Base-Promoted Dynamic Amide Exchange: Efficient Access to Isotopically Enriched Tertiary Amides

Supplementary Information

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I. Material and equipment

***Reactants and solvents**:*

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware. Commercially available chemicals were purchased from BLDpharm, ABCR, Acros Organics, Sigma-Aldrich, Alfa Aesar, Combi-Blocks, Carbolution, Fluorochem, TCI Europe and Eurisotop (for ^{2}H and ^{13}C labeled chemicals) and used as received unless otherwise stated. The following solvents were dried by distillation over the drying agents indicated in parentheses: THF (Sodium), Dichloromethane (CaH_2). Additional anhydrous solvents were purchased from Acros Organics, SigmaAldrich, Alfa Aesar and stored over molecular sieves under an argon atmosphere.

***Purifications**:*

Flash chromatography purifications were performed on silica gel (Merck Kieselgel 60, grading 40-63 µm) or using automate Puriflash XS 520 Plus with pre-packed column RediSep® Rf (grading 35-70 µm). Reverse phase HPLC purification were performed using a Waters Autopurify system equipped with a *2545* binary pump, a *2998* DAD and a QDa quadrupole for detection.

Analysis:

Reactions were monitored by TLC carried out on silica 0.25 mm (60 F254, Merck) using UV light as visualizing agent. For staining, the TLC plates were dipped into a solution basic aqueous permanganate (1 g $KMnO_4$, 6 g K_2CO_3 and 0.1 g KOH in 100 mL H_2O) and developed with a heat gun.

Nuclear Magnetic Resonance (NMR) Spectroscopy: ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) were measured on a Brucker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet, nonet, multiplet (m). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m).

LC-MS spectra were recorded on a Waters Acquity UPLC® equipped PDA eλ Detector and SQ Detector 2, mobile phase A: H_2O + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid.
High-Resolution Mass Spectra (HRMS) were performed on a Waters Xevo® G2-XS QTof mass spectrometer.

Infrared spectra (IR) were obtained on a Perkin Elmer UATR TWO FTIR spectrophotometer and are reported as wavelength numbers (cm^{-1}).

Melting points (Mp) were obtained on a BÜCHI Melting Point B-545 and are reported in °C.

<u>For Carbon-14 radiolabeling:</u>

Carbon-14 reagents and compounds were handled by experimentalist uniquely trained in working with radioactive materials and operating in specialized laboratories.

Carbon-14 radioactivity was measured either with a PerkinElmer Ultra Gold liquid scintillation cocktail or with a PerkinElmer 3110TR liquid scintillation analyzer.

RadioHPLC and HPLC-UV analyses were conducted with a Waters Alliance 2695 connected to a MS detector Waters ZQ 2000 and a Scintillation Analyzer Berthold 514 (column Xbridge BEH C18 100x4.6 mm, 3.5 µm). Alternatively, they were also conducted on a Waters Acquity UPLC® equipped PDA eλ Detector and SQ Detector 2, mobile phase A: H_2O + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid and a Scintillation Analyzer Berthold 509 (Xbridge BEH C18 50x2.1, 1.7).

Mass spectra (ESI) for the calculation of molar activities were performed on a Waters Micromass ZQ spectrometer, UP3HDO C18 column (100x4.6 mm; 3 µm) and a linear gradient of 5% B to 95% A over 8 min followed by 100% B over 5 min and 5% B to 95% A over 3 min (mobile phase A = water with 0.1% formic acid; mobile phase S5 B = acetonitrile with 0.1% formic acid; flow rate = 1 mL/min; desolvation gas = nitrogen; capillary temperature = 275 °C).

When using $^{14}CO_2$: $^{14}CO_2$ (2.172 GBq mmol-1) was generated using a $^{14}CO_2$ manifold system (RC Tritec AG). Mass spectra (ESI) for the calculation of specific activities were obtained using a Waters Micromass ZQ spectrometer. Radiochemical purities were determined by Thin Layer Chromatography on TLC silica gel 60F254 glass plates (Merck) using a RITA scanner (Raytest) for the radioactive detection.

Determination of Isotopic Enrichment (IE)

For the determination of IE, two different methods were utilized based on NMR and MS. Both methods were in agreement with each other.

Determination of Isotopic Enrichment (IE) by NMR Spectroscopy

In case of transamidations with deuterium-labeled amines, the degree of ^{2}H incorporation could be calculated by ^{1}H NMR spectroscopy by measuring the decrease of signal intensity of the amine moiety. Signal integrations were calibrated on position in which no proton-deuterium exchange was observed. In some cases, due to base-promoted deuteration of substrates, this method could not be performed (see part IV.).

In case of amide bond methathesis with ^{13}C-labeled amides, the IE were calculated with ^{13}C NMR spectroscopy, exploiting $^{2\text{-}4}J_{^{13}C\text{-}^{13}C}$ coupling constants. Due to the presence of two isotopologues, some ^{13}C signals appear as a singlet (^{12}C-amide isotopologue) and a doublet (^{13}C-amide isotopologue) and are reported as (s+d). The relative integration of the doublet to the total signal intensity allows the direct calculation of amide bond metathesis rate.

Determination of Isotopic Enrichment (IE) and Isotopic Exchange by LC-MS and LC-HRMS.

Isotopic enrichment and exchange were determined using by deconvolution of the integrated isotope patterns using the *Isopat 2* algorithm. When necessary, HRMS-MS experiments were conducted for selective isotopic enrichment calculation.

As MS experiments are considered more precise, and take into account the isotopic purity of the amine moiety for transamidations rate calculation, MS results are indicated in the manuscript. Results are confirmed with NMR experiments.

II. Investigation on the ^{13}C-NMR signals of amides containing pyperidine and morpholine substitution

During the characterization of the non-deuterated and deuterated substrates, in most cases, some ^{13}C-NMR signals were missing (or the signal/noise ratio was too low). Those signals correspond to the carbon in *alpha*, and sometimes in *beta* position, of the nitrogen atom of the amide (σ ca. 40-50 ppm, see Figure S1). This phenomenon is due to the free rotation of both the C-C and C-N bonds in *alpha* of carbonyl group.

To demonstrate this phenomenon a ^{13}C NMR spectrum was recorded at 223 °K and compared to a spectrum of the same sample recorded at room temperature (~298 °K (Figure S1)). As the temperature is lowered the rotations of the different bonds are limited. This is shown by the appearance of two new signals corresponding to the carbons in *alpha* of the amide nitrogen atom. As this phenomenon is well described in the literature[1,2] and shown by this example, the missing carbons are indicated when necessary. However, no additional cold NMR analysis were performed for the characterization of the other substrates and labeled products.

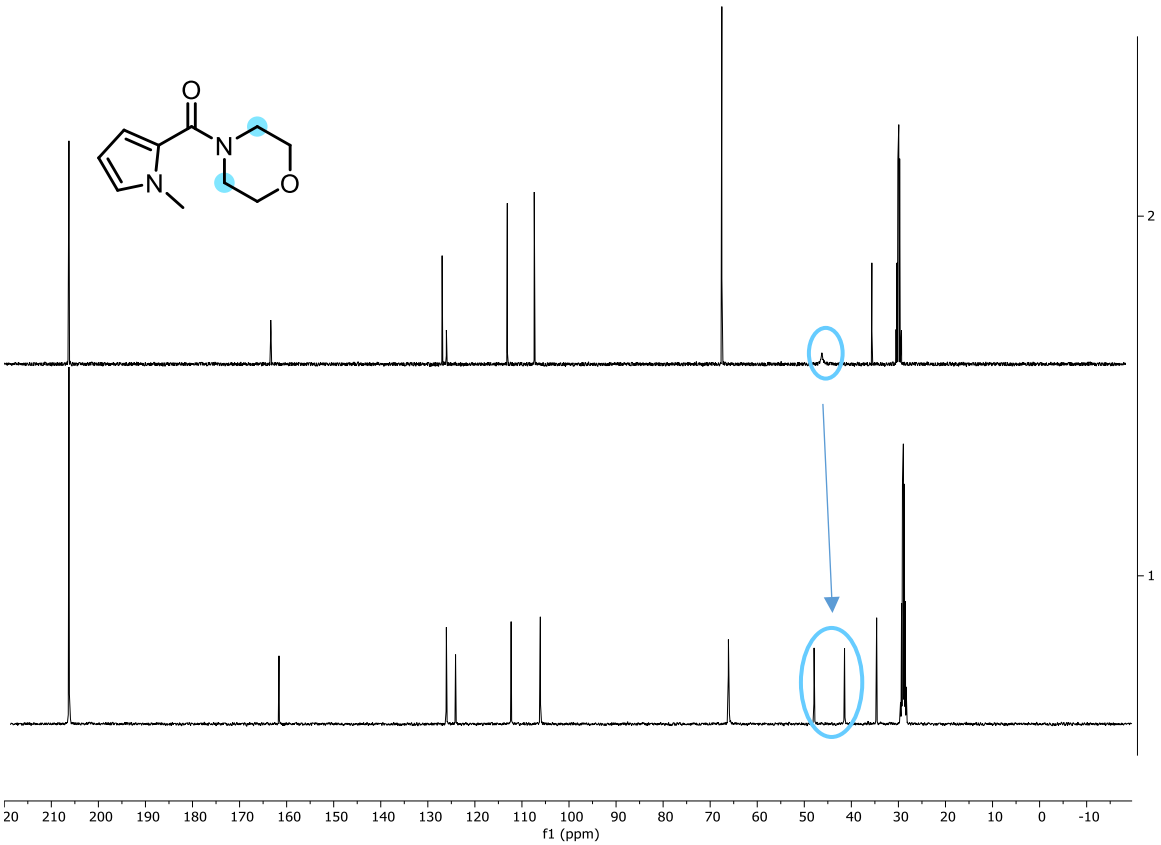


Figure S1: ^{13}C NMR spectra of the non-deuterated amide 20 (acetone-d6), BOTTOM- analysis performed at -50 °C, TOP- analysis performed at room temperature (~25 °C)

III. Synthetic procedure and analytical data of the starting materials

General procedure A: for the preparation unlabeled amides

In a 50 mL round bottom flask, a solution of carboxylic acid (1.0 equiv.) in anhydrous DCM (0.5 M) was stirred at room temperature under argon atmosphere. A catalytic amount of DMF (ca. 5 drops) was added, followed by the dropwise addition of oxalyl chloride (1.1 equiv.). The mixture was stirred at room temperature for 1h and then cooled at 0 °C. The amine (1.0 equiv.) was then added dropwise, followed by triethylamine (1.0 equiv.), and the reaction mixture was then stirred overnight at room temperature under argon. The reaction mixture was then diluted with water (10 mL) and dichloromethane (10 mL) and transferred into a separatory funnel. The organic layer was washed with NaOH (1M) twice, HCl (1M) and brine, then dried over $MgSO_4$, filtered and concentrated under vacuum. The pure amide was then obtained after purification on silica gel (cyclohexane/EtOAc as eluent, from 4/1 to 1/1).

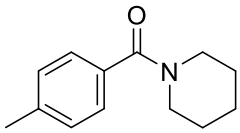
General procedure B: for the preparation of unlabeled amide with labile protons

In a 10 mL round bottom flask, a mixture of carboxylic acid (1.0 equiv.) and HCTU (1.1 equiv.) was stirred in anhydrous DMF (0.5 M) at room temperature under argon. Excess piperidine (2.5 equiv.) was then added, and the reaction mixture was stirred overnight at room temperature. After the night, 15mL of water were added to the reaction flask; the desired product precipitates (white powder) and was recovered by filtration with water washings.

General procedure C: for the preparation of unlabeled amides from acyl chloride

In a 50 mL round bottom flask, a solution of amine (1.2 equiv.) and triethylamine (1.2 equiv.) in anhydrous DCM (0.5 M) was cooled to 0 °C under argon atmosphere for 5 minutes. Benzoyl chloride (1.0 equiv.) was then added dropwise. The reaction mixture was then stirred overnight, slowly reaching room temperature. The reaction mixture was diluted with water (10 mL) and dichloromethane (10 mL) and transferred into a separatory funnel. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed with $NaHCO_3$ (sat.), HCl (1M) and brine, then dried over $MgSO_4$, filtered and concentrated under vacuum. The pure amide was then obtained after purification on silica gel (heptane/EtOAC as eluent, from 5/1 to 1/1).

piperidin-1-yl(p-tolyl)methanone (1)



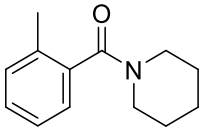
1

$C_{13}H_{17}NO$
MW: 203.29 g.mol^{-1}
White solid
Yield: 50%

Following the general procedure A, amide 1 was obtained as a white solid (1.017 g, 4.98 mmol, 50%). The spectral data (^{1}H-NMR) was consistent with reported one.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 2H), 3.69 (bs, 2H), 3.36 (bs, 2H), 2.39 (s, 3H), 1.66 (m, 4H), 1.53 (bs, 2H).

piperidin-1-yl(m-tolyl)methanone (3)



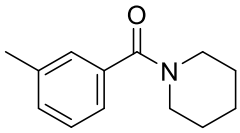
3

$C_{13}H_{17}NO$
MW: 203.29 g.mol^{-1}
White solid
Yield: 43%

Following the general procedure A, amide 3 was obtained as a white solid (266 mg, 1.31 mmol, 43%). The spectral data (^{1}H-NMR) was consistent with reported one.[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.23 (m, 1H), 7.22 – 7.12 (m, 3H), 3.89 – 3.76 (m, 1H), 3.74 – 3.63 (m, 1H), 3.22 – 3.12 (m, 2H), 2.31 (s, 3H), 1.66 (bs, 4H), 1.46 (bs, 2H).

piperidin-1-yl(o-tolyl)methanone (2)



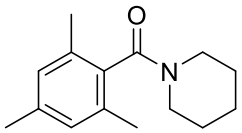
2

$C_{13}H_{17}NO$
MW: 203.29 g.mol^{-1}
White solid
Yield: 86%

Following the general procedure A, amide 2 was obtained as a white solid (876 mg, 4.31 mmol, 86%). The spectral data (^{1}H-NMR) was consistent with reported one.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 1H), 7.22 – 7.12 (m, 3H), 3.70 (bs, 2H), 3.34 (bs, 2H), 2.36 (s, 3H), 1.67 (bs, 4H), 1.52 (bs, 2H).

mesityl(piperidin-1-yl)methanone (37)



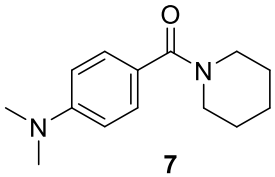
37

$C_{15}H_{21}NO$
MW: 231.34 g.mol^{-1}
Pale-yellow oil
Yield: 73%

Following the general procedure A, amide 37 was obtained as a pale-yellow oil (839 mg, 3.63 mmol, 73%).
The spectral data (^{1}H-NMR) was consistent with reported one.[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 2H), 3.77 (bs, 2H), 3.22 – 3.09 (m, 2H), 2.27 (s, 3H), 2.21 (s, 6H), 1.69 – 1.62 (m, 4H), 1.46 (bs, 2H).

(4-(dimethylamino)phenyl)(piperidin-1-yl)methanone (7)



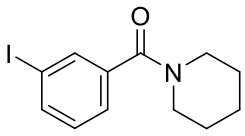
7

$C_{14}H_{20}N_2O$
MW: 232.33 g.mol^{-1}
White solid
Yield: 42%

Following the general procedure A, amide 7 was obtained as a white solid (97 mg, 0.42 mmol, 42%).
The spectral data (^{1}H-NMR) was consistent with reported one.[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.29 (m, 2H), 6.69 – 6.62 (m, 2H), 3.55 (bs, 4H), 2.97 (s, 6H), 1.70 – 1.62 (m, 2H), 1.62 – 1.52 (m, 4H).

(3-iodophenyl)(piperidin-1-yl)methanone (17)



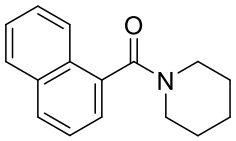
17

$C_{12}H_{14}INO$
MW: 315.15 g.mol^{-1}
White solid
Yield: 45%

Following the general procedure A, amide 17 was obtained as a white solid (141 mg, 0.45 mmol, 45%).
The spectral data (^{1}H-NMR) was consistent with reported one.[8]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 – 7.69 (m, 2H), 7.34 (ddd, *J* = 7.6, 1.5, 1.1 Hz, 1H), 7.13 (dd, *J* = 8.3, 7.6 Hz, 1H), 3.69 (bs, 2H), 3.32 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H).

naphthalen-1-yl(piperidin-1-yl)methanone (4)



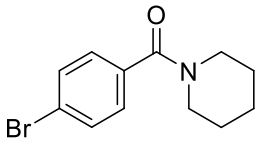
4

$C_{16}H_{17}NO$
MW: 239.32 g.mol^{-1}
White solid
Yield: 58%

Following the general procedure A, amide 4 was obtained as a white solid (139 mg, 0.58 mmol, 58%).
The spectral data (^{1}H-NMR) was consistent with reported one.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.81 (m, 3H), 7.55 – 7.43 (m, 3H), 7.42 – 7.36 (m, 1H), 3.97 – 3.78 (m, 2H), 3.12 (t, *J* = 5.2 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.70 – 1.61 (m, 2H), 1.45 – 1.31 (m, 2H).

(4-bromophenyl)(piperidin-1-yl)methanone (15)



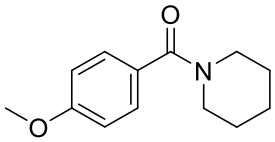
15

$C_{12}H_{14}BrNO$
MW: 268.15 g.mol^{-1}
Pale-yellow solid
Yield: 40%

Following the general procedure A, amide 15 was obtained as a pale-yellow solid (106 mg, 0.40 mmol, 40%).
The spectral data (^{1}H-NMR) was consistent with reported one.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 – 7.50 (m, 2H), 7.30 – 7.24 (m, 2H), 3.69 (bs, 2H), 3.32 (bs, 2H), 1.67 (bs, 4H), 1.51 (bs, 2H).

(4-methoxyphenyl)(piperidin-1-yl)methanone (8)



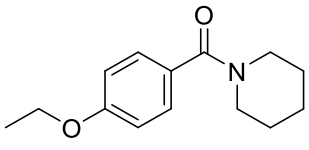
8

$C_{13}H_{17}NO_2$
MW: 219.28 g.mol^{-1}
Pale yellow oil
Yield: 54%

Following the general procedure A, amide 8 was obtained as a pale-yellow oil (592 mg, 2.70 mmol, 54%).
The spectral data (^{1}H-NMR) was consistent with reported one.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 2H), 6.93 – 6.87 (m, 2H), 3.83 (s, 3H), 3.74 – 3.29 (m, 4H), 1.71 – 1.63 (m, 2H), 1.60 (bs, 4H).

(4-ethoxyphenyl)(piperidin-1-yl)methanone (9)



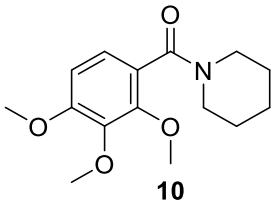
9

$C_{14}H_{19}NO_2$
MW: 233.31 g.mol^{-1}
White solid
Yield: 56%

Following the general procedure A, amide 9 was obtained as a white solid (130 mg, 0.56 mmol, 56%). The spectral data (^{1}H-NMR) was consistent with reported one.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 2H), 6.91 – 6.78 (m, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.78 – 3.20 (m, 4H), 1.66 – 1.59 (bs, 2H), 1.59 – 1.44 (m, 4H), 1.36 (t, *J* = 7.0 Hz, 3H).

piperidin-1-yl(2,3,4-trimethoxyphenyl)methanone (10)



10

$C_{15}H_{21}NO_4$
MW: 279.34 g.mol^{-1}
White solid
Yield: 70%

Following the general procedure A, amide 10 was obtained as a white solid (196 mg, 0.70 mmol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.5 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.76 (bs, 1H), 3.71 – 3.61 (m, 1H), 3.22 (bs, 2H), 1.72-1.54 (m, 5H), 1.44 (bs, 1H).

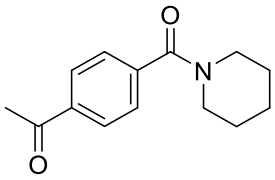
^{13}C NMR (101 MHz, $CDCl_3$): δ 167.5, 154.5, 150.2, 142.1, 124.3, 122.2, 107.7, 61.8, 61.2, 56.2, 48.4, 42.9, 26.5, 25.8, 24.7.

HRMS (ESI-TOF) m/z calc'd for $C_{15}H_{22}NO_4$: 280.1549 $[M+H]^+$; found 280.1549.

FTIR: 2998, 2936, 2854, 1619, 1594, 1500, 1448, 1428, 1408, 1274, 1220, 1125, 1092, 1036, 998, 949, 907, 890, 845, 822, 807, 751, 695, 682, 665, 626, 597, 567, 537, 474.

Melting Point: 52 – 55 °C.

1-(4-(piperidine-1-carbonyl)phenyl)ethan-1-one (11)



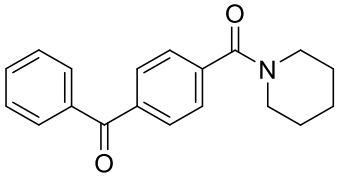
11

$C_{14}H_{17}NO_2$
MW: 231.30 g.mol^{-1}
White solid
Yield: 67%

Following the general procedure A, amide 11 was obtained as a white solid (155 mg, 0.67 mmol, 67%). The spectral data (^{1}H-NMR) was consistent with reported one.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.90 (m, 2H), 7.45 – 7.38 (m, 2H), 3.75 – 3.53 (m, 2H), 3.24 (bs, 2H), 2.56 (s, 3H), 1.71 – 1.55 (m, 4H), 1.53 – 1.36 (bs, 2H).

(4-benzoylphenyl)(piperidin-1-yl)methanone (12)



12

$C_{19}H_{19}NO_2$
MW: 293.37 g.mol^{-1}
White solid
Yield: 44%

Following the general procedure A, amide 12 was obtained as a white solid (129 mg, 0.44 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.77 (m, 4H), 7.65 – 7.56 (m, 1H), 7.54 – 7.44 (m, 4H), 3.74 (bs, 2H), 3.34 (bs, 2H), 1.70 (bs, 4H), 1.53 (bs, 2H).

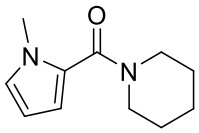
^{13}CNMR (101 MHz, CDCl3): δ 196.1, 169.2, 140.3, 138.4, 137.2, 132.7, 130.1 (2C), 130.0 (2C), 128.4 (2C), 126.7 (2C), 48.7, 43.2, 26.6, 25.6, 24.5.

HRMS (ESI-TOF) m/z calc'd for $C_{19}H_{20}NO_2$: 294.1494 $[M+H]^+$; found 294.1493.

FTIR: 2943, 2920, 2855, 1655, 1619, 1503, 1443, 1398, 1374, 1312, 1272, 1173, 1147, 1107, 1024, 999, 936, 919, 885, 850, 799, 764, 718, 699, 674, 643, 587, 560, 521, 471, 431.

Melting Point: 120 – 122 °C.

(1-methyl-1H-pyrrol-2-yl)(piperidin-1-yl)methanone (27)



27

$C_{11}H_{16}N_2O$
MW: 192.26 g.mol^{-1}
Colorless oil
Yield: 43%

Following the general procedure A, amide 27 was obtained as a colorless oil (166 mg, 0.86 mmol, 43%).

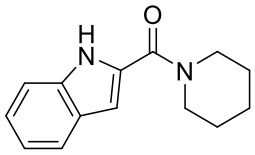
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (dd, *J* = 2.5, 1.8 Hz, 1H), 6.31 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.07 (dd, *J* = 3.8, 2.5 Hz, 1H), 3.76 (s, 3H), 3.69 – 3.64 (m, 4H), 1.73 – 1.65 (m, 2H), 1.65 – 1.55 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 125.9, 125.8, 112.2, 106.8, 35.7, 26.4 (2C), 24.9. (2 carbons missing due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calc'd for $C_{11}H_{17}N_2O$: 193.1341[M+H]$^+$; found 193.1337.

FTIR: 2936, 2854, 2239, 1611, 1532, 1470, 1436, 1366, 1307, 1255, 1235, 1163, 1128, 1106, 1059, 1020, 992, 955, 911, 869, 853, 823, 750, 722, 644, 608, 555, 496, 455.

(1H-indol-2-yl)(piperidin-1-yl)methanone (24)



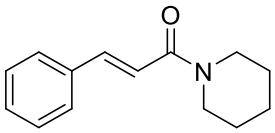
24

$C_{14}H_{16}N_2O$
MW: 228.30 g.mol^{-1}
White solid
Yield: 94%

Following the general procedure B, amide 24 was obtained as a white solid (214 mg, 0.94 mmol, 94%). The spectral data (^{1}H-NMR) was consistent with reported one.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (bs, 1H), 7.65 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.42 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.2 Hz,1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.77 (dd, *J* = 2.2, 1.0 Hz, 1H), 3.97 – 3.72 (m, 4H), 1.78 – 1.64 (m, 6H).

(E)-3-phenyl-1-(piperidin-1-yl)prop-2-en-1-one (36)



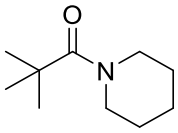
36

$C_{14}H_{17}NO$
MW: 215.3 g.mol^{-1}
White solid
Yield: 64%

Following the general procedure A, amide 36 was obtained as a white solid (137 mg, 0.64 mmol, 64%). The spectral data (^{1}H-NMR) was consistent with reported one.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 15.5 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.41 – 7.31 (m, 3H), 6.91 (d, *J* = 15.5 Hz, 1H), 3.79 – 3.47 (bs, 4H), 1.73 – 1.65 (m, 2H), 1.65 – 1.58 (m, 4H).

2,2-dimethyl-1-(piperidin-1-yl)propan-1-one (22)



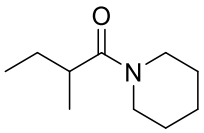
22

$C_{10}H_{19}NO$
MW: 169.27 g.mol^{-1}
Colorless oil
Yield: 55%

Following the general procedure A, amide 22 was obtained as a colorless oil (277 mg, 1.64 mmol, 55%). The spectral data (^{1}H-NMR) was consistent with reported one. [13]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 – 3.52 (m, 4H), 1.68 – 1.60 (m, 2H), 1.61 – 1.50 (m, 4H), 1.27 (s, 9H).

2-methyl-1-(piperidin-1-yl)butan-1-one (21)



21

$C_{10}H_{19}NO$
MW: 169.27 g.mol^{-1}
Colorless oil
Yield: 42%

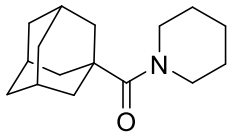
Following the general procedure A, amide 21 was obtained as a colorless oil (214 mg, 1.26 mmol, 42%).

1H NMR (400 MHz, $CDCl_3$): δ 3.69 – 3.32 (m, 4H), 2.61 (sextet, *J* = 6.8 Hz, 1H), 1.77 – 1.60 (m, 3H), 1.60 – 1.47 (m, 4H), 1.40 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 46.7, 43.0, 37.0, 27.2, 27.0, 25.9, 24.9, 17.5, 12.1.

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_{20}NO$: 170.1545 $[M+H]^+$; found 170.1546.

((3r,5r,7r)-adamantan-1-yl)(piperidin-1-yl)methanone (23)



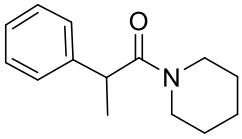
23

$C_{16}H_{25}NO$
MW: 247.38 g.mol^{-1}
White solid
Yield: 70%

Following the general procedure A, amide 23 was obtained as a white solid (174 mg, 0.70 mmol, 70%). The spectral data (^{1}H-NMR) was consistent with reported one.[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 – 3.57 (m, 4H), 2.07 – 1.98 (m, 8H), 1.72 (bs, 5H), 1.67 – 1.60 (m, 2H), 1.59 – 1.50 (m, 6H).

2-phenyl-1-(piperidin-1-yl)propan-1-one (19)



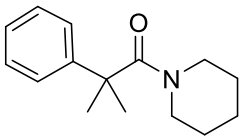
19

$C_{14}H_{19}NO$
MW: 217.31 g.mol^{-1}
White solid
Yield: 44%

Following the general procedure A, amide 19 was obtained as a white solid (194 mg, 0.89 mmol, 44%). The spectral data (^{1}H-NMR) was consistent with reported one.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 3.87 (q, *J* = 6.9 Hz, 1H), 3.79 – 3.67 (m, 1H), 3.47 – 3.35 (m, 1H), 3.35 – 3.23 (m, 2H), 1.58 – 1.47 (m, 3H), 1.47 – 1.39 (m, 4H), 1.38 – 1.26 (m, 1H), 1.05 – 0.90 (m, 1H).

2-methyl-2-phenyl-1-(piperidin-1-yl)propan-1-one (38)



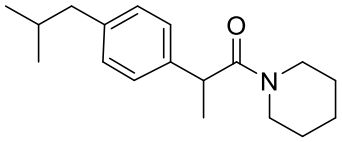
38

$C_{15}H_{21}NO$
MW: 231.34 g.mol^{-1}
White solid
Yield: 51%

Following the general procedure A, amide 38 was obtained as a white solid (235 mg, 1.02 mmol, 51%). The spectral data (^{1}H-NMR) was consistent with reported one.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 3.59 (bs, 2H), 2.95 (bs, 2H), 1.55 (s, 6H), 1.51 – 1.44 (m, 3H), 1.06 (bs, 3H).

2-(4-isobutylphenyl)-1-(piperidin-1-yl)propan-1-one (34)



34

$C_{18}H_{27}NO$
MW: 273.42 g.mol^{-1}
Colorless oil
Yield: 47%

Following the general procedure A, amide 24 was obtained as a colorless oil (128 mg, 0.47 mmol, 47%).

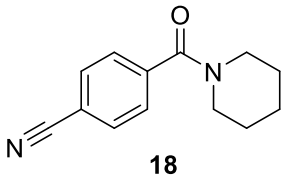
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.10 (m, 2H), 7.10 – 7.03 (m, 2H), 3.84 (q, *J* = 6.8 Hz, 1H), 3.79 – 3.70 (m, 1H), 3.43 – 3.22 (m, 3H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.83 (nonet, *J* = 6.8 Hz, 1H), 1.56 – 1.46 (m, 3H), 1.42 (d, *J* = 6.8 Hz, 4H), 1.36 – 1.24 (m, 1H), 1.01 – 0.91 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 139.9, 139.6, 129.5 (2C), 127.0 (2C), 46.6, 45.0, 43.1, 42.9, 30.2, 25.8, 25.5, 24.5, 22.3 (2C), 20.8.

HRMS (ESI-TOF) m/z calc'd for $C_{18}H_{28}NO$: 274.2171 $[M+H]^+$; found 274.2172.

FTIR (cm-1): 2930, 2856, 1732, 1639, 1510, 1433, 1383, 1366, 1262, 1226, 1186, 1138, 1087, 1061, 1012, 953, 889, 850, 802, 782, 732, 688, 589, 564, 506, 432.

4-(piperidine-1-carbonyl)benzonitrile (18)



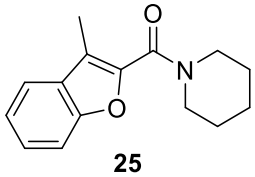
18

$C_{13}H_{14}N_2O$
MW: 214.27 g.mol^{-1}
White solid
Yield: 63%

Following the general procedure A, amide 18 was obtained as a white solid (270 mg, 1.26 mmol, 63%). The spectral data (^{1}H-NMR) was consistent with reported one.[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.67 (m, 2H), 7.52 – 7.45 (m, 2H), 3.84 – 3.57 (m, 2H), 3.39 – 3.17 (m, 2H), 1.77 – 1.61 (m, 4H), 1.58 – 1.42 (m, 2H).

(3-methylbenzofuran-2-yl)(piperidin-1-yl)methanone (25)



25

$C_{15}H_{17}N_2O_2$
MW: 243.31 g.mol^{-1}
White solid
Yield: 29%

Following the general procedure A, amide 25 was obtained as a white solid (38 mg, 0.16 mmol, 29%).

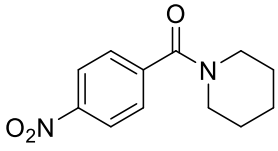
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (ddd, *J* = 7.7, 1.3, 0.8 Hz, 1H), 7.45 (ddd, *J* = 8.3, 1.1, 0.8 Hz, 1H), 7.36 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.27 (ddd, *J* = 7.7, 7.3, 1.1 Hz, 1H), 3.83 – 3.43 (m, 4H), 2.41 (s, 3H), 1.77 – 1.55 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.1, 153.7, 144.7, 129.3, 126.1, 123.0, 120.5, 119.8, 111.7, 24.8, 9.0. (4 carbons missing due to the free rotation of the amide bond, cf Figure S1)

HRMS (ESI-TOF) m/z calc'd for $C_{15}H_{18}N_2O_2$: 244.1338 $[M+H]^+$; found 244.1339.

FTIR (cm^{-1}): 2935, 2856, 1627, 1440, 1385, 1343, 1286, 1261, 1225, 1173, 1127, 1095, 1026, 1000, 954, 870, 853, 803, 746, 667, 544, 426.

(4-nitrophenyl)(piperidin-1-yl)methanone (40)



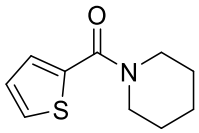
40

$C_{12}H_{14}N_2O_3$
MW: 234.26 $g.mol^{-1}$
White solid
Yield: 49%

Following the general procedure A, amide 40 was obtained as a white solid (230 mg, 0.98 mmol, 49%). The spectral data (^{1}H-NMR) was consistent with reported one.[16]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 2H), 7.56 – 7.49 (m, 2H), 3.70 (bs, 2H), 3.25 (bs, 2H), 1.74 – 1.59 (m, 4H), 1.57 – 1.41 (m, 2H).

piperidin-1-yl(thiophen-2-yl)methanone (26)



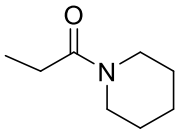
26

$C_{10}H_{13}NOS$
MW: 195.28 $g.mol^{-1}$
Colorless oil
Yield: 41%

Following the general procedure A, amide 26 was obtained as a colorless oil (160 mg, 0.82 mmol, 41%). The spectral data (^{1}H-NMR) was consistent with reported one.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.20 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.67 – 3.51 (m, 4H), 1.68 – 1.60 (m, 2H), 1.60 – 1.52 (m, 4H).

1-(piperidin-1-yl)propan-1-one (20)



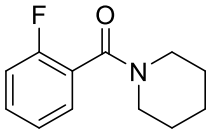
20

$C_8H_{15}NO$
MW: 141.21 $g.mol^{-1}$
Colorless oil
Yield: 61%

Following the general procedure A, amide 20 was obtained as a colorless oil (430 mg, 3.05 mmol, 61%). The spectral data (^{1}H-NMR) was consistent with reported one. [17]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (bs, 2H), 3.40 (bs, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.58 – 1.50 (m, 4H), 1.14 (t, *J* = 7.5 Hz, 3H).

(2-fluorophenyl)(piperidin-1-yl)methanone (39)



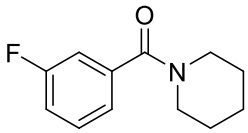
39

$C_{12}H_{14}FNO$
MW: 207.25 g.mol^{-1}
White solid
Yield: 86%

Following the general procedure A, amide 39 was obtained as a white solid (357 mg, 1.72 mmol, 86%). The spectral data (^{1}H-NMR) was consistent with reported one.[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.31 (m, 2H), 7.22 – 7.14 (ddd, *J* = 7.5, 6.4, 0.4 Hz, 1H), 7.07 (bs, 1H), 3.81 – 3.65 (m, 2H), 3.25 (bs, 2H), 1.70 – 1.42 (m, 6H).

(3-fluorophenyl)(piperidin-1-yl)methanone (16)



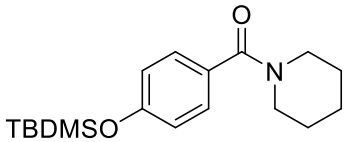
16

$C_{12}H_{14}FNO$
MW: 207.25 g.mol^{-1}
White solid
Yield: 29%

Following the general procedure A, amide 16 was obtained as a white solid (120 mg, 0.58 mmol, 29%). The spectral data (^{1}H-NMR) was consistent with reported one.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.31 (m, 1H), 7.15 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.12 – 7.05 (m, 2H), 3.69 (bs, 2H), 3.32 (bs, 2H), 1.74 – 1.43 (m, 6H).

(4-((tert-butyldimethylsilyl)oxy)phenyl)(piperidin-1-yl)methanone (6)



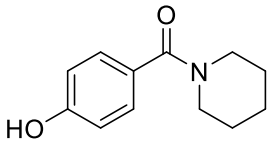
6

$C_{18}H_{29}NO_2Si$
MW: 319.52 g.mol^{-1}
White solid
Yield: 55%

Following the general procedure A, amide 6 was obtained as a white solid (350 mg, 1.10 mmol, 55%). The spectral data (^{1}H-NMR) was consistent with reported one.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 2H), 6.87 – 6.79 (m, 2H), 3.49 (bs, 4H), 1.67 (bs, 2H), 1.61 (bs, 4H), 0.98 (s, 9H), 0.20 (s, 6H).

(4-hydroxyphenyl)(piperidin-1-yl)methanone (5)



5

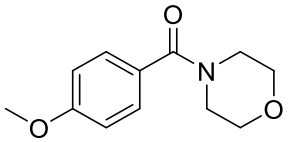
$C_{12}H_{15}NO_2$
MW: 205.26 g.mol^{-1}
White solid
Yield: 92%

To a solution of amide 32 (210 mg, 0.66 mmol) in freshly distilled THF (0.2 M, 3mL) was added TBAF, as a solution 1M in THF (0.73 mL, 0.73 mmol) at 0°C. The reaction was monitored by TLC using EtOAc/heptane (1/1) as eluent. After completion of the reaction (30 min) water and DCM (5mL each) were added to the reaction mixture. Extract the aqueous phase with DCM (twice, 10 mL each). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude was purified via silica column using Heptane/EtOAc as eluent (from 9/1 to 0/100) to yield a white solid. (125 mg, 0.61 mmol, 92%).

The spectral data (^{1}H-NMR) was consistent with reported one.[19]

^{1}H NMR (400 MHz, DMSO-*d*6): δ 9.80 (bs, 1H), 7.25 – 7.18 (m, 2H), 6.81 – 6.75 (m, 2H), 3.42 (bs, 4H), 1.59 (bs, 2H), 1.53 – 1.40 (m, 4H).

(4-methoxyphenyl)(morpholino)methanone (30)



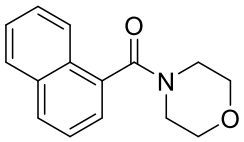
30

$C_{12}H_{15}NO_3$
MW: 221.26 g.mol^{-1}
White solid
Yield: 54%

Following the general procedure A, amide 30 was obtained as a white solid (230 mg, 1.04 mmol, 54%).
The spectral data (^{1}H-NMR) was consistent with reported one.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 2H), 6.95 – 6.87 (m, 2H), 3.83 (s, 3H), 3.80 – 3.46 (m, 8H).

morpholino(naphthalen-1-yl)methanone (29)



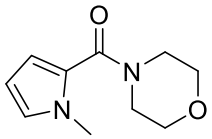
29

$C_{15}H_{15}NO_2$
MW: 241.29 g.mol^{-1}
Pale yellow oil
Yield: 32%

Following the general procedure A, amide 29 was obtained as a pale-yellow oil (77 mg, 0.32 mmol, 32%).
The spectral data (^{1}H-NMR) was consistent with reported one.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.82 (m, 3H), 7.59 – 7.46 (m, 3H), 7.42 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.06 – 3.98 (m, 1H), 3.95 – 3.82 (m, 3H), 3.57 – 3.48 (m, 2H), 3.25 – 3.16 (m, 2H).

(1-methyl-1H-pyrrol-2-yl)(morpholino)methanone (28)



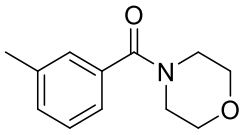
28

$C_{10}H_{14}N_2O_2$
MW: 194.23 g.mol^{-1}
White solid
Yield: 55%

Following the general procedure A, amide 28 was obtained as a white solid (219 mg, 1.13 mmol, 55%).
The spectral data (^{1}H-NMR) was consistent with reported one.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.32 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.08 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.82 – 3.74 (m, 7H), 3.74 – 3.68 (m, 4H).

morpholino(m-tolyl)methanone (31)



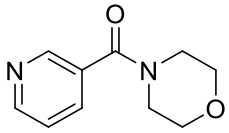
31

$C_{12}H_{15}NO_2$
MW: 205.26 g.mol^{-1}
Colorless oil
Yield: 23%

Following the general procedure A, amide 37 was obtained as a colorless oil (95 mg, 0.46 mmol, 23%).
The spectral data (^{1}H-NMR) was consistent with reported one.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.24 (m, 1H), 7.26 – 7.19 (m, 2H), 7.21 – 7.14 (m, 1H), 3.84 – 3.33 (m, 8H), 2.37 (s, 3H).

(4-methoxyphenyl)(morpholino)methanone (35)



35

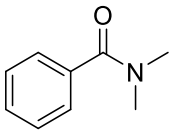
$C_{10}H_{12}N_2O_2$
MW: 192.22 g.mol^{-1}
Yellow oil
Yield: 16%

In a 25 mL round bottom flask nicotinic acid (0.5 g, 4 mmol) was solubilised in thionyl chloride (4 mL, 1M, 55 mmol), then refluxed for 2 hours under argon atmosphere. The mixture was concentrated in vacuo and the residue was taken in anhydrous dichloromethane (6 mL, 0.67M). To this solution was added dropwise at 0 °C a solution of morpholine (2.8 mL, 33 mmol) in anhydrous dichloromethane (3 mL, 11M) and stirred overnight. The reaction mixture was diluted in EtOAc and NaOH (5M), the aqueous layer was extracted thrice with NaOH 5M, the organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The pure amide was then obtained after purification on silica gel (DCM/MeOH as eluent, from 100/0 to 9/1) to yield 35 as a yellow oil. (122mg, 0.63 mmol, 16%).

The spectral data (^{1}H-NMR) was consistent with reported one.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (dd, *J* = 4.9, 2.2 Hz, 1H), 8.56 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.67 (ddd, *J* = 7.8, 2.2, 1.7 Hz, 1H), 7.28 (ddd, J = 7.8, 4.9, 0.9 Hz, 1H), 3.79 – 3.29 (m, 8H).

N,N-dimethylbenzamide (33)



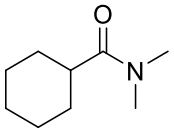
33

$C_9H_{11}NO$
MW: 149.19 g.mol^{-1}
Colorless oil
Yield: 68%

Following the general procedure A, amide 33 was obtained as a colorless oil (253 mg, 1.70 mmol, 68%). The spectral data (^{1}H-NMR) was consistent with reported one.[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (bs, 5H), 3.12 (bs, 3H), 2.98 (bs, 3H).

N,N-dimethylcyclohexanecarboxamide (32)



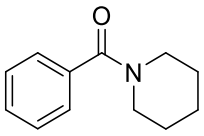
32

$C_9H_{17}NO$
MW: 155.24 g.mol^{-1}
Colorless oil
Yield: 60%

Following the general procedure A, amide 32 was obtained as a colorless oil (185 mg, 1.19 mmol, 60%). The spectral data (^{1}H-NMR) was consistent with reported one.[23]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 3H), 2.92 (s, 3H), 2.48 (tt, *J* = 11.5, 3.4 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.75 – 1.63 (m, 3H), 1.56 – 1.42 (m, 2H), 1.32 – 1.19 (m, 3H).

phenyl(piperidin-1-yl)methanone (44)



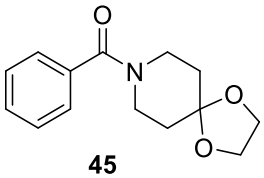
44

$C_{12}H_{15}NO$
MW: 189.26 g.mol^{-1}
White solid
Yield: 92%

Following the general procedure C, 44 was obtained as a white solid (697 mg, 3.68 mmol, 92%). The spectral data (^{1}H-NMR) was consistent with reported one.[24]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.31 (m, 5H), 3.71 (bs, 2H), 3.34 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H).

phenyl(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methanone (45)



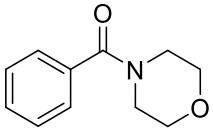
45

$C_{14}H_{17}NO_3$
MW: 247.29 g.mol^{-1}
White solid
Yield: 86%

Following the general procedure C,amide 45 was obtained as a white solid (529 mg, 2.14 mmol, 86%). The spectral data (^{1}H-NMR) was consistent with reported one.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.33 (m, 5H), 3.98 (s, 4H), 3.85 (bs, 2H), 3.48 (bs, 2H), 1.80 (bs, 2H), 1.62 (bs, 2H).

morpholino(phenyl)methanone (41)



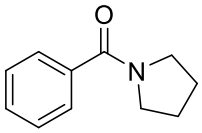
41

$C_{11}H_{13}NO_2$
MW: 191.23 g.mol^{-1}
White solid
Yield: 94%

Following the general procedure C, amide 41 was obtained as a white solid (369 mg, 1.93 mmol, 94%). The spectral data (^{1}H-NMR) was consistent with reported one.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.32 (m, 5H), 3.93 – 3.33 (m, 8H).

phenyl(pyrrolidin-1-yl)methanone (43)



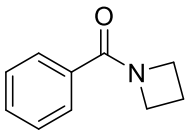
43

$C_{11}H_{13}NO$
MW: 175.23 g.mol^{-1}
Colorless oil
Yield: 83%

Following the general procedure C, amide 43 was obtained as a colorless oil (362 mg, 2.07 mmol, 83%). The spectral data (^{1}H-NMR) was consistent with reported one.[25]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.47 (m, 2H), 7.44 – 7.33 (m, 3H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.02 – 1.92 (m, 2H), 1.92 – 1.83 (m, 2H).

azetidin-1-yl(phenyl)methanone (42)



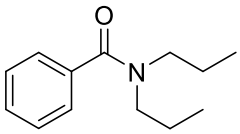
42

$C_{10}H_{11}NO$
MW: 161.20 g.mol^{-1}
Colorless oil
Yield: 91%

Following the general procedure C, amide 42 was obtained as a colorless oil (366 mg, 2.27 mmol, 91%). The spectral data (^{1}H-NMR) was consistent with reported one.[26]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 – 7.59 (m, 2H), 7.48 – 7.36 (m, 3H), 4.30 (t, *J* = 7.5 Hz, 2H), 4.23 (t, *J* = 7.7 Hz, 2H), 2.39 – 2.30 (tt, *J* = 7.7, 7.5 Hz, 2H).

N,N-dipropylbenzamide (48)



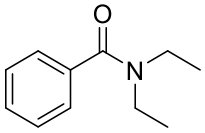
48

$C_{13}H_{19}NO$
MW: 205.30 g.mol^{-1}
Colorless oil
Yield: 95%

Following the general procedure C, amide 48 was obtained as a colorless oil (487 mg, 2.37 mmol, 95%). The spectral data (^{1}H-NMR) was consistent with reported one.[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.32 (m, 5H), 3.46 (bs, 2H), 3.16 (bs, 2H), 1.68 (bs, 2H), 1.53 (bs, 2H), 0.98 (bs, 3H), 0.74 (bs, 3H).

N,N-diethylbenzamide (47)



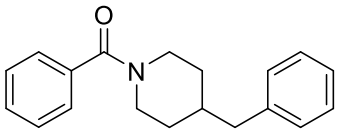
47

$C_{11}H_{15}NO$
MW: 177.25 g.mol^{-1}
Colorless oil
Yield: 73%

Following the general procedure C, amide 47 was obtained as a colorless oil (325 mg, 1.83 mmol, 73%). The spectral data (^{1}H-NMR) was consistent with reported one.[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 5H), 3.55 (bs, 2H), 3.25 (bs, 2H), 1.24 (bs, 3H), 1.11 (bs, 3H).

(4-benzylpiperidin-1-yl)(phenyl)methanone (53)



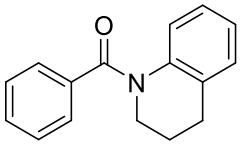
53

$C_{19}H_{21}NO$
MW: 279.38 g.mol^{-1}
White solid
Yield: 66%

Following the general procedure C, amide 53 was obtained as a white solid (556 mg, 1.99 mmol, 66%). The spectral data (^{1}H-NMR) was consistent with reported one.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 5H), 7.31 – 7.26 (m, 2H), 7.23 – 7.18 (m, 1H), 7.16 – 7.12 (m, 2H), 4.70 (bs, 1H), 3.72 (bs, 1H), 2.93 (bs, 1H), 2.71 (bs, 1H), 2.57 (bs, 2H), 1.86 – 1.70 (m, 2H), 1.60 (bs, 1H), 1.29 (s, 1H), 1.18 (bs, 1H).

(3,4-dihydroquinolin-1(2H)-yl)(phenyl)methanone (49)



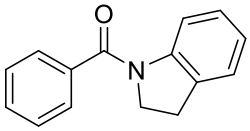
49

$C_{16}H_{15}NO$
MW: 237.30 g.mol^{-1}
White solid
Yield: 95%

Following the general procedure C, amide 49 was obtained as a white solid (672 mg, 2.83 mmol, 95%). The spectral data (^{1}H-NMR) was consistent with reported one.[28]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3 – 7.1 (m, 5H), 7.18 – 7.11 (m, 1H), 6.9 (td, *J* = 7.5, 1.3 Hz, 1H), 6.8 (td, *J* = 7.7 Hz, 1.53, 1H), 6.77 – 6.66 (m, 1H), 3.8 (dd, *J* = 6.6, 6.4 Hz, 2H), 2.8 (td, *J* = 6.6, 0.5 Hz, 2H), 2.0 – 1.9 (m, 2H).

indolin-1-yl(phenyl)methanone (50)



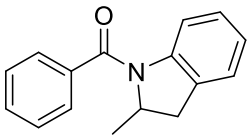
50

$C_{15}H_{13}NO$
MW: 223.28 g.mol^{-1}
Purple solid
Yield: >95%

Following the general procedure C, amide 50 was obtained as a purple solid (541 mg, 2.42 mmol, 97%). The spectral data (^{1}H-NMR) was consistent with reported one.[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 - 7.54 (m, 3H), 7.50 – 7.42 (m, 5H), 7.25 – 7.18 (m, 1H), 4.09 (bs, 2H), 3.12 (t, *J* = 8.3 Hz, 2H).

(2-methylindolin-1-yl)(phenyl)methanone (51)



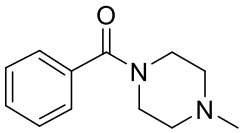
51

$C_{16}H_{15}NO$
MW: 237.30 g.mol^{-1}
Brown solid
Yield: 84%

Following the general procedure C, amide 51 was obtained as a brown solid (249 mg, 1.05 mmol, 84%). The spectral data (^{1}H-NMR) was consistent with reported one.[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.40 (m, 6H), 7.24 – 7.19 (m 1H), 7.09 – 6.92 (m, 2H), 4.74 (bs, 1H), 3.42 (dd, *J* = 15.7, 8.8 Hz, 1H), 2.64 (dd, *J* = 15.7, 1.1 Hz, 1H), 1.25 (s, 3H).

(4-methylpiperazin-1-yl)(phenyl)methanone (52)



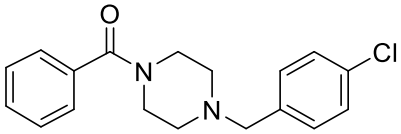
52

$C_{12}H_{16}N_2O$
MW: 177.20 g.mol^{-1}
Yellow solid
Yield: 74%

Following the general procedure C, amide 52 was obtained as a yellow solid (300 mg, 1.69 mmol, 74%). The spectral data (^{1}H-NMR) was consistent with reported one.[30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (bs, 5H), 3.80 (bs, 2H), 3.44 (bs, 2H), 2.49 (bs, 2H), 2.44 – 2.21 (m, 5H).

(4-(4-chlorobenzyl)piperazin-1-yl)(phenyl)methanone (54)



54

$C_{18}H_{19}ClN_2O$
MW: 314.81 g.mol^{-1}
White solid
Yield: 87%

Following the general procedure C, amide 54 was obtained as a white solid (176 mg, 0.56 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.22 (m, 5H), 7.19 – 7.08 (m, 4H), 3.65 (bs, 2H), 3.36 (bs, 4H), 2.30 (bs, 4H).

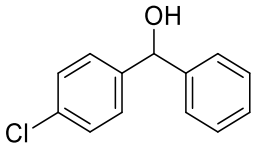
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 136.3, 135.9, 133.1, 130.4 (2C), 129.8, 128.6 (4C), 127.1 (2C), 62.2, 53.4, 52.8, 47.8, 42.2.

HRMS (ESI-TOF) m/z calcd for $C_{18}H_{20}ClN_2O$: 315.1264 $[M+H]^+$; found 315.1265.

FTIR (cm^{-1}): 2944, 2807, 1626, 1598, 1576, 1489, 1433, 1369, 1348, 1286, 1275, 1257, 1158, 1142, 1123, 1104, 1089, 1017, 1003, 938, 837, 813, 791, 735, 711, 668, 648, 599, 561, 501, 457, 440.

Melting Point: 97 - 100 °C.

(4-chlorophenyl)(phenyl)methanol (63a)



63a

$C_{13}H_{11}ClO$
MW: 218.68 g.mol^{-1}
Colorless oil
Yield: >95%

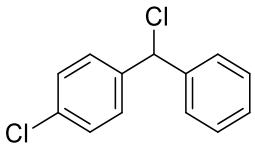
In a 250 mL round bottom flask, a solution of chlorobenzophenone (5.0 g, 23 mmol, 1.0 eq.) in anhydrous methanol (75 mL, 0.3 M) was stirred at 0 °C, then $NaBH_4$ (1.06 g, 28 mmol, 1.2 eq.) was added in 3 portions. The reaction solution was stirred for 3h at room temperature. Next, methanol was evaporated under reduced pressure. Then 30mL of 1M NaOH was added, and the mixture was extracted 3 times DCM (30mL). The combined DCM phase was washed with brine then dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure to afford compound as a colorless oil (5.0 g, 22.86 mmol, >95%).

The spectral data (^{1}H-NMR) was consistent with reported one.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 9H), 5.81 (d, *J* = 3.5 Hz, 1H), 2.26 (d, *J* = 3.5 Hz, 1H).

1-chloro-4-(chloro(phenyl)methyl)benzene (63b)



63b

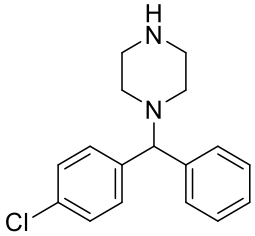
$C_{13}H_{10}Cl_2$
MW: 237.12 g.mol^{-1}
Yellow oil
Yield: 93%

In a 50 mL round bottom flask, to a stirred solution of (4-chlorophenyl)(phenyl)methanol 63a (4.0 g, 18 mmol, 1.0 eq.) in hydrochloric acid (37%, 20 mL, 1 M) was added calcium chloride (3.0 g, 27 mmol, 2.0 eq.) at room temperature. The resulting reaction mixture was refluxed for 18 h. After completion of the reaction as indicated by LCMS and TLC (Cyclo/EtOAc, 8/2), the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the compound without further purification as a yellow oil (3.96 g, 16.70 mmol, 93%).

The spectral data (^{1}H-NMR) was consistent with reported one.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.30 (m, 9H), 6.10 (s, 1H).

1-((4-chlorophenyl)(phenyl)methyl)piperazine (63c)



63c

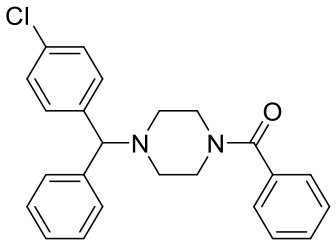
$C_{17}H_{19}ClN_2$
MW: 290.80 g.mol^{-1}
Colorless viscous oil
Yield: 70%

In a 50 mL round bottom flask, to a stirred solution of piperazine (550 mg, 6.3 mmol, 1.5 eq.) in CH_3CN (10 ml) was added K_2CO_3 (1.2 g, 8.4 mmol, 2 eq.) and benzyltriethyl ammonium bromide (BTEAB) (230 mg, 0.84 mmol, 20 mol%). After 15min of stirring, a solution of 1-chloro-4-(chloro(phenyl)methyl)benzene 63b (1.0 g, 4.2 mmol, 1.0 eq.) and KI (350 mg, 2.1 mmol, 0.5 eq.) in 10 mL of CH_3CN was added and the mixture was stirred to reflux overnight (18h). After completion of the reaction as indicated by TLC or LCMS, the reaction mixture was filtered. The combined filtrate was concentrated under reduced pressure, and the residue was acidified (HCl 1 M) to pH 2. The water phase was washed with ethyl acetate and then basified to pH 8 with $NaHCO_3$ sat., extracted with ethyl acetate. The combined ethyl acetate phase was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a colorless viscous oil (772 mg, 2.65 mmol, 70%).

The spectral data (^{1}H-NMR) was consistent with reported one.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 4H), 7.31 – 7.23 (m, 4H), 7.21 – 7.13 (m, 1H), 4.19 (s, 1H), 2.88 (bs, 4H), 2.34 (bs, 4H), labile N-H not observed.

(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(phenyl)methanone (55)



55

$C_{24}H_{23}ClN_2O$
MW: 390.91 g.mol^{-1}
White solid
Yield: >95%

Following the general procedure C using 63c as the amine partner, amide 55 was obtained as a white solid (399 mg, 1.02 mmol, >95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 8H), 7.31 – 7.23 (m, 5H), 7.23 – 7.17 (m, 1H), 4.24 (s, 1H), 3.82 (bs, 2H), 3.45 (bs, 2H), 2.50 (bs, 2H), 2.35 (bs, 2H).

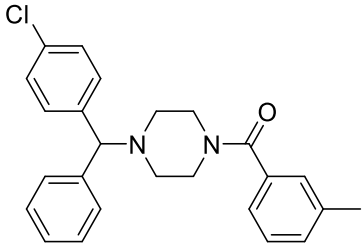
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 141.6, 140.8, 135.9, 132.9, 129.7, 129.2 (2C), 128.9 (2C), 128.8 (2C), 128.5 (2C), 127.9 (2C), 127.5, 127.1 (2C), 75.3, 52.0 (2C), 48.0, 42.4.

HRMS (ESI-TOF) m/z calcd for $C_{24}H_{24}ClN_2O$: 391.1577 $[M+H]^+$; found 391.1576.

FTIR (cm^{-1}): 3027, 2809, 2242, 1628, 1577, 1488, 1430, 1371, 1289, 1264, 1157, 1143, 1103, 1088, 1073, 1015, 998, 909, 849, 833, 803, 788, 758, 729, 709, 699, 645, 623, 570, 528, 498, 427.

Melting Point: 66 – 70 °C.

(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(m-tolyl)methanone (63)



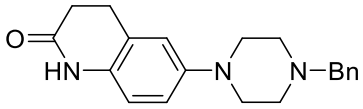
63

$C_{25}H_{25}ClN_2O$
MW: 404.94 g.mol^{-1}
White solid
Yield: 69%

Following the general procedure A using, amide 63 was obtained as a white solid (379 mg, 0.94 mmol, 69%).
The spectral data (^{1}H-NMR) was consistent with reported one.[16]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 4H), 7.29 – 7.21 (m, 6H), 7.20 – 7.16 (m, 2H), 7.13 (dt, *J* = 7.3, 1.8 Hz, 1H), 4.24 (s, 1H), 3.60 (bs, 4H), 2.34 (bs, 7H).

6-(4-benzylpiperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (66a)



66a

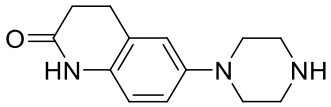
$C_{20}H_{23}N_3O$
MW: 321.42 g.mol^{-1}
Yellow solid
Yield: 68%

6-Bromo-3,4-dihydro-1H-quinolin-2-one (0.5 g, 2.21 mmol, 1.0 eq.), tris-(dibenzylideneacetone) dipalladium (i.e. $Pd_2(dba)_3$, 40 mg, 0.044 mmol, 2 mol%) and DavePhos (20 mg, 0.053 mmol, 2.4 mol%) were added to a flame dried flask (50 mL), which was evacuated and refilled with Ar (3x). *N*-benzylpiperazine was then added by syringe followed by LiHMDS (from a fresh new bottle, 5.0 mL, 1M in THF). After removing the Argon balloon, the red-brown solution was then heated to 65 °C and the reaction was stirred for 24 h. After cooling to room temperature, the reaction mixture was quenched by the addition of aqueous HCl (2 n, 20 mL) and then stirred at room temperature for 5 min. The resulting mixture was then basified by the addition of aqueous saturated sodium hydrogen carbonate solution (20 mL) and then extracted with ethyl acetate (4x 50 mL). The pure product was obtained after a purification on silica column using DCM/MeOH as eluent. A gradient of MeOH from 2% to 5% was performed to yield the pure product as a yellow solid (480 mg, 1.49 mmol, 68%).

The spectral data (^{1}H-NMR) was consistent with reported one.[32]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.38 – 7.30 (m, 4H), 7.30 – 7.24 (m, 1H), 6.80 – 6.68 (m, 3H), 3.57 (s, 2H), 3.18 – 3.04 (m, 4H), 2.91 (bs, 2H), 2.68 – 2.54 (m, 6H).

6-(piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (66b)



66b

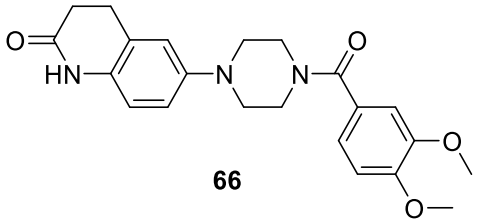
$C_{13}H_{17}N_3O$
MW: 231.30 g.mol^{-1}
Yellow oil
Yield: 86%

6-(4-Benzylpiperazin- 1-yl)-3,4-dihydro-1H-quinolin-2-one 66a (480 mg, 1.5 mmol, 1.0 eq.), 10 wt.-% palladium on carbon (239 mg, 0.225 mmol, 15 mol%), and methanol (1.5 mL, 1M) were added to a Parr reactor (10 mL). The reactor was filled with 5 bar H_2 and purged (3x). The H_2 pressure was then adjusted to 5 bar, and the reaction mixture heated to 80 °C for 16h. After completion of the reaction the reactor was cooled to room temperature, and the resulting mixture was filtered through a syringe filter (NYLON, 0.04 µm). The filtrate was evaporated in vacuo to dryness to give a residue as a yellow oil (300 mg, 1.29 mmol, 86%). The residue was engaged directly in the next step without further purification.

The spectral data (^{1}H-NMR) was consistent with reported one.[32]

^{1}H NMR (400 MHz, MeOD-*d*4): δ 6.89 – 6.72 (m, 3H), 3.15 – 3.08 (m, 4H), 3.08 – 3.01 (m, 4H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.52 (bs, 2H), the two labile N-H were not observed.

6-(4-(3,4-dimethoxybenzoyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (Vesnarinone) (66)



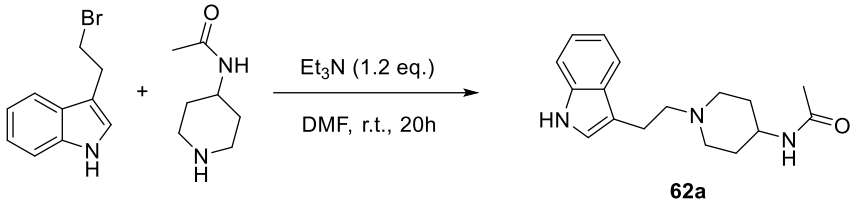
66

$C_{22}H_{25}N_3O_4$
MW: 395.46 g.mol^{-1}
Yellow solid
Yield: 37%

Following the general procedure A using 66b as the amine partner, amide 66 was obtained as a yellow solid (145 mg, 0.37 mmol, 37%) after purification on silica gel (eluent: DCM/MeOH from 99/1 to 95/5). The spectral data (^{1}H-NMR) was consistent with reported one.[32]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (bs, 1H), 7.02 (s, 1H), 7.01 (dd, *J* = 9.3, 2.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.84 – 6.74 (m, 2H), 6.68 (d, *J* = 8.3 Hz, 1H), 3.91 (t, *J* = 3.8 Hz, 6H), 3.78 (bs, 4H), 3.12 (bs, 4H), 2.93 (bs, 2H), 2.62 (bs, 2H).

N-(1-(2-(1H-indol-3-yl)ethyl)piperidin-4-yl)acetamide (62a)



62a

$C_{17}H_{23}N_3O$
MW: 285.39 g.mol^{-1}
White solid
Yield: 60%

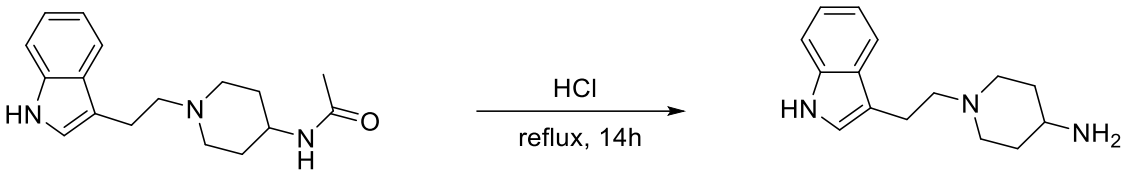
In a 10 mL round bottom flask, a mixture of 4-acetylamino-piperidine (0.94 g, 6.6 mmol, 1.1 eq.), 3(2-bromoethyl) indole (1.3 g, 6.0 mmol, 1.0 eq.) and triethylamine (1.0 mL, 7.2 mmol, 1.2 eq.), dissolved in 3 mL dimethylformamide, was stirred for 20 hours at room temperature. After completion of the reaction, the mixture was evaporated to dryness. The residue was dissolved in 10 mL of 10% ammonia solution, followed by three extractions with 20 mL of DCM. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered and concentrated under reduce pressure (yielding an orange viscous oil). The amine 62a was purified by trituration in cold acetonitrile (10 mL/g), the product crystallize to a white solid (1.0 g, 3.5 mmol, 60%).

^{1}H NMR (400 MHz, MeOD-*d*4): δ 7.53 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.32 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.03 (bs, 1H), 6.99 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 3.75 – 3.61 (m, 1H), 3.03 (bs, 2H), 2.98 – 2.89 (m, 2H), 2.72 – 2.61 (m, 2H), 2.17 (bs, 2H), 1.93 (s, 3H), 1.80 – 1.83 (m, 2H), 1.63 – 1.46 (m, 2H), both NH not observed.

^{13}C NMR (101 MHz, MeOD-*d*4): δ 172.6, 138.1, 128.7, 123.0, 122.3, 119.5, 119.2, 113.7, 112.2, 60.5, 53.4 (2C), 47.9, 32.3 (2C), 23.7, 22.6.

HRMS (ESI-TOF) m/z calcd for $C_{17}H_{24}N_3O$: 286.1919 $[M+H]^+$; found 286.1923.

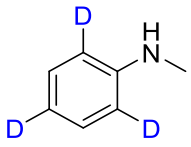
FTIR (cm^{-1}): 3267, 2929, 2814, 1633, 1551, 1456, 1370, 1340, 1308, 1245, 1140, 1093, 1048, 1009, 976, 926, 879, 799, 764, 739, 606, 579, 495, 464, 425.



62a **62b**

The intermediate 62a was next dissolved in 6M hydrochloric acid (10 mL, 10 mL/g), then the solution was progressively heated to reflux and held overnight (14h). After cooling the reaction to room temperature, the medium is filtered. Next, an aqueous sodium hydroxide solution (5M) was added to the filtrated solution (pH: 14). An oily precipitate appeared, which was recovered by filtration on a frit. The product 62b was used directly in the next step without further purification.

N-methylbenzen-2,4,6-d3-amine ([$^2H_3$]B)



[$^2H_3$]B

$C_7H_6D_3N$
MW: 110.17 g.mol^{-1}
Dark purple liquid
Yield: quantitative
IE: 1.84 D/molecule

An oven dried tube (10 mL) was filled with N-methylaniline (500 µL, 5.00 mmol, 1.0 eq.), D_2O (1 mL) and HCl conc. (300 µL). The tube was then sealed tightly and heated to 180 °C for 24h. The acidic mixture was quenched with NaOH (5 mL, 1M) the acqueous phase was extracted with DCM and the crude engaged again under the same conditions (D_2O: 1 mL, HCl: 300 µL, 180 °C, 24h). This cycle was done 5 times consecutively to obtain without further purification the desired labeled aniline.

The spectral data (^{1}H-NMR) was consistent with reported one.[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (bs, 2H), 6.7 (t, *J* = 7.3 Hz, 0.23H), 6.6 (d, *J* = 8.6 Hz, 0.51H), 2.8 (s, 3H).

HRMS (ESI-TOF) m/z calcd for $C_7H_{10}N$: 108.0813 $[M+H]^+$; found 108.0808.

Isotopic enrichment (measured by HRMS): 1.84 D/molecule.

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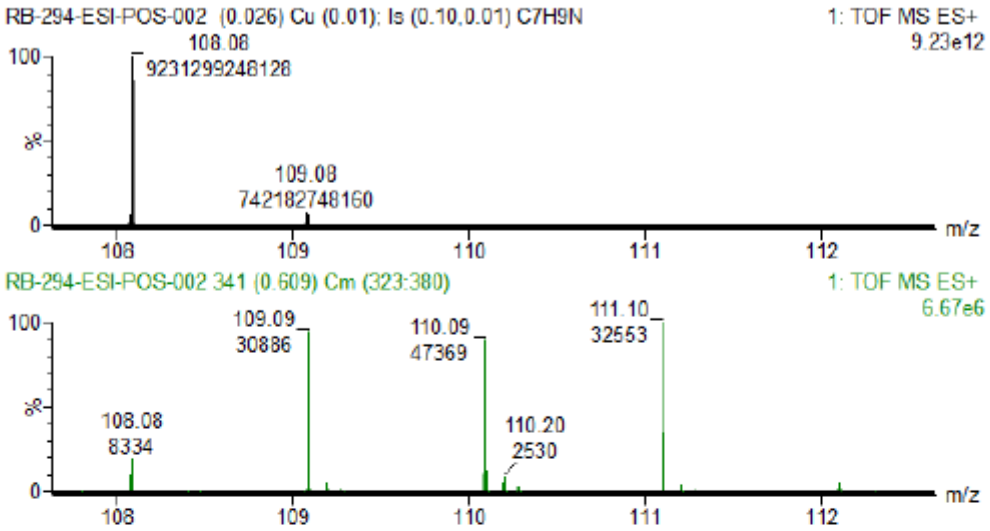
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	108	109	110	111	112	113	114	115
%	100,0	8,1	0,3	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	108	8334	0,00	8334,00	7,42
1	109	30886	674,22	30211,78	26,89
2	110	47369	24,17	44900,70	39,97
3	111	32553	0,00	28832,92	25,67
4	112	2526	0,00	63,20	0,06
5	113	79	0,00	-9,73	-0,01
6	114	0	0,00	0,60	0,00
7	115	0	0,00	-0,02	0,00
8	116	0	0,00	0,00	0,00
9	117	0	0,00	0,00	0,00
10	118	0	0,00	0,00	0,00
11	119	0	0,00	0,00	0,00
Total		121747		112333,46	100,00

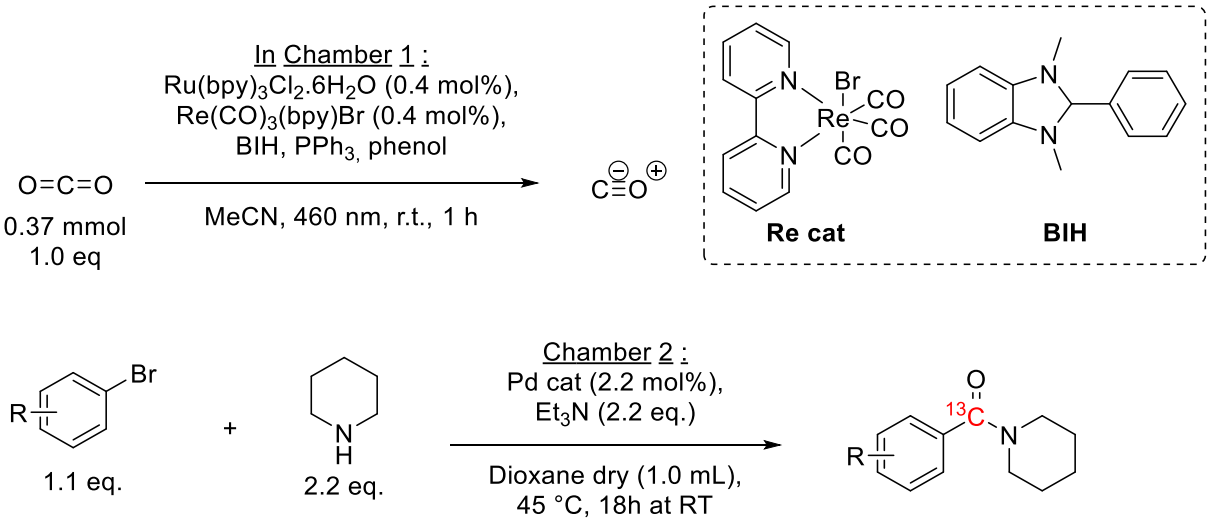
D/molecule	1,8

IV. Synthetic procedure and Analytical Data for the preparation of the Isotope carriers

General procedure D: preparation of ^{13}C-labeled carriers from the corresponding acid chloride

In a flame dried 25 mL round bottom flask, a mixture of [^{13}C]carboxylic acid (1.0 equiv.) in distilled DCM (0.375 M) under argon was stirred at room temperature and then, few drops of DMF were added, followed by oxalyl chloride (1.55 equiv.) dropwise. The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. An oven-dried 25 ml flask was charged with the amine (2.0 equiv.), triethylamine (2.0 equiv.) and distilled dichloromethane (1.5 M relative to the amine) and cooled to 0 °C. The [^{13}C]acyl chloride was then added slowly as a solution in distilled dichloromethane (0.5 M) and the reaction mixture was then stirred overnight at room temperature under argon. The reaction mixture was then diluted with water (10 mL) and dichloromethane (10 mL) and transferred into a separatory funnel. The organic layer was washed with NaOH (1M) twice, HCl (1M) and brine, then dried over $MgSO_4$, filtered and concentrated under vacuum. The pure amide was then obtained after purification on silica gel (cyclohexane/EtOAc as eluent, from 4/1 to 1/1)

General procedure E: Double chamber (adapted from the litterature[34,35])



Chamber 1:

The chamber was charge with 1.4 mL of stock solution A and 1.4 mL of Stock solution B. The chambers were sealed with a screwcap fitted with a Teflon®. The adaptor was then connected to the RC Tritec® system. The solution in Chamber 1 was frozen with a liquid nitrogen bath and the chambers were degassed with a vacuum pump connected with an RC Tritec manifold for 10 min. The stopcock was closed between the two chambers. [^{13}C]CO_2 (365 µmol, 1.0 eq) was then loaded into Chamber 1 using the RC Tritec® system and the stopcock was closed between Chamber 1 and the adaptor. The loaded Chamber 1 was then disconnected from the RC Tritec® system and the solution was warmed to room temperature. Chamber 1 was placed ca. 2 cm away from a 40 W A160WE Tuna Blue Kessil® LED lamp and photo-irradiated with the lower light intensity (164 W m-2) for 2h. [^{13}C]CO_2 is the limiting reagent.

Chamber 2:

A freshly prepared solution of Bromosubstrate (60 µL, 0.4 mmol, 1.1 eq), amine (80 µL, 0.8 mmol, 2.2 eq.), Pd Xantphos G3 precatalyst (7.5 mg, 8 µmol, 2.2 mol%) and Triethylamine (110 µL, 0.8 mmol, 2.2 eq.) in dry dioxane (1.0 mL, 0.4 M) under argon is injected via syringe, previously purged with argon, in Chamber 2 through the screwcap septum. The stopcock between the two chambers is open and the [^{13}C]CO produced in Chamber 1 can react in the aminocarbonylation in Chamber 2. The Two-Chamber Glassware was then held at 45 °C for 18h under constant vigorous stirring (>1200 rpm, in order to create a vortex).

After this time, the glassware is degassed and the crude mixture is transferred from Chamber 2 in a round bottom flask. The pure amide was then obtained after purification on silica gel (cyclohexane/EtOAc as eluent, from 8/2 to 1/1).

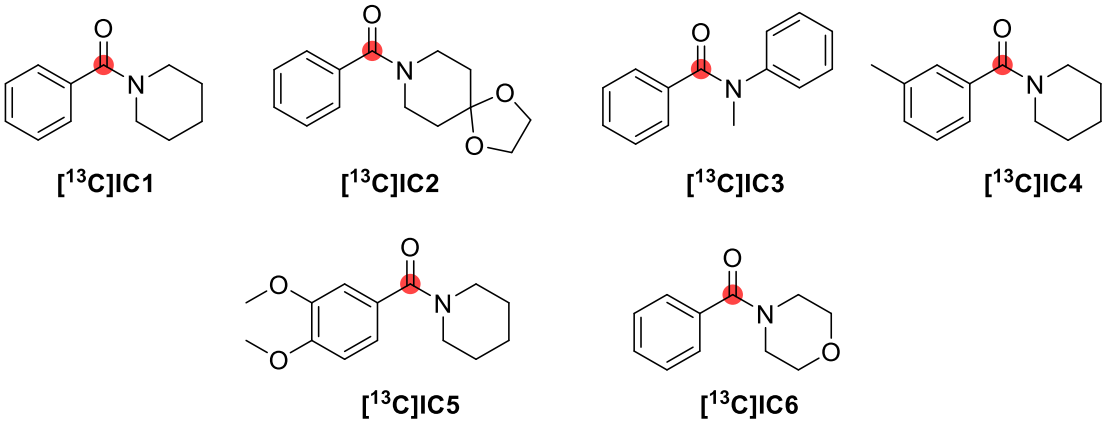
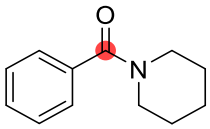


Figure S2: List of all carrier used in metathesis scope

[^{13}C] phenyl(piperidin-1-yl)methanone ([^{13}C]IC1)



[^{13}C]IC1

$C_{11}{}^{13}CH_{15}NO$
MW: 190.25 g.mol^{-1}
White solid
Yield: 81%

Following the general procedure D, [^{13}C]IC1 was obtained as a white solid (232 mg, 1.22 mmol, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.32 (m, 5H), 3.71 (bs, 2H), 3.34 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 136.7 (d, *J* = 66.2 Hz), 129.5 (d, *J* = 1.0 Hz), 128.6 (d, *J* = 4.1 Hz, 2C), 127.0 (d, *J* = 2.1 Hz, 2C), 48.9, 43.3, 26.7, 25.8, 24.8.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{11}H_{16}NO$: 191.1266 $[M+H]^+$; found 191.1266.

Isotopic purity (calculated by HRMS): (^{13}C) 98.7%.

FTIR (cm^{-1}): 2934, 2854, 1589, 1571, 1444, 1420, 1368, 1267, 1235, 1127, 1108, 1073, 1027, 997, 954, 879, 853, 781, 705, 631, 524, 421.

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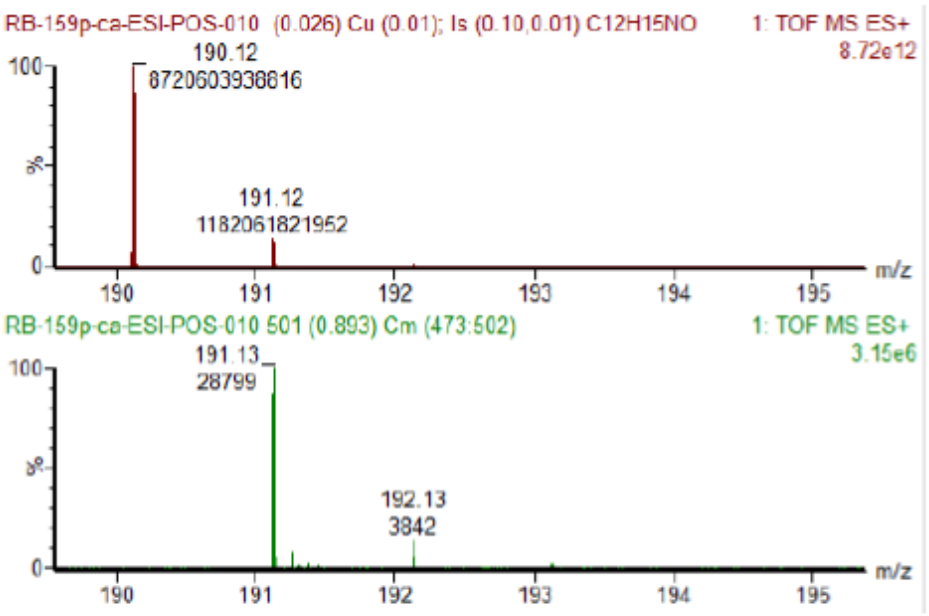
Isotopic Enrichment



theorical isotopic distribution

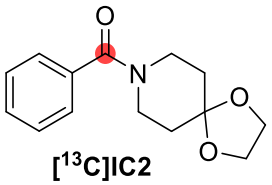
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	190	191	192	193	194	195	196	197
%	100,0	13,6	1,0	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	190	166	0,00	166,00	0,57
1	191	28799	22,58	28776,42	98,72
2	192	3842	1,66	-73,25	-0,25
3	193	599	0,00	321,20	1,10
4	194	0	0,00	-42,95	-0,15
5	195	0	0,00	2,63	0,01
6	196	0	0,00	0,07	0,00
7	197	0	0,00	-0,04	0,00
8	198	0	0,00	0,00	0,00
9	199	0	0,00	0,00	0,00
10	200	0	0,00	0,00	0,00
11	201	0	0,00	0,00	0,00
Total		33406		29150,09	100,00

% Isotopic enrichment : 98,7

[^{13}C] phenyl(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methanone ([^{13}C]IC2)



[^{13}C]IC2

$C_{13}{}^{13}CH_{17}NO_3$
MW: 248.28 g.mol^{-1}
White solid
Yield: 92%

Following the general procedure D, [^{13}C]IC2 was obtained as a white solid (274 mg, 1.10 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (bs, 5H), 4.03 – 3.78 (m, 6H), 3.55 – 3.37 (m, 2H), 1.87 – 1.62 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 136.5 (d, *J* = 66.3 Hz), 129.8 (d, *J* = 0.9 Hz), 128.7 (d, *J* = 4.2 Hz, 2C), 127.0 (d, *J* = 2.0 Hz, 2C), 107.1, 64.6 (2C), 45.8, 40.4 35.9 34.9.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{13}H_{18}NO_3$: 249.1321 $[M+H]^+$; found 249.1325.

Isotopic purity (calculated by HRMS): (^{13}C) 99.8%.

FTIR (cm^{-1}): 2959, 2878, 1673, 1591, 1573, 1421, 1360, 1338, 1266, 1245, 1162, 1127, 1085, 1031, 945, 912, 868, 782, 707, 662, 634, 527, 490.

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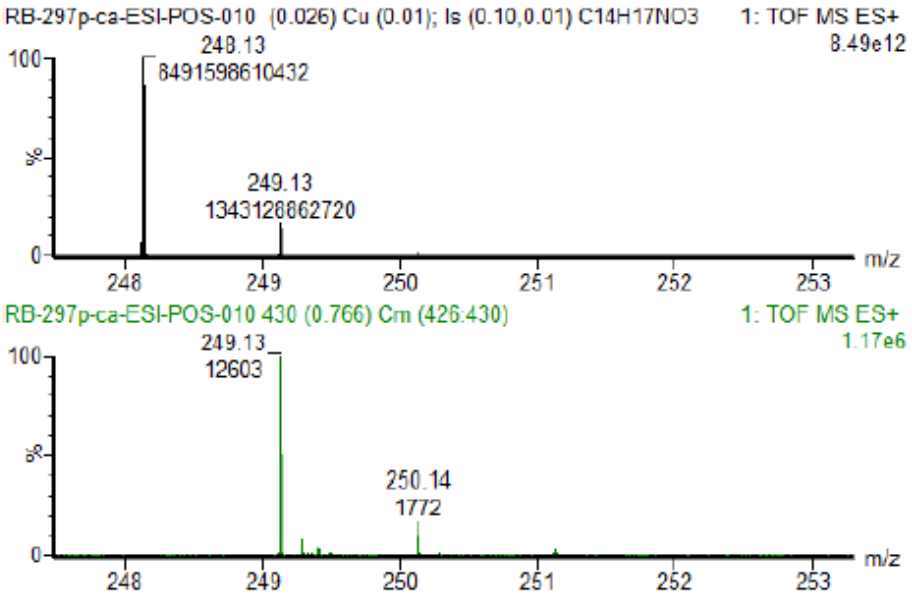
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

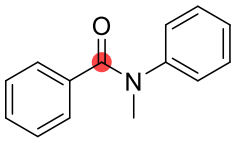
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	248	249	250	251	252	253	254	255
%	100,0	15,9	1,7	0,1	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	248	43	0,00	43,00	0,34
1	249	12603	6,84	12596,16	99,84
2	250	1772	0,73	-231,52	-1,84
3	251	388	0,04	210,63	1,67
4	252	44	0,00	1,85	0,01
5	253	0	0,00	-3,64	-0,03
6	254	0	0,00	0,34	0,00
7	255	0	0,00	0,01	0,00
8	256	0	0,00	0,00	0,00
9	257	0	0,00	0,00	0,00
10	258	0	0,00	0,00	0,00
11	259	0	0,00	0,00	0,00
Total		14850		12616,82	100,00

% Isotopic enrichment : 99,8

[^{13}C] N-methyl-N-phenylbenzamide ([^{13}C]IC3)



[^{13}C]IC3

$C_{13}{}^{13}CH_{13}NO_3$
MW: 212.26 g.mol^{-1}
Pale-yellow oil
Yield: >95%

Following the general procedure D, [^{13}C]IC3 was obtained as a pale-yellow oil (254 mg, 1.20 mmol, >95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.19 – 7.10 (m, 3H), 7.07 – 7.00 (m, 2H), 3.50 (d, J = 2.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8 (^{13}C-labeled), 145.1 (d, *J* = 2.3 Hz), 136.1 (d, *J* = 66.3 Hz), 129.7 (d, *J* = 0.9 Hz), 129.3 (2C), 128.8 (d, *J* = 2.1 Hz, 2C), 127.8 (d, *J* = 4.2 Hz, 2C), 127.0 (d, *J* = 1.2 Hz, 2C), 126.6, 38.5.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{13}H_{14}NO$: 213.1109 $[M+H]^+$; found 213.1111.

Isotopic purity (calculated by HRMS): (^{13}C) 96.2%.

FTIR (cm^{-1}): 2933, 1611, 1591, 1573, 1494, 1446, 1416, 1352, 1297, 1278, 1176, 1105, 1076, 1026, 995, 784, 769, 719, 698, 654, 578.

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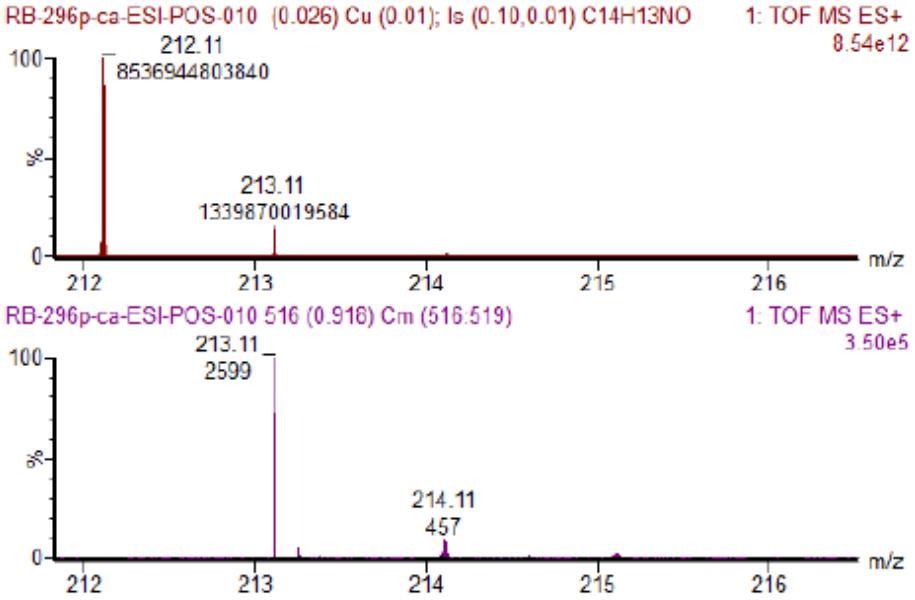
Isotopic Enrichment



theorical isotopic distribution

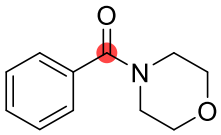
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	212	213	214	215	216	217	218	219
%	100,0	15,7	1,3	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	212	6	0,00	6,00	0,22
1	213	2599	0,94	2598,06	96,19
2	214	457	0,08	49,03	1,82
3	215	98	0,00	56,53	2,09
4	216	0	0,00	-9,51	-0,35
5	217	0	0,00	0,76	0,03
6	218	0	0,00	0,00	0,00
7	219	0	0,00	-0,01	0,00
8	220	0	0,00	0,00	0,00
9	221	0	0,00	0,00	0,00
10	222	0	0,00	0,00	0,00
11	223	0	0,00	0,00	0,00
Total		3160		2700,85	100,00

% Isotopic enrichment : 96,2

[^{13}C] morpholino(phenyl)methanone ([^{13}C]IC6)



[^{13}C]IC6

$C_{11}H_{13}NO_2$
MW: 192.22 g.mol^{-1}
White solid
Yield: 75%

Following the general procedure D, [^{13}C]IC6 was obtained as a white solid (214 mg, 1.11 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.32 (m, 5H), 3.93 – 3.33 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 135.3 (d, *J* = 66.5 Hz), 130.0 (d, *J* = 1.0 Hz), 128.72 (d, *J* = 4.3 Hz, 2C), 127.2 (d, *J* = 2.1 Hz, 2C), 67.05, 67.04, 48.4, 42.7.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{10}H_{14}NO_2$: 193.1059 $[M+H]^+$; found 193.1062.

Isotopic purity (calculated by HRMS): (^{13}C) 94.6%.

FTIR (cm^{-1}): 2922, 2855, 1594, 1573, 1446, 1419, 1300, 1274, 1251, 1155, 1114, 1067, 1011, 841, 782, 707, 549.

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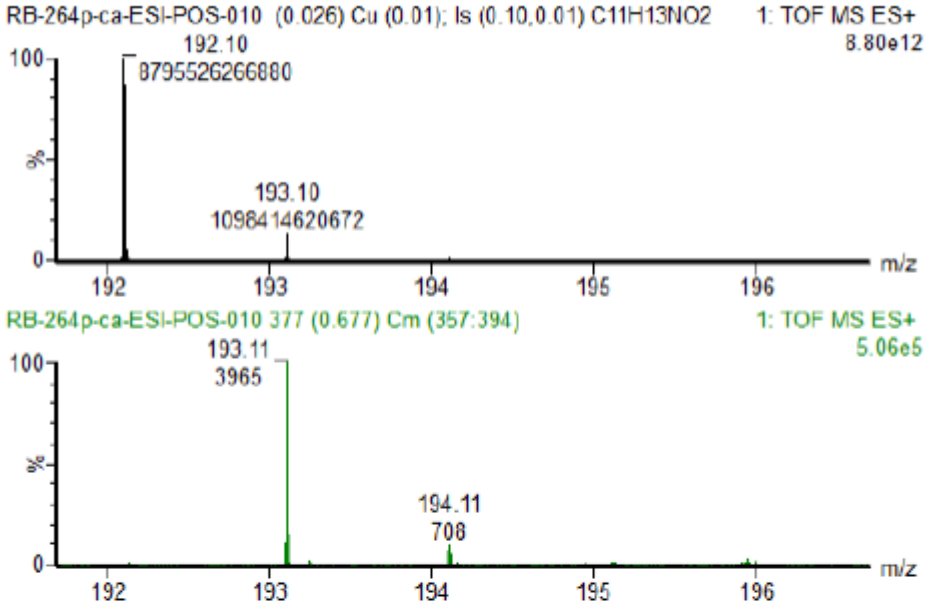
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

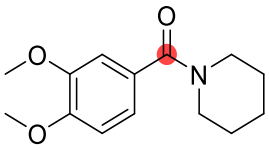
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	192	193	194	195	196	197	198	199
%	100,0	12,6	1,0	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	192	14	0,00	14,00	0,33
1	193	3965	1,76	3963,24	94,60
2	194	708	0,14	208,49	4,98
3	195	72	0,00	6,10	0,15
4	196	0	0,00	-2,85	-0,07
5	197	0	0,00	0,30	0,01
6	198	0	0,00	-0,01	0,00
7	199	0	0,00	0,00	0,00
8	200	0	0,00	0,00	0,00
9	201	0	0,00	0,00	0,00
10	202	0	0,00	0,00	0,00
11	203	0	0,00	0,00	0,00
Total		4759		4189,26	100,00

% Isotopic enrichment : 94,6

[^{13}C]-*(3,4-dimethoxyphenyl)(piperidin-1-yl)methanone ([^{13}C]IC5)*



[^{13}C]IC5

$C_{13}{}^{13}CH_{19}NO_3$
MW: 250.30 g.mol^{-1}
Brown oil
Yield: 88%

Following the general procedure E, [^{13}C]IC5 was obtained as a brown oil (80 mg, 0.32 mmol, 88%).

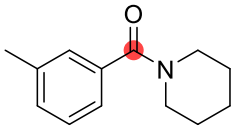
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 – 6.9 (m, 2H), 6.8 (d, *J* = 7.7 Hz, 1H), 3.90 – 3.78 (m, 6H), 3.8 – 3.2 (m, 4H), 1.7 – 1.4 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3 (^{13}C-labeled), 150.0 (d, *J* = 1.0 Hz), 149.0 (d, *J* = 5.1 Hz), 128.9 (d, *J* = 67.3 Hz), 119.9 (d, *J* = 2.1 Hz), 110.8 (d, *J* = 2.8 Hz), 110.6 (d, *J* = 5.1 Hz), 55.92, 55.90, 49.2, 43.6, 26.3 (2C), 24.8.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{13}H_{20}NO_3$: 251.1477 $[M+H]^+$; found 251.1478.

FTIR (cm^{-1}): 3000, 2934, 2854, 1593, 1571, 1515, 1463, 1443, 1421, 1368, 1350, 1328, 1261, 1239, 1222, 1183, 1138, 1108, 1025, 1005, 941, 902, 867, 854, 811, 767, 742, 723, 640, 610, 485.

[^{13}C]-*piperidin-1-yl(m-tolyl)methanone ([^{13}C]IC4)*



[^{13}C]IC4

$C_{12}{}^{13}CH_{17}NO$
MW: 204.28 g.mol^{-1}
Colorless oil
Yield: 35%

Following the general procedure E, [^{13}C]IC4 was obtained as a colorless oil (32 mg, 0.16 mmol, 35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 2H), 7.22 – 7.12 (m, 2H), 3.65 (bs, 2H) 3.30 (bs, 2H), 2.32 (s, 3H), 1.72 – 1.35 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 (^{13}C-labeled), 138.4 (d, *J* = 4.4 Hz), 136.6 (d, J = 65.9 Hz), 130.1 (d, *J* = 0.9 Hz), 128.3 (d, *J* = 4.4 Hz), 127.5 (d, *J* = 1.9 Hz), 123.8 (d, *J* = 2.0 Hz), 48.9, 43.2, 26.7, 25.7, 24.7, 21.5.

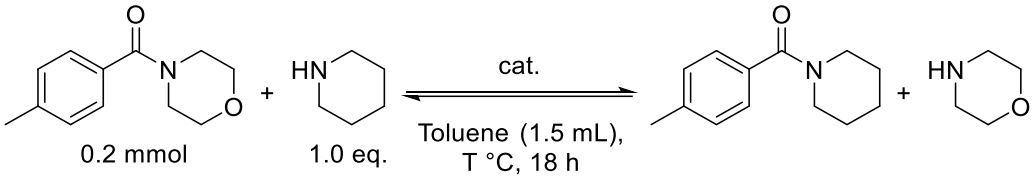
HRMS (ESI-TOF) m/z calcd for $^{13}CC_{12}H_{18}NO$: 205.1422 $[M+H]^+$; found 205.1422.

FTIR (cm^{-1}): 3040, 2934, 2855, 1591, 1578, 1426, 1368, 1350, 1273, 1209, 1154, 1128, 1109, 1091, 1028, 1001, 955, 897, 853, 812, 789, 728, 689, 635, 459, 419.

V. Synthetic procedure and analytical data for the amide exchange by transamidation

Preliminary attempts of transamidation:

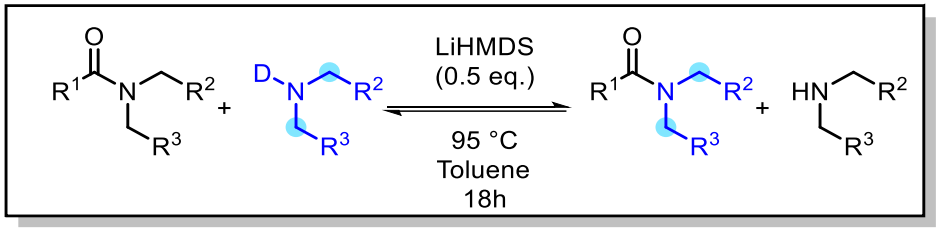
Based on the work published by the group of Stahl[26,36,37], initial attempts of transamidation and amide bond metathesis were made inspired by these procedures. The transamidation was investigated using commercially available tetrakis(dimethylamido) zirconium(IV) ($Zr(NMe_2)_4$) and tris(dimethylamino) aluminium dimer ($Al_2(NMe_2)_6$). Unfortunately, in our hands no exchange was observed on the model reaction represented in Figure S3.



Entry	Cat.	Cat quantity	T °C	Result
1	$Zr(NMe_2)_4$	2.5 %	25 °C	No exchange
2	$Zr(NMe_2)_4$	5.0 %	50 °C	No exchange
3	$Al_2(NMe_2)_6$	5.0 %	95 °C	No exchange

Figure S3 : Preliminary attempts of transamidation.

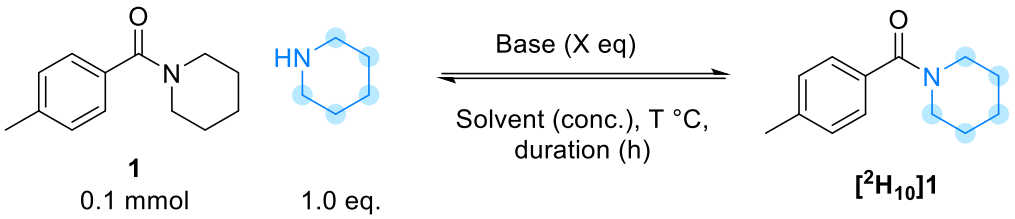
General procedure F: amide exchange by transamidation



An oven dried 5 mL micro-wave tube was cooled under vacuum then filled with nitrogen. The tube was charged with unlabeled amide (0.2 mmol, 1.0 eq.) and purged with 3 cycles vacuum/N_2. Then, dry toluene (2.0 mL, 0.1 M) was added, followed by fully deuterated amine (0.2 mmol, 1.0 eq.) and LiHMDS (1M in THF, between 0.1 and 0.5 mmol). The tube was then sealed and stirred at the desired temperature (between 55 °C or 95 °C) for 18h. After the indicated time, the reaction mixture was allowed to cool to room temperature, opened and 0.5 mL of methanol were slowly added, and the mixture was stirred for 5 minutes. The mixture was evaporated to dryness. The resulting crude was diluted in heptane/EtOAc (1/1) (sonication might be required), filtrated through a silica pad (ca. 300 mg) and washed 3 times with the same heptane/EtOAc mixture. The filtrate was concentrated under vacuum.

When required, a purification of the compound by a silica gel column chromatography was performed using heptane and ethyl acetate as eluent (from 4/1 to 1/1).

a. Optimisation



1
0.1 mmol

1.0 eq.

$[^2H_{10}]$**1**

Entry	Base	X eq.	T °C	Solvent (concentration)	Duration (h)	Yield (isolated)	IE (NMR)
1	LiHMDS	**0.75 eq.**	95 °C	Toluene (0.1M)	18 h	41%	*51%*
2	LiHMDS	**0.5 eq.**	95 °C	Toluene (0.1M)	18 h	85%	*51%*
3	LiHMDS	**0.25 eq.**	95 °C	Toluene (0.1M)	18 h	97%	*50%*
4	LiHMDS	**0.10 eq.**	95 °C	Toluene (0.1M)	18 h	97%	0%
5	LiHMDS	**0.05 eq.**	95 °C	Toluene (0.1M)	18 h	98%	0%
6	**NaHMDS**	0.25 eq.	95 °C	Toluene (0.1M)	18 h	79%	0%
7	***n*BuLi**	0.25 eq.	95 °C	Toluene (0.1M)	18 h	44%	*45%*
8	**KHMDS**	0.25 eq.	95 °C	Toluene (0.1M)	18 h	78%	0%
9	LiHMDS	0.25 eq.	95 °C	**THF** (0.1M)	18 h	91%	37%
10	LiHMDS	0.25 eq.	95 °C	**Chloroform** (0.1M)	18 h	70%	0%
11	LiHMDS	0.25 eq.	95 °C	**ACN** (0.1M)	18 h	75%	0%
12	LiHMDS	0.25 eq.	**55 °C**	Toluene (0.1M)	18 h	97%	51%
13	LiHMDS	0.25 eq.	**r.t.**	Toluene (0.1M)	18 h	96%	0%
14	LiHMDS	0.25 eq.	55 °C	Toluene (0.1M)	**2 h**	88%	26%
15	LiHMDS	0.25 eq.	55 °C	Toluene (0.1M)	**6 h**	96%	45%
16	LiHMDS	0.25 eq.	55 °C	Toluene (**0.2M**)	18 h	96%	47%
17	LiHMDS	0.25 eq.	55 °C	Toluene (**0.4M**)	18 h	93%	45%

Table S1 : Optimisation of the transamidation reaction

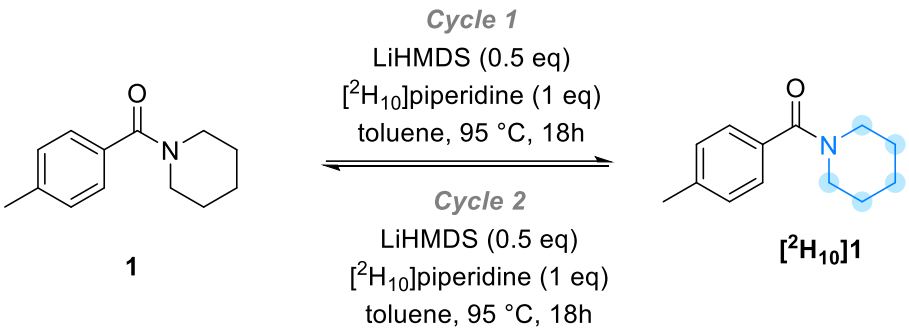
b. Effect of stoichiometry on isotopic enrichment

To examine the effect of deuterated amine stoichiometry on isotopic enrichment (IE), we employed two methods:

i) A sequential approach involving multiple transamidation cycles on a single amide;

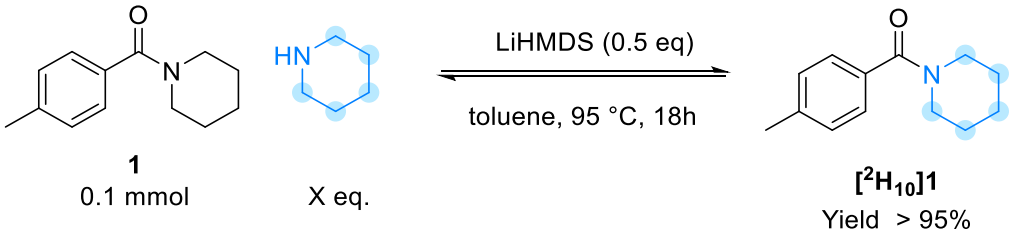
ii) An approach where the equivalent of deuterated amine was varied in a single reaction.

i. Sequential procedure (multiple cycles)



Following the general procedure F (described on page S52), a first labeling of the amide was achieved (IE_{Cycle1} = 50%). Without further purification (only filtration on silica pad), the crude mixture was transferred to a reactor tube and a second labeling following the general procedure F was achieved (IE_{Cycle2} = 63%). A high yield of 94% was obtained over two steps. After the second cycle we obtained a lower IE than expected (IE_{max} = 75%) which can be explained by the fact that the amide was not dry enough after the first cycle.

ii. Varying the stoichiometry of the ^{2}H-labeled amine



Following the general procedure F on a 0.20 mmol scale using 0.5, 1.0, 2.0 and 3 eq. of deuterated piperidine. The isotopic enrichments were measured by HRMS (ESI-TOF). As shown in Figure S4, the experimentally observed IE values closely align with the maximum theoretical values dictated by stoichiometry.

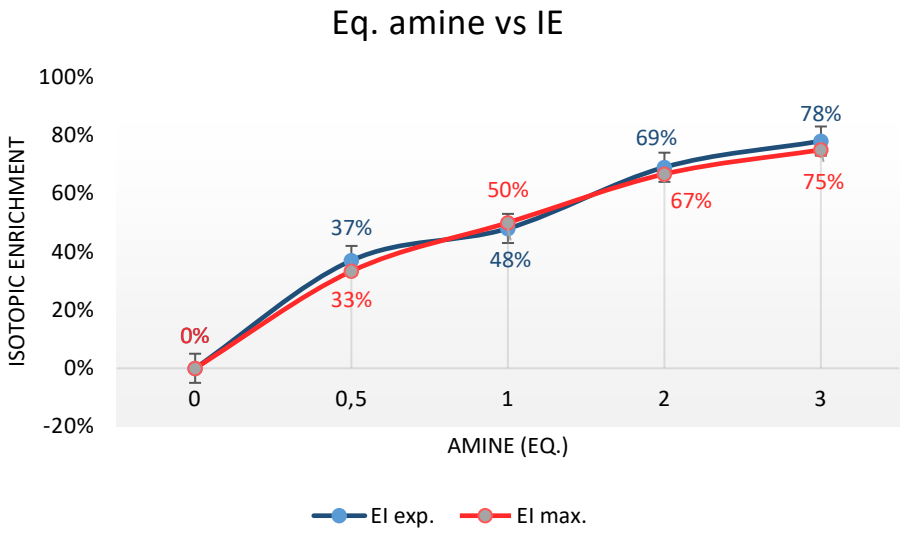


Figure S4: Impact of the number of equivalentsof labeled amine the IE. a comparison is shown between the maximal theoretical IE (Red, IEmax) and the values measured (Blue, IEexp, measurement error +/- 5%).

c. Base-promoted deuteration under the experimental conditions.

During our exploration of the transamidation reaction scope, we observed deuterium incorporation at sites other than the desired amine moiety of the amide product in certain substrates. This additional deuterium incorporation originates from the fully deuterated amines used as starting materials for transamidation, specifically from the labile deuterium atoms bound to nitrogen of the commercial reagent (*i.e.* R_1R_2N-D).

We observed partial deuterium incorporation at two types of positions:

- Acidic positions such as those *alpha* to a carbonyl of an ester/amide (pKa ~ 25) are deprotonated by the strong base LiHMDS (pKa ~ 26).
- Ortho positions of aromatic rings: These positions can be activated by a lithium chelate formed with the carbonyl group. This six-membered chelate ring enhances the acidity of the ortho proton, facilitating deuterium exchange with the labile deuterium from the commercial deuterated amine.[38]

In the 'Synthetic procedure and analytical data (transamidation)' section, we highlighted the positions of base-promoted deuteration with a lighter blue color and indicated the corresponding isotopic enrichment

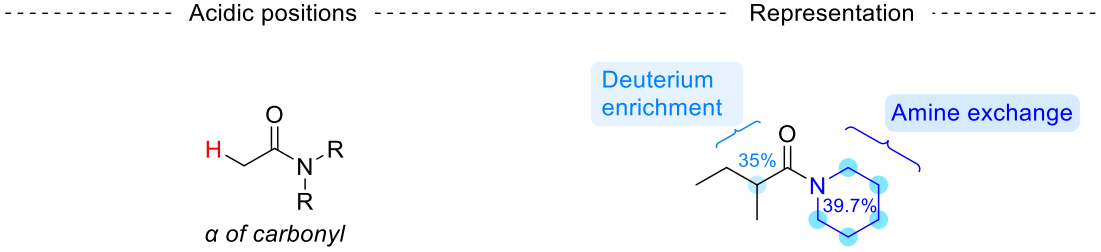
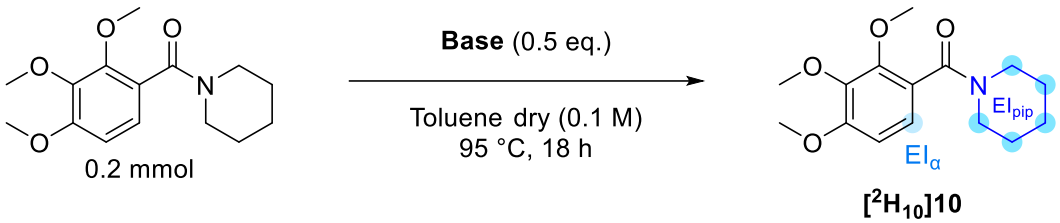


Figure S5: Examples of observed base-promoted deuterations under our experimental conditions.

We investigated other weak bases with the aim of preventing the unexpected deuteration while still performing the transamidation exchange. Taking the example [$^2H_{10}$]10 with a clear deuteration in *alpha* of the amide (IE_α = 42%) and a maximum enrichment on the piperidine moiety (IE_{pip} = 51%) with our standard transamidation conditions (General procedure F : LiHMDS 0.5 eq., 95 °C, 18 h, toluene dry) and tested 4 weaker bases : K_2CO_3, Et_3N, NaOtBu and Li_2CO_3.



[$^2H_{10}$]10

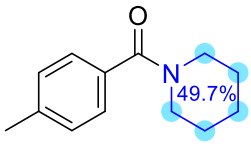
Entry	Base	Yield	IE_{pip} (NMR)	IE_α (NMR)
1	LiHMDS	97%	52%	42%
2	K_2CO_3	93%	0%	0%
3	Et_3N	93%	0%	0%
4	NaOtBu	>95%	0%	0%
5	Li_2CO_3	93%	0%	0%

Figure 6 : Investigation on aromatic deuteration

All bases tested didn't promote the aromatic deuteration in *ortho* to the amide, however the bases were also too weak to catalyze the amine exchange.

In conclusion, all bases resulted in a full recovery of the unlabeled amide.

(piperidin-1-yl-d_{10})(p-tolyl)methanone ([$^2H_{10}$]1)



[$^2H_{10}$]1

$C_{13}H_7D_{10}NO$
MW: 213.35 g.mol^{-1}
White solid
Yield: >95%
IE: 50%

Following the general procedure F, [$^2H_{10}$]1 was obtained as a white solid (43 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 55 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.21 – 7.14 (m, 2H), 3.80 – 3.21 (bs, 2.1H), 2.35 (s, 3H), 1.74 – 1.40 (m, 3.40H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 139.5, 133.6, 129.0 (2C), 127.0 (2C), 48.9, 43.2, 26.6, 25.7, 24.7, 21.4.

^{2}H NMR (61 MHz, $CHCl_3$): δ 4.01 – 2.90 (bs), 1.81 – 0.89 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_8D_{10}NO$: 214.2016 $[M+H]^+$; found 214.2013.

Isotopic exchange (calculated by ^{1}H NMR): 48%.

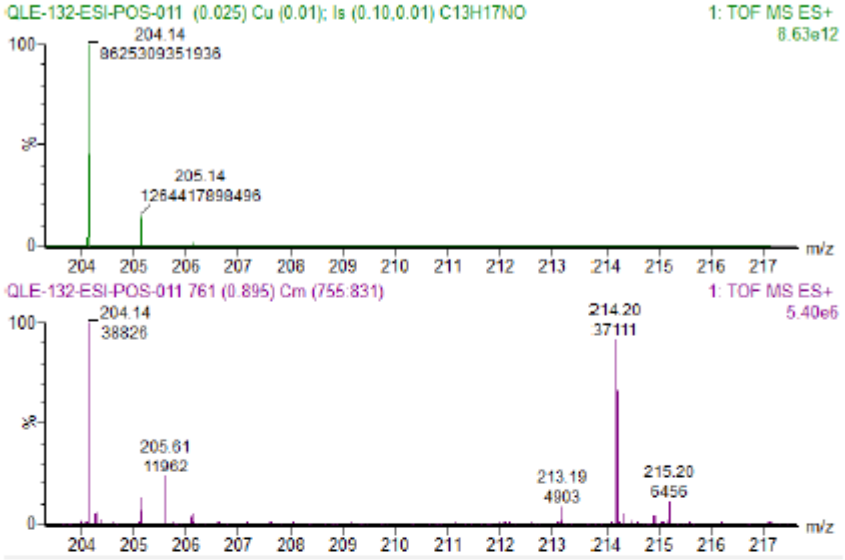
Isotopic exchange (calculated by HRMS): 49.7%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2211, 2111, 1622, 1510, 1401, 1274, 1240, 1211, 1182, 1129, 1107, 1026, 1001, 966, 898, 830, 790, 750, 668, 634.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

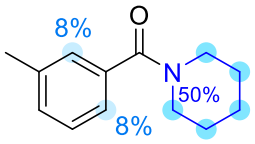
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	204	205	206	207	208	209	210	211
%	100	14,7	1,2	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	204	61727,602	0,00	61727,60	46,78
1	205	11351,101	9073,96	2277,14	1,73
2	206	1058,948	740,73	-16,52	-0,01
3	207	40,174	0,00	15,28	0,01
4	208	0	0,00	-2,05	0,00
5	209	0	0,00	0,12	0,00
6	210	0	0,00	0,01	0,00
7	211	0	0,00	0,00	0,00
8	212	528,922	0,00	528,92	0,40
9	213	7733,767	0,00	7656,02	5,80
10	214	59335,797	0,00	58204,02	44,11
11	215	10200,761	0,00	1552,90	1,18
12	216	963,613	0,00	36,89	0,03
13	217	0	0,00	-24,06	-0,02
14	218	0	0,00	3,09	0,00
Total		152940,69		1,32E+05	100,00

Echange %	49,7
Enrichissement %	3,7

(piperidin-1-yl-d10)(m-tolyl)methanone ([$^2H_{10}$]2)



[$^2H_{10}$]2

$C_{13}H_7D_{10}NO$
MW: 213.35 g.mol^{-1}
White solid
Yield: >95%
IE: 50%

Following the general procedure F, [$^2H_{10}$]2 was obtained as a white solid (42 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 1H), 7.22 – 7.12 (m, 2.85H), 3.70 (bs, 1.02H), 3.33 (bs, 1.01H), 2.36 (s, 3H), 1.66 (bs, 2.17H), 1.51 (bs, 1.09H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 138.3, 136.6, 130.1, 128.3, 127.5, 123.7, 48.8, 43.1, 26.6, 25.7, 24.7, 21.4.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.85 – 3.08 (m), 1.91 – 1.25 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_8D_{10}NO$: 214.2016 $[M+H]^+$; found 214.2019.

Isotopic exchange (calculated by ^{1}H NMR): 47%.

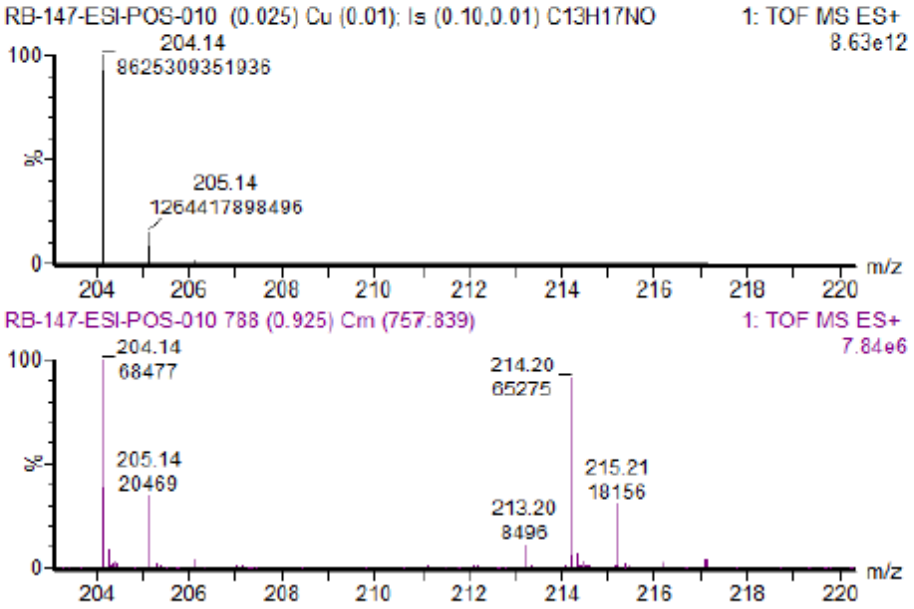
Isotopic exchange (calculated by HRMS): 50.0%.

Isotopic enrichment (calculated by HRMS): 13% monodeuteration (M+1), 1.6% bideuteration (M+2).

FTIR (cm^{-1}): 2933, 2854, 2212, 2110, 1624, 1584, 1429, 1398, 1279, 1258, 1211, 1154, 1128, 1108, 1091, 1028, 1000, 976, 955, 898, 872, 853, 813, 793, 740, 707, 690, 666, 636, 612, 524, 461, 439, 421.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

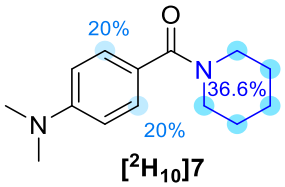
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	204	205	206	207	208	209	210	211
%	100	14,7	1,2	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	204	68477	0,00	68477,0	42,19
1	205	20469	10066,12	10402,88	6,41
2	206	3621	821,72	1270,05	0,78
3	207	625	0,00	313,47	0,19
4	208	0	0,00	-61,32	-0,04
5	209	0	0,00	5,25	0,00
6	210	0	0,00	-0,04	0,00
7	211	0	0,00	-0,06	0,00
8	212	0	0,00	0,01	0,00
9	213	8496	0,00	8496,00	5,24
10	214	65275	0,00	64026,09	39,45
11	215	18156	0,00	8642,21	5,33
12	216	2611	0,00	572,28	0,35
13	217	361	0,00	173,17	0,11
14	218	0	0,00	-32,32	-0,02
Total		188091		1,62E+05	100,00

Echange %	50,0
Enrichissement (+1D) %	13,0
Enrichissement (+2D) %	1,6

(4-(dimethylamino)phenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]7)



[$^2H_{10}$]7

$C_{14}H_{10}D_{10}N_2O$
MW: 242.39 g.mol^{-1}
White solid
Yield: >95%
IE: 36.6%

Following the general procedure F, [$^2H_{10}$]7 was obtained as a white solid (47 mg, 0.19 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 1.6H), 6.69 – 6.62 (m, 2H), 3.54 (bs, 2.19H), 2.97 (s, 6H), 1.70 – 1.50 (m, 3.38H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 151.4, 129.1 (2C), 123.5, 111.3 (2C), 40.3 (2C), 26.2 (2C), 24.8 (2 carbons missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.36 (bs), 3.50 (bs), 1.55 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{14}H_{11}D_{10}N_2O$: 243.2281 $[M+H]^+$; found 243.2280.

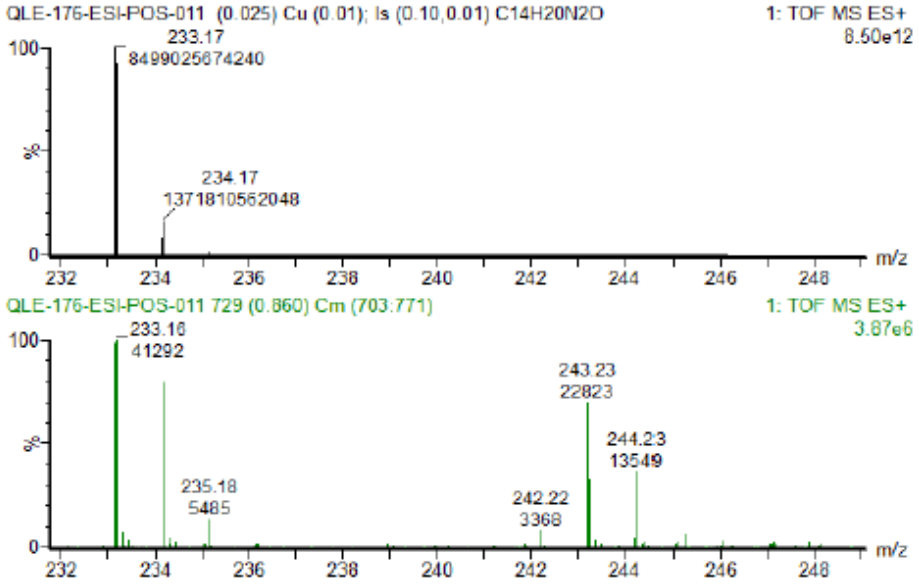
Isotopic exchange (calculated by HRMS): 36.6%.

Isotopic enrichment (calculated by HRMS): 28.5% monodeuteration (M+1), 3.5% bideuteration (M+2).

FTIR (cm^{-1}): 2936, 2850, 2811, 2206, 2109, 1601, 1525, 1482, 1442, 1413, 1385, 1359, 1292, 1273, 1230, 1211, 1193, 1169, 1159, 1124, 1100, 1063, 1022, 1009, 993, 970, 941, 894, 867, 847, 823, 764, 752, 709, 666, 632.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

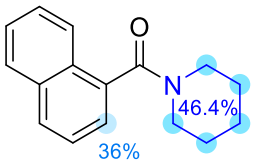
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	233	234	235	236	237	238	239	240
%	100	16,2	1,4	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	233	41292	0,00	41292,00	42,22
1	234	24018	6689,30	17328,70	17,72
2	235	5485	578,09	2099,66	2,15
3	236	885	0,00	302,25	0,31
4	237	63	0,00	-15,36	-0,02
5	238	0	0,00	-1,74	0,00
6	239	0	0,00	0,50	0,00
7	240	0	0,00	-0,06	0,00
8	241	0	0,00	0,00	0,00
9	242	3368	0,00	3368,00	3,44
10	243	22823	0,00	22277,38	22,78
11	244	13549	0,00	9892,91	10,11
12	245	3047	0,00	1132,46	1,16
13	246	460	0,00	138,04	0,14
14	247	37	0,00	-1,22	0,00
Total		115027		9,78E+04	100,00

Echange %	36,6
Enrichissement (+1D) %	28,5
Enrichissement (+2D) %	3,5

naphthalen-1-yl(piperidin-1-yl-d10)methanone ([$^2H_{10}$]4)



[$^2H_{10}$]4

$C_{16}H_7D_{10}NO$
MW: 249.38 g.mol^{-1}
White solid
Yield: >95%
IE: 46.4%

Following the general procedure F, [$^2H_{10}$]4 was obtained as a white solid (49 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 3H), 7.55 – 7.43 (m, 3H), 7.39 (dd, J = 6.9, 1.3 Hz, 0.63H), 3.87 (q, *J* = 5.5 Hz, 1.11H), 3.12 (dd, *J* = 6.2, 4.9 Hz, 1.11H), 1.70 (bs, 2.29H), 1.39 (bs, 1.11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 135.0, 133.6, 129.7, 128.9, 128.4, 126.9, 126.4, 125.3, 125.0, 123.5, 48.4, 42.8, 26.8, 25.9, 24.6.

^{2}H NMR (61 MHz, $CHCl_3$) δ 7.43 (bs), 3.83 (bs), 3.08 (bs), 1.64 (bs), 1.33 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{16}H_8D_{10}NO$: 250.2016 $[M+H]^+$; found 250.2013.

Isotopic exchange (calculated by ^{1}H NMR): 45%.

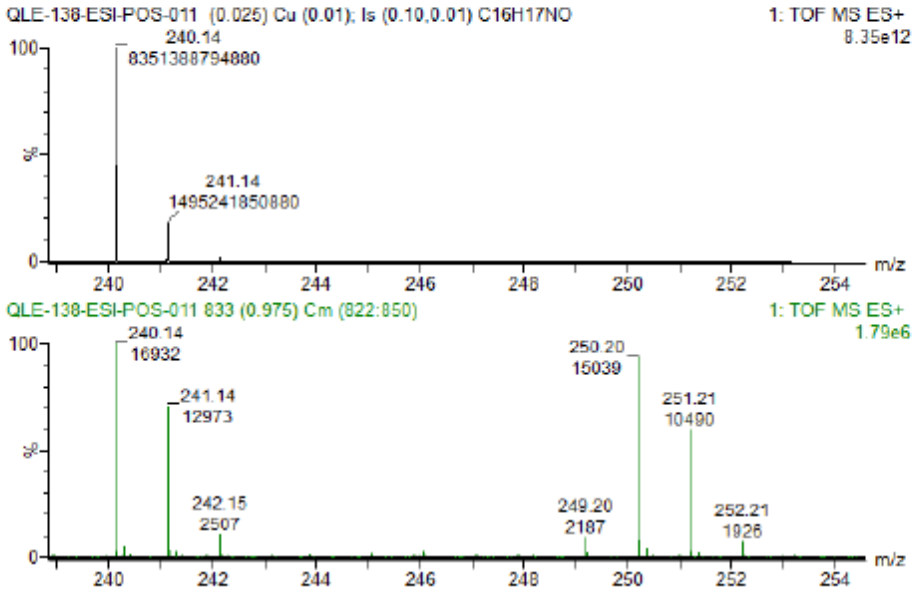
Isotopic exchange (calculated by HRMS): 46.4%.

Isotopic enrichment (calculated by HRMS): 36.4% monodeuteration (M+1), 1.6% bideuteration (M+2).

FTIR (cm^{-1}): 3046, 2933, 2856, 2206, 2109, 1616, 1505, 1472, 1439, 1386, 1365, 1281, 1214, 1134, 1069, 1023, 984, 953, 938, 872, 847, 814, 764, 741, 718, 688, 629.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

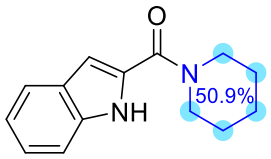
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	240	241	242	243	244	245	246	247
%	100	18	1,7	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	240	16932	0,00	16932,00	32,39
1	241	12973	3047,76	9925,24	18,99
2	242	2507	287,84	432,61	0,83
3	243	316	16,93	52,47	0,10
4	244	31	0,00	4,28	0,01
5	245	0	0,00	-2,09	0,00
6	246	0	0,00	0,25	0,00
7	247	0	0,00	-0,01	0,00
8	248	0	0,00	0,00	0,00
9	249	2187	0,00	2187,00	4,18
10	250	15039	0,00	14645,34	28,02
11	251	10490	0,00	7816,66	14,95
12	252	1926	0,00	267,84	0,51
13	253	199	0,00	3,26	0,01
14	254	17	0,00	4,04	0,01
Total		62617		5,23E+04	100,00

Echange %	46,4
Enrichissement (+1D) %	36,4
Enrichissement (+2D) %	1,6

(1H-indol-2-yl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]24)



[$^2H_{10}$]24

$C_{14}H_6D_{10}N_2O$
MW: 238.36 g.mol^{-1}
White solid
Yield: 68%
IE: 50.9%

Following the general procedure F, [$^2H_{10}$]24 was obtained as a white solid (32 mg, 0.13 mmol, 68%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (bs, 1H), 7.65 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.42 (dq, *J* = 8.2, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.2 Hz,1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.77 (dd, *J* = 2.2, 1.0 Hz, 1H), 3.89 (s, 2.2H), 1.72 (bs, 3.43H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 136.0, 129.9, 127.5, 124.0, 121.7, 120.3, 112.0, 104.8, 26.3 (2C), 24.8 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.84 (bs), 1.66 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{14}H_7D_{10}N_2O$: 239.1969 $[M+H]^+$; found 239.1968.

Isotopic exchange (calculated by ^{1}H NMR): 44%.

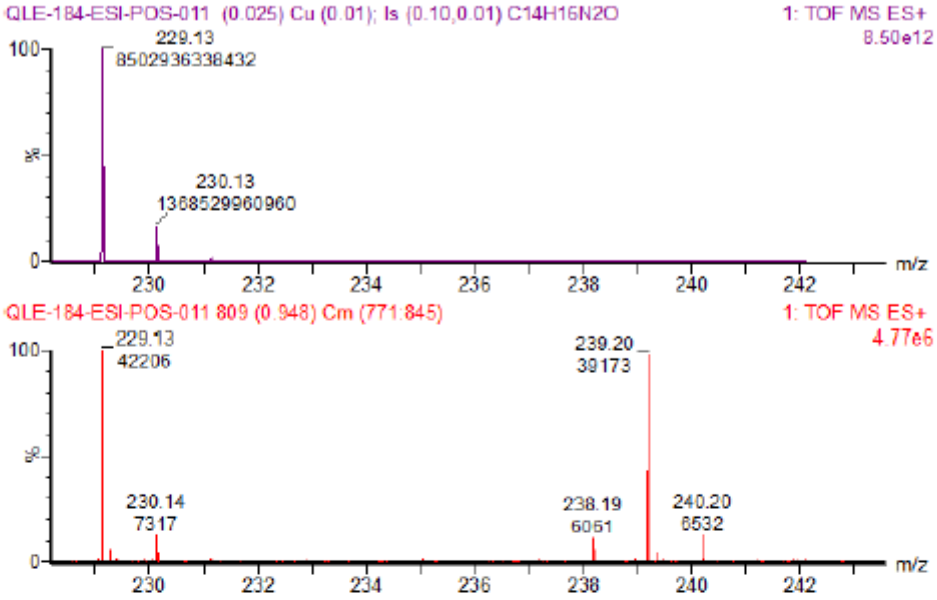
Isotopic exchange (calculated by HRMS): 50.9%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 3235, 2925, 2853, 2209, 2106, 1601, 1527, 1429, 1410, 1371, 1343, 1298, 1256, 1242, 1153, 1138, 1122, 1012, 954, 932, 900, 853, 832, 805, 766, 744, 731, 684, 665, 609.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

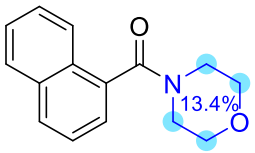
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	229	230	231	232	233	234	235	236
%	100	16,1	1,4	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	229	42206	0,00	42206,00	48,19
1	230	7317	6795,17	521,83	0,60
2	231	838	590,88	163,10	0,19
3	232	105	0,00	71,44	0,08
4	233	0	0,00	-13,78	-0,02
5	234	0	0,00	1,22	0,00
6	235	0	0,00	0,00	0,00
7	236	0	0,00	-0,02	0,00
8	237	0	0,00	0,00	0,00
9	238	6061	0,00	6061,00	6,92
10	239	39173	0,00	38197,18	43,62
11	240	6532	0,00	297,40	0,34
12	241	600	0,00	17,36	0,02
13	242	70	0,00	63,04	0,07
14	243	0	0,00	-10,39	-0,01
Total		102902		8,76E+04	100,00

Echange %	**50,9**
Enrichissement (+1D) %	**1,2**
Enrichissement (+2D) %	**0,4**

(morpholino-d8)(naphthalen-1-yl)methanone ([$^2H_{10}$]29)



[$^2H_{10}$]29

$C_{15}H_7D_8NO_2$
MW: 249.34 g.mol^{-1}
White solid
Yield: 68%
IE: 13.4%

Following the general procedure F, [$^2H_8$]29 was obtained as a white solid after purification (34 mg, 0.14 mmol, 68%) using 0.2 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.80 (m, 3H), 7.58 – 7.44 (m, 3H), 7.41 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.11 – 3.77 (m, 3.69H), 3.51 (bs, 1.82H), 3.26 – 3.11 (bs, 1.82H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.5, 133.7, 133.5, 129.6, 129.4, 128.6, 127.2, 126.6, 125.3, 124.7, 124.0, 67.2, 67.1, 47.7, 42.3.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.81 (bs), 3.48 (bs), 3.16 (bs).

Isotopic exchange (calculated by ^{1}H NMR): 9%.

Isotopic exchange (calculated by HRMS): 13.4%.

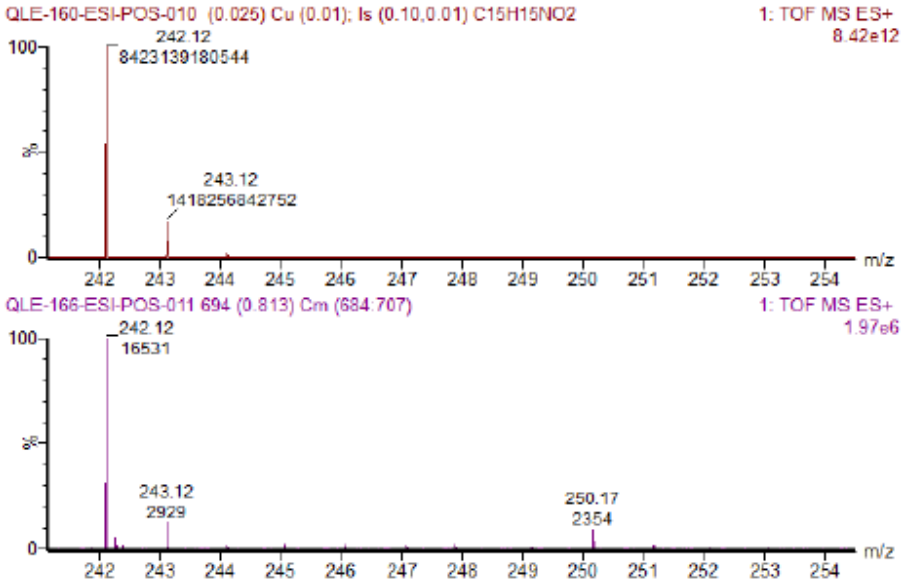
HRMS (ESI-TOF) m/z calc'd for $C_{15}H_8D_8NO_2$: 250.1683 $[M+H]^+$; found 250.1679.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 3053, 2963, 2899, 2852, 2089, 1956, 1630, 1592, 1507, 1465, 1428, 1388, 1362, 1342, 1300, 1280, 1267, 1248, 1207, 1155, 1111, 1067, 1044, 1018, 992, 940, 894, 865, 846, 798, 778, 745, 691, 655, 635.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

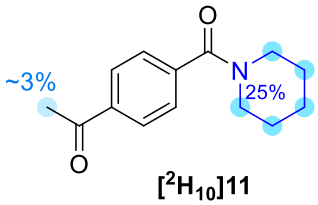
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	242	243	244	245	246	247	248	249
%	100	16,9	1,7	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	242	16531	0,00	16531,00	85,86
1	243	2929	2793,74	135,26	0,70
2	244	308	281,03	4,11	0,02
3	245	40	16,53	20,47	0,11
4	246	0	0,00	-3,67	-0,02
5	247	0	0,00	0,27	0,00
6	248	0	0,00	0,00	0,00
7	249	221	0,00	221,00	1,15
8	250	2354	0,00	2316,65	12,03
9	251	421	0,00	25,73	0,13
10	252	51	0,00	7,05	0,04
11	253	0	0,00	-3,95	-0,02
12	254	0	0,00	0,52	0,00
13	255	0	0,00	-0,03	0,00
14	256	0	0,00	0,00	0,00
Total		22855		1,93E+04	100,00

Echange %	13,4
Enrichissement (+1D) %	0,8
Enrichissement (+2D) %	0,0

1-(4-(piperidine-1-carbonyl-2,2,3,3,4,4,5,5,6,6-d10)phenyl)ethan-1-one ([$^2H_{10}$]11)



[$^2H_{10}$]11

$C_{14}H_7D_{10}NO_2$
MW: 241.36 g.mol^{-1}
White solid
Yield: 77%
IE: 25%

Following the general procedure F, [$^2H_{10}$]11 was obtained as a white solid after purification (37 mg, 0.15 mmol, 77%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.91 (m, 2H), 7.48 – 7.41 (m, 2H), 3.68 (bs, 1.54H), 3.26 (bs, 1.54H), 2.58 (s, 3H), 1.73 – 1.39 (m, 4.86H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 169.2, 141.0, 137.6, 128.5 (2C), 127.0 (2C), 48.7, 43.1, 26.8, 26.6, 25.6, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.44 (m), 2.59 (bs), 1.52 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{14}H_8D_{10}NO_2$: 242.1965 $[M+H]^+$; found 242.1963.

Isotopic exchange (calculated by ^{1}H NMR): 22%.

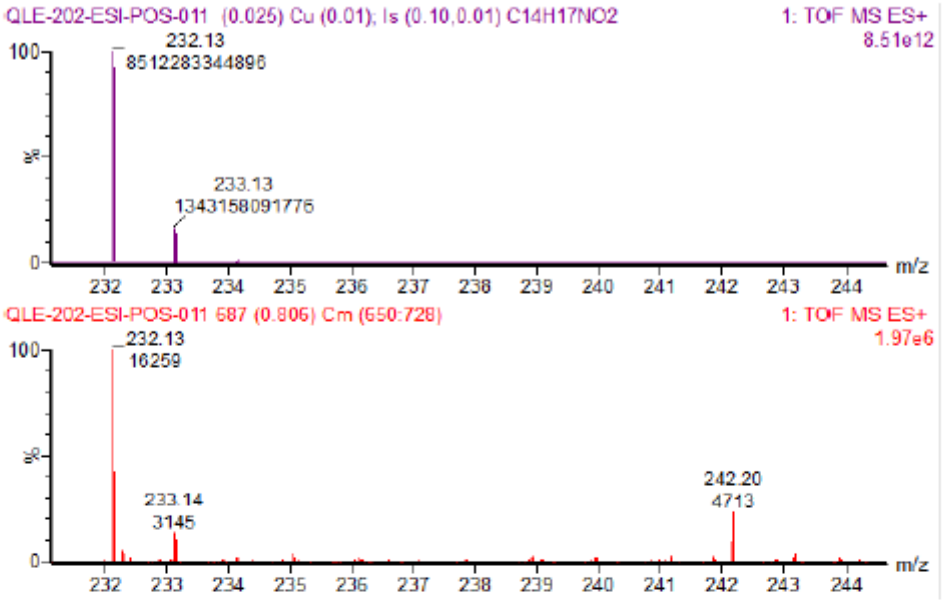
Isotopic exchange (calculated by HRMS): 25%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2934, 2854, 2210, 2110, 1678, 1616, 1504, 1440, 1420, 1357, 1269, 1130, 1110, 1030, 1004, 957, 888, 850, 761, 716, 668, 627.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

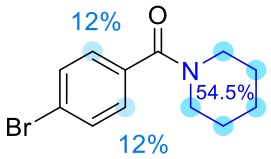
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	232	233	234	235	236	237	238	239
%	100	15,9	1,5	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	232	16259	0,00	16259,00	72,04
1	233	3145	2585,18	559,82	2,48
2	234	419	243,89	86,10	0,38
3	235	54	16,26	15,65	0,07
4	236	0	0,00	-4,34	-0,02
5	237	0	0,00	0,37	0,00
6	238	0	0,00	-0,01	0,00
7	239	0	0,00	0,00	0,00
8	240	0	0,00	0,00	0,00
9	241	734	0,00	734,00	3,25
10	242	4713	0,00	4596,29	20,37
11	243	941	0,00	199,18	0,88
12	244	226	0,00	124,65	0,55
13	245	27	0,00	-0,40	0,00
14	246	0	0,00	-2,00	-0,01
Total		26518		2,26E+04	100,00

Echange %	**25,0**
Enrichissement (+1D) %	**3,3**
Enrichissement (+2D) %	**0,5**

(4-bromophenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]15)



[$^2H_{10}$]15

$C_{12}H_4D_{10}BrNO$
MW: 278.22 g.mol^{-1}
Pale yellow solid
Yield: >95%
IE: 54.5%

Following the general procedure F, [$^2H_{10}$]15 was obtained as a pale-yellow solid (56 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 – 7.49 (m, 2H), 7.30 – 7.23 (m, 1.77H), 3.50 (bs, 2.17H), 1.75 – 1.43 (m, 3.57H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 135.3, 131.6 (2C), 128.6 (2C), 123.6, 49.1, 43.5, 26.7, 26.5, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.30 (bs), 3.46 (bs), 1.56 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_5D_{10}BrNO$: 278.0965 $[M+H]^+$; found 278.0962.

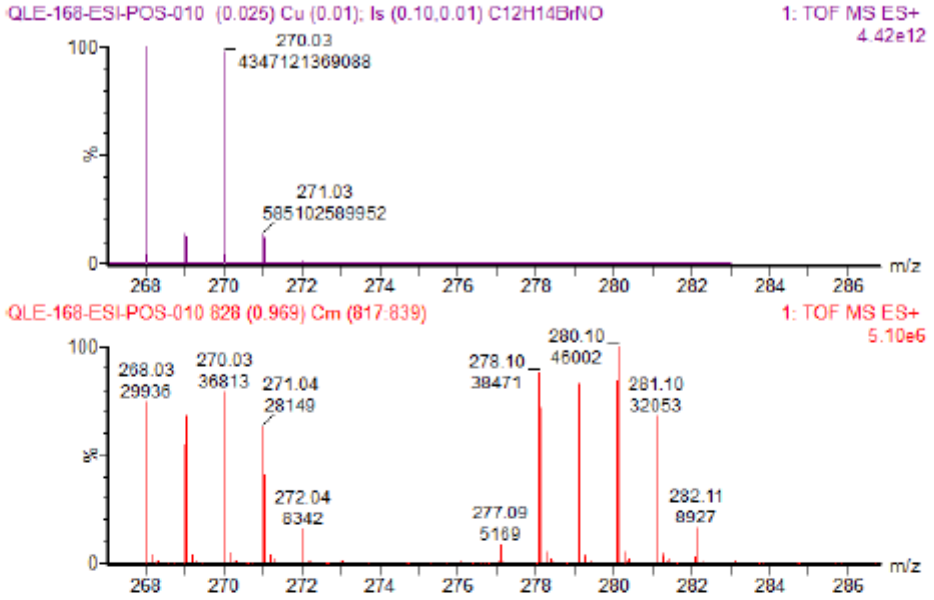
Isotopic exchange (calculated by HRMS): 54.5%.

Isotopic enrichment (calculated by HRMS): 41% monodeuteration (M+1), 7.1% bideuteration (M+2).

FTIR (cm^{-1}): 2934, 2853, 2212, 2110, 1612, 1438, 1416, 1273, 1238, 1194, 1126, 1105, 1070, 1028, 1000, 966, 942, 897, 830, 751, 732, 665.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

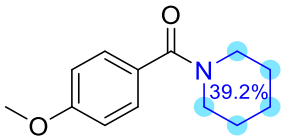
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	268	269	270	271	272	273	274	275
%	100	13,6	98,5	13,2	0,9	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	268	29936	0,00	29941,71	22,56
1	269	27809	4072,00	23697,27	17,86
2	270	36813	29492,06	4091,77	3,08
3	271	28149	3952,23	339,06	0,26
4	272	8342	269,47	873,91	0,66
5	273	1030	0,00	-217,89	-0,16
6	274	132	0,00	-786,81	-0,59
7	275	0	0,00	245,93	0,19
8	276	0	0,00	768,62	0,58
9	277	5169	0,00	4884,26	3,68
10	278	38471	0,00	37017,97	27,90
11	279	36405	0,00	26500,77	19,97
12	280	46002	0,00	5289,97	3,99
13	281	32053	0,00	253,97	0,19
14	282	8927	0,00	-155,97	-0,12
Total		299238		1,33E+05	100,04

Echange %	54,5
Enrichissement (+1D) %	41,0
Enrichissement (+2D) %	7,1

(4-methoxyphenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]8)



[$^2H_{10}$]8

$C_{13}H_7D_{10}NO_2$
MW: 229.35 g.mol^{-1}
White solid
Yield: >95%
IE: 39.2%

Following the general procedure F, [$^2H_{10}$]8 was obtained as a white solid (44 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 2H), 6.91 – 6.85 (m, 2H), 3.80 (s, 3H), 3.51 (bs, 2.26H), 1.71 – 1.47 (m, 3.59H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 160.6, 128.9 (2C), 128.7, 113.7 (2C), 55.4, 26.2 (2C), 24.7 (2 carbons missing due to due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.96 – 3.10 (m), 1.92 – .14 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_8D_{10}NO_2$: 230.1965 $[M+H]^+$; found 230.1963.

Isotopic exchange (calculated by ^{1}H NMR): 41%.

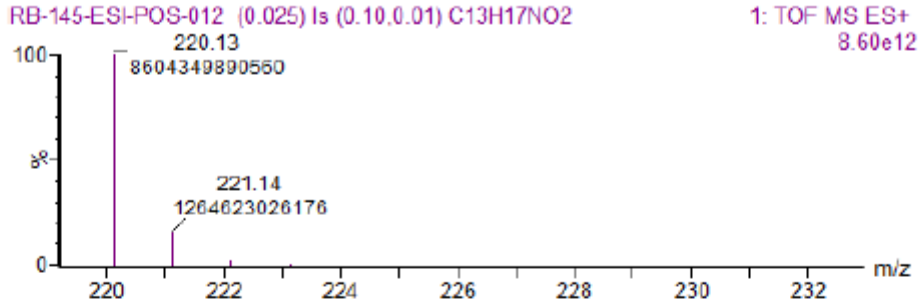
Isotopic exchange (calculated by HRMS): 39.2%.

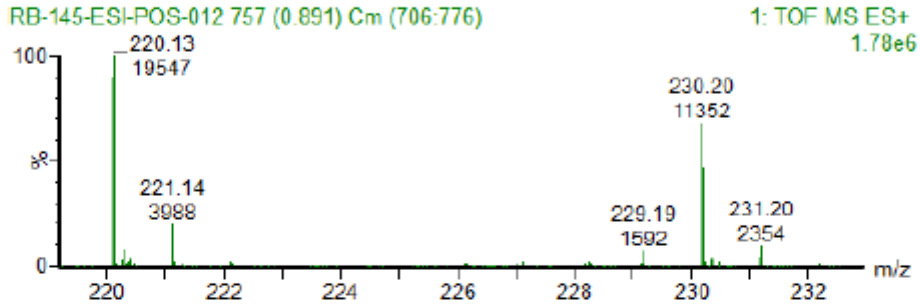
Isotopic enrichment (calculated by HRMS): 5.3% monodeuteration (M+1), 0.4% bideuteration (M+2).

FTIR (cm^{-1}): 2935, 2853, 2211, 1606, 1574, 1512, 1422, 1398, 1300, 1275, 1245, 1172, 1131, 1108, 1027, 1000, 967, 898, 886, 839, 792, 762, 713, 668, 643, 629, 592, 580, 532, 477, 425.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique





Profil isotopique théorique

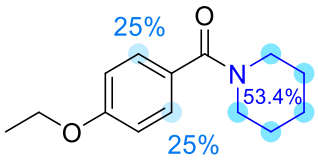
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	220	221	222	223	224	225	226	227
%	100	14,8	1,4	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	220	19547	0,00	19547,0	57,26
1	221	3988	2892,96	1095,04	3,21
2	222	519	273,66	83,28	0,24
3	223	44	19,55	-3,20	-0,01
4	224	0	0,00	-1,79	-0,01
5	225	0	0,00	0,23	0,00
6	226	0	0,00	-0,01	0,00
7	227	0	0,00	0,00	0,00
8	228	0	0,00	0,00	0,00
9	229	1592	0,00	1592,00	4,66
10	230	11352	0,00	11116,38	32,56
11	231	2354	0,00	686,49	2,01
12	232	305	0,00	46,18	0,14
13	233	0	0,00	-27,56	-0,08
14	234	0	0,00	2,75	0,01
Total		39701		3,41E+04	100,00

Echange %	39,2
Enrichissement (+1D) %	5,3
Enrichissement (+2D) %	0,4

(4-ethoxyphenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]9)



[$^2H_{10}$]9

$C_{14}H_9D_{10}NO_2$
MW: 243.37 g.mol^{-1}
White solid
Yield: 70%
IE: 53.4%

Following the general procedure F, [$^2H_{10}$]9 was obtained as a white solid after purification (34 mg, 0.14 mmol, 70%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 1.51H), 6.90 – 6.82 (m, 2H), 4.03 (q, J = 7.1, 2H), 3.86 – 3.06 (m, 1.94H), 1.80 – 1.45 (m, 2.85H), 1.40 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 159.9, 128.8 (2C), 114.1 (2C), 114.0, 63.5, 26.3 (2C), 24.7, 14.7 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.37 (bs), 3.48 (bs), 1.55 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{14}H_{10}D_{10}NO_2$: 244.2122 $[M+H]^+$; found 244.2121.

Isotopic exchange (calculated by ^{1}H NMR): 53%.

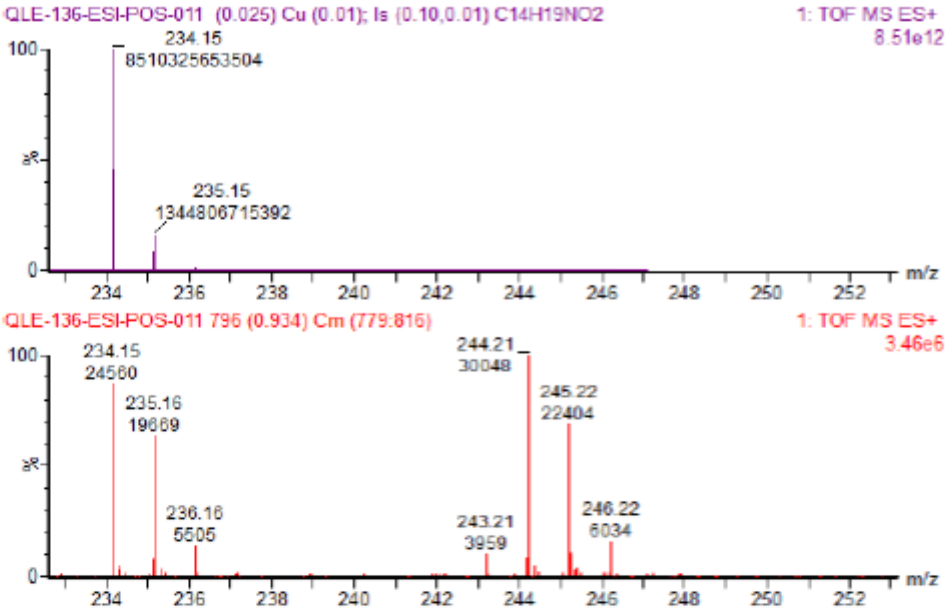
Isotopic exchange (calculated by HRMS): 53.4%.

Isotopic enrichment (calculated by HRMS): 36.9% monodeuteration (M+1), 6.6% bideuteration (M+2).

FTIR (cm^{-1}): 2924, 2206, 2109, 1732, 1603, 1509, 1467, 1392, 1288, 1233, 1172, 1114, 1045, 998, 972, 921, 896, 842, 762, 743, 657, 616.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

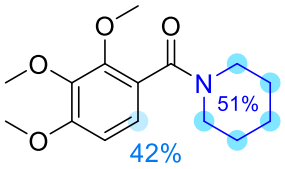
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	234	235	236	237	238	239	240	241
%	100	14,7	1,2	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	234	24560	0,00	24560,00	24,96
1	235	19669	3610,32	16058,68	16,32
2	236	5505	294,72	2849,65	2,90
3	237	836	0,00	224,40	0,23
4	238	100	0,00	32,82	0,03
5	239	0	0,00	-7,52	-0,01
6	240	0	0,00	0,71	0,00
7	241	0	0,00	-0,01	0,00
8	242	0	0,00	-0,01	0,00
9	243	3959	0,00	3959,00	4,02
10	244	30048	0,00	29466,03	29,95
11	245	22404	0,00	18024,99	18,32
12	246	6034	0,00	3030,73	3,08
13	247	829	0,00	167,18	0,17
14	248	102	0,00	41,06	0,04
Total		114046		9,84E+04	100,01

Echange %	53,4
Enrichissement (+1D) %	36,9
Enrichissement (+2D) %	6,6

(piperidin-1-yl-d10)(2,3,4-trimethoxyphenyl)methanone ([$^2H_{10}$]10)



[$^2H_{10}$]10

$C_{15}H_{11}D_{10}NO_4$
MW: 289.40 g.mol^{-1}
White solid
Yield: >95%
IE: 51.2%

Following the general procedure F, [$^2H_{10}$]10 was obtained as a white solid (56 mg, 0.19 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90 (d, *J* = 8.5 Hz, 0.58H), 6.70 – 6.61 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 – 3.59 (m, 1.17H), 3.20 (bs, 1.03H), 1.68 – 1.33 (m, 3.21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 154.4, 150.2, 142.1, 124.3, 122.2, 107.7, 61.7, 61.1, 56.2, 48.3, 42.8, 26.5, 25.8, 24.7.

^{2}H NMR (61 MHz, $CHCl_3$): δ 6.93 (bs), 3.65 (bs), 3.16 (bs), 1.56 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{15}H_{12}D_{10}NO$: 290.2177 $[M+H]^+$; found 290.2174.

Isotopic exchange (calculated by ^{1}H NMR): 49%.

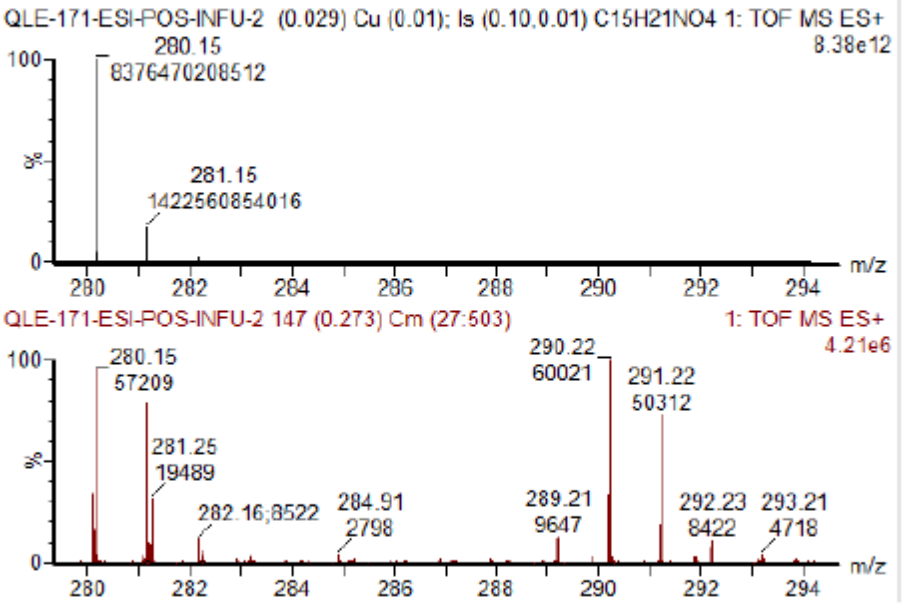
Isotopic exchange (calculated by HRMS): 51.2%.

Isotopic enrichment (calculated by HRMS): 40.8% monodeuteration (M+1), 0.7% bideuteration (M+2).

FTIR (cm^{-1}): 2937, 2854, 2212, 2110, 1622, 1594, 1495, 1462, 1442, 1409, 1276, 1222, 1193, 1134, 1094, 1038, 1001, 980, 955, 898, 878, 853, 804, 753, 726, 689.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

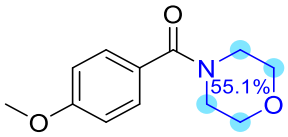
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	208	209	210	211	212	213	214	215
%	100	17,1	2,1	0,2	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	208	57209	0,00	57209,00	27,04
1	209	49132	9782,74	39349,26	18,60
2	210	8522	1201,39	591,89	0,28
3	211	4581	114,42	3539,03	1,67
4	212	0	0,00	-696,30	-0,33
5	213	0	0,00	43,56	0,02
6	214	0	0,00	0,09	0,00
7	215	0	0,00	0,46	0,00
8	216	0	0,00	-0,17	0,00
9	217	9647	0,00	9647,02	4,56
10	218	60021	0,00	58371,36	27,59
11	219	50321	0,00	40136,91	18,97
12	220	8422	0,00	313,50	0,15
13	221	4718	0,00	3704,77	1,75
14	222	0	0,00	-720,37	-0,34
Total		252573		2,11E+05	99,98

Echange %	51,2
Enrichissement (+1D) %	40,5
Enrichissement (+2D) %	0,6

(4-methoxyphenyl)(morpholino-d8)methanone ([$^2H_8$]30)



[$^2H_{10}$]30

$C_{12}H_7D_8NO_3$
MW: 229.30 g.mol^{-1}
White solid
Yield: 64%
IE: 55.1%

Following the general procedure F, [$^2H_8$]30 was obtained as a white solid (30 mg, 0.13 mmol, 64%) using 0.2 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 2H), 6.94 – 6.86 (m, 2H), 3.81 (s, 3H), 3.78 – 3.40 (m, 3.49H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 161.0, 129.3 (2C), 127.4, 113.8 (2C), 67.0 (2C), 55.4 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.61 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_8D_8NO_3$: 230.1632 $[M+H]^+$; found 230.1630.

Isotopic exchange (calculated by ^{1}H NMR): 56%.

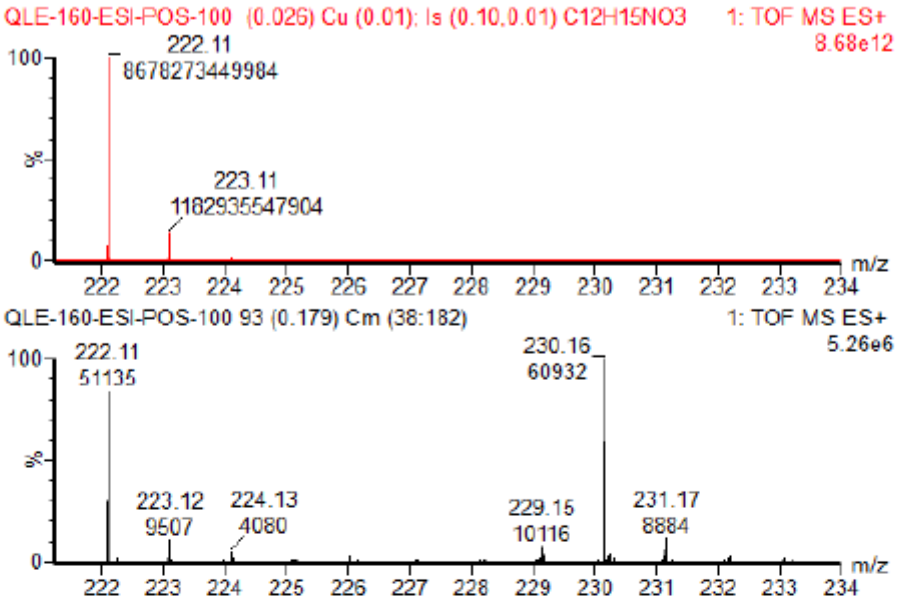
Isotopic exchange (calculated by HRMS): 55.1%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2922, 2846, 2229, 2091, 1607, 1512, 1418, 1398, 1300, 1278, 1246, 1174, 1108, 1067, 1022, 967, 950, 895, 839, 794, 761, 712, 647, 630, 611.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

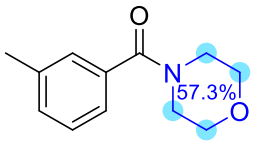
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	222	223	224	225	226	227	228	229
%	100	13,7	1,4	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	222	51135	0,00	51135,00	39,73
1	223	9507	7005,50	2501,51	1,94
2	224	4080	715,89	3021,40	2,35
3	225	862	51,14	361,91	0,28
4	226	0	0,00	-94,38	-0,07
5	227	0	0,00	4,84	0,00
6	228	0	0,00	0,30	0,00
7	229	0	0,00	-0,01	0,00
8	230	0	0,00	-0,01	0,00
9	231	10116	0,00	10116,00	7,86
10	232	60932	0,00	59546,11	46,26
11	233	8884	0,00	584,56	0,45
12	234	2444	0,00	1520,15	1,18
13	235	321	0,00	45,01	0,03
14	236	0	0,00	-28,03	-0,02
Total		148281		1,29E+05	100,00

Echange %	**55,1**
Enrichissement (+1D) %	**4,4**
Enrichissement (+2D) %	**5,3**

(morpholino-d8)(m-tolyl)methanone ([$^2H_8$]31)



[$^2H_{10}$]31

$C_{12}H_7D_8NO_2$
MW: 213.31 g.mol^{-1}
Colorless oil
Yield: 84%
IE: 57.3%

Following the general procedure F, [$^2H_8$]31 was obtained as a colorless oil after purification (36 mg, 0.17 mmol, 84%) using 0.2 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.14 (m, 1H), 3.75 (m, 3.94H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 138.6, 135.4, 130.7, 128.4, 127.8, 124.1, 67.0 (2C), 21.5 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.64 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_8D_8NO_2$: 214.1683 $[M+H]^+$; found 214.1680.

Isotopic exchange (calculated by ^{1}H NMR): 51%.

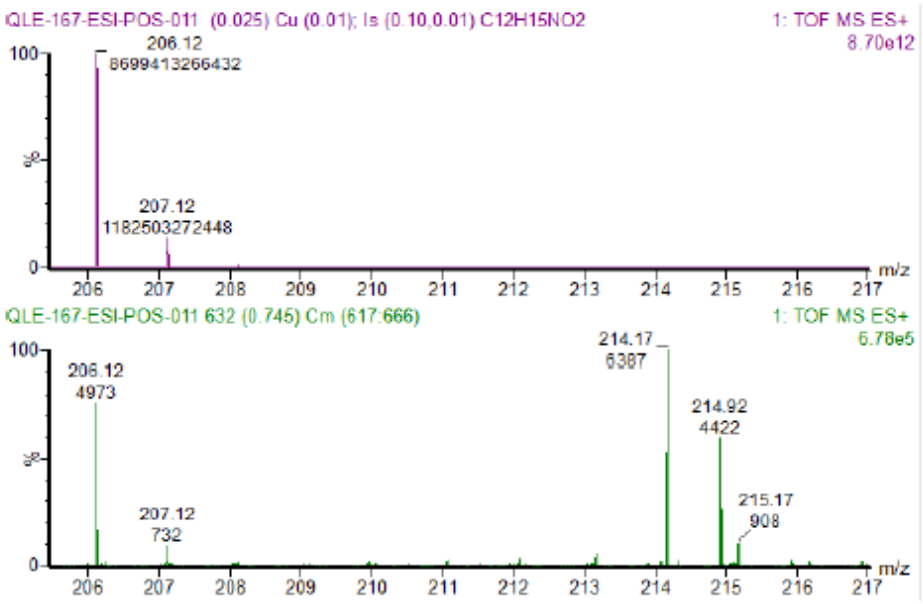
Isotopic exchange (calculated by HRMS): 57.3%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2961, 2920, 2855, 2226, 2090, 1628, 1584, 1486, 1426, 1397, 1300, 1279, 1262, 1208, 1170, 1154, 1108, 1069, 1055, 1026, 999, 974, 955, 901, 868, 822, 800, 740, 707, 676, 640, 613.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

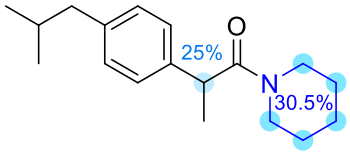
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	206	207	208	209	210	211	212	213
%	100	13,7	1,2	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	206	4973	0,00	4973,00	41,75
1	207	732	681,30	50,70	0,43
2	208	125	59,68	58,38	0,49
3	209	14	4,97	0,42	0,00
4	210	0	0,00	-0,81	-0,01
5	211	0	0,00	0,05	0,00
6	212	0	0,00	0,00	0,00
7	213	456	0,00	456,00	3,83
8	214	6387	0,00	6324,53	53,09
9	215	908	0,00	36,07	0,30
10	216	104	0,00	22,71	0,19
11	217	0	0,00	-9,87	-0,08
12	218	0	0,00	1,04	0,01
13	219	0	0,00	-0,05	0,00
14	220	0	0,00	0,00	0,00
Total		13699		1,19E+04	100,00

Echange %	57,3
Enrichissement (+1D) %	1,0
Enrichissement (+2D) %	1,1

2-(4-isobutylphenyl)-1-(piperidin-1-yl-d_{10})propan-1-one ([$^2H_{10}$]34)



[$^2H_{10}$]34

$C_{18}H_{17}D_{10}NO$
MW: 283.48 g.mol^{-1}
Colorless oil
Yield: 35%
IE: 30.5%

Following the general procedure F, [$^2H_{10}$]34 was obtained as a colorless oil after purification (20 mg, 0.07 mmol, 35%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.11 (m, 2H), 7.09 – 7.04 (m, 2H), 3.89 – 3.79 (m, 0.75H), 3.80 – 3.69 (m, 0.71H), 3.43 – 3.21 (m, 2.22H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.84 (nonet, *J* = 6.8 Hz, 1H), 1.57 – 1.45 (m, 2.32H), 1.42 (d, *J* = 6.7 Hz, 3.81H), 1.36 – 1.25 (m, 0.83H), 1.01 – 0.91 (m, 0.82H), 0.87 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 140.0, 139.8, 129.6 (2C), 127.1 (2C), 46.7, 45.2, 43.2, 43.0, 30.3, 26.0, 25.7, 24.7, 22.5, 20.9, 20.8.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.83 (s), 3.70 (s), 3.28 (s), 1.68 – 0.56 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{18}H_{18}D_{10}NO$: 284.2798 $[M+H]^+$; found 284.2796.

Isotopic exchange (calculated by ^{1}H NMR): 28%.

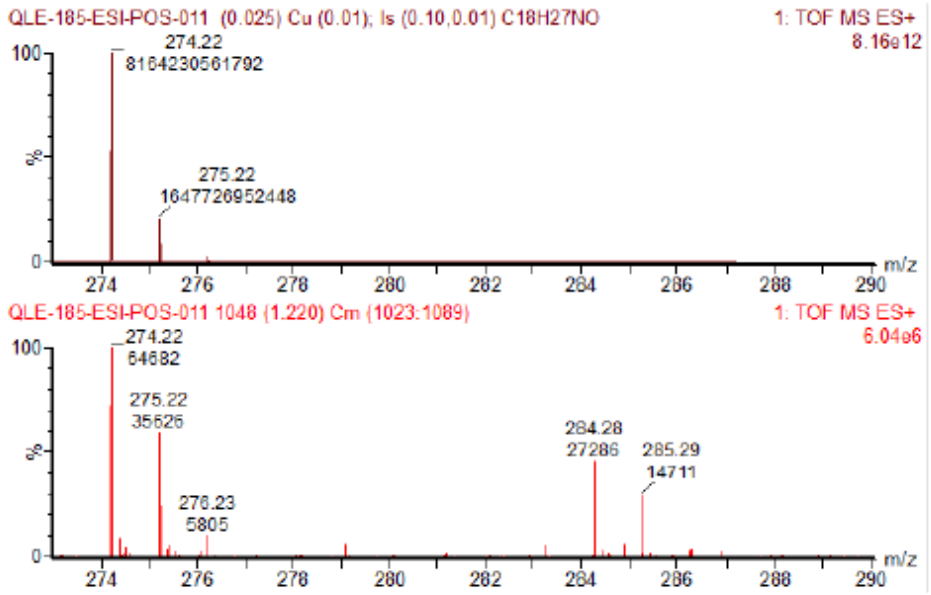
Isotopic exchange (calculated by HRMS): 30.5%.

Isotopic enrichment (calculated by HRMS): 25.8% monodeuteration (M+1).

FTIR (cm^{-1}): 2930, 2865, 2210, 2110, 1637, 1510, 1432, 1367, 1262, 1227, 1167, 1137, 1061, 1011, 975, 951, 896, 849, 802, 687.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

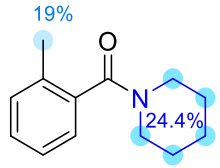
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	274	275	276	277	278	279	280	281
%	100	20,3	2,1	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	274	64682	0,00	64682,00	51,10
1	275	35626	13130,45	22495,55	17,77
2	276	5805	1358,32	-119,92	-0,09
3	277	616	64,68	103,26	0,08
4	278	0	0,00	-40,94	-0,03
5	279	0	0,00	6,26	0,00
6	280	0	0,00	-0,51	0,00
7	281	0	0,00	0,01	0,00
8	282	0	0,00	0,00	0,00
9	283	3589	0,00	3589,00	2,84
10	284	27286	0,00	26557,43	20,98
11	285	14711	0,00	9244,47	7,30
12	286	2459	0,00	21,08	0,02
13	287	219	0,00	-5,97	0,00
14	288	59	0,00	50,52	0,04
Total		155052		1,27E+05	100,01

Echange %	30,5
Enrichissement (+1D) %	25,8
Enrichissement (+2D) %	-0,1

(piperidin-1-yl-d10)(o-tolyl)methanone ([$^2H_{10}$]3)



[$^2H_{10}$]3

$C_{13}H_7D_{10}NO$
MW: 213.35 g.mol^{-1}
White solid
Yield: 89%
IE: 24.4%

Following the general procedure F, [$^2H_{10}$]3 was obtained as a white solid (38 mg, 0.18 mmol, 89%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 1H), 7.22 – 7.12 (m, 3H), 3.89 – 3.60 (m, 1.50H), 3.17 (td, *J* = 5.0, 2.0 Hz, 1.50H), 2.34 – 2.25 (m, 2.28H), 1.75 – 1.36 (m, 4.57H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 136.8, 134.0, 130.3, 128.6, 125.8, 125.6, 47.9, 42.4, 26.6, 25.7, 24.6, 19.0.

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.16 (bs), 3.72 (m), 3.10 (bs), 2.26 (bs), 1.47 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_8D_{10}NO$: 214.2016 $[M+H]^+$; found 214.2013.

Isotopic exchange (calculated by ^{1}H NMR): 25%.

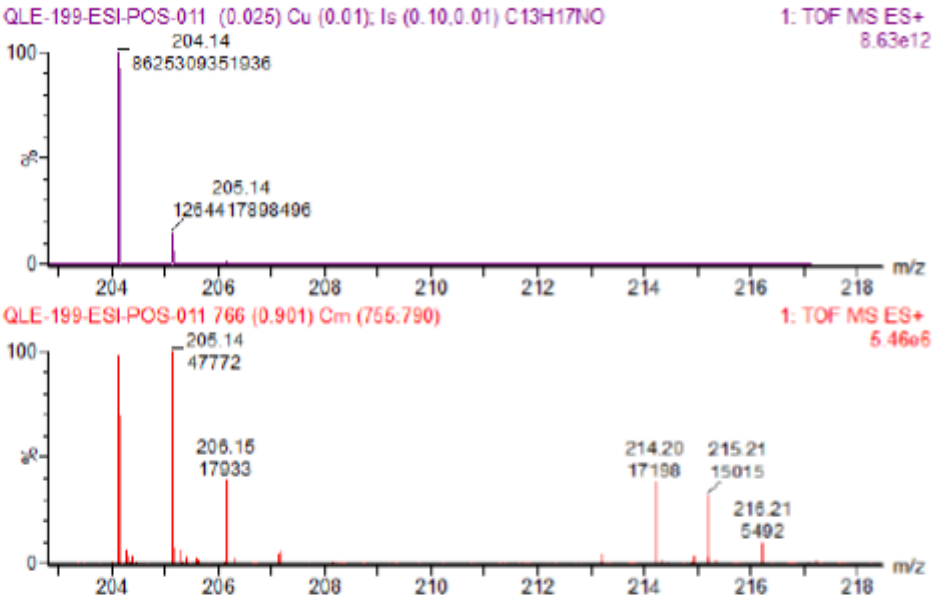
Isotopic exchange (calculated by HRMS): 24.4%.

Isotopic enrichment (calculated by HRMS): 40.0% monodeuteration (M+1), 11.2% bideuteration (M+2), 1.5% trideuteration (M+3).

FTIR (cm^{-1}): 2992, 2934, 2854, 2211, 2112, 1625, 1601, 1490, 1466, 1428, 1350, 1284, 1271, 1239, 1199, 1160, 1122, 1094, 1027, 1000, 968, 955, 898, 887, 853, 768, 742, 664, 635, 609.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

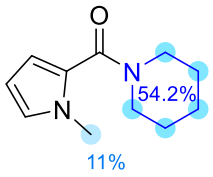
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	204	205	206	207	208	209	210	211
%	100	14,7	1,2	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	204	49478	0,00	49478,00	35,70
1	205	47772	7273,27	40498,73	29,22
2	206	17933	593,74	11385,95	8,21
3	207	3654	0,00	1494,28	1,08
4	208	378	0,00	21,71	0,02
5	209	61	0,00	39,88	0,03
6	210	0	0,00	-6,12	0,00
7	211	0	0,00	0,42	0,00
8	212	0	0,00	0,01	0,00
9	213	2508	0,00	2507,99	1,81
10	214	17198	0,00	16829,32	12,14
11	215	15015	0,00	12510,99	9,03
12	216	5492	0,00	3450,93	2,49
13	217	1033	0,00	375,58	0,27
14	218	129	0,00	32,38	0,02
Total		160651		1,39E+05	100,01

Echange %	24,4
Enrichissement (+1D) %	40,0
Enrichissement (+2D) %	11,2

(1-methyl-1H-pyrrol-2-yl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]27)



[$^2H_{10}$]27

$C_{11}H_6D_{10}N_2O$
MW: 202.32 g.mol^{-1}
White solid
Yield: >95%
IE: 54.2%

Following the general procedure F, [$^2H_{10}$]27 was obtained as a white solid (39 mg, 0.2 mmol, >95%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.32 - 6.26 (m, 1H), 6.08 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.75 (s, 2.85H), 3.68 – 3.63 (m, 2.13H), 1.72 – 1.54 (m, 3.4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 125.8, 112.1, 112.1, 106.8, 35.6, 26.4 (2C), 24.9 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 6.70 (m), 6.30 (m), 3.69 – 3.37 (m), 1.83 – 1.34 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{11}H_7D_{10}N_2O$: 203.1969 $[M+H]^+$; found 203.1968.

Isotopic exchange (calculated by ^{1}H NMR): 47%.

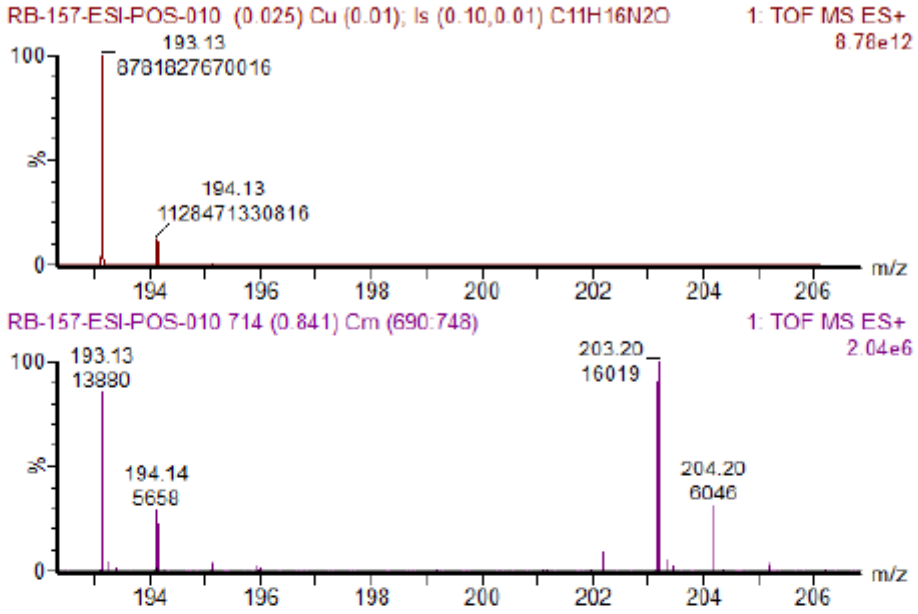
Isotopic exchange (calculated by HRMS): 54.2%.

Isotopic enrichment (calculated by HRMS): 21.1% monodeuteration (M+1), 3.0% bideuteration (M+2).

FTIR (cm^{-1}): 3104, 2934, 2853, 2211, 2110, 1612, 1531, 1468, 1429, 1385, 1298, 1255, 1235, 1196, 1175, 1129, 1105, 1062, 1021, 992, 958, 942, 899, 888, 869, 853, 822, 749, 722, 665, 633, 609, 555, 496, 420.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

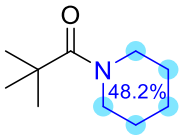
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	193	194	195	196	197	198	199	200
%	100	12,9	0,9	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	193	13880	0,00	13880,0	34,14
1	194	5658	1790,52	3867,48	9,51
2	195	1169	124,92	545,18	1,34
3	196	124	0,00	18,87	0,05
4	197	0	0,00	-7,34	-0,02
5	198	0	0,00	0,78	0,00
6	199	0	0,00	-0,03	0,00
7	200	0	0,00	0,00	0,00
8	201	0	0,00	0,00	0,00
9	202	2193	0,00	2193,00	5,39
10	203	16019	0,00	15736,10	38,70
11	204	6046	0,00	3996,31	9,83
12	205	1069	0,00	411,85	1,01
13	206	114	0,00	24,90	0,06
14	207	0	0,00	-6,92	-0,02
Total		46272		4,07E+04	100,00

Echange %	54,2
Enrichissement (+1D) %	21,1
Enrichissement (+2D) %	3,0

2,2-dimethyl-1-(piperidin-1-yl-d10)propan-1-one ([$^2H_{10}$]22)



[$^2H_{10}$]22

$C_{10}H_9D_{10}NO$
MW: 179.33 g.mol^{-1}
Colorless oil
Yield: 83%
IE: 48.2%

Following the general procedure F, [$^2H_{10}$]2 was obtained as a colorless oil after purification (30 mg, 0.17 mmol, 83%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 – 3.50 (m, 2.04H), 1.66 – 1.57 (m, 1.05H), 1.57 – 1.47 (m, 2.10H), 1.25 (d, *J* = 1.1 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 38.8, 28.6 (3C), 26.3 (2C), 24.9 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.52 (bs), 1.53 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_{11}D_{10}NO$: 180.2173 $[M+H]^+$; found 180.2171.

Isotopic exchange (calculated by ^{1}H NMR): 48%.

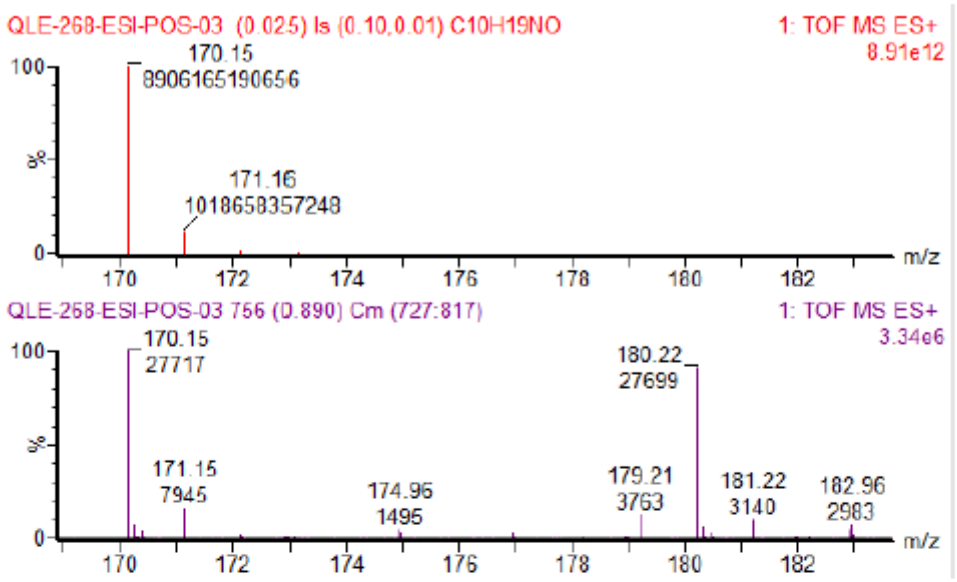
Isotopic exchange (calculated by HRMS): 48.2%.

Isotopic enrichment (calculated by HRMS): 14.6% monodeuteration (M+1), 0.4% bideuteration (M+2).

FTIR (cm^{-1}): 2933, 2856, 2210, 2109, 1620, 1478, 1404, 1362, 1268, 1194, 1125, 1070, 1026, 1007, 979, 923, 900, 854, 731, 678, 643, 560, 524, 411.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

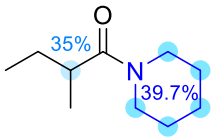
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	170	171	172	173	174	175	176	177
%	100	11,5	0,7	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	170	27717	0,00	27717,00	43,54
1	171	7945	3187,45	4757,55	7,47
2	172	872	194,02	130,86	0,21
3	173	55	0,00	6,65	0,01
4	174	0	0,00	-1,68	0,00
5	175	0	0,00	0,15	0,00
6	176	0	0,00	-0,01	0,00
7	177	0	0,00	0,00	0,00
8	178	0	0,00	0,00	0,00
9	179	3763	0,00	3763,00	5,91
10	180	27699	0,00	27266,26	42,83
11	181	3140	0,00	-21,96	-0,03
12	182	222	0,00	33,66	0,05
13	183	8	0,00	4,28	0,01
14	184	0	0,00	-0,73	0,00
Total		71421		6,37E+04	100,00

Echange %	48,2
Enrichissement (+1D) %	14,6
Enrichissement (+2D) %	0,4

2-methyl-1-(piperidin-1-yl-d10)butan-1-one ([$^2H_{10}$]21)



[$^2H_{10}$]21

$C_{10}H_9D_{10}NO$
MW: 179.33 g.mol^{-1}
Colorless oil
Yield: 69%
IE: 39.7%

Following the general procedure F, [$^2H_{10}$]21 was obtained as a colorless oil after purification (25 mg, 0.14 mmol, 69%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 – 3.31 (m, 2.02H), 2.64 – 2.53 (m, 0.65H), 1.72 – 1.59 (m, 2.01H), 1.59 – 1.45 (m, 2.19H), 1.46 – 1.30 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.86 (td, *J* = 7.4, 0.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 46.7, 42.9, 37.0, 27.2, 26.8, 25.9, 24.8, 17.4, 12.1.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.45 (m), 2.58 (bs), 1.52 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_{10}D_{10}NO$: 180.2173 $[M+H]^+$; found 180.2170.

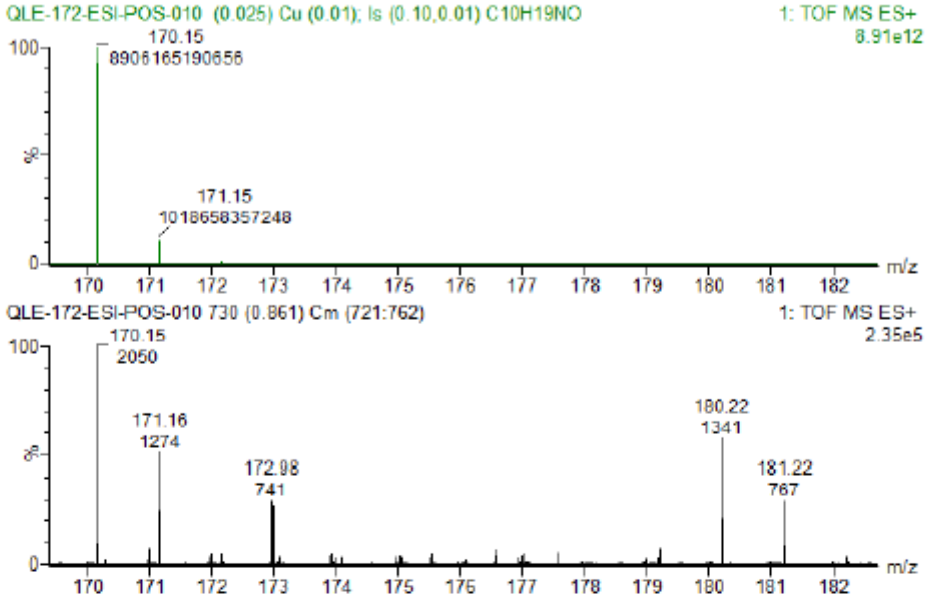
Isotopic exchange (calculated by HRMS): 39.7%.

Isotopic enrichment (calculated by HRMS): 33.3% monodeuteration (M+1), 1.1% bideuteration (M+2).

FTIR (cm^{-1}): 3369, 2925, 2855, 2211, 2111, 1731, 1615, 1443, 1367, 1251, 1230, 1174, 1131, 1012, 931, 899, 854, 801, 743, 721.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

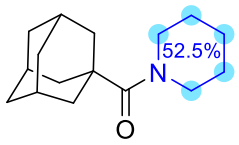
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	170	171	172	173	174	175	176	177
%	100	11,5	0,7	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	170	2050	0,00	2050,00	38,93
1	171	1274	235,75	1038,25	19,71
2	172	168	14,35	34,25	0,65
3	173	14	0,00	2,79	0,05
4	174	0	0,00	-0,56	-0,01
5	175	0	0,00	0,04	0,00
6	176	0	0,00	0,00	0,00
7	177	0	0,00	0,00	0,00
8	178	0	0,00	0,00	0,00
9	179	184	0,00	184,00	3,49
10	180	1341	0,00	1319,84	25,06
11	181	767	0,00	613,93	11,66
12	182	111	0,00	31,16	0,59
13	183	0	0,00	-7,88	-0,15
14	184	0	0,00	0,69	0,01
Total		5909		5,27E+03	100,00

Echange %	39,7
Enrichissement (+1D) %	33,3
Enrichissement (+2D) %	1,1

((3r,5r,7r)-adamantan-1-yl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]23)



[$^2H_{10}$]23

$C_{16}H_{15}D_{10}NO$
MW: 257.44 g.mol^{-1}
White solid
Yield: 89%
IE: 52.5%

Following the general procedure F, [$^2H_{10}$]23 was obtained as a white solid (46 mg, 0.18 mmol, 89%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 – 3.52 (m, 1.89H, IE), 2.04 – 1.91 (m, 9H), 1.73 – 1.64 (m, 6H), 1.65 – 1.56 (m, 1.03H), 1.55 – 1.46 (m, 2.07H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5, 46.4 (2C), 41.6, 39.1 (3C), 36.7 (3C), 28.6 (3C), 26.4 (2C), 24.8.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.53 (bs), 1.50 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{16}H_{16}D_{10}NO$: 258.2642 $[M+H]^+$; found 258.2637.

Isotopic exchange (calculated by ^{1}H NMR): 51%.

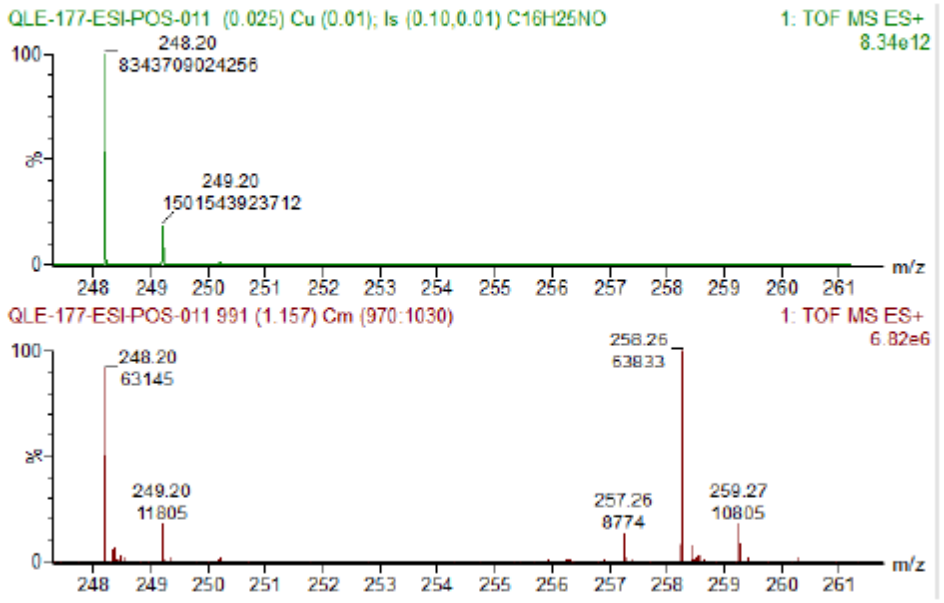
Isotopic exchange (calculated by HRMS): 52.5%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2900, 2848, 2205, 2110, 1702, 1611, 1443, 1412, 1382, 1343, 1311, 1277, 1264, 1248, 1223, 1196, 1182, 1162, 1143, 1124, 1101, 1084, 1042, 1028, 1012, 992, 976, 963, 935, 903, 868, 855, 816, 722, 696, 668, 646, 606.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

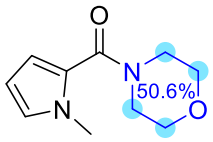
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	248	249	250	251	252	253	254	255
%	100	18,1	1,7	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	248	63145	0,00	63145,00	47,04
1	249	11805	11429,25	375,75	0,28
2	250	1305	1073,47	163,52	0,12
3	251	163	63,15	63,87	0,05
4	252	0	0,00	-14,72	-0,01
5	253	0	0,00	1,41	0,00
6	254	0	0,00	-0,07	0,00
7	255	0	0,00	0,00	0,00
8	256	0	0,00	0,00	0,00
9	257	8774	0,00	8774,00	6,54
10	258	63833	0,00	62244,91	46,37
11	259	10805	0,00	-610,49	-0,45
12	260	1057	0,00	100,56	0,07
13	261	73	0,00	2,93	0,00
14	262	0	0,00	-1,63	0,00
Total		160960		1,34E+05	100,00

Echange %	52,5
Enrichissement (+1D) %	0,6
Enrichissement (+2D) %	0,3

(1-methyl-1H-pyrrol-2-yl)(morpholino-d8)methanone ([$^2H_{10}$]28)



[$^2H_{10}$]28

$C_{10}H_6D_8N_2O_2$
MW: 202.28 g.mol^{-1}
White solid
Yield: 79%
IE: 50.6%

Following the general procedure F, [$^2H_8$]28 was obtained as a white solid after purification (32 mg, 0.16 mmol, 79%) using 0.2 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (ddq, *J* = 2.6, 1.7, 0.4 Hz, 1H), 6.30 (ddd, *J* = 3.9, 1.7, 1.0 Hz, 1H), 6.07 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.78 (t, *J* = 0.4 Hz, 3H), 3.77 – 3.73 (m, 1.87H), 3.72 – 3.66 (m, 1.87H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 126.6, 124.7, 113.1, 107.0, 67.1, 45.7 (2C), 35.8 (2C).

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.69 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_7D_8N_2O_2$: 203.1636 $[M+H]^+$; found 203.1636.

Isotopic exchange (calculated by ^{1}H NMR): 53%.

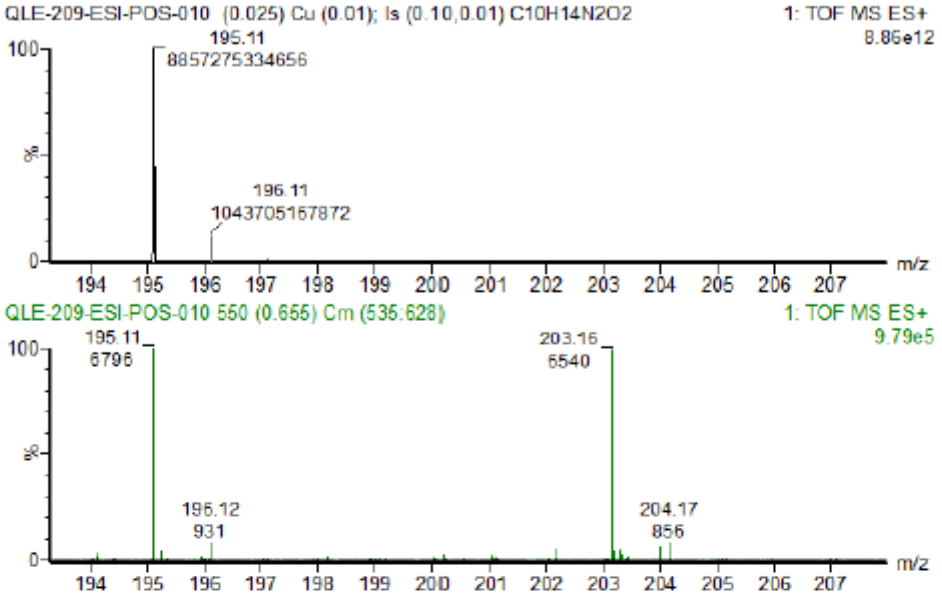
Isotopic exchange (calculated by HRMS): 50.6%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 3105, 2921, 2854, 2226, 2093, 1600, 1531, 1461, 1432, 1388, 1299, 1268, 1243, 1172, 1131, 1098, 1059, 1029, 1001, 943, 900, 884, 833, 745, 667, 634, 611.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

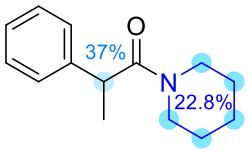
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	195	196	197	198	199	200	201	202
%	100	11,9	1	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	195	6796	0,00	6796,0	48,13
1	196	931	808,72	122,28	0,87
2	197	119	67,96	36,49	0,26
3	198	39	0,00	33,44	0,24
4	199	0	0,00	-4,34	-0,03
5	200	0	0,00	0,18	0,00
6	201	0	0,00	0,02	0,00
7	202	579	0,00	579,00	4,10
8	203	6540	0,00	6471,10	45,83
9	204	856	0,00	80,15	0,57
10	205	81	0,00	6,75	0,05
11	206	0	0,00	-1,60	-0,01
12	207	0	0,00	0,12	0,00
13	208	0	0,00	0,00	0,00
14	209	0	0,00	0,00	0,00
Total		15941		1,41E+04	100,00

Echange %	50,6
Enrichissement (+1D) %	1,8
Enrichissement (+2D) %	0,5

2-phenyl-1-(piperidin-1-yl-d10)propan-1-one ([$^2H_{10}$]19)



[$^2H_{10}$]19

$C_{14}H_9D_{10}NO$
MW: 227.37 g.mol^{-1}
White solid
Yield: 88%
IE: 22.8%

Following the general procedure F, [$^2H_{10}$]19 was obtained as a white solid after purification (40 mg, 0.18 mmol, 88%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.26 – 7.16 (m, 3H), 3.92 – 3.82 (m, 0.63H), 3.78 – 3.66 (m, 0.8H), 3.44 – 3.34 (m, 0.82H), 3.35 – 3.21 (m, 1.65H), 1.56 – 1.45 (m, 2.52H), 1.49 – 1.37 (m, 3.85H), 1.36 – 1.24 (m, 0.87H), 1.04 – 0.87 (m, 0.85H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 142.5, 128.9 (2C), 127.3 (2C), 126.7, 46.6, 43.3 (2C), 26.0, 25.6, 24.6, 20.9.

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.86 (bs), 3.68 (bs), 3.29 (m), 1.35 (m), 0.90 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{14}H_{10}D_{10}NO$: 228.2173 $[M+H]^+$; found 228.2170.

Isotopic exchange (calculated by ^{1}H NMR): 20%.

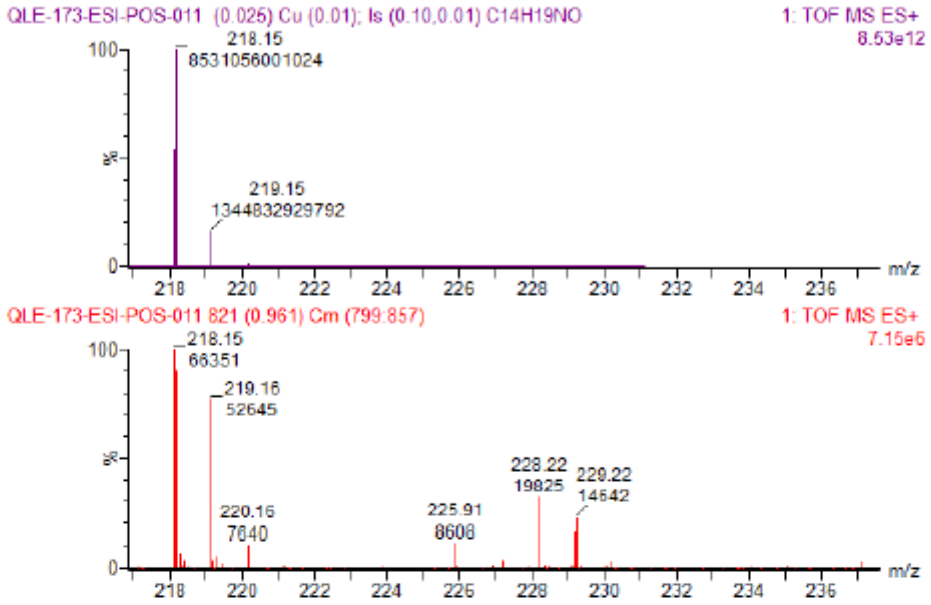
Isotopic exchange (calculated by HRMS): 22.8%.

Isotopic enrichment (calculated by HRMS): 38.8% monodeuteration (M+1), 0.1% bideuteration (M+2).

FTIR (cm^{-1}): 2932, 2856, 2211, 2110, 1631, 1493, 1432, 1368, 1263, 1228, 1183, 1137, 1091, 1061, 1027, 1010, 951, 897, 852, 749, 700, 664, 628, 569, 507, 479.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

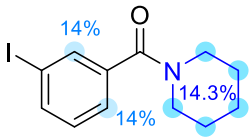
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	218	219	220	221	222	223	224	225
%	100	15,8	1,3	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	218	66351	0,00	66351,00	46,47
1	219	52645	10483,46	42161,54	29,53
2	220	7640	862,56	115,91	0,08
3	221	808	0,00	241,59	0,17
4	222	104	0,00	64,32	0,05
5	223	0	0,00	-13,30	-0,01
6	224	0	0,00	1,27	0,00
7	225	0	0,00	-0,03	0,00
8	226	0	0,00	-0,01	0,00
9	227	2644	0,00	2644,00	1,85
10	228	19825	0,00	19407,25	13,59
11	229	14642	0,00	11541,28	8,08
12	230	2298	0,00	222,18	0,16
13	231	225	0,00	39,86	0,03
14	232	0	0,00	-9,19	-0,01
Total		167182		1,43E+05	100,00

Echange %	22,8
Enrichissement (+1D) %	38,8
Enrichissement (+2D) %	0,1

(3-iodophenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]17)



[$^2H_{10}$]17

$C_{12}H_4D_{10}INO$
MW: 325.22 g.mol^{-1}
White solid
Yield: 63%
IE: 14.3%

Following the general procedure F, [$^2H_{10}$]17 was obtained as a white solid after purification (41 mg, 0.13 mmol, 63%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 1.74H), 7.35 – 7.28 (m, 1H), 7.12 (dd, *J* = 7.6, 8.5 Hz, 1H), 3.68 (bs, 1.75H), 3.31 (bs, 1.76H), 1.72 – 1.43 (m, 5.48H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 138.7, 138.4, 135.8, 130.2, 126.0, 94.3, 48.9, 43.3, 26.6, 25.7, 24.6.

^{2}H NMR (61 MHz, $CHCl_3$) δ 7.75 (bs), 3.45 (m), 1.56 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_5D_{10}INO$: 326.0826 $[M+H]^+$; found 326.0823.

Isotopic exchange (calculated by ^{1}H NMR): 13%.

Isotopic exchange (calculated by HRMS): 14.3%.

Isotopic enrichment (calculated by HRMS): 22.0% monodeuteration (M+1), 0.1% bideuteration (M+2).

FTIR (cm^{-1}): 3056, 2995, 2933, 2854, 2210, 2112, 1622, 1556, 1472, 1429, 1369, 1351, 1274, 1237, 1209, 1169, 1127, 1110, 1063, 1027, 999, 975, 955, 894, 853, 797, 747, 730, 690, 656, 632.

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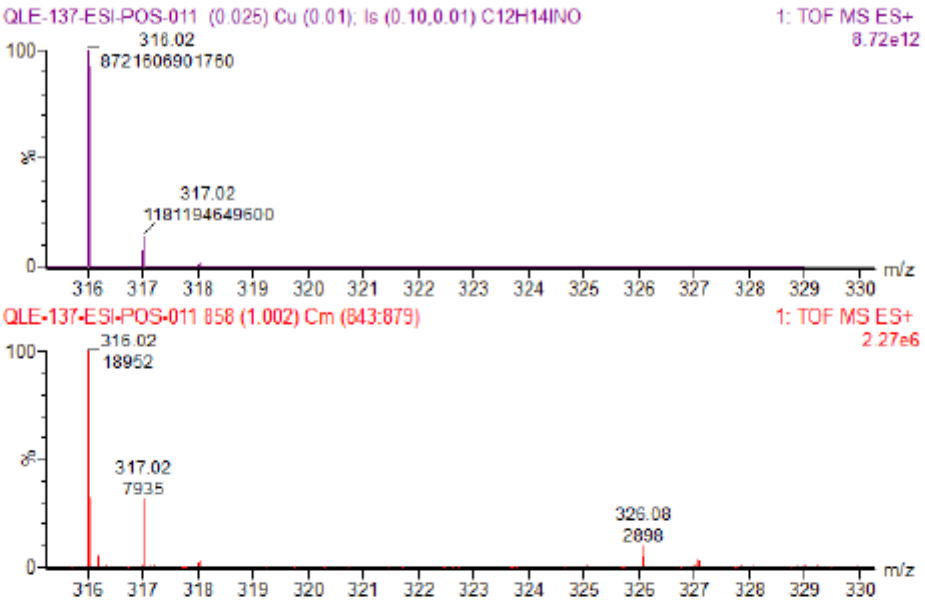
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

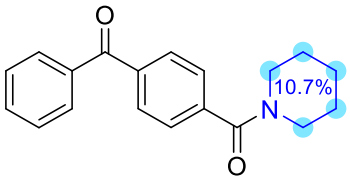
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	316	317	318	319	320	321	322	323
%	100	13,6	1	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	316	18952	0,00	18952,00	66,39
1	317	7935	2577,47	5357,53	18,77
2	318	947	189,52	28,86	0,10
3	319	79	0,00	21,50	0,08
4	320	0	0,00	-3,21	-0,01
5	321	0	0,00	0,22	0,00
6	322	0	0,00	0,00	0,00
7	323	0	0,00	0,00	0,00
8	324	0	0,00	0,00	0,00
9	325	407	0,00	407,00	1,43
10	326	2898	0,00	2842,65	9,96
11	327	1304	0,00	913,33	3,20
12	328	164	0,00	11,36	0,04
13	329	29	0,00	18,32	0,06
14	330	0	0,00	-2,61	-0,01
Total		32715		2,85E+04	100,00

Echange %	**14,3**
Enrichissement (+1D) %	**22,0**
Enrichissement (+2D) %	**0,1**

(4-benzoylphenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]12)



[$^2H_{10}$]12

$C_{19}H_9D_{10}NO_2$
MW: 303.43 g.mol^{-1}
White solid
Yield: 54%
IE: 10.7%

Following the general procedure F, [$^2H_{10}$]12 was obtained as a white solid after purification (33 mg, 0.11 mmol, 54%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 4H), 7.64 – 7.56 (m, 1H), 7.54 – 7.41 (m, 4H), 3.73 (bs, 1.87H), 3.46 – 3.18 (m, 1.88H), 1.69 (bs, 3.82H,), 1.52 (bs, 1.9H,).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 169.2, 140.3, 138.3, 137.2, 132.7, 130.12 (2C), 130.06 (2C), 128.4 (2C), 126.7 (2C), 48.7, 43.1, 26.6, 25.6, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.49 (m), 1.61 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{19}H_{10}D_{10}NO_2$: 304.2122 $[M+H]^+$; found 304.2117.

Isotopic exchange (calculated by ^{1}H NMR): 6%.

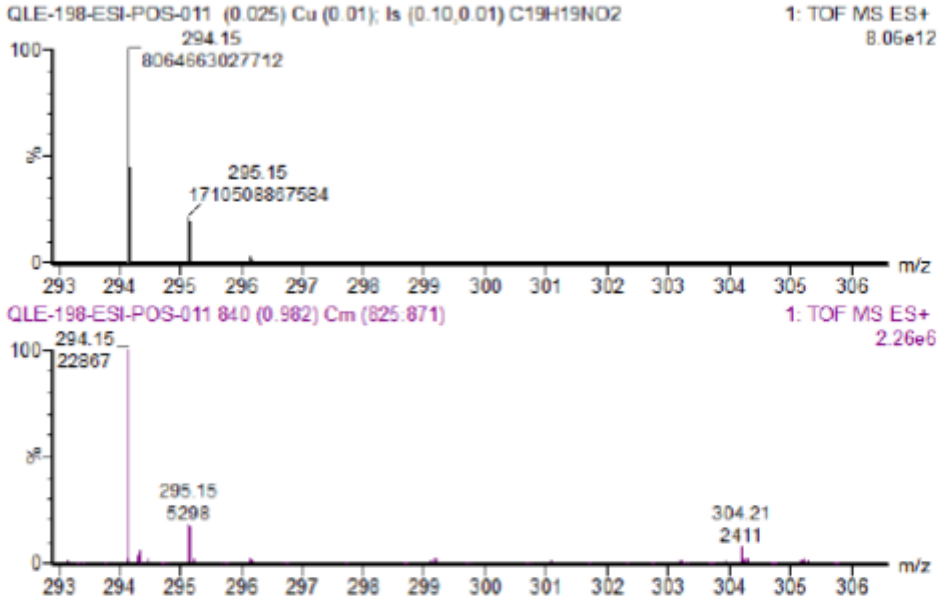
Isotopic exchange (calculated by HRMS): 10.7%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 3062, 3008, 2931, 2856, 2210, 2110, 1722, 1649, 1623, 1594, 1577, 1501, 1466, 1436, 1400, 1314, 1304, 1271, 1237, 1168, 1145, 1128, 1106, 1074, 1026, 1000, 967, 954, 936, 927, 886, 849, 826, 800, 766, 750, 716, 698, 675, 647, 616.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

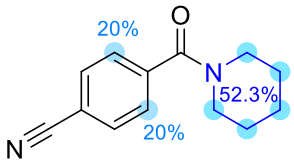
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	294	295	296	297	298	299	300	301
%	100	21,3	2,5	0,2	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	294	22867	0,00	22867,00	86,68
1	295	5298	4870,67	427,33	1,62
2	296	757	571,67	94,30	0,36
3	297	266	45,73	189,50	0,72
4	298	50	0,00	6,43	0,02
5	299	0	0,00	-6,29	-0,02
6	300	0	0,00	0,80	0,00
7	301	0	0,00	-0,03	0,00
8	302	0	0,00	0,00	0,00
9	303	409	0,00	409,00	1,55
10	304	2411	0,00	2323,88	8,81
11	305	570	0,00	64,79	0,25
12	306	85	0,00	12,29	0,05
13	307	0	0,00	-8,88	-0,03
14	308	0	0,00	1,46	0,01
Total		32713		2,64E+04	100,00

Echange %	10,7
Enrichissement (+1D) %	1,8
Enrichissement (+2D) %	0,4

4-(piperidine-1-carbonyl-2,2,3,3,4,4,5,5,6,6-d10)benzonitrile methanone ([$^2H_{10}$]18)



[$^2H_{10}$]18

$C_{13}H_4D_{10}N_2O$
MW: 224.33 g.mol^{-1}
White solid
Yield: 37%
IE: 52.3%

Following the general procedure F, [$^2H_{10}$]18 was obtained as a white solid after purification (17 mg, 0.08 mmol, 37%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 2H), 7.51 – 7.45 (m, 1.6H), 3.67 (bs, 1.12H), 3.27 (bs, 1.15H), 1.68 (bs, 3.25H), 1.51 (bs, 1.29H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 141.0, 132.5 (2C), 127.6 (2C), 118.3, 113.3, 48.8, 43.3, 26.6, 25.6, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$) δ 7.52 (bs), 3.63 (bs), 3.24 (bs), 1.57 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{13}H_5D_{10}N_2O$: 225.1812 $[M+H]^+$; found 225.1809.

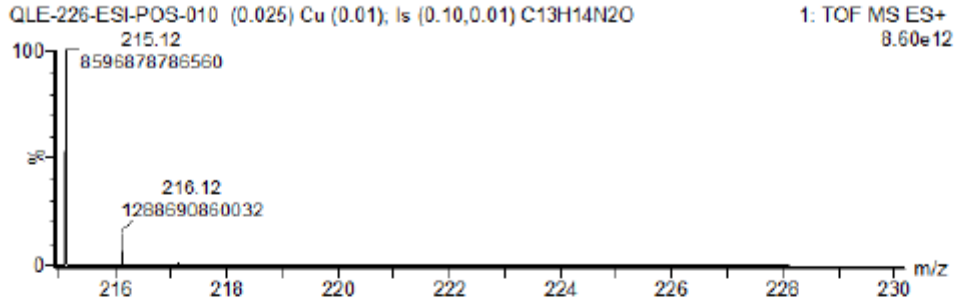
Isotopic exchange (calculated by HRMS): 52.3%.

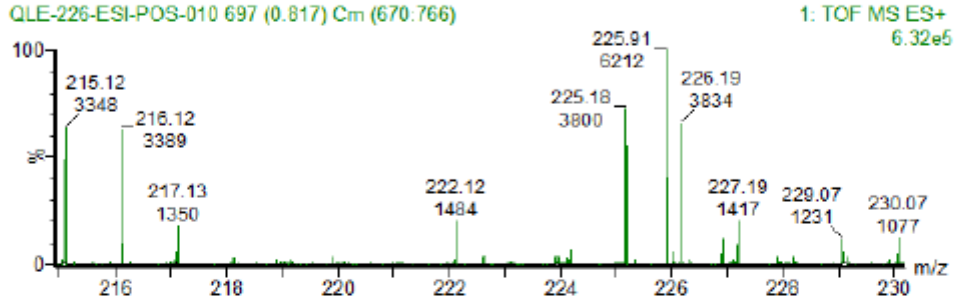
Isotopic enrichment (calculated by HRMS): 40.6% monodeuteration (M+1), 12.3% bideuteration (M+2).

FTIR (cm^{-1}): 2932, 2856, 2231, 2113, 1619, 1469, 1422, 1368, 1280, 1270, 1237, 1195, 1128, 1106, 1064, 1027, 1000, 969, 945, 934, 897, 885, 854, 840, 787, 759, 718, 667.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique





Profil isotopique théorique

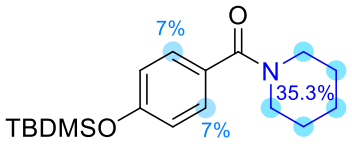
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	215	216	217	218	219	220	221	222
%	100	15	1,2	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	215	3348	0,00	3348,0	21,19
1	216	3389	502,20	2886,80	18,27
2	217	1350	40,18	876,80	5,55
3	218	274	0,00	107,84	0,68
4	219	55	0,00	28,30	0,18
5	220	0	0,00	-5,54	-0,04
6	221	0	0,00	0,49	0,00
7	222	0	0,00	-0,01	0,00
8	223	0	0,00	0,00	0,00
9	224	581	0,00	581,00	3,68
10	225	3800	0,00	3712,85	23,50
11	226	3834	0,00	3270,10	20,69
12	227	1417	0,00	881,93	5,58
13	228	314	0,00	142,47	0,90
14	229	0	0,00	-31,95	-0,20
Total		18362		1,58E+04	99,98

Echange %	52,3
Enrichissement (+1D) %	40,6
Enrichissement (+2D) %	12,3

(4-((tert-butyldimethylsilyl)oxy)phenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]6)



[$^2H_{10}$]6

$C_{18}H_{19}D_{10}NO_2Si$
MW: 329.58 g.mol^{-1}
White solid
Yield: 47%
IE: 35.3%

Following the general procedure F, [$^2H_{10}$]6 was obtained as a white solid after purification (31 mg, 0.09 mmol, 47%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 1.86H), 6.86 – 6.78 (m, 2H), 3.54 (bs, 2.44H), 1.75 – 1.36 (m, 3.74H), 0.97 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 156.9, 129.4, 128.8 (2C), 120.0, 119.8, 25.8 (3C), 24.8, 18.3, -4.3 (2C) (4 carbons missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$) δ 7.32 (bs), 3.49 (bs), 1.56 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{18}H_{20}D_{10}NO_2Si$: 330.2673 $[M+H]^+$; found 330.2673.

Isotopic exchange (calculated by ^{1}H NMR): 39%.

Isotopic exchange (calculated by HRMS): 35.3%.

Isotopic enrichment (calculated by HRMS): 13.1% monodeuteration (M+1).

FTIR (cm^{-1}): 2931, 2856, 2212, 2113, 1616, 1504, 1466, 1435, 1414, 1364, 1244, 1164, 1128, 1109, 1025, 1003, 969, 899, 841, 801, 779, 711, 682.

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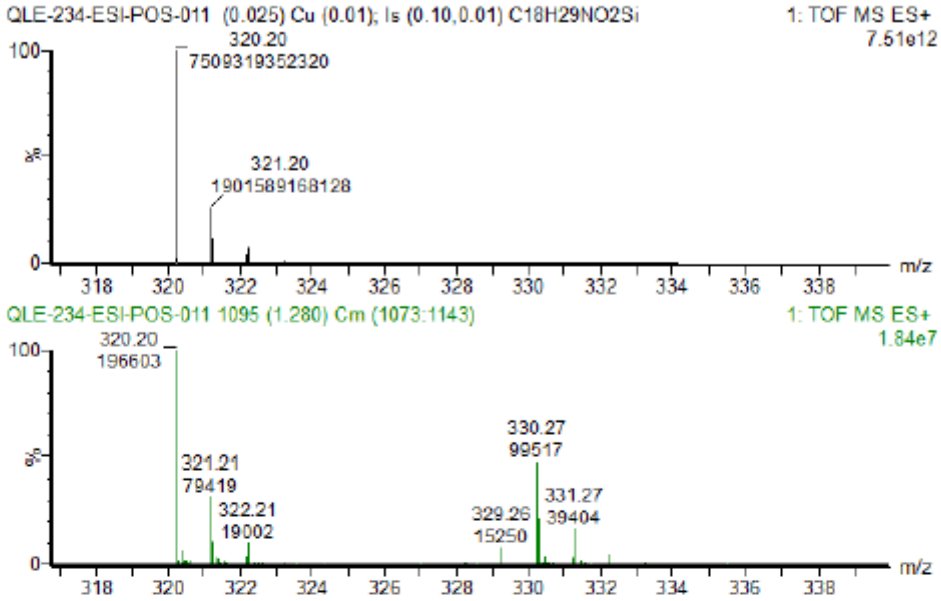
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

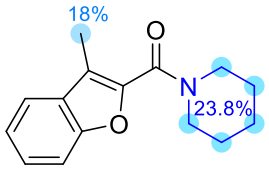
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	320	321	322	323	324	325	326	327
%	100	25,5	6,7	0,9	0,1	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	320	196603	0,00	196603,0	56,55
1	321	79419	50133,77	29285,24	8,42
2	322	19002	13172,40	-1638,14	-0,47
3	323	2574	1769,43	-739,81	-0,21
4	324	202	196,60	40,24	0,01
5	325	0	0,00	24,76	0,01
6	326	0	0,00	-0,71	0,00
7	327	0	0,00	-1,10	0,00
8	328	0	0,00	0,07	0,00
9	329	15250	0,00	15250,04	4,39
10	330	99517	0,00	95628,25	27,51
11	331	39404	0,00	13997,05	4,03
12	332	9783	0,00	-330,59	-0,10
13	333	1248	0,00	-481,41	-0,14
14	334	89	0,00	12,31	0,00
Total		463091		3,48E+05	100,00

Echange %	35,3
Enrichissement (+1D) %	13,1
Enrichissement (+2D) %	-0,7

(3-methylbenzofuran-2-yl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]25)



[$^2H_{10}$]25

$C_{15}H_7D_{10}NO_2$
MW: 253.37 g.mol^{-1}
Colorless oil
Yield: 66%
IE: 23.8%

Following the general procedure F, [$^2H_{10}$]25 was obtained as a colorless oil after purification (22 mg, 0.09 mmol, 66%) using 0.07 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 7.7, 1.3, 0.8 Hz, 1H), 7.46 (ddd, *J* = 8.3, 1.1, 0.8 Hz, 1H), 7.36 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.27 (ddd, J = 7.7, 7.3, 1.1 Hz, 1H), 3.66 (bs, 3.30H), 2.44 – 2.37 (m, 2.57H), 1.75 – 1.53 (m, 4.92H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 153.6, 144.7, 129.3, 126.1, 123.0, 120.4, 119.8, 111.7, 24.8, 8.9 (4C missing due to the free rotation of the amide bond, cf. Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.61 (bs), 2.41 (bs), 1.62 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{15}H_8D_{10}NO_2$: 254.1965 $[M+H]^+$; found 254.1962.

Isotopic exchange (calculated by ^{1}H NMR): 18%.

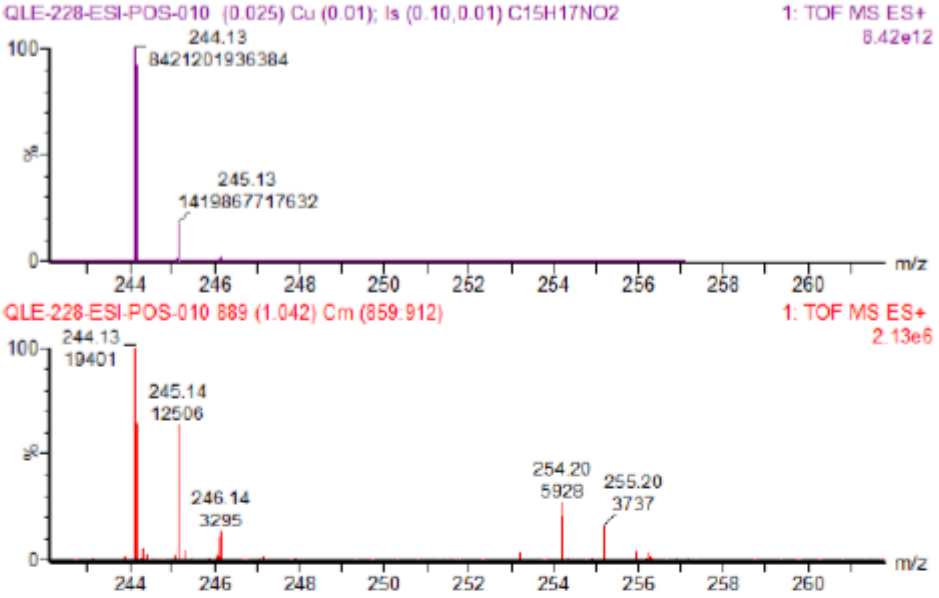
Isotopic exchange (calculated by HRMS): 23.8%.

Isotopic enrichment (calculated by HRMS): 30.7% monodeuteration (M+1), 4.7% bideuteration (M+2).

FTIR (cm^{-1}): 2939, 2854, 2210, 2111, 1612, 1444, 1387, 1339, 1285, 1260, 1224, 1172, 1113, 1093, 1061, 1025, 1000, 966, 941, 892, 870, 853, 828, 753, 671.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

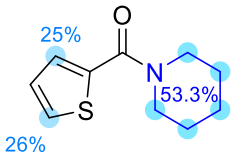
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	244	245	246	247	248	249	250	251
%	100	17	1,7	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	244	19401	0,00	19401,0	48,45
1	245	12506	3298,17	9207,83	22,99
2	246	3295	329,82	1399,85	3,50
3	247	550	19,40	136,09	0,34
4	248	76	0,00	19,86	0,05
5	249	0	0,00	-7,09	-0,02
6	250	0	0,00	0,73	0,00
7	251	0	0,00	-0,02	0,00
8	252	0	0,00	0,00	0,00
9	253	928	0,00	928,00	2,32
10	254	5928	0,00	5770,24	14,41
11	255	3737	0,00	2740,28	6,84
12	256	1011	0,00	446,13	1,11
13	257	142	0,00	13,80	0,03
14	258	0	0,00	-12,67	-0,03
Total		47574		4,00E+04	100,00

Echange %	23,8
Enrichissement (+1D) %	30,7
Enrichissement (+2D) %	4,7

(piperidin-1-yl-d10)(thiophen-2-yl)methanone ([$^2H_{10}$]26)



[$^2H_{10}$]26

$C_{10}H_3D_{10}NOS$
MW: 205.34 g.mol^{-1}
Colorless oil
Yield: 60%
IE: 53.3%

Following the general procedure F, [$^2H_{10}$]26 was obtained as a colorless oil after purification (25 mg, 0.12 mmol, 60%) using 0.1 mmol of LiHMDS (0.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 5.1, 1.2 Hz, 0.74H), 7.26 – 7.22 (m, 0.75H), 7.05 – 6.99 (m, 1H), 3.71 – 3.61 (m, 2.22H), 1.69 (bs, 1H), 1.63 (bs, 2.33H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 137.8, 128.4, 128.2, 126.6, 26.3 (2C), 24.7 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$) δ 7.46 (bs), 7.29 (bs), 7.06 (bs) 3.62 (bs), 1.59 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_4D_{10}NOS$: 206.1424 $[M+H]^+$; found 206.1422.

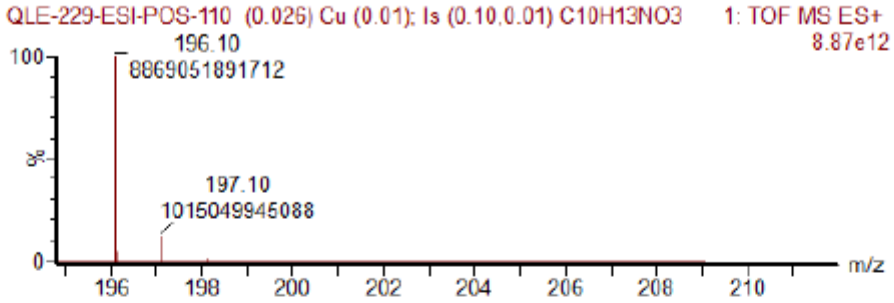
Isotopic exchange (calculated by HRMS): 57.5%.

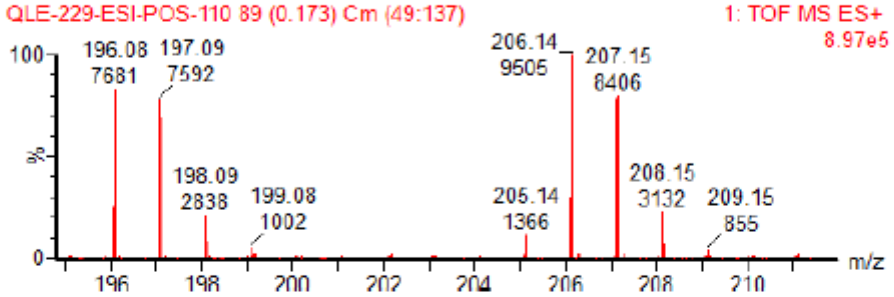
Isotopic enrichment (calculated by HRMS): 42.0% monodeuteration (M+1), 9.9% bideuteration (M+2).

FTIR (cm^{-1}): 2918, 2852, 2207, 2108, 1593, 1518, 1497, 1424, 1392, 1267, 1231, 1167, 1123, 1091, 1026, 989, 949, 929, 893, 868, 847, 812, 775, 733, 694, 662, 622, 593, 504, 443, 409.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique





Profil isotopique théorique

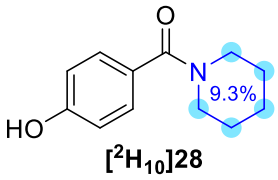
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	196	197	198	199	200	201	202	203
%	100	12,2	5,2	0,5	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	196	7681	0,00	7681,00	21,88
1	197	7592	937,08	6654,92	18,95
2	198	2838	399,41	1626,69	4,63
3	199	21	38,41	-561,92	-1,60
4	200	0	0,00	-49,31	-0,14
5	201	0	0,00	27,10	0,08
6	202	0	0,00	2,07	0,01
7	203	0	0,00	-1,41	0,00
8	204	0	0,00	-0,07	0,00
9	205	1366	0,00	1366,07	3,89
10	206	9505	0,00	9338,35	26,60
11	207	8406	0,00	7195,69	20,49
12	208	3132	0,00	1761,70	5,02
13	209	855	0,00	219,20	0,62
14	210	0	0,00	-154,33	-0,44
Total		41396		3,51E+04	99,98

Echange %	53,3
Enrichissement (+1D) %	41,7
Enrichissement (+2D) %	10,2

(4-hydroxyphenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]5)



[$^2H_{10}$]28

$C_{12}H_5D_{10}NO_2$
MW: 215.32 g.mol^{-1}
White solid
Yield: 56%
IE: 9.3%

Following the general procedure F, [$^2H_{10}$]5 was obtained as a white solid (24 mg, 0.11 mmol, 56%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.81 (bs, 1H), 7.25 – 7.17 (m, 2H), 6.82 – 6.74 (m, 2H), 3.6 - 3.38 (bs, 3.5H), 1.59 (bs, 1.90H), 1.55 – 1.41 (m, 3.67H).

^{13}C NMR (101 MHz, DMSO-*d*6) δ 169.1, 158.4, 128.8 (2C), 126.7, 114.8 (2C), 25.6 (2C), 24.1 (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, DMSO) δ 3.38 (bs), 1.41 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_6D_{10}NO_2$: 216.1809 $[M+H]^+$; found 216.1806.

Isotopic exchange (calculated by ^{1}H NMR): 7%.

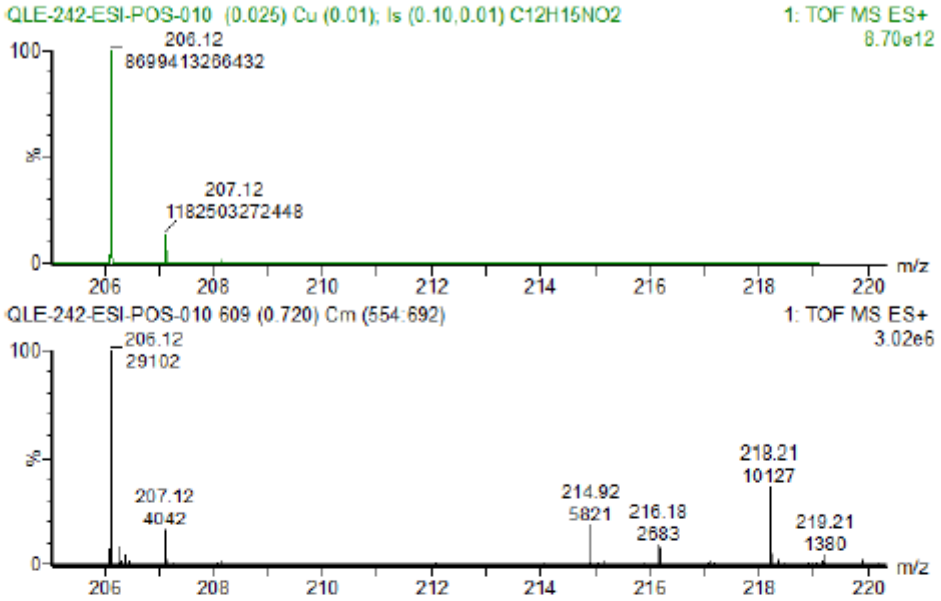
Isotopic exchange (calculated by HRMS): 9.3%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2918, 2852, 2207, 2108, 1593, 1518, 1497, 1424, 1392, 1267, 1231, 1167, 1123, 1091, 1026, 989, 949, 929, 893, 868, 847, 812, 775, 733, 694, 662, 622, 593, 504, 443, 409.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

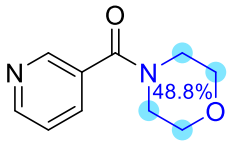
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	206	207	208	209	210	211	212	213
%	100	13,7	1,2	0,1	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	206	29102	0,00	29102,0	90,06
1	207	4042	3986,97	55,03	0,17
2	208	460	349,22	103,24	0,32
3	209	95	29,10	51,09	0,16
4	210	0	0,00	-8,29	-0,03
5	211	0	0,00	0,42	0,00
6	212	0	0,00	-0,01	0,00
7	213	399	0,00	399,00	1,23
8	214	2683	0,00	2628,34	8,13
9	215	379	0,00	14,13	0,04
10	216	0	0,00	-33,87	-0,10
11	217	0	0,00	1,84	0,01
12	218	0	0,00	0,14	0,00
13	219	0	0,00	-0,01	0,00
14	220	0	0,00	0,00	0,00
Total		37160		3,23E+04	100,00

Echange %	9,3
Enrichissement (+1D) %	0,2
Enrichissement (+2D) %	0,4

(morpholino-d8)(pyridin-3-yl)methanone ([$^2H_8$]35)



[$^2H_{10}$]35

$C_{10}H_4D_8N_2O_2$
MW: 200.27 g.mol^{-1}
Yellow oil
Yield: >95%
IE: 48.8%

Following the general procedure F, [$^2H_{10}$]35 was obtained as a yellow oil after purification (40 mg, 0.2 mmol, >95%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.9, 2.2 Hz, 1H), 8.56 (dd, *J* = 1.7, 0.9 Hz, 0.95H), 7.67 (ddd, *J* = 7.8, 2.2, 1.7 Hz, 1H), 7.28 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 3.96 – 3.27 (m, 4.08H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 151.1, 148.1, 135.2, 131.27, 123.6, 66.9(2C) (2C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.64 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{10}H_5D_8N_2O_2$: 201.1479 $[M+H]^+$; found 201.1474.

Isotopic exchange (calculated by ^{1}H NMR): 49%.

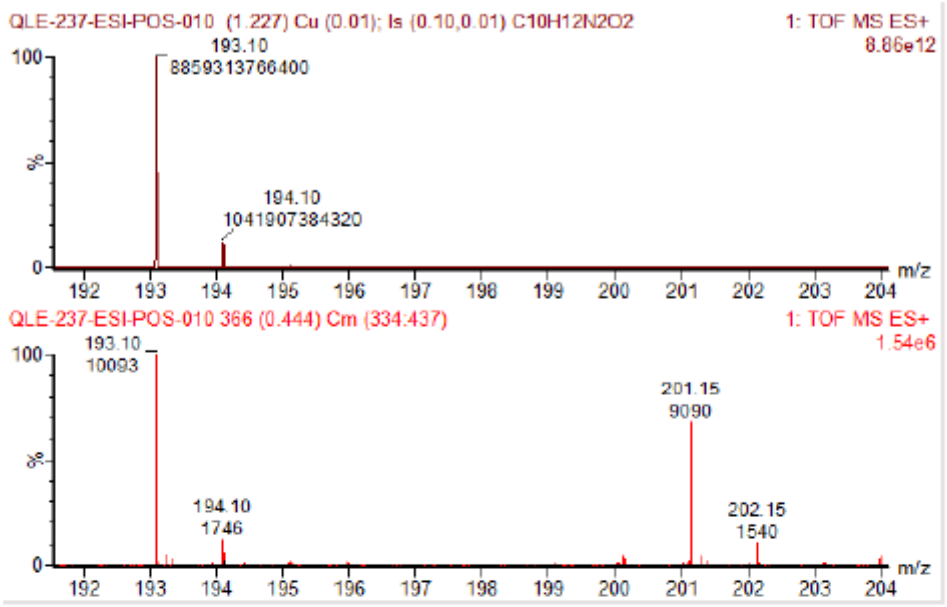
Isotopic exchange (calculated by HRMS): 48.8%.

Isotopic enrichment (calculated by HRMS): 5.2% monodeuteration (M+1).

FTIR (cm^{-1}): 2965, 2922, 2857, 2234, 2090, 1625, 1589, 1478, 1427, 1408, 1331, 1301, 1278, 1261, 1194, 1176, 1163, 1135, 1109, 1068, 1056, 1013, 969, 948, 920, 896, 819, 729, 647, 625, 607, 551, 489.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

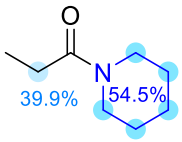
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	193	194	195	196	197	198	199	200
%	100	11,8	1	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	193	10093	0,00	10093,0	48,39
1	194	1746	1190,97	555,03	2,66
2	195	175	100,93	8,58	0,04
3	196	5	0,00	-1,56	-0,01
4	197	0	0,00	0,10	0,00
5	198	0	0,00	0,00	0,00
6	199	0	0,00	0,00	0,00
7	200	700	0,00	700,00	3,36
8	201	9090	0,00	9007,40	43,19
9	202	1540	0,00	470,13	2,25
10	203	166	0,00	20,45	0,10
11	204	12	0,00	4,89	0,02
12	205	0	0,00	-0,78	0,00
13	206	0	0,00	0,04	0,00
14	207	0	0,00	0,00	0,00
Total		23527		2,09E+04	100,00

Echange %	48,8
Enrichissement (+1D) %	5,2
Enrichissement (+2D) %	0,1

1-(piperidin-1-yl-d10)propan-1-one ([$^2H_{10}$]20)



[$^2H_{10}$]20

$C_8H_5D_{10}NO$
MW: 151.28 g.mol^{-1}
Colorless oil
Yield: 73%
IE: 54.5%

Following the general procedure F, [$^2H_{10}$]20 was obtained as a colorless oil after purification (22 mg, 0.15 mmol, 73%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (t, *J* = 5.6 Hz, 1.03H), 3.37 (t, *J* = 5.5 Hz, 1.01H), 2.32 (bs, 1.40H), 1.67 – 1.47 (m, 3.30H), 1.17 – 1.08 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 46.6, 42.7, 26.7, 26.6, 25.7, 24.7, 9.7.

^{2}H NMR (61 MHz, $CHCl_3$) δ 3.41 (m), 2.31 (bs), 1.51 (m).

HRMS (ESI-TOF) m/z calc'd for $C_8H_5D_{10}NO$: 152.1859 $[M+H]^+$; found 152.1855.

Isotopic exchange (calculated by ^{1}H NMR): 49%.

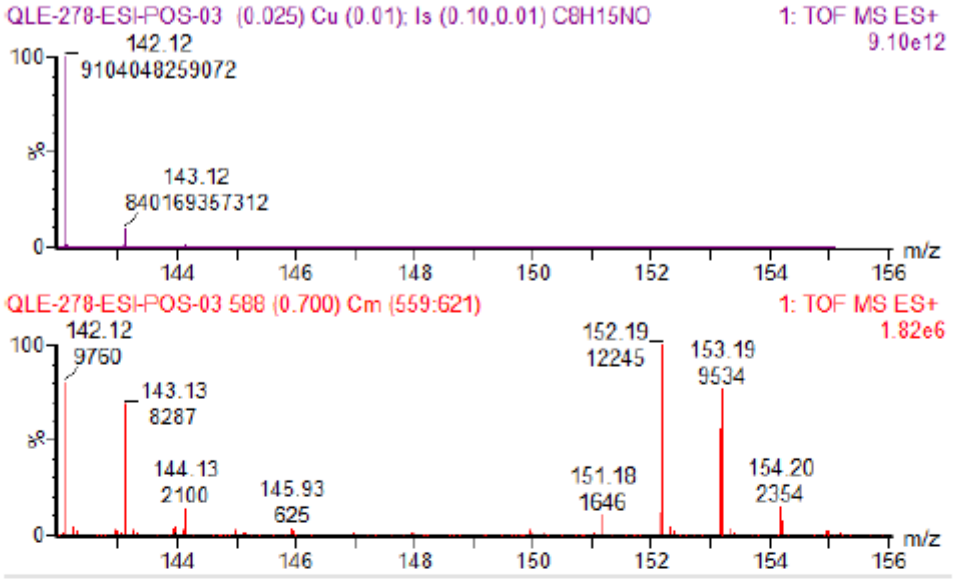
Isotopic exchange (calculated by HRMS): 54.5%.

Isotopic enrichment (calculated by HRMS): 39.9% monodeuteration (M+1), 7.4% bideuteration (M+2).

FTIR (cm^{-1}): 2935, 2856, 2210, 2110, 1728, 1633, 1426, 1310, 1279, 1251, 122.5, 1130, 1070, 1019, 973, 900, 853, 818, 748, 538, 477.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

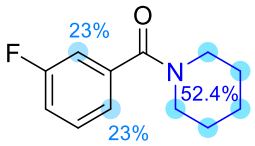
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	142	143	144	145	146	147	148	149
%	100	9,3	0,5	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	142	9760	0,00	9760,00	23,15
1	143	8287	907,68	7379,32	17,51
2	144	2100	48,80	1364,92	3,24
3	145	179	0,00	15,17	0,04
4	146	0	0,00	-8,24	-0,02
5	147	0	0,00	0,69	0,00
6	148	0	0,00	-0,02	0,00
7	149	0	0,00	0,00	0,00
8	150	0	0,00	0,00	0,00
9	151	1646	0,00	1646,00	3,90
10	152	12245	0,00	12091,92	28,68
11	153	9534	0,00	8401,22	19,93
12	154	2354	0,00	1512,23	3,59
13	155	181	0,00	-1,64	0,00
14	156	0	0,00	-7,41	-0,02
Total		46286		4,22E+04	100,00

Echange %	**54,5**
Enrichissement (+1D) %	**39,9**
Enrichissement (+2D) %	**7,4**

(3-fluorophenyl)(piperidin-1-yl-d10)methanone ([$^2H_{10}$]17)



[$^2H_{10}$]17

$C_{12}H_4D_{10}FNO$
MW: 217.31 g.mol^{-1}
White solid
Yield: 71%
IE: 52.4%

Following the general procedure F, [$^2H_{10}$]17 was obtained as a white solid after purification (31 mg, 0.14 mmol, 71%) using 0.3 mmol of LiHMDS (1.5 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 1H), 7.18 – 7.12 (m, 0.75H), 7.12 – 7.04 (m, 1.59H), 3.69 (bs, 0.98H), 3.31 (bs, 0.98H), 1.73 – 1.59 (m, 2.21H), 1.51 (bs, 1.12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 162.5 (d, $J_{13C\text{-}19F}$ = 247.7 Hz), 138.5, 130.2, 122.4 (d, J = 3.3 Hz), 116.4 (d, *J* = 21.2 Hz), 114.1 (d, *J* = 22.7 Hz), 48.7, 43.2, 26.6, 25.6, 24.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.18 (bs), 7.15 (m), 3.46 (m), 1.56 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_5D_{10}FNO$: 218.1765 $[M+H]^+$; found 218.1763.

Isotopic exchange (calculated by ^{1}H NMR): 51%.

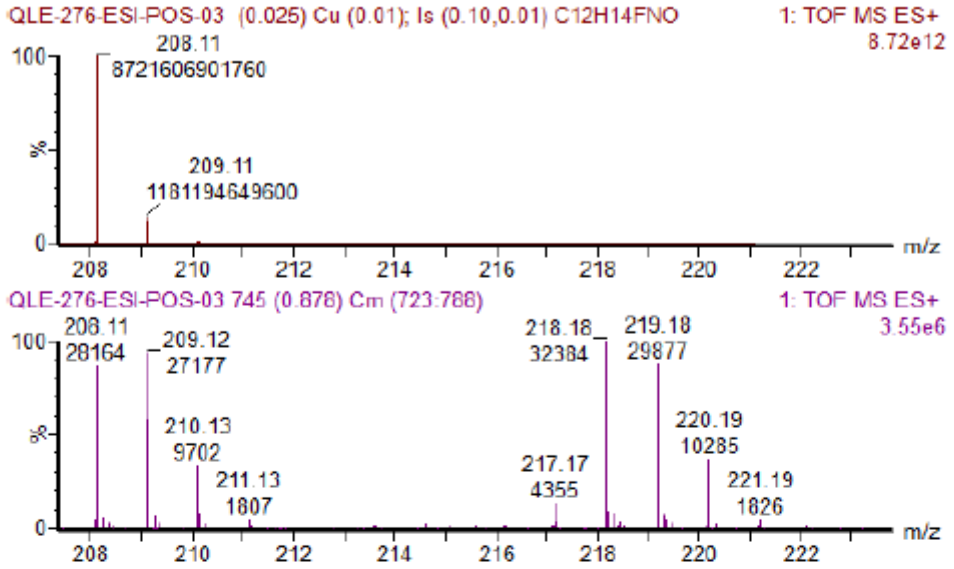
Isotopic exchange (calculated by HRMS): 52.4%.

Isotopic enrichment (calculated by HRMS): 40.4% monodeuteration (M+1), 10.8% bideuteration (M+2).

FTIR (cm^{-1}): 2937, 2856, 2213, 2112, 1625, 1581, 1436, 1403, 1273, 1253, 1214, 1150, 1124, 1104, 1079, 1027, 1007, 986, 941, 879, 851, 815, 795, 747, 701, 685, 672, 624, 586, 518, 478, 411.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

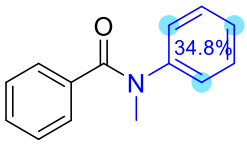
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	208	209	210	211	212	213	214	215
%	100	13,6	1	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	208	28164	0,00	28164,00	22,11
1	209	27177	3830,30	23346,70	18,33
2	210	9702	281,64	6245,21	4,90
3	211	1807	0,00	724,18	0,57
4	212	207	0,00	46,06	0,04
5	213	0	0,00	-13,51	-0,01
6	214	0	0,00	1,38	0,00
7	215	0	0,00	-0,05	0,00
8	216	0	0,00	-0,01	0,00
9	217	4355	0,00	4355,00	3,42
10	218	32384	0,00	31791,72	24,96
11	219	29877	0,00	25509,78	20,03
12	220	10285	0,00	6497,75	5,10
13	221	1826	0,00	687,21	0,54
14	222	181	0,00	22,56	0,02
Total		145965		1,27E+05	100,01

Echange %	52,4
Enrichissement (+1D) %	40,4
Enrichissement (+2D) %	10,8

N-methyl-N-(phenyl-2,4,6-d3)benzamide ([$^2H_3$]14)



[$^2H_{10}$]14

$C_{14}H_{10}D_3NO$
MW: 214.28 g.mol^{-1}
Pale-yellow oil
Yield: 85%
IE: 34.8%

Following the general procedure F, [$^2H_{10}$]14 was obtained as a pale-yellow oil after purification (18 mg, 0.08 mmol, 85%) using 0.1 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 1.87H), 7.25 – 7.11 (m, 5.81H), 7.07 – 7.01 (m, 1.45H), 3.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 145.2, 136.1, 129.7, 129.3 (2C), 128.8 (2C), 127.9 (2C), 127.0 (2C), 126.6, 38.5.

^{2}H NMR (61 MHz, $CDCl_3$): δ 7.4 – 6.6 (m).

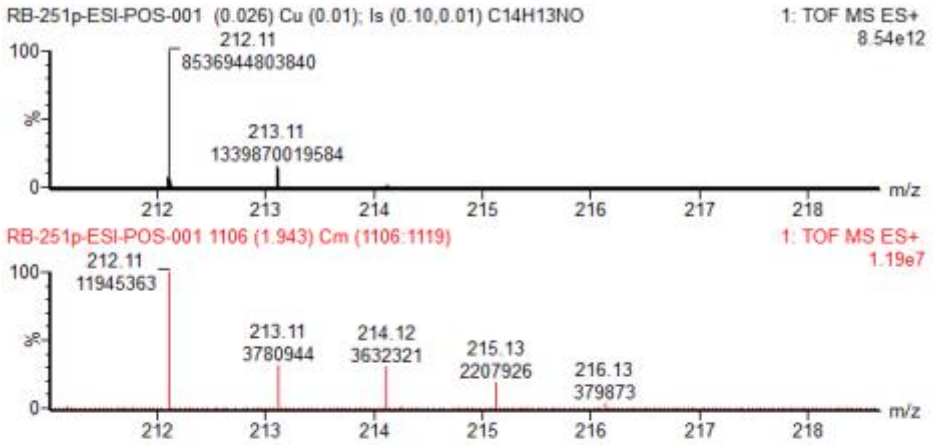
HRMS (ESI-TOF) m/z calcd for $C_{14}H_{11}D_3NO$: 215.1264 $[M+H]^+$; found 215.1259.

Isotopic exchange (calculated by HRMS): 34.8%.

FTIR (cm^{-1}): 3058, 2924, 2854, 1642, 1594, 1576, 1493, 1446, 1419, 1360, 1301, 1282, 1177, 1105, 1075, 1049, 1026, 1010, 999, 922, 875, 791, 769, 726, 697, 654, 639, 617, 578, 552, 518, 415.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

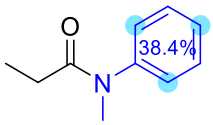
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	212	213	214	215	216	217	218	219
%	100	15,77	1,36	0,08	0	0	0	0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	212	11945363	0,00	11945363,00	63,78
1	213	3786944	1883783,75	1903160,25	10,16
2	214	3632321	162456,94	3169735,69	16,92
3	215	2207926	9556,29	1672619,41	8,93
4	216	379873	0,00	71469,99	**0,38**
5	217	0	0,00	-36554,23	**-0,20**
6	218	0	0,00	3454,51	**0,02**
7	219	0	0,00	-104,82	**0,00**
8	220	0	0,00	-1,21	**0,00**
9	221	0	0,00	-1,15	**0,00**
10	222	0	0,00	0,28	**0,00**
11	223	0	0,00	-0,03	**0,00**
12	224	0	0,00	0,00	**0,00**
13	225	0	0,00	0,00	**0,00**
14	226	0	0,00	0,00	**0,00**
Total		21952427		1,87E+07	100,00

Exchange (Aniline) %	**34,8**
Enrichment (+1D) %	**1,2**
Enrichment (+2D) %	**4,6**

N-methyl-N-(phenyl-2,4,6-d3)propionamide ([$^2H_3$]13)



[$^2H_{10}$]13

$C_{10}H_{10}D_3NO$
MW: 166.24 g.mol^{-1}
Colorless oil
Yield: 54%
IE: 38.4%

Following the general procedure F, [$^2H_{10}$]13 was obtained as a colorless oil after purification (9 mg, 0.05 mmol, 54%) using 0.1 mmol of LiHMDS (1.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.37 (m, 2H), 7.37 – 7.29 (m, 0.89H), 7.22 – 7.14 (m, 1.62H), 3.26 (s, 3H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 144.4, 129.9 (2C), 127.8, 127.4 (2C), 37.5, 27.7, 9.9.

^{2}H NMR (61 MHz, $CDCl_3$): δ 7.7 – 7.1 (m), 3.5 (s).

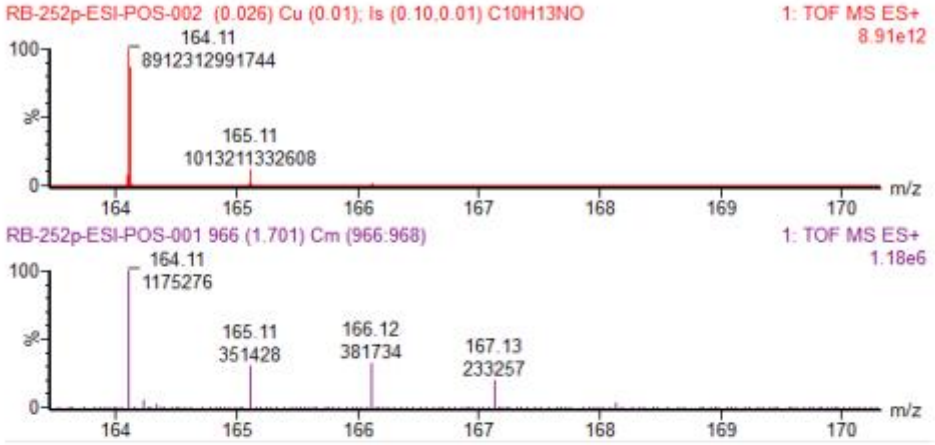
HRMS (ESI-TOF) m/z calc'd for $C_{10}H_{11}D_3NO$: 167.1264 $[M+H]^+$; found 167.1258.

Isotopic exchange (calculated by HRMS): 38.4%.

FTIR (cm^{-1}): 2977, 2938, 1652, 1595, 1496, 1462, 1420, 1376, 1273, 1124, 1095, 1071, 1034, 922, 808, 774, 701, 633, 617, 581, 559, 406.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

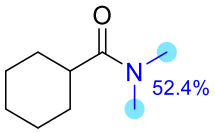
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	164	165	166	167	168	169	170	171
%	100	11,44	0,79	0,04	0	0	0	0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	164	1175276	0,00	1175276,00	60,49
1	165	351428	134451,57	216976,43	11,17
2	166	381734	9284,68	347627,22	17,89
3	167	233257	470,11	191304,22	9,85
4	168	35980	0,00	11261,75	**0,58**
5	169	3751	0,00	812,30	**0,04**
6	170	0	0,00	-258,42	**-0,01**
7	171	0	0,00	18,64	**0,00**
8	172	0	0,00	-0,42	**0,00**
9	173	0	0,00	0,00	**0,00**
10	174	0	0,00	0,00	**0,00**
11	175	0	0,00	0,00	**0,00**
12	176	0	0,00	0,00	**0,00**
13	177	0	0,00	0,00	**0,00**
14	178	0	0,00	0,00	**0,00**
Total		2181426		1,94E+06	100,00

Exchange (Aniline) %	**38,4**
Enrichment (+1D) %	**1,4**
Enrichment (+2D) %	**4,2**

N,N-bis(methyl-d3)cyclohexanecarboxamide ([$^2H_6$]32)



[$^2H_{10}$]32

$C_9H_{11}D_6NO$
MW: 161.28 g.mol^{-1}
Colorless oil
Yield: 68%
IE: 52.4%

Following the general procedure F, [$^2H_{10}$]32 was obtained as a colorless oil after purification (22 mg, 0.14 mmol, 68%) using 0.6 mmol of LiHMDS (3.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 1.45H), 2.89 (s, 1.49H), 2.45 (tdt, *J* = 11.5, 4.5, 3.3 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.73 – 1.58 (m, 3H), 1.54 – 1.40 (m, 2H), 1.32 – 1.16 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 40.7, 37.1, 35.6, 29.2 (2C), 25.95 (2C), 25.92.

^{2}H NMR (61 MHz, $CHCl_3$): δ 2.98 (bs), 2.87 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_9H_{12}D_6NO$: 162.1765 $[M+H]^+$; found 162.1760.

Isotopic exchange (calculated by HRMS): 52.4%.

Isotopic enrichment (calculated by HRMS): < 5%.

FTIR (cm^{-1}): 2927, 2853, 2207, 2073, 1629, 1495, 1447, 1418, 1398, 1359, 1348, 1291, 1246, 1186, 1155, 1116, 1053, 1030, 992, 893, 861, 837, 750, 664, 633, 602, 520, 495, 444.

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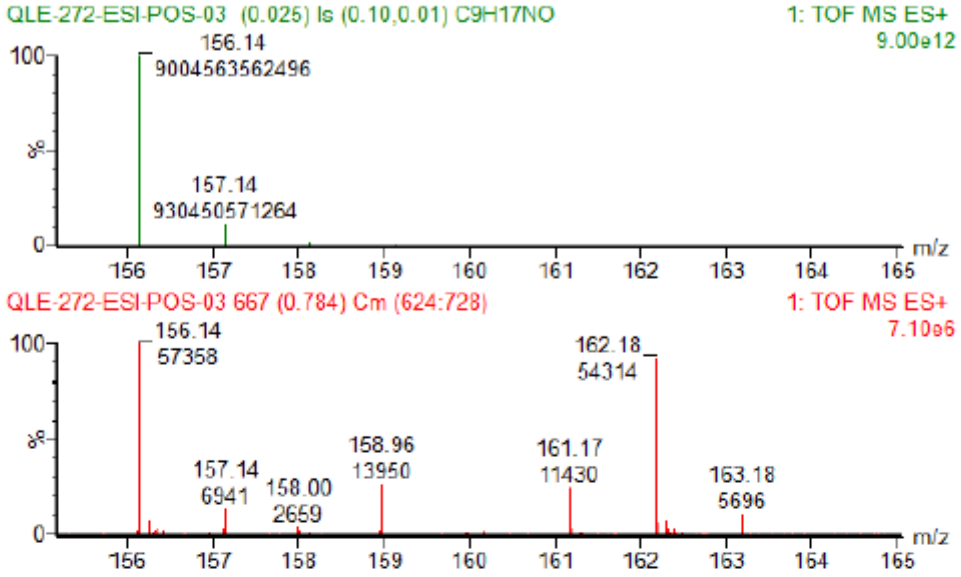
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

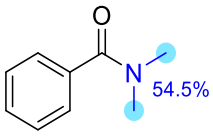
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	156	157	158	159	160	161	162	163
%	100	10,4	0,6	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	156	57358	0,00	57358,00	46,59
1	157	6941	5965,23	975,77	0,79
2	158	610	344,15	164,37	0,13
3	159	0	0,00	-22,95	-0,02
4	160	0	0,00	1,40	0,00
5	161	11430	0,00	11429,99	9,28
6	162	54314	0,00	53125,27	43,15
7	163	5696	0,00	102,39	0,08
8	164	311	0,00	-18,40	-0,01
9	165	0	0,00	1,30	0,00
10	166	0	0,00	-0,02	0,00
11	167	0	0,00	-0,01	0,00
12	168	0	0,00	0,00	0,00
13	169	0	0,00	0,00	0,00
14	170	0	0,00	0,00	0,00
Total		136660		1,23E+05	100,00

Echange %	52,4
Enrichissement (+1D) %	1,7
Enrichissement (+2D) %	0,3

N,N-bis(dimethyl-d3)benzamide ([$^2H_6$]33)



[$^2H_{10}$]33

$C_9H_5D_6NO$
MW: 155.230 g.mol^{-1}
Colorless oil
Yield: >95%
IE: 54.5%

Following the general procedure F, [$^2H_{10}$]33 was obtained as a colorless oil (15 mg, 0.1 mmol, >95%) using 0.6 mmol of LiHMDS (3.0 eq.) at 95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.37 (m, 5H), 3.11 (bs, 1.5H), 2.98 (bs, 1.46H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 136.5, 129.6, 128.5 (2C), 127.2 (2C), 29.8 (2C).

^{2}H NMR (61 MHz, $CDCl_3$): δ 3.3 – 2.7 (m).

HRMS (ESI-TOF) m/z calc'd for $C_9H_6D_6NO$: 156.1295 $[M+H]^+$; found 156.1295.

Isotopic exchange (calculated by ^{1}H NMR): 51%.

Isotopic exchange (calculated by HRMS): 54.5%.

Isotopic enrichment (calculated by HRMS): 11.0% monodeuteration (M+1), 0.3% bideuteration (M+2).

FTIR (cm^{-1}): 3058, 2928, 2215, 2074, 1622, 1576, 1505, 1483, 1445, 1417, 1393, 1265, 1247, 1216, 1179, 1113, 1084, 1074, 1027, 1002, 970, 928, 837, 788, 730, 704, 637, 620, 550, 436.

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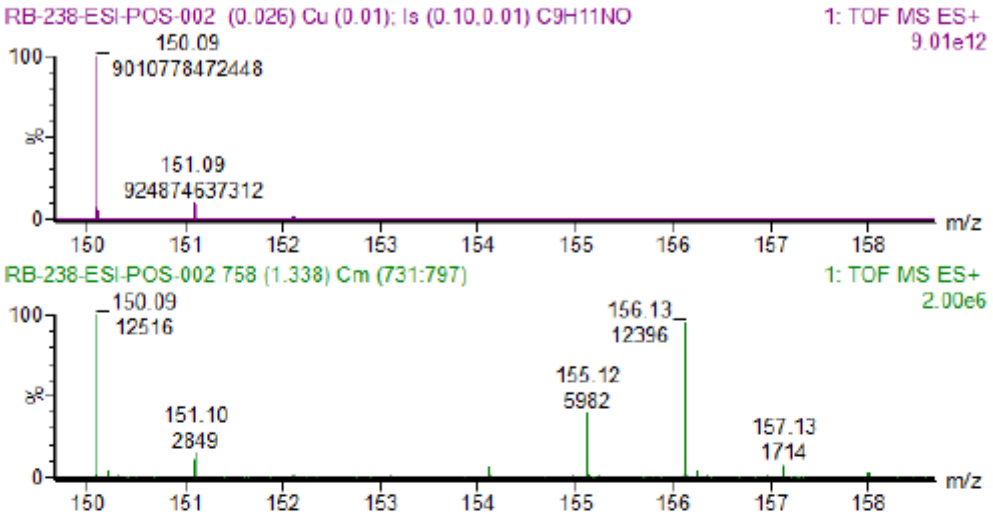
Plateforme d'Analyse

Enrichissement isotopique



Profil isotopique théorique

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	208	209	210	211	212	213	214	215
%	100	10,3	0,6	0	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	208	12516	0,00	12516,00	37,28
1	209	2849	1289,15	1559,85	4,65
2	210	284	75,10	48,24	0,14
3	211	0	0,00	-14,33	-0,04
4	212	1388	0,00	1389,19	4,14
5	213	5982	0,00	5839,00	17,39
6	214	12396	0,00	11786,25	35,11
7	215	1714	0,00	464,98	1,39
8	216	101	0,00	-17,61	-0,05
9	217	0	0,00	-0,98	0,00
10	218	0	0,00	0,21	0,00
11	219	0	0,00	-0,02	0,00
12	220	0	0,00	0,00	0,00
13	221	0	0,00	0,00	0,00
14	222	0	0,00	0,00	0,00
Total		37230		3,36E+04	100,00

Echange %	56,4
Enrichissement (+1D) %	11,0
Enrichissement (+2D) %	0,3

VI. Synthetic procedure and analytical data for amide metathesis

Preliminary attempts of amide bond metathesis:

The same result was observed using the zirconium catalyst in the amide bond metathesis reaction depicted in Figure S7. In light of these unsuccessful results, we did not investigate these strategy longer.

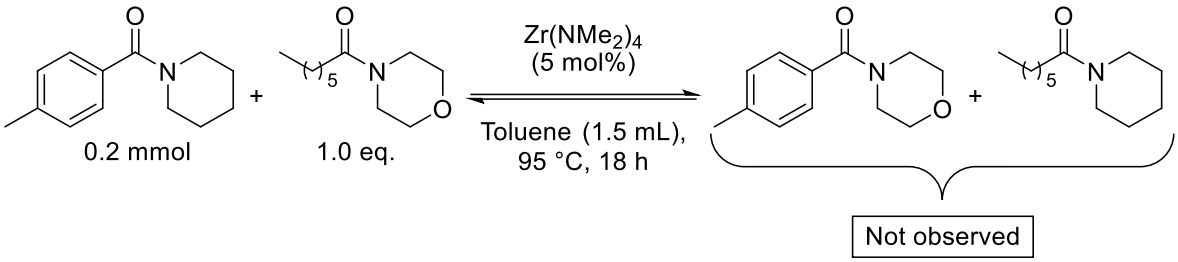
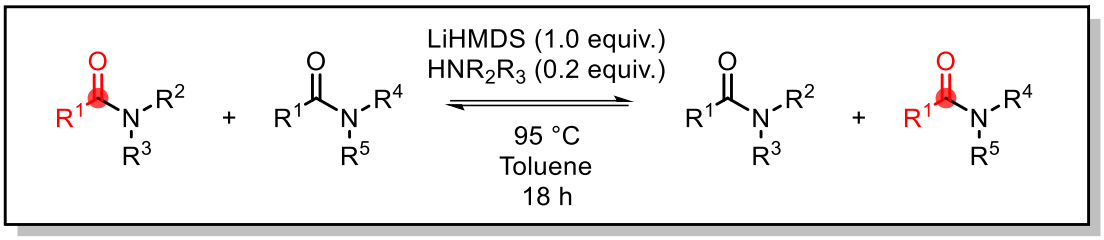


Figure S7 : Preliminary attempt of amide bond metathesis.

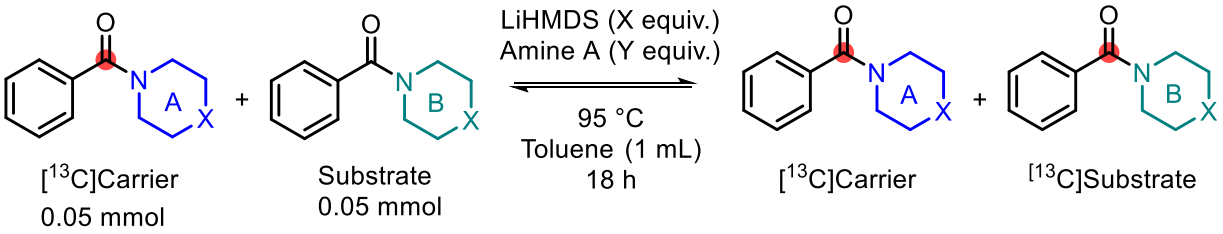
General procedure G: Amide Bond Metathesis



An oven-dried 5 mL micro-wave tube was cooled under vacuum then filled with nitrogen. The tube was then charged with the unlabeled amide (0.05 mmol, 1.0 equiv.) and the isotope carrier (0.05 mmol, 1.0 equiv.) and purged with 3 cycles vacuum/N_2. Then, dry toluene (1.0 mL, 0.05M) was added, followed by the catalytic amine* (0.01 mmol, added as a 0.1 M solution in dry toluene) and LiHMDS (1 M in THF, 0.05 mmol, 1.0 equiv.). The tube was then sealed and stirred at 95 °C for 18 h. The tube was then allowed to cool to room temperature, opened, and quenched by slow addition of 0.5 mL of methanol. The mixture was evaporated to dryness and the resulting crude was purified on silica gel column chromatography using heptane and ethyl acetate as eluent (from 5/1 to 2/1).

*the catalytic amine corresponds to the carrier (for C1, C5, C6: piperidine was used, for C2: 1,4-dioxa-8-azaspiro[4.5]decane, for C3: N-methylaniline, for C4: morpholine).

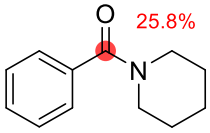
a. Optimisation



Entry	A	B	X eq.	Y eq.	T °C	Carrier recovery	Carrier IE	Substrate recovery	Substrate IE
1	Pipe.	Morpho.	**1.0**	50%	95 °C	>95%	Nd	65%	47%
2	Pipe.	Morpho.	**2.0**	50%	95 °C	>95%	Nd	34%	49%
3	Pipe.	Morpho.	1.0	**40%**	95 °C	90%	54%	54%	49%
4	Pipe.	Morpho.	1.0	**20%**	95 °C	92%	56%	62%	48%
5	Morpho.	Pipe.	1.0	**20%**	95 °C	74%	63%	>95%	38%
6	Morpho.	Pipe.	1.0	**40%**	95 °C	62%	48%	>95%	40%
7[a]	Morpho.	Pipe.	1.0	20%	95 °C	66%	55%	>95%	44%
8[a]	Pipe.	Morpho.	1.0	20%	95 °C	>95%	49%	70%	47%
9[a]	Pipe.	Morpho.	1.0	20%	**95 °C**	88%	49%	51%	42%
10[a]	Pipe.	Morpho.	1.0	20%	**55 °C**	>95%	62%	78%	23%
11[a]	Pipe.	Morpho.	1.0	20%	**20 °C**	84%	95%	68%	0%

Tableau 2 : Amide bond metathesis optimisation, pipe. = piperidine, morpho. = morpholine, [a]fresh toluene and fresh LiHMDS

[13C] phenyl(piperidin-1-yl)methanone ([13C]44)



[13C]44

$C_{11}{}^{13}CH_{15}NO$
MW: 190.25 g.mol^{-1}
White solid
Yield: 77%
IE: 25.8%

Following the general procedure G, [13C]44 was obtained as a white solid (7 mg, 0.037 mmol, 77%), using the isotopic carrier [13C]IC2 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 5H), 3.71 (bs, 2H), 3.34 (bs, 2H), 1.67 (bs, 4H), 1.51m (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C labeled), 136.7, 129.5, 128.5 (s + d, *J* = 4.1 Hz, 2C), 126.9 (s + d, *J* = 2.1 Hz, 2C), 48.9, 43.2, 26.7, 25.8, 24.8 (4 carbons broad signals due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{11}H_{16}NO$: 191.1266 $[M+H]^+$; found 191.1267.

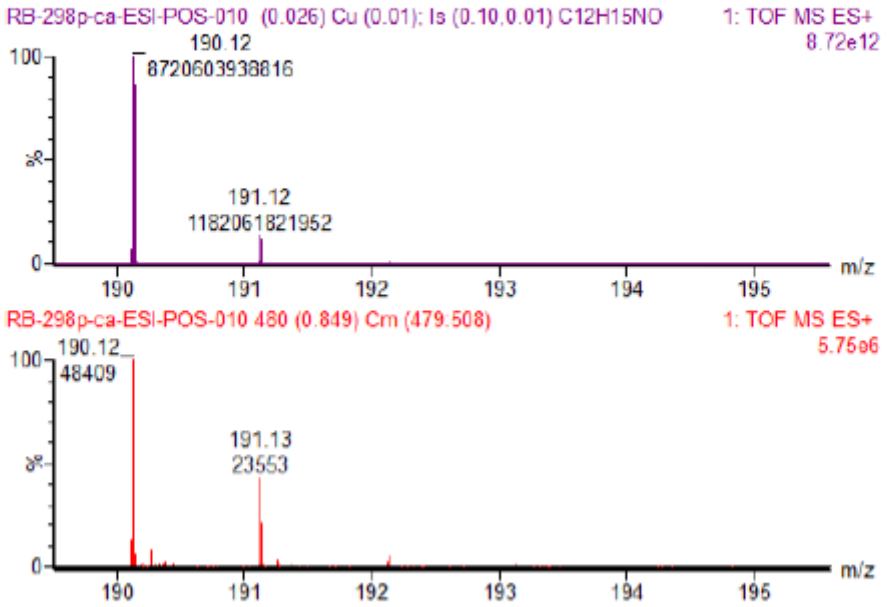
Isotopic exchange (calculated by ^{13}C NMR): 26%.

Isotopic exchange (calculated by HRMS): 25.8%.

FTIR (cm^{-1}): 2935, 2854, 1627, 1592, 1575, 1494, 1427, 1369, 1274, 1238, 1110, 1074, 1027, 1002, 955, 853, 784, 730, 706, 632, 524, 424.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

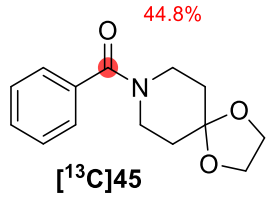
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	190	191	192	193	194	195	196	197
%	100,0	13,6	1,0	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	190	48409	0,00	48409,00	73,55
1	191	23553	6583,62	16969,38	25,78
2	192	2919	484,09	127,07	0,19
3	193	542	0,00	355,02	0,54
4	194	0	0,00	-49,55	-0,08
5	195	0	0,00	3,19	0,00
6	196	0	0,00	0,06	0,00
7	197	0	0,00	-0,04	0,00
8	198	0	0,00	0,00	0,00
9	199	0	0,00	0,00	0,00
10	200	0	0,00	0,00	0,00
11	201	0	0,00	0,00	0,00
Total		75423		65814,14	100,00

% Isotopic enrichment : 25,8

[^{13}C] phenyl(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methanone ([^{13}C]45)



[^{13}C]45

$C_{13}{}^{13}CH_{17}NO_3$
MW: 248.29 g.mol^{-1}
White solid
Yield: 80%
IE: 44.8%

Following the general procedure G, [^{13}C]45 was obtained as a white solid (10 mg, 0.040 mmol, 80%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.36 (m, 5H), 3.98 (s, 4H), 3.85 (bs, 2H), 3.48 (bs, 2H), 1.80 (bs, 2H), 1.64 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 136.1 (s + d, *J* = 66.4 Hz), 129.8, 128.6 (s + d, *J* = 4.2 Hz, 2C), 126.9 (s + d, *J* = 2.1 Hz, 2C), 107.1, 64.6, 45.8, 40.4, 35.8, 35.0 (4 carbons poorly defined due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{13}H_{18}NO_3$: 249.1321 $[M+H]^+$; found 249.1325.

Isotopic exchange (calculated by ^{13}C NMR): 42%.

Isotopic exchange (calculated by HRMS): 44.8%.

FTIR (cm^{-1}): 2959, 2879, 1631, 1593, 1574, 1466, 1424, 1360, 1338, 1267, 1250, 1162, 1127, 1087, 1031, 945, 913, 870, 783, 708, 662, 636, 527, 490.

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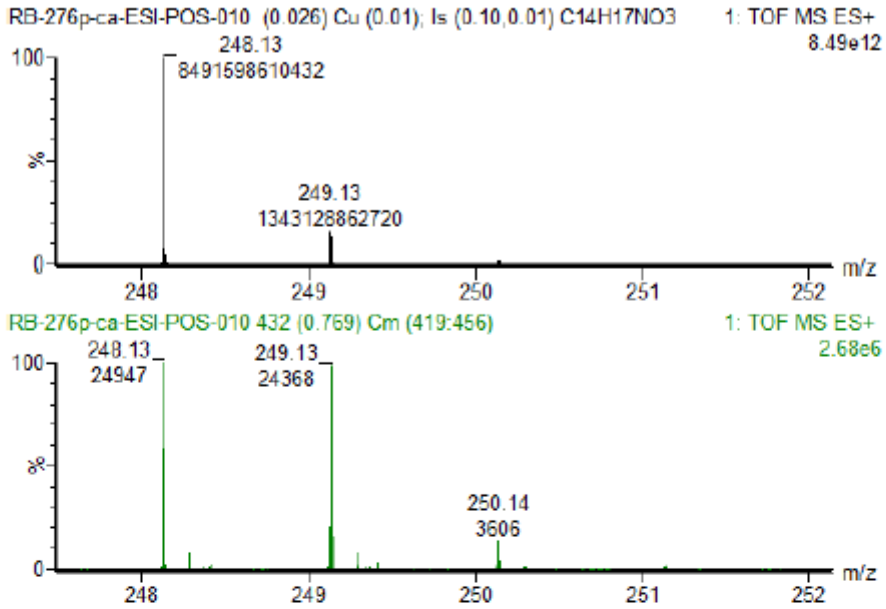
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

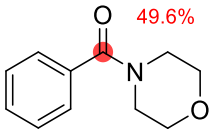
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	248	249	250	251	252	253	254	255
%	100,0	15,9	1,7	0,1	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	248	24947	0,00	24947,00	54,79
1	249	24368	3966,57	20401,43	44,81
2	250	3606	424,10	-61,93	-0,14
3	251	616	24,95	254,07	0,56
4	252	50	0,00	-9,75	-0,02
5	253	0	0,00	-2,71	-0,01
6	254	0	0,00	0,34	0,00
7	255	0	0,00	0,00	0,00
8	256	0	0,00	0,00	0,00
9	257	0	0,00	0,00	0,00
10	258	0	0,00	0,00	0,00
11	259	0	0,00	0,00	0,00
Total		53587		45528,46	100,00

% Isotopic enrichment : 44,8

[^{13}C] morpholino(phenyl)methanone ([^{13}C]41)



[^{13}C]41

$C_{10}{}^{13}CH_{13}NO_2$
MW: 192.22 g.mol^{-1}
White solid
Yield: 64%
IE: 49.6%

Following the general procedure G, [^{13}C]41 was obtained as a white solid (6 mg, 0.030 mmol, 64%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 5H), 3.98 – 3.31 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (^{13}C-labeled), 139.6, 130.0, 128.7 (s + d, *J* = 4.0 Hz, 2C), 127.3 (s + d, *J* = 2.0 Hz, 2C), 67.1 (2C) (2C missing due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{10}H_{14}NO_2$: 193.1059 $[M+H]^+$; found 193.1068.

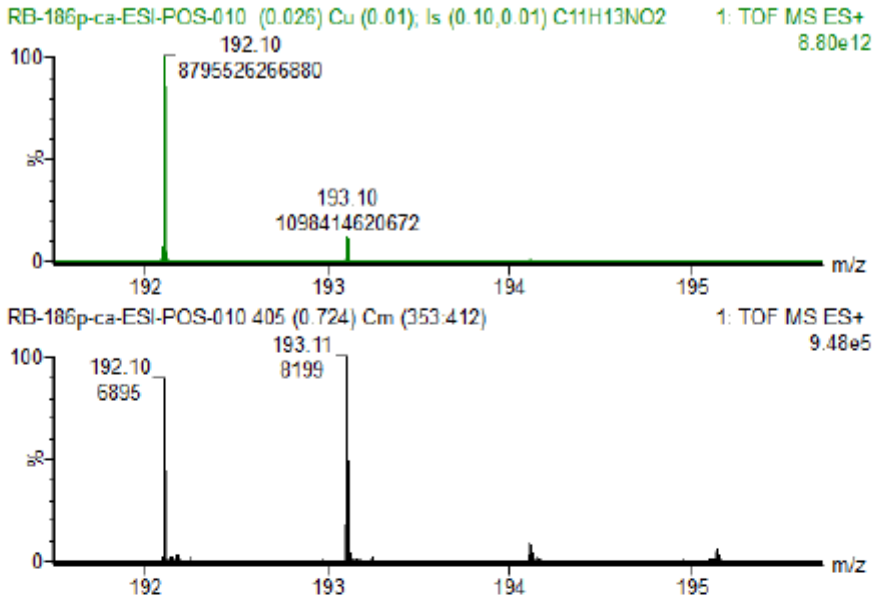
Isotopic exchange (calculated by ^{13}C NMR): 51%.

Isotopic exchange (calculated by HRMS): 49.6%.

FTIR (cm^{-1}): 2919, 2855, 1633, 1596, 1425, 1276, 1255, 1115, 1067, 1013, 842, 783, 733, 708, 548.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

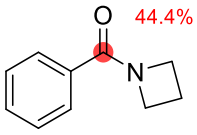
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	192	193	194	195	196	197	198	199
%	100,0	12,6	1,0	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	192	6895	0,00	6895,00	46,66
1	193	8199	868,77	7330,23	49,61
2	194	1525	68,95	532,44	3,60
3	195	166	0,00	25,61	0,17
4	196	0	0,00	-8,55	-0,06
5	197	0	0,00	0,82	0,01
6	198	0	0,00	-0,02	0,00
7	199	0	0,00	-0,01	0,00
8	200	0	0,00	0,00	0,00
9	201	0	0,00	0,00	0,00
10	202	0	0,00	0,00	0,00
11	203	0	0,00	0,00	0,00
Total		16785		14775,53	100,00

% Isotopic enrichment : 49,6

[^{13}C] azetidin-1-yl(phenyl)methanone ([^{13}C]42)



[^{13}C]42

$C_9{}^{13}CH_{11}NO$
MW: 162.20 g.mol^{-1}
Colorless oil
Yield: 47%
IE: 44.4%

Following the general procedure G, [^{13}C]42 was obtained as a colorless oil (4 mg, 0.025 mmol, 47%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H), 7.48 – 7.36 (m, 3H), 4.30 (t, *J* = 7.5 Hz, 2H), 4.23 (t, *J* = 7.7 Hz, 2H), 2.40 – 2.29 (quint, *J* = 7.7 Hz , 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5 (^{13}C-labeled), 133.5, 131.0, 128.5 (s + d, *J* = 4.0 Hz, 2C), 128.0 (s + d, *J* = 2.2 Hz, 2C), 53.5, 49.0, 16.2.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_9H_{12}NO$: 163.0953 $[M+H]^+$; found 163.0957.

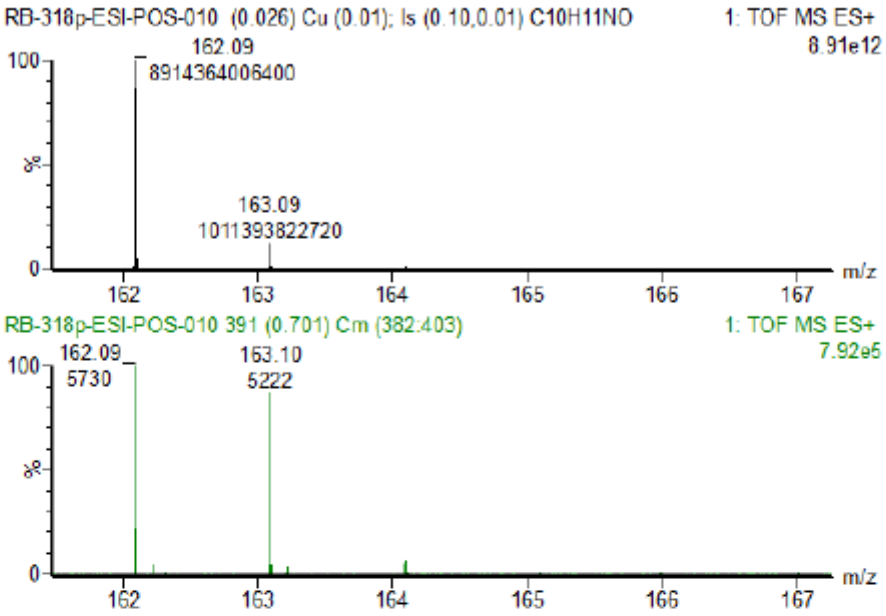
Isotopic exchange (calculated by 13C NMR): 46%.

Isotopic exchange (calculated by HRMS): 44.4%.

FTIR (cm^{-1}): 2954, 1628, 1597, 1570, 1448, 1411, 705.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

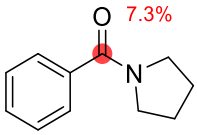
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	162	163	164	165	166	167	168	169
%	100,0	11,4	0,7	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	162	5730	0,00	5730,00	55,64
1	163	5222	653,22	4568,78	44,37
2	164	529	40,11	-31,95	-0,31
3	165	63	0,00	34,66	0,34
4	166	0	0,00	-3,73	-0,04
5	167	0	0,00	0,18	0,00
6	168	0	0,00	0,01	0,00
7	169	0	0,00	0,00	0,00
8	170	0	0,00	0,00	0,00
9	171	0	0,00	0,00	0,00
10	172	0	0,00	0,00	0,00
11	173	0	0,00	0,00	0,00
Total		11544		10297,95	100,00

% Isotopic enrichment : 44,4

[^{13}C] phenyl(pyrrolidin-1-yl)methanone ([^{13}C]43)



[^{13}C]43

$C_{10}{}^{13}CH_{13}NO$
MW: 176.22 g.mol^{-1}
Colorless oil
Yield: 85%
IE: 7.3%

Following the general procedure G, [^{13}C]43 was obtained as a colorless oil (8 mg, 0.043 mmol, 85%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.44 – 7.34 (m, 3H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 1.95 (quint, *J* = 6.8 Hz, 2H), 1.87 (quint, *J* = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (^{13}C-labeled), 137.4, 129.9, 128.4 (s + d, *J* = 3.8 Hz, 2C), 127.2 (2C), 49.7, 46.3, 26.5, 24.6.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{10}H_{14}NO$: 177.1109 $[M+H]^+$; found 177.1118.

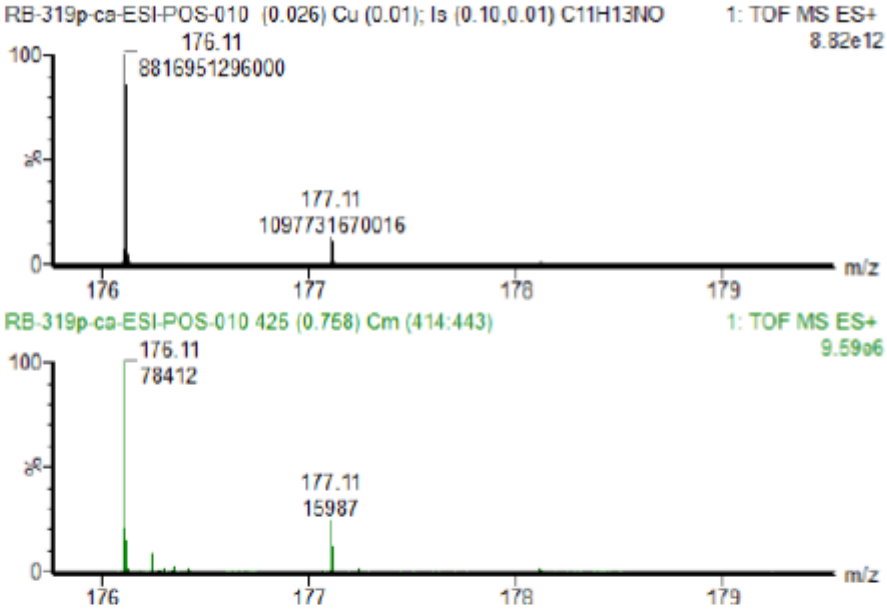
Isotopic exchange (calculated by ^{13}C NMR): 10%.

Isotopic exchange (calculated by HRMS): 7.3%.

FTIR (cm^{-1}): 2970, 2876, 1623, 1575, 1446, 1417, 1340, 1229, 1160, 1076, 1026, 791, 718, 700, 658, 471.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

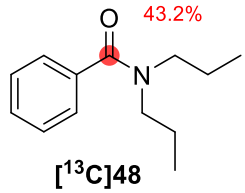
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	176	177	178	179	180	181	182	183
%	100,0	12,5	0,8	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	176	78412	0,00	78412,00	92,55
1	177	15987	9801,50	6185,50	7,30
2	178	1511	627,30	110,52	0,13
3	179	83	0,00	19,70	0,02
4	180	0	0,00	-3,35	0,00
5	181	0	0,00	0,26	0,00
6	182	0	0,00	-0,01	0,00
7	183	0	0,00	0,00	0,00
8	184	0	0,00	0,00	0,00
9	185	0	0,00	0,00	0,00
10	186	0	0,00	0,00	0,00
11	187	0	0,00	0,00	0,00
Total		95993		84724,62	100,00

% Isotopic enrichment : 7,3

[^{13}C] N,N-dipropylbenzamide ([^{13}C]48)



[^{13}C]48

$C_{12}{}^{13}CH_{19}NO$
MW: 206.29 g.mol^{-1}
Colorless oil
Yield: 79%
IE: 43.2%

Following the general procedure G, [^{13}C]48 was obtained as a colorless oil (8 mg, 0.039 mmol, 79%), using the isotopic carrier [^{13}C]IC2 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 5H), 3.46 (bs, *J* = 6.7 Hz, 2H), 3.15 (bs, 2H), 1.75 – 1.64 (m, *J* = 6.2 Hz, 2H), 1.58 – 1.44 (m, *J* = 6.4 Hz, 2H), 0.98 (bs, 3H), 0.74 (bs, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9 (^{13}C-labeled), 137.5, 129.1, 128.5 (2C), 126.6 (2C), 50.8, 46.4, 22.0, 20.9, 11.6, 11.2.

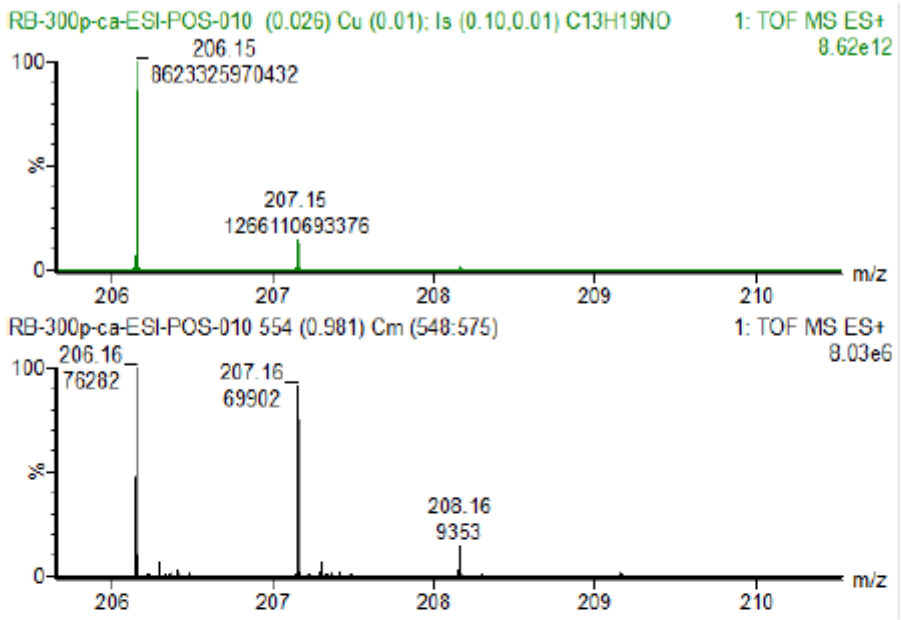
HRMS (ESI-TOF) m/z calcd for $^{13}CC_{12}H_{20}NO$: 207.1579 $[M+H]^+$; found 207.1585

Isotopic enrichment (calculated by HRMS): 43.2% of Carbone 13 (M+1)

FTIR (cm^{-1}): 2963, 2874, 1633, 1594, 1420, 1380, 1254, 1098, 1026, 782, 700.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

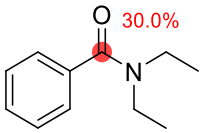
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	206	207	208	209	210	211	212	213
%	100,0	14,7	1,2	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	206	76282	0,00	76282,00	56,15
1	207	69902	11213,45	58688,55	43,20
2	208	9353	915,38	-189,60	-0,14
3	209	1779	0,00	1102,61	0,81
4	210	142	0,00	-17,81	-0,01
5	211	0	0,00	-10,61	-0,01
6	212	0	0,00	1,77	0,00
7	213	0	0,00	-0,13	0,00
8	214	0	0,00	0,00	0,00
9	215	0	0,00	0,00	0,00
10	216	0	0,00	0,00	0,00
11	217	0	0,00	0,00	0,00
Total		157458		135856,77	100,00

% Isotopic enrichment : 43,2

[^{13}C] N,N-diethylbenzamide ([^{13}C]47)



[^{13}C]47

$C_{10}{}^{13}CH_{15}NO$
MW: 178.24 g.mol^{-1}
Colorless oil
Yield: 60%
IE: 30.0%

Following the general procedure G, [^{13}C]47 was obtained as a colorless oil (5 mg, 0.030 mmol, 60%), using the isotopic carrier [^{13}C]IC2 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.33 (m, 5H), 3.55 (bs, 2H), 3.25 (bs, 2H), 1.25 (bs, 3H), 1.10 (bs, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (^{13}C-labeled), 137.4, 129.2, 128.5 (s + d, *J* = 4.0 Hz, 2C), 126.4 (s + d, *J* = 2.0 Hz, 2C), 43.4, 39.3, 14.4, 13.0.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{10}H_{16}NO$: 179.1266 $[M+H]^+$; found 179.1268.

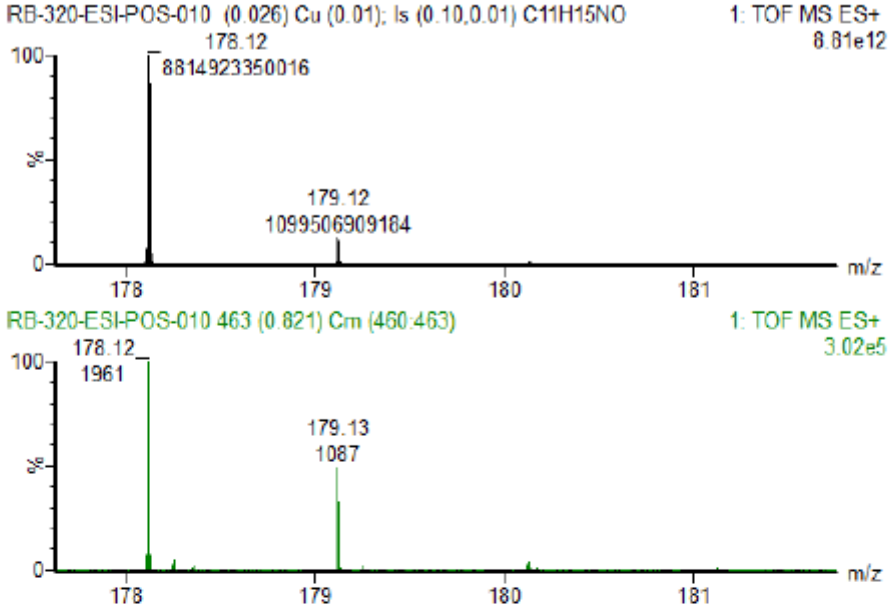
Isotopic exchange (calculated by ^{13}C NMR): 31%.

Isotopic exchange (calculated by HRMS): 30.0%.

FTIR (cm^{-1}): 2972, 2934, 1632, 1593, 1427, 1382, 1364, 1313, 1285, 1220, 1096, 1072, 1028, 943, 871, 785, 705, 628, 566.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

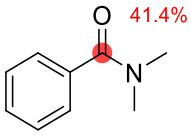
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	178	179	180	181	182	183	184	185
%	100,0	12,5	0,8	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	178	1961	0,00	1961,00	69,89
1	179	1087	245,13	841,88	30,00
2	180	115	15,69	-5,92	-0,21
3	181	16	0,00	10,01	0,36
4	182	0	0,00	-1,20	-0,04
5	183	0	0,00	0,07	0,00
6	184	0	0,00	0,00	0,00
7	185	0	0,00	0,00	0,00
8	186	0	0,00	0,00	0,00
9	187	0	0,00	0,00	0,00
10	188	0	0,00	0,00	0,00
11	189	0	0,00	0,00	0,00
Total		3179		2805,83	100,00

% Isotopic enrichment : 30,0

[^{13}C] N,N-dimethylbenzamide ([^{13}C]46)



[^{13}C]46

$C_8{}^{13}CH_{11}NO$
MW: 150.19 g.mol^{-1}
Colorless oil
Yield: 69%
IE: 41.4%

Following the general procedure G, [^{13}C]46 was obtained as a colorless oil (5 mg, 0.035 mmol, 69%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 5H), 3.11 (bs, 3H), 2.98 (bs, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (^{13}C-labeled), 136.5, 129.6, 128.5 (s + d, *J* = 4.1 Hz, 2C), 127.2 (s + d, *J* = 2.1 Hz, 2C), 39.7, 35.5.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_8H_{12}NO$: 151.0953 $[M+H]^+$; found 151.0955.

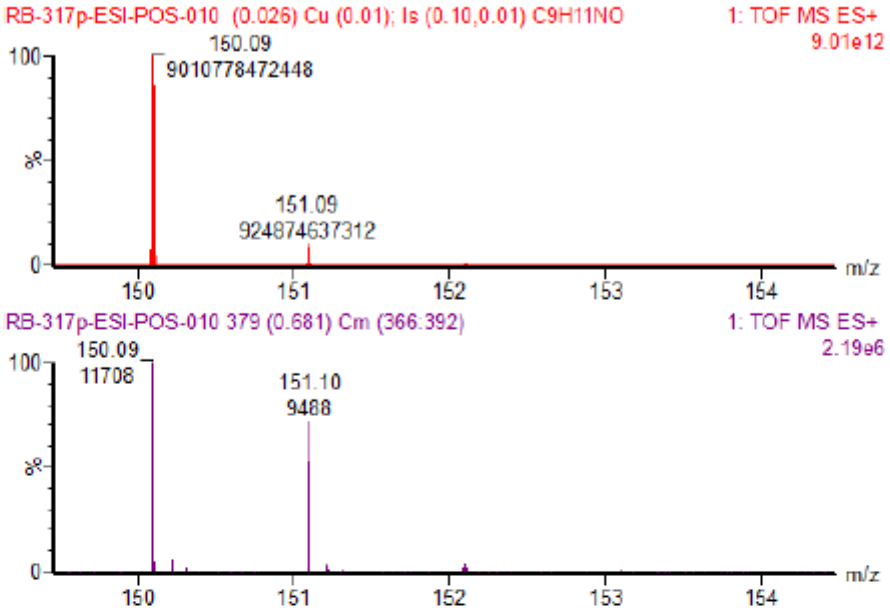
Isotopic exchange (calculated by ^{13}C NMR): 42%.

Isotopic exchange (calculated by HRMS): 41.4%.

FTIR (cm^{-1}): 2928, 1633, 1595, 1574, 1504, 1484, 1445, 1392, 1264, 1214, 1082, 1027, 786, 712, 637.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

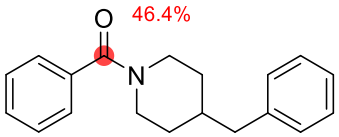
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	150	151	152	153	154	155	156	157
%	100,0	10,3	0,6	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	150	11708	0,00	11708,00	58,53
1	151	9488	1205,92	8282,08	41,40
2	152	850	70,25	-73,30	-0,37
3	153	139	0,00	96,86	0,48
4	154	0	0,00	-9,54	-0,05
5	155	0	0,00	0,40	0,00
6	156	0	0,00	0,02	0,00
7	157	0	0,00	0,00	0,00
8	158	0	0,00	0,00	0,00
9	159	0	0,00	0,00	0,00
10	160	0	0,00	0,00	0,00
11	161	0	0,00	0,00	0,00
Total		22185		20004,51	100,00

% Isotopic enrichment : 41,4

[^{13}C] (4-benzylpiperidin-1-yl)(phenyl)methanone ([^{13}C]53)



[^{13}C]53

$C_{18}{}^{13}CH_{21}NO$
MW: 280.38 g.mol^{-1}
White solid
Yield: 82%
IE: 46.4%

Following the general procedure G, [^{13}C]53 was obtained as a white solid (12 mg, 0.041 mmol, 82%), using the isotopic carrier [^{13}C]IC1 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (bs, 5H), 7.31 – 7.23 (m, 2H), 7.23 – 7.16 (m, 1H), 7.16 – 7.08 (m, 2H), 4.85 – 4.47 (m, 1H), 3.83 – 3.51 (m, 1H), 3.00 – 2.63 (m, 2H), 2.63 – 2.43 (m, 2H), 1.87 – 1.72 (m, 2H), 1.58 (bs, 1H), 1.37 – 1.11 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (^{13}C-labeled), 140.1, 136.5 (s + d, *J* = 66.3 Hz), 129.6, 129.2 (2C), 128.5 (s + d, *J* = 4.0 Hz, 2C), 128.4 (2C), 127.0 (s + d, *J* = 2.0 Hz, 2C), 126.2, 48.1, 43.1, 42.6, 38.5, 32.8, 32.0.

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{18}H_{22}NO$: 281.1736 $[M+H]^+$; found 281.1742.

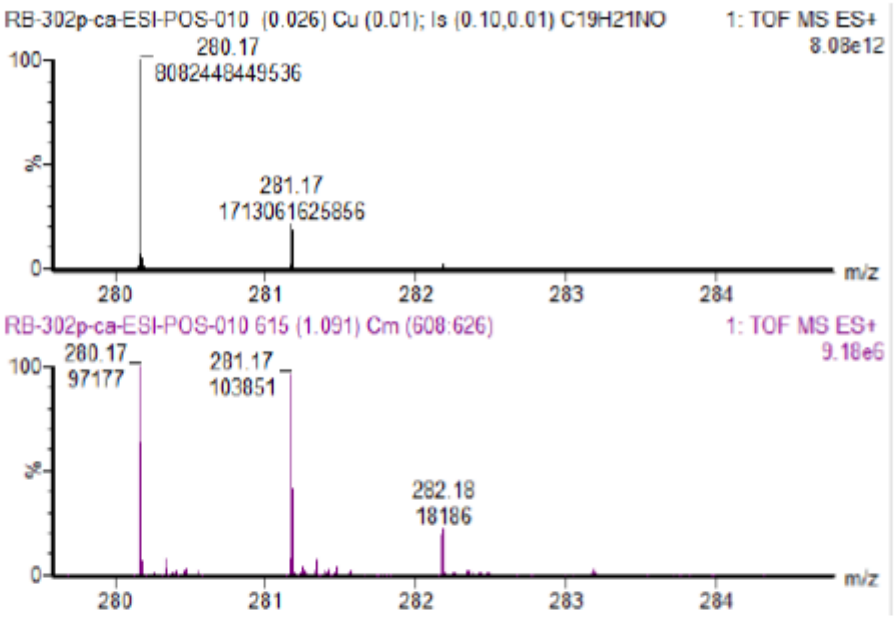
Isotopic exchange (calculated by ^{13}C NMR): 45%.

Isotopic exchange (calculated by HRMS): 46.4%.

FTIR (cm^{-1}): 3025, 2917, 2851, 1631, 1592, 1574, 1495, 1428, 1372, 1283, 1136, 1096, 1074, 1055, 1029, 966, 782, 747, 701, 634, 589, 491.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

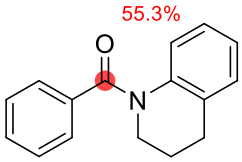
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	280	281	282	283	284	285	286	287
%	100,0	21,3	2,1	0,3	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	280	97177	0,00	97177,00	54,17
1	281	103851	20698,70	83152,30	46,35
2	282	18186	2040,72	-1566,16	-0,87
3	283	2514	291,53	809,86	0,45
4	284	180	0,00	-209,07	-0,12
5	285	0	0,00	32,22	0,02
6	286	0	0,00	-4,90	0,00
7	287	0	0,00	0,99	0,00
8	288	0	0,00	-0,21	0,00
9	289	0	0,00	0,04	0,00
10	290	0	0,00	-0,01	0,00
11	291	0	0,00	0,00	0,00
Total		221908		179392,08	100,00

% Isotopic enrichment : 46,4

[^{13}C] (3,4-dihydroquinolin-1(2H)-yl)(phenyl)methanone ([^{13}C]49)



[^{13}C]49

$C_{15}{}^{13}CH_{15}NO$
MW: 238.29 g.mol^{-1}
White solid
Yield: 71%
IE: 55.3%

Following the general procedure G, [^{13}C]49 was obtained as a white solid (9 mg, 0.036 mmol, 71%), using the isotopic carrier [^{13}C]IC3 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 3H), 7.31 – 7.26 (m, 2H), 7.18 – 7.13 (m, 1H), 6.99 (td, *J* = 7.5, 1.3 Hz, 1H), 6.86 (td, *J* = 7.8, 1.7 Hz, 1H), 6.75 – 6.66 (m, 1H), 3.91 (ts + td, *J* = 6.6, $J_{^{13}C\text{-}^{1}H}$ = 1.1 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.06 (quint, *J* = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (^{13}C-labeled), 165.8, 140.3, 136.5 (s + d, *J* = 66.1 Hz), 130.3, 128.8 (s + d, *J* = 2.2 Hz, 2C), 128.5, 128.2 (s + d, *J* = 4.3 Hz, 2C), 125.9, 125.6, 124.7, 27.1, 24.3 (2C).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{15}H_{16}NO$: 239.1266 $[M+H]^+$; found 239.1276.

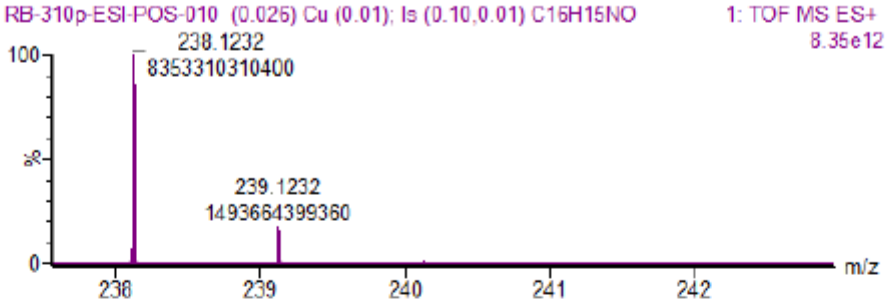
Isotopic exchange (calculated by ^{13}C NMR): 52%.

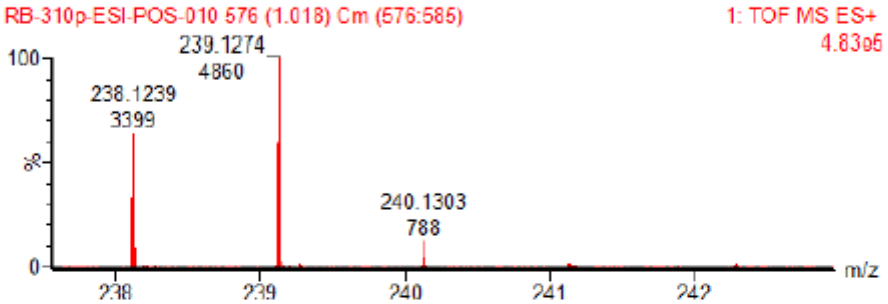
Isotopic exchange (calculated by HRMS): 55.3%.

FTIR (cm^{-1}): 2930, 1731, 1641, 1600, 1574, 1492, 1447, 1374, 1263, 1150, 1075, 1027, 939, 783, 757, 700, 651.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment





theorical isotopic distribution

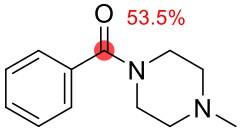
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	238	239	240	241	242	243	244	245
%	100,0	17,9	1,7	0,1	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	238	3399	0,00	3399,00	44,18
1	239	4860	608,42	4251,58	55,26
2	240	788	57,78	-30,82	-0,40
3	241	163	3,40	92,84	1,21
4	242	0	0,00	-20,35	-0,26
5	243	0	0,00	2,09	0,03
6	244	0	0,00	-0,12	0,00
7	245	0	0,00	0,01	0,00
8	246	0	0,00	0,00	0,00
9	247	0	0,00	0,00	0,00
10	248	0	0,00	0,00	0,00
11	249	0	0,00	0,00	0,00
Total		9210		7694,24	100,00

% Isotopic enrichment : 55,3

[^{13}C] (4-methylpiperazin-1-yl)(phenyl)methanone ([^{13}C]52)



[^{13}C]52

$C_{11}{}^{13}CH_{16}N_2O$
MW: 205.27 g.mol^{-1}
Yellow solid
Yield: 90%
IE: 53%

Following the general procedure G, [^{13}C]52 was obtained as a yellow solid (9 mg, 0.044 mmol, 90%), using the isotopic carrier [^{13}C]IC1 and 0.1 mmol of LiHMDS (2.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.31 (m, 5H), 3.80 (bs, 2H), 3.44 (bs, 2H), 2.55 – 2.26 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 135.9, 129.8, 128.6 (s + d, *J* = 4.2 Hz, 2C), 127.2 (s + d, *J* = 2.0 Hz, 2C) , 46.2 (4C missing due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $C_{12}H_{17}N_2O$: 206.1375 $[M+H]^+$; found 206.1376.

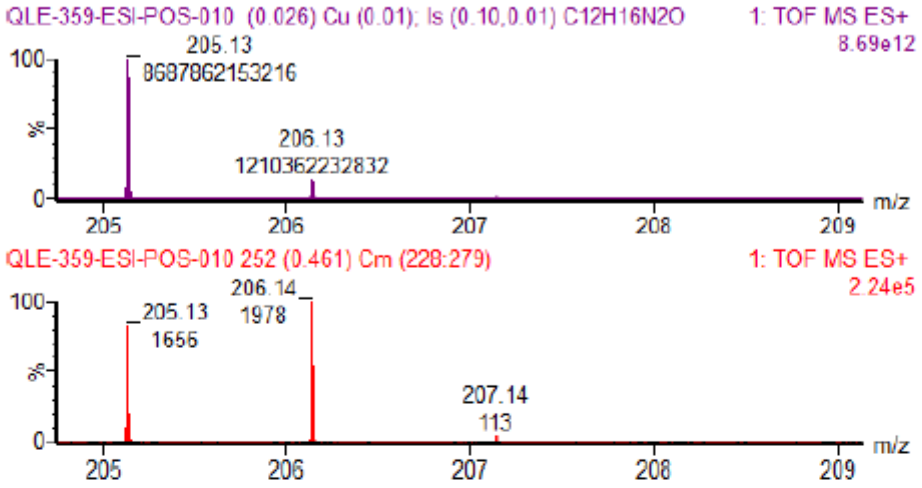
Isotopic exchange (calculated by ^{13}C NMR): 52%.

Isotopic exchange (calculated by HRMS): 53.5%.

FTIR (cm^{-1}): 2937, 2854, 2791, 1632, 1594, 1574, 1494, 1423, 1367, 1292, 1267, 1239, 1169, 1141, 1129, 1073, 1051, 1018, 1001, 926, 883, 781, 709, 637, 550, 423.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

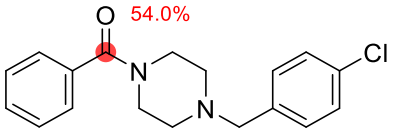
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	205	206	207	208	209	210	211	212
%	100,0	14,0	1,1	0,0	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	205	1656	0,00	1656,00	50,77
1	206	1978	231,84	1746,16	53,54
2	207	113	18,22	-149,68	-4,59
3	208	7	0,00	8,75	0,27
4	209	0	0,00	0,42	0,01
5	210	0	0,00	-0,16	0,00
6	211	0	0,00	0,02	0,00
7	212	0	0,00	0,00	0,00
8	213	0	0,00	0,00	0,00
9	214	0	0,00	0,00	0,00
10	215	0	0,00	0,00	0,00
11	216	0	0,00	0,00	0,00
Total		3754		3261,51	100,00

% Isotopic enrichment : 53,5

[^{13}C] (4-(4-chlorobenzyl)piperazin-1-yl)(phenyl)methanone ([^{13}C]54)



[^{13}C]54

$C_{17}{}^{13}CH_{19}ClN_2O$
MW: 315.81 g.mol^{-1}
White solid
Yield: 61%
IE: 54%

Following the general procedure G, [^{13}C]54 was obtained as a white solid (10 mg, 0.031 mmol, 61%), using the isotopic carrier [^{13}C]IC1 and 0.1 mmol of LiHMDS (2.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.36 (m, 5H), 7.31 – 7.23 (m, 4H), 3.79 (s, 2H), 3.53 – 3.32 (m, 4H), 2.59 – 2.26 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4 (^{13}C-labeled), 136.3, 133.1, 130.5 (2C), 129.8, 128.6 (2C), 128.5 (s + d, *J* = 4.2 Hz, 2C), 127.2 (s + d, *J* = 2.2 Hz, 2C), 62.2 (4C missing due to the free rotation of the amide bond, cf Figure S1, and 1Cq missing).

HRMS (ESI-TOF) m/z calcd for $C_{18}H_{20}ClN_2O$: 316.1298 $[M+H]^+$; found 316.1304.

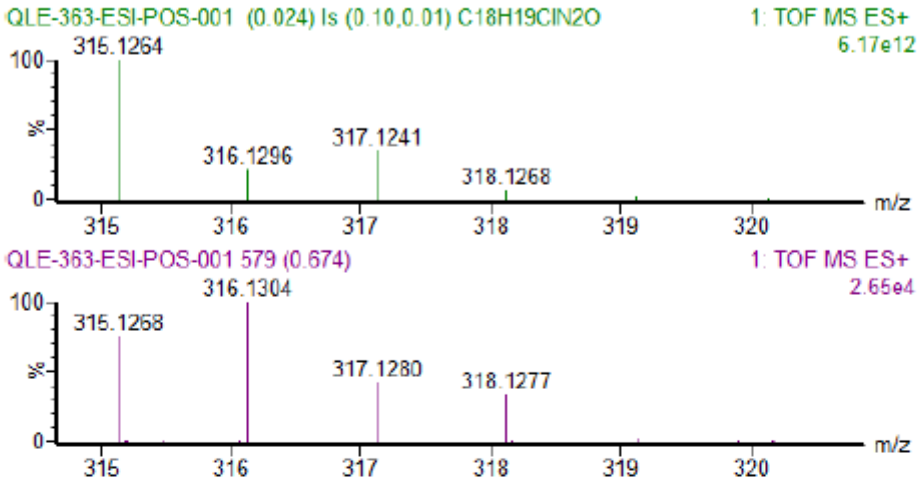
Isotopic exchange (calculated by ^{13}C NMR): 56%.

Isotopic exchange (calculated by HRMS): 54.0%.

FTIR (cm^{-1}): 2918, 2809, 1633, 1594, 1574, 1490, 1425, 1366, 1346, 1296, 1275, 1257, 1158, 1143, 1089, 1016, 1001, 811, 788, 709, 669, 634, 563, 509.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

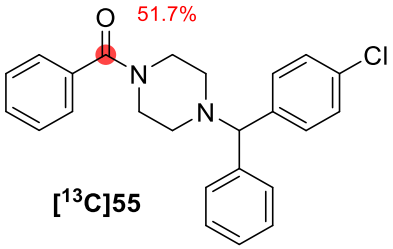
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	315	316	317	318	319	320	321	322
%	100,0	20,5	34,6	6,7	0,6	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	315	6700	0,00	6700,00	49,86
1	316	8629	1373,50	7255,50	54,00
2	317	3534	2318,20	-271,58	-2,02
3	318	2761	448,90	-142,63	-1,06
4	319	190	40,20	-213,11	-1,59
5	320	7	0,00	74,70	0,56
6	321	0	0,00	69,61	0,52
7	322	0	0,00	-24,98	-0,19
8	323	0	0,00	-22,69	-0,17
9	324	0	0,00	8,18	0,06
10	325	0	0,00	7,43	0,06
11	326	0	0,00	-2,68	-0,02
Total		21821		13437,75	100,01

% Isotopic enrichment : 54,0

[^{13}C] (4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(phenyl)methanone ([^{13}C]55)



[^{13}C]55

$C_{23}{}^{13}CH_{23}ClN_2O$
MW: 391.90 g.mol^{-1}
Colorless oil
Yield: 51%
IE: 51.7%

Following the general procedure G, [^{13}C]55 was obtained as a colorless oil (10 mg, 0.026 mmol, 50%), using the isotopic carrier [^{13}C]IC1 and 0.2 mmol of LiHMDS (4.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.32 (m, 9H), 7.31 – 7.23 (m, 4H), 7.23 – 7.17 (m, 1H), 4.24 (s, 1H), 3.79 (bs, 2H), 3.42 (bs, 2H), 2.50 – 2.26 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4 (^{13}C-labeled), 141.7, 140.9, 133.0, 129.8, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.6 (s + d, *J* = 4.2 Hz, 2C), 127.9 (2C), 127.6, 127.2 (s + d, *J* = 2.2 Hz, 2C), 75.4 (4C missing due to the free rotation of the amide bond, cf Figure S1, and 1 Cq missing).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{23}H_{24}ClN_2O$: 392.1611 $[M+H]^+$; found 392.1607.

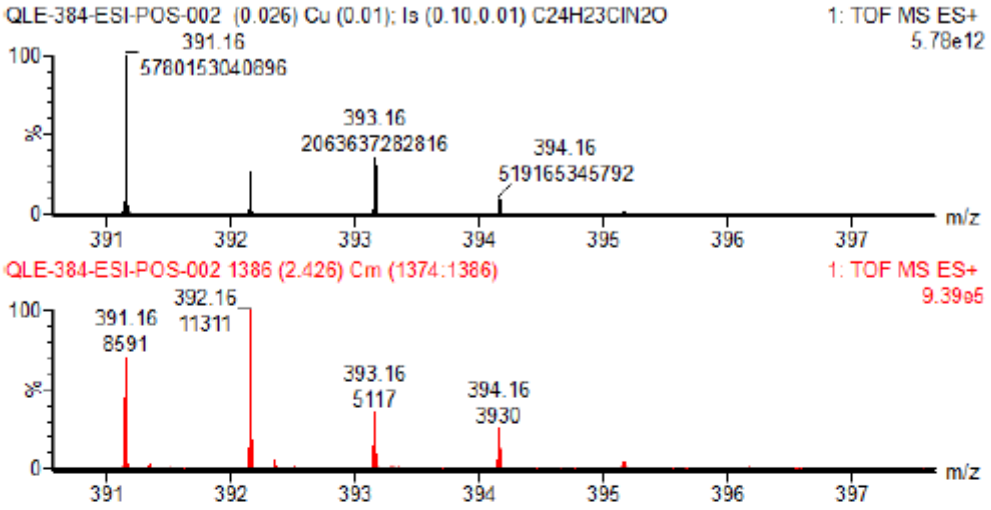
Isotopic exchange (calculated by ^{13}C NMR): 55%.

Isotopic exchange (calculated by HRMS): 51.7%.

FTIR (cm^{-1}): 3059, 2921, 2857, 2809, 1633, 1593, 1574, 1488, 1447, 1426, 1371, 1288, 1249, 1157, 1144, 1104, 1089, 1073, 1015, 998, 923, 833, 804, 782, 758, 733, 701, 636, 529, 499.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



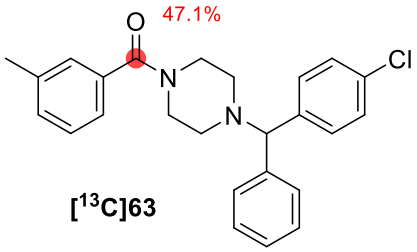
theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	391	392	393	394	395	396	397	398
%	100,0	27,1	36,1	9,1	1,2	0,1	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	391	8591	0,00	8591,00	49,45
1	392	11311	2328,16	8982,84	51,71
2	393	5117	3101,35	-418,70	-2,41
3	394	3930	781,78	18,88	0,11
4	395	932	103,09	157,50	0,91
5	396	165	8,59	37,22	0,21
6	397	111	0,00	38,38	0,22
7	398	0	0,00	-37,98	-0,22
8	399	0	0,00	-8,86	-0,05
9	400	0	0,00	12,01	0,07
10	401	0	0,00	2,90	0,02
11	402	0	0,00	-3,90	-0,02
Total		30157		17371,30	100,00
		% IE			51,7

[^{13}C] (4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)(m-tolyl)methanone ([^{13}C]63)



[^{13}C]63

$C_{24}{}^{13}CH_{25}ClN_2O$
MW: 405.93 g.mol^{-1}
Colorless oil
Yield: 66%
IE: 47.1%

Following the general procedure G, [^{13}C]63 was obtained as a colorless oil (13 mg, 0.033 mmol, 66%), using the isotopic carrier [^{13}C]IC6 and 0.1 mmol of LiHMDS (4.0 equiv.).

The isotopic carrier could be recovered (10 mg, 0.049 mmol, >95%) after purification, the enrichment was measured at 45% (measured by LCMS)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 4H), 7.31 – 7.11 (m, 9H), 4.24 (s, 1H), 3.78 (bs, 2H), 3.42 (bs, 2H), 2.45 (bs, 2H), 2.35 (s, 3H), 2.34 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 141.7, 140.9, 138.5 (s + d, *J* = 4.2 Hz), 135.9 (s + d, *J* = 66.7 Hz), 133.0, 130.5, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.3 (s + d, *J* = 4.4 Hz), 127.9 (2C), 127.7 (s + d, *J* = 2.0 Hz), 127.6, 124.1, 75.4, 21.5 (4C missing due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $^{13}CC_{24}H_{26}ClN_2O$: 406.1768 $[M+H]^+$; found 406.1768.

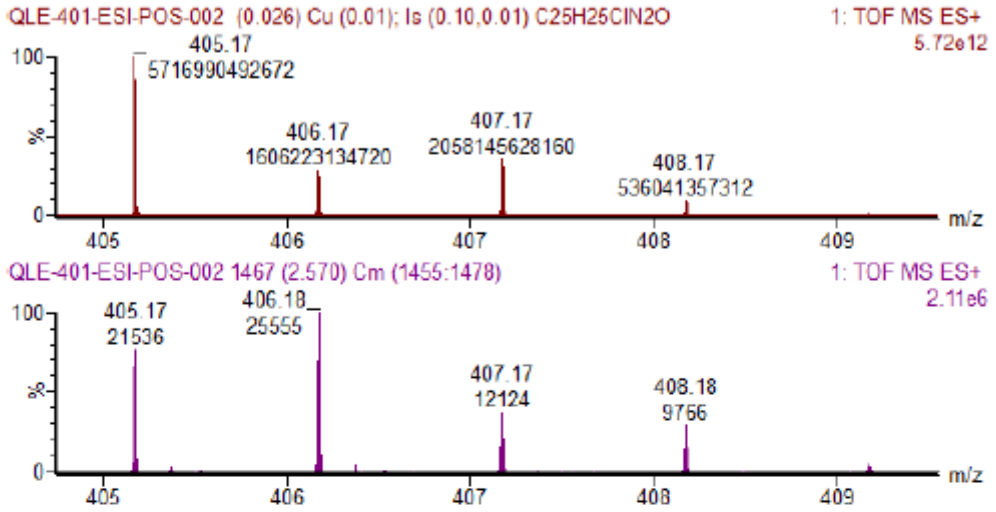
Isotopic exchange (calculated by ^{13}C NMR): 48%.

Isotopic exchange (calculated by HRMS): 47.1%.

FTIR (cm^{-1}): 3027, 2919, 2809, 2241, 1631, 1594, 1579, 1488, 1452, 1431, 1371, 1288, 1266, 1205, 1144, 1088, 1029, 1014, 998, 909, 851, 823, 803, 758, 728, 700, 643, 624, 533, 500, 448, 425.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment



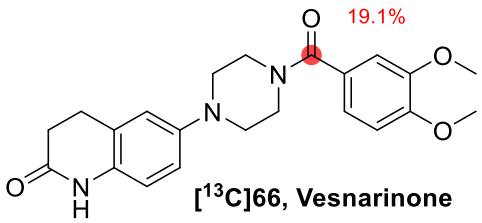
theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	405	406	407	408	409	410	411	412
%	100,0	28,2	36,4	9,5	1,3	0,1	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	405	21536	0,00	21536,00	52,10
1	406	25555	6073,15	19481,85	47,13
2	407	12124	7839,11	-1208,99	-2,92
3	408	9766	2045,92	969,62	2,35
4	409	2362	279,97	397,89	0,96
5	410	784	21,54	158,91	0,38
6	411	269	0,00	-16,52	-0,04
7	412	153	0,00	50,62	0,12
8	413	0	0,00	-29,50	-0,07
9	414	0	0,00	-11,00	-0,03
10	415	0	0,00	9,09	0,02
11	416	0	0,00	3,60	0,01
Total		72549		41341,57	100,01
			% IE		47,1

[^{13}C] 6-[4-(3,4-Dimethoxybenzoyl)piperazin-1-yl]-3,4-dihydro-1H-quinolin-2-one (Vesnarinone) ([^{13}C]66)



[^{13}C]66, Vesnarinone

$C_{21}{}^{13}CH_{25}N_3O_4$
MW: 396.45 g.mol^{-1}
Colorless oil
Yield: 34%
IE: 19.1%

Following the general procedure G, [^{13}C]66 was obtained as a colorless oil (7 mg, 0.018 mmol, 34%), using the isotopic carrier [^{13}C]IC5 and 0.2 mmol of LiHMDS (4.0 equiv.).

The isotopic carrier could be recovered (5 mg, 0.020 mmol, 40%) after purification, the enrichment was measured at 78% (measured by LCMS).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.04 – 6.98 (m, 2H), 6.91 – 6.84 (m, 1H), 6.81 – 6.73 (m, 2H), 6.73 – 6.67 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.79 (s, 4H), 3.11 (s, 4H), 2.93 (dd, *J* = 8.5, 6.5 Hz, 2H), 2.61 (dd, *J* = 8.6, 6.4 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (^{13}C-labeled), 166.8, 164.3, 150.6, 149.2, 147.3, 131.2, 127.9, 124.9, 120.3, 117.4, 116.3, 116.1, 111.1 (s + d, *J* = 4.5 Hz), 110.6 (s + d, *J* = 2.6 Hz), 56.2 (2C), 50.5 (2C), 30.9, 26.0. (2C missing due to the free rotation of the amide bond, cf Figure S1).

HRMS (ESI-TOF) m/z calcd for $C_{21}{}^{13}CH_{26}N_3O_4$: 397.1957 $[M+H]^+$; found 397.1956.

Isotopic exchange (calculated by ^{13}C NMR): 20%.

Isotopic exchange (calculated by HRMS): 19.1%.

FTIR (cm^{-1}): 3213, 2933, 1670, 619, 1581, 1508, 1461, 1429, 1370, 1321, 1263, 1230, 1180, 1137, 1021, 955, 810, 771, 730, 700, 671, 610, 520, 450.

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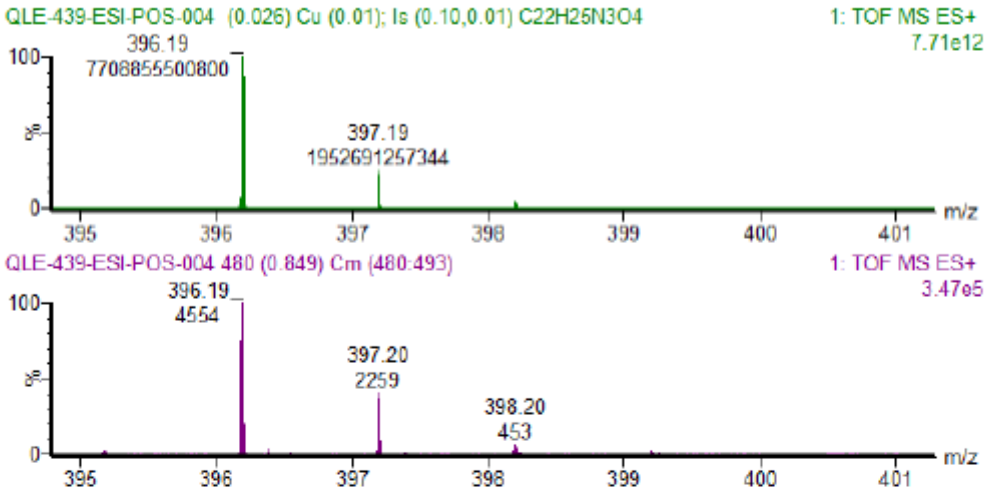
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

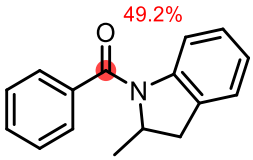
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	396	397	398	399	400	401	402	403
%	100,0	25,5	3,9	0,4	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	396	4554	0,00	4554,00	79,19
1	397	2259	1161,27	1097,73	19,09
2	398	453	177,61	-4,53	-0,08
3	399	162	18,22	102,13	1,78
4	400	36	0,00	5,74	0,10
5	401	0	0,00	-5,43	-0,09
6	402	0	0,00	0,75	0,01
7	403	0	0,00	0,00	0,00
8	404	0	0,00	-0,01	0,00
9	405	0	0,00	0,00	0,00
10	406	0	0,00	0,00	0,00
11	407	0	0,00	0,00	0,00
Total		7464		5750,39	100,00

IE % : 19,1

[^{13}C] (2-methylindolin-1-yl)(phenyl)methanone ([^{13}C]51)



[^{13}C]51

$C_{15}{}^{13}CH_{15}NO$
MW: 238.29 g.mol^{-1}
White solid
Yield: 71%
IE: 49.2%

Following the general procedure G, [^{13}C]51 was obtained as a white solid (9 mg, 0.036 mmol, 71%), using the isotopic carrier [^{13}C]IC3 and 0.05 mmol of LiHMDS (1.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.33 (m, 6H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.03 – 6.99 (m, 2H), 4.74 (bs, 1H), 3.42 (dd, *J* = 15.7, 8.8, 1H), 2.64 (dd, *J* = 15.8, 1.9 Hz, 1H), 1.24 (d, *J* = 5.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0 (^{13}C-labeled), 141.5, 137.2, 131.6, 130.3, 128.7 (s + d, *J* = 4.3 Hz, 2C), 127.2 (2C), 127.1, 125.6, 123.9, 117.1, 57.1, 36.0, 15.9.

HRMS (ESI-TOF) m/z calcd for $C_{15}{}^{13}CH_{16}NO$: 239.1266 $[M+H]^+$; found 239.1264.

Isotopic exchange (calculated by ^{13}C NMR): 52%.

Isotopic exchange (calculated by HRMS): 49.2%.

FTIR (cm^{-1}): 3058, 2971, 2925, 1637, 1596, 1479, 1462, 1445, 1386, 1326, 1287, 1262, 1226, 1177, 1153, 1105, 1072, 1025, 981, 922, 901, 856, 820, 782, 755, 728, 701, 674, 643, 604, 427.

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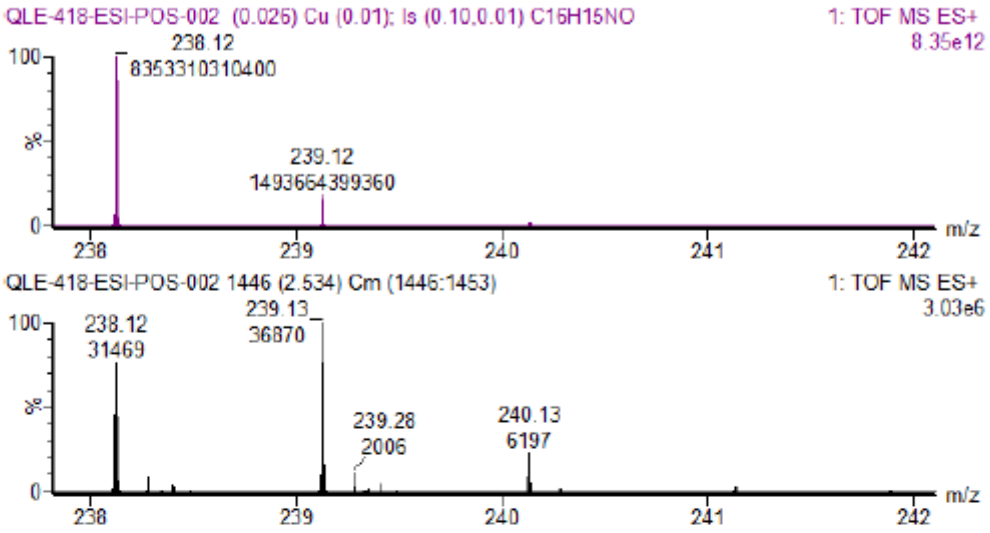
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	238	239	240	241	242	243	244	245
%	100,0	18,0	1,7	0,1	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	238	31469	0,00	31469,00	49,61
1	239	36870	5651,83	31218,17	49,22
2	240	6197	541,27	48,95	0,08
3	241	1241	34,62	660,64	1,04
4	242	202	0,00	48,17	0,08
5	243	0	0,00	-20,07	-0,03
6	244	0	0,00	2,05	0,00
7	245	0	0,00	-0,08	0,00
8	246	0	0,00	0,00	0,00
9	247	0	0,00	0,00	0,00
10	248	0	0,00	0,00	0,00
11	249	0	0,00	0,00	0,00
Total		75979		63426,83	100,00

% Isotopic enrichment : 49,2

VII. Limitations

a. Transamidation

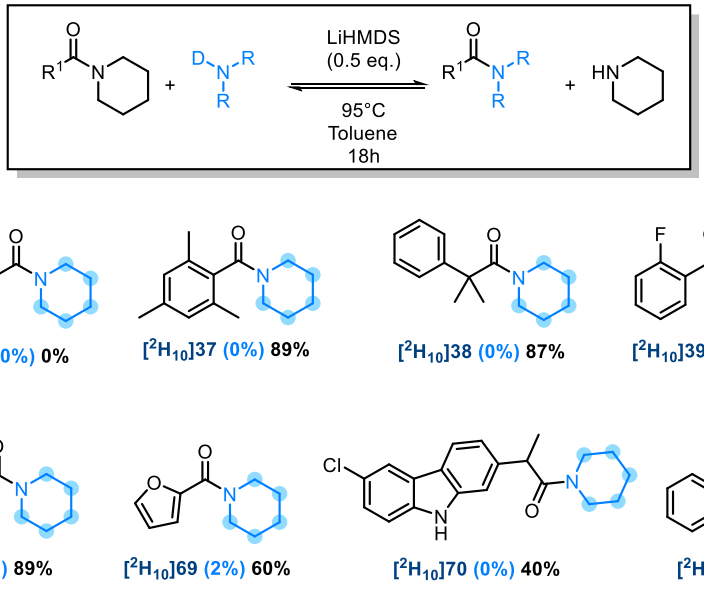


Figure S8 : Limitations of the transamidation

Unfortunately, we were e unable to label some substrate shown in Figure S8. Substrates [$^2H_{10}$]37 and [$^2H_{10}$]38 were recovered without any amine exchange observed du to steric hindrance close to the amide bond. With substrate [$^2H_{10}$]69 we observed only degradation under these conditions. Compounds [$^2H_{10}$]70 was not soluble in toluene and degraded, similar conditions in THF were tested, the amide solubility and recovery were improved however no exchange was observed. Compound [$^2H_{10}$]38 is a Michael acceptor, we observed degradation related to this reactivity. [$^2H_{10}$]40 is too deficient in electron. Finally, with compound [$^2H_{10}$]39 we observed a mixture of product related to the nucleophilic aromatic substitution of the fluorine by the free amine.

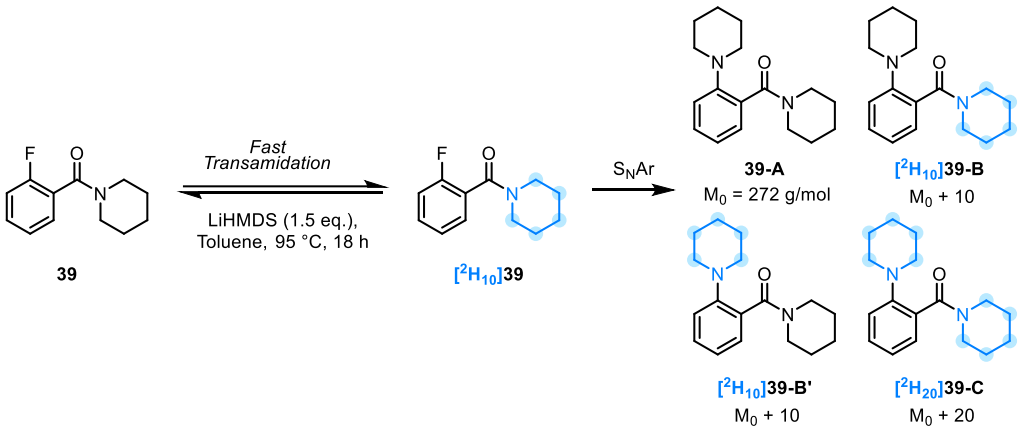


Figure 9 : Mixture of isotopologues of compound 39

Interestingly, we observed a statistic mixture between all four isotopologues: unlabeled (M_0 = 272 g/mol), labeled on amine or amide position (M_0 + 10) and labeled on both positions (M_0 + 20). This suggest that transamidation occurs, otherwise we shouldn't observe compound doubly labeled [$^2H_{20}$]39-C, however after the reaction time the S_NAr is complete.

b. Metathesis

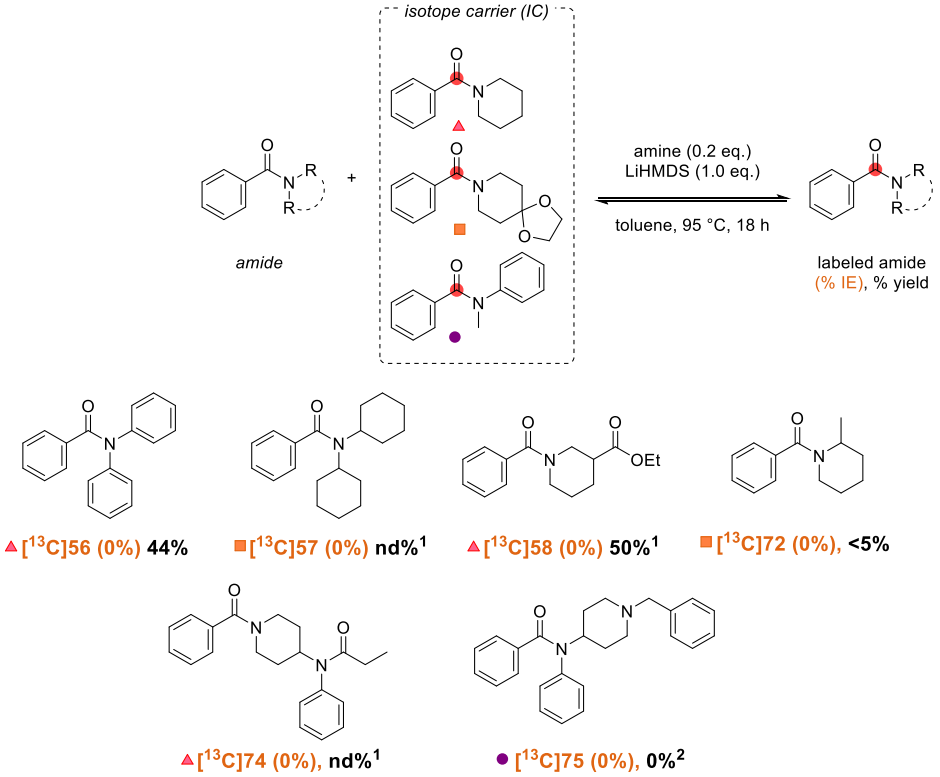
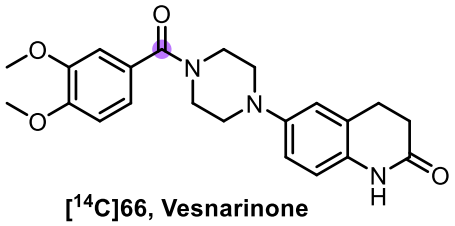


Figure 10 : Limitations of metathesis, [1]LiHMDS 3 eq., 120 °C, [2]LiHMDS 5 eq., 150 °C, "nd" stands for "no data" is indicated when the crude wasn't purified

Some substrates were subjected to the amide bond metathesis conditions without resulting in labeling. For [^{13}C]56, [^{13}C]57 and [^{13}C]72 we suspect a high steric hinderance to be the cause of an inefficient labeling. After no labeling under standard conditions, most of the substrates were submitted to harsher reaction conditions (cond. 1 : LiHMDS 3 eq., 120 °C ; cond. 2 : LiHMDS 5 eq., 150 °C). No exchange was observed and either partial or full degradation of the substrate occurred.

VIII. Vesnarinone radiolabeling (^{14}C)

[^{14}C]-Vesnarinone ([^{14}C]66)



[^{14}C]66, Vesnarinone

$C_{21}{}^{14}CH_{25}N_3O_4$
MW: 397.19 g.mol^{-1}
RCY: 18%
IE: 16%
White solid

To a 10 mL oven dried micro-wave tube containing a magnetic stirring bar, was added the ^{14}C-(3,4-dimethoxyphenyl)(piperidin-1-yl)methanone ([^{14}C]IC5) (101.05 MBq, 0.05 mmol, 1 eq., 40.76 MBq.mmol^{-1}) and the Vesnarinone (20 mg, 0.05 mmol, 1.0 eq.). The mixture was evaporated and dried under high vacuum for 2h. The tube was purged with 3 cycles vacuum/N_2. Dry toluene (1.0 mL, 0.05 M) was added, followed by the amine (0.2 mL of a toluene solution at 0.1 M freshly prepared) and LiHMDS (0.2 mL of a solution in THF, 1M). The tube was then sealed, replacing the rubber septum with a sealed stopper. The tube was heated at 95 °C for 18 hours. The resulting mixture was quenched with 0.5 mL of MeOH. The mixture was then evaporated to dryness and the resulting crude purified by silica column (a gradient was used starting with 99:1 DCM:MeOH, followed by 98:2 DCM:MeOH to finish with 95:5 DCM:MeOH) to afford **[^{14}C]-66** as a white solid further solubilized in ethanol to limit radiolysis (3.199 MBq, 639.73 kBq.mL^{-1}, 0.0086 mmol, radiochemical yield: 18%).

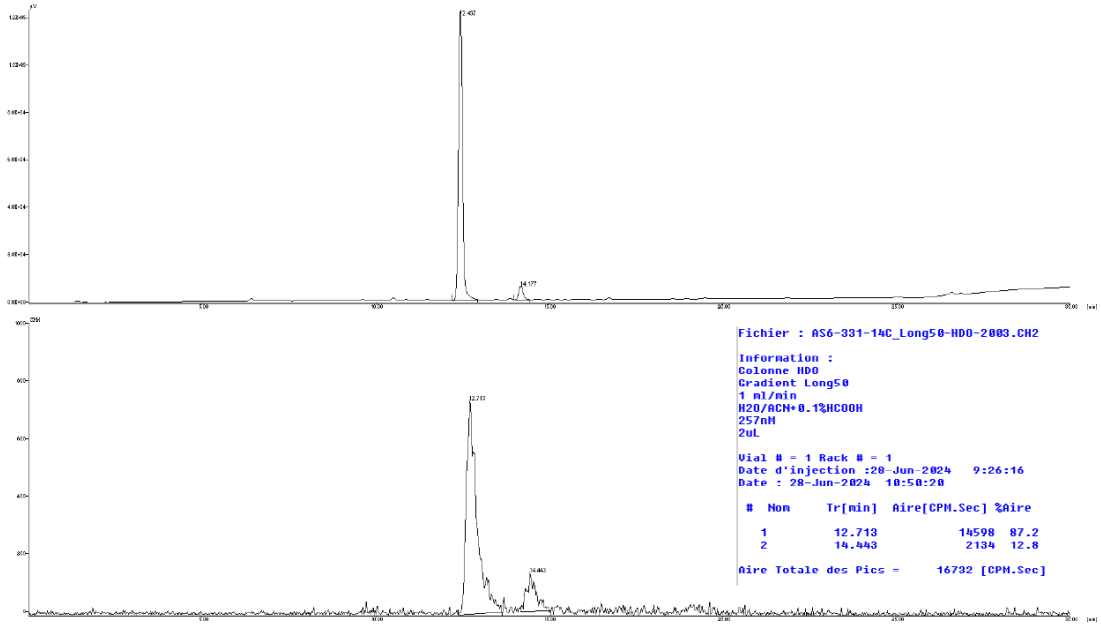
Molar activity (MS (ESI)): 369 MBq.mmol^{-1}.

Isotopic exchange (calculated by LCMS): 16 %.

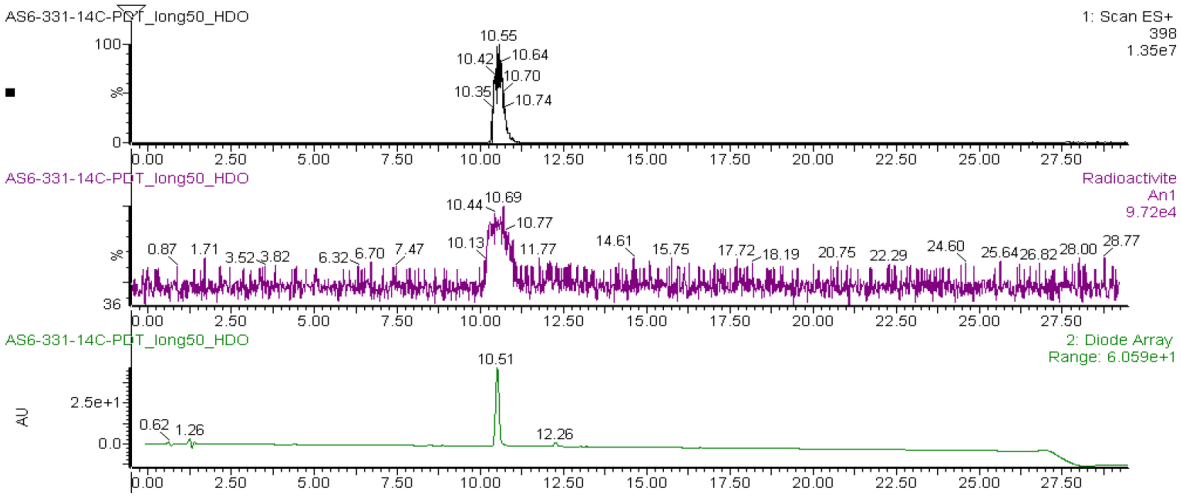
RadioTLC (silicagel 60F254, DCM/MeOH (95:5)) Rf = 0.3.

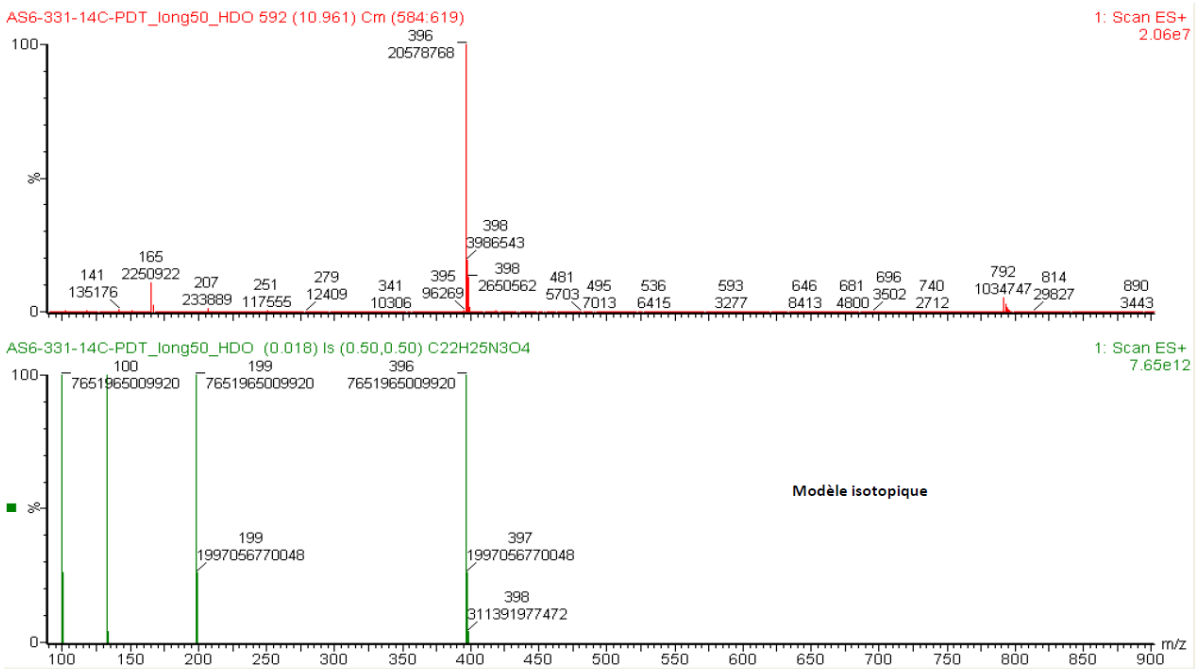
Radiochemical purity: ≥ 87%.

Radio HPLC (H_2O/ACN + 0.1% HCO_2H; t_0: 95/5 ; t_{15min}: 0/100 ; t_{16min}: 95/5, t_{20min}: 95/5): Retention Time = 12.713 min

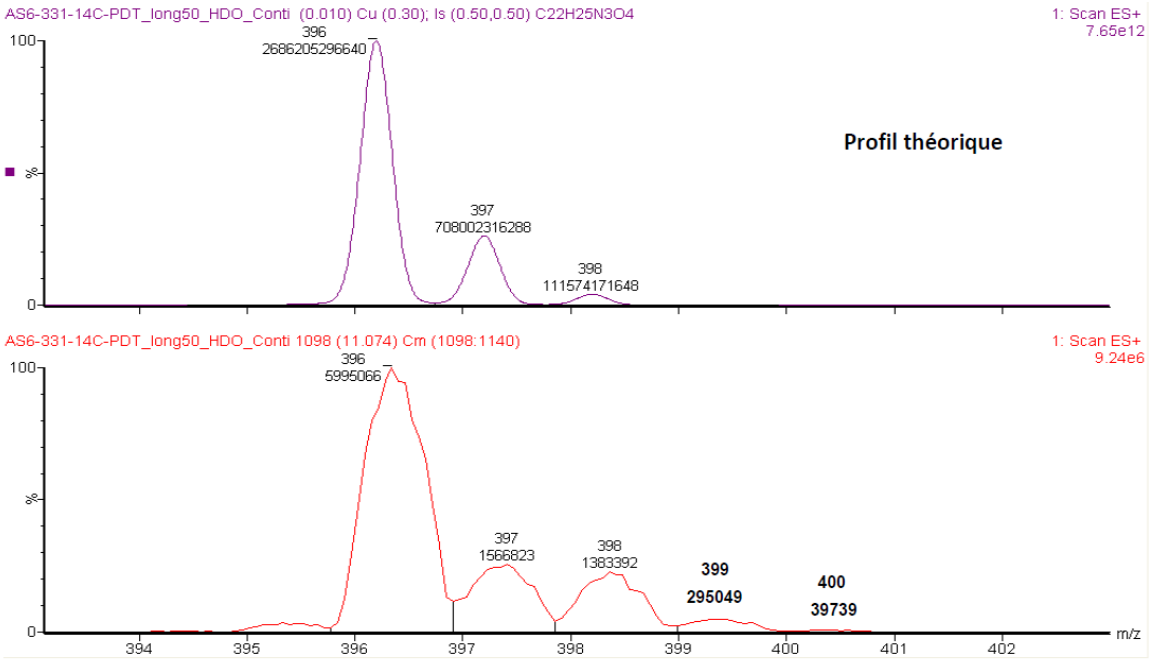


Isotopic enrichment: ^{14}C, [(M+2)+H]: 16 %




AS6-331-14C-PDT_long50_HDO 592 (10.961) Cm (584:619)
1: Scan ES+
2.06e7
100
%
0
396
20578768
398
3986543
398
2650562
165
2250922
141
135176
207
233889
251
117555
279
12409
341
10306
395
96269
481
5703
495
7013
536
6415
593
3277
646
8413
681
4800
696
3502
740
2712
792
1034747
814
29827
890
3443
AS6-331-14C-PDT_long50_HDO (0.018) Is (0.50,0.50) C22H25N3O4
1: Scan ES+
7.65e12
100
%
0
100
7651965009920
199
7651965009920
396
7651965009920
Modèle isotopique
199
1997056770048
397
1997056770048
398
311391977472
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
m/z

Zoom and EI calculation:



Profil isotopique théorique

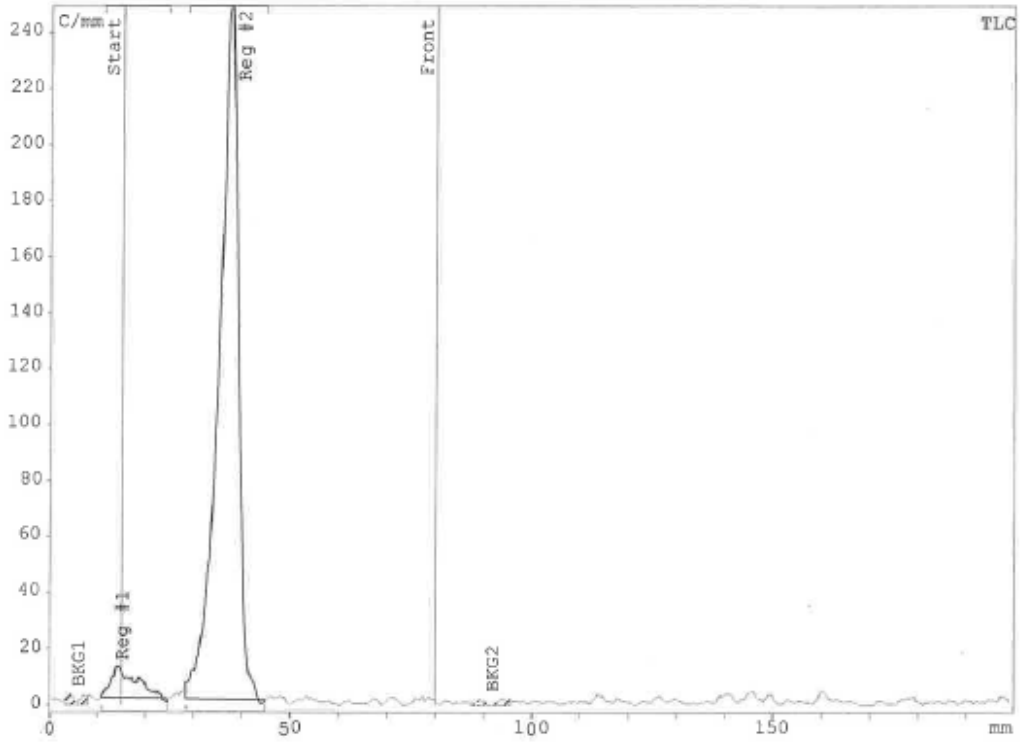
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	396	397	398	399	400	401	402	403
%	100	25,4	3,9	0,4	0	0	0	0

Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	396	5995066	0	6005691	84,06
1	398	1383392	234569	1144209	16,02
2	400	39739	0	-5681	-0,08
3	402	0	0	214	0,00
4	404	0	0	-8	0,00
5	406	0	0	0	0,00
6	408	0	0	0	0,00
7	410	0	0	0	0,00
Total		7418197		7144425,17	100,00

% Enrichissement isotopique : 16,0

RadioTLC (silica gel 60F254, DCM/MeOH (95/55)) Rf=0.3. Radiochemical purity: ≥94%



Description de l'échantillon

Etude:	ANTOINE		
Mesure:	AS6-331-14C-pur-31-32-33_01.r, commencé:		20/06/2024 05:59
Méthode:	C14 de:	01/01/2000	
Origine:	15 mm	Front 80 mm	
Meas. time:	1,0 min	Résolution:	0,4 mm
Détecteur de radioactivité: raytest RITA			
Autre Square flow cell #0			
Cell volume 0 ul			

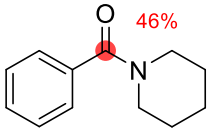
Intégration TLC

Substance	R/F	Type	Aire	%Aire
			Counts	%
Reg #1	-0,006	DD	67,183	5,52
Reg #2	0,345	DD	1150,692	94,48
Sum in ROI			1217,875	
Aire totale			1354,783	
Aire RF			1235,609	
BKG1			2,7273	
BKG2			1,0672	
Remainder RF			17,73	1,44
Remainder (Tot)			136,91	10,11

IX. Synthetic procedure and analytical data (other)

a. Scaling up

[^{13}C] phenyl(piperidin-1-yl)methanone ([^{13}C]59)



[^{13}C]59

$C_{11}{}^{13}CH_{15}NO$
MW: 190.25 g.mol^{-1}
Clear oil
Yield: 83%
IE: 46%

A flame dried flask (25 mL) was cooled under vacuum then filled with nitrogen. The tube was charged with the two amides (Substrate: 48 mg, 0.25 mmol, 1.0 eq.; Carrier [^{13}C]IC6: 48 mg, 0.25 mmol, 1.0 eq.) and purged with 3 cycles vacuum/N_2. Dry toluene (4.0 mL, 0.06M) was added, followed by the piperidine (as a 0.1 M solution in toluene, 0.05 mmol, 20 mol%) and LiHMDS (500 µL, 0.50 mmol, 2 eq.). The tube was then sealed, replacing the rubber septum with a sealed stopper. The tube was heated at 95 °C overnight (18h). Afterwards, 0.5 mL of MeOH was added and the mixture evaporated to dryness. The crude was dissolved in a mixture EtOAc/Cyclohexane (1/1) and filtered through a plug of silica. The gel was washed with the same mixture twice. After purification on silica gel column using the same eluent as the filtration, the pure ^{13}C labeled amide was obtained as a clear oil (40 mg, 0.21 mmol, 83%)

The spectral data (^{1}H-NMR) was consistent with previous exemple ([^{13}C]44).

Isotopic enrichment (calculated by LCMS): 46%

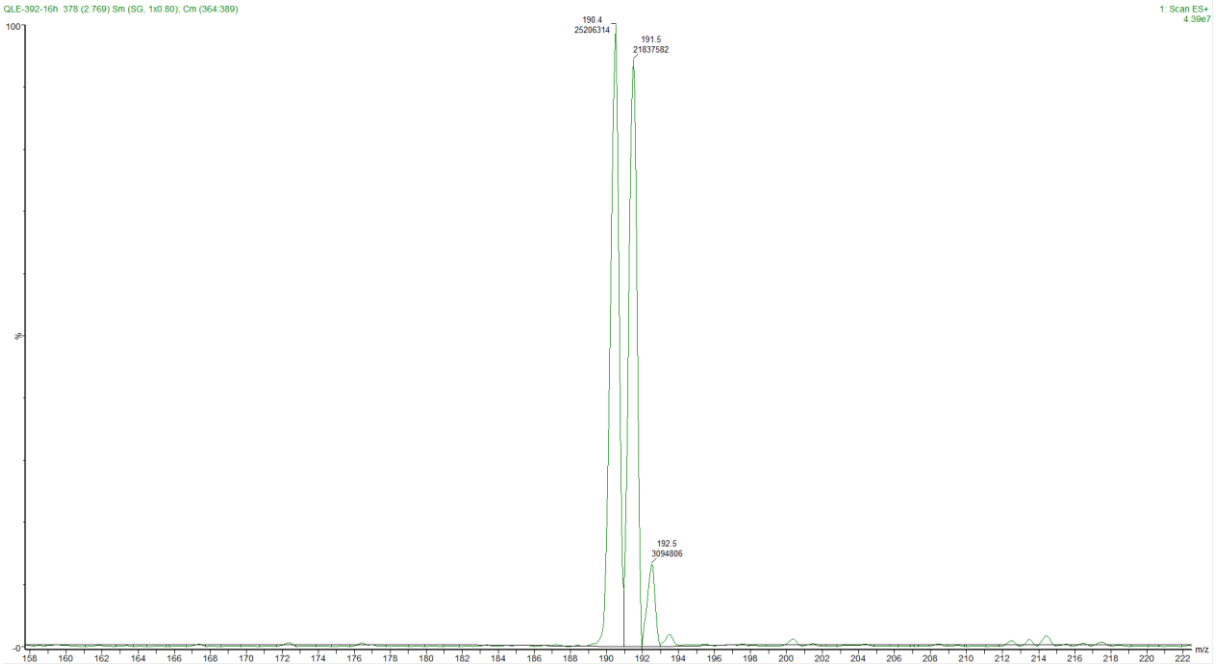
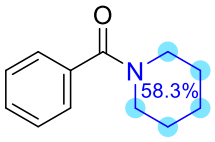


Figure S11: Mass spectrum of [^{13}C]59 (LCMS)

(piperidin-1-yl-d_{10})(p-tolyl)methanone ([$^2H_{10}$]59)



[$^2H_{10}$]59

$C_{12}H_5D_{10}NO$
MW: 199.32 g.mol^{-1}
Colorless oil
Yield: 92%
IE: 58.3%

A flame dried flask (25 mL) was cooled under vacuum then filled with nitrogen. The flask was charged with the amide (189.3 mg, 1.00 mmol, 1.0 eq.) and purged with 3 cycles vacuum/N_2. Dry toluene (10 mL, 0.1 M) was added, followed by deuterated-piperidine (100 µL, 1.00 mmol, 1.0 eq.) and LiHMDS (500 µL, 0.5 mmol, 0.5 eq.). The flask was disconnected from the vacuum/N_2 line, and a N_2 balloon was added. The flask was stirred at 95 °C overnight (18h). Afterwards, 0.5 mL of MeOH was added and the mixture evaporated to dryness. The crude was dissolved in a mixture EtOAc/Cyclohexane (1/1) and filtered through a plug of silica. The gel was washed with the same mixture twice. After evaporation of the solvent the pure deuterium labeled amide was obtained as a colorless oil (184 mg, 0.92 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (bs, 5H), 3.7 (bs, 1.03H), 3.3 (bs, 0.98H), 1.7 – 1.6 (bs, 2.37H), 1.5 (bs, 1.11H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 136.6, 129.4, 128.5 (2C), 126.9 (2C), 48.8, 43.2, 26.6, 25.7, 24.7.

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.41 (bs), 3.47 (m), 1.55 (m).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_6D_{10}NO$: 200.1859 $[M+H]^+$; found 200.1858.

Isotopic exchange (calculated by HRMS): 58.3%.

Isotopic enrichment (calculated by HRMS): 25.5% monodeuteration (M+1), 3.3% bideuteration (M+2).

FTIR (cm^{-1}): 3058, 2935, 2854, 2211, 2112, 1622, 1576, 1494, 1403, 1275, 1239, 1196, 1178, 1131, 1106, 1073, 1028, 1002, 967, 898, 853, 828, 785, 727, 703, 678, 666, 633, 604, 551, 525, 451, 422.

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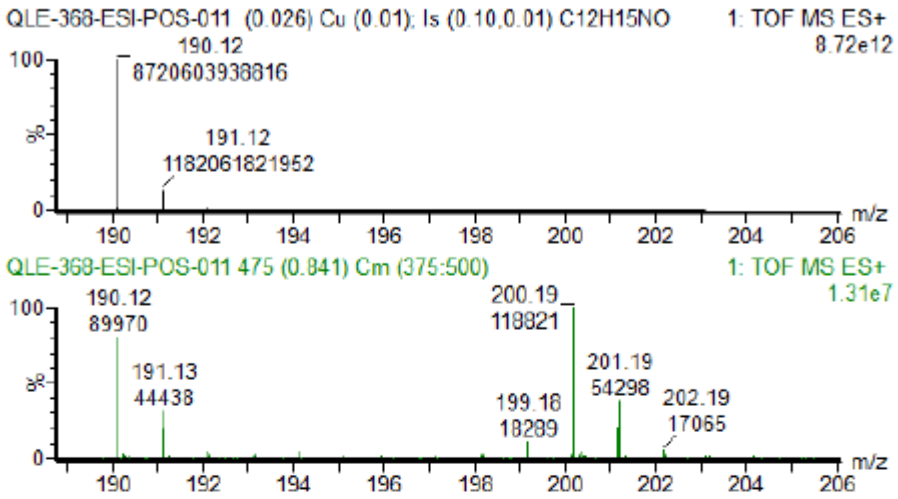
Enrichissement isotopique



Profil isotopique théorique

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	190	191	192	193	194	195	196	197
%	100	13,6	1	0	0	0	0	0

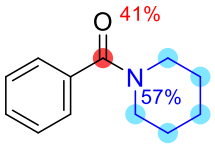
Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	190	89970	0,00	89970,0	29,10
1	191	44438	12235,92	32202,1	10,42
2	192	9399	899,70	4119,8	1,33
3	193	0	0,00	-882,3	-0,29
4	194	0	0,00	78,8	0,03
5	195	0	0,00	-1,9	0,00
6	196	0	0,00	-0,5	0,00
7	197	0	0,00	0,1	0,00
8	198	0	0,00	0,0	0,00
9	199	18289	0,00	18289,0	5,92
10	200	118821	0,00	116333,7	37,63
11	201	54298	0,00	38293,7	12,39
12	202	17065	0,00	10693,7	3,46
13	203	2007	0,00	169,7	0,05
14	204	0	0,00	-130,0	-0,04
Total		354287		3,09E+05	100,00

Echange %	58,3
Enrichissement (+1D) %	25,5
Enrichissement (+2D) %	3,3

b. Double labeling (^{13}C, $^{2}H_{10}$)

[^{13}C, $^{2}H_{10}$] phenyl(piperidin-1-yl-d10)methanone ([^{13}C,$^{2}H_{10}$]59)



[^{13}C,$^{2}H_{10}$]59

$C_{11}{}^{13}CH_5D_{10}NO$
MW: 200.31 g.mol^{-1}
Clear oil
Yield: >95%
IE (^{13}C): 41%
IE ($^{2}H_{10}$): 57%

Following the general procedure G, [^{13}C, $^{2}H_{10}$]59 was obtained as a colorless oil (10 mg, 0.050 mmol, >95%), using the isotopic carrier [^{13}C]IC6 and 0.1 mmol of LiHMDS (2.0 equiv.).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (bs, 5H), 3.7 (bs, 1.03H), 3.3 (bs, 0.98H), 1.7 – 1.6 (bs, 2.37H), 1.5 (bs, 1.11H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3 (^{13}C-labeled), 136.5, 129.3, 128.4 (s + d, *J* = 4.2 Hz, 2C), 126.8 (s + d, *J* = 2.0 Hz, 2C) , 24.6 (4C missing due to the free rotation of the amide bond, cf Figure S1).

^{2}H NMR (61 MHz, $CHCl_3$): δ 7.6 (m), 4.2 – 2.8 (m), 2.2 – 0.8 (m).

HRMS (ESI-TOF) m/z calc'd for $^{13}CC_{11}H_6D_{10}NO$: 201.1893 $[M+H]^+$; found 201.1901.

Isotopic exchange (amine bond metathesis, calculated by ^{13}C NMR): 44%.

Isotopic exchange (transamidation, calculated by ^{1}H NMR): 46%.

Isotopic exchange (amine bond metathesis, calculated by HRMS): 41%.

Isotopic exchange (transamidation, calculated by HRMS): 57%.

Isotopic enrichment (calculated by HRMS): 14% monodeuteration (M+1), 1.5% bideuteration (M+2).

FTIR (cm^{-1}): 3058, 2935, 2855, 2212, 2112, 1625, 1590, 1572, 1493, 1443, 1404, 1270, 1237, 1196, 1178, 1130, 1107, 1073, 1027, 1001, 965, 898, 853, 781, 703, 677, 666, 633, 603, 551, 451, 422.

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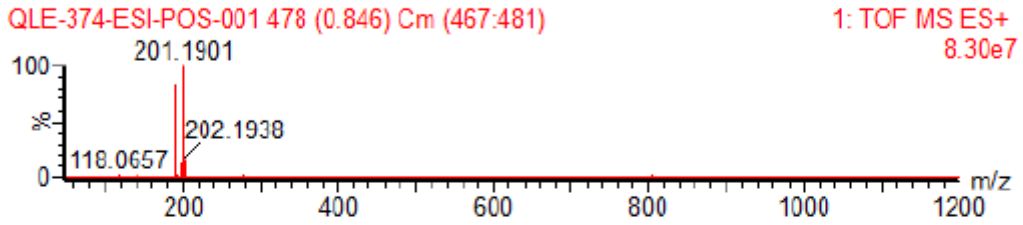
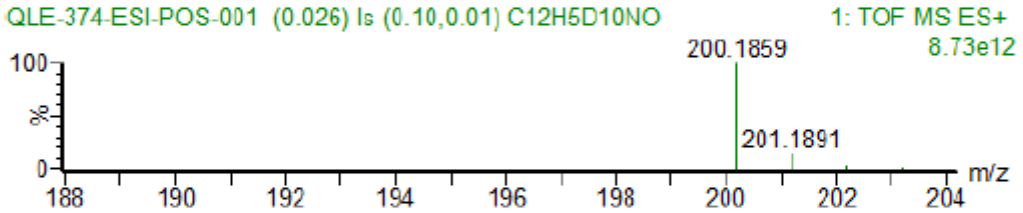
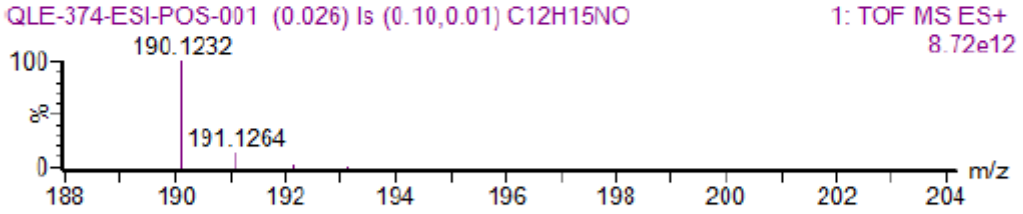
Spectrométrie de masse haute résolution

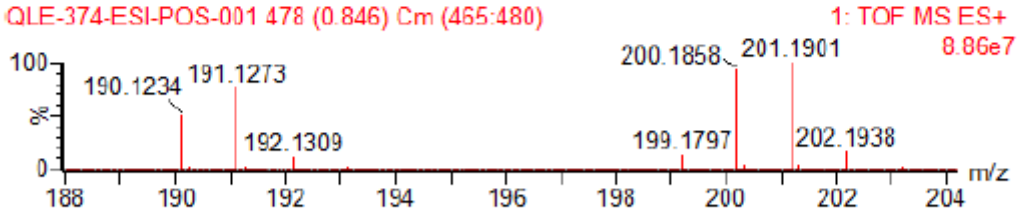
ANALYSE			
Échantillon	**QLE-374**	**Opérateur**	D'ANFRAY Timothée
Date	17/01/2024	**Demandeur**	LEMESRE Quentin
Instrument	Xevo G2-XS QTOF	**Encadrant**	AUDISIO Davide

ACQUISITION			
Source	ESI	**Polarité**	Positiv
Début scan	50 m/z	**Tension capillaire**	0.5 kV
Fin scan	1200 m/z	**Energie collision**	6 eV









m/z mesuré	z	Formule brute	m/z	erreur [mDa]	erreur [ppm]
190,1234	1	C12H16NO	190,1232	-0,2	-1,1
200,1858	1	C12H6D10NO	200,1859	0,1	0,5

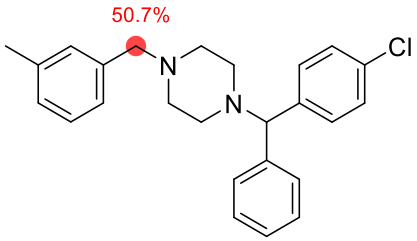
Echange (10D) %	**57**
Echange (13C)%	**41**
Enrichissement (+1D) %	**14**
Enrichissement (+2D) %	**1,5**

c. Amide reduction to amine

General procedure H for reduction of amide to amine:

A flame dried flask (10 mL) was charged with the amide and freshly distilled THF (0.05 M) followed by the addition $LiAlH_4$ (under argon atmosphere). The solution was stirred at RT until completion of the reaction (TLC and LCMS monitoring) usually 30min. Then a Fieser work up was performed using Rochelle's salt. Under high stirring, the excess $LiAlH_4$ was quench with 5 mL of EtOAc then add 5 mL of Rochelle's salt 1M solution (potassium sodium tartrate) and stirred for 12h, then separated the organic phase and washed it with water. The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure.

[^{13}C] 1-((4-chlorophenyl)(phenyl)methyl)-4-(3-methylbenzyl)piperazine ([^{13}C] Meclizine) ([^{13}C]64)



[^{13}C]64

$C_{24}{}^{13}CH_{27}ClN_2$
MW: 391.95 g.mol^{-1}
Colorless oil
Yield: 20%
IE: 50.7%

Following the general procedure H, on a 0.031 mmol scale of amide [^{13}C]63 using $LiAlH_4$ (20 mg, 0.5 mmol, 17 eq.), the desired compound was obtained as a colorless oil (a side product from the dehalogenation reaction was observed). A HPLC purification was performed on a column XSelectPFP (150 x 20 mm; 3 µm), using Solvent: A: H_2O + 0,1% HCOOH; B: ACN + 0,1% HCOOH Gradient (A/B): t = 0: 95/5; t = 24: 60/40; t = 24.10 min: 0/100; t = 30min: 0/100 (2 mg, 0.005 mmol, 20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 4H), 7.31 – 7.11 (m, 9H), 4.24 (s, 1H), 3.51 (s + d, *J* = 132 Hz, 2H), 2.47 (m, 5H), 2.32 (s, 3H), 1.6 (m, 3H).

HRMS (ESI-TOF) m/z calcd for $C_{24}{}^{13}CH_{28}ClN_2$: 392.1975 $[M+H]^+$; found 392.1973.

Isotopic exchange (calculated by HRMS): 50.7%;

FTIR (cm^{-1}): 3027, 2919, 2809, 2240, 1631, 1594, 1579, 1488, 1452, 1431, 1371, 1288, 1266, 1205, 1144, 1088, 1029, 1014, 998, 909, 851, 823, 803, 758, 728, 700, 643, 624, 533, 500, 448, 425.

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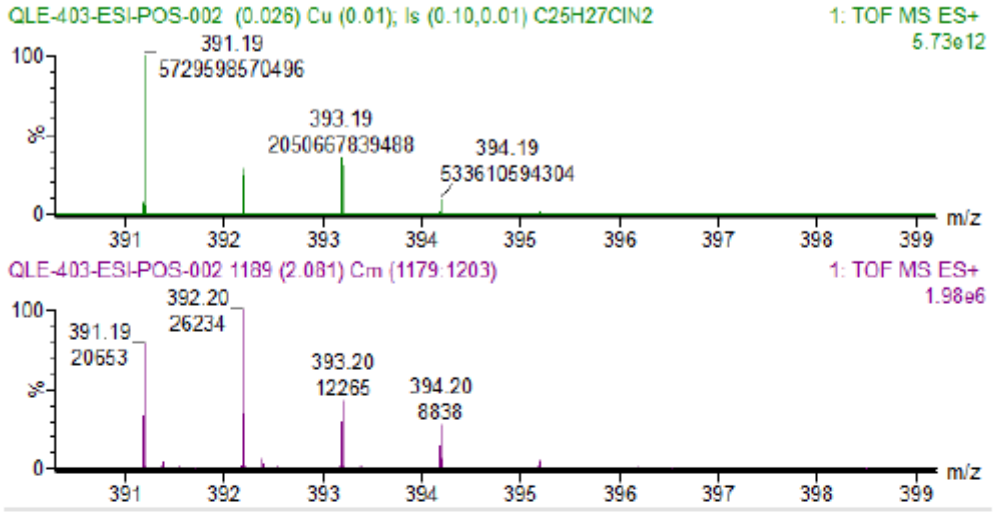
Isotopic Enrichment



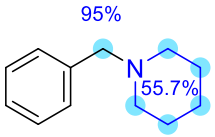
theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	391	392	393	394	395	396	397	398
%	100,0	28,2	36,2	9,4	1,2	0,1	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	391	20653	0,00	20653,00	51,31
1	392	26234	5824,14	20409,85	50,70
2	393	12265	7476,38	-966,96	-2,40
3	394	8838	1941,38	-219,07	-0,54
4	395	2114	247,84	359,46	0,89
5	396	307	20,65	110,26	0,27
6	397	72	0,00	-77,43	-0,19
7	398	0	0,00	-48,27	-0,12
8	399	0	0,00	27,18	0,07
9	400	0	0,00	15,40	0,04
10	401	0	0,00	-8,83	-0,02
11	402	0	0,00	-4,98	-0,01
Total		70483		40249,61	99,99
			% IE		50,7

1-(phenylmethyl-d2)piperidine-2,2,3,3,4,4,5,5,6,6-d10 ([$^2H_{12}$]60)



[$^2H_{12}$]60

$C_{12}H_5D_{12}N$
MW: 187.35 g.mol^{-1}
Colorless oil
Yield: 75%
IE: 55.7%

Following the general procedure H, using $LiAlD_4$ (95% deuterium enriched from Sigma, 80 mg, 2.0 mmol, 20 eq.) on a 0.1 mmol scale of amide [$^2H_{10}$]59, the desired compound was obtained as a colorless oil after filtration on a silica pad using Et_2O/Pentane (1/1) washing (14 mg, 0.075, 75%). Attention: the product is volatile (Careful evaporation was performed because of the volatility of the product, never under 100 mbar and higher than 40 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3 (m, 5H), 3.5 – 3.4 (m, 0.10H), 2.5 – 2.3 (m, 2.01H), 1.7 – 1.5 (m, 2.12H), 1.5 – 1.4 (m, 1.09H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 129.4 (2C), 128.2 (2C), 127.0, 54.5 (2C), 29.1, 26.1 (2C), 24.5.

^{2}H NMR (61 MHz, $CHCl_3$): δ 3.4 (bs), 2.2 (bs), 1.4 (bs), 1.3 (bs).

HRMS (ESI-TOF) m/z calc'd for $C_{12}H_6D_{12}N$: 188.2192 $[M+H]^+$; found 188.2193.

Isotopic exchange (calculated by HRMS): 55.7%.

FTIR (cm^{-1}): 3025, 2932, 2853, 2783, 2742, 2204, 2105, 2037, 1493, 1448, 1385, 1299, 1250, 1194, 1175, 1156, 1123, 1070, 1024, 991, 974, 929, 886, 856, 776, 720, 702, 632.

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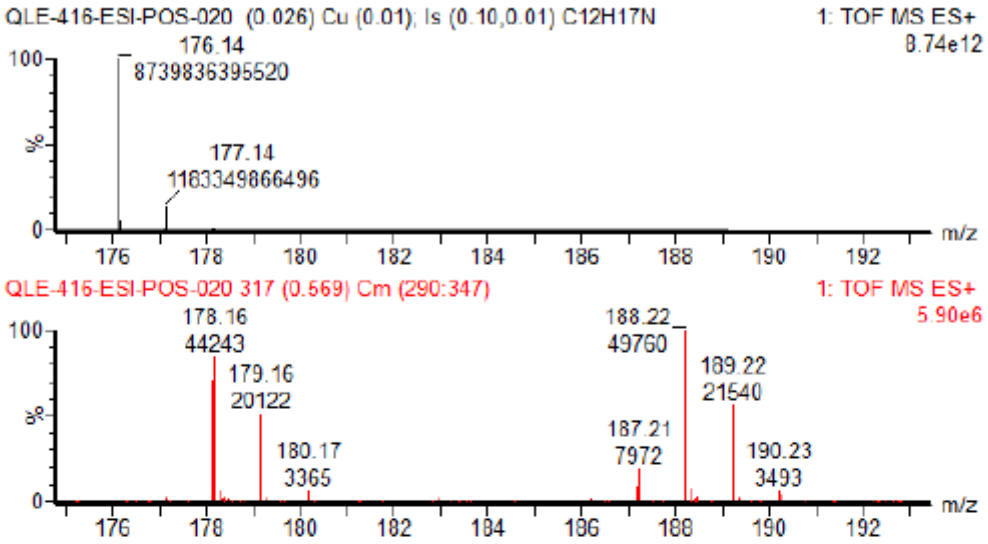
Enrichissement isotopique (total)



Profil isotopique théorique

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	176	177	178	179	180	181	182	183
%	100	13,6	0,8	0	0	0	0	0

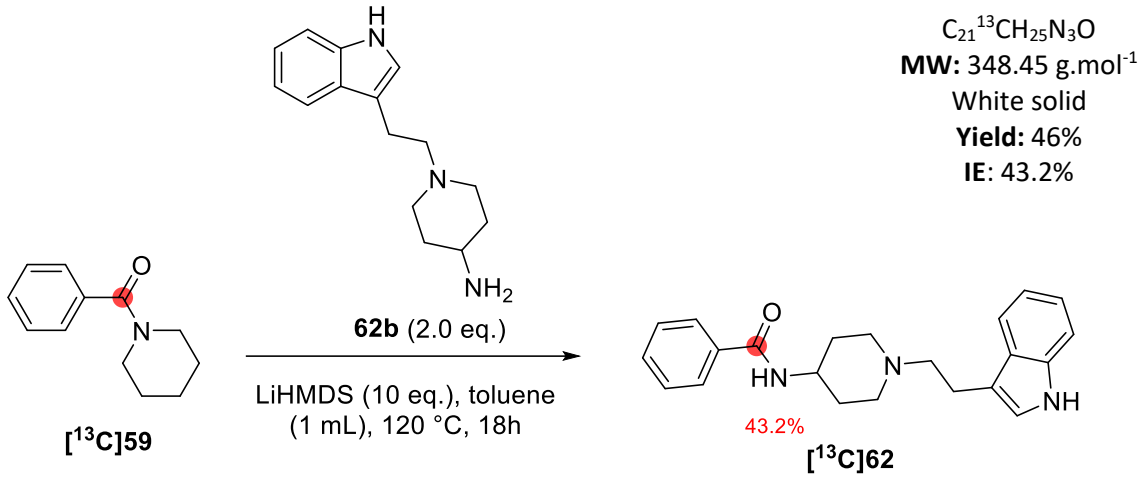
Calcul de l'enrichissement

Isotopomère	m/z	Aires	Correction isotopes naturels	Aires corrigées	Pureté isotopique (%)
0	176	10	0,00	10,00	**0,01**
1	177	1097	1,36	1095,64	**0,82**
2	178	44243	0,08	44093,91	**33,09**
3	179	20122	0,00	14116,46	**10,59**
4	180	3365	0,00	1092,41	**0,82**
5	181	154	0,00	-107,50	**-0,08**
6	182	0	0,00	5,88	**0,00**
7	183	0	0,00	0,06	**0,00**
8	184	0	0,00	-0,06	**0,00**
9	185	0	0,00	0,01	**0,00**
10	186	556	0,00	556,00	**0,42**
11	187	7972	0,00	7896,38	**5,92**
12	188	49760	0,00	48681,64	**36,53**
13	189	21540	0,00	14856,13	**11,15**
14	190	3493	0,00	1083,11	**0,81**
Total		152312		1,33E+05	100,08

Echange (Piperidine)% 55,7

d. Transamidation with primary amines

[^{13}C] N-(1-(2-(1H-indol-3-yl)ethyl)piperidin-4-yl)benzamide ([^{13}C]62)



$C_{21}{}^{13}CH_{25}N_3O$
MW: 348.45 g.mol^{-1}
White solid
Yield: 46%
IE: 43.2%

A flame dried microwave tube (10 mL) was cooled under vacuum then filled with nitrogen. The flask was charged with [^{13}C]phenyl(piperidin-1-yl)methanone ([^{13}C]59) (10 mg, 0.05 mmol, 1 eq.), amine 62b (20 mg, 0.1 mmol, 2 eq.) and purged with 3 cycles vacuum/N_2. Dry toluene (1 mL) was added followed by LiHMDS (0.5 mL, 0.5 mmol, 10 eq.). The tube was disconnected from the vacuum/N_2 line, and a N_2 balloon was added. The flask was stirred at 120 °C overnight (18h). Afterwards, 0.5mL of MeOH was added, the mixture was stirred for 5 min, filtered on a silica pad with DCM/MeOH (8/2). The pure product was obtained as a yellow solid via purification on a silica gel column using DCM/MeOH (gradient from 100/0 to 9/1) as eluent (8 mg, 0.023, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (s, 1H), 7.8 (m, 2H), 7.6 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.5 – 7.5 (m, 1H), 7.5 – 7.4 (m, 2H), 7.4 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.2 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H), 7.1 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.0 (d, *J* = 2.4 Hz, 1H), 6.2 – 6.0 (m, 1H), 4.2 – 4.0 (m, 1H), 3.2 – 2.9 (m, 4H), 2.8 – 2.7 (m, 2H), 2.3 (td, *J* = 11.7, 2.5 Hz, 2H), 2.1 – 2.0 (m, 2H), 1.8 – 1.6 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1 (^{13}C-labeled), 136.4, 134.7, 131.6, 128.7 (2C), 127.5, 127.0 (2C), 122.2, 121.7, 119.4, 118.9, 114.1, 111.3, 59.3, 52.6 (2C), 47.0, 32.2 (2C), 23.1.

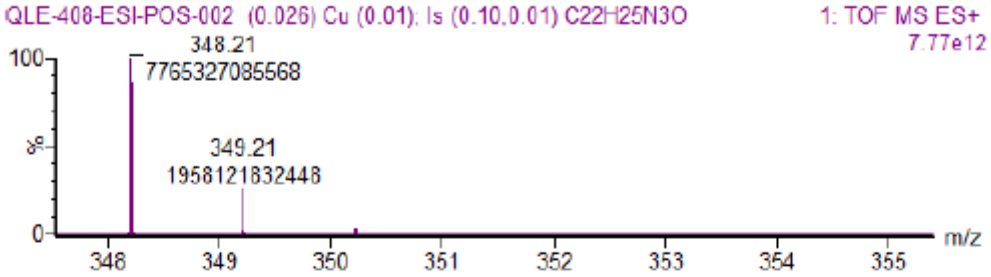
HRMS (ESI-TOF) m/z calcd for $C_{22}{}^{13}CH_{26}N_3O$: 349.2110 $[M+H]^+$; found 349.2104.

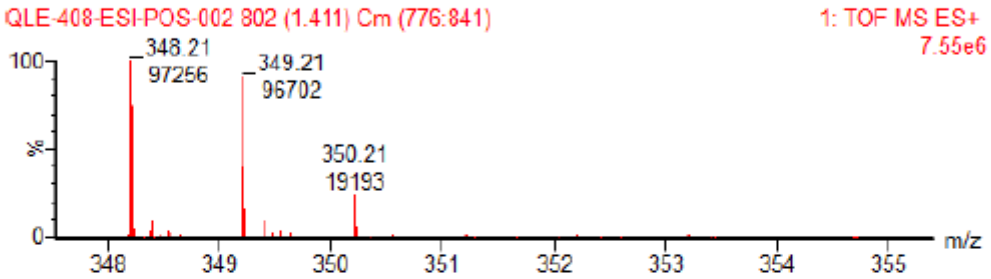
Isotopic exchange (calculated by HRMS): 43.2%.

FTIR (cm^{-1}): 3328, 2921, 2798, 1632, 1602, 1569, 1530, 1490, 1449, 1332, 1280, 1105, 1074, 973, 892, 804, 739, 708, 694, 645, 610, 583, 422.

Service de chimie bioorganique et de marquage (SCBM)
Plateforme d'Analyse

Isotopic Enrichment





theorical isotopic distribution

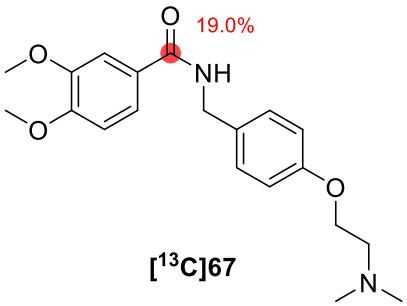
	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	348	349	350	351	352	353	354	355
%	100,0	25,3	3,3	0,2	0,0	0,0	0,0	0,0

Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	348	97256	0,00	97256,00	58,29
1	349	96702	24605,77	72096,23	43,21
2	350	19193	3209,45	-2256,79	-1,35
3	351	1755	194,51	-247,72	-0,15
4	352	0	0,00	-7,05	0,00
5	353	0	0,00	14,47	0,01
6	354	0	0,00	-2,93	0,00
7	355	0	0,00	0,28	0,00
8	356	0	0,00	0,00	0,00
9	357	0	0,00	0,00	0,00
10	358	0	0,00	0,00	0,00
11	359	0	0,00	0,00	0,00
Total		214906		166852,48	100,00
		% IE			43,2

[^{13}C] Itopride ([^{13}C]67)

Vesnarinone Recycling experiment:



[^{13}C]67

$C_{19}{}^{13}CH_{26}N_2O_4$
MW: 359.43 g.mol^{-1}
Yellow oil
Yield: 32%
IE: 19.0%

A flame dried microwave tube (10 mL) was cooled under vacuum and then filled with nitrogen. The flask was charged with [^{13}C]66 Vesnarinone previously labelled by metathesis (7.4 mg, 0.019 mmol, 1 eq.), 2-(4-(aminomethyl)phenoxy)-*N,N*-dimethylethan-1-amine (7.8 mg, 0.04 mmol, 2 eq.) and purged with 3 cycles vacuum/N_2. Dry toluene was added followed by LiHMDS (1M solution in toluene, 0.15 mL, 0.15 mmol, 8 eq.). The tube was disconnected from the vacuum/N_2 line, and a N_2 balloon was added. The flask was stirred at 120 °C overnight (18h). Afterwards, the mixture was cooled down to r.t., the tube opened, 0.5mL of MeOH was added and the mixture was stirred for 5 min. The purification was performed via preparative layered chromatography (PLC) using DCM/MeOH (9/1) as eluent ($RF_{product}$ = 0.3). The product was obtained as a yellow solid oil (2.2 mg, 0.006 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (d, *J* = 2.1 Hz, 1H), 7.3 – 7.3 (m, 3H), 6.9 (d, *J* = 8.8 Hz, 2H), 6.8 (d, *J* = 8.3 Hz, 1H), 6.3 (s, 1H), 4.6 (d, *J* = 5.6 Hz, 2H), 4.1 (t, *J* = 5.6 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 2.9 (t, *J* = 5.6 Hz, 2H), 2.4 (s, 6H).

HRMS (ESI-TOF) m/z calcd for $C_{19}{}^{13}CH_{27}N_2O_4$: 360.2005 $[M+H]^+$; found 360.2010.

Isotopic exchange (calculated by HRMS): 19.0%.

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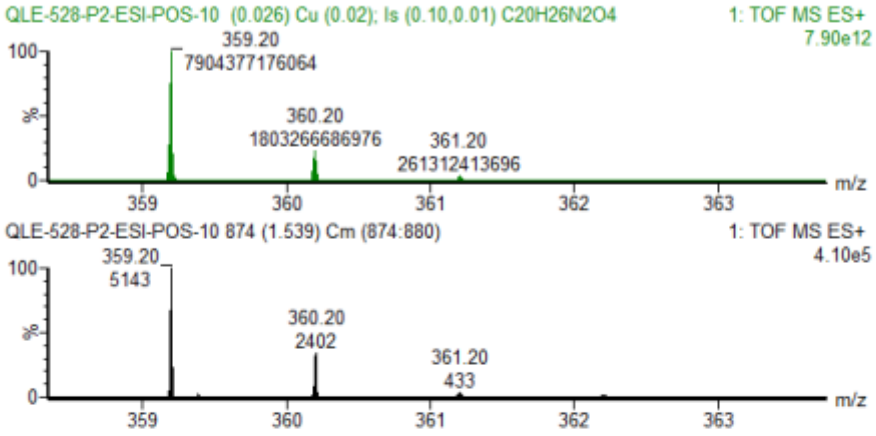
Plateforme d'Analyse

Isotopic Enrichment



theorical isotopic distribution

	M	M+1	M+2	M+3	M+4	M+5	M+6	M+7
m/z	359	360	361	362	363	364	365	366
%	100,0	22,9	3,3	0,3	0,0	0,0	0,0	0,0

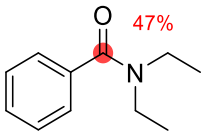
Enrichment calculation

Isotopomer	m/z	Area	natural isotope correction	Corrected area	Isotopic purity (%)
0	359	5143	0,00	5143,00	79,76
1	360	2402	1177,75	1224,25	18,99
2	361	433	169,72	-17,07	-0,26
3	362	155	15,43	103,08	1,60
4	363	24	0,00	-2,71	-0,04
5	364	0	0,00	-2,73	-0,04
6	365	0	0,00	0,41	0,01
7	366	0	0,00	0,01	0,00
8	367	0	0,00	-0,01	0,00
9	368	0	0,00	0,00	0,00
10	369	0	0,00	0,00	0,00
11	370	0	0,00	0,00	0,00
Total		8157		6448,22	100,00

Isotopic enrichment% : 19,0

e. Transamidation with excess of amine (10 eq.)

[^{13}C] N,N-Diethylbenzamide ([^{13}C]61)



[^{13}C]61

$C_{10}{}^{13}CH_{15}NO$
MW: 178.24 g.mol^{-1}
Colorless oil
Calculated Yield: 67%
IE: 47% (LCMS)

An oven dried microwave tube was put under vacuum then filled with nitrogen. The flask was charged with the amide [^{13}C]59 (from metathesis scale up) (9.5 mg, 0.05 mmol, 1.0 eq.) and purged with 3 cycles vacuum/N_2. Dry toluene was added, followed by diethylamine (50 µL, 0.5 mmol, 10 eq.) and LiHMDS (200 µL, 0.2 mmol, 4 eq.). The flask was disconnected from the vacuum/N_2 line, and a N_2 balloon was added. The flask was stirred at 95 °C over the night (18h). After the night 0.5 mL of MeOH was added and the mixture evaporated to dryness. The mixture was transferred to a flask and evaporated to dryness, the crude was then filtrated through silica gel (via a pasteur pipette), the gel was washed with Cyclohexane/EtOAc (1/1) to obtain a mixture of ^{13}C labeled [^{13}C]25 (67%) and the Carrier [^{13}C]18 (33%) was obtained as a colorless oil (10 mg). The two amides aren't separable.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 3.48 (bs, 2H), 3.18 (bs, 2H), 1.23 – 1.13 (bs, 4H), 1.04 (bs, 2H).

Isotopic exchange (calculated by LCMS): 47%

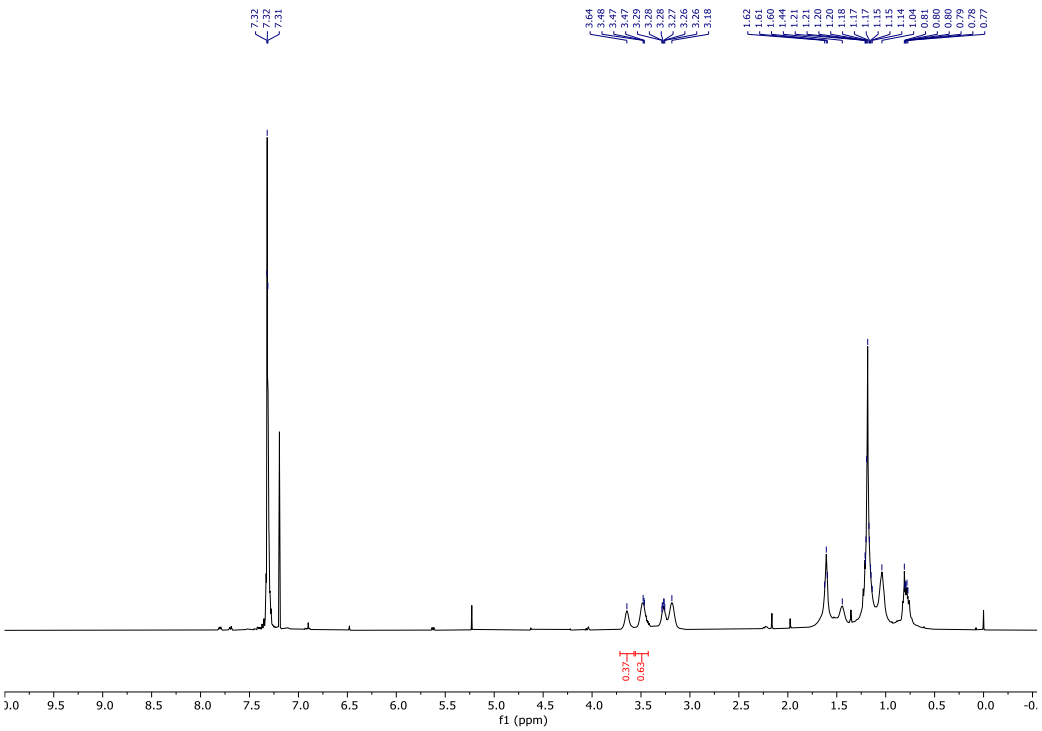


Figure S12: ^{1}HNMR of the two-amide mixture after purification

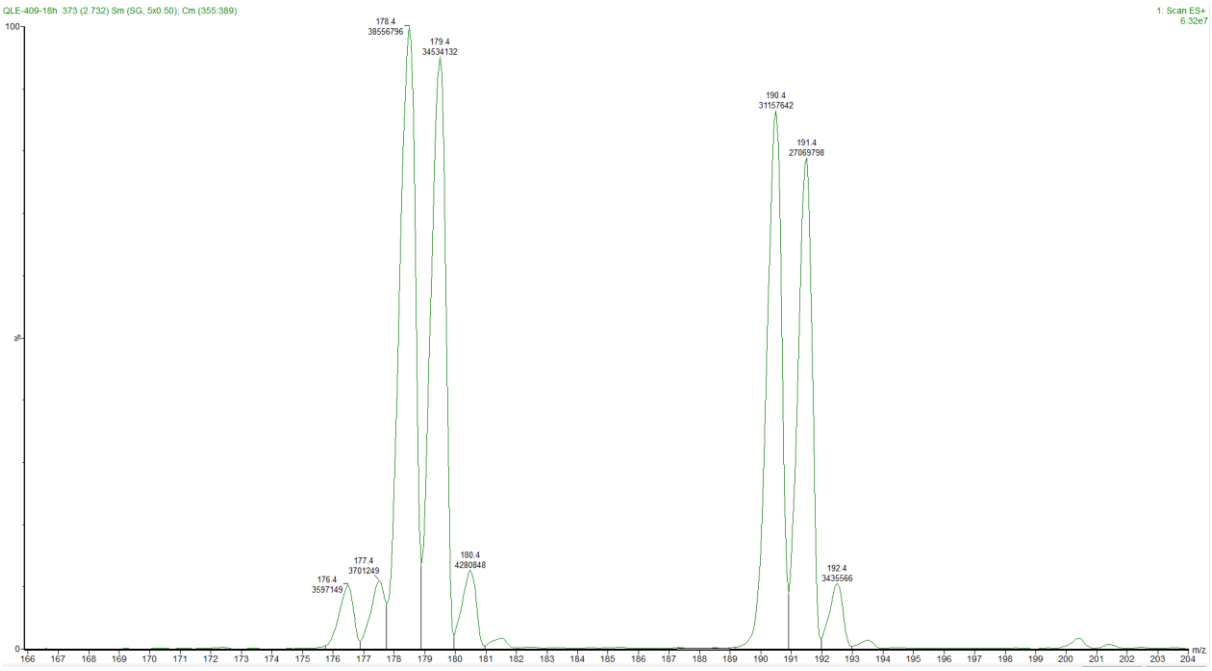


Figure S13: Mass sprectrum of [^{13}C]61 (LCMS)

X. Graphical guide for the amide exchange procedures by transamidation and metathesis.

Transamidation/metathesis

Figure S14 : Glassware used and reagents for all exchange experiments, 5 mL microwave tube with stirring bar and seal.

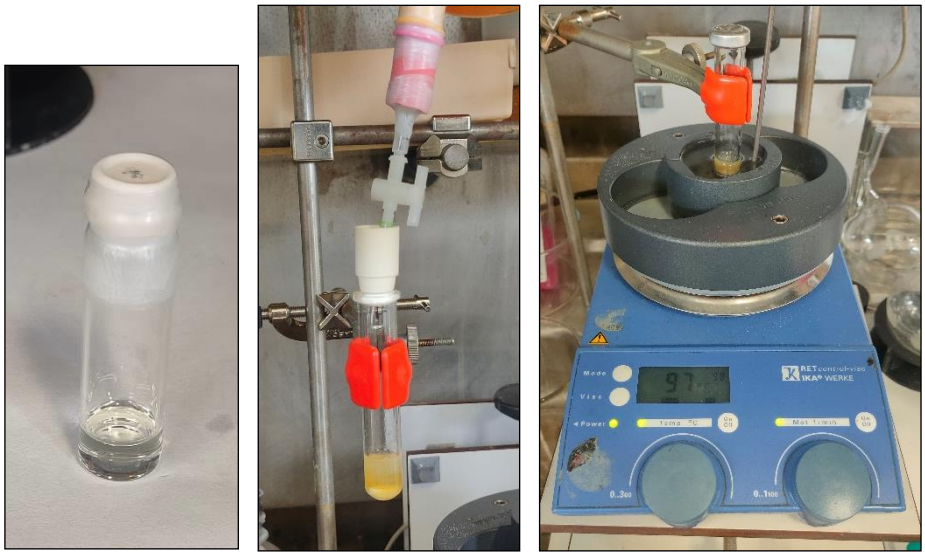


Figure S15 : amine solution freshly prepared under argon (left), mixture of amides, amine, LiHMDS in toluene ready to be sealed and heated (middle, some amide are more soluble than in the picture), heated solution in oil bath (right, heating block was also used for condition screening).

Vesnarinone

Figure S16 : after evaporation of DCM (only for Vesnarinone)

XI. References

[1] T. Kozlecki, P. M. Tolstoy, A. Kwocz, M. A. Vovk, A. Kochel, I. Polowczyk, P. Yu. Tretyakov, A. Filarowski, *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.* **2015**, *149*, 254–262.

[2] R. Wodtke, J. Steinberg, M. Köckerling, R. Löser, C. Mamat, *RSC Adv.* **2018**, *8*, 40921–40933.

[3] T. T. Dang, Y. Zhu, J. S. Y. Ngiam, S. C. Ghosh, A. Chen, A. M. Seayad, *ACS Catal.* **2013**, *3*, 1406–1410.

[4] S. L. Zultanski, J. Zhao, S. S. Stahl, *J. Am. Chem. Soc.* **2016**, *138*, 6416–6419.

[5] S. W. Krabbe, V. S. Chan, T. S. Franczyk, S. Shekhar, J. G. Napolitano, C. A. Presto, J. A. Simanis, *J. Org. Chem.* **2016**, *81*, 10688–10697.

[6] T. Furukawa, M. Tobisu, N. Chatani, *Bull. Chem. Soc. Jpn.* **2017**, *90*, 332–342.

[7] G. Wu, Y. Li, X. Yu, Y. Gao, H. Chen, *Adv. Synth. Catal.* **2017**, *359*, 687–692.

[8] X. Zhao, F. Yang, S.-Y. Zou, Q.-Q. Zhou, Z.-S. Chen, K. Ji, *ACS Catal.* **2022**, DOI 10.1021/acscatal.1c05439.

[9] S. Das, D. Addis, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 1770–1771.

[10] S. Srinivas Kotha, S. Badigenchala, G. Sekar, *Adv. Synth. Catal.* **2015**, *357*, 1437–1445.

[11] C. Bal Reddy, S. Ram, A. Kumar, R. Bharti, P. Das, *Chem. – Eur. J.* **2019**, *25*, 4067–4071.

[12] N. Tsunoji, M. V. Opanasenko, M. Kubů, J. Čejka, H. Nishida, S. Hayakawa, Y. Ide, M. Sadakane, T. Sano, *ChemCatChem* **2018**, *10*, 2536–2540.

[13] G. Pandey, S. Koley, R. Talukdar, P. K. Sahani, *Org. Lett.* **2018**, *20*, 5861–5865.

[14] X. Zhou, G. Zhang, B. Gao, H. Huang, *Org. Lett.* **2018**, *20*, 2208–2212.

[15] T. Wakikawa, D. Sekine, Y. Murata, Y. Bunno, M. Kojima, Y. Nagashima, K. Tanaka, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2022**, *61*, e202213659.

[16] Y. Zhang, D. Riemer, W. Schilling, J. Kollmann, S. Das, *ACS Catal.* **2018**, *8*, 6659–6664.

[17] P. V. Joshi, A. A. Sayed, A. RaviKumar, V. G. Puranik, S. S. Zinjarde, *Eur. J. Med. Chem.* **2017**, *136*, 246–258.

[18] X.-Q. Ning, S.-J. Lou, Y.-J. Mao, Z.-Y. Xu, D.-Q. Xu, *Org. Lett.* **2018**, *20*, 2445–2448.

[19] Sk. S. Shah, M. Shee, Y. Venkatesh, A. K. Singh, S. Samanta, N. D. P. Singh, *Chem. – Eur. J.* **2020**, *26*, 3703–3708.

[20] Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu, X. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 3231–3235.

[21] Z. Wu, K. L. Hull, *Chem. Sci.* **2016**, *7*, 969–975.

[22] R. S. Mane, B. M. Bhanage, *Adv. Synth. Catal.* **2017**, *359*, 2621–2629.

[23] J. S. Pallesen, D. Narayanan, K. T. Tran, S. M. Ø. Solbak, G. Marseglia, L. M. E. Sørensen, L. J. Høj, F. Munafò, R. M. C. Carmona, A. D. Garcia, H. L. Desu, R. Brambilla, T. N. Johansen, G. M. Popowicz, M. Sattler, M. Gajhede, A. Bach, *J. Med. Chem.* **2021**, *64*, 4623–4661.

[24] J.-F. Soulé, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, *133*, 18550–18553.

[25] T. Ben Halima, J. Masson-Makdissi, S. G. Newman, *Angew. Chem. Int. Ed.* **2018**, *57*, 12925–12929.

[26] S. E. Eldred, D. A. Stone, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 3422–3423.

[27] T. Alam, A. Rakshit, H. N. Dhara, A. Palai, B. K. Patel, *Org. Lett.* **2022**, *24*, 6619–6624.

[28] W. I. Nicholson, F. Barreteau, J. A. Leitch, R. Payne, I. Priestley, E. Godineau, C. Battilocchio, D. L. Browne, *Angew. Chem. Int. Ed.* **2021**, *60*, 21868–21874.

[29] R. Sreedharan, T. Gandhi, *J. Org. Chem.* **2023**, *88*, 8480–8492.

[30] C.-P. Xu, Z.-H. Xiao, B.-Q. Zhuo, Y.-H. Wang, P.-Q. Huang, *Chem. Commun.* **2010**, *46*, 7834–7836.

[31] T. Yu, H. Dong, Z. Shi, L. Cheng, X. Guo, X. Lian, F. Liu, *Lett. Org. Chem.* **2018**, *15*, 485–490.

[32] Y. Y. See, T. T. Dang, A. Chen, A. M. Seayad, *Eur. J. Org. Chem.* **2014**, *2014*, 7405–7412.

[33] S. Zhou, J. Wang, F. Zhang, C. Song, J. Zhu, *Org. Lett.* **2016**, *18*, 2427–2430.

[34] S. Monticelli, A. Talbot, P. Gotico, F. Caillé, O. Loreau, A. Del Vecchio, A. Malandain, A. Sallustrau, W. Leibl, A. Aukauloo, F. Taran, Z. Halime, D. Audisio, *Nat. Commun.* **2023**, *14*, 4451.

[35] S. D. Friis, T. Skrydstrup, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 4296–4299.

[36] J. M. Hoerter, K. M. Otte, S. H. Gellman, S. S. Stahl, **n.d.**

[37] J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui, S. S. Stahl, **n.d.**

[38] P. Beak, R. A. Brown, *J. Org. Chem.* **1982**, *47*, 34–46.

XII. NMR Spectra unlabeled amides

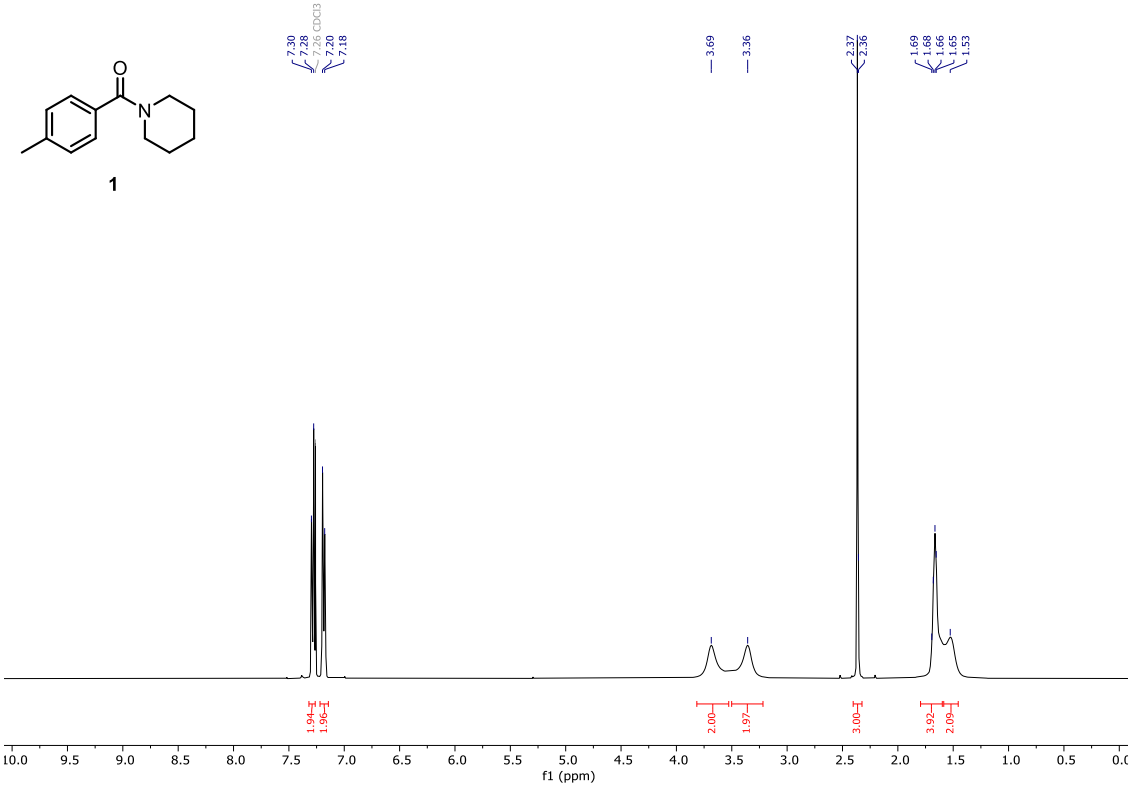


Figure S17: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

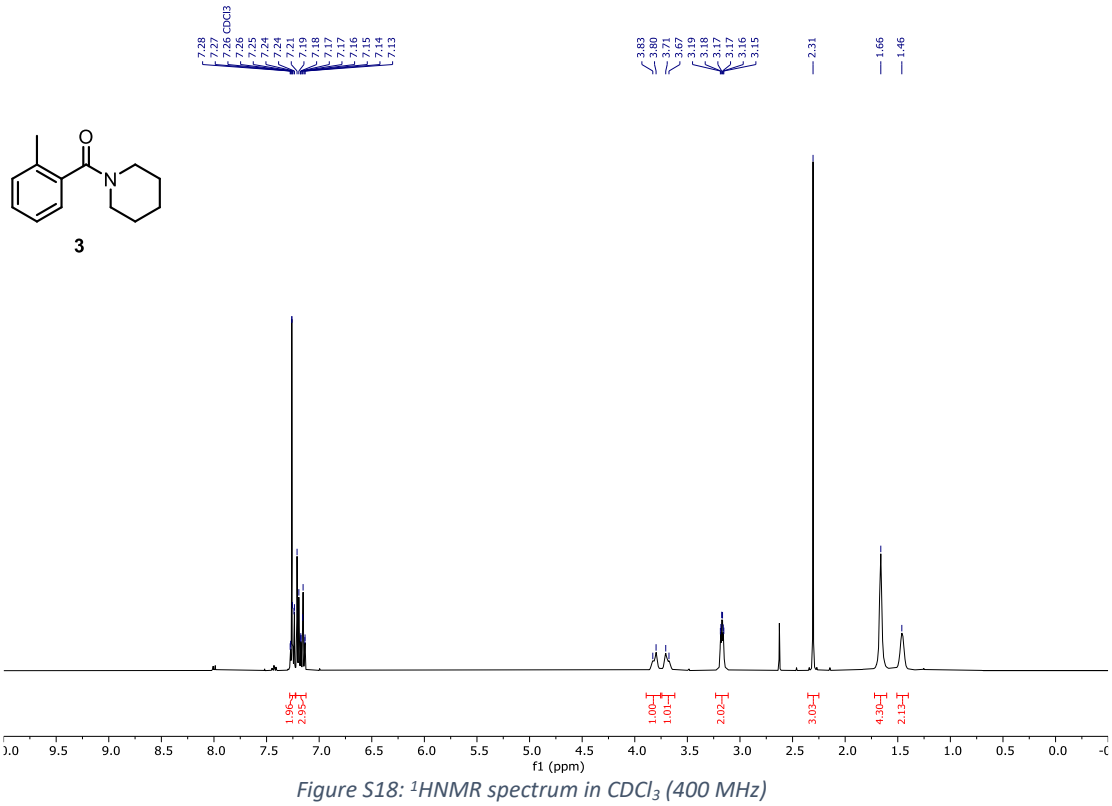


Figure S18: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

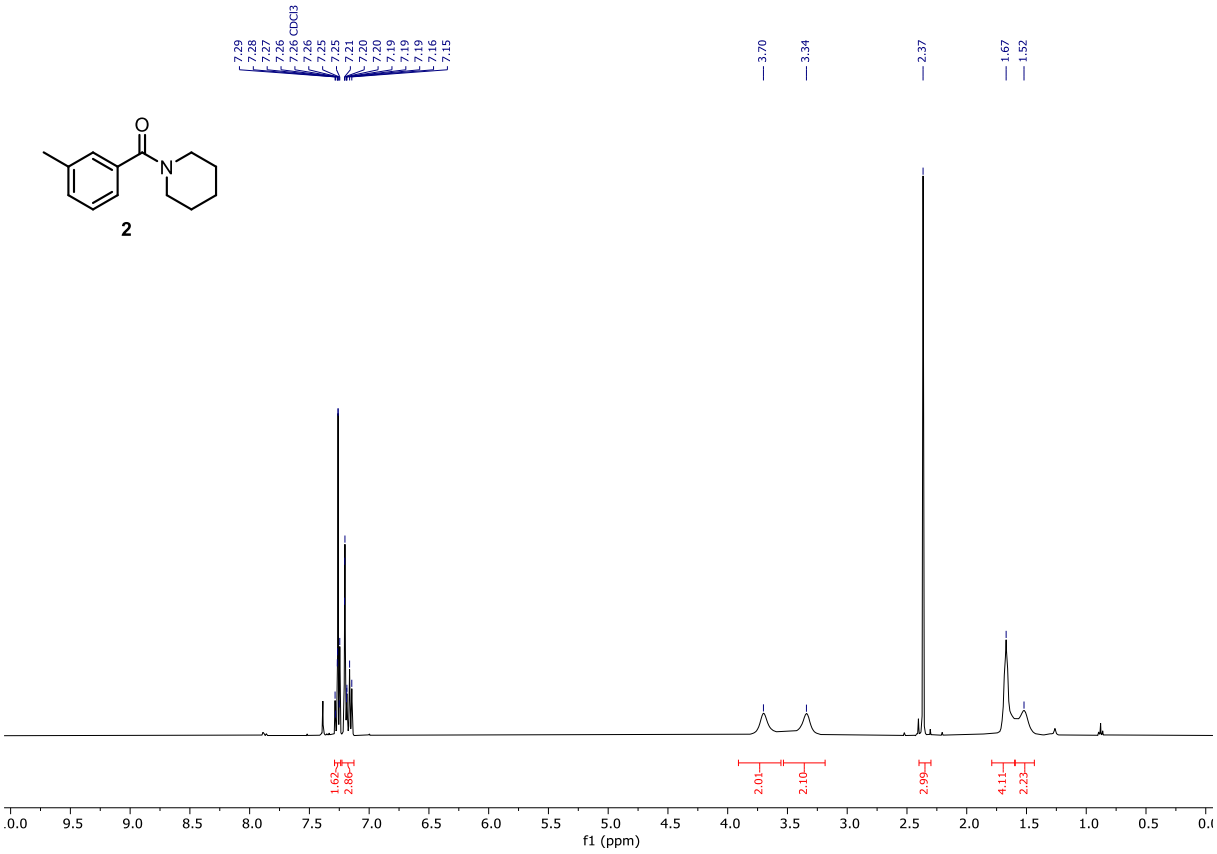


Figure S19: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

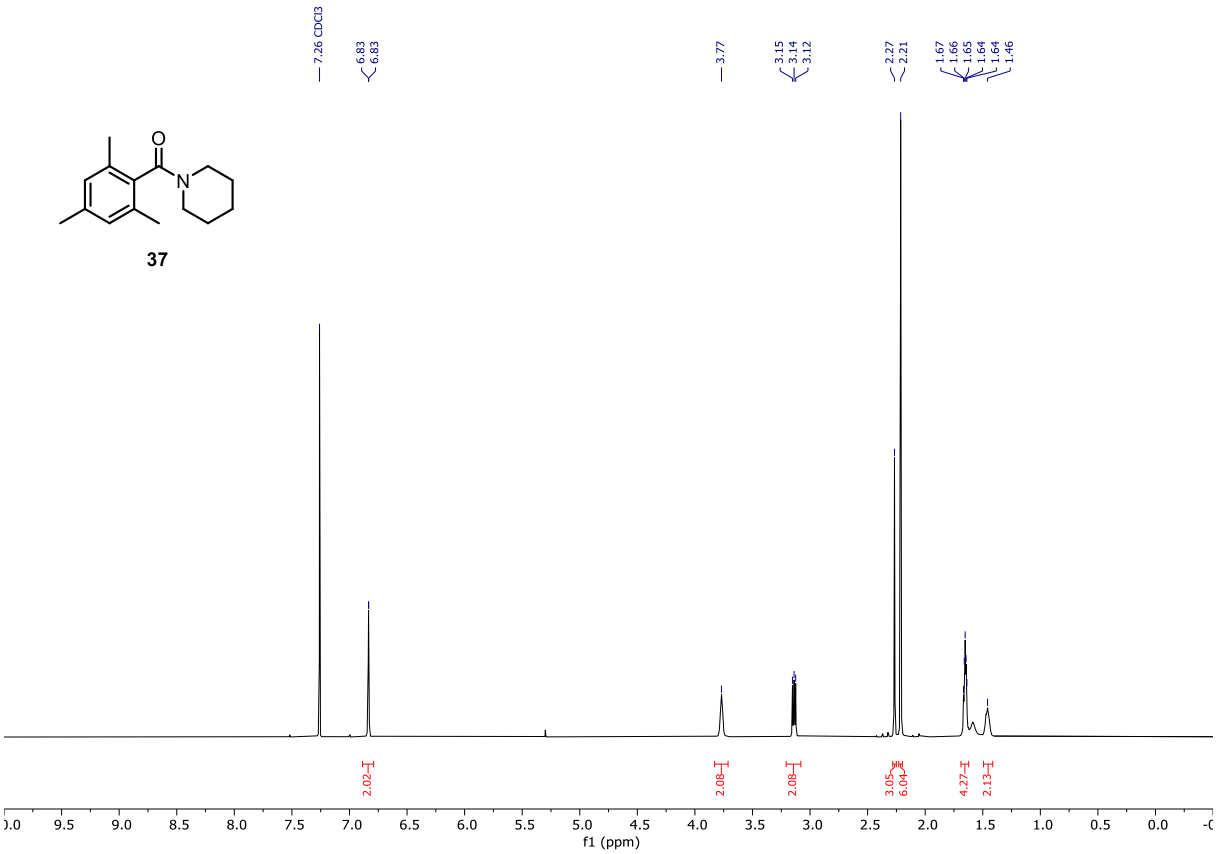


Figure S20: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

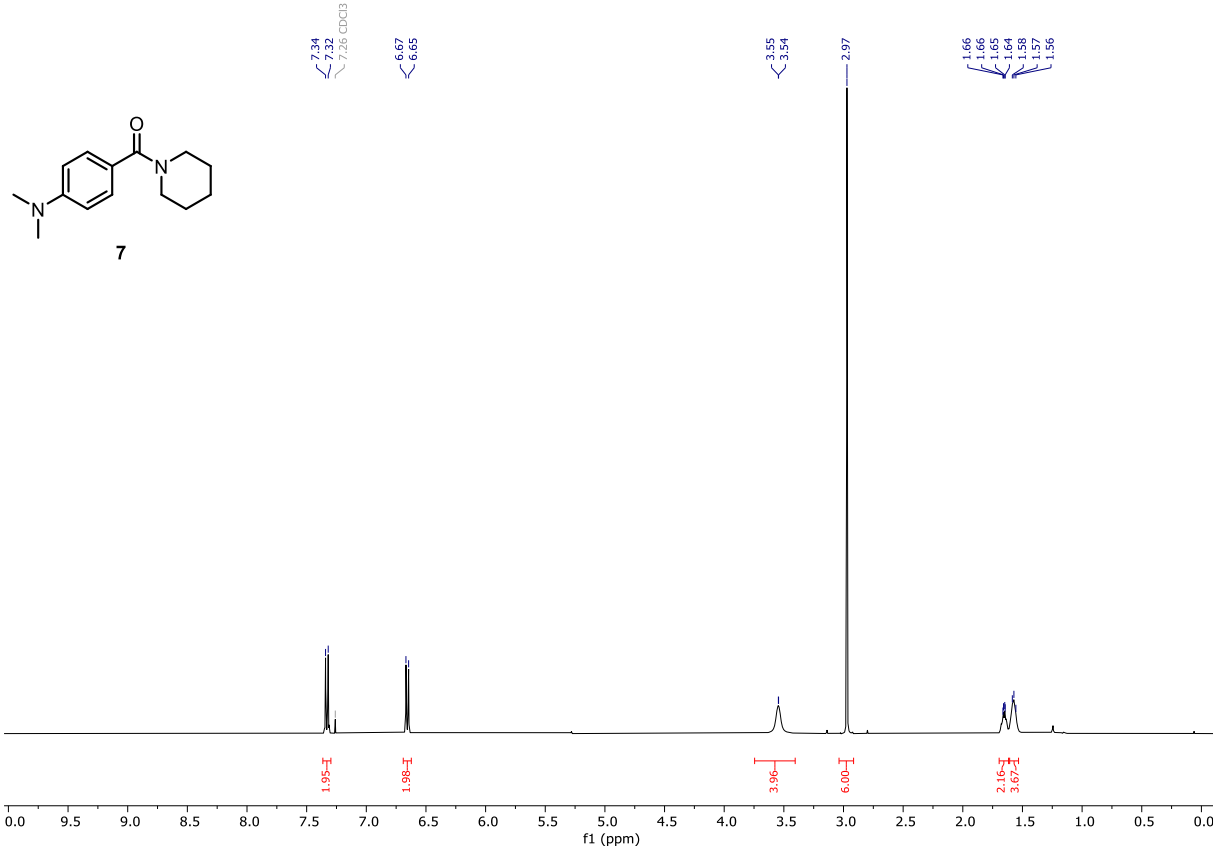


Figure S21: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

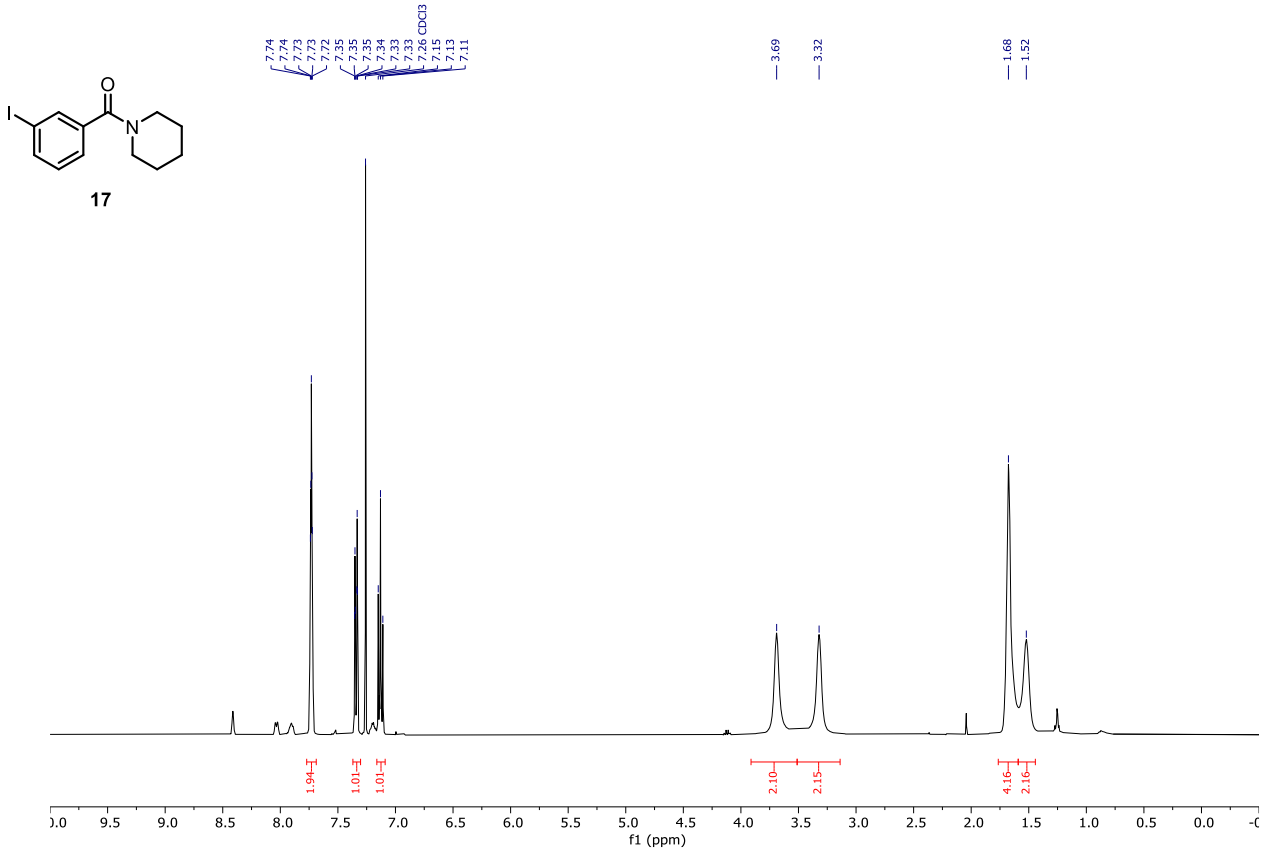


Figure S22: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

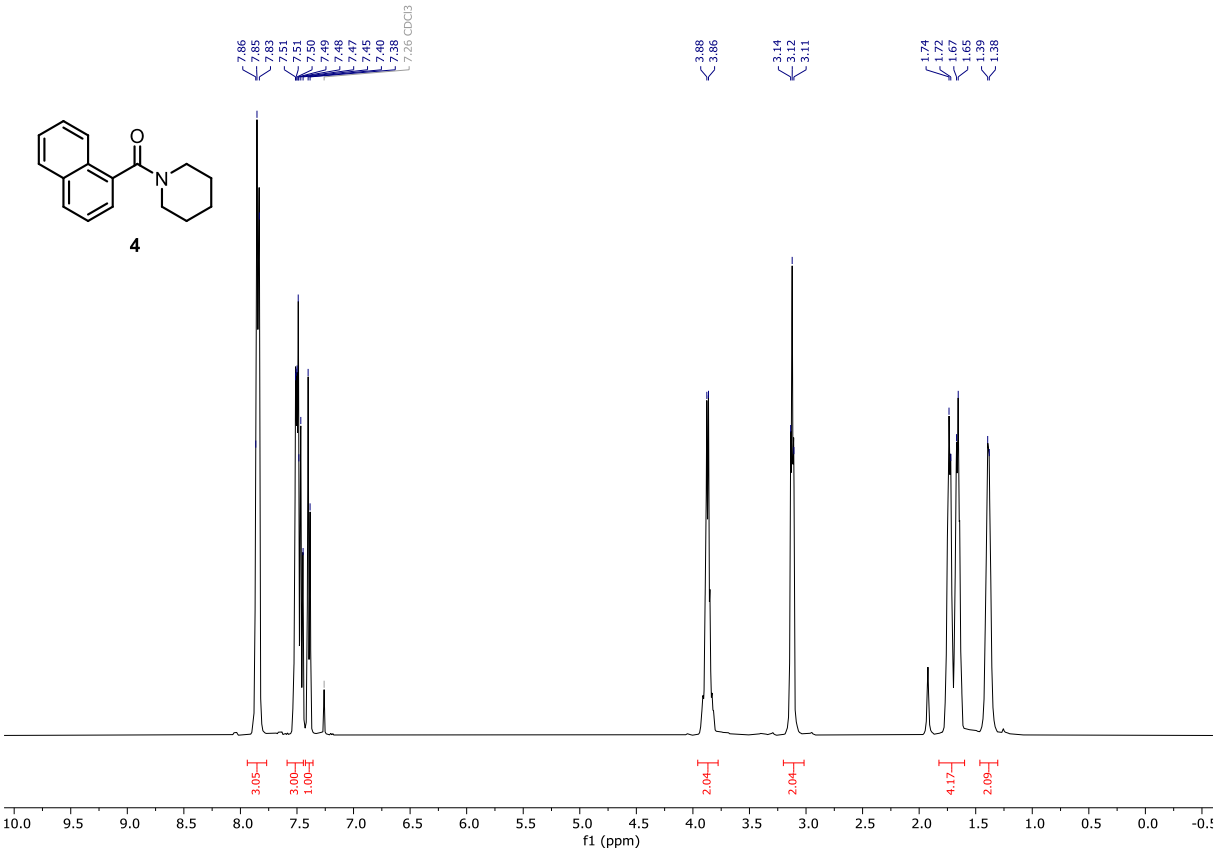


Figure S23: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

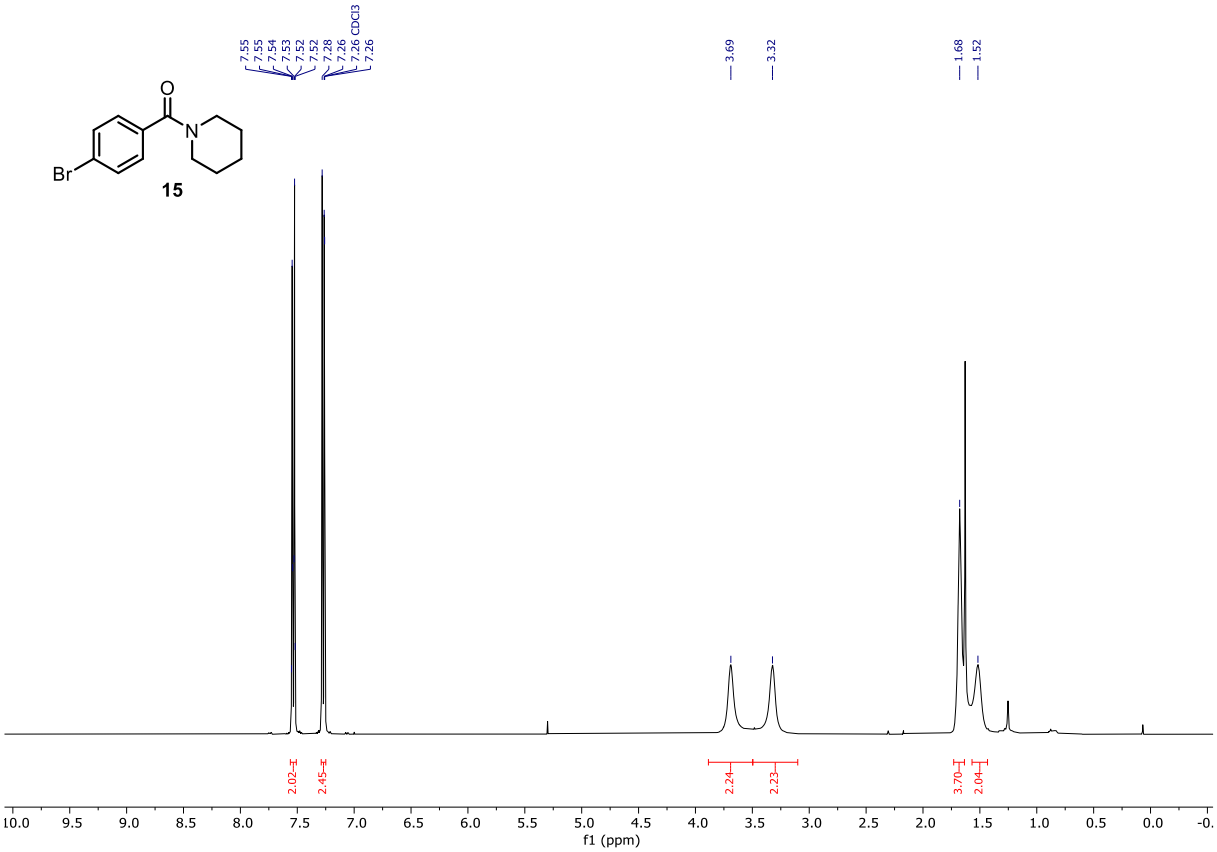


Figure S24: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

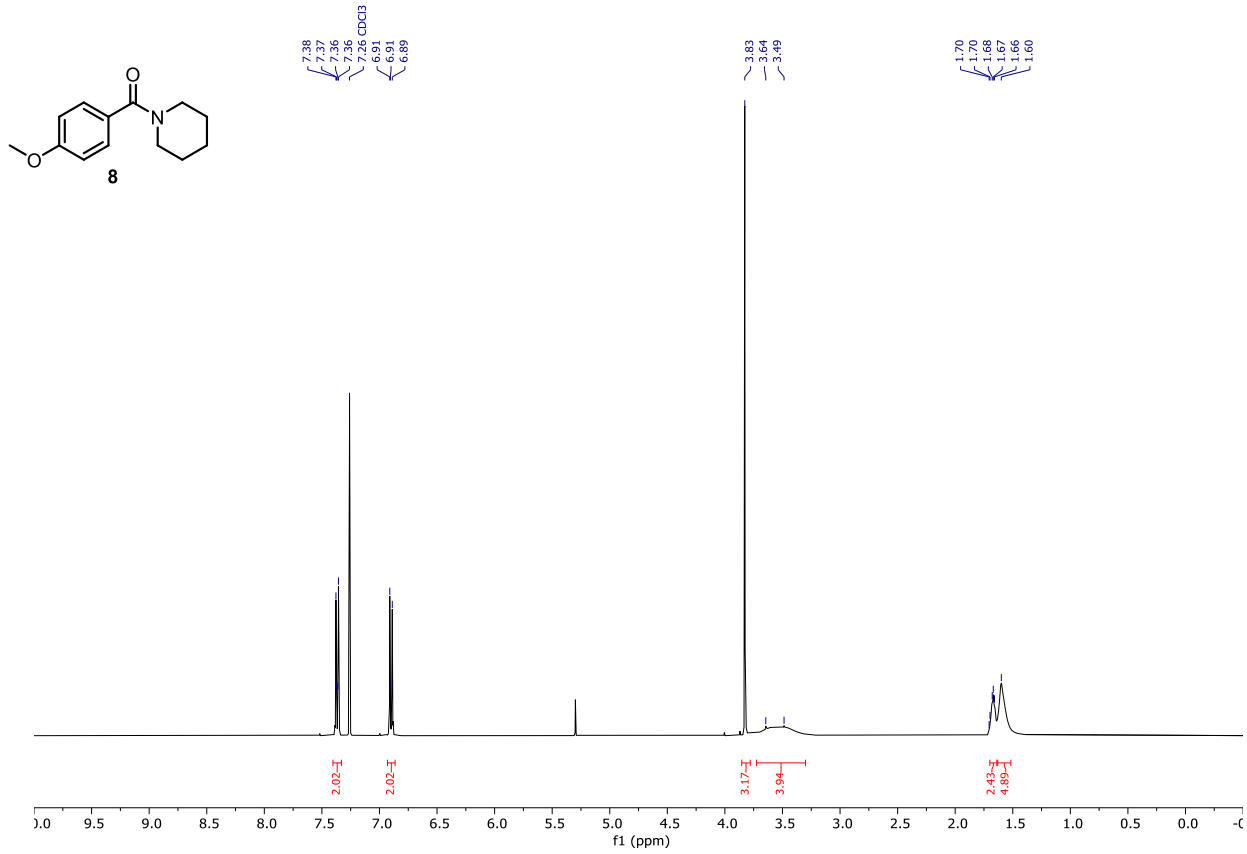


Figure S25: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

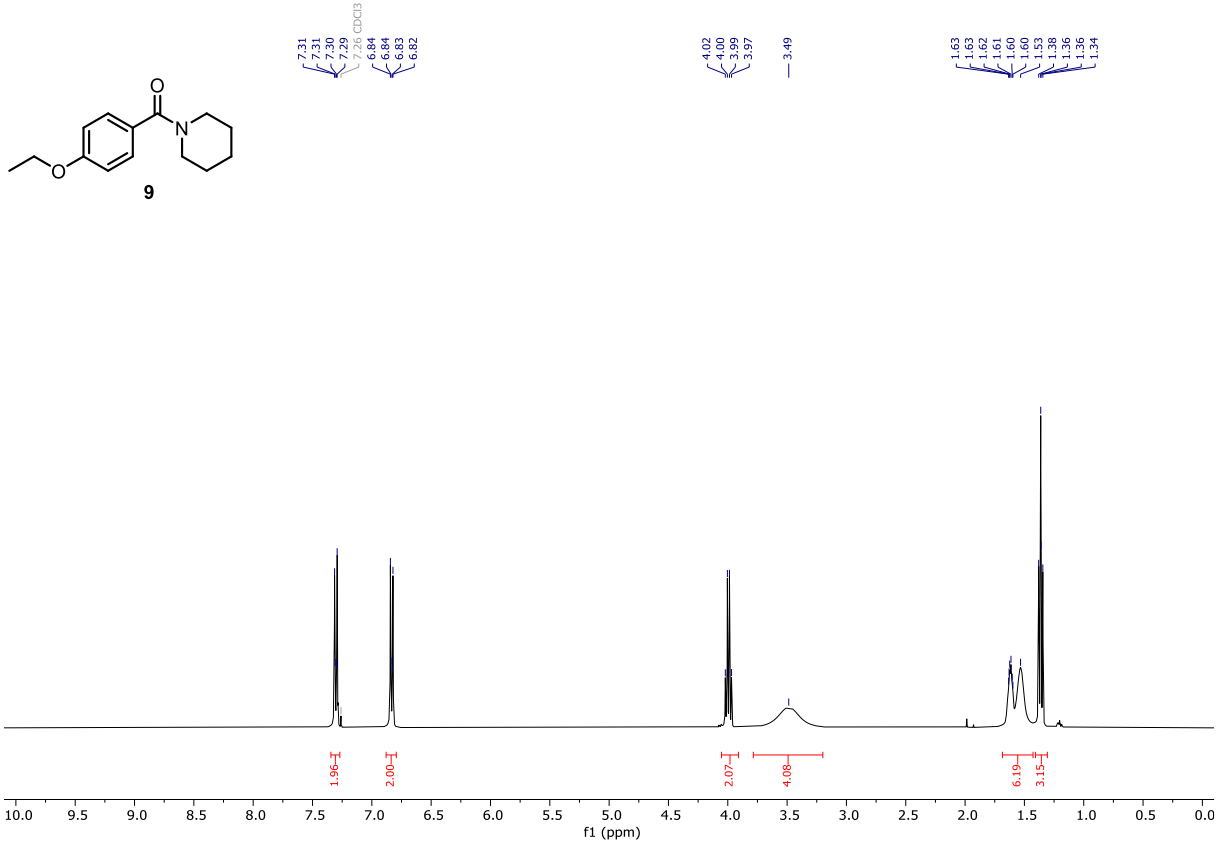


Figure S26: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

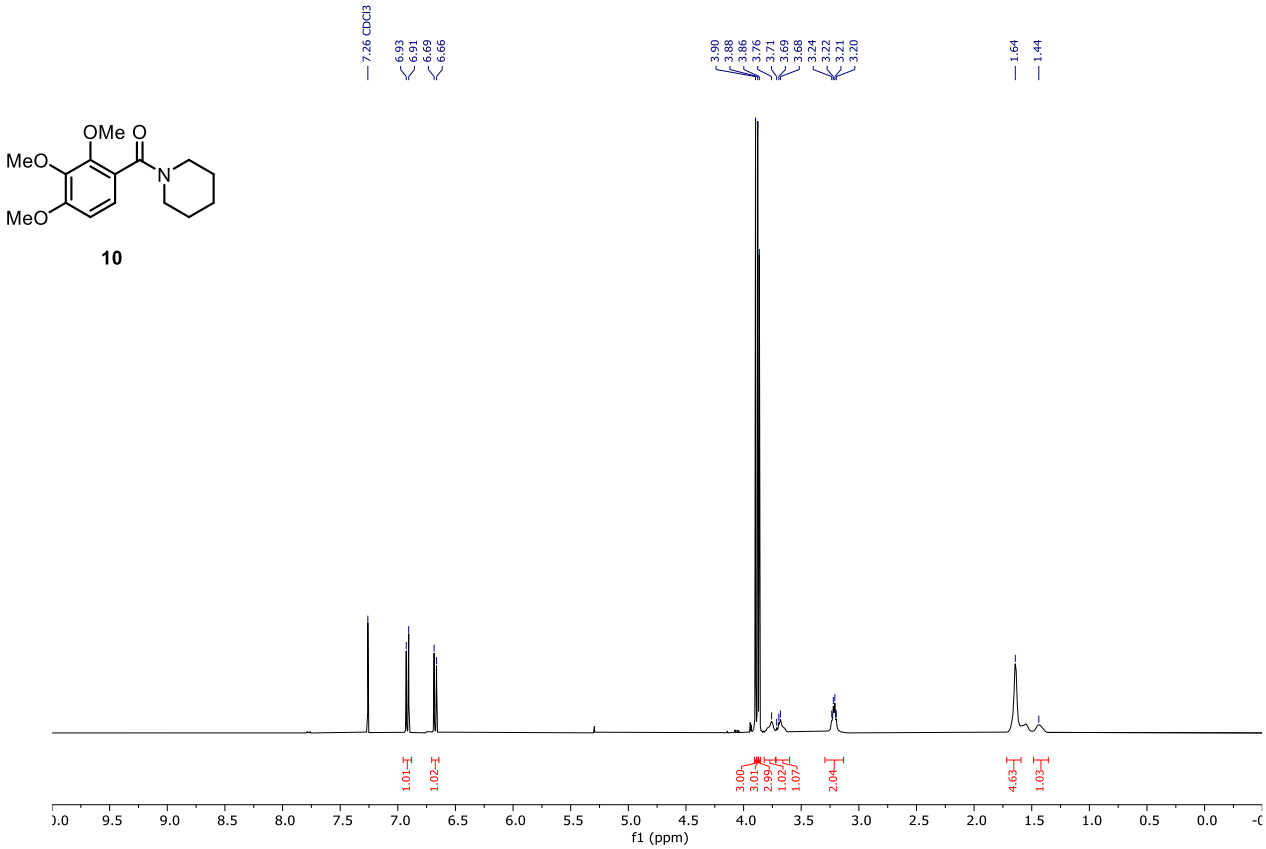


Figure S27: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

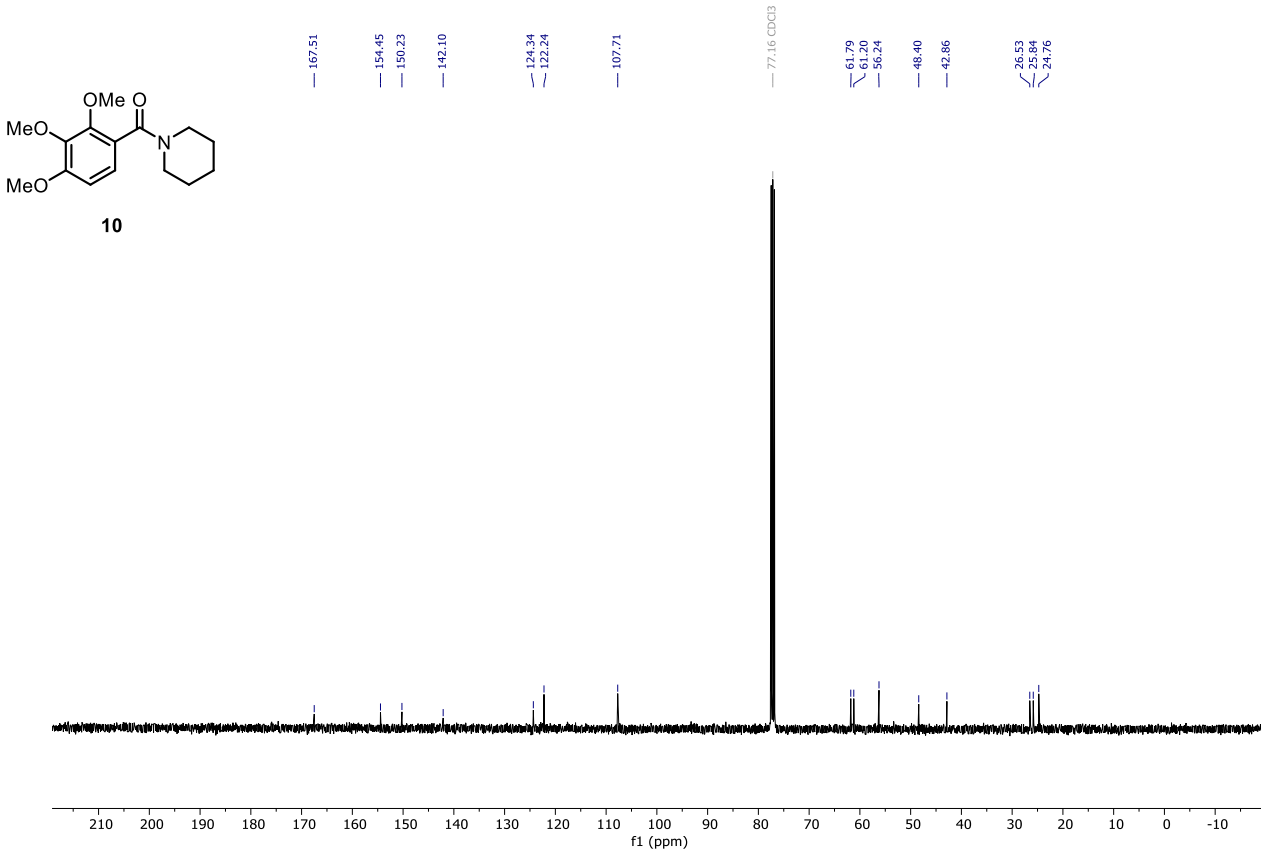


Figure S28: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

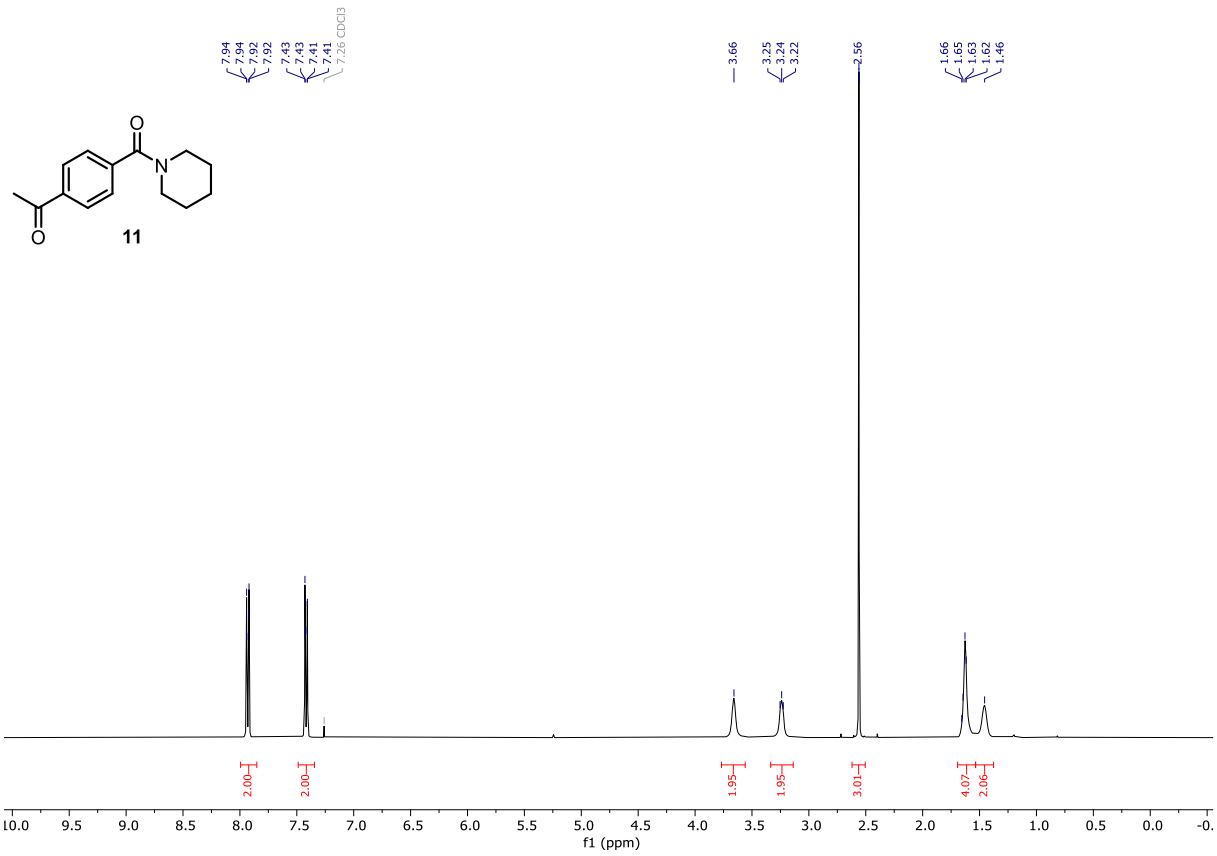


Figure S29: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

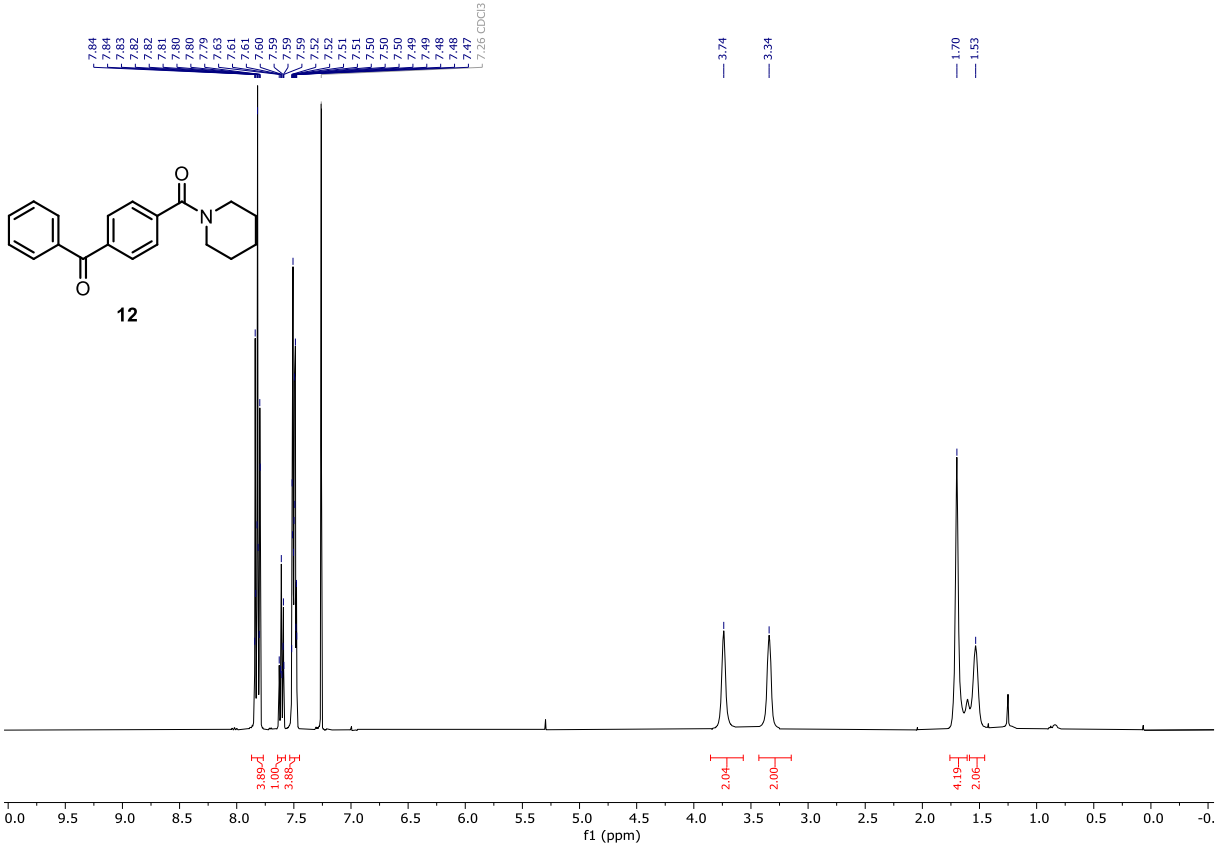


Figure S30: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

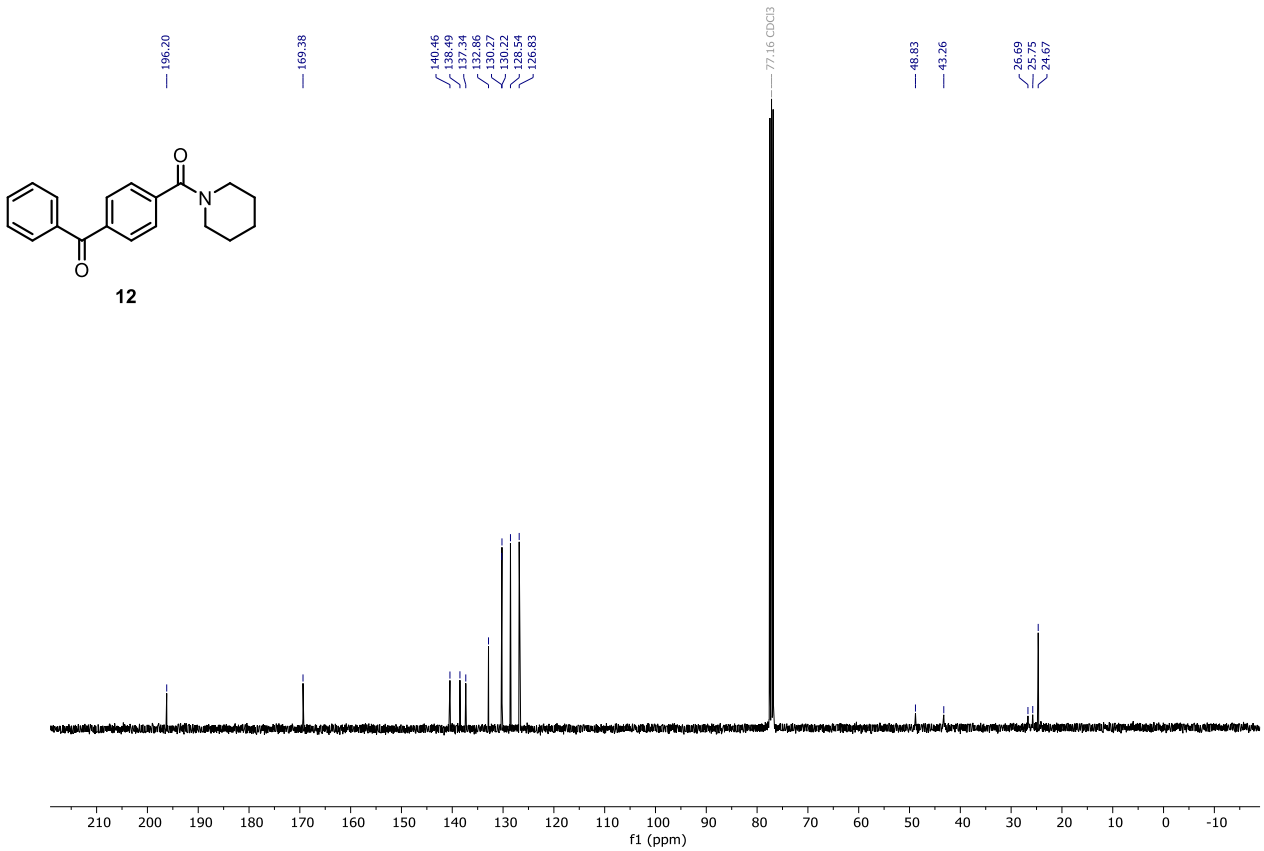


Figure S31: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

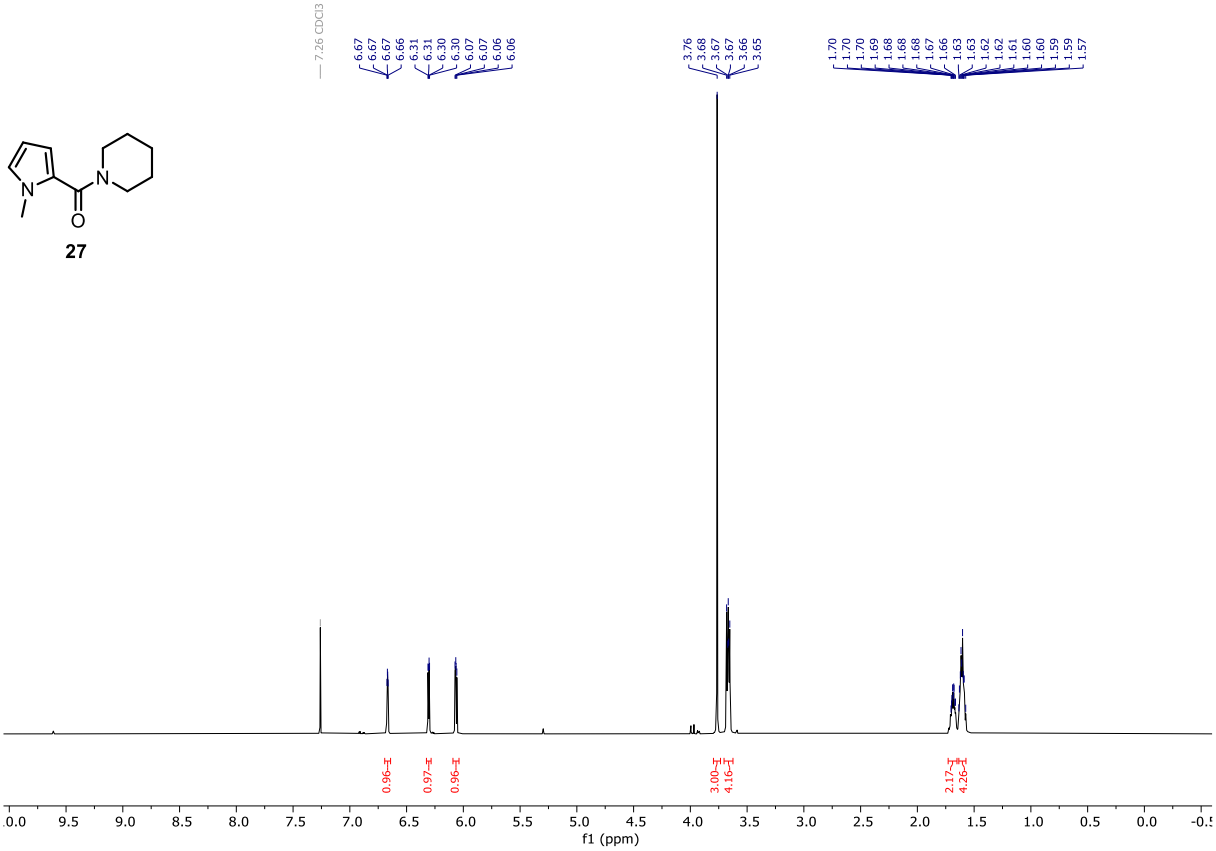


Figure S32: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

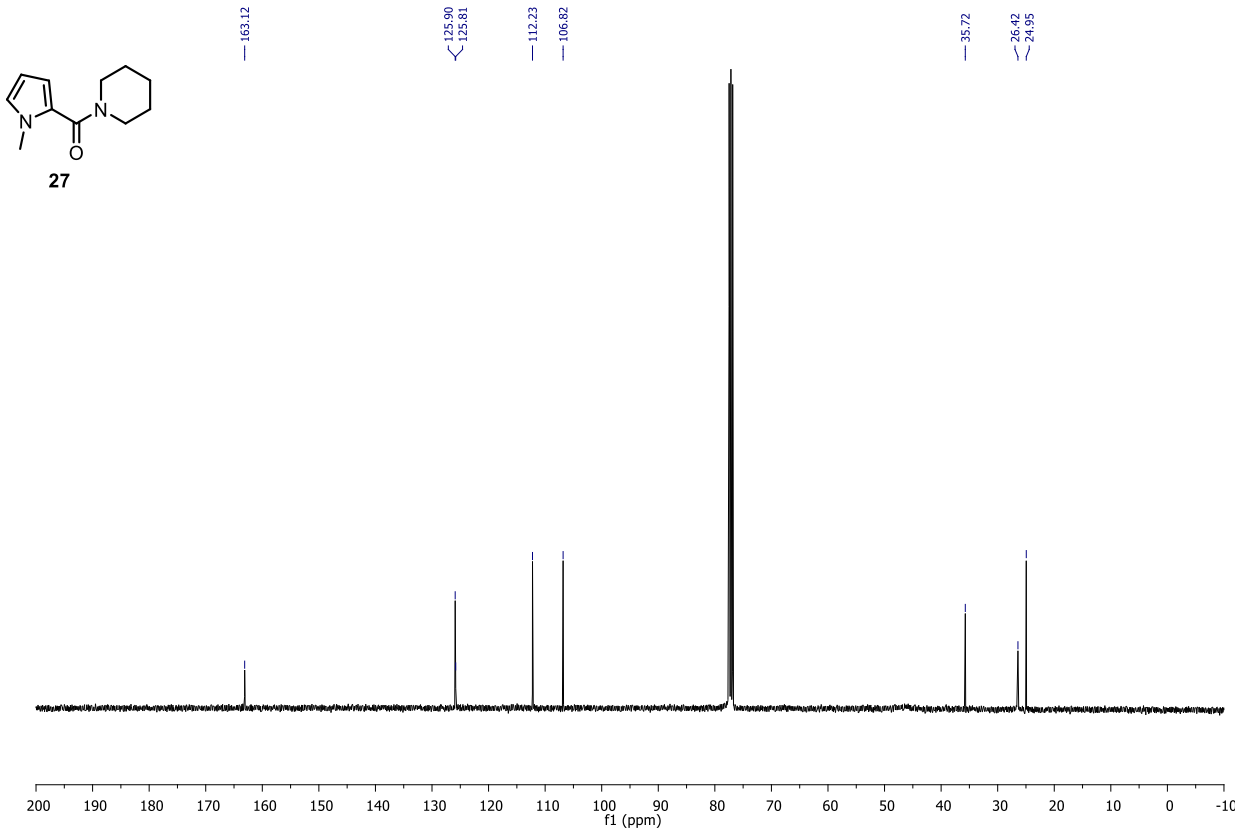


Figure S33: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

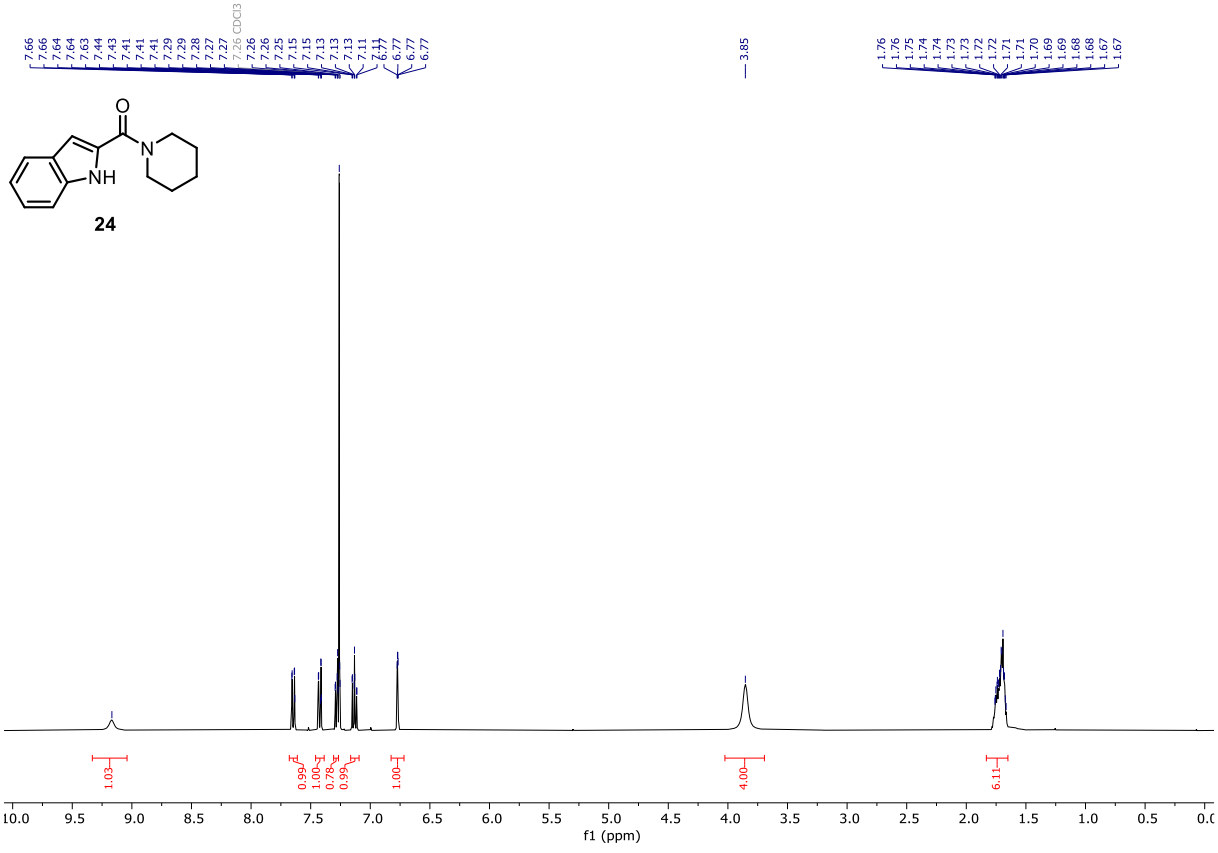


Figure S34: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

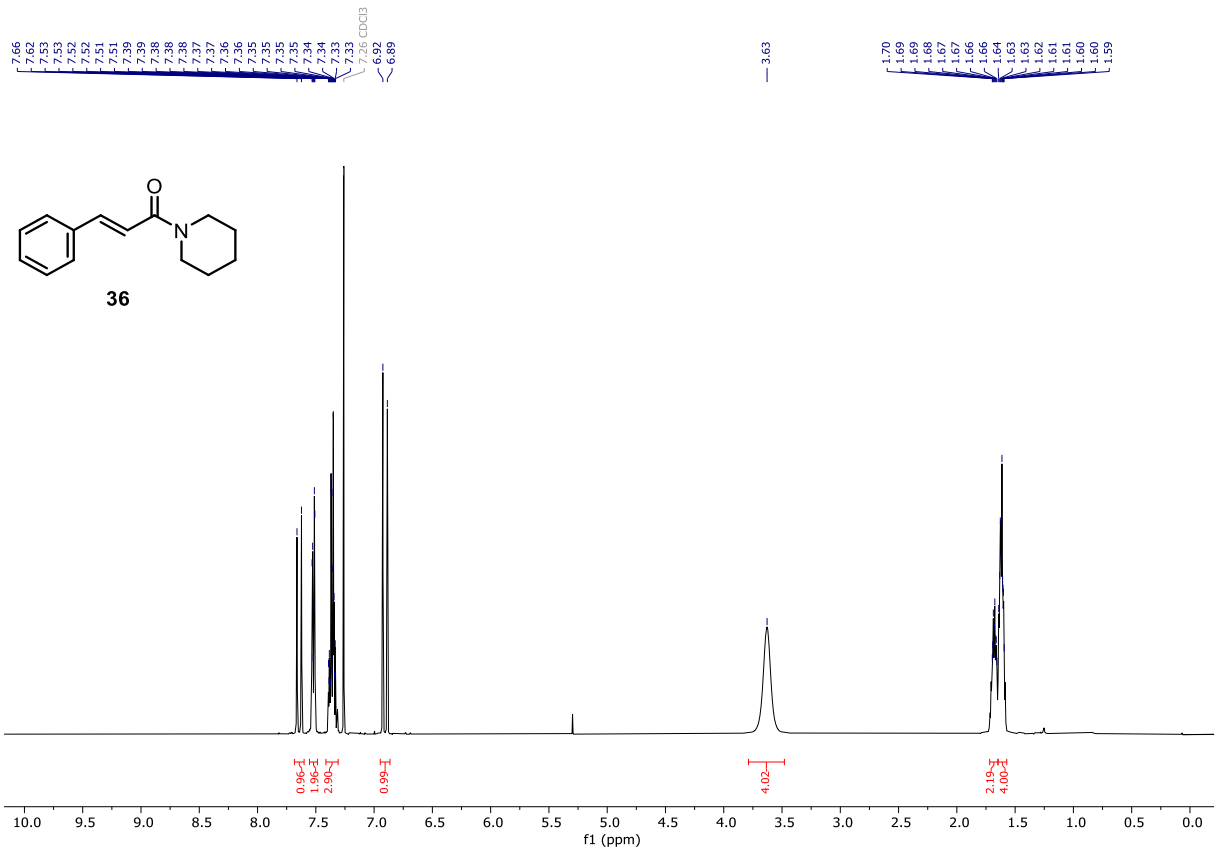


Figure S35: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

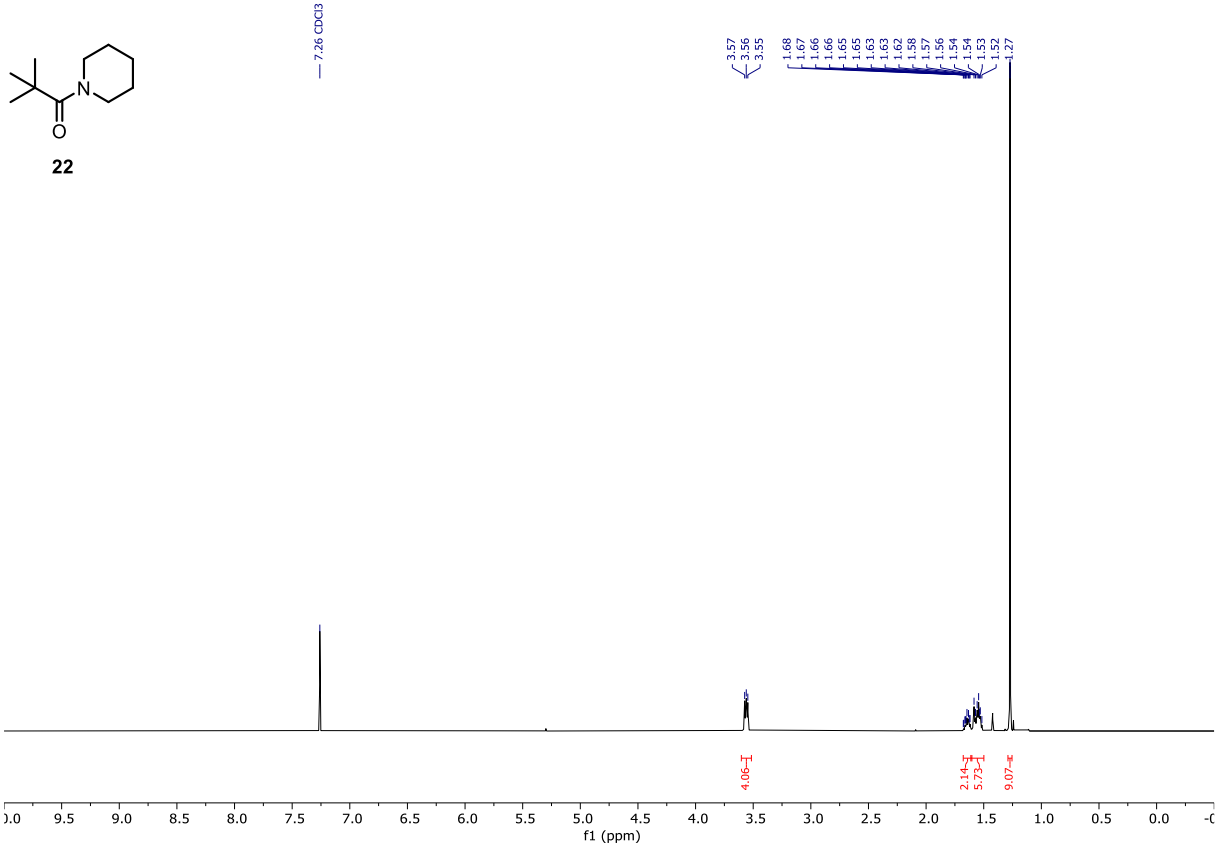


Figure S36: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

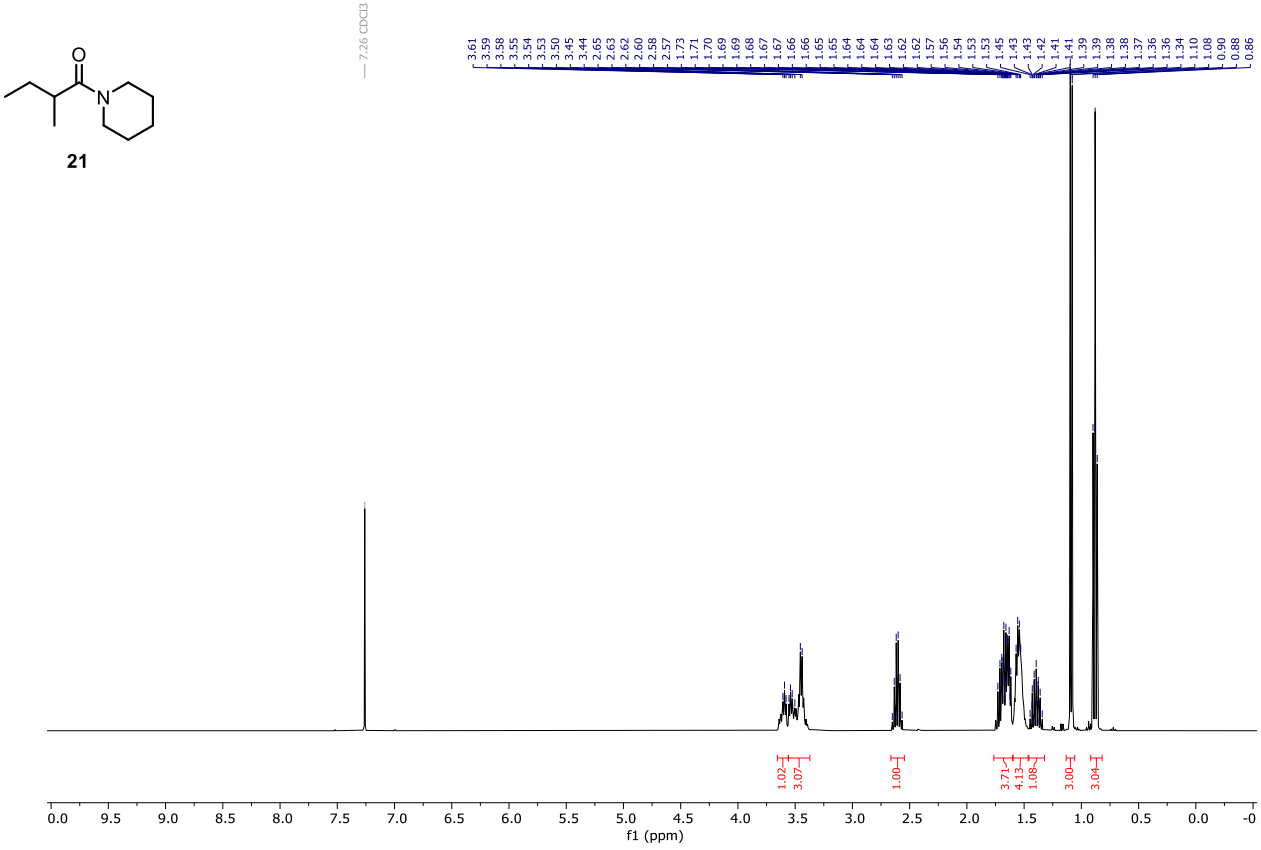


Figure S37: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

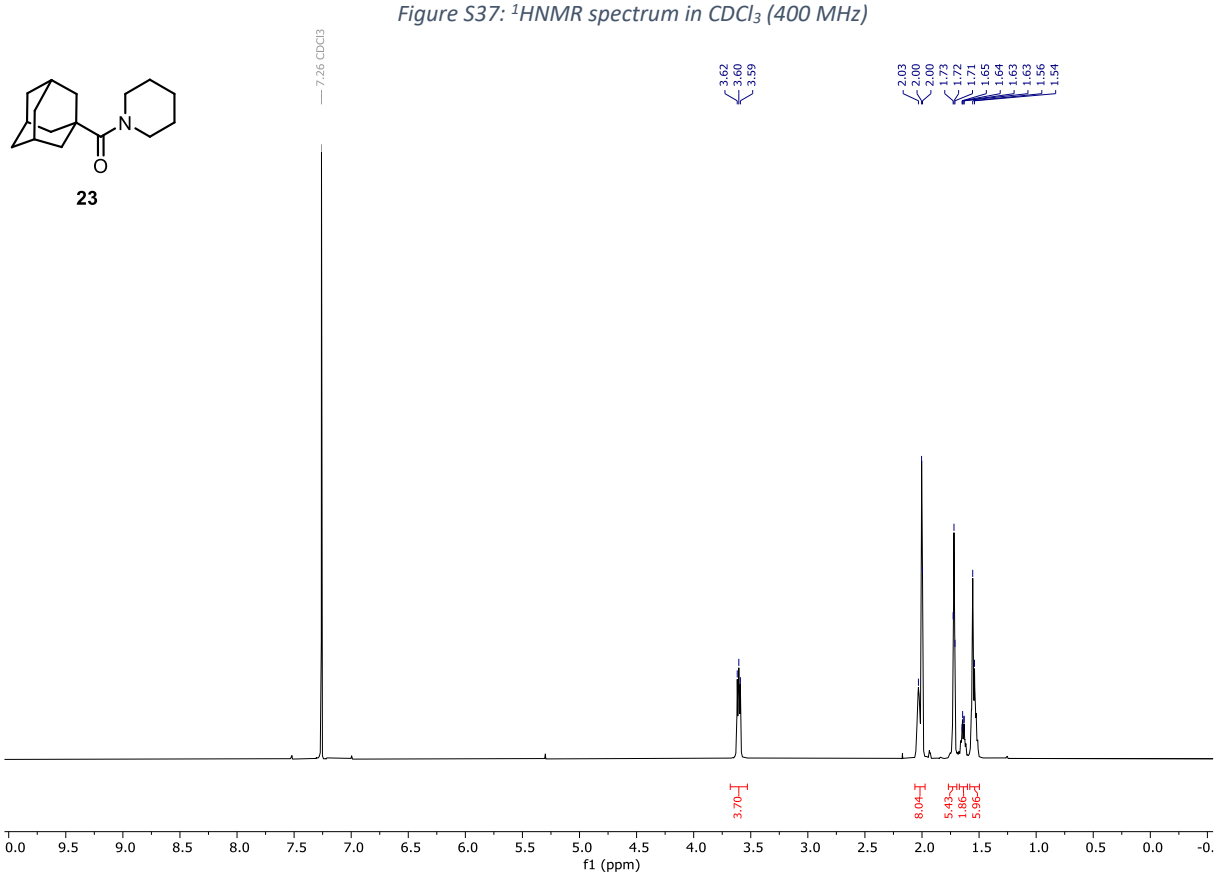


Figure S38: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

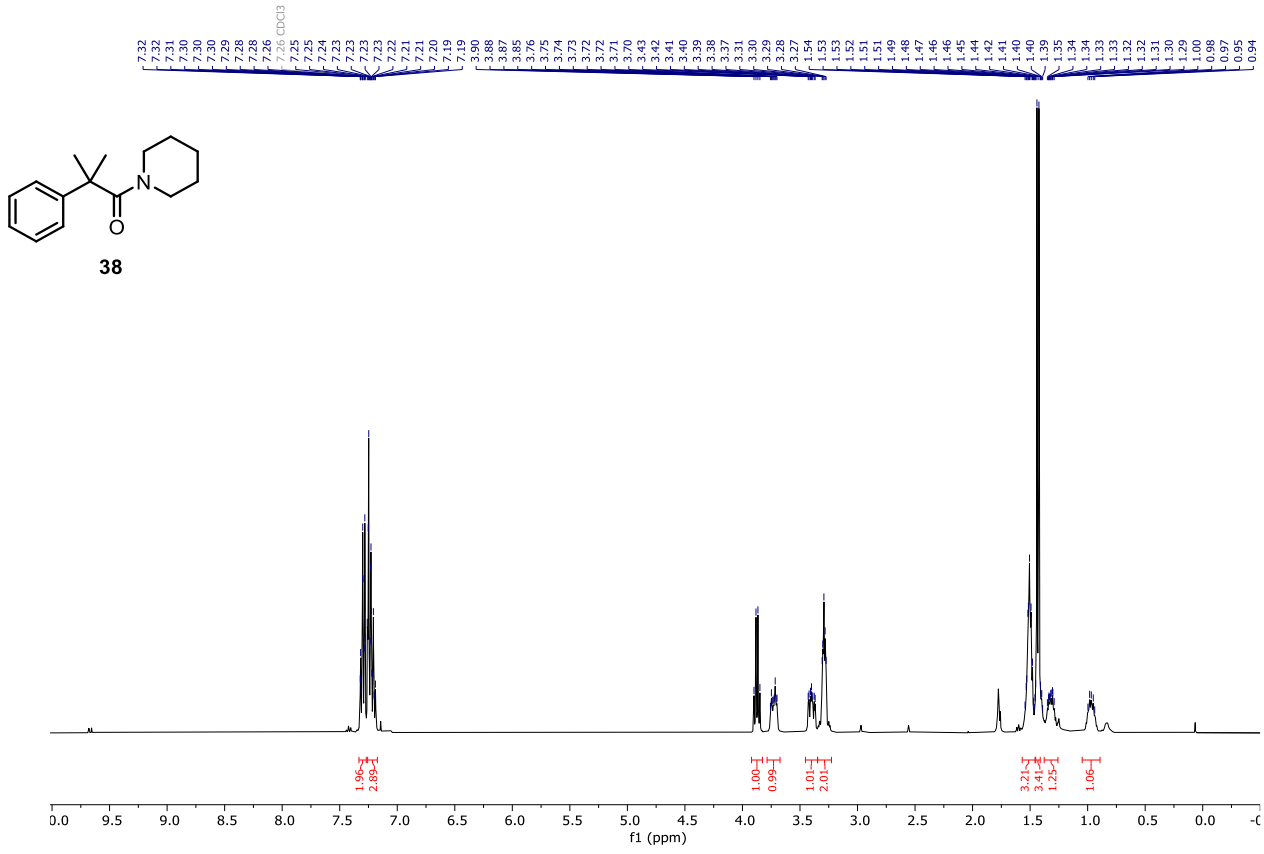


Figure S39: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

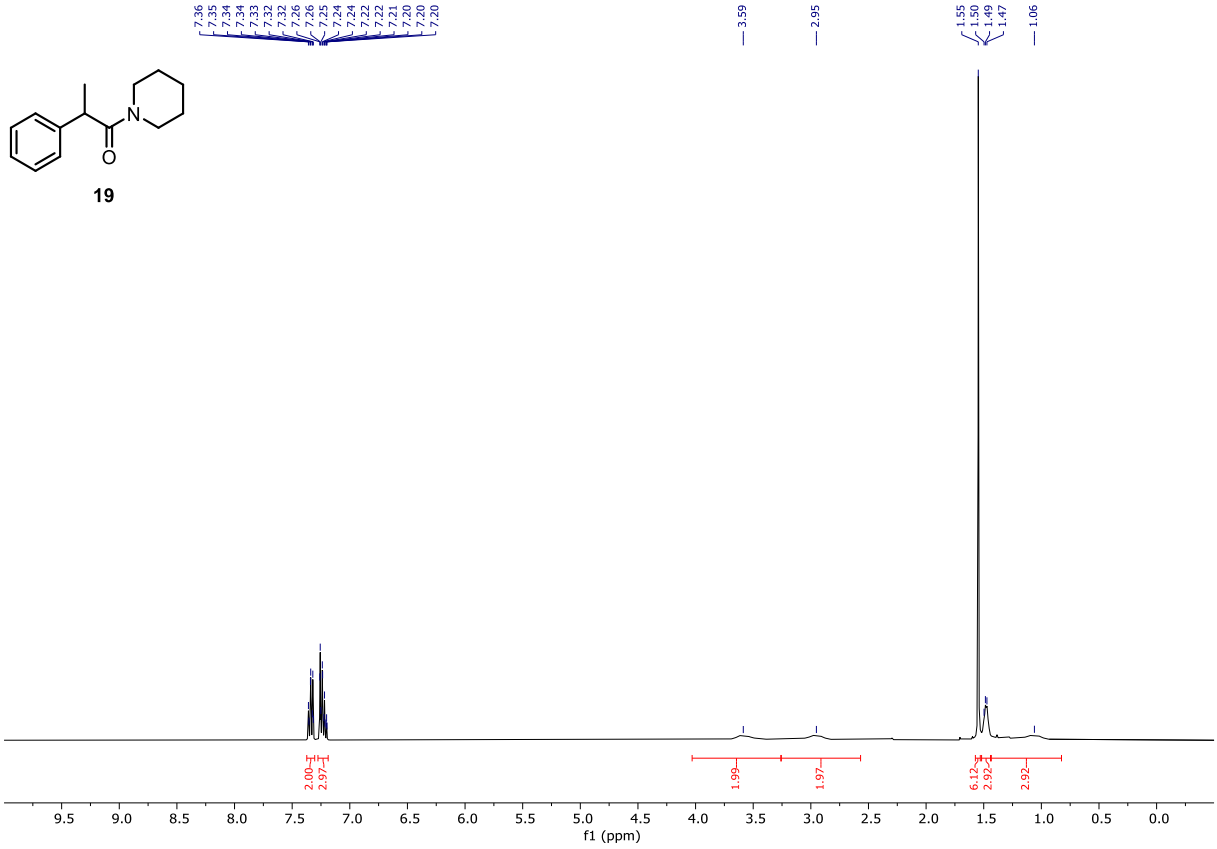


Figure S40: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

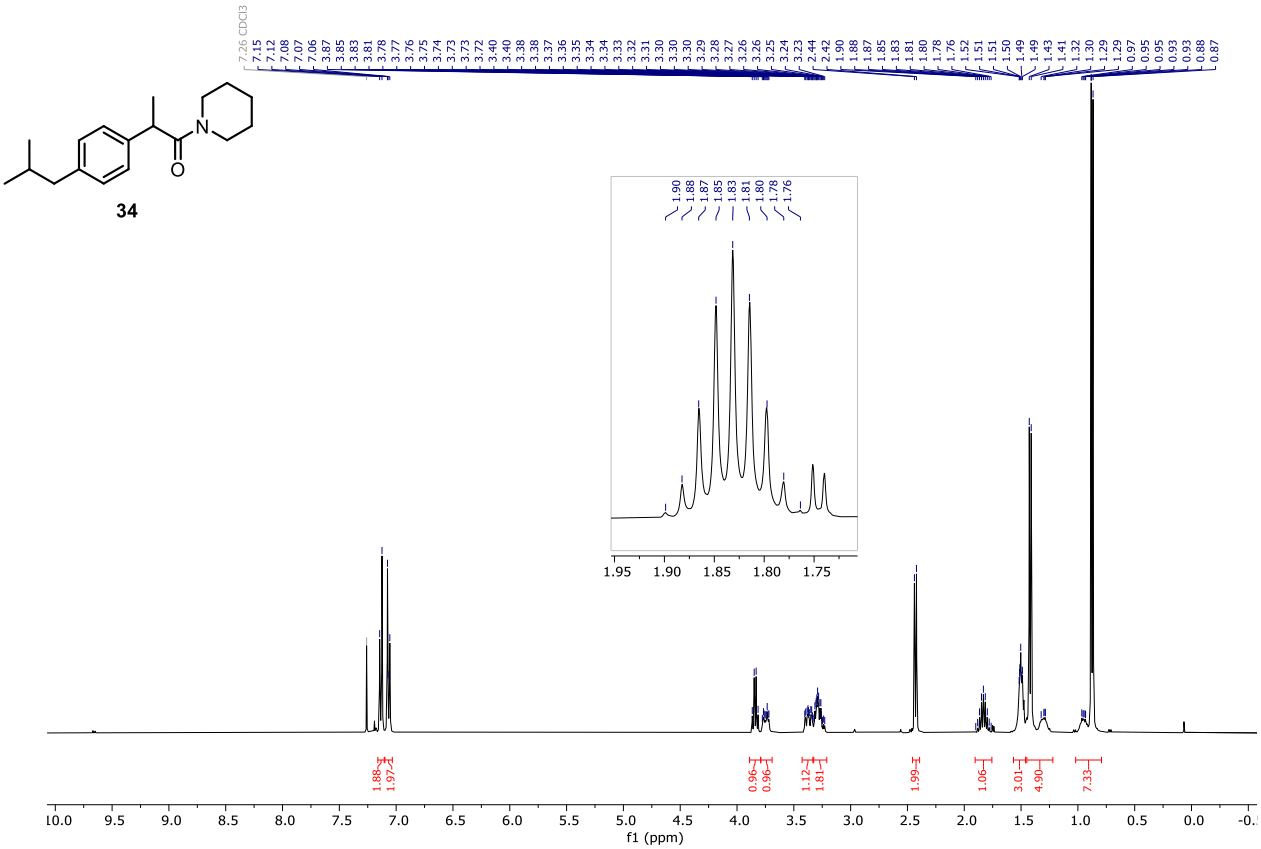


Figure S41: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

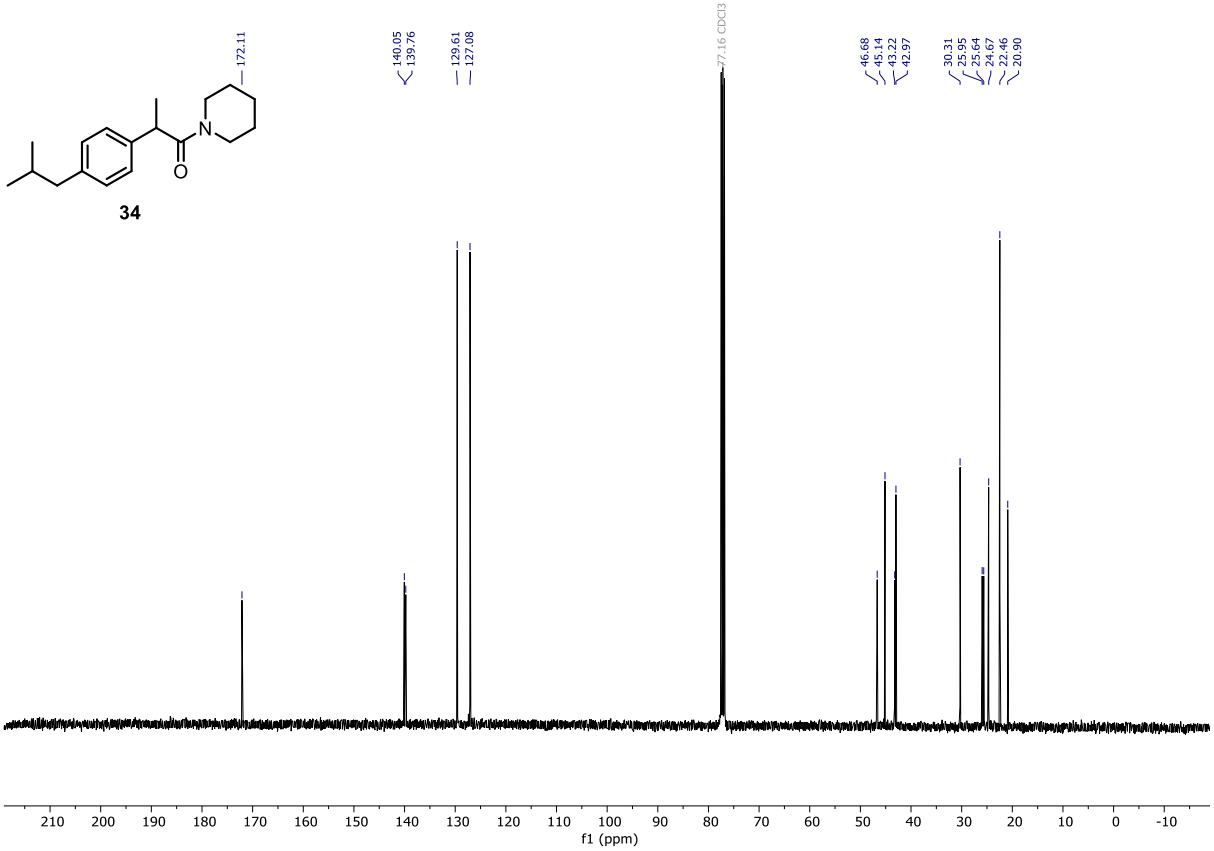


Figure S42: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

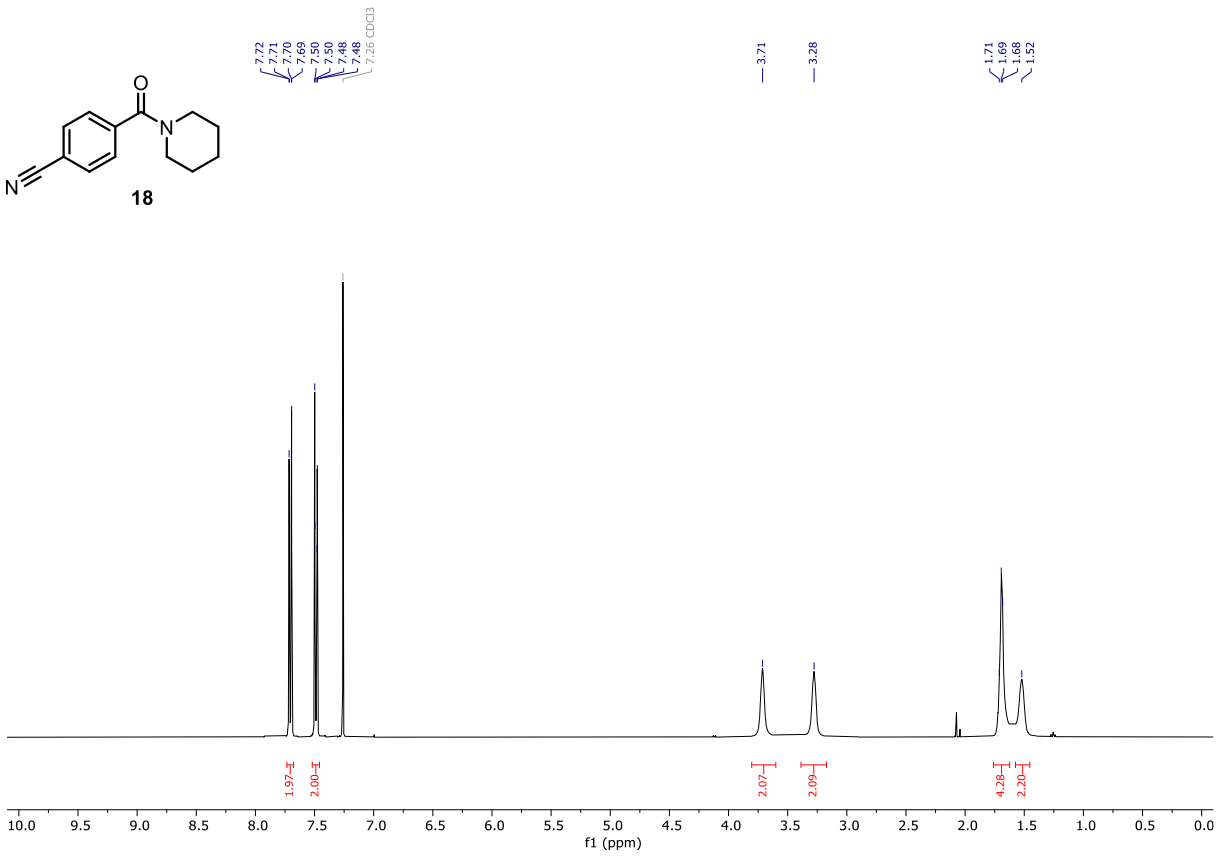


Figure S43: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

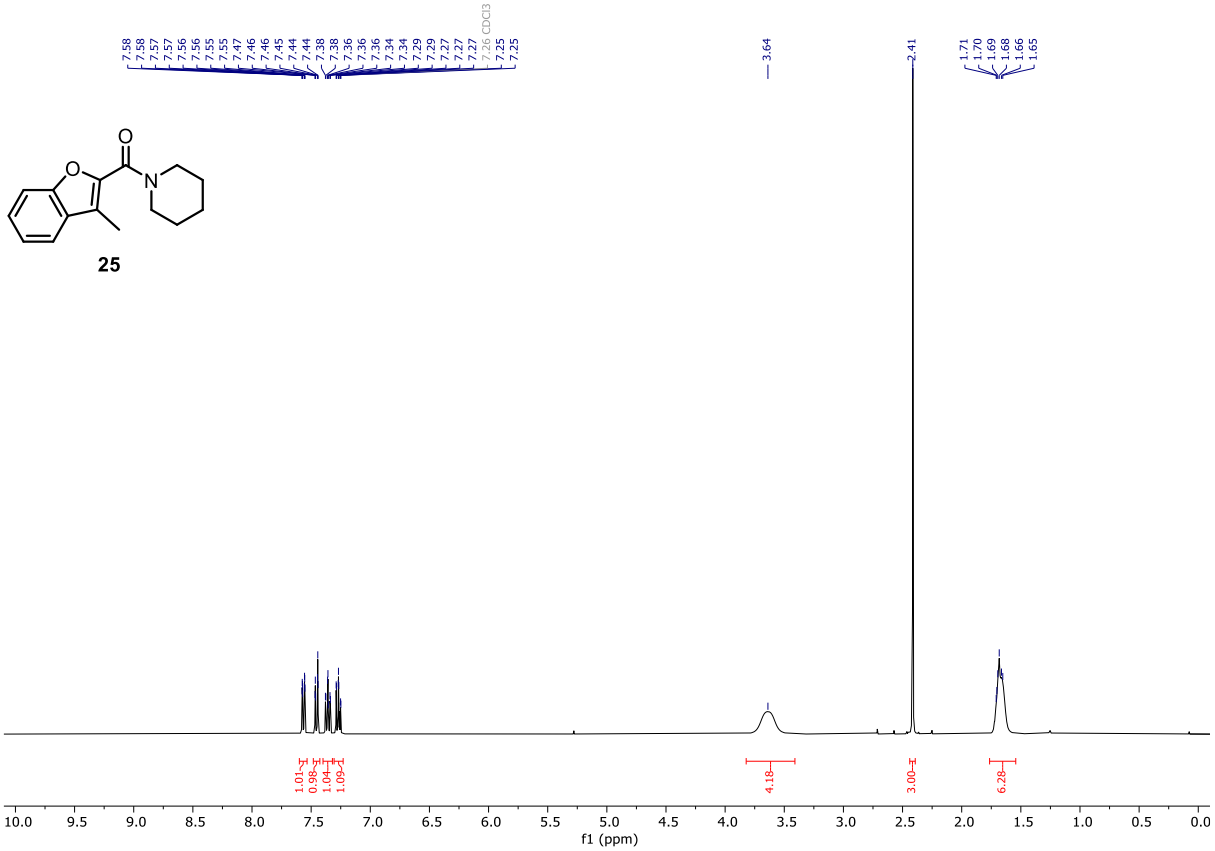


Figure S44: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

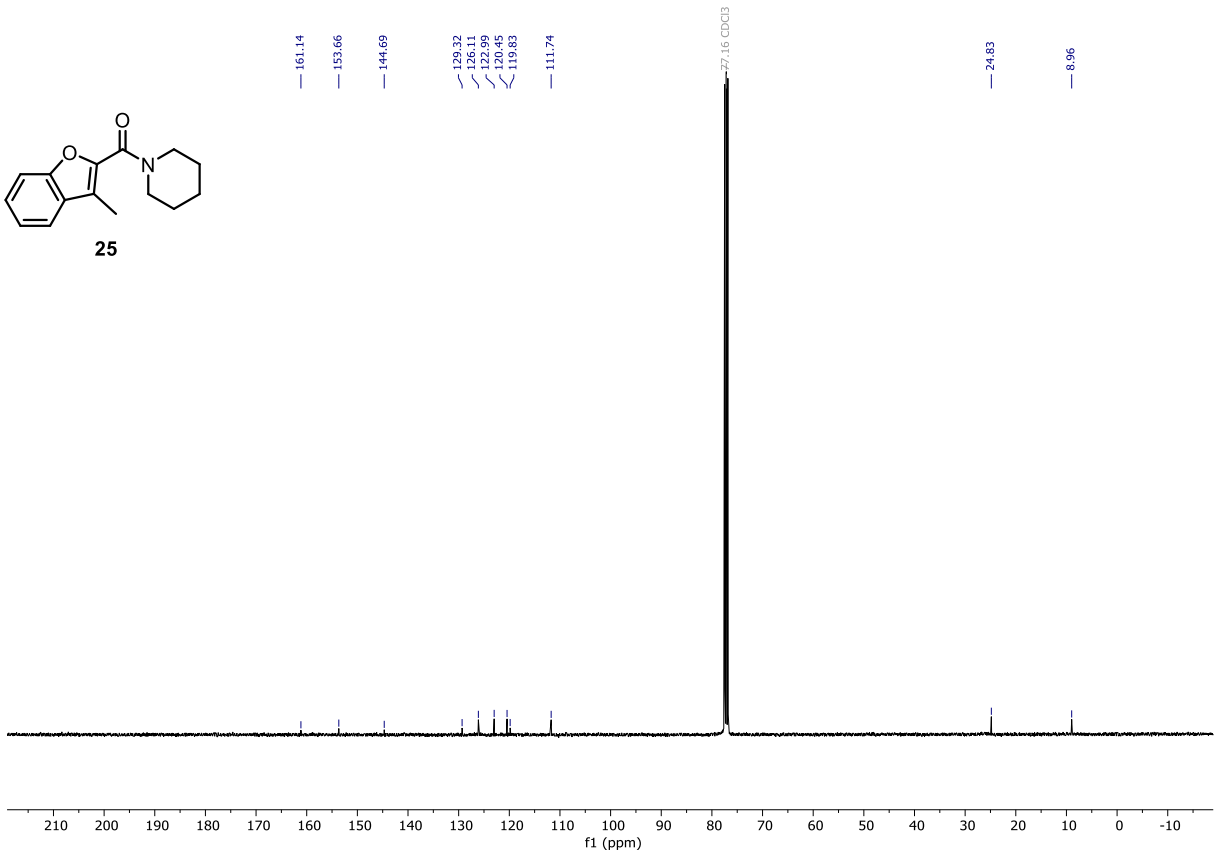


Figure S45: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

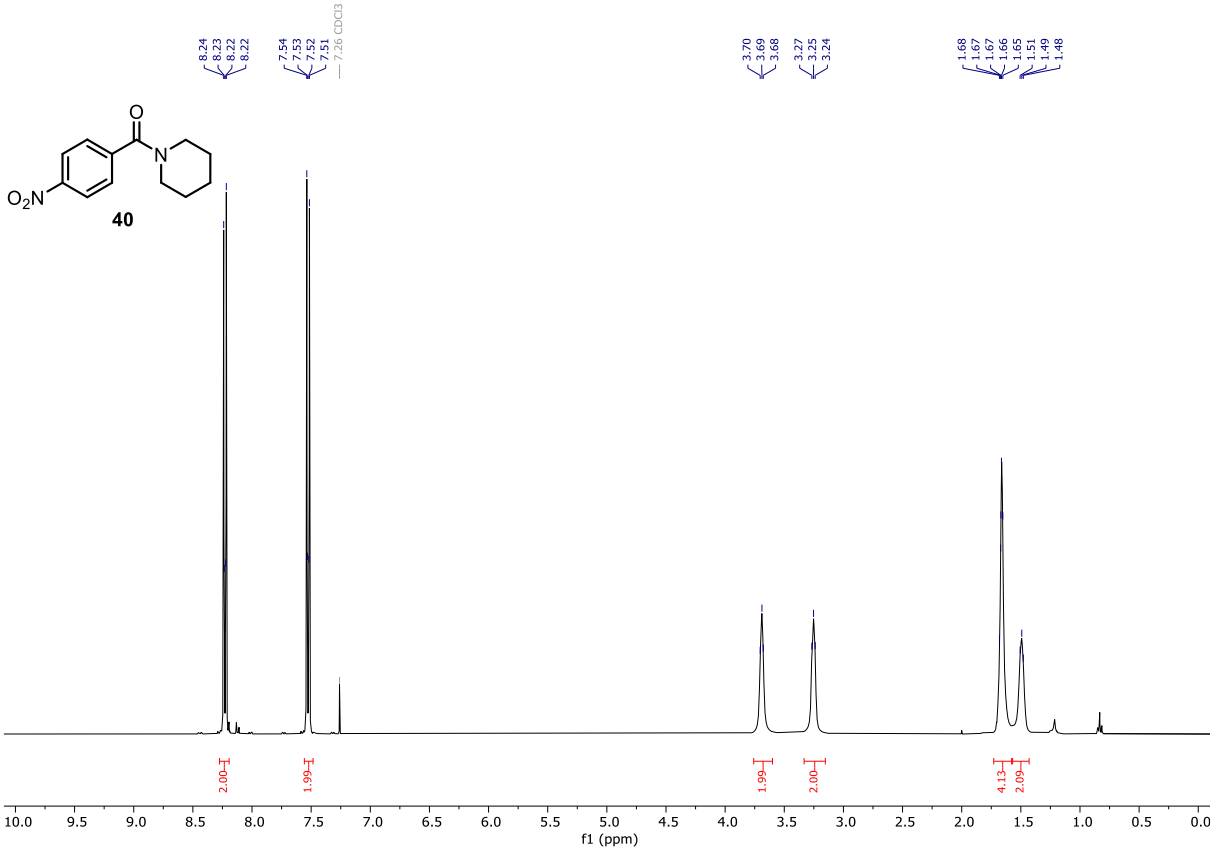


Figure S46: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

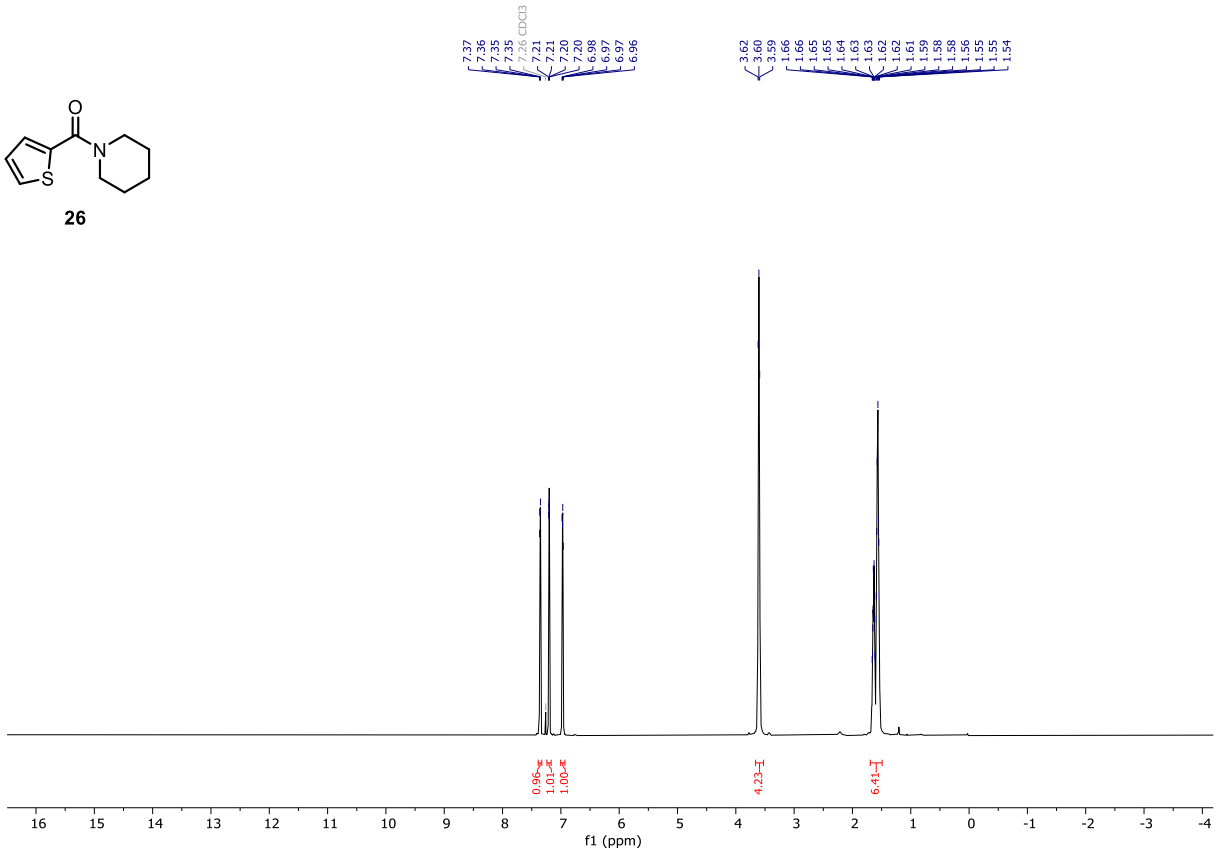


Figure S47: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

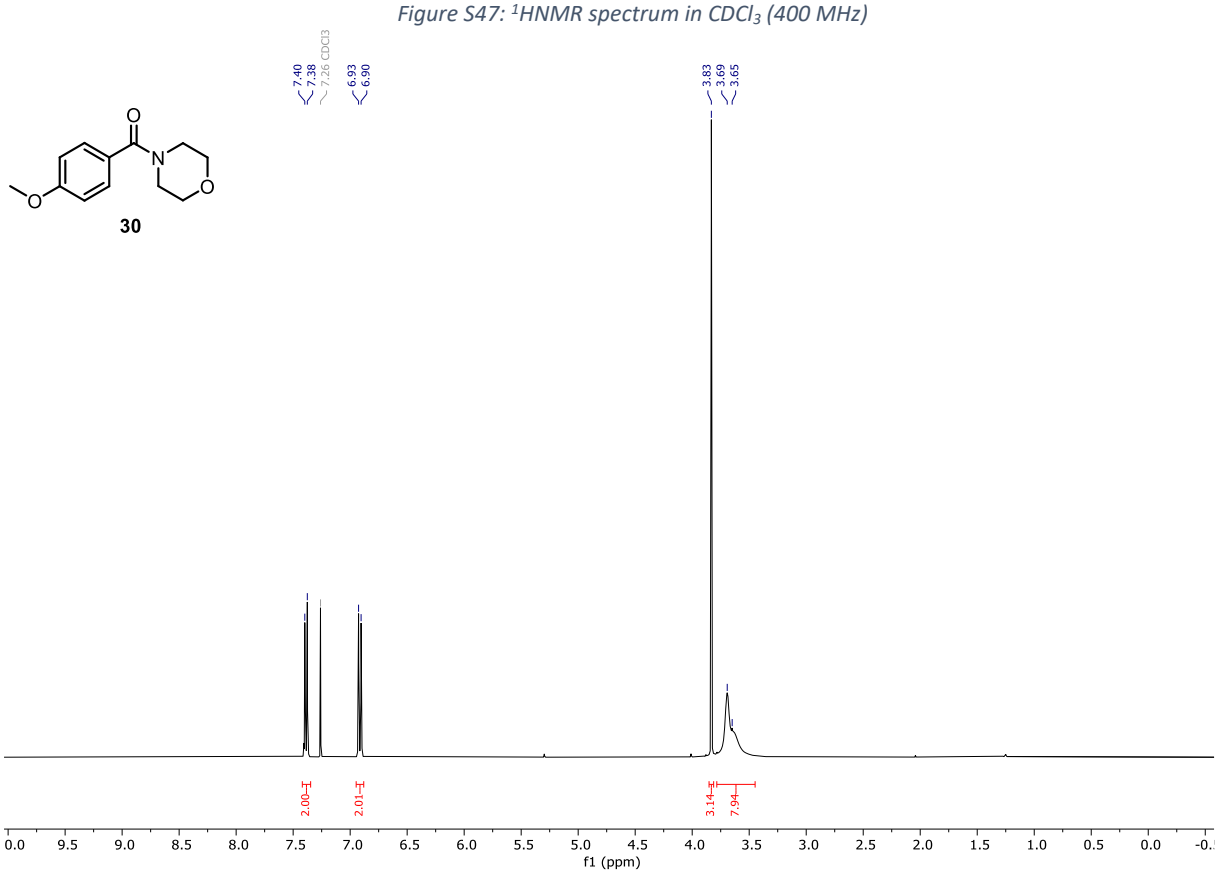


Figure S48: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

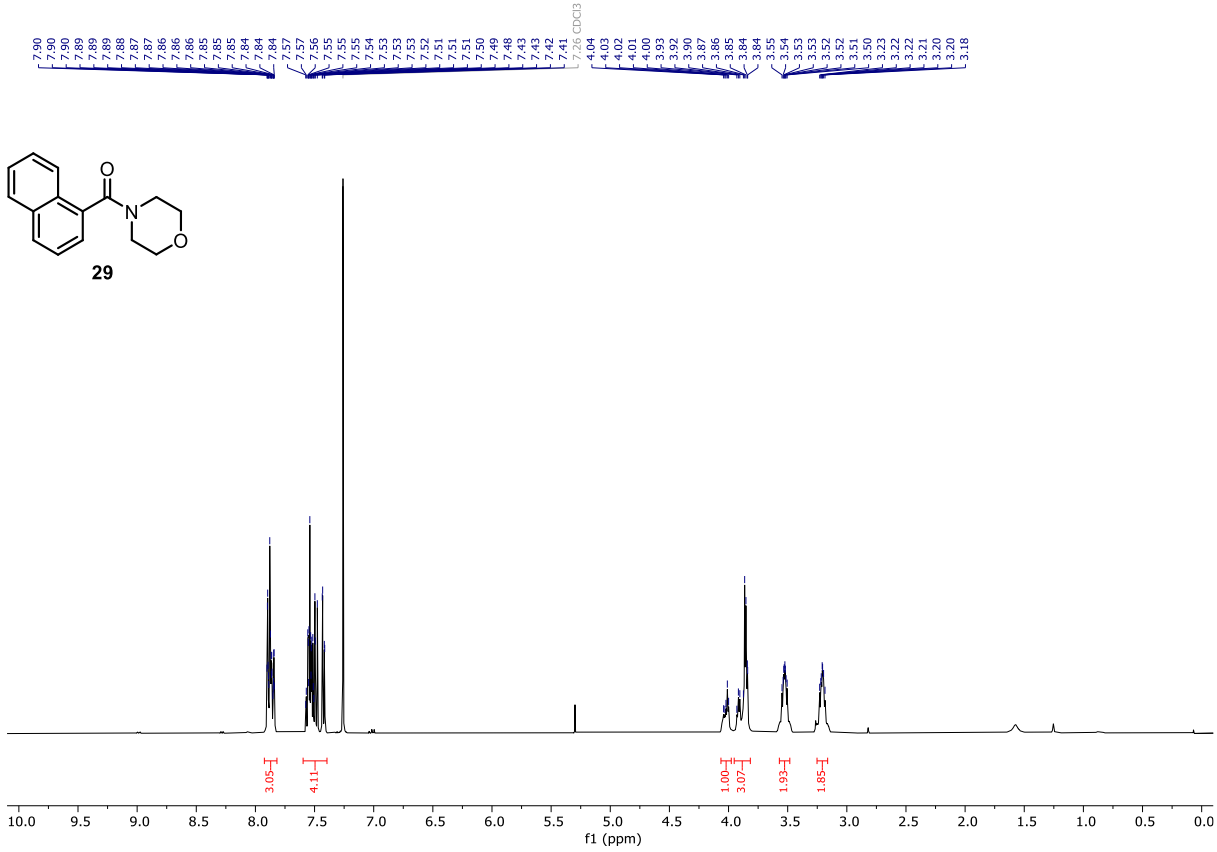


Figure S49: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

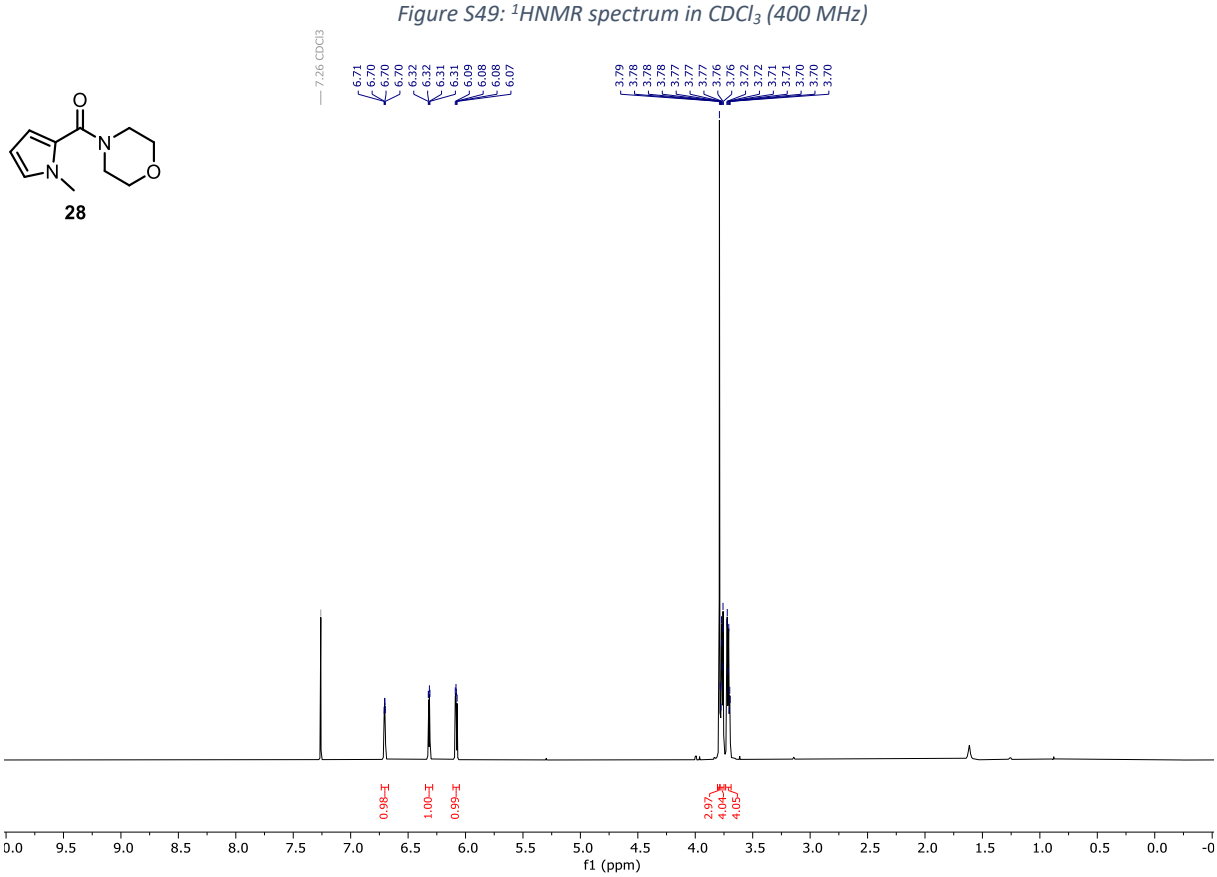


Figure S50: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

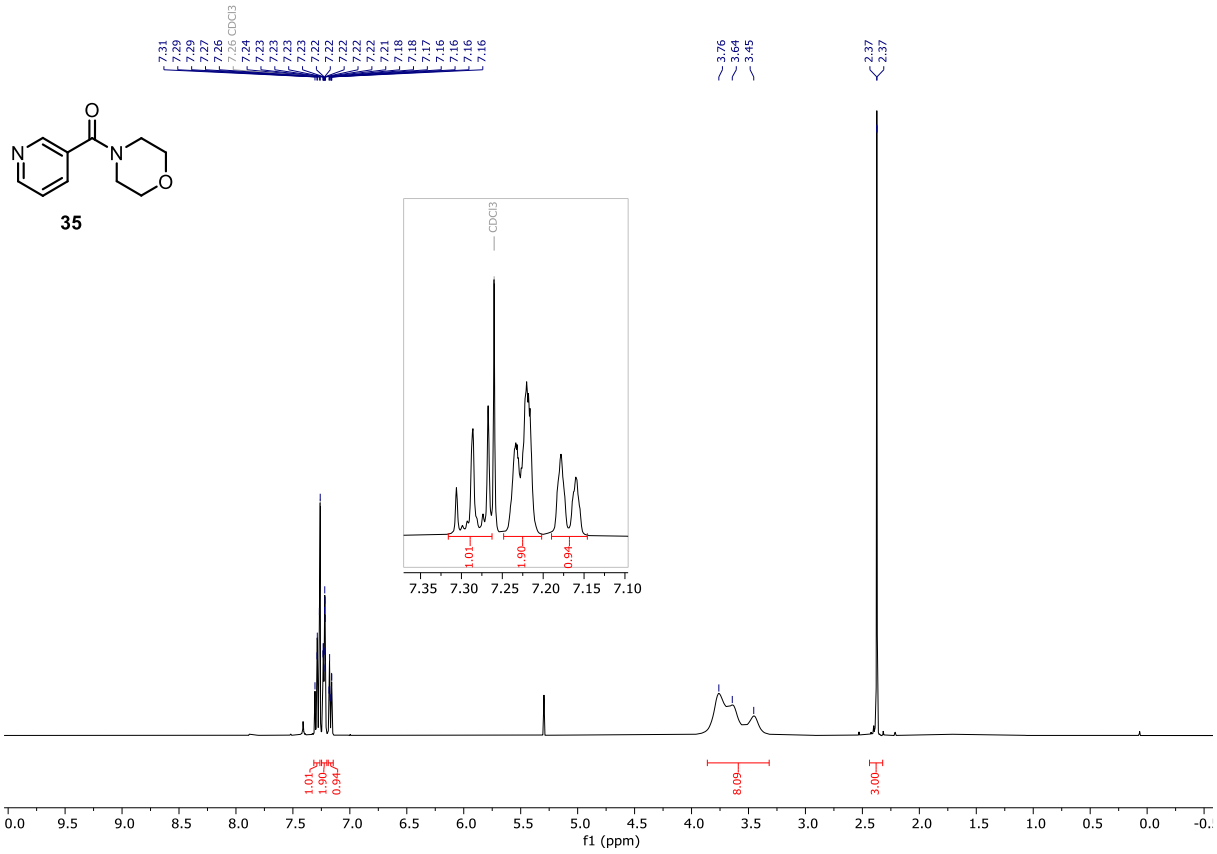


Figure S51: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

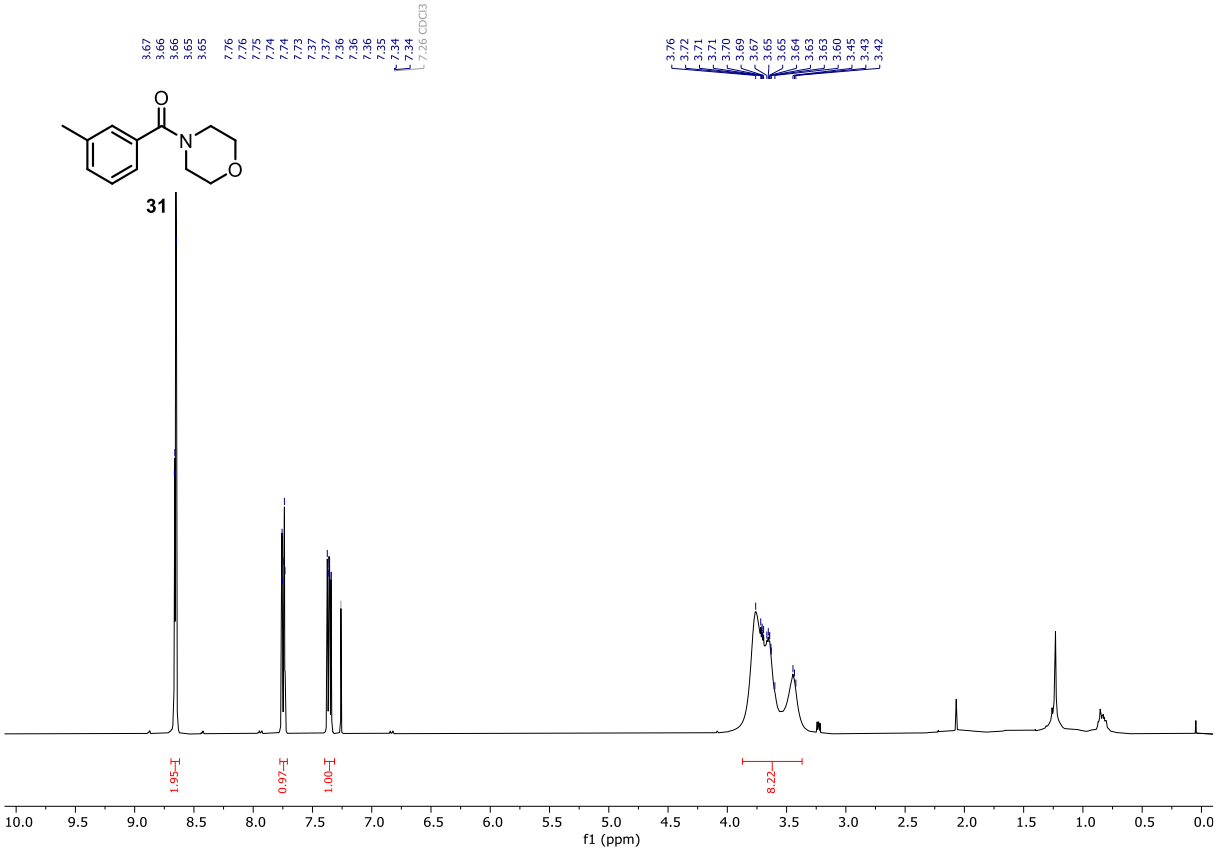


Figure S52: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

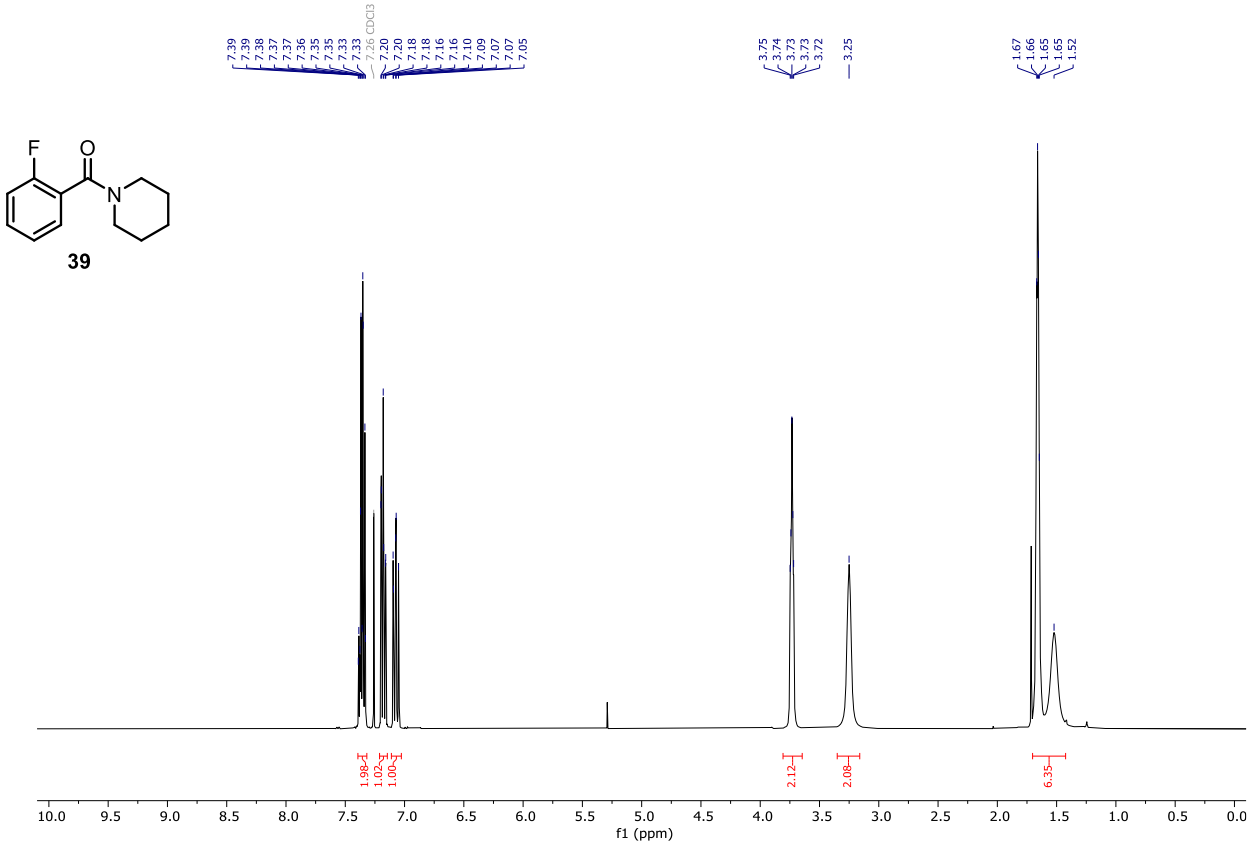


Figure S53: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

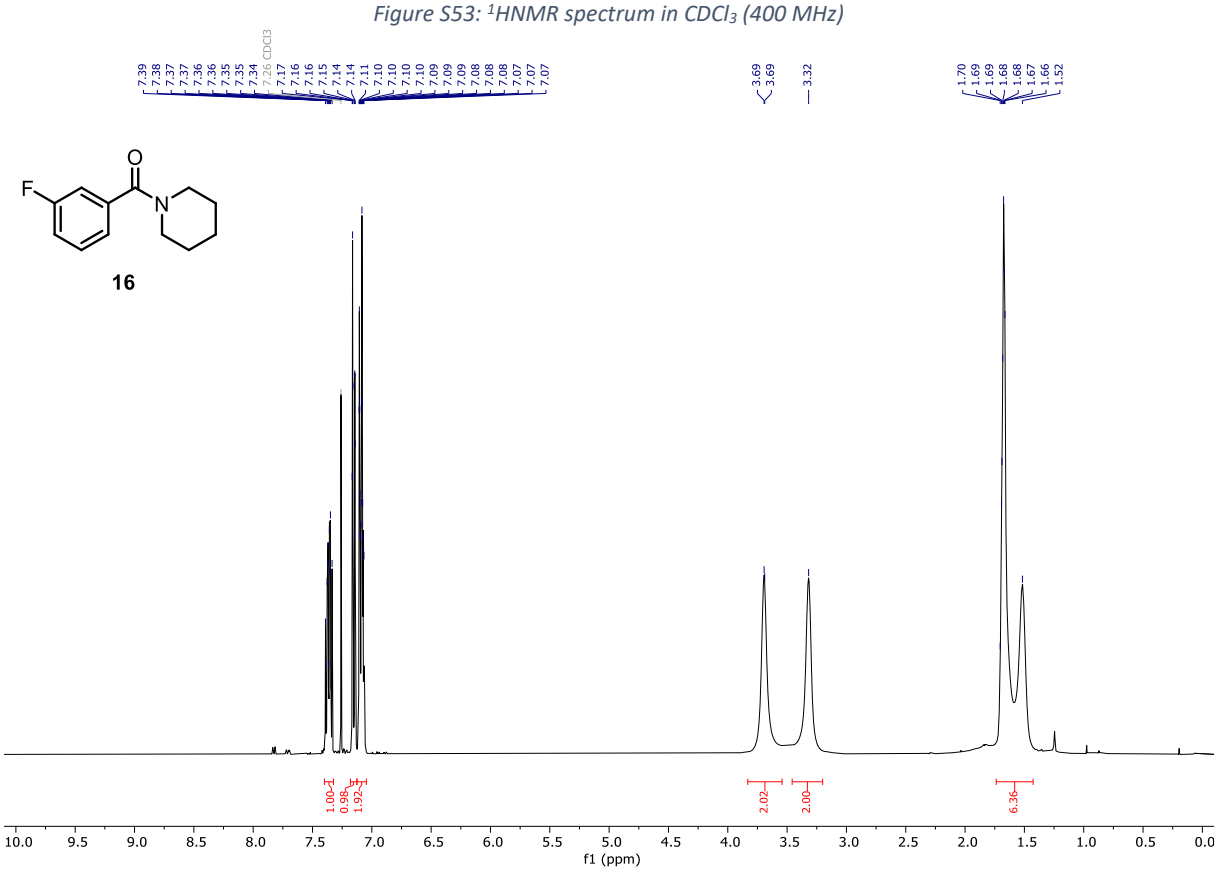


Figure S54: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

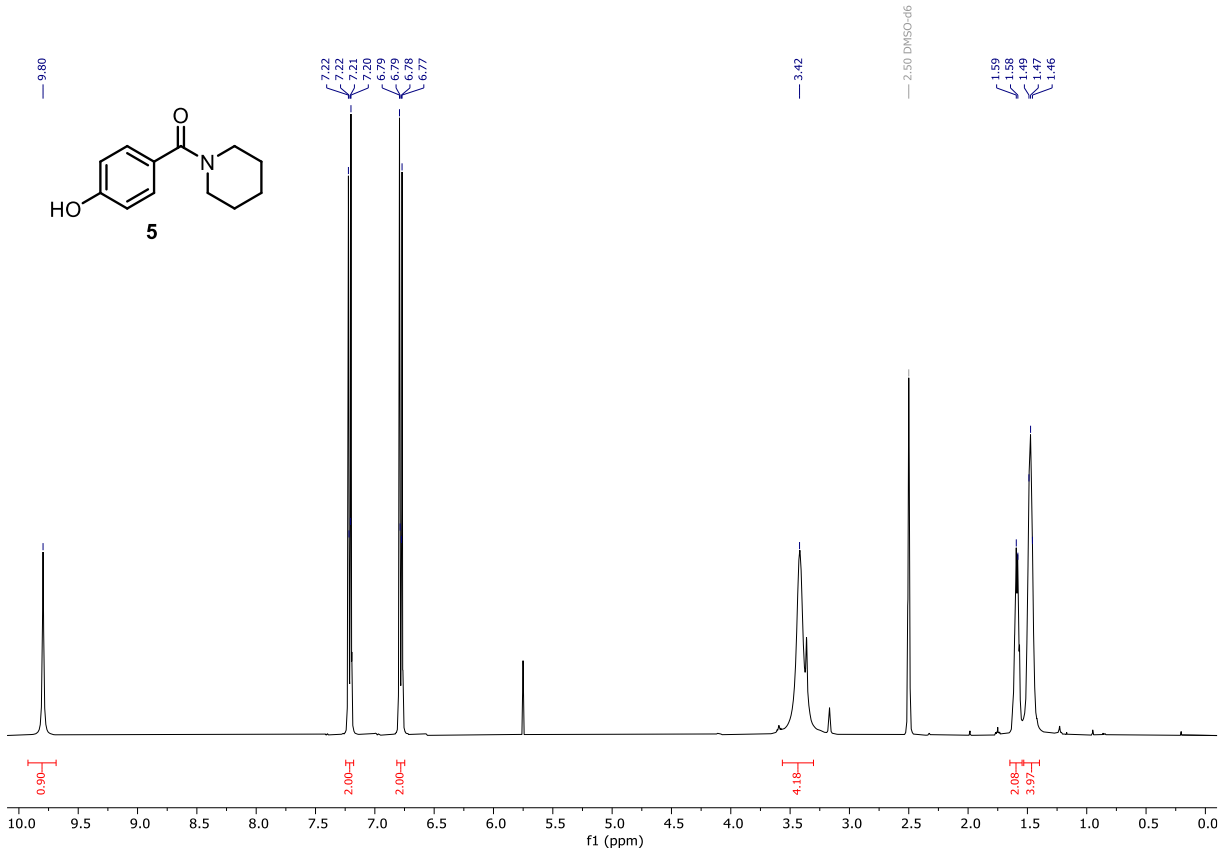


Figure S55: ^{1}HNMR spectrum in DMSO-d_6 (400 MHz)

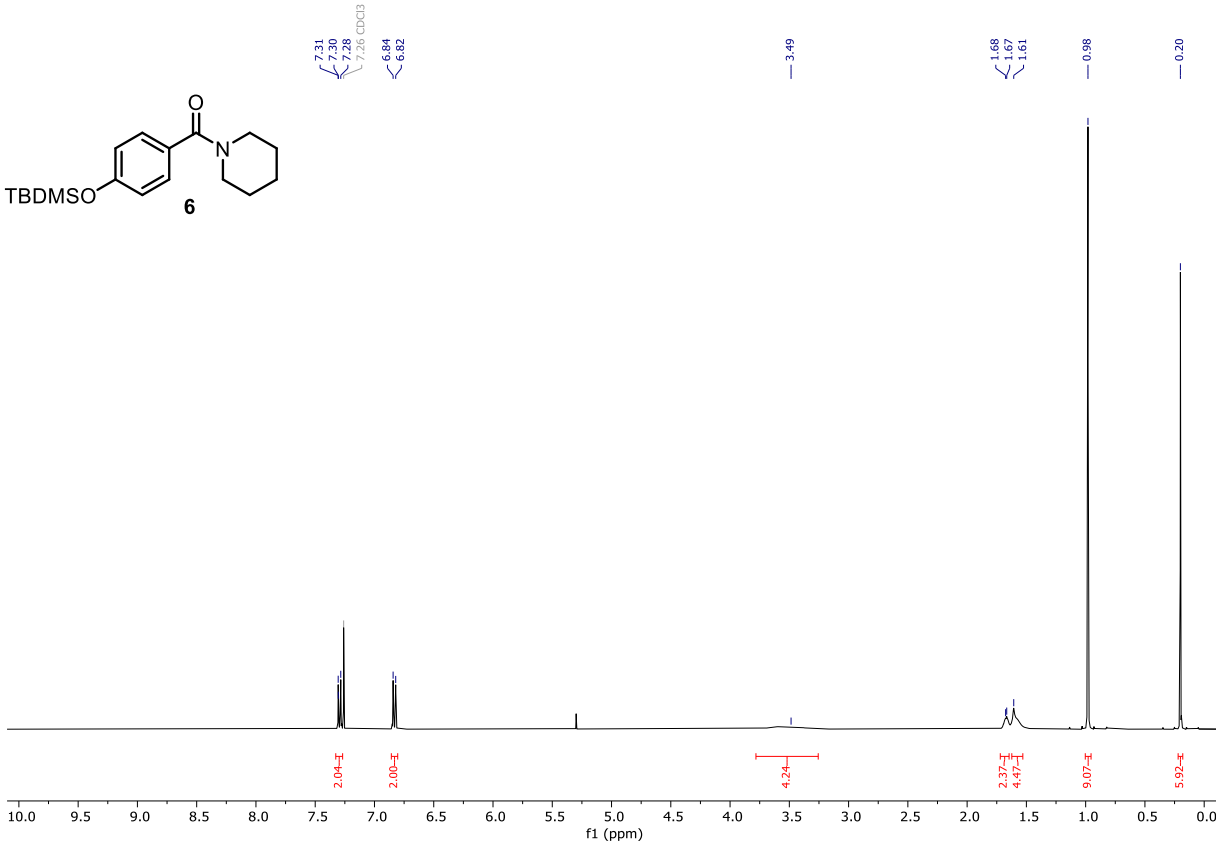


Figure S56:

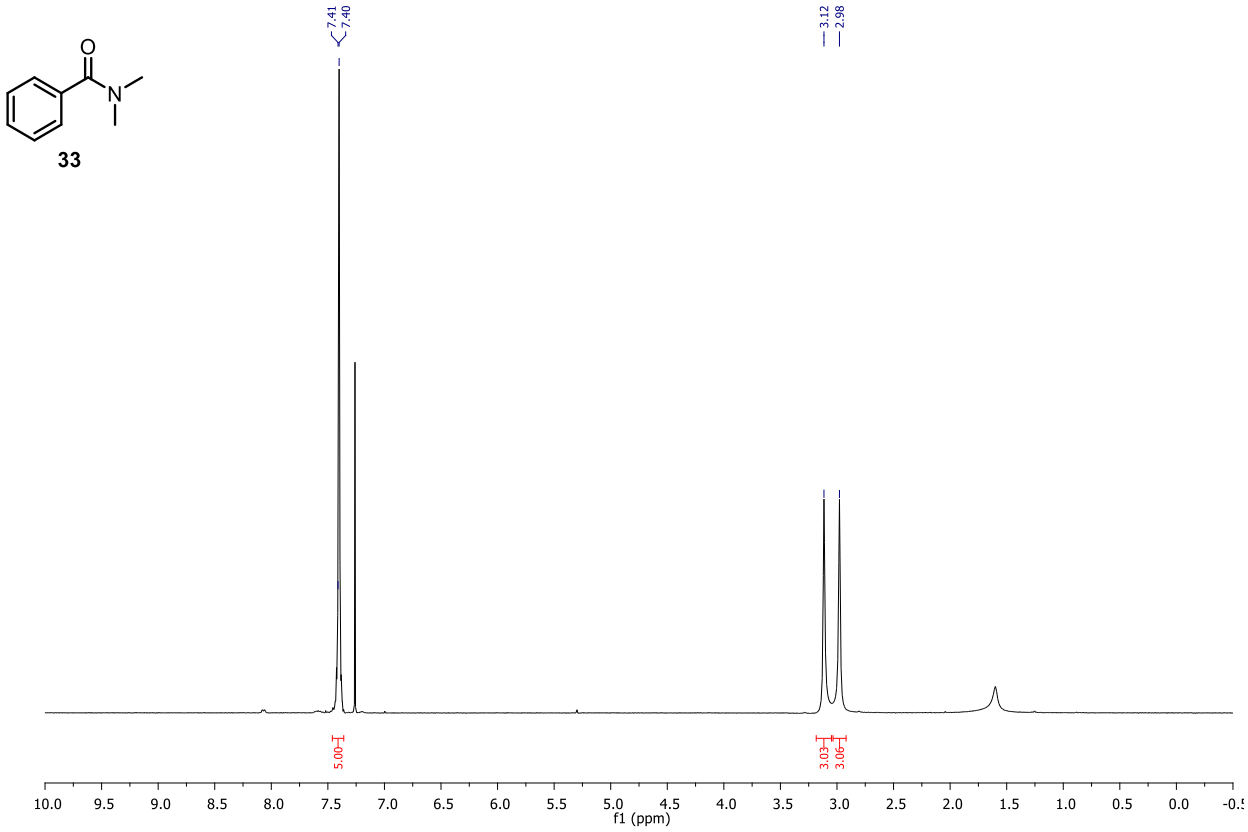


Figure S57: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

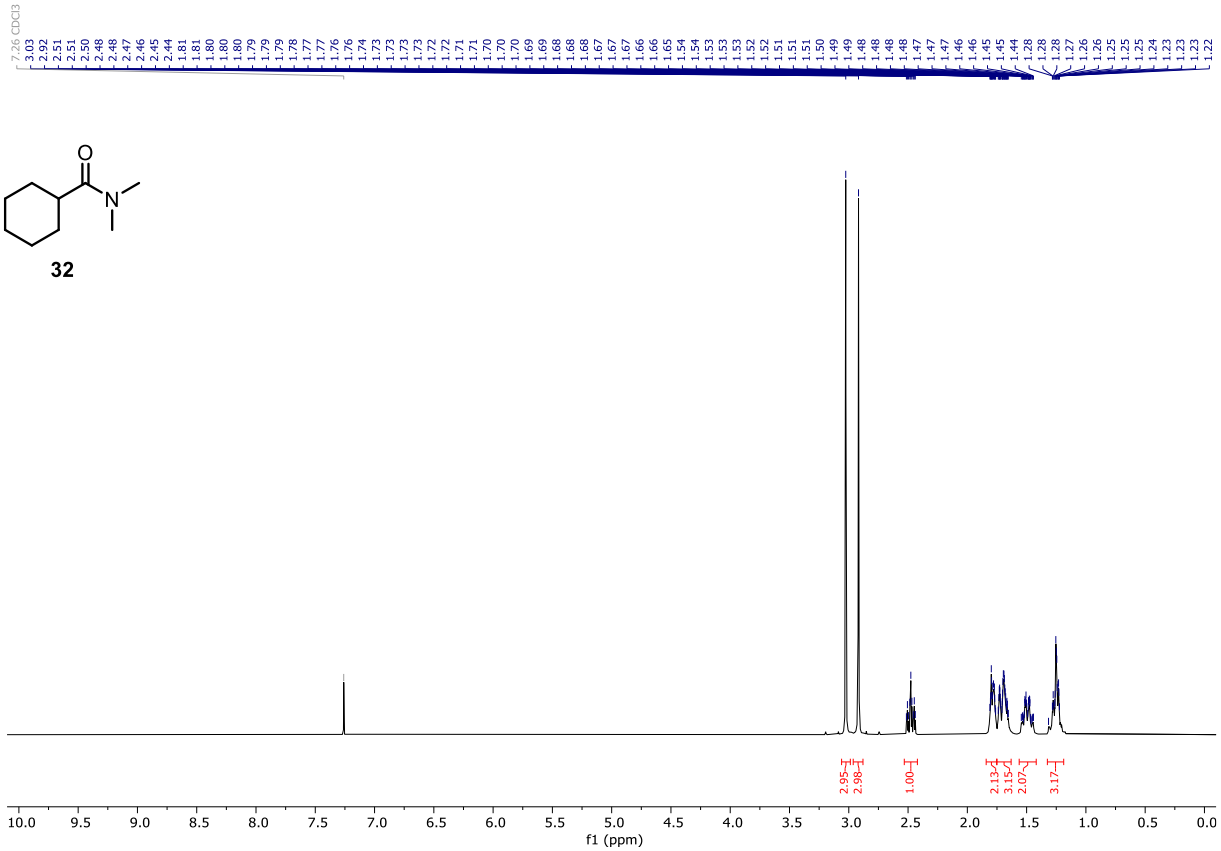


Figure S58: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

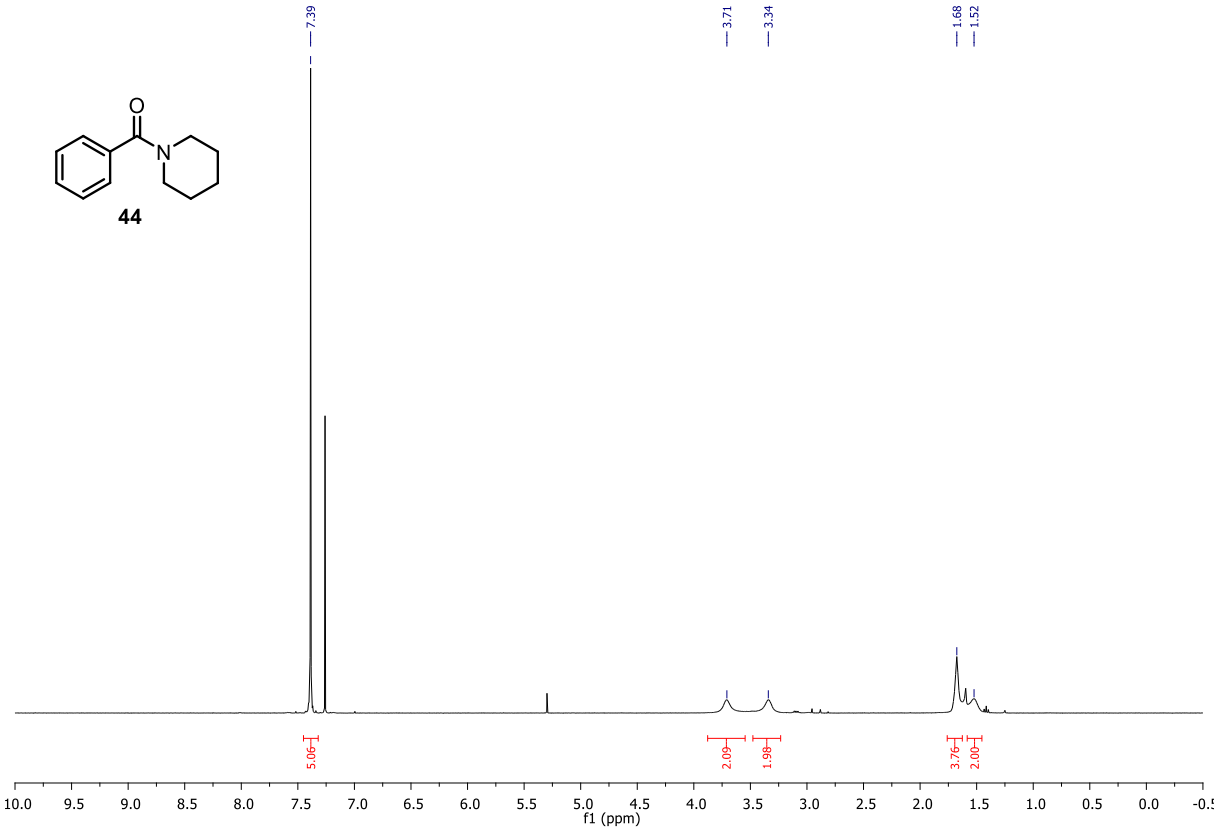


Figure S59: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

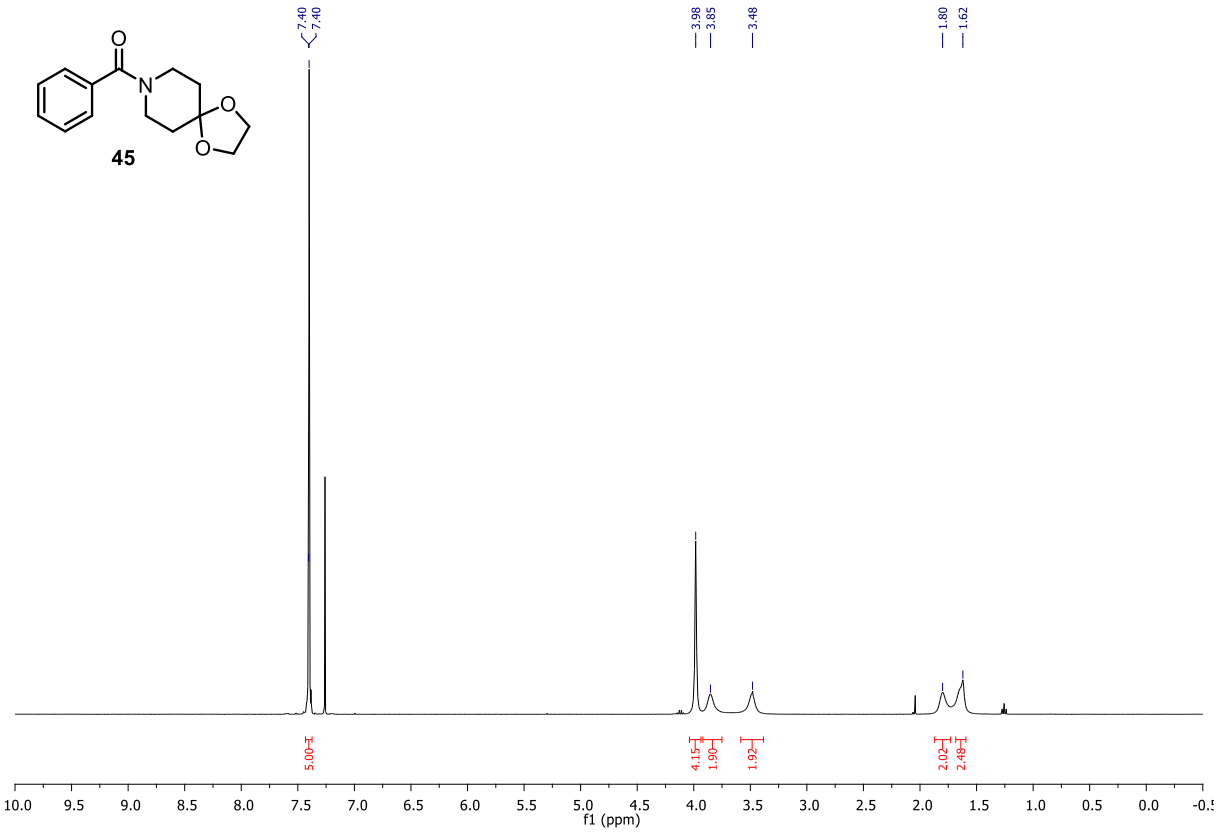


Figure S60: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

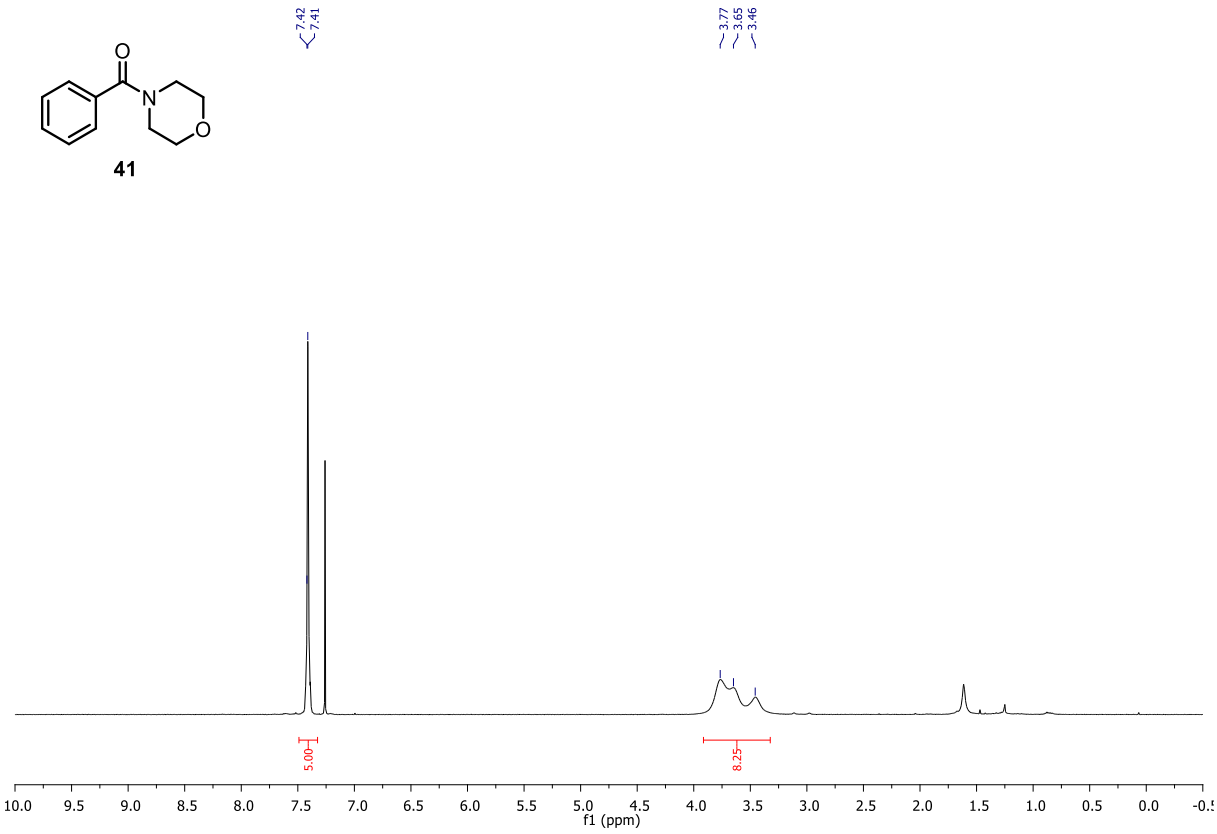


Figure S61: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

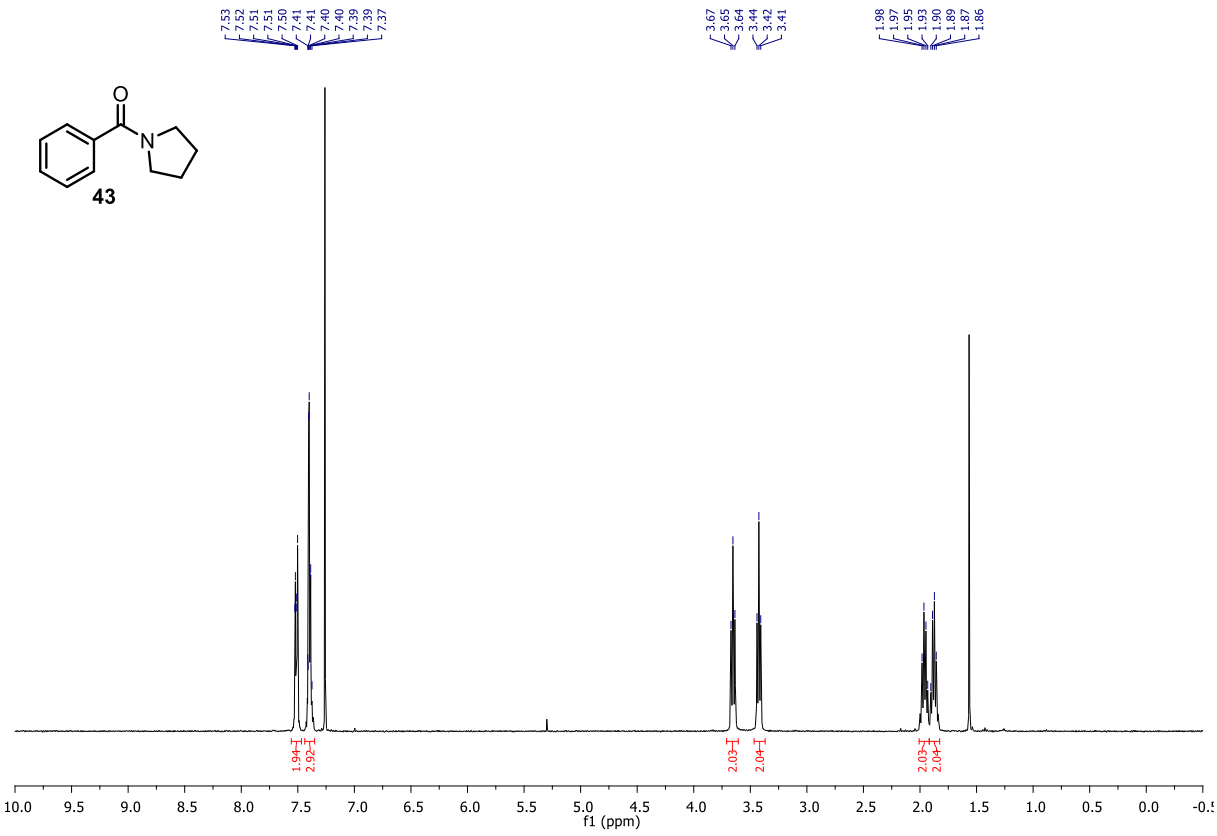


Figure S62: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

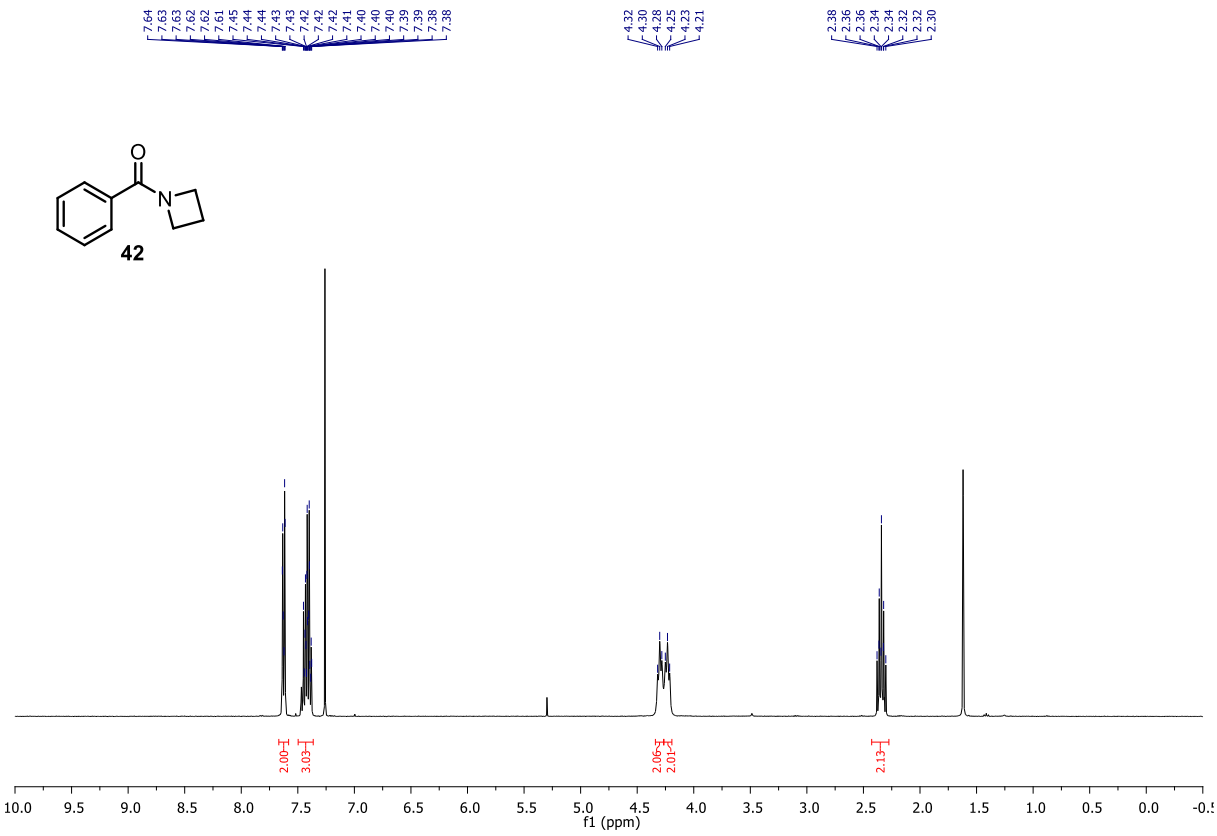


Figure S63: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

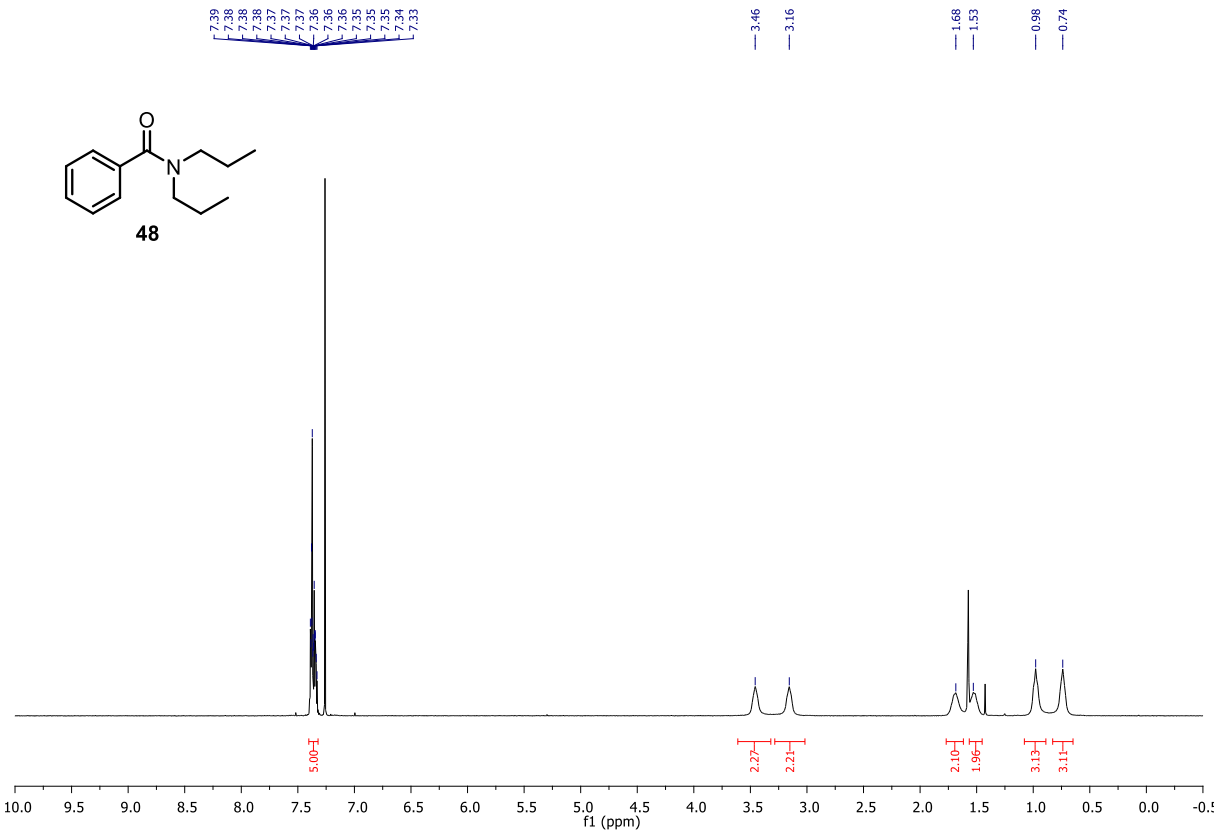


Figure S64: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

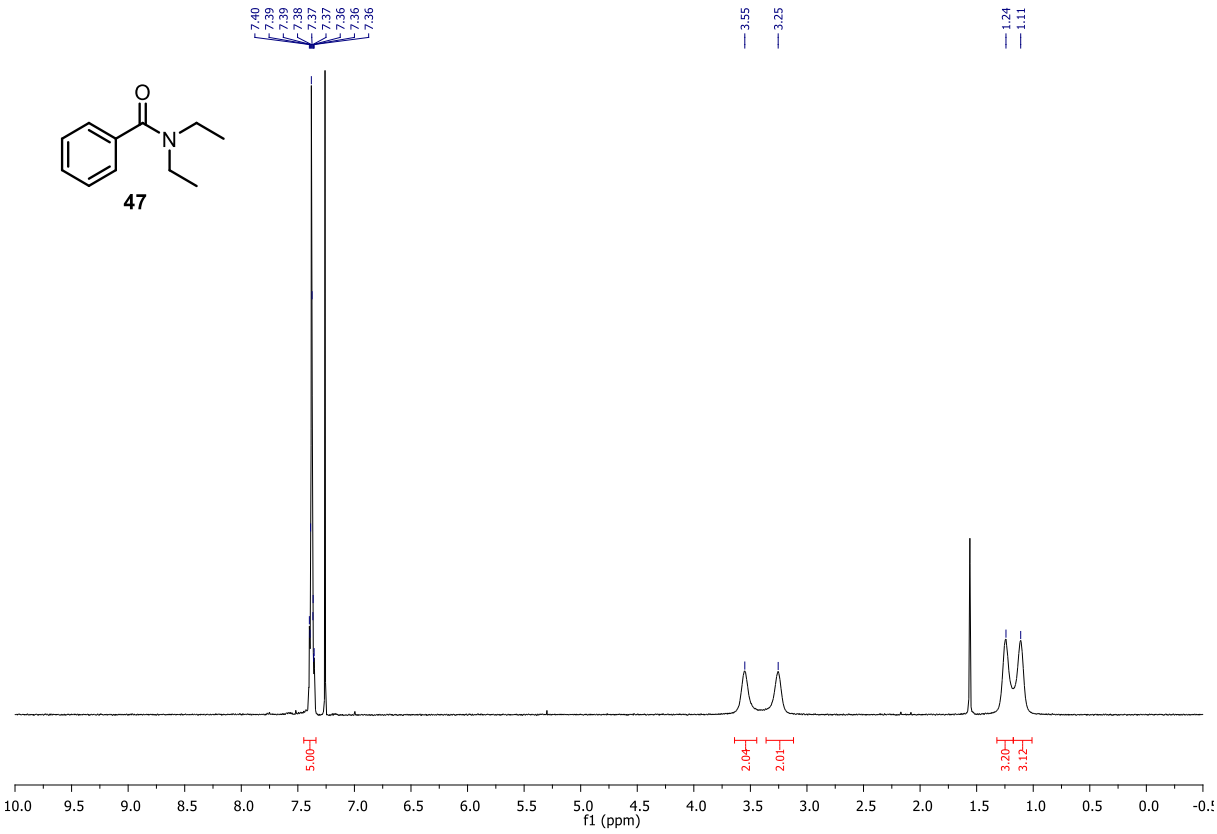


Figure S65: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

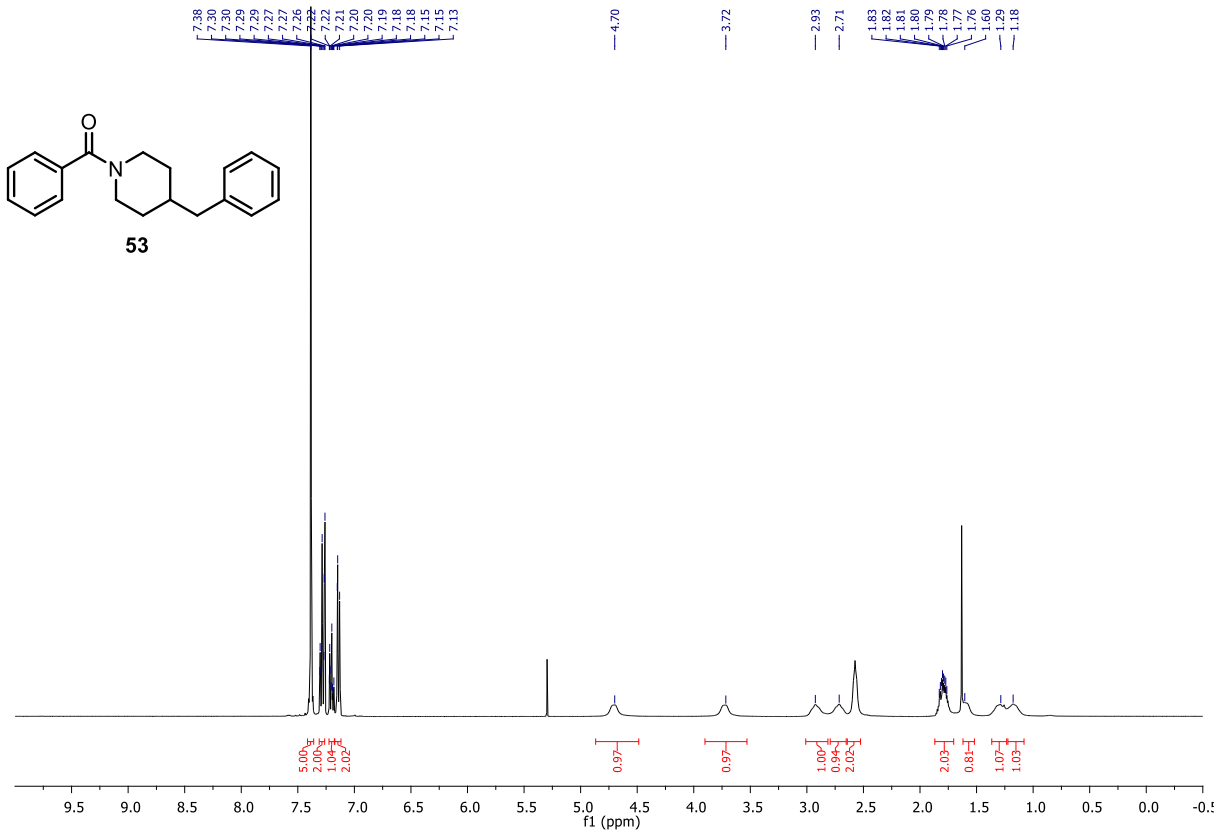


Figure S66: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

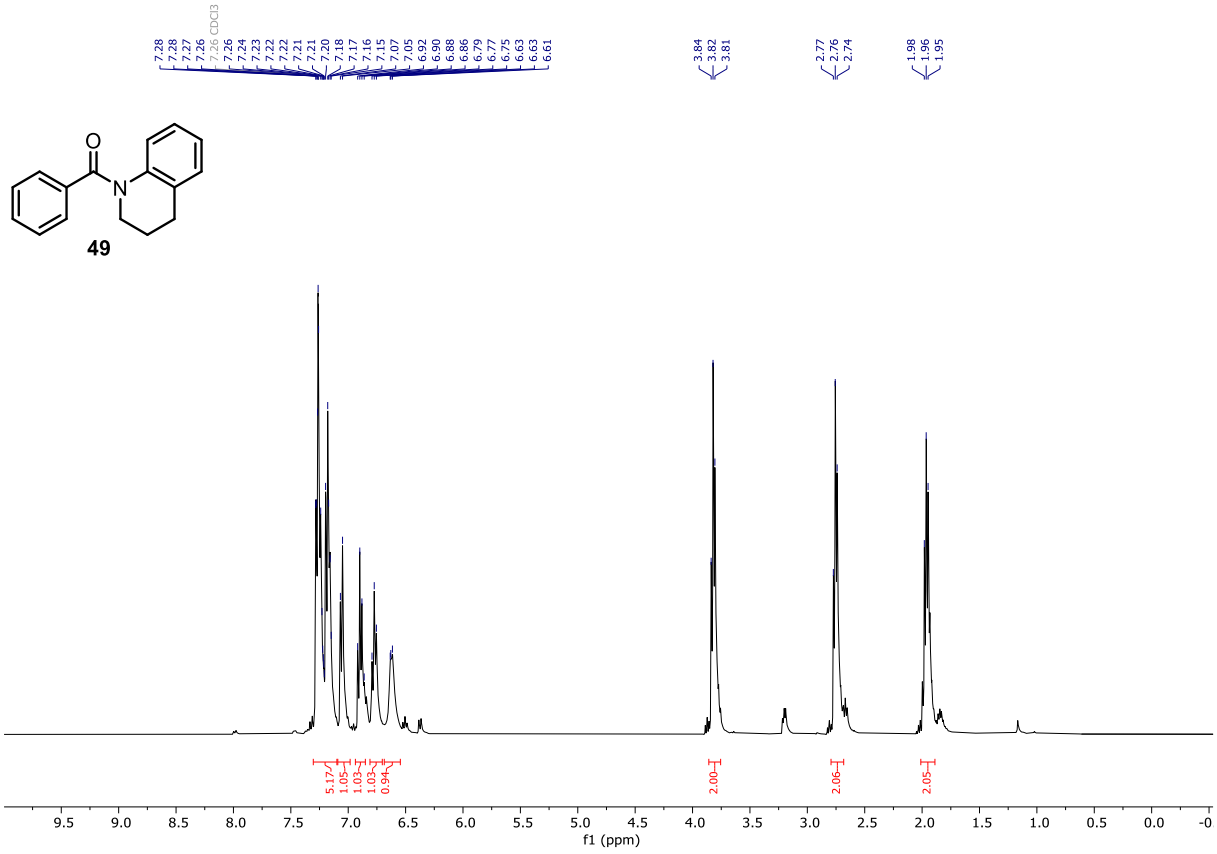


Figure S67: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

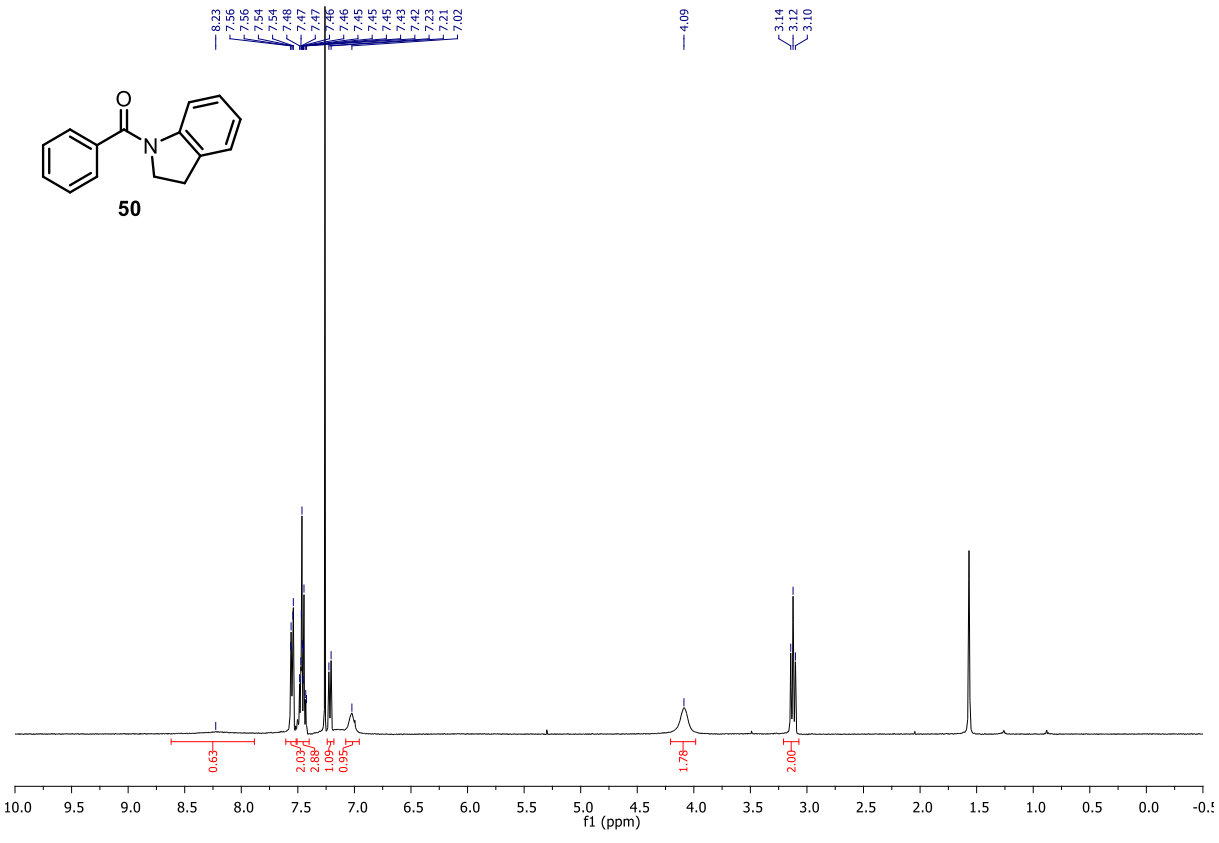


Figure S68: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

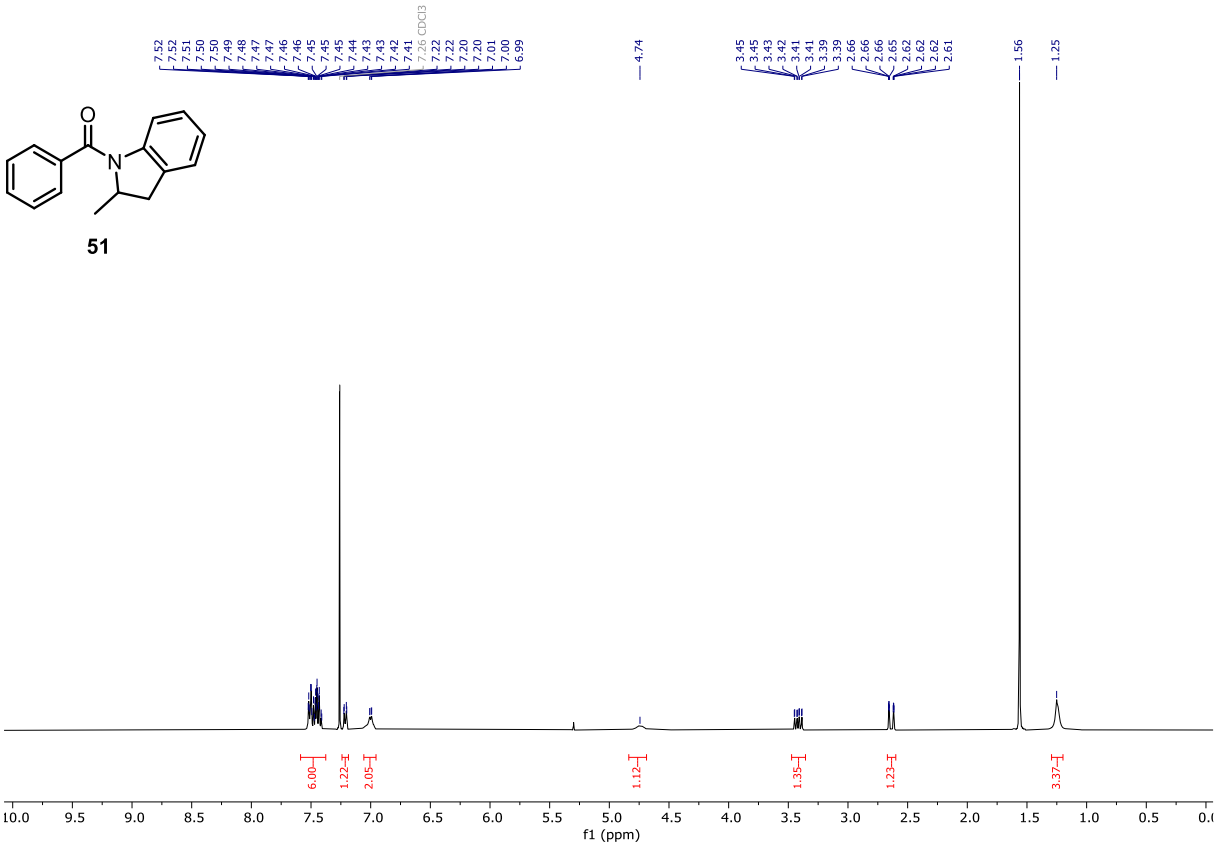


Figure S69: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

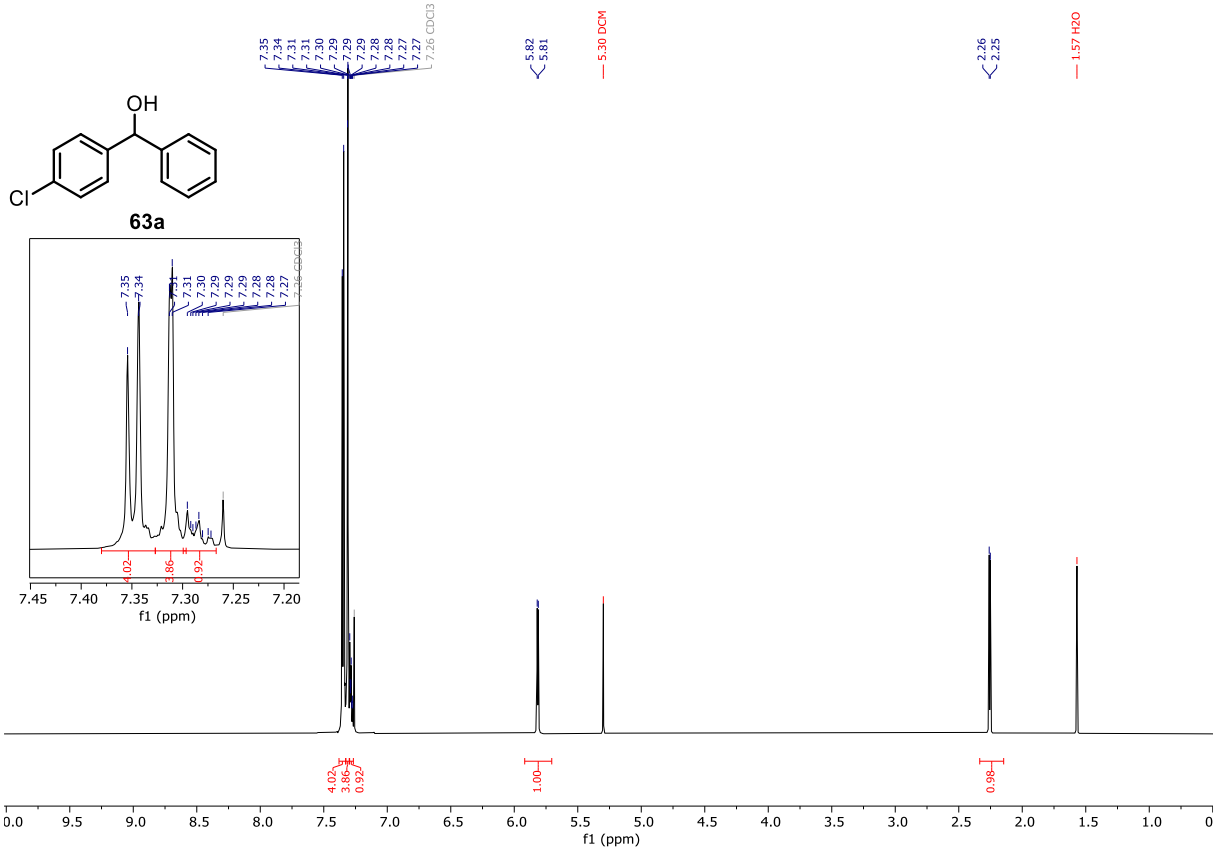


Figure S70: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

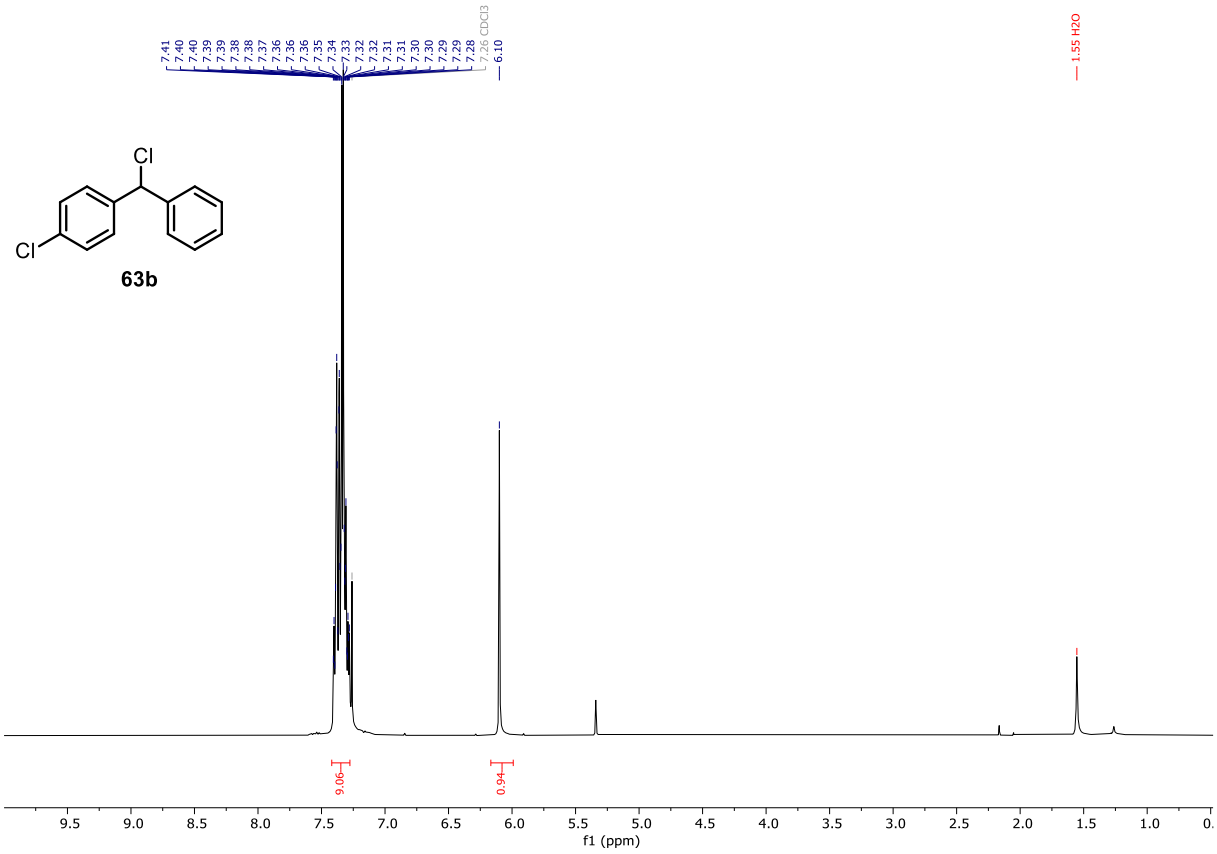


Figure S71: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

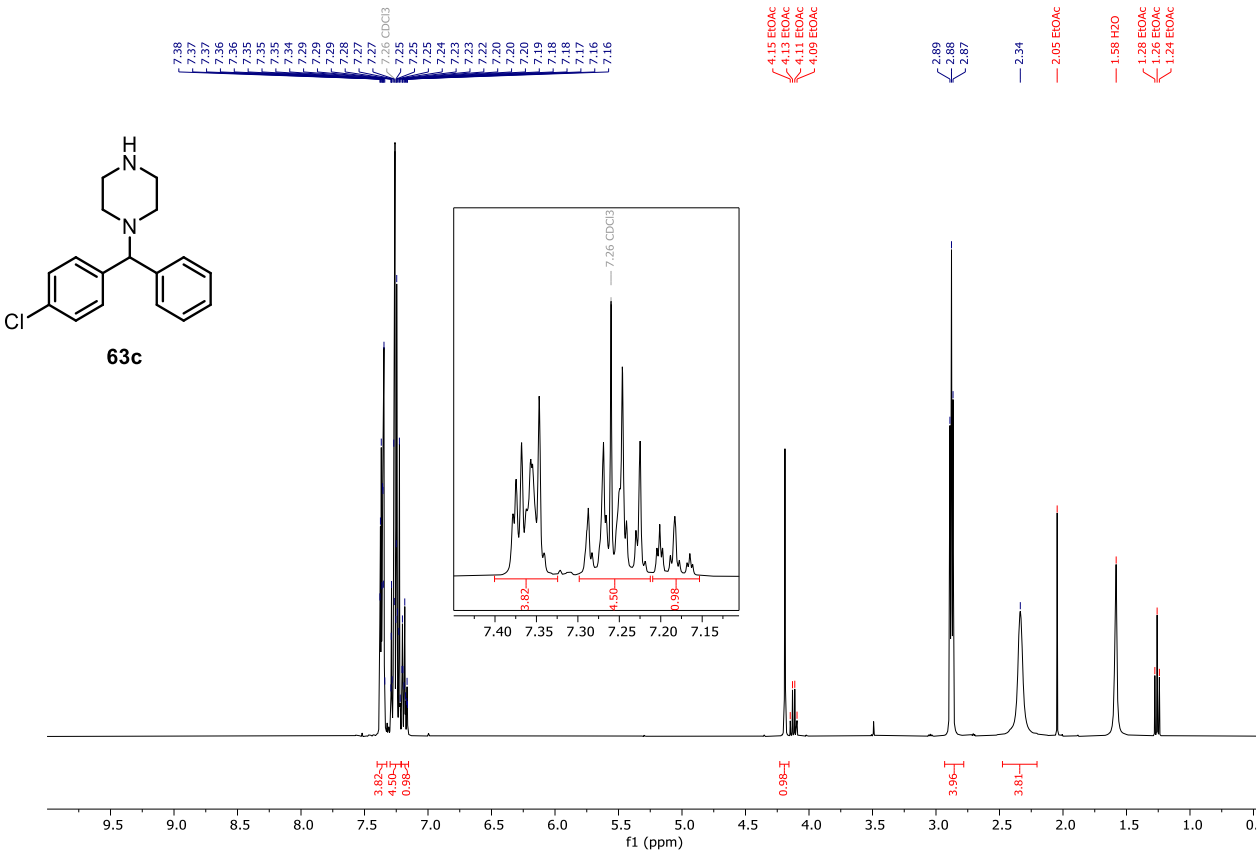


Figure S72: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

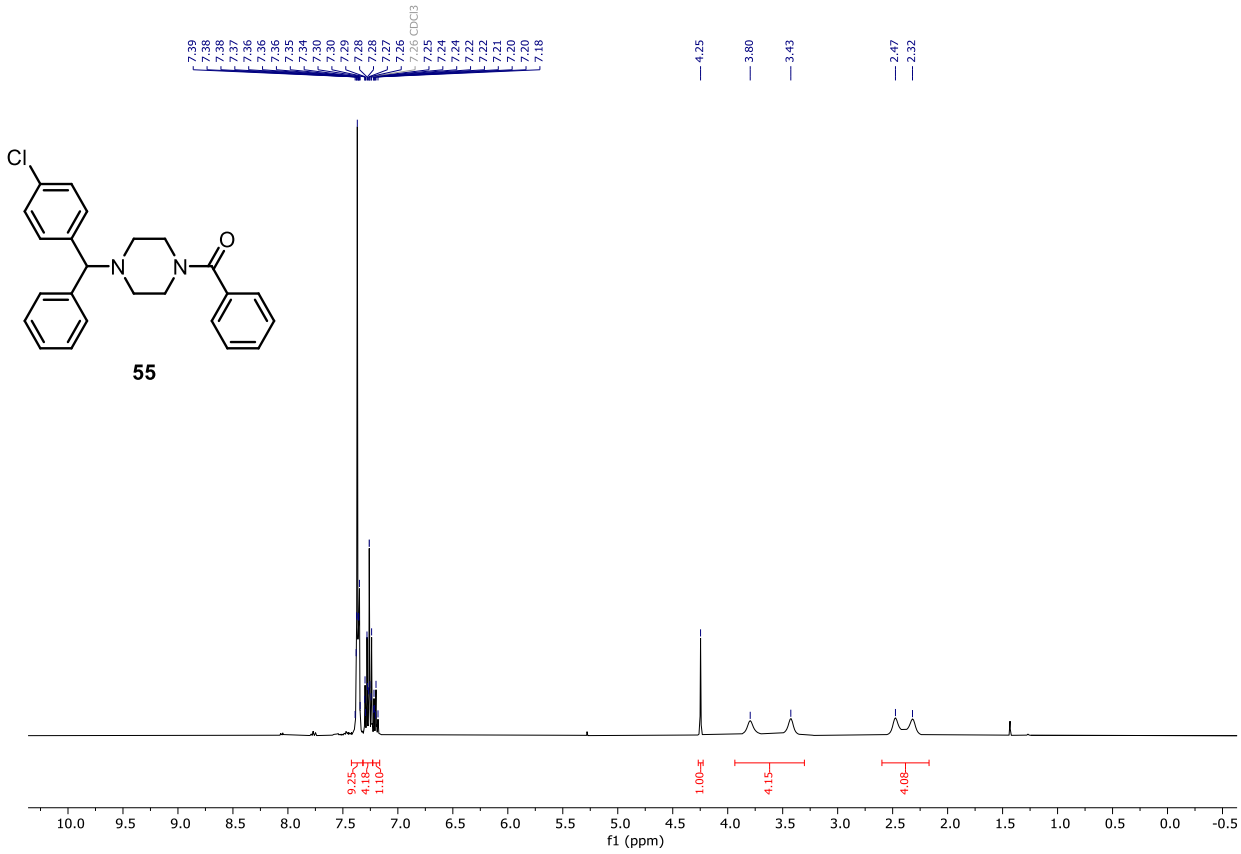


Figure S73: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

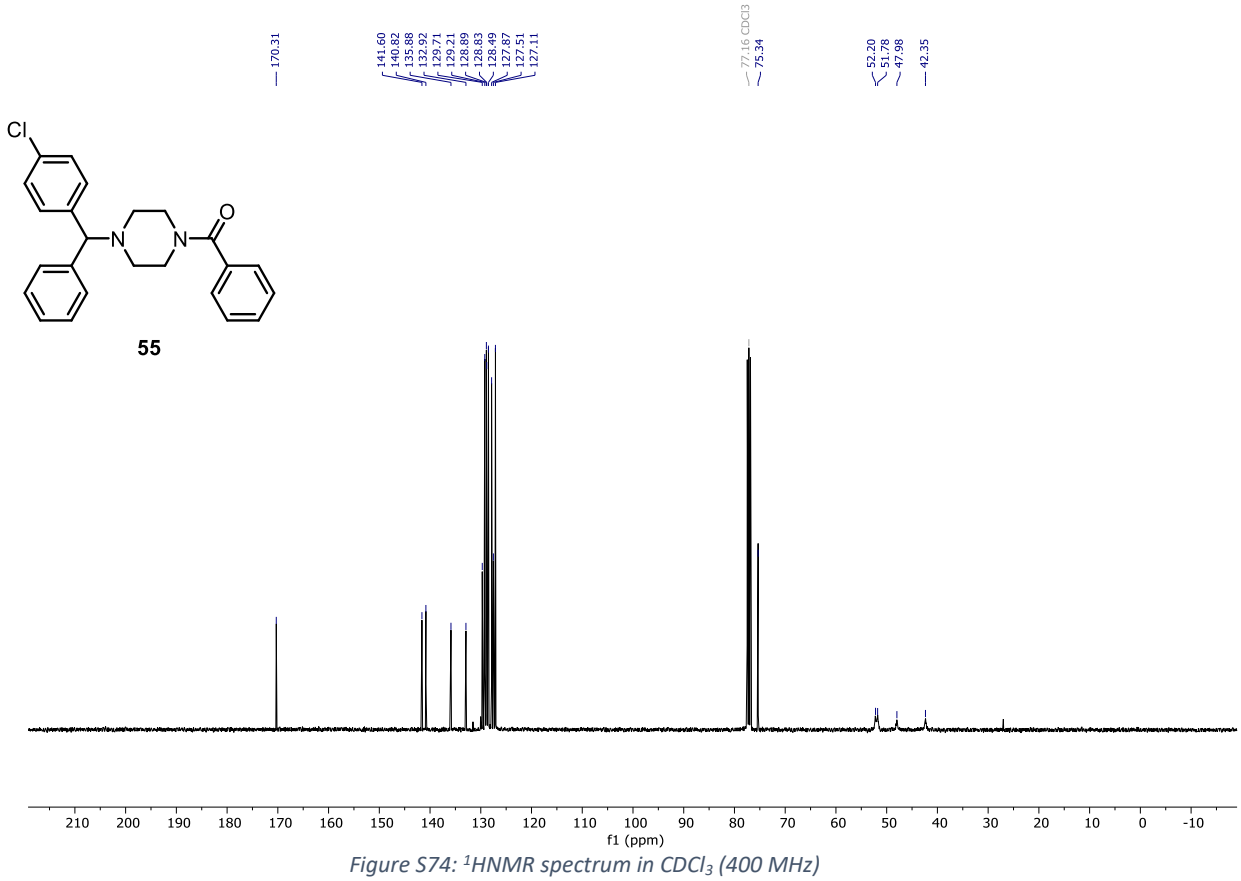


Figure S74: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

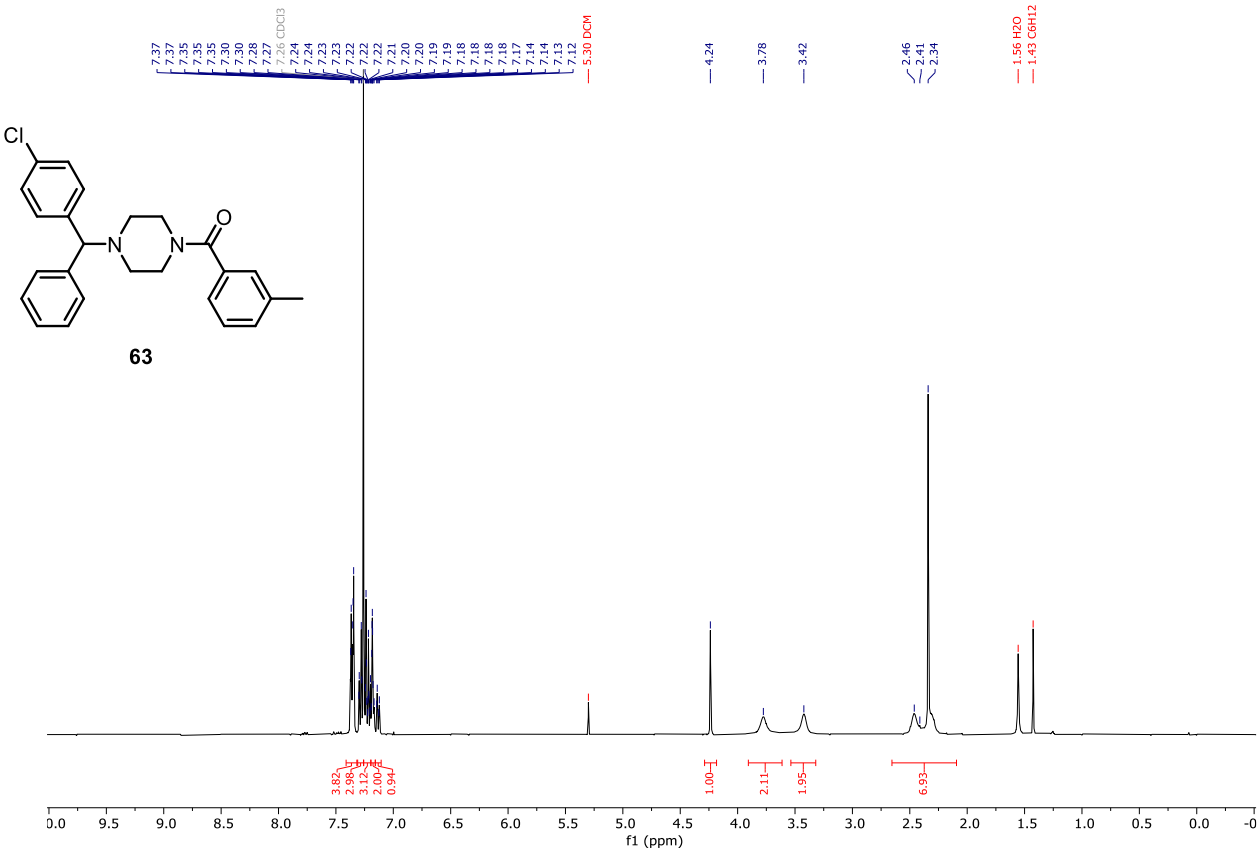


Figure S75: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

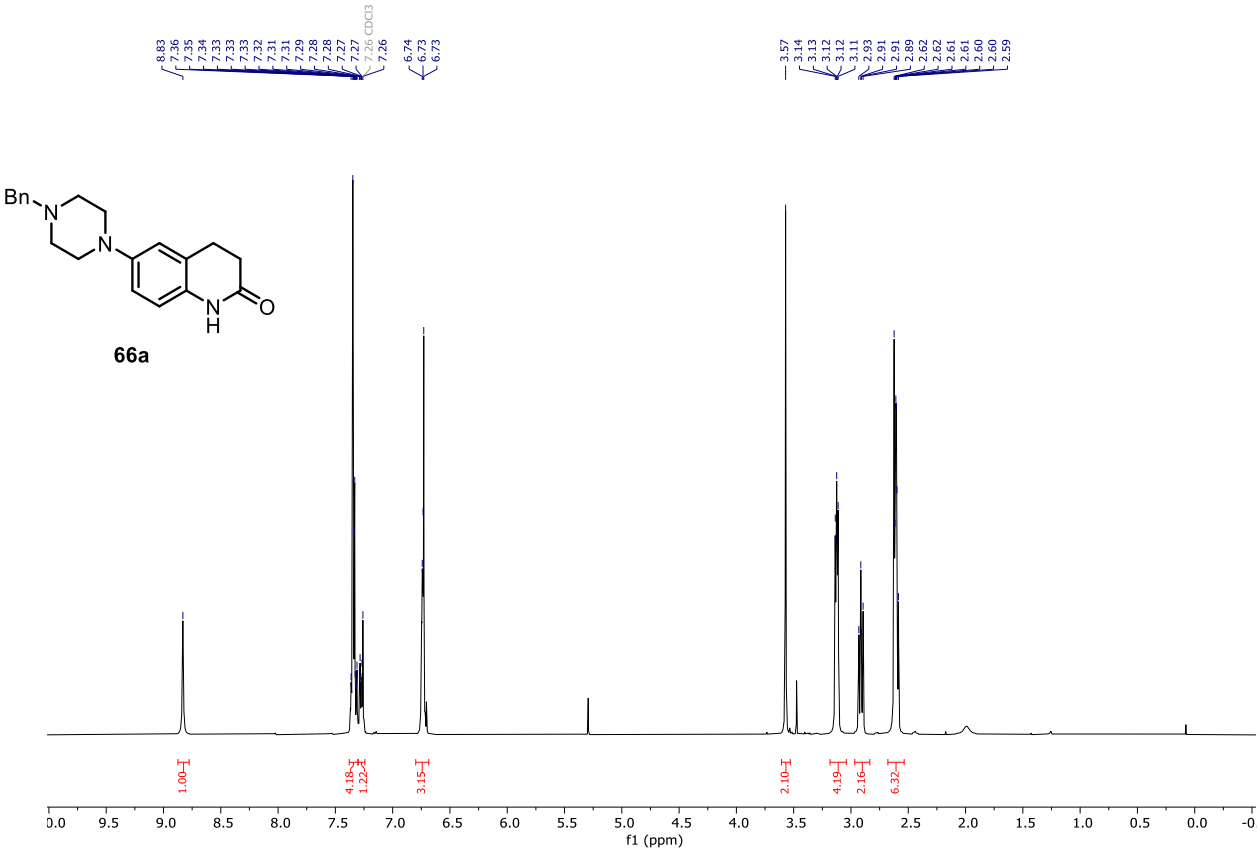


Figure S76: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

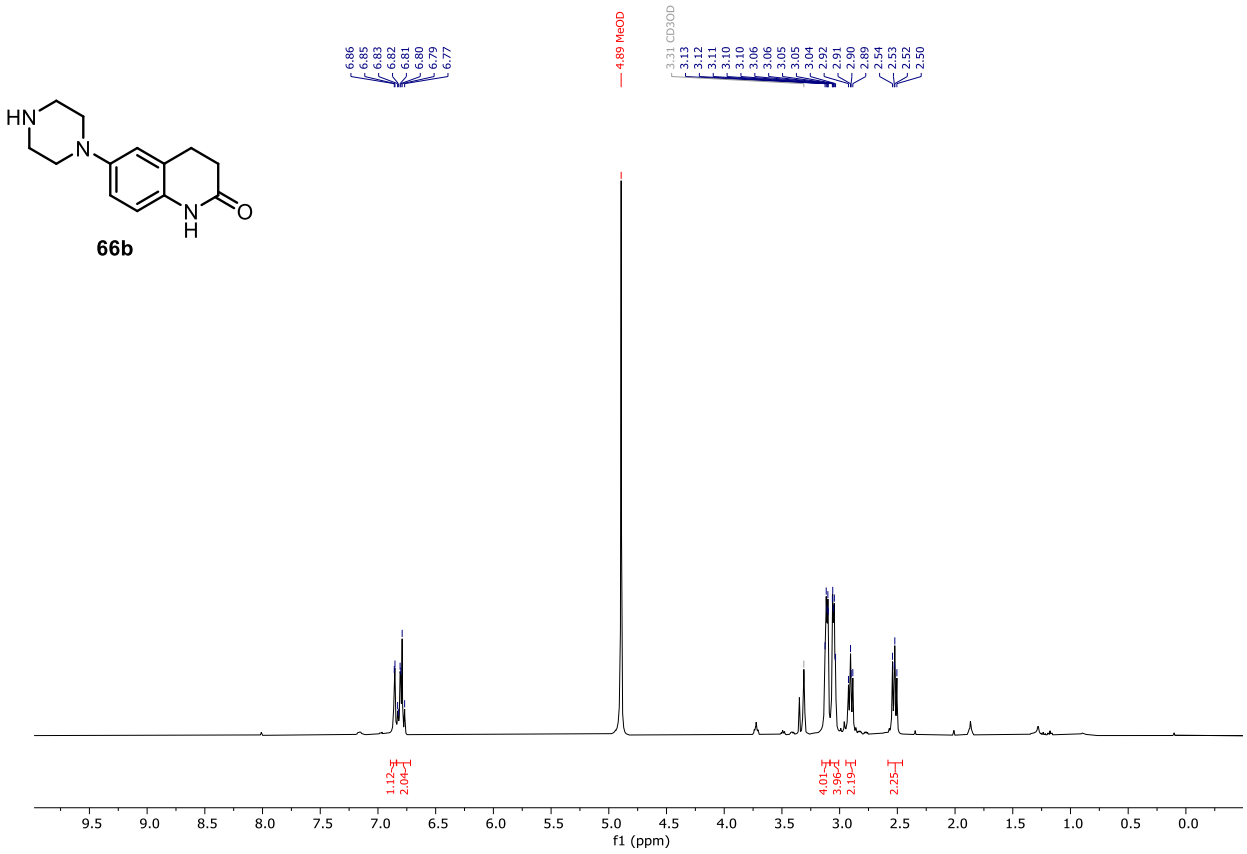


Figure 77: ^{1}HNMR spectrum in MeOD-d_4 (400 MHz)

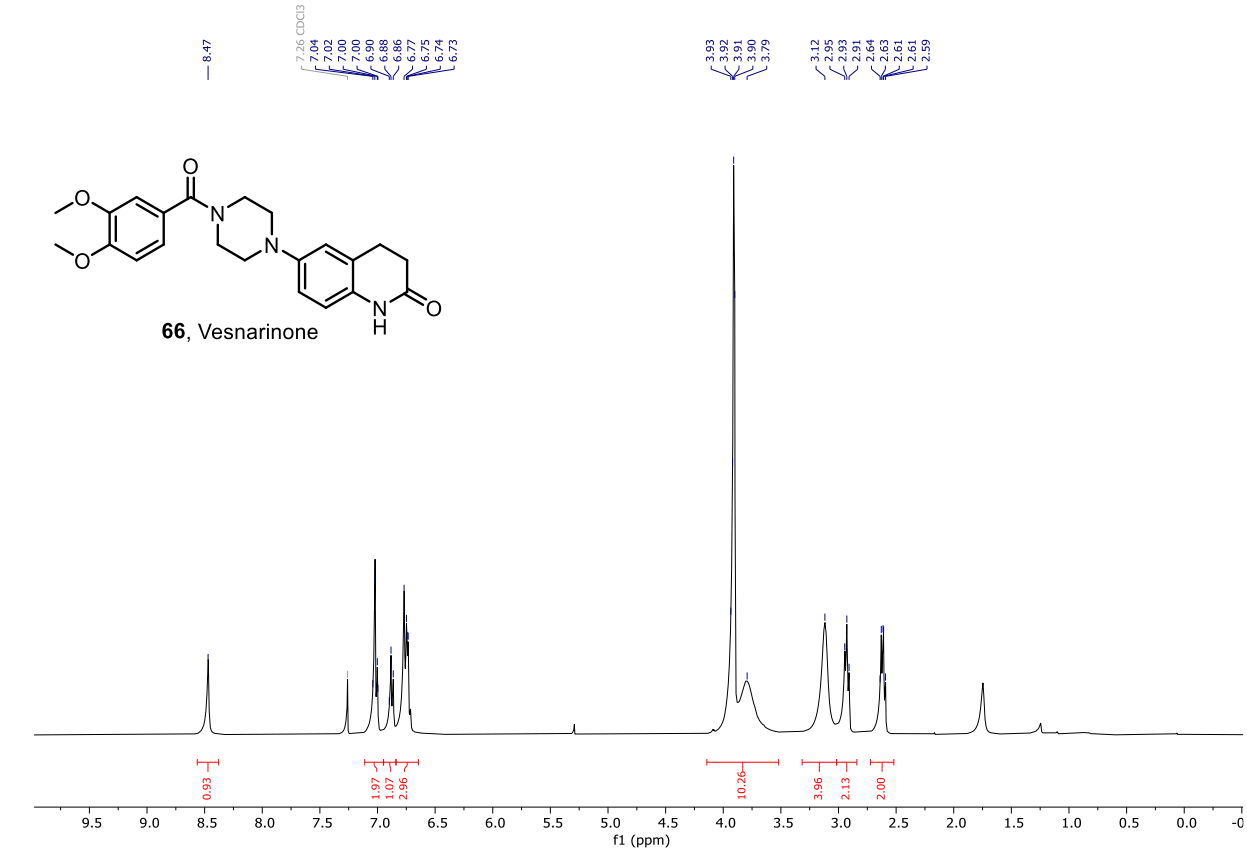


Figure S78: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

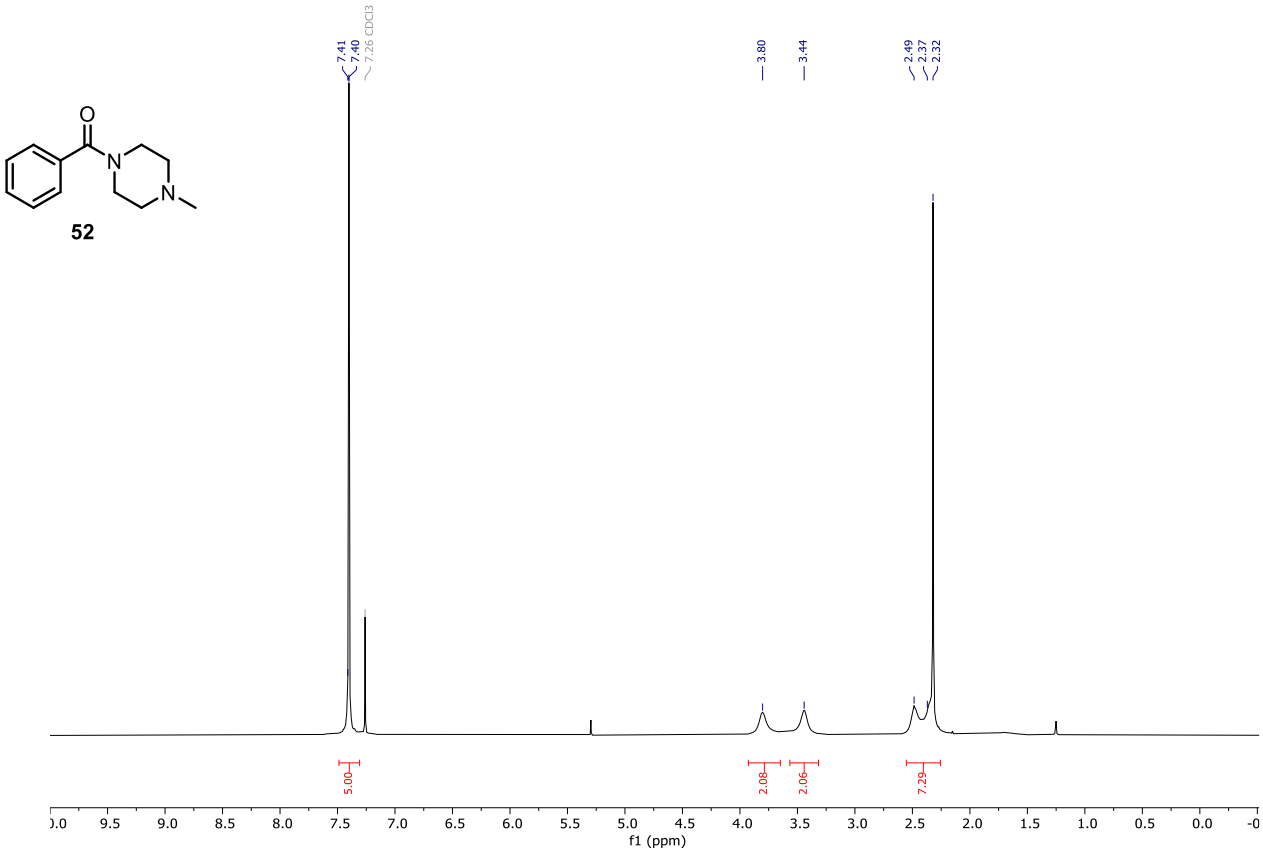


Figure S79: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

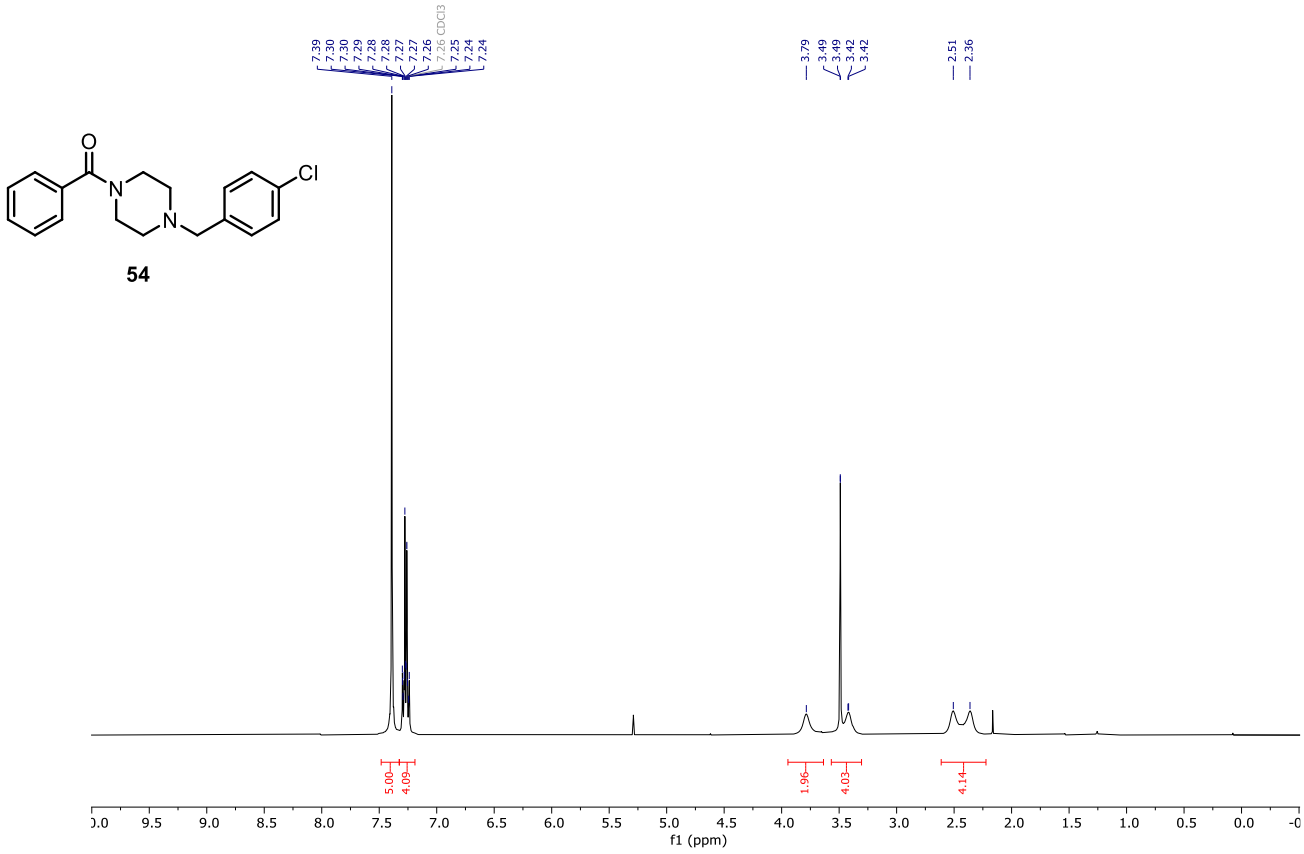


Figure S80: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

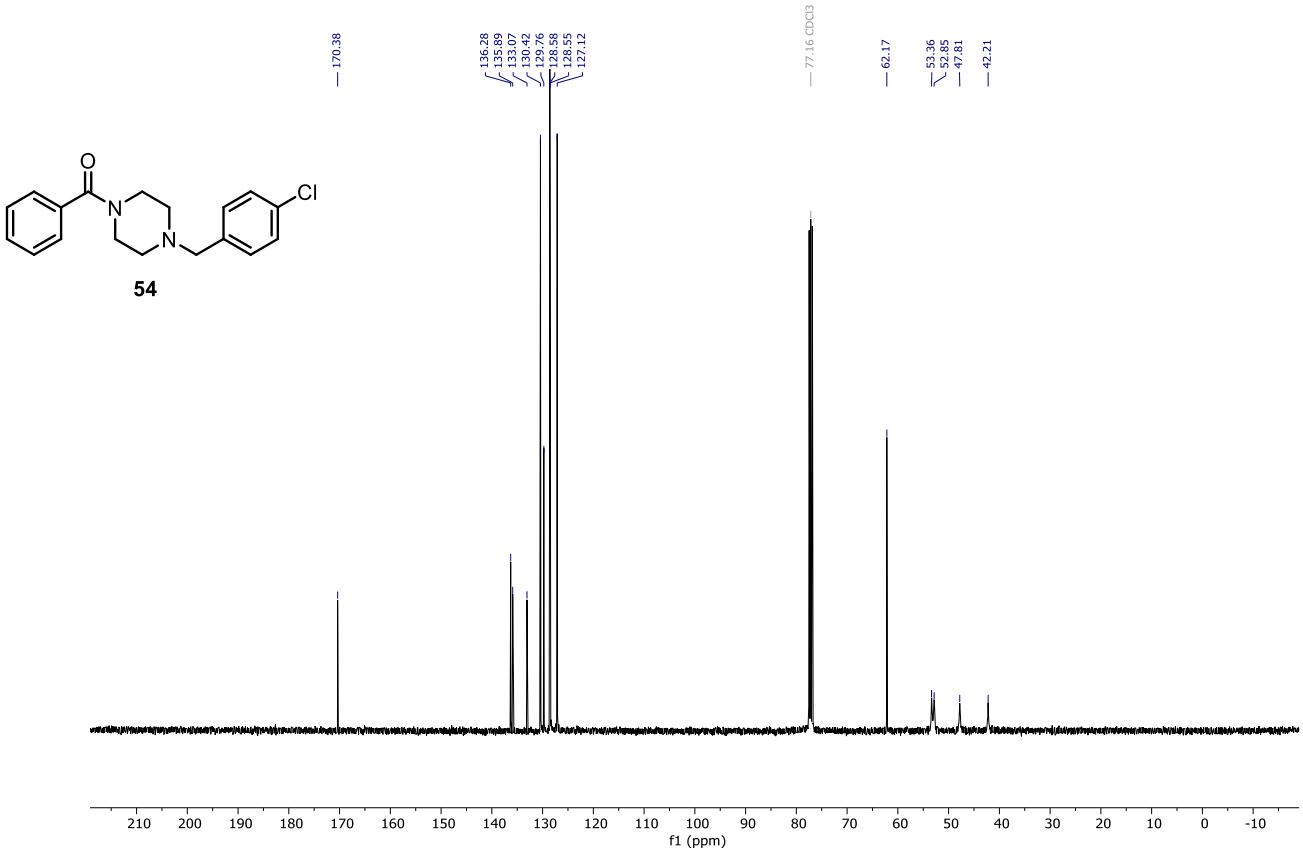


Figure S81: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

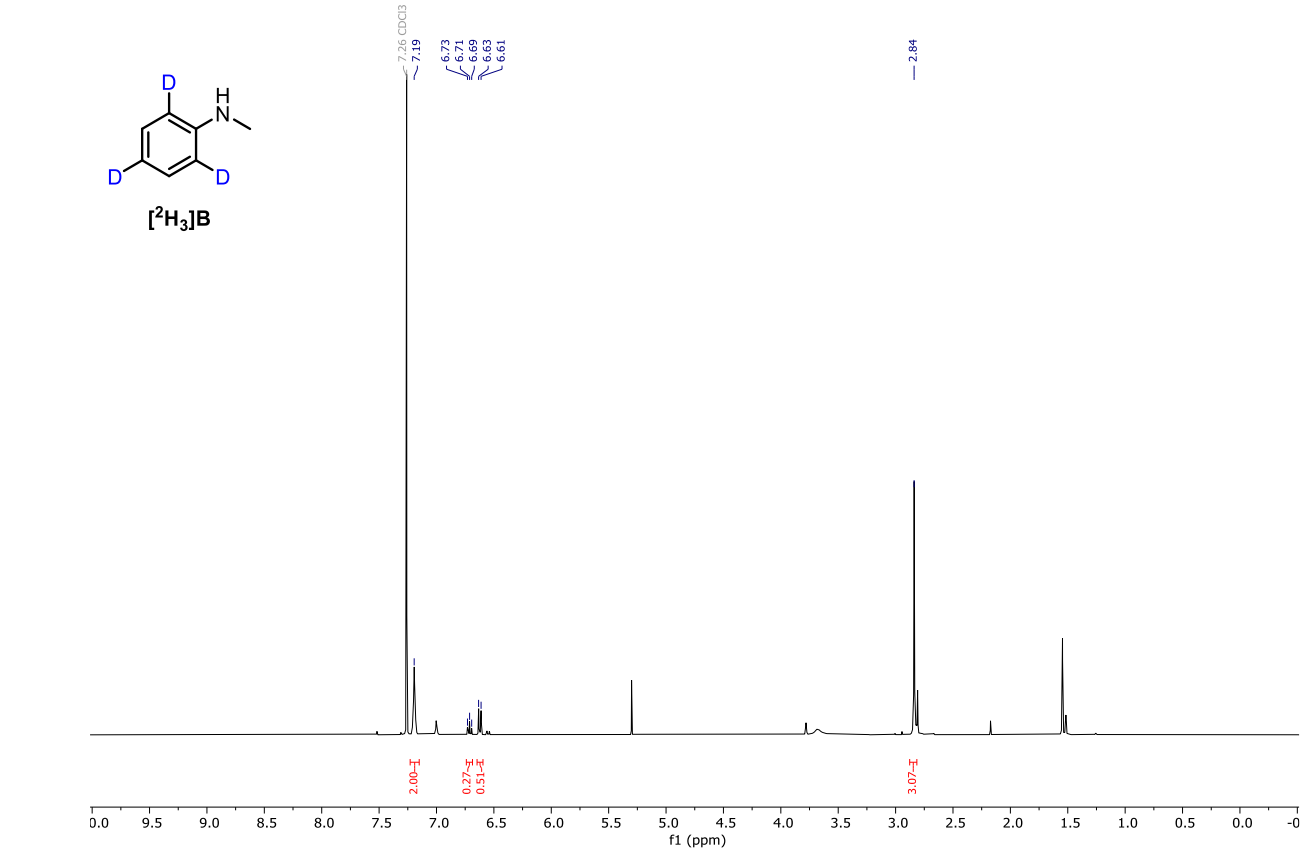


Figure S82: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

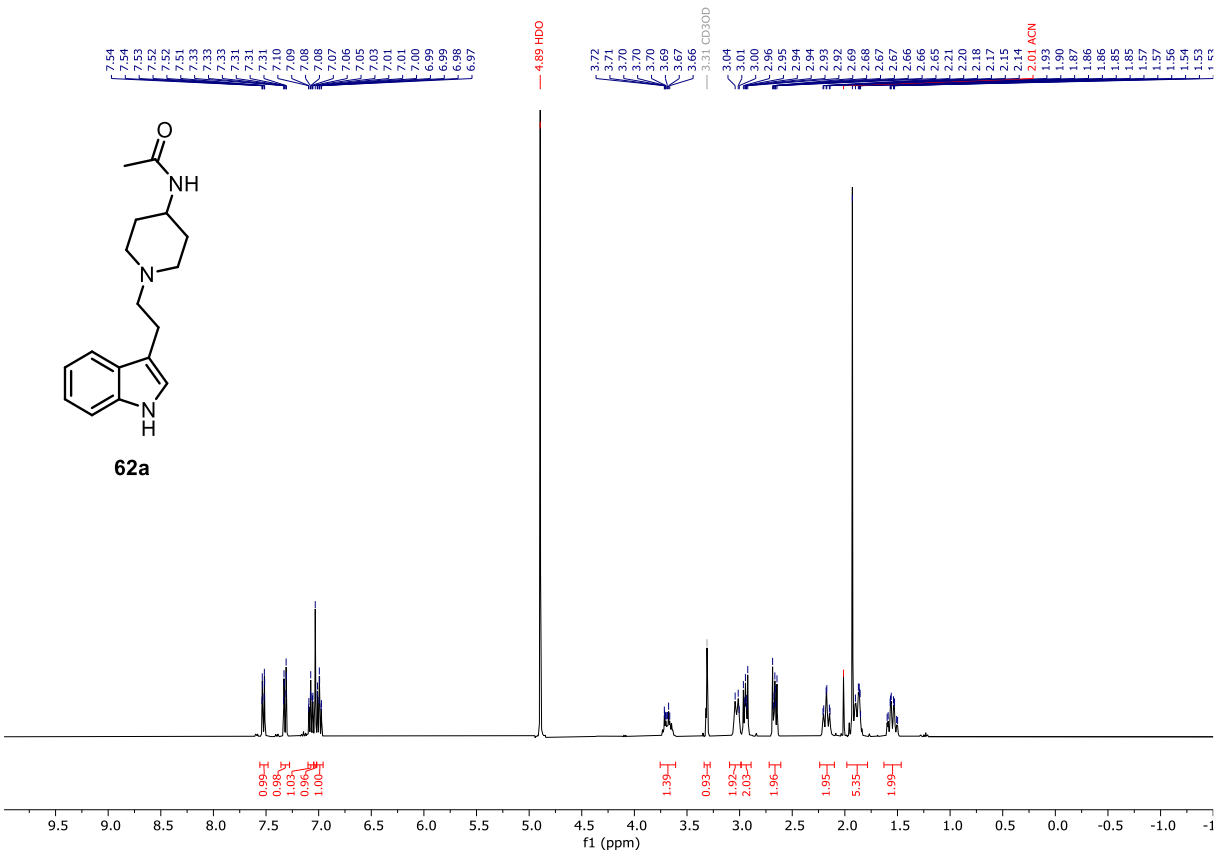


Figure 83: ^{1}HNMR spectrum in MeOD-d_4 (400 MHz)

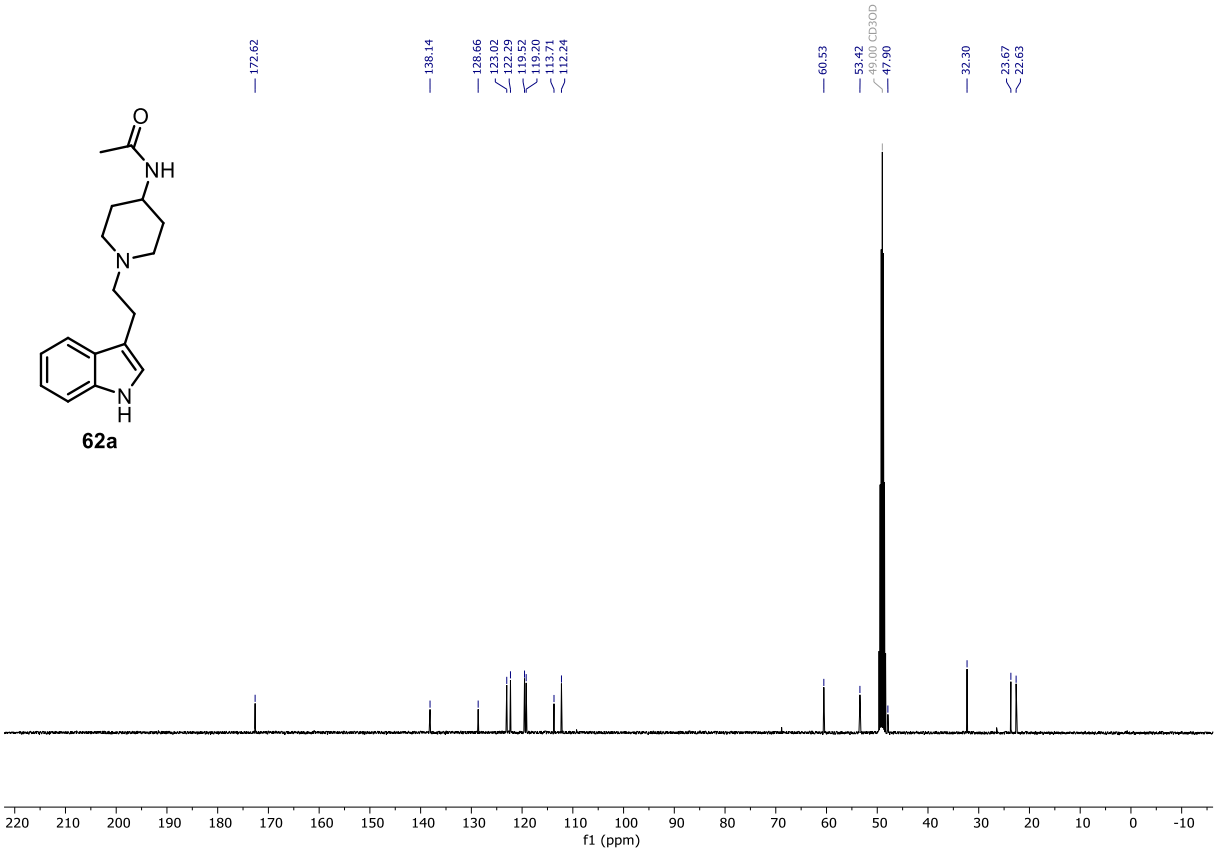


Figure 84: ^{13}CNMR spectrum in MeOD-d_4 (101 MHz)

XIII. NMR Spectra Isotope Carrier

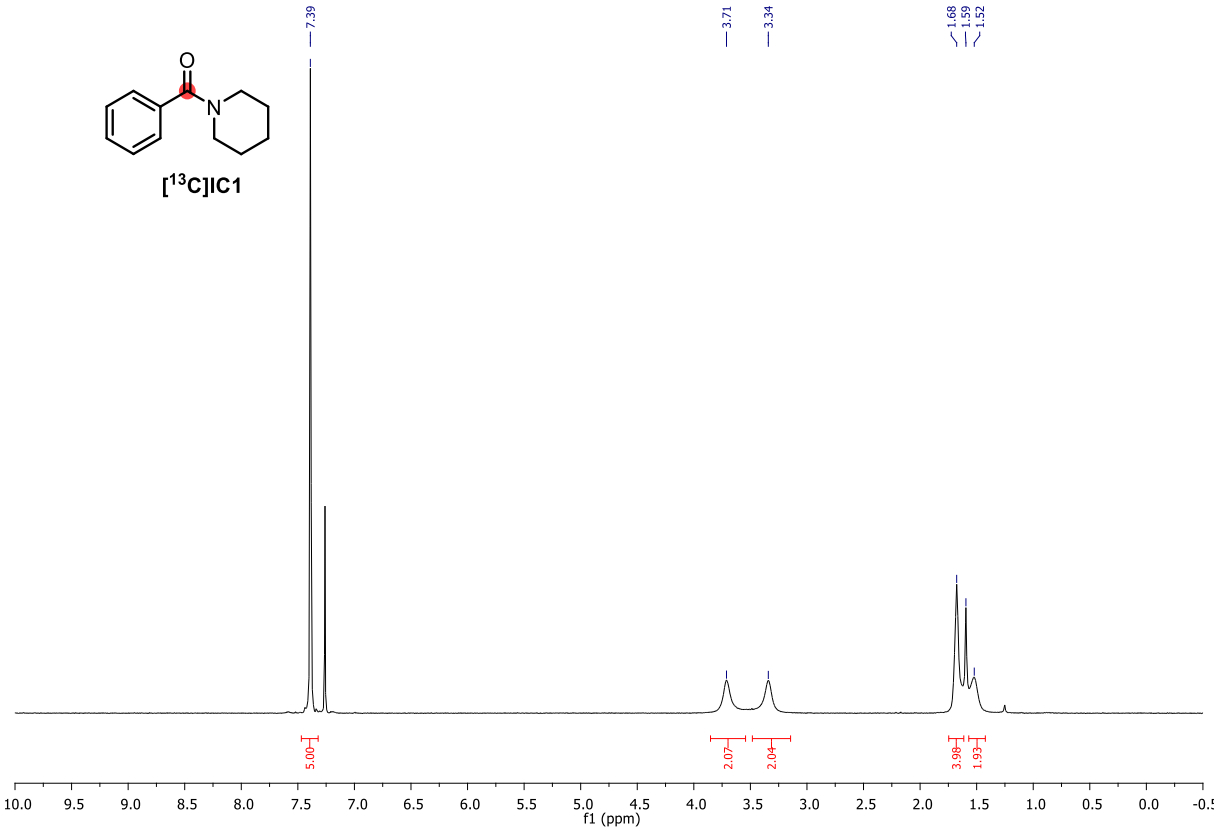


Figure S85: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

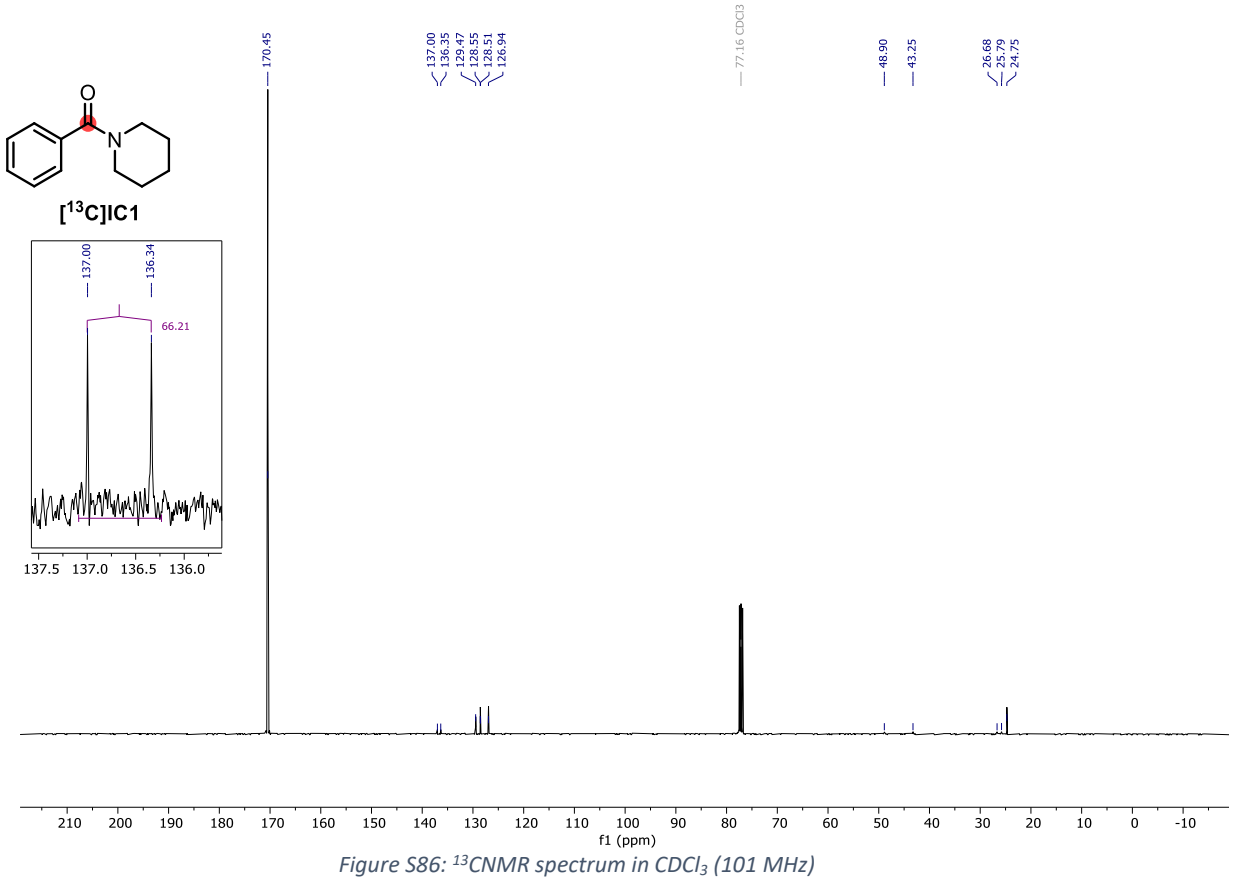


Figure S86: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

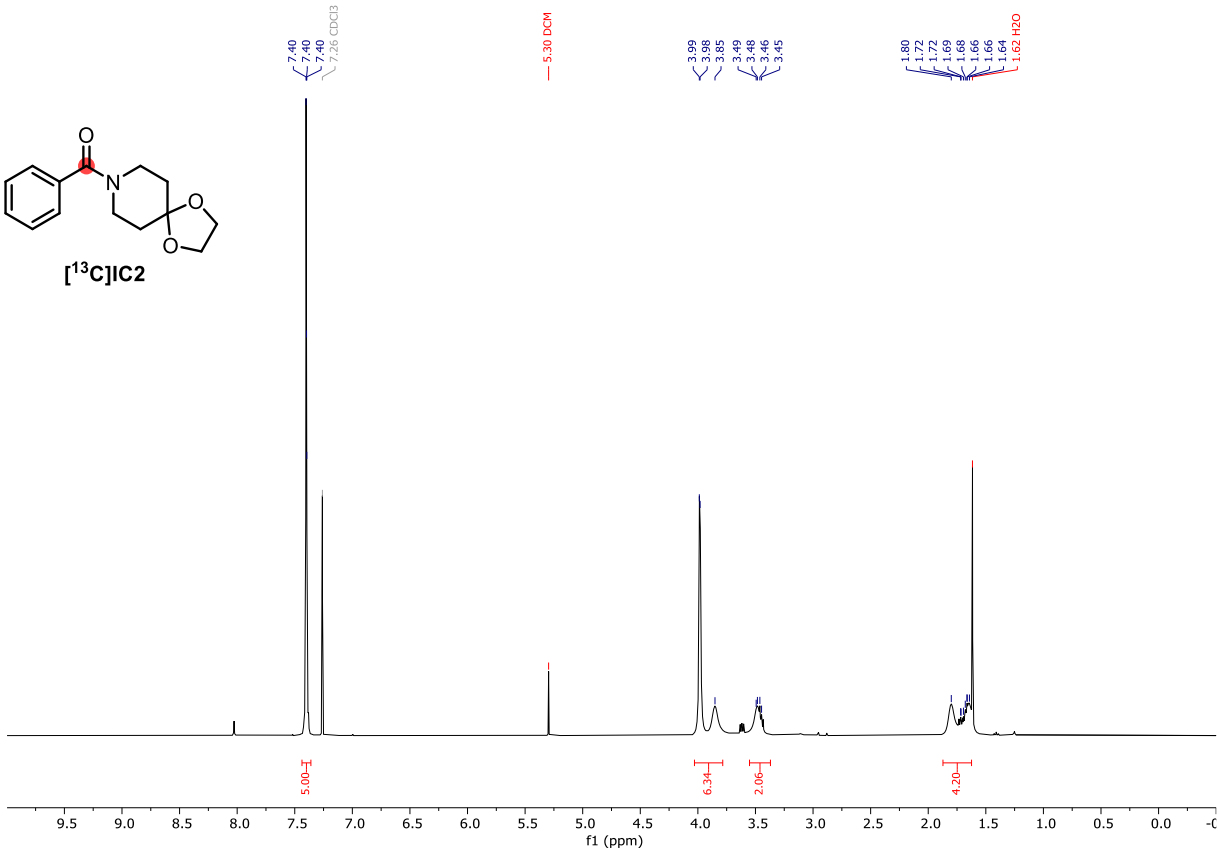


Figure S87: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

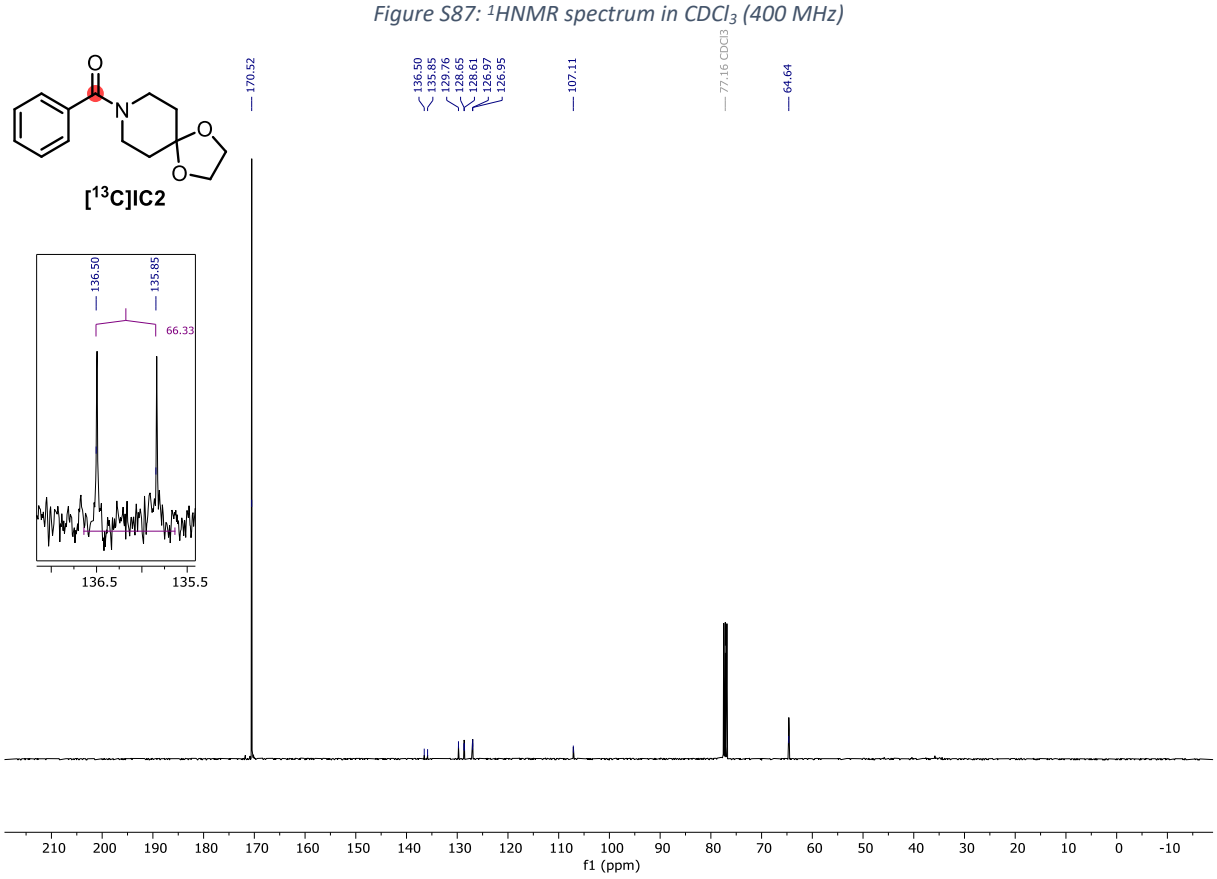


Figure S88: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

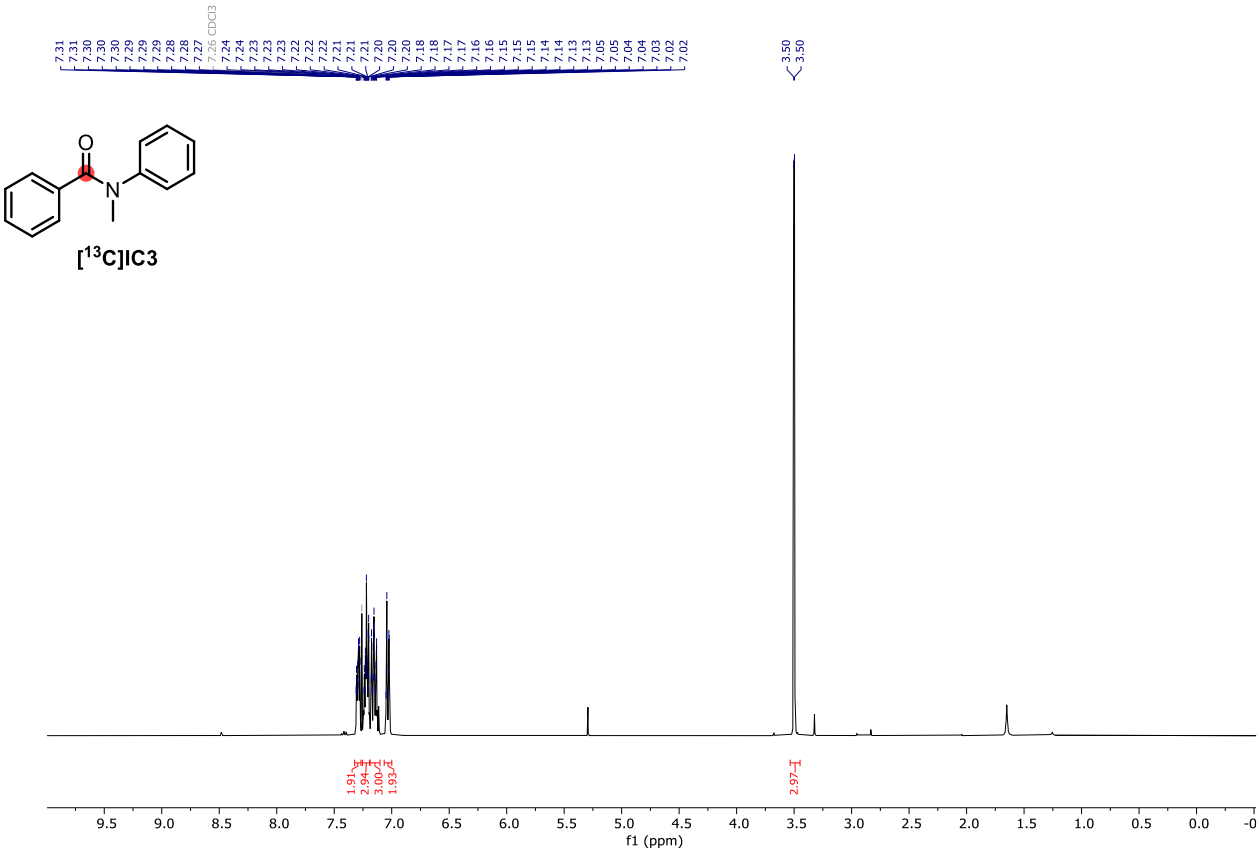


Figure S89: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

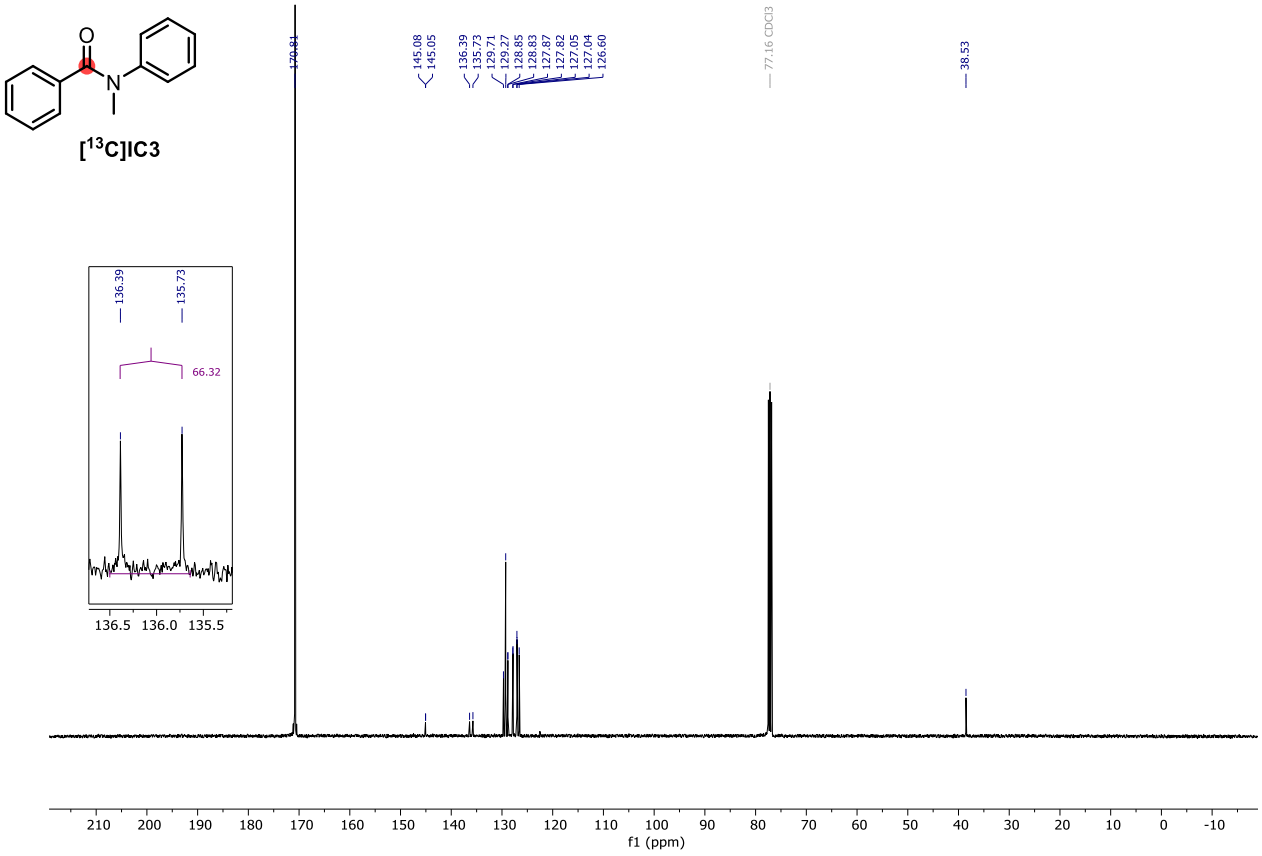


Figure S90: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

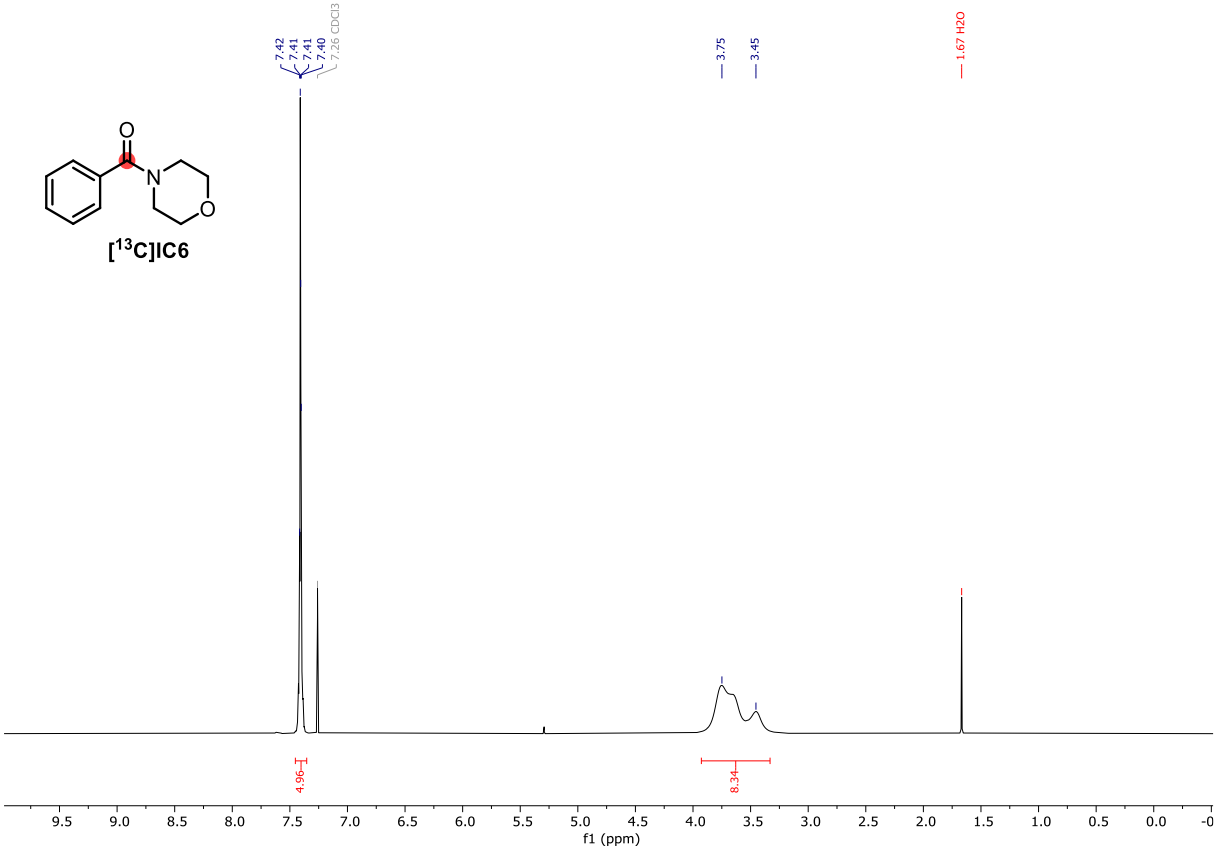


Figure S91: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

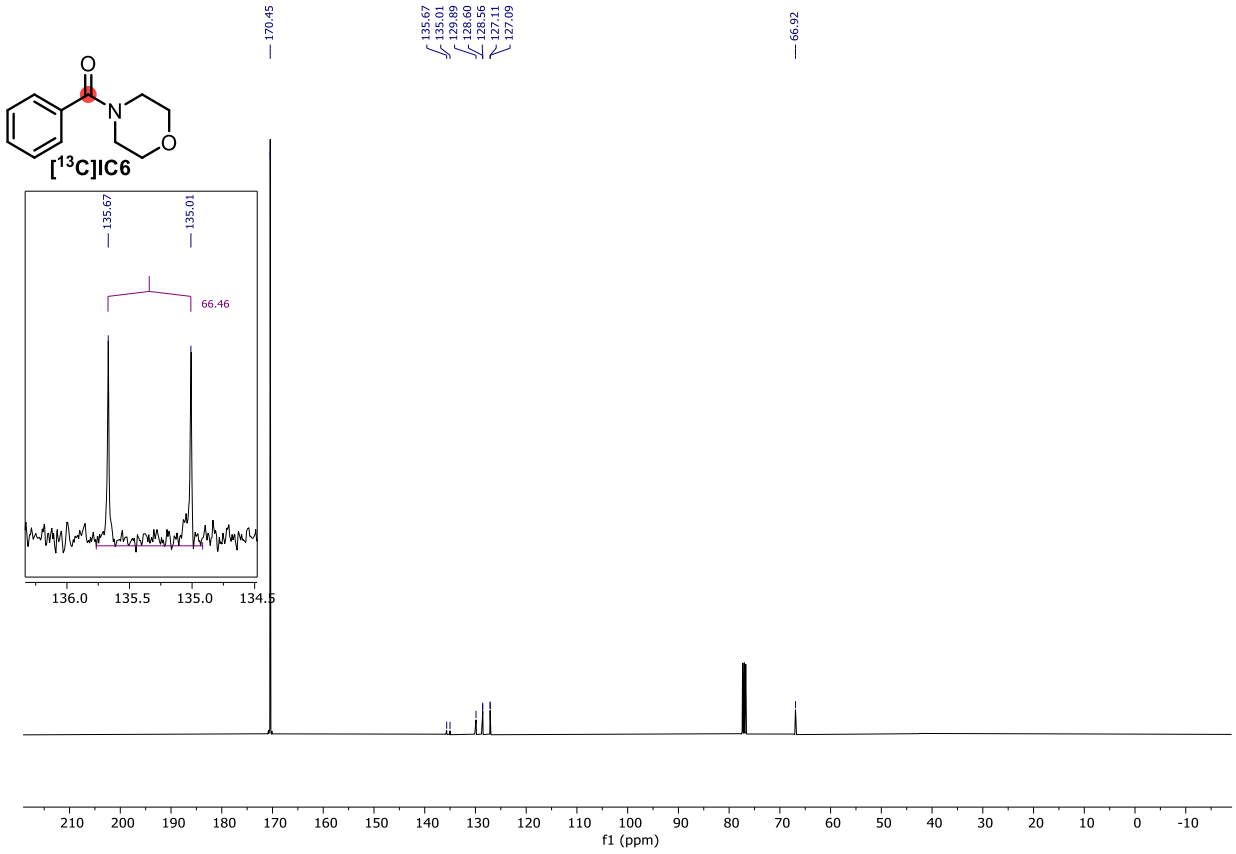


Figure S92: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

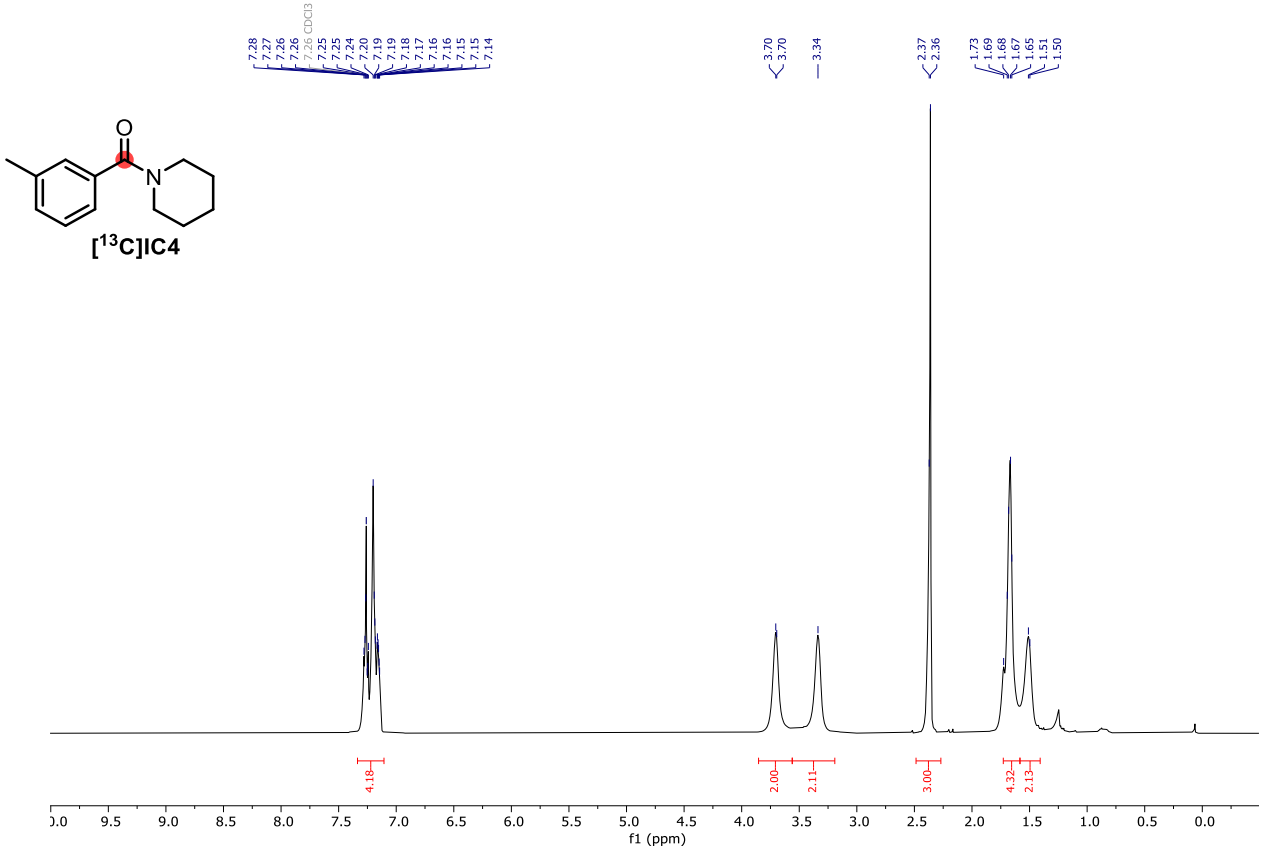


Figure S93: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

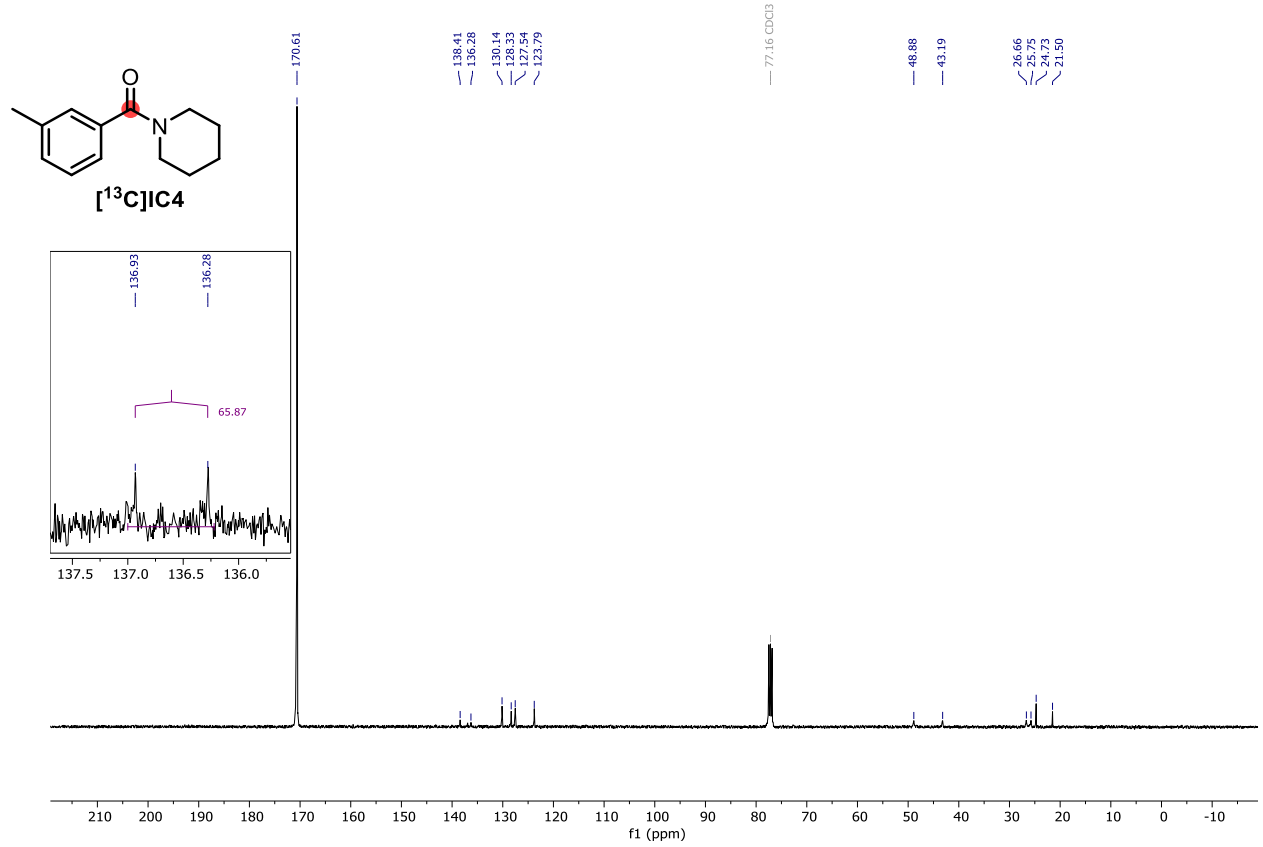


Figure S94: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

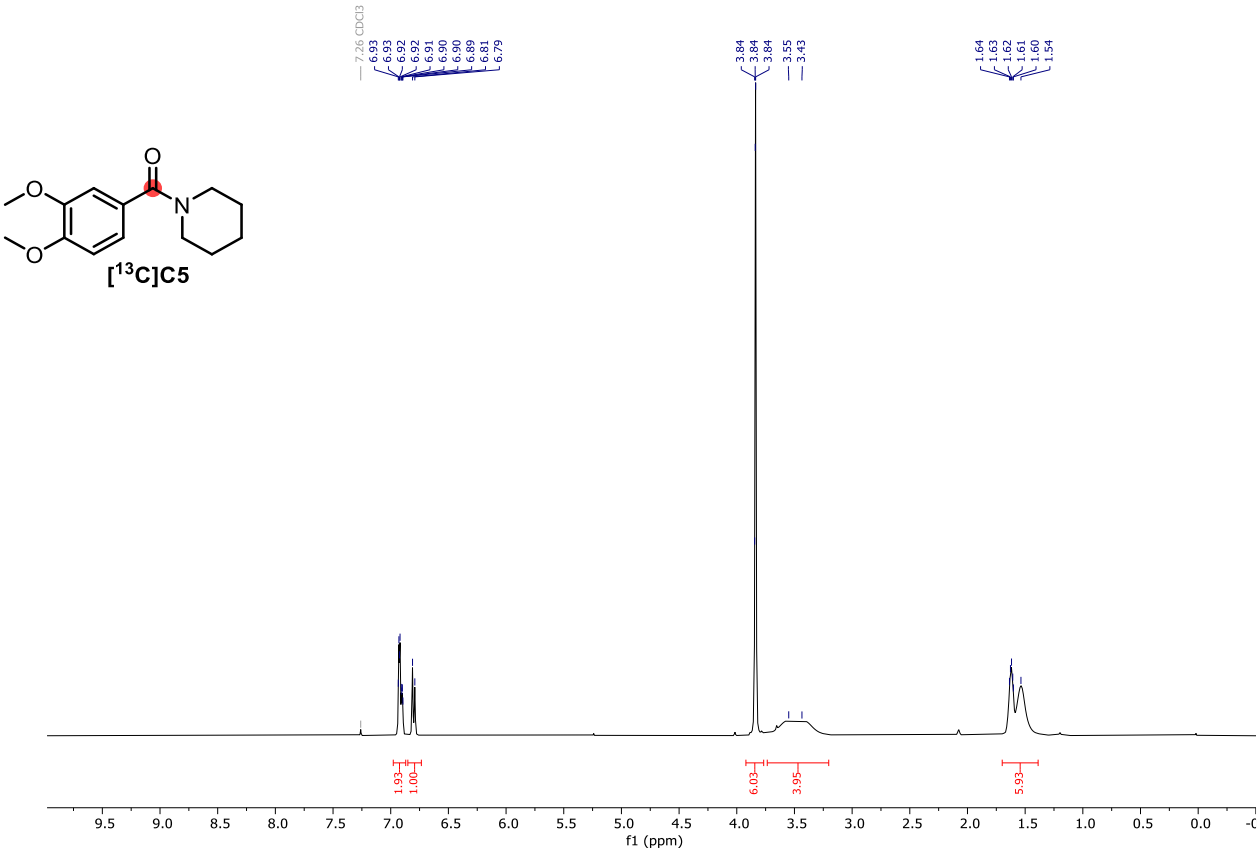


Figure S95: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

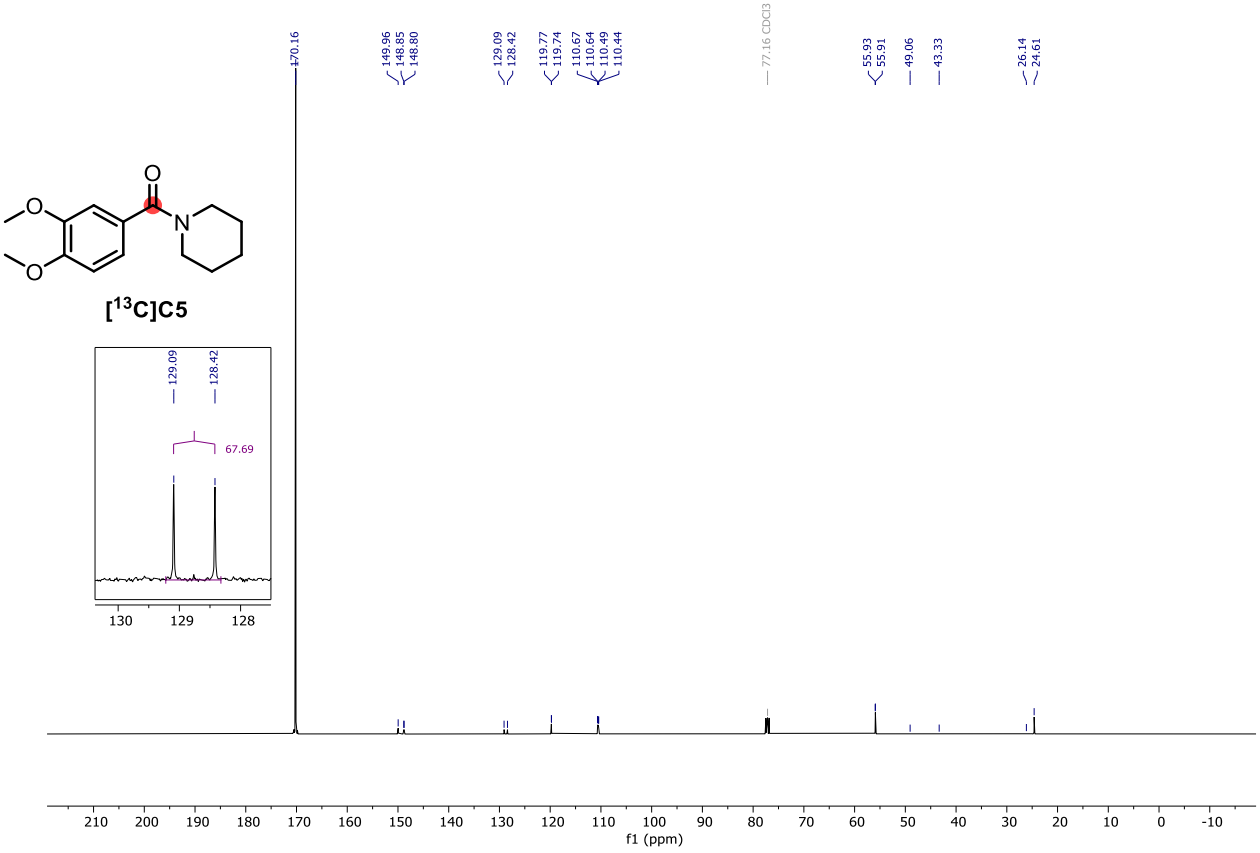
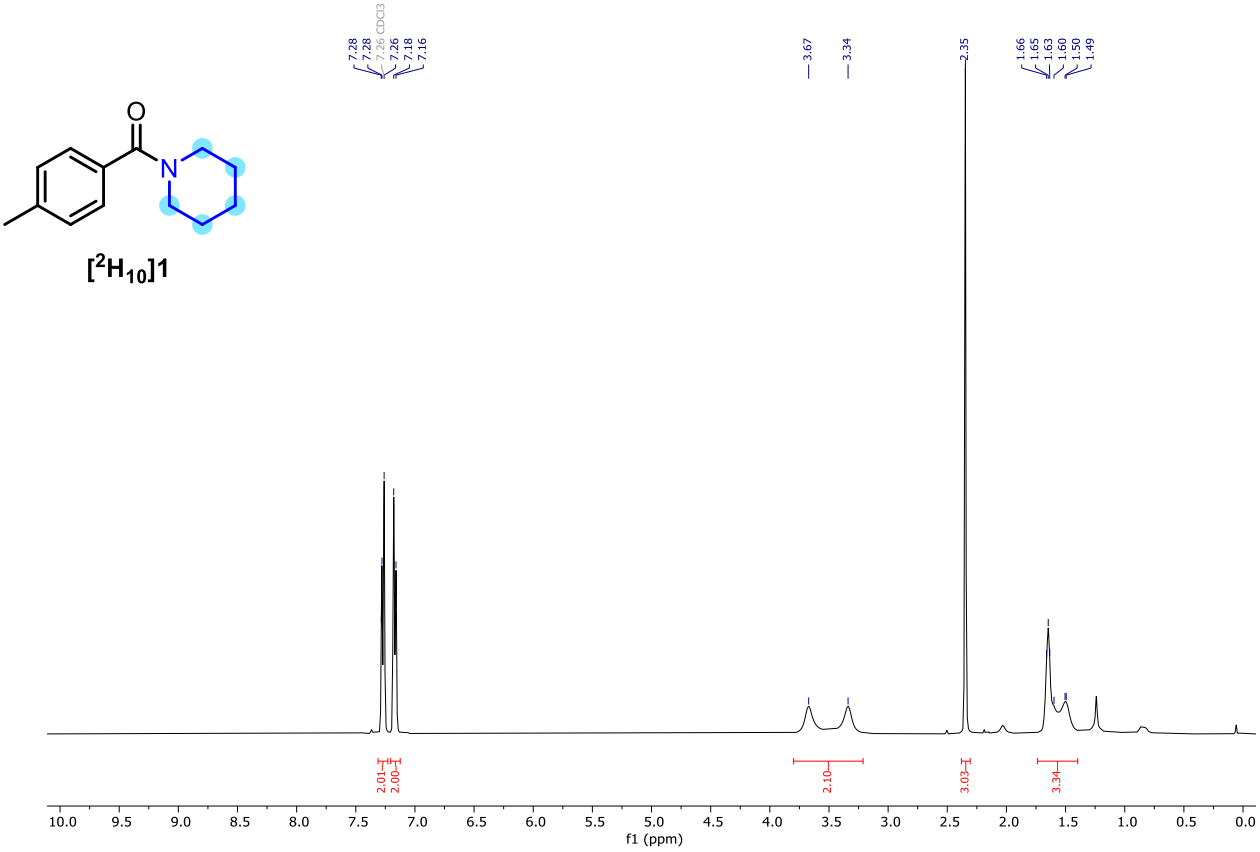


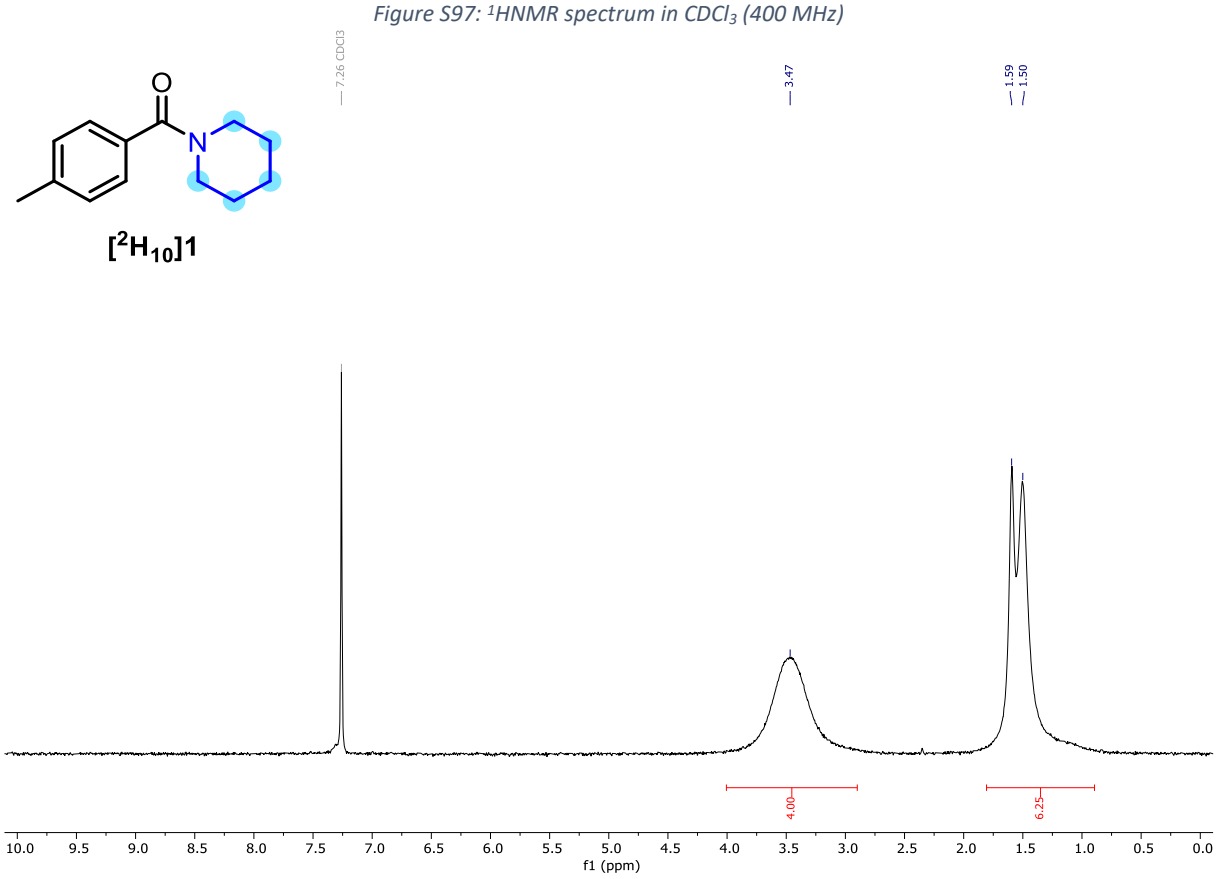
Figure S96: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

XIV. NMR Spectra deuterium labeled amides (transamidation)



$[^2H_{10}]1$

Figure S97: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)



$[^2H_{10}]1$

Figure S98: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

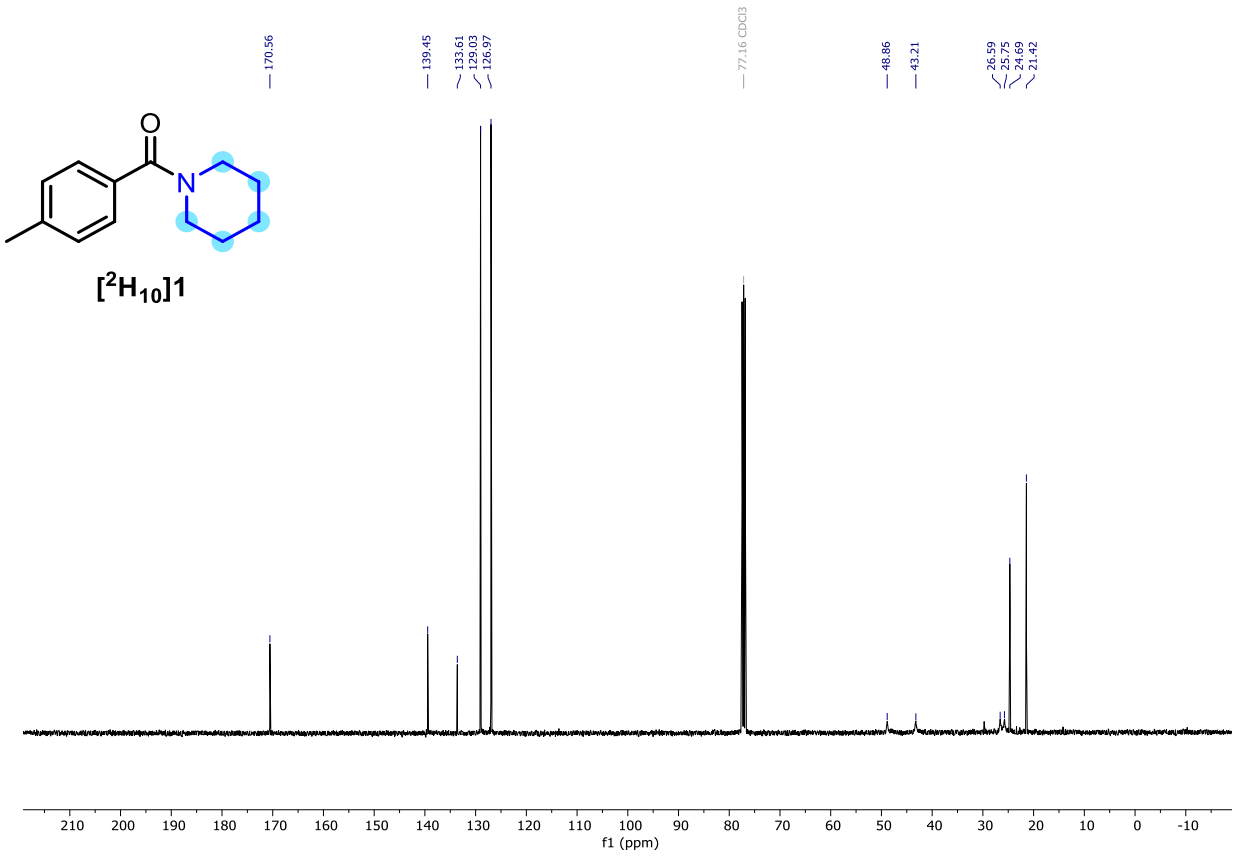


Figure S99: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

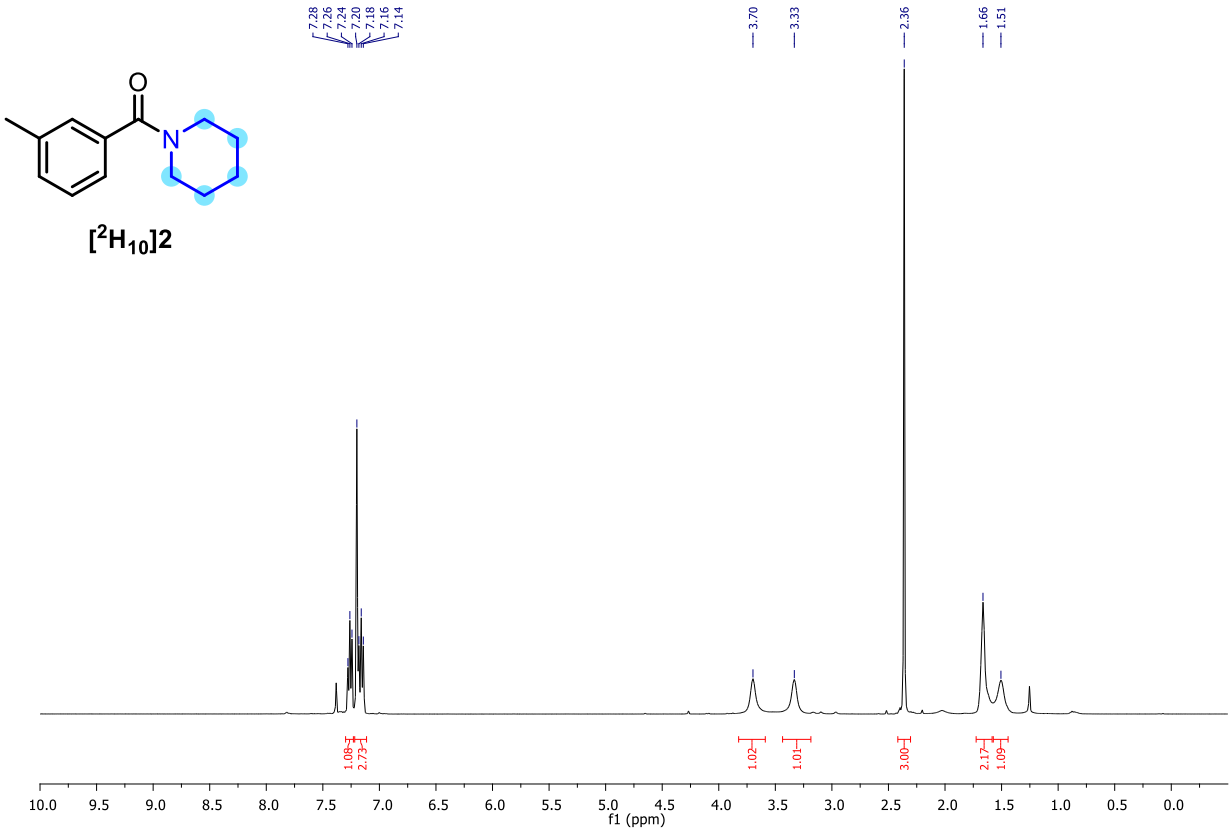


Figure S100: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

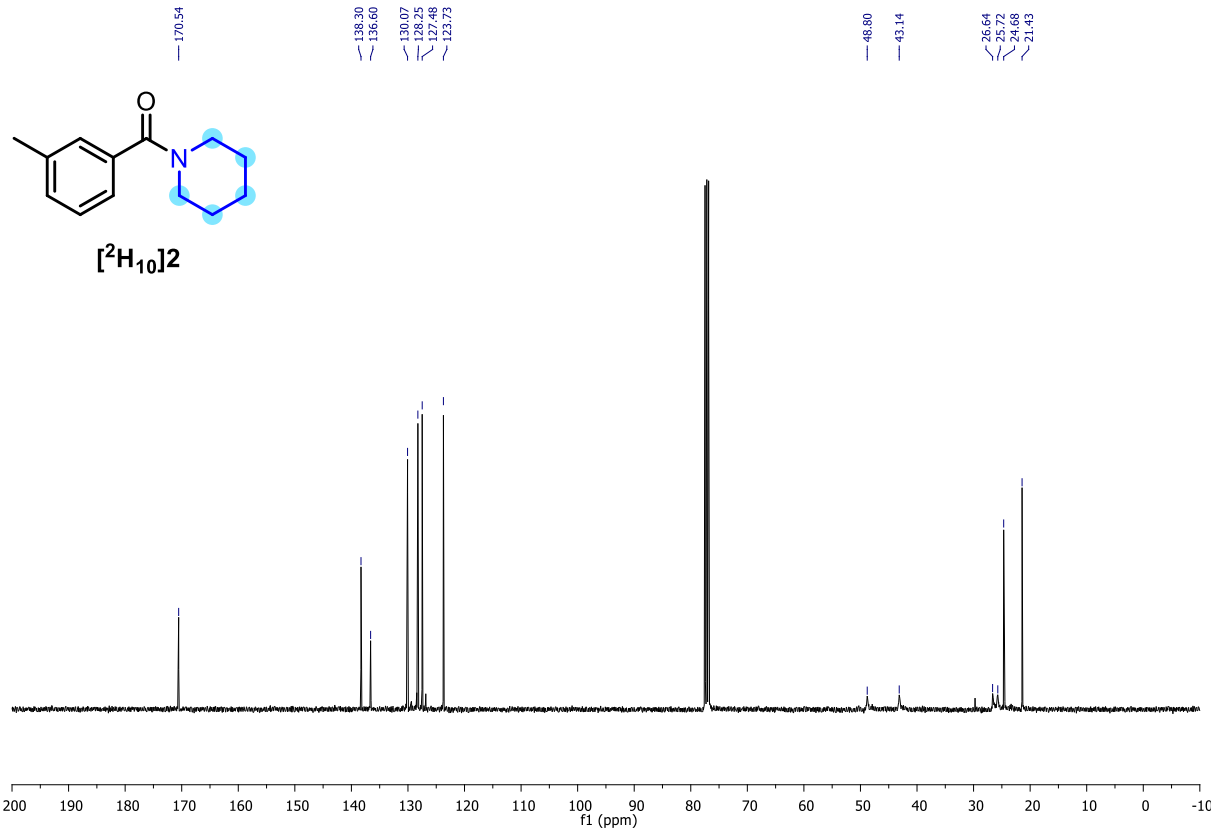


Figure S101: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

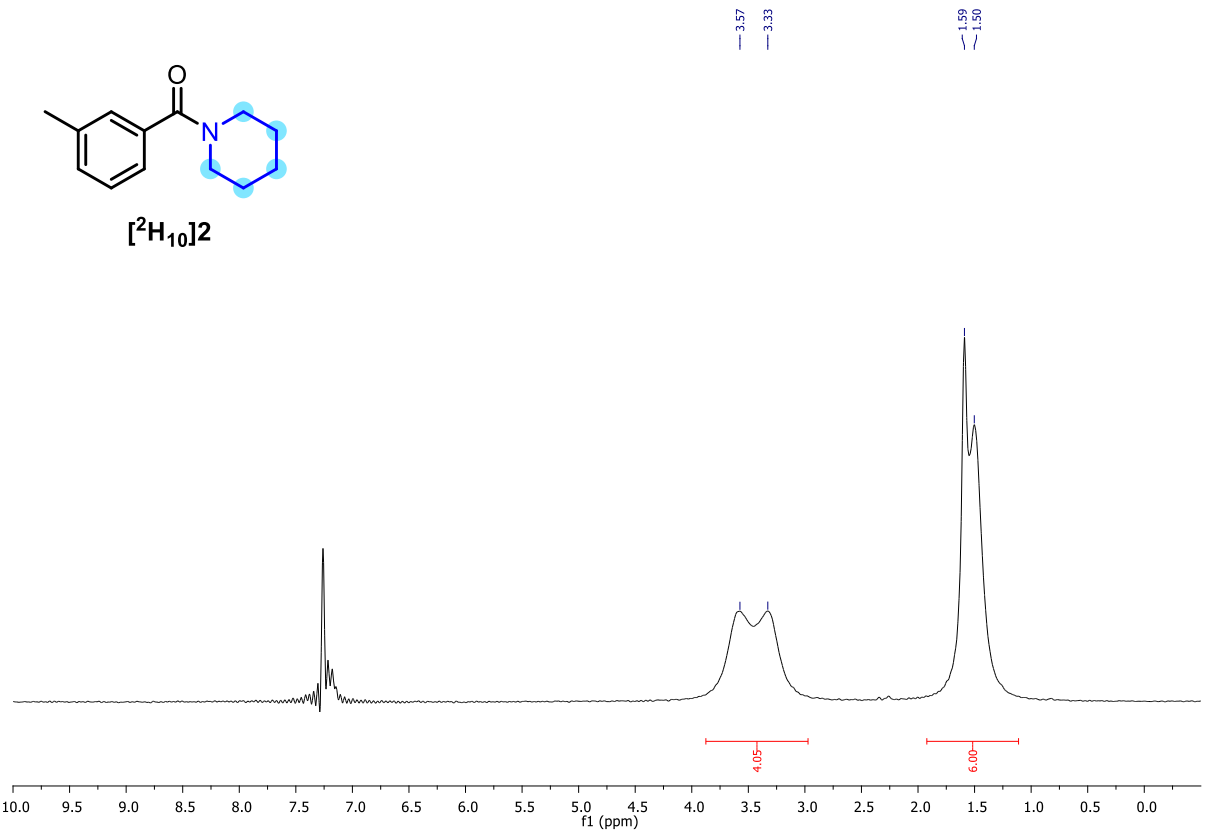


Figure S102: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

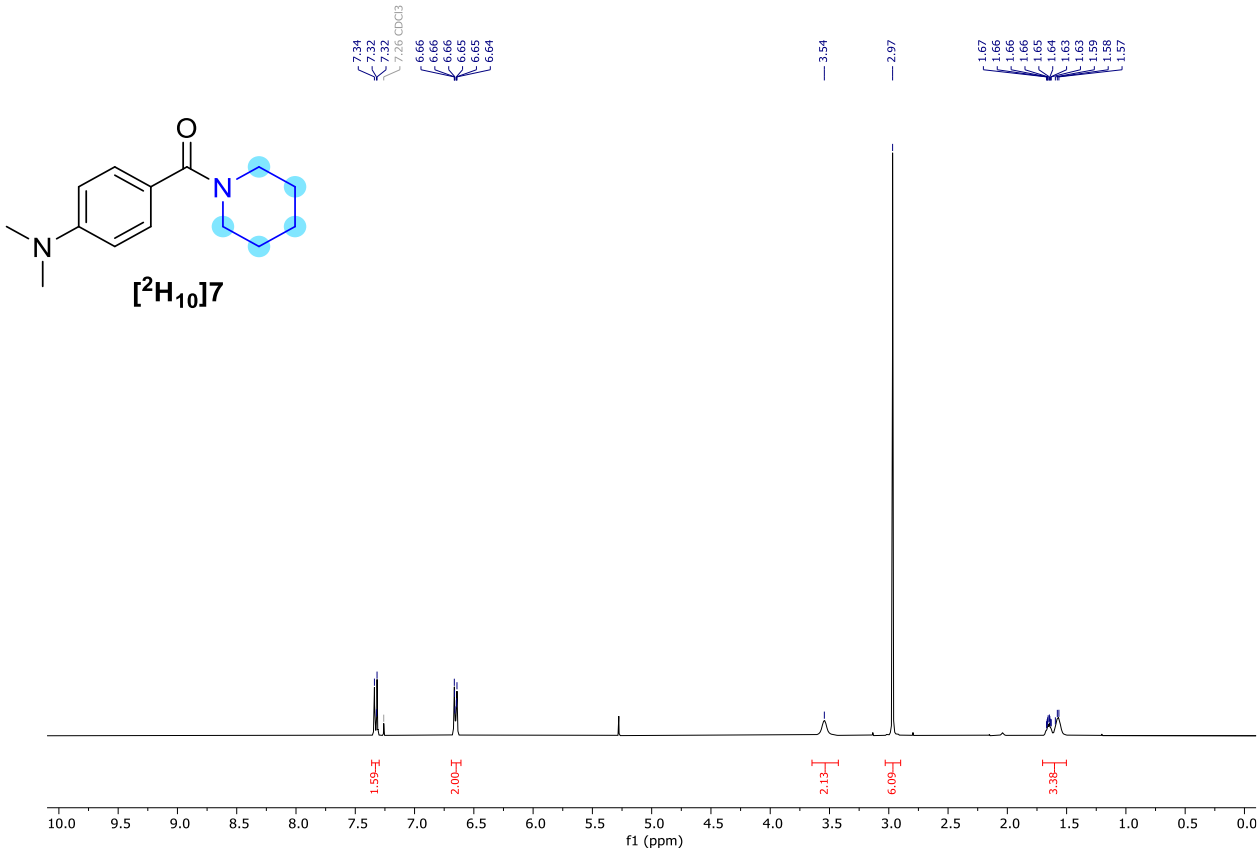


Figure S103: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

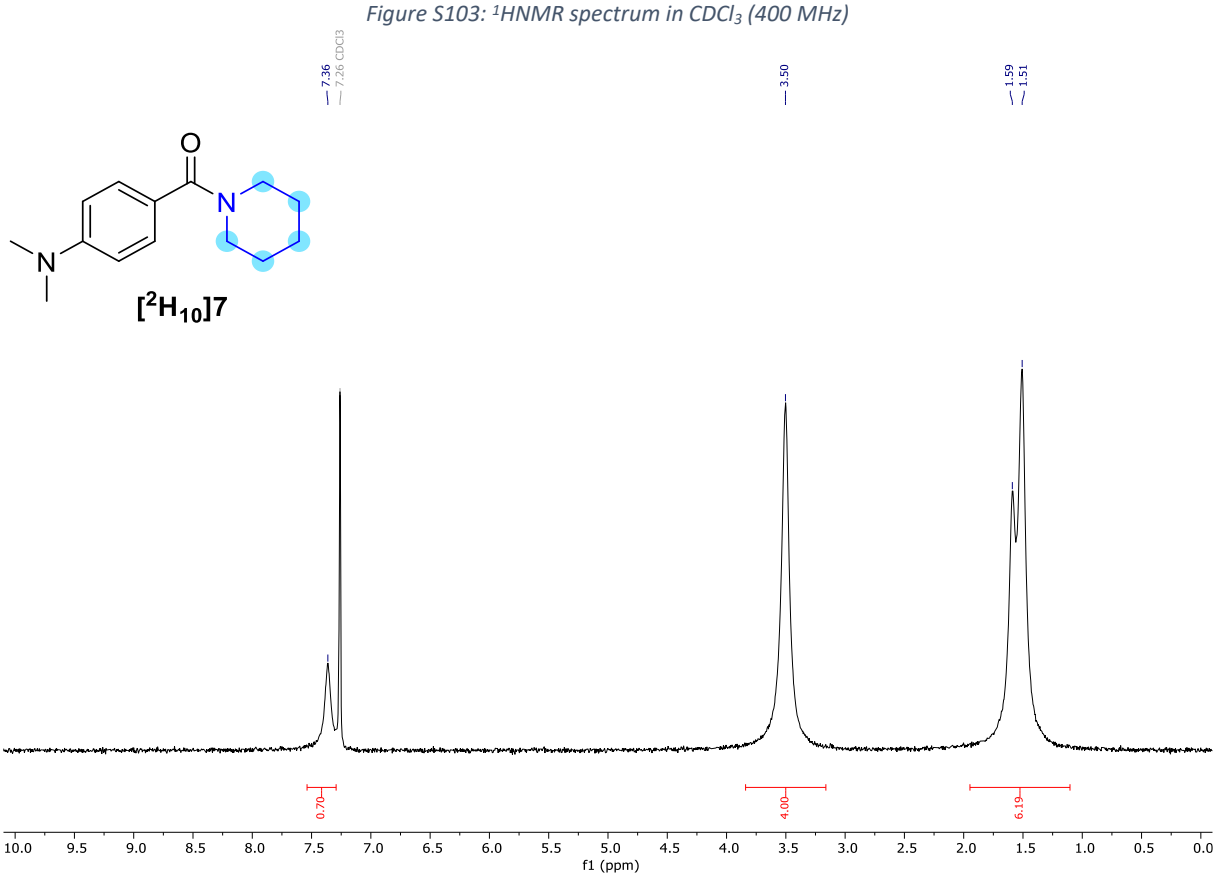


Figure S104: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

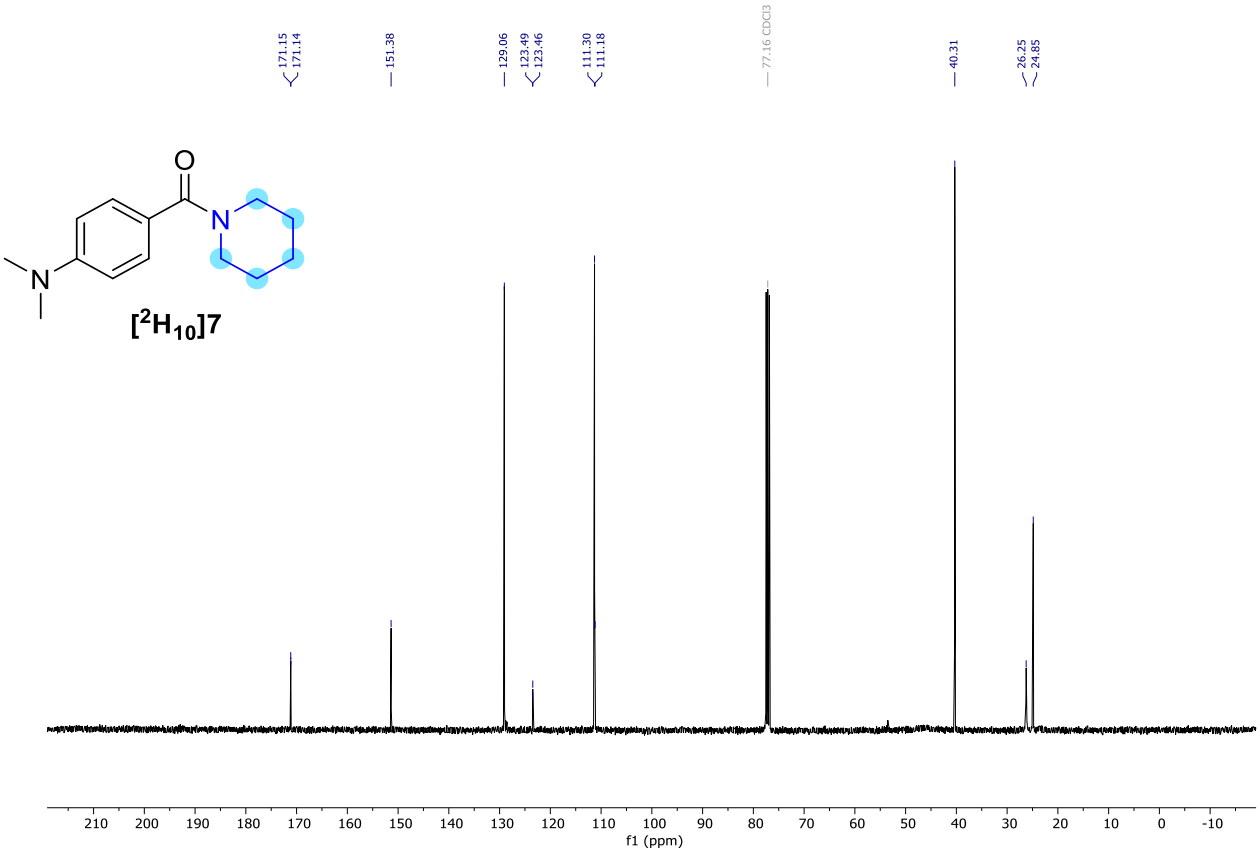


Figure S105: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

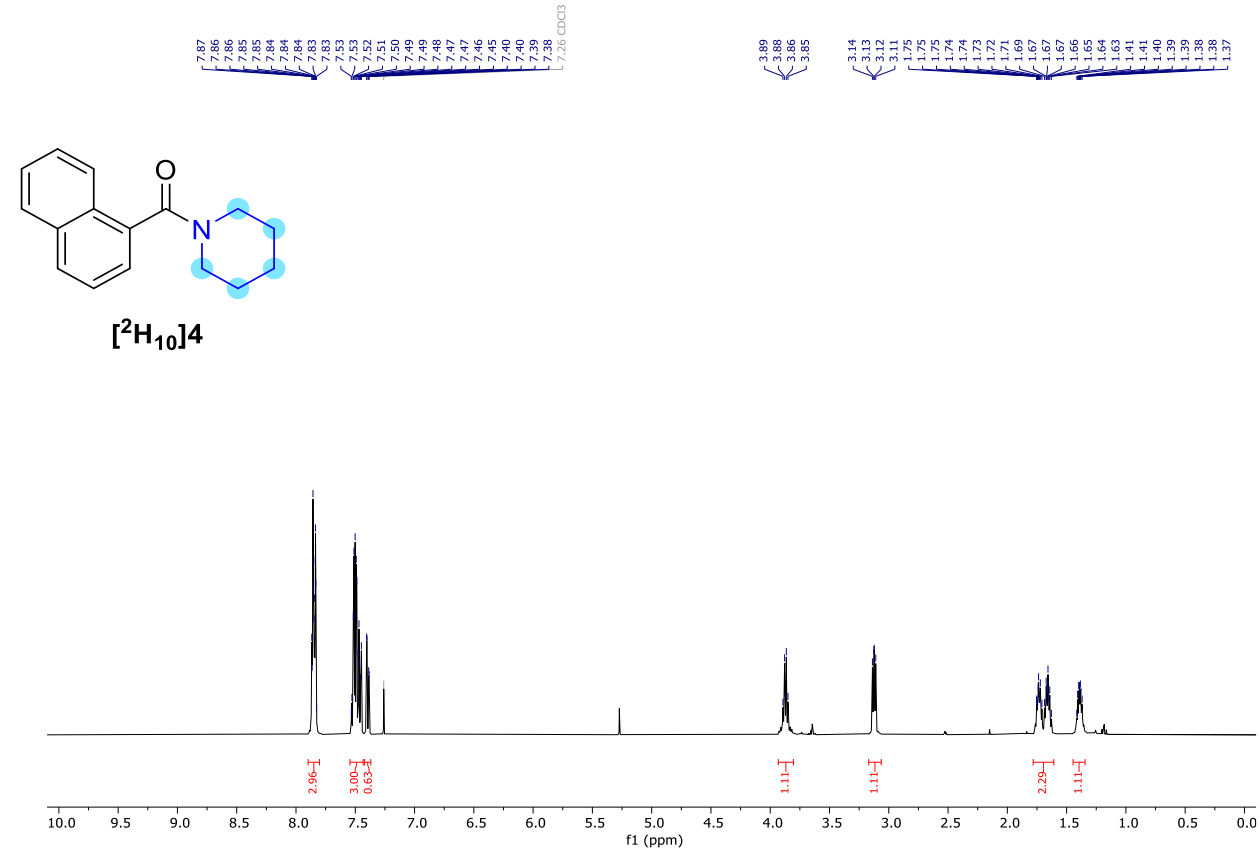


Figure S106: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

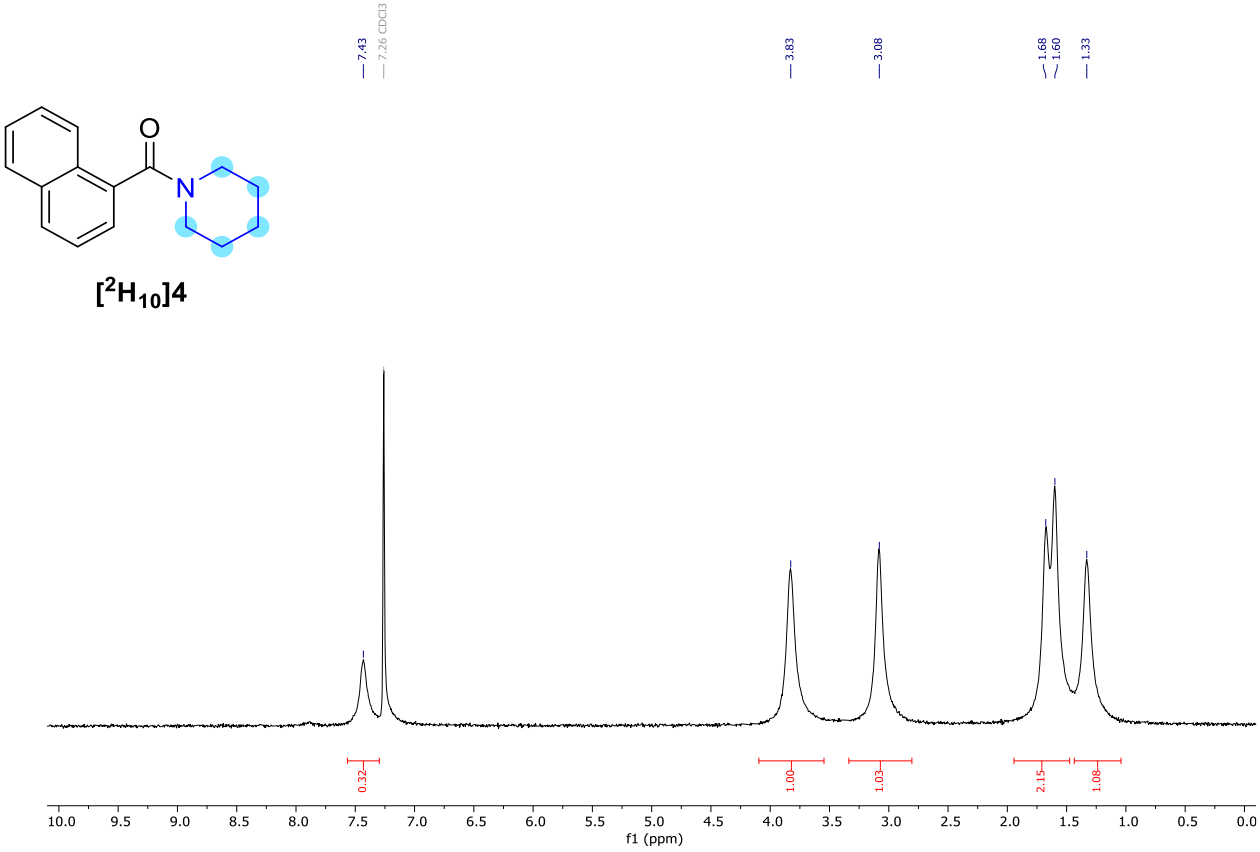


Figure S107: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

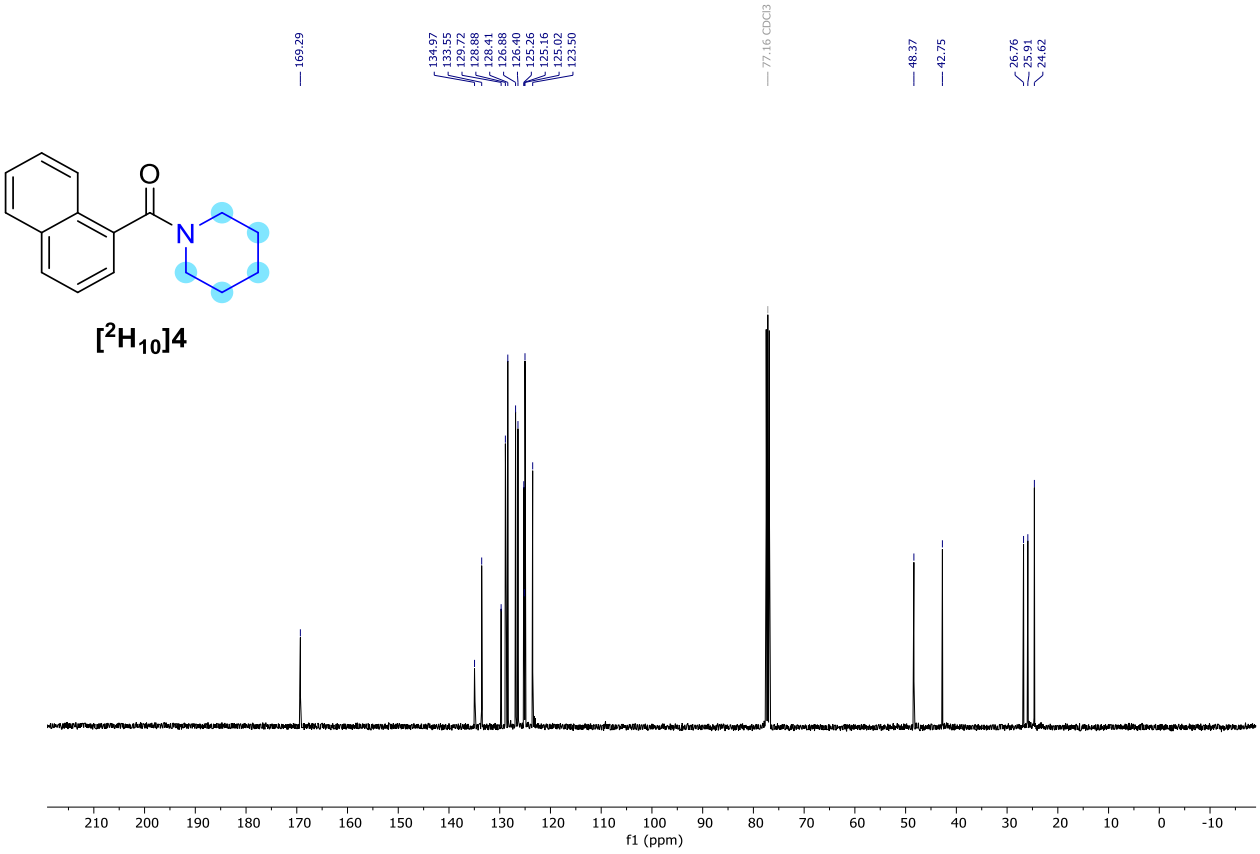


Figure S108: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

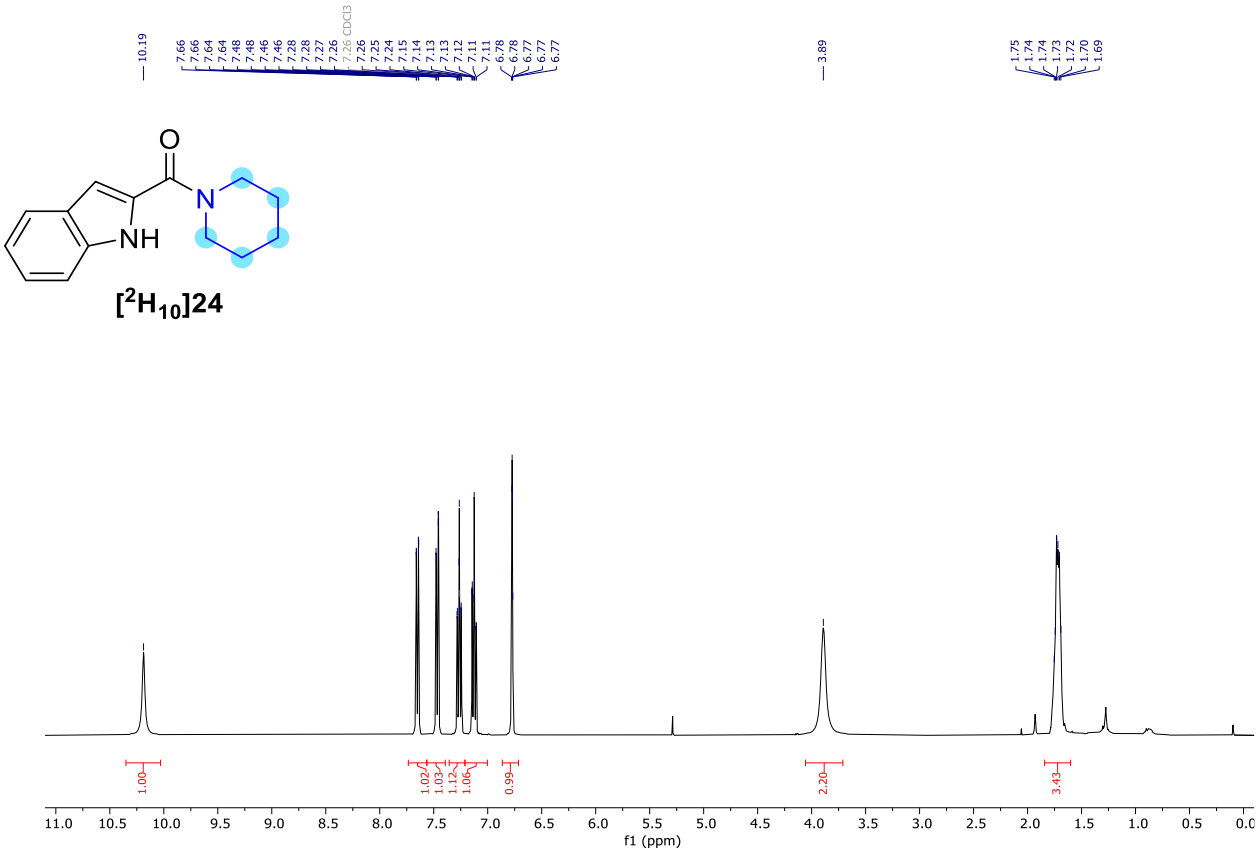


Figure S109: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

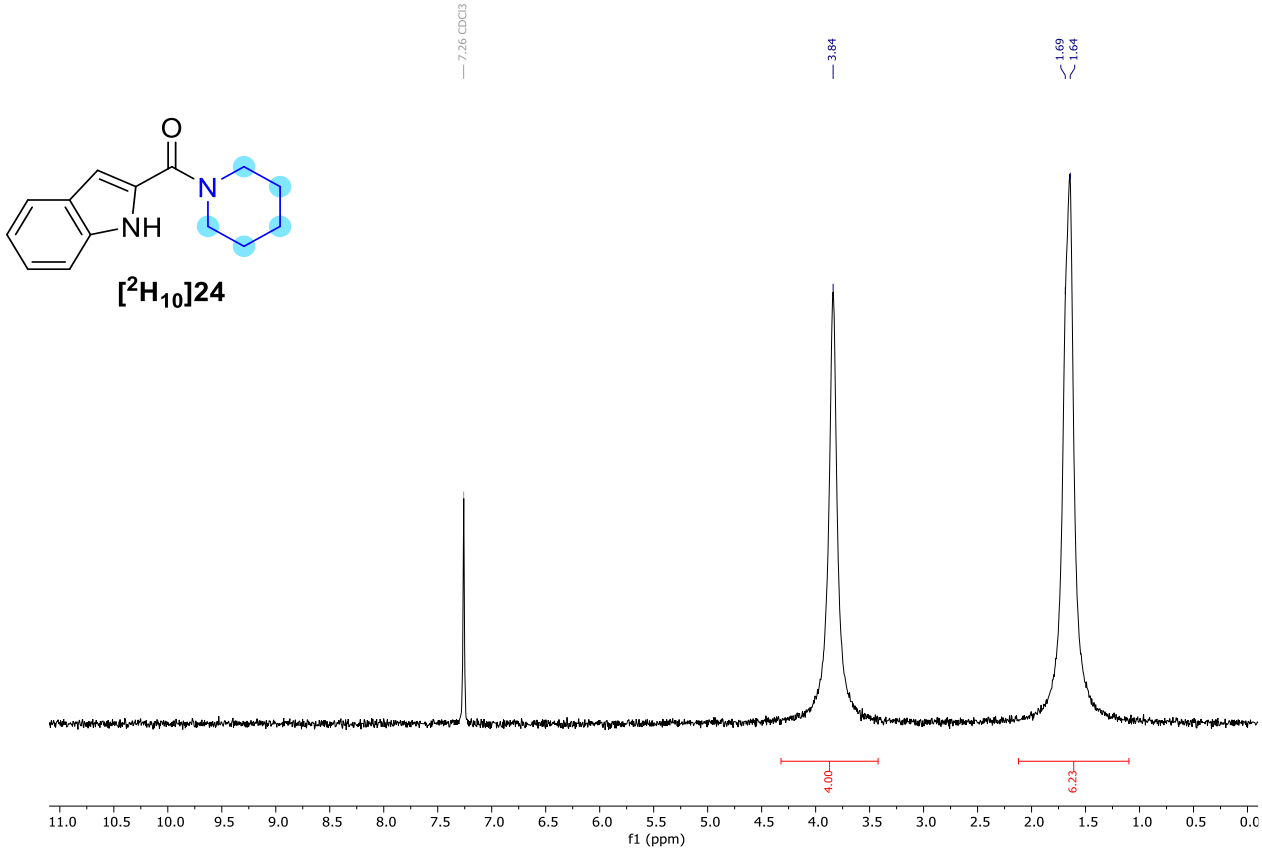


Figure S110: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

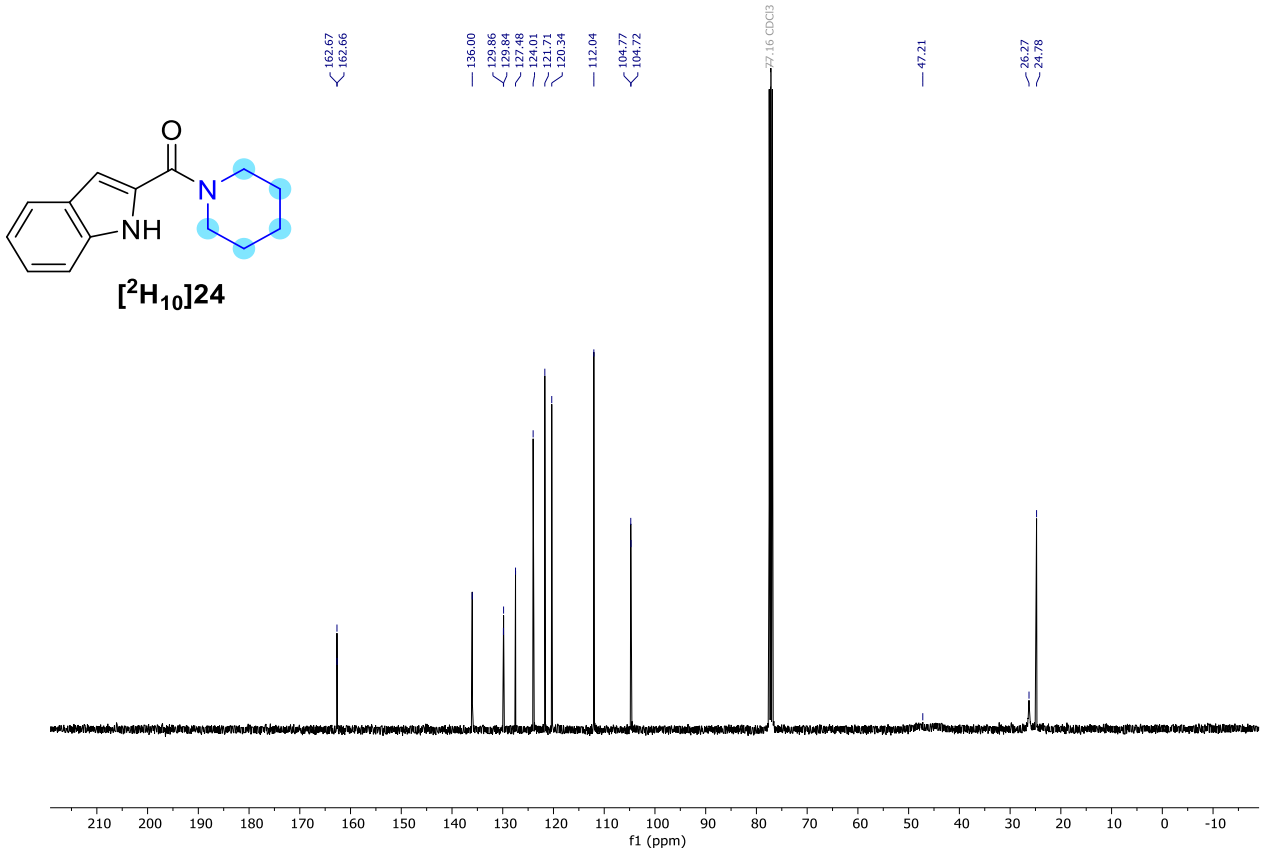
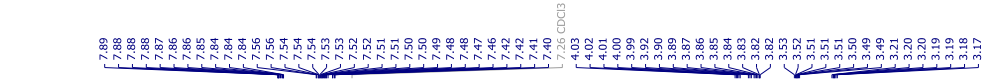
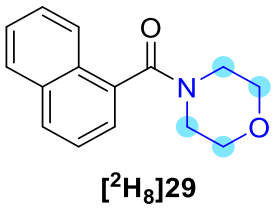


Figure S111: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)





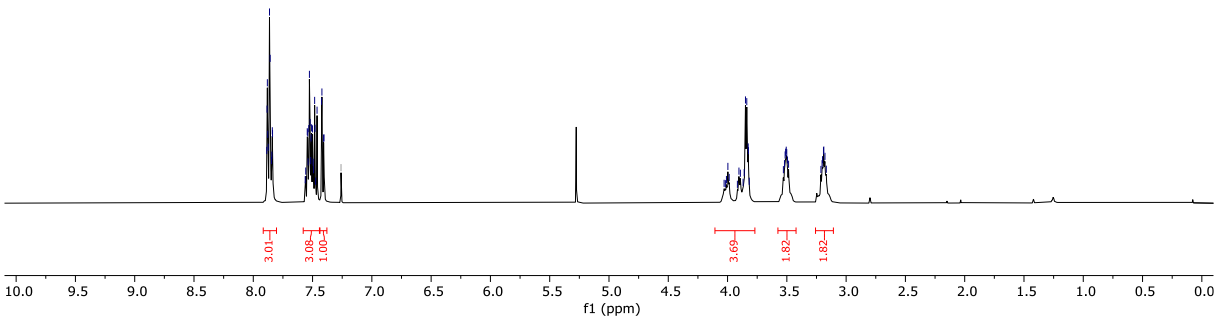


Figure S112: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

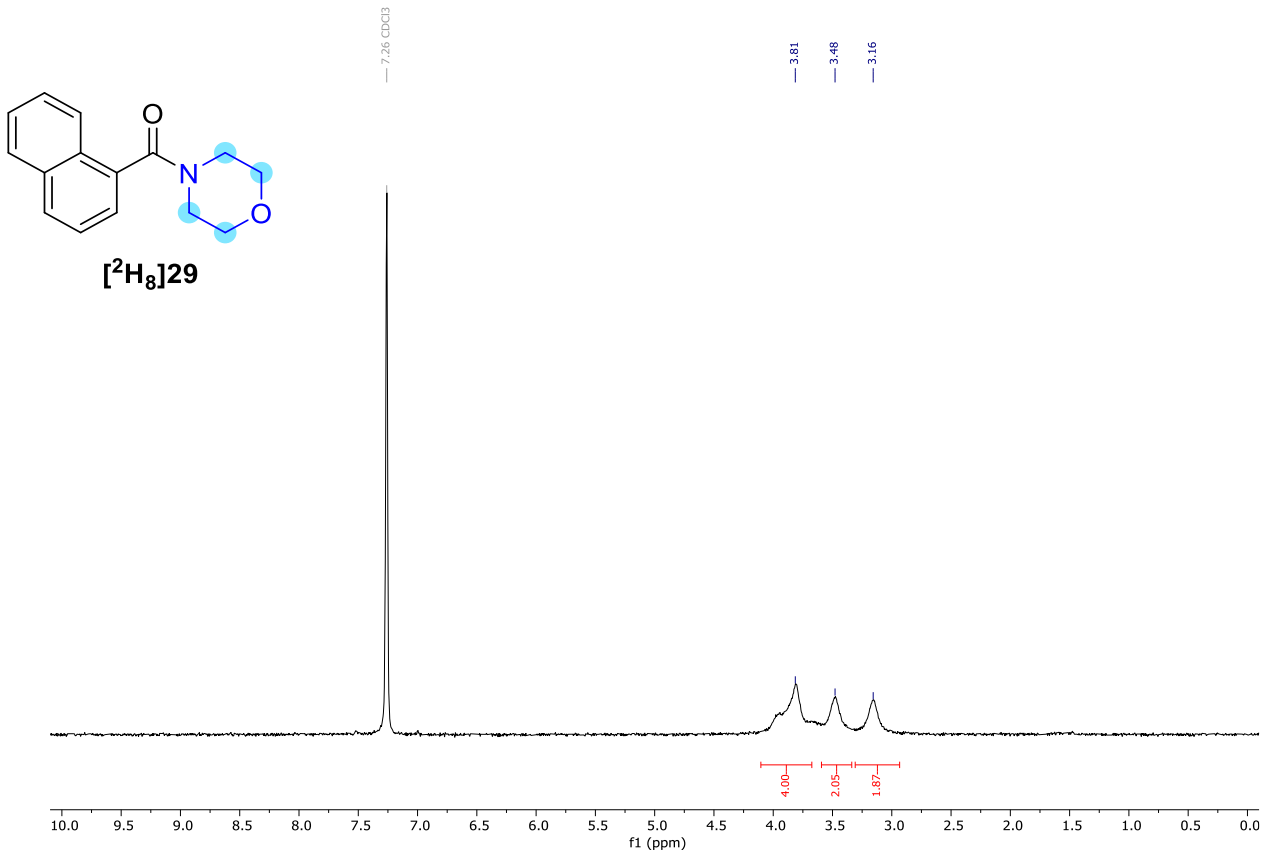


Figure S113: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

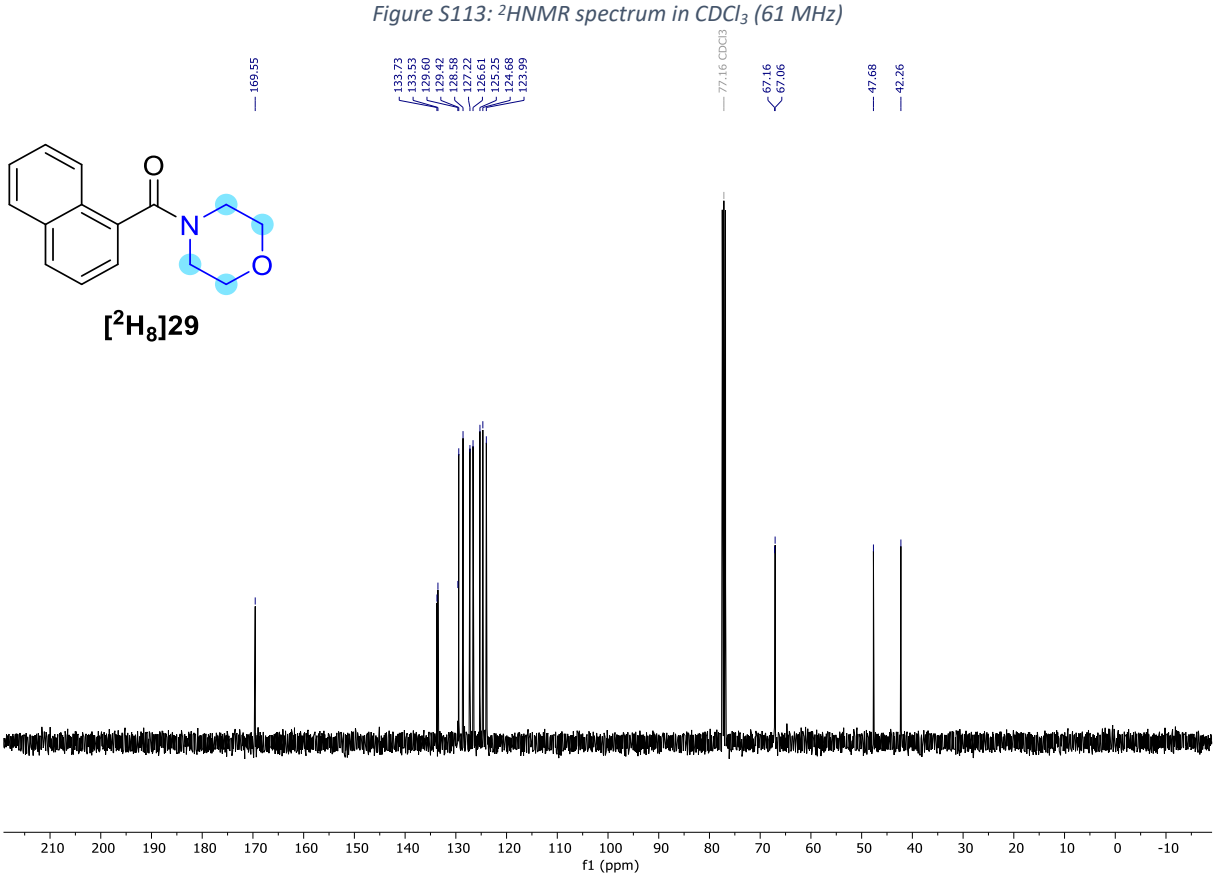


Figure S114: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

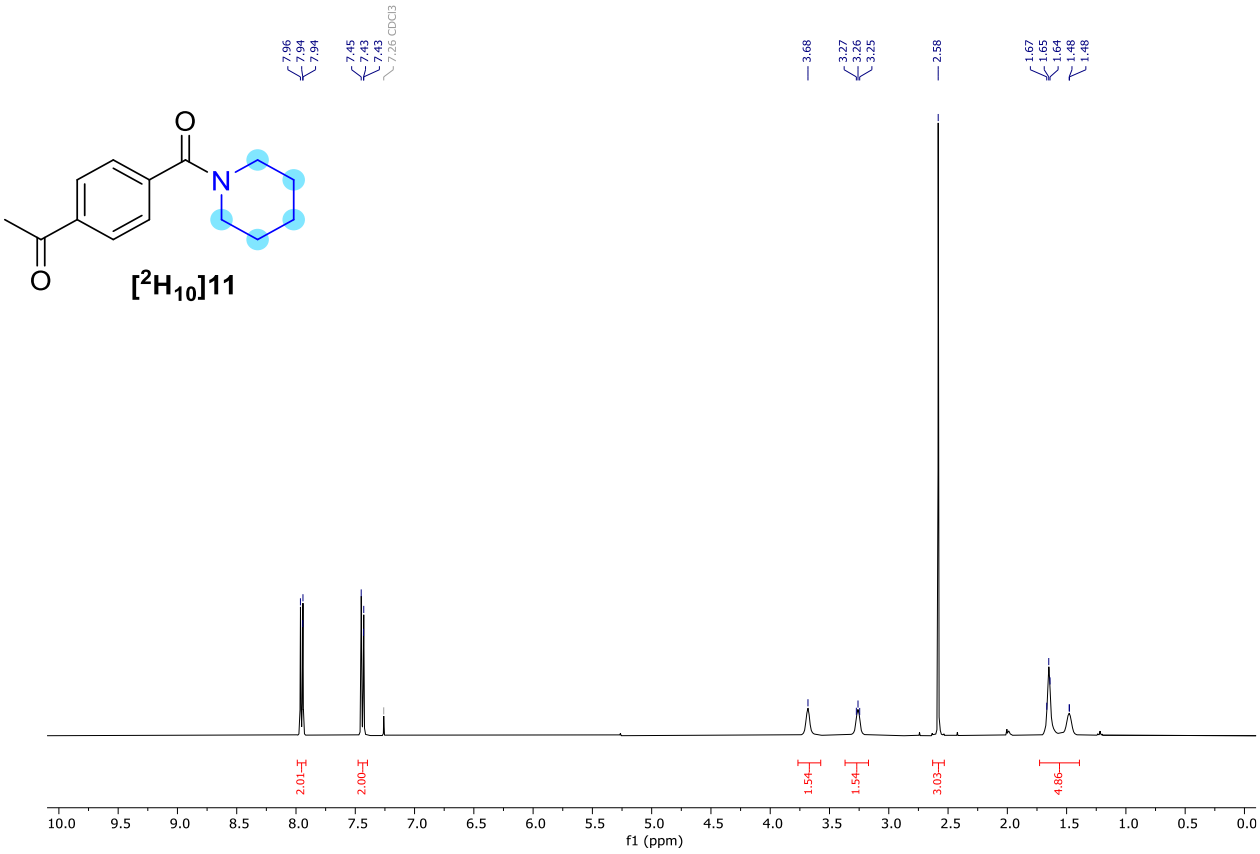


Figure S115: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

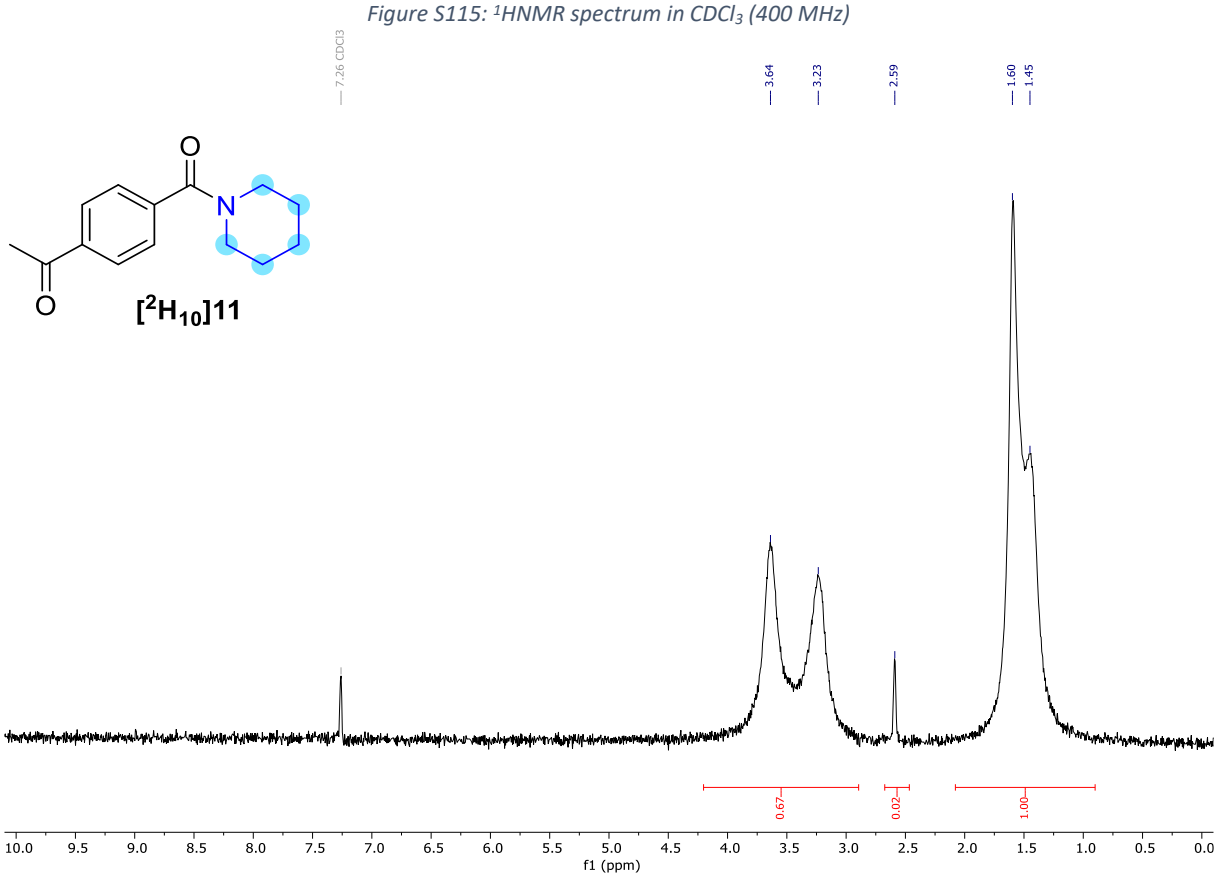


Figure S116: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

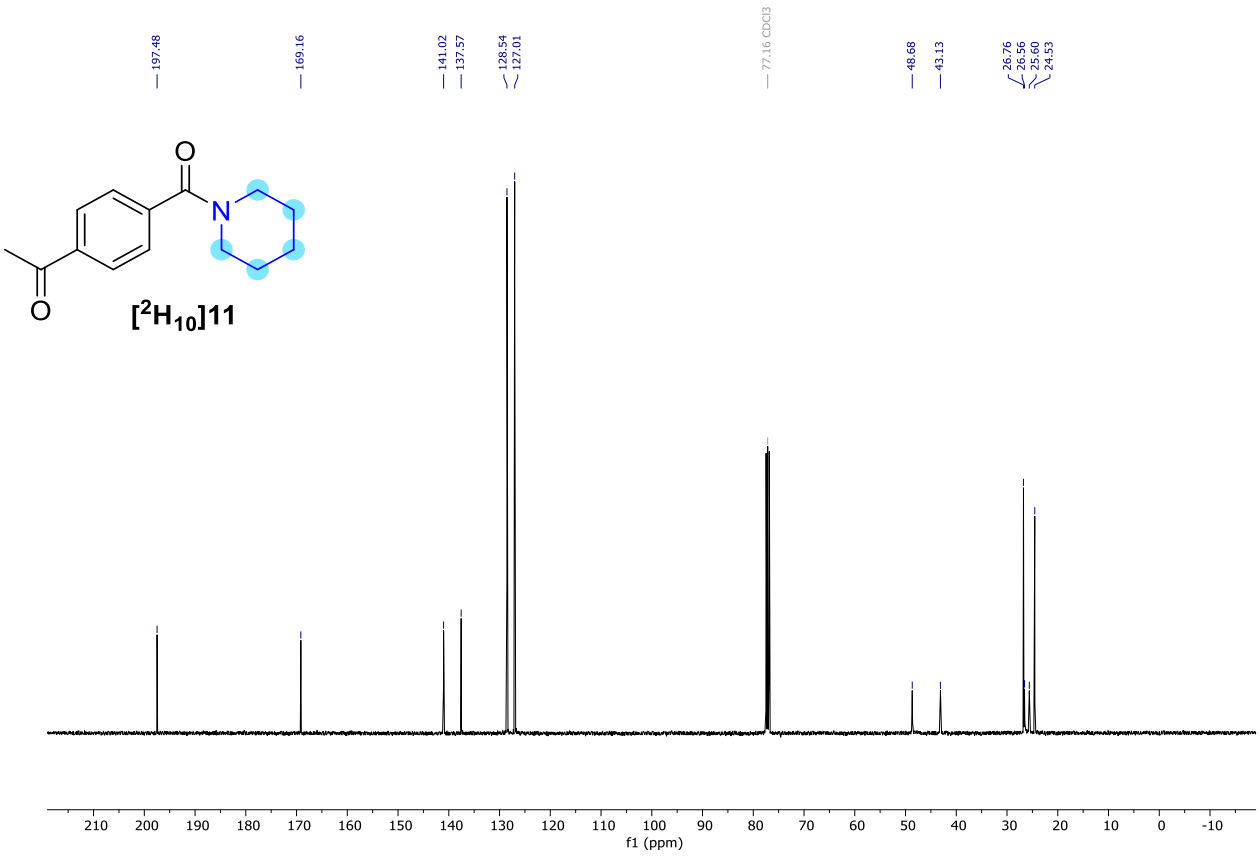


Figure S117: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

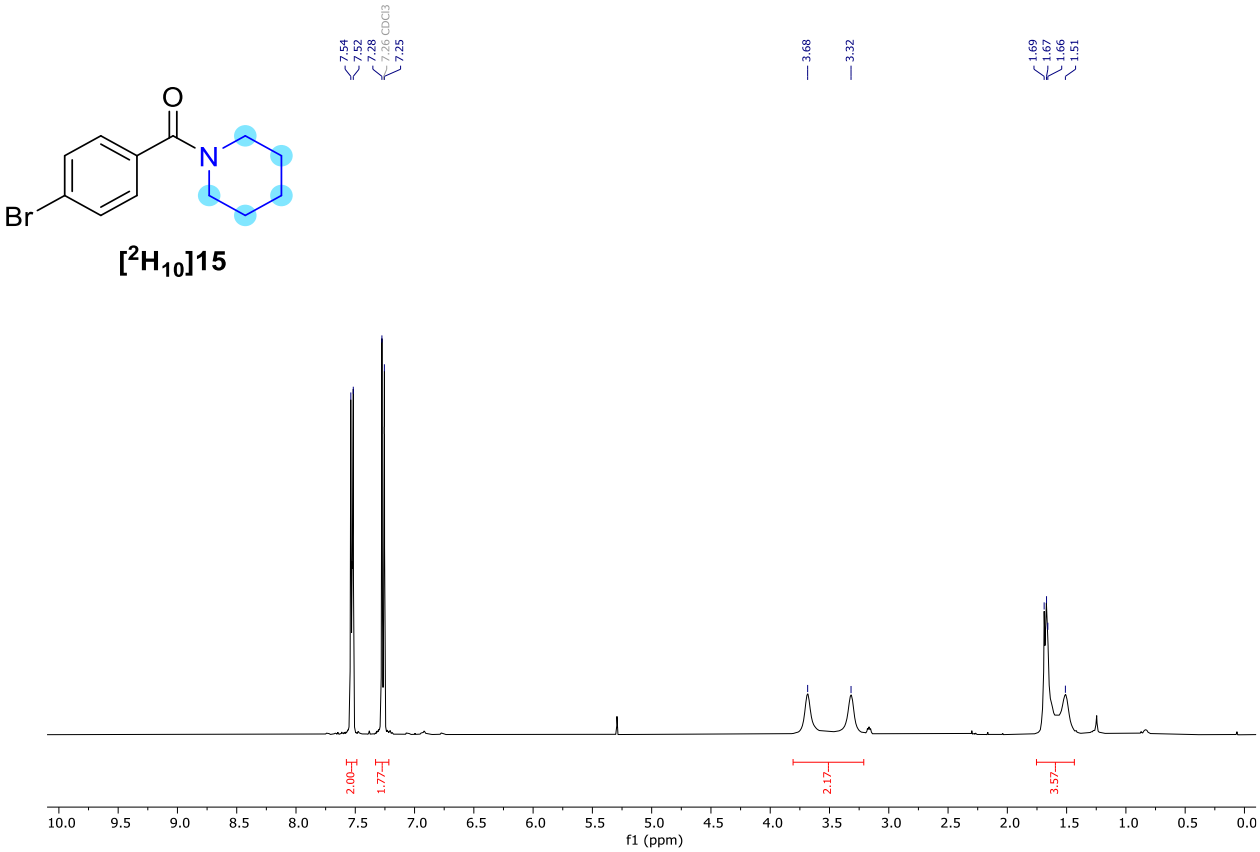


Figure S118: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

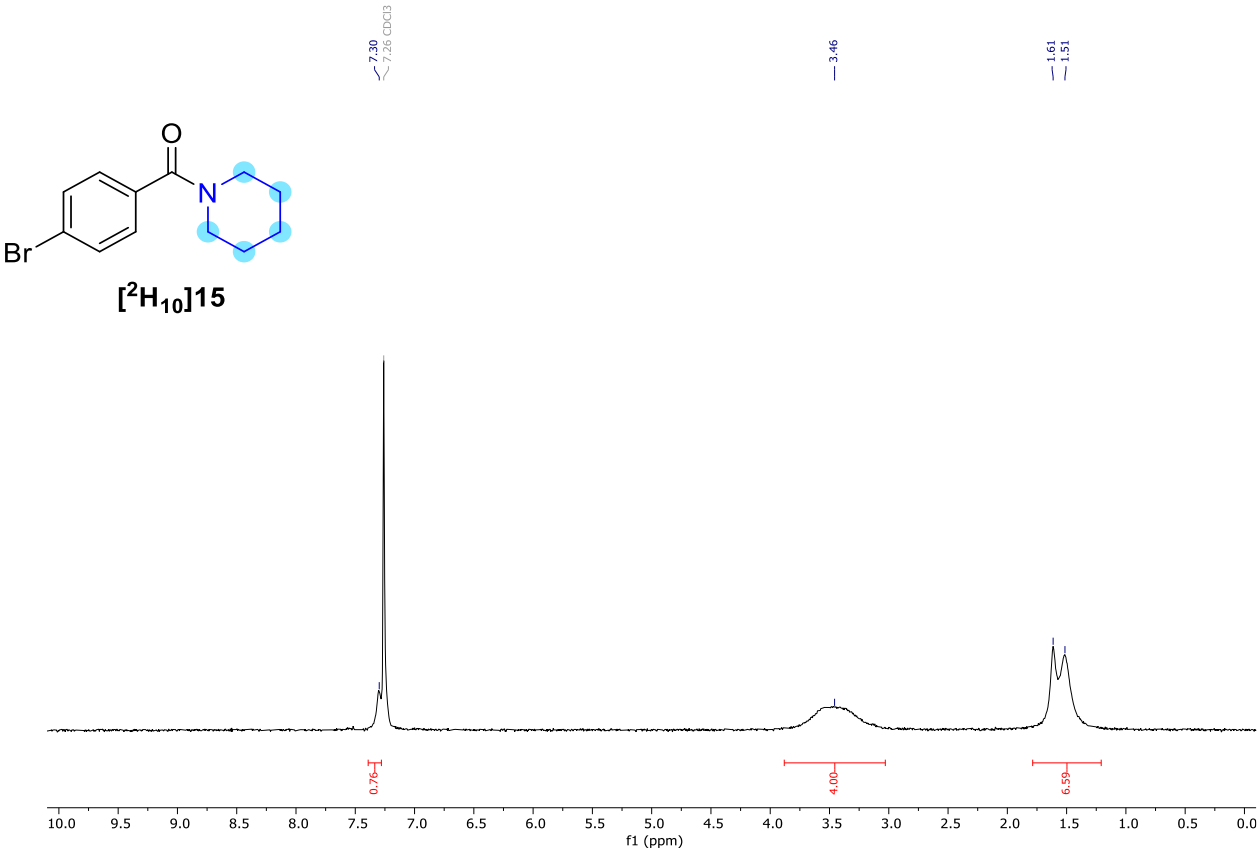


Figure S119: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

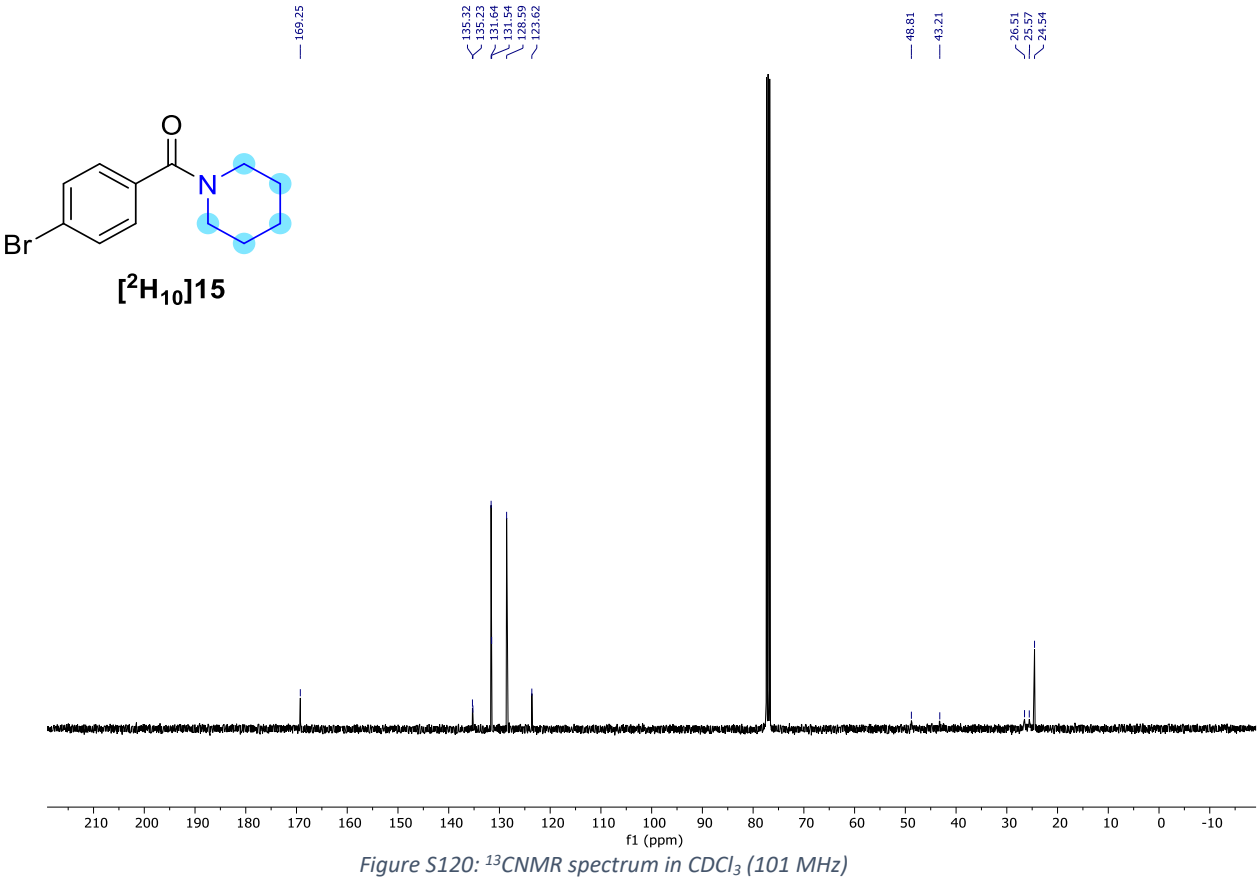


Figure S120: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

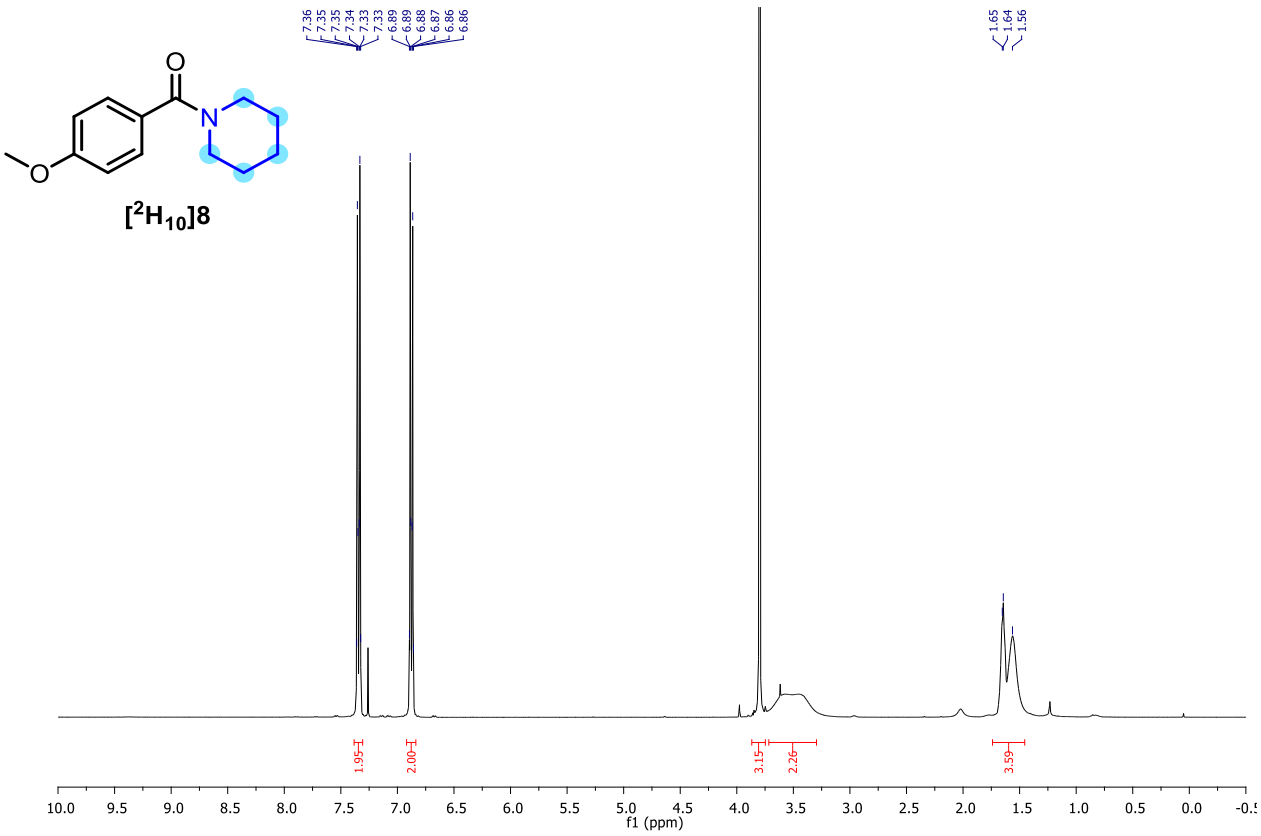


Figure S121: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

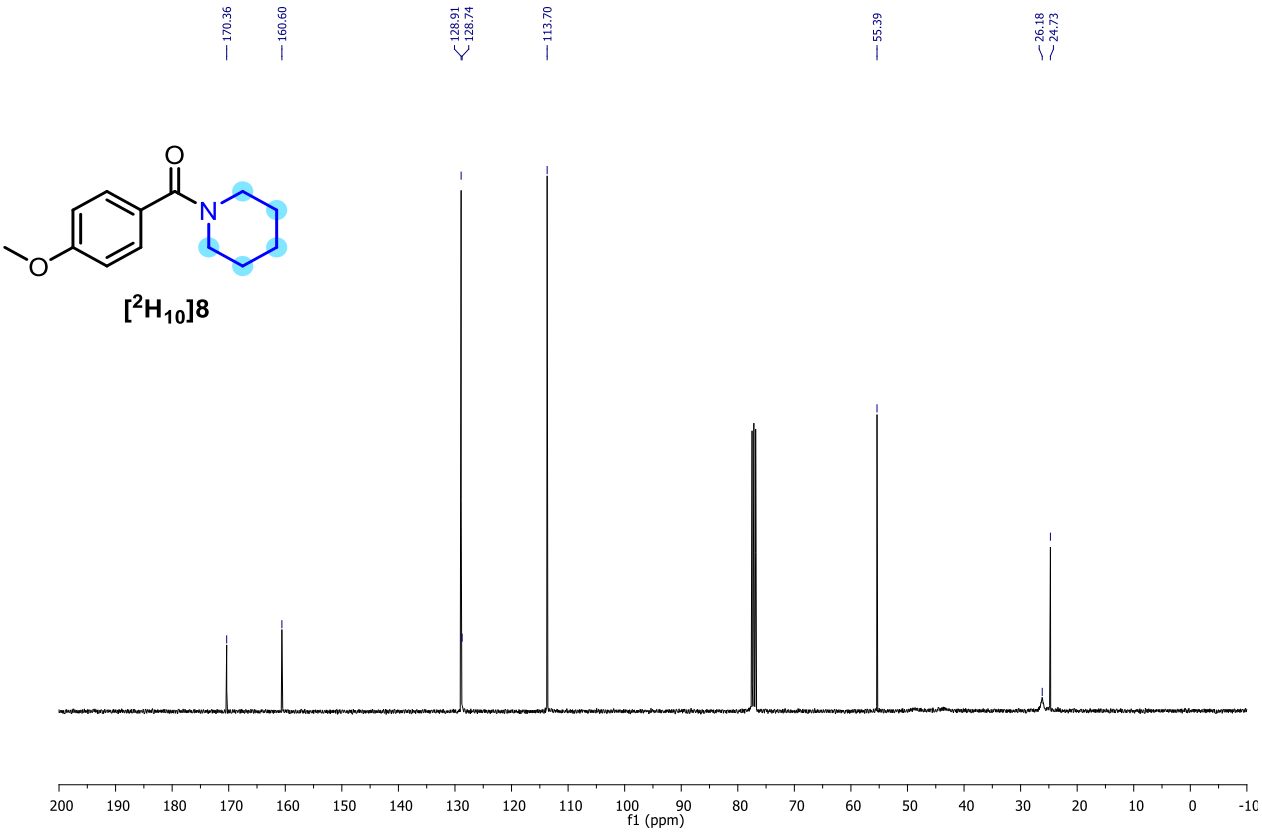
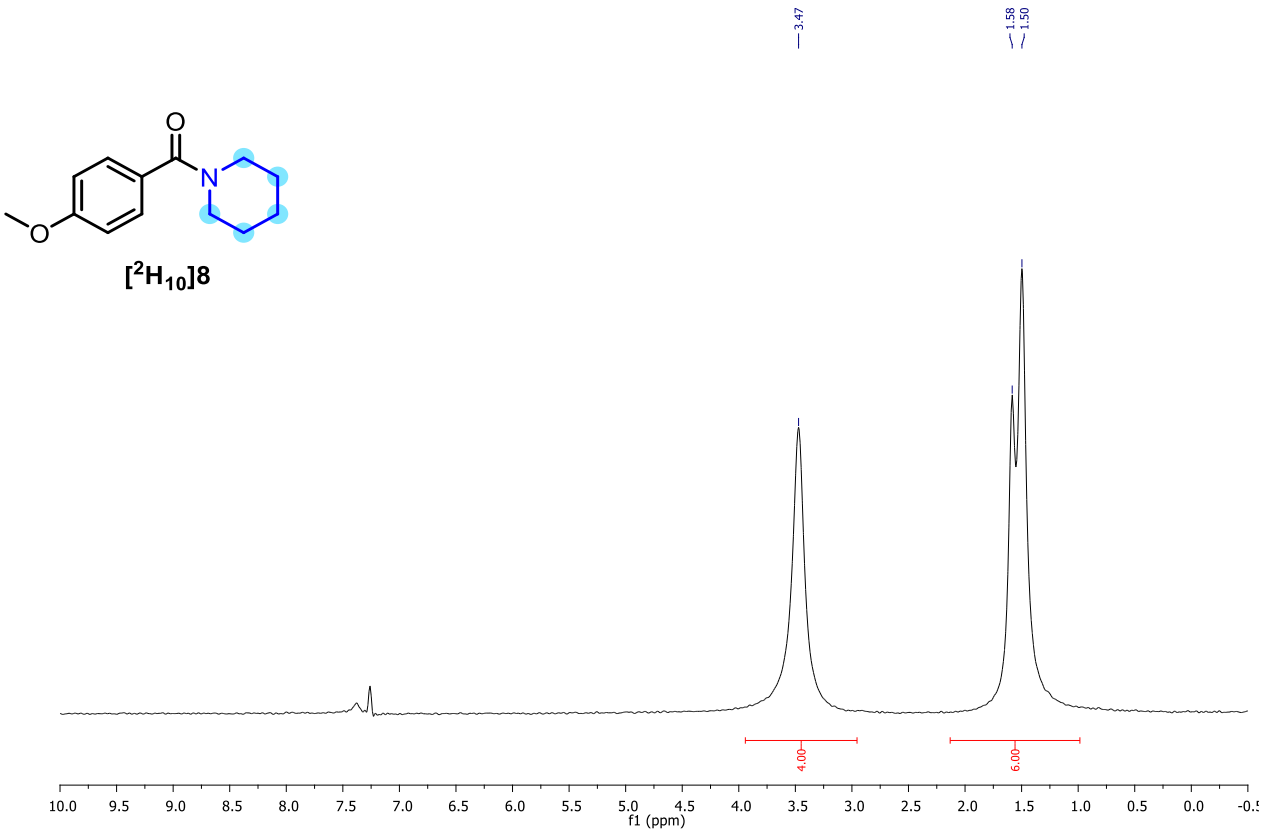
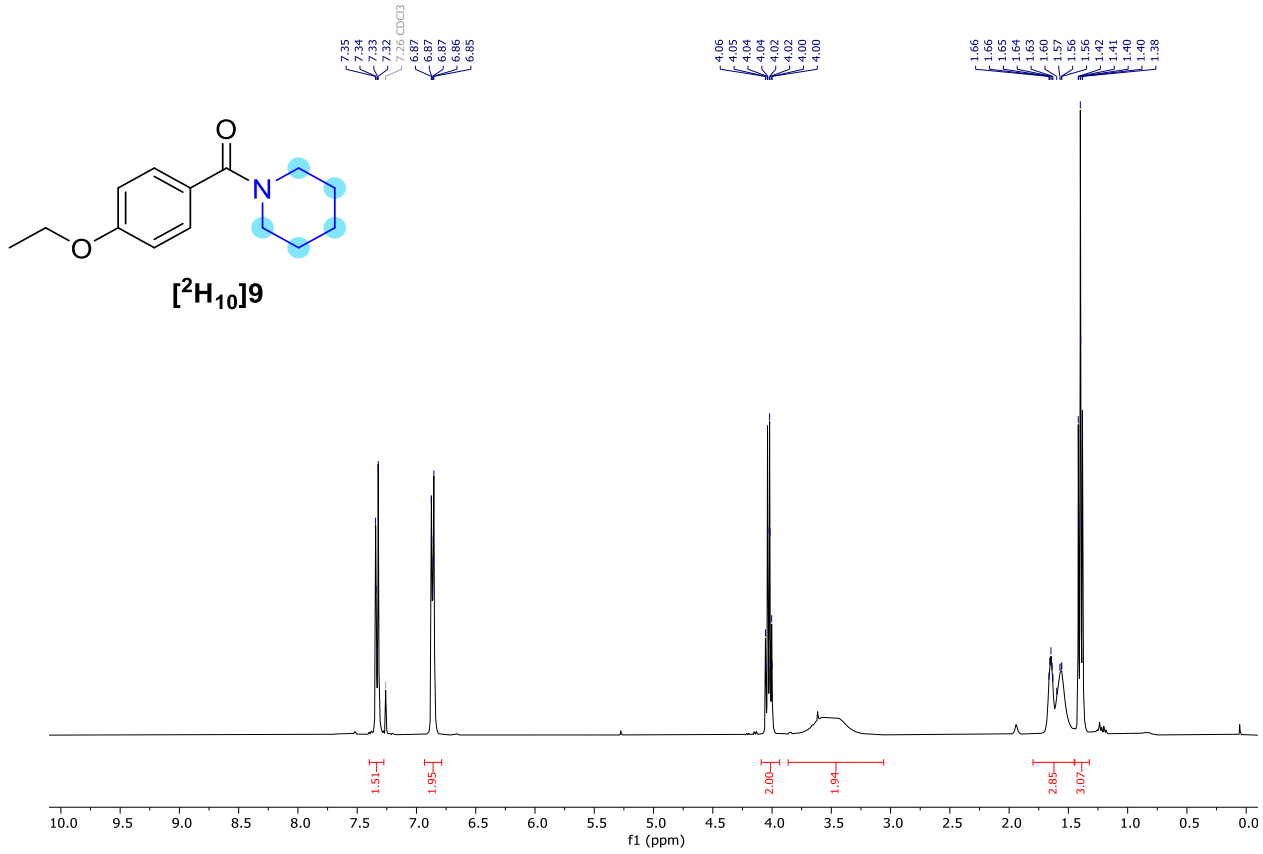


Figure S122: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)



$[^2H_{10}]$8

Figure S123: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)



$[^2H_{10}]$9

Figure S124: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

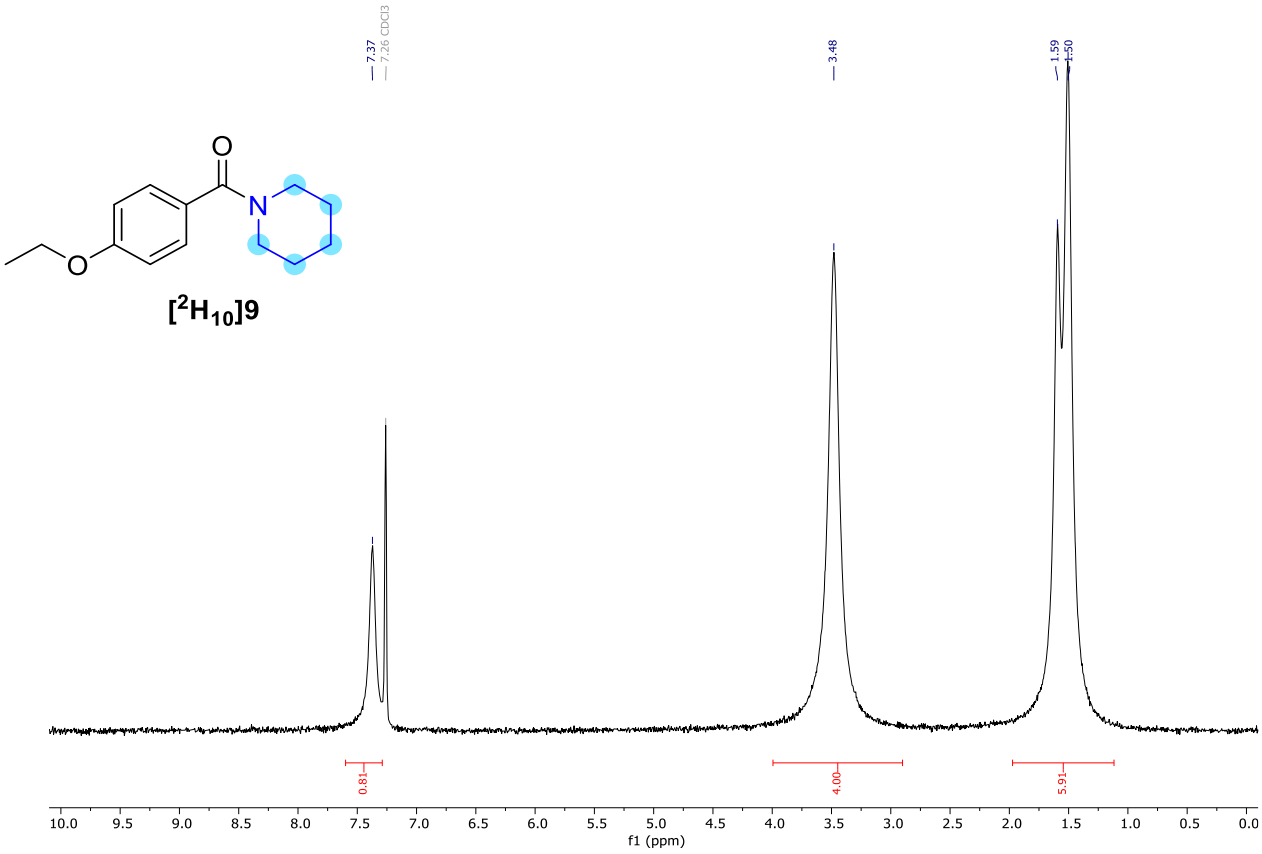


Figure S125: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

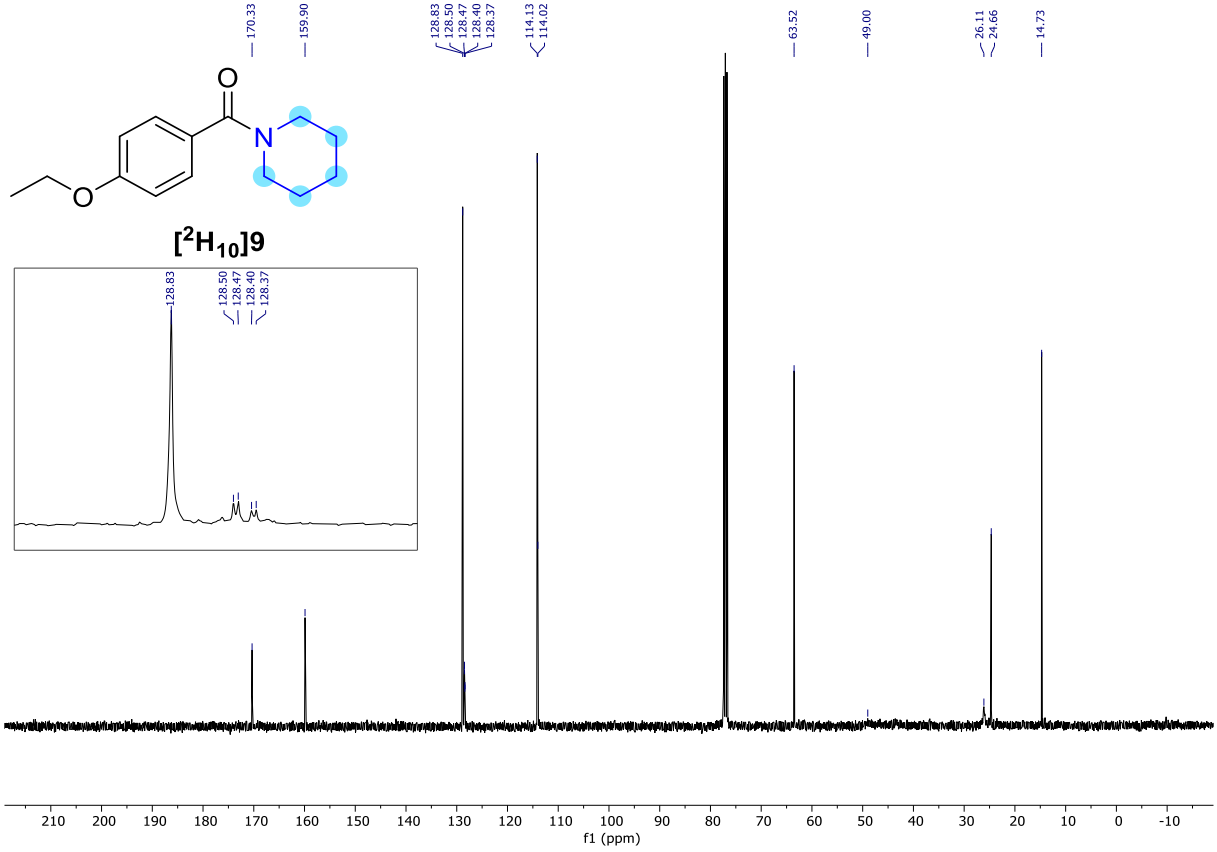


Figure S126: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

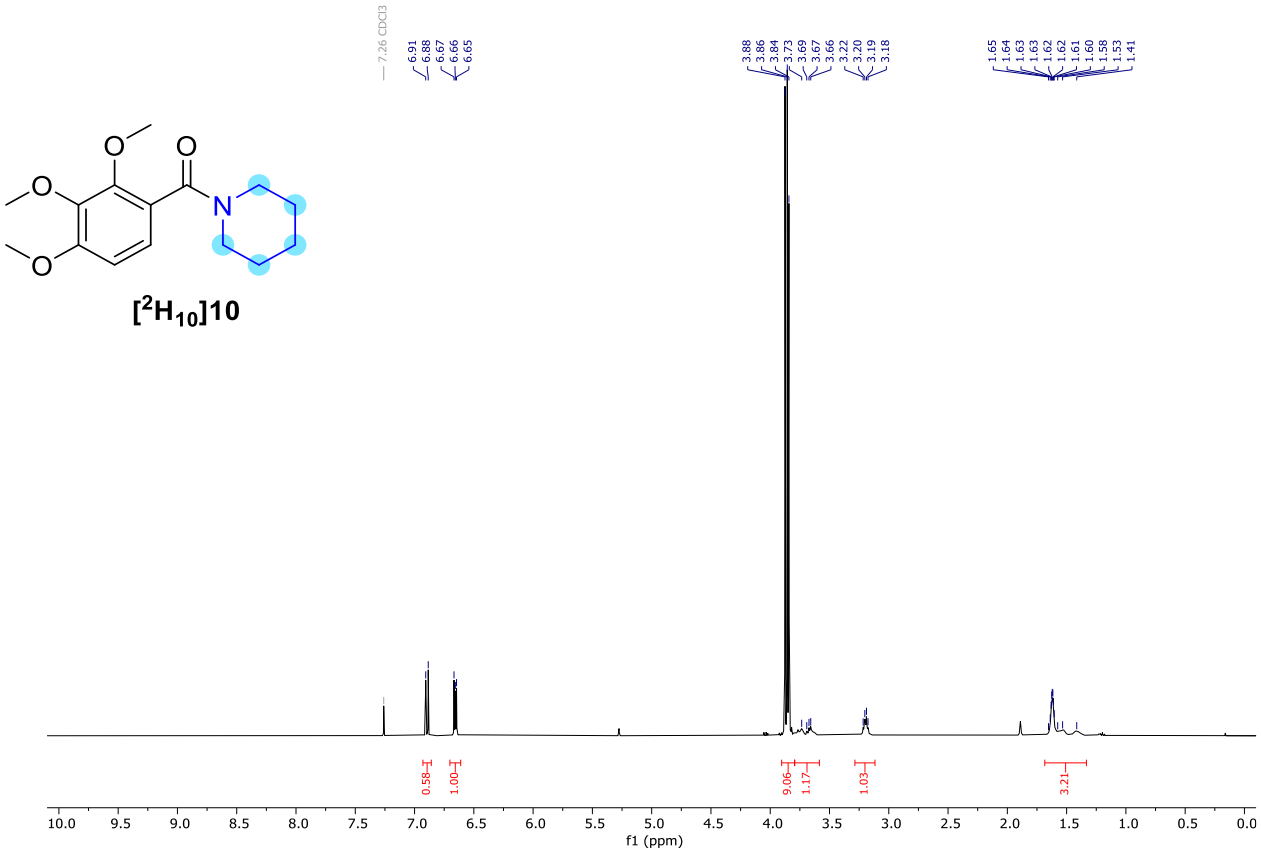


Figure S127: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

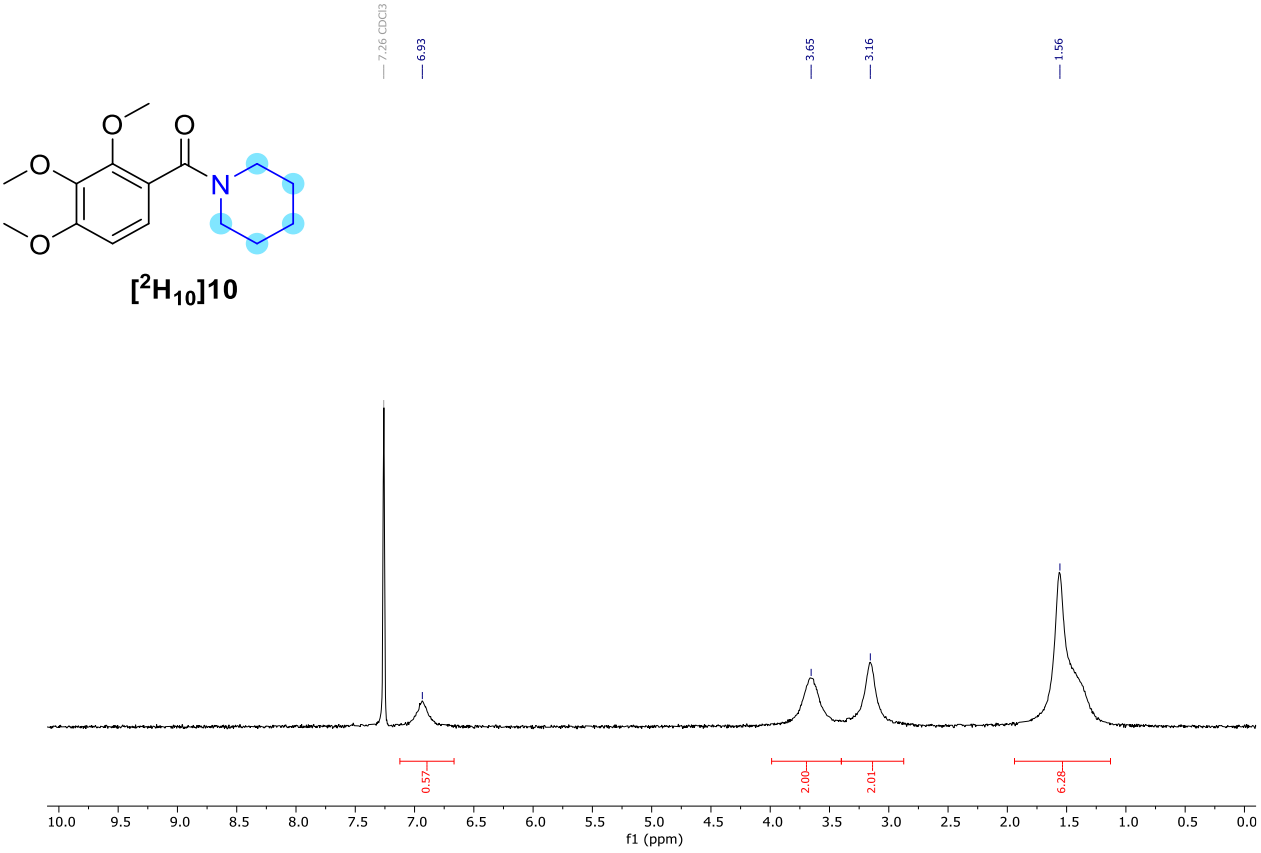


Figure S128: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

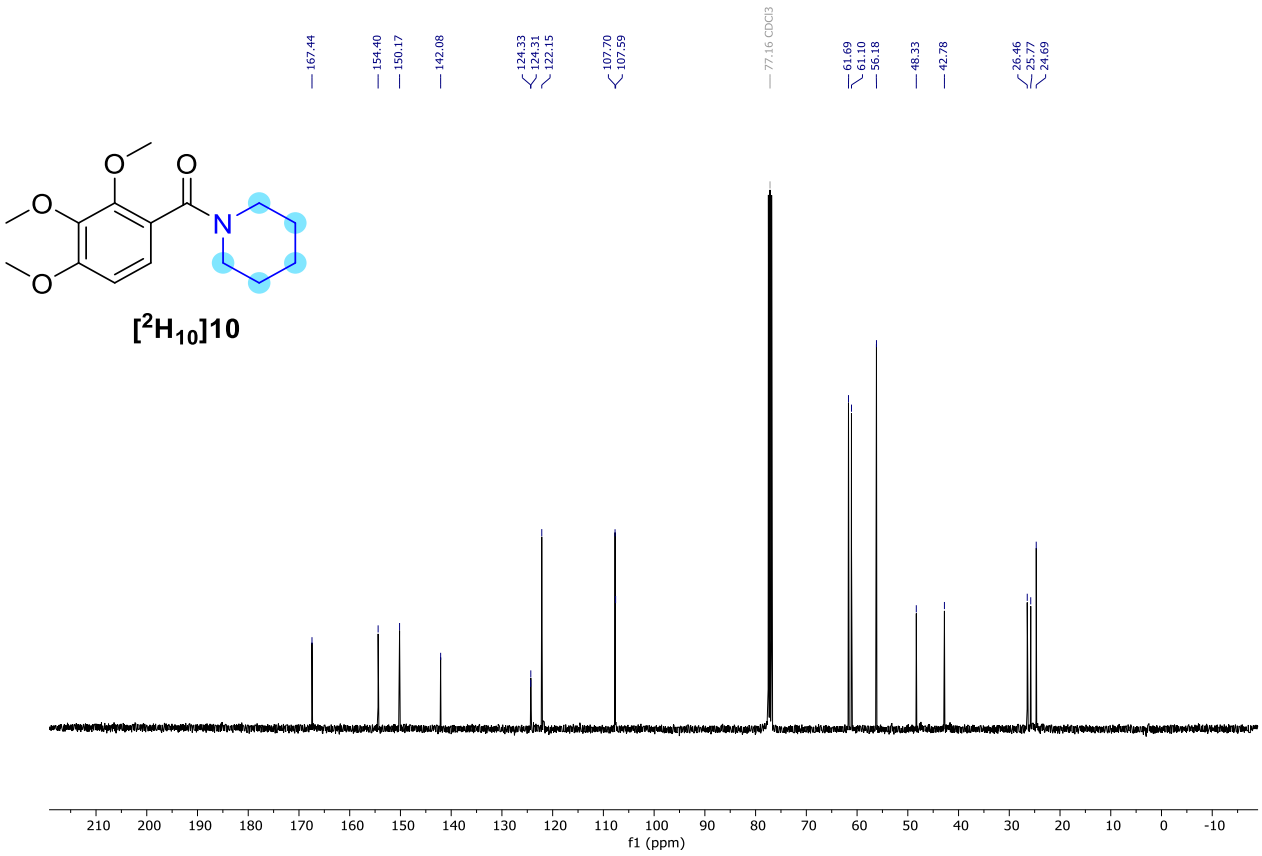


Figure S129: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

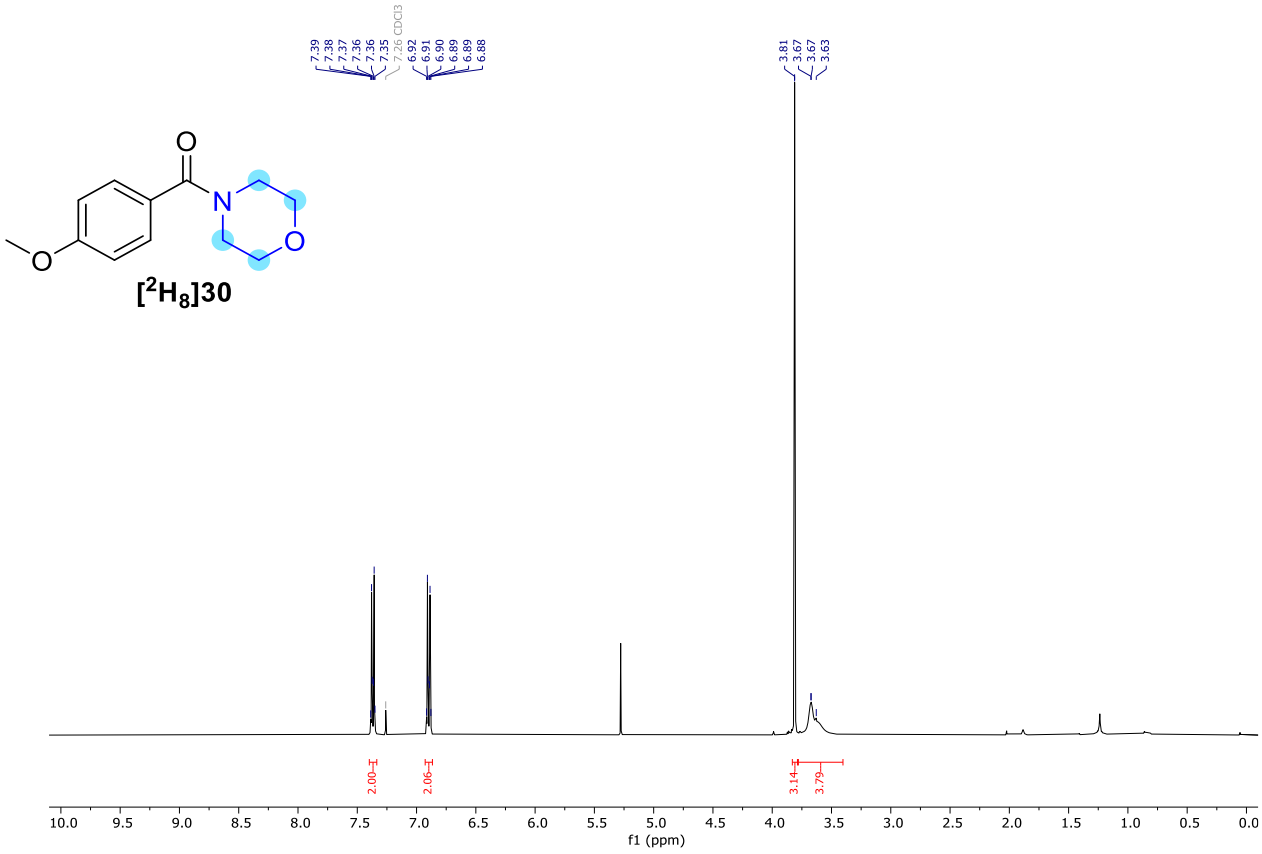


Figure S130: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

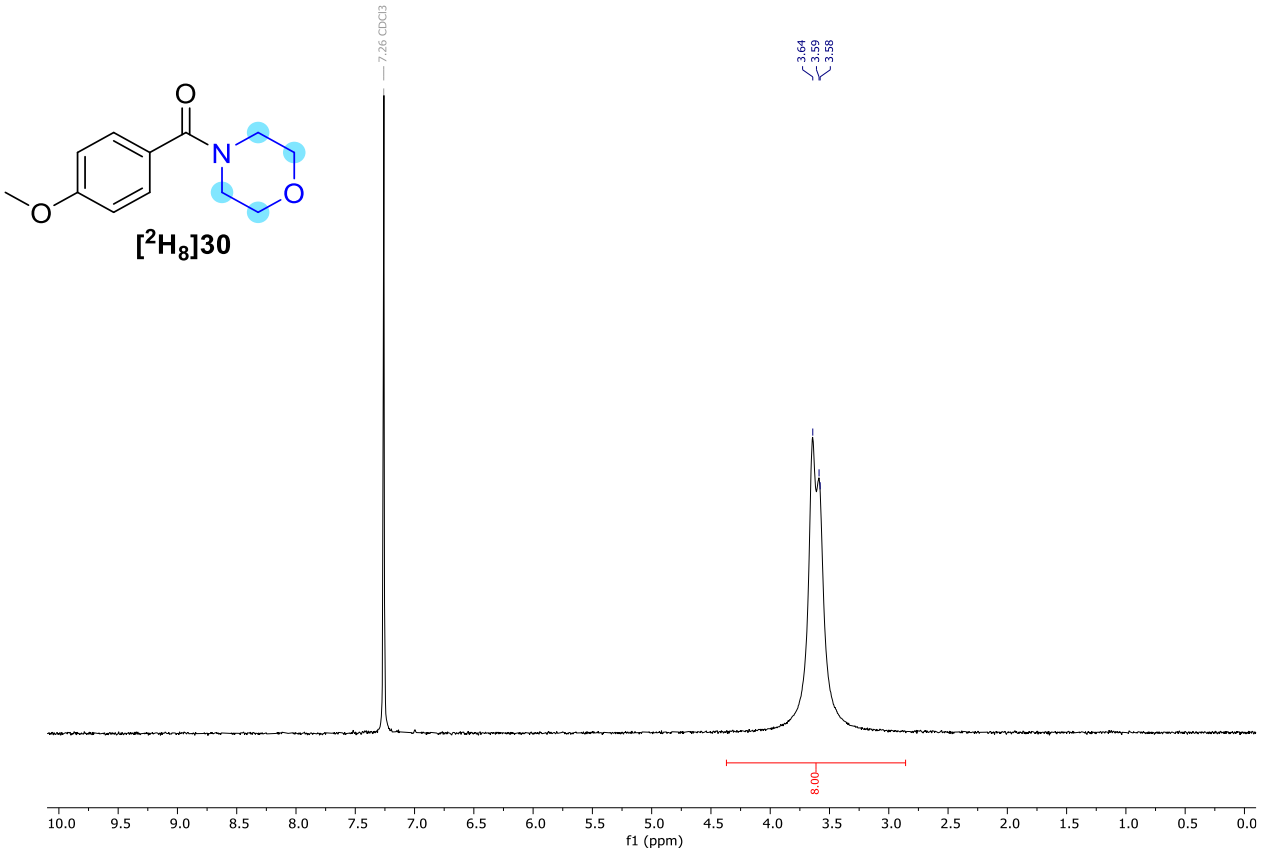


Figure S131: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

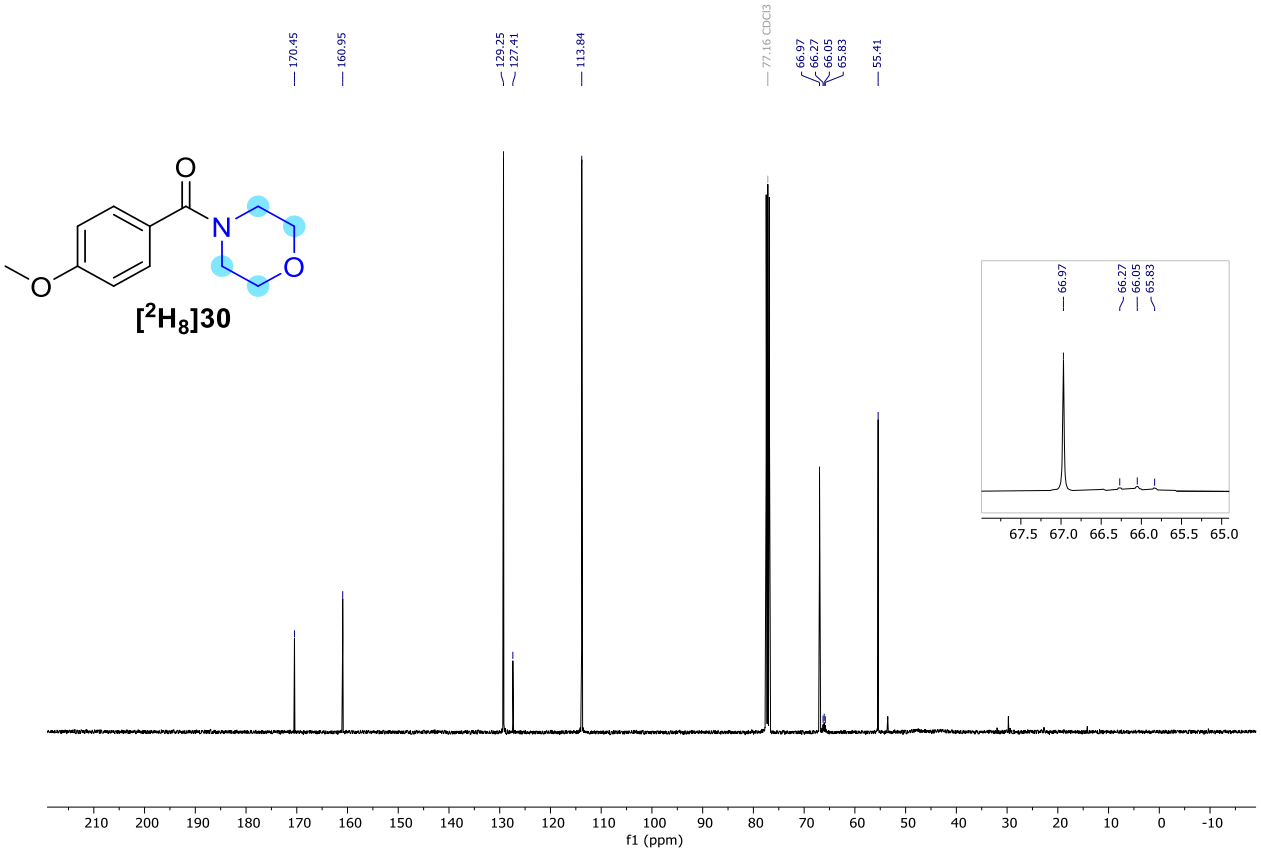


Figure S132: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

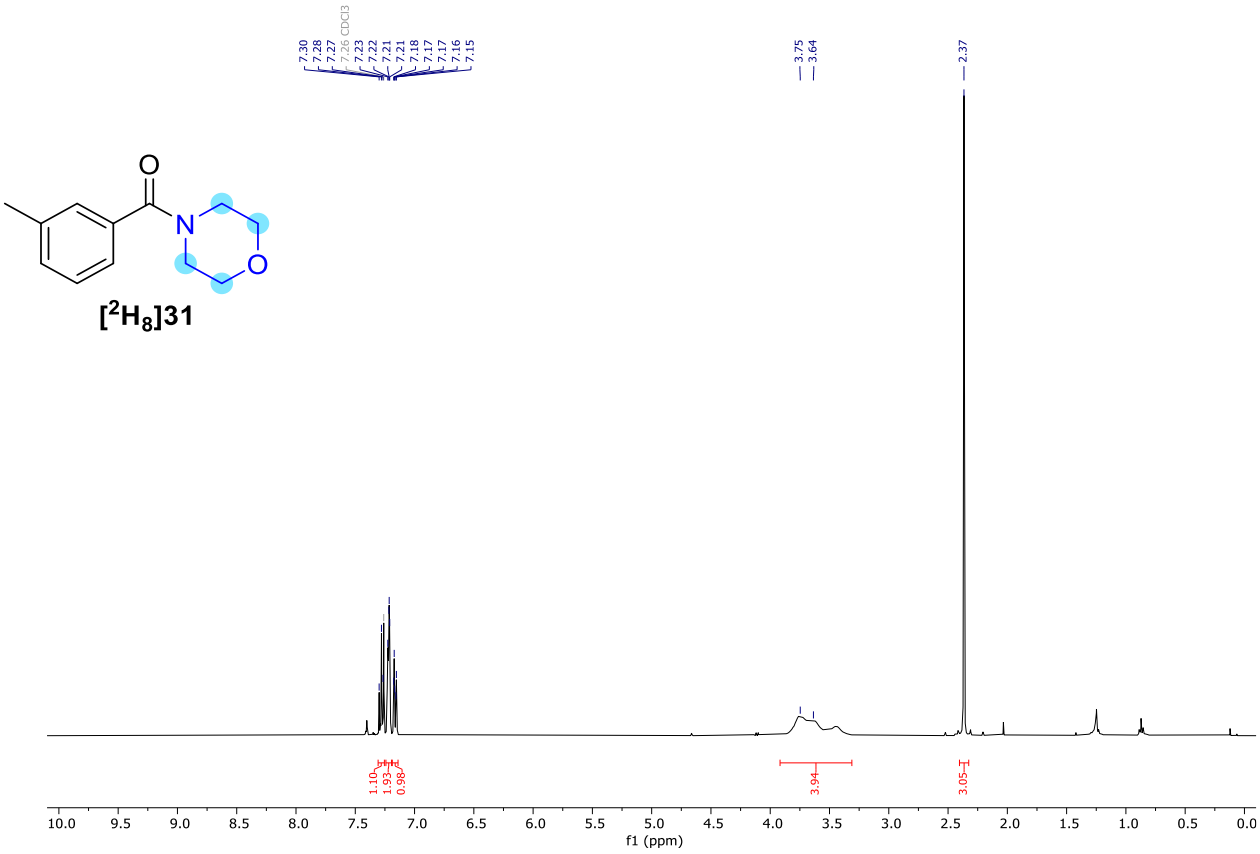


Figure S133: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

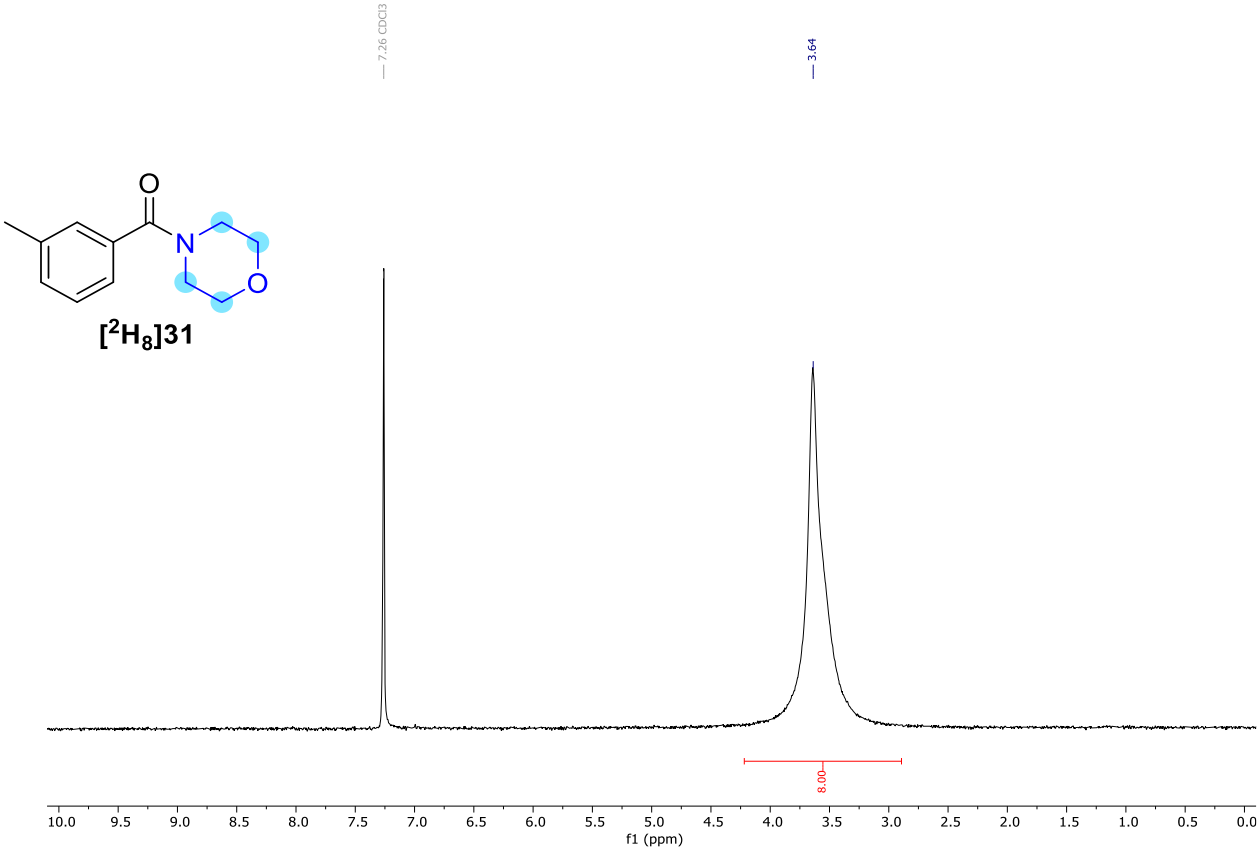


Figure S134: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

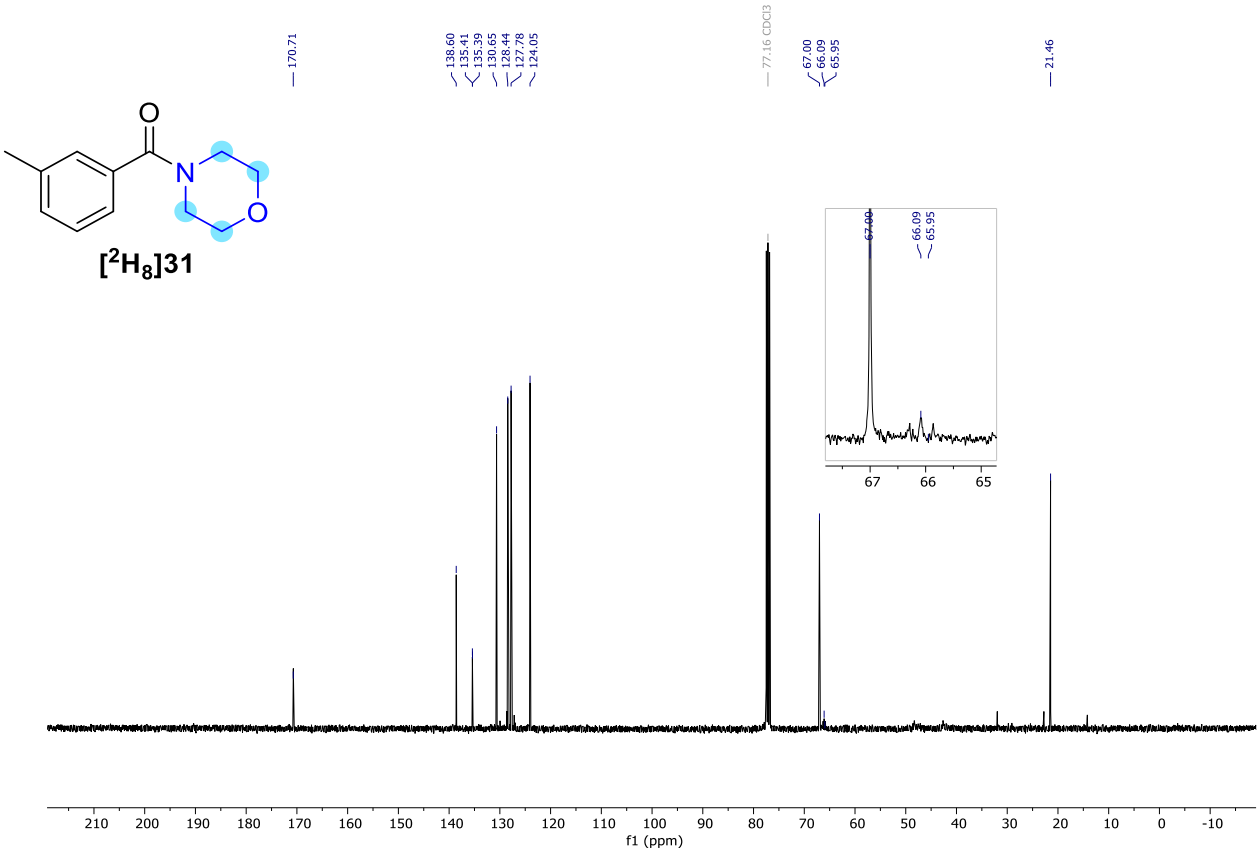


Figure S135: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

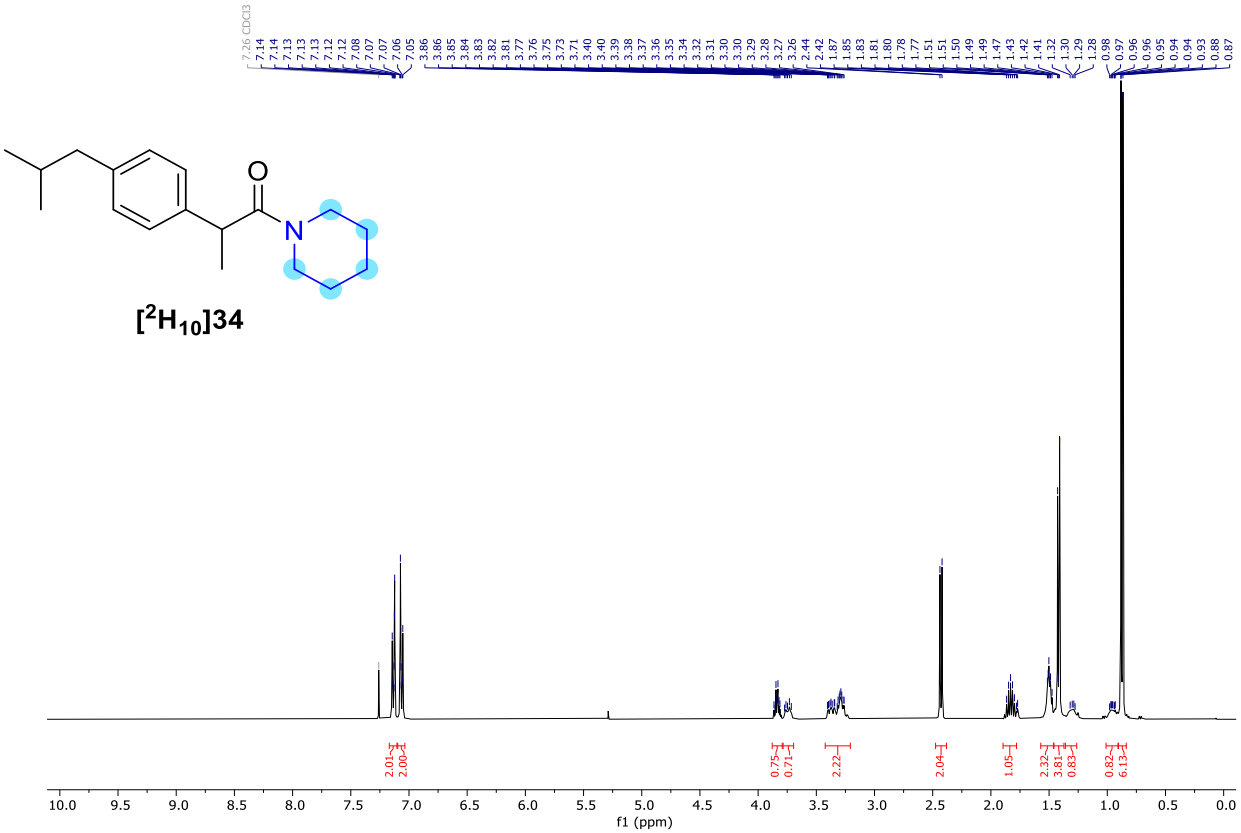


Figure S136: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

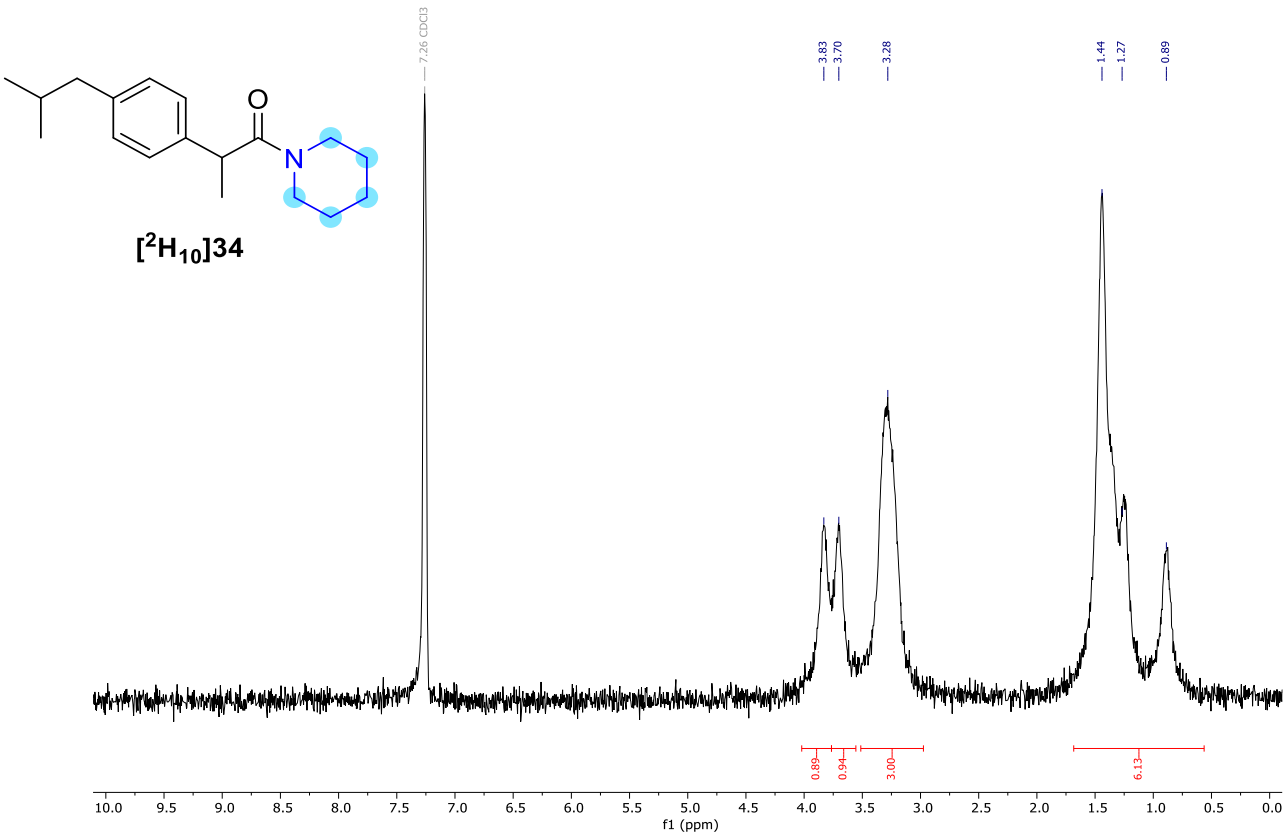


Figure S137: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

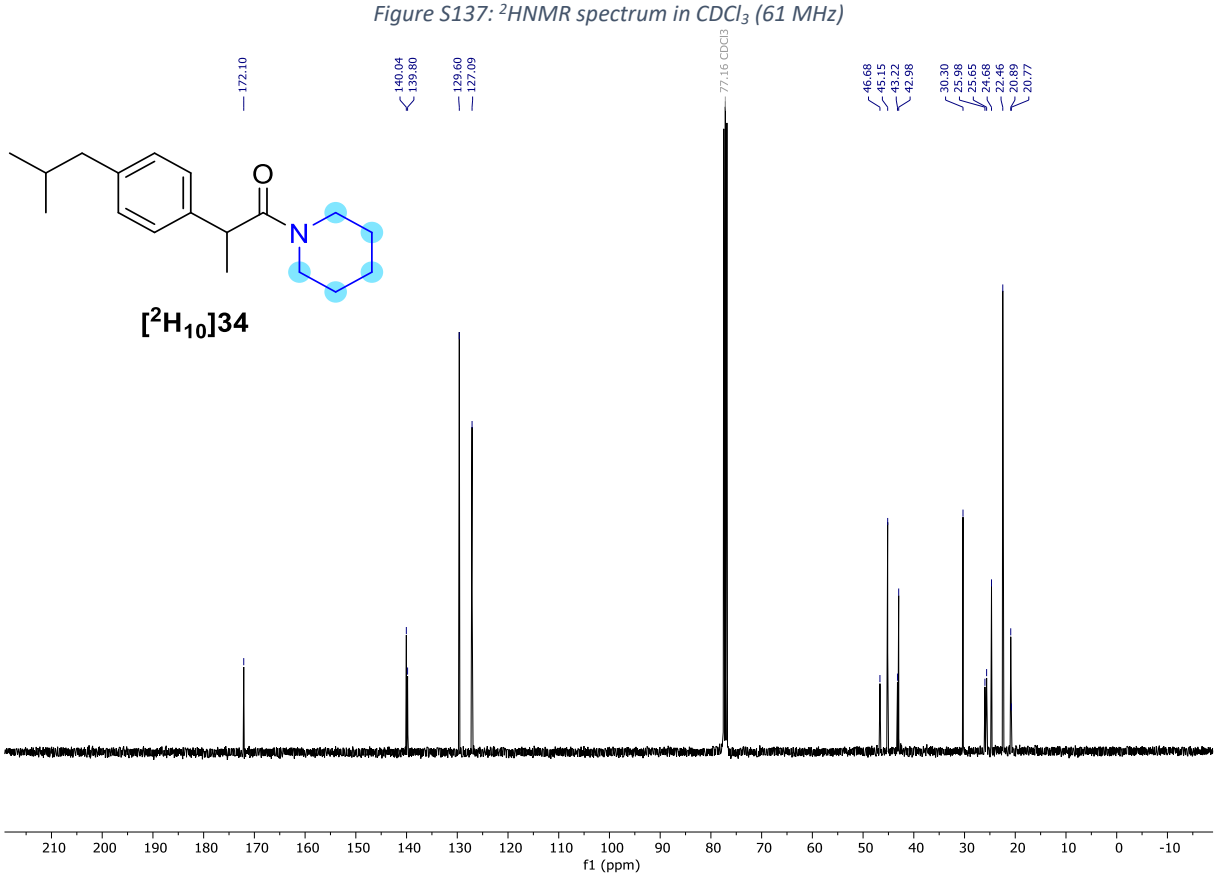


Figure S138: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

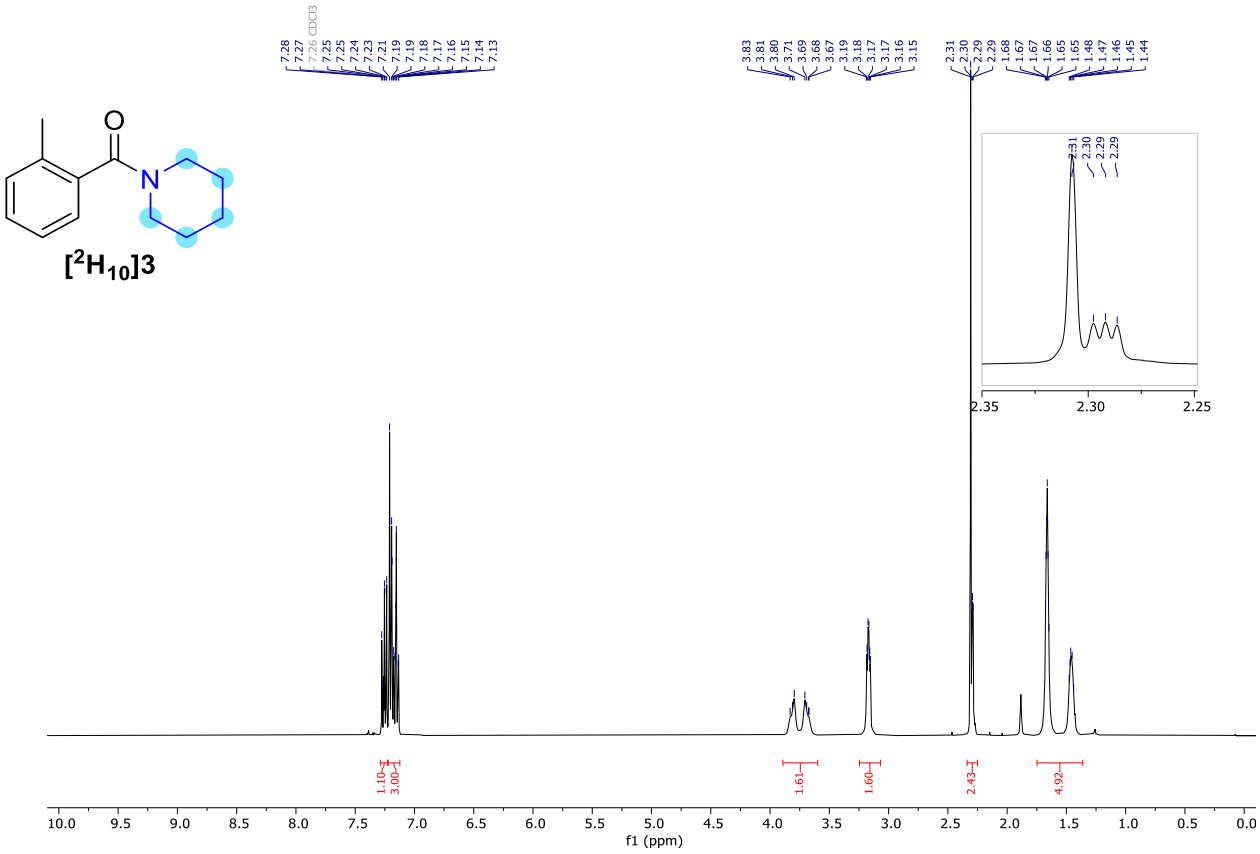


Figure S139: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

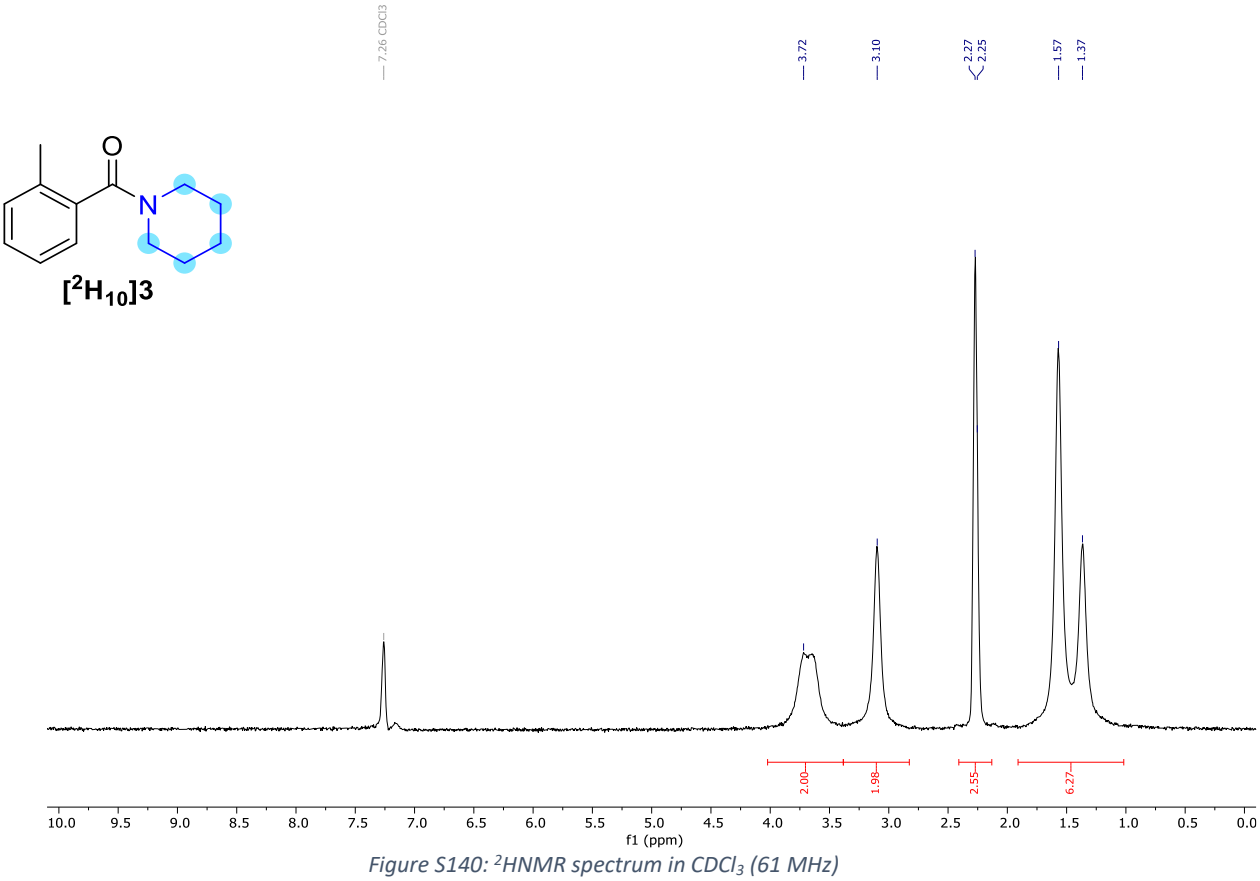


Figure S140: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

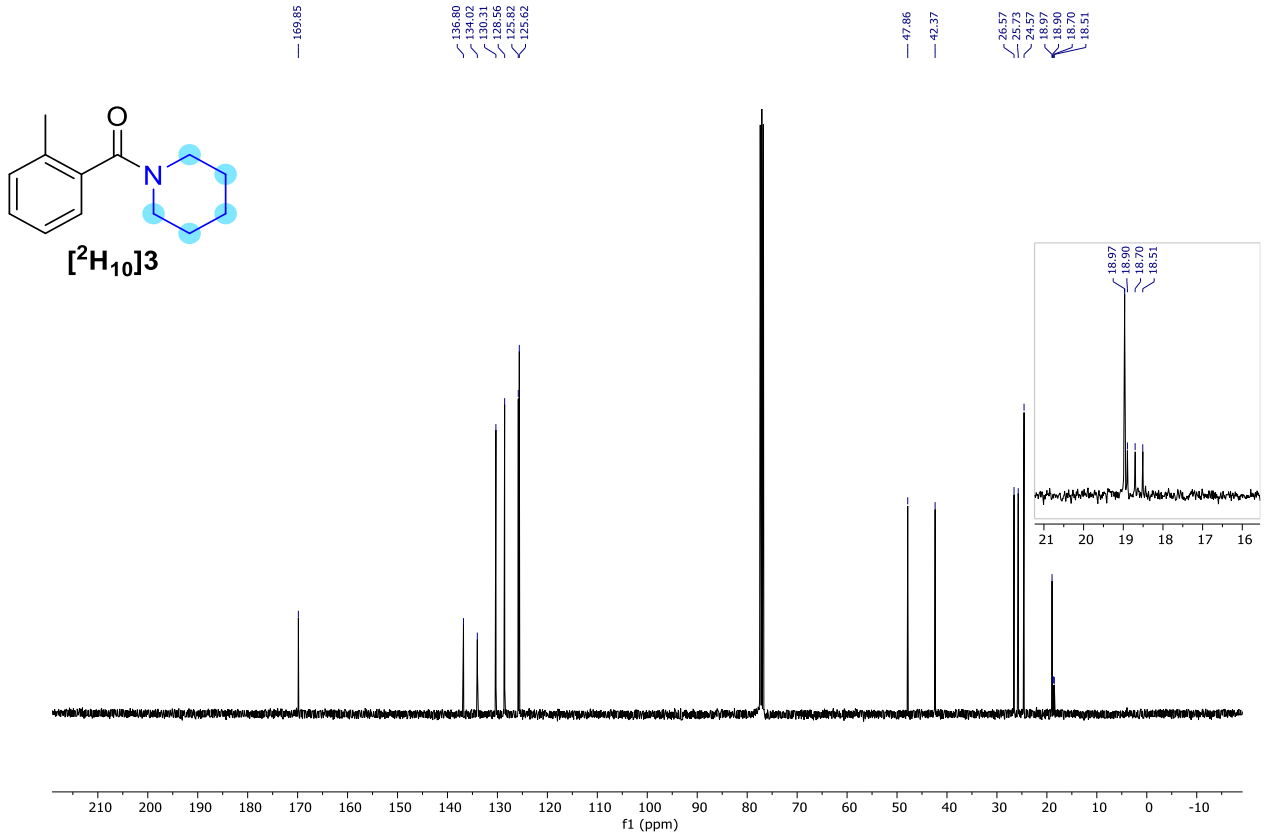


Figure S141: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

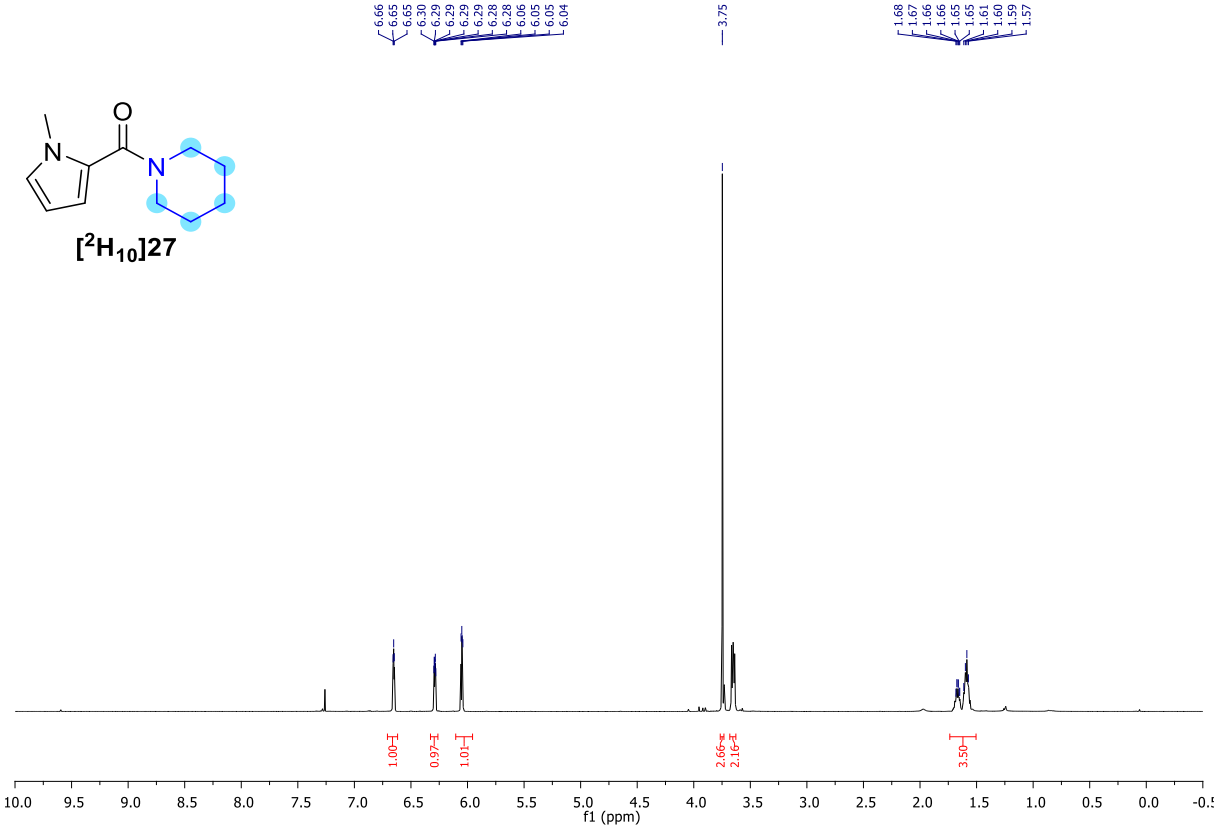


Figure S142: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

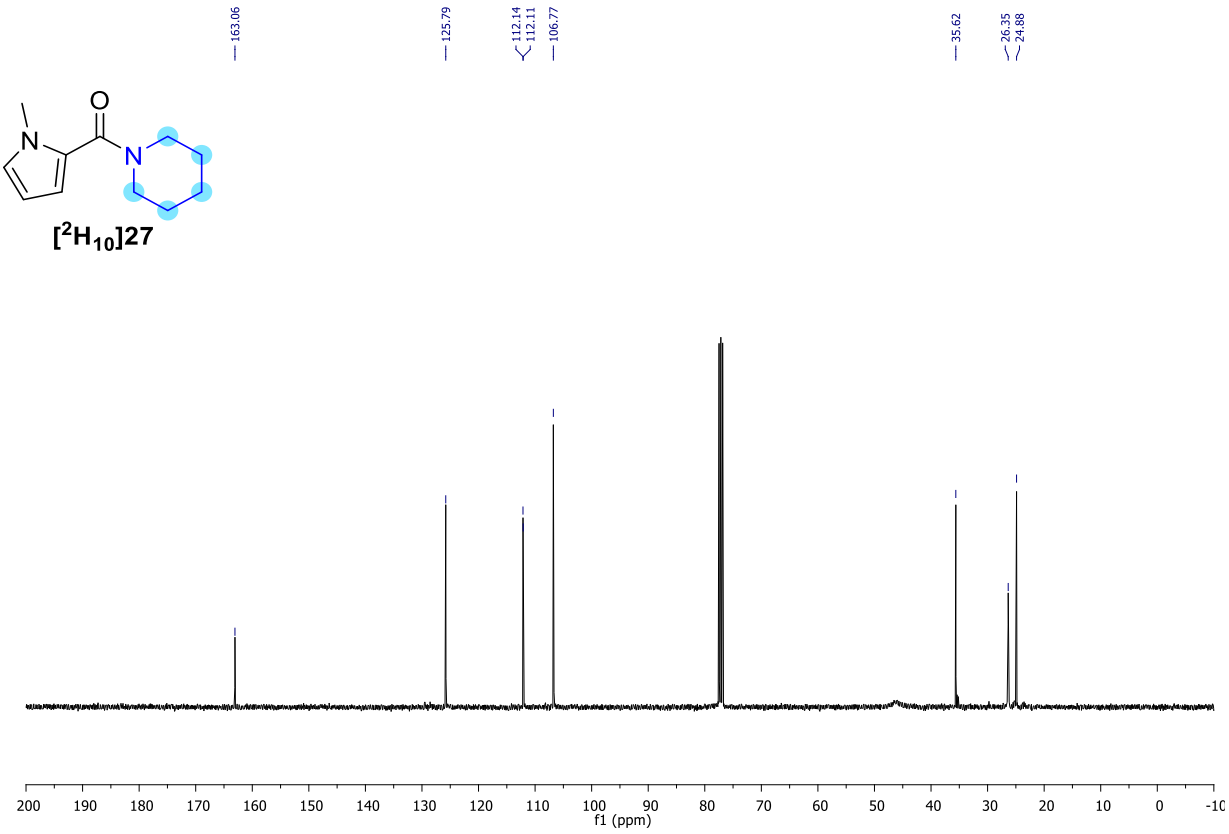


Figure S143: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

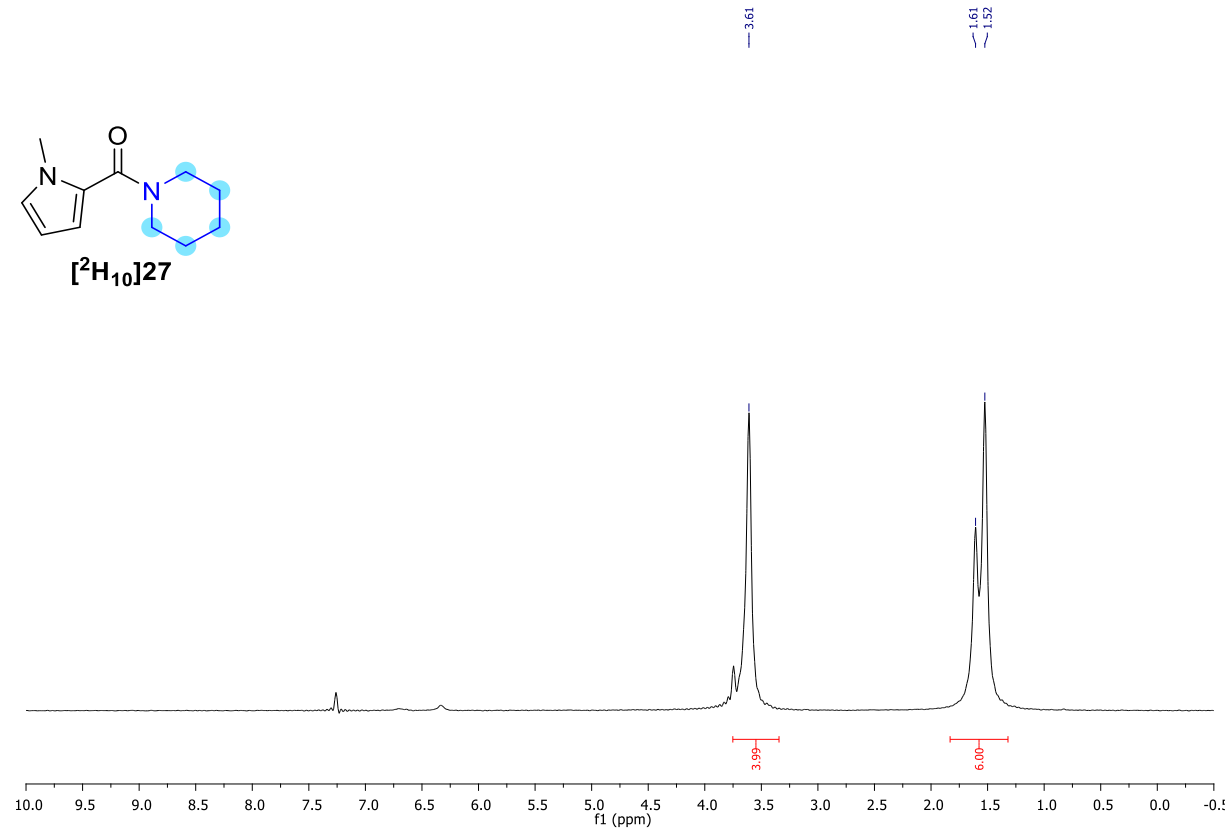


Figure S144: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

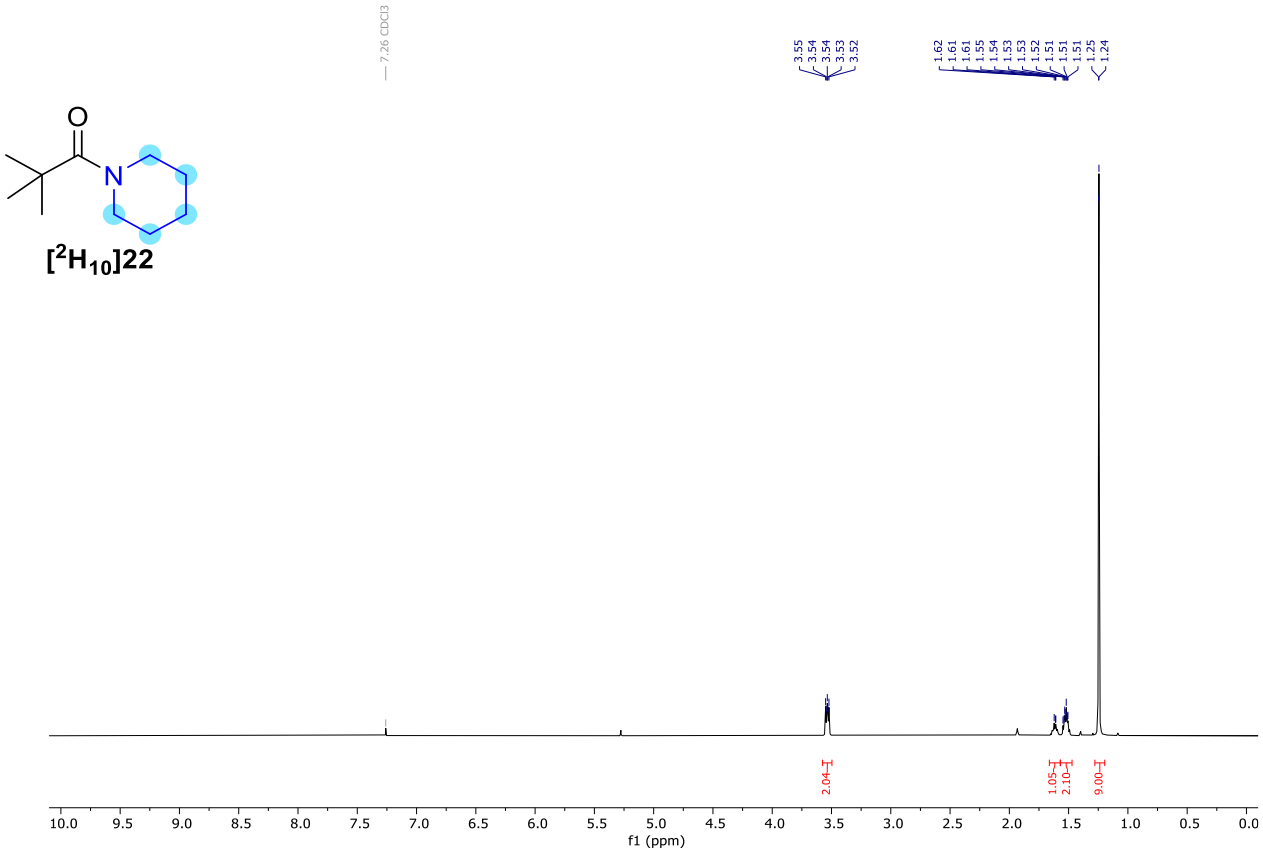


Figure S145: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

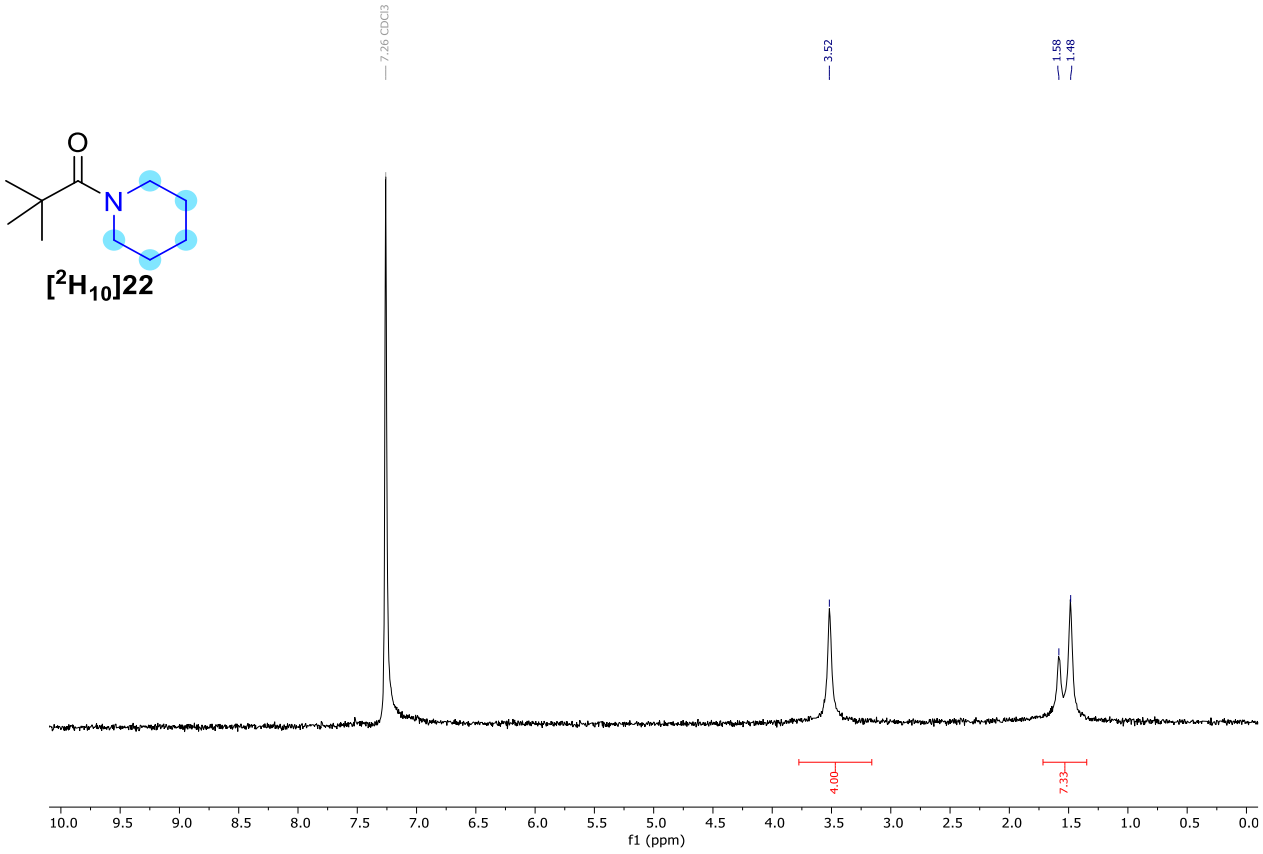


Figure S146: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

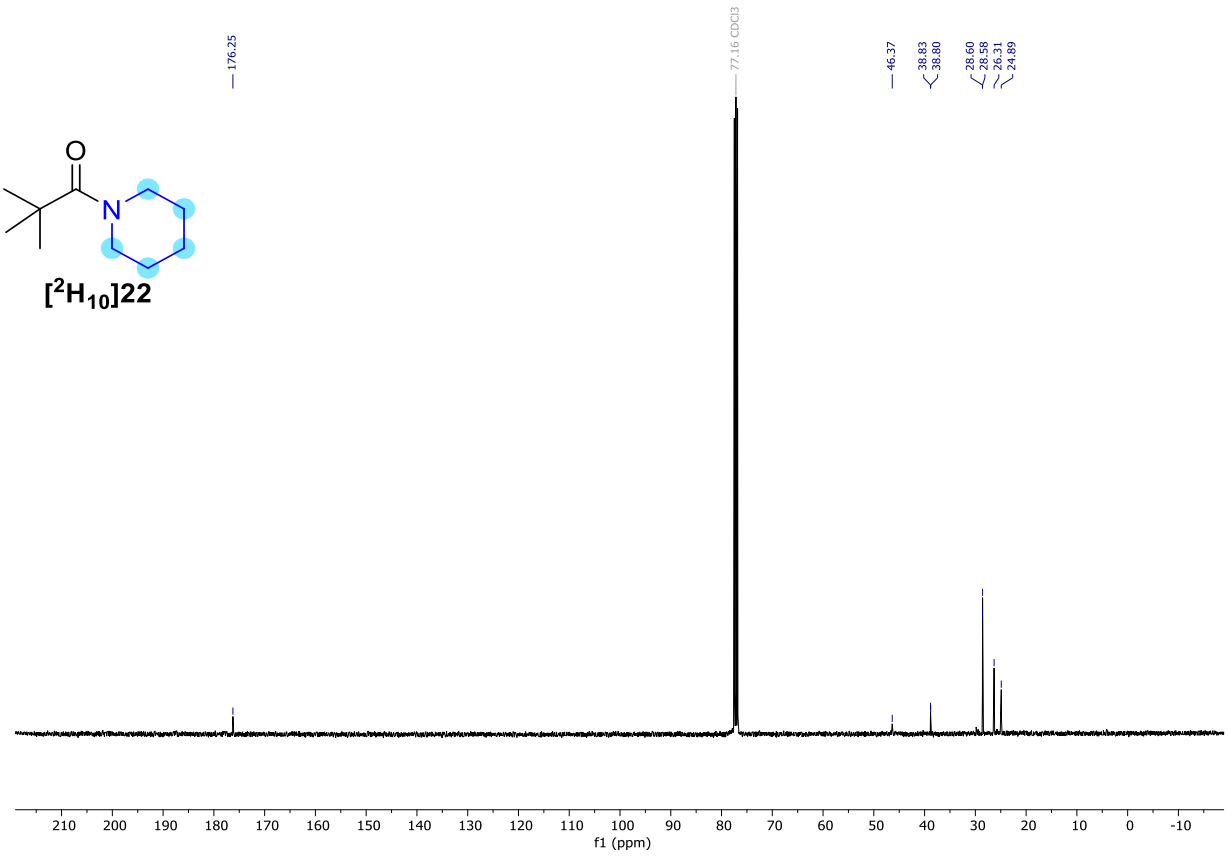


Figure S147: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

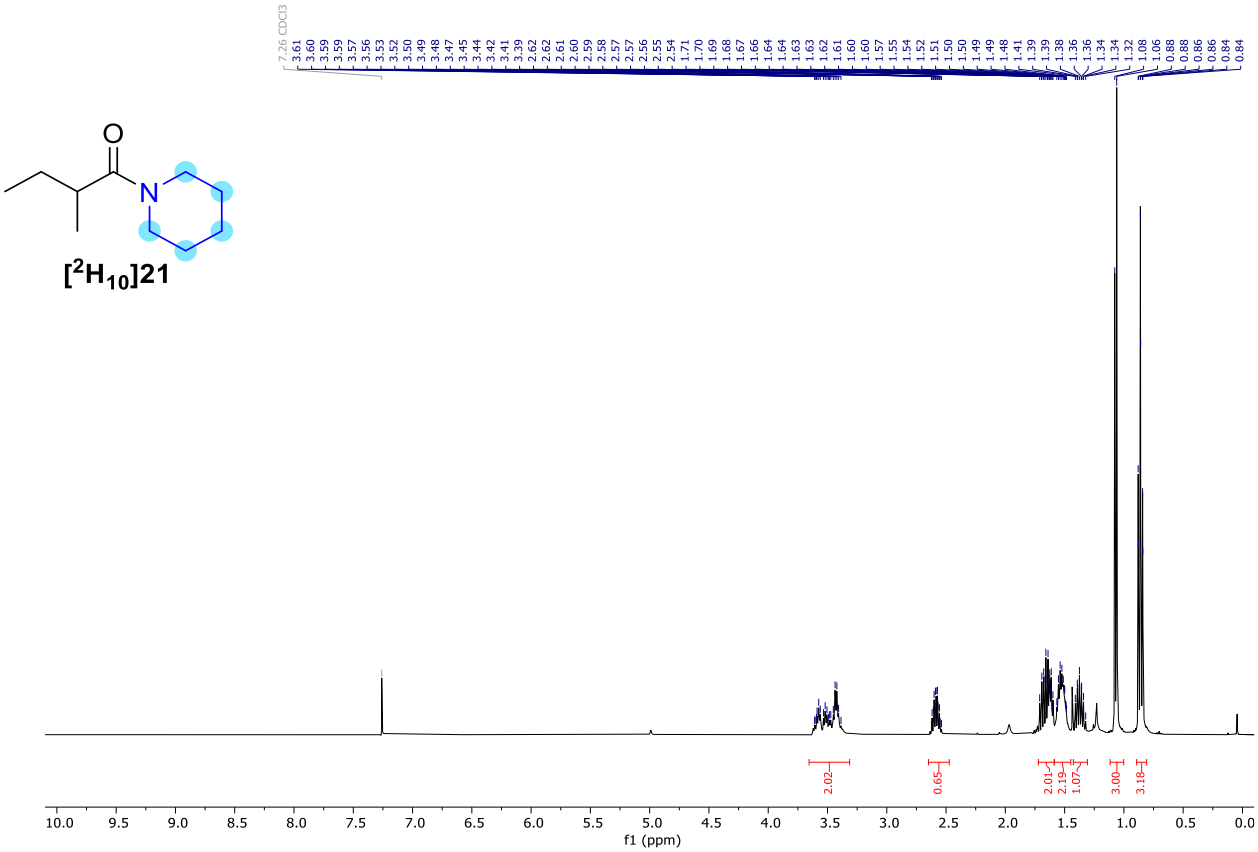


Figure S148: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

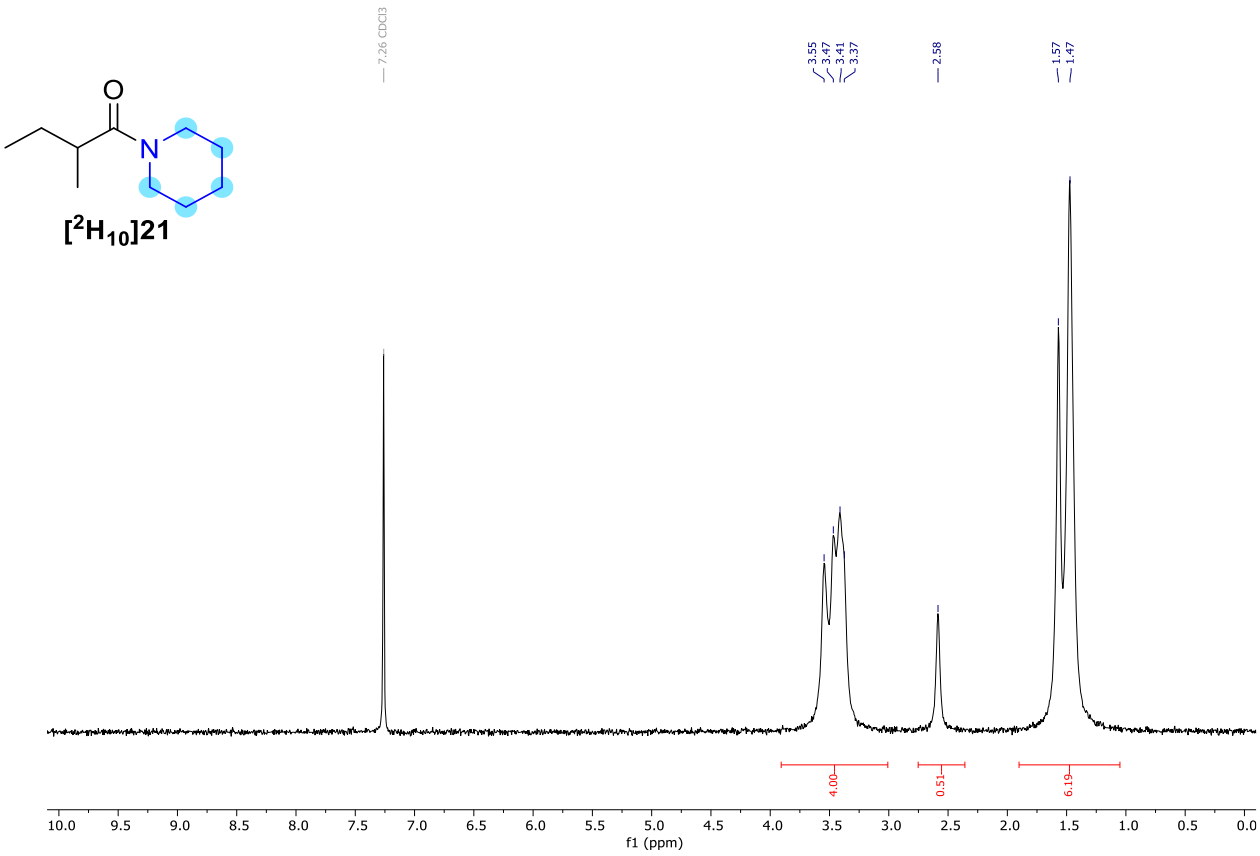


Figure S149: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

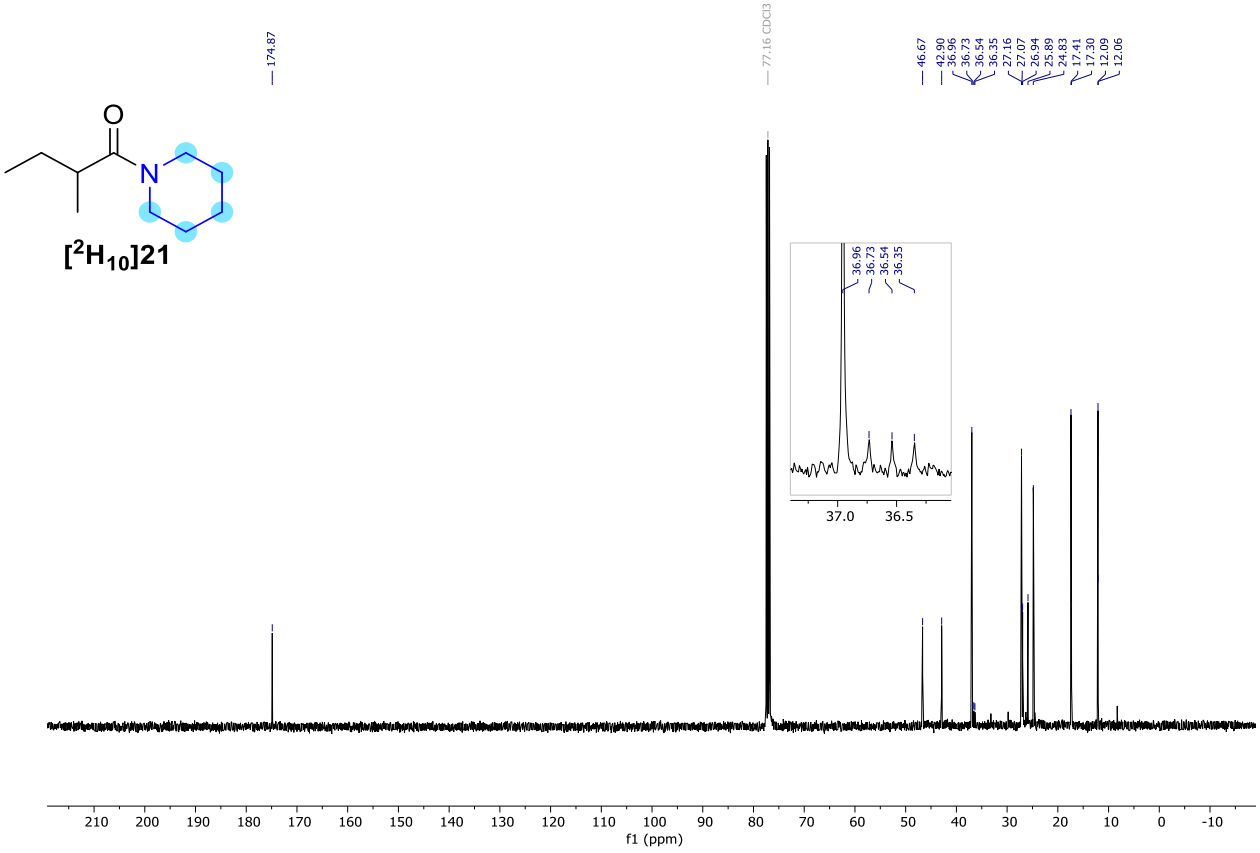


Figure S150: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

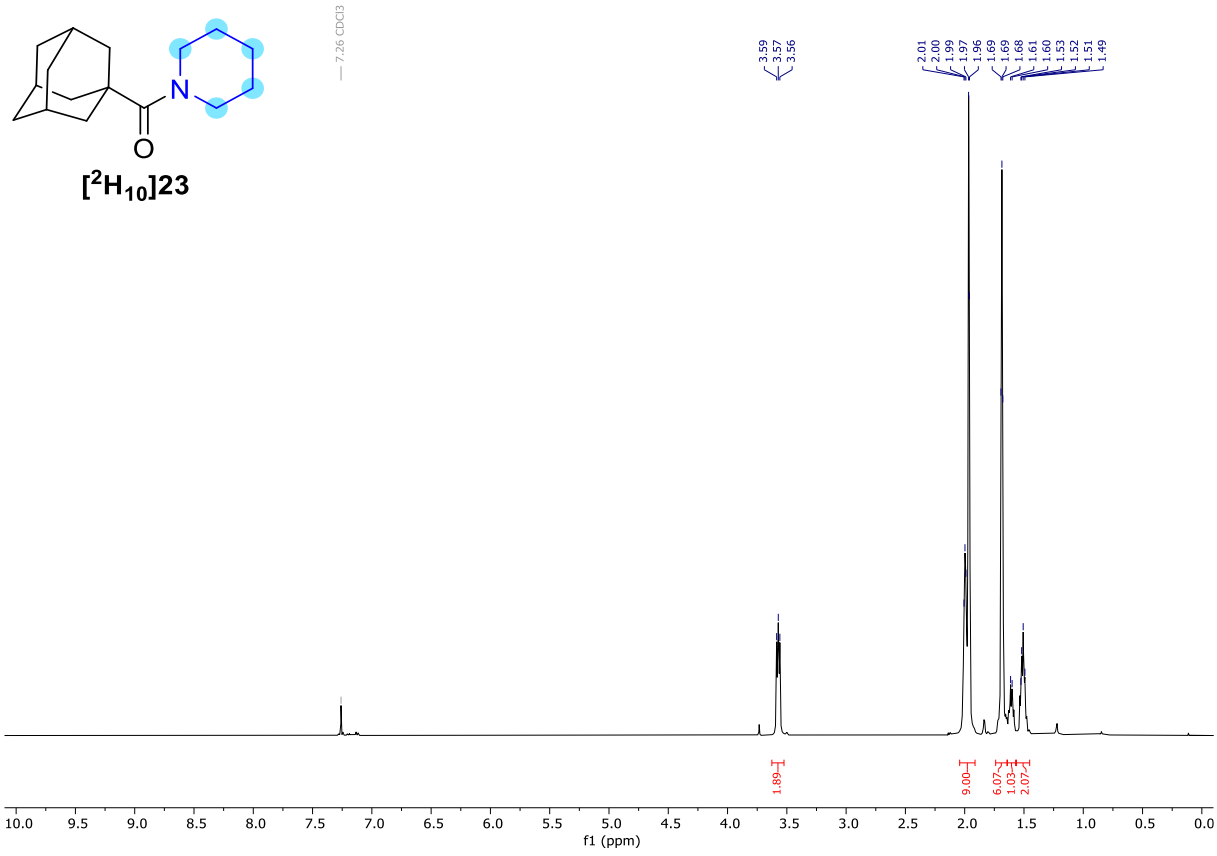


Figure S151: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

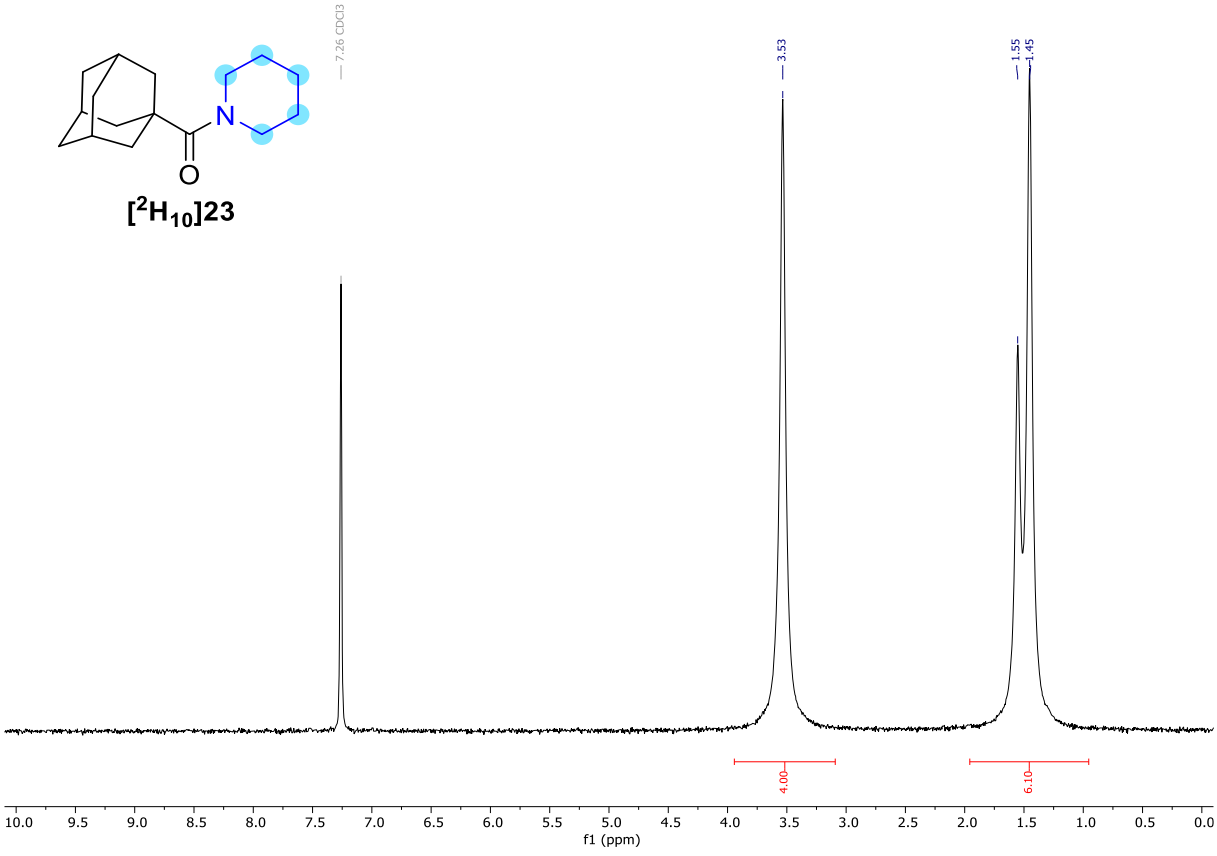


Figure S152: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

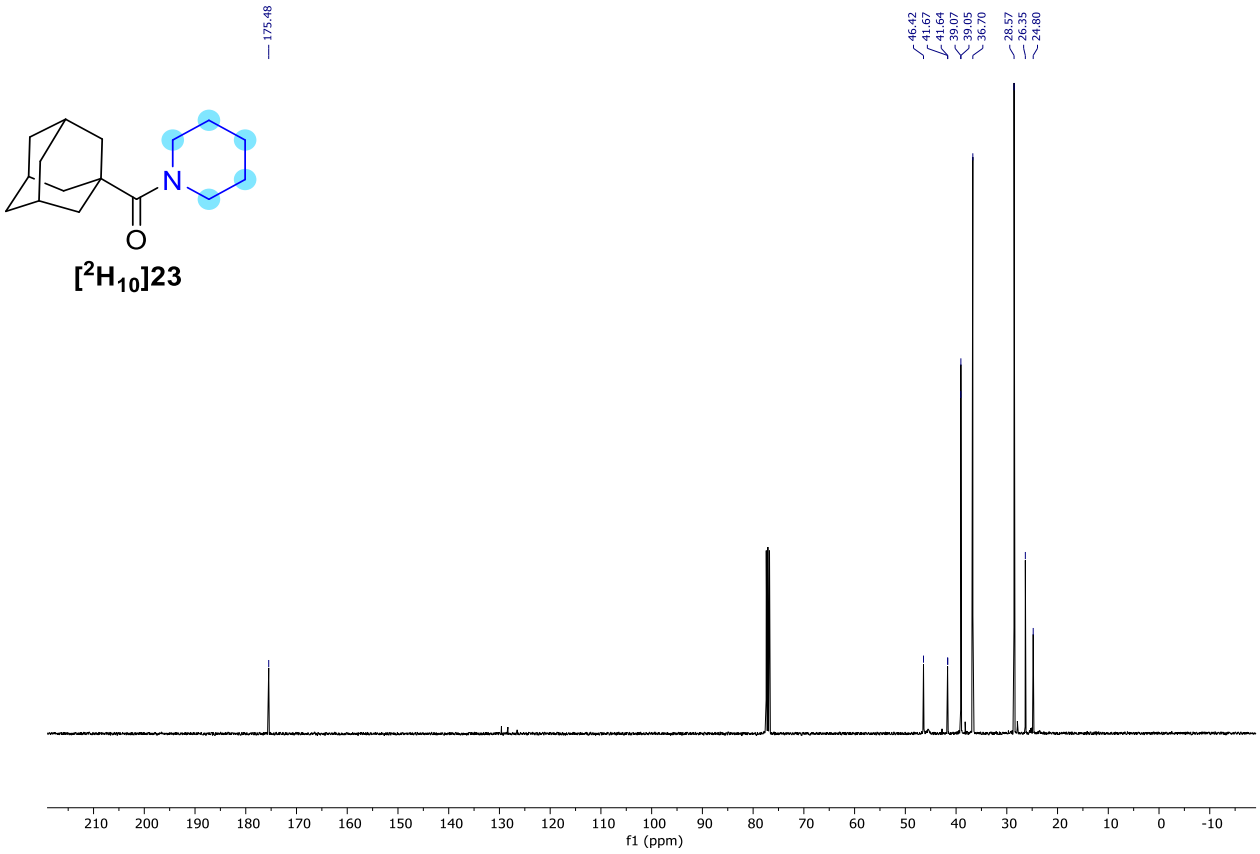


Figure S153: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

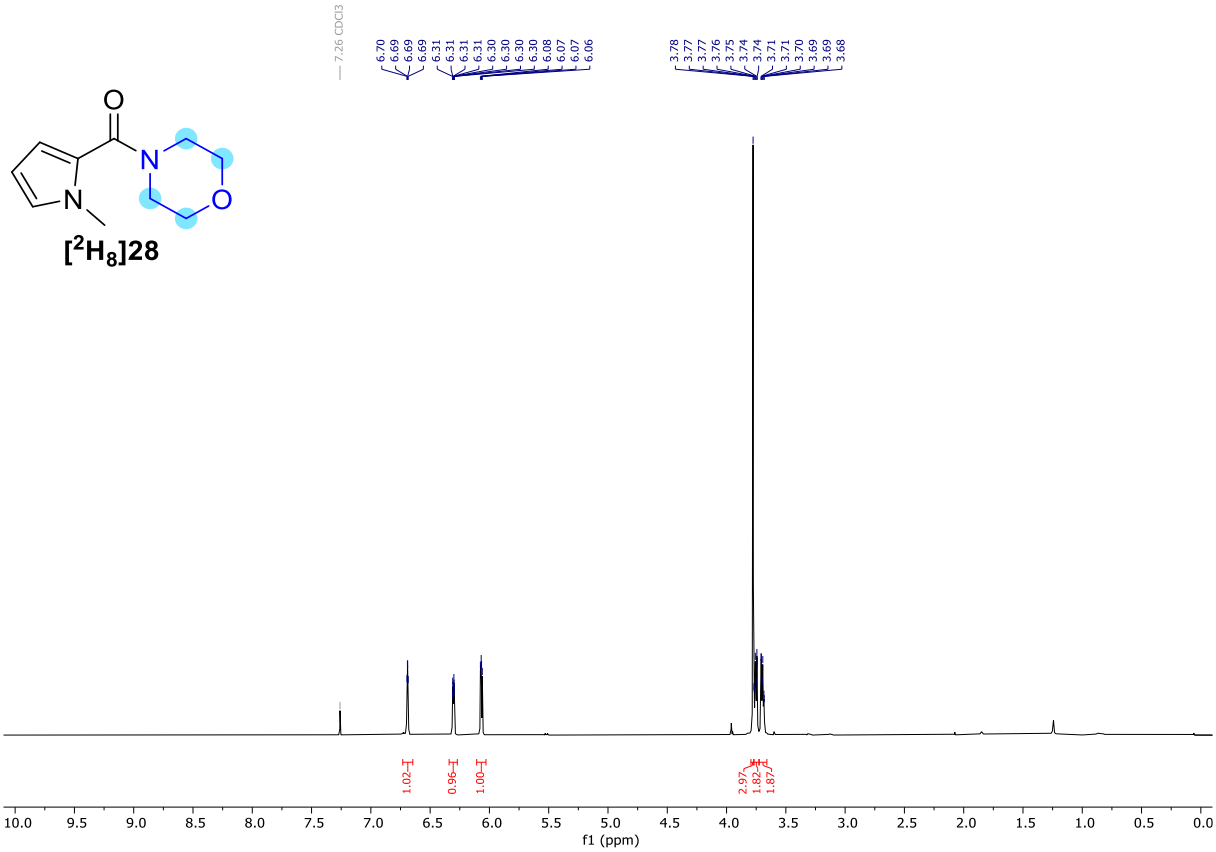


Figure S154: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

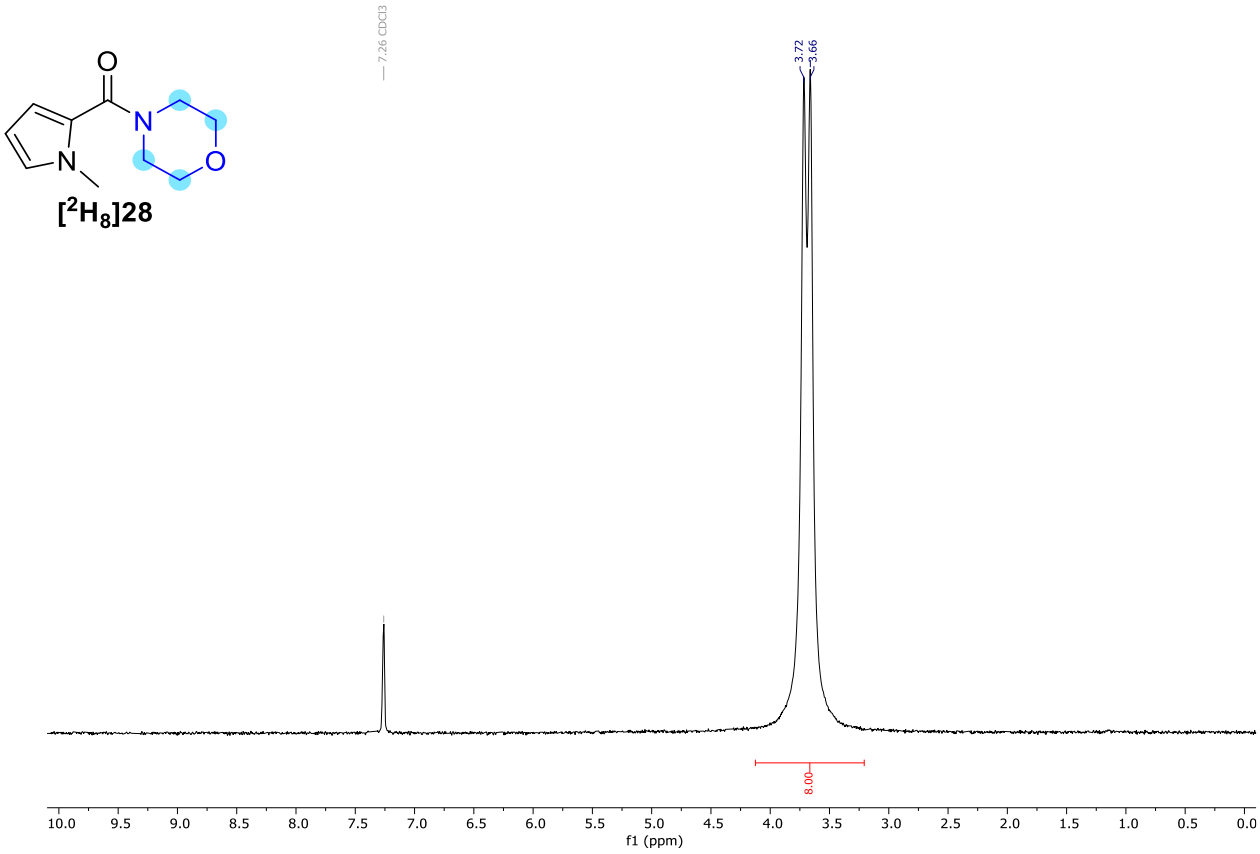


Figure S155: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

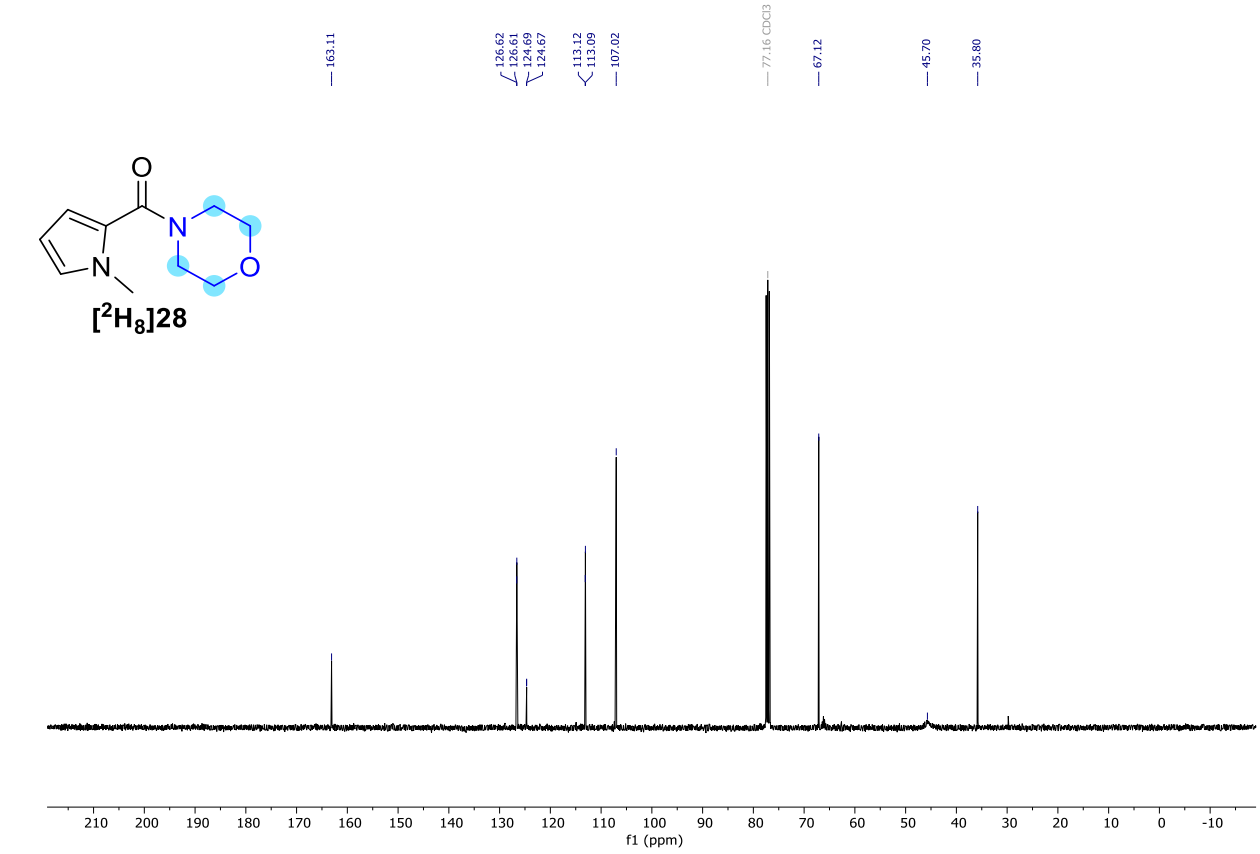


Figure S156: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

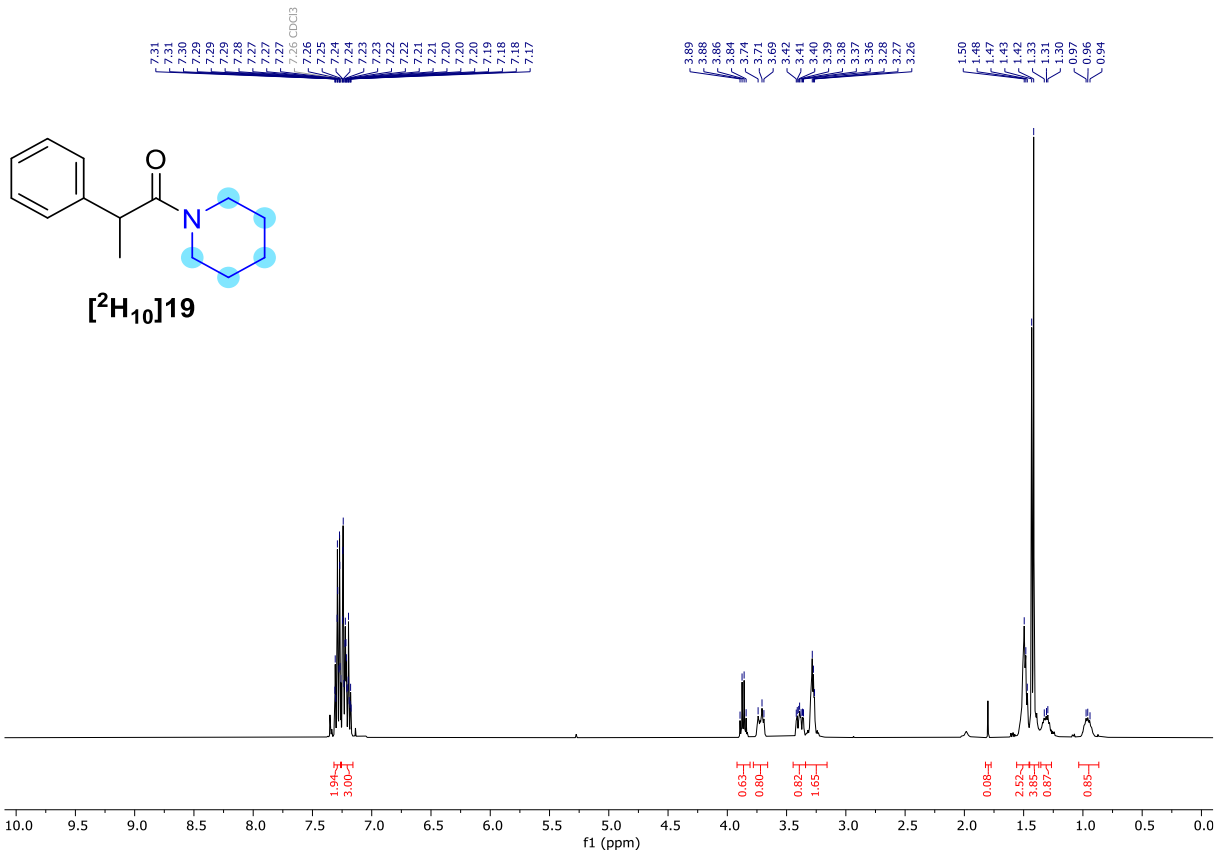


Figure S157: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

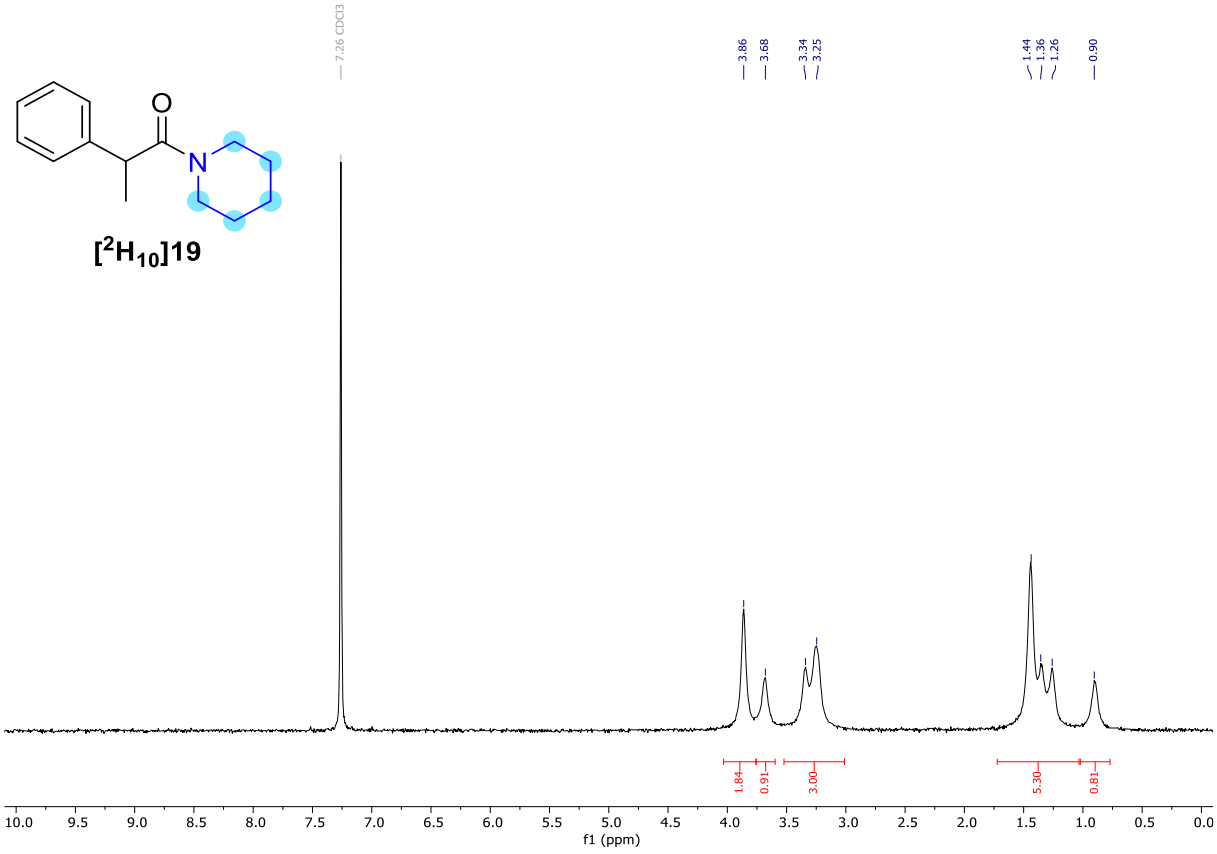


Figure S158: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

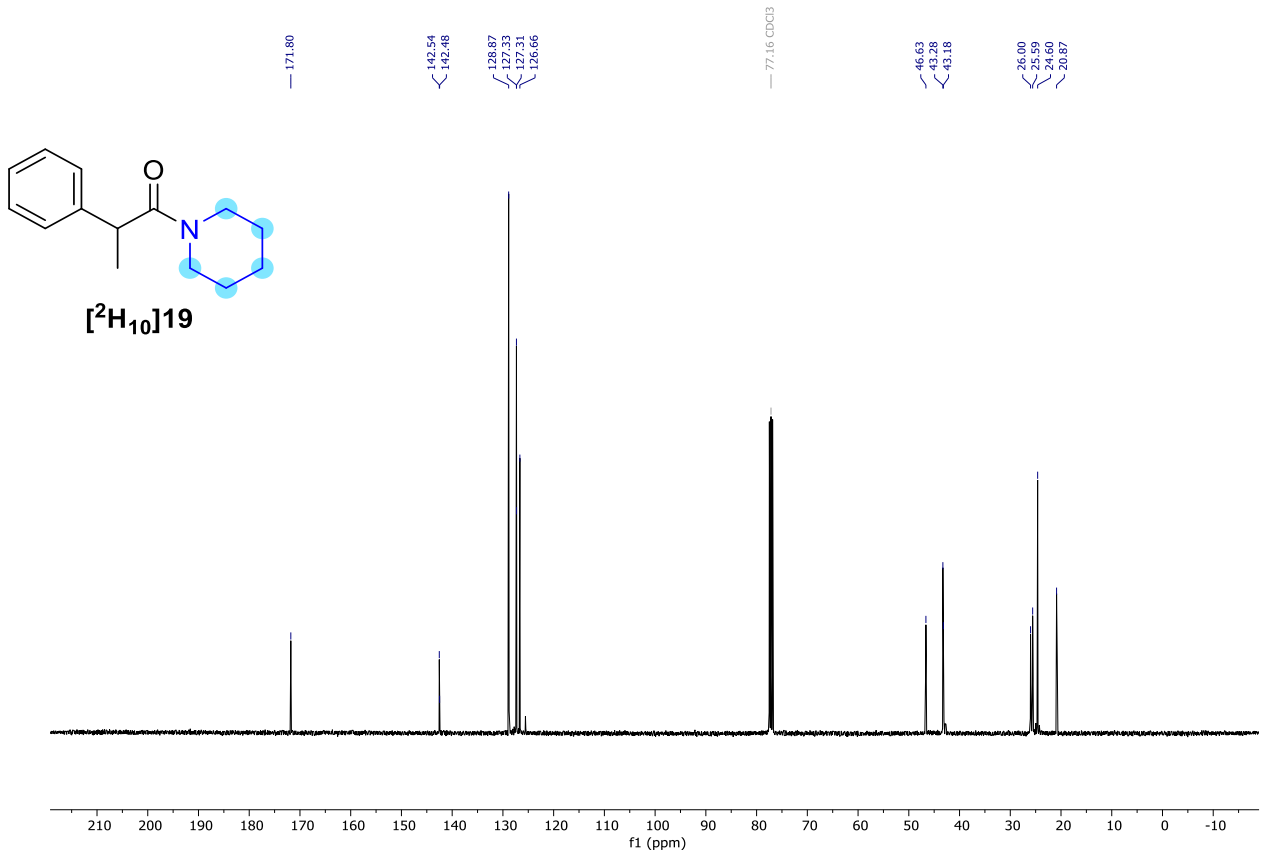


Figure S159: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

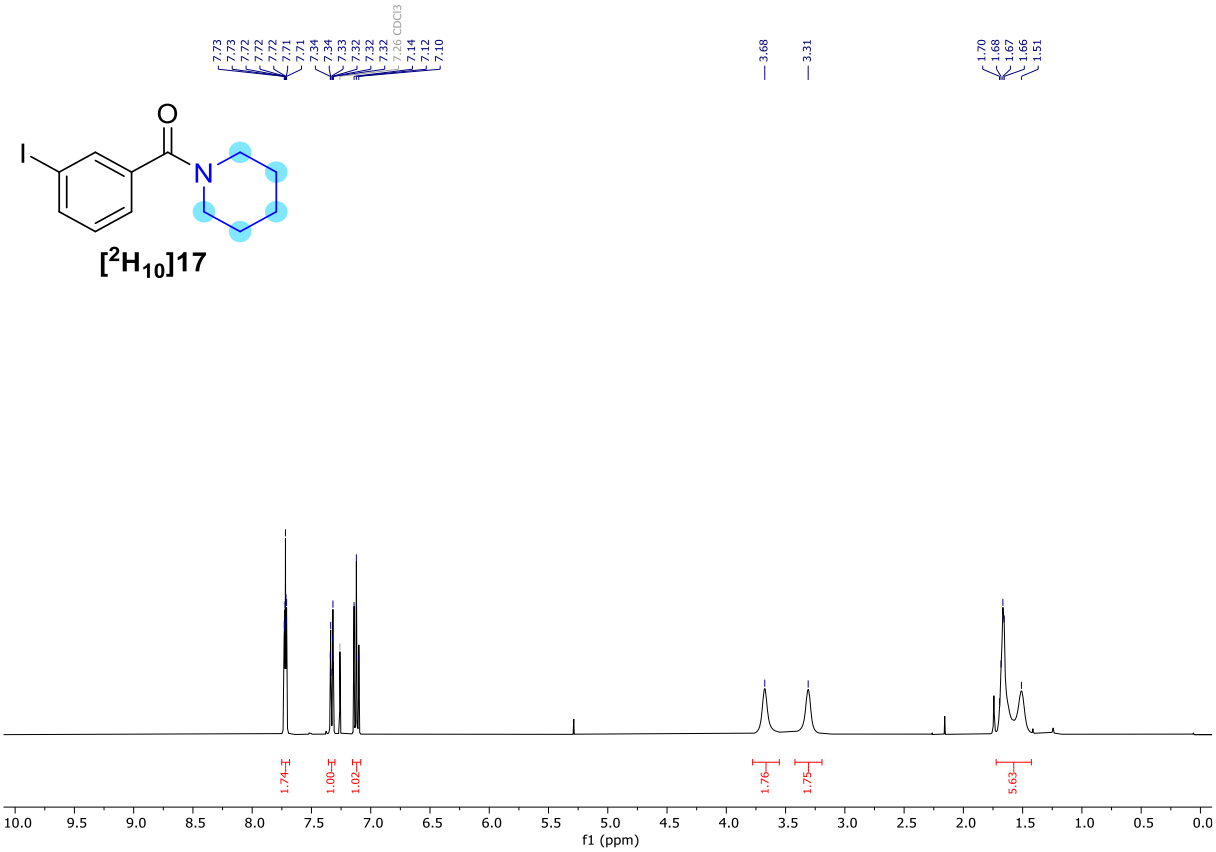


Figure S160: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

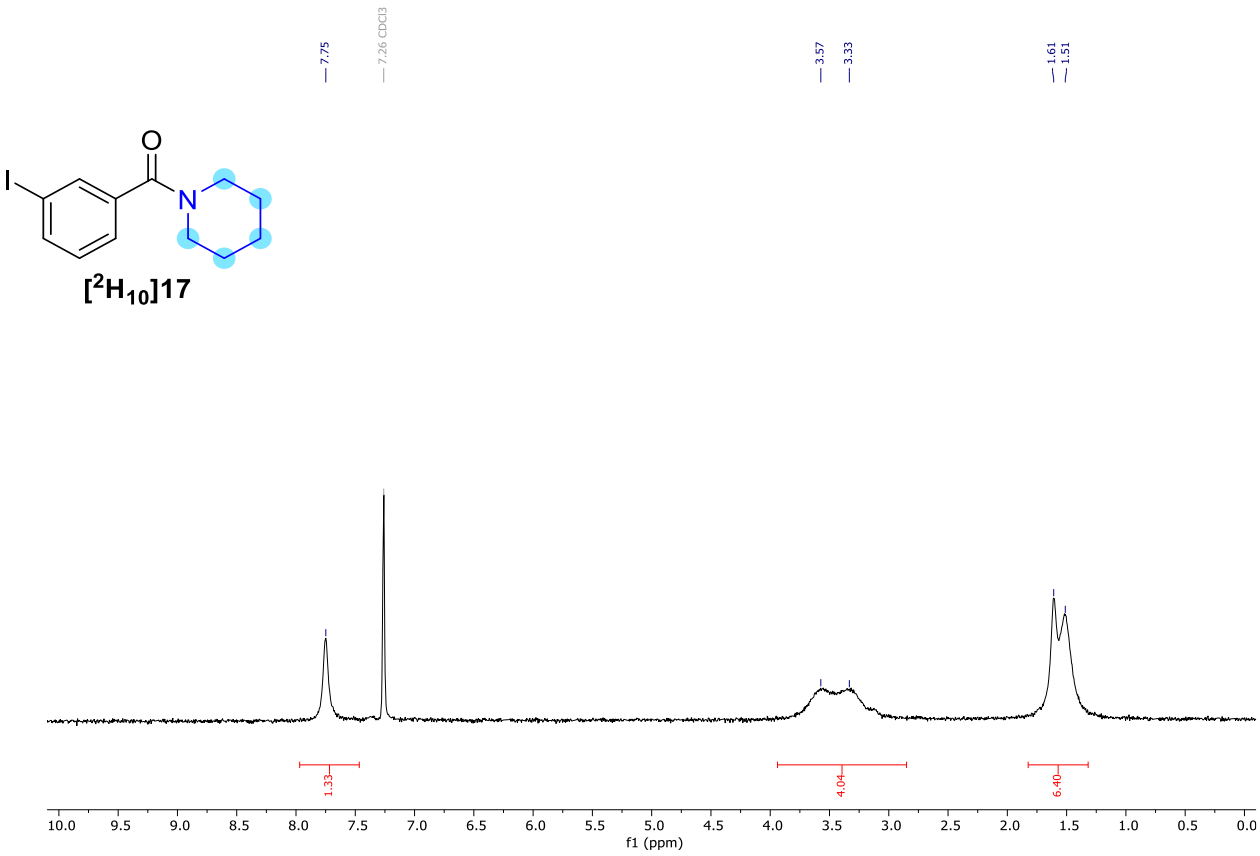


Figure S161: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

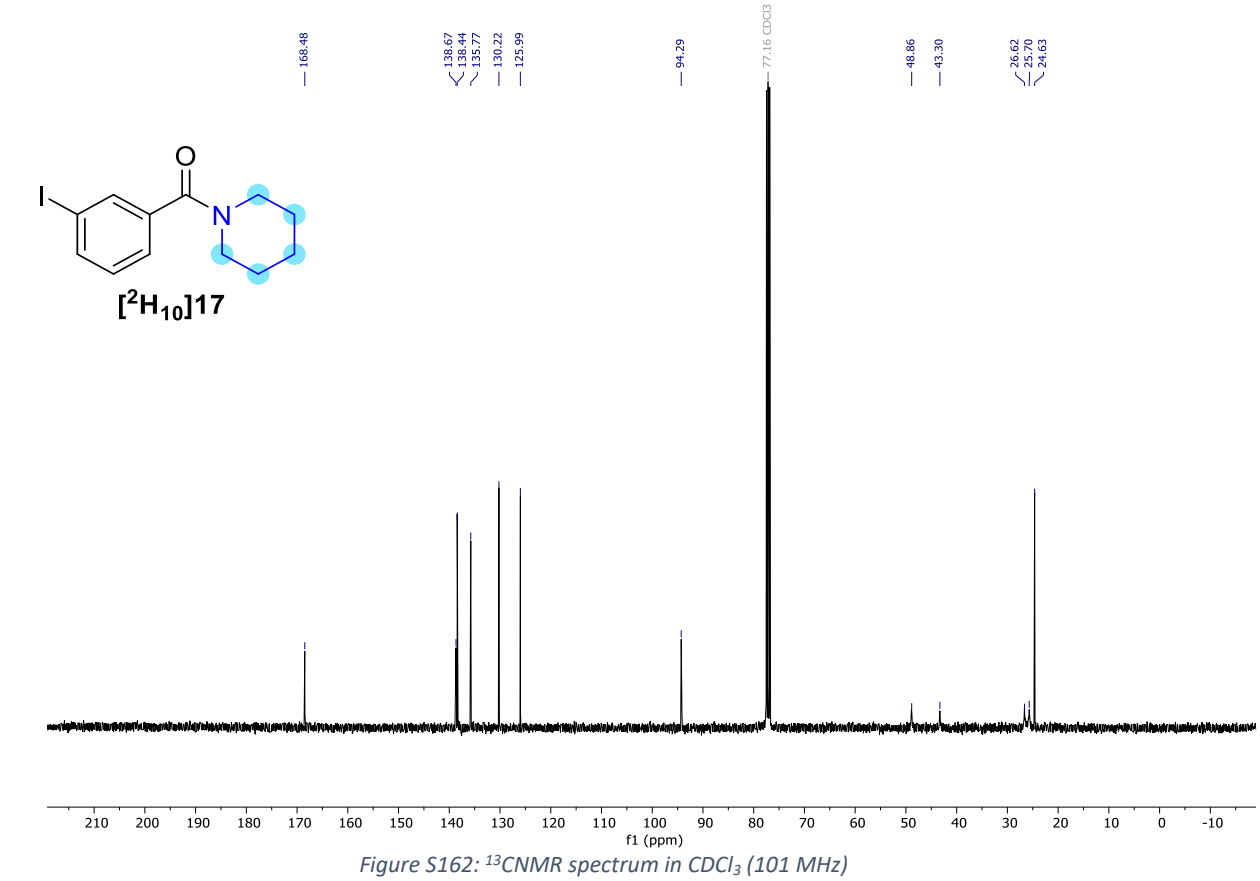


Figure S162: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

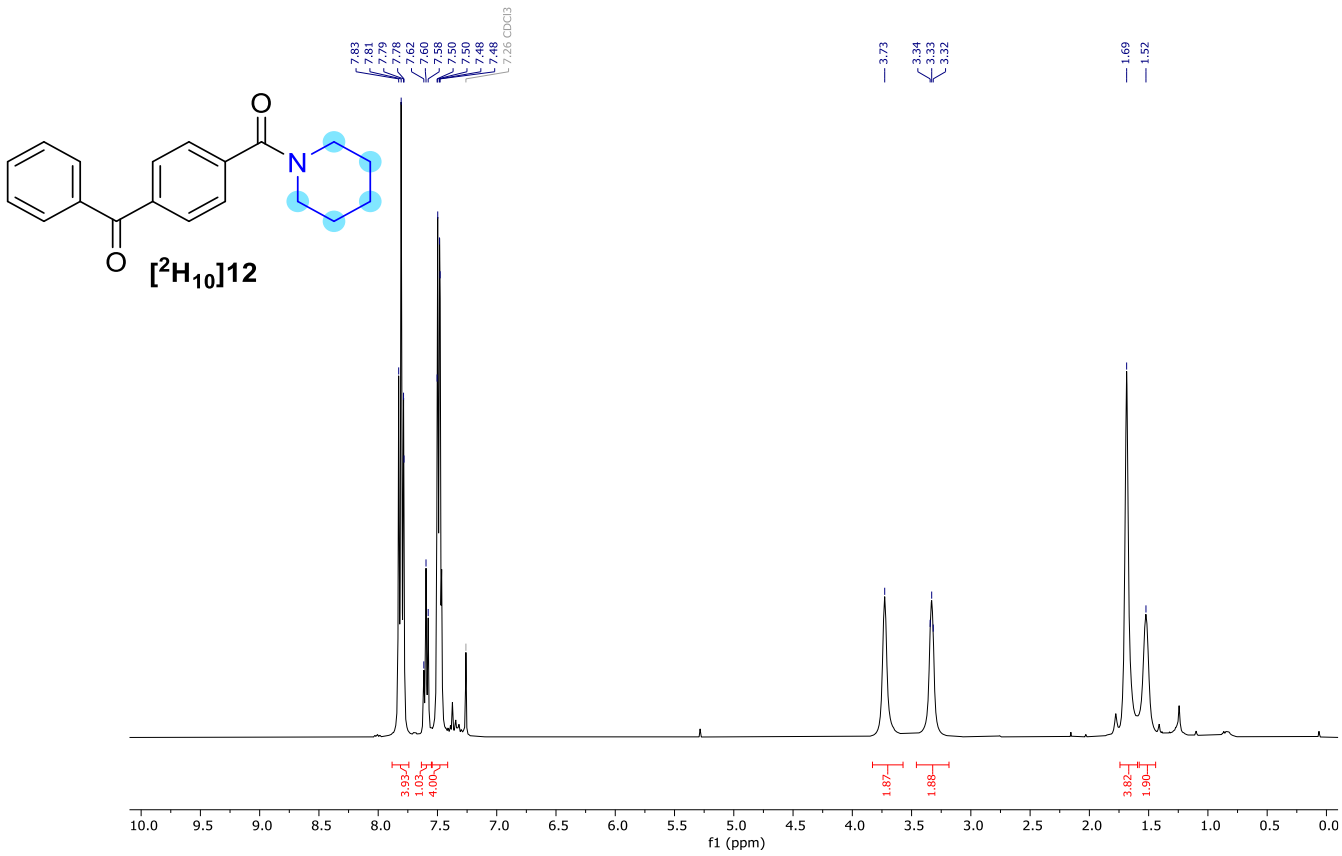


Figure S163: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

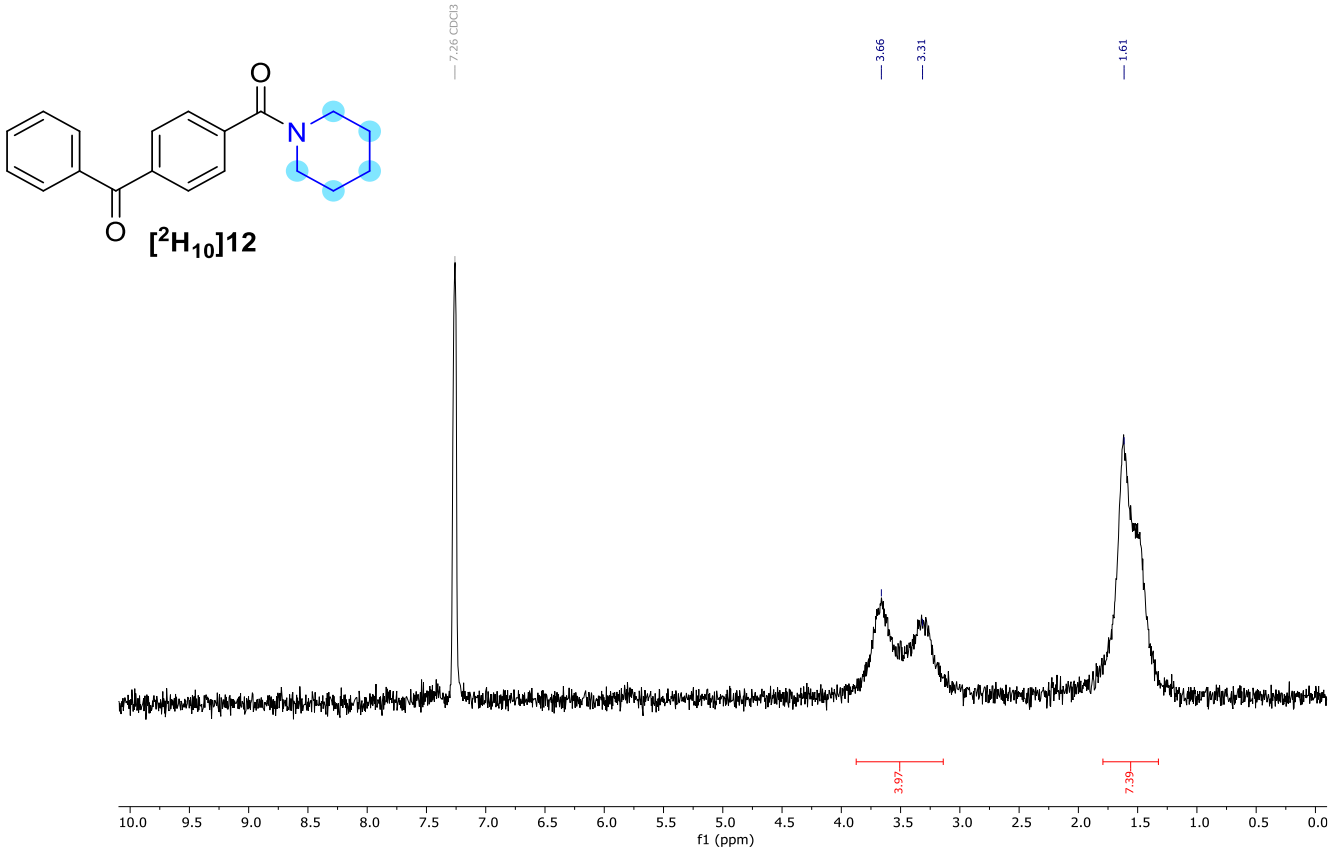


Figure S164: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

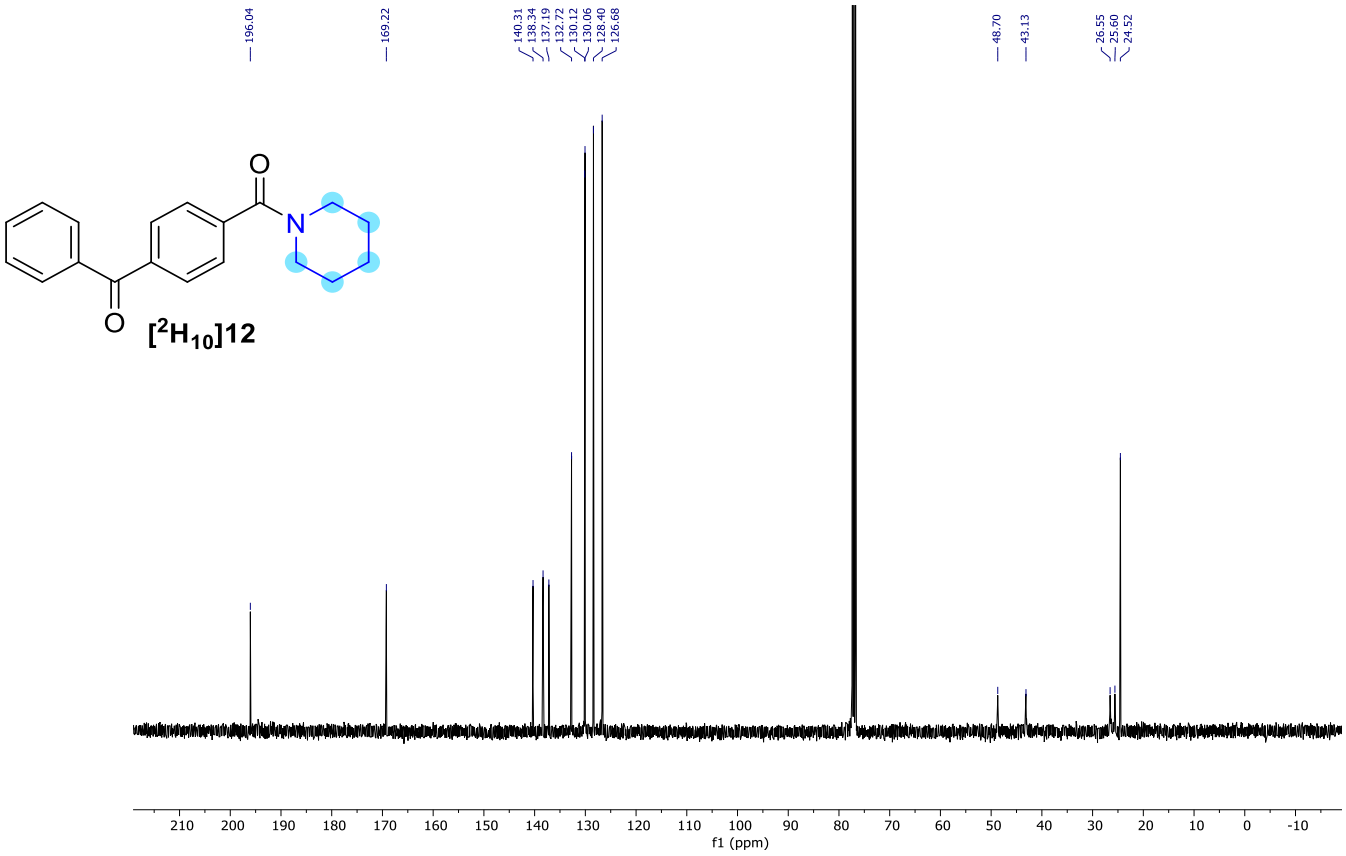


Figure S165: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

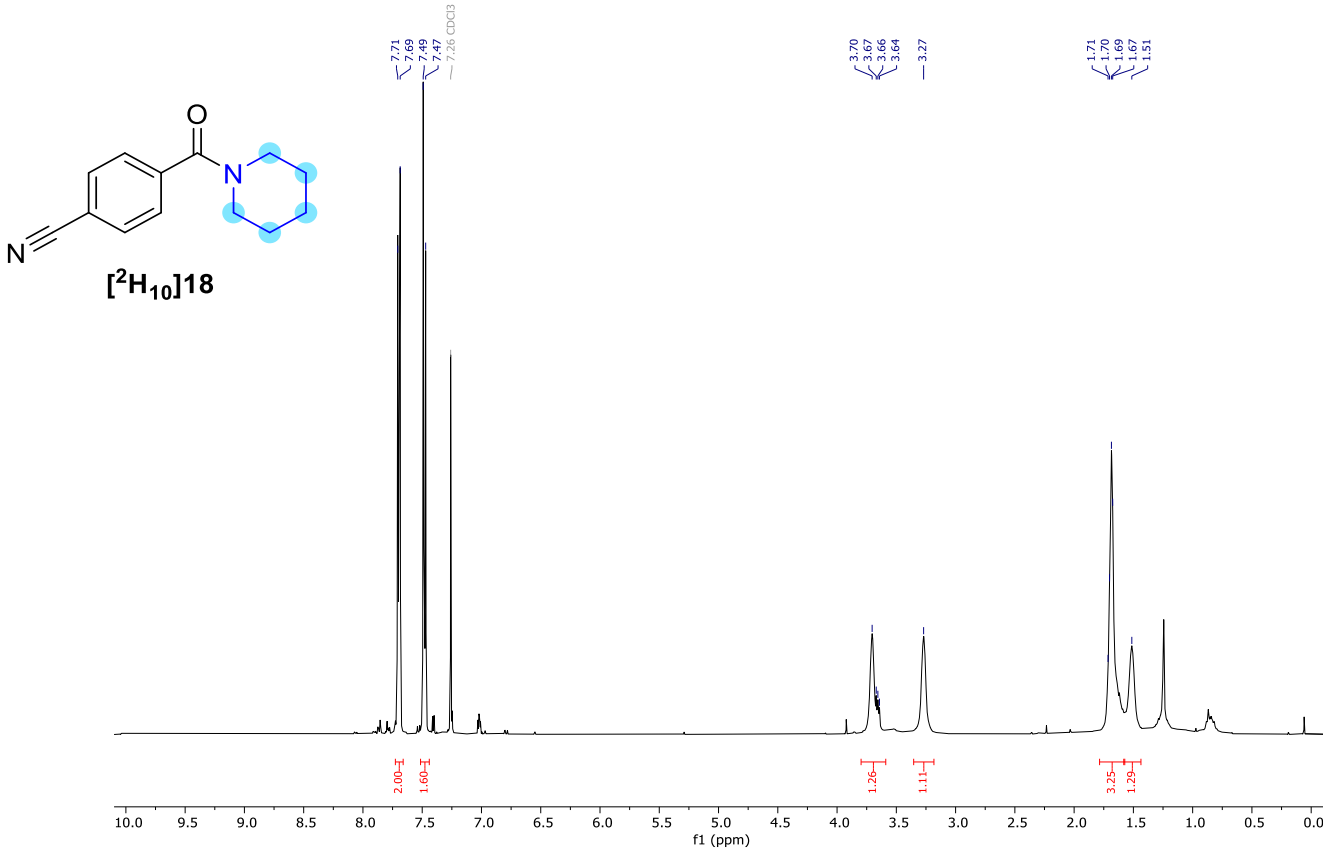


Figure S166: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

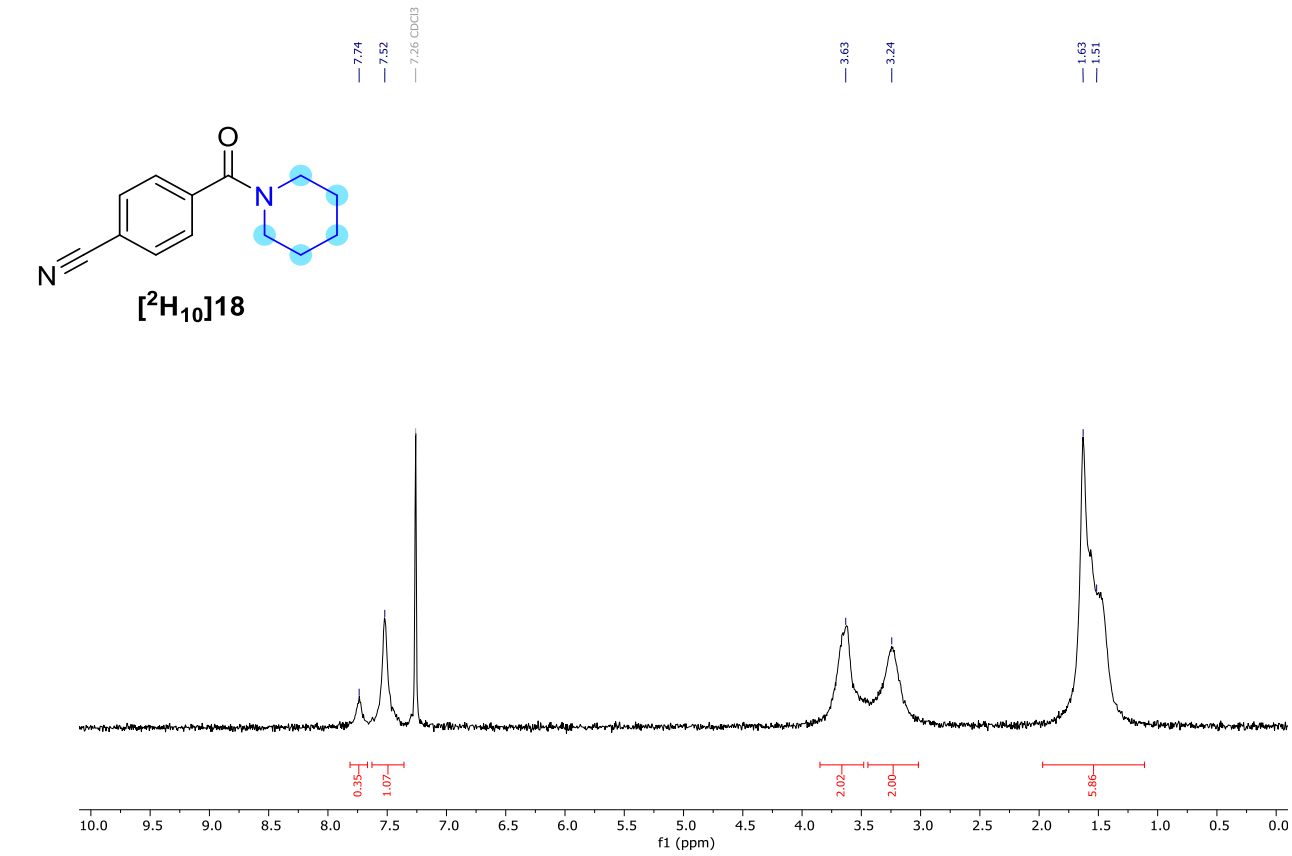


Figure S167: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

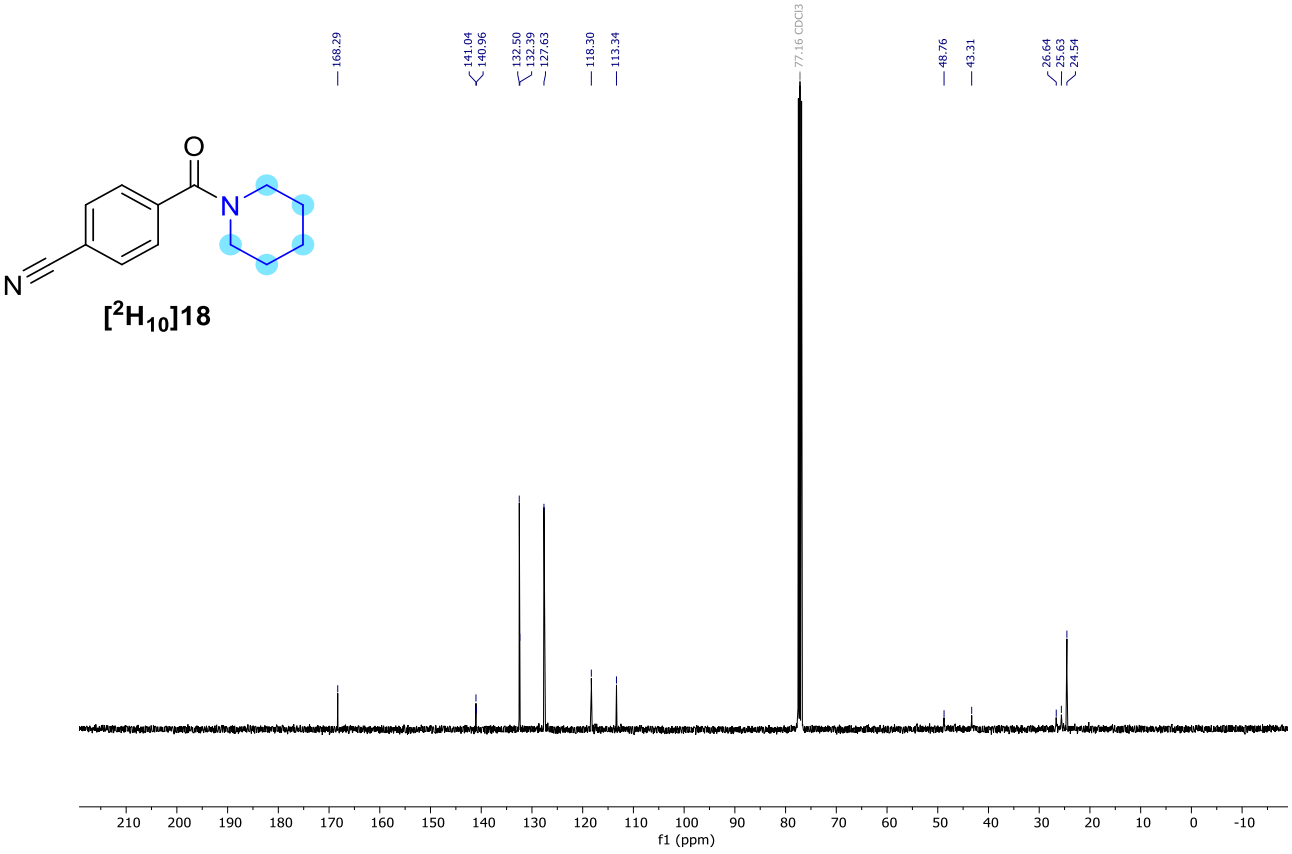


Figure S168: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

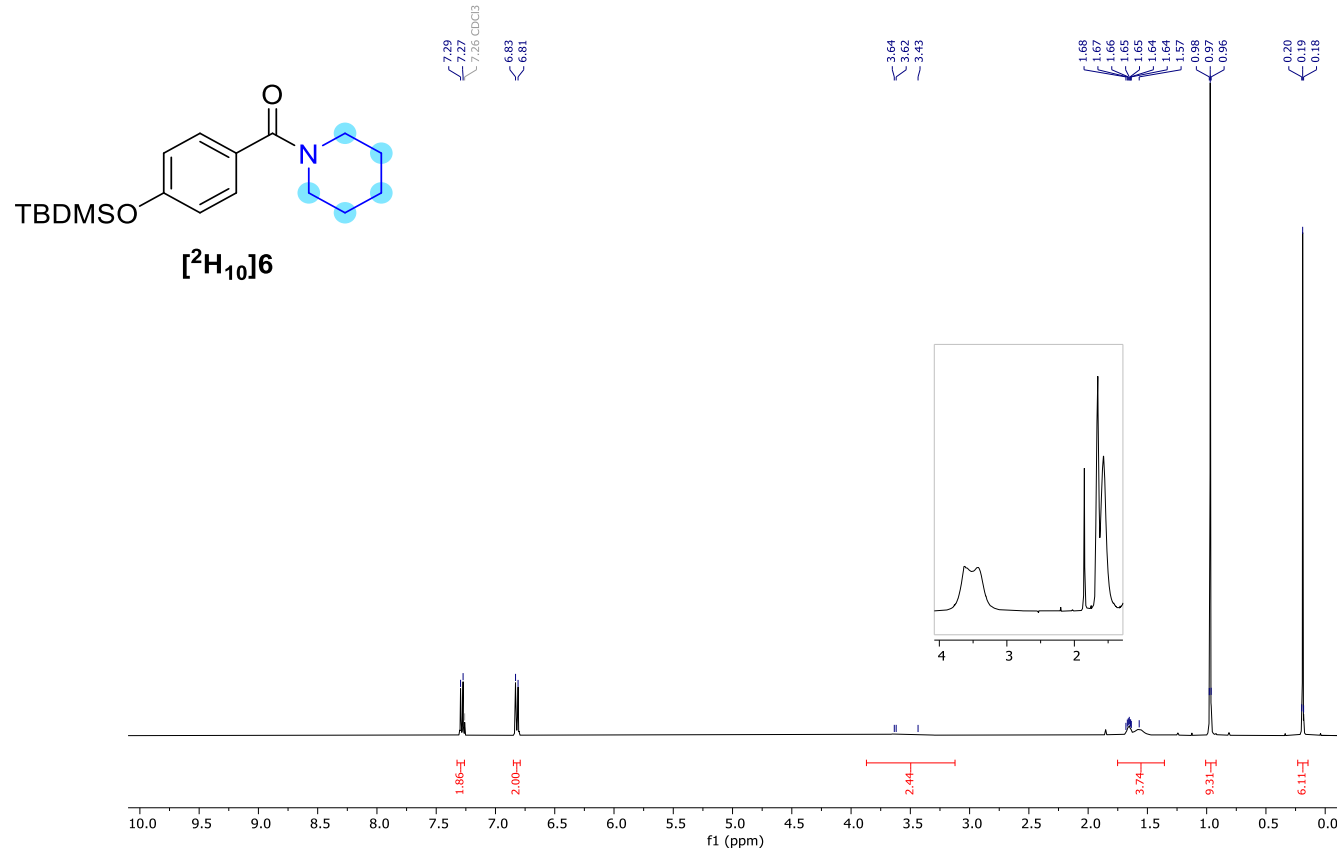


Figure S169: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

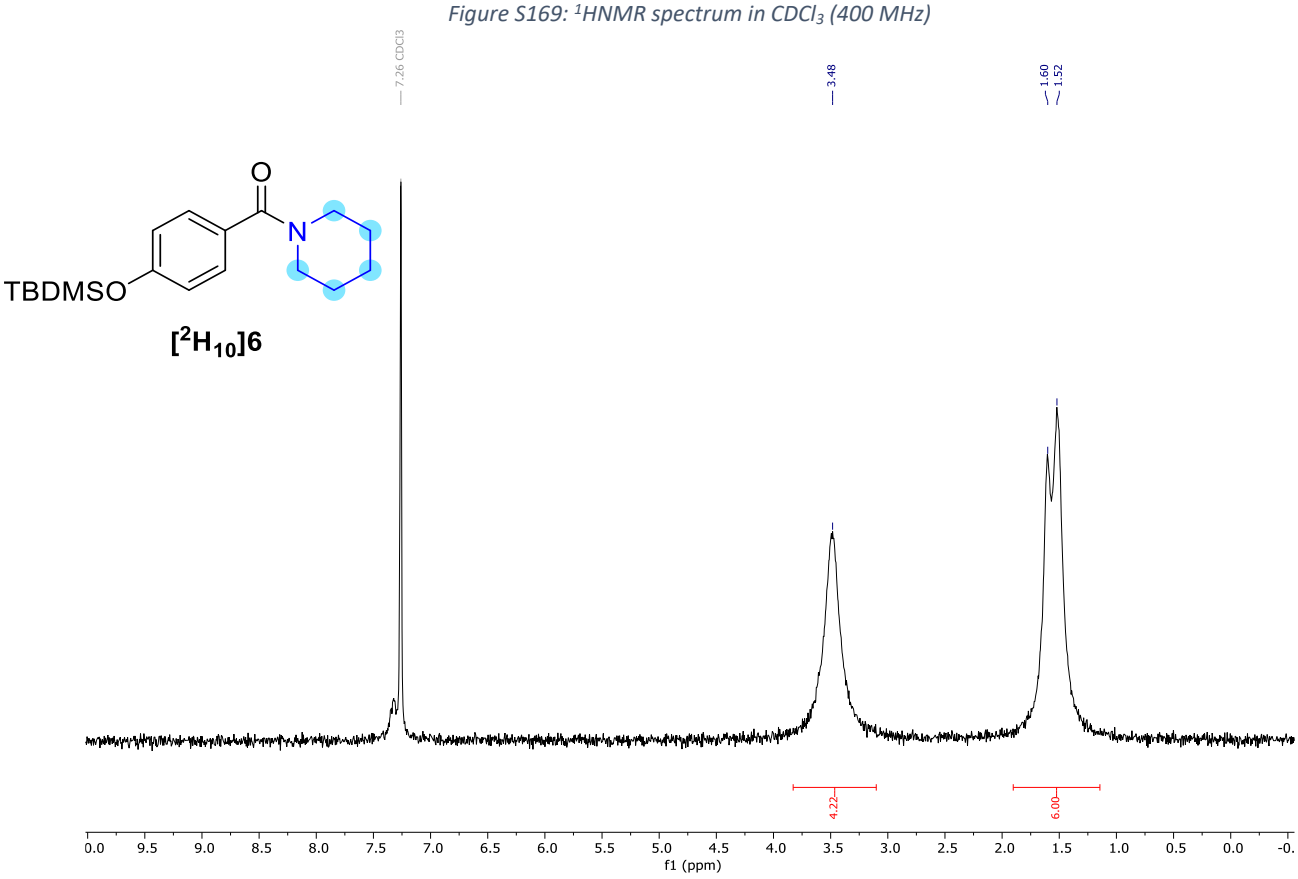


Figure S170: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

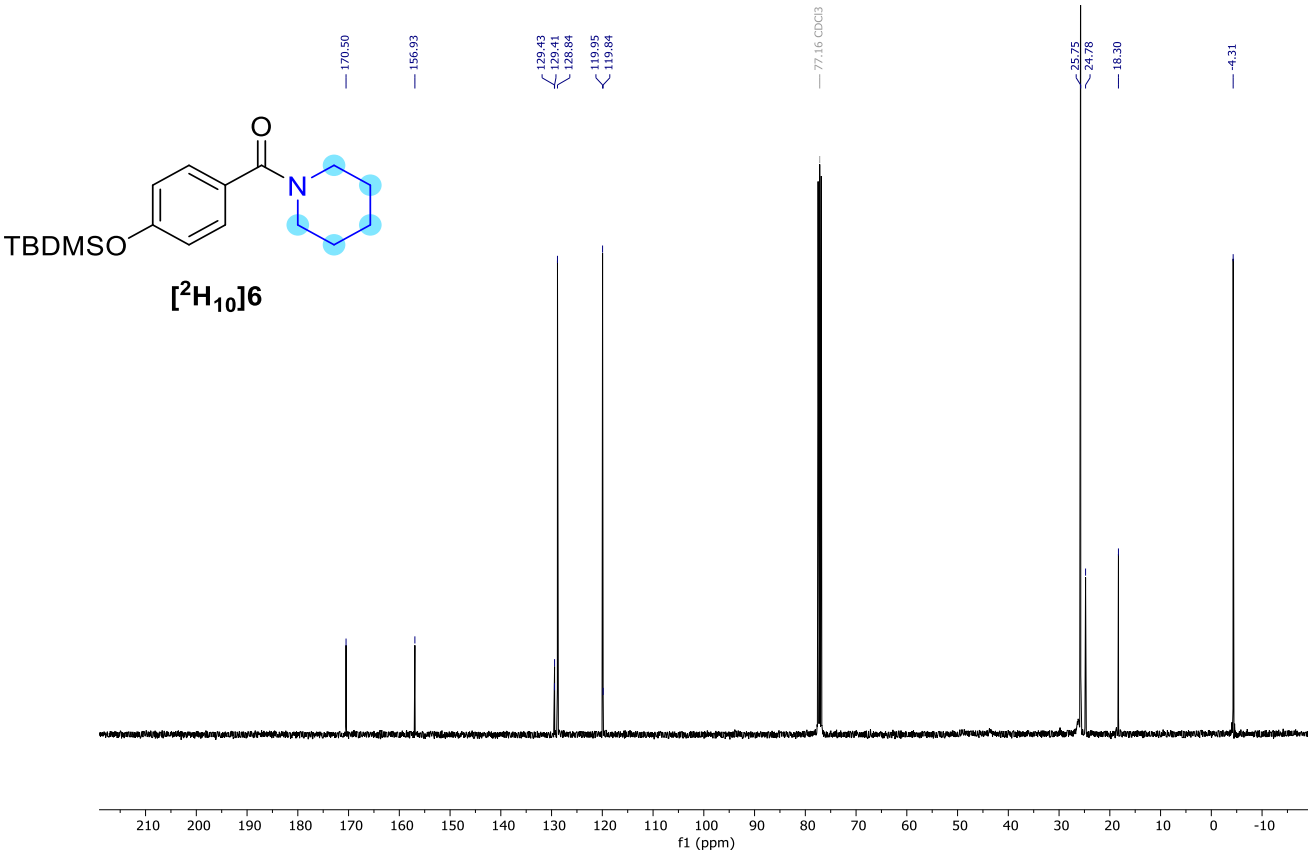


Figure S171: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

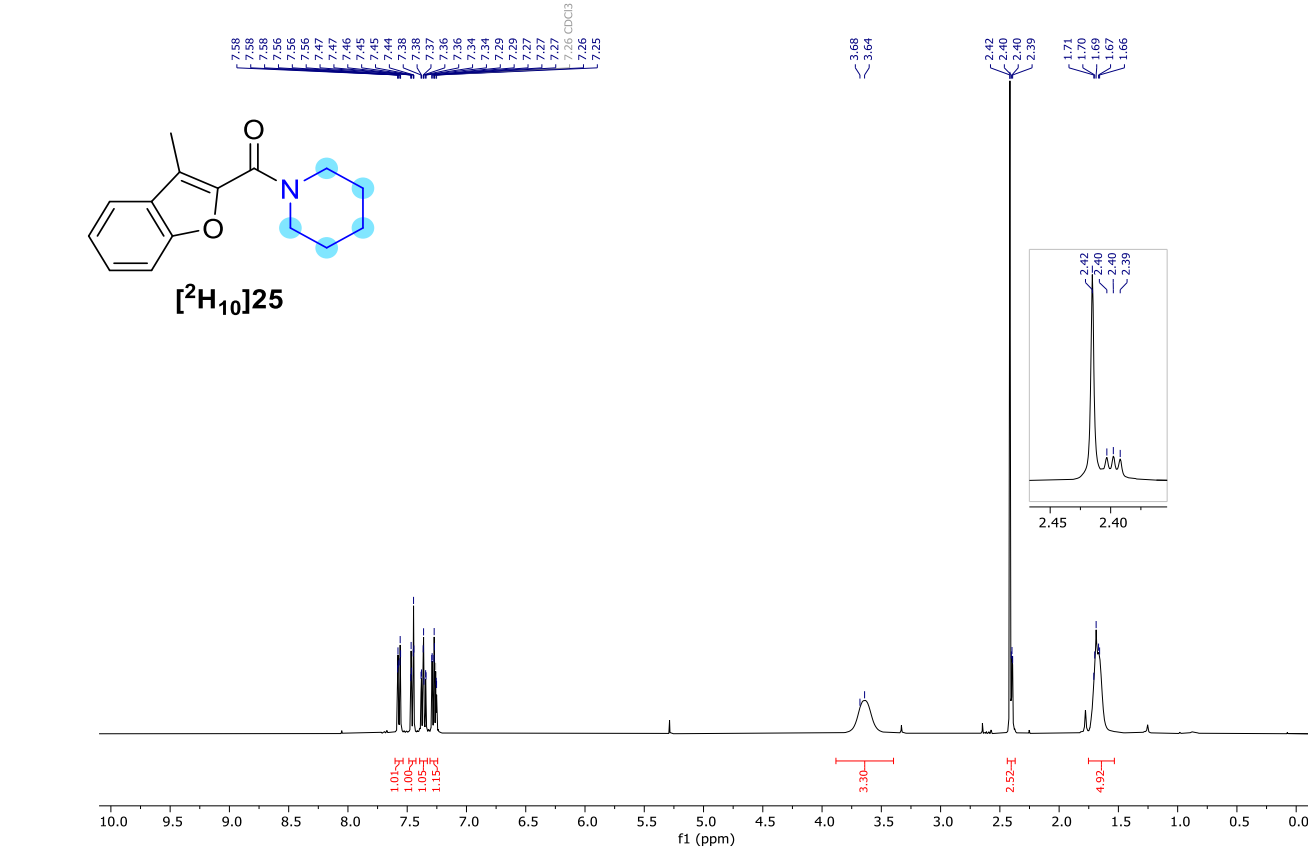


Figure S172: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

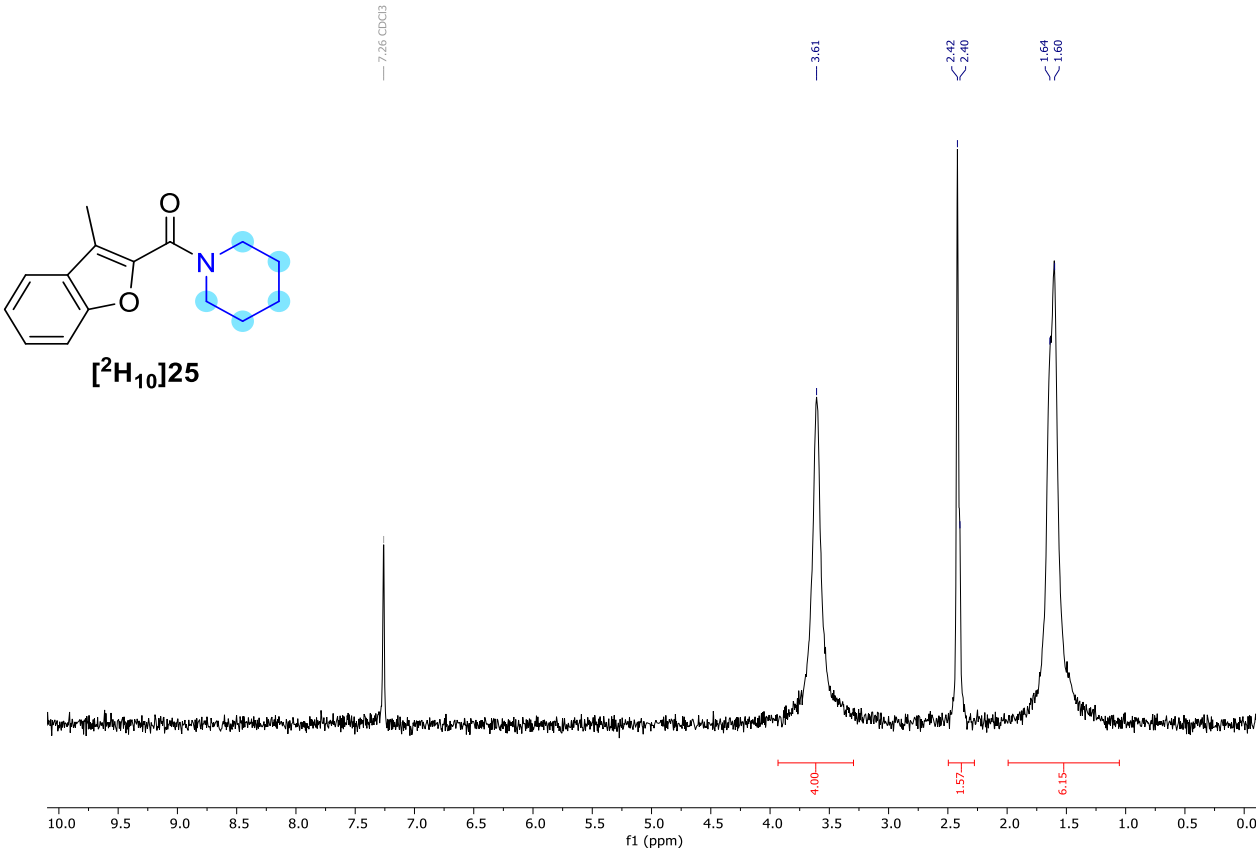


Figure S173: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

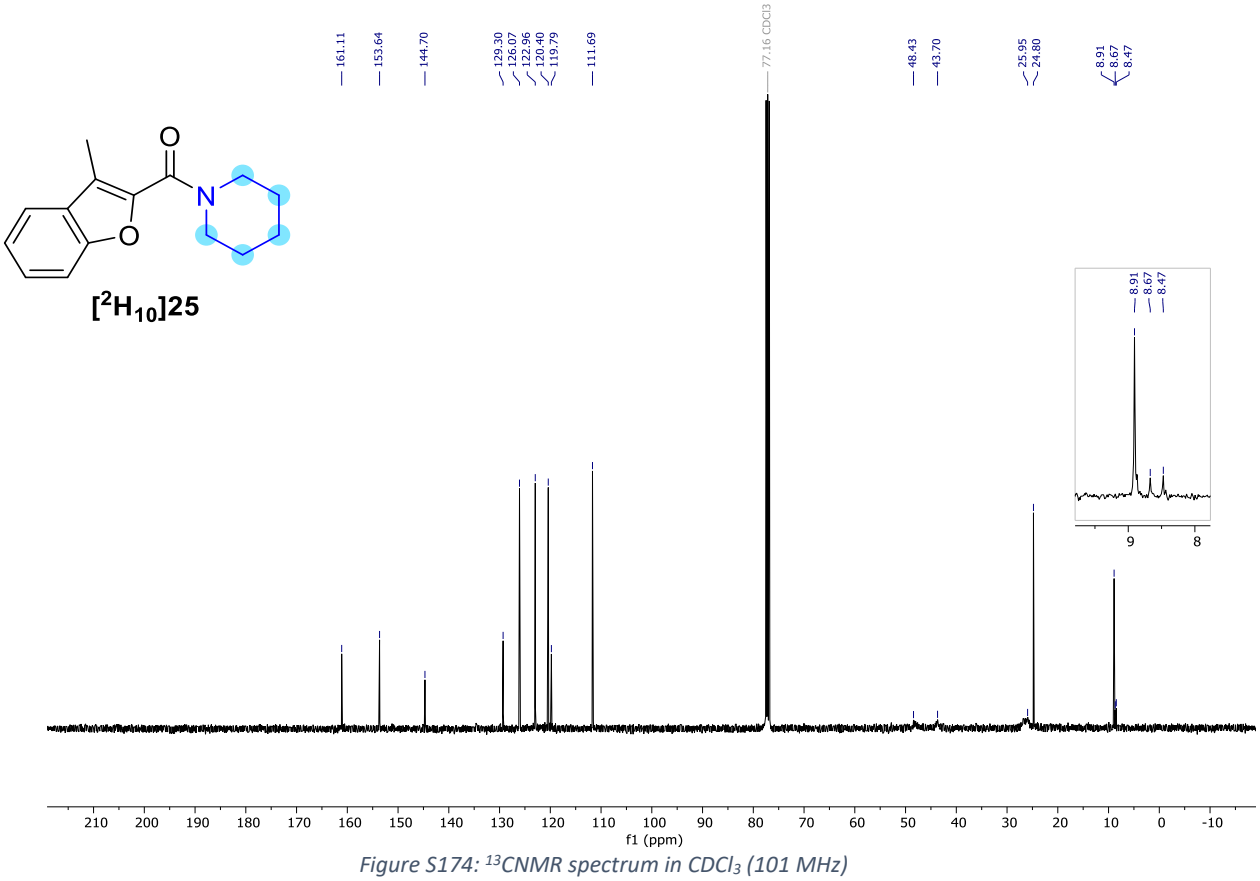


Figure S174: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

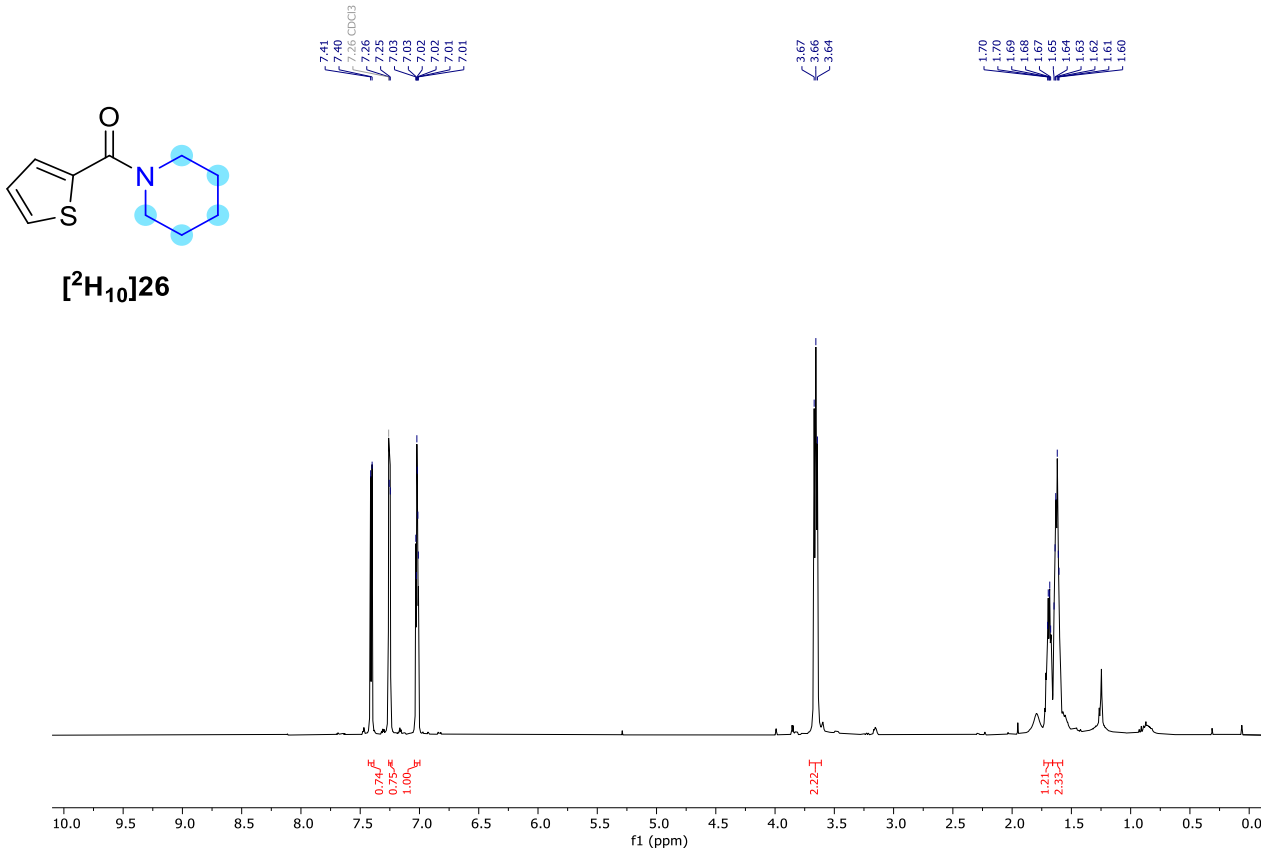


Figure S175: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

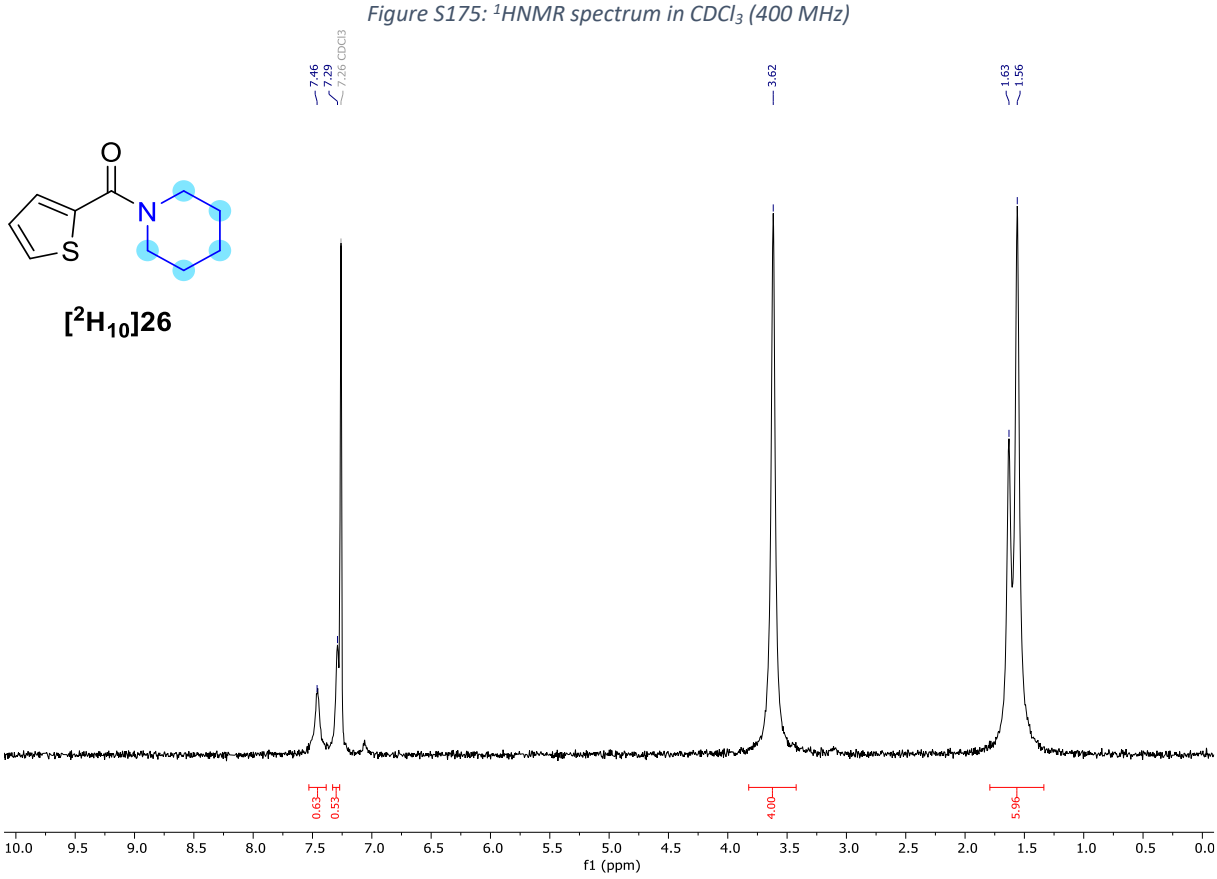


Figure S176: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

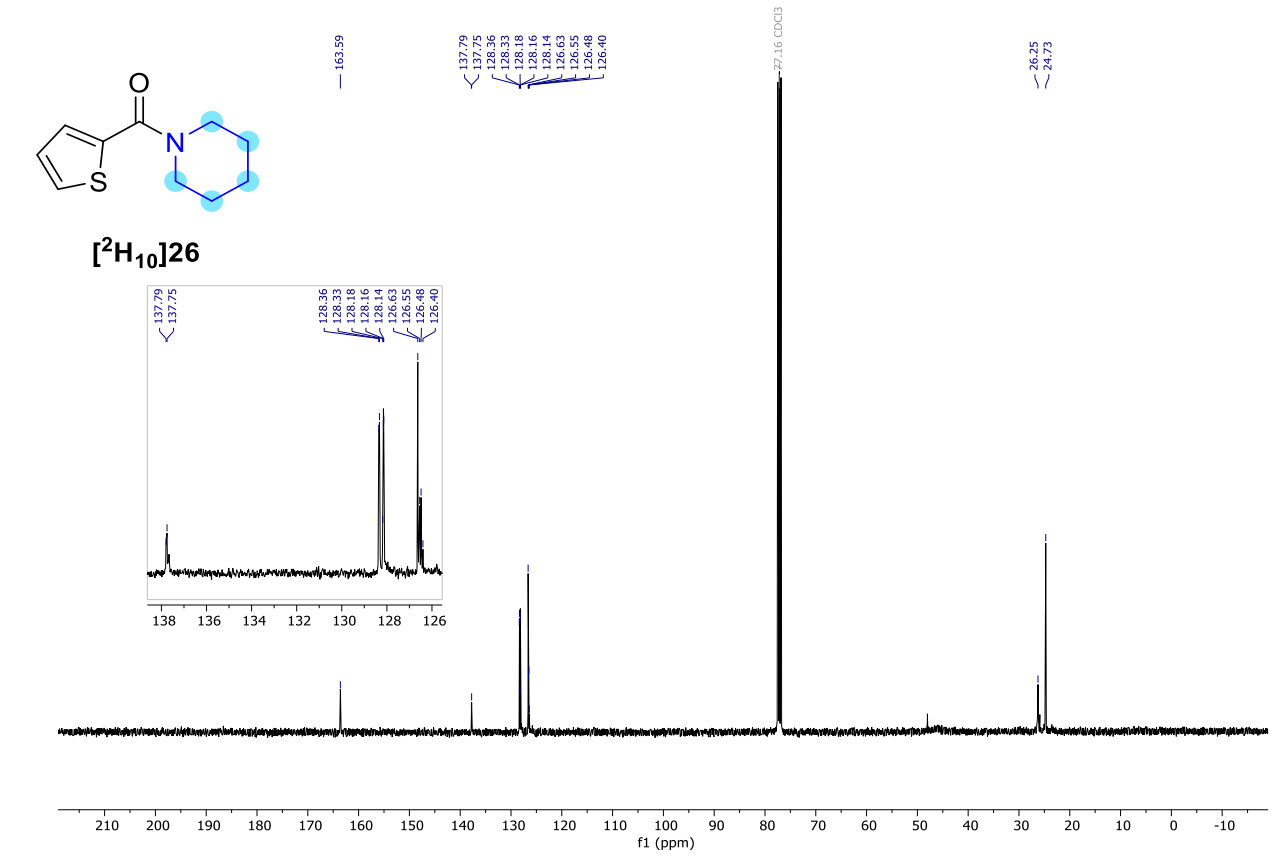


Figure S177: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

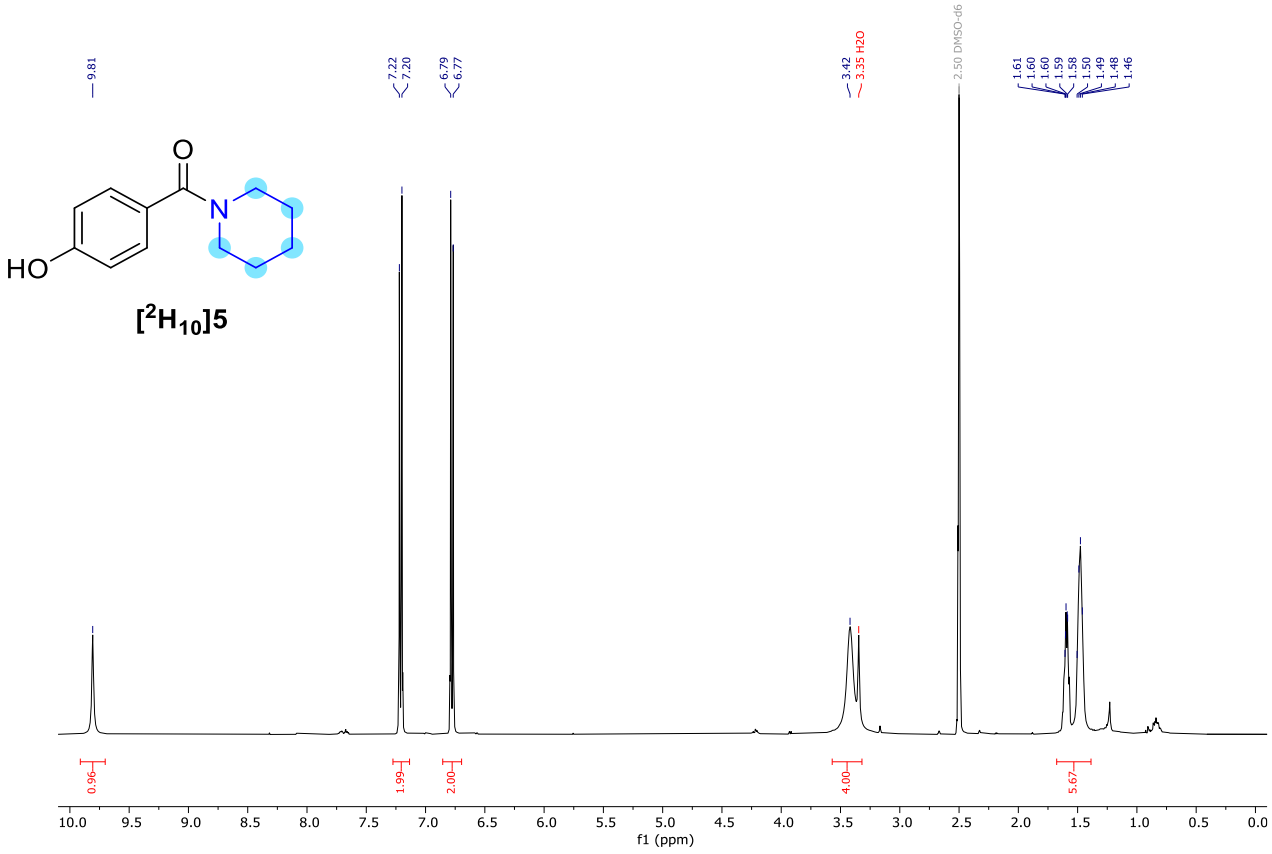


Figure 178: ^{1}HNMR spectrum in DMSO-d_6 (400 MHz)

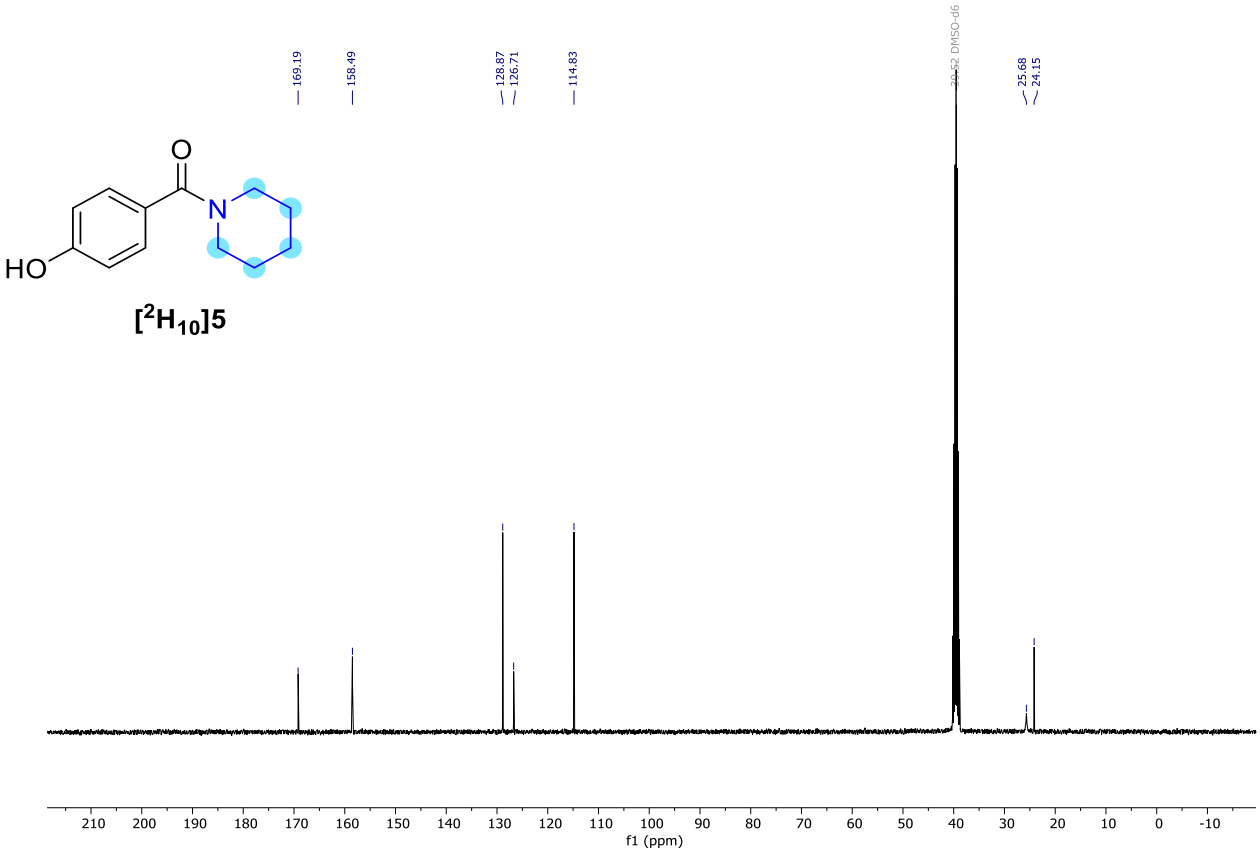


Figure 179: ^{13}CNMR spectrum in DMSO-d_6 (101 MHz)

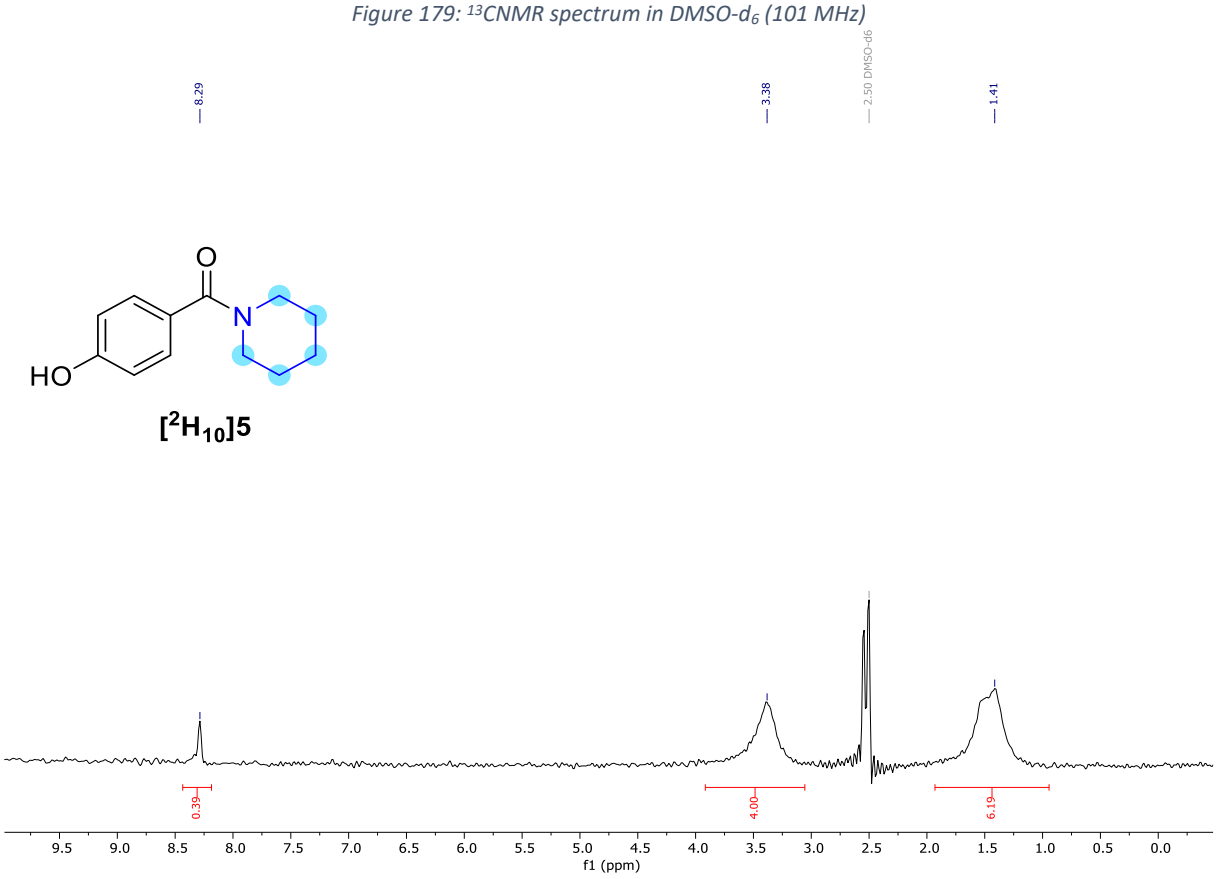


Figure 180: ^{2}HNMR spectrum in DMSO (61 MHz)

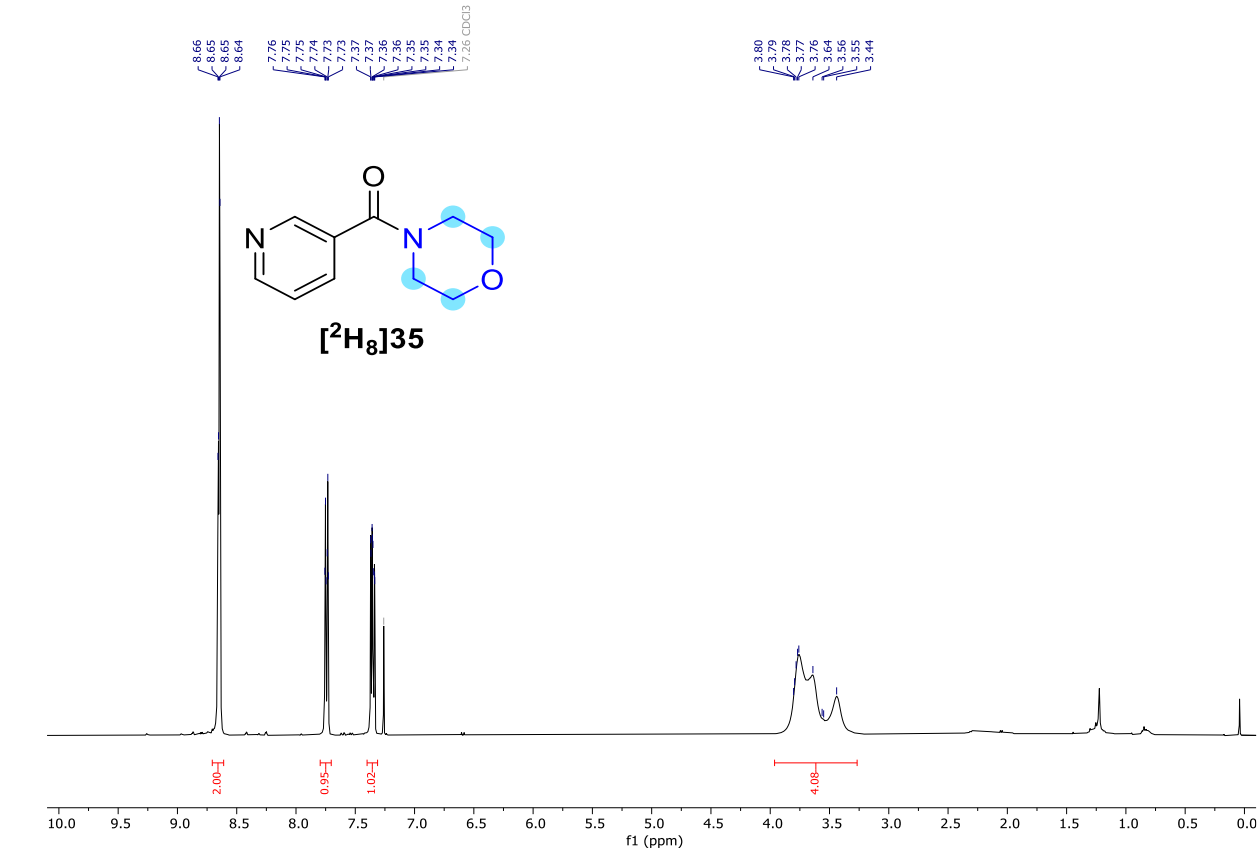


Figure S181: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

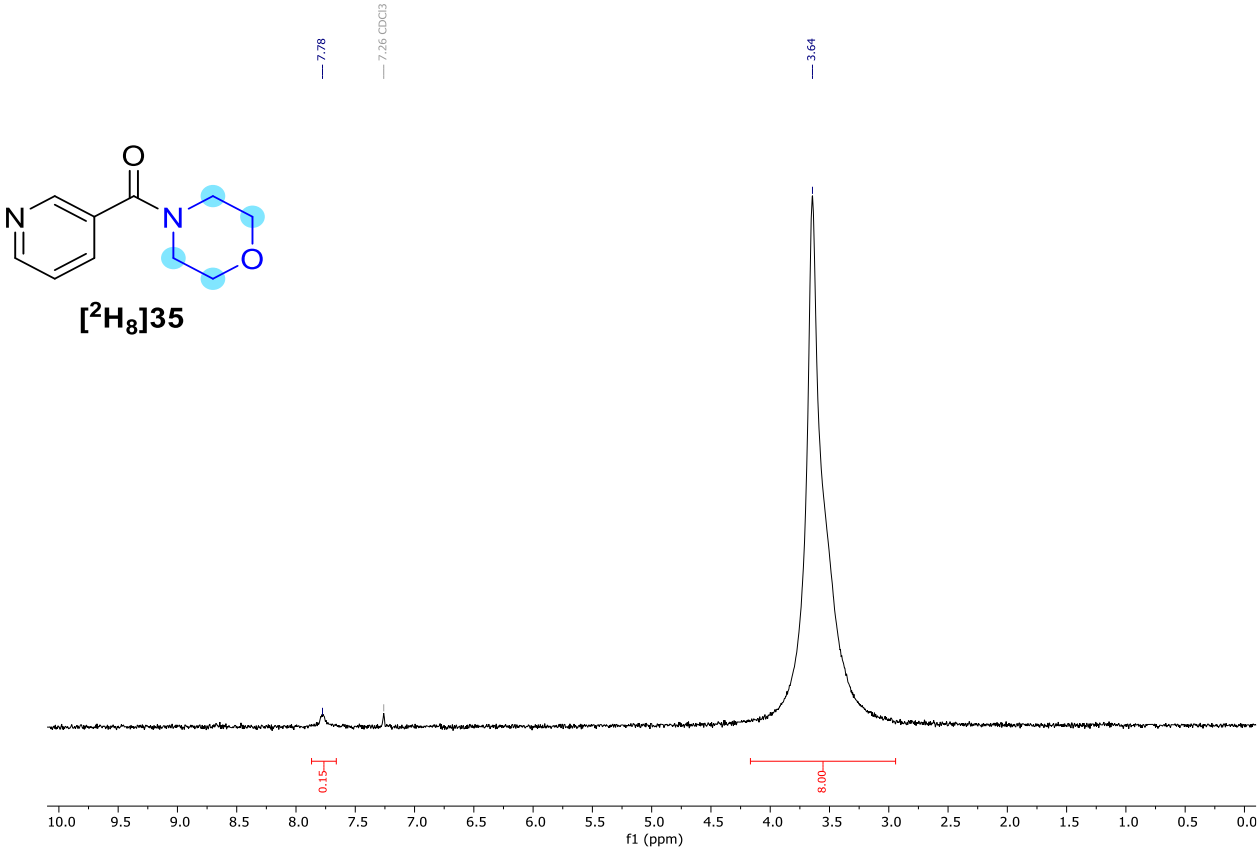


Figure S182: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

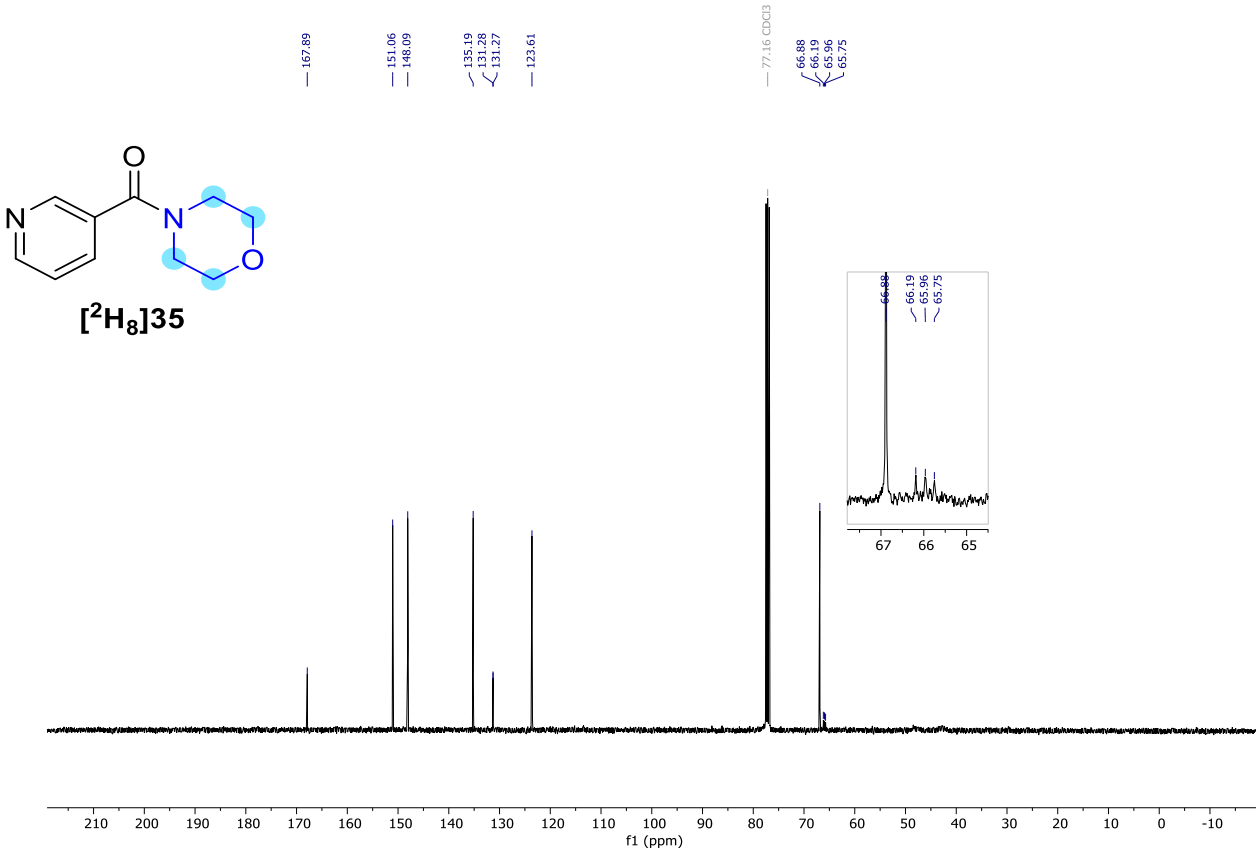


Figure S183: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

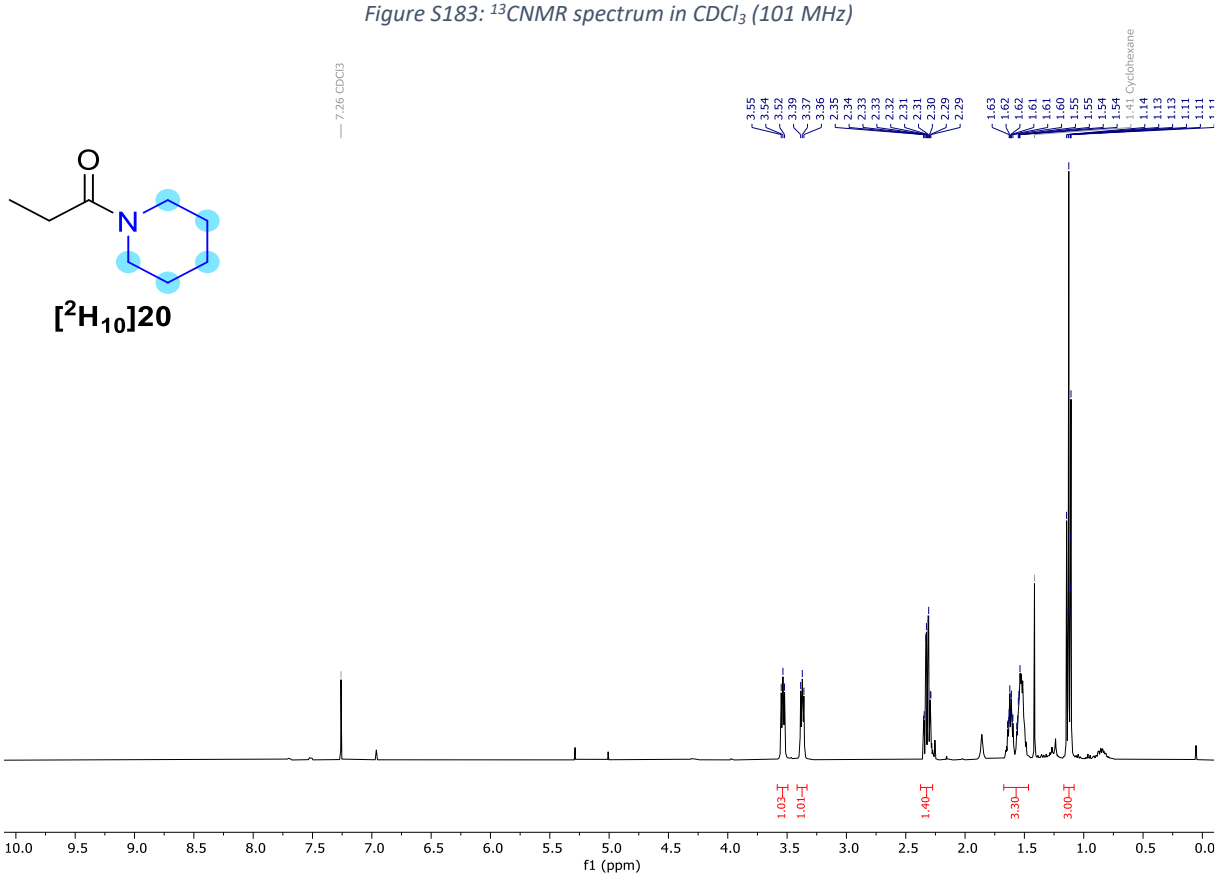


Figure S184: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

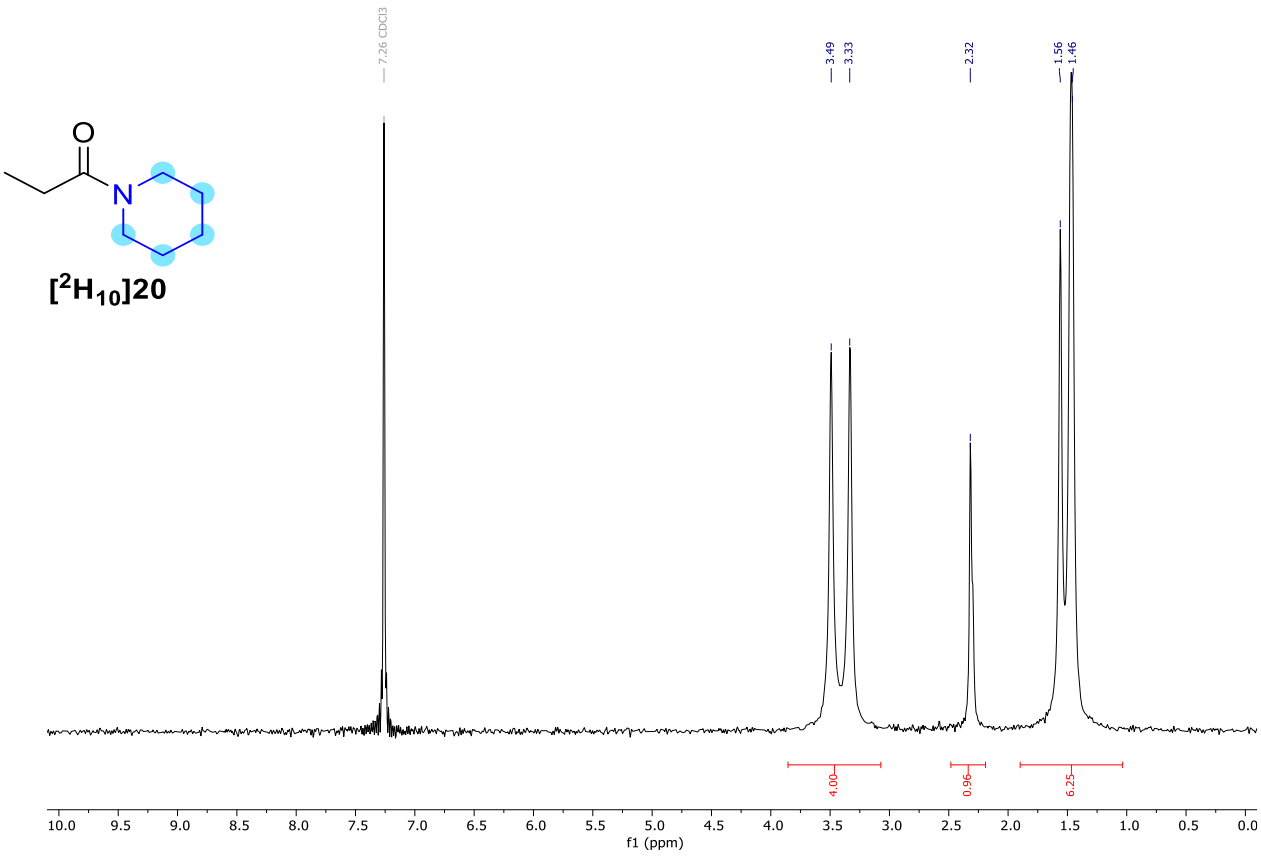


Figure S185: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

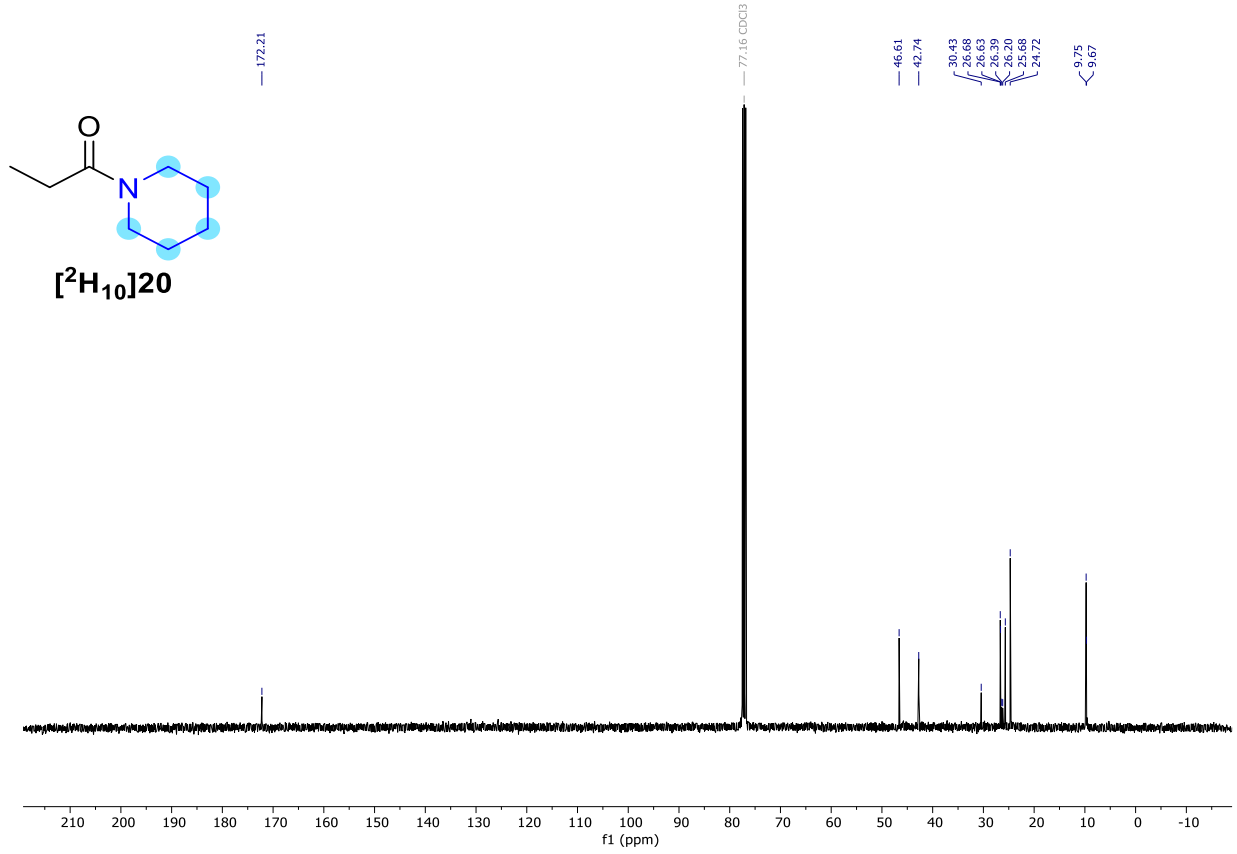


Figure S186: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

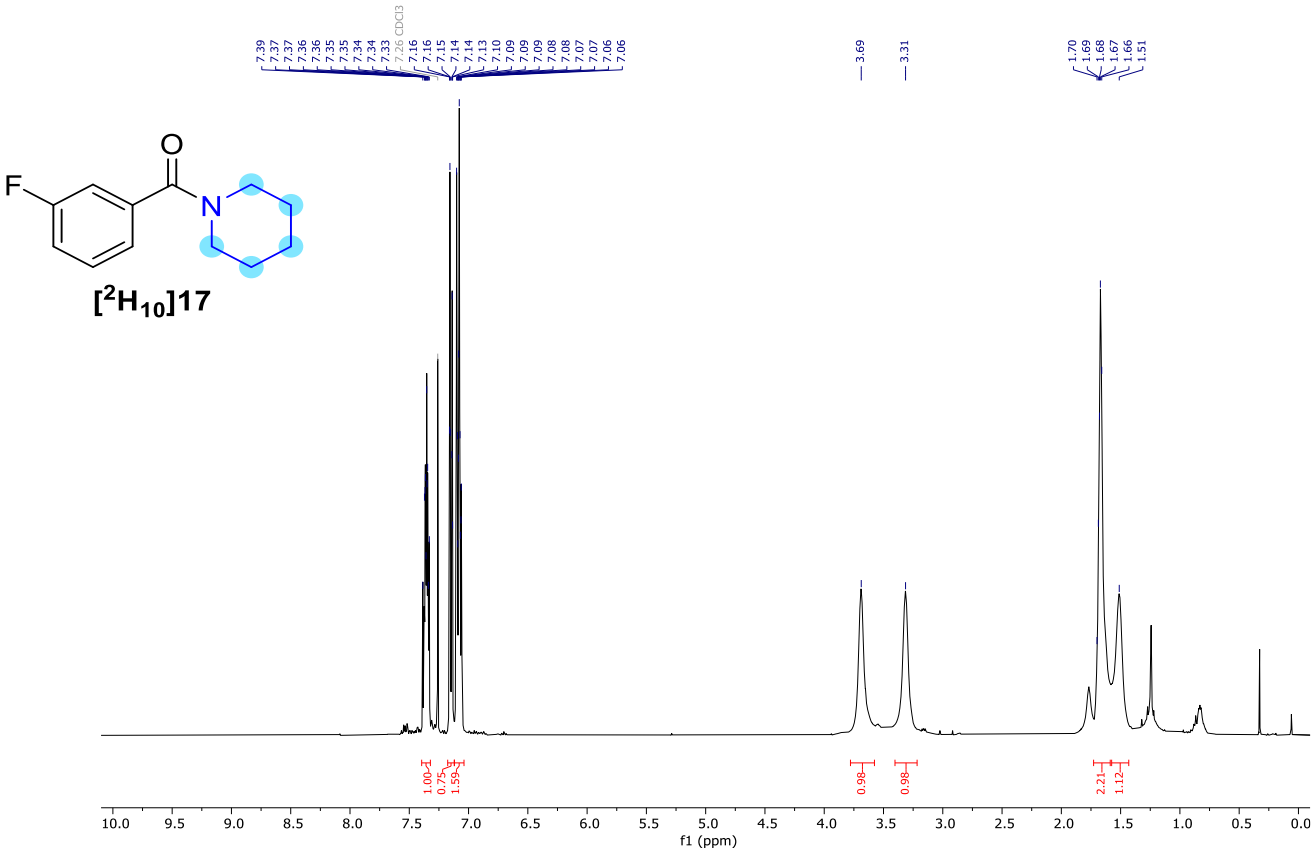


Figure S187: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

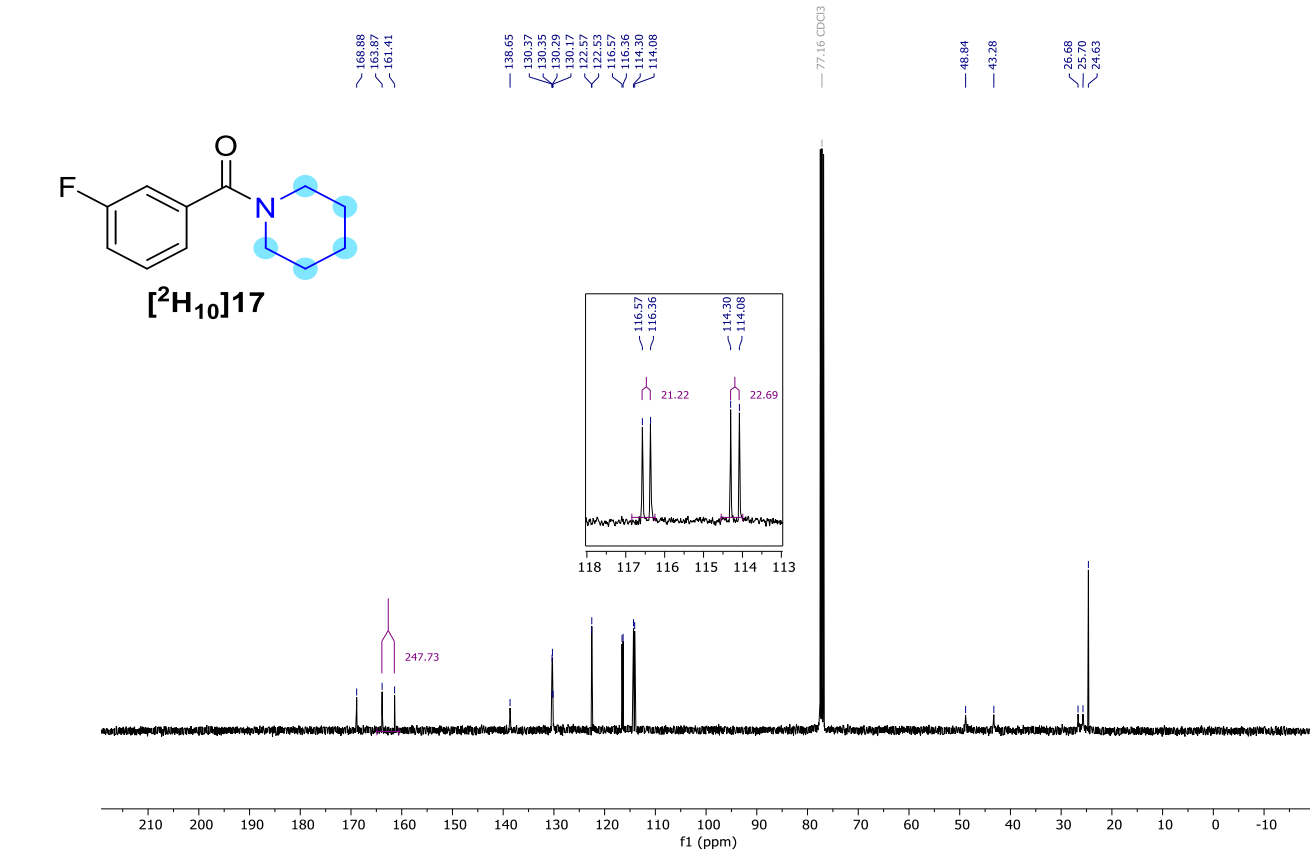


Figure S188: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

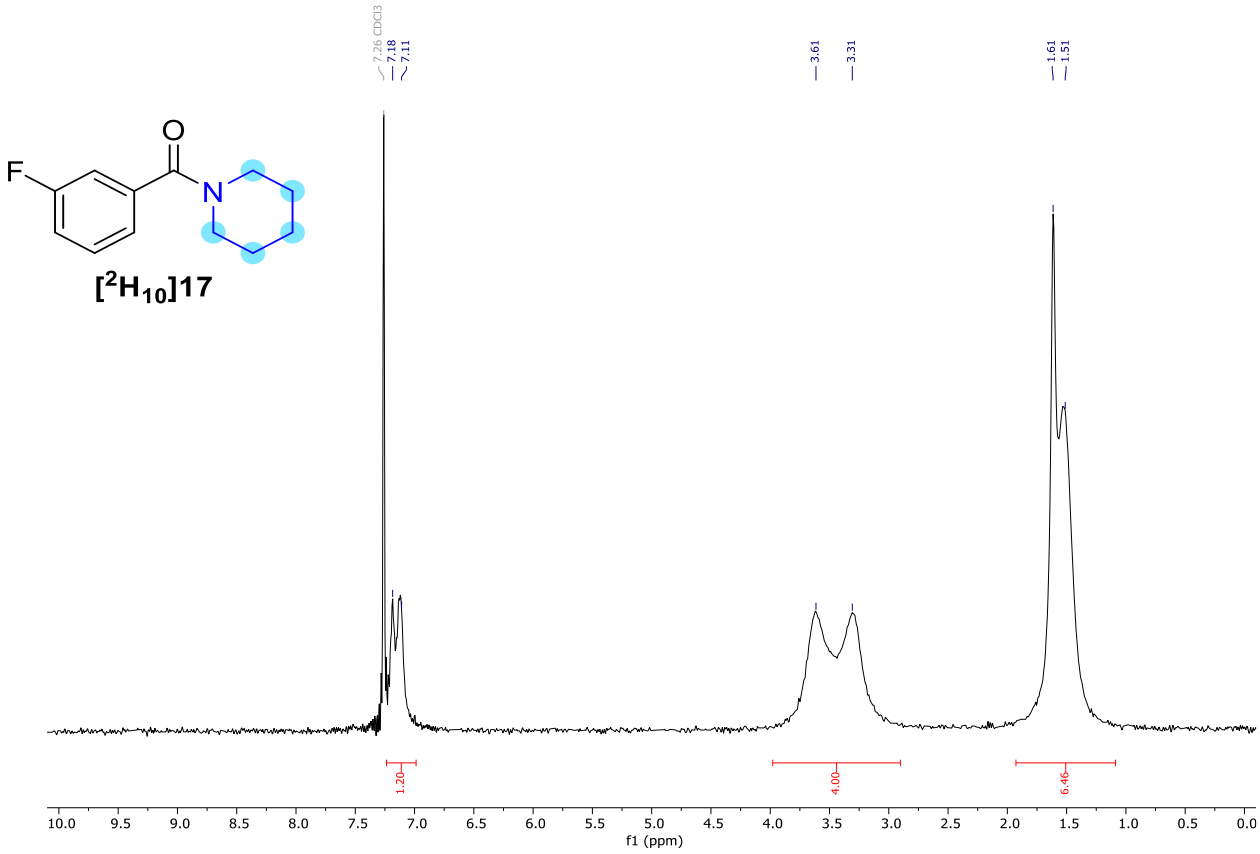


Figure S189: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

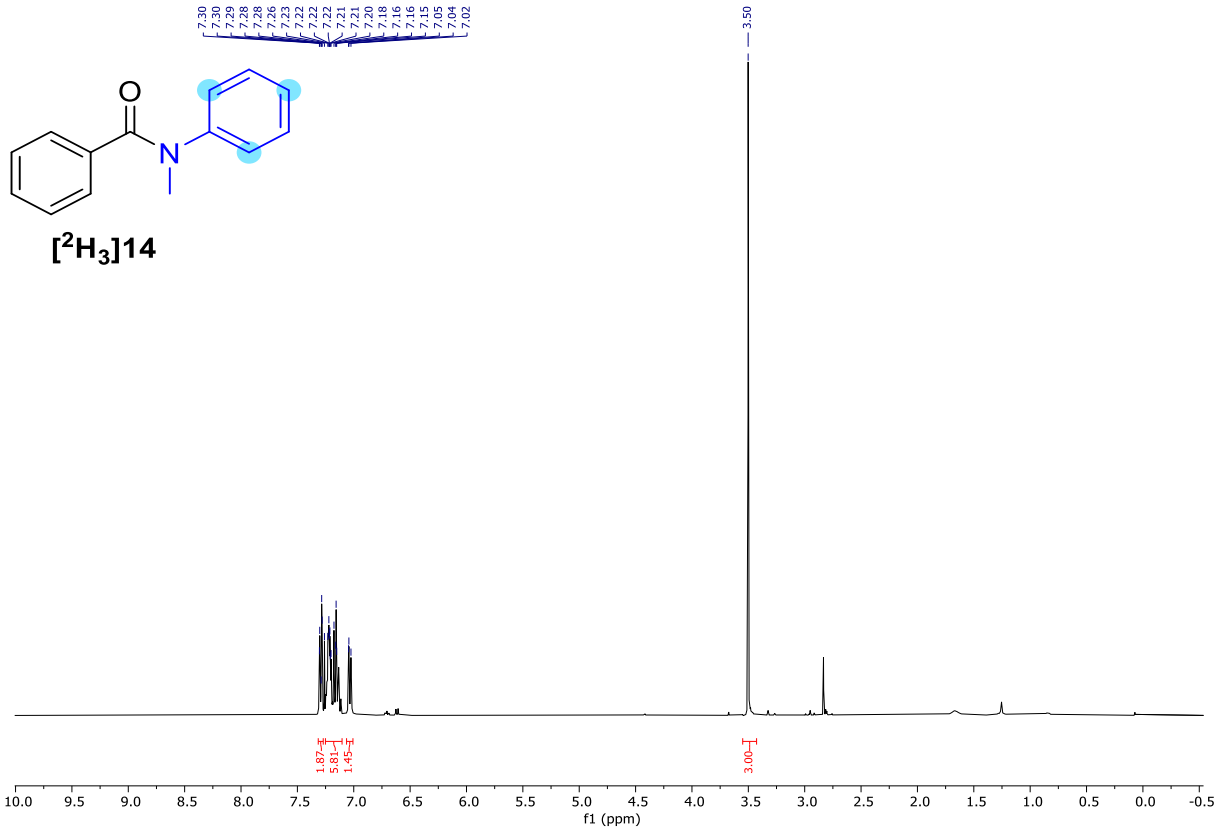


Figure S190: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

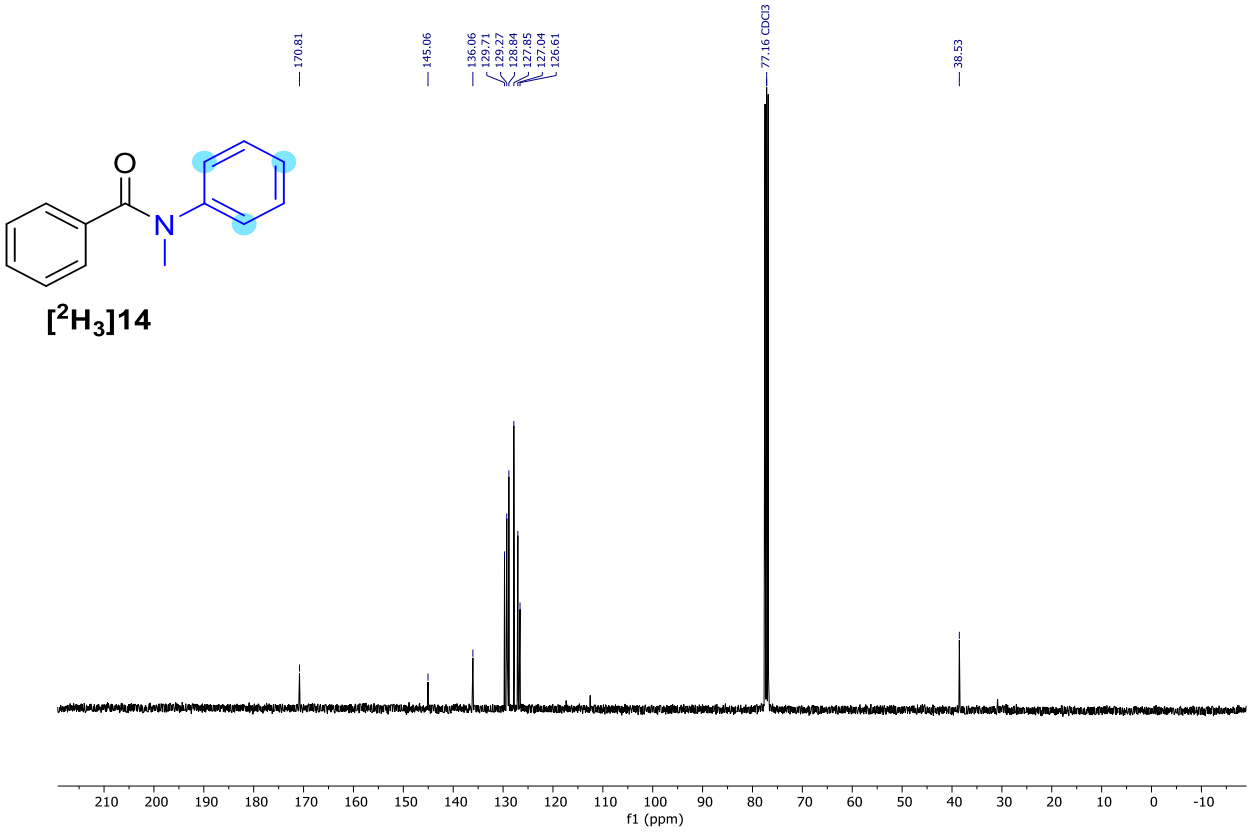


Figure S191: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

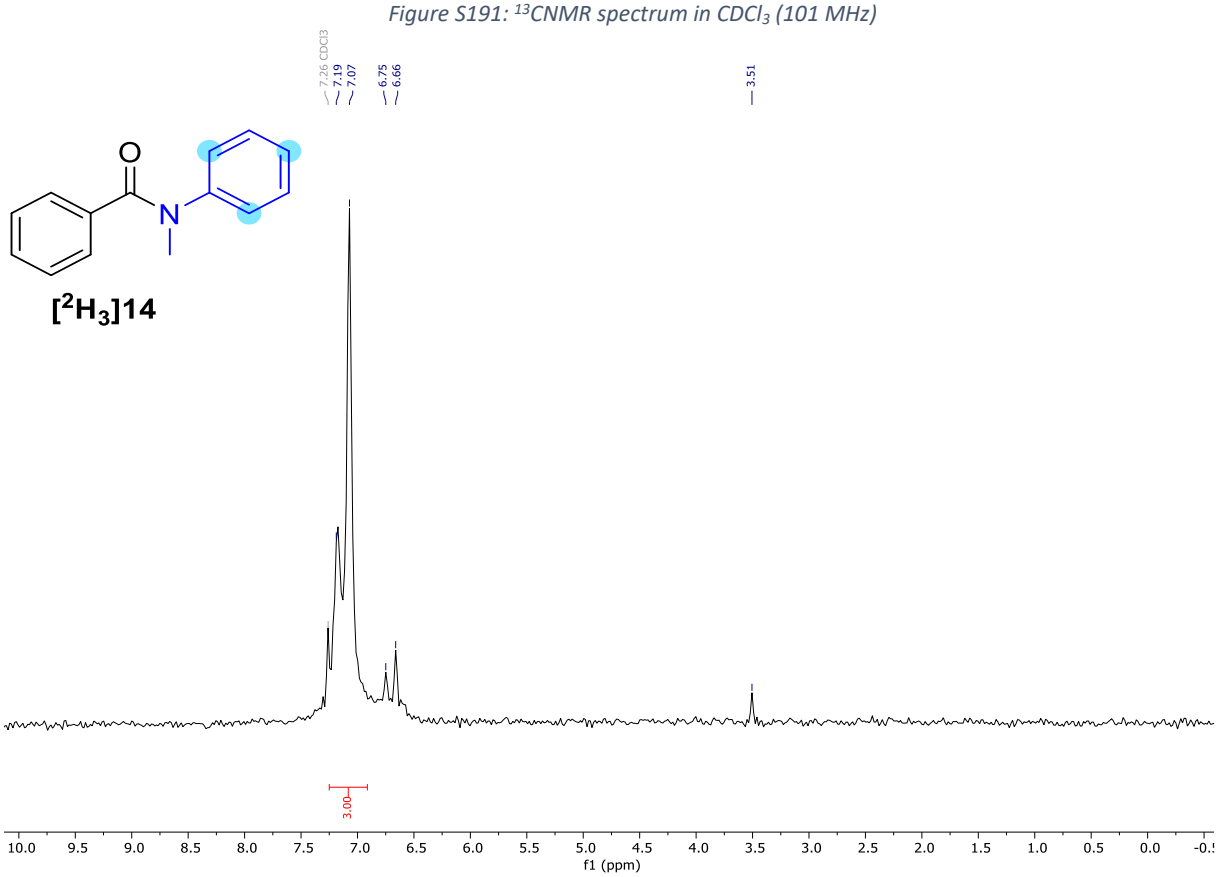


Figure S192: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

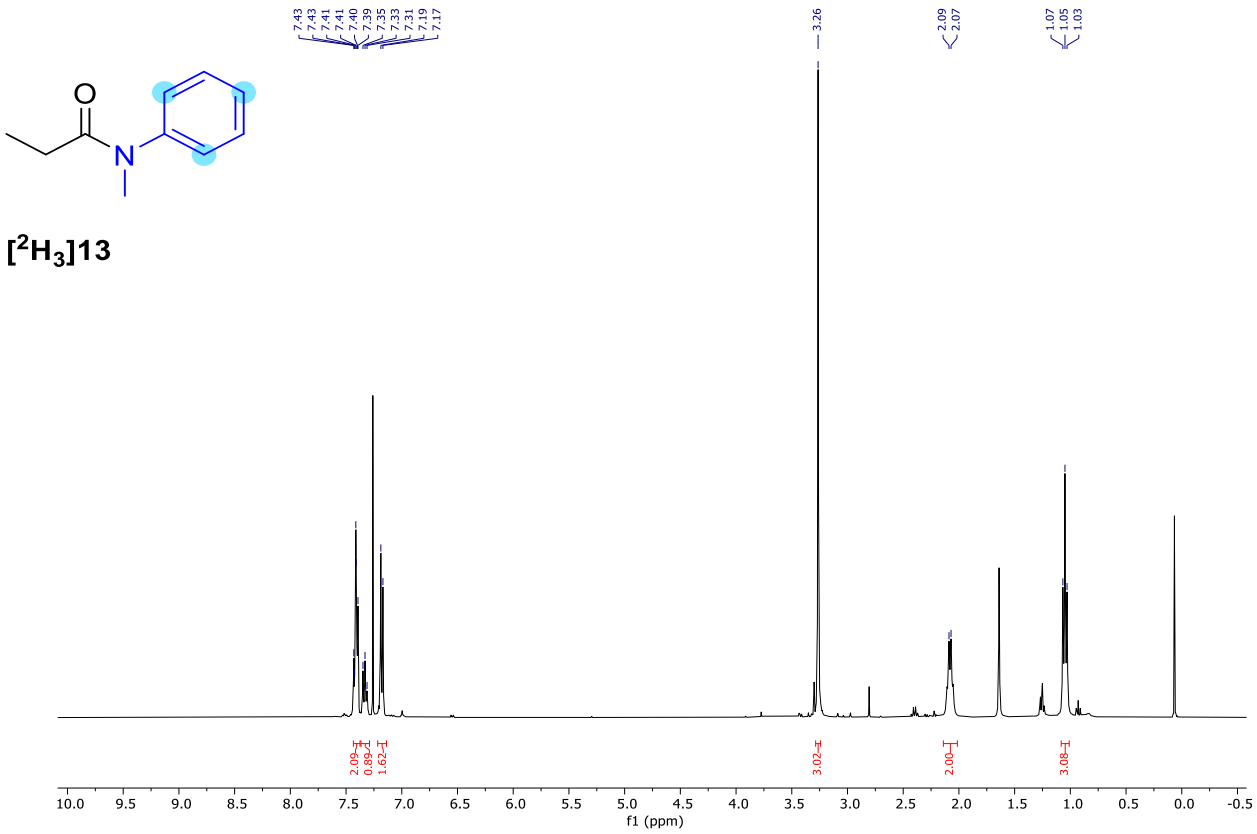


Figure S193: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

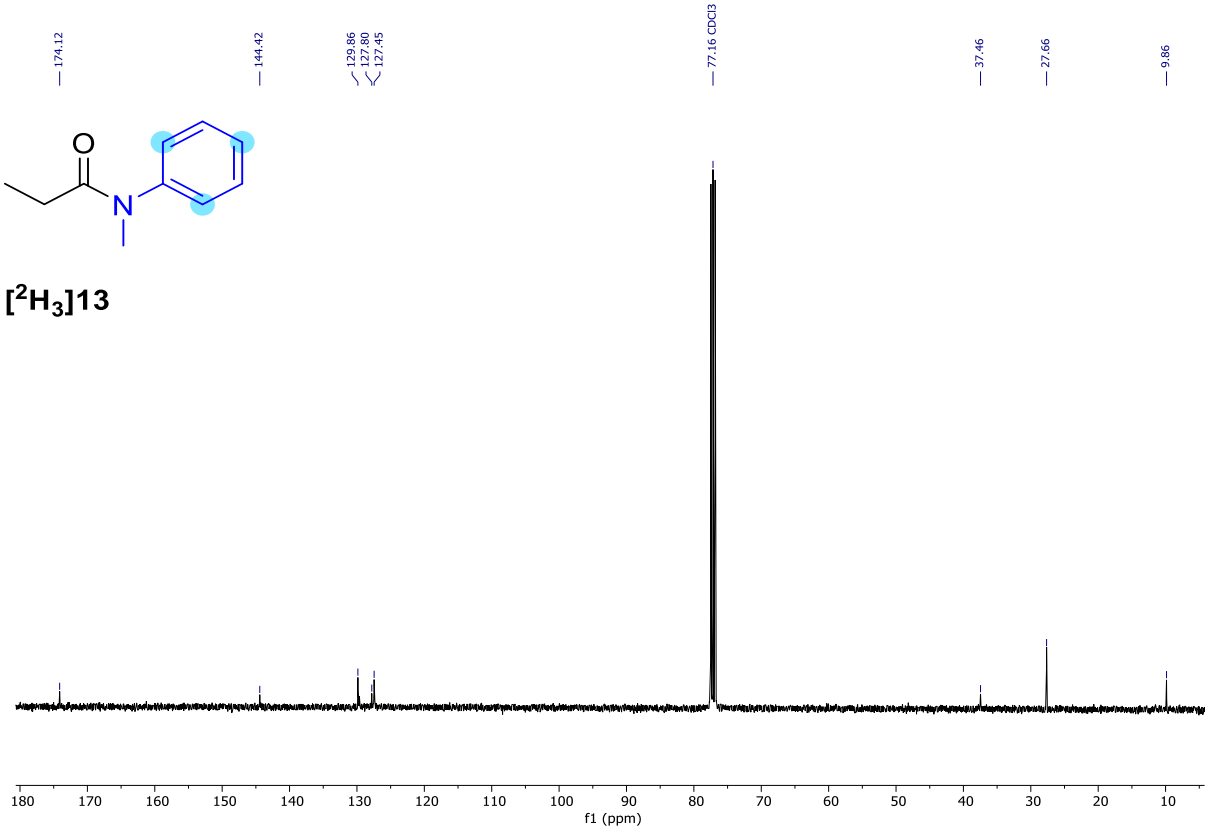
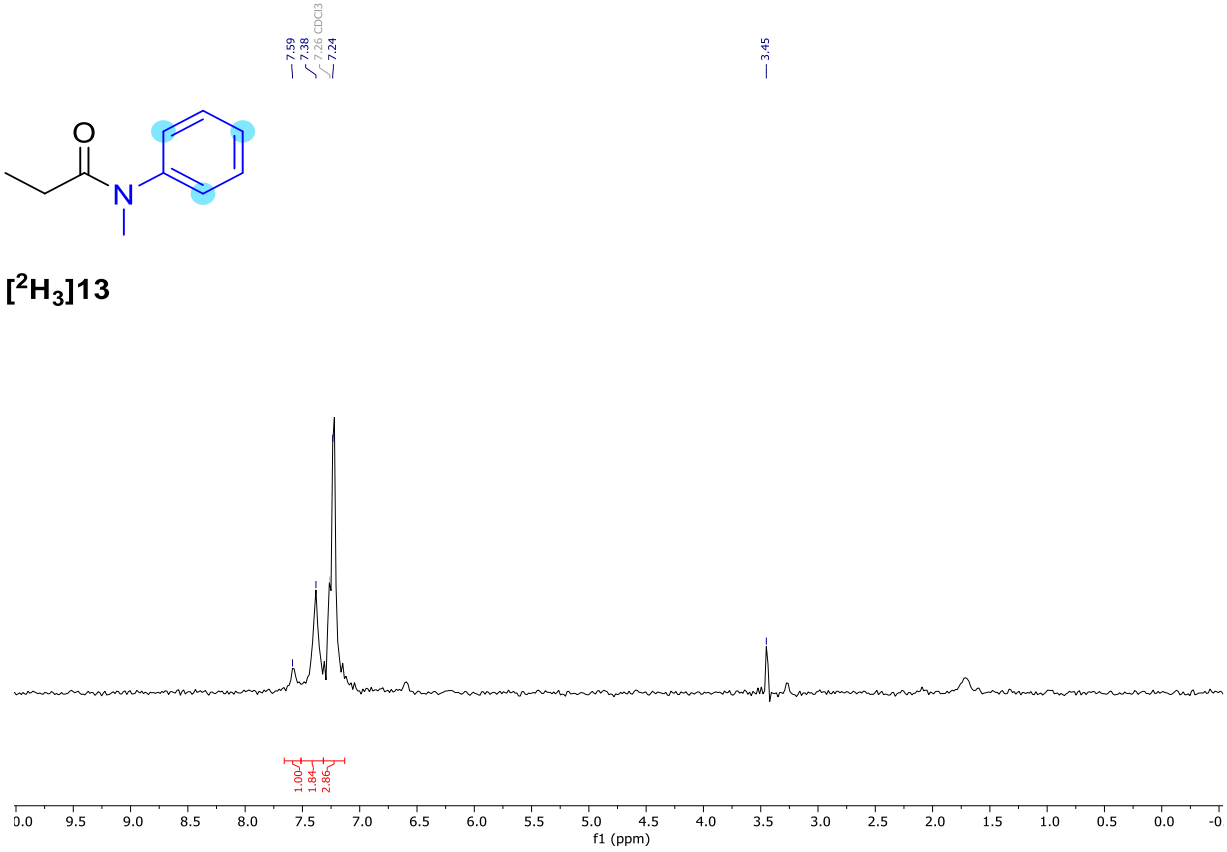
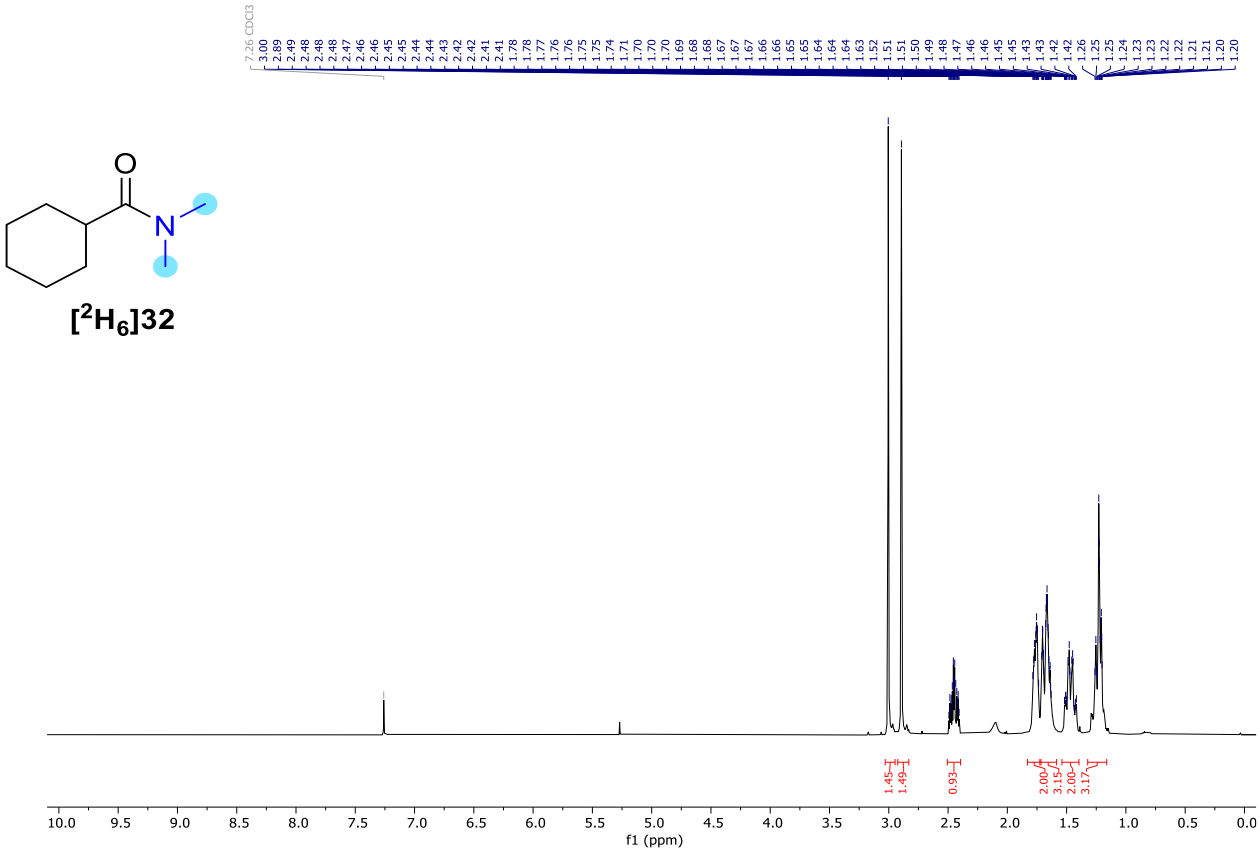


Figure S194: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)



[$^2H_3$]13

Figure S195: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)



[$^2H_6$]32

Figure S196: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

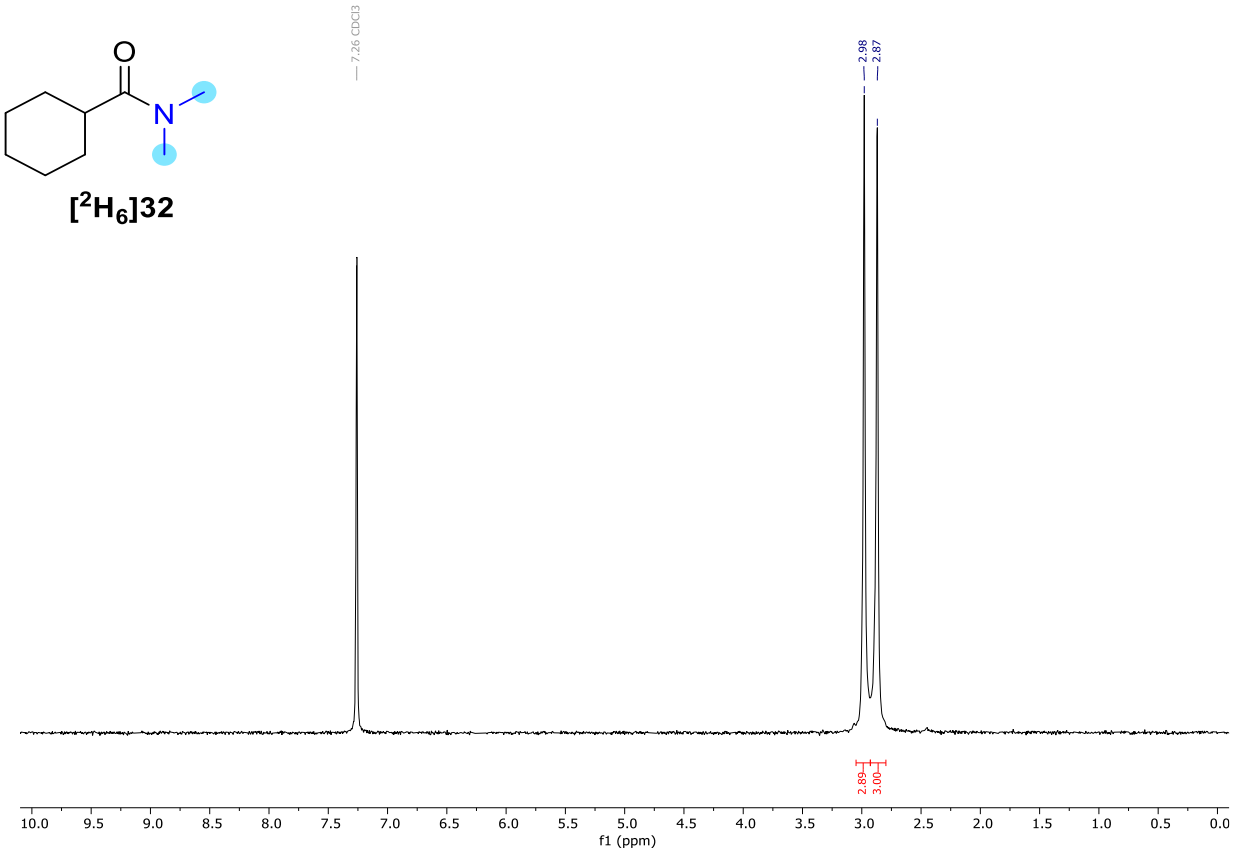


Figure S197: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

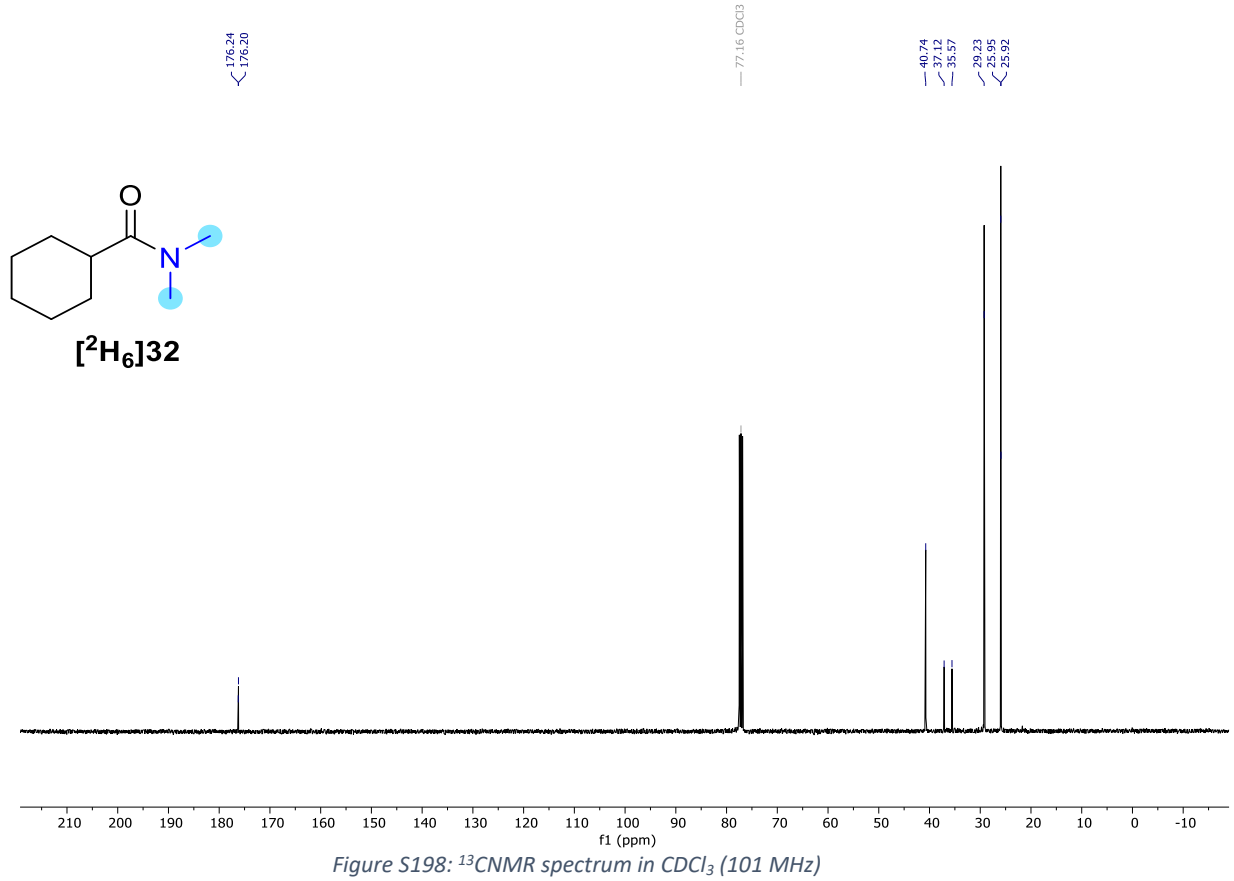


Figure S198: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

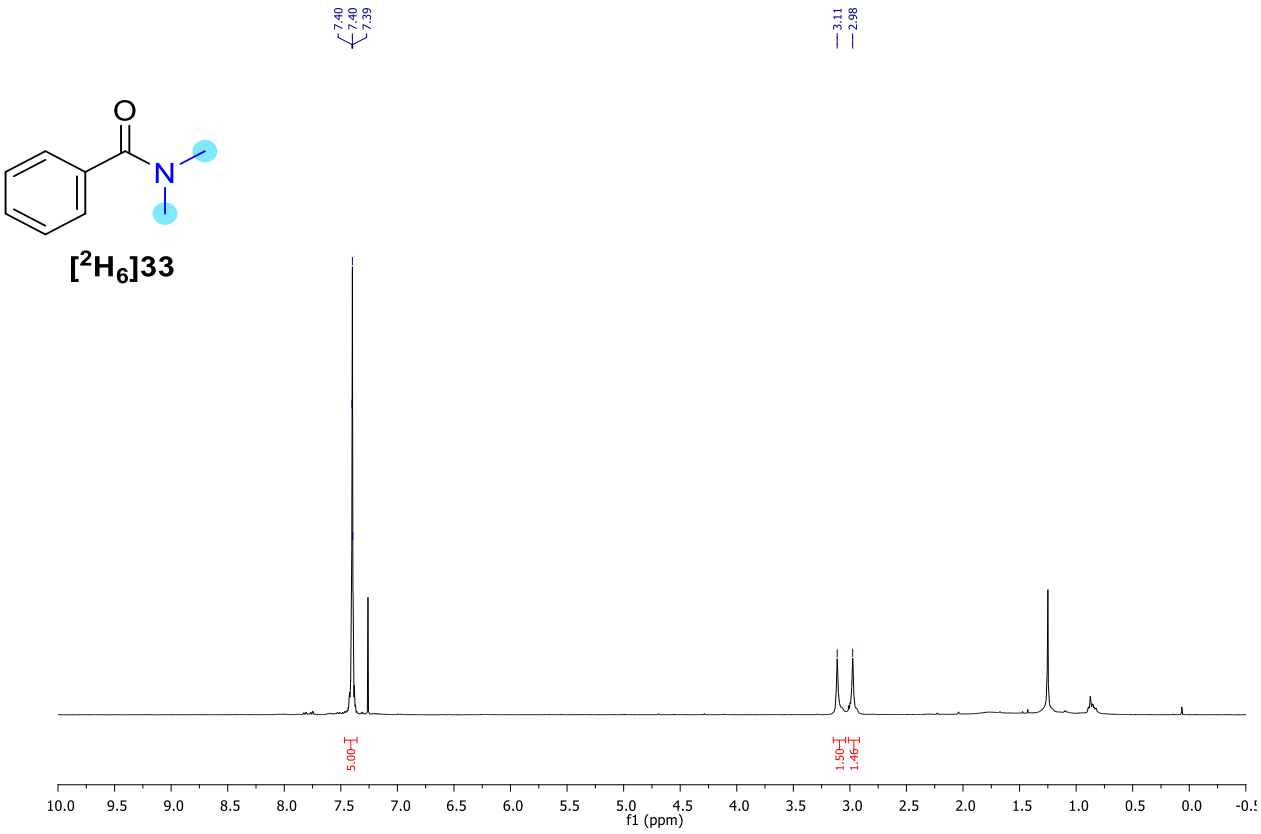


Figure S199: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

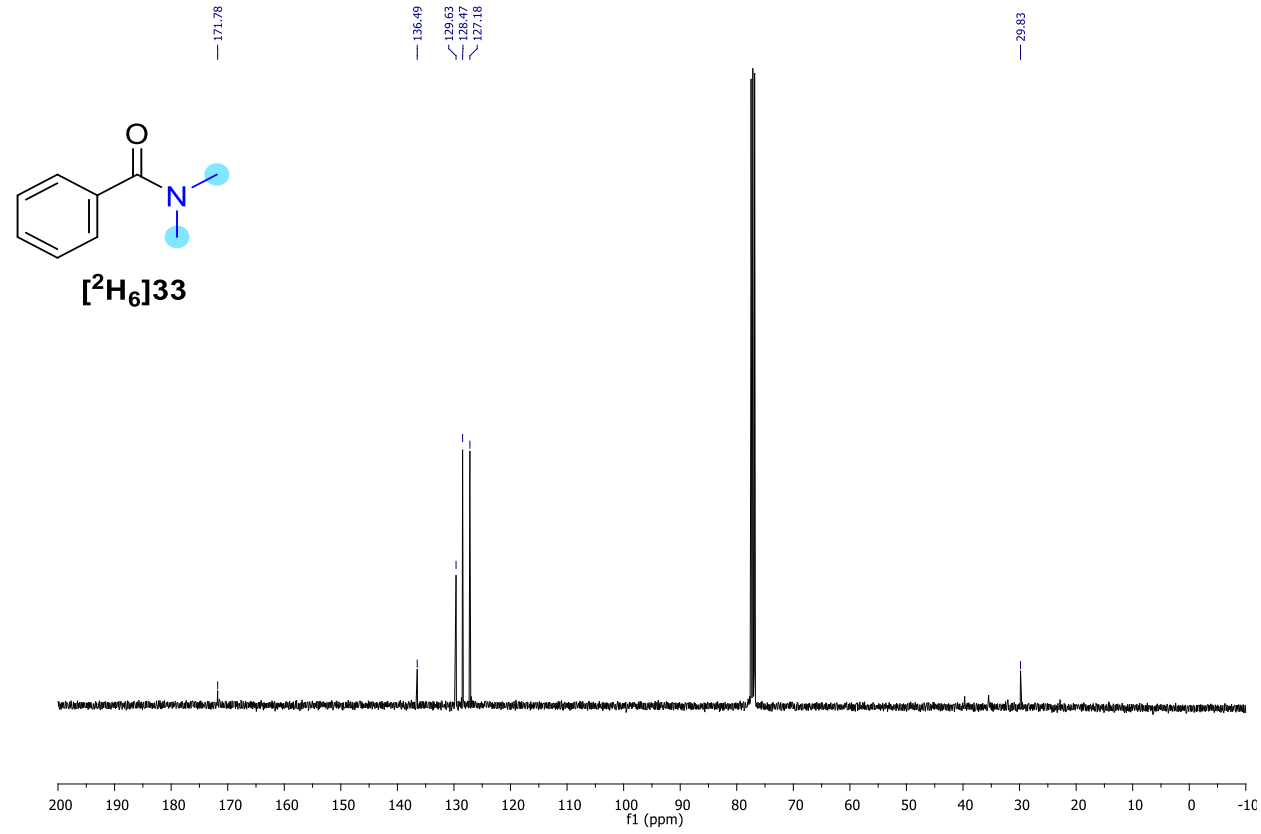


Figure S200: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

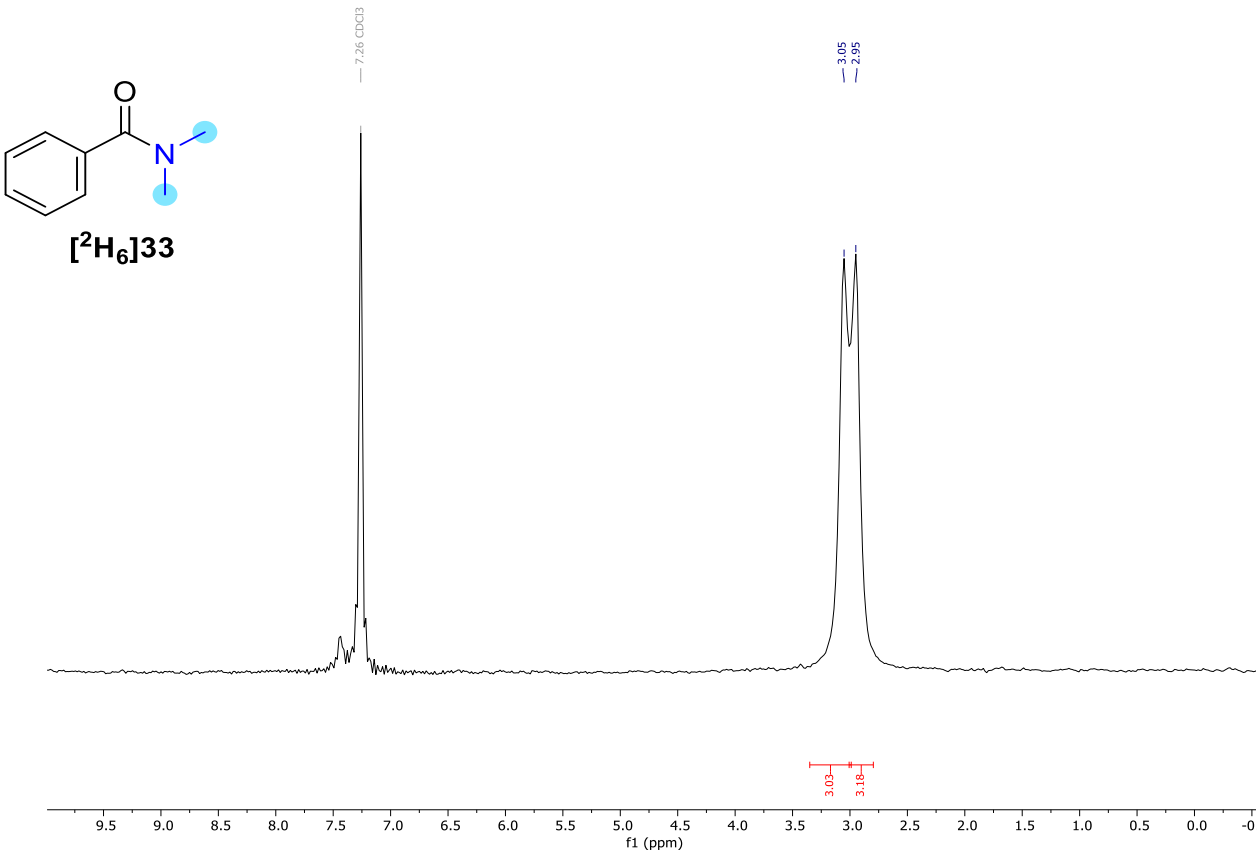


Figure S201: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

XV. NMR Spectra carbon-13 labeled amides (metathesis)

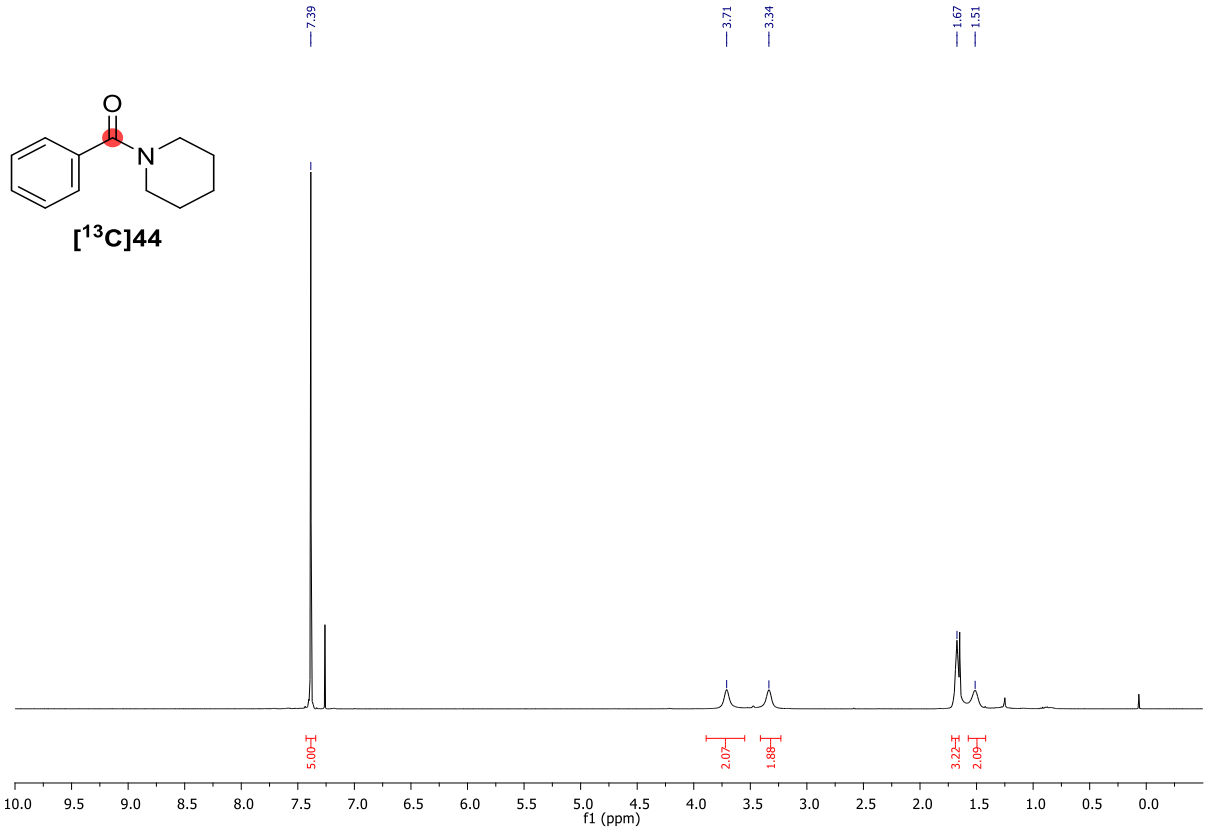


Figure S202: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

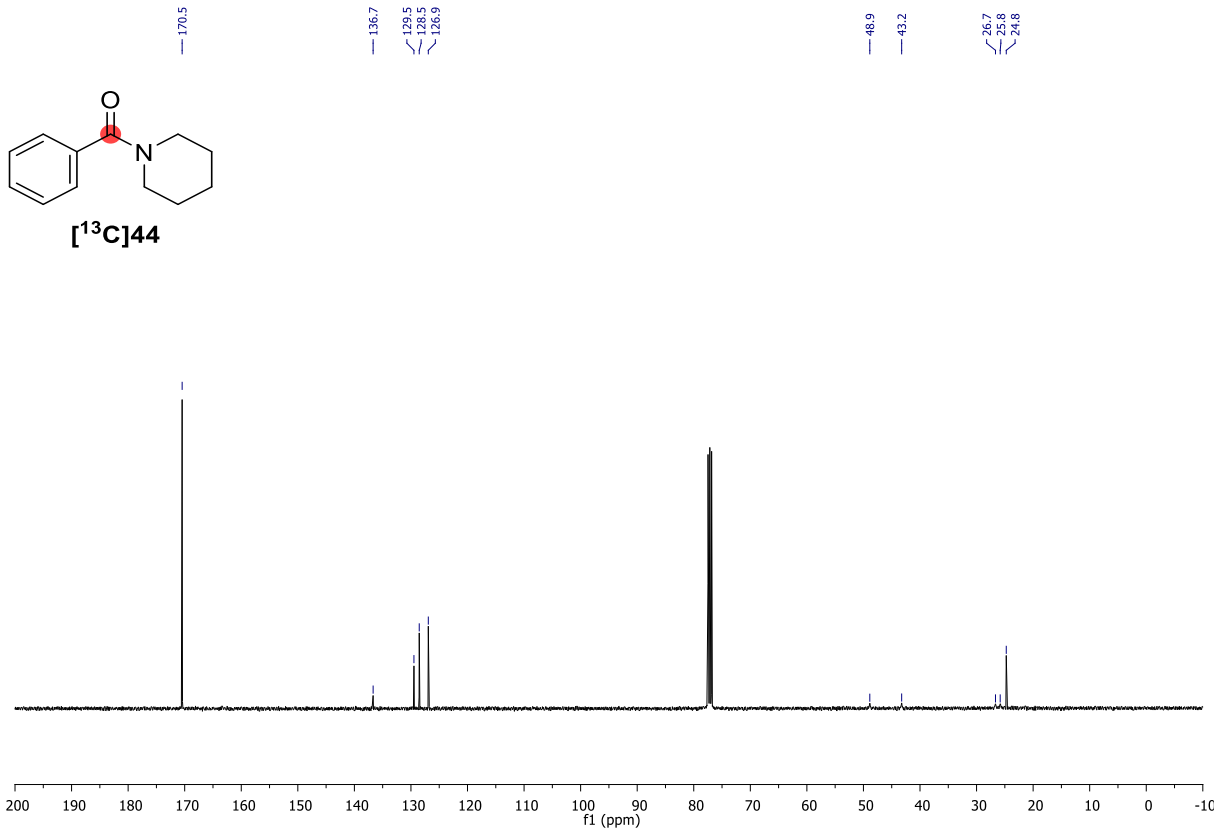


Figure S203: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

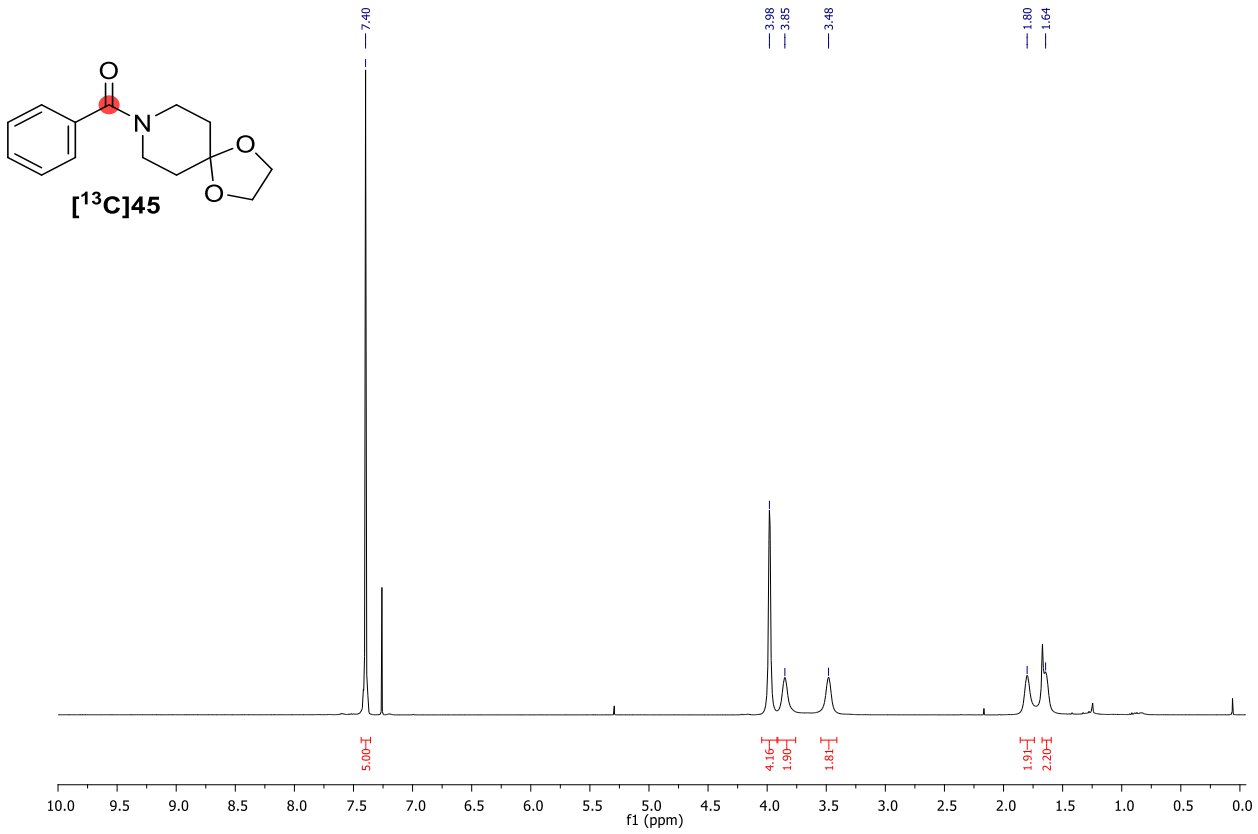


Figure S204: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

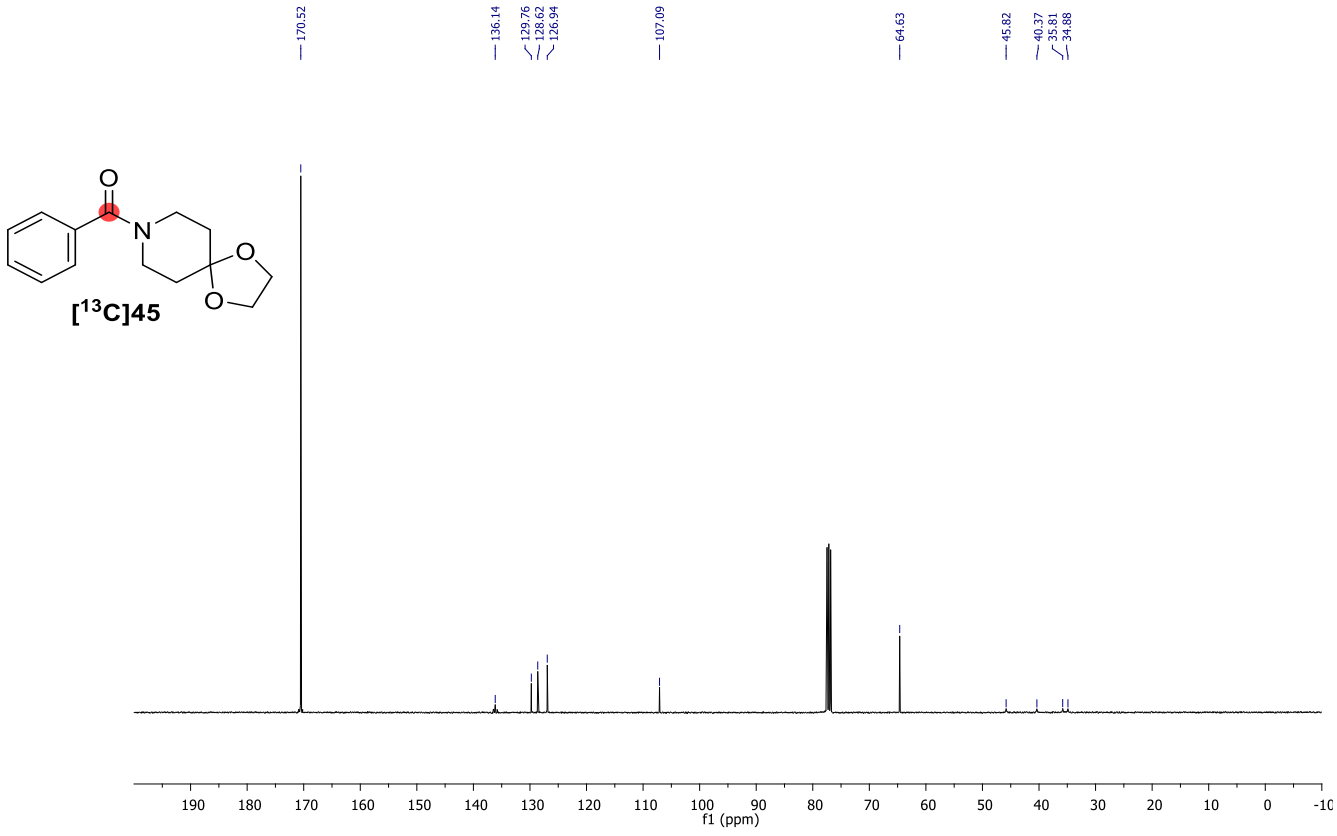


Figure S205: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

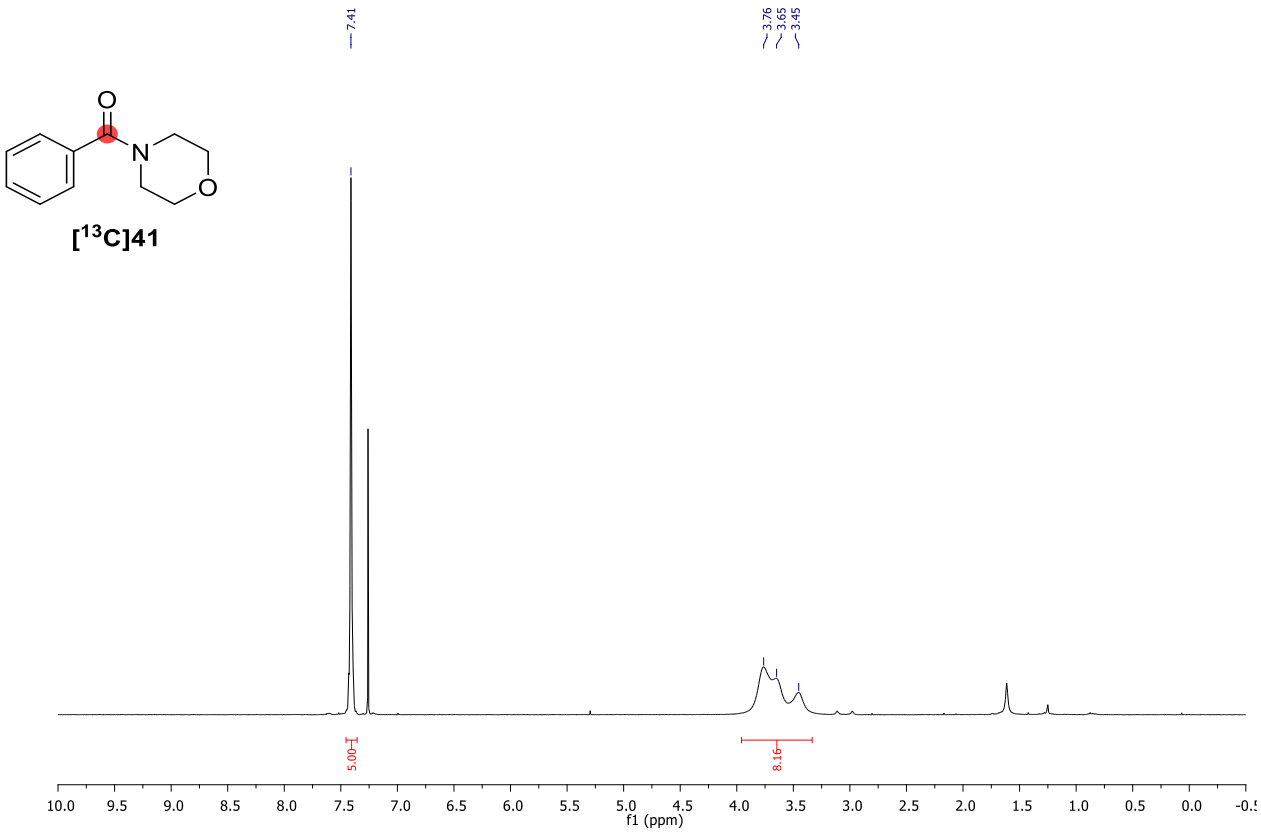


Figure S206: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

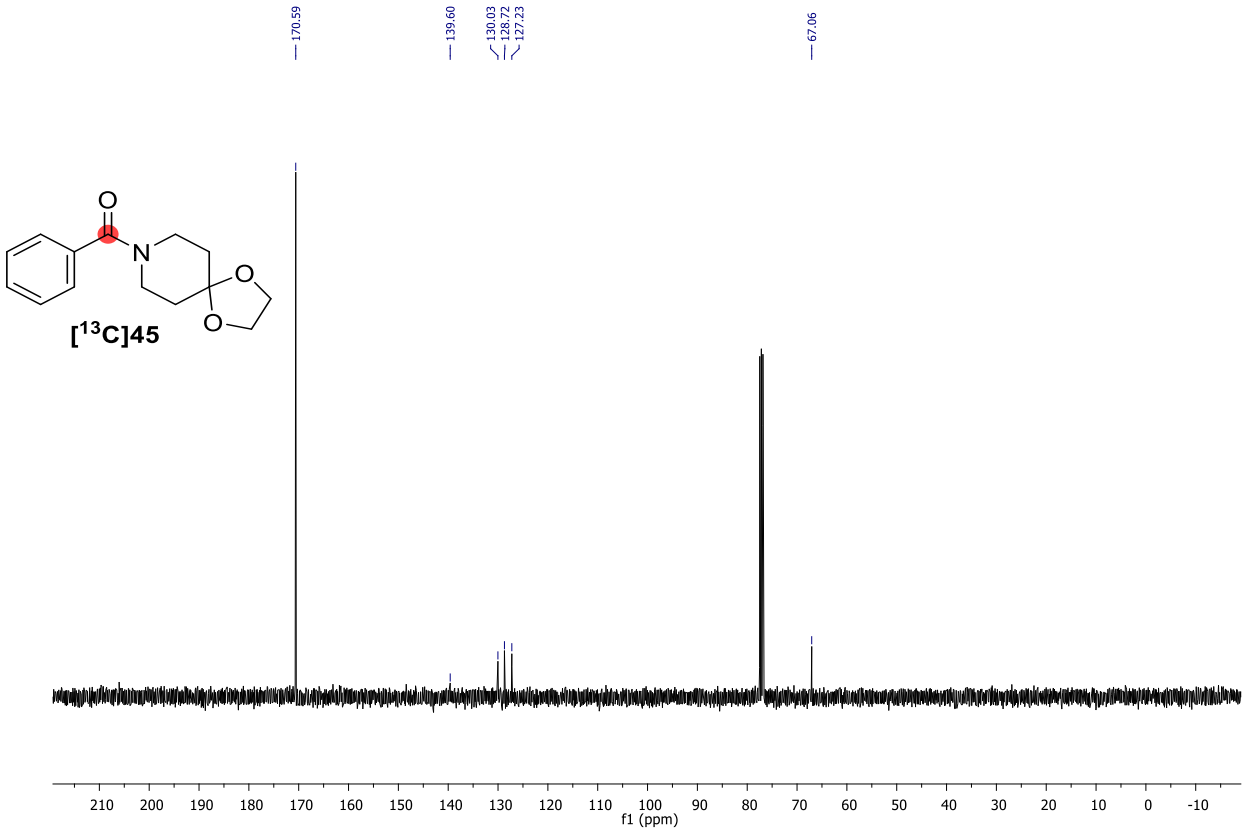


Figure S207: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

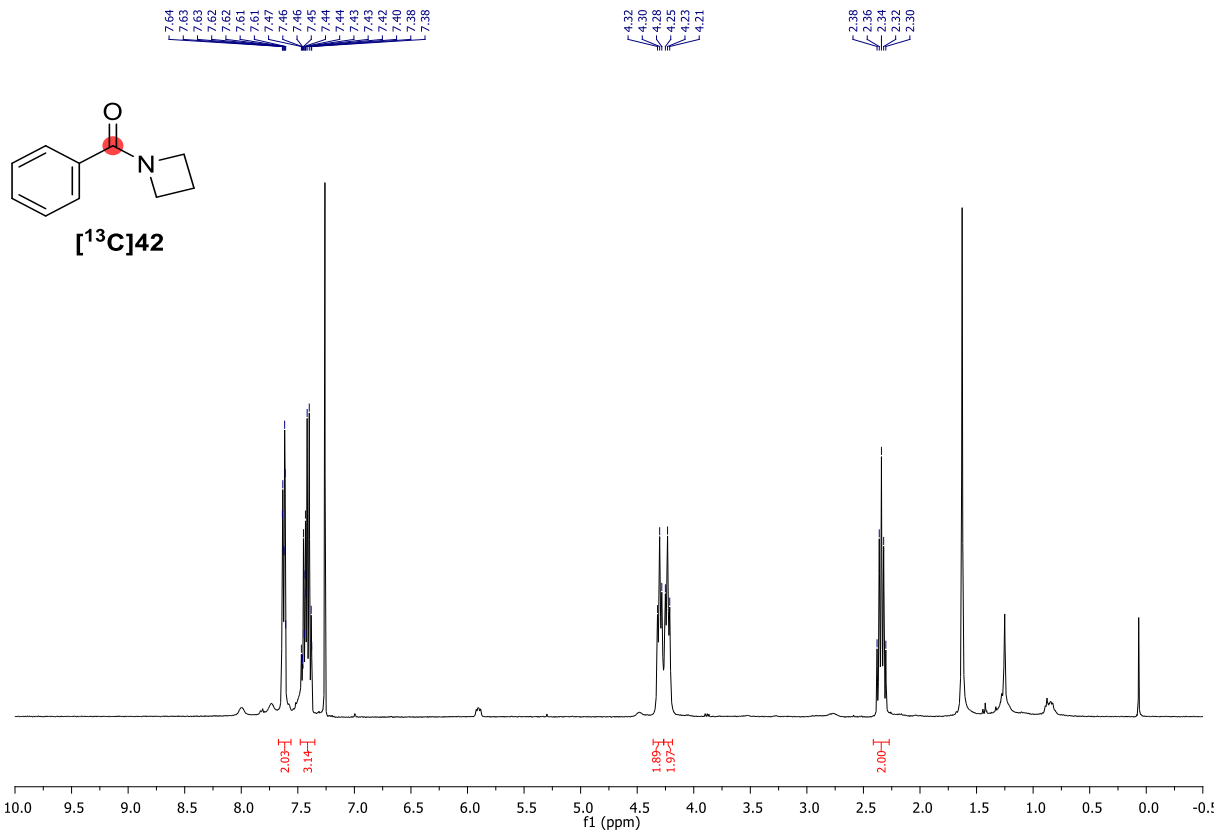


Figure S208: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

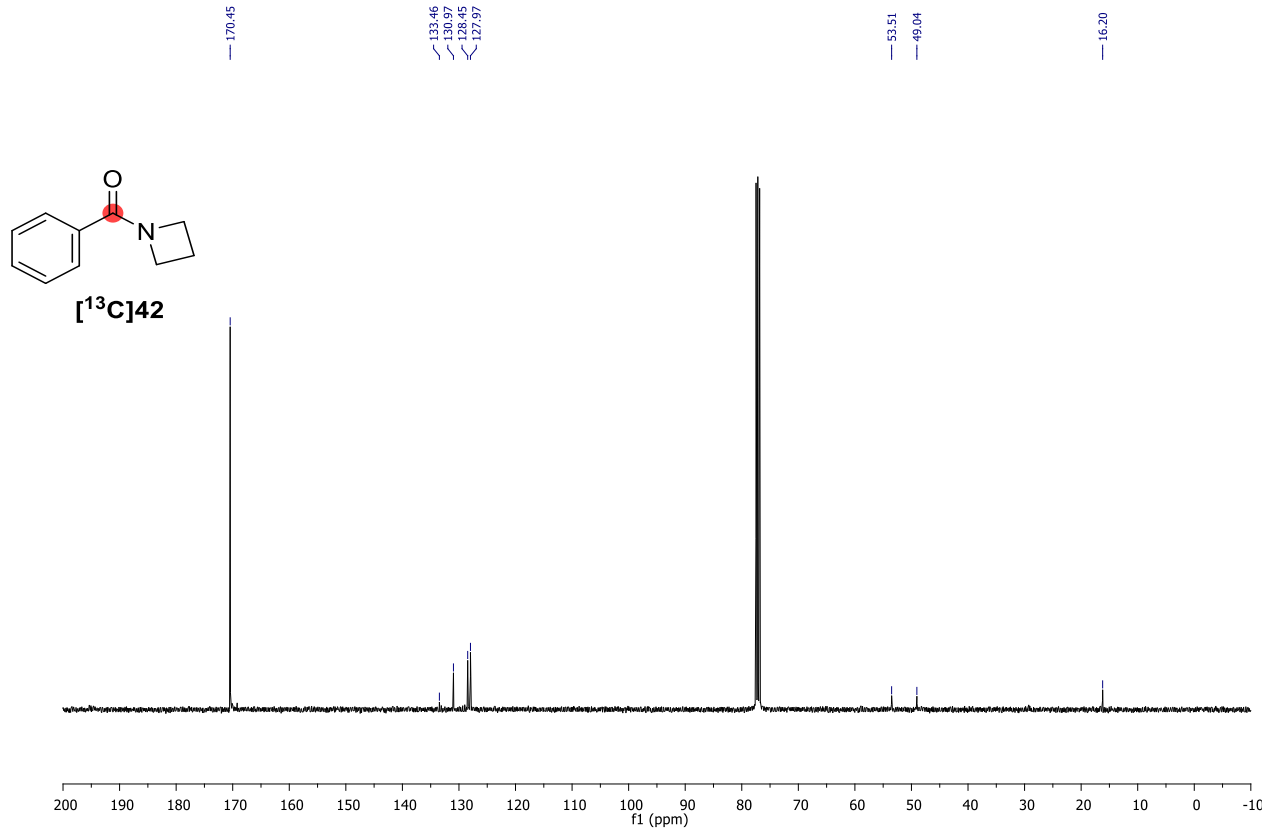


Figure S209: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

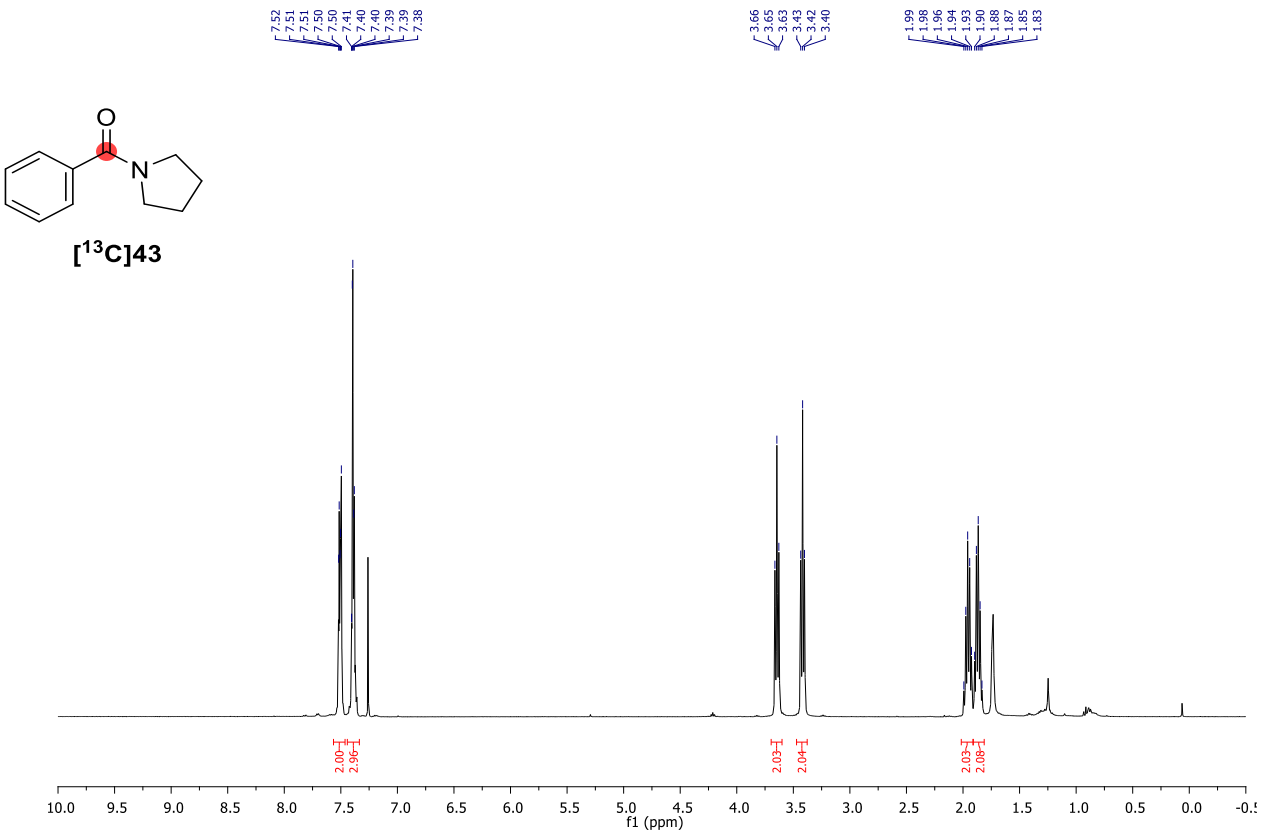


Figure S210: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

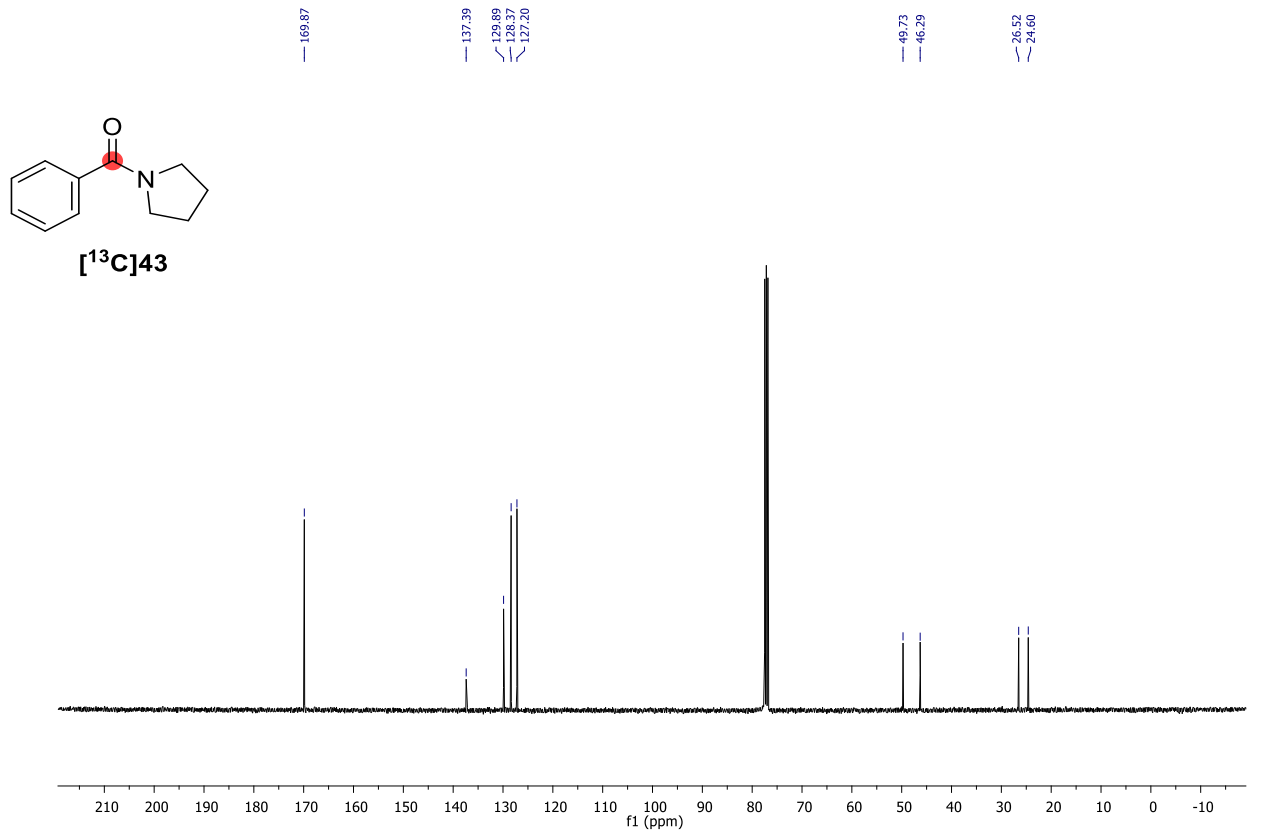


Figure S211: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

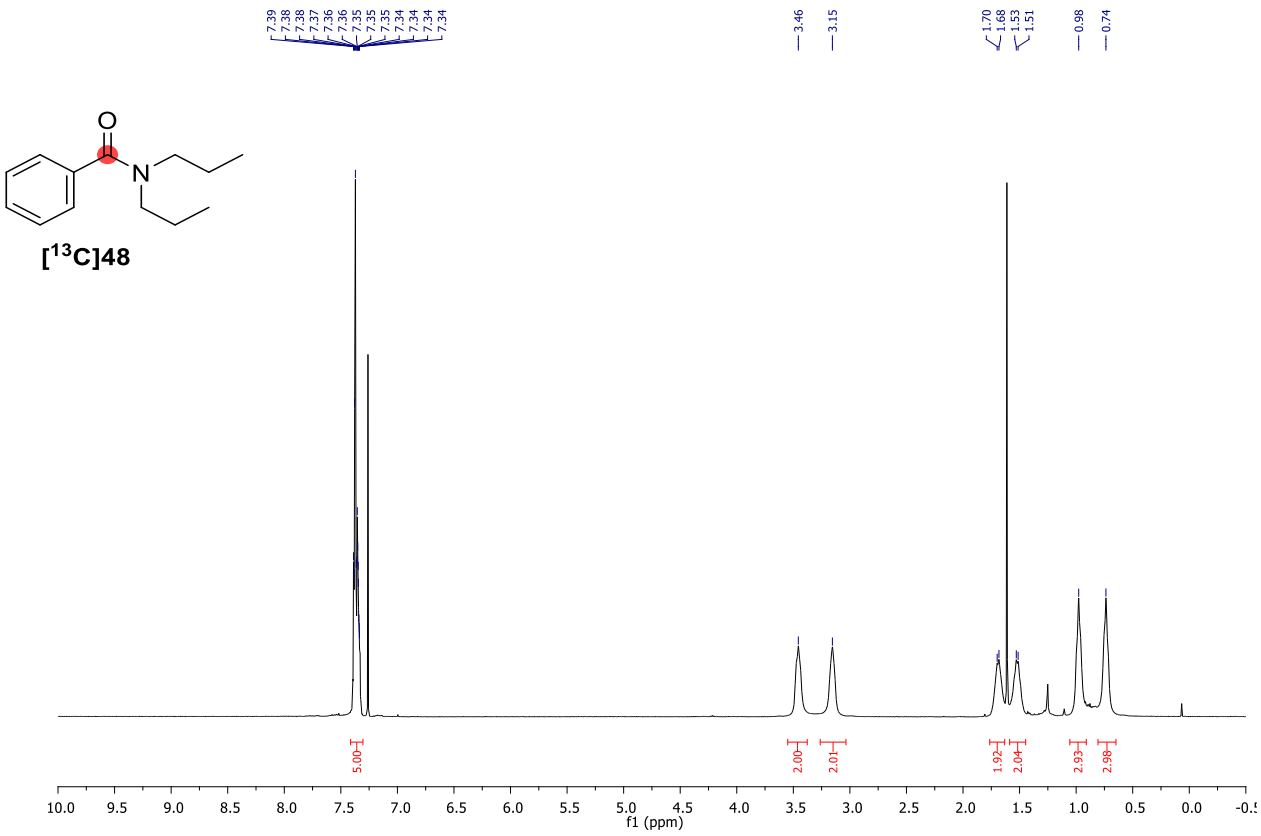


Figure S212: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

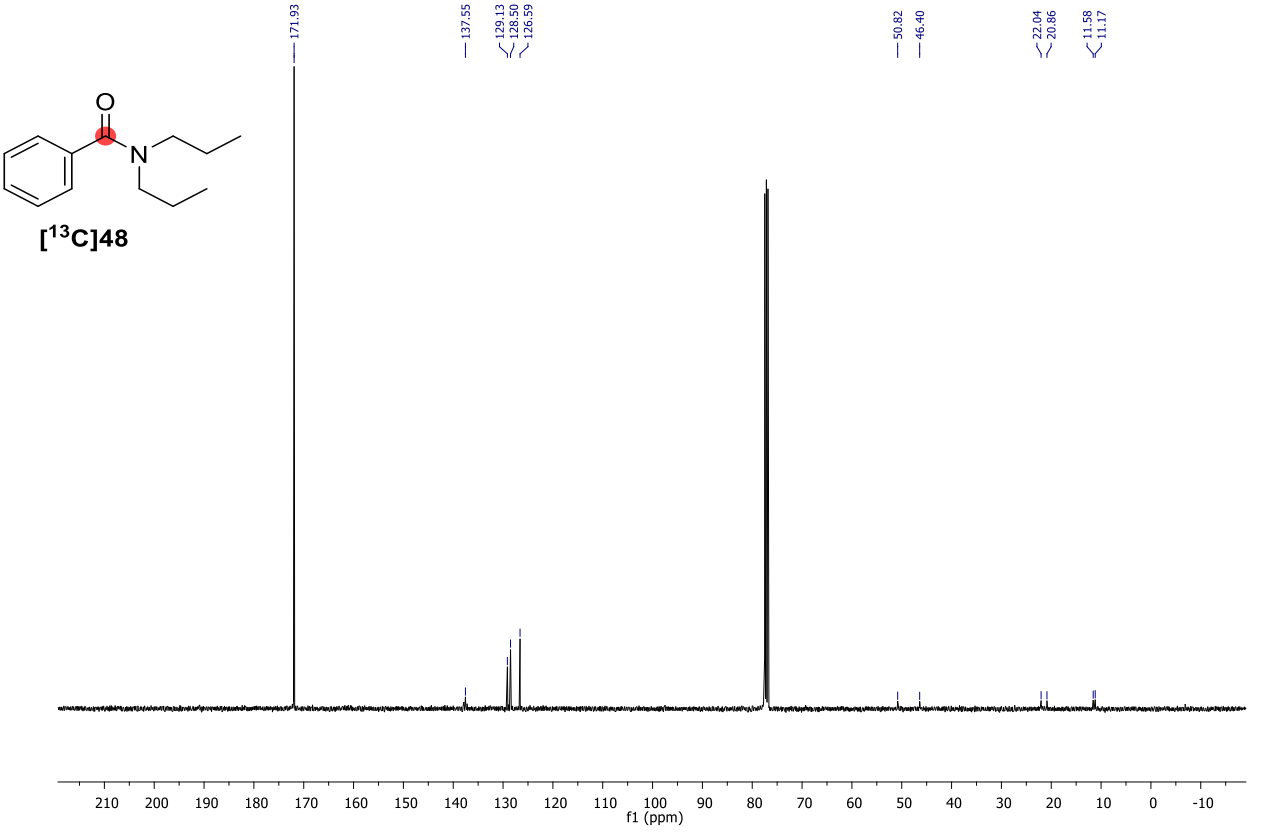


Figure S213: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

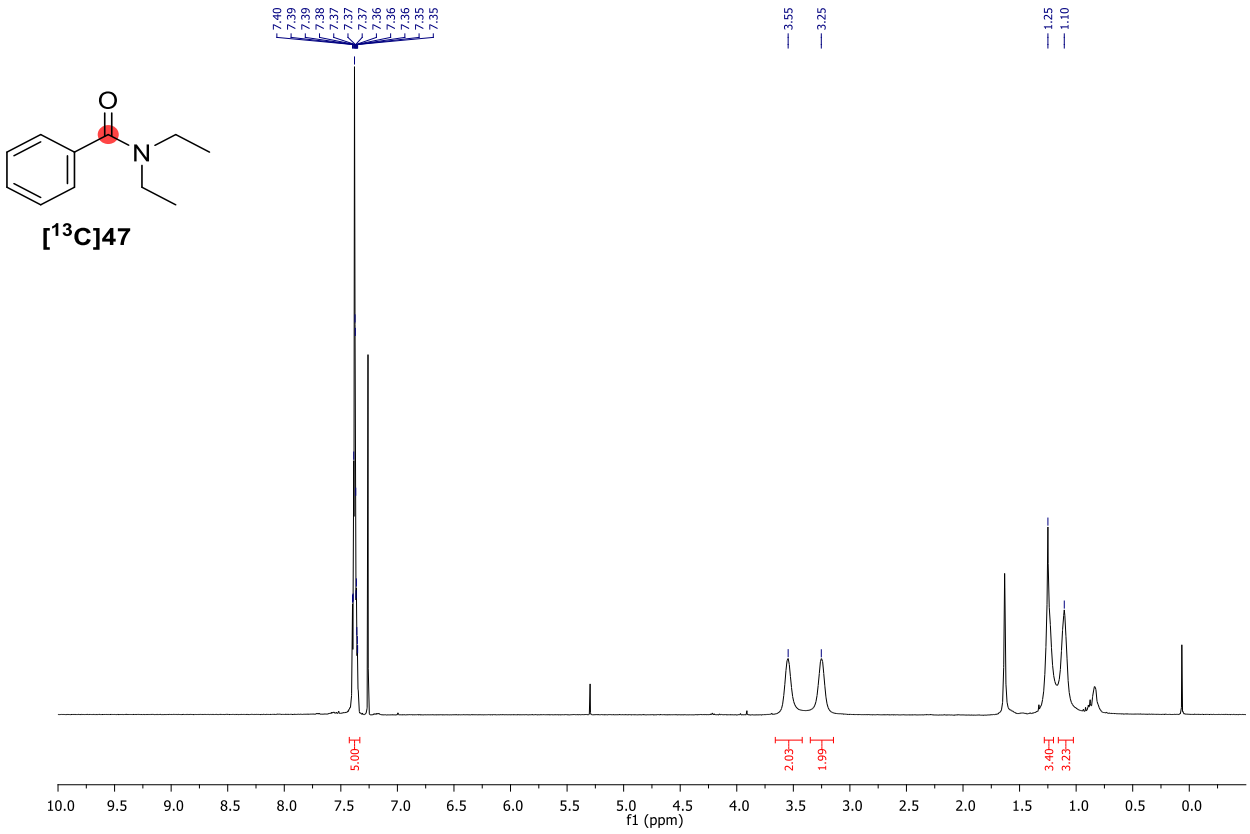


Figure S214: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

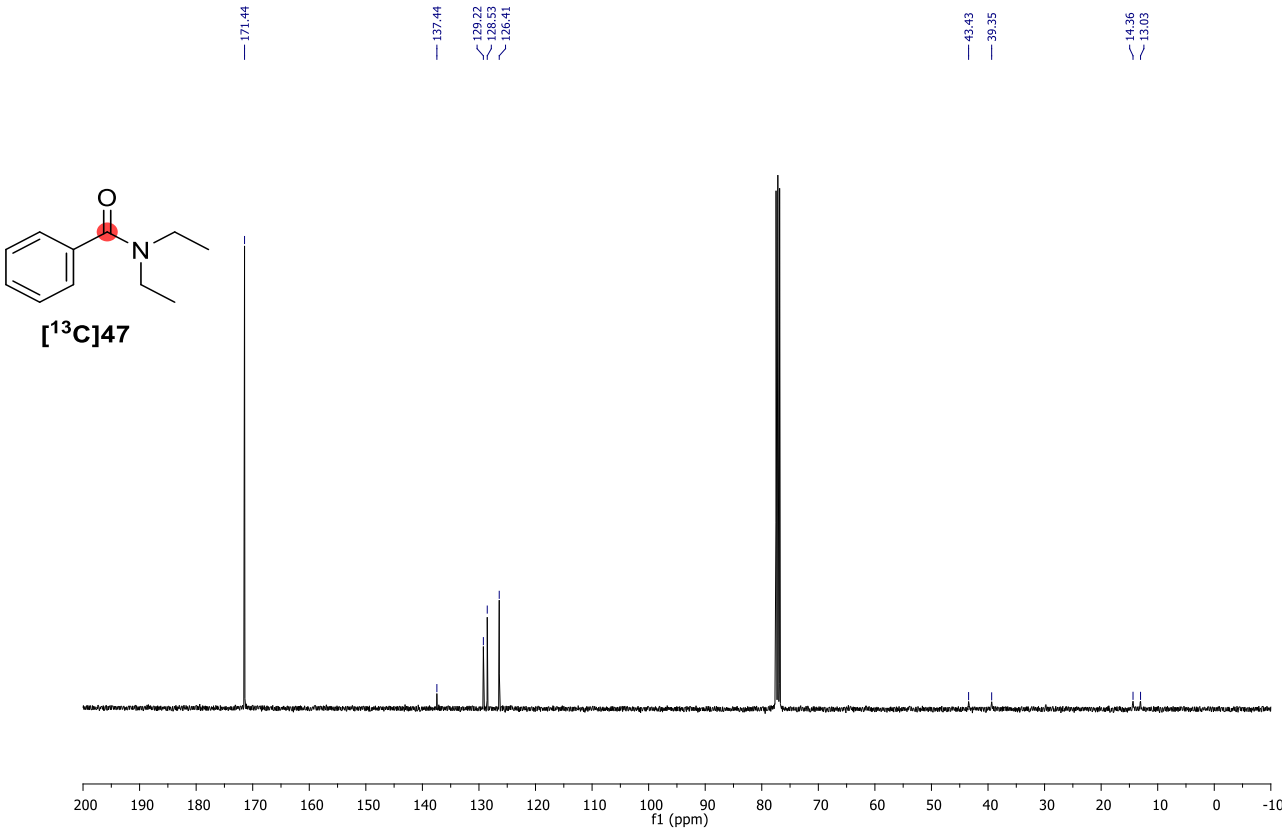


Figure S215: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

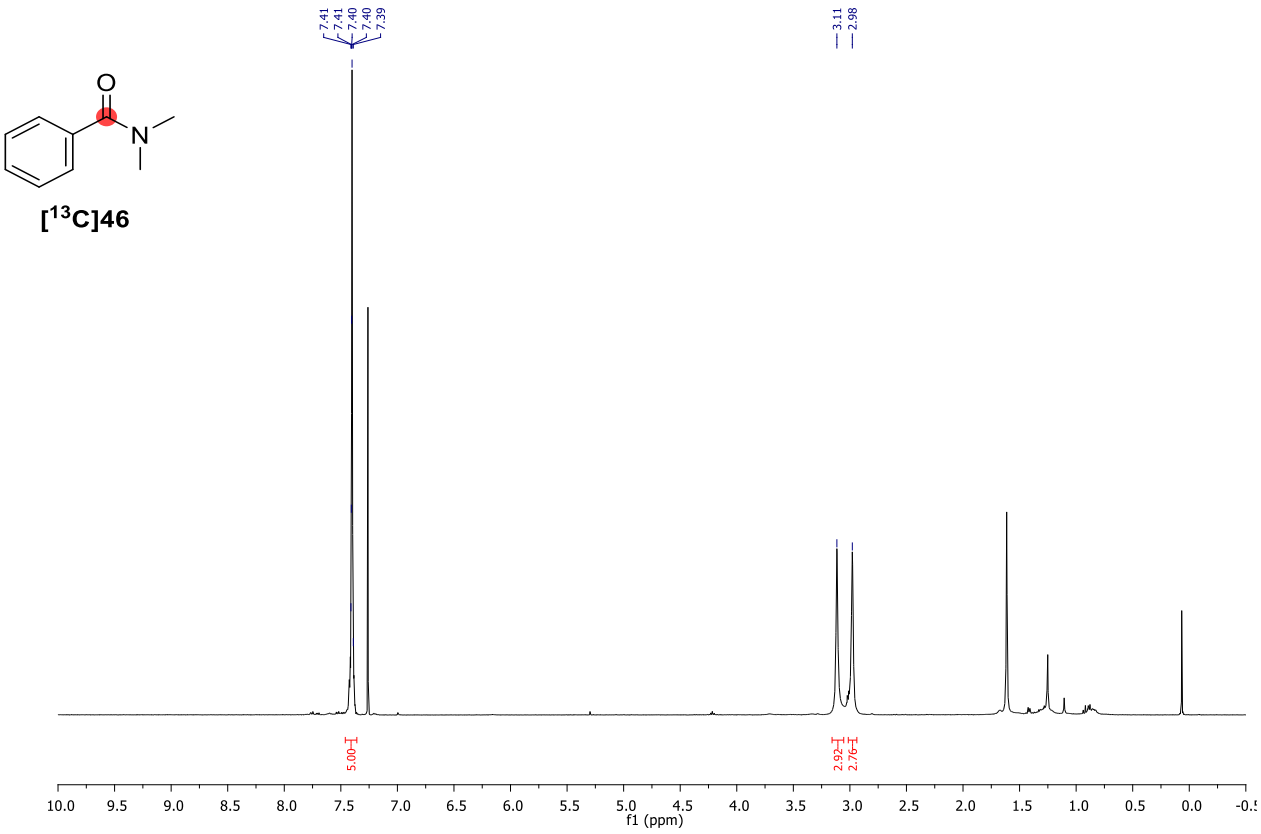


Figure S216: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

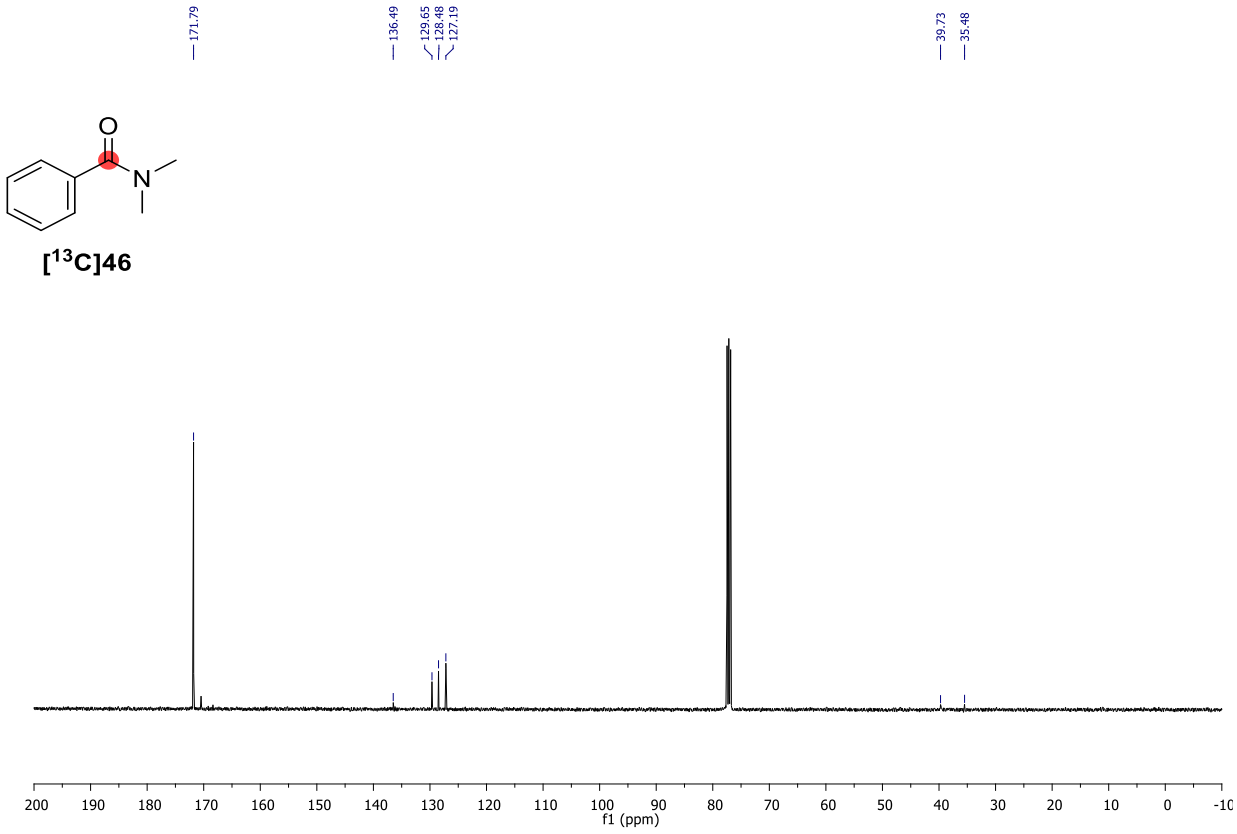


Figure S217: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

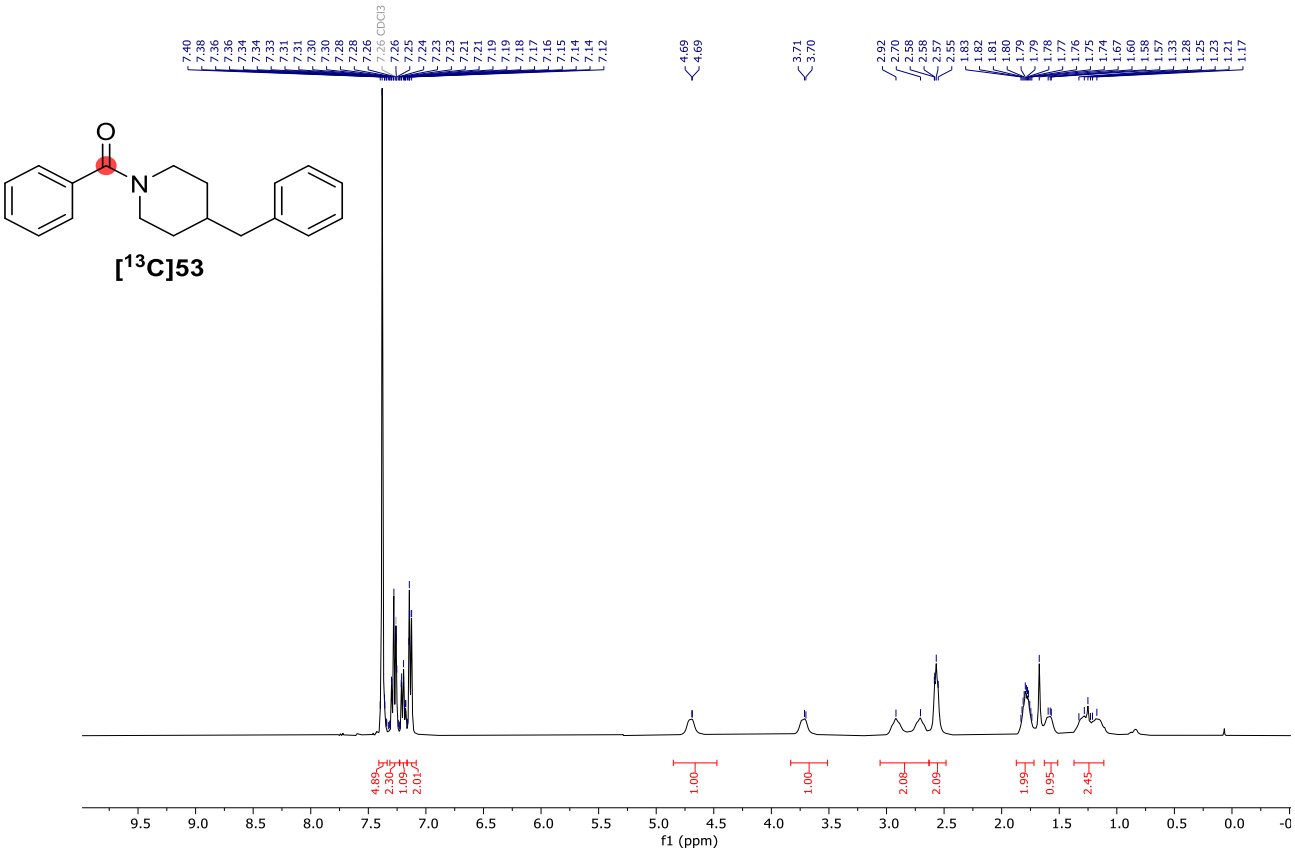


Figure S218: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

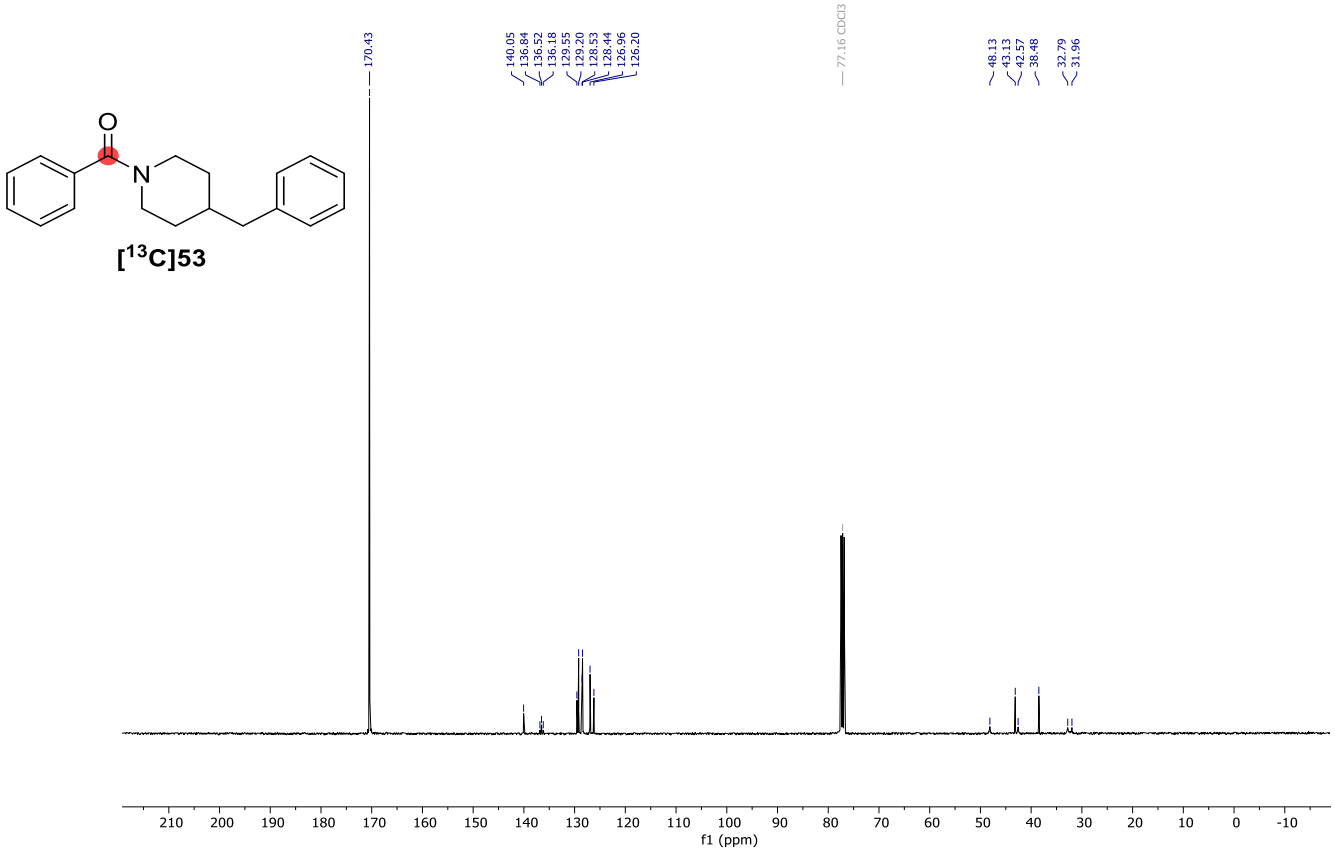


Figure S219: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

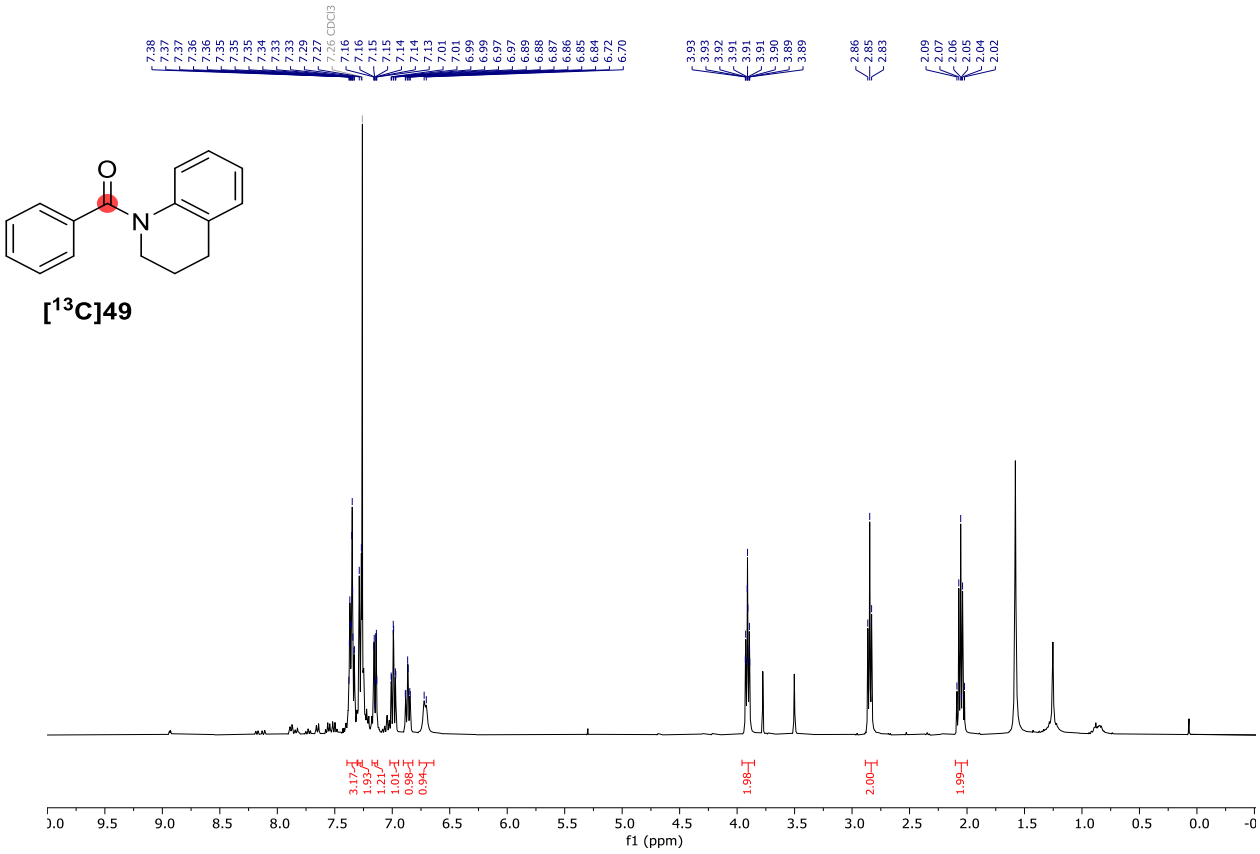


Figure S220: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

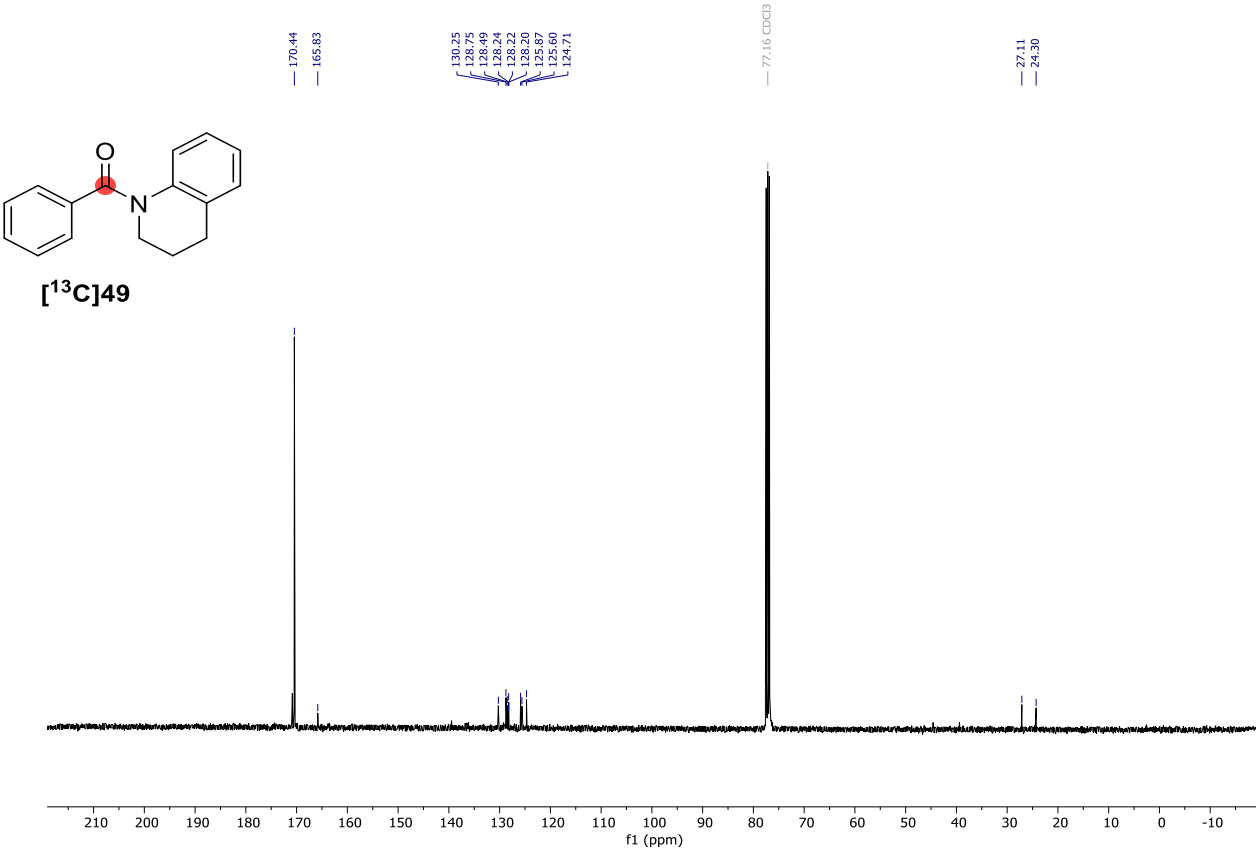


Figure S221: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

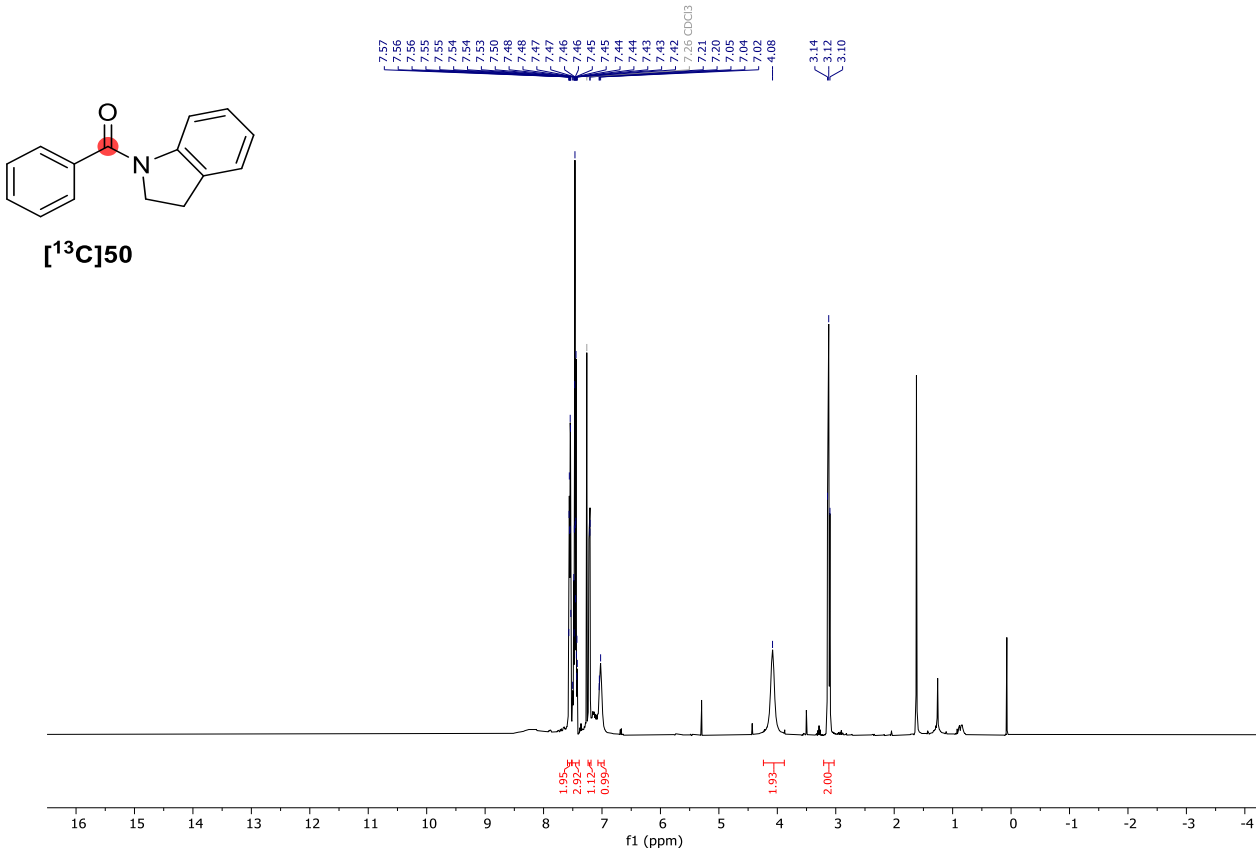


Figure S222: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

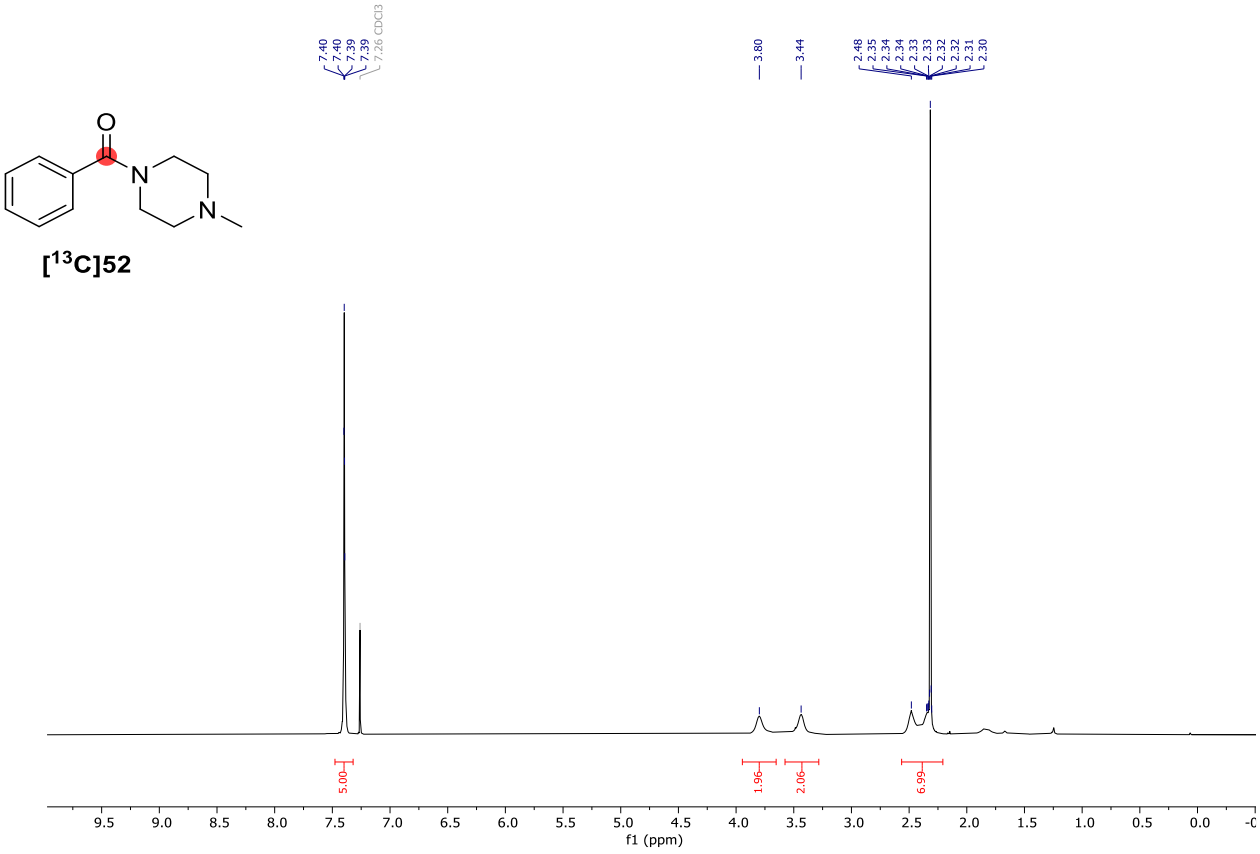


Figure S223: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

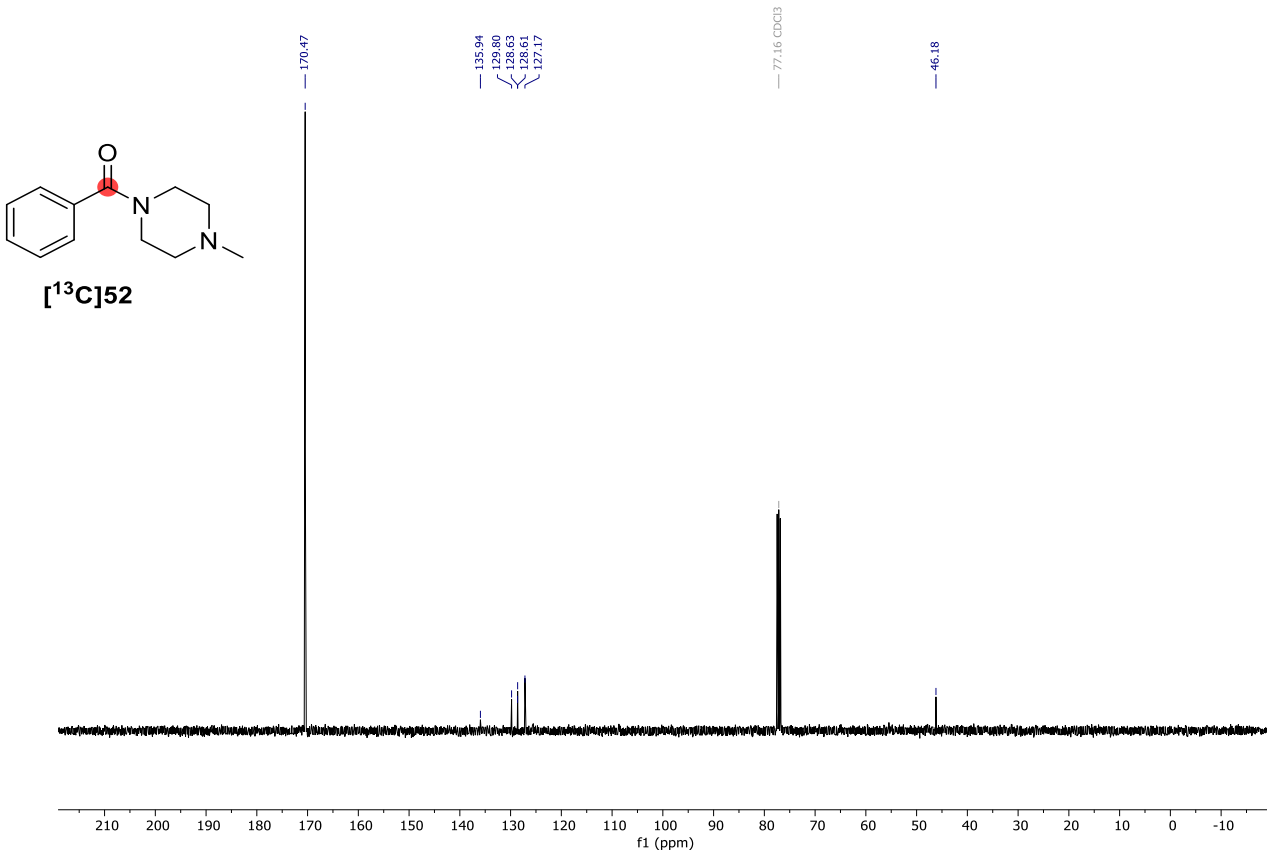


Figure S224: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

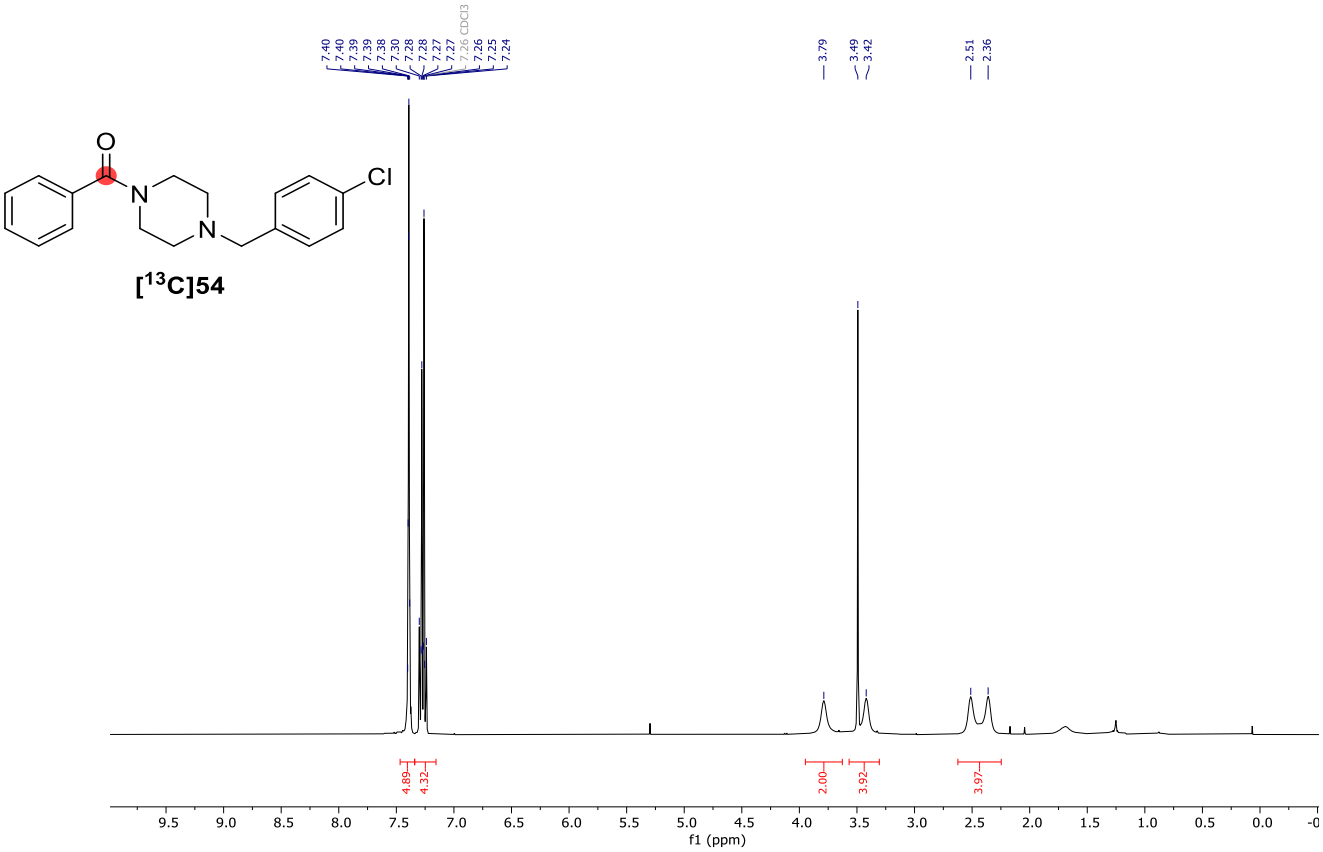


Figure S225: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

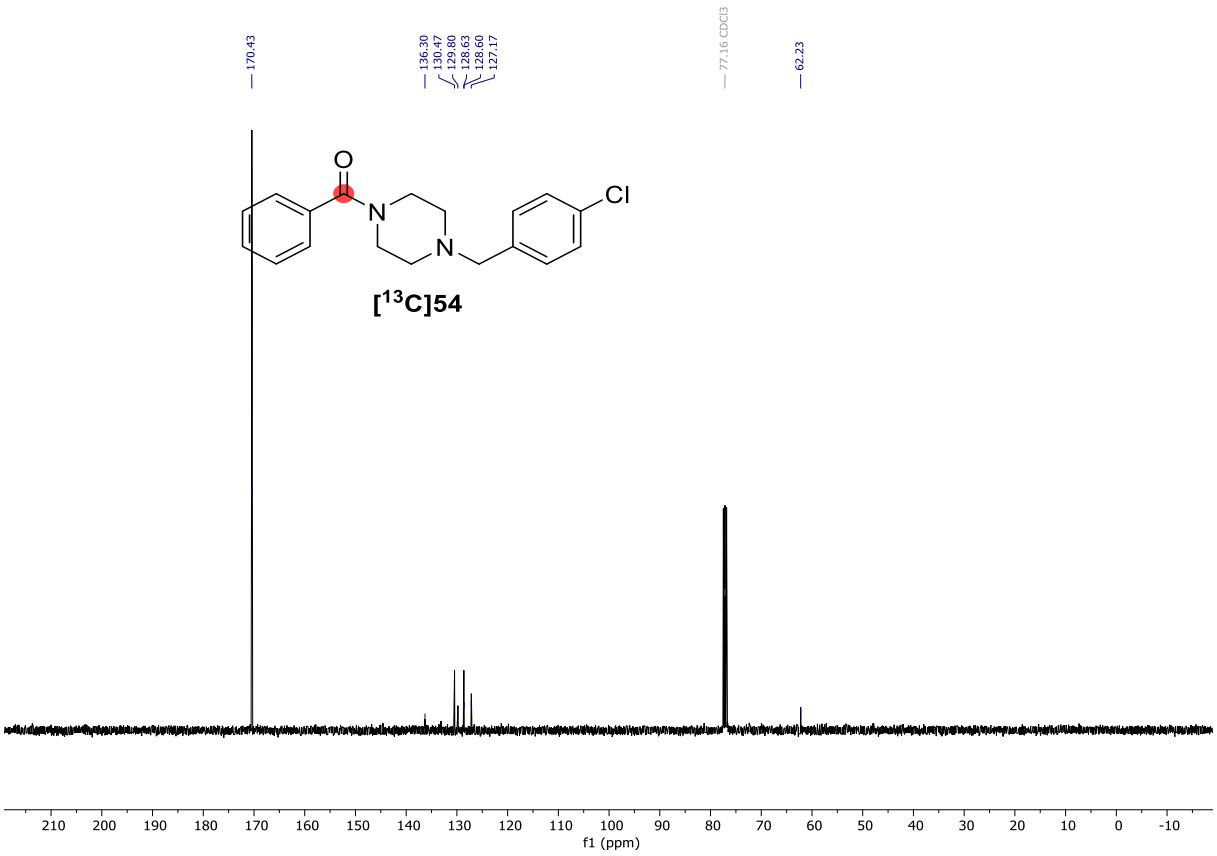


Figure S226: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

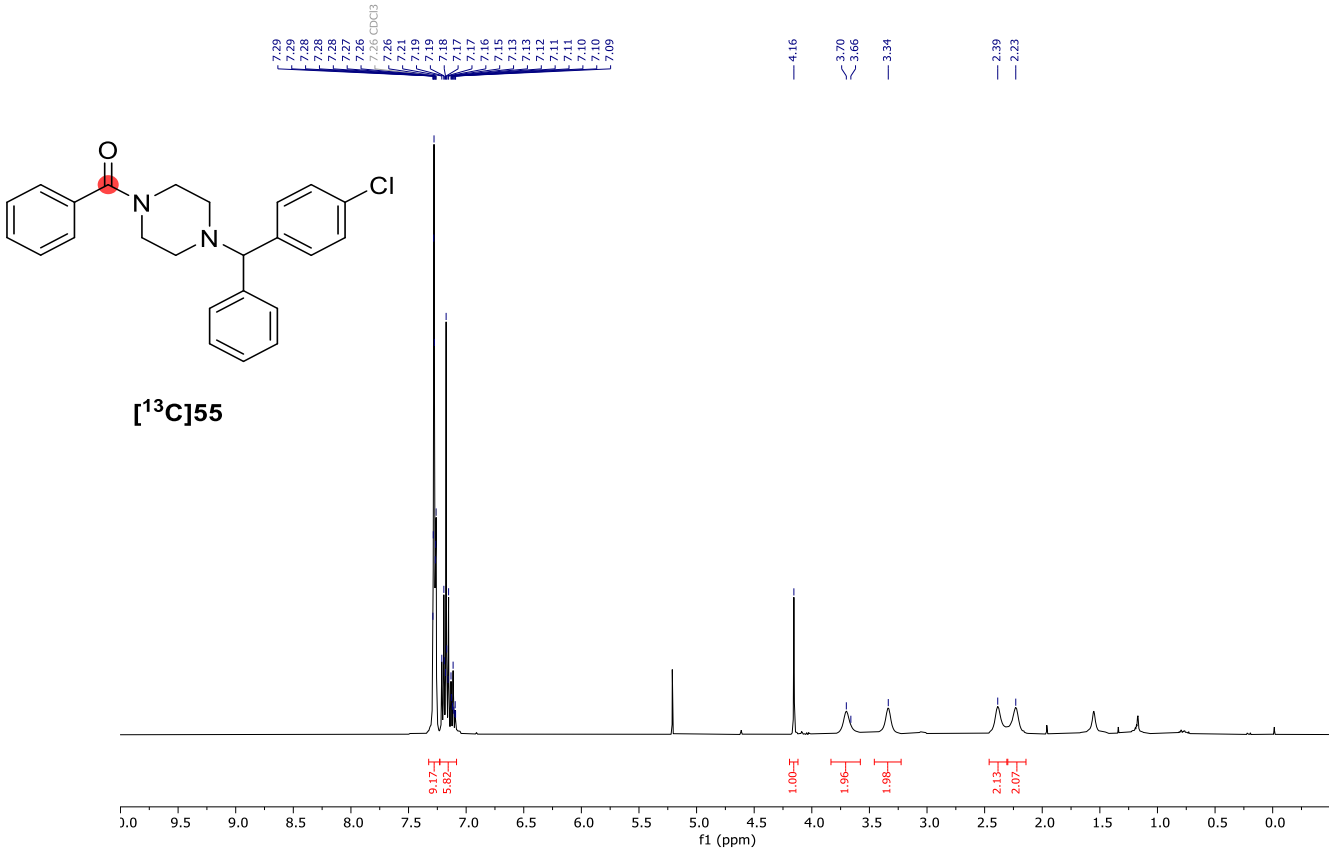


Figure S227: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

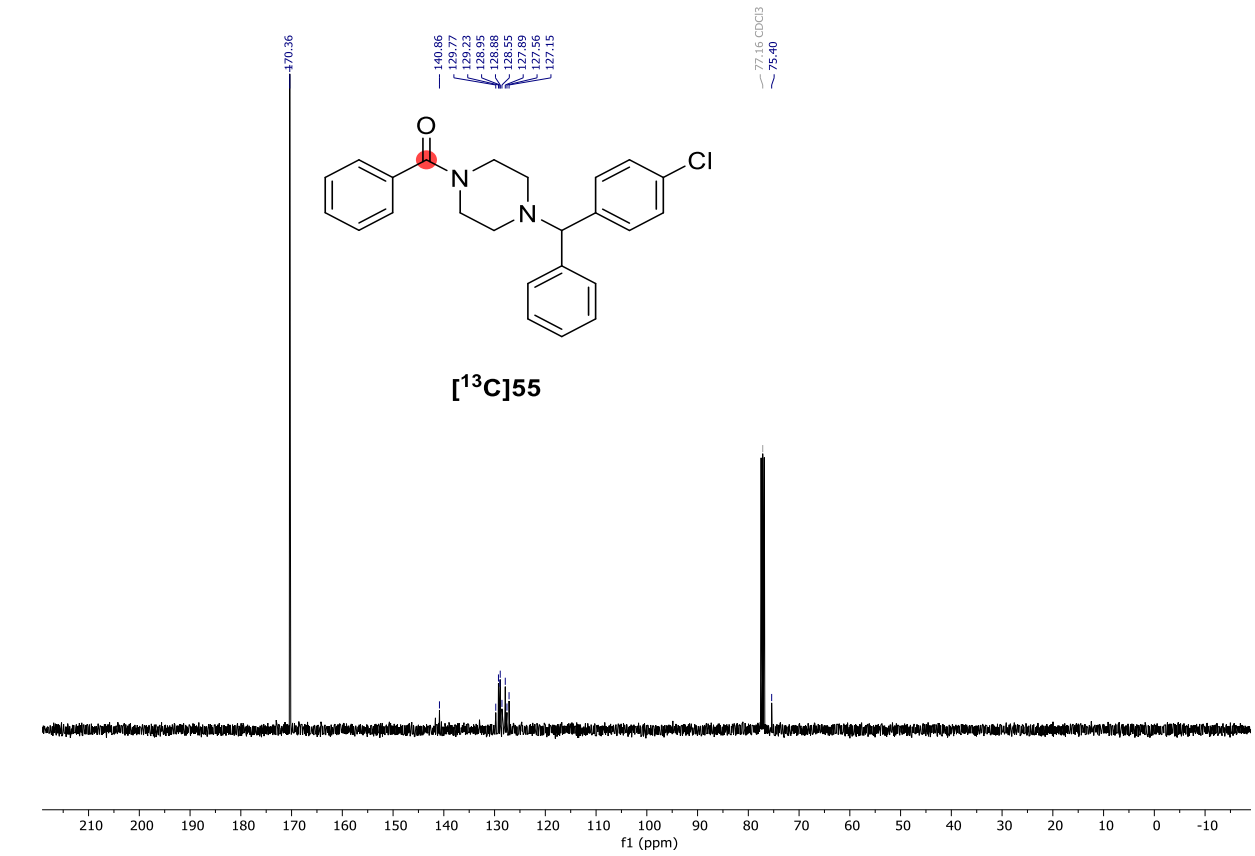


Figure S228: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

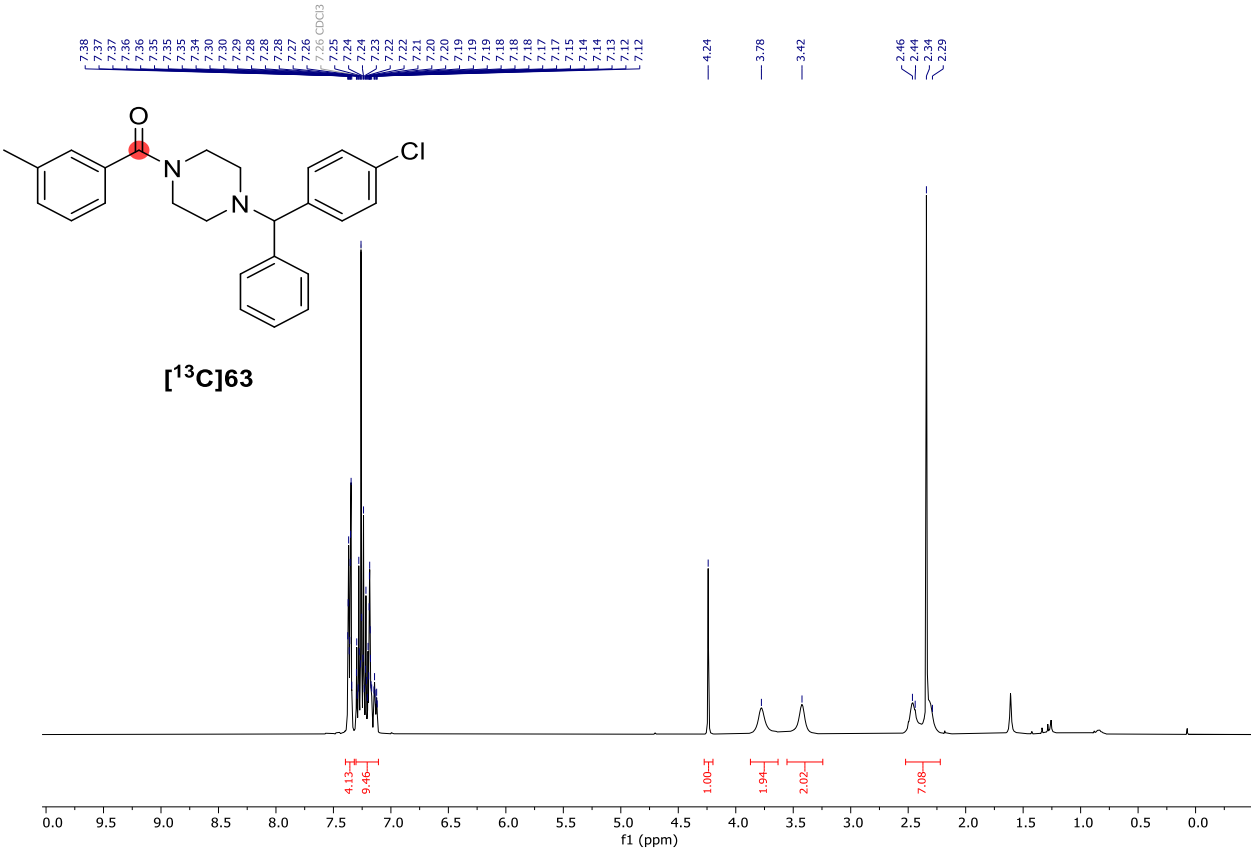


Figure S229: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

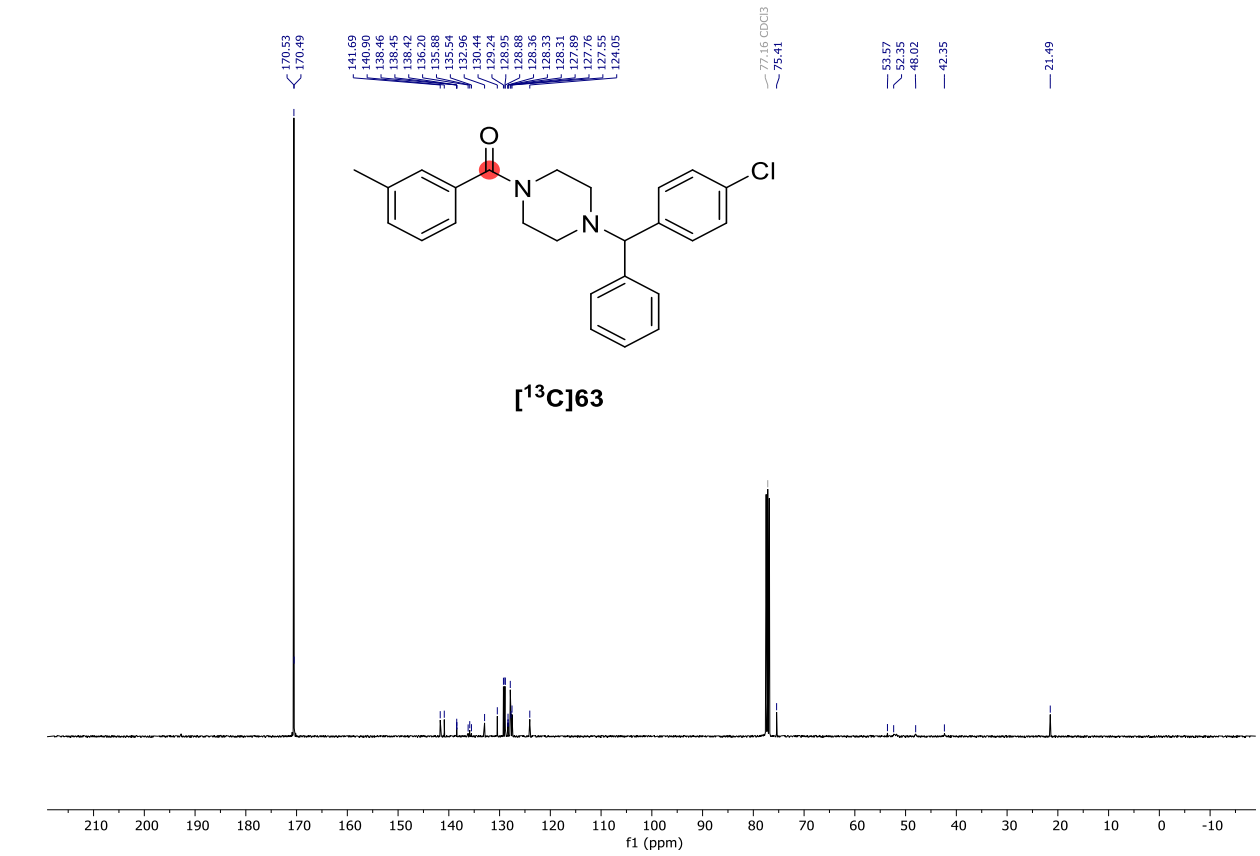


Figure S230: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

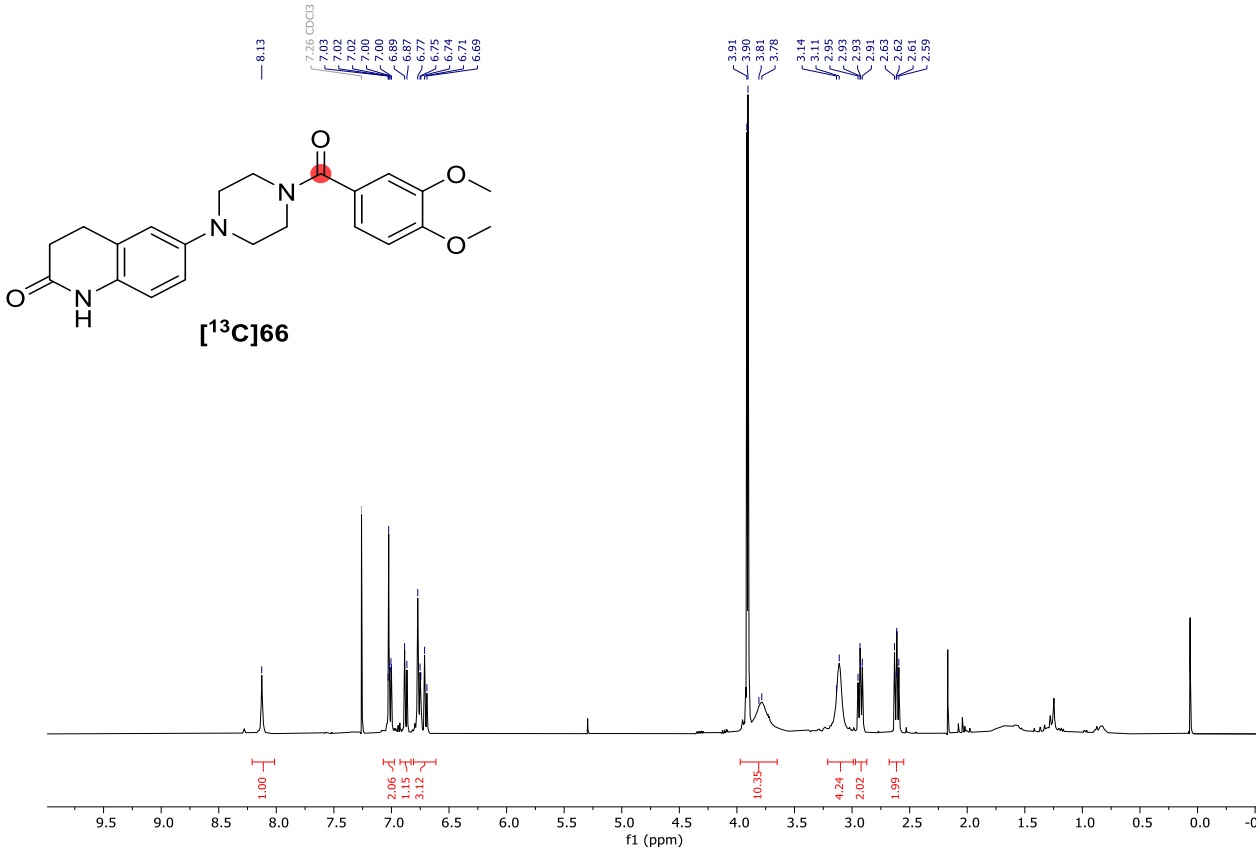


Figure S231: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

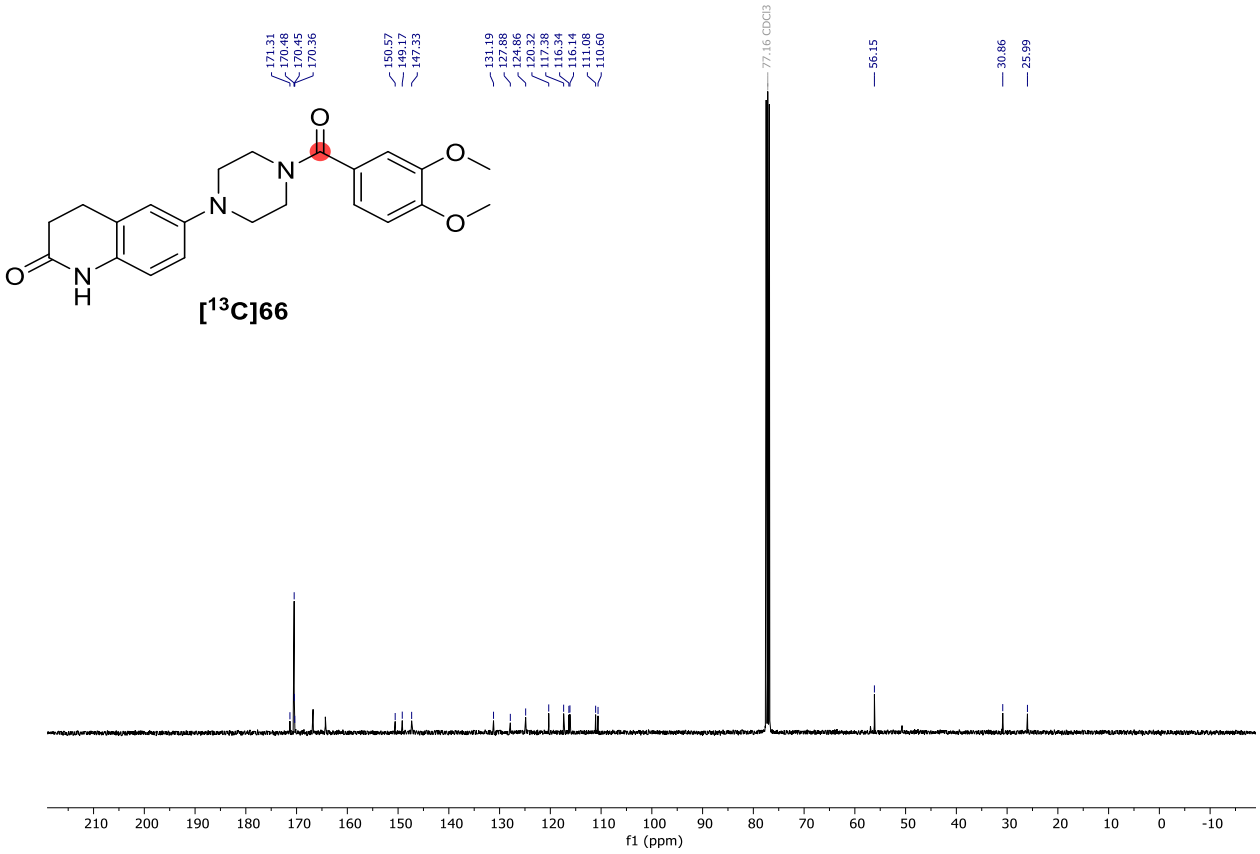


Figure S232: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

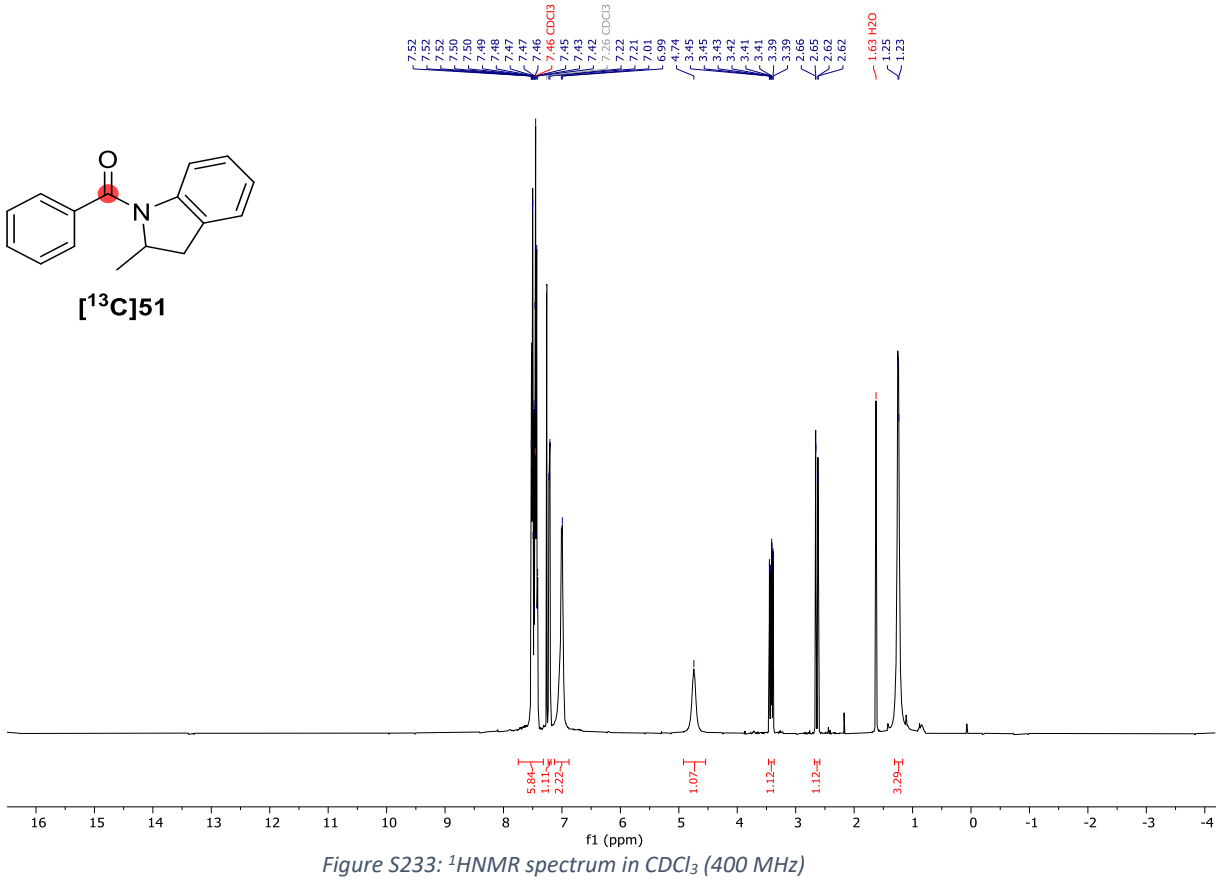


Figure S233: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

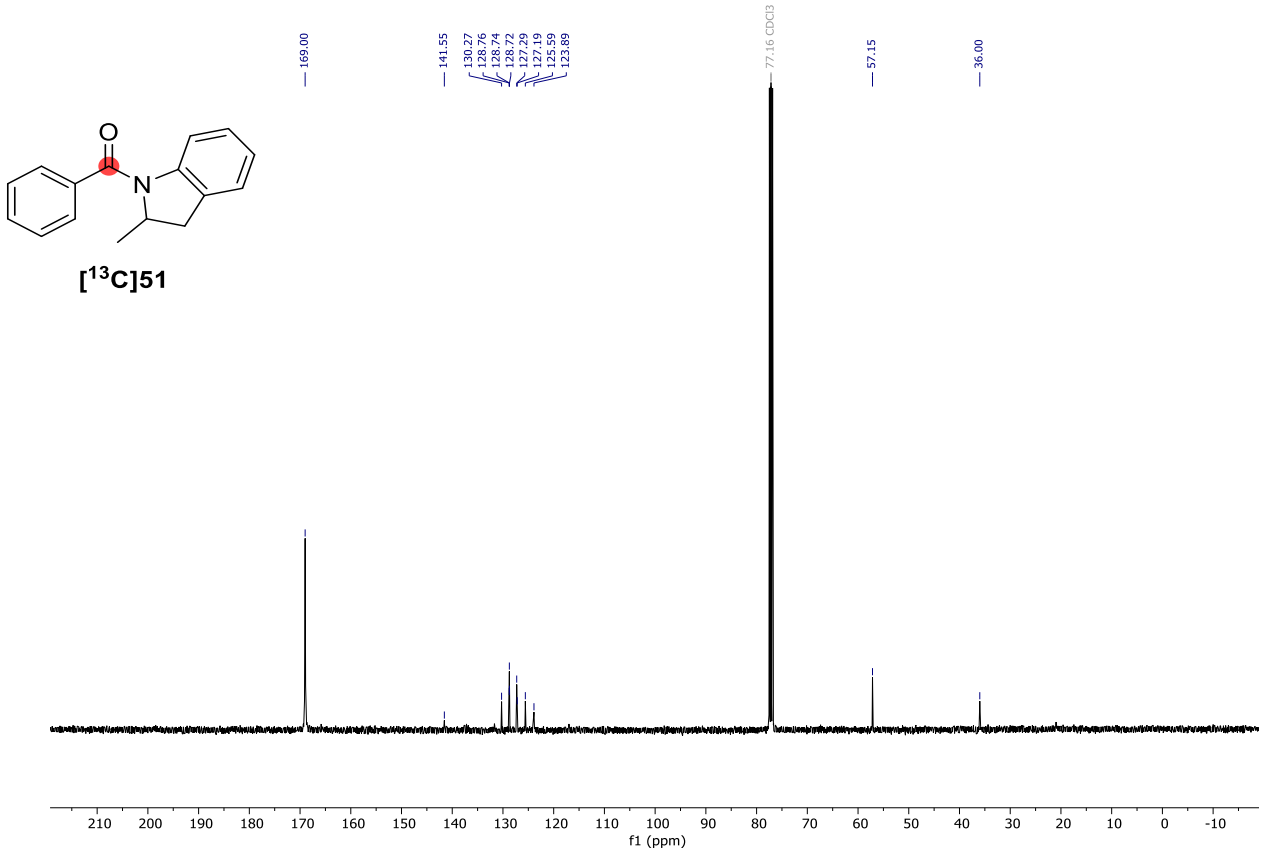


Figure S234: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

XVI. NMR Spectra labeled amides (Other)

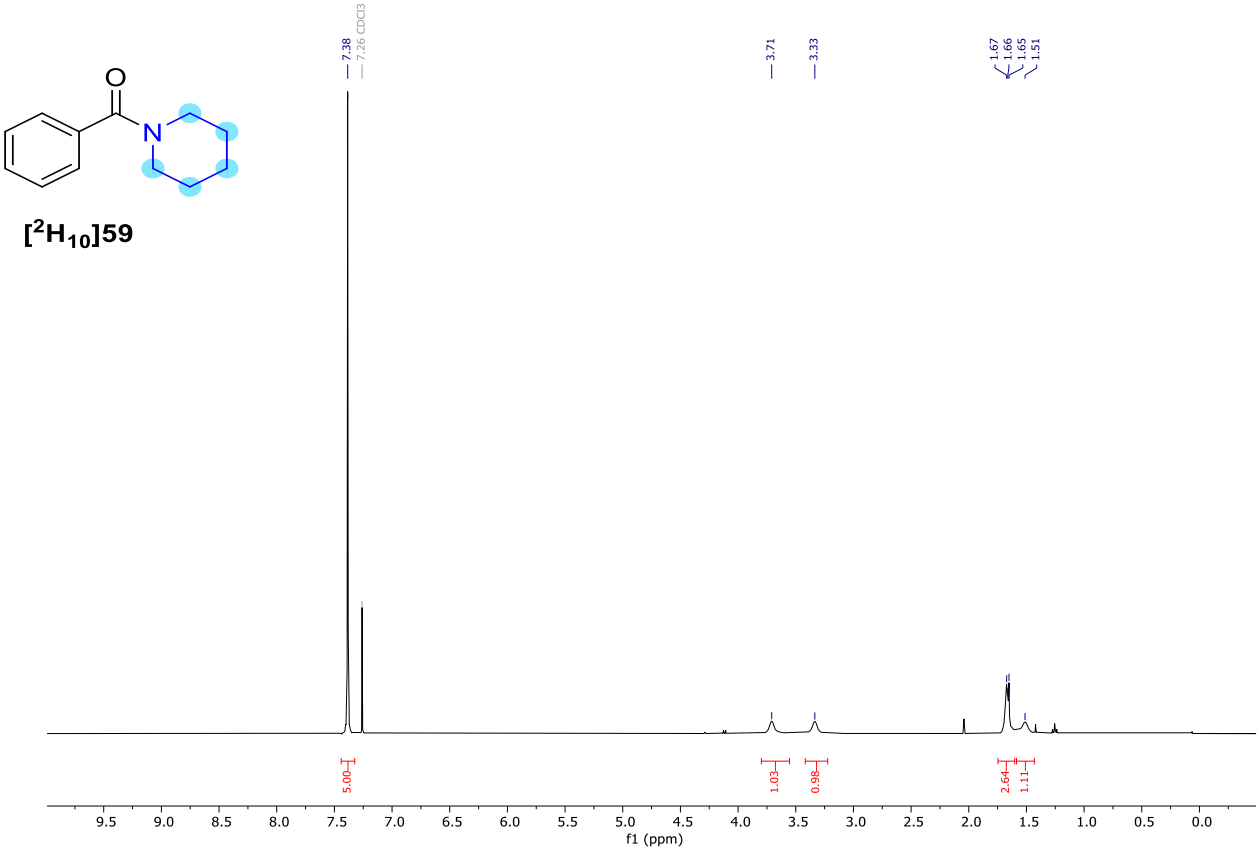


Figure S235: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

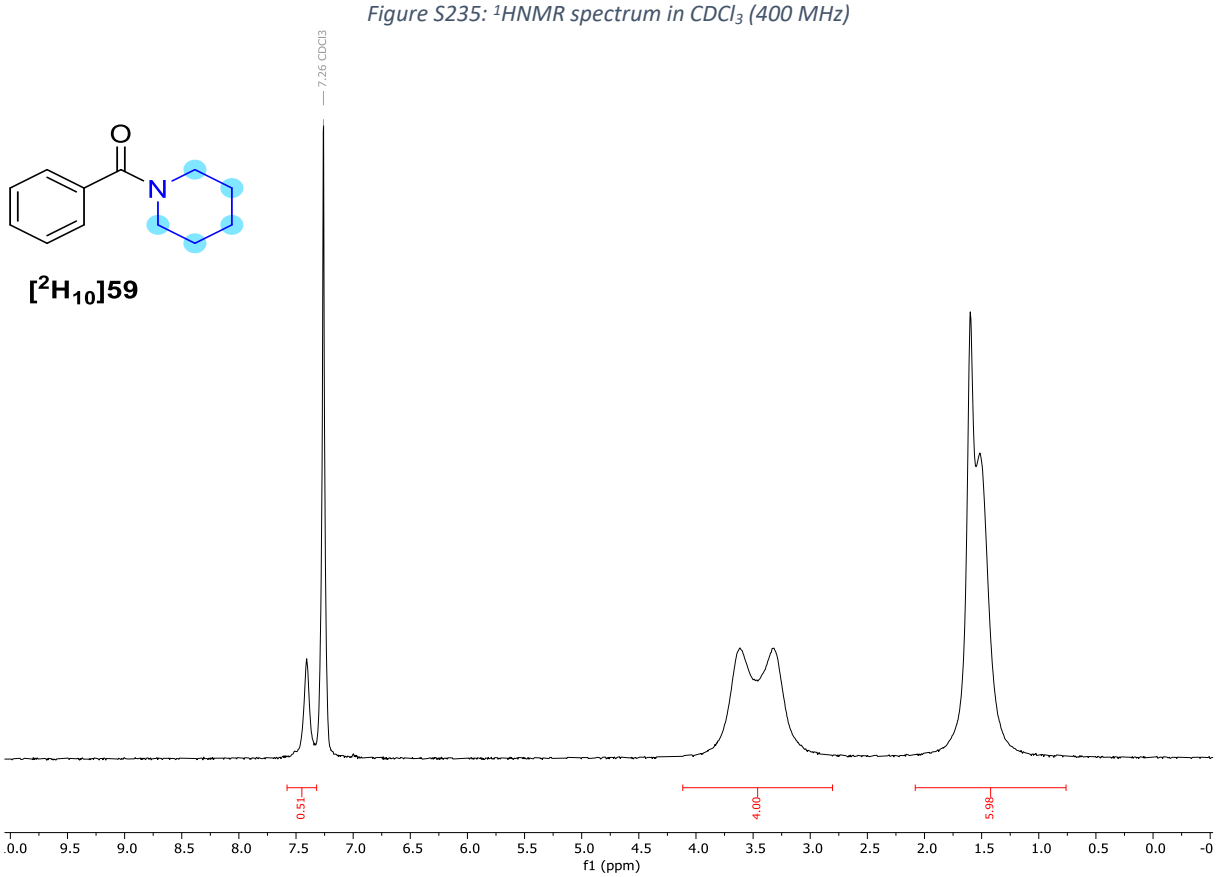


Figure S236: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)

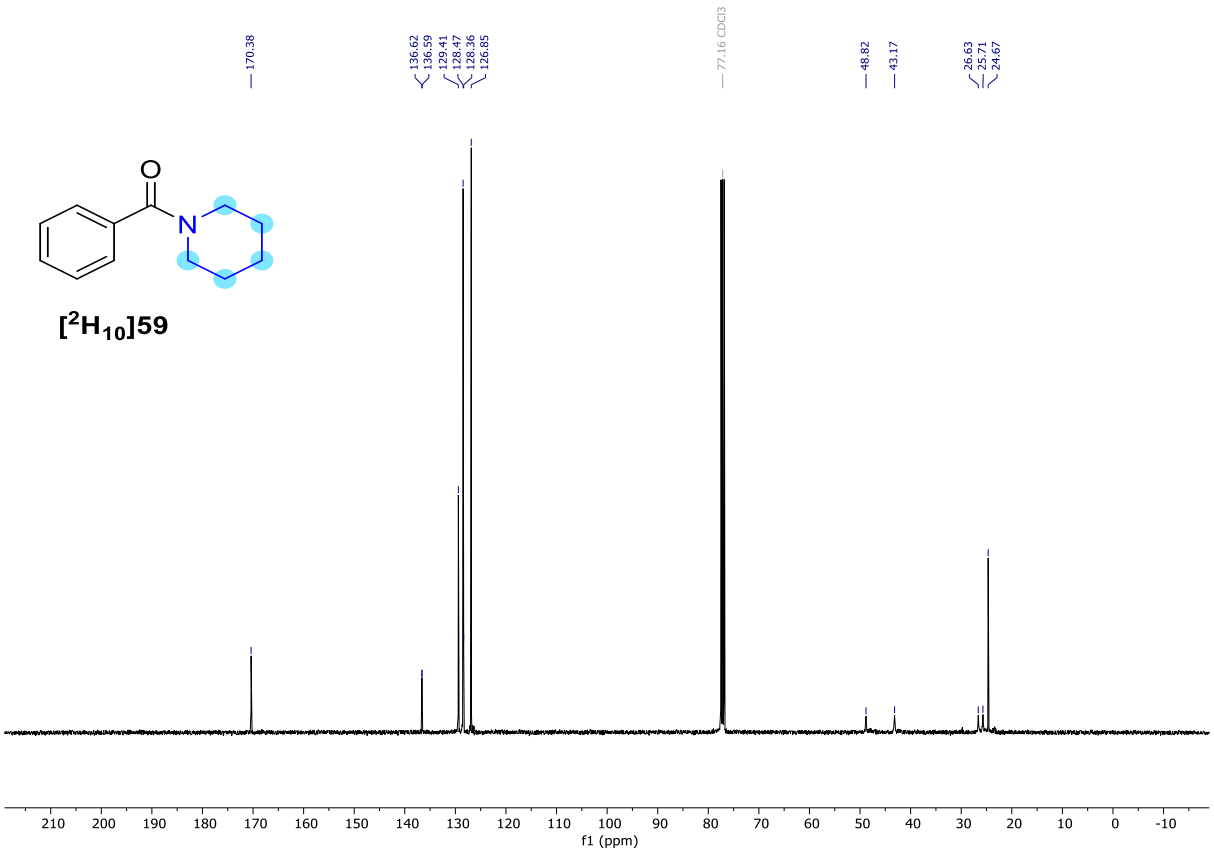


Figure S237: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

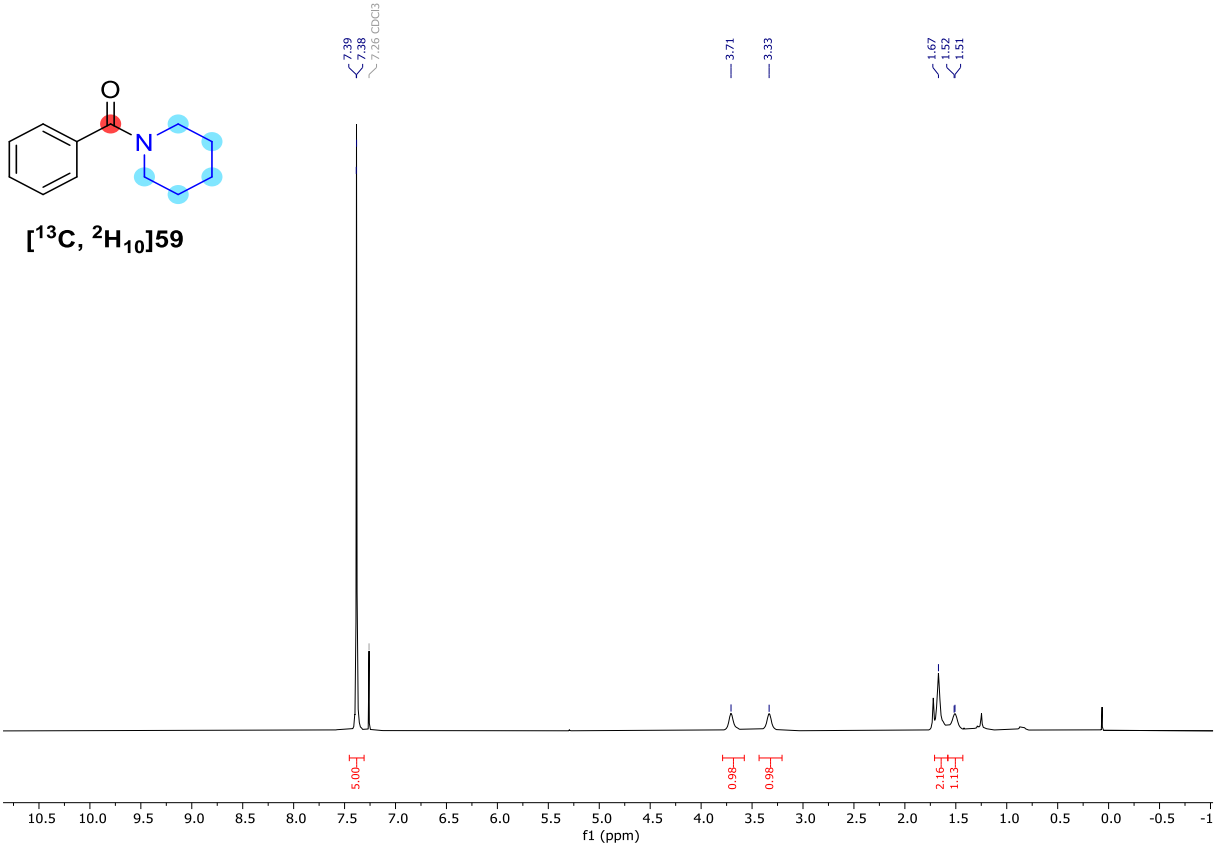
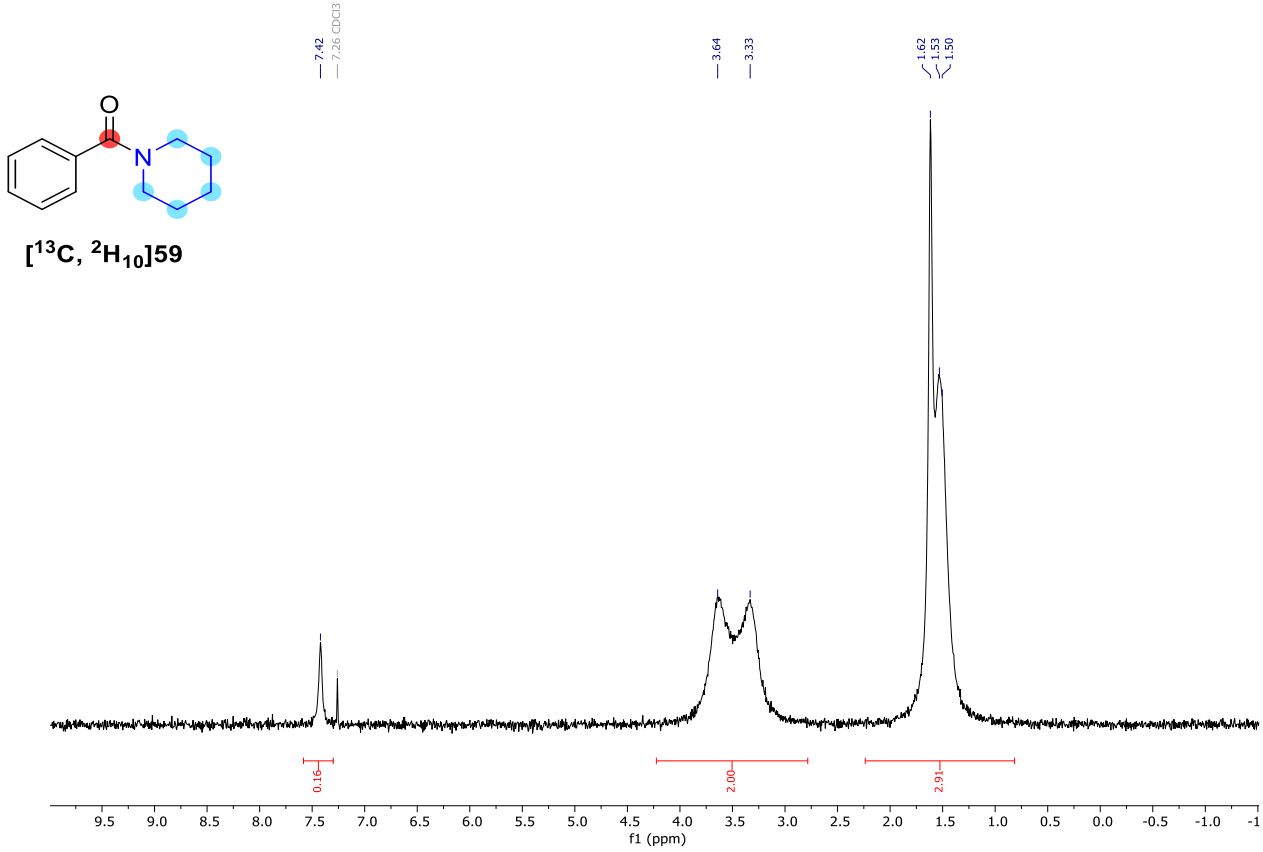
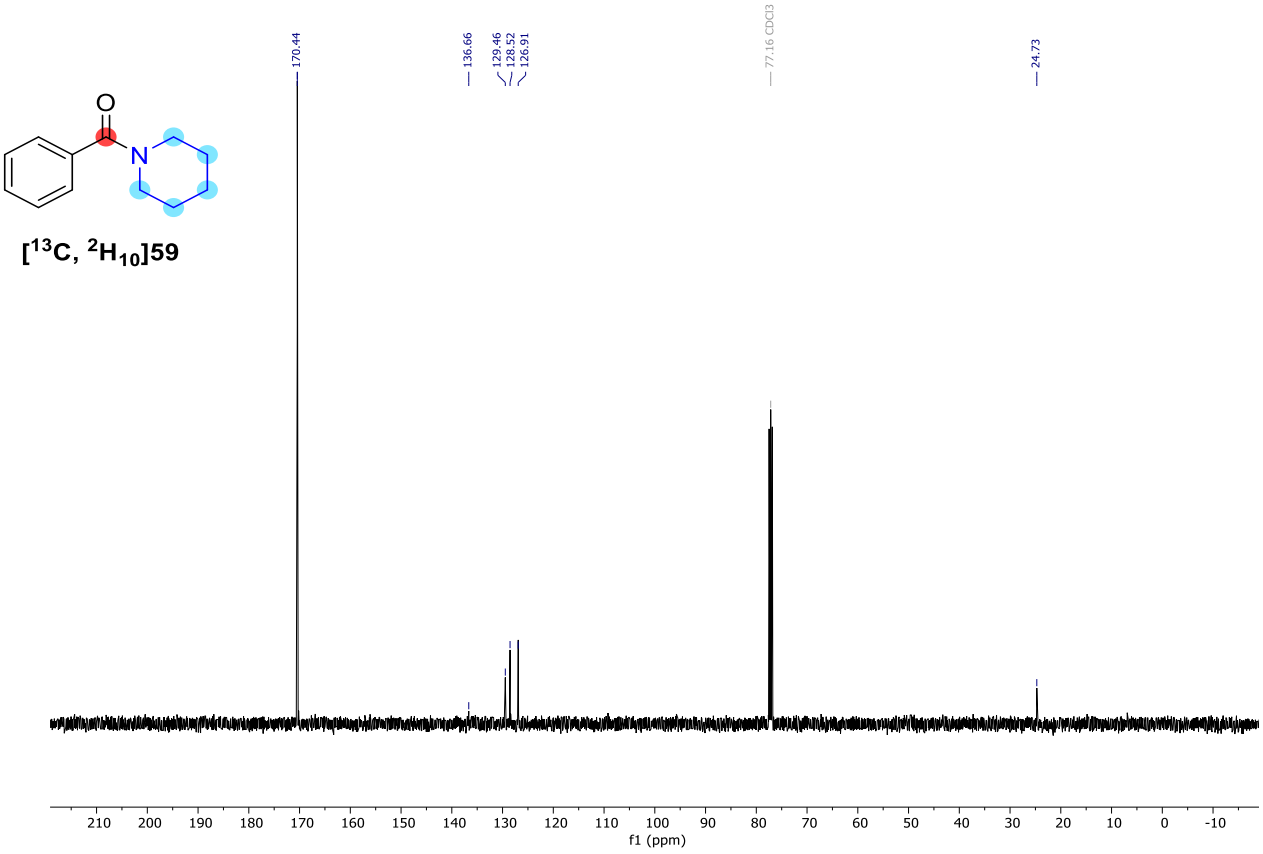


Figure S238: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)



$[^{13}C, {}^{2}H_{10}]$59

Figure S239: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)



$[^{13}C, {}^{2}H_{10}]$59

Figure S240: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

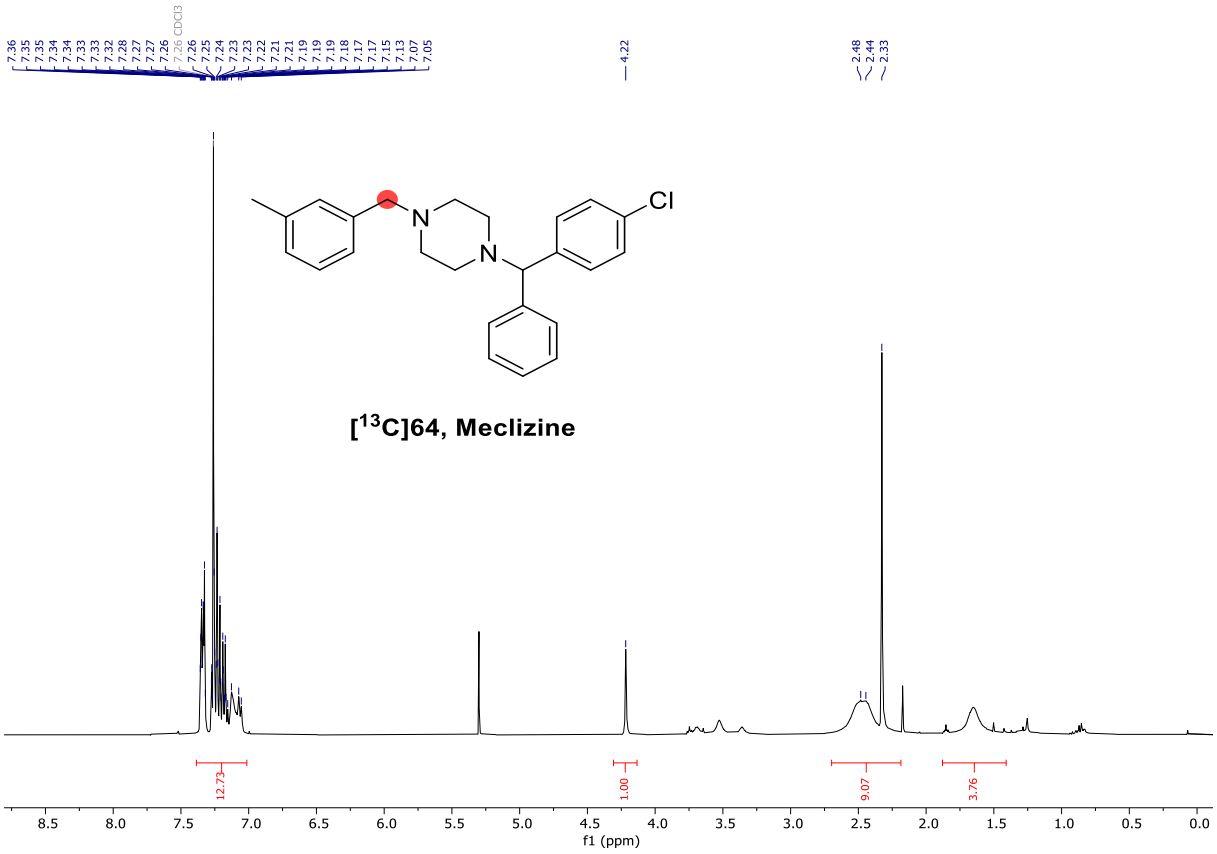


Figure S241: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

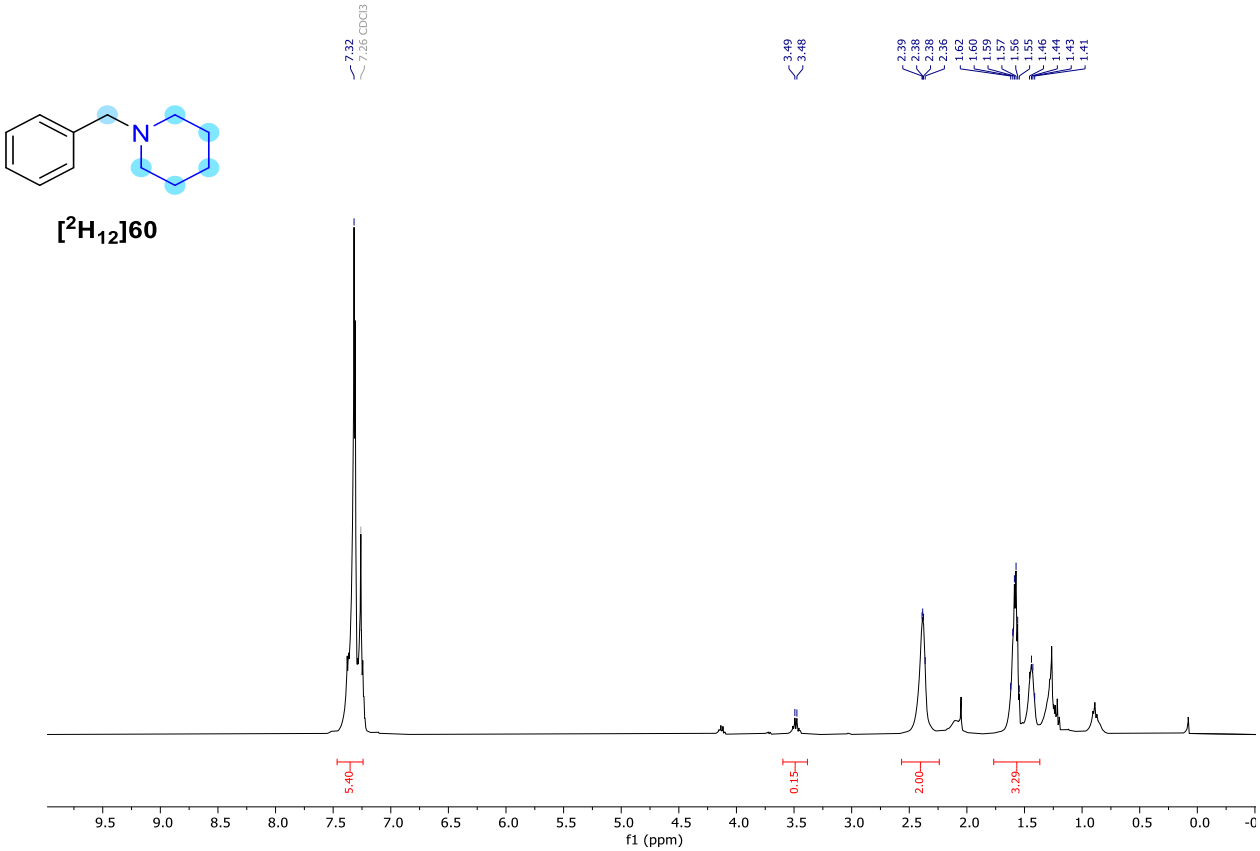
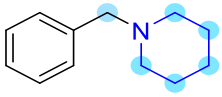
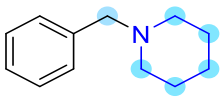


Figure S242: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)



[$^{2}H_{12}$]60

Figure S243: ^{2}HNMR spectrum in $CDCl_3$ (61 MHz)



[$^{2}H_{12}$]60

Figure S244: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

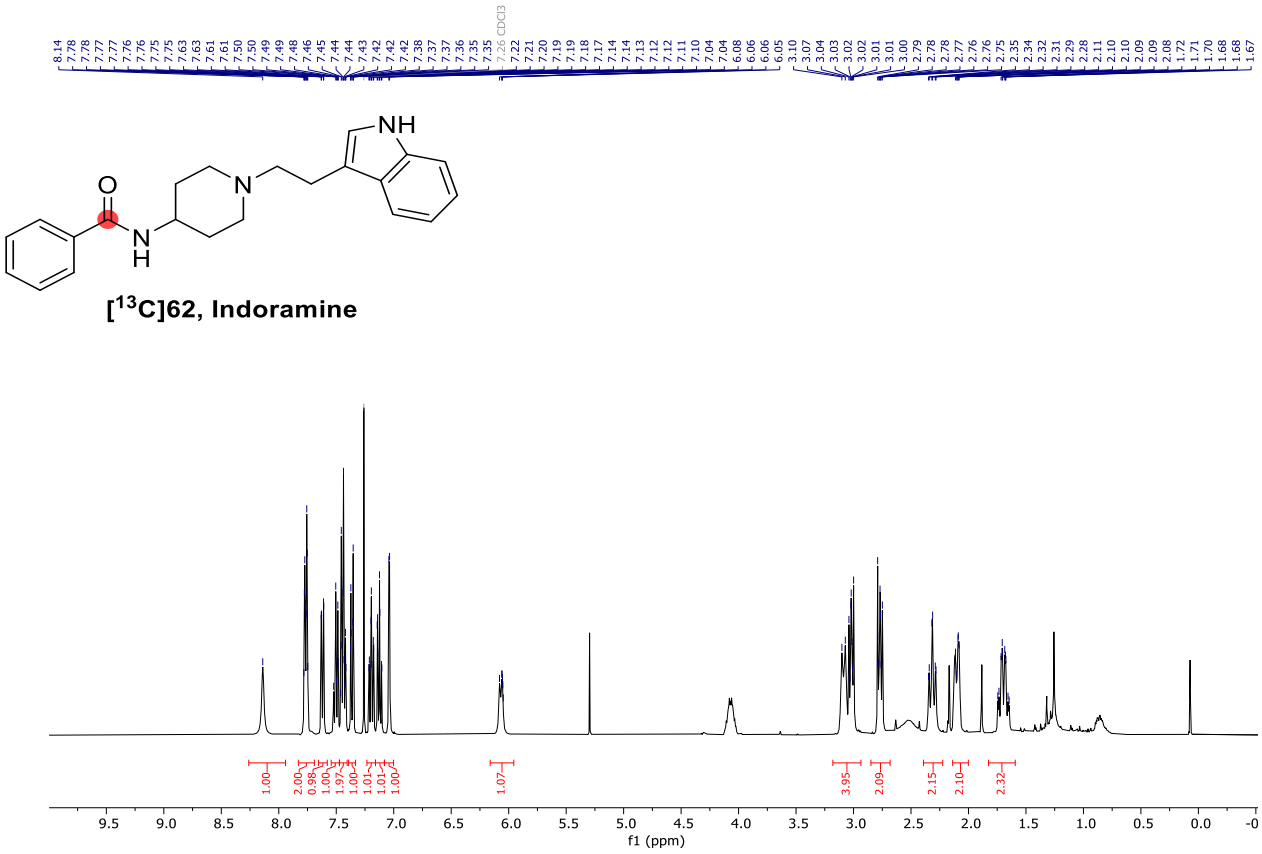


Figure S245: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

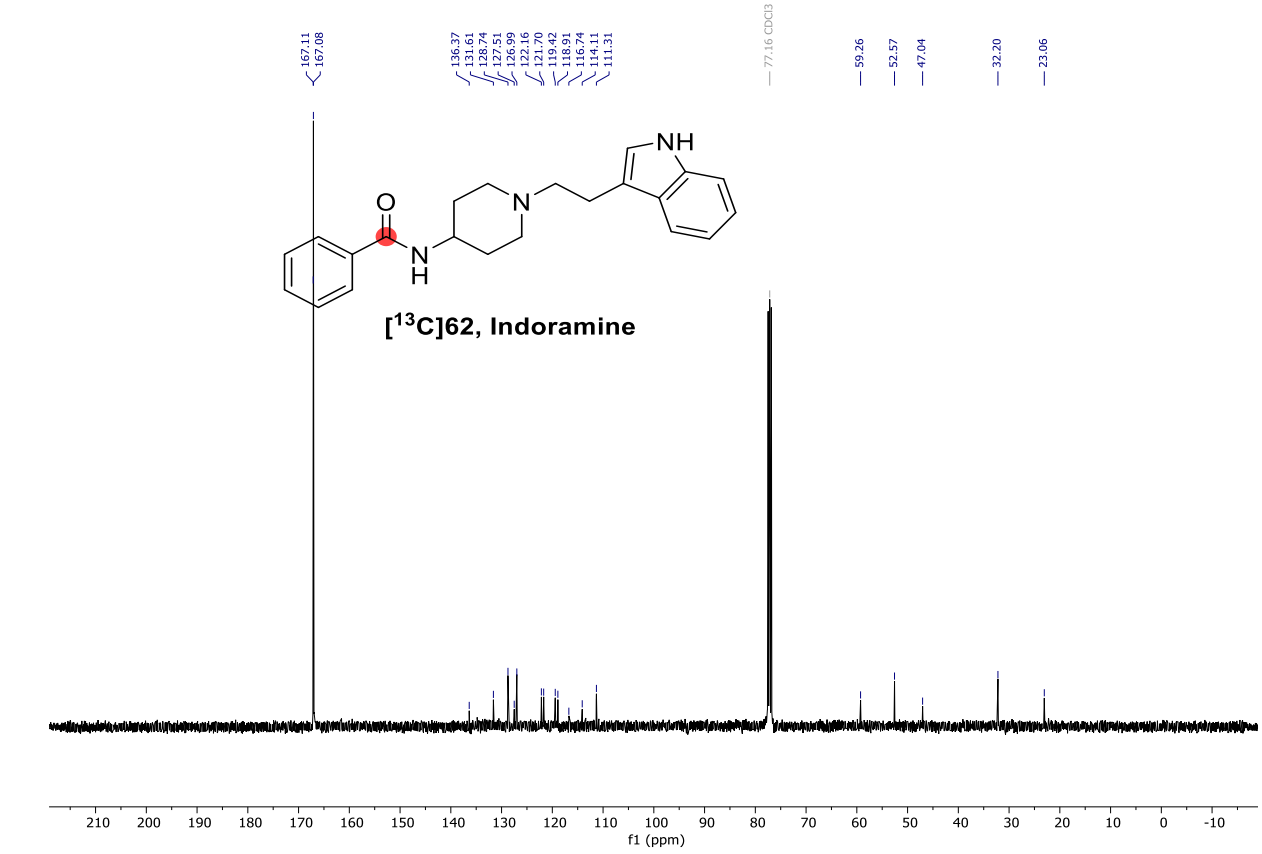


Figure S246: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)

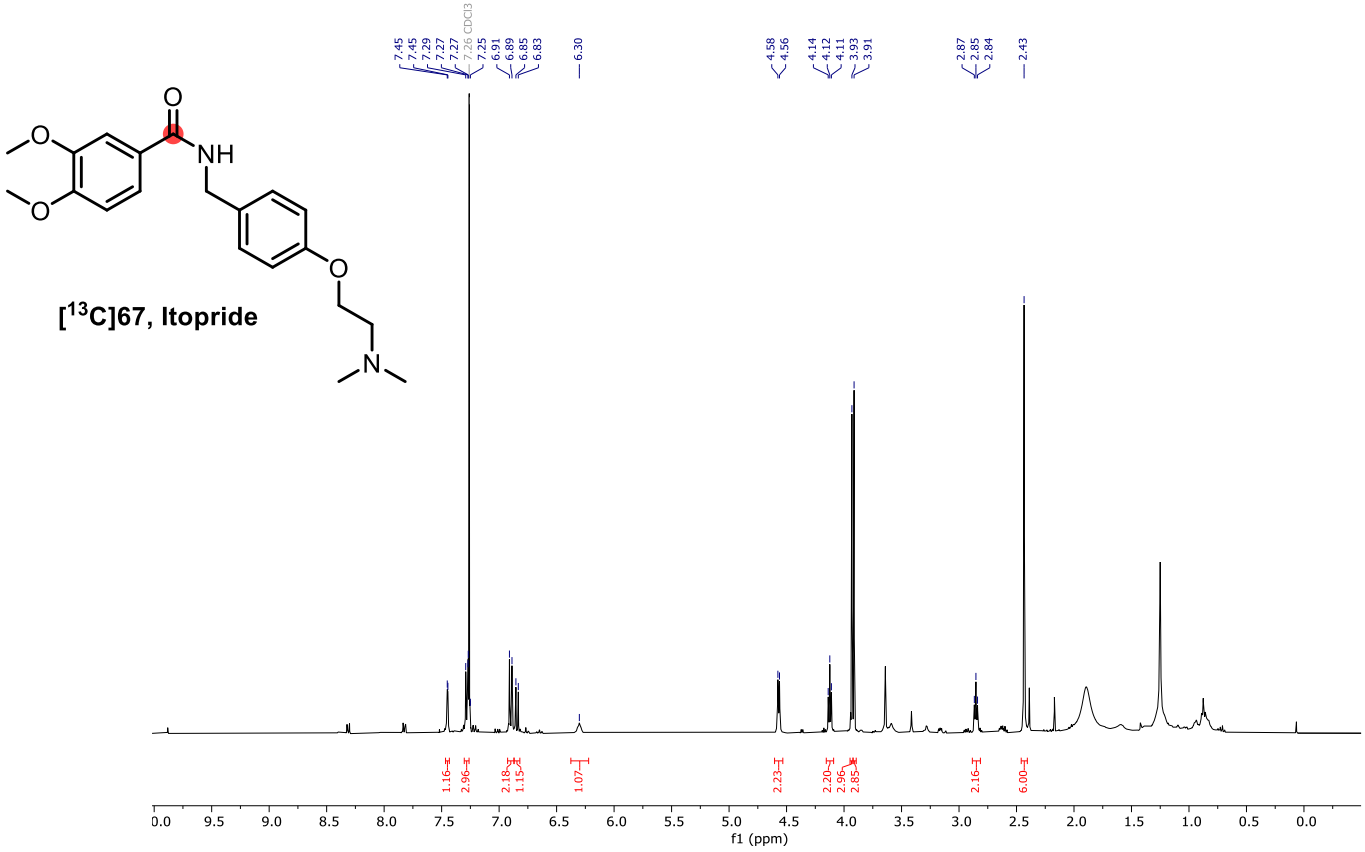


Figure S247: ^{1}HNMR spectrum in $CDCl_3$ (400 MHz)

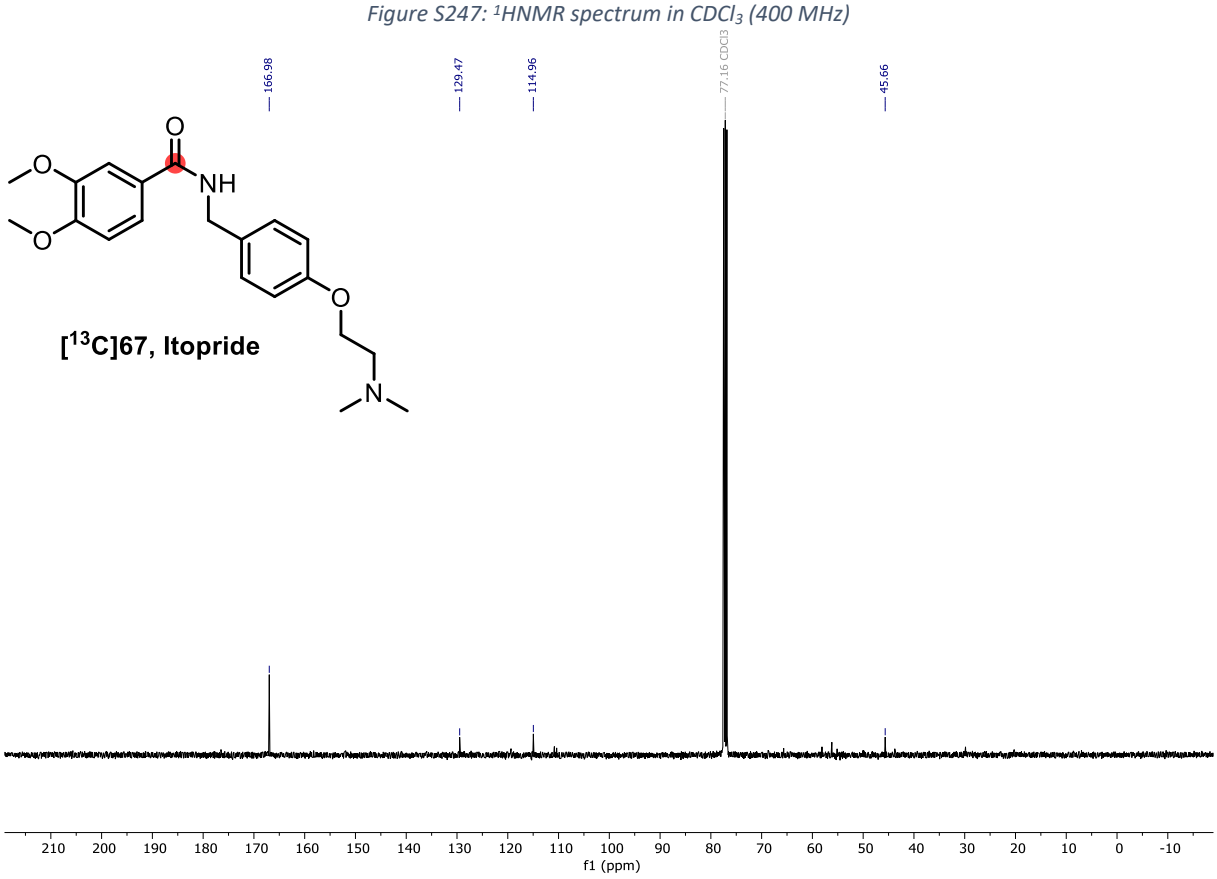


Figure S248: ^{13}CNMR spectrum in $CDCl_3$ (101 MHz)