Supporting Information for

Practical preparation of challenging amides from non-nucleophilic amines and esters under flow conditions

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Experimental part

^{1}H NMR spectra

Bruker 300 Avance (300 MHz), Bruker DPX-400 (400 MHz) and Bruker 500 Avance III (500 MHz) with tetramethylsilane as internal standard with $CDCl_3$ and DMSO or with the deuterated solvent as internal standard. The δ-values are expressed in ppm.

^{13}C NMR spectra

Bruker 300 Avance (working at 75 MHz), Bruker DPX-400 (working at 100 MHz) and Bruker 500 Avance III (working at 125 MHz) with the deuterated solvent as internal standard ($CDCl_3$: 77.16 ppm, triplet; DMSO: 39.52 ppm, quintet). The δ-values are expressed in ppm.

IR spectra

Bruker Alpha-T FT-IR spectrometer with universal sampling module. Data processing using Opus software.

Mass spectra

HRMS: Electron-impact (EI): Kratos MS50TC machine with ionization energy of 70 eV and at 150 - 250 °C, as required, coupled to a MASSPEC II data acquiring system. The High resolution EI-mass spectra were recorded with a resolution of 10000.

Melting Points

Reichert-Jung Thermovar (the measurements are not corrected).

Flow chemistry equipment

- Vapourtec R2+R4
- CHEMTRIX Labtrix Start syringe pump.
- 1 ml Sigma-Aldrich Starter Kit microreactor.
- Dolomite PTFE tubing and ETFE connectors.

Chromatography

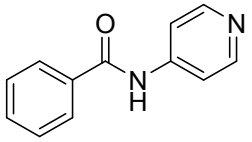
- TLC plates: pre-coated TLC-plates SIL G-25 (with fluorescence-indicator 254 nm): layer thickness 0.25 mm; average pore diameter 60 Å; 20x20 cm glass plates
- Silica gel for column chromatography: MP Silica 32-63, average pore diameter 60 Å, Ecochron

Exploration of substrate scope ester reagent

General procedure

Two solutions, ester (0.45 M), amine (0.5 M; 1.1 equiv) in dry DMF and commercially available LHMDS (1M; 2.2 equiv) in dry THF were both pumped at 0.25 mL/min using syringe pumps. The mixed solution was allowed to reside in a 1 mL microreactor at 25 °C (t_R = 2 min), after which the reaction mixture was quenched in NH_4Cl solution (1 M). The reaction was extracted with DCM (3x), the organic layers were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was either washed with iPr$_2$O (**3a**, **3c**, **3d**, **3e**), or purified using silica gel chromatography (heptane/EtOAc gradient) (**3f**, **3g**, **3h, 3i**).

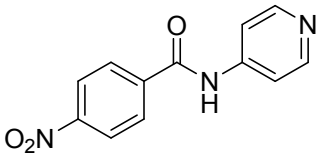
N-(pyridin-4-yl)benzamide[1] 3a



Yield: 84% (152 mg) (from 0.91 mmol ethyl benzoate **1a**); 78% (141 mg) (from 2,4,6-trichlorophenyl benzoate **4**)
The experiment was carried out following the general procedure. 137 mg () of ester compound was used as limiting reagent.

Melting point: 141.6 °C – 143.2 °C
FT-IR (cm^{-1}): 1675
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.56 (s, 1H), 8.44 (d, 2H, *J* = 5.0 Hz), 7.93 (d, 2H, *J* = 7.1 Hz), 7.76 (d, 2H, 7.9 Hz), 7.58 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, 7.8 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): δ 166.5 (C), 150.3 (CH), 146.0 (C), 134.3 (C), 132.1 (CH), 128.5 (CH), 127.9 (CH), 114.1 (CH)
HRMS: mass calculated for $C_{12}H_{10}N_2O_1$: 198.0793; found: 198.0798

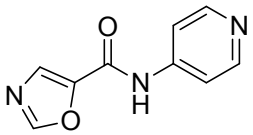
4-nitro-N-(pyridin-4-yl)benzamide[2] 3b



Yield: 100% (222 mg)
The experiment was carried out following the general procedure. 177 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 235.1 °C – 239.6 °C
FT-IR (cm^{-1}): 1680
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.83 (s, 1H), 8.46 (d, 2H, *J* = 4.8 Hz), 8.33 (d, 2H, *J* = 9.0 Hz), 8.14 (d, 2H, *J* = 9.0 Hz), 7.74 (d, 2H, *J* = 4.9 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): δ 164.9 (C), 150.4 (CH), 149.4 (C), 145.6 (C), 139.8 (C), 129.5 (CH), 123.6 (CH), 114.2 (CH)
HRMS: mass calculated for $C_{12}H_9N_3O_3$: 243.0644; found: 243.0621

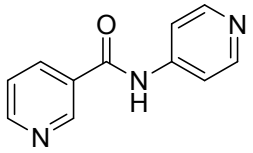
Amide **3b** was found to precipitate from the quenched reaction mixture. After filtration, the compound was washed with H_2O and *i*Pr_2O.

N-(pyridin-4-yl)-1,3-oxazole-5-carboxamide 3c



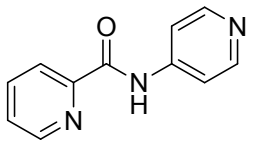
Yield: 92% (159 mg)
The experiment was carried out following the general procedure. 128 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 185.3 °C – 187.1 °C
FT-IR (cm^{-1}): 1680
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.73 (s, 1H), 8.64 (s, 1H), 8.44 (d, 2H, *J* = 4.9 Hz), 8.01 (s, 1H), 7.69 (d, 2H, *J* = 4.9 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): δ 155.7 (C), 154.3 (C), 150.4 (CH), 145.1 (C), 144.7 (CH), 131.1 (CH), 114.2 (CH)
HRMS: mass calculated for $C_9H_7N_3O_2$: 189.0538; found: 189.0535

N-(pyridin-4-yl)pyridine-3-carboxamide[3] 3d



Yield: 87% (157 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 162.2 °C – 165.1 °C
FT-IR (cm^{-1}): 1676
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.74 (s, 1H), 9.08 (s, 1H), 8.75 (d, 1H, *J* = 4.9 Hz), 8.46 (d, 2H, *J* = 4.8 Hz), 8.26 (d, 1H, *J* = 7.9 Hz), 7.74 (d, 2H, *J* = 4.9 Hz), 7.54 (m, 1H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 165.1 (C), 152.6 (CH), 150.4 (CH), 148.9 (CH), 145.7 (C), 135.7 (CH), 130.1 (C), 123.6 (CH), 114.1 (CH)
HRMS: mass calculated for $C_{11}H_9N_3O_1$: 199.0746; found: 199.0747

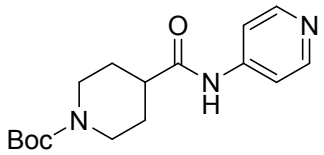
N-(pyridin-4-yl)pyridine-2-carboxamide[3] 3e



Yield: 76% (172 mg)
The experiment was carried out following a modified procedure shown below. 172 mg (1.136 mmol) of ester compound was used as limiting reagent.
Melting point: 115.7 °C – 117.3 °C
FT-IR (cm^{-1}): 1687
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.95 (s, 1H), 8.71 (s, 1H), 8.46 (d, 2H, *J* = 4.9 Hz), 8.13 (d, 1H, *J* = 7.8 Hz), 8.04 (m, 1H), 7.91 (d, 2H, *J* = 4.8 Hz), 7.66 (m, 1H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 163.7 (C), 150.3 (CH), 149.3 (C), 148.6 (CH), 145.2 (C), 138.26 (CH), 138.25 (CH), 127.4 (CH), 122.8 (CH), 114.2 (CH)
HRMS: mass calculated for $C_{11}H_9N_3O_1$: 199.0746; found: 199.0739

As the insolubility of a reaction intermediate caused blockage of the microreactor, the solvent ratio DMF:THF was raised from 1:1 to 2:1. Thus; two solutions, **ester (0.227 M)**, **amine (0,250 M; 1.1 equiv)** in dry DMF and commercially available **LHMDS (1 M; 2.2 equiv)** in dry THF were pumped at **0.333 mL/min** and **0.167 mL/min** respectively.

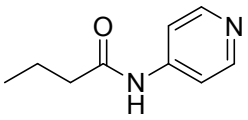
tert-butyl 4-[(pyridin-4-yl)carbamoyl]piperidine-1-carboxylate[4] 3f



Yield: 83% (231 mg)

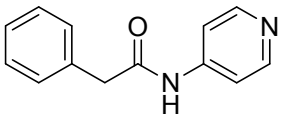
The experiment was carried out following the general procedure. 234 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 148.5 °C – 151.4 °C
FT-IR (cm^{-1}): 1677
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.29 (s, 1H), 8.38 (d, 2H, *J* = 4.9 Hz), 7.55 (d, 2H, *J* = 4.9 Hz), 3.98 (s, 2H), 2.76 (s, 2H), 2.58-2.47 (m, 1H), 1.78 (d, 2H, *J* = 12.7 Hz), 1.53-1.33 (m, 2H), 1.39 (s, 9H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 174.3 (C), 153.9 (C), 150.3 (CH), 145.8 (C), 113.2 (CH), 78.7 (C), 42.8 (CH), 28.1 (CH_3), 28.0 (CH_2)
HRMS: mass calculated for $C_{16}H_{23}N_3O_3$: 305.1739; found: 305.1716

N-(pyridin-4-yl)butanamide[5] 3g



Yield: 78% (116 mg)
The experiment was carried out following the general procedure. 106 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 132.3 °C – 134.0 °C
FT-IR (cm^{-1}): 1700
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.19 (s, 1H), 8.34 (d, 2H, *J* = 4.9 Hz), 7.50 (d, 2H, *J* = 4.9 Hz), 2.32 (t, 2H, *J* = 7.3 Hz), 1.60 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): 172.5 (C), 150.3 (CH), 145.8 (C), 113.1 (CH), 38.4 (CH_2), 18.3 (CH_2), 13.6 (CH_3)
HRMS: mass calculated for $C_9H_{12}N_2O_1$: 164.0950; found: 164.0935

2-phenyl-N-(pyridin-4-yl)acetamide[6] 3h

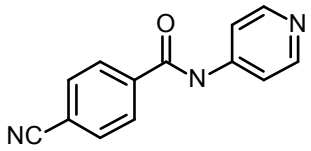


Yield: 46% (89 mg)
The experiment was carried out following the general procedure. 149 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: not determined, as the compound appears as two tautomers.
FT-IR (cm^{-1}): 1684

Note: the compound was observed in NMR experiments as a mixture of two tautomers. In the case of the ^{1}H NMR data provided beneath, the nine aromatic proton resonances arising from both tautomers were given a total integration value nine, other proton resonances were integrated accordingly. In the case of the ^{13}C NMR data, the carbon resonances arising from the main tautomer are reported.
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.64-10.34 (m, 1.30 1H), 9.00 (s, 0.14 1H), 8.45-8.28 (m, 2.8 2H), 7.58-7.40 (m, 2.2 8H), 7.32-7.10 (m, 4.0 2H), 3.68 (s, 1.60 1H)
^{13}C NMR (125 MHz, DMSO, ppm): 170.4 (C), 150.4 (CH), 145.8 (C), 135.4 (C), 129.2 (CH), 128.4 (CH), 126.7 (CH), 113.2 (CH), 43.4 (CH_2)

HRMS: mass calculated for $C_{13}H_{12}N_2O_1$: 212.0950; found: 212.0948

4-cyano-N-(pyridin-4-yl)acetamide 3i



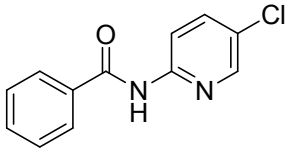
Yield: 81% (58 mg)
The experiment was carried out following the general procedure. 61 mg (0.32 mmol) of ester compound was used as limiting reagent.
Melting point: 201.1 ºC
FT-IR (cm^{-1}): 1688
^{1}H NMR (400 MHz, DMSO, ppm): δ 10.82 (s, 1H), 8.51 (d, 2H, *J* = 6.2 Hz), 8.12 (d, 2H, *J* = 8.6 Hz), 8.06 (d, 2H, *J* = 8.8 Hz), 7.78 (d, 2H, *J* = 6.2 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): δ 165.2 (C), 150.4 (CH), 145.5 (C), 138.2 (C), 132.6 (CH), 128.7 (CH), 118.2 (C), 114.3 (C), 114.1 (CH)
HRMS: mass calculated for $C_{13}H_9N_3O_1$: 223.0746; found: 223.0821

Exploration of substrate scope amide reagent

General procedure

Two solutions, ester (0.45 M), amine (0.5 M; 1.1 equiv) in dry DMF and commercially available LHMDS (1M; 2.2 equiv) in dry THF were both pumped at 0.25 mL/min using syringe pumps. The mixed solution was allowed to reside in a 1 mL microreactor at 25 °C (t_R = 2 min), after which the reaction mixture was quenched in NH_4Cl solution (1 M). The reaction was extracted with DCM (3x), the organic layers were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was either washed with *i*Pr_2O (**3j**, **3l**, **3o**, **3p**), or purified using silica gel chromatography (heptane/EtOAc gradient) (**3k**, **3m**, **3n**, **3q**, **3r**, **3s, 3t, 3u, 3v, 3w, 3x**).

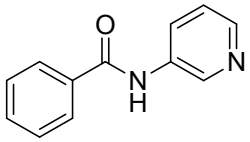
N-(5-chloropyridin-2-yl)benzamide[7] 3j



Yield: 50% (106 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 107.4 °C – 110.9 °C
FT-IR (cm^{-1}): 1674
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.94 (s, 1H), 8.40 (d, 1H, *J* = 8.5 Hz), 8.22 (d, 1H, *J* = 8.9 Hz), 8.01 (d, 2H, *J* = 7.2 Hz), 7.92 (d, 1H, *J* = 8.9 Hz), 7.57 (t, 1H, *J* = 7.3 Hz), 7.49 (t, 2H, *J* = 7.6 Hz)

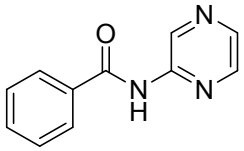
^{13}C NMR (125 MHz, DMSO, ppm): δ 166.1 (C), 150.9 (C), 146.3 (CH), 137.8 (CH), 133.9 (C), 132.1 (CH), 128.4 (CH), 128.1 (CH), 125.6 (C), 115.8 (CH)
HRMS: mass calculated for $C_{12}H_9N_2O_1Cl_1$: 232.0403; found: 232.0329

N-(pyridin-3-yl)benzamide[8] 3k



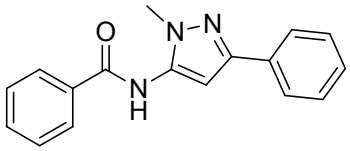
Yield: 60% (108 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 98.9 °C – 102.3 °C
FT-IR (cm^{-1}): 1646
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.43 (s, 1H), 8.90 (s, 1H), 8.28 (d, 1H, *J* = 4.6 Hz), 8.16 (d, 1H, *J* = 8.3 Hz), 7.94 (d, 2H, *J* = 7.7 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 7.35 (m, 1H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 166.0 (C), 144.6 (CH), 142.0 (CH), 135.9 (C), 134.4 (C), 131.9 (CH), 128.5 (CH), 127.8 (CH), 127.4 (CH), 123.6 (CH)
HRMS: mass calculated for $C_{12}H_{10}N_2O_1$: 198.0793; found: 198.0790

N-(pyrazin-2-yl)benzamide[9] 3l



Yield: 63% (114 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 167.3 °C – 169.8 °C
FT-IR (cm^{-1}): 1676
^{1}H NMR (500 MHz, DMSO, ppm): δ 11.09 (s, 1H), 9.43 (d, 1H, *J* = 1.4 Hz), 8.45 (m, 1H), 8.40 (d, 1H, *J* = 2.6 Hz), 8.05 (d, 2H, *J* = 8.1 Hz), 7.60 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.6 Hz)
^{13}C NMR (100 MHz, DMSO, ppm): δ 166.3 (C), 149.2 (C), 142.7 (CH), 140.0 (CH), 137.6 (CH), 133.5 (C), 132.4 (CH), 128.5 (CH), 128.3 (CH)
HRMS: mass calculated for $C_{11}H_9N_3O_1$: 199.0746; found: 199.0744

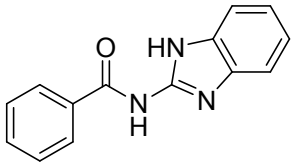
N-(1-methyl-3-phenyl-1H-pyrazol-5-yl)benzamide[10] 3m



Yield: 69% (174 mg)

The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 167.2 °C – 168.5 °C
FT-IR (cm^{-1}): 1652
^{1}H NMR (300 MHz, DMSO, ppm): δ 10.44 (s, 1H), 8.02 (d, 2H, *J* = 7.9 Hz), 7.80 (d, 2H, *J* = 7.2 Hz), 7.69-7.51 (m, 3H), 7.41 (t, 2H, *J* = 7.4 Hz), 7.30 (t, 1H, *J* = 7.3 Hz), 6.73 (s, 1H), 3.76 (s, 3H)
^{13}C NMR (75 MHz, DMSO, ppm): δ 165.7 (C), 148.2 (C), 137.6 (C), 133.4 (C), 133.3 (C), 132.2 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 124.8 (CH), 97.8 (CH), 35.9 (CH_3)
HRMS: mass calculated for $C_{17}H_{15}N_3O_1$: 277.1215; found: 277.1214

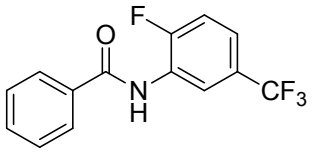
N-(1H-1,3-benzodiazol-2-yl)benzamide[11] 3n



Yield: 42% (60 mg) (Reaction carried out at 25 °C); 45% (65 mg) (Reaction carried out at 50 °C)
The experiment was carried out following a modified procedure shown below. 91 mg (0.606 mmol) of ester compound was used as limiting reagent.
Melting point: 240.1 °C – 244.6 °C
FT-IR (cm^{-1}): 1662
^{1}H NMR (300 MHz, DMSO, ppm): δ 12.32 (s, 2H), 8.18 (d, 2H, *J* = 7.9 Hz), 7.67-7.44 (m, 5H), 7.16 (m, 2H)
^{13}C NMR (75 MHz, DMSO, ppm): δ 168.4 (C), 148.9 (C), 134.4 (C), 132.0 (CH), 128.30 (CH), 128.38 (CH), 121.5 (CH), 113.4 (CH)
HRMS: mass calculated for $C_{14}H_{11}N_3O_1$: 237.0902; found: 237.0900

As the substrate contains an additional acidic proton, 3.3 equiv LHMDS were used to increase conversion. Thus; two solutions, **ester (0.303 M)**, **amine (0.333 M; 1.1 equiv)** in dry DMF and commercially available **LHMDS (1 M; 3.3 equiv)** in dry THF were both pumped at 0.25 mL/min.

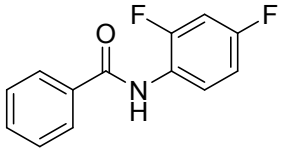
N-[2-fluoro-5-(trifluoromethyl)phenyl]benzamide[1] 3o



Yield: 61% (156 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 123.6 °C – 125.7 °C
FT-IR (cm^{-1}): 1660

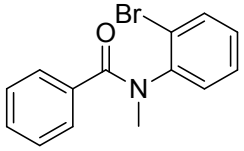
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.32 (s, 1H), 8.06 (d, 1H, J = 6.8 Hz), 7.95 (d, 2H, J = 8.0 Hz), 7.62-7.53 (m, 2H), 7.52-7.44 (m, 3H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 165.8 (C), 157.4 (C, d, $J_{C\text{-}F}$ = 249.7 Hz), 133.6 (C), 132.1 (CH), 128.5 (CH), 127.9 (CH), 126.99 (C, d, $J_{C\text{-}F}$ = 12.9 Hz), 125.3 (C, qd, $J_{C\text{-}F}$ = 32.2 Hz & $J_{C\text{-}F}$ = 3.5 Hz), 123.85 (CH, m), 123.77 (C, q, $J_{C\text{-}F}$ = 268.6 Hz), 123.6 (CH, m), 117.1 (CH, d, $J_{C\text{-}F}$ = 21.5 Hz)
HRMS: mass calculated for $C_{14}H_9N_1O_1F_4$: 283.0620; found: 283.0574

N-(2,4-difluorophenyl)benzamide[12] 3p



Yield: 78% (165 mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 114.5 °C – 117.1 °C
FT-IR (cm^{-1}): 1650
^{1}H NMR (500 MHz, DMSO, ppm): δ 10.07 (s, 1H), 7.93 (d, 2H, J = 7.5 Hz), 7.59-7.51 (m, 2H), 7.48 (t, 2H, J = 7.5 Hz), 7.30 (t, 1H, J = 9.8 Hz), 7.07 (t, 1H, J = 8.6 Hz)
^{13}C NMR (125 MHz, DMSO, ppm): δ 165.6 (C), 159.7 (C, dd, $J_{C\text{-}F}$ = 234.6 Hz & $J_{C\text{-}F}$ = 10.1 Hz), 156.1 (C, dd, $J_{C\text{-}F}$ = 240.9 Hz & $J_{C\text{-}F}$ = 12.9 Hz), 133.8 (C), 131.9 (CH), 128.57 (CH, dd, $J_{C\text{-}F}$ = 7.4 Hz & $J_{C\text{-}F}$ = 2.8 Hz), 128.50 (CH), 127.8 (CH), 122.3 (C, dd, $J_{C\text{-}F}$ =12.8 & $J_{C\text{-}F}$ = 3.7), 111.2 (CH, dd, $J_{C\text{-}F}$ = 21.1 Hz, $J_{C\text{-}F}$ = 3.7 Hz), 104.4 (CH, t, $J_{C\text{-}F}$ = 26.6 Hz)
HRMS: mass calculated for $C_{13}H_9N_1O_1F_2$: 233.0652; found: 233.0646

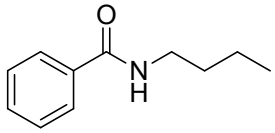
N-(2-bromophenyl)-N-methylbenzamide[13] 3q



Yield: 36% (192 mg) (Reaction carried out at 25 °C); 82% (443 mg) (Reaction carried out at 50 °C)
The experiment was carried out following a modified procedure shown below. 273 mg (1.818 mmol) of ester compound was used as limiting reagent.
Melting point: 104.0 °C – 105.9 °C
FT-IR (cm^{-1}): 1637
^{1}H NMR (300 MHz, DMSO, ppm): δ 7.54 (d, 1H, J = 7.7 Hz), 7.35 (d, 2H, J = 7.4 Hz), 7.29-6.99 (m, 6H), 3.39 (s, 3H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 169.7 (C), 143.0 (C), 135.9 (C), 133.3 (CH), 131.2 (CH), 129.64 (CH), 129.61 (CH), 128.9 (CH), 127.6 (CH), 122.2 (C), 36.6 (CH_3)
HRMS: mass calculated for $C_{14}H_{12}N_1O_1Br_1$: 289.0102; found: 289.0128

The reaction was carried out in THF using 1.1 equiv of LHMDS. Thus; two solutions, **ester (0.909 M)**, **amine (1 M; 1.1 equiv)** in dry **THF** and commercially available **LHMDS (1 M; 1.1 equiv)** in dry THF were both pumped at 0.25 mL/min.

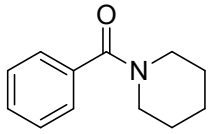
N-butylbenzamide[12] 3r



Yield: 33% (53 mg) (Reaction carried out at 25 °C); 58% (103 mg) (Reaction carried out at 55 °C)
The experiment was carried out following a modified procedure shown below. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: oil
FT-IR (cm^{-1}): 1635
^{1}H NMR (500 MHz, DMSO, ppm): δ 8.41 (s, 1H), 7.79 (d, 2H, *J* = 7.7 Hz), 7.48 (t, 1H, *J* = 7.3 Hz), 7.42 (t, 2H, *J* = 7.4 Hz), 3.25 (m, 2H), 1.50 (m, 2H), 1.32 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz)
^{13}C NMR (100 MHz, DMSO, ppm): δ 166.2 (C), 134.8 (C), 131.1 (CH), 128.3 (CH), 127.1 (CH), 31.3 (CH_2), 13.7 (CH_2), 13.8 (CH_3)
HRMS: mass calculated for $C_{11}H_{15}N_1O_1$: 177.1154; found: 177.1155

The reaction was carried out in THF. Thus; two solutions, ester (0.45 M), amine (0.5 M; 1.1 equiv) in dry **THF** and commercially available LHMDS (1 M; 2.2 equiv) in dry THF were both pumped at 0.25 mL/min.

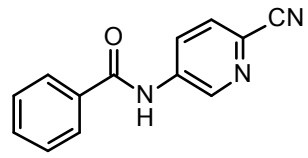
1-benzoylpiperidine[12] 3s



Yield: 33% (56 mg) (Reaction carried out at 25 °C); 56% (106 mg) (Reaction carried out at 55 °C)
The experiment was carried out following a modified procedure shown below. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: oil
FT-IR (cm^{-1}): 1624
^{1}H NMR (500 MHz, DMSO, ppm): δ 740-7.34 (m, 3H), 7.32-7.26 (m, 2H), 3.57 (s, 2H), 3.25 (s, 2H), 1.66-1.35 (m, 6H)
^{13}C NMR (100 MHz, DMSO, ppm): δ 169.0 (C), 136.6 (C), 129.3 (CH), 128.5 (CH), 126.6 (CH), 48.1 (CH_2), 42.3 (CH_2), 26.0 (CH_2), 25.3 (CH_2), 24.1 (CH_2)
HRMS: mass calculated for $C_{12}H_{15}N_1O_1$: 189.1154; found: 189.1124

The reaction was carried out in THF using 1.1 equiv of LHMDS. Thus; two solutions, ester (0.45 M), amine (0.5 M; 1.1 equiv) in dry **THF** and commercially available **LHMDS (1 M; 1.1 equiv)** in dry THF were pumped at **0.333 mL/min** and **0.167 mL/min** respectively.

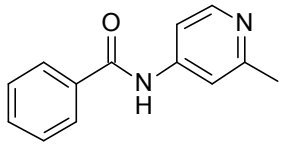
N-(6-cyanopyridin-3-yl)benzamide[14] 3t



Yield: 45% (35 mg) (Reaction carried out at 25 °C); 61% (47 mg) (Reaction carried out at 50 °C)

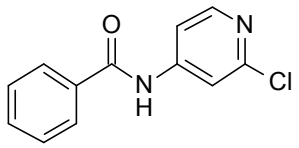
The experiment was carried out following the general procedure. 50 mg (0.35 mmol) of ester compound was used as limiting reagent.
Melting point: 162.4 ºC
FT-IR (cm^{-1}): 1649
^{1}H NMR (400 MHz, DMSO, ppm): δ 10.87 (s, 1H), 9.10 (d, 2H, *J* = 2.5 Hz), 8.46 (dd, 2H, *J* = 8.6 Hz, *J* = 2.5 Hz), 8.04 (d, 2H, *J* = 8.6 Hz), 8.01–7.98 (m, 2H), 7.68-7.63 (m, 1H), 7.60-7.58 (m, 2H)
^{13}C NMR (125 MHz, DMSO, ppm): δ 166.4 (C), 142.9 (CH), 139.2 (C), 133.8 (C), 132.4 (CH), 129.5 (CH), 128.6 (CH), 127.9 (CH), 126.8 (CH), 126.2 (C), 117.7 (C)
HRMS: mass calculated for $C_{13}H_9N_3O$: 223.0746; found: 223.0824

N-(2-methylpyridin-4-yl)benzamide 3u



Yield: 76% (113 mg)
The experiment was carried out following the general procedure. 105 mg (0.70 mmol) of ester compound was used as limiting reagent.
Melting point: oil
FT-IR (cm^{-1}): 1674
^{1}H NMR (400 MHz, DMSO, ppm): δ 8.41 (d, 1H, *J* = 5.78 Hz), 8.14 (s, 1H), 7.88-7.85 (m, 2H), 7.60-7.37 (m, 4H), 7.38 (dd, 2H, *J* = 5.5 Hz, *J* = 1.85 Hz), 2.54 (s, 3H)
^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 166.6 (C), 160.2 (C), 150.5 (CH), 145.8 (C), 134.6 (C), 132.9 (CH), 129.3 (CH), 127.6 (CH), 127.9 (CH), 113.5 (CH), 111.6 (CH), 25 (CH_3)
HRMS: mass calculated for $C_{13}H_{12}N_2O$: 212.0950; found: 212.1091

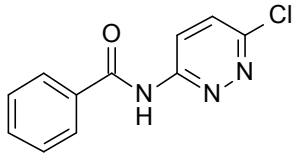
N-(2-chloropyridin-4-yl)benzamide[15] 3v



Yield: 59% (96.7 mg) (Reaction carried out at 25 °C); 75% (121.8 mg) (Reaction carried out at 50 °C)

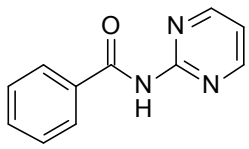
The experiment was carried out following the general procedure. 105 mg (0.70 mmol) of ester compound was used as limiting reagent.
Melting point: 278.6 ºC
FT-IR (cm^{-1}): 1662
^{1}H NMR (400 MHz, DMSO, ppm): δ 8.30 (d, 1H, *J* = 5.55 Hz), 8.10 (s, 1H), 7.88-7.85 (m, 2H), 7.78 (d, 1H, *J* = 1.85 Hz), 7.63-7.59 (m, 1H), 7.53-7.49 (m, 3H)
^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 166.5 (C), 153.0 (C), 150.7 (CH), 147.5 (C), 134.0 (C), 133.2 (CH), 129.5 (CH), 127.6 (CH), 114.1 (CH), 113.1 (CH)
HRMS: mass calculated for $C_{12}H_9ClN_2O$: 232.0403; found: 232.0482

N-(6-chloropyridazin-3-yl)benzamide 3w



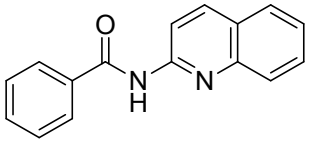
Yield: 31% (51.1 mg) (Reaction carried out at 25 °C); 57% (93 mg) (Reaction carried out at 50 °C)
The experiment was carried out following the general procedure. 105 mg (0.70 mmol) of ester compound was used as limiting reagent.
Melting point: 221.3 ºC
FT-IR (cm^{-1}): 1667
^{1}H NMR (400 MHz, DMSO, ppm): δ 9.16 (s, 1H), 8.67 (d, 2H, *J* = 8.3 Hz), 7.96 (m, 2H), 7.65–7.61 (m, 1H), 7.58-7.52 (m, 3H)
^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 166.5 (C), 155.0 (C), 152.9 (C), 133.5 (CH), 133.4 (C), 130.4 (CH), 129.5 (CH), 127.8 (CH), 121.6 (CH)
HRMS: mass calculated for $C_{11}H_8ClN_3O$: 233.0356; found: 233.0443

N-(pyrimidin-2-yl)benzamide[16] 3x



Yield: 24% (34 mg) (Reaction carried out at 25 °C); 68% (94.7 mg) (Reaction carried out at 50 °C)
The experiment was carried out following the general procedure. 105 mg (0.70 mmol) of ester compound was used as limiting reagent.
Melting point: 139.9 ºC
FT-IR (cm^{-1}): 1697
^{1}H NMR (400 MHz, DMSO, ppm): δ 8.75 (s, 1H), 8.66 (d, 2H, *J* = 4.86 Hz), 7.96-7.94 (m, 2H), 7.61-7.57 (m, 1H), 7.53-7.49 (m, 2H), 7.07 (t, 1H, *J* = 4.86 Hz)
^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 165.2 (C), 158.9 (CH), 158.2 (C), 134.7 (C), 132.9 (CH), 129.3 (CH), 127.9 (CH), 117.3 (CH)
HRMS: mass calculated for $C_{11}H_9N_3O$: 199.0746; found: 199.0823

N-(quinolin-2-yl)benzamide[17] 3y



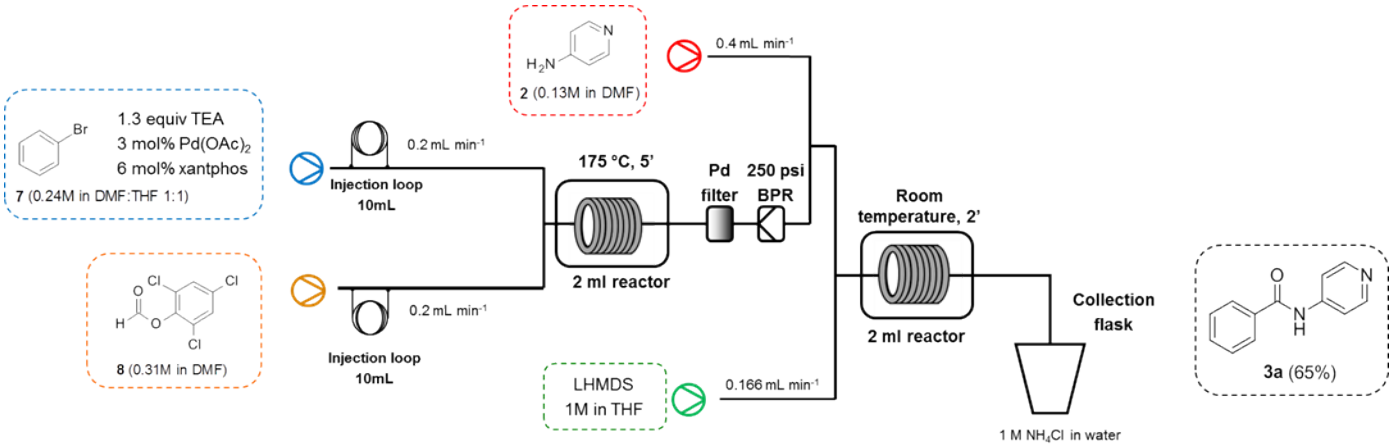
Yield: 75% (170mg)
The experiment was carried out following the general procedure. 137 mg (0.91 mmol) of ester compound was used as limiting reagent.
Melting point: 122.2 °C – 122.9 °C
FT-IR (cm^{-1}): 1675
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.94 (s, 1H), 8.59 (d, 1H, *J* = 9.0 Hz), 8.22 (d, 1H, *J* = 8.9 Hz), 8.02-7.92 (m, 2H), 7.81 (t, 2H, *J* = 8.4 Hz), 7.70-7.62 (m, 1H), 7.61-7.40 (m, 4H)
^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.1 (C), 151.1 (C), 146.6 (C), 138.7 (CH), 134.2 (C), 132.4 (CH), 130.0 (CH), 128.8 (CH), 127.6 (CH), 127.3 (CH), 126.4 (C), 125.2 (CH), 114.4 (CH)
HRMS: mass calculated for $C_{16}H_{12}N_2O$: 248.0950; found: 248.0954

Carbonylation /amidation cascade reaction

A schematic representation of the reaction setup is provided beneath. Both flow rates and reactor volumes are described for the implemented reaction setup, but can be changed proportionally. Prior to use, all reagent channels are stabilised with their respective solvent mixtures.

- A) Blue channel: solution of $Pd(OAc)_2$ (0.0071 M; 0.03 equiv) and xantphos (0.0143 M; 0.06 equiv) in dry THF:dry DMF (1:1), then bromobenzene (0.238 M) and triethylamine (0.309 M; 1.3 equiv) were added.
- B) Orange channel: solution of trichlorophenyl formiate (0.309 M; 1.3 equiv) in dry DMF.
- C) Red channel: solution of 4-aminopyridine (0.131 M; 1.1 equiv) in dry DMF.
- D) Green channel: commercially available solution of LHMDS (1 M; 3.5 equiv) in THF.

Solutions A and B were both pumped at 0.2 mL/min using a Vapourtec R2+R4 system. The mixed solution was allowed to reside in a 2 mL stainless steel coil reactor at 175 °C (t_R = 5 min), after which the reaction mixture was passed through a Pd-filter and 250psi BPR. Subsequently this reaction mixture was mixed with a solution C (0.4 mL/min) and a solution D (0.166 mL/min), both pumped using syringe pumps. The resulting mixture was allowed to reside in a second 2 mL microreactor at room temperature (t_R = approx. 2 min), after which the reaction mixture was quenched in NH_4Cl solution (1 M). The reaction was extracted with DCM (3x), the organic layers were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified using silica gel chromatography (heptane/EtOAc gradient). When the reaction was carried out with 378 mg (2.375 mmol) bromobenzene, N-(pyridin-4-yl)benzamide **3a** was isolated in 65% yield (304 mg).



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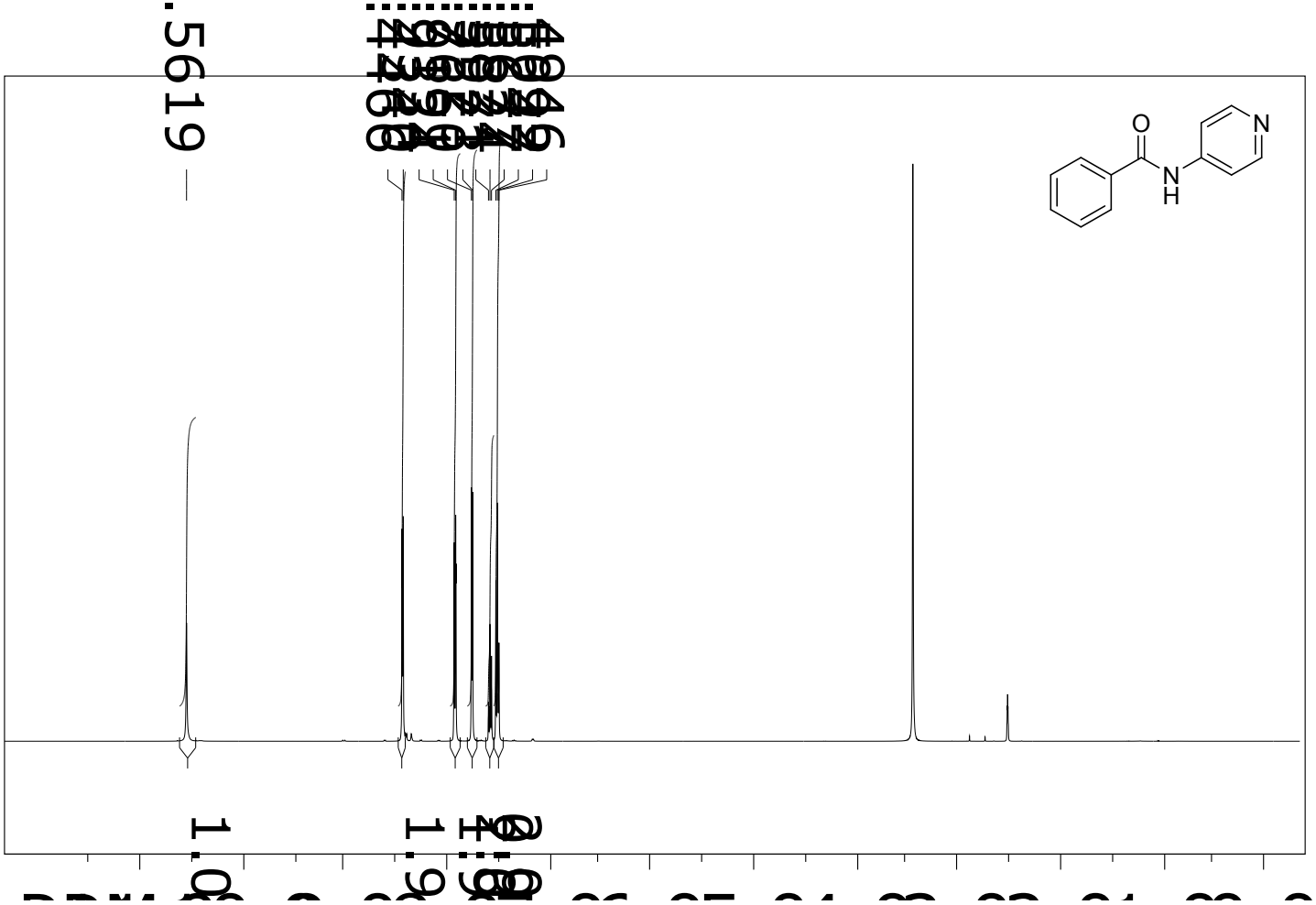
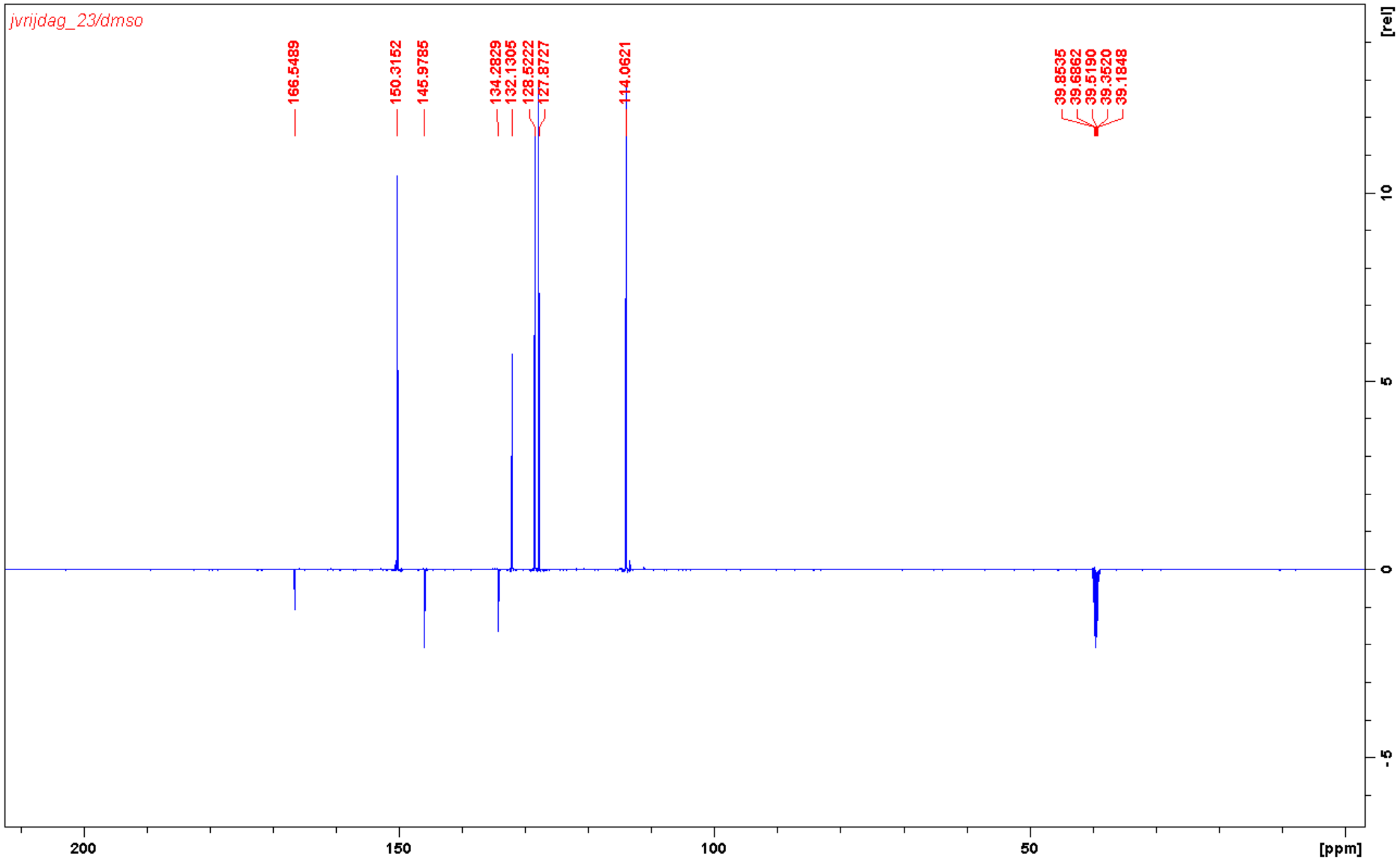
NMR spectra

N-(pyridin-4-yl)benzamide 3a

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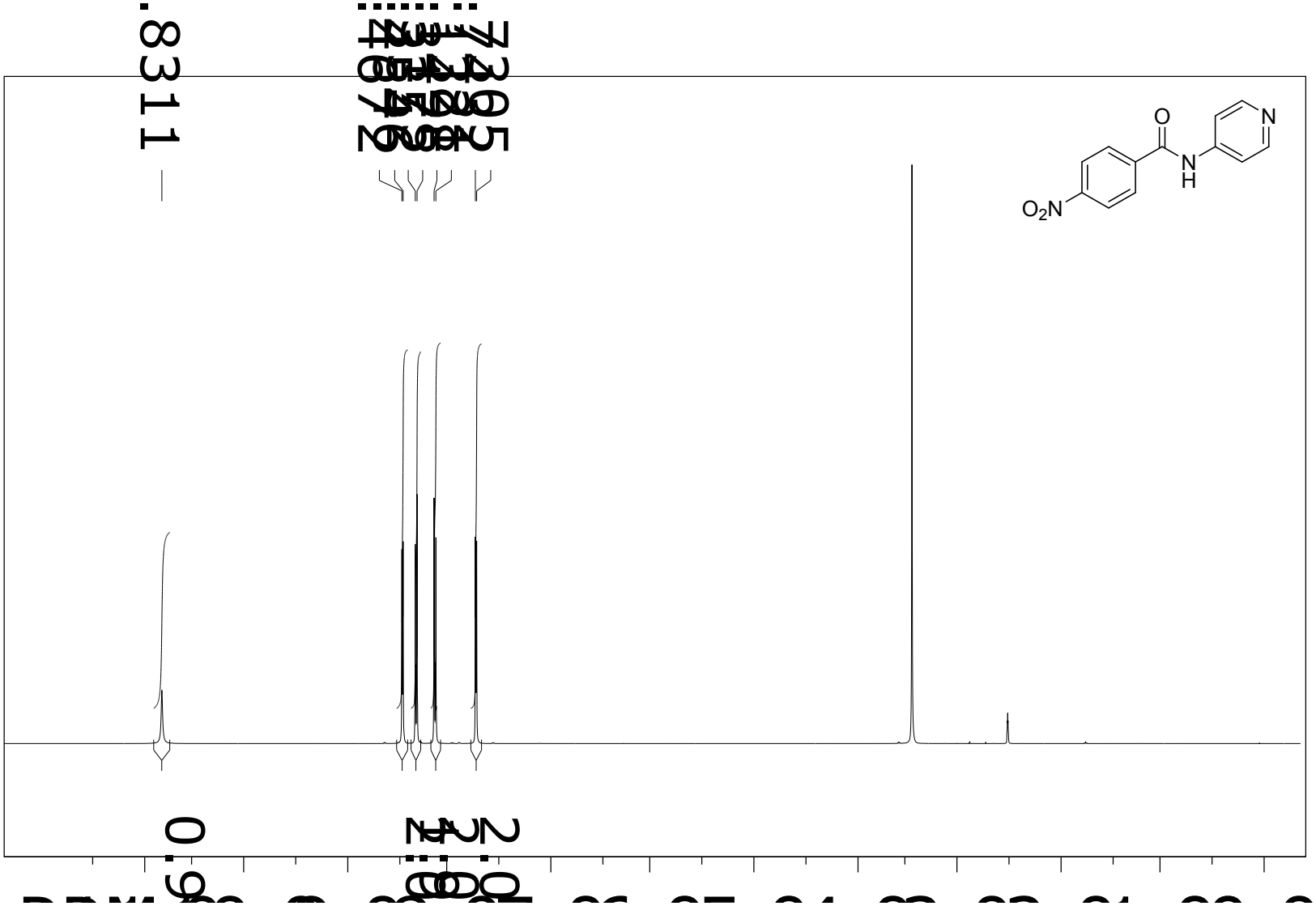
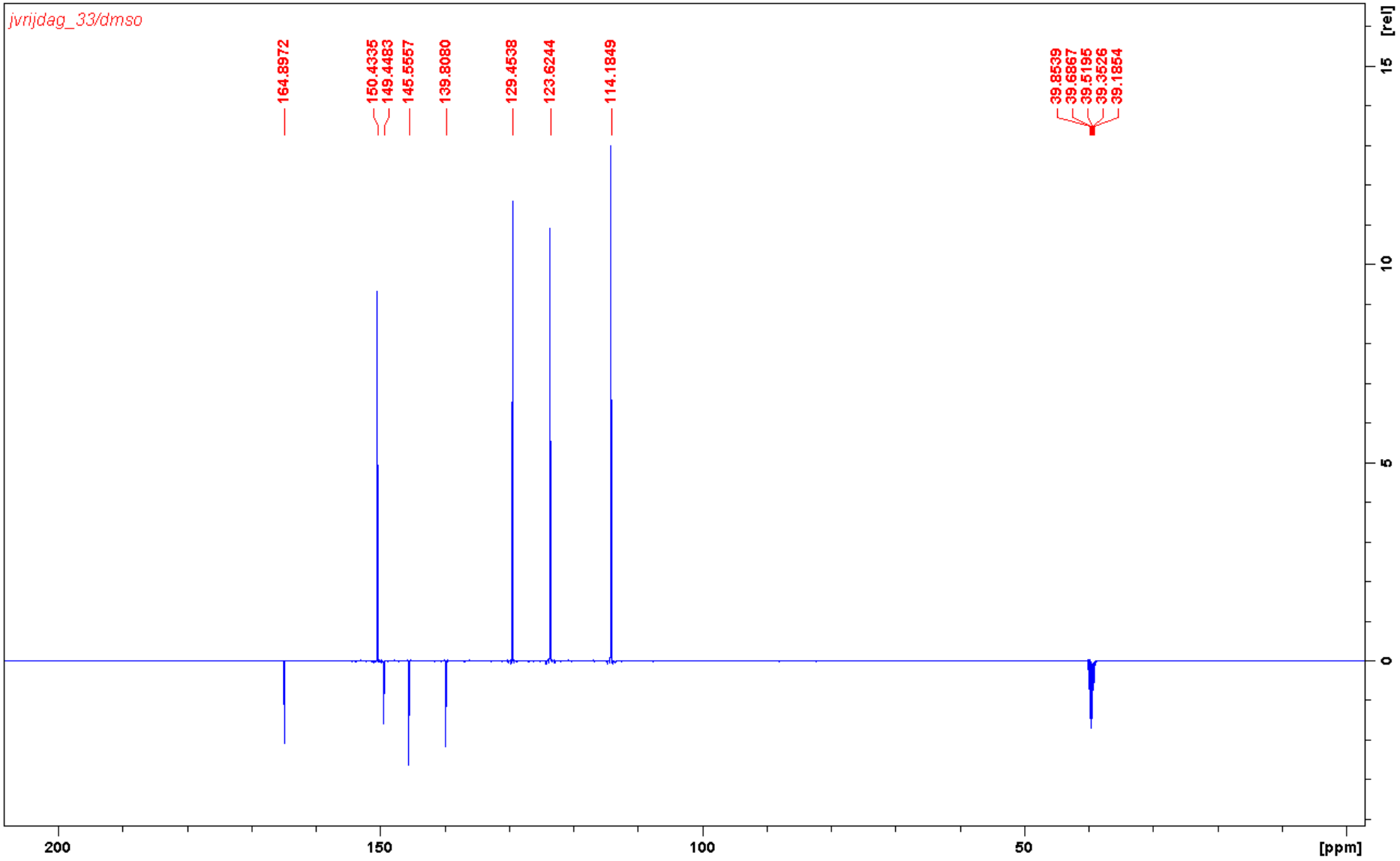
39.5190
39.3520
39.1848
[rel]
10
5
0
-5
200
150
100
50
[ppm]

4-nitro-N-(pyridin-4-yl)benzamide 3b

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39.6867
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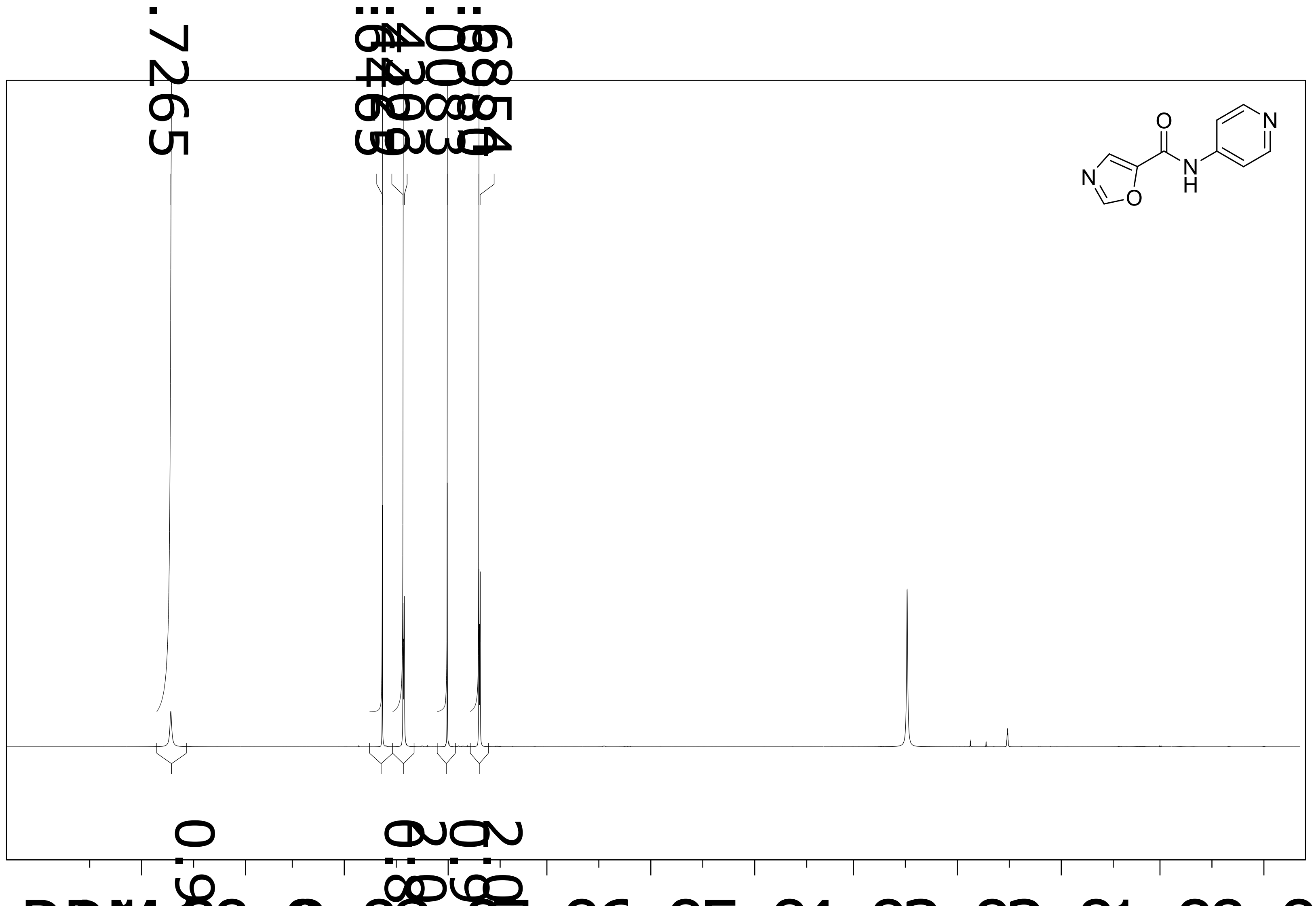
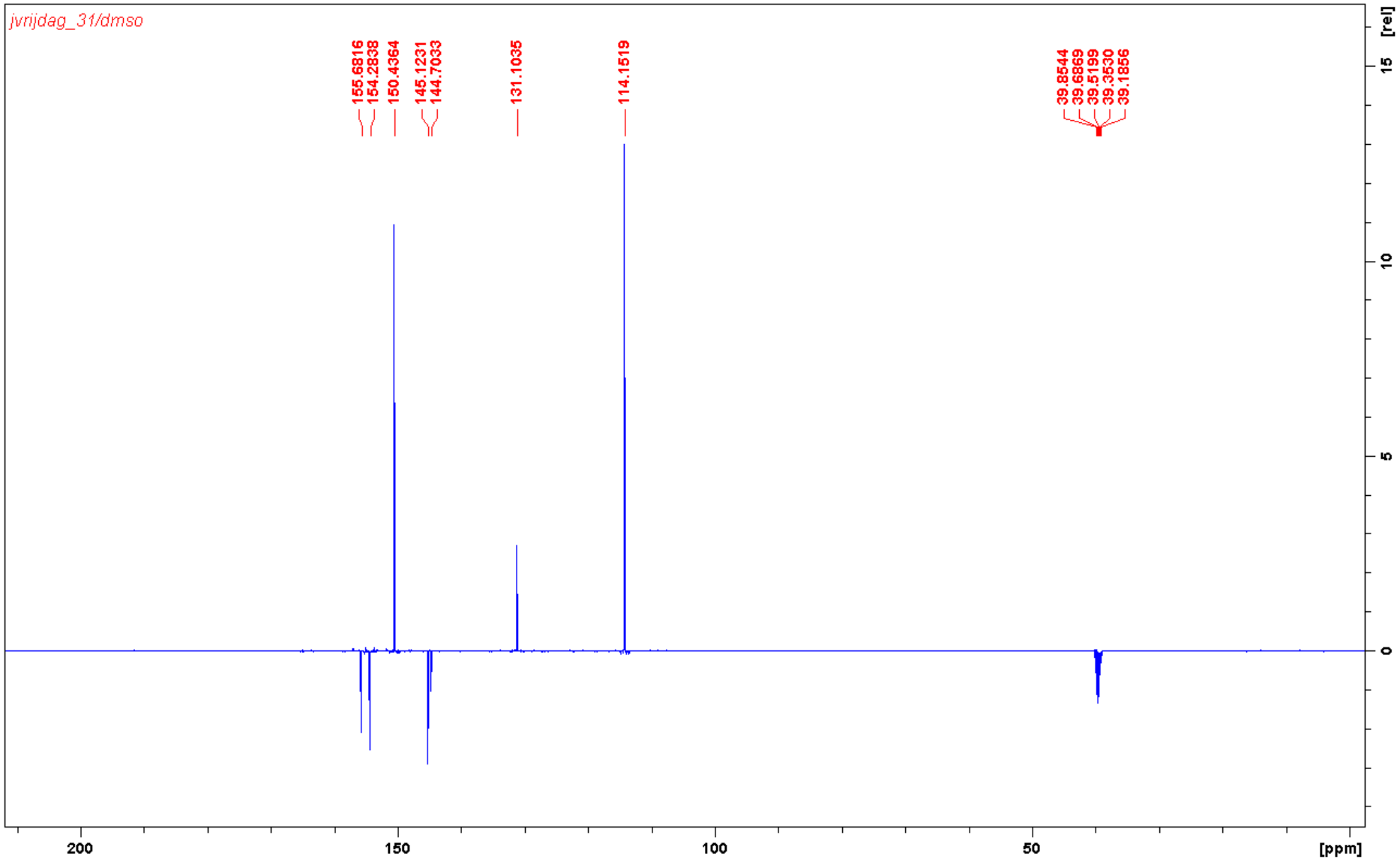
39.3526
39.1854
[rel]
15
10
5
0
200
150
100
50
[ppm]

N-(pyridin-4-yl)-1,3-oxazole-5-carboxamide 3c

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39.5199
39.3530
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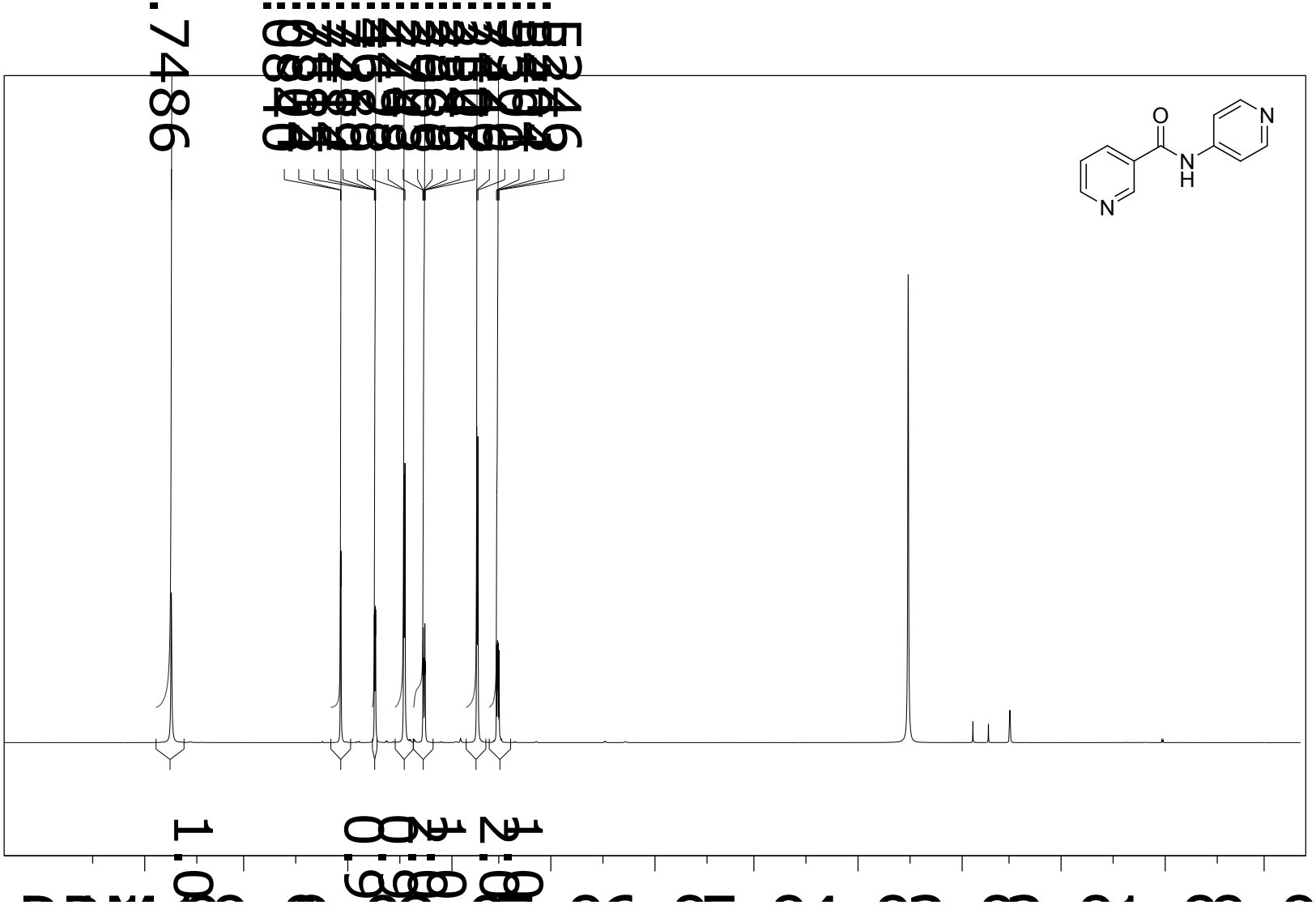
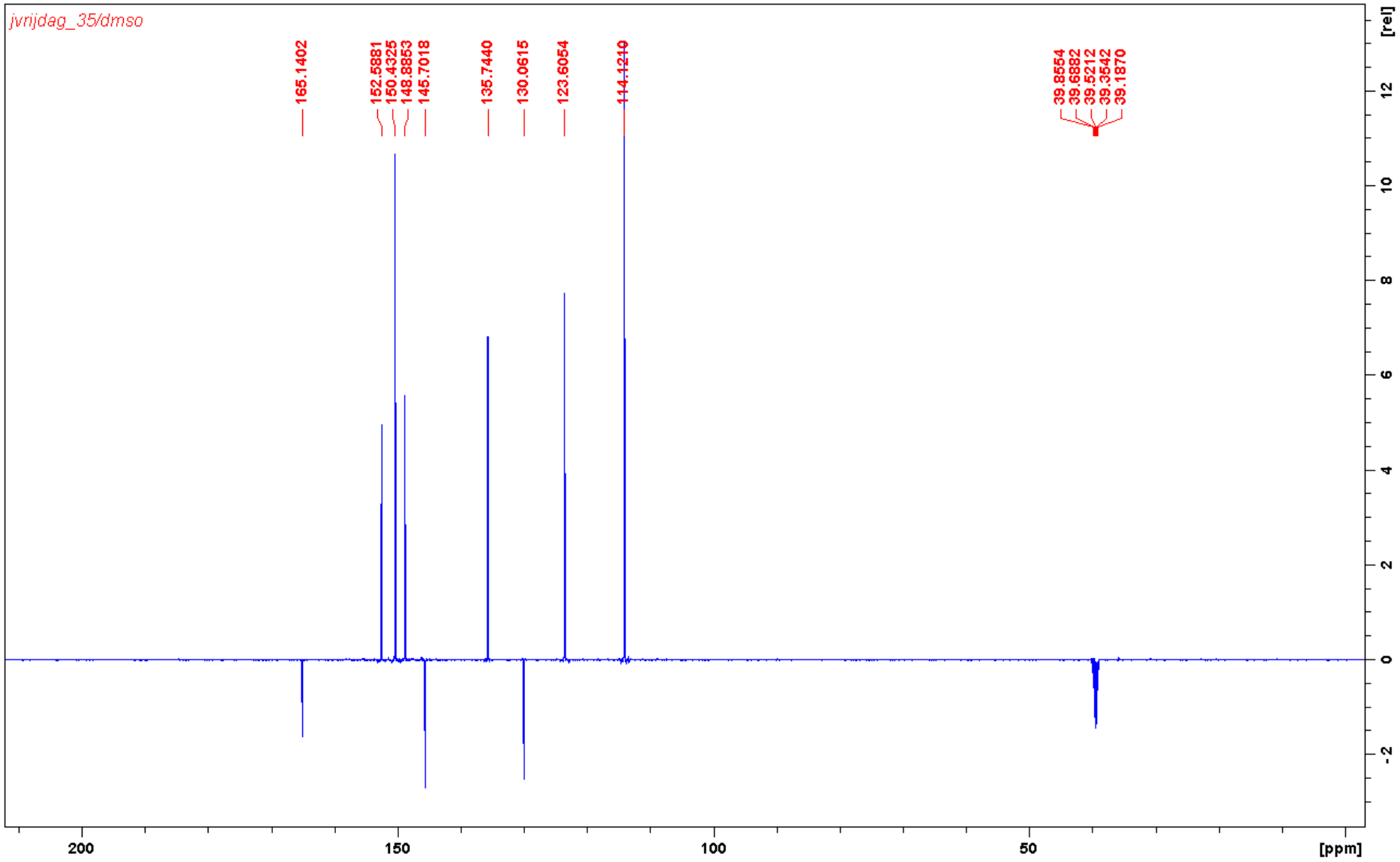
[rel]
15
10
5
0
200
150
100
50
[ppm]

N-(pyridin-4-yl)pyridine-3-carboxamide 3d

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12
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8
6
4
2
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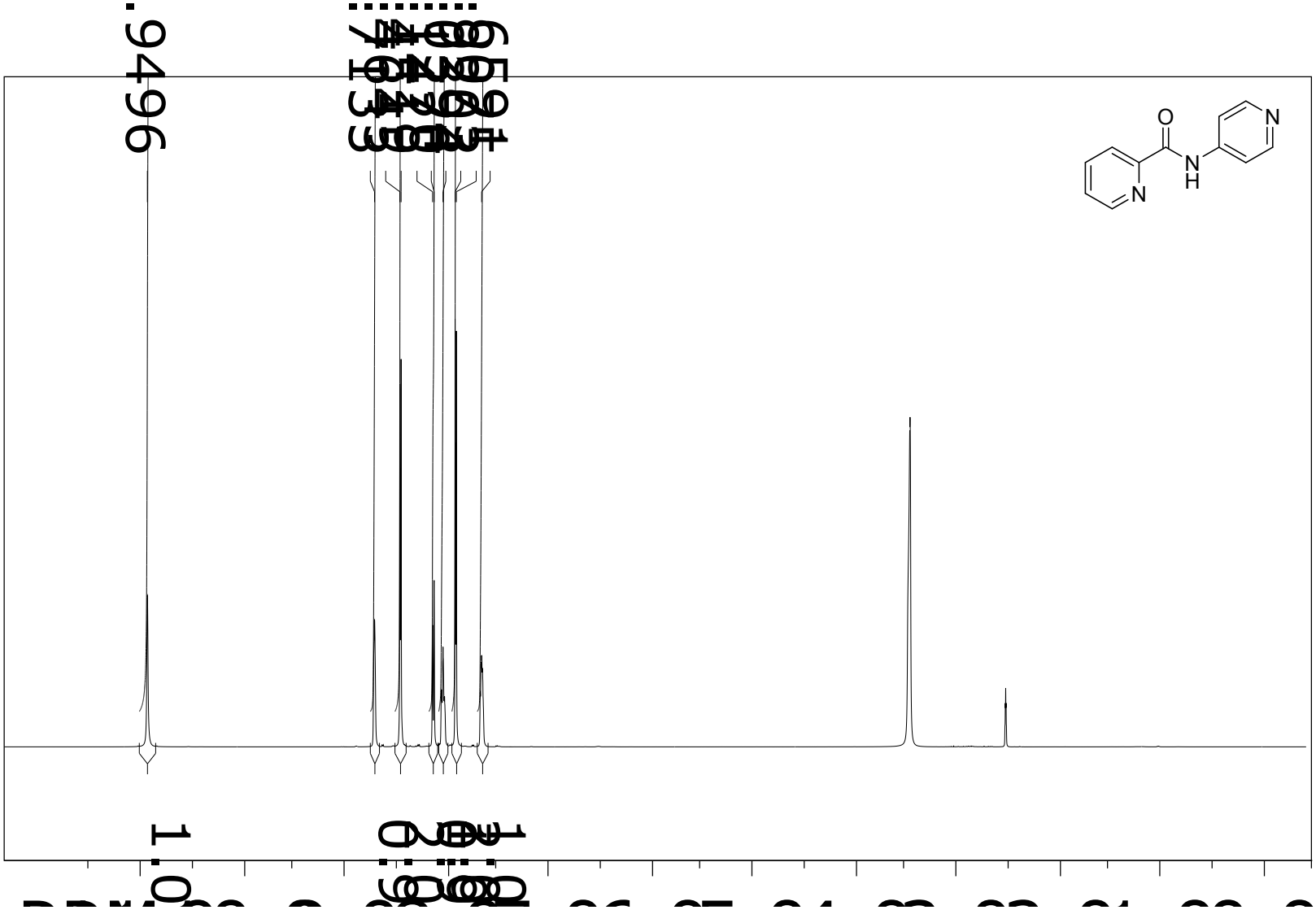
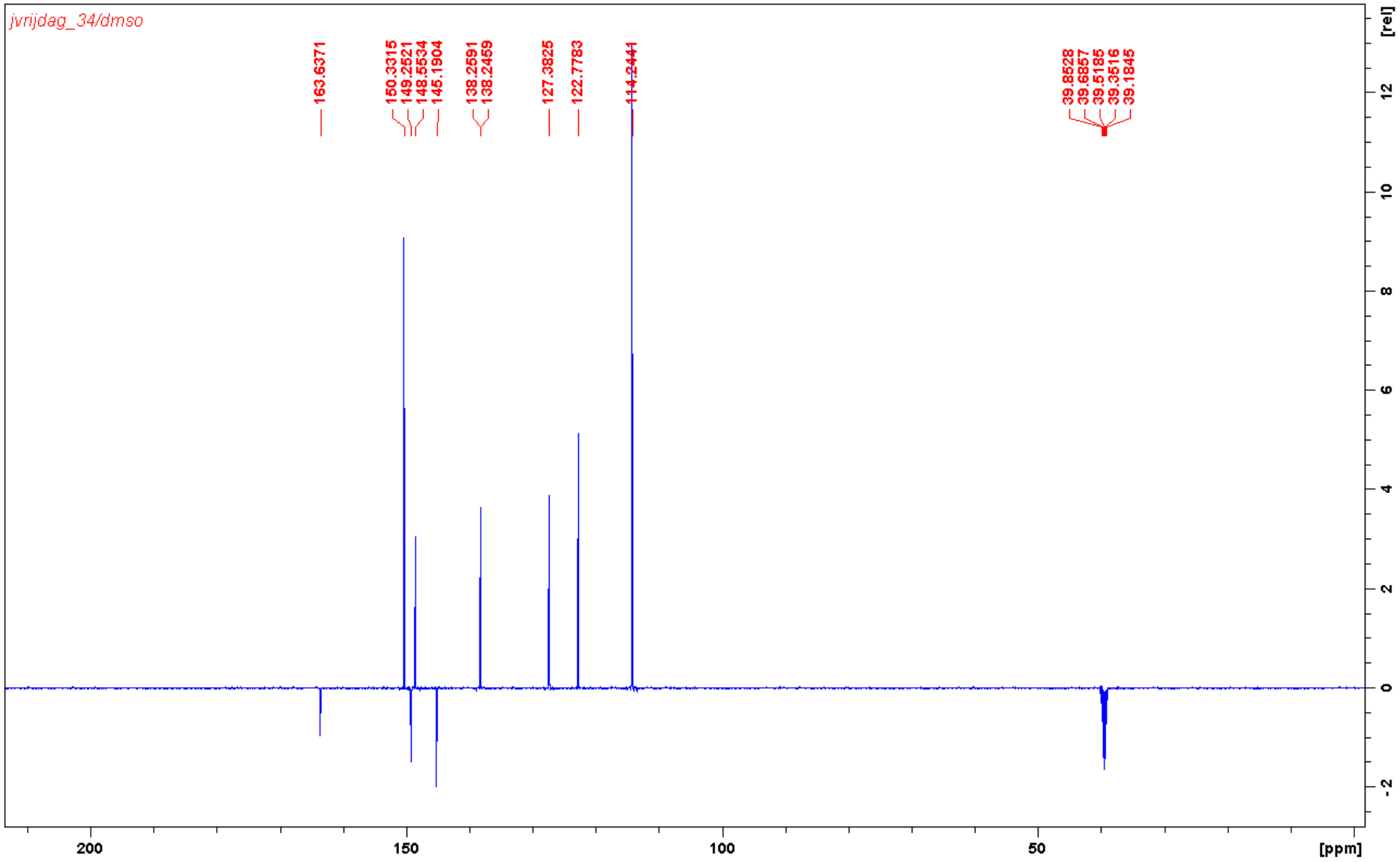
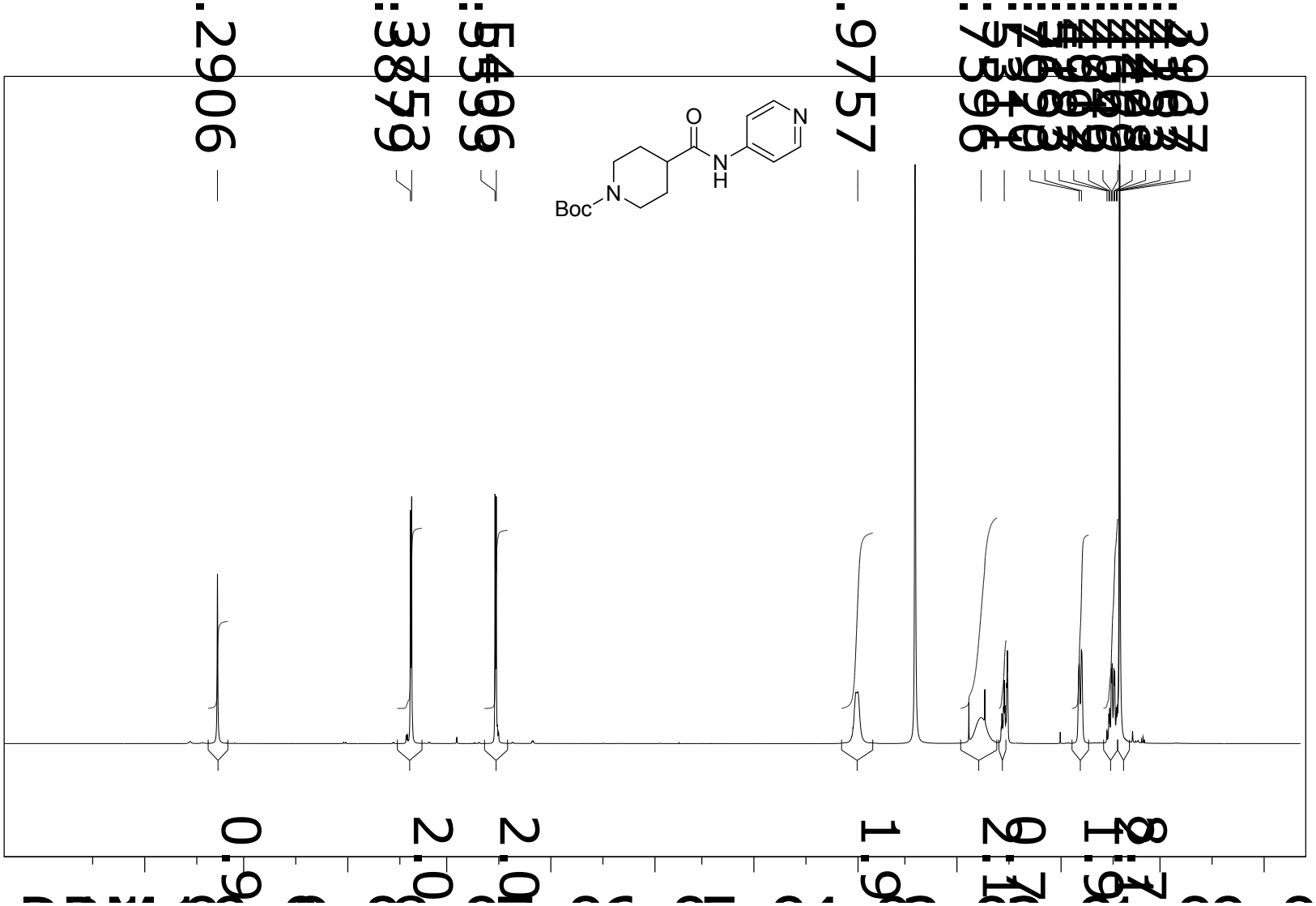
-2
200
150
100
50
[ppm]

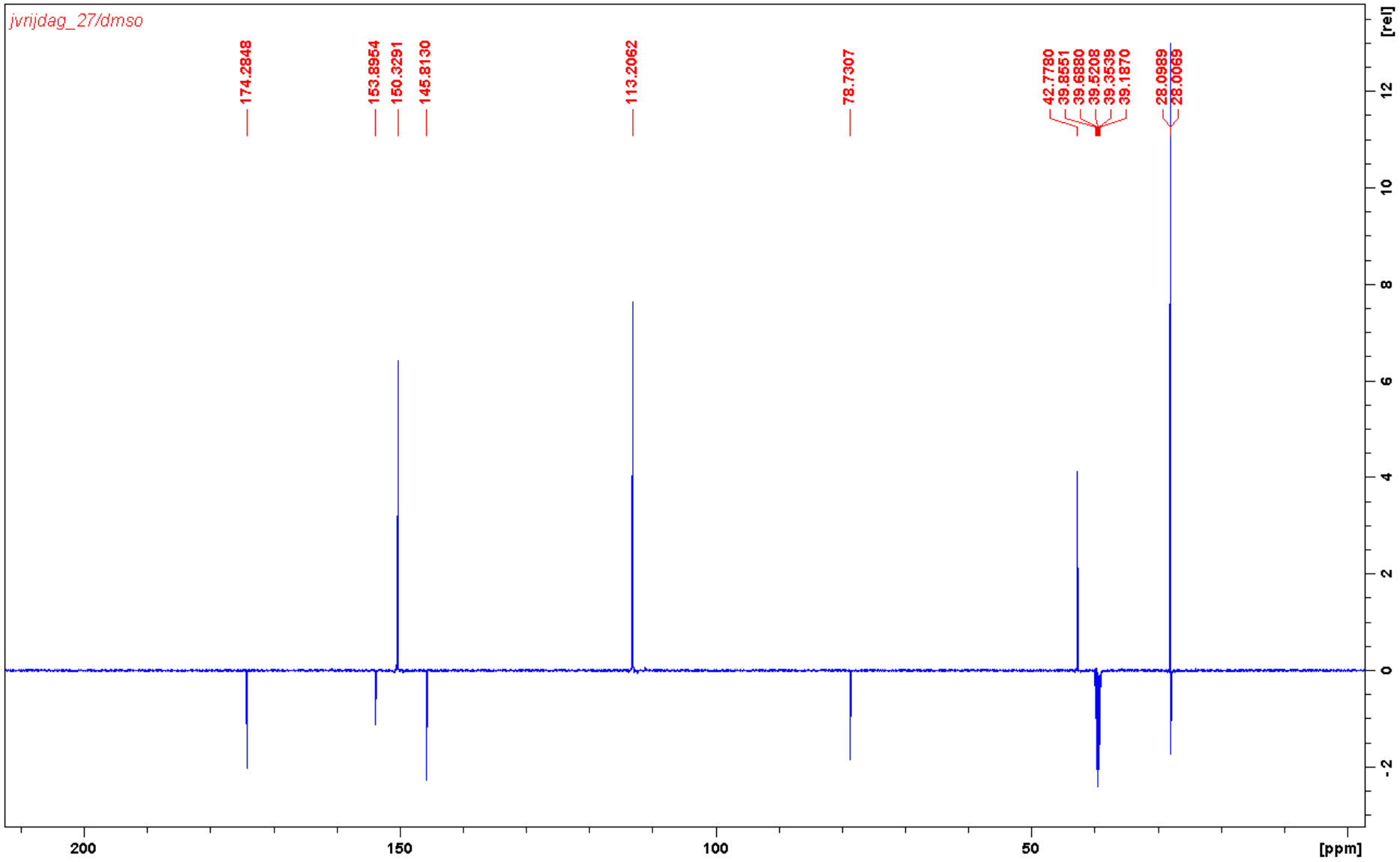
N-(pyridin-4-yl)pyridine-2-carboxamide 3e



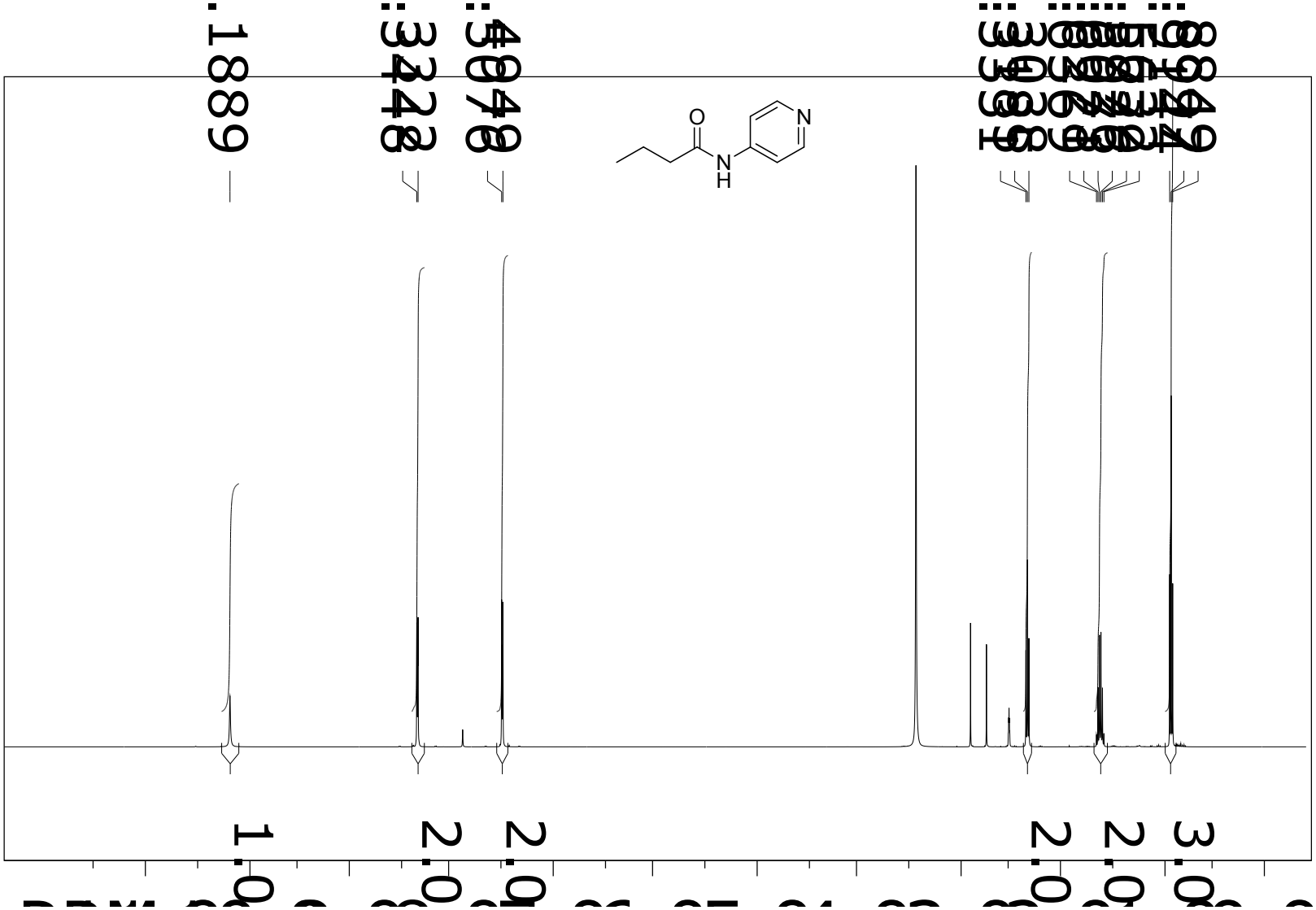

jvnjdag_34/dmso
163.6371
150.3315
149.2521
148.5534
145.1904
138.2591
138.2459
127.3825
122.7783
114.2441
39.8528
39.6857
39.5185
39.3516
39.1845
[rel]
12
10
8
6
4
2
0
-2
200
150
100
50
[ppm]

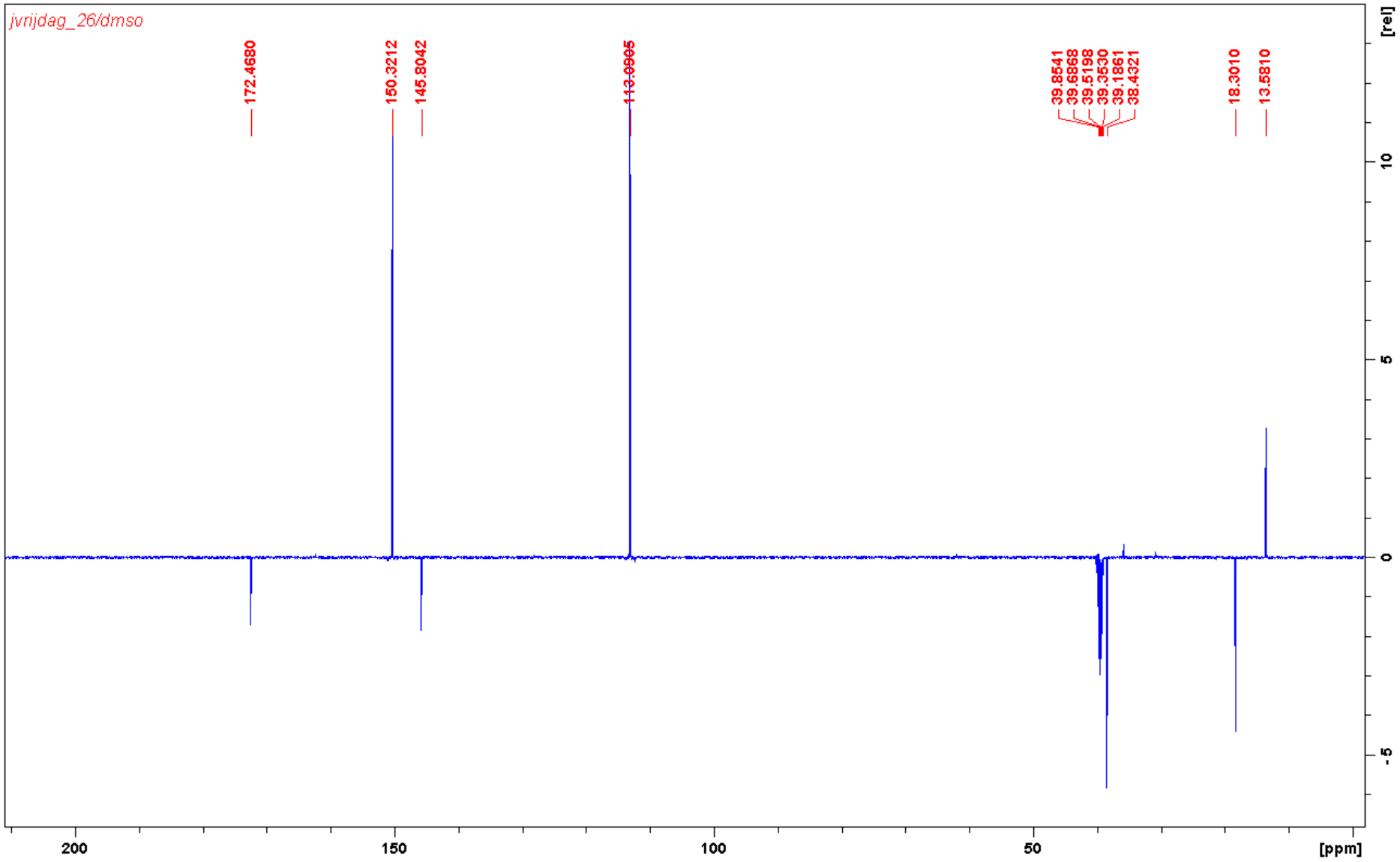
tert-butyl 4-[(pyridin-4-yl)carbamoyl]piperidine-1-carboxylate 3f



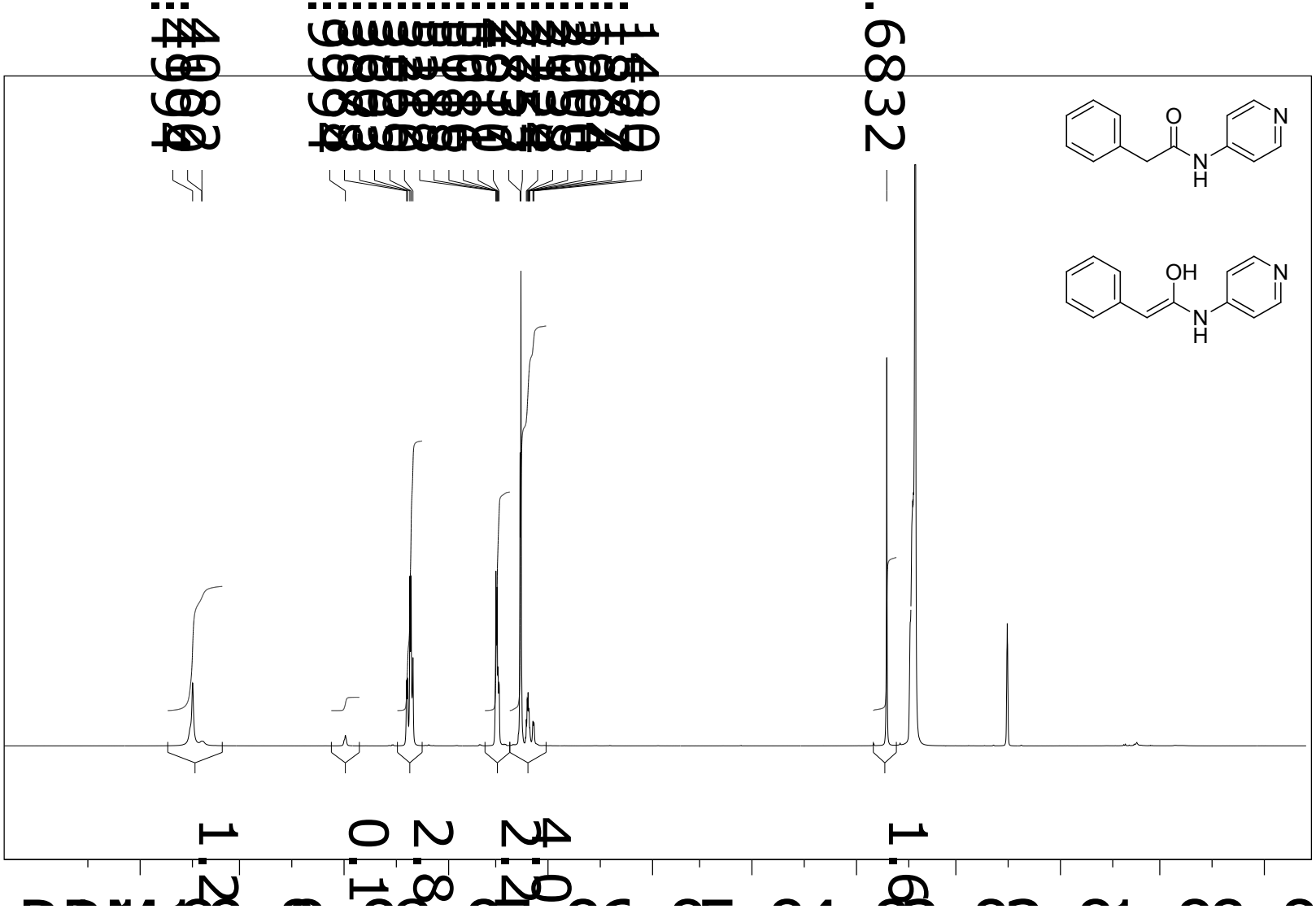

jvnjdag_27/dmso
174.2848
153.8954
150.3291
145.8130
113.2062
78.7307
42.7780
39.8551
39.6880
39.5208
39.3539
39.1870
28.0989
28.0069
[rel]
12
10
8
6
4
2
0
-2
200
150
100
50
[ppm]

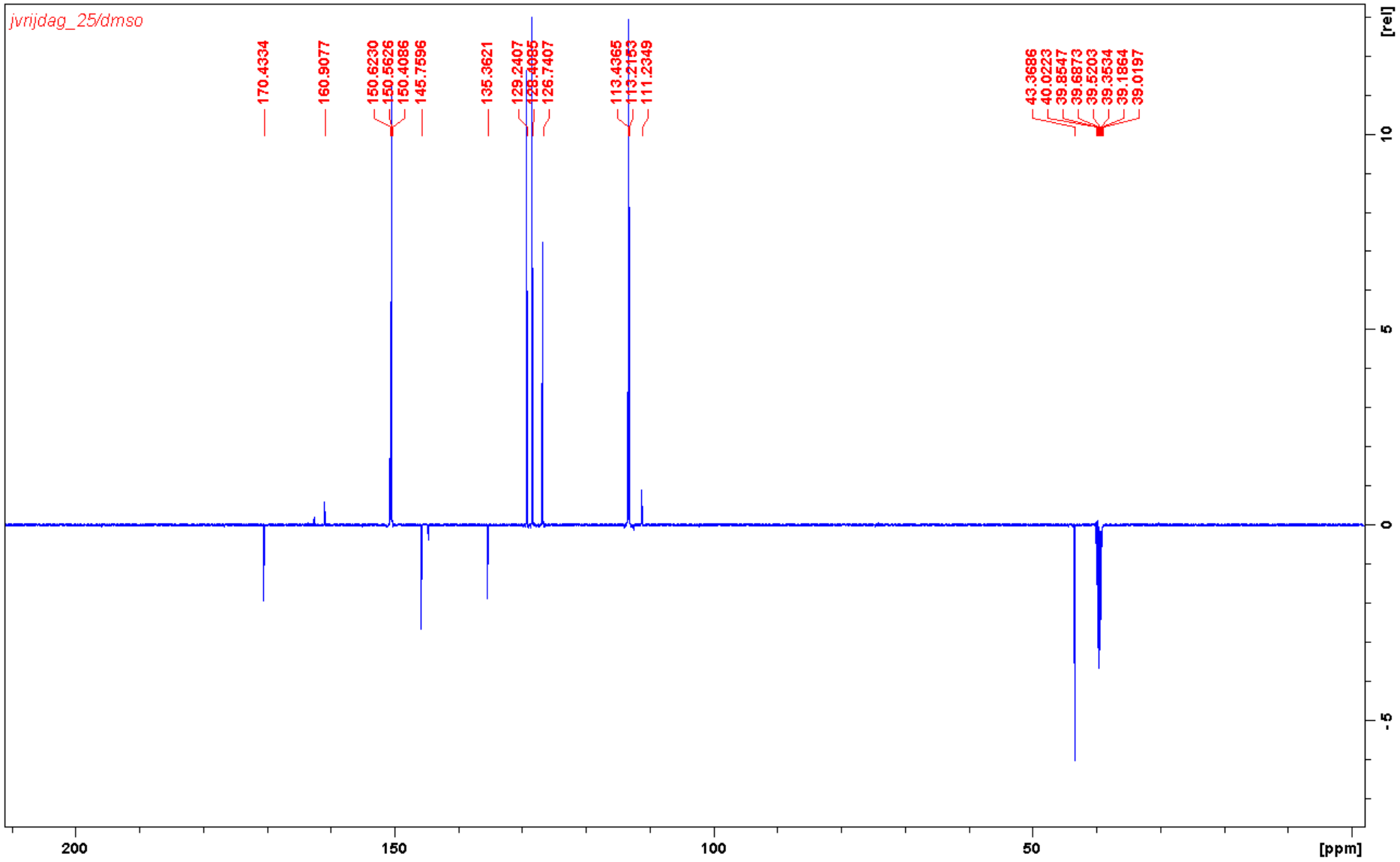
N-(pyridin-4-yl)butanamide 3g



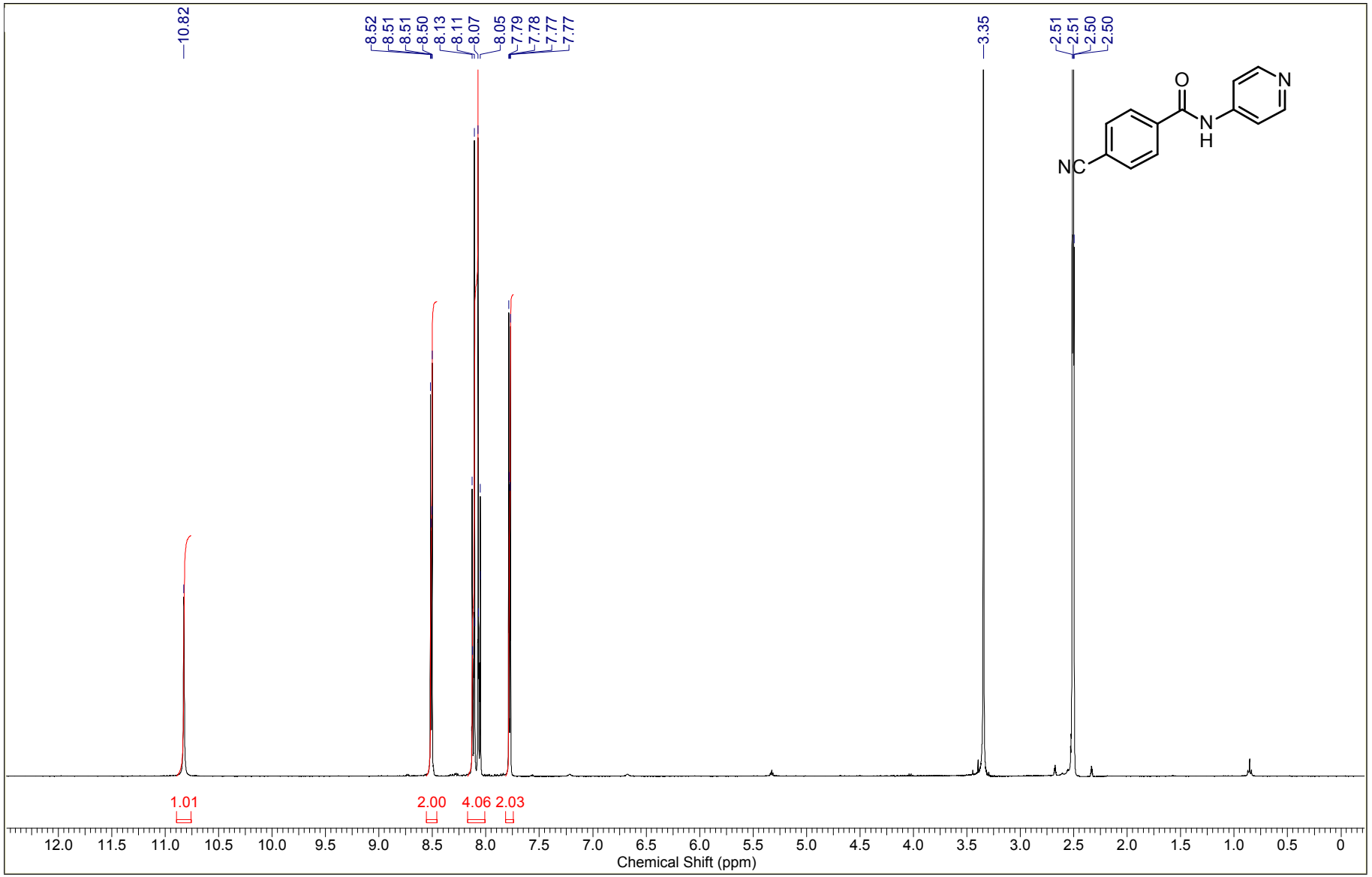

jvnjdag_26/dmso
172.4680
150.3212
145.8042
113.0905
39.8541
39.6868
39.5198
39.3530
39.1861
38.4321
18.3010
13.5810
[rel]
10
5
0
-5
200
150
100
50
[ppm]

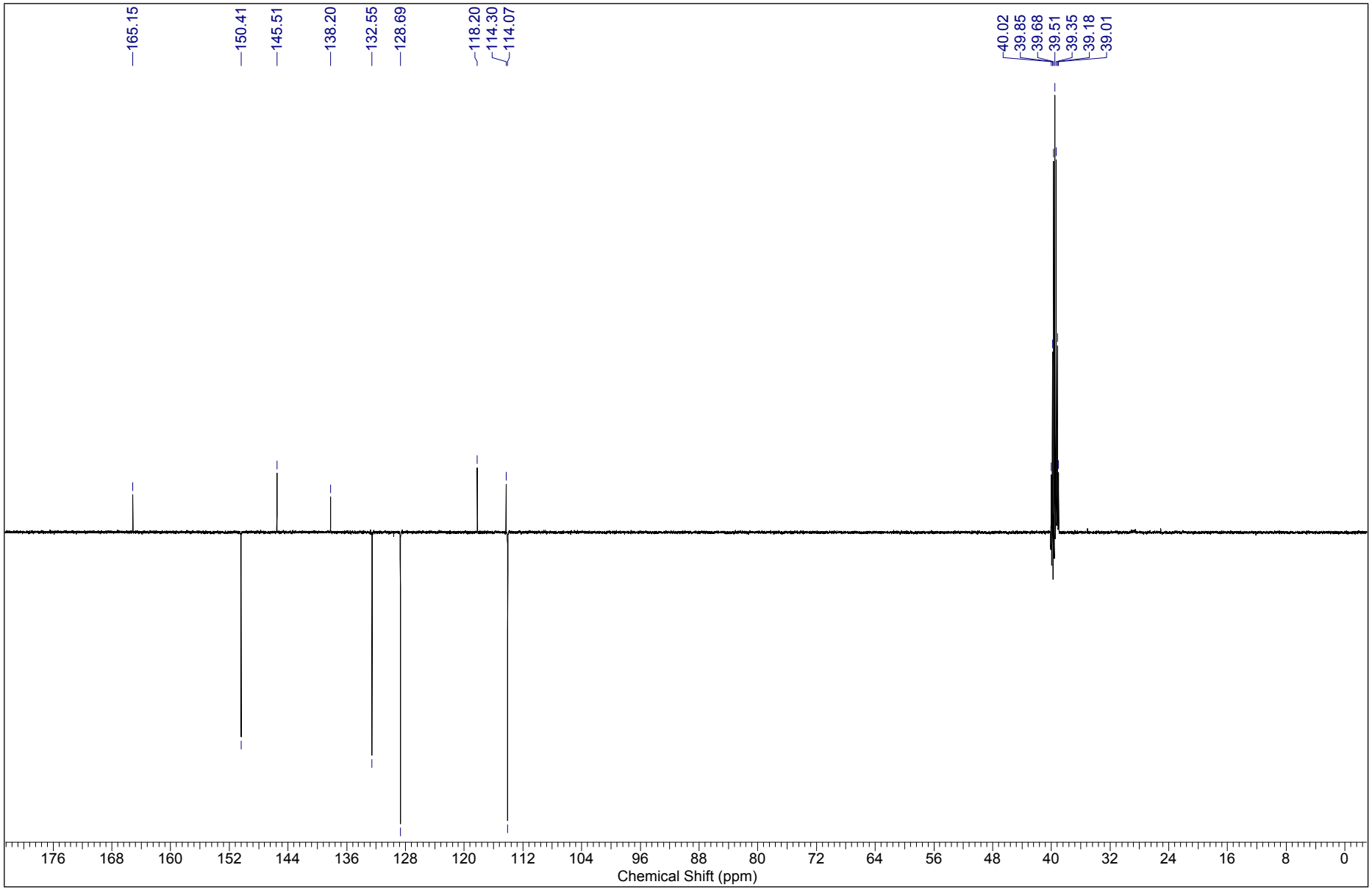
2-phenyl-N-(pyridin-4-yl)acetamide 3h



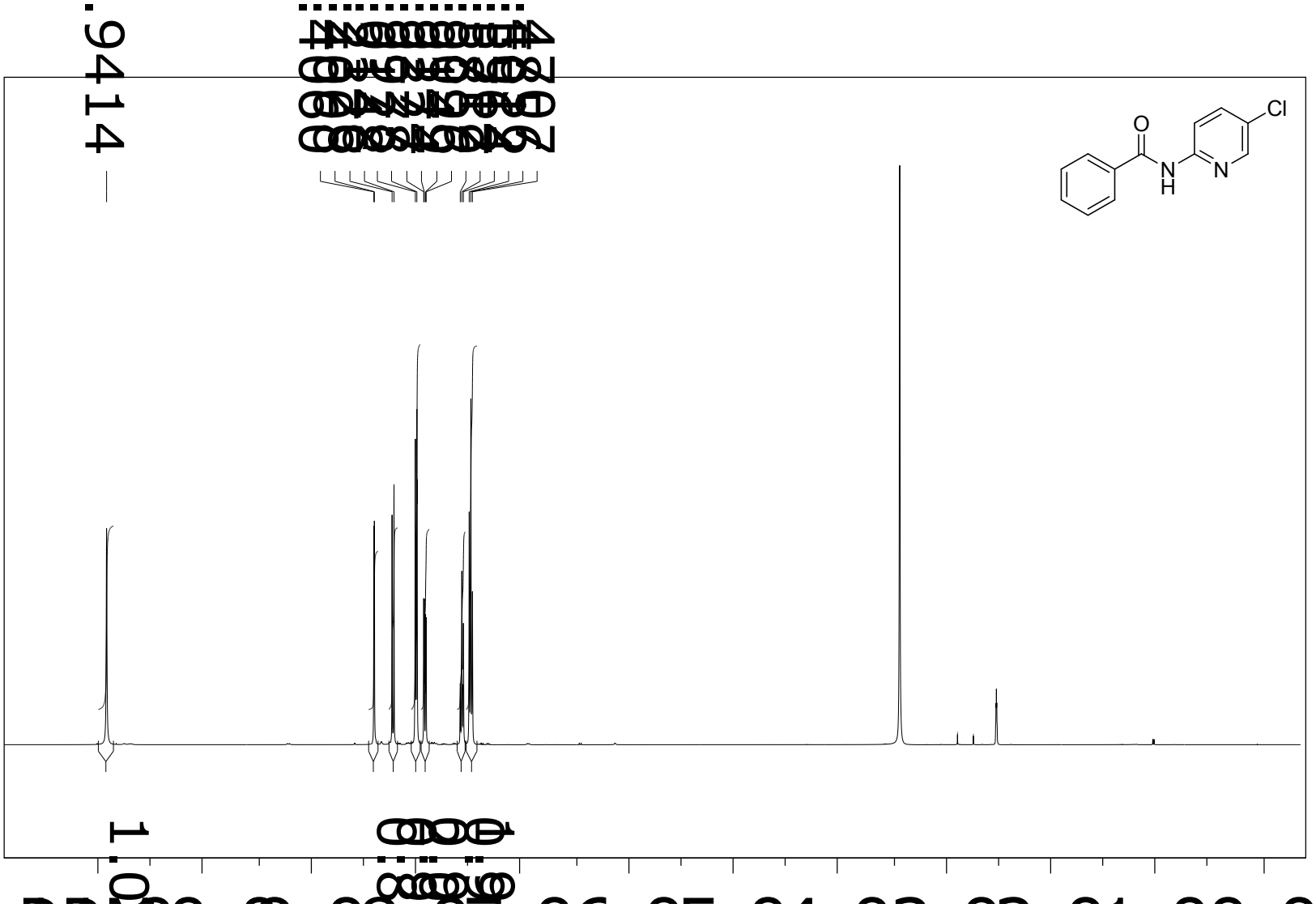

jvnjdag_25/dmso
170.4334
160.9077
150.6230
150.5626
150.4086
145.7596
135.3621
129.2407
128.4085
126.7407
113.4365
113.2153
111.2349
43.3686
40.0223
39.8547
39.6873
39.5203
39.3534
39.1864
39.0197
[rel]
10
5
0
-5
200
150
100
50
[ppm]

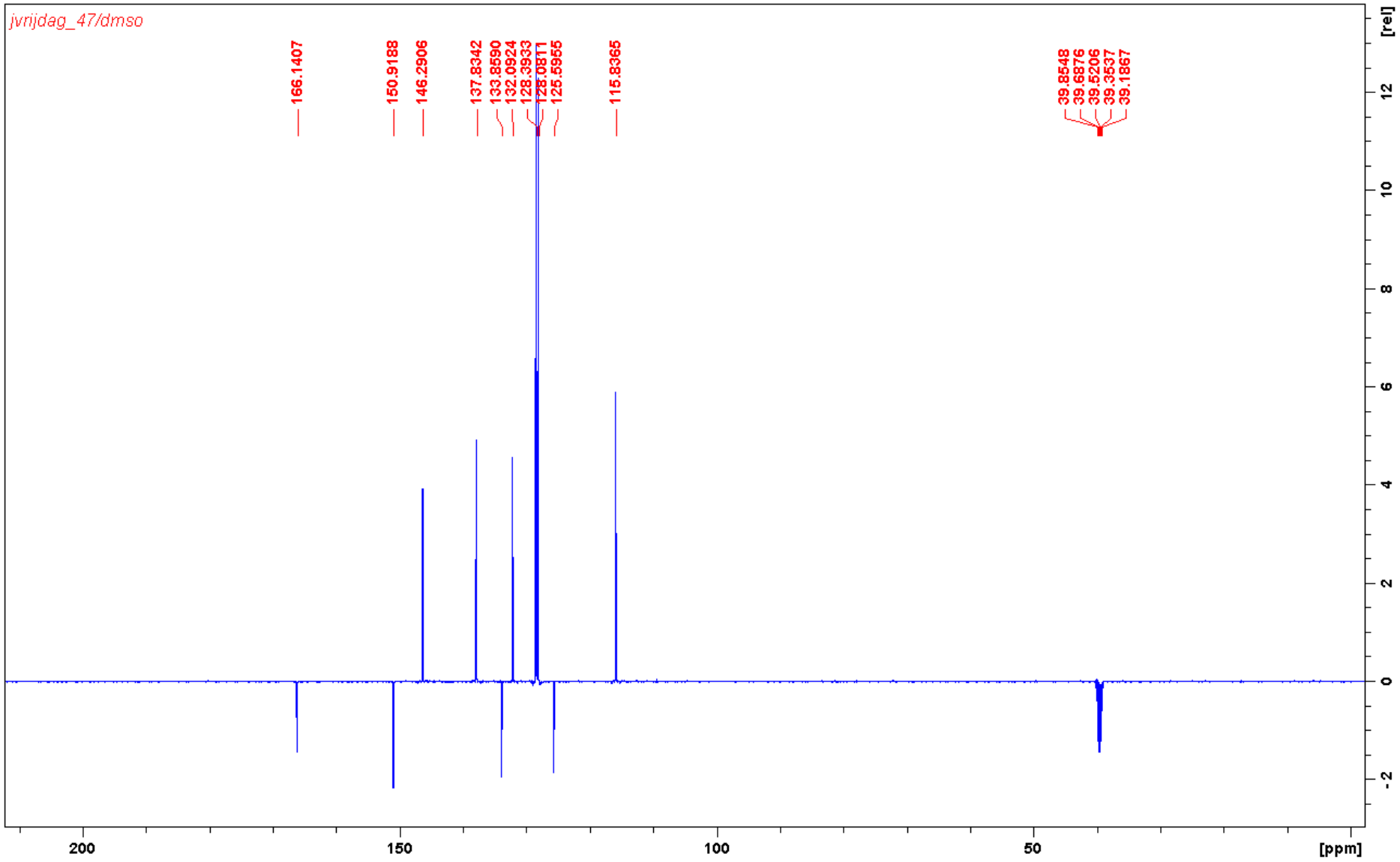
4-cyano-N-(pyridin-4-yl)acetamide 3i



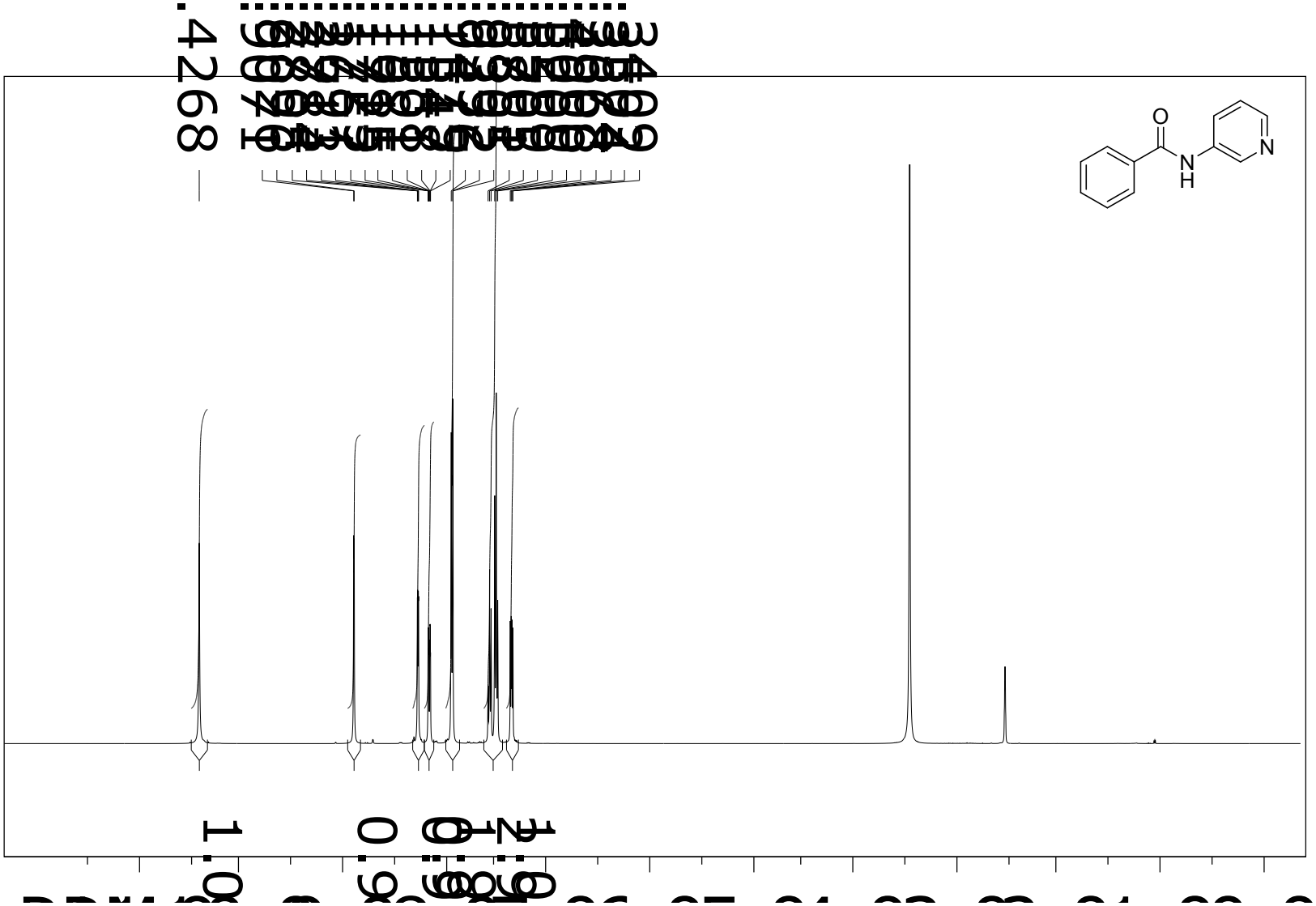

165.15
150.41
145.51
138.20
132.55
128.69
118.20
114.30
114.07
40.02
39.85
39.68
39.51
39.35
39.18
39.01
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

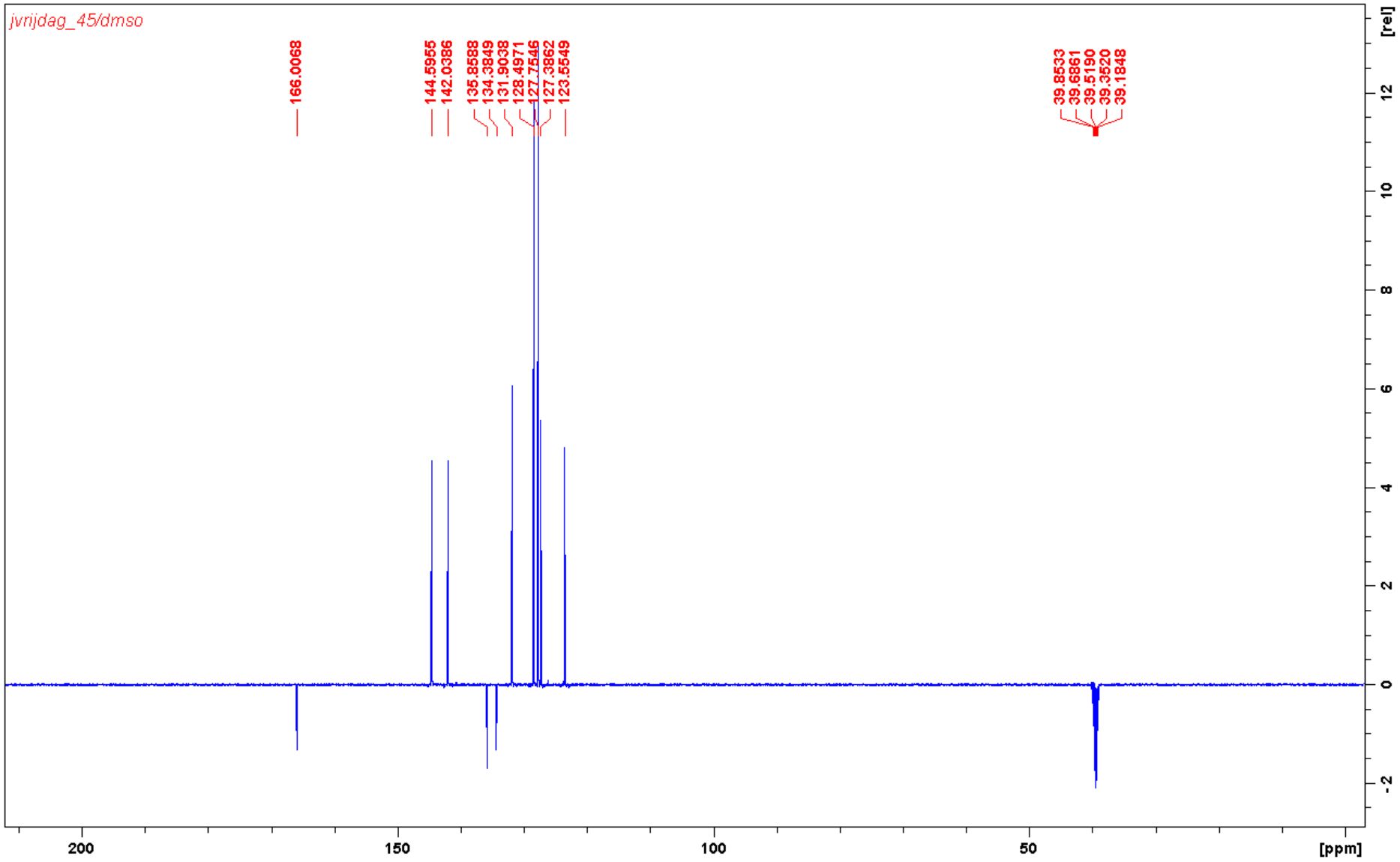
N-(5-chloropyridin-2-yl)benzamide 3j



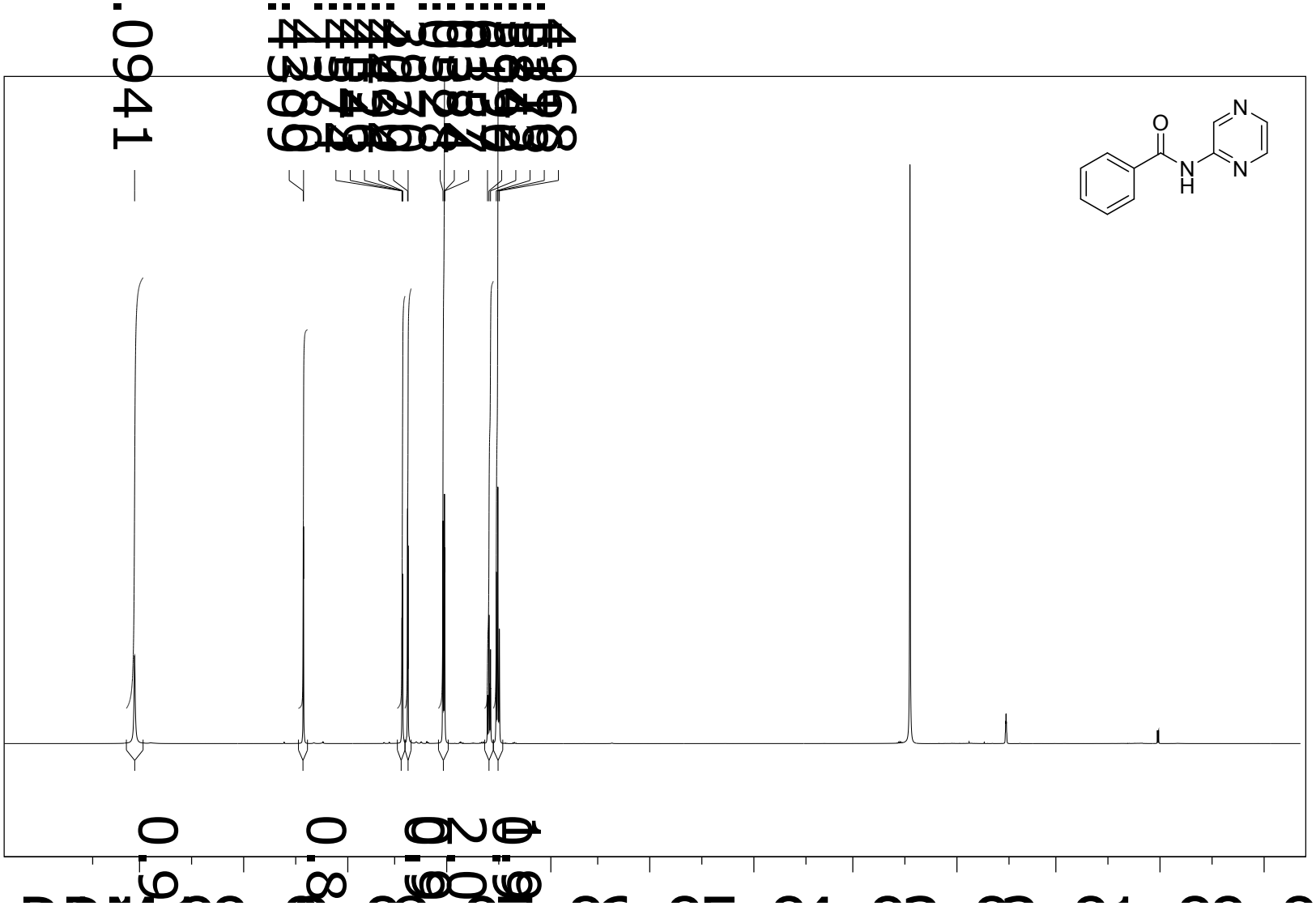

jvnjdag_47/dmso
166.1407
150.9188
146.2906
137.8342
133.8590
132.0924
128.3933
128.0811
125.5955
115.8365
39.8548
39.6876
39.5206
39.3537
39.1867
[rel]
12
10
8
6
4
2
0
-2
200
150
100
50
[ppm]

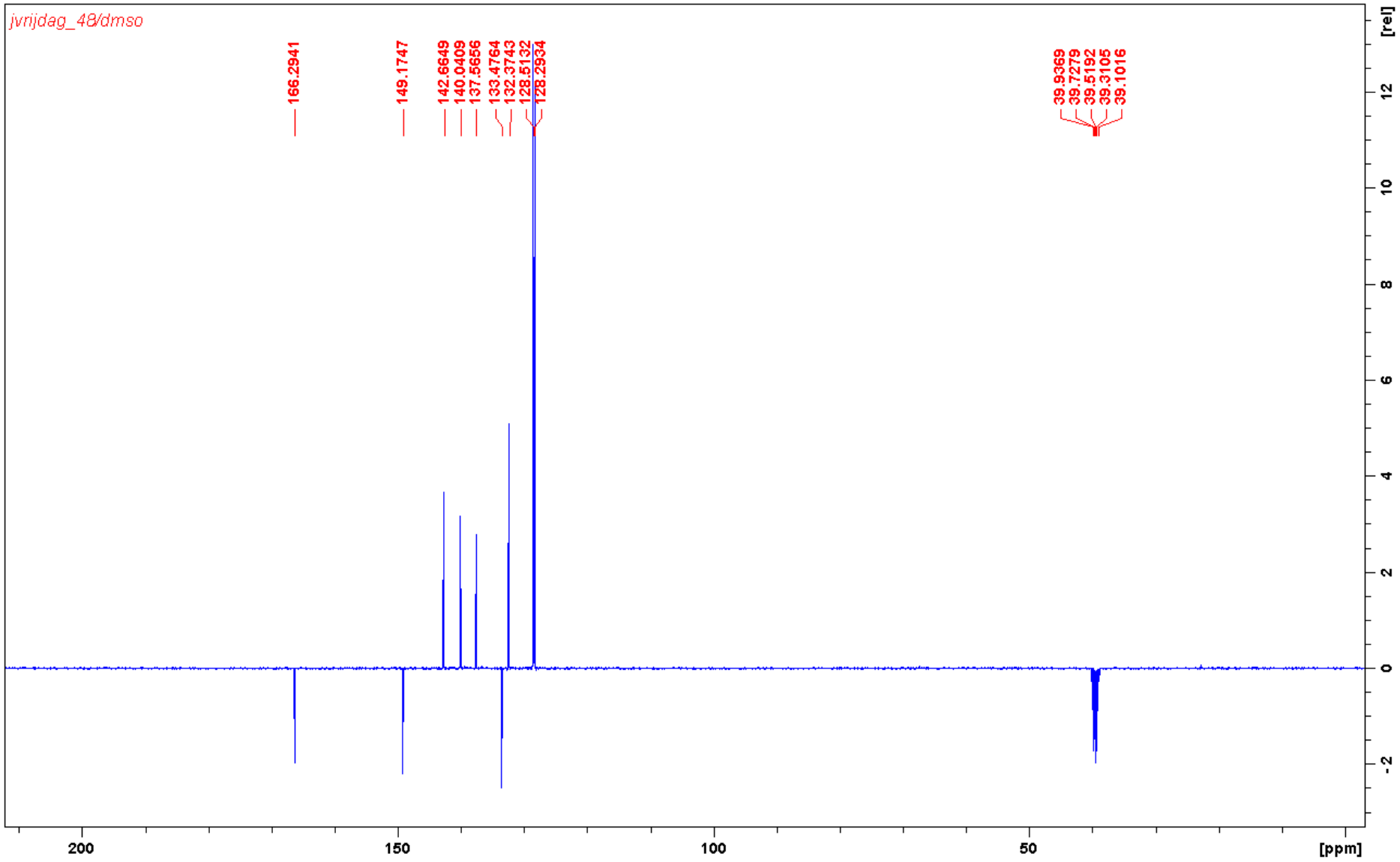
N-(pyridin-3-yl)benzamide 3k



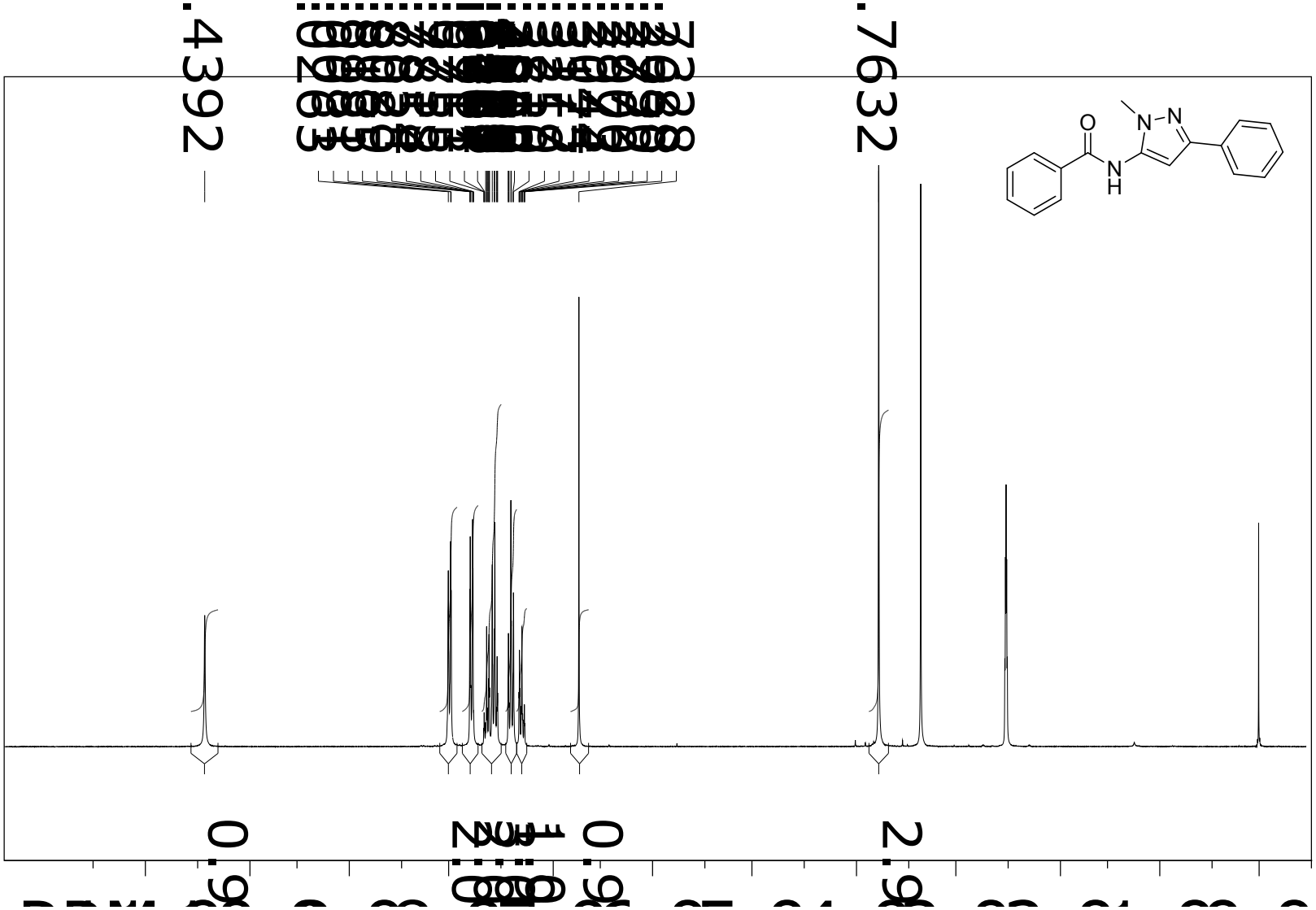

jvnjdag_45/dmso
166.0068
144.5955
142.0386
135.8588
134.3849
131.9038
128.4971
127.7546
127.3862
123.5549
39.8533
39.6861
39.5190
39.3520
39.1848
[rel]
12
10
8
6
4
2
0
-2
200
150
100
50
[ppm]

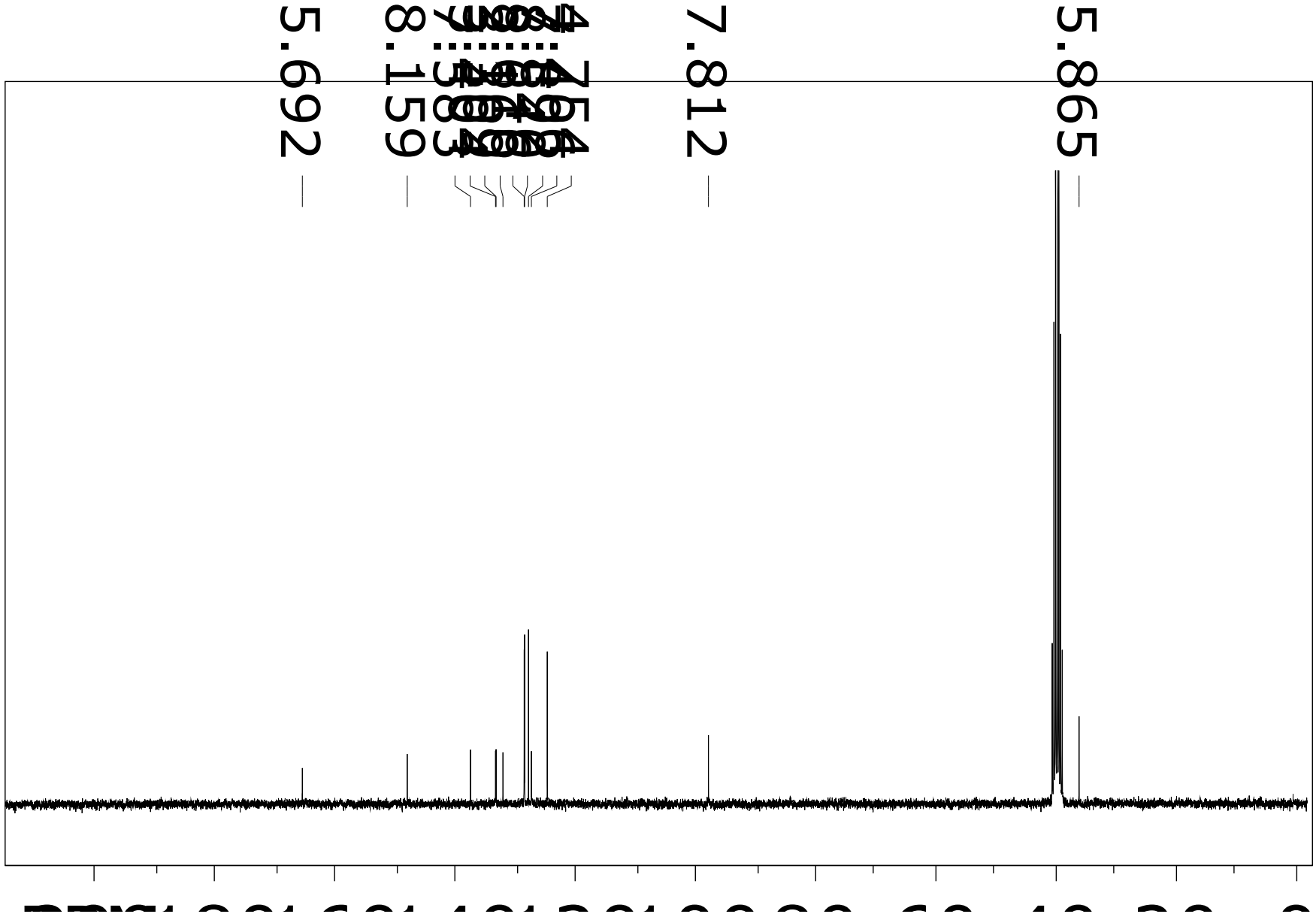
N-(pyrazin-2-yl)benzamide 3l



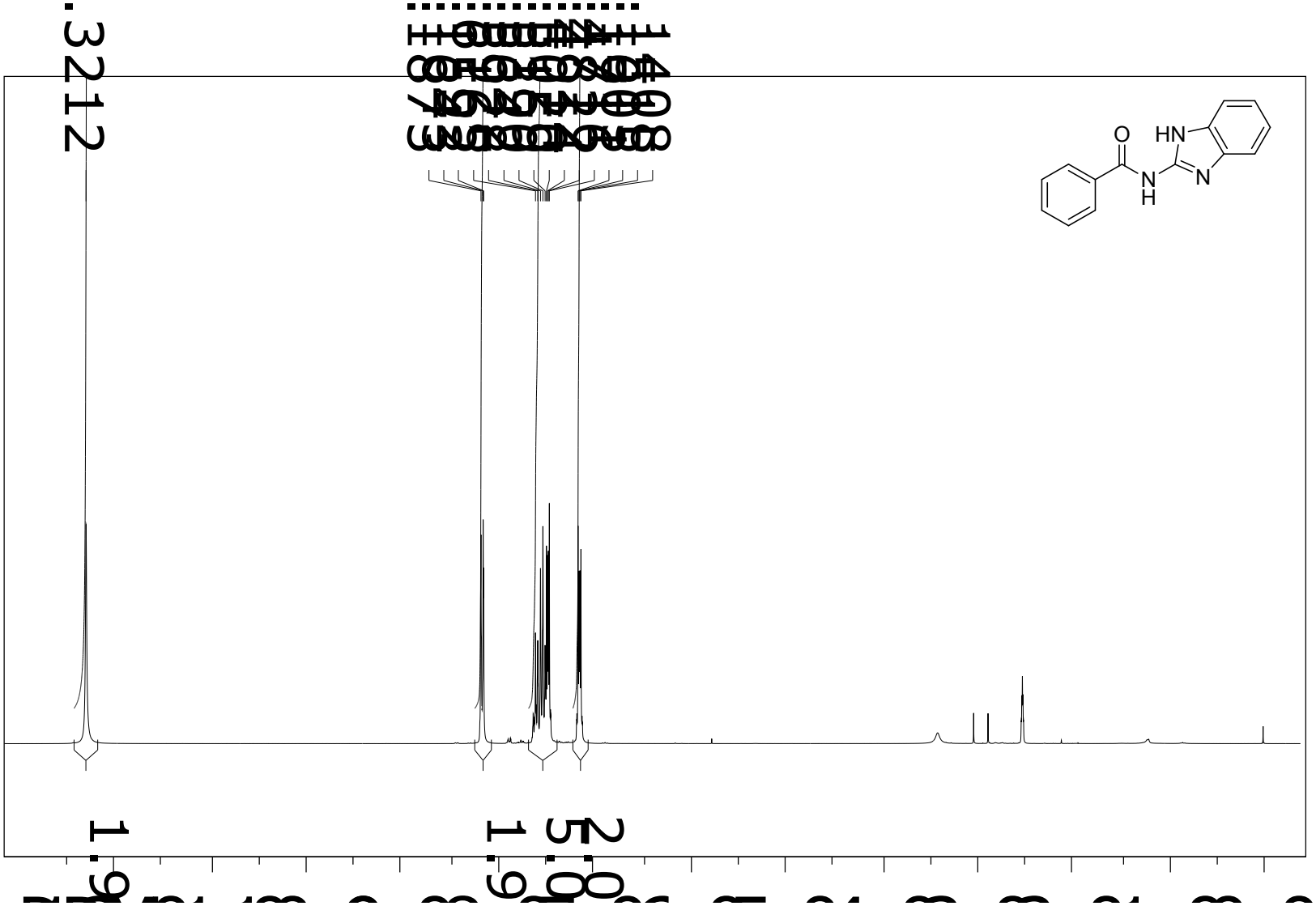

jvnjdag_48/dmso
166.2941
149.1747
142.6649
140.0409
137.5656
133.4764
132.3743
128.5132
128.2934
39.9369
39.7279
39.5192
39.3105
39.1016
[rel]
12
10
8
6
4
2
0
-2
200
150
100
50
[ppm]

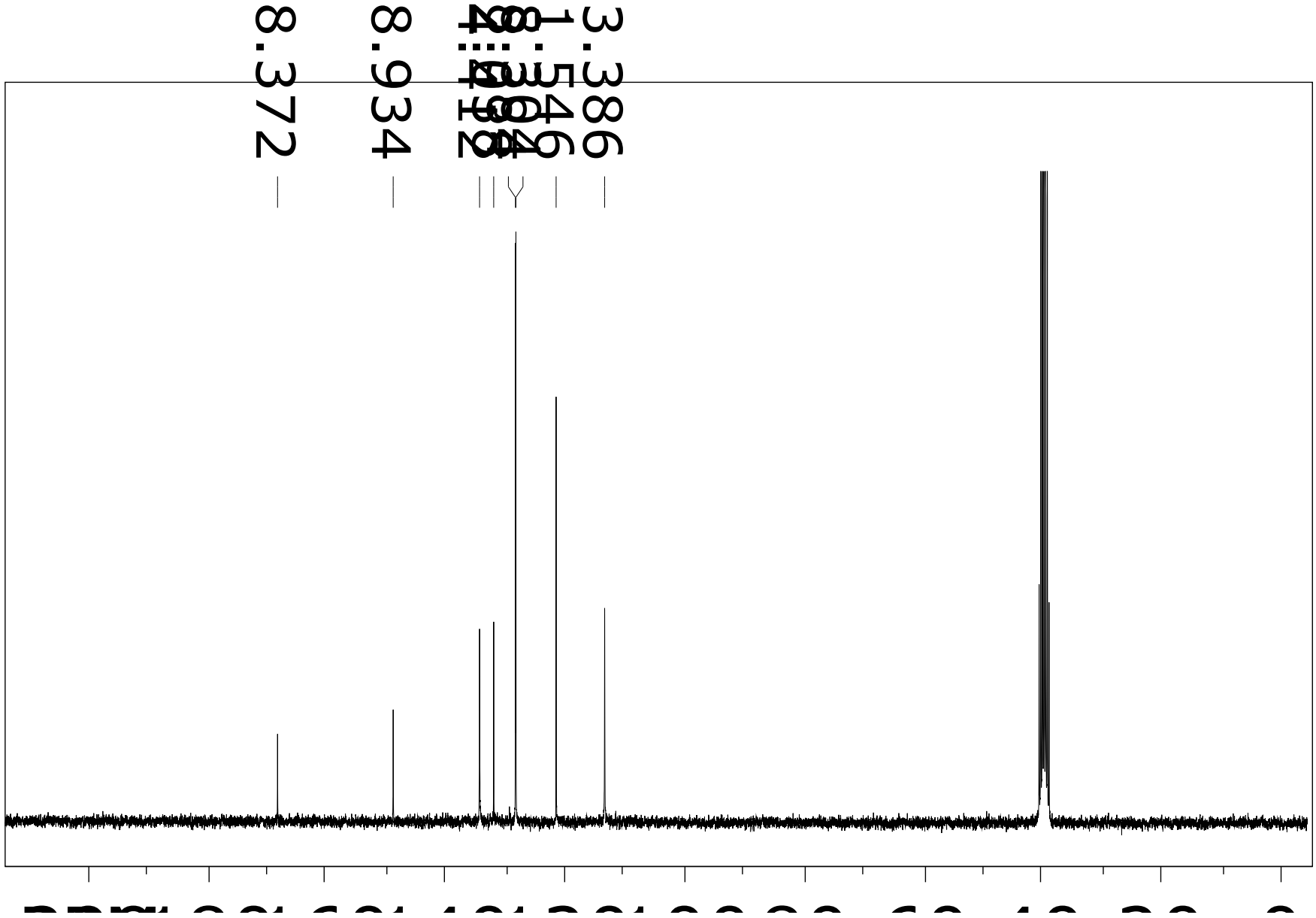
N-(1-methyl-3-phenyl-1H-pyrazol-5-yl)benzamide 3m



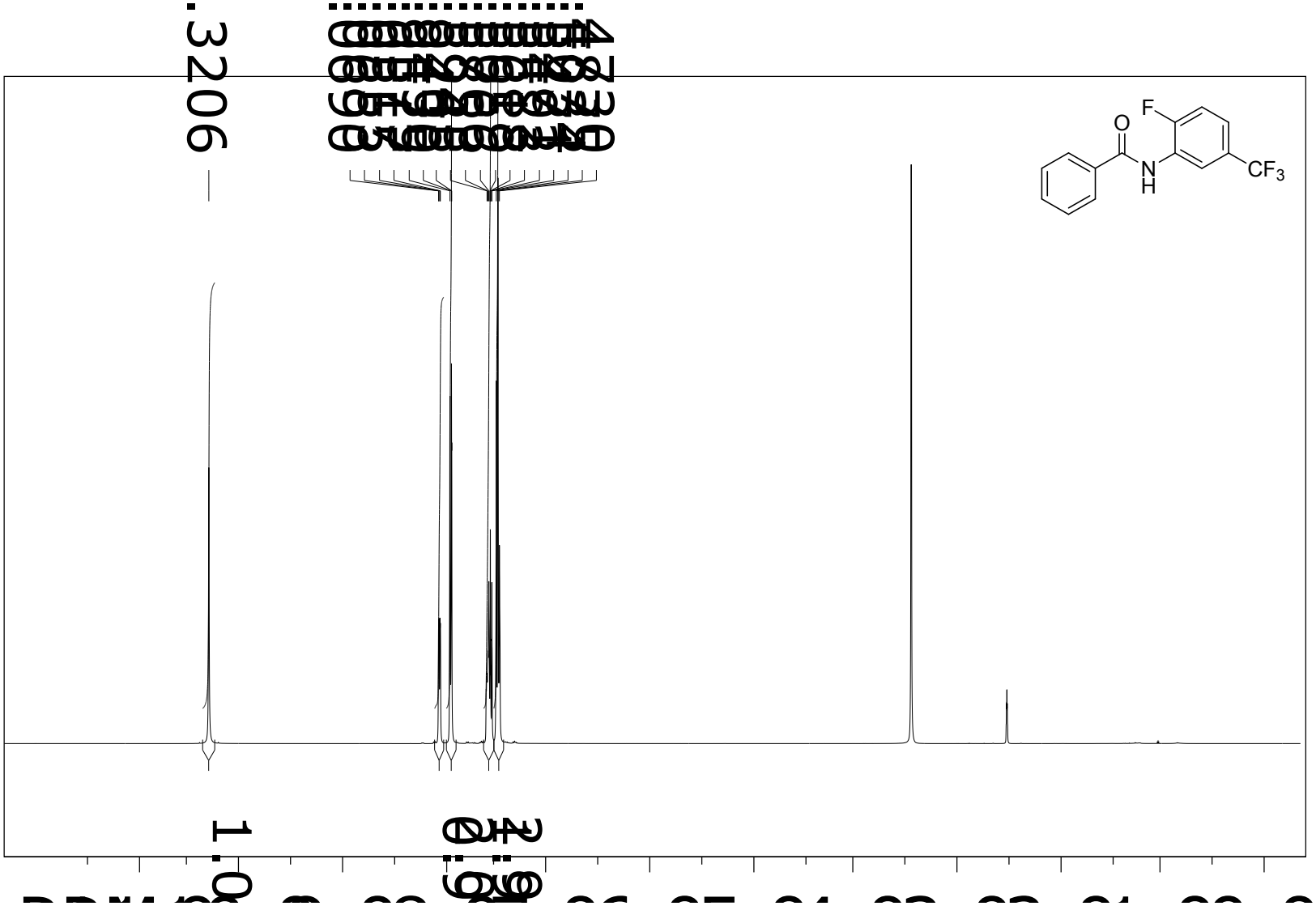

5.692
8.156
7.812
5.865

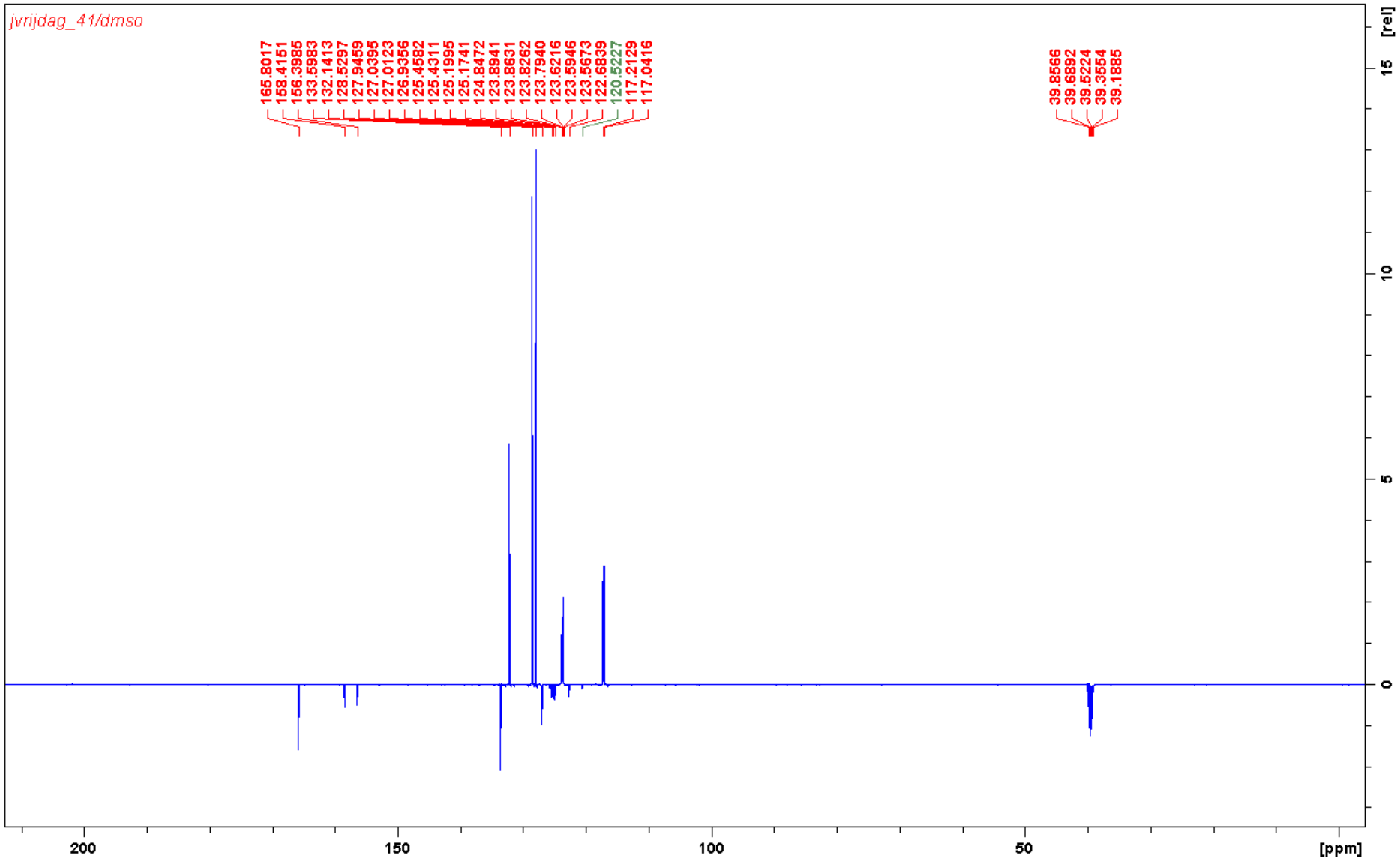
N-(1H-1,3-benzodiazol-2-yl)benzamide 3n



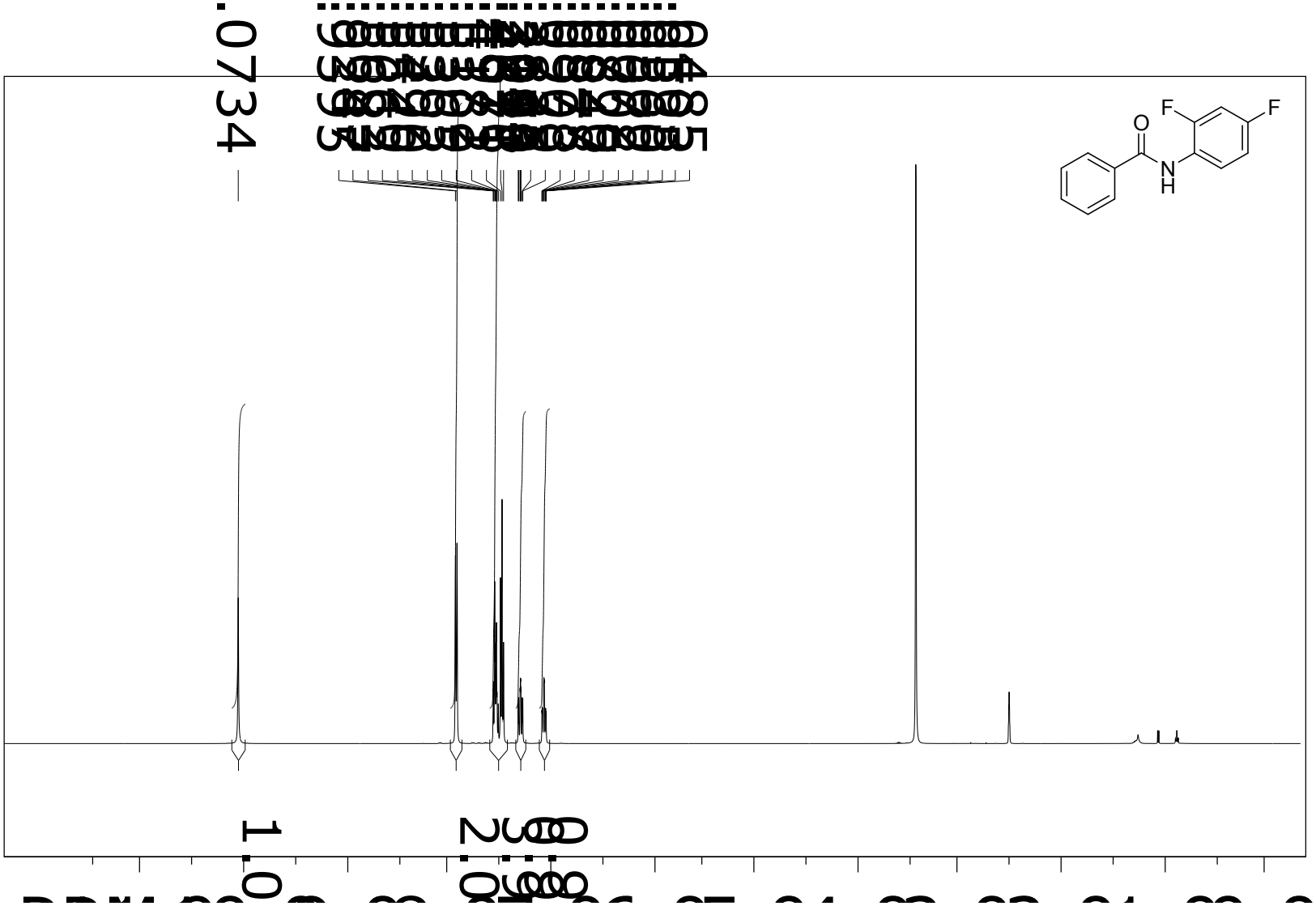

8.372
8.634
3.386

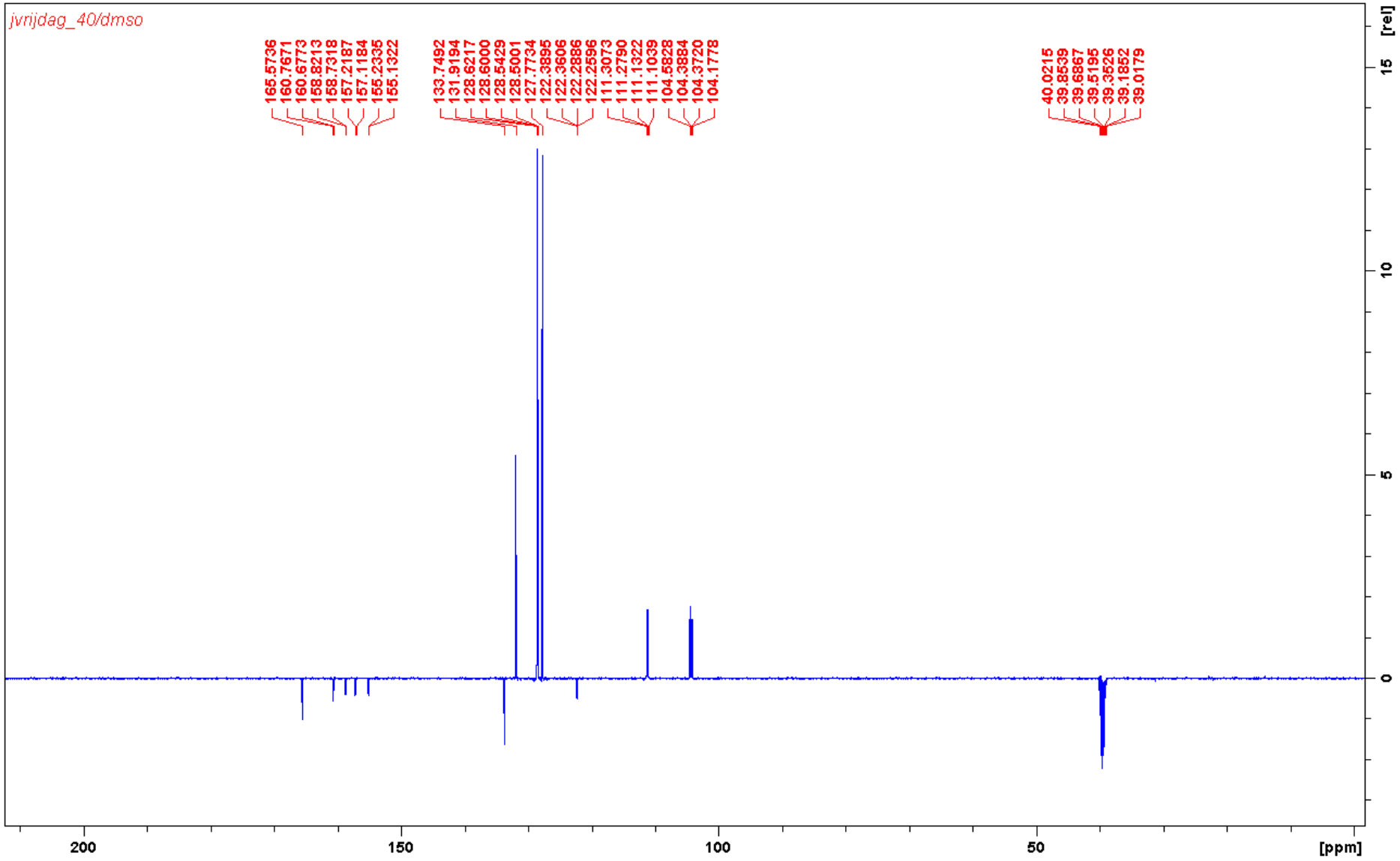
N-[2-fluoro-5-(trifluoromethyl)phenyl]benzamide 3o



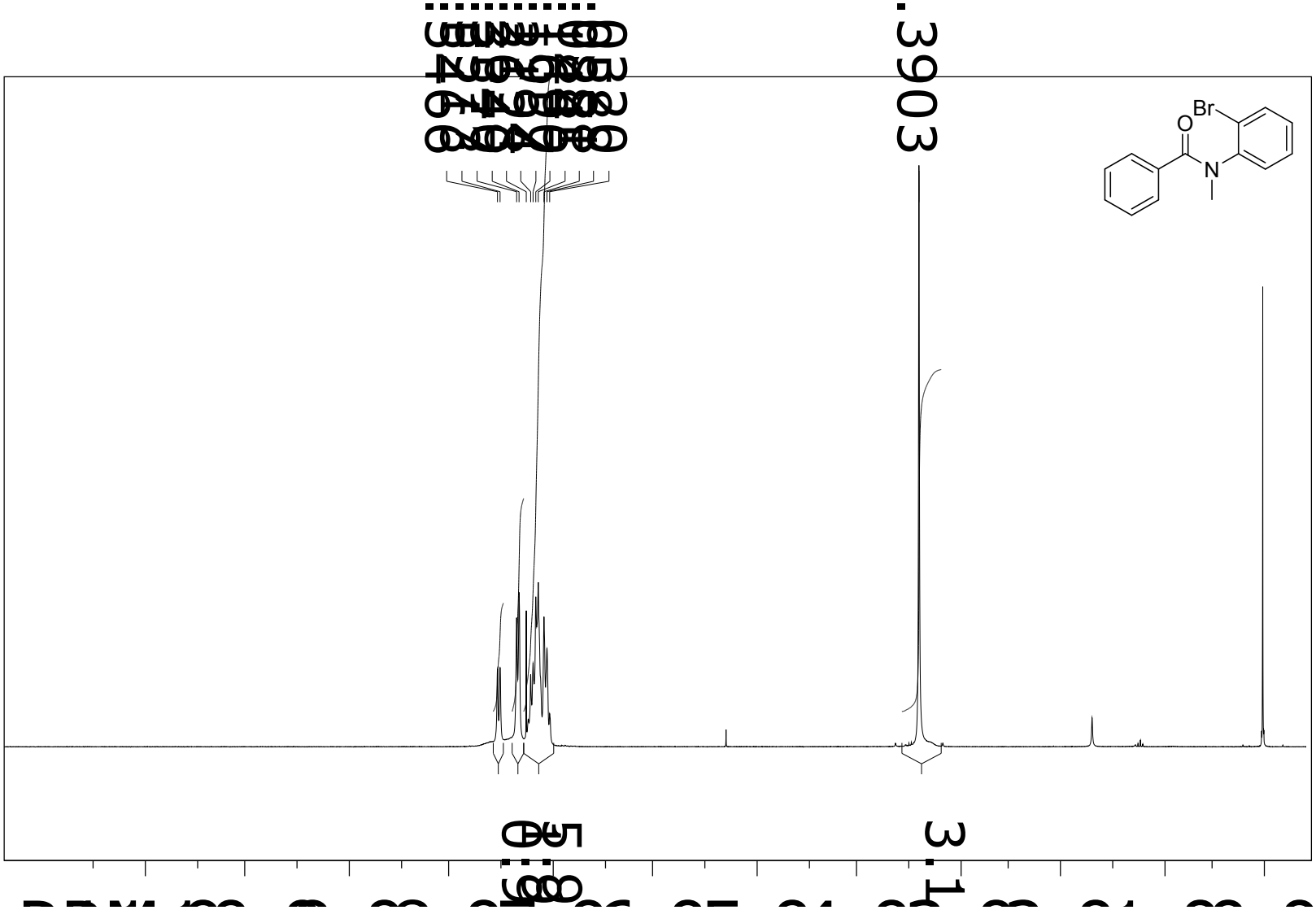

jvnjdag_41/dmso
165.8017
158.4151
156.3985
133.5983
132.1413
128.5297
127.9459
127.0395
127.0123
126.9356
125.4582
125.4311
125.1995
125.1741
124.8472
123.8941
123.8631
123.8262
123.7940
123.6216
123.5946
123.5673
122.6839
120.5227
117.2129
117.0416
39.8566
39.6892
39.5224
39.3554
39.1885
[rel]
15
10
5
0
200
150
100
50
[ppm]

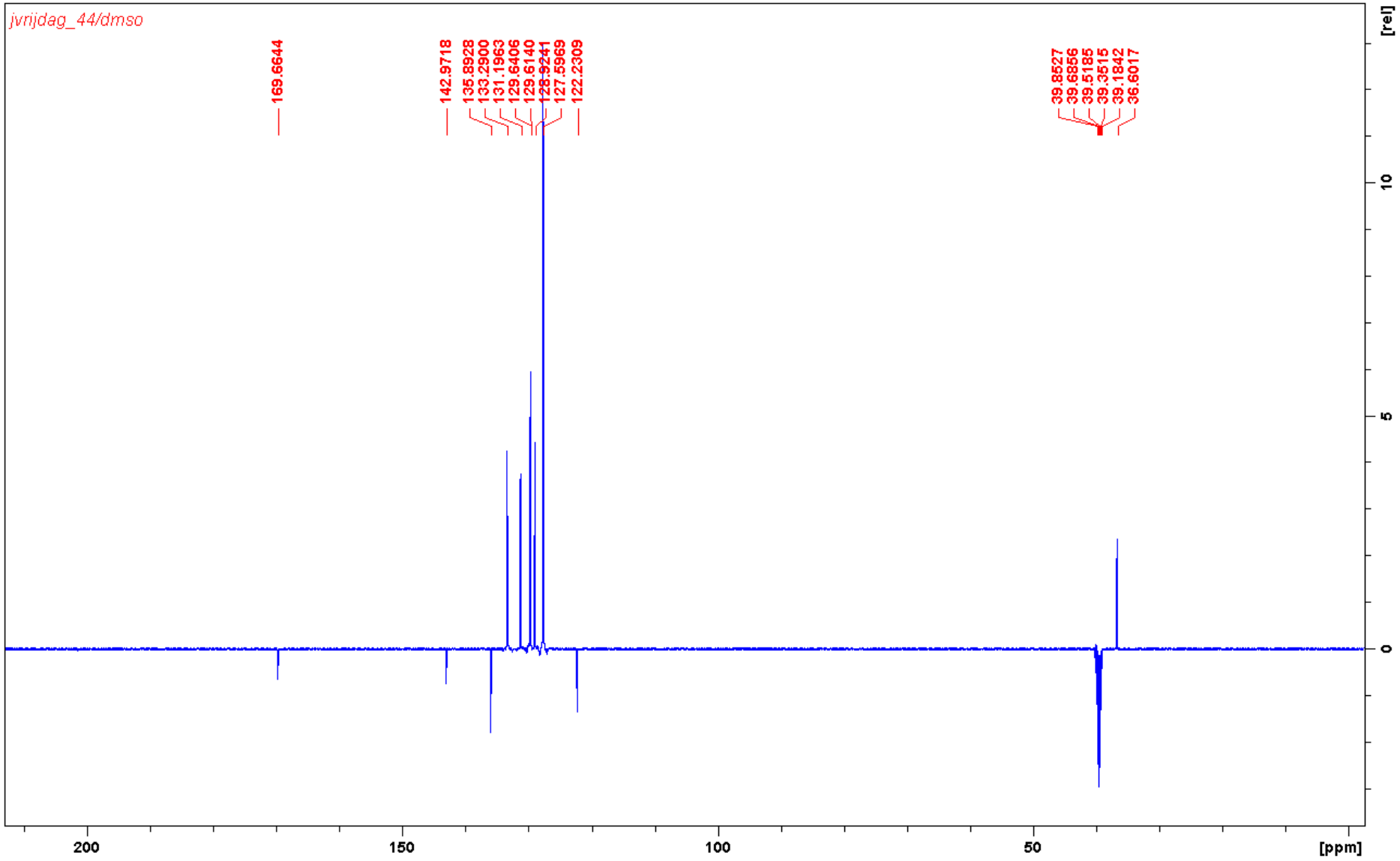
N-(2,4-difluorophenyl)benzamide 3p



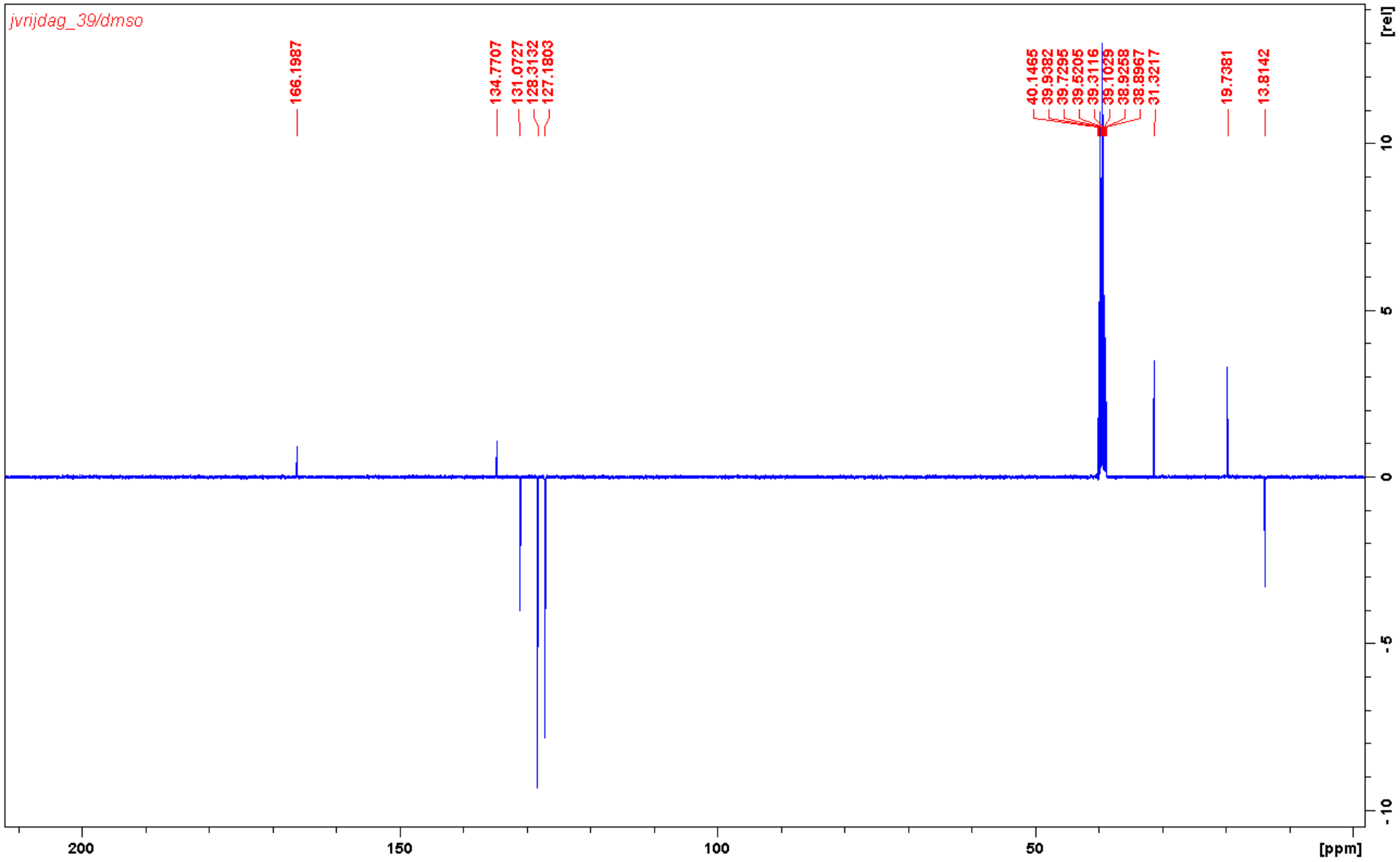

jvnjdag_40/dmso
165.5736
160.7671
160.6773
158.8213
158.7318
157.2187
157.1184
155.2335
155.1322
133.7492
131.9194
128.6217
128.6000
128.5429
128.5001
127.7734
122.3895
122.3606
122.2886
122.2596
111.3073
111.2790
111.1322
111.1039
104.5828
104.3884
104.3720
104.1778
40.0215
39.8539
39.6867
39.5195
39.3526
39.1852
39.0179
[rel]
15
10
5
0
200
150
100
50
[ppm]

N-(2-bromophenyl)-N-methylbenzamide 3q

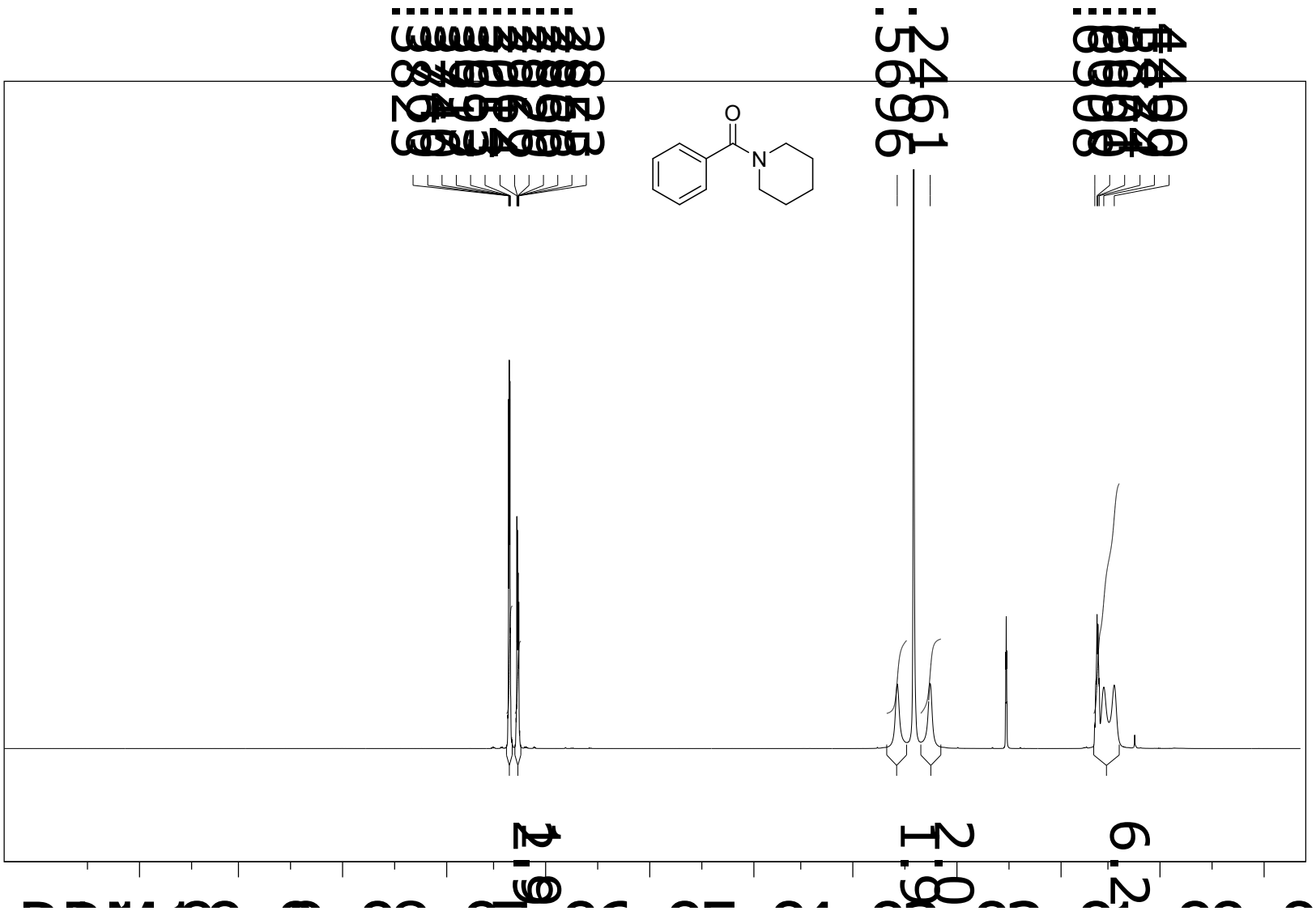


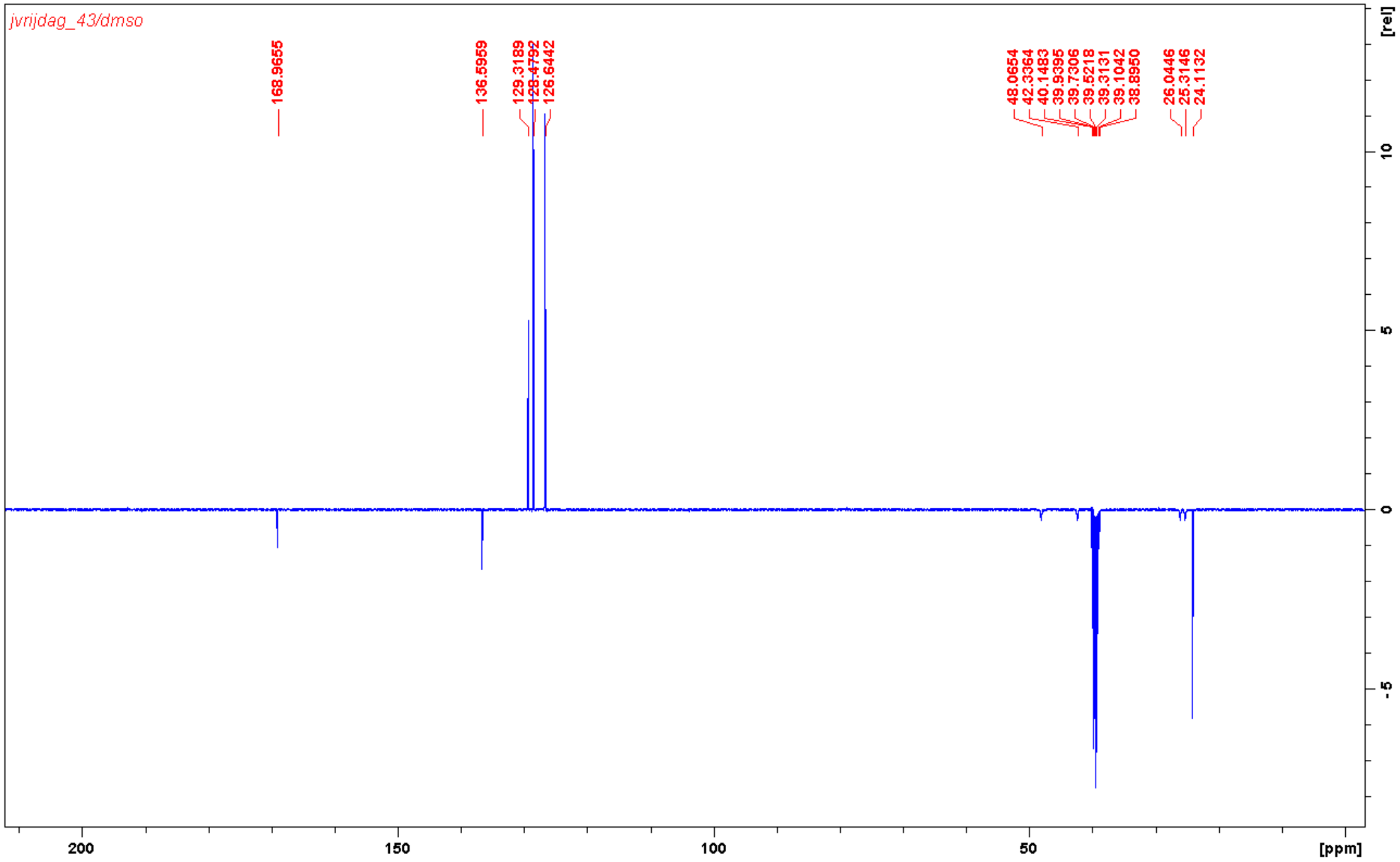

jvnjdag_44/dmso
169.6644
142.9718
135.8928
133.2900
131.1963
129.6406
129.6140
128.9241
127.5969
122.2309
39.8527
39.6856
39.5185
39.3515
39.1842
36.6017
[rel]
10
5
0
200
150
100
50
[ppm]

N-butylbenzamide 3r

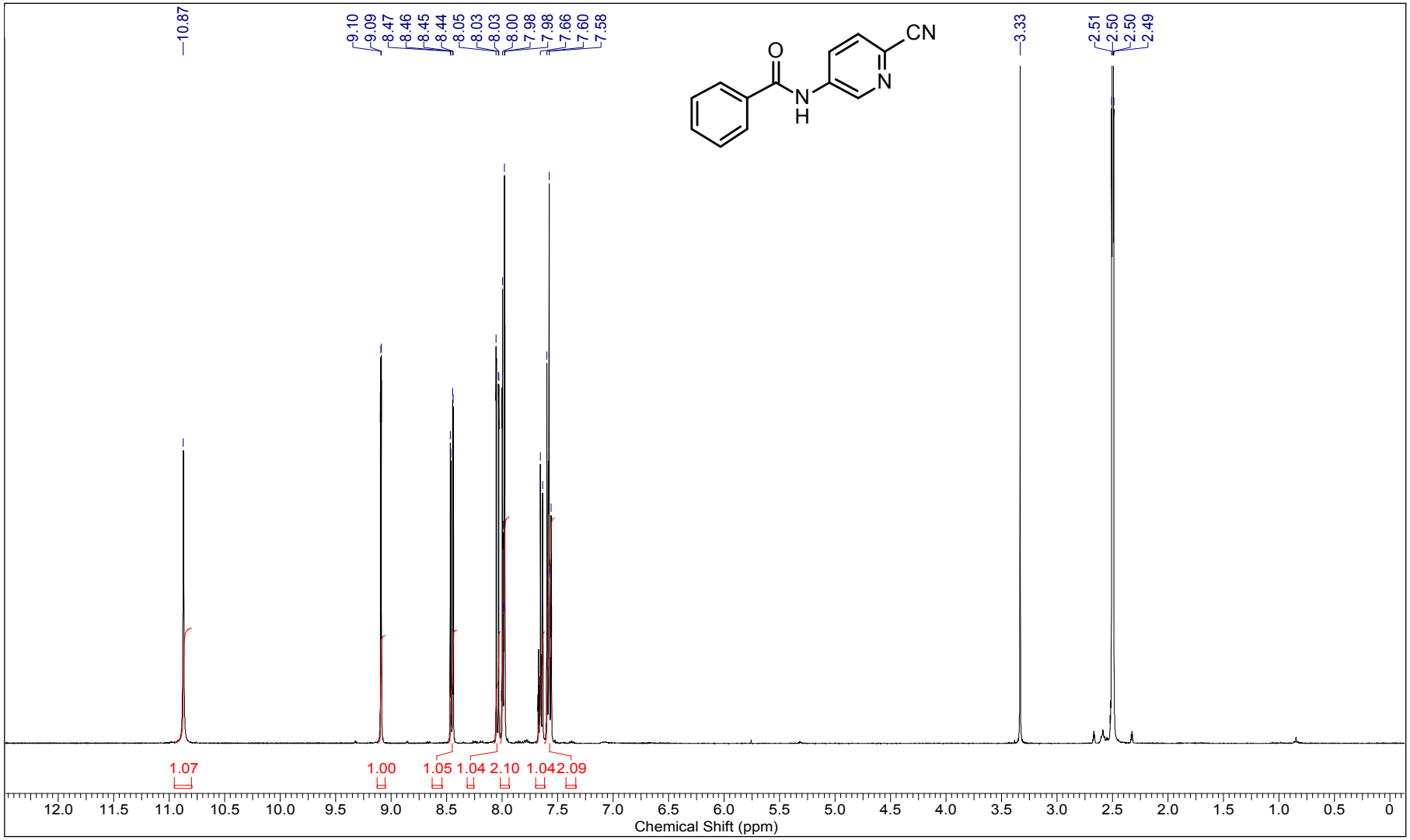

jvnjdag_39/dmso
166.1987
134.7707
131.0727
128.3132
127.1803
40.1465
39.9382
39.7295
39.5205
39.3116
39.1029
38.9258
38.8967
31.3217
19.7381
13.8142
[rel]
10
5
0
-5
-10
200
150
100
50
[ppm]

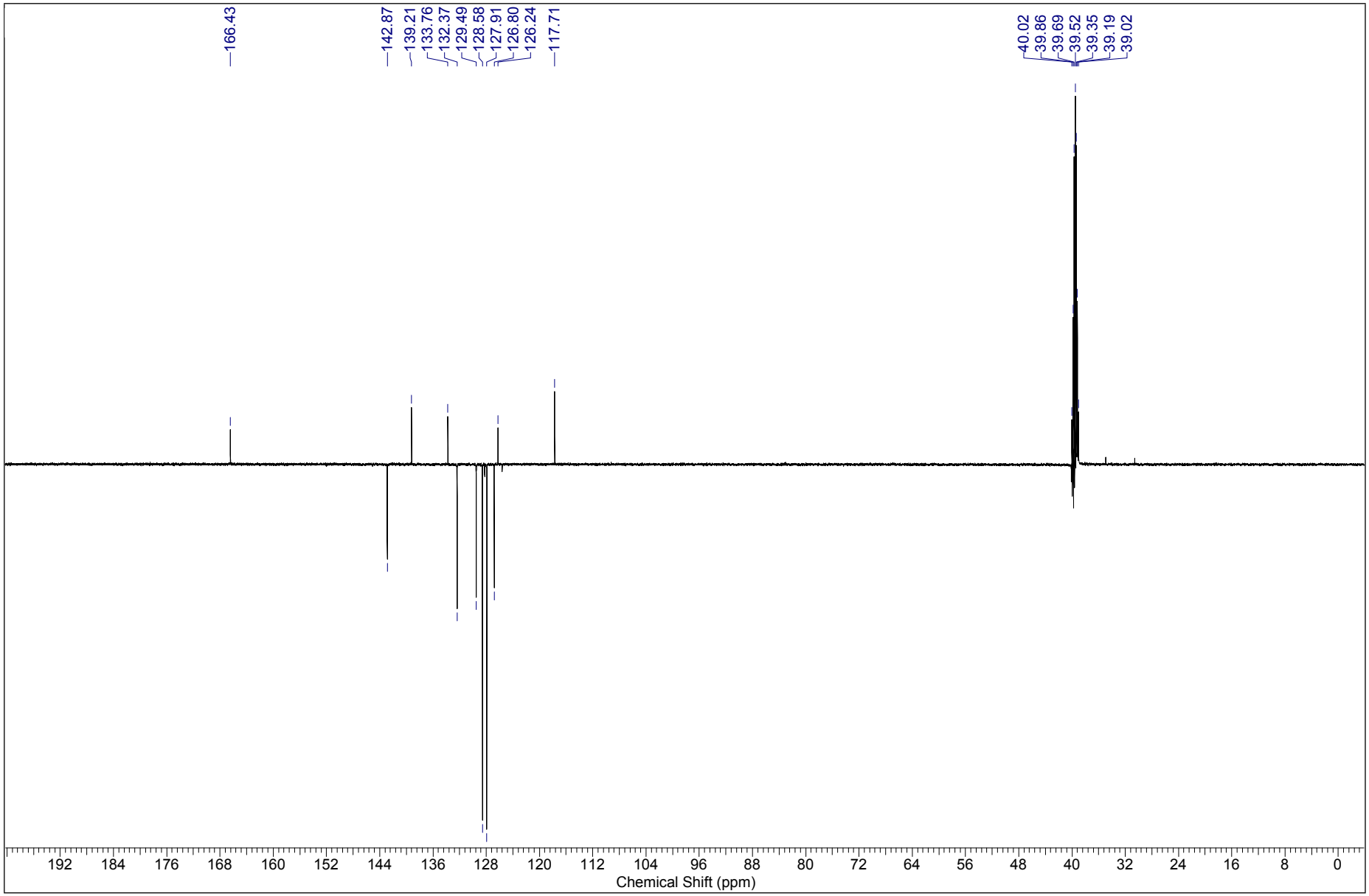
1-benzoylpiperidine 3s



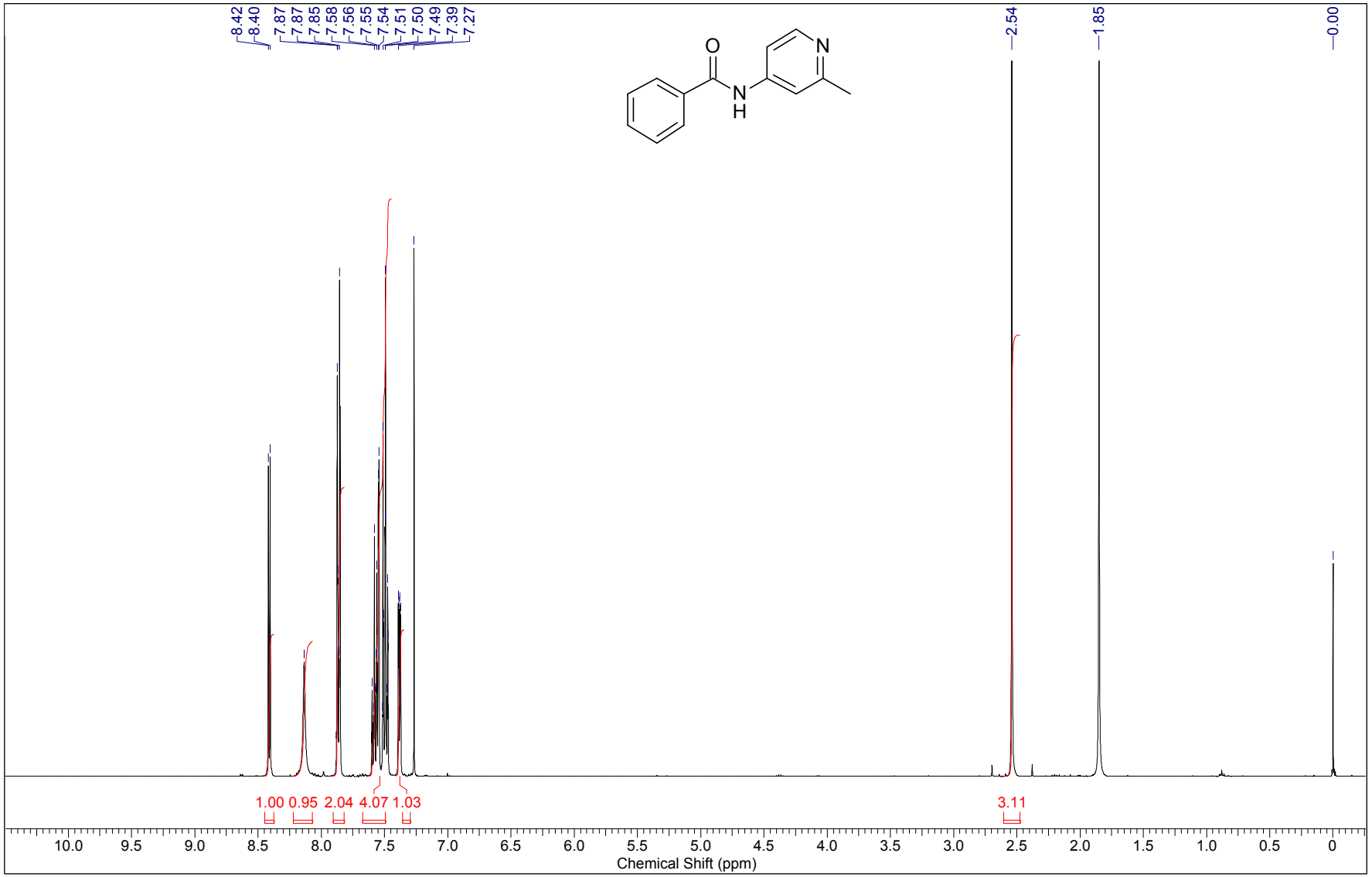

jvnjdag_43/dmso
168.9655
136.5959
129.3189
128.4792
126.6442
48.0654
42.3364
40.1483
39.9395
39.7306
39.5218
39.3131
39.1042
38.8950
26.0446
25.3146
24.1132
[rel]
10
5
0
-5
200
150
100
50
[ppm]

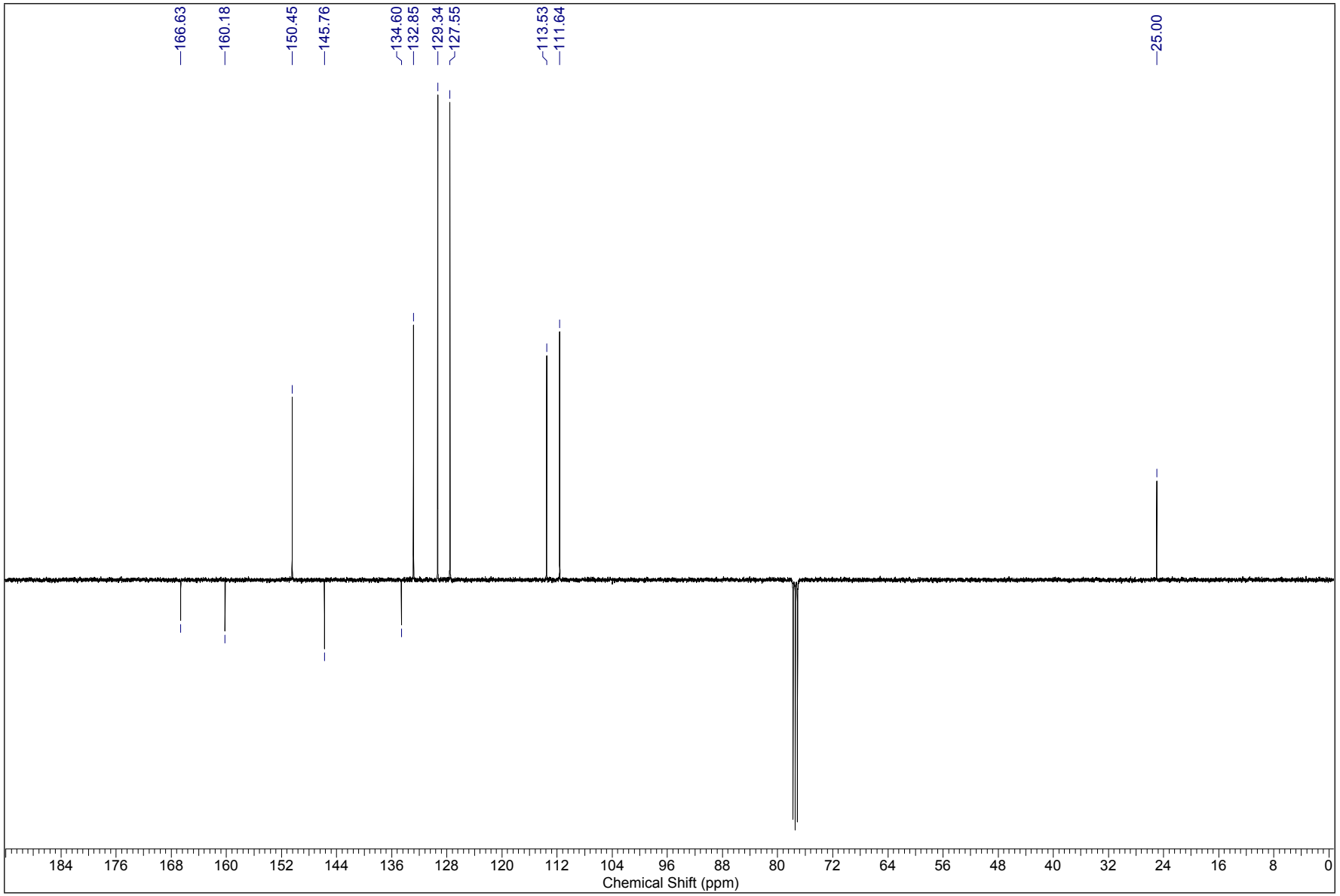
N-(6-cyanopyridin-3-yl)benzamide 3t



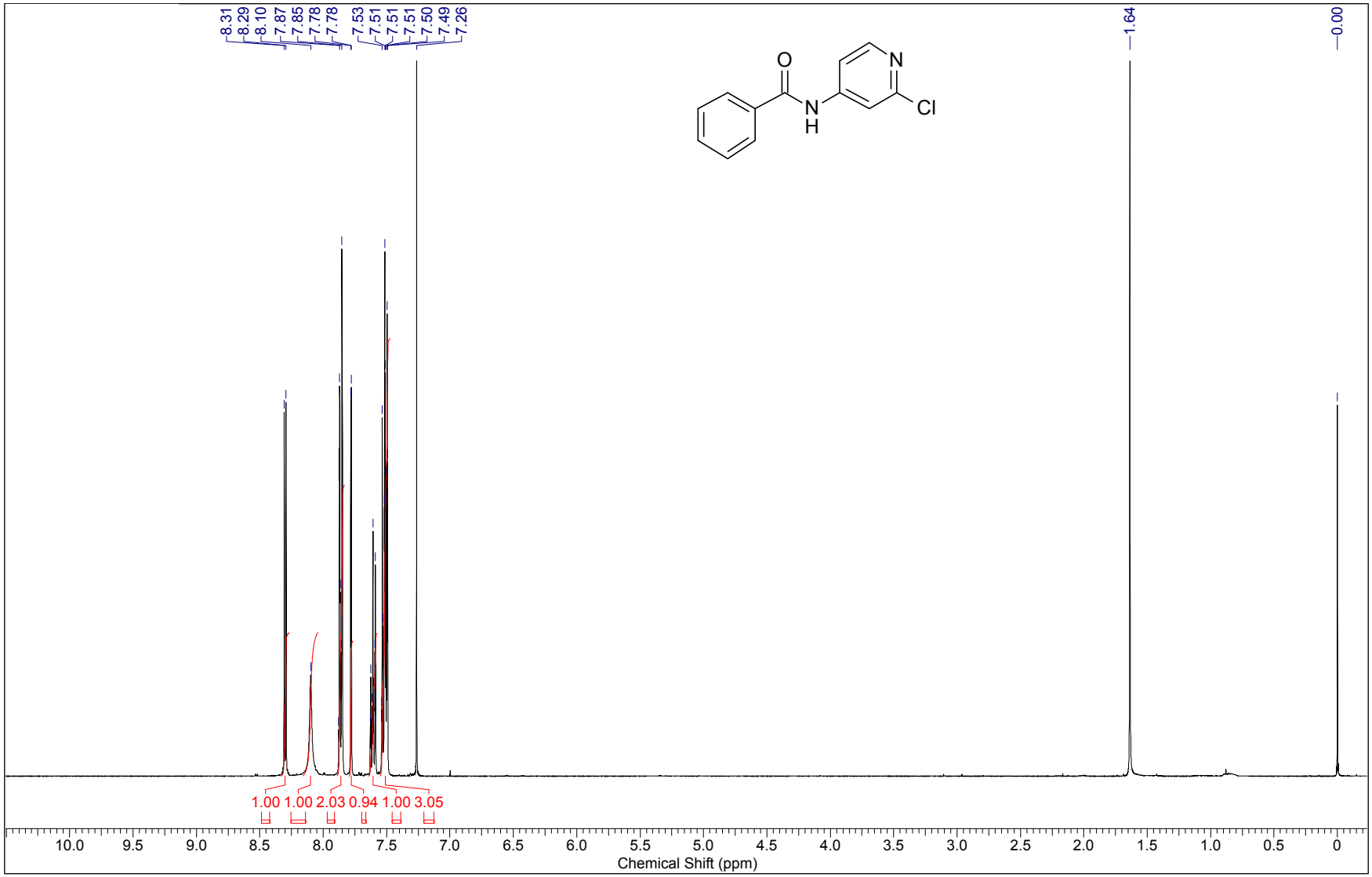

166.43
142.87
139.21
133.76
132.37
129.49
128.58
127.91
126.80
126.24
117.71
40.02
39.86
39.69
39.52
39.35
39.19
39.02
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

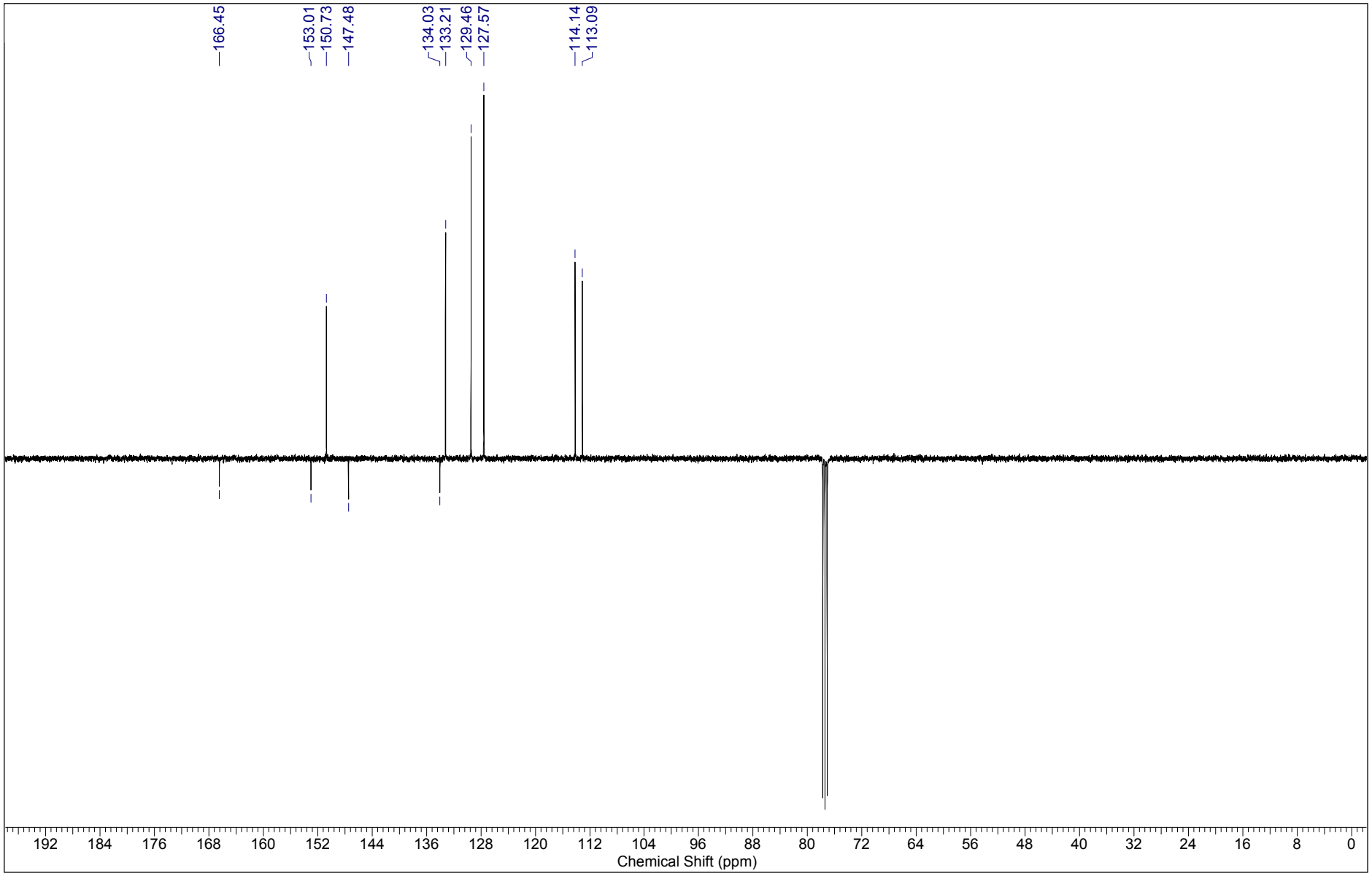
N-(2-methylpyridin-4-yl)benzamide 3u



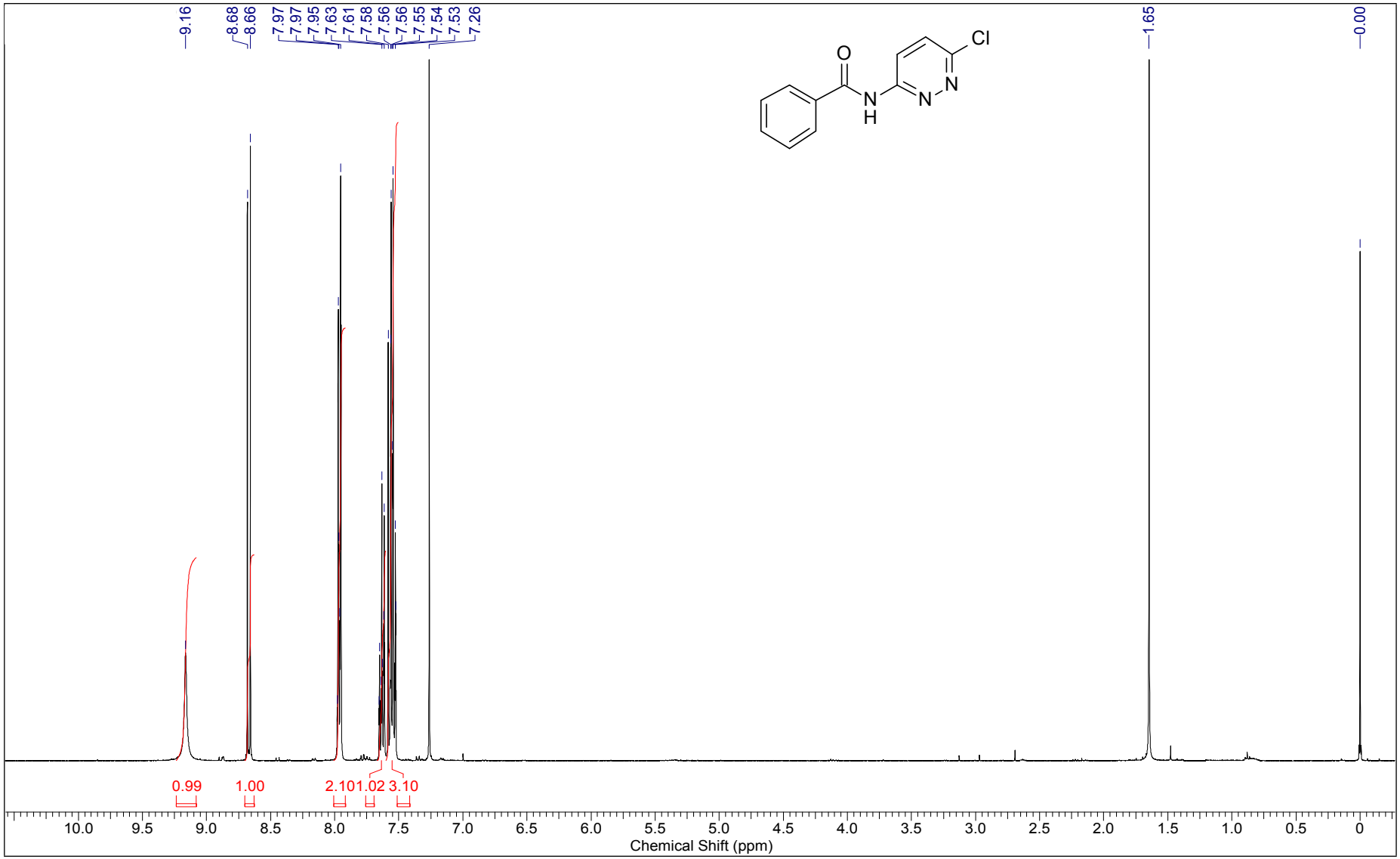

166.63
160.18
150.45
145.76
134.60
132.85
129.34
127.55
113.53
111.64
25.00
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

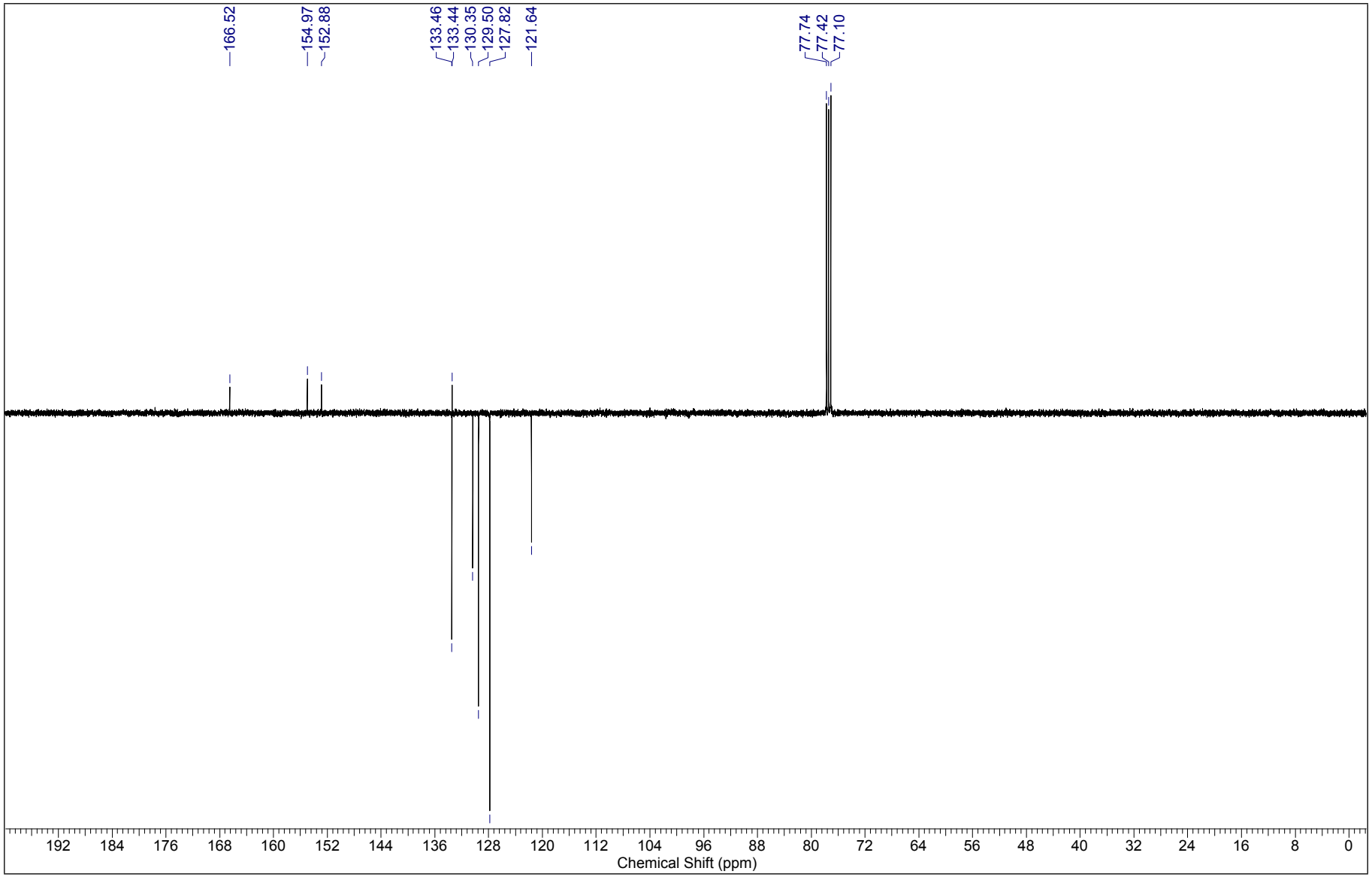
N-(2-chloropyridin-4-yl)benzamide 3v



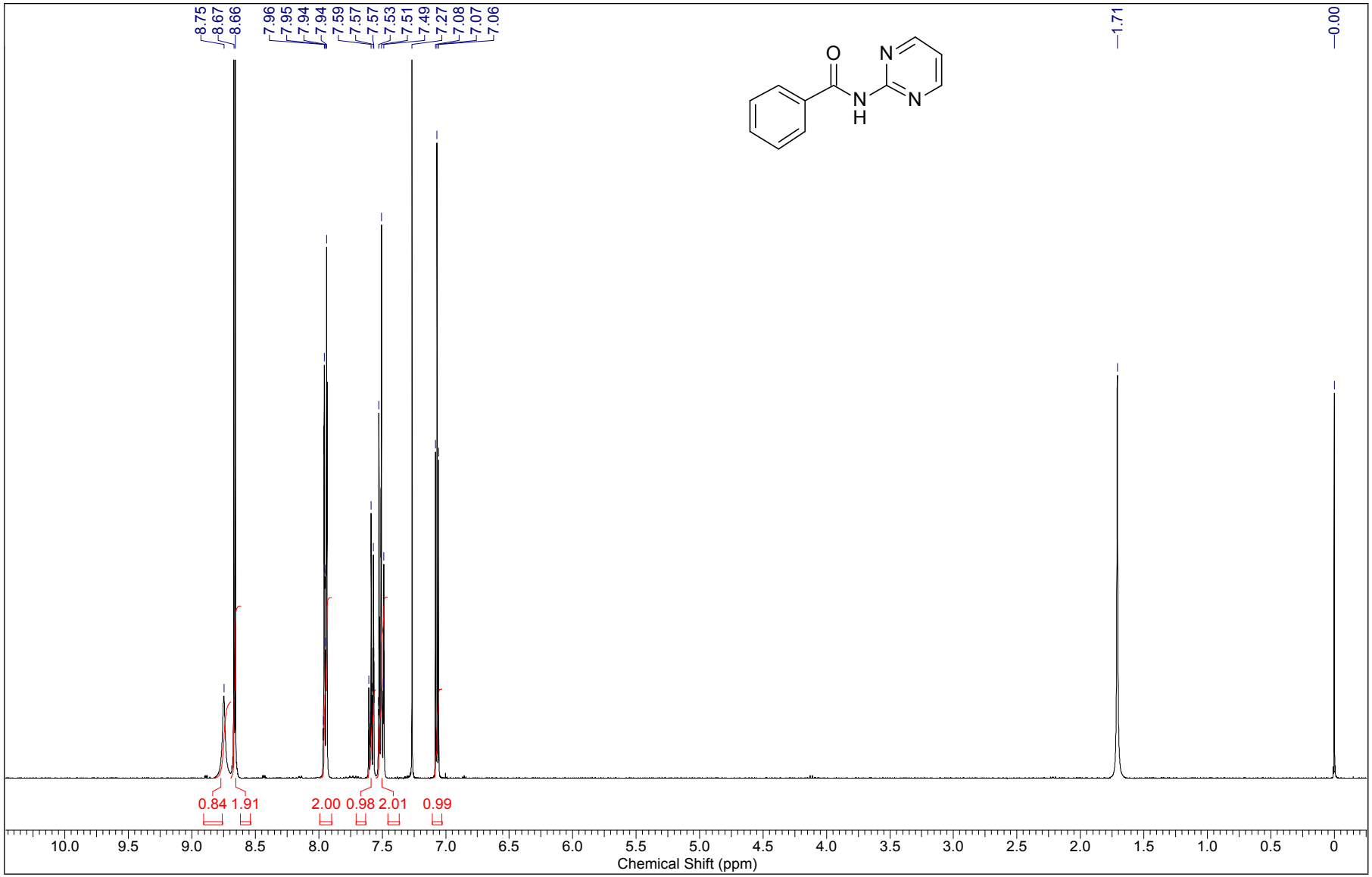

166.45
153.01
150.73
147.48
134.03
133.21
129.46
127.57
114.14
113.09
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

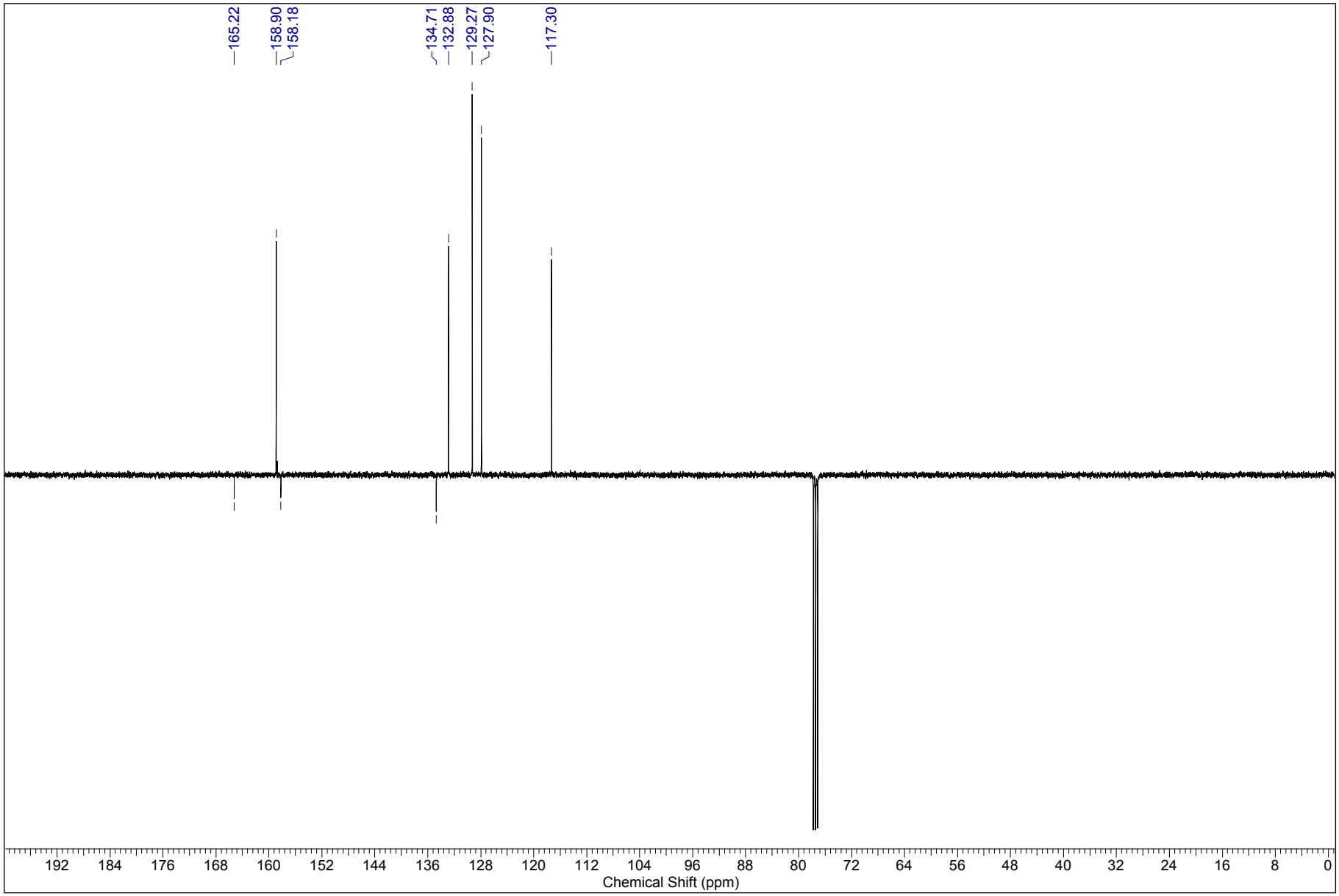
N-(6-chloropyridazin-3-yl)benzamide 3w




166.52
154.97
152.88
133.46
133.44
130.35
129.50
127.82
121.64
77.74
77.42
77.10
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

N-(pyrimidin-2-yl)benzamide 3x




165.22
158.90
158.18
134.71
132.88
129.27
127.90
117.30
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

N-(quinolin-2-yl)benzamide 3y