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Direct, facile synthesis of *N*-acyl-α-amino amides from α-keto esters and ammonia

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EXPERIMENTAL PROCEDURES, OPTIMIZATION STUDIES, CHARACTERIZATION DATA and NMR SPECTRA

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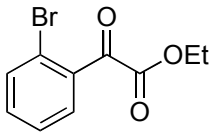
General Information. Ethyl benzoyl formate (**1a**), ethyl pyruvate (**1l**) and ethyl 3-methyl-2-oxobutyrate (**1m**) were purchased from Aldrich. α-Keto esters **1b**, **1c**, **1e**, **1g** and **1h** were prepared as previously described.[1] α-Keto esters **1n** was synthesized from phenyl pyruvic acid as previously described.[2] α-Keto esters **1d**, **1f**, **1i-k** were prepared according to the procedure developed by Shimizu and Murakami.[1] All other reagents were used as received (Aldrich, Acros). MeOH was dried over magnesium methoxide and distilled prior to use. Melting points are uncorrected, and were measured on a Fisher-Johns melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz respectively on a Bruker Spectrospin 300 or 500 MHz spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in $(CD_3)_2SO$ or CD_3OD (δ 2.50 and 3.31 respectively). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $(CD_3)_2SO$ or CD_3OD (δ 39.52 and 49.00 respectively). Infrared spectra were obtained on a Bruker VECTOR22 FT-IR spectrometer.

I. Preparation of α-keto esters

α-Keto esters **1d**, **1f**, **1i-k** were prepared by exactly following the procedure developed by Shimizu and Murakami:[1]
A solution of the aryl boronic acid (0.60 mmol, 1.2 equiv), H_3BO_2 (1.00 mmol, 2.0 equiv), $[Rh(OH)(cod)]_2$ (0.0125 mmol, 2.5 mol%) and ethyl cyanoformate (0.5 mmol, 1.0 equiv) in 1,4-dioxane (1.0 mL) was stirred for 30 min at rt and then at 60 °C for 3 h under argon. The reaction mixture was then cooled to rt and diluted with EtOAc (10 mL) and citric acid (10% in water, 5.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic extracts was washed with water (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude α-keto ester, which was subsequently purified by silica gel chromatography (hexanes/EtOAc).

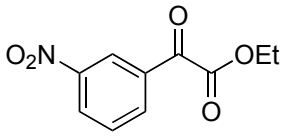
Ethyl 2-(2-bromophenyl)-2-oxoacetate (1d)



1d

1d isolated as a brown oil: ^{1}H NMR [C_6D_6, 500 MHz] δ 7.41 (1H, dd, *J* = 7.5, 1.5 Hz), 7.07 (1H, d, *J* = 7.5 Hz), 6.67 (1H, t, *J* = 7.5 Hz), 6.58 (1H, dt, *J* = 7.5 1.5 Hz), 3.98 (2H, q, *J* = 7.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR [C_6D_6, 75 MHz] δ 187.43, 162.88, 136.29, 133.60, 131.81, 130.18, 130.02, 121.71, 62.48, 18.62.

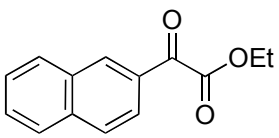
Ethyl 2-(3-nitrophenyl)-2-oxoacetate (1f)



1f

1f isolated as a yellow oil: ^{1}H NMR [$CDCl_3$, 300 MHz] δ 8.86 (1H, s), 8.51 – 8.47 (1H, d, *J* = 8.0 Hz), 8.48 (1H, d, *J* = 8.0 Hz), 7.75 (1H, t, *J* = 8.0 Hz), 4.48 (2H, q, *J* = 7.0 Hz), 1.44 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.63, 162.25, 148.49, 135.58, 134.01, 130.34, 128.94, 125.04, 63.15, 14.12.

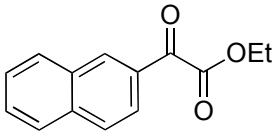
Ethyl 2-(naphthalen-1-yl)-2-oxoacetate (1i)



1i

1i isolated as a pale yellow solid: m.p. = 79-82 °C; ^{1}H NMR [$CDCl_3$, 300 MHz] δ 9.04 (1H, d, *J* = 8.0 Hz), 8.13 (1H, d, *J* = 8.0 Hz), 7.96 (1H, d, *J* = 7.5 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.73 – 7.68 (1H, m), 7.63 – 7.54 (2H, m), 4.50 (2H, q, *J* = 7.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz); ^{13}C NMR [$CDCl_3$, 75 MHz] δ 188.90, 164.67, 135.83, 134.04, 133.92, 131.09, 129.31, 128.80, 128.40, 127.10, 125.71, 124.36, 62.43, 14.20.

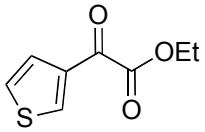
Ethyl 2-(naphthalen-2-yl)-2-oxoacetate (1j)



1j

1j isolated as a dark brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (1H, s), 8.04 (1H, d, *J* = 8.5 Hz), 7.97 – 7.85 (3H, m), 7.76 – 7.53 (2H, m), 4.52 (2H, q, *J* = 7.0 Hz), 1.46 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.46, 164.06, 136.44, 133.57, 132.35, 130.08, 129.90, 129.67, 129.03, 128.01, 127.26, 124.03, 62.50, 14.26.

Ethyl 2-oxo-2-(thiophen-3-yl)acetate (1k)



1k

1k isolated as a yellow oil; ^{1}H NMR (C_6D_6, 300 MHz) δ 8.14 (1H, dd, *J* = 3.0, 1.0 Hz), 7.53 (1H, dd, *J* = 5.0, 1.0 Hz), 6.50 (1H, dd, *J* = 5.0, 3.0 Hz), 3.89 (2H, q, *J* = 7.0 Hz), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (C_6D_6, 75 MHz) δ 182.13, 162.97, 138.24, 137.21, 125.21, 124.59, 61.96, 13.35.

II. General experimental procedure for the synthesis of *N*-acyl-α-amino amides (Table 2)

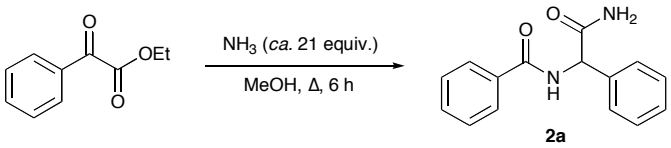
CAUTION: The procedure described below generates pressure in a closed reaction vessel. The reaction vessel should be placed behind a blast shield in a well-ventilated fume hood.

To a solution of ammonia in methanol (*ca*. 7M in MeOH, 3.0 mL, *ca*. 21 equiv.) in a Swagelock® 50 mL stainless steel cylinder or an Ace® pressure tube was added the α-keto ester (1.00 mmol). The cylinder (or tube) was sealed and heated in an oil bath at 60 °C or 80 °C for 6 h or 12 h respectively. The cylinder (or tube) was then removed was allowed to cool to room temperature (1 h), and then cooled further in a –40 °C bath. The Swagelock® cylinder (or pressure tube) was opened and the contents were transferred to a small Erlenmeyer flask (50 mL). A steady stream of air was blown over the reaction mixture until some precipitation was observed. The reaction mixture was then heated slightly to redissolve all solid matter, and allowed to stand at room

temperature for 2 h. The precipitated product was filtered off through a scintered glass funnel, and washed with ice-cold methanol (*ca*. 5 ml).

II. Optimization Studies

Table 3. Effect of Reaction Time and Temperature on the Isolated Yield of **2a**

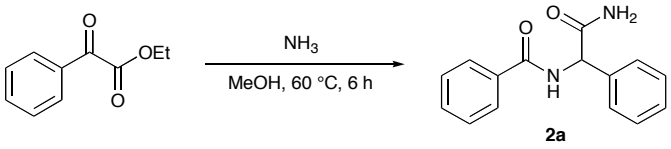


2a

Entry	Temperature/°C	Time/h	Yield/%[a]
1	20	6	<10
2	20	18	13
3	35	6	15
4	35	18	29
5	50	6	63
6	50	18	80
7	60	6	90
8	60	18	82
9	90	6	84
10	90	18	68

[a] Isolated Yield

Table 4. Effect of Equivalence of Ammonia on the Isolated Yield of **2a**

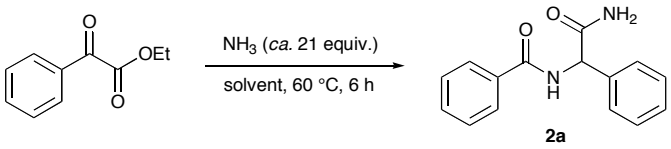


2a

Entry	Equivalence of Ammonia[b]	Yield/%[a]
1	3	9
2	7	17
3	14	49
4	21	90

[a] Isolated Yield; [b] Approximate

Table 5. Effect of Solvent on the Isolated Yield of **2a**



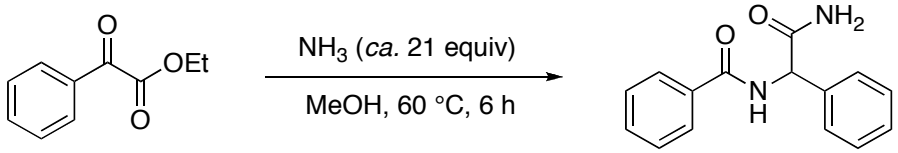
2a

Entry	Solvent[b]	Yield/%[a]
1	H_2O	29
2	MeOH	90
3	EtOH	84
4	$PhCH_3$	<10
5	DMSO	<10
6	THF	24
7	DME	34

[a] Isolated Yield; [b] Solutions of *ca*. 7M ammonia were made by adding the appropriate volume of liquid ammonia to the solvent.

III. Characterization Data

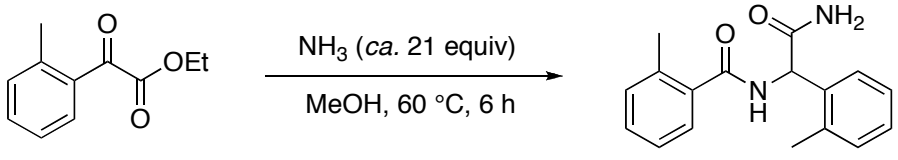
N-(2-Amino-2-oxo-1-phenylethyl)benzamide (2a)[3]



1a **2a**

2a isolated as a white solid: m.p. = 199-201 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 500 MHz] δ 8.70 (1H, d, *J* = 8.0 Hz), 7.91 (2H, d, *J* = 7.0 Hz), 7.90 (1H, br s), 7.57 – 7.50 (3H, m), 7.46 (2H, t, *J* = 7.5 Hz), 7.36 (2H, t, *J* = 7.5 Hz), 7.30 (1H, t, *J* = 7.5 Hz), 7.24 (1H, br s), 5.63 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 172.16, 166.42, 139.30, 134.47, 131.89, 128.72 (two signals overlapped), 128.10, 127.98 (two signals overlapped), 56.42; IR (KBr) υ 3372, 3321, 3169, 3056, 1698, 1650 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{15}H_{14}N_2O_2$ (M^+) 254.1055, found 254.1057.

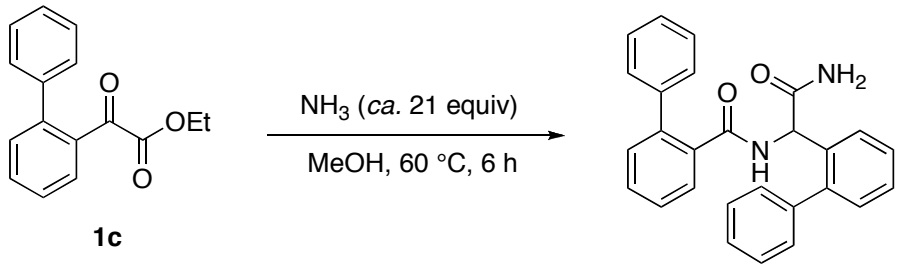
N-[2-Amino-1-(2-methylphenyl)-2-oxoethyl]-2-methylbenzamide (2b)



1b **2b**

2b isolated as a white solid: m.p. = 205-207 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 500 MHz] δ 8.62 (1H, d, *J* = 8.0 Hz), 7.48 (1H, br s), 7.43 – 7.28 (3H, m), 7.25 – 7.13 (6H, m), 5.74 (1H, d, *J* = 8.0 Hz), 2.44 (3H, s), 2.32 (3H, s); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 172.06, 168.69, 136.75, 136.60 (two signals overlapped), 135.35, 130.24, 130.14, 129.29, 127.58, 127.52, 127.35, 125.86, 125.28, 53.70, 19.38, 19.11; IR (KBr) υ 3431, 3284, 1680, 1629 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368, found 282.1366.

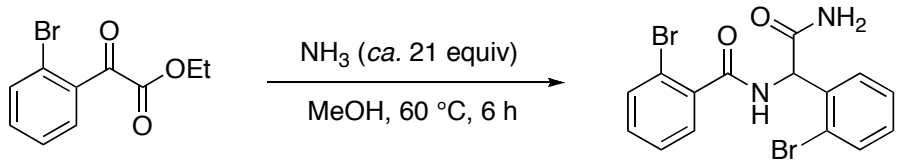
***N*-[2-Amino-1-(biphenyl-2-yl)-2-oxoethyl]biphenyl-2-carboxamide (2c)**



1c **2c**

2c isolated as a white solid: m.p. = 108-109 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 8.78 (1H, d, *J* = 7.5 Hz), 7.55 – 7.15 (19H, m), 6.83 (1H, br s), 5.42 (1H, d, *J* = 7.5 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 172.03, 168.39, 141.85, 140.41, 140.01, 139.35, 136.26, 135.32, 129.89, 129.75, 129.45, 129.21, 128.35, 128.28, 128.08, 128.04, 127.90, 127.51, 127.43, 127.06, 126.97, 126.79, 54.21; IR (KBr) υ 3430, 3253, 3057, 1689, 1631 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{27}H_{22}N_2O_2$ (M^+) 406.1681, found 406.1684.

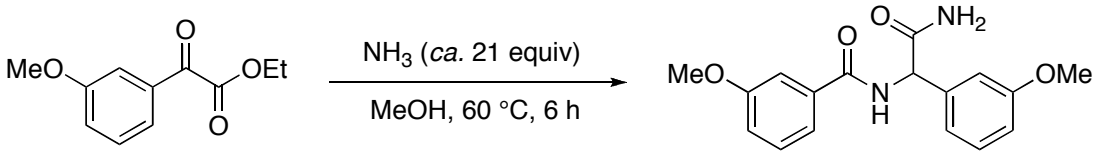
***N*-[2-Amino-1-(2-bromophenyl)-2-oxoethyl]-2-bromobenzamide (2d)**



1d **2d**

2d isolated as a white solid: m.p. = 181-183 °C (MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.70 – 7.15 (11H, m), 6.05 (1H, s);^{13}C NMR (CD_3OD, 75 MHz) δ 173.49, 169.91, 138.77, 137.47, 134.14, 134.06, 132.23, 130.99, 130.53, 130.00, 128.86, 128.37, 125.43, 120.33, 58.41; IR (KBr) υ 3433, 3304, 1669, 1621 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{15}H_{12}Br^{79}{}_2N_2O_2$ (M^+) 409.9266, found 409.9261.

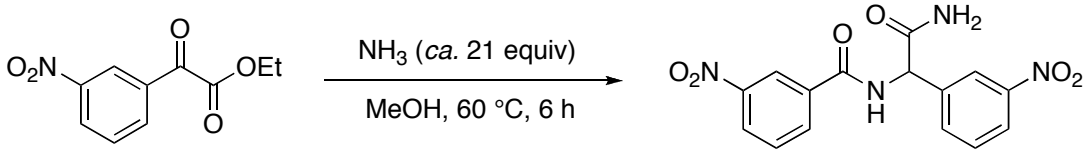
***N*-[2-Amino-1-(3-methoxyphenyl)-2-oxoethyl]-3-methoxybenzamide (2e)**



1e **2e**

2e isolated as a white solid: m.p. = 144-146 °C (MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.47 – 7.25 (4H, m), 7.13 – 7.05 (3H, m), 6.93 – 6.87 (1H, m), 5.64 (1H, s) [N-H signals absent]; ^{13}C NMR (CD_3OD, 75 MHz) δ 175.02, 169.61, 161.60, 161.42, 140.60, 136.69, 130.97, 130.83, 121.10, 120.78, 119.02, 115.02, 114.57, 113.92, 59.03, 56.03, 55.88; IR (KBr) υ 3303, 3154, 1697, 1630 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{18}N_2O_4$ (M^+) 314.1267, found 314.1266.

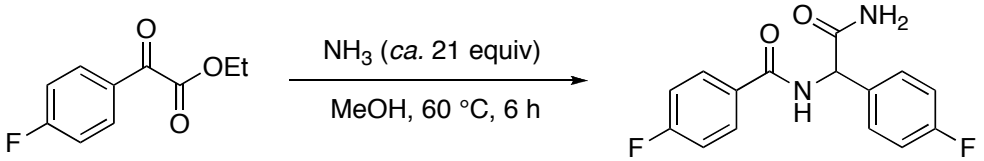
***N*-[2-Amino-1-(3-Nitrophenyl)-2-oxoethyl]-3-nitrobenzamide (2f)**



1f **2f**

2f isolated as a white solid: m.p. = 178-179 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.55 (1H, d, *J* = 8.0 Hz), 8.78 (1H, t, *J* = 2.0 Hz), 8.46 (1H, t, *J* = 2.0 Hz), 8.40 – 8.25 (2H, m), 8.20 (1H, dt, *J* = 8.0, 2.0 Hz), 8.00 (1H, d, *J* = 8.0 Hz), 7.93 (1H, br s), 7.82 – 7.62 (2H, m), 7.43 (1H, br s), 5.84 (1H, d, *J* = 8.0 Hz) ;^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 170.60, 164.34, 147.74, 147.63, 140.69, 135.13, 134.70, 134.37, 129.99, 129.90, 126.15, 122.71, 122.65, 122.53, 56.41; IR (KBr) υ 3310, 3150, 1698, 1635, 1606, 1535, 1348 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{15}H_{12}N_4O_6$ (M^+) 344.0757, found 344.0760.

***N*-[2-Amino-1-(4-fluorophenyl)-2-oxoethyl]-4-fluorobenzamide (2g)**

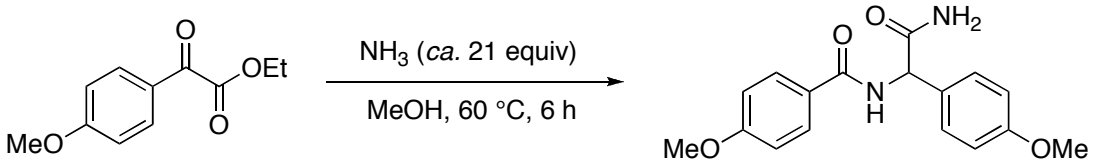


1g **2g**

2g isolated as a white solid: m.p. = 202-204 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 8.72 (1H, d, *J* = 7.5 Hz), 7.87 (2H, app t, *J* = 7.5 Hz), 7.60 (1H, br s), 7.44 (2H, app t, *J* = 7.5 Hz), 7.30 – 7.00 (5H, m), 5.50 (1H, d, *J* = 7.5 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 171.59, 165.03, 164.47 (d, *J* = 182 Hz), 161.21 (d, *J* = 177 Hz), 134.96, 134.93, 130.43 (d, *J* = 9 Hz), 129.67 (d, *J* = 8 Hz), 115.20 (d, *J* = 6.5 Hz), 114.92 (d, *J* = 6.5 Hz), 56.21; IR (KBr) υ 3425, 3338, 1699,

1637 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{15}H_{12}F_2N_2O_2$ (M^+) 290.0867, found 290.0869. [app = apparent]

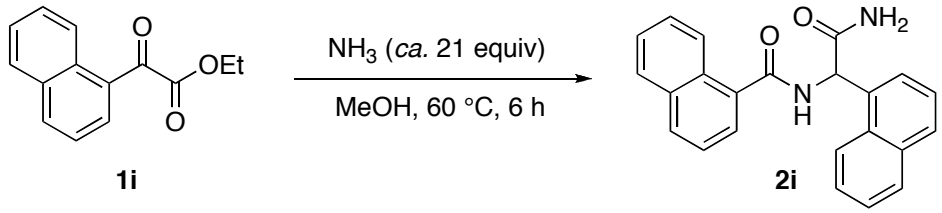
***N*-[2-Amino-1-(4-methoxyphenyl)-2-oxoethyl]-4-methoxybenzamide (2h)**



1h **2h**

2h isolated as a clear, colourless, crystalline solid: m.p. = 253-255 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 8.48 (1H, d, *J* = 8.0 Hz), 7.91 (2H, d, *J* = 8.5 Hz), 7.63 (1H, br s), 7.44 (2H, d, *J* = 8.5 Hz), 7.20 (1H, br s), 6.99 (2H, d, *J* = 8.5 Hz), 6.92 (2H, d, *J* = 8.5 Hz), 5.56 (1H, d, *J* = 8.0 Hz), 3.80 (3H, s), 3.74 (3H, s); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 172.20, 165.28, 161.70, 158.70, 130.98, 129.46, 128.74, 126.22, 113.63, 113.40 56.16, 55.33, 55.10; IR (KBr) υ 3365, 3321, 1696, 1646, 1622 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{18}N_2O_4$ (M^+) 314.1267, found 314.1267.

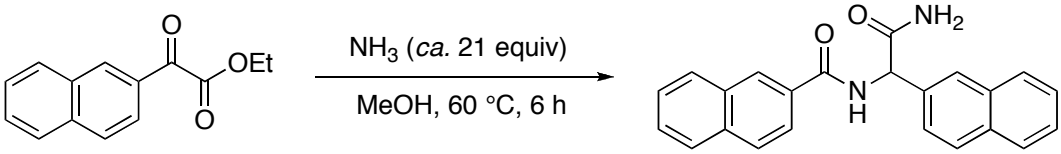
***N*-[2-Amino-1-(naphthalen-1-yl)-2-oxoethyl]-1-naphthamide (2i)**



1i **2i**

2i isolated as a white solid: m.p. = 245-247 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.22 (1H, d, *J* = 8.0 Hz), 8.40 – 8.28 (2H, m), 8.05 – 7.90 (4H, m), 7.81 (1H, br s), 7.75 – 7.42 (9H, m), 6.54 (1H, d, *J* = 8.0 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 171.99, 168.19, 134.16, 134.05, 133.41, 132.96, 131.26, 129.81, 129.73, 128.57, 128.24, 128.03, 126.50, 126.37, 126.03, 125.75, 125.70, 125.53, 125.41, 125.27, 124.74, 123.57, 53.65; IR (KBr) υ 3445, 3286, 1685, 1633 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{23}H_{18}N_2O_2$ (M^+) 354.1368, found 354.1367.

***N*-[2-Amino-1-(naphthalen-2-yl)-2-oxoethyl]-2-naphthamide (2j)**

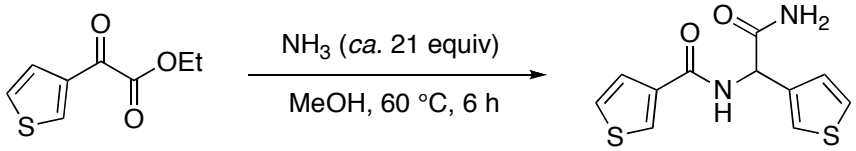


1j **2j**

2j isolated as a white solid: m.p. = 230-232 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 9.06 (1H, d, *J* = 7.0 Hz), 8.65 (1H, br s), 8.30 – 7.65 (10H, m), 7.60 – 7.25 (5H, m), 5.94 (1H, d, *J* =

7.0 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 171.74, 166.10, 136.39, 134.27, 132.75, 132.46, 132.12, 131.25, 128.93, 128.00, 127.89, 127.80 (2 signals overlapped), 127.68, 127.61, 127.55, 126.70, 126.38, 126.32, 126.09, 125.89, 124.55, 57.17; IR (KBr) υ 3301, 3142, 1678, 1645 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{23}H_{18}N_2O_2$ (M^+) 354.1368, found 354.1370.

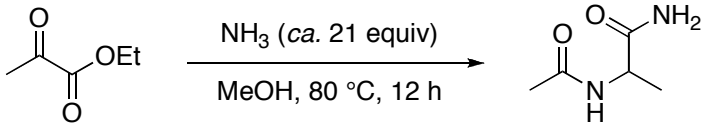
_N_-[2-Amino-2-oxo-1-(thiophen-3-yl)ethyl]thiophene-3-carboxamide (2k)



1k **2k**

2k isolated as a clear, crystalline solid: m.p. = 216-218 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 8.63 (1H, d, *J* = 8.5 Hz), 8.35 (1H, t, *J* = 1.0 Hz), 7.69 (1H, br s), 7.65 – 7.47 (4H, m), 7.28 – 7.22 (2H, m), 5.73 (1H, d, *J* = 8.5 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 172.09, 162.13, 139.60, 137.62, 129.94, 127.87, 127.80, 126.97, 126.58, 123.28, 53.16; IR (KBr) υ 3386, 3276, 1678, 1633 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{11}H_{10}N_2O_2S_2$ (M^+) 266.0184, found 266.081.

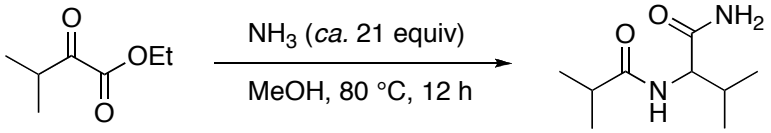
2-Acetamidopropanamide (2l)[4]



1l **2l**

2l isolated as a clear, crystalline solid: m.p. = 157-159 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 7.96 (1H, d, *J* = 7.5 Hz), 7.33 (1H, br s), 6.97 (1H, br s), 4.17 (1H, pentet, *J* = 7.5 Hz), 1.81 (3H, s), 1.15 (3H, d, *J* = 7.5 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 174.78, 169.15, 48.04, 22.61, 18.36; IR (KBr) υ 3338, 3267, 1697, 1611 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_5H_{10}N_2O_2$ (M^+) 130.0742, found 130.0742.

3-Methyl-2-[(2-Methylpropanoyl)amino]butanamide (2m)

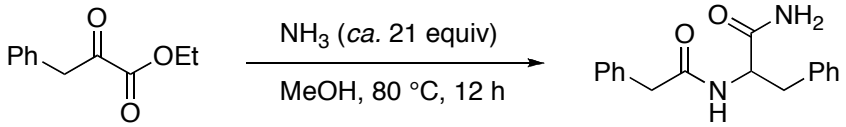


1m **2m**

2m isolated as a white solid: m.p. = 175-177 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 300 MHz] δ 7.64 (1H, d, *J* = 9.0 Hz), 7.37 (1H, br s), 7.01 (1H, br s), 4.11 (1H, dd, *J* = 9.0, 7.0 Hz), 2.53 (1H, heptet, *J* = 7.0 Hz), 1.94 (1H, octet, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.84 (3H, d, *J* = 7.0 Hz), 0.82 (3H, d, *J* = 7.0 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 176.13,

173.34, 57.14, 33.63, 30.41, 20.07, 19.32, 19.25, 18.01; IR (KBr) υ 3335, 3270, 1690, 1638 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_9H_{18}N_2O_2$ (M^+) 186.1368, found 186.1370.

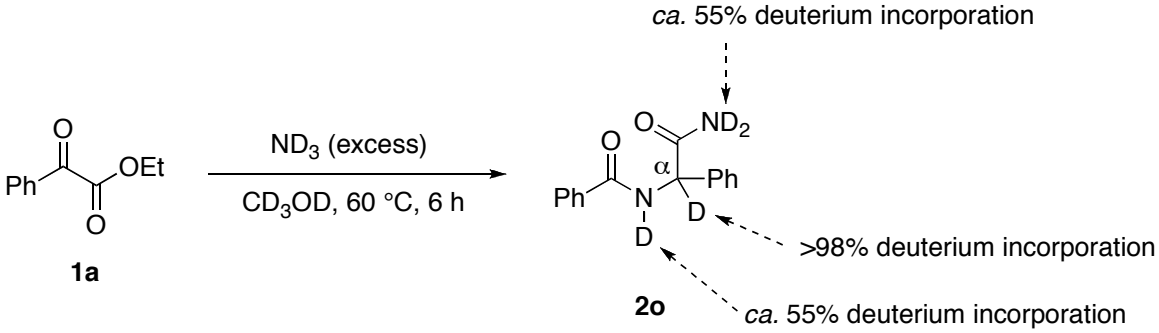
3-Phenyl-2-(2-phenylacetamido)propanamide (2n)[5]



1n **2n**

2n isolated as a white solid: m.p. = 204-206 °C (MeOH); ^{1}H NMR [$(CD_3)_2SO$, 500 MHz] δ 8.19 (1H, d, *J* = 8.5 Hz), 7.46 (1H, br s), 7.25 – 7.13 (8H, m), 7.09 (2H, d, *J* = 7.5 Hz), 7.05 (1H, br s), 4.46 (1H, app dt, *J* = 9.0, 4.5 Hz), 3.43 (1H, d, *J* = 14.0 Hz), 3.37 (1H, d, *J* = 14.0 Hz), 3.01 (1H, dd, *J* = 13.5, 4.5 Hz), 2.77 (1H, dd, *J* = 13.5, 9.5 Hz); ^{13}C NMR [$(CD_3)_2SO$, 75 MHz] δ 173.10, 169.80, 137.98, 136.31, 129.18, 128.94, 128.00 (two signals overlapped), 126.15 (two signals overlapped), 53.76, 42.12, 37.73; IR (KBr) υ 3380, 3297, 1637 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368, found 282.1364. [app = apparent]

Deuterated 2o

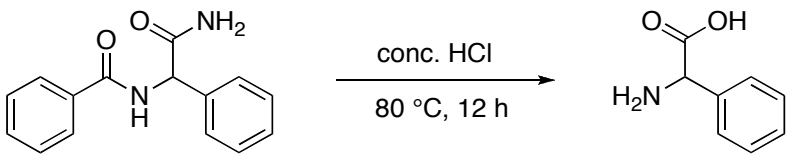


1a **2o**

2o isolated as a white solid: m.p. = 178-180 °C (CD_3OD); ^{1}H NMR [$(CD_3)_2SO$, 500 MHz] δ 8.78 (0.45H, br s), 7.98 (2H, d, *J* = 7.5 Hz), 7.80 (0.45H, br s), 7.65 – 7.15 (8.45H, m), 5.72 (0.01H, m); ^{13}C NMR (CD_3OD, 75 MHz) δ 171.87, 166.10, 138.77, 134.00, 131.53, 128.34 (two signals overlapped), 127.69 (two signals overlapped), 127.57, 56.61 (t, *J* = 20 Hz).

The deuterium incorporation at the α-position was calculated by integrating the ^{1}H NMR signal at δ 5.72 versus the aromatic signals. The deuterium incorporation of the amide protons were calculated by integrating the ^{1}H NMR signal at δ 8.78 or 7.80 versus the aromatic signals

2-Amino-2-phenylacetic acid [2-Phenylglycine] (3)[6]



2a **3**

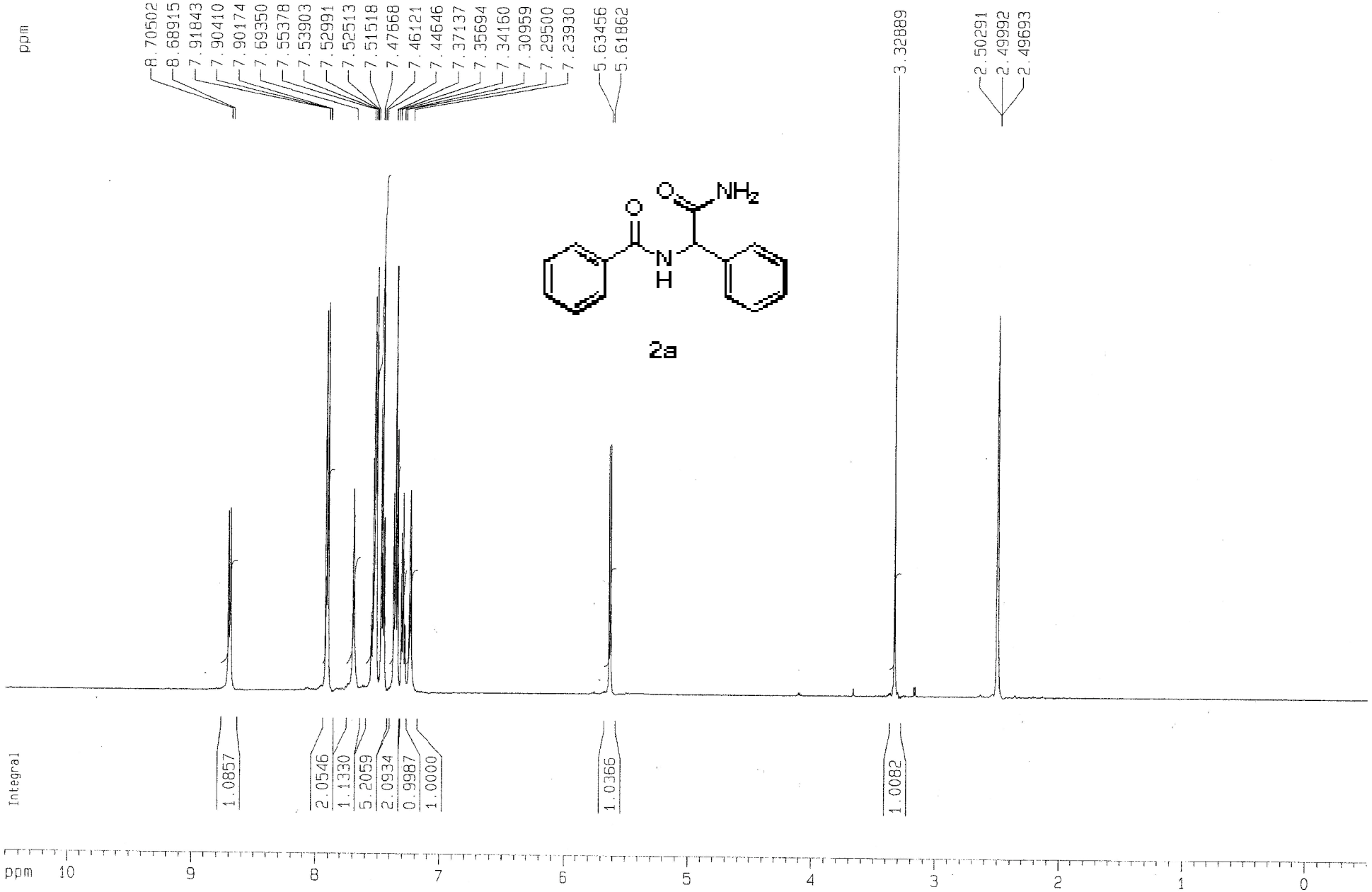
A solution of **2a** (254 mg, 1.00 mmol) in concentrated, aqueous HCl (1 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature and poured into a column containing Dowex 50W-X8 (15 mL, acid form, 50-100 mesh). The column first washed with 50% aqueous isopropanol (50 mL), and the water (50 mL). The amino acid was then eluted with aqueous ammonia (1 M). The eluent was collected and all volatiles were removed *in vacuo* to afford **3** (130 mg, 94%) as a white solid.

3: m.p. = 285-290 °C (H_2O); ^{1}H NMR [DCl/D_2O/$(CD_3)_2SO$, 300 MHz] δ 8.10 (3H, s), 7.25 – 7.07 (5H, m), 4.80 (1H, s); ^{13}C NMR [DCl/D_2O/$(CD_3)_2SO$, 75 MHz] δ 171.83, 133.97, 132.89, 132.13, 130.92, 58.55.

References

1. H. Shimizu and M. Murakami, *Chem. Commun.*, 2007, 2855.
2. J. M. Domagala, *Tetrahedron Lett.*, 1980, **21**, 4997.
3. W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, 1963, **28**, 2018.
4. R. Pascal, A. Rousset and A. Commeyras, *New. J. Chem.*, 1989, **13**, 205.
5. H. Yanagawa, Y. Makino, K. Sato, M. Nishizawa and F. Egami, *Origins of Life*, 1984, **14**, 163.
6. M. Kitamura, D. Lee, S. Hayashi, S. Tanaka and M. Yoshimura, *J. Org. Chem.*, 2002, **67**, 8685.

^{1}H and ^{13}C NMR Spectra of **2** and **3**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7.52513
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7.47668
7.46121
7.44646
7.37137
7.35694
7.34160
7.30959
7.29500
7.23930
5.63456
5.61862
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2.49693
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N
H
2a
Integral
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5.2059
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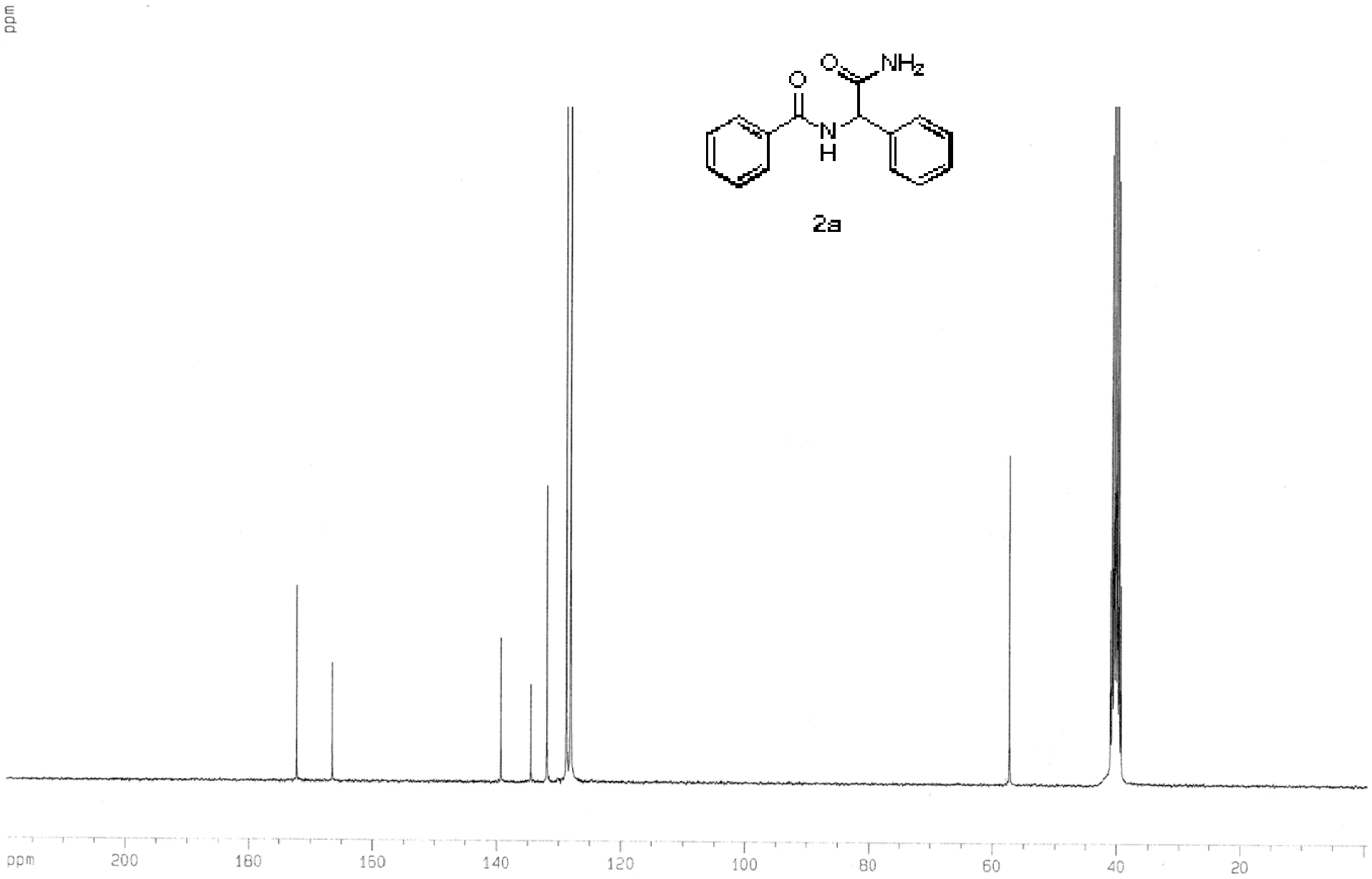
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80
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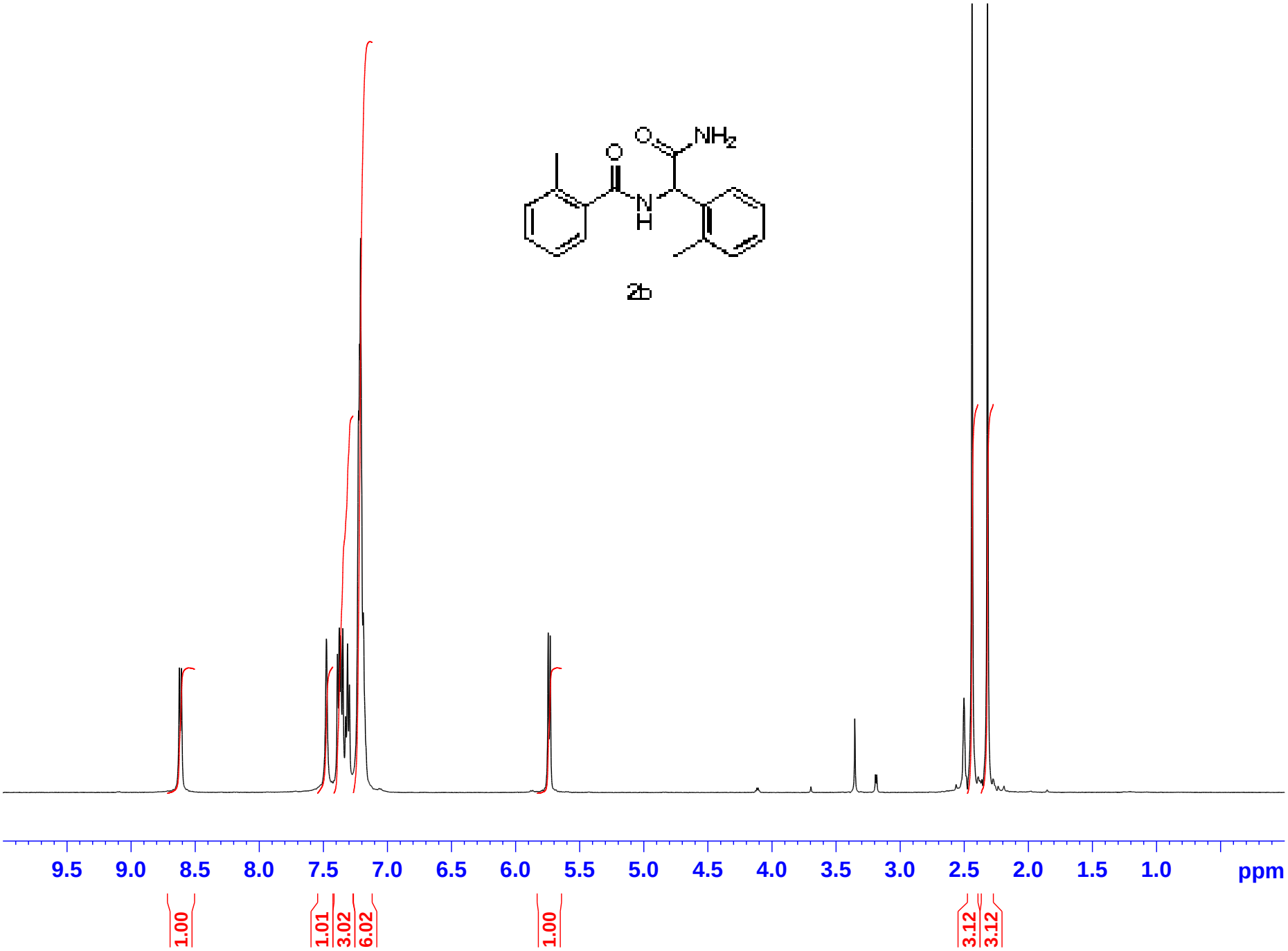
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N
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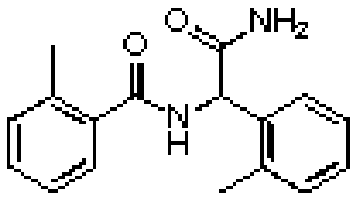
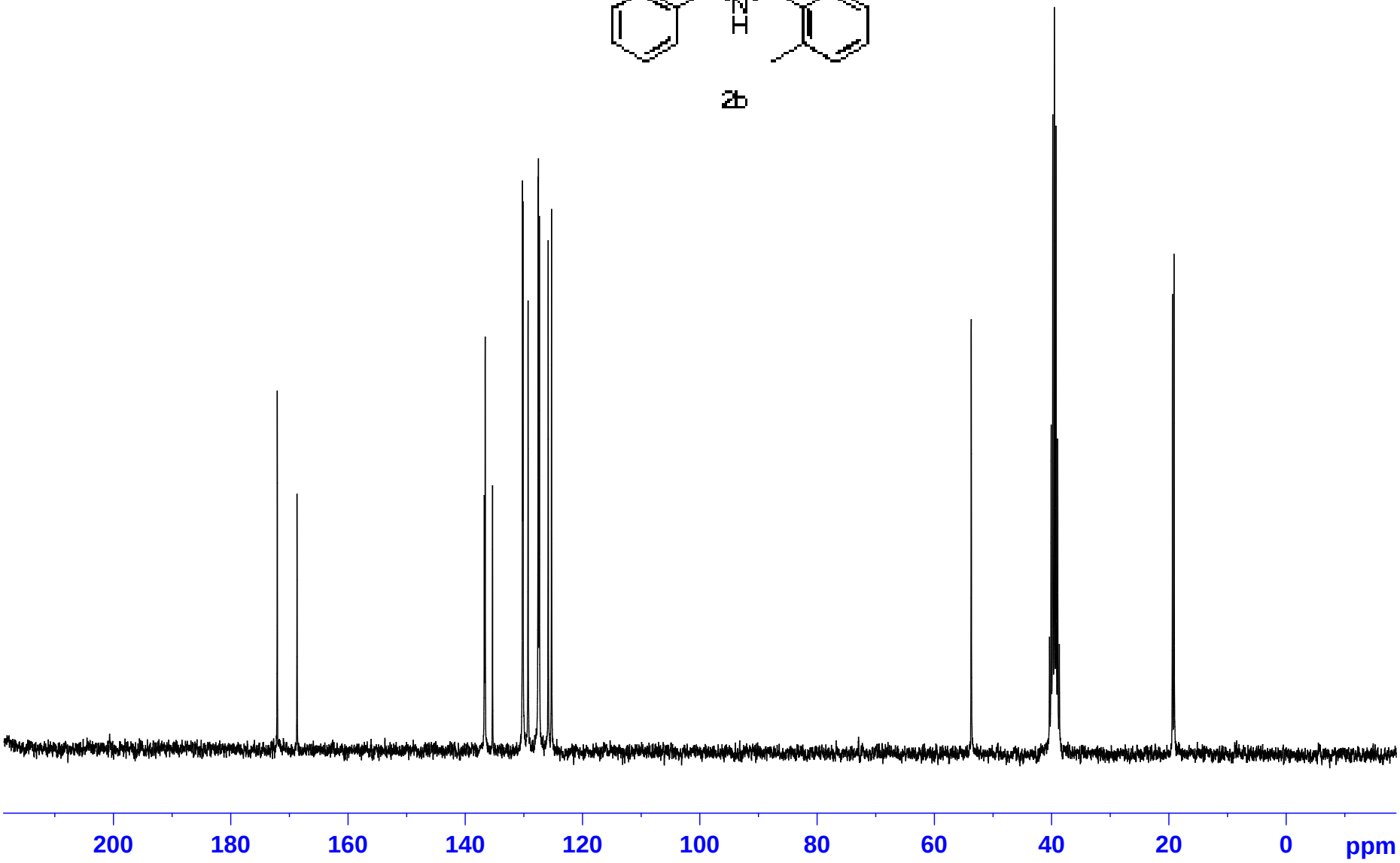
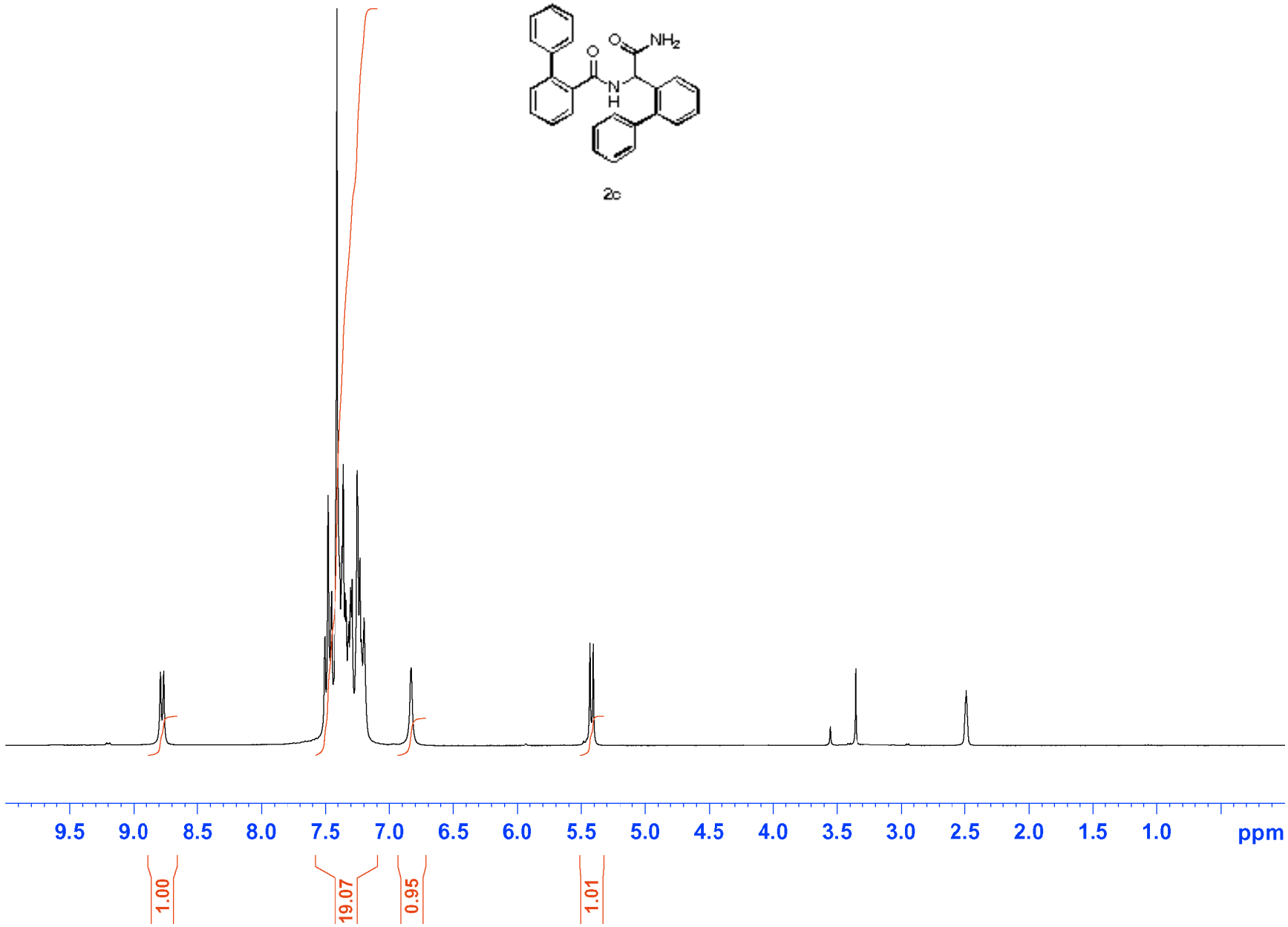


2b

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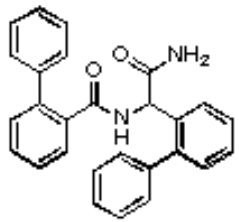
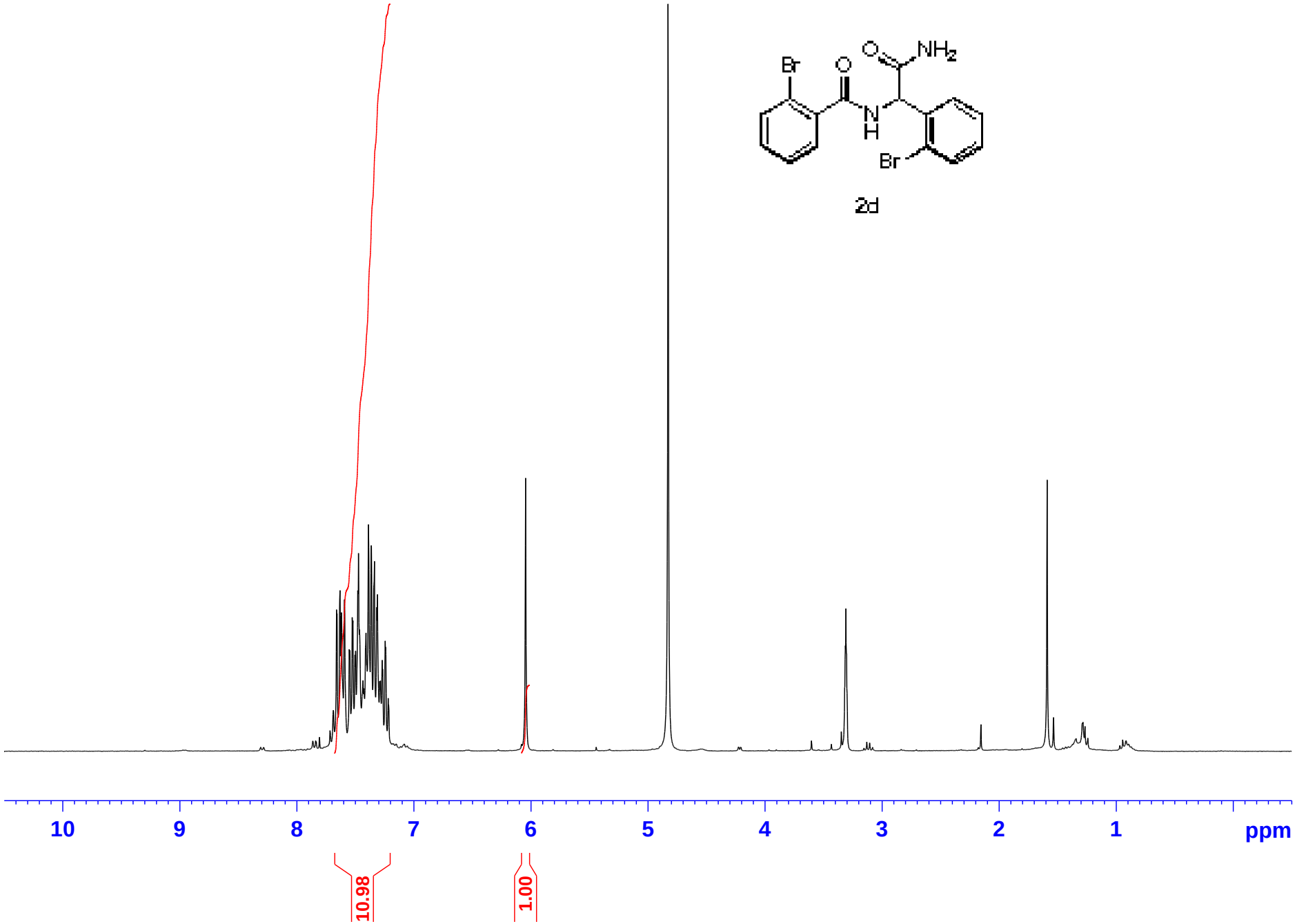


2c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O
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N
H
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7
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4
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1
ppm
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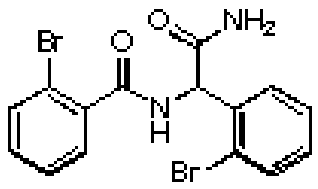

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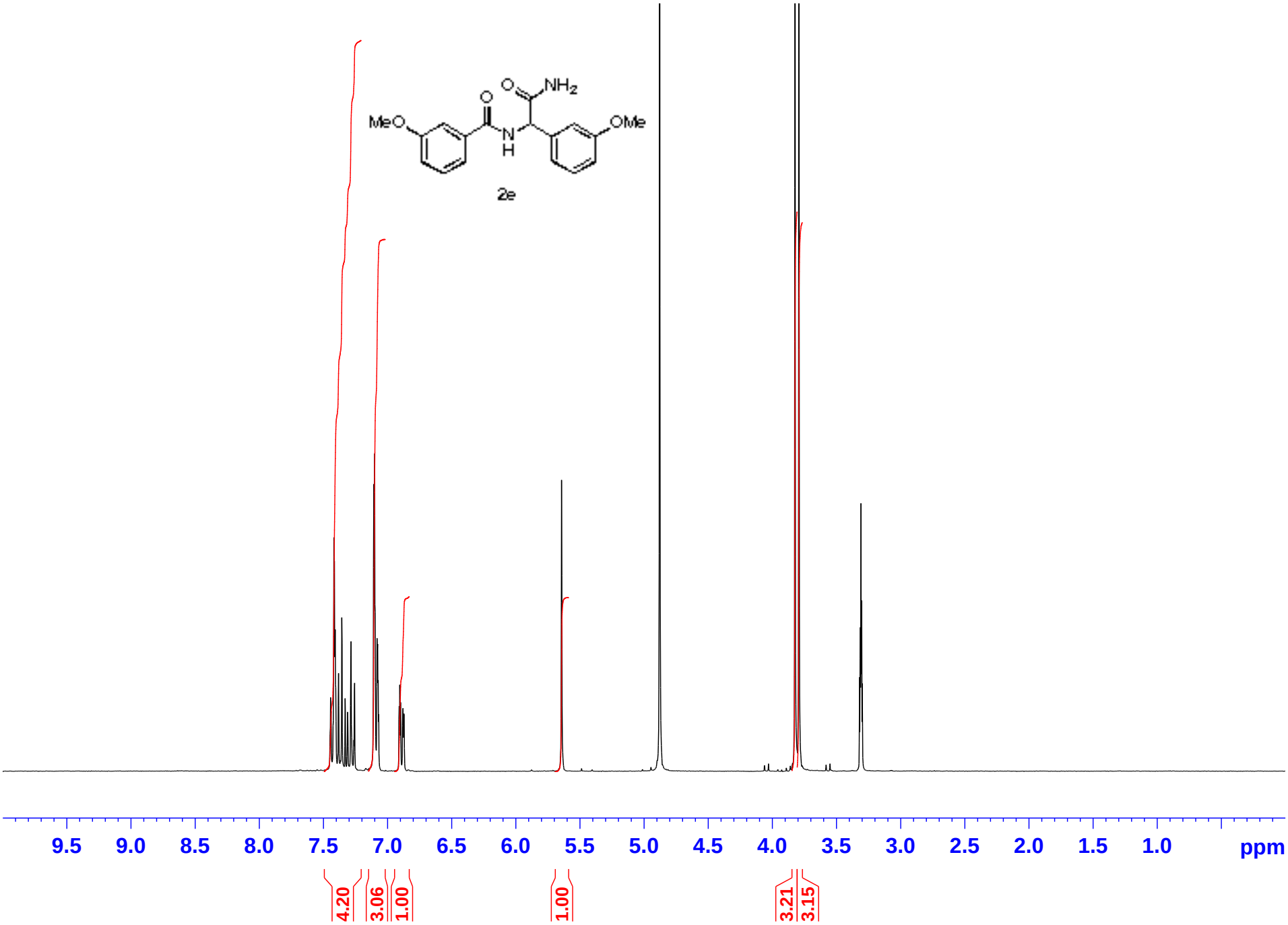
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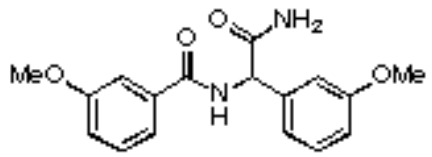

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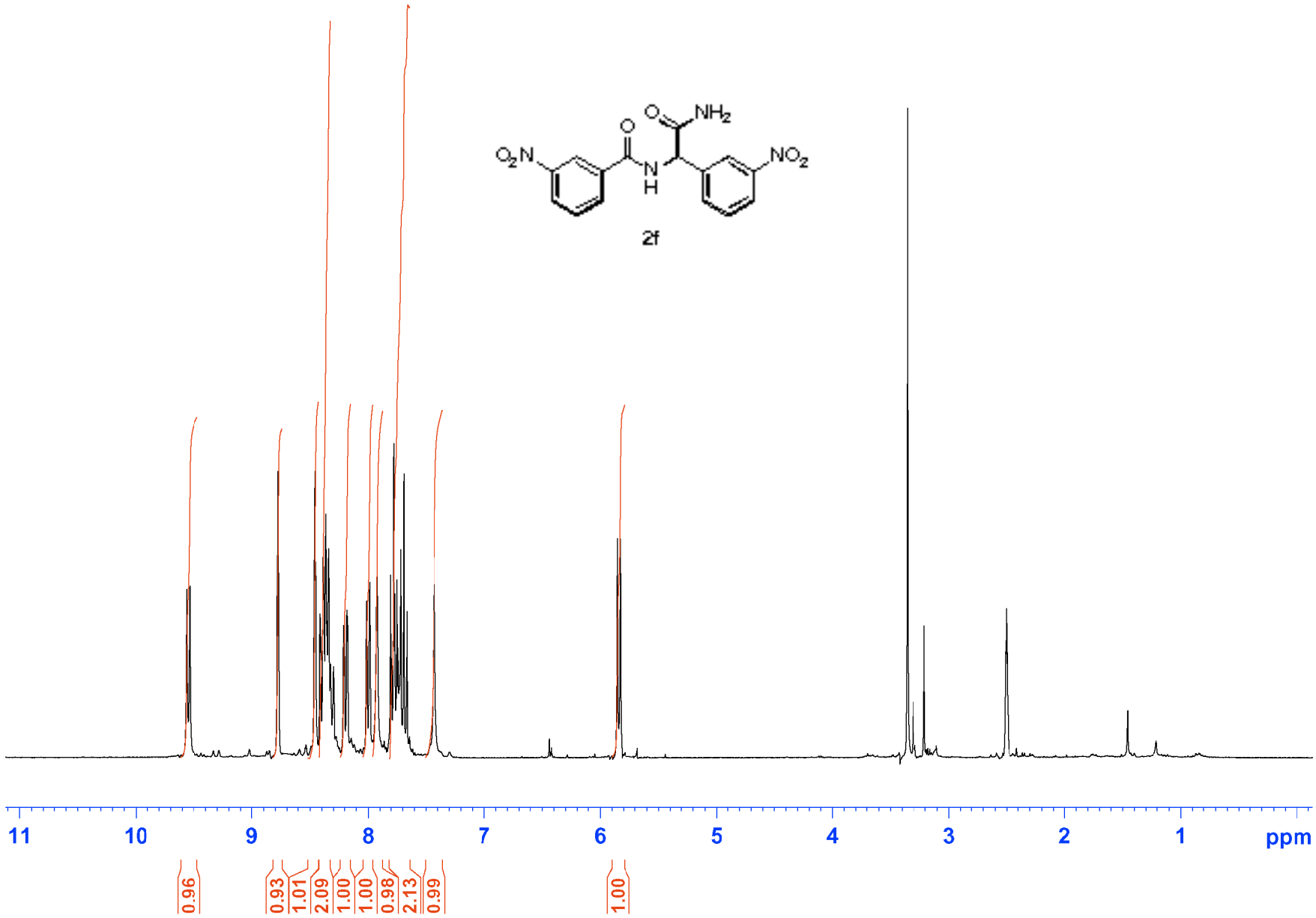
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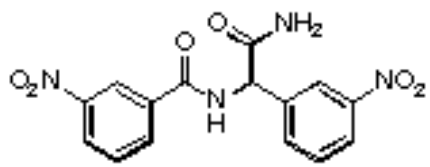

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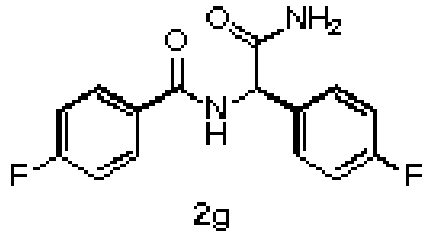
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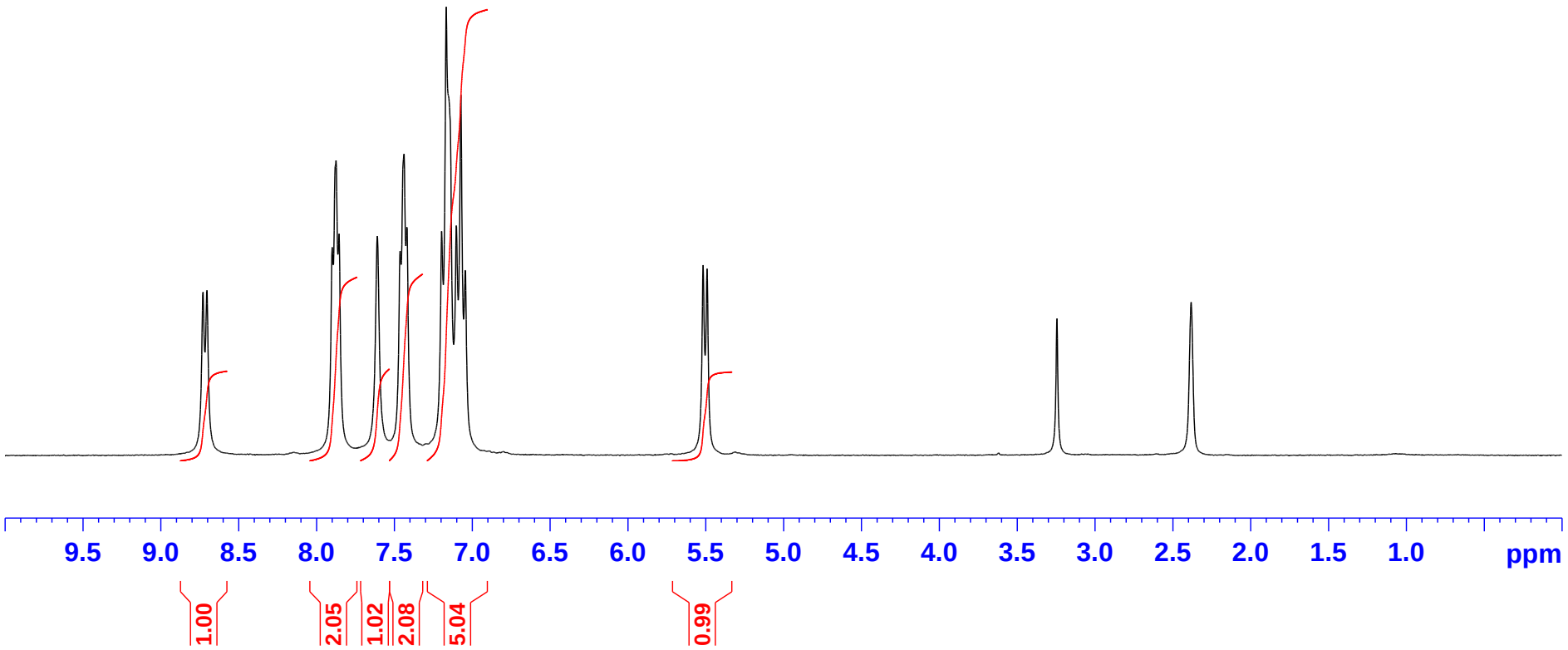
F
F

2g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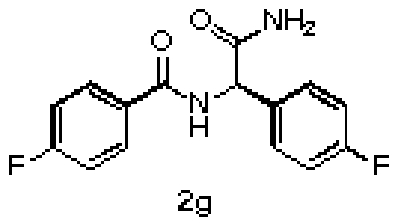
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2g

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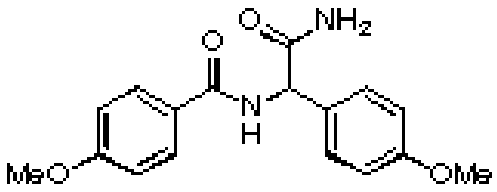
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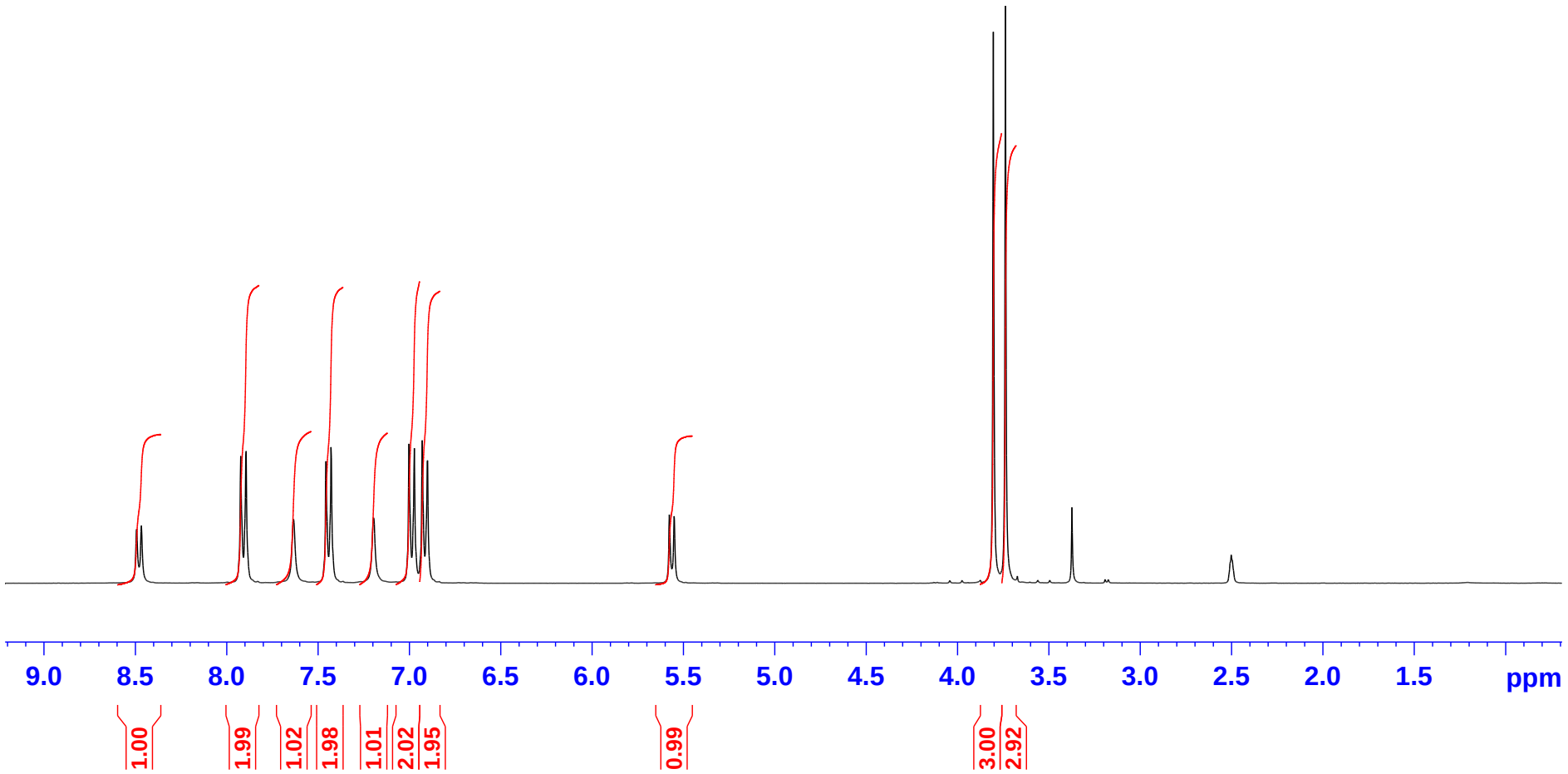
2h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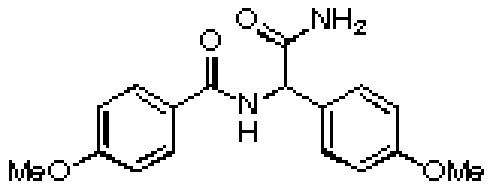

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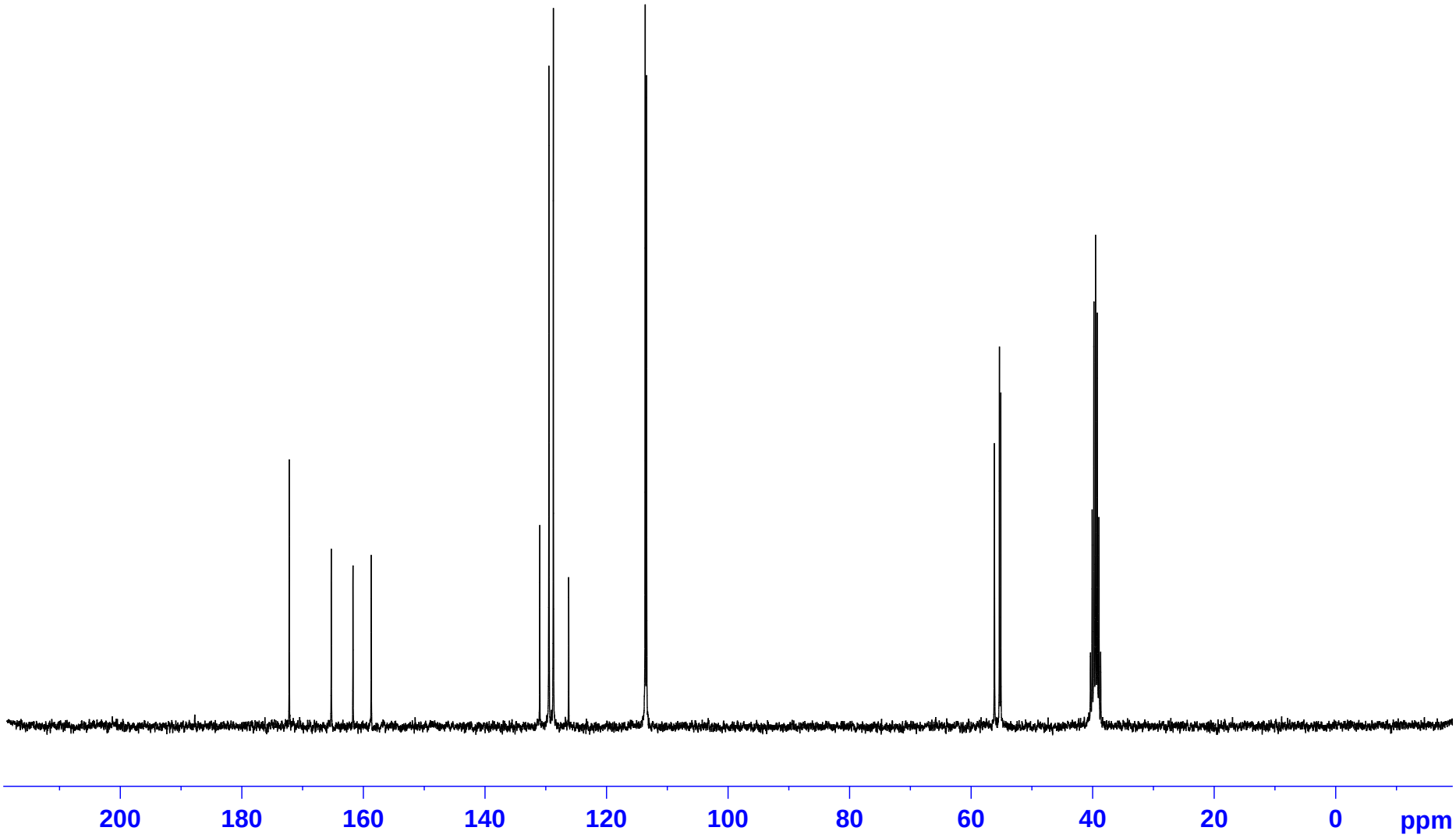

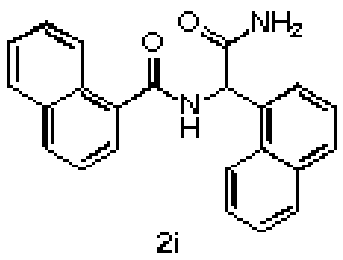

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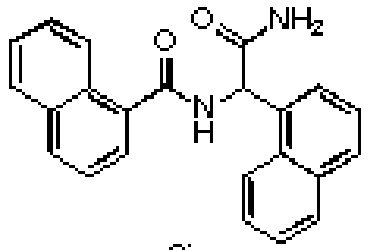

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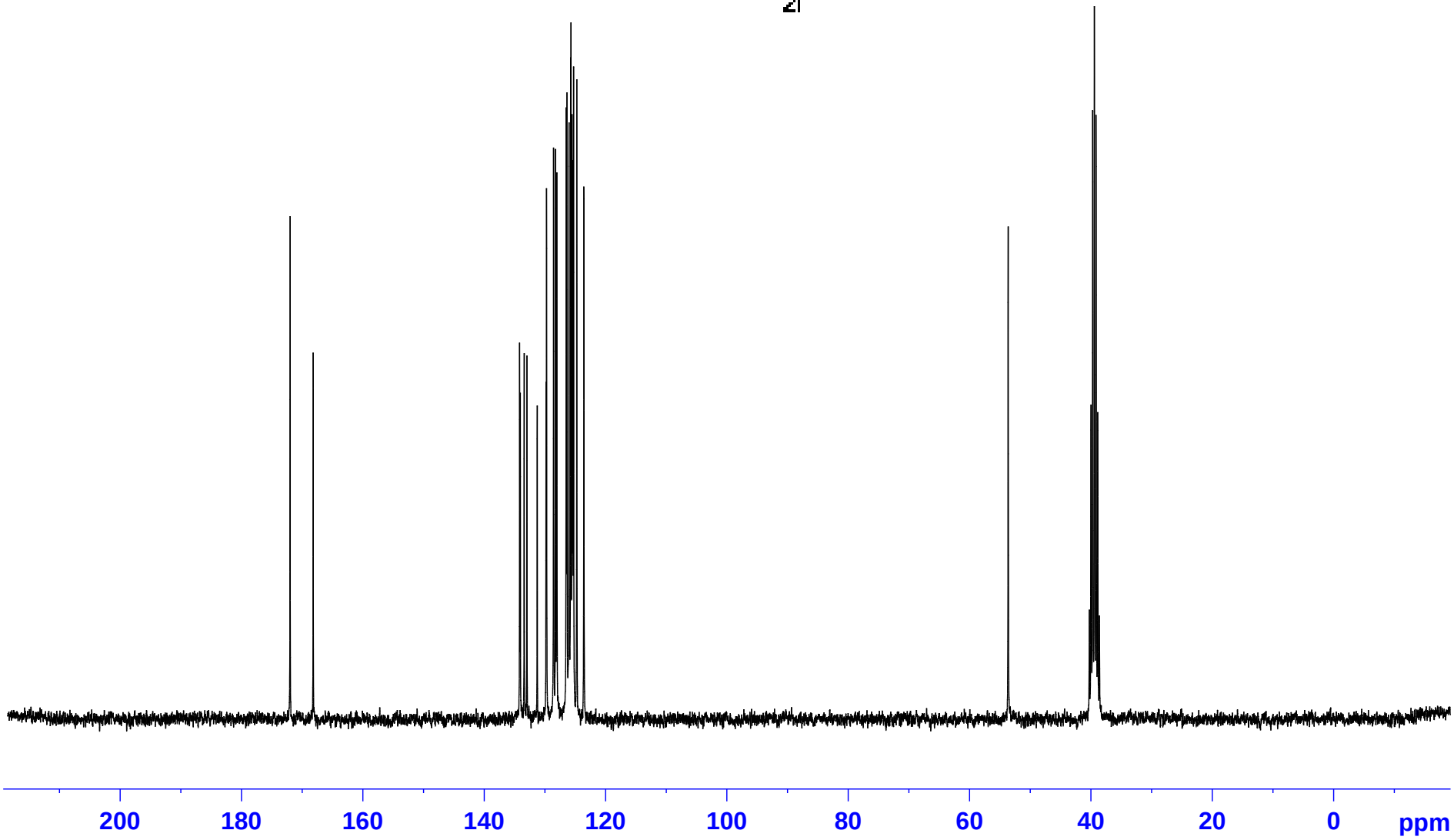

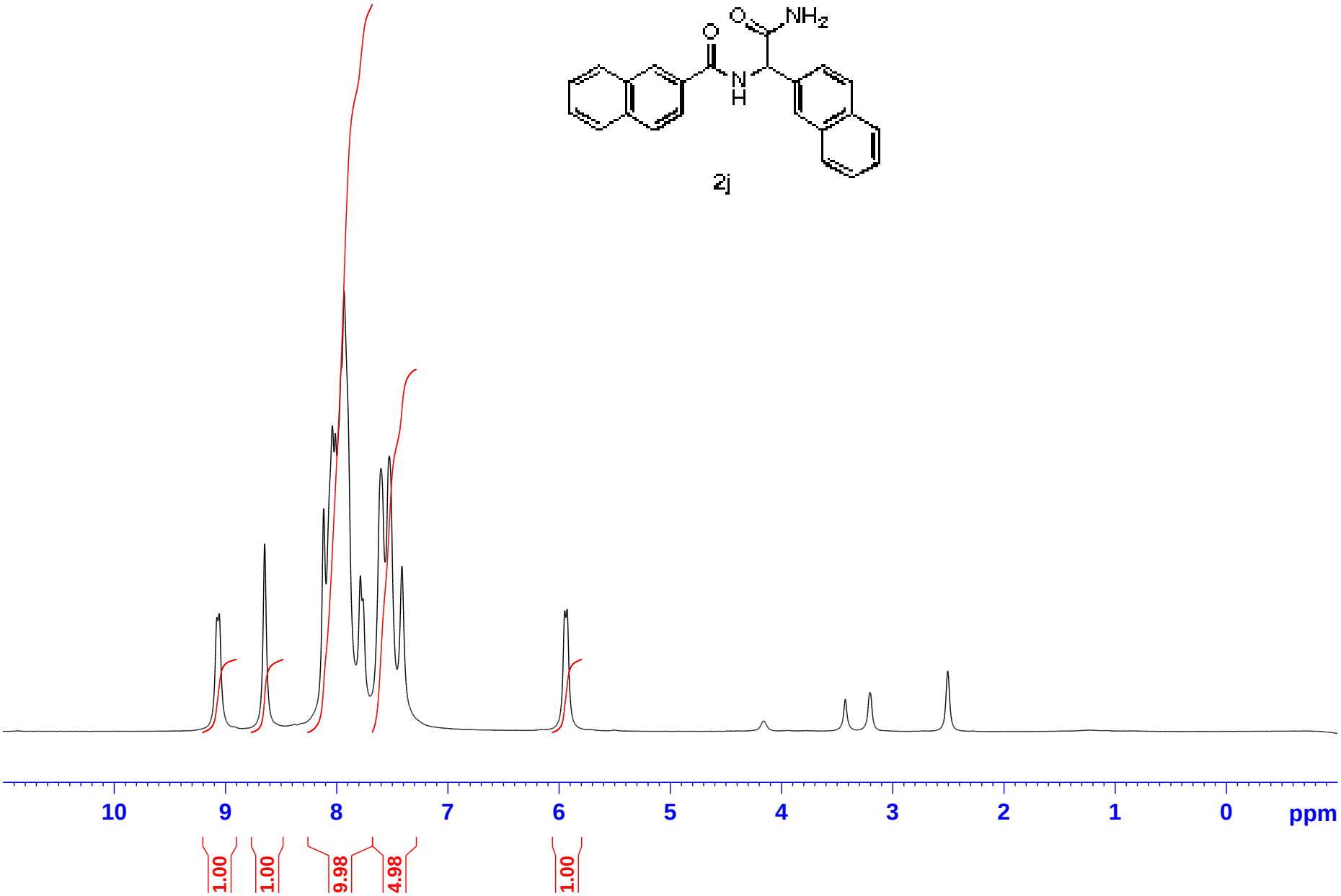

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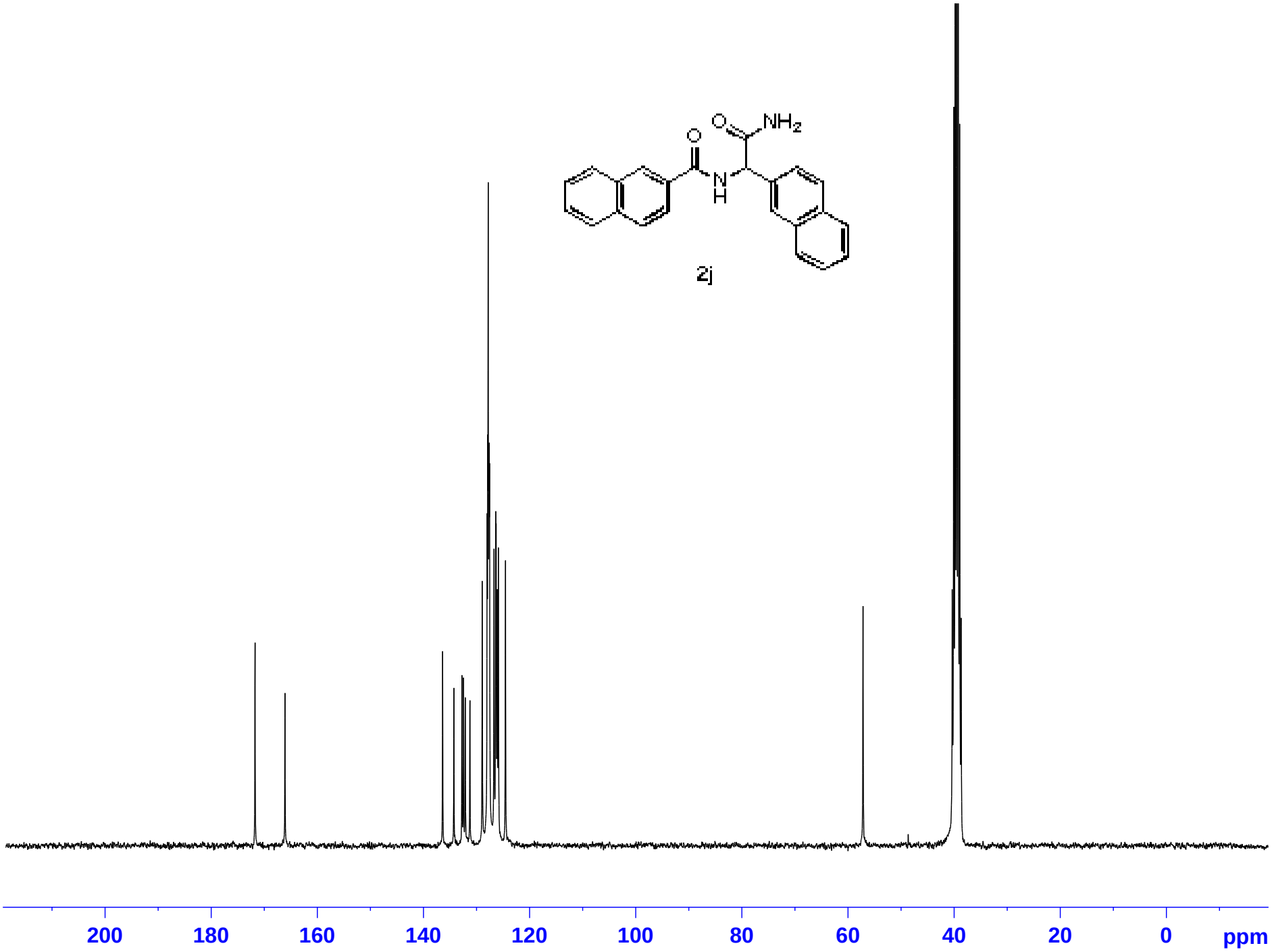
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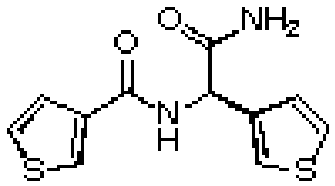
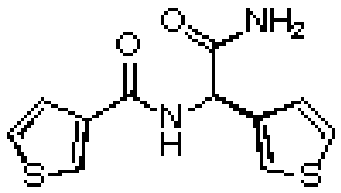
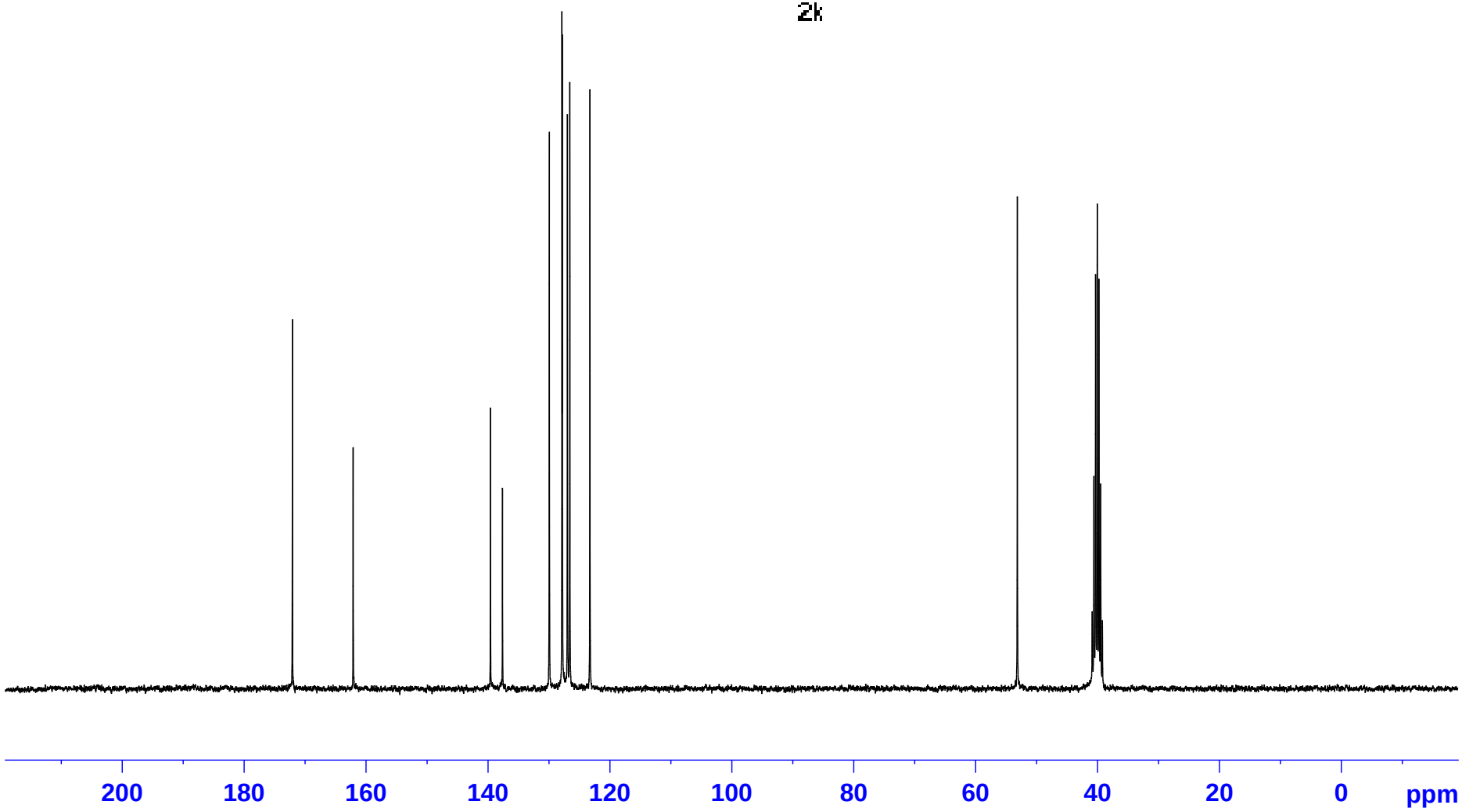
0
ppm

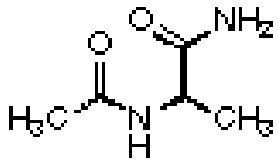


2k



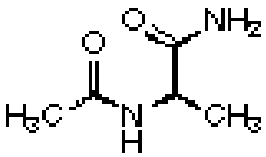
2k



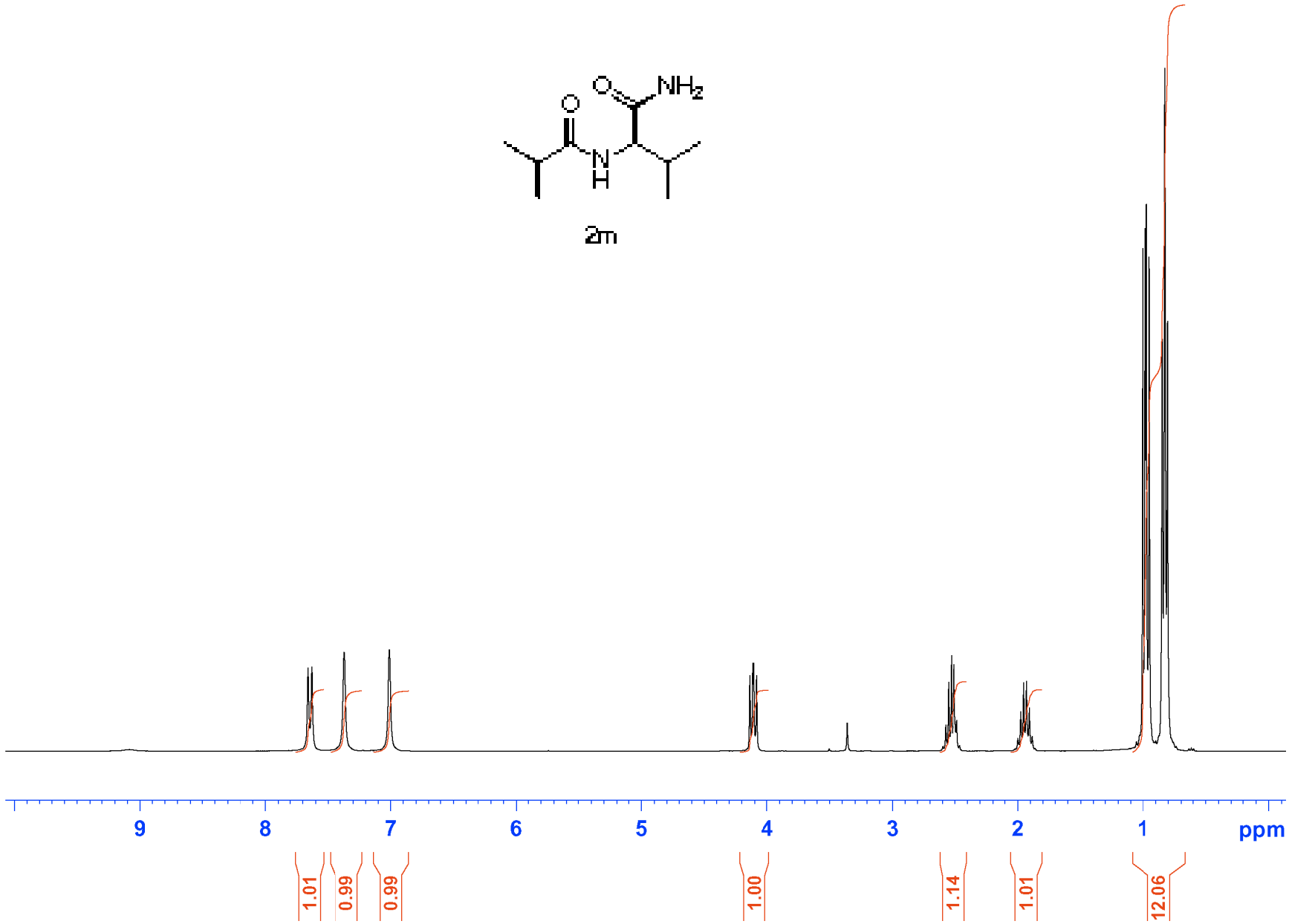

O
NH2
O
H3C
N
H
CH3

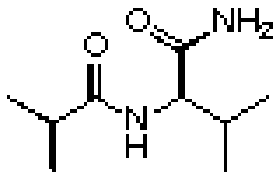
2

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.00
1.02
1.00
3.04
3.08

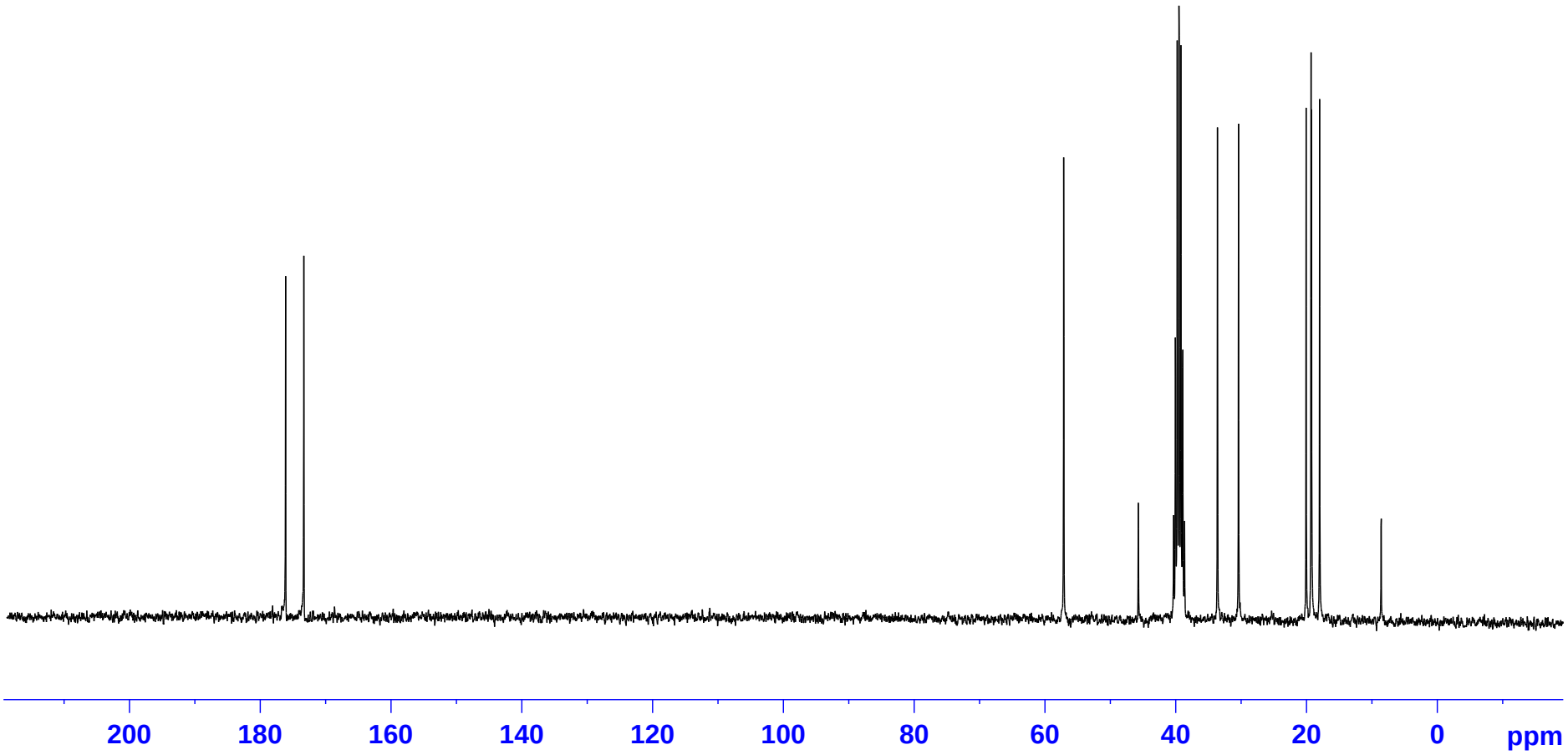


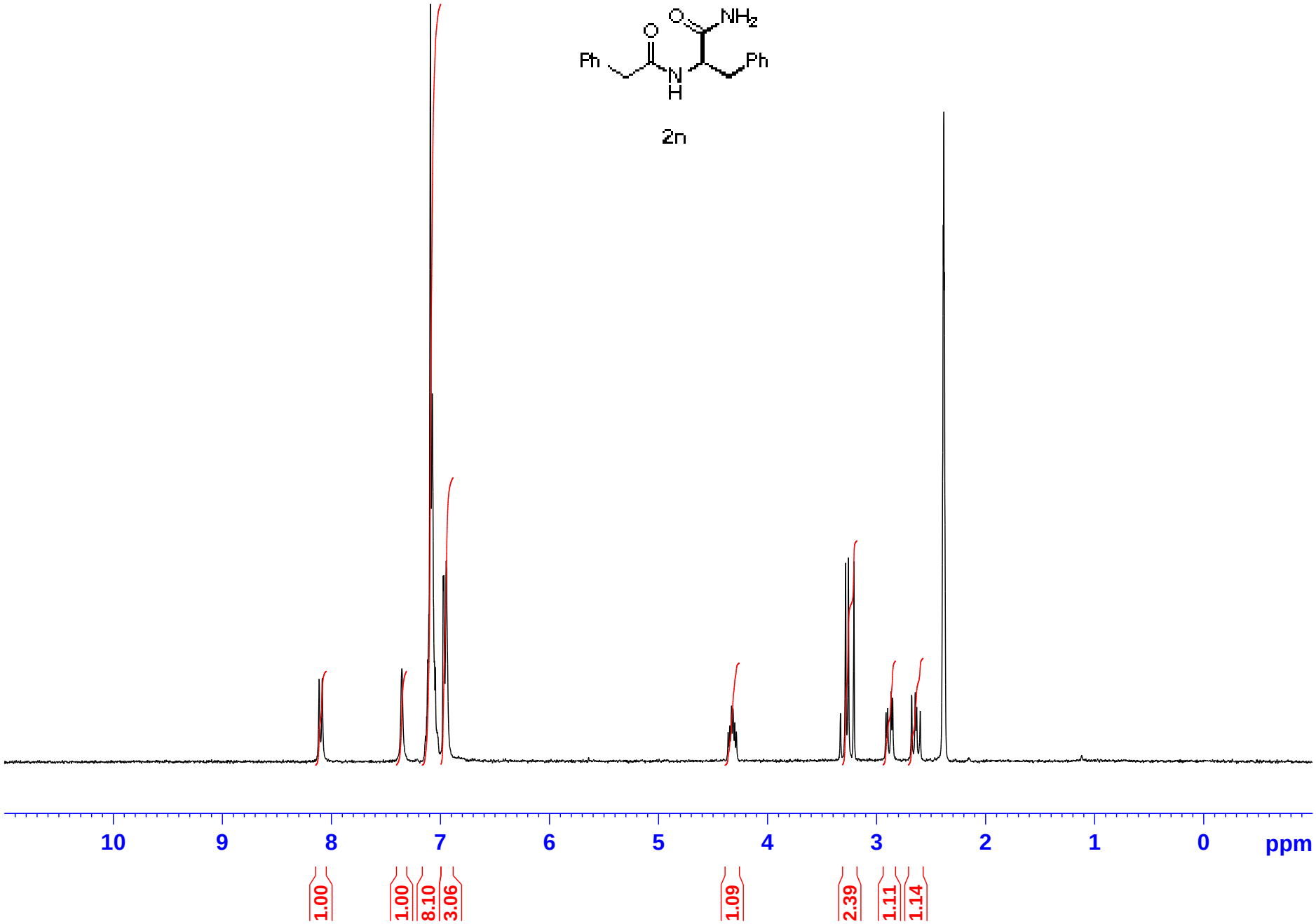
2

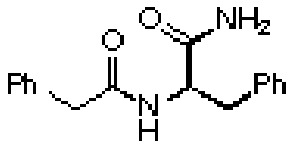

NH2
O
O
N
H
2m
9
8
7
6
5
4
3
2
1
ppm
1.01
0.99
0.99
1.00
1.14
1.01
12.06



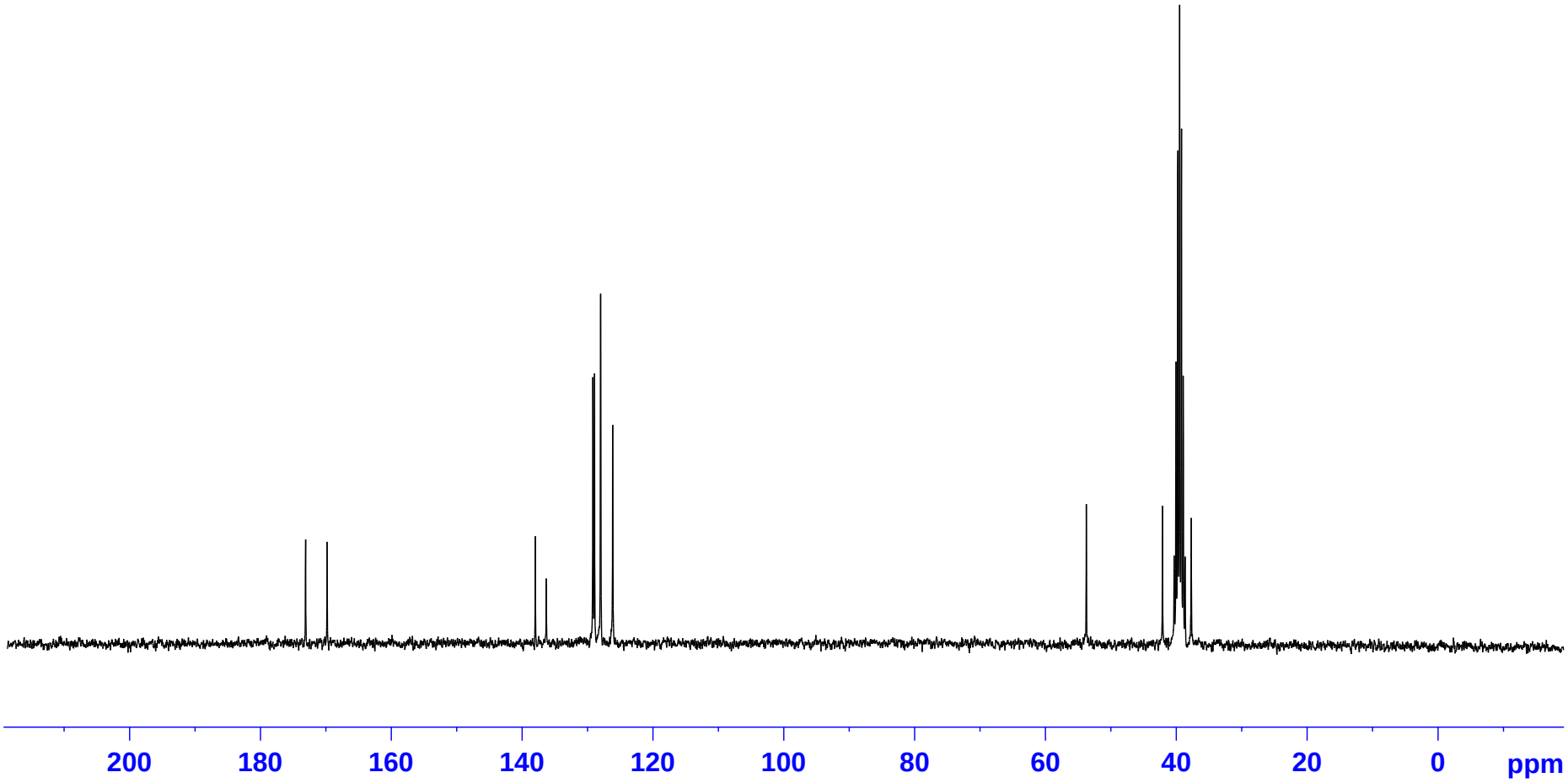
2m

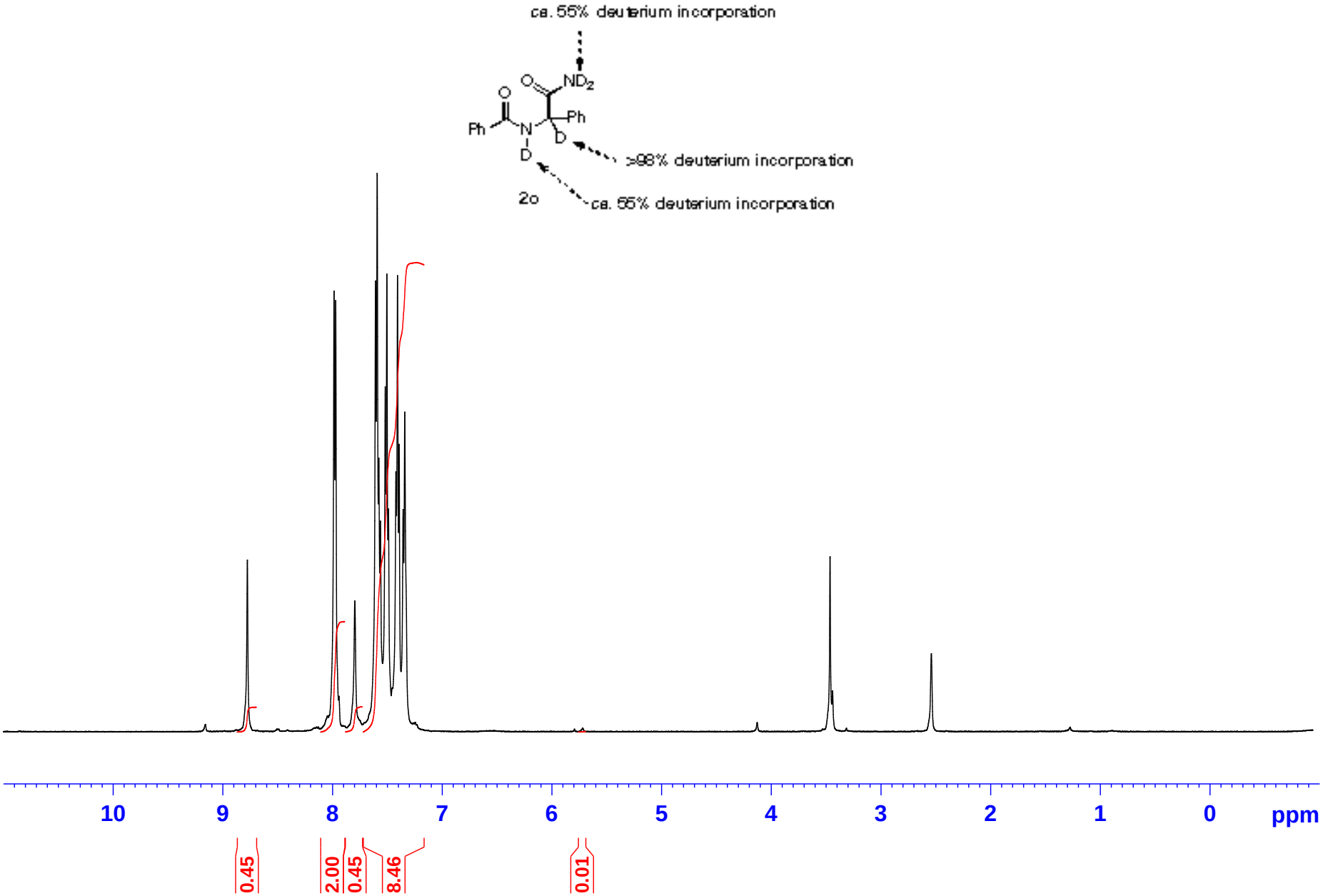


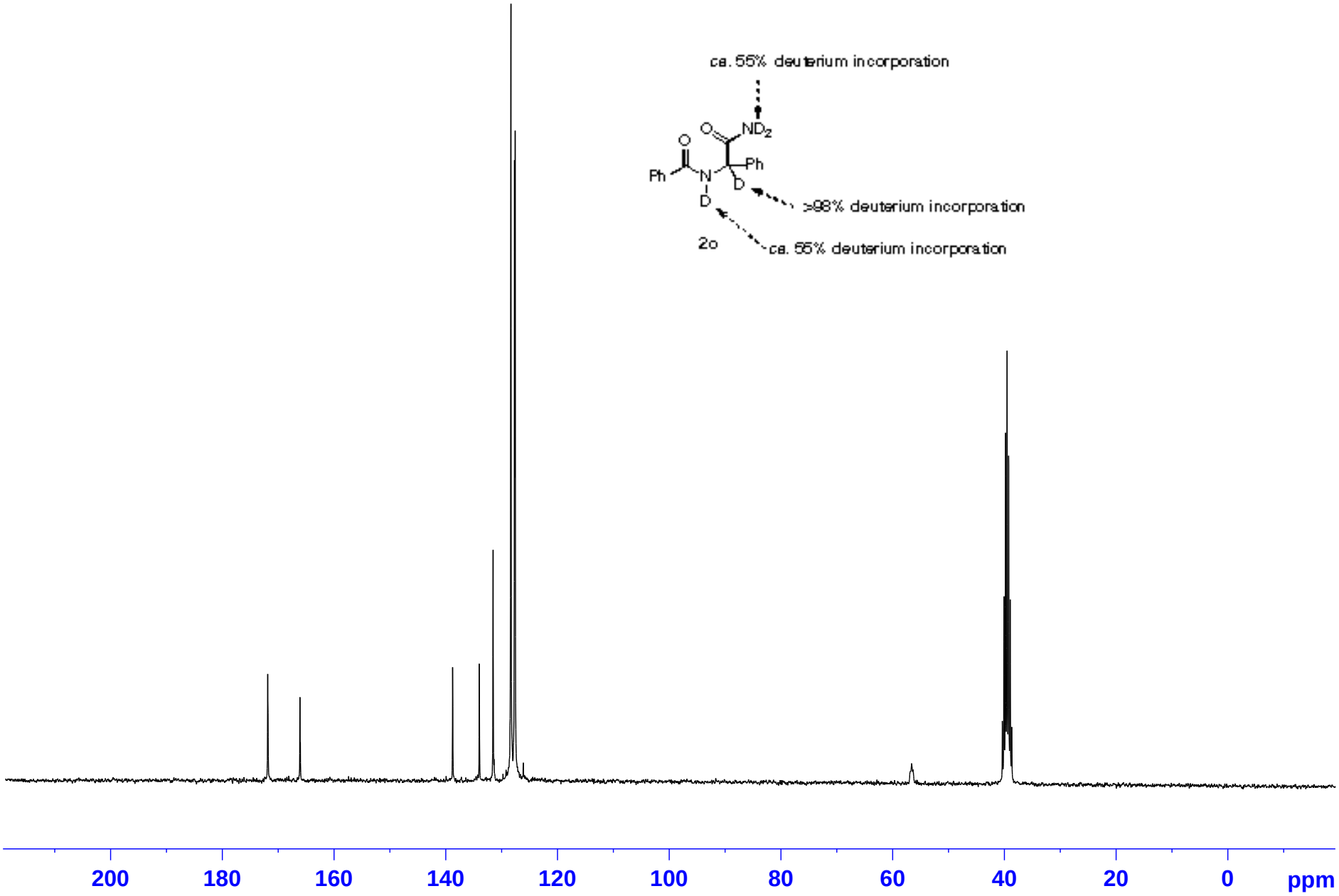

NH2
O
O
Ph
N
H
Ph
2n
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
8.10
3.06
1.09
2.39
1.11
1.14

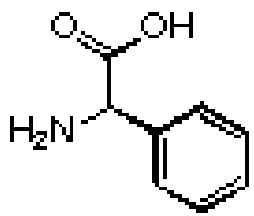


2n

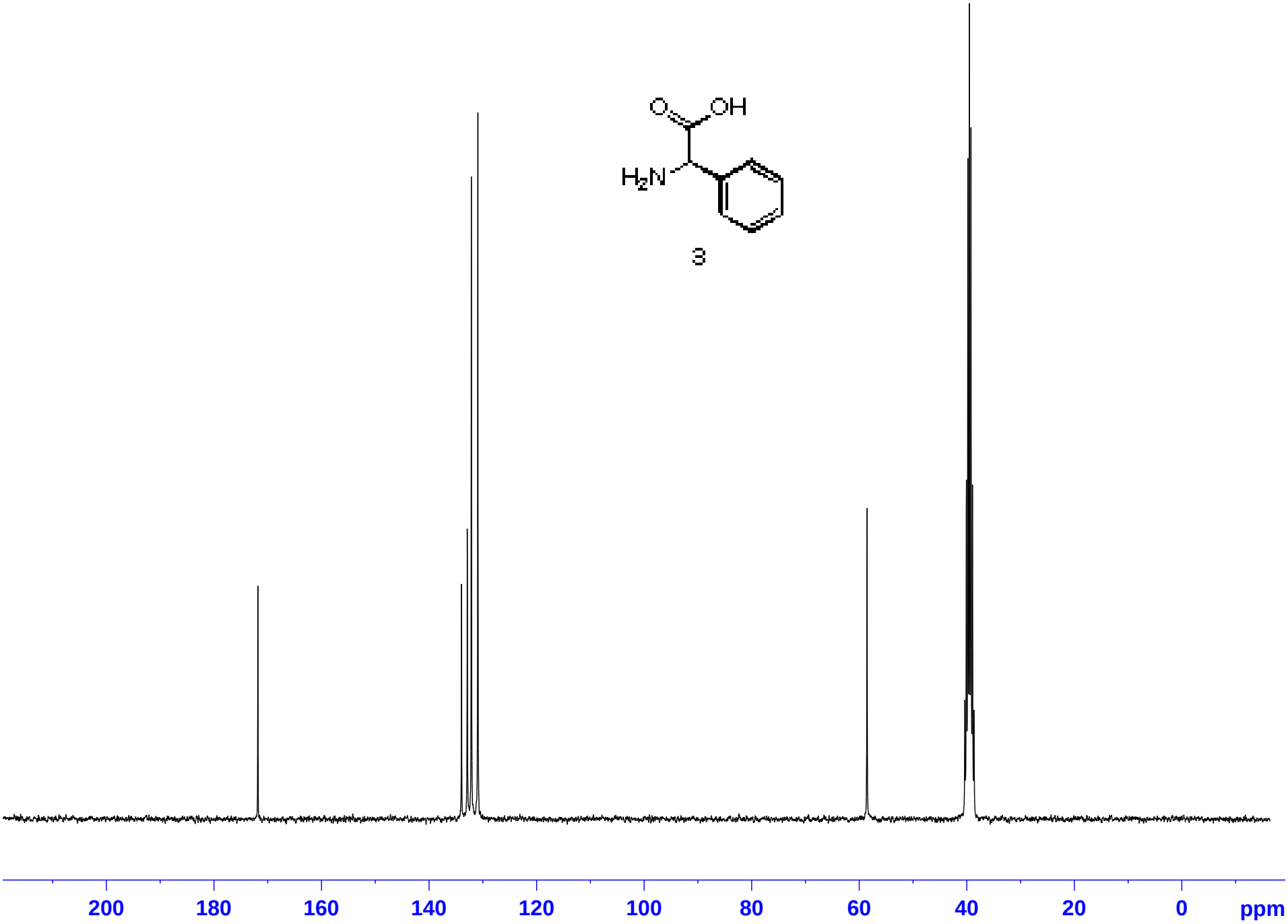



ca. 55% deuterium incorporation
ND2
O
O
Ph
N
Ph
D
D
>98% deuterium incorporation
2o
ca. 55% deuterium incorporation
10
9
8
7
6
5
4
3
2
1
0
ppm
0.45
2.00
0.45
8.46
0.01


ca. 55% deuterium incorporation
ND2
O
Ph
N
D
Ph
D
≥98% deuterium incorporation
ca. 55% deuterium incorporation
2o
200
180
160
140
120
100
80
60
40
20
0
ppm



3



3