Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information for

The sustainable synthesis of peptidomimetics via chemoenzymatic tandem oxidation-Ugi reaction

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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).

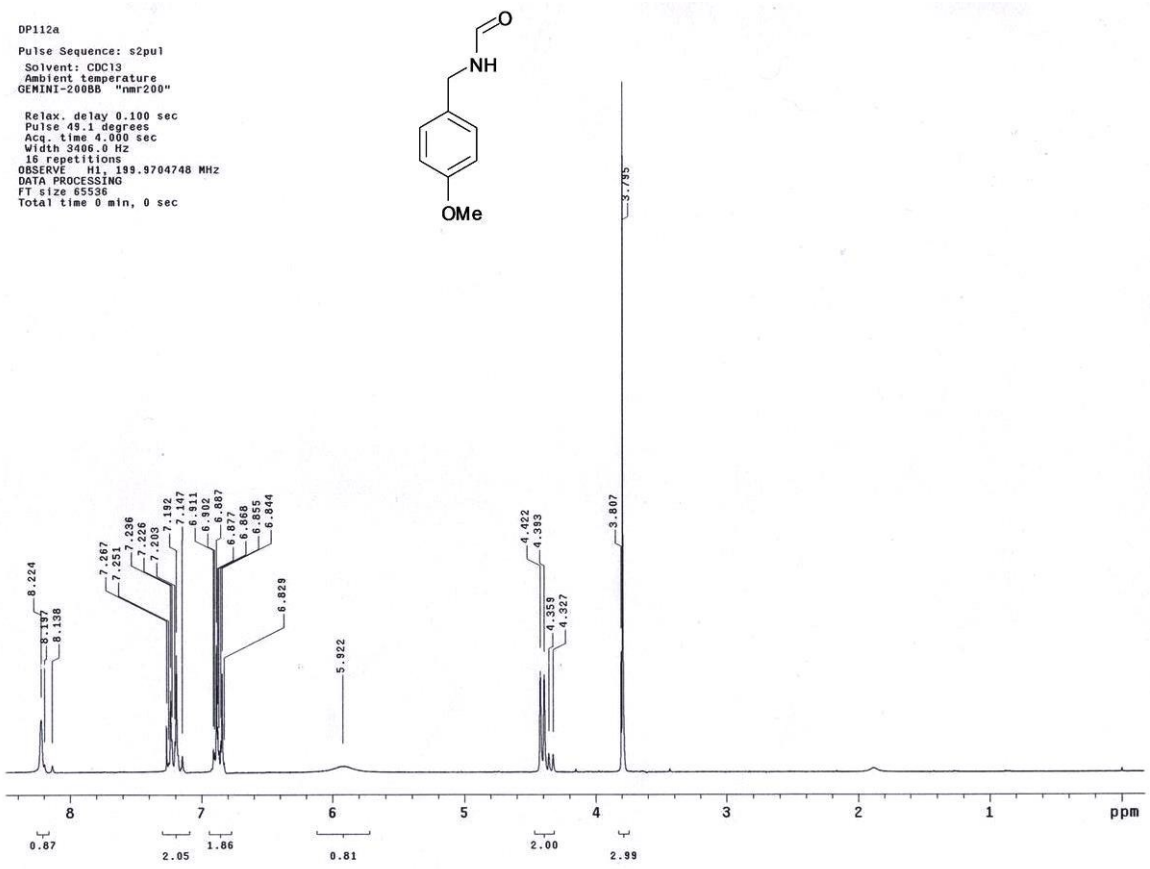

Figure 1[1]H NMR spectrum of *N*-(4-methoxybenzyl)formamide (200 MHz, $CDCl_3$).

Synthesis of *p*-methoxybenzylisocyanide (5a):

I Method:

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 (8.5:1.5 / v:v) as an eluent. Yield 80 % (1.88 g).

II Method (PTC condition):

Reaction conditions: To a mixture of sodium hydroxide (2.5 g), *t*-butyl ammonium bromide (0.19 g) in distilled water (2.5 mL) was added the solution of 4-methoxybenzylamine (6mmol, 750 µL) in chloroform (20 mL). After 18 h of stirring at room temperature, the reaction mixture was quenched by adding distilled water, then extracted with dichloromethane (3x20 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 (8.5:1.5 / v:v) as an eluent. Yield 66 % (582.4 mg).

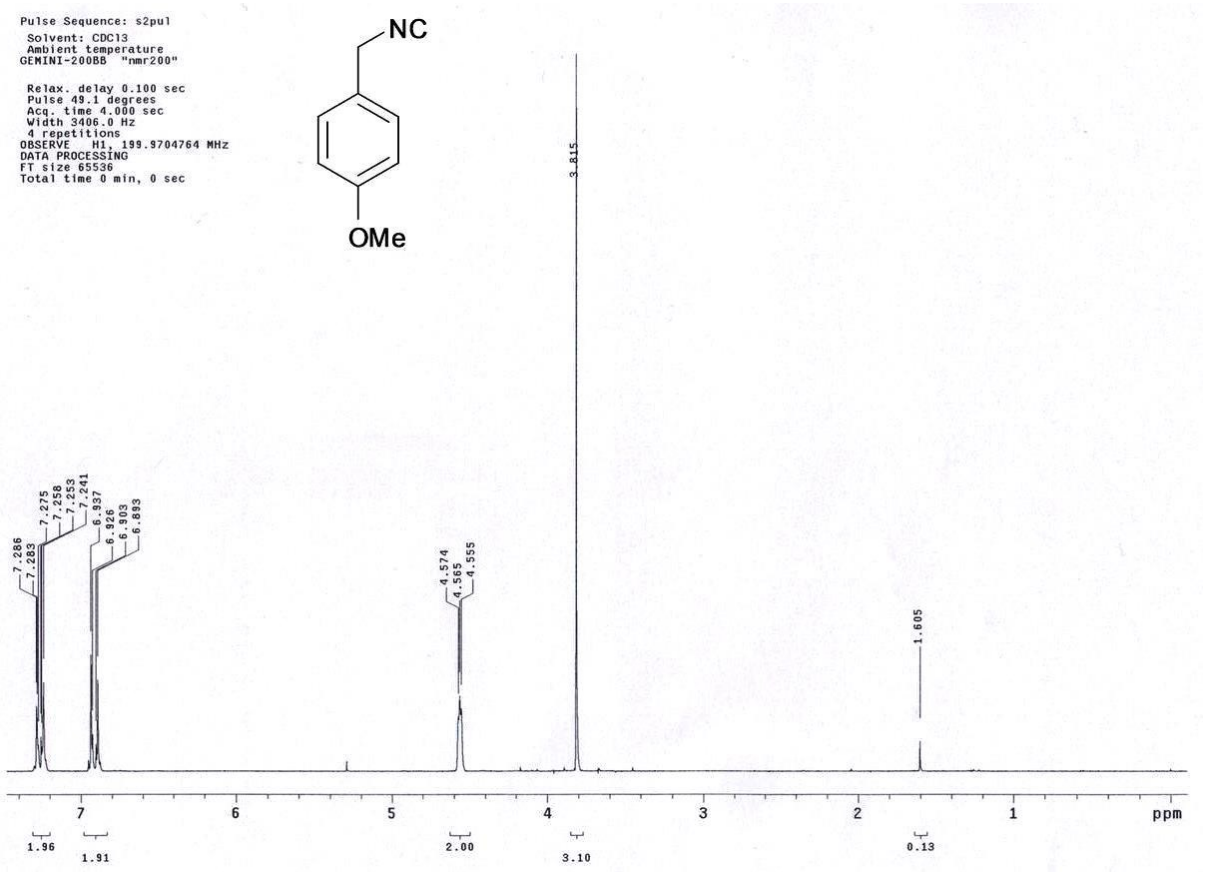

Figure 2. ^{1}H NMR spectrum of compound **4a** (200 MHz, $CDCl_3$).

Appearance of the aqueous Ugi multicomponent reaction samples containing SDS

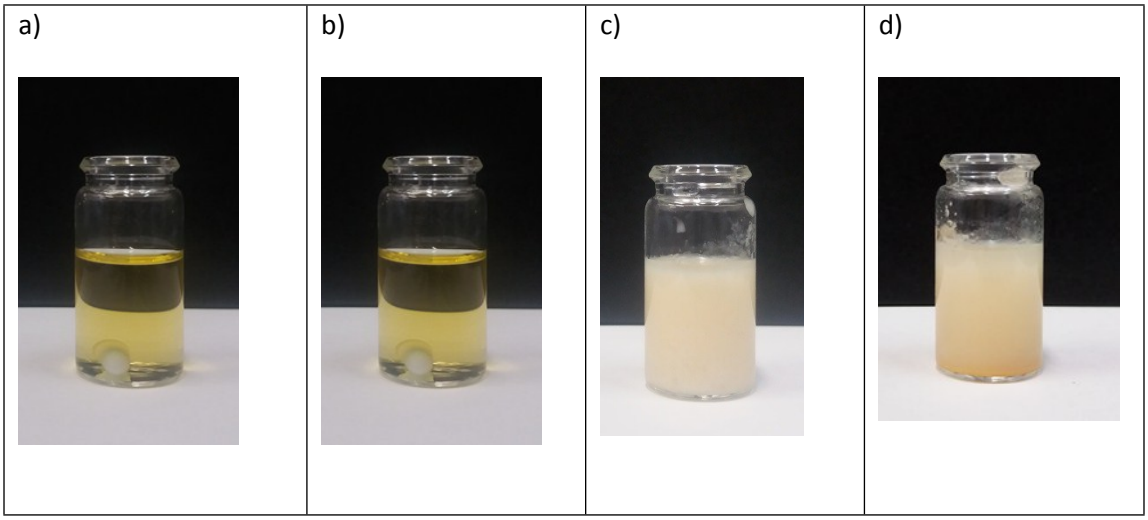

Figure 3. Photographic images of the Ugi multicomponent reaction samples (reaction with benzyl alcohol**1a** (0.5mmol), *p*-methoxybenzylamine**3a** (0.5 mmol) and *p*-methoxybenzylisocyanide**5a** (0.5 mmol)) in phosphate buffer 5.2 pH (5 mL), with the addition of SDS, TEMPO and LTv in 25 °C. The reaction was carried out in an open vessel.

a) suspension of SDS, TEMPO and LTv in phosphate buffer 5.2 pH after 10 minutes of stirring with a magnetic stirrer.

b) Reaction mixture in suspension of SDS, TEMPO, LTv after addition of **1a**

c) Reaction mixture in suspension of SDS, TEMPO, LTv and **1a** 10 minutes after addition of **3a**next day.

d) Reaction mixture in suspension of SDS, TEMPO, LTv and **1a** 10 minutes after addition of **3a**, **4a** and **5a** next day.

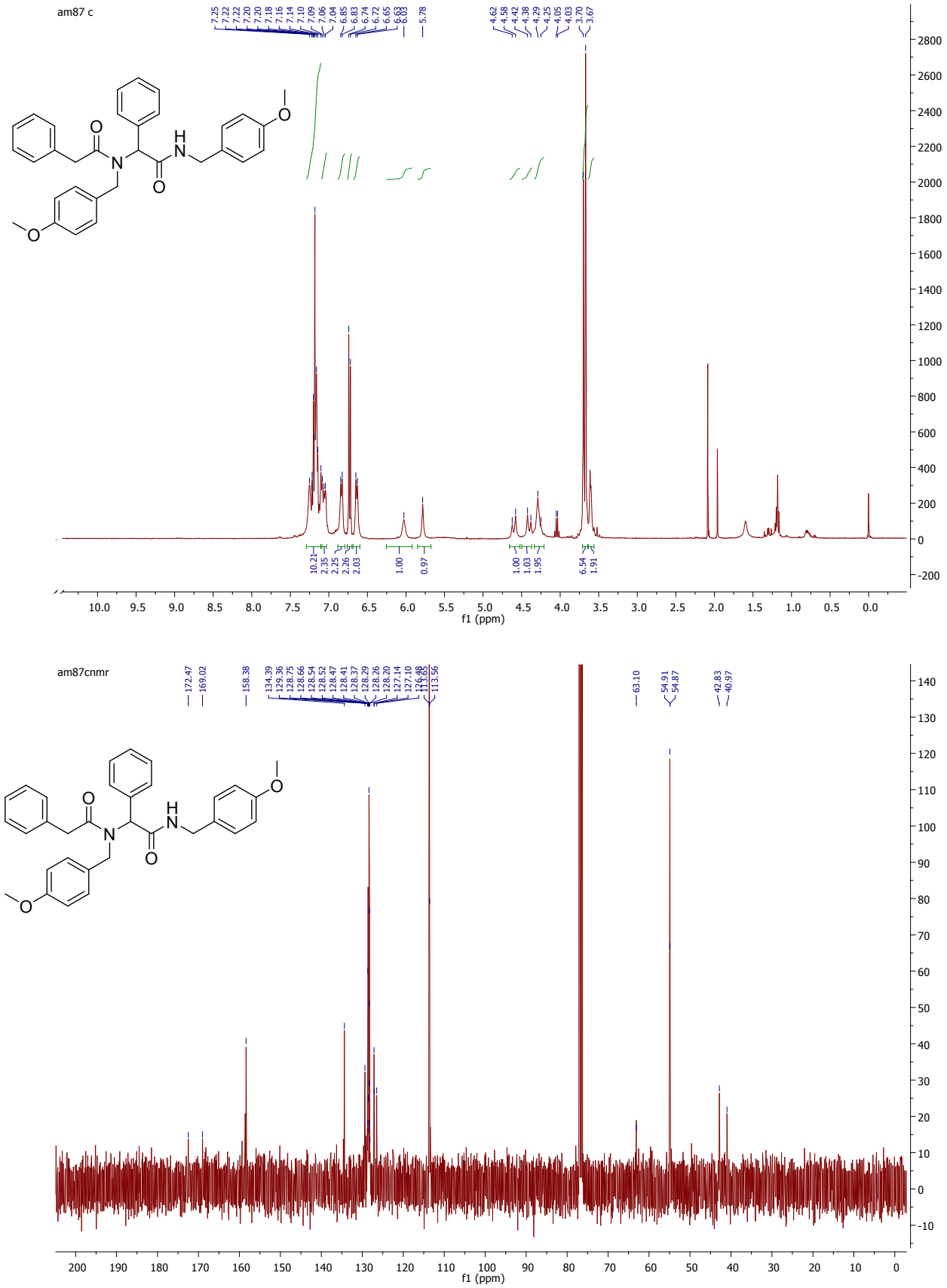

Figure 4. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6a** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

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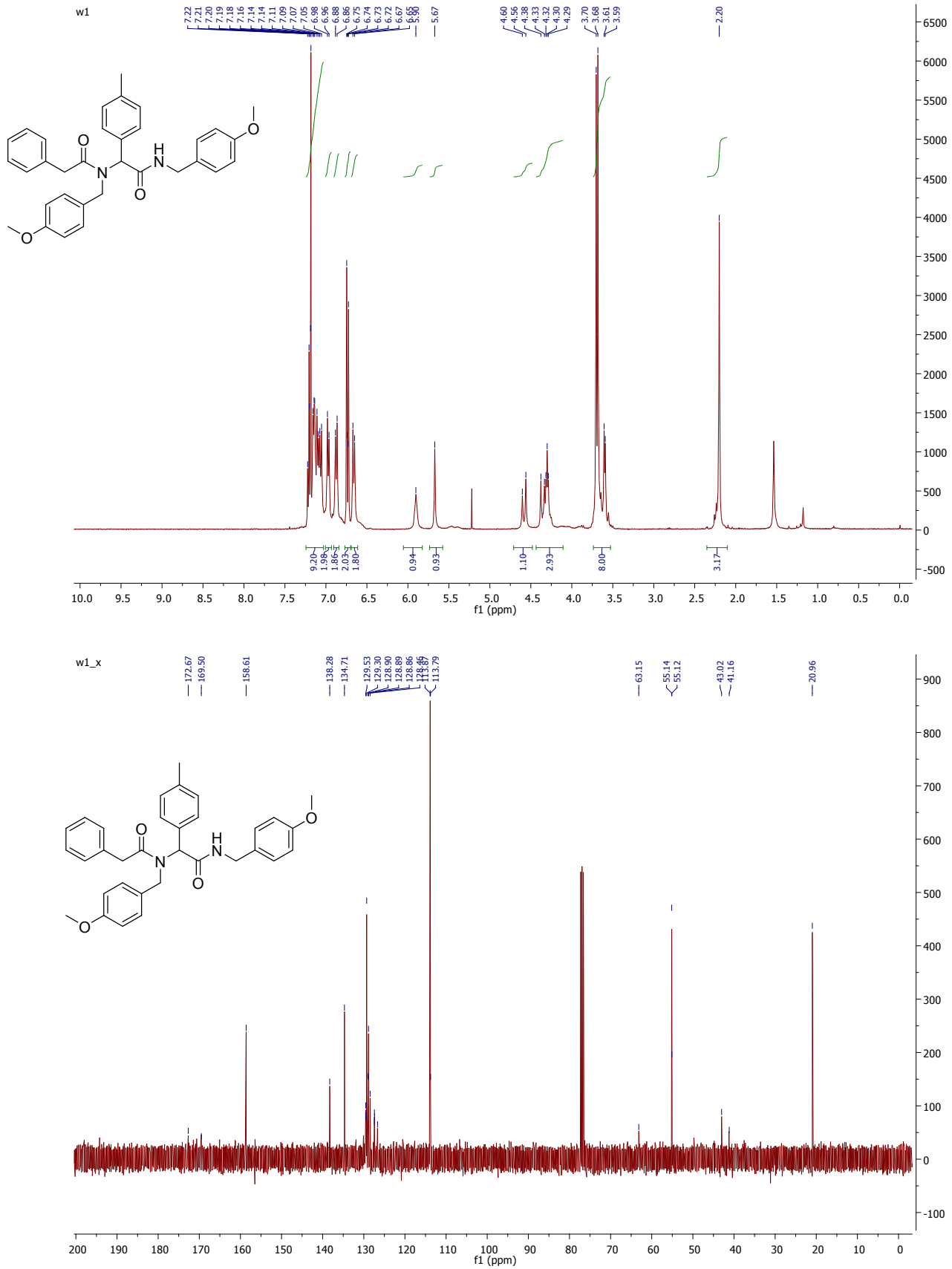


Figure 5. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6b** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl(2-phenylacetylo)amino]-2-[4-methylphenyl)acetamide (400 MHz, $CDCl_3$).

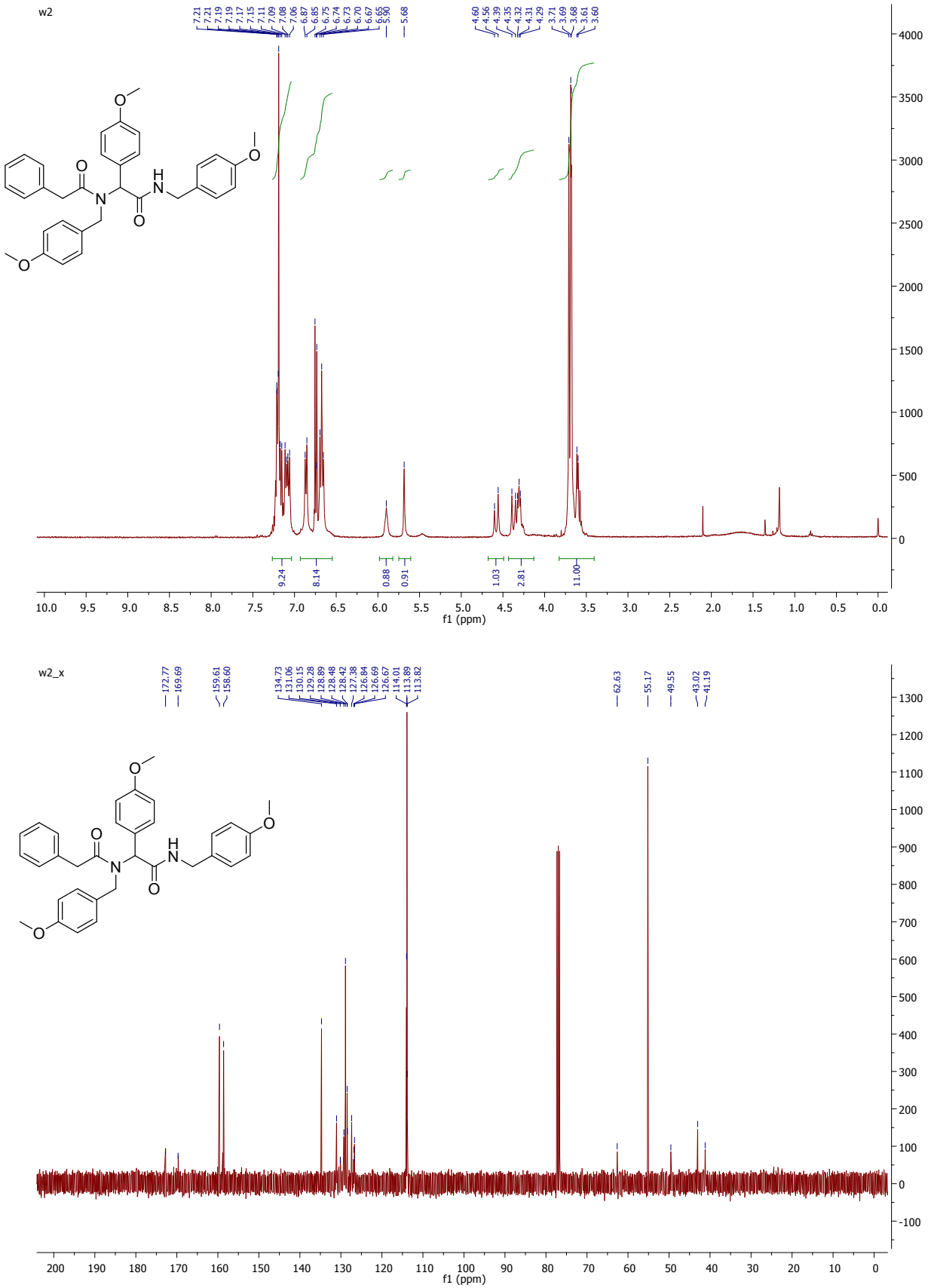


Figure 6. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6c** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-[4-methoxyphenyl)acetamide (400 MHz, $CDCl_3$).

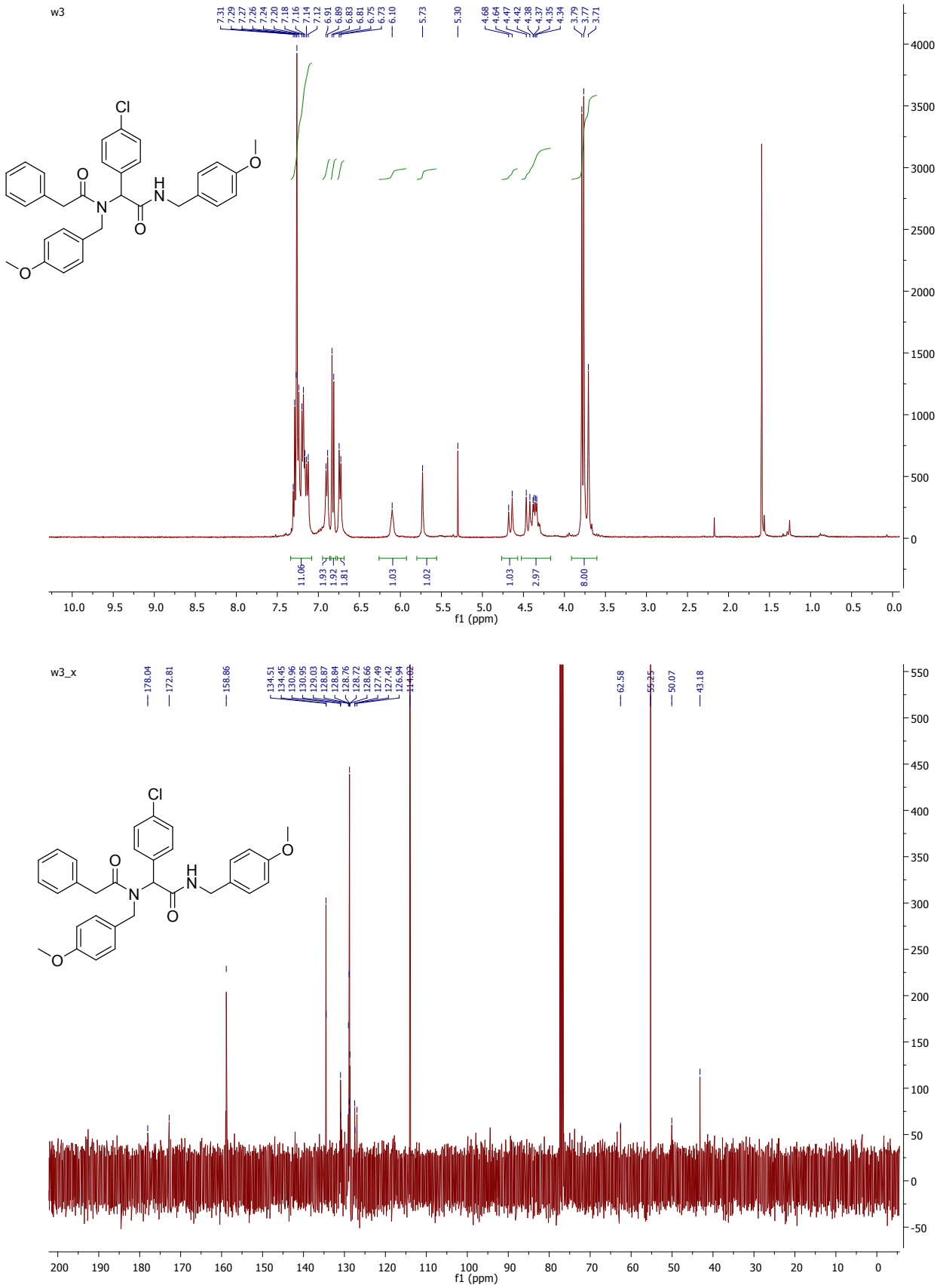


Figure 7. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6d** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-[4-chlorophenyl)acetamide(400 MHz, $CDCl_3$).

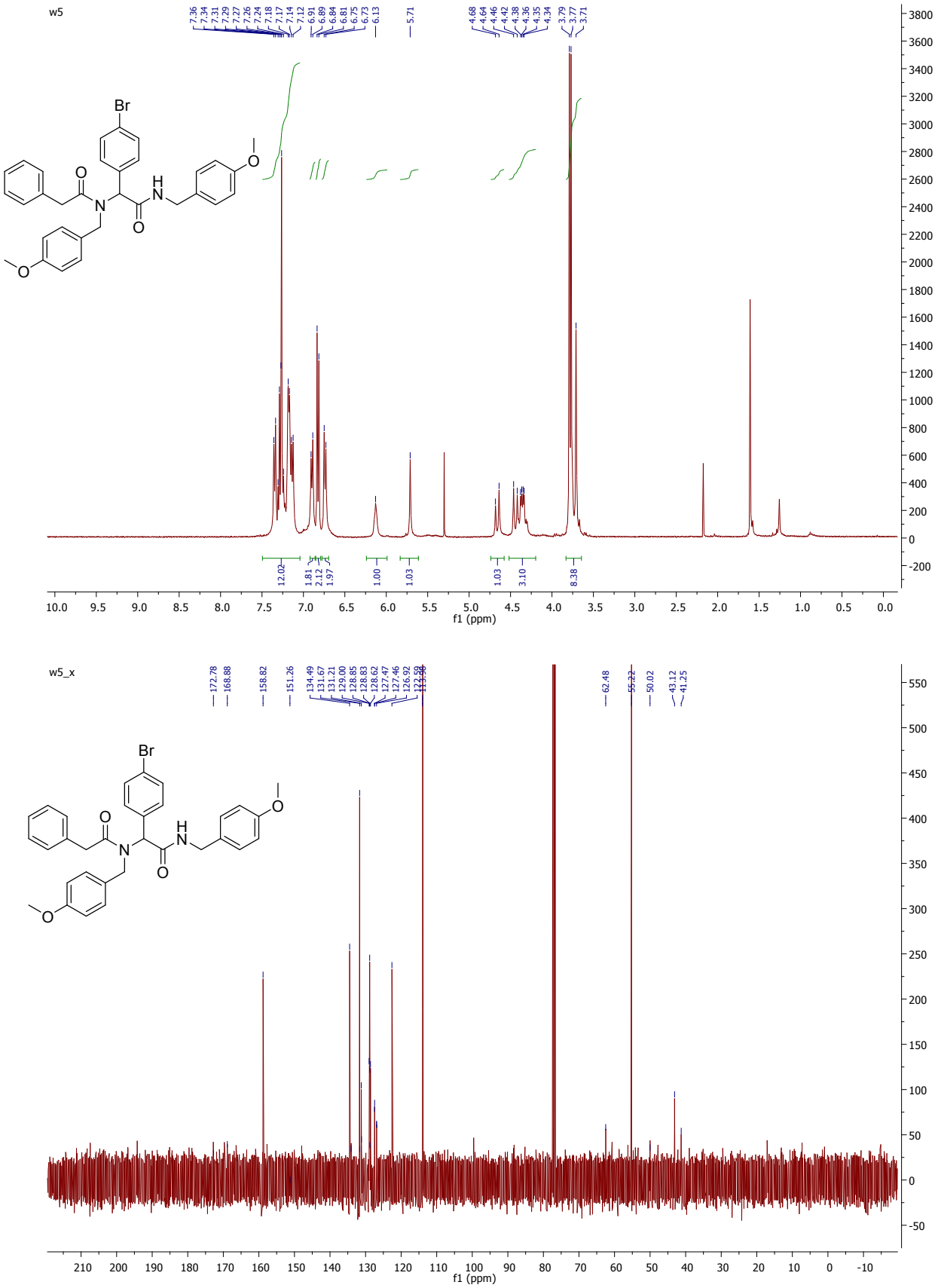


Figure 8. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6e** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-[4-bromophenyl)acetamide (400 MHz, $CDCl_3$).

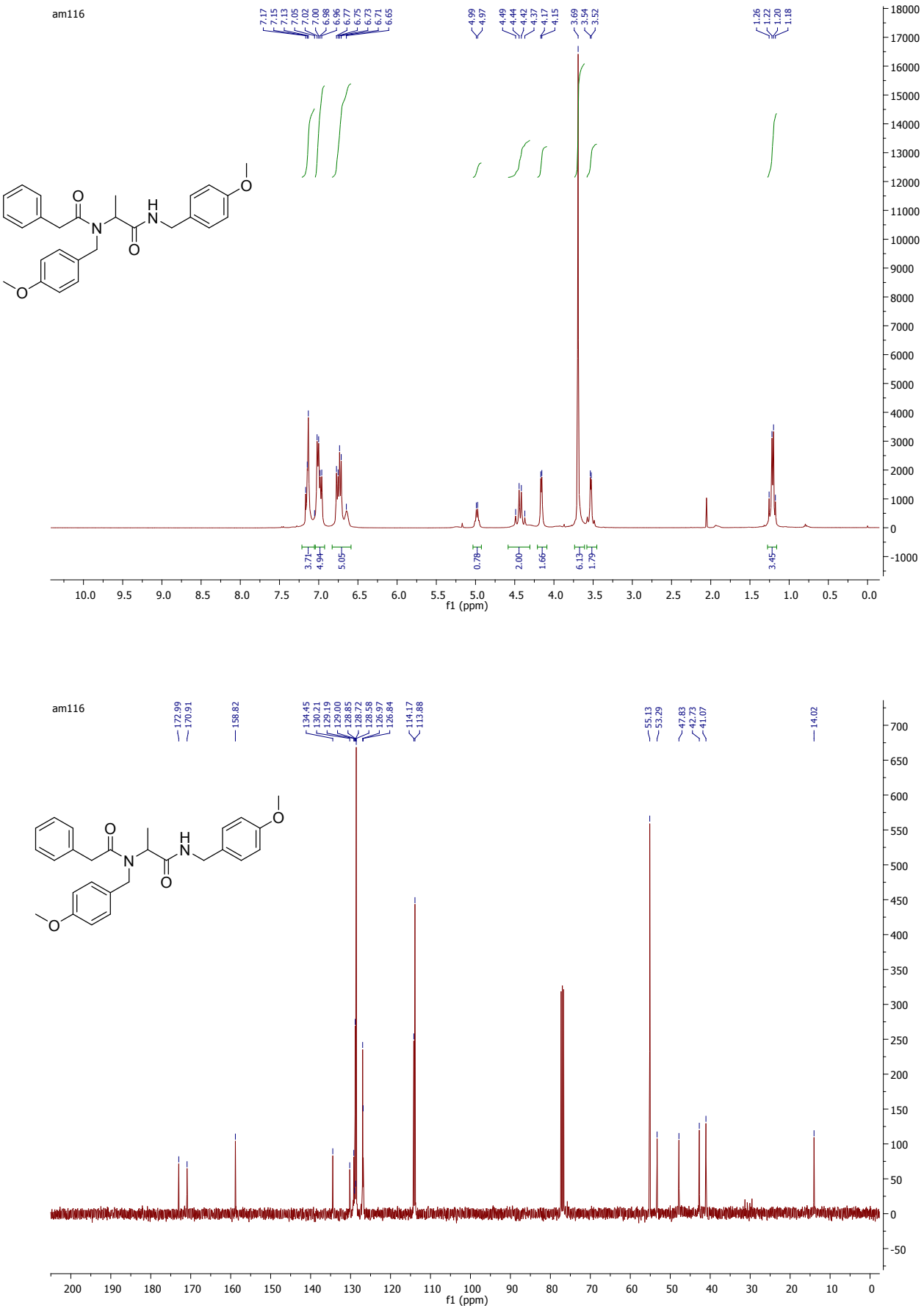


Figure 9. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6g** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-propionamide (400 MHz, $CDCl_3$).

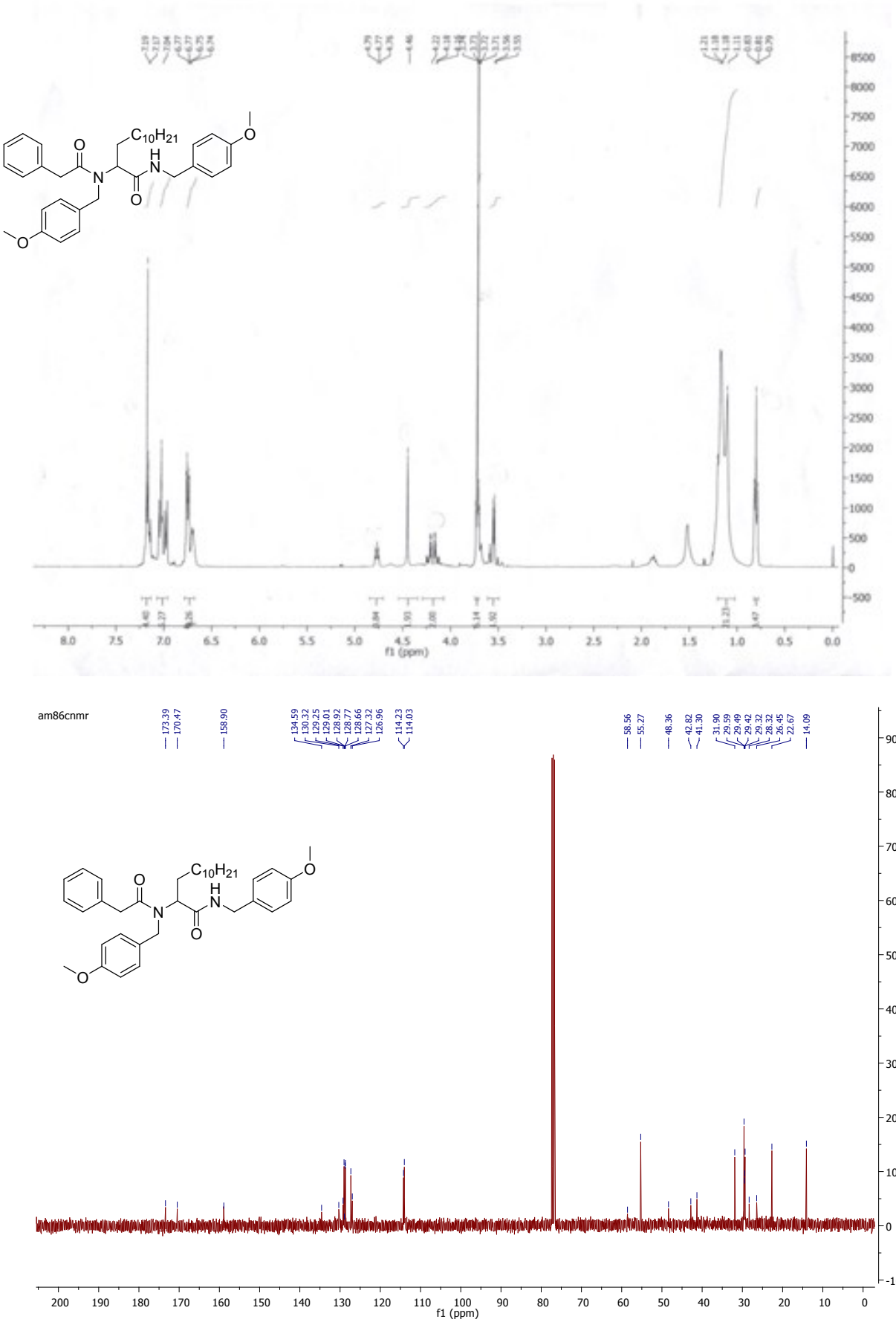


Figure 10. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6i** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-dodecanamide (400 MHz, $CDCl_3$).

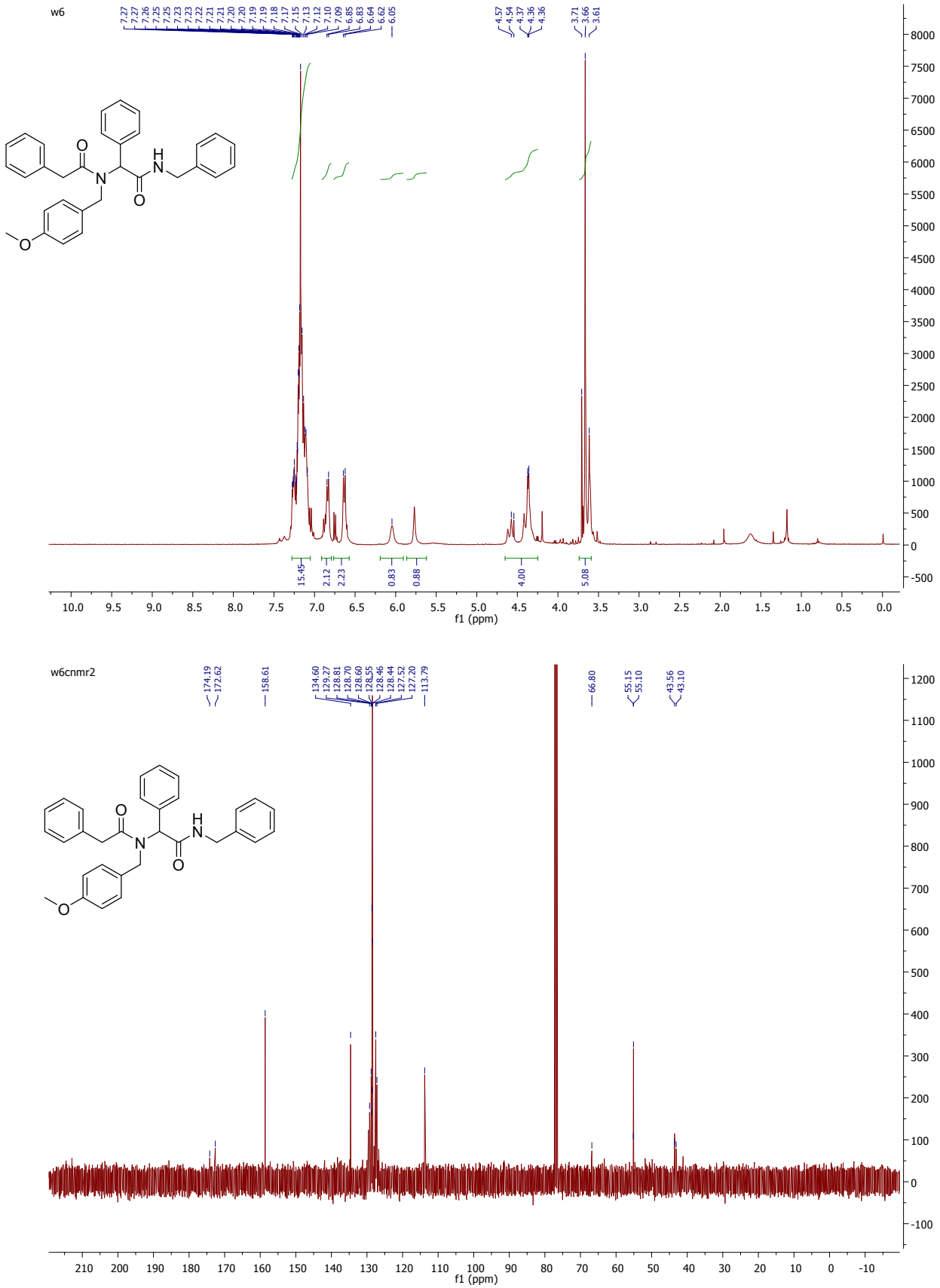


Figure 11. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6j** N-benzyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

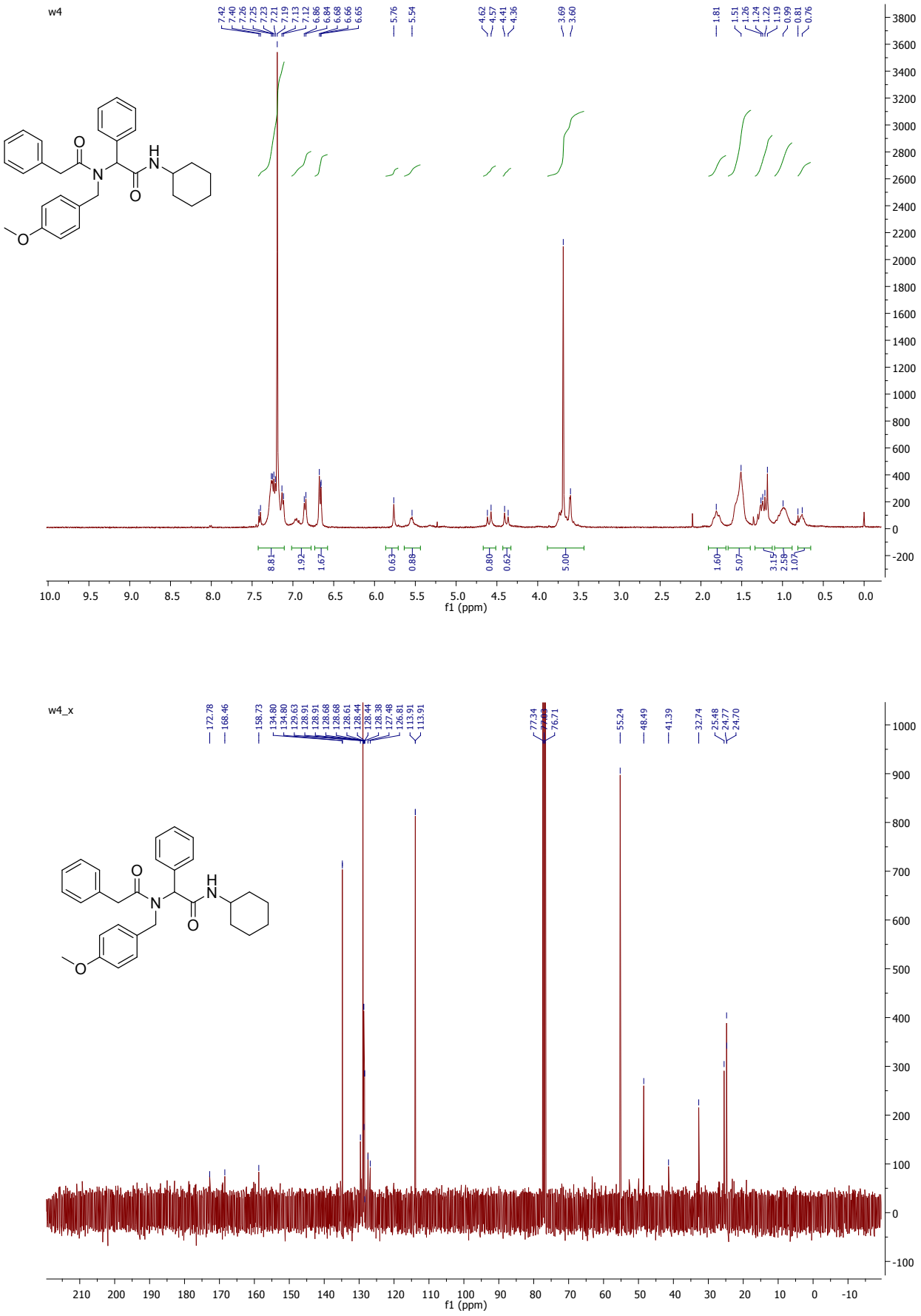


Figure 12. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6k** N-cyclohexyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

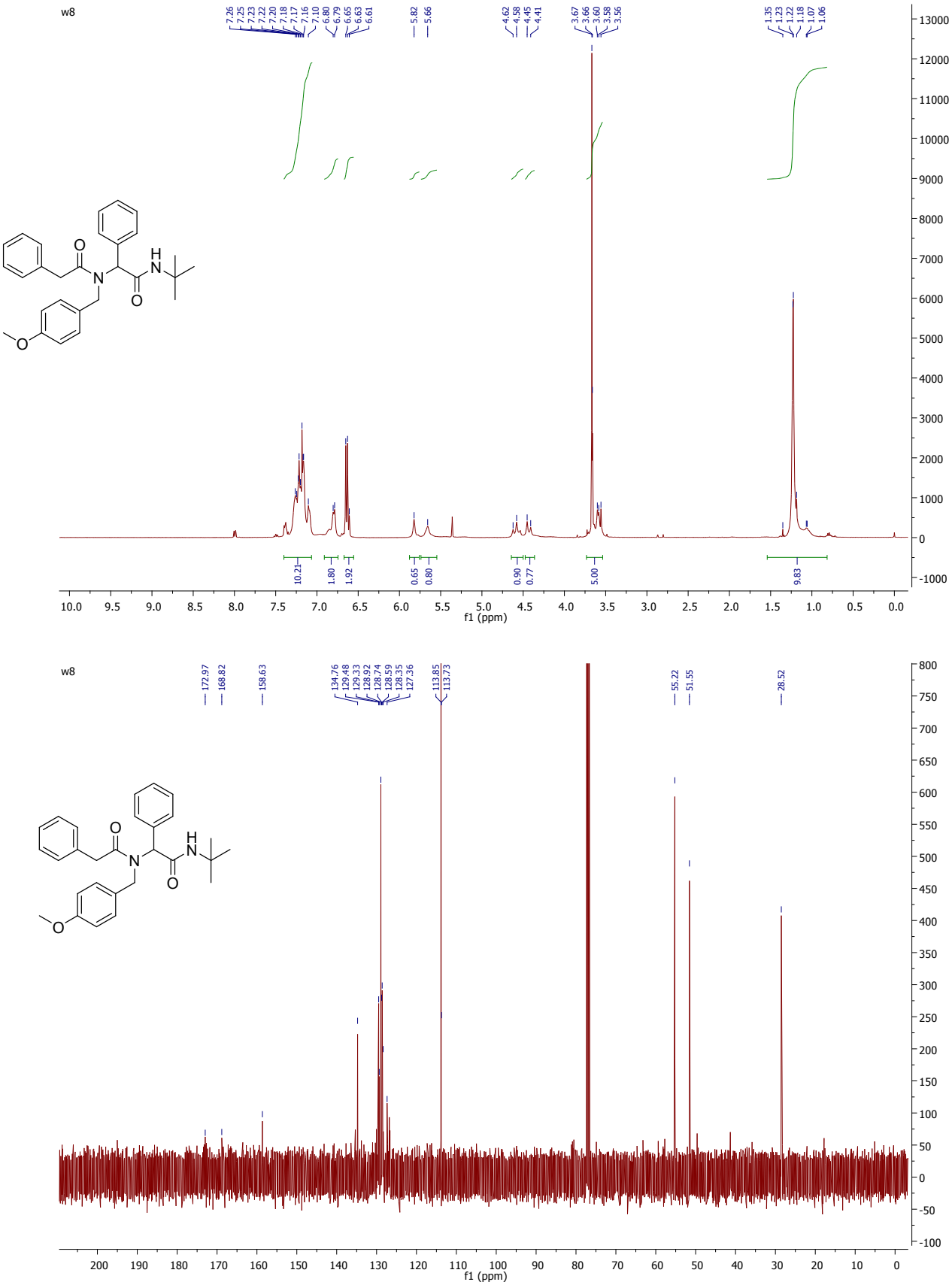


Figure 13. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6l** N-*t*-butyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

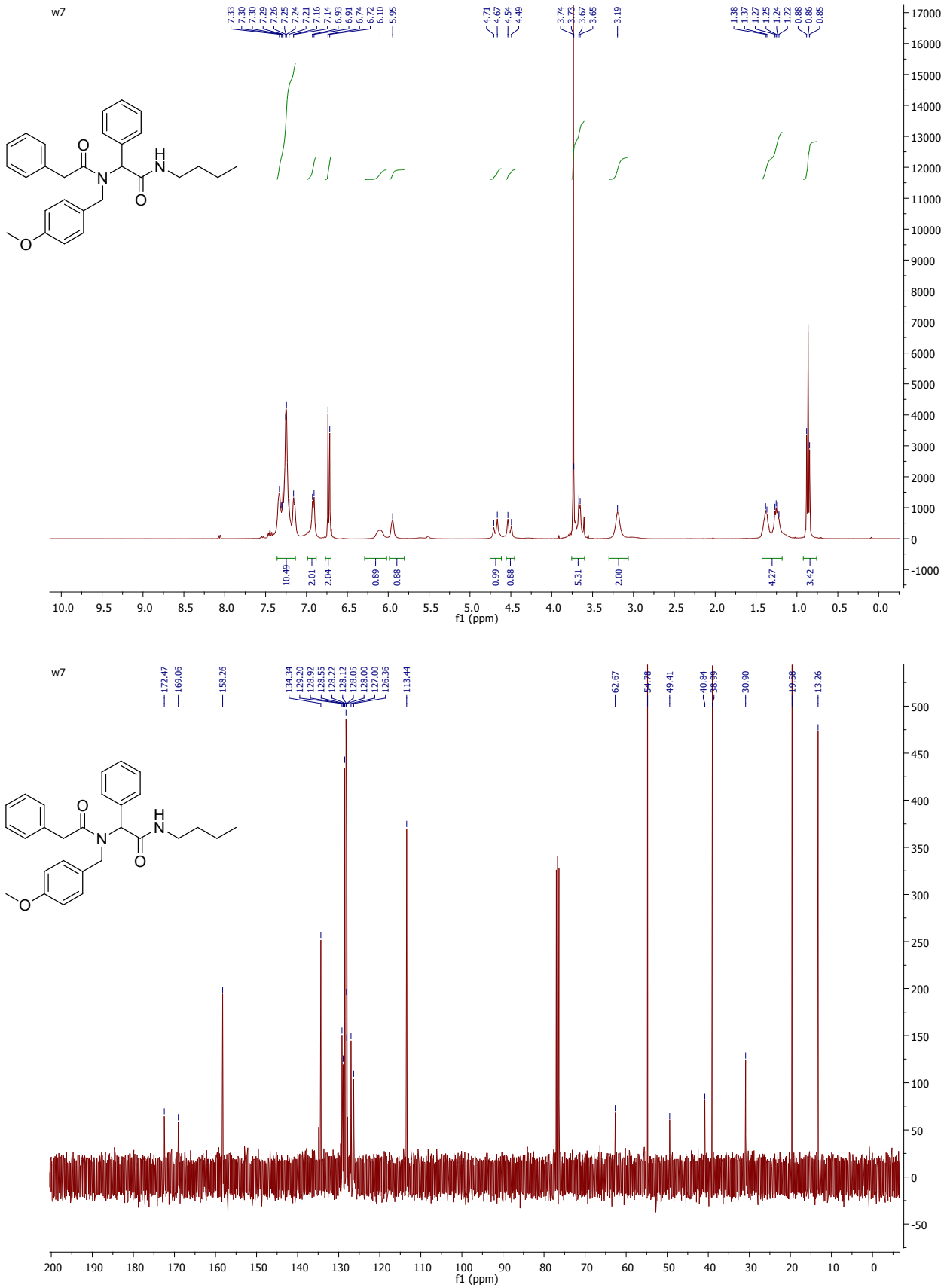


Figure 14. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6m** N-*n*-butyl-2-[(4-methoxyphenyl)methyl-(2-phenylacetylo)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

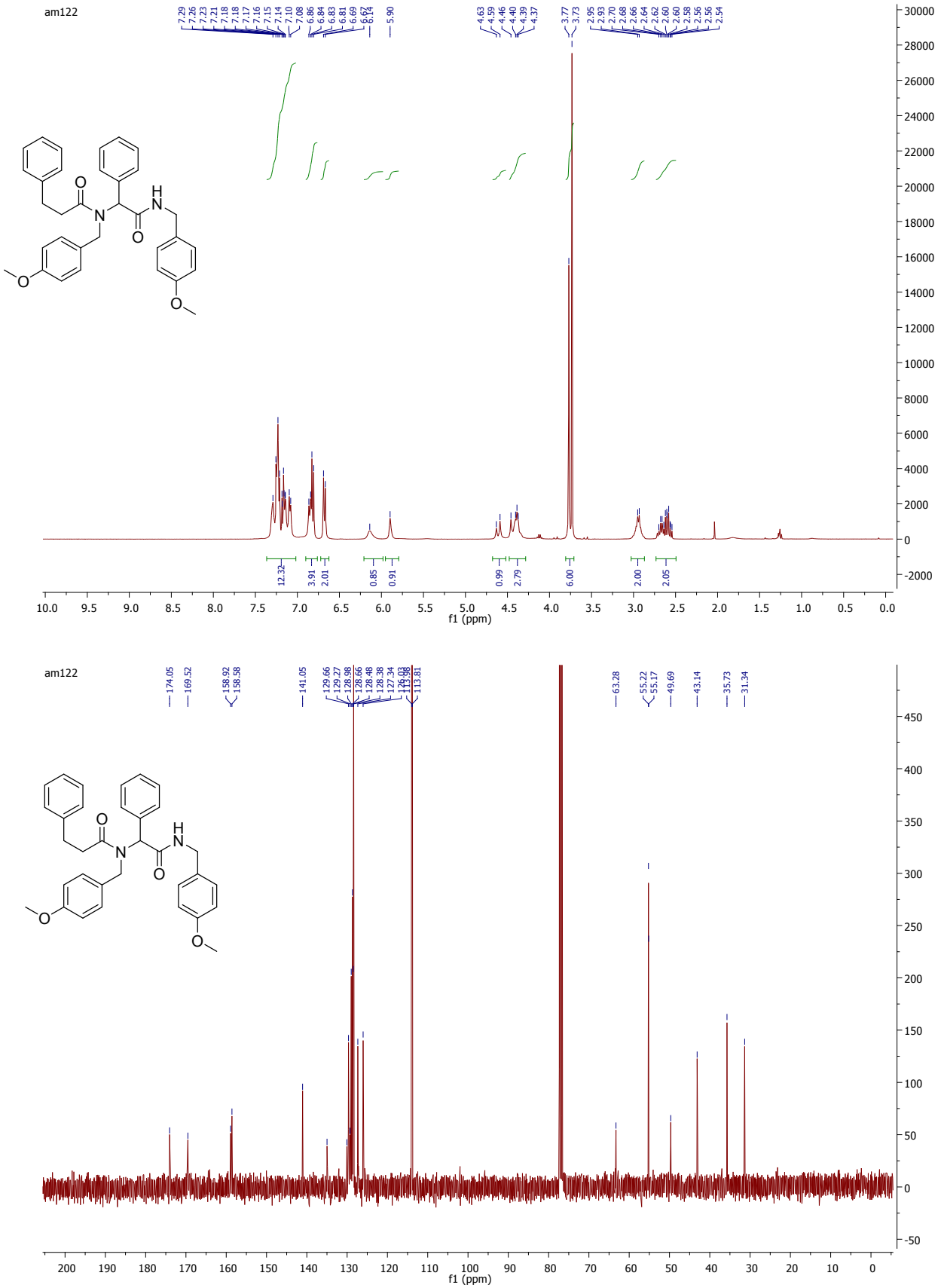
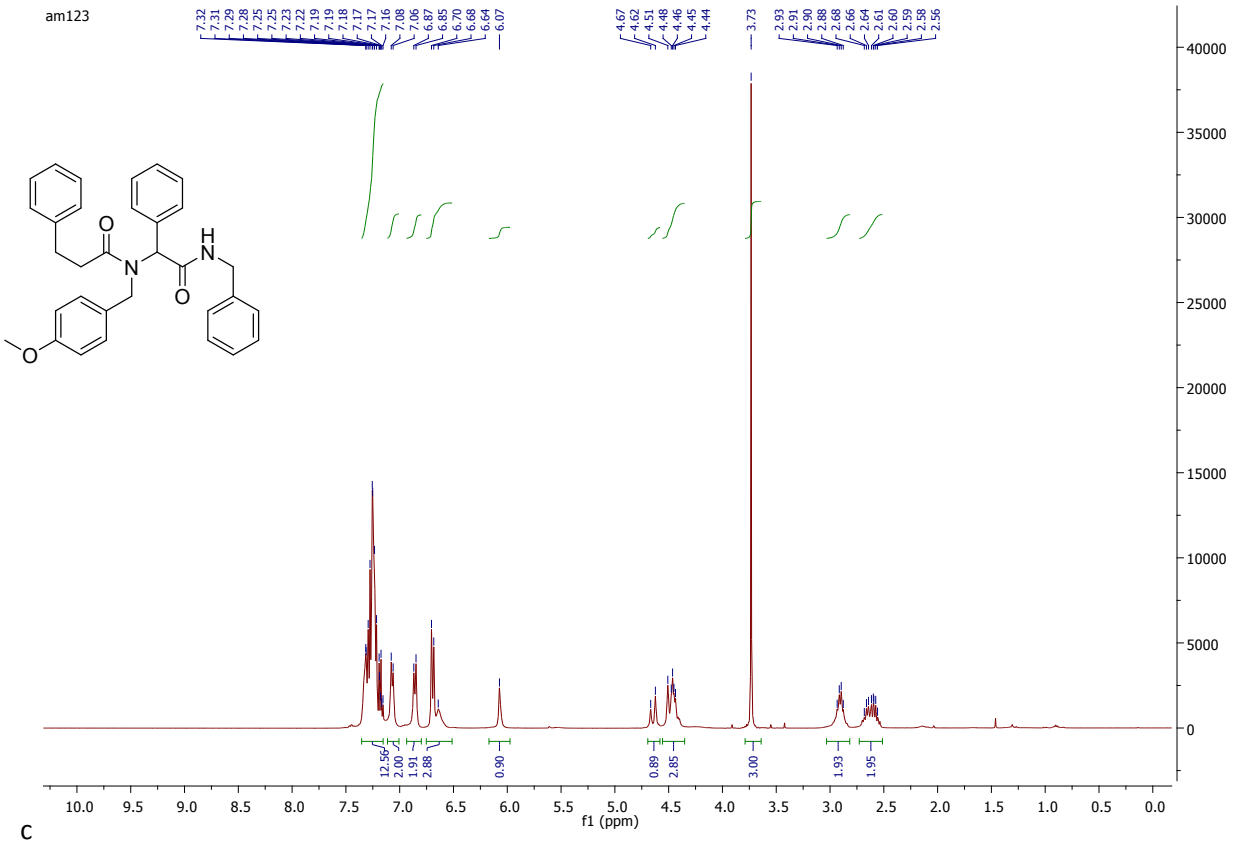


Figure 15. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6n** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-3-(phenylpropionyl)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).



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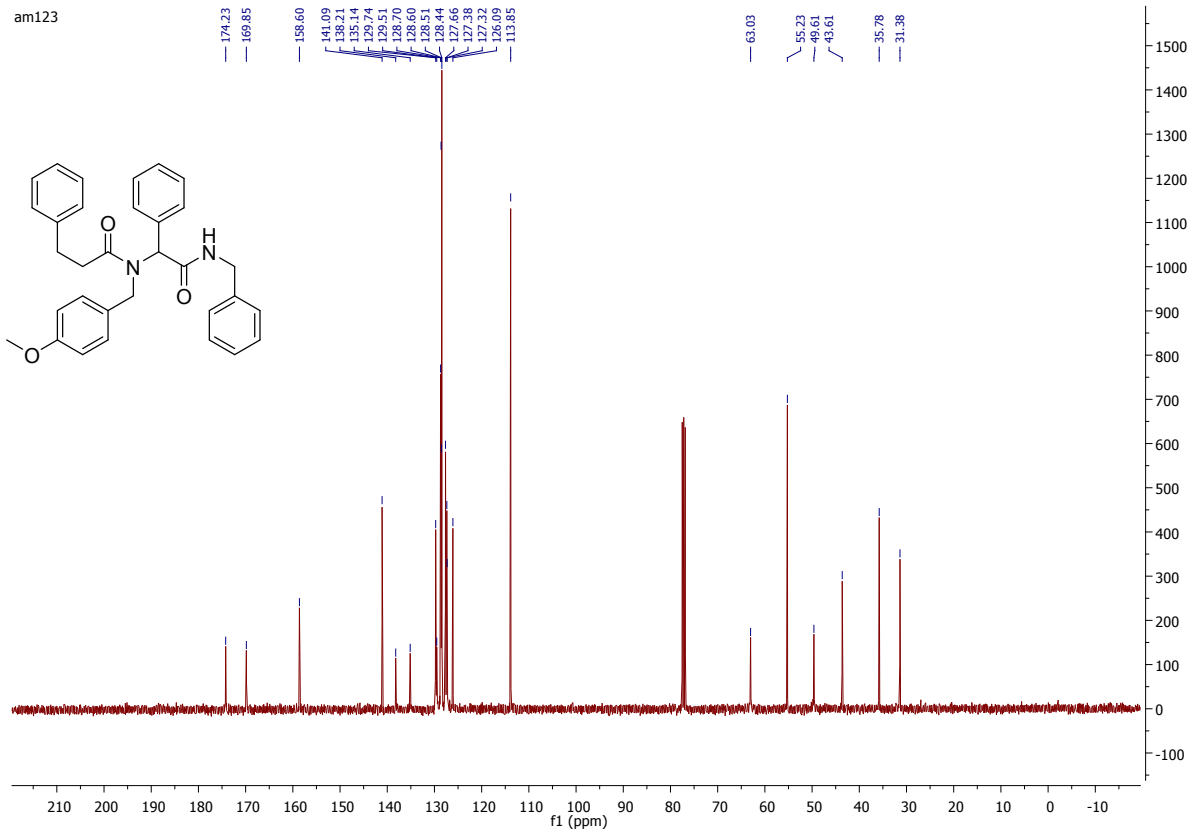

Figure 16. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6o** N-benzyl-2-[(4-methoxyphenyl)methyl-4-(phenylprobutyryl)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

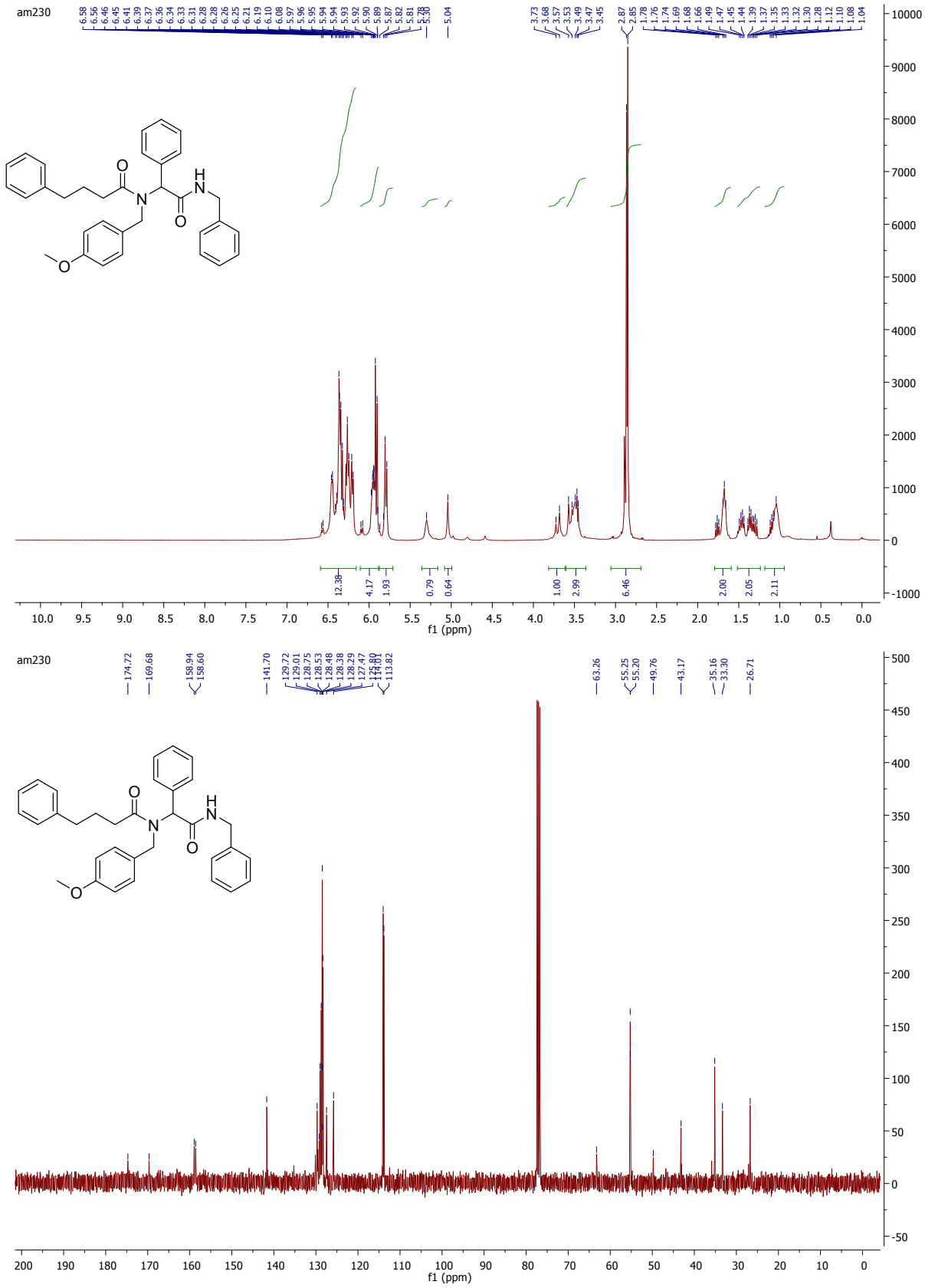

Figure 17. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6p** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-4-(phenylbutyryl)amino]-2-phenylacetamide (400 MHz, $CDCl_3$).

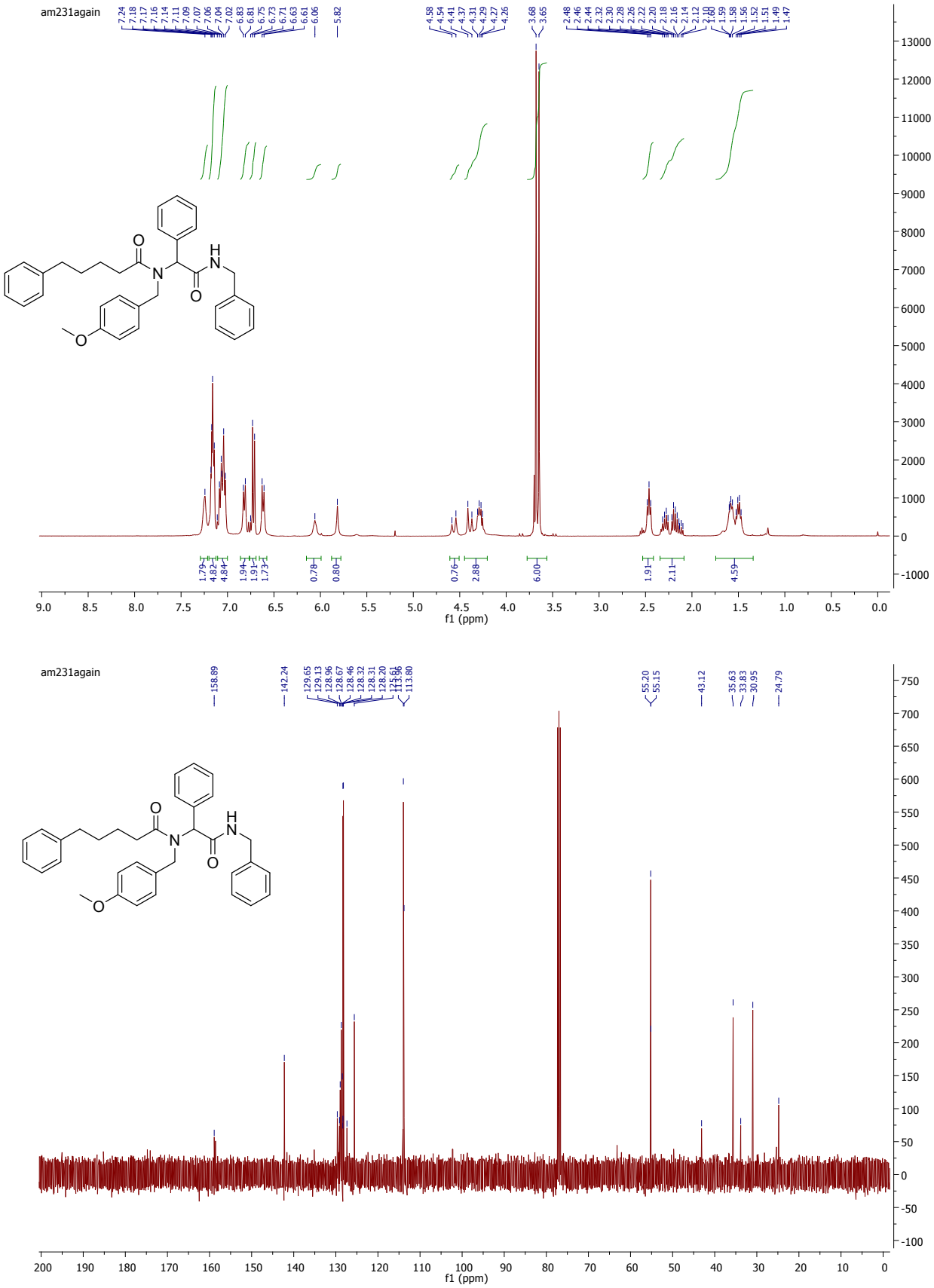

Figure 18. ^{1}HNMR (above) and ^{13}CNMR (below) spectra of compounds **6r** N-[(4-methoxyphenyl)metyl]-2-[(4-methoxyphenyl)methyl-4-(phenylpentyl)amino]-2-phenylacetamide (400 MHz, $CDCl_3$.