Supporting Information

Efficient Catalyst-Free Direct Amidation of Non-Activated Carboxylic Acids from Carbodiimides

Mehmet Mart[a], Janusz Jurczak[a]*, Idris Karakaya[b]*

[a]Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka, 44/52, 01-224, Warsaw, Poland
[b]Department of Chemistry, College of Basic Sciences, Gebze Technical University, 41400 Gebze, Turkey
Email: karakaya@gtu.edu.tr; jjurczak@icho.edu.pl

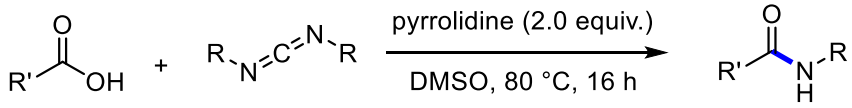
General considerations

All substrates were purchased commercially and used without purification. NMR measurements were carried out on a 400 MHz Bruker or 500 or 600 MHz Varian Mercury spectrometer. High-resolution mass spectra were performed using a Mariner mass spectrometry device from PerSeptive Biosystem. Thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F254 precoated aluminum-backed plates (0.25 mm). Flash chromatography was applied on silica gel (230–400 mesh).

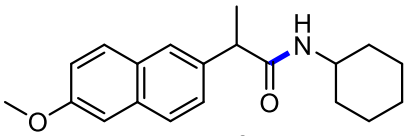
Synthesis of *N,N'*-diphenylcarbodiimide (2c)[1]

A 100 mL round bottom flask was filled with diphenylthiourea (2.19 mmol, 500 mg) and $AgNO_3$ (1.05 equiv., 2.30 mmol, 390 mg). Then, 30 mL of the mixed solvent (ACN/DCM, 1:1) were added and the reaction mixture cooled in a dry ice bath. Subsequently, Et_3N (1.05 equiv., 2.30 mmol, 0.32 mL) were added. The resulted mixture was stirred for 16 h at ambient temperature. Afterwards, the mixed solvent was removed, the desired product was collected by column chromatography purification. Obtained as a yellowish liquid (212 mg, 50%), ^{1}H NMR (DMSO, 400 MHz): δ 7.44 – 7.34 (m, 4H), 7.31 – 7.18 (m, 6H).

General procedure of amidation

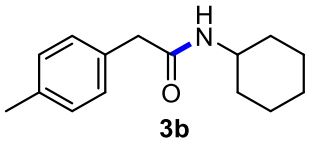


A 100 mL round-bottom flask was filled with acid (0.5 mmol) and carbodiimide (0.6 mmol). Then, 4 mL of the DMSO was added. The resulted solution was stirred for 2 h at 80 °C. Afterwards, pyrrolidine (1.0 mmol) was added. The resulted solution was stirred for 16 h at 80 °C. Subsequently, 20 mL of H_2O was added and products were extracted with 3x10 mL DCM, the desired product was collected by column chromatography purification.



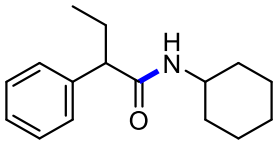
3a

***N*-Cyclohexyl-2-(6-methoxynaphthalen-2-yl)propanamide (3a)**: Obtained as a white solid (143 mg, 92%), mp = 104-106 °C, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 – 7.69 (m, 2H), 7.65 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.12 (s, 1H), 5.27 (d, *J* = 6.1 Hz, 1H), 3.91 (s, 3H), 3.77 – 3.70 (m, 1H), 3.64 (q, *J* = 6.8 Hz, 1H), 1.90 – 1.75 (m, 3H), 1.57 (d, *J* = 7.1 Hz, 3H), 1.34 – 1.27 (m, 3H), 1.07 – 0.88 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.32, 157.73, 136.84, 133.70, 129.23, 129.01, 127.45, 126.31, 126.04, 119.06, 105.71, 55.32, 48.21, 47.15, 32.97, 32.90, 25.47, 24.80, 24.73, 18.64; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{26}NO_2$, 312.1964; found 312.1969.



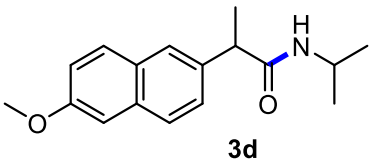
3b

***N*-Cyclohexyl-2-(*p*-tolyl)acetamide (3b)**[2]: Obtained as a white solid (101 mg, 88%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.30 (s, 1H), 3.77 – 3.68 (m, 1H), 3.48 (s, 2H), 2.32 (s, 3H), 1.84 – 1.76 (m, 2H), 1.63 – 1.50 (m, 3H), 1.33 – 1.27 (m, 2H), 1.10 – 1.04 (m, 1H), 1.02 – 0.96 (m, 2H).



3c

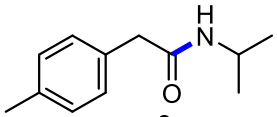
***N*-Cyclohexyl-2-phenylbutanamide (3c)**[3]: Obtained as a white solid (98 mg, 80%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.23 (m, 5H), 5.27 (d, *J* = 5.7 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.18 (t, *J* = 7.6 Hz, 1H), 2.24 – 2.13 (m, 1H), 1.92 – 1.84 (m, 1H), 1.81 – 1.72 (m, 2H), 1.65 – 1.54 (m, 3H), 1.39 – 1.25 (m, 2H), 1.16 – 0.94 (m, 3H), 0.89 (t, *J* = 7.4 Hz, 3H).



3d

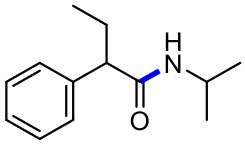
***N*-Isopropyl-2-(6-methoxynaphthalen-2-yl)propanamide (3d)**: Obtained as a white solid (118 mg, 87%), mp = 133-135 °C, ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70 (dd, *J* = 8.6, 3.4 Hz, 2H), 7.64 (s, 1H), 7.35 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.12 (d, *J* = 2.1

Hz, 1H), 5.13 (d, *J* = 5.1 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.91 (s, 3H), 3.62 (q, *J* = 7.1 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ173.32, 157.69, 136.70, 133.65, 129.19, 128.95, 127.46, 126.26, 126.04, 119.07, 105.62, 55.30, 47.11, 41.39, 22.60, 22.53, 18.60; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{22}NO_2$, 294.1470; found 294.1469.



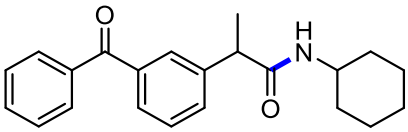
3e

***N*-Isopropyl-2-(*p*-tolyl)acetamide (3e)**[4]: Obtained as a white solid (79 mg, 82%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 5.19 (s, 1H), 4.12 – 4.00 (m, 1H), 3.50 (s, 2H), 2.35 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 6H).



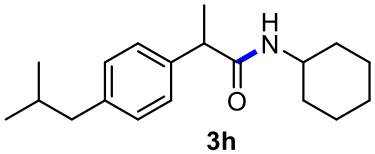
3f

***N*-Isopropyl-2-phenylbutanamide (3f)**[5]**:** Obtained as a white solid (79 mg, 77%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.23 (m, 5H), 5.27 (s, 1H), 4.09 – 4.01 (m, 1H), 3.17 (t, *J* = 7.6 Hz, 1H), 2.23 – 2.12 (m, 1H), 1.81 – 1.72 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).



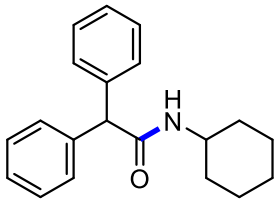
3g

2-(3-Benzoylphenyl)-*N*-cyclohexylpropanamide (3g)[6]**:** Obtained as a white solid (119 mg, 71%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, *J* = 7.4 Hz, 2H), 7.73 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.53 – 7.41 (m, 3H), 5.31 (d, *J* = 7.1 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.57 (q, *J* = 7.1 Hz, 1H), 1.89 – 1.79 (m, 2H), 1.67 – 1.57 (m, 3H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.38 – 1.27 (m, 2H), 1.16 – 0.96 (m, 3H).



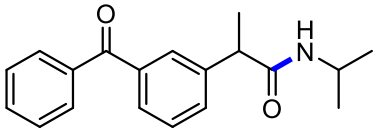
3h

***N*-Cyclohexyl-2-(4-isobutylphenyl)propanamide (3h)[7]:** Obtained as a white solid (101 mg, 70%), mp = 90-93 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.19 (d, *J* = 6.3 Hz, 1H), 3.81 – 3.66 (m, 1H), 3.49 (q, *J* = 7.2 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.91 – 1.76 (m, 3H), 1.61 – 1.53 (m, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.38 – 1.26 (m, 2H), 1.15 – 0.96 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.48, 140.55, 138.84, 129.54, 127.29, 47.98, 46.84, 45.01, 32.87, 32.78, 30.15, 25.50, 24.64, 24.60, 22.34, 18.49; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{30}NO$, 288.2327; found 288.2336.



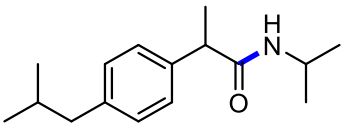
3i

***N*-Cyclohexyl-2,2-diphenylacetamide (3i)[8]:** Obtained as a white solid (98 mg, 67%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.25 (m, 10H), 5.44 (s, 1H), 4.90 (s, 1H), 3.93 – 3.77 (m, 1H), 1.89 (d, *J* = 9.3 Hz, 2H), 1.69 – 1.53 (m, 3H), 1.43 – 1.28 (m, 2H), 1.19 – 1.01 (m, 3H).



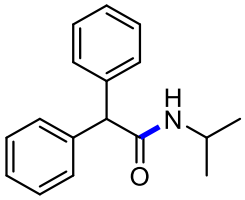
3j

2-(3-Benzoylphenyl)-*N*-isopropylpropanamide (3j)[9]: Obtained as a white solid (115 mg, 78%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 – 7.77 (m, 2H), 7.73 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.50 – 7.43 (m, 3H), 5.32 (d, *J* = 6.3 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.56 (q, *J* = 7.1 Hz, 1H), 1.52 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H).



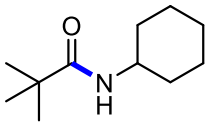
3k

2-(4-Isobutylphenyl)-*N*-isopropylpropanamide (3k)[10]: Obtained as a white solid (95 mg, 77%), ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.16 (d, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 2H), 5.08 (s, 1H), 4.04 – 3.99 (m, 1H), 3.46 (q, *J* = 6.8 Hz, 1H), 2.44 (d, *J* = 7.0 Hz, 2H), 1.86 – 1.82 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.2 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 6H).



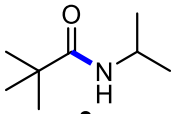
3l

***N*-Isopropyl-2,2-diphenylacetamide (3l)[8]:** Obtained as a white solid (79 mg, 62%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 – 7.30 (m, 4H), 7.26 (d, *J* = 7.3 Hz, 6H), 5.41 (s, 1H), 4.88 (s, 1H), 4.19 – 4.11 (m, 1H), 1.12 (d, *J* = 6.6 Hz, 6H).



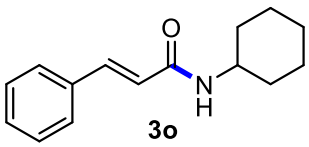
3m

***N*-Cyclohexylpivalamide (3m)[11]:** Obtained as a white solid (62 mg, 68%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.44 (s, 1H), 3.78 – 3.69 (m, 1H), 1.94 – 1.83 (m, 2H), 1.74 – 1.55 (m, 3H), 1.43 – 1.30 (m, 2H), 1.17 (s, 9H), 1.12 – 1.08 (m, 3H).



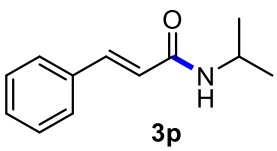
3n

***N*-Isopropylpivalamide (3n)[12]:** Obtained as a white solid (52 mg, 73%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.37 (s, 1H), 4.08 – 4.04 (m, 1H), 1.18 (s, 9H), 1.14 (d, *J* = 6.4 Hz, 6H).



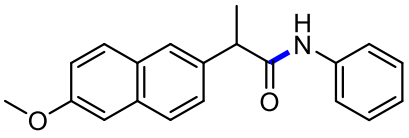
3o

***N*-Cyclohexylcinnamamide (3o)[13]:** Obtained as a white solid (70 mg, 61%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.43 – 7.29 (m, 3H), 6.40 (d, *J* = 15.6 Hz, 1H), 5.67 (d, *J* = 7.1 Hz, 1H), 3.97 – 3.88 (m, 1H), 2.05 – 1.98 (m, 2H), 1.81 – 1.68 (m, 2H), 1.70 – 1.59 (m, 1H), 1.48 – 1.34 (m, 2H), 1.28 – 1.12 (m, 3H).



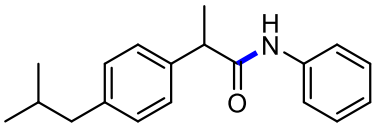
3p

***N*-Isopropylcinnamamide (3p)**[14]**:** Obtained as a white solid (61 mg, 64%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, *J* = 15.6 Hz, 1H), 7.51 – 7.30 (m, 5H), 6.40 (d, *J* = 15.6 Hz, 1H), 5.77 (s, 1H), 4.31 – 4.18 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 6H).



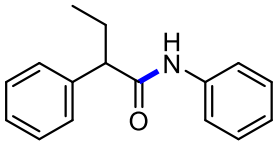
3q

2-(6-methoxynaphthalen-2-yl)-*N*-phenylpropanamide (3q)[15]**:** Obtained as a white solid (137 mg, 90%), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 – 7.65 (m, 3H), 7.37 – 7.32 (m, 3H), 7.19 – 7.16 (m, 2H), 7.10 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.04 (s, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 3.85 (s, 3H), 3.78 (q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H).



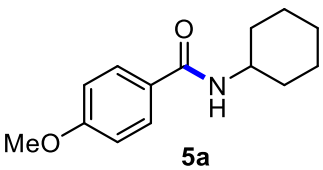
3r

2-(4-isobutylphenyl)-N-phenylpropanamide (3r)[16]**:** Obtained as a white solid (107 mg, 76%), ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.39 (d, *J* = 7.9 Hz, 2H), 7.27 – 7.23 (m, 4H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 3.68 (q, *J* = 7.2 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.90 – 1.81 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H).



3s

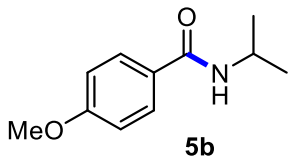
***N*,2-diphenylbutanamide (3s)**[17]**:** Obtained as a white solid (105 mg, 88%), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 4.4 Hz, 4H), 7.24 – 7.16 (m, 3H), 7.05 (s, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.32 (t, *J* = 7.5 Hz, 1H), 2.26 – 2.16 (m, 1H), 1.85 – 1.75 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H).



5a

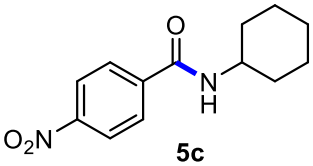
***N*-Cyclohexyl-4-methoxybenzamide (5a)**[18]**:** Obtained as a white solid (85 mg, 73%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.95 (d, *J* = 5.3 Hz,

1H), 4.04 – 3.89 (m, 1H), 3.84 (s, 3H), 2.02 (d, *J* = 9.4 Hz, 2H), 1.80 – 1.61 (m, 3H), 1.47 – 1.38 (m, 2H), 1.30 – 1.13 (m, 3H).



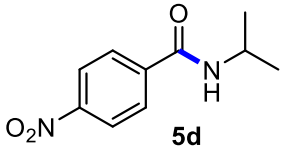
5b

***N*-Isopropyl-4-methoxybenzamide (5b)**[19]**:** Obtained as a white solid (85 mg, 88%), ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 5.85 (s, 1H), 4.30 – 4.20 (m, 1H), 3.83 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 6H).



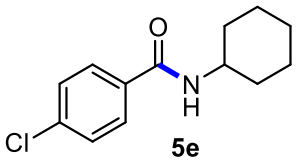
5c

***N*-Cyclohexyl-4-nitrobenzamide (5c)**[20]**:** Obtained as a white solid (93 mg, 75%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 6.00 (d, *J* = 5.7 Hz, 1H), 4.05 – 3.95 (m, 1H), 2.08 – 2.04 (m, 2H), 1.84 – 1.64 (m, 3H), 1.53 – 1.39 (m, 2H), 1.34 – 1.18 (m, 3H).



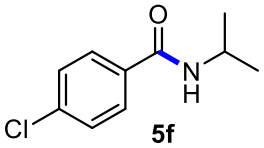
5d

***N*-Isopropyl-4-nitrobenzamide (5d)**[21]**:** Obtained as a white solid (84 mg, 81%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 5.98 (s, 1H), 4.40 – 4.30 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 6H).



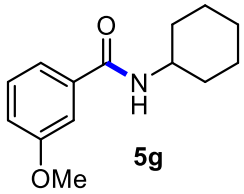
5e

4-Chloro-*N*-cyclohexylbenzamide (5e)[13]**:** Obtained as a white solid (113 mg, 95%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 5.97 (s, 1H), 4.01 – 3.92 (m, 1H), 2.05 – 2.01 (m, 2H), 1.81 – 1.71 (m, 2H), 1.68 – 1.64 (m, 1H), 1.49 – 1.35 (m, 2H), 1.30 – 1.16 (m, 3H).



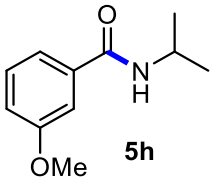
5f

4-Chloro-*N*-isopropylbenzamide (5f)[22]**:** Obtained as a white solid (84 mg, 86%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.01 (s, 1H), 4.31 – 4.22 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 6H).



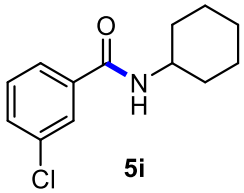
5g

***N*-Cyclohexyl-3-methoxybenzamide (5g)**[23]**:** Obtained as a white solid (90 mg, 77%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.05 – 6.98 (m, 1H), 6.00 (s, 1H), 4.03 – 3.91 (m, 1H), 3.85 (s, 3H), 2.05 – 2.01 (m, 2H), 1.78 – 1.64 (m, 3H), 1.50 – 1.36 (m, 2H), 1.29 – 1.19 (m, 3H).



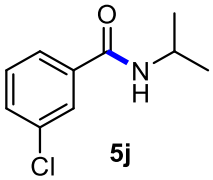
5h

***N*-Isopropyl-3-methoxybenzamide (5h)**[24]**:** Obtained as a white solid (80 mg, 83%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.23 (m, 3H), 7.03 – 7.00 (m, 1H), 6.00 (s, 1H), 4.34 – 4.21 (m, 1H), 3.84 (s, 3H), 1.26 (d, *J* = 6.6 Hz, 6H).



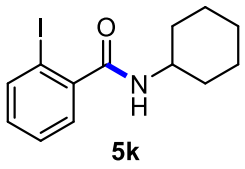
5i

3-Chloro-*N*-cyclohexylbenzamide (5i)[23]**:** Obtained as a white solid (57 mg, 48%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 5.95 (s, 1H), 3.99 – 3.93 (m, 1H), 2.09 – 1.98 (m, 2H), 1.80 – 1.65 (m, 3H), 1.47 – 1.37 (m, 2H), 1.29 – 1.17 (m, 3H).



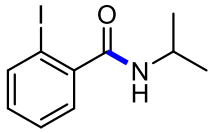
5j

3-Chloro-*N*-isopropylbenzamide (5j)[25]**:** Obtained as a white solid (57 mg, 58%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 4.33 – 4.24 (m, 1H), 1.28 (d, *J* = 6.6 Hz, 6H).



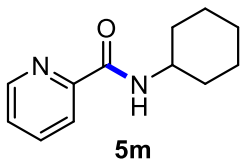
5k

***N*-Cyclohexyl-2-iodobenzamide (5k)**[26]**:** Obtained as a white solid (58 mg, 35%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.38 (q, *J* = 7.5 Hz, 2H), 7.15 – 7.01 (m, 1H), 5.64 (s, 1H), 4.10 – 3.91 (m, 1H), 2.10 – 2.07 (m, 2H), 1.80 – 1.62 (m, 3H), 1.49 – 1.40 (m, 2H), 1.33 – 1.19 (m, 3H).



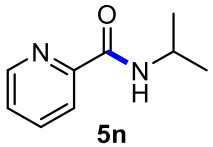
5l

2-Iodo-*N*-isopropylbenzamide (5l)[25]**:** Obtained as a white solid (65 mg, 45%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 – 7.81 (m, 1H), 7.45 – 7.31 (m, 2H), 7.11 – 7.06 (m, 1H), 5.59 (s, 1H), 4.38 – 4.22 (m, 1H), 1.29 (d, *J* = 6.6 Hz, 6H).



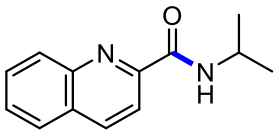
5m

***N*-Cyclohexylpicolinamide (5m)**[27]**:** Obtained as a white solid (74 mg, 73%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.25 – 8.17 (m, 1H), 7.96 (s, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 4.04 – 3.92 (m, 1H), 2.07 – 1.97 (m, 2H), 1.82 – 1.71 (m, 2H), 1.71 – 1.61 (m, 1H), 1.52 – 1.18 (m, 5H).



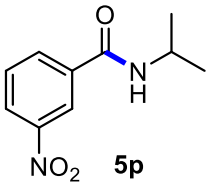
5n

***N*-Isopropylpicolinamide (5n)**[28]**:** Obtained as a white solid (67 mg, 82%), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.21 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.89 (s, H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 – 7.40 (m, 1H), 4.35 – 4.23 (m, 1H), 1.30 (d, *J* = 6.6 Hz, 6H).



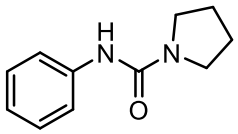
5o

***N*-isopropylquinoline-2-carboxamide (5o)**[29]**:** Obtained as a white solid (72 mg, 67%), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 – 8.29 (m, 2H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.2, Hz, 1H), 7.79 – 7.75 (m, 1H), 7.64 – 7.59 (m, 1H), 4.40 – 4.29 (m, 1H), 1.35 (d, *J* = 6.6 Hz, 6H).



5p

***N*-isopropyl-3-nitrobenzamide (5p)**[2]**:** Obtained as a white solid (66 mg, 63%), ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.55 (s, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 6.03 (s, 1H), 4.35 – 4.28 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 6H).



26

***N*-phenylpyrrolidine-1-carboxamide (urea, 26)**[30]**:** Obtained as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.9 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.21 (s, 1H), 3.46 (t, *J* = 6.6 Hz, 4H), 1.97 (t, *J* = 6.6 Hz, 4H).

References

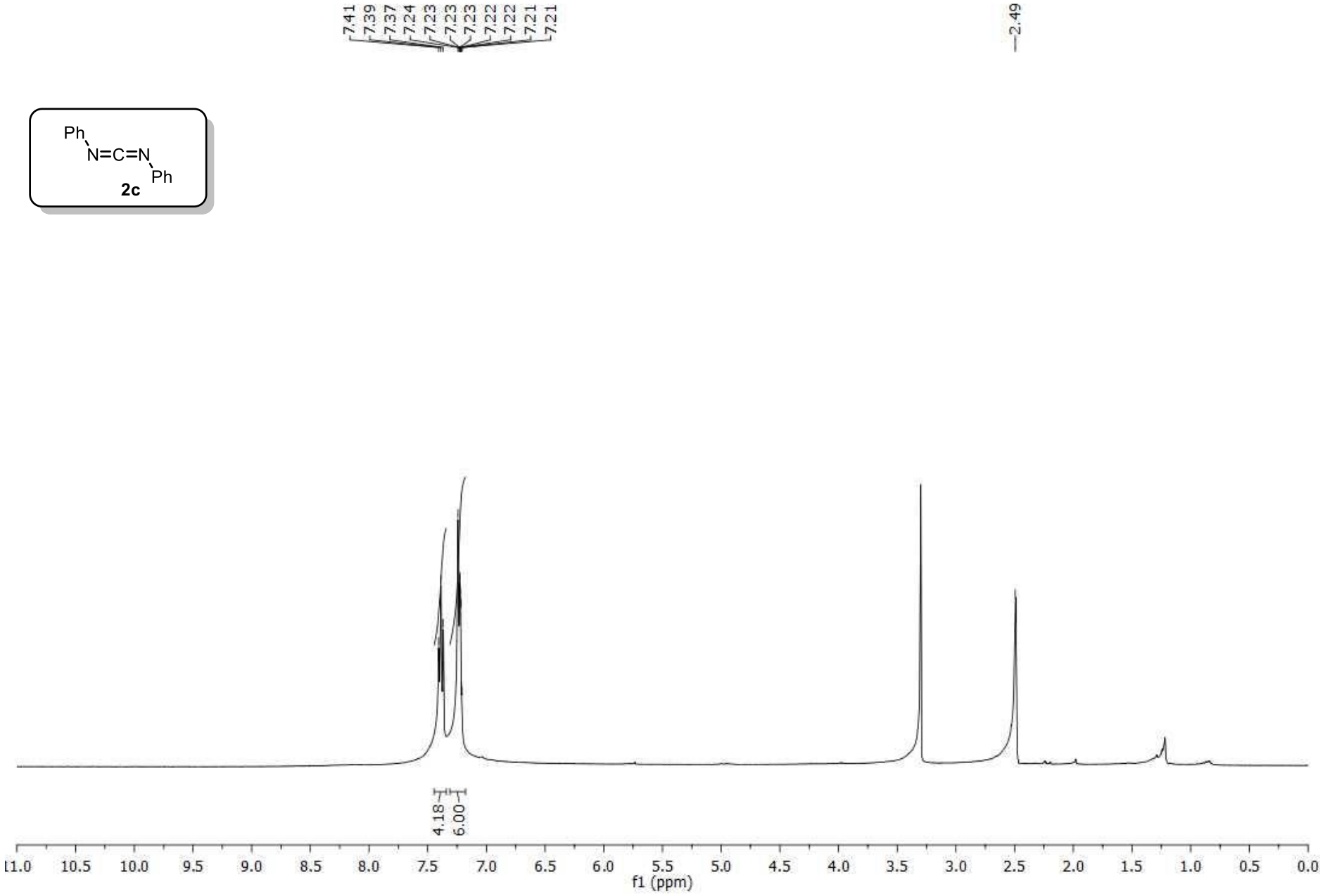
1. A. M. Camelio, A. Krasovskiy, B. Bailey and A. Davis, *J. Org. Chem.*, 2022, **87**, 2022-2044.
2. F. Panahi, F. Jamedi and N. Iranpoor, *Eur. J. Org. Chem.*, 2016, **2016**, 780-788.
3. L. M. Mori-Quiroz, K. W. Shimkin, S. Rezazadeh, R. A. Kozlowski and D. A. Watson, *Chem-Eur. J.*, 2016, **22**, 15654-15658.
4. D. G. Pintori and M. F. Greaney, *Org. Lett.*, 2011, **13**, 5713-5715.
5. X. Y. Hu, S. H. Hao, Y. Wei, Z. L. Wang, H. M. Wang, Y. C. Feng and Q. X. Qin, *Tetrahedron Lett.*, 2022, **95**, 153731

6. Z. Rajic, D. Hadjipavlou-Litina, E. Pontiki, M. Kralj, L. Suman and B. Zorc, *Chem. Biol. Drug. Des.*, 2010, **75**, 641-652.
7. Y. Yuan, F. Q. Zhao and X. F. Wu, *Chem. Sci.*, 2021, **12**, 12676-12681.
8. X. Jin, M. Willeke, R. Lucchesi, C. G. Daniliuc, R. Frohlich, B. Wibbeling, W. Uhl and E. U. Wurthwein, *J. Org. Chem.*, 2015, **80**, 6062-6075.
9. Bhardwaj, Tilak Raj; et al, India, IN2008DE02354 A 2010-04-23
10. S. A. N. Mehta, S. Thareja, P. Malla, M. Misra, T. Bhardwaj and M. Kumar, *ChemTech.*, 2010, **2**, 233-238.
11. H. Q. Do, S. Bachman, A. C. Bissember, J. C. Peters and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 2162-2167.
12. T. T. Chen, A. E. Wang and P. Q. Huang, *Org. Lett.*, 2019, **21**, 3808-3812.
13. C. Duangkamol, S. Jaita, S. Wangngae, W. Phakhodee and M. Pattarawarapan, *RSC Adv.*, 2015, **5**, 52624-52628.
14. T. Sato, A. Ohno, S. M. Sarkar, Y. Uozumi and Y. M. A. Yamada, *Chemcatchem.*, 2015, **7**, 2141-2148.
15. Y. H. Yao, H. Y. Yang, M. Chen, F. Wu, X. X. Xu and Z. H. Guan, *J. Am. Chem. Soc.*, 2021, **143**, 85-91.
16. Q. Gou, Q. Chen, Q. Tan, M. Zhu, H. Huang, M. Deng, W. Yi and S. He, *Org. Lett.*, 2022, **24**, 3549-3554.
17. Y. P. Zhu, S. Sergeyev, P. Franck, R. V. Orru and B. U. Maes, *Org. Lett.*, 2016, **18**, 4602-4605.
18. S. Wangngae, C. Duangkamol, M. Pattarawarapan and W. Phakhodee, *RSC Adv.*, 2015, **5**, 25789-25793.
19. J. Kraiem and T. Ollevier, *Green Chem.*, 2017, **19**, 1263-1267.
20. C. Dankers, J. Tadros, D. G. Harman, J. R. Aldrich-Wright, T. V. Nguyen and C. P. Gordon, *ACS Comb. Sci.*, 2020, **22**, 255-267.
21. R. N. Ram, N. Kumar and N. Singh, *J. Org. Chem.*, 2010, **75**, 7408-7411.
22. S. H. Lee and G. I. Nikonov, *Dalton T.*, 2014, **43**, 8888-8893.
23. X. D. Lang and L. N. He, *Chemsuschem.*, 2018, **11**, 2062-2067.
24. C. G. Jorgensen, B. Frolund, J. Kehler and A. A. Jensen, *Chemmedchem.*, 2011, **6**, 725-736.
25. M. T. Shea, G. T. Rohde, Y. A. Vlasenko, P. S. Postnikov, M. S. Yusubov, V. V. Zhdankin, A. Saito and A. Yoshimura, *Molecules*, 2021, **26**.
26. F. Chahdoura, S. Mallet-Ladeira and M. Gomez, *Org. Chem. Front.*, 2015, **2**, 312-318.

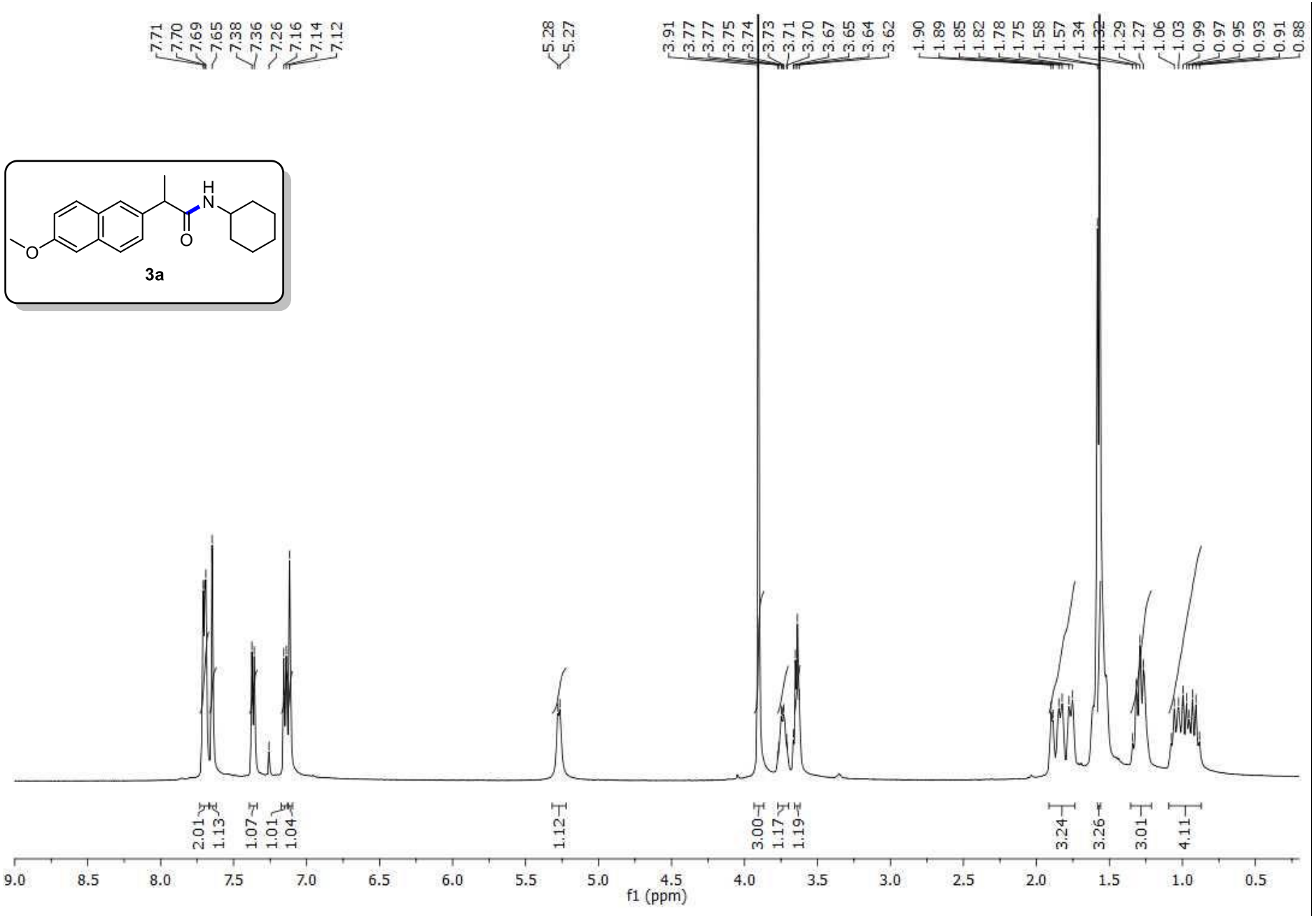
27. E. T. Nadres, G. I. F. Santos, D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2013, **78**, 9689-9714.
28. A. C. Maguire, V. Kumar and S. J. Connon, *Chem. Commun.*, 2019, **55**, 13526-13529.
29. T. Gonec, P. Bobal, J. Sujan, M. Pesko, J. H. Guo, K. Kralova, L. Pavlacka, L. Vesely, E. Kreckova, J. Kos, A. Coffey, P. Kollar, A. Imramovsky, L. Placek and J. Jampilek, *Molecules*, 2012, **17**, 613-644.
30. L. Mistry, K. Mapesa, T. W. Bousfield and J. E. Camp, Synthesis of ureas in the bio-alternative solvent Cyrene, *Green Chem.*, 2017, **19**, 2123-2128.

Spectral Data

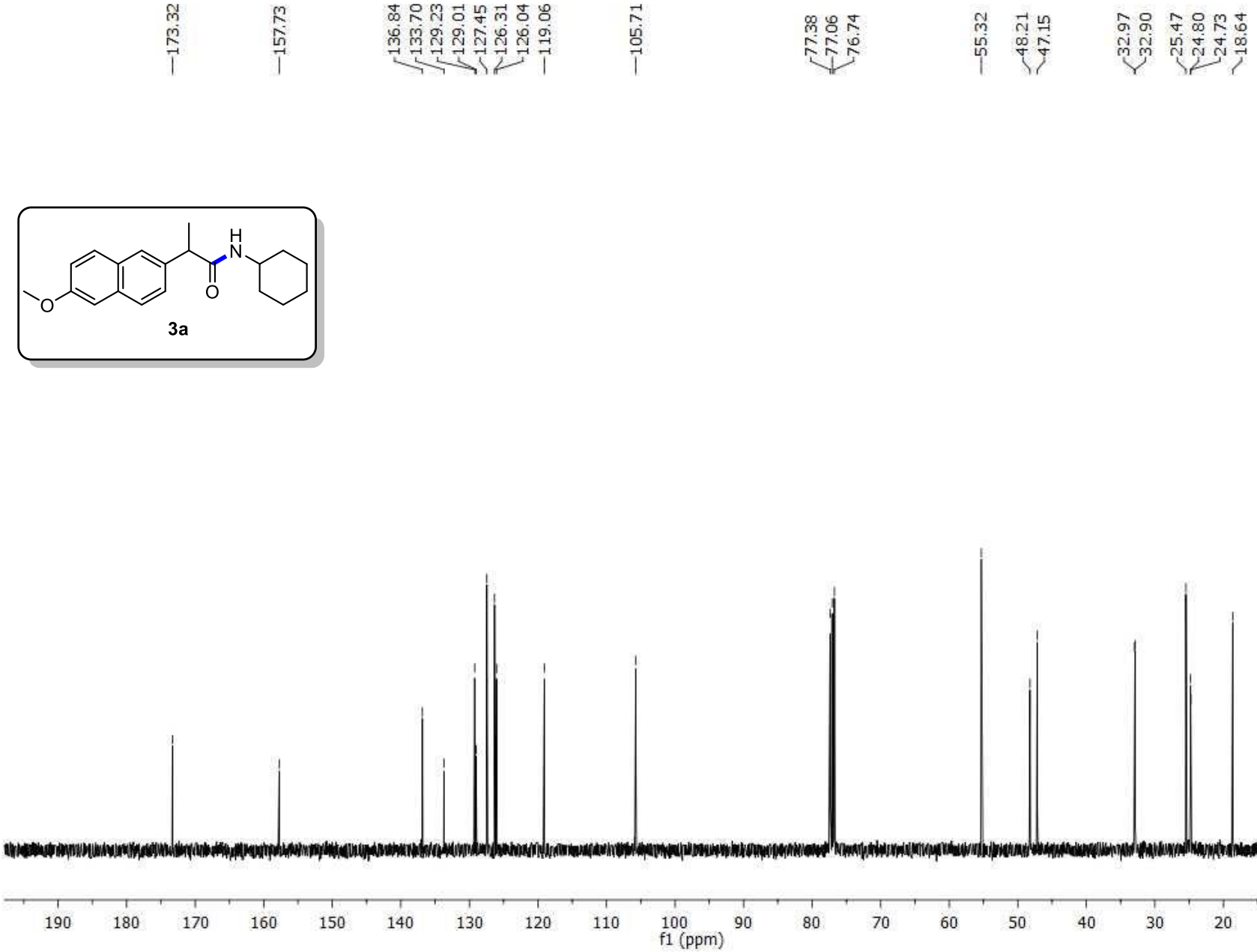
^{1}H NMR (DMSO, 400 MHz) spectrum of *N*,*N'*-diphenylcarbodiimide **(2c)**



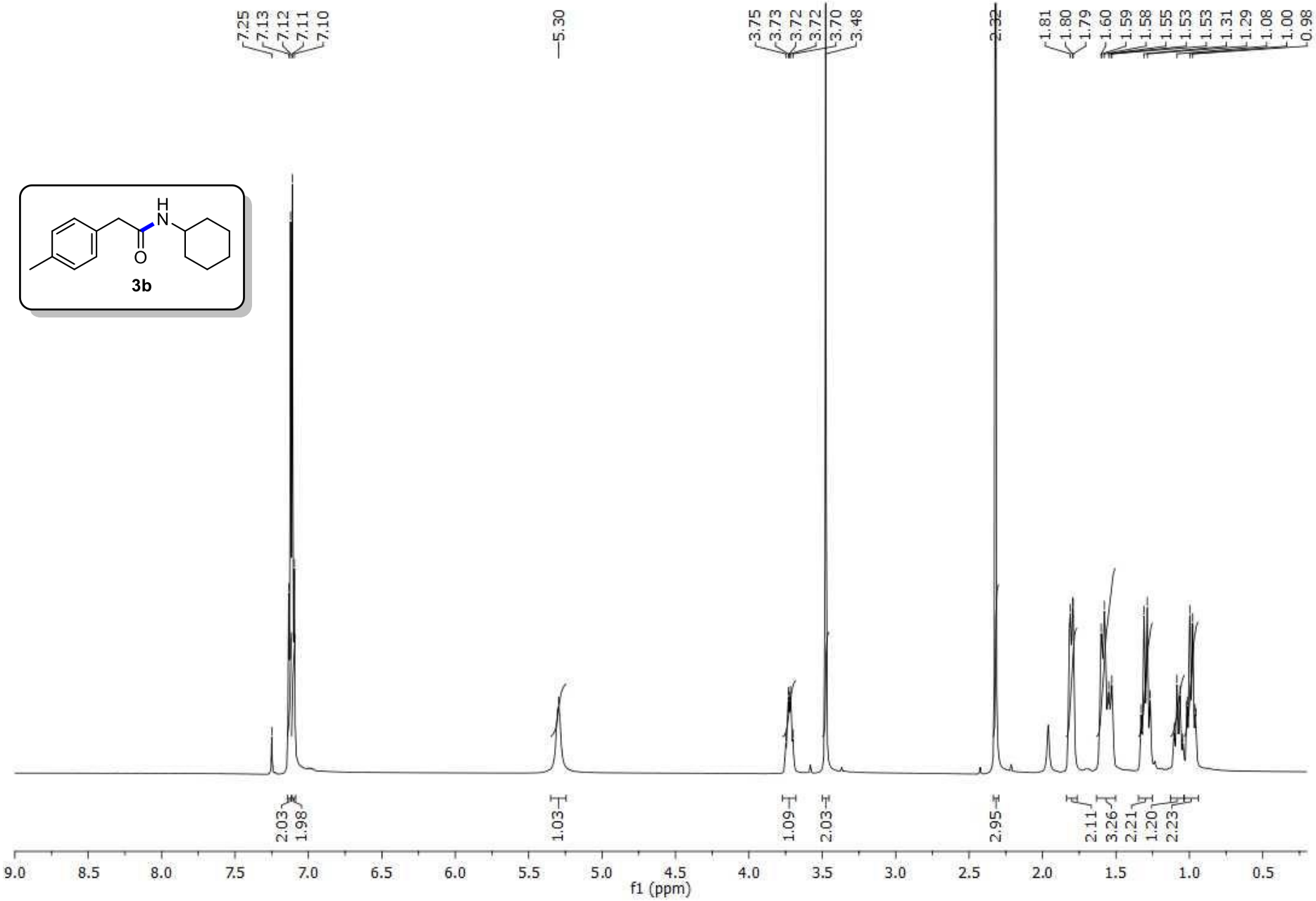
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2-(6-methoxynaphthalen-2-yl)propanamide (**3a**)



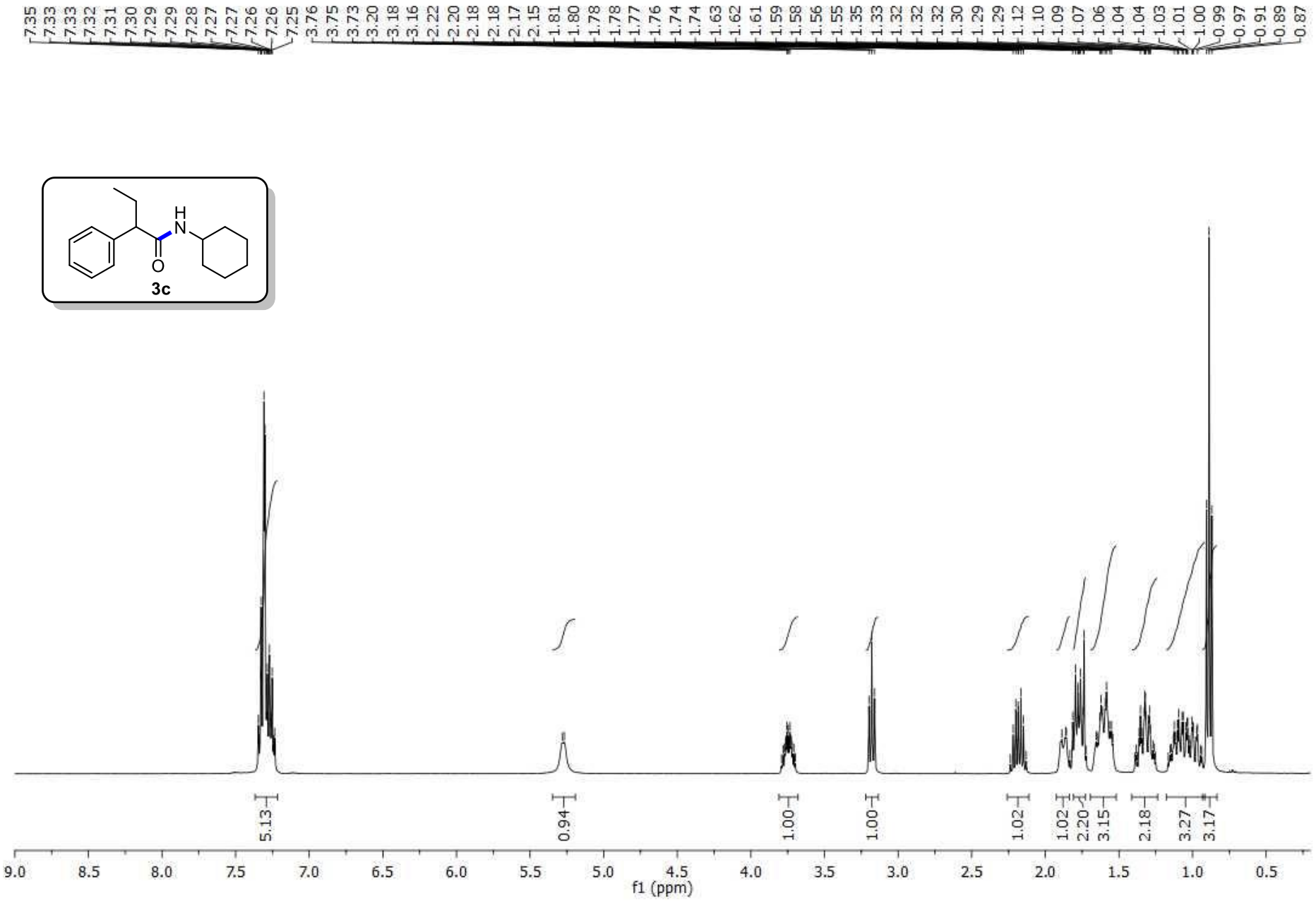
^{13}C NMR ($CDCl_3$, 101 MHz) spectrum of *N*-Cyclohexyl-2-(6-methoxynaphthalen-2-yl)propanamide (**3a**)



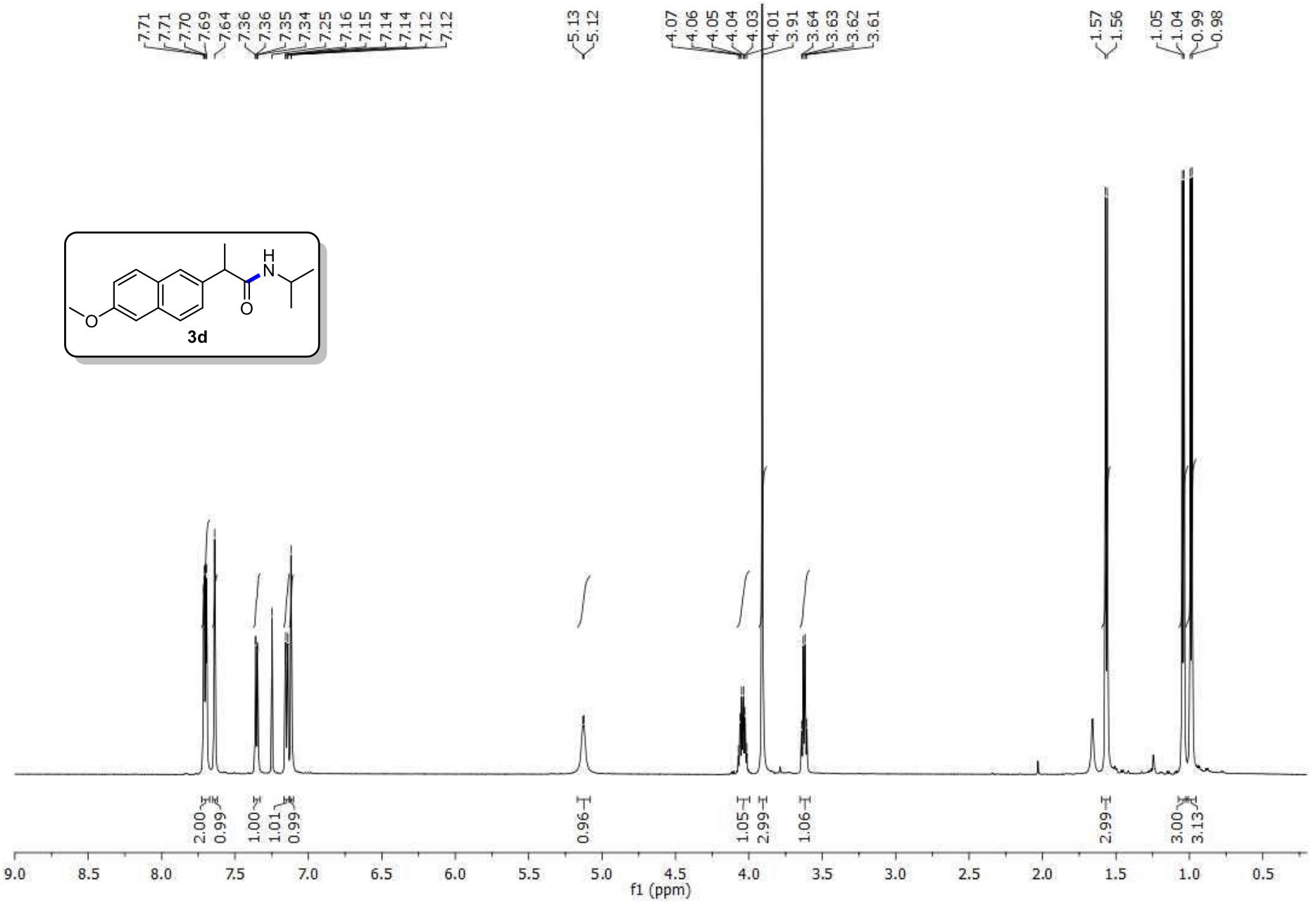
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2-(p-tolyl)acetamide (**3b**)



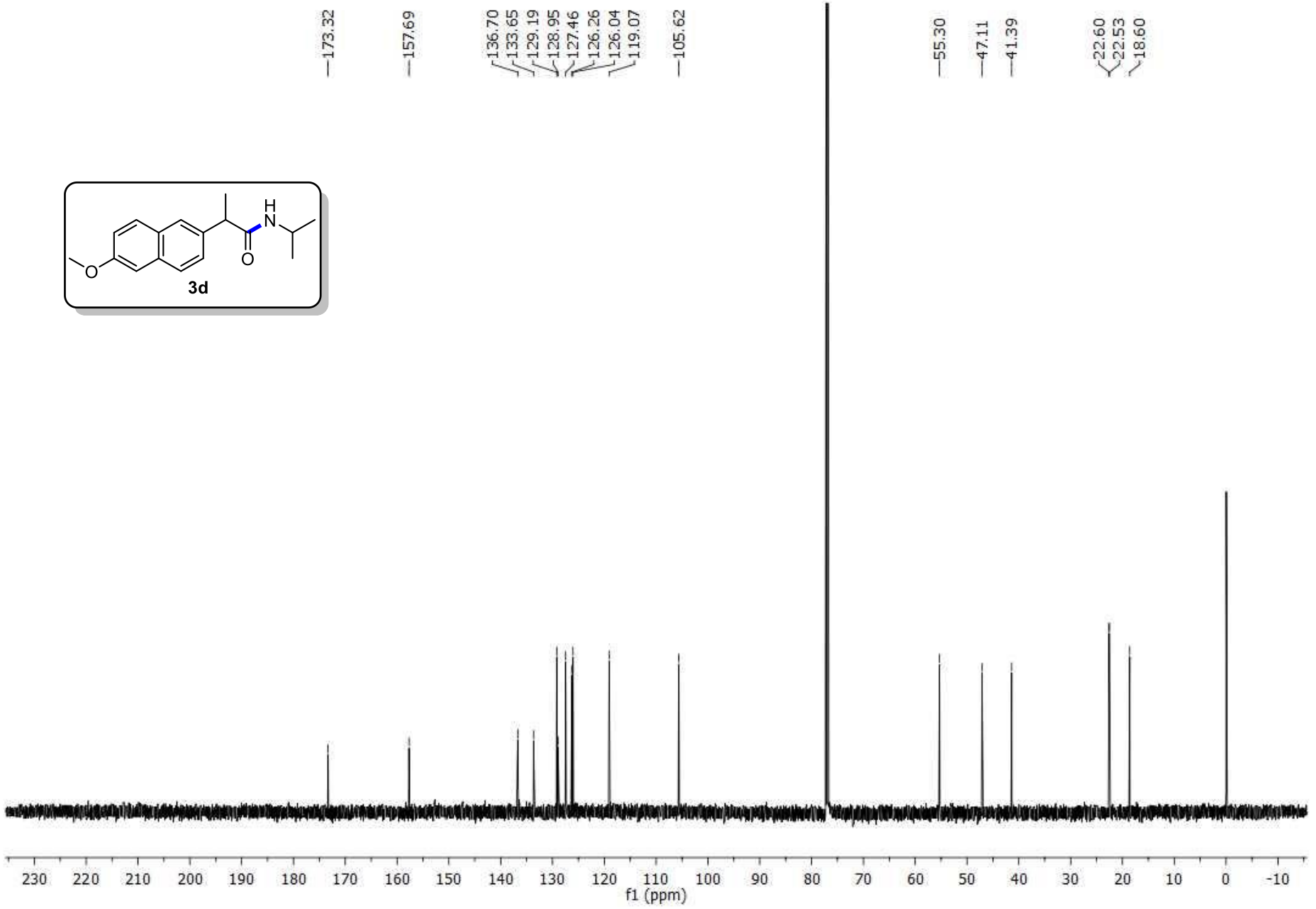
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2-phenylbutanamide **(3c)**



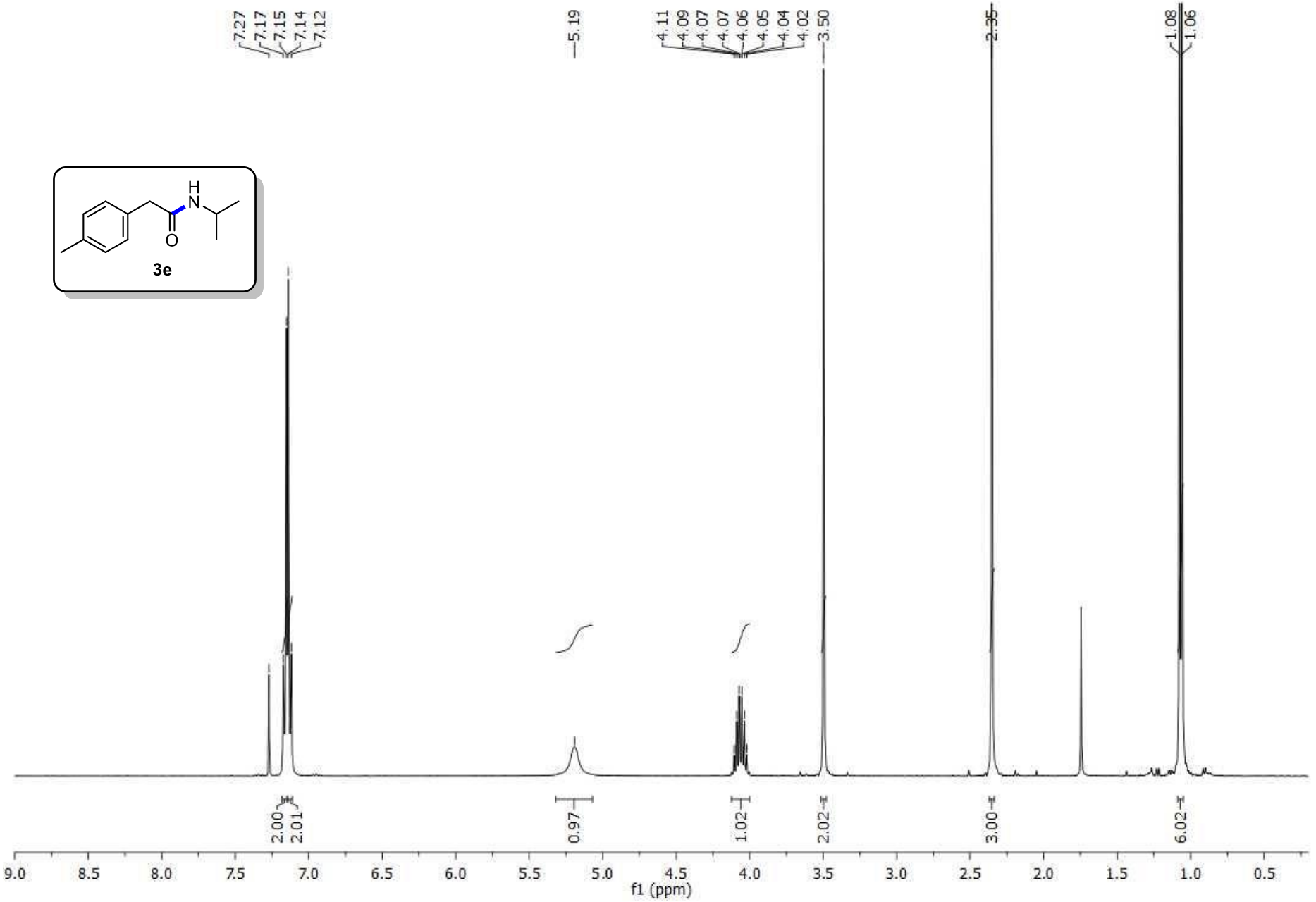
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of *N*-Isopropyl-2-(6-methoxynaphthalen-2-yl)propanamide **(3d)**



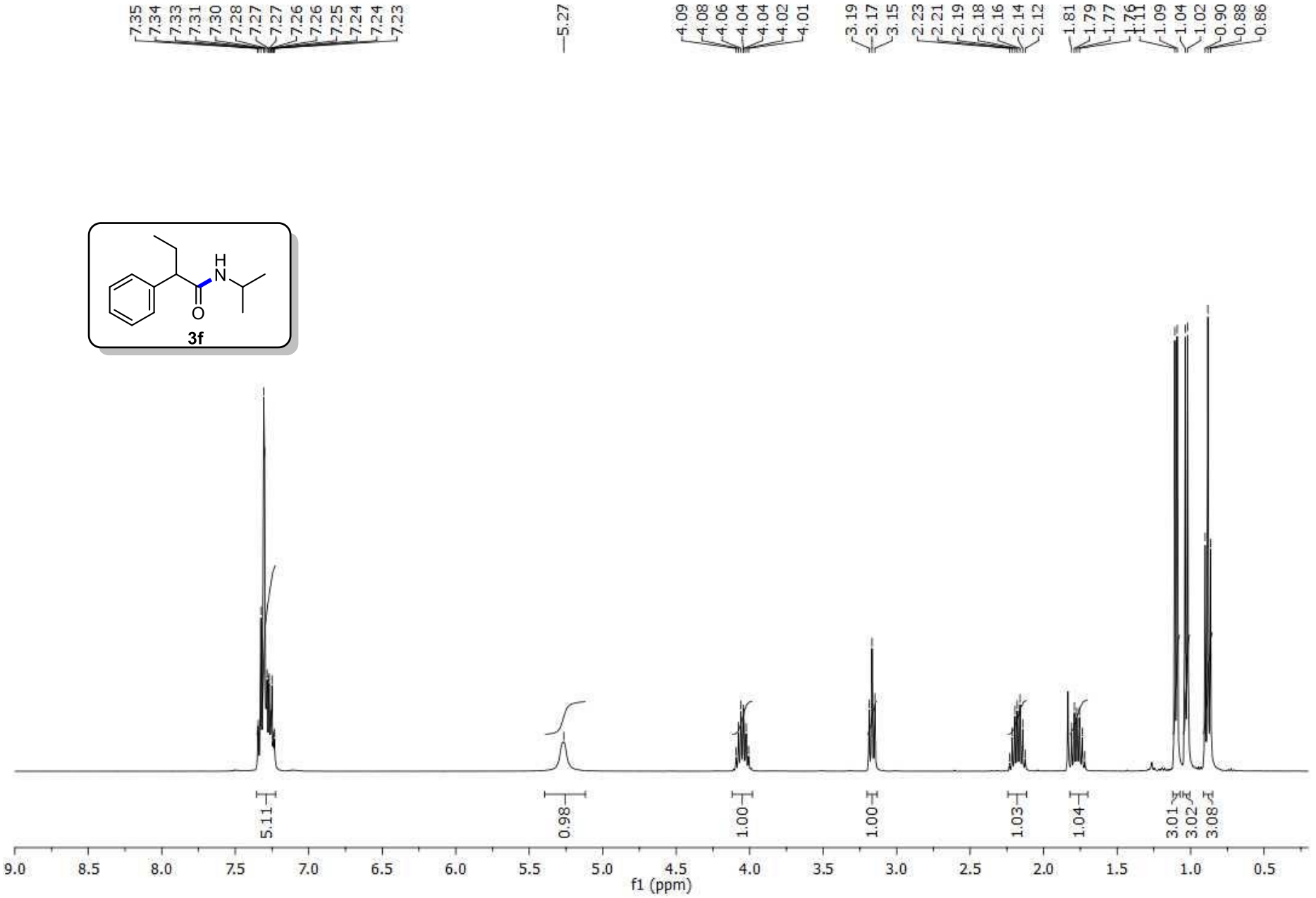
^{13}C NMR (151 MHz, $CDCl_3$) spectrum of *N*-Isopropyl-2-(6-methoxynaphthalen-2-yl)propanamide **(3d)**



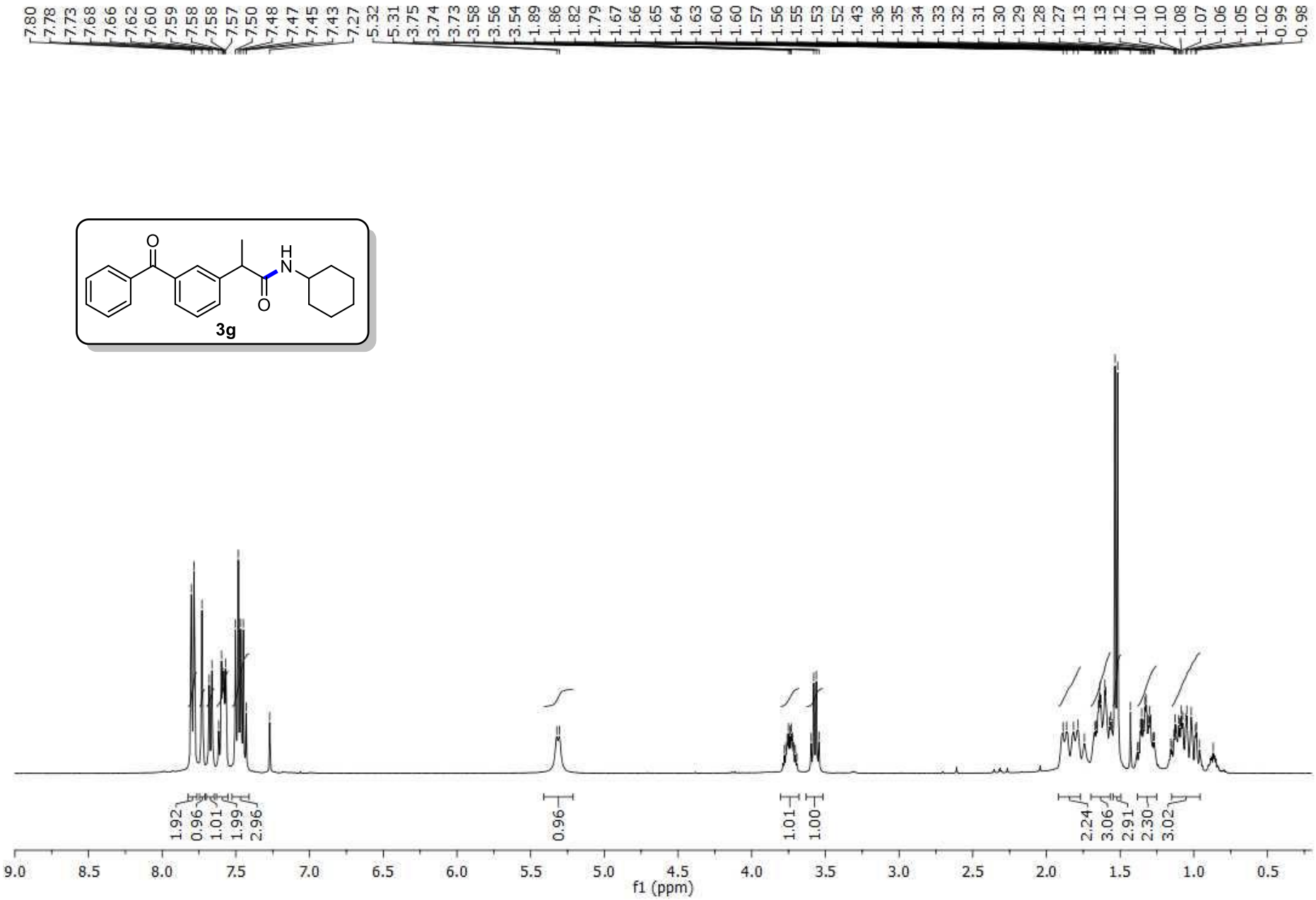
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropyl-2-(*p*-tolyl)acetamide **(3e)**



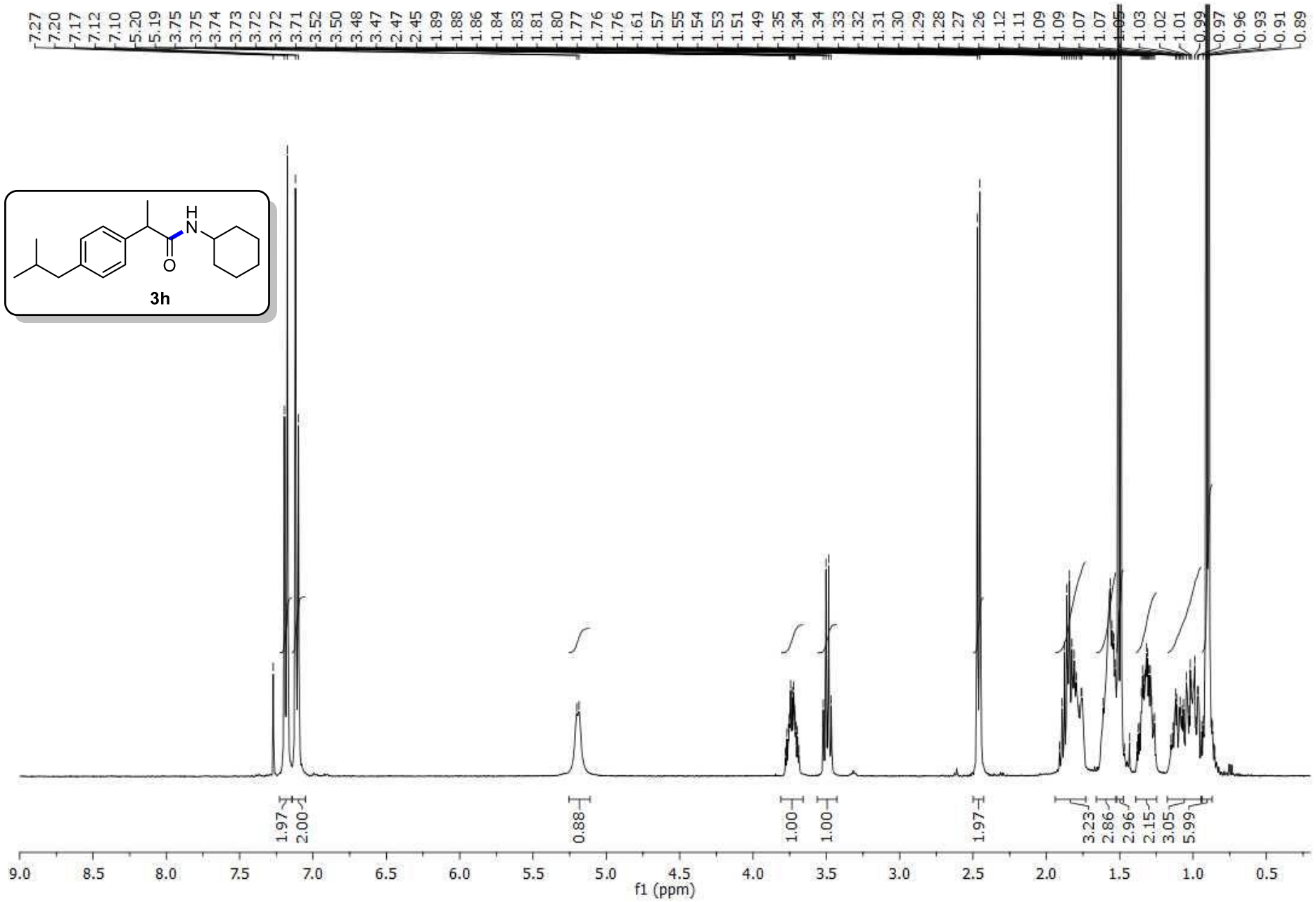
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropyl-2-phenylbutanamide **(3f)**



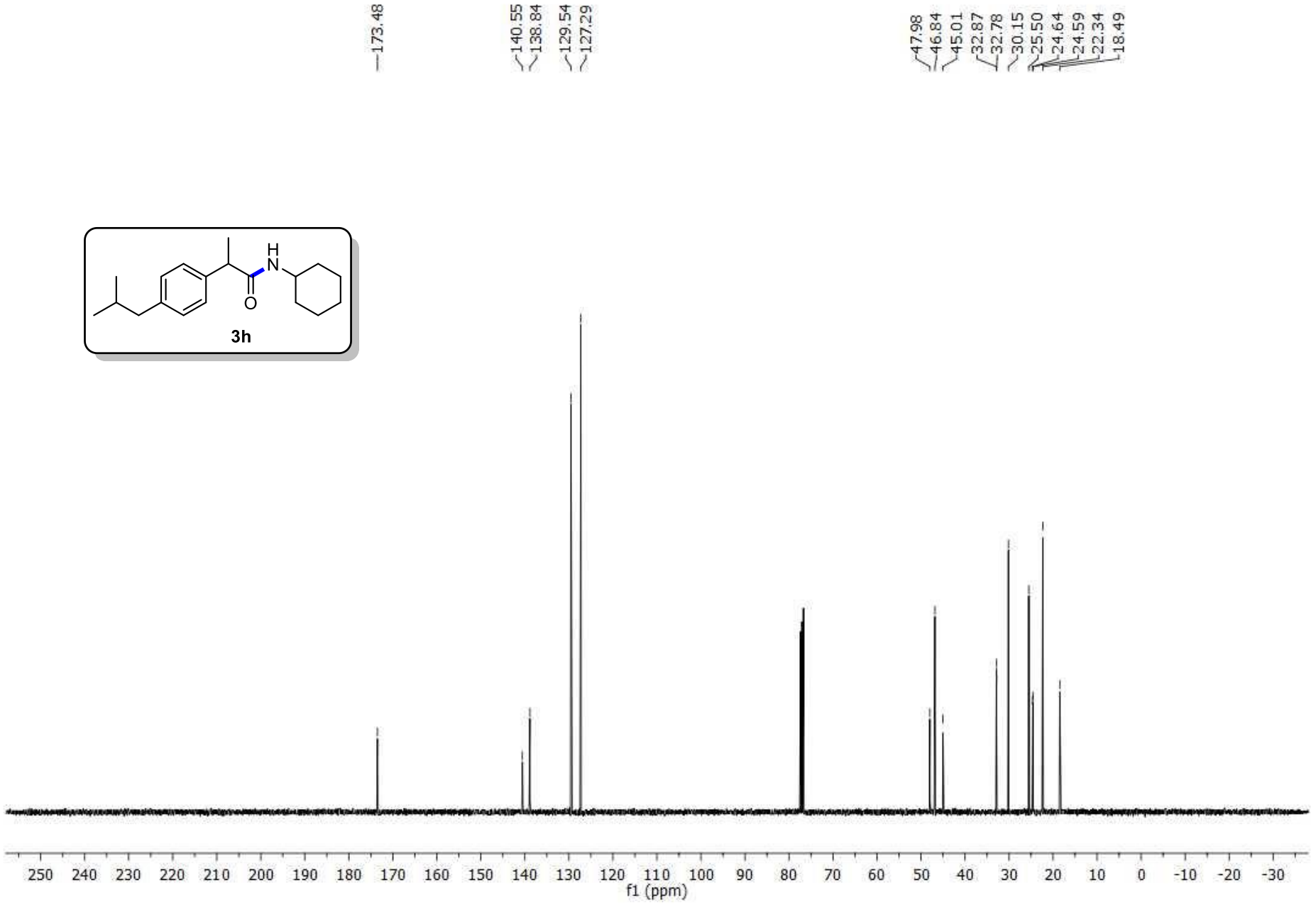
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2-(3-Benzoylphenyl)-*N*-cyclohexylpropanamide **(3g)**



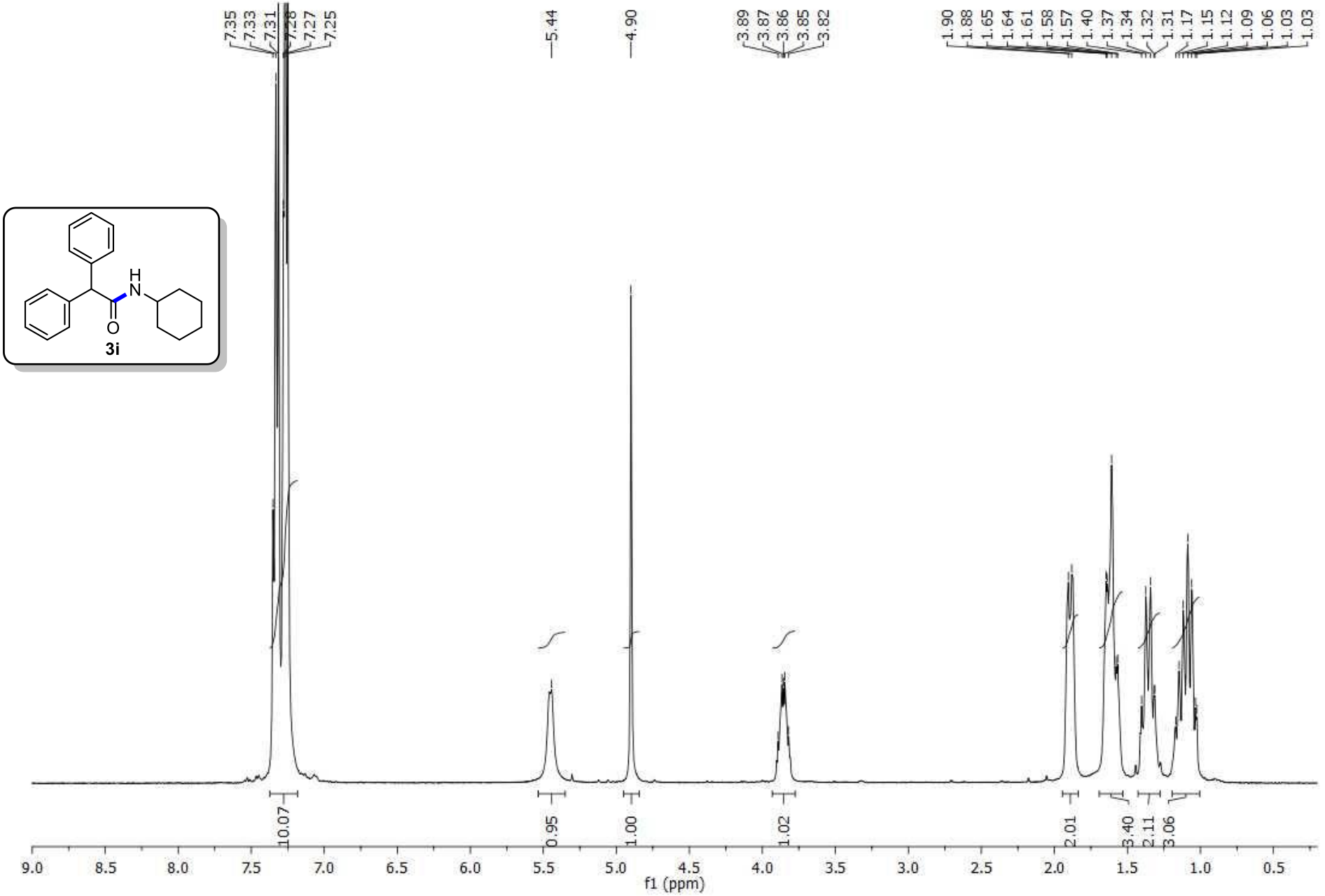
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2-(4-isobutylphenyl)propanamide **(3h)**



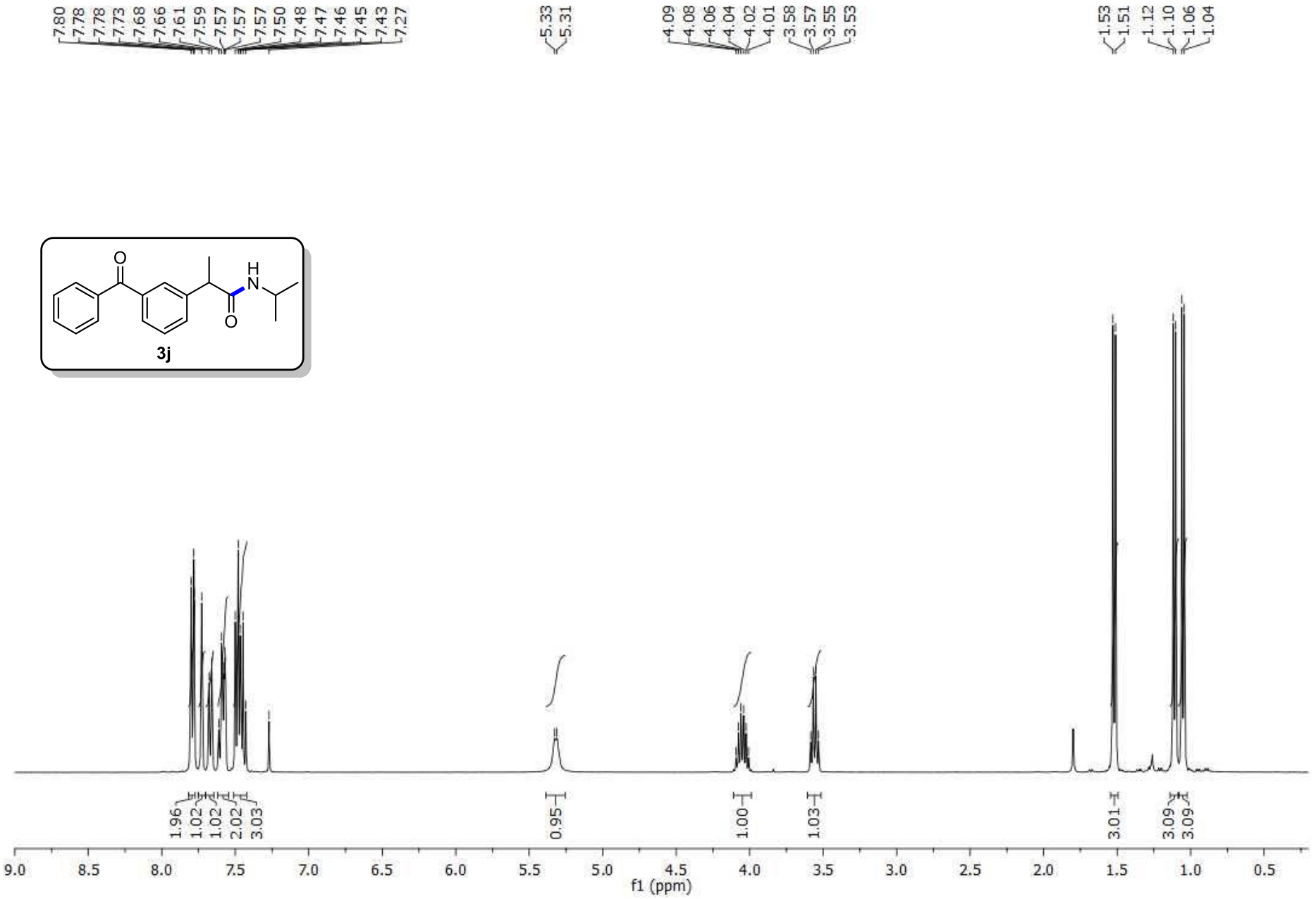
^{13}C NMR ($CDCl_3$, 101 MHz) spectrum of *N*-Cyclohexyl-2-(4-isobutylphenyl)propanamide **(3h)**



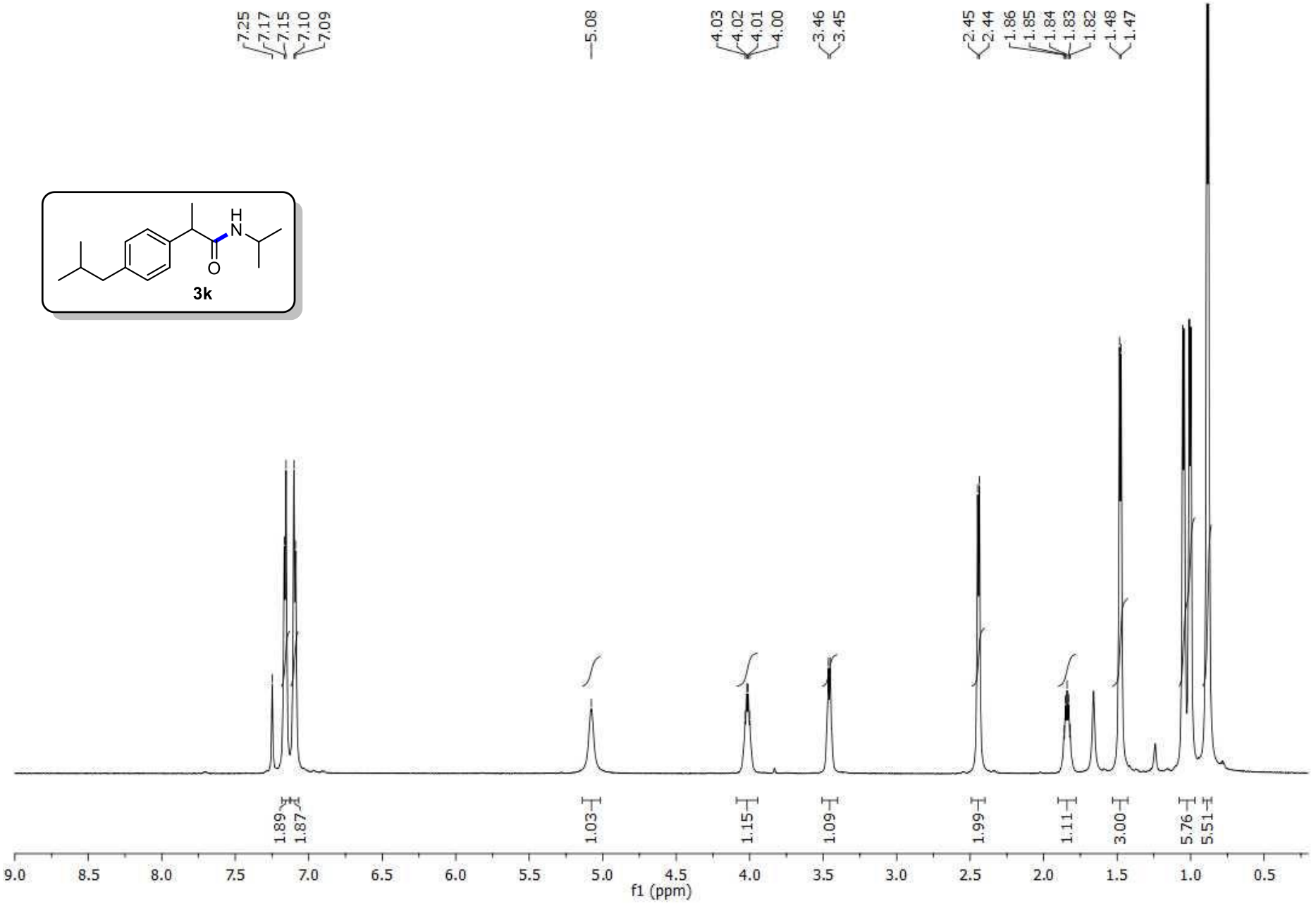
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2,2-diphenylacetamide **(3i)**



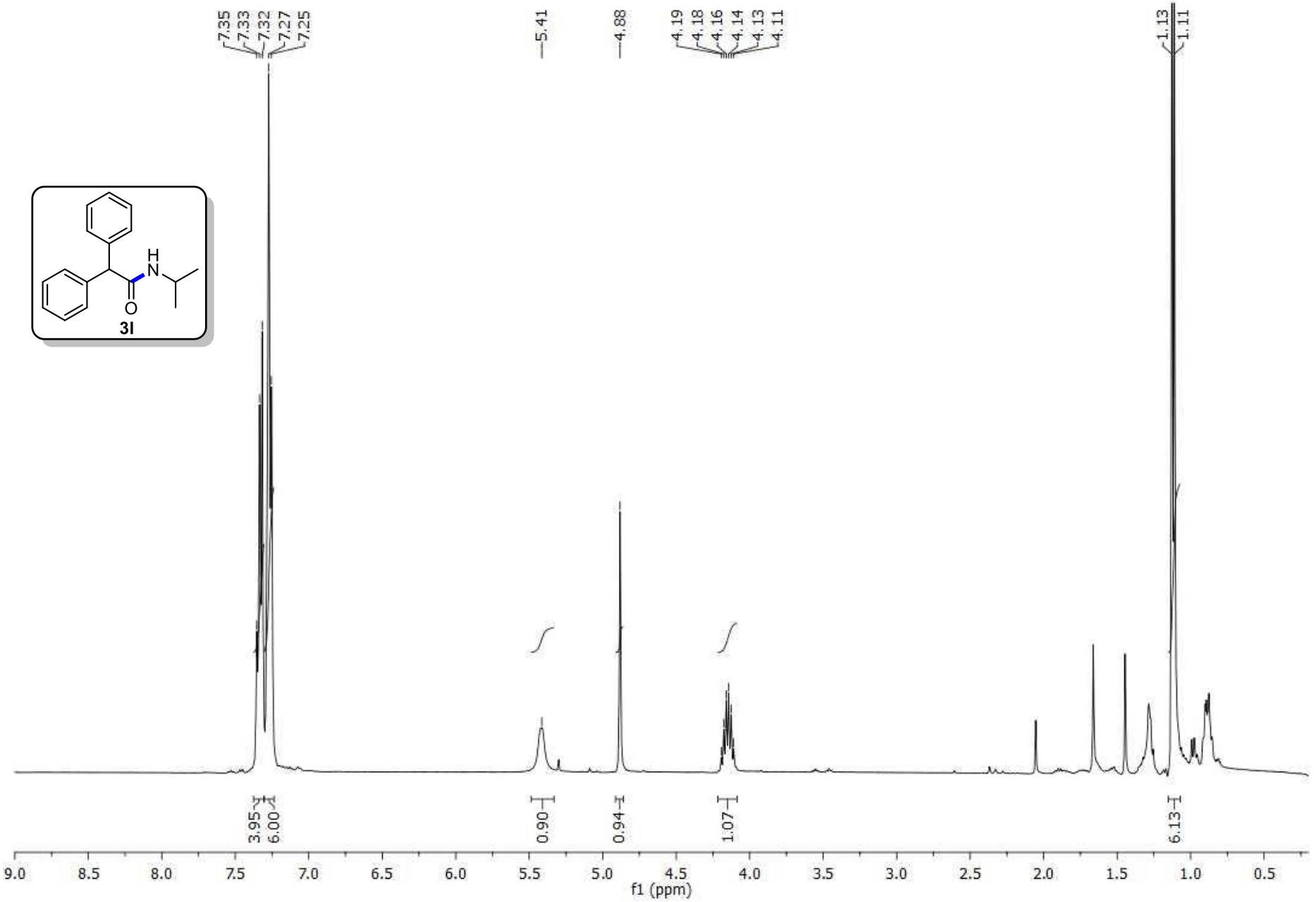
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2-(3-Benzoylphenyl)-*N*-isopropylpropanamide **(3j)**



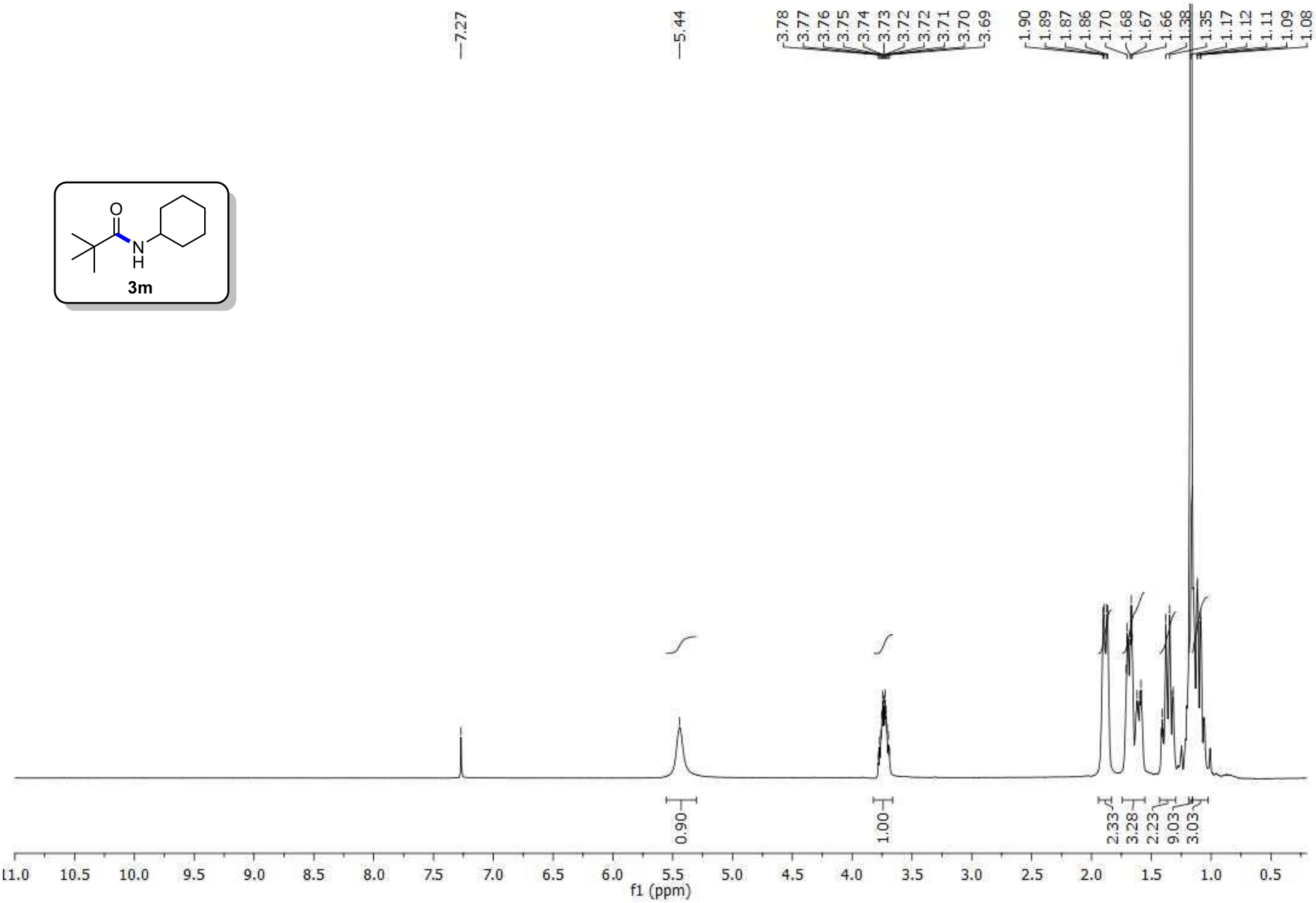
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of 2-(4-Isobutylphenyl)-*N*-isopropylpropanamide **(3k)**



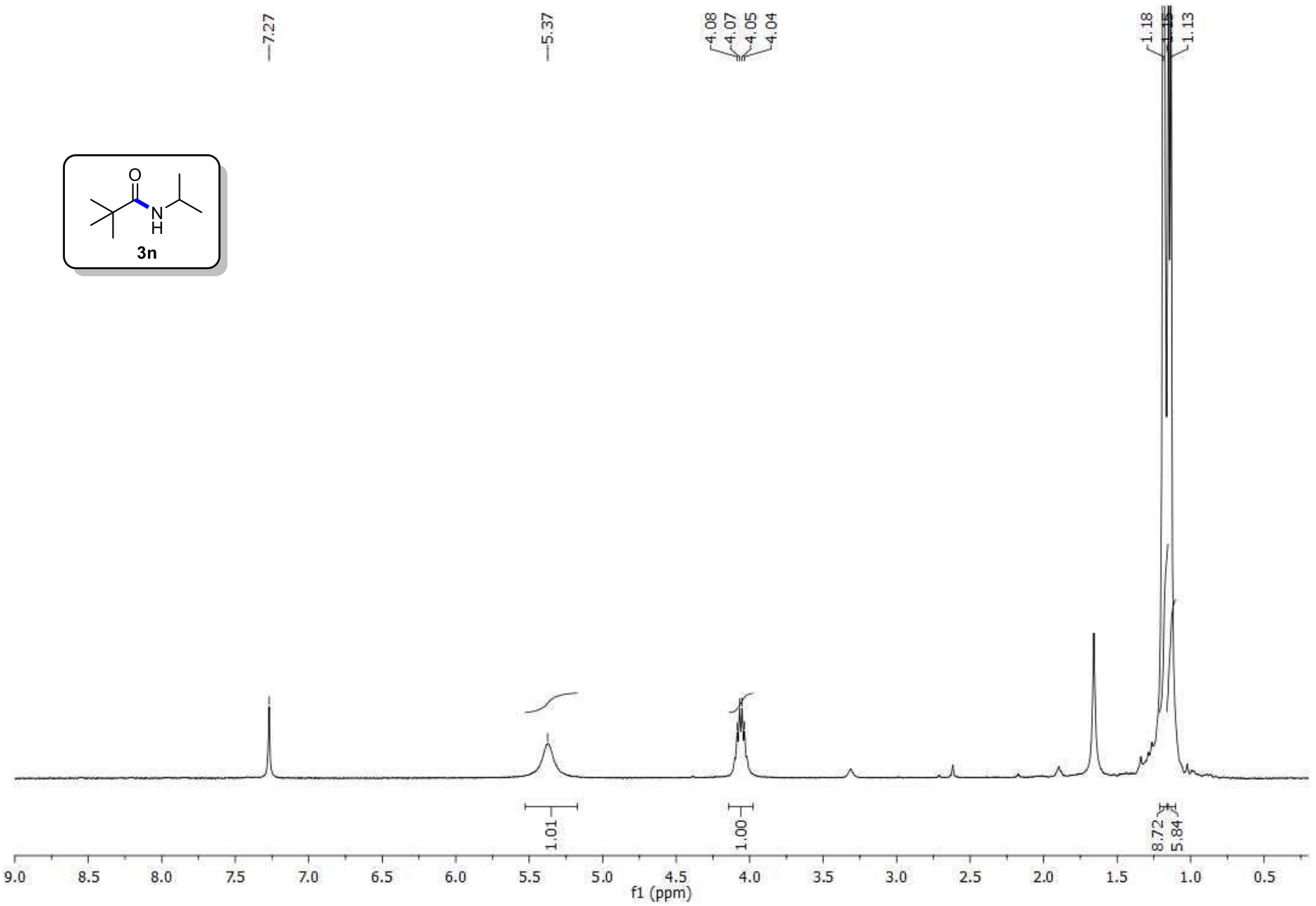
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropyl-2,2-diphenylacetamide **(3l)**



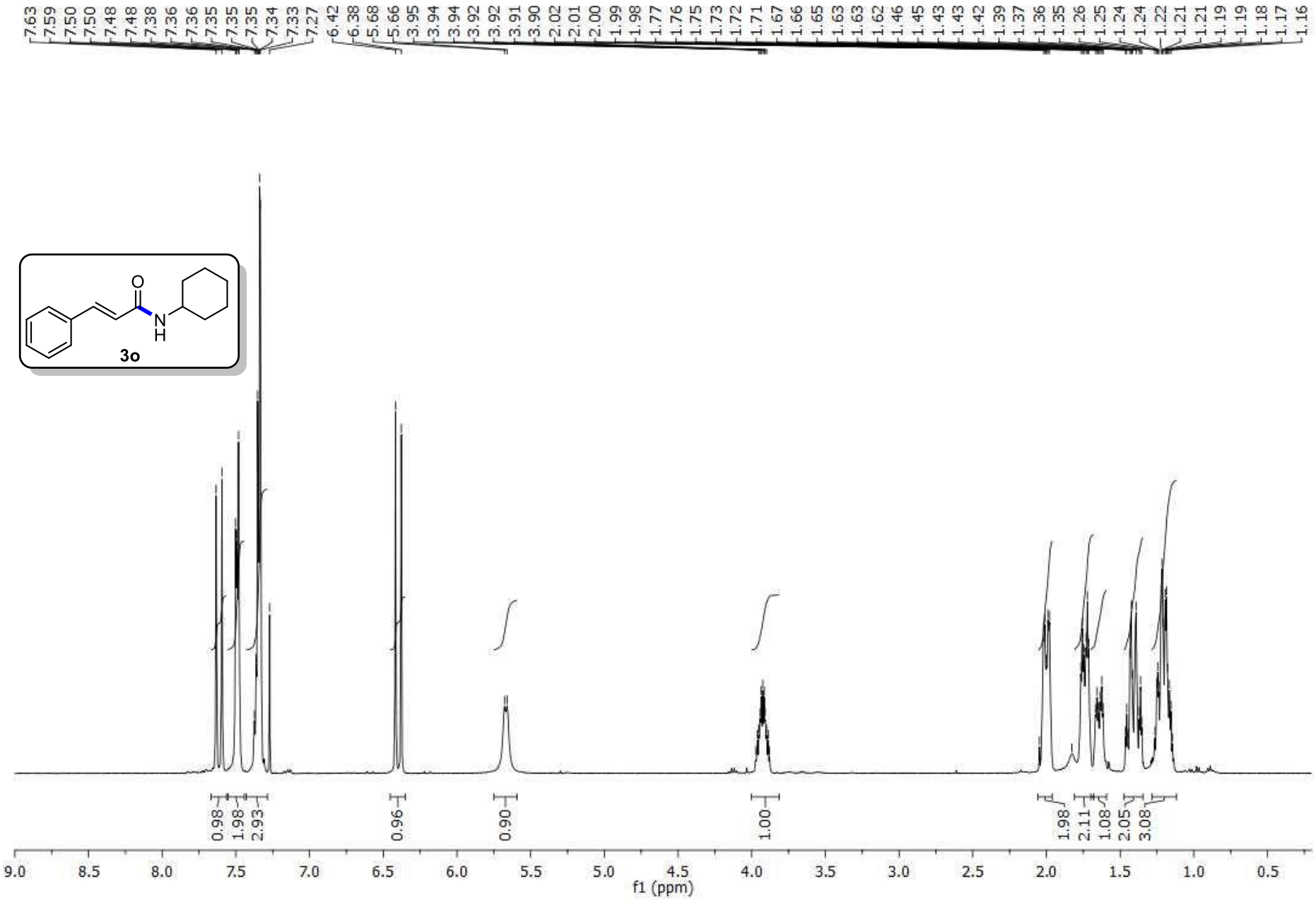
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexylpivalamide **(3m)**



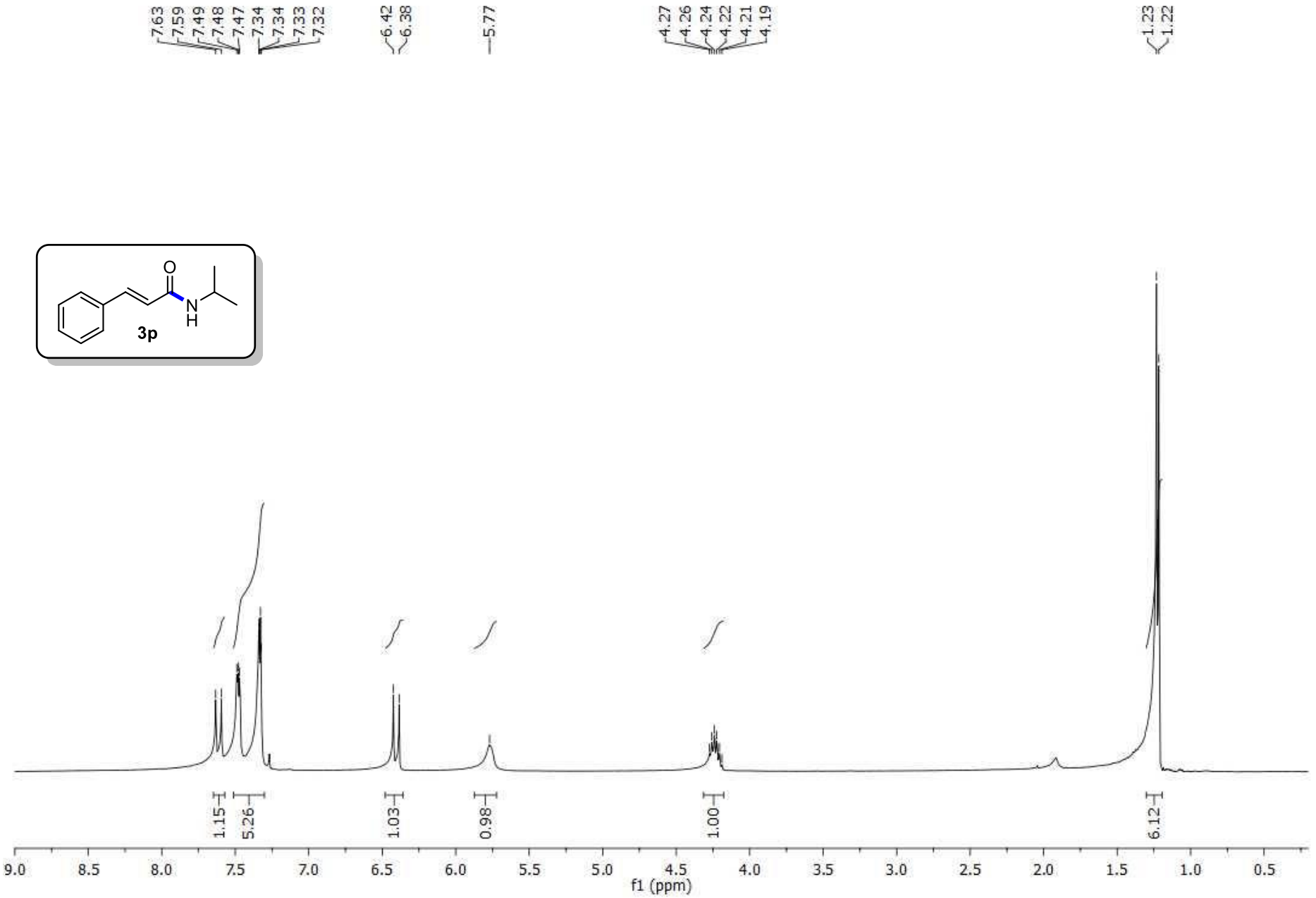
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropylpivalamide **(3n)**



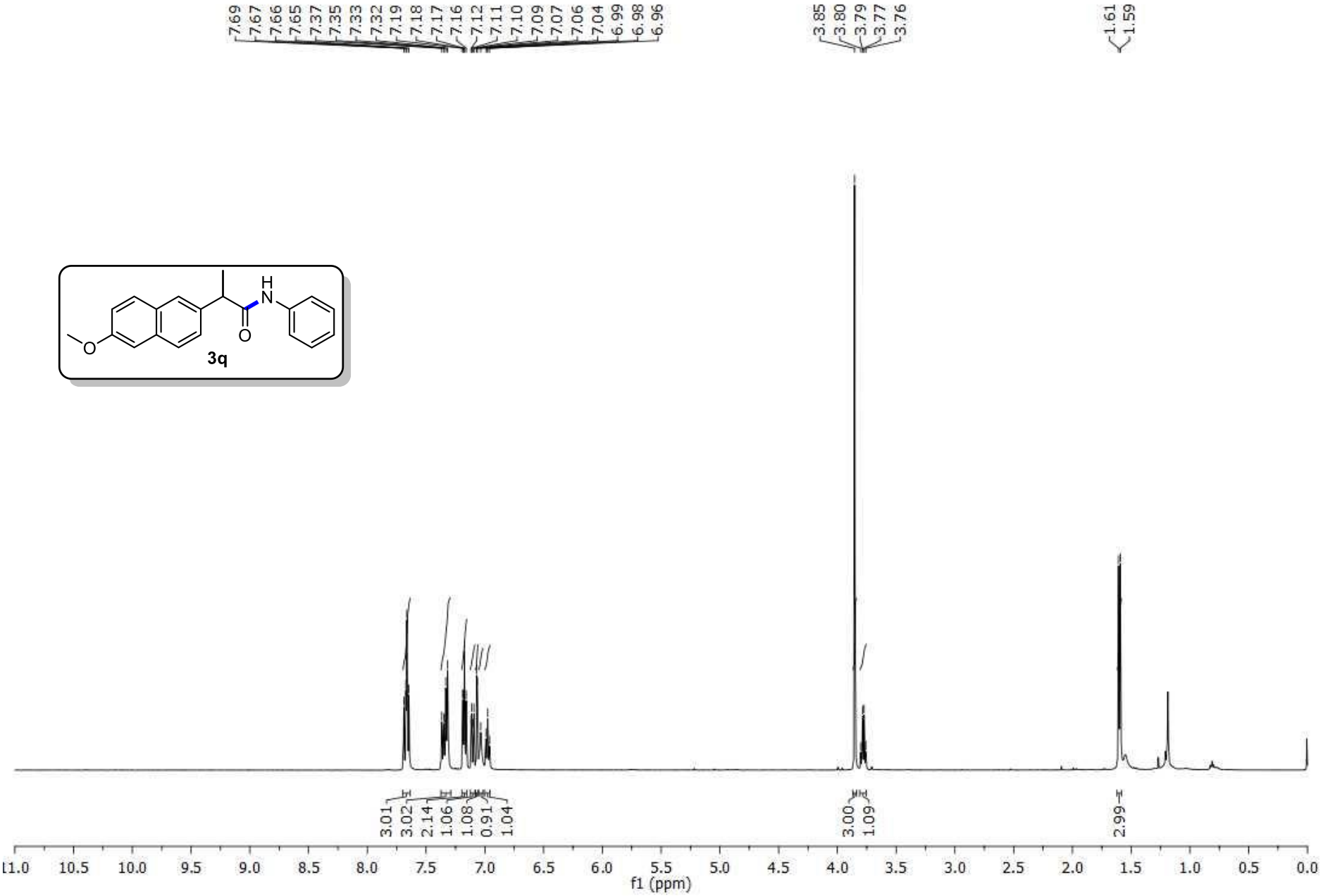
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexylcinnamamide **(3o)**



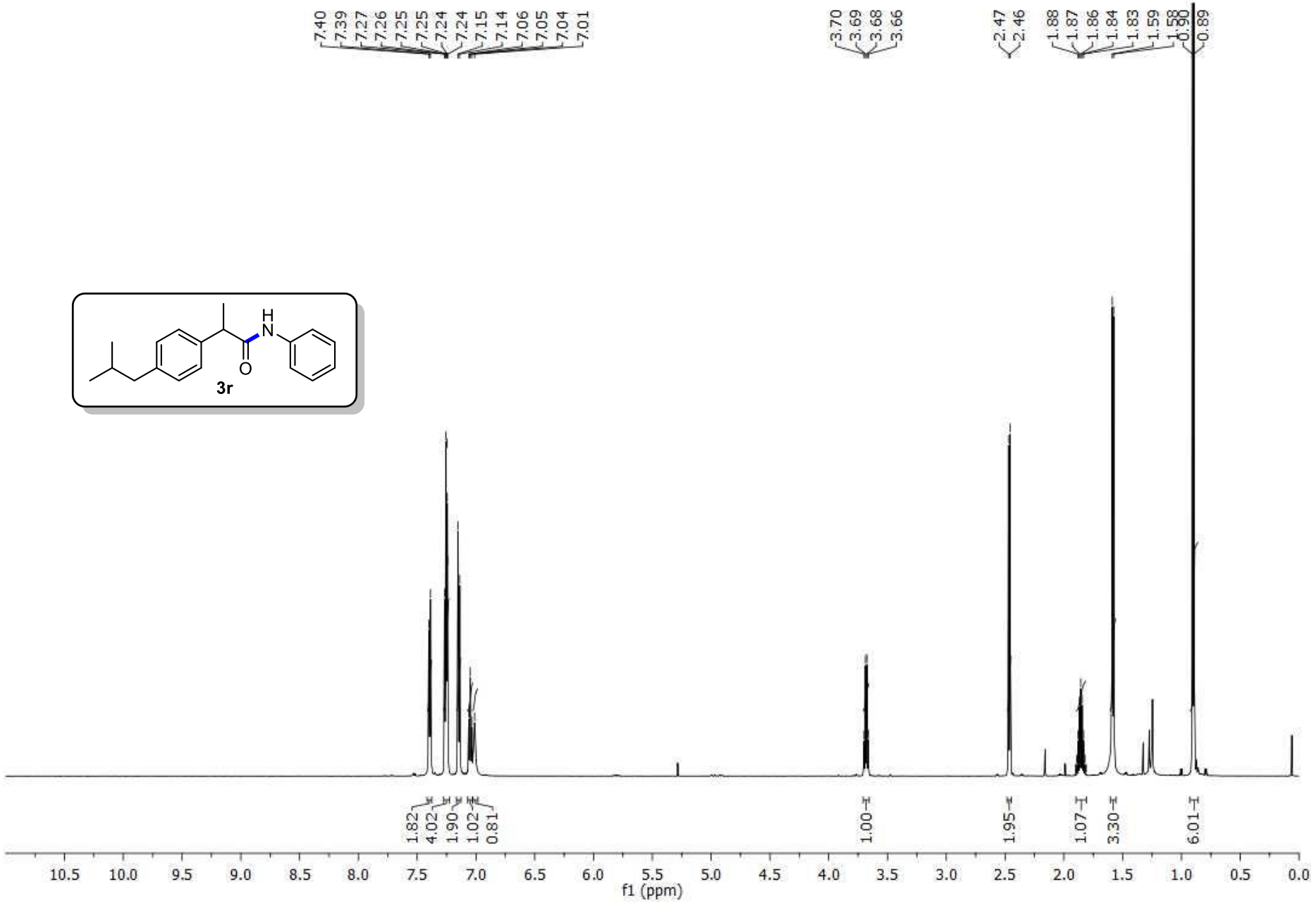
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropylcinnamamide **(3p)**



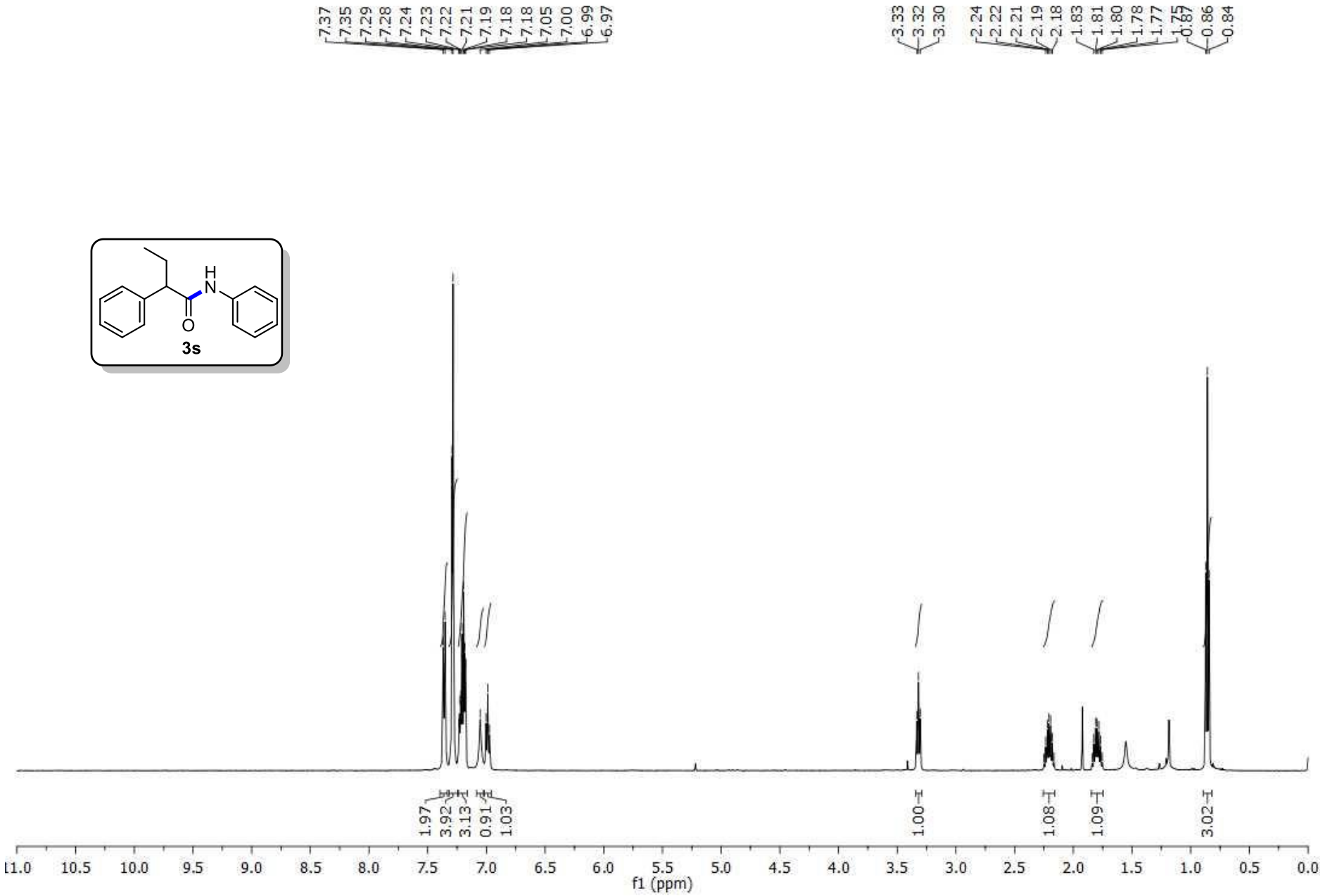
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of 2-(6-methoxynaphthalen-2-yl)-*N*-phenylpropanamide **(3q)**



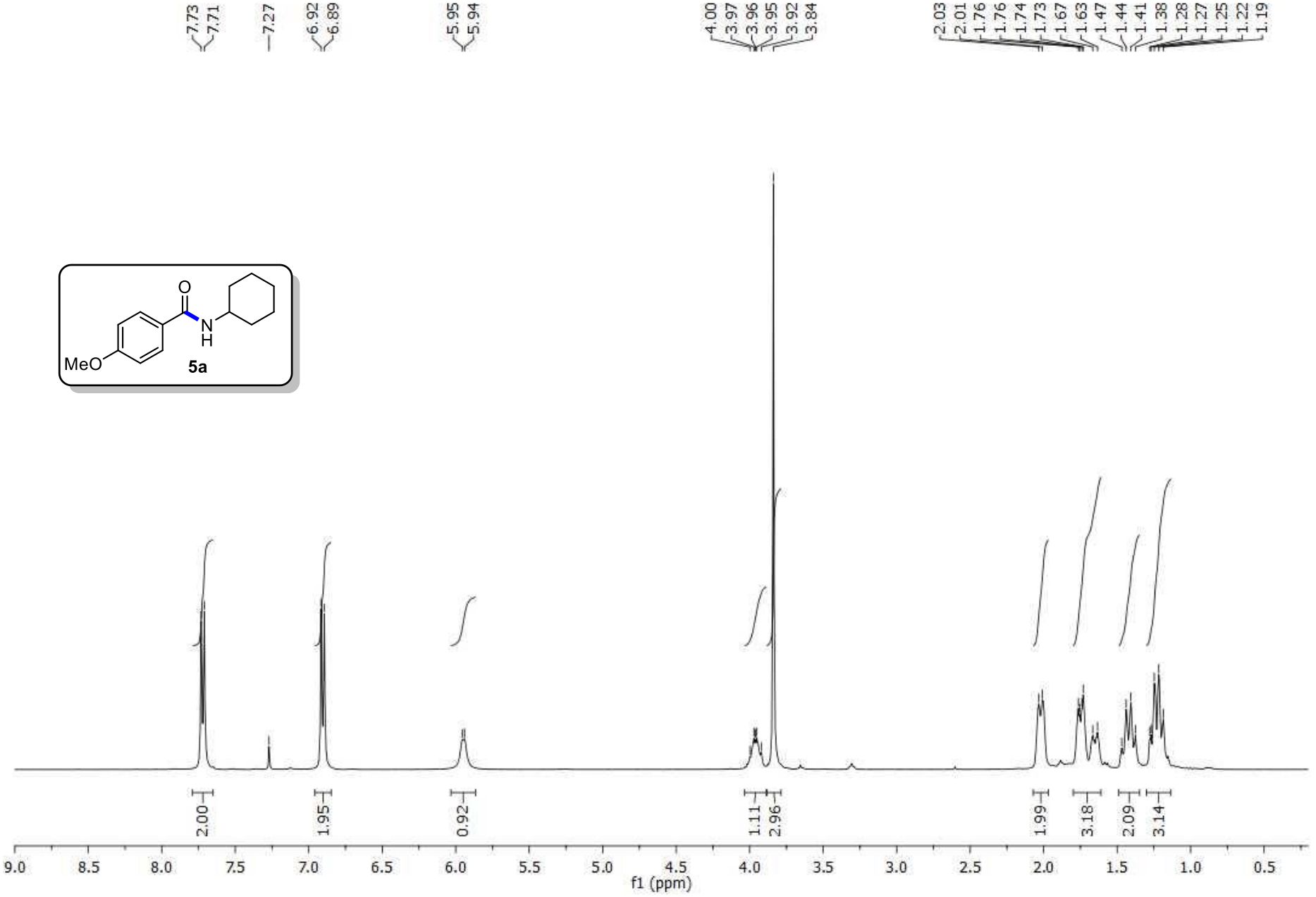
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of 2-(4-isobutylphenyl)-N-phenylpropanamide **(3r)**



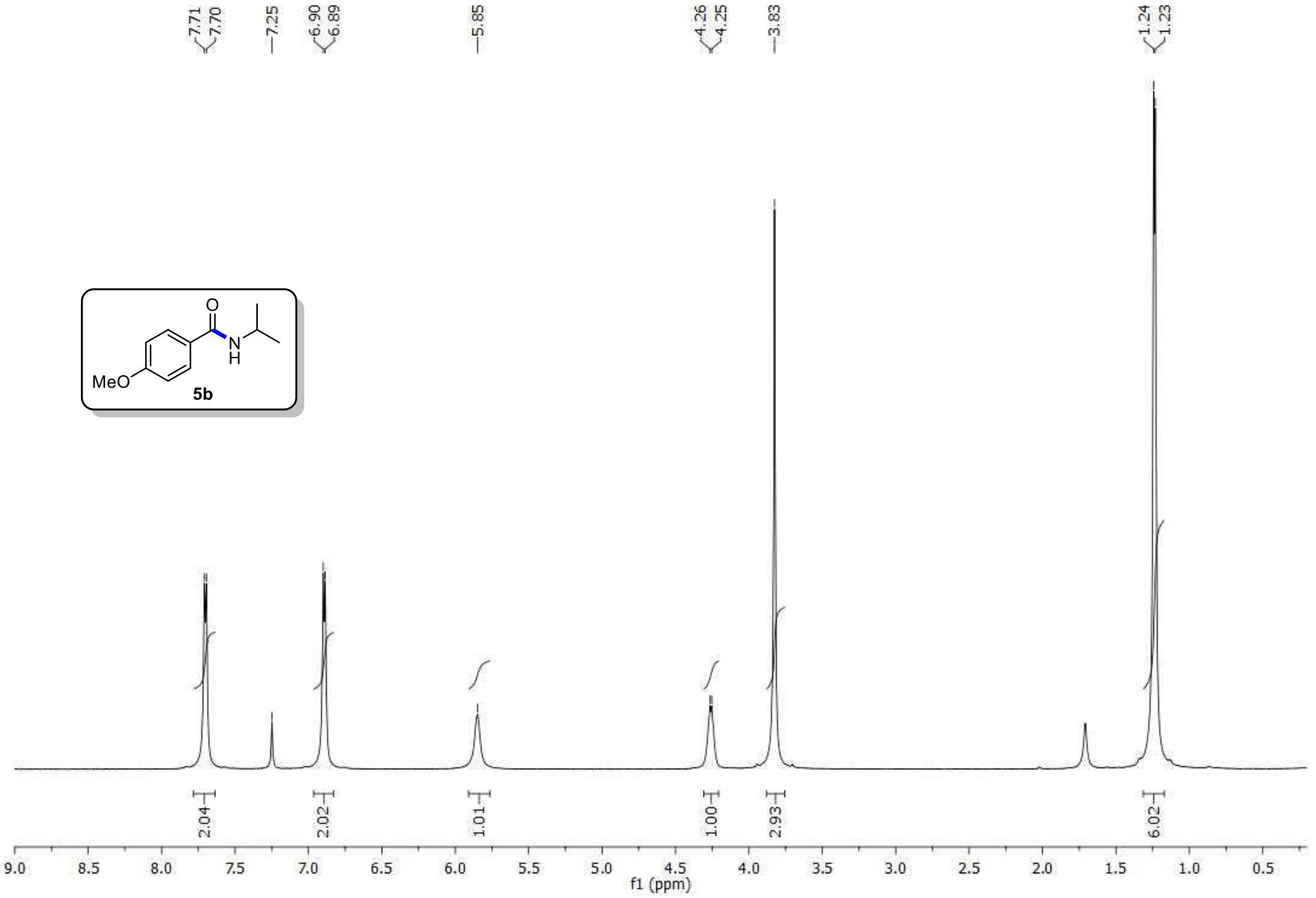
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *N*,2-diphenylbutanamide **(3s)**



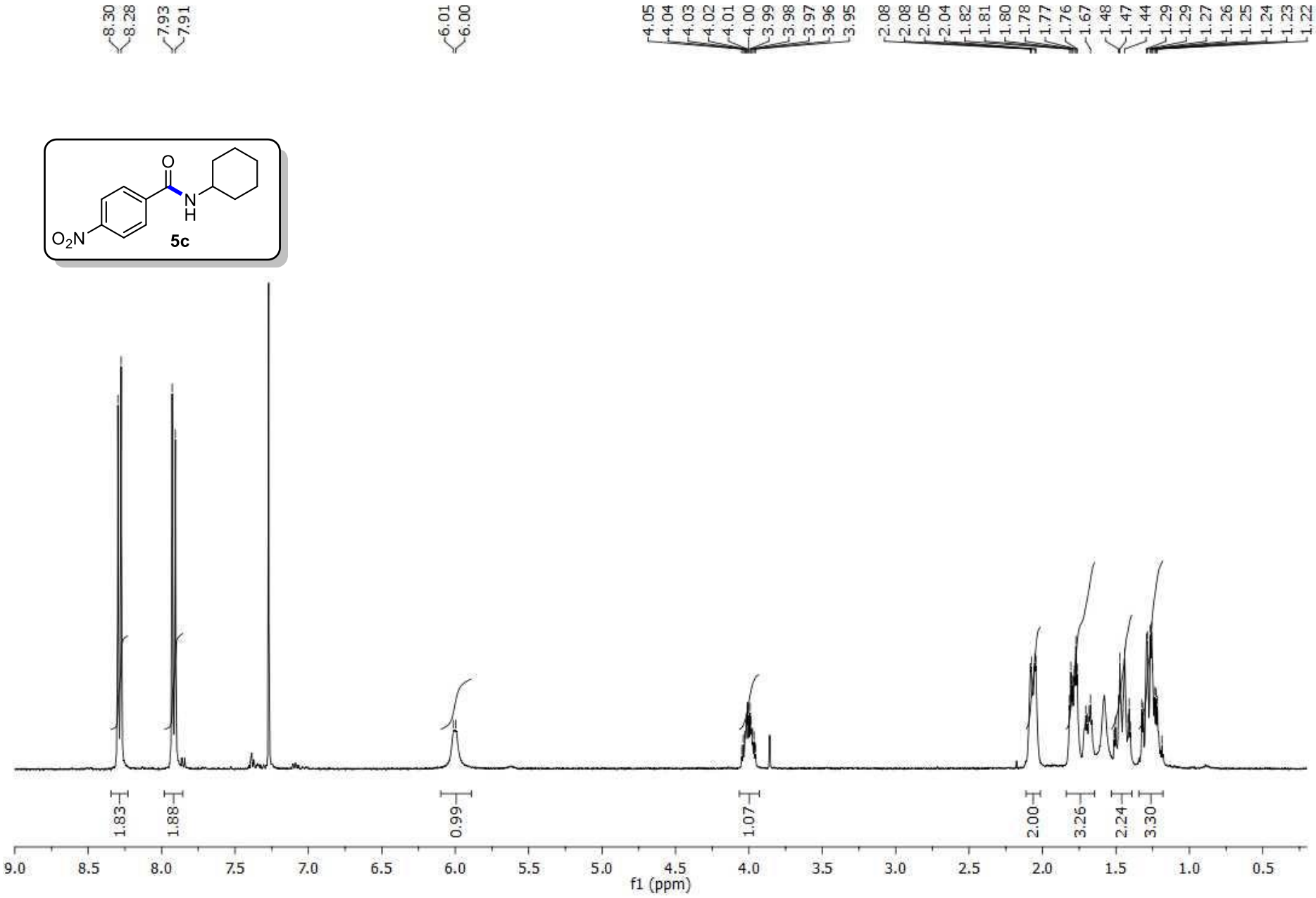
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-4-methoxybenzamide **(5a)**



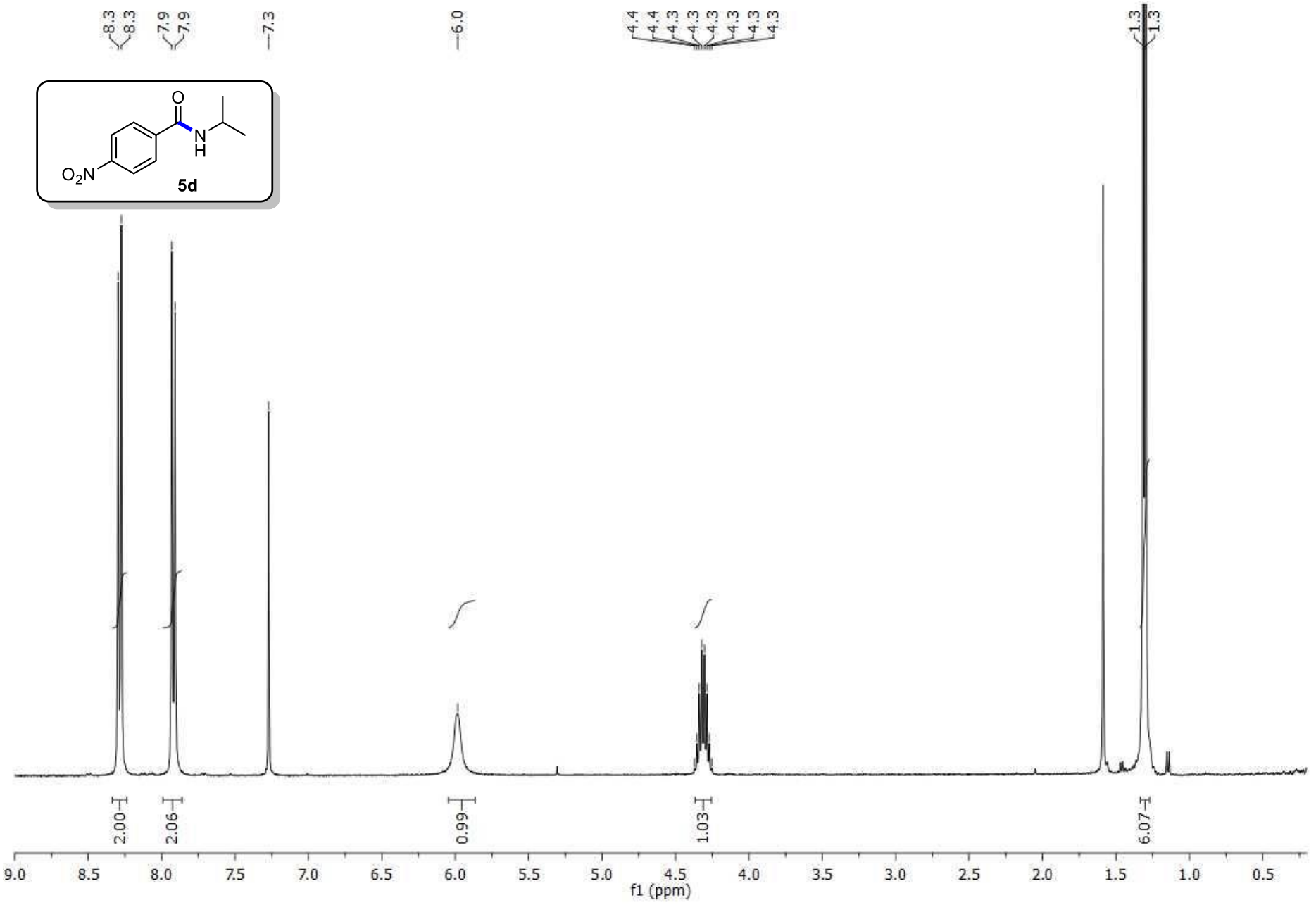
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of *N*-Isopropyl-4-methoxybenzamide **(5b)**



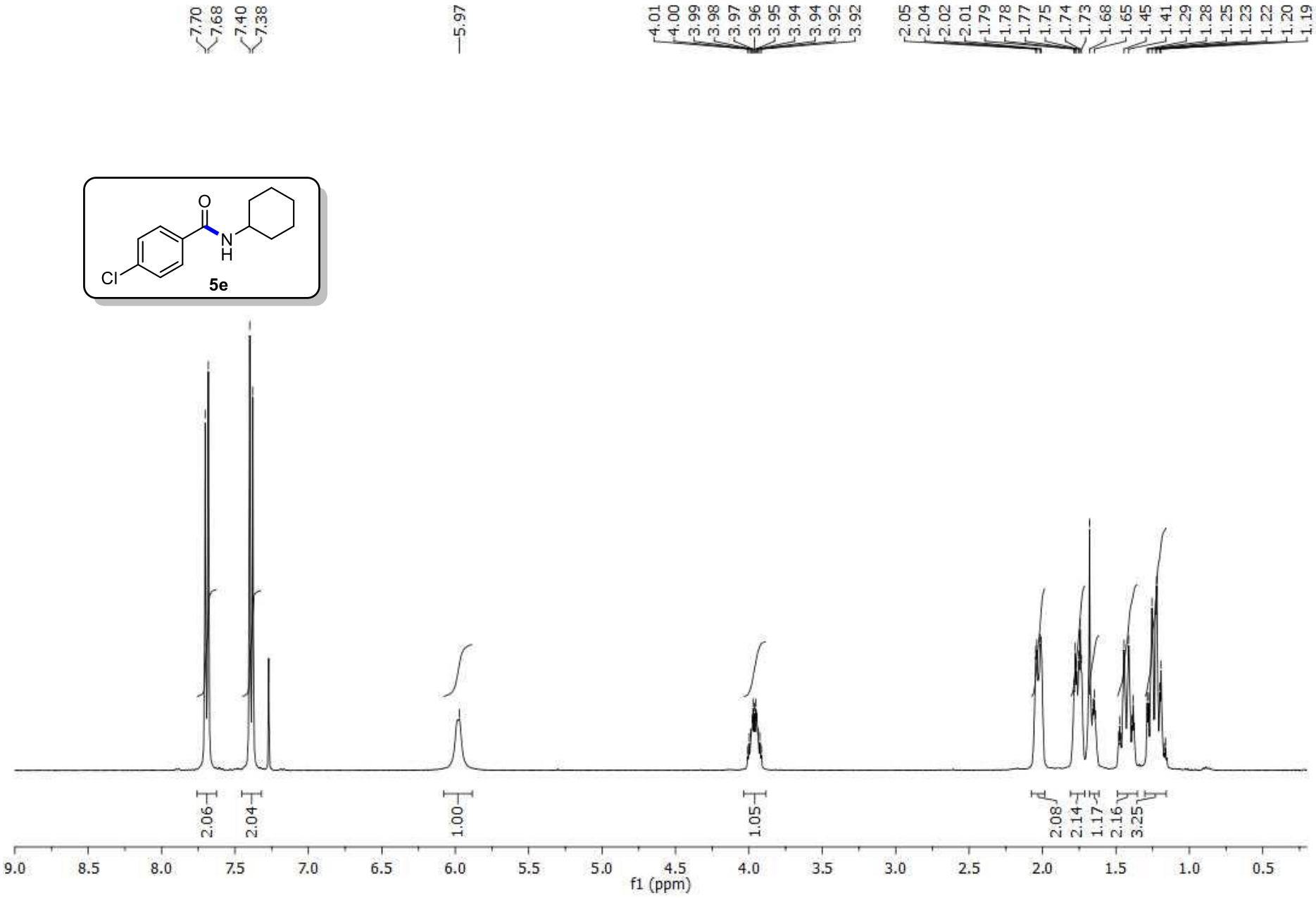
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-4-nitrobenzamide **(5c)**



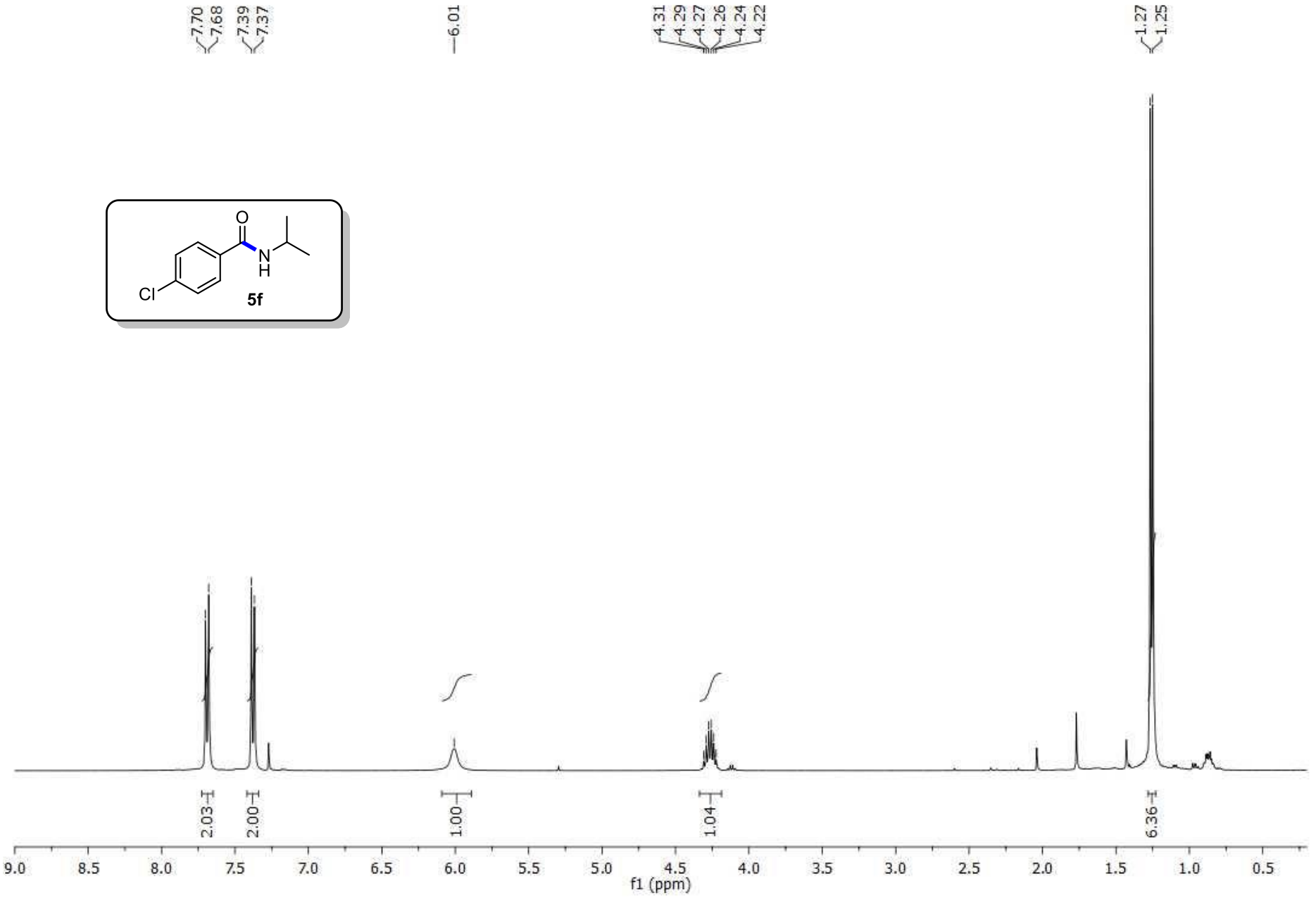
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropyl-4-nitrobenzamide **(5d)**



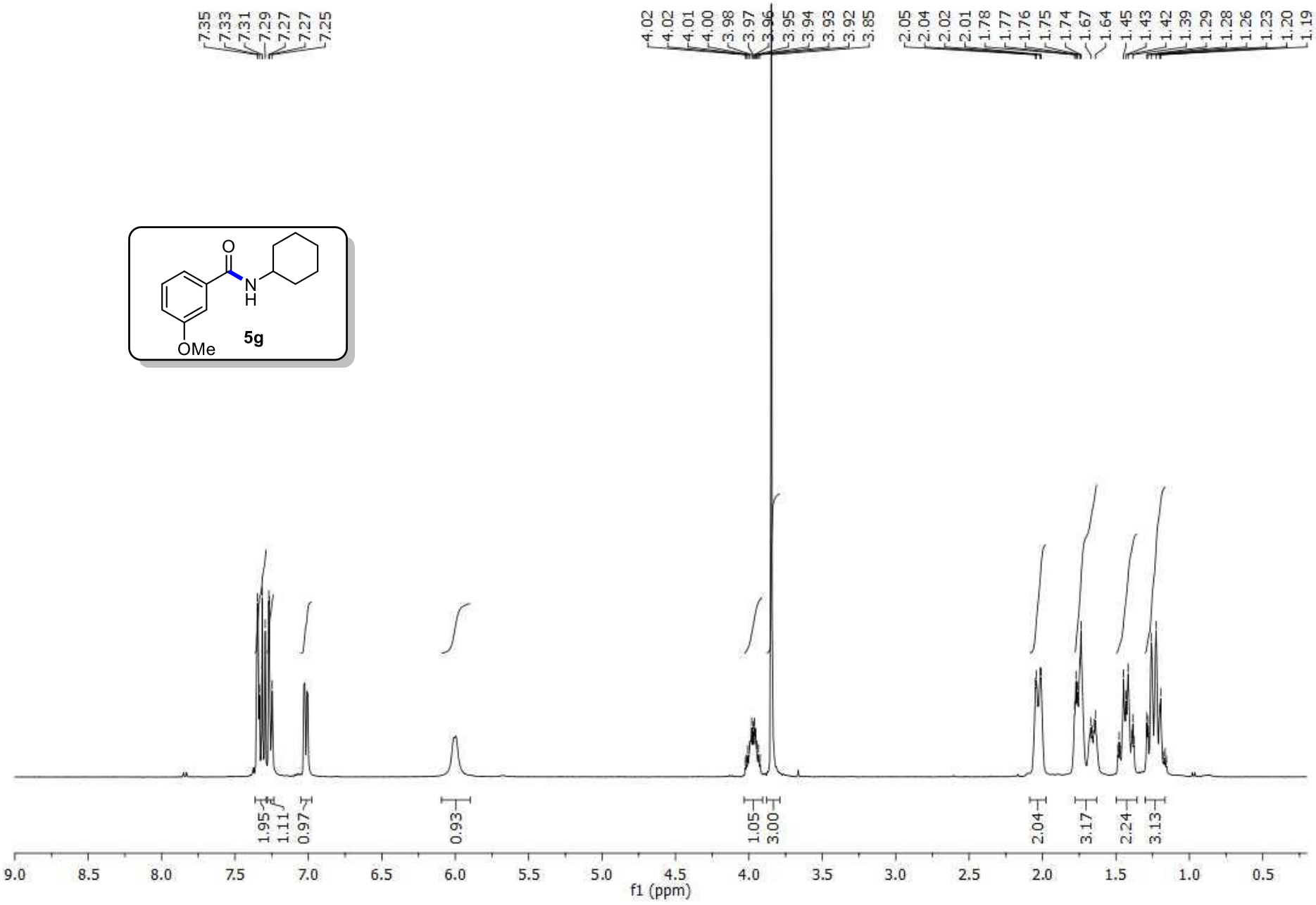
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 4-Chloro-*N*-cyclohexylbenzamide **(5e)**



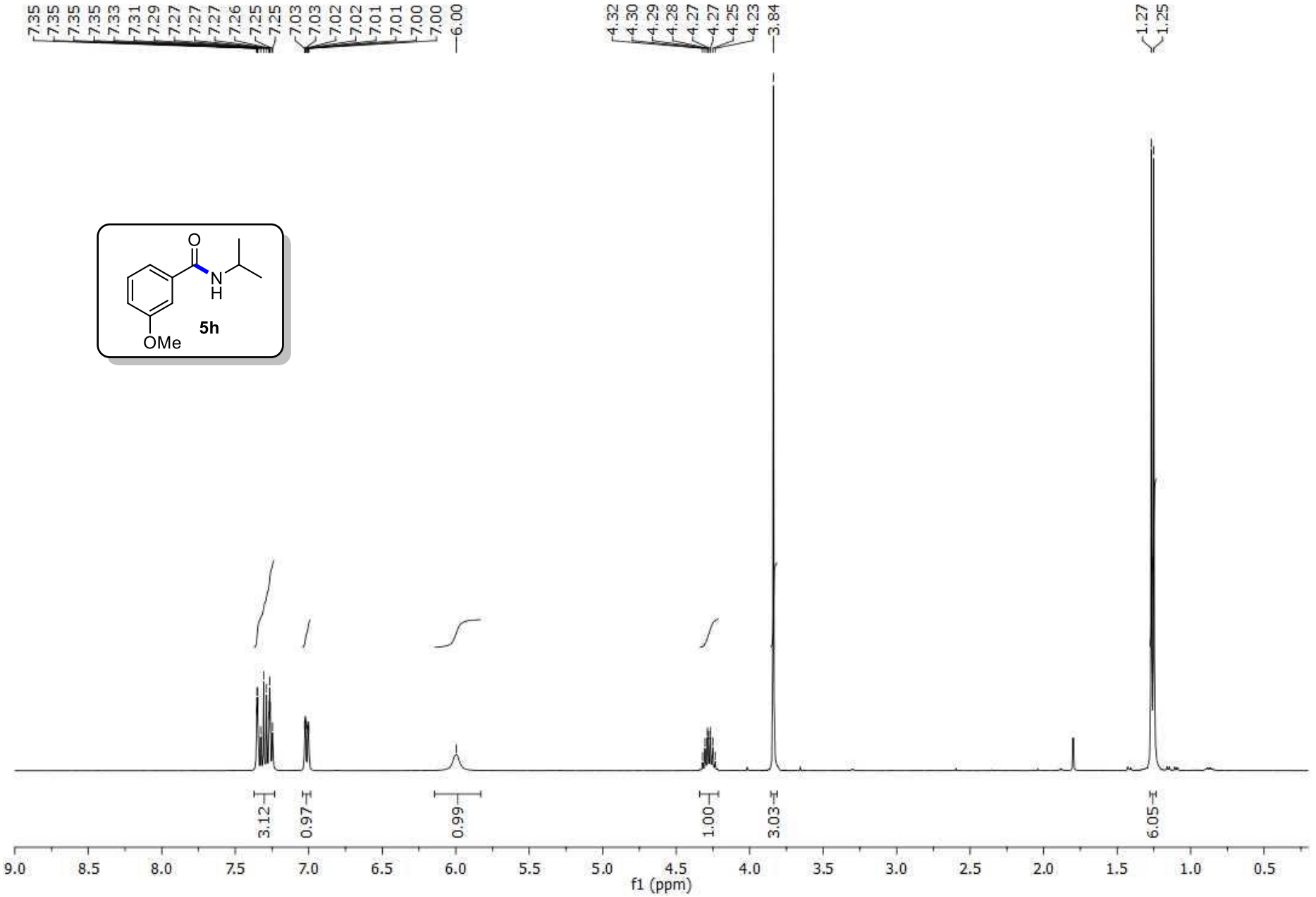
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 4-Chloro-*N*-isopropylbenzamide **(5f)**



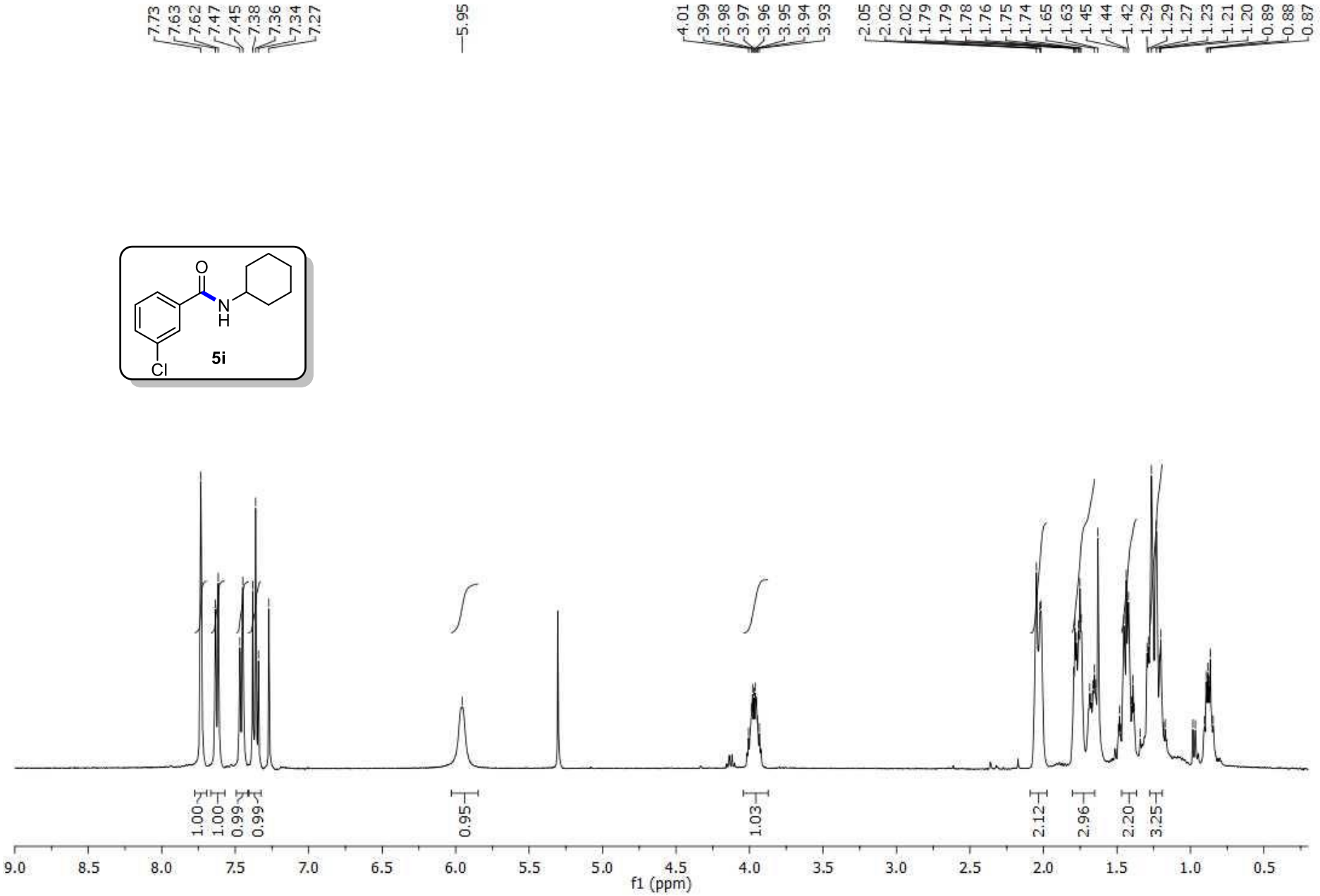
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-3-methoxybenzamide **(5g)**



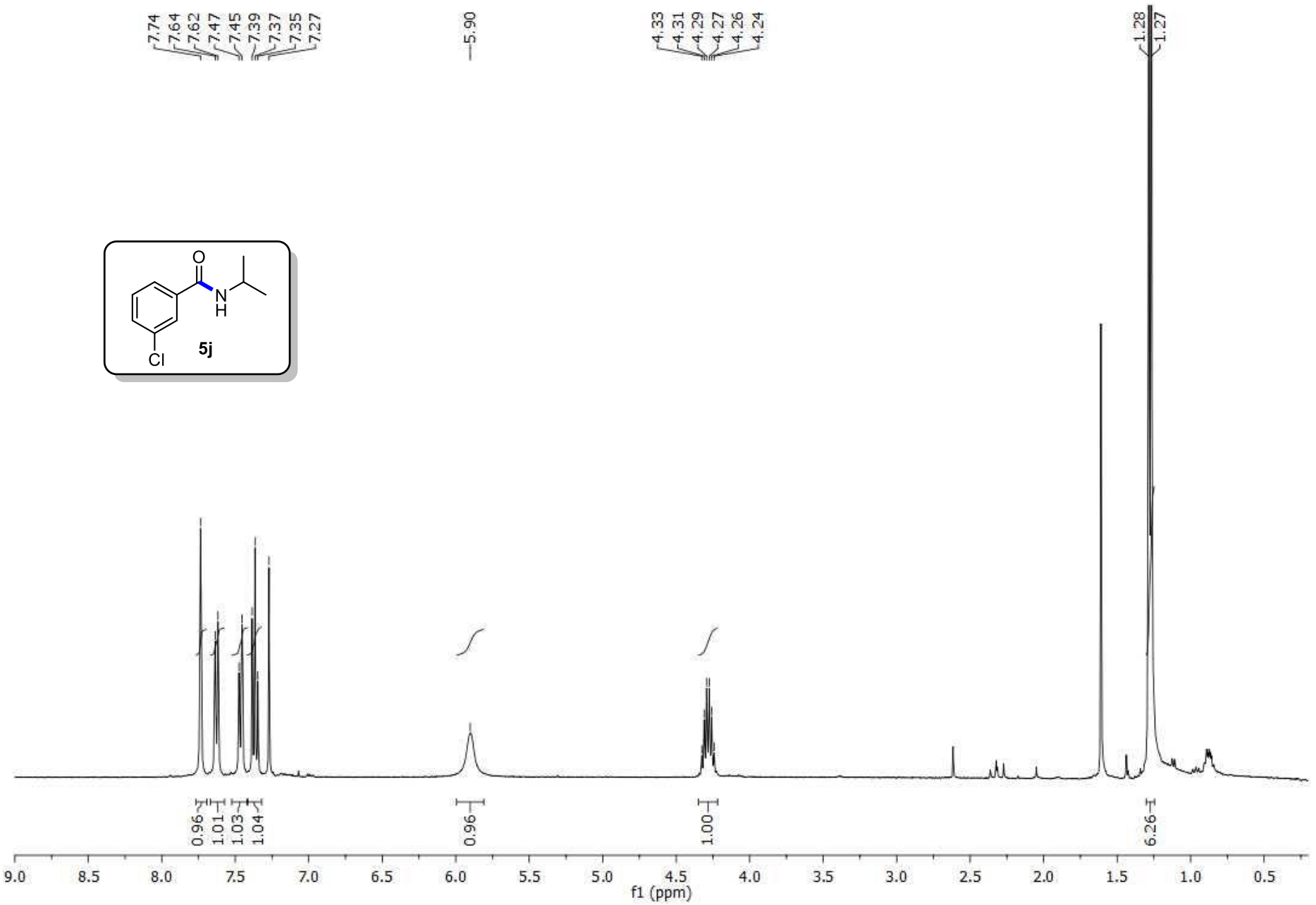
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropyl-3-methoxybenzamide **(5h)**



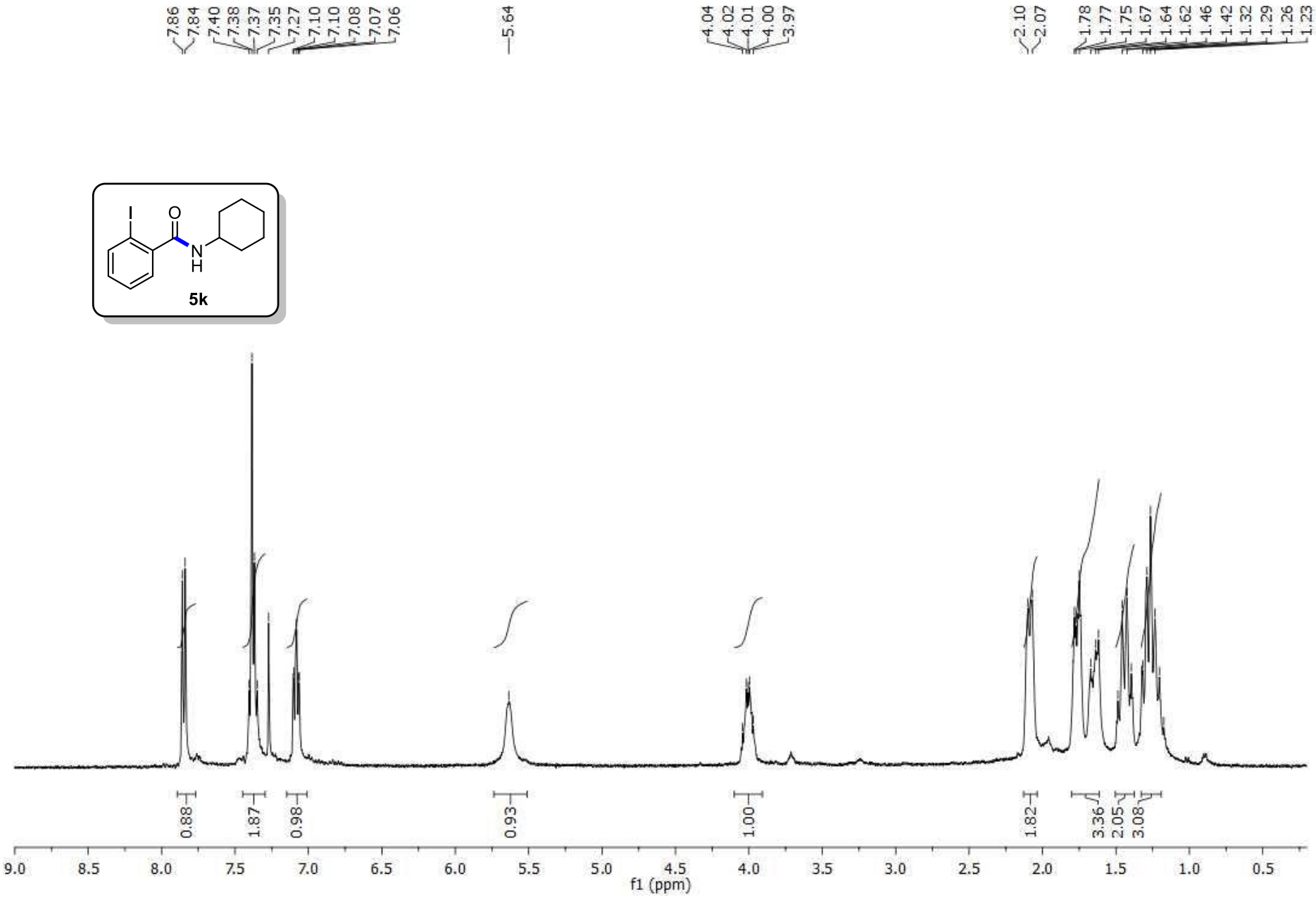
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 3-Chloro-*N*-cyclohexylbenzamide **(5i)**



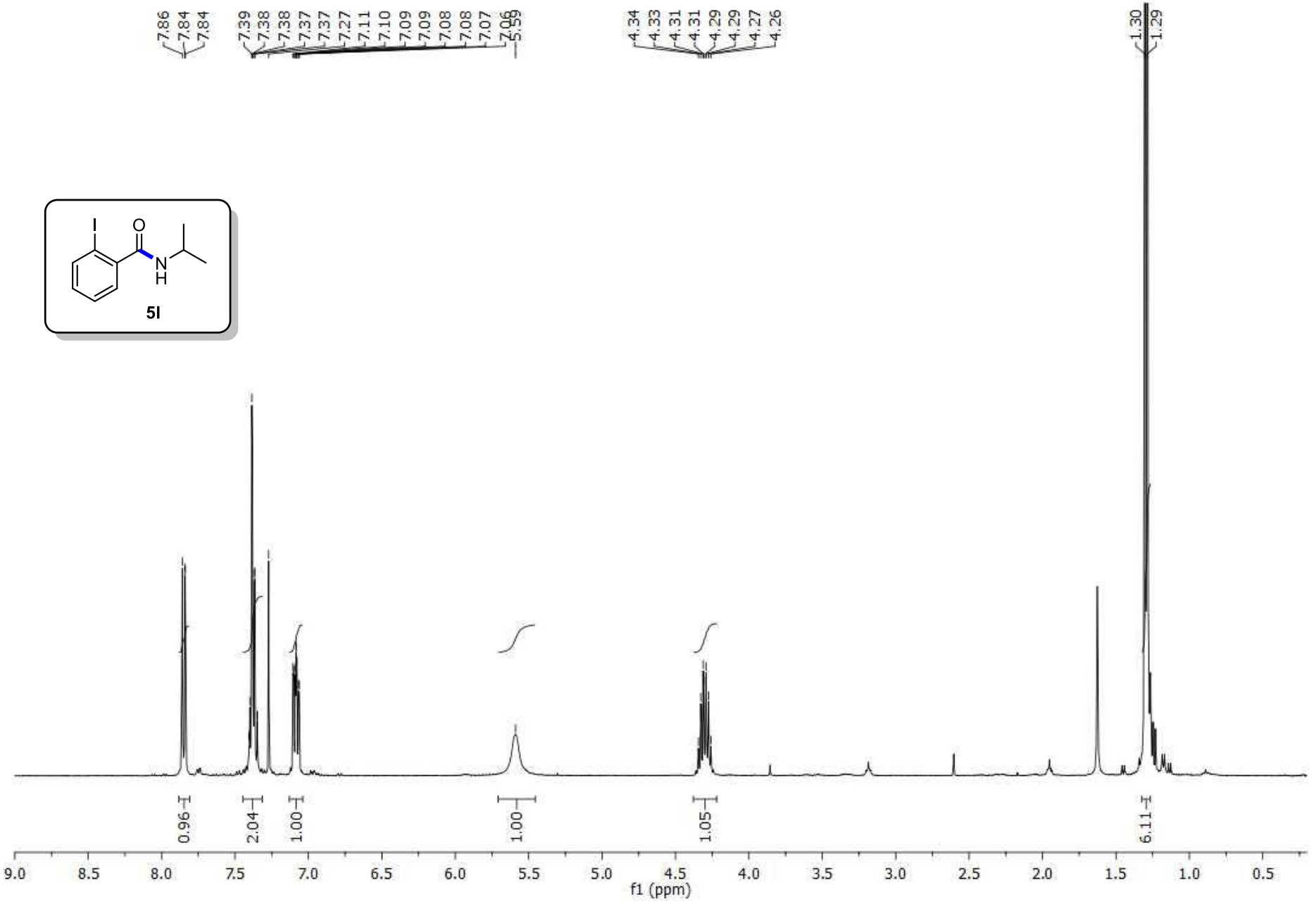
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 3-Chloro-*N*-isopropylbenzamide **(5j)**



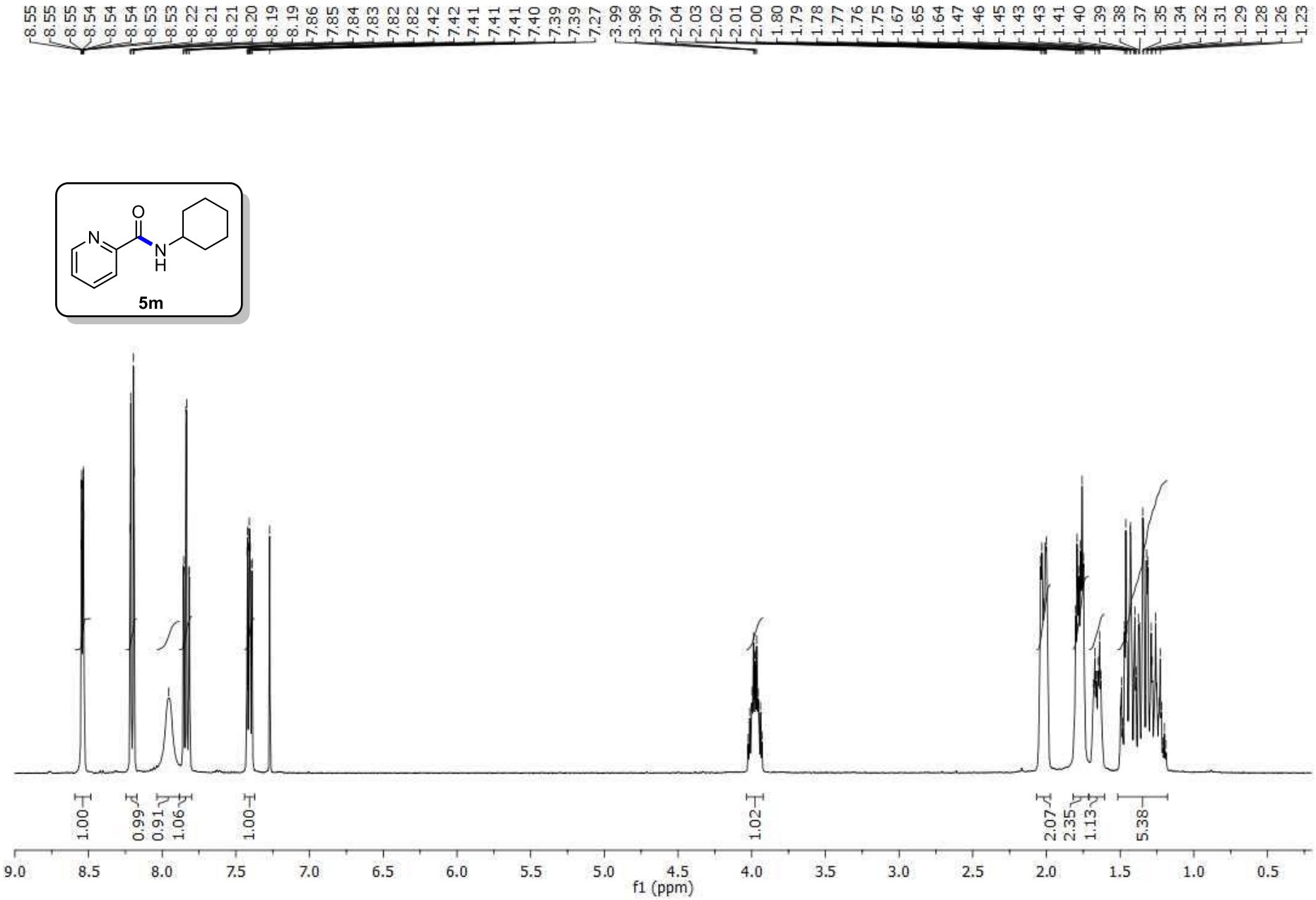
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexyl-2-iodobenzamide **(5k)**



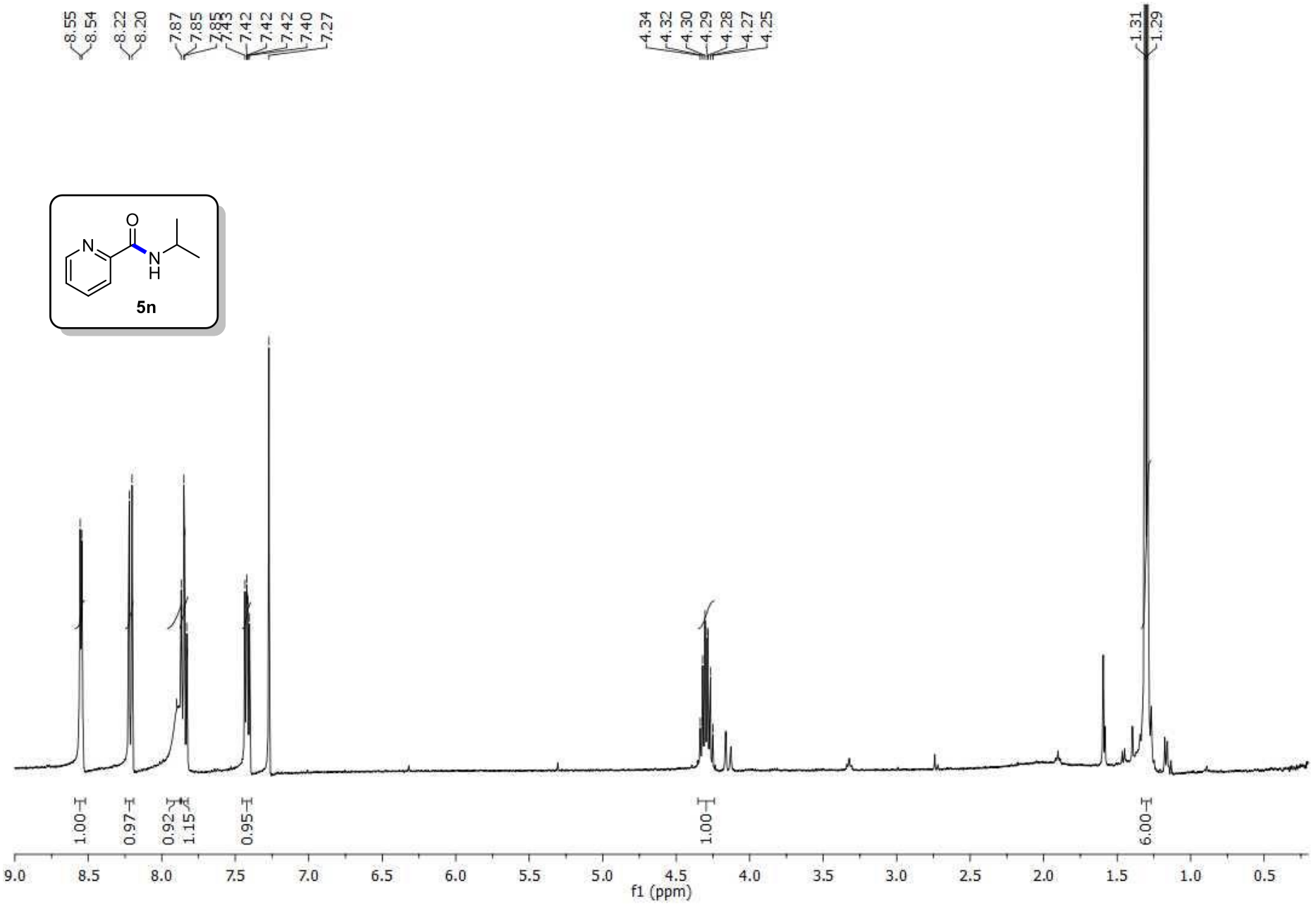
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2-Iodo-*N*-isopropylbenzamide **(5l)**



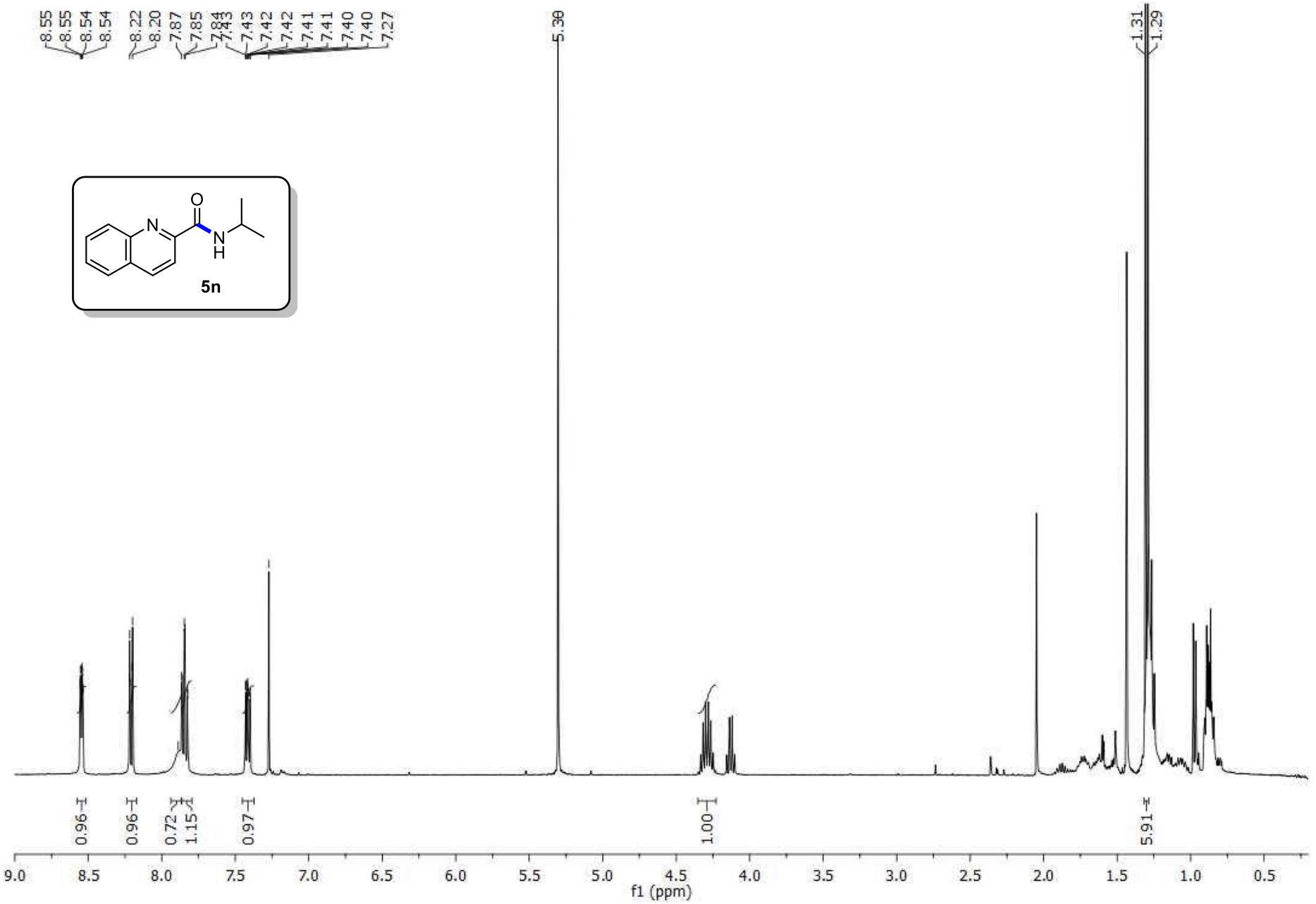
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Cyclohexylpicolinamide **(5m)**



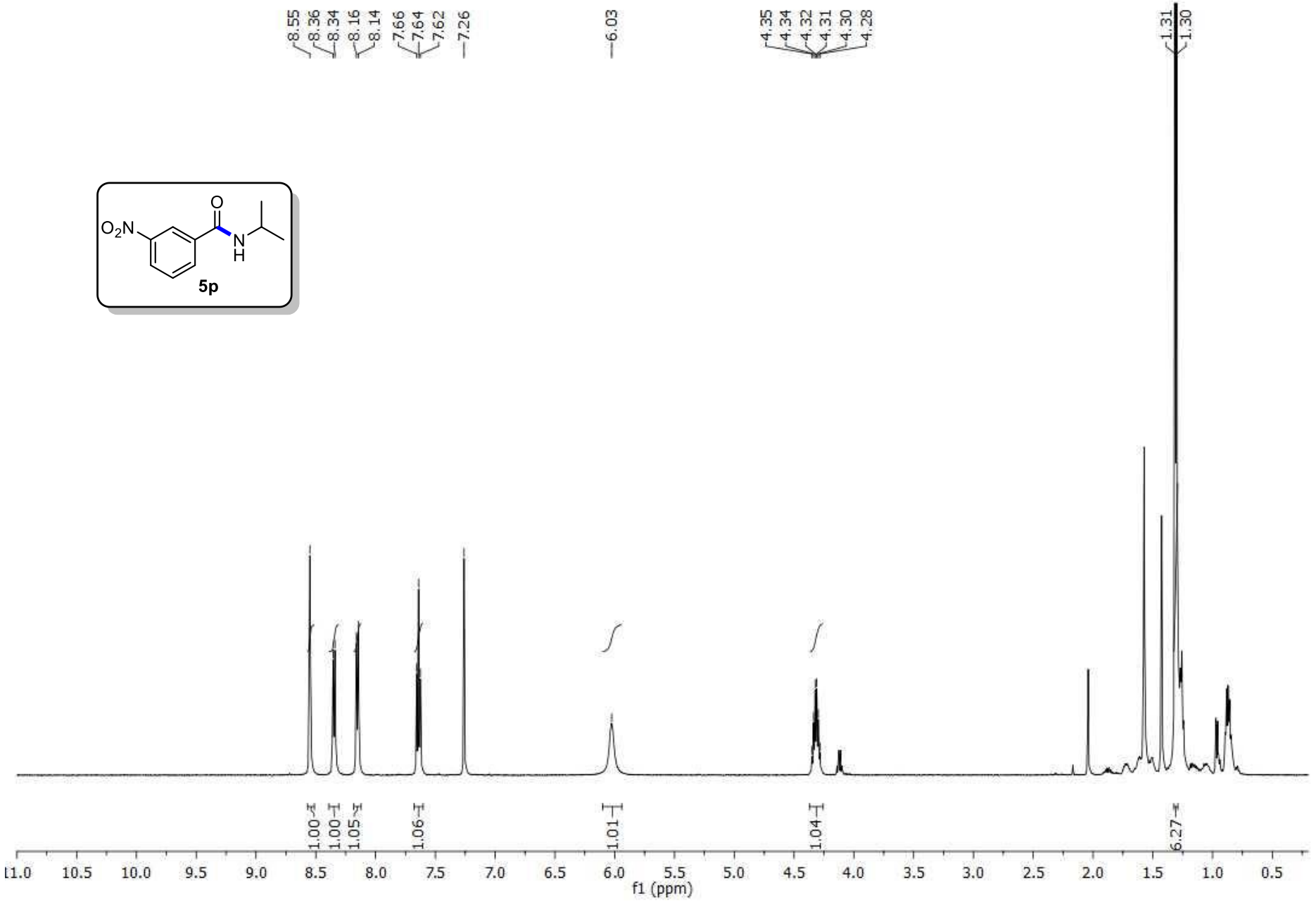
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*-Isopropylpicolinamide **(5n)**



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *N*-isopropylquinoline-2-carboxamide **(5o)**



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *N*-isopropyl-3-nitrobenzamide **(5p)**



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of *N*-phenylpyrrolidine-1-carboxamide **(26)**