

Supporting Information
for
Consecutive hydrazino-Ugi-azide reactions:
synthesis of acylhydrazines bearing 1,5-
disubstituted tetrazoles

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Detailed experimental procedures, NMR and mass spectra

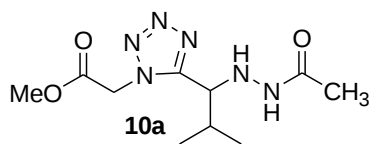
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General information

NMR spectra were recorded on a Bruker Ascend instrument using a 5 mm internal diameter probe operating at 600 MHz for ^1H and at 150 MHz for ^{13}C in the presence of TMS as internal standard. High resolution ESIMS analyses were carried out on a triple TOF 5600+ (AB Sciex) with internal calibration and direct solution (1 ppm) infusion in positive ion mode. TLC plates were revealed by treatment with a 10% solution of phosphomolybdic acid in ethanol, followed by heating. Melting points were recorded on a Marconi melting point and are uncorrected. Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. Compounds were analyzed by ^1H NMR, ^{13}C NMR and high resolution ESI mass spectra giving data consistent with the proposed structures. Compounds names were given based on ChemDraw® software 7.0.

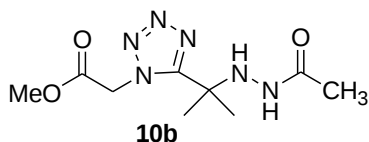
General procedure for the hydrazino-Ugi-azide reactions: To a stirred solution of hydrazide **2a–c** (0.40 mmol) in TFE (1.0 mL) were added successively oxo compound **7a–h** (0.40 mmol, 0.80 mmol when a ketone was used), trimethylsilylazide (**8**, TMS azide, 0.40 mmol), methyl isocyanoacetate (**9**, 0.40 mmol) and ZnCl_2 (10 mol %). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the Ugi tetrazole product.



{5-[1-(*N'*-Acetylhydrazino)-2-methylpropyl]

tetrazol-1-yl}acetic acid methyl ester (10a): Prepared following the general procedure using acetylhydrazide (**2a**, 0.73 mmol, 0.054 g), isobutyraldehyde (**7a**, 0.73 mmol, 0.053 g), trimethylsilyl azide (**8**, 0.73 mmol, 0.084 g), methyl isocynoacetate (**9**, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10a** in 44% yield (0.086 g, 0.32 mmol) as a yellow oil. *R*_f (CH₂Cl₂/MeOH 5%) 0.28.

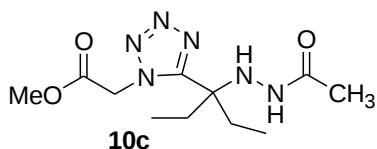
¹H NMR (600 MHz, CDCl₃) δ 7.47 (br s, 1H), 5.39 (s, 2H), 5.06 (br s, 1H), 4.31 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 2.08-2.01 (m, 1H), 1.88 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 169.8, 167.6, 154.9, 63.0, 53.4, 48.8, 30.7, 20.9, 19.6, 19.2. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₀H₁₈N₆O₃Na: 293.1338; found: 293.1342.



{5-[1-(*N'*-Acetylhydrazino)-1-methylethyl]-tetrazol-

1-yl}acetic acid methyl ester (10b): Prepared following the general procedure using acetylhydrazide (**2a**, 0.73 mmol, 0.054 g), acetone (**7b**, 0.146 mmol, 0.107 mL), trimethylsilyl azide (**8**, 0.73 mmol, 0.084 g), methyl isocynoacetate (**9**, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10b** in 36% yield (0.067 g, 0.26 mmol) as a white solid. Mp 112–114 °C; *R*_f (CH₂Cl₂/MeOH 5%) 0.34.

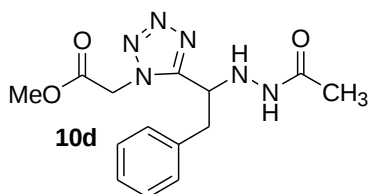
¹H NMR (600 MHz, CDCl₃) δ 7.18 (br s, 1H), 5.47 (s, 2H), 4.98 (br s, 1H), 3.86 (s, 3H), 1.92 (s, 3H), 1.63 (s, 6H). ¹³C NMR (150 MHz, CDCl₃): δ 169.8, 168.2, 158.3, 57.4, 53.4, 49.7, 24.8, 20.8. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₉H₁₆N₆O₃Na: 279.1182; found: 279.1184.



{5-[1-(*N'*-Acetylhydrazino)-1-ethylpropyl]-tetrazol-

1-yl}acetic acid methyl ester (10c**):** Prepared following the general procedure using acetylhydrazide (**2a**, 0.40 mmol, 0.030 g), 3-pentanone (**7c**, 0.40 mmol, 0.034 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.0054 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10c** in 47% yield (0.053 g, 0.19 mmol) as a white solid. Mp 130–132 °C; R_f (CH₂Cl₂/MeOH 5%) 0.31.

¹H NMR (600 MHz, CDCl₃) δ 7.08 (br s, 1H), 5.54 (s, 2H), 5.26 (br s, 1H), 3.84 (s, 3H), 2.04–1.98 (m, 2H), 1.96–1.90 (m, 2H), 1.89 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃): δ 169.1, 168.4, 157.2, 63.6, 53.4, 49.9, 24.9, 21.0, 7.2. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₁H₂₀N₆O₃Na: 307.1495; found: 307.1500.

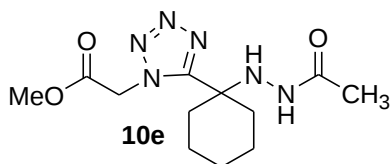


{5-[1-(*N'*-Acetylhydrazino)-2-phenylethyl]-tetrazol-

1-yl}acetic acid methyl ester (10d**):** Prepared following the general procedure using acetylhydrazide (**2a**, 0.73 mmol, 0.054 g), phenylacetaldehyde (**7d**, 0.73 mmol, 0.098 g), trimethylsilyl azide (**8**, 0.73 mmol, 0.084 g), methyl isocyanoacetate (**9**, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10d** in 30% yield (0.069 g, 0.22 mmol) as a yellow oil. R_f (CH₂Cl₂/MeOH 5%) 0.39.

¹H NMR (600 MHz, CDCl₃) δ 7.50 (s, 1H), 7.30–7.27 (m, 3H), 7.08–7.06 (m, 2H), 4.94 and 4.91 (2s, 1H, rotamers), 4.87 (t, *J* = 7.0 Hz, 1H), 4.79 and 4.76 (2s, 1H, rotamers), 3.79 (s, 3H), 3.23–3.15 (m, 2H), 1.85 (s, 3H). ¹³C NMR (150

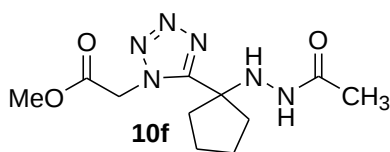
MHz, CDCl₃): δ 170.1, 167.2, 155.1, 135.0, 129.2, 128.9, 127.6, 57.1, 53.3, 48.0, 38.9, 20.9. HRMS (ESI) m/z : calcd. for [M+Na]⁺ C₁₄H₁₈N₆O₃Na: 341.1338; found: 341.1344.



{5-[1-(N'-Acetylhydrazino)cyclohexyl]-tetrazol-1-yl}acetic acid methyl ester (10e):

Prepared following the general procedure using acetylhydrazide (**2a**, 0.73 mmol, 0.054 g), cyclohexanone (**7e**, 0.73 mmol, 0.072 g), trimethylsilyl azide (**8**, 0.73 mmol, 0.084 g), methyl isocyanoacetate (**9**, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10e** in 40% yield (0.093 g, 0.29 mmol) as a white solid. Mp 116–118 °C, R_f (CH₂Cl₂/MeOH 5%) 0.32.

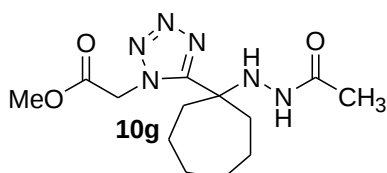
¹H NMR (600 MHz, CDCl₃) δ 7.17 (d, J = 5.9 Hz, 1H), 5.51 (s, 2H), 5.30 (d, J = 7.3 Hz, 1H), 3.84 (s, 3H), 2.19–2.15 (m, 2H), 1.89 (s, 3H), 1.86–1.82 (m, 2H), 1.77–1.71 (m, 2H), 1.65–1.59 (m, 2H), 1.51–1.48 (m, 2H). ¹³C NMR (150 MHz, CDCl₃): δ 169.5, 168.1, 157.6, 59.5, 53.4, 49.8, 33.1, 24.9, 21.8, 20.9. HRMS (ESI) m/z : calcd. for [M+Na]⁺ C₁₂H₂₀N₆O₃Na: 319.1495; found: 319.1501.



{5-[1-(N'-Acetylhydrazino)cyclopentyl]-tetrazol-1-yl}acetic acid methyl ester (10f):

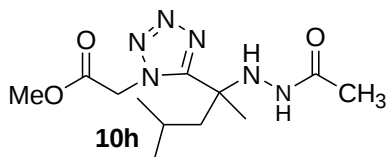
Prepared following the general procedure using acetylhydrazide (**2a**, 0.73 mmol, 0.054 g), cyclopentanone (**7f**, 0.73 mmol, 0.061 g), trimethylsilyl azide (**8**, 0.73 mmol, 0.084 g), methyl isocyanoacetate (**9**, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10f** in 36% yield (0.074 g, 0.26 mmol) as a yellow solid. Mp 105–107 °C; R_f (CH₂Cl₂/MeOH 5%) 0.36.

^1H NMR (600 MHz, CDCl_3) δ 7.21 (d, J = 7.5 Hz, 1H), 5.41 (s, 2H), 5.15 (d, J = 7.7 Hz, 1H), 3.84 (s, 3H), 2.29-2.24 (m, 2H), 2.08-2.04 (m, 1H), 1.97-1.92 (m, 2H), 1.90 (s, 3H), 1.84-1.77 (m, 2H). ^{13}C NMR (150 MHz, CDCl_3): δ 170.0, 168.1, 158.4, 67.6, 53.4, 49.3, 35.0, 27.0, 24.8, 23.9, 20.9. HRMS (ESI) m/z : calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{18}\text{N}_6\text{O}_3\text{Na}$: 305.1338; found: 305.1350.



{5-[1-(*N'*-Acetylhydrazino)cycloheptyl]-tetrazol-1-yl}acetic acid methyl ester (10g**):** Prepared following the general procedure using acetylhydrazide (**2a**; 0.40 mmol, 0.030 g), cycloheptanone (**7g**, 0.40 mmol, 0.045 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl_2 (0.040 mmol, 0.005 g). Purification by column chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow 2\% \text{ MeOH}/\text{CH}_2\text{Cl}_2$) furnished product **10g** in 53% yield (0.066 g, 0.21 mmol) as a white solid. Mp 102–104 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5%) 0.44.

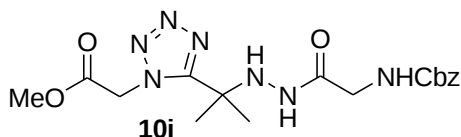
^1H NMR (600 MHz, CDCl_3) δ 7.17 (br s, 1H), 5.49 (s, 2H), 5.24 (d, J = 8.1 Hz, 1H), 3.85 (s, 3H), 2.32-2.26 (m, 2H), 1.97-1.93 (m, 2H), 1.90 (s, 3H), 1.70-1.66 (m, 4H), 1.61-1.56 (m, 4H). ^{13}C NMR (150 MHz, CDCl_3): δ 169.6, 168.6, 158.8, 63.8, 53.5, 49.9, 35.2, 30.4, 22.3, 20.9. HRMS (ESI) m/z : calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{22}\text{N}_6\text{O}_3\text{Na}$: 333.1651; found: 333.1650.



{5-[1-(*N'*-Acetylhydrazino)-1,3-dimethyl-butyl]-tetrazol-1-yl}acetic acid methyl ester (10h**):** Prepared following the general procedure using acetylhydrazide (**2a**, 0.40 mmol, 0.030 g), methyl isobutyl ketone (**7h**, 0.40 mmol, 0.040 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g),

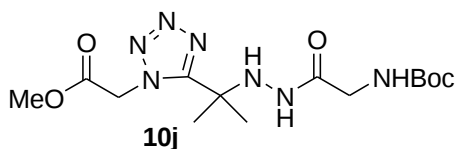
methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10h** in 47% yield (0.056 g, 0.19 mmol) as a white solid. Mp 94–96 °C; R_f (CH₂Cl₂/MeOH 5%) 0.42.

¹H NMR (600 MHz, CDCl₃) δ 7.15 (br s, 1H), 5.54 (d, *J* = 17.0 Hz, 1H), 5.38 (s, *J* = 17.0 Hz, 1H), 5.03 (br s, 1H), 3.86 (s, 3H), 1.91 (s, 3H), 1.72 (s, 3H), 1.70–1.66 (m, 3H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.52 (d, *J* = 6.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 169.9, 168.4, 157.7, 60.7, 53.5, 49.7, 47.2, 24.7, 24.2, 23.2, 21.2, 20.9. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₂H₂₂N₆O₃Na: 321.1651; found: 321.1650.



(5-{1-[N'-(2-(Benzyloxycarbonyl-amino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-yl)acetic acid methyl ester (10i): Prepared following the general procedure using Cbz-glycine hydrazide (**2b**, 0.40 mmol, 0.089 g), acetone (**7b**, 0.80 mmol, 0.046 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10i** in quantitative yield (0.162 g, 0.40 mmol) as a white solid. Mp 120–122 °C; R_f (CH₂Cl₂/MeOH 5%) 0.36.

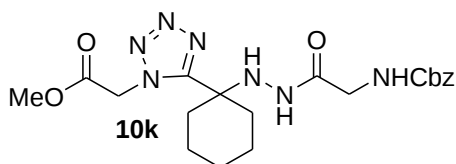
¹H NMR (600 MHz, CDCl₃) δ 7.77 (d, *J* = 7.4 Hz, 1H), 7.35–7.29 (m, 5H), 5.47 (s, 2H), 5.45 (br s, 1H), 5.09 (s, 2H), 4.92 (d, *J* = 7.4 Hz, 1H), 3.83 (d, *J* = 5.9 Hz, 2H), 3.80 (s, 3H), 1.60 (s, 6H). ¹³C NMR (150 MHz, CDCl₃): δ 169.1, 168.3, 158.1, 156.5, 136.0, 128.5, 128.2, 128.1, 67.2, 57.5, 53.6, 49.8, 43.3, 24.9. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₇H₂₃N₇O₅Na: 428.1658; found: 428.1666.



(5-{1-[N'-(2-(tert-

Butoxycarbonylamino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-yl)acetic acid methyl ester (10j): Prepared following the general procedure using Boc-glycine hydrazide (**2c**, 0.40 mmol, 0.076 g), acetone (**7b**, 0.80 mmol, 0.046 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10j** in 97% yield (0.144 g, 0.39 mmol) as a colorless oil. R_f (CH₂Cl₂/MeOH 5%) 0.34.

¹H NMR (600 MHz, CDCl₃) δ 7.72 (br s, 1H), 5.47 (s, 2H), 5.04 (br s, 1H), 4.93 (br s, 1H), 3.84 (s, 3H), 3.77 (d, J = 5.9 Hz, 2H), 1.62 (s, 6H), 1.41 (s, 9H). ¹³C NMR (150 MHz, CDCl₃): δ 169.6, 167.9, 158.1, 155.9, 80.2, 57.3, 53.4, 49.8, 42.9, 28.1, 24.8. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₄H₂₅N₇O₅Na: 394.1815; found: 394.1814.

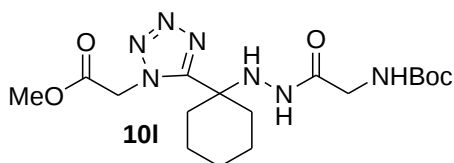


(5-{1-[N'-(2-

(Benzyloxycarbonylamino)acetyl)hydrazino]-cyclohexyl}-tetrazol-1-yl)acetic acid methyl ester (10k): Prepared following the general procedure using Cbz-glycine hydrazide (**2b**, 0.40 mmol, 0.089 g), cyclohexanone (**7e**, 0.40 mmol, 0.039 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product **10k** in 85% yield (0.151 g, 0.34 mmol) as a white solid. Mp 62–64 °C; R_f (CH₂Cl₂/MeOH 5%) 0.42.

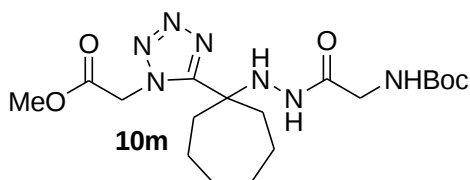
¹H NMR (600 MHz, CDCl₃) δ 7.62 (br s, 1H), 7.36-7.29 (m, 5H), 5.49 (s, 2H), 5.32 (br s, 1H), 5.23 (br s, 1H), 5.08 (s, 2H), 3.80 (s, 5H), 2.18-2.14 (m, 2H), 1.86-1.79 (m, 2H), 1.75-1.69 (m, 2H), 1.64-1.57 (m, 2H), 1.51-1.47 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 168.8, 168.3, 157.5, 156.4, 136.0, 128.5, 128.2, 128.1, 67.2, 59.7, 53.6, 49.9, 43.3, 33.2, 25.0, 21.8. HRMS (ESI) m/z : calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{20}\text{H}_{27}\text{N}_7\text{O}_5\text{Na}$: 468.1971; found: 468.1974.



(5-{1-[N'-(2-(tert-butoxycarbonylamino)acetyl)hydrazino]-cyclohexyl}-tetrazol-1-yl)acetic acid methyl ester (10l): Prepared following the general procedure using Boc-glycine hydrazide (**2c**, 0.40 mmol, 0.076 g), cyclohexanone (**7e**, 0.40 mmol, 0.039 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl_2 (0.040 mmol, 0.005 g). Purification by column chromatography ($\text{CH}_2\text{Cl}_2 \rightarrow 3\% \text{ MeOH}/\text{CH}_2\text{Cl}_2$) furnished product **10l** in 57% yield (0.094 g, 0.23 mmol) as a white solid. Mp 68–70 °C; R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5%) 0.41.

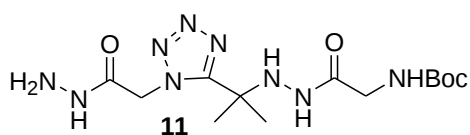
^1H NMR (600 MHz, CDCl_3) δ 7.67 (s, 1H), 5.50 (s, 2H), 5.01 (s, 1H), 3.82 (s, 3H), 3.74 (s, 2H), 2.21–2.17 (m, 2H), 1.87–1.82 (m, 2H), 1.76–1.70 (m, 2H), 1.65–1.59 (m, 2H), 1.51–1.47 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (150 MHz, CDCl_3): δ 169.3, 168.1, 157.3, 155.8, 80.4, 59.7, 53.5, 49.9, 43.0, 33.2, 28.2, 24.9, 21.8. HRMS (ESI) m/z : calcd. for $[\text{M}+\text{Na}]^+$ $\text{C}_{17}\text{H}_{29}\text{N}_7\text{O}_5\text{Na}$: 434.2128; found: 434.2143.



(5-{1-[N'-(2-(tert-butoxycarbonylamino)acetyl)hydrazino]-cycloheptyl}-tetrazol-1-yl)acetic acid methyl ester (10m): Prepared following the general procedure using Boc-

glycine hydrazide (**2c**, 0.40 mmol, 0.076 g), cycloheptanone (**7g**, 0.40 mmol, 0.045 g), trimethylsilyl azide (**8**, 0.40 mmol, 0.046 g), methyl isocyanoacetate (**9**, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product **10n** in 62% yield (0.106 g, 0.25 mmol) colorless oil. R_f (CH₂Cl₂/MeOH 5%) 0.50.

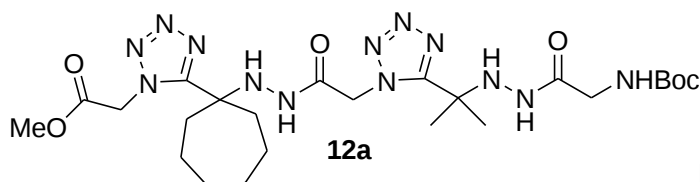
¹H NMR (600 MHz, CDCl₃) δ 7.68 (s, 1H), 5.49 (s, 2H), 5.04 (s, 1H), 3.83 (s, 3H), 3.76 (d, *J* = 5.5 Hz, 2H), 2.32-2.28 (m, 2H), 1.96-1.92 (m, 2H), 1.68-1.53 (m, 8H), 1.40 (s, 9H). ¹³C NMR (150 MHz, CDCl₃): δ 169.3, 168.2, 158.6, 155.8, 80.3, 63.8, 53.5, 50.8, 49.9, 43.8, 35.3, 30.4, 28.2, 24.3, 22.3. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₈H₃₁N₇O₅Na: 448.2284; found: 448.2296.



{N'-[1-(1-Hydrazinocarbonylmethyl-1H-

tetrazol-5-yl)-1-methylethyl]-hydrazinocarbonylmethyl}carbamic acid *tert*-butyl ester (11**):** To a solution of compound **10j** (0.371 g, 1.00 mmol) in 2.0 mL of ethanol was added hydrazine hydrate (0.200 g, 4.00 mmol). After refluxing for 5 h, the residue was concentrated in vacuum and purified by column chromatography (CH₂Cl₂ → 10% MeOH/CH₂Cl₂) furnishing product **6** in 55% yield (0.204 g, 0.55 mmol) as a white solid. Mp 44–46 °C; R_f (CH₂Cl₂/MeOH 15%) 0.39.

¹H NMR (600 MHz, DMSO-*d*₆) δ 9.59 (s, 1H), 9.00 (d, *J* = 5.9 Hz, 1H), 6.95 (t, *J* = 6.1 Hz, 1H), 5.51 (s, 2H), 5.37 (d, *J* = 5.9 Hz, 1H), 4.39 (br, 1H), 3.43 (d, *J* = 5.9 Hz, 2H), 1.46 (s, 6H), 1.35 (s, 9H). ¹³C NMR (150 MHz, DMSO-*d*₆): δ 169.1, 165.2, 158.3, 155.8, 78.1, 56.5, 49.5, 34.7, 28.2, 25.1, 18.6, 13.9. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₁₃H₂₅N₉O₄Na: 394.1927; found: 394.1923.



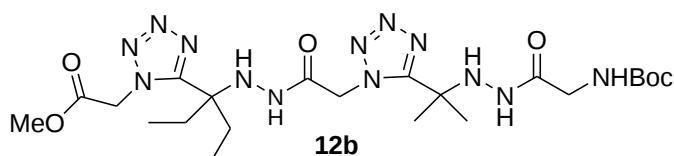
[5-(1-{N'-[2-(5-{1-[N'-(2-(tert-

Butoxycarbonylamino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-

yl)acetyl]hydrazino}-cycloheptyl)-tetrazol-1-yl]acetic acid methyl ester

(12a): Prepared following the general procedure using hydrazide **11** (0.13 mmol, 0.048 g), cycloheptanone (**7g**, 0.13 mmol, 0.014 g), trimethylsilyl azide (**8**, 0.13 mmol, 0.015 g), methyl isocyanoacetate (**9**, 0.13 mmol, 0.013 mL) and ZnCl₂ (0.013 mmol, 0.002 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product **12a** in 68% yield (0.055 g, 0.090 mmol) as a white solid. Mp 105–107 °C; R_f (CH₂Cl₂/MeOH 10%) 0.52.

¹H NMR (600 MHz, DMSO-*d*₆) δ 9.59 (d, *J* = 4.4 Hz, 1H), 8.94 (d, *J* = 5.1 Hz, 1H), 6.88 (s, 1H), 5.87 (s, 2H), 5.64 (d, *J* = 4.4 Hz, 1H), 5.45 (s, 2H), 5.27 (d, *J* = 5.5 Hz, 1H), 3.71 (s, 3H), 3.39 (d, *J* = 5.9 Hz, 2H), 2.17-2.13 (m, 2H), 1.96-1.92 (m, 2H), 1.65-1.59 (m, 2H), 1.53-1.48 (m, 4H), 1.41-1.30 (m, 17H). ¹³C NMR (150 MHz, DMSO-*d*₆): δ 169.0, 167.6, 165.6, 158.0 (2C), 155.7, 78.0, 62.4, 56.1, 54.9, 52.7, 49.6, 49.3, 45.7, 41.7, 35.0, 29.6, 28.1, 24.9, 21.9. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₂₄H₄₁N₁₃O₆Na: 630.3200; found: 630.3230.



[5-(1-{N'-[2-(5-{1-[N'-(2-(tert-

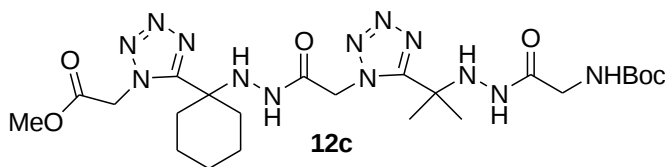
Butoxycarbonylamino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-

yl)acetyl]hydrazino}-1-ethylpropyl)-tetrazol-1-yl]acetic acid methyl ester

(12b): Prepared following the general procedure using hydrazide **11** (0.35 mmol, 0.130 g), 3-pentanone (**7c**, 0.35 mmol, 0.030 g), trimethylsilyl azide (**8**, 0.35 mmol, 0.040 g), methyl isocyanoacetate (**9**, 0.35 mmol, 0.032 mL) and

ZnCl₂ (0.035 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 5% MeOH/CH₂Cl₂) furnished product **12b** in 54% yield (0.110 g, 0.19 mmol) as a yellow solid. Mp 101–103 °C; R_f (CH₂Cl₂/MeOH 10%) 0.43.

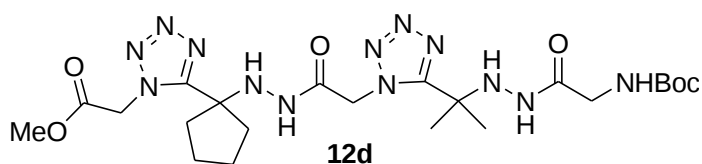
¹H NMR (600 MHz, DMSO-*d*₆) δ 9.47 (br s, 1H), 8.95 (d, *J* = 5.5 Hz, 1H), 6.88 (t, *J* = 6.1 Hz, 1H), 5.93 (s, 2H), 5.66 (br s, 1H), 5.46 (s, 2H), 5.25 (d, *J* = 5.5 Hz, 1H), 3.70 (s, 3H), 3.39 (d, *J* = 5.9 Hz, 2H), 1.96–1.90 (m, 2H), 1.80–1.74 (m, 2H), 1.35 and 1.33 (2s, 15H), 0.69 (t, *J* = 7.5 Hz, 6H). ¹³C NMR (150 MHz, DMSO-*d*₆): δ 169.0, 167.6, 165.7, 158.0, 156.4, 155.7, 78.0, 62.5, 56.0, 52.7, 49.8, 49.3, 45.7, 41.7, 28.1, 24.8, 24.7, 20.0, 7.03. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₂₂H₃₉N₁₃O₆Na: 604.3044; found: 604.3035.



[5-(1-{N'-[2-(5-{1-[N'-(2-(tert-

Butoxycarbonylamino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-yl)acetyl]hydrazino}-cyclohexyl)-tetrazol-1-yl]acetic acid methyl ester (12c**):** Prepared following the general procedure using hydrazide **11** (0.26 mmol, 0.095 g), cyclohexanone (**7e**, 0.26 mmol, 0.025 g), trimethylsilyl azide (**8**, 0.26 mmol, 0.030 g), methyl isocyanoacetate (**9**, 0.26 mmol, 0.024 mL) and ZnCl₂ (0.026 mmol, 0.004 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product **12c** in 70% yield (0.108 g, 0.18 mmol) as a yellow solid. Mp 119–121 °C; R_f (CH₂Cl₂/MeOH 10%) 0.47.

¹H NMR (600 MHz, DMSO-*d*₆) δ 9.59 (br s, 1H), 8.92 (d, *J* = 5.3 Hz, 1H), 6.88 (s, 1H), 5.84 (s, 2H), 5.67 (s, 1H), 5.41 (s, 2H), 5.25 (d, *J* = 5.3 Hz, 1H), 3.70 (s, 3H), 3.40 (d, *J* = 5.9 Hz, 2H), 2.05–1.99 (m, 2H), 1.80–1.77 (m, 2H), 1.69–1.60 (m, 2H), 1.47–1.39 (m, 4H), 1.35 and 1.33 (2s, 15H). ¹³C NMR (150 MHz, DMSO-*d*₆): δ 169.0, 167.6, 165.6, 158.0, 156.8, 155.7, 78.0, 58.2, 56.1, 52.7, 49.5, 49.2, 45.7, 41.7, 32.8, 28.1, 24.9, 21.4. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₂₃H₃₉N₁₃O₆Na: 616.3044; found: 616.3033.



[5-(1-{N'-[2-(5-{1-[N'-(2-(tert-

Butoxycarbonylamino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-

yl)acetyl]hydrazino}-cyclopentyl)-tetrazol-1-yl]acetic acid methyl ester

(12d): Prepared following the general procedure using hydrazide **11** (0.30 mmol, 0.110 g), cyclopentanone (**7f**, 0.30 mmol, 0.025 g), trimethylsilyl azide (**8**, 0.30 mmol, 0.034 g), methyl isocyanoacetate (**9**, 0.30 mmol, 0.027 mL) and ZnCl₂ (0.030 mmol, 0.004 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product **12d** in 45% yield (0.079 g, 0.14 mmol) as a yellow solid. Mp 114–116 °C; R_f (CH₂Cl₂/MeOH 10%) 0.47.

¹H NMR (600 MHz, CDCl₃) δ 8.44 (d, *J* = 7.0 Hz, 1H), 8.39 (br s, 1H), 5.47 (s, 2H), 5.41 (s, 2H), 5.27 (br s, 1H), 5.14 (br s, 1H), 4.75 (br s, 1H), 3.86 (s, 3H), 3.77 (d, *J* = 5.9 Hz, 1H), 2.29–2.24 (m, 1H), 2.09–2.02 (m, 1H), 1.95–1.88 (m, 2H), 1.78–1.76 (m, 2H), 1.59 (s, 6H), 1.43 (s, 9H). ¹³C NMR (150 MHz, CDCl₃): δ 169.9, 168.1, 165.6, 158.2, 157.9, 156.0, 80.3, 67.6, 57.5, 53.7, 49.9, 49.4, 42.9, 35.2, 29.7, 28.3, 25.2, 23.8, 14.1. HRMS (ESI) *m/z*: calcd. for [M+Na]⁺ C₂₂H₃₇N₁₃O₆Na: 602.2887; found: 602.2879.

Spectra of compounds

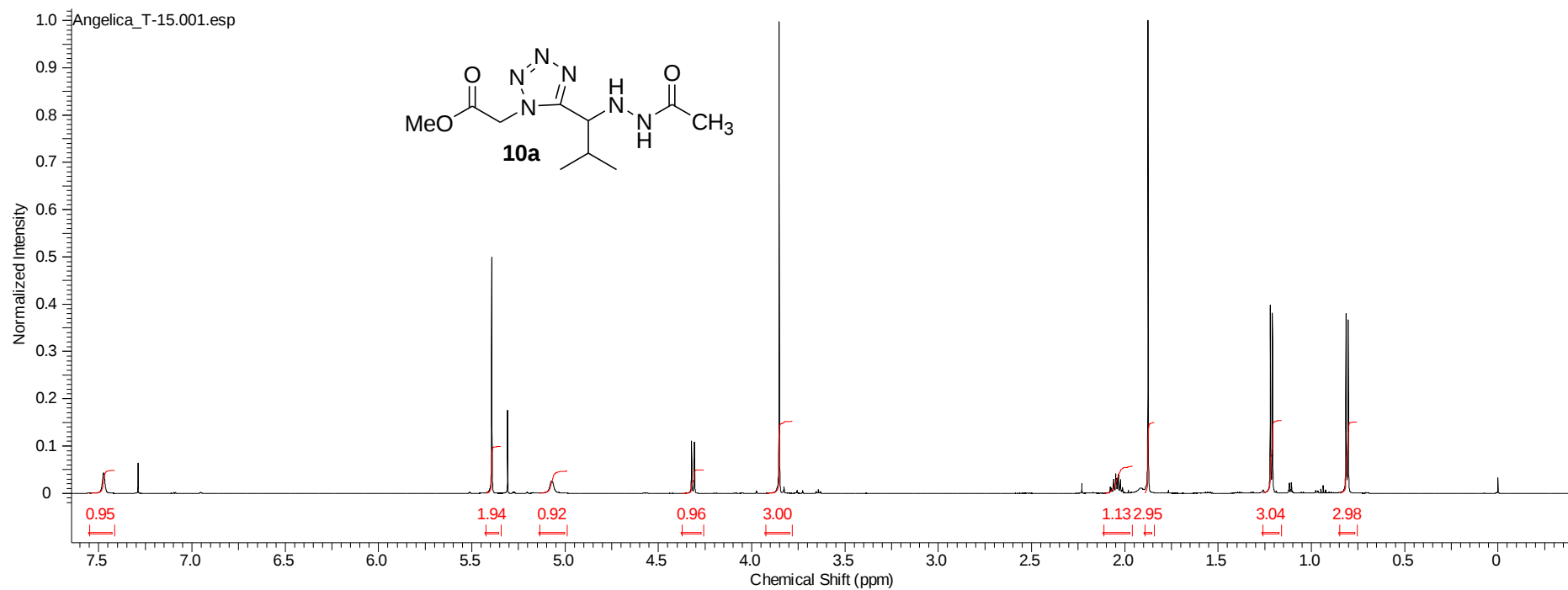


Figure S1: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10a**.

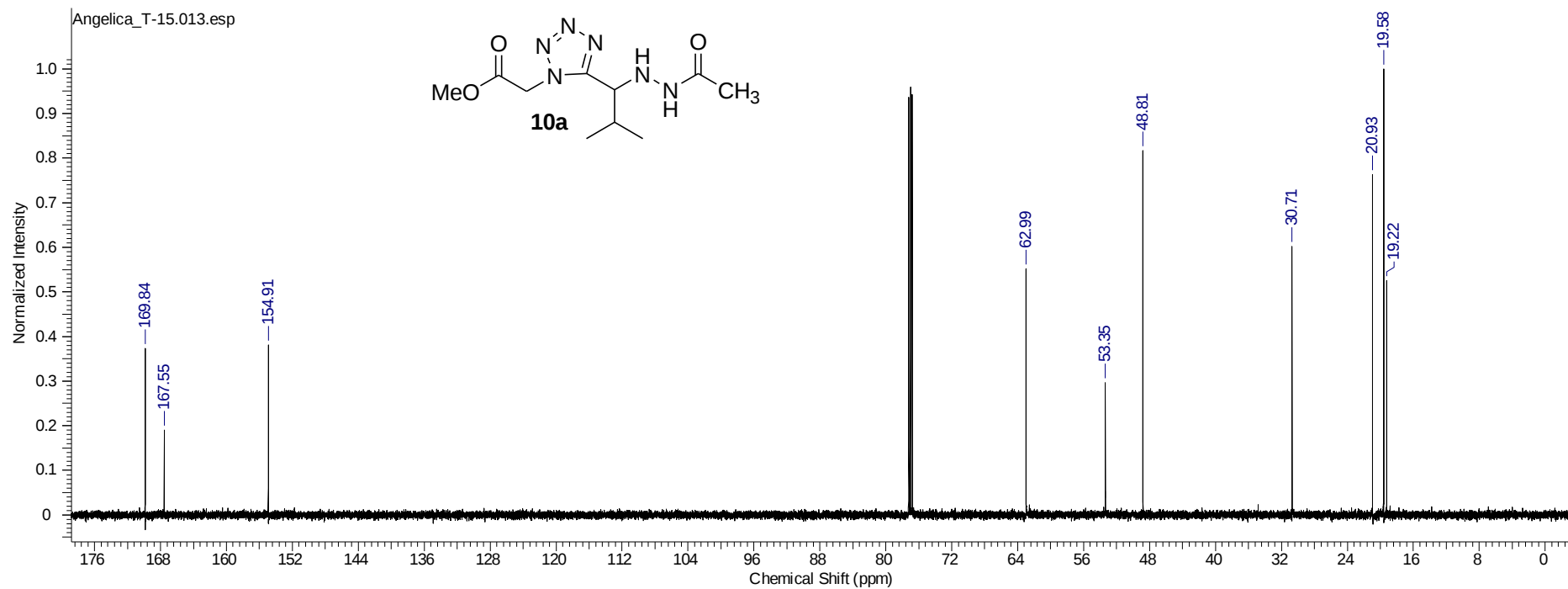


Figure S2: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10a**.

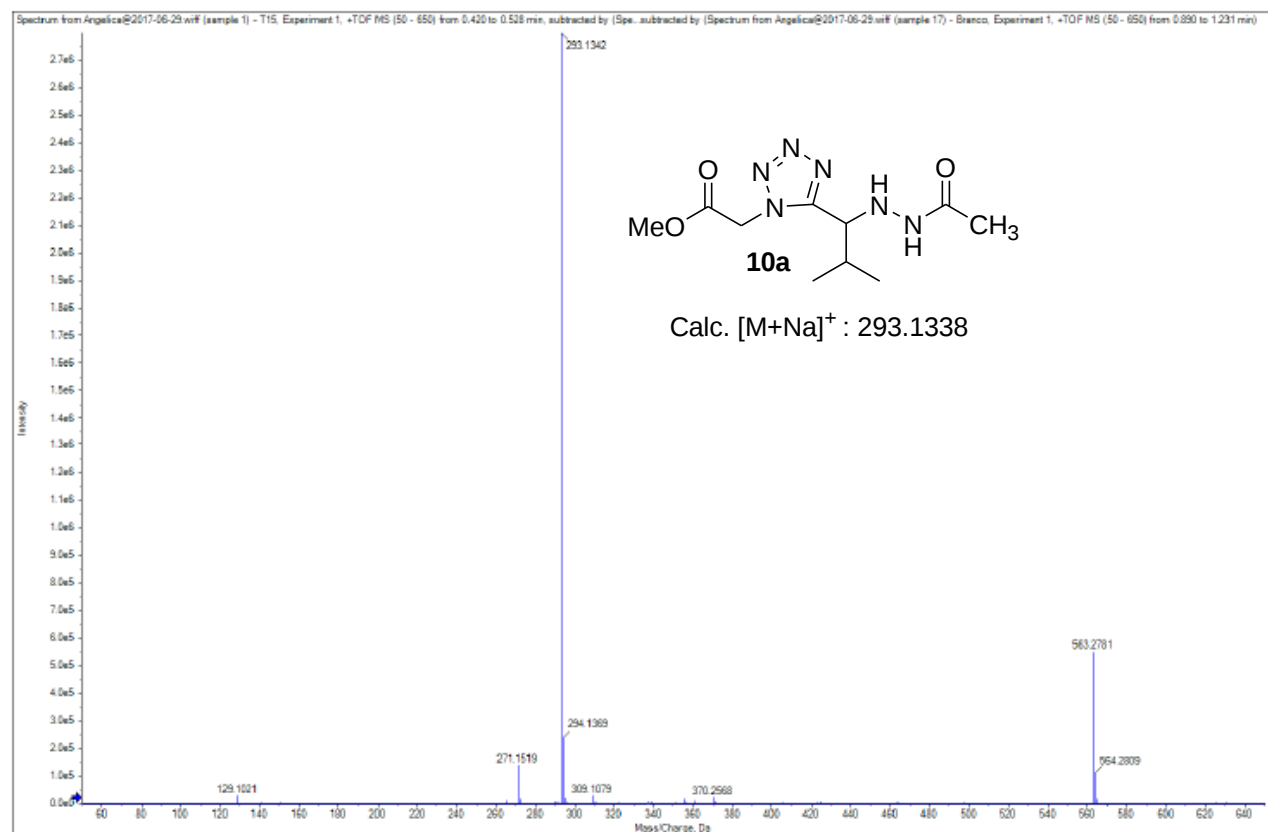


Figure S3: ESI-HRMS of compound **10a**.

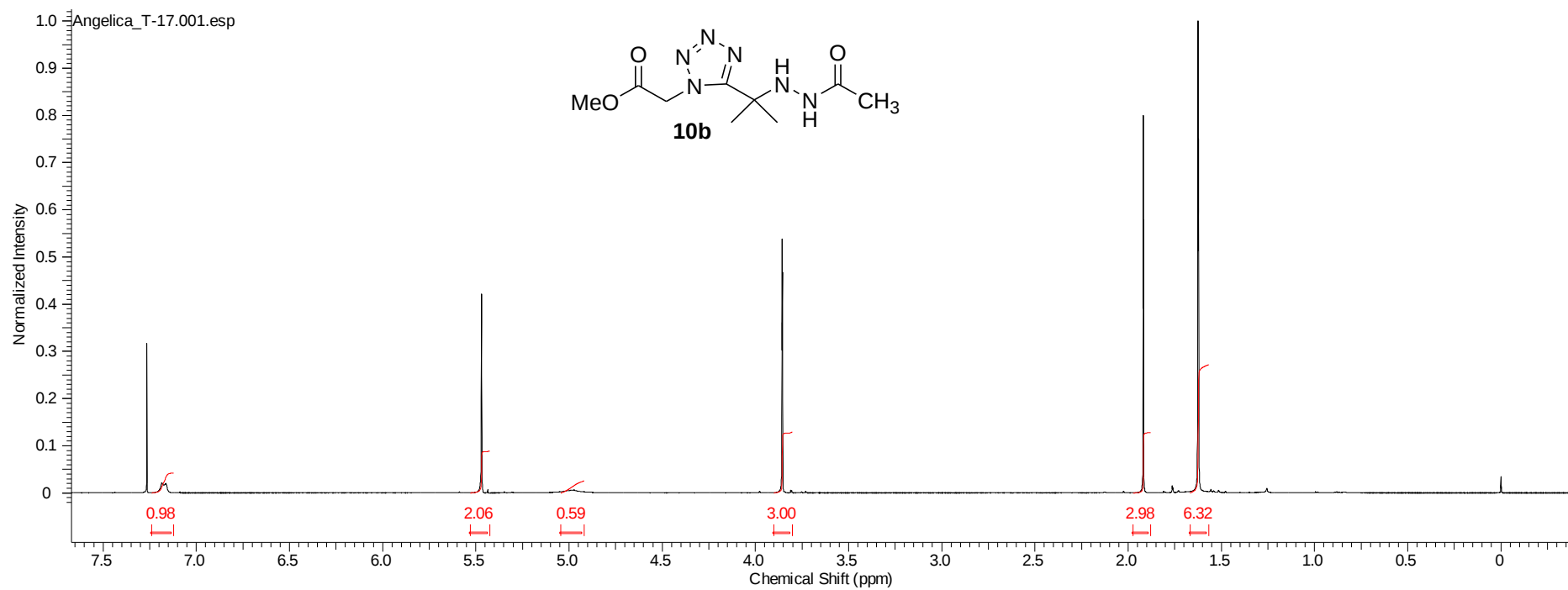


Figure S4: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10b**.

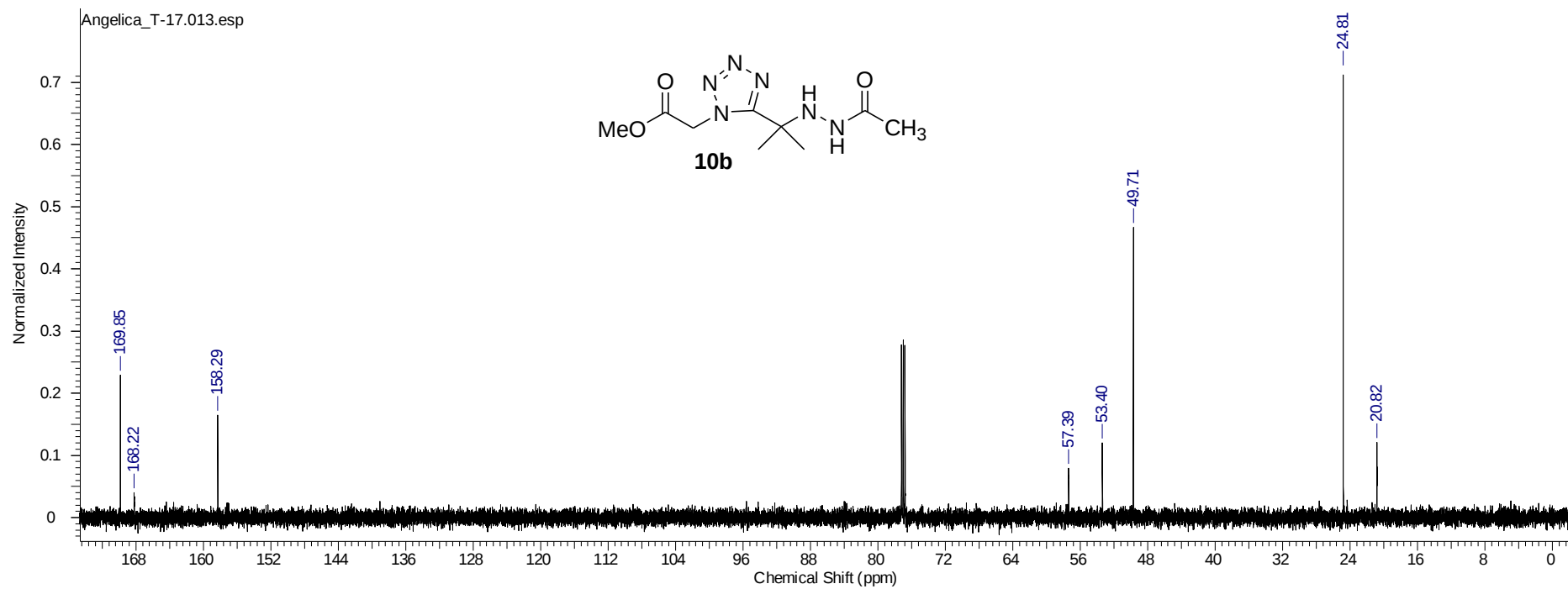


Figure S5: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10b**.

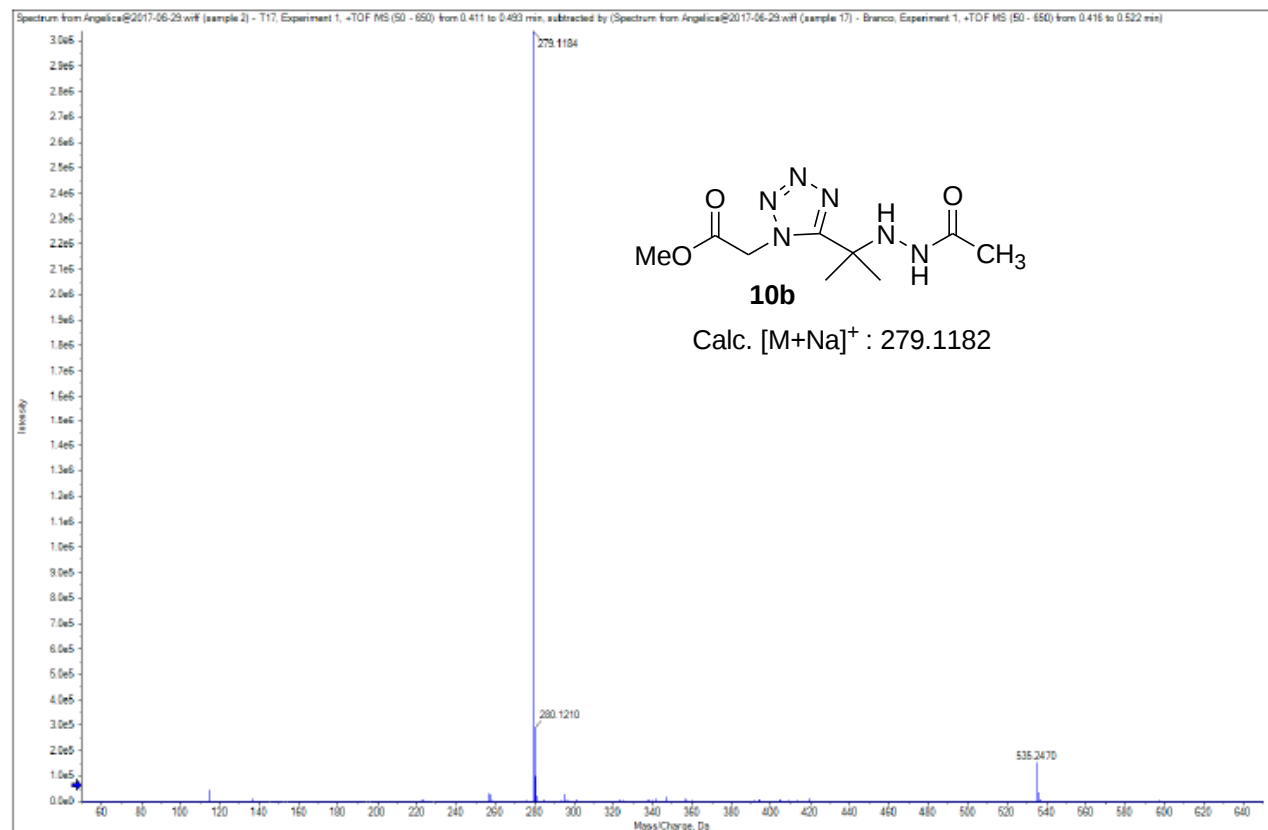


Figure S6: ESI-HRMS of compound **10b**.

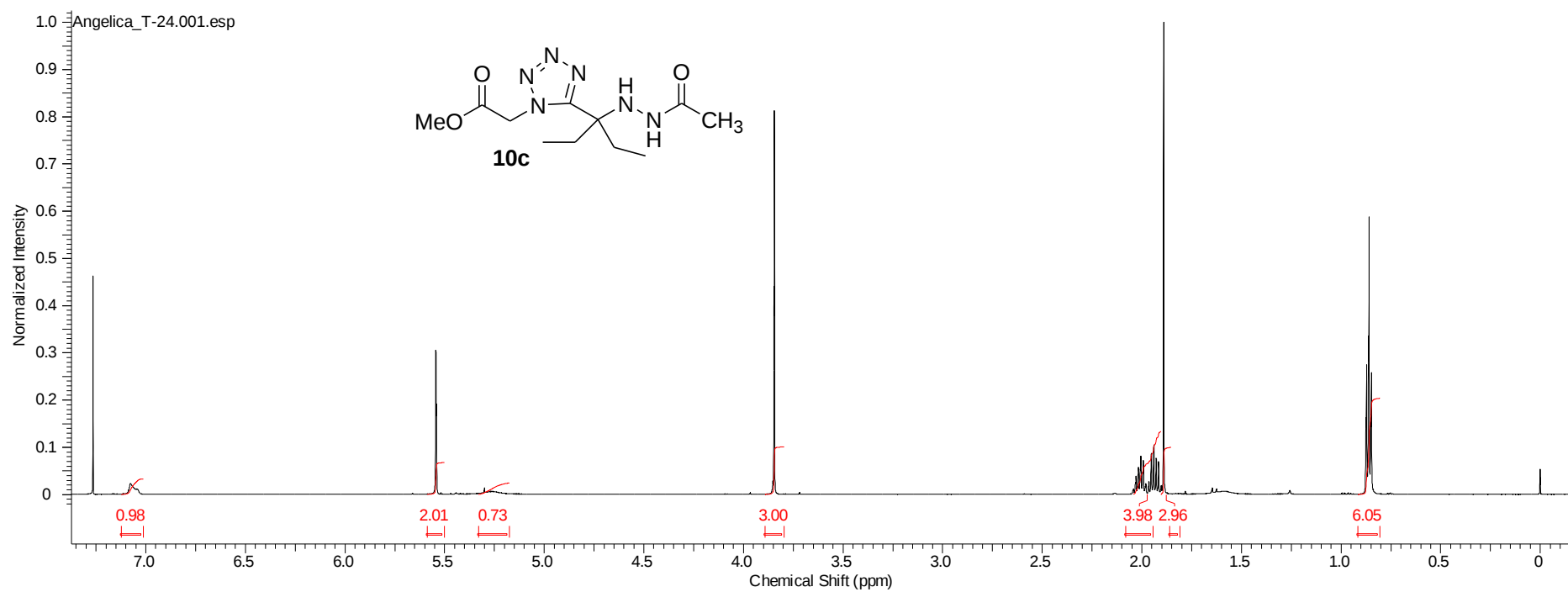


Figure S7: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10c**.

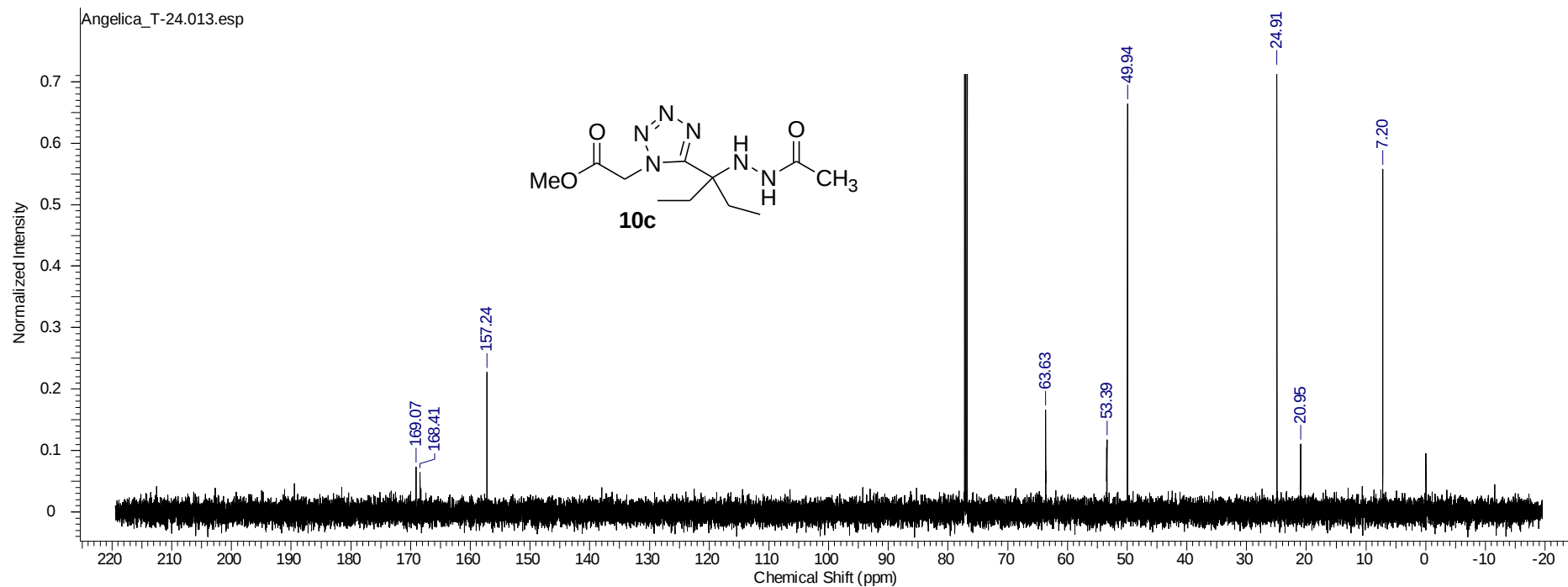


Figure S8: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10c**.

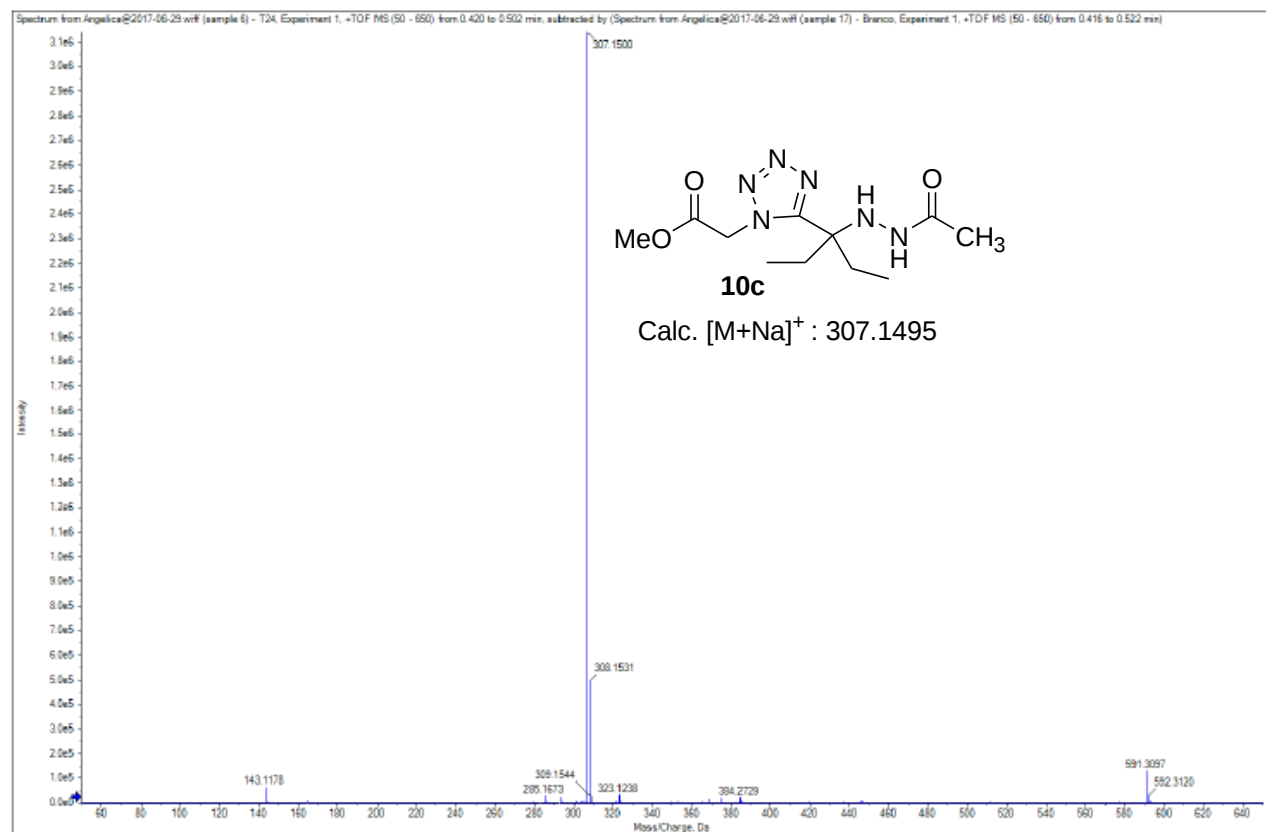


Figure S9: ESI-HRMS of compound **10c**.

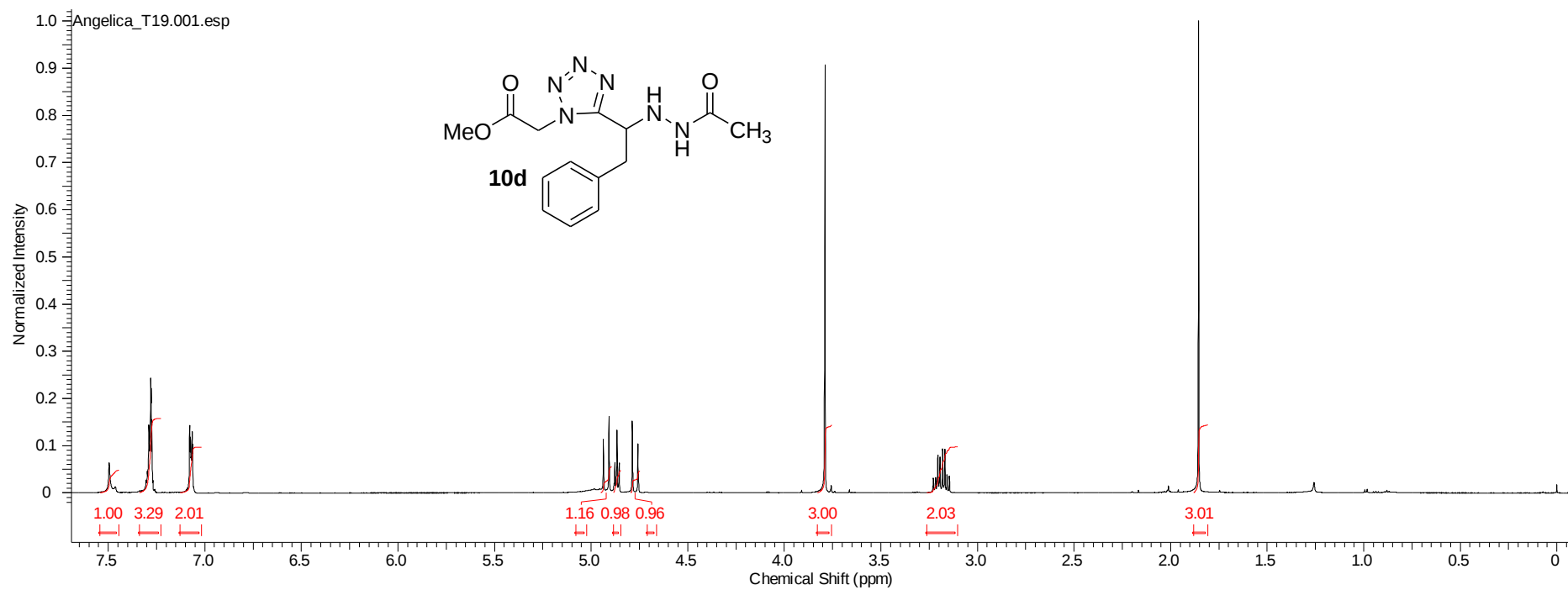


Figure S10: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10d**.

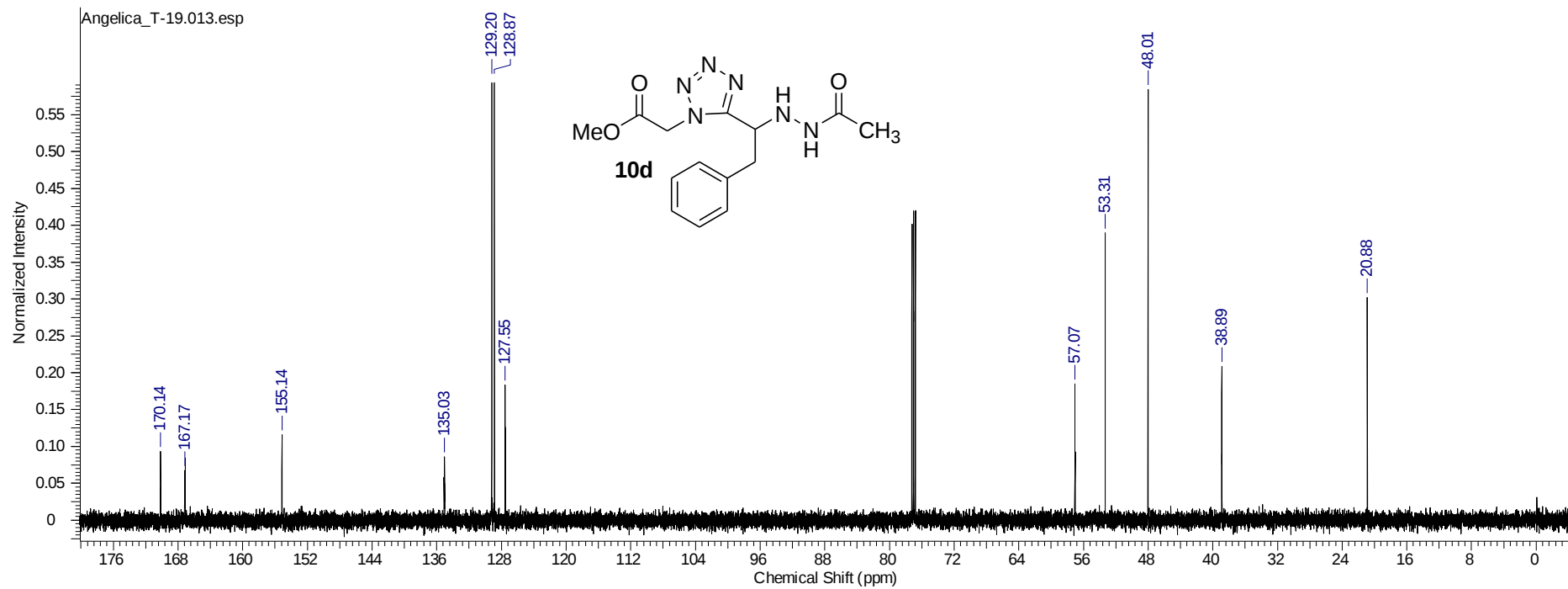


Figure S11: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10d**.

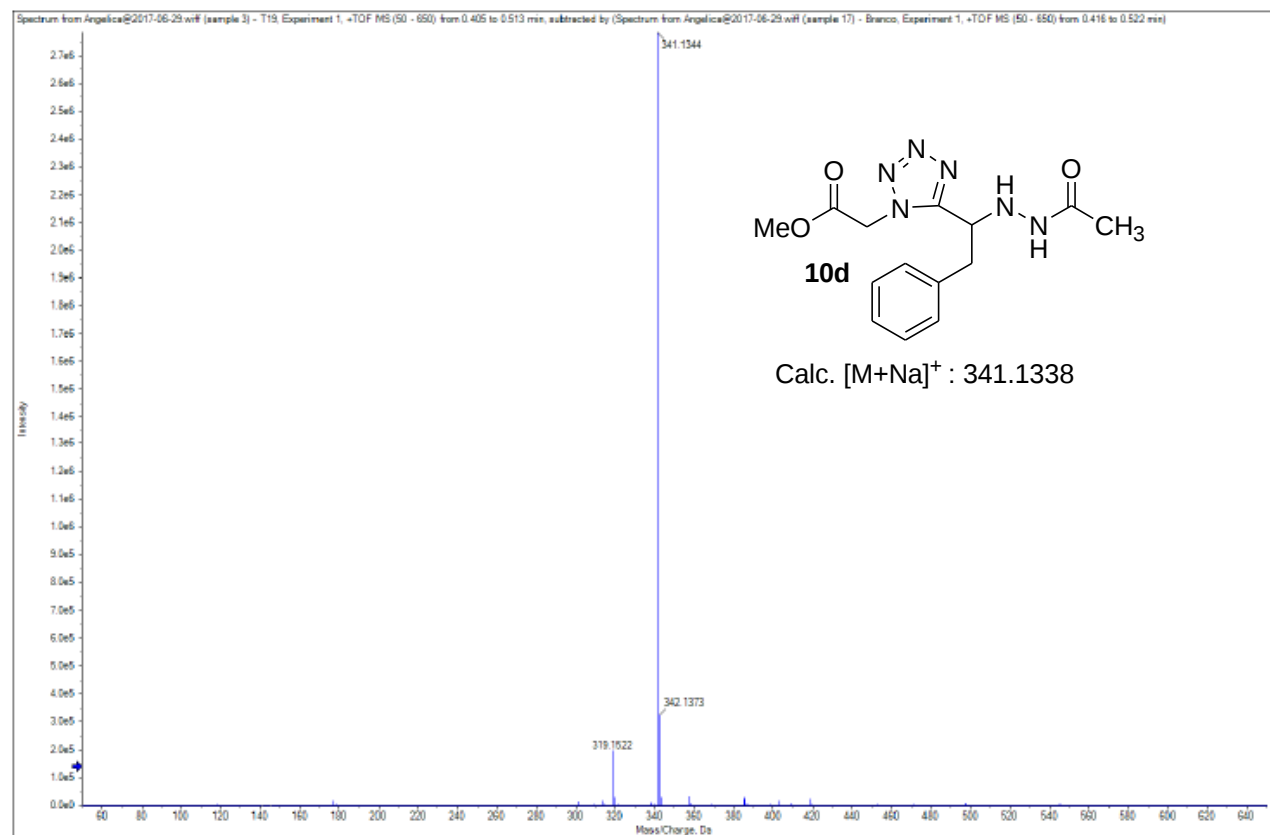


Figure S12: ESI-HRMS of compound **10d**.

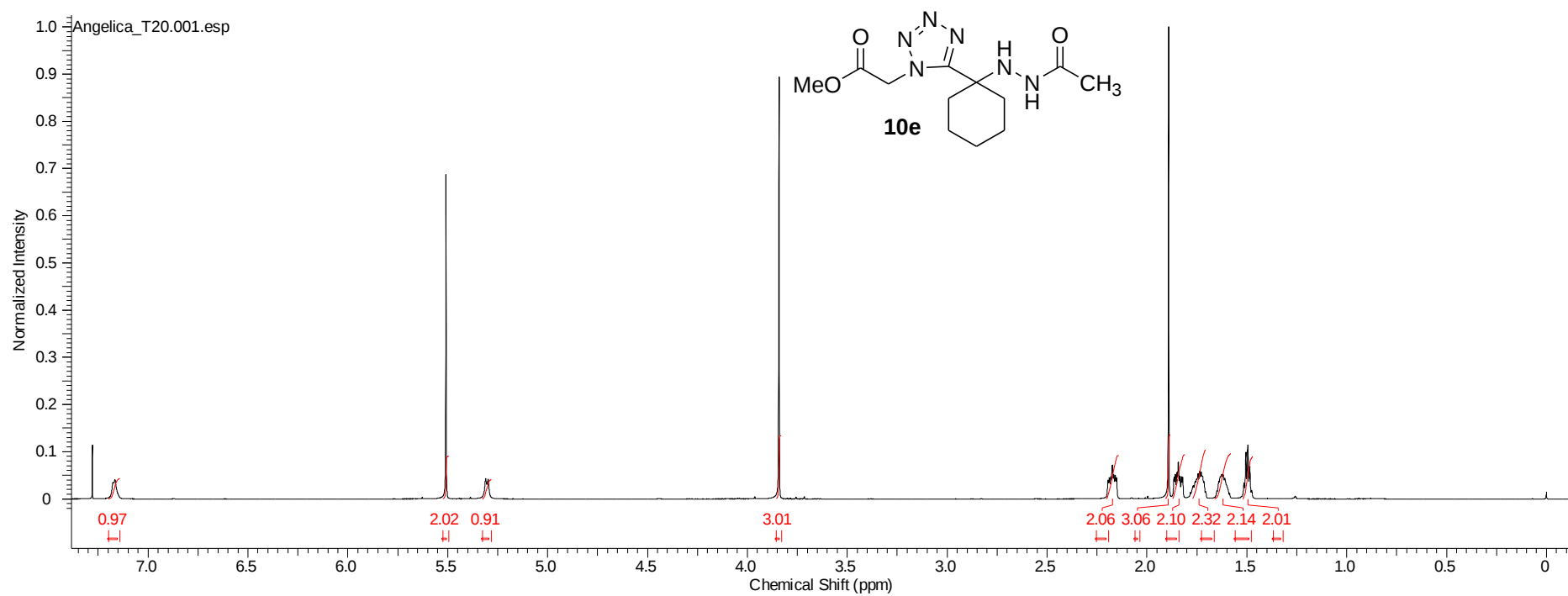


Figure S13: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10e**.

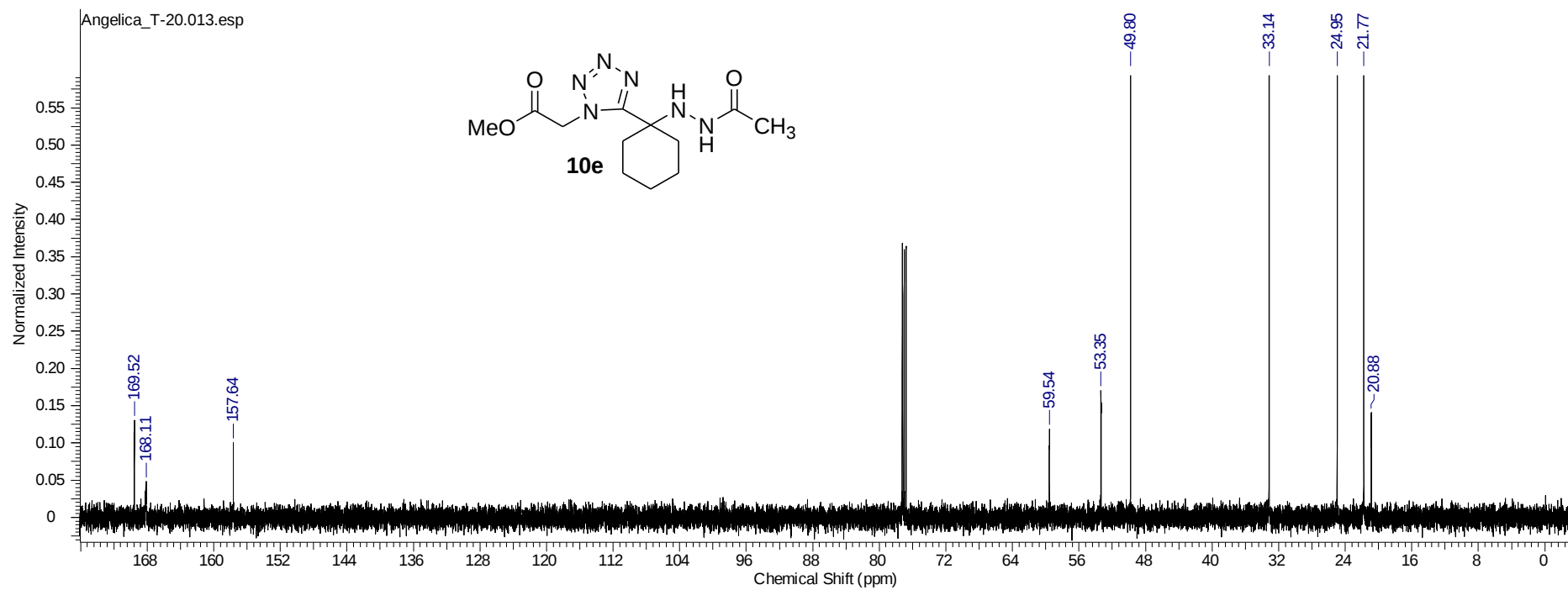


Figure S14: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10e**.

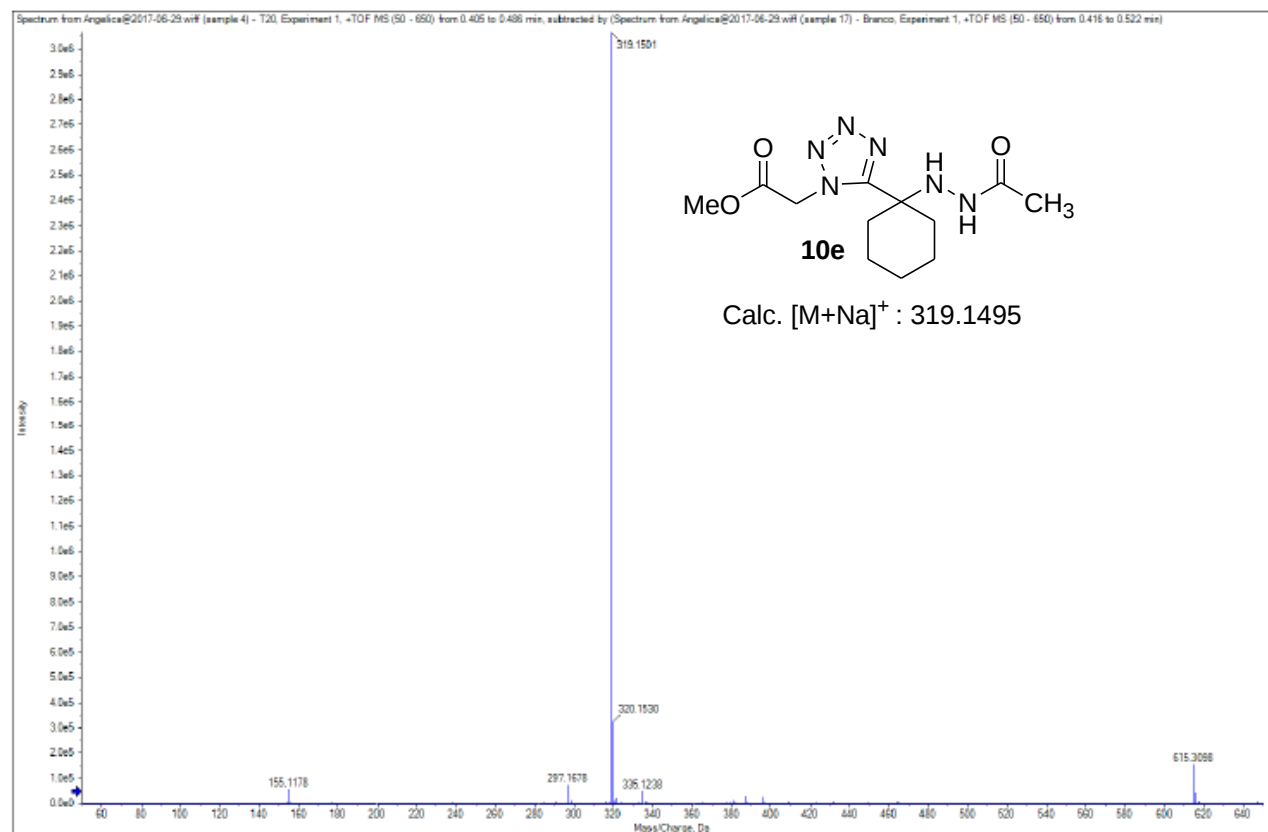


Figure S15: ESI-HRMS of compound **10e**.

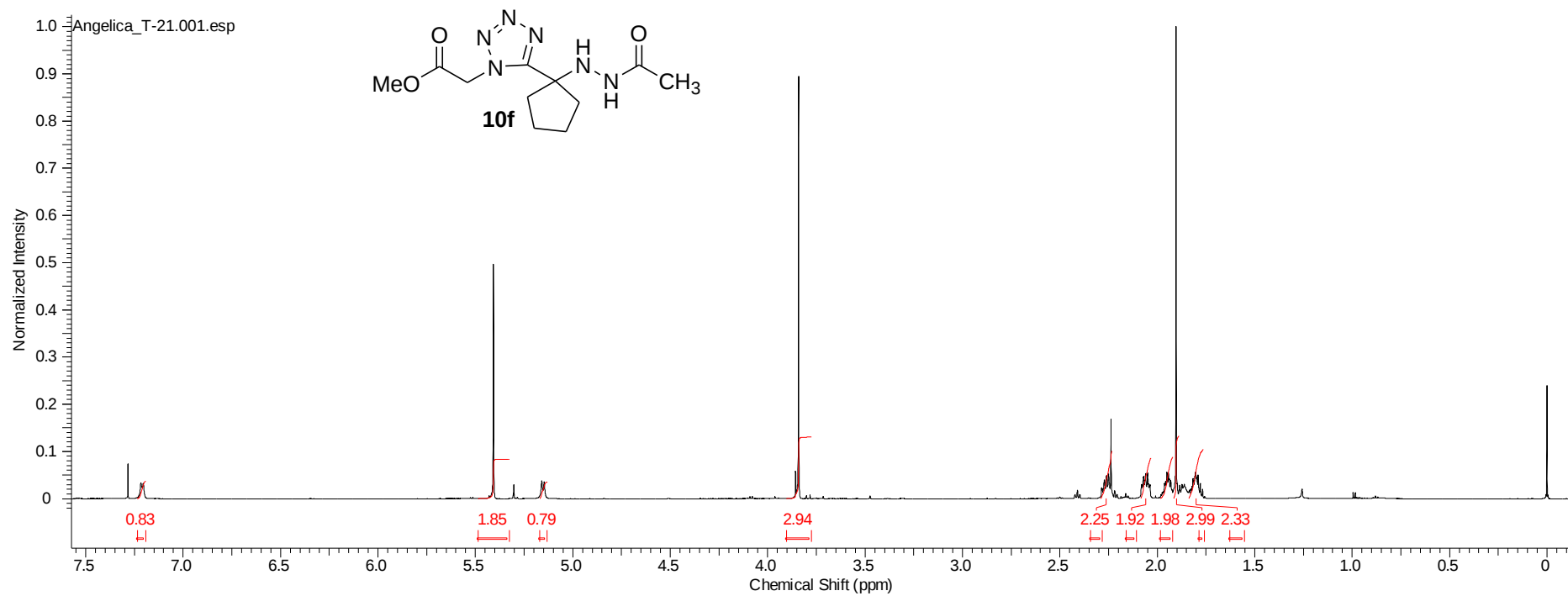


Figure S16: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10f**.

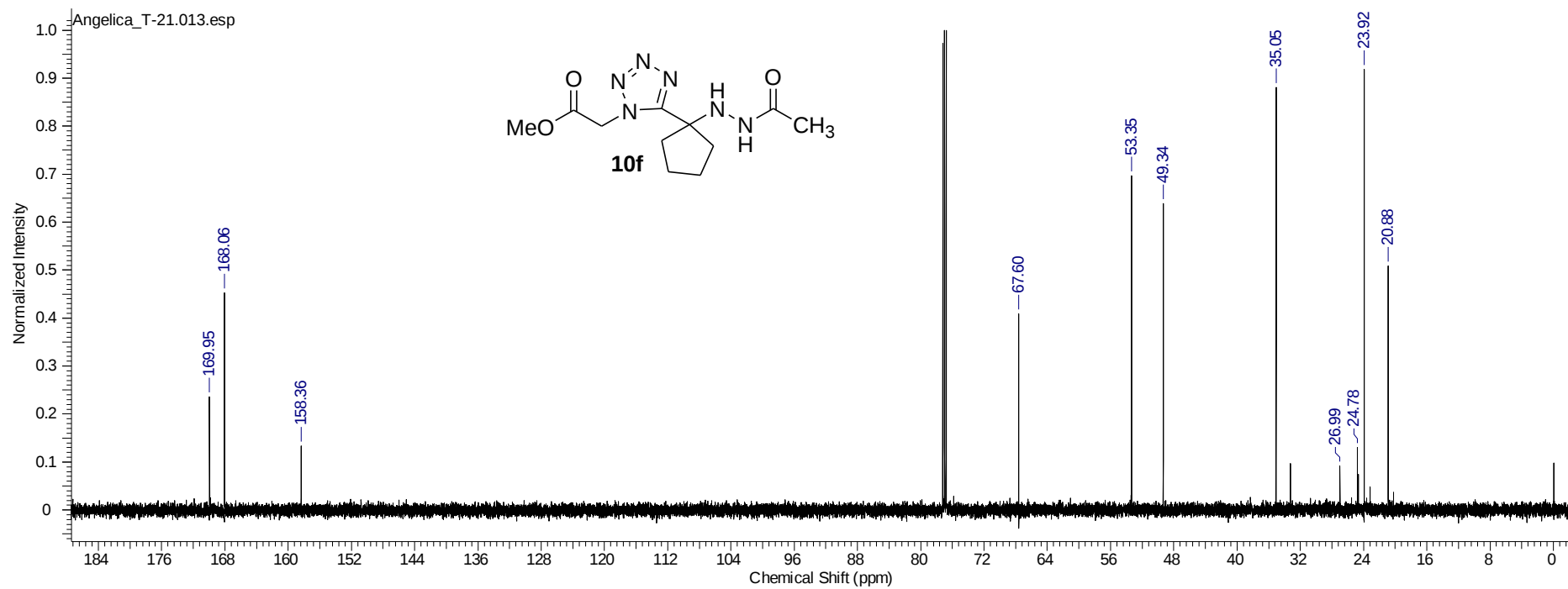


Figure S17: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10f**.

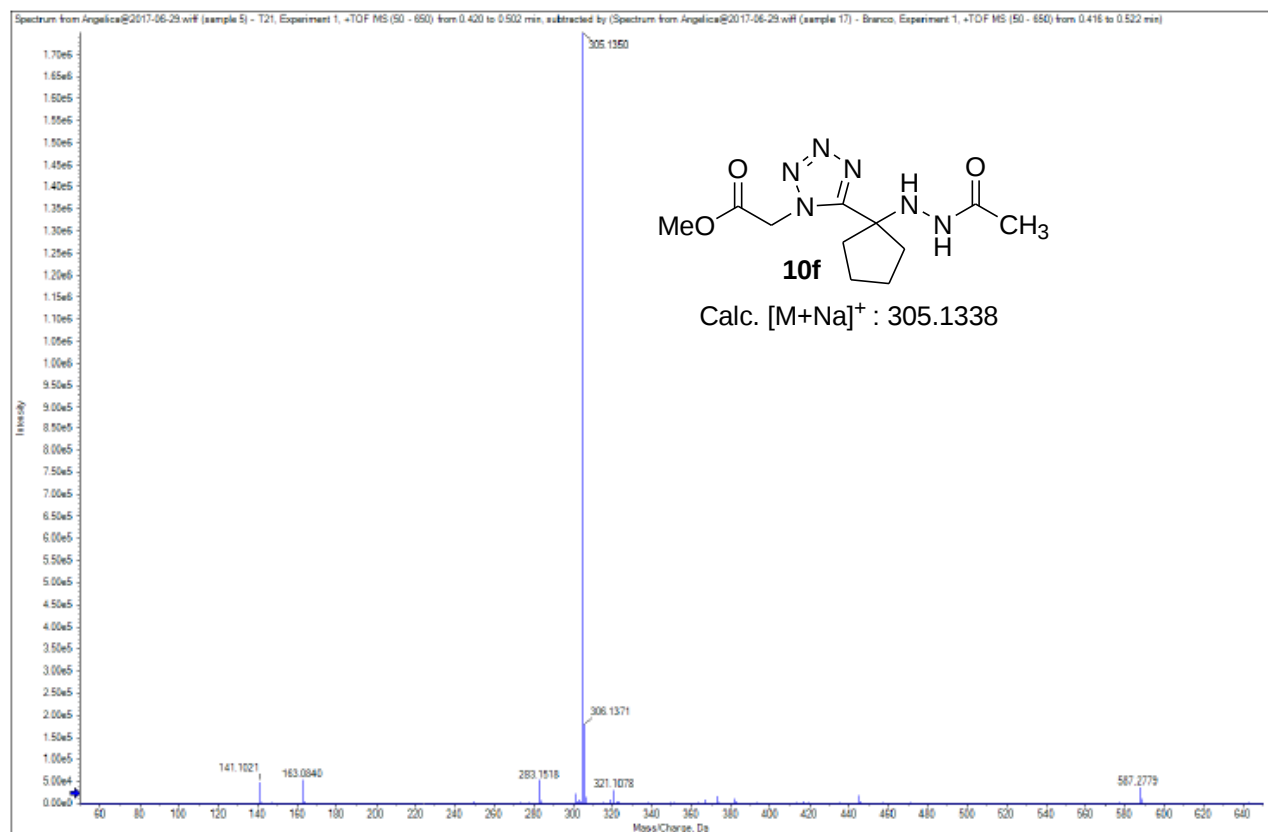


Figure S18: ESI-HRMS of compound **10f**.

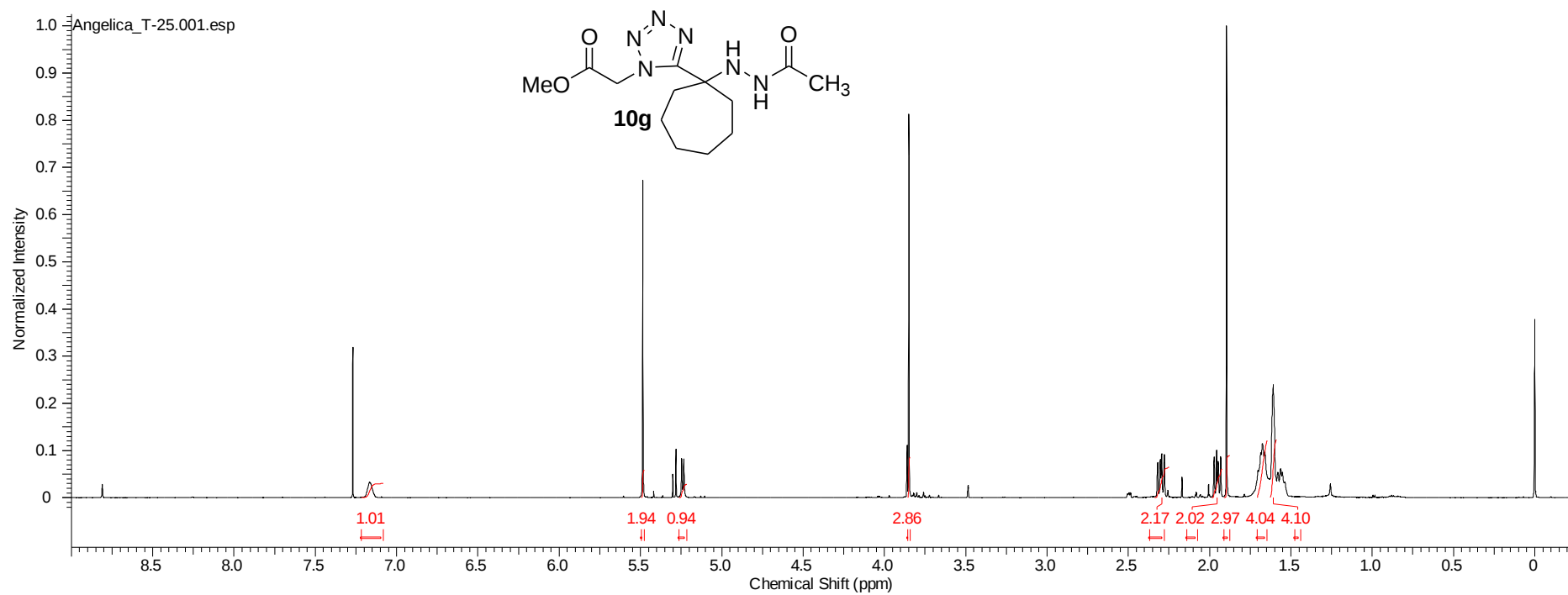


Figure S19: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10g**.

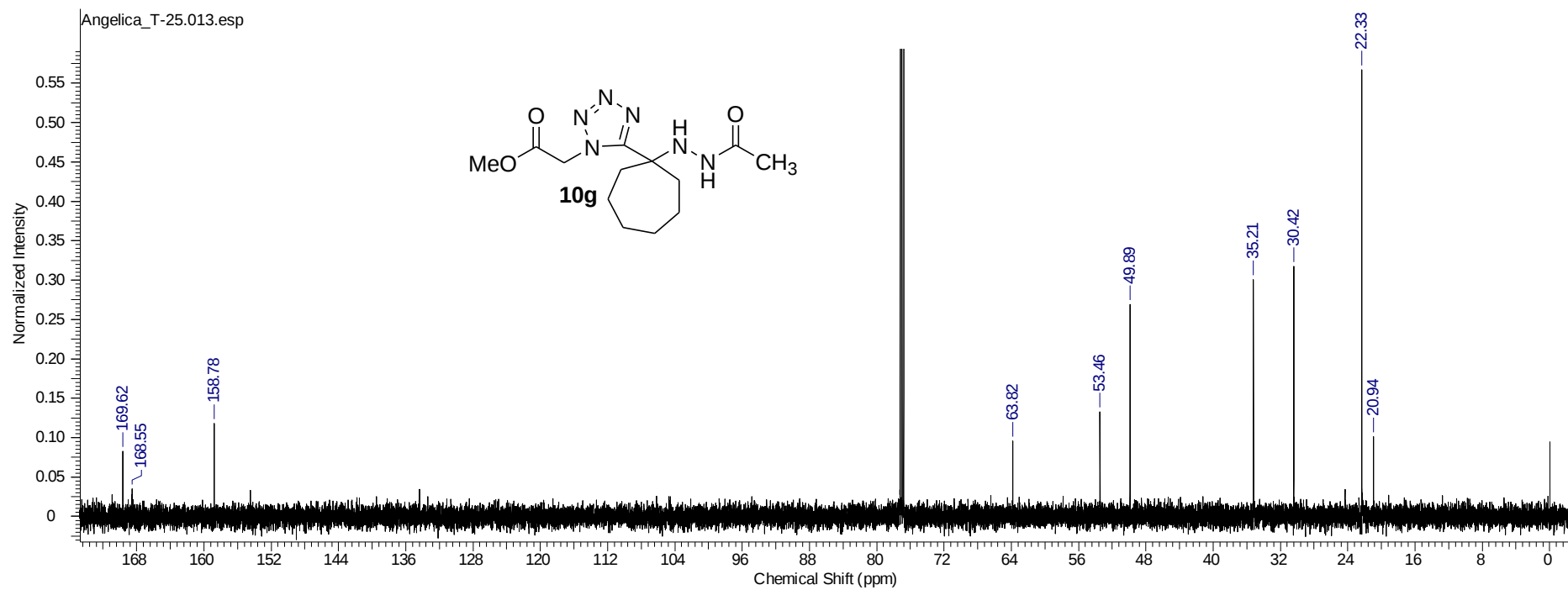


Figure S20: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10g**.

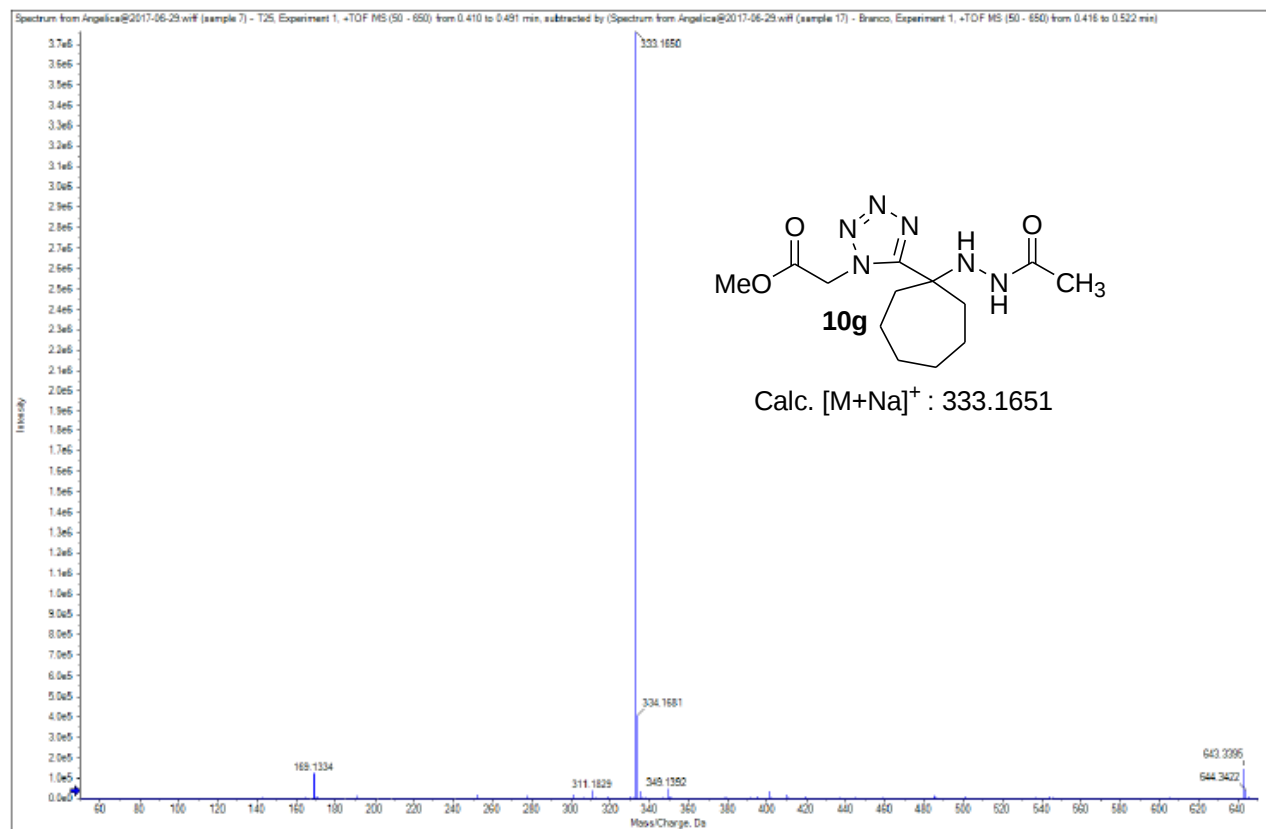


Figure S21: ESI-HRMS of compound **10g**.

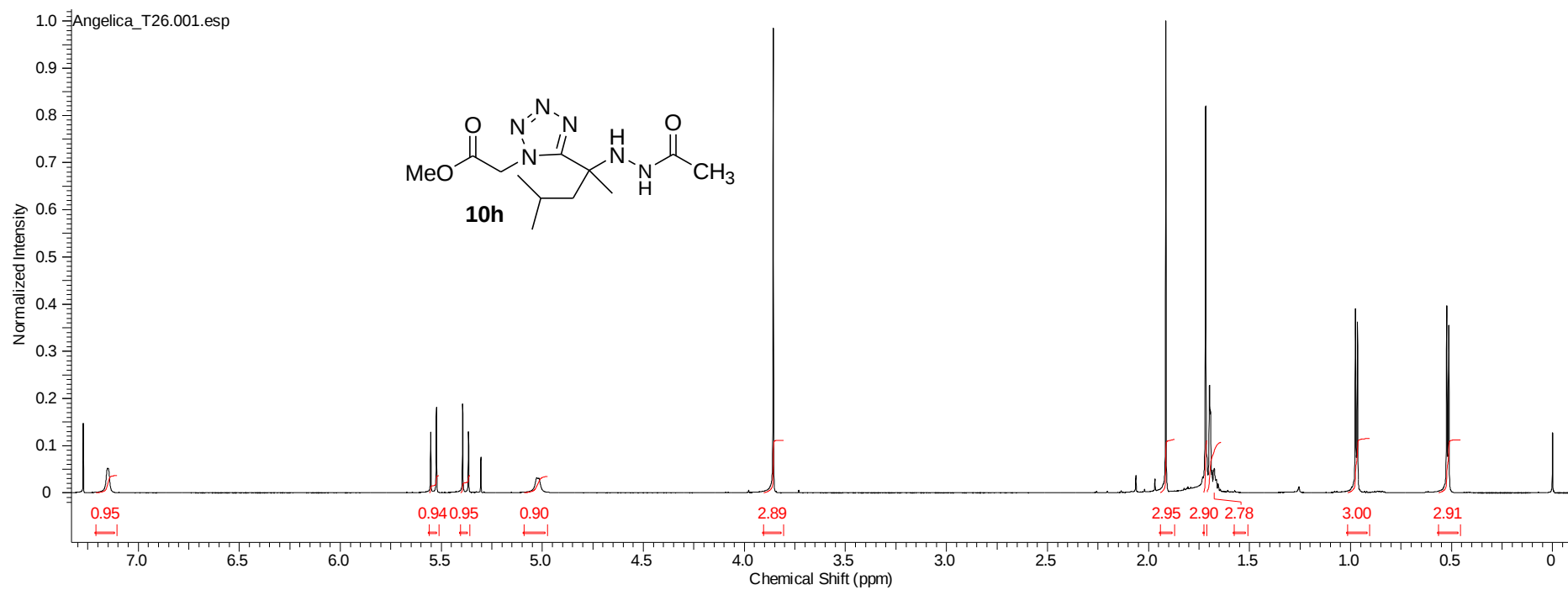


Figure S22: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10h**.

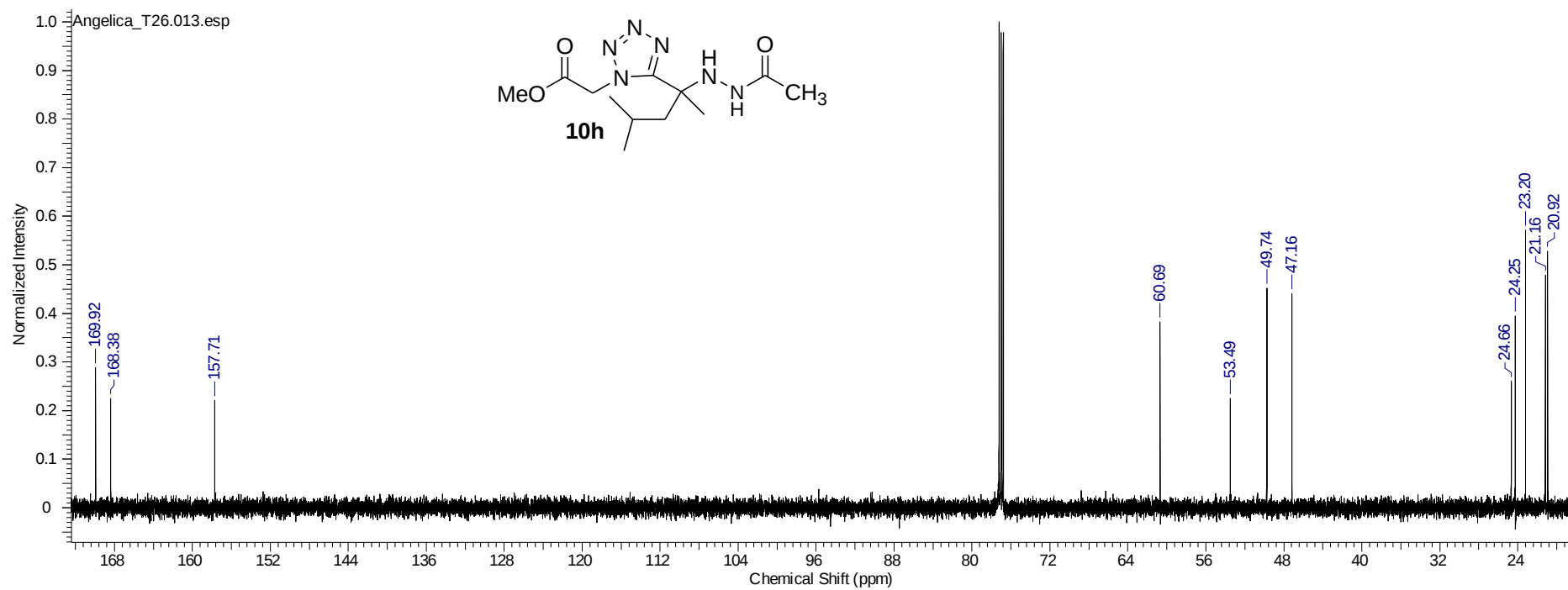


Figure S23: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10h**.

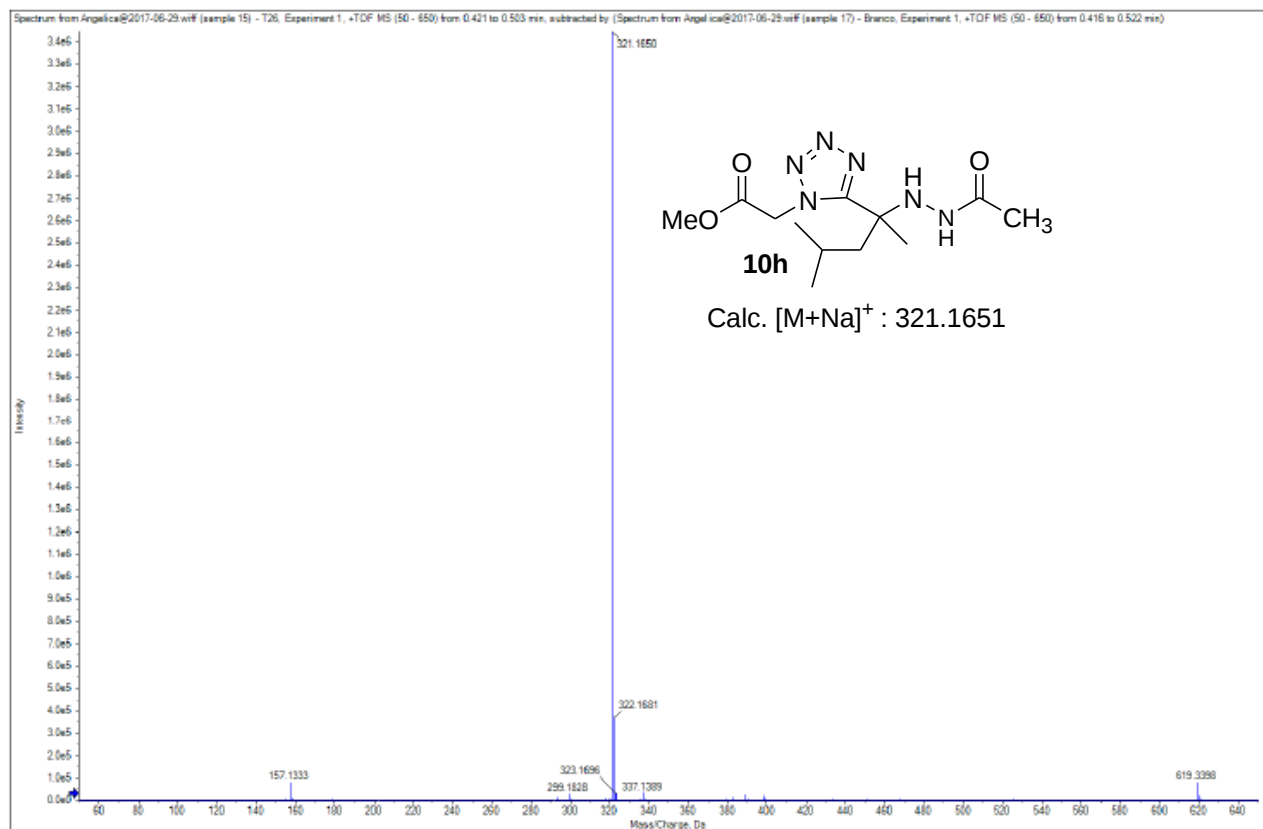


Figure S24: ESI-HRMS of compound **10h**.

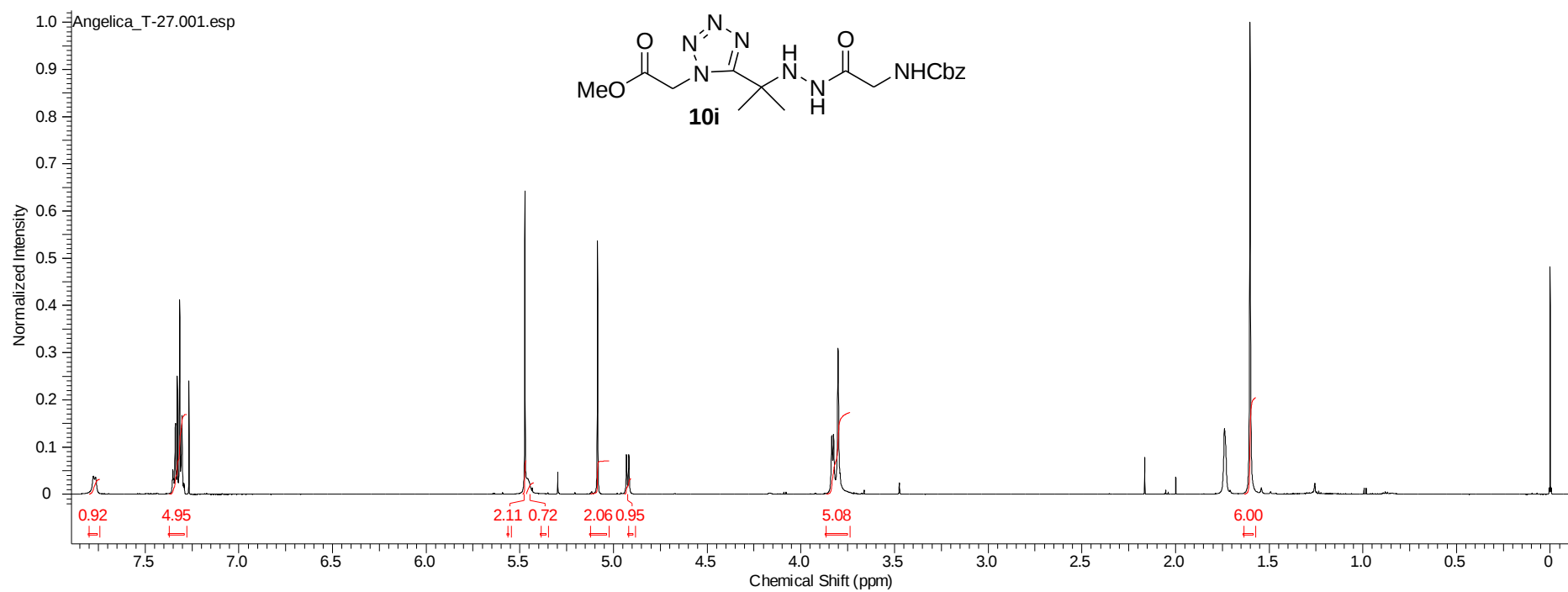


Figure S25: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10i**.

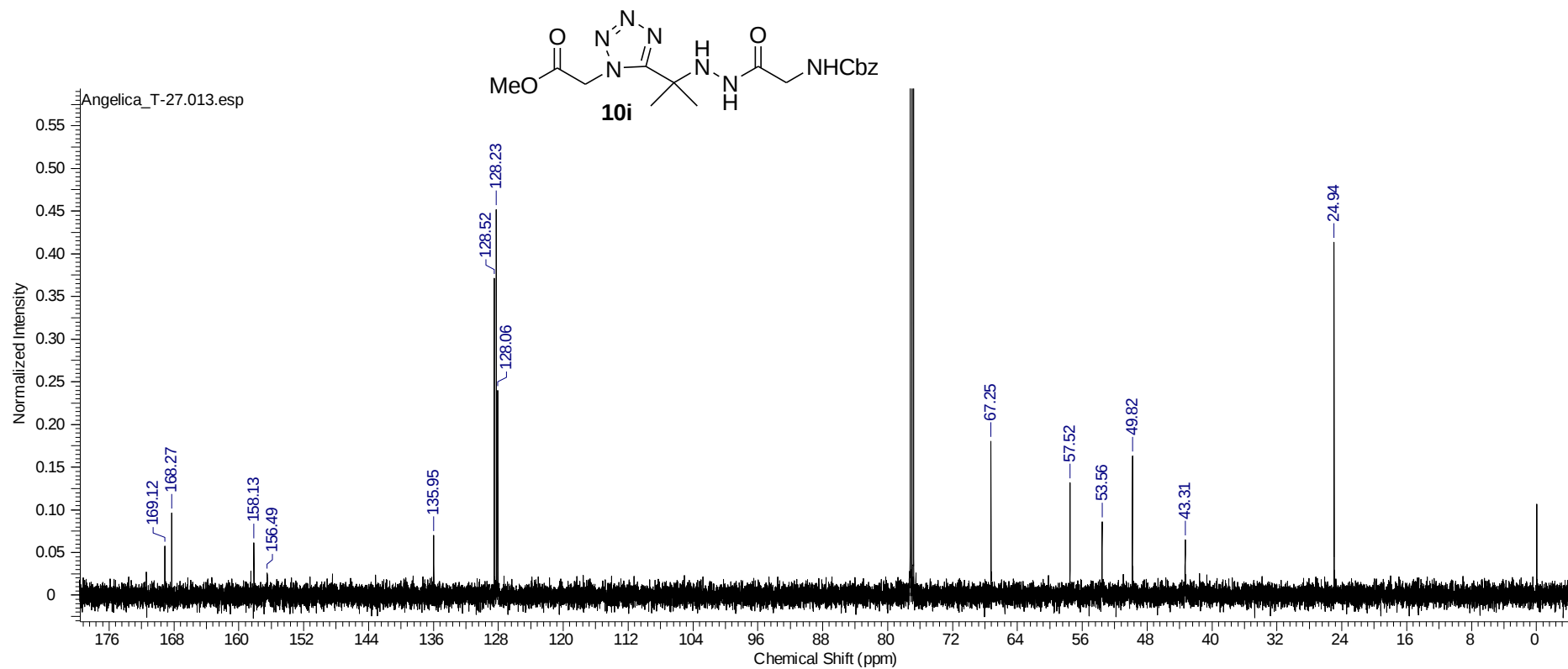


Figure S26: ¹³C NMR (150 MHz, CDCl₃) spectrum of compound **10i**.

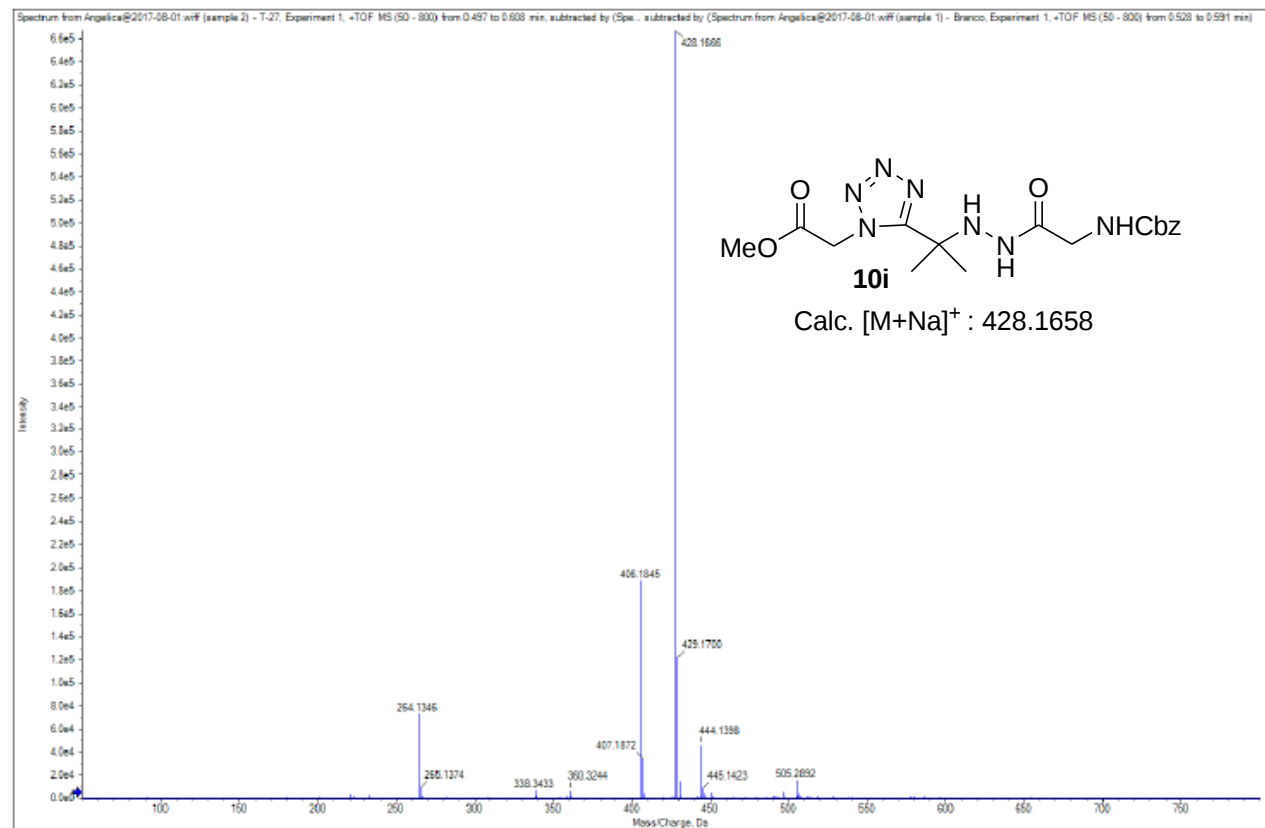


Figure S27: ESI-HRMS of compound **10i**.

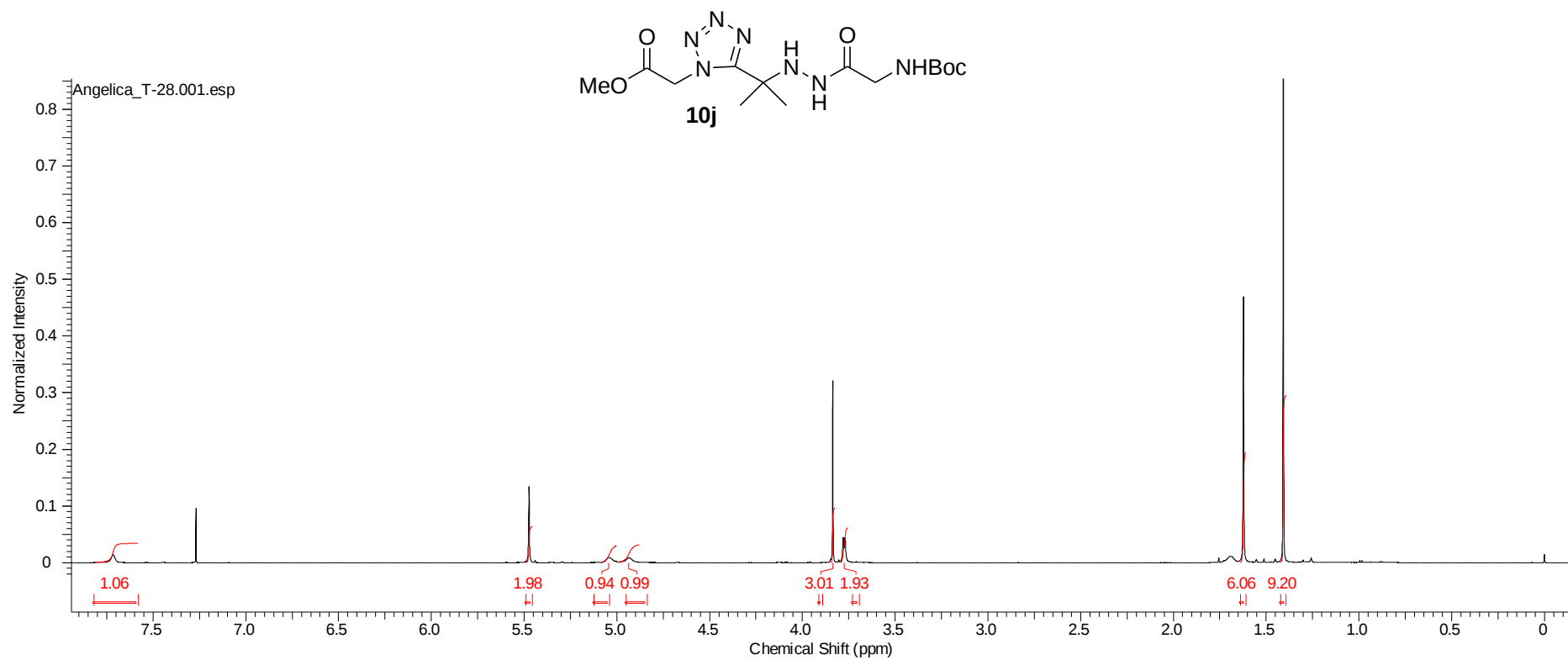


Figure S28: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10j**.

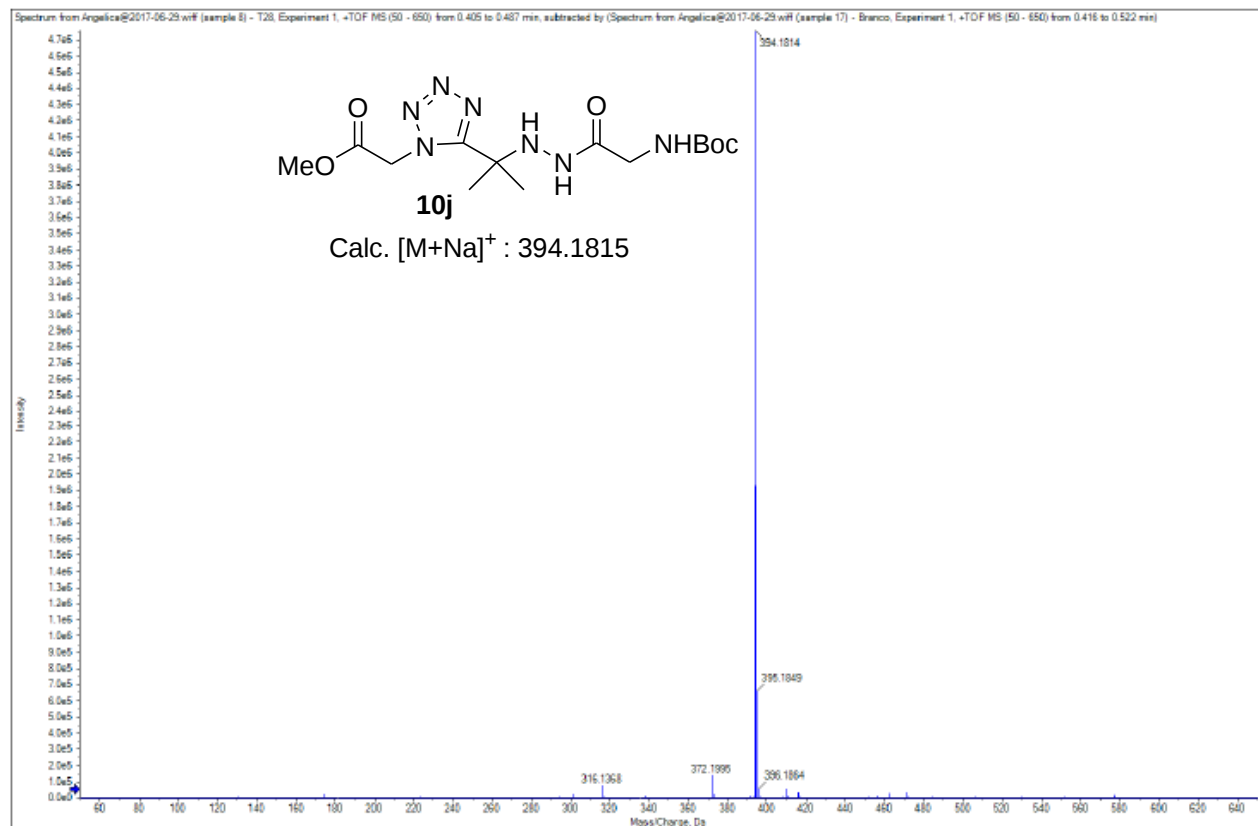


Figure S30: ESI-HRMS of compound **10j**.

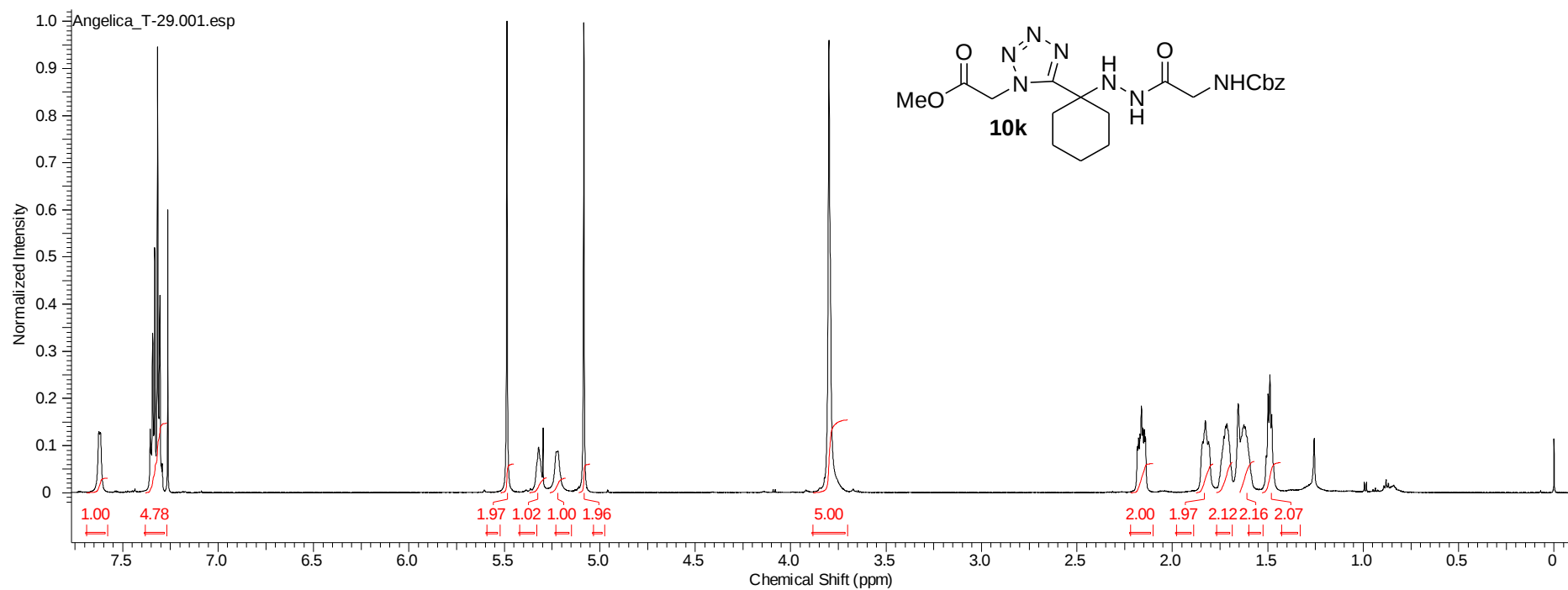


Figure S31: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10k**.

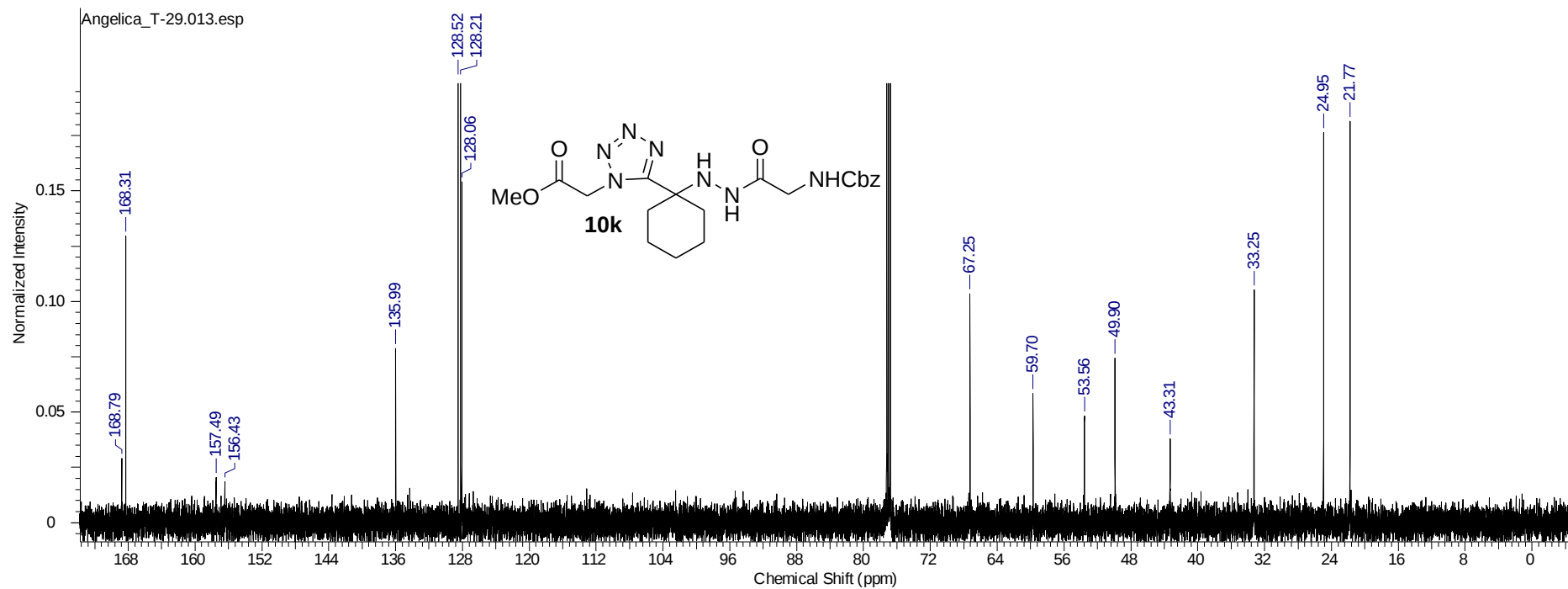


Figure S32: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10k**.

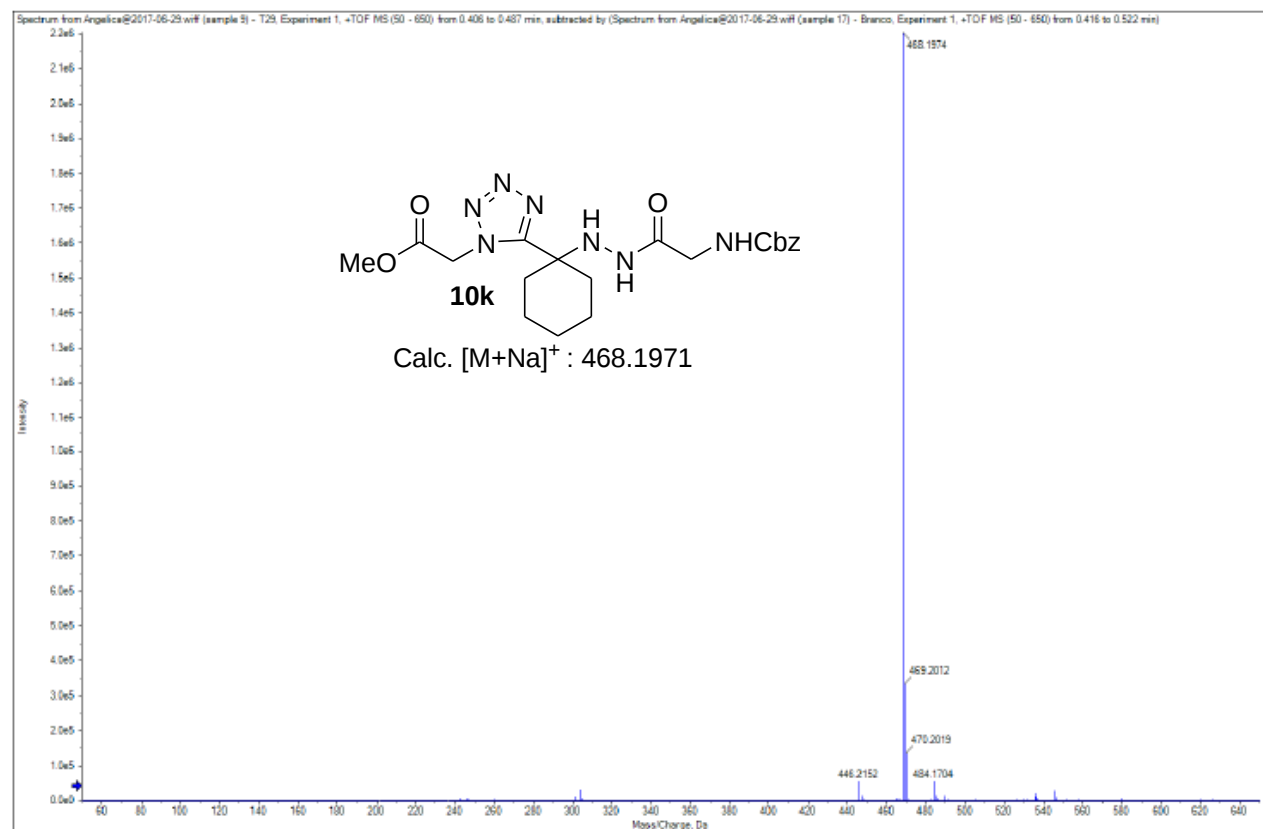


Figure S33: ESI-HRMS of compound **10k**.

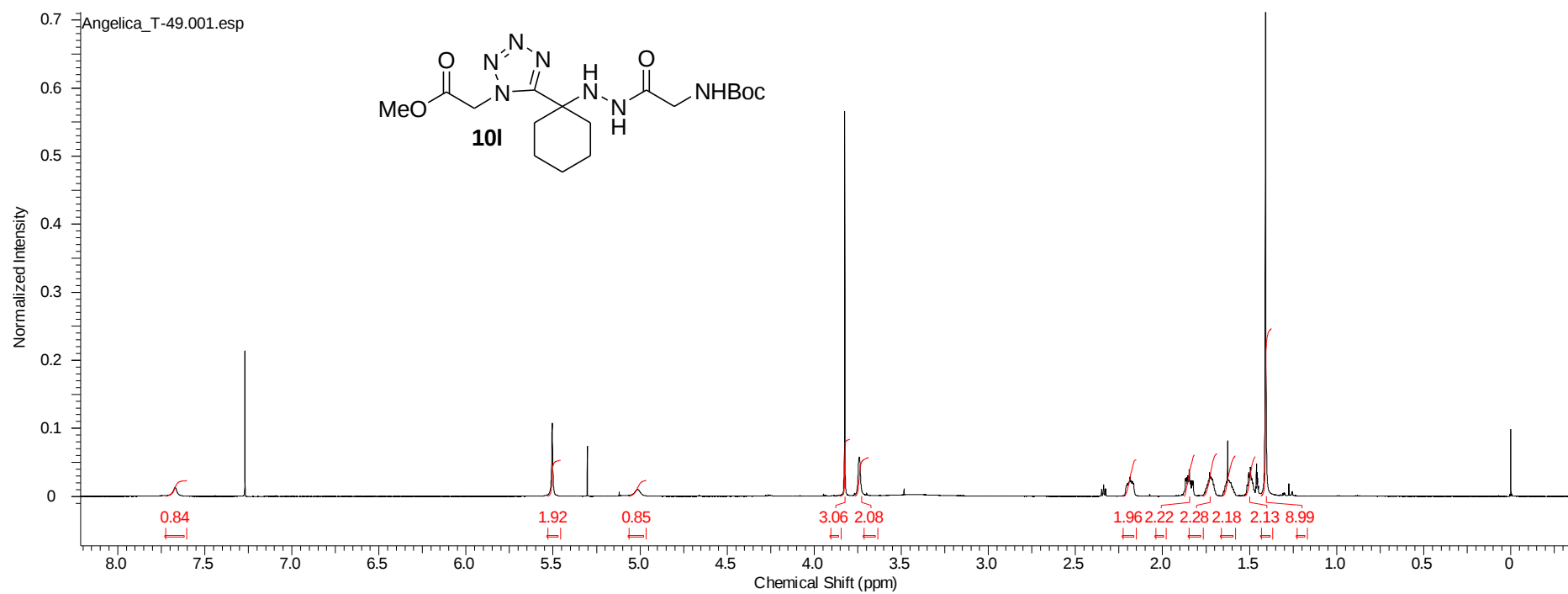


Figure S34: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10I**.

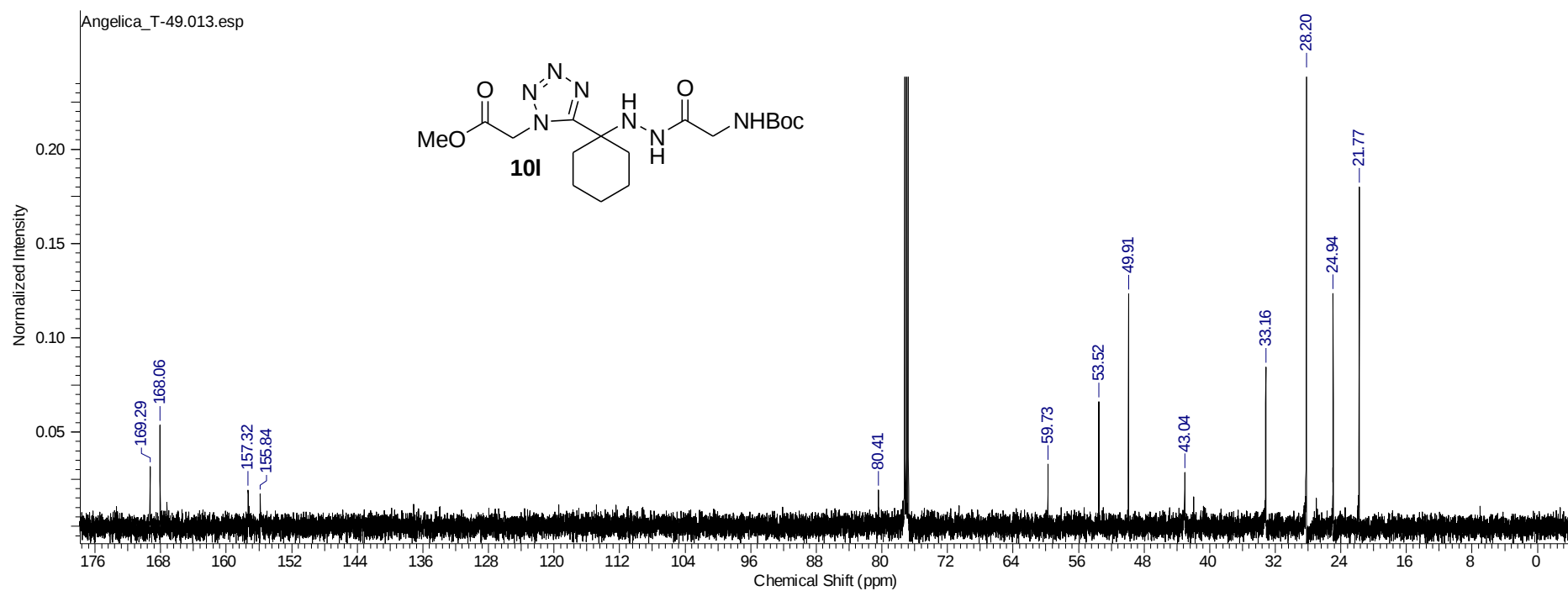


Figure S35: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10I**.

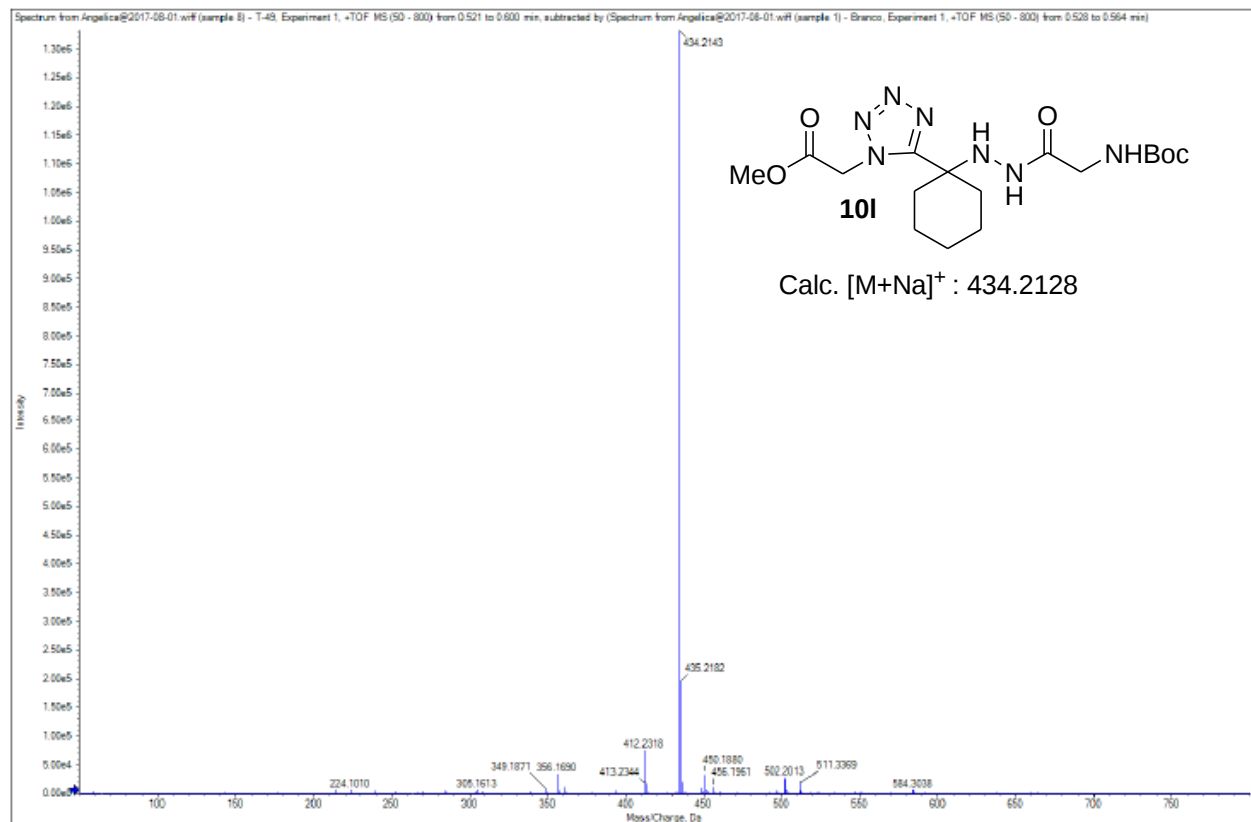


Figure S36: ESI-HRMS of compound **10I**.

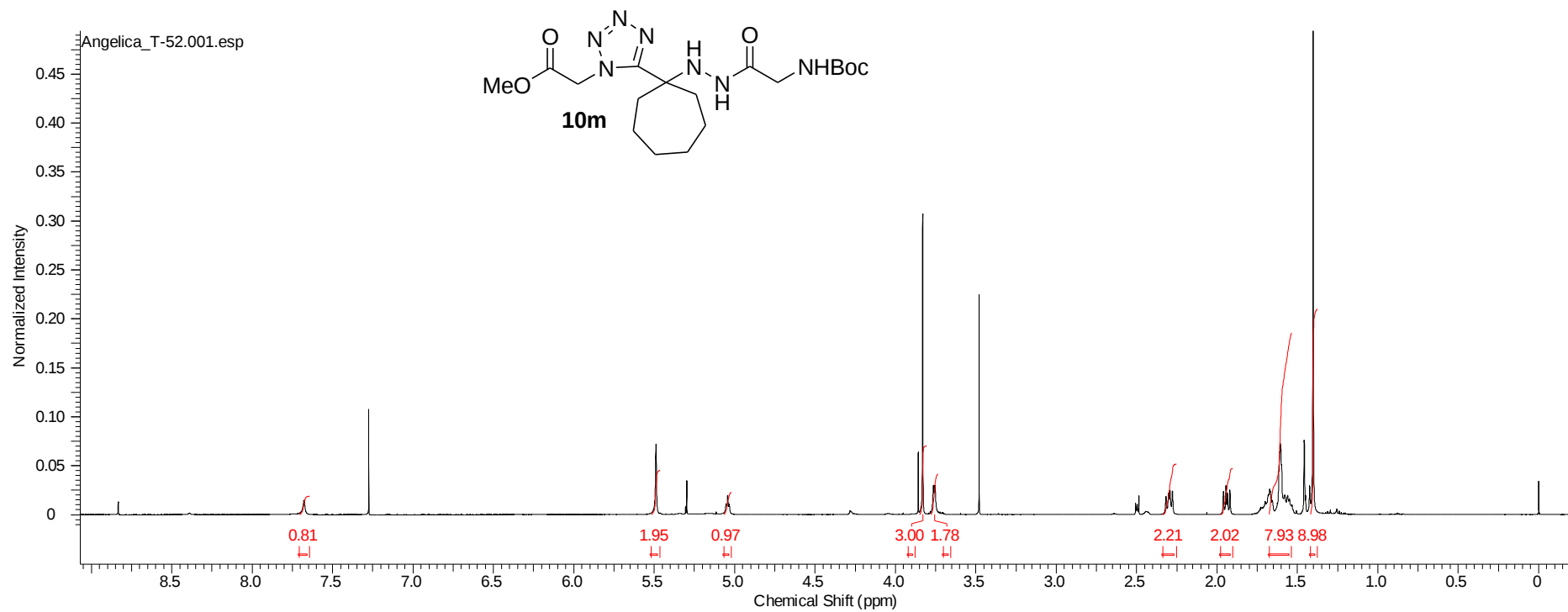


Figure S37: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **10m**.

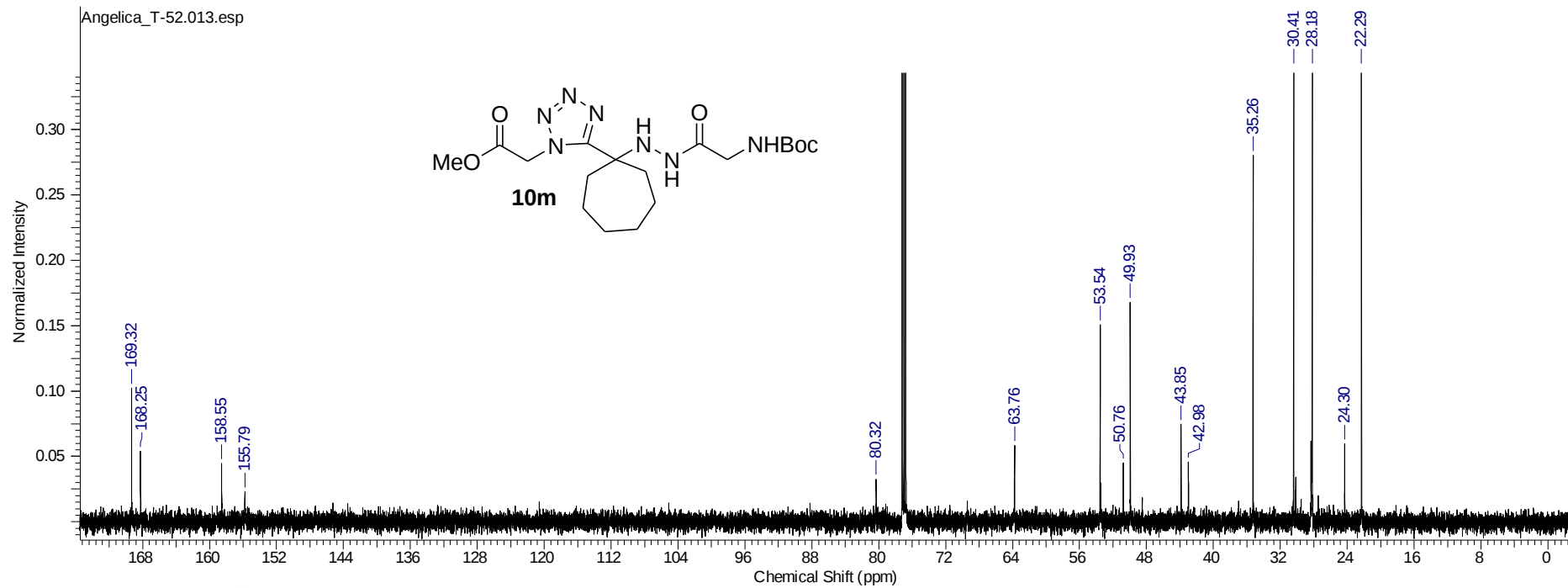


Figure S38: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **10m**.

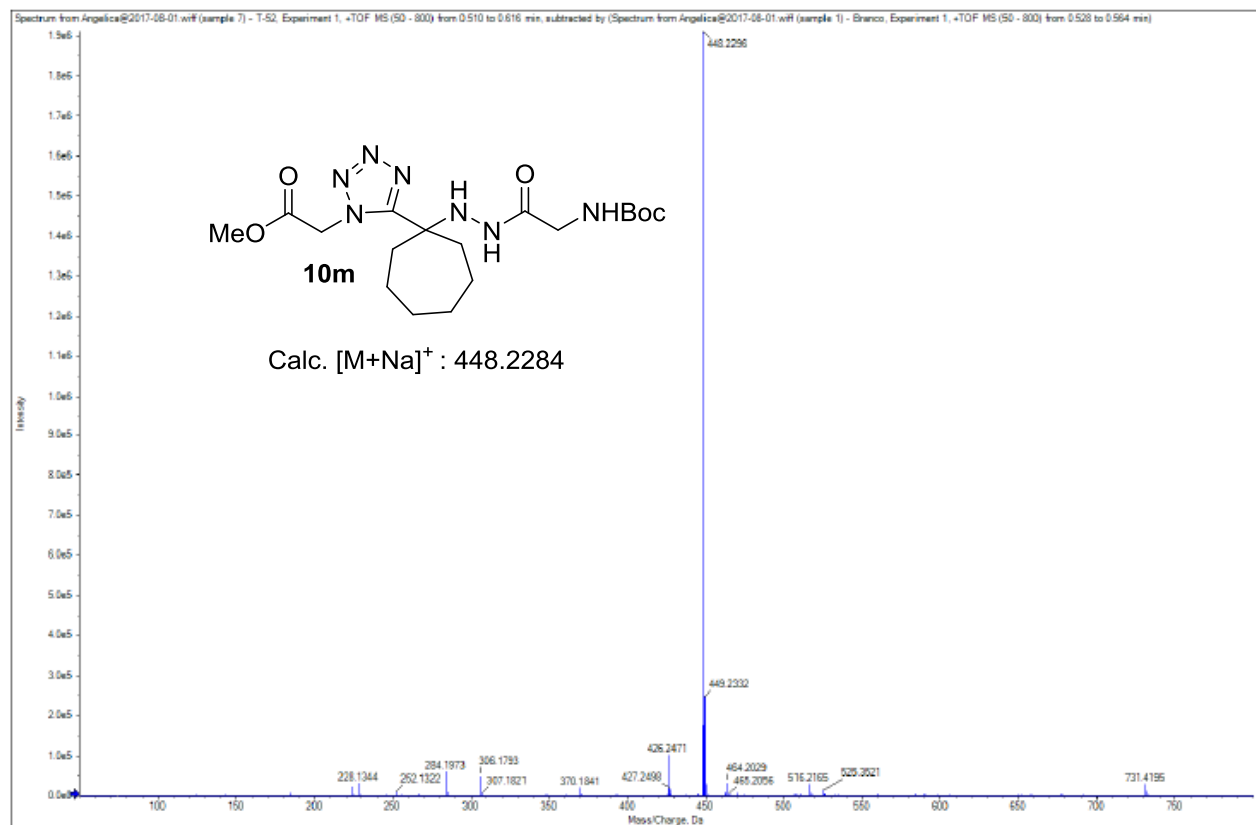


Figure S39: ESI-HRMS of compound **10m**.

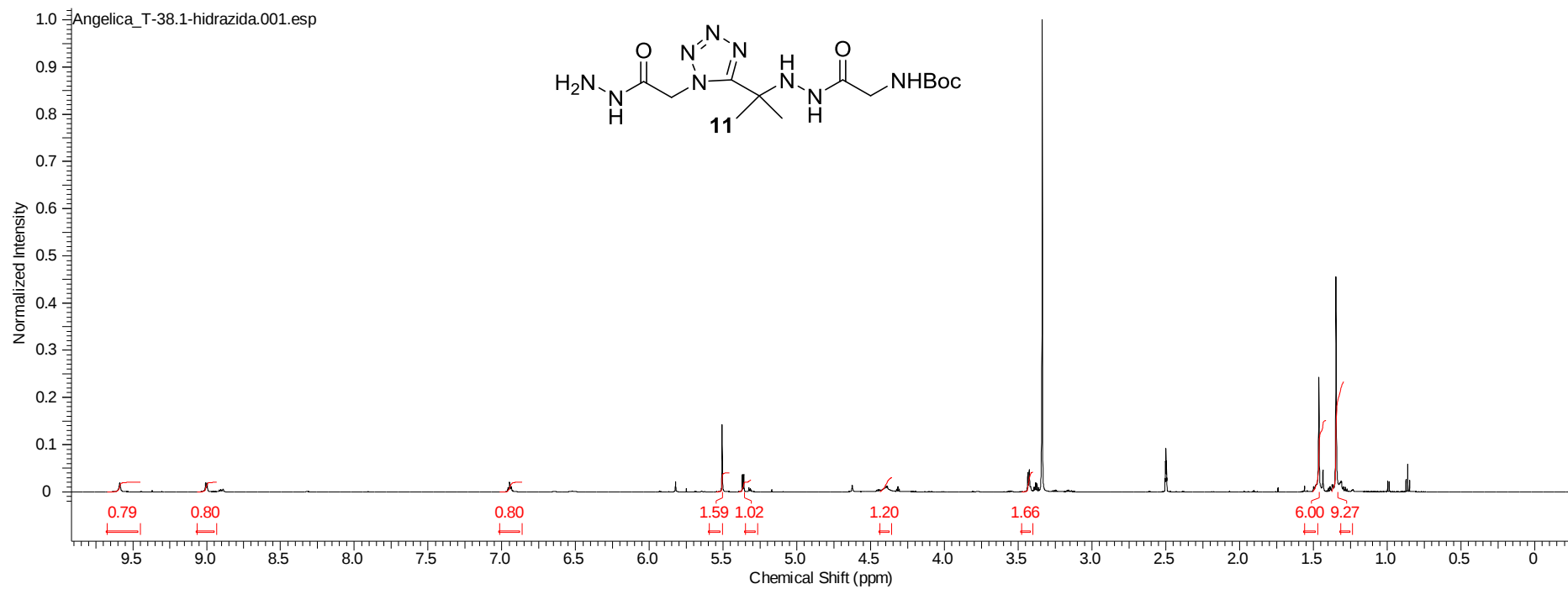


Figure S40: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) spectrum of compound **11**.

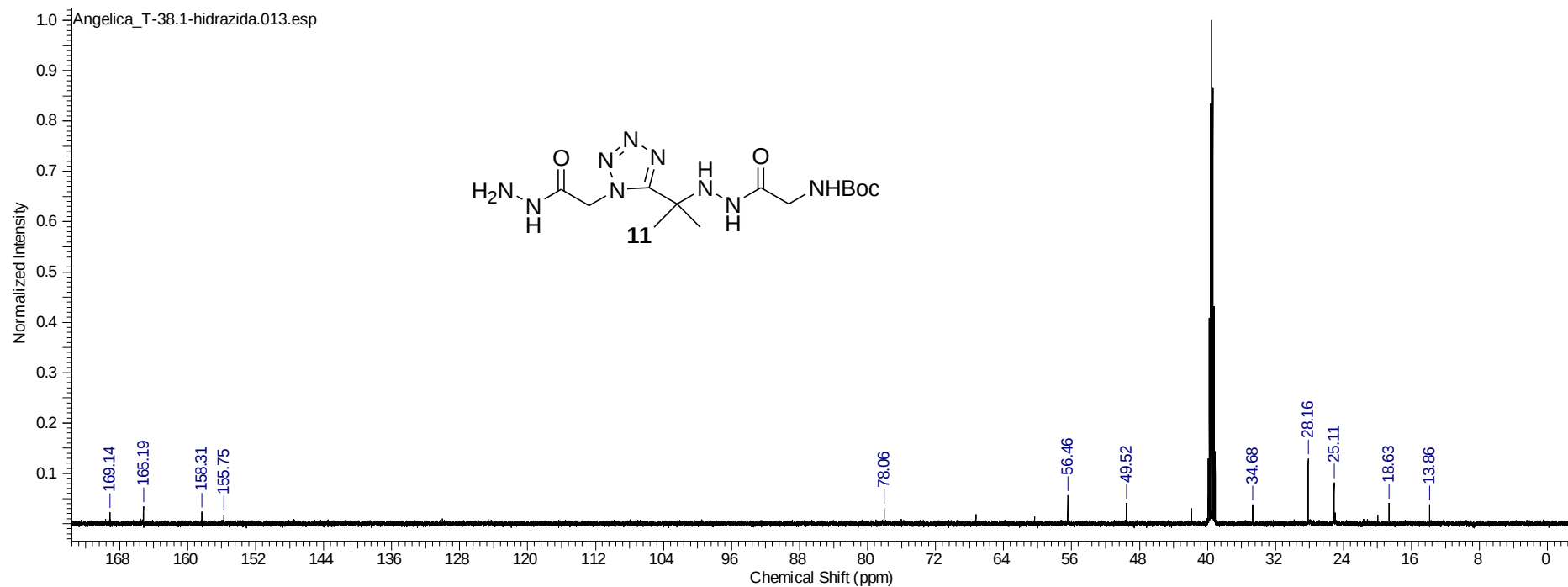


Figure S41: ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) spectrum of compound **11**.

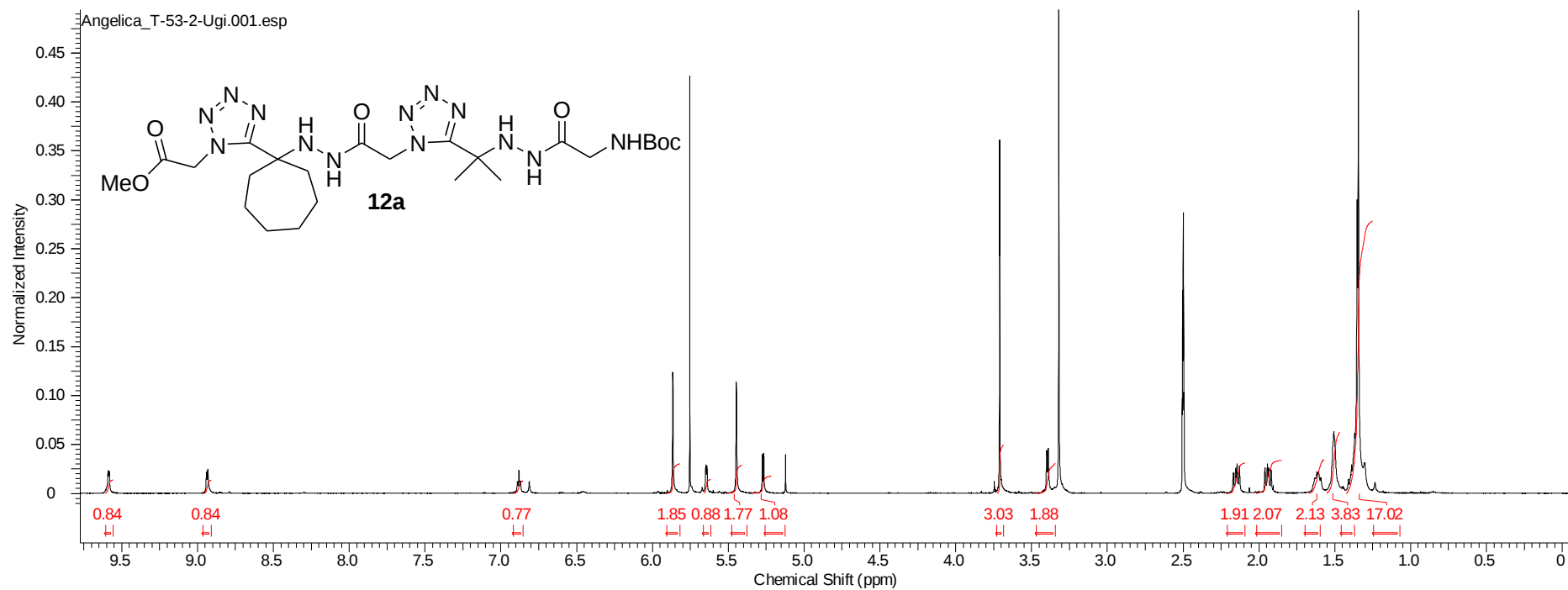


Figure S42: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) spectrum of compound **12a**.

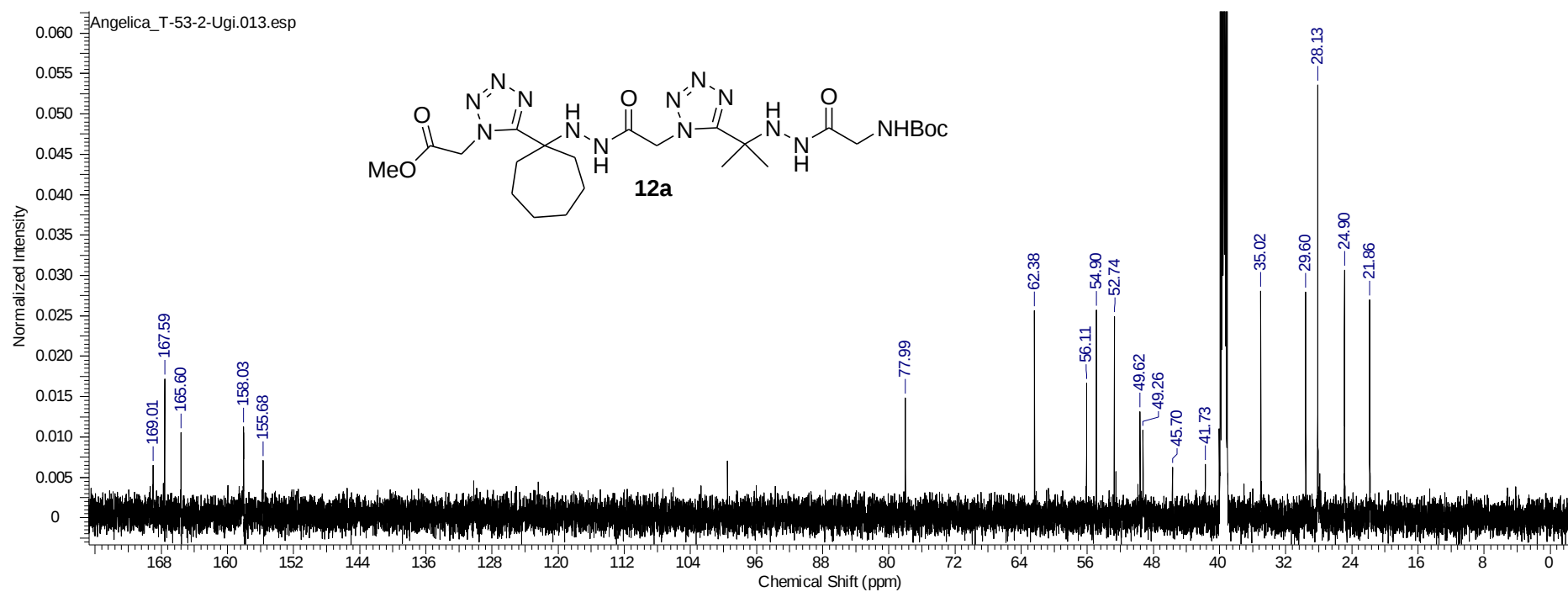


Figure S43: ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) spectrum of compound **12a**.

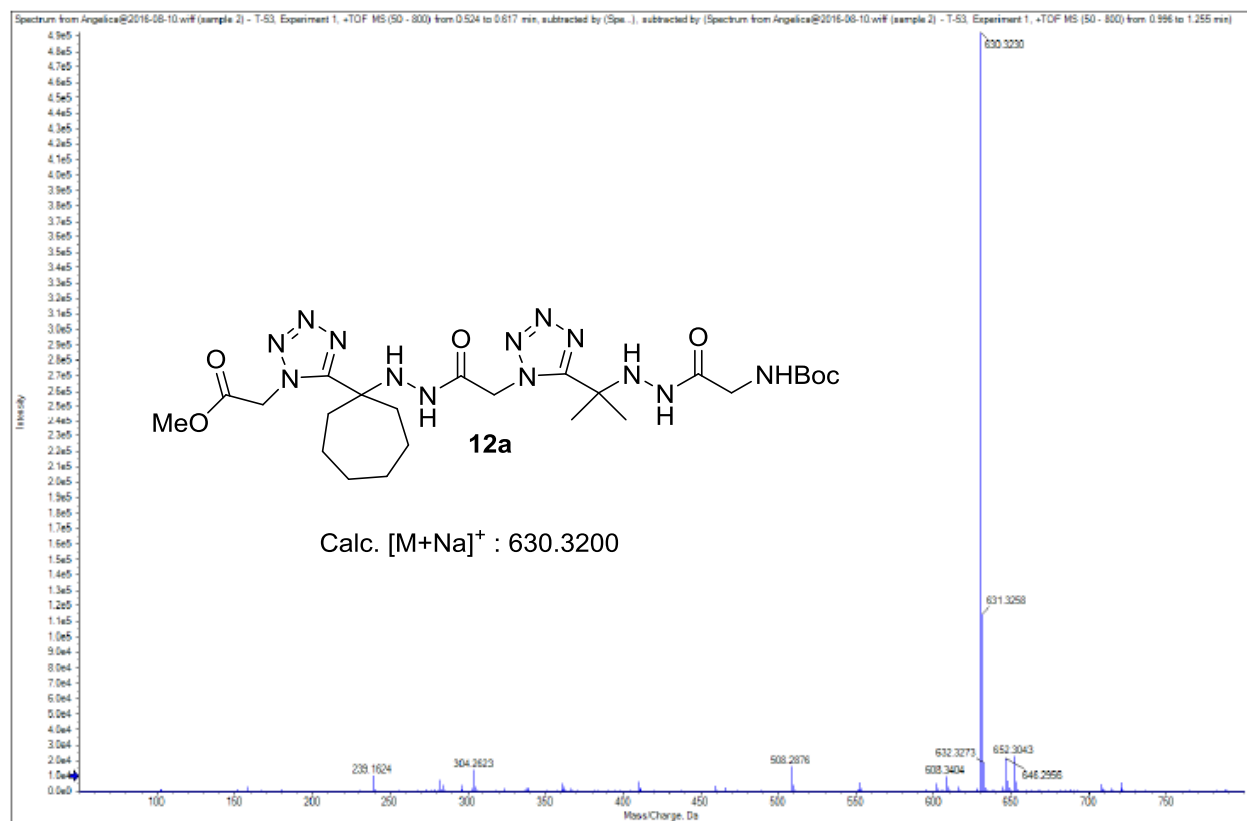


Figure S44: ESI-HRMS of compound **12a**.

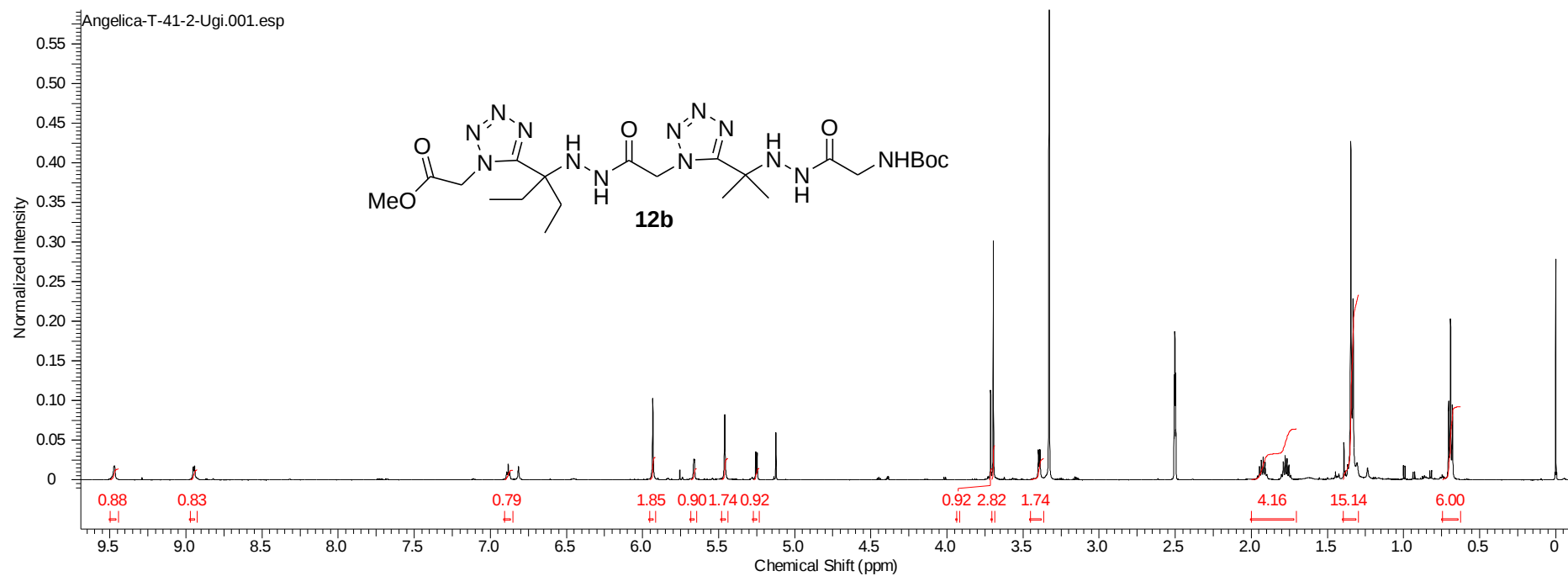


Figure S45: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) spectrum of compound **12b**.

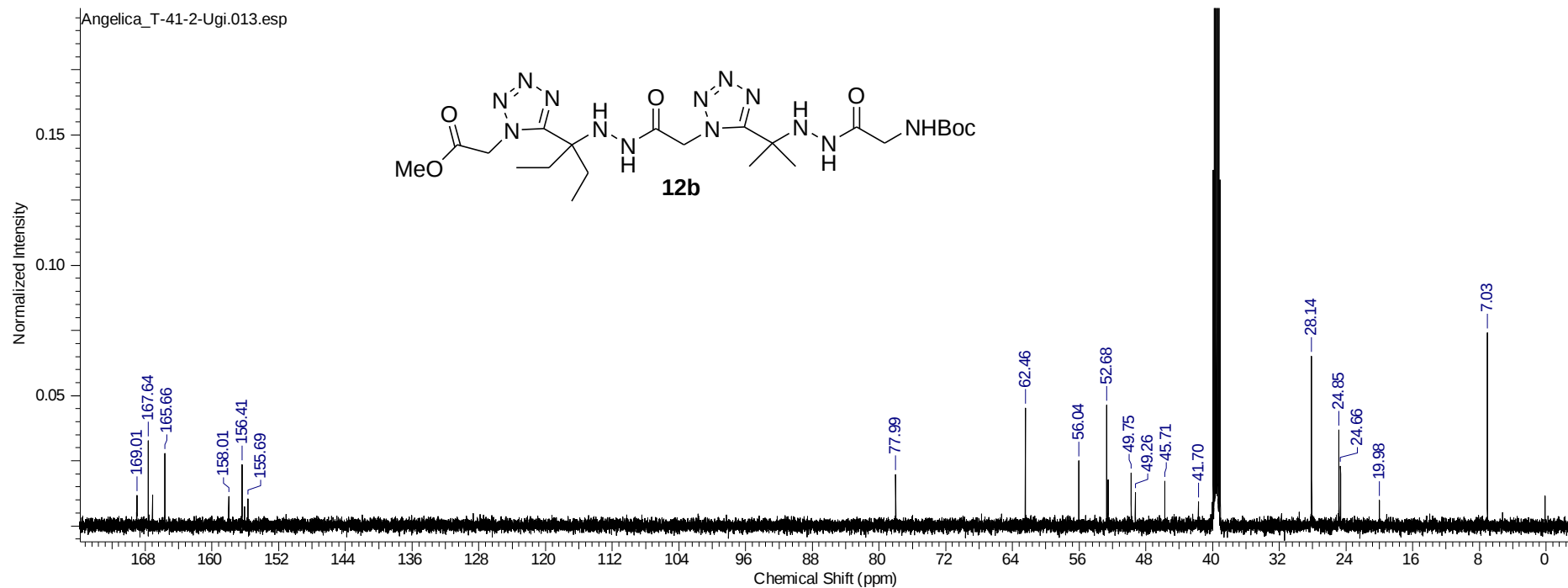


Figure S46: ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) spectrum of compound **12b**.

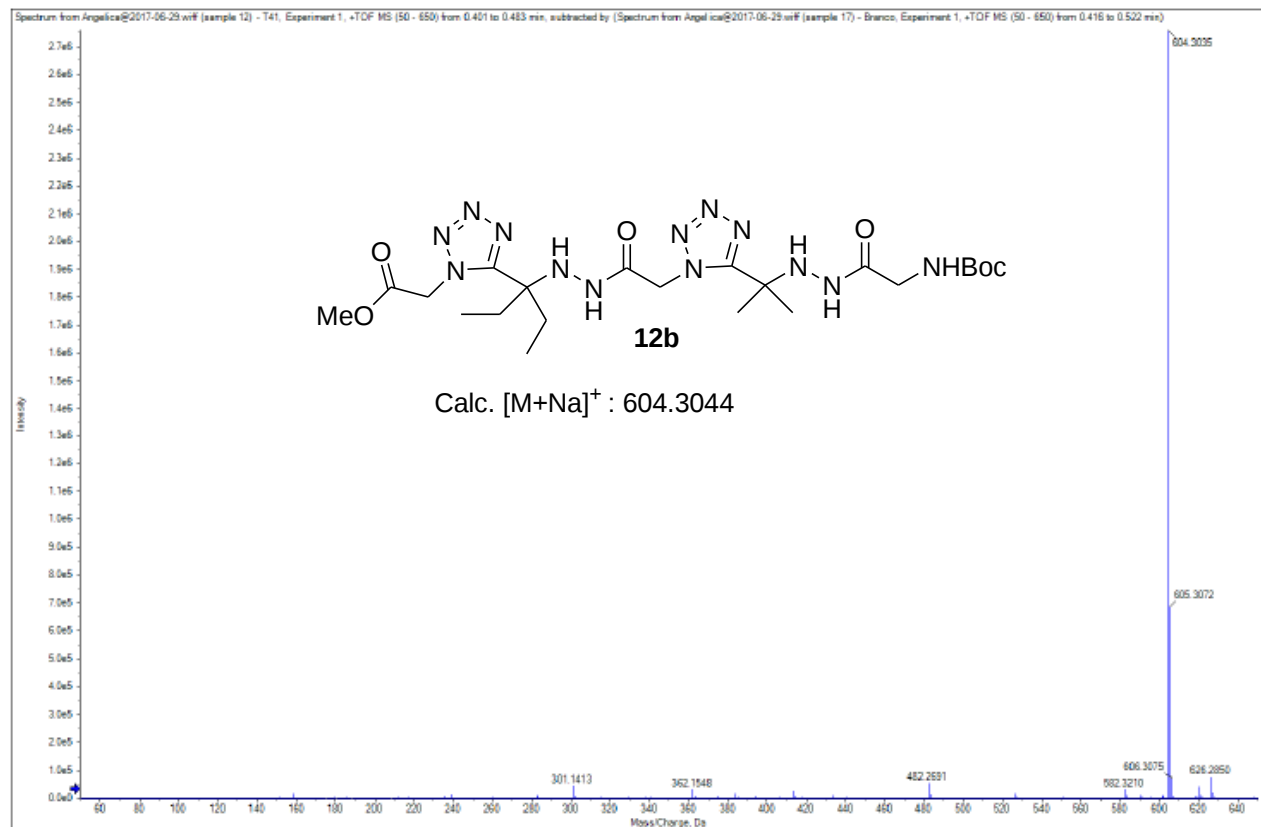


Figure S47: ESI-HRMS of compound **12b**.

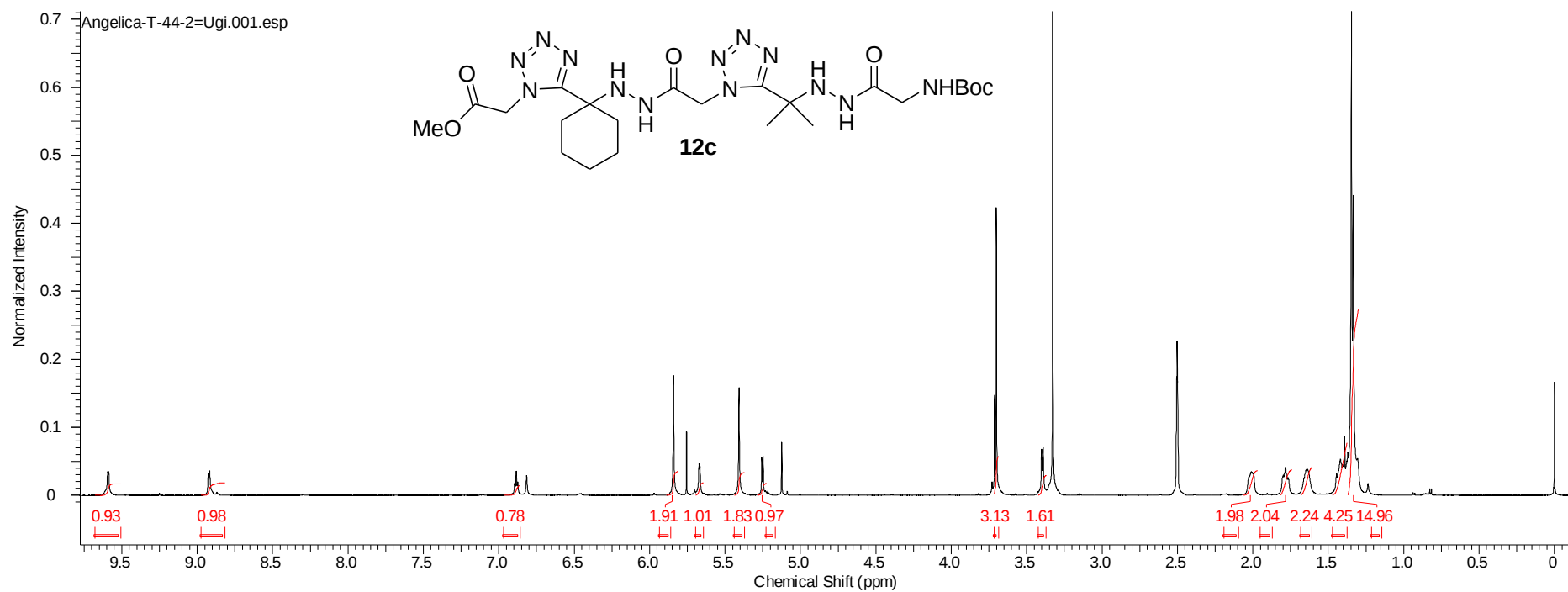


Figure S48: ^1H NMR (600 MHz, DMSO- d_6) spectrum of compound **12c**.

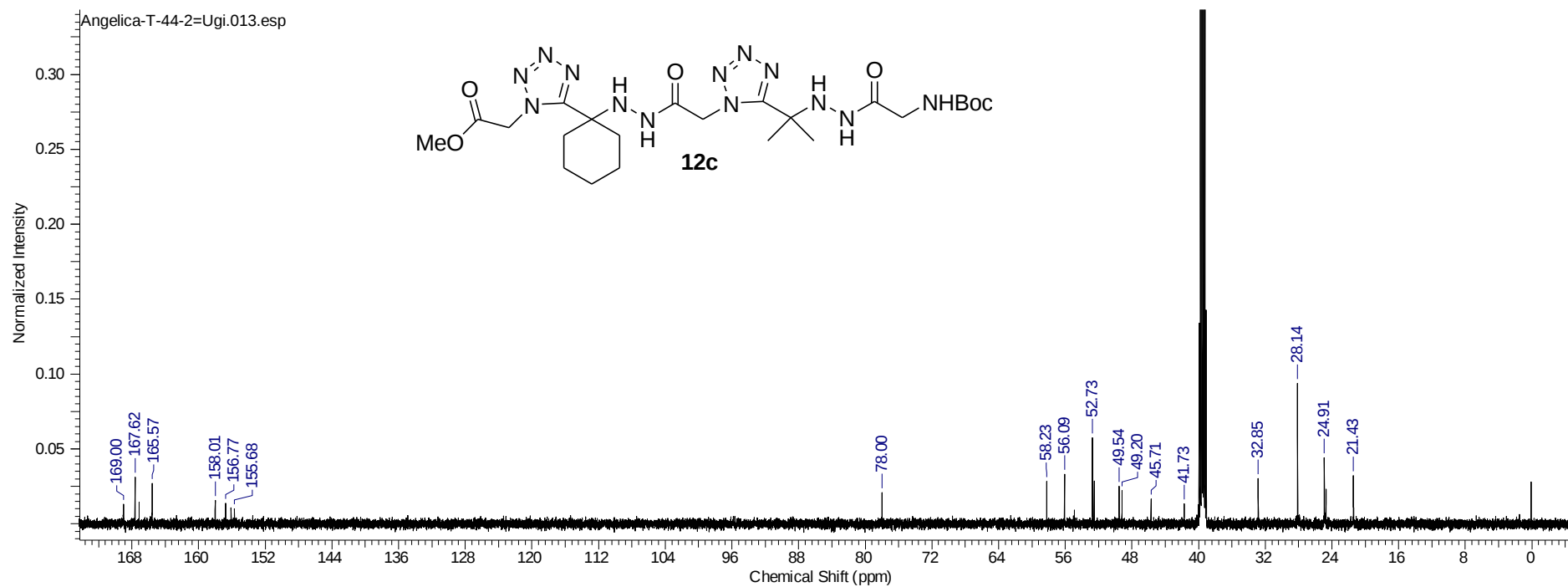


Figure S49: ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) spectrum of compound **12c**.

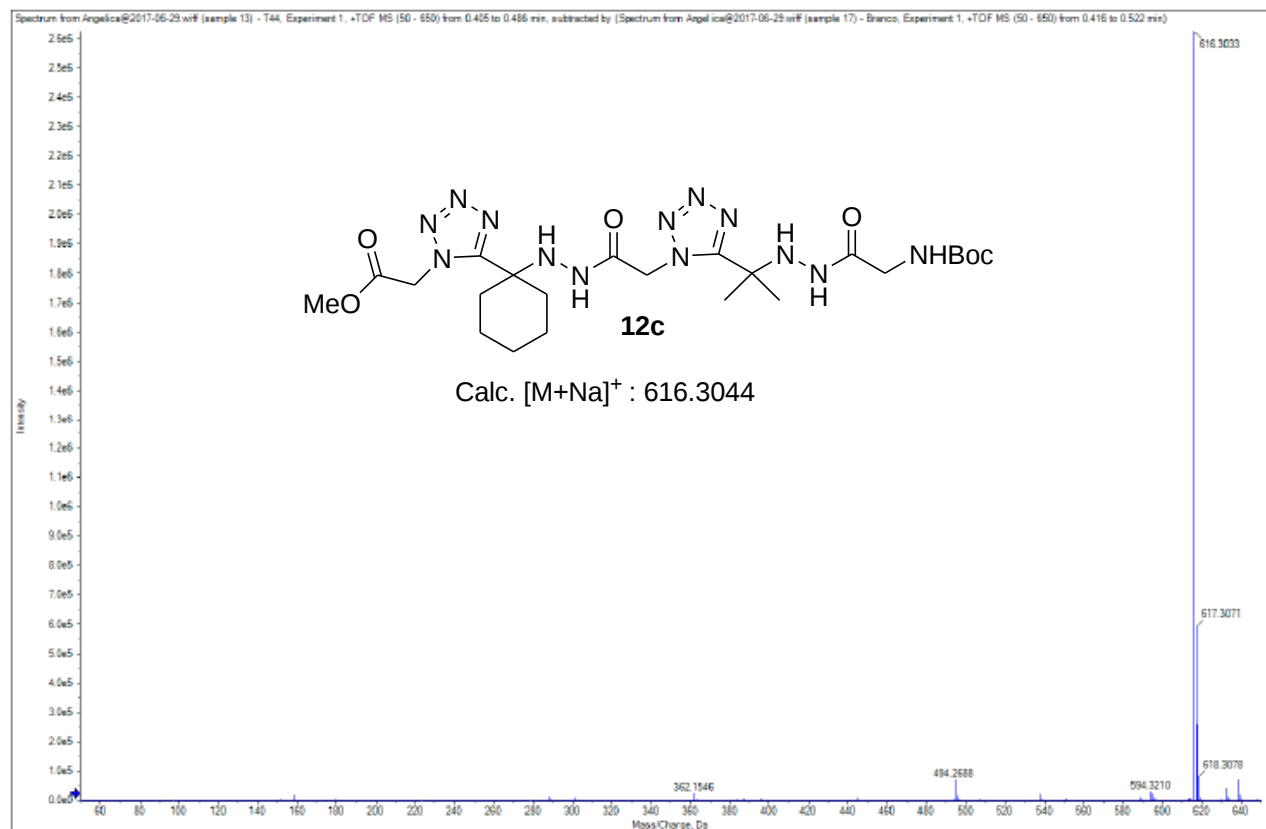


Figure S50: ESI-HRMS of compound **12c**.

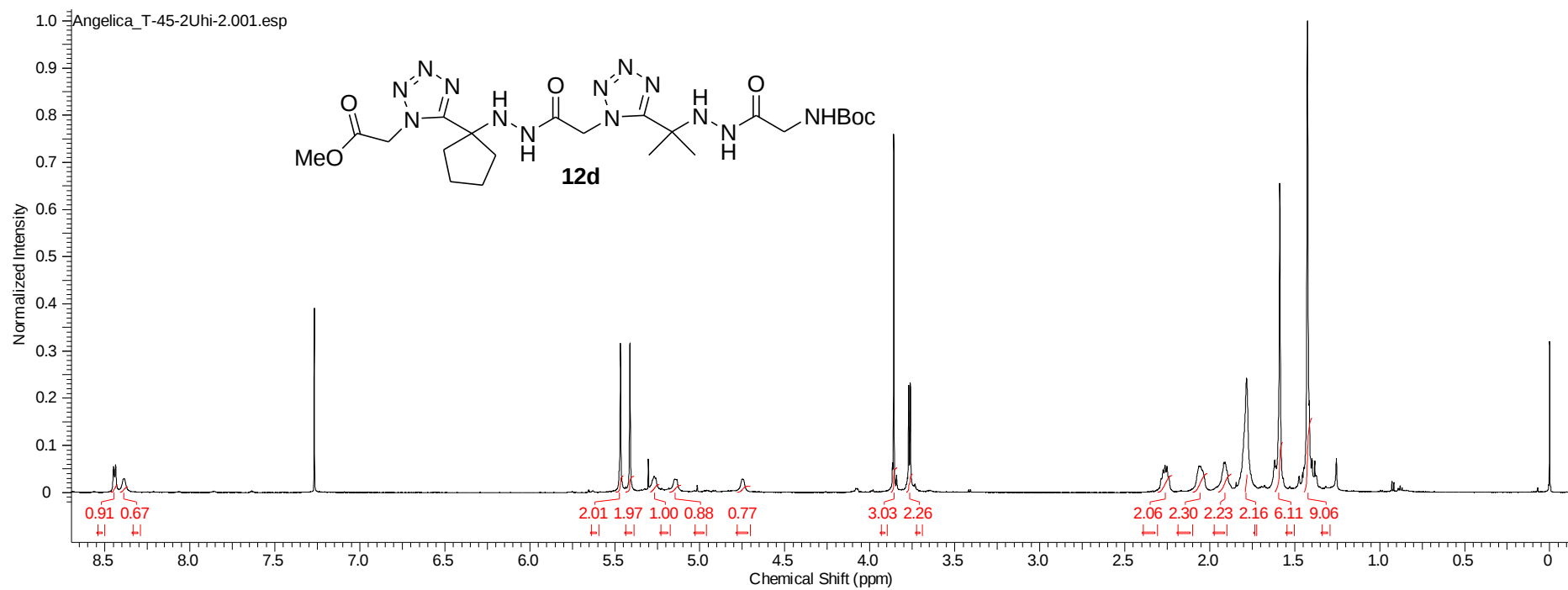


Figure S51: ^1H NMR (600 MHz, CDCl_3) spectrum of compound **12d**.

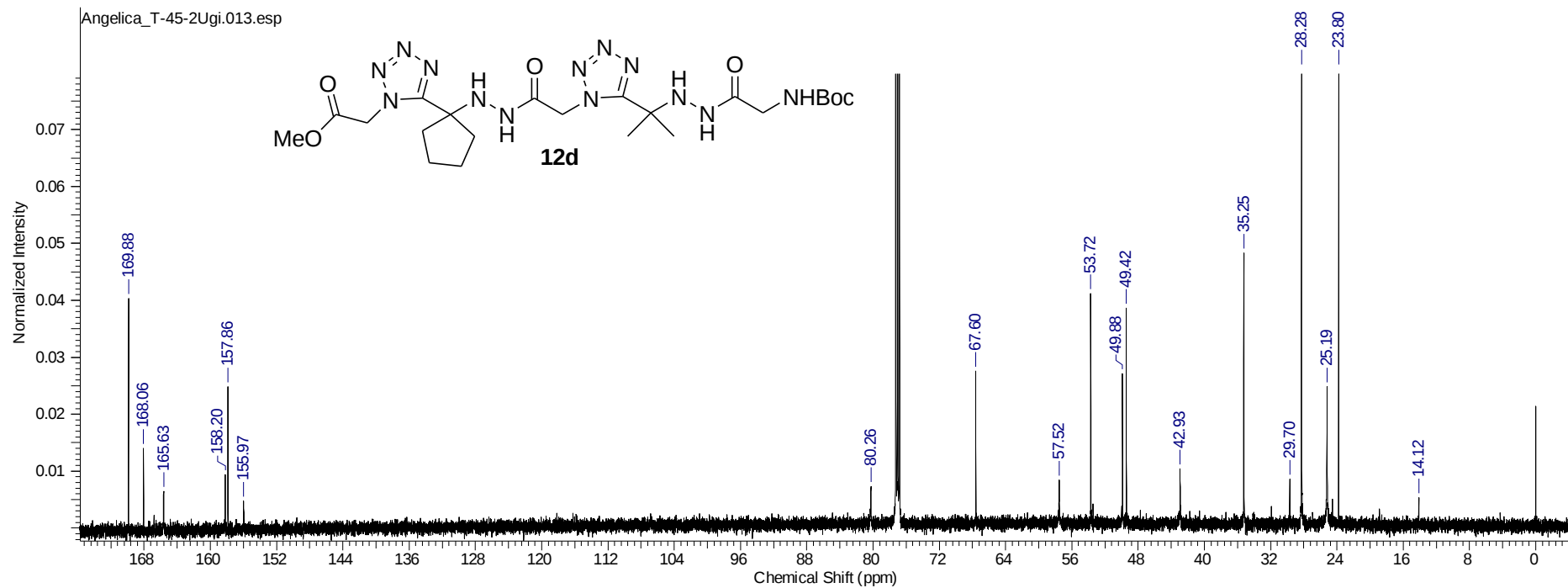


Figure S52: ^{13}C NMR (150 MHz, CDCl_3) spectrum of compound **12d**.

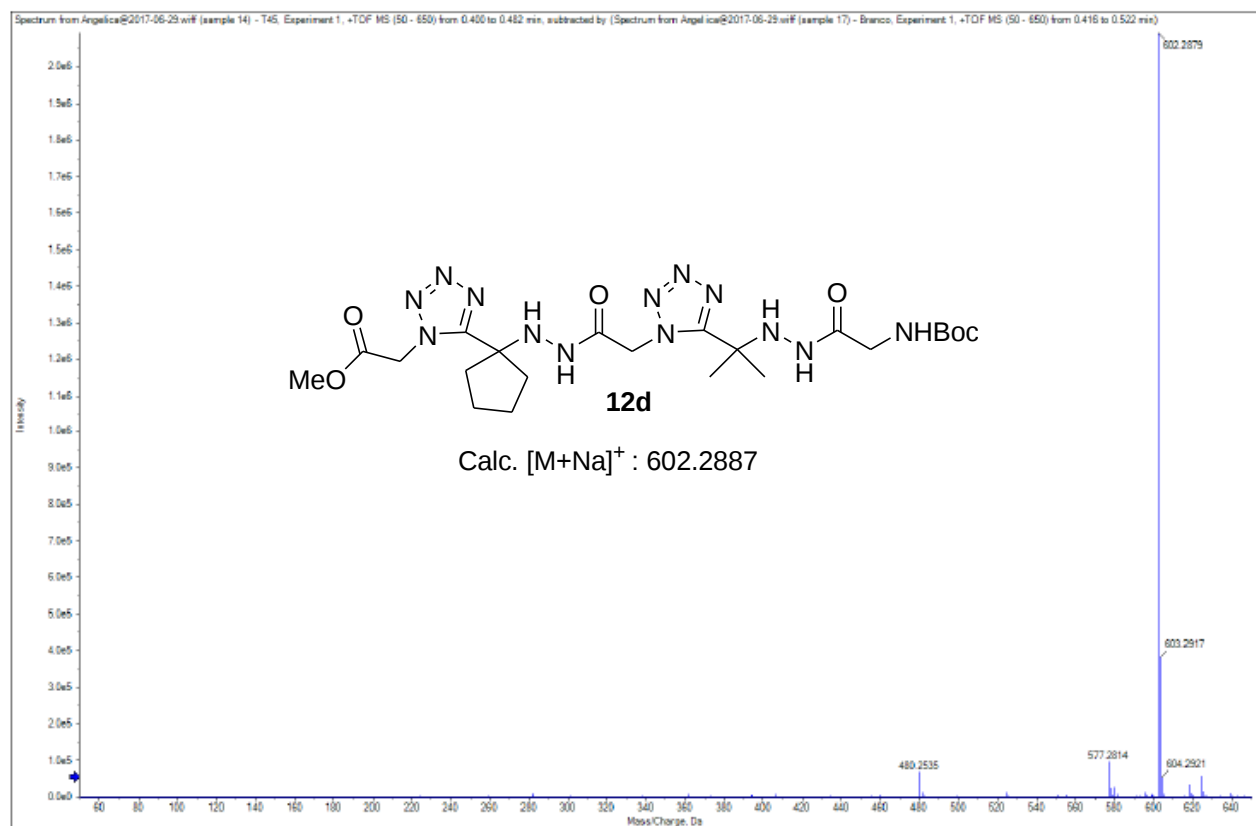


Figure S53: ESI-HRMS of compound **12d**.