

# Development of Novel Alaninamide Derivatives with Anticonvulsant Activity and Favorable Safety Profiles in Animal Models

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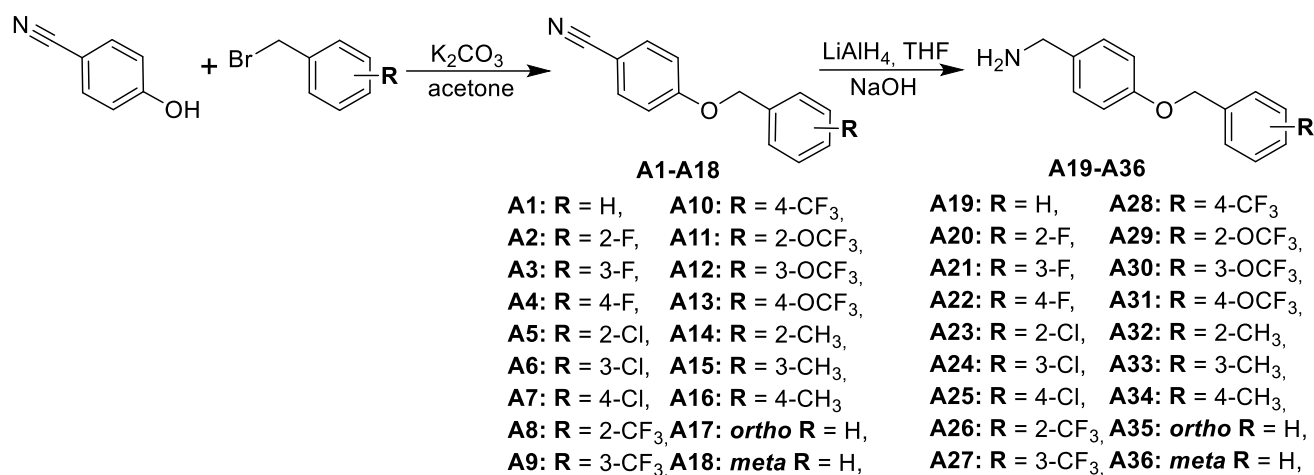
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**Table S1.** Anticonvulsant activity screening data in the MES and 6 Hz (32 mA) seizure models in mice *i.p.* (dose of 100 mg/kg) pretreatment time–0.5 h.

Compd	R	R <sup>1</sup>	MES test <sup>a</sup>	6 Hz (32 mA) test <sup>a</sup>
<b>Pyrrolidine-2,5-dione derivatives</b>				
<b>5</b>	H	H	<b>4/4</b>	<b>2/4</b>
<b>6</b>	2-F	H	<b>4/4</b>	<b>4/4</b>
<b>7</b>	3-F	H	1/4	<b>4/4</b>
<b>8</b>	4-F	H	<b>2/4</b>	<b>2/4</b>
<b>9</b>	2-Cl	H	<b>4/4</b>	<b>3/4</b>
<b>10</b>	3-Cl	H	<b>4/4</b>	<b>3/4</b>
<b>11</b>	4-Cl	H	<b>0/4</b>	<b>1/4</b>
<b>12</b>	2-CF <sub>3</sub>	H	<b>4/4</b>	<b>3/4</b>
<b>13</b>	3-CF <sub>3</sub>	H	<b>4/4</b>	<b>4/4</b>
<b>14</b>	4-CF <sub>3</sub>	H	<b>2/4</b>	<b>2/4</b>
<b>15</b>	2-OCF <sub>3</sub>	H	<b>2/4</b>	<b>1/4</b>
<b>16</b>	3-OCF <sub>3</sub>	H	<b>4/4</b>	<b>2/4</b>
<b>17</b>	4-OCF <sub>3</sub>	H	<b>4/4</b>	<b>3/4</b>
<b>18</b>	2-CH <sub>3</sub>	H	<b>3/4</b>	<b>3/4</b>
<b>19</b>	3-CH <sub>3</sub>	H	1/4	1/4
<b>20</b>	4-CH <sub>3</sub>	H	0/4	0/4
<b>21</b>	H	CH <sub>3</sub>	1/4	0/4
<b>22</b>	H	H	1/4	0/4
<b>23</b>	H	H	1/4	0/4
<b>Pyrrolidin-2-one derivatives</b>				
<b>36</b>	H	H	<b>4/4</b>	1/4
<b>37</b>	2-CF <sub>3</sub>	H	<b>4/4</b>	<b>2/4</b>
<b>38</b>	3-CF <sub>3</sub>	H	<b>4/4</b>	<b>3/4</b>
<b>39</b>	4-OCF <sub>3</sub>	H	<b>4/4</b>	<b>4/4</b>

Ratios where at least 50% of animals were protected have been highlighted in bold for easier data interpretation.

<sup>a</sup> Data indicate: number of mice protected / number of mice tested. The animals were examined at one pretreatment time–0.5 h. MES – the maximal electroshock seizure test. 6 Hz (32 mA) seizure test,.



**Scheme S1.** Synthesis of intermediates benzonitrile **A1–A18** and amines **A19–A36**.

### General synthetic procedure for (benzyloxy)benzonitrile **A1–A18**

The appropriate cyanophenol (3.57 g, 30 mmol, 1 eq) was dissolved in acetone (100 ml). Anhydrous potassium carbonate (16.58 g, 120 mmol, 4 eq) was added, followed by the dropwise addition of the appropriate benzyl bromide (30 mmol, 1 eq). The reaction mixture was heated to 60°C and stirred for 12 hours. After the reaction was complete, the solvent was evaporated, and the resulting derivative was crystallized from anhydrous ethanol.

#### 4-(benzyloxy)benzonitrile (**A1**)

White solid. Yield: 83% (5.2 g); UPLC (purity: 98.2%):  $t_R$  = 3.89 min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>11</sub>NO (M+H)<sup>+</sup> 210.08, found 210.10. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.12 (s, 2 H), 6.95–7.08 (m, 2 H), 7.21–7.46 (m, 5 H), 7.52–7.65 (m, 2 H).

#### 4-((2-fluorobenzyl)oxy)benzonitrile (**A2**)

White solid. Yield: 78% (5.31 g); UPLC (purity: 97.5%):  $t_R$  = 3.93 min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>10</sub>FNO (M+H)<sup>+</sup> 228.07, found 228.2. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.12 (s, 2 H), 6.97–7.11 (m, 2 H), 7.31–7.48 (m, 4 H), 7.52–7.67 (m, 2 H).

#### 4-((3-fluorobenzyl)oxy)benzonitrile (**A3**)

White solid. Yield: 80% (5.44 g); UPLC (purity: 99.2%):  $t_R$  = 3.98 min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>10</sub>FNO (M+H)<sup>+</sup> 228.07, found 228.1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.11 (s, 2 H), 6.93–7.09 (m, 3 H), 7.09–7.43 (m, 3 H), 7.52–7.66 (m, 2 H).

#### 4-((4-fluorobenzyl)oxy)benzonitrile (**A4**)

White solid. Yield: 77% (5.24 g); UPLC (purity: 98.4%):  $t_R$  = 3.97 min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>10</sub>FNO (M+H)<sup>+</sup> 228.07, found 228.1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.12 (s, 2 H), 6.97–7.11 (m, 2 H), 7.31–7.48 (m, 4 H), 7.52–7.67 (m, 2 H).

#### **4-((2-chlorobenzyl)oxy)benzonitrile (A5)**

White solid. Yield: 74% (5.54 g); UPLC (purity: 98.8%):  $t_R$  = 3.96 min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{10}ClNO$  ( $M+H$ )<sup>+</sup> 244.05, found 244.2. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.13 (s, 2 H), 6.98–7.13 (m, 2 H), 7.25–7.37 (m, 2 H), 7.39–7.54 (m, 2 H), 7.56–7.65 (m, 2 H).

#### **4-((3-chlorobenzyl)oxy)benzonitrile (A6)**

White solid. Yield: 81% (5.91 g); UPLC (purity: 99.5%):  $t_R$  = 3.95 min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{10}ClNO$  ( $M+H$ )<sup>+</sup> 244.05, found 244.1. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.08 (s, 2 H), 6.82–7.07 (m, 2 H), 7.24–7.36 (m, 3 H), 7.41 (s, 1 H), 7.53–7.65 (m, 2 H).

#### **4-((4-chlorobenzyl)oxy)benzonitrile (A7)**

White solid. Yield: 75% (5.48 g); UPLC (purity: 99.7%):  $t_R$  = 3.94 min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{10}ClNO$  ( $M+H$ )<sup>+</sup> 244.05, found 244.1. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.08 (s, 2 H), 6.89–7.10 (m, 2 H), 7.19–7.46 (m, 4 H), 7.49–7.76 (m, 2 H).

#### **4-((2-(trifluoromethyl)benzyl)oxy)benzonitrile (A8)**

White solid. Yield: 74% (6.14 g); UPLC (purity: 98.7%):  $t_R$  = 4.31 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO$  ( $M+H$ )<sup>+</sup> 278.07, found 278.2. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.12 (s, 2 H), 6.97–7.11 (m, 2 H), 7.31–7.48 (m, 4 H), 7.52–7.67 (m, 2 H).

#### **4-((3-(trifluoromethyl)benzyl)oxy)benzonitrile (A9)**

White solid. Yield: 76% (6.30 g); UPLC (purity: 99.8%):  $t_R$  = 4.32 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO$  ( $M+H$ )<sup>+</sup> 278.07, found 278.2. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.16 (s, 2 H), 6.94–7.11 (m, 2 H), 7.26 (s, 1 H), 7.44–7.78 (m, 5 H).

#### **4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile (A10)**

White solid. Yield: 68% (5.64 g); UPLC (purity: 98.9%):  $t_R$  = 4.32 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO$  ( $M+H$ )<sup>+</sup> 278.07, found 278.2. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.18 (s, 2 H), 6.86–7.08 (m, 2 H), 7.27 (s, 1 H), 7.42–7.90 (m, 5 H).

#### **4-((2-(trifluoromethoxy)benzyl)oxy)benzonitrile (A11)**

White solid. Yield: 74% (6.49 g); UPLC (purity: 99.5%):  $t_R$  = 4.42 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO_2$  ( $M+H$ )<sup>+</sup> 294.07, found 294.1. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.12 (s, 2 H), 6.95–7.14 (m, 2 H), 7.32–7.48 (m, 4 H), 7.56–7.69 (m, 2 H).

#### **4-((3-(trifluoromethoxy)benzyl)oxy)benzonitrile (A12)**

White solid. Yield: 69% (6.05 g); UPLC (purity: 99.1%):  $t_R$  = 4.41 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO_2$  ( $M+H$ )<sup>+</sup> 294.07, found 294.2. <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  5.13 (s, 2 H), 6.94–7.11 (m, 2 H), 7.30–7.51 (m, 4 H), 7.58–7.74 (m, 2 H).

#### **4-((4-(trifluoromethoxy)benzyl)oxy)benzonitrile (A13)**

White solid. Yield: 78% (6.84 g); UPLC (purity: 98.7%):  $t_R$  = 4.43 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{10}F_3NO_2$  (M+H)<sup>+</sup> 294.07, found 294.2. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.12 (s, 2 H), 6.91–7.14 (m, 2 H), 7.29–7.54 (m, 4 H), 7.59–7.77 (m, 2 H).

#### **4-((2-methylbenzyl)oxy)benzonitrile (A14)**

White solid. Yield: 71% (4.74 g); UPLC (purity: 99.3%):  $t_R$  = 4.21 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{13}NO$  (M+H)<sup>+</sup> 224.10, found 224.2. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.35 (s, 3 H), 5.13 (s, 2 H), 6.87–7.12 (m, 2 H), 7.29–7.50 (m, 3 H), 7.59–7.80 (m, 3 H).

#### **4-((3-methylbenzyl)oxy)benzonitrile (A15)**

White solid. Yield: 79% (5.27 g); UPLC (purity: 98.2%):  $t_R$  = 4.25 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{13}NO$  (M+H)<sup>+</sup> 224.10, found 224.2. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.36 (s, 3 H), 5.12 (s, 2 H), 6.85–7.11 (m, 2 H), 7.26–7.47 (m, 4 H), 7.61–7.77 (m, 3 H).

#### **4-((4-methylbenzyl)oxy)benzonitrile (A16)**

White solid. Yield: 83% (5.48 g); UPLC (purity: 97.6%):  $t_R$  = 4.28 min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{13}NO$  (M+H)<sup>+</sup> 224.10, found 224.2. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.35 (s, 3 H), 5.12 (s, 2 H), 6.84–7.09 (m, 2 H), 7.25–7.49 (m, 3 H), 7.62–7.78 (m, 3 H).

#### **2-(benzyloxy)benzonitrile (A17)**

White solid. Yield: 85% (5.30 g); UPLC (purity: 99.4%):  $t_R$  = 3.81 min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{11}NO$  (M+H)<sup>+</sup> 209.25, found 209.3.

#### **3-(benzyloxy)benzonitrile (A18)**

White solid. Yield: 81% (5.06 g); UPLC (purity: 98.7%):  $t_R$  = 3.87 min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{11}NO$  (M+H)<sup>+</sup> 209.25, found 209.3.

## General synthetic procedure for (benzyloxy)phenylmethanamine A19–A36

In a dry round-bottom flask placed in an ice bath under an inert gas atmosphere, a solution of 2.4 M LiAlH<sub>4</sub> (60 mmol, 3 eq) in THF was added. Then, a solution of the appropriate nitrile (20 mmol, 1 eq) in 20 ml THF was added dropwise. After 10 minutes, the reaction was continued at room temperature under an argon atmosphere. The reaction progress was monitored using HPLC. After one hour, the reaction mixture was cooled in an ice bath again, and sequentially, 4 ml of distilled water, 2 ml of 10% NaOH, and another 4 ml of distilled water were added. The mixture was stirred for 2 hours, then filtered through Celite, concentrated, and extracted with a DCM/H<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure.

### (4-(benzyloxy)phenyl)methanamine (A19)

White solid. Yield: 84% (3.58 g); UPLC (purity: 89.4%):  $t_R = 7.13$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>15</sub>NO (M+H)<sup>+</sup> 214.12, found 214.2.

### (4-((2-fluorobenzyl)oxy)phenyl)methanamine (A20)

White solid. Yield: 81% (3.74 g); UPLC (purity: 99.1%):  $t_R = 6.83$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>FNO (M+H)<sup>+</sup> 232.11, found 232.2.

### (4-((3-fluorobenzyl)oxy)phenyl)methanamine (A21)

White solid. Yield: 77% (3.55 g); UPLC (purity: 98.4%):  $t_R = 6.94$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>FNO (M+H)<sup>+</sup> 232.11, found 232.2.

### (4-((4-fluorobenzyl)oxy)phenyl)methanamine (A22)

White solid. Yield: 69% (3.18 g); UPLC (purity: 97.2%):  $t_R = 6.96$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>FNO (M+H)<sup>+</sup> 232.11, found 232.2.

### (4-((2-chlorobenzyl)oxy)phenyl)methanamine (A23)

White solid. Yield: 78% (3.85 g); UPLC (purity: 96.5%):  $t_R = 7.73$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>ClNO (M+H)<sup>+</sup> 248.08, found 248.1.

### (4-((3-chlorobenzyl)oxy)phenyl)methanamine (A24)

White solid. Yield: 72% (3.55 g); UPLC (purity: 98.5%):  $t_R = 7.75$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>ClNO (M+H)<sup>+</sup> 248.08, found 248.2.

### (4-((4-chlorobenzyl)oxy)phenyl)methanamine (A25)

White solid. Yield: 83% (4.10 g); UPLC (purity: 97.6%):  $t_R = 7.76$  min, LC-MS (ESI):  $m/z$  calcd for C<sub>14</sub>H<sub>14</sub>ClNO (M+H)<sup>+</sup> 248.08, found 248.2.

### (4-((2-(trifluoromethyl)benzyl)oxy)phenyl)methanamine (A26)

White solid. Yield: 78% (4.38 g); UPLC (purity: 99.3%):  $t_R = 7.82$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO$  (M+H)<sup>+</sup> 282.10, found 282.2.

**(4-((3-(trifluoromethyl)benzyl)oxy)phenyl)methanamine (A27)**

White solid. Yield: 82% (4.60 g); UPLC (purity: 97.4%):  $t_R = 6.74$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO$  (M+H)<sup>+</sup> 282.10, found 282.2.

**(4-((4-(trifluoromethyl)benzyl)oxy)phenyl)methanamine (A28)**

White solid. Yield: 68% (3.88 g); UPLC (purity: 98.5%):  $t_R = 7.83$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO$  (M+H)<sup>+</sup> 282.10, found 282.2.

**(4-((2-(trifluoromethoxy)benzyl)oxy)phenyl)methanamine (A29)**

White solid. Yield: 81% (4.81 g); UPLC (purity: 95.4%):  $t_R = 7.89$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO_2$  (M+H)<sup>+</sup> 298.10, found 298.2.

**(4-((3-(trifluoromethoxy)benzyl)oxy)phenyl)methanamine (A30)**

White solid. Yield: 77% (4.57 g); UPLC (purity: 96.2%):  $t_R = 7.71$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO_2$  (M+H)<sup>+</sup> 298.10, found 298.2.

**(4-((4-(trifluoromethoxy)benzyl)oxy)phenyl)methanamine (A31)**

White solid. Yield: 83% (4.93 g); UPLC (purity: 100%):  $t_R = 7.87$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{14}F_3NO_2$  (M+H)<sup>+</sup> 298.10, found 298.2.

**(4-((2-methylbenzyl)oxy)phenyl)methanamine (A32)**

White solid. Yield: 80% (3.63 g); UPLC (purity: 98.7%):  $t_R = 7.10$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{17}NO$  (M+H)<sup>+</sup> 228.13, found 228.2.

**(4-((3-methylbenzyl)oxy)phenyl)methanamine (A33)**

White solid. Yield: 84% (3.81 g); UPLC (purity: 96.8%):  $t_R = 7.08$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{17}NO$  (M+H)<sup>+</sup> 228.13, found 228.2.

**(4-((4-methylbenzyl)oxy)phenyl)methanamine (A34)**

White solid. Yield: 82% (3.72 g); UPLC (purity: 97.6%):  $t_R = 7.12$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{15}H_{17}NO$  (M+H)<sup>+</sup> 228.13, found 228.2.

**(2-(benzyloxy)phenyl)methanamine (A35)**

White solid. Yield: 81% (3.49 g); UPLC (purity: 99.1%):  $t_R = 7.02$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{15}NO$  (M+H)<sup>+</sup> 214.12, found 214.2.

**(3-(benzyloxy)phenyl)methanamine (A36)**

White solid. Yield: 78% (3.42 g); UPLC (purity: 98.7%):  $t_R = 7.08$  min, LC-MS (ESI):  $m/z$  calcd for  $C_{14}H_{15}NO$  (M+H)<sup>+</sup> 214.12, found 214.2.



**Table S2.** Inhibitory effects of obtained compounds on MAO-B.

<b>Compound</b>	<b>% inhibition MAO-B (1 <math>\mu</math>M) <sup>a</sup></b>	<b>IC<sub>50</sub> <math>\pm</math> SEM [nM] <sup>b</sup></b>
<b>5</b>	0	-
<b>6</b>	0	-
<b>7</b>	0	-
<b>8</b>	0	-
<b>9</b>	0	-
<b>10</b>	0	-
<b>11</b>	0	-
<b>12</b>	0	-
<b>13</b>	0	-
<b>14</b>	0	-
<b>15</b>	0	-
<b>16</b>	31	-
<b>17</b>	0	-
<b>18</b>	0	-
<b>19</b>	0	-
<b>20</b>	0	-
<b>21</b>	0	-
<b>22</b>	0	-
<b>23</b>	0	-
<b>36</b>	0	-
<b>37</b>	0	-
<b>38</b>	2	-
<b>39</b>	0	-
<b>Positive control (Safinamide)</b>	100	8 $\pm$ 1
<b>Positive control (Rasagiline)</b>	100	25 $\pm$ 6

<sup>a</sup> % of inhibition at 1  $\mu$ M; mean values of two independent experiments. <sup>b</sup> IC<sub>50</sub> values were determined by fluorometric method using human recombinant MAO-B and rasagiline [1  $\mu$ M] as a positive control.

**Table S3.** The general information of radioligand binding/functional assays.

Binding studies	Ref.
Na <sup>+</sup> channel (site 2)	[1]
Ca <sup>2+</sup> channel (L, dihydropyridine site) (antagonist radioligand)	[2]
Ca <sup>2+</sup> channel (L, diltiazem site) (antagonist radioligand)	[3]
Ca <sup>2+</sup> channel (L, verapamil site) (antagonist radioligand)	[4]
N-type Ca <sup>2+</sup> [ <sup>3</sup> H] Gabapentin binding (antagonist radioligand)	[5]
GABA transporter (antagonist radioligand)	[6]
GLYT1 (glycine transporter binding) (antagonist radioligand)	[7]
Potassium channel (hERG)	[8]
Functional studies	
Cav <sub>1.2</sub> (L-type) ( <i>h</i> ) calcium ion channel cell based antagonist calcium flux assay	[9,10]

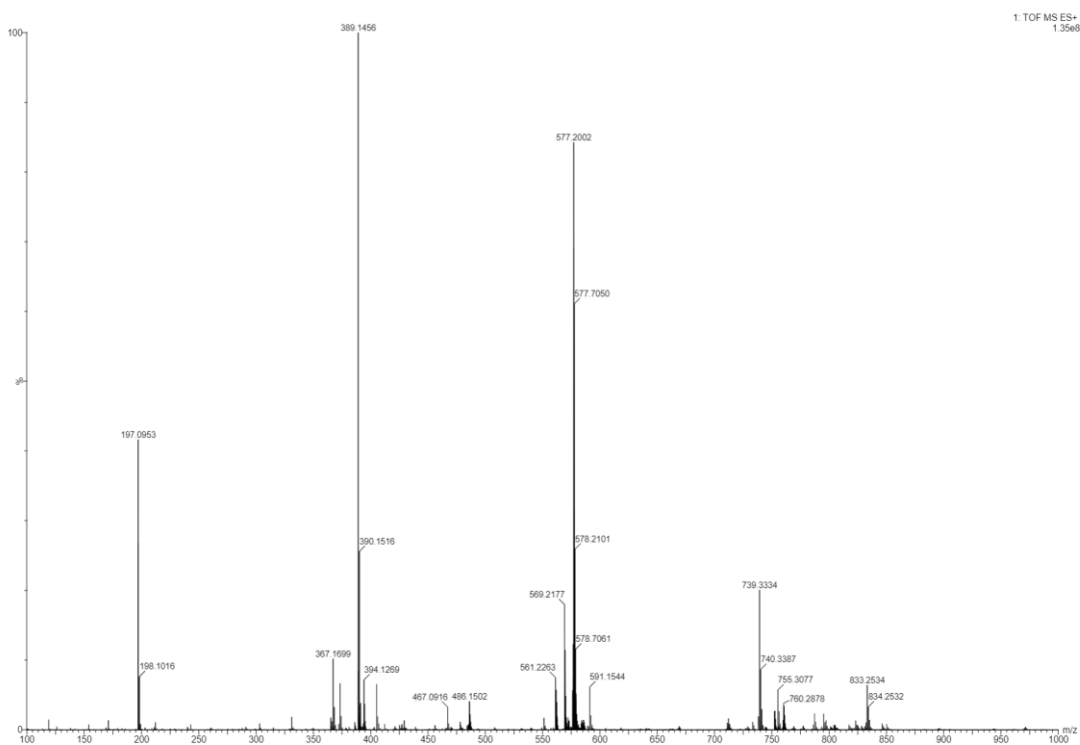
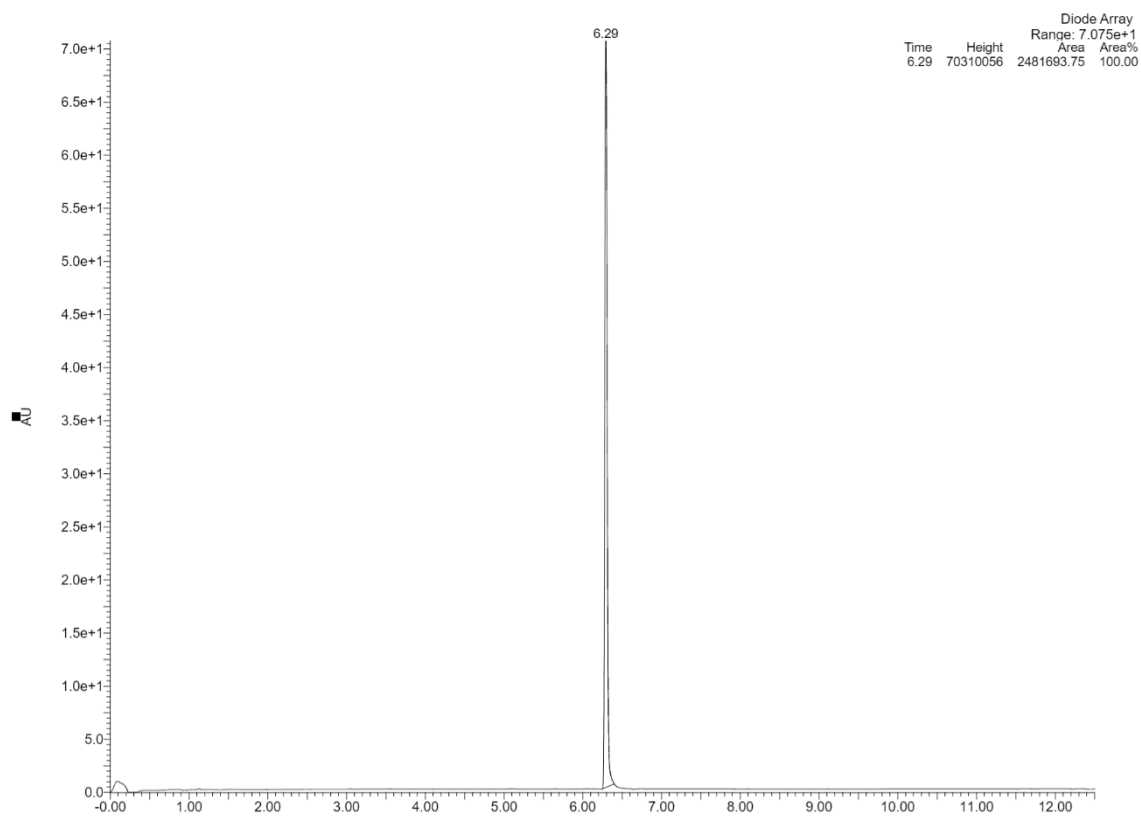
Assays were performed commercially in Eurofins Cerep SA (Celle l'Evescault, France) and Eurofins Panlabs Discovery Services Taiwan, Ltd. (New Taipei City, Taiwan), using procedures describe elsewhere:

## References

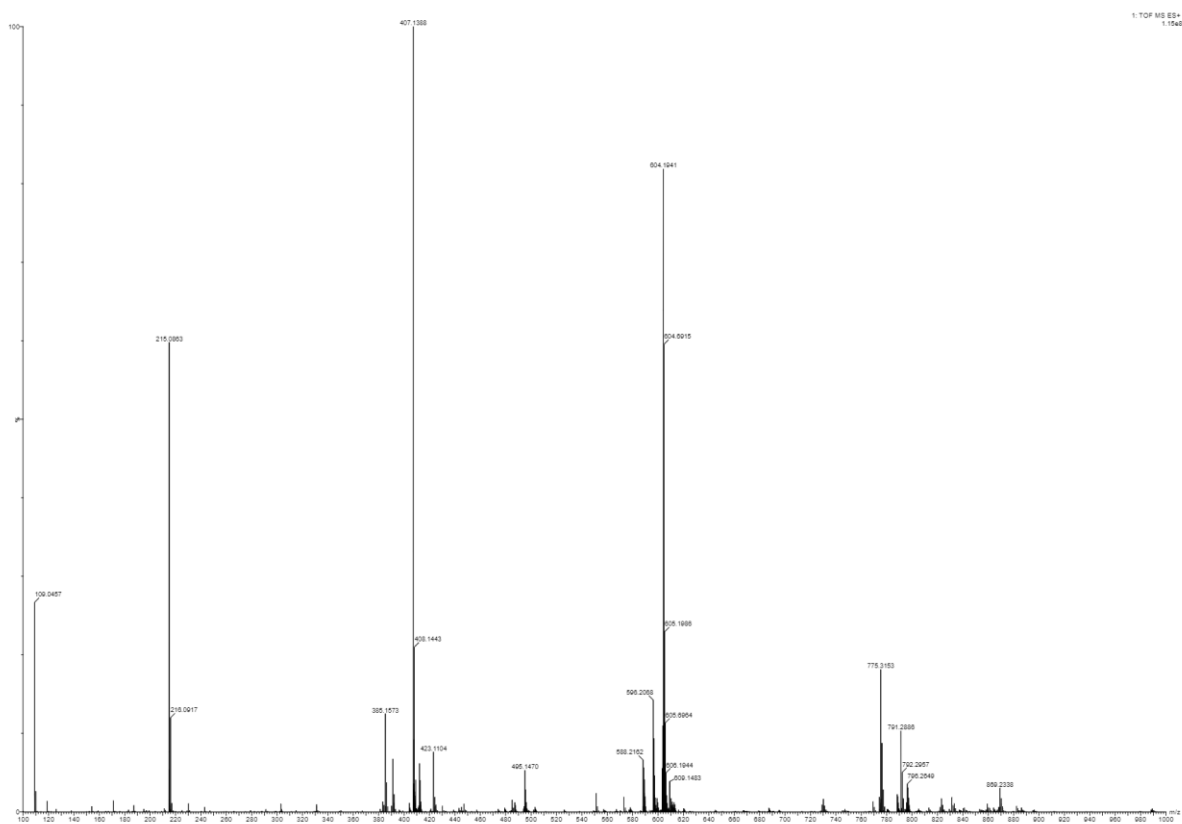
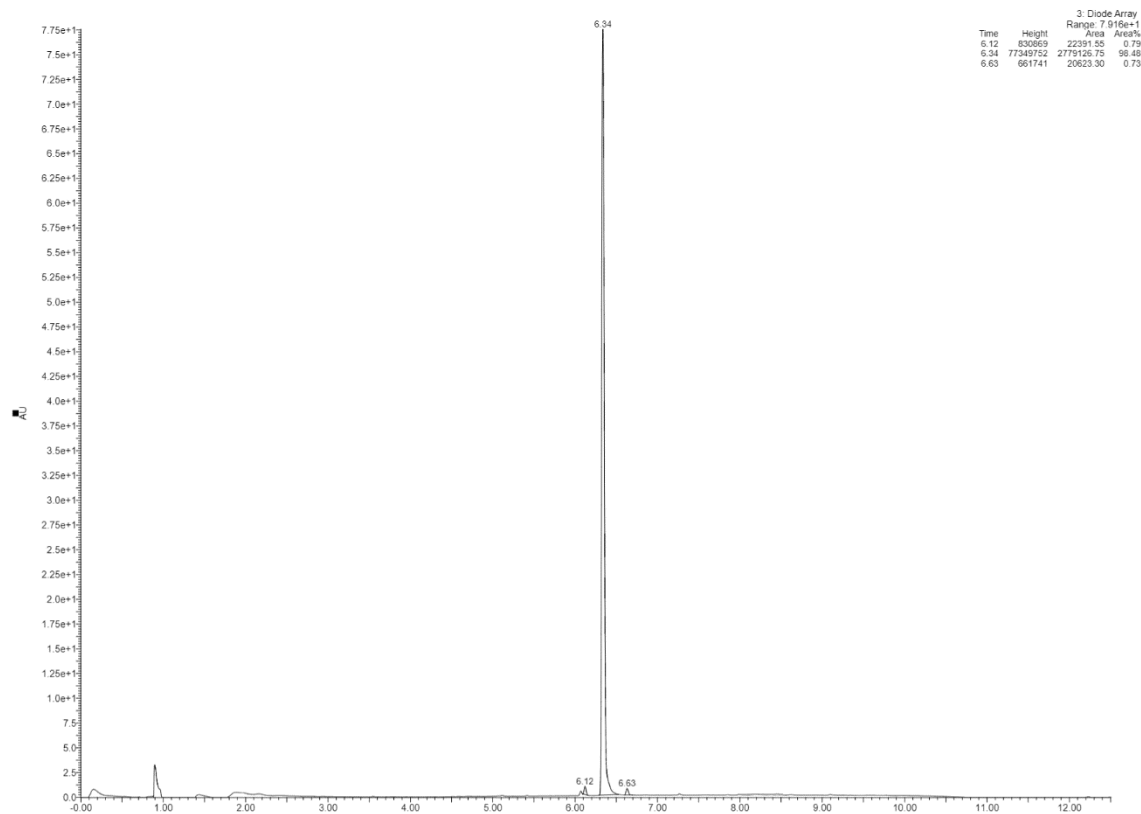
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## UPLC/HRMS traces for target final compounds

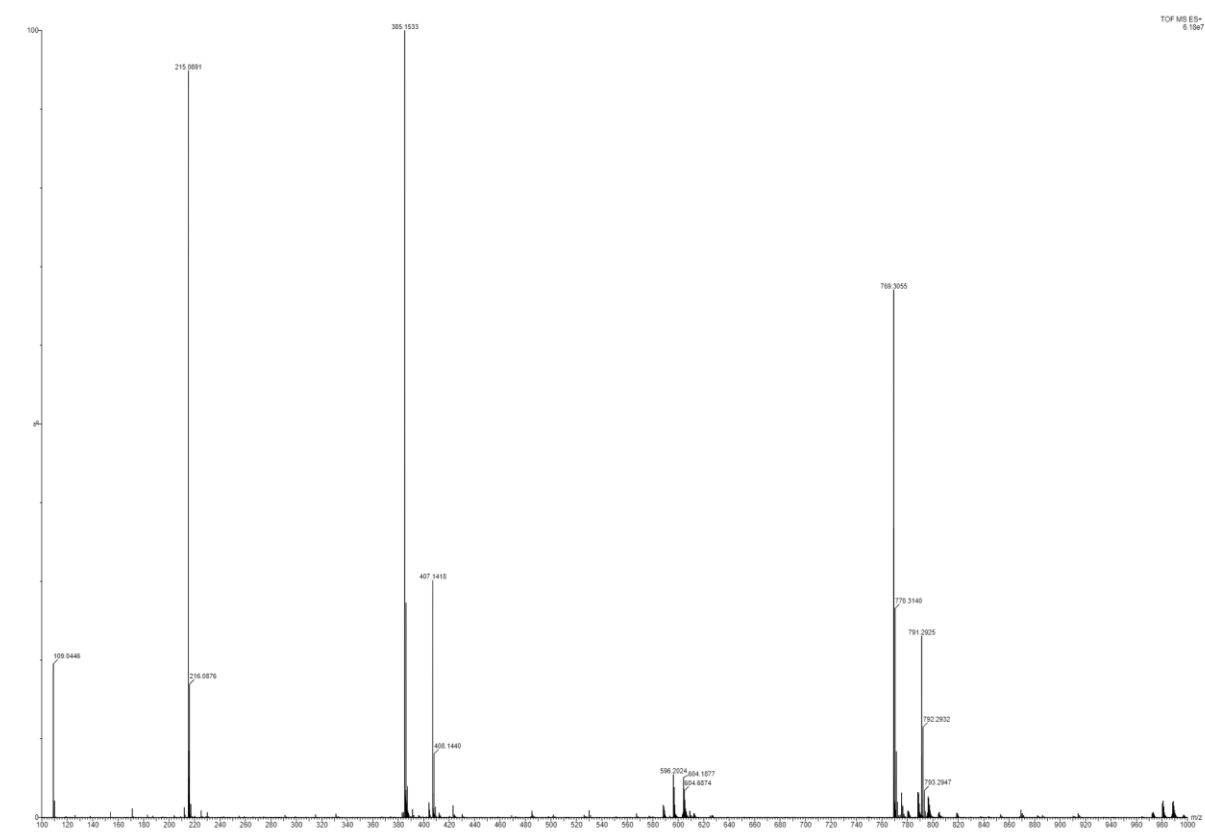
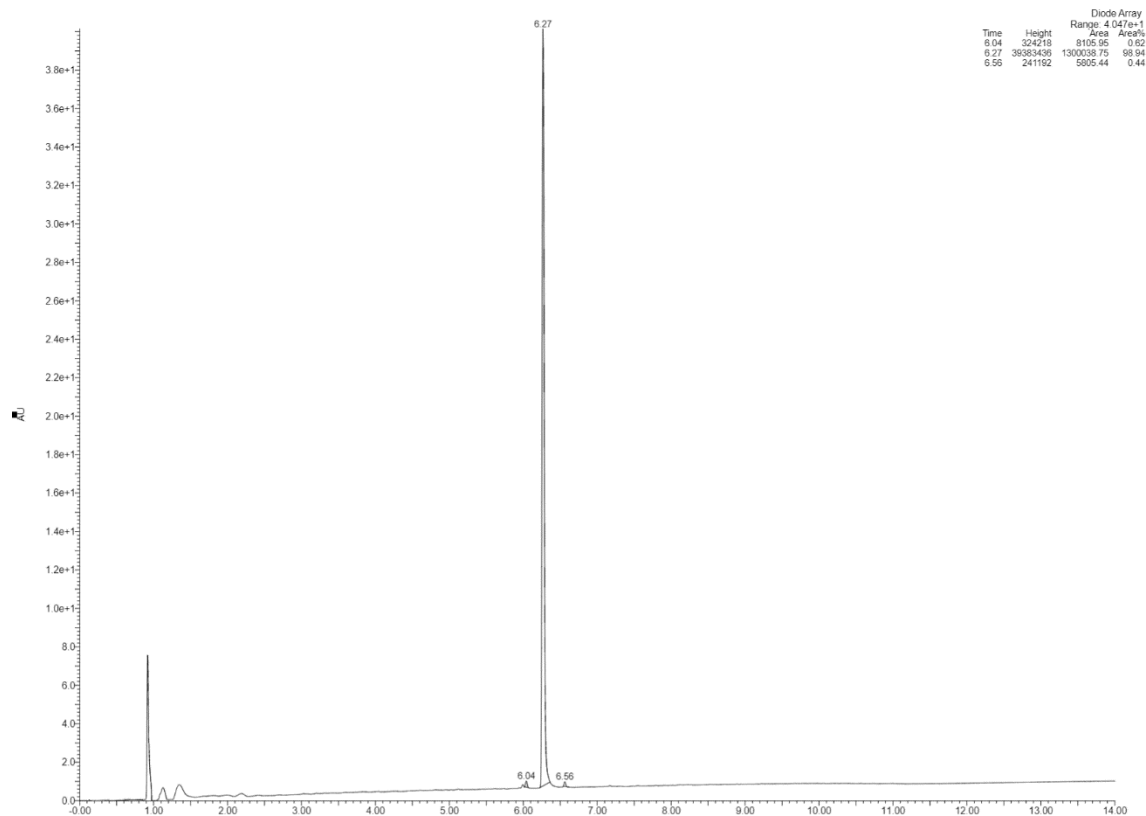
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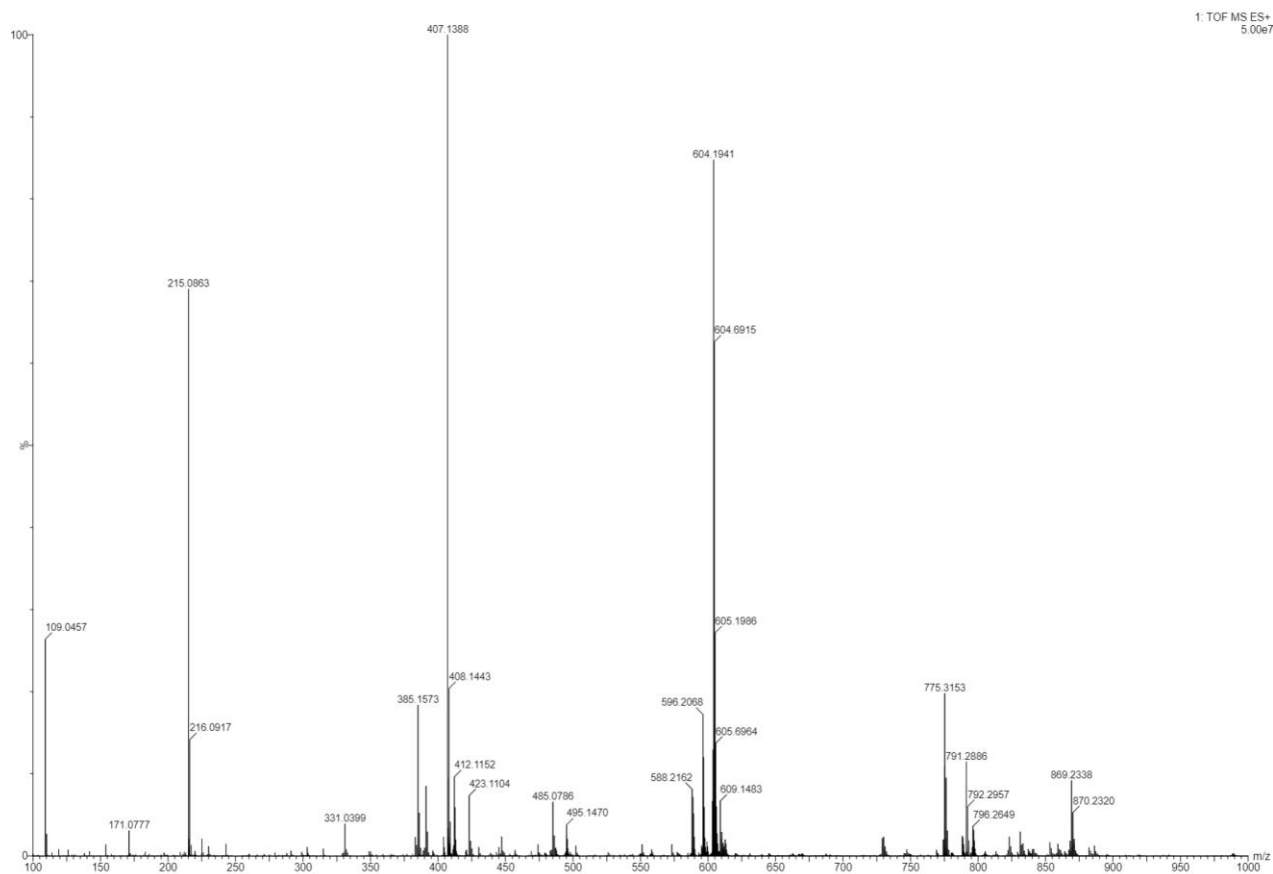
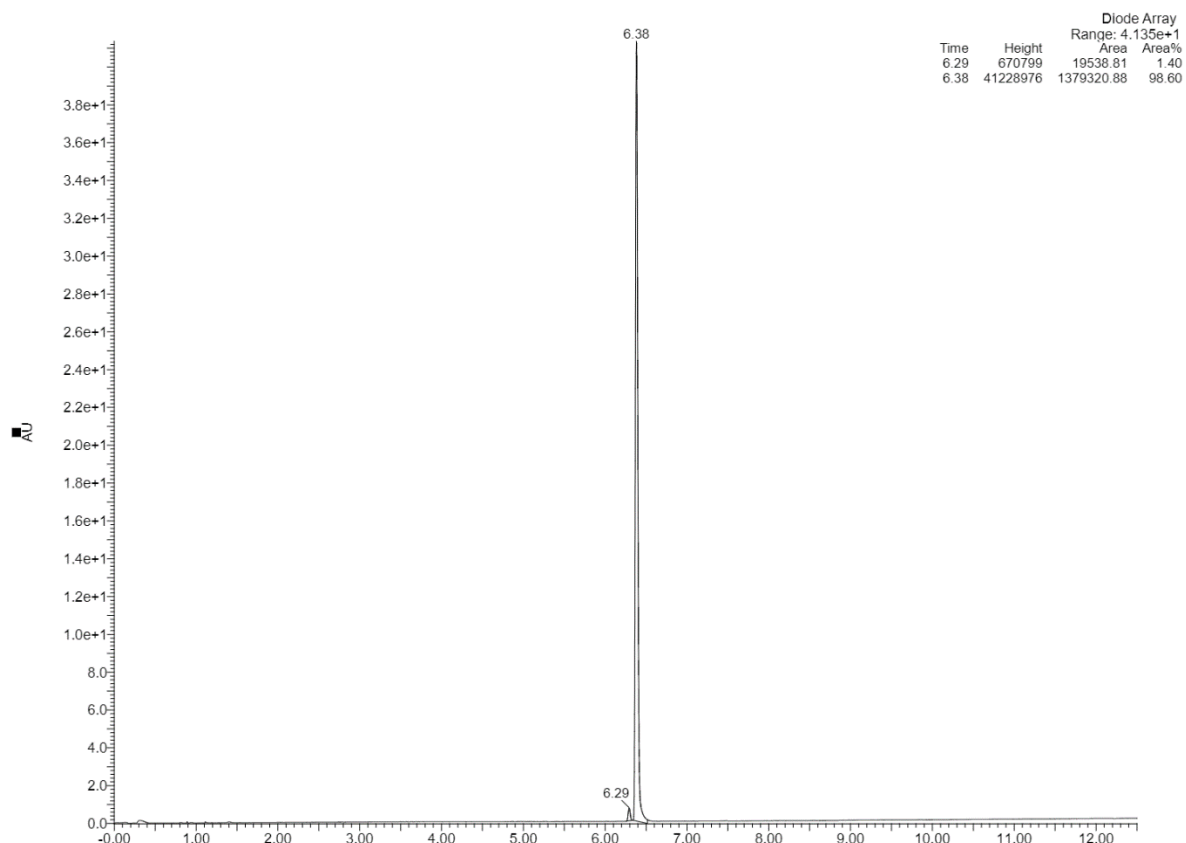
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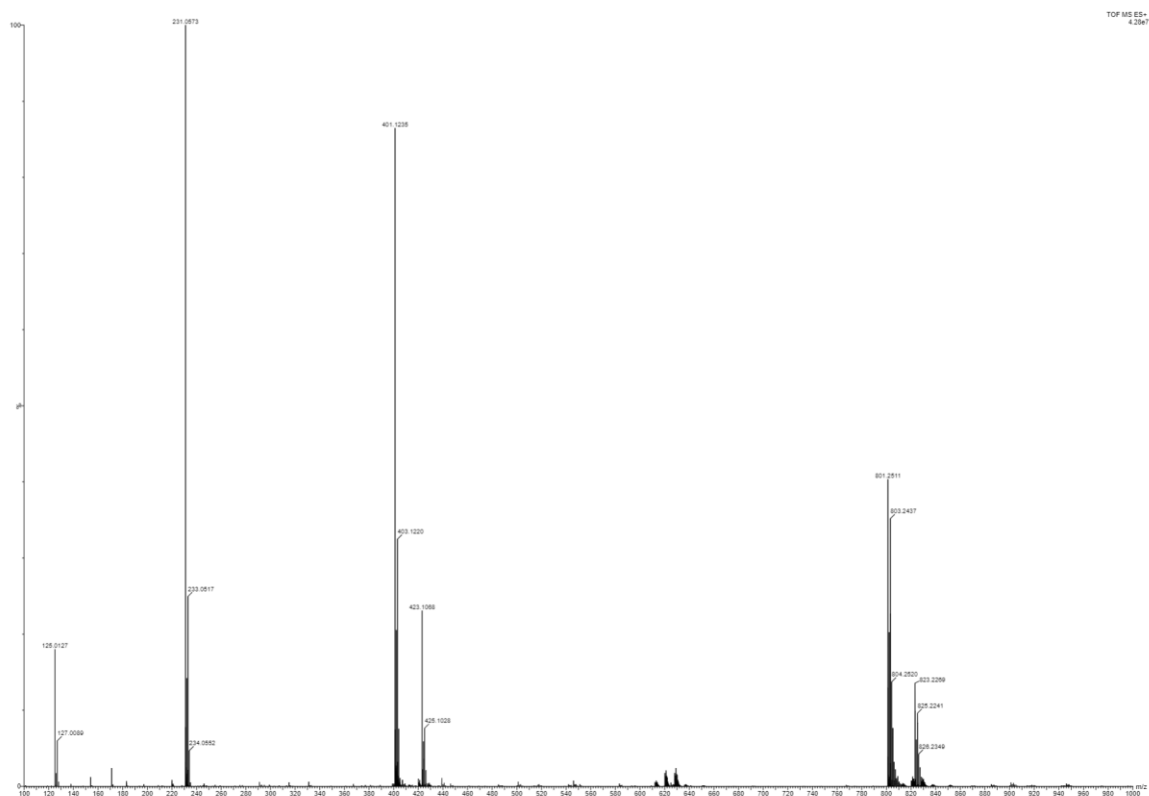
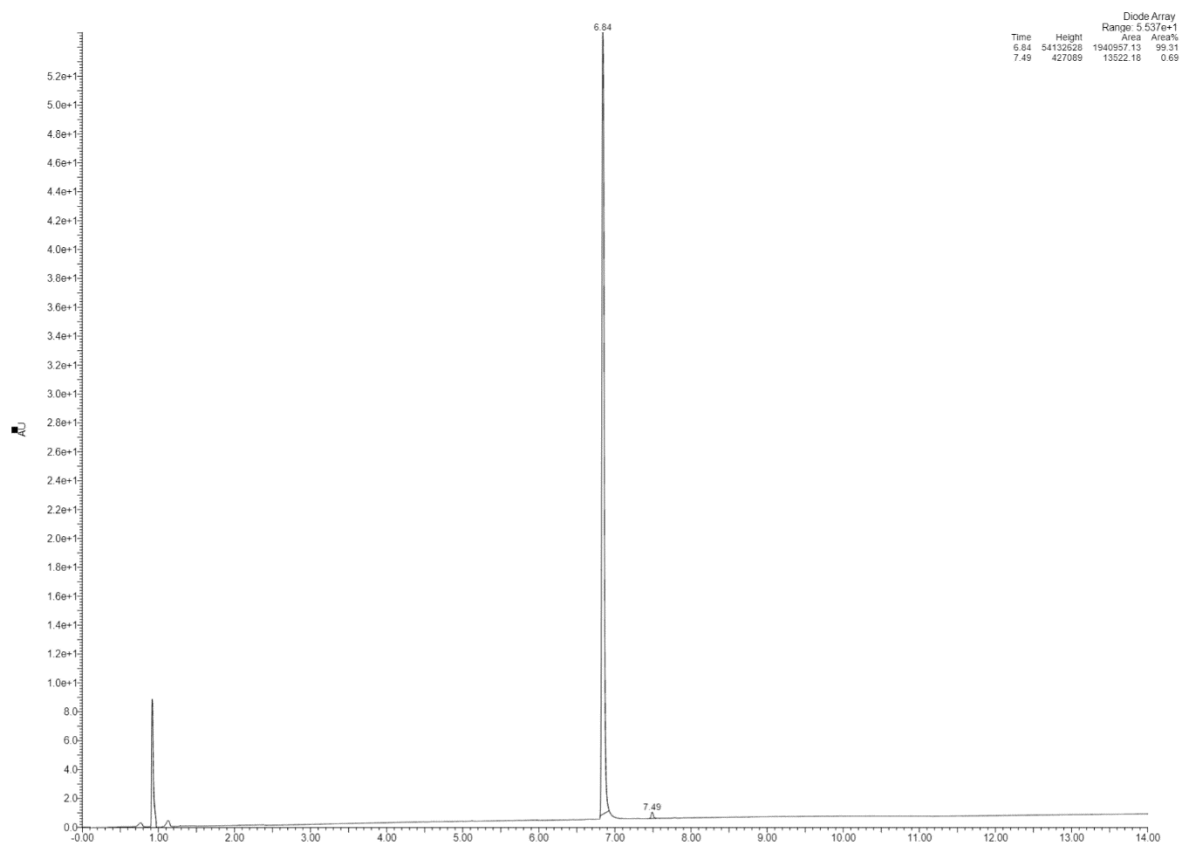
## 2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-fluorobenzyl)oxy)benzyl)propanamide (7)



# 2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-fluorobenzyl)oxy)benzyl)propanamide (8)

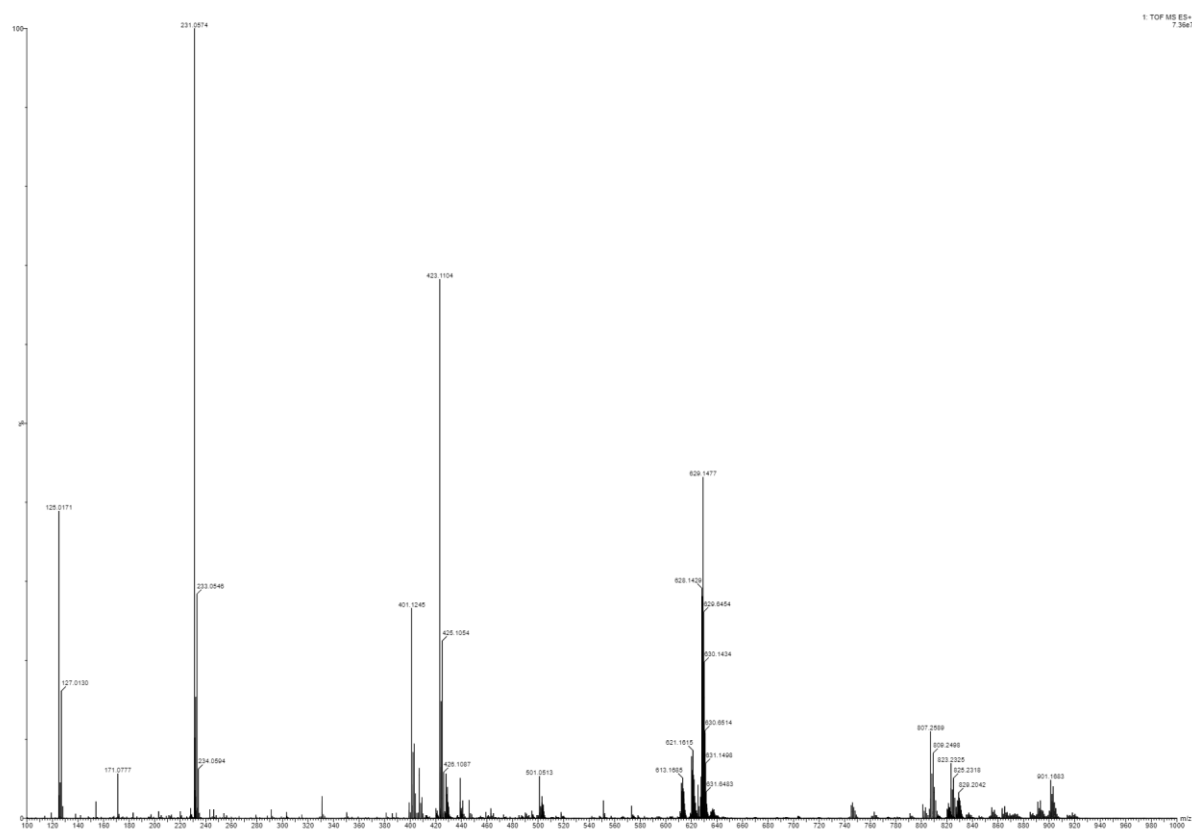
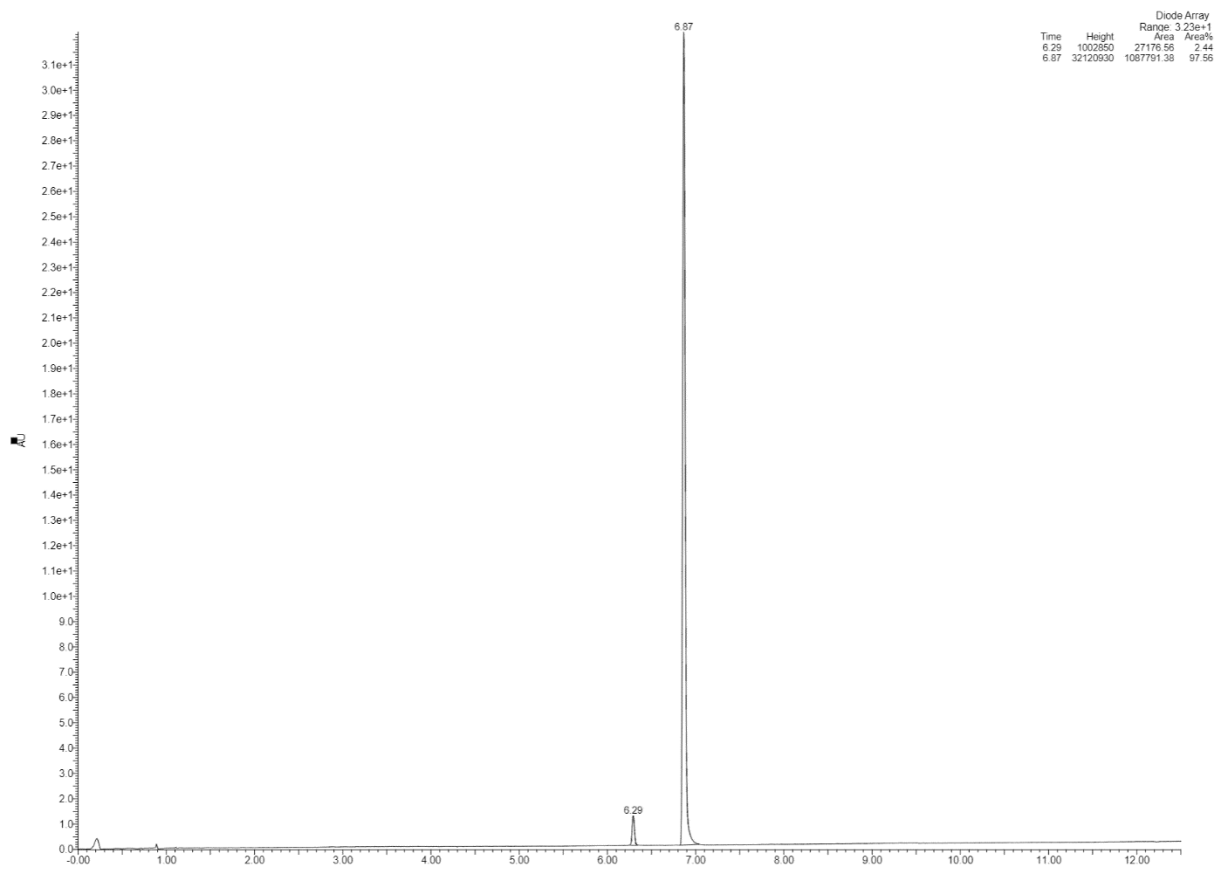


# ***N*-(4-((2-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (9)**

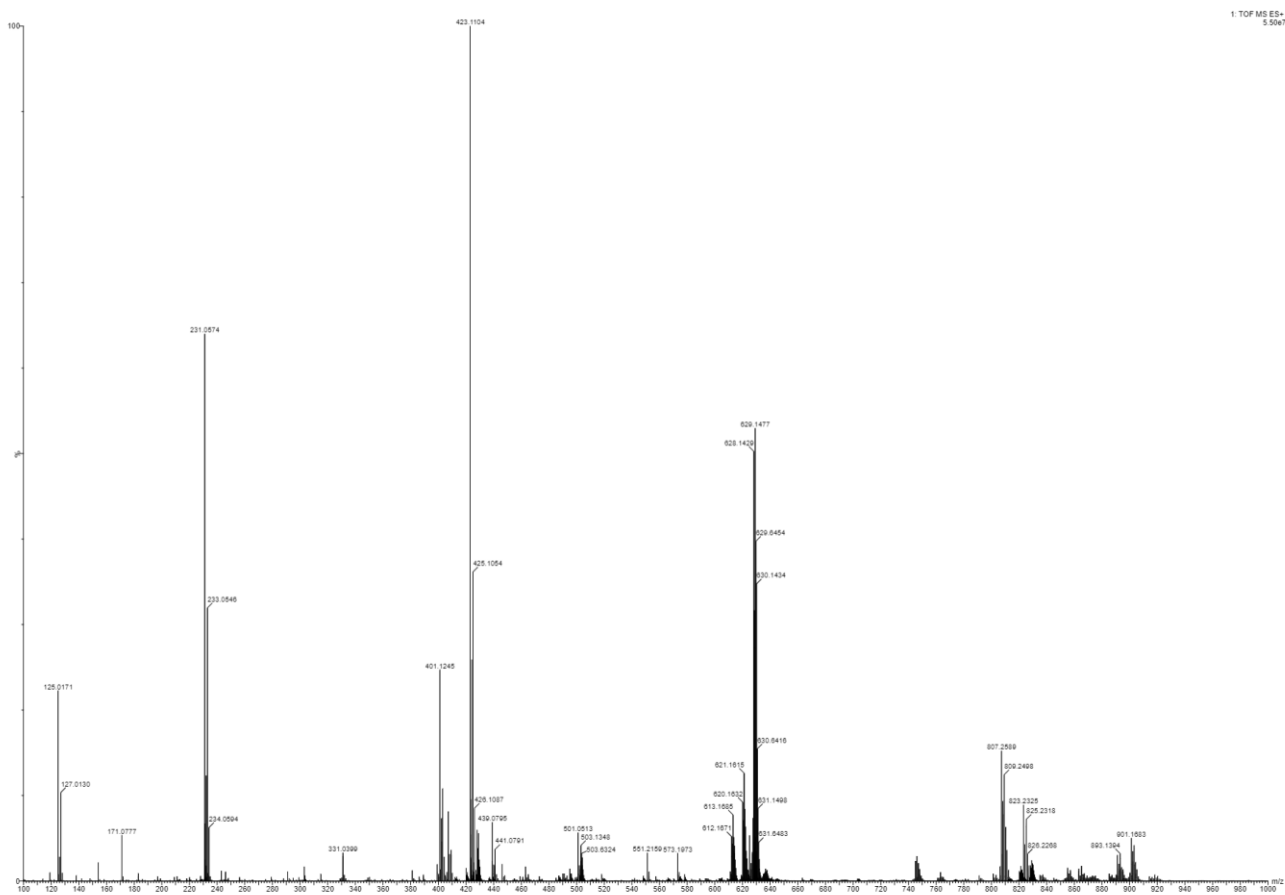
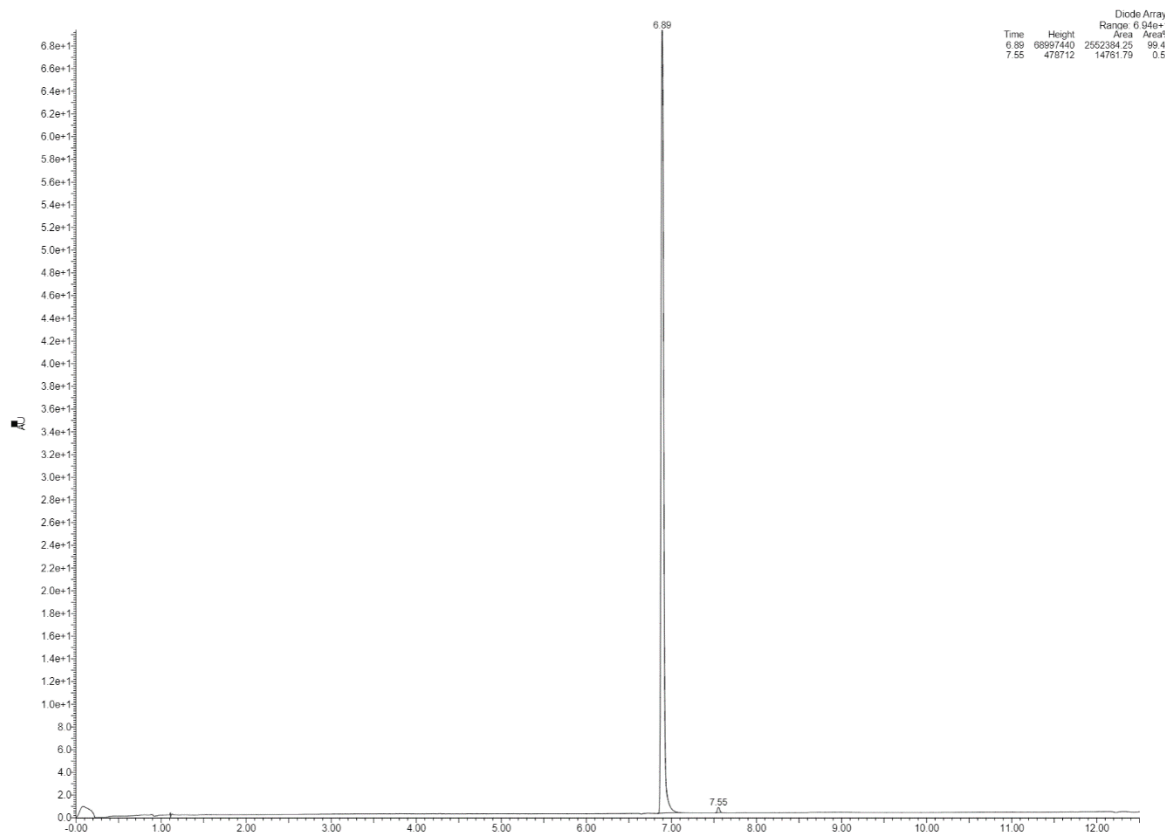




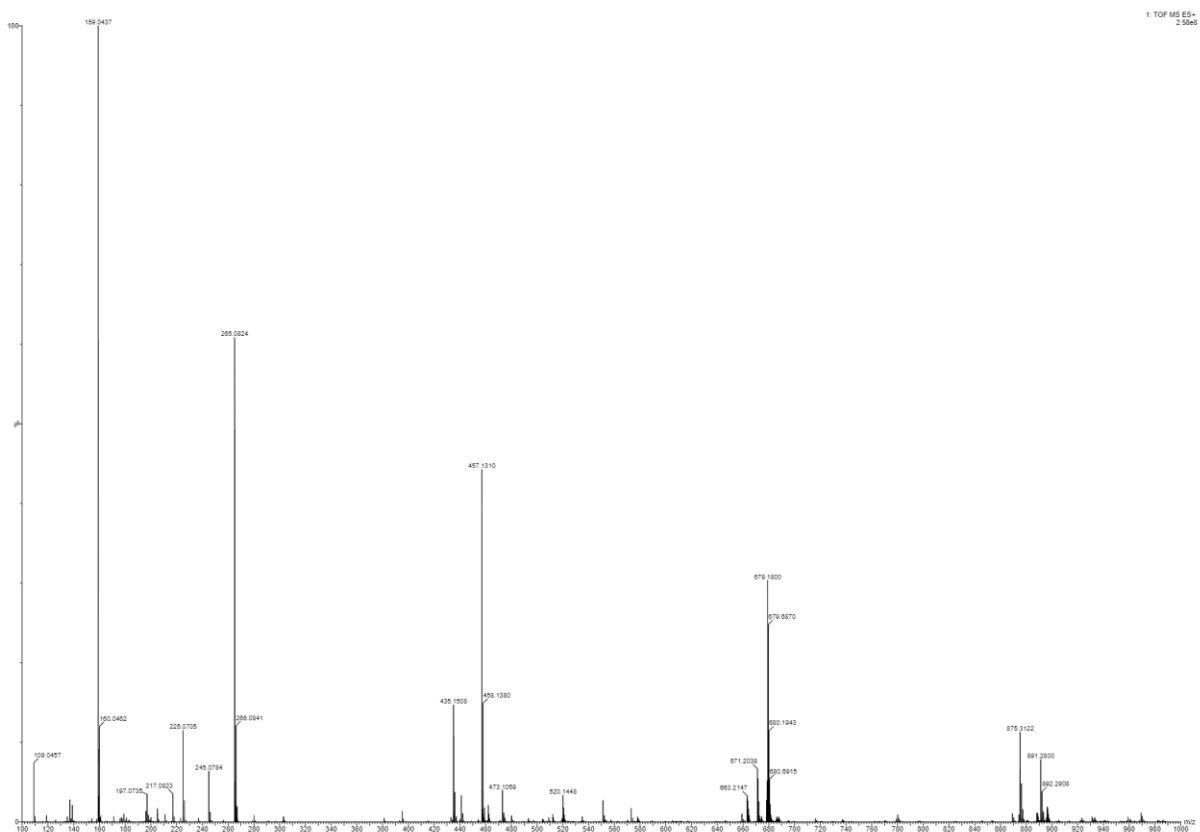
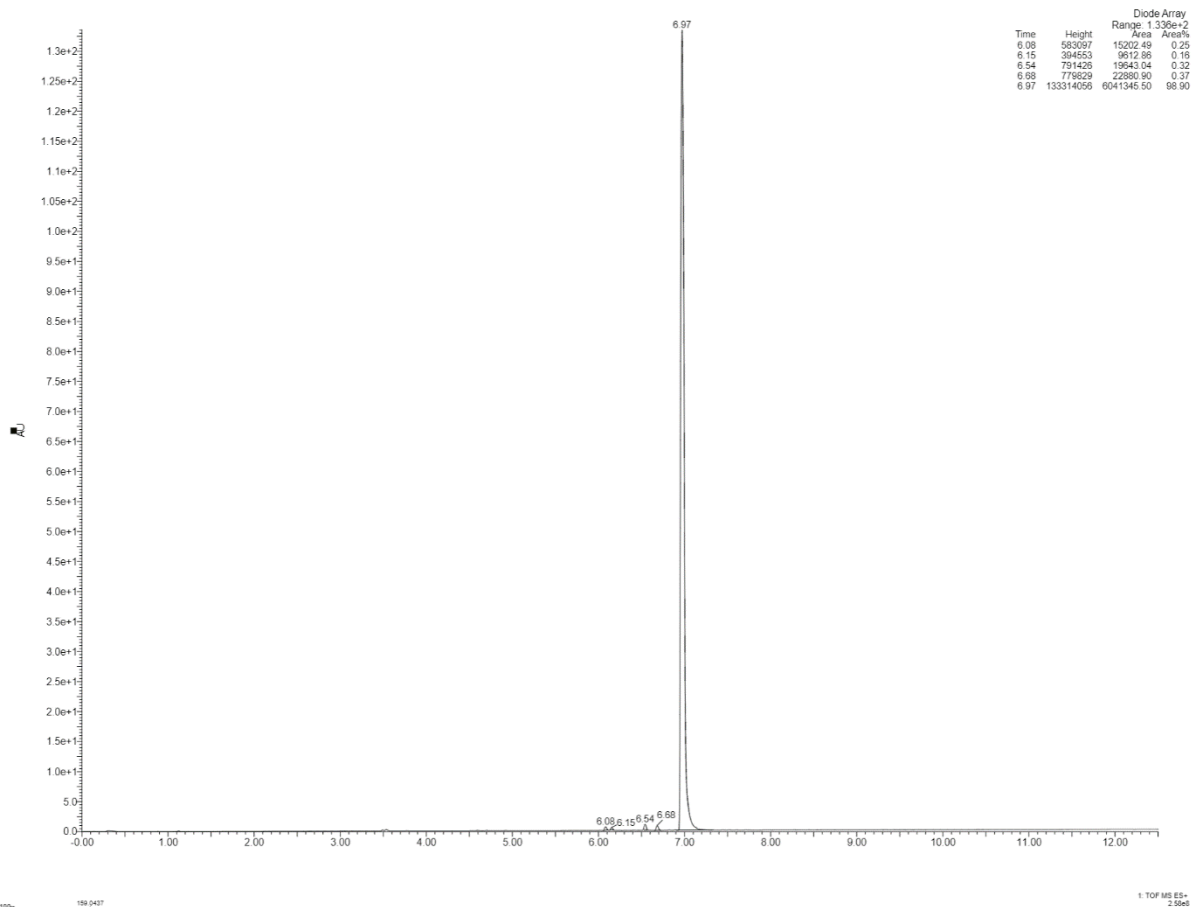
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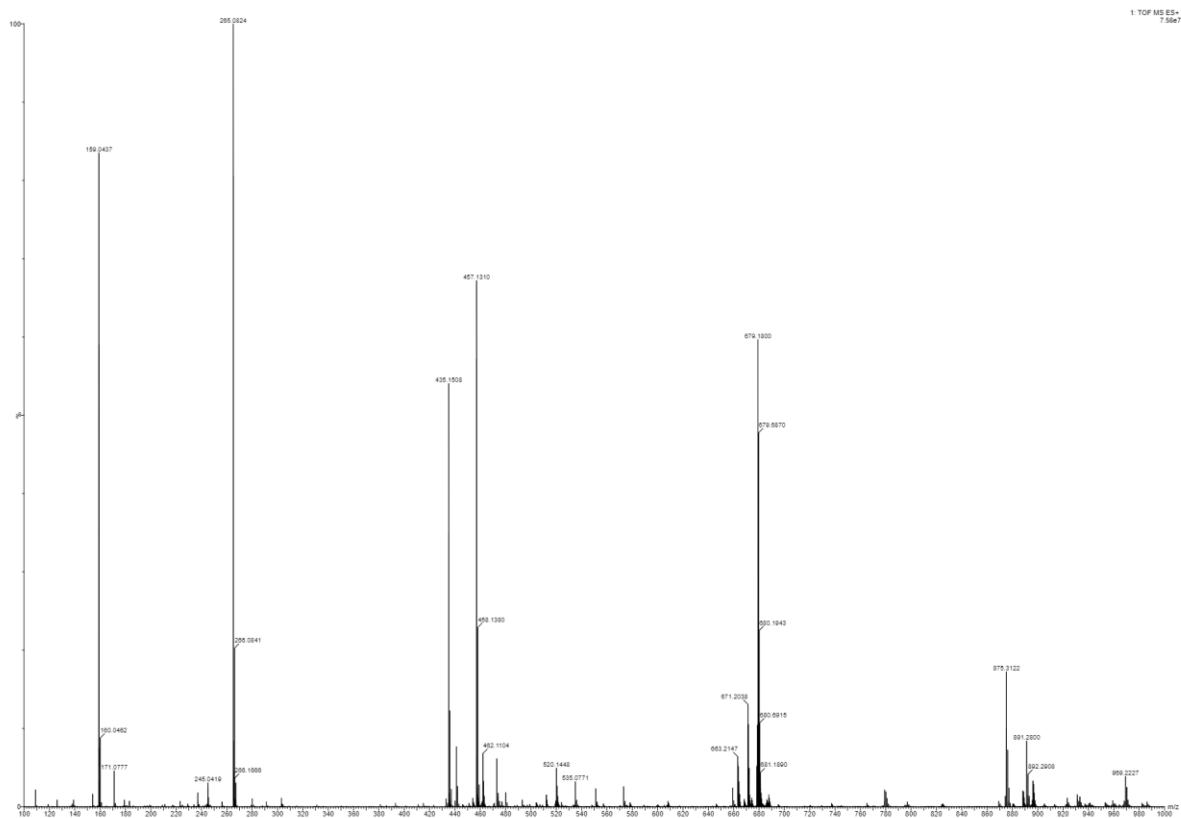
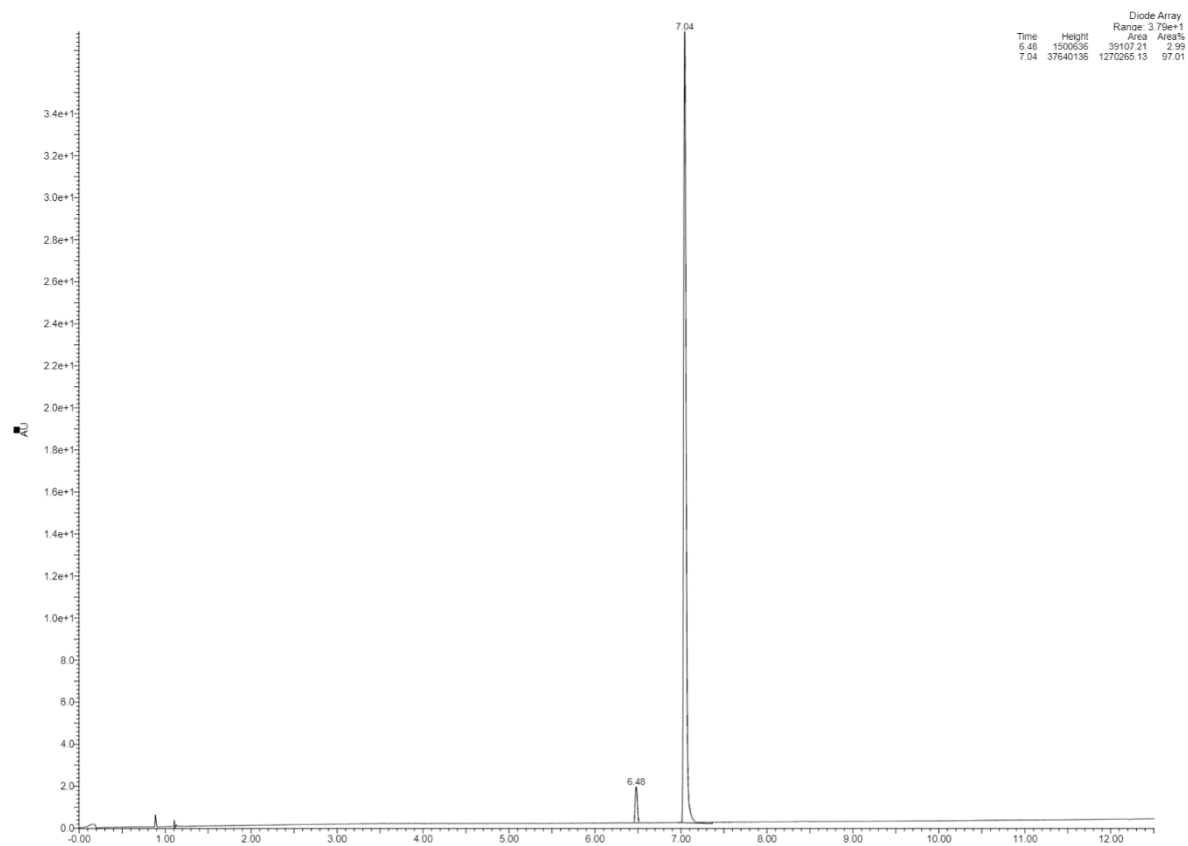
***N*-(4-((4-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (11)**



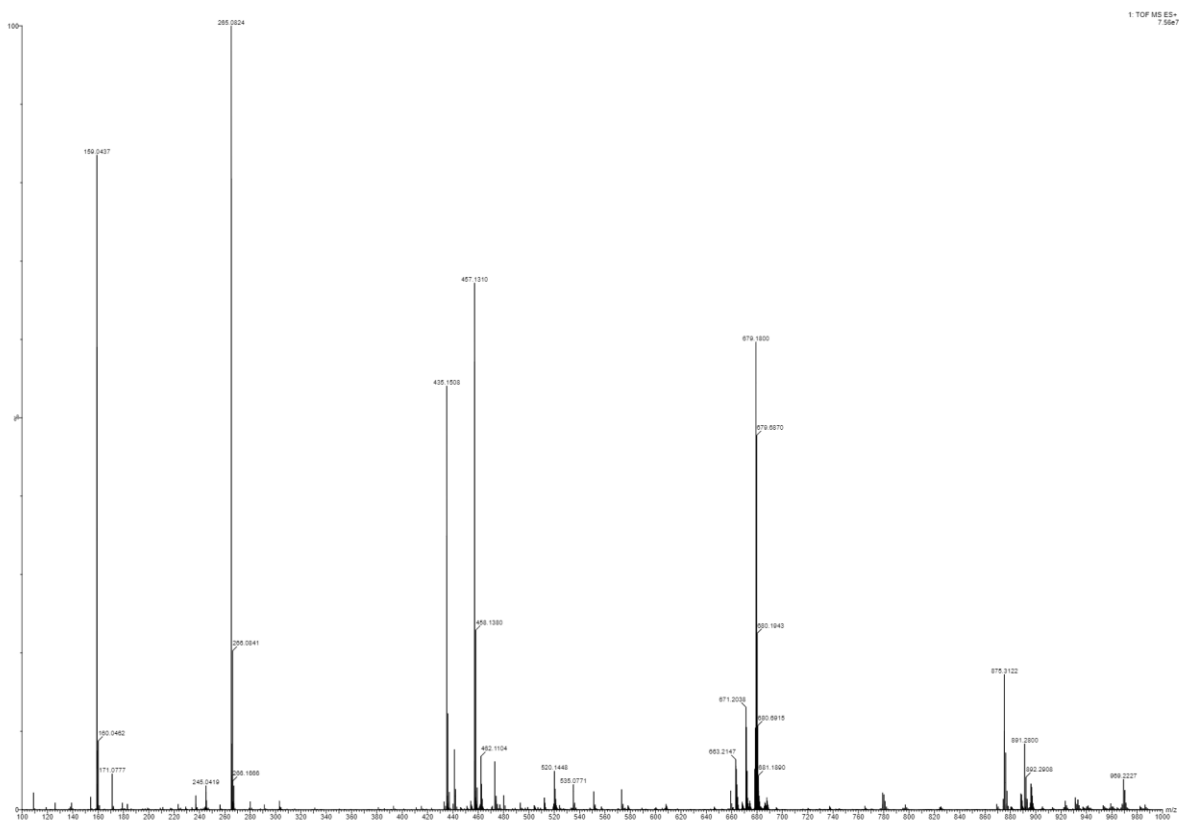
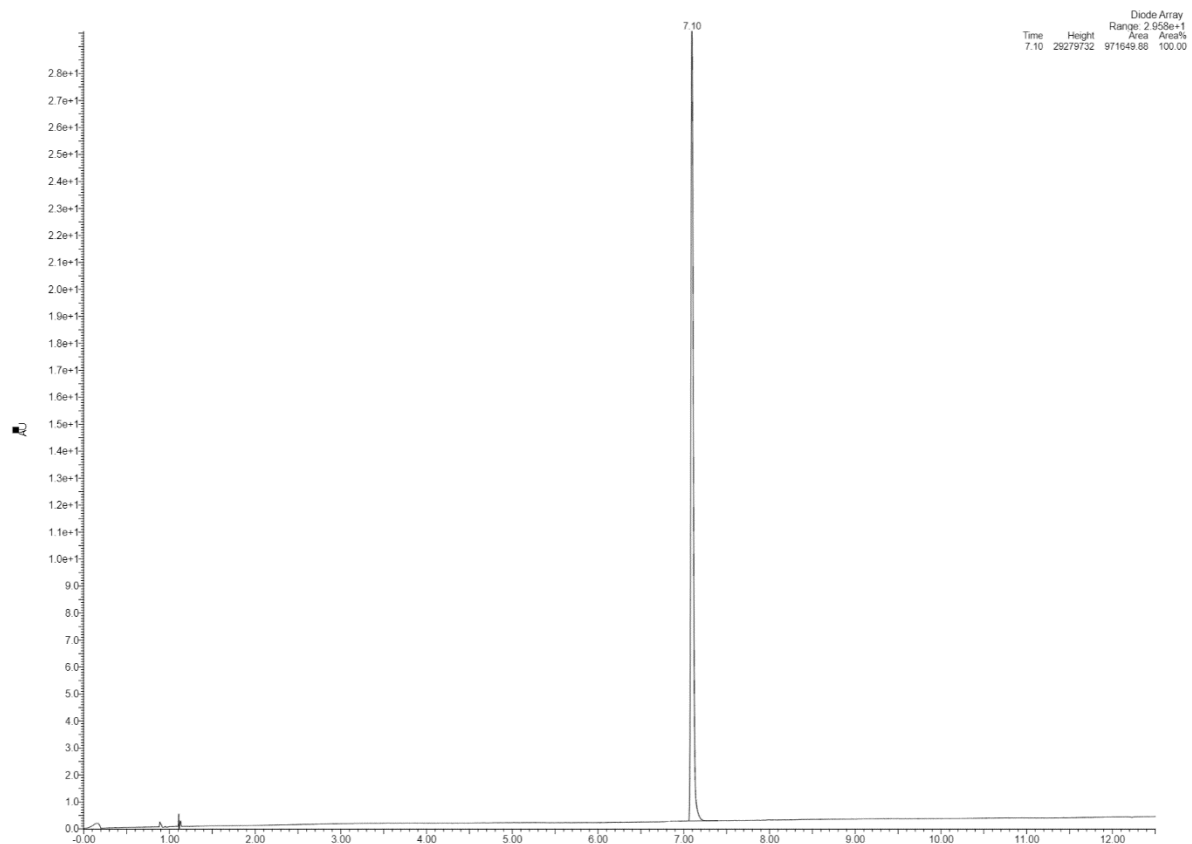
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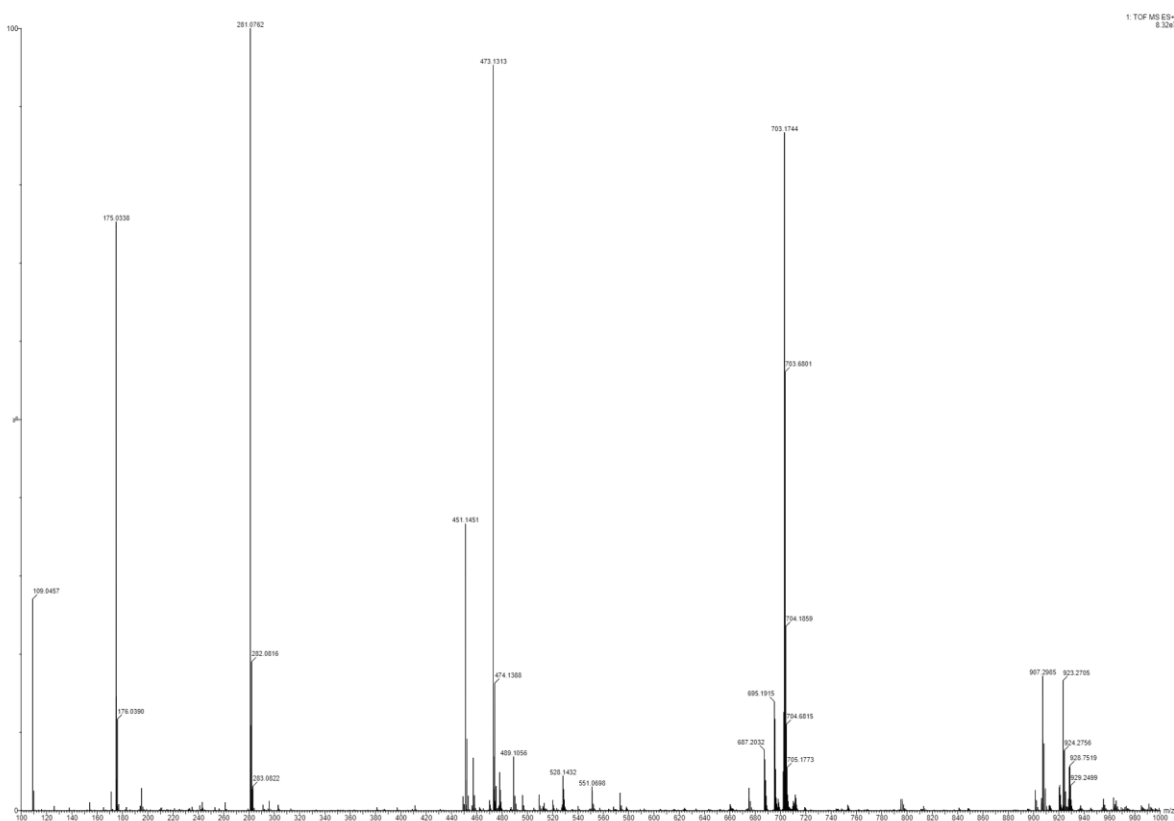
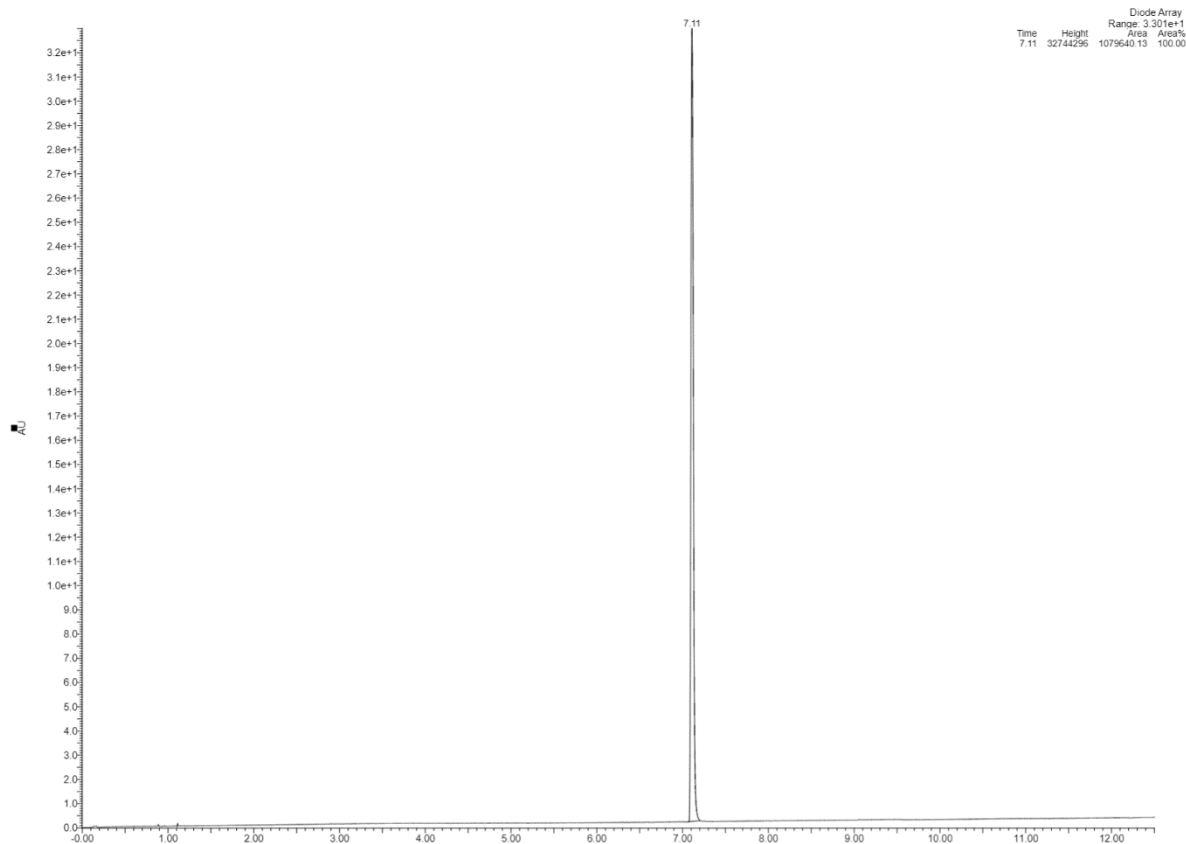
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethyl)benzyl)oxy)benzyl)propenamide  
(13)**



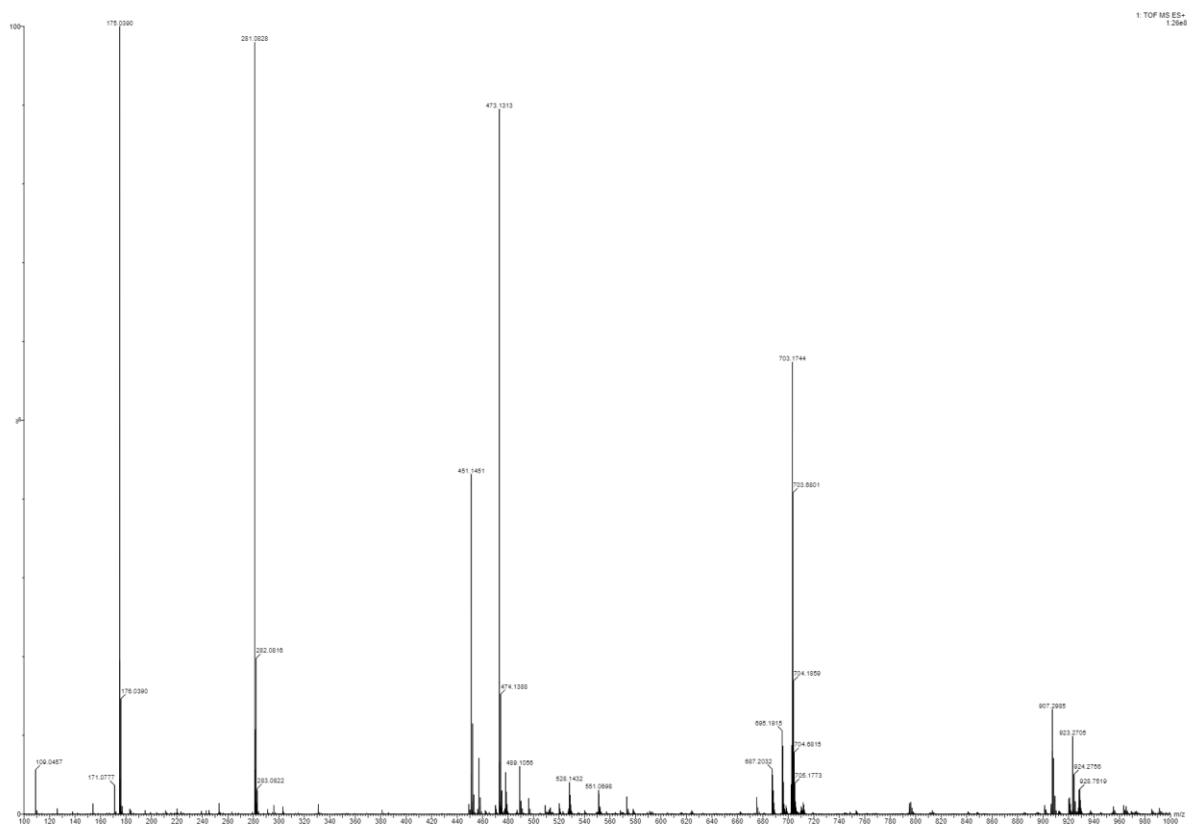
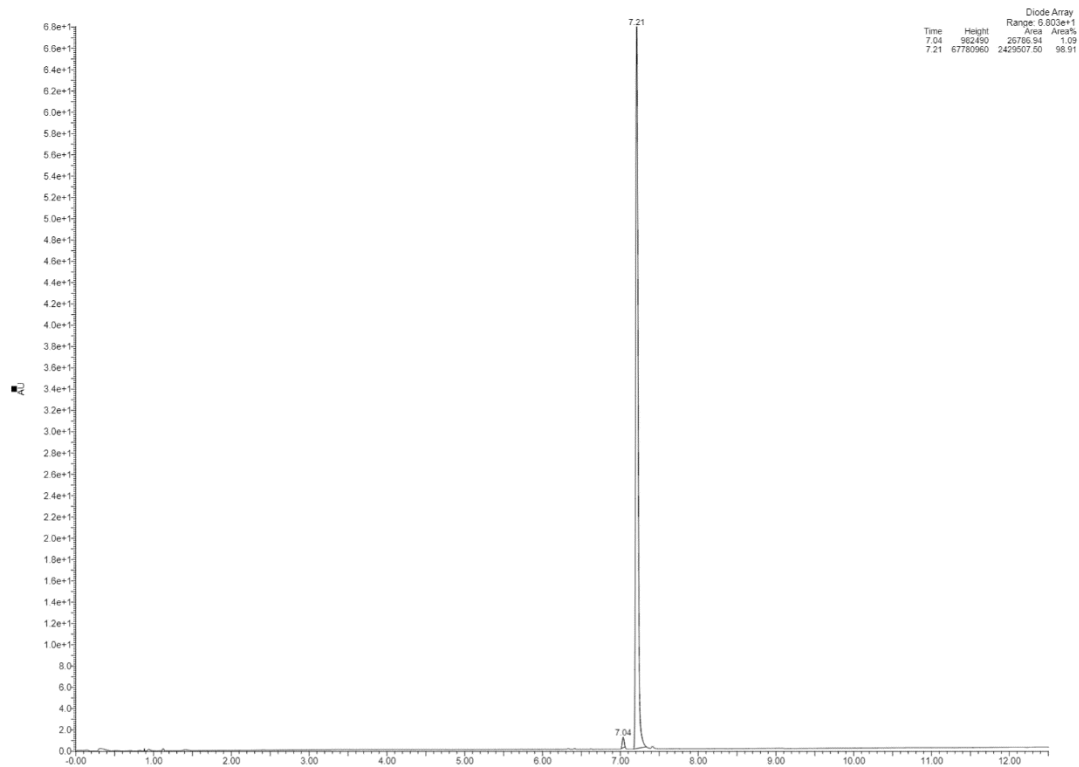
# **2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)propenamide (14)**



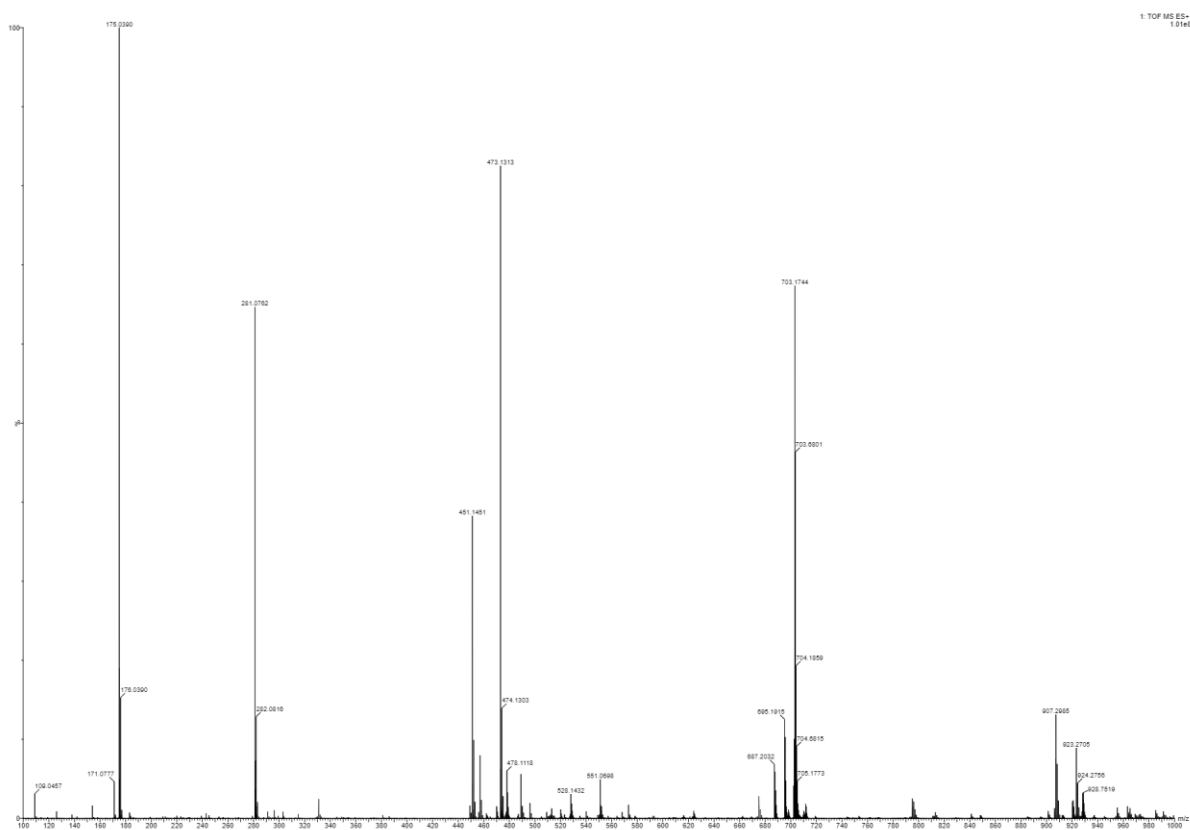
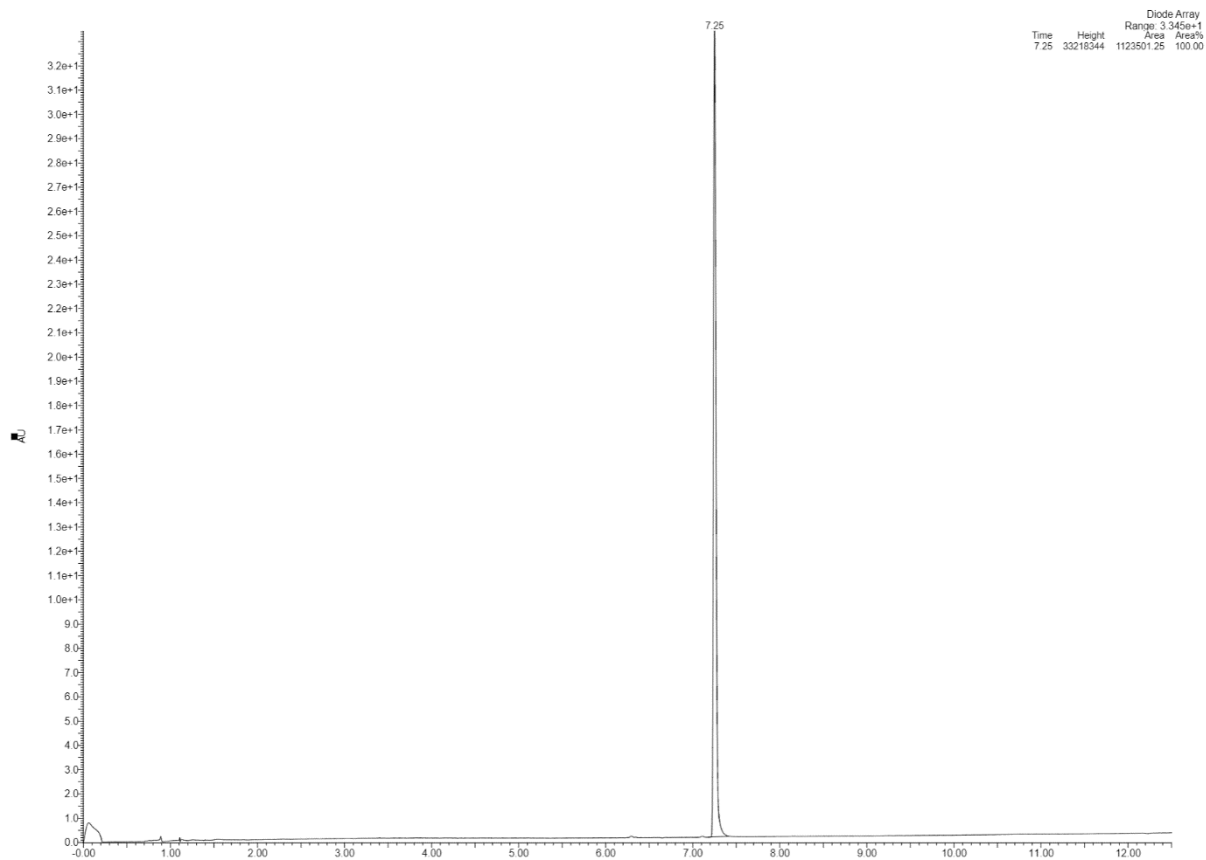
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide  
(15)**



# 2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethoxy)benzyl)oxy)benzyl)propenamide (16)

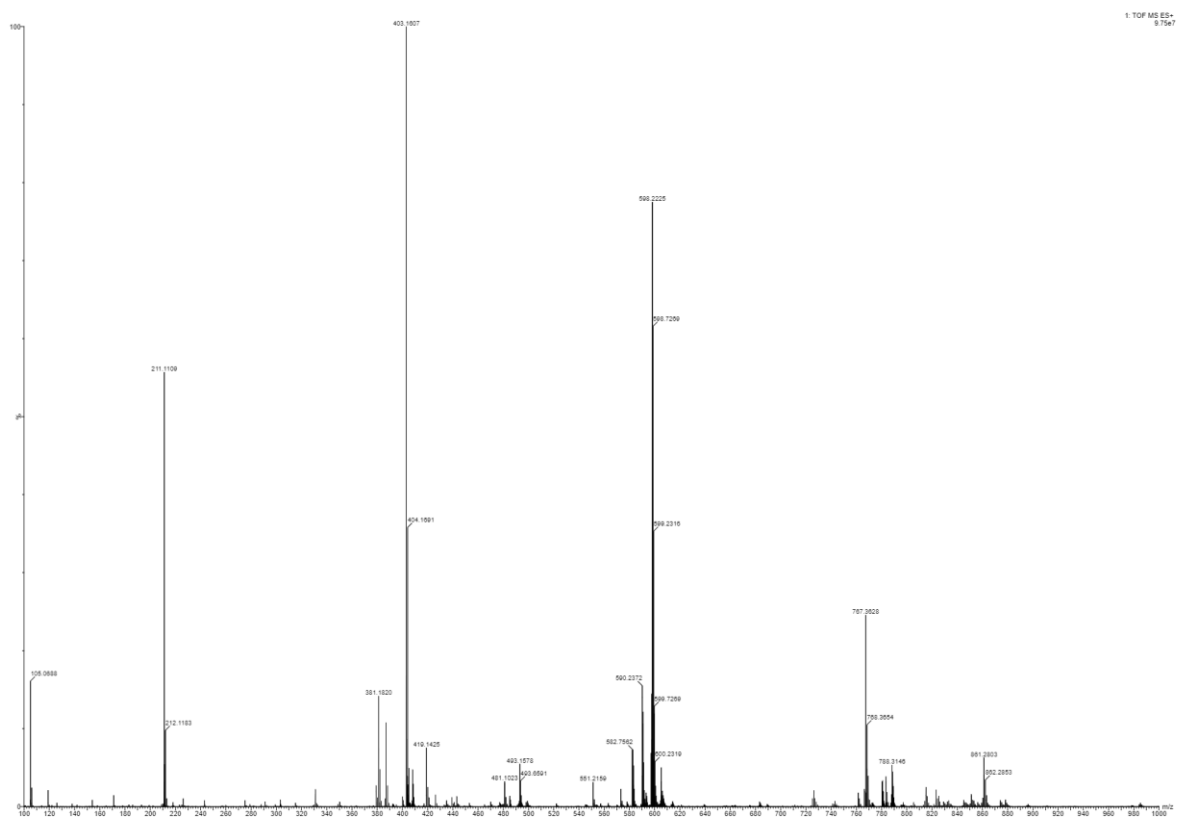
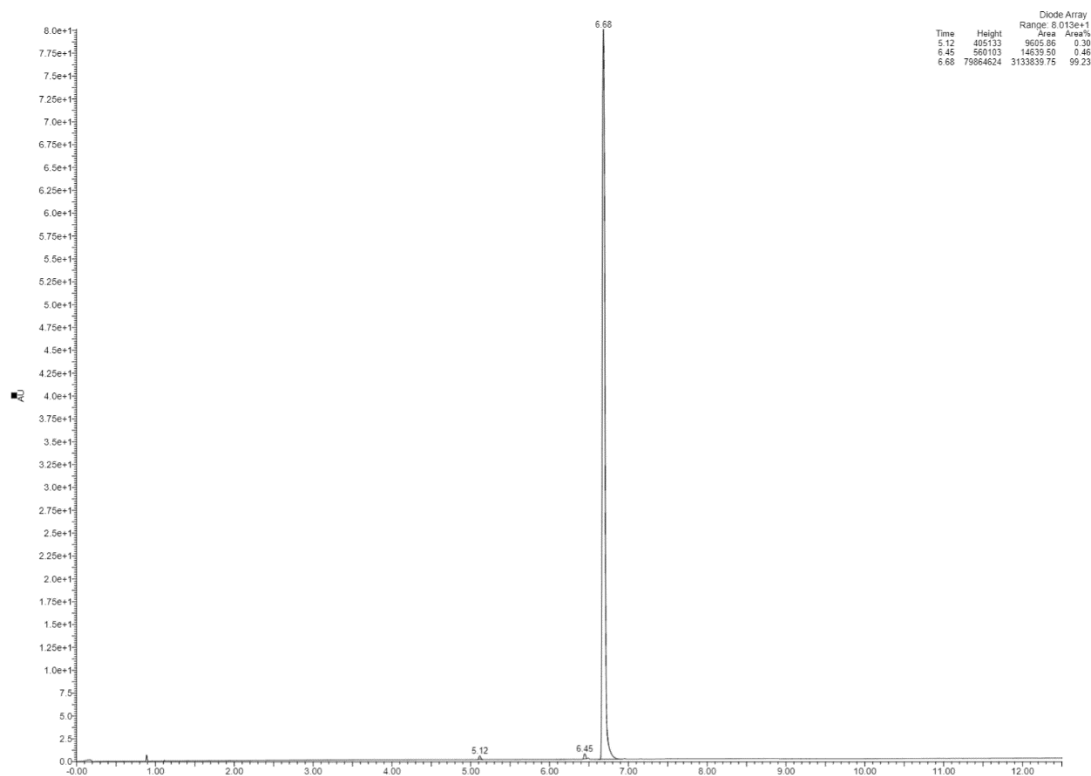


**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide  
(17)**

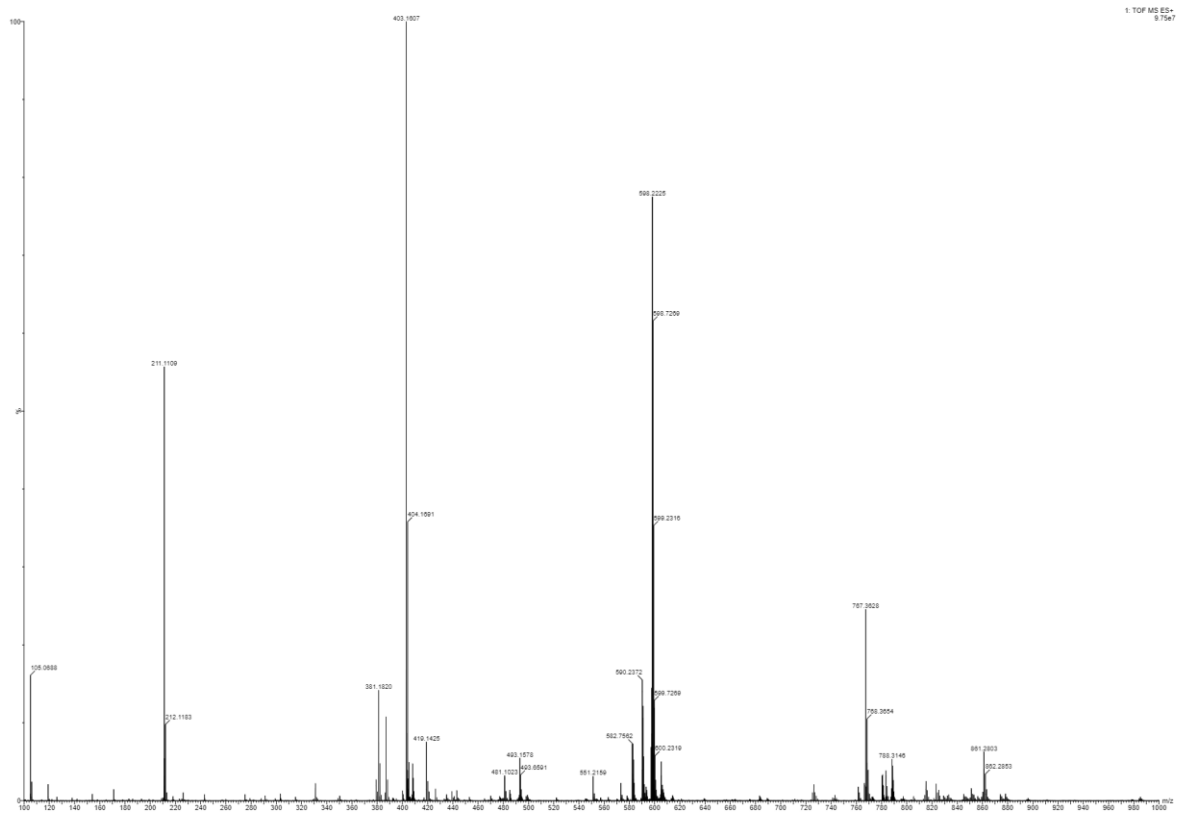
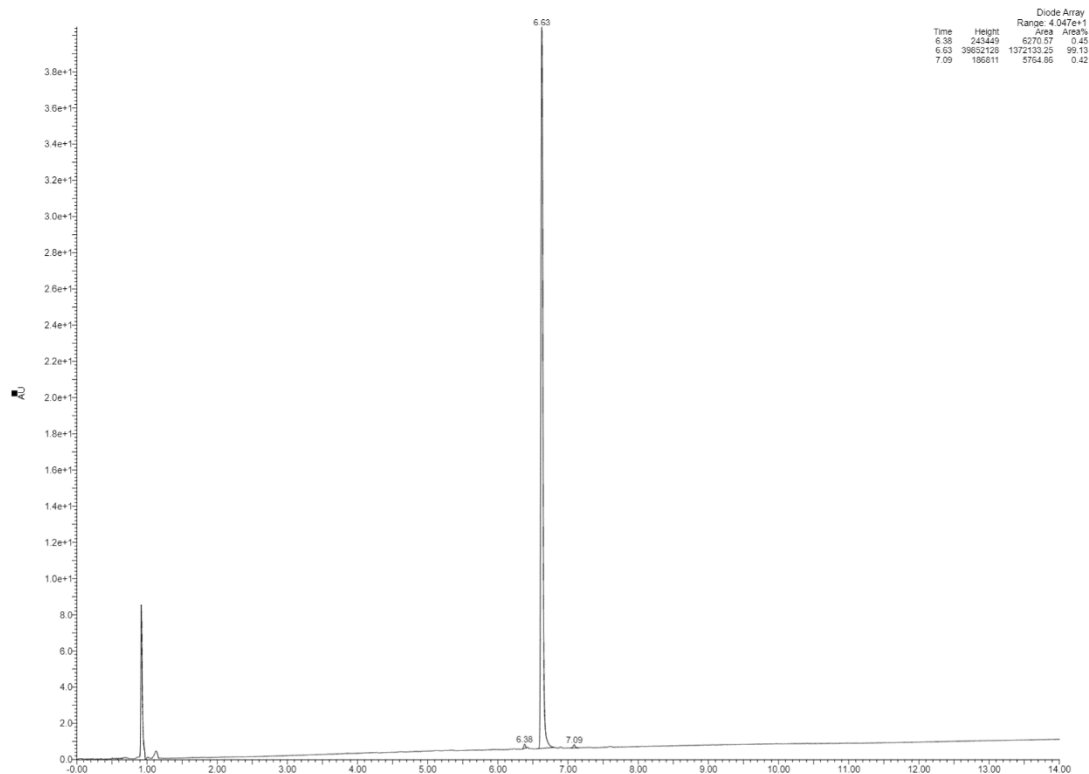




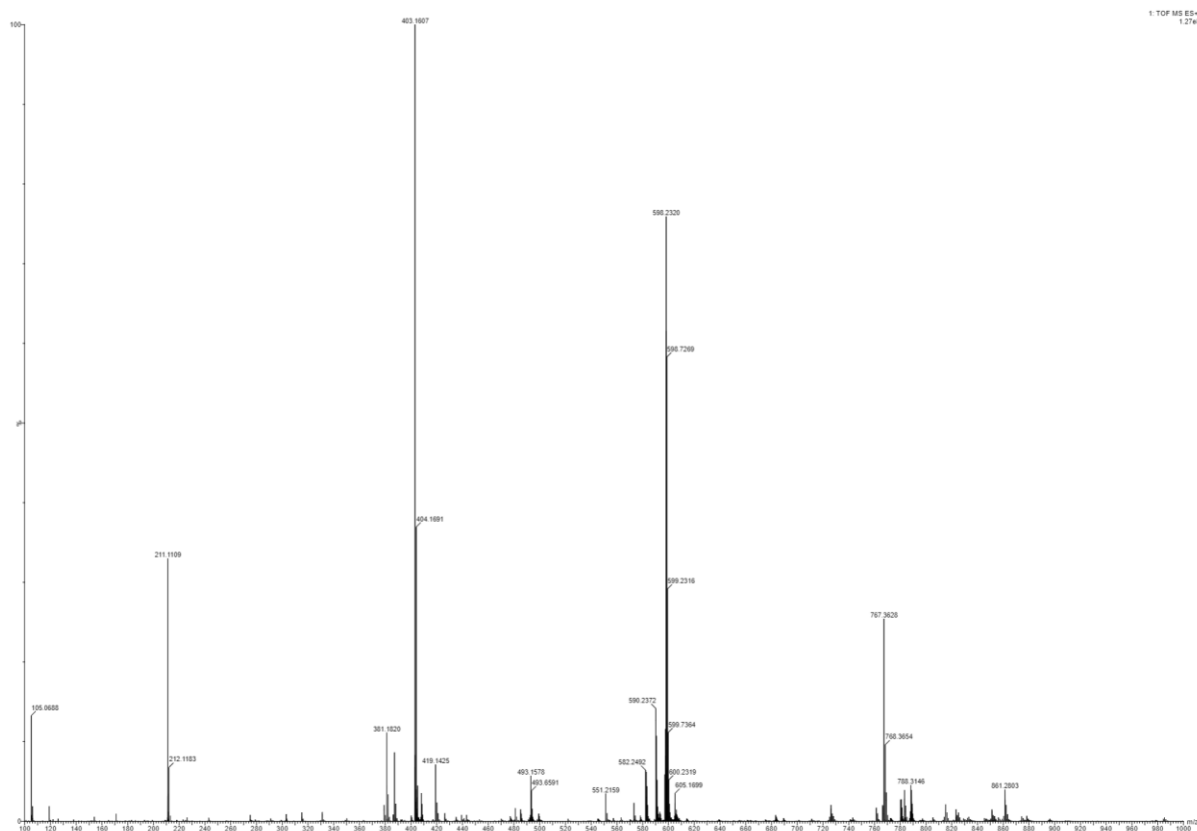
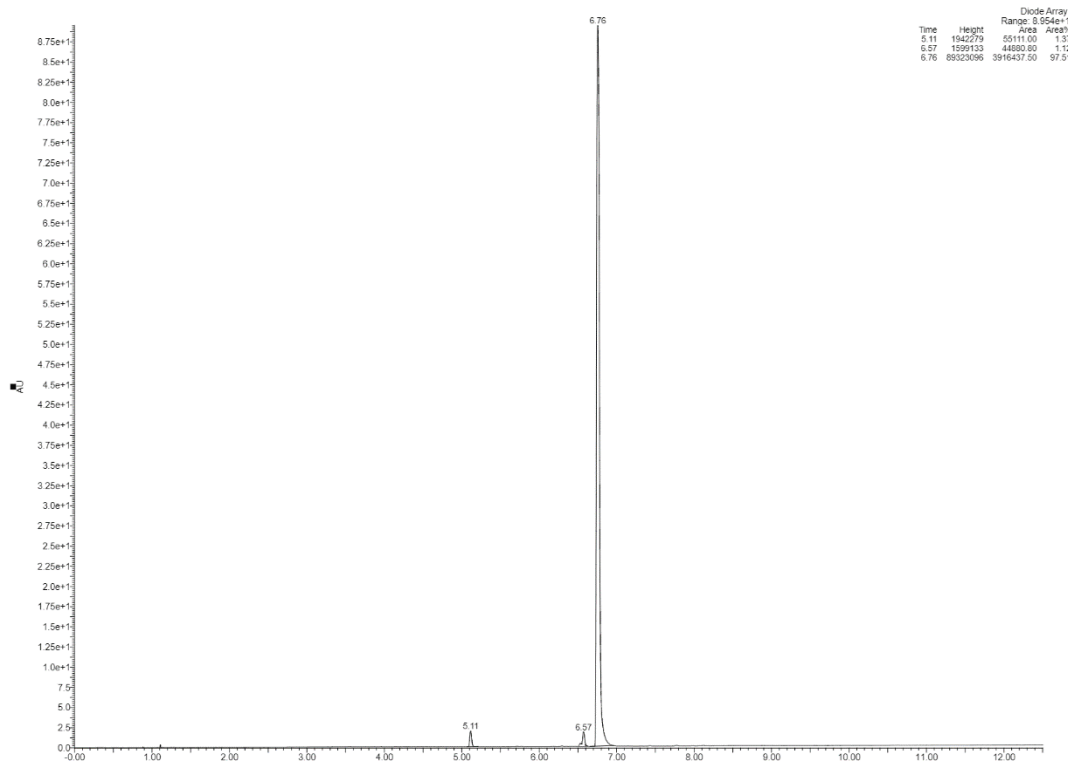
## 2-(2,5-dioxopyrrolidin-1-yl)-N-((2-methylbenzyl)oxy)benzylpropanamide (18)



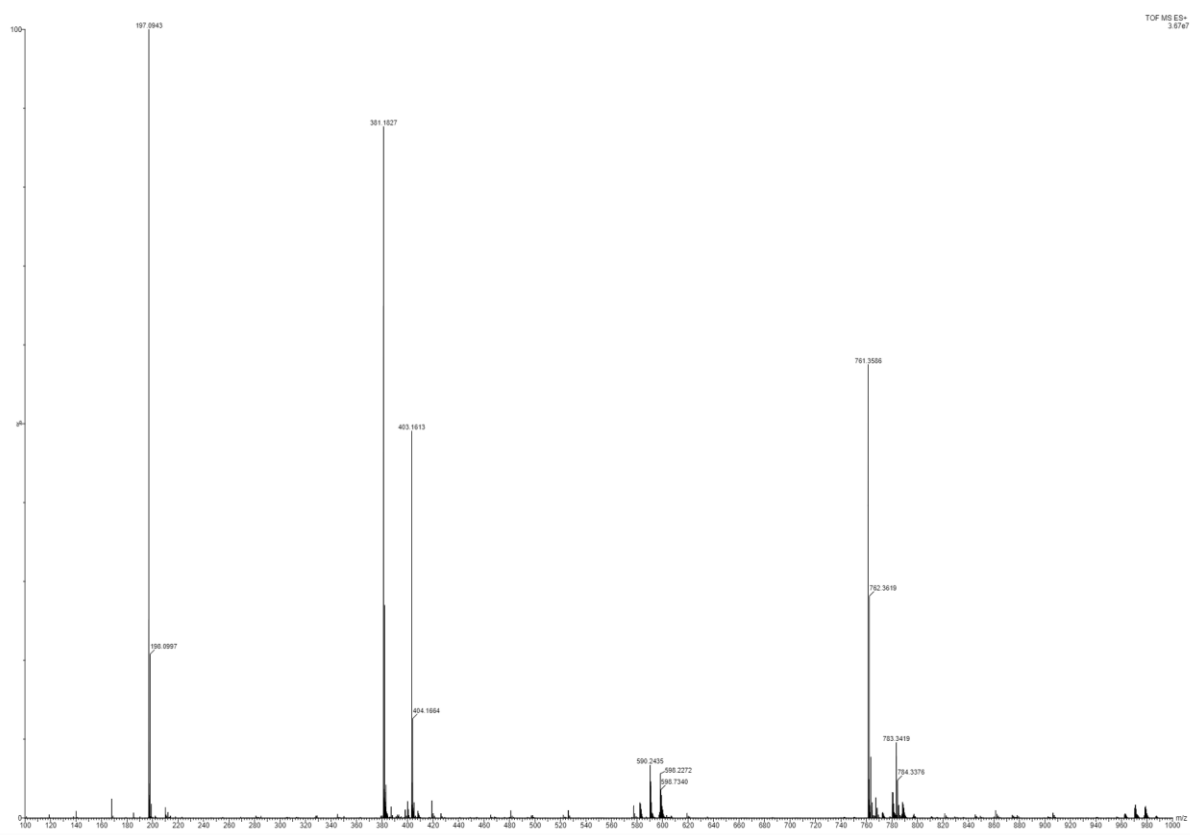
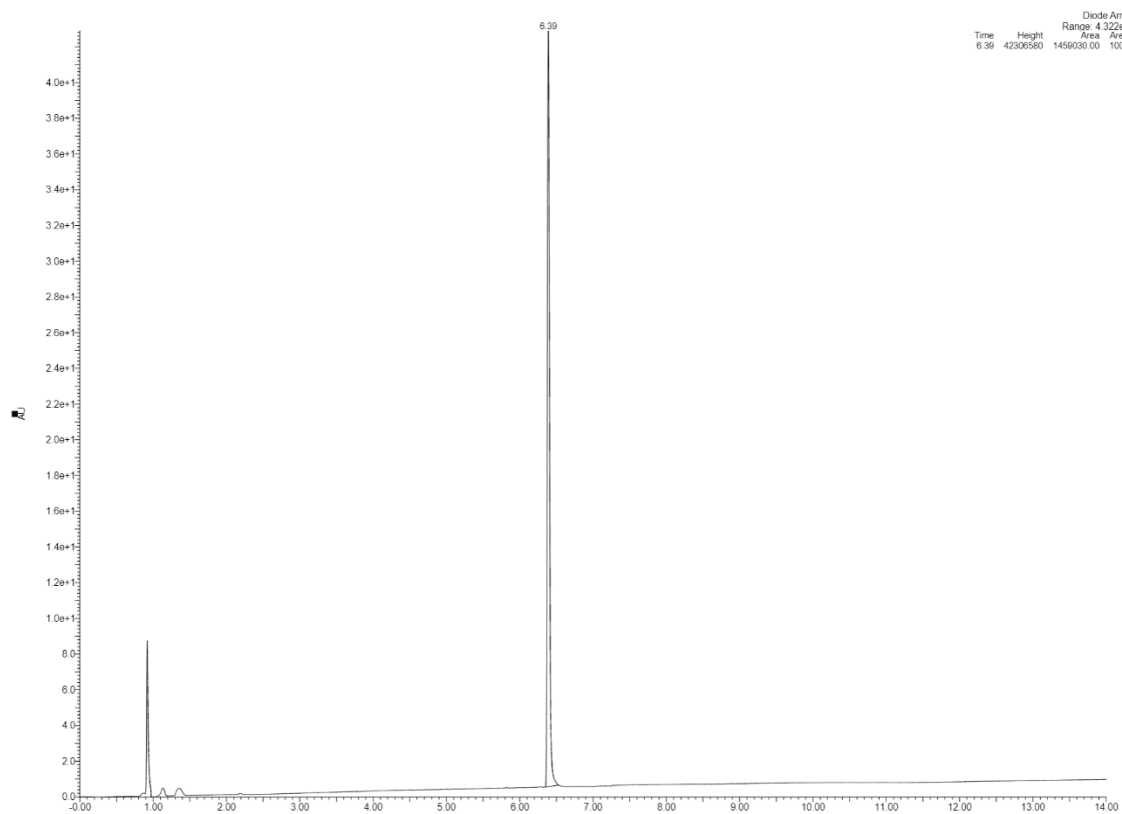
## 2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-methylbenzyl)oxy)benzyl)propanamide (19)



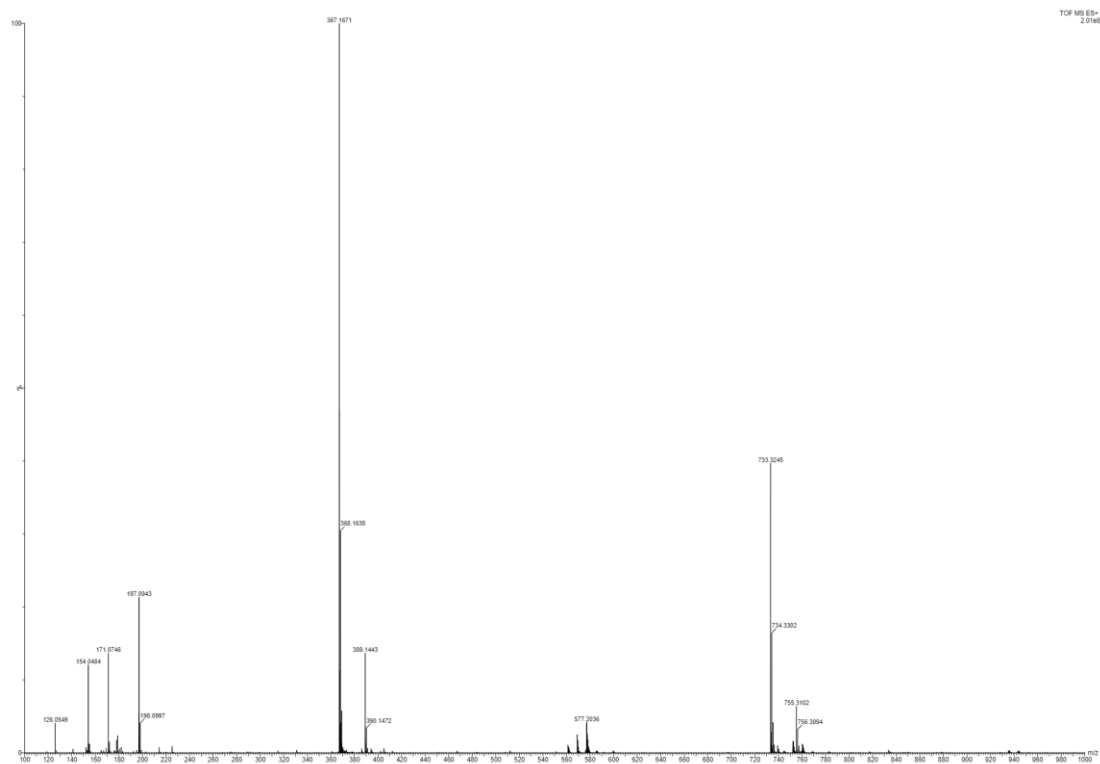
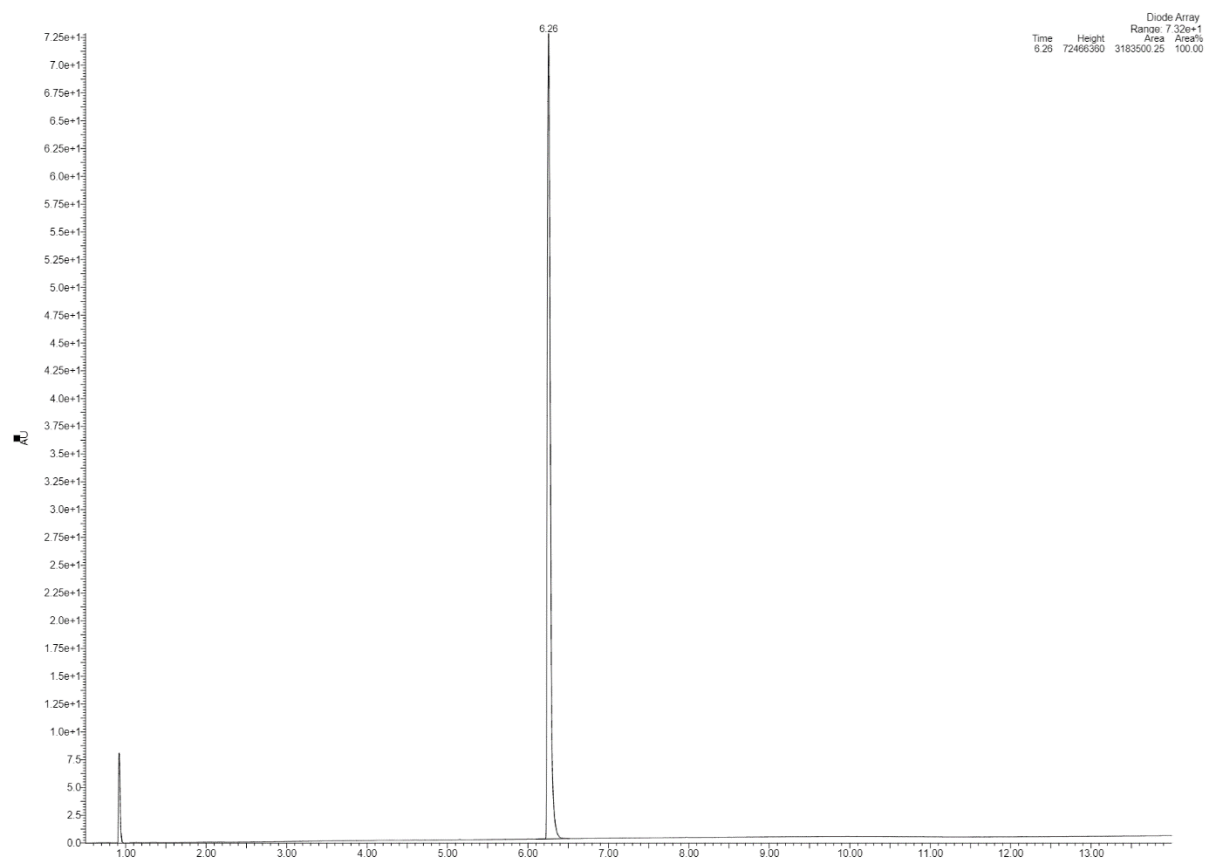
## 2-(2,5-dioxopyrrolidin-1-yl)-N-((4-(4-methylbenzyl)oxy)benzyl)propanamide (20)



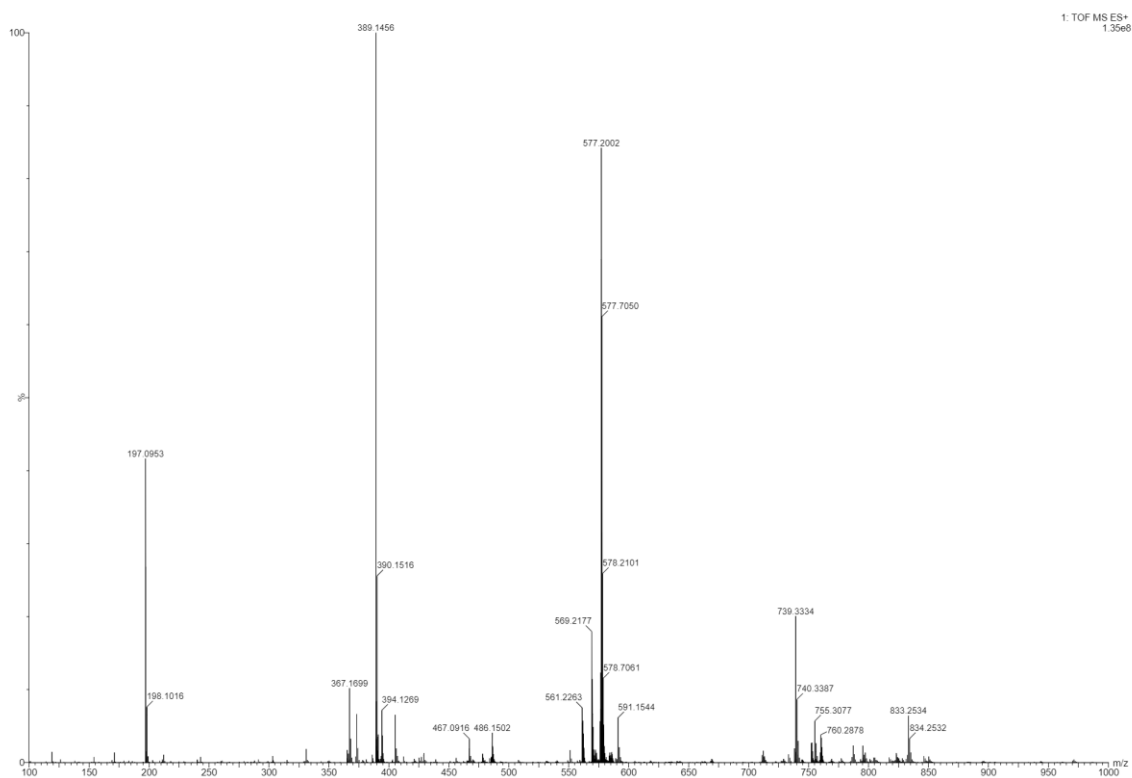
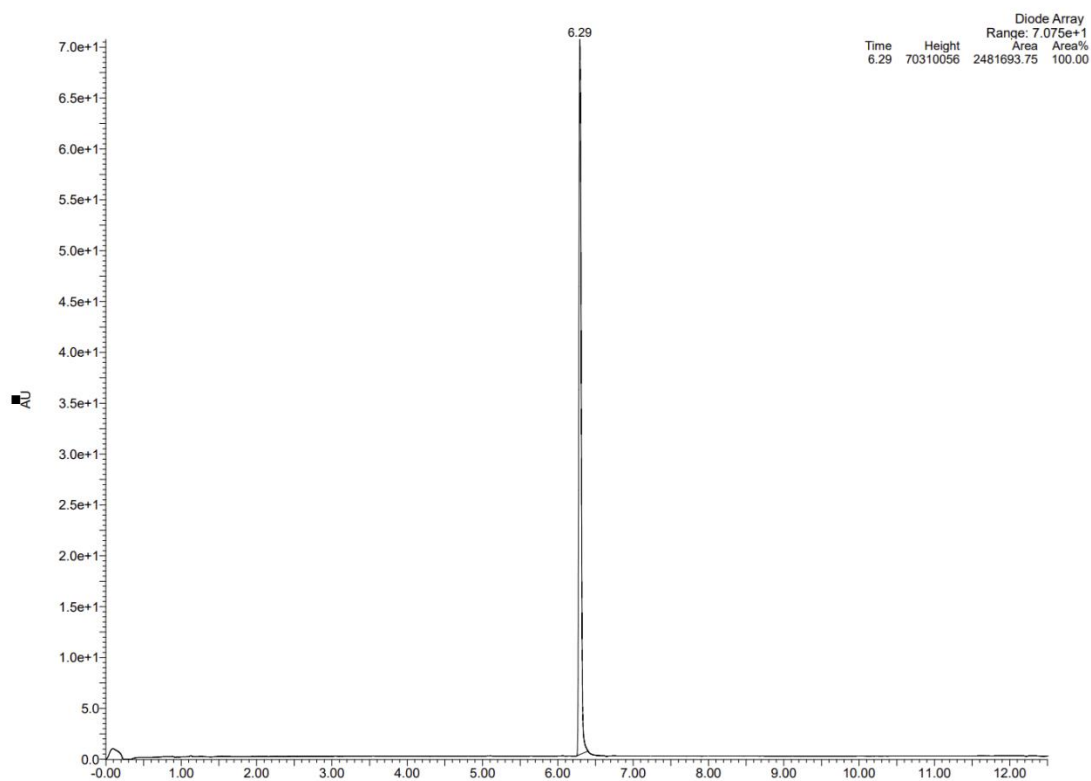
# ***N*-(4-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)-2-methylpropanamide (21)**



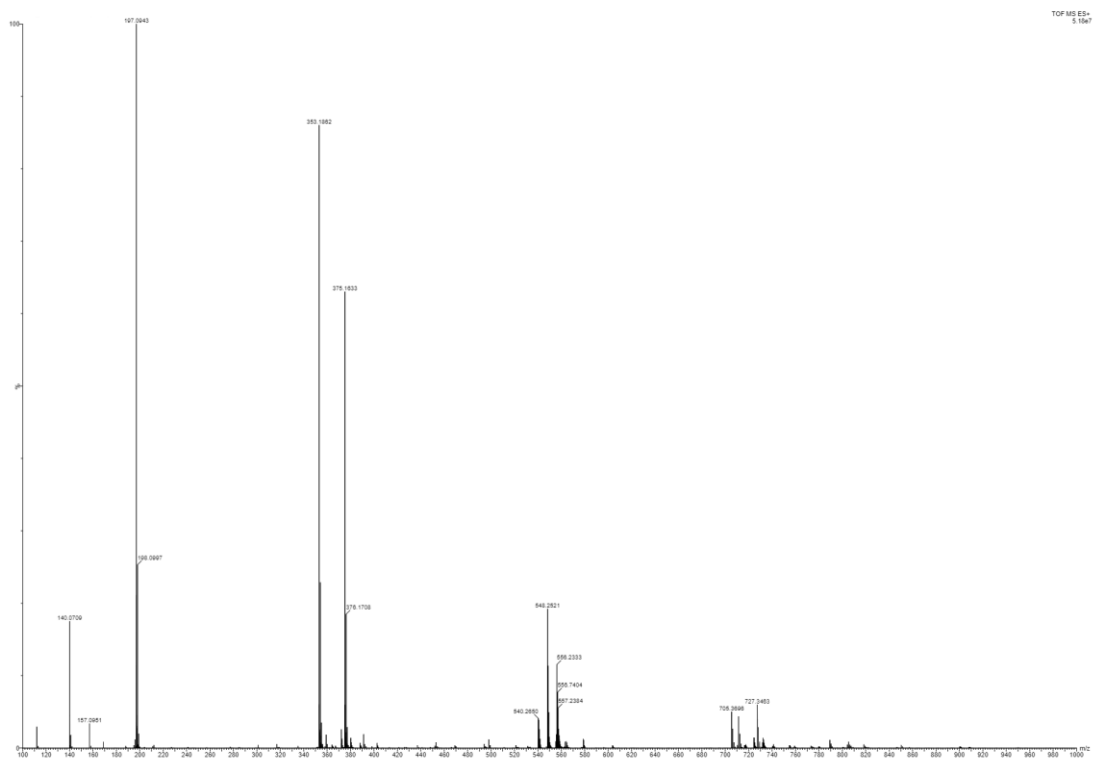
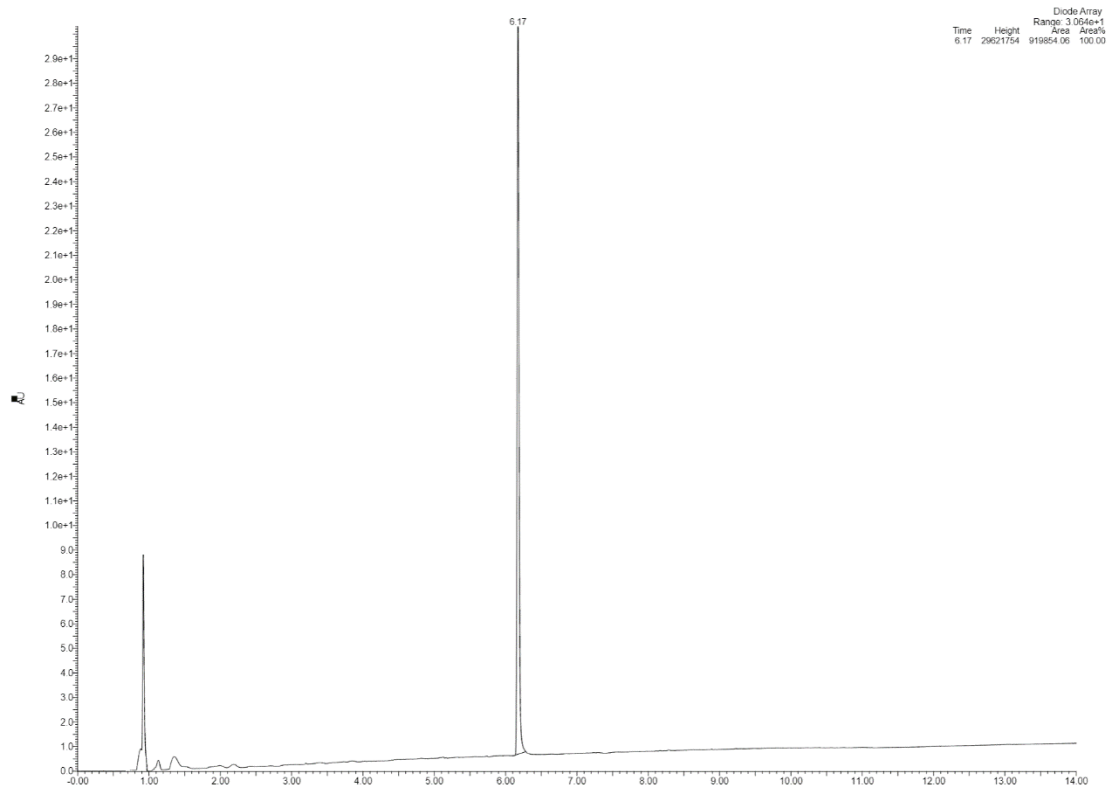
***N*-(3-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (22)**



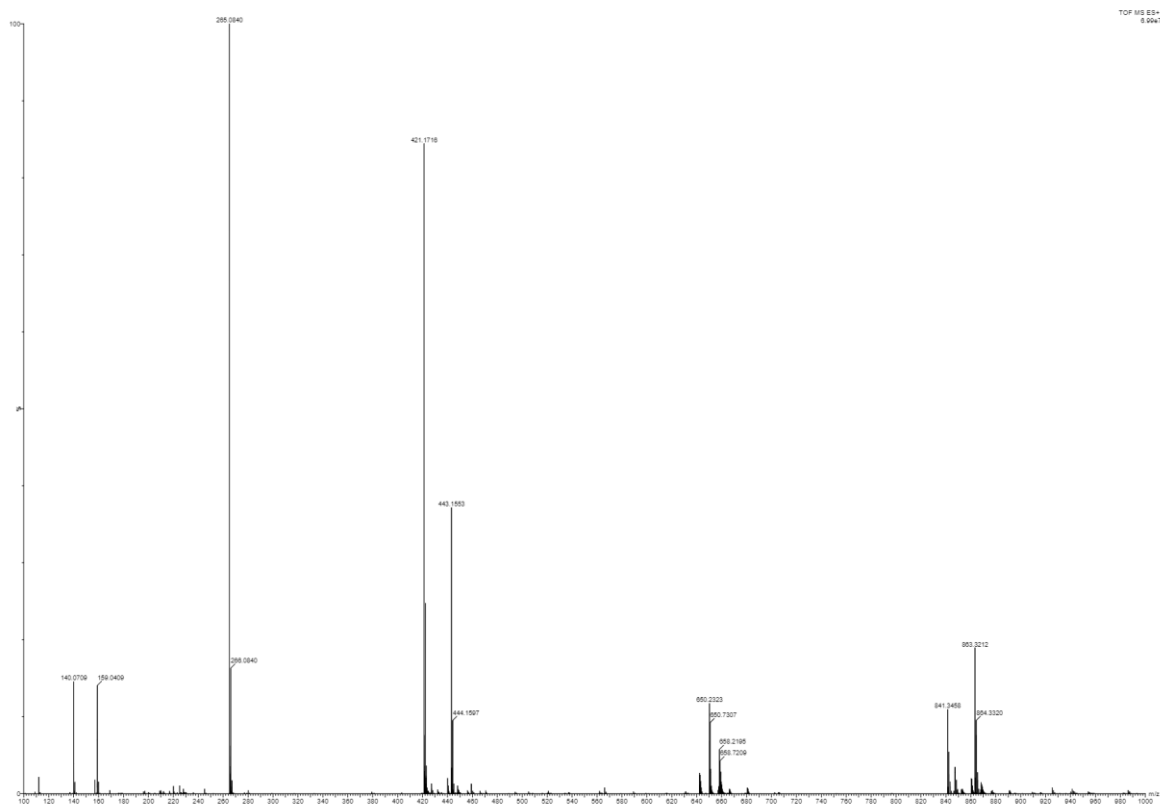
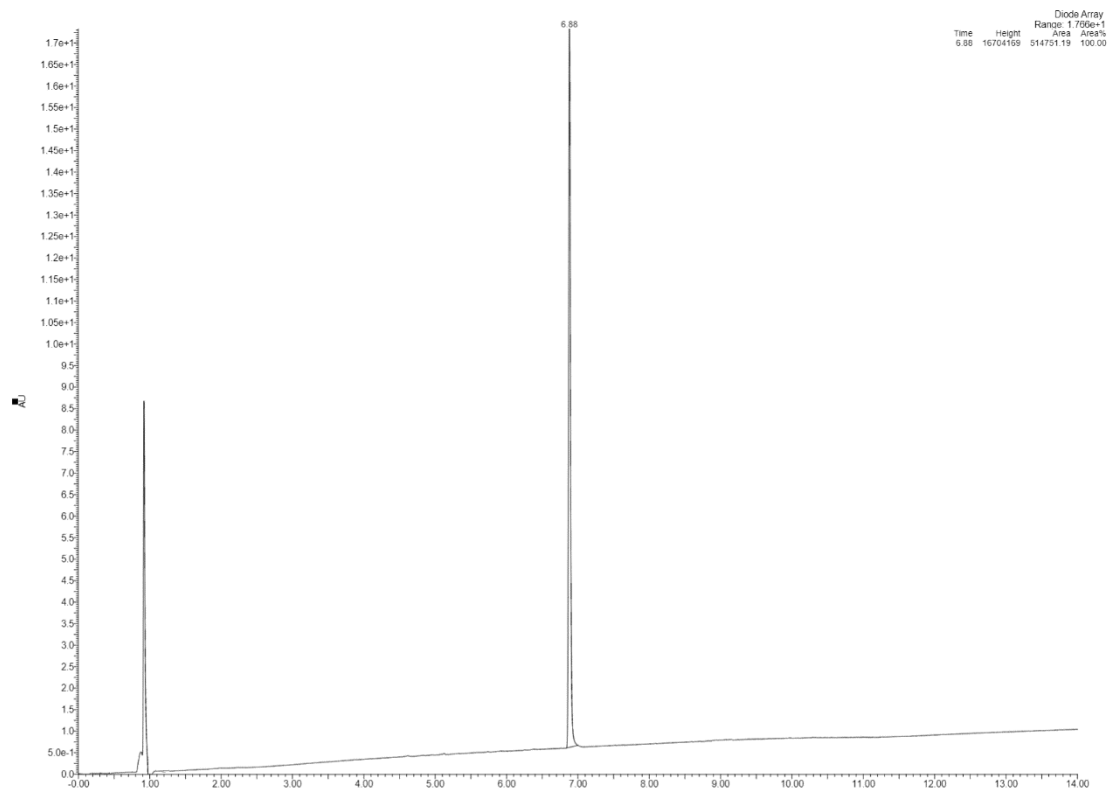
***N*-(2-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (AS-35) (23)**



# ***N*-(4-(benzyloxy)benzyl)-2-(2-oxopyrrolidin-1-yl)propanamide (36)**

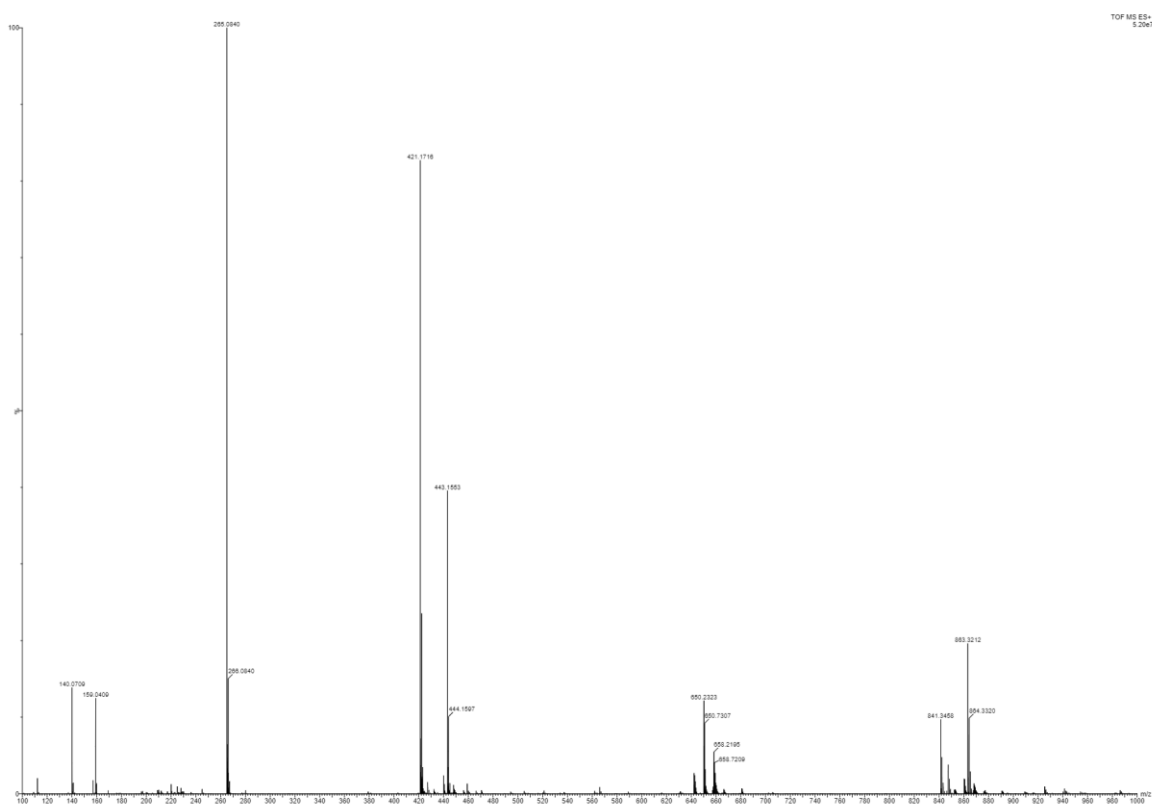
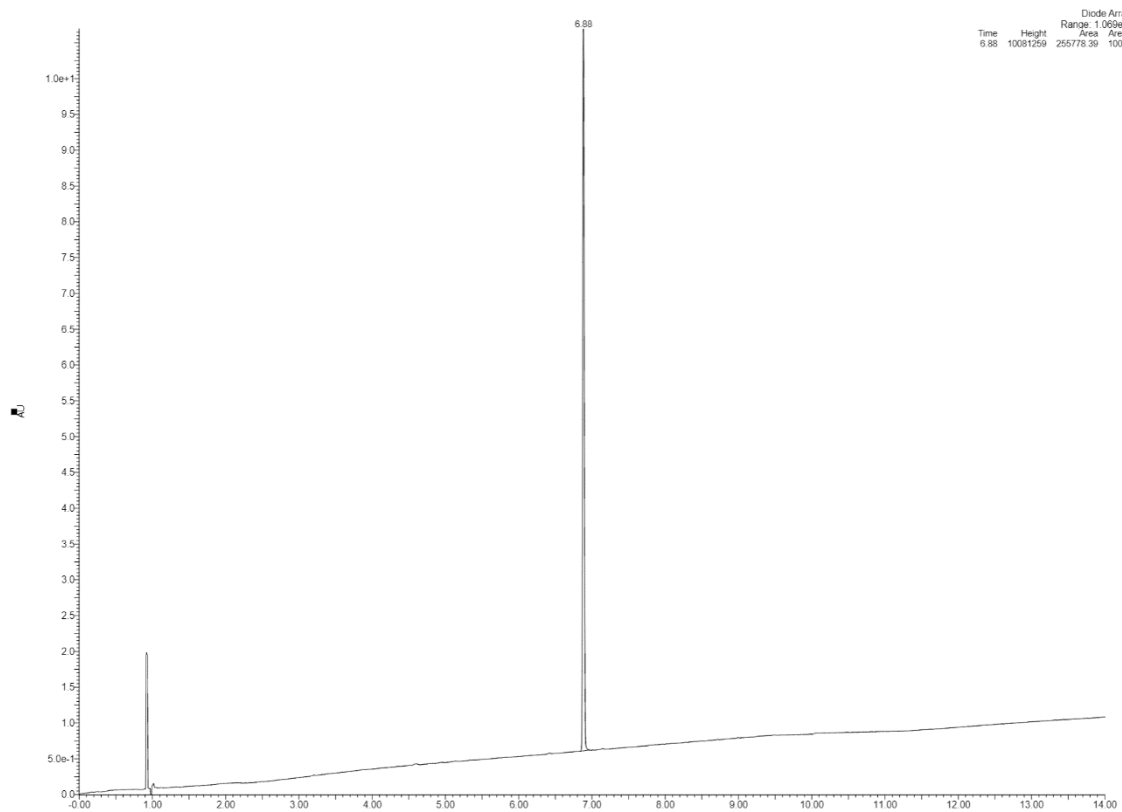


## 2-(2-oxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (37)

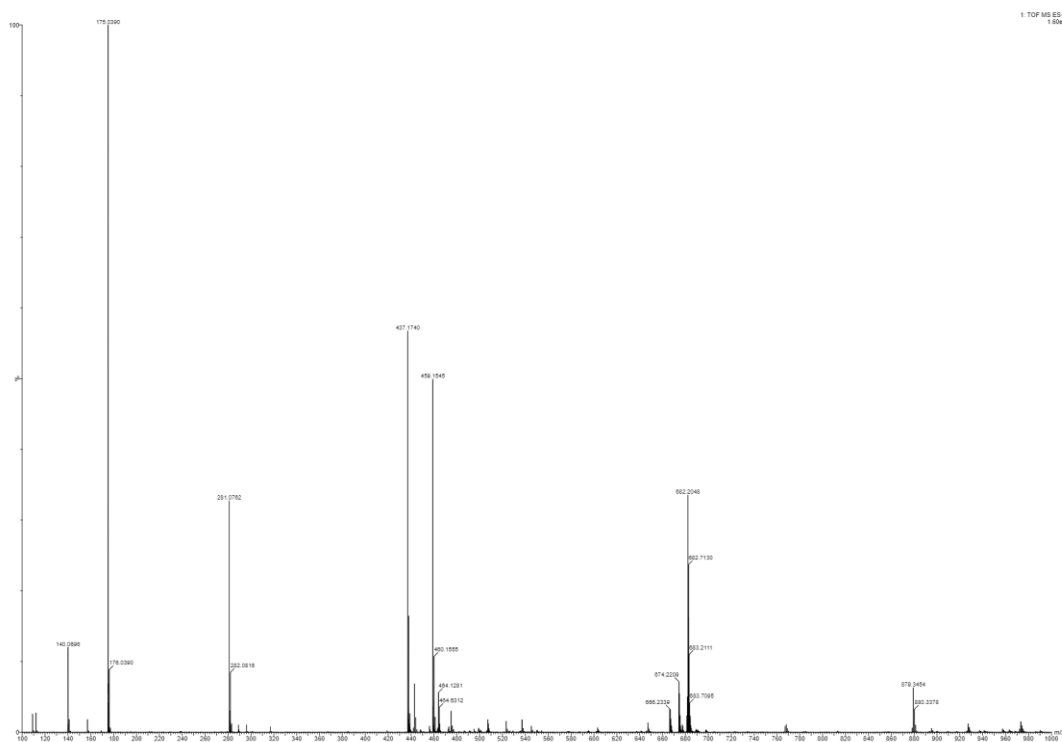
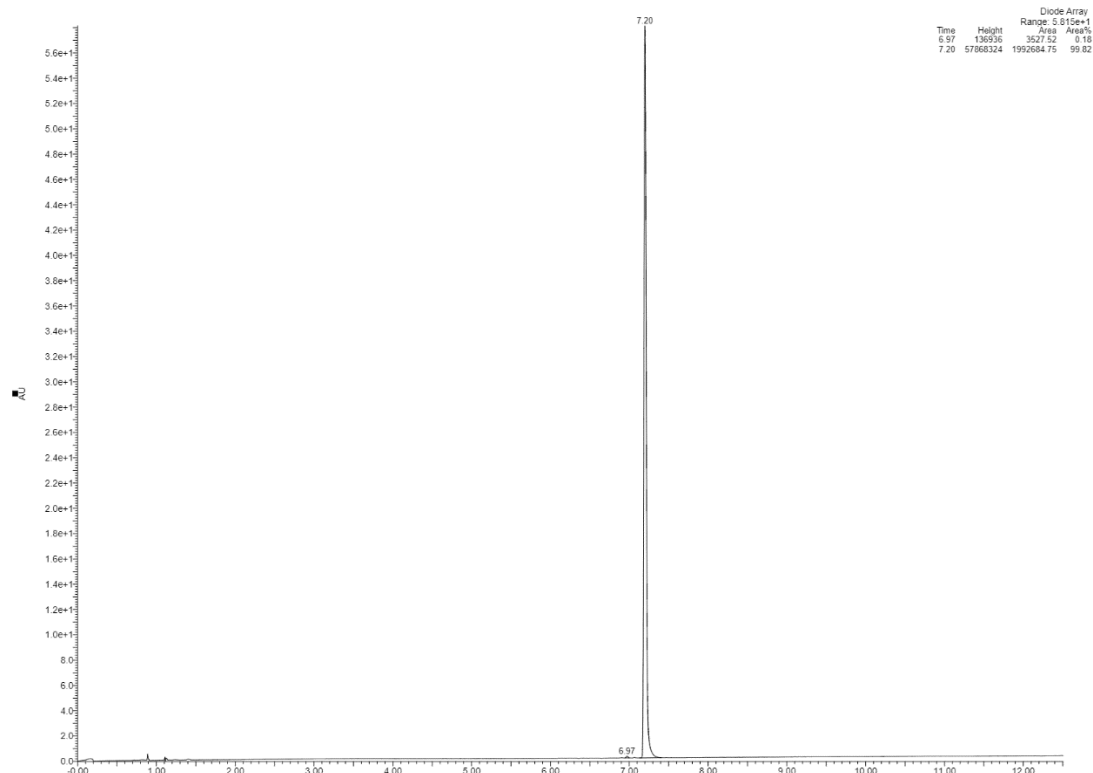




## 2-(2-oxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (38)

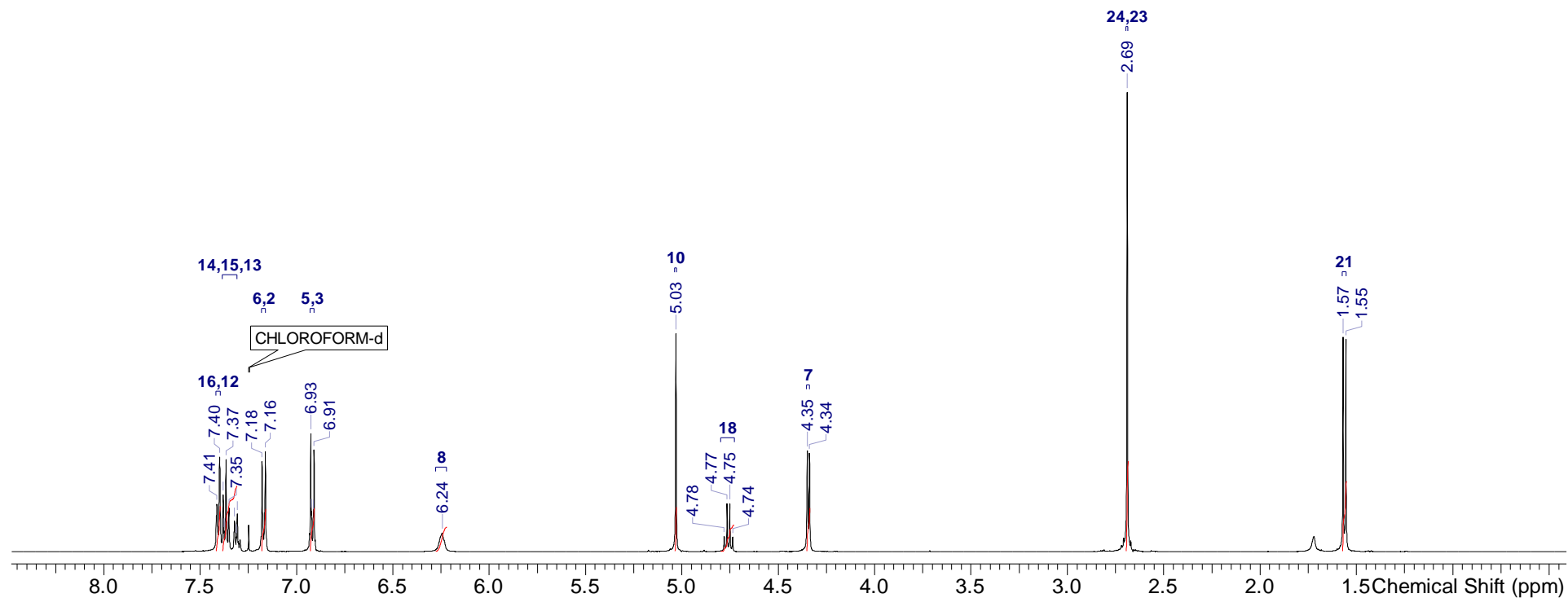
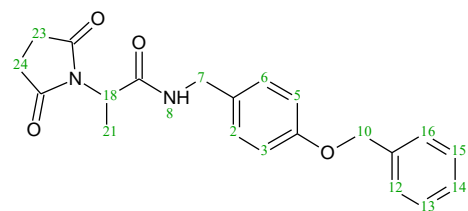


**2-(2-oxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide**  
(39)

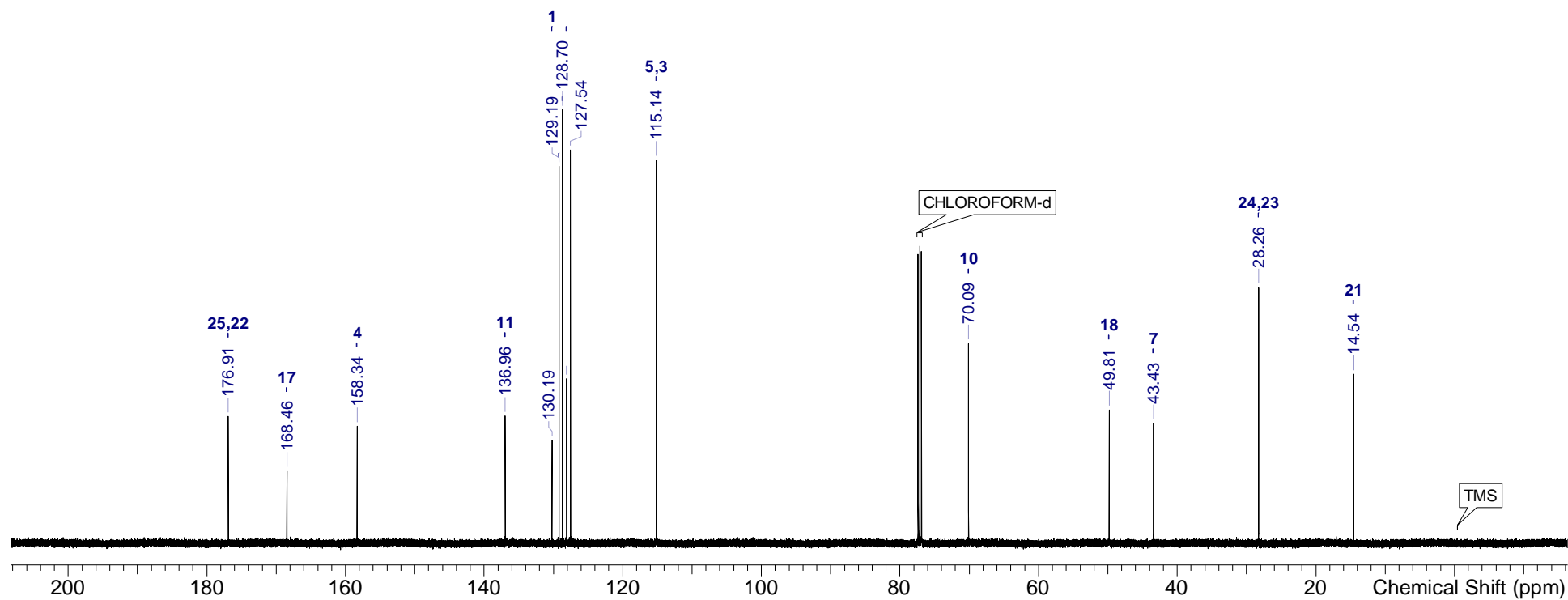
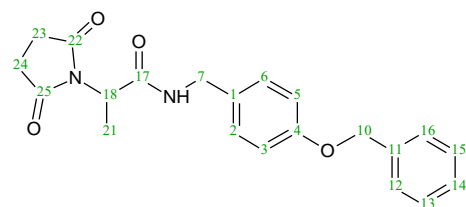


**$^1\text{H}$  NMR,  $^{13}\text{C}$  NMR spectra for all final compounds**

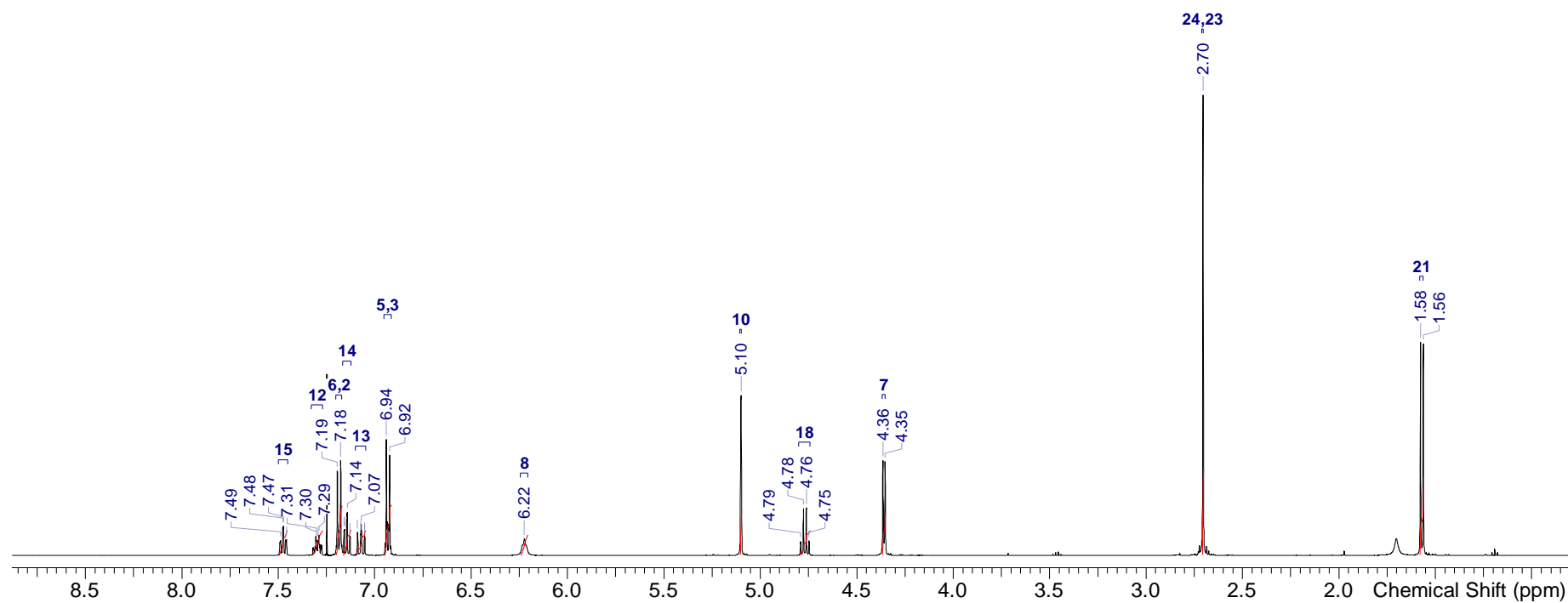
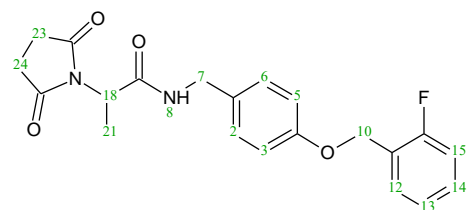
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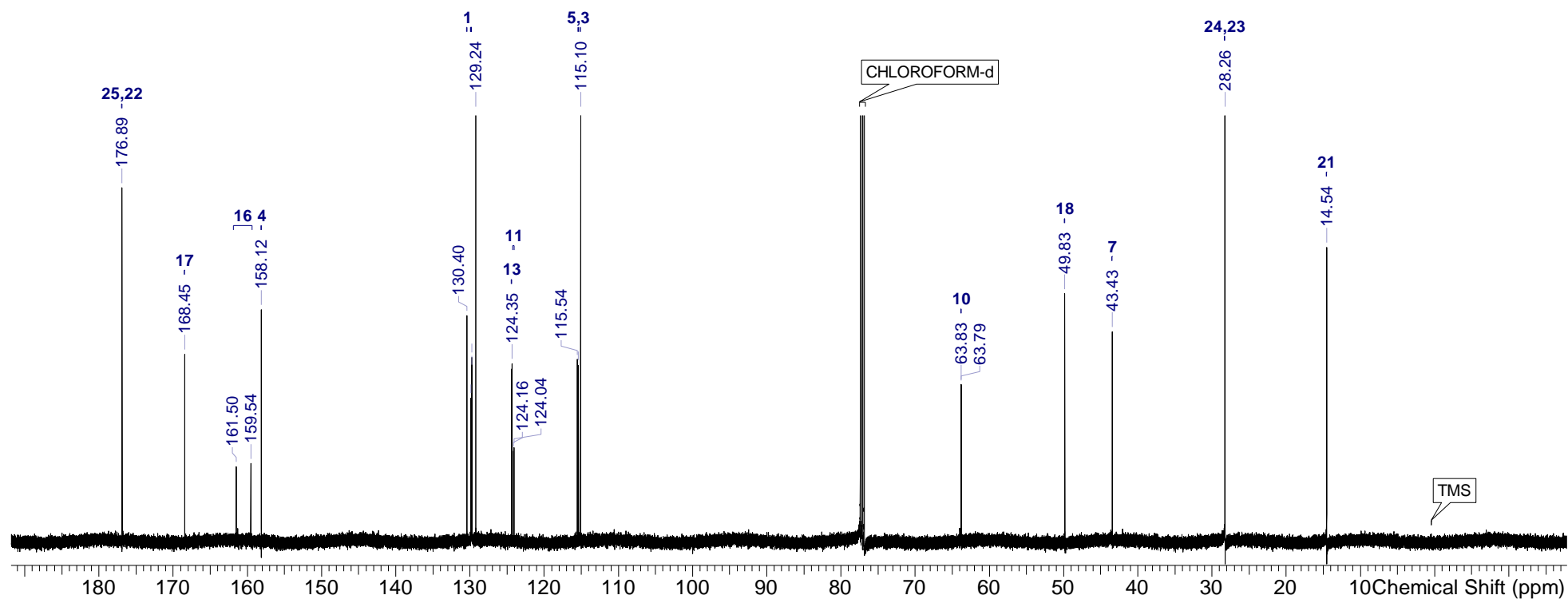
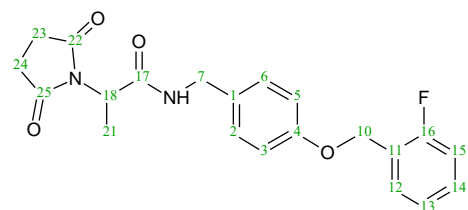
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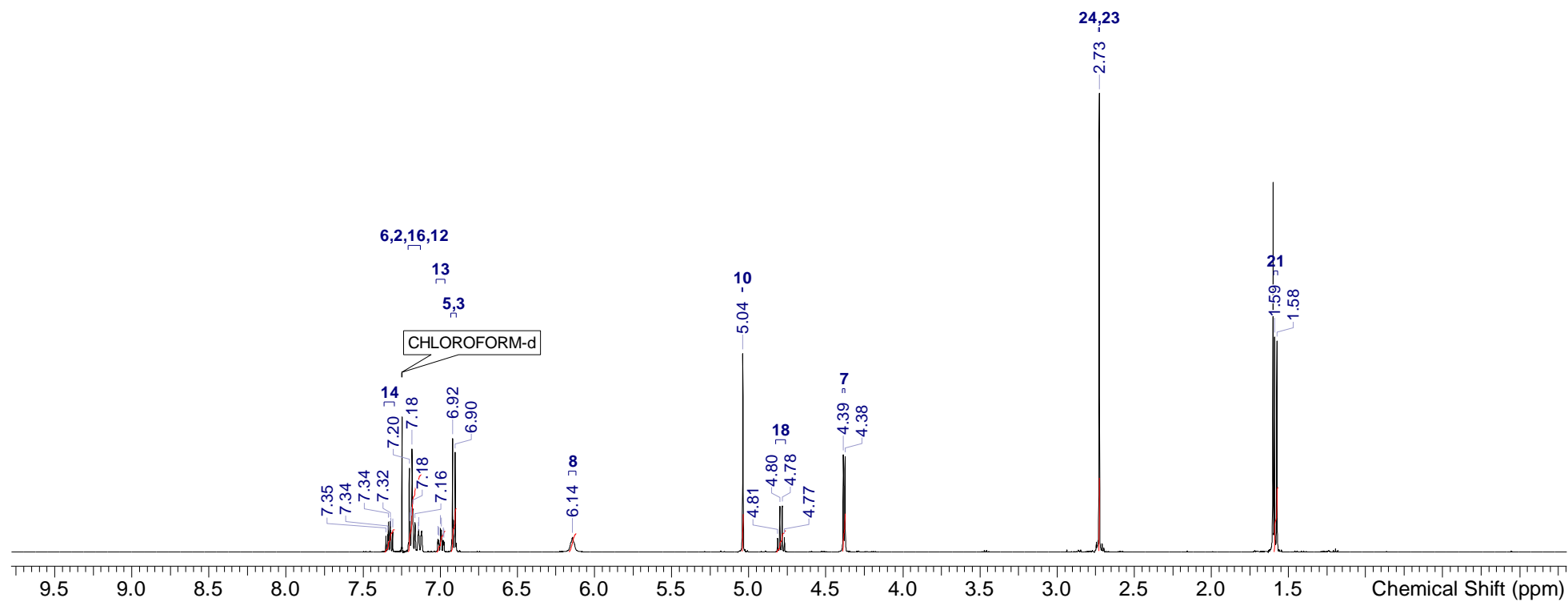
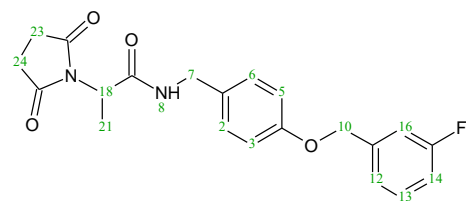
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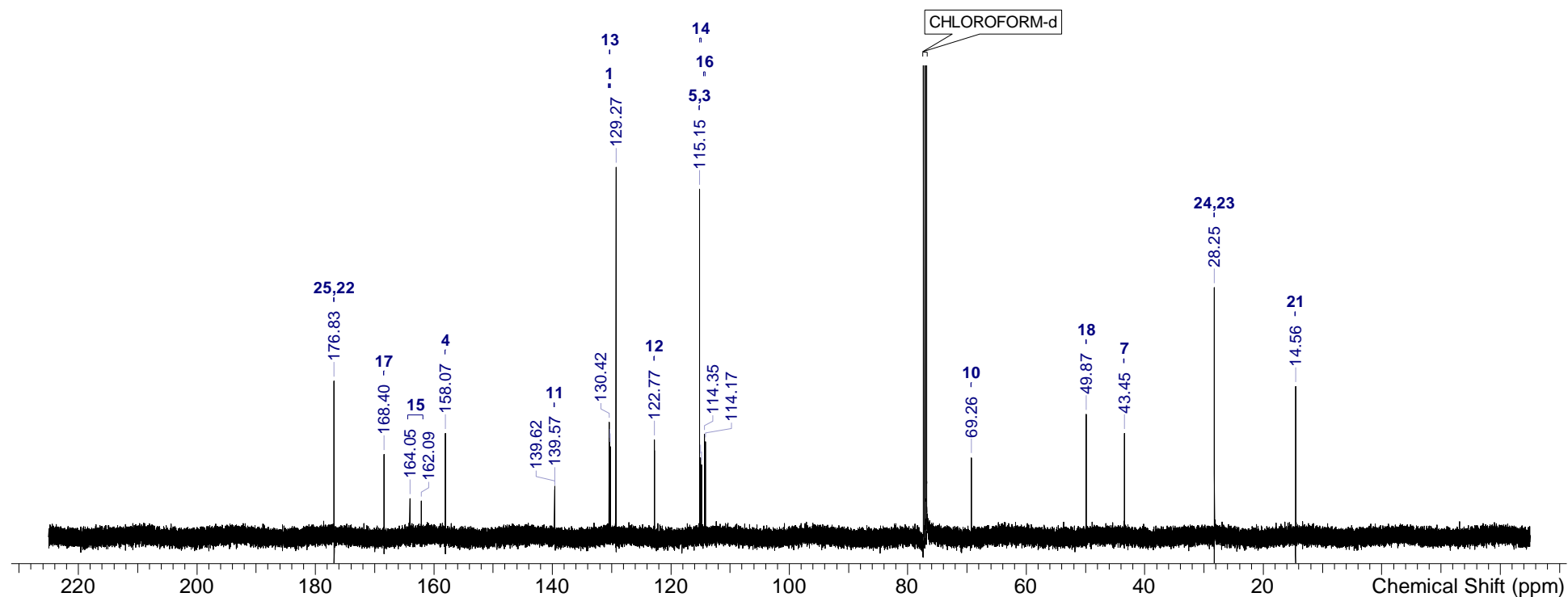
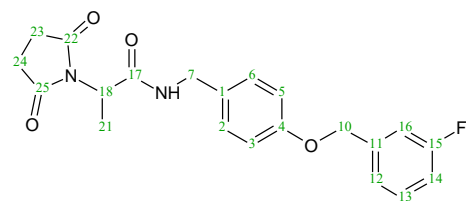
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-fluorobenzyl)oxy)benzyl)propanamide (6) –  $^{13}\text{C}$  NMR



**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-fluorobenzyl)oxy)benzyl)propanamide (7) – <sup>1</sup>H NMR**

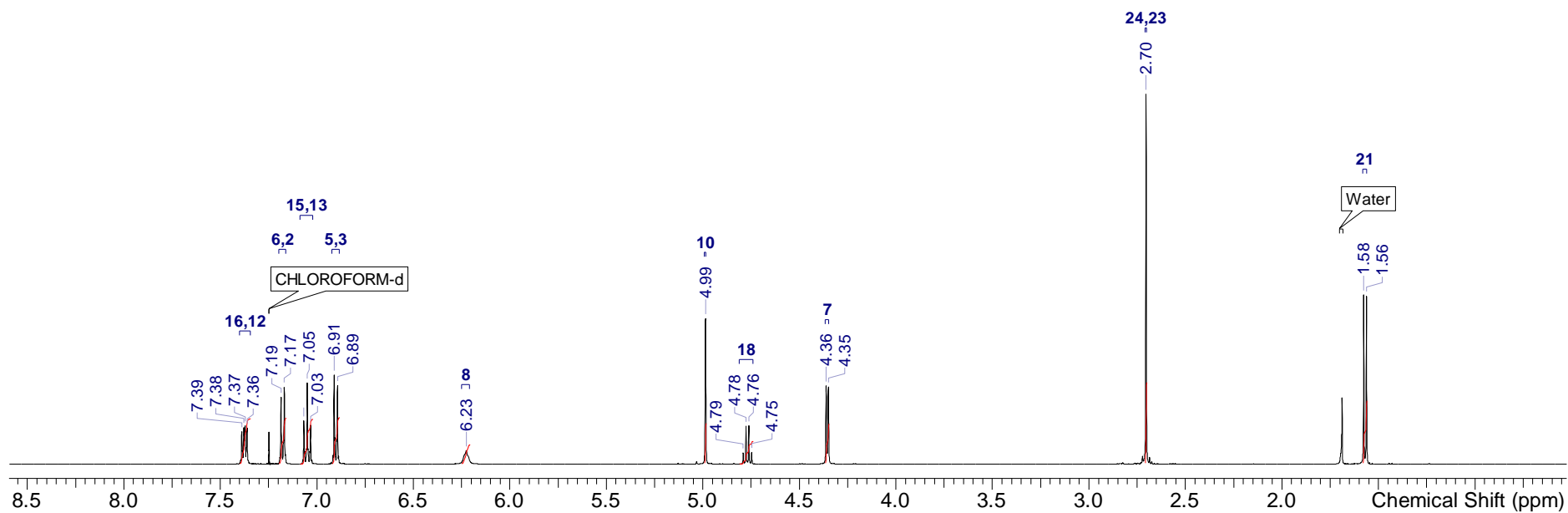
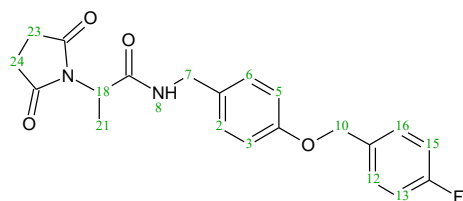


2-(2,5-dioxypyrrolidin-1-yl)-N-(4-((3-fluorobenzyl)oxy)benzyl)propanamide (7) –  $^{13}\text{C}$  NMR

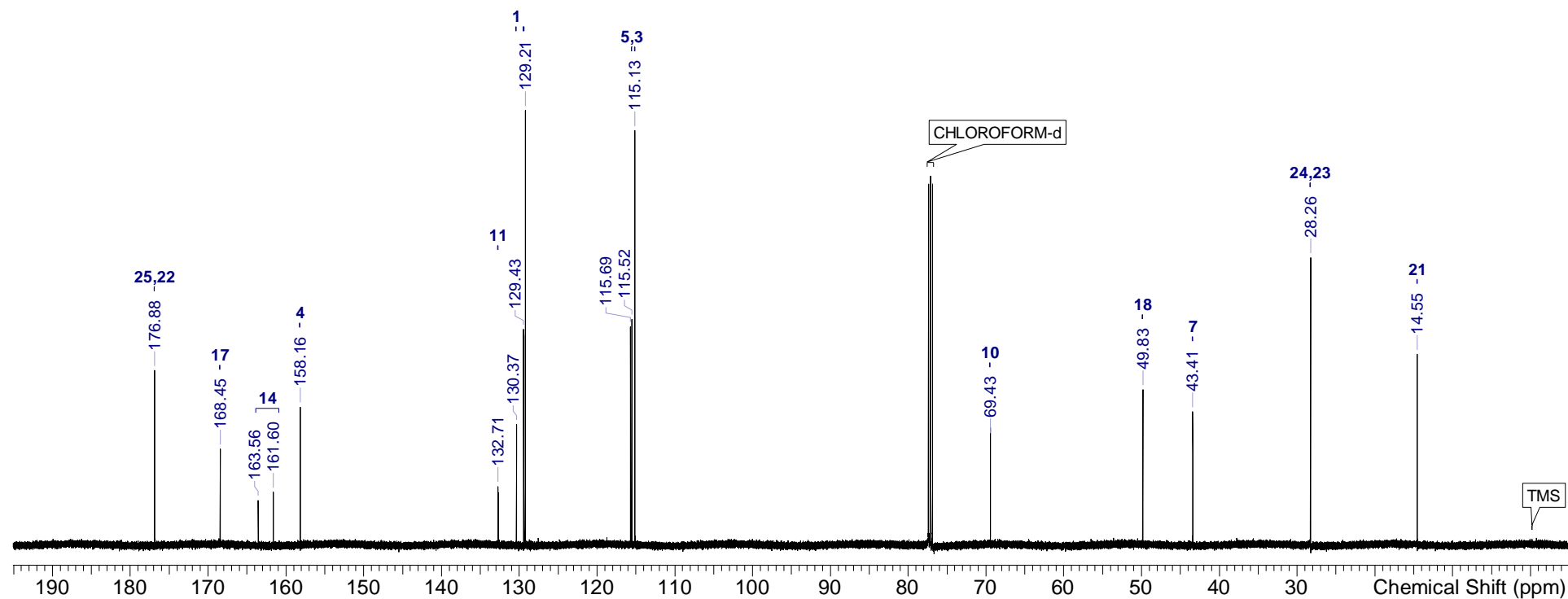
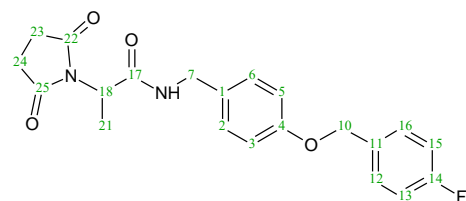




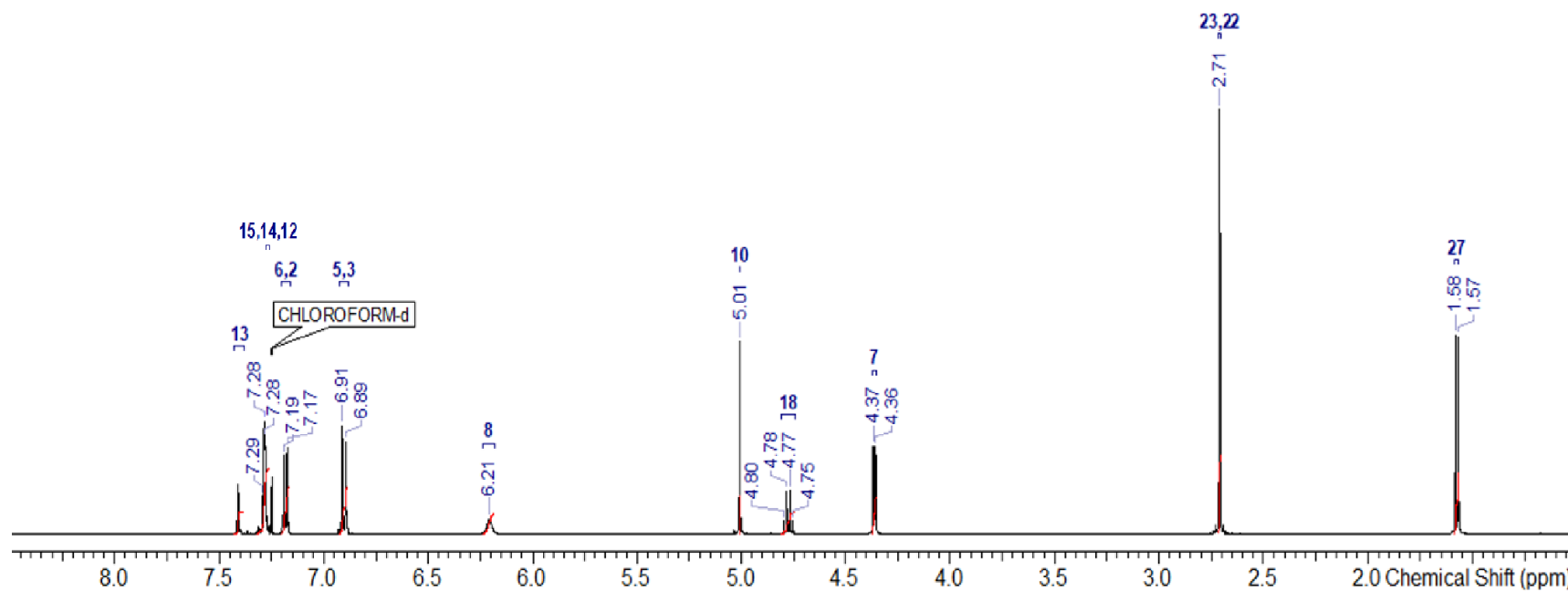
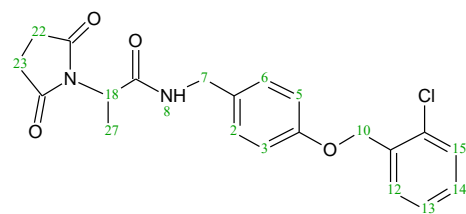
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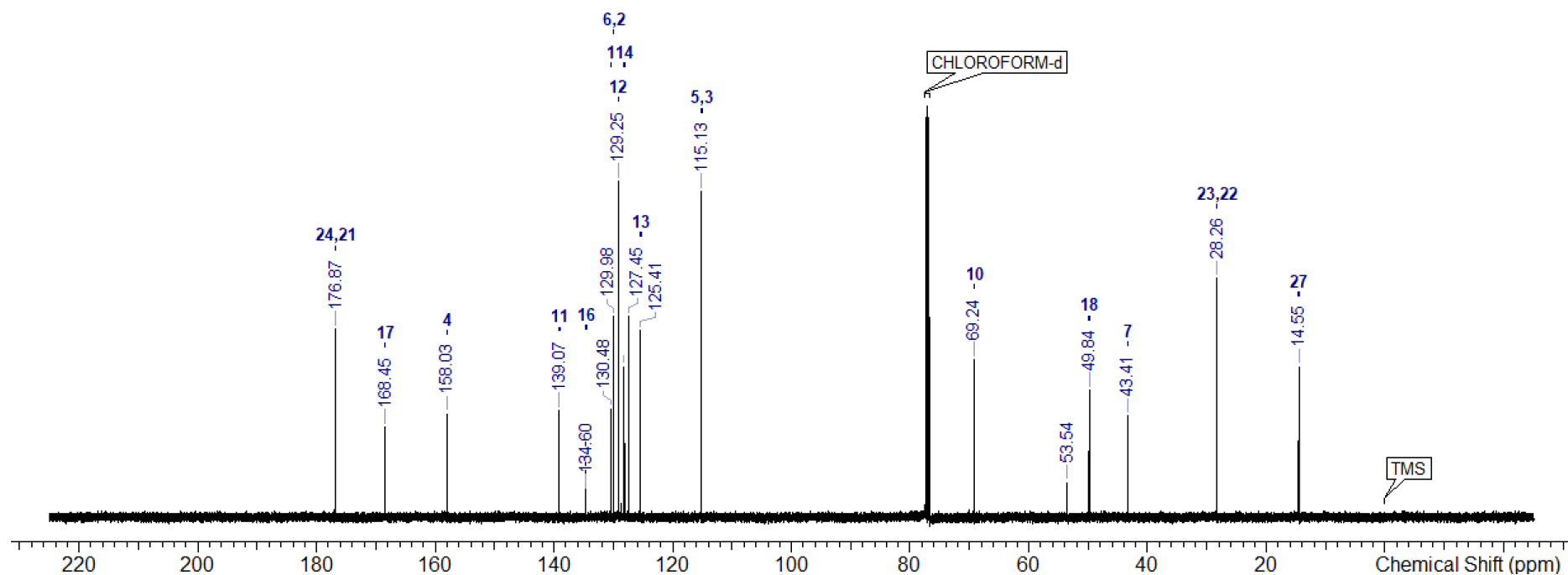
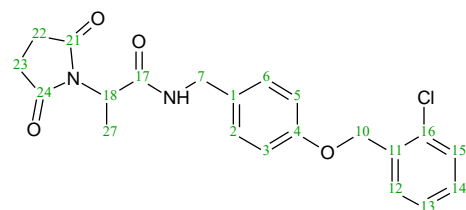
2-(2,5-dioxypyrrolidin-1-yl)-N-(4-((4-fluorobenzyl)oxy)benzyl)propanamide (8) –  $^{13}\text{C}$  NMR



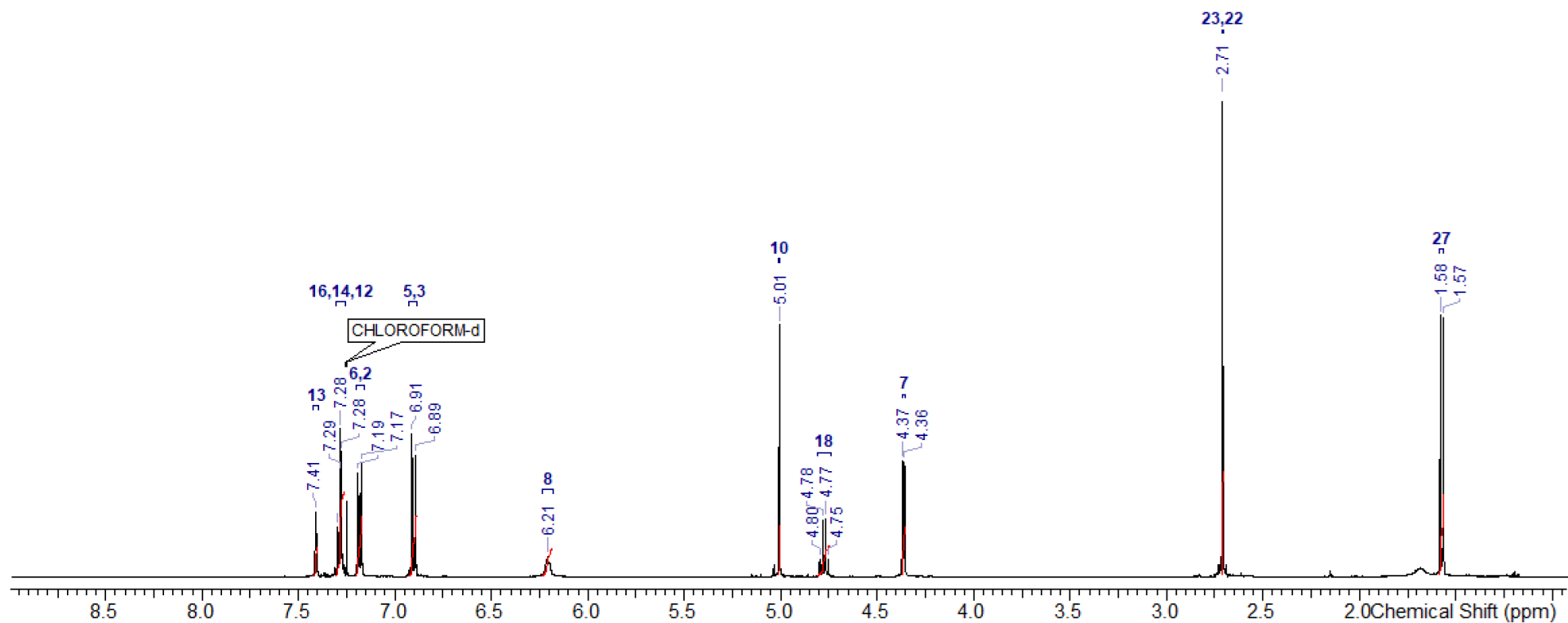
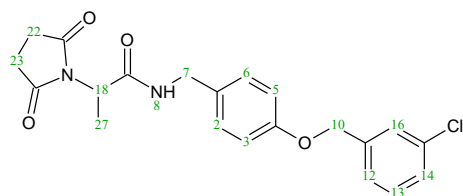
***N*-(4-((2-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (9) –  $^1\text{H}$  NMR**



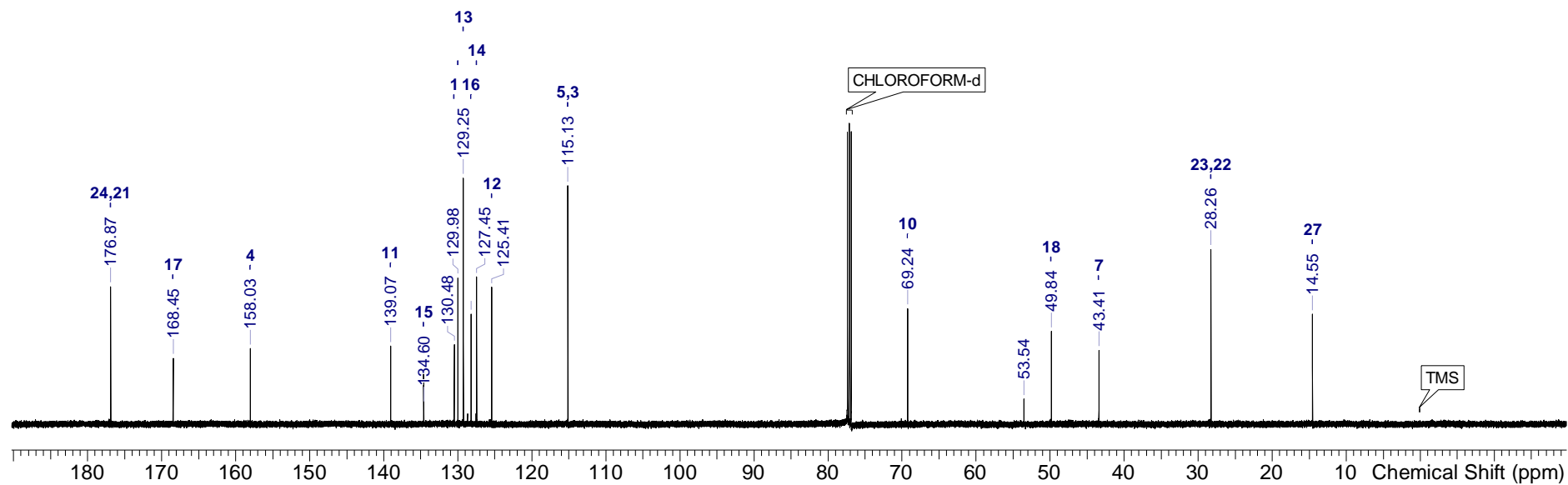
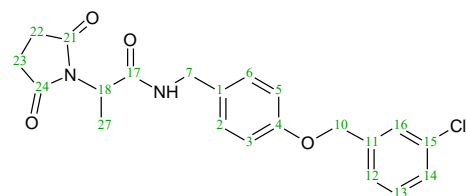
***N*-(4-((2-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (9) –  $^{13}\text{C}$  NMR**



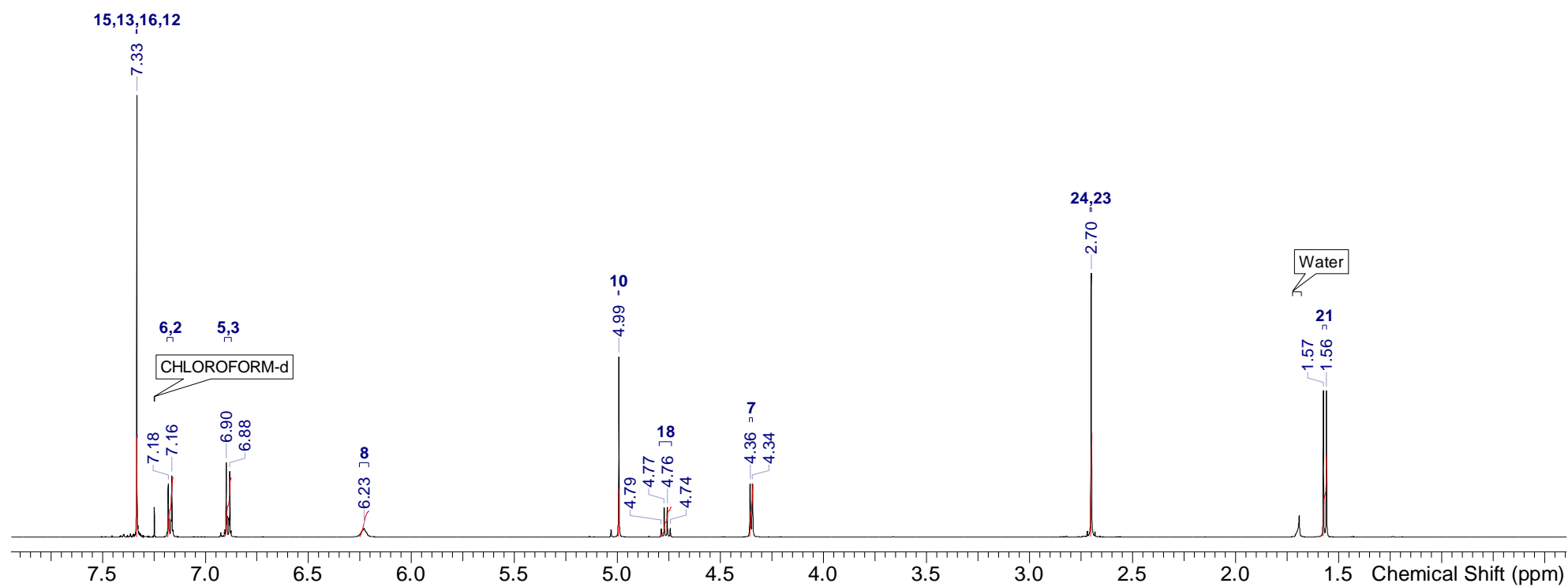
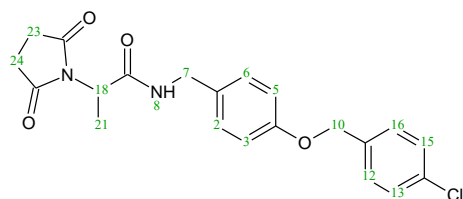
***N*-(4-((3-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (10) –  $^1\text{H}$  NMR**



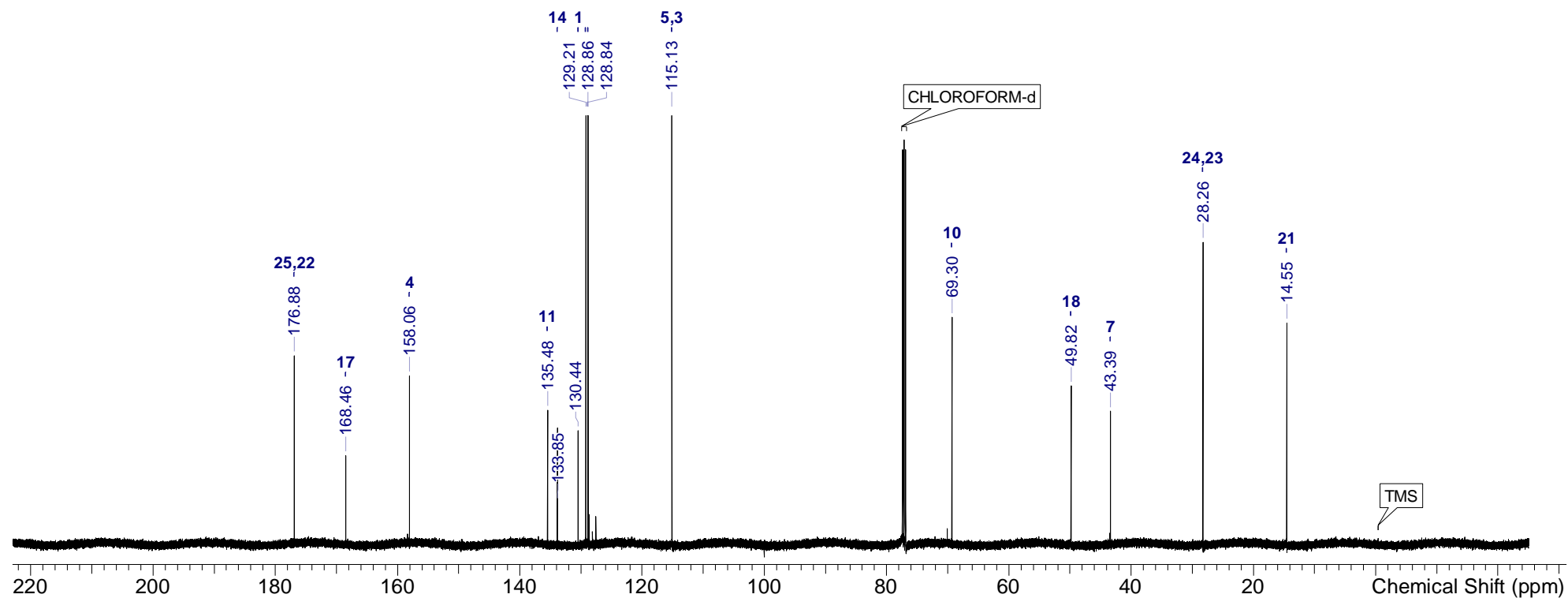
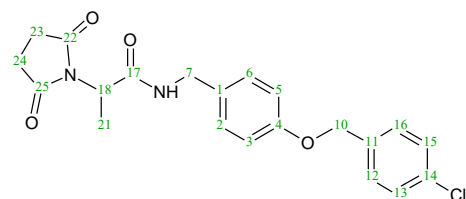
***N*-(4-((3-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (10) –  $^{13}\text{C}$  NMR**



***N*-(4-((4-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (11) –  $^1\text{H}$  NMR**

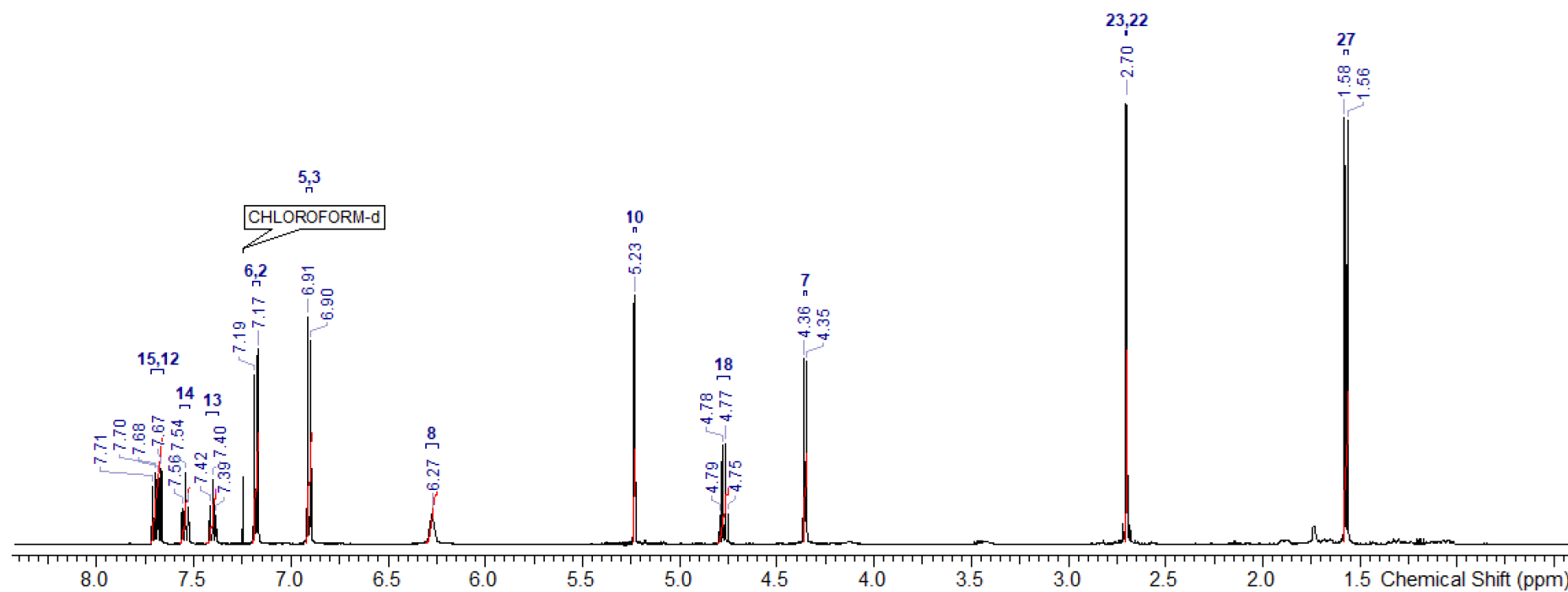
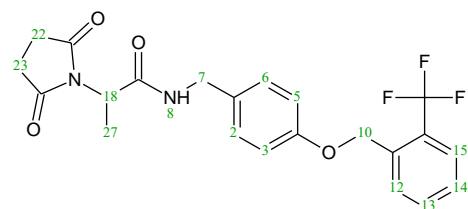


***N*-(4-((4-chlorobenzyl)oxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (11) –  $^{13}\text{C}$  NMR**

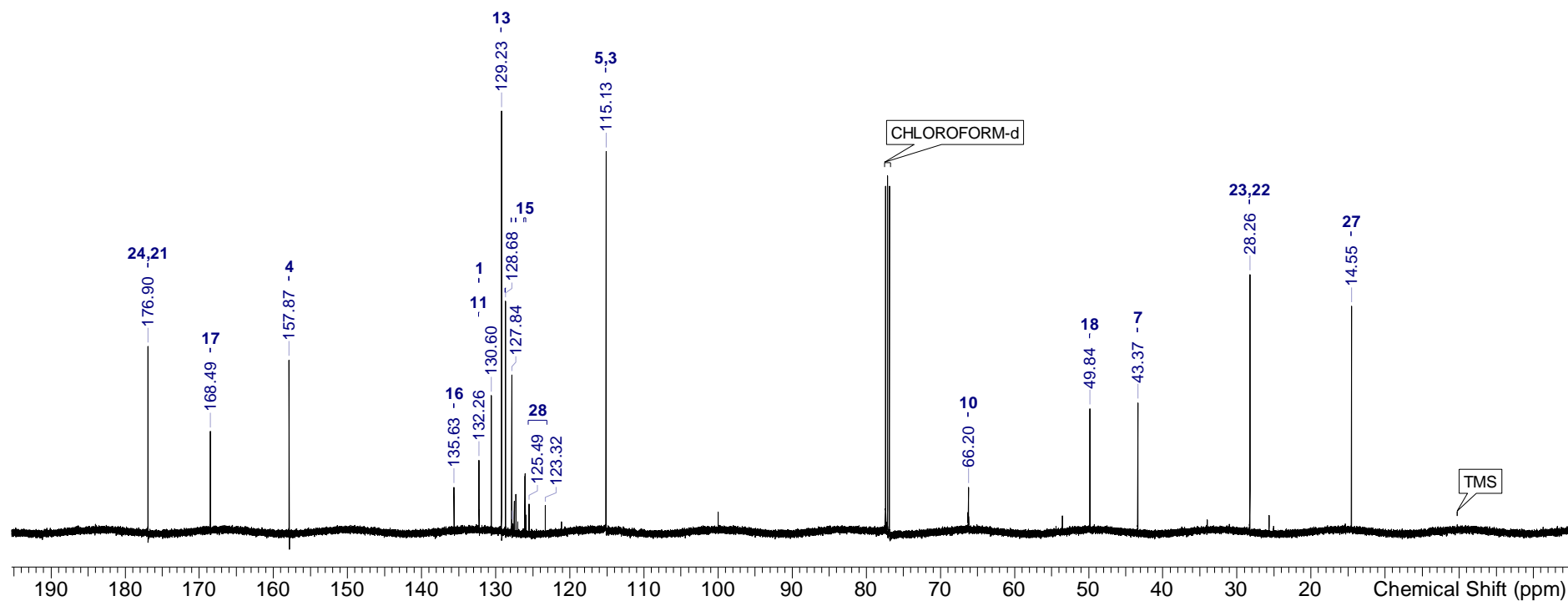
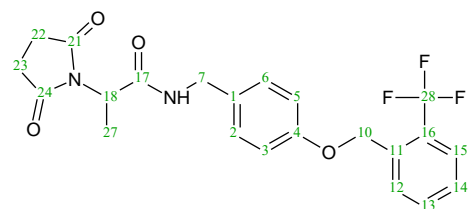




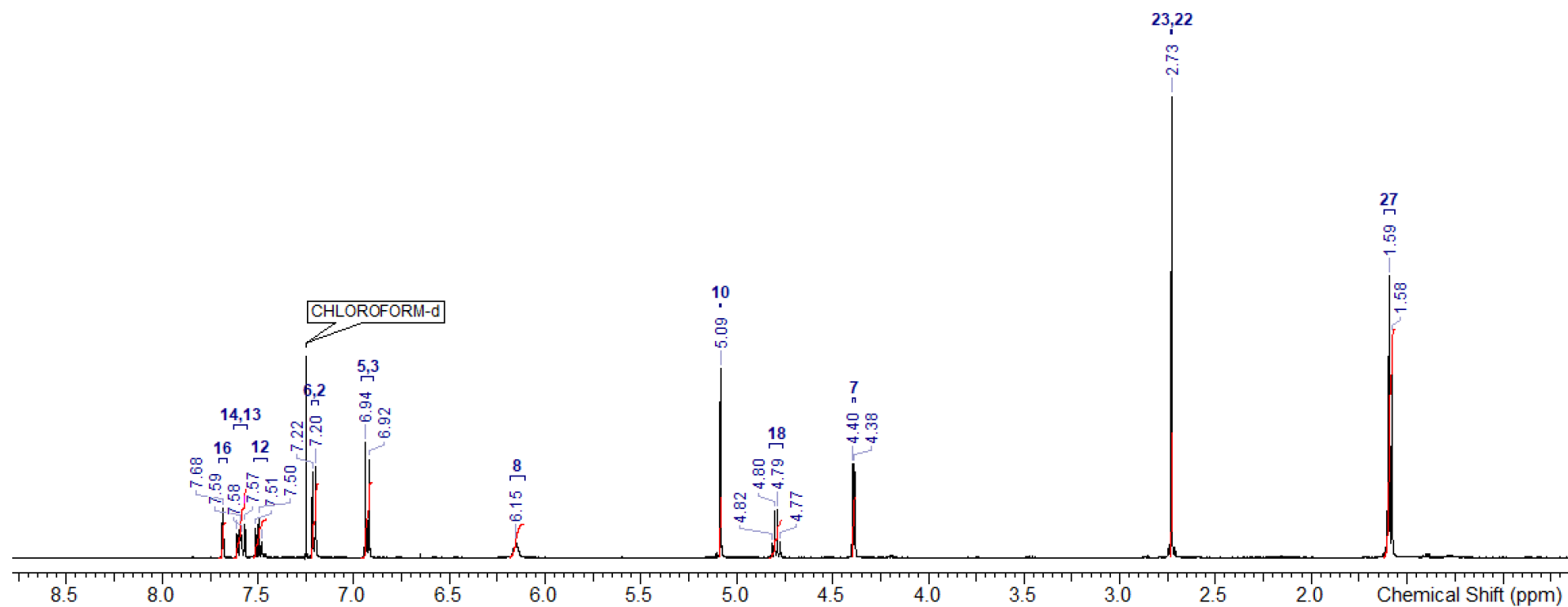
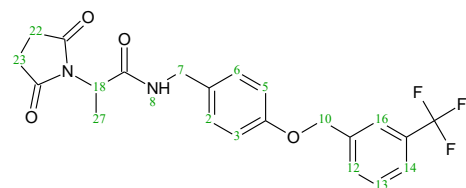
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (12) –  $^1\text{H}$  NMR



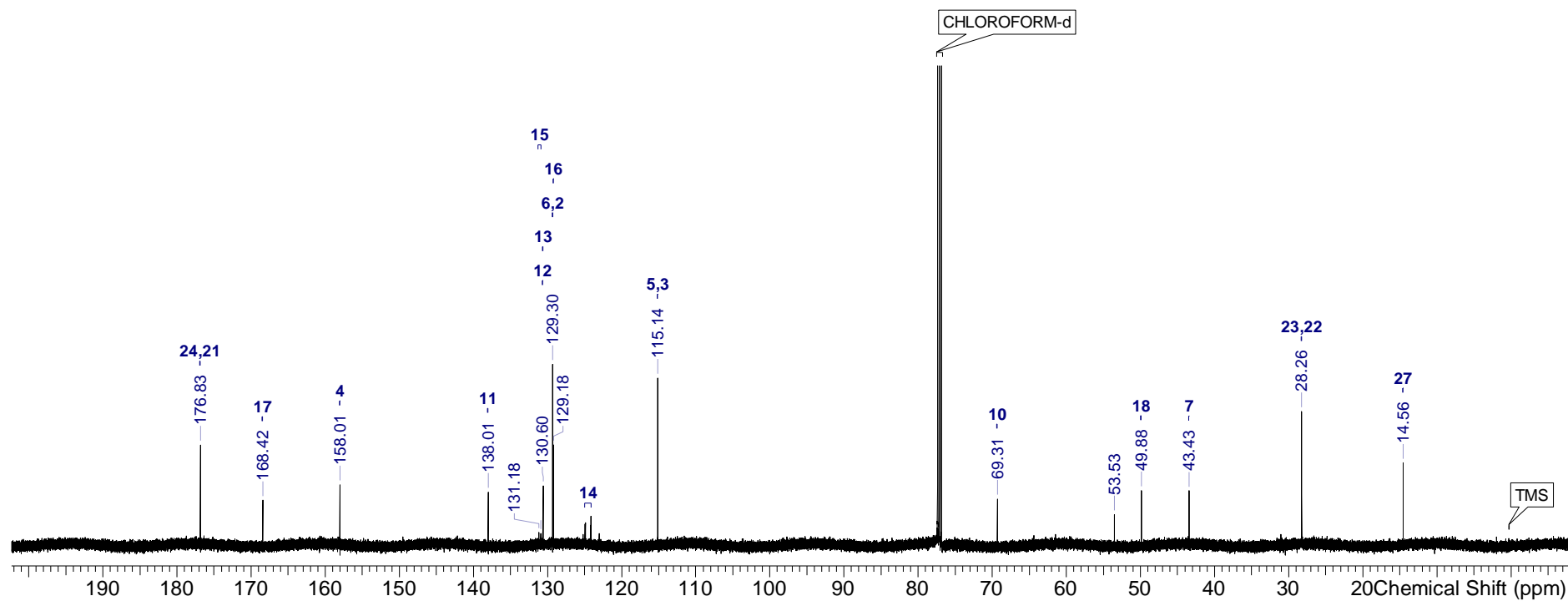
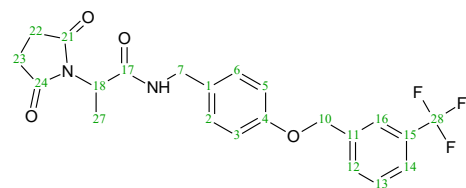
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (12) –  $^{13}\text{C}$  NMR



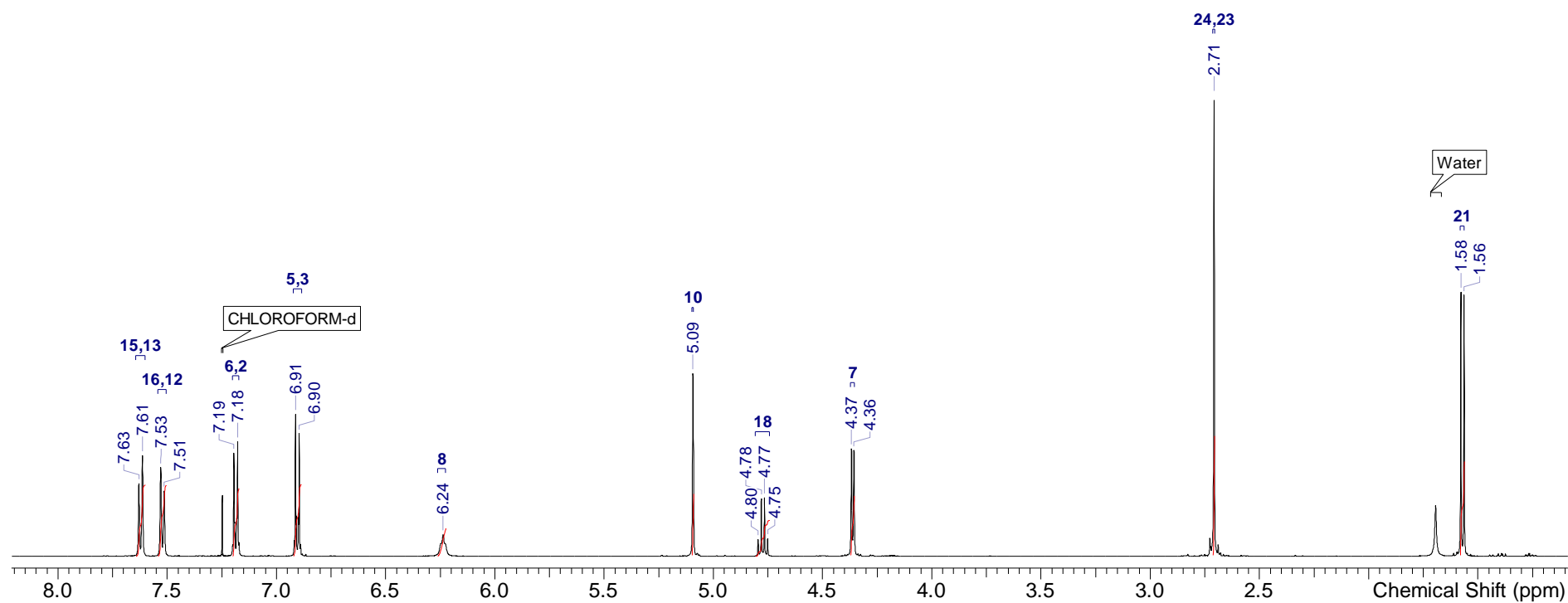
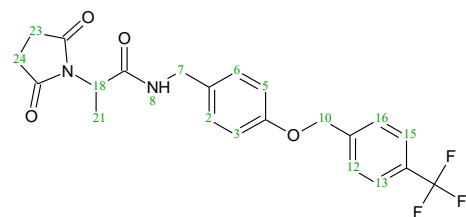
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (13) –  $^1\text{H}$  NMR**



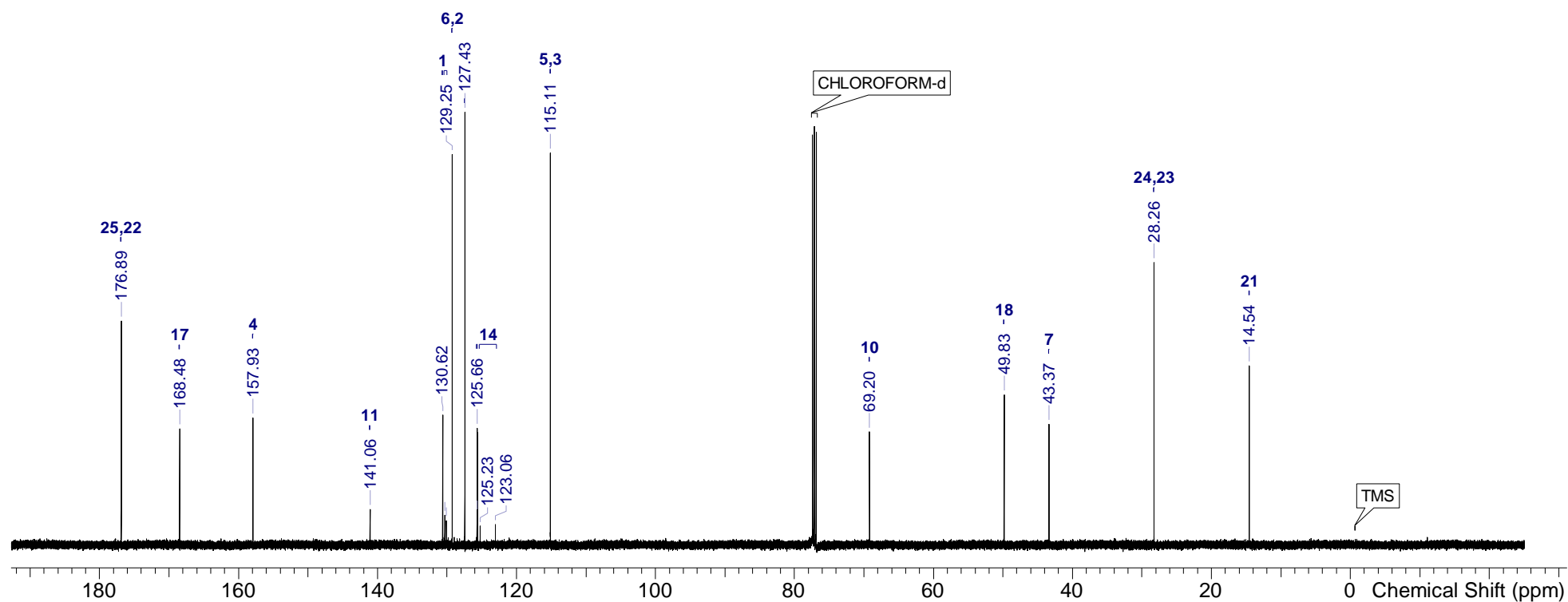
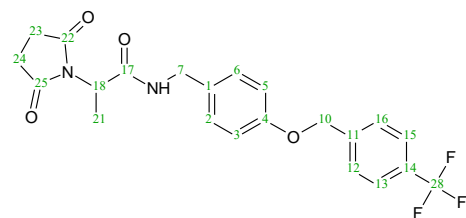
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (13) –  $^{13}\text{C}$  NMR**



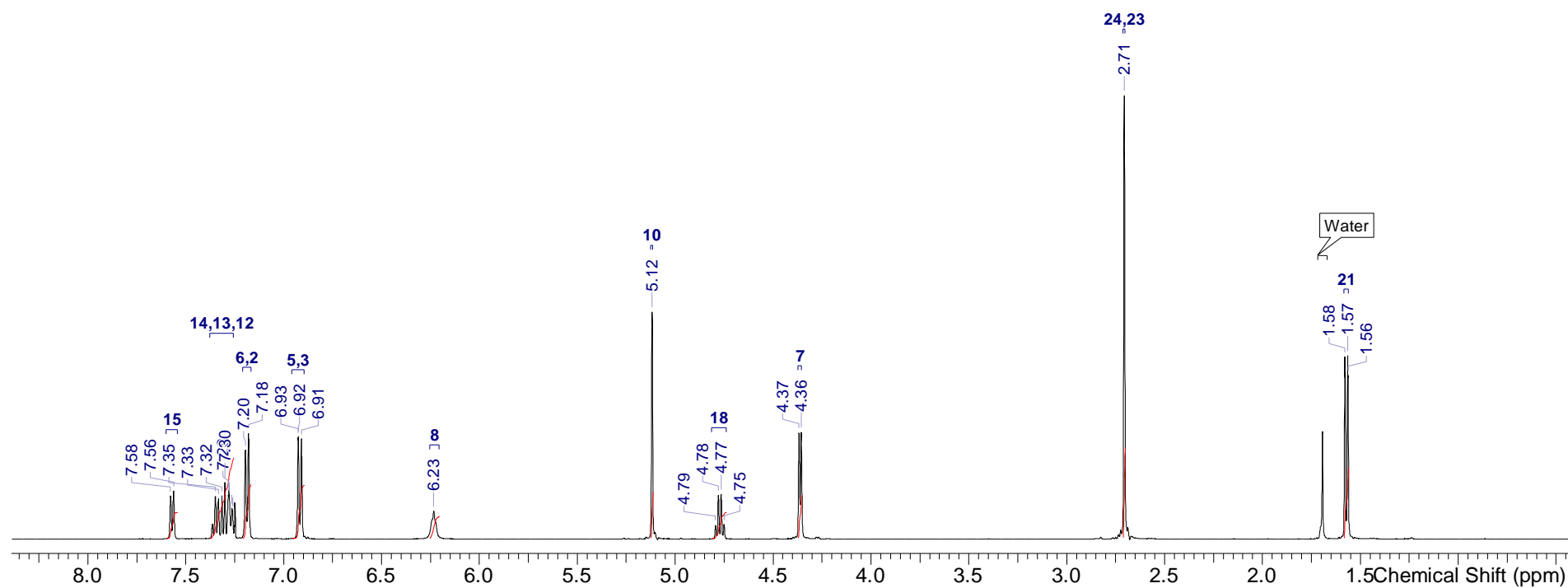
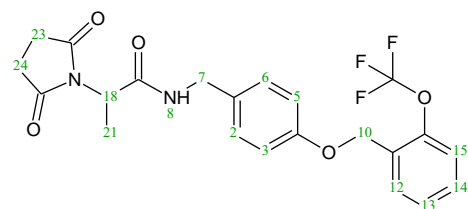
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (14) –  $^1\text{H}$  NMR**



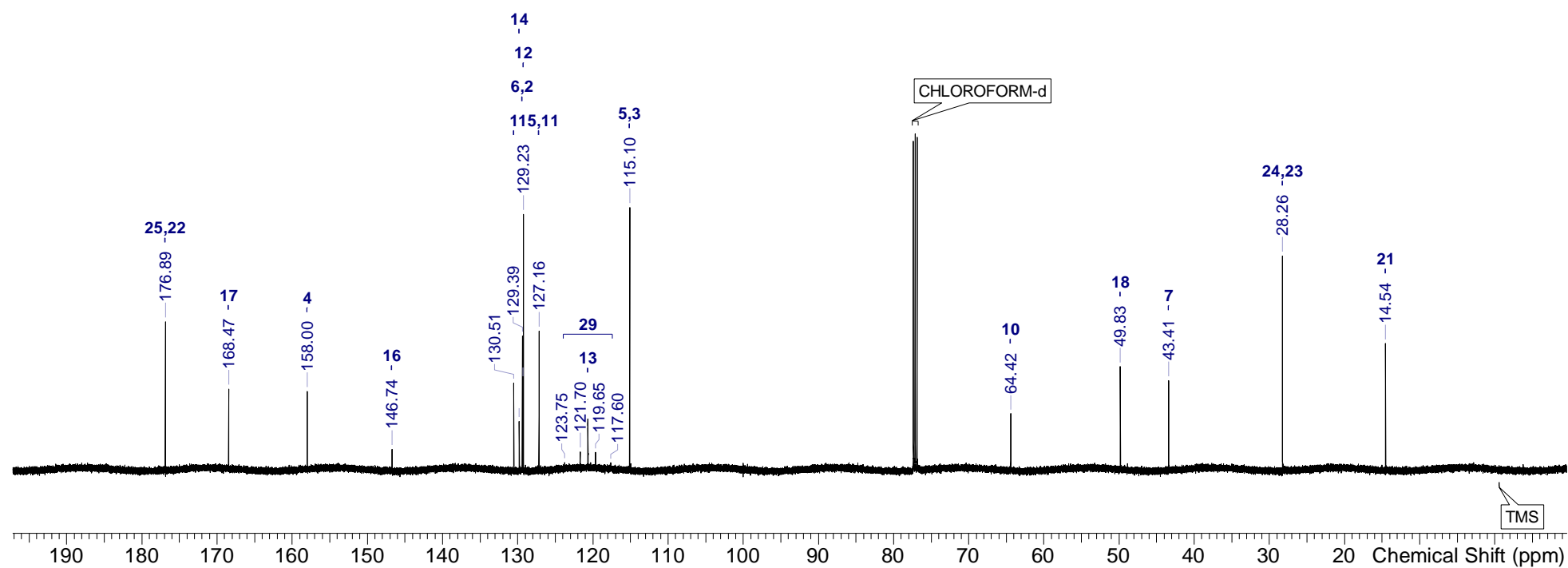
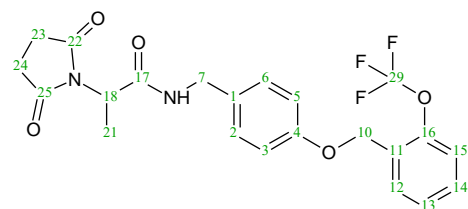
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (14) –  $^{13}\text{C}$  NMR



**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (15) –  $^1\text{H}$  NMR**

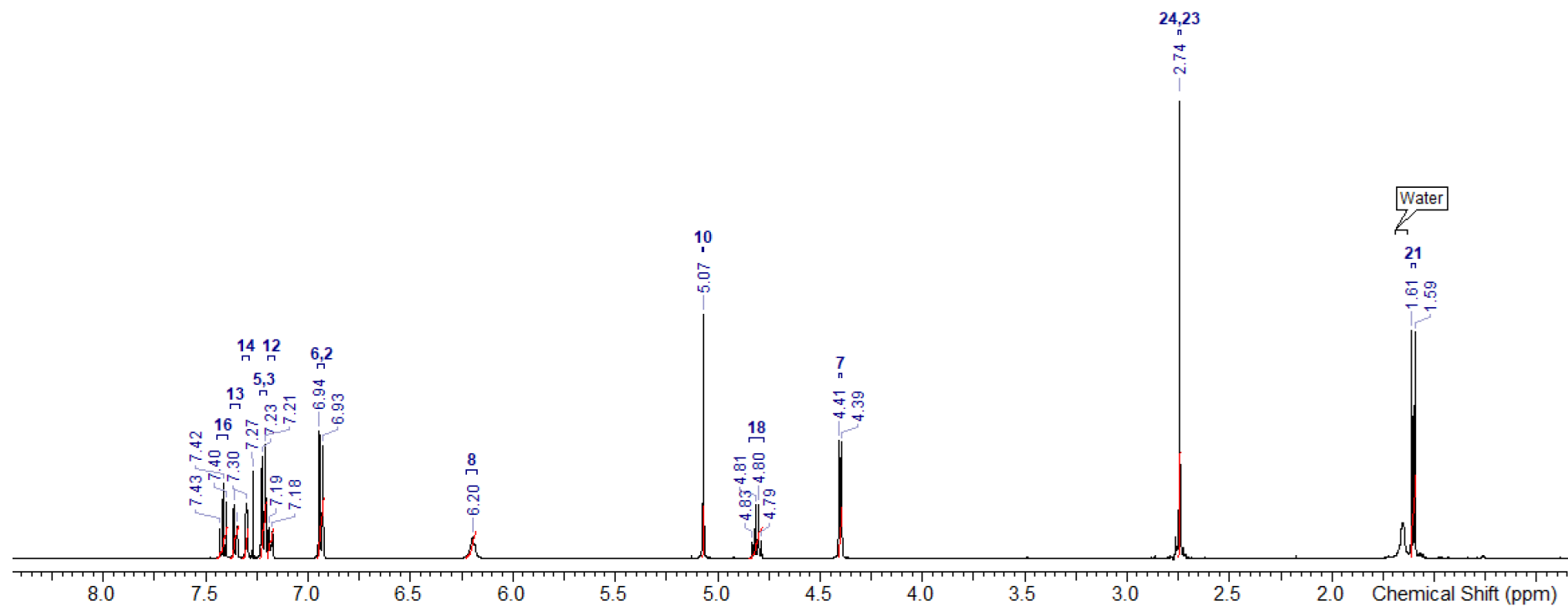


2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (15) –  $^{13}\text{C}$  NMR

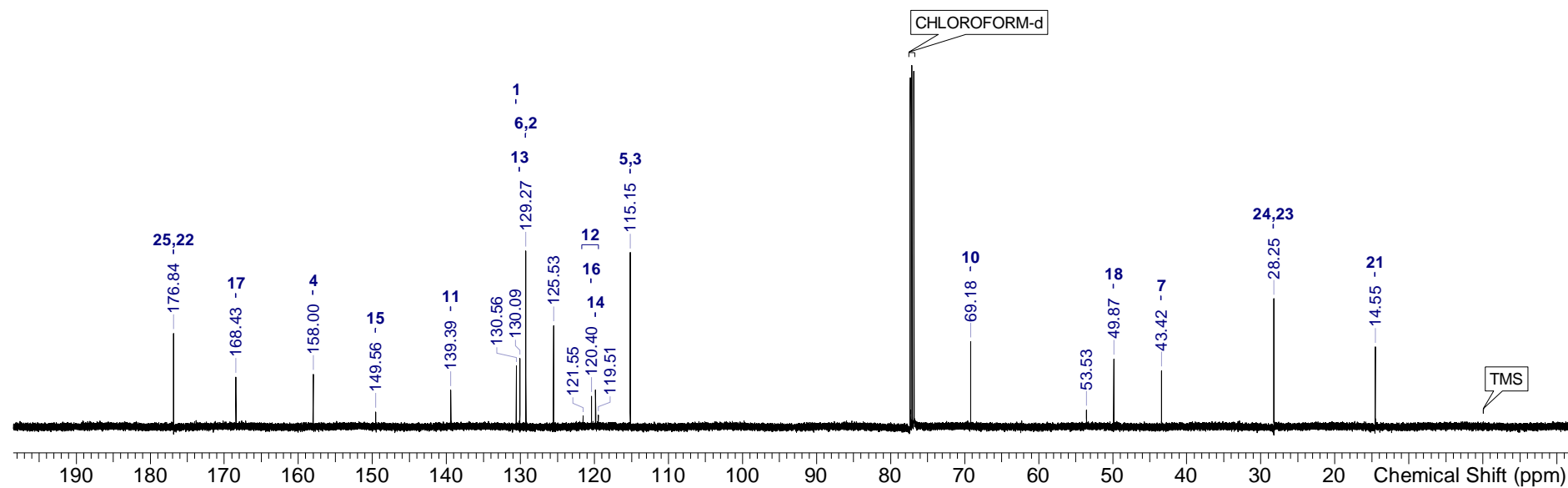
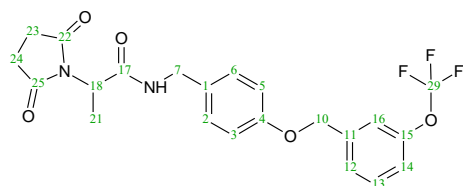




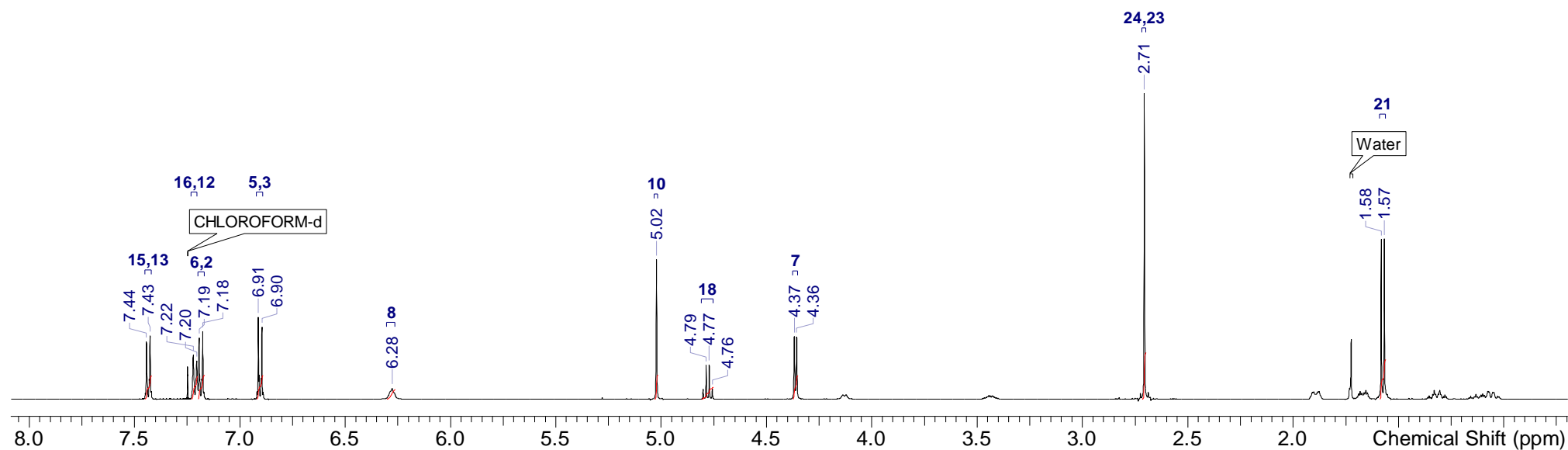
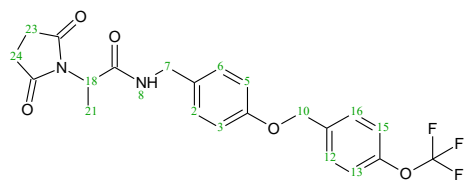
The chemical structure shows a 2,4-difluorophenyl group connected via an ether linkage to a 4-((2-oxo-2,3-dihydro-1H-imidazo[5,1-b]pyridin-5-yl)amino)phenyl group. The atoms are numbered as follows: 1-10 for the imidazopyridine system, 11-16 for the central phenyl ring, and 17-24 for the 2,4-difluorophenyl group. The numbering starts at the nitrogen of the imidazole ring (1), goes around the fused pyridine ring (2-10), then through the central phenyl ring (11-16), and finally through the 2,4-difluorophenyl group (17-24).



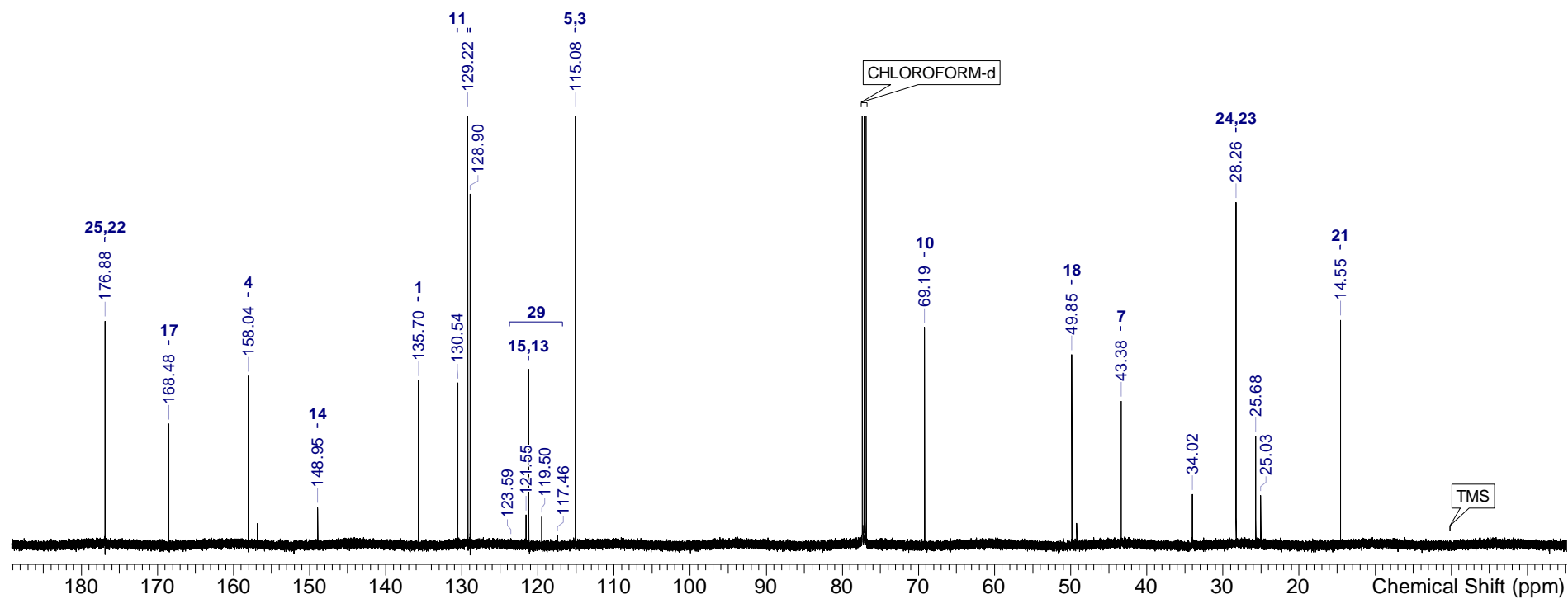
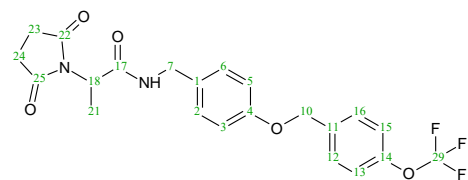
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (16) –  $^{13}\text{C}$  NMR**



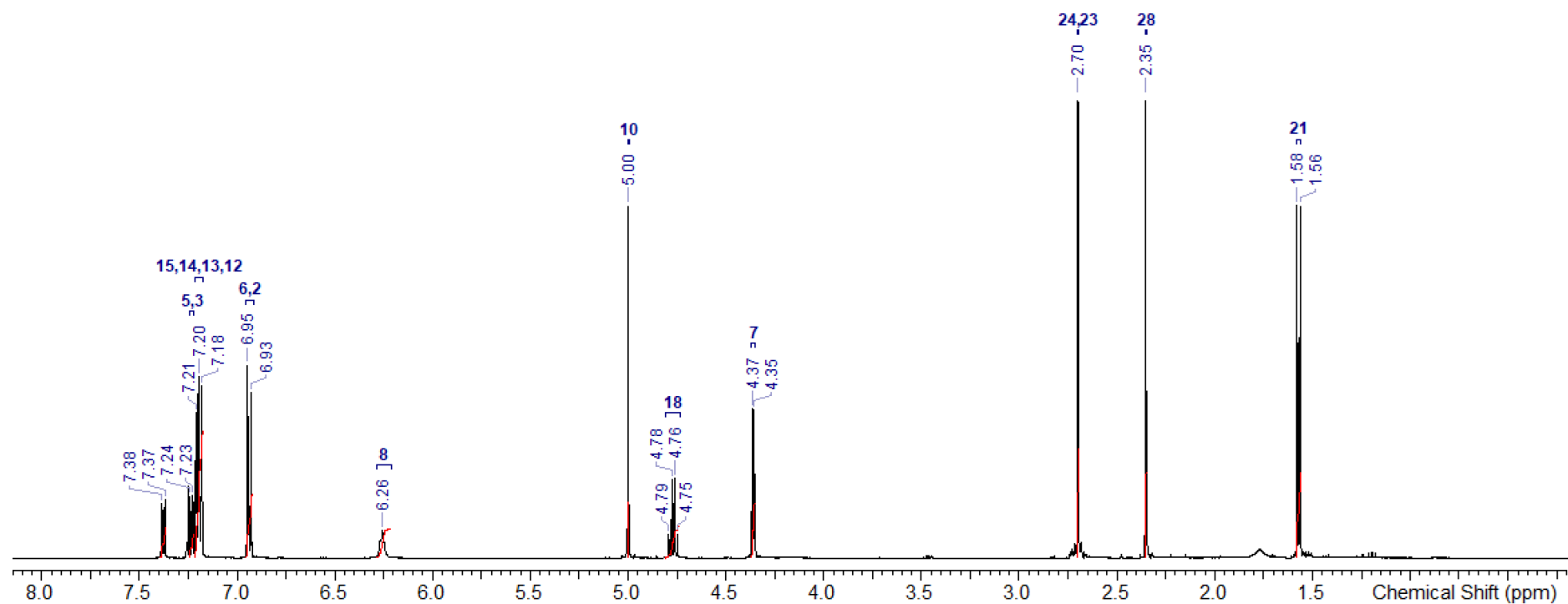
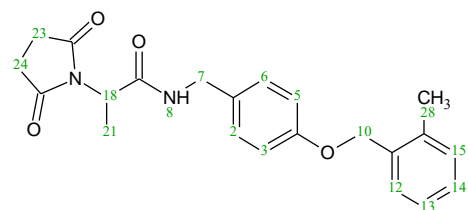
**2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (17) –  $^1\text{H}$  NMR**



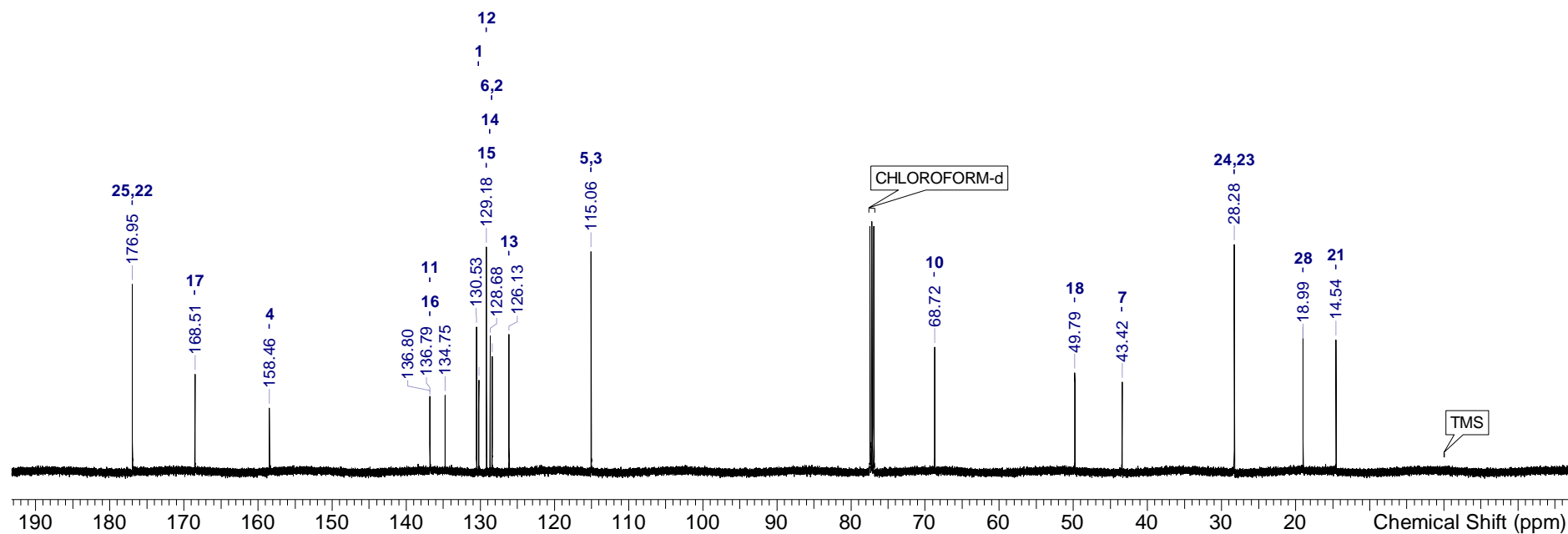
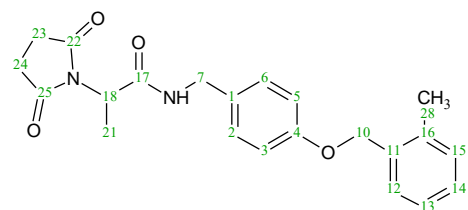
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (17) –  $^{13}\text{C}$  NMR



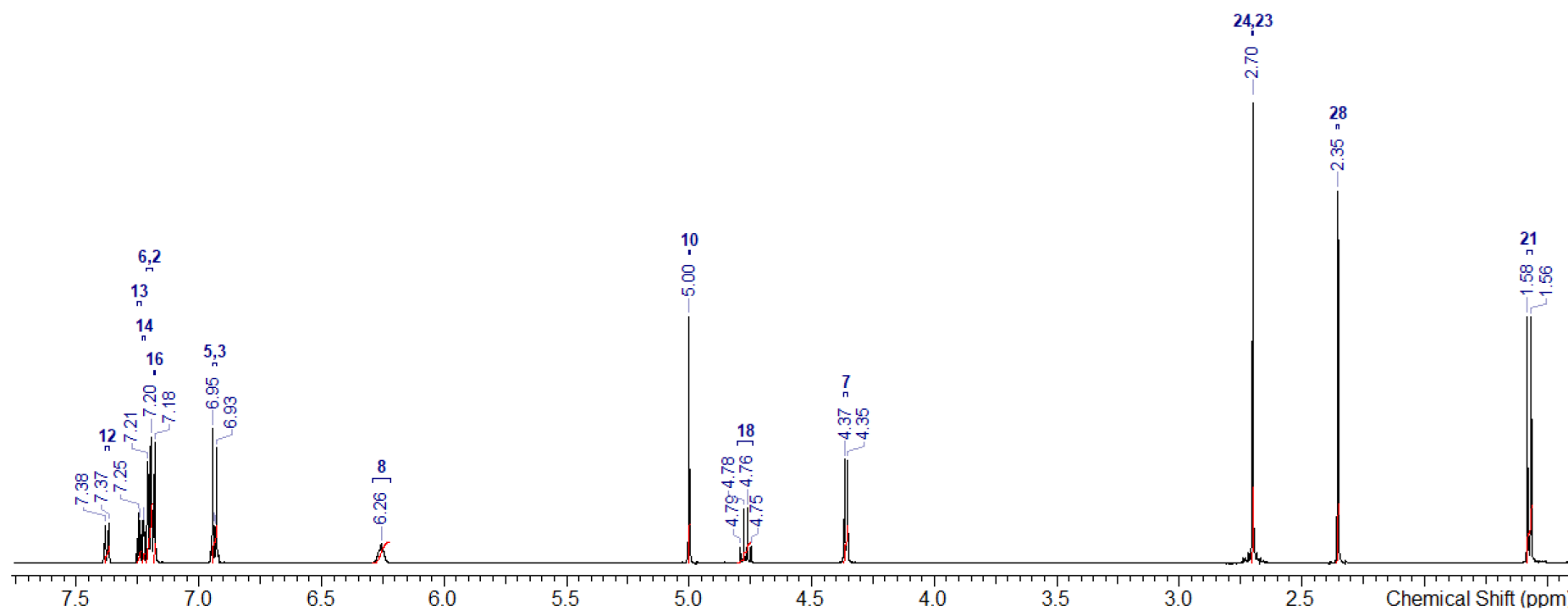
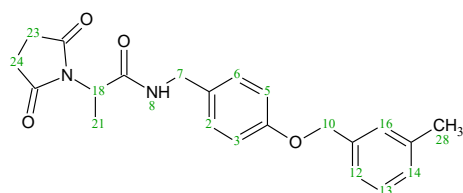
**2-(2,5-dioxypyrrolidin-1-yl)-N-(4-((2-methylbenzyl)oxy)benzyl)propanamide (18) –  $^1\text{H}$  NMR**



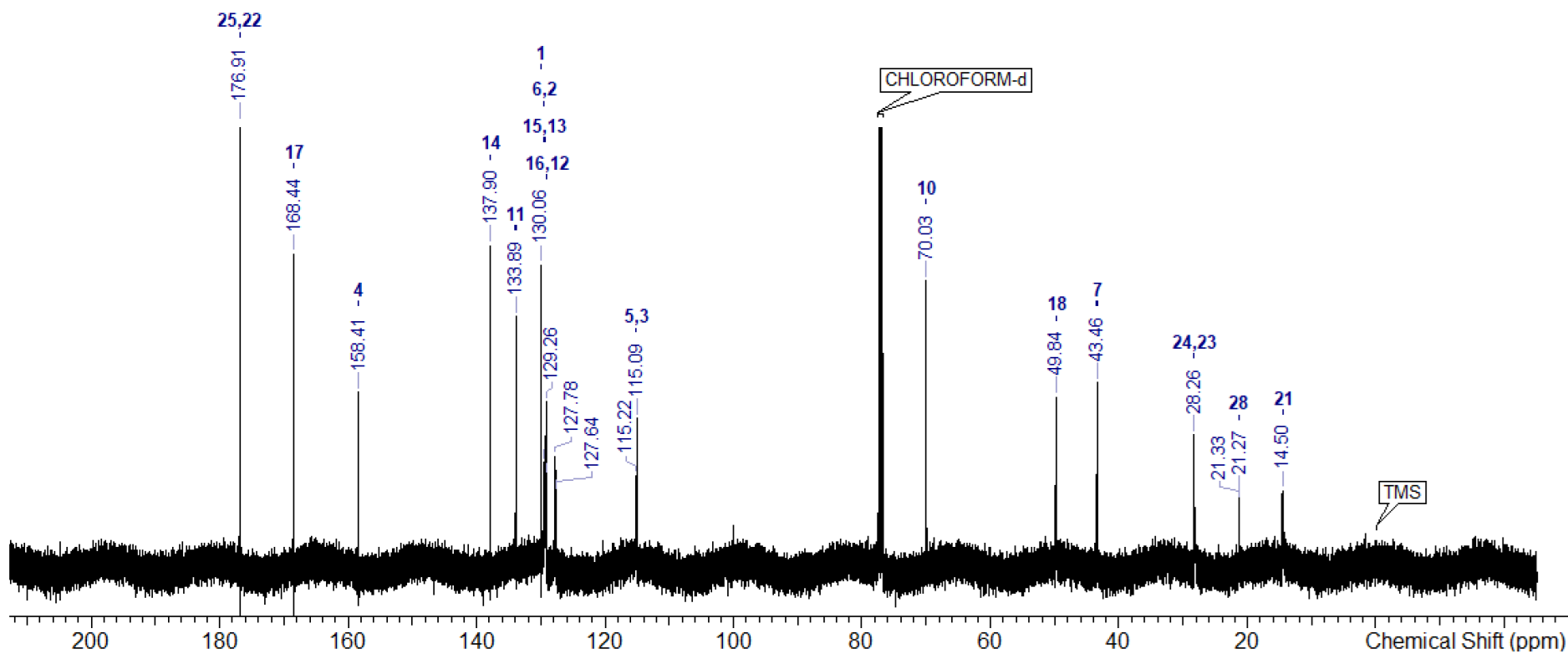
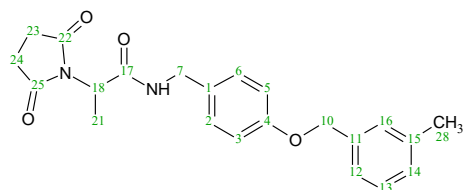
2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((2-methylbenzyl)oxy)benzyl)propanamide (18) –  $^{13}\text{C}$  NMR



2-(2,5-dioxypyrrolidin-1-yl)-N-(4-((3-methylbenzyl)oxy)benzyl)propanamide (19) –  $^1\text{H}$  NMR

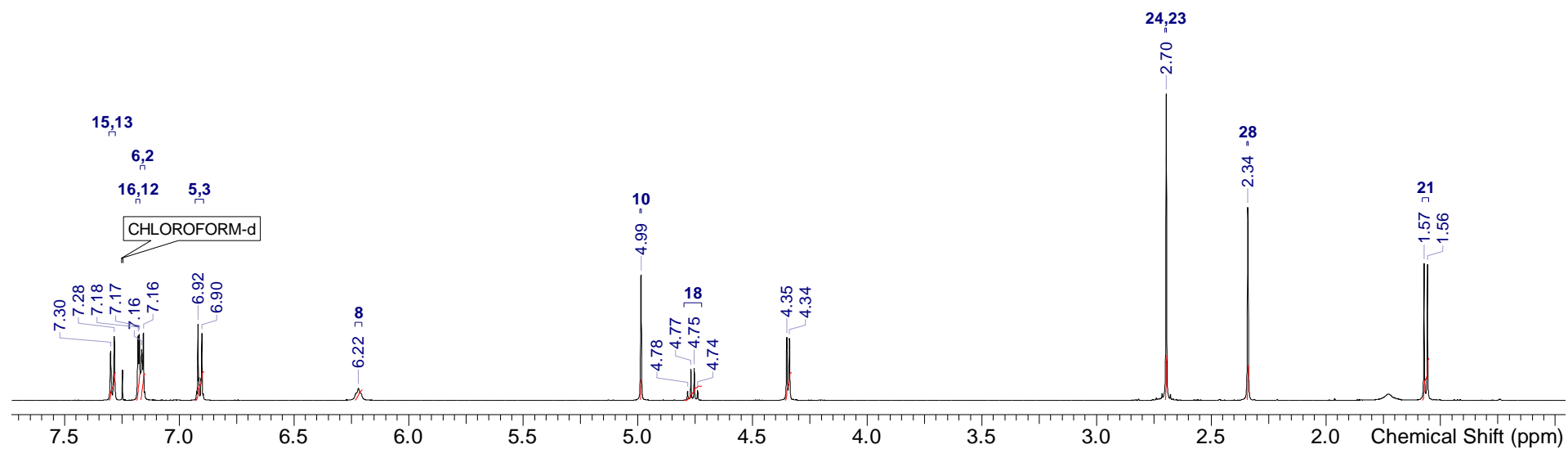
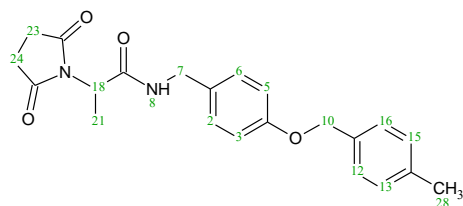


2-(2,5-dioxopyrrolidin-1-yl)-N-(4-((3-methylbenzyl)oxy)benzyl)propanamide (19) –  $^{13}\text{C}$  NMR

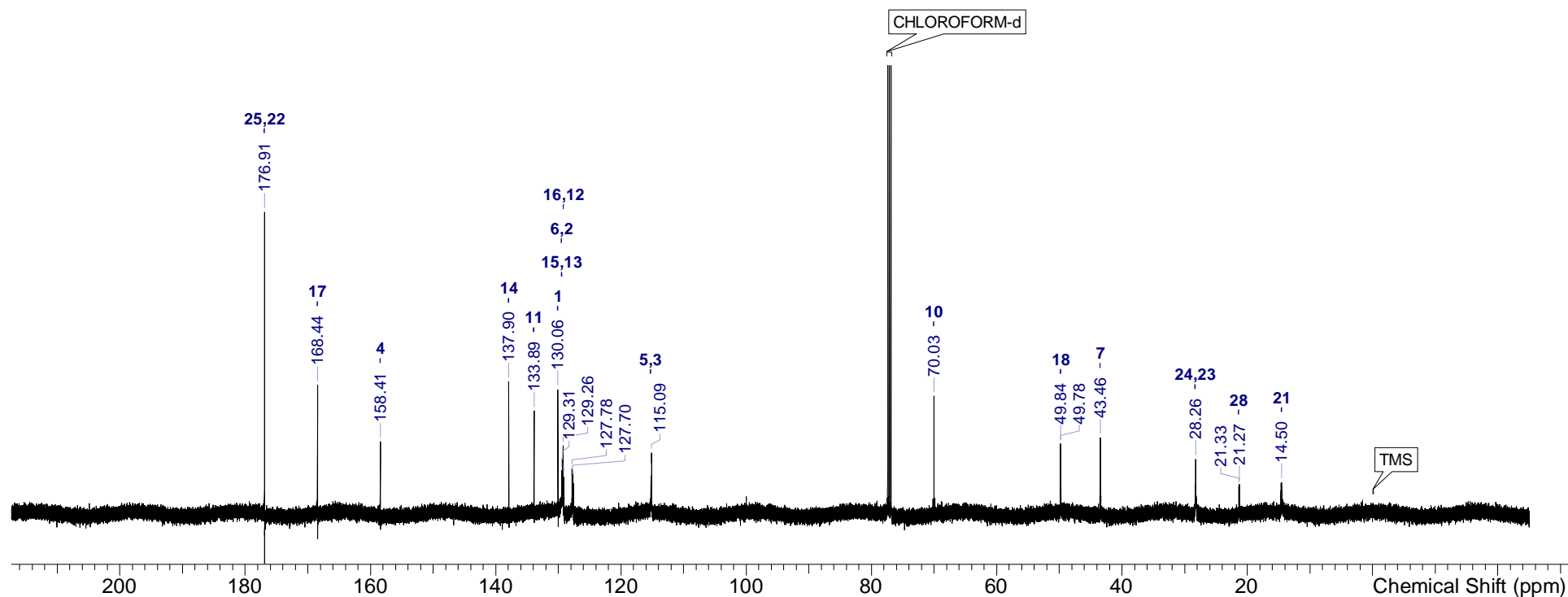
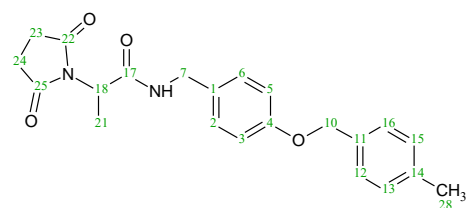




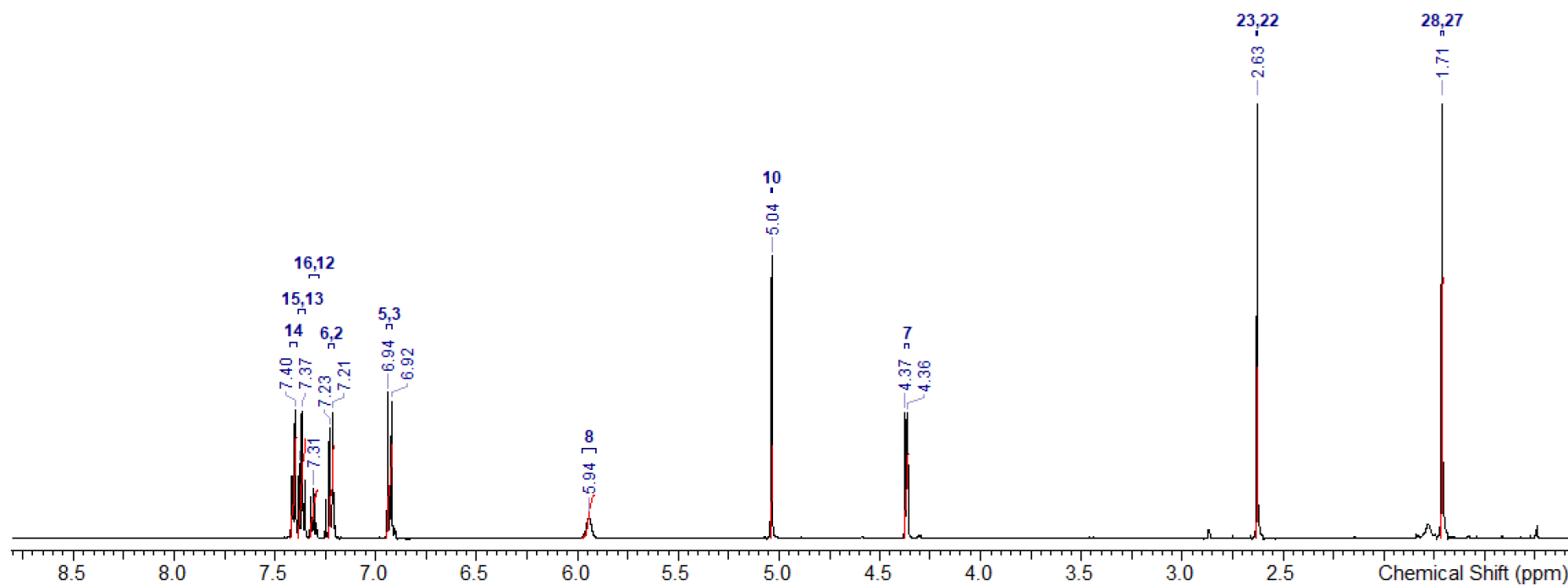
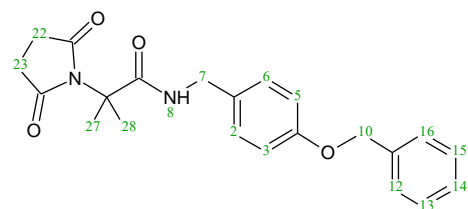
2-(2,5-dioxypyrrolidin-1-yl)-N-(4-((4-methylbenzyl)oxy)benzyl)propanamide (20) –  $^1\text{H}$  NMR



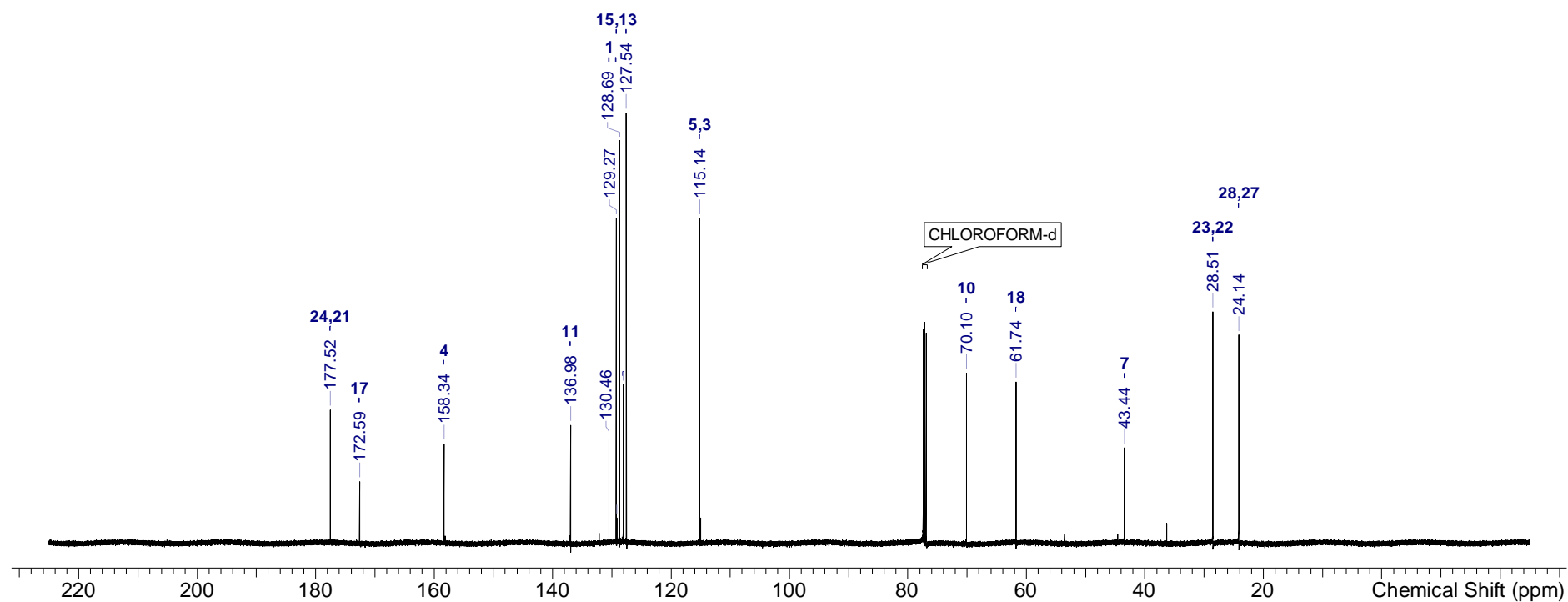
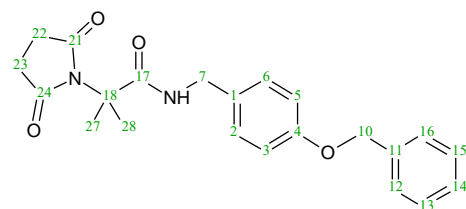
2-(2,5-dioxopyrrolidin-1-yl)-N-((4-(4-methylbenzyl)oxy)benzyl)propanamide (20) –  $^{13}\text{C}$  NMR



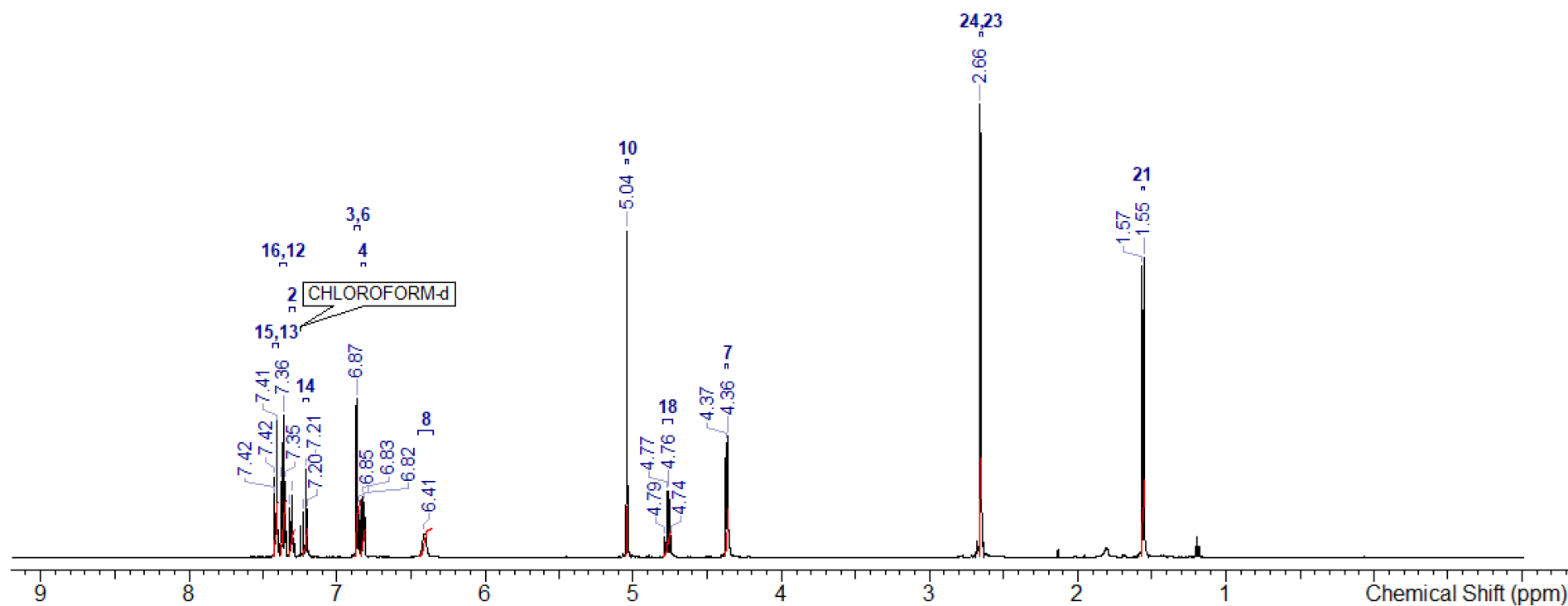
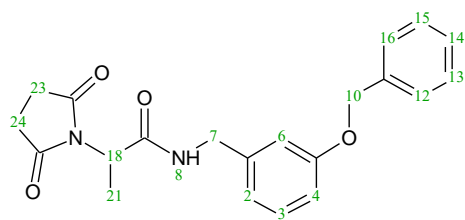
***N*-(4-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)-2-methylpropanamide (21) –  $^1\text{H}$  NMR**



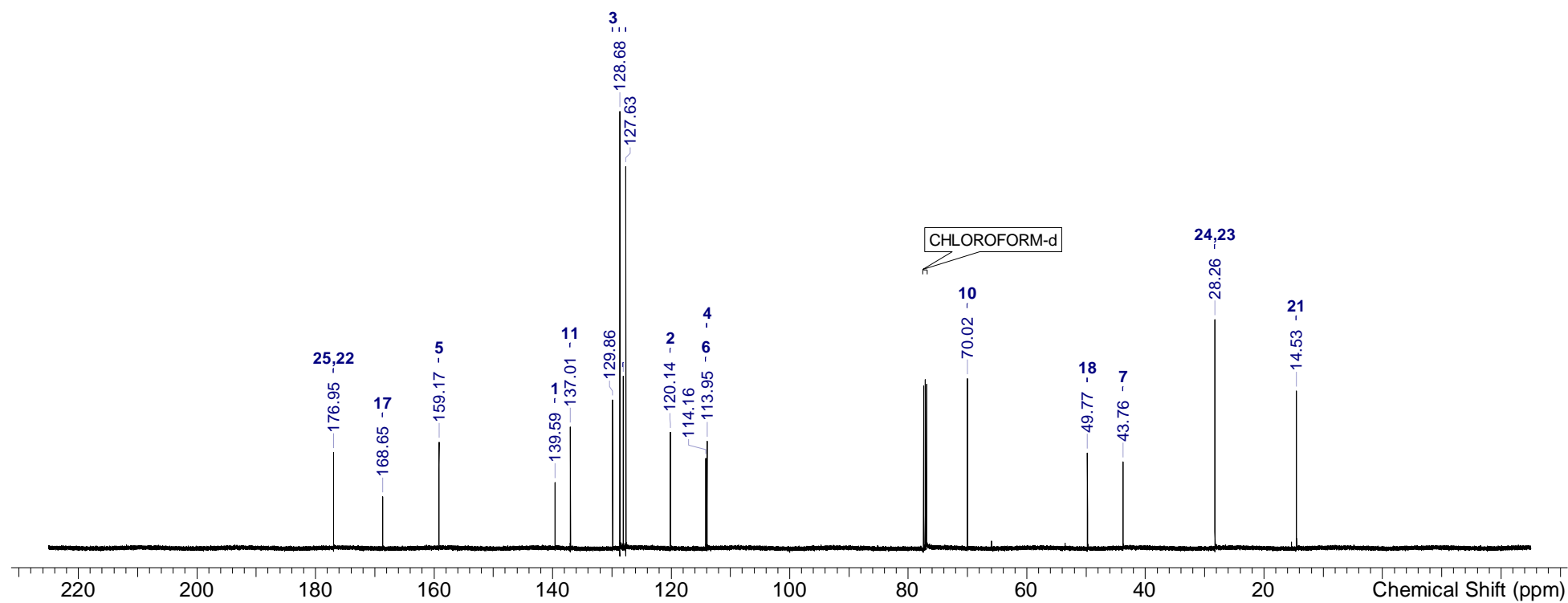
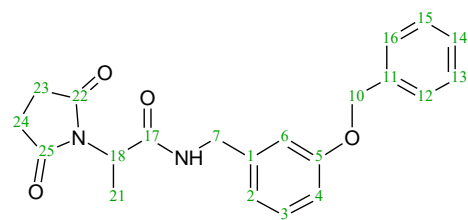
***N*-(4-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)-2-methylpropanamide (21) –  $^{13}\text{C}$  NMR**



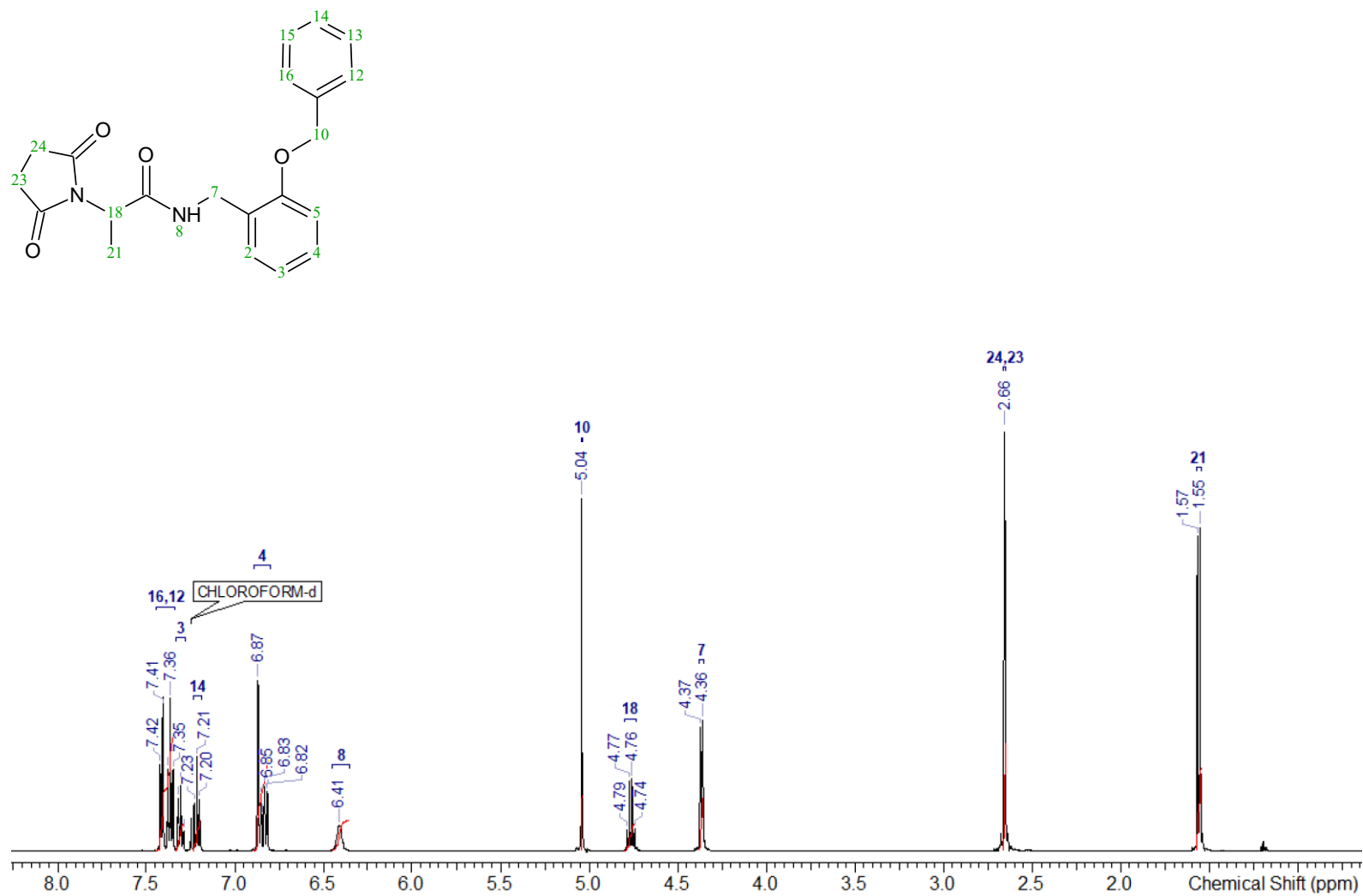
***N*-(3-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (22) –  $^1\text{H}$  NMR**



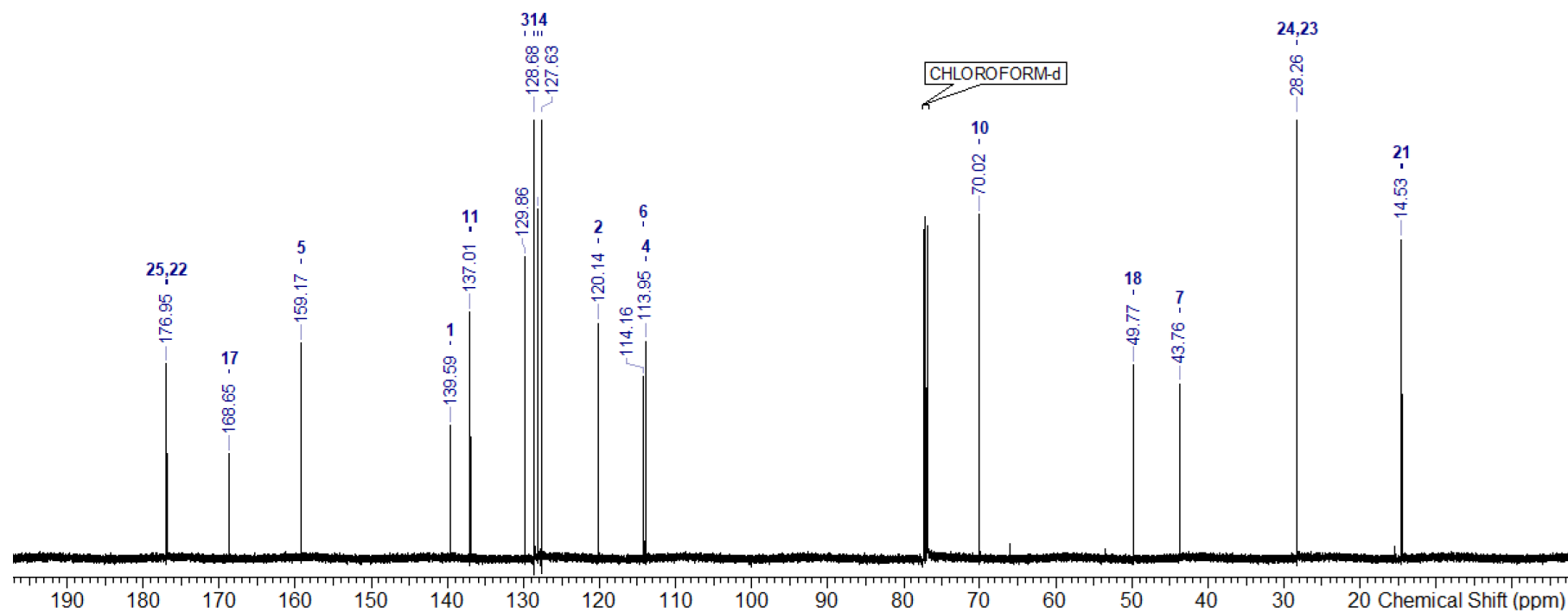
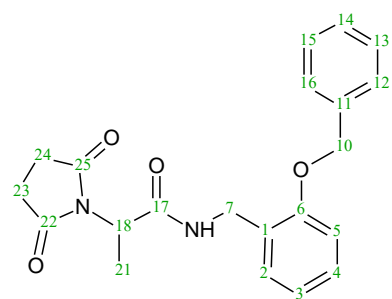
***N*-(3-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (22) –  $^{13}\text{C}$  NMR**



***N*-(2-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (23) –  $^1\text{H}$  NMR**

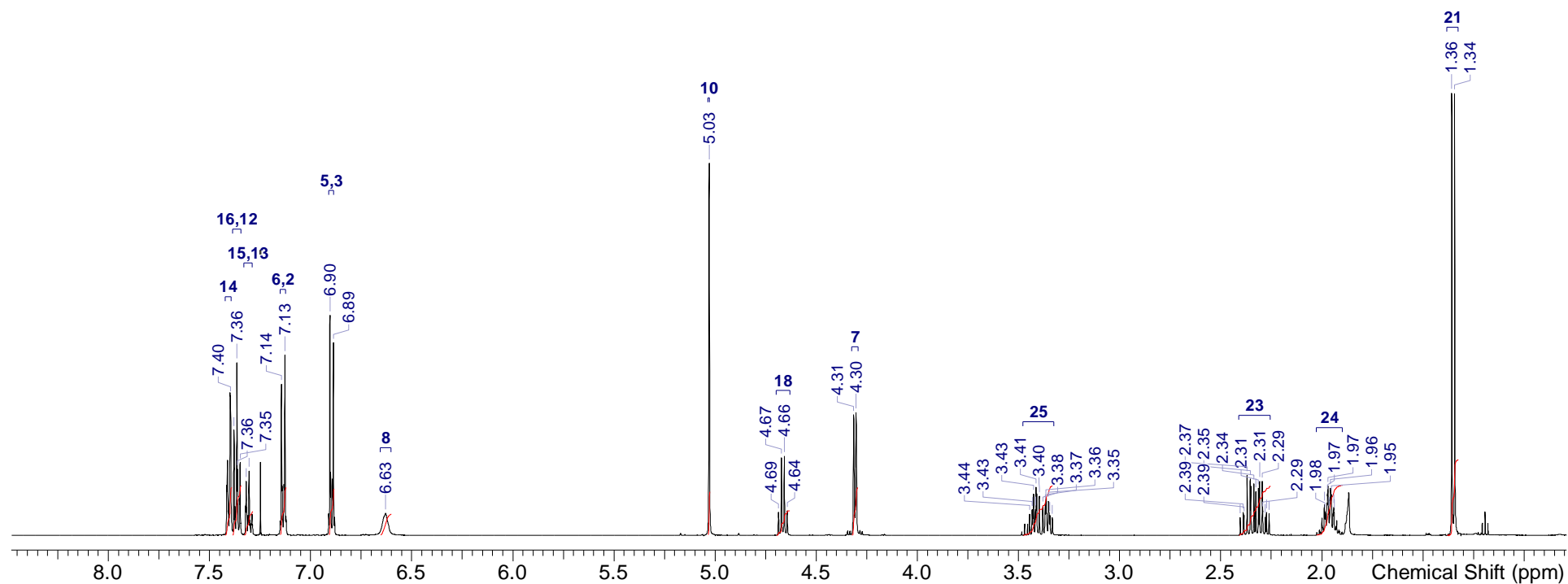
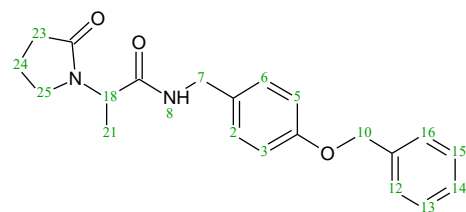


***N*-(2-(benzyloxy)benzyl)-2-(2,5-dioxopyrrolidin-1-yl)propanamide (23) –  $^{13}\text{C}$  NMR**

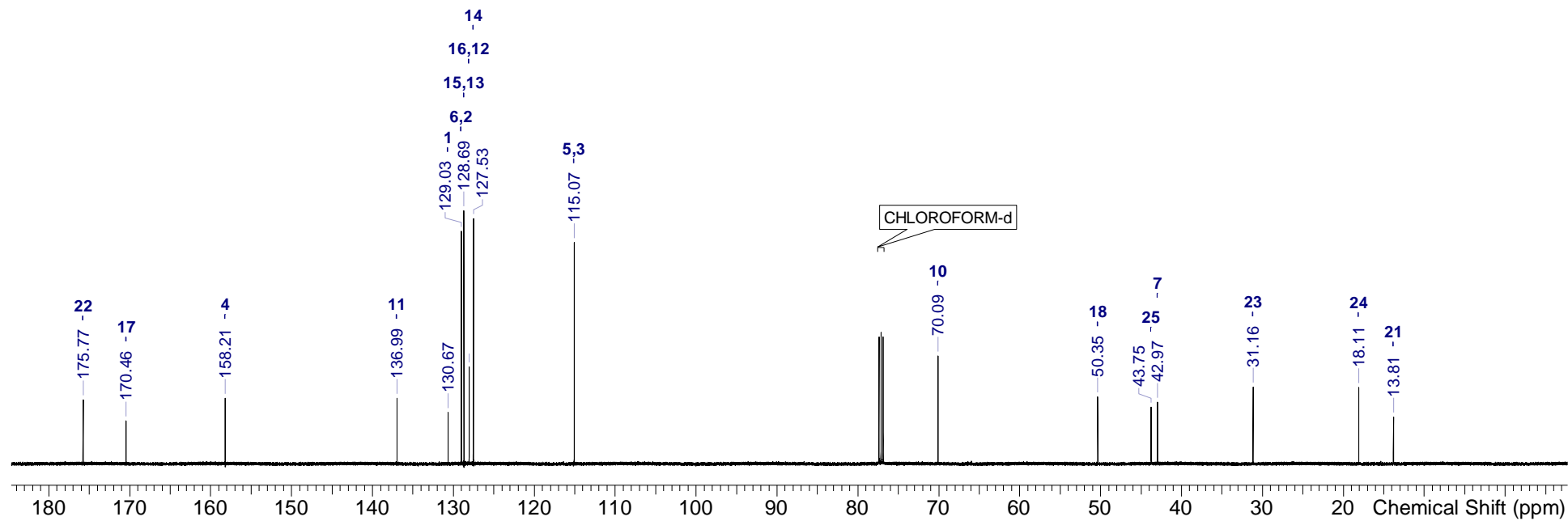
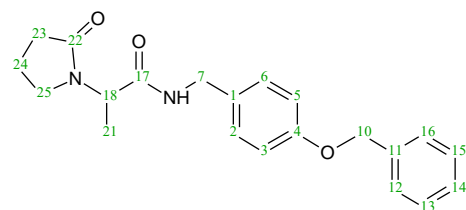




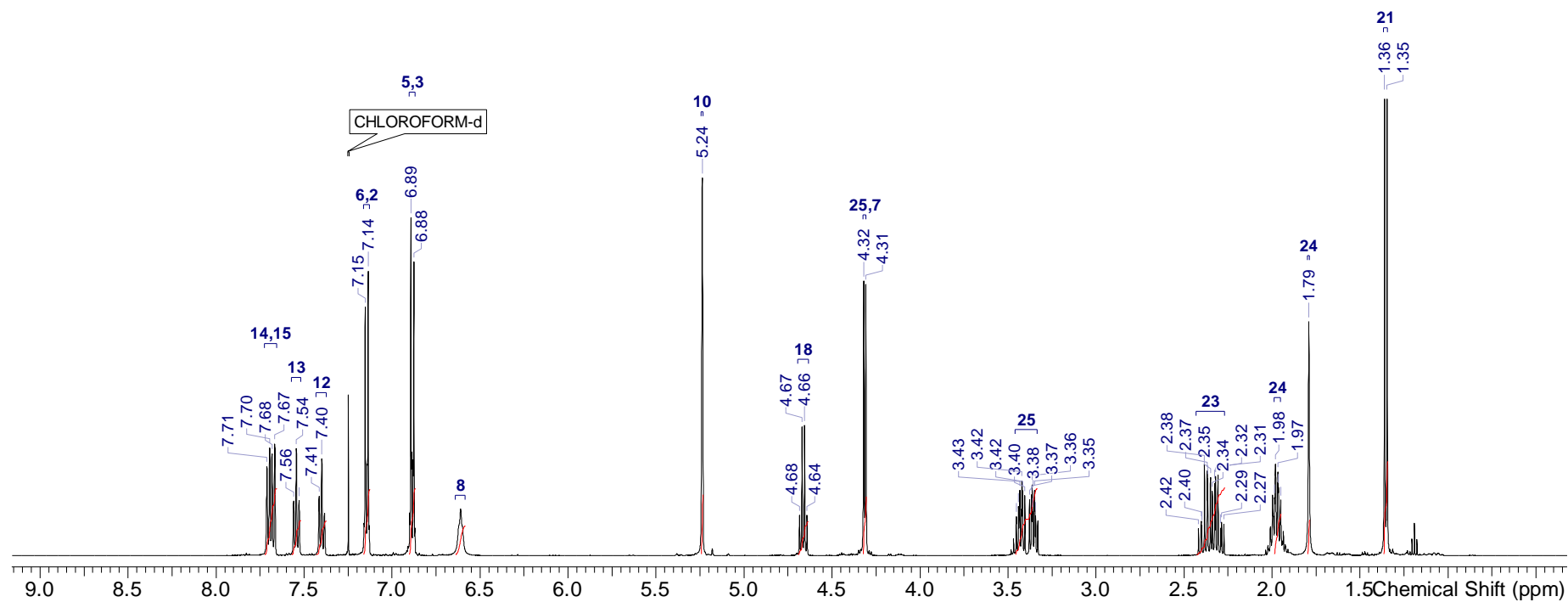
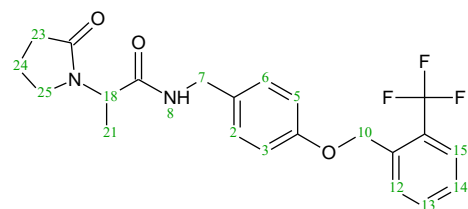
***N*-(4-(benzyloxy)benzyl)-2-(2-oxopyrrolidin-1-yl)propanamide (36) – <sup>1</sup>H NMR**



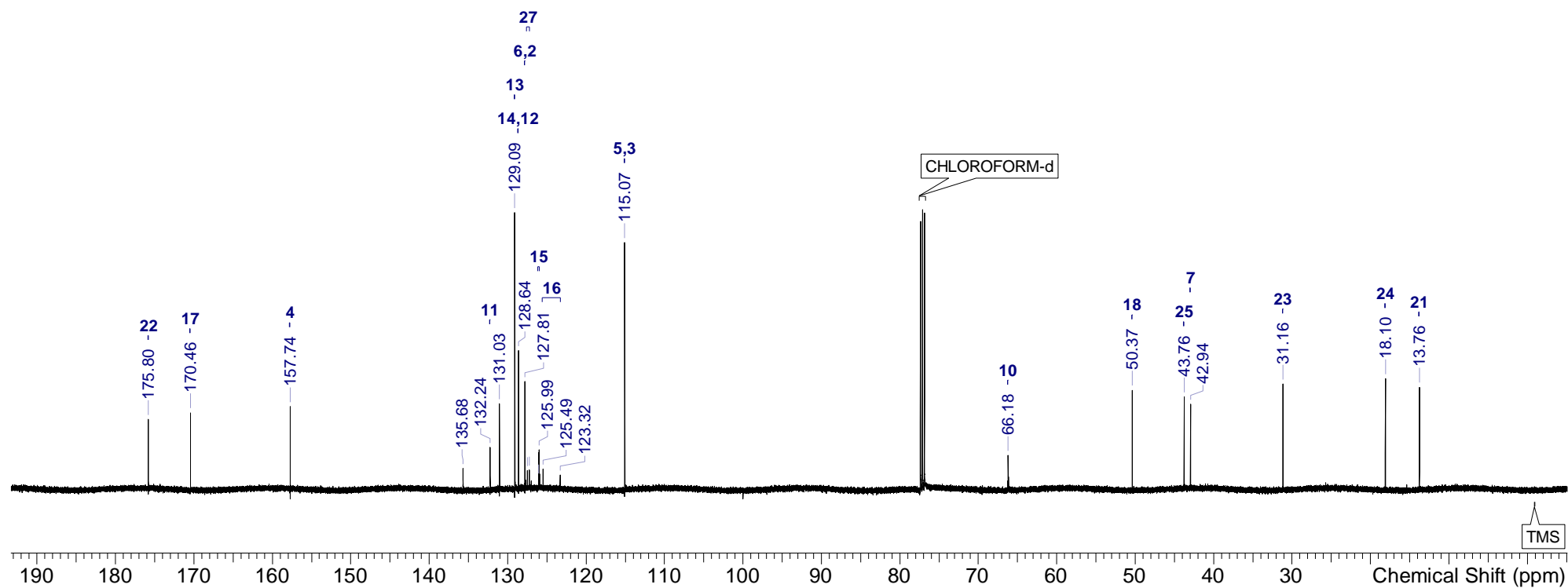
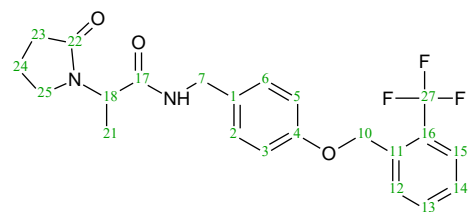
***N*-(4-(benzyloxy)benzyl)-2-(2-oxopyrrolidin-1-yl)propanamide (36) –  $^{13}\text{C}$  NMR**



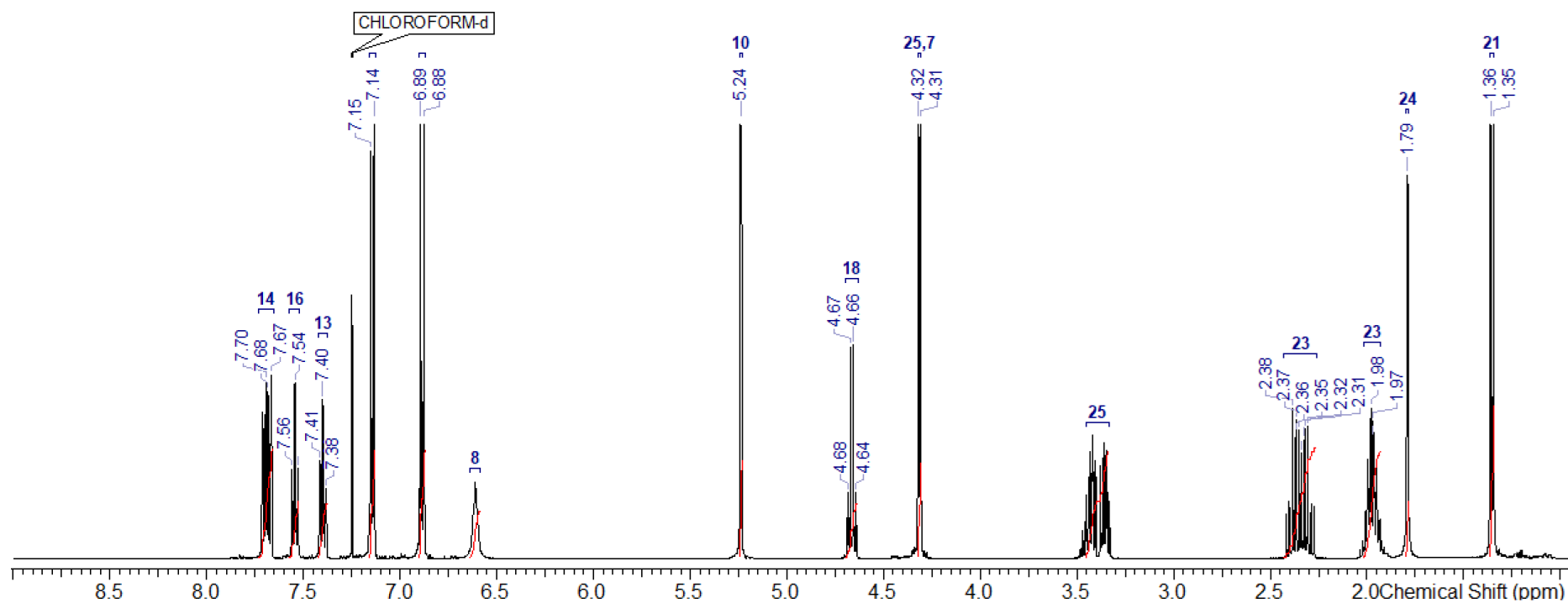
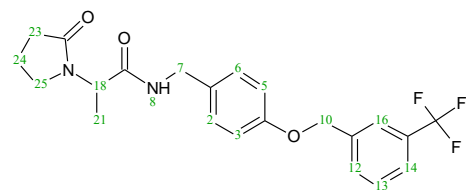
**2-(2-oxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (37) –  $^1\text{H}$  NMR**



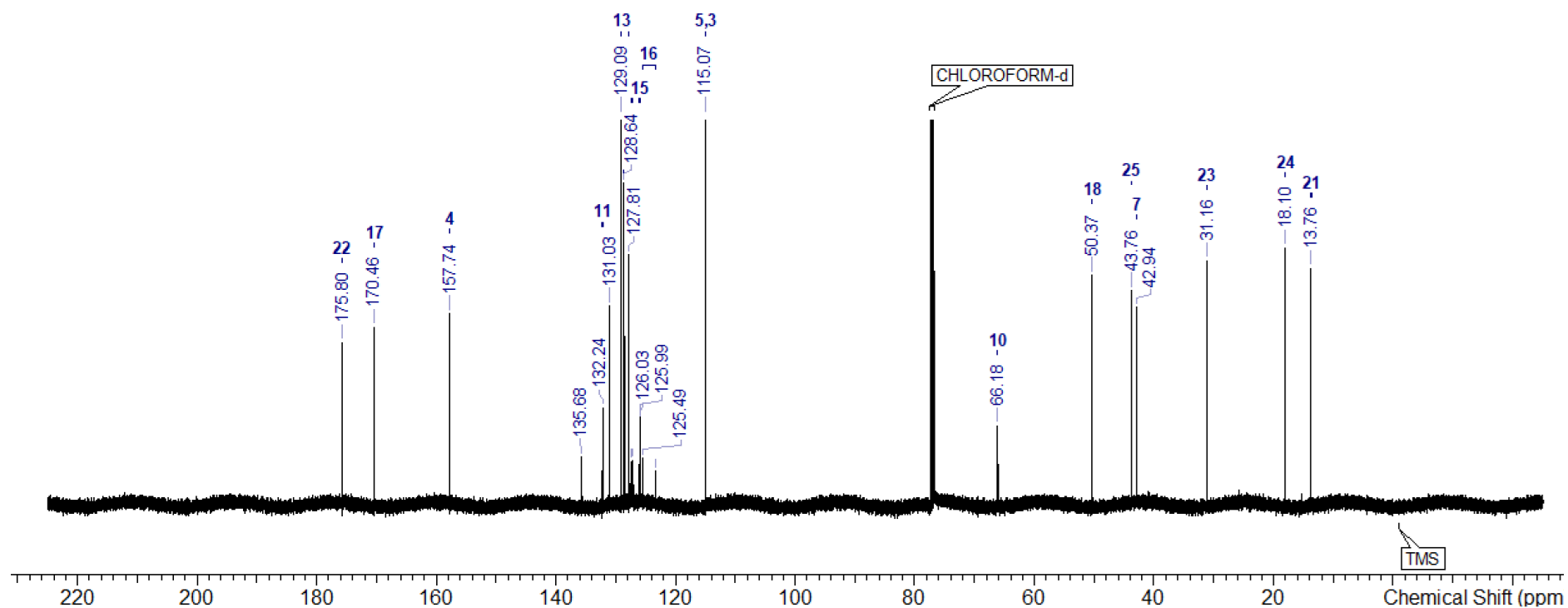
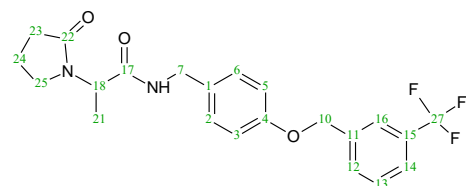
**2-(2-oxopyrrolidin-1-yl)-N-(4-((2-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (37) –  $^{13}\text{C}$  NMR**



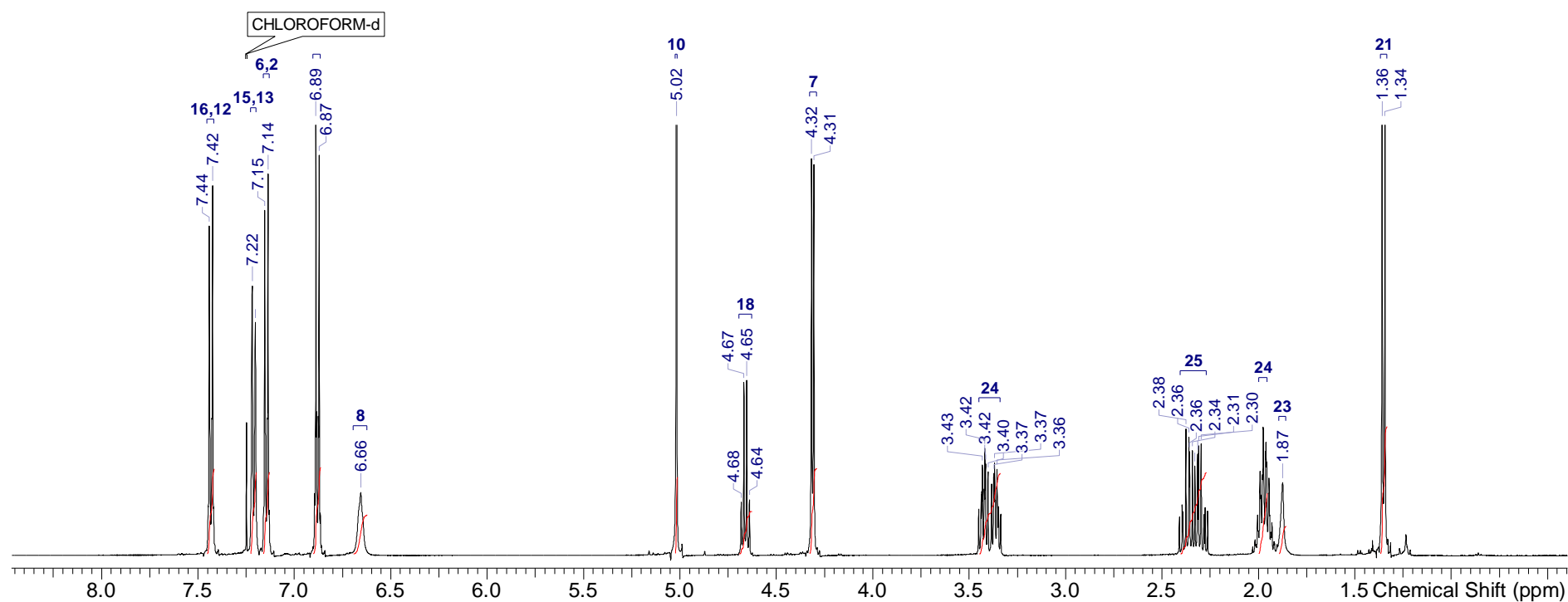
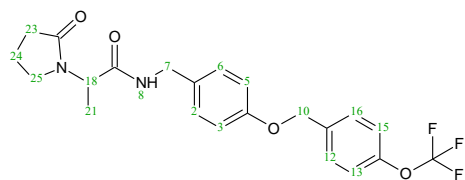
**2-(2-oxopyrrolidin-1-yl)-N-(4-((3-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (38) –  $^1\text{H}$  NMR**



**2-(2-oxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethyl)benzyl)oxy)benzyl)propanamide (38) –  $^{13}\text{C}$  NMR**



**2-(2-oxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (39) –  $^1\text{H}$  NMR**



**2-(2-oxopyrrolidin-1-yl)-N-(4-((4-(trifluoromethoxy)benzyl)oxy)benzyl)propanamide (39) –  $^{13}\text{C}$  NMR**

