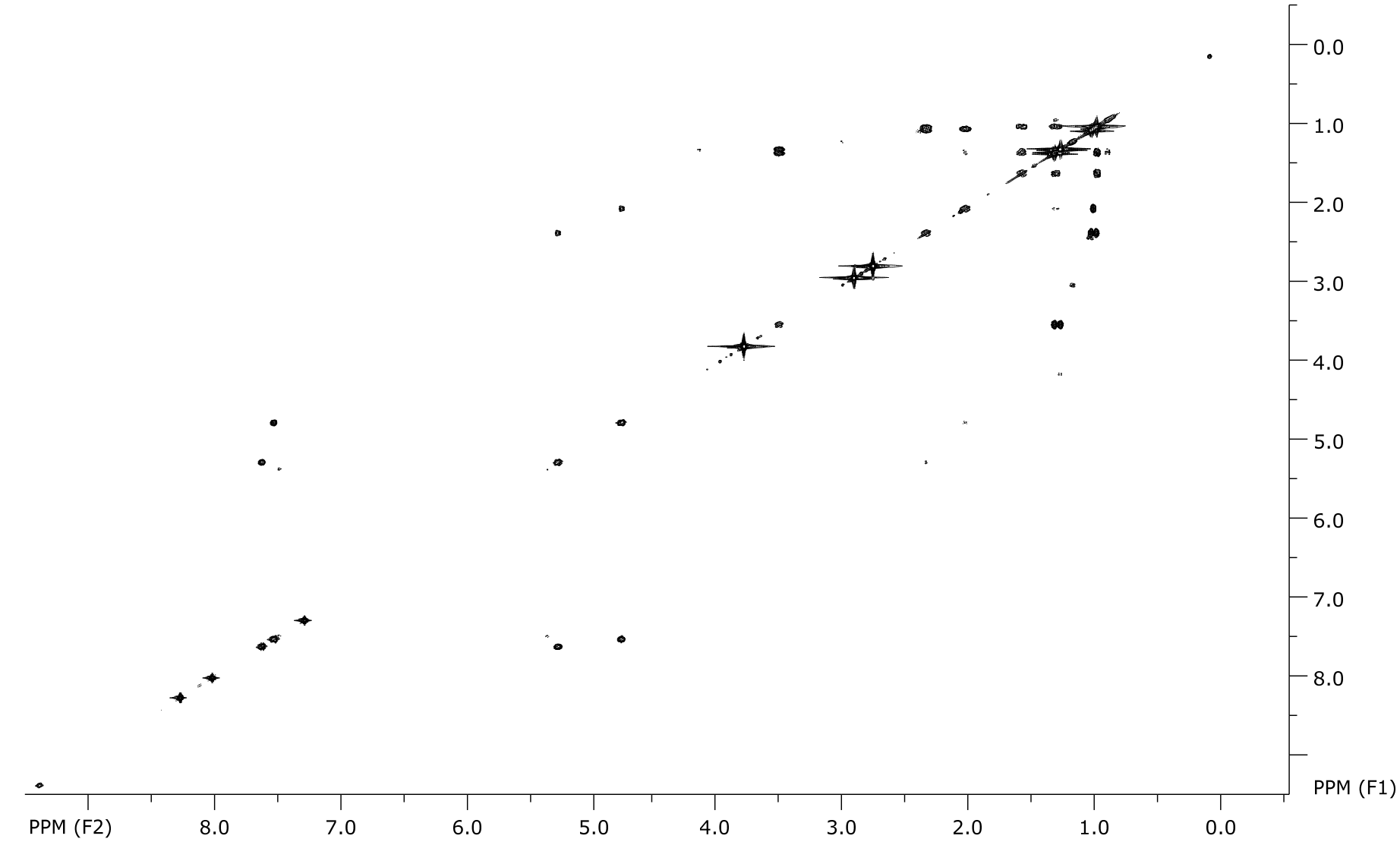
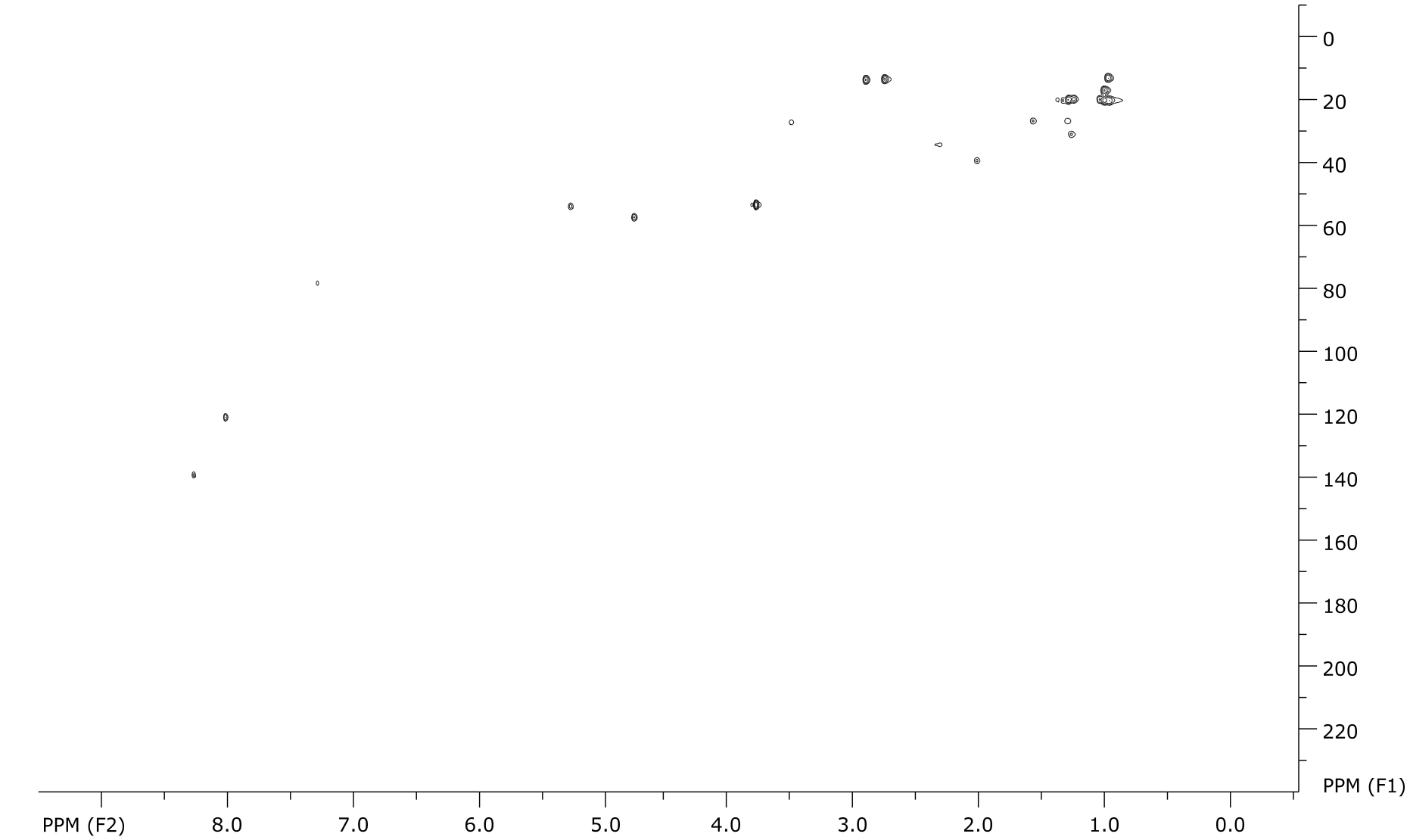
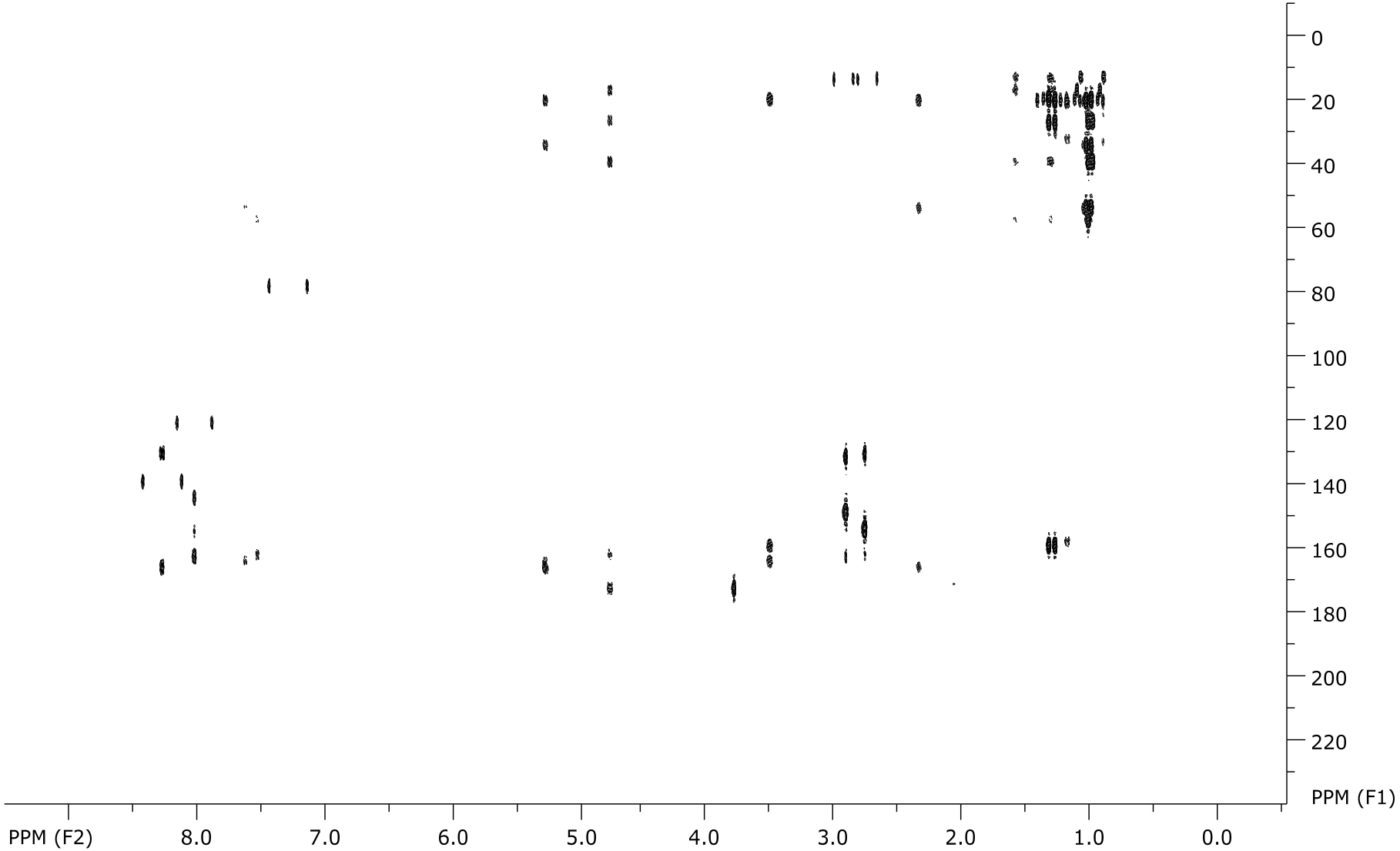


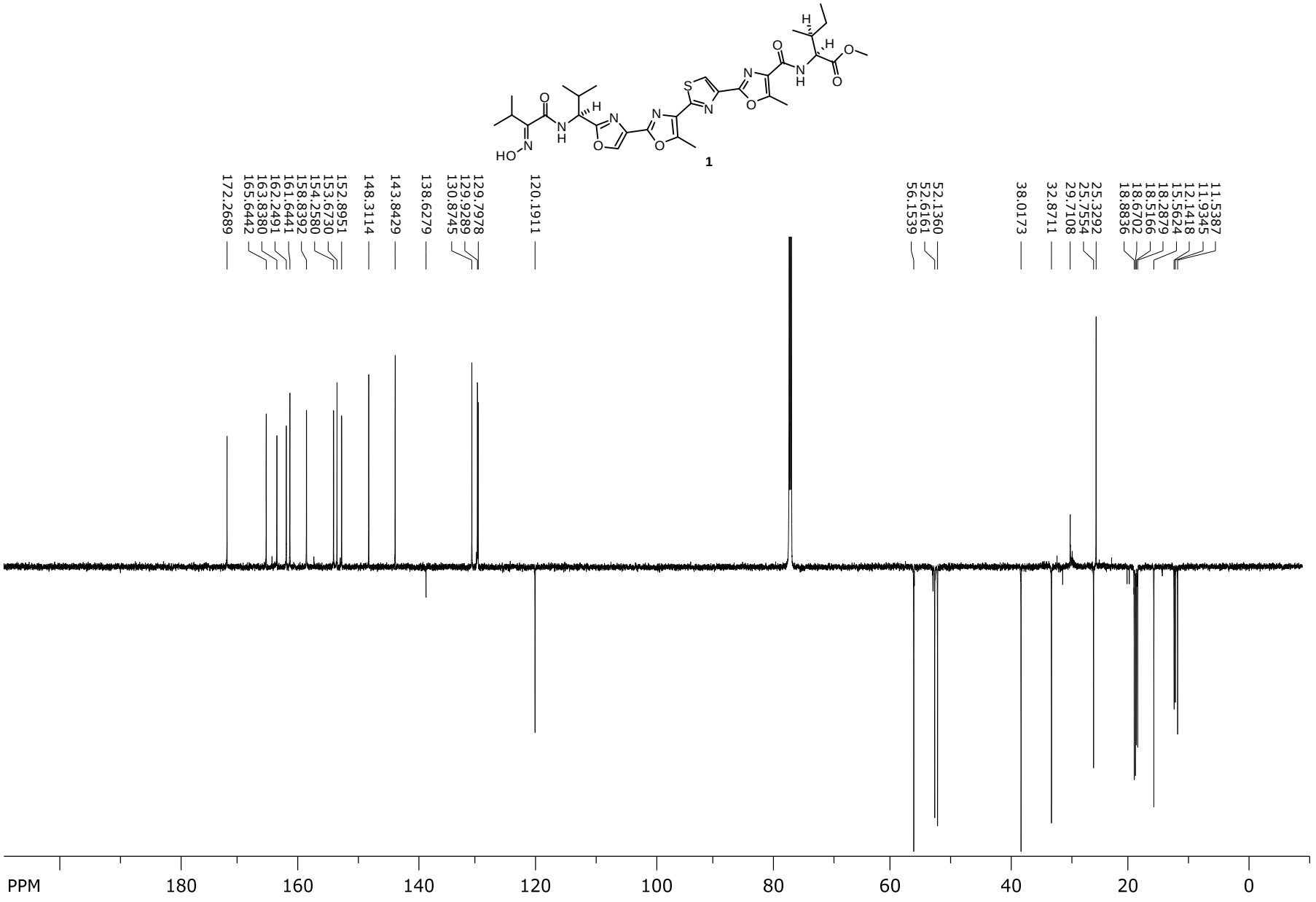
COSY


0
20
40
60
80
100
120
140
160
180
200
220
PPM (F1)
PPM (F2)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

HMQC


0
20
40
60
80
100
120
140
160
180
200
220
PPM (F1)
PPM (F2)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

HMBC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153.6730
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143.8429
138.6279
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129.9289
129.7978
120.1911
56.1539
52.6161
52.1360
38.0173
32.8711
29.7108
25.7554
25.3292
18.8836
18.6702
18.5166
18.2879
15.5624
12.1418
11.9345
11.5387
PPM
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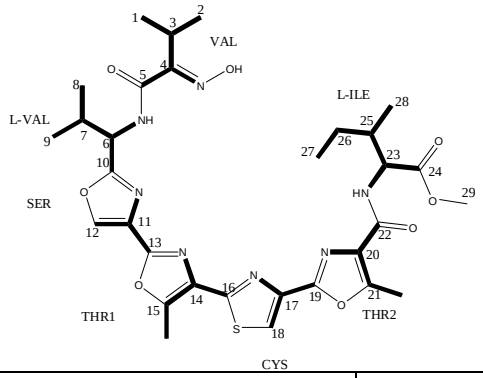
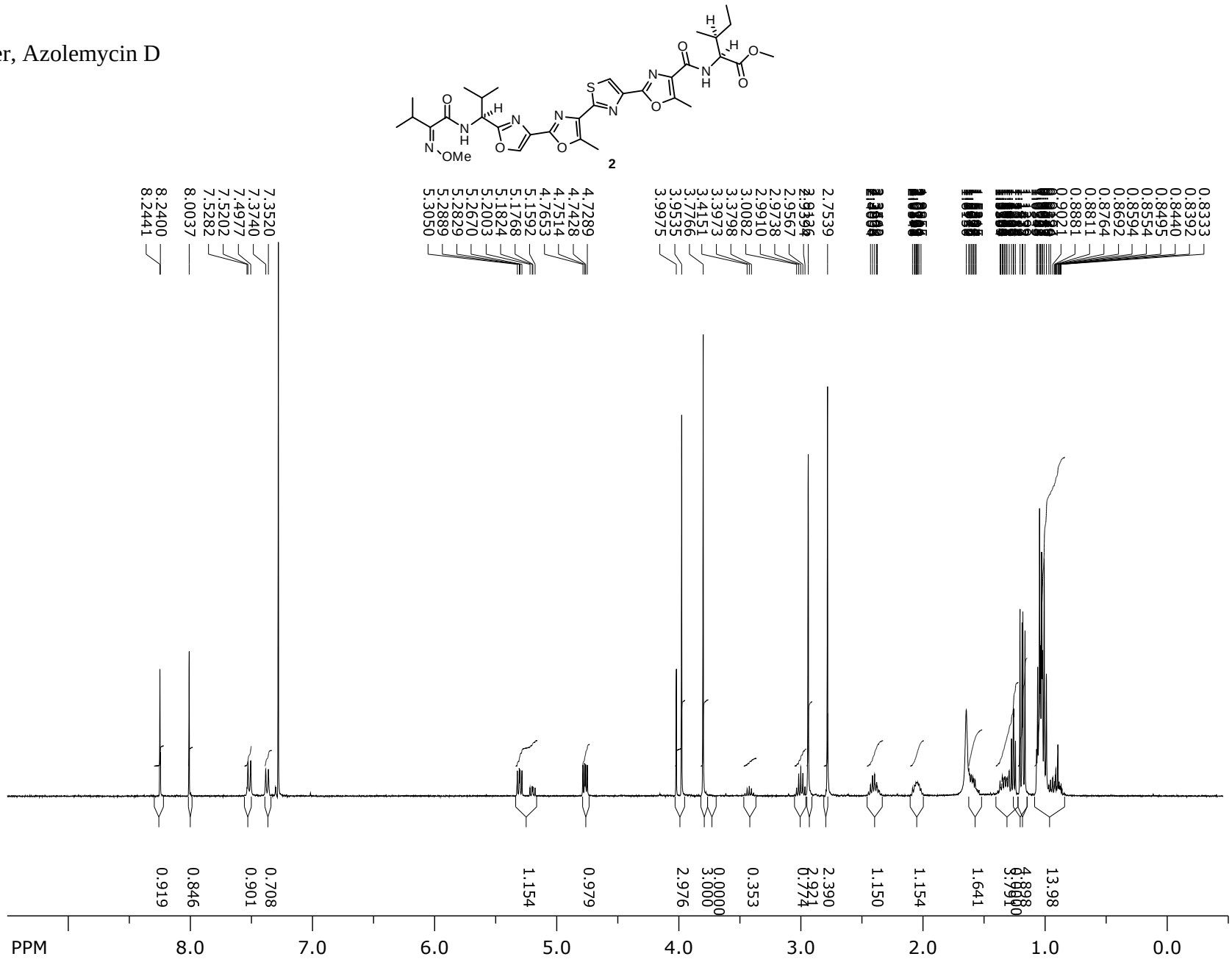
160
140
120
100
80
60
40
20
0

Comparison of Natural and Synthetic Azolemycin A *E* isomer ^{1}H and ^{13}C NMR

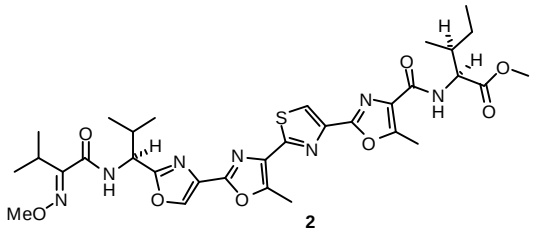


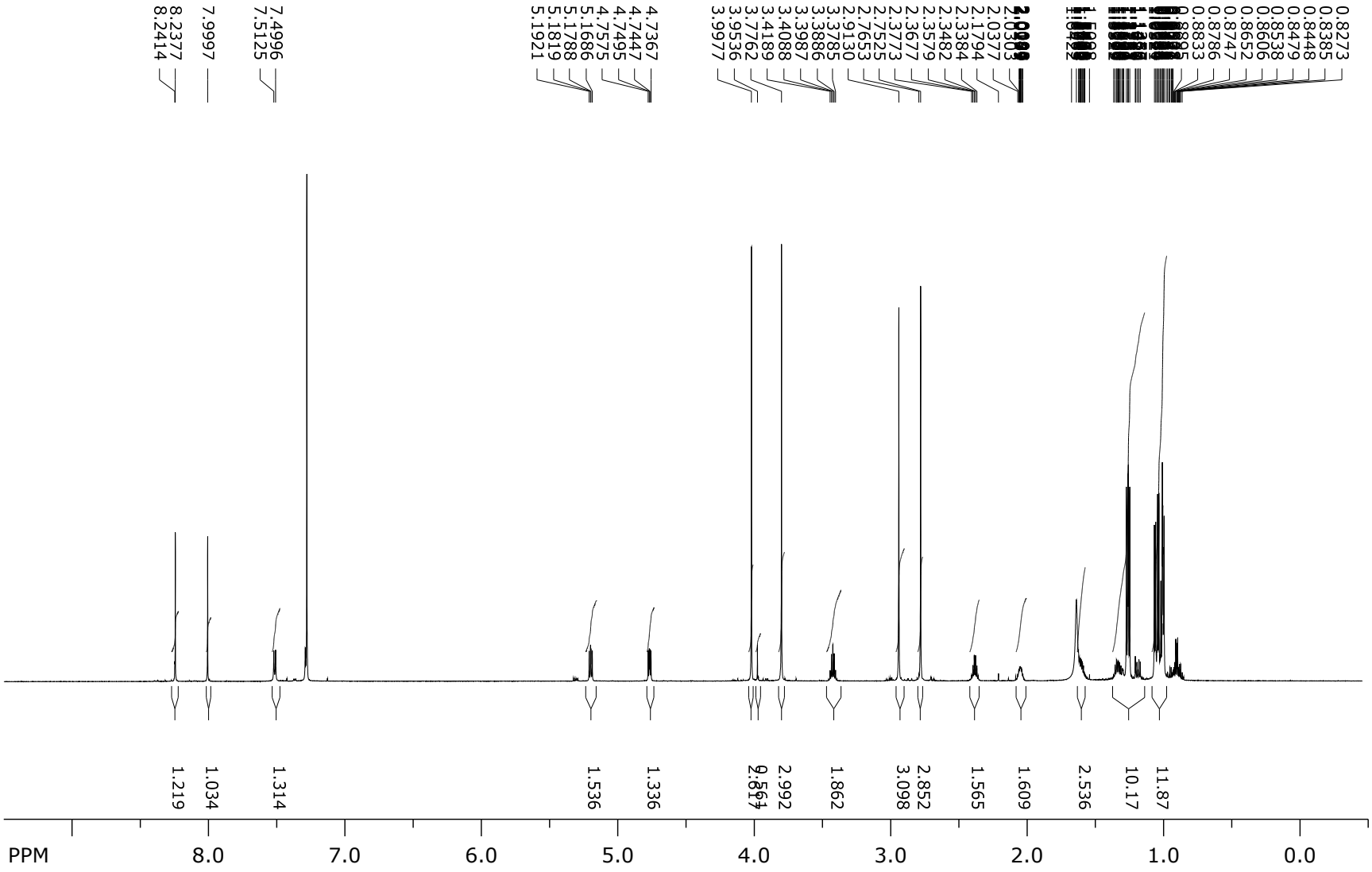
	Natural Product *E*		Synthesised Product	
C/N positions	1H (ppm, J Hz)	13C (ppm)	1H (ppm, J Hz)	13C (ppm)
1	1.28 (d, 7.0)	18.8	1.31 (d, 7.0)	18.7
2	1.25 (d, 7.0)	18.2	1.26 (d, 7.0)	18.3
3	3.47 (m)	25.6	3.50 (sept., 7.0)	25.8
4		158.8		158.8
N-OH	10.02 (s, b)		9.37 (s, b)	
5		163.5		163.8
NH	7.65 (b)		7.60 (d, 10.0)	
6	5.25 (dd, 6.5, 8.7)	52.7	5.25 (6.2, 9.4)	52.6
7	2.30 (m)	33.0	2.33 (oct, 6.6)	32.9
8/9	0.98 (d, 6.7)	19.0	1.00 (d, 6.8)	18.9
8/9	1.00 (d, 6.7)	18.4	1.02 (d, 6.9)	18.5
10		165.4		
11		129.8		
12	8.24 (s)	138.7	8.26 (s)	138.6
13		153.0		152.9
14		130.9		130.9
15		148.4		148.3
15-Me	2.89 (s)	12.2	2.90 (s)	12.1
16		162.2		162.3
17		143.9		143.8
18	7.99 (s)	120.2	8.00 (s)	120.2
19		154.4		154.3
20		129.9		129.9
21		153.7		153.7
21-Me	2.74 (s)	11.8	2.75 (s)	11.8
22		161.6		161.6
NH	7.52 (d, 8.8)		7.51 (d, 9.0)	
23	4.73 (dd, 5.4, 8.8)	56.3	4.75 (dd, 5.6, 8.9)	56.2
24		172.2		172.3
25	2.00 (m)	37.9	2.02 (m)	38.0
26	1.28/1.56 (m)	25.6	1.30 (m)/1.57 (dqd, 4.8, 7.5, 14.9)	25.3
27	0.96 (t, 7.4)	11.5	0.97 (t, 7.5)	11.5
28	0.97 (d, 6.3)	15.6	0.98 (d, 6.7)	15.6
29	3.76 (s)	52.6	3.78	52.1

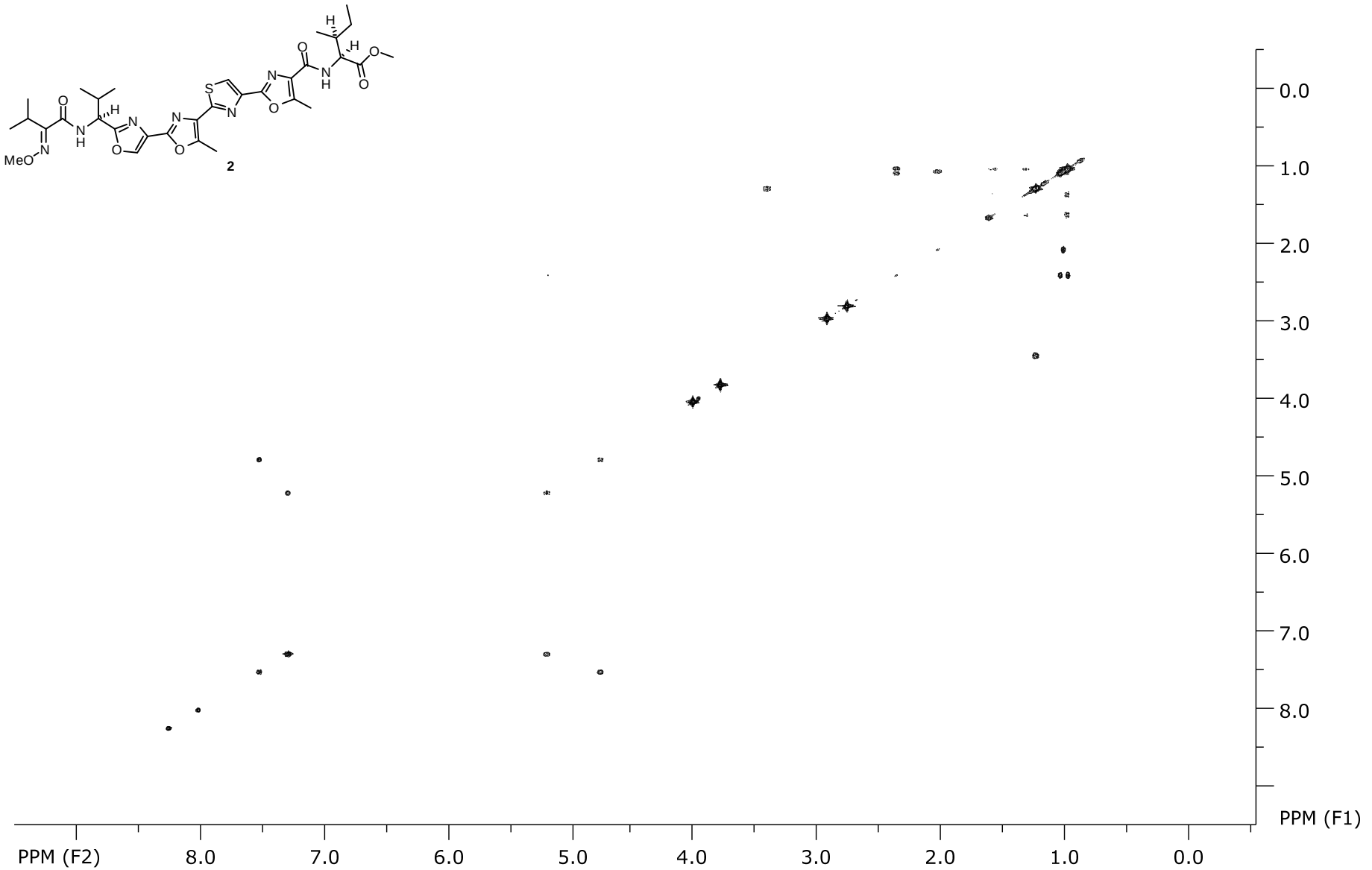
Z- isomer, Azolemycin D



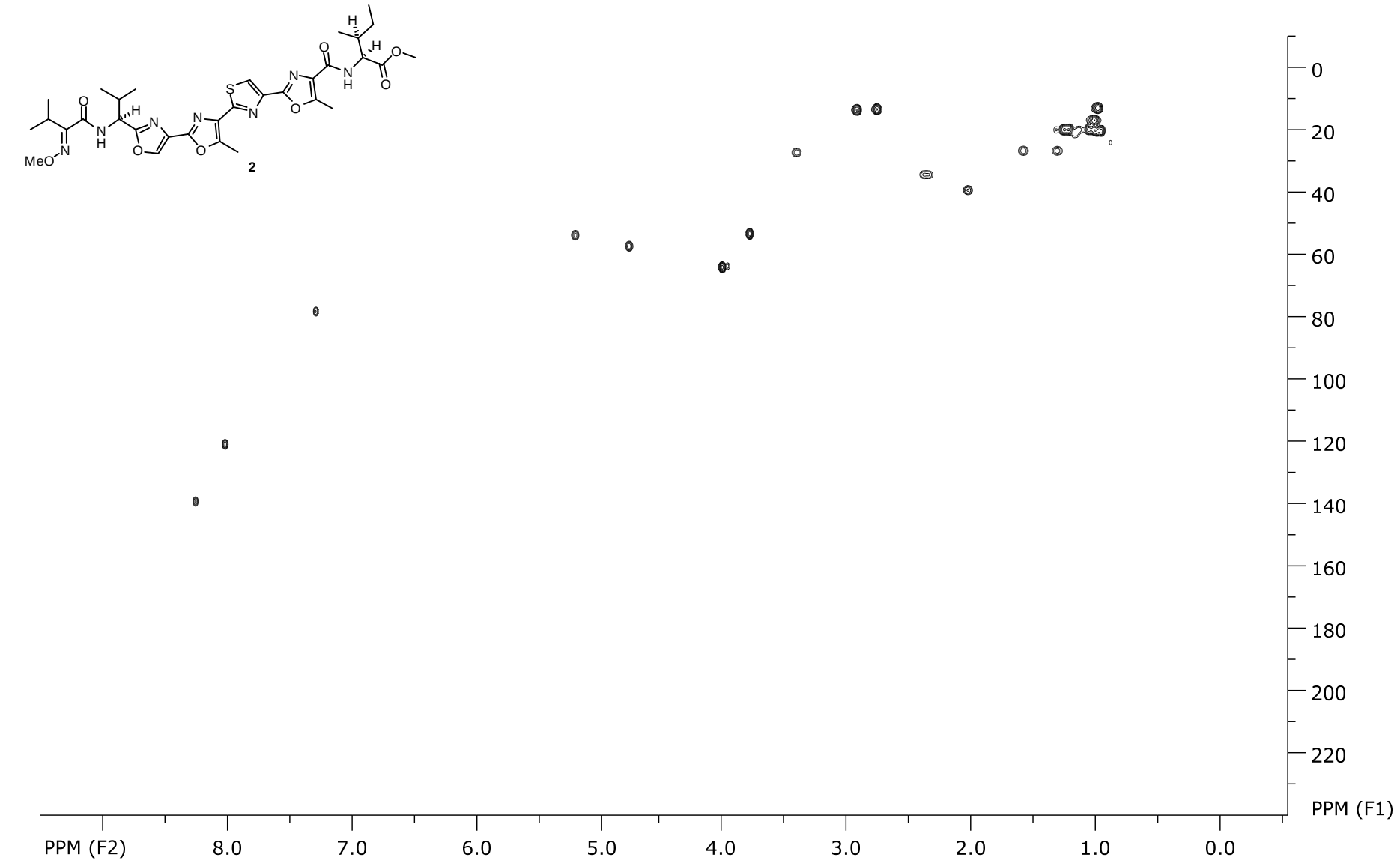
E-isomer, Azolemycin C



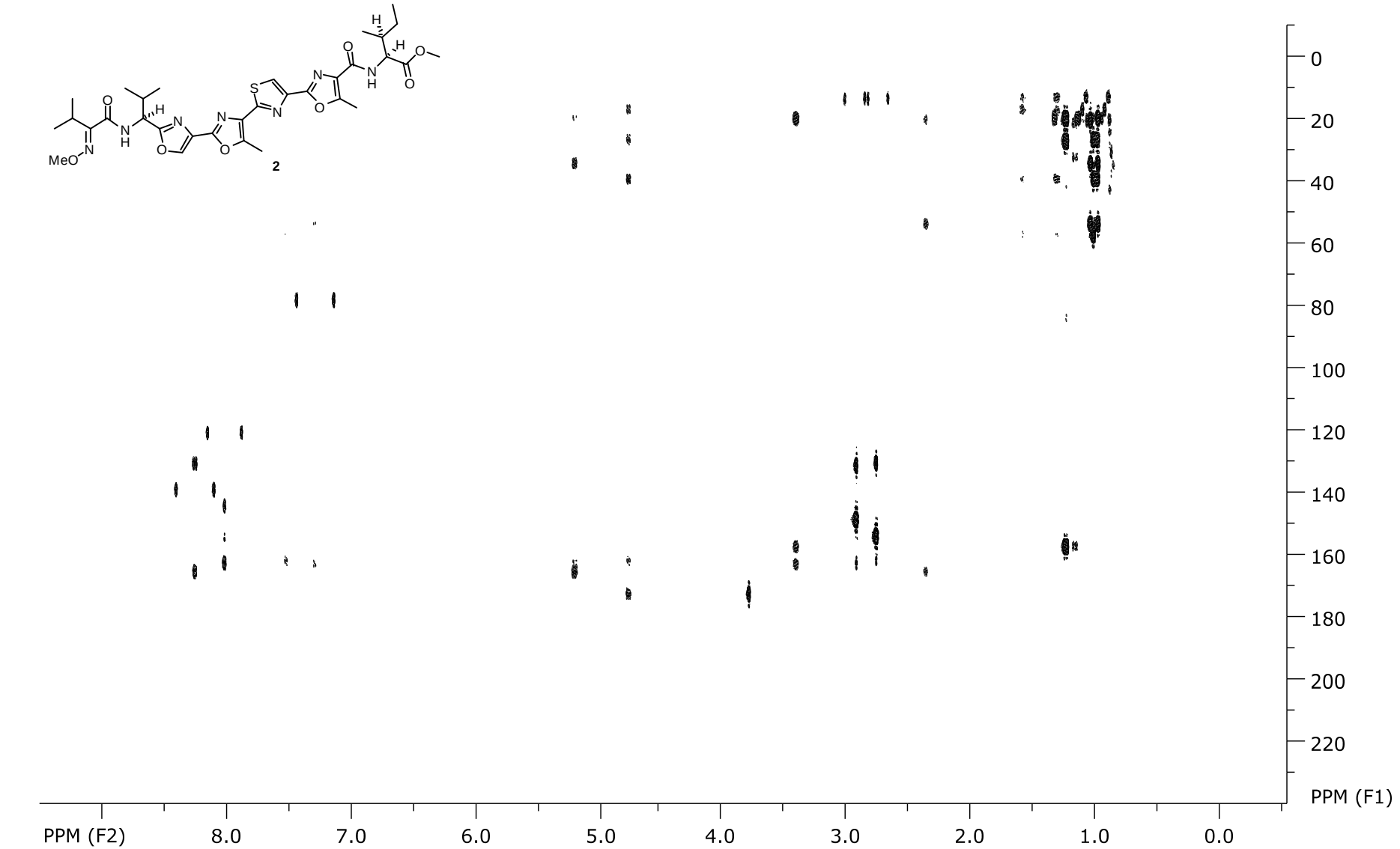




COSY


MeO
2
0
20
40
60
80
100
120
140
160
180
200
220
PPM (F1)
PPM (F2)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

HMQC


MeO
2
0
20
40
60
80
100
120
140
160
180
200
220
PPM (F1)
PPM (F2)
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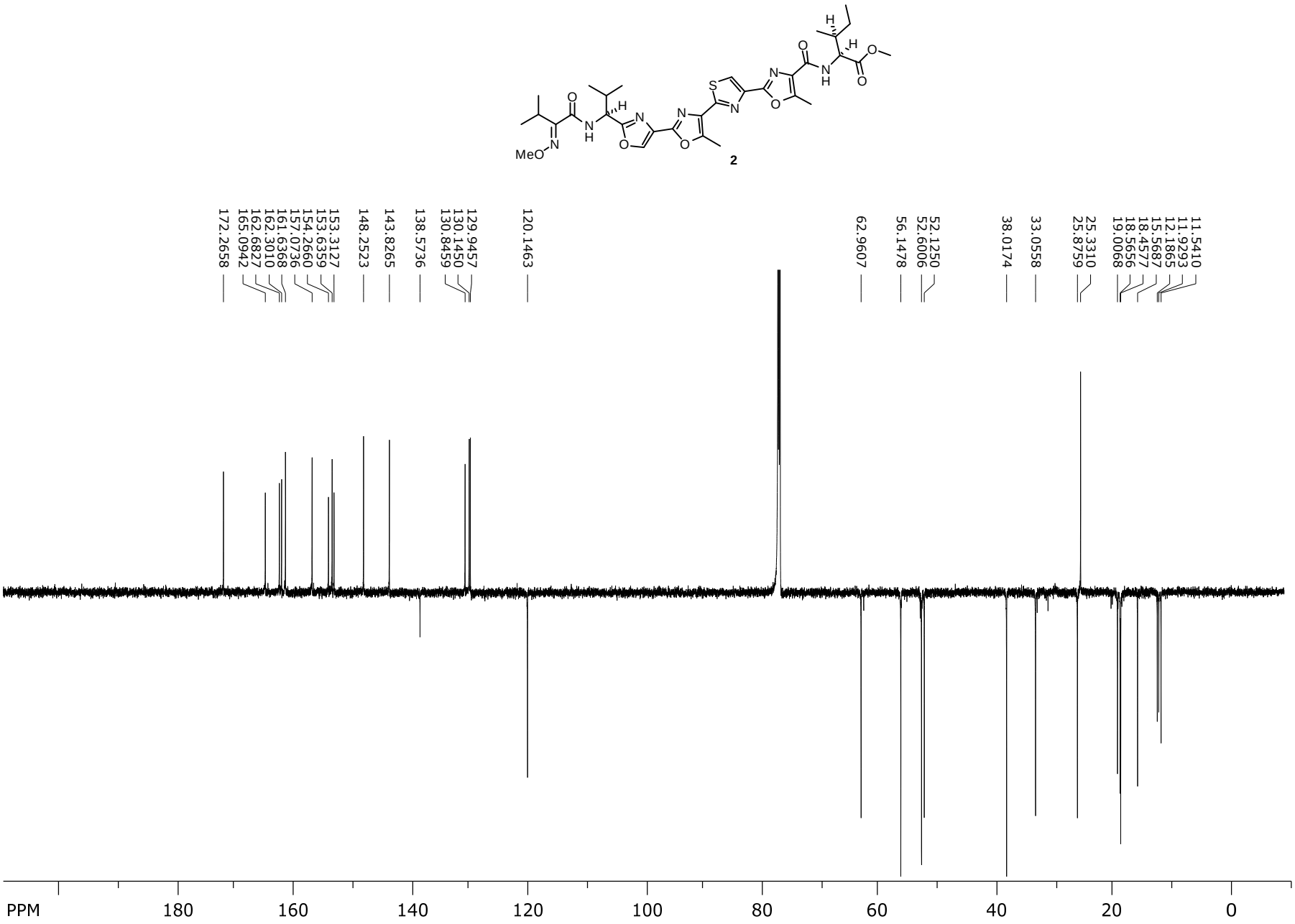
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

HMBC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138.5736
130.8459
130.1450
129.9457
120.1463
62.9607
56.1478
52.6006
52.1250
38.0174
33.0558
25.8759
25.3310
19.0068
18.5656
18.4577
15.5687
12.1865
11.9293
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PPM
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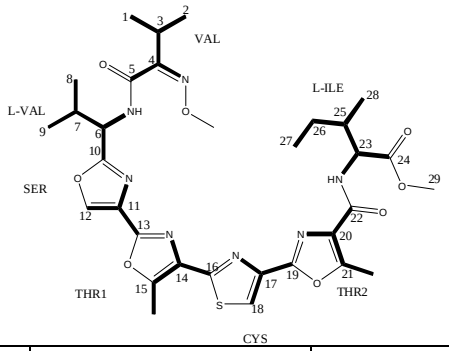
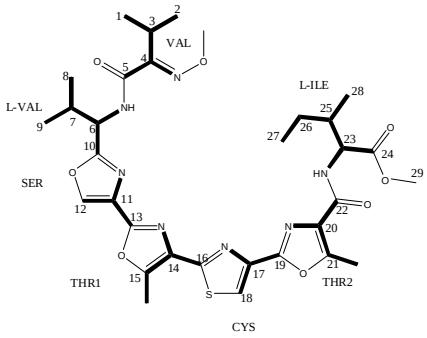
160
140
120
100
80
60
40
20
0

Comparison of Natural and Synthetic Azolemycin D *Z*-isomer ^{1}H NMR

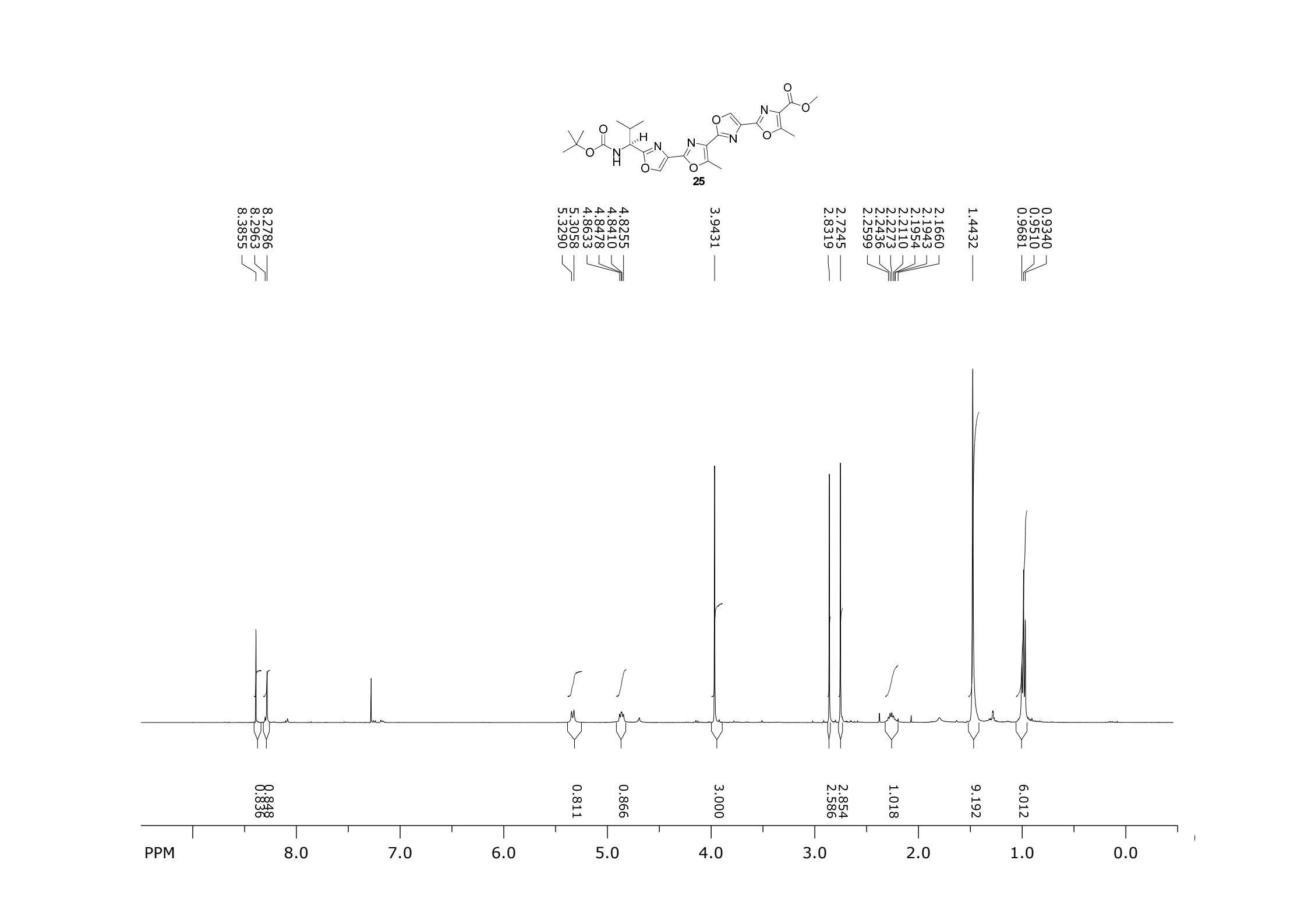


	Natural	Synthetic
C/N positions	^{1}H (ppm, *J* Hz)	^{1}H (ppm, *J* Hz)
1	1.14 (d, 7.0)	1.13 (d, 6.9)
2	1.15 (d, 7.0)	1.15 (d, 7.0)
3	2.97 (m)	2.96 (sept., 6.8)
4		
N-O-Me	3.95 (s)	3.94 (s)
5		
NH	7.38 (d, 8.9)	7.35(d, 9.0)
6	5.28 (dd, 6.4, 8.9)	5.28(dd, 6.4, 8.8)
7	2.35 (m)	2.36(m)
8	1.00 (d, 6.7)	0.99(d, 6.8)
9	1.03 (d, 6.7)	1.00 (d, 6.2)
10		
11		
12	8.23(s)	8.23(s)
13		
14		
15		
15-Me	2.90(s)	2.90(s)
16		
17		
18	7.99(s)	7.99(s)
19		
20		
21		
21-Me	2.74(s)	2.74(s)
22		
NH	7.51(d, 8.6)	7.50(d, 8.8)
23	4.74 (dd, 5.4, 8.6)	4.74 (dd, 5.6, 9.0)
24		
25	2.00 (m)	2.00 (m)
26	1.28/1.56(m)	1.29/1.56(m)
27	0.96(t, 7.4)	0.96(t, 7.2)
28	0.97(d, 6.3)	0.97(d, 6.6)
29	3.77(s)	3.77(s)

Comparison of Natural and Synthetic Azolemycin C *E*-isomer ^{1}H and ^{13}C NMR



	Natural Product		Synthetic Product	
C/N positions	^{1}H (ppm, *J* Hz)	^{13}C (ppm)	^{1}H (ppm, *J* Hz)	^{13}C (ppm)
1	1.24 (d, 7.0)	18.5	1.21 (d, 7.1)	18.6
2	1.20 (d, 7.0)	18.4	1.19 (d, 7.0)	18.5
3	3.39 (m)	25.6	3.38 (sept., 7.0)	23.9
4		157.6		157.1
N-O-Me	3.99 (s)	62.7	3.98 (s)	63.0
5		162.8		162.7
NH	7.29 (d, 8.8)		7.48 (d, 9.0)	
6	5.19 (dd, 6.4, 8.8)	52.6	5.16 (dd, 7.2, 9.4)	52.6
7	2.30 (m)	32.9	2.33 (oct., 6.8)	33.0
8	0.98 (d, 6.7)	19.0	0.98(d, 6.8)	19.0
9	1.00 (d, 6.7)	18.4	1.00 (d, 6.8)	19.0
10		165.3		165.1
11		129.8		129.9
12	8.23 (s)	138.6	8.22 (s)	138.6
13		153.0		153.3
14		130.9		130.8
15		148.2		148.3
15-Me	2.88 (s)	11.8	2.89 (s)	12.2
16		161.9		162.3
17		143.9		143.8
18	7.99 (s)	120.1	7.98 (s)	120.1
19		154.3		154.3
20		129.8		130.0
21		153.7		153.6
21-Me	2.74 (s)	11.4	2.73(s)	11.9
22		161.7		161.6
NH	7.51 (d, 8.7)		7.25 (d, 9.0)	
23	4.74 (dd, 5.4, 8.7)	56.1	4.73 (dd, 5.7, 9.0)	56.1
24		172.1		172.3
25	2.00 (m)	37.9	1.99 (m)	38.0
26	1.28/1.56 (m)	25.4	1.28/1.56(m)	25.3
27	0.96 (t, 7.4)	11.6	0.95 (t, 7.4)	11.5
28	0.97 (d, 6.3)	15.5	0.95 (d, 6.8)	15.6
29	3.77 (s)	52.6	3.76(s)	52.6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5.3290
5.3058
4.8633
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4.8410
4.8255
3.9431
2.8319
2.7245
2.2599
2.2436
2.2273
2.2110
2.1954
2.1943
2.1660
1.4432
0.9681
0.9510
0.9340
0.836
0.848
0.811
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3.000
2.586
2.854
1.018
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6.0
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4.0
3.0
2.0
1.0
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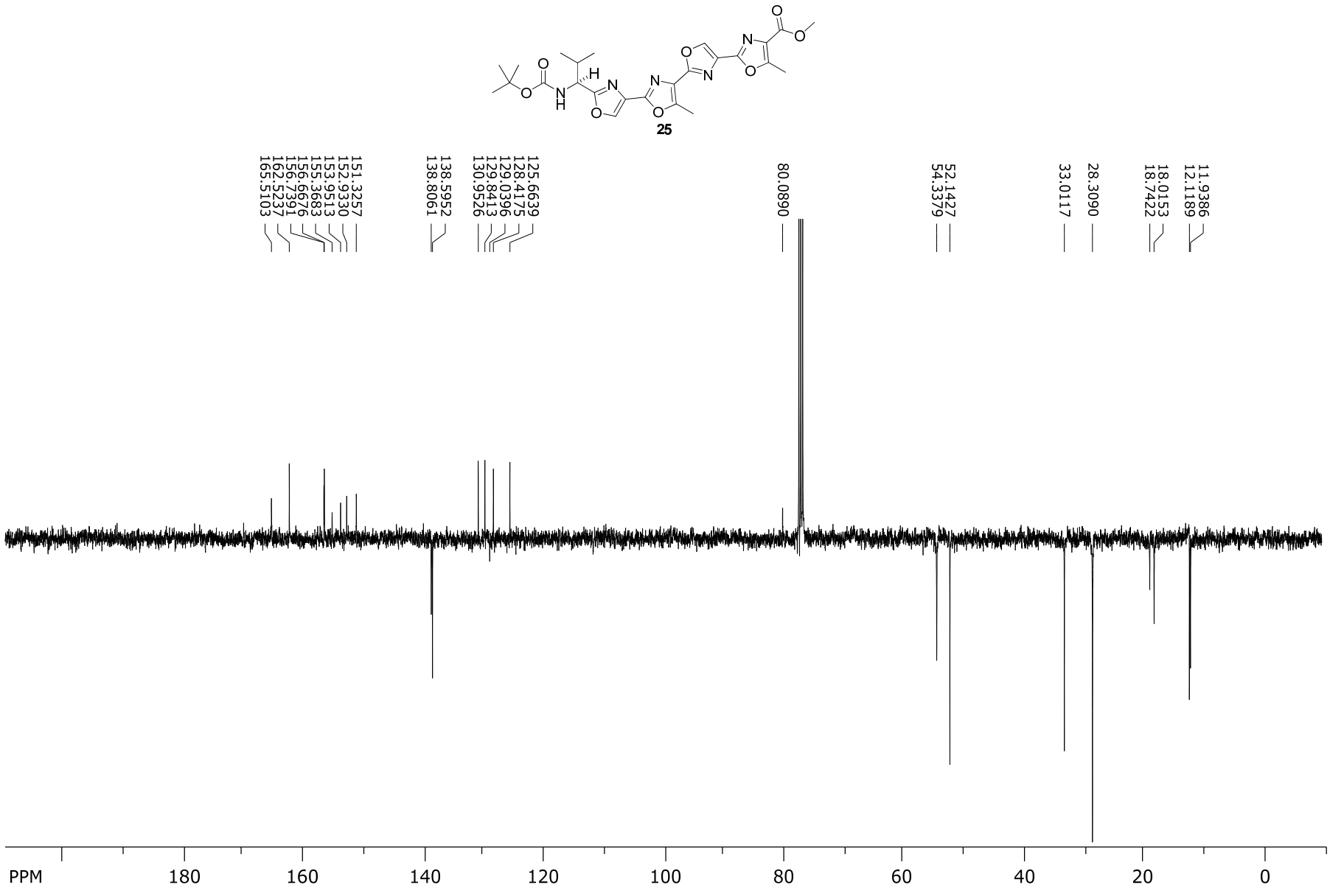
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128.4175
125.6639
80.0890
54.3379
52.1427
33.0117
28.3090
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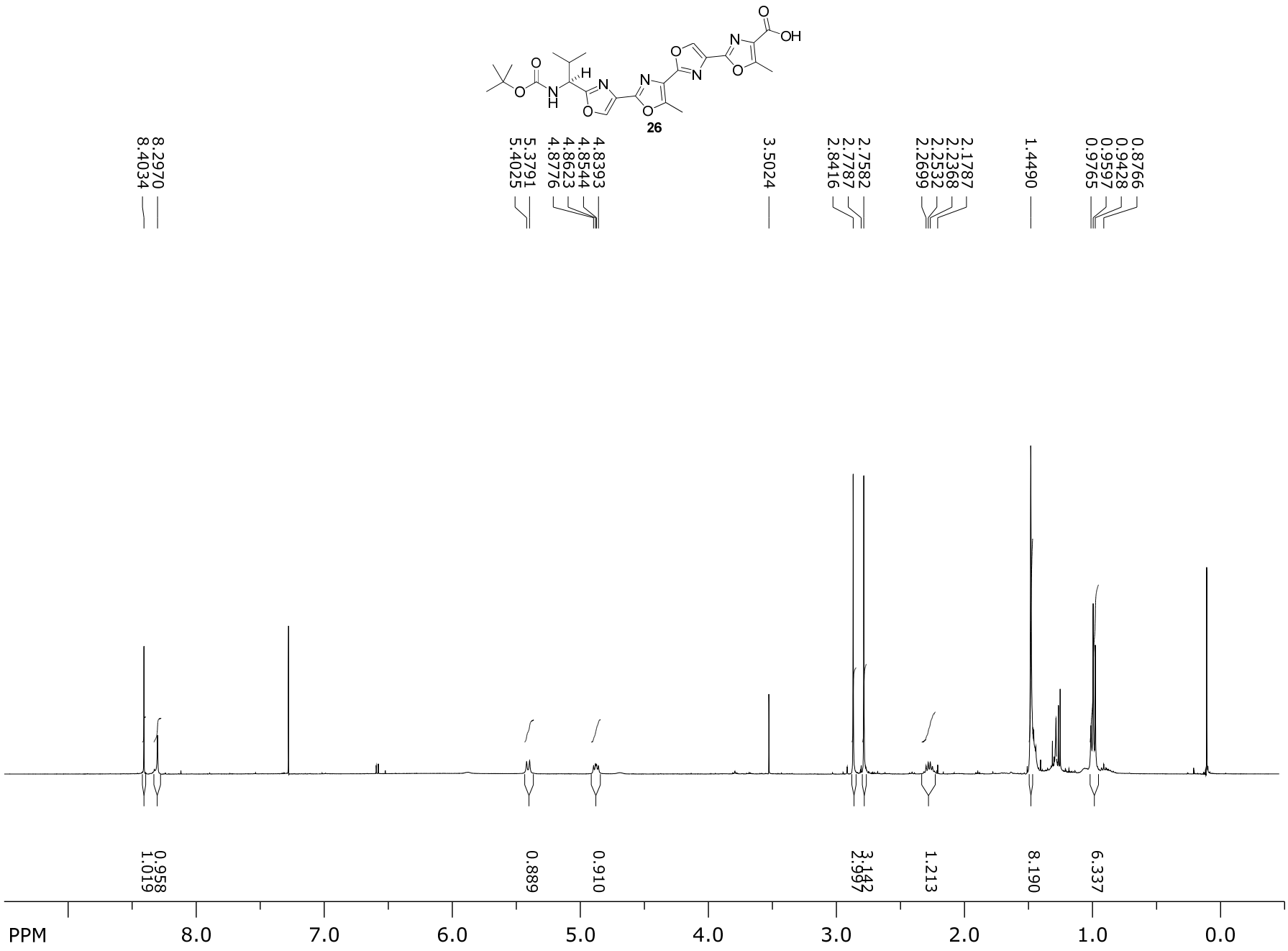
140
120
100
80
60
40
20
0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4.8544
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3.5024
2.7582
2.7787
2.8416
2.1787
2.2368
2.2532
2.2699
1.4490
0.8766
0.9428
0.9597
0.9765
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0.910
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2.997
1.213
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4.0
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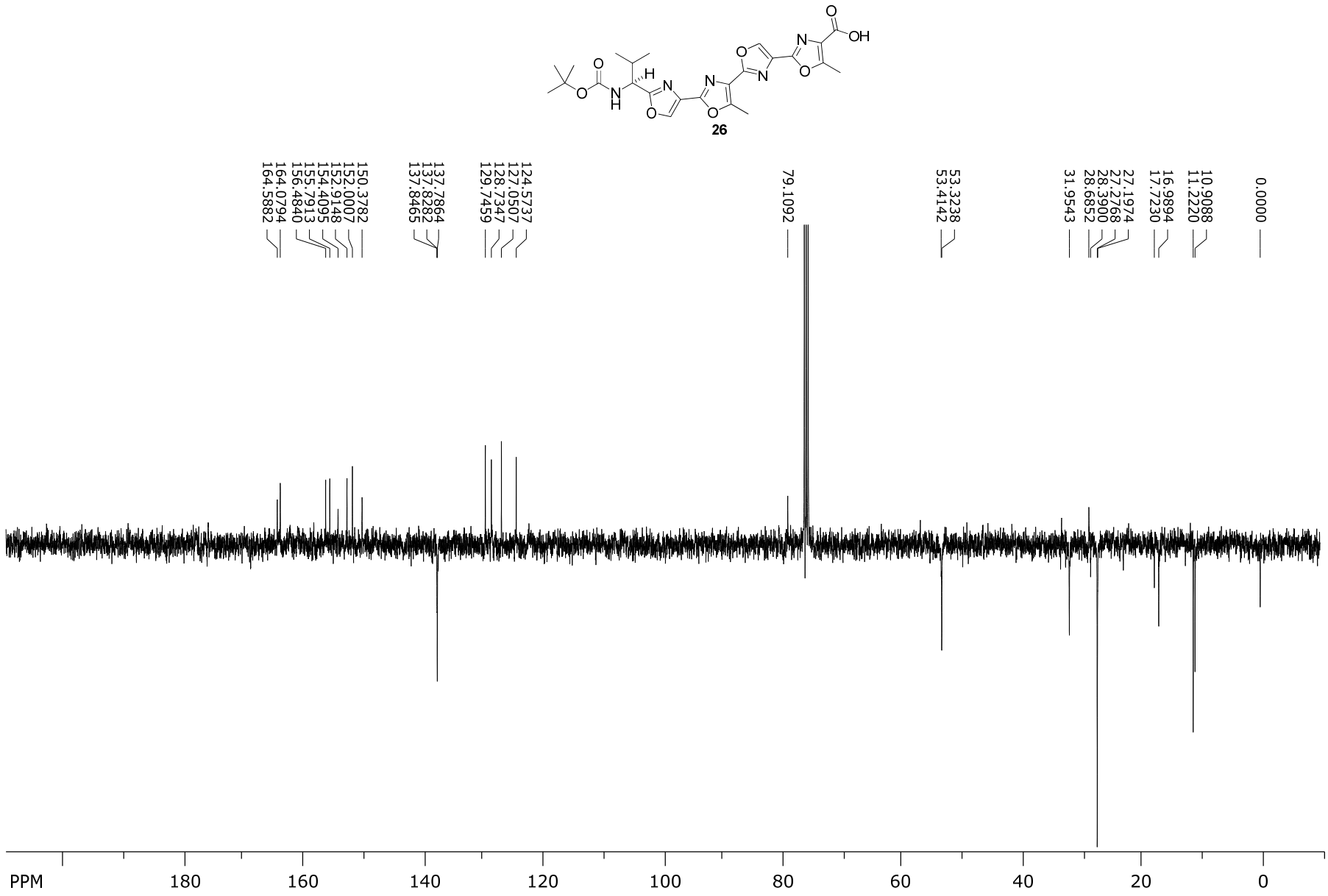
2.0
1.0
0.0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155.7913
154.4095
152.9148
152.0007
150.3782
137.8465
137.8282
137.7864
129.7459
128.7347
127.0507
124.5737
79.1092
53.4142
53.3238
31.9543
28.6852
28.3900
27.2768
27.1974
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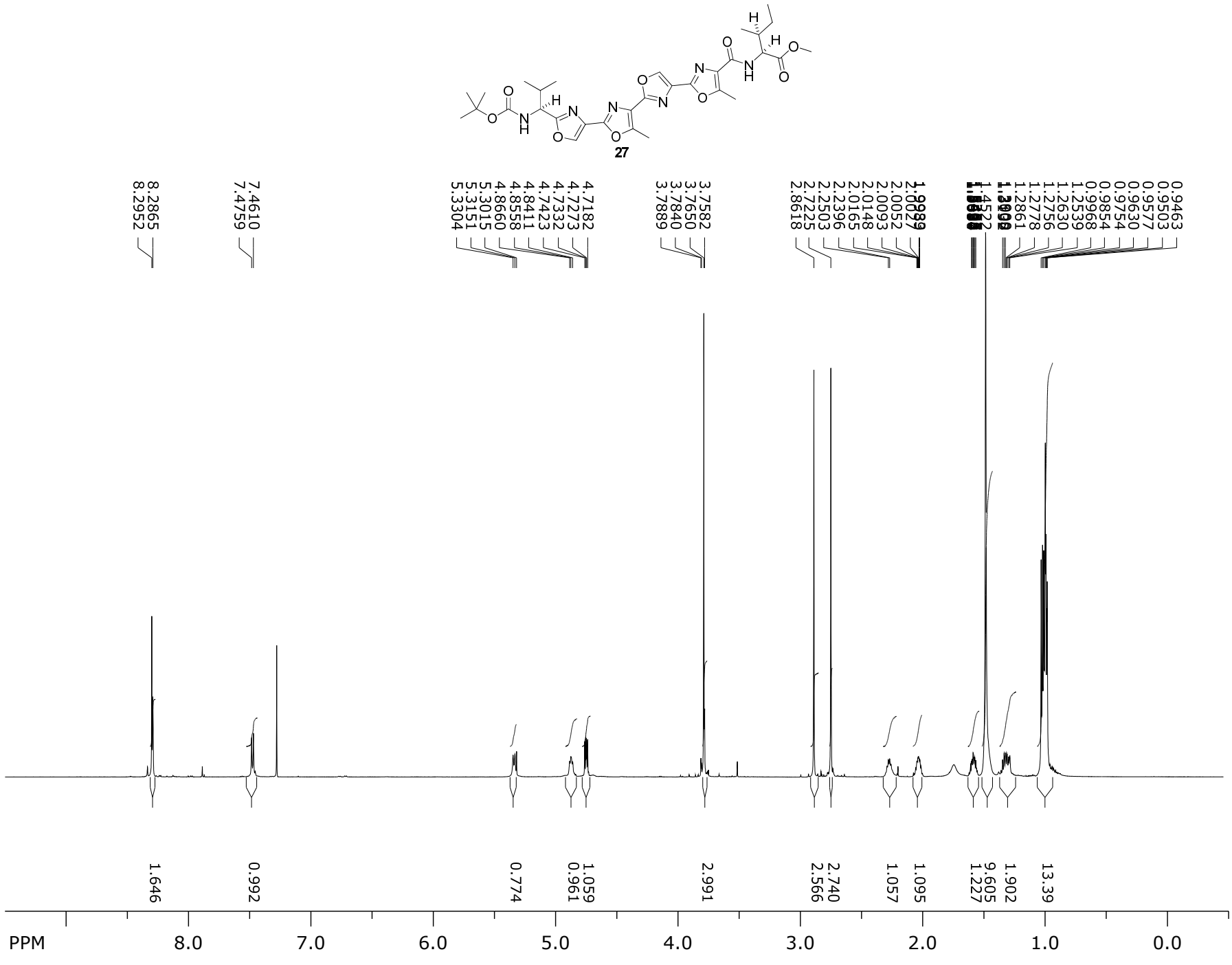
140
120
100
80
60
40
20
0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4.7273
4.7182
3.7889
3.7840
3.7650
3.7582
2.8618
2.7225
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2.0148
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2.0052
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0.9854
0.9968
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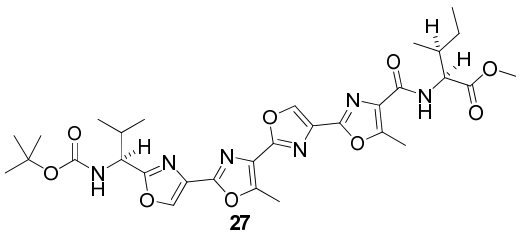

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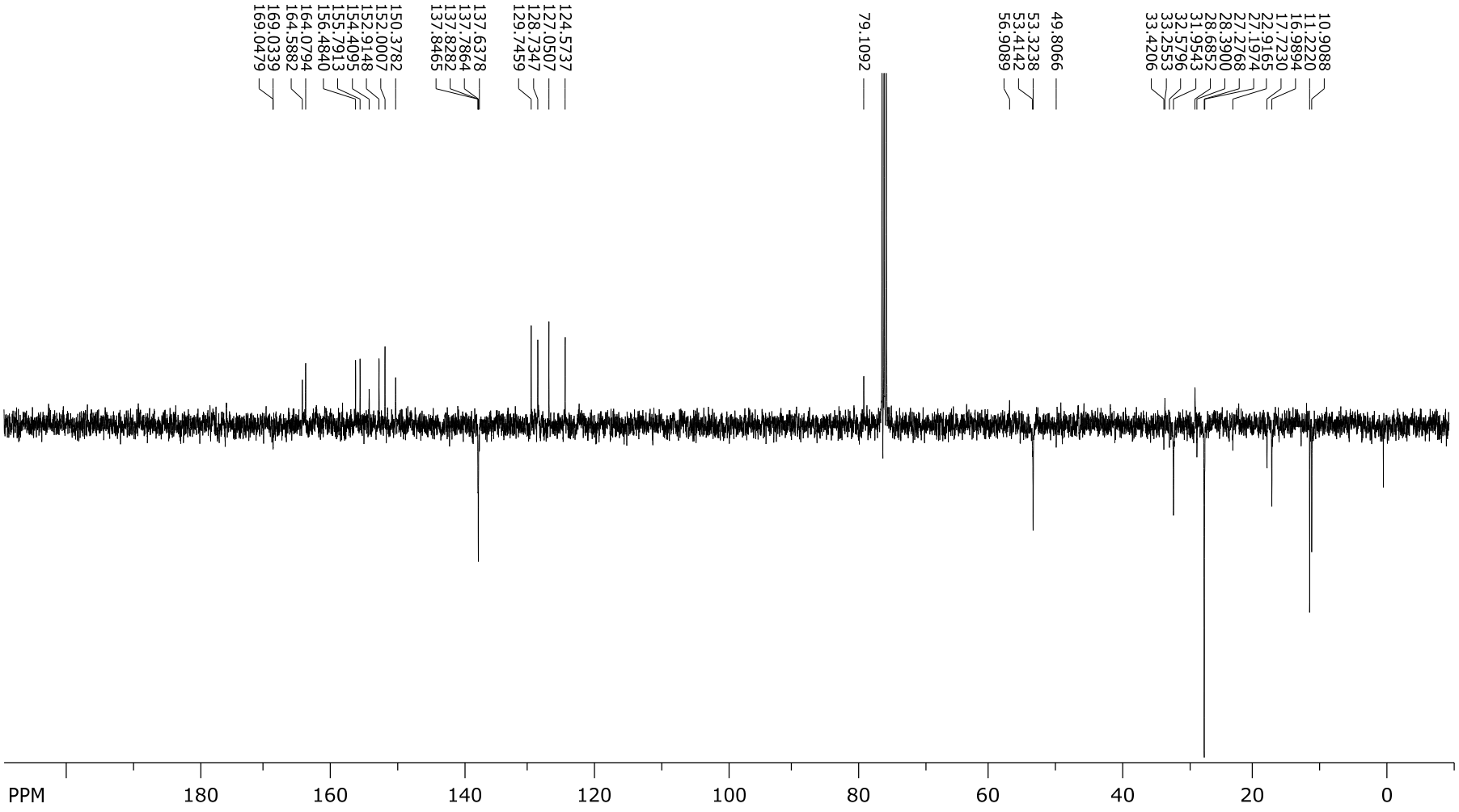
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124.5737
79.1092
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33.2553
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31.9543
28.6852
28.3900
27.2768
27.1974
22.9165
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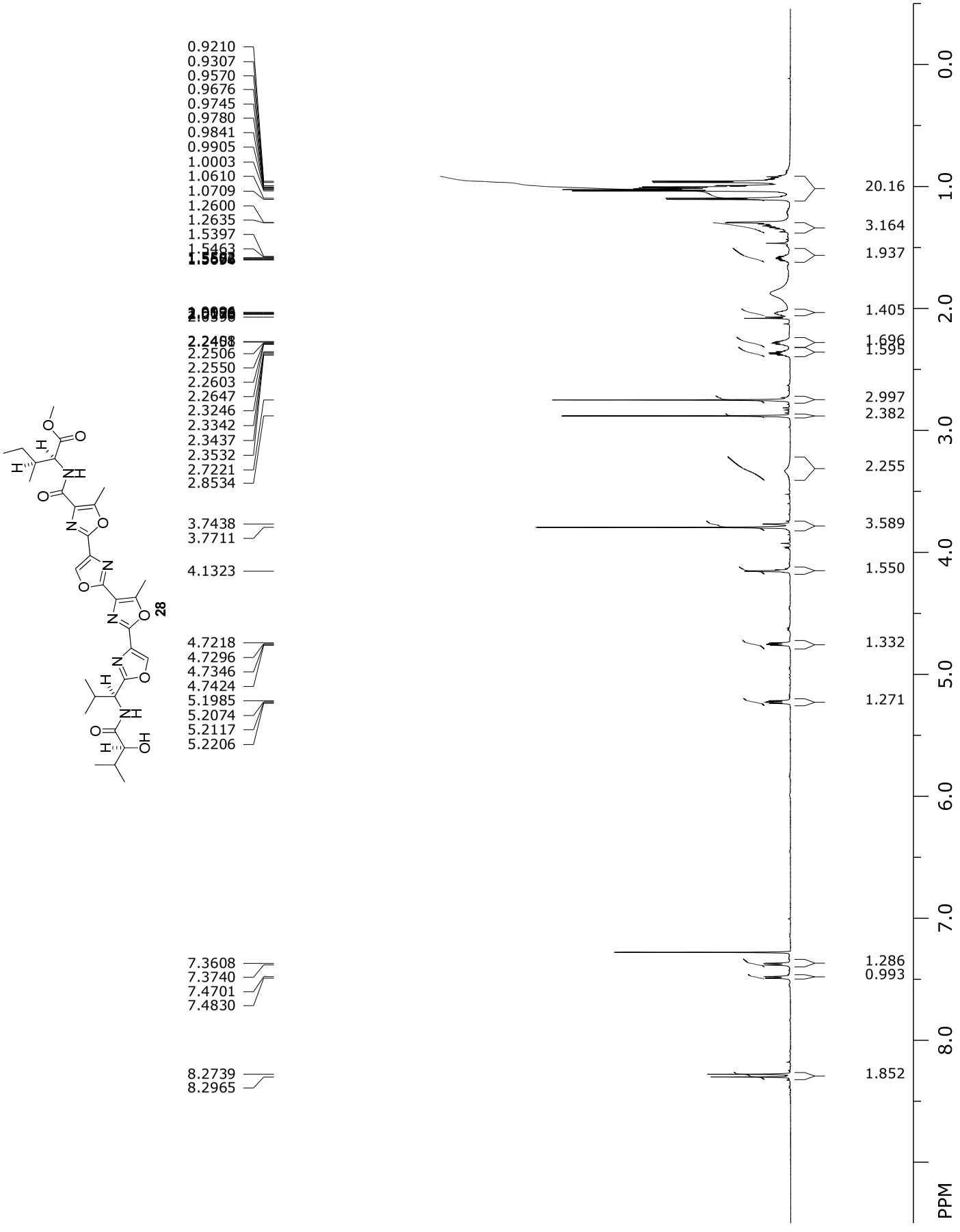
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1.5397
1.5463
2.2506
2.2550
2.2603
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2.3342
2.3437
2.3532
2.7221
2.8534
3.7438
3.7711
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4.7218
4.7296
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4.7424
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1.550
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1.286
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5.0
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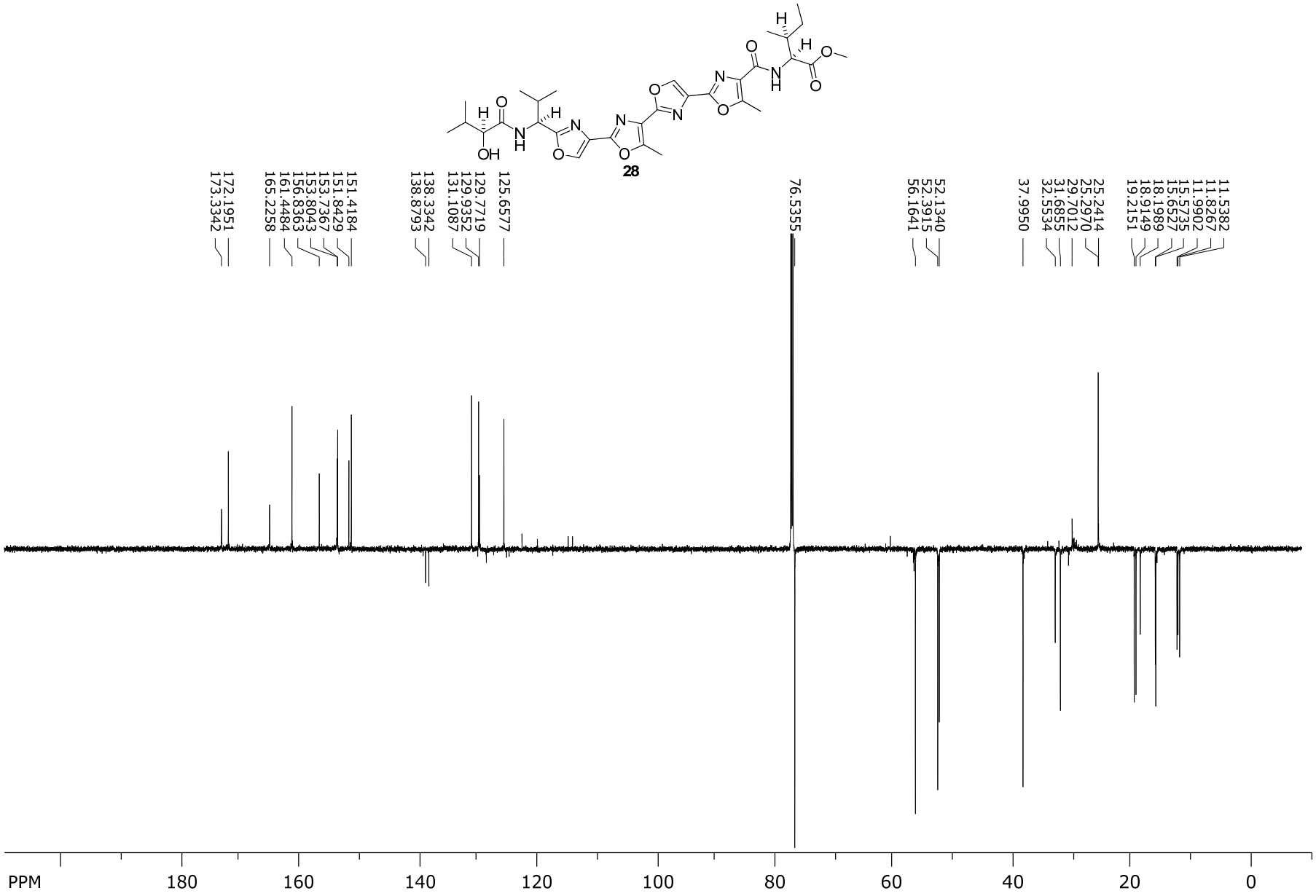
PPM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120
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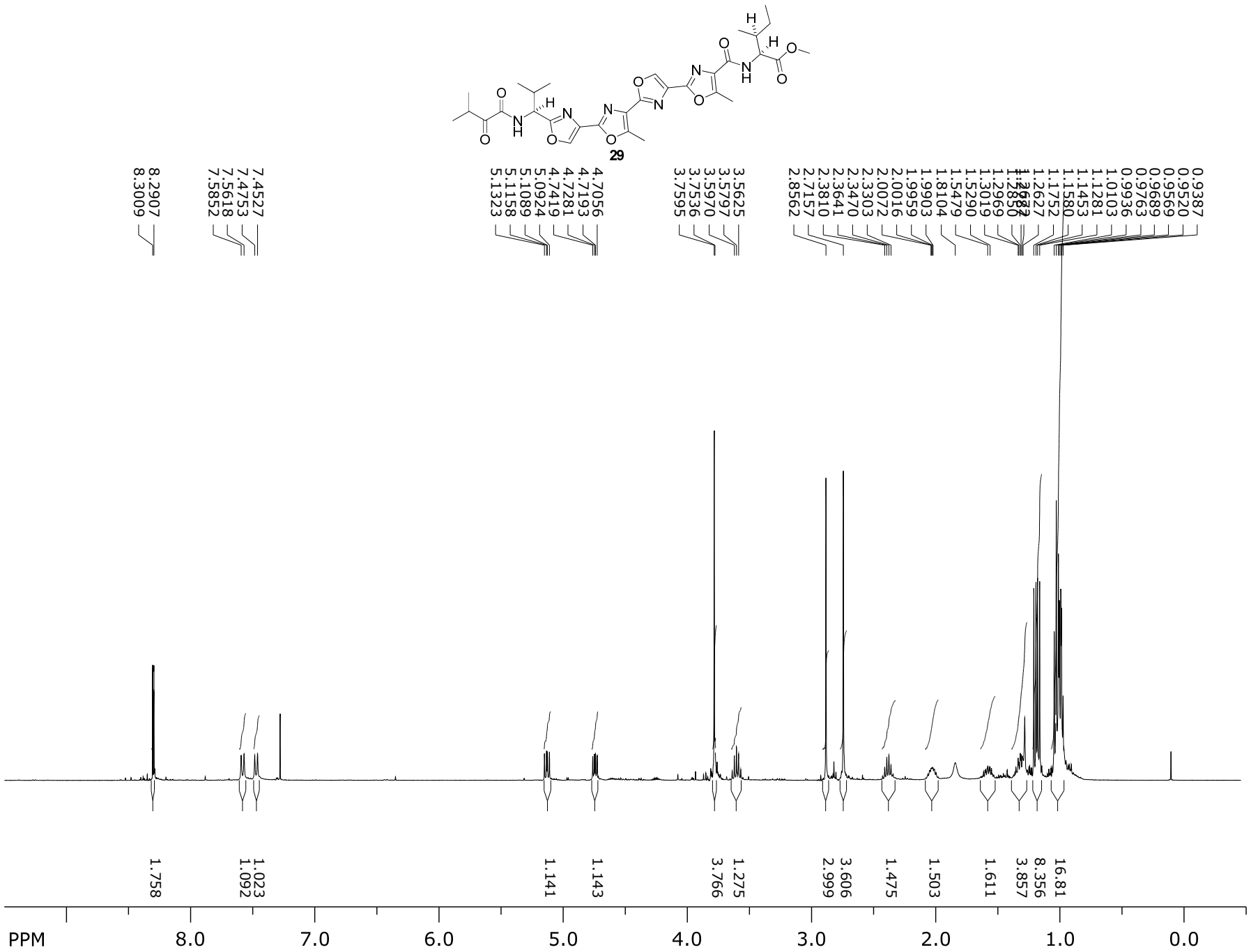
20
0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3.5625
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1.275
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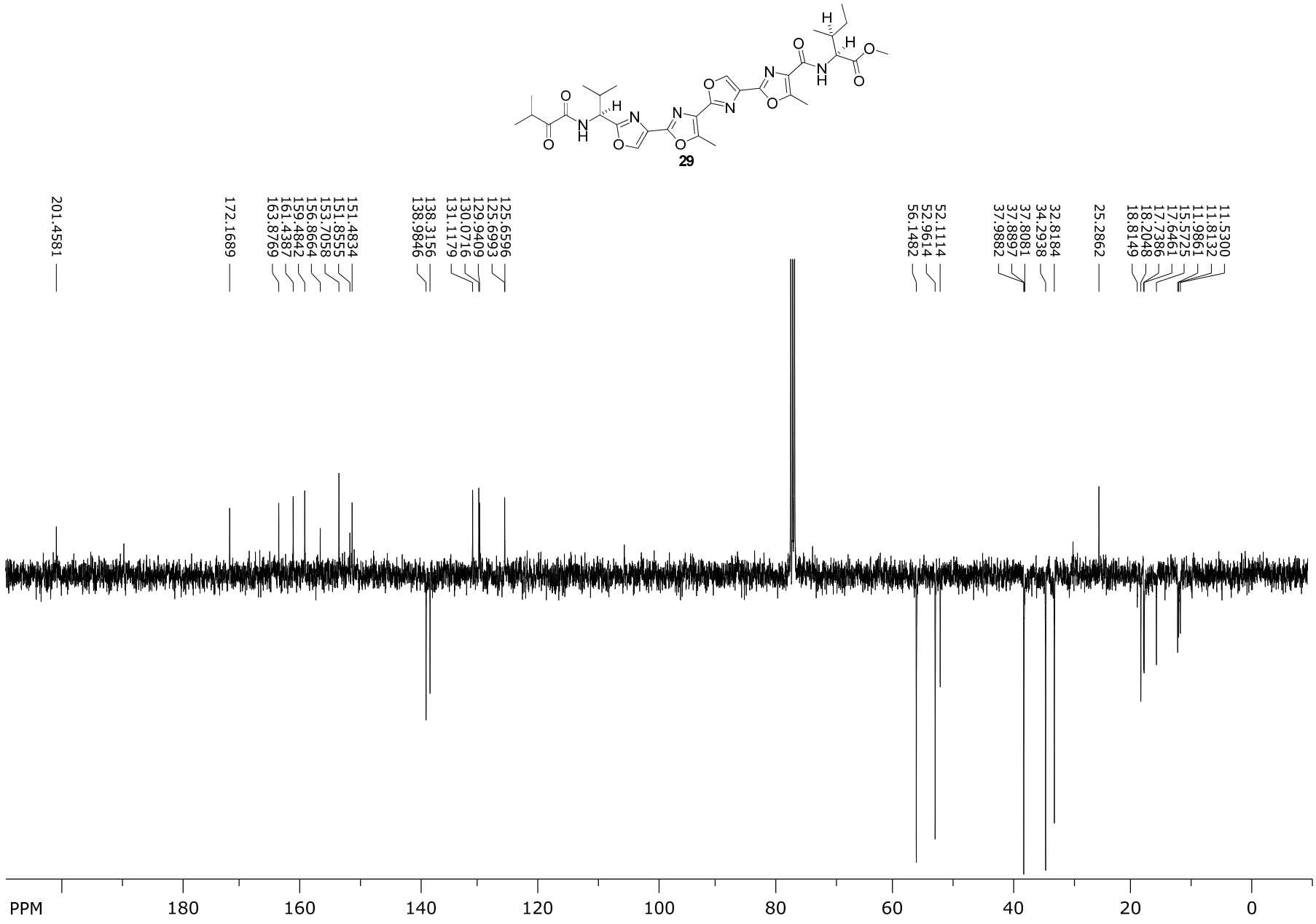
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32.8184
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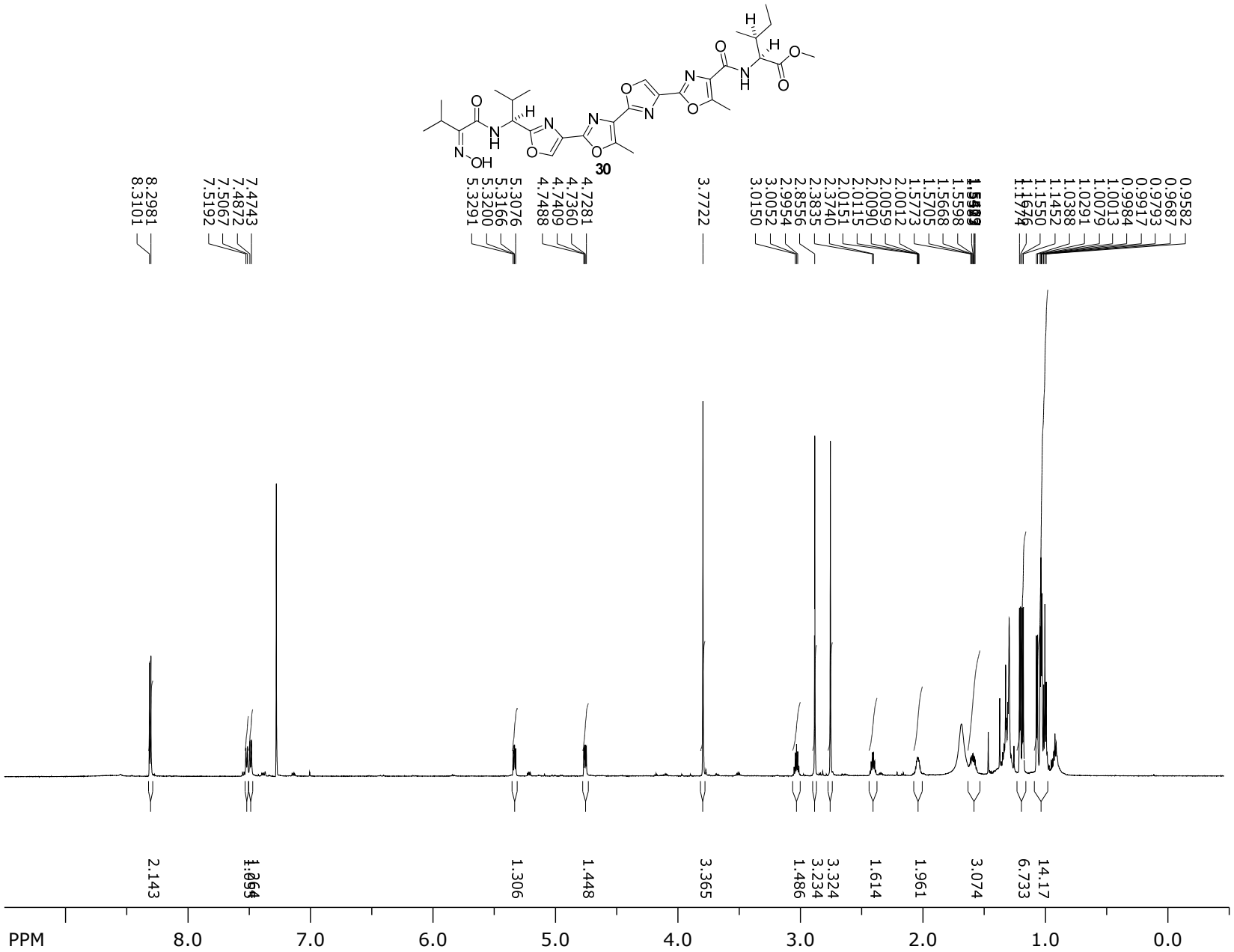
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3.0052
2.9954
2.8556
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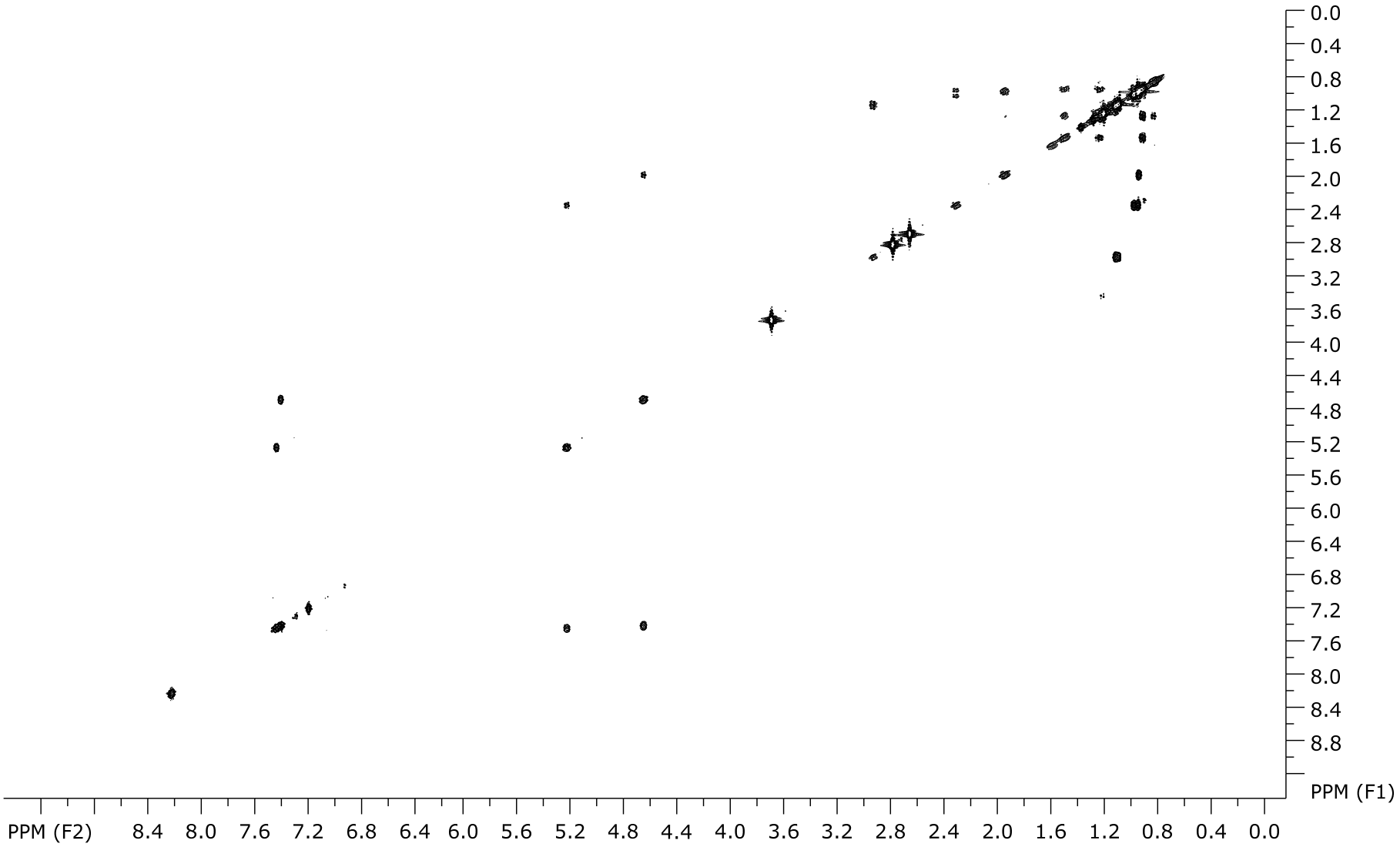
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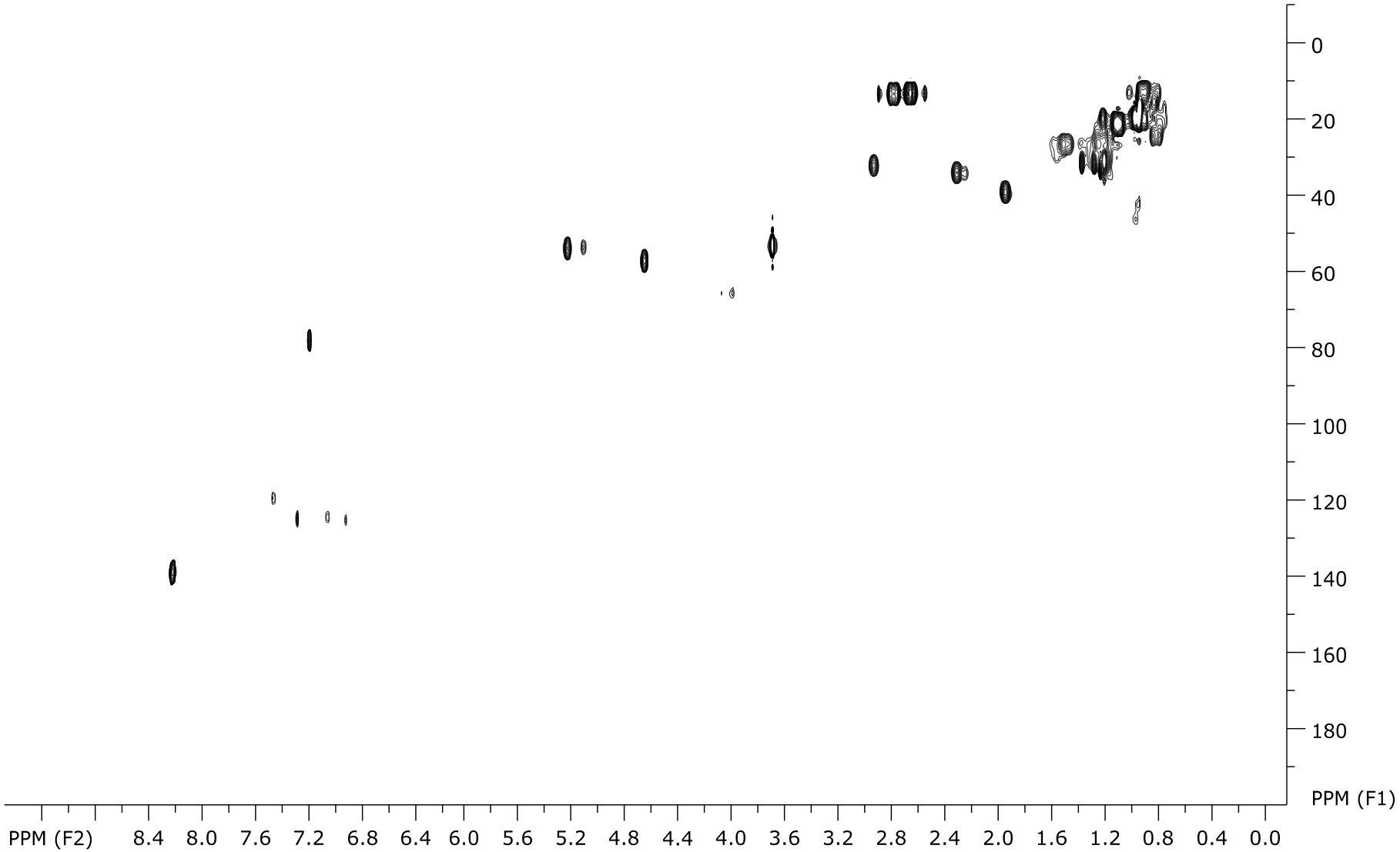
8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0
PPM (F1)
0.0 0.4 0.8 1.2 1.6 2.0 2.4 2.8 3.2 3.6 4.0 4.4 4.8 5.2 5.6 6.0 6.4 6.8 7.2 7.6 8.0 8.4 8.8

COSY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40
60
80
100
120
140
160
180
PPM (F1)
PPM (F2)
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8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
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3.2
2.8
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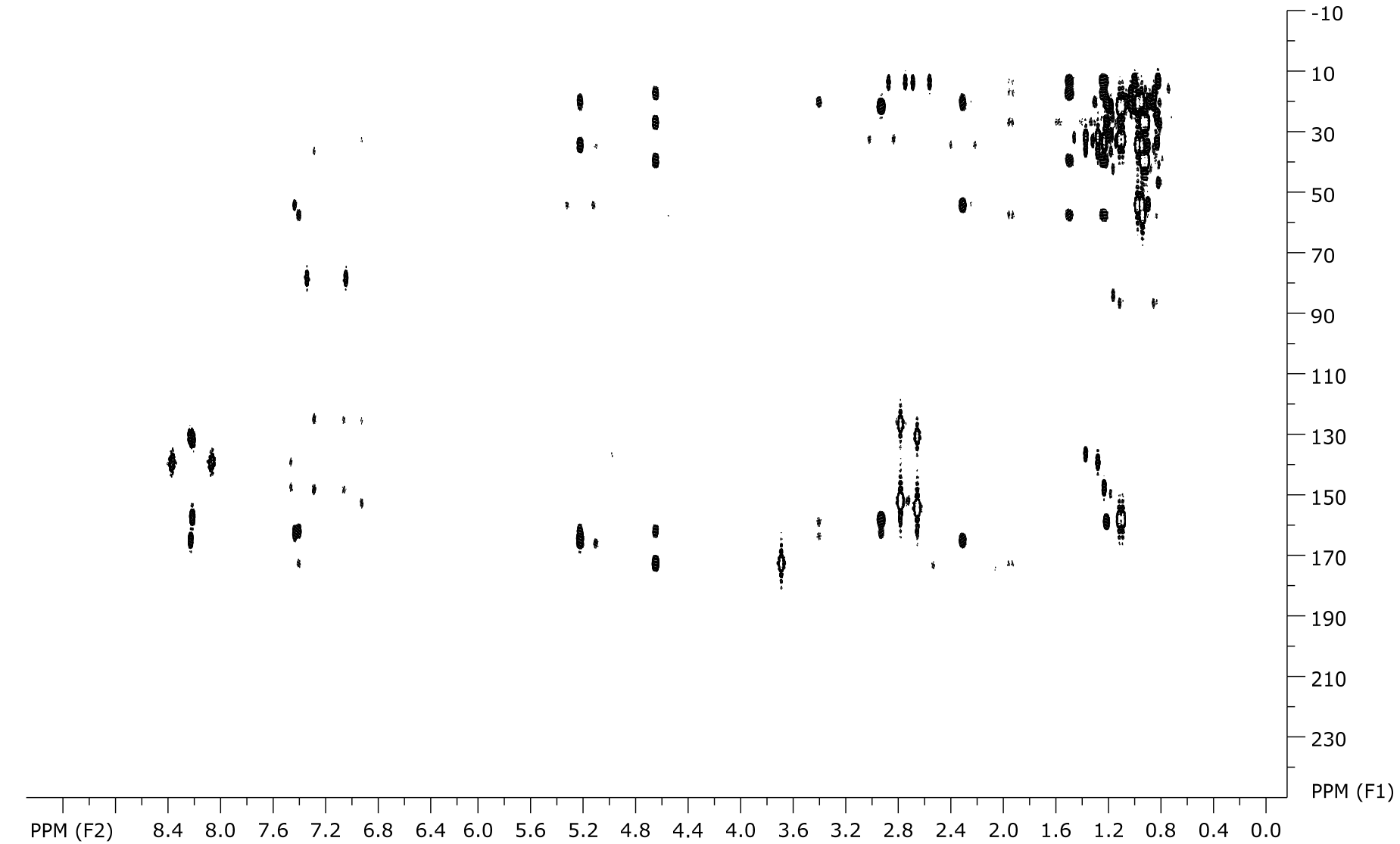
2.0
1.6
1.2
0.8
0.4
0.0

HMQC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PPM (F2)
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8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
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1.2
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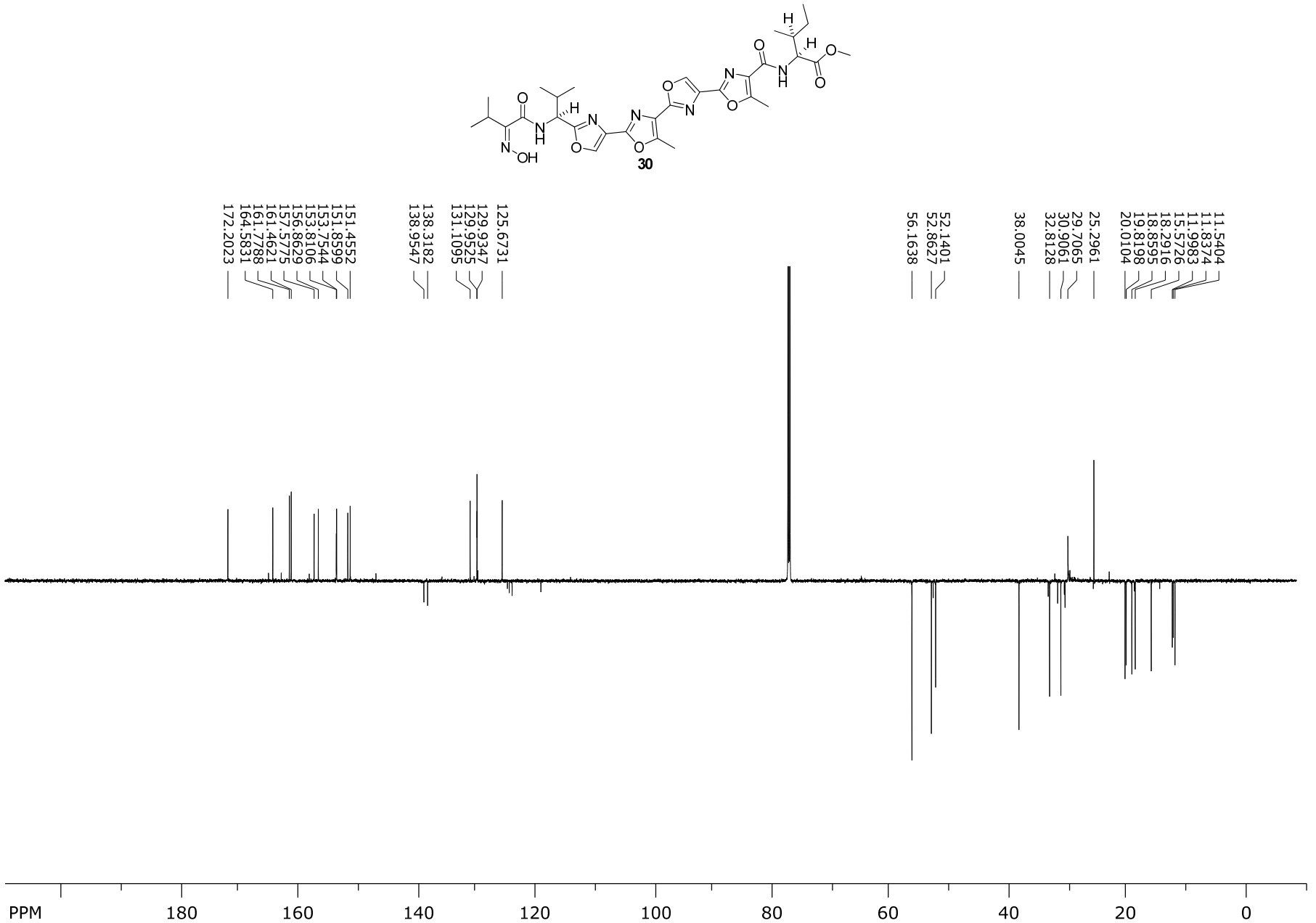
BC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PPM
180
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140
120
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80
60
40
20
0