

Supporting Information

Catalyst-Free Facile Synthesis of 2-Substituted Benzothiazoles

Siva S. Panda,^a Mohamed A. Ibrahim,^{a,b} Alexander A. Oliferenko,^a Abdullah M. Asiri^{c,d} and

Alan R. Katritzky^{a,c*}

^a*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida,*

Gainesville, FL 32611-7200

^b*Department of Organic Chemistry, College of Pharmacy, Misr University for Science and*

Technology, Al-Motamayez District, P.O. Box: 77, Egypt

^c*Chemistry Department, King Abdulaziz University, Jeddah, 21589 Saudi Arabia*

^d*Center of Excellence for Advance Materials Research (CEAMR), King Abdulaziz University,*

Jeddah, 21589 Saudi Arabia

Fax: 352-392-9199; Tel: 352-392-0554; E-mail: katritzky@chem.ufl.edu

1. General information	S2
2. Experimental Section	S3
3. ¹ H, ¹³ C, CHN/HRMS and HPLC spectra of all new compounds	S11

General Information

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in CDCl₃ or DMSO-*d*₆, on Mercury or Gemini NMR spectrometers operating at 300 MHz for ¹H (with TMS as an internal standard) and 75 MHz for ¹³C. Elemental analyses were performed on a Carlo Erba-EA1108 instrument. All microwave assisted reactions were carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). The reaction mixtures were transferred into a 10 mL glass pressure microwave tube equipped with a magnetic stirring bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation (Discover mode; run time: 60 sec.; PowerMax-cooling mode).

To elucidate the mechanism and range of applicability, **5f** (Cbz-Ala-Bt) was selected for coupling with 2-aminothiophenol in five organic solvents, tap and distilled water, and also under solvent-free conditions. The yields and purity are shown in Table S4.

Table S4 Reaction of 2-aminothiophenol and Cbz-Ala-Bt in different solvents

Entry	Solvent	Yield (%) ^a	Purity (%) ^b
1	Ethanol	44	56
2	THF	58	49
3	DMF	58	45
4	Toluene	61	51
5	Tap water	78	95
6	Distilled water	79	96

^aCrude yield after workup with aq.NaCO₃ and 4 N HCl

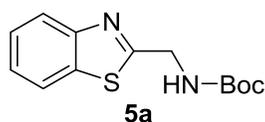
^bPurity of the crude product was checked using HPLC

^c2-aminothiophenol in excess

Experimental Section

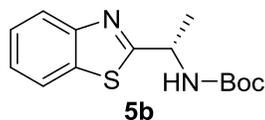
Typical procedure: A mixture of 2-aminothiophenol (0.1 g, 0.085 mL, 0.80 mmol) and N-protected aminoacylbenzotriazole or N-protected peptidylbenzotriazole (0.80 mmol) was subjected to microwave irradiation (50 W, 70 °C) in water (3 mL) for 1 h. After completion of the reaction, aqueous NaCO₃ solution was added and the mixture was extracted with ethyl acetate followed by washing with 4 N HCl. When the supernatant water retained the product in a colloidal form, the product was isolated by extraction with ethyl acetate. The organic phase was dried over MgSO₄ and then evaporated to obtain the desired product.

tert-Butyl (benzo[*d*]thiazol-2-ylmethyl)carbamate (Boc-Gly-BZT, 5a)



Light yellow solid (84%); mp. 68–70 °C. ¹H NMR (CDCl₃) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.78 (br s, 1H), 4.73 (d, *J* = 6.9 Hz, 2H), 1.48 (s, 9H); ¹³C NMR (CDCl₃) δ 170.4, 155.9, 153.0, 135.1, 126.2, 125.2, 122.9, 121.8, 80.3, 43.1, 28.4; HRMS (+ESI-TOF) *m/z* for C₁₃H₁₆N₂O₂S [M+Na]⁺ calcd. 287.0836, found 287.0825.

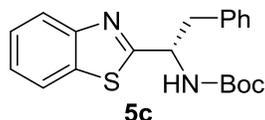
tert-Butyl (*S*)- (1-(benzo[*d*]thiazol-2-yl)ethyl)carbamate (Boc-Ala-BZT, 5b)



Brown solid (82%); mp. 70–72 °C. ¹H NMR (CDCl₃) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 5.50–5.60 (m, 1H), 5.19 (br s, 1H),

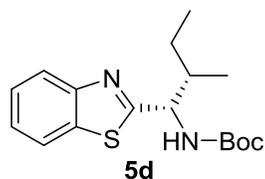
1.66 (d, $J = 6.9$ Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (CDCl_3) δ 170.1, 155.2, 153.2, 135.0, 126.2, 125.1, 123.0, 121.8, 80.2, 49.4, 28.5, 21.8; HRMS (+ESI-TOF) m/z for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 301.0981, found 301.0991.

***tert*-Butyl (*S*)-(1-(benzo[*d*]thiazol-2-yl)-2-phenylethyl)carbamate (Boc-Phe-BZT, 5c)**



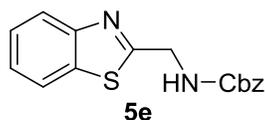
Light yellow solid (83%); mp. 99–101 °C. ^1H NMR (CDCl_3) δ 7.99 (d, $J = 8.1$ Hz, 1H), 7.80 (d, $J = 7.7$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.28–7.16 (m, 5H), 5.57–5.50 (m, 1H), 5.42–5.35 (m, 1H), 3.46–3.26 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (CDCl_3) δ 173.4, 155.2, 153.2, 136.4, 134.9, 129.6, 128.6, 127.0, 126.2, 125.1, 123.0, 121.8, 80.2, 54.4, 41.6, 28.4; HRMS (+ESI-TOF) m/z for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 377.1294, found 377.1299.

***tert*-Butyl ((1*S*,2*S*)-1-(benzo[*d*]thiazol-2-yl)-2-methylbutyl)carbamate (Boc-Ile-BZT, 5d)**



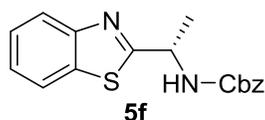
Yellow solid (80%); mp. 130–132 °C. ^1H NMR (CDCl_3) δ 8.73–8.69 (m, 1H), 8.33–8.27 (m, 1H), 7.41–7.26 (m, 1H), 7.05–6.95 (m, 1H), 5.25 (br s, 1H), 4.13–4.09 (m, 1H), 2.07–1.97 (m, 1H), 1.48 (br s, 9H), 1.25–0.87 (m, 8H); ^{13}C NMR (CDCl_3) δ 170.3, 155.9, 139.2, 136.3, 131.8, 124.6, 121.6, 115.5, 80.3, 60.3, 37.2, 28.6, 25.0, 16.0, 11.8; HRMS (+ESI-TOF) m/z for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 343.1451, found 343.1453.

Benzyl (benzo[*d*]thiazol-2-ylmethyl)carbamate (Cbz-Gly-BZT, 5e)



White solid (82%); mp. 123–125 °C. ¹H NMR (CDCl₃) δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.36–7.24 (m, 6H), 6.16 (br s, 1H), 5.14 (s, 2H), 4.76 (br s, 2H); ¹³C NMR (CDCl₃) δ 169.7, 156.6, 152.7, 136.2, 135.0, 128.6, 128.3, 128.3, 126.3, 125.4, 122.8, 121.8, 67.4, 43.4; Anal. calcd for C₁₆H₁₄N₂O₂S: C, 64.41; H, 4.73; N, 9.39; found: C, 64.70; H, 4.93; N, 9.07.

Benzyl (*S*)-(1-(benzo[*d*]thiazol-2-yl)ethyl)carbamate (Cbz-L-Ala-BZT, 5f)



White solid (78%); mp. 92–94 °C. ¹H NMR (CDCl₃) δ 7.95 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.35–7.22 (m, 6H), 6.07–6.03 (m, 1H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.12 (s, 1H), 5.11 (s, 1H), 1.63 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 174.0, 155.8, 153.0, 136.3, 134.9, 128.5, 128.3, 128.2, 126.2, 125.2, 122.9, 121.8, 67.1, 49.8, 21.8; HRMS (+ESI-TOF) *m/z* for C₁₇H₁₆N₂O₂S [M+H]⁺ calcd. 313.1005, found 313.1014.

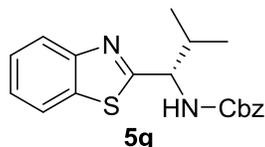
Benzyl (1-(benzo[*d*]thiazol-2-yl)ethyl)carbamate (Cbz-dl-Ala-BZT, 5f+5f')



Drak brown solid (73%); mp. 88–90 °C. ¹H NMR (CDCl₃) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.35–7.22 (m, 6H), 6.27–6.23 (m, 1H), 5.26 (t, *J* = 6.6

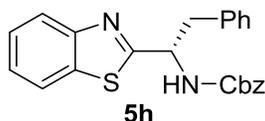
Hz, 1H), 5.12 (s, 1H), 5.11 (s, 1H), 1.63 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 175.6, 174.6, 155.6, 152.4, 136.3, 136.2, 134.5, 128.4, 128.1, 126.3, 125.2, 122.7, 121.8, 67.0, 66.8, 49.7, 49.6, 21.6, 18.6; HRMS (+ESI-TOF) m/z for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 335.0825, found 335.0841.

Benzyl (S)- (1-(benzo[d]thiazol-2-yl)-2-methylpropyl)carbamate (Cbz-L-Val-BZT, 5g)



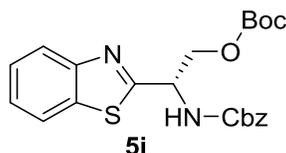
White solid (78%); mp. 220–222 °C. ^1H NMR (CDCl_3) δ 8.51 (s, 1H), 8.25 (d, $J = 8.1$ Hz, 1H), 7.35–7.23 (m, 7H), 7.06–6.95 (m, 1H), 5.14 (s, 2H), 4.11 (t, $J = 6.6$ Hz, 1H), 2.24–2.13 (m, 1H), 1.00–0.90 (m, 6H); ^{13}C NMR (CDCl_3) δ 170.1, 156.8, 139.2, 136.4, 132.0, 128.8, 128.5, 128.4, 128.4, 125.1, 124.9, 121.8, 67.5, 61.4, 30.9, 19.6, 17.9. ; HRMS (+ESI-TOF) m/z for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 341.1318, found 341.1316.

Benzyl (S)- (1-(benzo[d]thiazol-2-yl)-2-phenylethyl)carbamate (Cbz-L-Phe-BZT, 5h)



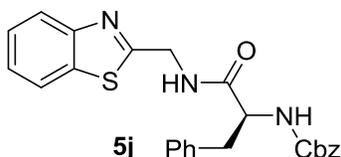
Off white solid (70%); mp. 180–182 °C. ^1H NMR ($\text{DMSO}-d_6$) δ 10.02 (s, 1H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.37–7.19 (m, 12H), 4.97 (s, 2H), 4.56–4.47 (m, 1H), 3.19–3.13 (m, 1H), 2.94–2.86 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 171.2, 156.2, 137.9, 137.0, 135.6, 131.8, 129.4, 129.0, 128.4, 128.3, 127.8, 127.6, 127.2, 126.9, 126.5, 126.1, 65.5, 56.7, 37.5 ; HRMS (+ESI-TOF) m/z for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 389.1318, found 389.1314.

Benzyl (S)-(1-(benzo[d]thiazol-2-yl)-2-(tert-butoxy)ethyl)carbamate (Z-Ser(tBu)-BZT, 5i)



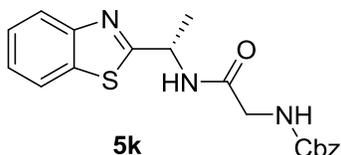
Yellow oil (88%). ^1H NMR (CDCl_3) δ 7.97 (d, $J = 8.0$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.43–7.30 (m, 7H), 6.10 (br s, 1H), 5.27 (br s, 1H), 5.15 (s, 2H), 3.94 (br s, 1H), 3.78–3.73 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (CDCl_3) δ 172.2, 156.0, 153.1, 136.3, 135.2, 128.6, 128.3, 128.0, 125.9, 124.9, 122.9, 121.6, 73.8, 67.4, 67.2, 63.6, 54.6, 27.3; HRMS (+ESI-TOF) m/z for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 385.1580, found 385.1576.

Benzyl (S)-(1-((benzo[d]thiazol-2-ylmethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (Cbz-Phe-Gly-BZT, 5j)



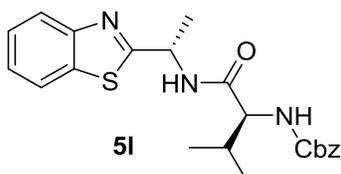
Dark brown solid (76%); mp. 149–151 °C. ^1H NMR (CDCl_3) δ 7.85 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.69–7.64 (m, 1H), 7.41–7.31 (m, 2H), 7.22–7.10 (m, 10H), 5.98–5.94 (m, 1H), 5.01–4.89 (m, 2H), 4.69 (s, 2H), 4.64–4.61 (m, 1H), 3.14–3.02 (m, 2H); ^{13}C NMR (CDCl_3) δ 171.8, 168.3, 156.2, 152.7, 136.3, 136.1, 135.2, 129.4, 128.6, 128.5, 128.2, 127.9, 127.0, 126.2, 125.3, 122.9, 121.8, 67.1, 56.3, 41.6, 38.7; HRMS (+ESI-TOF) m/z for $\text{C}_{25}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ calcd. 468.1352, found 468.1364.

Benzyl (S)-(2-((1-(benzo[d]thiazol-2-yl)ethyl)amino)-2-oxoethyl)carbamate (Cbz-Gly-Ala-BZT, 5k)



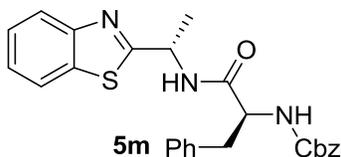
Off white solid (78%); mp. 114–116 °C. ¹H NMR (CDCl₃) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 6.9 Hz, 2H), 7.38–7.21 (m, 6H), 5.87–5.79 (m, 1H), 5.52–5.45 (m, 1H), 5.09 (s, 2H), 3.97 (s, 2H), 1.64 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (CDCl₃) δ 173.1, 168.9, 156.8, 152.7, 136.2, 134.9, 128.6, 128.3, 128.2, 126.4, 125.4, 122.9, 121.9, 67.4, 48.0, 44.7, 21.6; HRMS (+ESI-TOF) *m/z* for C₁₉H₂₁N₃O₃S [M+Na]⁺ calcd. 370.1220, found 370.1248.

Benzyl ((S)-1-(((S)-1-(benzo[d]thiazol-2-yl)ethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Cbz-Val-Ala-BZT, 5l)



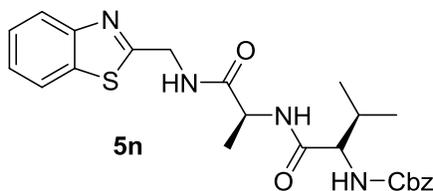
Light orange solid (70%); mp. 179–181 °C. ¹H NMR (CDCl₃) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.38–7.25 (m, 6H), 5.53–5.40 (m, 1H), 5.12 (s, 2H), 4.14–4.06 (m, 1H), 3.64–3.43 (m, 1H), 1.67 (d, *J* = 6.6 Hz, 3H), 1.01–0.93 (m, 6H); ¹³C NMR (CDCl₃) δ 170.9, 156.6, 153.0, 136.3, 135.1, 128.7, 128.7, 128.4, 128.3, 126.4, 125.4, 123.2, 121.9, 67.4, 60.6, 48.2, 31.4, 29.9, 21.9, 19.6; HRMS (+ESI-TOF) *m/z* for C₂₂H₂₇N₃O₃S [M+Na]⁺ calcd. 434.1509, found 434.1509.

Benzyl ((S)-1-(((S)-1-(benzo[d]thiazol-2-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate (Cbz-Phe-Ala-BZT, 5m)



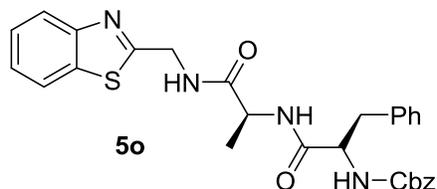
Whits solid (89%); mp. 184–186 °C. ^1H NMR (CDCl_3) δ 7.90 (d, $J = 8.1$ Hz, 1H), 7.81 (d, $J = 7.3$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 1H), 7.36 (t, $J = 7.1$ Hz, 1H), 7.28–6.98 (m, 11H), 5.62–5.51 (m, 1H), 5.45–5.35 (m, 1H), 5.05 (br s, 2H), 4.60–4.50 (m, 1H), 3.09 (br s, 2H), 1.57 (d, $J = 4.9$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 170.6, 170.6, 156.1, 153.0, 136.2, 135.1, 129.5, 128.9, 128.8, 128.7, 128.4, 128.2, 127.1, 126.3, 125.3, 123.1, 121.8, 67.3, 56.4, 48.0, 38.8, 21.5; HRMS (+ESI-TOF) m/z for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 460.1689, found 460.1681.

Benzyl ((2S)-1-((1-((benzo[d]thiazol-2-yl)methyl)amino)-1-oxopropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Cbz-Val-Ala-Gly-BZT, 5n)

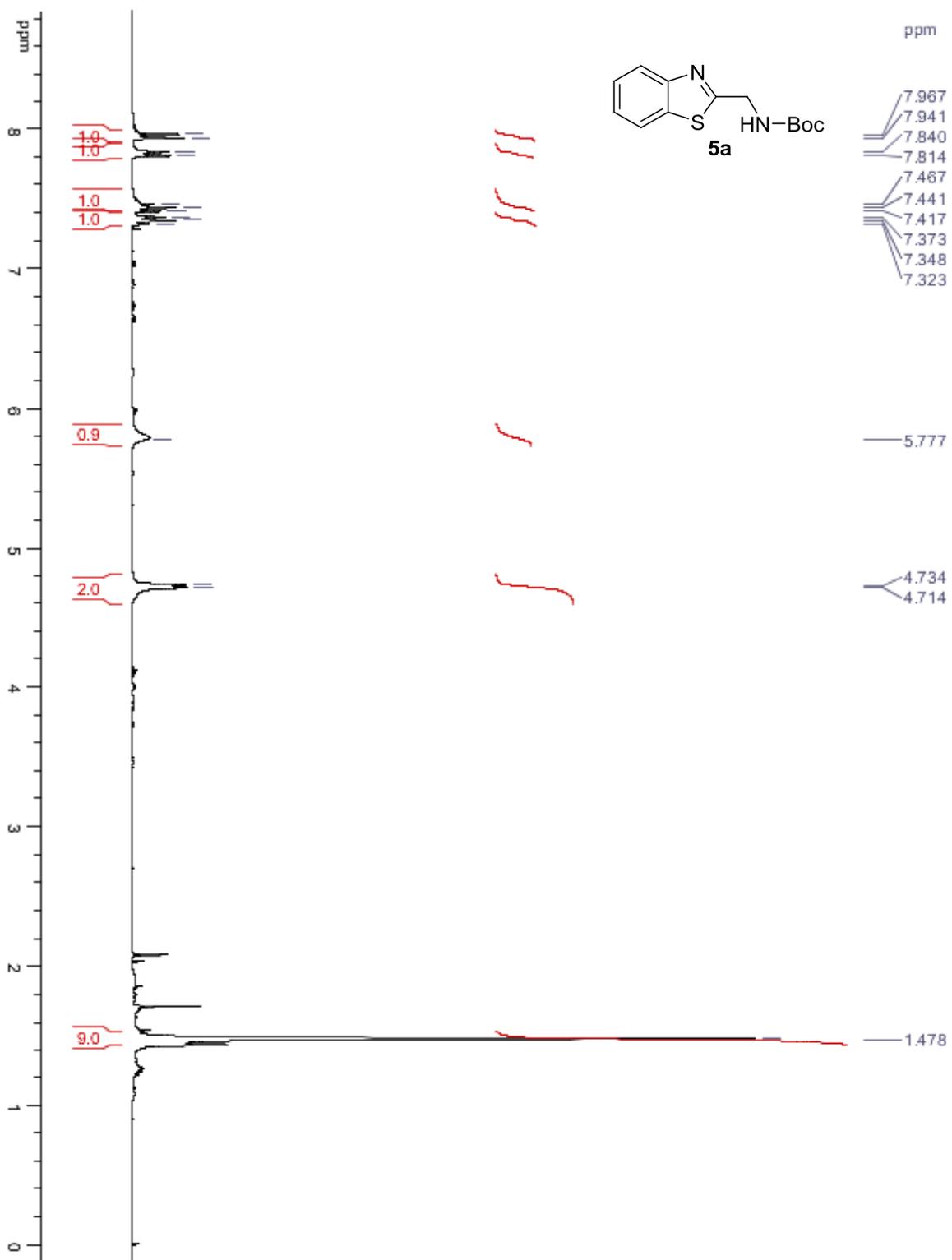


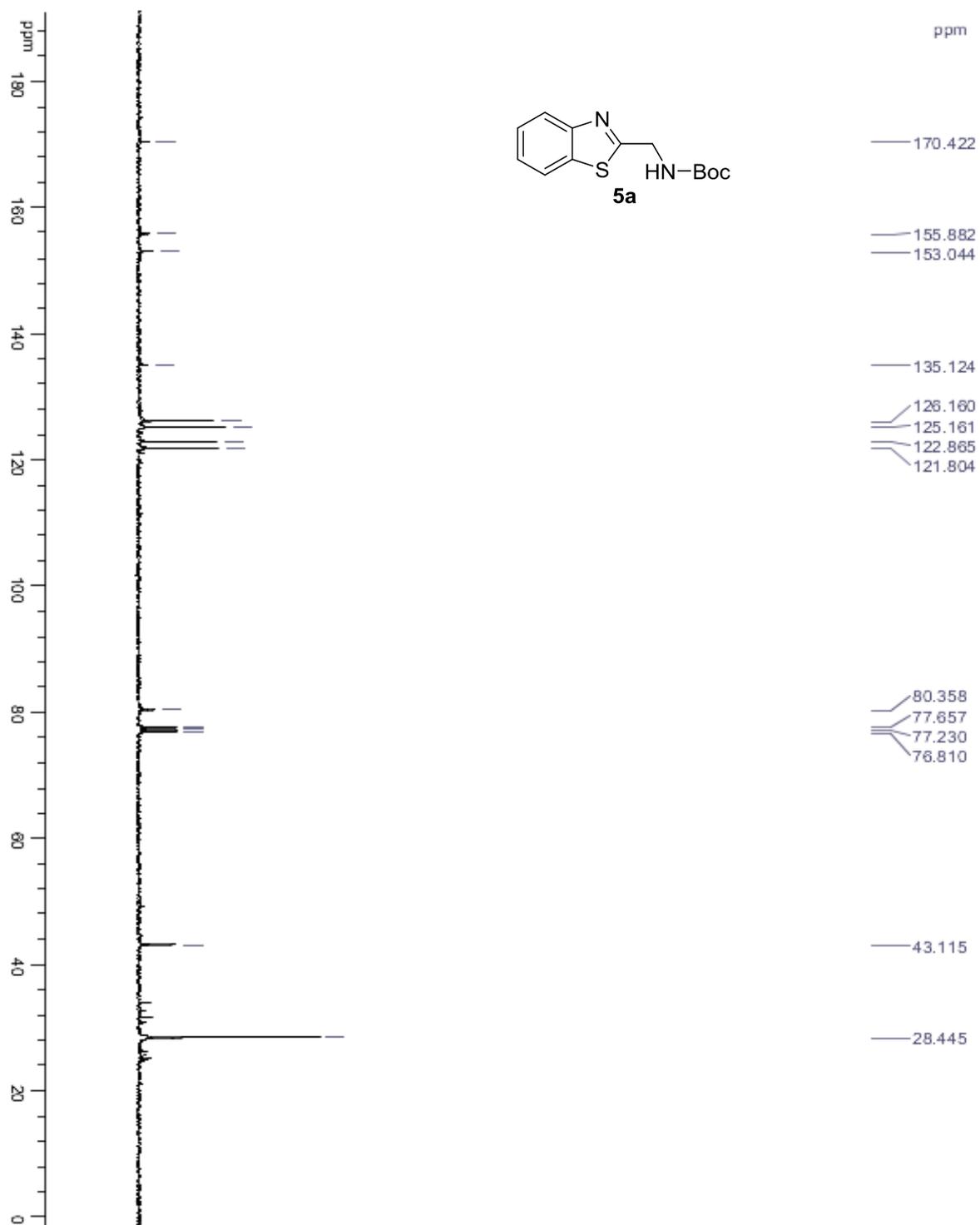
Brown solid (75%); mp. 110–112 °C. ^1H NMR (CDCl_3) δ 7.97 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.32–7.26 (m, 6H), 6.72 (d, $J = 7.5$ Hz, 1H), 5.42 (d, $J = 7.5$ Hz, 1H), 5.11–5.04 (m, 2H), 4.85 (br s, 2H), 4.61 (t, $J = 7.0$ Hz, 1H), 4.02 (t, $J = 8.2$ Hz, 1H), 2.17–2.09 (m, 1H), 1.43 (d, $J = 6.7$ Hz, 3H), 1.02–0.87 (m, 6H); ^{13}C NMR (CDCl_3) δ 172.6, 171.6, 169.6, 156.9, 151.6, 136.2, 134.7, 128.7, 128.4, 128.2, 126.8, 125.8, 122.6, 122.0, 67.4, 60.9, 49.1, 41.7, 31.1, 19.5, 18.1, 18.0; HRMS (+ESI-TOF) m/z for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ calcd. 469.1904, found 469.1900.

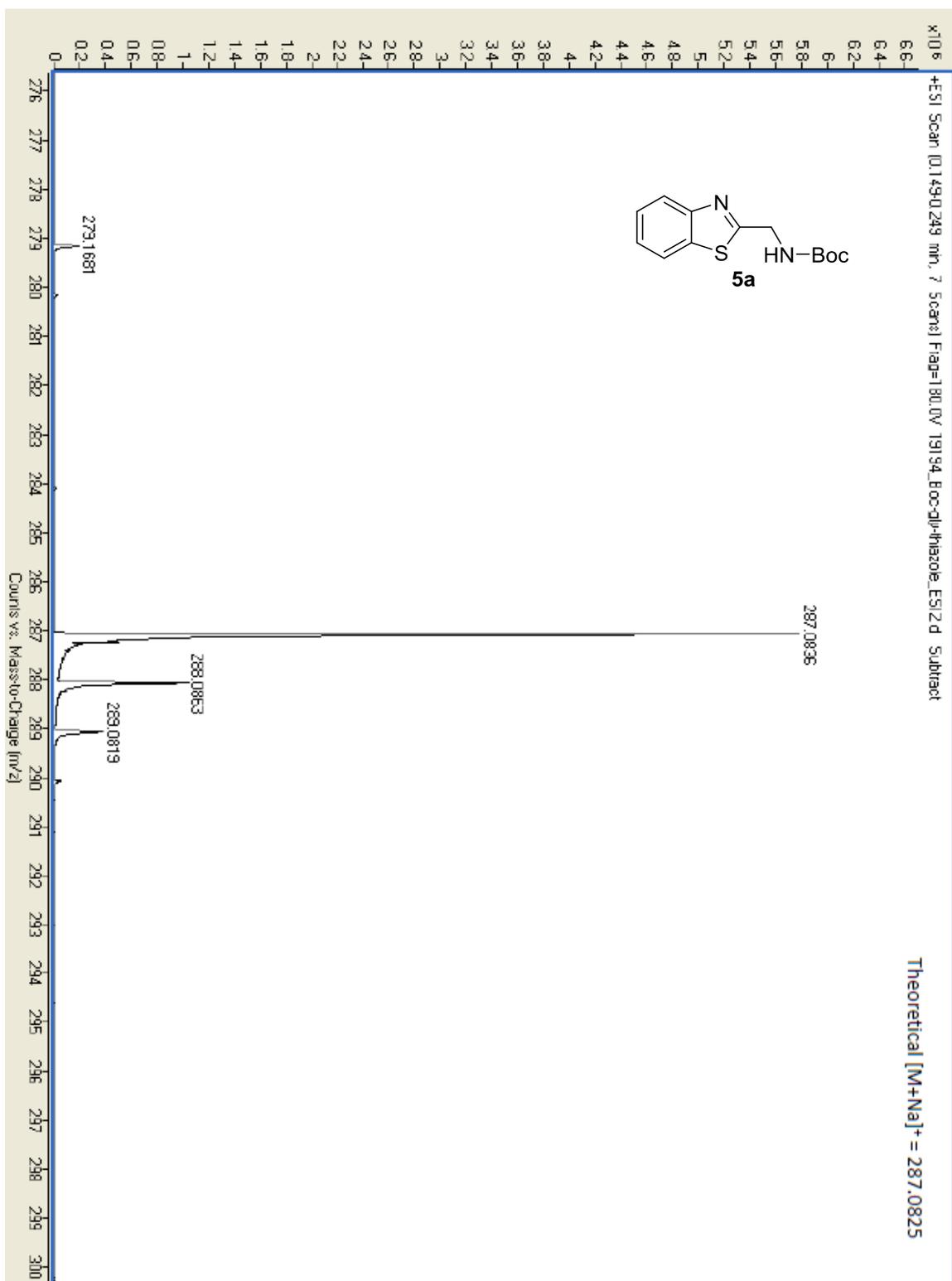
Benzyl ((2*S*)-1-((1-((benzo[*d*]thiazol-2-ylmethyl)amino)-1-oxopropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (Cbz-Phe-Ala-Gly-BZT, **5o)**

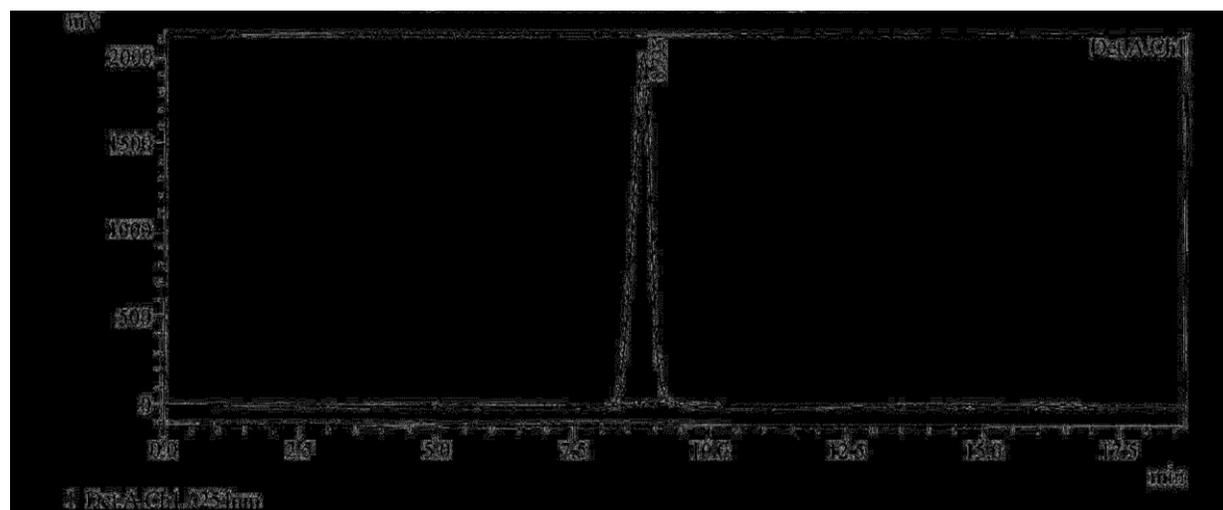


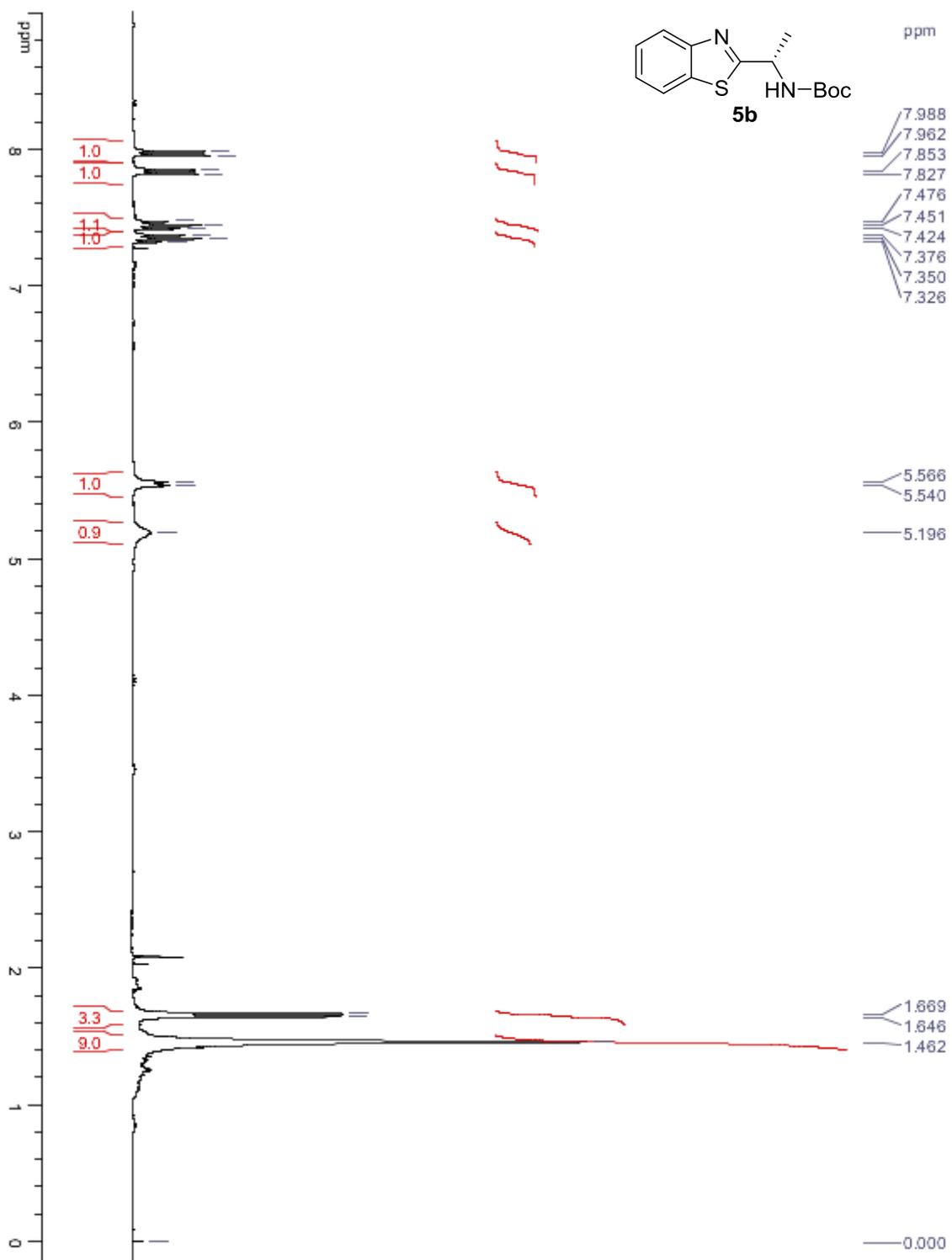
Light brown solid (88%); mp. 163–165 °C. ¹H NMR (CDCl₃) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 5.3 Hz, 1H), 7.42–7.12 (m, 13H), 5.99 (d, *J* = 7.8 Hz, 1H), 5.04–4.88 (m, 2H), 4.78–4.60 (m, 4H), 3.09–2.95 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃) δ 172.4, 171.5, 169.0, 156.4, 153.0, 136.3, 136.2, 135.2, 129.4, 128.8, 128.6, 128.2, 128.0, 127.2, 126.3, 125.3, 123.0, 121.9, 67.2, 56.4, 49.1, 41.9, 38.8, 18.4; HRMS (+ESI-TOF) *m/z* for C₂₈H₂₈N₄O₄S [M+H]⁺ calcd. 539.1723, found 539.1749.

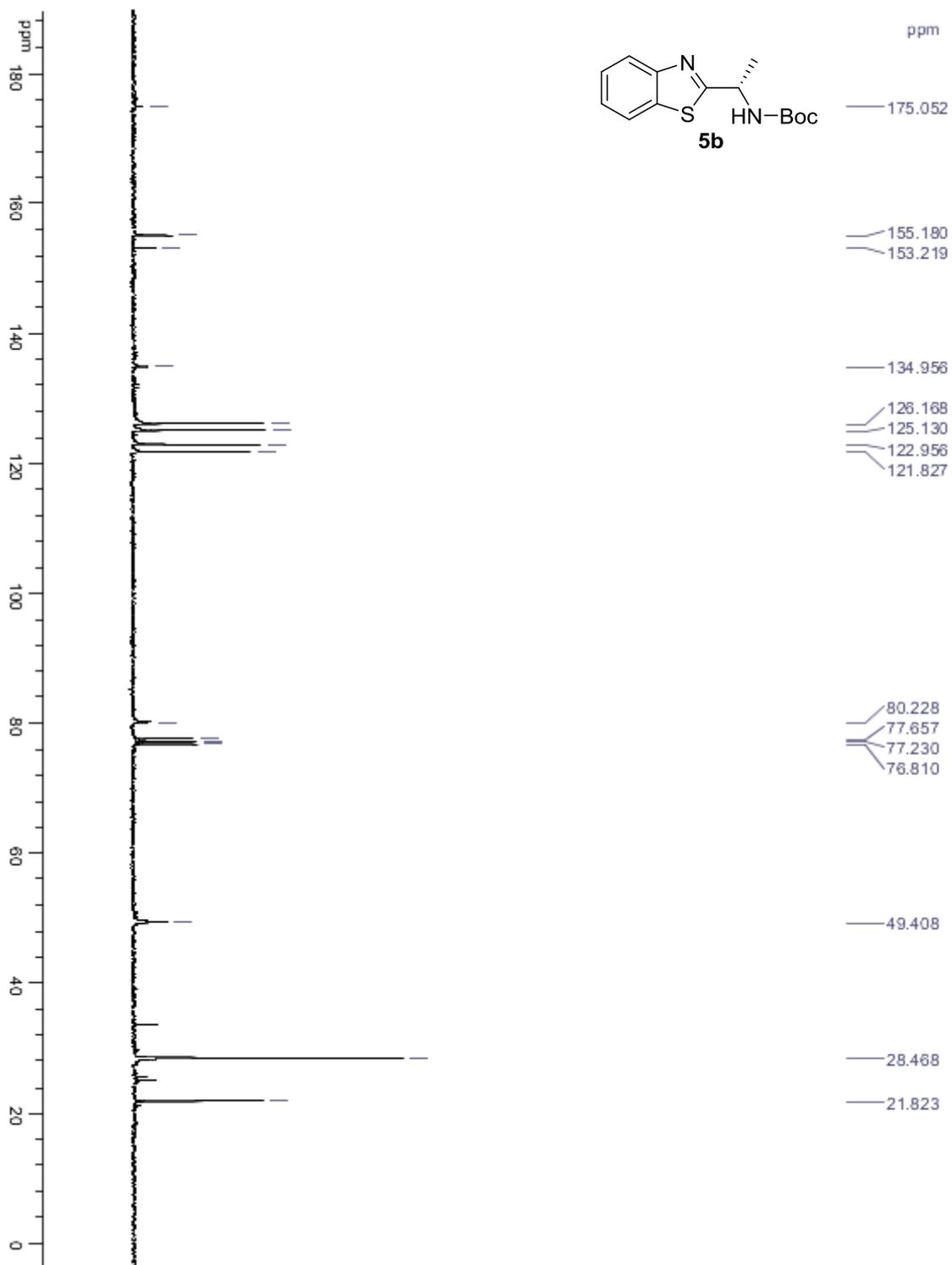


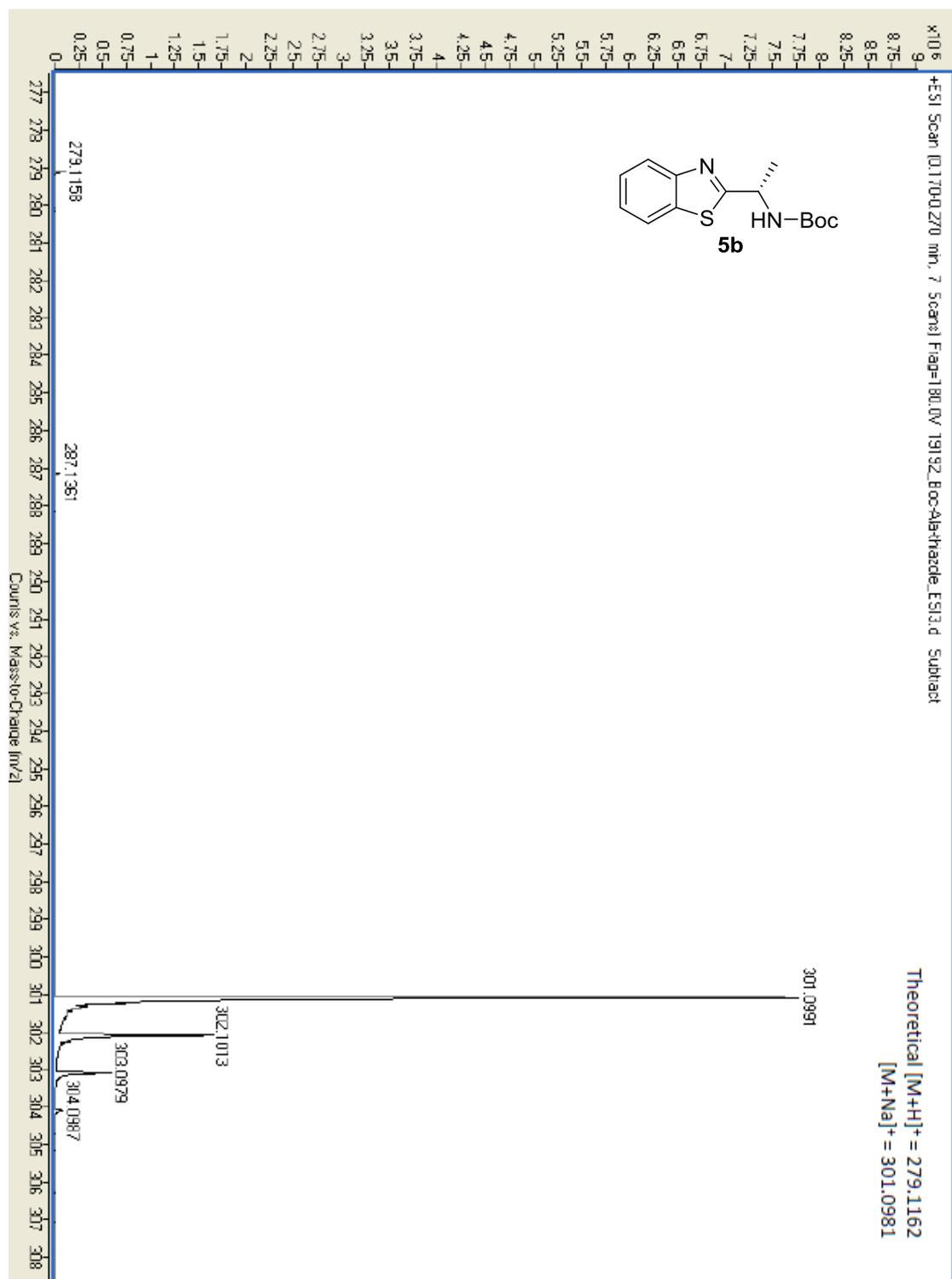


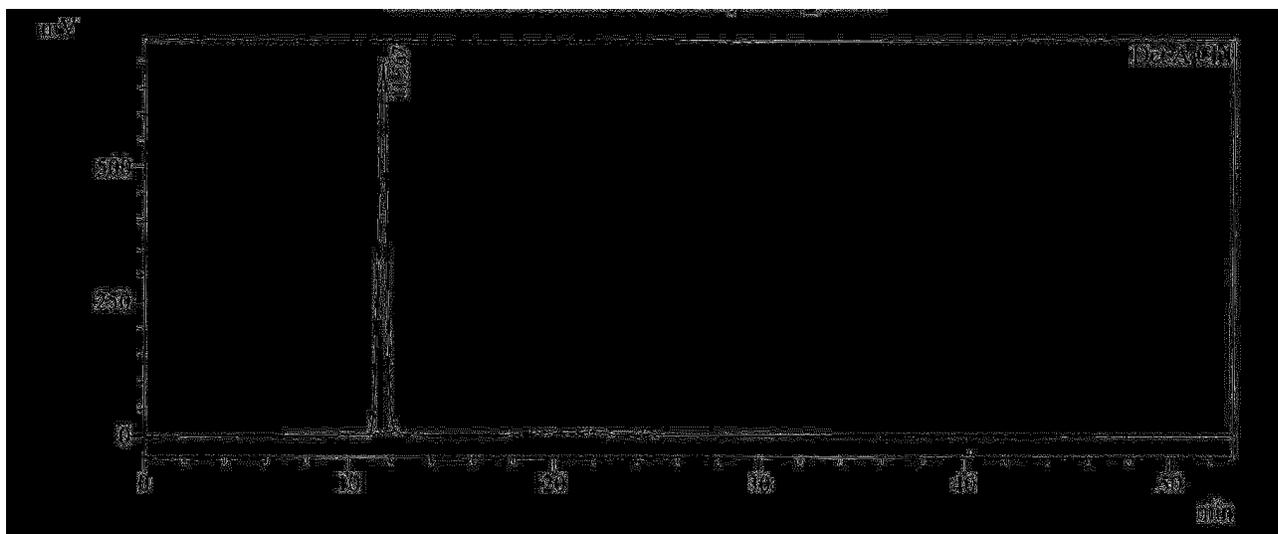


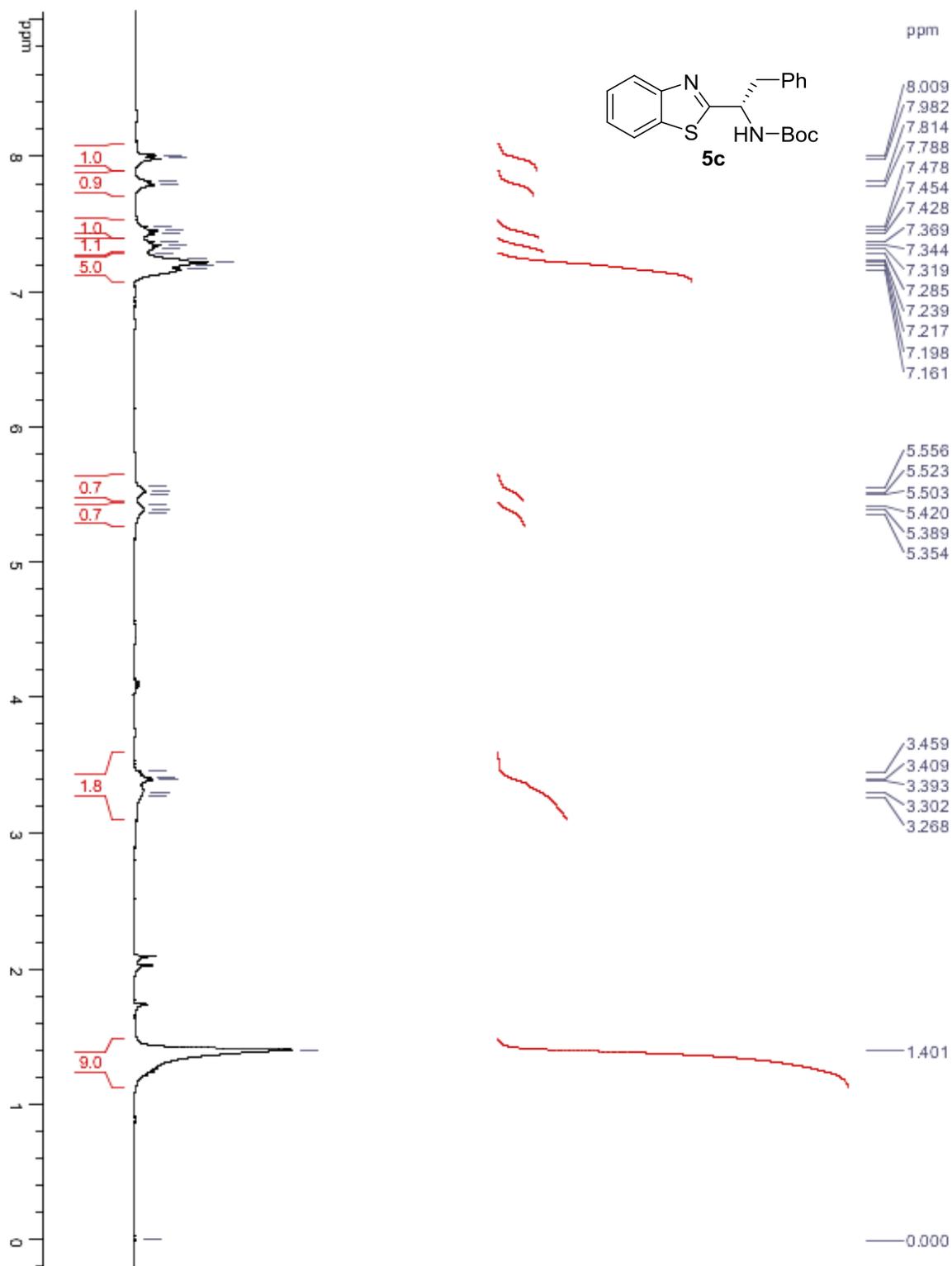


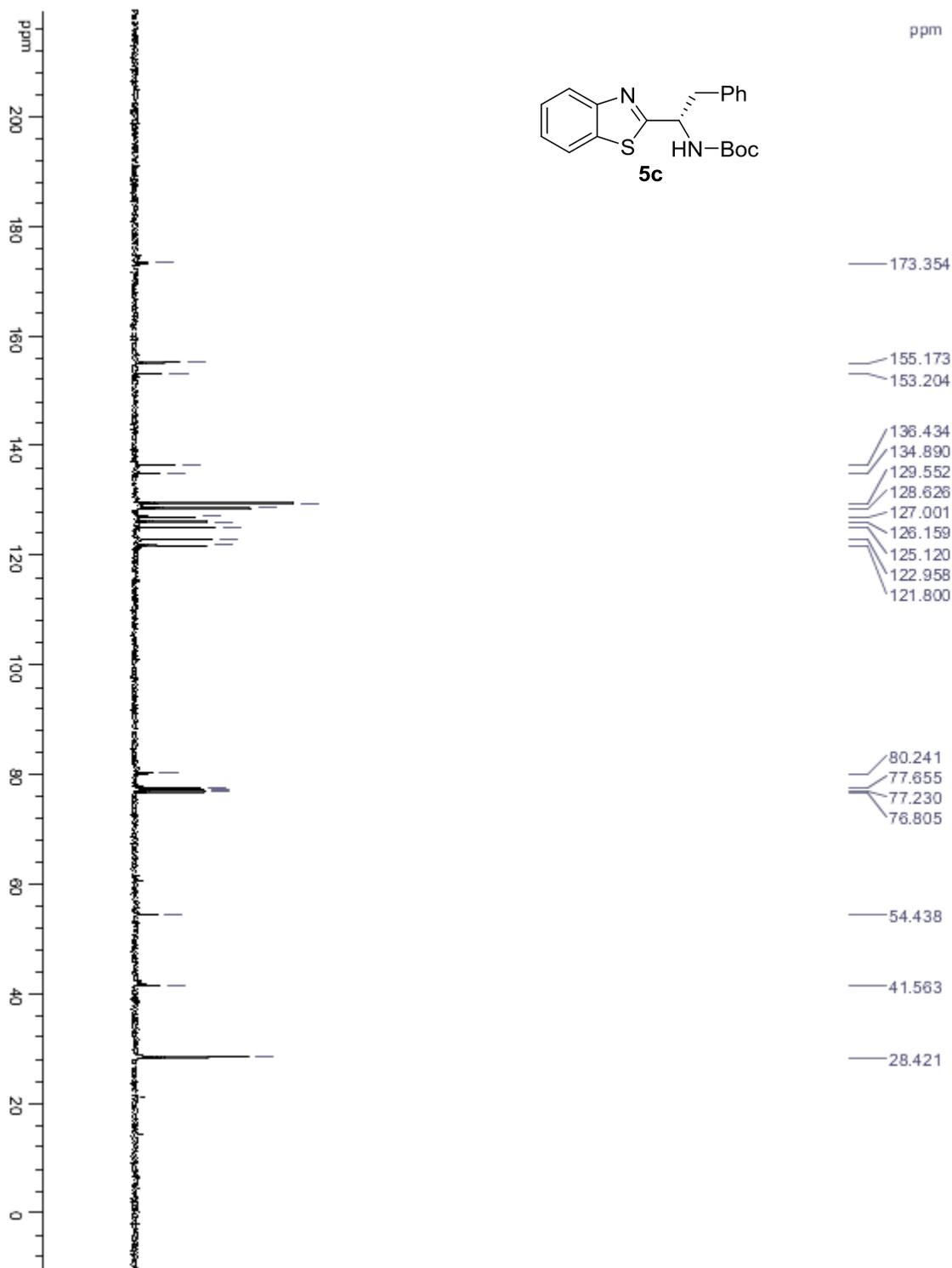


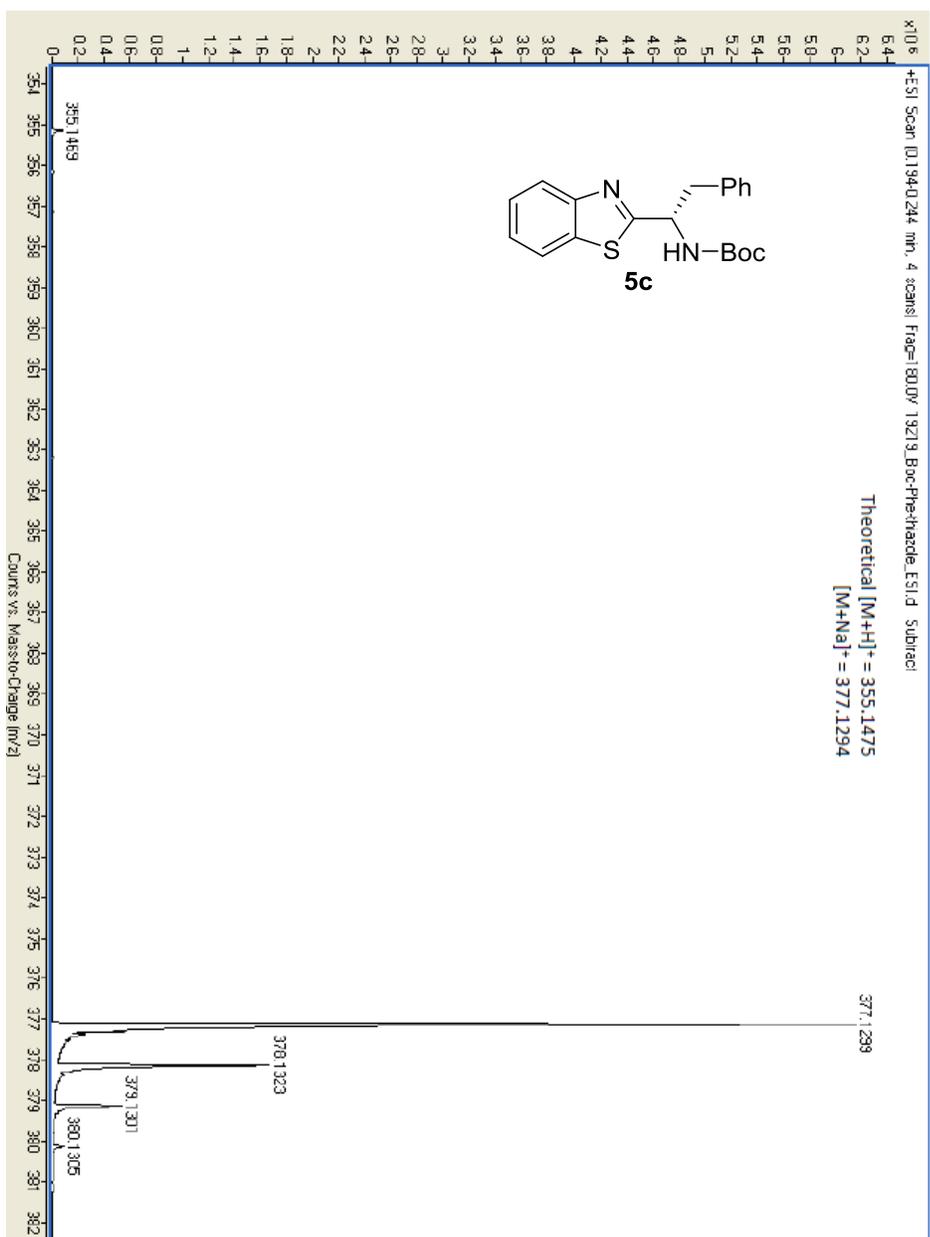


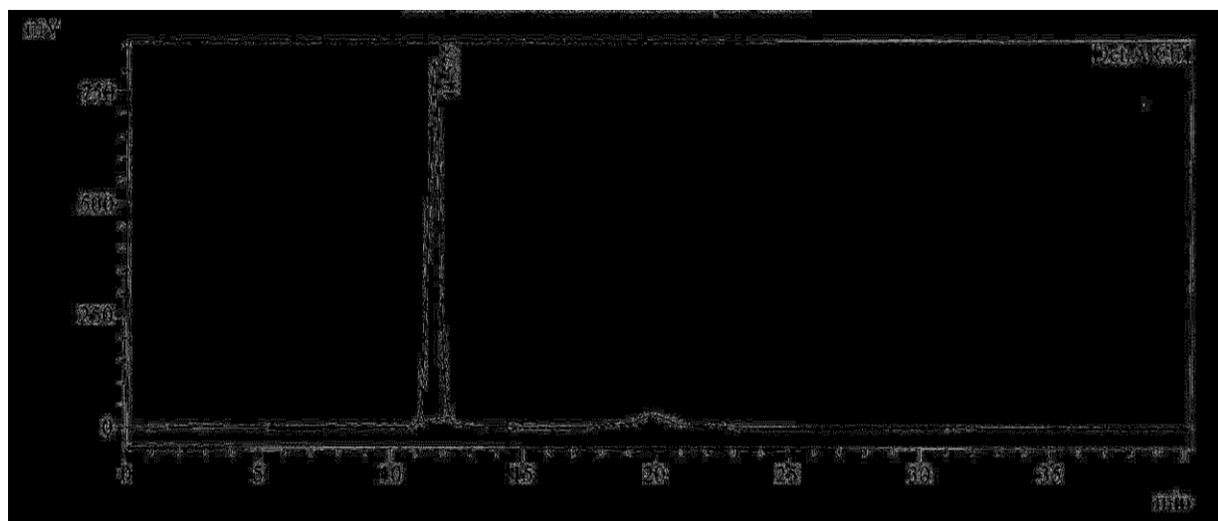


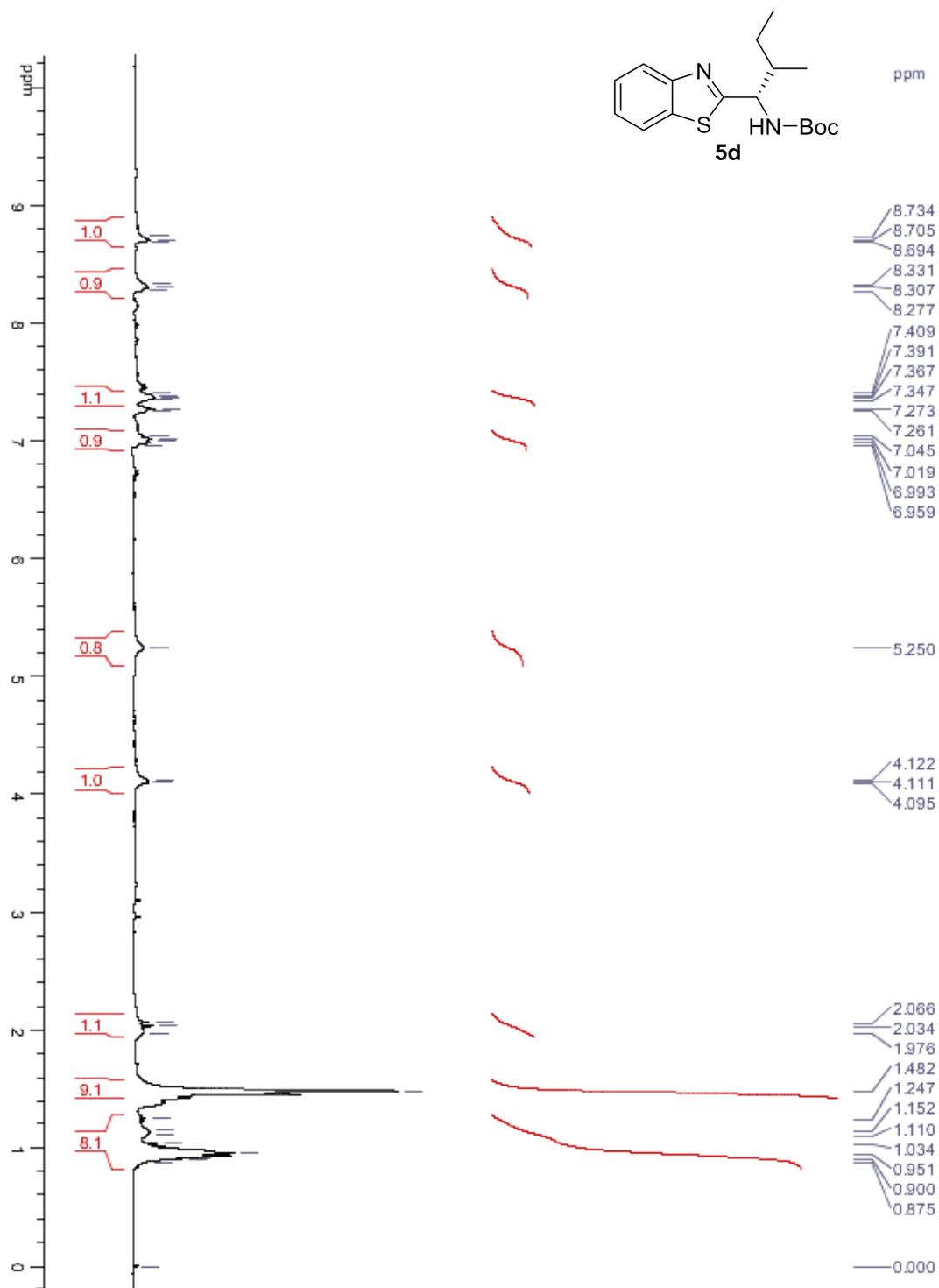


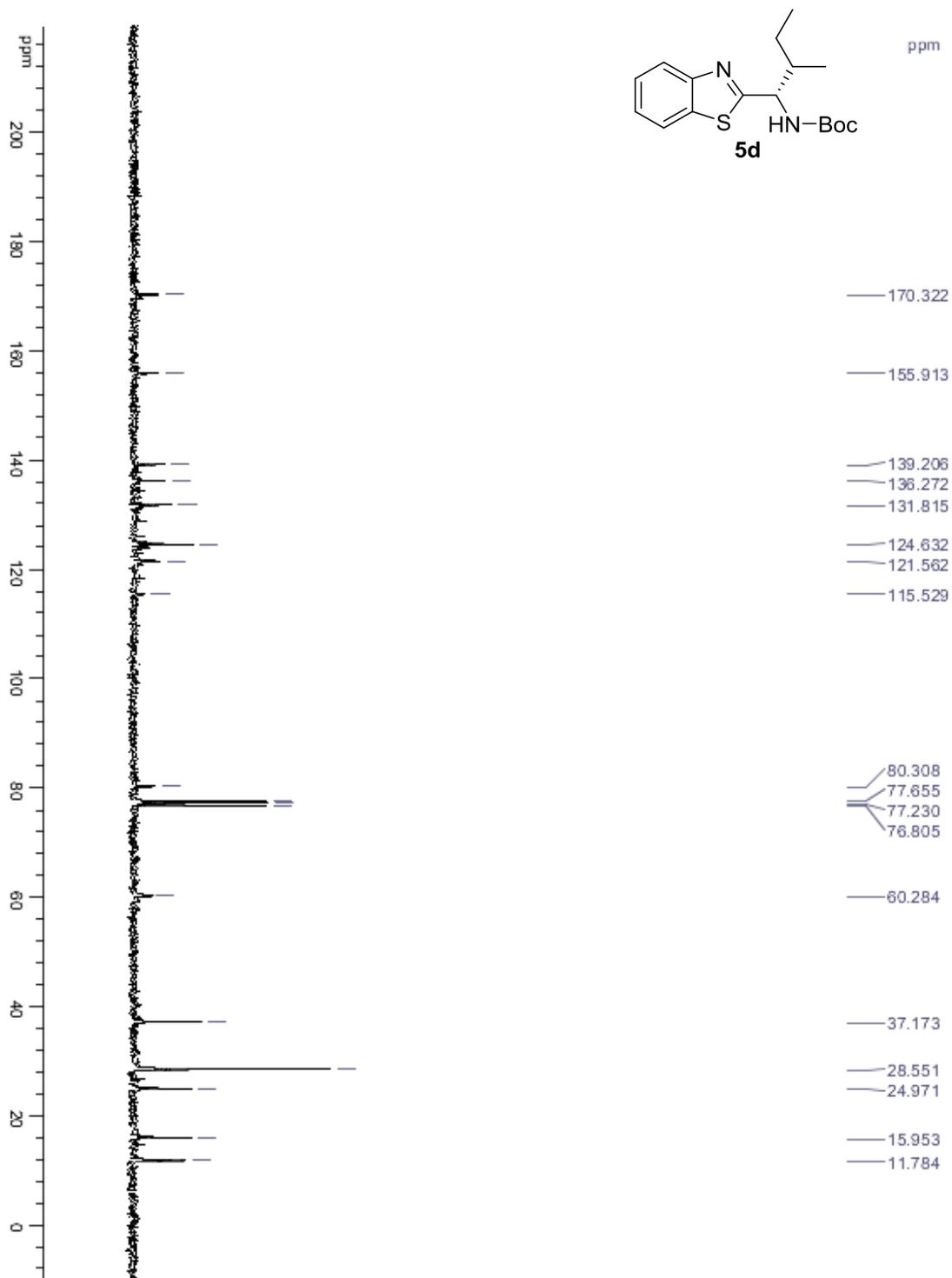


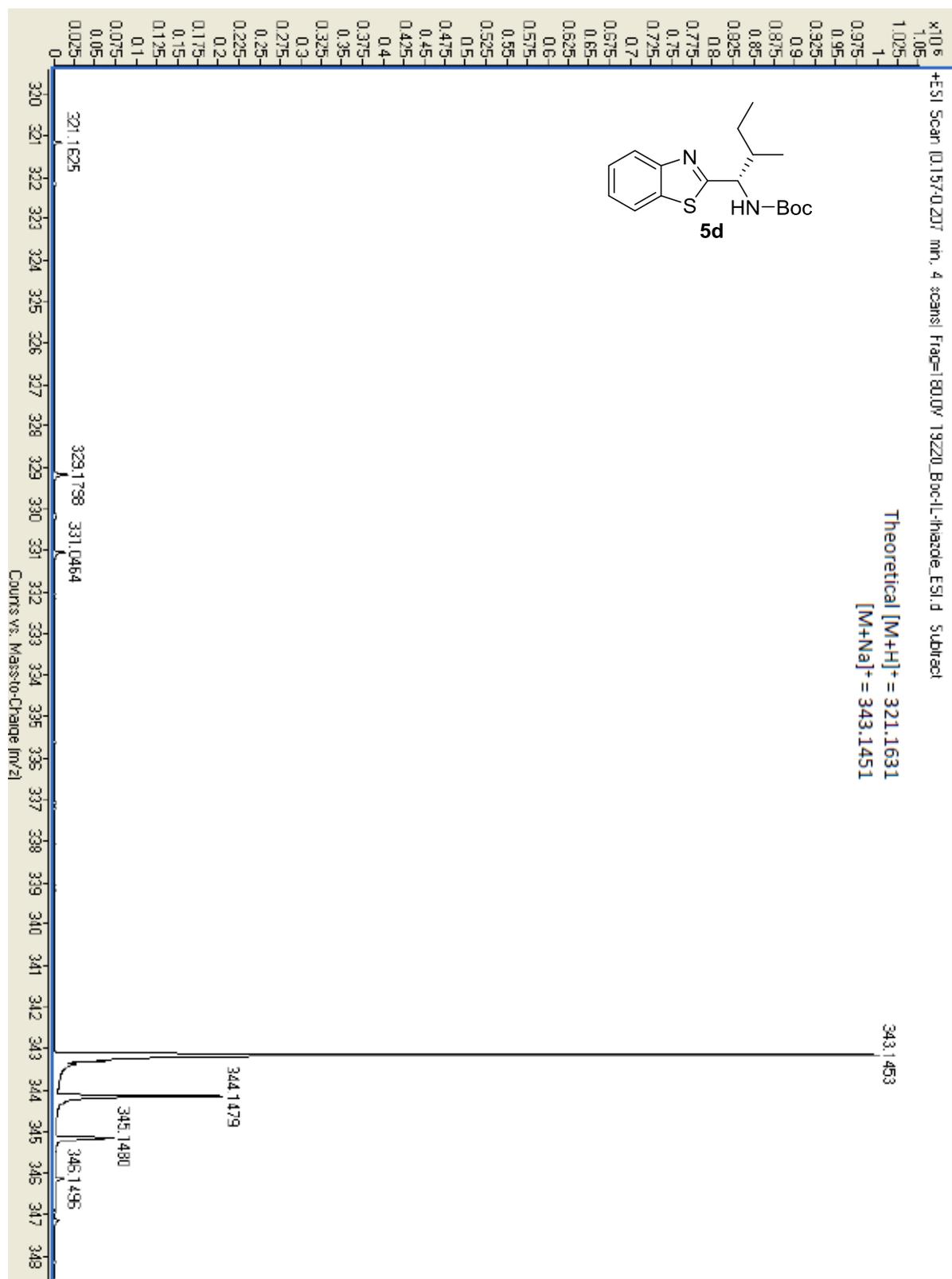


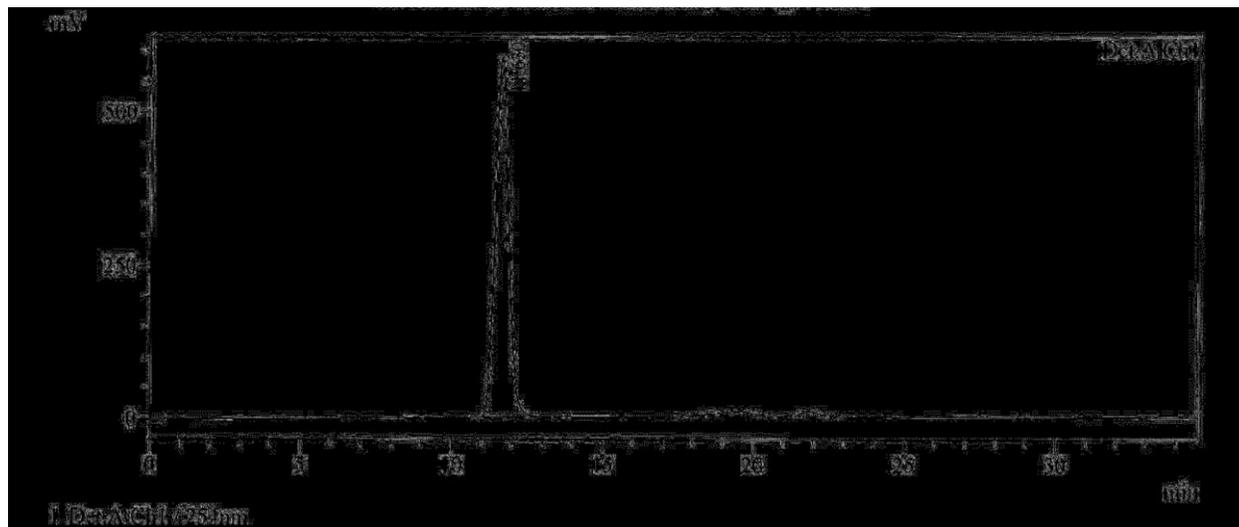


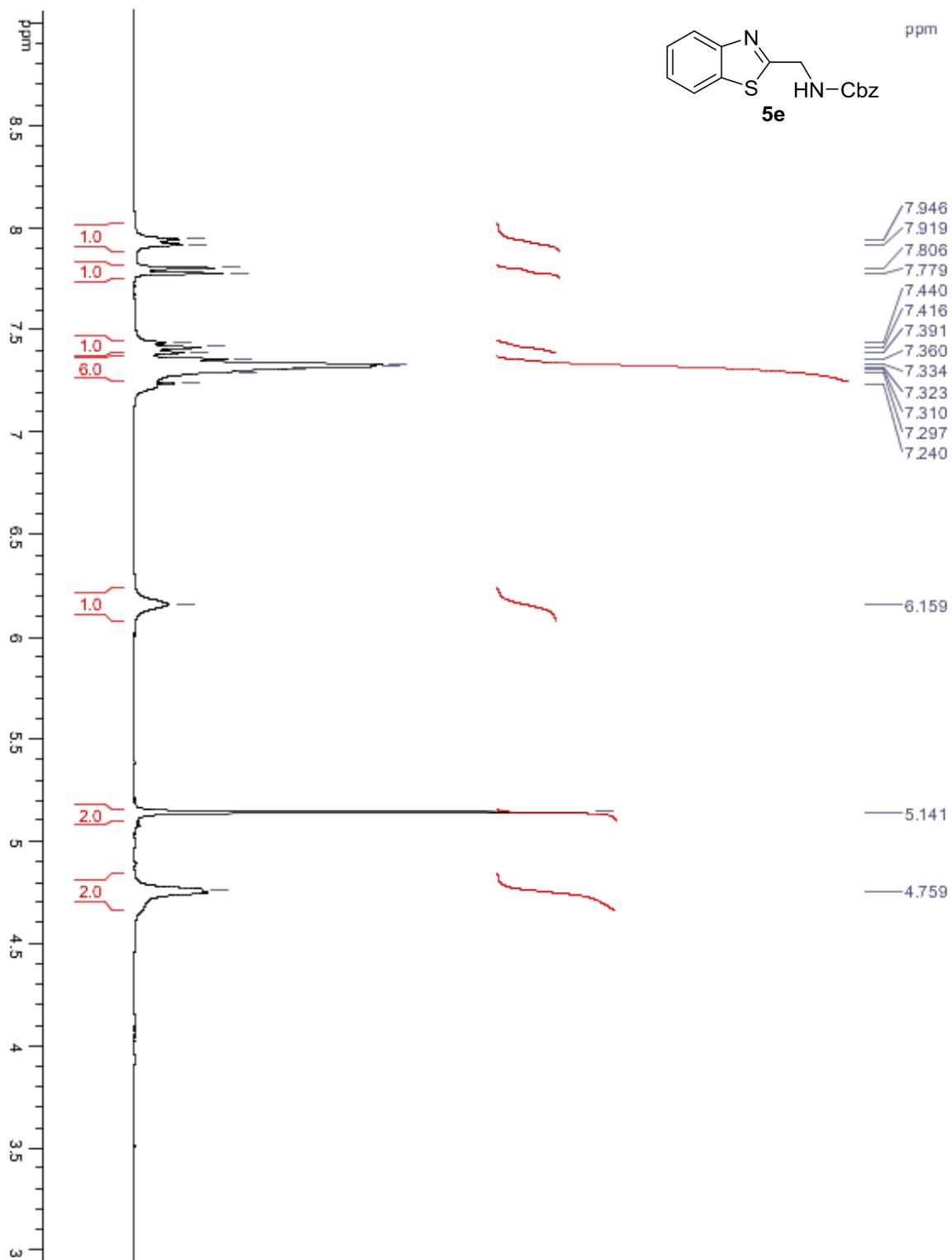


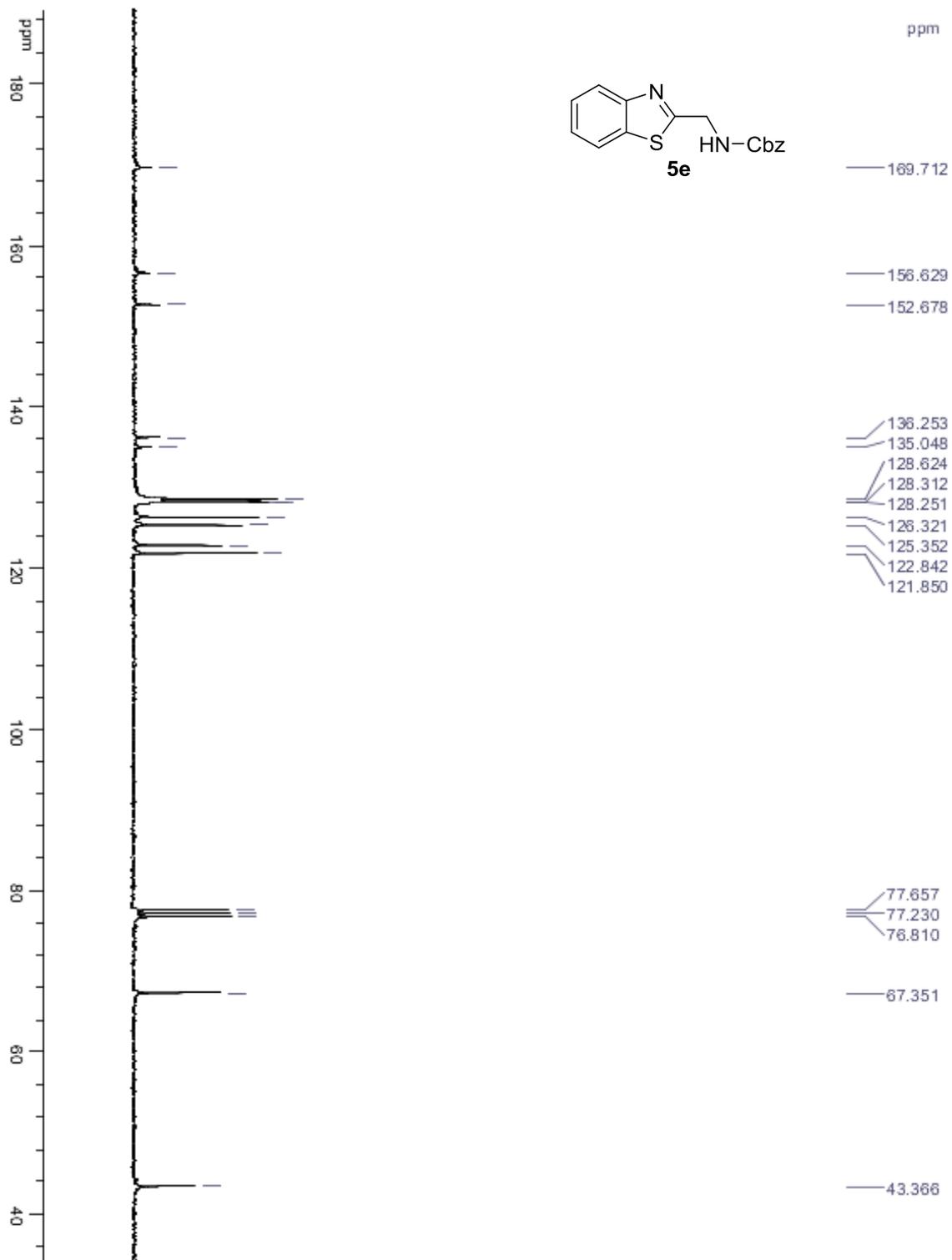






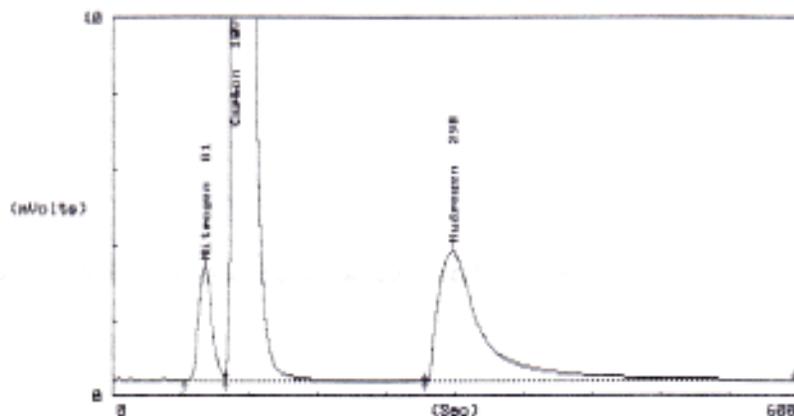
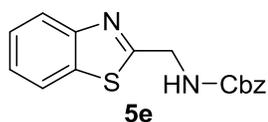






EAGER 200 Stripchart

Sample Ident. : 12 ~~thazo~~ *2-thazo* Filename : 276012
 Analysed : 01-17-13 05:45:36 Printed : 01-17-2013 05:55:38



EAGER 200 Peak Integration Report

Instrument name : Instrument #1 Bline drift (fV): 2.8
 Company Name : U of Florida Operator Ident. : KOU
 Analysed : 01-17-13 05:45:36 Printed : 01-17-2013 05:55:39
 Sample Ident. : 12 thazo Filename : 276012
 Sample Weight : 2.141 Calc.method: using 'K. Factors'

No. (#)	Type (#)	Start (Sec)	End (Sec)	Ret Time (Sec)	Height (fV)	Area (fV*Sec)	Area % (%)	Name	
1	FU	63	98	81	3015.0	38095	3.98	Nitrogen	
2	FU	98	274	107	53511.9	760133	79.39	Carbon	
3	RS	274	597	298	3455.6	159180	16.63	Hydrogen	
							957408	100.00	

EAGER 200 Unk Report

Instrument name : Instrument #1 Bline drift (fV): 2.8
 Company Name : U of Florida Operator Ident. : KOU
 Analysed : 01-17-13 05:45:36 Printed : 01-17-2013 05:55:39
 Sample Ident. : 12 thazo Filename : 276012
 Sample Weight : 2.141 Calc.method: using 'K. Factors'

Pk. (#)	Ret Time (Sec)	Area (fV*Sec)	Element % (%)	Area Ratio	Name
1	81	38095	9.075	.199537E+02	Nitrogen
2	107	760133	64.700	.100000E+01	Carbon
3	298	159180	4.929	.477531E+01	Hydrogen

