Supporting Information for

Efficient Ugi reactions in an aqueous vesicle system

Arleta Madej,[a] Daniel Paprocki,[a] Dominik Koszelewski,[a] Anna Żądło-Dobrowolska,[a] Anna Brzozowska,[b] Peter Walde[c] and Ryszard Ostaszewski[a]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

[b] Institute of Physical Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

[c] Laboratory of Polymer Chemistry, Department of Materials, ETH Zurich, Vladimir-Prelog-Weg 5, 8093 Zurich, Switzerland

Synthesis of *N*-(4-methoxybenzyl)formamide:

Reaction conditions: 4-methoxybenzylamine (30 mmol; 3.8 ml) and ethyl formate (12.5 ml) were heated under reflux overnight. After cooling the reaction mixture to room temperature, 5 ml hexane were added. The precipitate was filtered and washed with hexane. Yield 78 % (3.86 g).

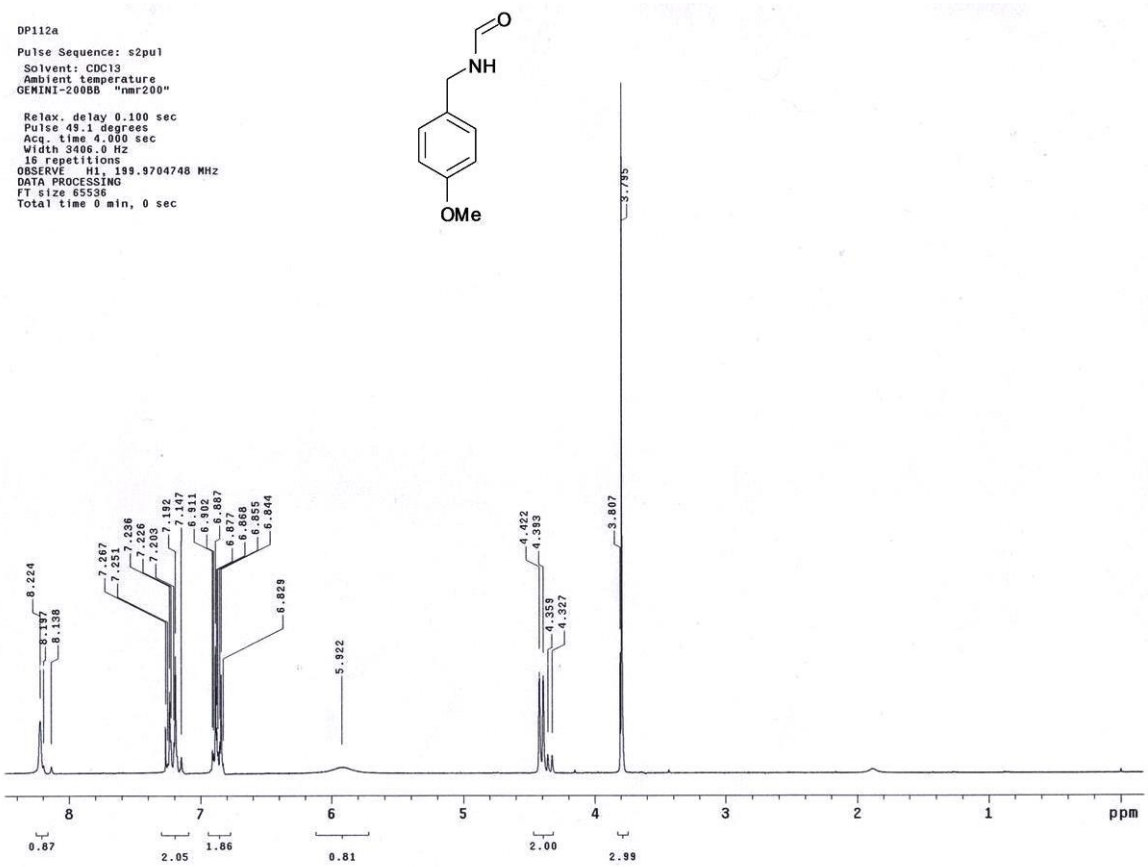


Figure 1 ^{1}H NMR spectrum of *N*-(4-methoxybenzyl)formamide (200 MHz, $CDCl_3$).

Synthesis of *p*-methoxybenzylisocyanide (3a):

Reaction conditions: To a solution of *N*-(4-methoxybenzyl)formamide (16 mmol; 2.64 g) and triethylamine (48 mmol; 6.7 ml) in dry dichloromethane (20 ml) at -78°C phosphoryl oxychloride (20 mmol; 1.85 ml) was added dropwise. After 1 h of stirring at room temperature, the reaction mixture was quenched by adding a saturated solution of $NaHCO_3$ (20 mL), then extracted with dichloromethane (2×20 mL). The combined organic layers were dried with $MgSO_4$ and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as an eluent. Yield 80 % (1.88 g).

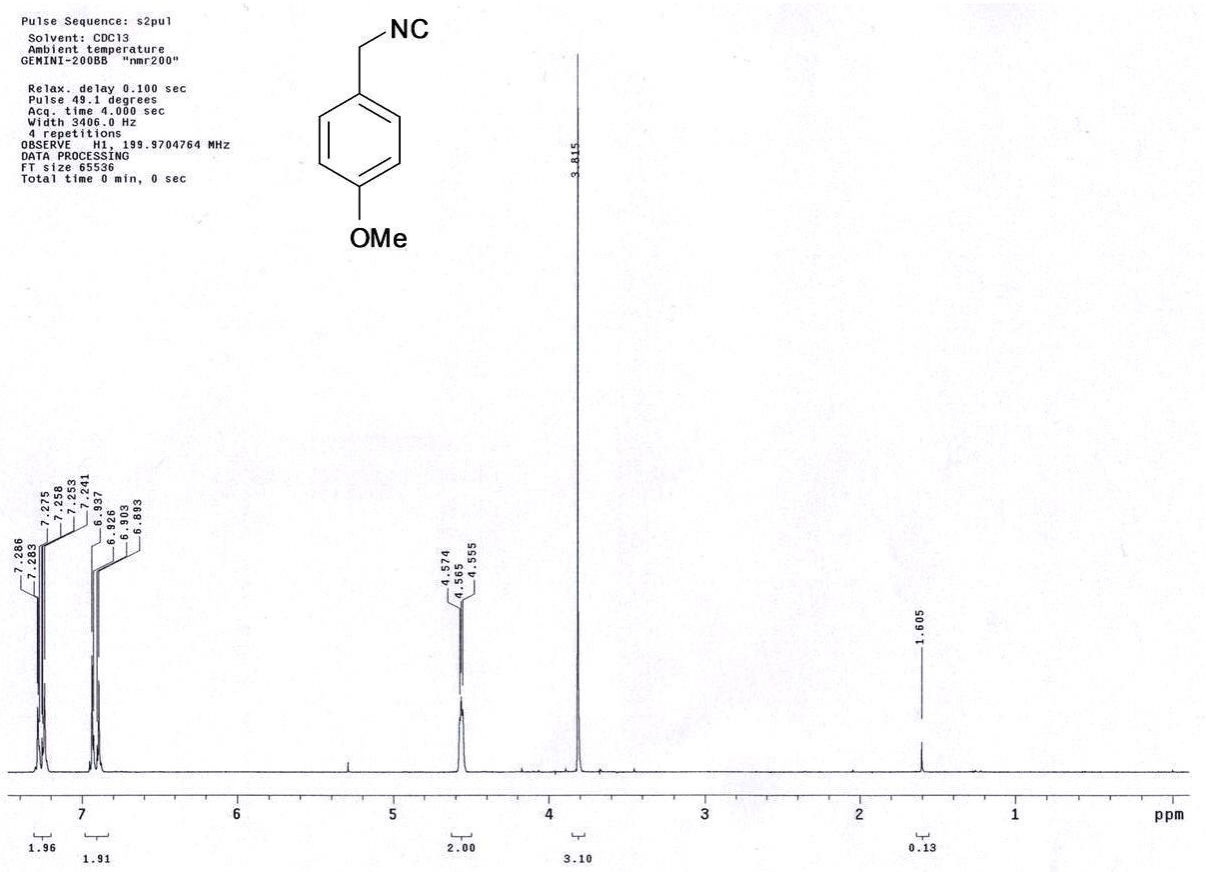


Figure 2 ^{1}H NMR spectrum of compound **4a** (200 MHz, $CDCl_3$).

Synthesis of *N*-hexylformamide:

Reaction conditions: 4-methoxybenzylamine (30 mmol; 3.8 ml) and ethyl formate (12.5 ml) were heated under reflux overnight. After cooling the reaction mixture to room temperature, solvent was evaporated. The product was purified by column chromatography (silica gel, hexane/AcOEt). Yield 90% (3.49 g).

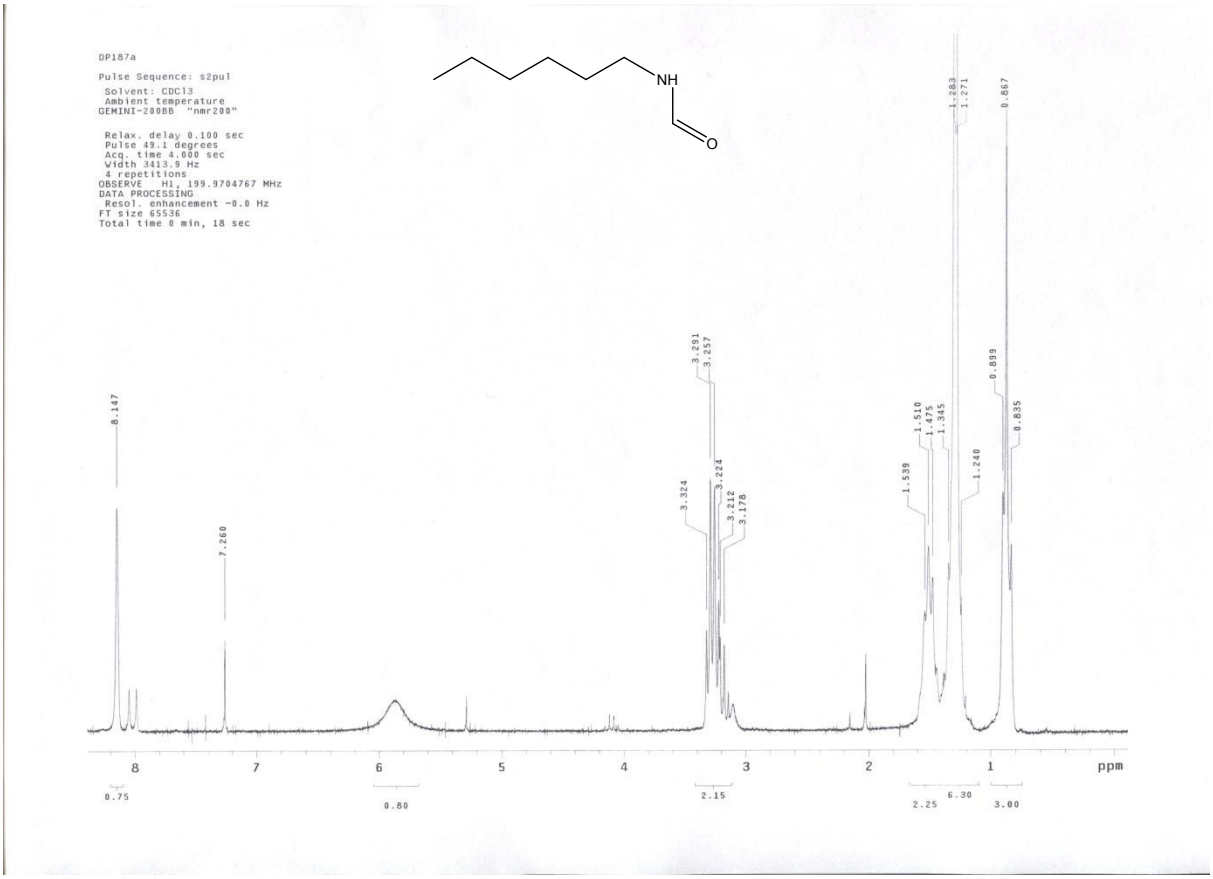


Figure 3 ^{1}H NMR spectrum of *N*-hexyl formamide (200 MHz, $CDCl_3$).

Synthesis of hexylisocyanide:

Reaction conditions: To a solution of *N*-hexyl formamide (16 mmol) and triethylamine (48 mmol; 6.7 ml) in dry dichloromethane (20 ml) at -78°C phosphoryl oxychloride (20 mmol; 1.85 ml) was added dropwise. After 1 h of stirring at room temperature, the reaction mixture was quenched by adding a saturated solution of $NaHCO_3$ (20 mL), then extracted with dichloromethane (2×20 mL). The combined organic layers were dried with $MgSO_4$ and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as an eluent. Yield 54% (482,5 mg)

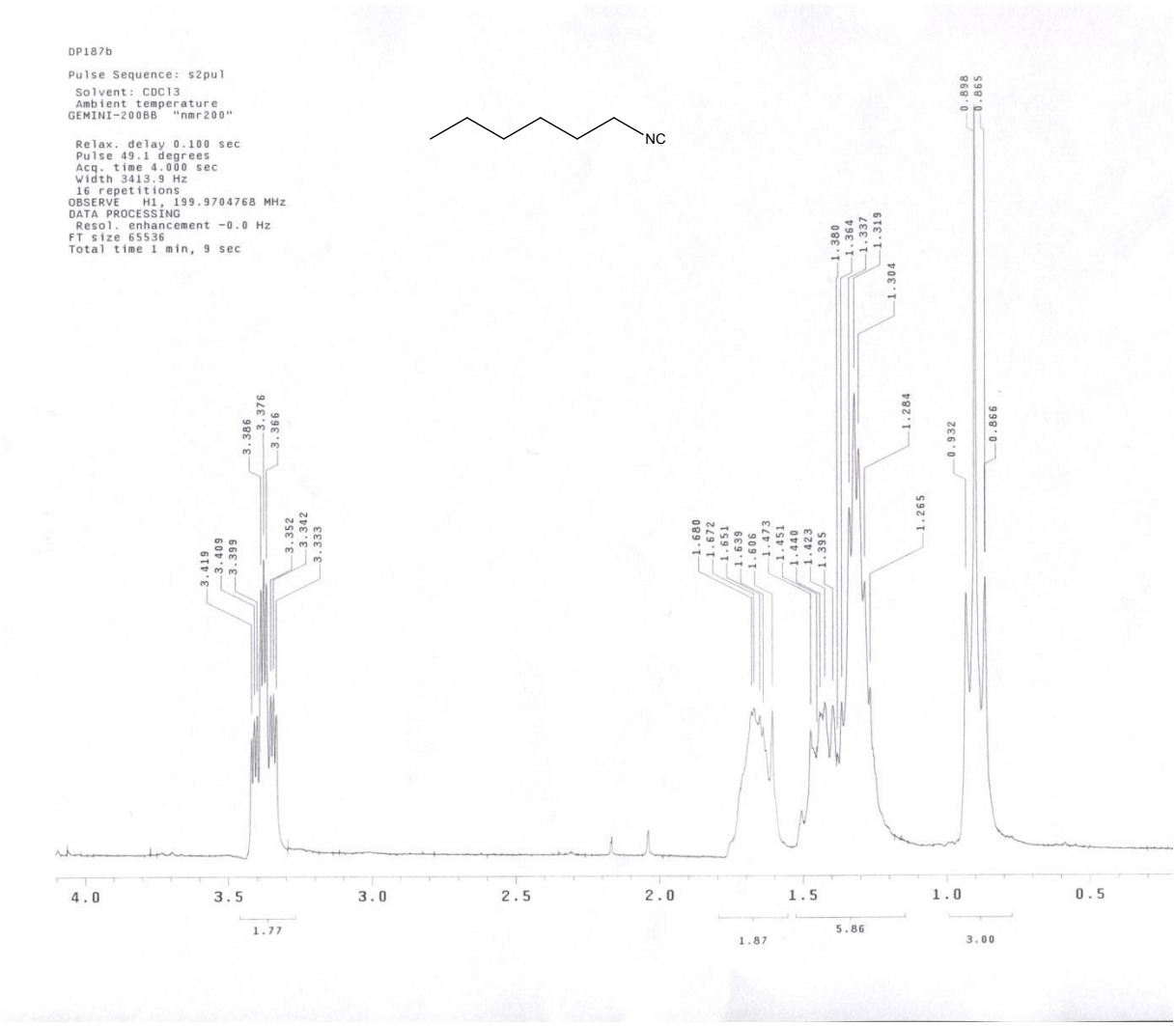


Figure 4 ^{1}H NMR spectrum of hexylisocyanide (200 MHz, $CDCl_3$).

Synthesis of N-(2,4-dimethoxybezyl)formamide:

Reaction conditions: 4-methoxybenzylamine (30 mmol; 3.8 ml) and ethyl formate (12.5 ml) were heated under reflux overnight. After cooling the reaction mixture to room temperature, 5 ml hexane were added. The precipitate was filtered and washed with hexane. Yield 80 % (4.69 g).

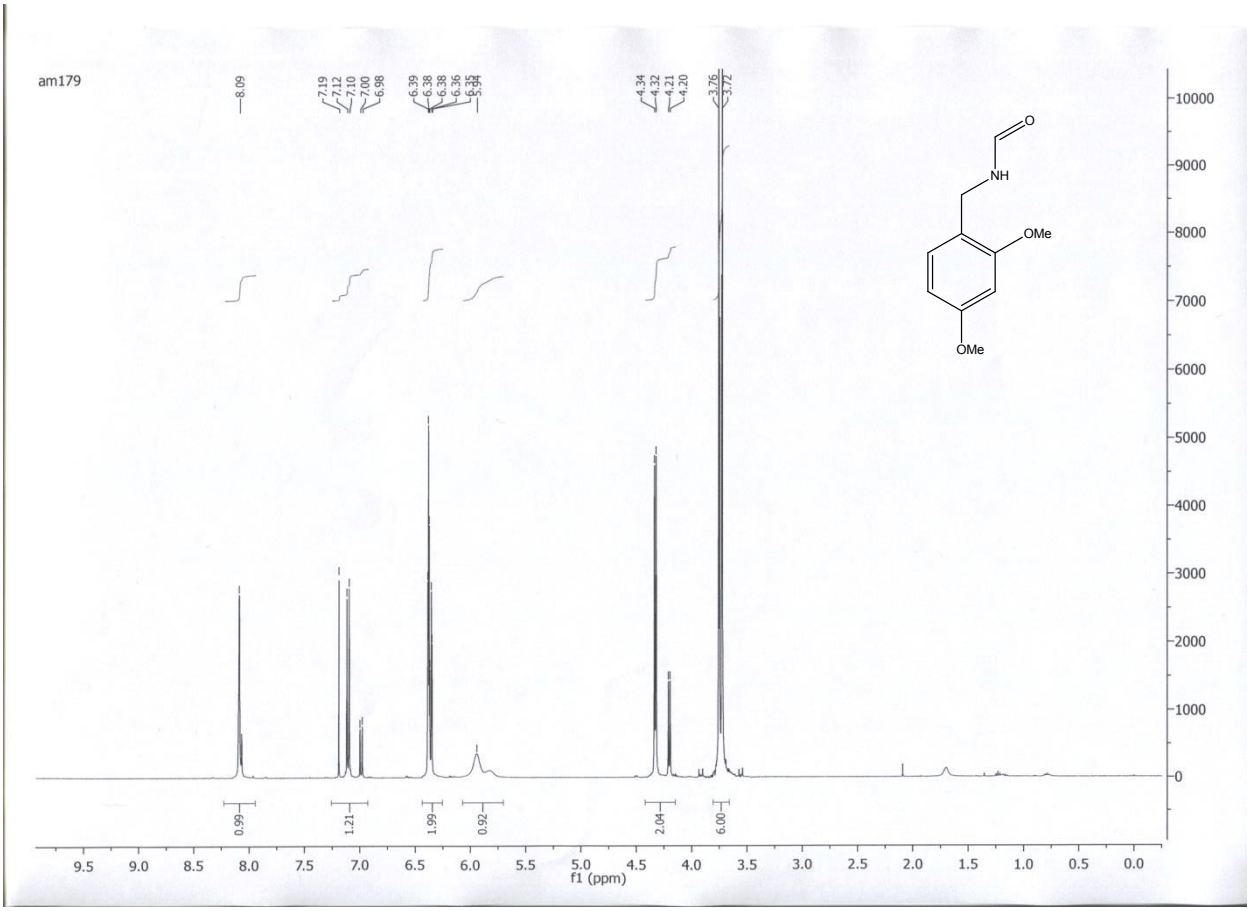


Figure 5 ^{1}H NMR spectrum of *N*-(2,4-dimethoxybezyl)formamide (400 MHz, $CDCl_3$).

Synthesis of 2,4-dimethoxybezylisocyanide:

Reaction conditions: To a solution of *N*-(2,4-dimethoxybezyl)formamide (16 mmol) and triethylamine (48 mmol; 6.7 ml) in dry dichloromethane (20 ml) at -78°C phosphoryl oxychloride (20 mmol; 1.85 ml) was added dropwise. After 1 h of stirring at room temperature, the reaction mixture was quenched by adding a saturated solution of $NaHCO_3$ (20 mL), then extracted with dichloromethane (2×20 mL). The combined organic layers were dried with $MgSO_4$ and residuals of solvent were distilled under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/AcOEt as an eluent. Yield 80 % (4.25 g)

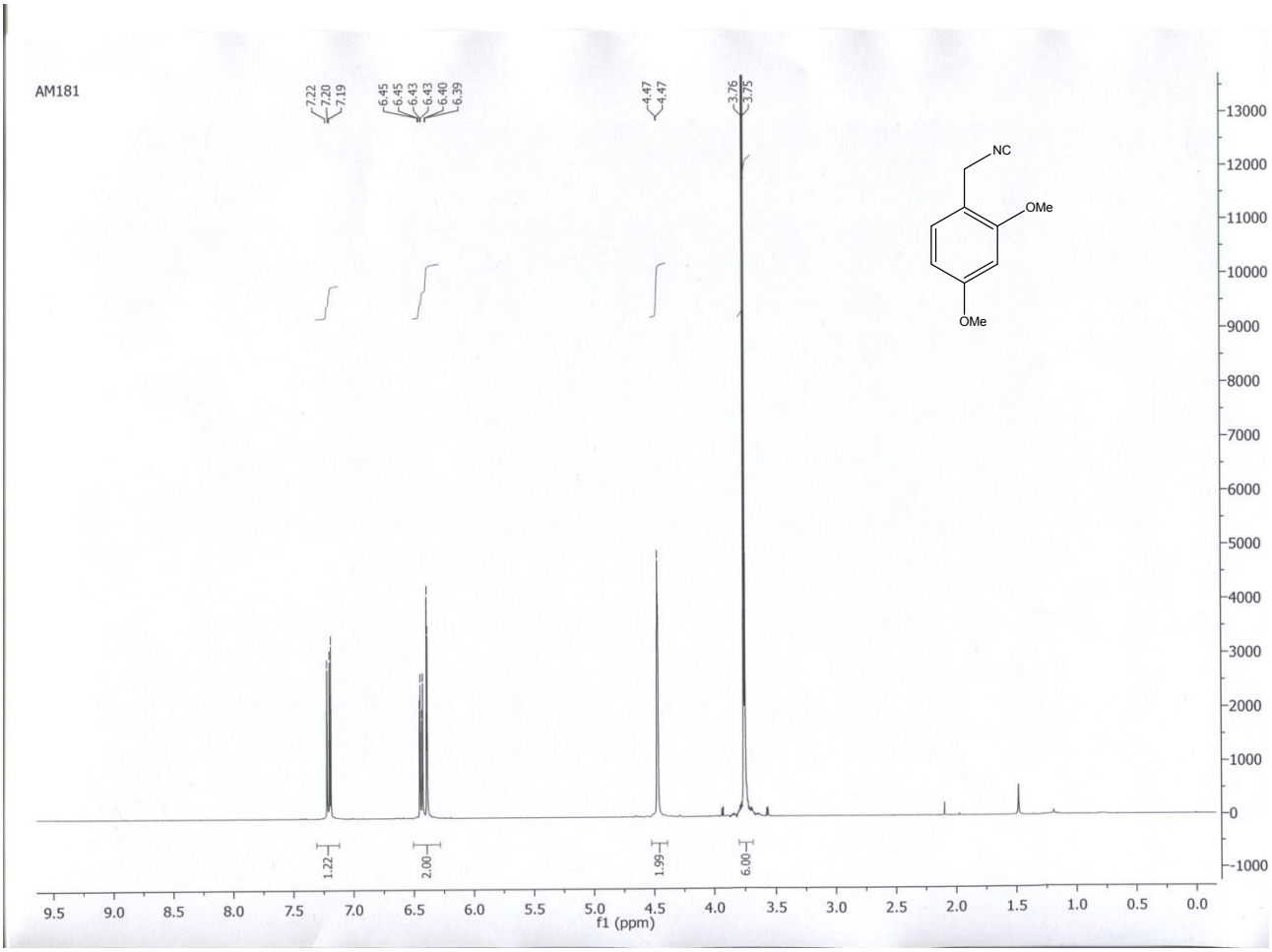


Figure 6 ^{1}H NMR spectrum of 2,4-dimethoxybezylisicyanide (400 MHz, $CDCl_3$).

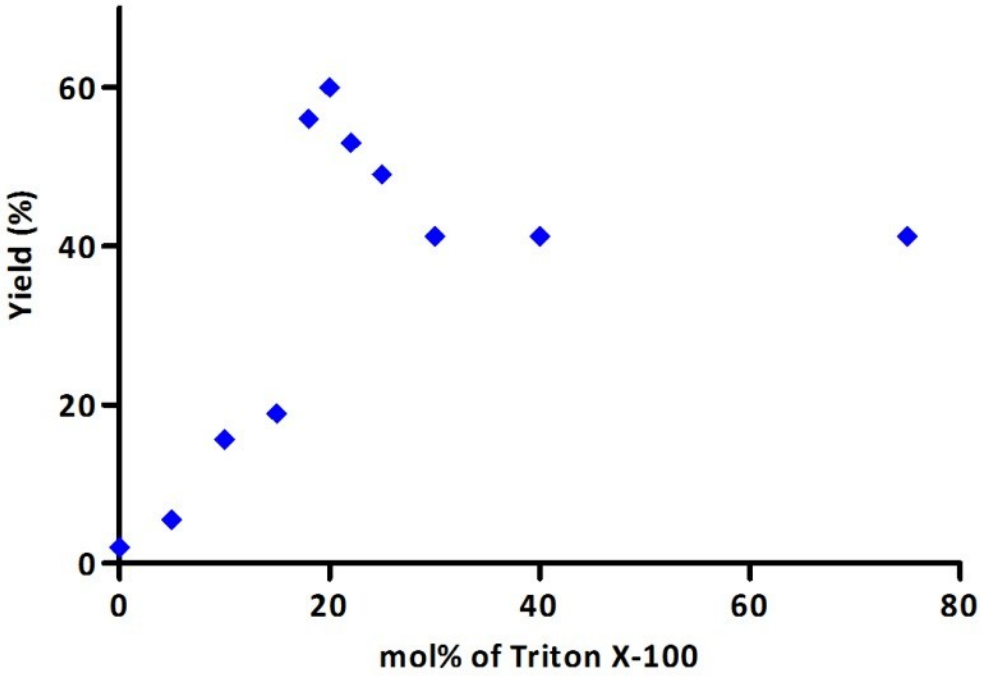


Figure 7 Effect of amount of Triton X-100 on the yield of 5a in the model Ugi reaction.

REACTION CONDITIONS: p-methoxybenzylamine (3A, 0.5 mmol), isovaleraldehyde (2a, 0.5 mmol), phenylacetic acid (1a, 0.5 mmol), *p*-methoxybenzyl isocyanide (4a, 0.5 mmol) and surfactant (0.1 mmol) in 5 mL distilled water for 48 h. mol% Triton X-100 corresponds to the amount of substrates (0.1 M).

Appearance of the aqueous Ugi multicomponent reaction samples containing DDAB and Triton X-100.

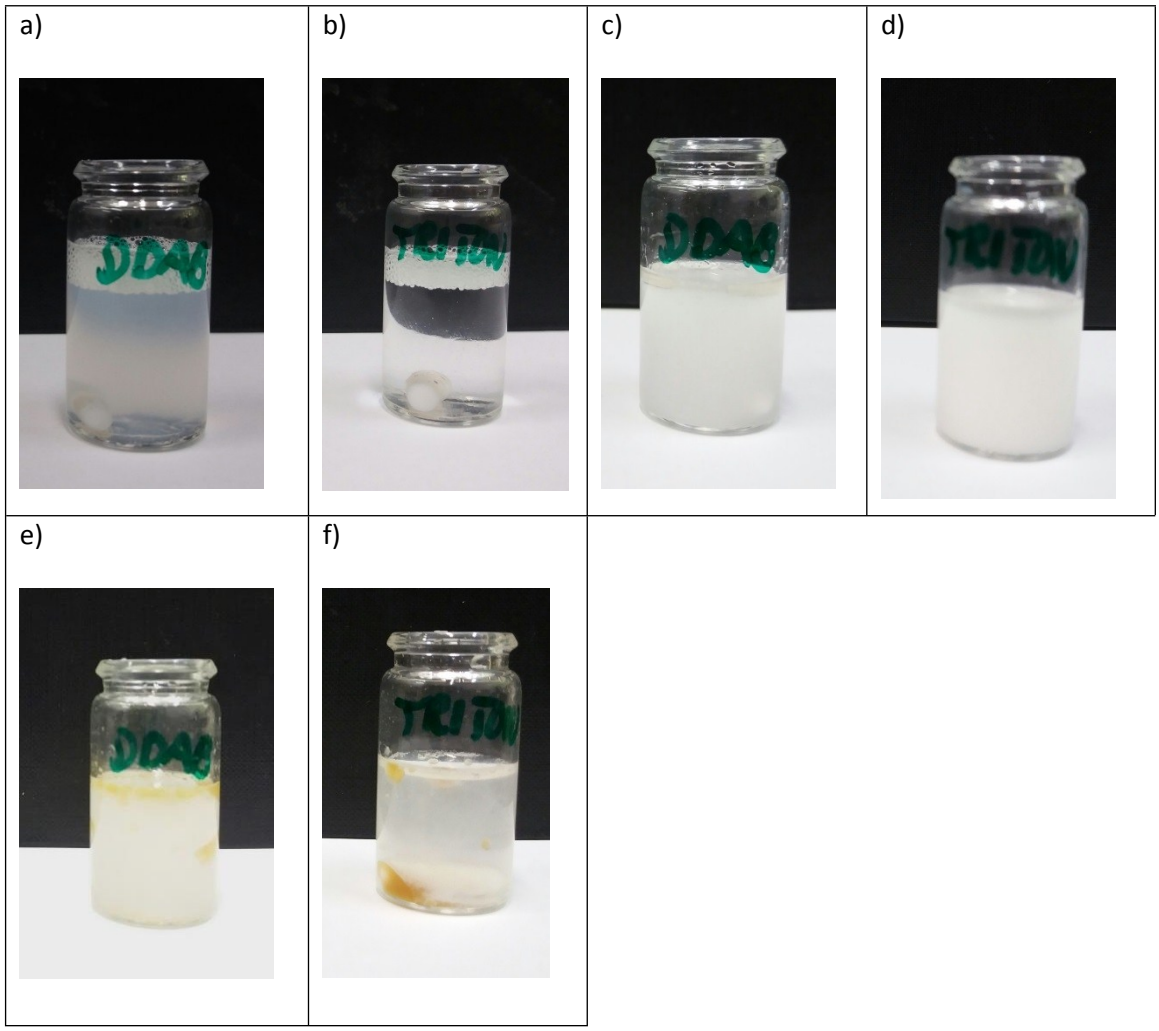


Figure 8. Photographic images of the Ugi multicomponent reaction samples (reaction with phenylacetic acid **1a** (0.5 mmol), isovalerial aldehyde **2a** (0.5 mmol), *p*-methoxybenzylamine **3a** (0.5 mmol) and *p*-methoxybenzyl isocyanide **4a** (0.5 mmol)) in distilled water (5 mL), with the addition of DDAB or Triton X-100 (0.1 mmol), 25 °C.

a) Suspension of DDAB in distilled water after 10 minutes of stirring with a magnetic stirrer.

b) Suspension of Triton X-100 in distilled water after 10 minutes of stirring with a magnetic stirrer.

c) Reaction mixture in suspension of DDAB after addition of **2a** and **3a.**

d) Reaction mixture in suspension of Triton X-100 after addition of **2a** and **3a.**

e) Reaction mixture in suspension of DDAB 10 minutes after addition of **1a**, **2a**, **3a** and **4a.**

f) Reaction mixture in suspension of Triton X-100 10 minutes after addition of **1a**, **2a**, **3a** and **4a.**

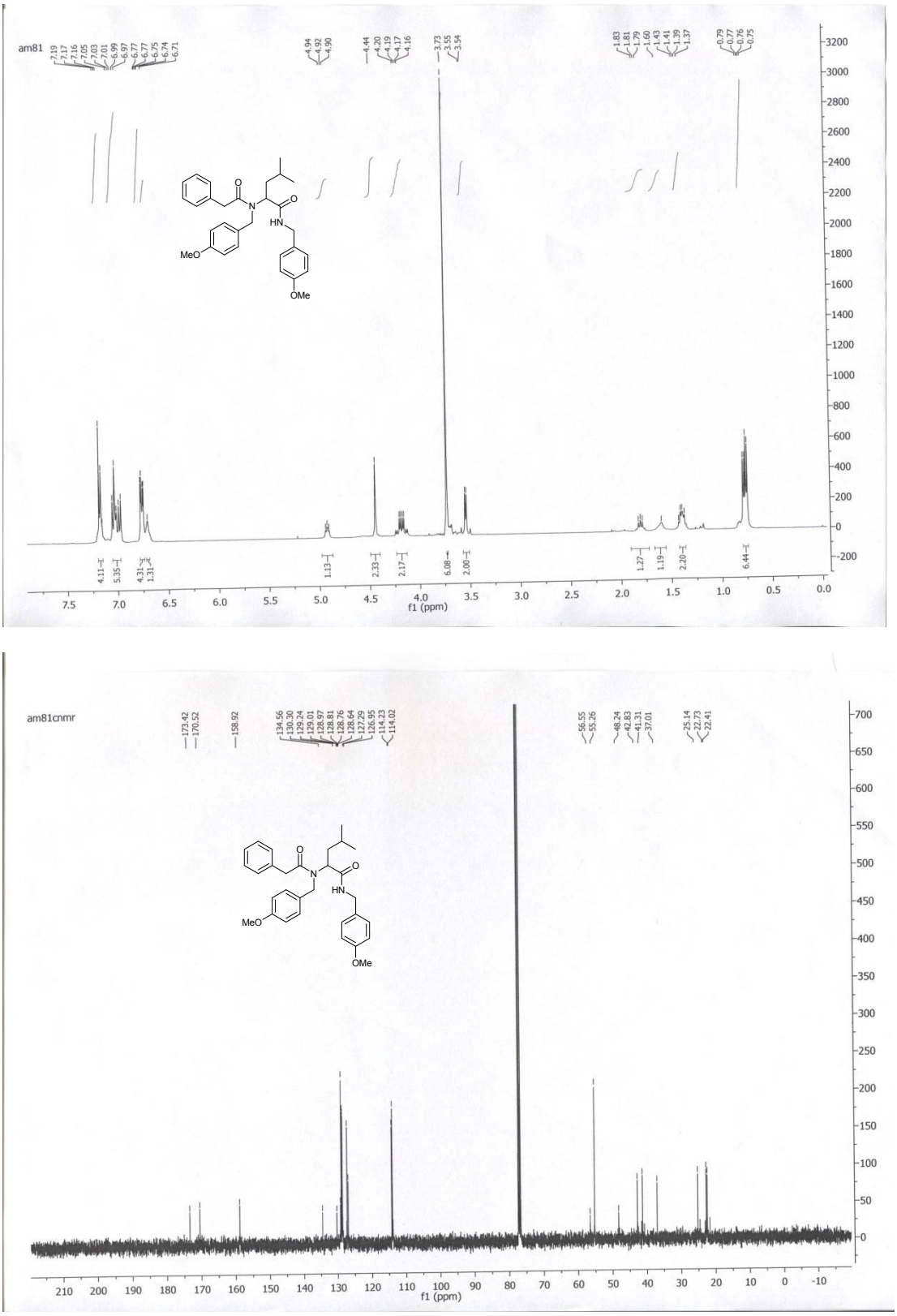
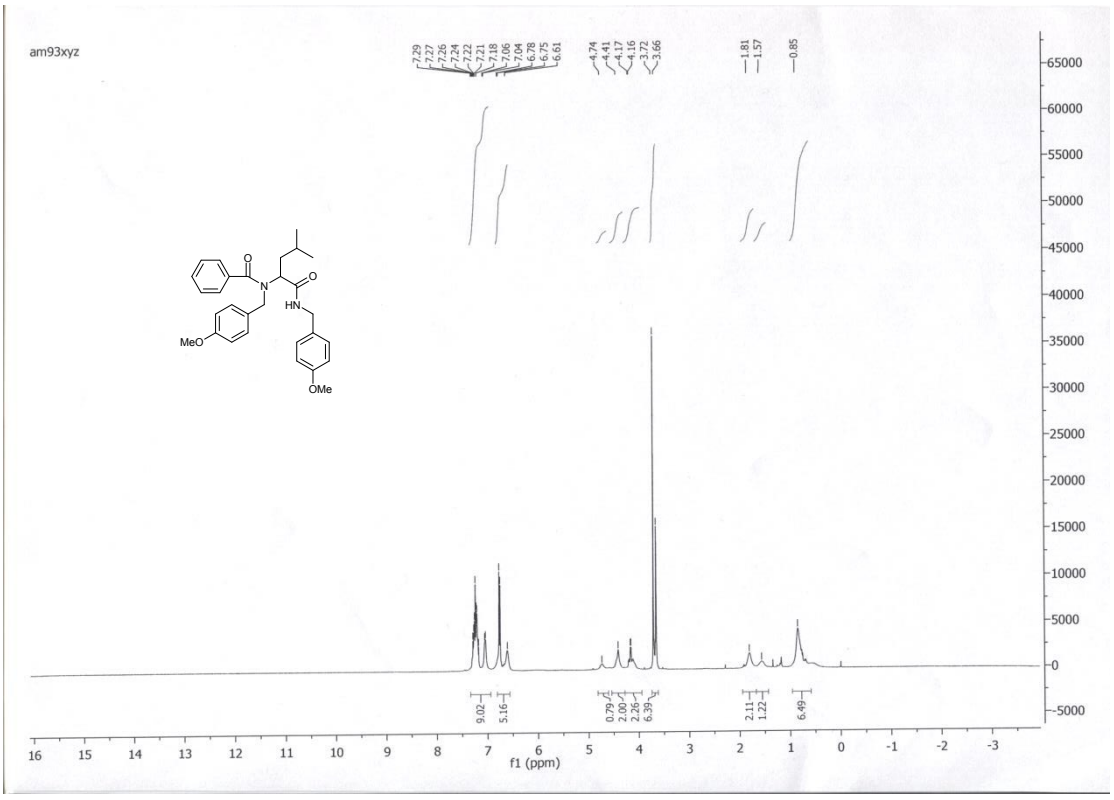


Figure 9 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5a** (400 MHz, $CDCl_3$).



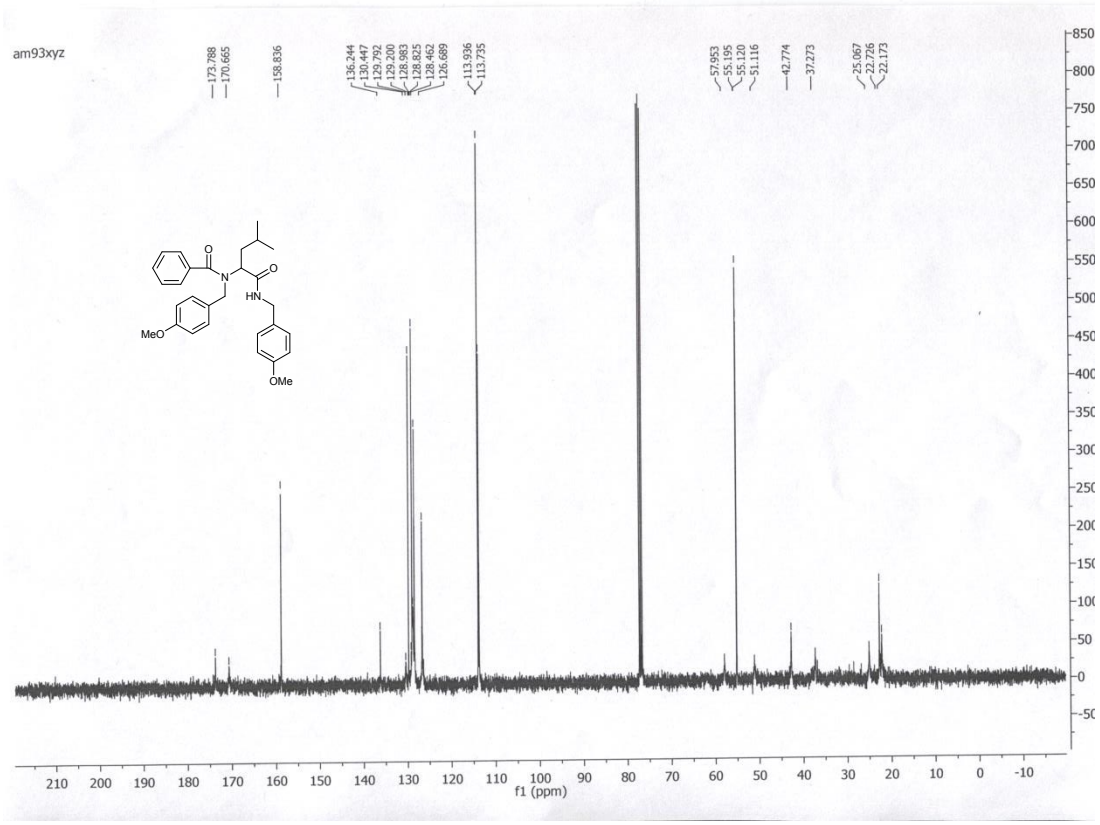


Figure 10 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5b** (400 MHz, $CDCl_3$).

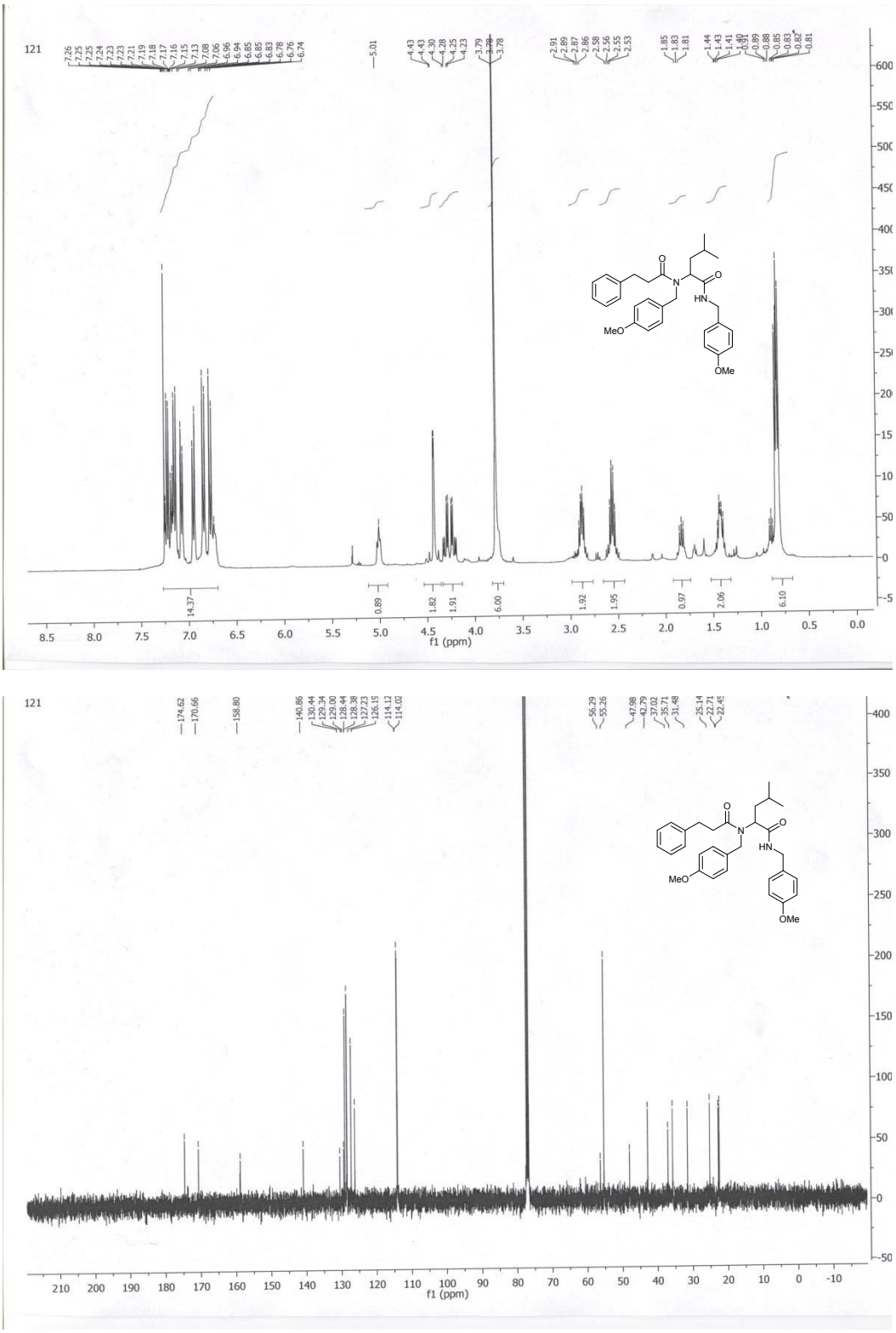


Figure 11 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5c** (400 MHz, $CDCl_3$).

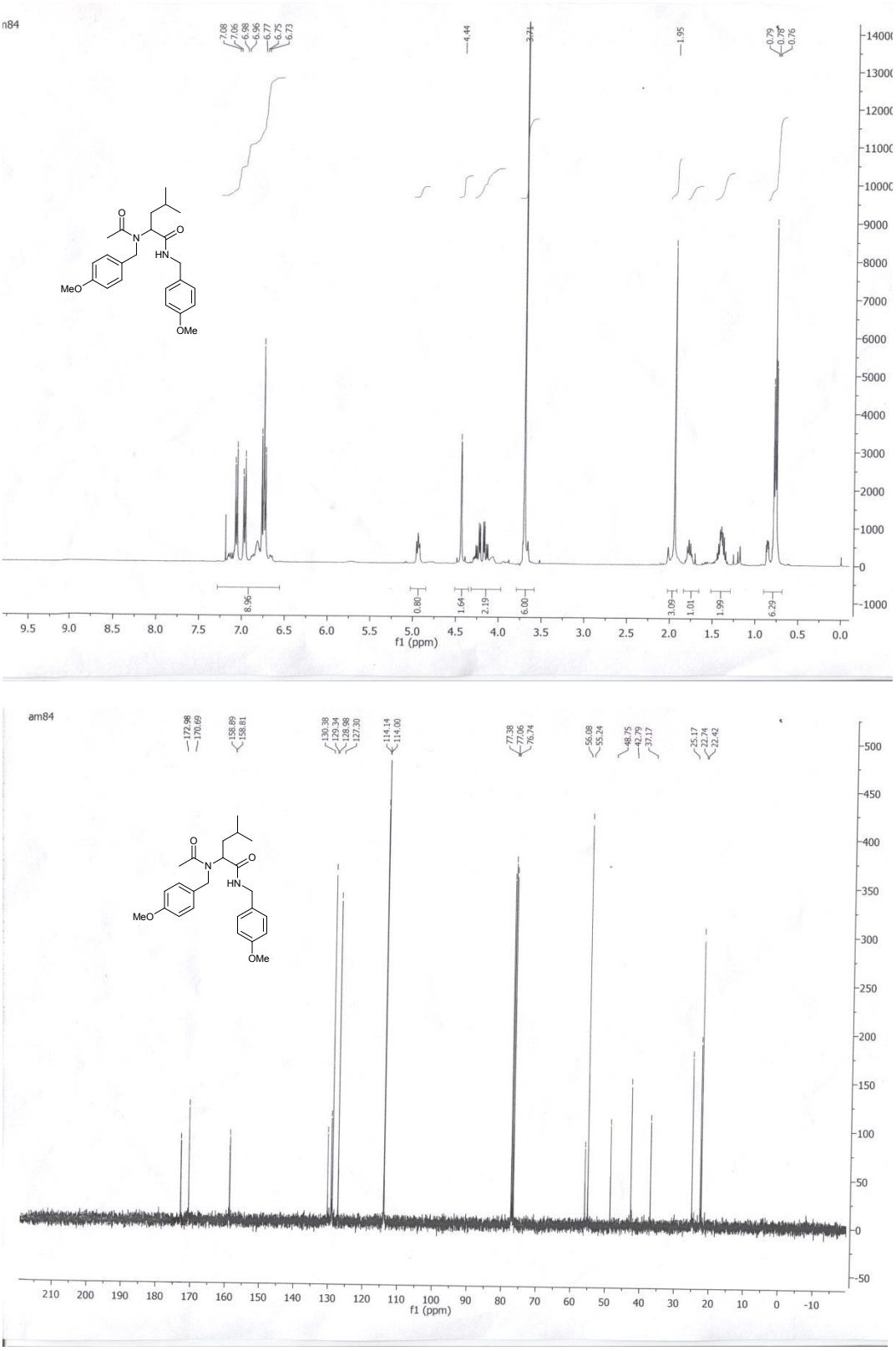
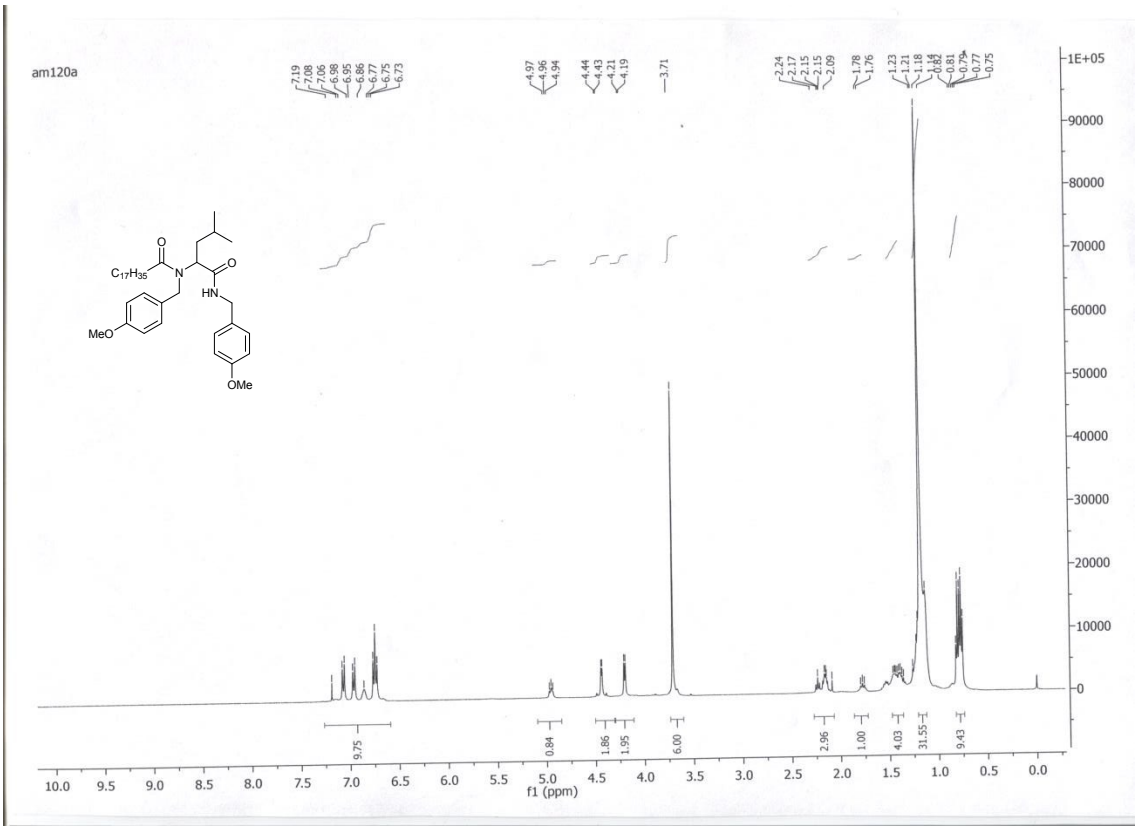


Figure 12 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5d** (400 MHz, $CDCl_3$).



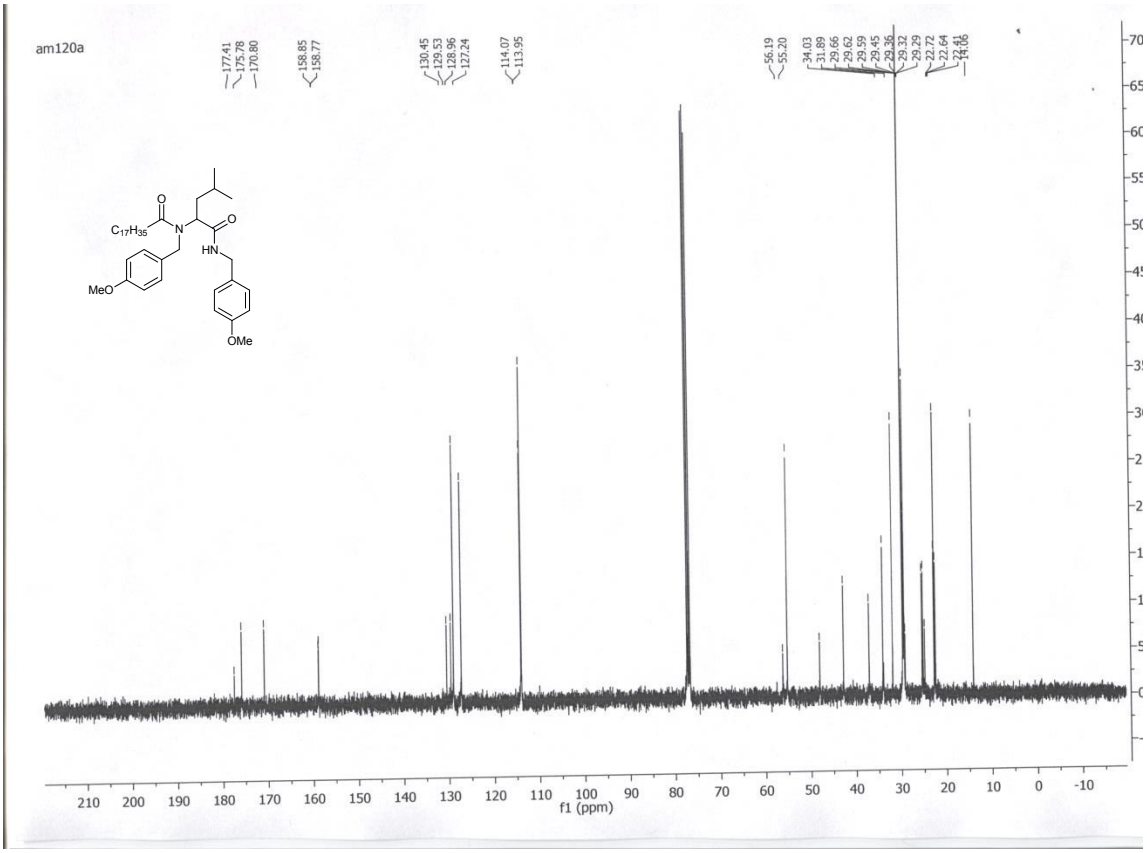


Figure 13 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5e** (400 MHz, $CDCl_3$).

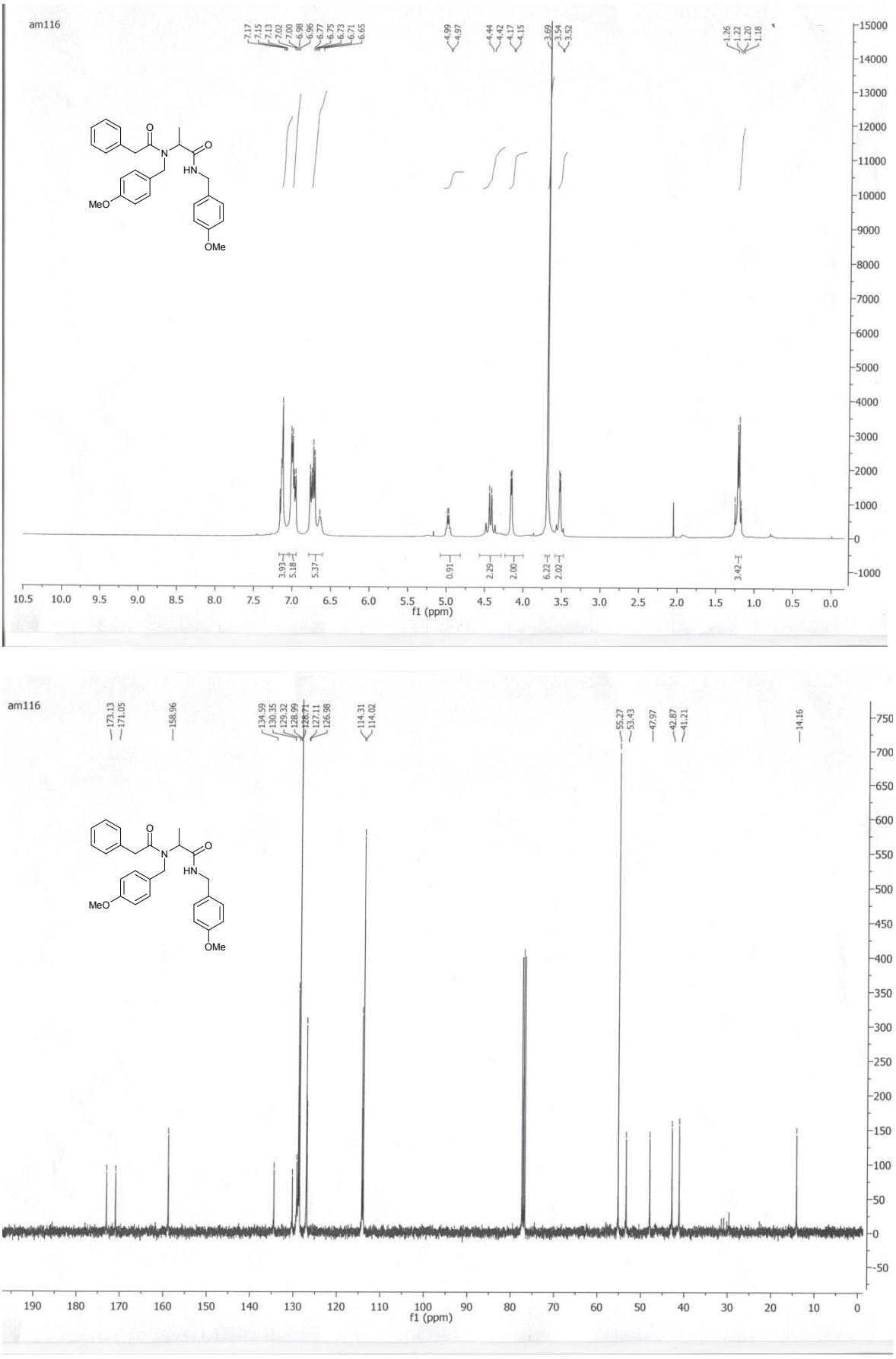


Figure 14 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5f** (400 MHz, $CDCl_3$).

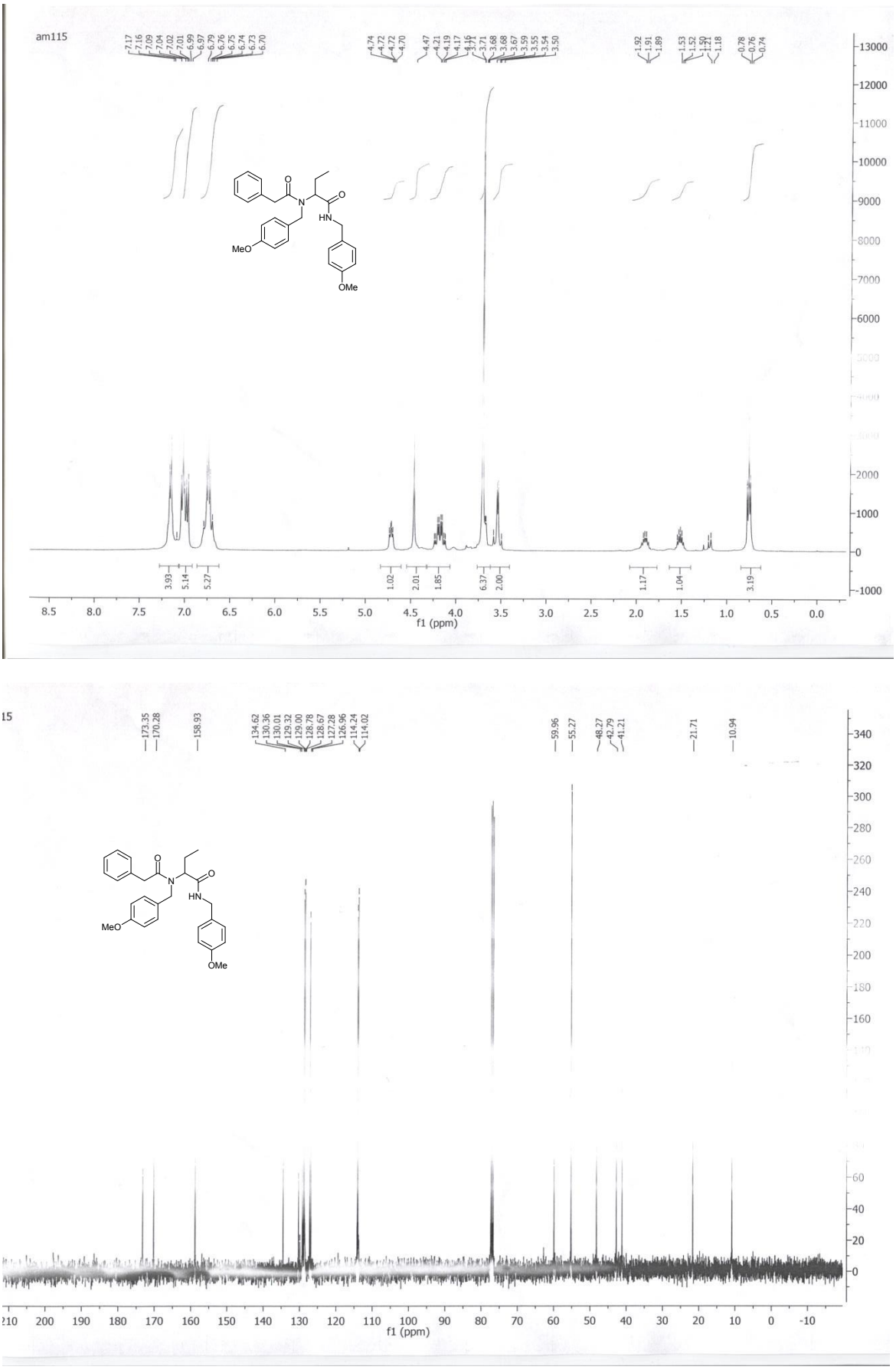


Figure 15 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5g** (400 MHz, $CDCl_3$).

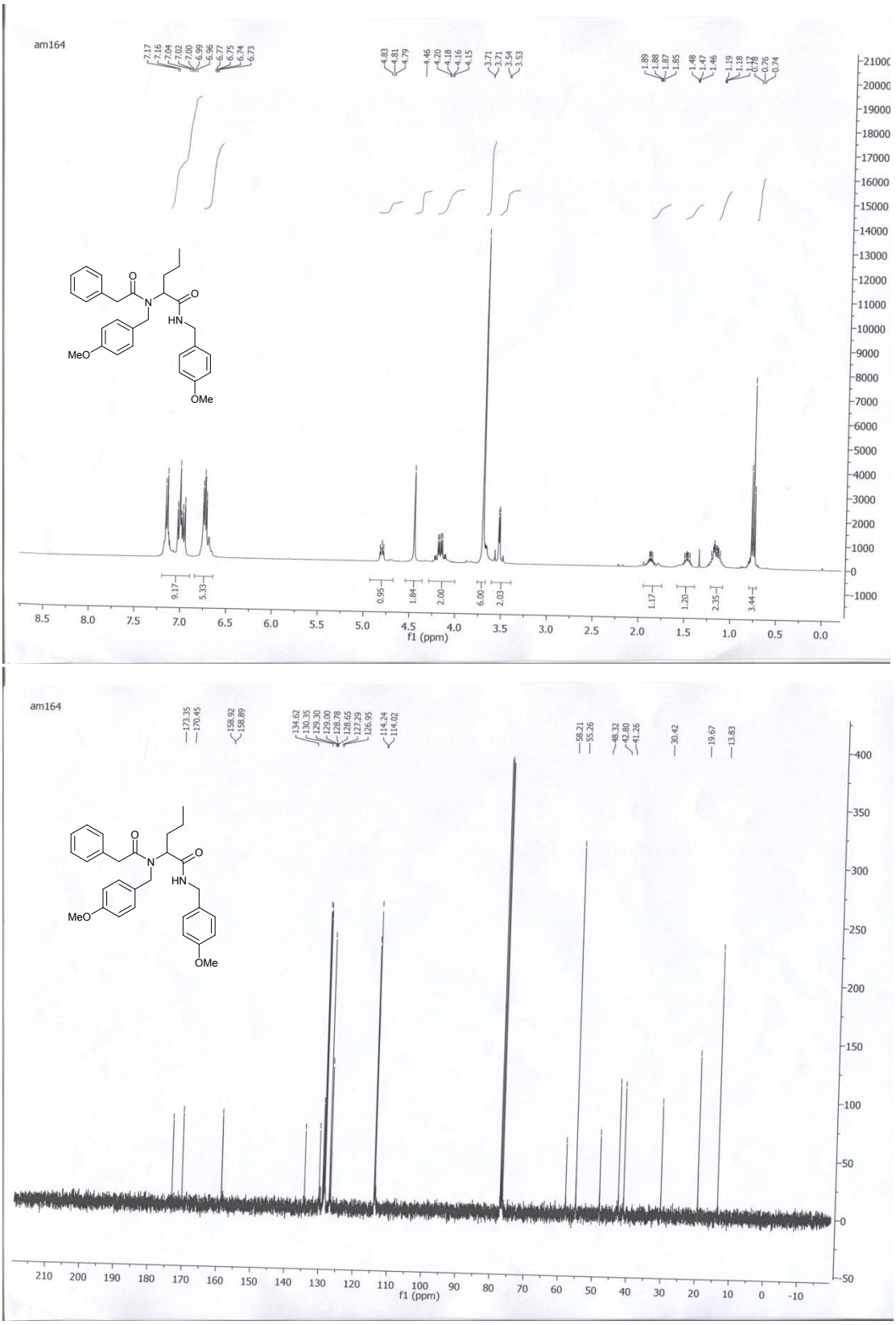
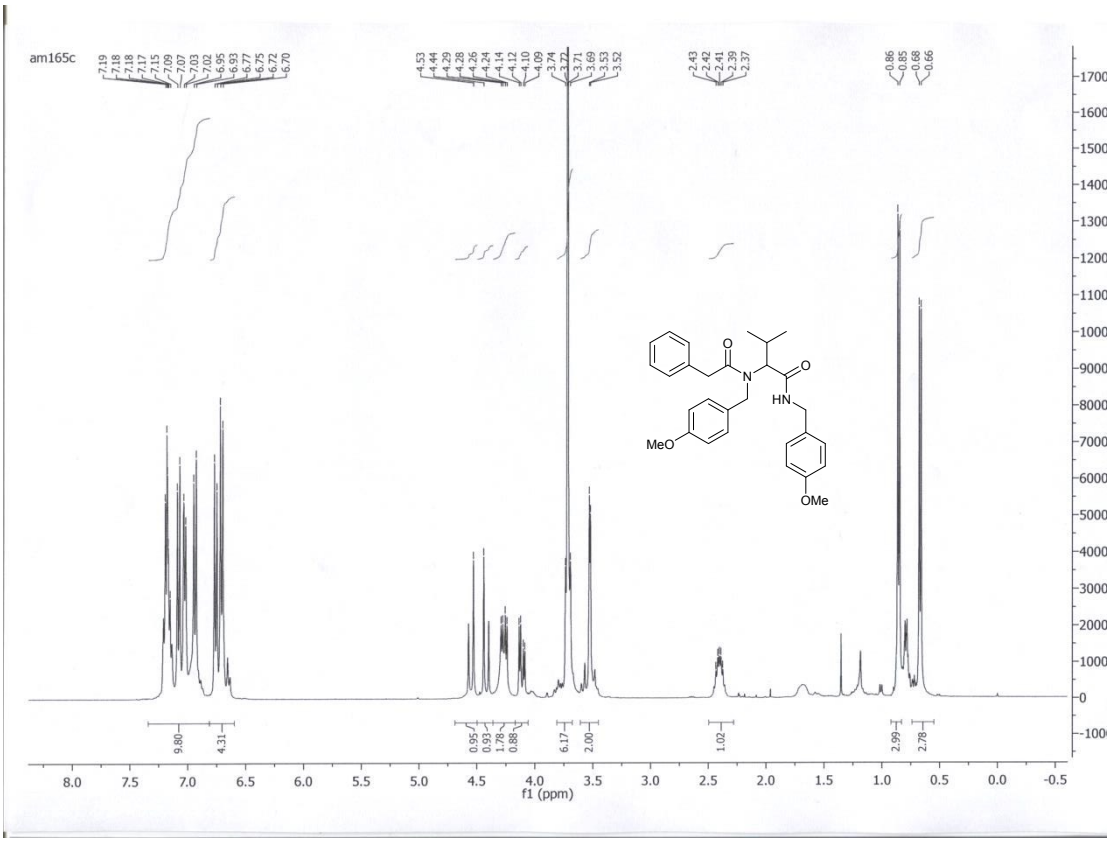


Figure 16 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5h** (400 MHz, $CDCl_3$).


am165c
7.19
7.18
7.18
7.17
7.15
7.09
7.07
7.03
7.02
6.93
6.77
6.75
6.72
6.70
4.53
4.44
4.29
4.28
4.26
4.14
4.12
4.10
4.09
3.74
3.72
3.71
3.69
3.53
3.52
2.43
2.42
2.41
2.39
2.37
0.86
0.85
0.68
0.66
O
N
O
HN
MeO
OMe
9.80
4.31
0.95
0.93
1.78
0.88
6.17
2.00
1.02
2.99
2.78
f1 (ppm)

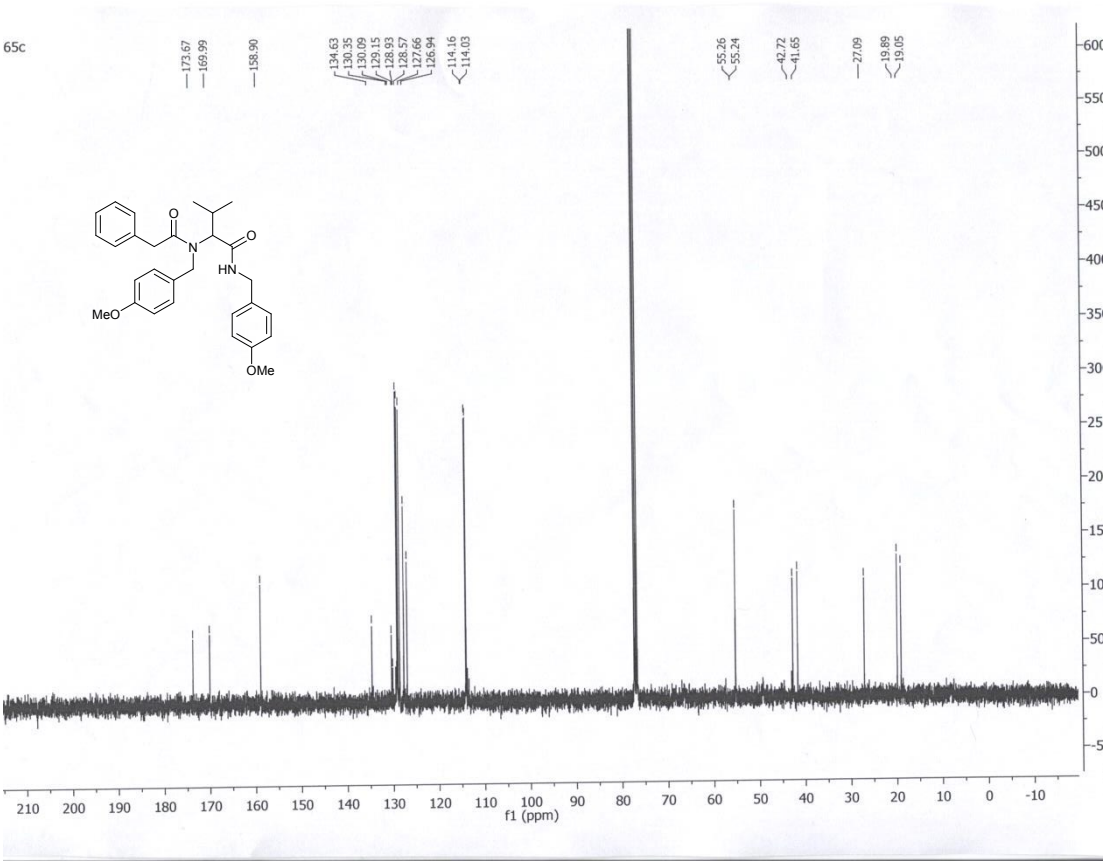


Figure 17 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5i** (400 MHz, $CDCl_3$

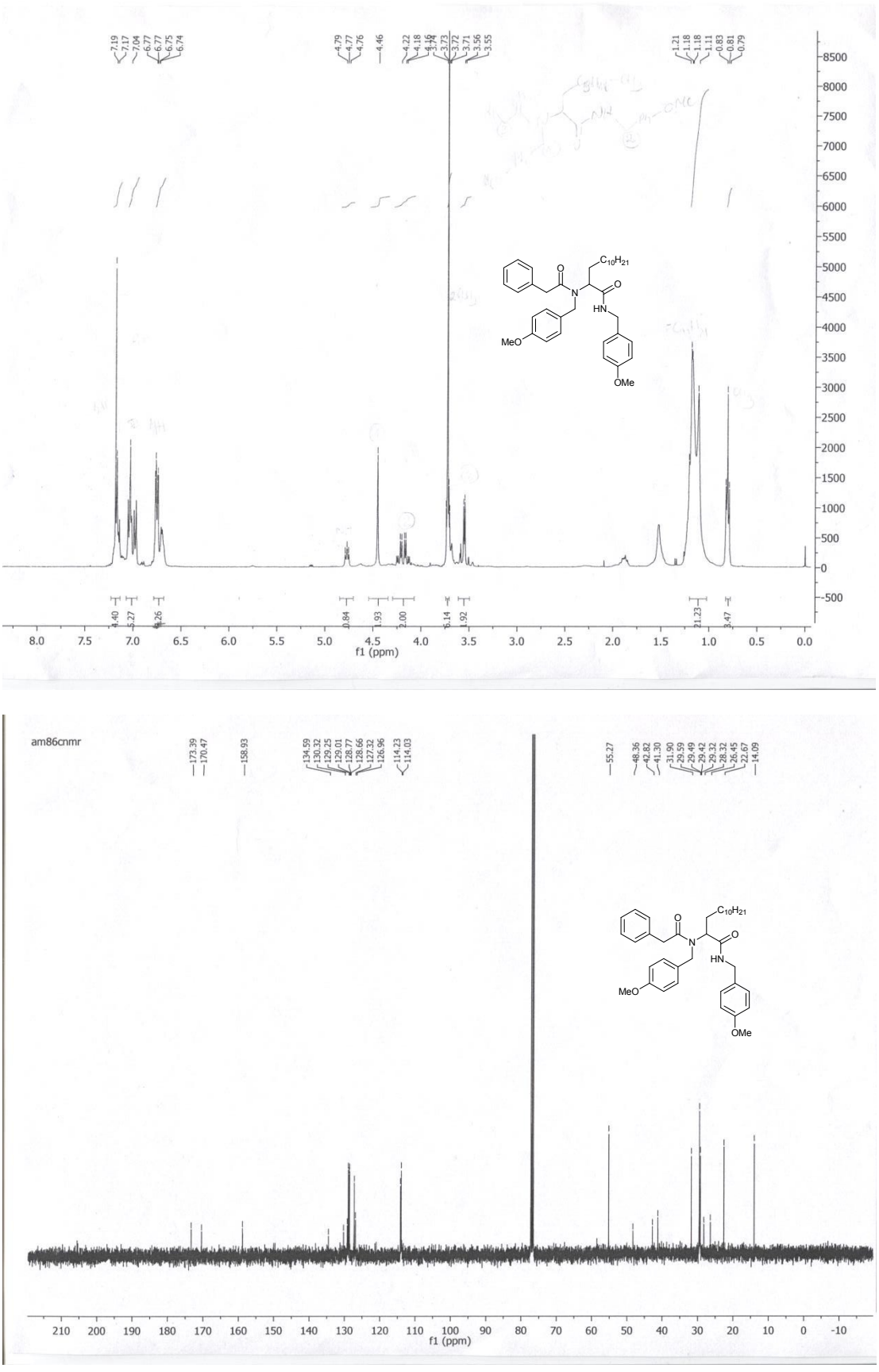


Figure 18 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5j** (400 MHz, $CDCl_3$).

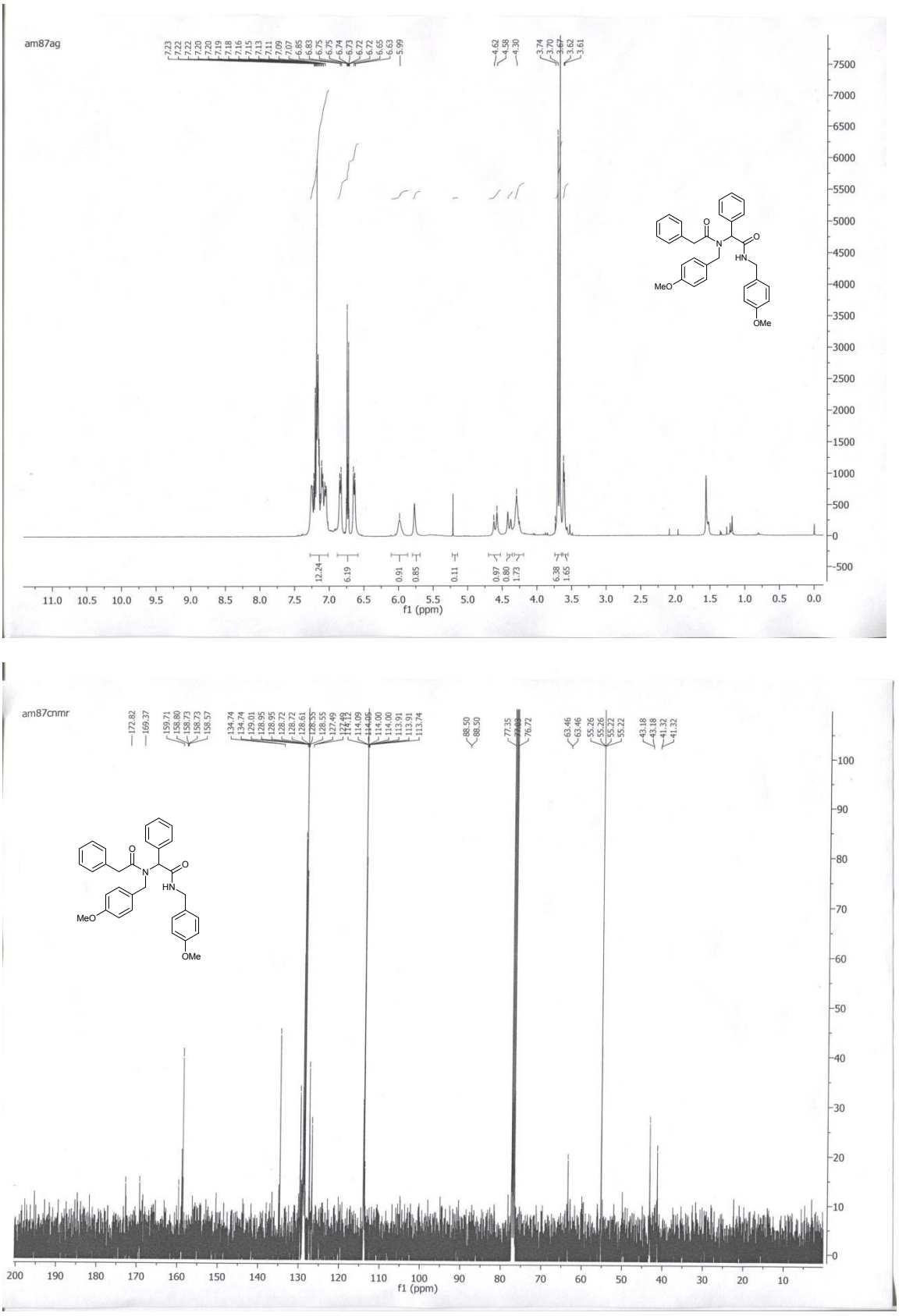


Figure 19 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5k** (400 MHz, $CDCl_3$).

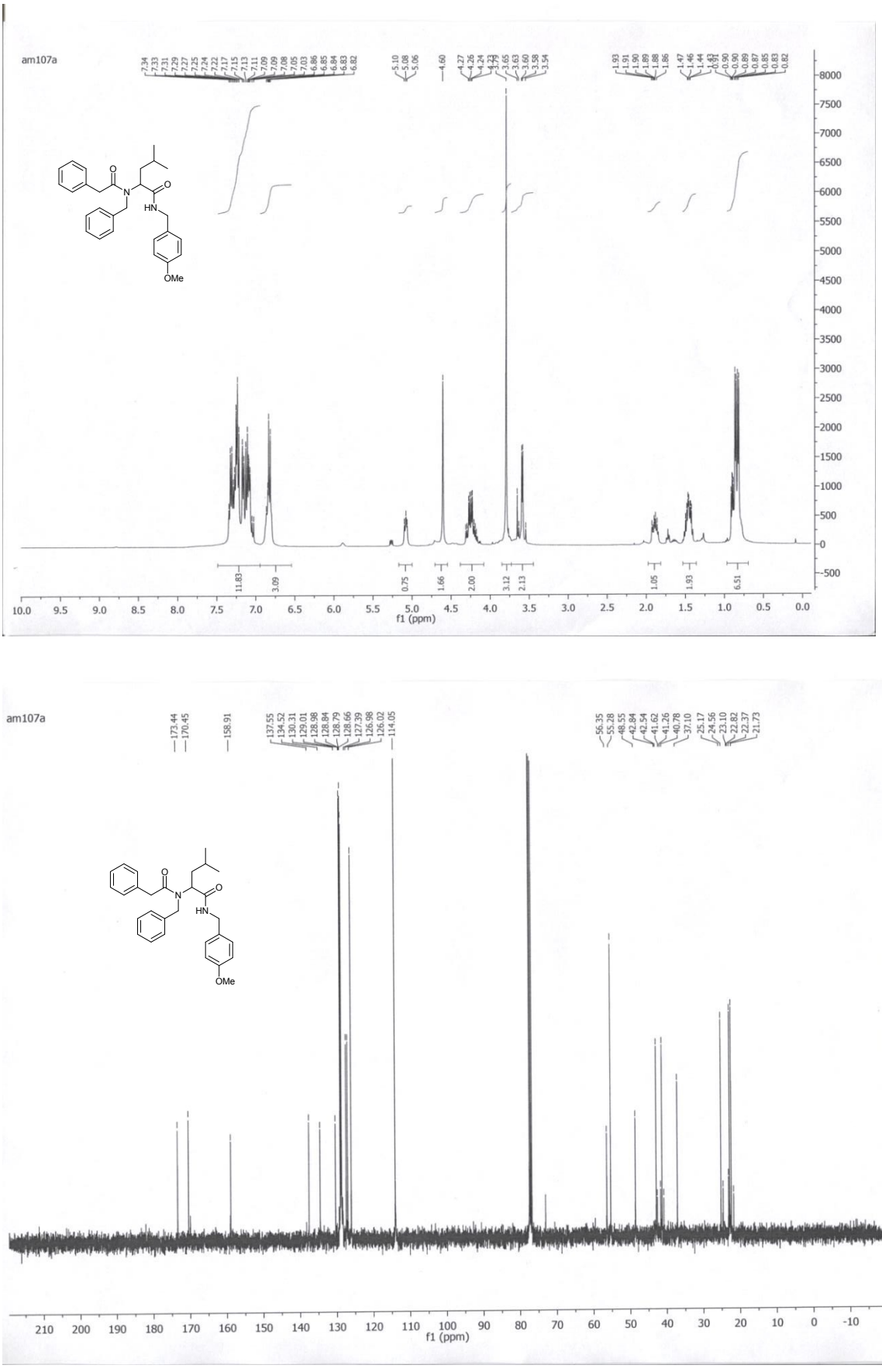
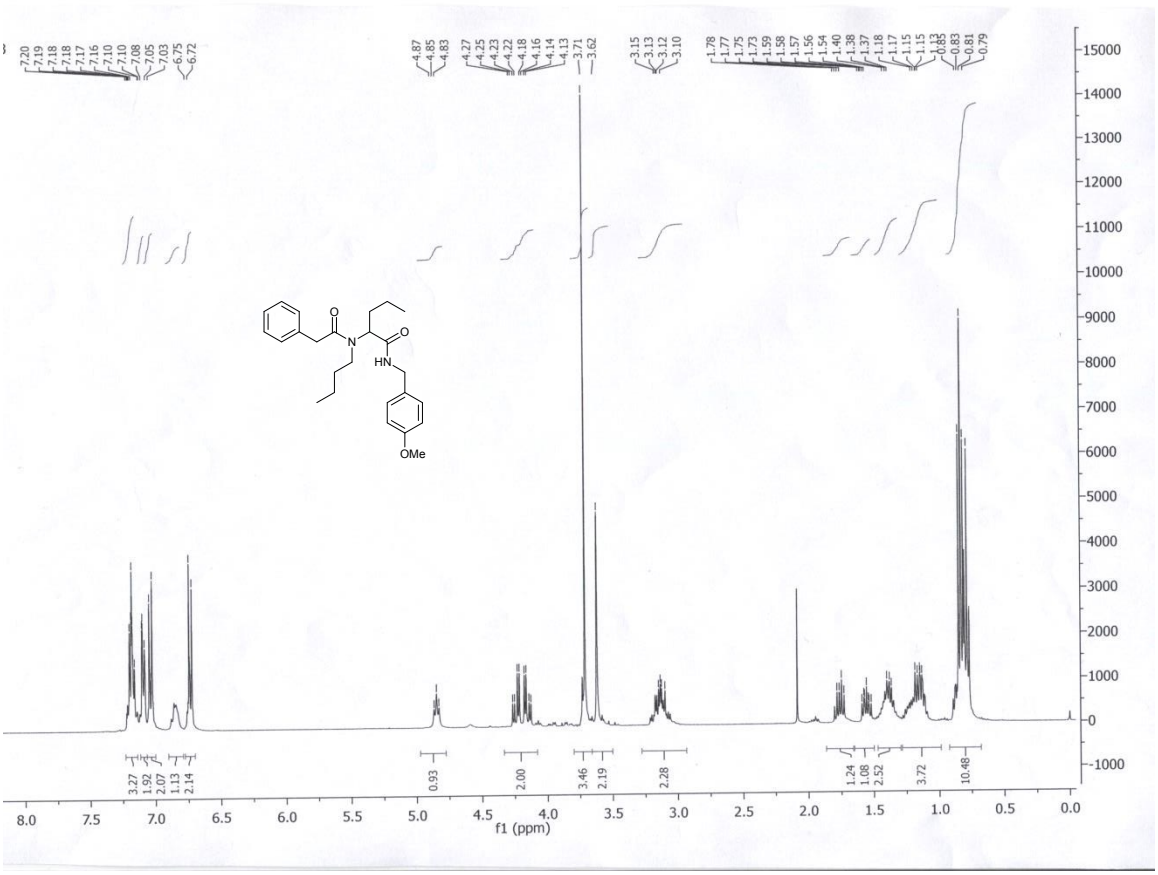


Figure 20 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5l** (400 MHz, $CDCl_3$).



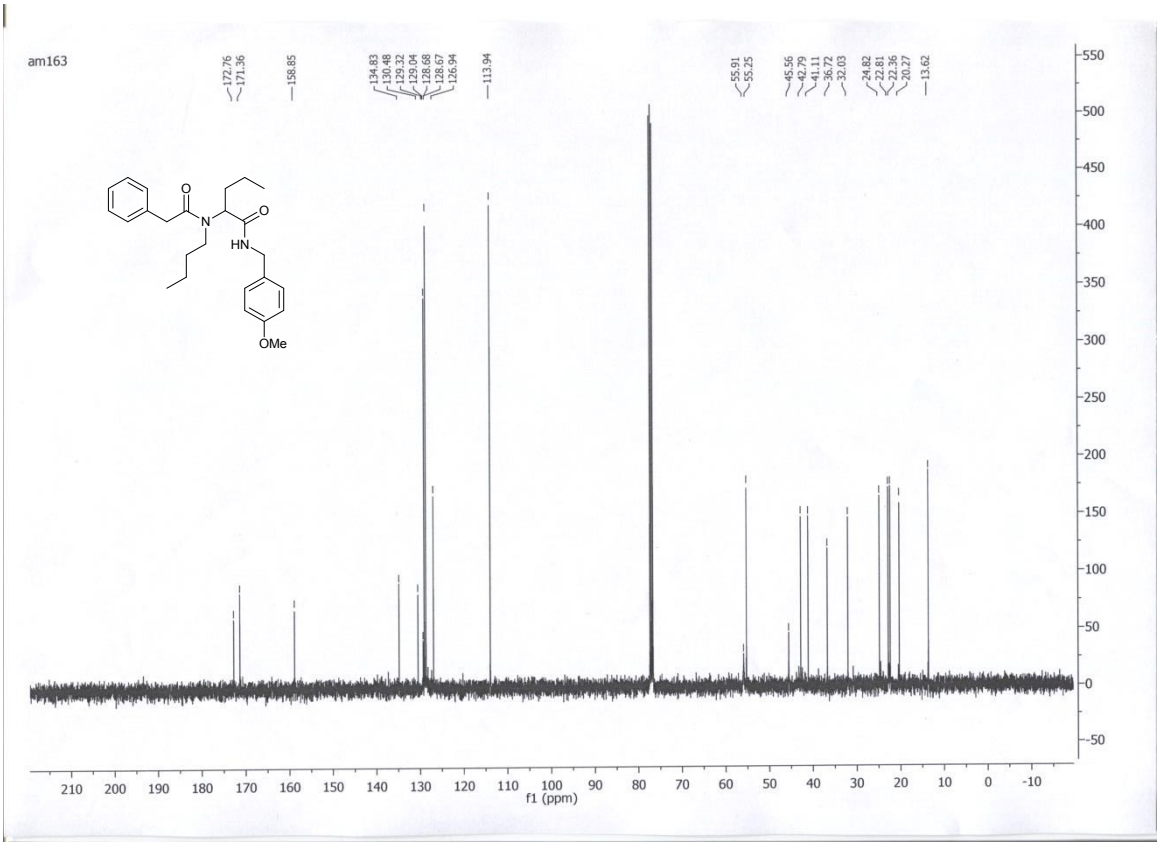


Figure 21 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5m** (400 MHz, $CDCl_3$).

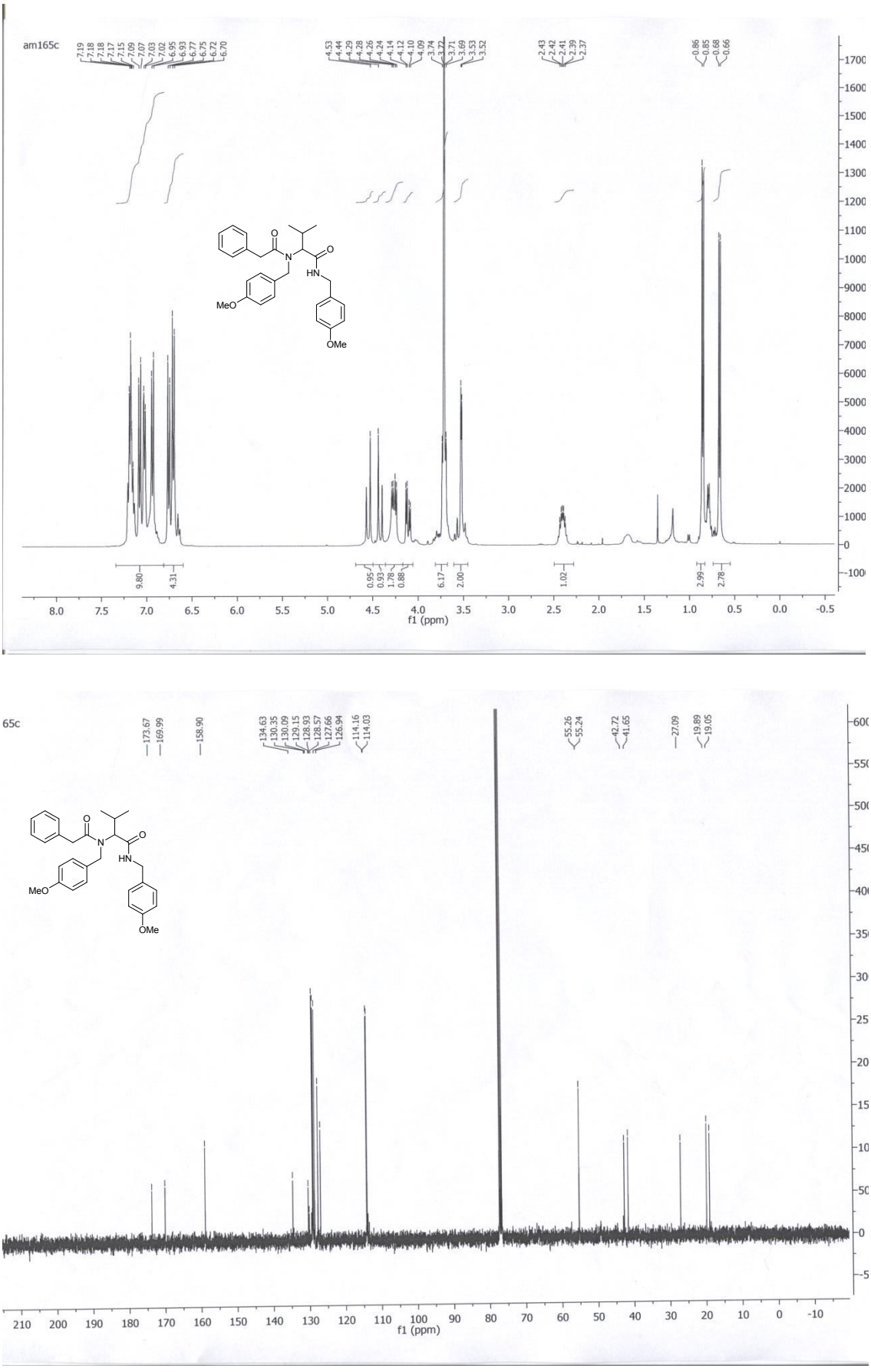
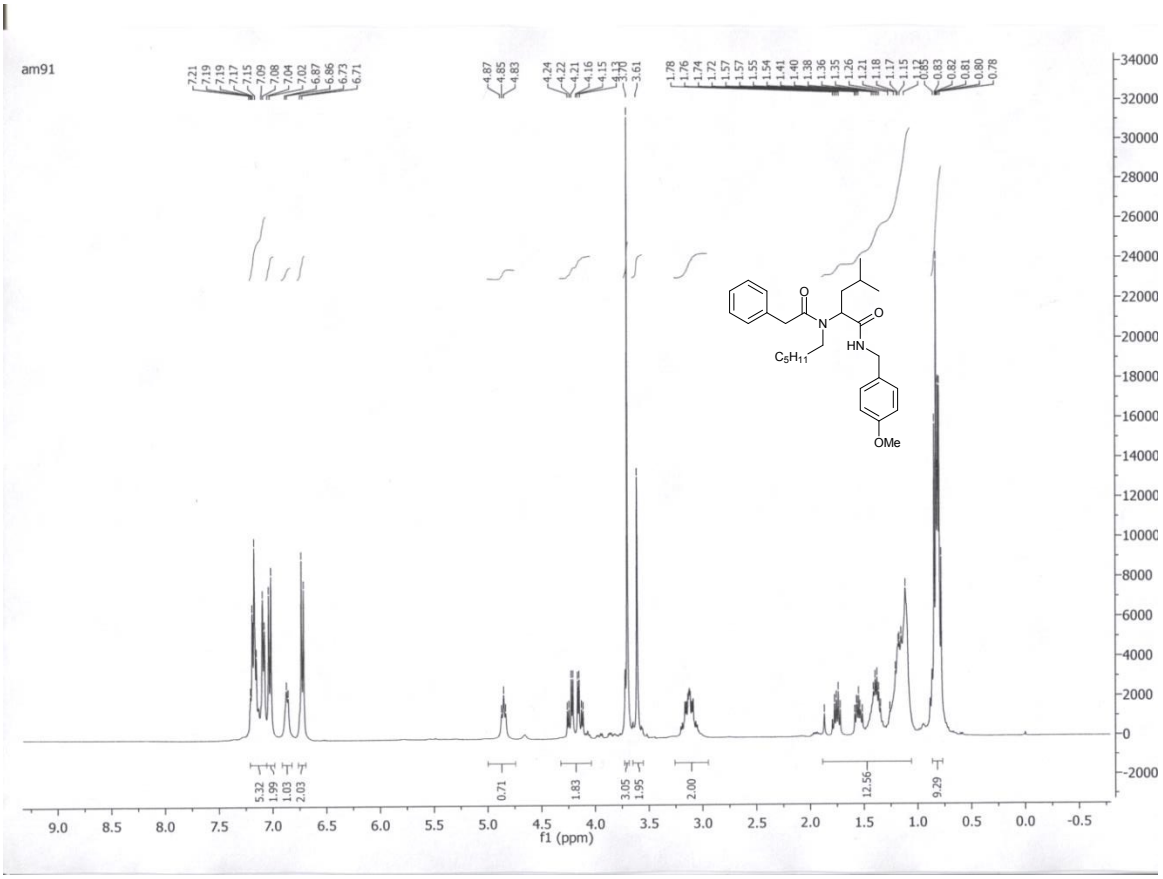


Figure 22 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5n** (400 MHz, $CDCl_3$).


am91
7.21
7.19
7.19
7.17
7.15
7.09
7.08
7.04
7.02
6.87
6.86
6.73
6.71
4.87
4.85
4.83
4.24
4.22
4.21
4.16
4.15
3.63
3.61
1.78
1.76
1.74
1.72
1.57
1.57
1.55
1.54
1.41
1.40
1.38
1.36
1.35
1.26
1.21
1.18
1.17
1.15
0.85
0.83
0.82
0.81
0.80
0.78
5.32
1.99
1.03
2.03
0.71
1.83
3.05
1.95
2.00
12.56
9.29
f1 (ppm)
O
N
O
HN
C5H11
OMe

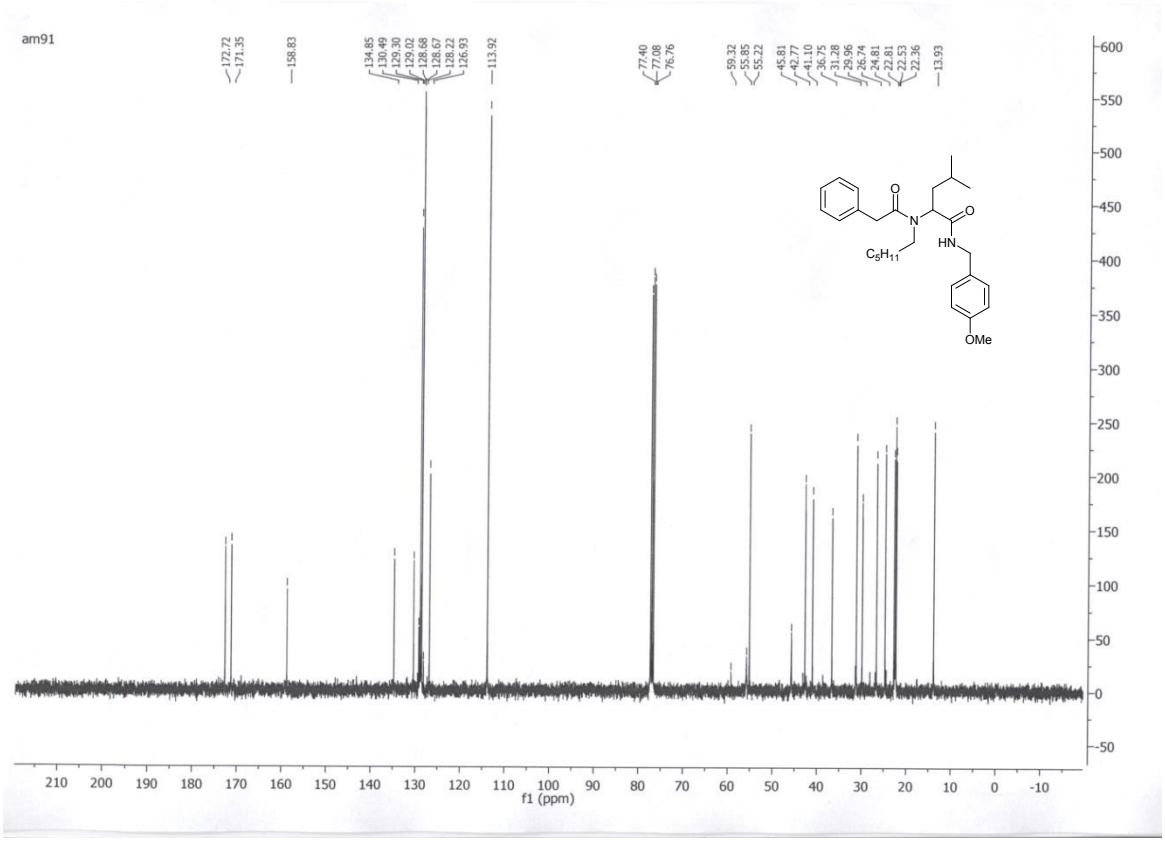
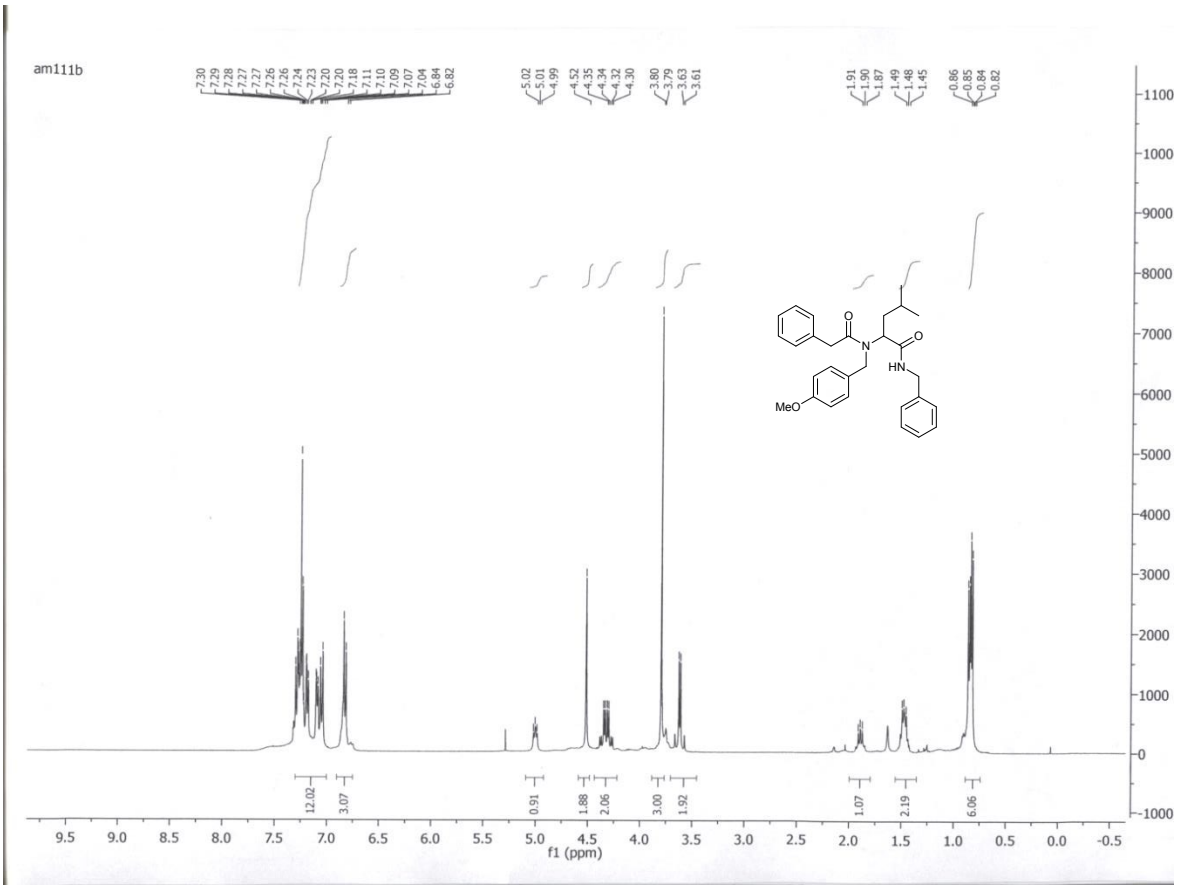

am91
172.72
171.35
158.83
134.85
130.49
129.30
129.02
128.68
128.67
128.22
126.93
113.92
77.40
77.08
76.76
59.32
55.85
55.22
45.81
42.77
41.10
36.75
31.28
29.96
26.74
24.81
22.81
22.53
22.36
13.93
f1 (ppm)
O
N
O
HN
C5H11
OMe

Figure 23 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5o** (400 MHz, $CDCl_3$).



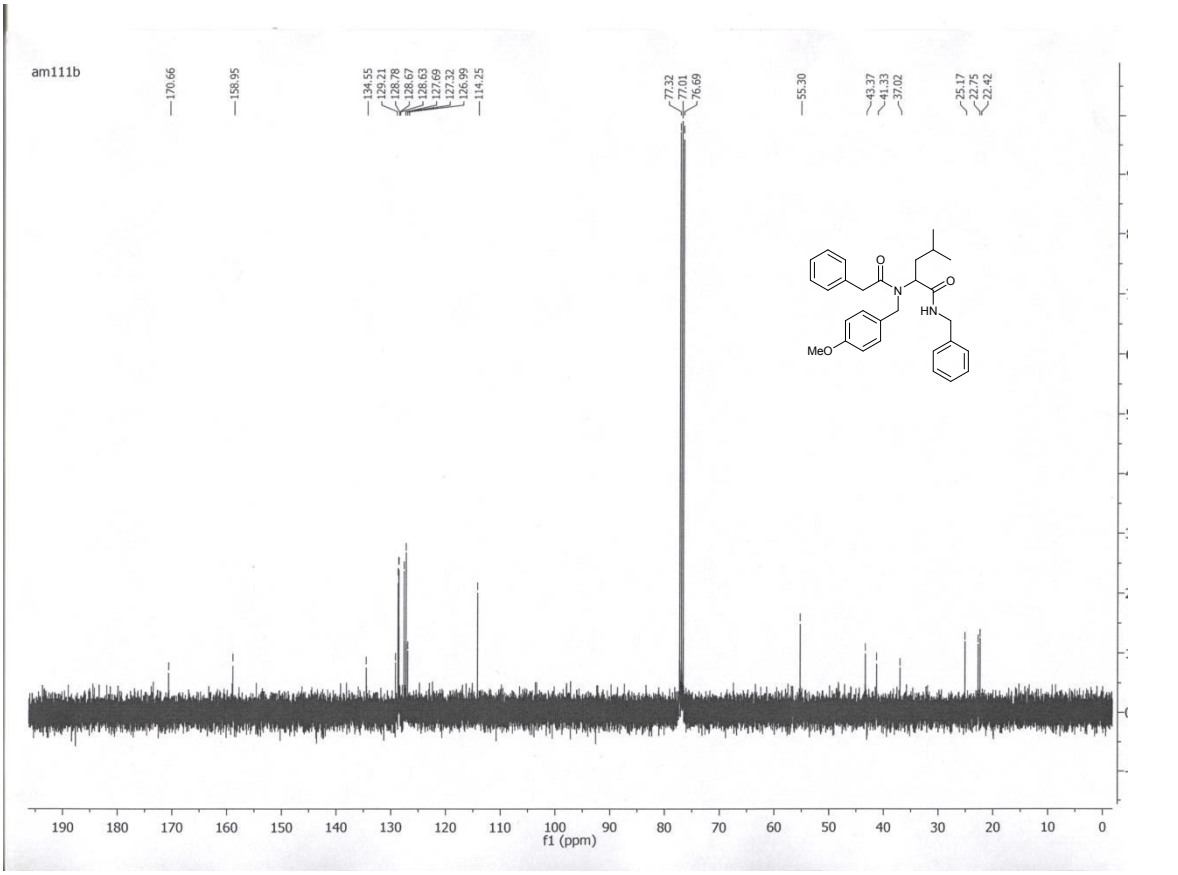


Figure 24 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5p** (400 MHz, $CDCl_3$).

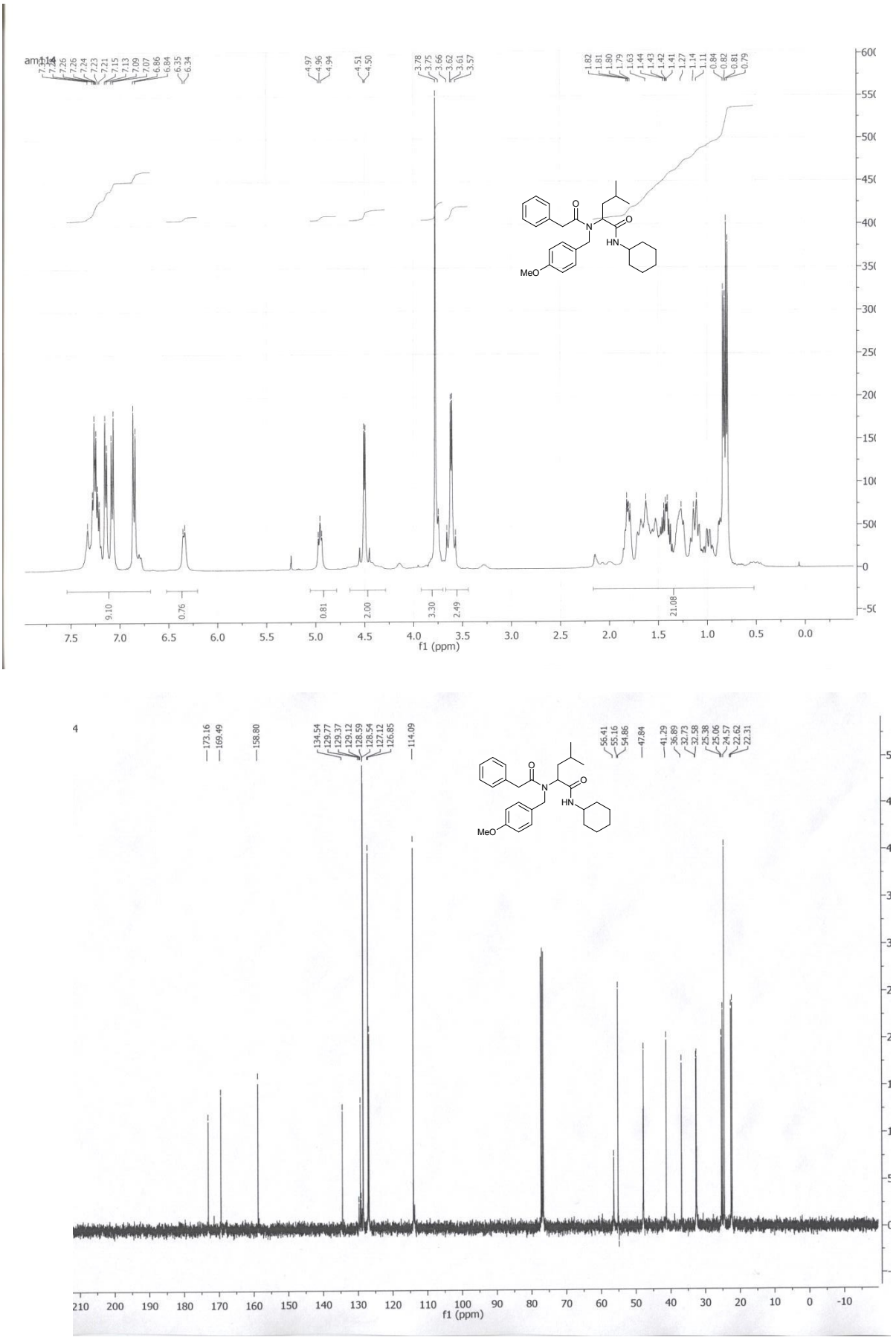
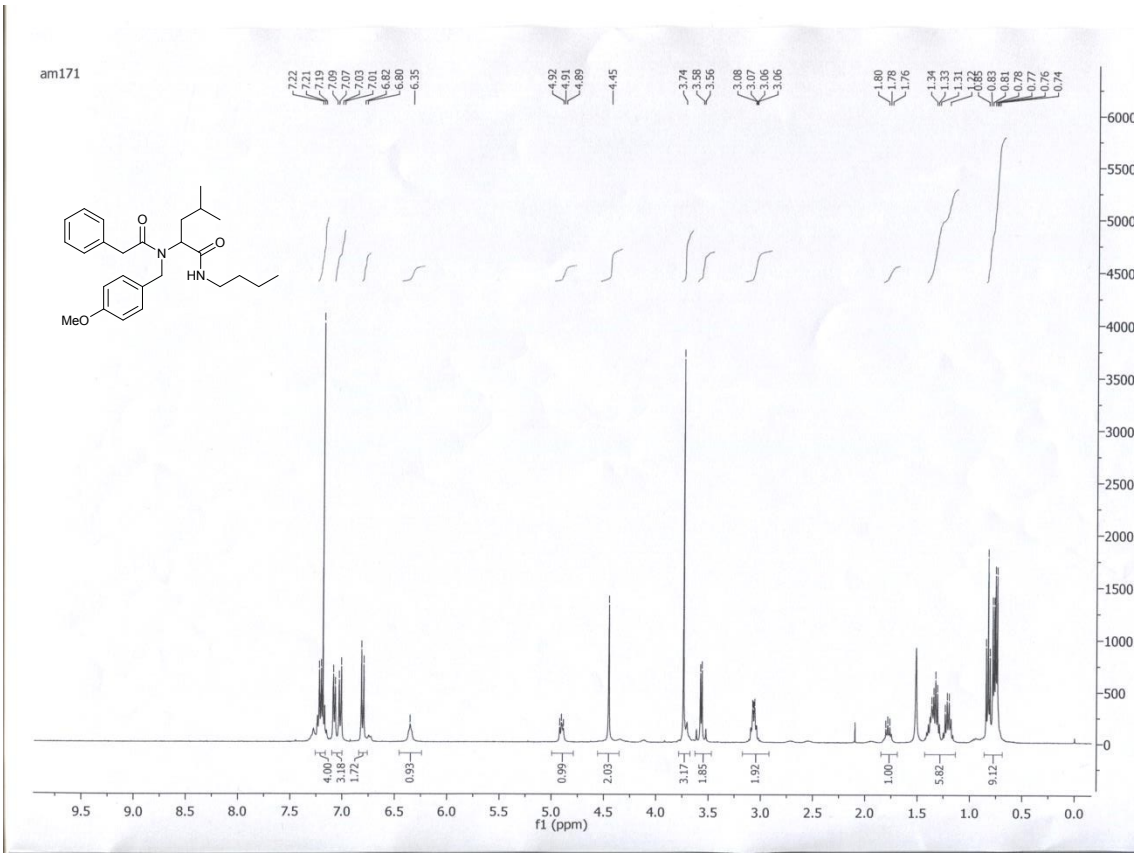


Figure 25 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5t** (400 MHz, $CDCl_3$).



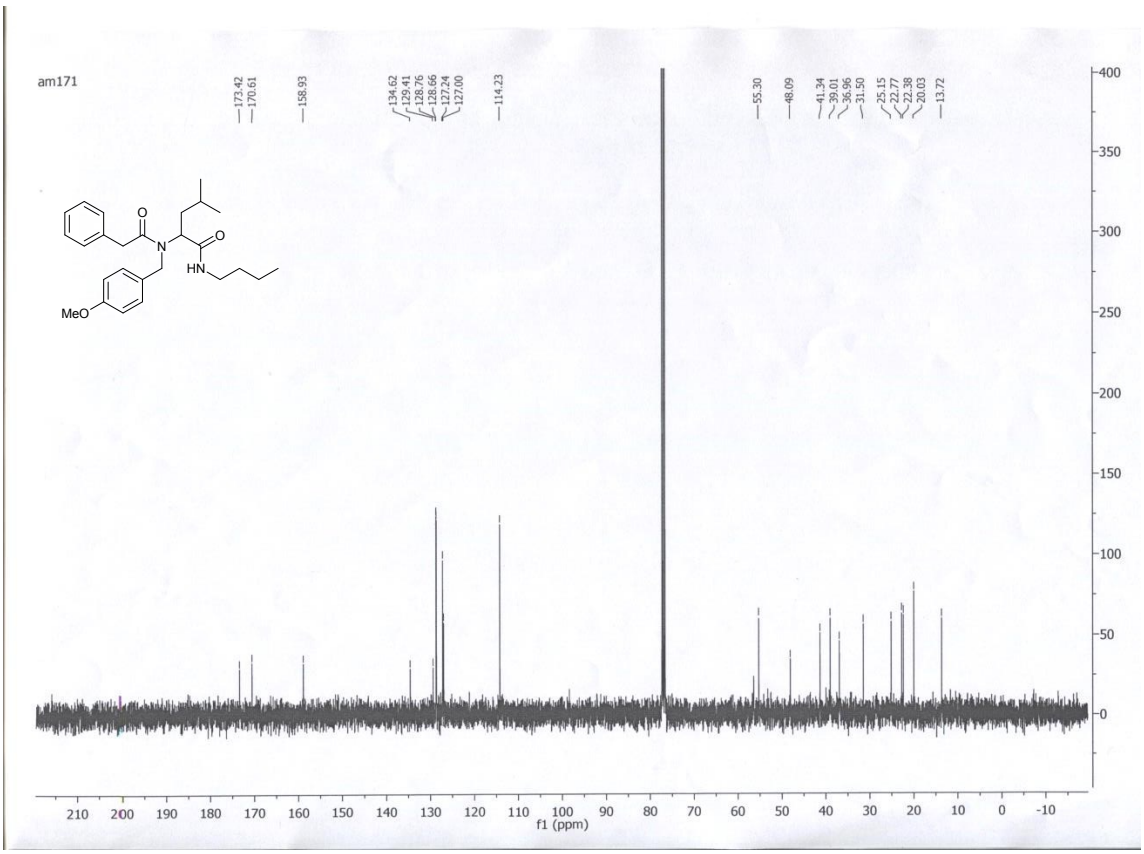
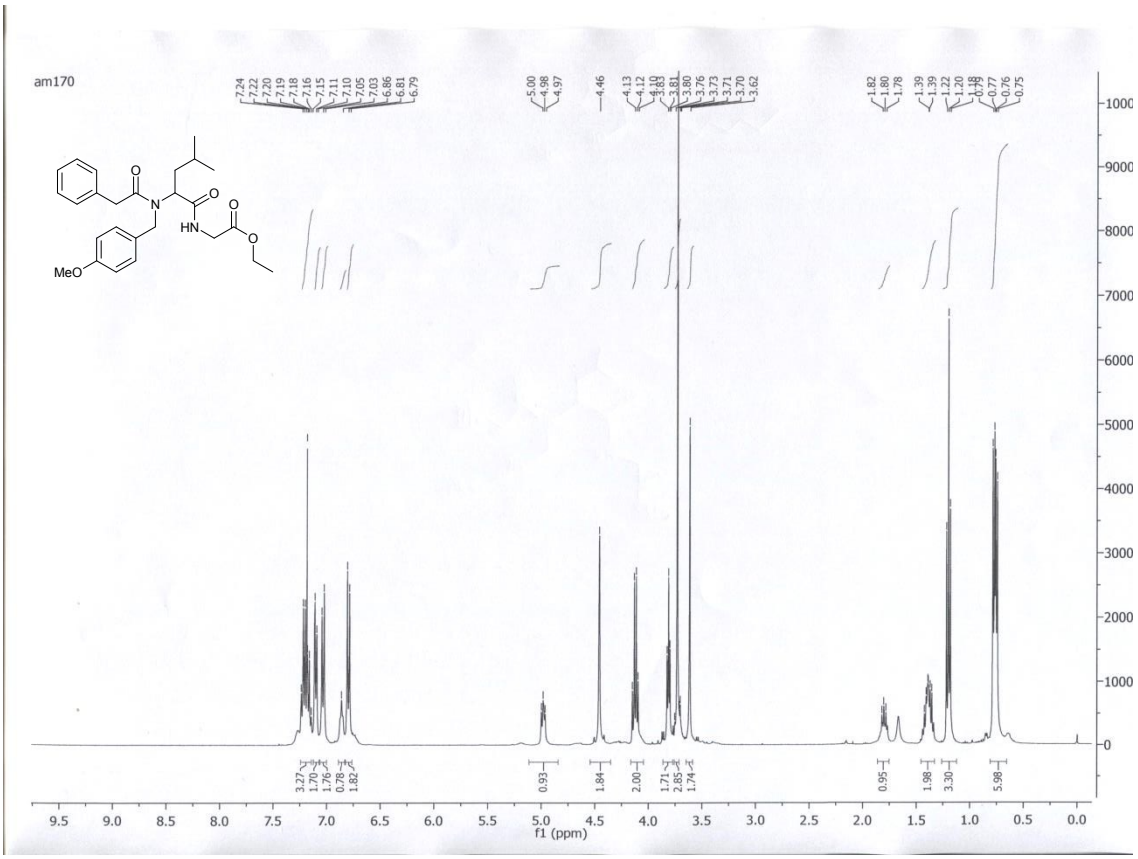


Figure 26 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5u** (400 MHz, $CDCl_3$).


am170
MeO
HN
f1 (ppm)

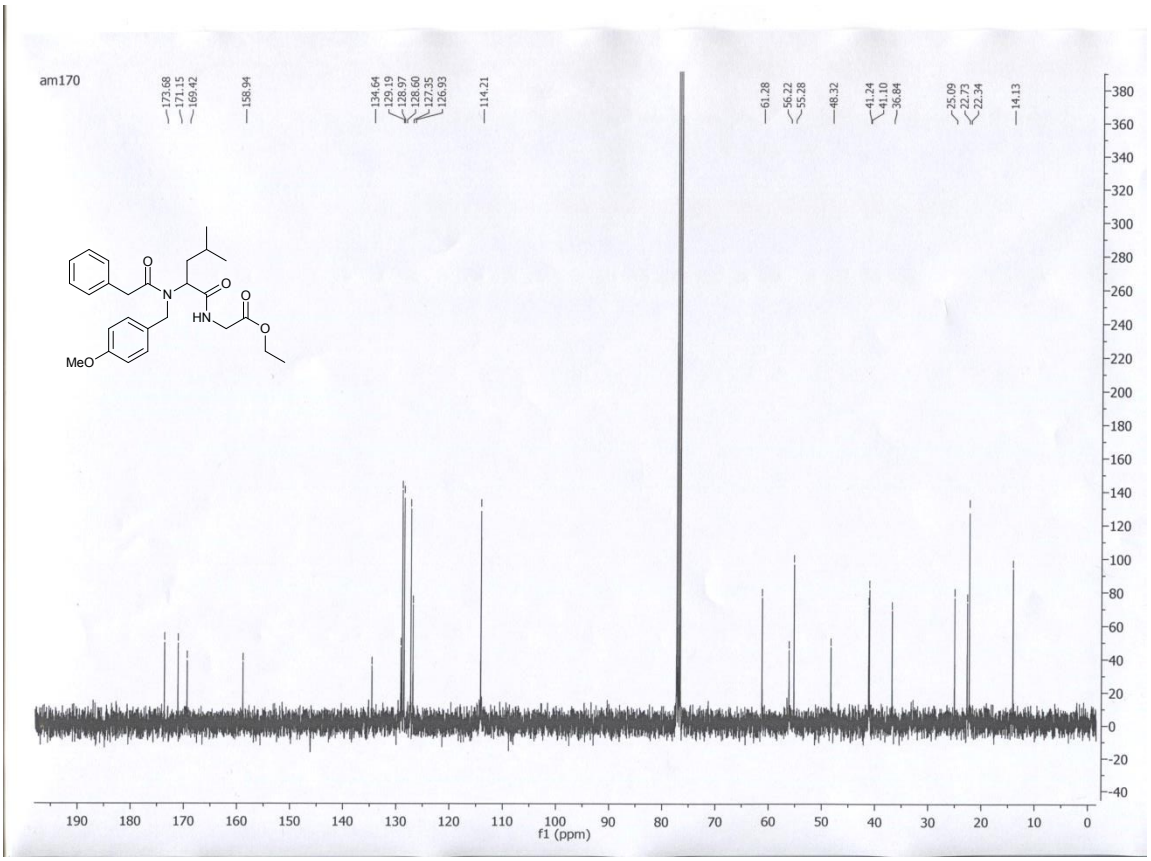


Figure 27 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5w** (400 MHz, $CDCl_3$).

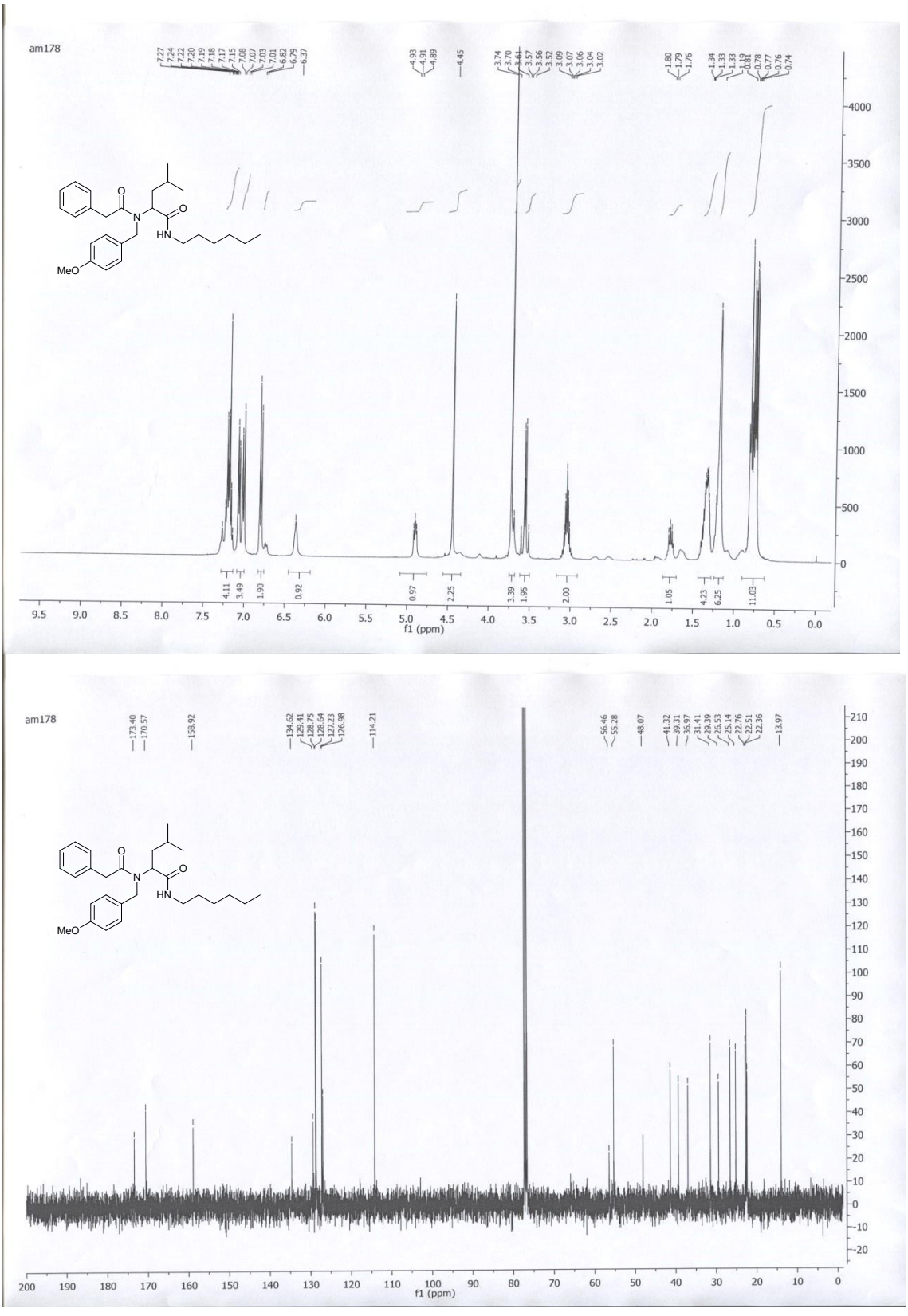


Figure 28 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5v** (400 MHz, $CDCl_3$).

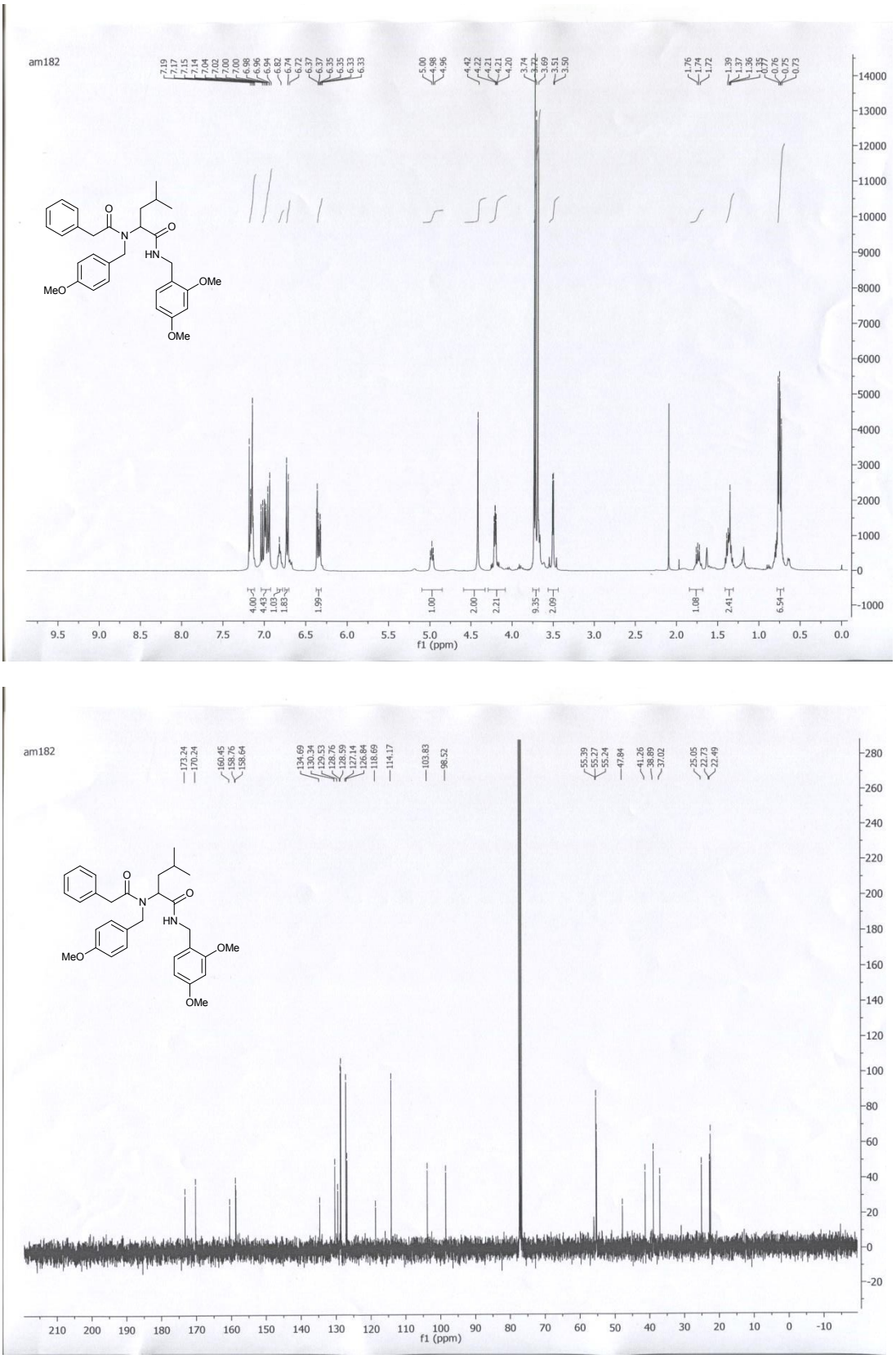


Figure 29 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5x** (400 MHz, $CDCl_3$).

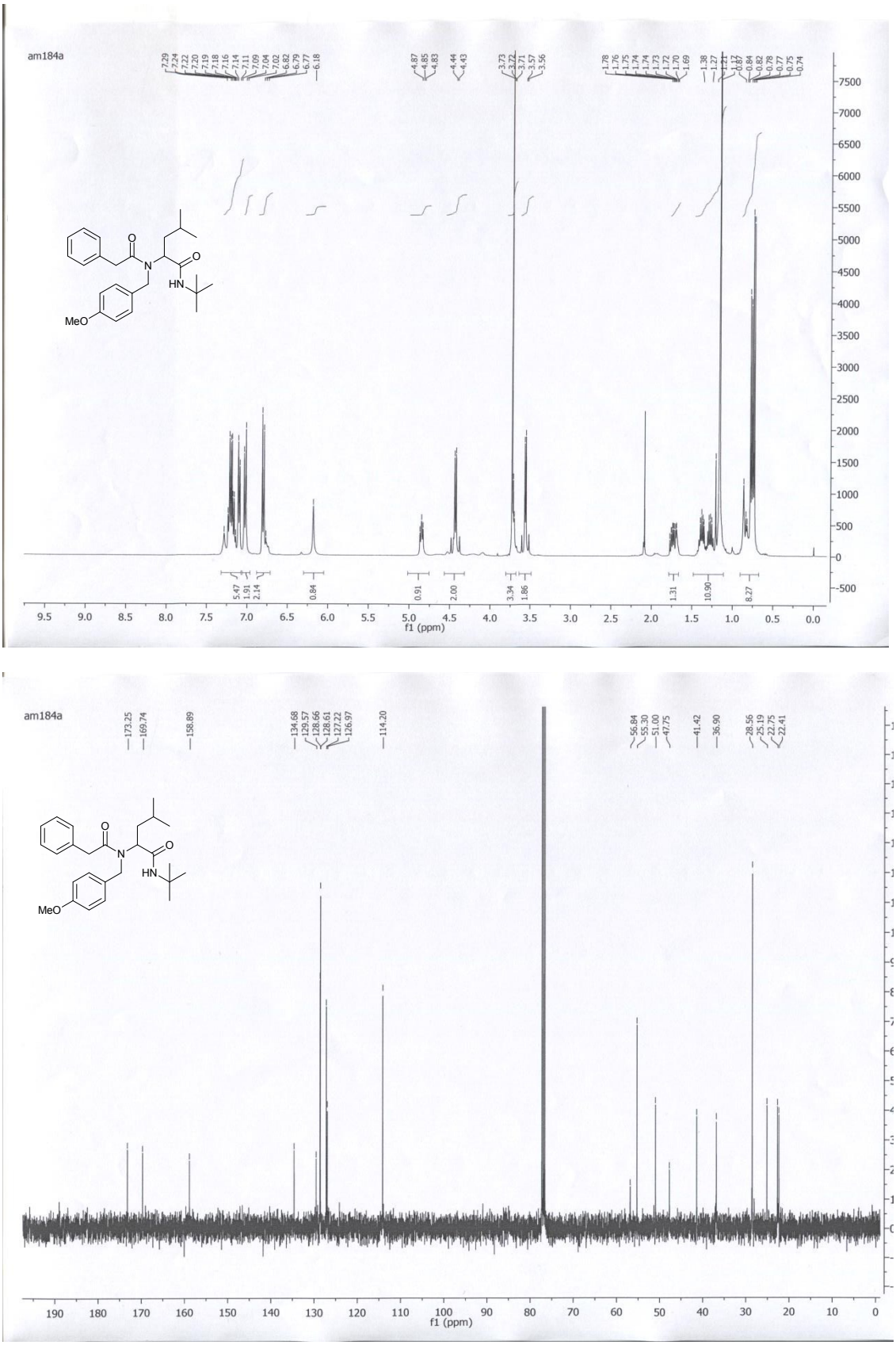
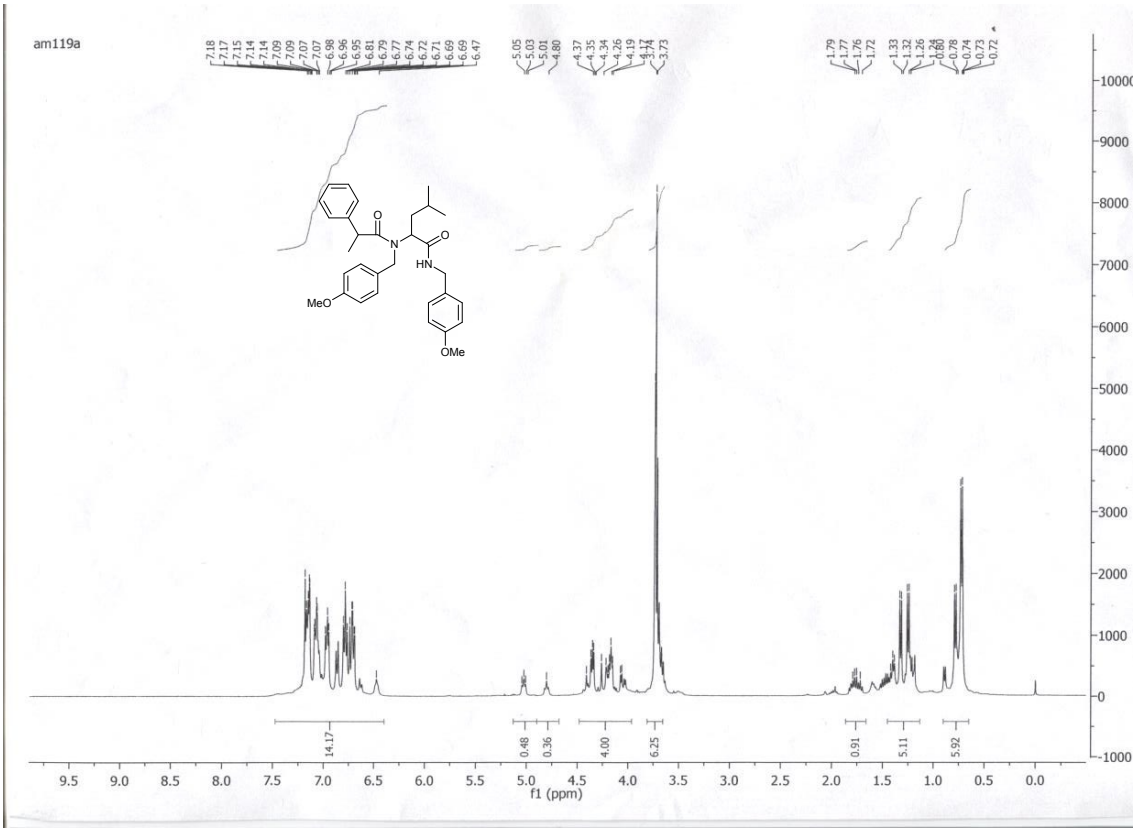


Figure 30 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5y** (400 MHz, $CDCl_3$).


am119a
7.18
7.17
7.15
7.14
7.14
7.09
7.09
7.07
7.07
6.98
6.96
6.95
6.81
6.79
6.77
6.74
6.72
6.71
6.69
6.69
6.47
5.05
5.03
5.01
4.80
4.37
4.35
4.34
4.26
4.19
3.74
3.73
1.79
1.77
1.76
1.72
1.33
1.32
1.26
1.24
0.80
0.78
0.74
0.73
0.72
MeO
OMe
HN
14.17
0.48
0.36
4.00
6.25
0.91
5.11
5.92
f1 (ppm)

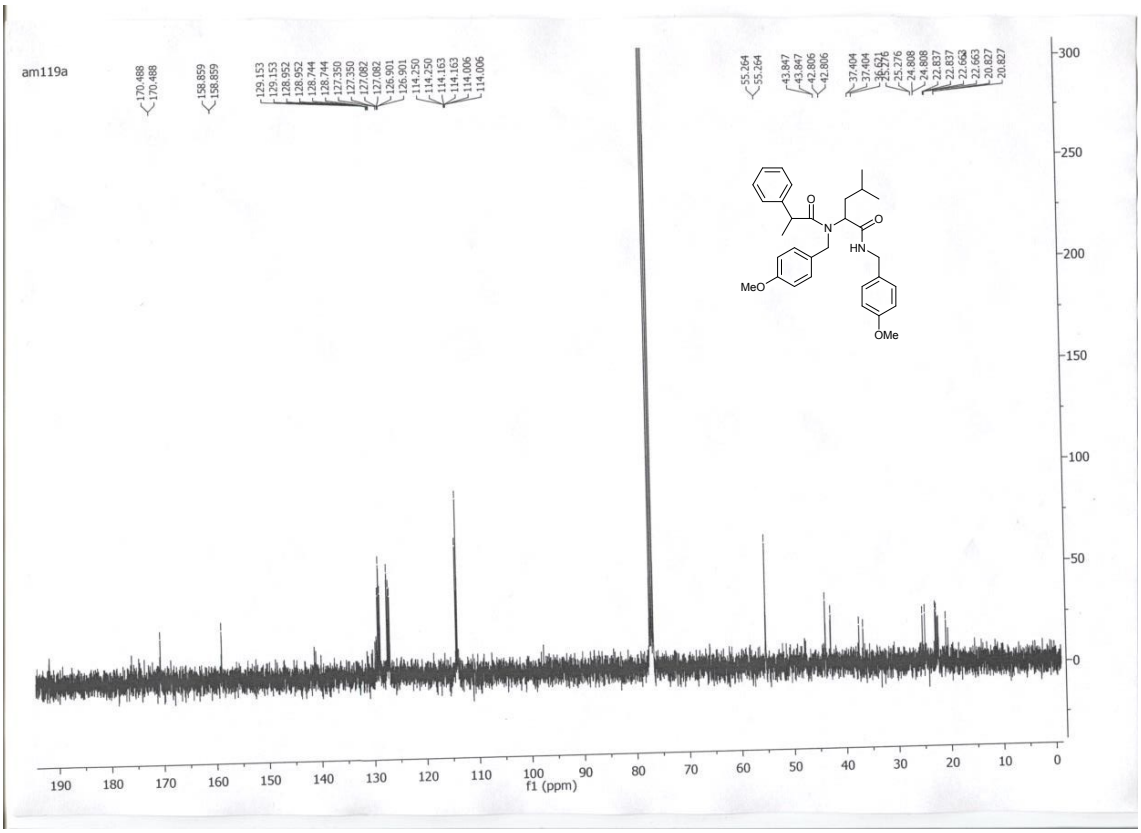

am119a
170.488
170.488
158.859
158.859
129.153
129.153
128.952
128.952
128.744
128.744
127.350
127.350
127.082
127.082
126.901
126.901
114.250
114.250
114.163
114.163
114.006
114.006
55.264
55.264
43.847
43.847
42.806
42.806
37.404
37.404
26.111
26.111
25.276
25.276
24.808
24.808
22.837
22.837
22.663
22.663
20.827
20.827
MeO
OMe
HN
f1 (ppm)

Figure 31 ^{1}H NMR (above) and ^{13}C NMR (below) spectra of compound **5z** (400 MHz, $CDCl_3$).