Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Nickel-Catalyzed Cross-Coupling Aminations via High-Throughput Mechanochemistry Enabled by Resonant Acoustic Mixing

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1. General Information:

Unless otherwise stated, all reactions were carried out under an inert atmosphere in screw cap reaction vials or 96 well plate sealed with a silicone/PTFE cap mat . All the reagents and solvents were bought from Sigma Aldrich, Strem Chemicals, and Alfa Aesar in a sure-seal bottle and were used as received. For column chromatography, silica gel (100–200 mesh) from Aldrich was used. A gradient elution using *n*-Hexane and Ethyl Acetate were performed based on Merck aluminum TLC sheets (silica gel 60 F_{254}). They were visualized under UV light (254 nm) or by staining with aqueous potassium permanganate or vanillin alcoholic solutions. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath at 50 °C.

All isolated compounds are characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectroscopy. ^{1}H NMR spectra were recorded in deuterated solvents on Bruker Avance-II spectrometers at 400 or 500 MHz, with residual protic solvent as the internal standard. ^{13}C NMR spectra were recorded in deuterated solvents on Bruker Avance-II spectrometers at 101 or 125 MHz, with the central peak of the deuterated solvent as the internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz) rounded to the nearest 0.1 Hz. The ^{1}H NMR spectra are reported as δ/ppm downfield from tetramethylsilane (multiplicity, number of protons, assignment, coupling constant J/Hz). The ^{13}C NMR spectra are reported as δ/ppm and were obtained with ^{1}H decoupling (note: $CDCl_3$ referenced at δ 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets and dt = doublet of triplets respectively).

All GCMS analysis was done by Agilent 7890A GC system connected with 5975C inert XL EI/CI MSD (with triple axis detector). High-resolution mass spectra (HRMS) analysis was performed using Bruker micro Time-of-Flight (TOF)-MS equipped with an ESI source.

2. Designed and Customized 96-well Collection Plate holder for RAM (HTE)

Synthesis of all the compounds were carried out in a LabRAM II (Resodyn) using a 1mL 96-well collection plate with round well bottoms in polypropylene and silicone/PTFE cap mat purchased from Analytical Sales and Services, Inc. (Figure S1a). To ensure reproducibility and perform the 96 reactions simultaneously, an in-house 96-well collection plate holder was designed, and 3D printed (Figure S1b) and mounted on the LabRAM II instrument, (Figure S1c)

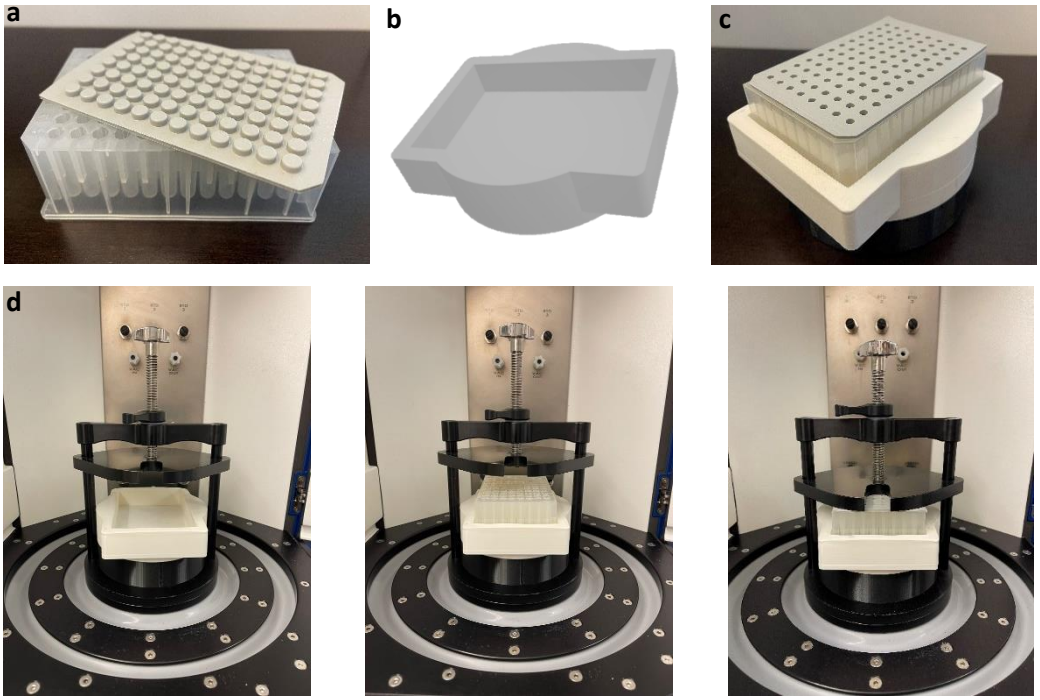
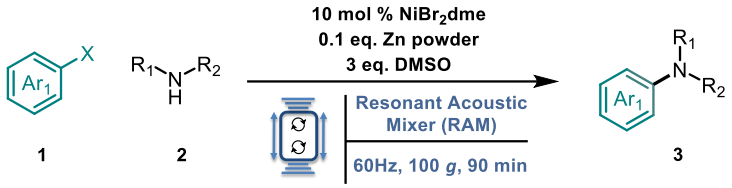


Figure S1: Picture of: **a)** 1 mL 96-well polypropylene collection plate with a silicone/PTFE cap mat; **b)** in-house designed 3D printed sample holder for the 96-well plate placed; **c)** 96-well plate placed in the in-house designed 3D printed sample holder made of ABS (Acrylonitrile butadiene styrene); **c)** 96-well plate in the in-house designed sample holder mounted on the LabRAM II instrument.

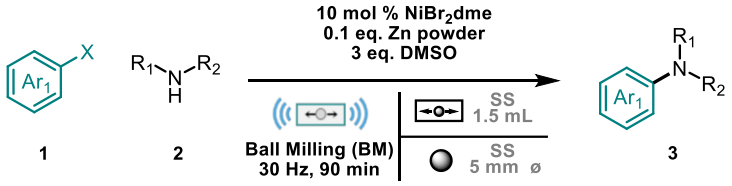
3. General Procedure for the Catalytic Reactions

3.1 General Procedure for the Cross-coupling of aryl halide and amines using RAM



All reactions were conducted in a Resodyn LabRAM II instrument at 60 Hz, in a 1 mL 96-well collection plate. aryl halide **1** (0.2 mmol, 1 eq.), amine **2** (0.6 mmol, 3 eq.), $NiBr_2$dme (0.1 mmol, 0.1 eq.), Zn powder (0.1 mmol, 0.1 eq.), and 55 µL of DMSO were added in glovebox. The 96-well plate was sealed with the silicone/PTFE cap mat and placed in the in-house holder. After being mounted in LabRAM II instrument, the plate was mixed at an acceleration of 100 *g* for 90 min. Upon completion, the reaction mixture was transferred to a flask and filtered with DCM. The crude product was purified by flash column chromatography using hexane/EtOAc as eluent to obtain the desired product **3**.

3.2 General Procedure for the Cross-coupling of aryl halide and amines using BM



All reactions were conducted in a Retsch MM400 Mixer milling, using a Ø 5mm stainless-steel ball in a 1.5 mL stainless-steel jar at 30 Hz. aryl halide **1** (0.2 mmol, 1 eq.), amine **2** (0.6 mmol, 3 eq.), $NiBr_2$dme (0.1 mmol, 0.1 eq.), Zn powder (0.1 mmol, 0.1 eq.), 55 µL of DMSO, and stainless-steel ball were added in the jar inside glovebox. The jar was sealed, mounted in Ball Milling instrument, and mixed for 90 min. Upon completion, the reaction mixture was transferred to a flask and filtered with DCM. The crude product was purified by flash column chromatography using hexane/EtOAc as eluent to obtain the desired product **3**.

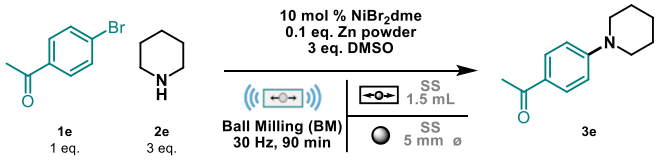
4. Control Experiments

4.1 Control experiments LabRAM II

Entry	Variables	Yield (%)[a]	Entry	Variables	Yield (%)[a]
1	**none**	**98 (97)**	7	30 *g*, 60 g	61, 78
2	No nickel	NR	8	30 min, 60 min	87, 92
3	No zinc	NR	9	2 eq. DMSO	63
4	No liquid additive (LA) DMSO	8	10	0.05 eq $NiBr_2$dme and 0.05 eq. Zn	26
5	Overnight, stirring at r.T.	NR	11	0.05 eq. $NiBr_2$dme	39
6	Overnight, stirring at 60 ºC	38	12	0.05 eq. Zn	trace

Table S1: Control experiments for the Cross-coupling of aryl halide and amines using RAM. 1-(4-bromophenyl)ethan-1-one **1e** (0.2 mmol), aniline **2e** (0.6 mmol), $NiBr_2$·dme (0.01 mmol), Zn (0.01 mmol), in DMSO (0.8 mmol), under an inert atmosphere for 90 min at 100 *g*; [a]GC yield using dodecane as an internal standard. Isolated yield in parentheses.

4.2 Control experiments Ball Milling



Entry	Variables	Yield (%)[a]
1	**none**	**97 (96)**
2	No nickel	NR
3	No zinc	NR
4	No liquid additive (LA)	NR
5	No ball	23
6	30 min, 60 min	36, 70

Table S2 Control experiments for the Cross-coupling of aryl halide and amines using BM. 1-(4-bromophenyl)ethan-1-one **1e** (0.2 mmol), aniline **2e** (0.6 mmol), $NiBr_2$·dme (0.01 mmol), Zn (0.01 mmol), in DMSO (0.8 mmol), under an inert atmosphere for 90 min at 30 Hz. [a]GC yield using dodecane as an internal standard. Isolated yield in parentheses.

4.3 1mL 96-well collection plate HTE-RAM[a]

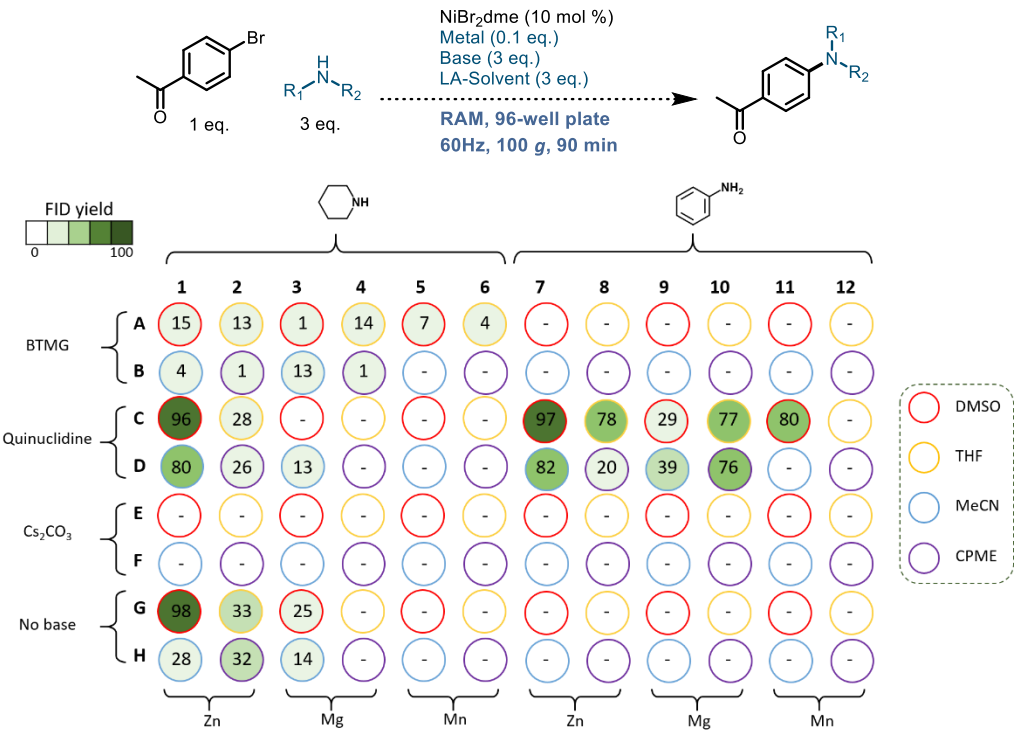


Figure S2 Mechanochemical HTE cross-coupling amination optimization screening. Reaction setup for the nickel-catalyzed cross-coupling included two amines (piperidine and aniline; 3 eq.), three bases (2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG), quinuclidine, and Cs_2CO_3;3 eq.), three metal powders (zinc, magnesium, and manganese; 0.1 eq.), and four liquid-assisted (LA) solvents (DMSO, THF, MeCN, and CPME, 3 eq.), using 1-(4-bromophenyl)ethan-1-one (1 eq.) as a coupling partner and $NiBr_2$dme (0.1 eq.) as a catalyst, at 100 *g*, 60 Hz, per 90 min. [a]GCMS-FID yield using dodecane as an internal standard. Heatmap visualization generated using GCMS-FID data after min-max normalization.

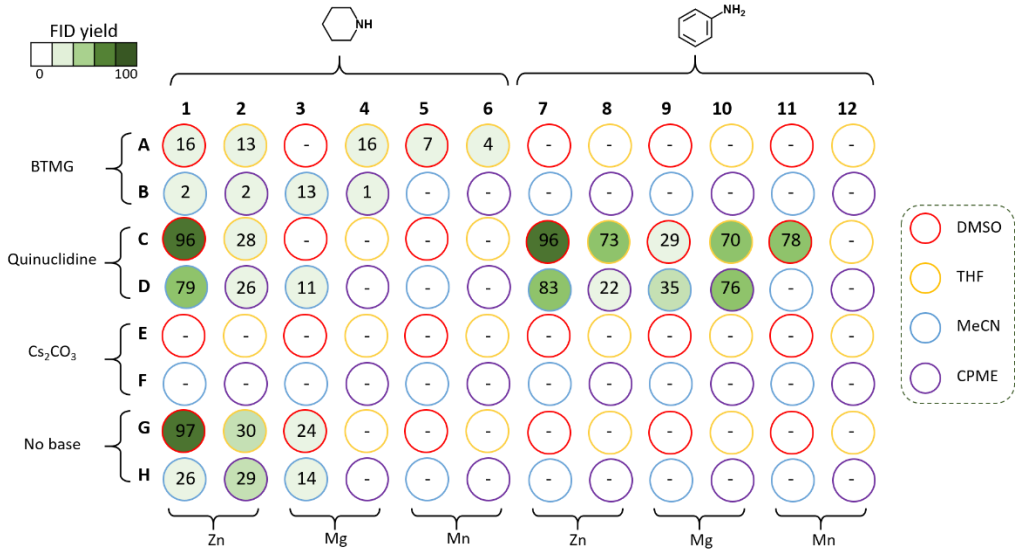
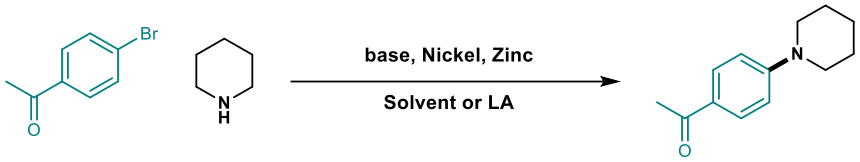


Figure S3: Repeated mechanochemical HTE cross-coupling amination optimization screening. [a]GCMS-FID yield using dodecane as an internal standard. Heatmap visualization generated using GCMS-FID data after min-max normalization.

5. Green metric: Process Mass Intensity (PMI)

Green chemistry metrics assess the efficiency and environmental impact of chemical processes, promoting less use of solvents and reducing loading of reagents and waste. To demonstrate the sustainability of our method (A) compared to the solution-based reaction (B),[5] we calculated the green metric Process Mass Intensity (PMI). PMI measures the total mass in kilograms of raw materials used (input) to produce 1 kilogram of product (output). When comparing two processes, the one with the lowest PMI highlights its superior environmental benefits and increased efficiency, making it the greenest.

PMI calculation for the C-N bond cross-coupling amination of the selected reaction:



A) Solution-based process[5] (product 11):

Light-free amination protocol (18 h): aryl halide (0.2 mmol, 1 eq.), amine (0.4 mmol, 2 eq.), base (0.36 mmol, 1.8 eq.), $NiBr_2$dme (0.01 mmol, 0.05 eq.), zinc powder (0.02 mmol, 0.1 eq.), and 27 eq. of DMA.

B) Our mechanochemistry process (product 3e):

RAM amination protocol (90 min): aryl halide (0.2 mmol, 1 eq.), amine (0.6 mmol, 3 eq.), base (0.6 mmol, 3 eq.), $NiBr_2$dme (0.02 mmol, 0.1 eq.), Zn powder (0.02 mmol, 0.1 eq.), and 55 µL of DMSO.

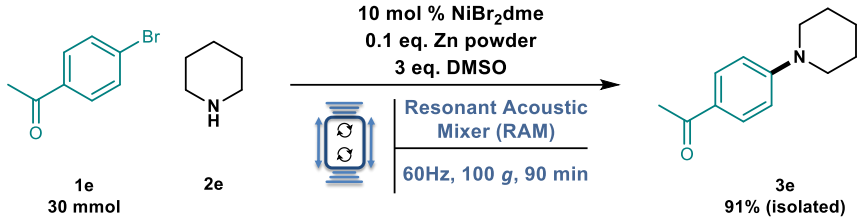
Process Mass Intensity (PMI):

$$\text{PMI} = \frac{\text{Total mass used in the process [kg]}}{\text{Mass of product [kg]}}$$

Process	Aryl halide	Amine	Base	Nickel	Zinc	Solvent or LA	Yield	PMI
A	0.0398	0.0341	0.04	0.00309	0.00131	0.47	93% (38g)	15.5
B	0.0398	0.0511	0.0605	0.00617	0.00131	0.0667	97 % (39.5g)	**5.7**

6. Scale-up Reaction

Scale-up of RAM-accelerated Nickel cross-coupling amination reaction achieved in 30 mmol scale using standard condition, exemplifying the high efficiency and practicality of this amination protocol.



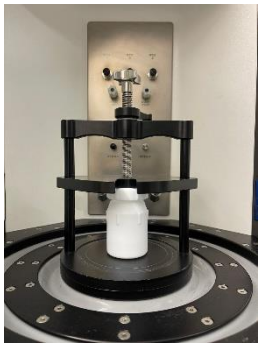
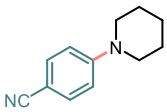


Figure S4: *Picture of 100 mL Teflon vial mounted in LabRAM II*

The reaction of 4-bromoacetophenone **1e** with piperidine **2e** was conducted in a Resodyn LabRAM II instrument at 60 Hz, in a Teflon vial (100 mL). Aryl halide **1e** (30 mmol, 1 eq.), amine **2e** (90 mmol, 3 eq.), $NiBr_2$dme (0.3 mmol, 0.01 eq.), Zn powder (0.3 mmol, 0.01 eq.), and 3 eq of DMSO as a liquid assisted solvent were added in the vial under inert atmosphere. The Teflon vial was sealed and mounted in LabRAM II instrument. The vial was mixed at an acceleration of 100 *g* for 90 min. Upon completion, the reaction mixture was transferred to a flask and filtered with DCM. The crude product was purified by flash column chromatography using hexane/EtOAc as eluent to obtain the desired product **3e** in a 91% (5.55g) isolated yield.

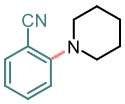
7. Spectroscopic Data of the Products

4-(piperidin-1-yl)benzonitrile (3a):



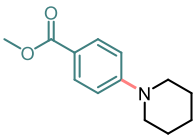
The title compound was prepared according to general procedure and isolated as a white solid in 86% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.40 (d, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.32 (t, J = 4.9 Hz, 4H), 1.67 (d, J = 3.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.60, 133.56, 120.45, 114.19, 99.05, 48.56, 25.30, 24.30. The spectral data were consistent with those reported in the literature. [1]

2-(piperidin-1-yl)benzonitrile (3b):



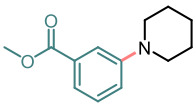
The title compound was prepared according to general procedure and isolated as a colorless oil in 79% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.7, 1.7 Hz, 1H), 7.44 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.03 – 6.89 (m, 2H), 3.20 – 3.11 (m, 4H), 1.78 (q, J = 5.6 Hz, 4H), 1.64 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.96, 134.37, 133.72, 127.75, 121.16, 118.82, 105.94, 53.24, 26.19, 24.14. The spectral data were consistent with those reported in the literature.[2]

Methyl 4-(piperidin-1-yl)benzoate (3c):



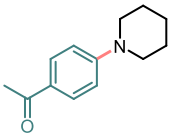
The title compound was prepared according to general procedure and isolated as a light yellow solid in 90% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 6.88 – 6.80 (m, 2H), 3.85 (s, 3H), 3.35 – 3.27 (m, 4H), 1.70 – 1.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.34, 154.57, 131.31, 118.75, 113.67, 51.63, 48.88, 25.46, 24.42. The spectral data were consistent with those reported in the literature.[3]

Methyl 3-(piperidin-1-yl)benzoate (3d):



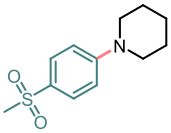
The title compound was prepared according to general procedure and isolated as a white solid in 92% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 2.6, 1.6 Hz, 1H), 7.47 (dt, J = 7.6, 1.3 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.12 (dd, J = 8.4, 2.7 Hz, 1H), 3.89 (s, 3H), 3.24 – 3.13 (m, 4H), 1.70 (q, J = 5.8 Hz, 4H), 1.62 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.67, 152.14, 130.92, 129.09, 120.99, 120.24, 117.19, 52.15, 50.53, 25.78, 24.30. The spectral data were consistent with those reported in the literature.[4]

1-[4-(piperidin-1-yl)phenyl]ethan-1-one (3e):



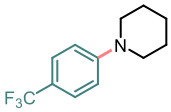
The title compound was prepared according to general procedure and isolated as a white solid in 97% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.77 (m, 2H), 6.88 – 6.77 (m, 2H), 3.34 (t, J = 4.9 Hz, 4H), 2.49 (s, 3H), 1.71 – 1.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.47, 154.43, 130.52, 126.67, 113.29, 48.65, 26.11, 25.37, 24.39. The spectral data were consistent with those reported in the literature.[5]

1-[4-(methylsulfonyl)phenyl]piperidine (3f):



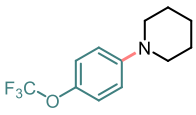
The title compound was prepared according to general procedure and isolated as a white solid in 72% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.34 (t, J = 4.3 Hz, 4H), 2.99 (s, 3H), 1.63 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.49, 129.16, 127.48, 113.83, 48.71, 45.06, 25.28, 24.29. The spectral data were consistent with those reported in the literature.[5]

1-[4-(trifluoromethyl)phenyl]piperidine (3g):



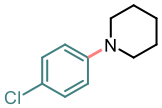
The title compound was prepared according to general procedure and isolated as a colorless oil in 88% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 3.35 – 3.19 (m, 4H), 1.75 – 1.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.87, 125.02 (q, J = 271.7 Hz), 119.73 (q, J = 32.3 Hz), 114.77, 49.49, 25.53, 24.38. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.20 (s, 3F). The spectral data were consistent with those reported in the literature.[5]

1-[4-(trifluoromethoxy)phenyl]piperidine (3h):



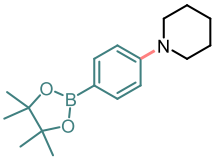
The title compound was prepared according to general procedure and isolated as a colorless oil in 76% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.8 Hz, 2H), 6.97 – 6.84 (m, 2H), 3.20 – 3.08 (m, 4H), 1.71 (q, J = 5.7 Hz, 4H), 1.63 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.99, 141.80, 122.02, 120,8 (q, J = 256.5 Hz), 117.19, 50.90, 25.85, 24.24. ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.22. The spectral data were consistent with those reported in the literature.[6]

1-(4-chlorophenyl)piperidine (3i):



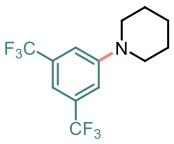
The title compound was prepared according to general procedure and isolated as a white solid in 86% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 6.90 – 6.82 (m, 2H), 3.15 – 3.08 (m, 4H), 1.71 (p, J = 5.8 Hz, 4H), 1.61 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.86, 128.95, 124.07, 117.81, 50.82, 25.80, 24.26. The spectral data were consistent with those reported in the literature.[6]

1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (3j):



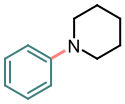
The title compound was prepared according to general procedure and isolated as a white solid 62% yield after column chromatography using a mixture of 1:10 EtOAc/Hexane as eluent (Ball milling yield 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 2H), 6.91 (d, J = 8.2 Hz, 2H), 3.30 – 3.20 (m, 4H), 1.68 (q, J = 5.5 Hz, 4H), 1.60 (dt, J = 7.2, 4.0 Hz, 2H), 1.33 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.96, 136.21, 131.07, 114.73, 83.39, 49.66, 25.61, 24.96, 24.50. The spectral data were consistent with those reported in the literature.[7]

1-[3,5-bis(trifluoromethyl)phenyl]piperidine (3k):



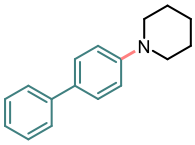
The title compound was prepared according to general procedure and isolated as a white solid in 54% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 7.22 (s, 1H), 3.29 – 3.26 (m, 4H), 1.75 – 1.70 (m, 4H), 1.67 – 1.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.25, 132.35 (q, J = 32.6 Hz), 123.82 (q, J = 272.7 Hz), 115.04, 111.40, 49.73, 25.49, 24.13. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.06. The spectral data were consistent with those reported in the literature.[8]

1-phenylpiperidine (3l):



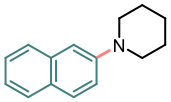
The title compound was prepared according to general procedure and isolated as a colorless oil in 50% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 3.20 – 3.13 (m, 4H), 1.75 (p, J = 5.8 Hz, 4H), 1.59 (q, J = 5.5, 4.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.02, 129.21, 119.32, 116.96, 51.21, 25.84, 24.31. The spectral data were consistent with those reported in the literature.[6]

1-(9-4-yl)piperidine (3m):



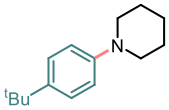
The title compound was prepared according to general procedure and isolated as a white solid in 78% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.80 – 7.73 (m, 2H), 7.65 (t, J = 7.7 Hz, 2H), 7.56 – 7.47 (m, 1H), 7.30 – 7.23 (m, 2H), 3.50 – 3.42 (m, 4H), 2.03 – 1.94 (m, 4H), 1.89 – 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.44, 141.13, 131.87, 128.78, 127.77, 126.59, 126.42, 116.63, 50.61, 25.87, 24.42. The spectral data were consistent with those reported in the literature.[8]

1-(naphthalen-2-yl)piperidine (3n):



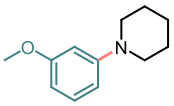
The title compound was prepared according to general procedure and isolated as a colorless oil in 68% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, J = 9.1 Hz, 3H), 7.50 (ddd, J = 8.2, 6.7, 1.3 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.26 (s, 1H), 3.42 – 3.32 (m, 4H), 1.89 (q, J = 5.7 Hz, 4H), 1.74 (q, J = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.08, 134.80, 128.64, 128.51, 127.51, 126.82, 126.24, 123.30, 120.30, 110.64, 51.24, 25.97, 24.45. The spectral data were consistent with those reported in the literature.[9]

1-[4-(tert-butyl)phenyl]piperidine (3o):



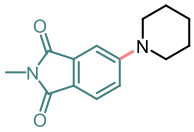
The title compound was prepared according to general procedure and isolated as a pale yellow solid in 51% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.01 – 6.85 (m, 2H), 3.18 – 3.08 (m, 4H), 1.75 (d, J = 5.5 Hz, 4H), 1.57 (q, J = 6.6 Hz, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.88, 141.61, 125.94, 116.52, 51.21, 34.07, 31.60, 26.05, 24.38. The spectral data were consistent with those reported in the literature.[10]

1-(3-methoxyphenyl)piperidine (3p):



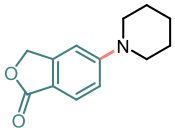
The title compound was prepared according to general procedure and isolated as a colorless oil in 52% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.2 Hz, 1H), 6.57 (dd, J = 8.2, 2.3 Hz, 1H), 6.50 (t, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.2, 2.4 Hz, 1H), 3.79 (s, 3H), 3.20 – 3.13 (m, 4H), 1.71 (p, J = 5.8 Hz, 4H), 1.59 (dd, J = 7.2, 4.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.65, 153.58, 129.77, 109.51, 104.23, 102.95, 55.28, 50.79, 25.87, 24.45. The spectral data were consistent with those reported in the literature.[11]

2-methyl-5-(piperidin-1-yl)isoindoline-1,3-dione (3q):



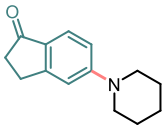
The title compound was prepared according to general procedure and isolated as a bright yellow solid in 74% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 2.3 Hz, 1H), 6.97 (dd, J = 8.5, 2.4 Hz, 1H), 3.43 – 3.34 (m, 4H), 3.09 (s, 3H), 1.71 – 1.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.28, 168.75, 155.31, 134.86, 124.78, 119.33, 117.34, 108.42, 49.06, 25.29, 24.27, 23.82. The spectral data were consistent with those reported in the literature.[12]

5-(piperidin-1-yl)isobenzofuran-1(3H)-one (3r):



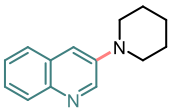
The title compound was prepared according to general procedure and isolated as a colorless oil in 73% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.8 Hz, 1H), 6.96 (dd, J = 8.7, 2.2 Hz, 1H), 6.78 (s, 1H), 5.16 (s, 2H), 3.41 – 3.32 (m, 4H), 1.72 – 1.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 155.59, 149.56, 126.76, 115.76, 113.99, 105.56, 69.27, 49.18, 25.36, 24.32. HRMS (ESI-TOF) for $C_{13}H_{15}NO_2$: calculated for $[M-H]^-$ 218.1181, found 218.1182.

5-(piperidin-1-yl)-2,3-dihydro-1H-inden-1-one (3s):



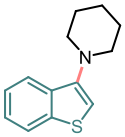
The title compound was prepared according to general procedure and isolated as a colorless oil in 55% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 8.9, 2.3 Hz, 1H), 6.77 (d, J = 2.3 Hz, 1H), 3.39 (t, J = 5.0 Hz, 4H), 3.05 – 2.99 (m, 2H), 2.65 – 2.58 (m, 2H), 1.68 (d, J = 3.8 Hz, 6H).. ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.98, 158.17, 156.18, 126.98, 125.25, 114.39, 109.59, 49.02, 36.57, 26.05, 25.50, 24.52. The spectral data were consistent with those reported in the literature.[13]

3-(piperidin-1-yl)quinolone (3t):



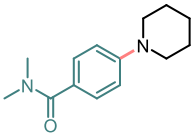
The title compound was prepared according to general procedure and isolated as a light yellow solid in 84% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 2.9 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.64 (dd, J = 7.7, 1.8 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.32 (d, J = 2.8 Hz, 1H), 3.29 – 3.21 (m, 4H), 1.76 (t, J = 5.7 Hz, 4H), 1.67 – 1.55 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.80, 145.65, 142.54, 129.08, 128.82, 126.88, 126.58, 126.20, 116.82, 50.67, 25.72, 24.15. The spectral data were consistent with those reported in the literature. [14]

1-(benzo[b]thiophen-3-yl)piperidine (3u):



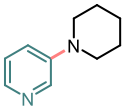
The title compound was prepared according to general procedure and isolated as a pale yellow solid in 70% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H), 7.40 – 7.31 (m, 2H), 6.58 (s, 1H), 3.13 – 3.06 (m, 4H), 1.83 (p, J = 5.6 Hz, 4H), 1.65 (q, J = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.32, 139.36, 135.01, 124.49, 123.58, 123.32, 122.22, 106.44, 53.95, 26.39, 24.61. The spectral data were consistent with those reported in the literature.[15]

N,N-dimethyl-4-(piperidin-1-yl)benzamide (3v):



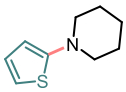
The title compound was prepared according to general procedure and isolated as a yellowish solid in 55% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.7, 1.5 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 3.22 (t, J = 5.4 Hz, 4H), 3.05 (s, 6H), 1.71 – 1.65 (m, 4H), 1.60 (q, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.08, 152.87, 129.09, 125.61, 114.85, 49.79, 25.67, 24.43. HRMS (ESI-TOF) for $C_{14}H_{20}N_2O$: calculated for $[M+Na]^+$ 255.1474, found 255.1473.

3-(piperidin-1-yl)pyridine (3w):



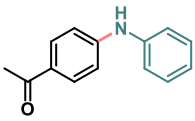
The title compound was prepared according to general procedure and isolated as a pail yellow oil in 60% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 2.7 Hz, 1H), 8.03 (d, J = 4.1 Hz, 1H), 7.21 – 7.10 (m, 2H), 3.23 – 3.12 (m, 4H), 1.70 (q, J = 5.7 Hz, 4H), 1.64 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.87, 139.84, 138.77, 123.60, 122.87, 49.94, 25.63, 24.18. The spectral data were consistent with those reported in the literature.[16]

1-(thiophen-2-yl)piperidine (3x):



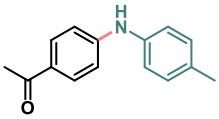
The title compound was prepared according to general procedure and isolated as a colorless oil in 65% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 5.4, 3.8 Hz, 1H), 7.04 (dd, J = 5.4, 1.2 Hz, 1H), 6.59 – 6.54 (m, 1H), 3.61 – 3.56 (m, 4H), 2.19 (p, J = 5.7 Hz, 4H), 2.06 – 1.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.44, 126.22, 111.83, 104.95, 53.03, 25.54, 23.92. The spectral data were consistent with those reported in the literature.[17]

1-[4-(phenylamino)phenyl]ethan-1-one (3y):



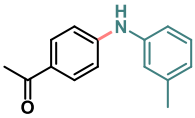
The title compound was prepared according to general procedure and isolated as a light yellow solid in 86% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.77 (m, 2H), 7.45 – 7.28 (m, 2H), 7.23 – 7.14 (m, 2H), 7.07 (t, J = 7.3 Hz, 1H), 7.03 – 6.93 (m, 2H), 6.37 (s, 1H), 2.60 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.63, 148.60, 140.76, 130.72, 129.59, 128.94, 123.36, 120.75, 114.47, 26.24. The spectral data were consistent with those reported in the literature.[18]

1-[4-(p-tolylamino)phenyl]ethan-1-one (3z):



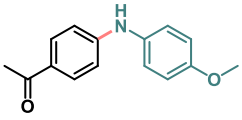
The title compound was prepared according to general procedure and isolated as an orange solid in 88% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.96 – 6.89 (m, 2H), 2.52 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.57, 149.20, 137.89, 133.51, 130.77, 130.16, 128.58, 121.66, 113.96, 26.23, 20.95. The spectral data were consistent with those reported in the literature.[19]

1-[4-(m-tolylamino)phenyl]ethan-1-one (3aa):



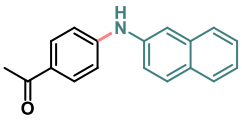
The title compound was prepared according to general procedure and isolated as a solid in 95% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 2H), 7.23 (t, J = 8.1 Hz, 1H), 7.06 – 6.94 (m, 4H), 6.90 (d, J = 7.5 Hz, 1H), 2.53 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.62, 148.63, 140.60, 139.57, 130.73, 129.41, 128.90, 124.30, 121.47, 117.86, 114.52, 26.26, 21.57. The spectral data were consistent with those reported in the literature.[20]

1-{4-[(4-methoxyphenyl)amino]phenyl}ethan-1-one (3ab):



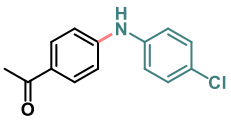
The title compound was prepared according to general procedure and isolated as a white solid in 89% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.11 (s, 1H), 3.81 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.52, 156.70, 150.25, 133.30, 130.81, 128.10, 124.62, 114.86, 113.20, 55.62, 26.18. The spectral data were consistent with those reported in the literature.[21]

1-[4-(naphthalen-2-ylamino)phenyl]ethan-1-one (3ac):



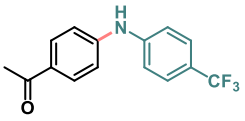
The title compound was prepared according to general procedure and isolated as a light yellow solid in 67% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.81 (t, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.40 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.13 – 7.04 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.58, 148.33, 138.37, 134.40, 130.80, 130.37, 129.59, 129.47, 127.86, 127.02, 126.84, 124.79, 121.48, 116.09, 114.94, 26.33. The spectral data were consistent with those reported in the literature.[22]

1-{4-[(4-chlorophenyl)amino]phenyl}ethan-1-one (3ad):



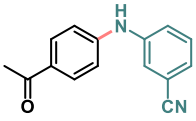
The title compound was prepared according to general procedure and isolated as a white solid in 92% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.76 (m, 2H), 7.34 – 7.26 (m, 2H), 7.16 – 7.06 (m, 2H), 7.02 – 6.92 (m, 2H), 6.13 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.60, 148.03, 139.43, 130.78, 129.69, 129.53, 128.27, 121.91, 114.76, 26.34. The spectral data were consistent with those reported in the literature.[23]

1-{4-{[4-(trifluoromethyl)phenyl]amino}phenyl}ethan-1-one (3ae):



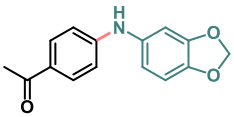
The title compound was prepared according to general procedure and isolated as a yellow solid in 82% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.08 (m, 2H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.82, 146.68, 144.46, 130.70, 130.46, 126.92 (q, *J* = 3.8 Hz), 124.41 (q, *J* = 271.69 Hz), 123.99 (q, *J* = 33.33 Hz), 118.27, 116.27, 26.40. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.97. The spectral data were consistent with those reported in the literature.[24]

3-[(4-acetylphenyl)amino]benzonitrile (3af):



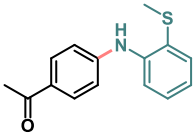
The title compound was prepared according to general procedure and isolated as a solid in 56% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.8, 1.9 Hz, 2H), 7.50 – 7.39 (m, 3H), 7.35 – 7.30 (m, 1H), 7.11 (dd, *J* = 8.7, 2.0 Hz, 2H), 6.41 (s, 1H), 2.60 (d, *J* = 1.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.66, 146.56, 142.27, 130.78, 130.69, 130.59, 125.95, 123.52, 122.02, 118.70, 116.03, 113.62, 26.42. HRMS (ESI-TOF) for $C_{15}H_{12}N_2O$: calculated for $[M-H]^-$ 237.1028, found 237.1025.

1-[4-(benzo[d][1,3]dioxol-5-ylamino)phenyl]ethan-1-one (3ag):



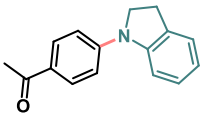
The title compound was prepared according to general procedure and isolated as a colorless oil in 56% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 2H), 6.86 – 6.81 (m, 2H), 6.79 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.76 – 6.71 (m, 1H), 6.65 (dt, *J* = 8.2, 1.6 Hz, 1H), 5.99 (s, 1H), 5.98 (d, *J* = 1.0 Hz, 2H), 2.51 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.55, 149.86, 148.47, 144.64, 134.63, 130.82, 128.49, 116.04, 113.57, 108.78, 104.89, 101.53, 26.24. HRMS (ESI-TOF) for $C_{15}H_{13}NO_3$: calculated for $[M+Na]^+$ 278.0793, found 278.0784.

1-{4-{[2-(methylthio)phenyl]amino}phenyl}ethan-1-one (3ah):



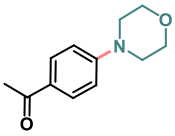
The title compound was prepared according to general procedure and isolated as a yellowish solid in 85% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.82 (m, 2H), 7.40 (ddd, *J* = 13.9, 7.9, 1.5 Hz, 2H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H), 7.10 – 6.96 (m, 3H), 6.59 (s, 1H), 2.53 (s, 3H), 2.38 (d, *J* = 2.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.52, 148.00, 140.08, 131.02, 130.64, 129.53, 128.75, 127.57, 123.59, 119.67, 115.23, 26.28, 17.28. HRMS (ESI-TOF) for $C_{15}H_{15}NOS$: calculated for $[M+Na]^+$ 280.0772, found 280.0776.

1-[4-(indolin-1-yl)phenyl]ethan-1-one (3ai):



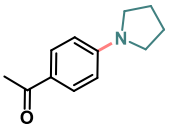
The title compound was prepared according to general procedure and isolated as a yellowish solid in 73% yield after column chromatography using a mixture of 20:80 EtOAc/Hexane as eluent (Ball milling yield 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.96 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 4.06 (t, *J* = 8.4 Hz, 2H), 3.21 (t, *J* = 8.3 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.49, 147.99, 145.16, 132.17, 130.28, 128.92, 127.23, 125.44, 120.63, 115.25, 109.88, 51.84, 28.08, 26.26. HRMS (ESI-TOF) for $C_{16}H_{15}NO$: calculated for $[M+Na]^+$ 260.1052, found 260.1051.

1-(4-morpholinophenyl)ethan-1-one (3aj):



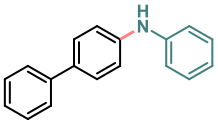
The title compound was prepared according to general procedure and isolated as a orange solid in 94% yield after column chromatography using a mixture of 1:1 EtOAc/Hexane as eluent (Ball milling yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 2H), 6.91 – 6.78 (m, 2H), 3.86 – 3.80 (m, 4H), 3.31 – 3.25 (m, 4H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.64, 154.28, 130.41, 128.16, 113.33, 66.60, 47.56, 26.23. The spectral data were consistent with those reported in the literature.[25]

1-[4-(pyrrolidin-1-yl)phenyl]ethan-1-one (3ak):



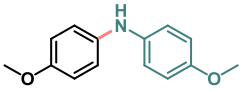
The title compound was prepared according to general procedure and isolated as a yellow solid in 79% yield after column chromatography using a mixture of 10:90 EtOAc/Hexane as eluent (Ball milling yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.75 (m, 2H), 6.53 – 6.44 (m, 2H), 3.38 – 3.31 (m, 4H), 2.49 (s, 3H), 2.05 – 1.98 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.45, 151.05, 130.77, 124.89, 110.71, 47.62, 26.03, 25.51. The spectral data were consistent with those reported in the literature.[26]

N-phenyl-[1,1'-biphenyl]-4-amine (3al):



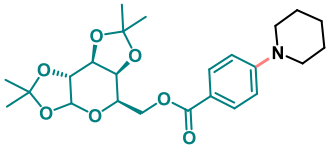
The title compound was prepared according to general procedure and isolated as a white solid in 82% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 2H), 7.59 – 7.53 (m, 2H), 7.50 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 7.17 (td, J = 7.8, 7.3, 1.7 Hz, 4H), 7.01 (td, J = 7.3, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.88, 142.59, 140.92, 133.85, 129.52, 128.86, 128.08, 126.72, 126.64, 121.38, 118.22, 117.92. The spectral data were consistent with those reported in the literature.[27]

bis(4-methoxyphenyl)amine (3am):



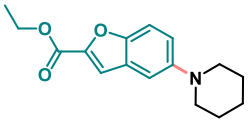
The title compound was prepared according to general procedure and isolated as a pale yellow solid in 83% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 – 6.75 (m, 8H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.44, 138.04, 119.72, 114.84, 55.76. The spectral data were consistent with those reported in the literature.[22]

((5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl 4-(piperidin-1-yl)benzoate (3an):



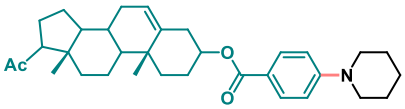
The title compound was prepared according to general procedure and isolated as a pale yellow solid in 84% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.7 Hz, 2H), 6.99 – 6.71 (m, 2H), 5.56 (d, J = 4.9 Hz, 1H), 4.64 (dd, J = 7.9, 2.5 Hz, 1H), 4.48 (dd, J = 11.4, 5.1 Hz, 1H), 4.39 – 4.30 (m, 3H), 4.15 (ddd, J = 7.1, 5.1, 1.8 Hz, 1H), 3.32 (t, J = 5.1 Hz, 4H), 1.66 (d, J = 12.6 Hz, 6H), 1.49 (d, J = 15.2 Hz, 6H), 1.34 (d, J = 9.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.58, 131.53, 113.74, 109.72, 108.91, 96.45, 71.29, 70.83, 70.69, 66.38, 63.31, 49.00, 26.17, 26.10, 25.41, 25.14, 24.61, 24.41. HRMS (ESI-TOF) for $C_{24}H_{33}NO_7$: calculated for $[M+Na]^+$ 470.2155, found 470.2157.

ethyl 5-(piperidin-1-yl)benzofuran-2-carboxylate (3ao):



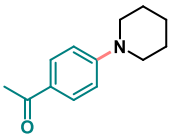
The title compound was prepared according to general procedure and isolated as a yellowish solid 61% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 2H), 7.24 – 7.07 (m, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 5.4 Hz, 4H), 1.77 (p, *J* = 5.2 Hz, 4H), 1.59 (q, *J* = 5.5, 5.0 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.81, 146.08, 127.59, 120.96, 114.08, 112.64, 61.55, 52.80, 26.10, 24.18, 14.49. HRMS (ESI-TOF) for $C_{16}H_{19}NO_3$: calculated for $[M+Na]^+$ 296.1263, found 296.1264.

(10R,13S)-17-acetyl-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(piperidin-1-yl)benzoate (3ap):



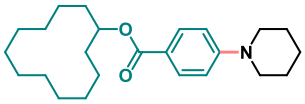
The title compound was prepared according to general procedure and isolated in 76% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 2H), 5.40 (d, *J* = 5.1 Hz, 1H), 4.81 (tt, *J* = 10.9, 6.0 Hz, 1H), 3.31 (t, *J* = 5.1 Hz, 4H), 2.62 – 2.40 (m, 3H), 2.22 – 2.15 (m, 1H), 2.12 (s, 3H), 2.07 – 1.95 (m, 3H), 1.90 (dt, *J* = 13.4, 3.5 Hz, 1H), 1.77 – 1.58 (m, 11H), 1.54 – 1.43 (m, 3H), 1.20 (ddd, *J* = 19.8, 11.4, 4.9 Hz, 3H), 1.05 (s, 4H), 0.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.75, 166.21, 140.02, 131.72, 131.29, 122.32, 113.83, 63.80, 56.95, 50.00, 49.11, 44.11, 38.91, 38.41, 37.20, 36.77, 31.95, 31.90, 31.70, 28.06, 25.39, 24.60, 24.38, 22.92, 21.16, 19.50, 13.35. HRMS (ESI-TOF) for $C_{33}H_{45}NO_3$: calculated for $[M+Na]^+$ 526.3297, found 526.3293.

1-[4-(piperidin-1-yl)phenyl]ethan-1-one (3aq):



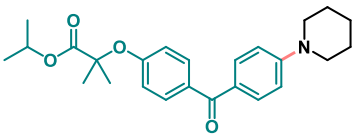
The title compound was prepared according to general procedure and isolated as a solid in 70% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.81 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.35 (t, *J* = 5.2 Hz, 4H), 2.50 (s, 3H), 1.67 (d, *J* = 7.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.54, 154.44, 130.58, 126.92, 113.41, 48.78, 26.18, 25.41, 24.43. The spectral data were consistent with those reported in the literature.[5]

cyclododecyl 4-(piperidin-1-yl)benzoate (3ar):



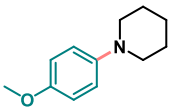
The title compound was prepared according to general procedure and isolated in 55% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 2H), 6.87 (s, 2H), 5.21 (ddd, J = 11.9, 7.2, 4.7 Hz, 1H), 3.32 (t, J = 5.2 Hz, 4H), 1.79 (dt, J = 13.5, 6.8 Hz, 2H), 1.73 – 1.56 (m, 8H), 1.51 – 1.30 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.27, 113.89, 72.14, 29.32, 25.41, 24.33, 24.11, 23.50, 23.31, 21.04. HRMS (ESI-TOF) for $C_{24}H_{37}NO_2$:calculated for $[M-H]^-$ 372.2902, found 372.2904.

isopropyl 2-methyl-2-{4-[4-(piperidin-1-yl)benzoyl]phenoxy}propanoate (3as):



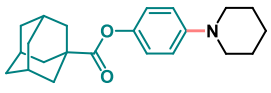
The title compound was prepared according to general procedure and isolated in 62% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 2H), 7.71 – 7.67 (m, 2H), 6.93 – 6.81 (m, 4H), 5.08 (hept, J = 6.3 Hz, 1H), 3.36 (t, J = 5.0 Hz, 4H), 1.64 (s, 12H), 1.20 (d, J = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.20, 173.48, 158.75, 132.46, 132.13, 131.58, 117.30, 113.43, 69.36, 48.89, 25.49, 25.44, 24.42, 21.65. HRMS (ESI-TOF) for $C_{24}H_{31}NO_4$: calculated for $[M+Na]^+$ 432.2151, found 432.2152.

1-(4-methoxyphenyl)piperidine (3at):



The title compound was prepared according to general procedure and isolated in 63% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 51%).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.5 Hz, 2H), 6.86 – 6.81 (m, 2H), 3.77 (s, 3H), 3.07 – 2.99 (m, 4H), 1.75 (p, J = 5.6 Hz, 4H), 1.56 (q, J = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 119.08, 114.47, 55.69, 52.70, 26.11, 24.19. The spectral data were consistent with those reported in the literature.[10]

4-(piperidin-1-yl)phenyl (3r,5r,7r)-adamantane-1-carboxylate (3au):



The title compound was prepared according to general procedure and isolated in 58% yield after column chromatography using a mixture of EtOAc/Hexane as eluent (Ball milling yield 56%).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, J = 5.3, 2.0 Hz, 4H), 3.10 (t, J = 5.5 Hz, 4H), 2.09 – 2.01 (m, 9H), 1.78 – 1.67 (m, 10H), 1.57 (d, J = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.76, 150.23, 143.94, 121.85, 117.58, 51.42, 41.06, 38.93, 36.63, 28.08, 26.01, 24.31. HRMS (ESI-TOF) for $C_{22}H_{29}NO_2$:calculated for $[M-H]^-$ 340.2276, found 340.2276.

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8. References

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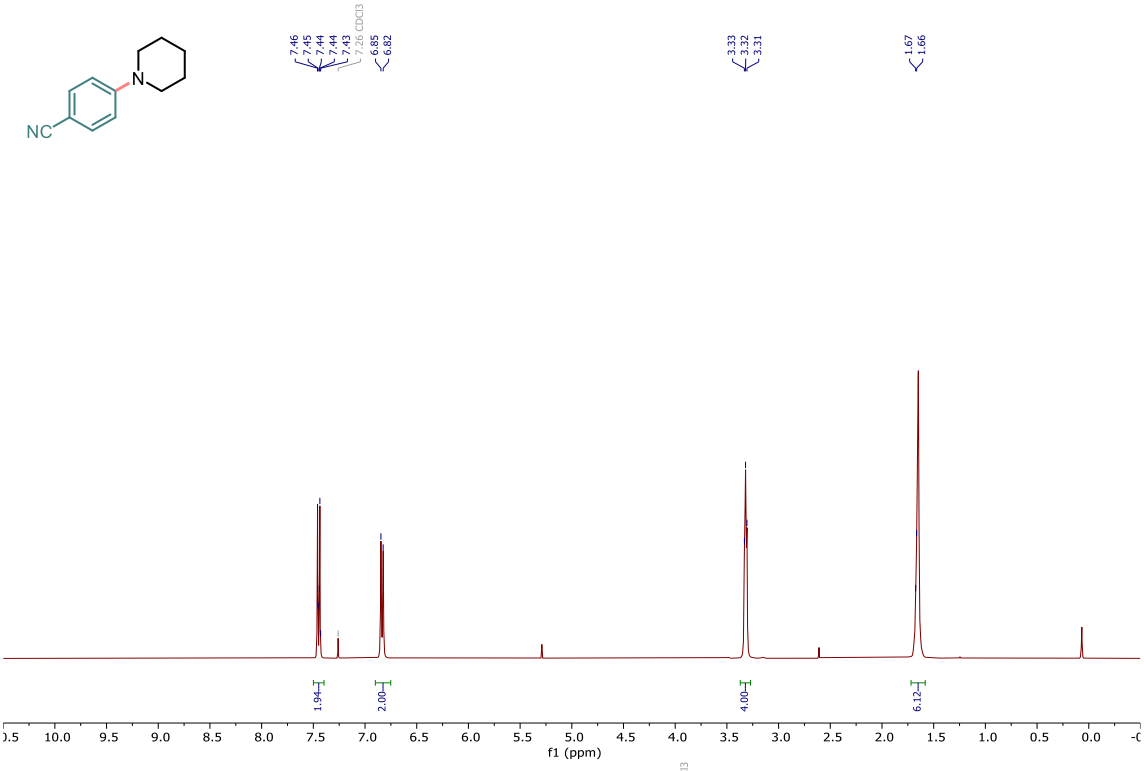
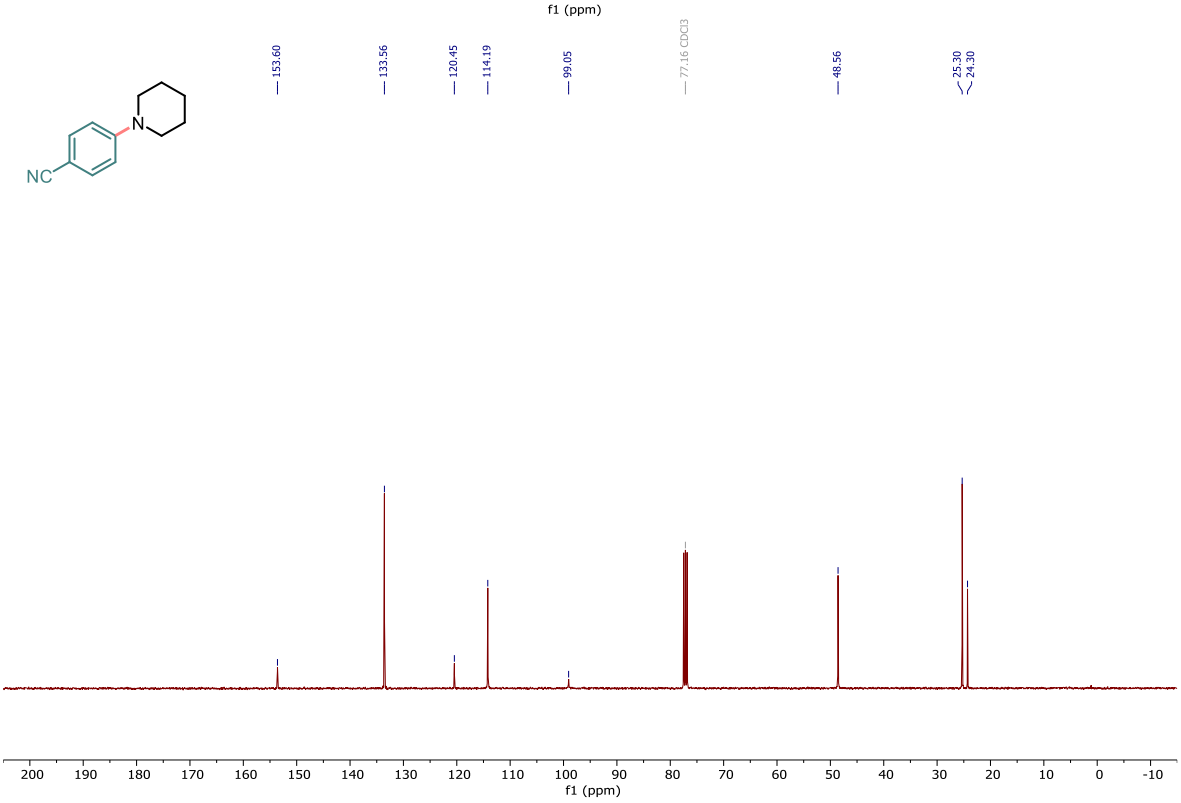
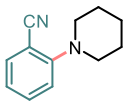
9. Copies of the ^{1}H-, ^{13}C-, and ^{19}F-NMR Spectra for Isolated Products

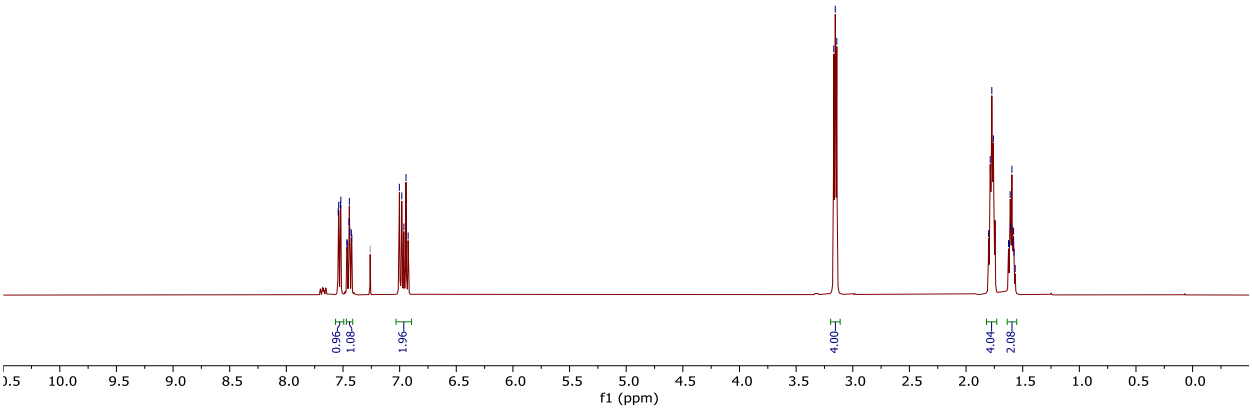
4-(piperidin-1-yl)benzonitrile (3a):

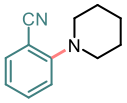


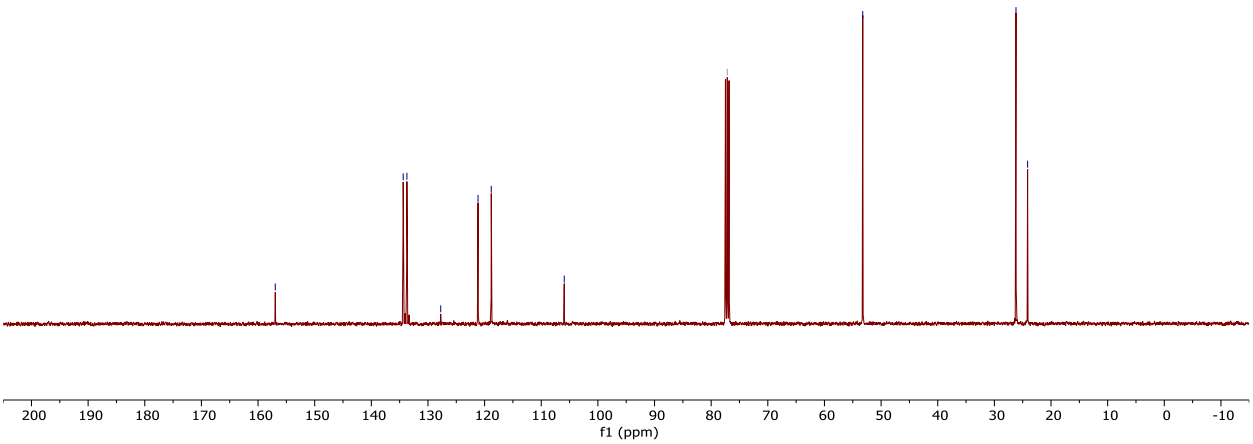


2-(piperidin-1-yl)benzonitrile (3b):

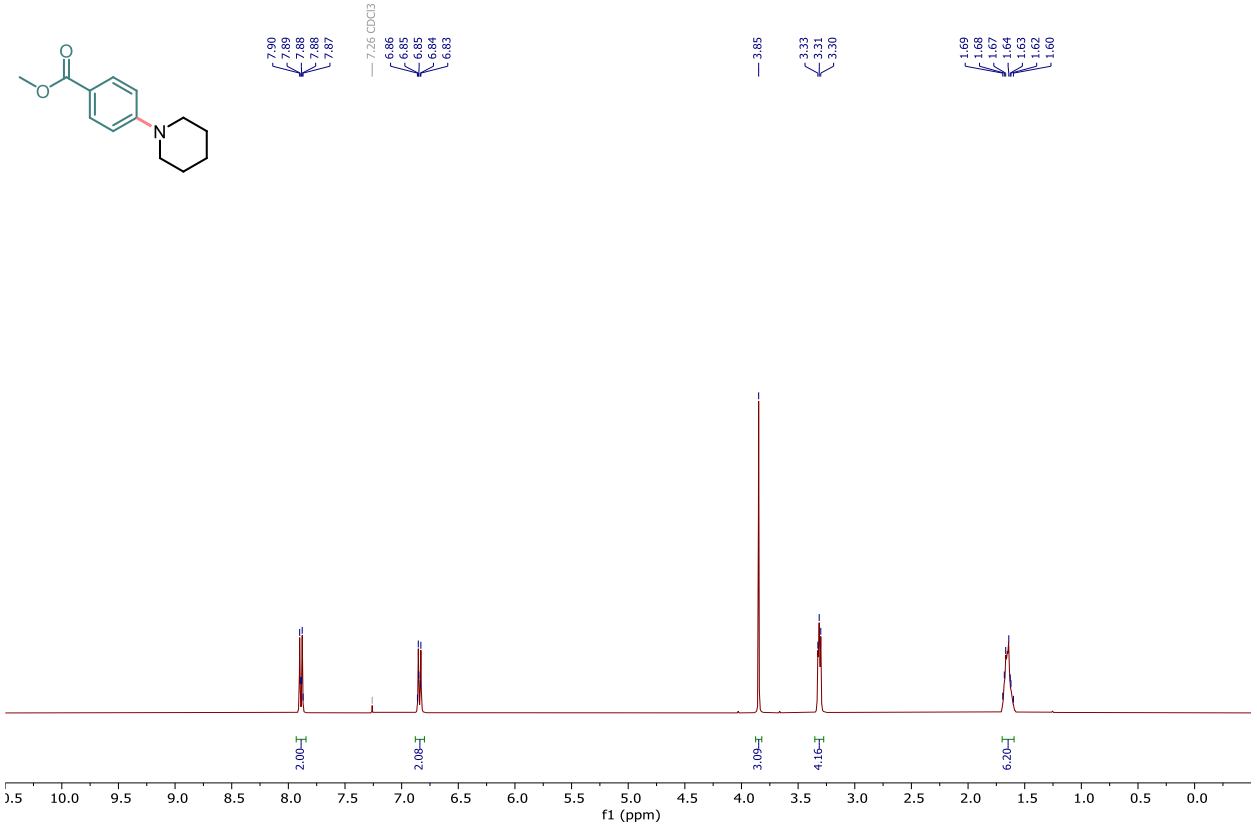


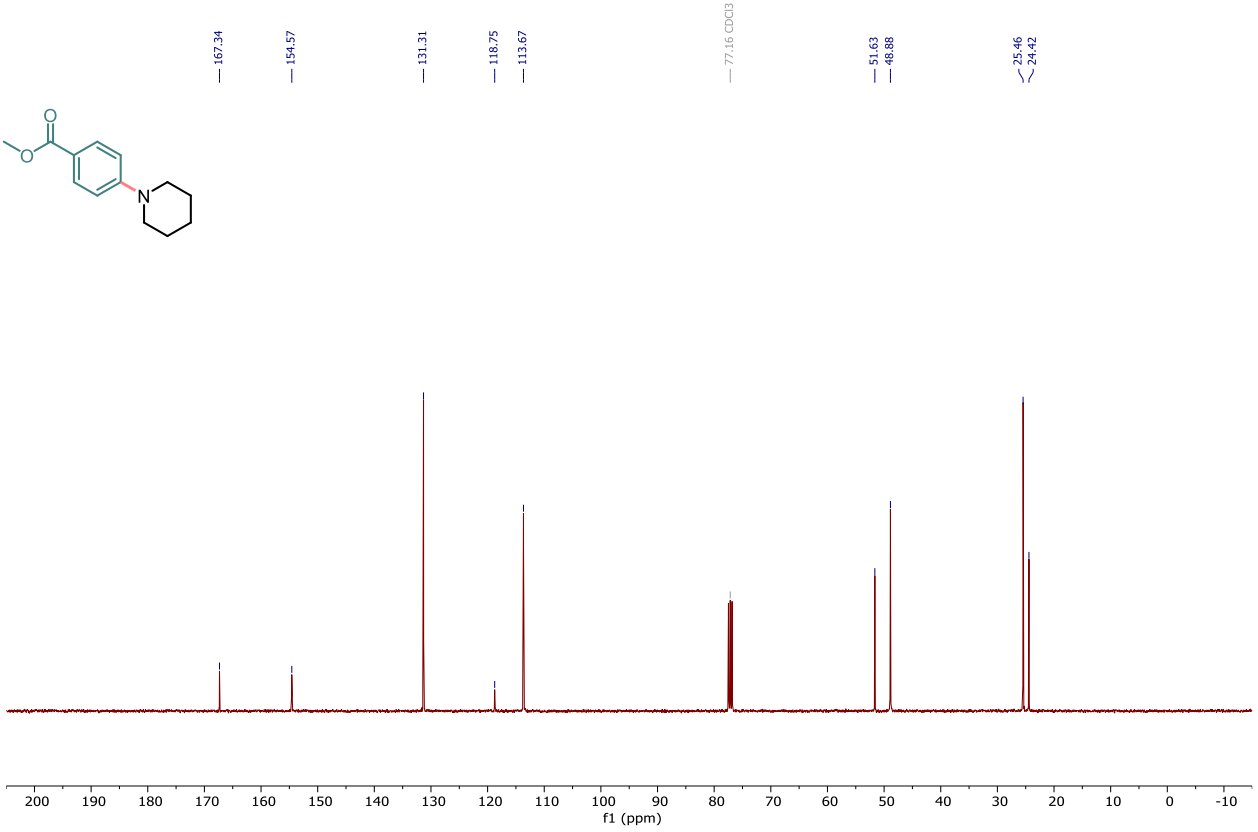




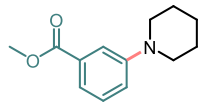


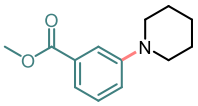
Methyl 4-(piperidin-1-yl)benzoate (3c):



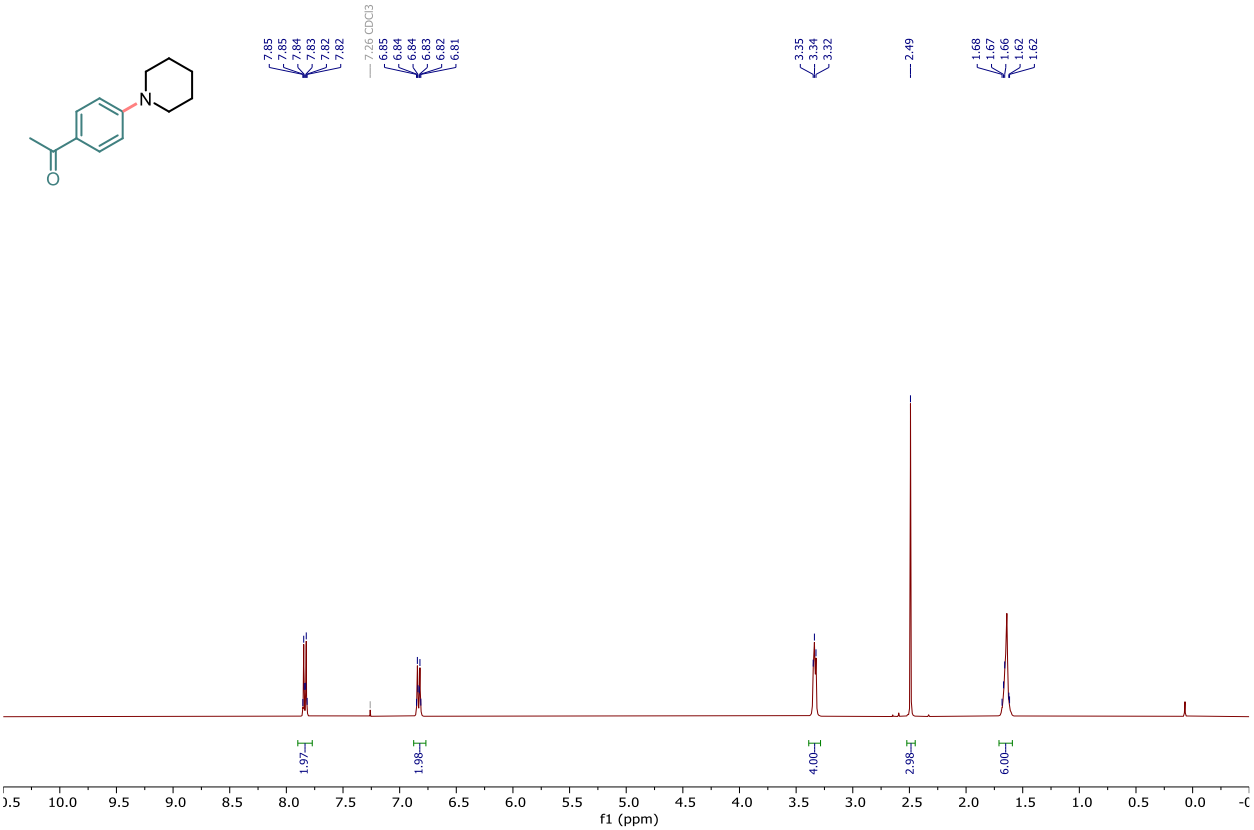


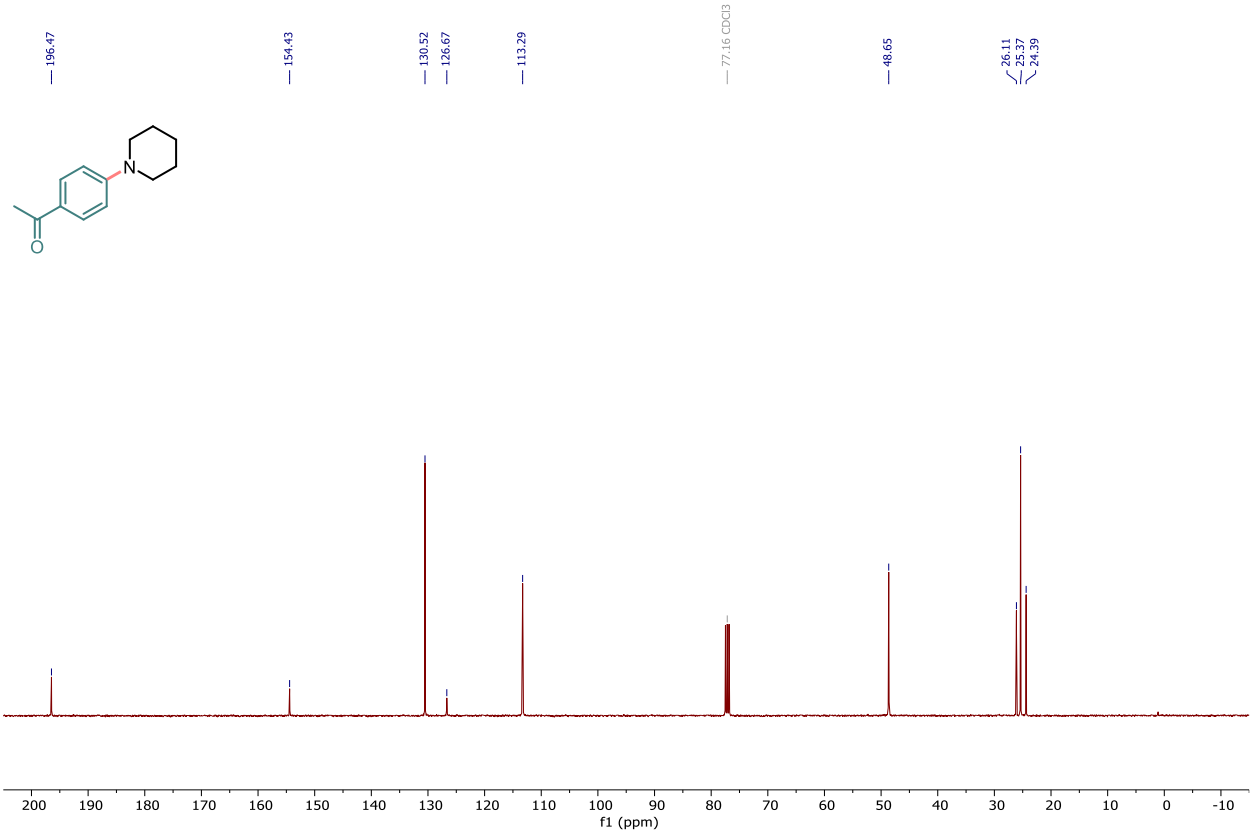
Methyl 3-(piperidin-1-yl)benzoate (3d):



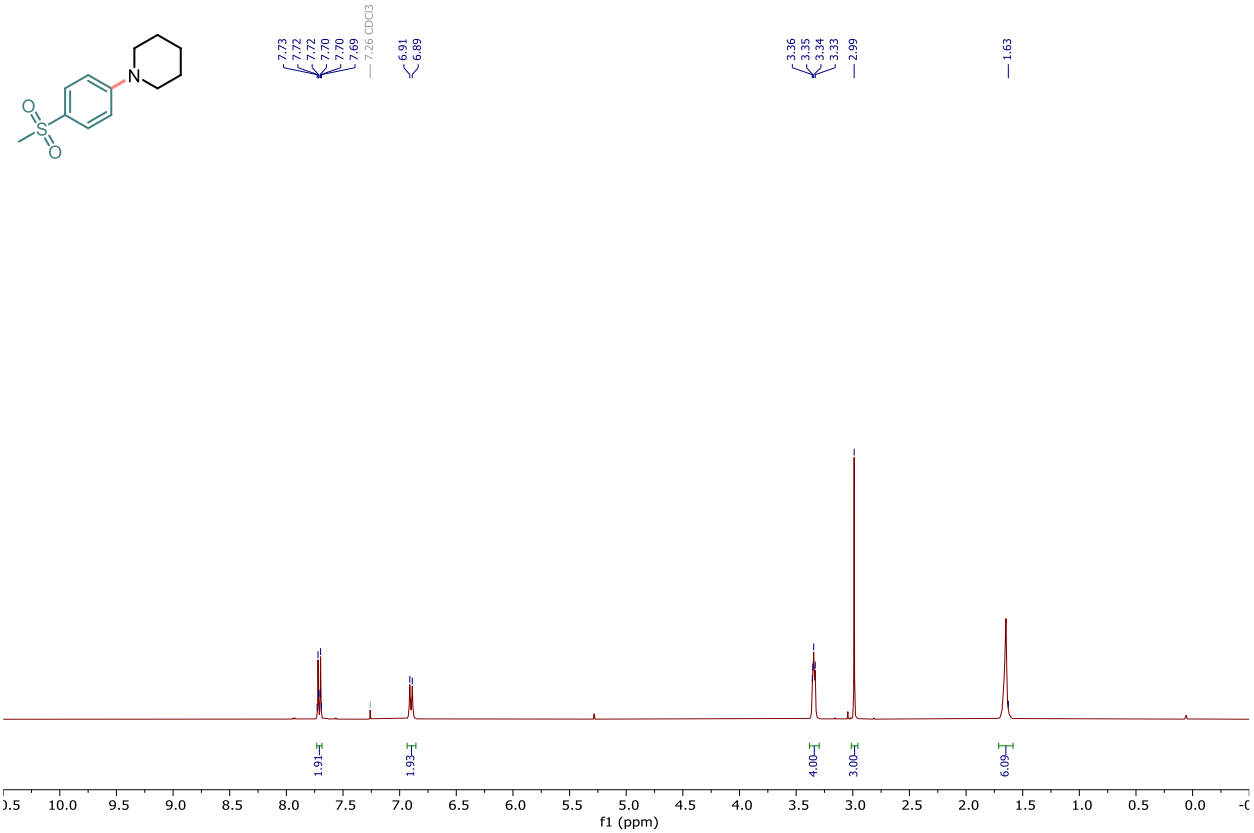


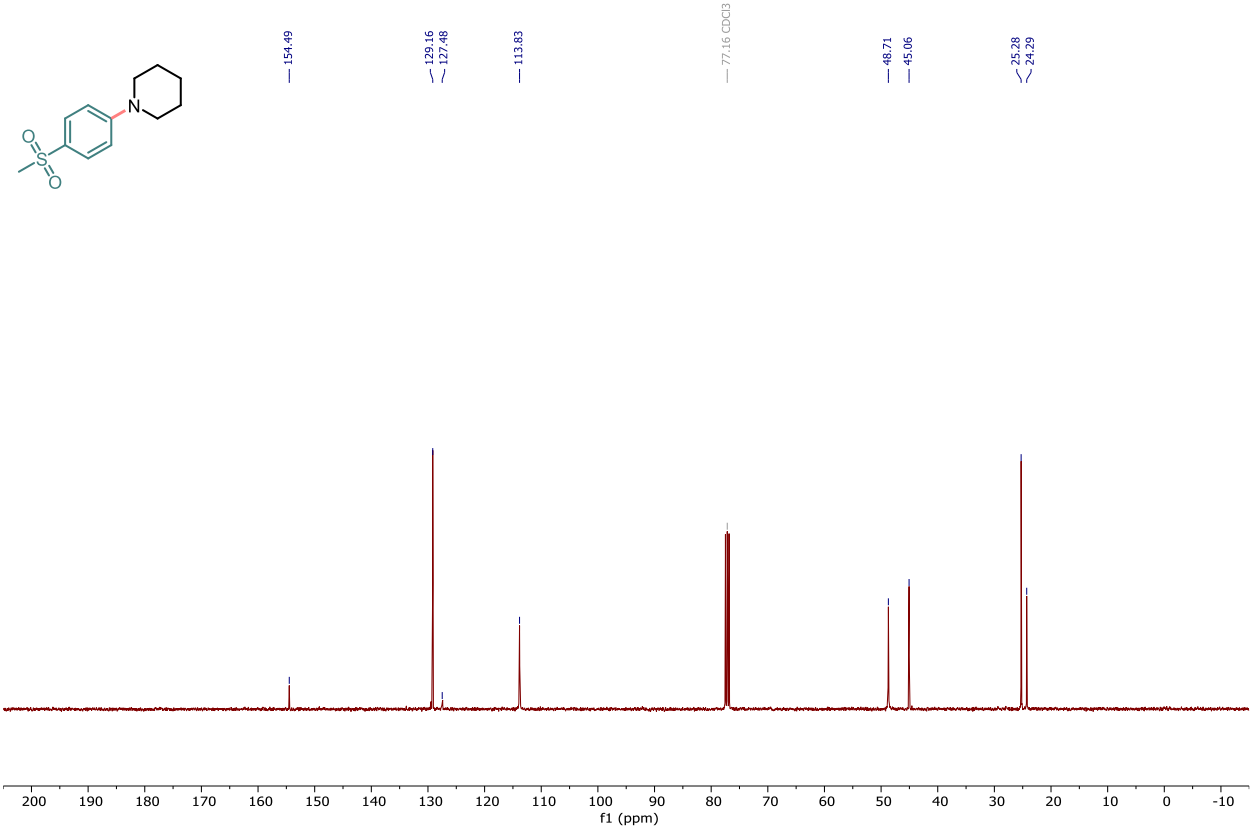
1-[4-(piperidin-1-yl)phenyl]ethan-1-one (3e):



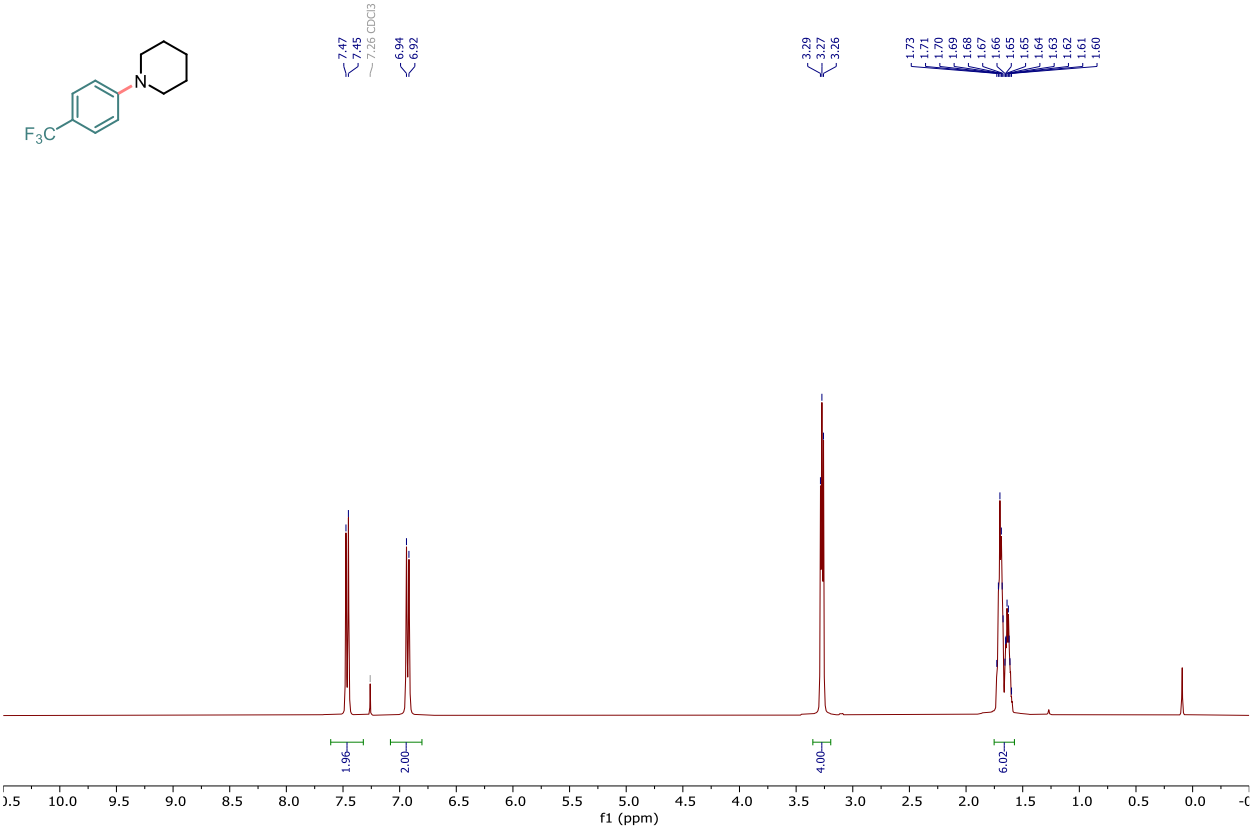


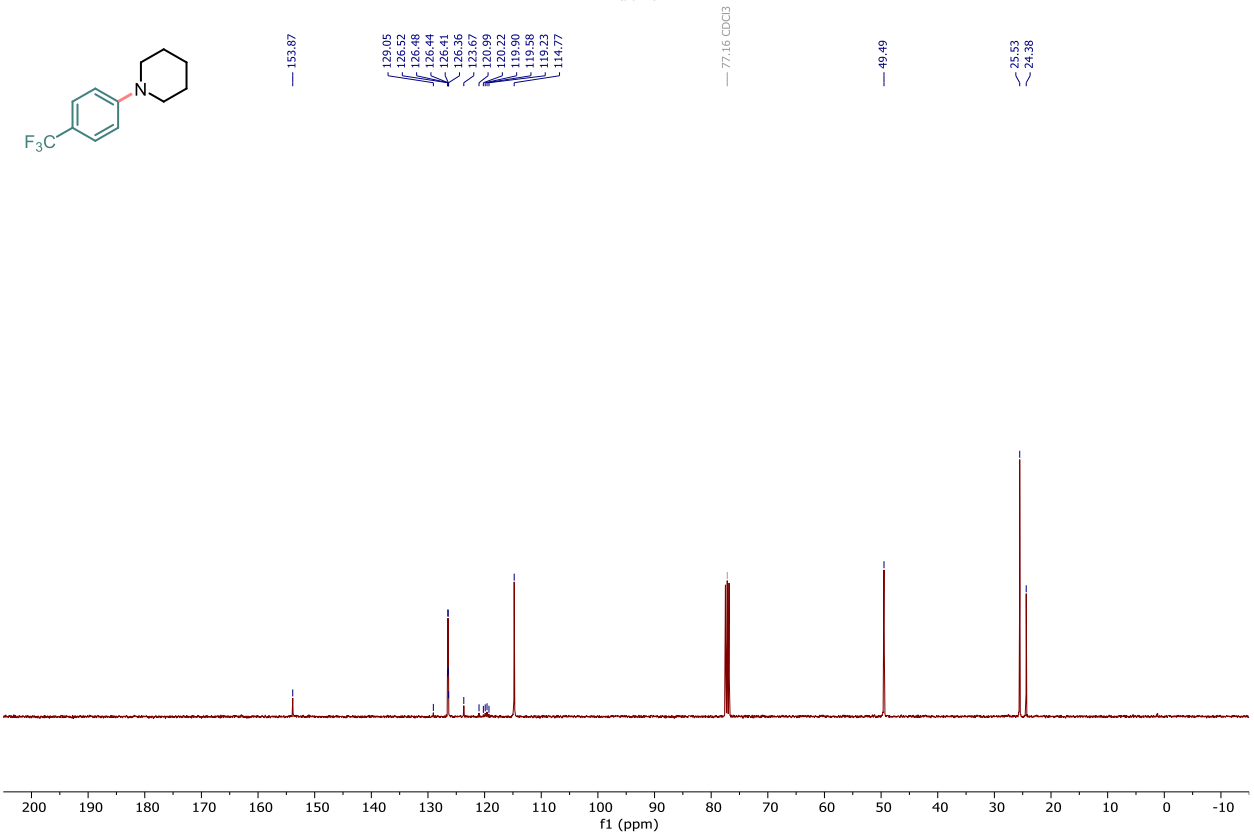
1-[4-(methylsulfonyl)phenyl]piperidine (3f):

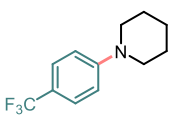




1-[4-(trifluoromethyl)phenyl]piperidine (3g):

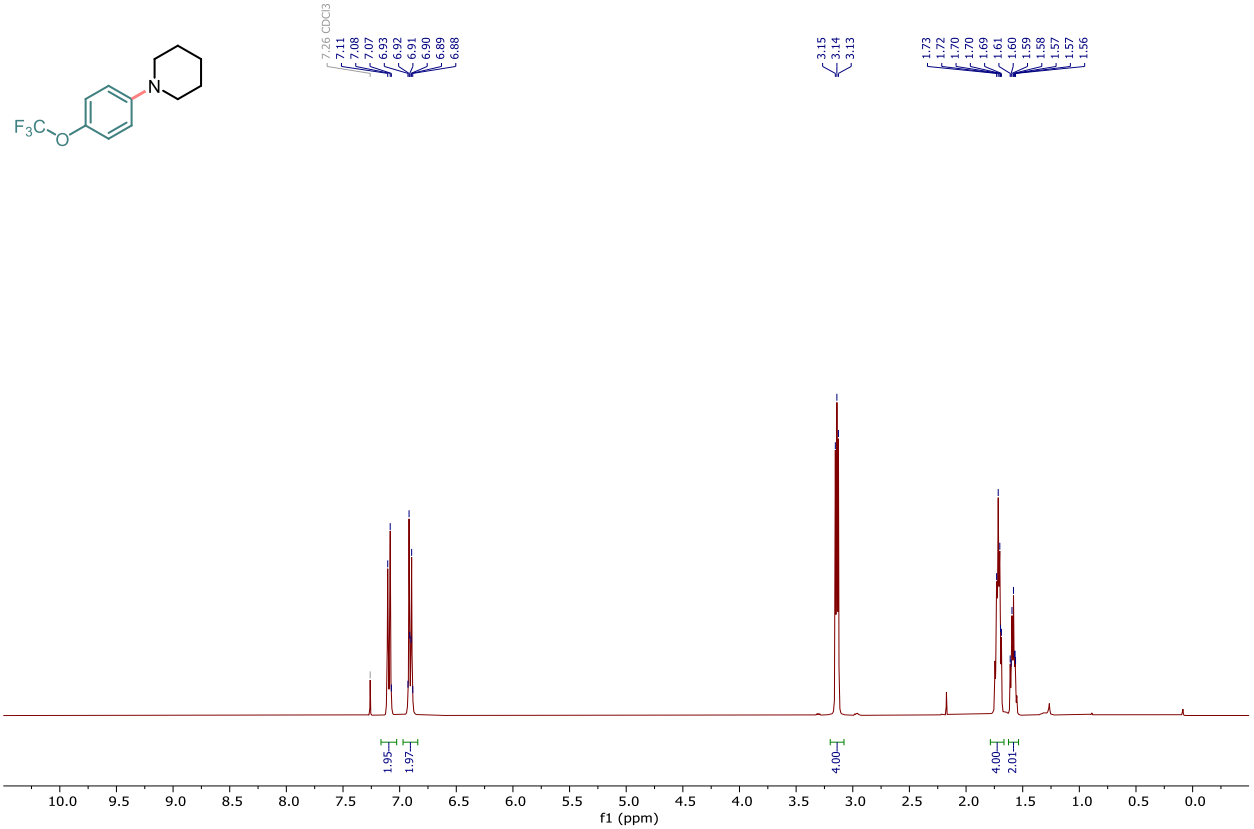


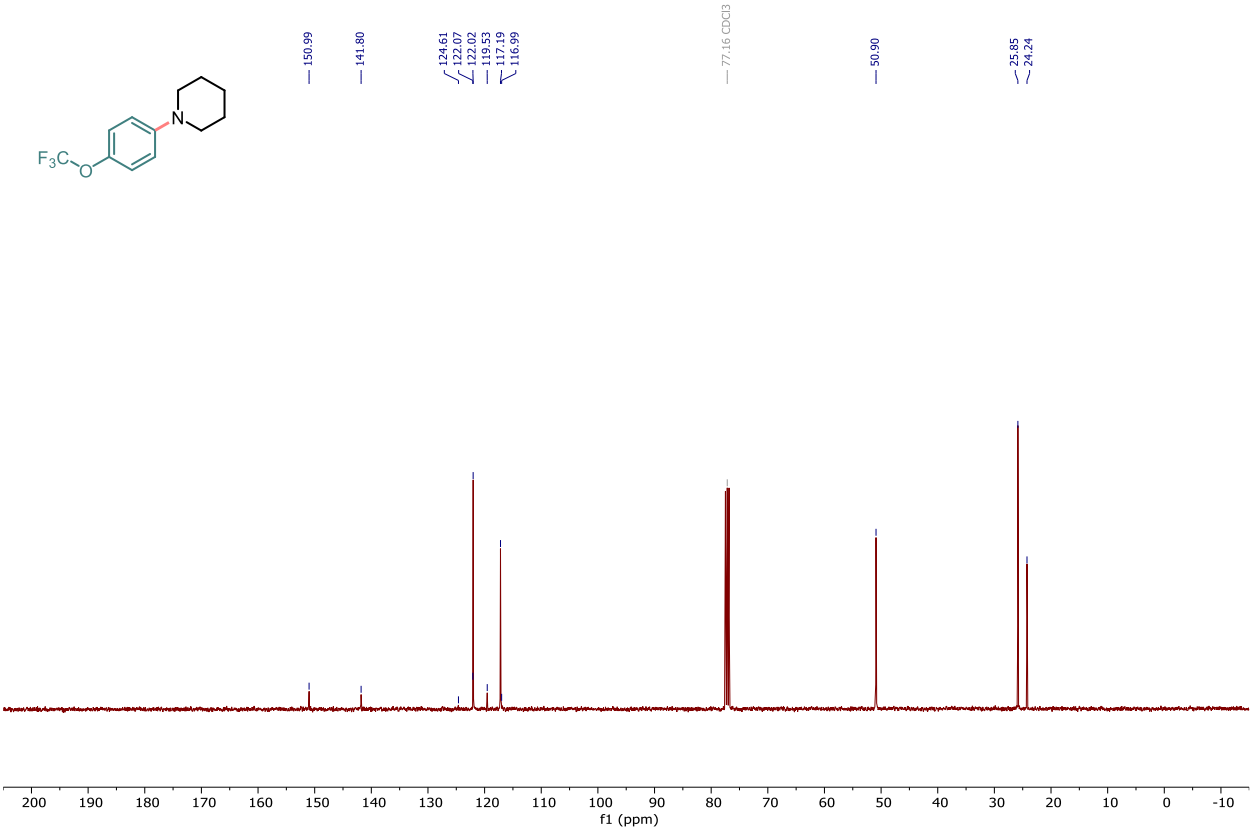


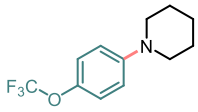

N
F3C

-61.20
-59.2 -59.4 -59.6 -59.8 -60.0 -60.2 -60.4 -60.6 -60.8 -61.0 -61.2 -61.4 -61.6 -61.8 -62.0 -62.2 -62.4 -62.6 -62.8 -63.0 -63.2 -63.4 -63.6 -63.8 -64.0 -64.2 -64.4 -64.6 -64.8
f1 (ppm)

1-[4-(trifluoromethoxy)phenyl]piperidine (3h):

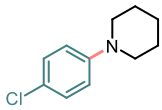


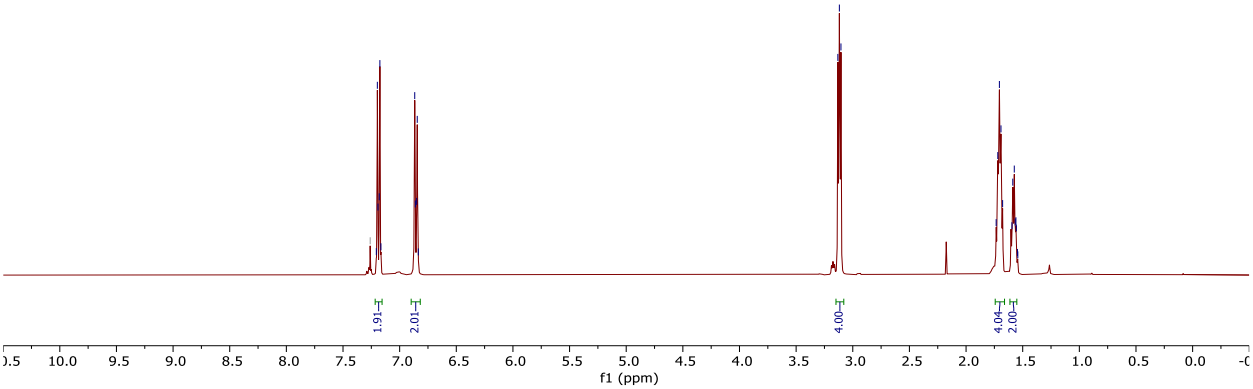


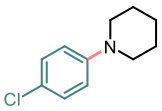

F3C
O
N

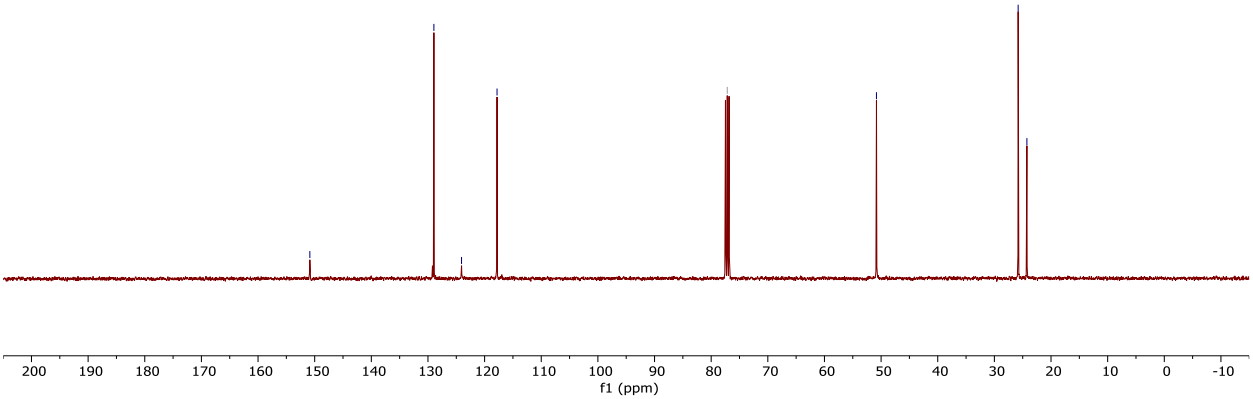
-58.22
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
f1 (ppm)

1-(4-chlorophenyl)piperidine (3i):

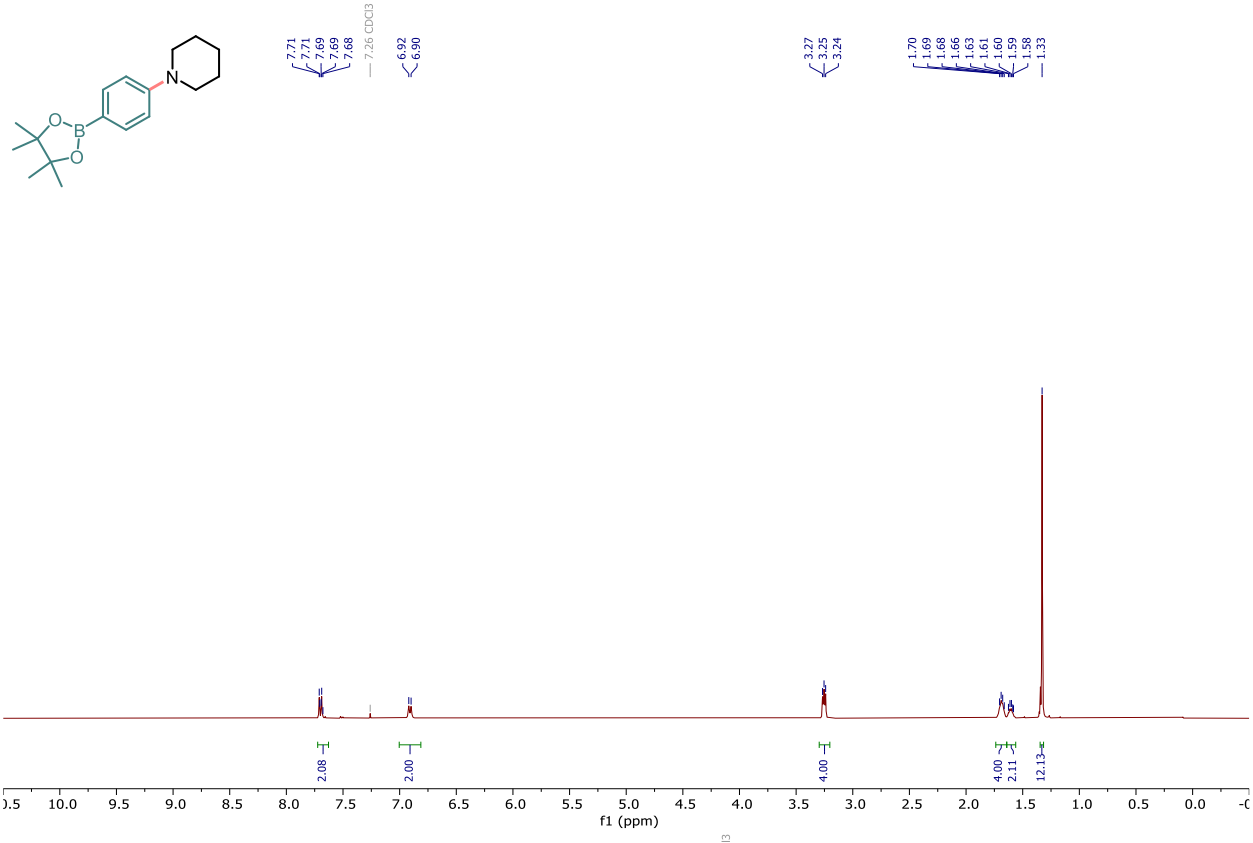


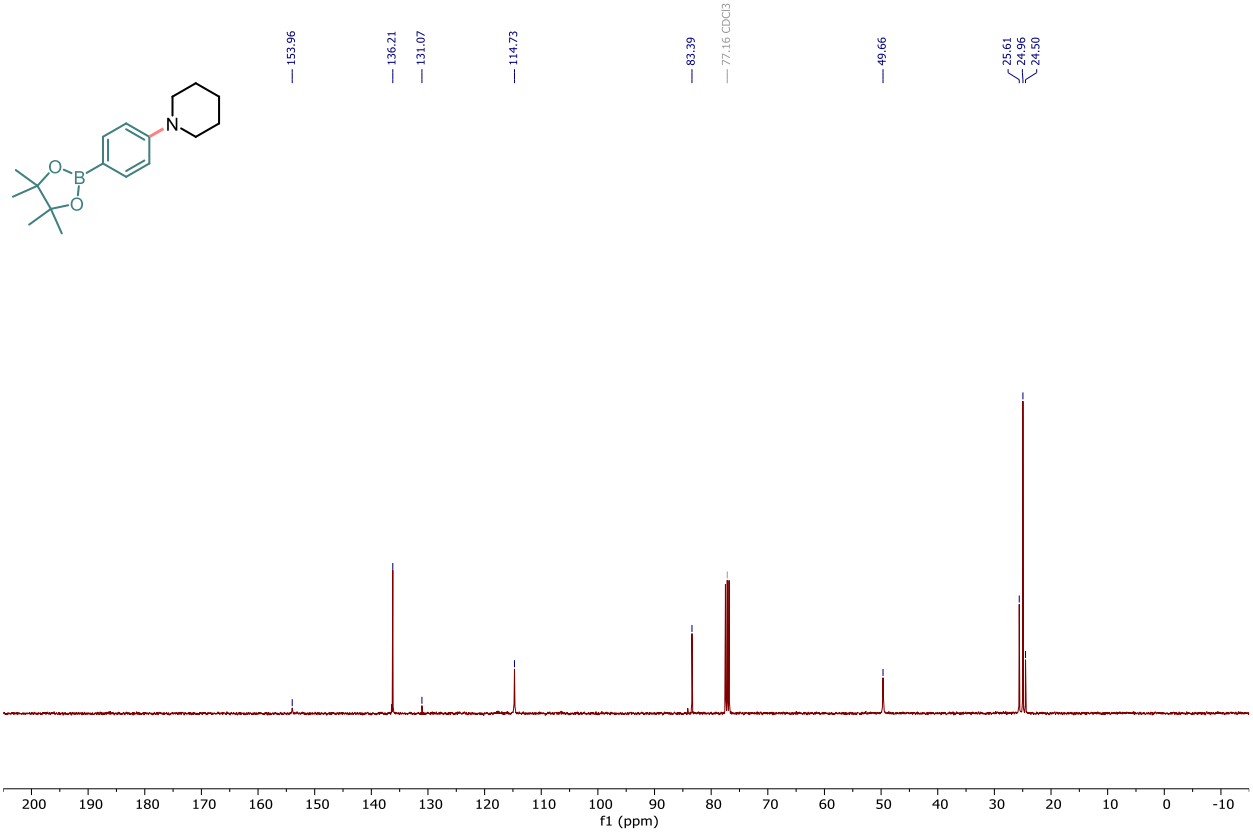




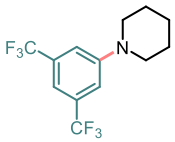


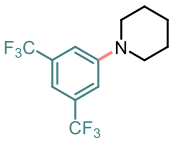
1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (3j):

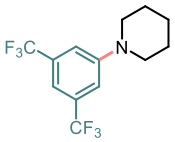




1-[3,5-bis(trifluoromethyl)phenyl]piperidine (3k):

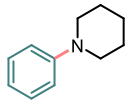


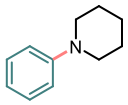



F3C
N
CF3

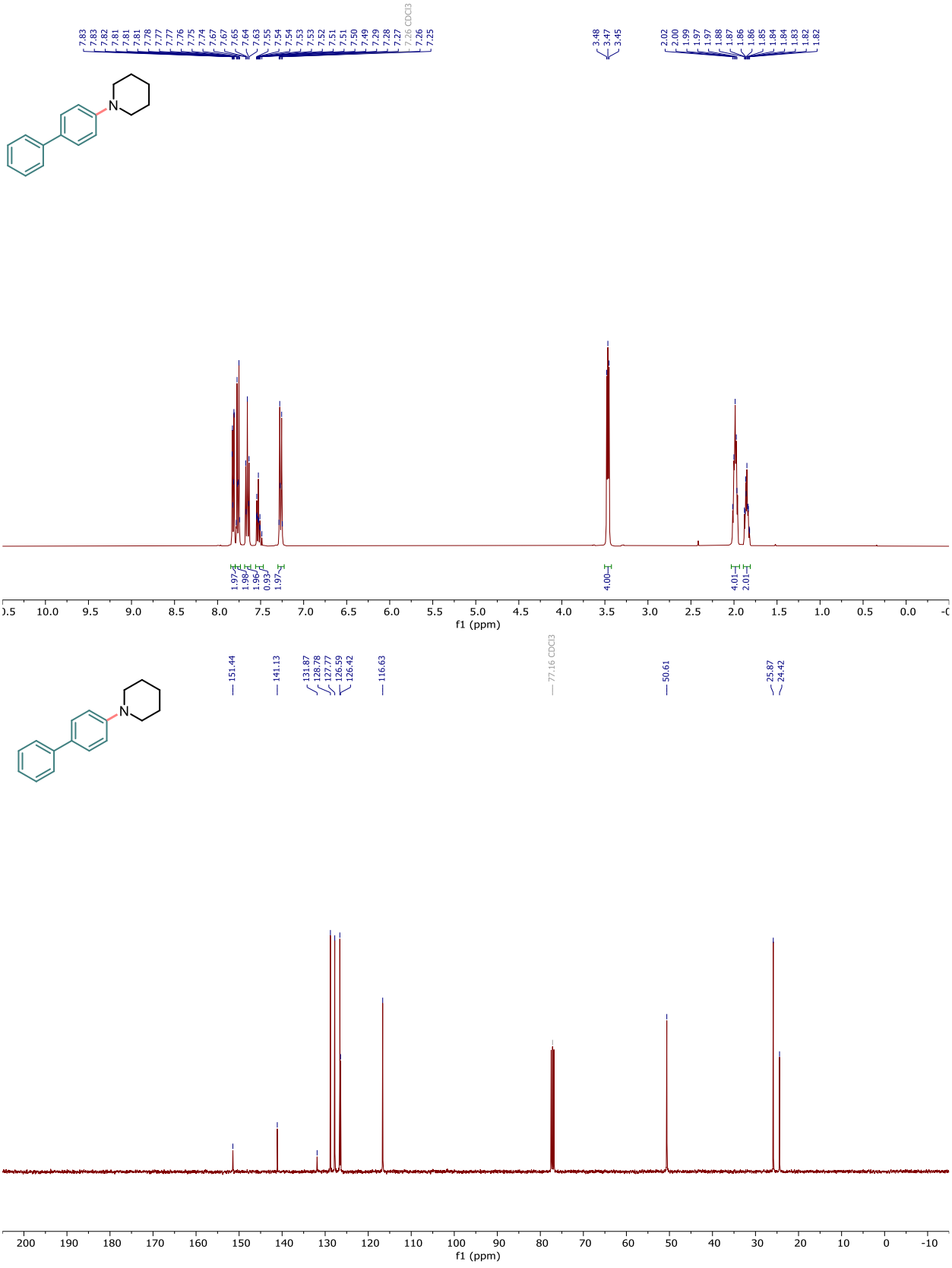
-63.06
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
f1 (ppm)

1-phenylpiperidine (3l):

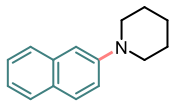


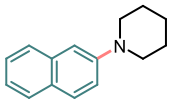


1-([1,1'-biphenyl]-4-yl)piperidine (3m):

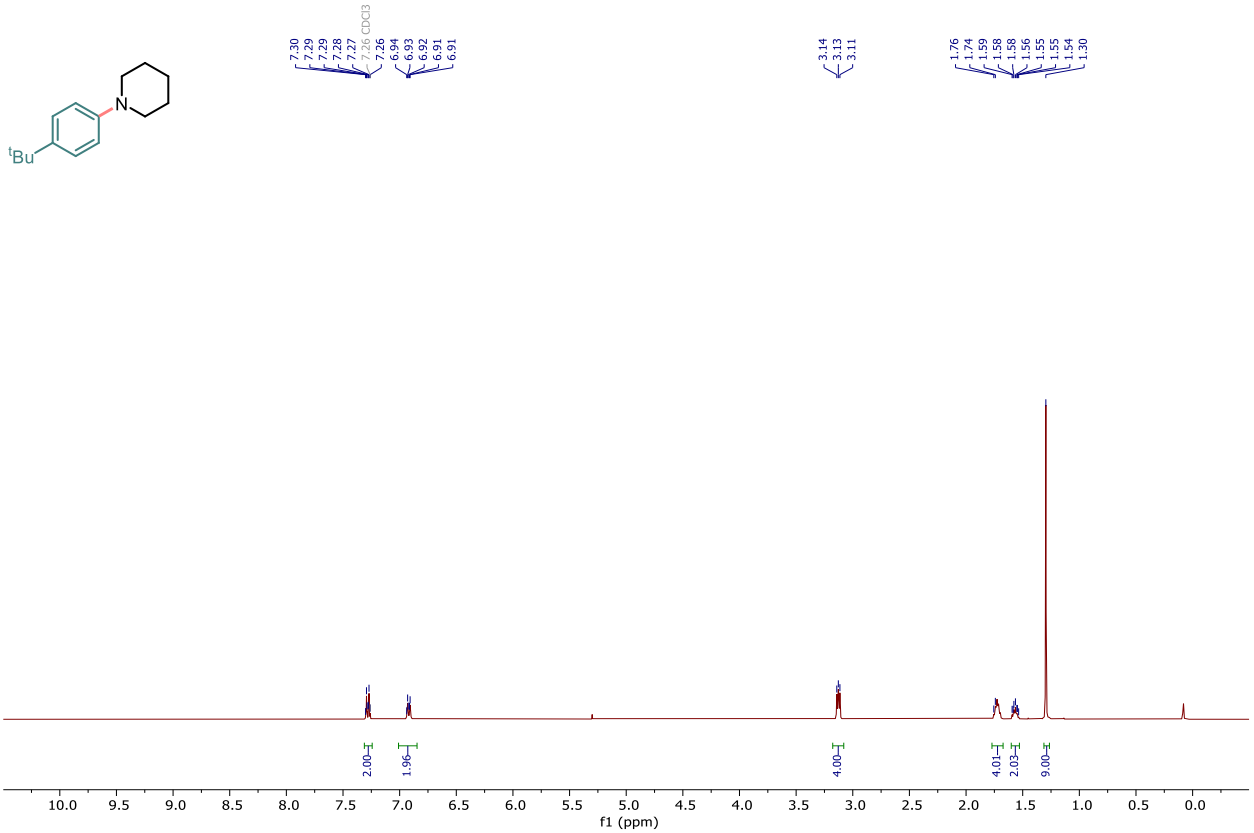


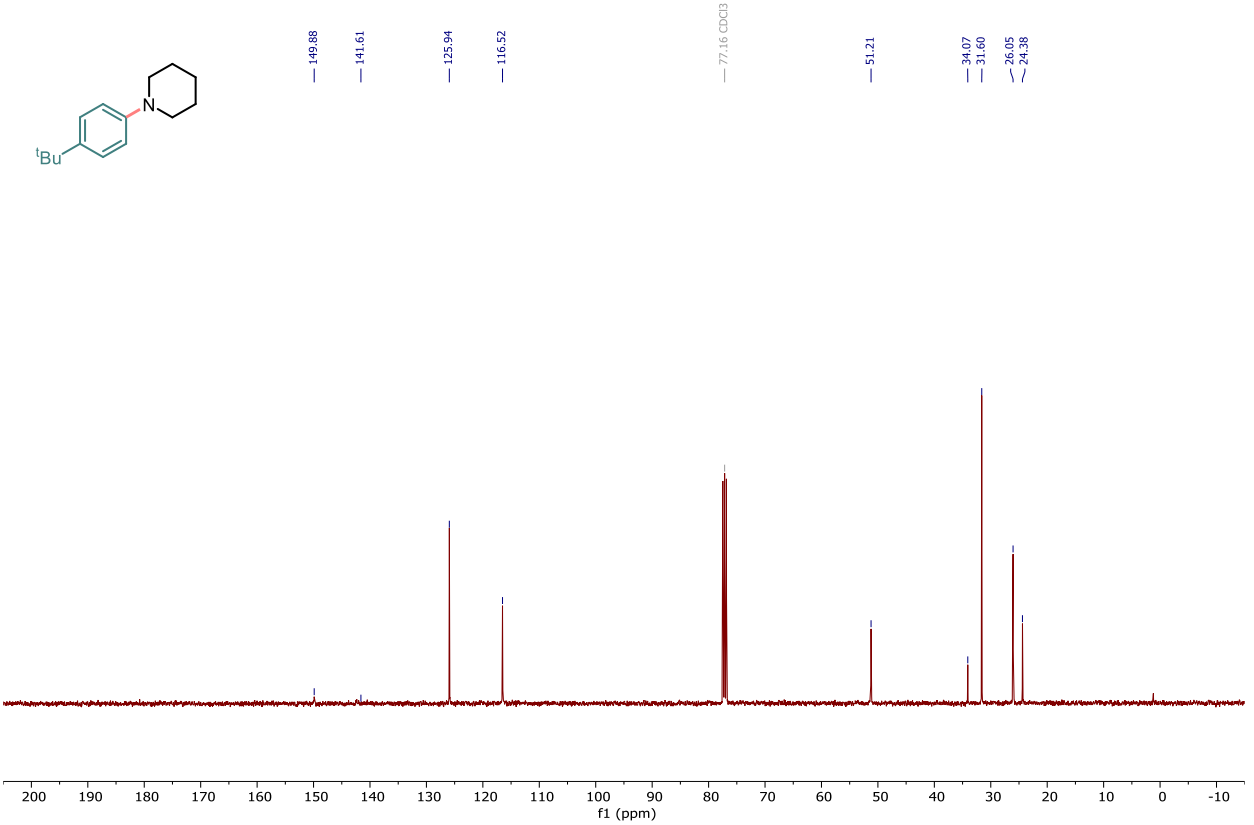
1-(naphthalen-2-yl)piperidine (3n):



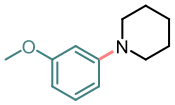


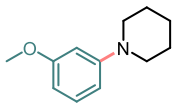
1-[4-(tert-butyl)phenyl]piperidine (3o):



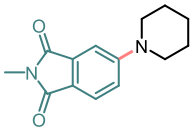


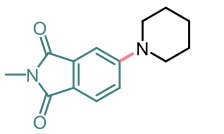
1-(3-methoxyphenyl)piperidine (3p):



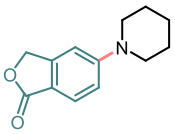


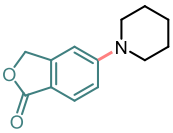
2-methyl-5-(piperidin-1-yl)isoindoline-1,3-dione (3q):



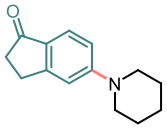


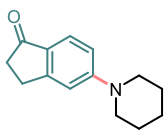
5-(piperidin-1-yl)isobenzofuran-1(3H)-one (3r):



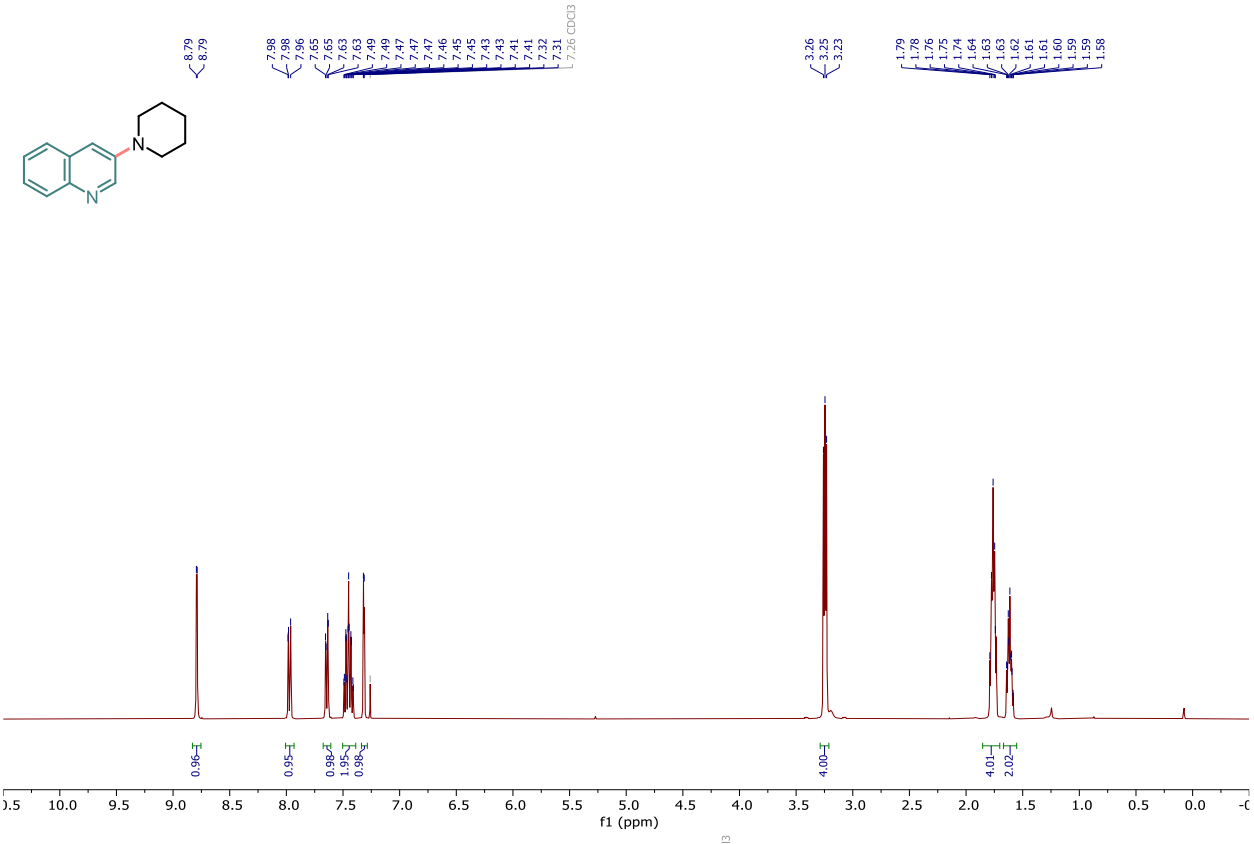


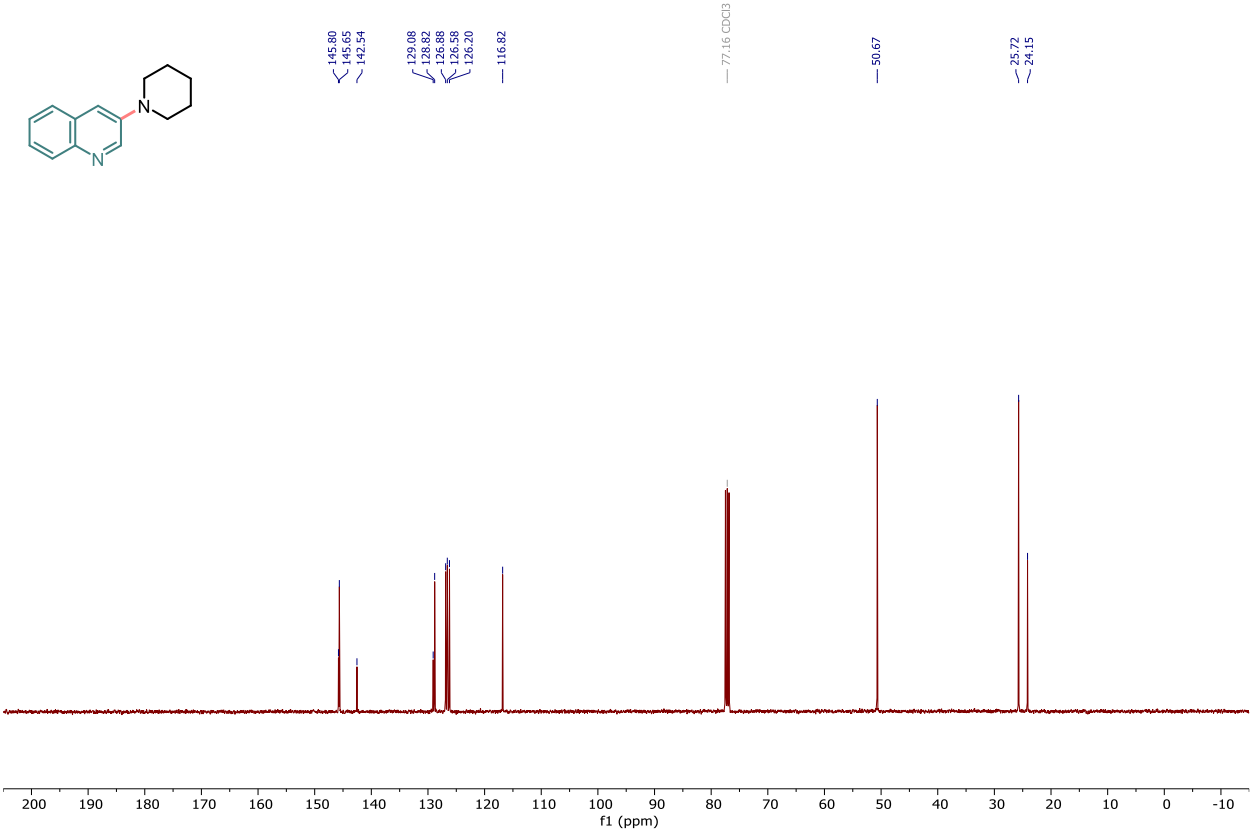
5-(piperidin-1-yl)-2,3-dihydro-1H-inden-1-one (3s):



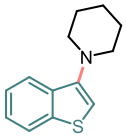


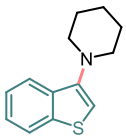
3-(piperidin-1-yl)quinolone (3t):



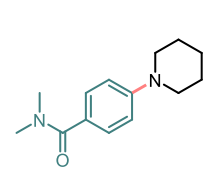


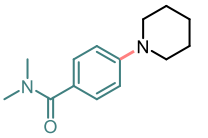
1-(benzo[b]thiophen-3-yl)piperidine (3u):



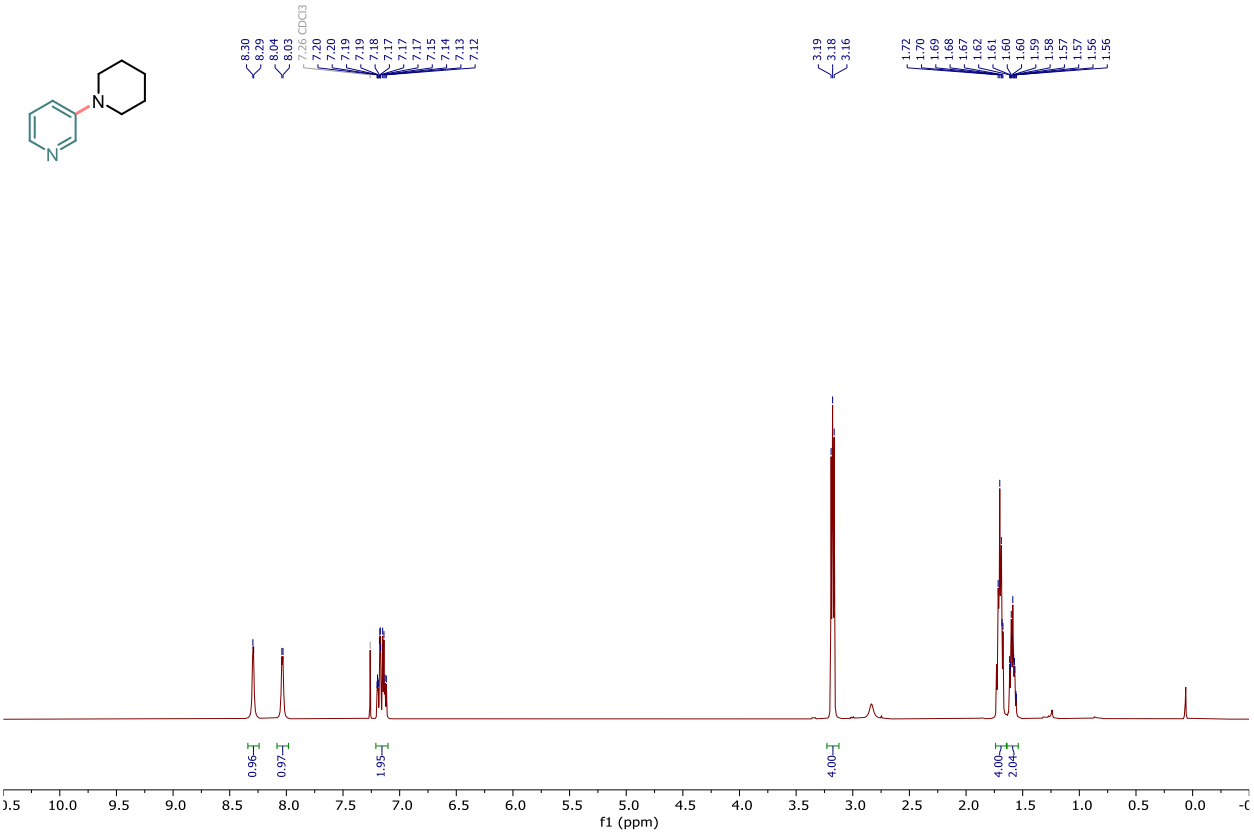


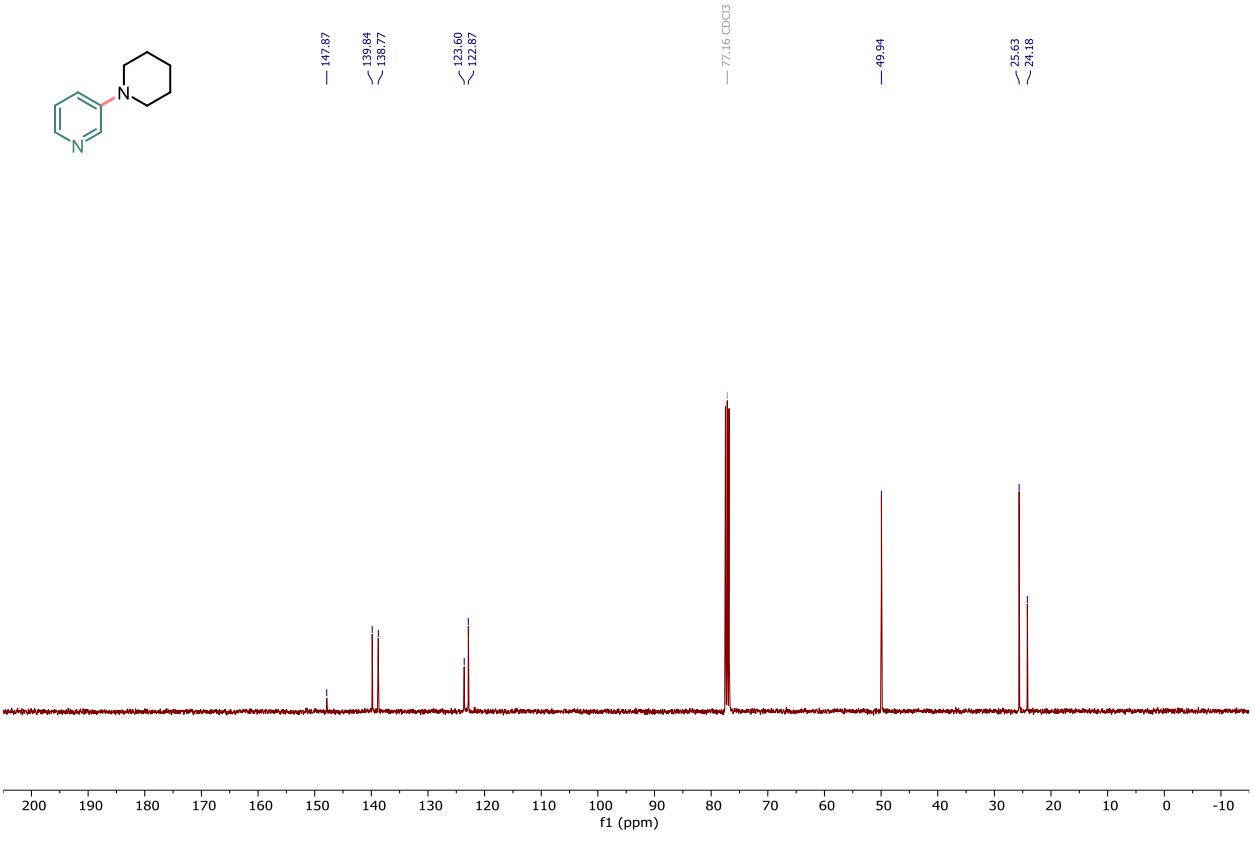
N,N-dimethyl-4-(piperidin-1-yl)benzamide (3v):



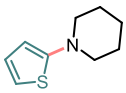


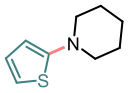
3-(piperidin-1-yl)pyridine (3w):



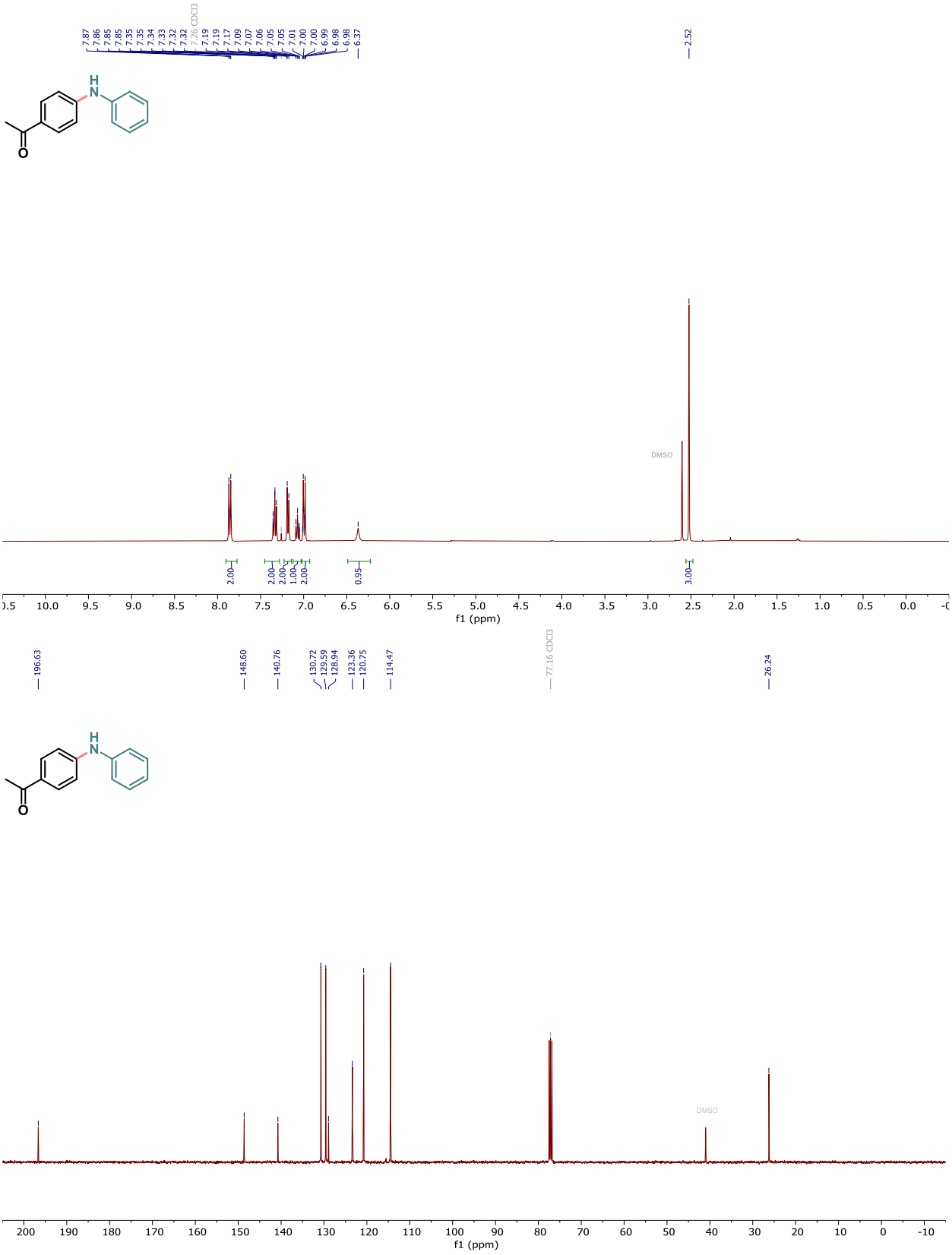


1-(thiophen-2-yl)piperidine (3x):

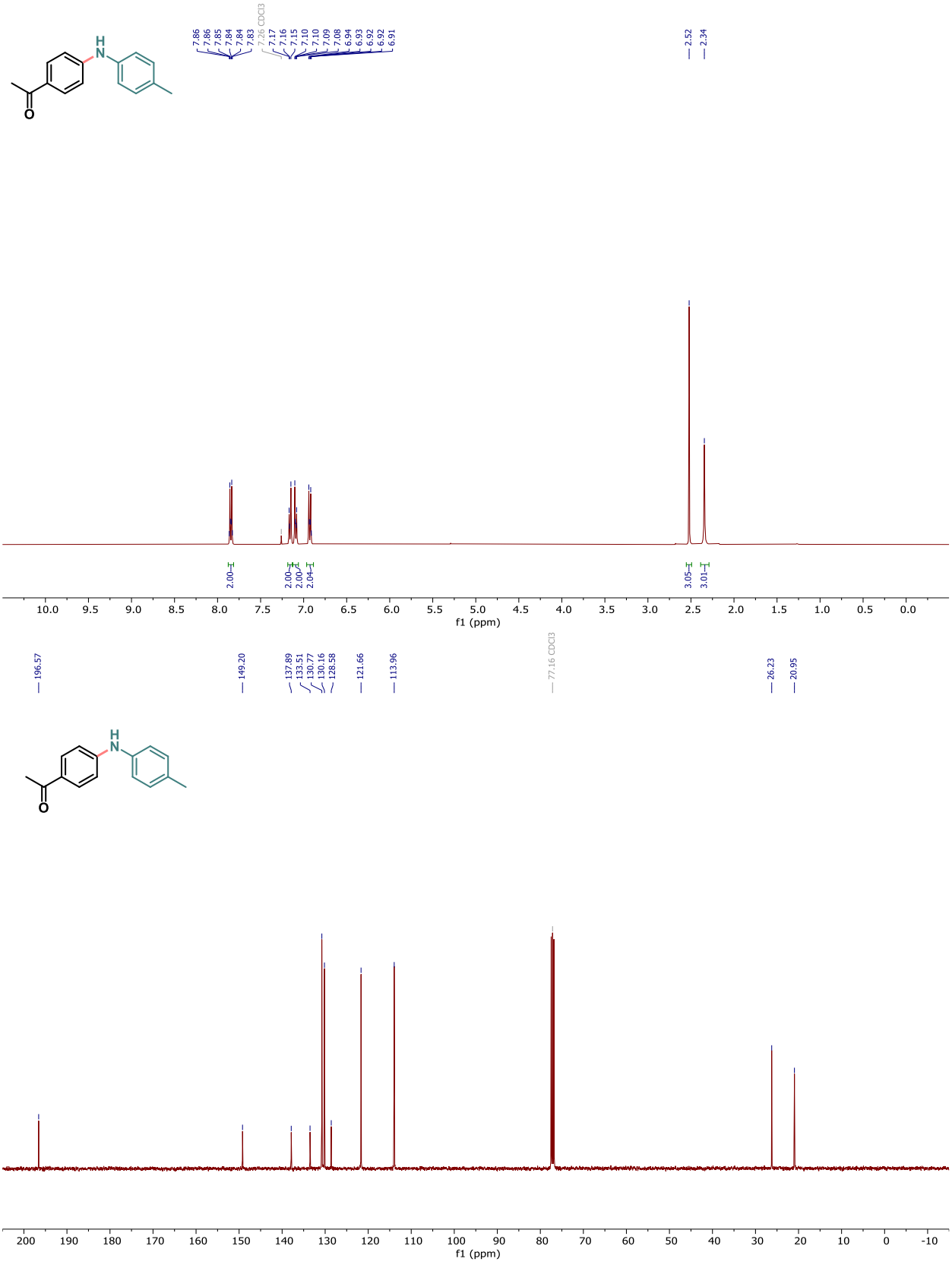




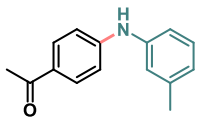
1-[4-(phenylamino)phenyl]ethan-1-one (3y):

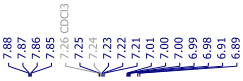


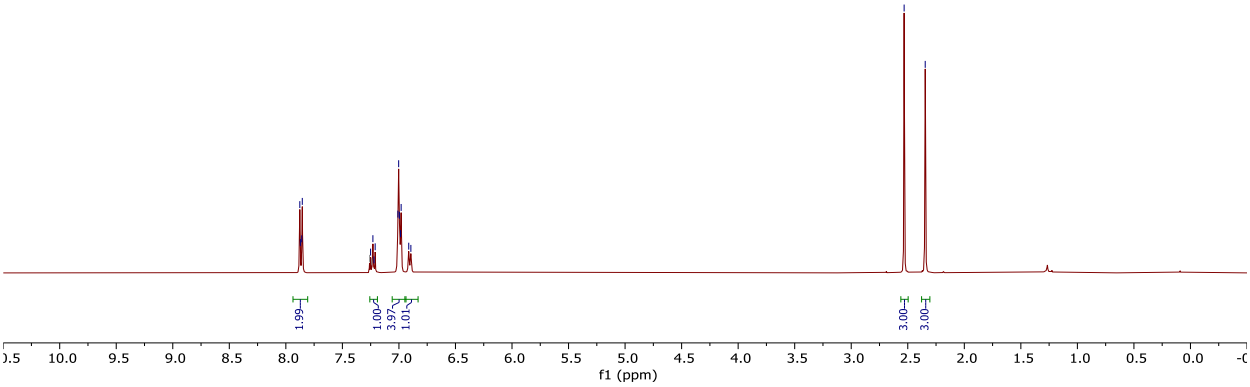
1-[4-(p-tolylamino)phenyl]ethan-1-one (3z):

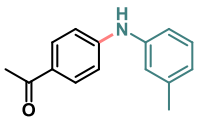


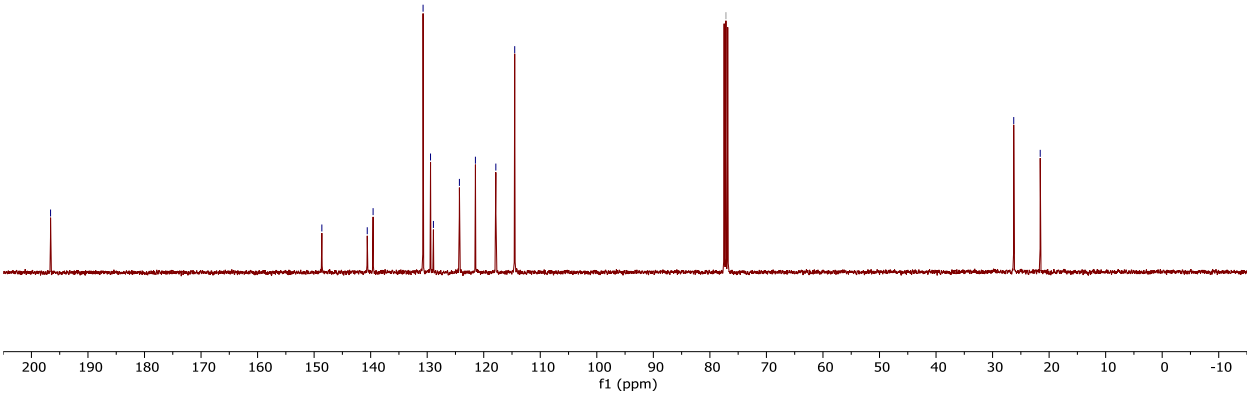
1-[4-(m-tolylamino)phenyl]ethan-1-one (3aa):



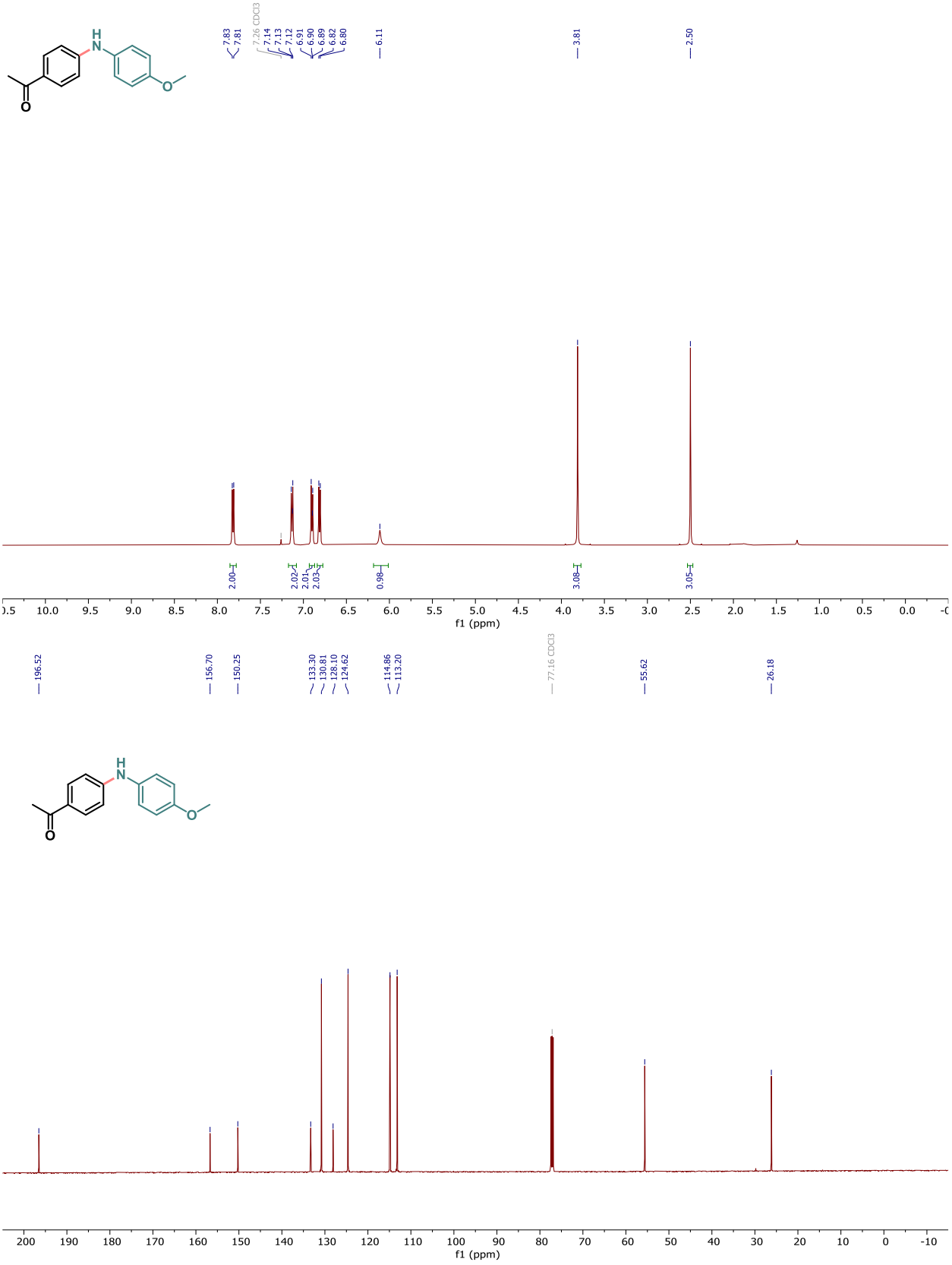




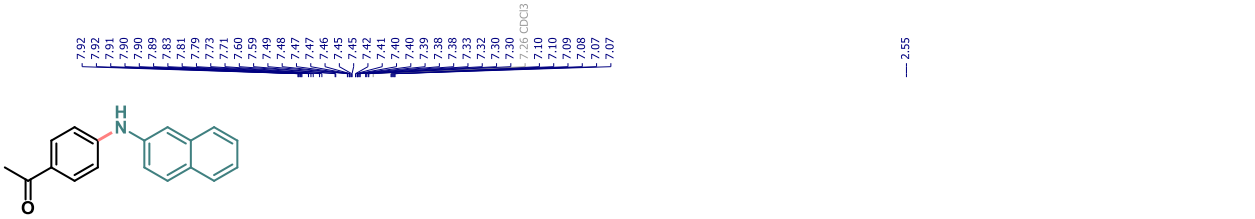


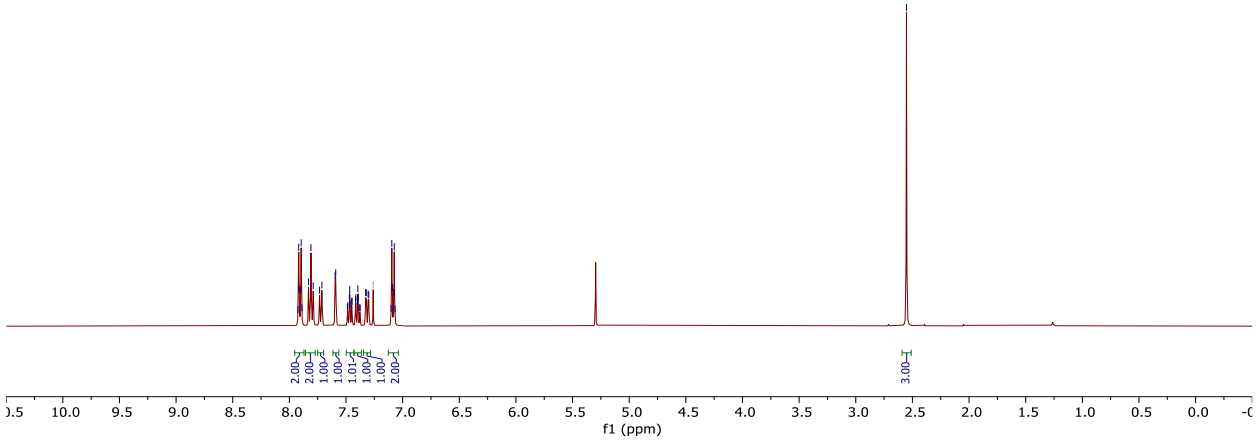


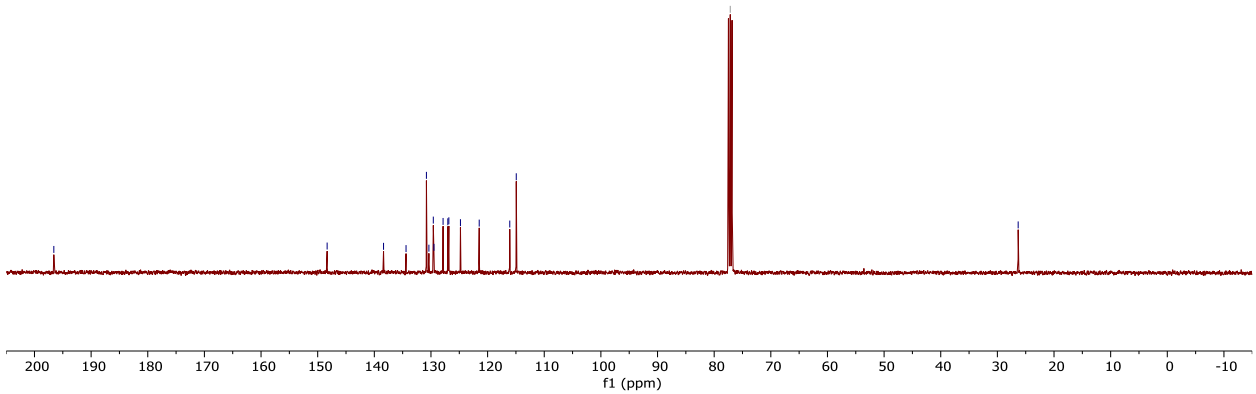
1-{4-[(4-methoxyphenyl)amino]phenyl}ethan-1-one (3ab):



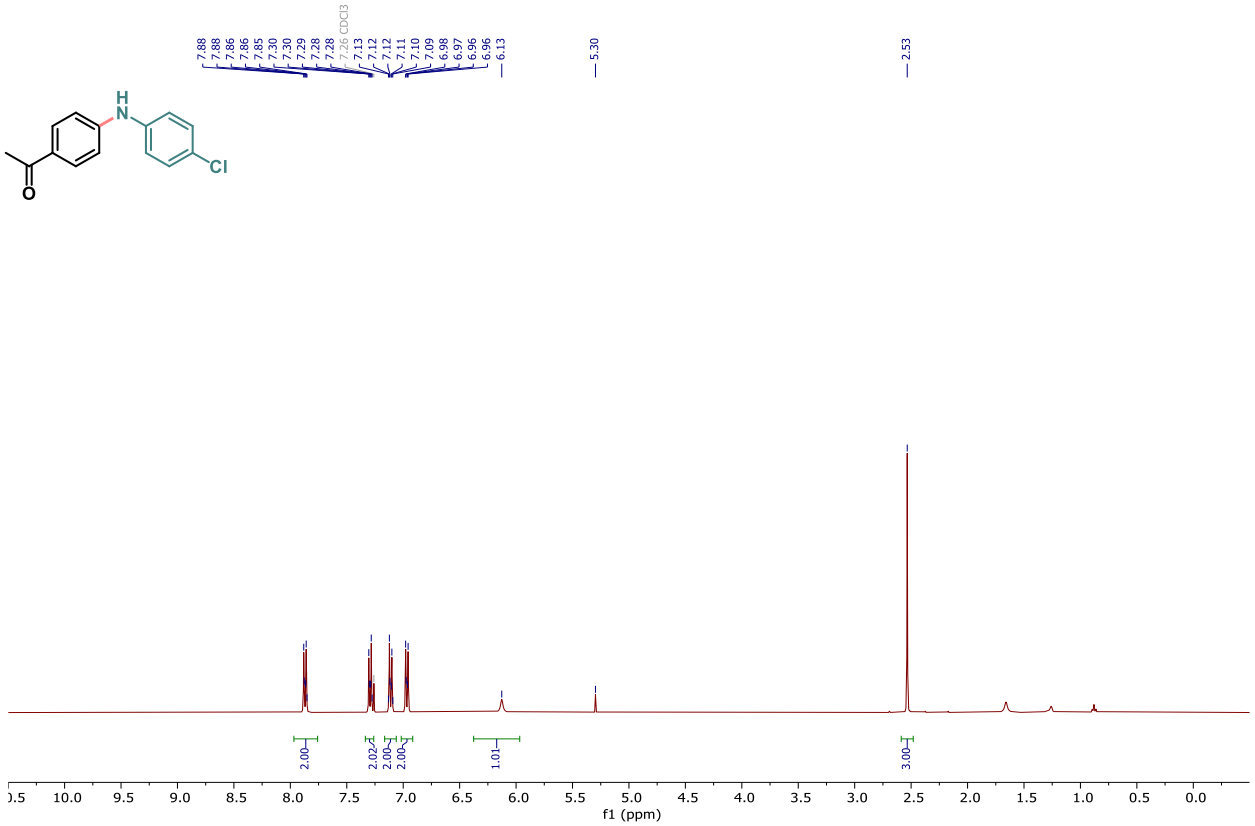
1-[4-(naphthalen-2-ylamino)phenyl]ethan-1-one (3ac):

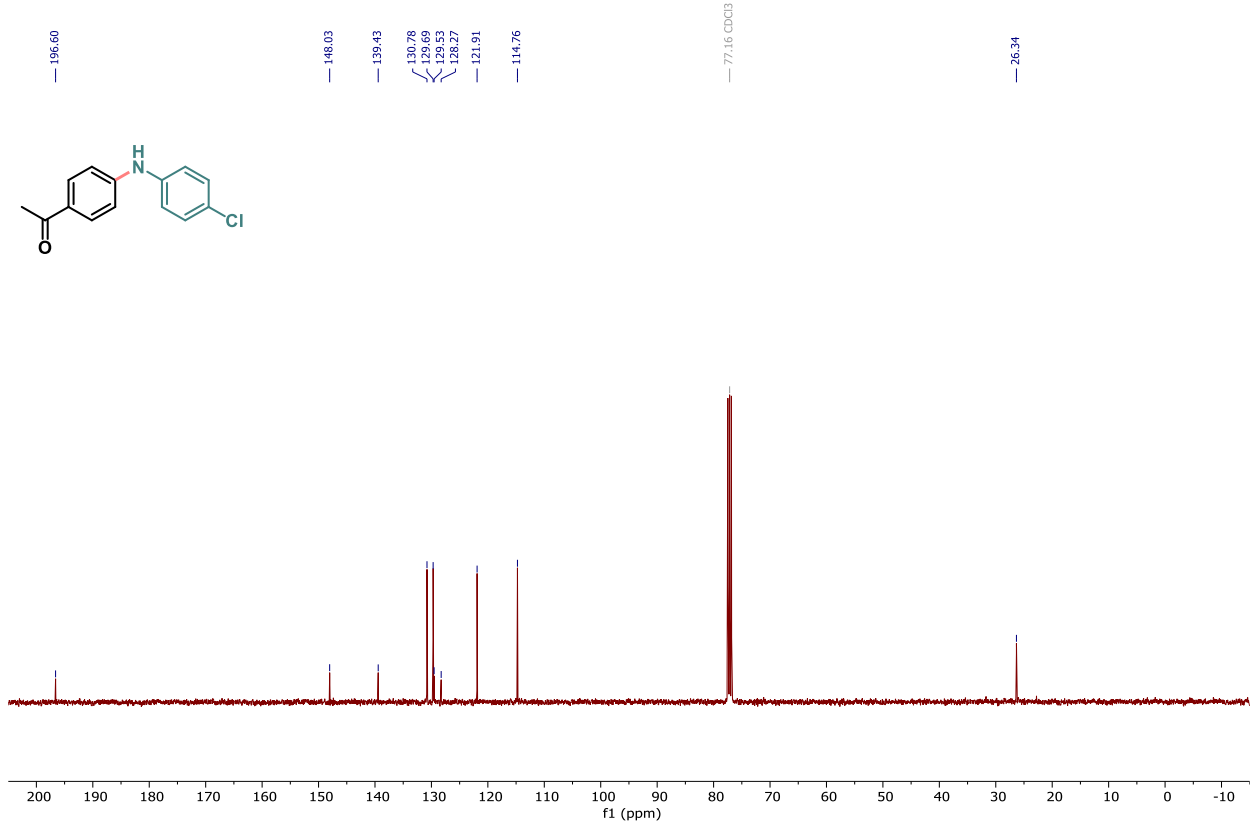




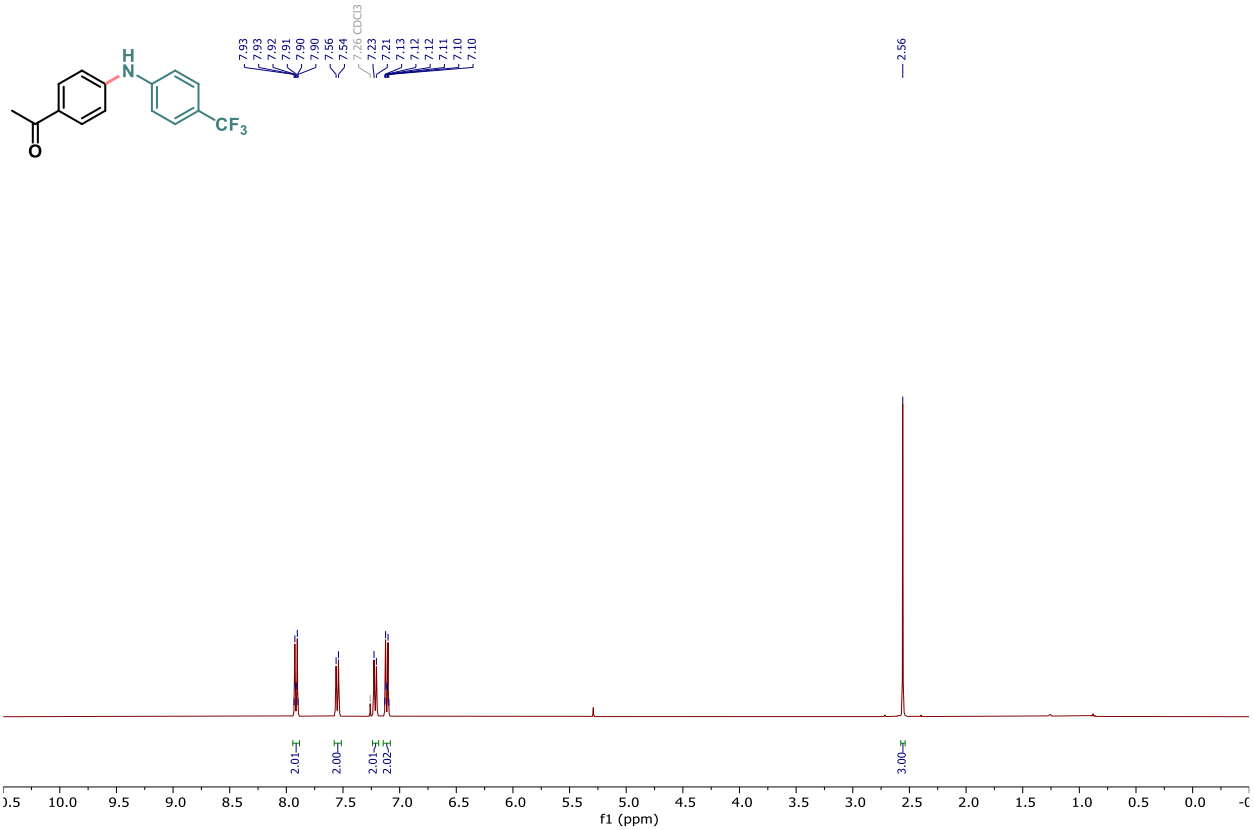


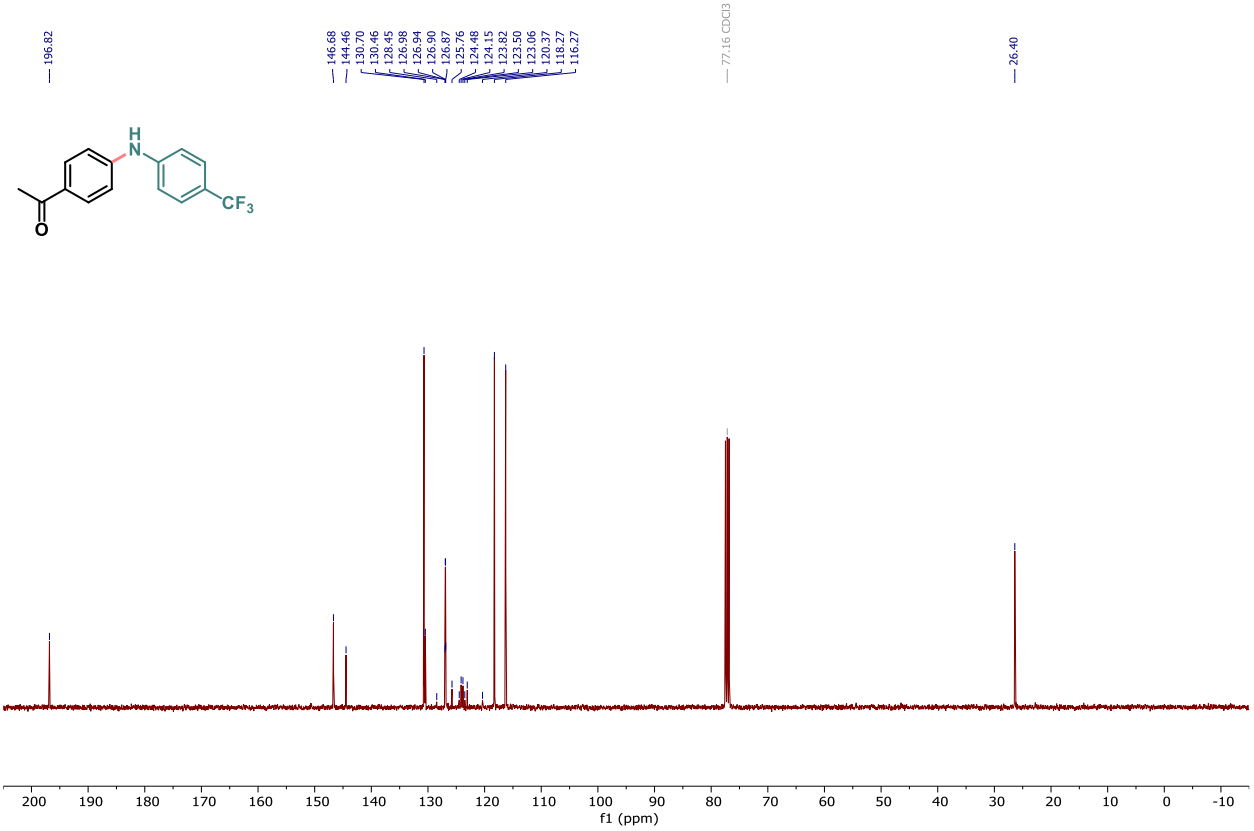
1-{4-[(4-chlorophenyl)amino]phenyl}ethan-1-one (3ad):

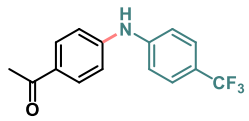




1-{4-{[4-(trifluoromethyl)phenyl]amino}phenyl}ethan-1-one (3ae):

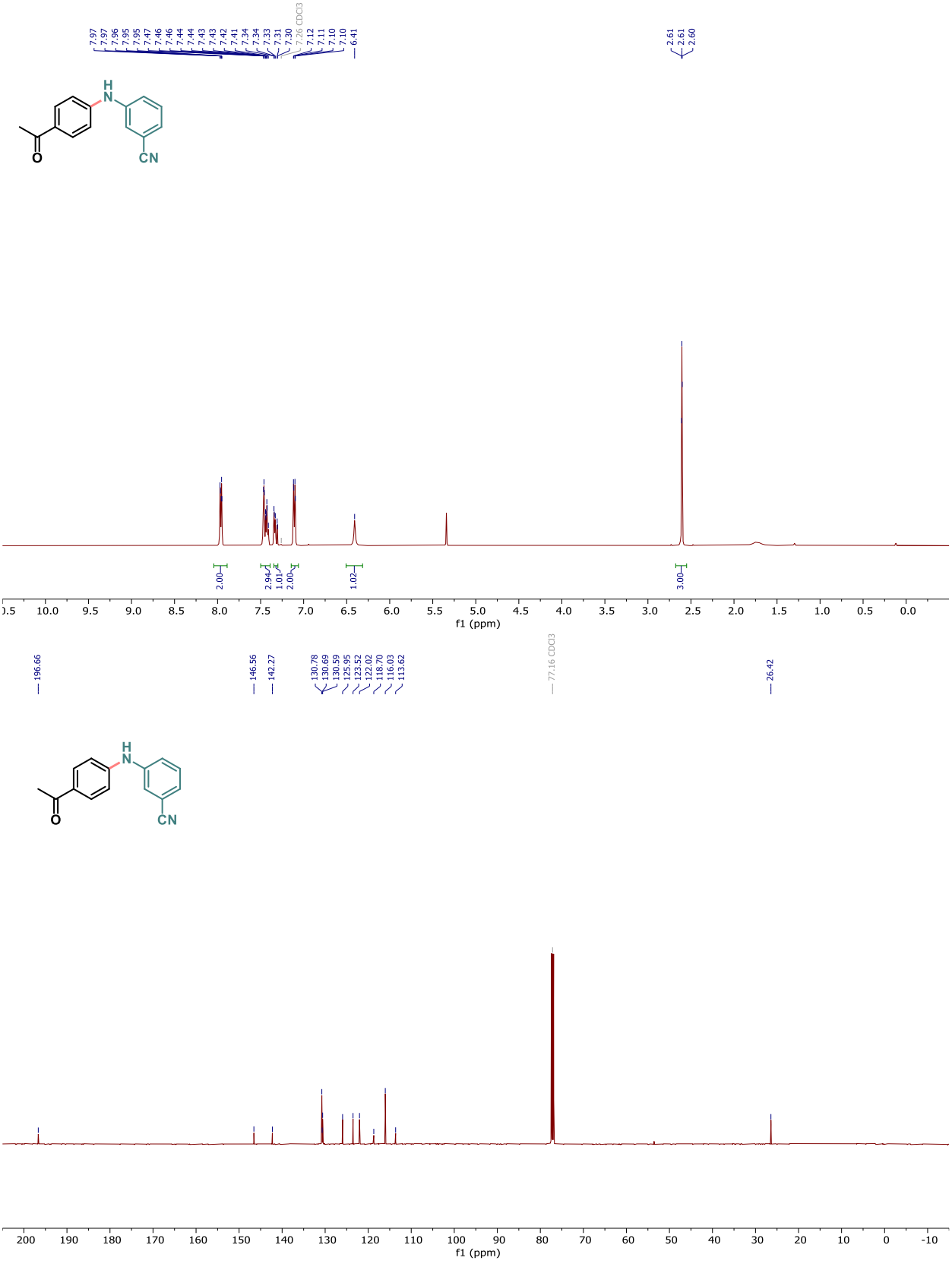




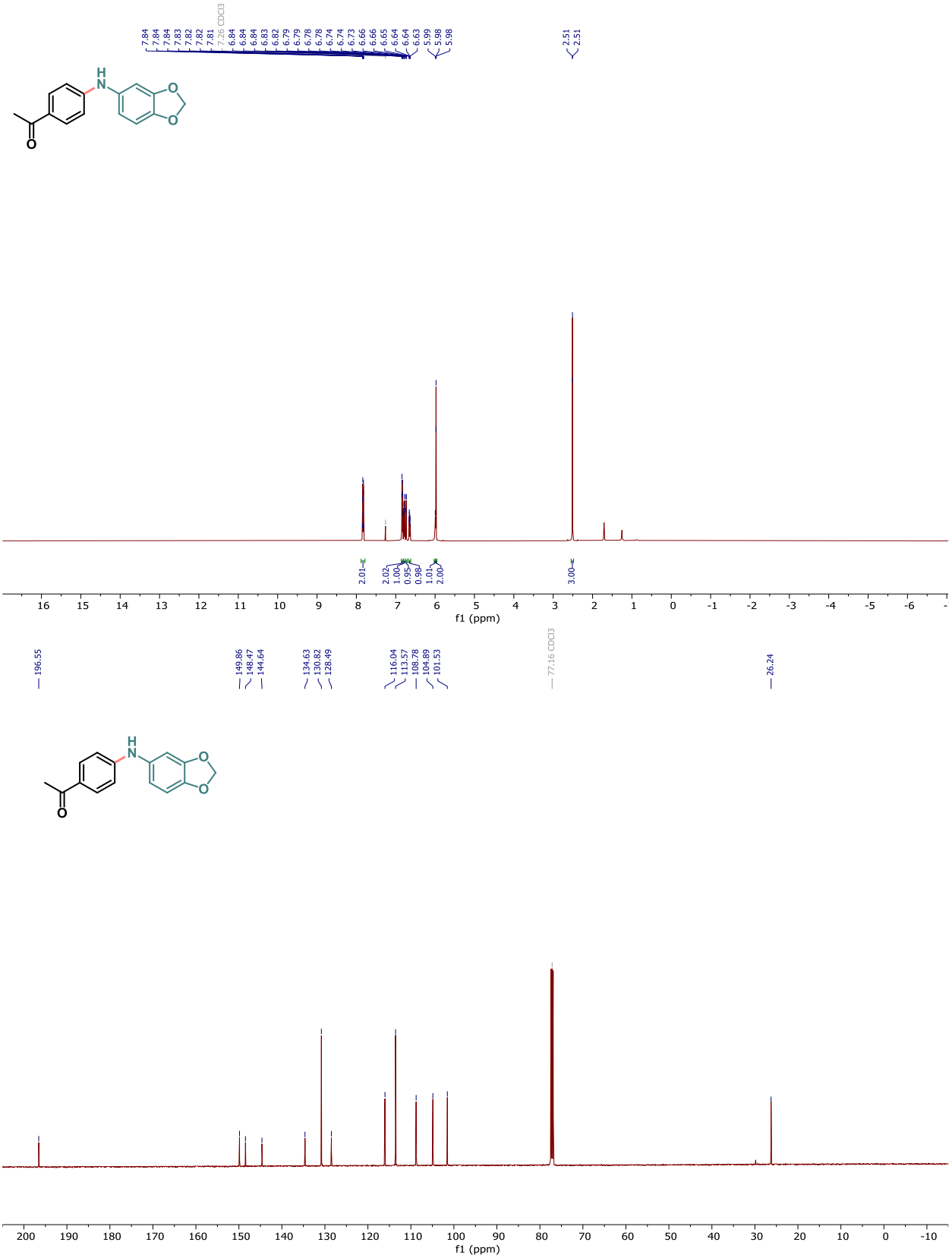

H
N
O
CF3

-61.97
200
150
100
50
0
-50
-100
-150
-200
-250
-300
-350
f1 (ppm)

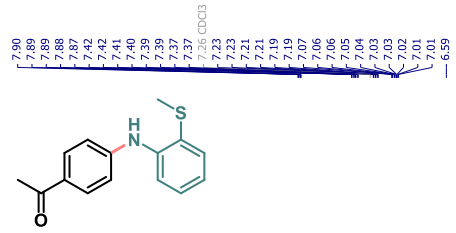
3-[(4-acetylphenyl)amino]benzonitrile (3af):

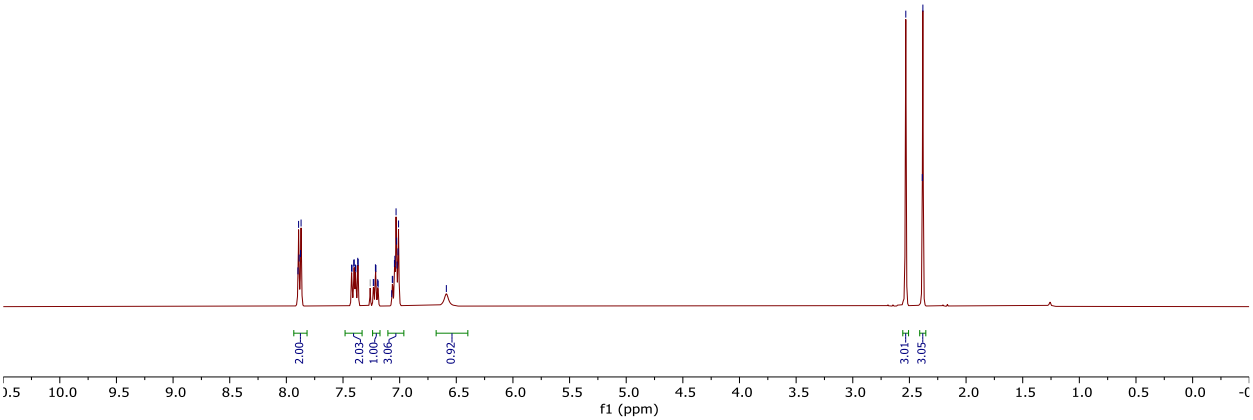


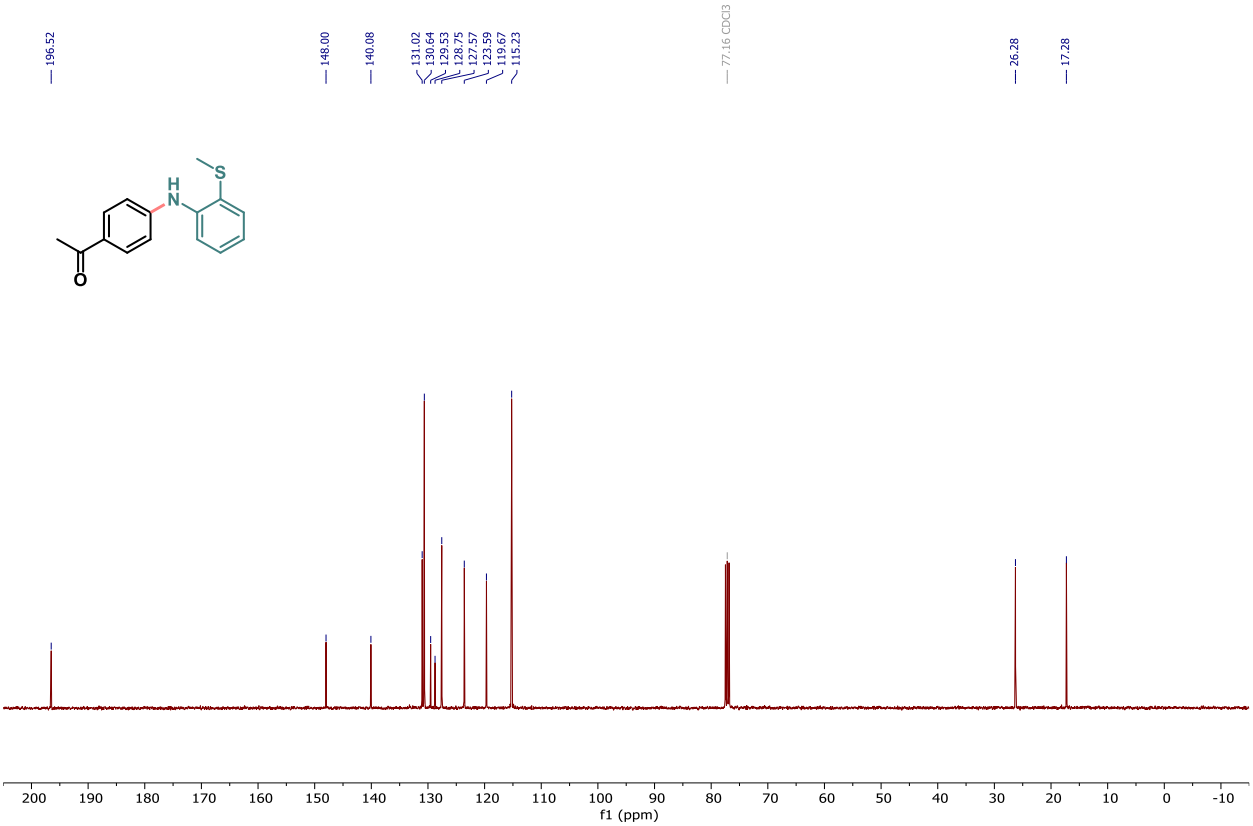
1-[4-(benzo[d][1,3]dioxol-5-ylamino)phenyl]ethan-1-one (3ag):



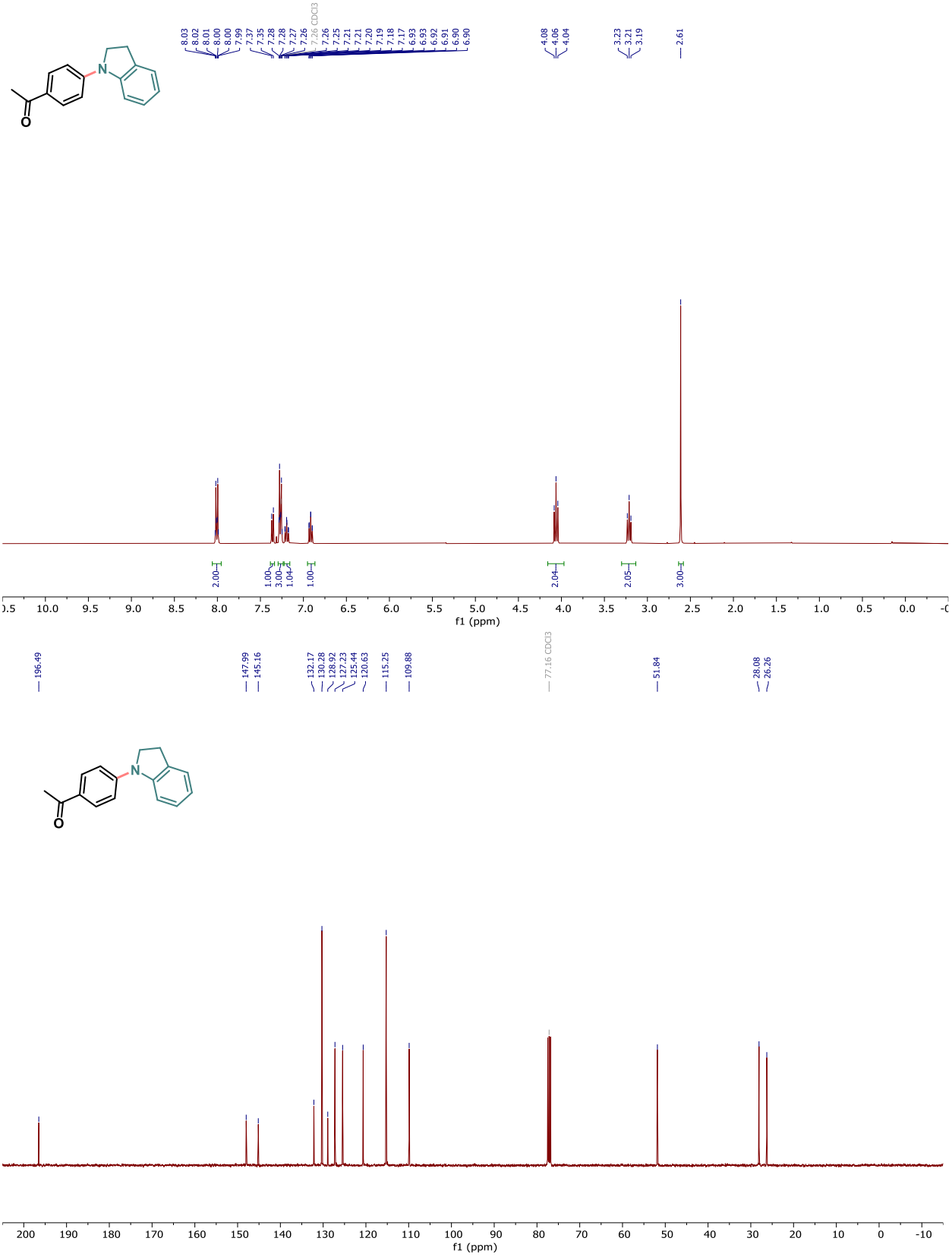
1-{4-{[2-(methylthio)phenyl]amino}phenyl}ethan-1-one (3ah):



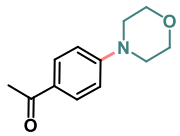


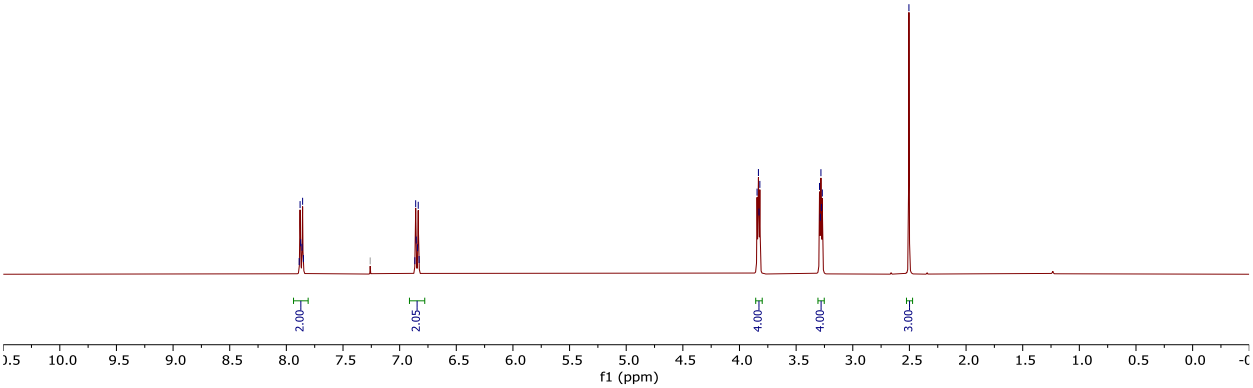


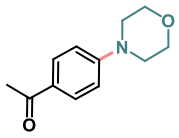
1-[4-(indolin-1-yl)phenyl]ethan-1-one (3ai):

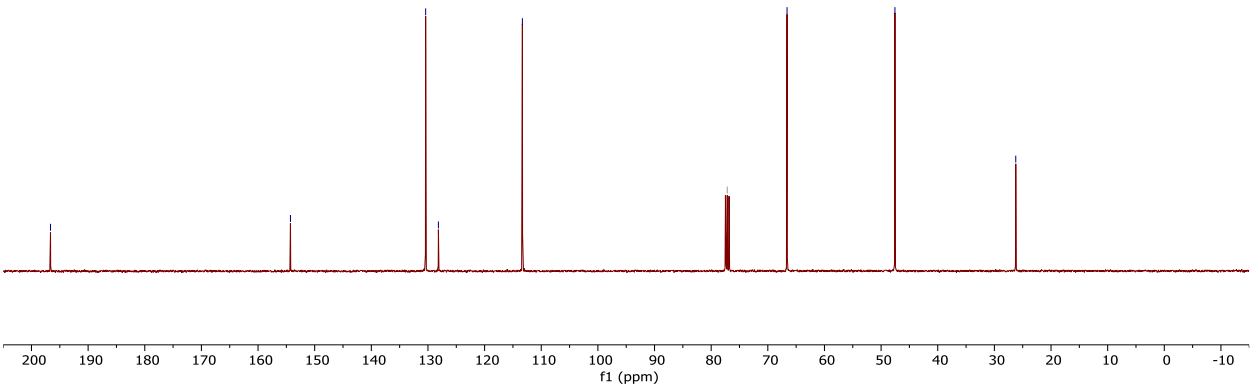


1-(4-morpholinophenyl)ethan-1-one (3aj):

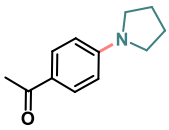


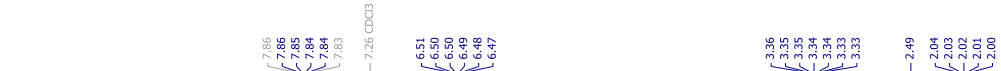


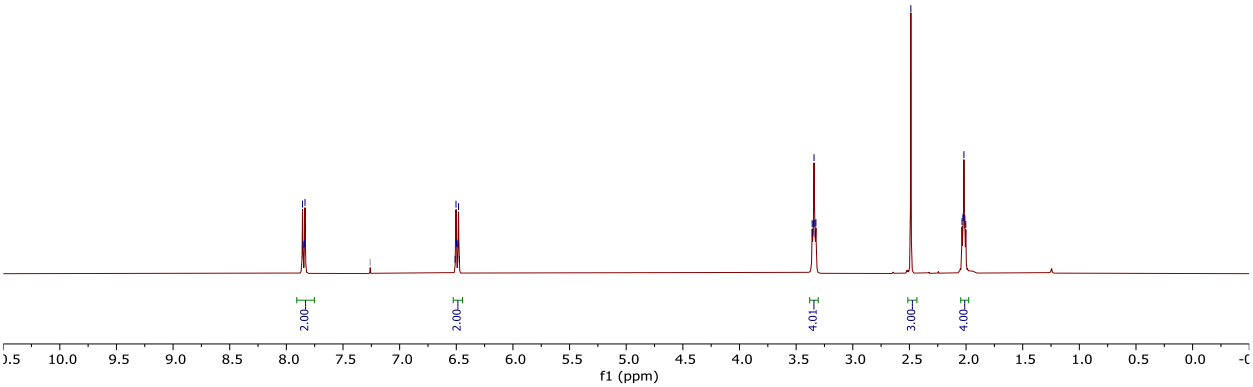


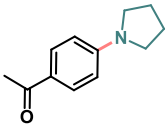


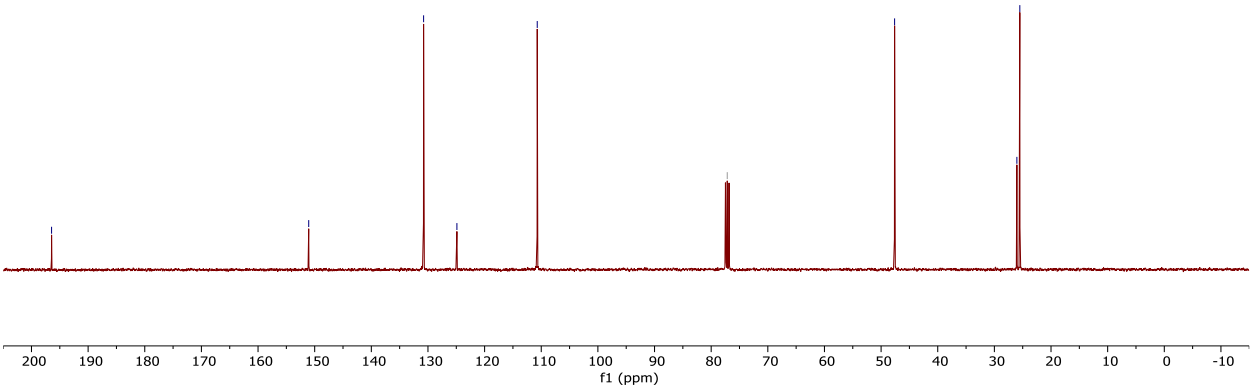
1-[4-(pyrrolidin-1-yl)phenyl]ethan-1-one (3ak):



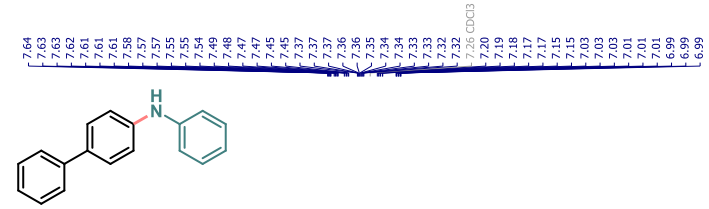


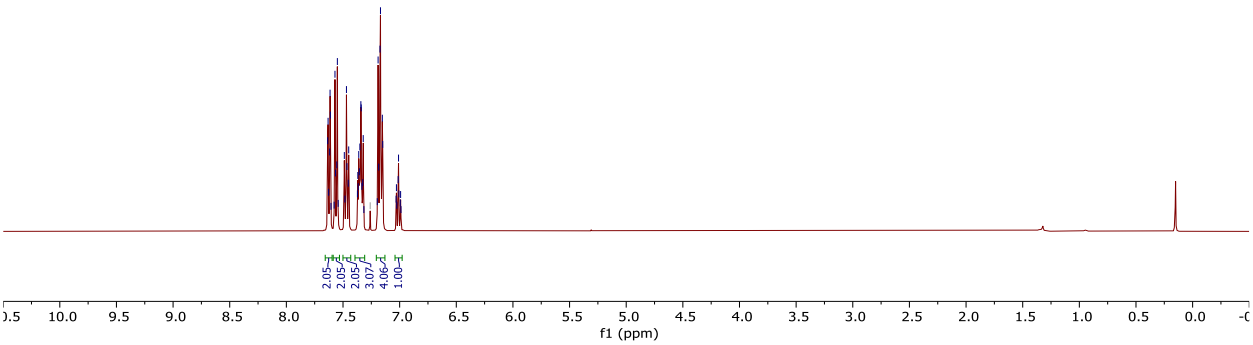


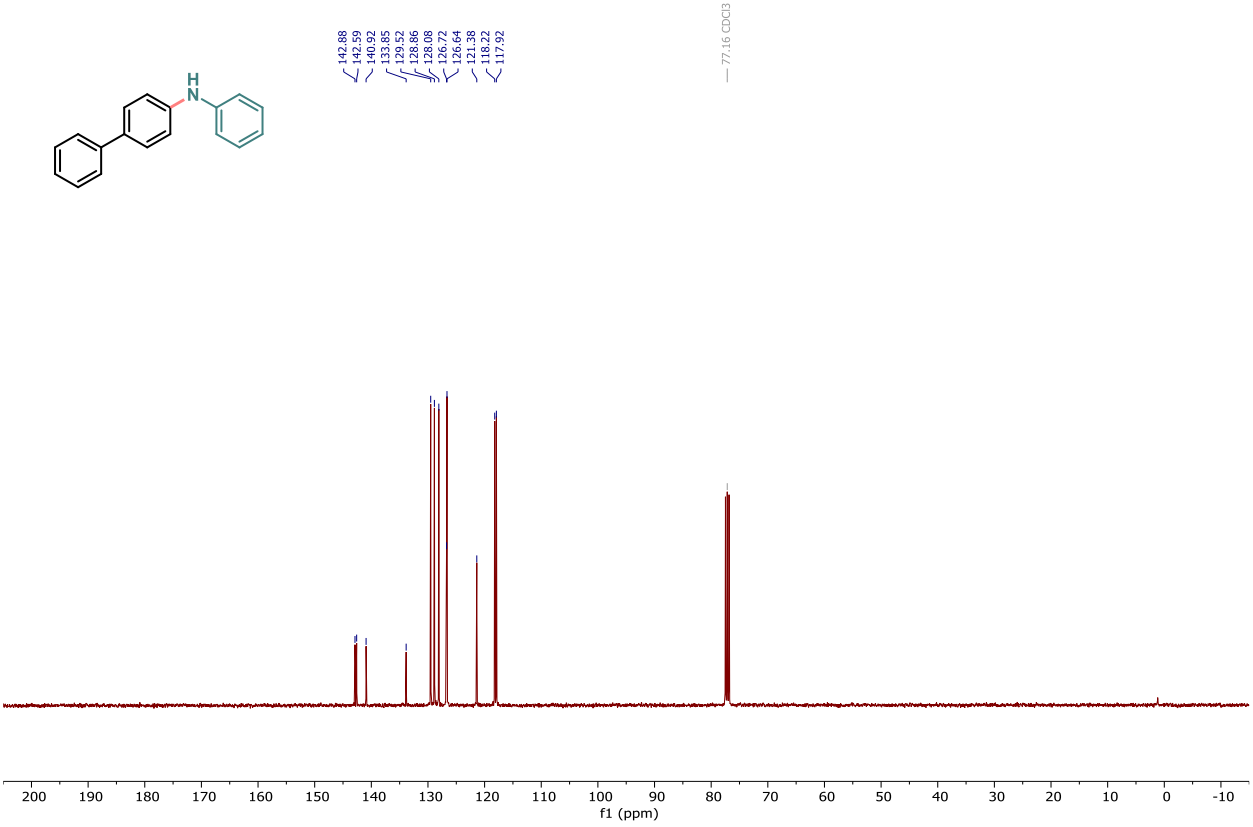




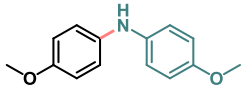
N-phenyl-[1,1'-biphenyl]-4-amine (3al):

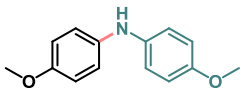




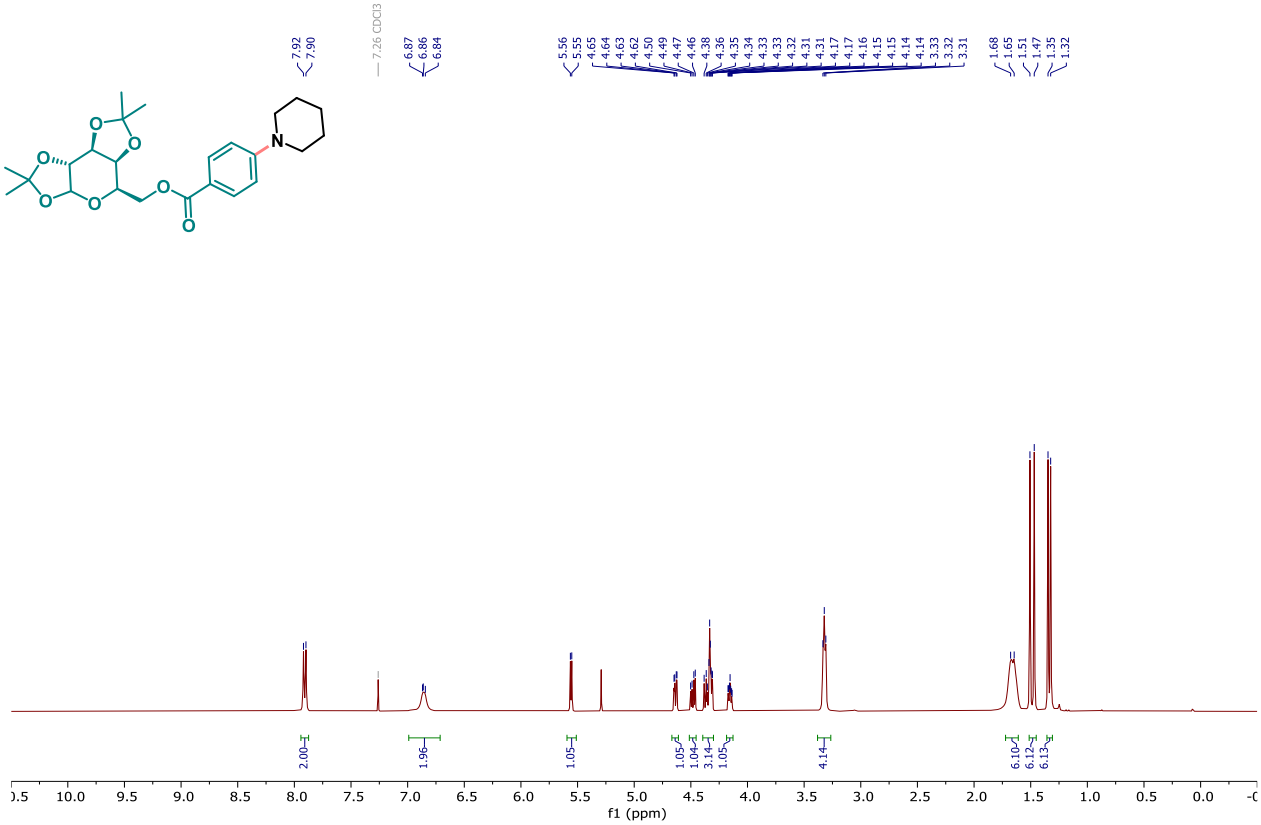


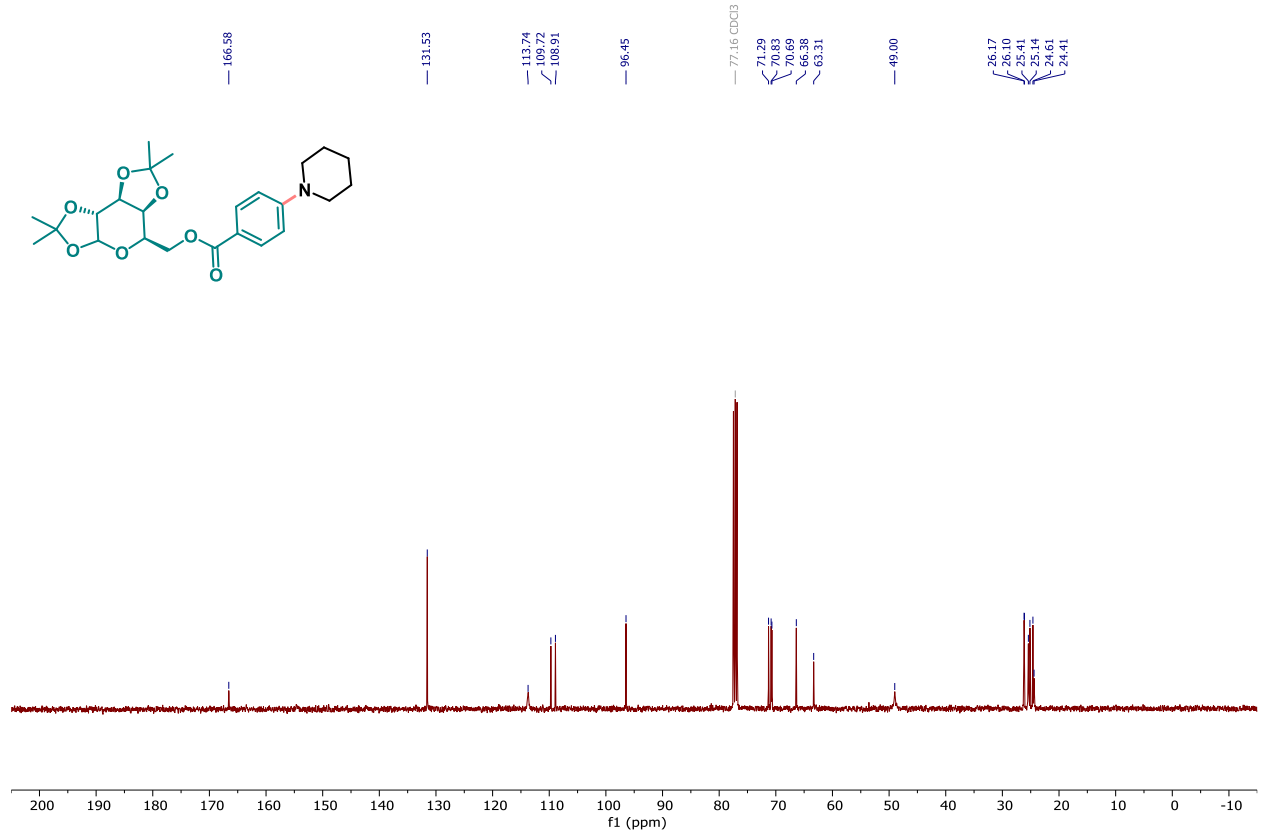
bis(4-methoxyphenyl)amine (3am):



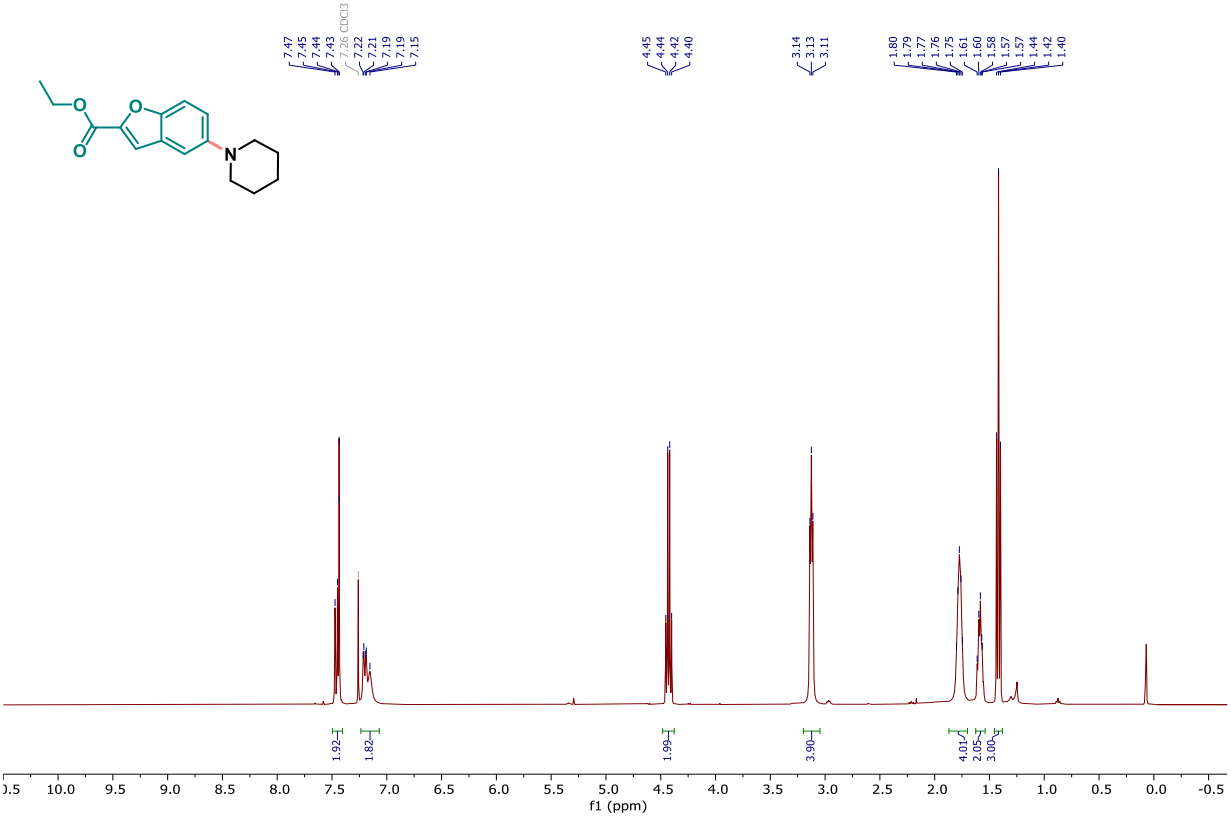


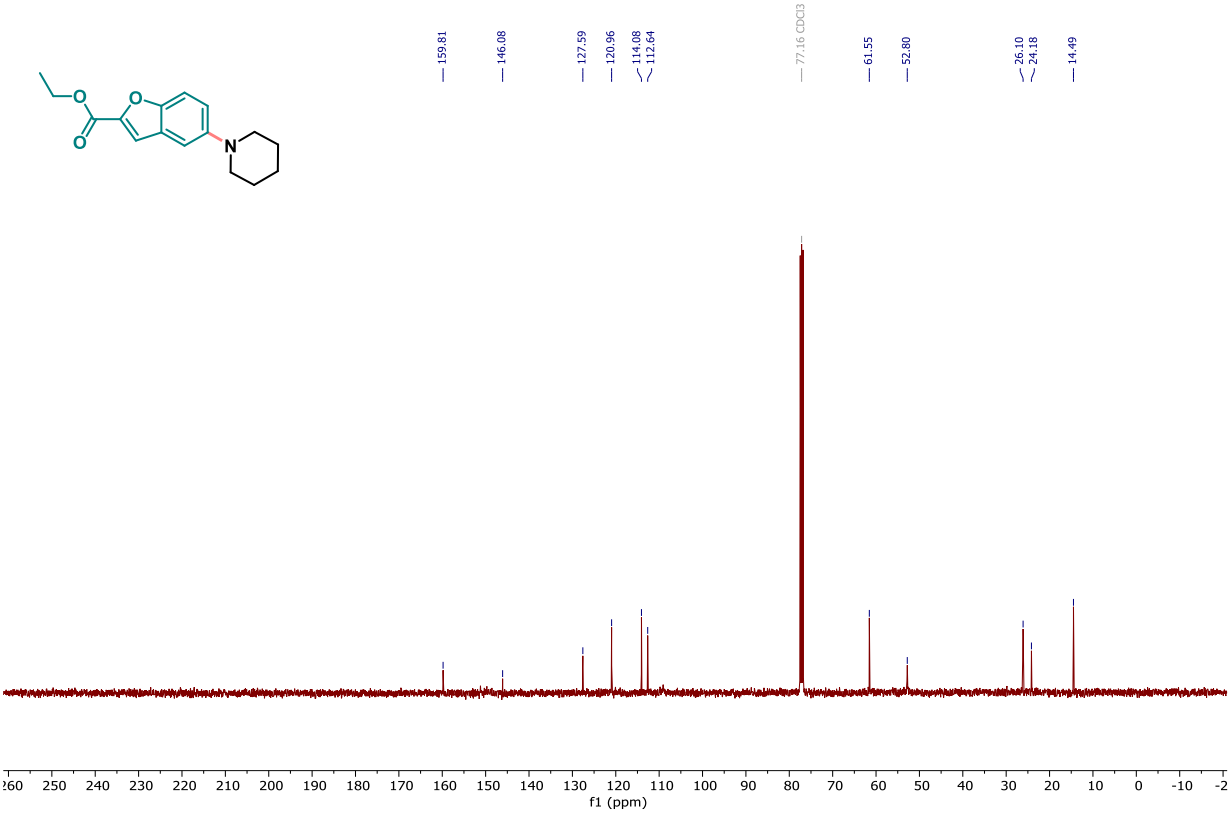
((5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl 4-(piperidin-1-yl)benzoate (3an):



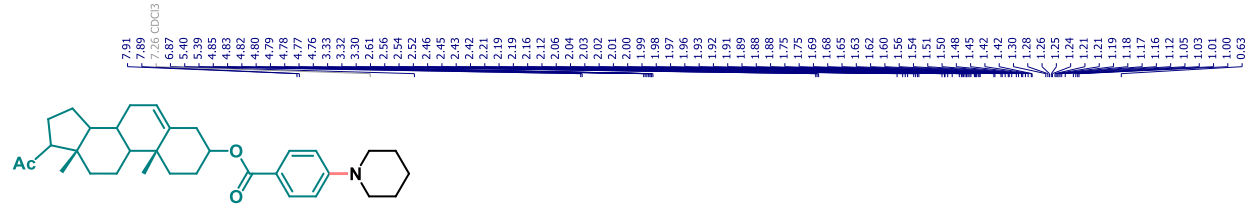


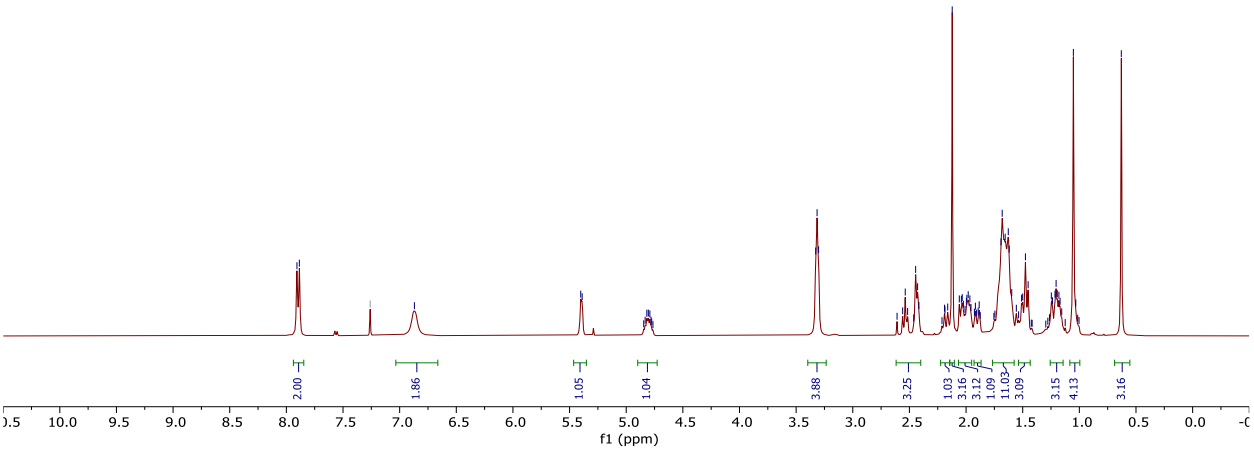
ethyl 5-(piperidin-1-yl)benzofuran-2-carboxylate (3ao):

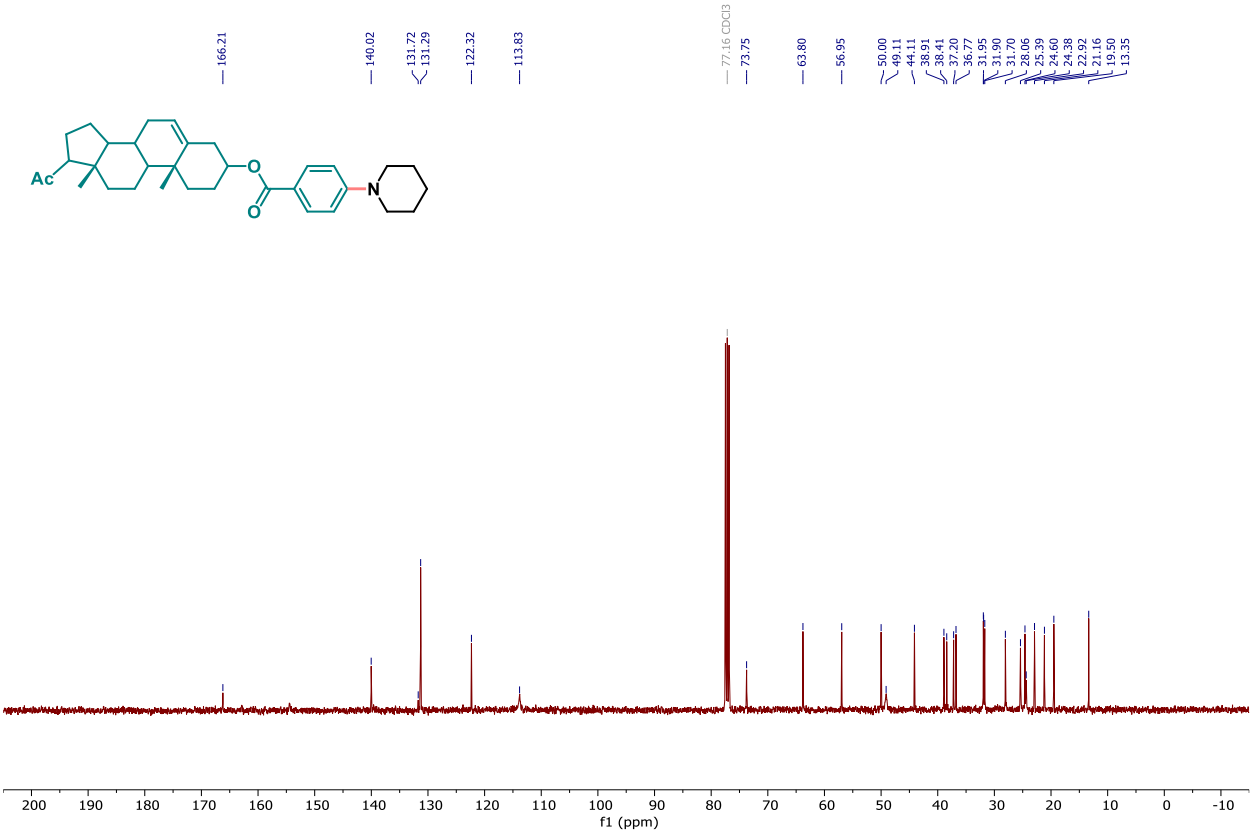




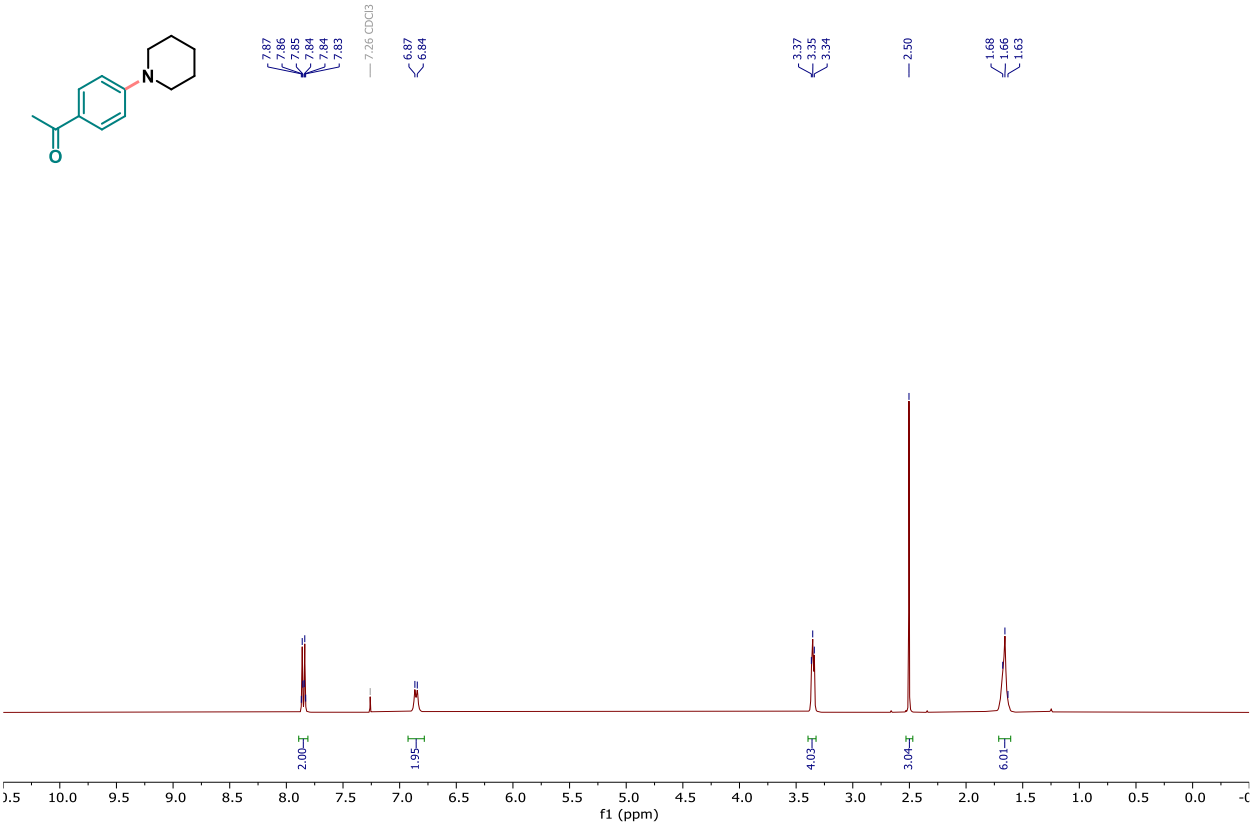
(10R,13S)-17-acetyl-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(piperidin-1-yl)benzoate (3ap):

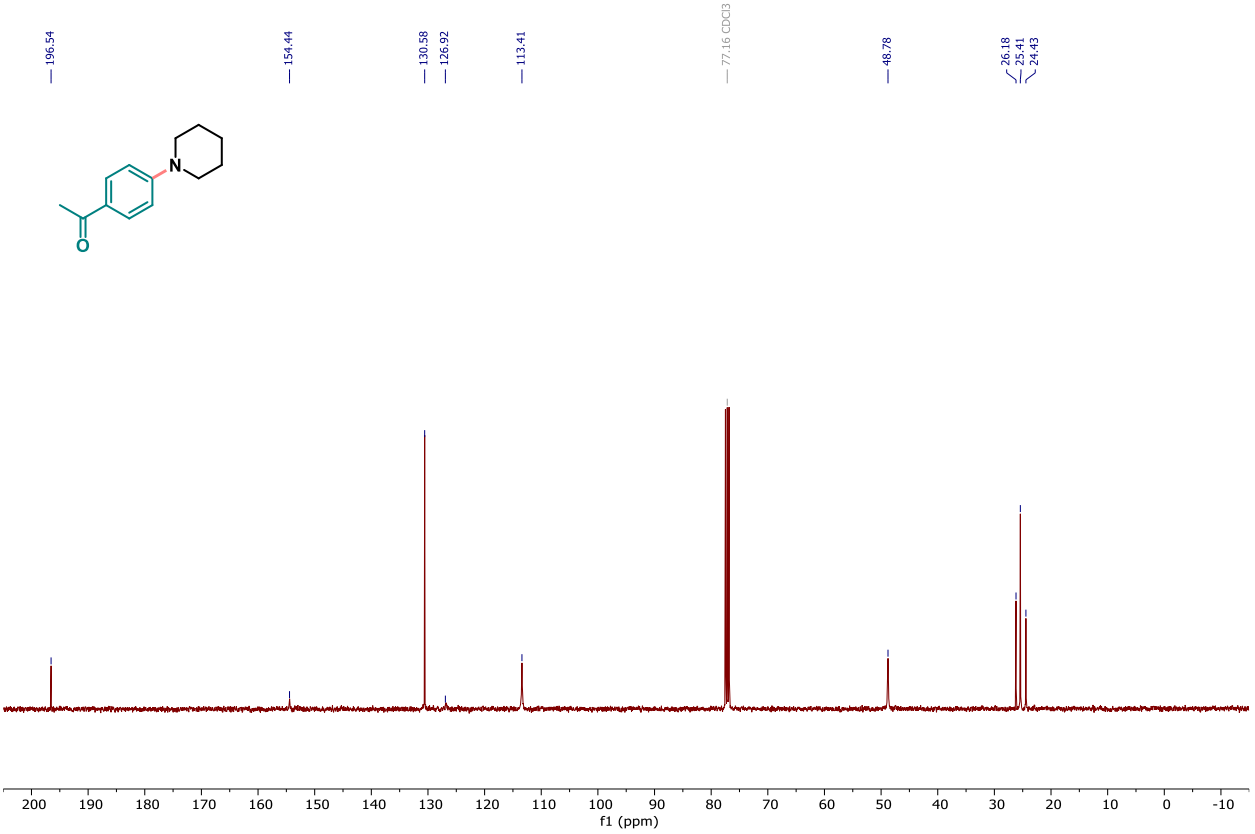




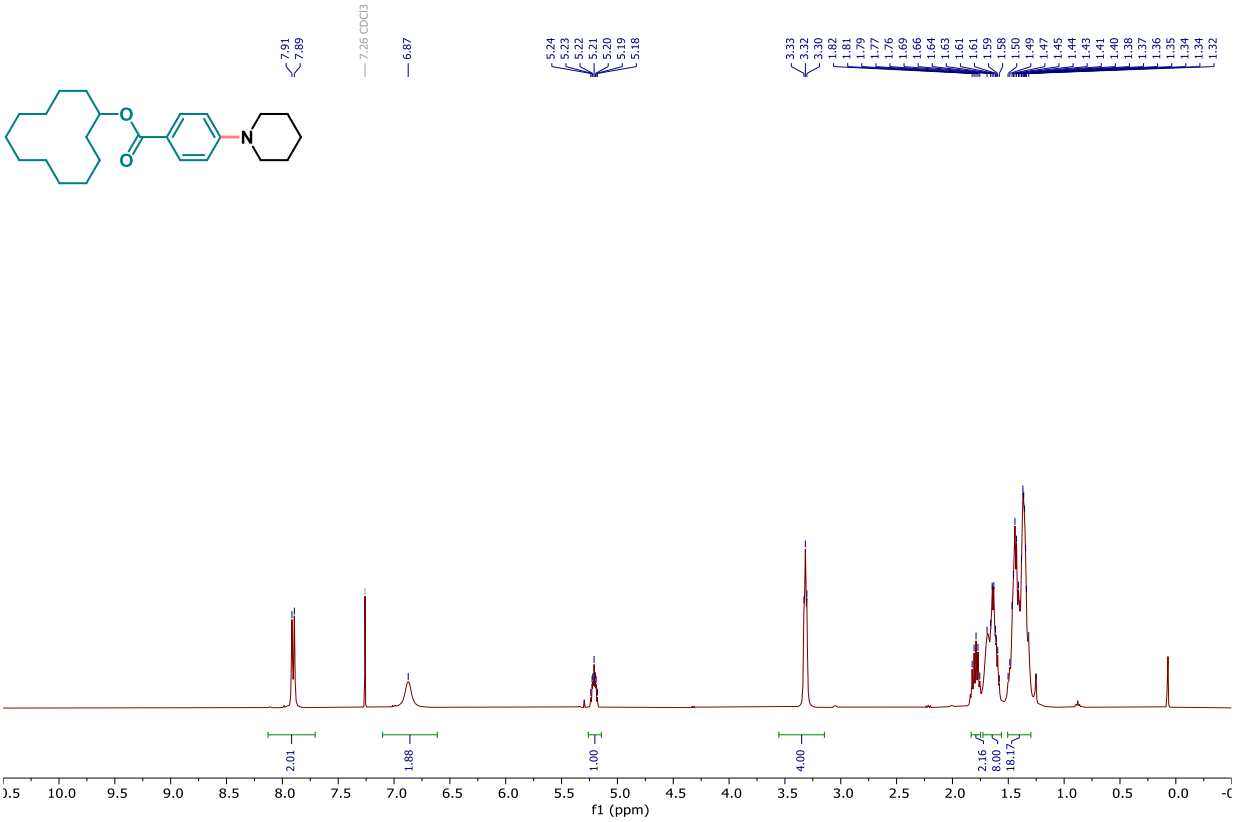


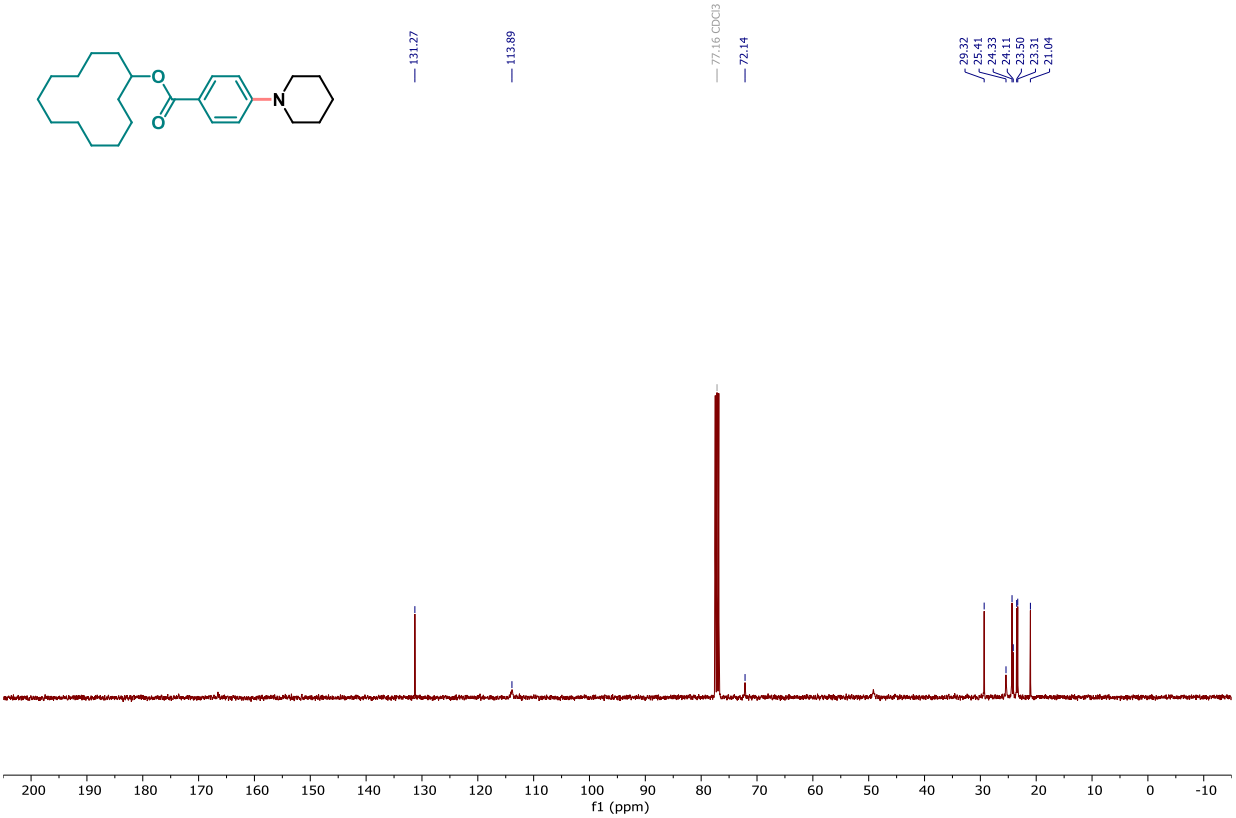
1-[4-(piperidin-1-yl)phenyl]ethan-1-one (3aq):



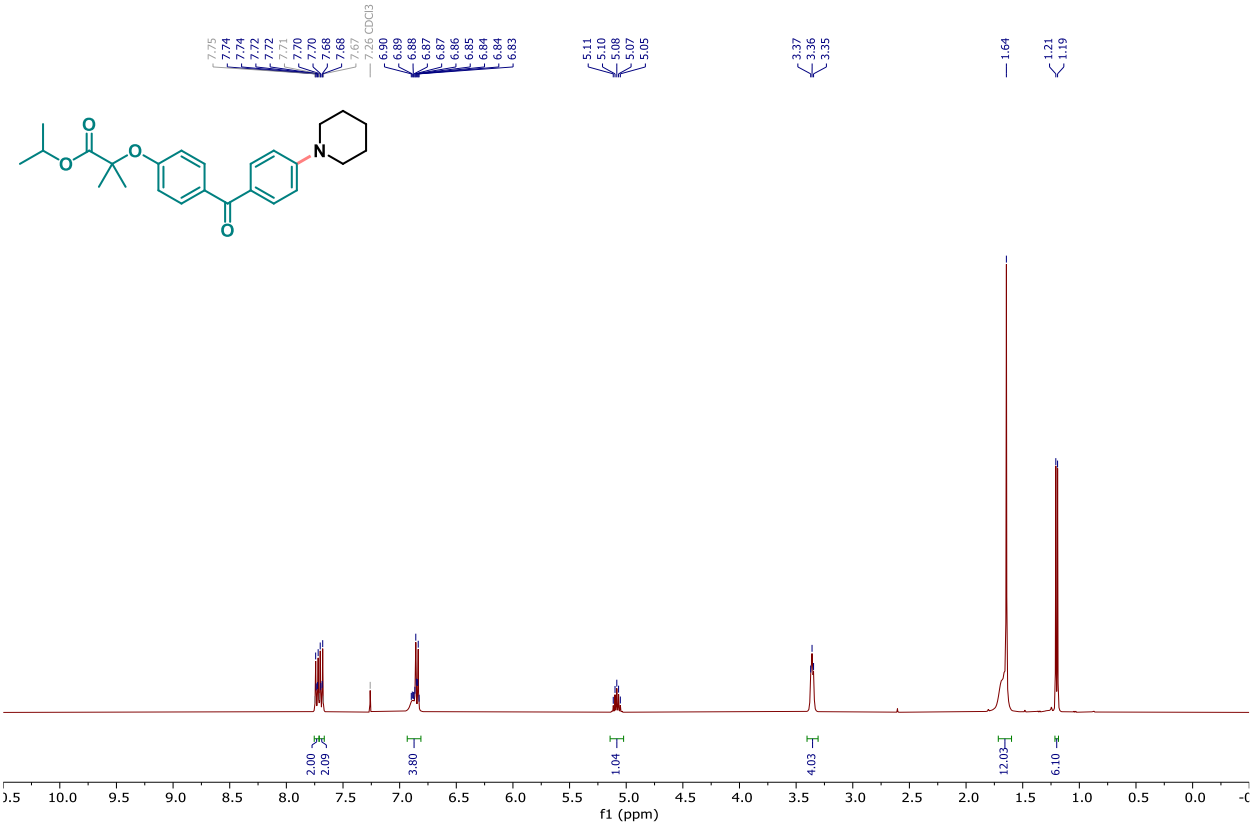


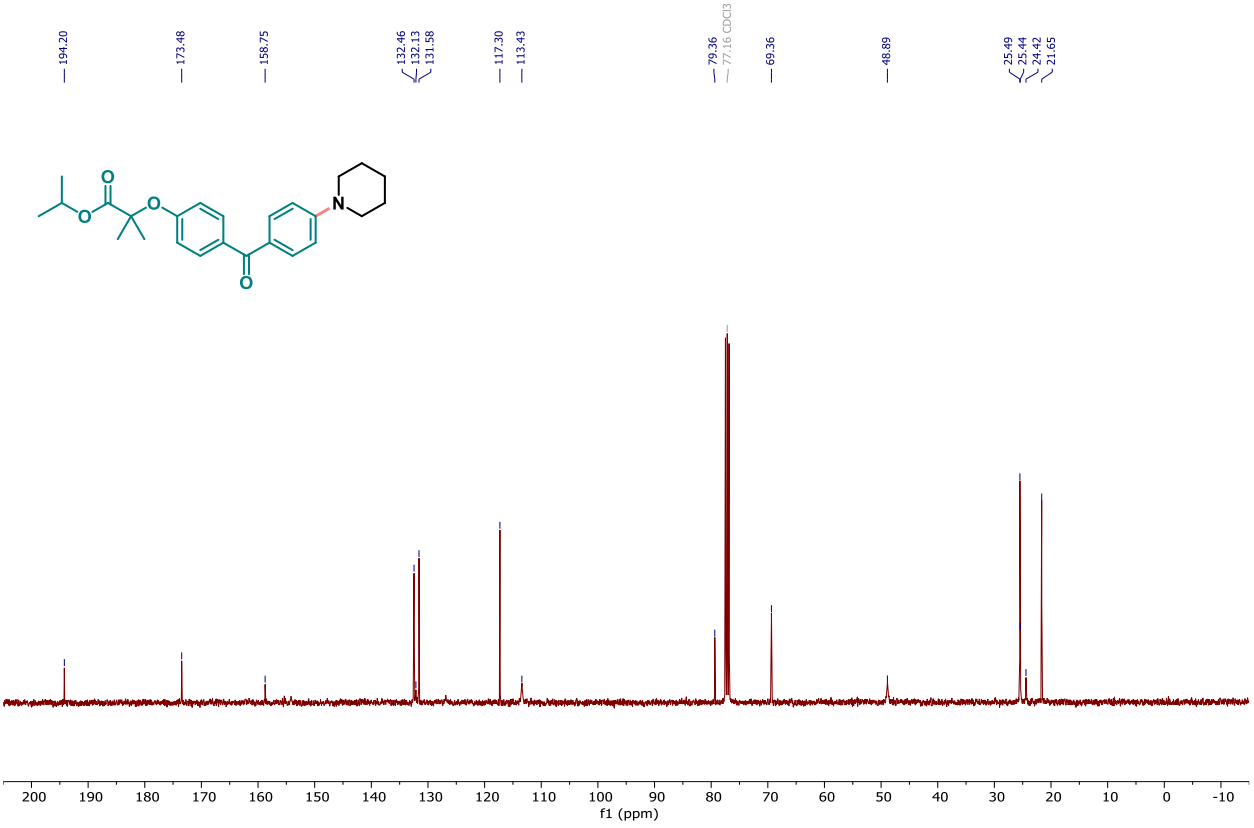
cyclododecyl 4-(piperidin-1-yl)benzoate (3ar):



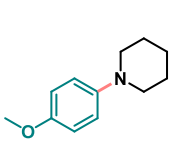


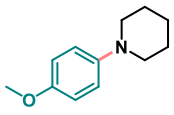
isopropyl 2-methyl-2-{4-[4-(piperidin-1-yl)benzoyl]phenoxy}propanoate (3as):





1-(4-methoxyphenyl)piperidine (3at):





4-(piperidin-1-yl)phenyl (3r,5r,7r)-adamantane-1-carboxylate (3au):