Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supplementary Information

For

Imido-Substituted Triazines as Dehydrative Condensing Reagents for the Chemoselective Formation of Amides in the Presence of Free Hydroxy Groups

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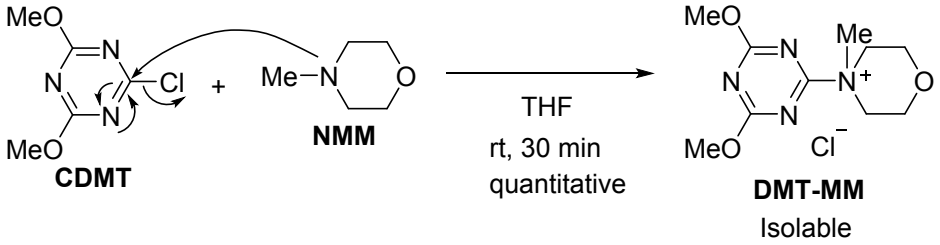
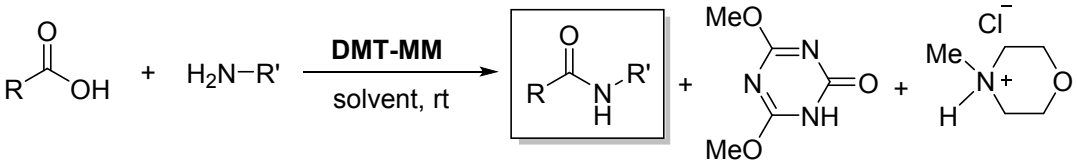
Contents

1. The Detailed Reaction Mechanism

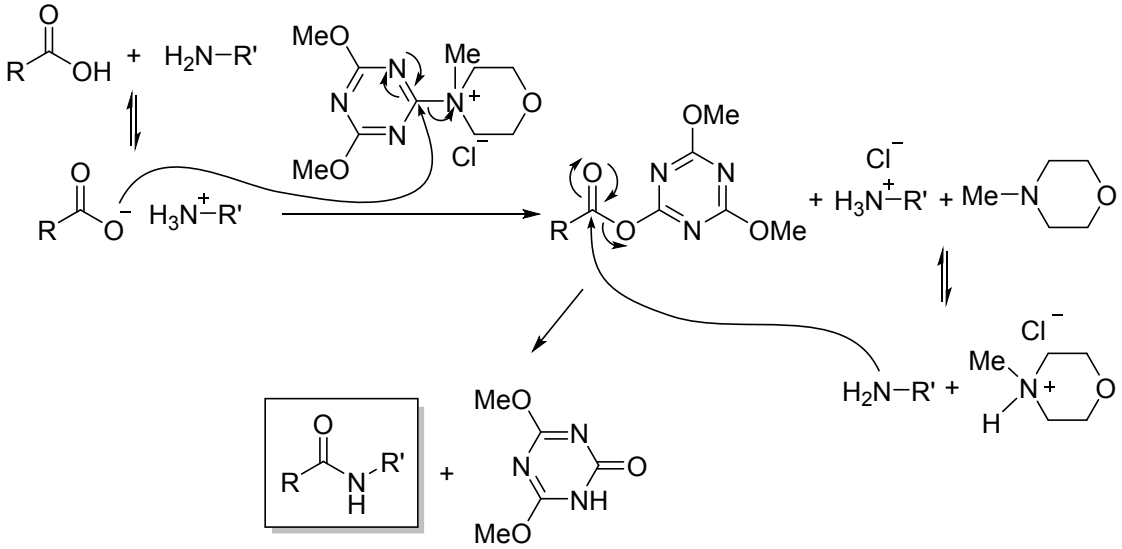
Formation of DMT-MM



A General Scheme for the Amide-Forming Reactions using DMT-MM

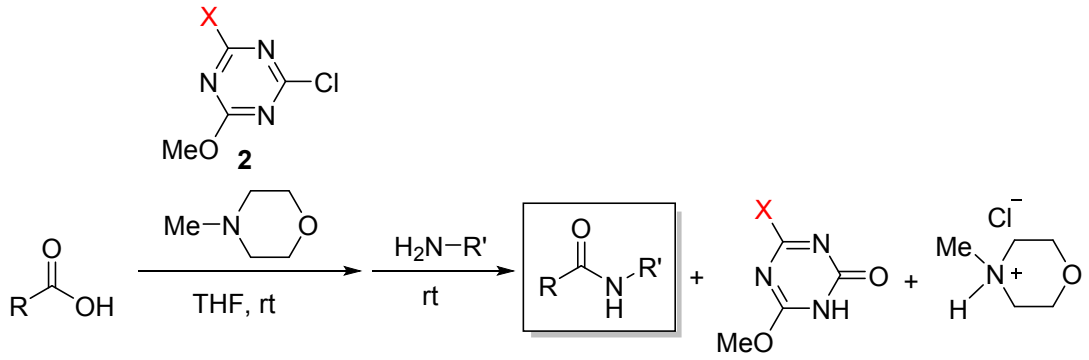


A Reaction Mechanism



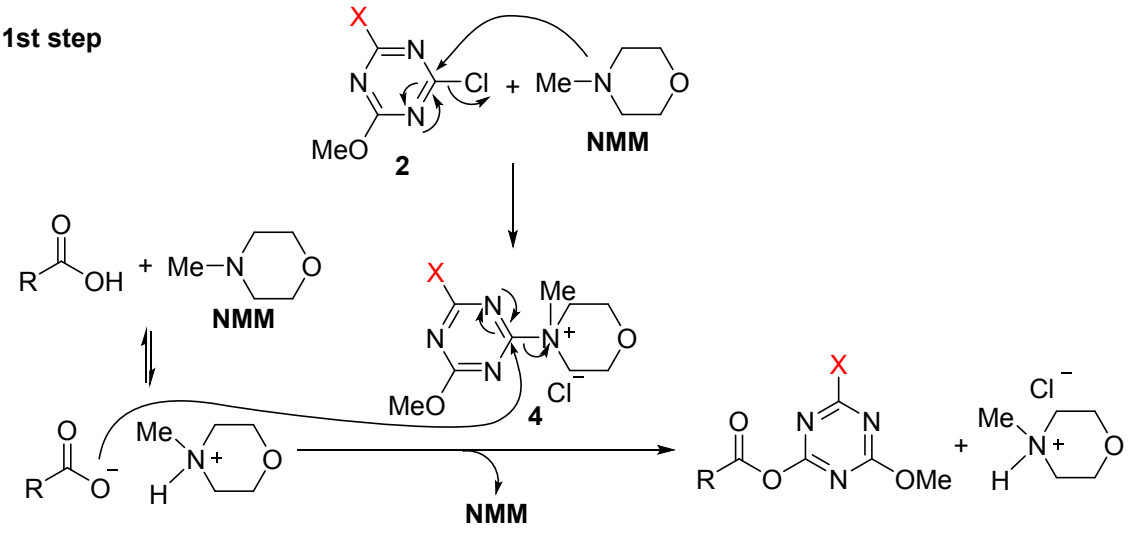
When the imido-substituted chlorotriazine **2** was used, the corresponding **4** was not isolated and was generated in situ.

A General Scheme for the Amide-Forming Reactions using chlorotriazine (2)

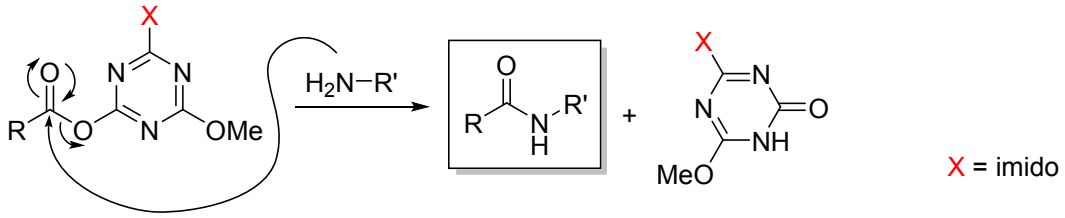


A Reaction Mechanism

1st step



2nd step

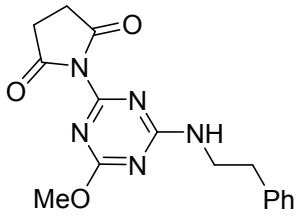


2. General Methods

Nuclear magnetic resonance [^{1}H NMR (400 or 600 MHz) and ^{13}C NMR (100 or 150 MHz)] spectra were determined on JEOL JNM-ECS400 and JEOL JNM-ECA600 spectrometers. Chemical shifts for ^{1}H NMR are reported as δ values relative to TMS as an internal standard. Coupling constants for ^{1}H NMR are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR were reported as δ values relative to the center line of a triplet at 77.16 ppm for deuterochloroform. Mass spectra were measured on a JEOL JMS-T100TD spectrometer (DART- and ESI-MS). Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Flash chromatography separation was performed on Kanto Chemical silica gel 60 N (spherical, neutral, 40–100 mesh) unless otherwise noted. Reagents were of commercial grade and were used without any purification unless otherwise noted. Dehydrated THF and toluene were purchased from commercial sources. All reactions that are sensitive to oxygen or moisture were conducted under a N_2 atmosphere.

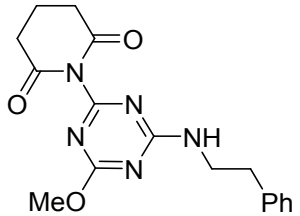
3. Experimental Procedure and Characterization Data for Products

2-Methoxy-4-phenethylamino-6-succinimido-1,3,5-triazine (8A)



To a CH_2Cl_2 solution (2 mL) of **2A** (97 mg, 0.40 mmol), phenethylamine (126 μL, 1.0 mmol) was added under a N_2 atmosphere at ambient temperature. After stirring for 20 min, the reaction mixture was quenched with 1 M $KHSO_4$ (4 mL), and the mixture was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified using preparative TLC (AcOEt) to afford the title compound (86 mg, 66% yield) as a white solid. Mp 57–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.20 (m, 5H), 5.82 (br s, 0.67H), 5.72 (br s, 0.33H), 4.01 (s, 2.01H), 3.92 (s, 0.99H), 3.74 (q, J = 6.9 Hz, 2.01H), 3.70 (q, J = 6.8 Hz, 0.99H), 2.91 (t, J = 6.9 Hz, 2.01H), 2.91 (t, J = 6.8 Hz, 0.99H), 2.89 (s, 1.32H), 2.85 (s, 2.68H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.49 (major), 174.34 (minor), 172.55 (major), 171.91 (minor), 168.15 (minor), 167.99 (major), 162.65 (minor), 162.09 (major), 138.43 (minor), 138.27 (major), 128.83 (major or minor), 128.80 (major or minor), 128.77 (major), 128.73 (minor), 126.78 (major), 126.67 (minor), 55.18 (major), 55.09 (minor), 42.44 (major and minor), 35.31 (minor), 35.21 (major), 28.93 (minor), 28.89 (major); IR (KBr): 3440, 3039, 3018, 1730, 1591, 1541, 1481, 1396, 1254, 1049, 928, 1487, 1452, 1435, 1346, 1327, 1306, 1282 cm^{-1}; HRMS (DART) m/z: $[M + H]^+$ Calcd for $C_{16}H_{18}N_5O_3$ 328.1410; Found: 328.1394.

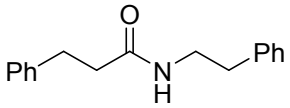
2-Glutarimido-4-methoxy-6-phenethylamino-1,3,5-triazine (8D)



To a CH_3CN (1 mL) solution of **2D** (26 mg, 0.10 mmol), phenethylamine (25 μL, 0.2 mmol) was added under a N_2 atmosphere at ambient temperature. After stirring for 10 min, the reaction mixture was concentrated *in vacuo*. The residue was purified using preparative TLC (AcOEt) to afford the title compound (30 mg, 88% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (t, J = 7.6 Hz, 2H), 7.25–7.19 (m, 3H), 5.70 (br s, 0.7H), 5.65 (br s, 0.3H), 4.00 (s,

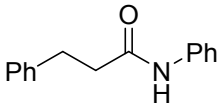
2.1H), 3.90 (s, 0.9H), 3.74 (q, *J* = 6.8 Hz, 1.4H), 3.69 (q, *J* = 6.6 Hz, 0.6H), 2.91 (t, *J* = 7.2 Hz, 1.4H), 2.88 (t, *J* = 6.9 Hz, 0.6H), 2.76 (t, *J* = 6.5 Hz, 1.2H), 2.72 (t, *J* = 6.5 Hz, 2.8H), 2.08 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.92 (major), 172.20 (minor), 171.39 (major), 171.37 (minor), 168.50 (minor), 168.24 (major), 165.90 (minor), 165.28 (major), 138.45 (minor), 138.25 (major), 128.88 (major), 128.86 (minor), 128.83 (major), 128.80 (minor), 126.85 (major), 126.73 (minor), 55.21 (major), 55.08 (minor), 42.44 (major), 42.35 (minor), 35.33 (minor), 35.28 (major), 32.47 (minor), 32.41 (major), 17.22 (minor), 17.18 (major); IR (KBr): 3356, 3026, 2960, 2939, 1741, 1695, 1589, 1539, 1479, 1350, 1319, 1255, 1178, 1140, 1007, 920, 816, 752, 702, 588, 555, 498, 444 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}N_5NaO_3$ 364.1386; Found: 364.1366.

_N_-Phenethyl-3-phenylpropanamide (7a) [1]



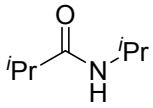
The title compound (83 mg, 83% yield) was obtained by flash column chromatography (hexane/AcOEt = 7 : 3 to pure AcOEt) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27–7.16 (m, 8H), 7.07 (d, *J* = 7.2 Hz, 2H), 5.58 (br s, 1H), 3.45 (q, *J* = 6.6 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.40 (t, *J* = 7.7 Hz, 2H).

_N_,3-Diphenylpropanamide (7b) [2,3]



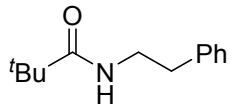
The title compound (81 mg, 90% yield) was obtained by flash column chromatography (hexane/AcOEt = 8 : 2 to 7 : 3) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.25–7.13 (m, 6H), 7.05 (t, *J* = 7.3 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H).

_N_-Isopropylisobutyramide (7d) [4]



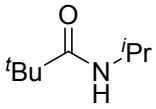
The title compound (36 mg, 69% yield) was obtained by column chromatography (hexane/AcOEt = 9 : 1 to 7 : 3) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41 (br s, 1H), 4.11–4.03 (m, 1H), 2.30 (sep, *J* = 6.9 Hz, 1H), 1.15 (d, *J* = 2.3 Hz, 6H), 1.13 (d, *J* = 2.3 Hz, 6H).

_N_-Phenethylpivalamide (7e)[5]



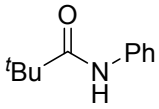
The title compound (52 mg, 63% yield) was obtained by flash column chromatography (hexane/AcOEt = 8 : 2 to 6 : 4) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 6.9 Hz, 2H), 5.71 (br s, 1H), 3.49 (q, J = 6.4 Hz, 2H), 2.81 (t, J = 6.9 Hz, 2H), 1.14 (s, 9H).

_N_-Isopropylpivalamide (7f)[6]



The title compound (43 mg, 75% yield) was obtained by flash column chromatography (hexane/AcOEt = 9 : 1 to 7 : 3) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (br s, 1H), 4.12–4.00 (m, 1H), 1.18 (s, 9H), 1.14 (d, J = 6.4 Hz, 6H).

_N_-Phenylpivalamide (7g)[7]

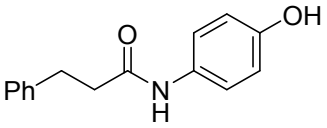


The title compound (43 mg, 60% yield) was obtained by flash column chromatography (hexane/AcOEt = 9 : 1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.8 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 1.32 (s, 9H).

Boc-Leu-Phe-OMe (7i)[8]

The title compound (141 mg, 90% yield) was obtained by flash column chromatography (hexane/AcOEt = 8 : 2 to 7 : 3) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 6.68 (br d, J = 6.2 Hz, 1H), 5.00 (br d, J = 6.5 Hz, 1H), 4.86–4.82 (m, 1H), 4.12 (br s, 1H), 3.69 (s, 3H), 3.14 (dd, J = 13.7, 5.8 Hz, 1H), 3.07 (dd, J = 13.7, 5.8 Hz, 1H), 1.66–1.60 (m, 2H), 1.43 (s, 9H), 1.41–1.39 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H).

_N_-(4-Hydroxyphenyl)-3-phenylpropanamide (7m)[9]



The title compound (70 mg, 73% yield) was obtained by flash column chromatography (hexane/AcOEt = 99 : 1 to 95 : 5) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.63 (s, 1H), 9.14 (s, 1H), 7.33 (d, J = 9.0 Hz, 2H), 7.30–7.23 (m, 4H), 7.18 (t, J = 6.9 Hz, 1H), 6.67 (d, J = 9.0 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.55 (t, J = 7.8 Hz, 2H).

Boc-Tyr-Gly-O^{t}Bu (7n)[10]

The title compound (113 mg, 71% yield) was obtained by flash column chromatography (hexane/AcOEt = 7 : 3 to 5 : 5) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$ with 5 drops of CD_3OD): δ 7.18 (br s, 1H), 7.02 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 8.2 Hz, 2H), 5.58–5.56 (m, 1H), 4.33–4.32 (m, 1H), 3.90 (dd, J = 18.2, 4.4 Hz, 1H), 3.82 (dd, J = 18.2, 4.6 Hz, 1H), 3.64 (s, 1H), 3.02 (dd, J = 13.5, 5.3 Hz, 1H), 2.87 (dd, J = 13.5, 5.8 Hz, 1H), 1.46 (s, 9H), 1.38 (s, 9H).

4. References

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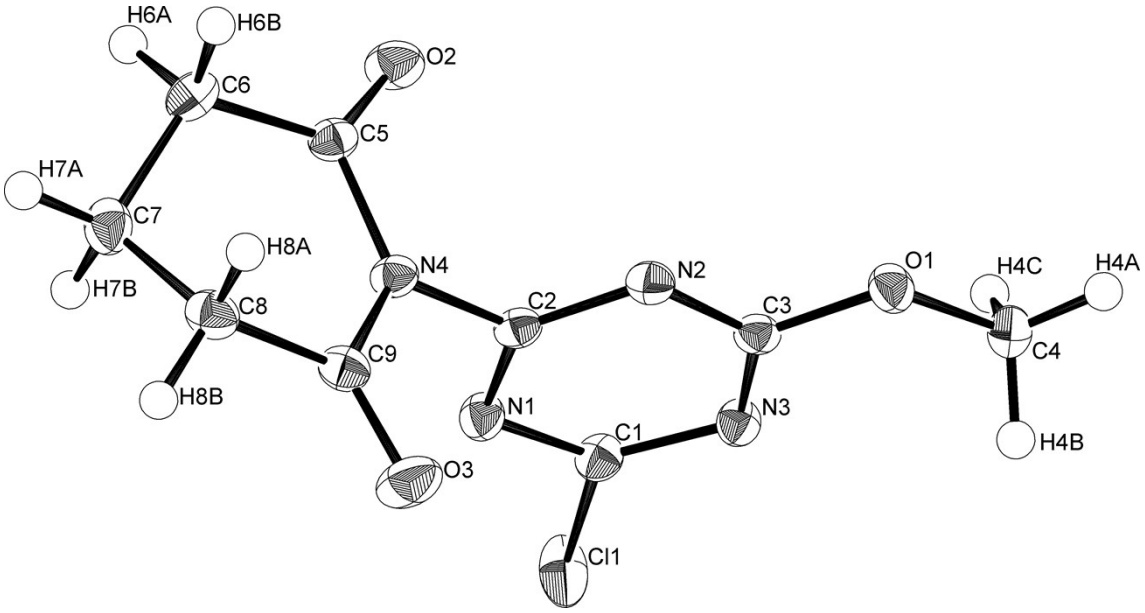
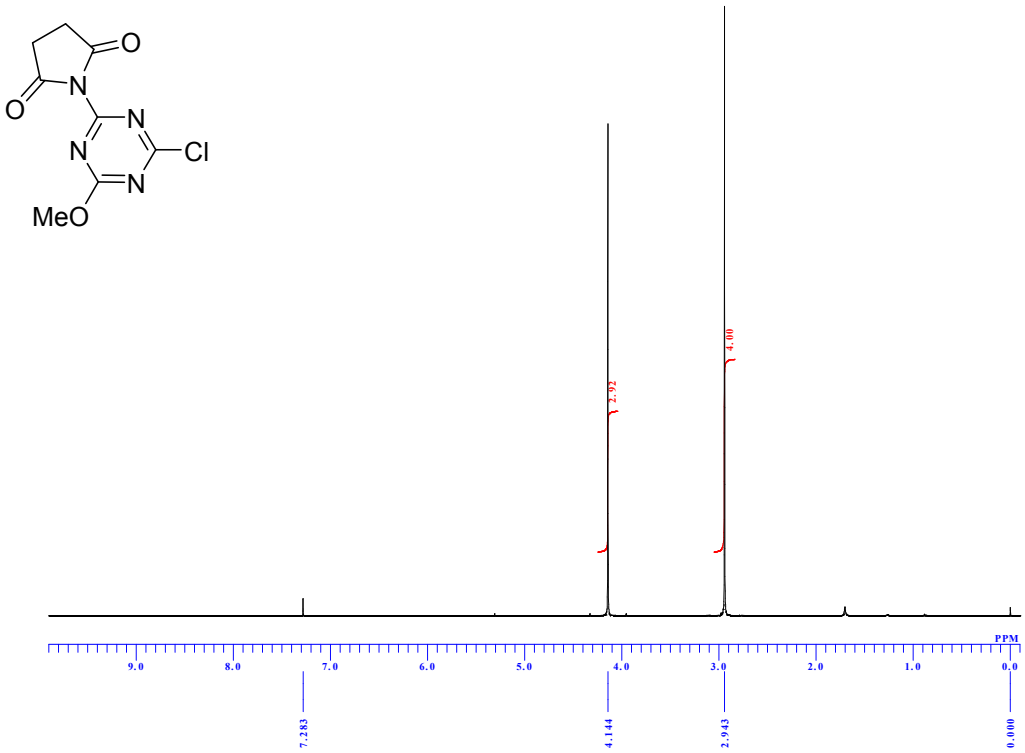
5. X-ray Single Crystal Structure Analysis of Chlorotriazine (2D)

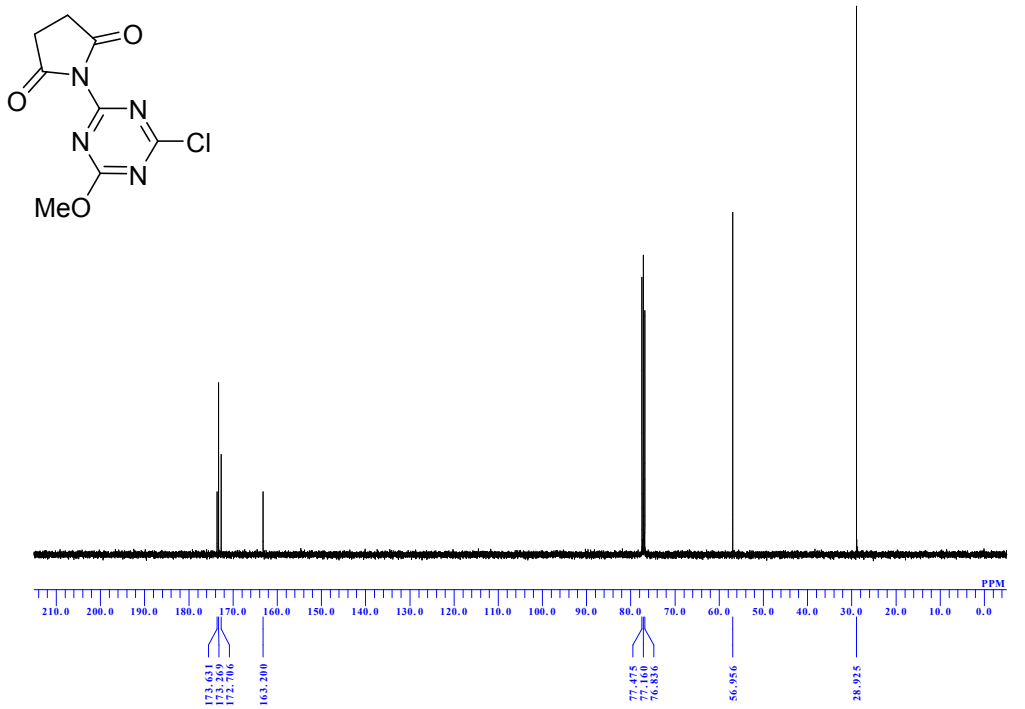


Crystallographic data of **2D** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1834905.

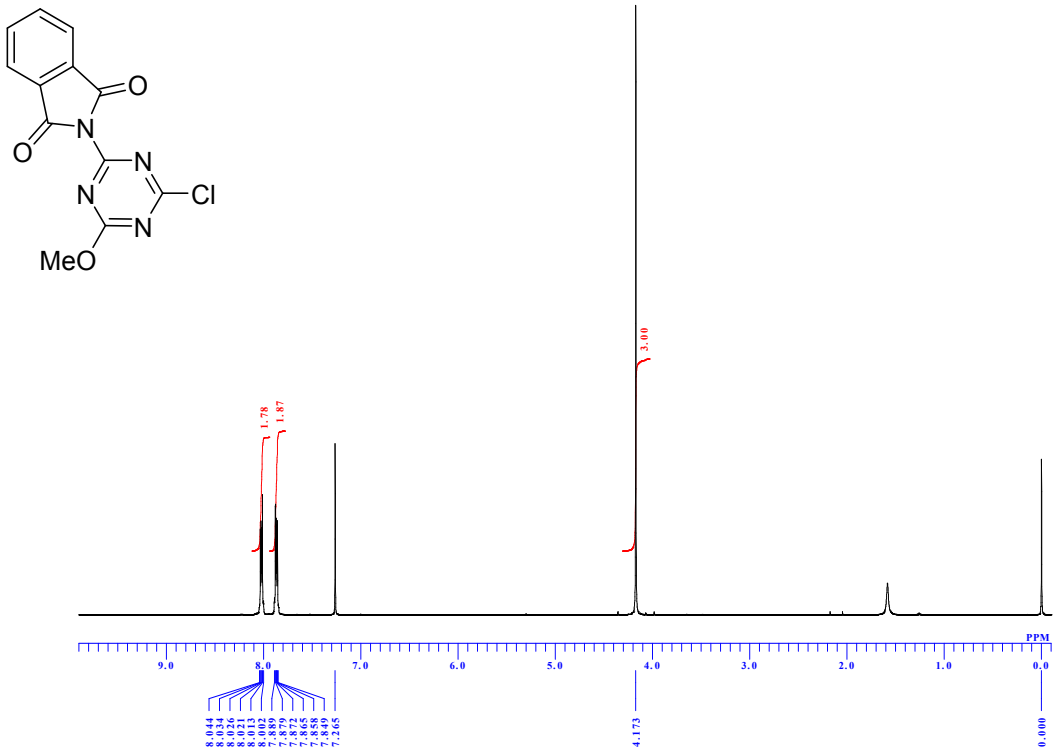
6. ^{1}H and ^{13}C NMR Spectra

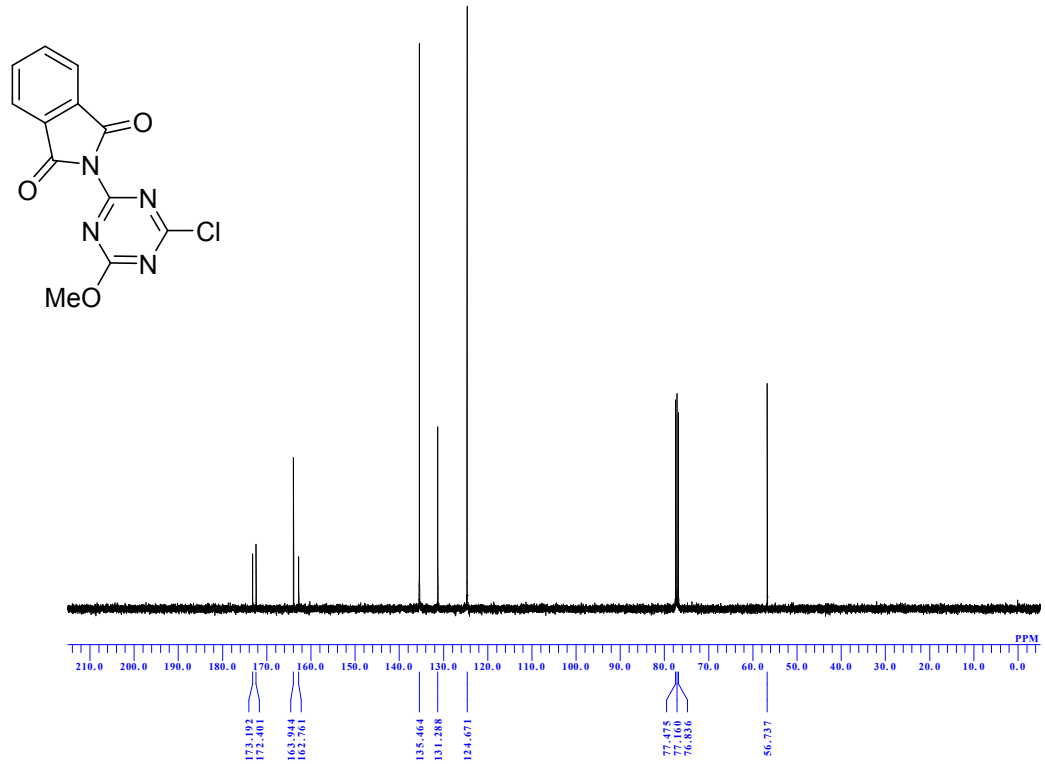
2-Chloro-4-methoxy-6-succinimido-1,3,5-triazine (2A)



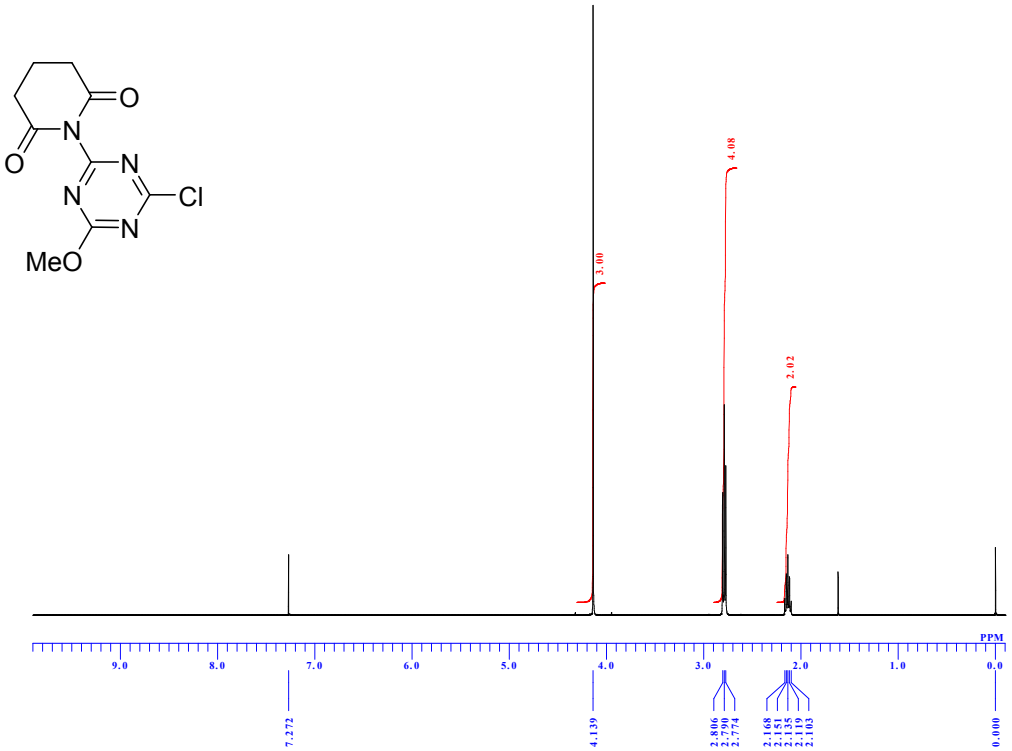


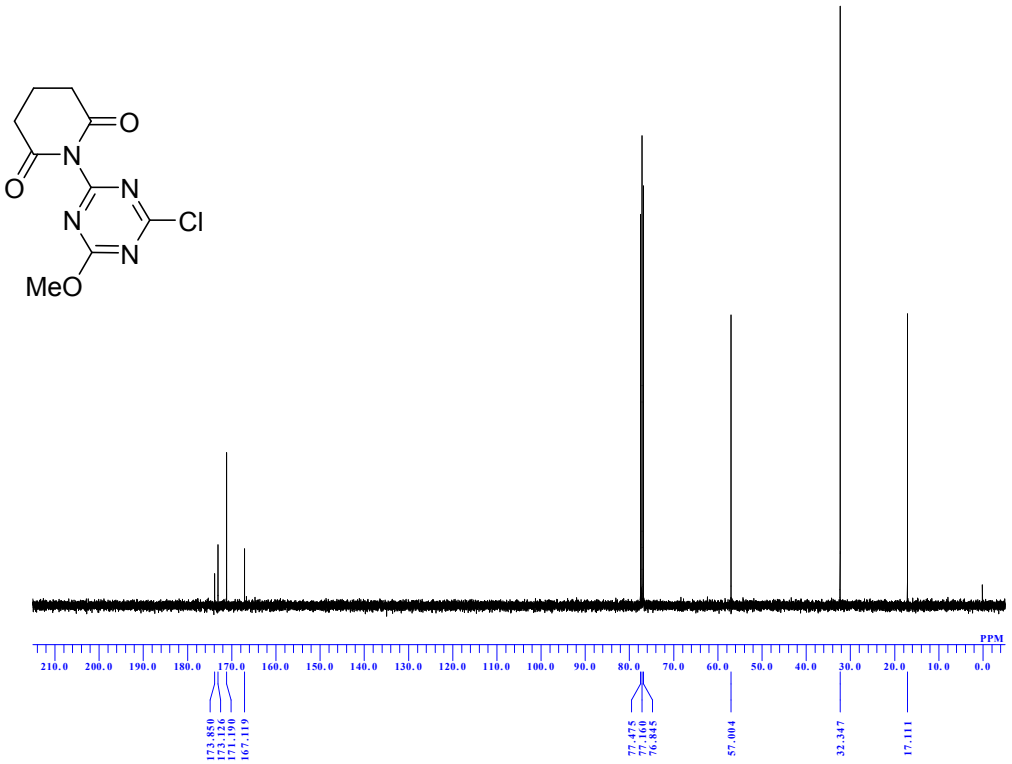
2-Chloro-4-methoxy-6-phthalimido-1,3,5-triazine (2B)



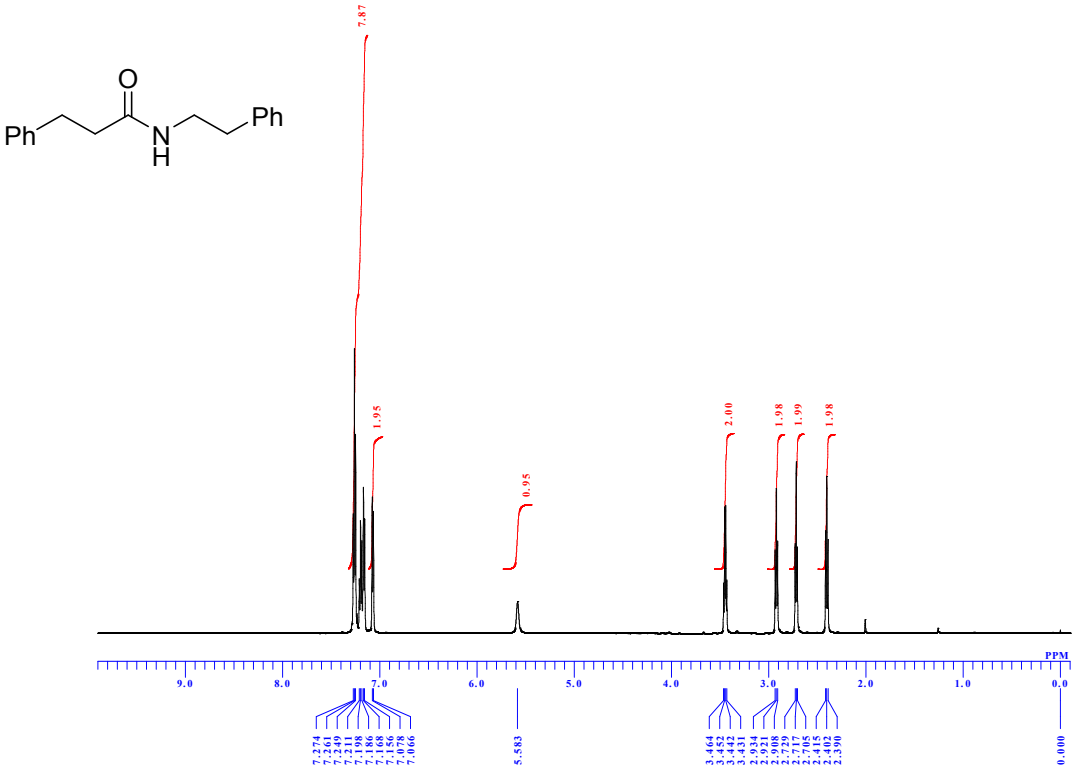


2-Chloro-4-glutarimido-6-methoxy-1,3,5-triazine (2D)

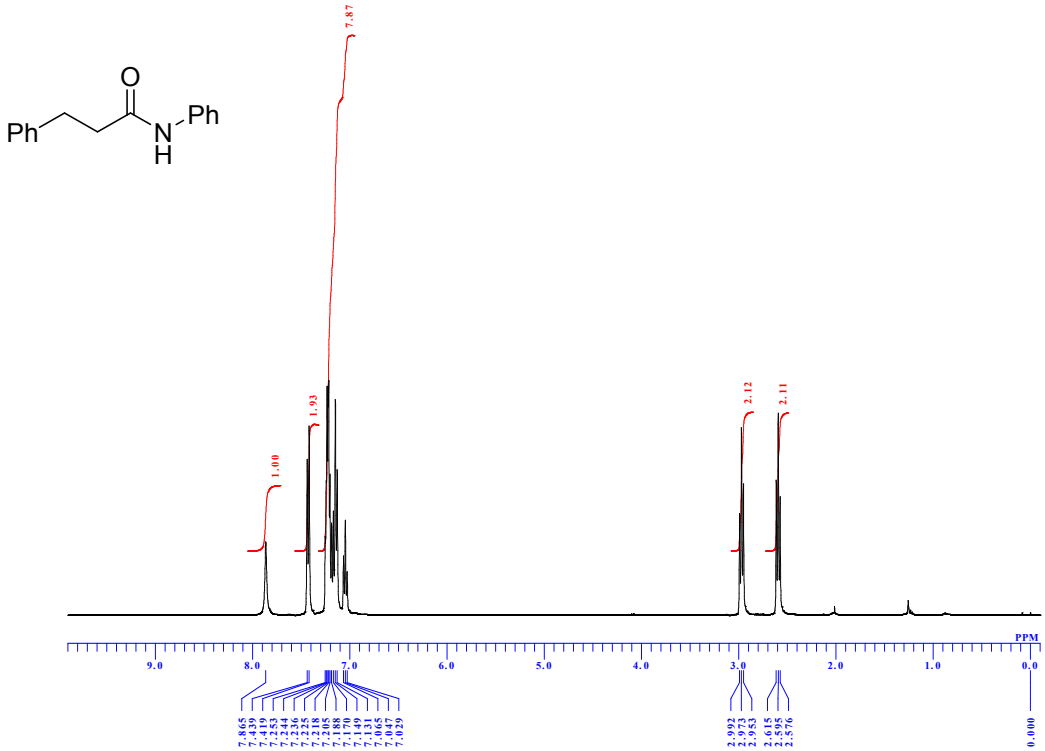




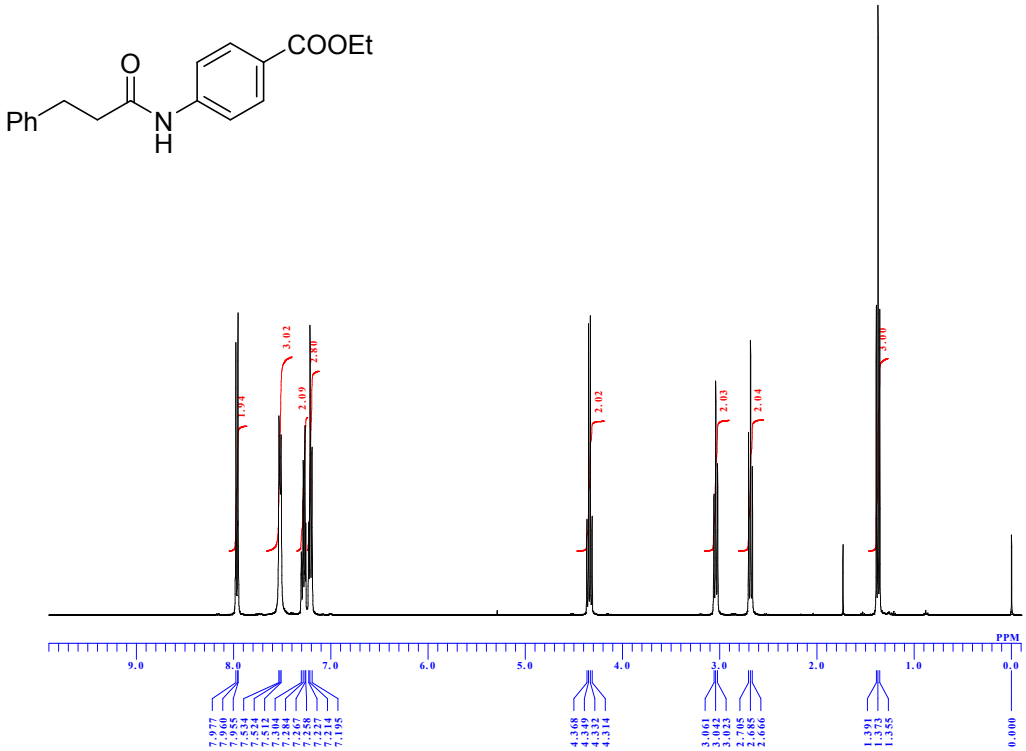
***N*-Phenethyl-3-phenylpropanamide (7a)**

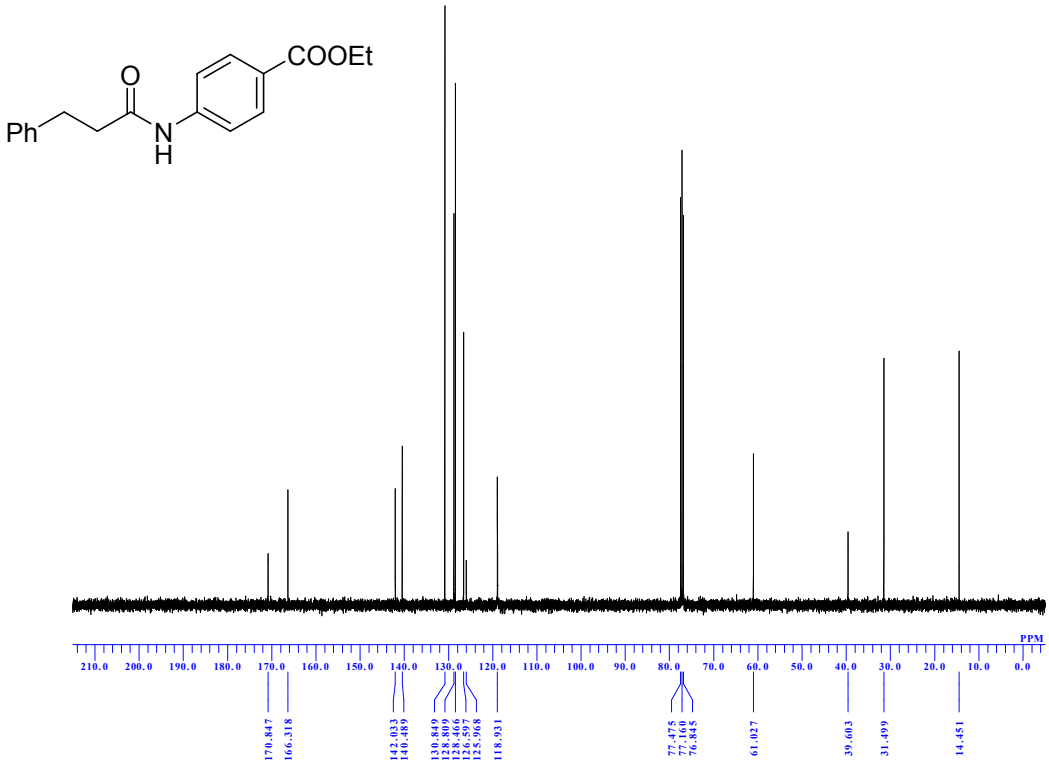


***N*,3-Diphenylpropanamide (7b)**

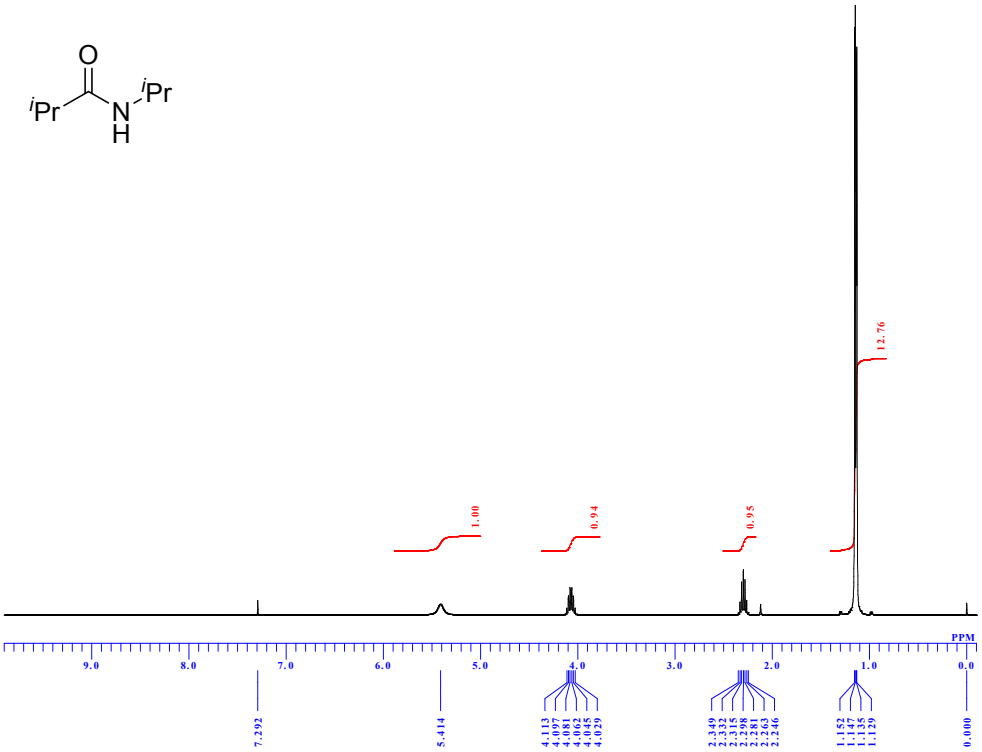


***N*-(4-Ethoxycarbonylphenyl)-3-phneylpropionamide (7c)**

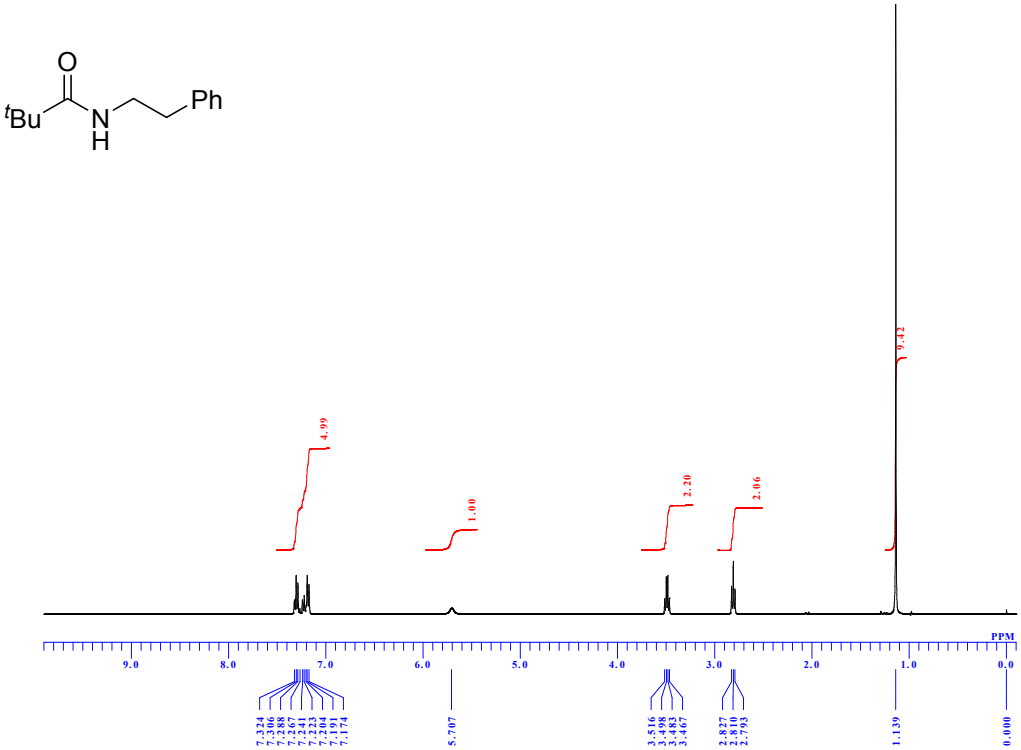




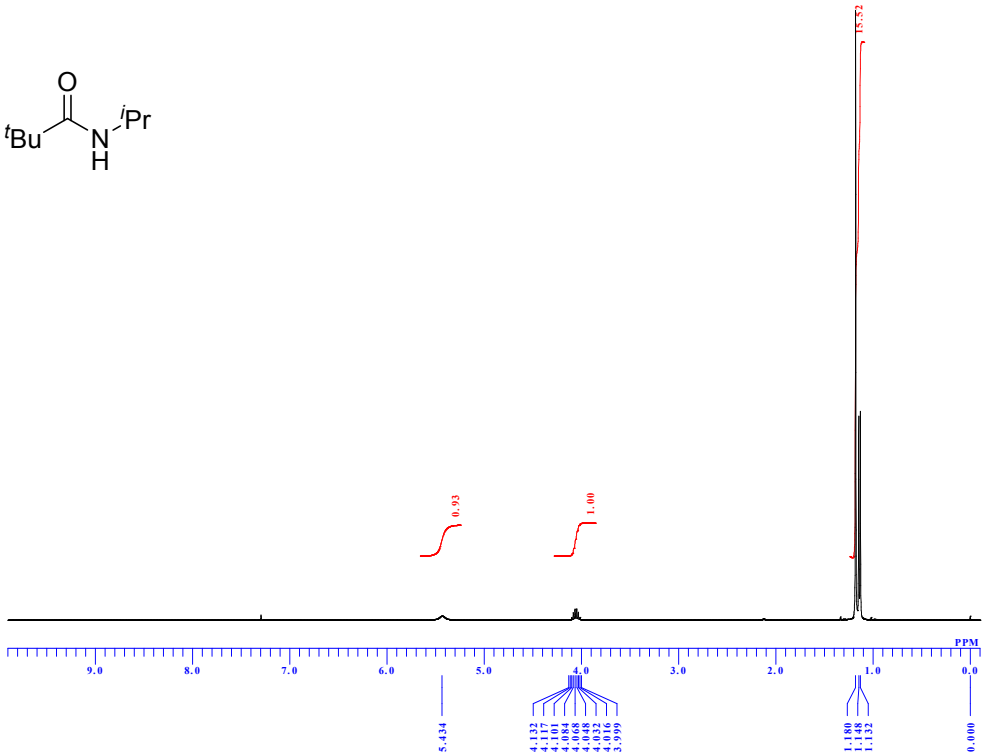
_N_-Isopropylisobutyramide (7d)



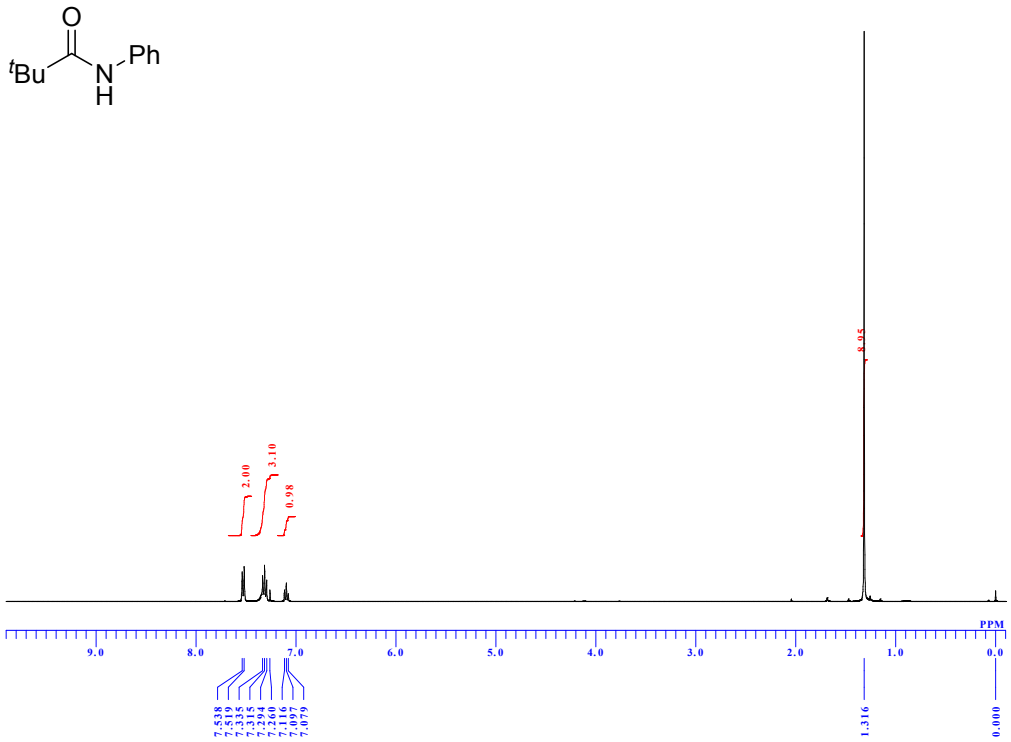
_N_-Phenethylpivalamide (7e)



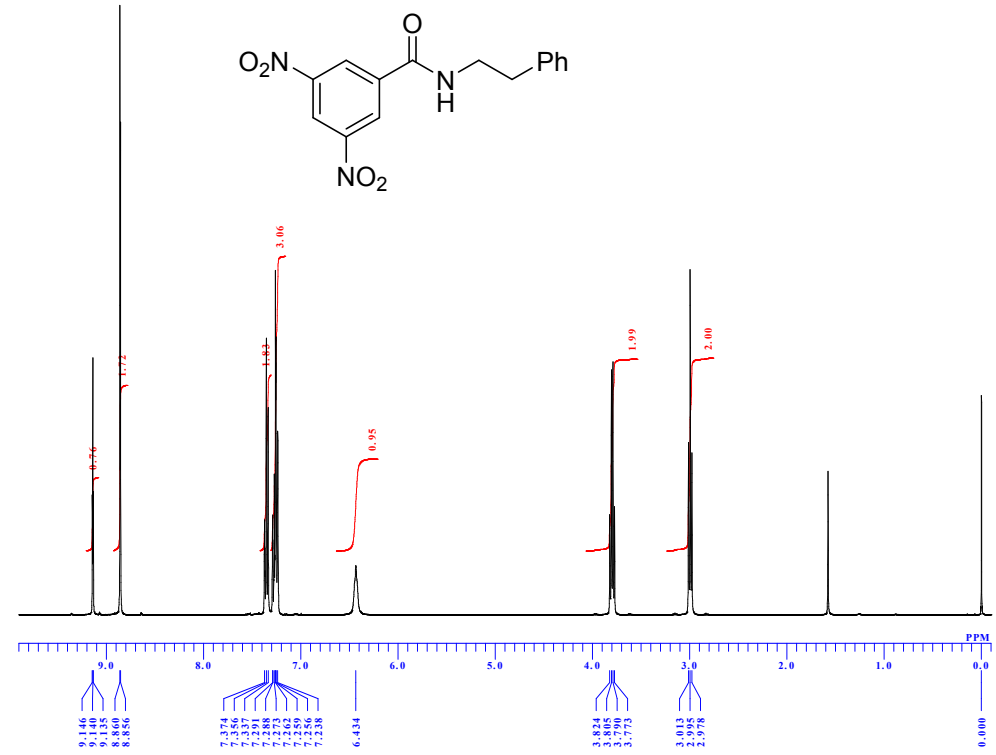
***N*-Isopropylpivalamide (7f)**

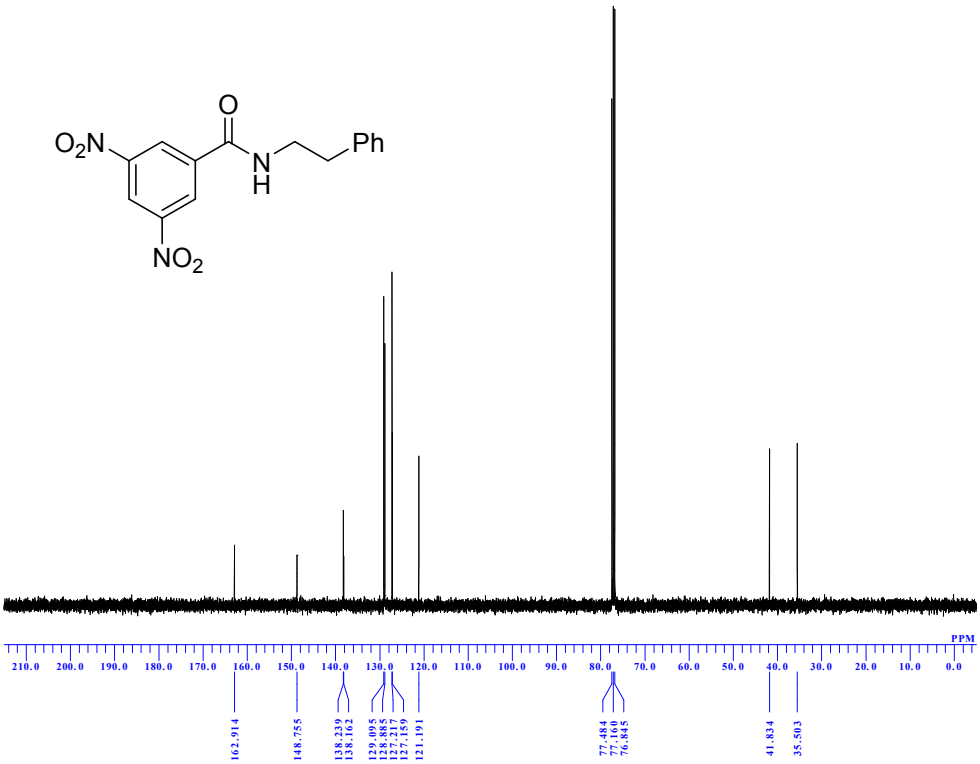


***N*-Phenylpivalamide (7g)**

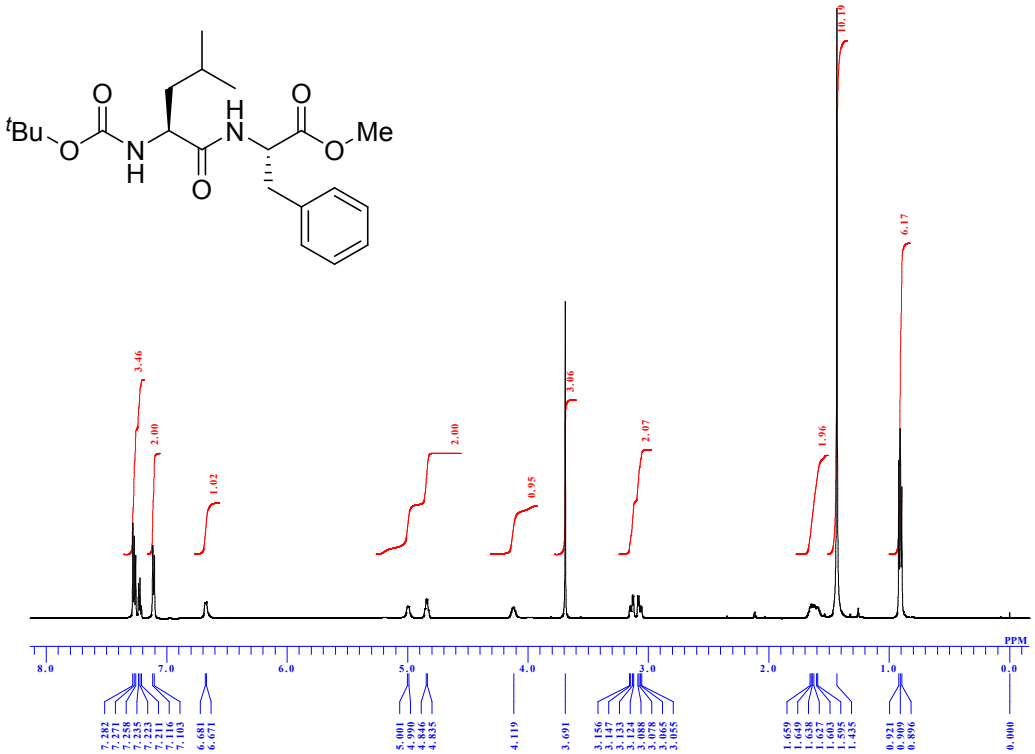


3,5-Dinitro-*N*-(2-phenethyl)benzamide (7h)

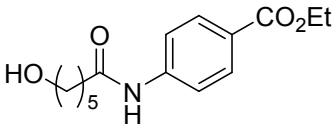


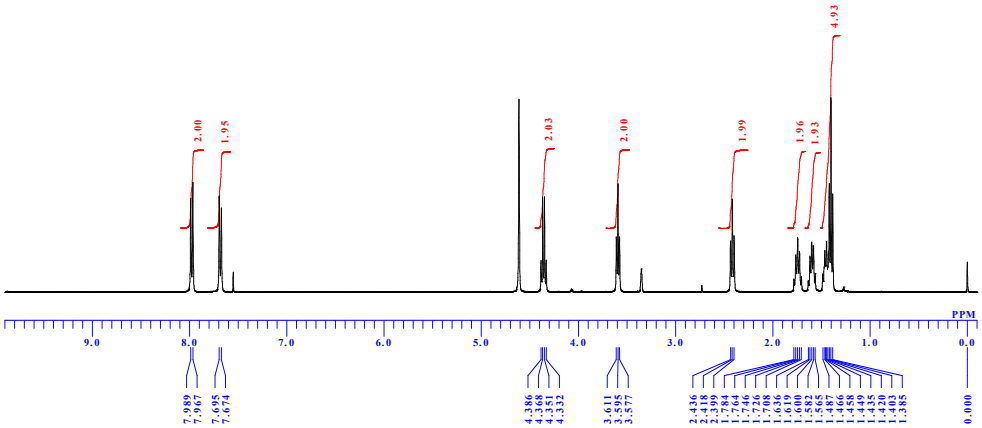


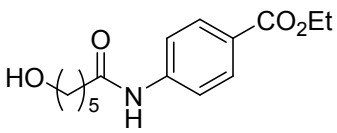
Boc-Leu-Phe-OMe (7i)



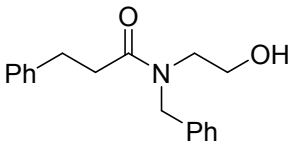
***N*-(4-Ethoxycarbonylphenyl)-6-hydroxyhexanamide (7j)**

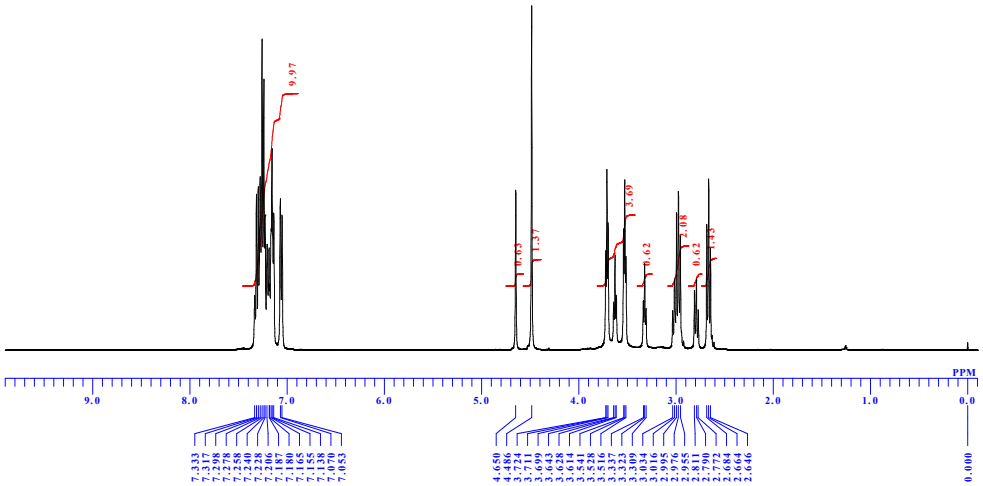


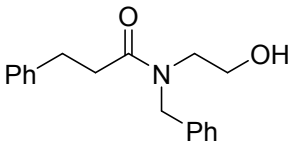




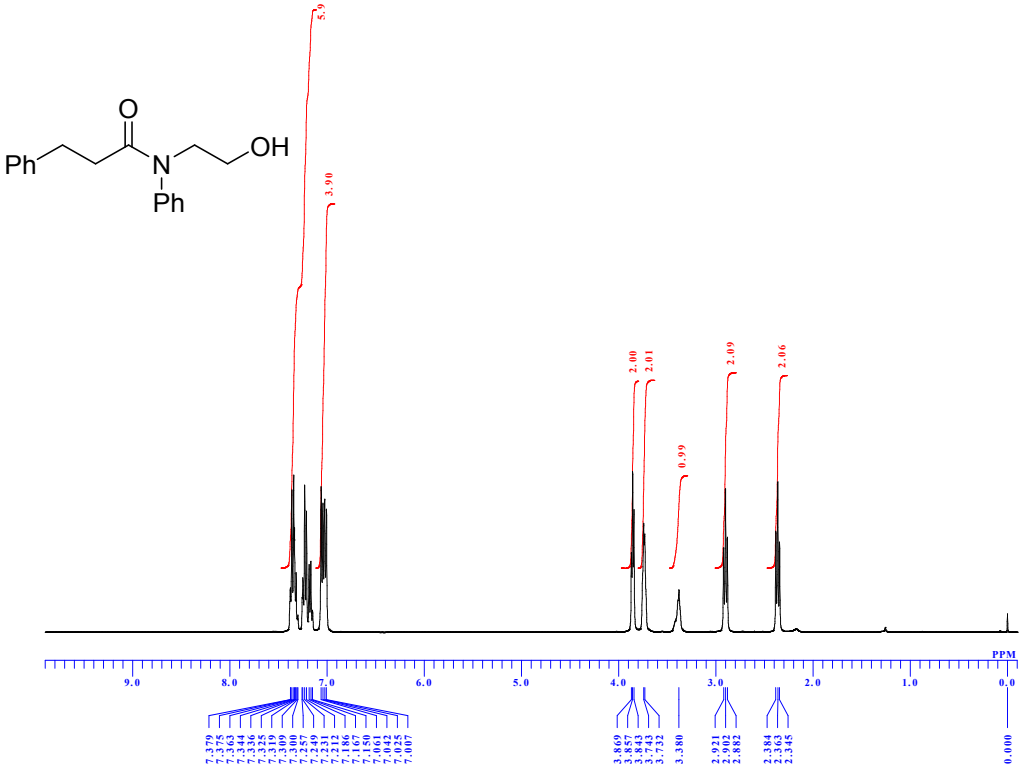
***N*-Benzyl-*N*-(2-hydroxyethyl)-3-phenylpropanamide (7k)**

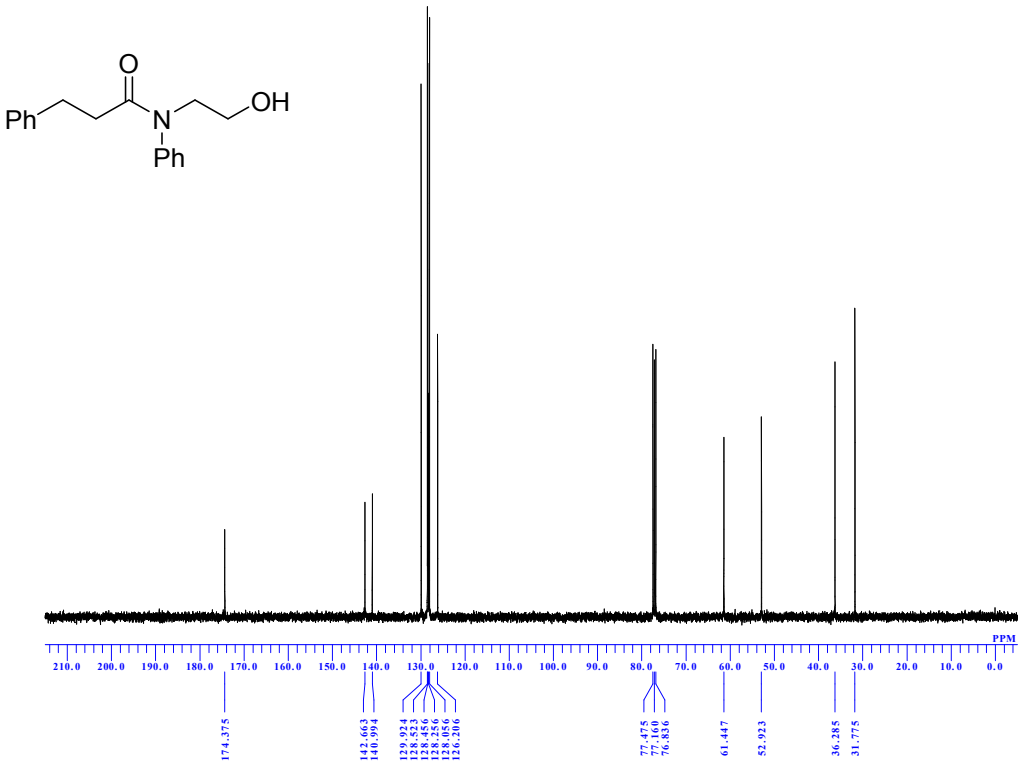




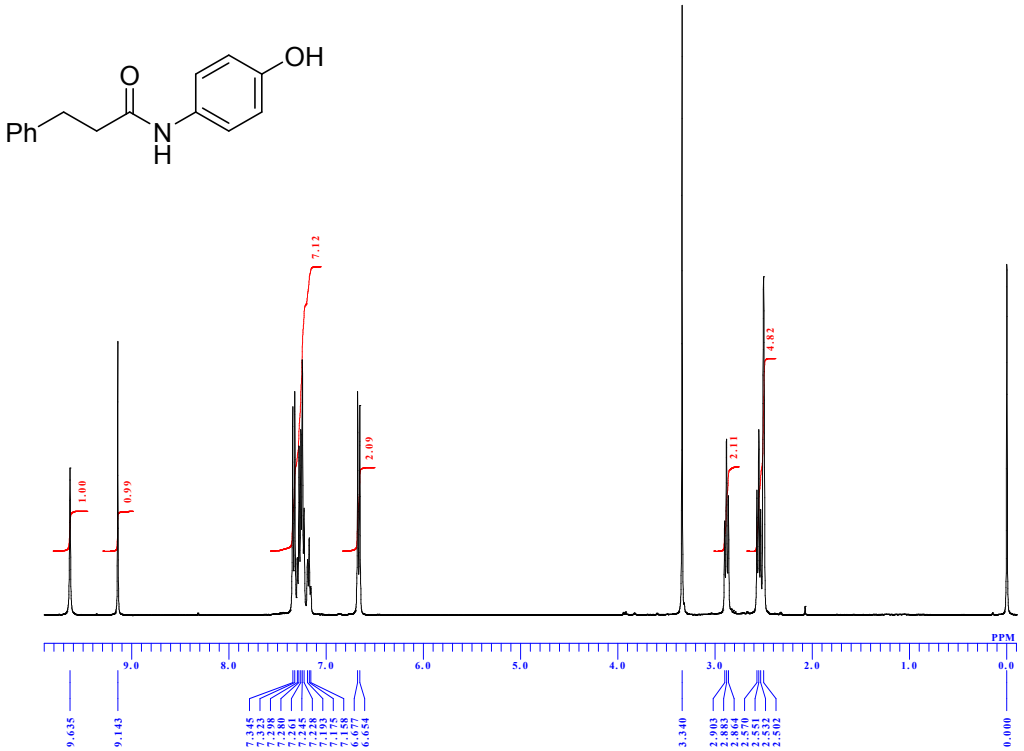


***N*-(2-Hydroxyethyl)-*N*-phenyl-3-phenylpropanamide (7l)**

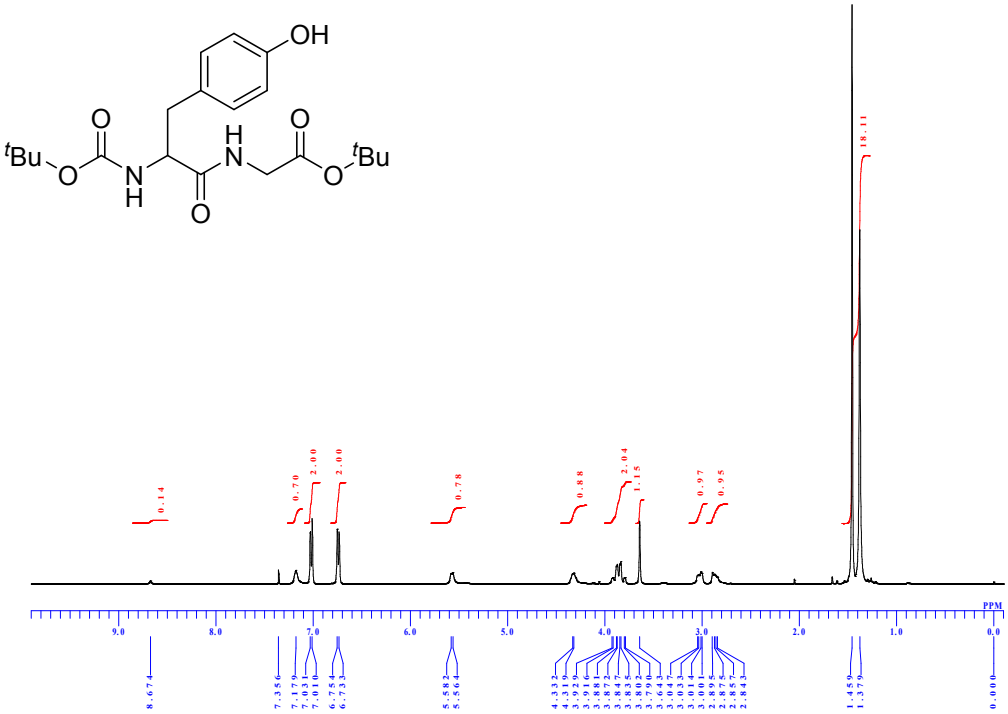




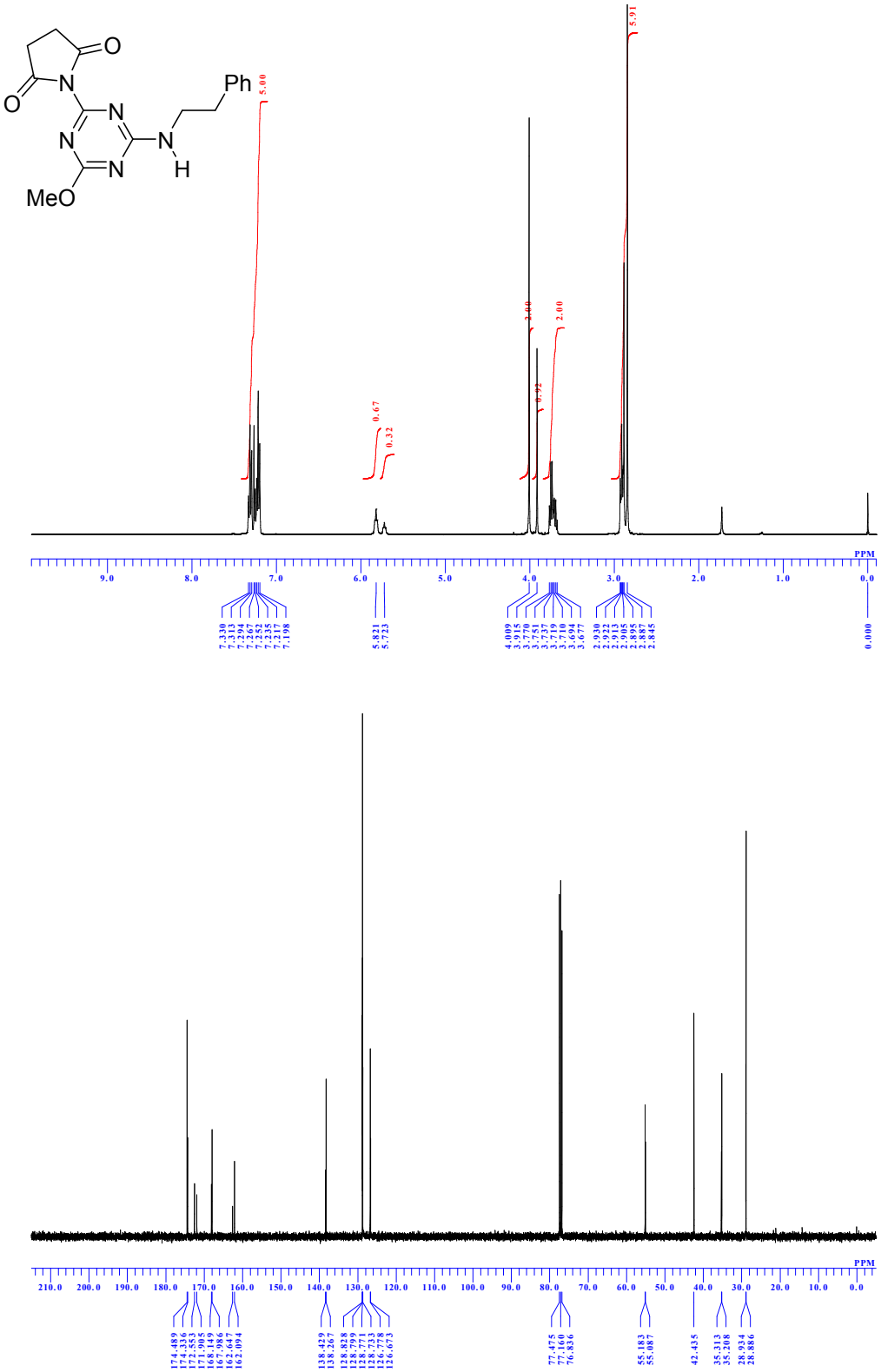
***N*-(4-Hydroxyphenyl)-3-phenylpropanamide (7m)**



Boc-Tyr-Gly-O^{t}Bu (7n)



2-Methoxy-4-phenethylamino-6-succinimido-1,3,5-triazine (8A)



2-Glutarimido-4-methoxy-6-phenethylamino-1,3,5-triazine (8D)