

**Supporting Information for  
Direct Asymmetric Reductive Amination**

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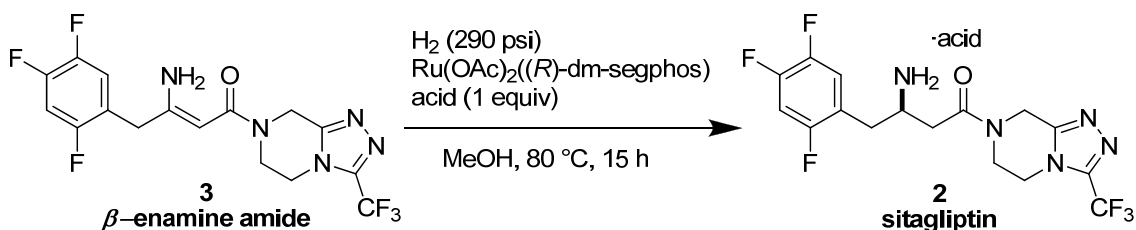
### Complete References 4(d) and 5

- (4) (d) Hansen, K.B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.-K.; Spindler, F.; Malan, C.; Grabowski, E.J.J.; Armstrong, J.D., *J. Am. Chem. Soc.* **2009**, *131*, 8798.
- (5) Kim, D.; Wang, L.; Beconi, M.; Eiermann, G. J.; Fisher, M. H.; He, H.; Hickey, G. J.; Kowalchick, J. E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M. E.; Patel, R. A.; Petrov, A.; Scapin, G.; Patel, S. B.; Roy, R. S.; Wu, J. K.; Wyvratt, M. J.; Zhang, B. B.; Zhu, L.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2005**, *48*, 141.

**General.** Reactions were carried out under a nitrogen atmosphere containing a Teflon coated stirrer bar. Methanol were distilled from Mg prior to use.  $\beta$ -Enamine amide **3** (Clausen, A. M.; Dziadul, B.; Cappuccio, K. L.; Kaba, M.; Starbuck, C.; Hsiao, Y.; Dowling, T. M. *Org. Process Res. Dev.* **2006**, *10*, 723–726) and  $\beta$ -keto amide **1** (Xu, F.; Armstrong, J. D.; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002–13009) were provided by Merck Process Research. Acetoacetanilide **5a** was purchased from Wako Pure Chemical Industries, Ltd. and benzoylacetanilide **5d** was purchased from Tokyo Kasei Kogyo Co., Ltd. Other  $\beta$ -keto amide **5** were synthesized according to known literature procedures (**5b**, **5e**, **5f**, **5h**: Kibler, C. J.; Weissverger, A. *Org. Syn. Collect. Vol. 3*, 108; **5c**, **5g**: Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Ganzer, E.; Kerekjarto, B. v.; Kessler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61–70). NMR spectra were obtained on Bruker DRX500 ( $^1\text{H}$ : 500.13 MHz,  $^{13}\text{C}$ : 125.77 MHz). Optical rotation was obtained on Jasco P-1020. IR spectra were obtained using Avatar 360 FT-IR. Melting points were obtained on Yanaco MP500D. HRMS was obtained on Shimadzu LCMS-IT-TOF.

### General procedure for asymmetric hydrogenation of $\beta$ -enamine amide (**3**)

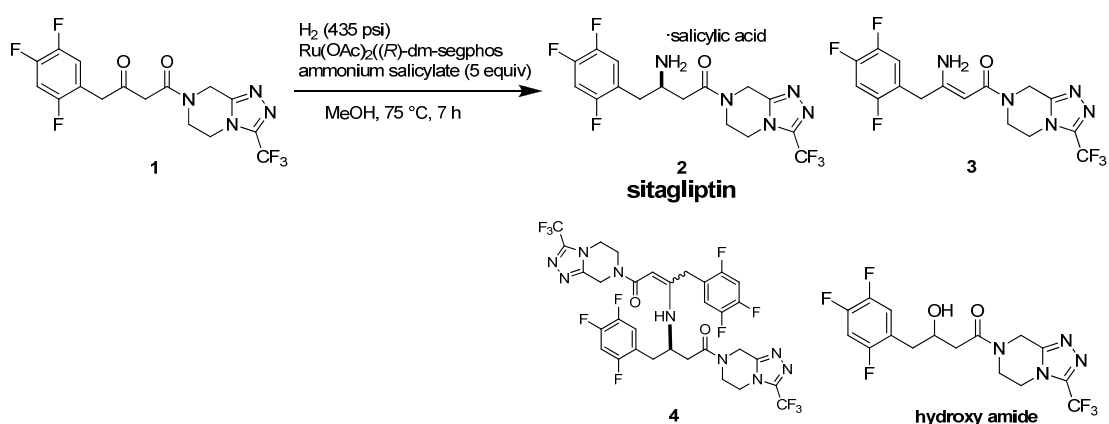
(Table 1)



To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed  $\text{Ru}(\text{OAc})_2((R)\text{-dm-segphos})$  (2.4 mg, 0.025 mmol),

$\beta$ -enamine amide **3** (202.7 mg, 0.500 mmol) and acid (0.500 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of MeOH (2 mL). Hydrogen was initially introduced into the autoclave at a pressure of 145 psi, before being reduced to 14.5 psi by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 290 psi and the solution was stirred at 80 °C for 15 h. The solution was cooled to 20 °C then hydrogen gas was carefully released. Assay yield and optical purity were determined by HPLC (see Analytical Information (S5)).

**Representative procedure for asymmetric reductive amination of  $\beta$ -keto amide (1) (Table 2, entry 1)**



To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed  $\text{Ru}(\text{OAc})_2((R)\text{-dm-segphos})$  (4.7 mg, 0.005 mmol),  $\beta$ -keto amide **1** (203.2 mg, 0.500 mmol) and ammonium salicylate (387.9 mg, 2.500 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of MeOH (2 mL). Hydrogen was initially introduced into the autoclave at a pressure of 145 psi, before being reduced to 14.5 psi by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 435 psi. The autoclave was placed in a pre-warmed oil-bath set at 80 °C, and the mixture was stirred for 7 h. The solution was cooled to 20 °C then hydrogen gas was carefully released. Assay yield and optical purity were determined by HPLC (see Analytical Information (S5)).

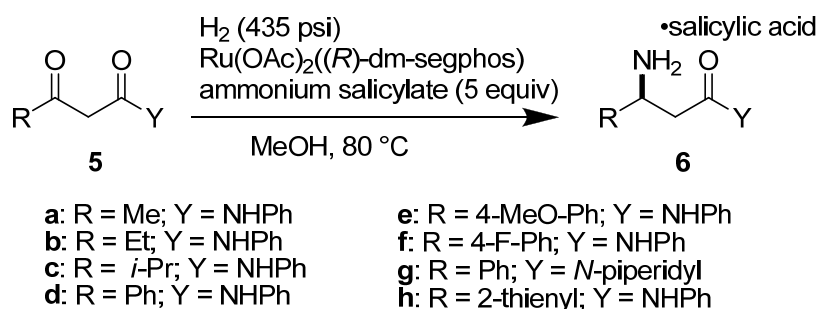
**Concentration profile for reductive amination of  $\beta$ -keto amide (1) (Figure 1c)**

To a 100-mL hastelloy autoclave equipped with a mechanical stirrer, thermometer and a sampling needle was placed  $\text{Ru}(\text{OAc})_2((R)\text{-dm-segphos})$  (115.9 mg, 0.123 mmol),  $\beta$ -keto amide **1** (5.00 g, 12.3 mmol) and ammonium salicylate (9.55 g, 61.5 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of MeOH (50

mL). Hydrogen was initially introduced into the autoclave at a pressure of 145 psi, before being reduced to 14.5 psi by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 435 psi. The reaction mixture was stirred and heated to 70 °C. Time when temperature reached 70 °C was assumed to be beginning time. Reaction sample were obtained at every 1 h (2 drops into a 1.5 mL MeOH), and the concentration of the products determined by HPLC (see Analytical Information (S5)).

### General procedure for asymmetric reductive amination of $\beta$ -keto amide (**5**)

(Table 3)



To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed Ru(OAc)<sub>2</sub>((*R*)-dm-segphos) (23.5 mg, 0.025 mmol),  $\beta$ -keto amide **5** (2.500 mmol) and ammonium salicylate (1.939 g, 12.50 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of MeOH (5 mL). Hydrogen was initially introduced into the autoclave at a pressure of 145 psi, before being reduced to 14.5 psi by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 435 psi and the solution was stirred at 80 °C for 15 h (entry 1–7) or 24 h (entry 8). The solution was cooled to 20 °C then hydrogen gas was carefully released. Assay yield of  $\beta$ -amino amide **6** in the reaction mixture was determined by HPLC (see Analytical Information (S5)).

After evaporation of solvent, 1N HCl (20 mL) was added to the residue, and washed with ethyl acetate (20 mL). The aqueous solution was basified with Na<sub>2</sub>CO<sub>3</sub> (3 g), and extracted with ethyl acetate (20 mL  $\times$  2). The combined organic layer was washed with brine, dried over with Na<sub>2</sub>SO<sub>4</sub>, and then evaporated. The residue was purified by flash chromatography on silica gel using a 95:5:3 mixture of ethyl acetate, methanol, and triethylamine to afford the pure free  $\beta$ -amino amide. Optical purity was determined by chiral HPLC (see Analytical Information (S5)).

**Analytical Information:**

- Assay yield

The analytically pure free  $\beta$ -amino amides were used as the standard sample.

HPLC separation of  $\beta$ -amino amide (**2**):

Column: Agilent Zorbax Extend C-18, i.d. 5  $\mu$ m, 4.6  $\times$  150 mm

Temperature: 23  $^{\circ}$ C

UV Detection: 215 nm

Solvent A: H<sub>2</sub>O/MeOH = 80/20 (v/v), 10 mM TRIS

Solvent B: H<sub>2</sub>O/MeOH = 20/80 (v/v), 10 mM TRIS

Gradient Profile Description: 1.5 mL/min

Time (min)	%A	%B
0	55	45
8	24	76
15	24	76
15.1	55	45

Retention times:

Compound	Time (min)
<b>salicylic acid, ammonium salicylate</b>	0.9
<b>3</b>	6.1
<b>2</b>	4.5
<b>1, hydroxy amide</b>	4.9
<b>4</b>	11.9

HPLC separation of  $\beta$ -amino amides (**6**):

Column: GL Sciences, Inc. Inertsil ODS-3V, i.d. 5  $\mu$ m, 4.6  $\times$  250 mm

Temperature: 40  $^{\circ}$ C

UV Detection: 220 nm

Solvent A: 0.1 vol% HClO<sub>4</sub> in H<sub>2</sub>O

Solvent B: CH<sub>3</sub>CN

Gradient Profile Description: 1.0 mL/min

Time (min)	%A	%B
0	75	25
10	25	75
15	25	75
15.1	75	25

Retention times:

Compound	Time (min)
<b>6a</b>	4.3
<b>6b</b>	4.9
<b>6c</b>	6.0
<b>6d</b>	7.1
<b>6e</b>	7.4
<b>6f</b>	7.5
<b>6g</b>	7.8
<b>6h</b>	6.2
<b>salicylic acid, ammonium salicylate</b>	10.0

- Enantiomeric excess assay

HPLC separation of  $\beta$ -amino amide (**2**):

Column: Daicel Chiralpak AD-H, i.d. 5  $\mu$ m, 4.6  $\times$  250 mm

Temperature: 35  $^{\circ}$ C

UV Detection: 268 nm

Eluent: hexane/ethanol/diethylamine = 40/60/0.1

Method Description: 0.8 mL/min

Retention times:

minor isomer (min)	Sitagliptin (min)
12.3	14.3

HPLC separation of  $\beta$ -amino amides (**6**)

Column: Daicel Chiralpak AD-H, i.d. 5  $\mu$ m, 4.6  $\times$  250 mm

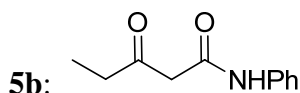
Temperature: 35  $^{\circ}$ C

UV Detection: 254 nm

Method Description:

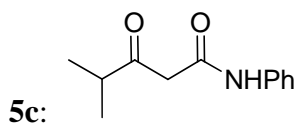
Compound	Flow (mL/min)	i-PrOH %	EtOH %	hexane %	Et <sub>2</sub> NH %	<i>t</i> <sub>1</sub> (min)	<i>t</i> <sub>2</sub> (min)
<b>6a</b>	0.5	0	10	90	0.1	24.6	26.7
<b>6b</b>	0.5	20	0	80	0.1	10.1	12.0
<b>6c</b>	0.5	20	0	80	0.1	10.0	12.3

<b>6d</b>	0.8	0	60	40	0.1	7.8	11.7
<b>6e</b>	0.5	30	0	70	0.1	12.1	14.7
<b>6f</b>	0.5	0	60	40	0.1	11.2	12.3
<b>6g</b>	0.5	10	0	90	0.1	21.4	22.9
<b>6h</b>	0.5	0	60	40	0.1	12.1	15.4



### 3-Oxo-N-phenylpentanamide

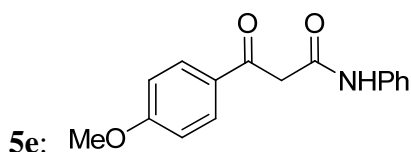
mp: 85.2–86.9 °C; IR (KBr) 3289, 3256, 3196, 3136, 3081, 2976, 1715, 1660, 1599, 1561, 1501, 1445, 1415, 1364, 759, 743, 692; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.17 (s, 1H), 7.54–7.57 (m, 2H), 7.31–7.36 (m, 2H), 7.10–7.15 (m, 1H), 3.58 (s, 2H), 2.63 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 208.1, 163.4, 137.5, 129.0, 124.5, 120.1, 48.7, 37.5, 7.4; HRMS (ESI+) *m/z* calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>Na, [M + Na]<sup>+</sup> 214.0839, found 214.0840.



### 4-Methyl-3-oxo-N-phenylpentanamide

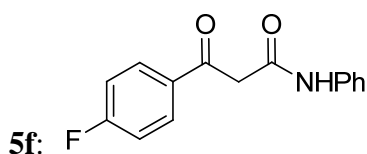
(lit.: Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Kerekjarto, B. v.; Kessler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61-70.)

bp: 154–156 °C/67–80 Pa; IR (neat) 3305, 3201, 3140, 3062, 2972, 2934, 2875, 1716, 1661, 1600, 1549, 1499, 1467, 1445, 1412, 1385, 1331, 1250, 1178, 1157, 1072, 1047, 756, 693; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.21 (s, 1H), 7.54–7.57 (m, 2H), 7.30–7.35 (m, 2H), 7.09–7.14 (m, 1H), 3.73 (s, 2H), 2.74 (sept, J = 6.9 Hz, 1H), 1.17 (d, J = 6.9 Hz, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 211.5, 163.6, 137.5, 129.0, 124.5, 120.1, 46.9, 42.3, 17.7; HRMS (ESI+) *m/z* calcd for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>Na, [M + Na]<sup>+</sup> 228.0995, found 228.0991.



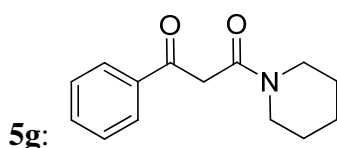
### 3-(4-Methoxyphenyl)-3-oxo-N-phenylpropanamide

mp: 129.9–131.9 °C; IR (KBr) 3291, 3249, 3073, 2941, 1672, 1650, 1598, 1573, 1541, 1512, 1446, 1423, 1336, 1309, 1288, 1258, 1180, 1162, 1111, 1021, 963, 854, 758, 696; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.39 (s, 1H), 8.00–8.04 (m, 2H), 7.56–7.61 (m, 2H), 7.30–7.36 (m, 2H), 7.09–7.14 (m, 1H), 6.95–7.00 (m, 2H), 4.06 (s, 2H), 3.89 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.8, 164.6, 137.6, 131.1, 129.0, 129.0, 124.4, 120.1, 114.2, 55.6, 45.1; HRMS (ESI+) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>Na, [M + Na]<sup>+</sup> 292.0944, found 292.0946.



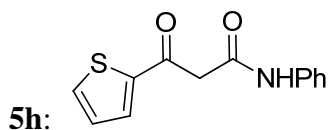
### 3-(4-Fluorophenyl)-3-oxo-N-phenylpropanamide

mp: 131.5–133.0 °C; IR (KBr) 3293, 3065, 1683, 1662, 1592, 1533, 1507, 1499, 1236, 1204, 1159, 1012, 839, 754, 688; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.16 (s, 1H), 8.05–8.10 (m, 2H), 7.55–7.59 (m, 2H), 7.31–7.36 (m, 2H), 7.16–7.21 (m, 2H), 7.10–7.15 (m, 1H), 4.08 (s, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.7, 166.5 (d, 257.8 Hz), 163.4, 137.5, 132.5 (d, 3.8 Hz), 131.5 (d, J = 8.8 Hz), 129.0, 124.6, 120.1, 116.2 (d, J = 22.6 Hz), 45.7; HRMS (ESI+) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>NO<sub>2</sub>FNa, [M + Na]<sup>+</sup> 280.0744, found 280.0752.



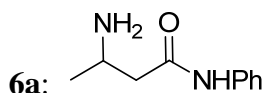
### 3-Oxo-1-phenyl-3-piperidin-1-ylpropan-1-one

bp: 172–173 °C/67–80 Pa; IR (neat) 3061, 3003, 2938, 2857, 1689, 1633, 1481, 1445, 1382, 1270, 1226, 1139, 1020, 953, 853, 762, 691; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ (ca. 3:2 keto-enol mixture) 15.47 (s, 2/5 of 1H, enol OH), 8.01–8.05 (m, 3/5 of 2H, keto aromatic Hs), 7.76–7.79 (m, 2/5 of 2H, enol aromatic Hs), 7.56–7.60 (m, 3/5 of 1H, keto aromatic H), 7.45–7.50 (m, 3/5 of 2H, keto aromatic Hs), 7.37–7.43 (m, 2/5 of 3H, enol aromatic Hs), 5.83 (s, 2/5 of 1H, enol olefinic H), 4.10 (s, 3/5 of 2H, CH<sub>2</sub>), 3.55–3.62 (m, 3/5 of 2H and 2/5 of 4H, keto and enol CH<sub>2</sub>N), 3.40–3.45 (m, 3/5 of 2H, keto CH<sub>2</sub>N), 1.52–1.72 (m, 6H, both remaining piperidino Hs); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.0, 171.5, 165.0, 136.2, 135.2, 133.6, 130.5, 128.7, 128.7, 128.4, 125.9, 84.3, 47.7, 46.1, 43.0, 26.3, 25.5, 24.5, 24.5, 24.4; HRMS (ESI+) *m/z* calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>Na, [M + Na]<sup>+</sup> 254.1152, found 254.1147.



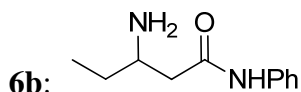
**3-Oxo-N-phenyl-3-(thiophen-2-yl)propanamide**

mp: 130.6–132.9 °C; IR (KBr) 3311, 3196, 3144, 3087, 1667, 1655, 1606, 1551, 1498, 1443, 1416, 1346, 1309, 1279, 1249, 1155, 1061, 998, 959, 759, 735, 728, 693; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.28 (s, 1H), 7.88 (dd, J = 1.1, 3.9 Hz, 1H), 7.78 (dd, J = 1.1, 4.9 Hz, 1H), 7.56–7.59 (m, 2H), 7.31–7.36 (m, 2H), 7.20 (dd, J = 3.9, 4.9 Hz, 1H), 7.10–7.15 (m, 1H), 4.06 (s, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 188.8, 163.1, 143.1, 137.5, 136.1, 134.1, 129.0, 128.7, 124.6, 120.1, 46.0; HRMS (ESI+) *m/z* calcd for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>SNa, [M + Na]<sup>+</sup> 268.0403, found 268.0416.



**(-)-3-Amino-N-phenylbutanamide**

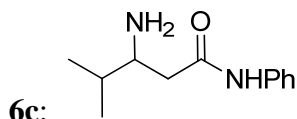
mp: 72.0–74.0 °C; [α]<sub>D</sub><sup>20</sup> -23.0 (*c* 0.22, MeOH); 94.7% ee determined by HPLC (Chiralpak AD-H, hexane:EtOH:diethylamine = 90:10:0.1, 0.5 mL/min, λ = 254 nm, *t*<sub>1</sub> (minor) = 24.6 min, *t*<sub>2</sub> (major) = 26.7 min); IR (KBr) 3347, 3288, 3240, 3184, 2954, 2880, 1672, 1602, 1575, 1557, 1499, 1443, 1404, 1339, 1296, 1254, 1187, 1086, 961, 757, 693; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.21 (s, 1H), 7.52–7.56 (m, 2H), 7.27–7.32 (m, 2H), 7.04–7.09 (m, 1H), 3.30–3.43 (m, 1H), 2.46 (dd, J = 3.1, 15.8 Hz, 1H), 2.28 (dd, J = 8.9, 15.8 Hz, 1H), 1.54 (s, 2H), 1.22 (d, J = 6.4 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 170.2, 138.5, 128.9, 123.7, 119.7, 45.2, 44.5, 25.1; HRMS (ESI+) *m/z* calcd for C<sub>10</sub>H<sub>15</sub>N<sub>2</sub>O, [M + H]<sup>+</sup> 178.1179, found 179.1182.



**(-)-3-Amino-N-phenylpentanamide**

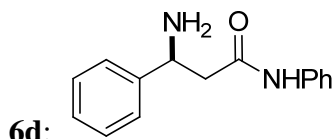
[α]<sub>D</sub><sup>20</sup> -36.0 (*c* 0.21, MeOH); 98.1% ee determined by HPLC (Chiralpak AD-H, hexane:2-propanol:diethylamine = 80:20:0.1, 0.5 mL/min, λ = 254 nm, *t*<sub>1</sub> (major) = 10.1 min, *t*<sub>2</sub> (minor) = 12.0 min); IR (KBr) 3310, 3195, 3134, 3057, 2962, 2877, 1669, 1602, 1556, 1499, 1442, 1383, 1343, 1313, 1177, 755, 692; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.41 (s, 1H), 7.52–7.57 (m, 2H), 7.27–7.32 (m, 2H), 7.04–7.08 (m, 1H), 3.04–3.11 (m, 1H), 2.48 (dd, J = 2.7, 15.9 Hz, 1H), 2.27 (dd, J = 9.5, 15.9 Hz, 1H), 1.51–1.60 (m, 1H), 1.52 (br, 2H), 1.37–1.47 (m, 1H), 0.97 (t, J = 7.5 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

$\delta$  170.4, 138.6, 128.9, 123.6, 119.7, 50.4, 43.3, 31.7, 10.2; HRMS (ESI+)  $m/z$  calcd for  $C_{11}H_{17}N_2O$ ,  $[M + H]^+$  193.1335, found 193.1335.



**(-)-3-Amino-4-methyl-N-phenylpentanamide**

mp: 37.5–39.0 °C;  $[\alpha]_D^{20}$  -42.3 (*c* 0.22, MeOH); 98.9% ee determined by HPLC (Chiralpak AD-H, hexane:2-propanol:diethylamine = 80:20:0.1, 0.5 mL/min,  $\lambda$  = 254 nm,  $t_1$  (major) = 10.0 min,  $t_2$  (minor) = 12.3 min); IR (KBr) 3347, 3277, 3177, 3128, 3061, 2961, 2876, 1663, 1599, 1546, 1499, 1443, 1369, 1314, 1251, 756, 694;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  10.60 (s, 1H), 7.53–7.57 (m, 2H), 7.27–7.32 (m, 2H), 7.03–7.08 (m, 1H), 2.95 (ddd, *J* = 2.3, 5.4, 10.7 Hz, 1H), 2.41 (dd, *J* = 2.3, 15.9 Hz, 1H), 2.27 (dd, *J* = 10.7, 15.9 Hz, 1H), 1.61–1.72 (m, 1H), 1.40–1.60 (br, 2H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  170.9, 138.6, 128.8, 123.6, 119.7, 54.2, 41.3, 34.5, 18.7, 17.3; HRMS (ESI+)  $m/z$  calcd for  $C_{12}H_{19}N_2O$ ,  $[M + H]^+$  207.1492, found 207.1487.

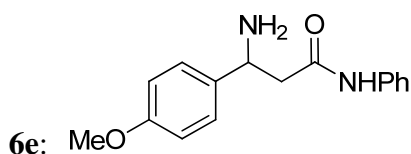


**(3S)-3-Amino-N,3-diphenylpropanamide**

(lit. Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.)

mp: 135.8–138.2 °C;  $[\alpha]_D^{20}$  +25.4 (*c* 0.20, MeOH); 99.2% ee determined by HPLC (Chiralpak AD-H, hexane:EtOH:diethylamine = 40:60:0.1, 0.8 mL/min,  $\lambda$  = 254 nm,  $t_1$  (*R* isomer) = 7.0 min,  $t_2$  (*S* isomer) = 9.3 min); IR (KBr) 3316, 1657, 1599, 1529, 1498, 1442, 1327, 756, 702;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  9.82 (s, 1H), 7.52–7.56 (m, 2H), 7.26–7.39 (m, 7H), 7.06–7.11 (m, 1H), 4.38 (dd, *J* = 5.4, 7.9 Hz, 1H), 2.62–2.74 (m, 2H), 1.83 (br, 2H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  169.6, 145.0, 138.3, 128.9, 128.9, 127.6, 125.6, 123.9, 119.8, 53.0, 45.7; HRMS (ESI+)  $m/z$  calcd for  $C_{15}H_{17}N_2O$ ,  $[M + H]^+$  241.1335, found 241.1331. The absolute configuration was established by converting the amine into (3*S*)-3-acetamido-*N*,3-diphenylpropanamide (Ac<sub>2</sub>O, triethylamine,  $CH_2Cl_2$ ). An authentic sample was prepared from ethyl (3*S*)-3-amino-3-phenylpropanoate hydrochloride by acylation of the amino group

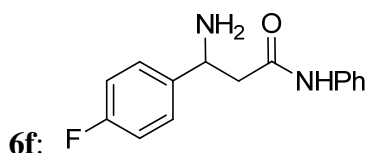
(Ac<sub>2</sub>O-triethylamine), hydrolysis of the ester group (NaOH–EtOH) and followed by EDC coupling with aniline,  $[\alpha]_D^{20} -21.6$  (*c* 0.26, EtOH).



**(+)-3-Amino-3-(4-methoxyphenyl)-N-phenylpropanamide**

(lit. Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.)

mp: 146.2–148.1 °C;  $[\alpha]_D^{20} +36.4$  (*c* 0.20, MeOH); 99.6% ee determined by HPLC (Chiralpak AD-H, hexane:2-propanol:diethylamine = 70:30:0.1, 0.5 mL/min,  $\lambda = 254$  nm,  $t_1$  (major) = 12.1 min,  $t_2$  (minor) = 14.7 min); IR (KBr) 3305, 3057, 2943, 2868, 2840, 1859, 1599, 1530, 1519, 1442, 1249, 1084, 1036, 830, 751, 701; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.82 (s, 1H), 7.52–7.56 (m, 2H), 7.29–7.34 (m, 2H), 7.22–7.26 (m, 2H), 7.06–7.11 (m, 1H), 6.87–6.91 (m, 2H), 4.34 (dd, *J* = 5.3, 8.0 Hz, 1H), 3.80 (s, 3H), 2.62–2.70 (m, 2H), 1.79 (br, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  169.7, 158.9, 138.3, 137.2, 128.9, 126.7, 123.9, 119.8, 114.2, 55.3, 52.4, 45.8; HRMS (ESI+) *m/z* calcd for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>,  $[M + H]^+$  271.1441, found 271.1453.

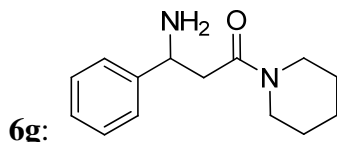


**(+)-3-Amino-3-(4-fluorophenyl)-N-phenylpropanamide**

(lit. Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.)

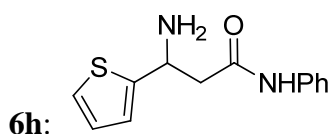
mp: 146.7–149.0 °C;  $[\alpha]_D^{20} +26.5$  (*c* 0.22, MeOH); 99.4% ee determined by HPLC (Chiralpak AD-H, hexane:EtOH:diethylamine = 40:60:0.1, 0.5 mL/min,  $\lambda = 254$  nm,  $t_1$  (minor) = 11.2 min,  $t_2$  (major) = 12.3 min); IR (KBr) 3318, 3063, 2942, 2869, 1655, 1600, 1582, 1630, 1510, 1500, 1443, 1410, 1329, 1226, 1179, 833, 753, 727, 702; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.54 (s, 1H), 7.50–7.55 (m, 2H), 7.27–7.34 (m, 4H), 7.07–7.12 (m, 1H), 7.01–7.06 (m, 2H), 4.40 (m, 1H), 2.63–2.67 (m, 2H), 1.81 (br, 2H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  169.4, 162.0 (d, *J* = 246.5 Hz), 140.7 (d, *J* = 3.8 Hz),

138.1, 129.0, 127.3 (d,  $J = 7.5$  Hz), 124.1, 119.9, 115.7 (d,  $J = 21.4$  Hz), 52.3, 45.9; HRMS (ESI+)  $m/z$  calcd for  $C_{15}H_{16}N_2OF$ ,  $[M + H]^+$  259.1241, found 259.1249.



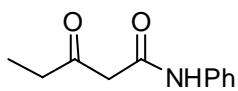
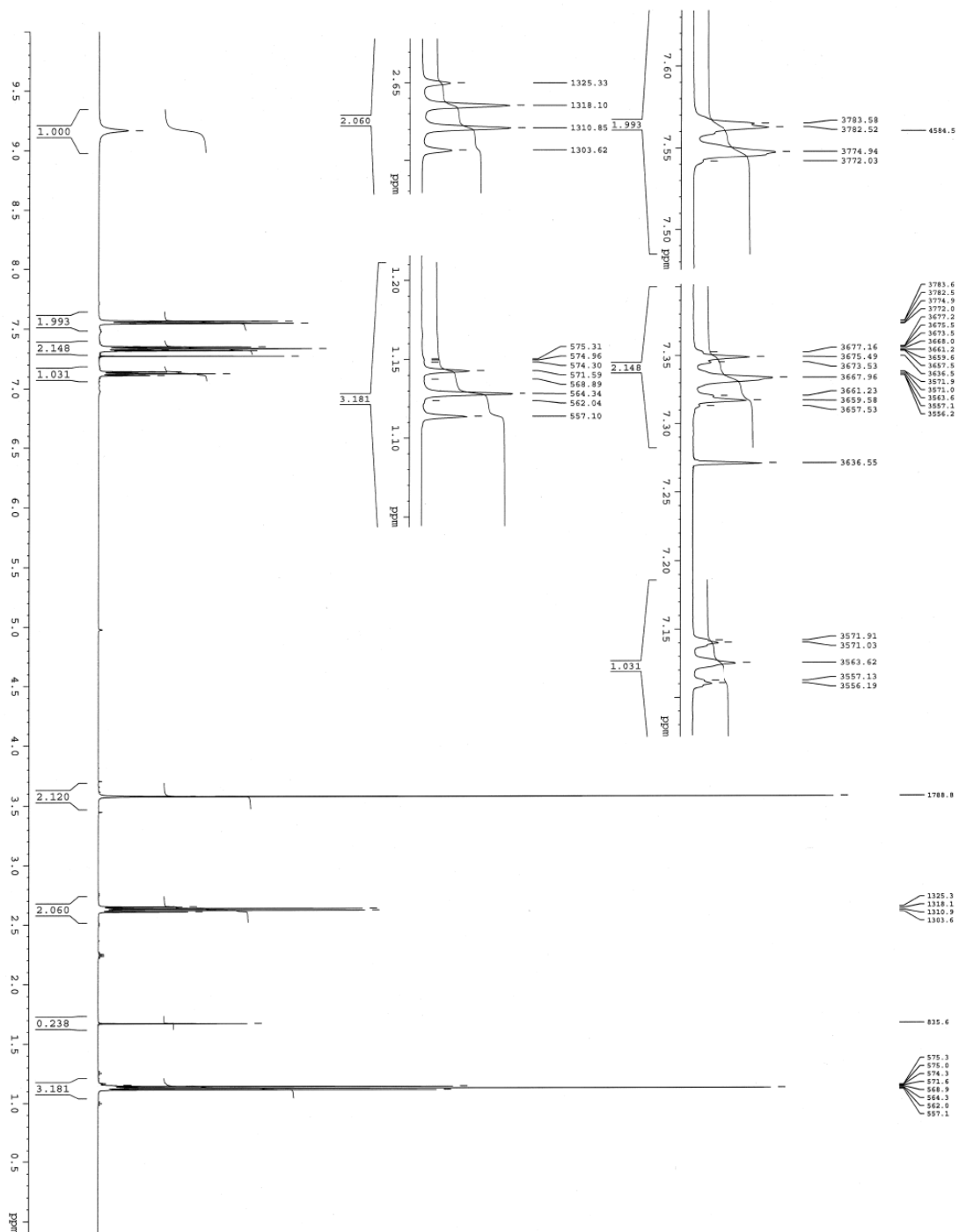
**(-)-3-Amino-3-phenyl-1-(piperidin-1-yl)propan-1-one**

$[\alpha]_D^{20}$   $-7.5$  ( $c$  0.21, MeOH); 97.9% ee determined by HPLC (Chiralpak AD-H, hexane:2-propanol:diethylamine = 90:10:0.1, 0.5 mL/min,  $\lambda = 254$  nm,  $t_1$  (major) = 21.4 min,  $t_2$  (minor) = 22.9 min); IR (neat) 3371, 3300, 3026, 2935, 2856, 1634, 1492, 1444, 1370, 1351, 1281, 1250, 1219, 1137, 1021, 954, 916, 853, 766, 703;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.38–7.42 (m, 2H), 7.31–7.35 (m, 2H), 7.23–7.27 (m, 1H), 4.51 (dd,  $J = 4.1, 8.8$  Hz, 1H), 3.49–3.61 (m, 2H), 3.25–3.35 (m, 2H), 2.54–2.65 (m, 2H), 1.91 (br, 2H), 1.57–1.64 (m, 2H), 1.37–1.55 (m, 4H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  169.4, 145.3, 128.5, 127.2, 126.4, 52.7, 46.4, 43.2, 42.6, 26.2, 25.5, 24.5; HRMS (ESI+)  $m/z$  calcd for  $C_{14}H_{21}N_2O$ ,  $[M + H]^+$  233.1648, found 233.1645.

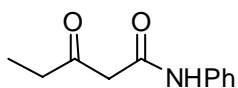
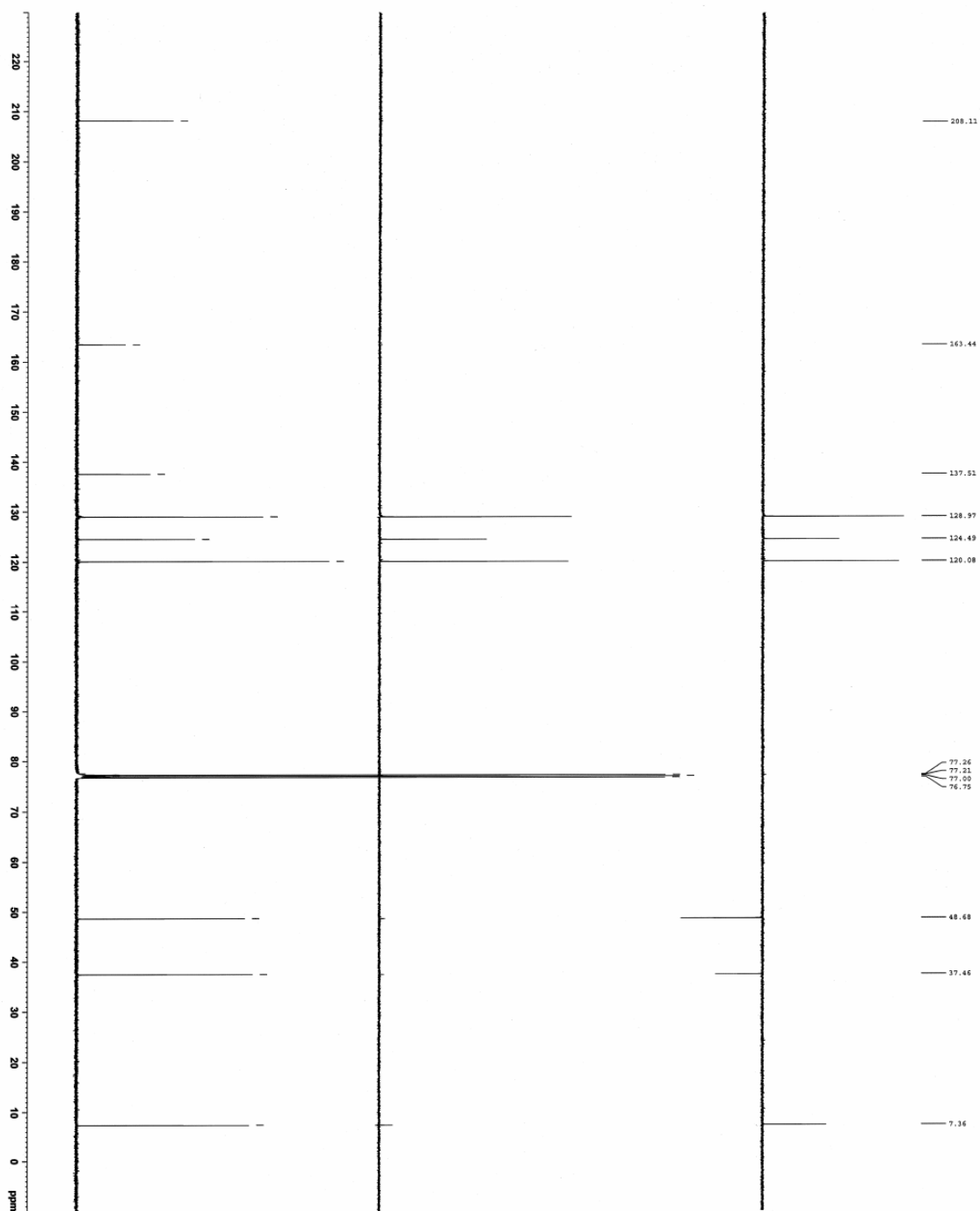


**(+)-3-Amino-N-phenyl-3-(thiophen-2-yl)propanamide**

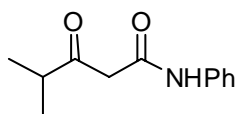
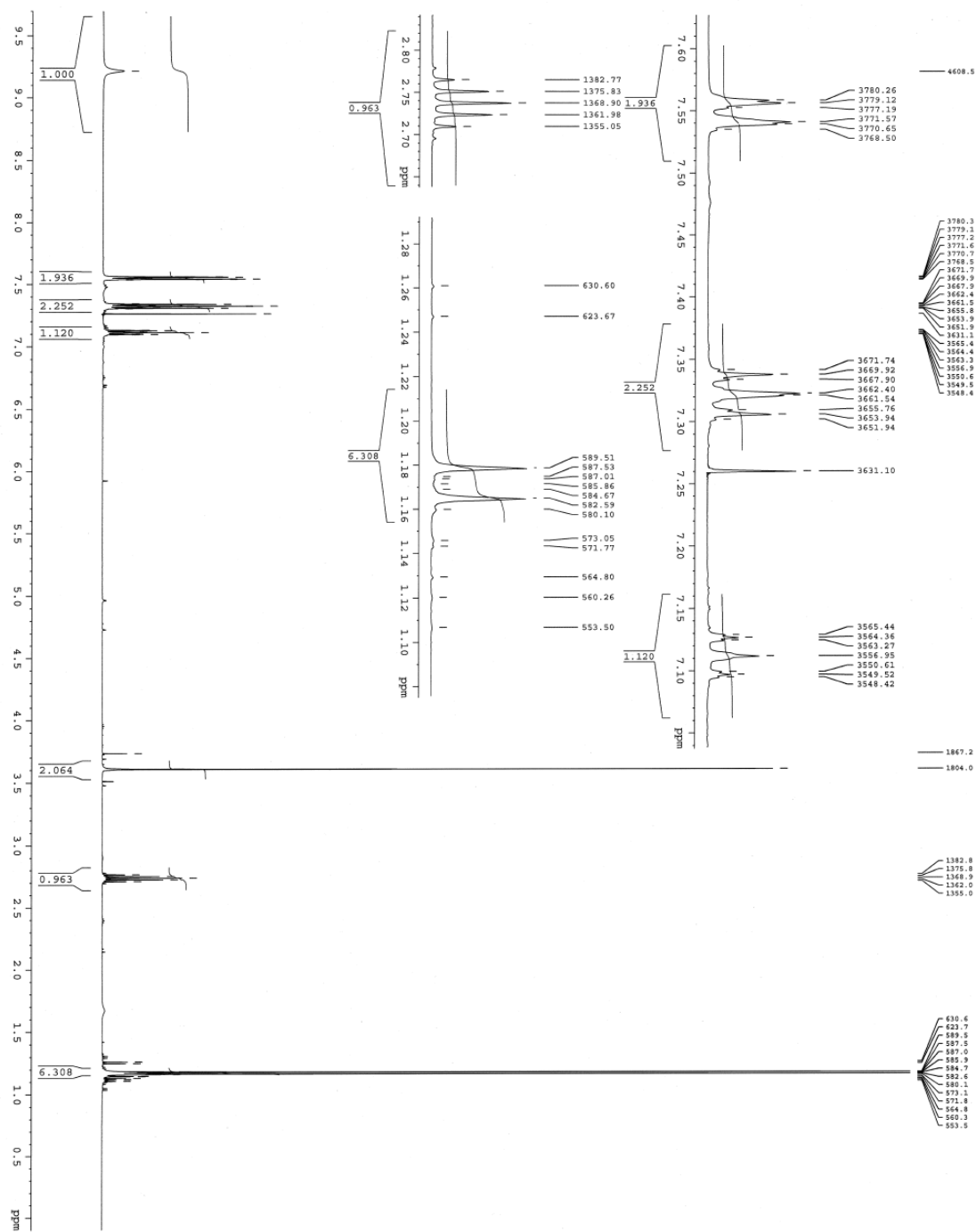
mp: 140.5–142.4 °C;  $[\alpha]_D^{20}$   $+26.8$  ( $c$  0.21, MeOH); 99.6% ee determined by HPLC (Chiralpak AD-H, hexane:EtOH:diethylamine = 40:60:0.1, 0.5 mL/min,  $\lambda = 254$  nm,  $t_1$  (minor) = 12.1 min,  $t_2$  (major) = 15.4 min); IR (KBr) 3344, 3271, 3247, 3189, 3126, 3097, 3063, 3021, 2977, 1673, 1622, 1611, 1559, 1490, 1444, 1255, 1173, 1025, 906, 838, 761, 738, 704, 694;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  9.57 (s, 1H), 7.51–7.55 (m, 2H), 7.29–7.34 (m, 2H), 7.21–7.24 (m, 1H), 7.07–7.12 (m, 1H), 6.95–6.98 (m, 2H), 4.69 (dd,  $J = 3.5, 9.6$  Hz, 1H), 2.83 (dd,  $J = 3.5, 15.7$  Hz, 1H), 2.74 (dd,  $J = 9.6, 15.7$  Hz, 1H), 1.94 (br, 2H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  169.0, 149.4, 138.1, 128.9, 127.0, 124.1, 124.1, 123.0, 119.9, 48.9, 46.2; HRMS (ESI+)  $m/z$  calcd for  $C_{13}H_{15}N_2OS$ ,  $[M + H]^+$  247.0900, found 247.0905.



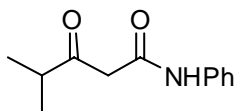
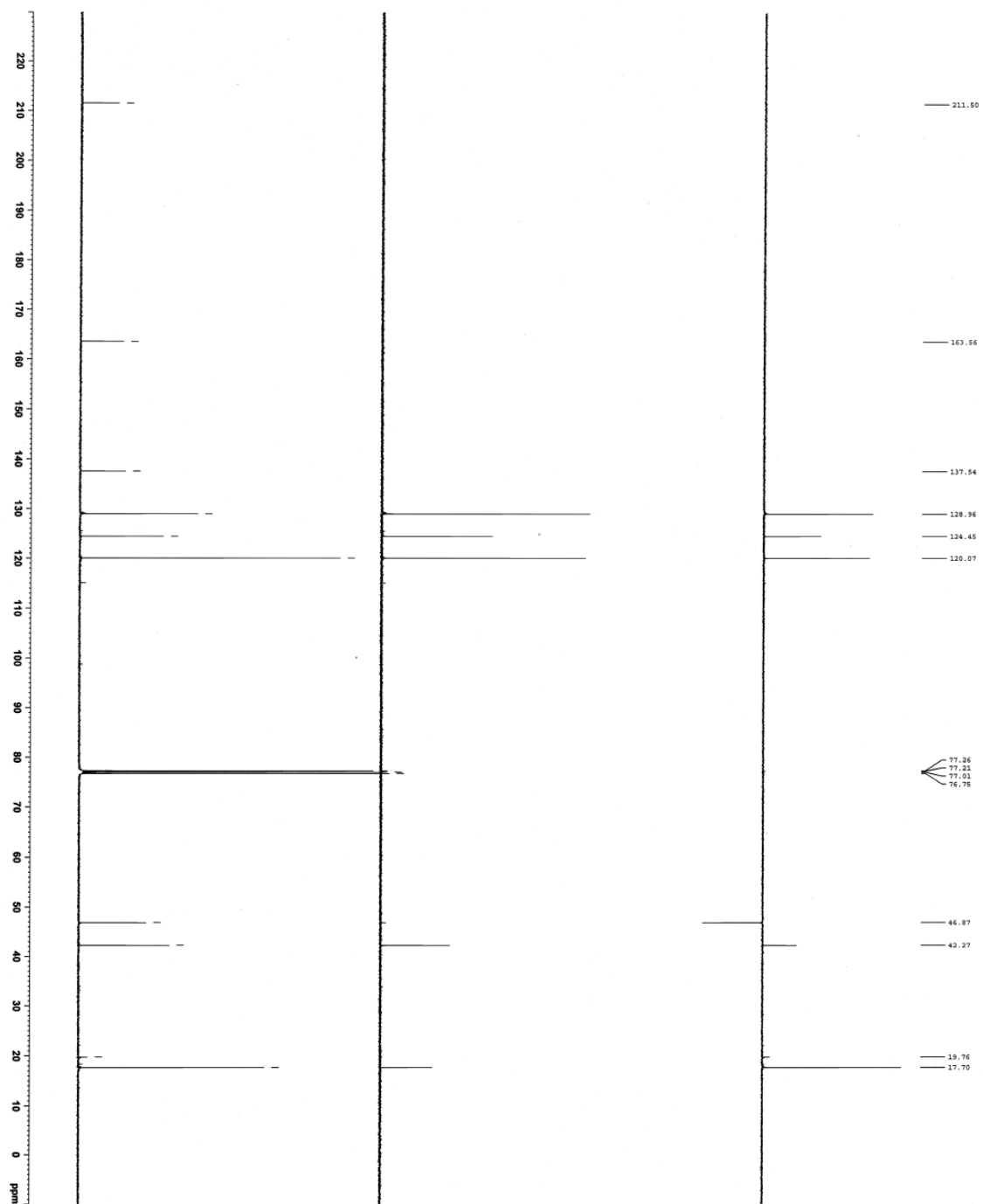
3-Oxo-N-phenylpentanamide **5b**  
 $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



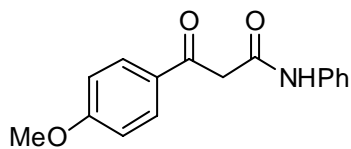
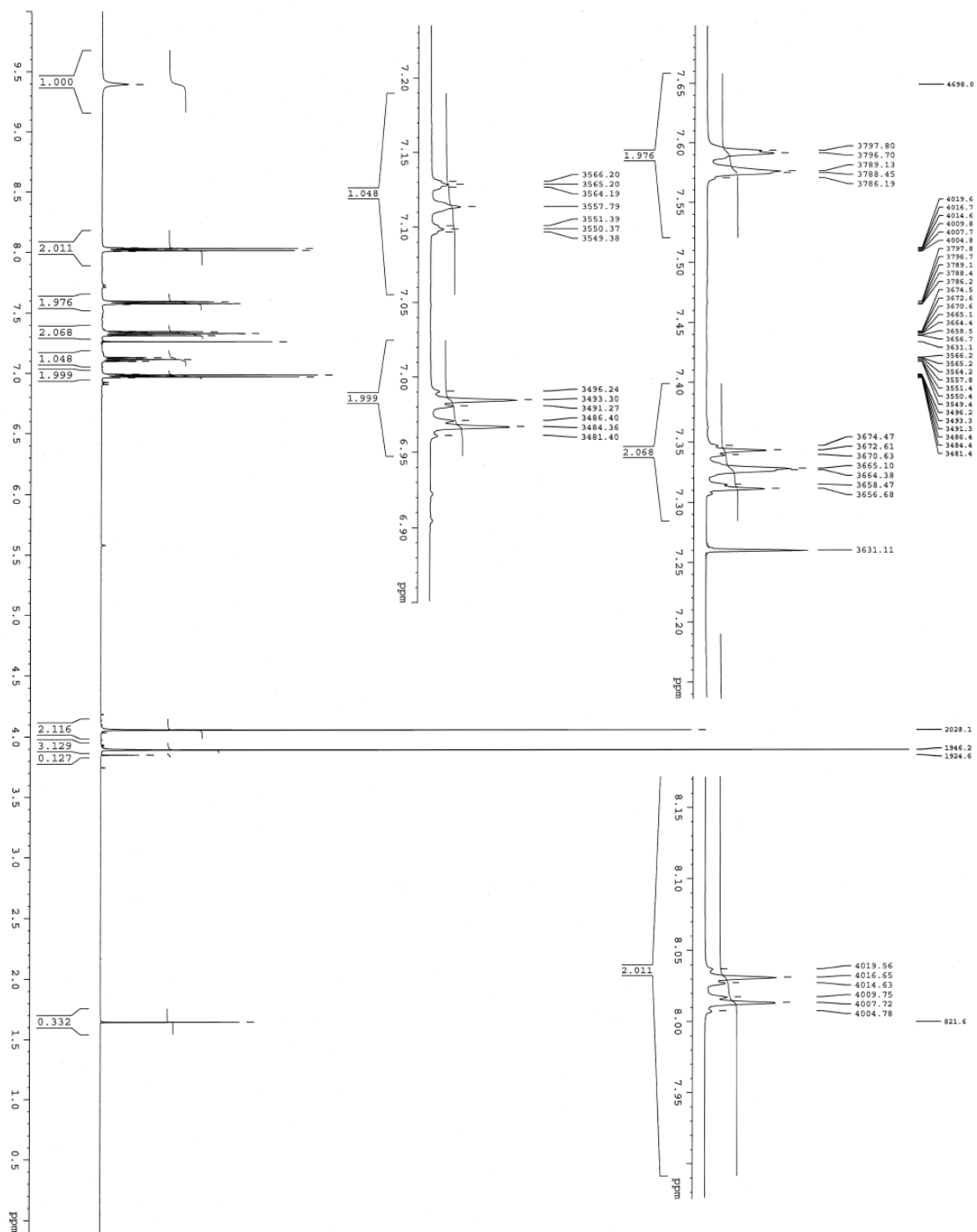
3-Oxo-*N*-phenylpentanamide **5b**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



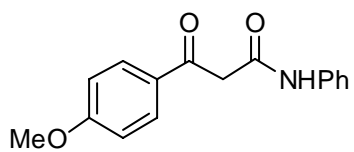
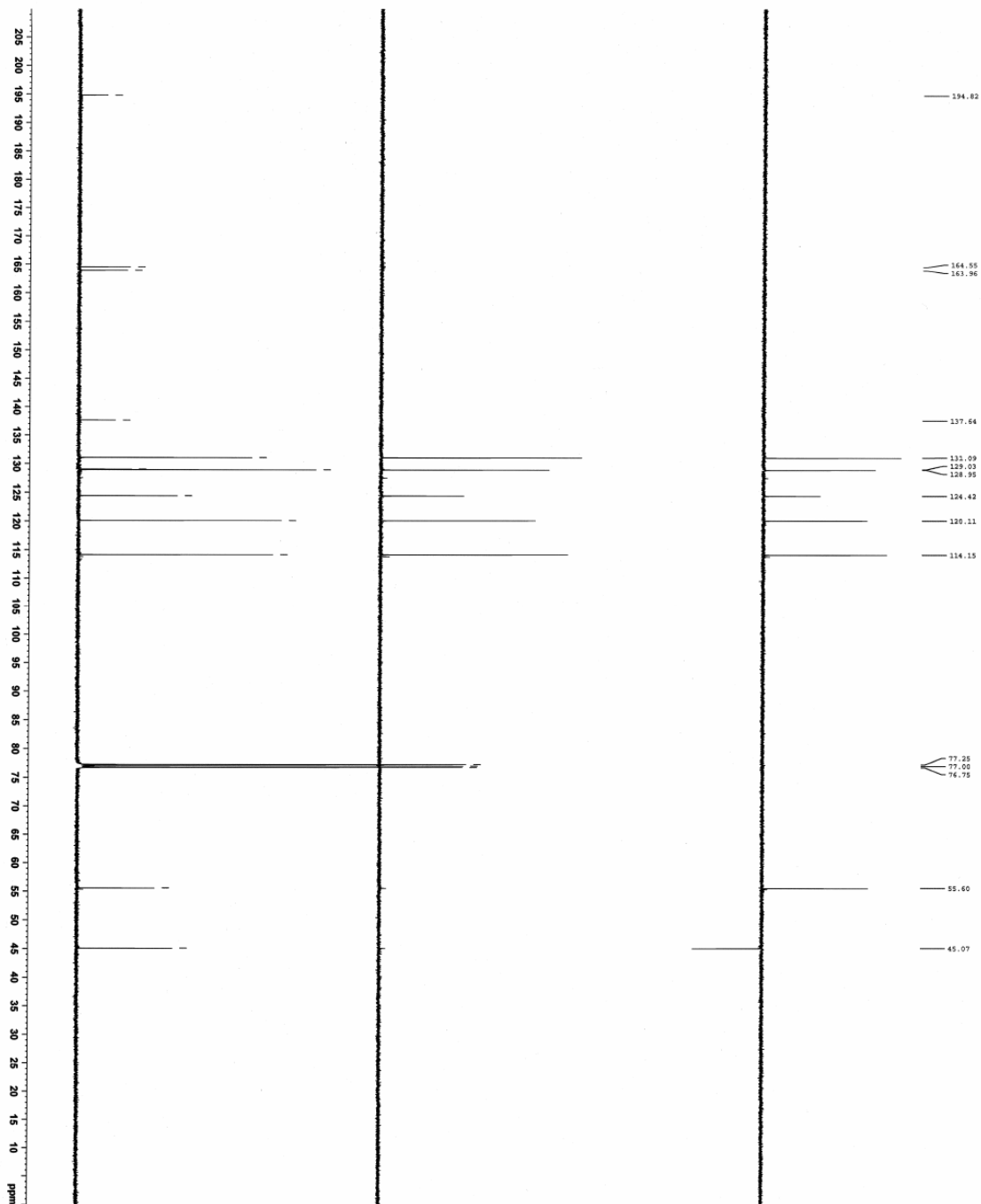
4-Methyl-3-oxo-N-phenylpentanamide **5c**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



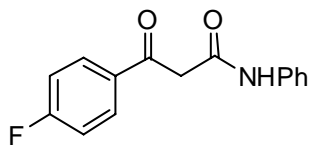
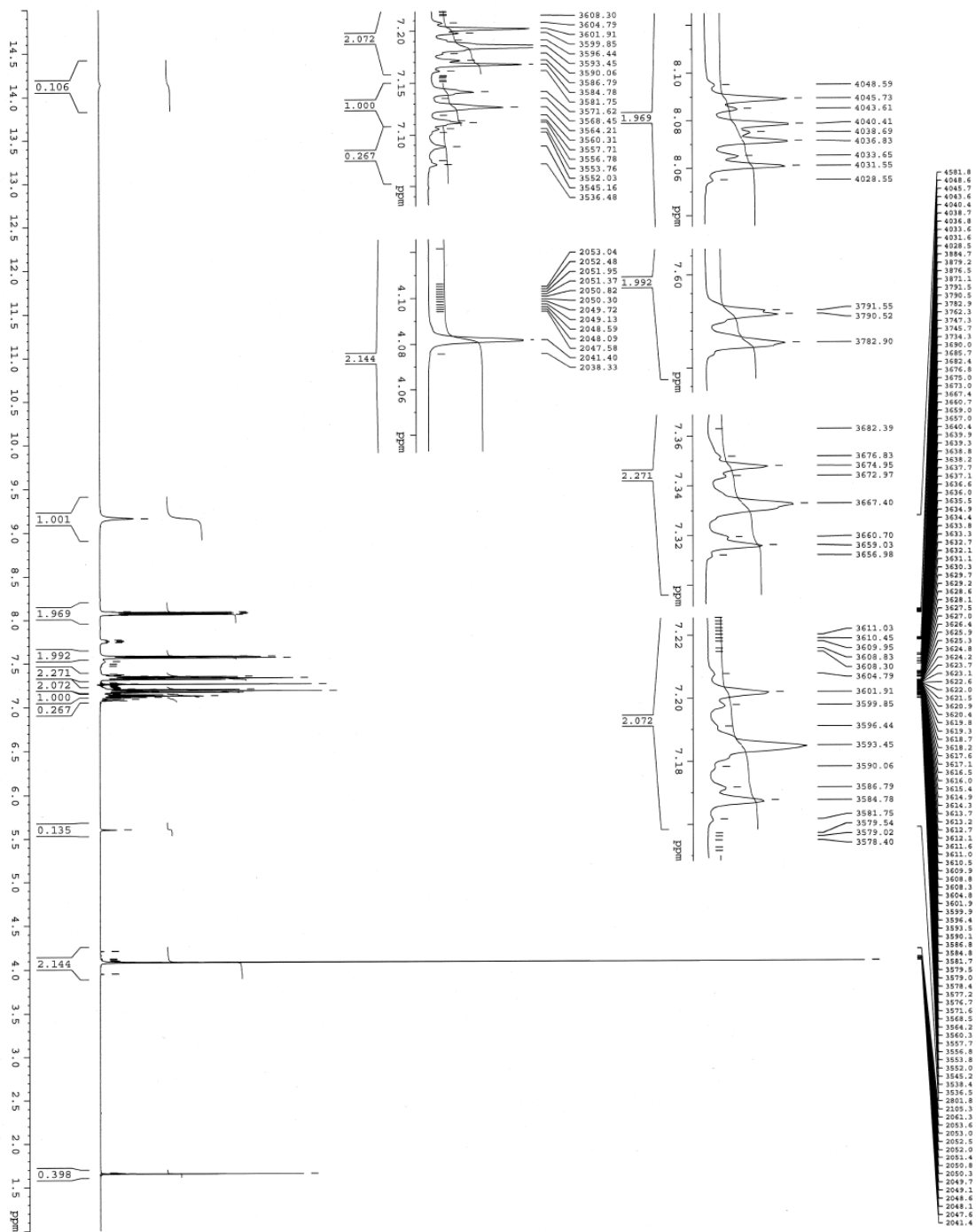
4-Methyl-3-oxo-N-phenylpentanamide **5c**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



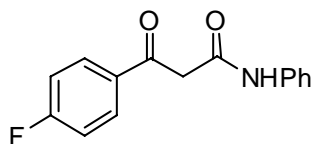
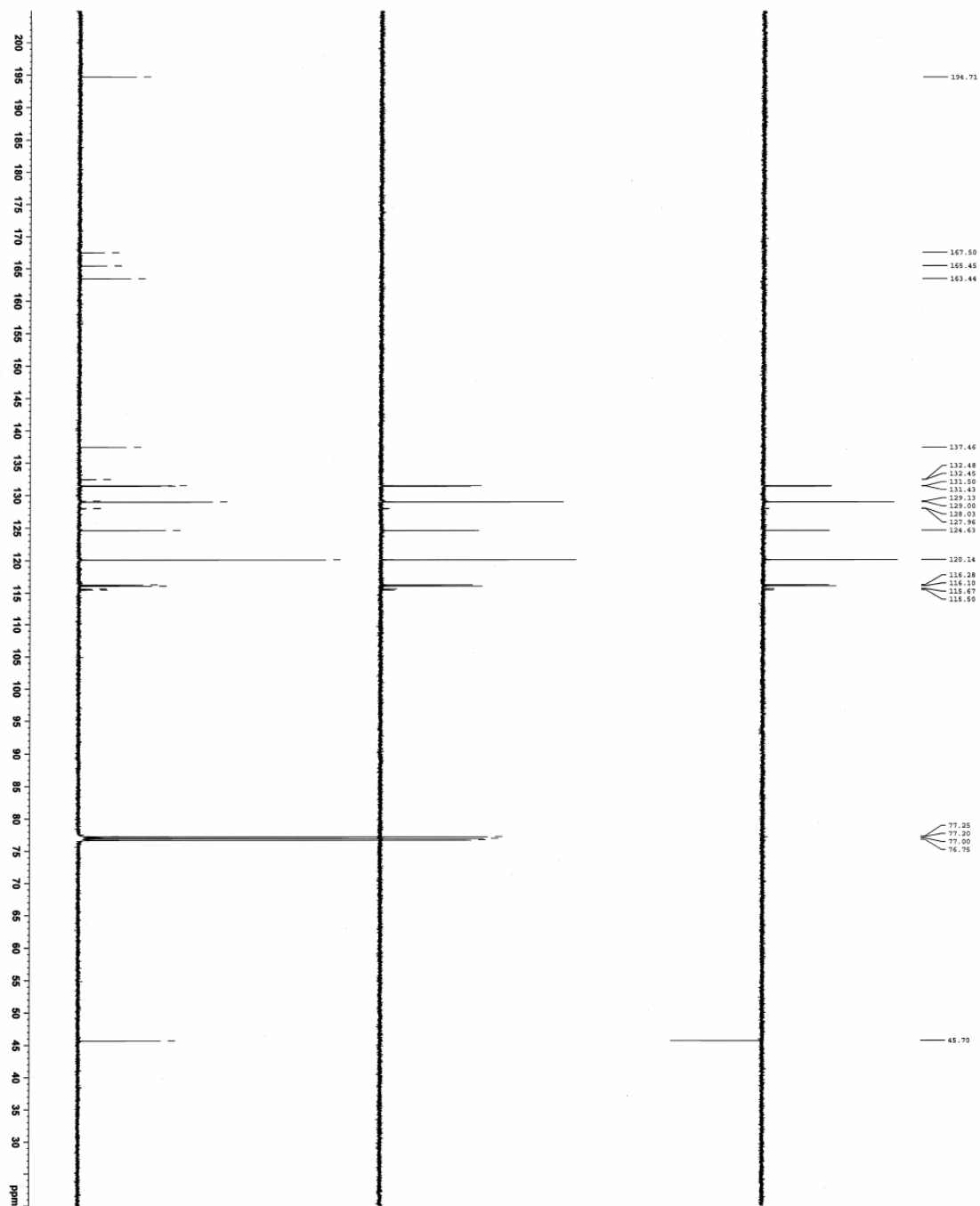
3-(4-Methoxyphenyl)-3-oxo-N-phenylpropanamide **5e**  
 $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



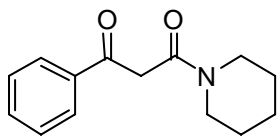
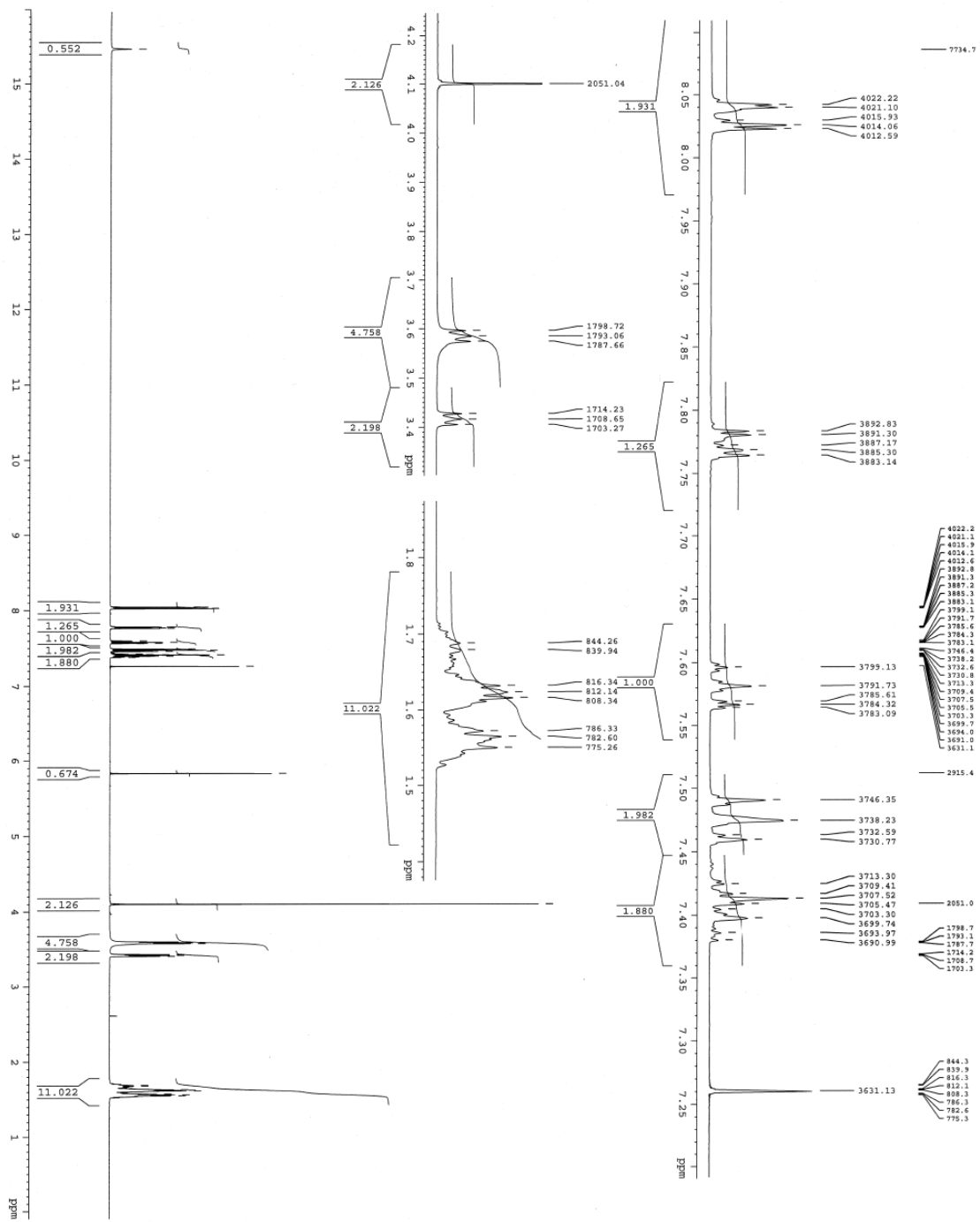
3-(4-Methoxyphenyl)-3-oxo-N-phenylpropanamide **5e**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



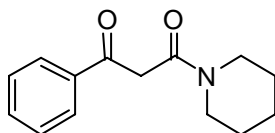
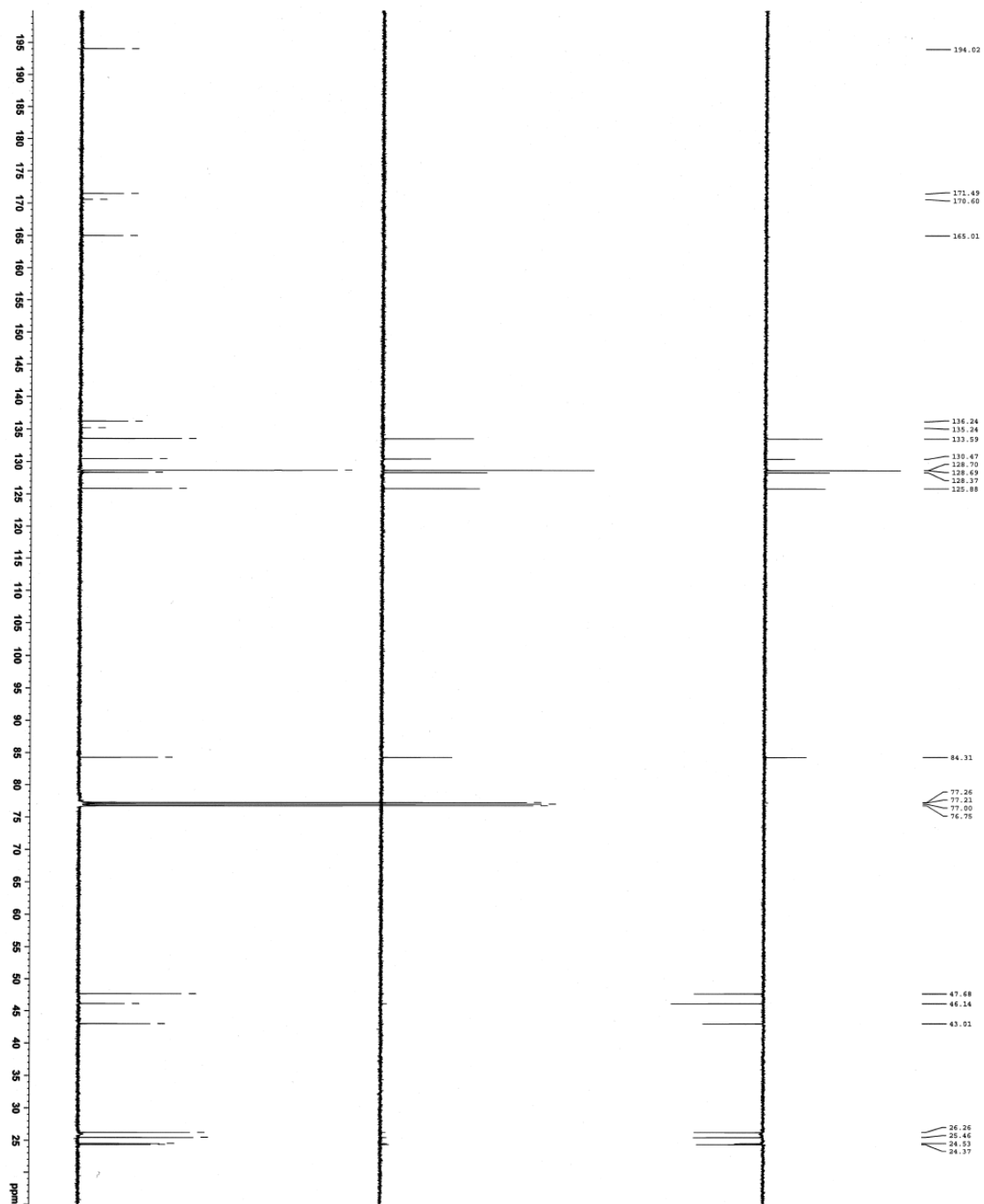
3-(4-Fluorophenyl)-3-oxo-N-phenylpropanamide **5f**  
 $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



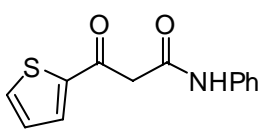
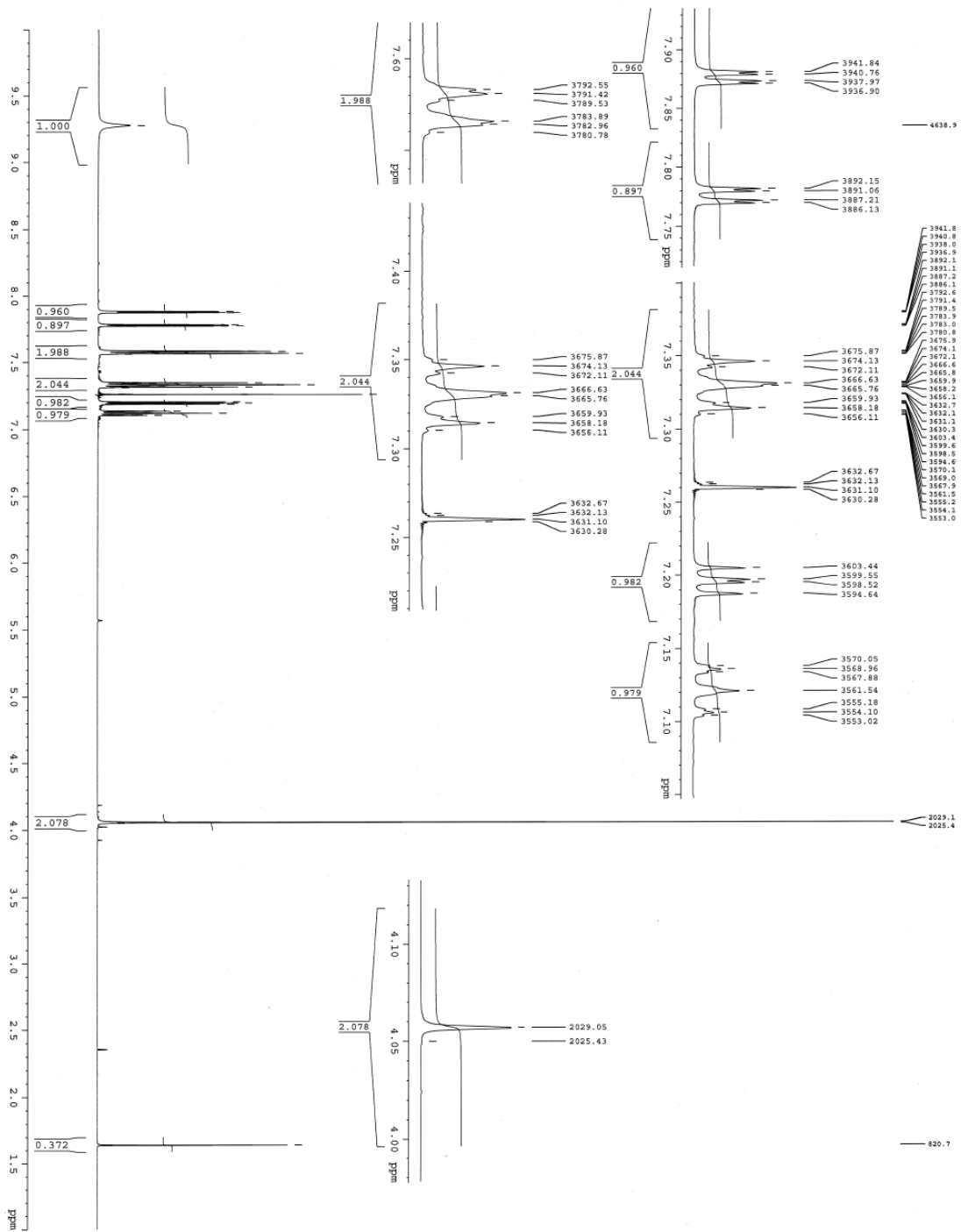
3-(4-Fluorophenyl)-3-oxo-N-phenylpropanamide **5f**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



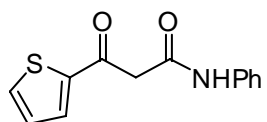
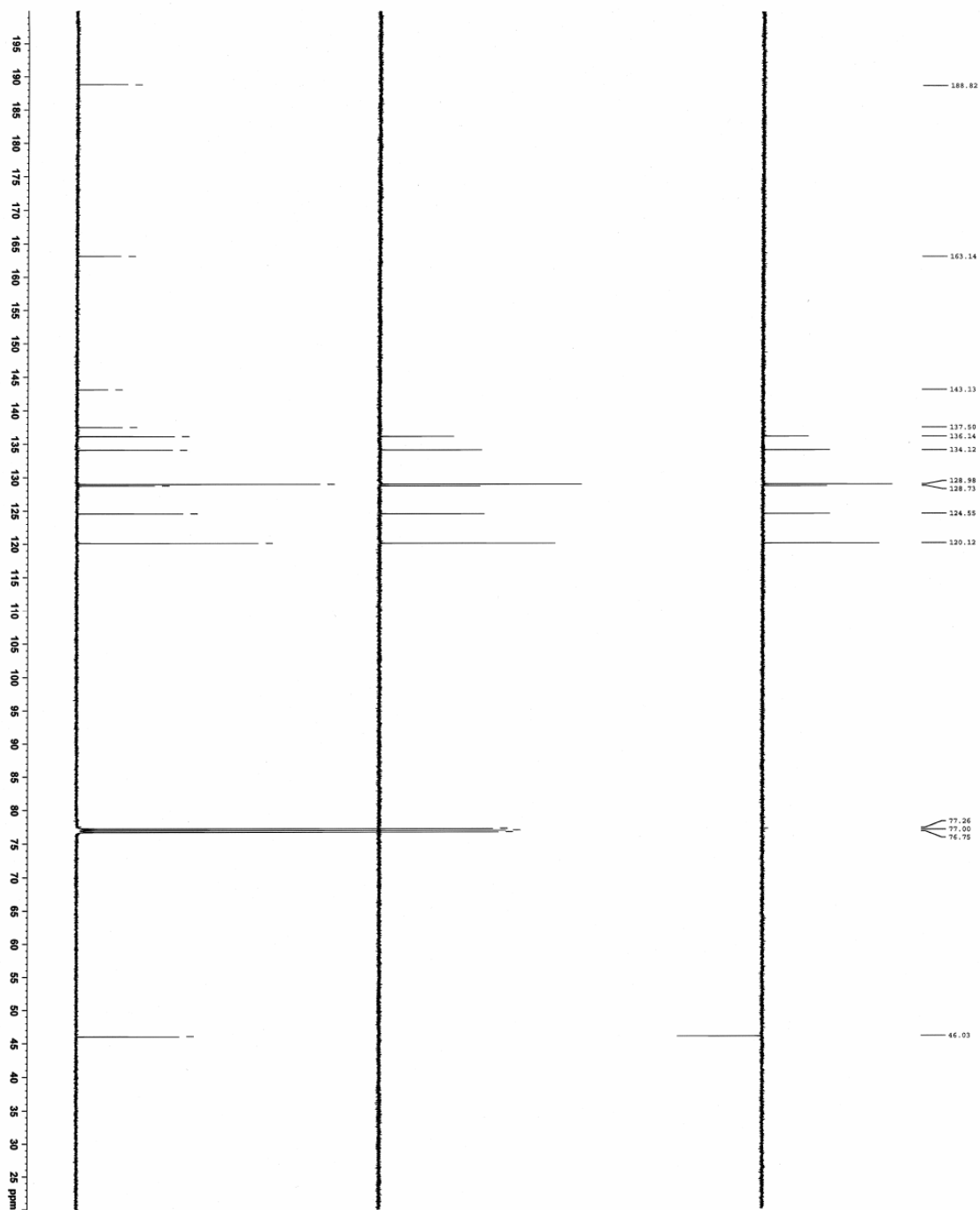
3-Oxo-1-phenyl-3-piperidin-1-ylpropan-1-one **5g**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



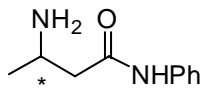
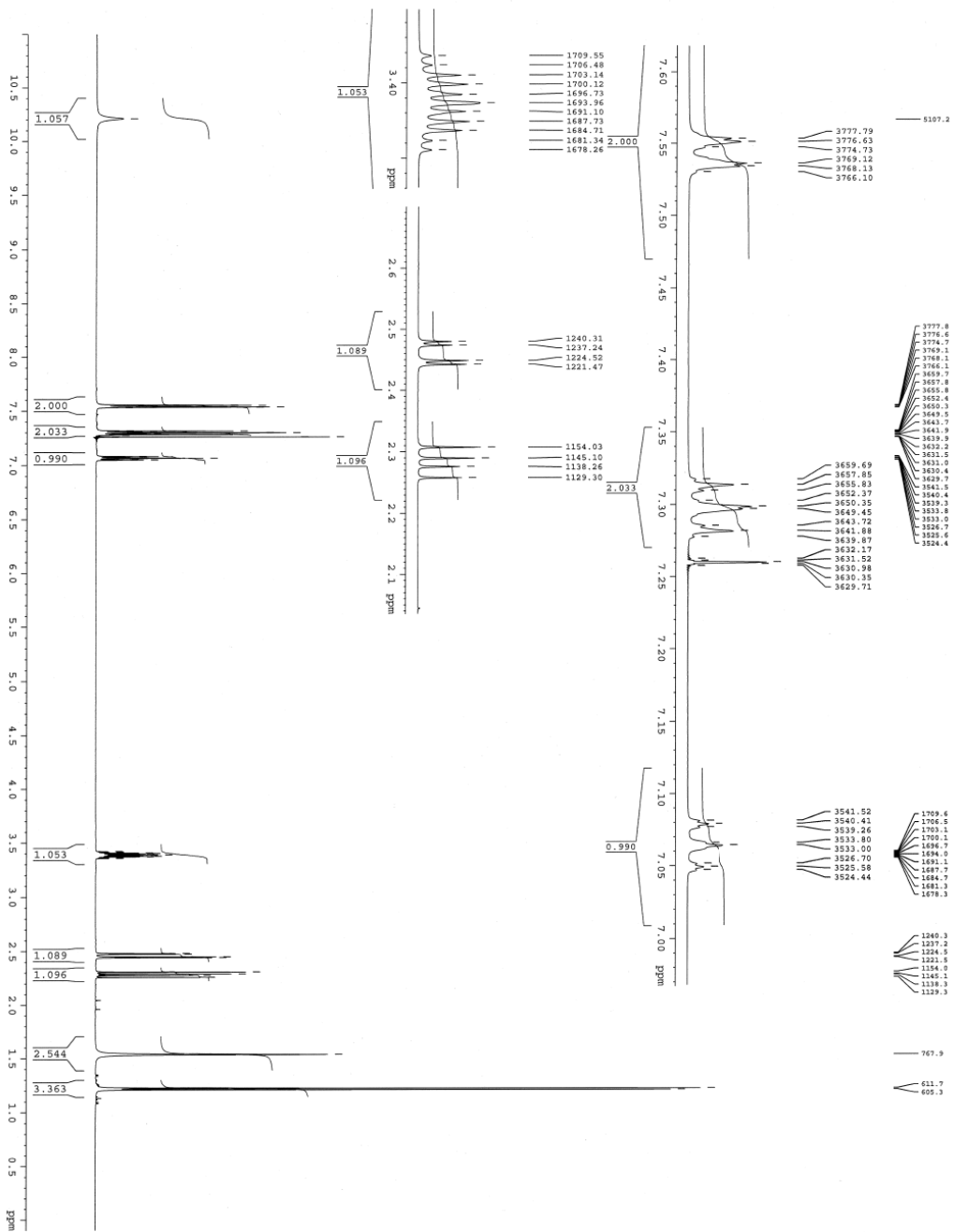
3-Oxo-1-phenyl-3-piperidin-1-ylpropan-1-one **5g**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



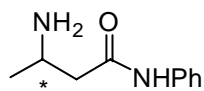
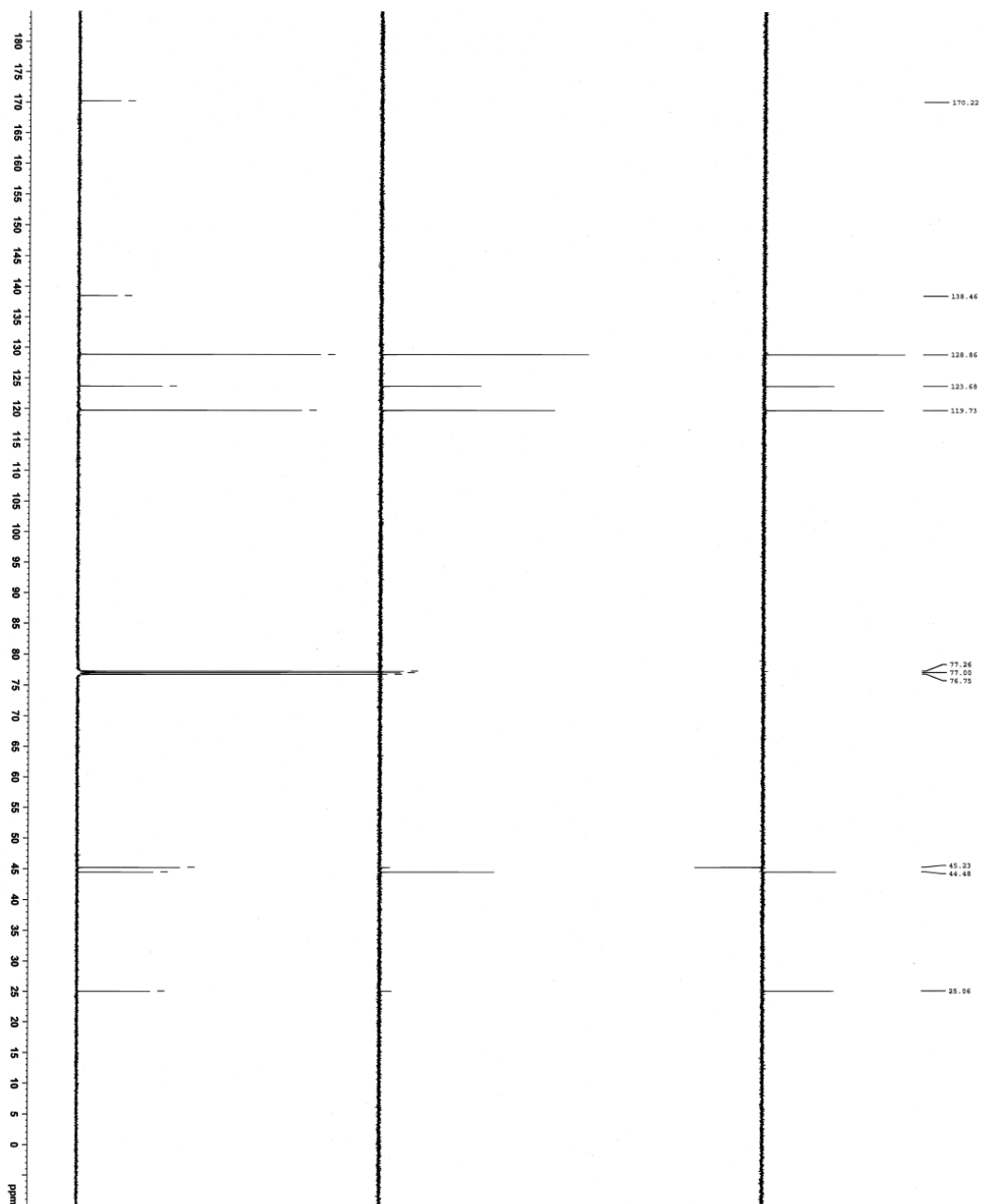
3-Oxo-N-phenyl-3-(thiophen-2-yl)propanamide **5h**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



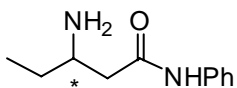
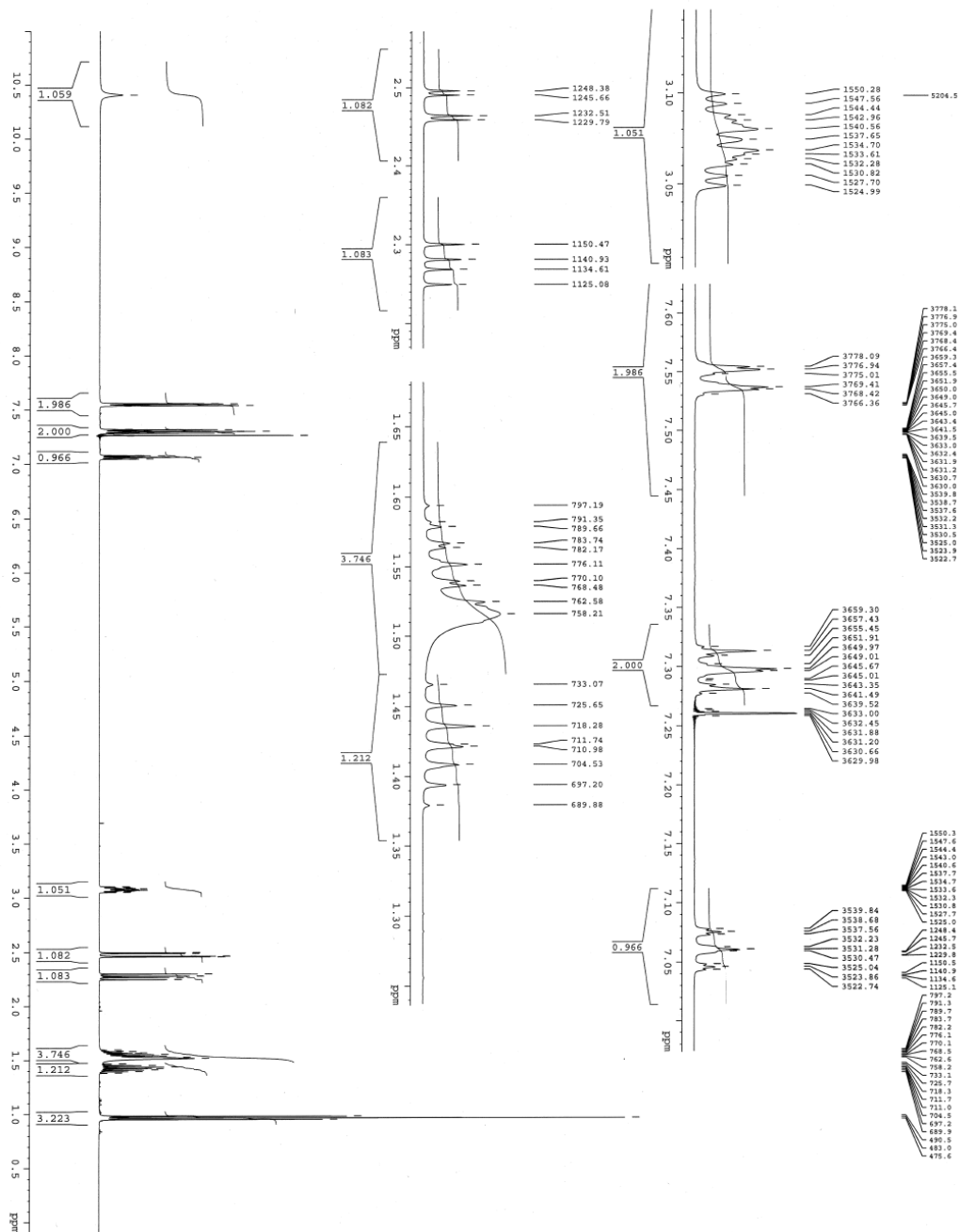
3-Oxo-N-phenyl-3-(thiophen-2-yl)propanamide **5h**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



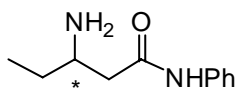
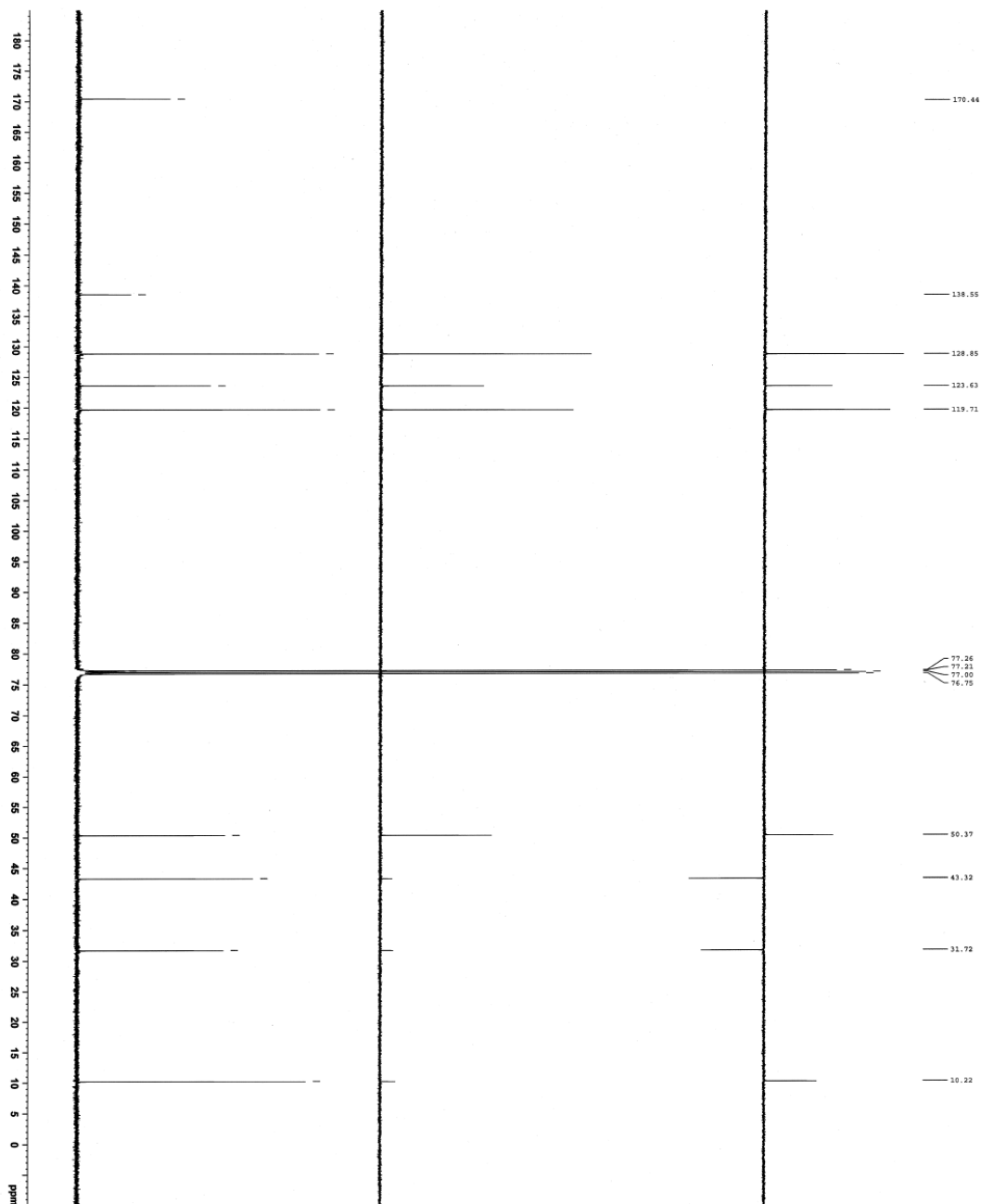
(-)-3-Amino-N-phenylbutanamide **6a**  
 $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



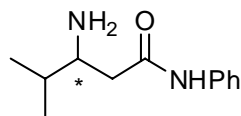
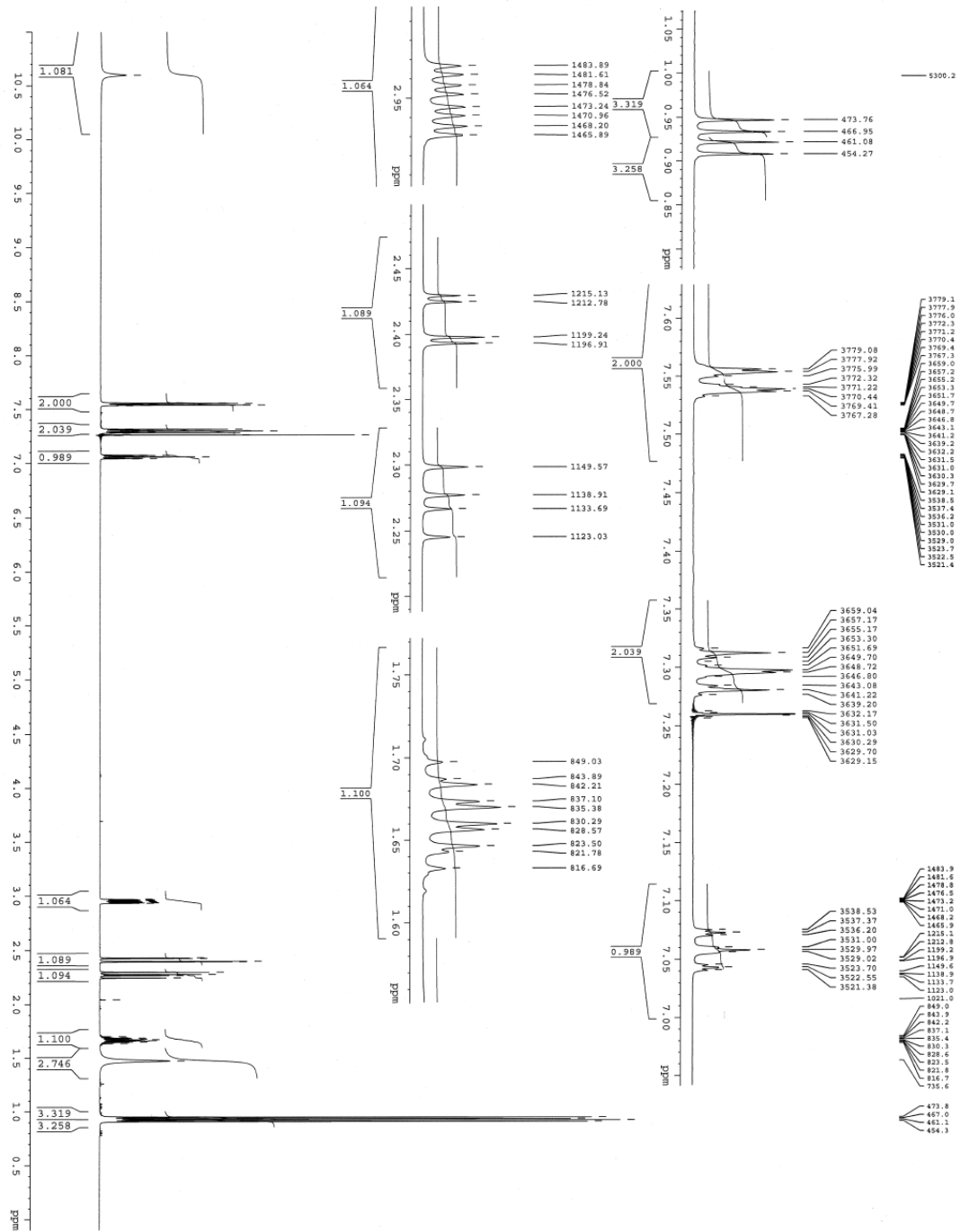
(-)-3-Amino-N-phenylbutanamide **6a**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



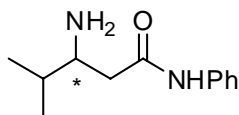
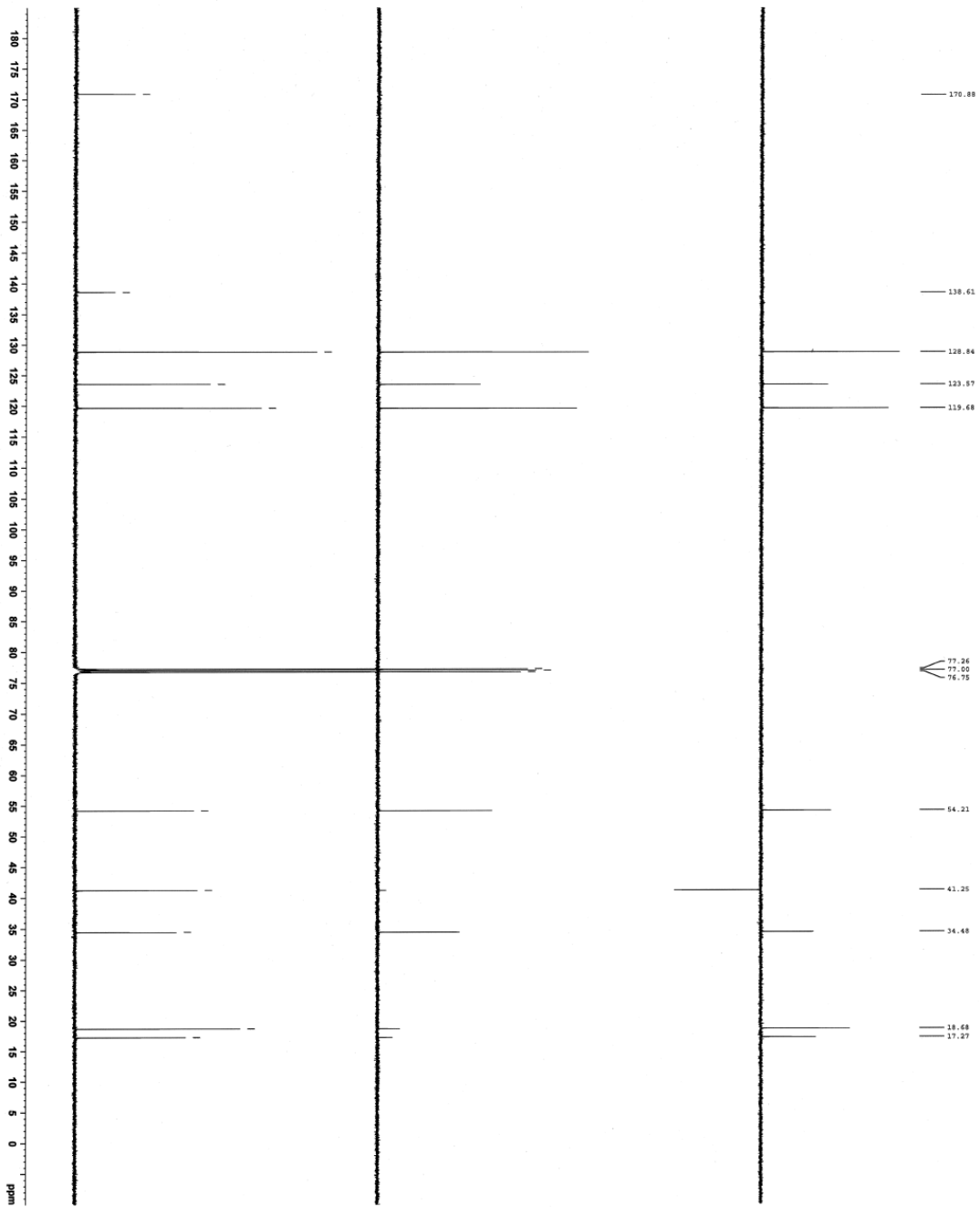
(-)-3-Amino-N-phenylpentanamide **6b**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



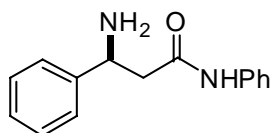
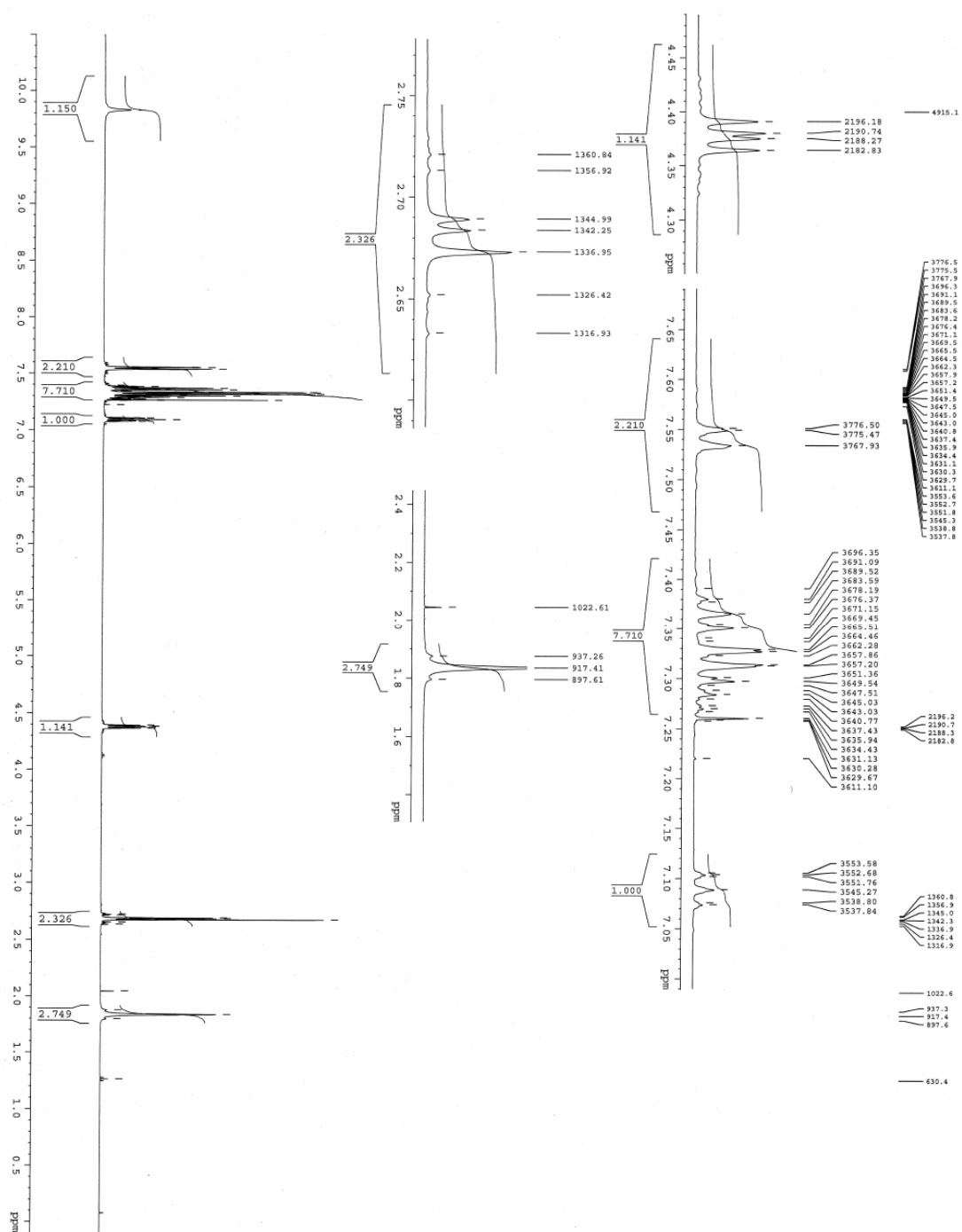
(-)-3-Amino-N-phenylpentanamide **6b**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



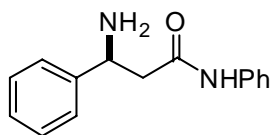
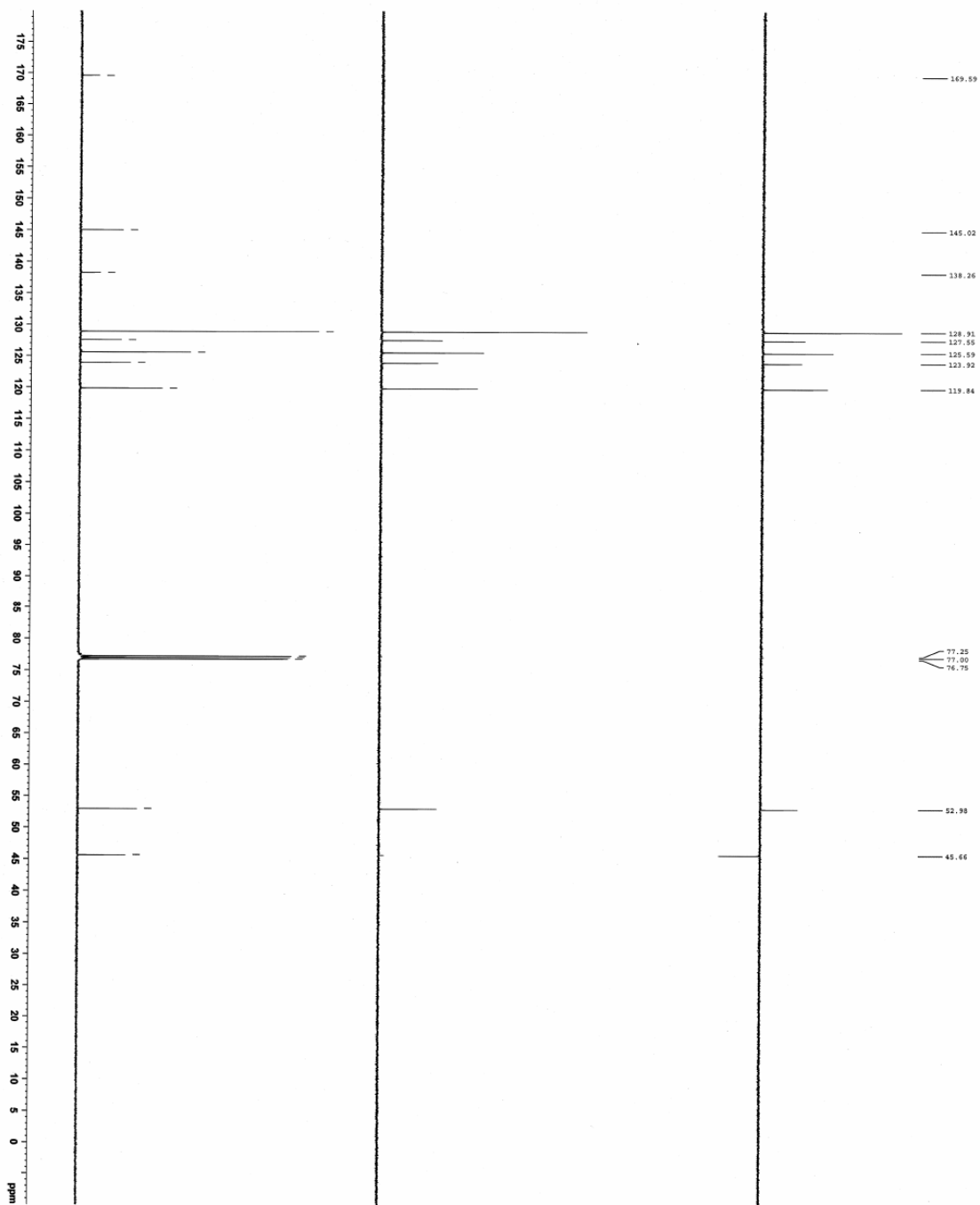
(-)-3-Amino-4-methyl-N-phenylpentanamide **6c**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



(-)-3-Amino-4-methyl-*N*-phenylpentanamide **6c**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )

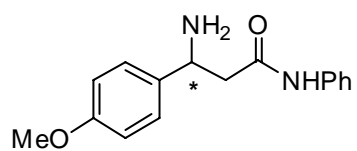
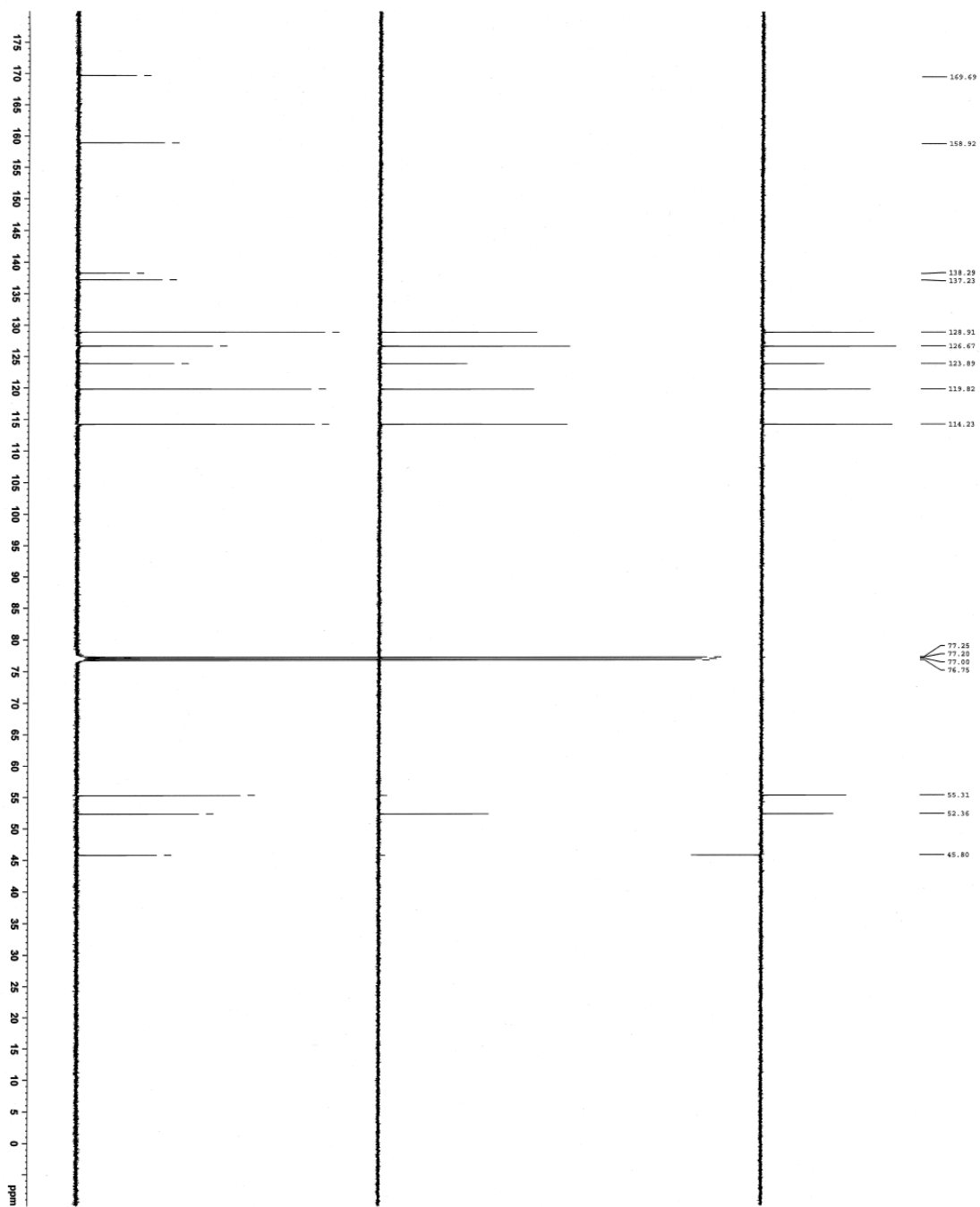


(3S)-3-amino-N,3-diphenylpropanamide **6d**  
 $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )



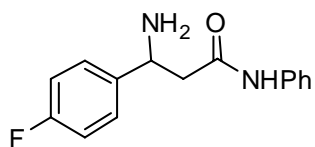
(3S)-3-Amino-*N*,3-diphenylpropanamide **6d**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )





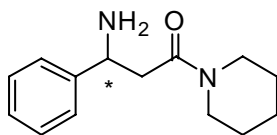
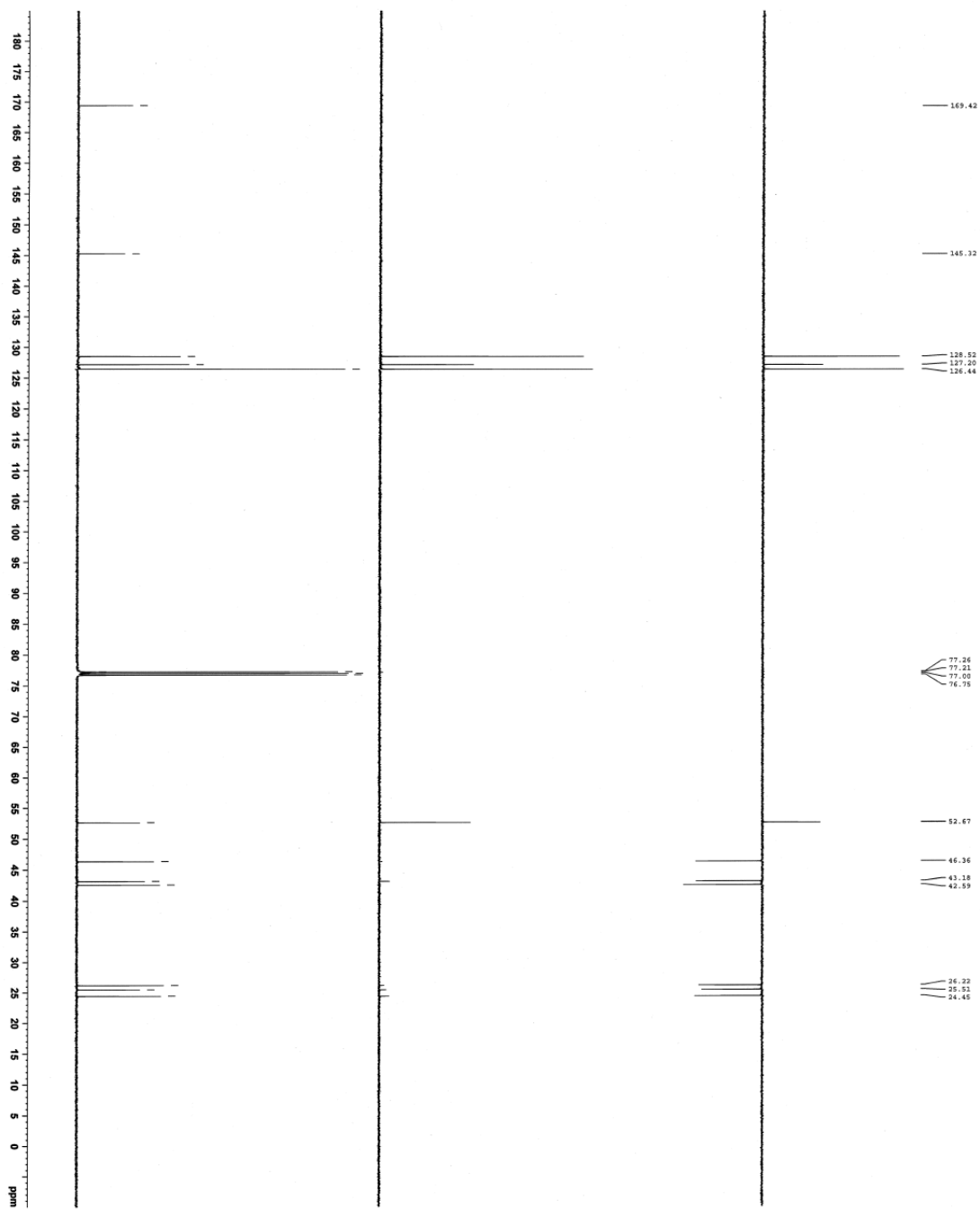
(+)-3-Amino-3-(4-methoxyphenyl)-N-phenylpropanamide **6e**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)



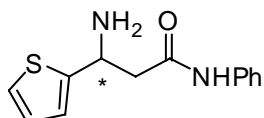
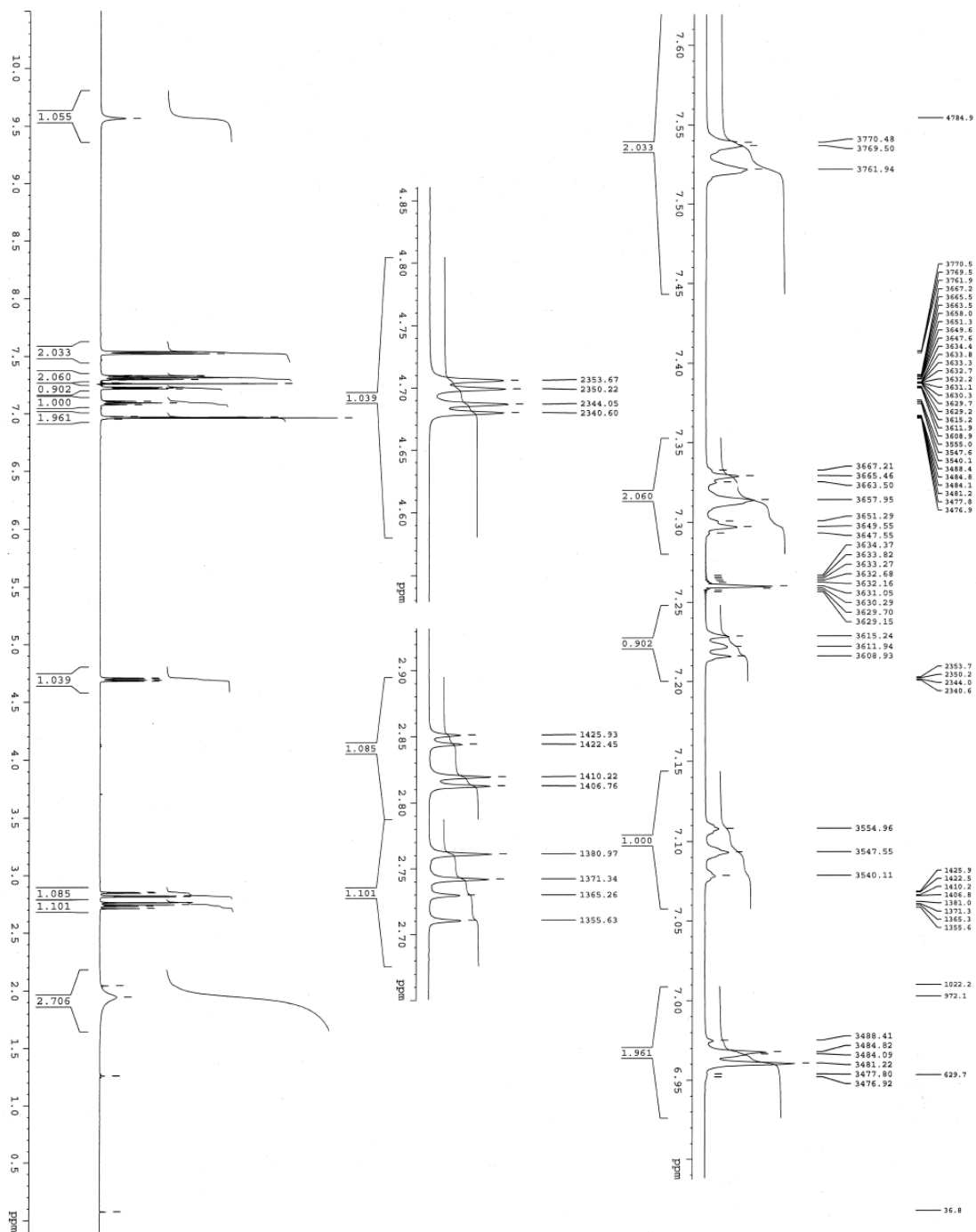


(+)-3-Amino-3-(4-fluorophenyl)-*N*-phenylpropanamide **6f**  
<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)

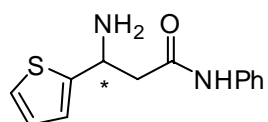
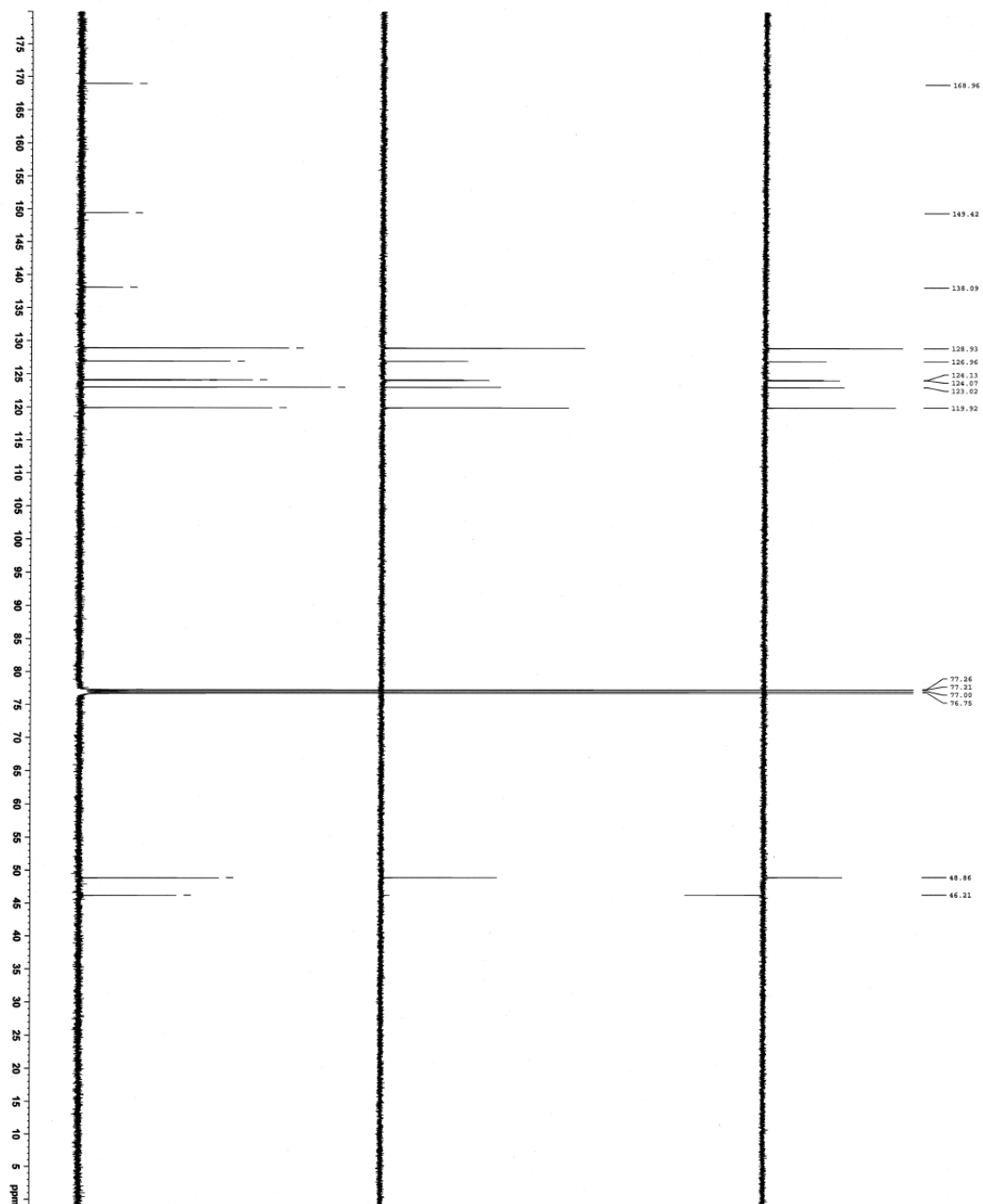




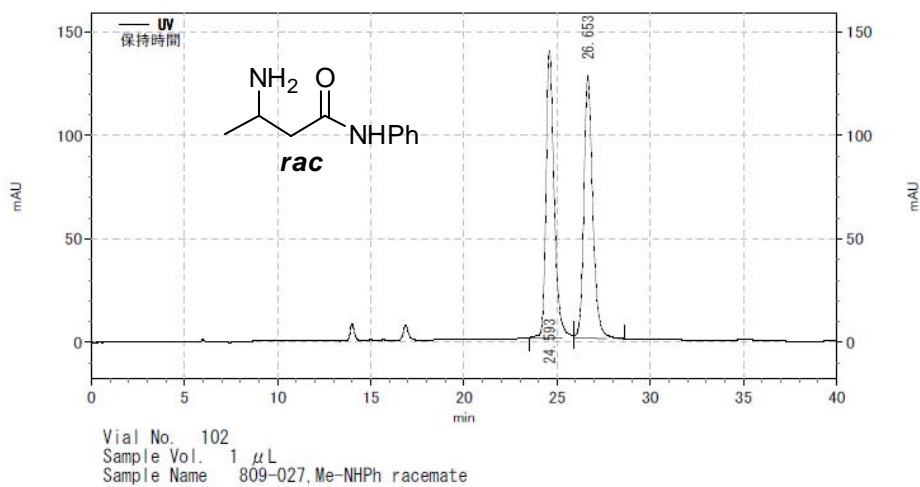
(-)-3-Amino-3-phenyl-1-(piperidin-1-yl)propan-1-one **6g**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



(+)-3-Amino-N-phenyl-3-(thiophen-2-yl)propanamide **6h**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)

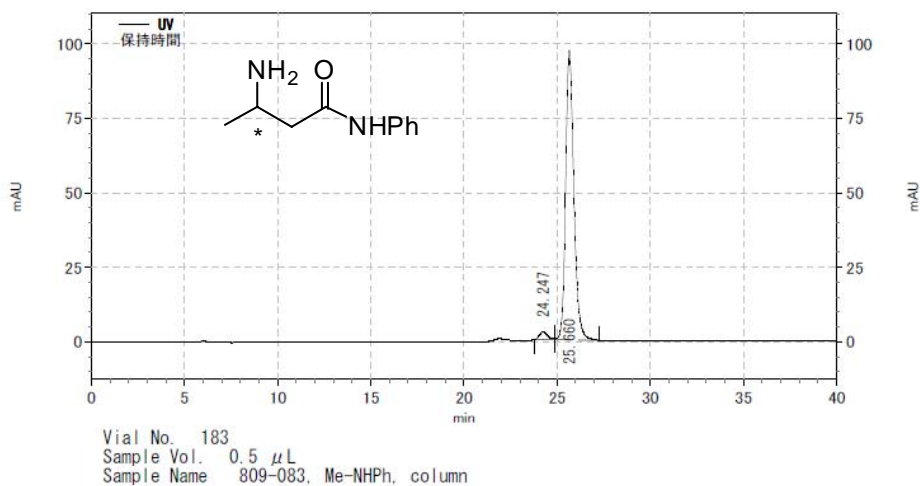


(+)-3-Amino-*N*-phenyl-3-(thiophen-2-yl)propanamide **6h**  
 $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )



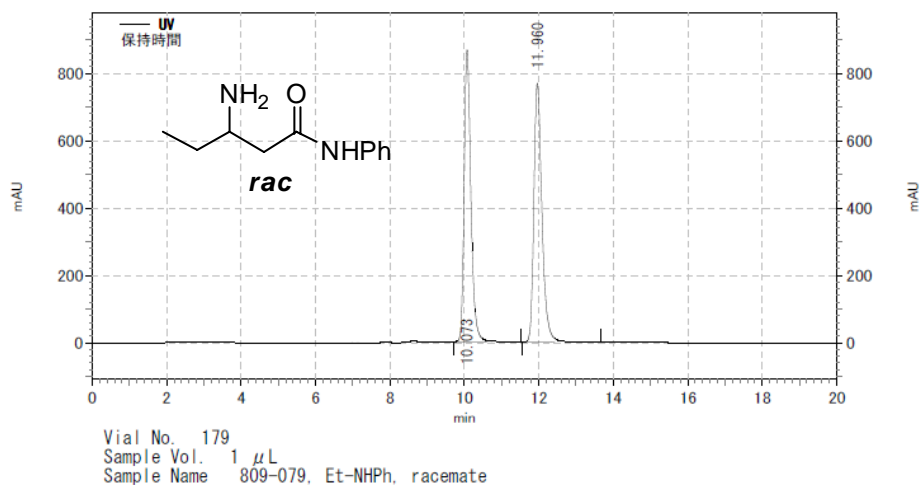
UV結果 Pk #	保持時間	面積	面積%	ペーシングコード
1	24.59	16929563	50.221	BV
2	26.65	16780763	49.779	VB
トータル		33710326	100.000	

*rac*-3-Amino-*N*-phenylbutanamide



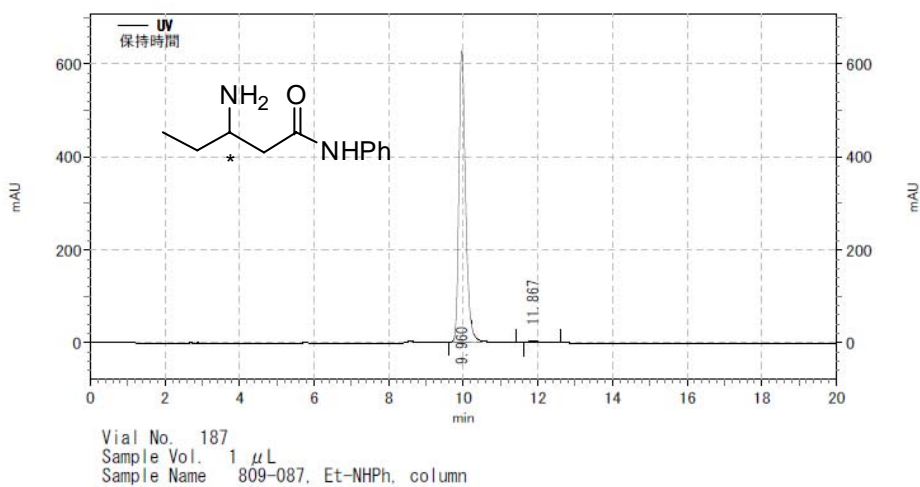
UV結果 Pk #	保持時間	面積	面積%	ペーシングコード
1	24.25	322535	2.633	BV
2	25.66	11925083	97.367	VB
トータル		12247618	100.000	

(-)-3-Amino-*N*-phenylbutanamide (**6a**, Table 3, Entry 1)



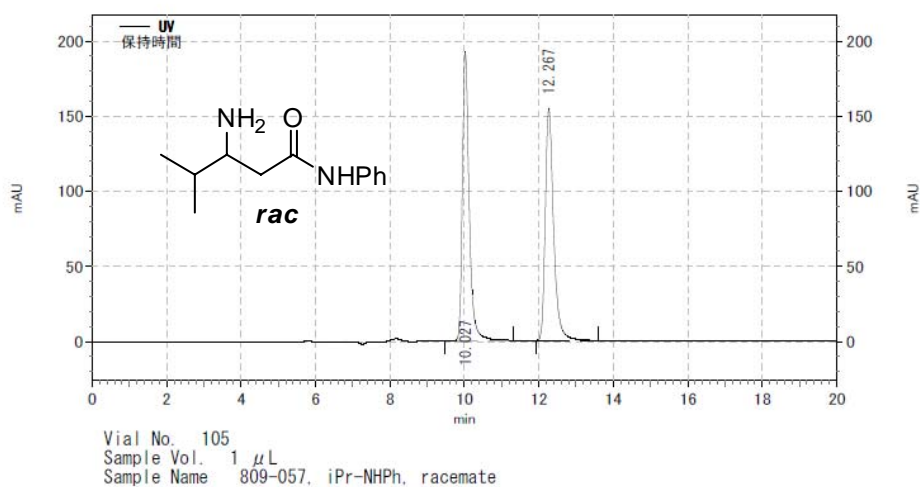
UV結果 Pk #	保持時間	面積	面積%	ヘーシイコード
1	10.07	43592794	48.526	BB
2	11.96	46240864	51.474	BB
トータル		89833658	100.000	

*rac*-3-Amino-*N*-phenylpentanamide



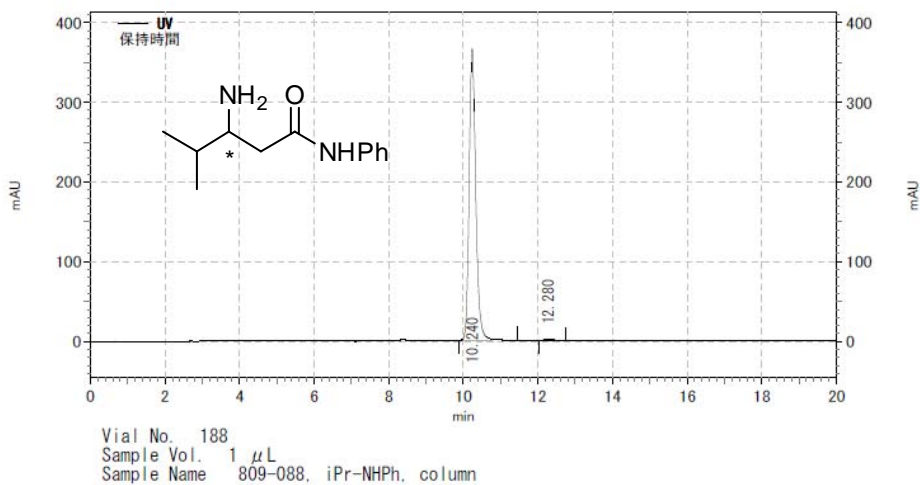
UV結果 Pk #	保持時間	面積	面積%	ヘーシイコード
1	9.96	31438370	99.050	BB
2	11.87	301610	0.950	BB
トータル		31739980	100.000	

(-)-3-Amino-*N*-phenylpentanamide (**6b**, Table 3, Entry 2)



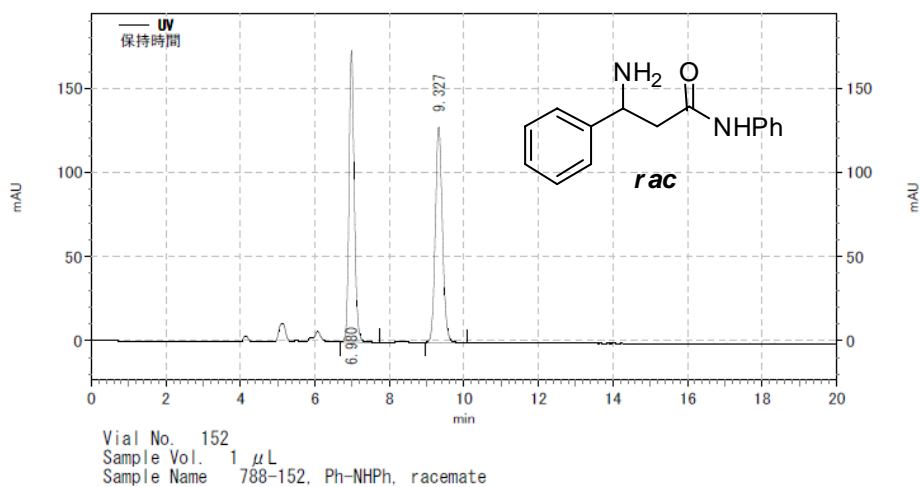
UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	10.03	9772069	50.419	BB
2	12.27	9609813	49.581	BB
トータル		19381882	100.000	

*rac*-3-Amino-4-methyl-*N*-phenylpentanamide



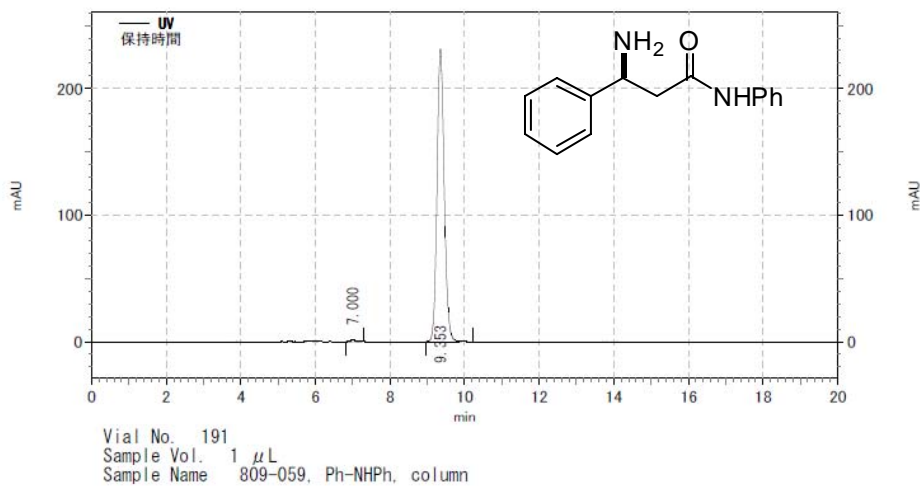
UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	10.24	18169368	99.431	BB
2	12.28	104055	0.569	BB
トータル		18273423	100.000	

(-)-3-Amino-4-methyl-*N*-phenylpentanamide (**6c**, Table 3, Entry 3)



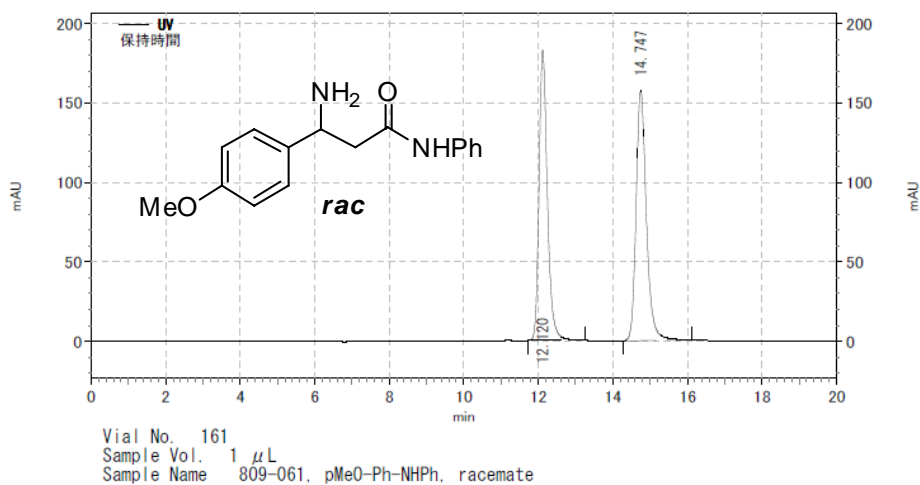
UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	6.98	6816660	50.010	BB
2	9.33	6813851	49.990	BB
トータル		13630511	100.000	

*rac*-3-Amino-*N*,3-diphenylpropanamide



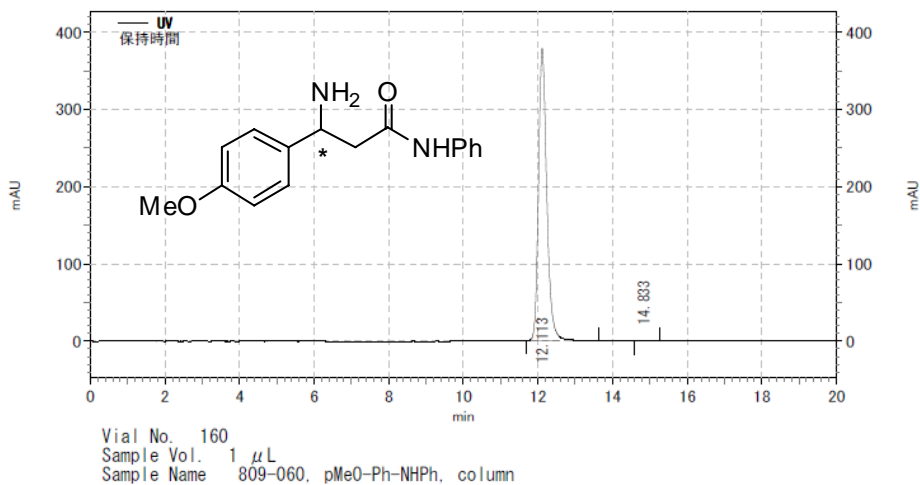
UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	7.00	53100	0.426	BB
2	9.35	12413828	99.574	BB
トータル		12466928	100.000	

(3*S*)-3-Amino-*N*,3-diphenylpropanamide (**6d**, Table 3, Entry 4)



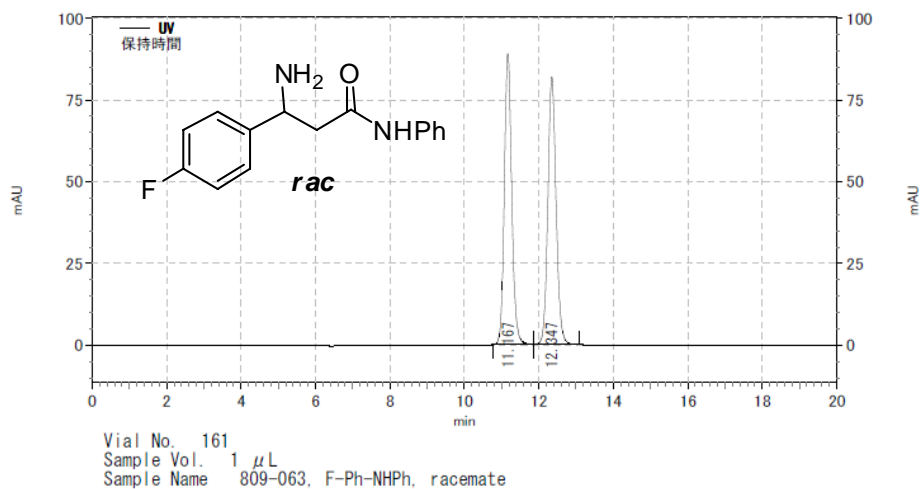
UV結果 Pk #	保持時間	面積	面積%	ヘキサインコード
1	12.12	11362588	48.565	BB
2	14.75	12034302	51.435	BB
トータル		23396890	100.000	

*rac*-3-Amino-3-(4-methoxyphenyl)-*N*-phenylpropanamide



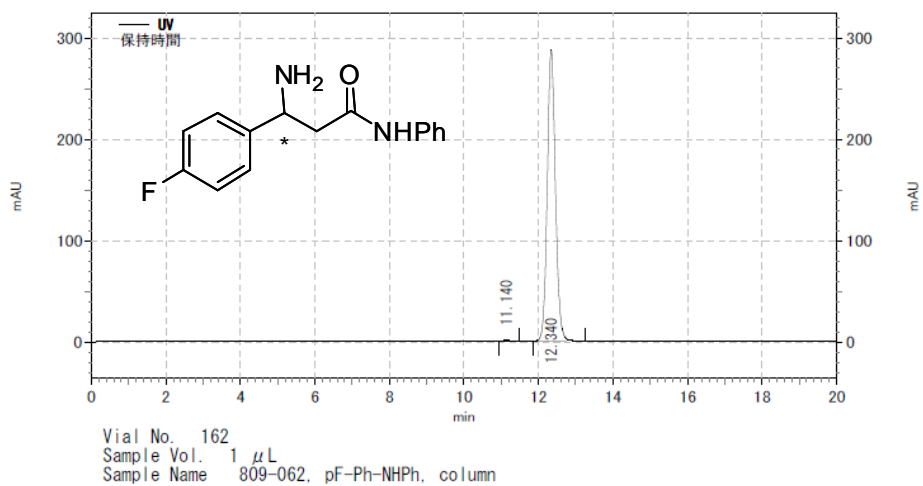
UV結果 Pk #	保持時間	面積	面積%	ヘキサインコード
1	12.11	23298693	99.798	BB
2	14.83	47202	0.202	BB
トータル		23345895	100.000	

(+)-3-Amino-3-(4-methoxyphenyl)-*N*-phenylpropanamide (**6e**, Table 3, Entry 5)



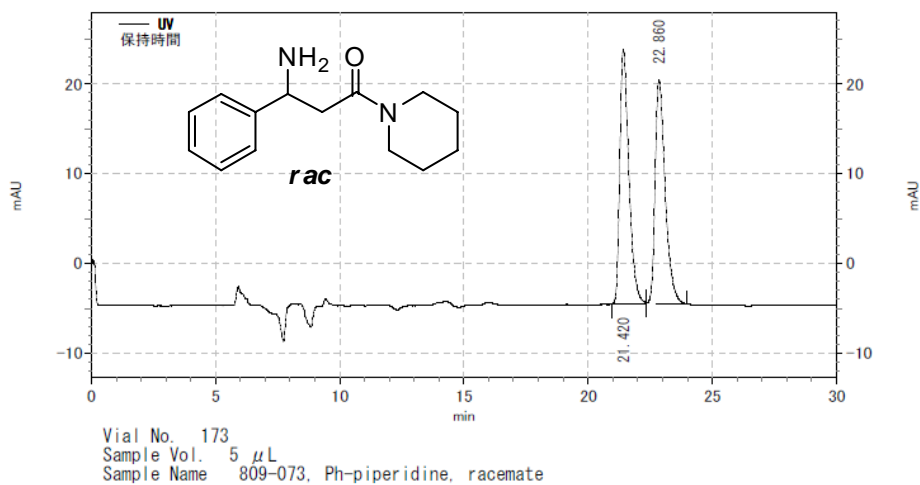
UV結果 Pk #	保持時間	面積	面積%	ヘーシイコード
1	11.17	4942784	49.522	BV
2	12.35	5038273	50.478	VB
トータル		9981057	100.000	

*rac*-3-Amino-3-(4-fluorophenyl)-*N*-phenylpropanamide



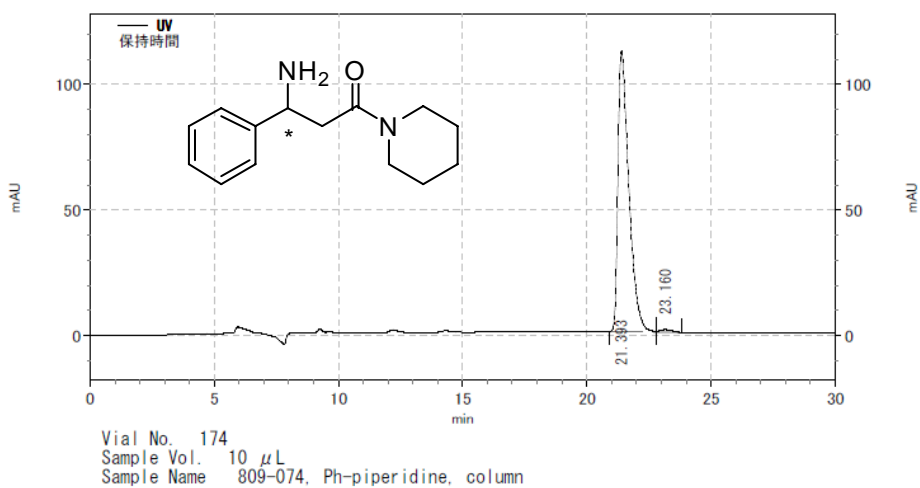
UV結果 Pk #	保持時間	面積	面積%	ヘーシイコード
1	11.14	53303	0.303	BB
2	12.34	17563878	99.697	BB
トータル		17617181	100.000	

(+)-3-Amino-3-(4-fluorophenyl)-*N*-phenylpropanamide (**6f**, Table 3, Entry 6)



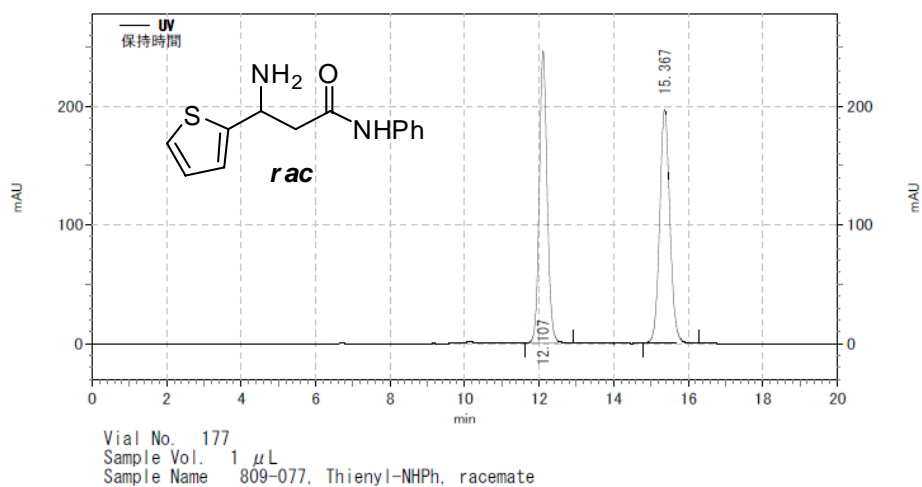
UV結果 Pk #	保持時間	面積	面積%	ヘキサインコード
1	21.42	2874441	50.689	BV
2	22.86	2796314	49.311	VB
トータル		5670755	100.000	

*rac*-3-Amino-3-phenyl-1-(piperidin-1-yl)propan-1-one



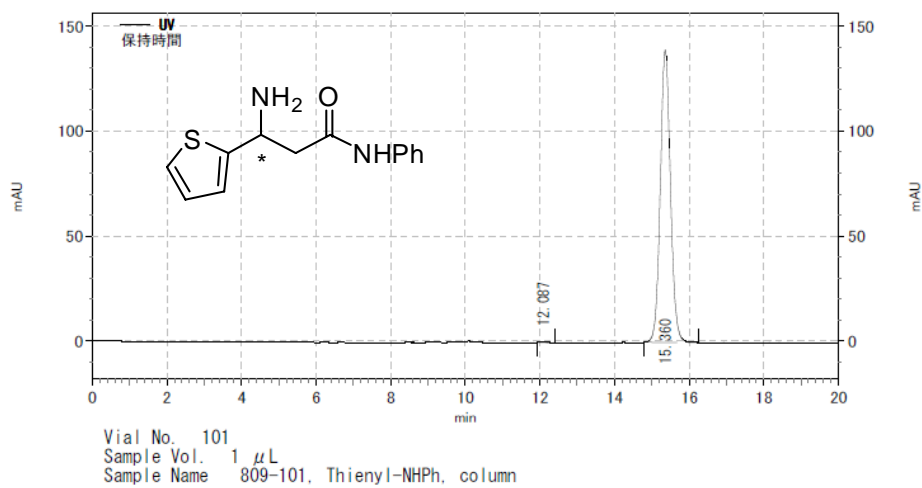
UV結果 Pk #	保持時間	面積	面積%	ヘキサインコード
1	21.39	13593519	98.970	BV
2	23.16	141413	1.030	VB
トータル		13734932	100.000	

(-)-3-Amino-3-phenyl-1-(piperidin-1-yl)propan-1-one (**6g**, Table 3, Entry 7)



UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	12.11	14461103	49.126	BB
2	15.37	14975394	50.874	BB
トータル		29436497	100.000	

*rac*-3-Amino-*N*-phenyl-3-(thiophen-2-yl)propanamide



UV結果 Pk #	保持時間	面積	面積%	ピークコード
1	12.09	22462	0.212	BB
2	15.36	10552160	99.788	BB
トータル		10574622	100.000	

(+)-3-Amino-*N*-phenyl-3-(thiophen-2-yl)propanamide (**6h**, Table 3, Entry 8)