Electronic Supplementary Material (ESI) for Chemical Communications

A Simple Base-Mediated Amidation of Aldehydes with Azides

Sameer S. Kulkarni, Xiangdong Hu, and Roman Manetsch*

Department of Chemistry, University of South Florida,
4202 E. Fowler Ave, Tampa, FL - 33620

manetsch@usf.edu

SUPPORTING INFORMATION

TABLE OF CONTENTS

SECTION TITLE **PAGE**

General: ...…….……...…….....2

Synthesis of azides: ……..…….3

Screening of various non-nucleophilic bases for amidation…….……...……5

Synthesis of amides: …….…....……...5

Experiment involving benzaldehyde-α-d_1: …….…...…16

References: ……...….17

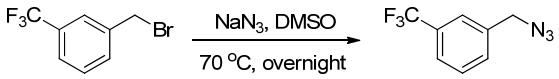
^{1}H and ^{13}C NMR Spectra: 18

General: All reagents and solvents were purchased from commercial sources and used without further purification. All reactions were run under an Argon atmosphere unless otherwise indicated. Prior to use of solvents in reactions, they were purified by passing the degassed solvents through a column of activated alumina and transferred by an oven-dried syringe or cannula. Thin layer chromatography was performed on Merck TLC plates (silica gel 60 F_{254}). ^{1}H NMR and ^{13}C NMR were recorded on a Varian Inova 400 (400 MHz) or a Bruker Avance DPX-250 (250 MHz) instrument. The HRMS data were measured on an Agilent 1100 Series MSD/TOF with electrospray ionization.

The azides **1a**,[1] **1b**,[2] **1d**,[3] **1e**,[4] **1f**,[5] **1i**,[6] **1j**,[7] **1l**,[8] and an aldehyde **2n**[9] were synthesized as previously reported in the literature. The *t*-BuOK (sublimed grade) was purchased from Sigma Aldrich.

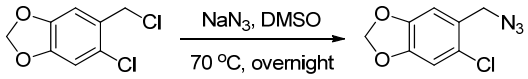
1. Synthesis of azides:

1.1 **1-(azidomethyl)-3-(trifluoromethyl)benzene (1c):**



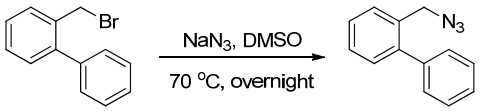
To a solution of 1-(bromomethyl)-3-(trifluoromethyl)benzene (1.0 g, 4.18 mmol) in DMSO (15 mL), was added sodium azide (326 mg, 5.0 mmol, 1.2 eq) and the resulting reaction mixture was stirred overnight at 70 °C. The reaction was then treated with H_2O (40 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (30 mL × 3), dried with Na_2SO_4 and concentrated under reduced pressure. The azide **1c** was then obtained by flash chromatography. Yield = 76%. R_f = 0.31 in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.55 (m, 2H), 7.51 – 7.48 (m, 2H), 4.42 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.74, 131.48, 131.42 (q, *J* = 32.5 Hz), 129.53, 125.25 (q, *J* = 3.7 Hz), 124.94 (q, *J* = 3.7 Hz), 124.12 (q, *J* = 272.4 Hz), 54.31 ppm.

1.2 **5-(azidomethyl)-6-chlorobenzo[*d*][1,3]dioxole (1g):**



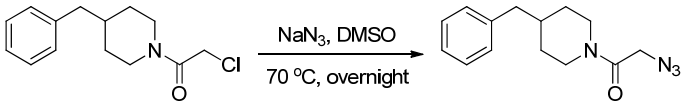
The azide **1g** was prepared following the procedure described for the synthesis of azide **1c**. Yield = 73%. R_f = 0.62 in hexanes : EtOAc = 5:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82 (s, 1H), 5.98 (s, 2H), 4.36 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.47, 147.14, 126.41, 126.12, 110.29, 109.85, 102.22, 52.35 ppm.

1.3 **2-(azidomethyl)-1,1'-biphenyl (1h):**



The azide **1h** was synthesized following the procedure described for the synthesis of azide **1c**. Yield = 83%. R_f = 0.22 in hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.42 – 7.37 (m, 4H), 7.36 – 7.30 (m, 3H), 4.28 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.42, 140.45, 132.99, 130.64, 129.76, 129.39, 128.53, 127.99, 127.65, 52.80 ppm.

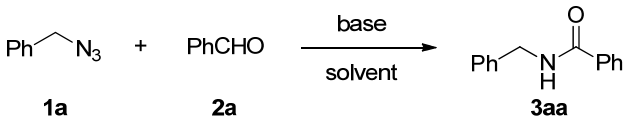
1.4 **2-azido-1-(4-benzylpiperidin-1-yl)ethanone (1k):**



The azide **1k** was prepared following the procedure described for the synthesis of azide **1c**, starting from 1-(4-benzylpiperidin-1-yl)-2-chloroethanone.[10] Yield = 54%. R_f = 0.3 in hexanes : EtOAc = 2:1. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.09 (m, 5H), 4.58 (d, *J* = 13.3 Hz, 1H), 3.92 (s, 2H), 3.61 (d, *J* = 13.7 Hz, 1H), 3.05 – 2.87 (m, 1H), 2.67 – 2.47 (m, 3H), 1.90 – 1.65 (m, 3H), 1.19 (q, *J* = 11.8 Hz, 2H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.20, 139.61, 128.95, 128.20, 125.98, 50.47, 45.11, 42.66, 42.31, 37.83, 32.18, 31.43 ppm. HRMS (ESI) calcd for $C_{14}H_{18}N_4O$ $[M+H]^+$: 259.1553, found: 259.1557

2. Screening of various non-nucleophilic bases for amidation:

Following additional bases were screened using benzyl azide (**1a**) and benzaldehyde (**2a**) as substrates.



1a **2a** **3aa**

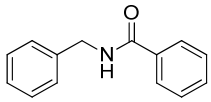
Entry	Base	Solvent	Reaction Temp.	Yield (%)[a]
1	DABCO	DMF	rt	-
2	TEA	DMF	rt	-
3	DMAP	DMF	rt	-
4	2,6-lutidine	DMF	rt	-
5	NaH	DMF	rt	-
6	*t*-BuLi	THF	-78 °C to rt[b]	-
7	LDA	THF	-78 °C to rt[b]	10

General reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (0.75 mmol), solvent (2.5 mL), 15 min; [a] Isolated yield based on **1a**; [b] warmed up to rt over 1 h.

3. Synthesis of amides:

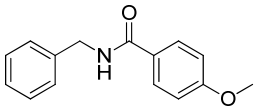
General Procedure: To a mixture of the azide (0.5 mmol) and an aldehyde (0.6 mmol, 1.2 eq) in DMF (2.5 mL) at room temperature, *t*-BuOK (1.0 or 2.0 mmol, 2 or 4 eq) was carefully added and bubbling was observed immediately. After the completion of reaction, (monitored by TLC) water (10 mL) was added and the pH was adjusted to 7.0 using saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc (20 mL × 2) and the combined organic layers were washed with brine (30 mL × 3), dried with Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash chromatography.

3.1 ***N*-benzylbenzamide (3aa):**



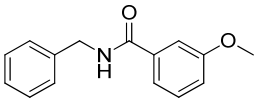
Yield = 72%. R_f = 0.41 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.46 – 7.37 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.20 (m, 4H), 4.52 (d, *J* = 5.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.68, 138.49, 134.37, 131.39, 128.59, 128.43, 127.68, 127.30, 127.16, 43.87 ppm. HRMS (ESI) calcd for $C_{14}H_{13}NO$ $[M+H]^+$: 212.1070, found: 212.1068

3.2 ***N*-benzyl-4-methoxybenzamide (3ab):**



Yield = 81%. R_f = 0.31 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.35 – 7.18 (m, 5H), 7.07 (s, 1H), 6.84 – 6.77 (m, 2H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.76 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.16, 162.19, 138.74, 128.99, 128.65, 127.79, 127.35, 126.75, 113.71, 55.41, 43.94 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, found: 242.1172

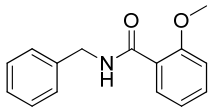
3.3 ***N*-benzyl-3-methoxybenzamide (3ac):**



Yield = 81%. R_f = 0.35 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 1H), 7.32 (d, *J* = 0.5 Hz, 1H), 7.32 – 7.29 (m, 3H), 7.29 – 7.28 (m, 1H), 7.28 – 7.24 (m, 2H), 7.03 – 6.97 (m, 1H), 6.61 (s, 1H), 4.59 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.42, 159.99, 138.35, 136.02, 129.71,

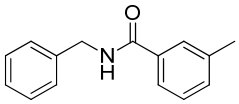
128.91, 128.03, 127.74, 118.89, 117.92, 112.57, 55.59, 44.29 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, found: 242.1175

3.4 ***N*-benzyl-2-methoxybenzamide (3ad):**



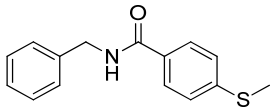
Yield = 45%. R_f = 0.39 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.36 – 7.28 (m, 4H), 7.27 – 7.21 (m, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 4.66 (d, *J* = 5.7 Hz, 2H), 3.83 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.33, 157.48, 138.77, 132.79, 132.20, 128.57, 127.42, 127.16, 121.19, 111.37, 55.87, 43.66 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, found: 242.1177

3.5 ***N*-benzyl-3-methylbenzamide (3ae):**



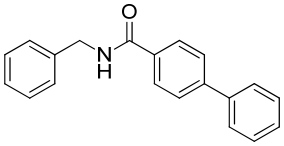
Yield = 75%. R_f = 0.51 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 3H), 7.29 – 7.16 (m, 7H), 4.51 (d, *J* = 5.9 Hz, 2H), 2.28 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.84, 138.57, 138.06, 134.31, 132.01, 128.43, 128.19, 127.86, 127.55, 127.11, 124.14, 43.71, 21.17 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO$ $[M+H]^+$: 226.1226, found: 226.1230

3.6 ***N*-benzyl-4-(methylthio)benzamide (3af):**



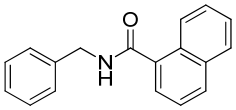
Yield = 83%. R_f = 0.37 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 2H), 7.34 – 7.25 (m, 5H), 7.23 – 7.20 (m, 2H), 6.42 (s, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 2.48 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.00, 143.65, 138.44, 130.63, 128.92, 128.05, 127.74, 127.57, 125.58, 44.25, 15.21 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NOS$ $[M+H]^+$: 258.0947, found: 258.0951

3.7 ***N*-benzyl-[1,1'-biphenyl]-4-carboxamide (3ag):**



Yield = 74%. R_f = 0.49 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 6.5 Hz, 4H), 7.44 (t, *J* = 6.4 Hz, 2H), 7.41 – 7.22 (m, 6H), 6.96 (s, 1H), 4.62 (d, *J* = 4.5 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.34, 144.40, 140.11, 138.48, 133.18, 129.04, 128.87, 128.47, 128.12, 127.99, 127.73, 127.31, 44.23 ppm. HRMS (ESI) calcd for $C_{20}H_{17}NO$ $[M+H]^+$: 288.1383, found: 288.1384

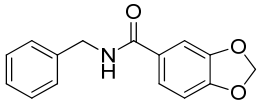
3.8 ***N*-benzyl-1-naphthamide (3ah):**



Yield = 67%. R_f = 0.49 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.34 – 7.21 (m, 6H), 6.85 (s, 1H), 4.52 (d, *J* = 5.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.49,

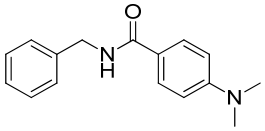
138.34, 134.19, 133.62, 130.51, 130.18, 128.68, 128.26, 127.75, 127.43, 126.99, 126.33, 125.46, 125.00, 124.62, 43.85 ppm. HRMS (ESI) calcd for $C_{18}H_{15}NO$ $[M+H]^+$: 262.1226, found: 262.1224

3.9 ***N*-benzylbenzo[*d*][1,3]dioxole-5-carboxamide (3ai):**



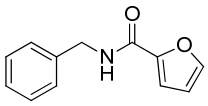
Yield = 86%. R_f = 0.32 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 7H), 6.76 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.52 (s, 1H), 5.97 (s, 2H), 4.56 (d, *J* = 5.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.84, 150.49, 148.11, 138.48, 128.89, 128.76, 128.01, 127.69, 121.76, 108.12, 107.86, 101.83, 44.28 ppm. HRMS (ESI) calcd for $C_{15}H_{13}NO_3$ $[M+H]^+$: 256.0968, found: 256.0966

3.10 ***N*-benzyl-4-(dimethylamino)benzamide (3aj):**



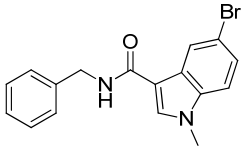
Yield = 83%. R_f = 0.26 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 9.0 Hz, 2H), 7.35 – 7.25 (m, 5H), 6.64 (d, *J* = 9.0 Hz, 2H), 6.26 (s, 1H), 4.61 (d, *J* = 5.7 Hz, 2H), 2.99 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.44, 152.63, 139.05, 128.81, 128.63, 128.01, 127.49, 121.25, 111.21, 44.04, 40.27 ppm. HRMS (ESI) calcd for $C_{16}H_{18}N_2O$ $[M+H]^+$: 255.1492, found: 255.1500

3.11 ***N*-benzylfuran-2-carboxamide (3ak):**



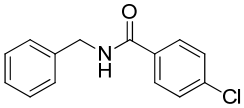
Yield = 86%. R_f = 0.48 in hexanes : EtOAc = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.30 – 7.18 (m, 4H), 7.06 (d, *J* = 3.2 Hz, 2H), 6.43 – 6.37 (m, 1H), 4.53 (d, *J* = 5.9 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.39, 147.89, 143.96, 138.17, 128.58, 127.73, 127.39, 114.18, 111.99, 42.99 ppm. HRMS (ESI) calcd for $C_{12}H_{11}NO_2$ $[M+H]^+$: 202.0863, found: 202.0862

3.12 ***N*-benzyl-5-bromo-1-methyl-1*H*-indole-3-carboxamide (3al):**



Yield = 72%. R_f = 0.25 in hexanes : EtOAc = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 1H), 7.51 (s, 1H), 7.36 – 7.25 (m, 6H), 7.16 – 7.13 (m, 1H), 6.22 (s, 1H), 4.63 (d, *J* = 5.8 Hz, 2H), 3.71 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.69, 138.99, 136.00, 132.47, 128.90, 127.97, 127.60, 127.56, 125.78, 123.53, 115.27, 111.51, 110.43, 43.65, 33.59 ppm. HRMS (ESI) calcd for $C_{17}H_{15}BrN_2O$ $[M+H]^+$: 343.0441, found: 343.0440

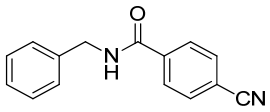
3.13 ***N*-benzyl-4-chlorobenzamide (3am):**



Yield = 80%. R_f = 0.55 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.25 (m, 7H), 6.54 (s, 1H), 4.59 (d, *J* = 5.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.53, 138.17, 137.98, 132.95, 129.02, 128.63,

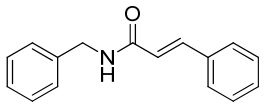
128.10, 127.90, 44.41 ppm. HRMS (ESI) calcd for $C_{14}H_{12}ClNO$ $[M+H]^+$: 246.0680, found: 246.0678

3.14 ***N*-benzyl-4-cyanobenzamide (3an):**



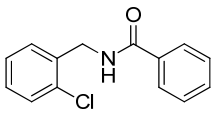
Yield = 37%. R_f = 0.35 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.25 (m, 5H), 7.00 (s, 1H), 4.56 (d, *J* = 5.7 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.85, 138.36, 137.75, 132.49, 128.95, 127.93, 127.91, 118.14, 115.10, 44.37 ppm. HRMS (ESI) calcd for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1022, found: 237.1023

3.15 ***N*-benzylcinnamamide (3ao):**



Yield = 19%. R_f = 0.38 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 15.6 Hz, 1H), 7.43 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.35 – 7.22 (m, 8H), 6.52 (s, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.14, 141.36, 138.40, 134.97, 129.79, 128.92, 128.83, 128.16, 127.95, 127.62, 120.80, 43.93 ppm. HRMS (ESI) calcd for $C_{16}H_{15}NO$ $[M+H]^+$: 238.1226, found: 238.1223

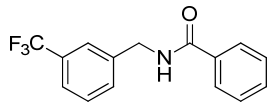
3.16 ***N*-(2-chlorobenzyl)benzamide (3ba):**



Yield = 78%. R_f = 0.5 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 2H), 7.49 – 7.33 (m, 5H), 7.23 – 7.18 (m, 2H), 6.75 (s, 1H), 4.69 (d, *J* =

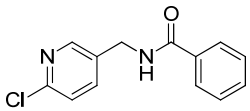
6.0 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.55, 135.79, 134.42, 133.84, 131.76, 130.48, 129.73, 129.17, 128.75, 127.32, 127.17, 42.20 ppm. HRMS (ESI) calcd for $C_{14}H_{12}ClNO$ $[M+H]^+$: 246.0680, found: 246.0677

3.17 ***N*-(3-(trifluoromethyl)benzyl)benzamide (3ca):**



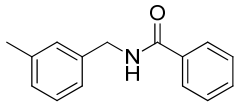
Yield = 52%. R_f = 0.37 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2H), 7.57 – 7.46 (m, 4H), 7.45 – 7.37 (m, 3H), 6.75 (s, 1H), 4.65 (d, *J* = 5.9 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.79, 139.56, 134.21, 131.96, 131.37 (q, *J* = 1.3 Hz), 131.22 (q, *J* = 32.2 Hz), 129.42, 128.85, 127.19, 124.70 – 124.50 (m, two quartets being merged, *J* = 3.8 Hz), 124.20 (q, *J* = 272.4 Hz), 43.73 ppm. HRMS (ESI) calcd for $C_{15}H_{12}F_3NO$ $[M+H]^+$: 280.0944, found: 280.0949

3.18 ***N*-((6-chloropyridin-3-yl)methyl)benzamide (3da):**



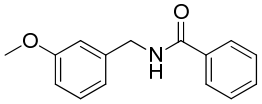
Yield = 65%. R_f = 0.33 in hexanes : EtOAc = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.77 – 7.72 (m, 2H), 7.61 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.40 – 7.34 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.08 (s, 1H), 4.53 (d, *J* = 6.0 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.96, 150.68, 149.07, 138.83, 133.88, 133.37, 132.06, 128.82, 127.19, 124.48, 40.85 ppm. HRMS (ESI) calcd for $C_{13}H_{11}ClN_2O$ $[M+H]^+$: 247.0633, found: 247.0635

3.19 ***N*-(3-methylbenzyl)benzamide (3ea):**



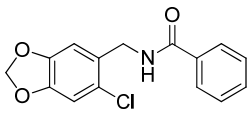
Yield = 58%. R_f = 0.45 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.50 – 7.44 (m, 1H), 7.42 – 7.36 (m, 2H), 7.24 – 7.19 (m, 1H), 7.15 – 7.06 (m, 3H), 6.58 (s, 1H), 4.57 (d, *J* = 5.7 Hz, 2H), 2.32 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.49, 138.63, 138.30, 134.59, 131.65, 128.83, 128.83, 128.71, 128.49, 127.16, 125.10, 44.27, 21.55 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO$ $[M+H]^+$: 226.1226, found: 226.1231

3.20 ***N*-(3-methoxybenzyl)benzamide (3fa):**



Yield = 75%. R_f = 0.32 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2H), 7.51 – 7.44 (m, 1H), 7.42 – 7.36 (m, 2H), 7.27 – 7.22 (m, 1H), 6.93 – 6.86 (m, 2H), 6.81 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.60 (s, 1H), 4.58 (d, *J* = 5.7 Hz, 2H), 3.77 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.56, 160.09, 139.98, 134.53, 131.70, 129.97, 128.74, 127.15, 120.26, 113.65, 113.17, 55.41, 44.23 ppm. HRMS (ESI) calcd for $C_{15}H_{15}NO_2$ $[M+H]^+$: 242.1176, found: 242.1179

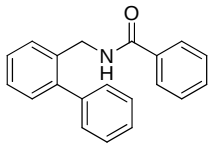
3.21 ***N*-((6-chlorobenzo[*d*][1,3]dioxol-5-yl)methyl)benzamide (3ga):**



Yield = 77%. R_f = 0.4 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.49 – 7.43 (m, 1H), 7.41 – 7.35 (m, 2H), 6.91 (s, 1H), 6.80 (s, 1H), 6.70 (s, 1H), 5.92 (s, 2H), 4.57 (d, *J* = 6.0 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$)

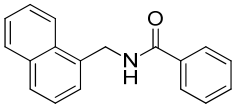
δ 167.56, 147.91, 147.04, 134.39, 131.77, 129.03, 128.75, 127.16, 125.61, 110.30, 110.03, 102.03, 42.08 ppm. HRMS (ESI) calcd for $C_{15}H_{12}ClNO_3$ $[M+H]^+$: 290.0578, found: 290.0583

3.22 ***N*-([1,1'-biphenyl]-2-ylmethyl)benzamide (3ha):**



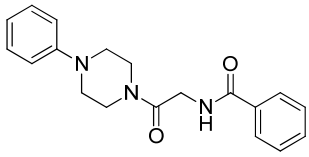
Yield = 78%. R_f = 0.53 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.60 (m, 2H), 7.49 – 7.40 (m, 4H), 7.38 – 7.32 (m, 7H), 7.29 – 7.26 (m, 1H), 6.26 (s, 1H), 4.61 (d, *J* = 5.6 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.20, 141.89, 140.95, 135.61, 134.51, 131.57, 130.44, 129.15, 129.03, 128.67, 128.65, 128.03, 127.73, 127.58, 127.02, 42.27 ppm. HRMS (ESI) calcd for $C_{20}H_{17}NO$ $[M+H]^+$: 288.1383, found: 288.1383

3.23 ***N*-(naphthalen-1-ylmethyl)benzamide (3ia):**



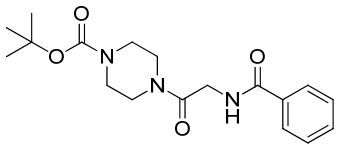
Yield = 60%. R_f = 0.47 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 1H), 7.89 – 7.85 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.55 – 7.45 (m, 3H), 7.45 – 7.39 (m, 2H), 7.38 – 7.32 (m, 2H), 6.48 (s, 1H), 5.05 (d, *J* = 5.3 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.36, 134.46, 134.09, 133.58, 131.68, 131.66, 128.98, 128.91, 128.71, 127.15, 127.04, 126.91, 126.22, 125.59, 123.68, 42.54 ppm. HRMS (ESI) calcd for $C_{18}H_{15}NO$ $[M+H]^+$: 262.1226, found: 262.1225

3.24 ***N*-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)benzamide (3ja):**



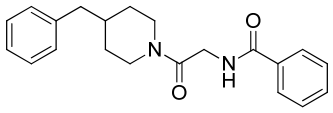
Yield = 56%. R_f = 0.17 in hexanes : EtOAc = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 7.35 (s, 1H), 7.30 – 7.25 (m, 2H), 6.93 – 6.88 (m, 3H), 4.28 (d, *J* = 4.0 Hz, 2H), 3.83 – 3.79 (m, 2H), 3.62 – 3.58 (m, 2H), 3.21 – 3.15 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.38, 166.74, 150.89, 134.05, 131.85, 129.47, 128.74, 127.26, 121.02, 116.99, 49.77, 49.53, 44.58, 42.22, 41.90 ppm. HRMS (ESI) calcd for $C_{19}H_{21}N_3O_2$ $[M+H]^+$: 324.1707, found: 324.1716

3.25 ***tert*-butyl 4-(2-benzamidoacetyl)piperazine-1-carboxylate (3ka):**



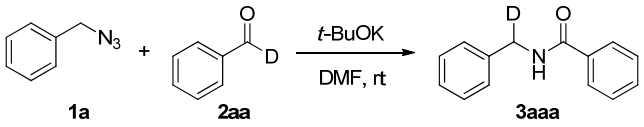
Yield = 45%. R_f = 0.12 in hexanes : EtOAc = 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.46 (ddd, *J* = 6.4, 3.7, 1.3 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.31 (s, 1H), 4.22 (d, *J* = 4.0 Hz, 2H), 3.63 – 3.56 (m, 2H), 3.48 – 3.37 (m, 6H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.39, 166.95, 154.55, 133.94, 131.85, 128.71, 127.23, 80.70, 44.45, 42.05, 41.89, 28.50 ppm. HRMS (ESI) calcd for $C_{18}H_{25}N_3O_4$ $[M+Na]^+$: 370.1737, found: 370.1738

3.26 ***N*-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)benzamide (3la):**



Yield = 76%. R_f = 0.14 in hexanes : EtOAc = 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 2H), 7.51 – 7.46 (m, 1H), 7.45 – 7.37 (m, 3H), 7.31 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 7.14 – 7.10 (m, 2H), 4.62 – 4.52 (m, 1H), 4.29 – 4.12 (m, 2H), 3.80 – 3.70 (m, 1H), 2.96 (tt, *J* = 15.6, 8.0 Hz, 1H), 2.65 – 2.52 (m, 3H), 1.84 – 1.67 (m, 3H), 1.26 – 1.11 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.30, 166.26, 139.79, 134.13, 131.73, 129.20, 128.67, 128.51, 127.22, 126.31, 44.85, 42.97, 42.69, 41.85, 38.24, 32.36, 31.73 ppm. HRMS (ESI) calcd for $C_{21}H_{24}N_2O_2$ $[M+H]^+$: 337.1911, found: 337.1904

4. Experiment involving benzaldehyde-α-d_1:



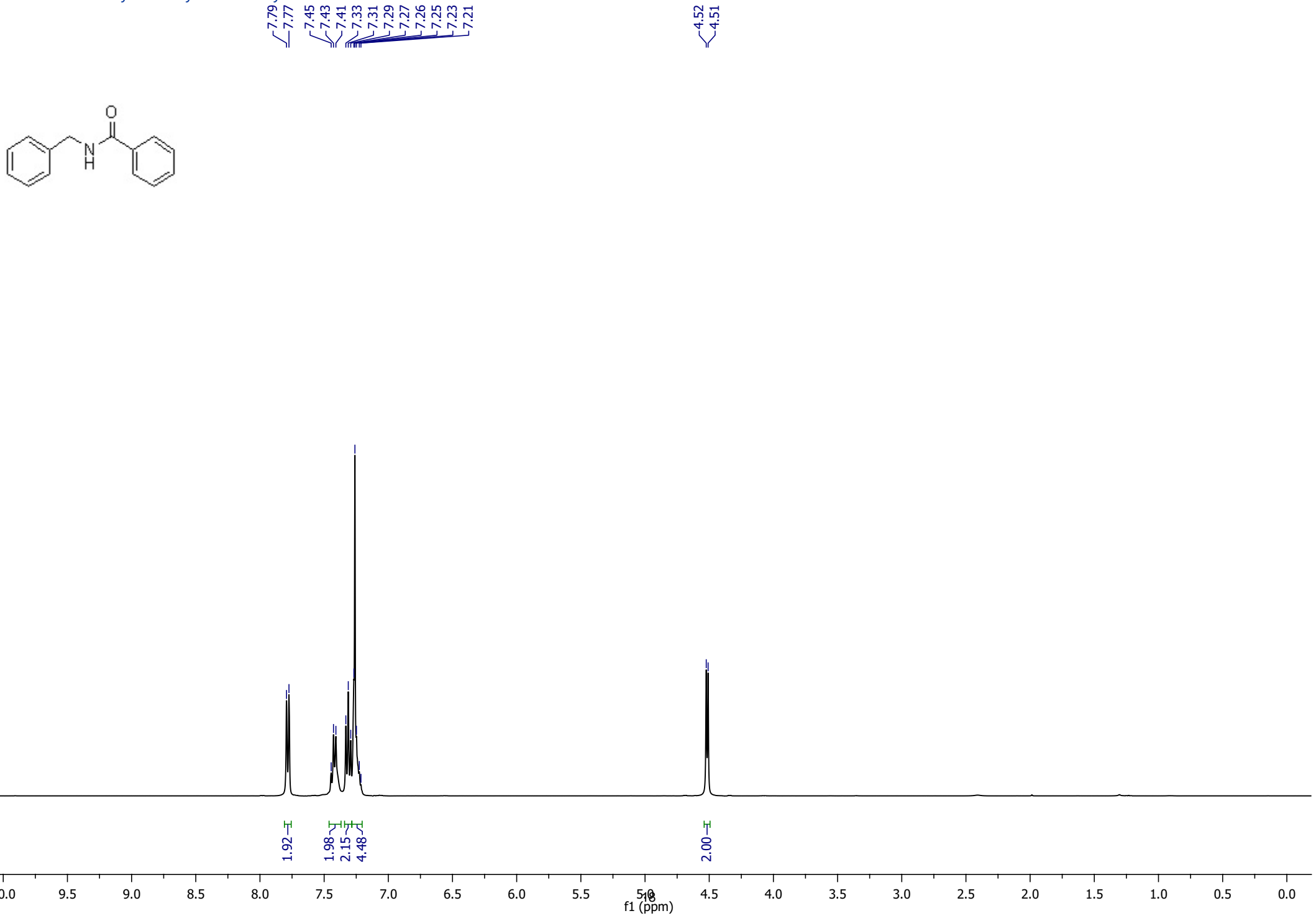
1a **2aa** **3aaa**

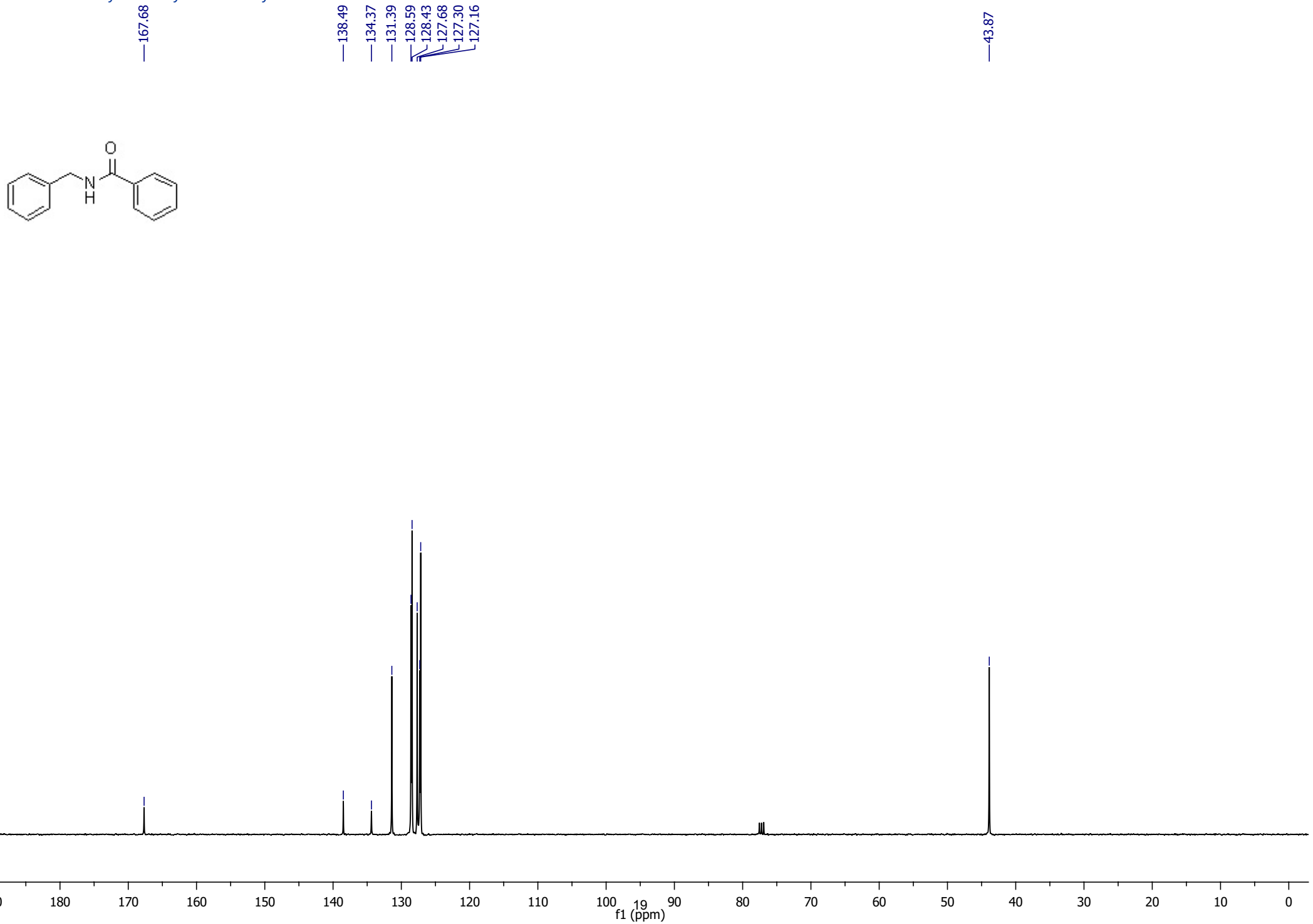
All the spectral data (^{1}H, ^{13}C, and ^{2}H NMR) is included (see pages 78 – 80). From the ^{1}H NMR spectroscopy, 50% deuterium incorporation was observed (see page 78). HRMS (ESI) calcd for $C_{14}H_{12}DNO$ $[M+H]^+$: 213.1133, found: 213.1132

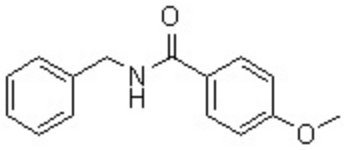
(Note: ^{1}H NMR spectrum was recorded on a Agilent Technologies Direct Drive 500 MHz instrument with a cryogenic triple resonance (TR) 5mm indirect detection probe, while ^{13}C and ^{2}H NMR spectra were recorded on a Varian Inova 400 MHz instrument.)

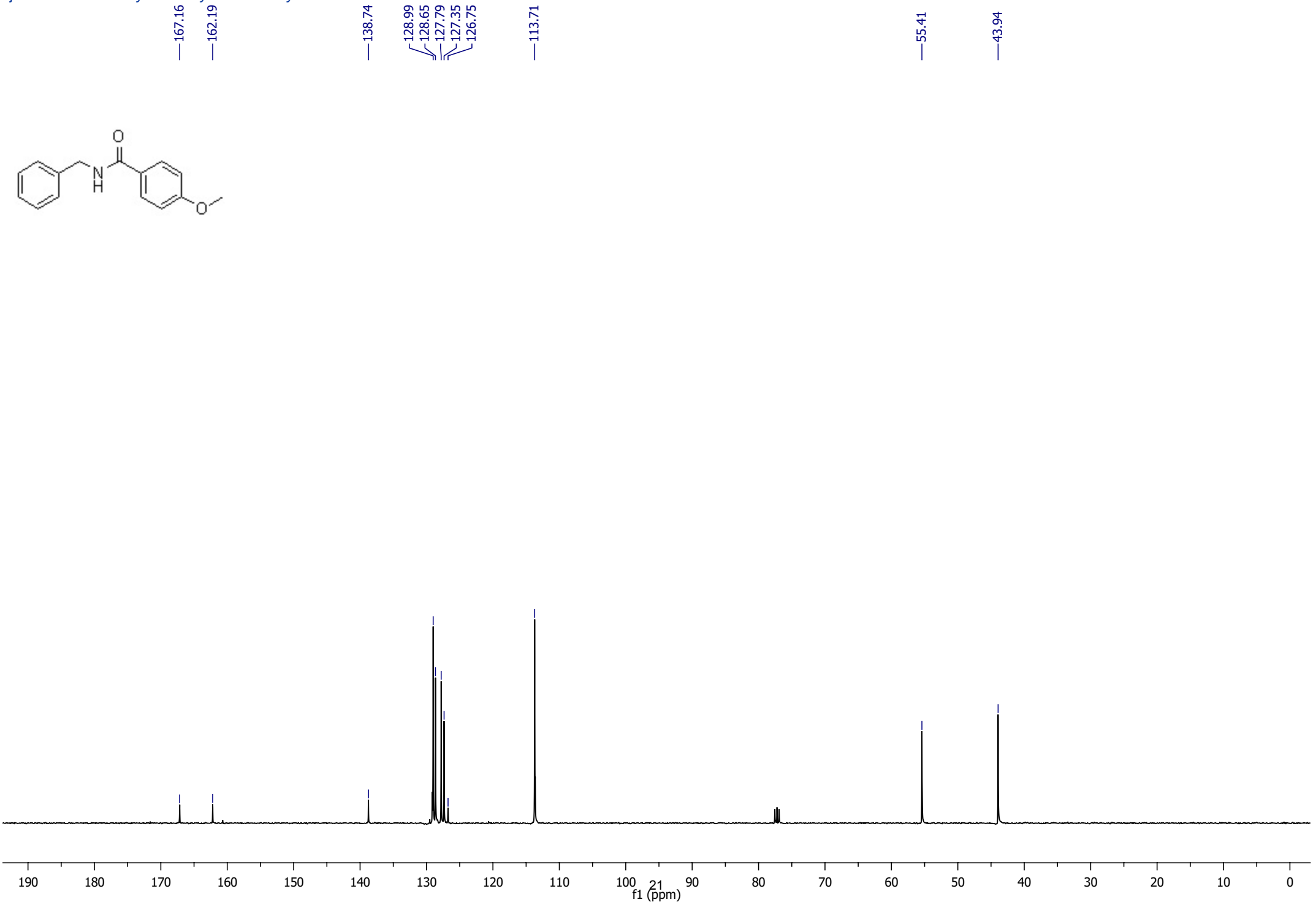
References:

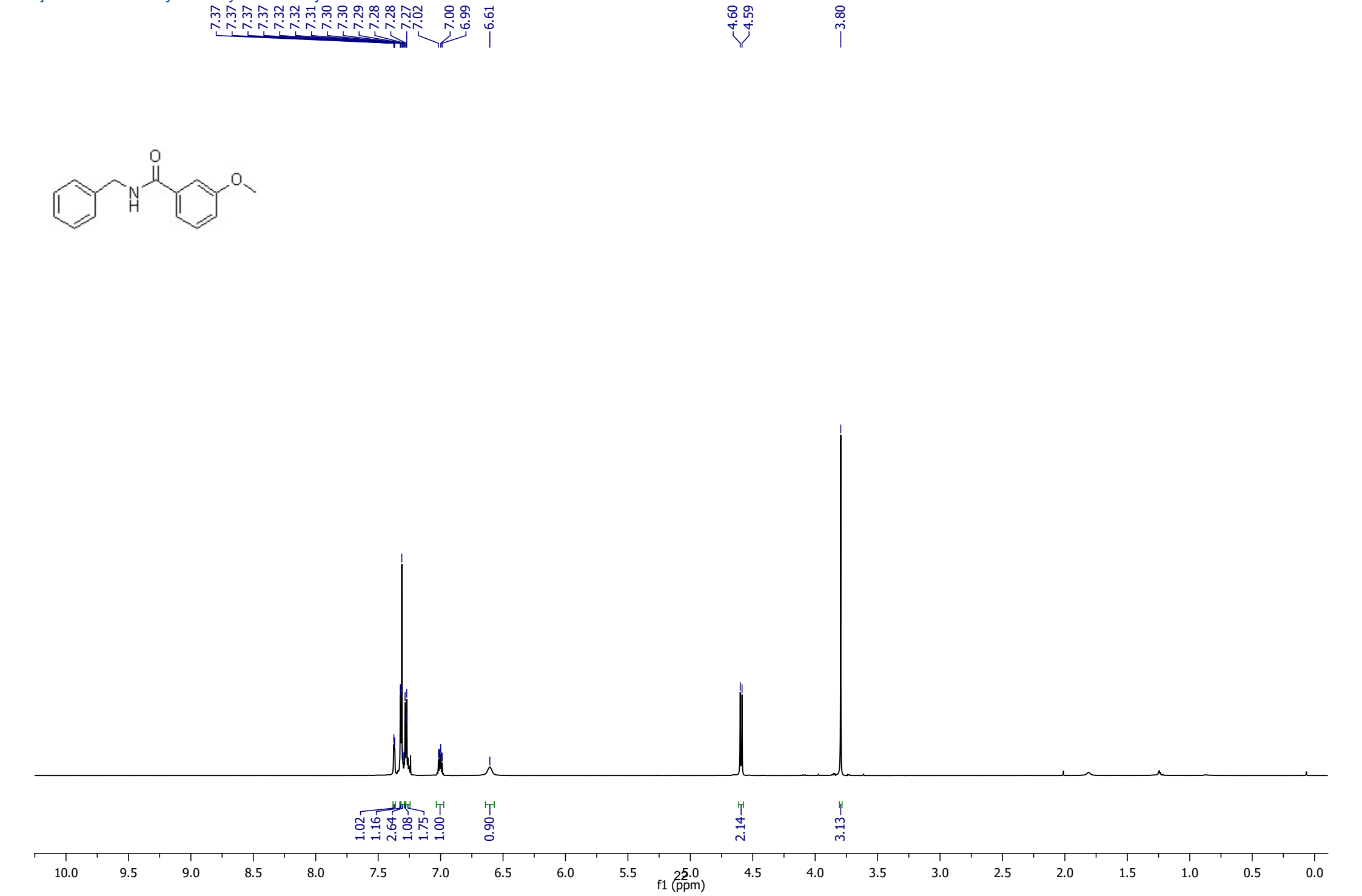
1. S. G. Alvarez and M. T. Alvarez, *Synthesis*, 1997, 413-414.
2. A. Chakraborty, S. Dey, S. Sawoo, N. N. Adarsh and A. Sarkar, *Organometallics*, 2010, **29**, 6619-6622.
3. W. Tang and D. Q. Shi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 496-502.
4. X. L. Wang, K. Wan and C. H. Zhou, *Eur. J. Med. Chem.*, 2010, **45**, 4631-4639.
5. J. A. Stefely, R. Palchaudhuri, P. A. Miller, R. J. Peterson, G. C. Moraski, P. J. Hergenrother and M. J. Miller, *J. Med. Chem.*, 2010, **53**, 3389-3395.
6. T. Suzuki, Y. Ota, Y. Kasuya, M. Mutsuga, Y. Kawamura, H. Tsumoto, H. Nakagawa, M. G. Finn and N. Miyata, *Angew. Chem., Int. Ed.*, 2010, **49**, 6817-6820.
7. X. R. Zhang, X. H. Yang and S. S. Zhang, *Synth. Commun.*, 2009, **39**, 830-844.
8. Y. Angell, D. Chen, F. Brahimi, H. U. Saragovi and K. Burgess, *J. Am. Chem. Soc.*, 2008, **130**, 556-565.
9. M. Chakrabarty, R. Basak, Y. Harigaya and H. Takayanagi, *Tetrahedron*, 2005, **61**, 4173-4173.
10. J. M. Contreras, I. Parrot, W. Sippl, Y. M. Rival and C. G. Wermuth, *J. Med. Chem.*, 2001, **44**, 2707-2718.

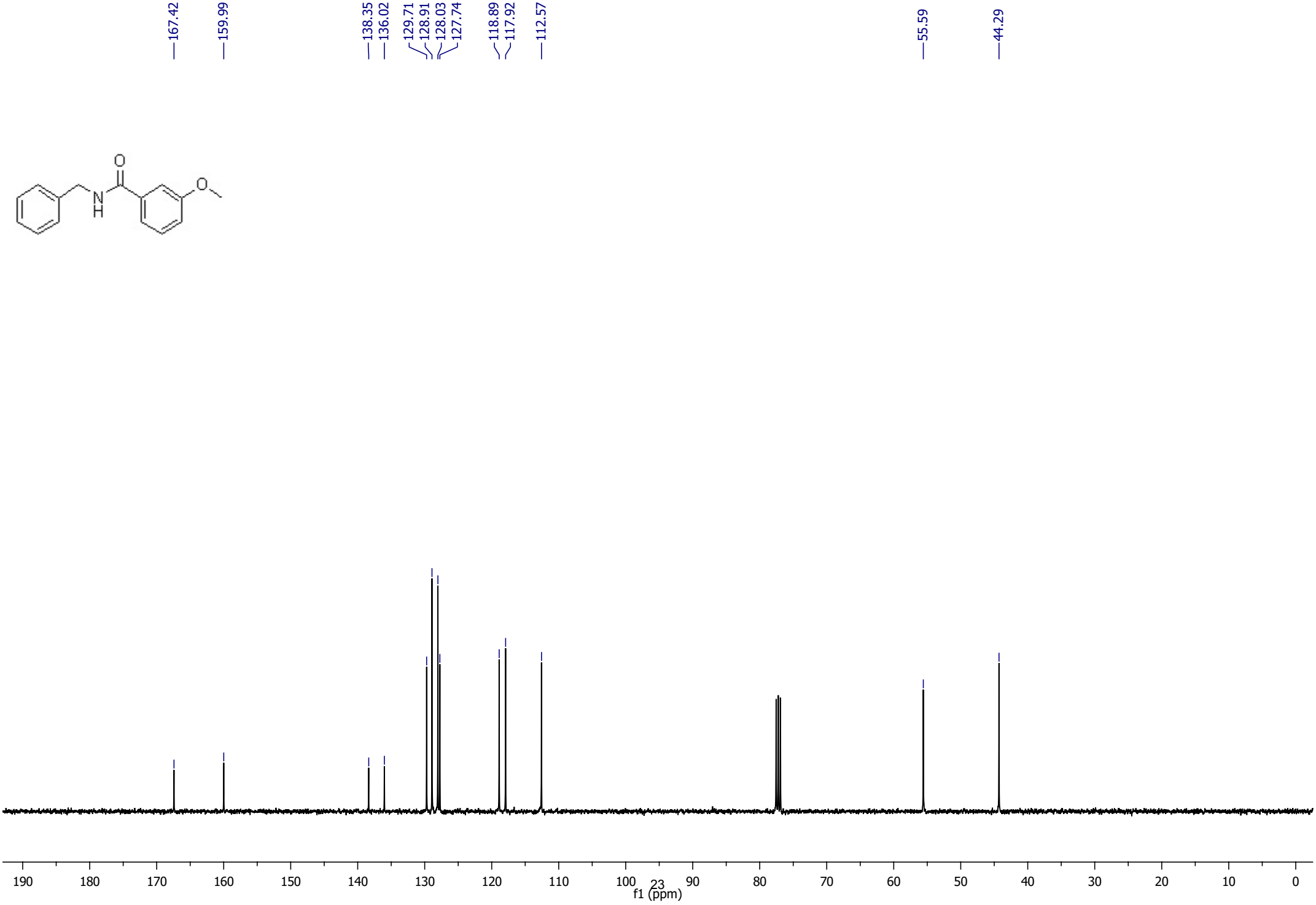


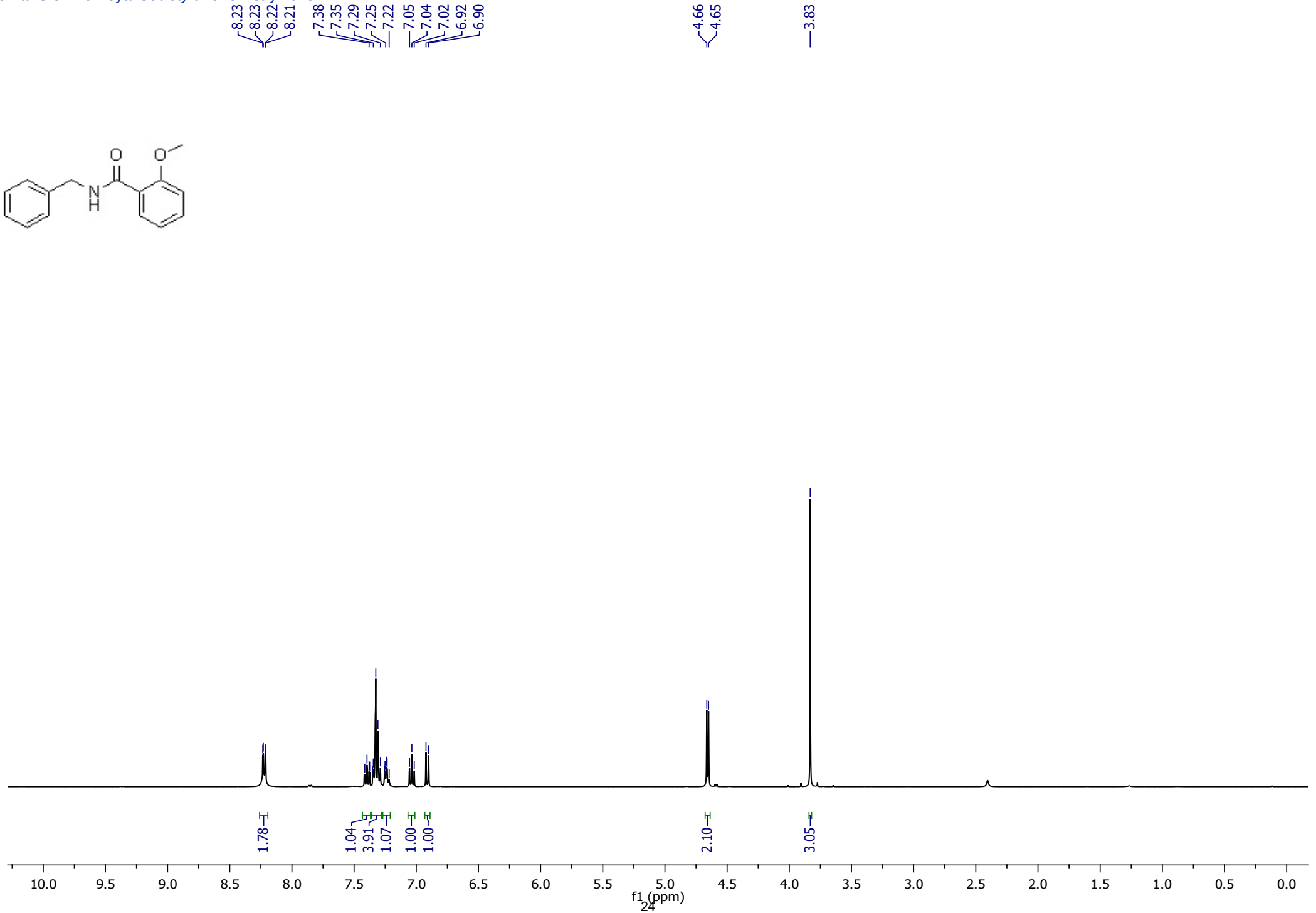


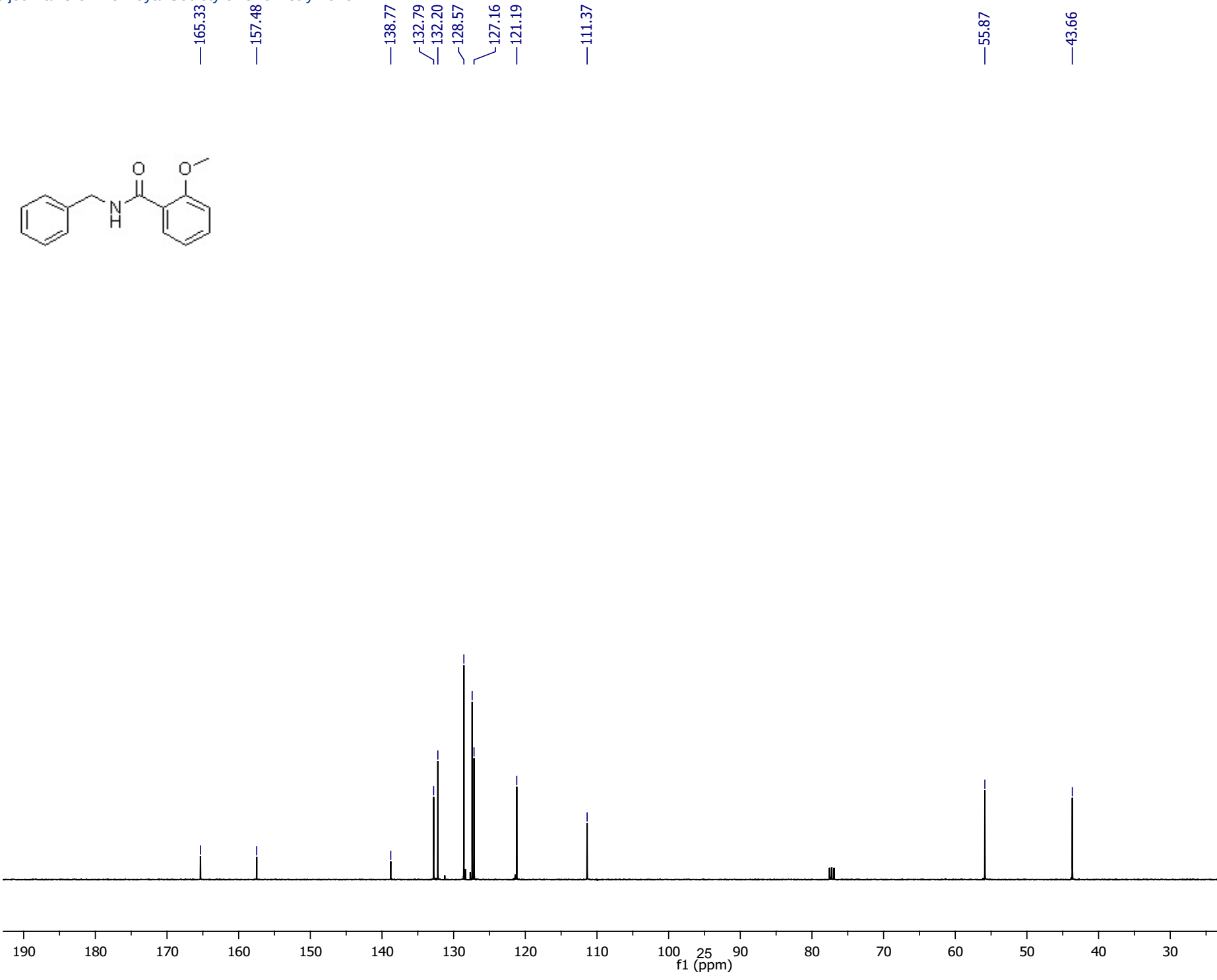


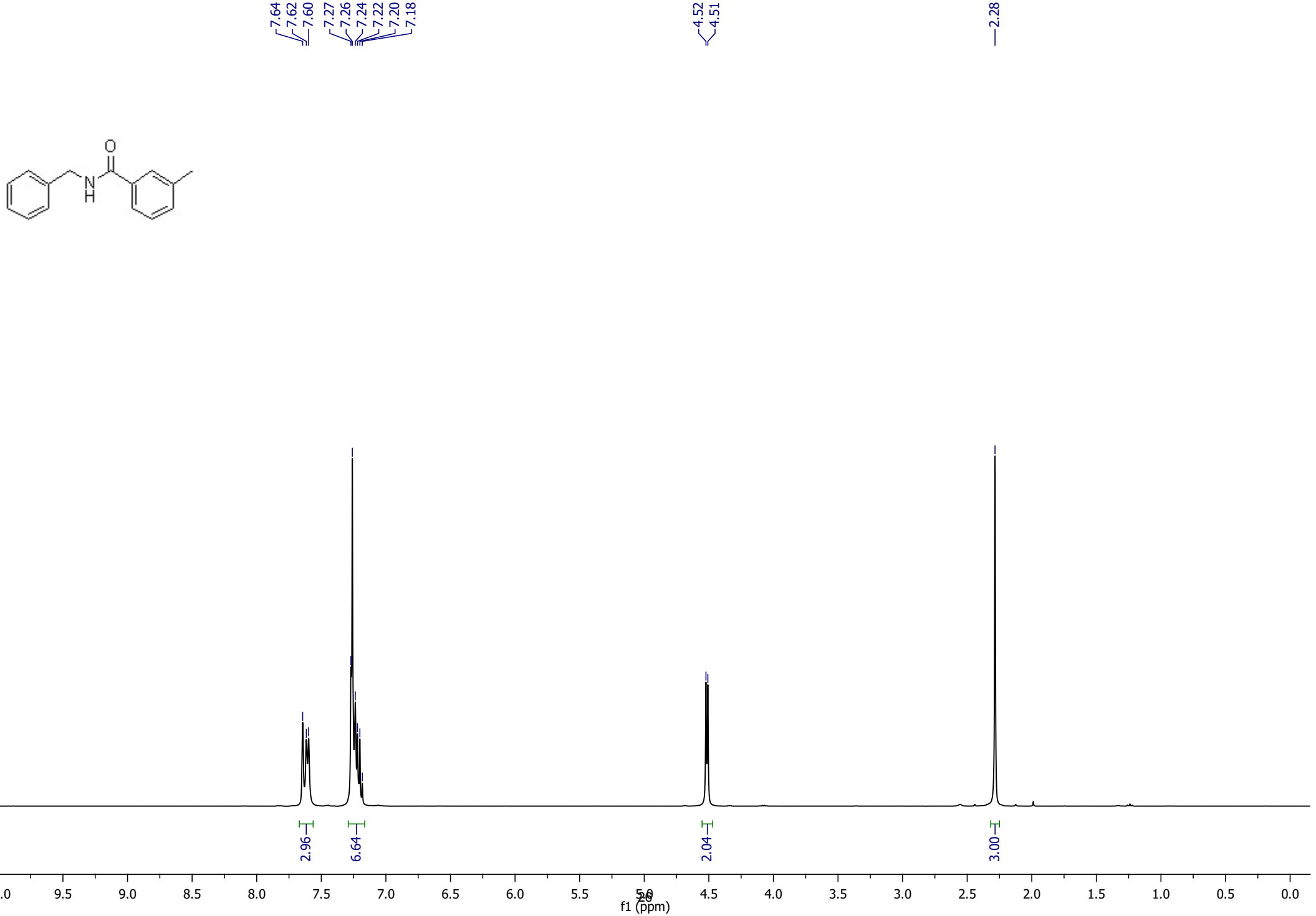


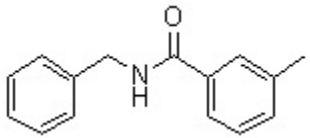


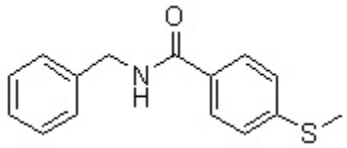


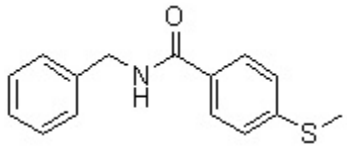


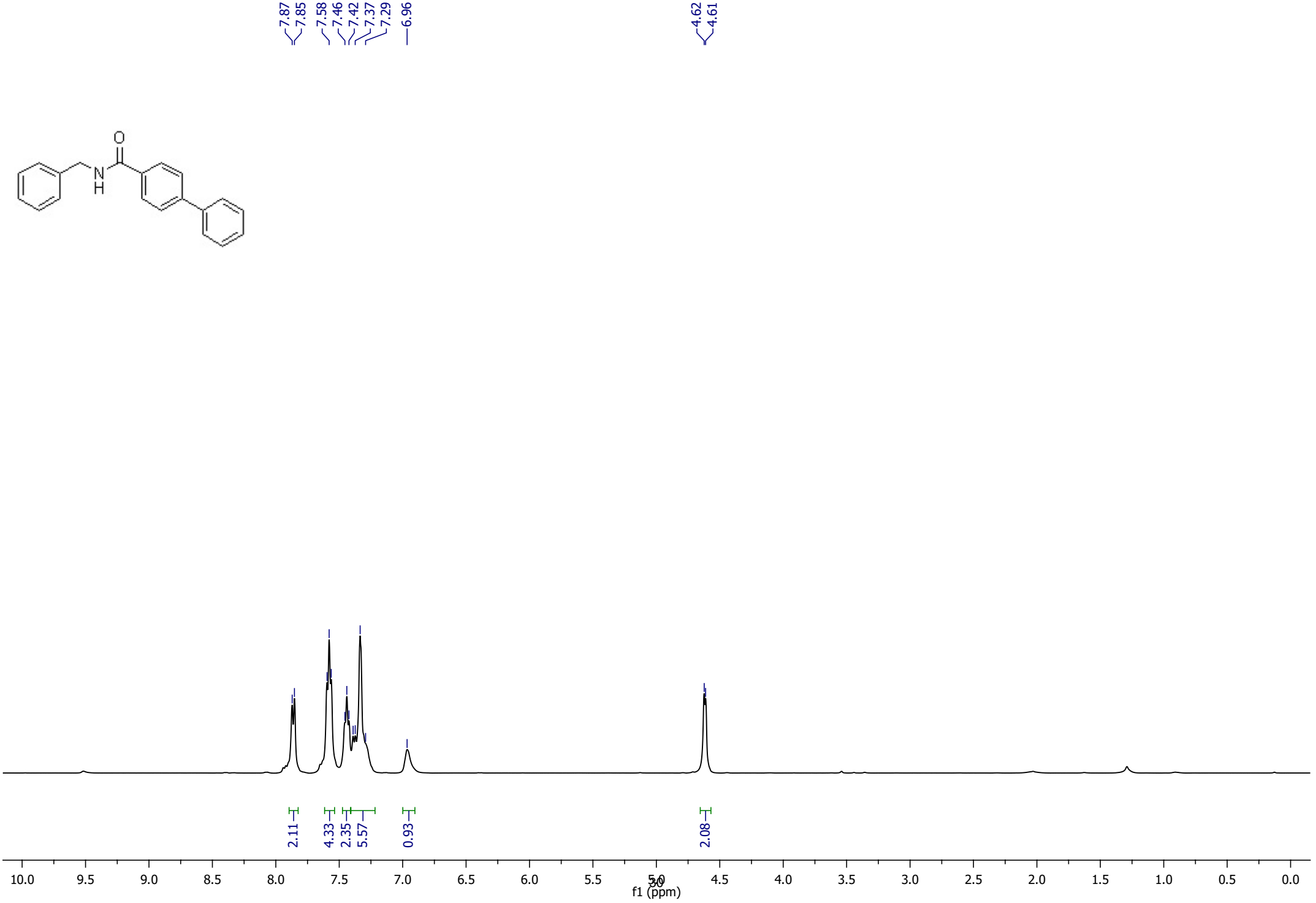


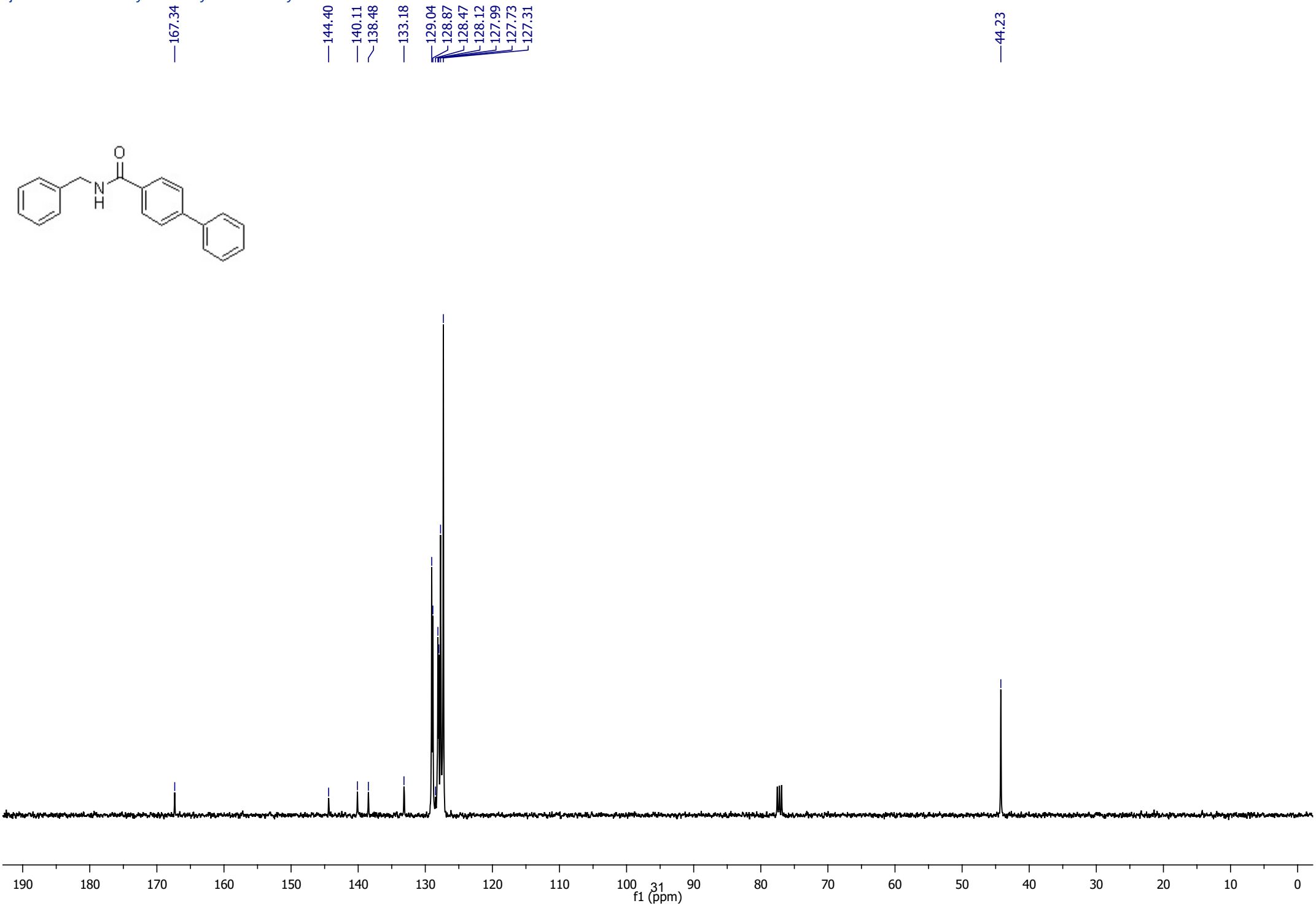


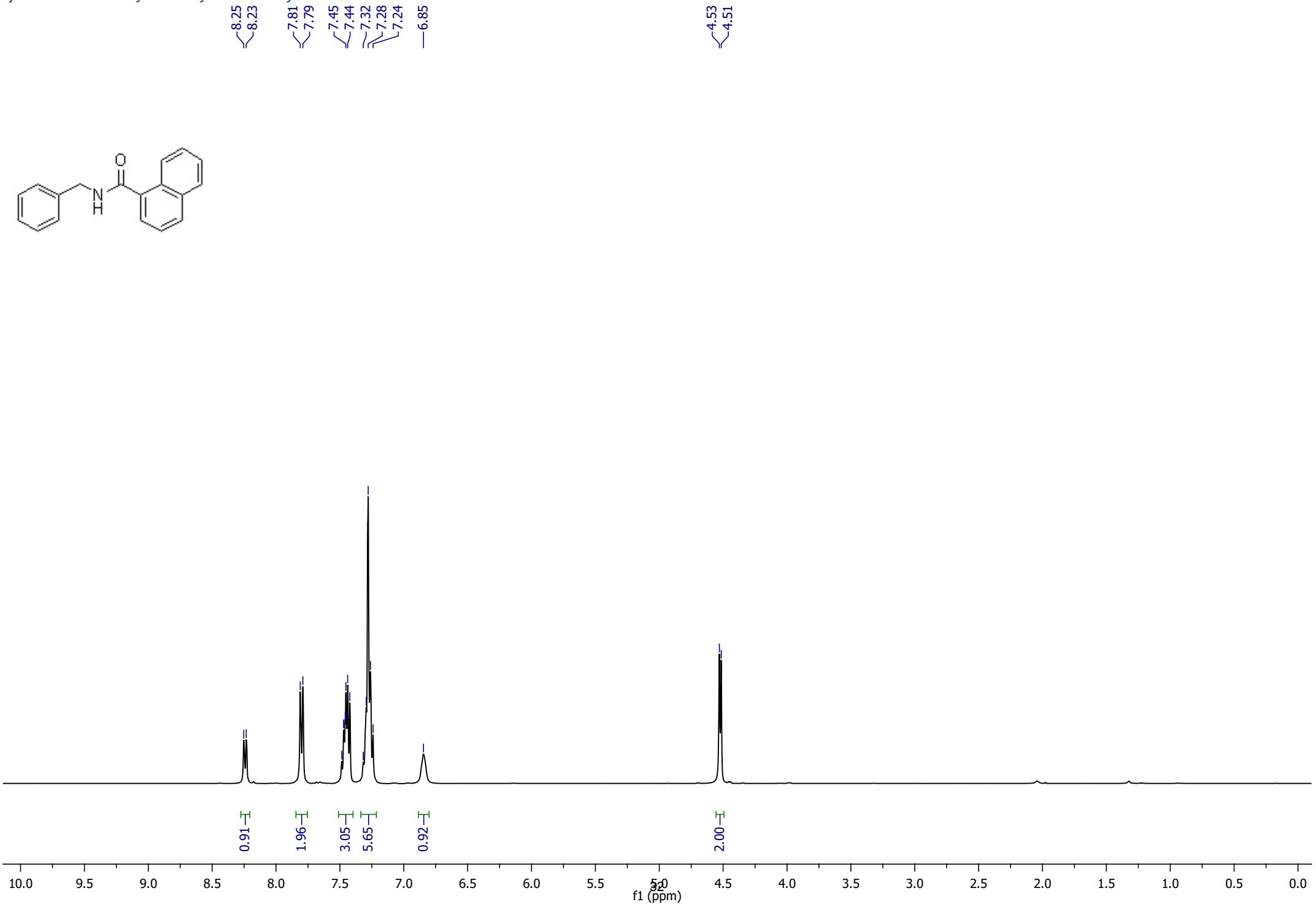


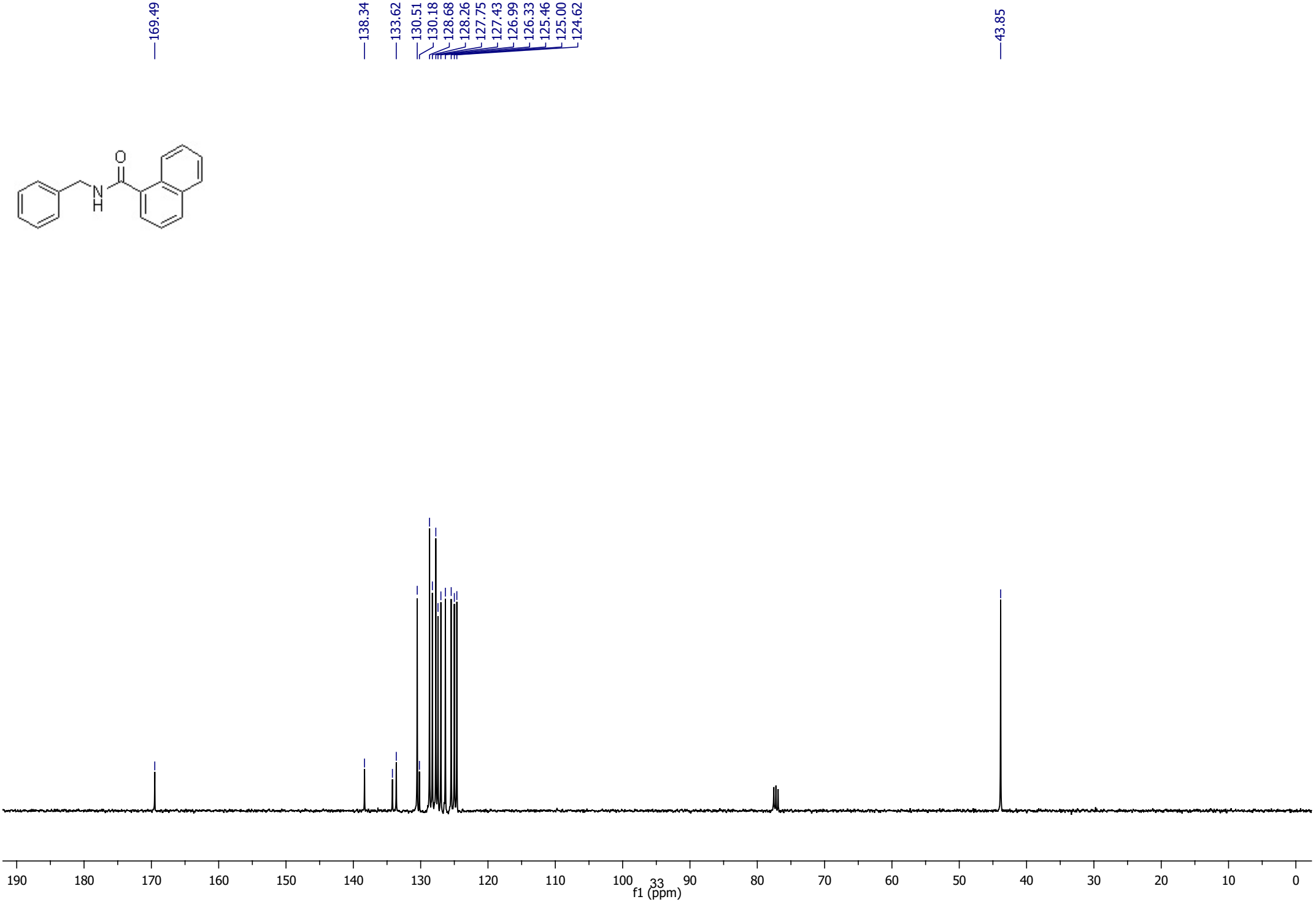


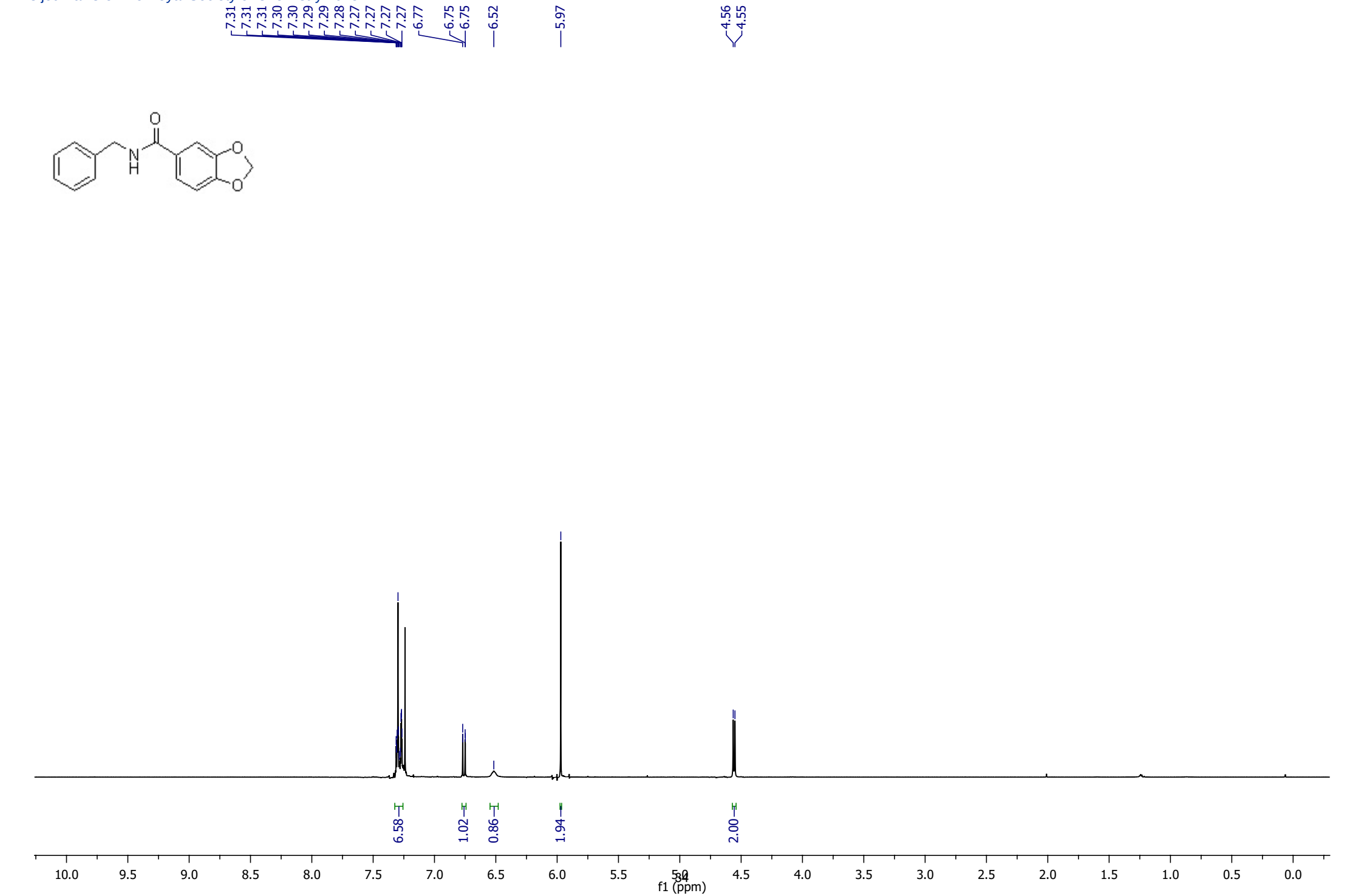











7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.27
7.27
6.77
6.75
6.75
6.52
5.97
4.56
4.55
O
N
H
O
O
6.58
1.02
0.86
1.94
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)