

Supplementary Information for
Development of a triazinedione-based dehydrative condensing
reagent containing 4-(dimethylamino)pyridine as an acyl transfer
catalyst

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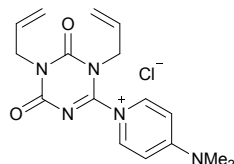
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1. General information

Nuclear magnetic resonance [^1H NMR (400 MHz), ^{13}C NMR (100 MHz)] spectra were recorded in CDCl_3 on a JEOL JNM-ECS400 spectrometer. Chemical shifts for ^1H NMR are reported as δ values relative to tetramethylsilane as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of a triplet at 77.16 ppm for CDCl_3 . Reactions under microwave irradiation were performed with a Biotage Initiator. Mass spectra were measured on JMS-T100TD (DART-TOF or ESI-TOF). Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Flash chromatography separations were performed using silica gel (KANTO CHEMICAL Silica Gel 60 N, spherical, neutral, 40–100 mesh) or amine-functionalized silica gel (Chromatorex NH-DM2035, Fuji Silysia Chemical). Amino acid derivative **6e** was purchased from Watanabe chemical industries and used without further purification. Other reagents were commercial grades and were used without any purification unless otherwise noted. All reactions sensitive to oxygen or moisture were conducted under a N_2 atmosphere. Known compounds (**4**¹ and **11**²) were prepared according to the reported procedure.

2. Experimental procedure and characterization data

Synthesis of ATD-DMAP



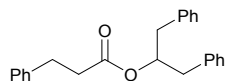
A solution of **4** (1.132 g, 4.97 mmol) and $\text{PdCl}_2(\text{PhCN})_2$ (9.2 mg, 0.024 mmol) in THF (10.0 mL) was heated at reflux for 4 h and then cooled to room temperature. A solution of DMAP (446.3 mg, 3.65 mmol) in THF (10.0 mL) was added. After 2 h, the precipitate was separated from the supernatant and washed with THF to afford a pale yellow solid (1.155 g, 93%). ^1H NMR: δ 8.85–8.78 (m, 2H), 7.29–7.21 (m, 2H), 5.97–5.79 (m, 2H), 5.42 (d, $J = 16.9$ Hz, 1H), 5.28 (d, $J = 10.1$ Hz, 1H), 5.23 (d, $J = 10.6$ Hz, 1H), 5.14 (d, $J = 16.9$ Hz, 1H), 4.73 (d, $J = 5.5$ Hz, 2H), 4.54 (d, $J = 6.0$ Hz, 2H), 3.46 (s, 6H); ^{13}C NMR: δ 157.5, 154.9, 152.9, 149.9, 140.3, 130.5, 130.1, 119.6, 118.7, 108.2, 49.9, 45.3, 41.5; HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_5\text{O}_2^+$ ($[\text{M} - \text{Cl}]^+$): 314.1617; found: 314.1631.

General procedure for esterification using ATD-DMAP (GP-1)

A solution of ATD-DMAP (1.2 equiv.) in CH_2Cl_2 (1.50 mL) was added to a mixture of a carboxylic acid (0.4 mmol, 1 equiv.), an alcohol (1.2 equiv.), and NMM (1.2 equiv.) in CH_2Cl_2 (0.50 mL) at room temperature. After 10 min, the reaction mixture was quenched by addition of *N,N*-dimethylethylenediamine (1 equiv.). After 5 min, the reaction mixture was diluted with CHCl_3 (30 mL) and washed with aqueous HCl (1 M, 30 mL), saturated aqueous NaHCO_3 (20 mL), and brine (70 mL). The organic layer was dried (MgSO_4) and filtered. The filtrate was

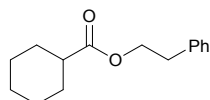
concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired ester.

1,3-Diphenylpropan-2-yl 3-phenylpropanoate (**8ab**)³



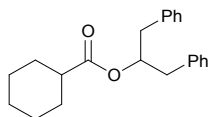
GP-1 was followed using **6a** (60.2 mg, 0.40 mmol) and **7b** (98 μ L, 0.49 mmol). Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (123.4 mg, 89%).

2-Phenethyl cyclohexanecarboxylate (**8ba**)³



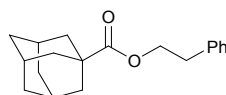
GP-1 was followed using **6b** (51.4 mg, 0.40 mmol) and **7a** (58 μ L, 0.48 mmol). Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (87.8 mg, 94%).

1,3-Diphenylpropan-2-yl cyclohexanecarboxylate (**8bb**)³



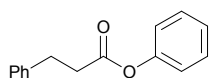
GP-1 was followed using **6b** (51.5 mg, 0.40 mmol), **7b** (98 μ L, 0.49 mmol), and *i*-Pr₂EtN (84 μ L, 0.48 mmol) instead of NMM. Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (120.8 mg, 93%).

2-Phenethyl adamantane-1-carboxylate (**8ca**)³



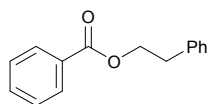
A mixture of **6c** (72.7 mg, 0.40 mmol), **7a** (58 μ L, 0.48 mmol), NMM (54 μ L, 0.49 mmol), and ATD-DMAP (169.7 mg, 0.49 mmol) in CH₂Cl₂ (2.00 mL) was heated under microwave irradiation conditions (130 $^{\circ}$ C, 20 min), and then cooled to room temperature. *N,N*-dimethylethylenediamine (43 μ L, 0.40 mmol) was added. The reaction mixture was diluted with CHCl₃ (30 mL) and washed with aqueous HCl (1 M, 30 mL), saturated aqueous NaHCO₃ (20 mL), and brine (70 mL). The organic layer was dried (MgSO₄) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica, hexane/EtOAc = 9:1) to afford the title compound (95.1 mg, 83%).

Phenyl 3-phenylpropanoate (**8ac**)³



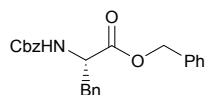
GP-1 was followed using **6a** (59.8 mg, 0.40 mmol) and **7c** (45.6 mg, 0.48 mmol). Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (77.2 mg, 86%).

2-Phenethyl benzoate (**8da**)³



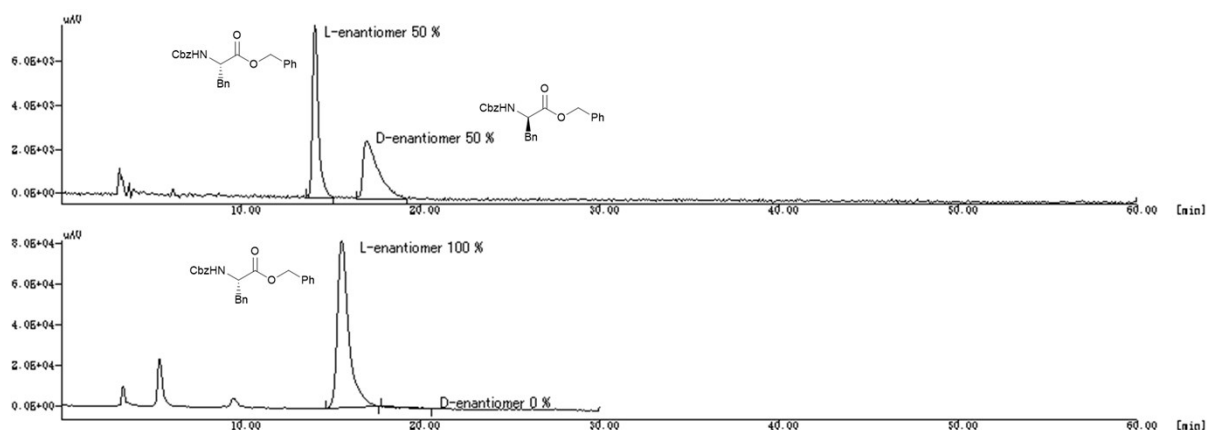
GP-1 was followed using **6d** (48.7 mg, 0.40 mmol) and **7a** (58 μ L, 0.48 mmol). Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (85.2 mg, 94%).

N-[(Benzyloxy)carbonyl]-*L*-phenylalanine benzyl ester (**8ed**)³

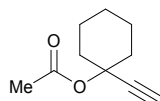


GP-1 was followed using **6e** (119.8 mg, 0.40 mmol) and **7d** (50 μ L, 0.48 mmol). Column chromatography (silica, hexane/EtOAc = 9:1) afforded the title compound (>99%ee) in quantitative yield.

HPLC analysis of **8ed**: Chiralpak IB-3 4.6 \times 25 cm, 1.0 mL/min (hexane/2-propanol = 95:5), and detection at 254 or 208 nm.



1-Ethynylcyclohexyl acetate (**8fe**)⁴



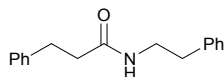
GP-1 was followed using **6f** (46 μ L, 0.80 mmol), **7e** (50.1 mg, 0.40 mmol), NMM (88 μ L, 0.80 mmol), ATD-DMAP (210.3 mg, 0.60 mmol), and molecular sieves 4A (51.6 mg). The reaction mixture was stirred for 30 h. Column chromatography (silica, hexane/CH₂Cl₂ = 7:3) afforded the title compound (42.6 mg, 64%).

General procedure for amidation using ATD-DMAP (GP-2)

A solution of ATD-DMAP (1.1 equiv.) in CH₂Cl₂ (1.50 mL) was added to a mixture of a carboxylic acid (0.4 mmol, 1 equiv.) and an amine (1.1 equiv.) in CH₂Cl₂ (0.50 mL) at room temperature. After 10 min, the reaction mixture was diluted with CHCl₃ (30 mL) and washed with aqueous HCl (1 M, 30 mL), saturated aqueous NaHCO₃ (20 mL), and brine (70 mL). The

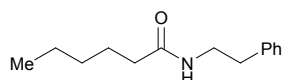
organic layer was dried (MgSO₄) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to afford the desired amide.

***N*-(2-Phenethyl)-3-phenylpropanamide (10aa)²**



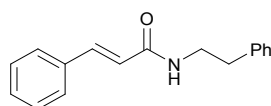
GP-2 was followed using **6a** (60.3 mg, 0.40 mmol) and **9a** (56 μL, 0.44 mmol). Column chromatography (silica, hexane/EtOAc = 7:3) afforded the title compound (94.5 mg, 93%).

***N*-(2-Phenethyl)hexanamide (10ha)⁵**



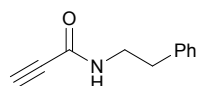
GP-2 was followed using **6h** (50 μL, 0.40 mmol) and **9a** (56 μL, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 4:1) afforded the title compound (85.7 mg, 98%).

***N*-(2-Phenethyl)cinnamamide (10ia)⁵**



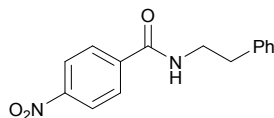
GP-2 was followed using **6i** (60.5 mg, 0.41 mmol) and **9a** (56 μL, 0.44 mmol). Column chromatography (silica, hexane/EtOAc = 4:1) afforded the title compound (95.8 mg, 93%).

***N*-Phenethylpropiolamide (10ja)⁵**



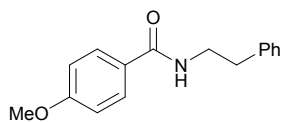
GP-2 was followed using **6j** (25 μL, 0.41 mmol) and **9a** (56 μL, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 7:3) afforded the title compound (56.7 mg, 81%).

4-Nitro-*N*-(2-phenethyl)benzamide (10ka)²



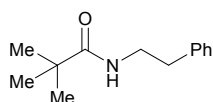
GP-2 was followed using **6k** (67.5 mg, 0.40 mmol) and **9a** (56 μL, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 7:3) afforded the title compound (99.0 mg, 91%).

4-Methoxy-*N*-(2-phenethyl)benzamide (10la)²



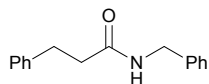
GP-2 was followed using **6l** (61.7 mg, 0.41 mmol) and **9a** (56 μ L, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 4:1) afforded the title compound (95.3 mg, 92%).

***N*-(2-Phenethyl)pivalamide (10ma)²**



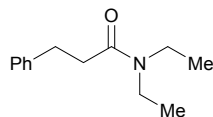
GP-2 was followed using **6m** (43.0 mg, 0.42 mmol) and **9a** (56 μ L, 0.44 mmol). The reaction mixture was stirred for 3 h. Column chromatography (amine-functionalized silica, hexane/EtOAc = 4:1) afforded the title compound (78.3 mg, 91%).

***N*-Benzyl-3-phenylpropanamide (10ab)⁵**



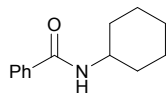
GP-2 was followed using **6a** (60.9 mg, 0.40 mmol) and **9b** (48 μ L, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 7:3) afforded the title compound (90.9 mg, 94%).

***N,N*-Diethyl-3-phenylpropanamide (10ac)²**



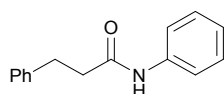
GP-2 was followed using **6a** (61.0 mg, 0.41 mmol) and **9c** (46 μ L, 0.44 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 7:3) afforded the title compound (83.7 mg) in quantitative yield.

***N*-Cyclohexylbenzamide (10dd)⁵**



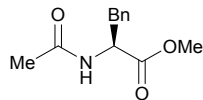
GP-2 was followed using **6d** (49.2 mg, 0.40 mmol) and **9d** (52 μ L, 0.45 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 7:3) afforded the title compound (82.1 mg) in quantitative yield.

***N*,3-Diphenylpropanamide (10ae)⁶**



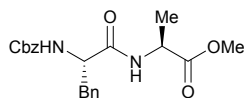
GP-2 was followed using **6a** (61.4 mg, 0.41 mmol) and **9e** (36 μ L, 0.39 mmol). The reaction mixture was stirred for 3 h. Column chromatography (amine-functionalized silica, hexane/EtOAc = 9:1) afforded the title compound (86.1 mg, 97%).

N-Acetyl-L-phenylalanine methyl ester (**10nf**)⁵



GP-2 was followed using **6n** (40.3 mg, 0.49 mmol) and **9f** (88.6 mg, 0.41 mmol). Column chromatography (amine-functionalized silica, hexane/EtOAc = 4:1) afforded the title compound (92.0 mg) in quantitative yield.

Methyl (benzyloxy)carbonyl-L-phenylalanyl-L-alaninate (**10eg**)²



GP-2 was followed using **6e** (119.7 mg, 0.40 mmol), **9g** (61.4 mg, 0.44 mmol), Et₃N (61 μ L, 0.44 mmol), and ATD-DMAP (168.8 mg, 0.48 mmol). The reaction time was 15 min. Column chromatography (amine-functionalized silica, hexane/EtOAc = 1:1) afforded the title compound (141.1 mg, 92%).

Fig. S1 Crude ¹H NMR spectrum of **10eg**.

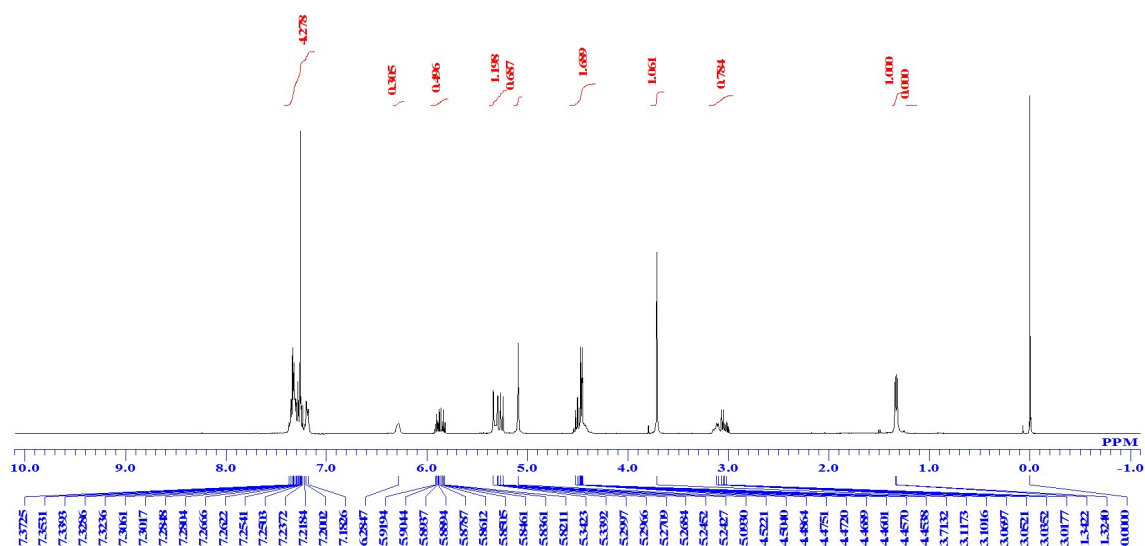
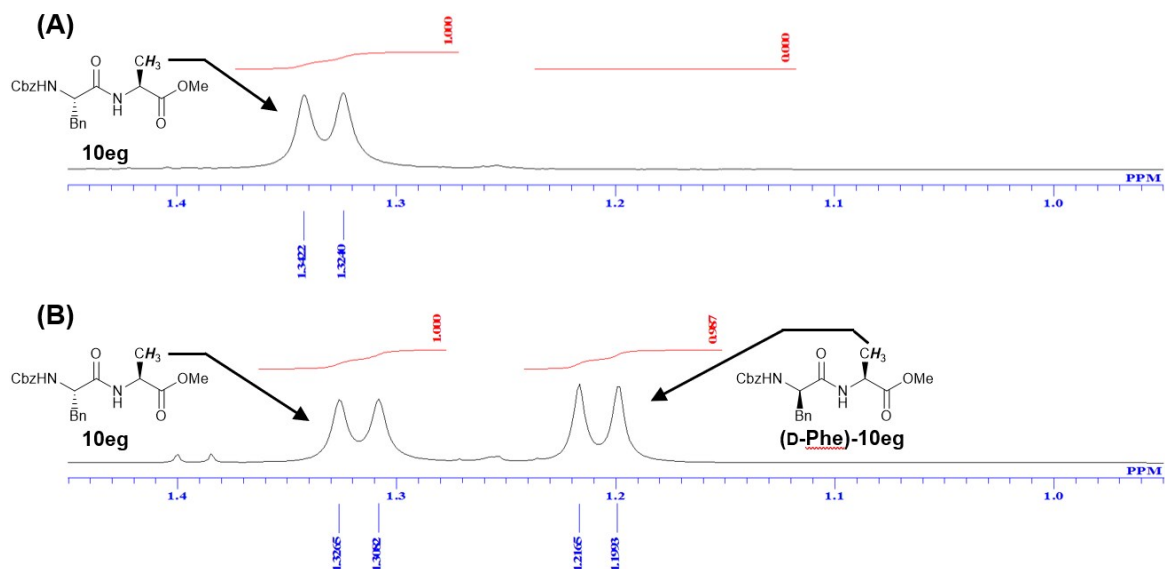
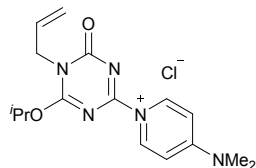


Fig S2 Comparison of ^1H NMR spectra of (A) the crude mixture of **10eg** prepared using ATD-DMAP and (B) a 1:1 mixture of **10eg** and (**D-Phe**)-**10eg** (our previous data from Ref. 2).

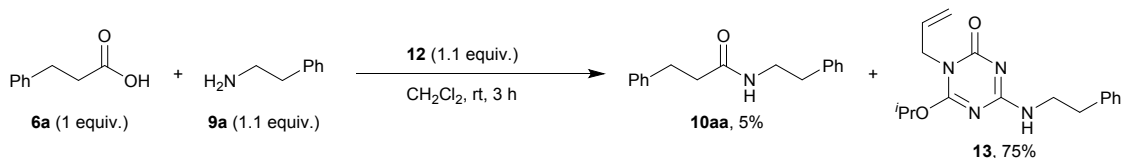


Synthesis of triazinone-based dehydrative condensing reagent **12**.



DMAP (293.0 mg, 2.4 mmol) was added to a solution of **4** (503.0 mg, 2.2 mmol) in THF (5.0 mL) at room temperature. After 2 h, the precipitate was filtered and washed with THF to afford **12** (723.4 mg, 94%) as a pale yellow solid. ^1H NMR: δ 9.38–9.33 (m, 2H), 7.54–7.47 (m, 2H), 5.96–5.80 (m, 2H), 5.37–5.29 (m, 2H), 4.64–4.58 (m, 2H), 3.57 (s, 6H), 1.52 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR: δ 163.4, 160.2, 158.8, 154.7, 137.0, 129.4, 120.3, 109.0, 79.0, 45.2, 42.0, 21.9; HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_5\text{O}_2^+$ ($[\text{M} - \text{Cl}]^+$): 316.3845; found: 316.3851.

Attempted amidation using **12**.



Dehydrative condensing reagent **12** (154.6 mg, 0.44 mmol) was added to a solution of **6a** (60.1 mg, 0.40 mmol) and **9a** (55.5 μL , 0.44 mmol) in CH_2Cl_2 (2.00 mL) at room temperature. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous HCl (1 M, 7 mL), saturated aqueous NaHCO_3 (10 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1 to 1:3) and amine-

functionalized silica gel column chromatography (EtOAc) to afford **10aa** (5.3 mg, 5%) and **13** (103.8 mg, 75%) as a white solid.

1-Allyl-6-isopropoxy-4-(2-phenethylamino)-1,3,5-triazin-2(1H)-one (13)

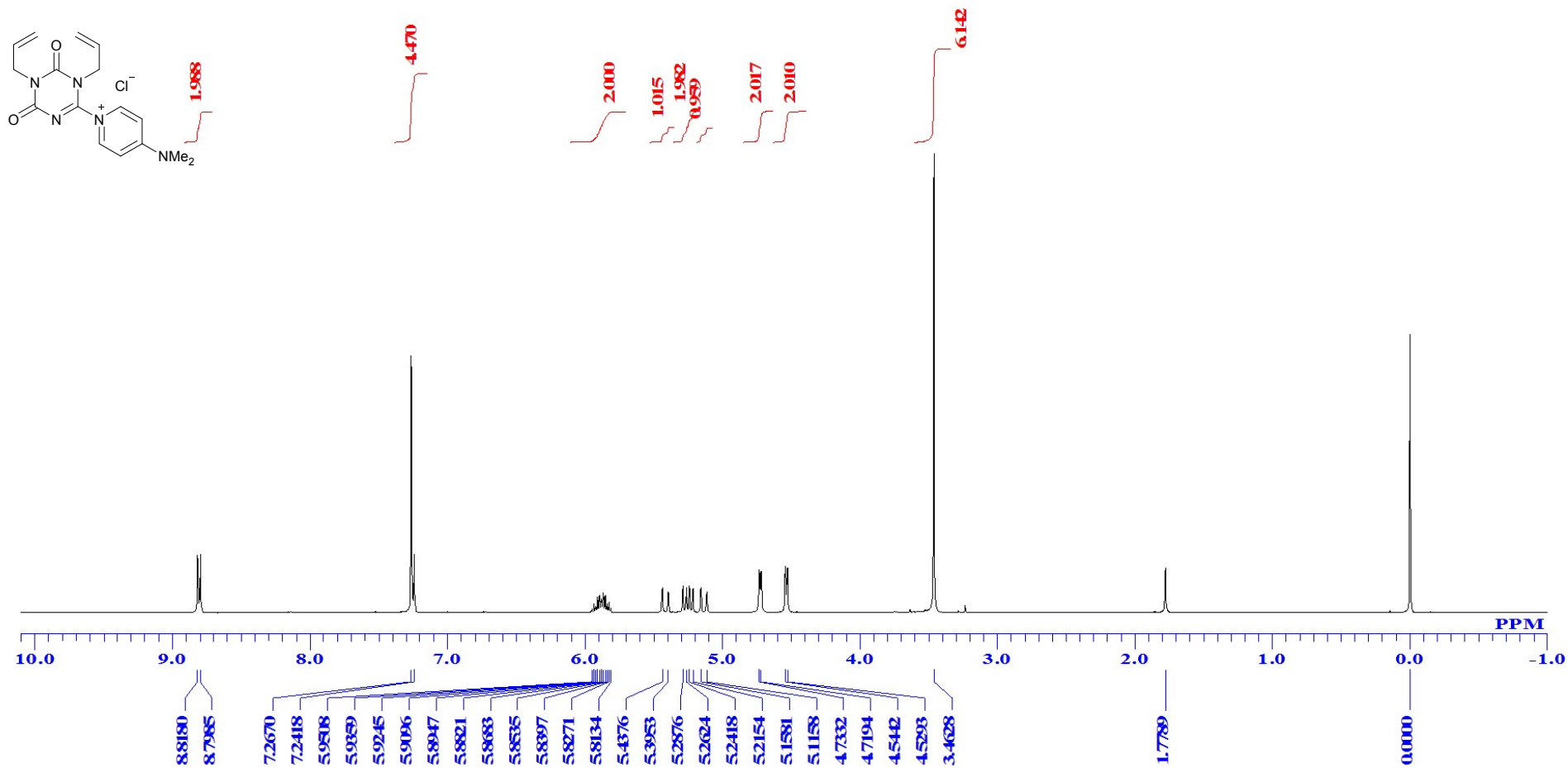
¹H NMR (mixture of rotamers): δ 7.36–7.17 (m, 5H), 6.42–6.28 (m, 0.4 H), 5.92–5.78 (m, 1H), 5.40–5.02 (m, 3.6H), 4.53–4.44 (m, 2H), 3.74 (dt, $J = 6.6, 6.6$ Hz, 1.2H), 3.65 (dt, $J = 6.7, 6.7$ Hz, 0.8H), 2.94–2.85 (m, 2H), 1.39 (d, $J = 6.0$ Hz, 2.4H), 1.32 (d, $J = 6.4$ Hz, 3.6H); ¹³C NMR (mixture of rotamers): δ 164.2, 163.7, 160.6, 160.1, 156.6, 155.6, 139.4, 138.8, 131.9, 131.8, 128.9, 128.7, 128.4, 128.2, 126.3, 126.0, 117.5, 117.3, 73.3, 73.1, 43.6, 43.4, 42.5, 42.0, 36.4, 35.3, 21.6, 21.5; HRMS (DART-TOF) Calcd for C₁₇H₂₃N₄O₂ ([M + H]⁺): 315.1821; found: 315.1840.

3. References

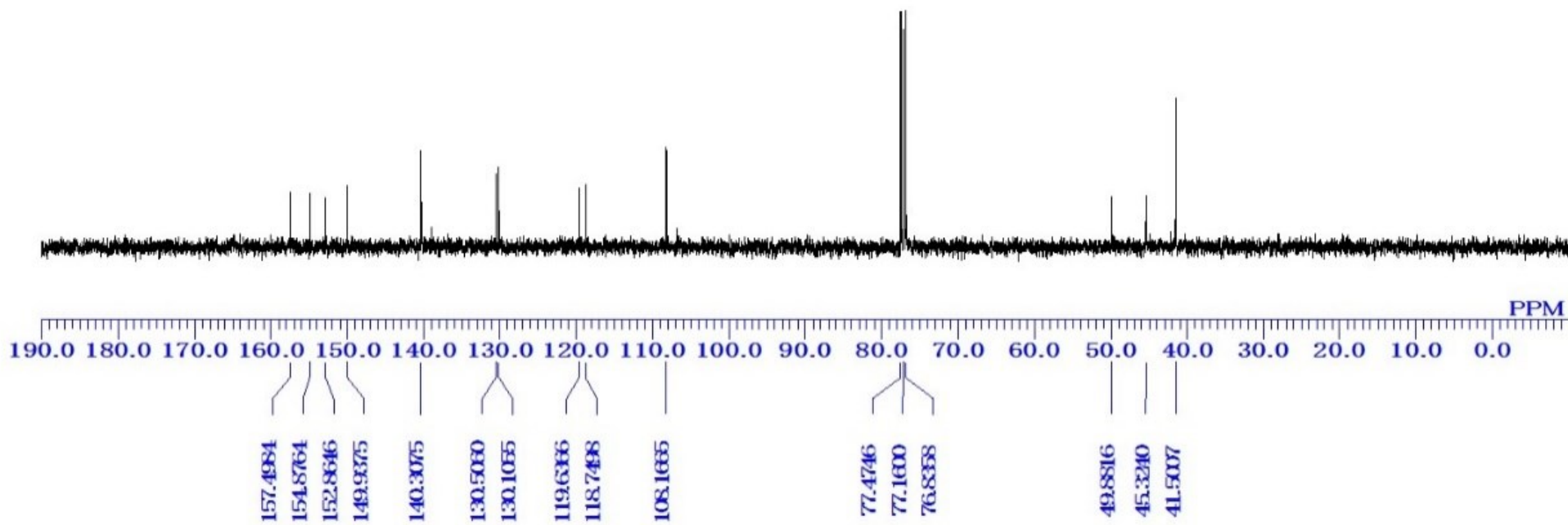
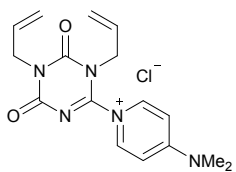
- (1) H. Fujita, R. Yamashita, T. Fujii, K. Yamada, M. Kitamura and M. Kunishima, *Eur. J. Org. Chem.*, 2019, 4436–4446.
- (2) K. Yamada, M. Kota, K. Takahashi, H. Fujita, M. Kitamura and M. Kunishima, *J. Org. Chem.*, 2019, **84**, 15042–15051.
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4. ^1H and ^{13}C NMR spectra

^1H NMR
ATD-DMAP

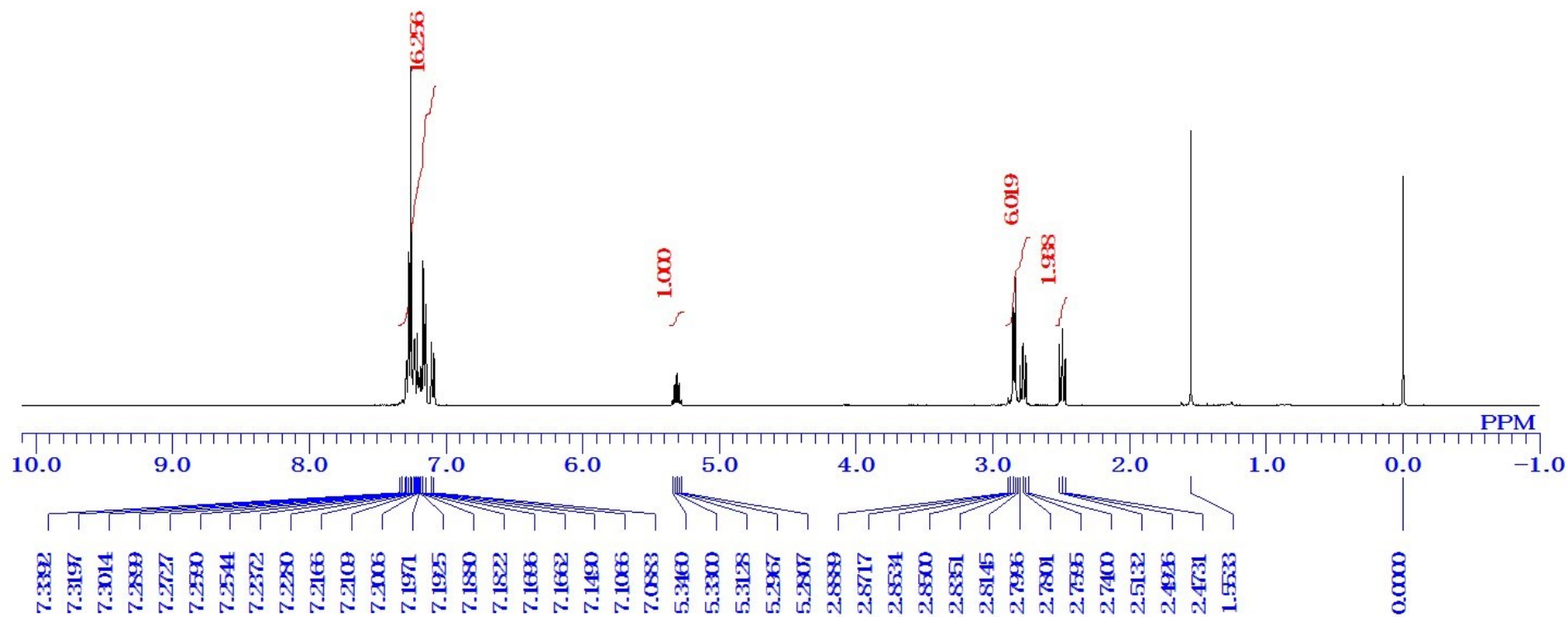
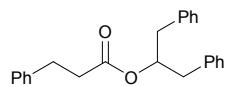


¹³C NMR
ATD-DMAP

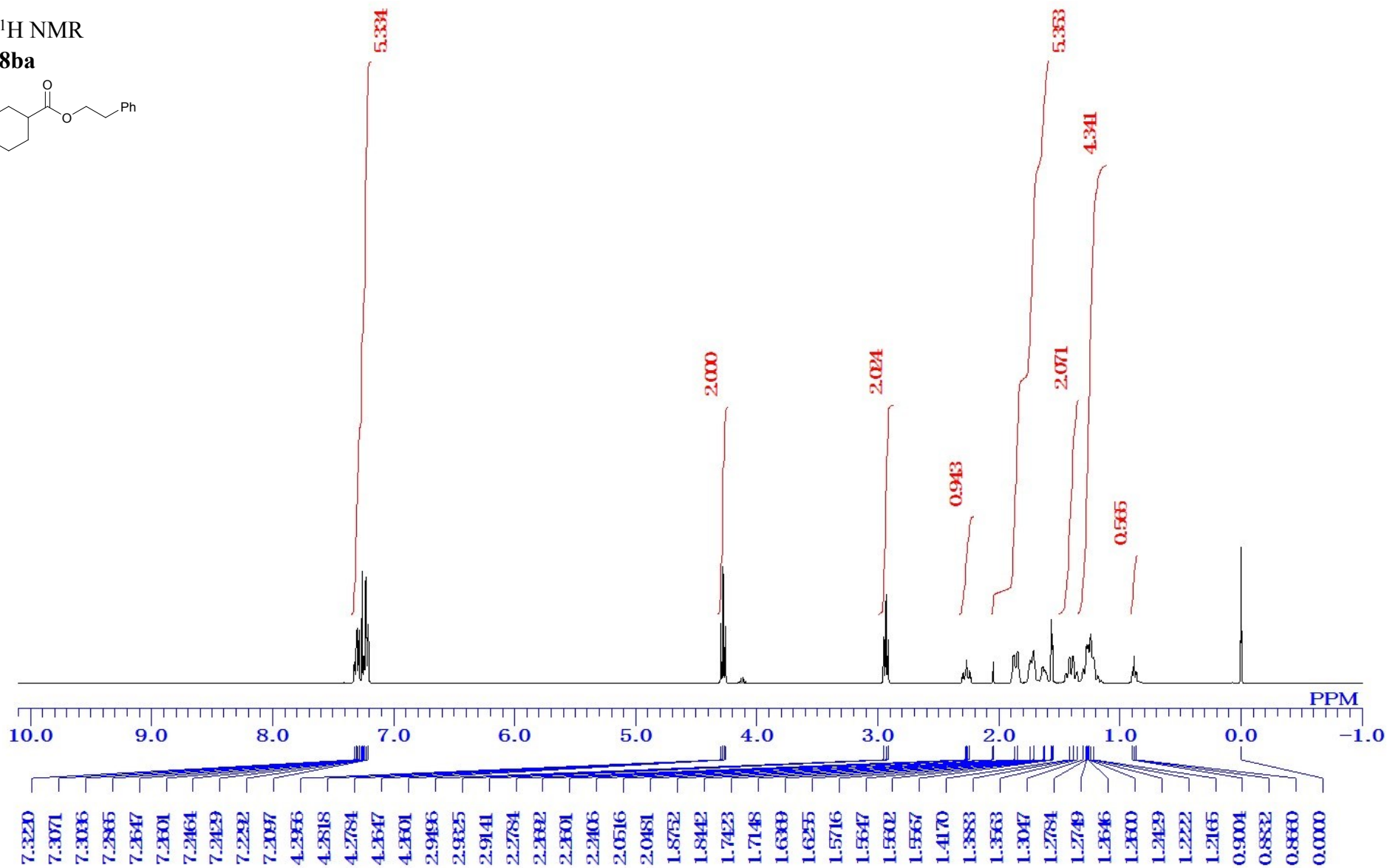
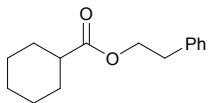


¹H NMR

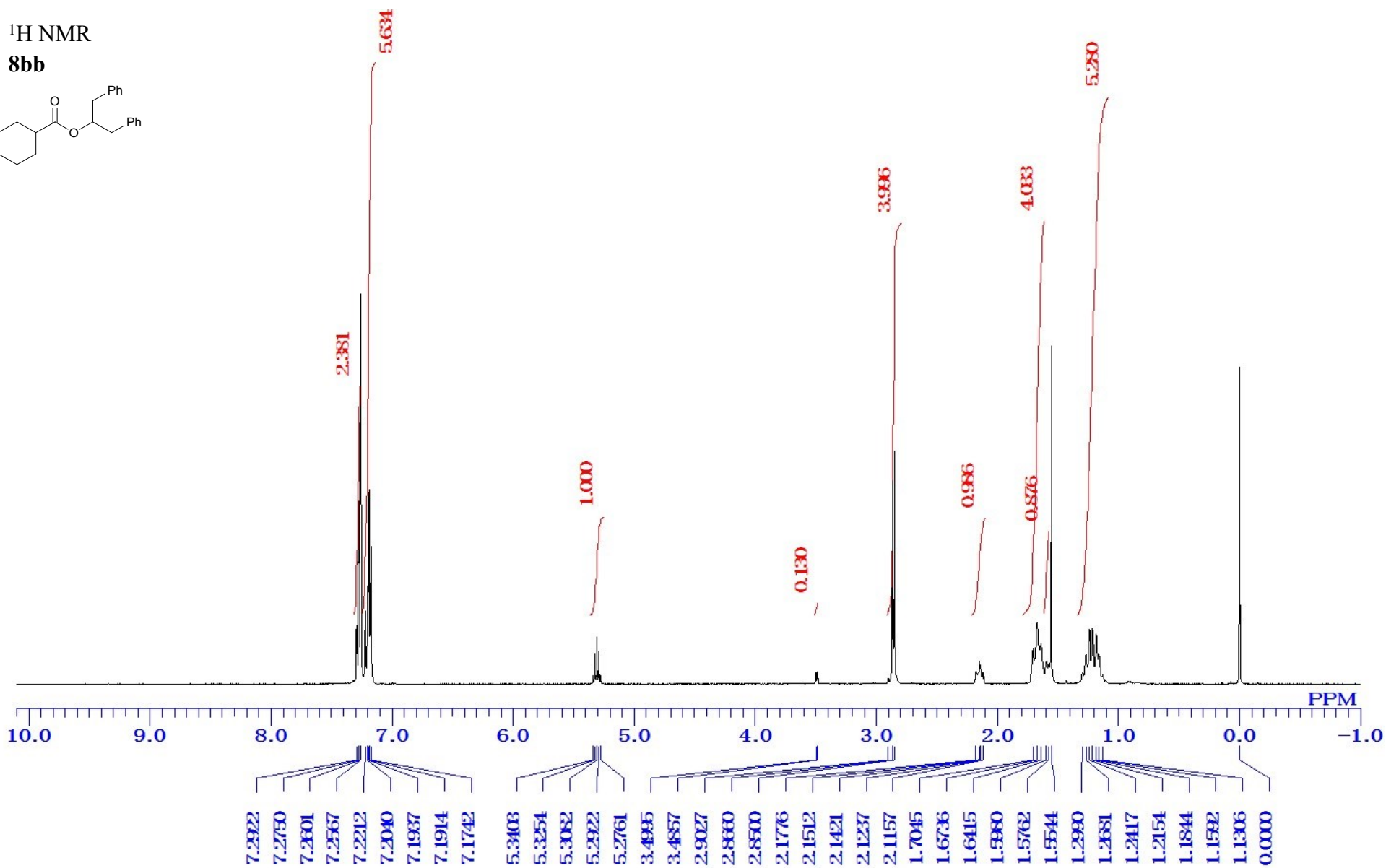
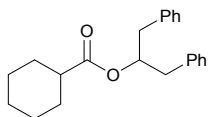
8ab



¹H NMR
8ba

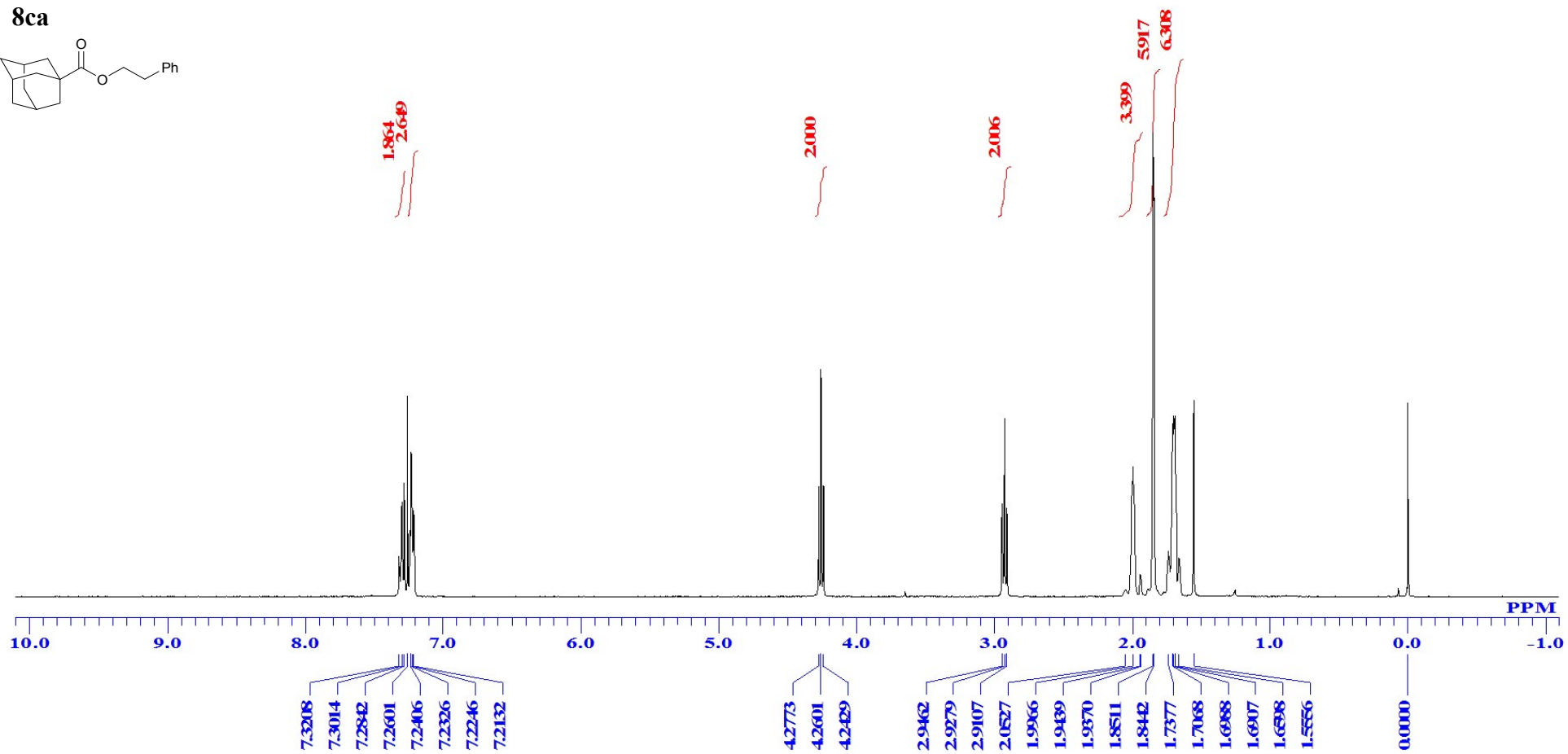
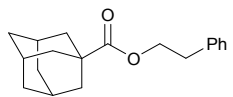


¹H NMR
8bb



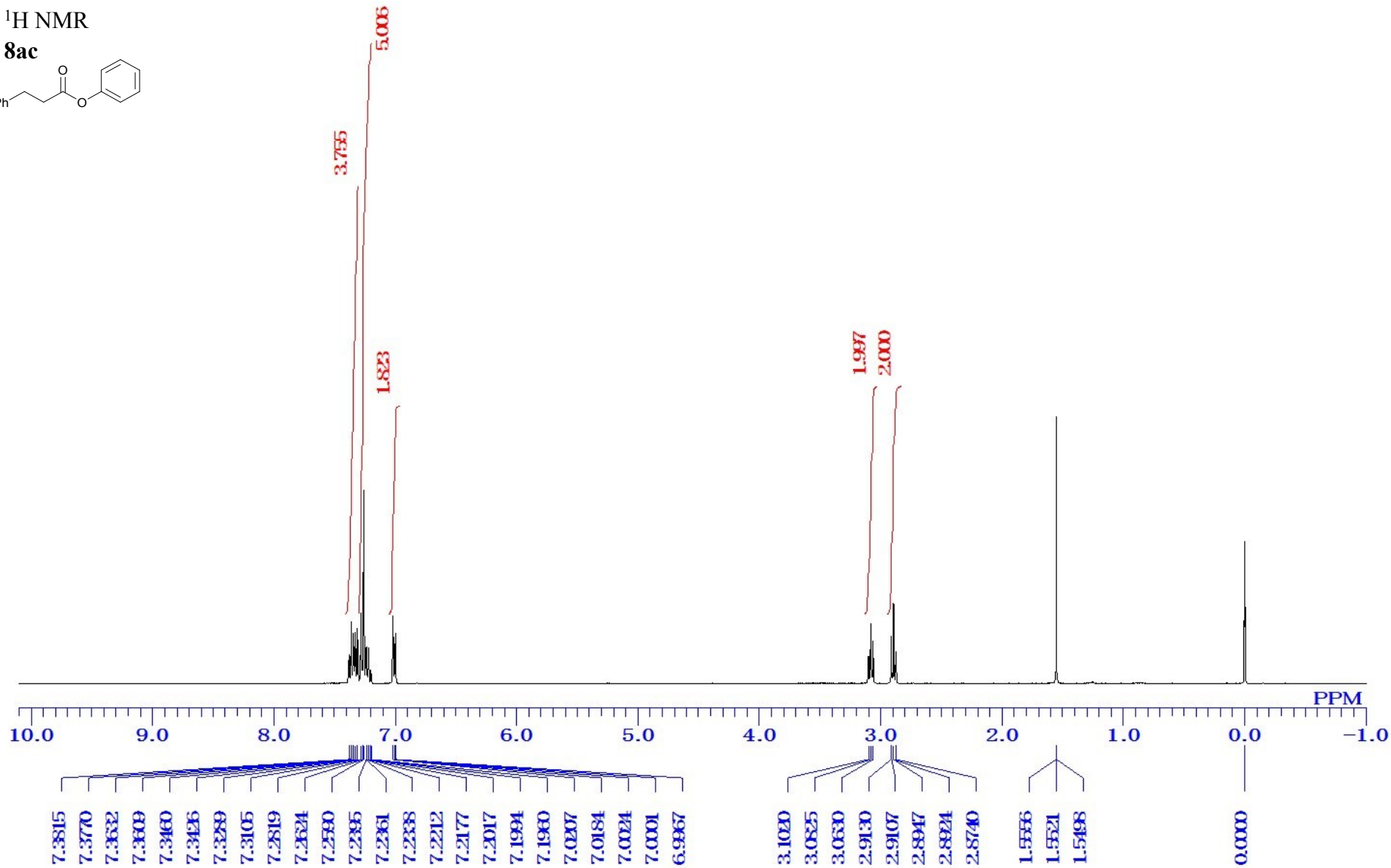
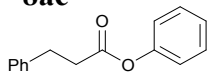
¹H NMR

8ca



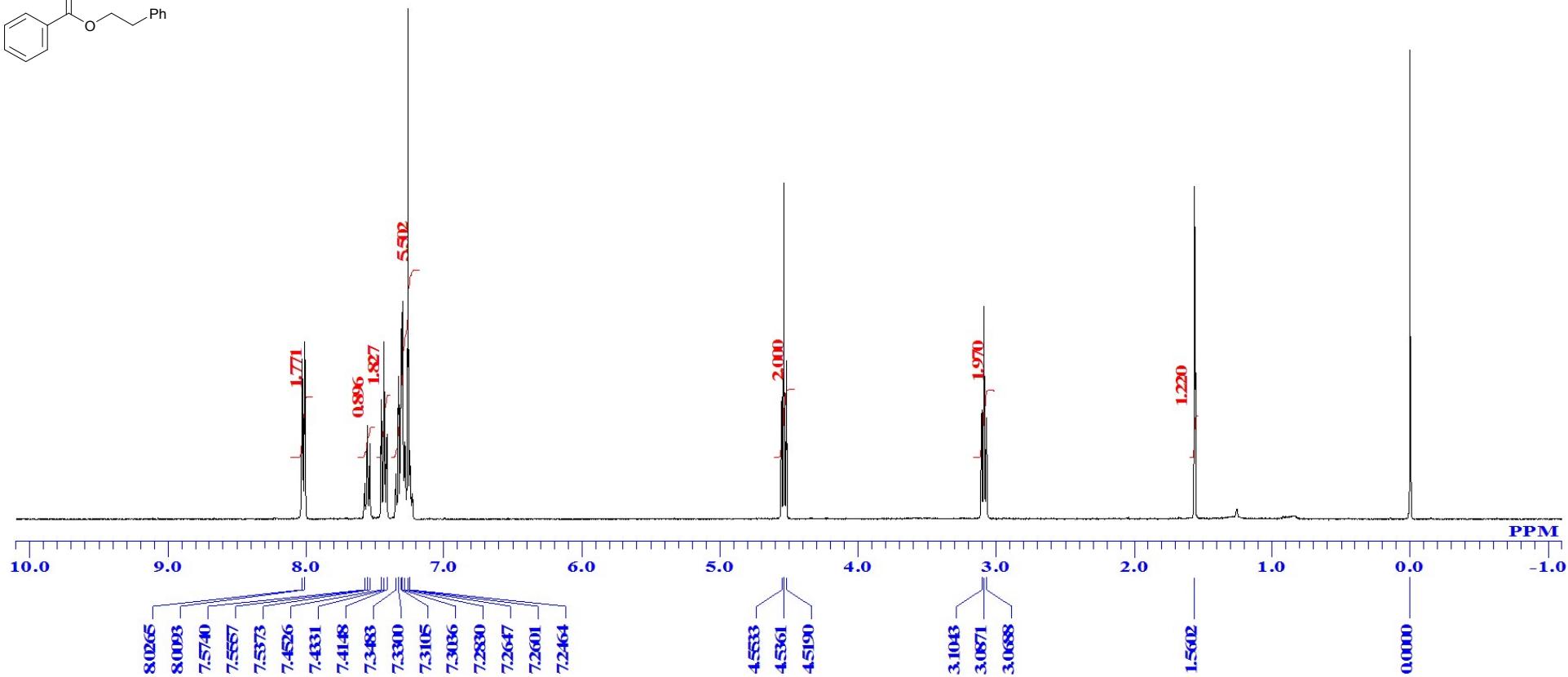
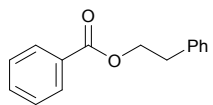
¹H NMR

8ac



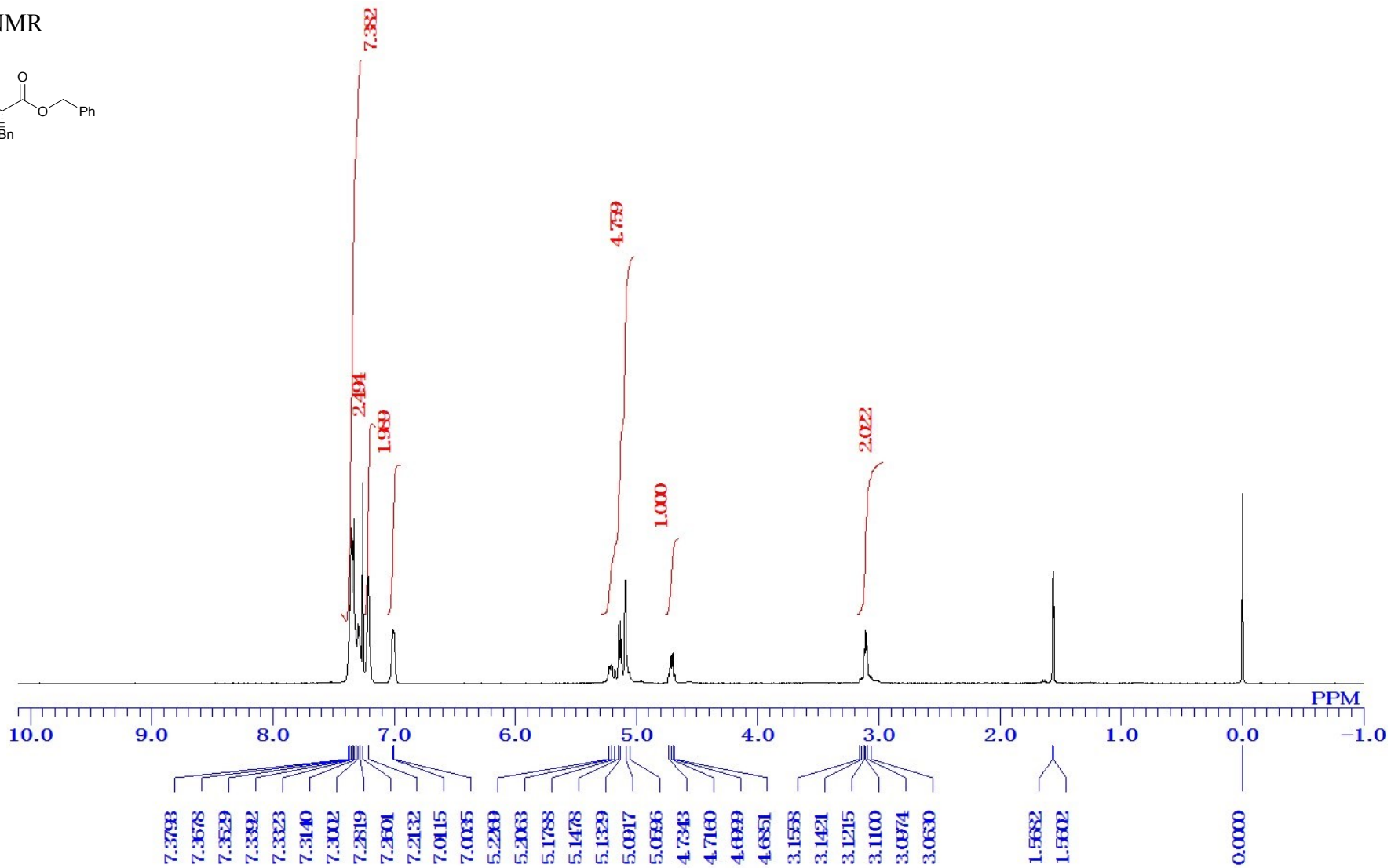
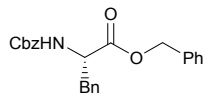
¹H NMR

8da

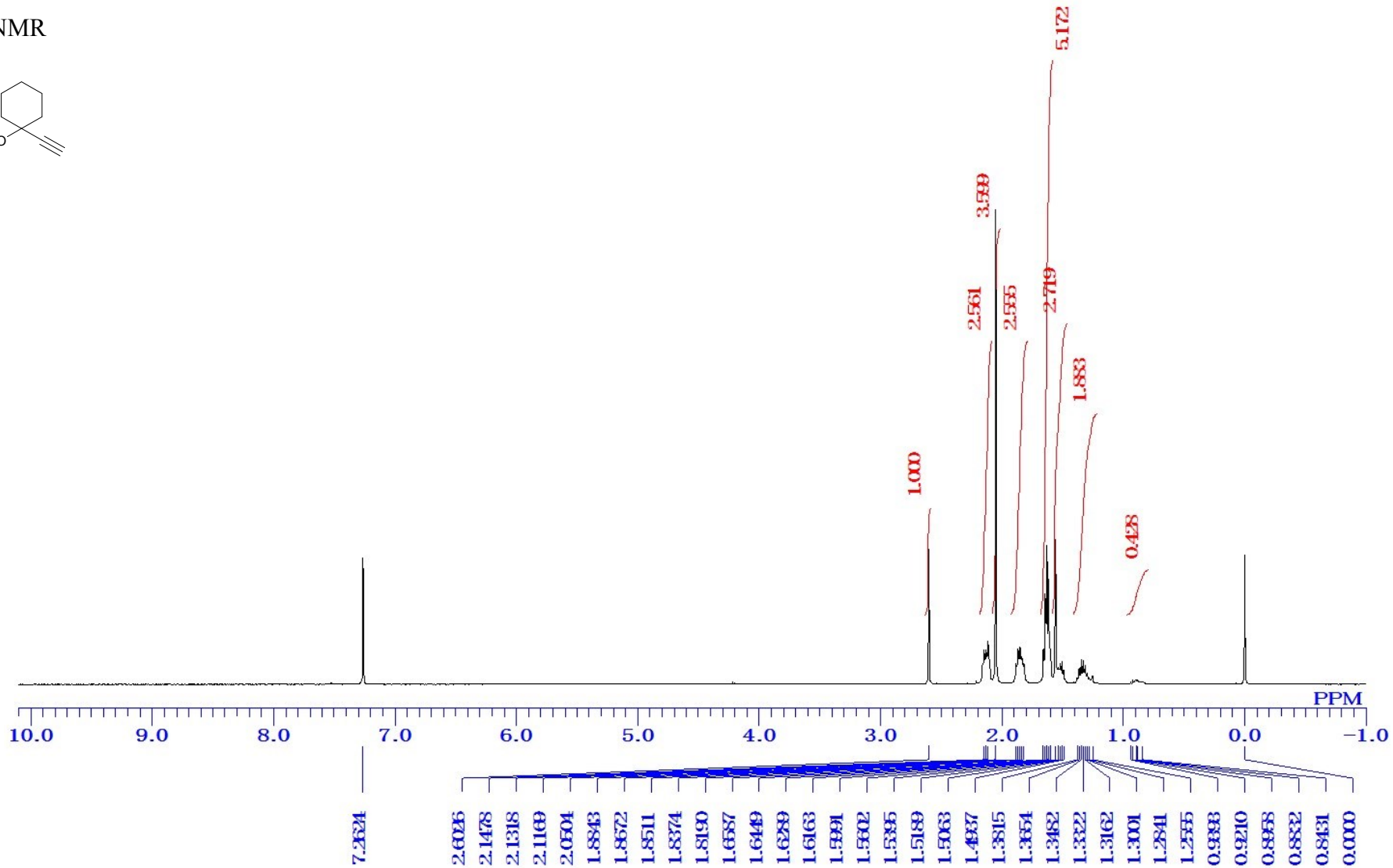
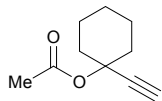


¹H NMR

8ed

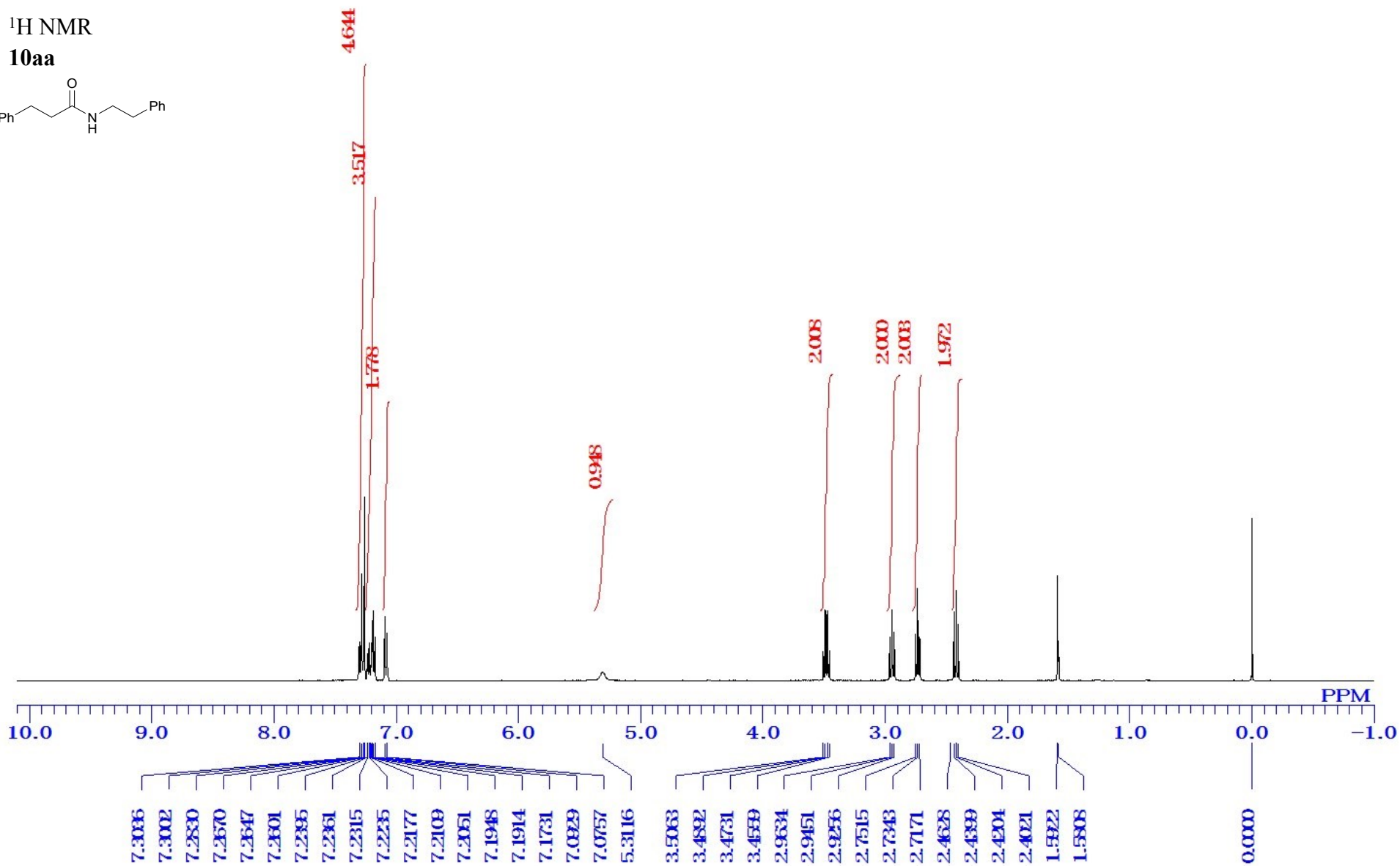
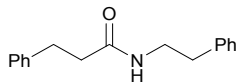


¹H NMR
8fe

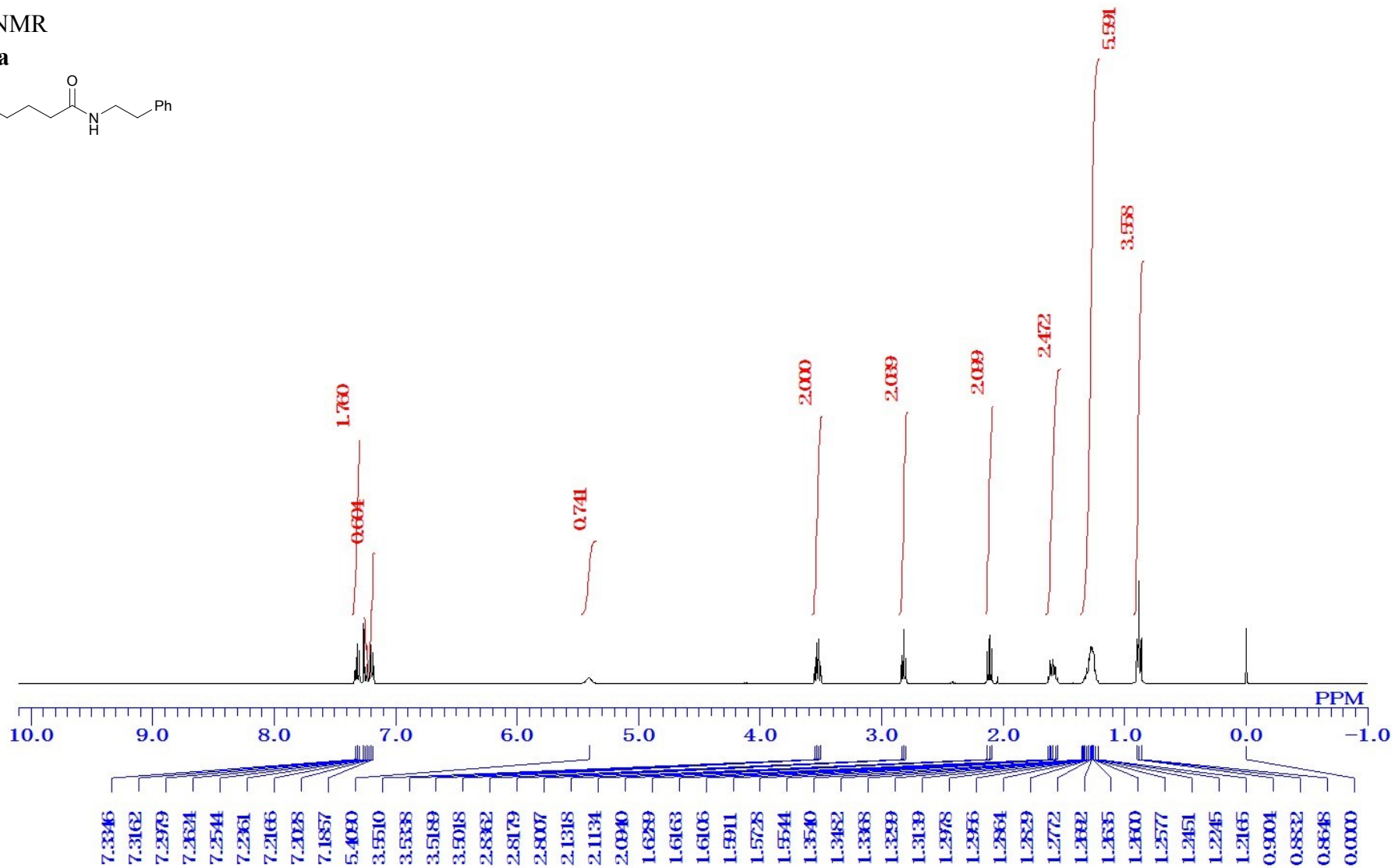
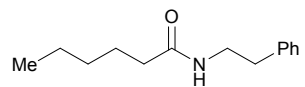


¹H NMR

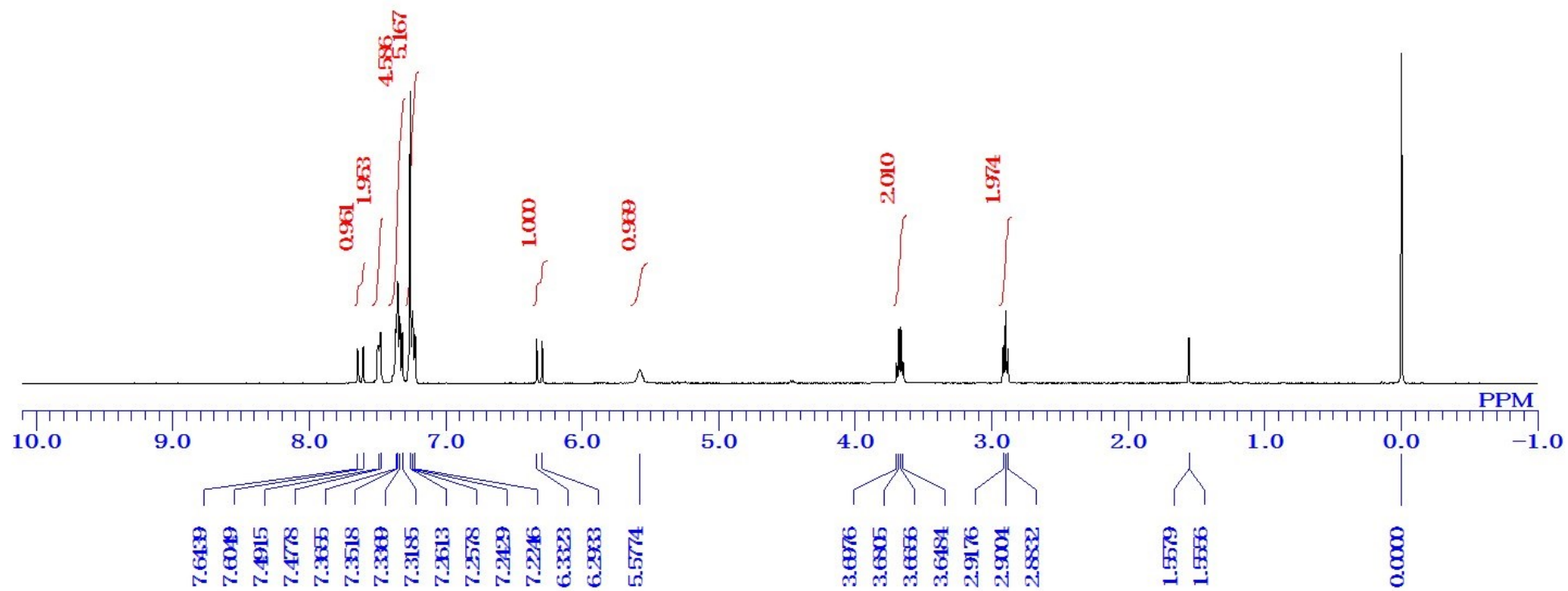
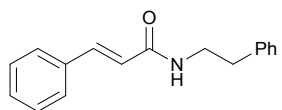
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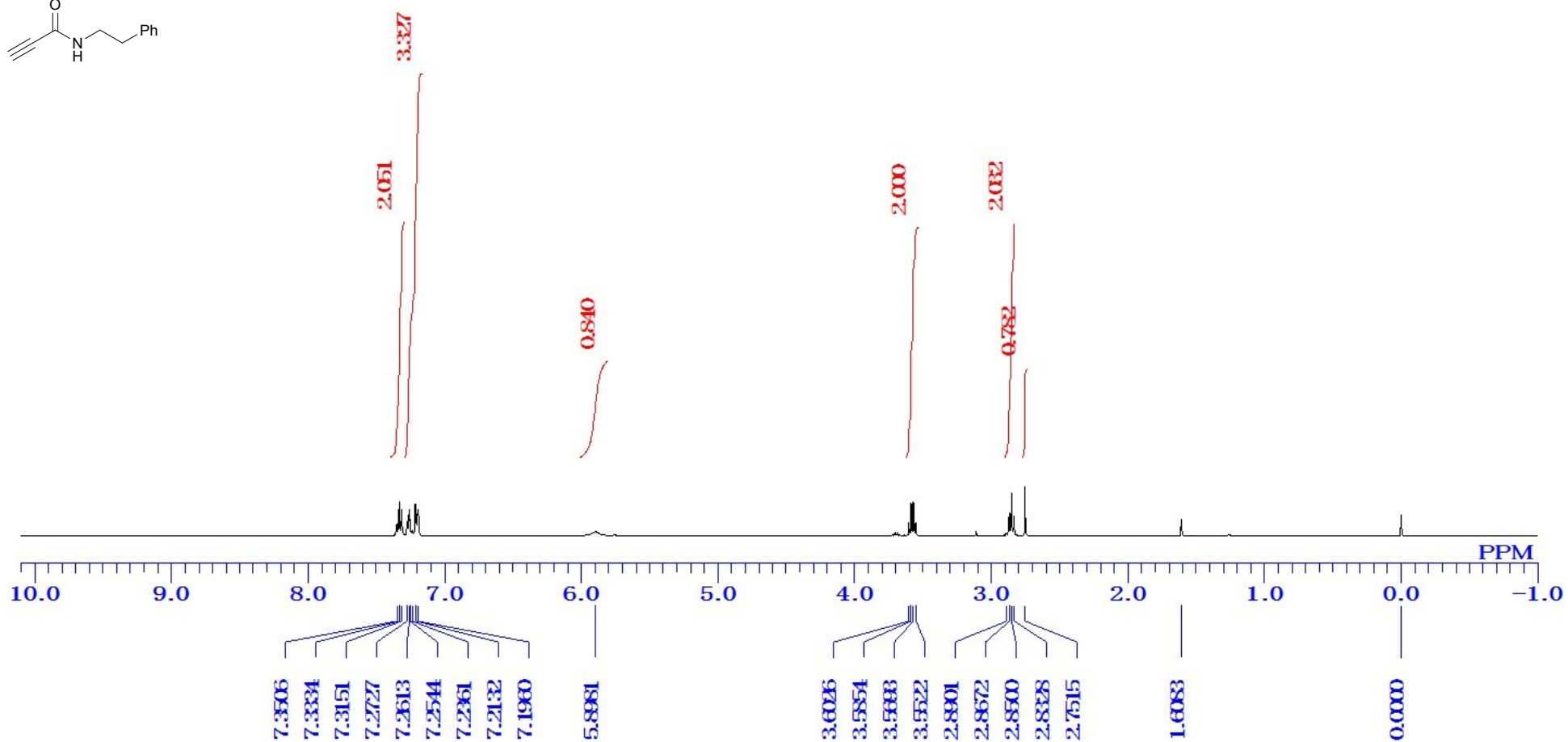
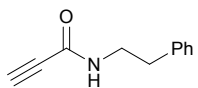
¹H NMR
10ha



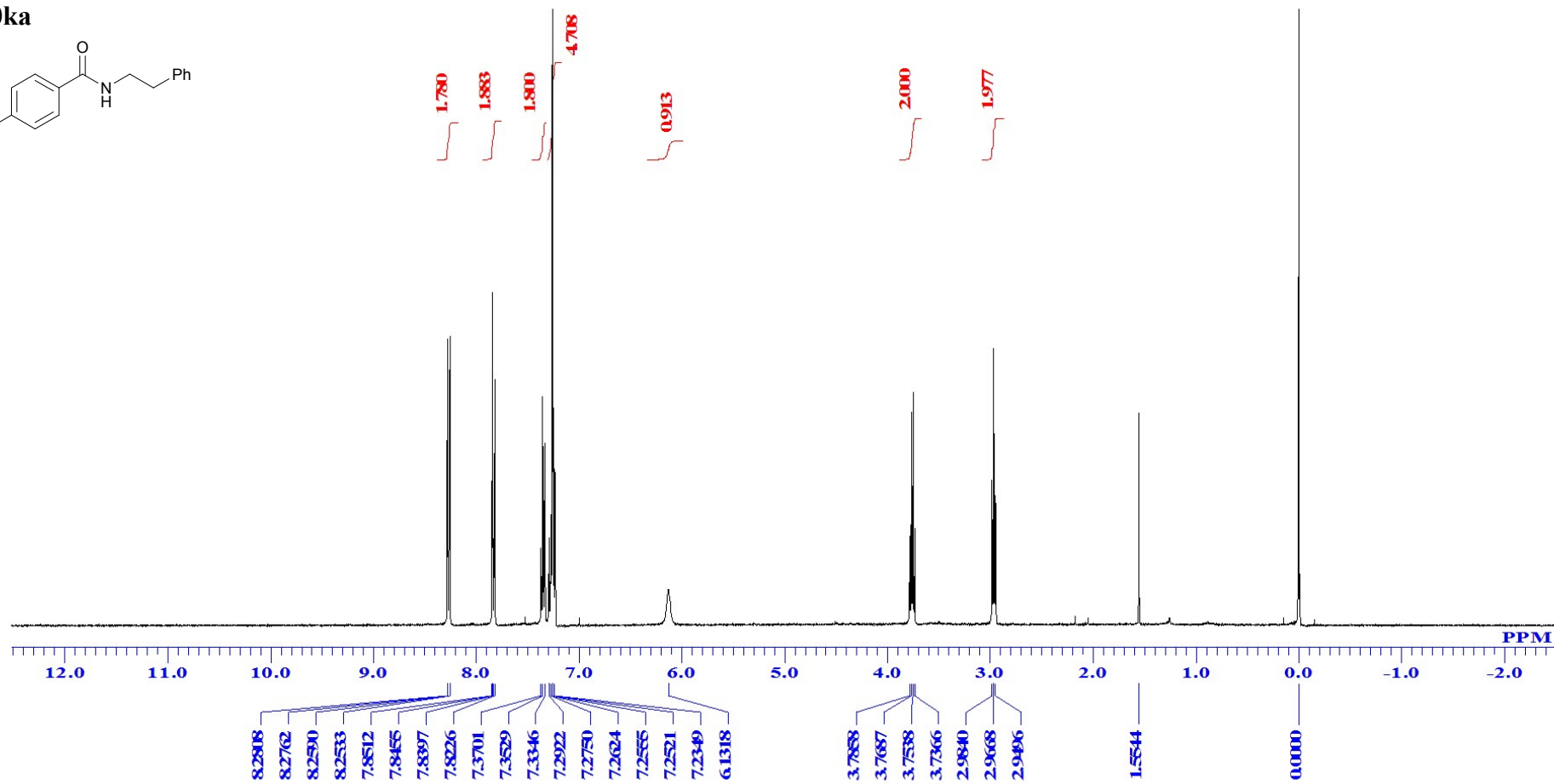
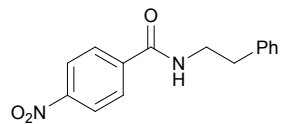
¹H NMR
10ia



¹H NMR
10ja

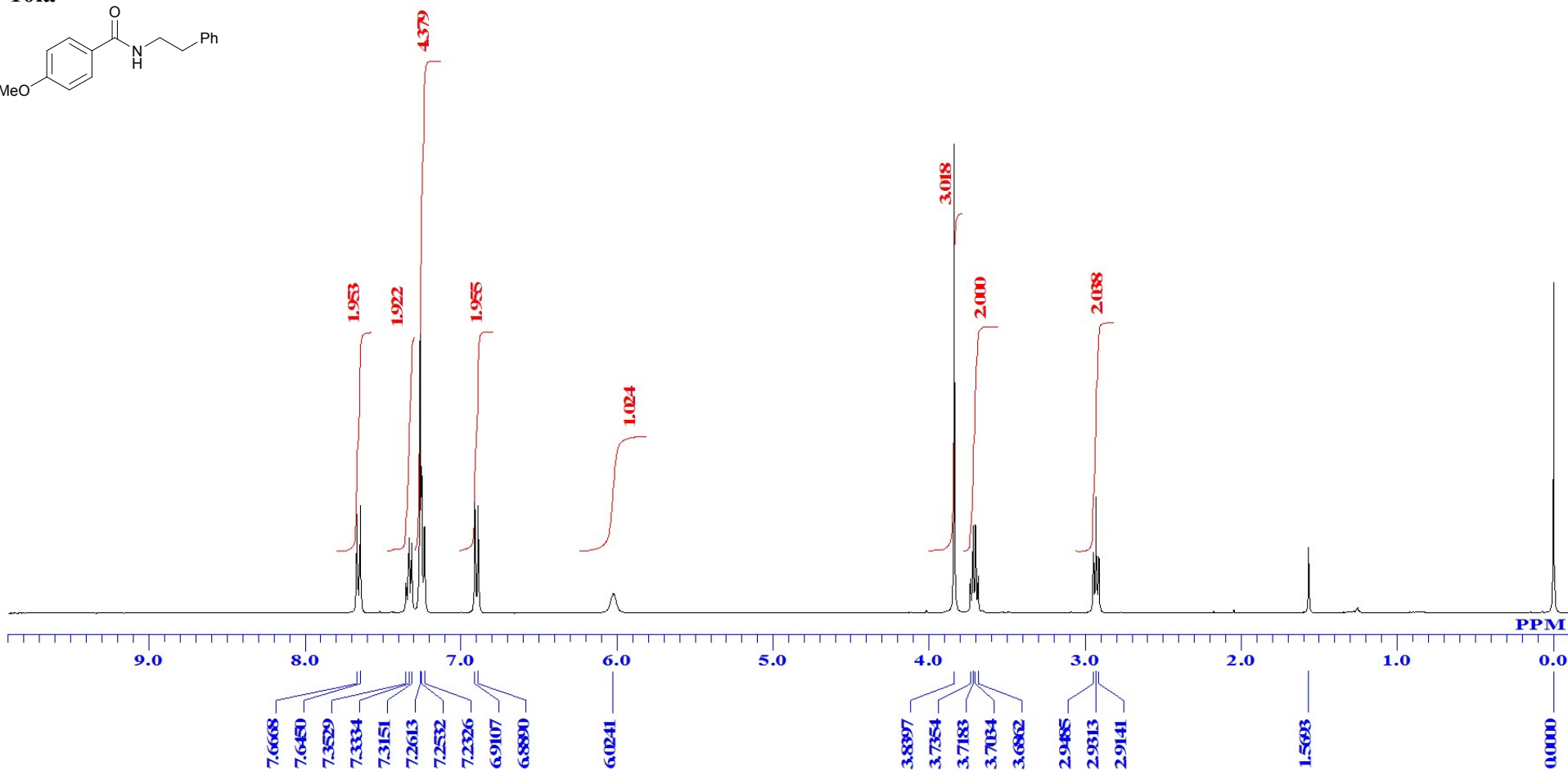
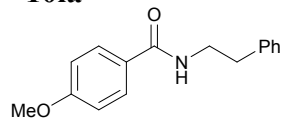


¹H NMR
10ka



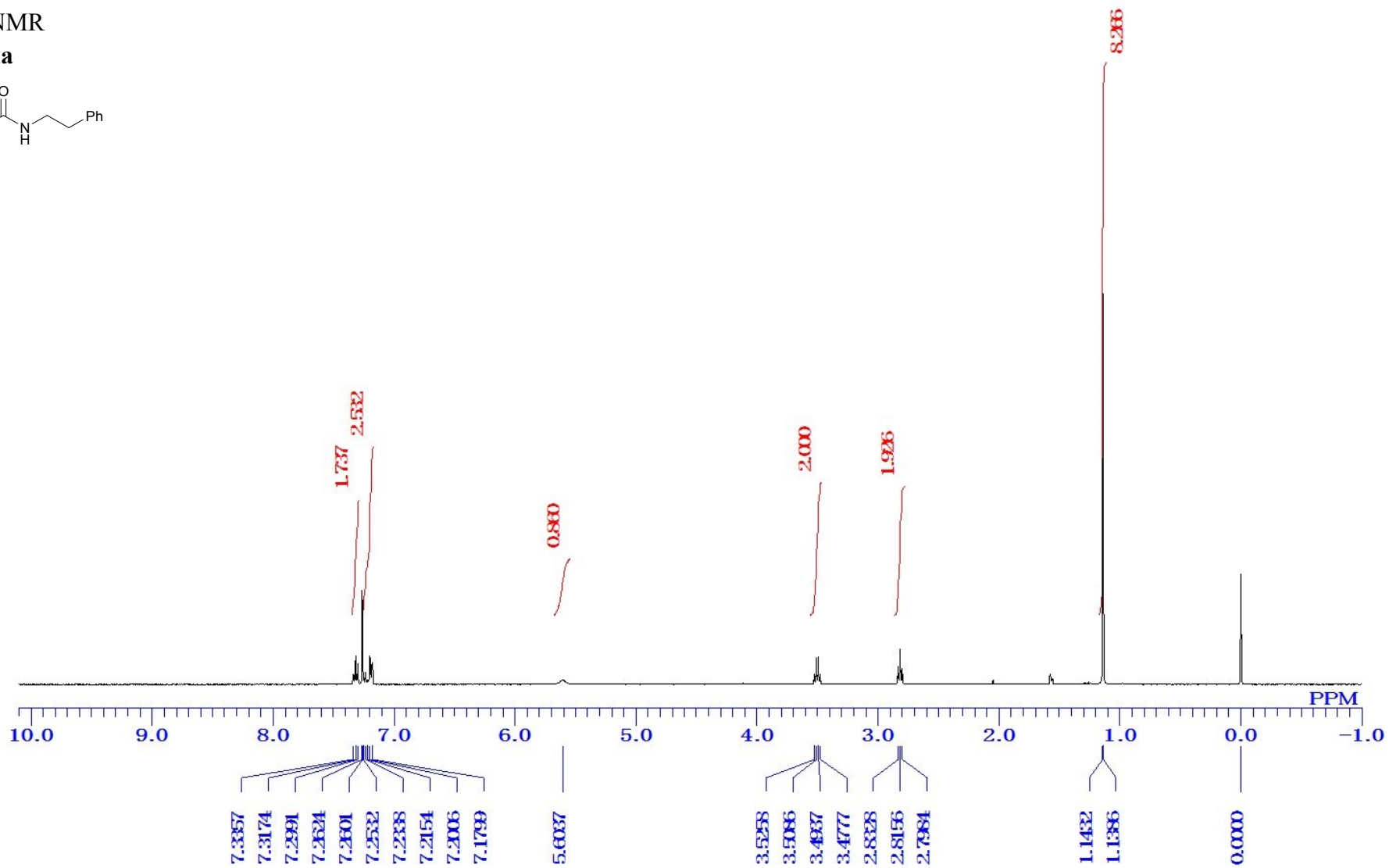
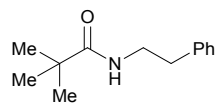
¹H NMR

10a



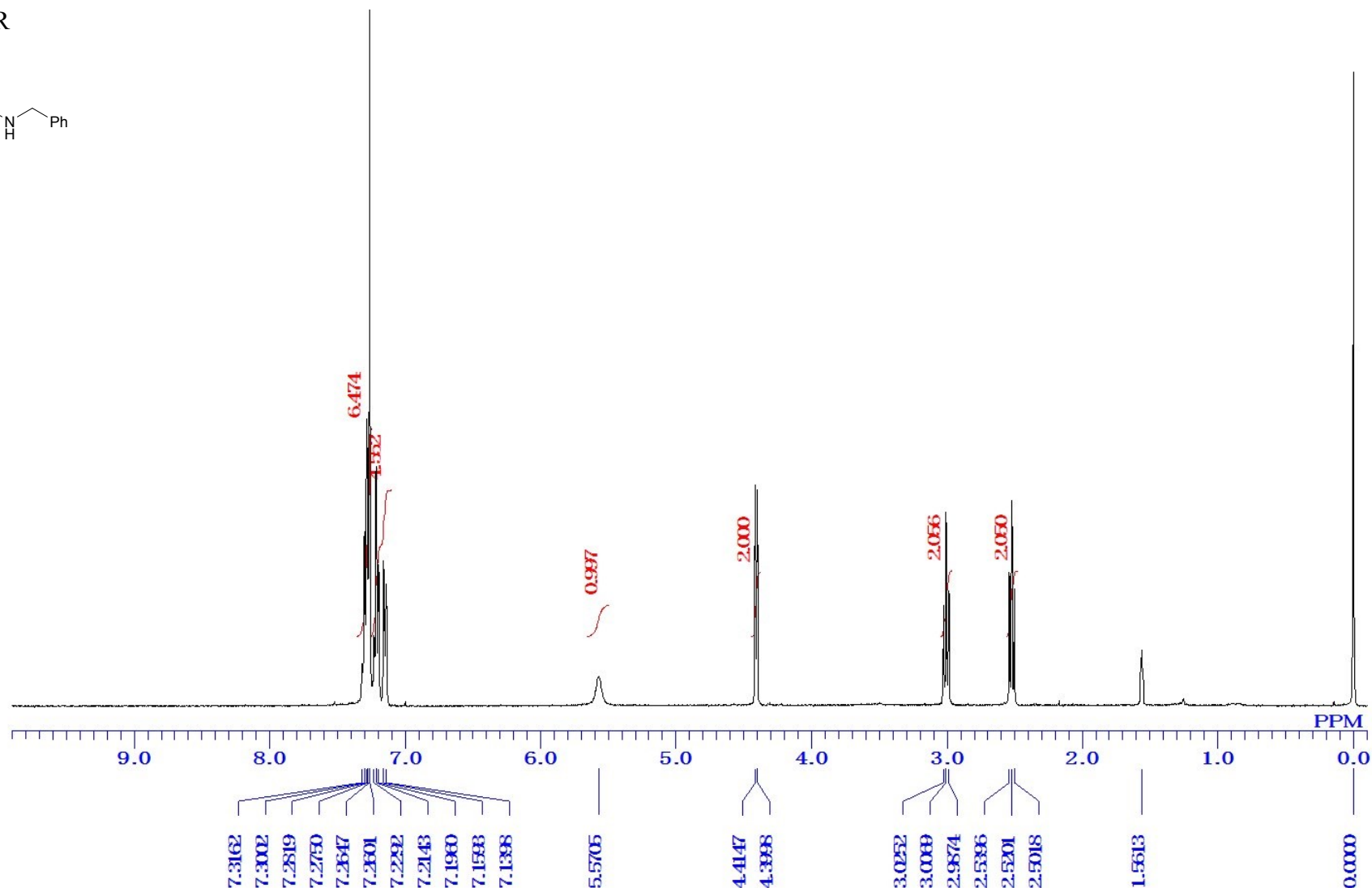
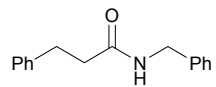
¹H NMR

10ma

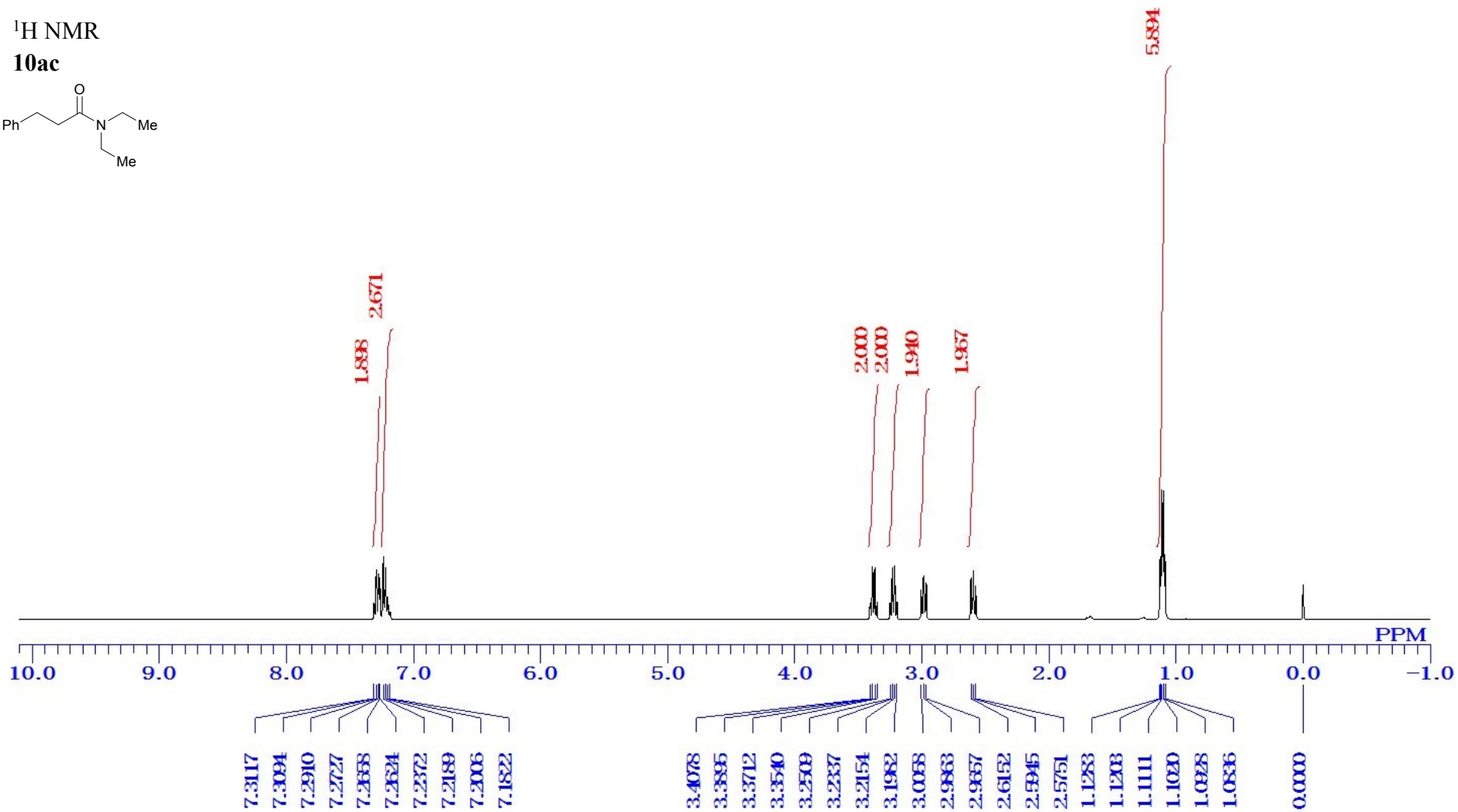
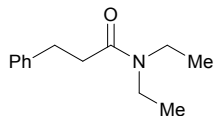


¹H NMR

10ab

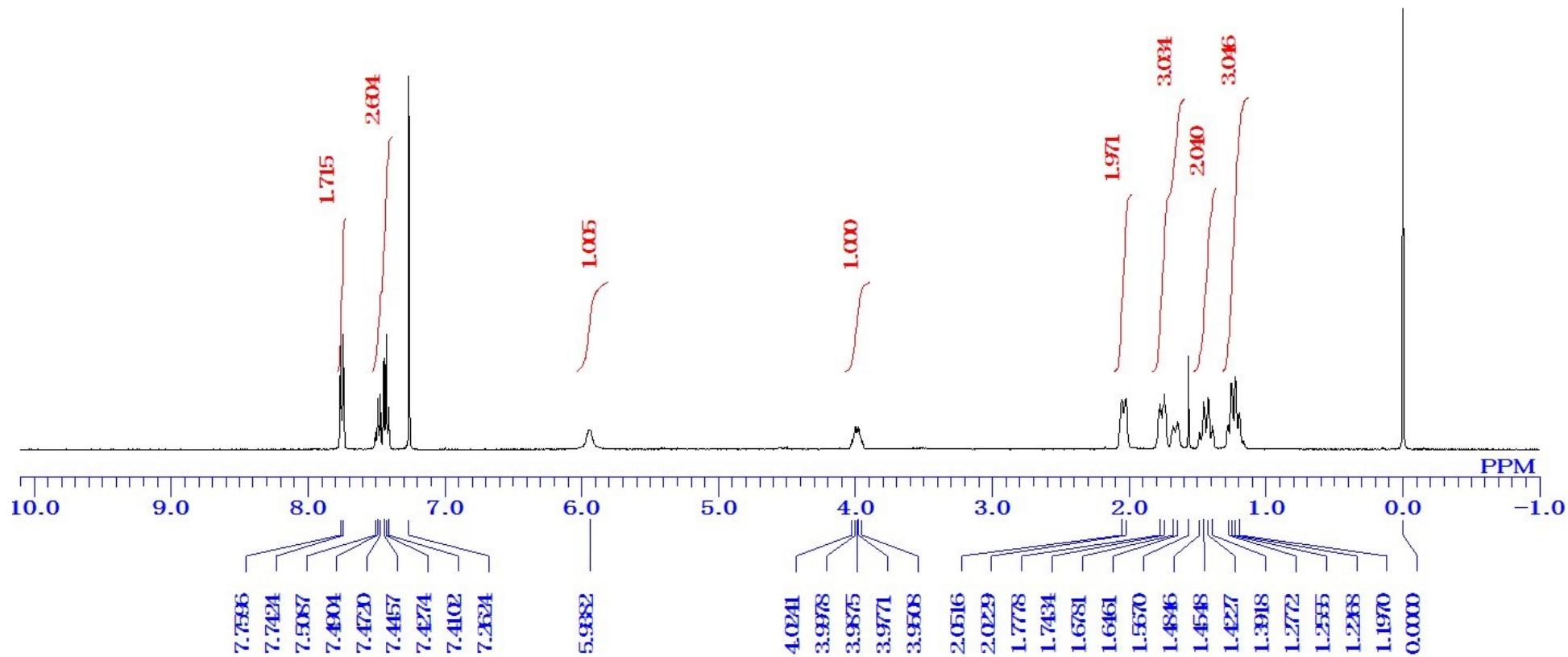
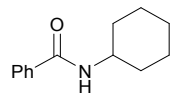


¹H NMR
10ac



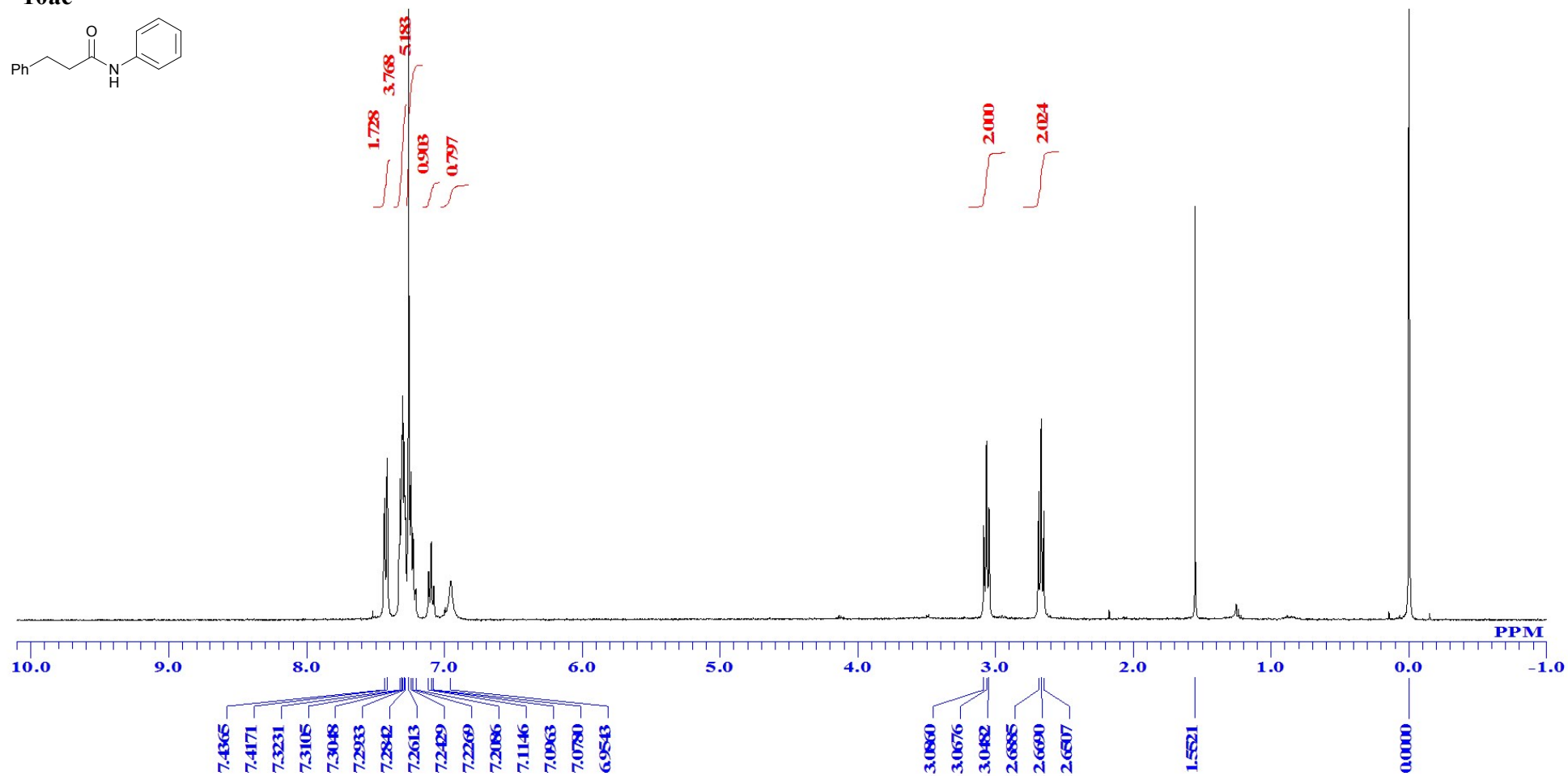
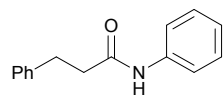
¹H NMR

10dd



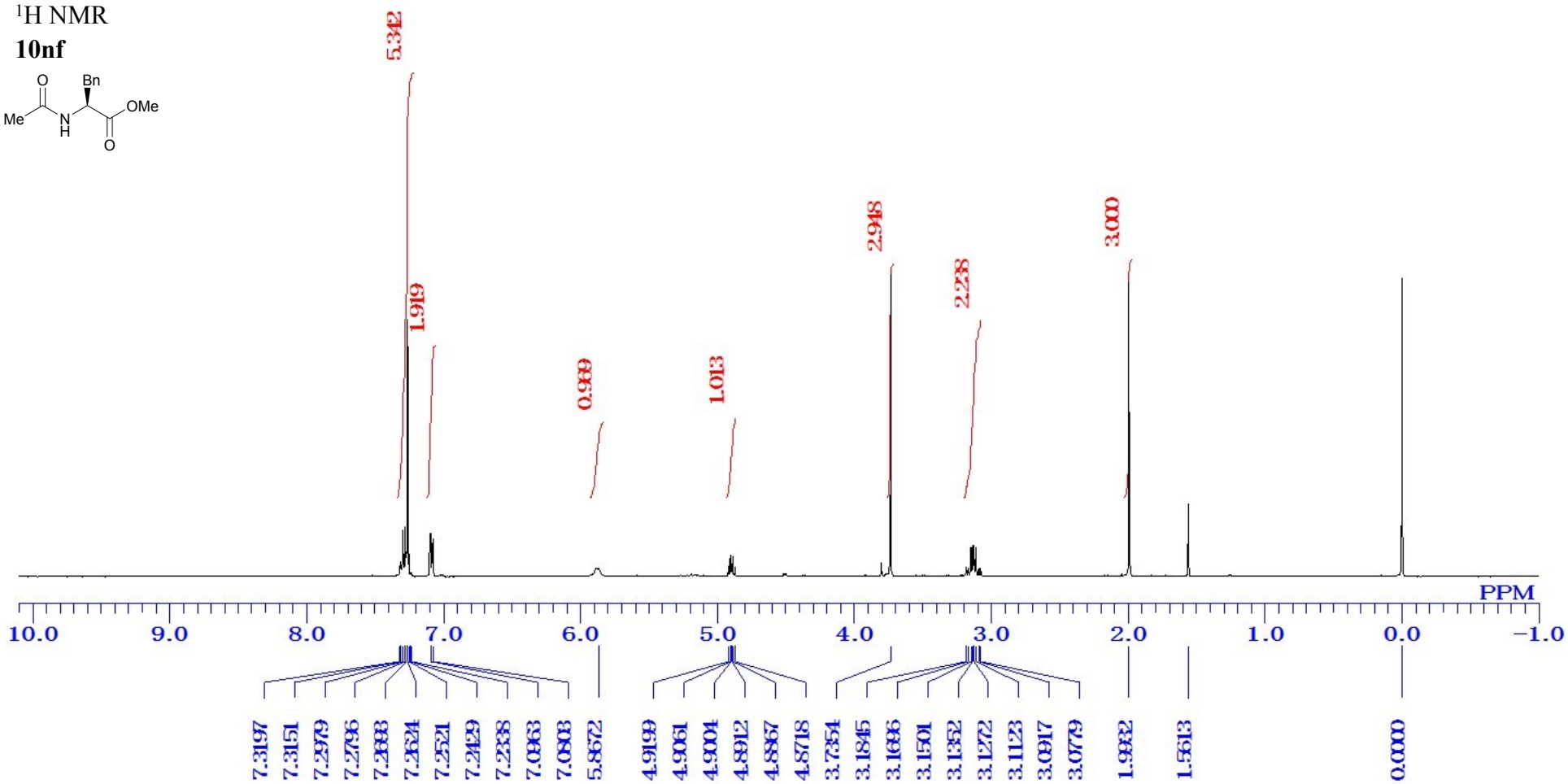
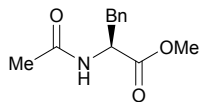
¹H NMR

10ae

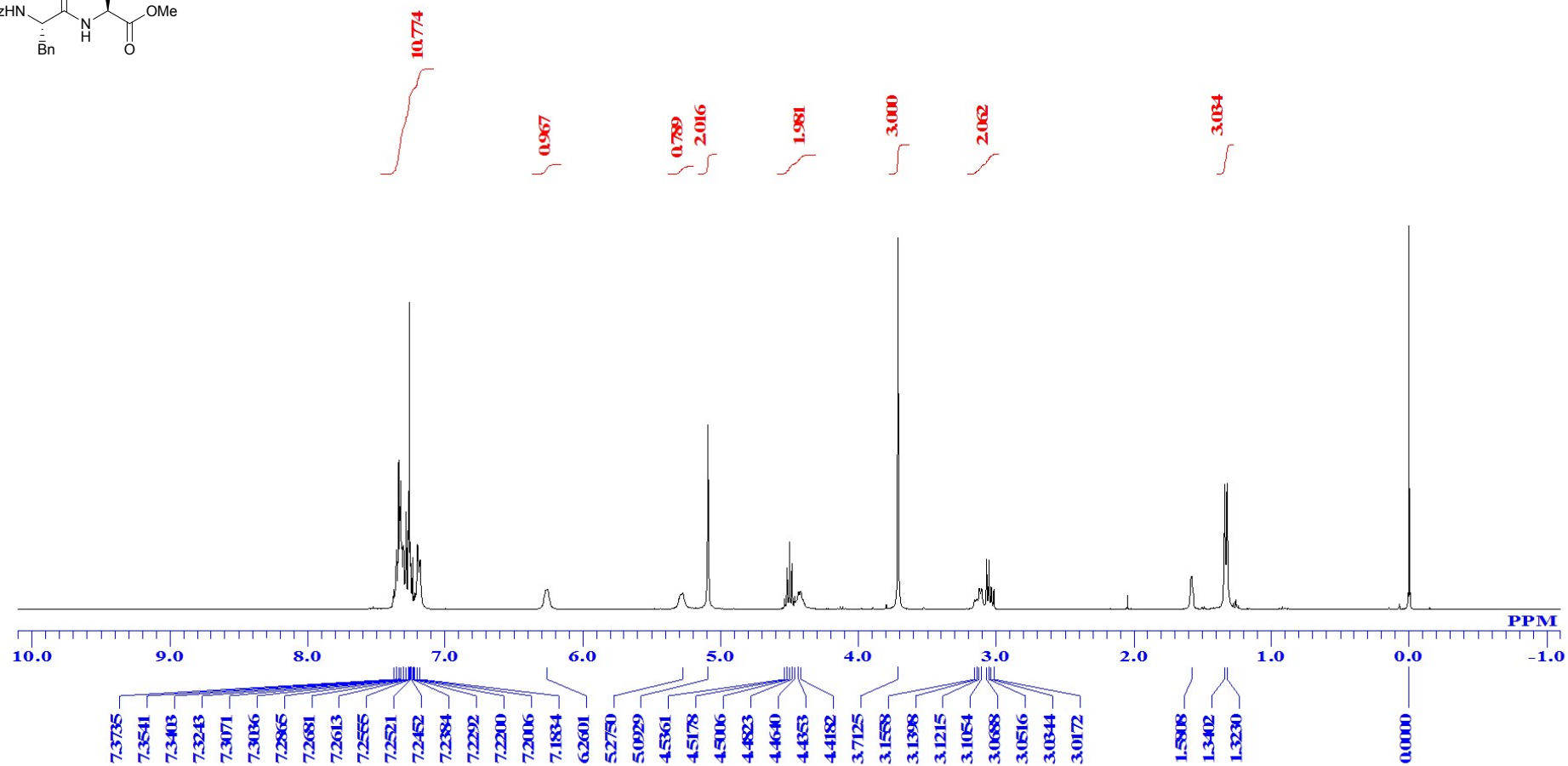
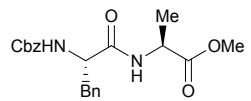


¹H NMR

10nf

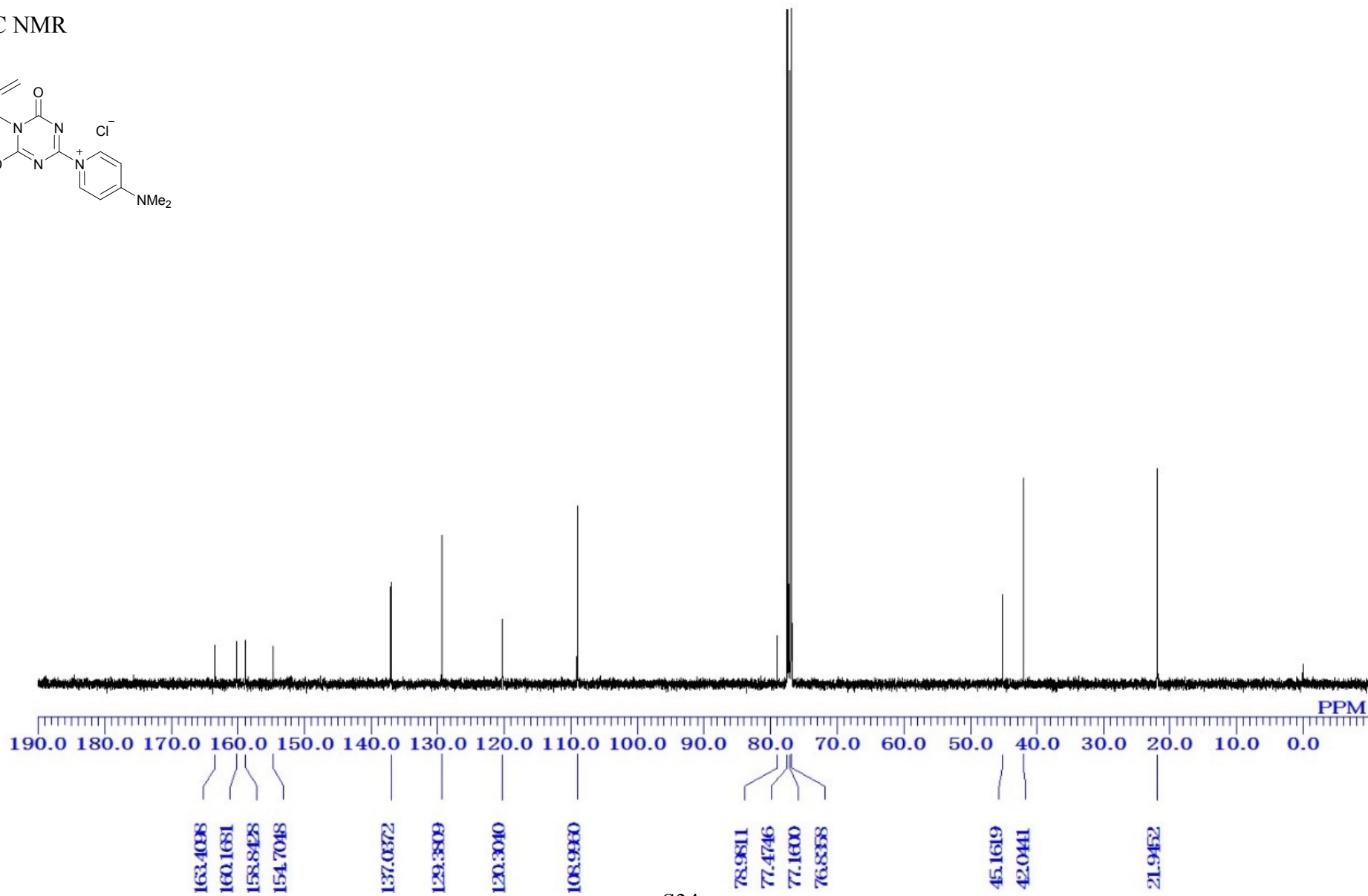
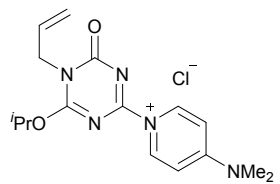


¹H NMR
10eg



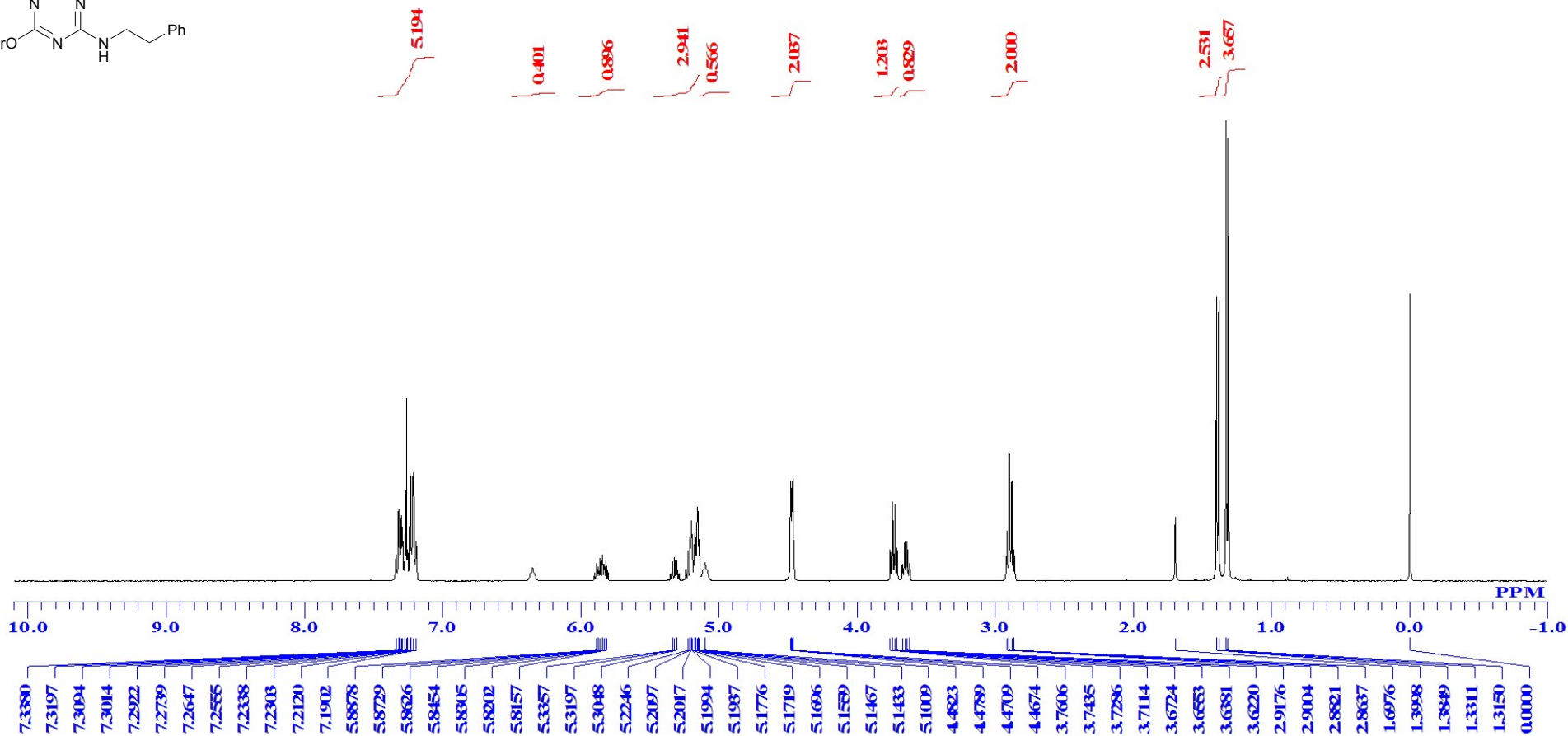
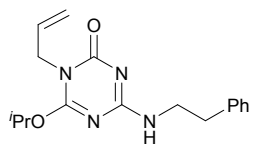
¹³C NMR

12



S34

¹H NMR
13



¹³C NMR

13

