Supporting Information

Nucleophilic Aromatic Substitution Reactions under Aqueous, Mild Conditions Using Polymeric Additive HPMC

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General Information

All reagents were purchased from commercial suppliers and used without further purifications. Hydroxypropyl methylcellulose was obtained from *Gustav Parmentier GmbH* (HPMC Mantrocel® E5, 4.0–6.0 mPa·s (2% aq. sol. 20 °C), 28–30% methoxy substitution, 7–12% hydroxypropyl substitution). Millipore water was obtained with an EMD Millipore Milli-QTM Advantage A10 water purification system. Reactions were conducted in 8 mL microwave vials from *Biotage*®. Reaction progress was monitored by LC-MS and/or thin layer chromatography. LC-MS monitoring was performed on *Agilent*® 1100 series instruments controlled by *Agilent*® ChemStation Software. For detection Single-Quadrupole MS (ESI or APCI, positive mode) or DAD were used. Conversions and product ratios were determined using an Infinity II 1260 device from *Agilent*® (column: Meteoric core C18, 50x2.1 mm, 2.7 µm; eluents: (A) water + 0.1% formic acid, (B) MeCN + 0.1% formic acid; gradient: 5–100% (B) in 1.8 min, isocrat. 100% (B) for 0.9 min, flow: 1 mL/min; T = 50 °C; detection: UV at 254 nm). TLC monitoring was performed on Silica gel 60 F_{254} aluminum plates from *Merck*® using UV-light (254 nm) for visualization of the aromatic compounds. CHROMABOND® empty cartridges with a PTS (for DCM) or PTL (for EtOAc) membranes from *Macherey Nagel*® were used for parallel work-up of the products. Automated flash chromatography was performed on a GRACE system from *Büchi*® using prepacked FlashPure Silica columns (4 g, 15 ml/min, max. pressure 245 psi, 4–800 mg sample). For detection ELSD and/or DAD were used. Very polar substances were purified using reversed phase flash chromatography on a puriFlash® system from *Interchim*® (column: Waters Xselect CSH C18, 150x30 mm, 5 µm; eluents: (A) water + 0.1% formic acid, (B) MeCN + 0.1% formic acid,flow: 50 mL/min, T = 23 °C). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on *Bruker* Avance III 500 MHz or 600 MHz spectrometers at 23 °C (if not stated otherwise). Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the solvent peaks (^{1}H: δ = 7.26 ($CDCl_3$),5.13 (CD_2Cl_2), 2.50 (DMSO-d_6) ppm; ^{13}C = 77.16 ($CDCl_3$), 53.84 (CD_2Cl_2), 39.52 (DMSO-d_6) ppm). ^{19}F chemical shifts are reported relative to $CFCl_3$ (0 ppm). The following abbreviations are used to report the multiplicity of the peaks: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex. = sextet, sep. = septet and combinations thereof, br = broad signal, m = multiplet). For the unambiguous assignment of the peaks two-dimensional homo- and heteronuclar spectra were recorded (COSY, HSQC, HMBC, NOESY). HMBC and NOESY spectra were used to determine the connectivity for products where different chemo- or regioisomers could have formed. High resolution spectra were obtained on a Xevo G2-S QTof device from *Waters*. Permanent mass calibration is achieved using a locksolvent (5 mM sodium formiate in 90/10 *iso*-propanol/water).

Preparation of 2 wt% HPMC solution in Millipore water (100 mL)

Millipore water (66 mL) was heated to 70 °C. HPMC Mantrocel® E5 (2.0 g) was added to give a cloudy solution. Subsequently Millipore water (34 mL) was added, and the stirred mixture was then allowed to cool to room temperature to give a clear solution.

Preparation of 1 wt% HPMC solution in Millipore water (100 mL)

Millipore water (66 mL) was heated to 70 °C. HPMC Mantrocel® E5 (1.0 g) was added to give a cloudy solution. Subsequently Millipore water (34 mL) was added, and the stirred mixture was then allowed to cool to room temperature to give a clear solution.

Preparation of 0.1 wt% HPMC solution in Millipore water (100 mL)

Millipore water (66 mL) was heated to 70 °C. HPMC Mantrocel® E5 (100 mg) was added to give a cloudy solution. Subsequently Millipore water (34 mL) was added, and the stirred mixture was then allowed to cool to room temperature to give a clear solution.

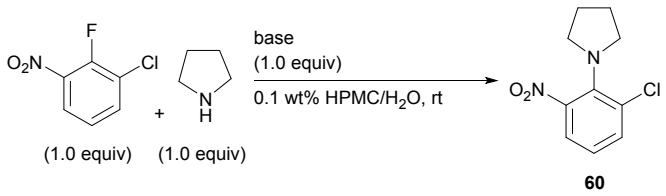
Optimization of the S_NAr reaction

Investigation of the base (cf. Table 1, entries 1–7)

In order to explore suitable bases for the S_NAr reaction in HPMC/water, HPMC solution (2 wt% in Millipore water, 1.0 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and the corresponding base (0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. Samples were taken after 10 s, 1 min, 5 min, 15 min, 30 min and 1 h. Conversion as well as the ratio between the desired product **3** and the hydrolysis side product **4** were determined by integration of the peaks of 2,4,5-trichloropyrimidine (**1**, r_t = 1.28 min), 2,5-dichloro-4-(pyrrolidin-1-yl)pyrimidine (**3**, r_t = 1.43 min) and 2,5-dichloro-4-hydroxypyrimidine (**4**, r_t = 0.38 min) at 254 nm.

Investigation of the role of the counterion

In order to explore the influence of different counterion of the hydroxide anion, four different hydroxides were investigated. For this purpose, HPMC solution (0.1 wt% HPMC in Millipore water, 0.5 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2-fluoro-3-chloronitrobenzene (88 mg, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and the corresponding base (0.5 mmol, 1.0 equiv). The reaction was stirred at rt for 4 h. Reaction progress was monitored by LC-MS. Samples of the reaction mixture were taken after 5 min, 10 min, 15 min, 30 min, 1 h, 2.5 h and 4 h. Conversion was determined by integration of the peaks of 2-fluoro-3-chloronitrobenzene (r_t = 1.36 min) and 1-(2-chloro-6-nitrophenyl)pyrrolidine (**60**, r_t = 1.76 min) at 254 nm.



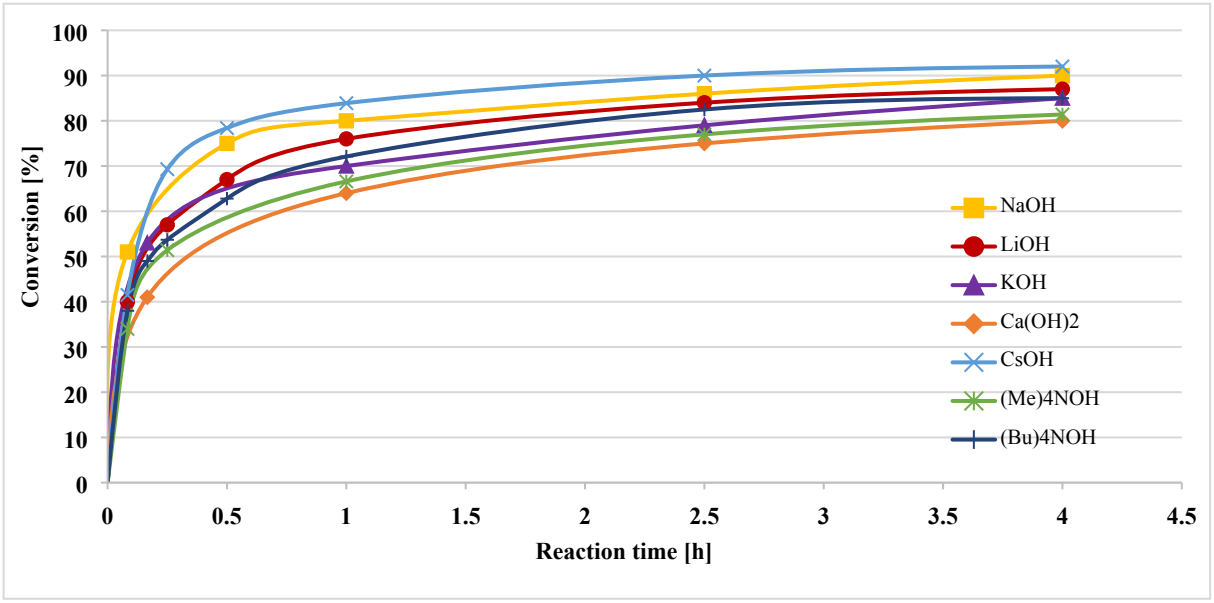


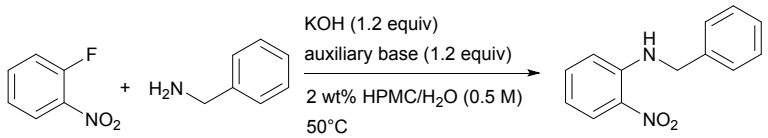
Figure S1 Investigation of the role of the counterion.

Investigation of different auxiliary bases

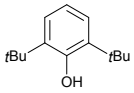
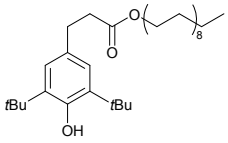
In order to explore the influence of lipophilic auxiliary bases on the conversion and reaction kinetics, different silanols and phenols were screened. HPMC solution (0.1 wt% HPMC in Millipore water, 0.9 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar and KOH (34 mg, 0.6 mmol, 1.2 equiv) and the corresponding auxiliary base (0.6 mmol, 1.2 equiv) were added. The mixture was stirred for 30 min at rt. Another 8 mL microwave vial was loaded with HPMC solution (0.1 wt% in Millipore water, 0.1 mL). 2-fluoro-1-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv) was added, followed by benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv).

The stock solution of HPMC containing KOH and the auxiliary base (0.9 mL) was added and the reaction was stirred at rt for 7 h. Reaction progress was monitored by LC-MS. Samples of the reaction mixture were taken after 30 min, 4 h and 7 h. Conversion was determined by integrating the peaks of 2-fluoro-1-nitrobenzene (**5**, r_t = 1.16 min) and *N*-benzyl-2-nitroaniline (**7**, r_t = 1.62 min).

Table S1 Investigation of different lipophilic auxiliary bases.



5 (1.0 equiv) **6** (1.0 equiv) **7**

Entry	Auxiliary Base		cLogP*	Conv. [%]
1	-	-	-	85
2	Tri-*iso*-propylsilanol		3.9	55
3	2,6-di-*tert*-butylphenol		4.5	60
4	Triphenylsilanol		4.8	53
5	Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate		13.4	55

* calculated index for the lipophilicity (ChemDraw)

(A) KOH

(B) KOH + triphenylsilanol

Investigation of the amount of HPMC needed in the reaction (cf. Table 1, entries 7–10)

In order to determine the minimal required amount of HPMC for the S_NAr reactions in aqueous medium, HPMC solution (0–2 wt% HPMC in Millipore water, 1.0 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and sodium *tert*-butoxide (48 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. Samples of the reaction mixture were taken after 10 s, 1 min, 5 min, 15 min, 30 min and 1 h. Conversion, as well as the ratio between the desired product **3** and the hydrolysis side product **4**, were determined by integration of the peaks of 2,4,5-trichloropyrimidine (**1**, r_t = 1.28 min), 2,5-dichloro-4-(pyrrolidin-1-yl)pyrimidine (**3**, r_t = 1.43 min) and 2,5-dichloro-4-hydroxypyrimidine (**4**, r_t = 0.38 min) at 254 nm.

Investigation of the order of addition of the reactants (cf. Table 1, entries 9 and 11)

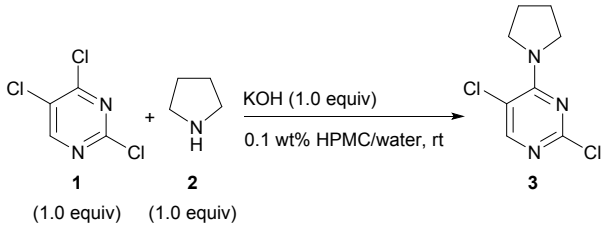
In order to explore the influence of the order of addition on the S_NAr reaction in HPMC/water and the ratio between the desired product **3** and the hydrolysis side-product **4**, HPMC solution (0.1 w% HPMC in Millipore water, 1.0 mL)

was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and sodium *tert*-butoxide (48 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. Samples of the reaction mixture were taken after 10 s, 1 min, 5 min, 15 min, 30 min and 1 h. Conversion, as well as the ratio between the desired product **3** and the hydrolysis side product **4**, were determined by integration of the peaks of 2,4,5-trichloropyrimidine (**1**, r_t = 1.28 min), 2,5-dichloro-4-(pyrrolidin-1-yl)pyrimidine (**3**, r_t = 1.43 min) and 2,5-dichloro-4-hydroxypyrimidine (**4**, r_t = 0.384 min) at 254 nm.

Investigation of the reaction molarity

In order to determine the maximal possible reaction molarity for the S_NAr reactions in HPMC/water, HPMC solution (0.1 wt% HPMC in Millipore water, 170 µL–1.0 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt for 20 min. After completion of the reaction, DCM (3 mL) was added, and reaction mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges with a PTS membrane (*Macherey Nagel*®). The organic layer was evaporated, and the crude product was adsorbed on silica prior to column chromatography (4 g silica, 15 mL/min, 0–8 % EtOAc in heptane). The desired product **3** was obtained as a white solid.

Table S2 Optimization of the reaction molarity.



1 (1.0 equiv) **2** (1.0 equiv) **3**

Entry	Molarity [M]	Time [min]	Yield [%][a]
1	0.5	10 s	76
2	1.0	10 s	90
3	3.0	10 s	82*

[a] isolated yields. * reduced stirrability due to the formation of clumps (see picture).

(Entry 2) 1.0 M

(Entry 3) 3.0 M

Stability of HPMC

After optimization of the reaction conditions, stability of HPMC under these conditions was evaluated using NMR. Since a 0.1 wt% solution of HPMC would not contain enough HPMC for NMR analysis, a 2 wt% HPMC solution was prepared. For this purpose, HPMC (100 mg) was dissolved in D_2O (5 mL) to obtain a 2 wt% solution of HPMC. KOH (281 mg, 5.0 mmol) was added to obtain a 1 M solution in the HPMC/water mixture. The mixture was stirred at 50 °C for 24 h. NMR samples (500 µL) were taken after 0 h, 1 h, 2 h, 4 h, 8 h, and 24 h and the proton spectra were compared to investigate whether HPMC decomposes under our standard reaction conditions (see Figure S2). As no change of the NMR spectra over time was detectable, we concluded that HPMC is chemically stable under the reaction conditions applied in this work.

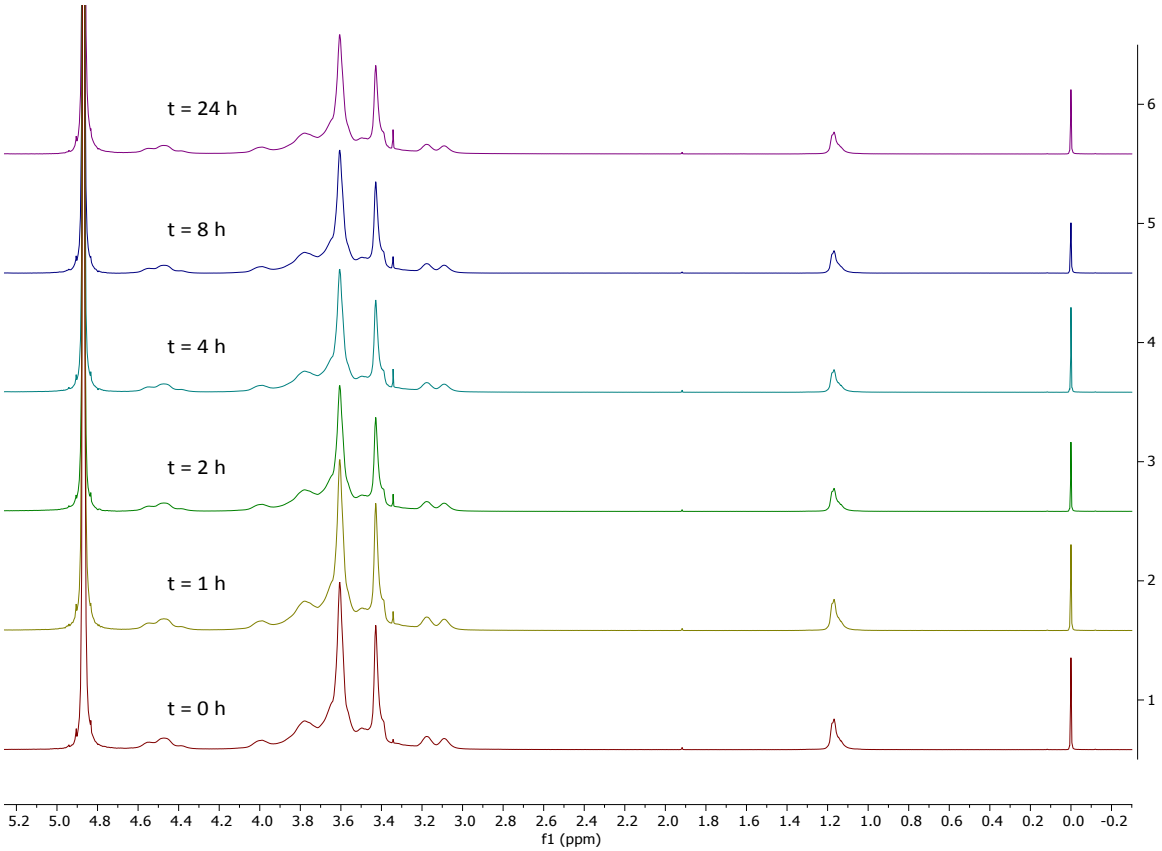


Figure S2 Stability of HPMC under basic conditions at 50 °C. (1) 2 wt% HPMC in D_2O, KOH (1 M), t = 0 h. (2) 2 wt% HPMC in D_2O, KOH (1 M), t = 1 h. (3) 2 wt% HPMC in D_2O, KOH (1 M), t = 2 h. (4) 2 wt% HPMC in D_2O, KOH (1 M), t = 4 h. (5) 2 wt% HPMC in D_2O, KOH (1 M), t = 8 h. (6) 2 wt% HPMC in D_2O, KOH (1 M), t = 24 h.

Comparison of different methodologies for the S_NAr reaction (cf. Figure 2)

In order to compare our new methodology with other different approaches, 2-fluoro-1-nitrobenzene (**5**) was reacted with benzylamine (**6**) following four different reaction procedures. Reaction progress was monitored by LC-MS and conversion was determined by integrating the peaks of 2-fluoro-1-nitrobenzene (**5**, r_t = 1.16 min) and *N*-benzyl-2-nitroaniline (**7**, r_t = 1.622 min). Samples of the reaction mixture were taken after 5 min, 1.5 h, 2.5 h, 5 h and 23 h.

Reaction in HPMC/water: 2-fluoro-1-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv) was loaded into an 8 mL microwave tube equipped with a magnetic stirring bar. HPMC solution (0.1 wt% in Millipore water, 0.5 mL) was added and the mixture was stirred 1–2 min until a homogeneous suspension has been formed. Benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) was added, followed by KOH (28 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. Upon completion of the reaction, DCM (3 mL) was added, and the mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges with a PTS membrane from *Macherey Nagel*®. The organic layer was evaporated, and the crude product was adsorbed on silica prior to column chromatography (4 g silica, 15 mL/min, 0–7 % EtOAc in heptane). The desired product **7** was isolated as an orange oil (102 mg, 90%).

Reaction in DMF: 2-fluoro-1-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv) was loaded into an 8 mL microwave tube equipped with a magnetic stirring bar. Anhydrous, degassed DMF (0.5 mL) and benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) were added, followed by K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. The reaction mixture was diluted with water and extracted with EtOAc (3x). Combined org. layers were washed with water (2x), the org. layer was dried over Na_2SO_4, and concentrated under vacuum. Crude was purified using column chromatography (4 g silica, 15 mL/min, 0–7 % EtOAc in heptane). The desired product **7** was isolated as an orange oil (105 mg, 92%).

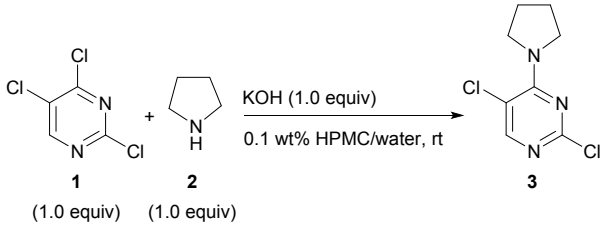
Reaction in TPGS-750-M/water: 2-fluoro-1-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv) was loaded into an 8 mL microwave tube equipped with a magnetic stirring bar. TPGS-750-M solution (2 wt% in Millipore water, 0.5 mL) and benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) were added, followed by K_3PO_4 (54 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. The aqueous layer was extracted with EtOAc (3x). Combined org. layers were dried over Na_2SO_4, concentrated under vacuum, and purified using column chromatography (4 g silica, 15 mL/min, 0–7 % EtOAc in heptane). The desired product **7** was isolated as an orange oil (84 mg, 74%).

Reaction in water: 2-fluoro-1-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv) was loaded into an 8 mL microwave tube equipped with a magnetic stirring bar. Millipore water (0.5 mL) and benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) were added, followed by KOH (28 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt and reaction progress was monitored by LC-MS. The aqueous layer was extracted with EtOAc (3x). Combined org. layers were dried over Na_2SO_4, concentrated under vacuum, and purified using column chromatography (4 g silica, 15 mL/min, 0–7 % EtOAc in heptane). The desired product **7** was isolated as an orange oil (74 mg, 64%).

Investigation of different work-up solvents

As DCM is not an environmentally friendly solvent,[1] its replacement for extraction of the S_NAr products was investigated. Therefore, HPMC solution (0.1 wt% HPMC in Millipore water, 0.5 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt for 20 min. After completion of the reaction, extraction solvent (3 mL) was added, and the mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges with either a PTS membrane (for DCM) or PTL membrane (for EtOAc) from *Macherey Nagel*®. The organic layer was evaporated, and the crude product was adsorbed on silica prior to column chromatography (4 g silica, 15 mL/min, 0–8 % EtOAc in heptane). The desired product **3** was obtained as a white solid.

Table S3 Comparison of different work-up solvents.



Entry	Work-up solvent	Yield [%][a]
1	DCM	90
2	EtOAc	86

[a] isolated yields.

In order to investigate if not only the final products but also HPMC itself is extracted during the work-up procedure, DCM and EtOAc were analyzed for their capacity to dissolve HPMC. This would lead to undesired residual HPMC in the final products. For this purpose, HPMC solution (0.1 wt% HPMC in Millipore water, 5.0 mL, contains 5 mg HPMC) was extracted either with DCM (3 x 20 mL) or EtOAc (3 x 20 mL). The combined organic layers of each extraction solvent were dried over Na_2SO_4 and evaporated to dryness. Both aqueous layers were lyophilized. The residues of each layer were dissolved in D_2O and ^1H NMR spectra were recorded and compared to a spectrum of HPMC in D_2O (see Figure S3–S4). For both extraction solvents, a major part of HPMC was found to be present in the aqueous layer (82–92% of total 5 mg HPMC, see Table S4). In the organic layer of the EtOAc extraction no residual HPMC was detected. In the organic layer of the DCM extraction only 0.7 mg of HPMC was detected.

Table S4 Residual amount of HPMC in different layers after extraction with DCM or EtOAc.

Entry	Extraction solvent	Layer	HPMC amount [mg]
1	DCM	org.	0.7
2	DCM	aq.	4.1
3	EtOAc	org.	0.1
4	EtOAc	aq.	4.6

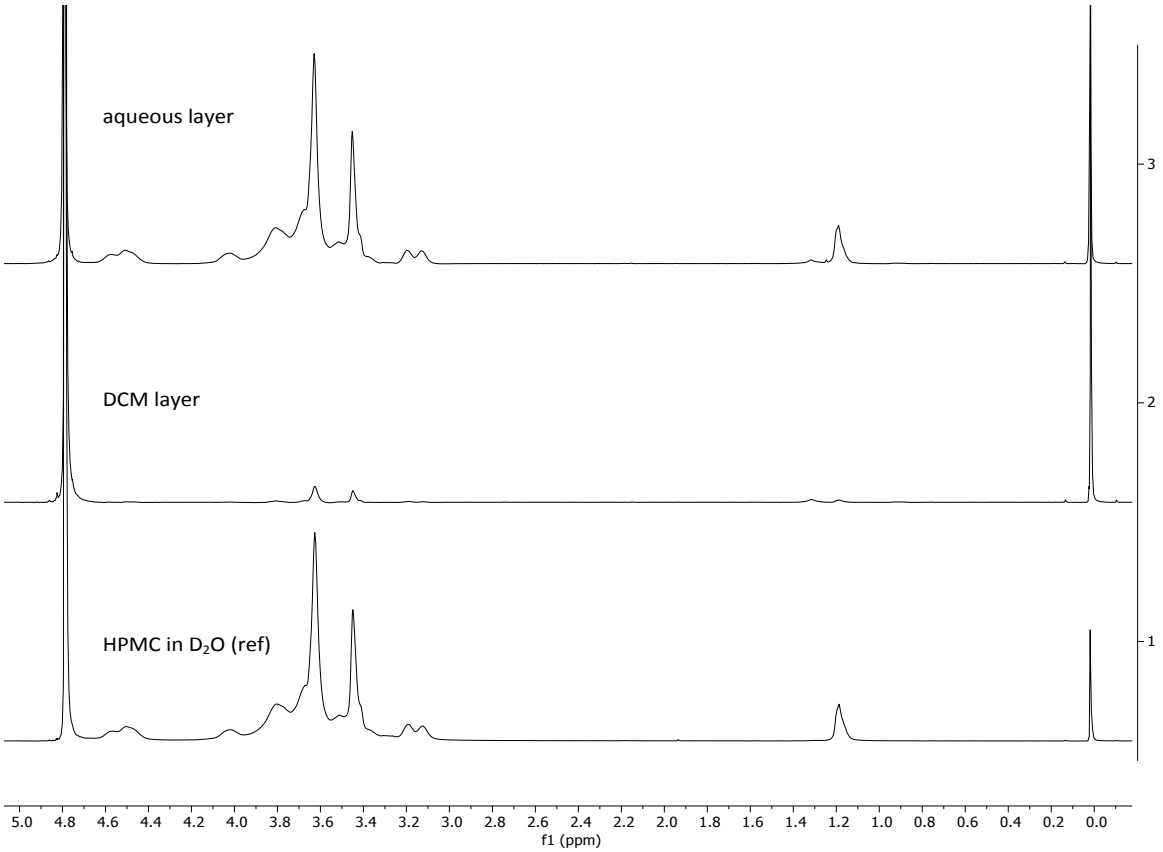


Figure S3 NMR spectra of different layers resulting from the extraction with DCM. (1) Reference spectrum of HPMC in D_2O. (2) NMR spectrum of organic DCM layer. (3) NMR spectrum of the aqueous layer after extraction with DCM.

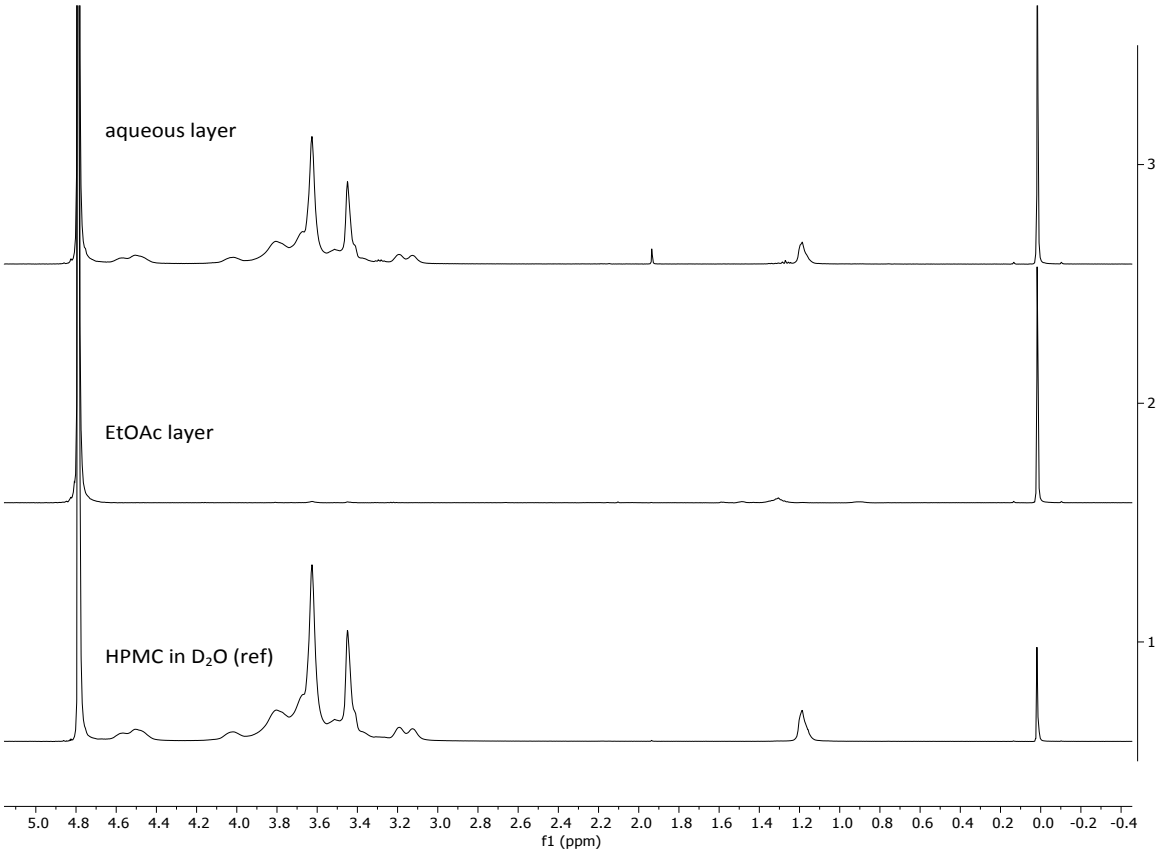


Figure S4 NMR spectra of different layers resulting from the extraction with EtOAc. (1) Reference spectrum of HPMC in D_2O. (2) NMR spectrum of organic EtOAc layer. (3) NMR spectrum of the aqueous layer after extraction with EtOAc.

Recycling study (cf. Scheme 1)

In order to explore whether it is possible to recycle the aqueous reaction medium containing HPMC in multiple consecutive reactions, three distinct reactions were conducted using the same reaction solvent.

HPMC solution (0.1 wt% HPMC in Millipore water, 1.0 mL) was loaded into an 8 mL microwave vial equipped with a magnetic stirring bar. 2,4,5-trichloropyrimidine (**1**, 115 µL, 1.0 mmol, 1.0 equiv) was added, followed by pyrrolidine (**2**, 83 µL, 1.0 mmol, 1.0 equiv) and KOH (56 mg, 0.5 mmol, 1.0 equiv). The reaction was stirred at rt for 10 min. EtOAc (3 mL) was added to the reaction and the mixture was stirred vigorously for 5–10 min. Layers were allowed to separate. The org. layer was removed using a syringe and the procedure was repeated one more time. Combined org. layers were dried over Na_2SO_4 and concentrated under vacuum. 2,5-dichloro-4-(pyrrolidine-1-yl)pyrimidine (**3**) was obtained spectroscopically clean as a white solid (196 mg, 90%). The aqueous layer remained in the microwave vial and the same reaction procedure was repeated using this solvent from the first reaction. After isolation 2,5-dichloro-4-(pyrrolidine-1-yl)pyrimidine (**3**) was obtained spectroscopically pure as a white solid (187 mg, 86%).

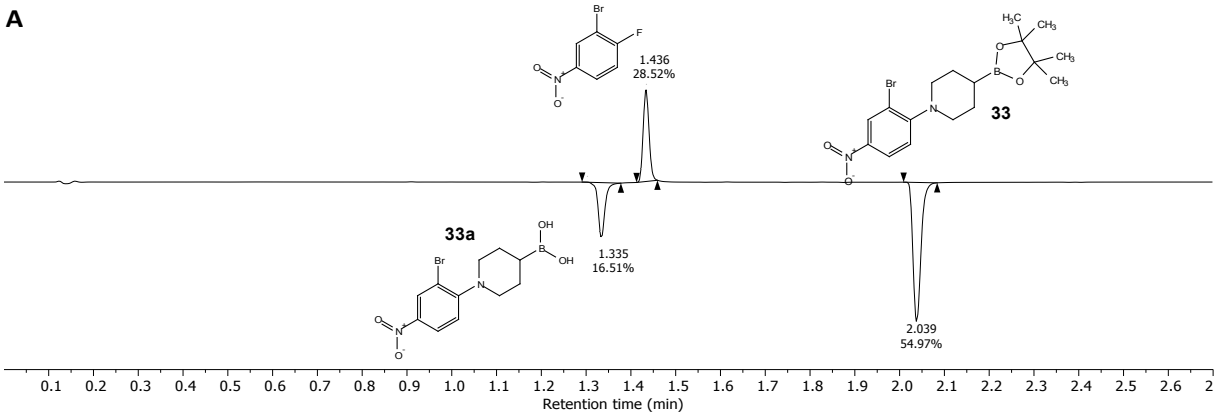
The aqueous layer remained in the microwave vial and 2,4,5-trichloropyrimidine (**1**, 115 µL, 1.0 mmol, 1.0 equiv.) was added, followed by 2-(3,4-dimethoxyphenyl)ethanamine (169 µL, 1.0 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 1.0 equiv). The reaction was stirred at rt for 10 min. EtOAc (3 mL) was added to the reaction and the mixture was stirred vigorously for 5–10 min. Layers were allowed to separate. The org. layer was removed using a syringe and the procedure was repeated one more time. Combined org. layers were dried over Na_2SO_4 and concentrated under vacuum. 2,5-dichloro-*N*-(3,4-dimethoxyphenethyl)pyrimidine-4-amine (**10**) was obtained spectroscopically clean as a yellow oil (320 mg, 80%). Analytical data for compound **10** are in accordance with previously reported data in the literature.[2]

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.93 (t, *J* = 5.8 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 8.1 Hz, 2.0 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.62–3.55 (m, 2H), 2.80 (t, *J* = 7.3 Hz, 2H) ppm.

Control experiments in organic solvents

Stability of alkyl boronic esters

In order to verify that the low decomposition rate observed for products **31**–**33** in reactions of different boronic esters is related to HPMC/water as a solvent, reaction of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine with 1-fluoro-2-bromo-4-nitrobenzene was conducted in an organic solvent (DMF). The reaction was monitored by LC-MS and the ratio between the desired boronic ester (**33**, r_t = 2.0 min) and the boronic acid (**33a**, r_t = 1.3 min) was determined by integration of the corresponding peaks in the UV-chromatogram (280 nm). For the reaction in DMF a ratio of 77:23 (**33**:**33a**) was observed after 22 h (see Figure S5). For the reaction in HPMC/water a ratio of 95:5 (**33**:**33a**) was observed after 22 h (see Figure S6).



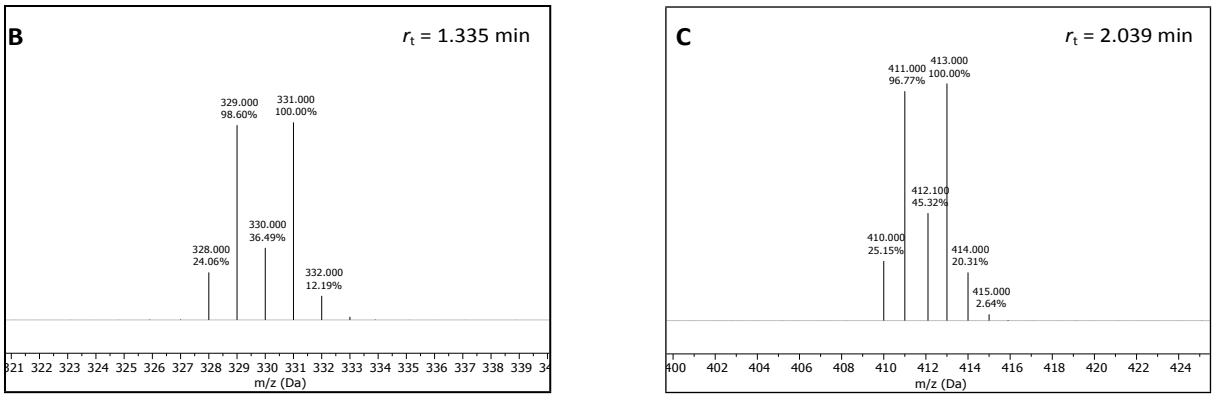


Figure S5 Reaction of 1-fluoro-2-bromo-4-nitrobenzene with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine in DMF. **A.** UV-chromatogram at 280 nm after 22 h. **B.** MS-spectrum at 1.335 min, m/z $[M+H]^+$ calcd. for $C_{11}H_{15}BBrN_2O_4^+$ 329.03; found: 329.00. **C.** MS-spectrum at 2.039 min, m/z $[M+H]^+$ calcd. for $C_{17}H_{25}BBrN_2O_4^+$ 411.11; found: 411.00.

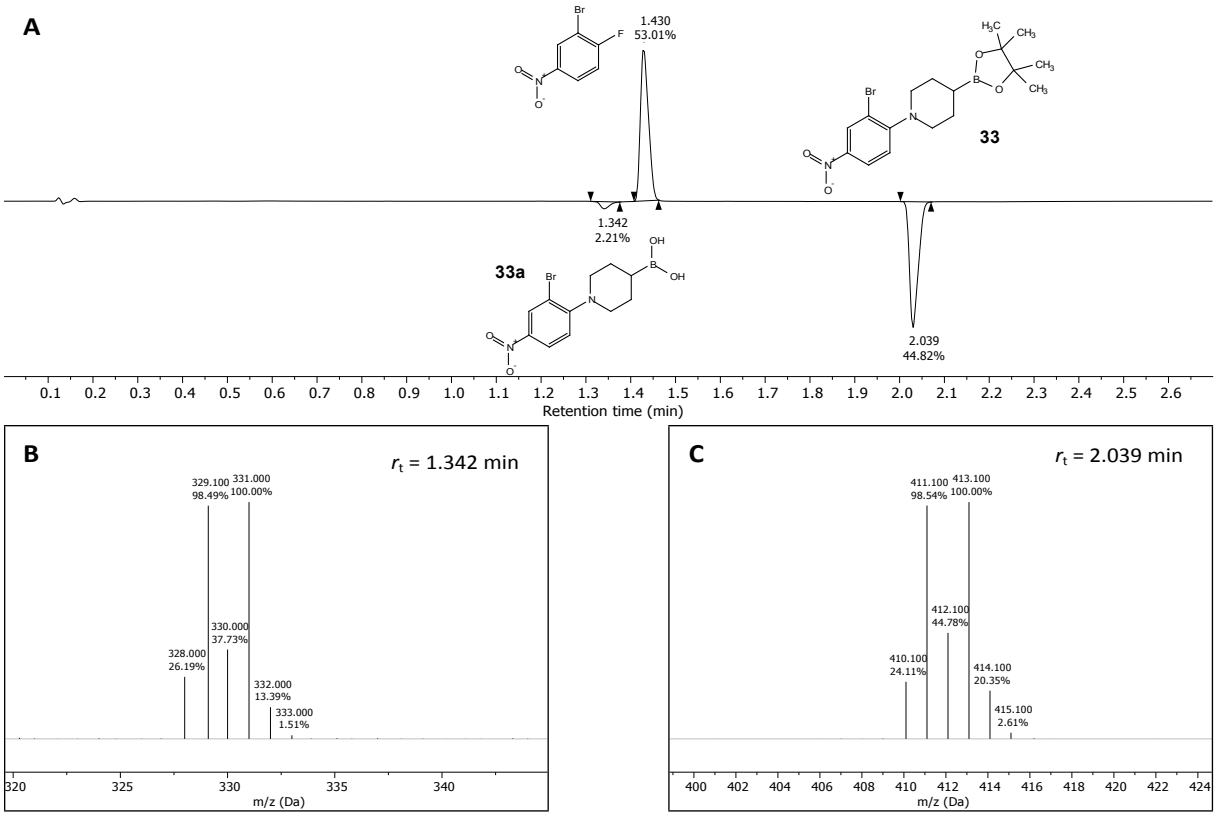


Figure S6 Reaction of 1-fluoro-2-bromo-4-nitrobenzene with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine in HPMC/water. **A.** UV-chromatogram at 280 nm after 22 h. **B.** MS-spectrum at 1.342 min, m/z $[M+H]^+$ calcd. for $C_{11}H_{15}BBrN_2O_4^+$ 329.03; found: 329.10. **C.** MS-spectrum at 2.039 min, m/z $[M+H]^+$ calcd. for $C_{17}H_{25}BBrN_2O_4^+$ 411.11; found: 411.10.

N-over O-selectivity for amino alcohols

To determine that the remarkable chemoselectivity observed for products **19**–**24** in reactions of various aminoalcohols with different electrophiles is related to HPMC/water as reaction solvent, the reaction of 2-fluoro-5-cyanopyridine with 4-aminobutanol was conducted in an organic solvent (DMF). The reaction was monitored by LC-MS and the ratio between the desired *N*-substituted product (**24**, r_t = 0.68 min) and the *N*,*O*-disubstituted (**24a**, r_t = 1.30 min) was determined by integration of the corresponding peaks in the UV-chromatogram (280 nm). For the reaction in DMF a ratio of 38:62 (**24**:**24a**) with an overall conversion of 96% was observed after 2 h (see Figure S7). For the reaction in HPMC/water a ratio of 95:5 (**24**:**24a**) with an overall conversion of 94% was observed after 5 h (see Figure S8). *O*-substituted product was observed in neither of the two solvents.

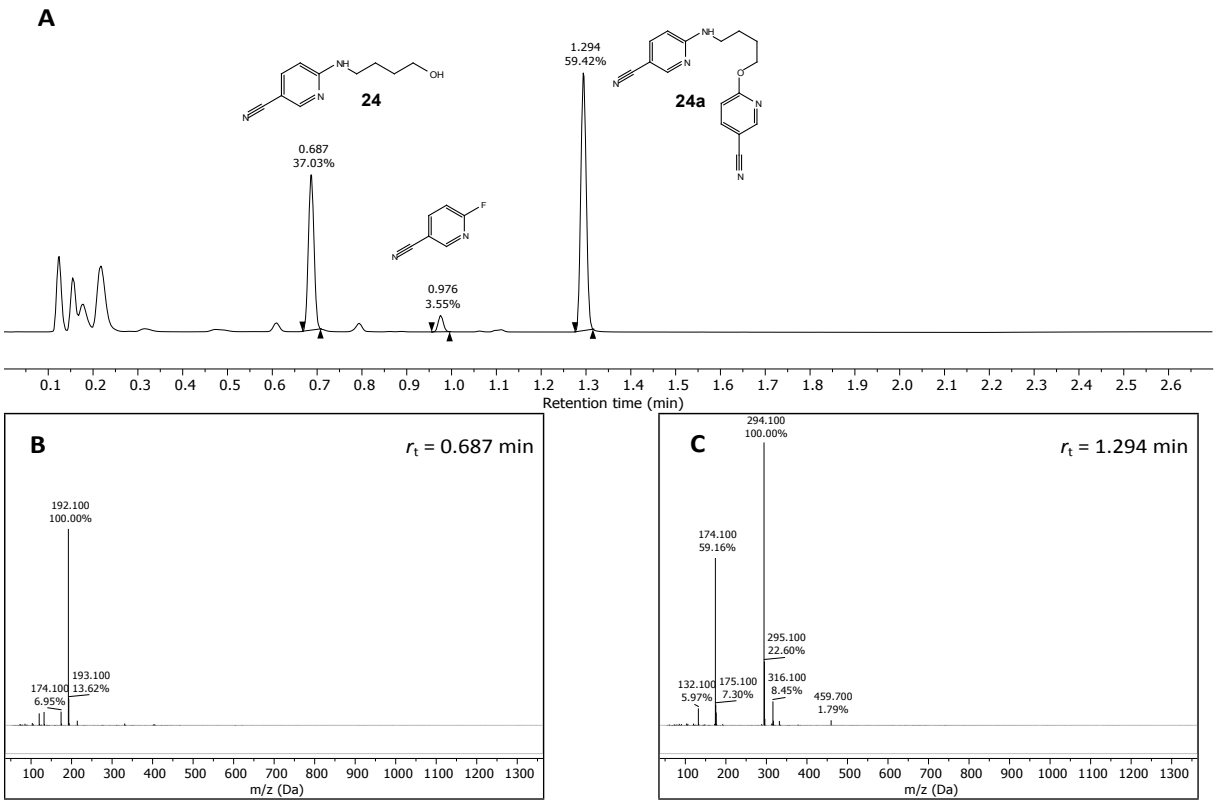


Figure S7 Reaction of 2-fluoro-5-cyanopyridine with 4-aminobutanol in DMF. **A.** UV-chromatogram at 280 nm after 2 h. **B.** MS-spectrum at 0.687 min, m/z $[M+H]^+$ calcd. for $C_{10}H_{14}N_3O^+$ 192.11; found: 192.10. **C.** MS-spectrum at 1.294 min, m/z $[M+H]^+$ calcd. for $C_{16}H_{16}N_5O^+$ 294.13; found: 294.10.

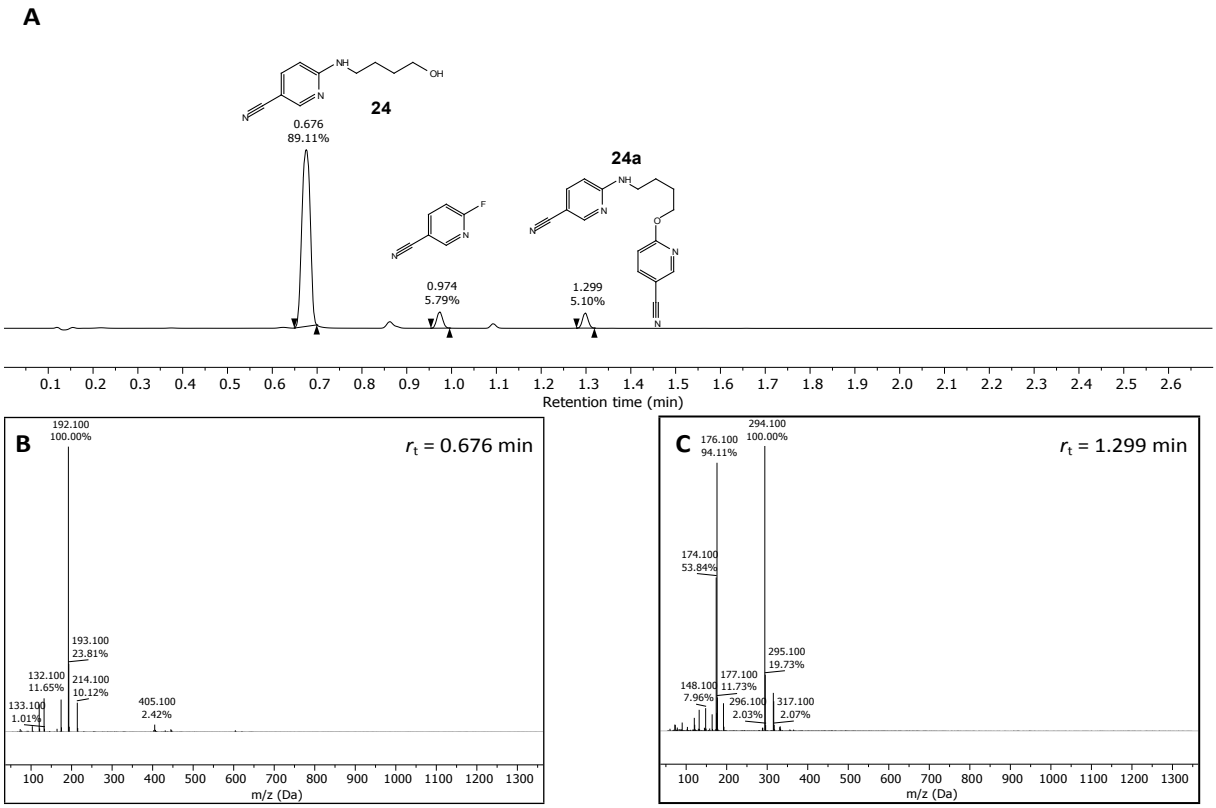


Figure S8 Reaction of 2-fluoro-5-cyanopyridine with 4-aminobutanol in HPMC/water. **A.** UV-chromatogram at 280 nm after 5 h. **B.** MS-spectrum at 0.676 min, m/z $[M+H]^+$ calcd. for $C_{10}H_{14}N_3O^+$ 192.11; found: 192.10. **C.** MS-spectrum at 1.299 min, m/z $[M+H]^+$ calcd. for $C_{16}H_{16}N_5O^+$ 294.13; found: 294.10.

Regioselectivity of 2,4,5-trichloropyrimidines

In order to verify that the remarkable regioselectivity observed for the reactions of 2,4,5-trichloropyrimidine (**1**) with various amines (**3**, **11**–**14**) is a consequence of using HPMC/water as a reaction solvent, reaction of 2,4,5-trichloropyrimidine (**1**) with pyrrolidine (**2**) was conducted in an organic solvent (DMF). The reaction was monitored by LC-MS and the ratio between the desired 4-subsituted product (**3**, r_t = 1.46 min), the 2-substituted regioisomer (**3a**, r_t = 1.66 min) and the undesired 2,4-disubstituted product (**3b**, r_t = 0.96 min) was determined by integration of the corresponding peaks in the UV-chromatogram (254 nm). For the reaction in DMF a ratio of 65:29:6 (**3**:**3a**:**3b**) with an overall conversion of 95% was observed after 1 h (see Figure S9). For the reaction in HPMC/water a ratio of 94:6:0 (**3**:**3a**:**3b**) with an overall conversion of 99% was observed after 1 h (see Figure S10).

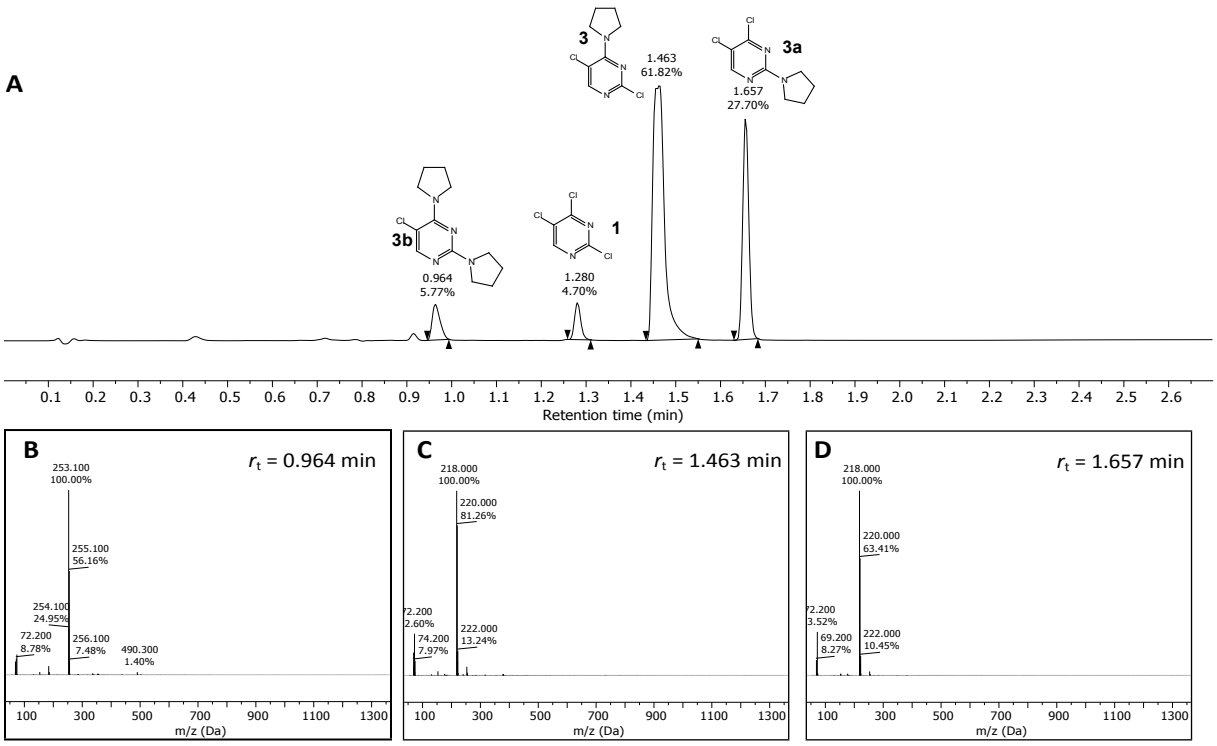
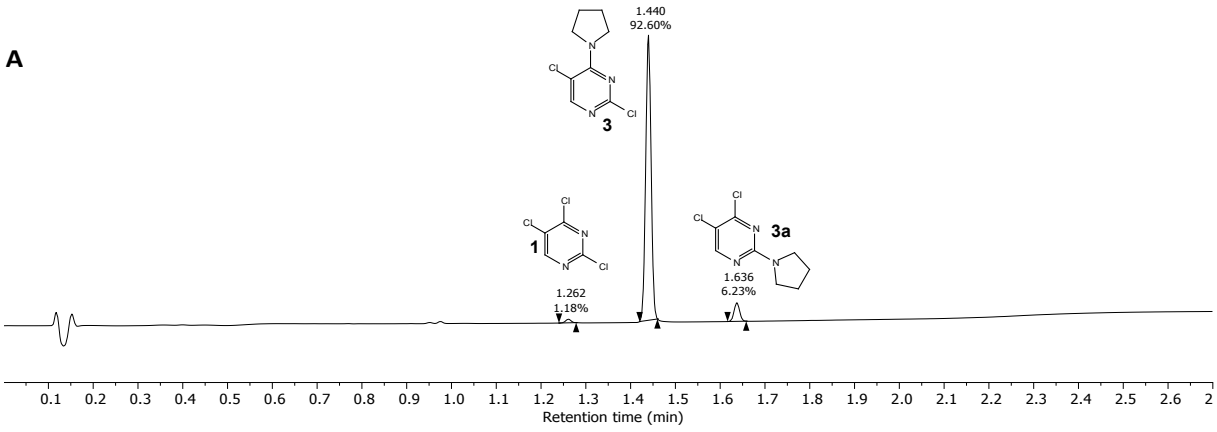


Figure S9 Reaction of 2,4,5-trichloropyrimidine (**1**) with pyrrolidine (**2**) in DMF. **A.** UV-chromatogram at 254 nm after 1 h reaction time. **B.** MS-spectrum at 0.964 min, m/z $[M+H]^+$ calcd. for $C_{12}H_{18}ClN_4^+$ 253.12; found: 253.10. **C.** MS-spectrum at 1.463 min, m/z $[M+H]^+$ calcd. for $C_8H_{10}Cl_2N_3^+$ 218.02; found: 218.00. **D.** MS-spectrum at 1.657 min, m/z $[M+H]^+$ calcd. for $C_8H_{10}Cl_2N_3^+$ 218.02; found: 218.00.



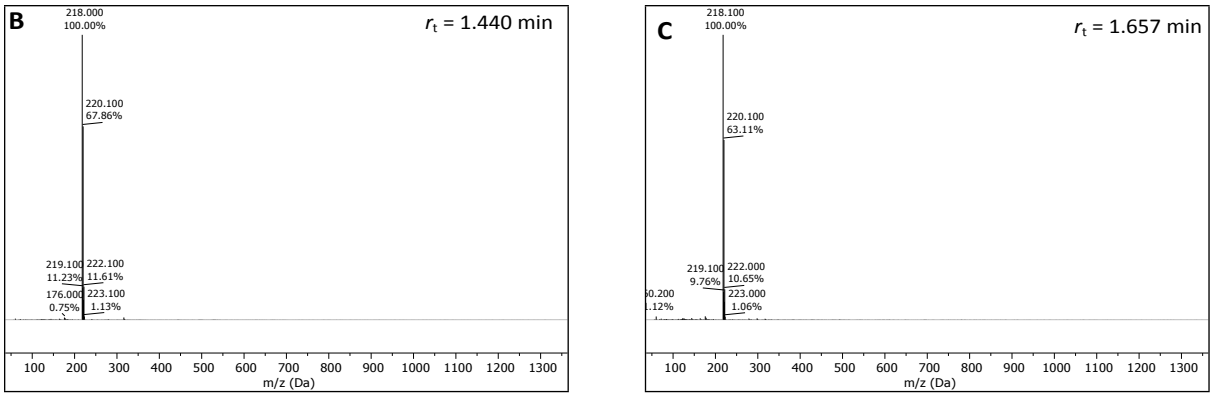
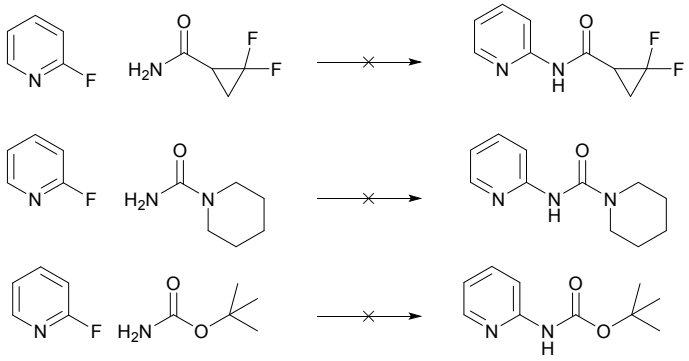


Figure S10 Reaction of 2,4,5-trichloropyrimidine (**1**) with pyrrolidine (**2**) in HPMC/water. **A.** UV-chromatogram at 254 nm after 1 h reaction time. **B.** MS-spectrum at 1.440 min, m/z $[M+H]^+$ calcd. for $C_8H_{10}Cl_2N_3^+$ 218.02; found: 218.00. **C.** MS-spectrum at 1.657 min, m/z $[M+H]^+$ calcd. for $C_8H_{10}Cl_2N_3^+$ 218.02; found: 218.00.

Limitations of the S_NAr reaction in HPMC/water

Reaction with non-nucleophilic amines

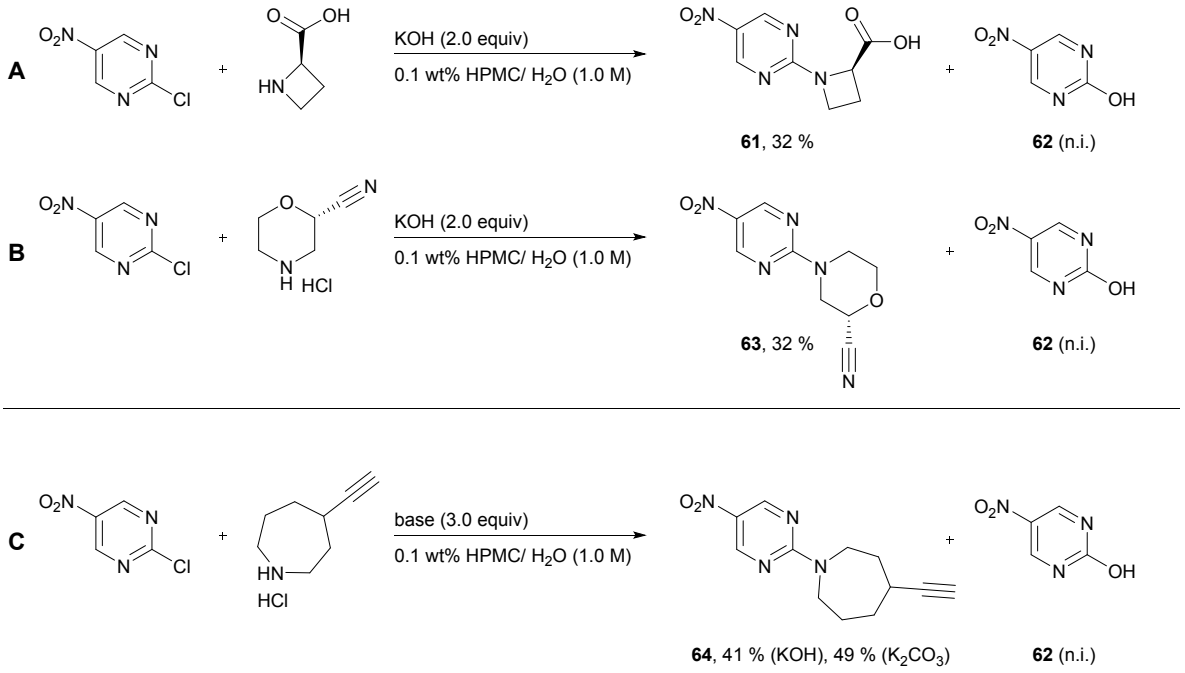
In order to verify that the reactivity of the nucleophile in aq. medium is comparable to the one in organic medium, three control experiments with non-nucleophilic NH_2-groups were conducted. General procedure I was followed by reacting 2-fluoropyridine (43 µL, 0.5 mmol, 1.0 equiv), either 2,2-difluorocyclopropane-1-carboxamide (61 mg, 0.5 mmol, 1.0 equiv), piperidine-1-carboxamide (64 mg, 0.5 mmol, 1.0 equiv) or *tert*-butyl carbamate (59 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 24 h. Using LC-MS analysis no product formation was detected.



Scheme S1 Control experiments with non-nucleophilic NH_2-groups (amide, urea, carbamate). No product formation was observed by LC-MS analysis

Reactions with 2-chloro-5-nitropyrimidine

To evaluate if some electron deficient amines, that have proven to be relatively unreactive during our studies, need a more activated electrophile to give the desired products in good yields, two challenging amines were reacted with 2-chloro-5-nitropyrimidine (Scheme S2, **A–B**). Despite using a more activated electrophile, desired products **61** and **63** were obtained in low yields only. We hypothesized that this could be explained by competing hydrolysis of this highly activated electrophile to 2-hydroxy-5-nitropyrimidine (**62**). To examine this hypothesis, 4-ethynylazepam, which was known to be reactive in S_NAr reactions in HPMC/water, was reacted with 2-chloro-5-nitropyrimidine (Scheme S2, **C**). However, this reaction also delivered product **64** in moderate yield only. The same experiment was also conducted with a weaker base in order to suppress the hydrolysis of the starting material, but this only led to a small increase in the yield. This led to a conclusion that highly activated electrophiles present a limitation of the S_NAr reaction in HPMC/water due to competing hydrolysis of these substrates.



Scheme S2 Reactions of different electrondeficient amines with 2-chloro-5-nitropyrimidine (**A-B**). (**C**) Control reaction with a known nucleophile. n.i.: not isolated.

Synthesis

General Procedure I

The electrophile (0.5 mmol, 1.0 equiv) was weighed into an 8 mL microwave tube equipped with a magnetic stirring bar. HPMC solution (0.1 wt% in Millipore water, 0.5 mL) was added and the mixture was stirred 1–2 min until a homogeneous solution or suspension was formed. The amine (0.5 mmol, 1.0 equiv) was added, followed by inorganic base. The reaction mixture was stirred at rt or 50 °C and reaction progress was monitored by LC-MS. After the reaction was completed, DCM (3 mL) was added, and the mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges containing a PTS membrane (*Macherey Nagel*®). The organic layer was evaporated, and crude product was adsorbed on silica gel prior to column chromatography (4 g silica, 15 mL/min).

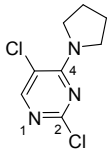
General Procedure II

The nucleophile (0.5 mmol, 1.0 equiv) and KOH (0.5 mmol, 1.0 equiv) were weighed into a 4 mL reaction vial equipped with a magnetic stirring bar. HPMC solution (0.1 wt% in Millipore water, 1.0 mL) was added and the mixture was stirred 5 min until a homogeneous solution or suspension was formed. The electrophile (0.5 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 60 °C. Reaction progress was monitored by TLC or GC-MS until complete consumption of starting material. The reaction mixture was allowed to cool down to rt, EtOAc (1.0 mL) was added and the mixture was stirred vigorously for 5–10 min. Stirring was stopped, and the organic layer was removed with a syringe. As required, a second extraction step was performed. The organic layer was dried

over Na2SO4 and was evaporated to obtain crude product. If necessary, flash chromatography using EtOAc/hexanes was performed for further purification.

Synthesis of the S_NAr Products

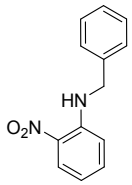
2,5-dichloro-4-(pyrrolidin-1-yl)pyrimidine (3)



General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 10 min. LCMS analysis of the completed reaction revealed a ratio of 94:6 of the two possible regioisomers (4-position vs. 2-position). Purification was performed using column chromatography (0–8% EtOAc in heptane). The desired product **3** was obtained as a white solid (98 mg, 90%). Analytical data for compound **3** is in accordance with previously reported data in the literature.[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 3.93–3.73 (m, 4H), 2.01–1.89 (m, 4H) ppm.

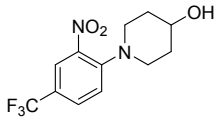
***N*-benzyl-2-nitroaniline (7)**



General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv), benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **7** was obtained as a yellow oil (94 mg, 82%). Analytical data for compound **7** is in accordance with previously reported data in the literature.[4]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 8.20 (dd, *J* = 8.6 Hz, 1.6 Hz, 1H), 7.44–7.27 (m, 6H), 6.82 (dd, *J* = 8.6 Hz, 1.2 Hz, 1H), 6.67 (ddd, *J* = 8.4 Hz, 6.9 Hz, 1.2 Hz, 1H), 4.55 (d, *J* = 5.6 Hz, 2H) ppm.

1-(4-nitro-3-(trifluoromethyl)phenyl)piperidin-4-ol (8)



General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), piperidin-4-ol (51 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 15 min. The desired product **8** was obtained as a yellow solid (112 mg, 81%). Analytical data match those of the commercially available compound (CAS: 702650-29-1).

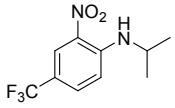
***R*$_f$** = 0.31 (1:9, EtOAc/hexanes); **Melting point:** 140–146 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.17 (d, *J* = 8 Hz, 1H), 3.98–3.94 (m, 1H), 3.38–3.35 (m, 2H), 3.06–3.00 (m, 2H), 2.02 (m, 2H), 1.78–1.70 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 140.1, 130.2, 124.6, 124.3, 120.6, 77.3, 77.0, 76.7, 66.5, 48.3, 33.8 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.12 (3F) ppm.

***N*-*iso*-propyl-2-nitro-4-(trifluoromethyl)aniline (9)**



General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), *iso*-propylamine (43 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 15 min. The desired product **9** was obtained as a yellow solid (113 mg, 91%).

***R*$_f$** = 0.30 (1:9, EtOAc/hexanes); **Melting point:** 104–105 °C.

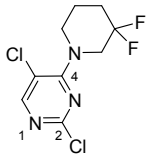
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.22 (s, 1H), 7.59 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 3.88 (q, *J* = 8 Hz, 1H), 1.36 (d, *J* = 8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 132.1, 130.8, 125.3, 125.3, 121.1 (q, *J* = 270 Hz), 117.1 (q, *J* = 34 Hz), 114.9, 44.5, 22.7 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.02 (3F) ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{10}H_{11}F_3N_2O_2$ 248.0767, found: 248.0771.

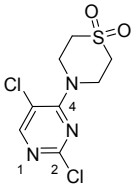
2,5-dichloro-4-(3,3-difluoropiperidin-1-yl)pyrimidine (11)



General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), 3,3-difluoropiperidine hydrochloride (79 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 2.5 h. LCMS analysis of the completed reaction revealed a ratio of 78:22 of the two possible regioisomers (4-position vs. 2-position). Purification was performed using column chromatography (0–10% EtOAc in heptane). The desired product **11** was obtained as a colorless oil (98 mg, 73%).

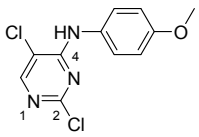
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 4.00 (t, J = 11.5 Hz, 2H), 3.79–3.70 (m, 2H), 2.16–2.05 (m, 2H), 1.98–1.90 (m, 2H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 158.7, 157.7, 119.1 (t, *J* = 244.9 Hz, 1C), 115.2, 52.3 (t, *J* = 32.5 Hz, 1C), 46.9, 32.4 (t, *J* = 23.3 Hz, 1C), 21.5 (t, *J* = 4.8 Hz, 1C) ppm.
^{19}F NMR (471 MHz, $CDCl_3$) δ -101.7 (p, *J* = 11.5 Hz, 2F) ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_9H_{10}Cl_2F_2N_3^+$ 268.0215, found: 268.0221

4-(2,5-dichloropyrimidin-4-yl)thiomorpholine 1,1-dioxide (12)



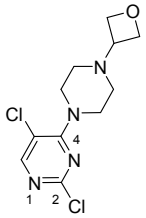
General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), thiomorpholine 1,1-dioxide (68 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 22 h. LCMS analysis of the completed reaction revealed only formation of the desired 4-regioisomer (no substitution at 2-position). Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **12** was obtained as a white solid (105 mg, 74%).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H), 4.21–4.05 (m, 4H), 3.40–3.32 (m, 4H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6) δ 159.6, 159.0, 156.4, 115.2, 50.9, 45.6 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_8H_{10}Cl_2N_3O_2S^+$ 281.9865, found: 281.9872.

2,5-dichloro-*N*-(4-methoxyphenyl)pyrimidin-4-amine (13)



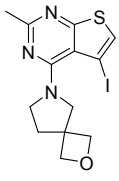
General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), *p*-ansidine (58 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 22 h. LCMS analysis of the completed reaction revealed a ratio of 98:0.5:1.5 of the two possible regioisomers and the double substituted product (4-position vs. 2-position vs. 2,4-double substituted). Purification was performed using column chromatography (0–20% EtOAc in heptane). The desired product **13** was obtained as a white solid (122 mg, 90%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.54–7.43 (m 2H), 7.15 (br s, 1H), 6.99–6.88 (m, 2H), 3.82 (s, 3H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 157.3, 156.8, 154.4, 129.7, 123.5, 114.5, 113.6, 55.6 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{10}Cl_2N_3O^+$ 270.0196, found: 270.0203.

2,5-dichloro-4-(4-(oxetan-3-yl)piperazin-1-yl)pyrimidine (14)



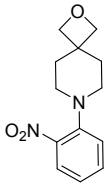
General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), 1-oxetan-3-yl-piperazine (71 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 10 min. LCMS analysis of the completed reaction revealed a ratio of 95:4:1 of the two possible regioisomers and the double substituted product (4-position vs. 2-position vs. 2,4-double substituted). Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **14** was obtained as a white solid (137 mg, 94%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 4.69 (t, *J* = 6.6 Hz, 2H), 4.64 (t, *J* = 6.2 Hz, 2H), 3.87 (t, *J* = 5.0 Hz, 2H), 3.54 (p, *J* = 6.4 Hz, 1H), 2.45 (t, *J* = 5.0 Hz, 2H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2, 158.5, 157.8, 119.9, 75.3, 59.1, 49.5, 46.9 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{15}Cl_2N_4O^+$ 289.0617, found: 289.0626.

6-(5-iodo-2-methylthieno[2,3-*d*]pyrimidin-4-yl)-2-oxa-6-azaspiro[3.4]octane (15)



General procedure I was followed by reacting 4-chloro-5-iodo-2-methylthieno[2,3-*d*]pyrimidine (155 mg, 0.5 mmol, 1.0 equiv), 2-oxa-6-azaspiro[3.4]octane (52 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 20 h. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **15** was obtained as a slightly yellow solid (159 mg, 82%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 4.71 (d, *J* = 6.1 Hz, 2H), 4.62 (d, *J* = 6.1 Hz, 2H), 4.07 (s, 2H), 3.85 (t, *J* = 6.9 Hz, 2H), 2.58 (s, 3H), 2.20 (t, *J* = 6.9 Hz) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 161.8, 160.1, 126.6, 116.3, 81.1, 69.6, 60.3, 52.2, 45.2, 35.8, 25.5 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{13}H_{15}IN_3OS^+$ 387.9975, found: 387.9967.

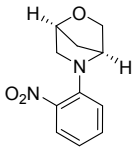
7-(2-nitrophenyl)-2-oxa-7-azaspiro[3.5]nonane (16)



General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv), 2-oxa-7-azaspiro[3.5]nonane (61 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **16** was obtained as an orange oil (98 mg, 79%). Analytical data for compound **16** is in accordance with previously reported data in the literature.[5]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.45 (ddd, *J* = 8.7 Hz, 7.4 Hz, 1.7 Hz, 1H), 7.10 (dd, *J* = 8.4 Hz, 1.3 Hz), 7.02 (ddd, *J* = 8.4 Hz, 7.3 Hz, 1.3 Hz), 4.47 (s, 4H), 3.01–2.90 (m, 4H), 2.07–1.98 (m, 4H) ppm.

(1*S*,4*S*)-5-(2-nitrophenyl)-2-oxa-5-azabicyclo[2.2.1]heptane (17)



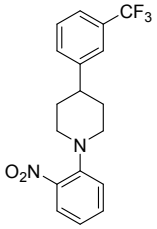
General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv), (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (68 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–75% EtOAc in heptane). The desired product **17** was obtained as a yellow solid (57 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2 Hz, 1.7 Hz, 1H), 7.36 (ddd, *J* = 8.7 Hz, 7.1 Hz, 1.7 Hz, 1H), 6.83 (dd, *J* = 8.6 Hz, 1.2 Hz, 1H), 6.78 (ddd, *J* = 8.2 Hz, 7.1 Hz, 1.1 Hz, 1H), 4.63–4.58 (m, 1H), 4.45–4.39 (m, 1H), 4.00 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H), 3.87 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 3.62 (dd, *J* = 10.0 Hz, 1.7 Hz, 1H), 2.62 (dd, *J* = 10.0 Hz 1.6 Hz, 1H), 2.07 (dd, *J* = 10.0 Hz, 2.4 Hz), 2.02–1.95 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9, 138.5, 133.1, 127.2, 117.2, 117.1, 76.4, 71.4, 59.9, 59.7, 36.8 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{13}N_2O_3^+$ 221.0921, found: 221.0922.

1-(2-nitrophenyl)-4-(3-(trifluoromethyl)phenyl)piperidine (18)



General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv), 4-(3-trifluoromethylphenyl)piperidine hydrochloride (133 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 2.5 h. Purification was performed using column chromatography (0–10% EtOAc in heptane). The desired product **18** was obtained as a yellow oil (164 mg, 94%).

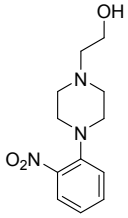
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.1 Hz, 1.6 Hz, 1H), 7.55–7.41 (m, 5H), 7.19 (dd, *J* = 8.3 Hz, 1.2 Hz), 7.04 (ddd, *J* = 8.4 Hz, 7.3 Hz, 1.2 Hz), 3.46–3.36 (m, 2H), 3.02–2.91 (m, 2H), 2.79–2.67 (m, 2H), 2.03–1.89 (m, 4H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7, 143.4, 133.6, 131.0 (q, *J* = 31.5 Hz, 1C), 130.4, 129.1, 126.1, 124.1 (q, *J* = 271.4, 1C), 123.9 (q, *J* = 3.8 Hz, 1C), 123,4 (q, *J* = 3.8 Hz, 1C), 121.6, 121.4, 52.9, 42.4, 33.4 ppm.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5 (s, 3F) ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{18}H_{18}F_3N_2O_2^+$ 351.1315, found: 351.1317.

2-(4-(2-nitrophenyl)piperazin-1-yl)ethan-1-ol (19)



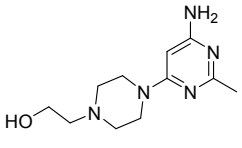
General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (**5**, 53 µL, 0.5 mmol, 1.0 equiv), *N*-(2-hydroxyethyl)piperazine (61 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–100% EtOAc in heptane, then 0-10% MeOH in EtOAc). The desired product **19** was obtained as a yellow oil (92 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.48 (ddd, *J* = 8.7 Hz, 7.4 Hz, 1.7 Hz, 1H), 7.15 (dd, *J* = 8.2 Hz, 1.2 Hz, 1H), 7.05 (ddd, *J* = 8.3 Hz, 7.4 Hz, 1.2 Hz, 1H), 3.71–3.60 (m, 2H), 3.17–3.04 (m, 4H), 2.74–2.66 (m, 4H), 2.65–2.60 (m, 2H), 2.33 (br s, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0, 143.7, 133.6, 126.0, 122.1, 121.2, 59.4, 57.8, 52.9, 51.9 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{18}N_3O_3^+$ 252.1343, found: 252.1343.

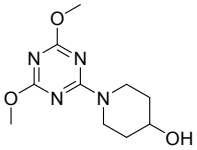
2-(4-(6-amino-2-methylpyrimidin-4-yl)piperazin-1-yl)ethanol (20)



General procedure I was followed by reacting 4-amino-6-chloro-2-methylpyrimidine (144 mg, 1.0 mmol, 1.0 equiv), *N*-(2-hydroxyethyl)piperazine (123 µL, 1.0 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 50 °C for 48 h. Reaction solvent was evaporated and DCM (10 mL) were added. A white solid precipitated and was filtered off. The desired product **20** was obtained as a white solid (191 mg, 80%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 6.06 (br s, 2H), 5.42 (s, 1H), 4.45 (br s, 1H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.38 (t, *J* = 5.0 Hz, 4H), 2.46–2.36 (m, 6H), 2.15 (s, 3H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 164.5, 162.8, 79.5, 60.3, 58.5, 52.9, 43.6, 25.7 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{20}N_5O^+$ 238.1662, found: 238.1671.

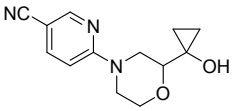
1-(4,6-dimethoxy-1,3,5-triazin-2-yl)piperidin-4-ol (21)



General procedure II was followed by reacting 2-chloro-4,6-dimethoxy-1,3,5-triazine (88 mg, 0.5 mmol, 1.0 equiv), piperidin-4-ol (51 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **21** was obtained as an off-white solid (83 mg, 69%).
R_f = 0.31 (4:3, EtOAc/hexanes); **Melting point:** 140–146 °C

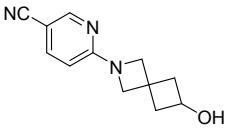
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35–4.30 (m, 2H), 3.99–3.96 (m, 1H), 3.94 (s, 6H), 3.45–3.40 (m, 2H), 1.94–1.91 (m, 2H), 1.61 (br s, 1H), 1.57–1.51 (m, 2H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 166.5, 67.6, 54.6, 41.0, 34.1 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{10}H_{17}N_4O_3^+$ 241.1295, found: 241.1252.

6-(2-(1-hydroxycyclopropyl)morpholino)nicotinonitrile (22)



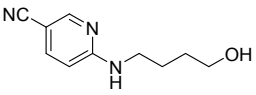
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 1-(morpholin-2-yl)cyclopropanol hydrochloride (90 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 2 h. Purification was performed using column chromatography (0–75% EtOAc in heptane). The desired product **22** was obtained as a white solid (75 mg, 61%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 2.3 Hz, 0.8 Hz, 1H), 7.64 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 6.62 (dd, *J* = 9.0 Hz, 0.8 Hz, 1H), 4.32–4.17 (m, 2H), 4.09 (ddd, *J* = 11.6 Hz, 3.7 Hz, 1.4 Hz, 1H), 3.67 (td, *J* = 11.8 Hz, 2.9 Hz, 1H), 3.25 (dd, *J* = 13.1 Hz, 10.9 Hz, 1H), 3.15–3.03 (m, 2H), 0.93–0.83 (m, 2H), 0.76–0.58 (m, 2H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 152.7, 140.1, 118.5, 106.2, 97.1, 79.7, 66.5, 56.2, 46.0, 44.4, 13.1, 10.6 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{13}H_{16}N_3O_2^+$ 246.1237, found: 246.1243.

6-(6-hydroxy-2-azaspiro[3.3]heptan-2-yl)nicotinonitrile (23)



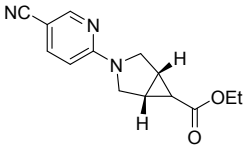
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 2-azaspiro[3.3]heptan-6-ol (57 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 1 h. Purification was performed using column chromatography (0–30% MeOH in DCM). The desired product **23** was obtained as a white solid (94 mg, 87%).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (dd, *J* = 2.3 Hz, 0.8 Hz, 1H), 7.78 (dd, *J* = 8.8 Hz, 2.3 Hz, 1H), 6.37 (dd, *J* = 8.8 Hz, 0.8 Hz, 1H), 5.05 (d, *J* = 6.2 Hz, 1H), 4.05–3.95 (m, 5H), 2.49–2.44 (m, 2H), 2.06–1.97 (m, 2H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6) δ 159.7, 152.9, 139.2, 118.9, 105.2, 94.9, 62.3, 60.9, 60.6, 43.7, 30.2 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{14}N_3O^+$ 216.1131, found: 216.1142.

6-((4-hydroxybutyl)amino)nicotinonitrile (24)



General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4-aminobutanol (46 µL, 0.5 mmol, 1.0 equiv) and K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 5 h. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **24** was obtained as a white solid (59 mg, 62%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37–8.28 (m, 1H), 7.54 (dd, *J* = 8.8 Hz, 2.3 Hz, 1H), 6.37 (dd, *J* = 8.8 Hz, 0.8 Hz, 1H), 5.42 (br s, 1H), 3.70 (t, *J* = 6.1 Hz, 2H), 3.38 (q, *J* = 6.5 Hz, 2H), 2.07 (br s, 1H), 1.80–1.58 (m, 4H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 153.3, 139.7, 118.8, 106.9, 96.7, 62.4, 41.7, 29.8, 25.9 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{10}H_{14}N_3O^+$ 192.1131, found: 192.1130.

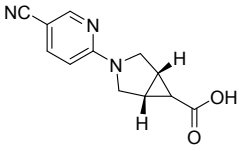
ethyl (1*R*,5*S*)-3-(5-cyanopyridin-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxylate (25)



General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), ethyl 3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (96 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 20 h. Purification was performed using column chromatography (0–50% EtOAc in heptane). The desired product **25** was obtained as a white solid (111 mg, 86%).

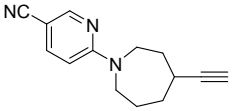
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 2.3 Hz, 0.8 Hz, 1H), 7.56 (dd, *J* = 8.9 Hz, 2.3 Hz, 1H), 6.30 (dd, *J* = 9.0 Hz, 0.8 Hz, 1H), 3.93 (q, *J* = 7.1 Hz, 2H), 3.89–3.77 (m, 2H), 3.74–3.55 (m, 2H), 2.16 (ddd, *J* = 8.1 Hz, 3.2 Hz, 1.5 Hz, 2H), 1.88 (t, *J* = 8.1 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 157.0, 153.0, 139.4, 119.1, 106.6, 96.0, 60.7, 46.8, 23.7, 23.2, 22.6, 14.2 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{14}H_{16}N_3O_2^+$ 258.1237, found: 258.1243.

(1*R*,5*S*)-3-(5-cyanopyridin-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (26)



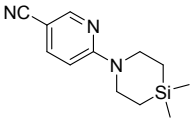
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 3-azabicyclo[3.1.0]hexane-6-carboxylic acid hydrochloride (82 mg, 0.5 mmol, 1.0 equiv) and KOH (84 mg, 1.5 mmol, 3.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 20 h. After completion of the reaction the mixture was diluted with MeOH and adsorbed on silica gel. Purification was performed using column chromatography (0–100 % MeOH in DCM). The desired product **26** was obtained as a white solid (113 mg, 97%).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (dd, *J* = 2.4 Hz, 0.7 Hz, 1H), 7.81 (dd, *J* = 8.9 Hz, 2.3 Hz, 1H), 6.53 (dd, *J* = 9.0 Hz, 0.7 Hz, 1H), 3.91–3.60 (m, 2H), 3.55–3.46 (m, 2H), 2.15–1.98 (m, 2H), 1.34–1.28 (m, 1H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6) δ 173.7, 157.7, 152.7, 139.3, 118.9, 107.0, 94.8, 48.9, 26.6, 25.0 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{12}N_3O_2^+$ 230.0924, found: 230.0933.

6-(4-ethynylazepan-1-yl)nicotinonitrile (27)



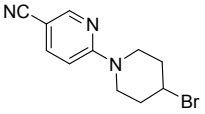
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4-ethynylazepane hydrochloride (80 mg, 0.5 mmol, 1.0 equiv) and KOH (84 mg, 1.5 mmol, 3.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 20 h. Purification was performed using column chromatography (0–30% EtOAc in heptane). The desired product **27** was obtained as a colorless oil (77 mg, 68%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 7.56 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 6.47 (dd, *J* = 9.0 Hz, 0.8 Hz, 1H), 4.00–3.48 (m, 4H), 2.80–2.73 (m, 1H), 2.08 (d, *J* = 2.5 Hz, 1H), 2.07–1.75 (m, 5H), 1.72–1.61 (m, 1H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 153.0, 139.6, 119.2, 105.1, 95.4, 86.5, 70.2, 47.3, 44.9, 33.3, 31.9, 29.6, 24.3 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{14}H_{16}N_3^+$ 226.1339, found: 226.1340.

6-(4,4-dimethyl-1,4-azasilinan-1-yl)nicotinonitrile (28)



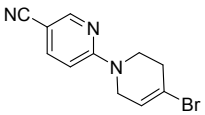
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4,4-dimethyl-1,4-azasilinane hydrochloride (83 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–20% EtOAc in heptane). The desired product **28** was obtained as a white solid (97 mg, 84%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 2.4 Hz, 0.7 Hz, 1H), 7.56 (dd, *J* = 9.1 Hz, 2.4 Hz, 1H), 6.58 (dd, *J* = 9.1 Hz, 0.8 Hz, 1H), 3.92–3.81 (m, 4H), 0.88–0.76 (m, 4H), 0.11 (s, 6H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 153.3, 139.7, 119.2, 105.5, 95.2, 44.9, 13.1, -2.8 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{18}N_3Si^+$ 232.1265, found: 232.1266.

6-(4-bromopiperidin-1-yl)nicotinonitrile (29)



General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4-bromopiperidine hydrobromide (122 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 3 h. Purification was performed using column chromatography (0–35% EtOAc in heptane). The desired product **29** was obtained as a white solid (103 mg, 77%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 2.3 Hz, 0.8 Hz, 1H), 7.61 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 6.62 (dd, *J* = 9.0 Hz, 0.8 Hz, 1H), 4.47 (sept, *J* = 7.4 Hz, 1H), 4.00–3.89 (m, 2H), 3.71–3.60 (m, 2H), 2.25–2.14 (m, 2H), 2.09–1.98 (m, 2H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 152.9, 140.1, 118.7, 105.8, 96.6, 49.2, 43.1, 35.3 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{13}BrN_3^+$ 266.0287, found: 266.0295.

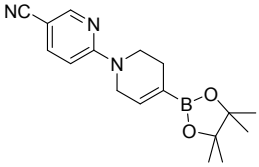
4-bromo-3,6-dihydro-2*H*-[1,2'-bipyridine]-5'-carbonitrile (30)



General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4-bromo-1,2,3,6-tetrahydropyridine hydrochloride (99 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 3 h. Purification was performed using column chromatography (0–35% EtOAc in heptane). The desired product **30** was obtained as a white solid (120 mg, 91%).

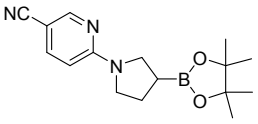
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J* = 2.3 Hz, 1H), 7.89 (dd, *J* = 9.1 Hz, 2.3 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 6.26–6.17 (m, 1H), 4.18–4.09 (m, 2H), 3.89 (t, *J* = 5.7 Hz, 2H), 2.63–2.53 (m, 2H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6) δ 159.3, 152.9, 140.6, 126.8, 119.3, 119.1, 107.1, 96.1, 46.2, 42.4, 34.7 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{11}BrN_3^+$ 264.0131, found: 264.0140.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2*H*-[1,2'-bipyridine]-5'-carbonitrile (31)



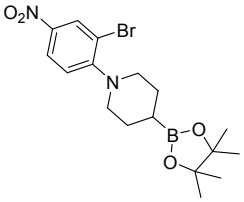
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride (123 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 3 h. Purification was performed using column chromatography (0–35% EtAOc in heptane). The desired product **31** was obtained as a white solid (103 mg, 66%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.4 Hz, 1H), 7.60 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 6.62–6.51 (m, 2H), 4.10 (m, 2H), 3.76 (t, *J* = 5.7 Hz, 2H), 2.41–2.33 (m, 2H), 1.28 (s, 12H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 152.8, 139.7, 138.1, 128.7, 119.0, 105.7, 96.0, 83.8, 45.8, 41.0, 26.1, 25.0 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{17}H_{23}BN_3O_2^+$ 312.1878, found: 312.1888.

6-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl)nicotinonitrile (32)



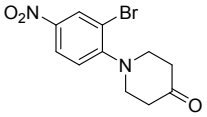
General procedure I was followed by reacting 5-cyano-2-fluoropyridine (61 mg, 0.5 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrrolidine hydrochloride (117 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 3 h. Purification was performed using column chromatography (0–35% EtAOc in heptane). The desired product **32** was obtained as a white solid (70 mg, 47%).
^{1}H NMR (500 MHz, DMSO-d_6, 360 K) δ 8.40 (dd, *J* = 2.3 Hz, 0.8 Hz, 1H), 7.72 (dd, *J* = 8.9 Hz, 2.3 Hz, 1H), 6.52 (d, *J* = 8.9 Hz, 0.8 Hz, 1H), 3.69–3.61 (m, 1H), 3.60–3.51 (m, 1H), 3.40–3.28 (m, 2H), 2.15–2.07 (m, 1H), 1.92–1.83 (m, 1H), 1.76–1.67 (m, 1H), 1.22 (s, 12H) ppm.
^{13}C NMR (126 MHz, DMSO-d_6, 278 K) δ 157.2, 152.8, 139.1, 119.2, 106.6, 93.8, 83.3, 48.8, 47.3, 27.1, 24.9 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{16}H_{23}BN_3O_2^+$ 300.1878, found: 300.1882.

1-(2-bromo-4-nitrophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine (33)



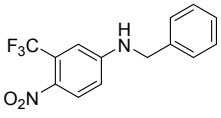
General procedure I was followed by reacting 3-bromo-4-fluoronitrobenzene (110 mg, 0.5 mmol, 1.0 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine hydrochloride (106 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 4 h. Purification was performed using column chromatography (0–30% EtOAc in heptane). The desired product **33** was obtained as a yellow solid (141 mg, 67%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.7 Hz, 1H), 8.11 (dd, *J* = 8.9 Hz, 2.7 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H) 3.46–3.38 (m, 2H), 2.90–2.79 (m, 2H), 1.91–1.73 (m, 4H), 1.26 (s, 12H), 1.19–1.09 (m, 1H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 142.1, 130.0, 124.0, 119.8, 117.6, 83.4, 53.1, 27.2, 24.9, 19.3 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{17}H_{25}BBrN_2O_4^+$ 411.1805, found: 411.1086.

1-(2-bromo-4-nitrophenyl)piperidin-4-one (34)



General procedure I was followed by reacting 3-bromo-4-fluoronitrobenzene (110 mg, 0.5 mmol, 1.0 equiv), piperidin-4-one hydrochloride (68 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–50% EtOAc in heptane). The desired product **34** was obtained as a yellow solid (18 mg, 12%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.6 Hz, 1H), 8.17 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 1H) 3.48 (t, *J* = 6.0 Hz, 4H), 2.69 (t, *J* = 6.0 Hz, 4H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 207.0, 155.8, 143.2, 129.9, 124.1, 120.4, 118.3, 51.2, 41.6 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{12}BrN_2O_3^+$ 299.0026, found: 299.0026.

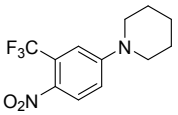
***N*-benzyl-4-nitro-3-(trifluoromethyl)aniline (35)**



General procedure II was followed by reacting 4-fluoro-1-nitro-2-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **35** was obtained as a yellow solid (97 mg, 69%). Analytical data match those of the commercially available compound (CAS: 393-11-1).

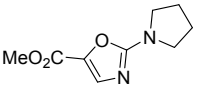
***R*f** = 0.39 (1:4, EtOAc/hexanes)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8 Hz, 1H), 7.41–7.32 (m, 5H), 6.95 (d, *J* = 4 Hz, 1H), 6.68 (dd, *J* = 6 Hz, J = 4 Hz, 1H), 4.94 (br s, 1H), 4.44 (s, 2H) ppm.
^{19}F NMR (376 MHz, CDCl3) δ -60.44 (3F) ppm.

1-(4-nitro-3-(trifluoromethyl)phenyl)piperidine (36)



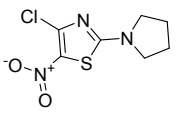
General procedure II was followed by reacting 4-fluoro-1-nitro-2-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), piperidine (50 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **36** was obtained as a yellow solid (108 mg, 79%).
***R*f** = 0.33 (1:9, EtOAc/hexanes); **Melting point:** 70–72 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 10 Hz, 1H), 7.12 (s, 1H), 6.99–6.88 (m, 1H), 3.45 (br s, 4H), 1.71 (br s, 6H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 136.1, 129.0, 126.3, 122.6 (q, *J* = 273 Hz), 114.4, 112.0 (q, *J* = 7 Hz),48.5, 25.3, 24.2 ppm.
^{19}F NMR (376 MHz, $CDCl_3$) δ -60.26 (3F) ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{13}F_3N_2O_2$ 274.0924, found: 274.0924.

methyl 2-(pyrrolidin-1-yl)oxazole-5-carboxylate (37)



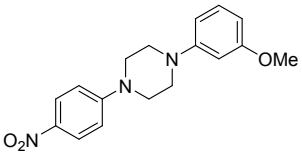
General procedure I was followed by reacting methyl 2-chlorooxazole-5-carboxylate (81 mg, 0.5 mmol, 1.0 equiv), pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 1.5 h. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **37** was obtained as a white solid (75 mg, 76%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 3.83 (s, 3H), 3.67–3.53 (m, 4H), 2.09–1.94 (m, 4H) ppm.
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 158.7, 137.9, 136.4, 51.6, 47.6, 25.7 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_9H_{12}N_2O_3^+$ 197.0921, found: 197.0927.

4-chloro-5-nitro-2-(pyrrolidine-1-yl)thiazole (38)



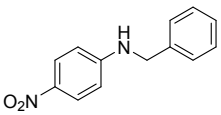
General procedure I was followed by reacting methyl 2,4-dichloro-5-nitrothiazole (100 mg, 0.5 mmol, 1.0 equiv), pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and K_2CO_3 (69 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 1.5 h.. Purification was performed using column chromatography (0–100% EtOAc in heptane). The desired product **38** was obtained as an orange solid (78 mg, 67%). The double substituted by-product, 5-nitro-2,4-di(pyrrolidin-1-yl)thiazole, was isolated as well (16 mg, 12%).
^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.85–3.57 (m, 2H), 3.46–3.16 (m, 2H), 2.28–1.98 (m, 4H) ppm.
^{13}C NMR (126 MHz, CD_2Cl_2) δ 164.3, 142.5, 119.5, 50.6, 50.0, 25.9 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_7H_9ClN_3O_2S^+$ 234.0099, found: 234.0107.

1-(3-methoxyphenyl)-4-(4-nitrophenyl)piperazine (39)



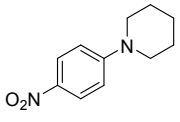
General procedure II was followed by reacting 1-fluoro-4-nitrobenzene (71 mg, 0.5 mmol, 1.0 equiv), 1-(3-methoxyphenyl)piperazine (96 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 15 min. The desired product **39** was obtained as an off-white solid (124 mg, 79%).
***R*f** = 0.22 (1:4, EtOAc/hexanes); **Melting point:** 138–140 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 5 Hz, 2H), 7.20 (d, *J* = 10 Hz, 1H), 6.87 (d, *J* = 10 Hz, 2H), 6.58–6.56 (m, 1H), 6.49–6.47 (m, 2H), 3.81 (bs, 3H), 3.58 (t, *J* = 5 Hz, 4H), 3.36 (t, *J* = 5 Hz, 4H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 154.8, 152.2, 138.8, 130.1, 126.1, 112.8, 109.1, 105.1, 102.9, 55.4, 48.8, 47.1 ppm.
HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{17}H_{20}N_3O_3^+$ 314.1499, found: 314.1503.

***N*-benzyl-4-nitroaniline (40)**



General procedure II was followed by reacting 1-fluoro-4-nitrobenzene (71 mg, 0.5 mmol, 1.0 equiv), benzylamine (**6**, 55 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **40** was obtained as a yellow solid (72 mg, 68%). Analytical data for compound **40** is in accordance with previously reported data in the literature.[6]
***R*f** = 0.30 (1:4, EtOAc/hexanes).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8 Hz, 2H), 7.38–7.33 (m, 5H), 6.58 (d, *J* = 8 Hz, 2H), 4.43 (s, 2H) ppm.

1-(4-nitrophenyl)piperidine (41)

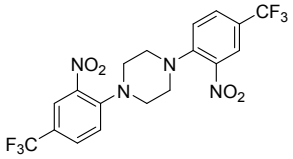


General procedure II was followed by reacting 1-fluoro-4-nitrobenzene (71 mg, 0.5 mmol, 1.0 equiv), piperidine (50 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **41** was obtained as a yellow solid (76 mg, 74%). Analytical data for compound **41** is in accordance with previously reported data in the literature.[7]

***R*f** = 0.33 (1:9, EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 10 Hz, 2H), 6.80 (d, *J* = 10 Hz, 2H), 3.44 (s, 4H), 1.69 (s, 6H) ppm.

1,4-bis(2-nitro-4-(trifluoromethyl)phenyl)piperazine (42)



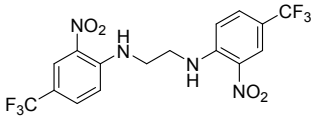
General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (209 mg, 1.0 mmol, 2.0 equiv), piperazine (43 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at rt for 15 min. The desired product **42** was obtained as a yellow solid (195 mg, 84%). Analytical data for compound **42** is in accordance with previously reported data in the literature.[8]

***R*f** = 0.31 (1:4, EtOAc/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.72 (d, *J* = 12 Hz, 2H), 7.23 (d, *J* = 12 Hz, 2H), 3.35 (br s, 8H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.02 (6F) ppm.

***N*^{1},*N*^{2}-bis(2-nitro-4-(trifluoromethyl)phenyl)ethane-1,2-diamine (43)**



General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (209 mg, 1.0 mmol, 2.0 equiv), ethylenediamine (33 µL, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 25 min. The desired product **43** was obtained as a yellow solid (159 mg, 70%).

***R*f** = 0.29 (1:9, EtOAc/hexanes); **Melting point:** 216–218 °C.

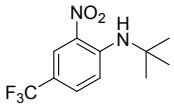
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 2H), 8.40 (br s, 2H), 7.68 (d, *J* = 8 Hz, 2H), 7.00 (d, *J* = 8 Hz, 2H), 3.78–3.77 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 131.6, 125.2, 123.9, 123.8 (q, *J* = 270 Hz), 116.1, 114.9, 41.3 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.06 (6F) ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{16}H_{13}F_6N_4O_4^+$ 439.0757, found: 439.0759.

***N*-(*tert*-butyl)-2-nitro-4-(trifluoromethyl)aniline (44)**



General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), *tert*-butylamine (52 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 25 min. The desired product **44** was obtained as a yellow solid (92 mg, 70%).

***R*f** = 0.25 (1:9, EtOAc/hexanes); **Melting point:** 171–173 °C.

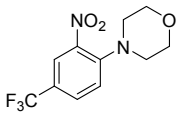
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 8.48 (s, 1H), 7.56 (d, *J* = 8 Hz, 1H), 7.18 (d, *J* = 8 Hz, 1H), 1.53 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 131.4, 125.6, 116.4, 52.4, 29.7 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.05 (3F) ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{11}H_{14}F_3N_2O_2^+$ 263.1002, found: 263.1005.

4-(2-nitro-4-(trifluoromethyl)phenyl)morpholine (45)



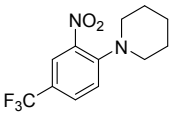
General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), morpholine (44 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at rt for 10 min. The desired product **45** was obtained as a yellow solid (114 mg, 82%). Analytical data for compound **45** is in accordance with previously reported data in the literature.[9]

***R*f** = 0.37 (1:4, EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.62 (d, *J* = 4 Hz, 1H), 7.11 (d, *J* = 4 Hz, 1H), 3.78 (br s, 4H), 3.08 (br s, 4H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.46 (3F) ppm.

1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine (46)



General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), piperidine (50 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **46** was obtained as a yellow solid (110 mg, 80%). Analytical data for compound **46** is in accordance with previously reported data in the literature.[10]

R_f = 0.29 (1:9, EtOAc/hexanes); **Melting point:** 68–70 °C.

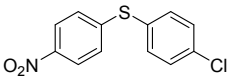
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.61 (dd, *J* = 10 Hz, 5 Hz, 1H), 7.14 (d, *J* = 10 Hz, 1H), 3.12(t, *J* = 5 Hz, 4H), 1.74–1.62 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.8, 130.0, 124.5, 124.4, 123.6 (q, *J* = 270 Hz), 120.6, 52.2, 25.7, 23.9 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -60.30 (3F) ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{13}F_3N_2O_2$ 274.0924, found: 274.0922.

(4-chlorophenyl)(4-nitrophenyl)sulfane (56)

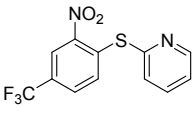


General procedure II was followed by reacting 1-fluoro-4-nitrobenzene (71 mg, 0.5 mmol, 1.0 equiv), 4-chlorobenzenethiol (72 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 20 min. The desired product **56** was obtained as a yellow solid (96 mg, 72%). Analytical data for compound **56** is in accordance with previously reported data in the literature.[11]

R_f = 0.23 (1:9, EtOAc/hexanes.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 10 Hz, 2H), 7.48–7.42 (m, 4H), 7.19 (d, *J* = 10 Hz, 2H) ppm.

2-((2-nitro-4-(trifluoromethyl)phenyl)thio)pyridine (57)



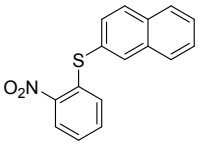
General procedure II was followed by reacting 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (105 mg, 0.5 mmol, 1.0 equiv), pyridine-2-thiol (56 mg, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 1.0 mL) at 60 °C for 25 min. The desired product **57** was obtained as a yellow solid (105 mg, 70%). Analytical data for compound **57** is in accordance with previously reported data in the literature.[12]

R_f = 0.28 (1:9, EtOAc/hexanes.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29–8.28 (m, 1H), 8.06 (s, 1H), 7.44–7.39 (m, 1H), 7.25 (d, *J* = 8.0, 2H), 7.00–6.97 (m, 2H) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.27 (3F) ppm.

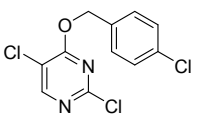
naphthalen-2-yl(2-nitrophenyl)sulfane (58)



General procedure I was followed by reacting 1-fluoro-2-nitrobenzene (53 µL, 0.5 mmol, 1.0 equiv), 2-naphthalenethiol (71 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 22 h. Purification was performed using column chromatography (0–20% EtOAc in heptane). The desired product **58** was obtained as a yellow solid (125 mg, 89%). Analytical data for compound **58** is in accordance with previously reported data in the literature.[13]

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34–8.16 (m, 1H), 8.08–7.91 (m, 1H), 7.68–7.42 (m, 4H), 7,41–7.28 (m, 1H), 6.95–6.81 (m, 1H) ppm.

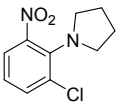
2,5-dichloro-4-((4-chlorobenzyl)oxy)pyrimidine (59)



General procedure I was followed by reacting 2,4,5-trichloropyrimidine (**1**, 57 µL, 0.5 mmol, 1.0 equiv), 4-chlorobenzyl alcohol (71 mg, 0.5 mmol, 1.0 equiv) and KOH (34 mg, 0.6 mmol, 1.2 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 2 h. Purification was performed using column chromatography (5–20% EtOAc in heptane). The desired product **59** was obtained as a white solid (68 mg, 47%). Analytical data for compound **59** is in accordance with previously reported data in the literature.[2]

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 7.55–7.48 (m, 4H), 5.50 (s, 2H) ppm.

1-(2-chloro-6-nitrophenyl)pyrrolidine (60)



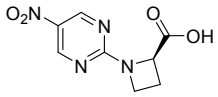
General procedure I was followed by reacting 3-chloro-2-fluoronitrobenzene (88 mg, 0.5 mmol, 1.0 equiv), pyrrolidine (**2**, 41 µL, 0.5 mmol, 1.0 equiv) and KOH (28 mg, 0.5 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 20 h. Purification was performed using column chromatography (0–5 % EtOAc in heptane). The desired product **60** was obtained as a yellow oil (108 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.48 (dd, *J* = 8.1 Hz, 1.6 Hz, 1H), 7.07 (t, *J* = 8.1 Hz, 1H), 3.29–3.22 (m, 4H), 2.01–1.91 (m, 4H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 140.0, 135.0, 134.1, 124.0, 123.0, 50.5, 26.1 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{10}H_{12}ClN_2O_2^+$ 227.0582, found: 227.0586.

(*R*)-1-(5-nitropyrimidin-2-yl)azetidine-2-carboxylic acid (61)



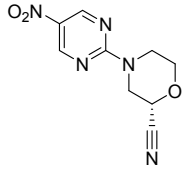
General procedure I was followed by reacting 2-chloro-5-nitropyrimidine (80 mg, 0.5 mmol, 1.0 equiv), (*R*)-azetidine-2-carboxylic acid (51 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 2 h. Purification was performed using reversed phase column chromatography (solvents: (A) water + 0.1% FA, (B) acetonitrile + 0.1 % FA; gradient: 5% (B), isocrat. for 1.5 min, 11–21% (B) in 20 min). The desired product **61** was obtained as a brown solid (36 mg, 32%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 9.11 (s, 2H), 4.90 (dd, *J* = 9.5 Hz, 5.3 Hz, 1H), 4.30–4.11 (m, 2H), 2.76 (dtd, *J* = 11.3 Hz, 9.3 Hz, 6.4 Hz, 1H), 2.31 (ddt, *J* = 11.2 Hz, 8.9 Hz, 5.6 Hz, 1H) ppm.

^{13}C NMR (126 MHz, DMSO-d_6) δ 171.5, 160.9, 155.2, 154.8, 134.4, 61.1, 48.6, 20.7 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_8H_9N_4O_4^+$ 225.0618, found: 225.0620.

(*S*)-4-(5-nitropyrimidin-2-yl)morpholine-2-carbonitrile (63)



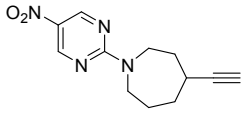
General procedure I was followed by reacting 2-chloro-5-nitropyrimidine (80 mg, 0.5 mmol, 1.0 equiv), (*S*)-morpholine-2-carbonitrile hydrochloride (74 mg, 0.5 mmol, 1.0 equiv) and KOH (56 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 3 h. Purification was performed using column chromatography (0–35% EtOAc in heptane). The desired product **63** was obtained as a white solid (37 mg, 32%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s, 2H), 5.19 (t, *J* = 3.5 Hz, 1H), 4.64 (ddd, *J* = 14.0 Hz, 3.2 Hz, 1.5 Hz, 1H), 4.44 (dtd, *J* = 13.7 Hz, 3.2 Hz, 1.5 Hz, 1H), 3.95 (dt, *J* = 12.1 Hz, 3.5 Hz, 2H), 3.64–3.49 (m, 1H) ppm.

^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4, 155.2, 134.3, 116.9, 63.5, 63.2, 45.9, 43.6 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_9H_{10}N_5O_3^+$ 236.0778, found: 236.0783.

4-ethynyl-1-(5-nitropyrimidin-2-yl)azepane (64)



General procedure I was followed by reacting 2-chloro-5-nitropyrimidine (80 mg, 0.5 mmol, 1.0 equiv), ethynylazepane hydrochloride (80 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (207 mg, 1.5 mmol, 3.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at 50 °C for 20 h. Purification was performed using column chromatography (0–20% EtOAc in heptane). The desired product **64** was obtained as a slightly yellow solid (60 mg, 49%).

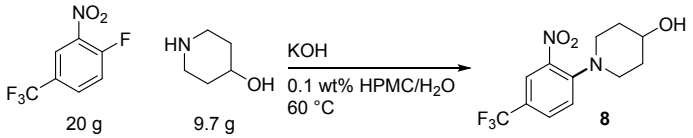
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (m, 2H), 4.04–3.80 (m, 4H), 2.85–2.76 (m, 1H), 2.16–1.77 (m, 6H), 1.74–1.65 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 154.9, 154.8, 133.6, 86.3, 70.3, 47.7, 45.5, 33.2, 31.9, 29.5, 24.1 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{12}H_{15}N_4O_2^+$ 247.1190, found: 247.1196.

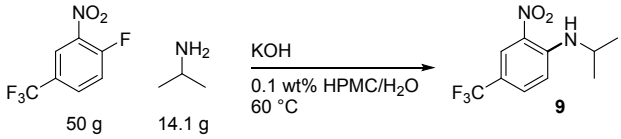
Scale-up experiments

Synthesis of 1-(4-nitro-3-(trifluoromethyl)phenyl)piperidin-4-ol (8) on 20 g scale



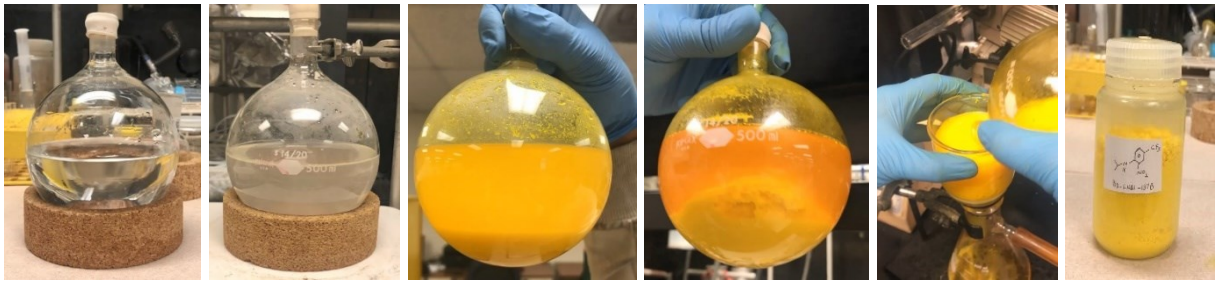
In an oven-dried 250 mL round-bottom flask containing a PTFE-coated stir bar, 4-hydroxy piperidine (9.7 g, 96.0 mmol, 1.0 equiv), KOH (5.4 g, 96.0 mmol, 1.0 equiv) and HPMC solution (0.1 wt% in Millipore water, 96.0 mL) were added sequentially. The reaction mixture was stirred at rt for 5 min. 4-fluoro-3-nitrobenzotrifluoride (20 g, 96.0 mmol, 1.0 equiv) was then added and the reaction mixture was stirred at 60 °C. Reaction progress was monitored by TLC. Upon complete consumption of the starting materials, reaction was allowed to cool to rt. Reaction mixture was then filtered and the resulting solid was washed with water (3 x 10 mL). The pure product **8** was obtained as a yellow solid (23.9 g, 86%). Analytical data are in accordance with those on small scale (see section above).

Synthesis of *N-iso*-propyl-2-nitro-4-(trifluoromethyl)aniline (9) on 50 g scale



50 g 14.1 g

In an oven-dried 500 mL round-bottom flask containing a PTFE-coated stir bar, *iso*-propylamine (14.14 g, 239.2 mmol, 1.0 equiv), KOH (13.4 g, 239.2 mmol, 1.0 equiv) and HPMC solution (0.1 wt% in Millipore water, 239.0 mL) were added sequentially. The reaction mixture was stirred at rt for 5 min. 4-fluoro-3-nitrobenzotrifluoride (50 g, 239.2 mmol, 1.0 equiv) was then added. The reaction mixture was stirred at 60 °C and reaction progress was monitored by TLC. After complete consumption of the starting materials, reaction was allowed to cool to rt. Reaction mixture was then filtered and the resulting solid was washed with water (3 x 10 mL). The pure product **9** was obtained as a yellow solid (57.1 g, 96%). Analytical data are in accordance with those on small scale (see section above).



A **B** **C** **D** **E** **F**

Figure S11 Synthesis of *N-iso*-propyl-2-nitro-4-(trifluoromethyl)aniline (**9**) on 50 g scale. **A** 0.1 wt% HPMC/water; **B** After addition of KOH and iso-propylamine; **C** After addition of 4-fluoro-3-nitrobenzotrifluoride; **D** After 20 minutes reaction time; **E** Filtration of product; **F** Isolated product **9**.

Process Mass Intensity (PMI) calculation

For both reactions on scale PMI calculations were performed taking into account the reagents and substrates (table S5, entry 1), water (reaction solvent and washing step, entry 2), and the organic solvent (entry 3). The PMIs for the scale-up reactions towards compounds **8** and **9** were found to be lower compared to three reference S_NAr reactions in aqueous medium that were published on gram to kilogram scale.[14, 15] The PMI for reagents and substrates was found to be slightly reduced for the reactions conducted in HPMC/water. This finding can be attributed to the equimolar amounts of all reagents and superior atom economy of KOH compared to K_2PO_4 which used for the reactions in TPGS-750-M. The major difference, however, was found to result from the PMI for organic solvents because the use of organic solvents could be completely circumvented in the procedure presented herein. Comparing combined PMIs of multiple reactions types that were performed under aqueous conditions to ones performed under classical reaction conditions, revealed a reduction of PMI of approx. 30%[15, 16]–80%[17, 18]. Therefore, this work presents not only a significant improvement compared to S_NAr reactions using organic solvents, but also a further optimization of reaction conditions in aqueous medium.

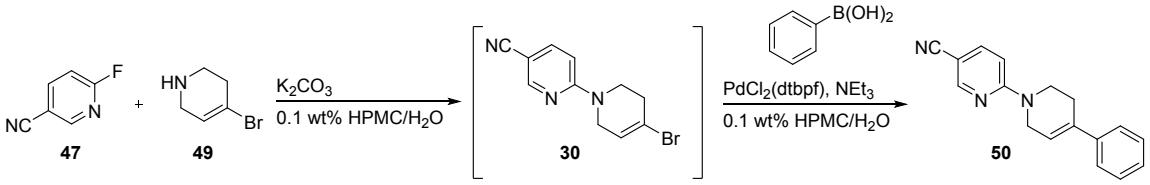
Table S5 PMI calculations for two reactions in HPMC/water and three reference reactions in TPGS-750-M/water.

PMI	Reaction to cmpd. 8	Reaction to cmpd. 9	Reference reactions in TPGS-750-M[a]
Reagents + Substrates	1.47	1.36	2.18–3.11
Water	5.27	4.71	6.08–6.65
Solvents	0	0	11.64–19.16[b]
combined	6.74	6.07	19.90–28.92

[a] PMIs were calculated for two reported S_NAr reactions on 10 g scale[14] and were reported for one S_NAr reaction on kilogram scale.[15] [b] column chromatography not included for the reactions on 10 g scale.

Two-steps-one-pot reactions

Synthesis of 4-phenyl-3,6-dihydro-2*H*-[1,2'bipyridine]-5'-carbonitrile (50) starting from vinyl bromide



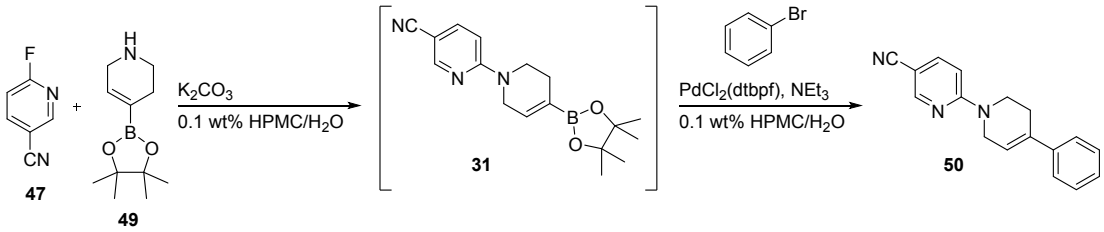
For the S_NAr reaction, general procedure I was followed by reacting 5-cyano-2-fluoropyridine (**47**, 61 mg, 0.5 mmol, 1.0 equiv), 4-bromo-1,2,3,6-tetrahydropyridine hydrochloride (**49**, 99 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 1.5 h. After LCMS-analysis showed completion of the S_NAr reaction towards intermediate **30**, phenylboronic acid (122 mg, 1.0 mmol, 2.0 equiv), $PdCl_2$(dtbpf) (6.5 mg, 10 µmol, 0.02 equiv) and triethylamine (209 µL, 1.5 mmol, 3.0 equiv) were added to the reaction mixture. The reaction was stirred open to air for 1 h at rt. DCM (3 mL) was added and the reaction mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges that contain a PTS membrane (*Macherey Nagel*®). The organic layer was evaporated, and crude product was adsorbed on silica gel prior to column chromatography (20 g silica, 30 mL/min, 0–20% EtOAc in heptane). The desired product **50** was obtained as a slightly yellow solid (117 mg, 90% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 7.64 (dd, *J* = 9.0 Hz, 2.3 Hz, 1H), 7.43–7.39 (m, 2H), 7.38–7.32 (m, 2H), 7.30–7.26 (m, 1H), 6.61 (dd, *J* = 9.0 Hz, 0.8 Hz, 1H), 6.15 (tt, *J* = 3.4 Hz, 1.5 Hz, 1H), 4.22 (q, *J* = 2.8 Hz, 2H), 3.99 (t, *J* = 5.7 Hz, 2H), 2.68 (ttd, *J* = 5.6 Hz, 2.6 Hz, 1.5 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 152.8, 140.3, 139.9, 136.4, 128.7, 127.7, 125.1, 120.1, 118.9, 105.8, 96.3, 45.2, 41.1, 27.4 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{17}H_{16}N_3^+$ 262.1339, found: 262.1346.

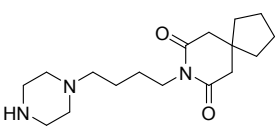
Synthesis of 4-phenyl-3,6-dihydro-2*H*-[1,2'bipyridine]-5'-carbonitrile (0353) starting from vinyl boronic ester



For the S_NAr reaction, general procedure I was followed by reacting 5-cyano-2-fluoropyridine (**47**, 61 mg, 0.5 mmol, 1.0 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-1,2,3,6-tetrahydropyridine hydrochloride (**49**, 123 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.5 mL) at rt for 7 h. After LCMS-analysis showed completion of the S_NAr reaction towards intermediate **31**, bromobenzene (105 µL, 1.0 mmol, 2.0 equiv), $PdCl_2$(dtbpf) (6.5 mg, 10 µmol, 0.02 equiv) and triethylamine (209 µL, 1.5 mmol, 3.0 equiv) were added to the reaction mixture. The reaction was stirred open to air for 1 h at rt. DCM (3 mL) was added and the reaction mixture was stirred vigorously for 5–10 min. Phase separation was performed using 6 mL cartridges that contain a PTS membrane (*Macherey Nagel*®). The organic layer was evaporated, and crude product was adsorbed on silica gel prior to column chromatography (20 g silica, 30 mL/min, 0–30% EtOAc in heptane). The desired product **50** was obtained as a slightly yellow solid (100 mg, 77% over two steps). Analytical data are in accordance with those of the reaction starting from the vinyl bromide (see section above).

Synthesis of active pharmaceutical ingredients (APIs) using HPMC/water

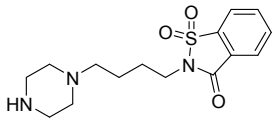
Synthesis of 8-(4-(piperazin-1-yl)butyl)-8-azaspiro[4.5]decane-7,9-dione (52)



The synthesis of intermediate 52 was performed starting from 3,3-tetramethyleneglutarimide, 1,4-dibromobutane, and piperazine in a two-step synthesis following literature known procedures. The isolated yields were comparable to those published.[19]

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.62 (t, *J* = 7.0 Hz, 2H), 2.83 (t, *J* = 5.0 Hz, 4H), 2.60 (s, 4H), 2.41–2.31 (m, 4H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.66–1.56 (m, 4H), 1.45–1.30 (m, 8H) ppm.

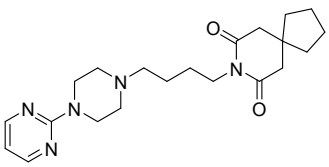
Synthesis of 2-(4-(piperazin-1-yl)butyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (53)



The synthesis of intermediate 53 was performed starting from saccharin, 1,4-dibromobutane, and piperazine in a two-step synthesis following literature known procedures. The isolated yields were comparable to those published.[20]

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.08–8.03 (m, 1H), 8.02–7.97 (m, 1H), 3.74 (t, *J* = 7.2 Hz, 2H). 3.00 (t, *J* = 5.0 Hz, 4H), 2.57–2.18 (m, 4H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.75 (p, *J* = 7.4 Hz, 2H), 1.51 (p, *J* = 7.4 Hz, 2H) ppm.

Synthesis of 8-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)-8-azaspiro[4.5]decane-7,9-dione (Buspirone, 54)



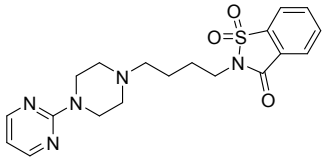
General procedure I was followed by reacting 2-fluoropyrimidine (**51**, 12 mg, 0.125 mmol, 1.0 equiv), 8-(4-(piperazin-1-yl)butyl)-8-azapiro[4.5]decane-7,9-dione (38 mg, 0.125 mmol, 1.0 equiv) and K_2CO_3 (17 mg, 0.125 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.25 mL) at rt for 30 min. Purification was performed using column chromatography (0–15% MeOH in DCM). The desired product **54** was obtained as a white solid (30 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.7 Hz, 2H), 6.43 (t, *J* = 4.7 Hz, 1H), 3.82–3.71 (m, 6H), 2.55 (s, 4H), 2.49–2.42 (m, 4H), 2.39–2.31 (m, 2H), 1.72–1.62 (m, 4H), 1.56–1.41 (m, 8H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 161.7, 157.8, 109.8, 58.4, 53.2, 45.0, 43.7, 39.6, 39.4, 37.6, 26.1, 24.3, 24.2 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{21}H_{32}N_5O_2^+$ 386.2551, found: 386.2557.

Synthesis of 2-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (Ipsapirone, 55)



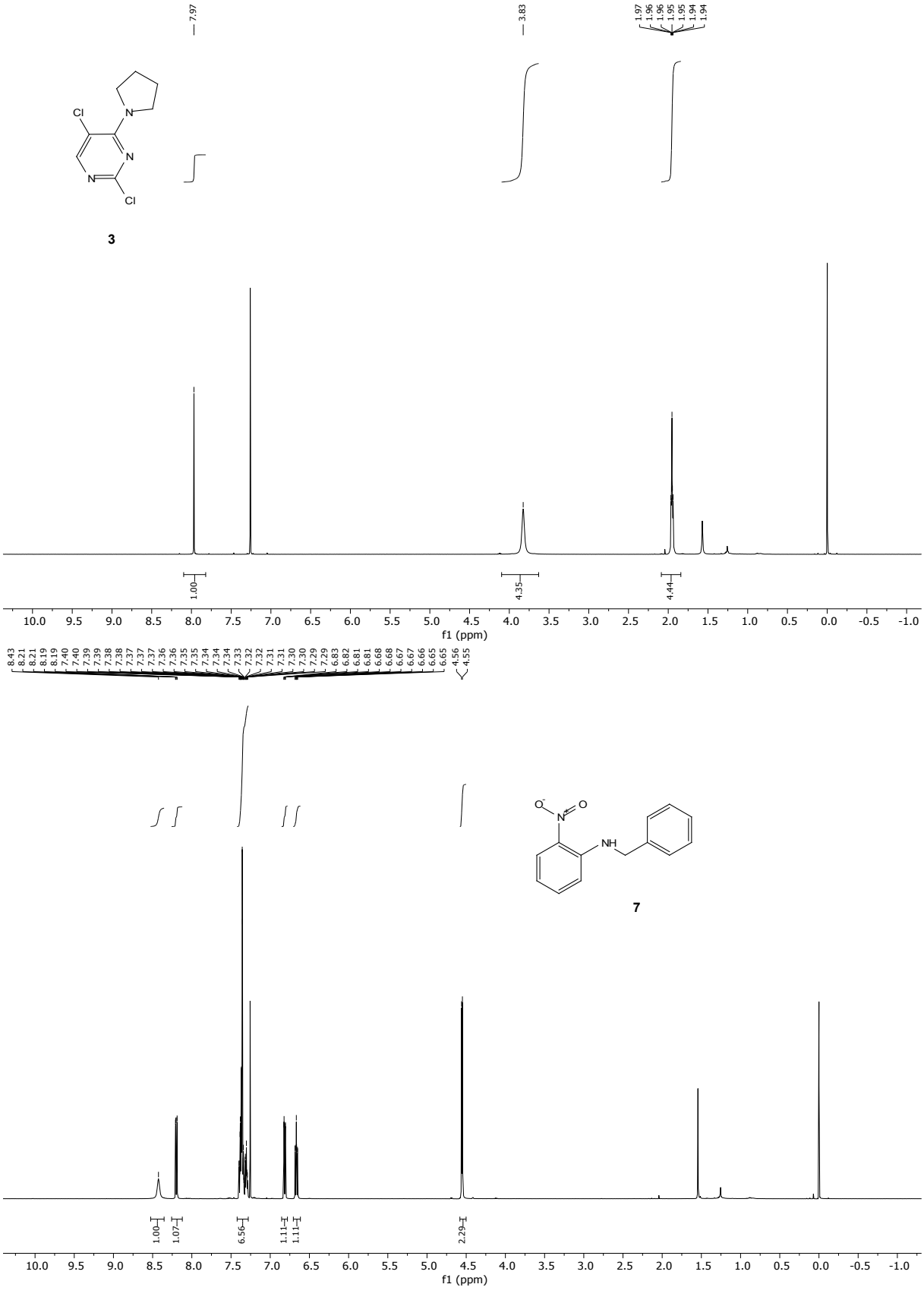
General procedure I was followed by reacting 2-fluoropyrimidine (**51**, 12 mg, 0.125 mmol, 1.0 equiv), 2-(4-(piperazin-1-yl)benzo[*d*]isothiazol-3(2*H*)one 1,1-dioxide (40 mg, 0.125 mmol, 1.0 equiv) and K_2CO_3 (17 mg, 0.125 mmol, 1.0 equiv) in HPMC solution (0.1 wt% in Millipore water, 0.25 mL) at rt for 30 min. Purification was performed using column chromatography (0–15% MeOH in DCM). The desired product **55** was obtained as a colorless oil (38 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 4.7 Hz, 2H), 8.07–8.00 (m, 1H), 7.94–7.88 (m, 1H), 7.85 (td, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.81 (td, *J* = 7.5 Hz, 1.4 Hz, 1H), 6.45 (t, *J* = 4.7 Hz, 1H), 3.85–3.74 (m, 6H), 2.51–2.46 (m, 4H), 2.44–2.39 (m, 2H), 1.90 (p, *J* = 7.5 Hz, 2H), 1.63 (p, *J* = 7.5 Hz, 2H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 159.1, 157.8, 137.8, 134.8, 134.4, 127.5, 125.2, 121.0, 109.9, 58.0, 53.2, 43.8, 39.3, 26.6, 24.1 ppm.

HRMS (ESI-TOF) m/z = $[M+H]^+$ calcd. for $C_{19}H_{24}N_5O_3S^+$ 402.1594, found: 402.1600.

NMR-data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1.97
1.96
1.96
1.95
1.95
1.94
1.94
Cl
N
N
N
Cl
3
1.00
4.35
4.44
f1 (ppm)
8.43
8.21
8.21
8.19
8.19
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.36
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7.35
7.35
7.34
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
6.83
6.82
6.81
6.81
6.68
6.68
6.67
6.67
6.66
6.65
6.65
4.56
4.55
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N
O
NH
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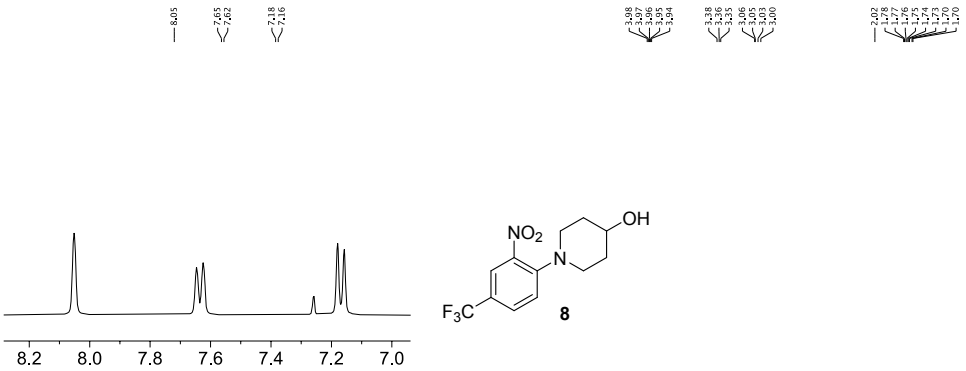
6.56
1.11
1.11
2.29
f1 (ppm)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7.16
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3.97
3.96
3.95
3.94
3.38
3.36
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3.06
3.05
3.03
3.00
2.02
1.78
1.77
1.76
1.75
1.74
1.73
1.70
1.70
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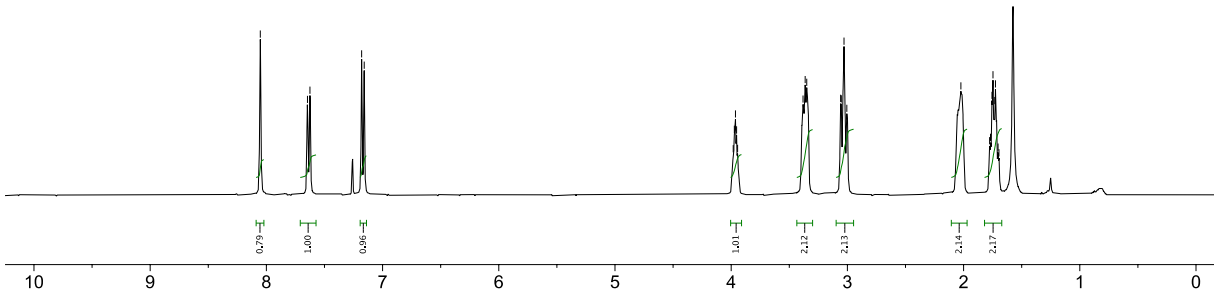
N
F3C
8
8.2
8.0
7.8
7.6
7.4
7.2
7.0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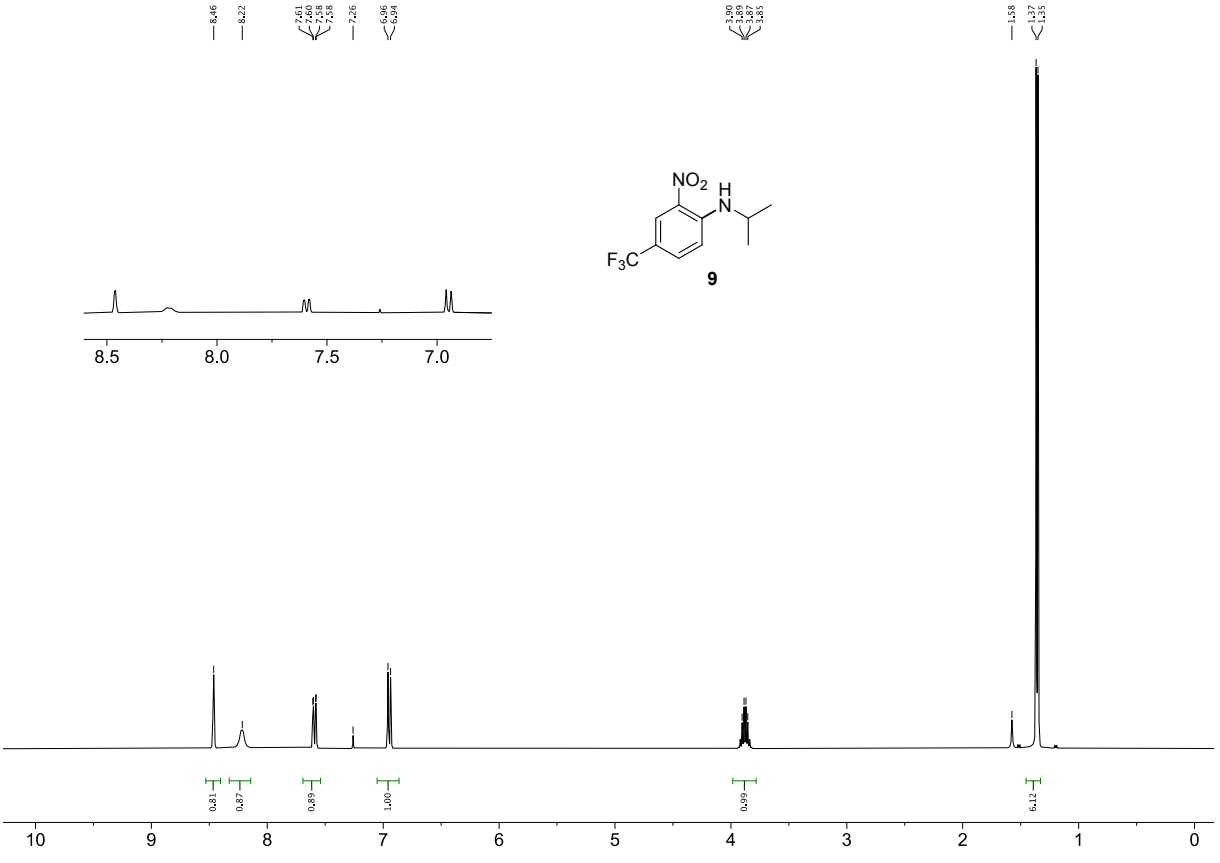
1.00
0.96
1.01
2.12
2.13
2.14
2.17
10
9
8
7
6
5
4
3
2
1
0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7.58
7.26
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6.94
3.90
3.89
3.87
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1.58
1.37
1.35
NO2
H
N
F3C
9
8.5
8.0
7.5
7.0
0.81
0.87
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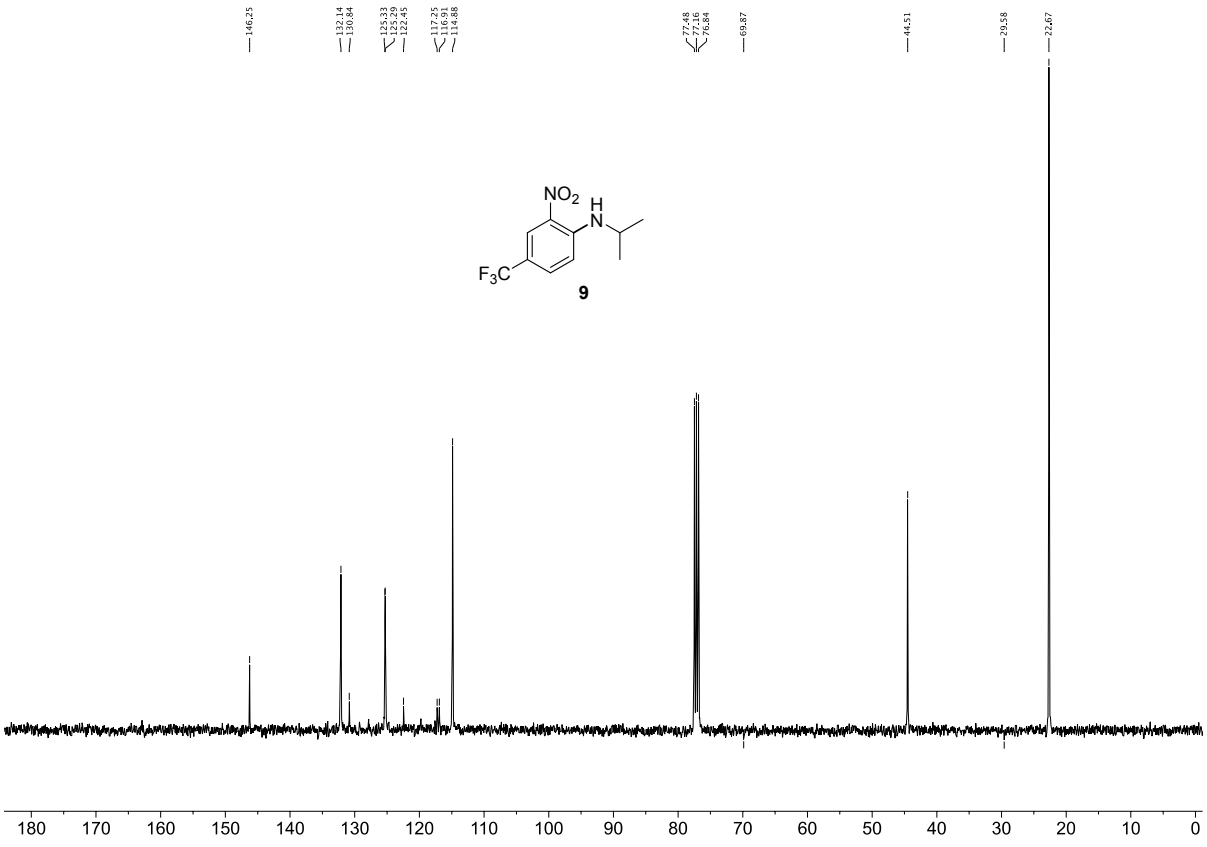
1.00
0.99
6.12
10
9
8
7
6
5
4
3
2
1
0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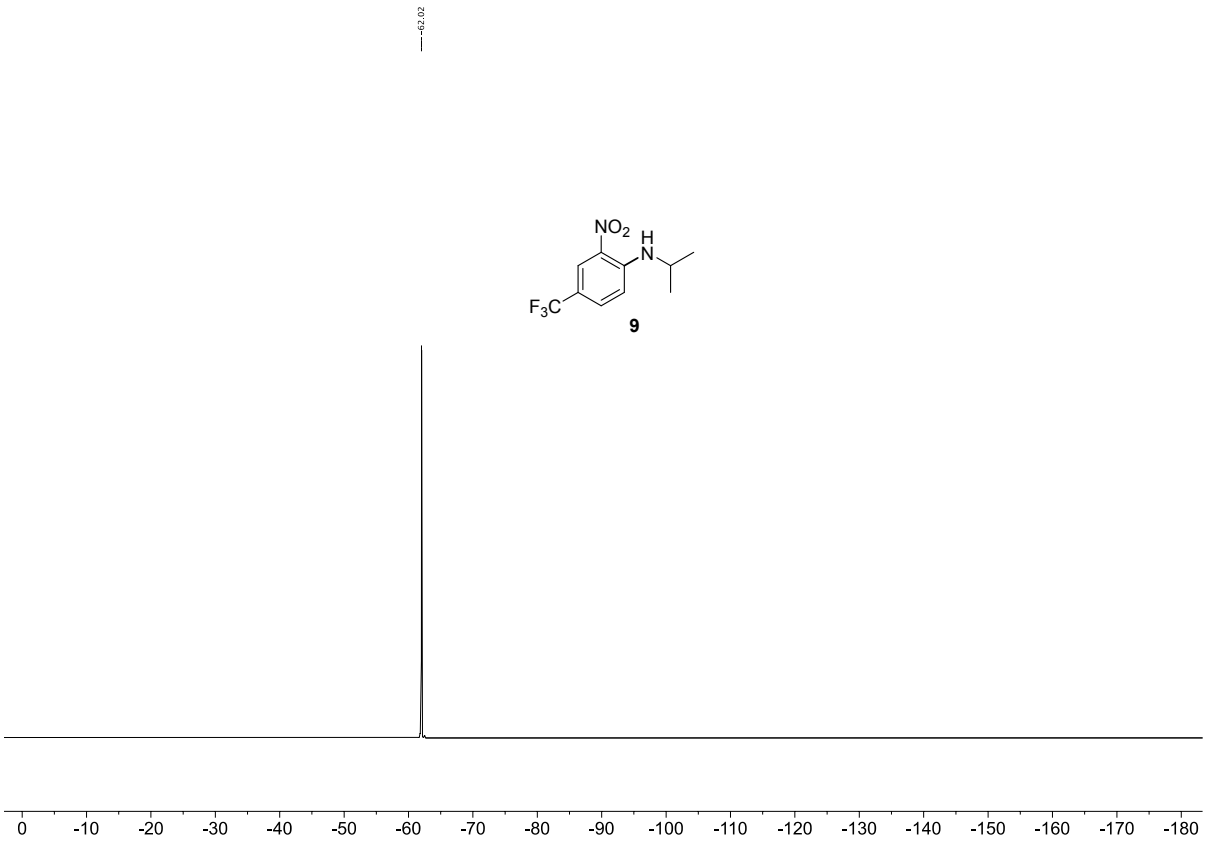
132.14
130.84
125.33
125.29
122.45
117.55
114.88
77.48
77.16
76.84
69.87
44.51
29.58
22.67
NO2
H
N
F3C
9
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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N
F3C
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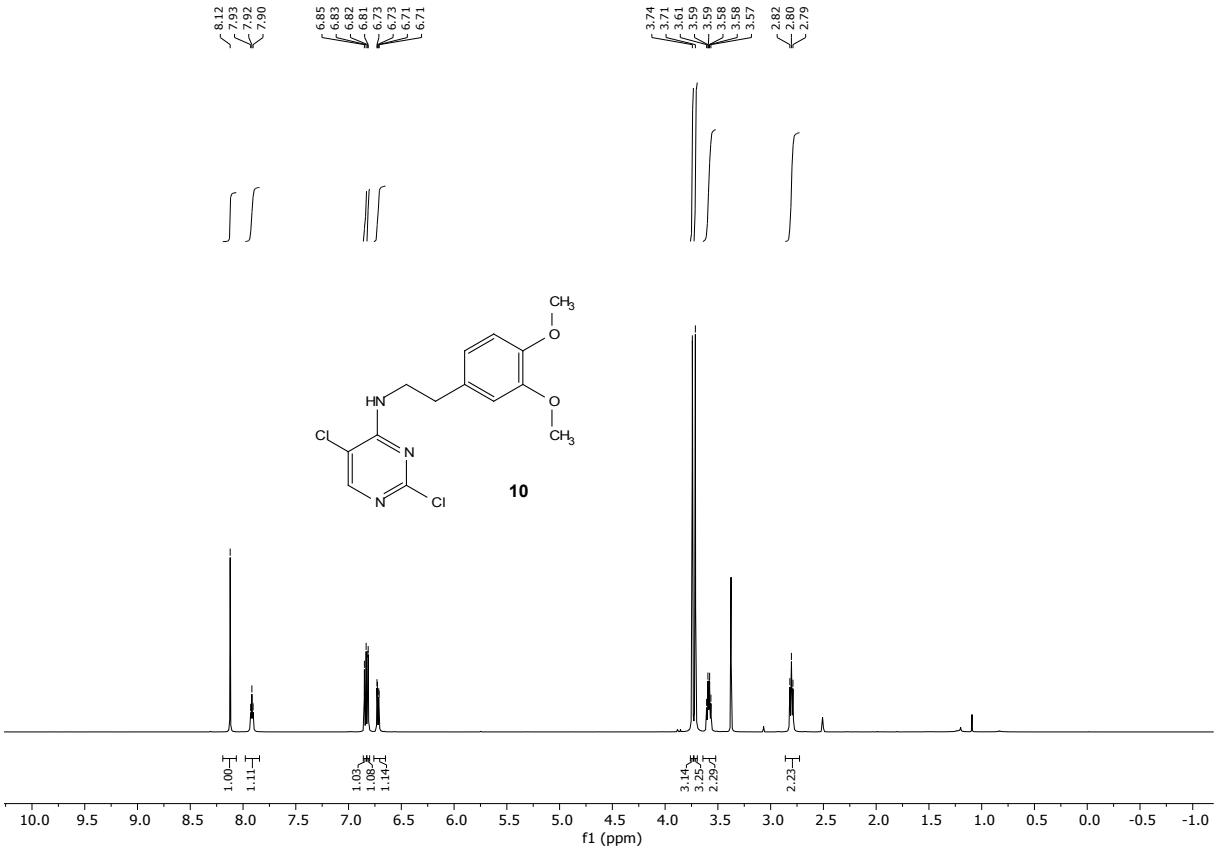
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7.90
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6.83
6.82
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6.71
6.71
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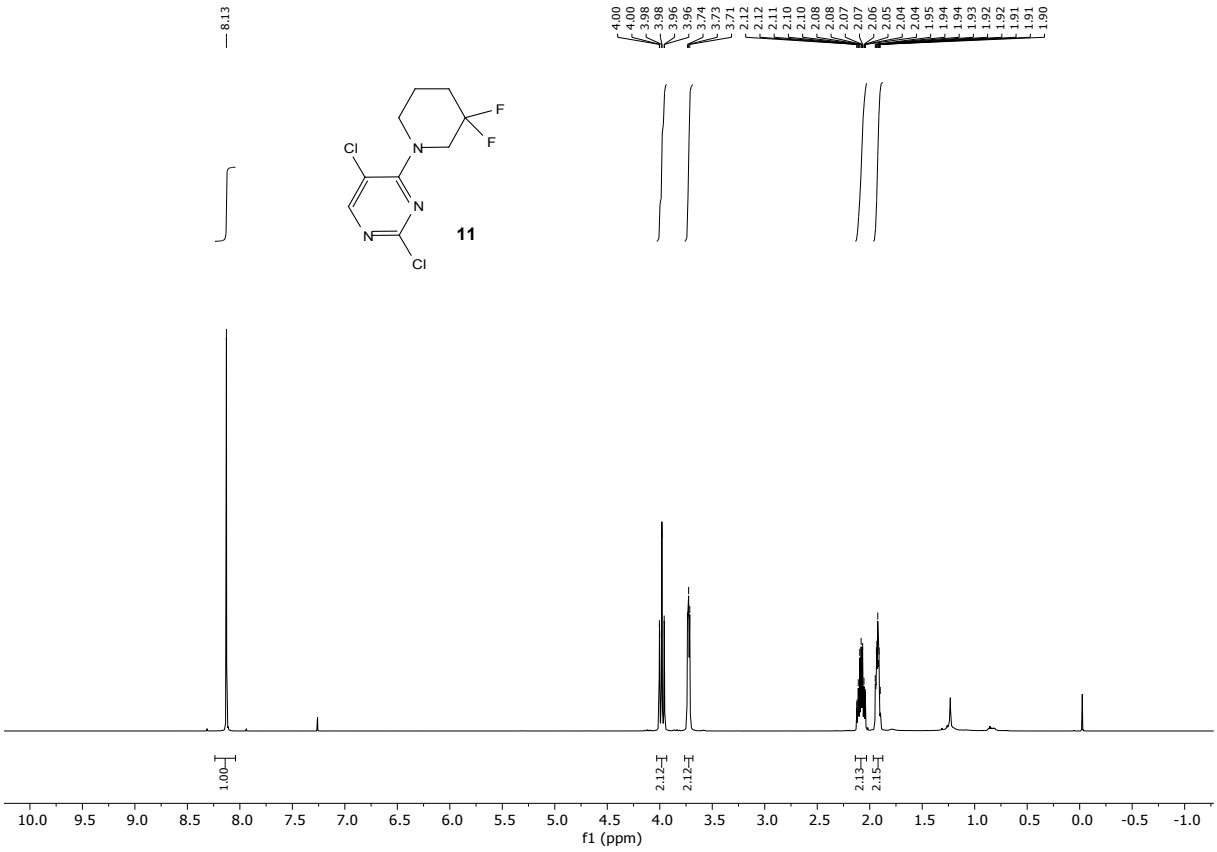
3.71
3.61
3.59
3.59
3.58
3.58
3.57
2.82
2.80
2.79
CH3
O
HN
O
CH3
Cl
N
N
Cl
10
1.00
1.11
1.03
1.08
1.14
3.14
3.25
2.29
2.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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4.00
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3.98
3.96
3.96
3.74
3.73
3.71
2.12
2.12
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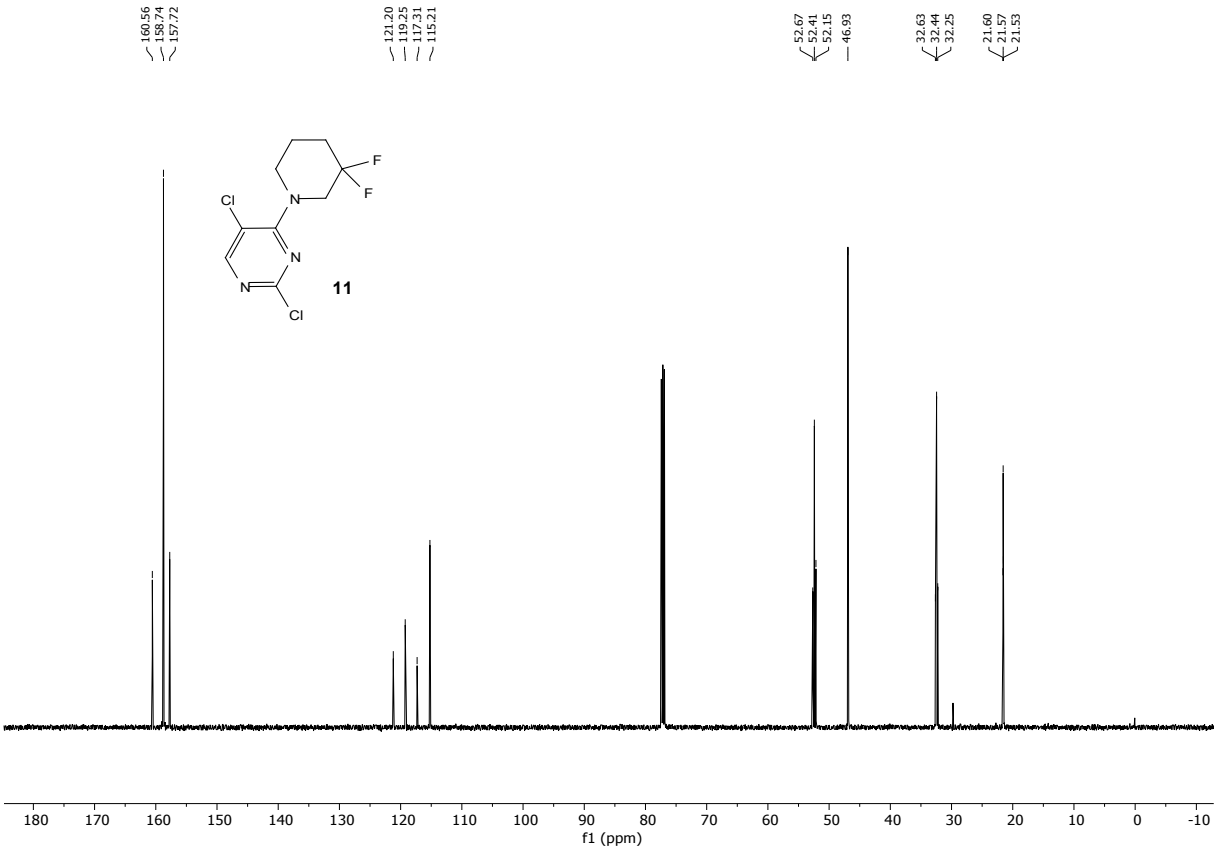
2.10
2.10
2.08
2.08
2.07
2.07
2.06
2.05
2.04
2.04
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.91
1.90
F
F
Cl
N
N
N
Cl
11
1.00
2.12
2.12
2.13
2.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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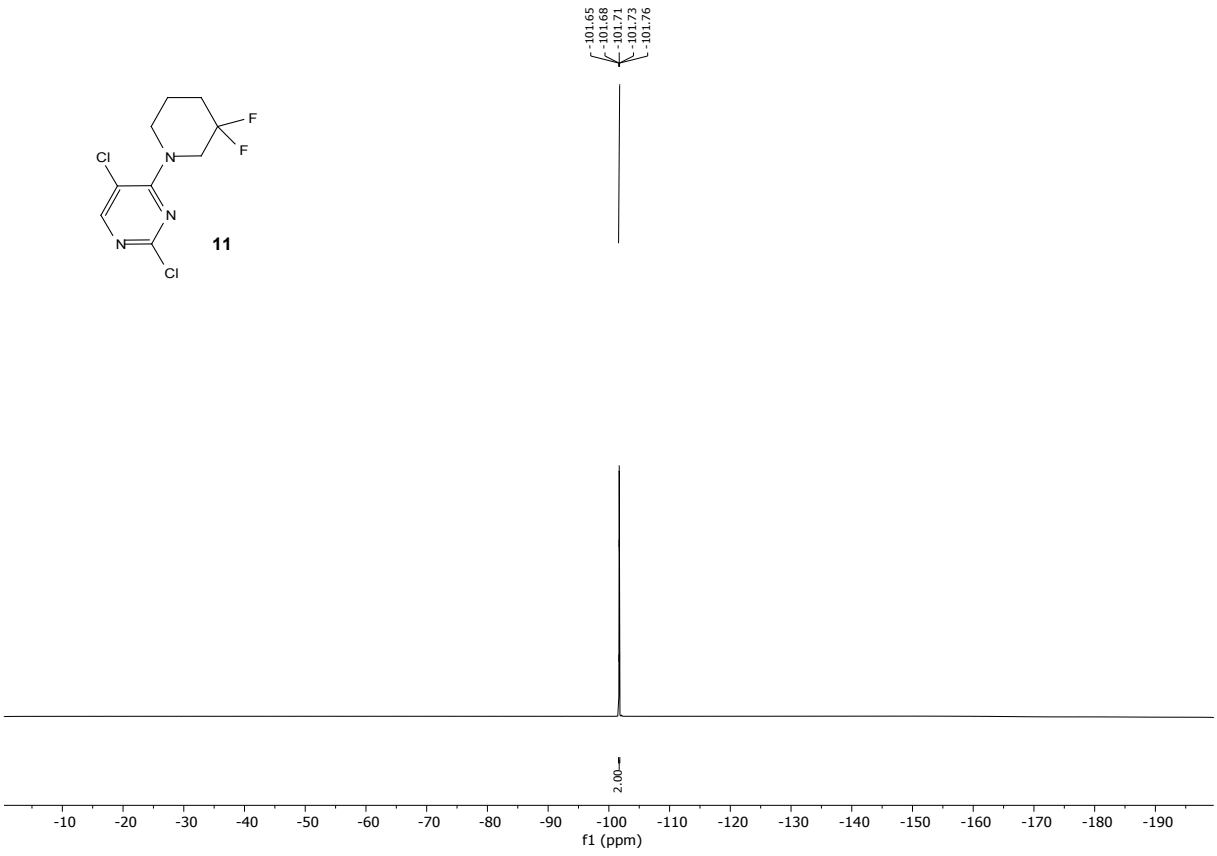
157.72
121.20
119.25
117.31
115.21
52.67
52.41
52.15
46.93
32.63
32.44
32.25
21.60
21.57
21.53
F
F
Cl
N
N
N
Cl
11
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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-101.68
-101.71
-101.73
-101.76
F
F
Cl
N
N
N
Cl
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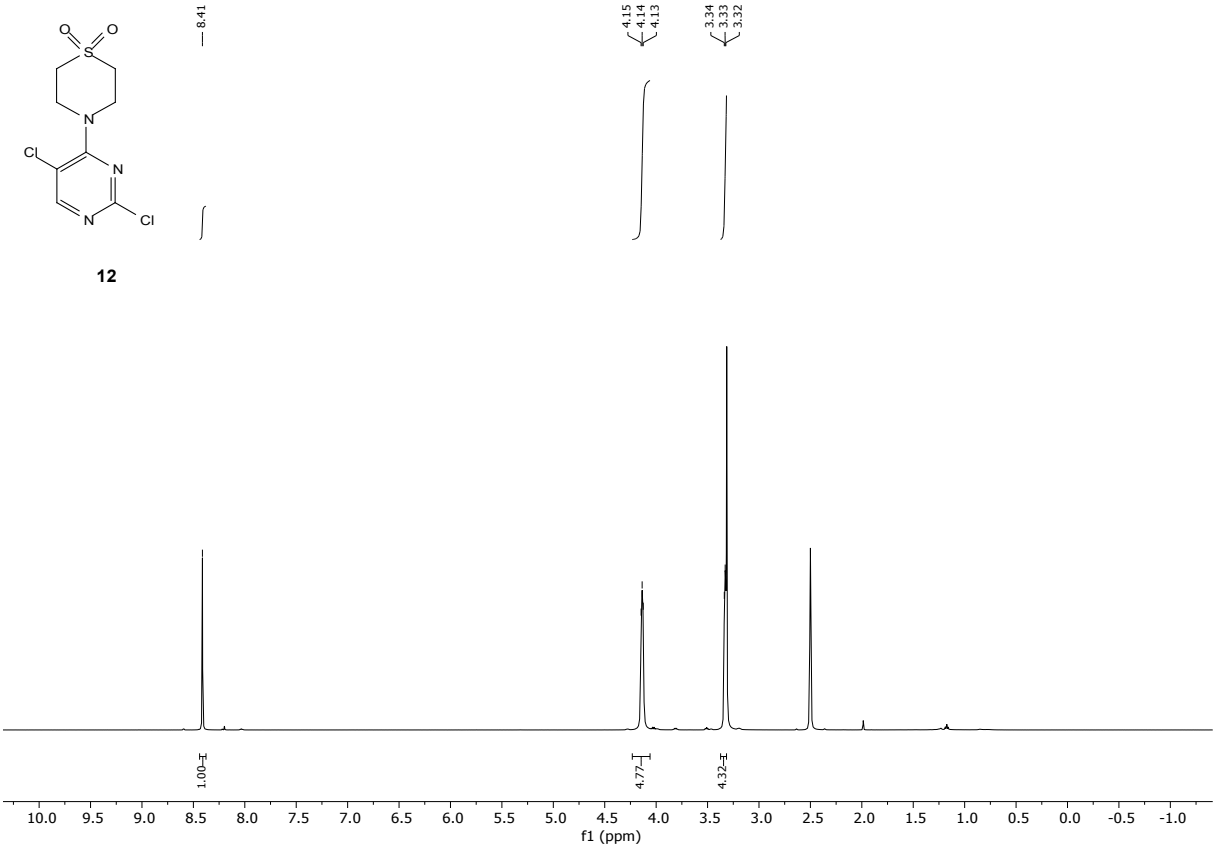
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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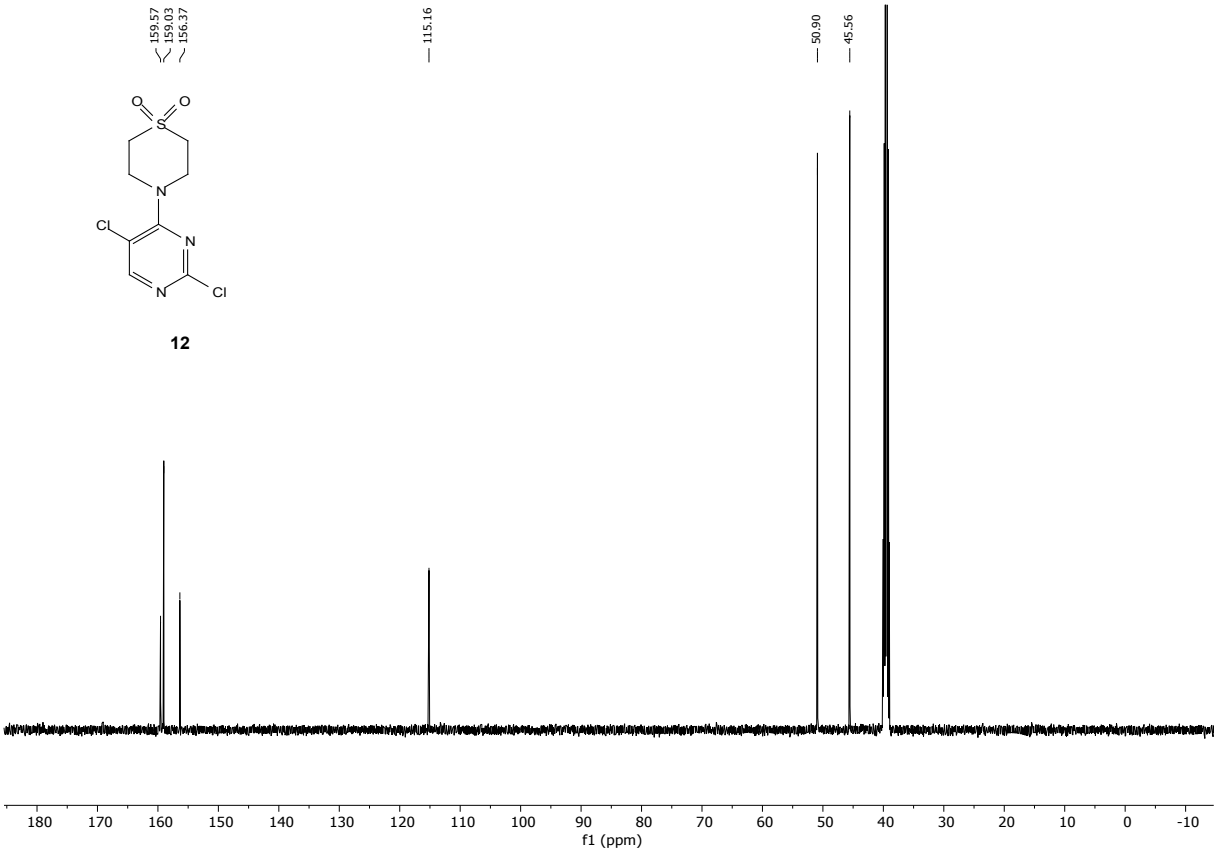
4.13
3.34
3.33
3.32
1.00
4.77
4.32
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

12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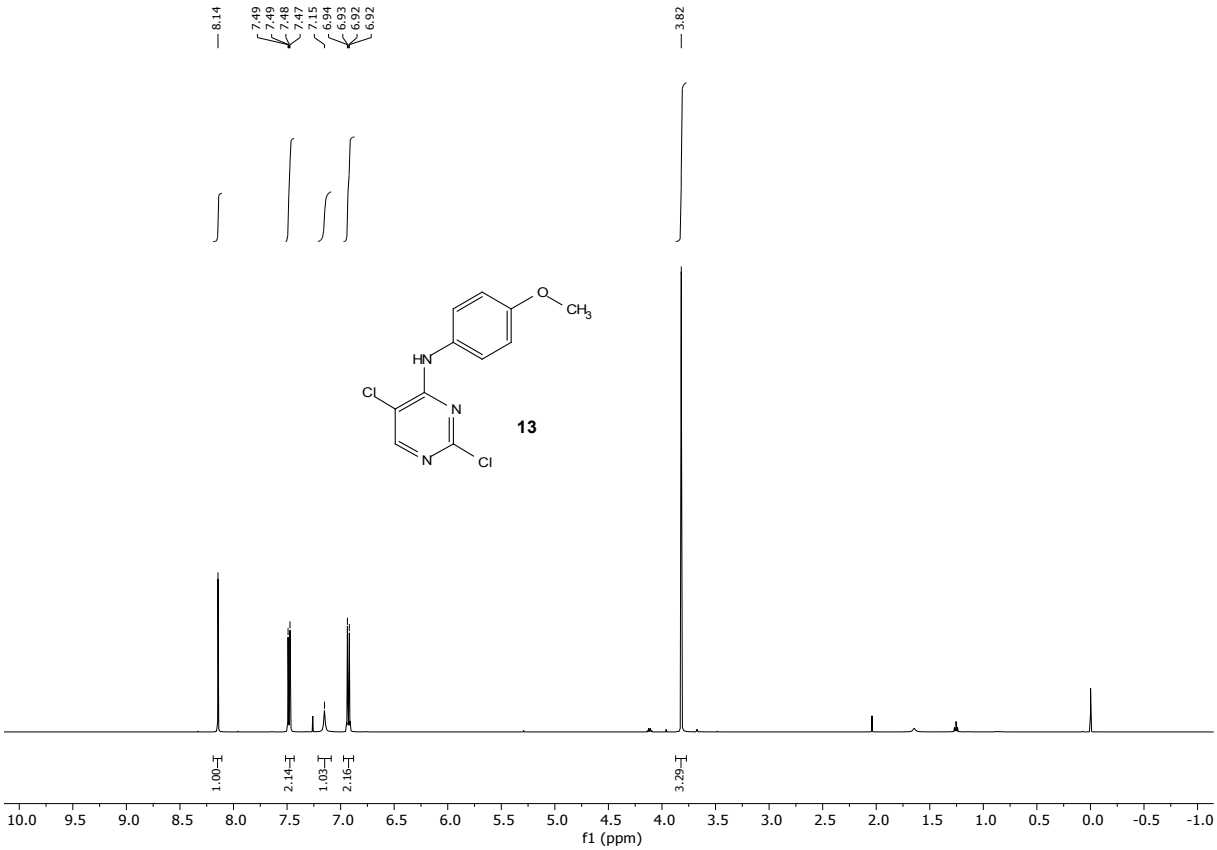
159.03
156.37
115.16
50.90
45.56
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

12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7.47
7.15
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6.93
6.92
6.92
3.82
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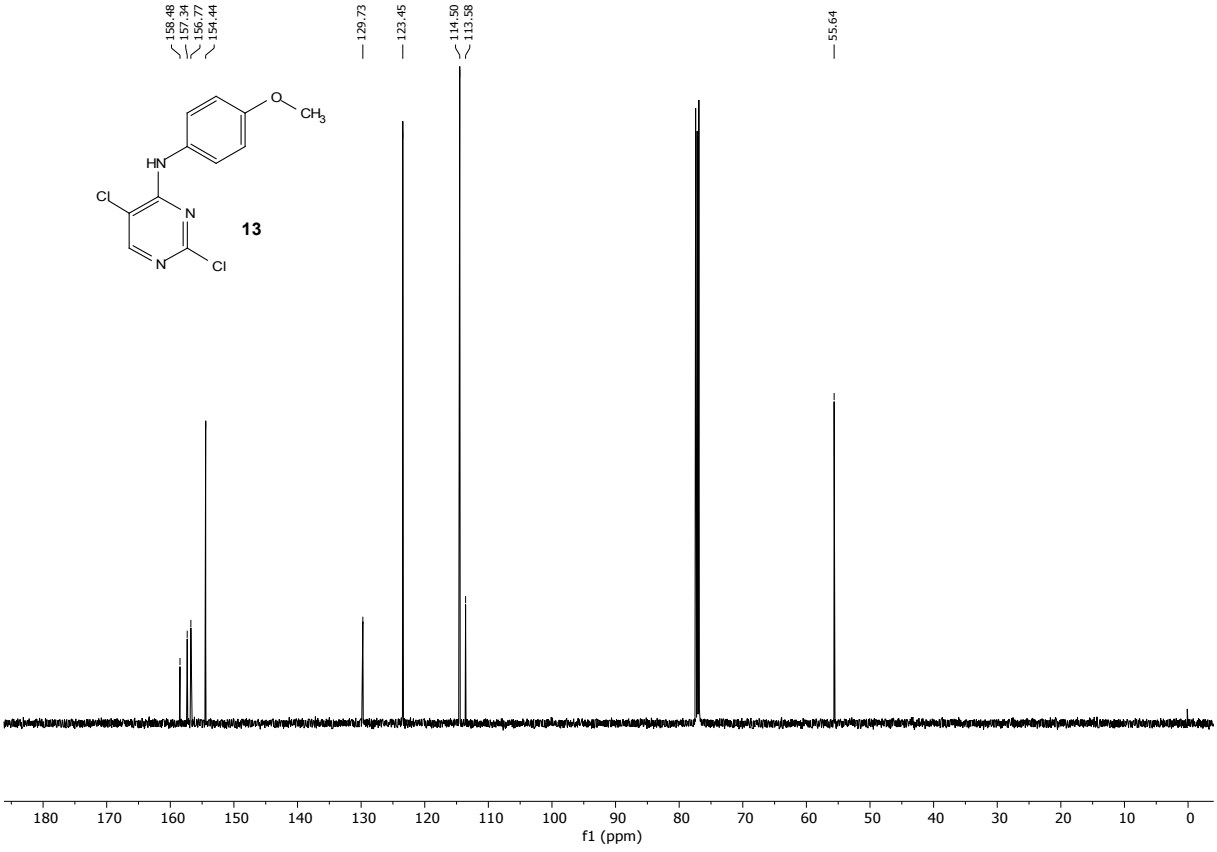
Cl
N
N
Cl
O
CH3
13
1.00
2.14
1.03
2.16
3.29
f1 (ppm)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Cl
N
N
Cl
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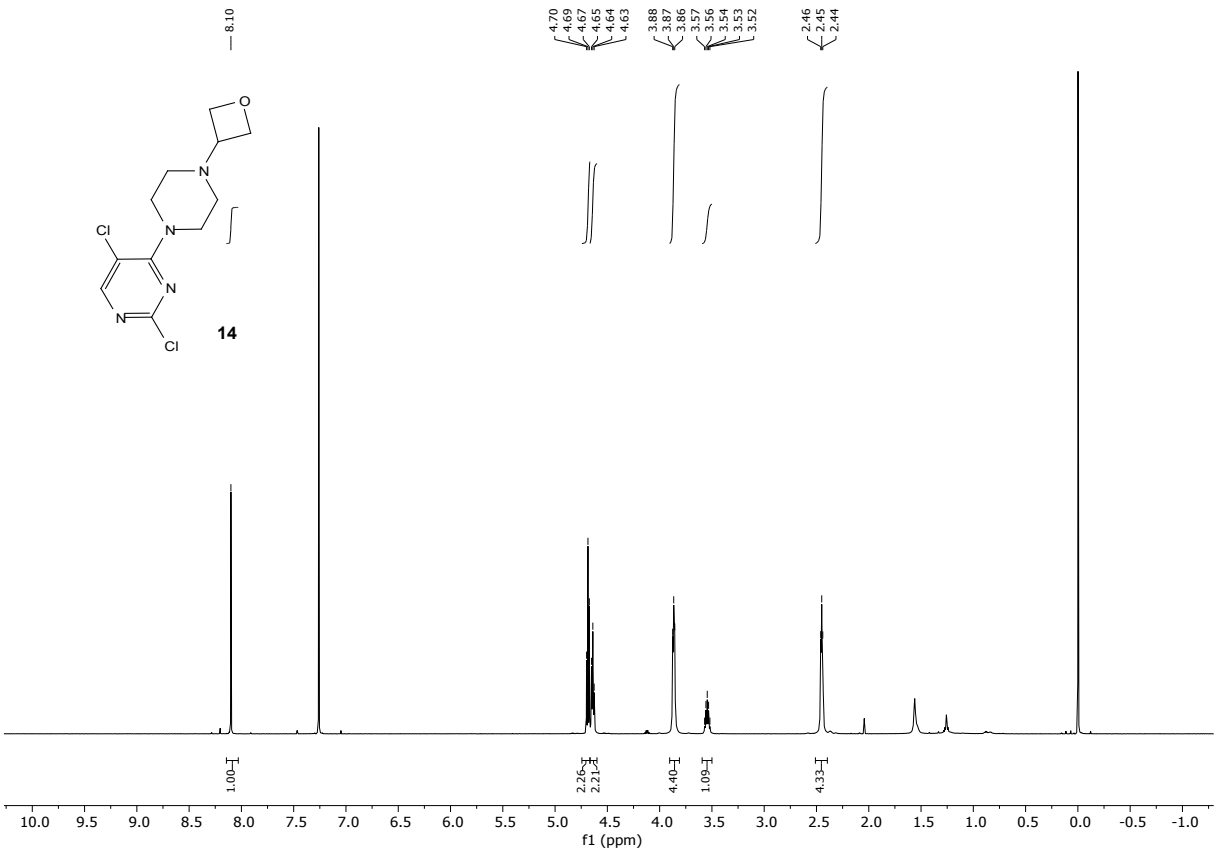
CH3
13
f1 (ppm)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4.65
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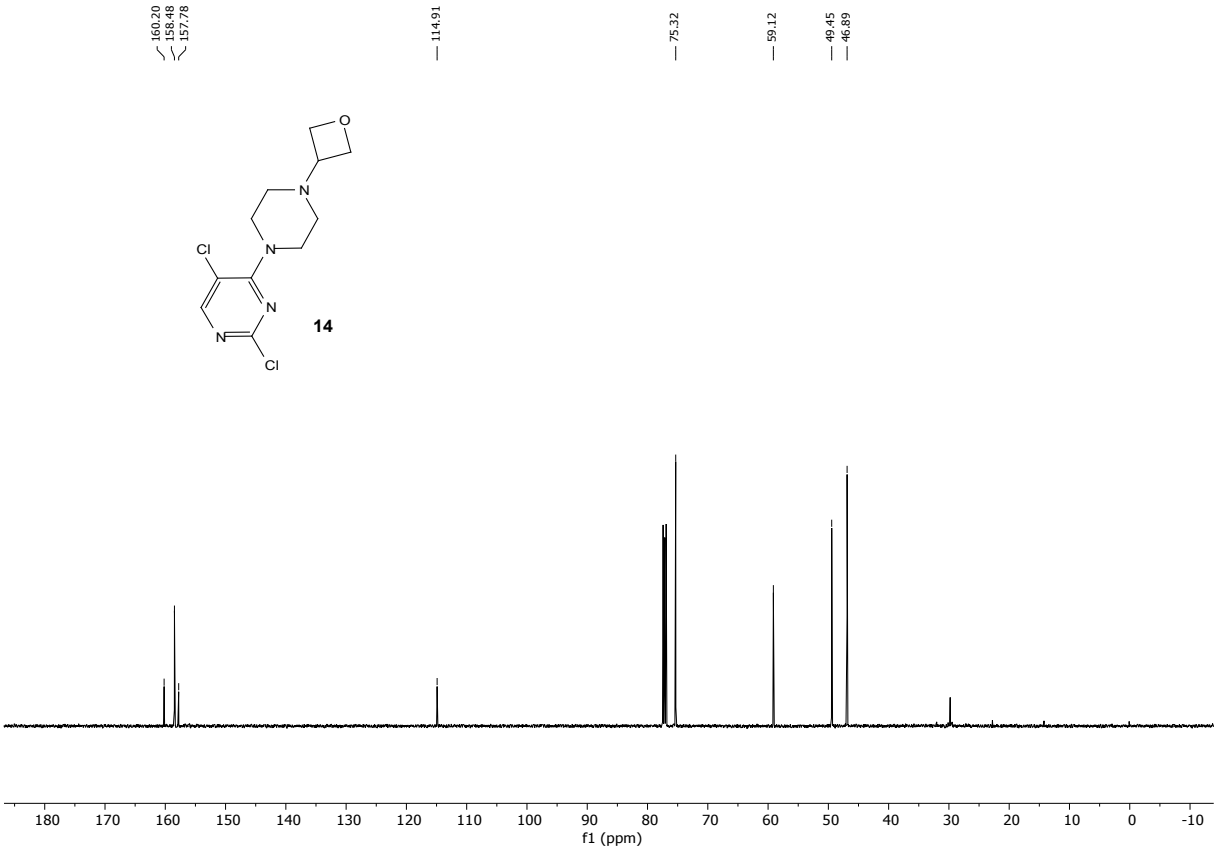
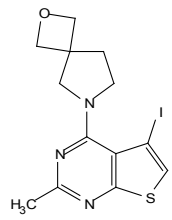
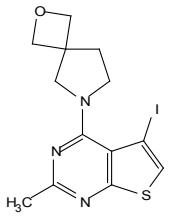
3.88
3.87
3.86
3.57
3.56
3.54
3.53
3.52
2.46
2.45
2.44
O
N
N
Cl
N
N
Cl
14
1.00
2.26
2.21
4.40
1.09
4.33
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


160.20
158.48
157.78
114.91
75.32
59.12
49.45
46.89
O
N
N
Cl
N
N
Cl
14
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



15

7.47
4.71
4.70
4.63
4.62
4.07
3.86
3.85
3.84
2.58
2.21
2.20
2.18
1.00
2.24
2.21
2.18
2.24
3.36
2.24
f1 (ppm)



15

169.08
161.79
160.12
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116.28
81.09
69.58
60.26
52.19
45.24
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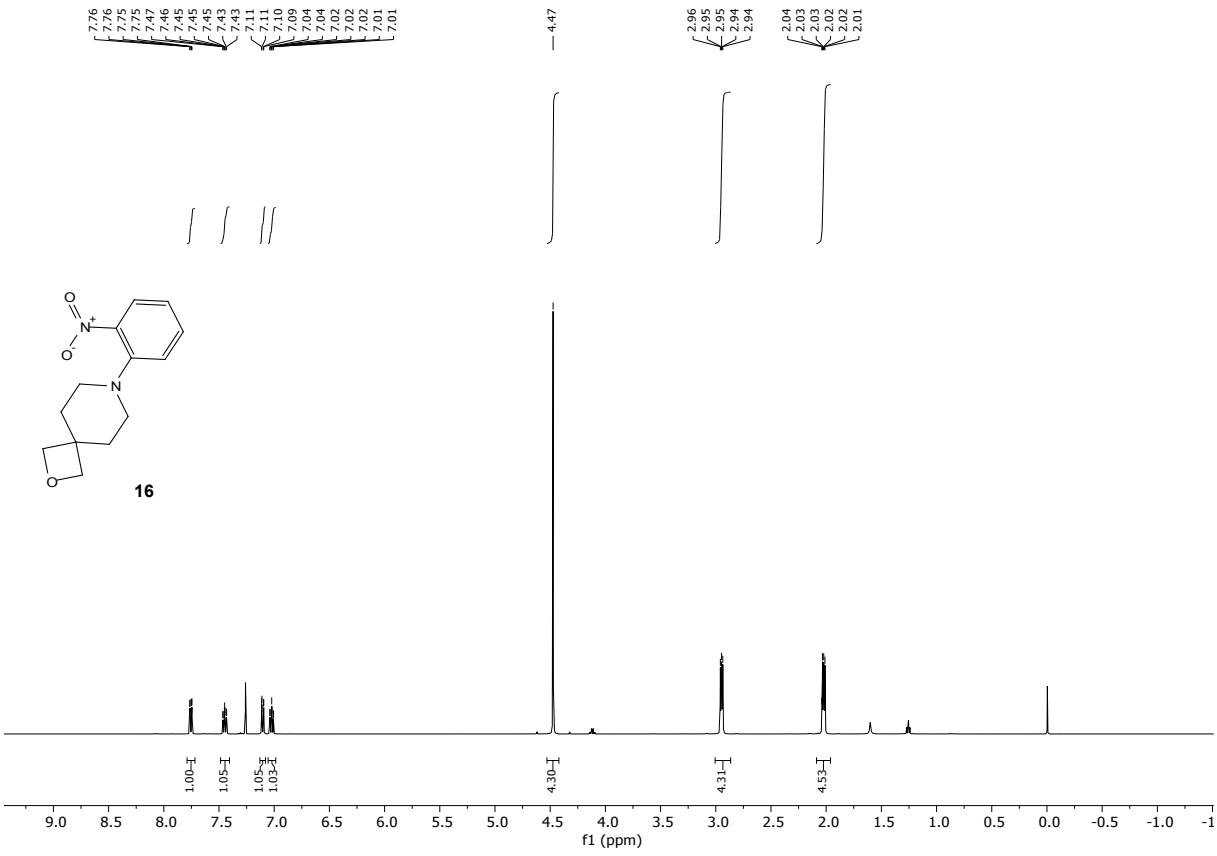
25.49
f1 (ppm)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7.76
7.75
7.75
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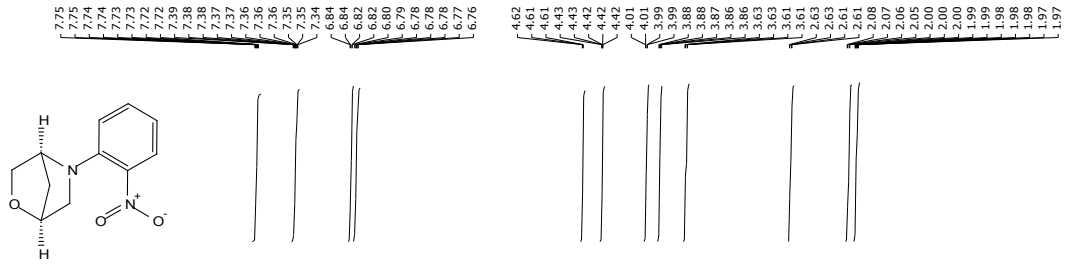
7.45
7.45
7.43
7.43
7.11
7.10
7.09
7.04
7.04
7.02
7.02
7.01
7.01
4.47
2.96
2.95
2.95
2.94
2.94
2.04
2.03
2.03
2.02
2.02
2.01
16
1.00
1.05
1.05
1.03
4.30
4.31
4.53
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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7.75
7.74
7.74
7.73
7.72
7.72
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
6.84
6.84
6.82
6.82
6.80
6.79
6.78
6.78
6.78
6.77
6.76
4.62
4.61
4.61
4.61
4.43
4.43
4.42
4.42
4.42
4.01
4.01
3.99
3.99
3.88
3.88
3.87
3.86
3.86
3.63
3.63
3.61
3.61
2.63
2.63
2.61
2.61
2.08
2.07
2.06
2.05
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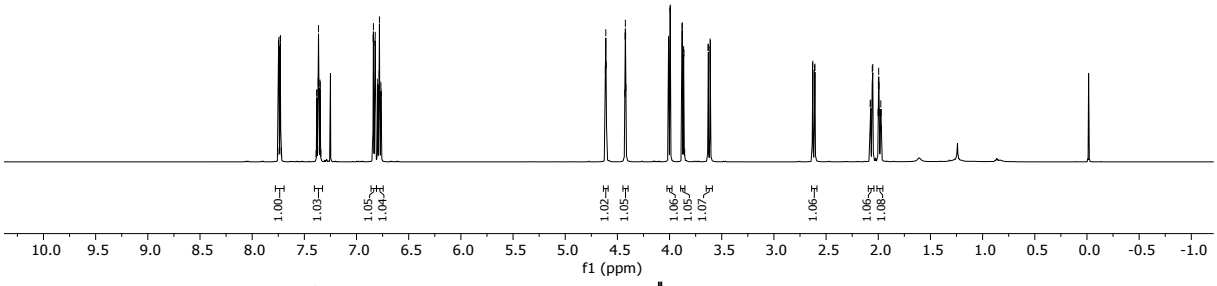
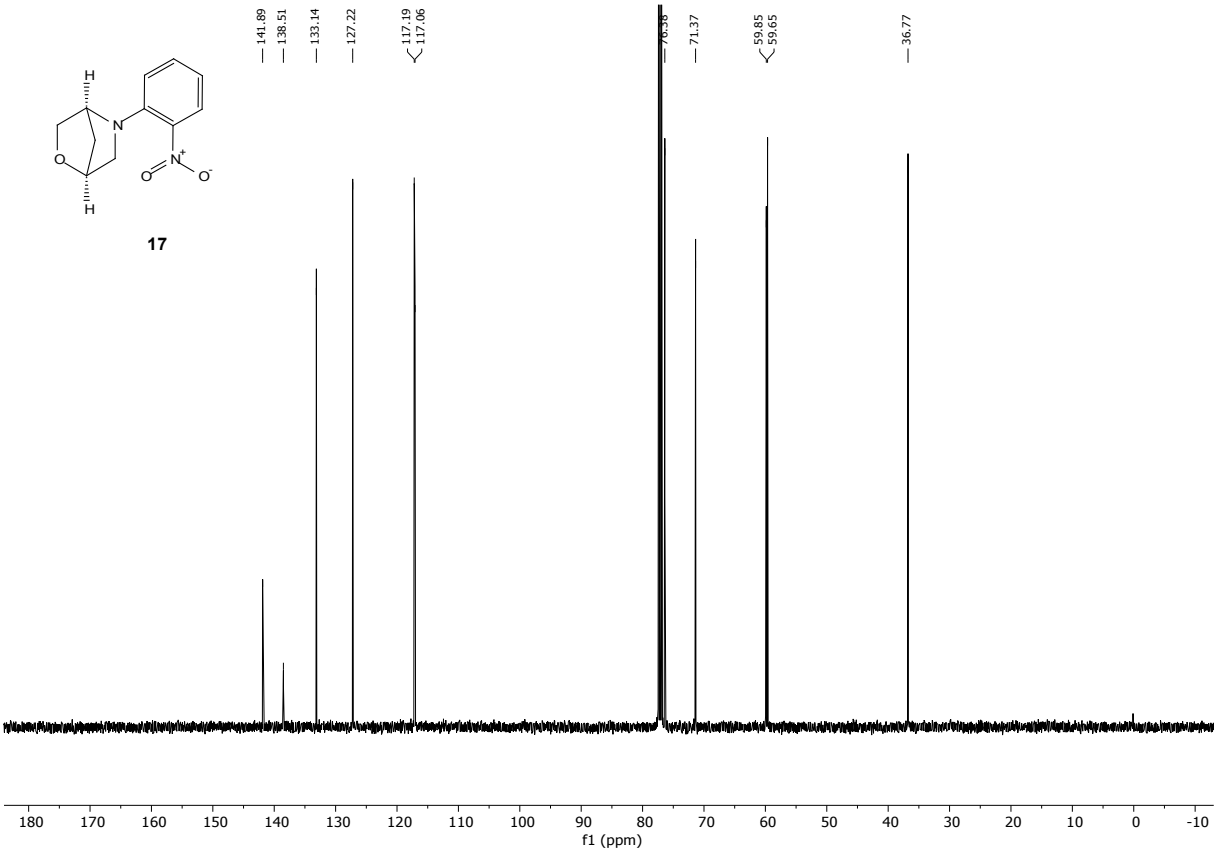
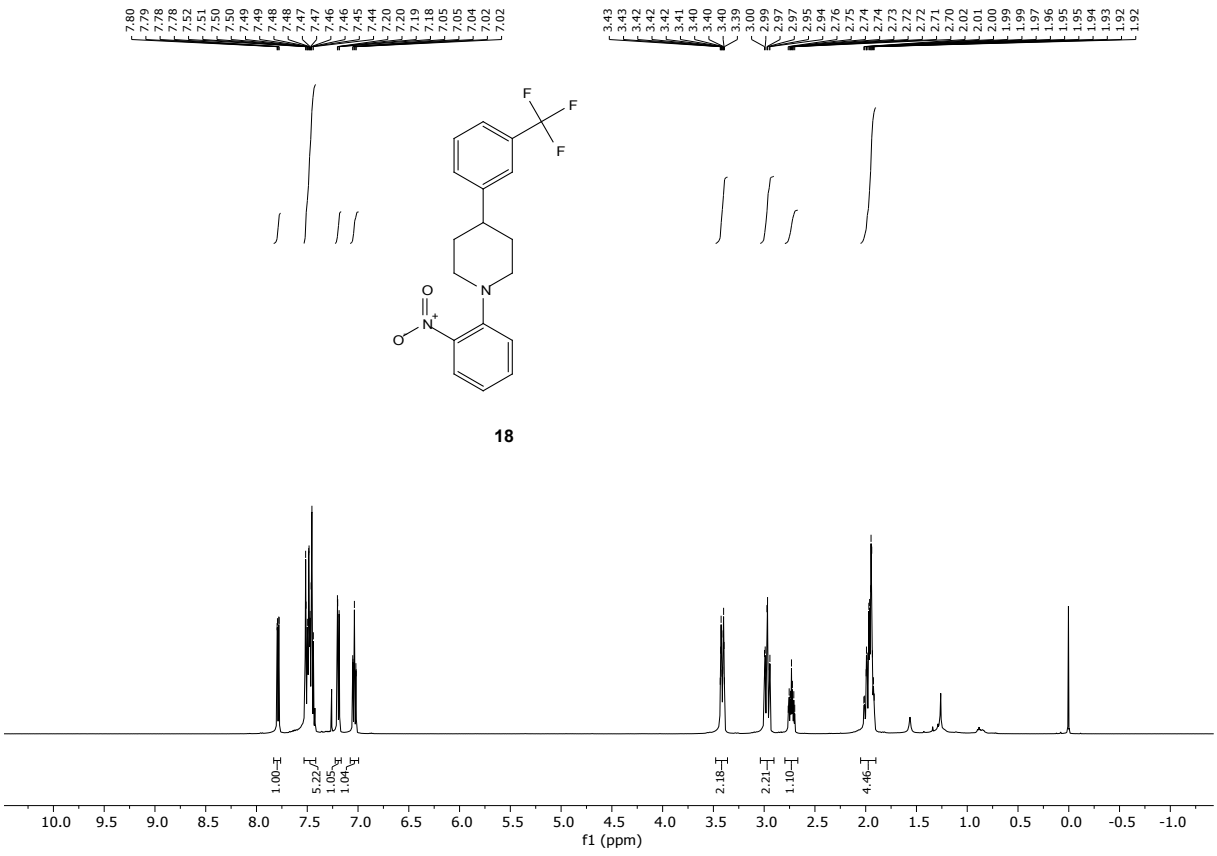
2.00
2.00
1.99
1.99
1.98
1.98
1.98
1.97
1.97

17


1.00
1.03
1.05
1.04
1.02
1.05
1.06
1.05
1.07
1.06
1.06
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


141.89
138.51
133.14
127.22
117.19
117.06
76.38
71.37
59.85
59.65
36.77
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

17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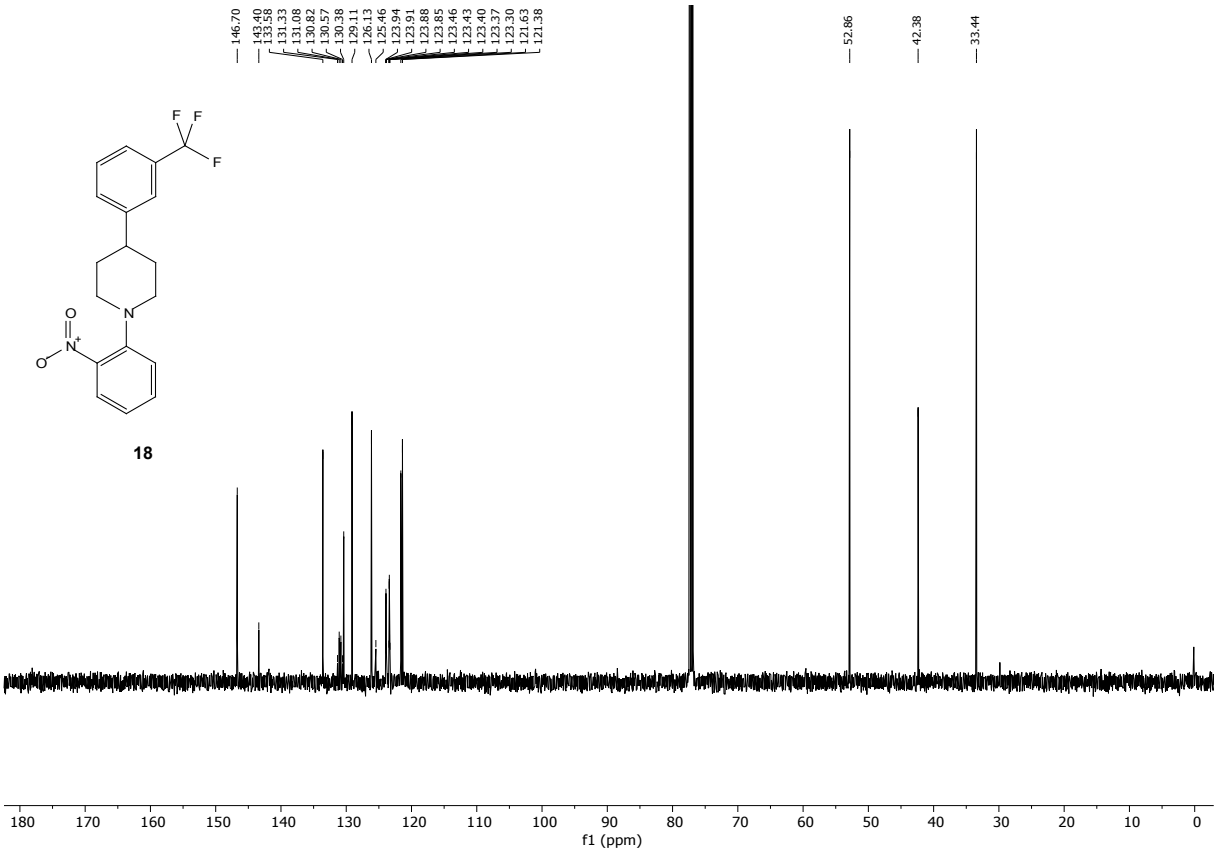
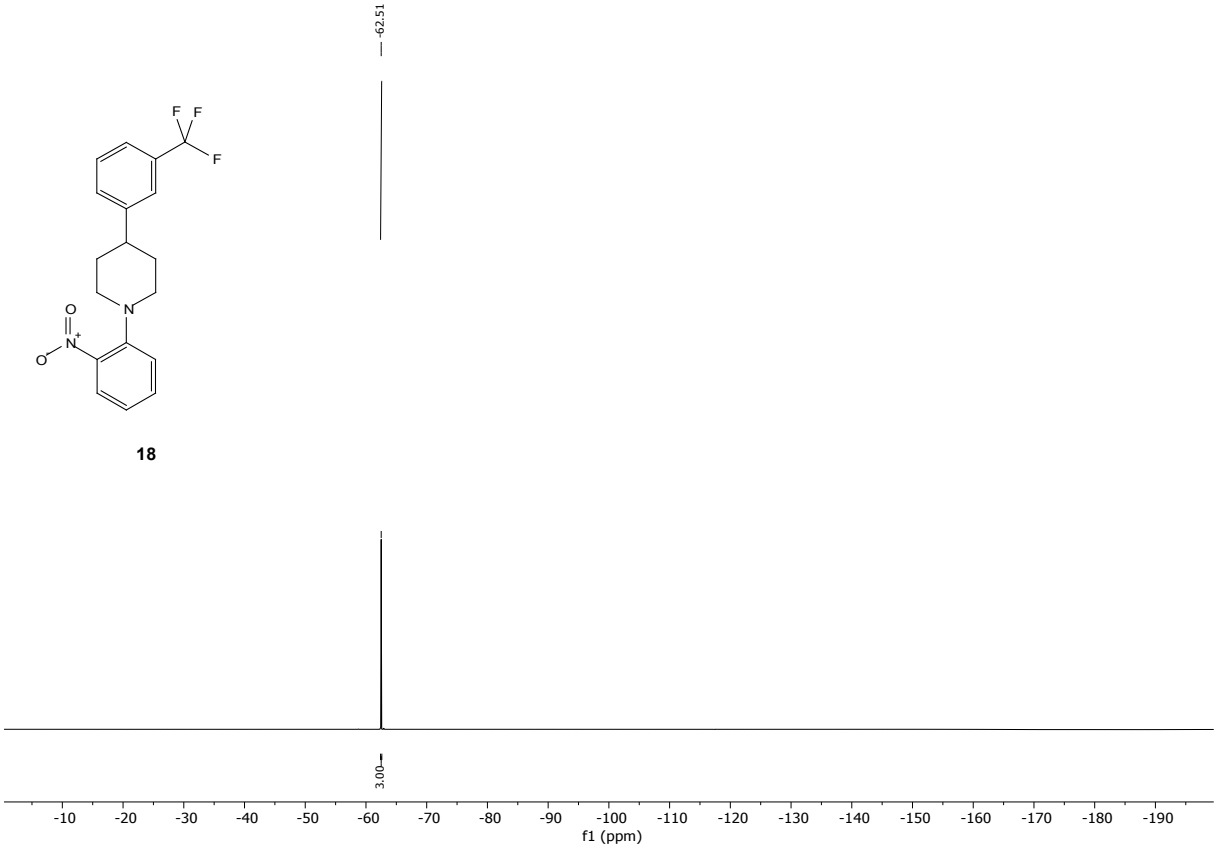
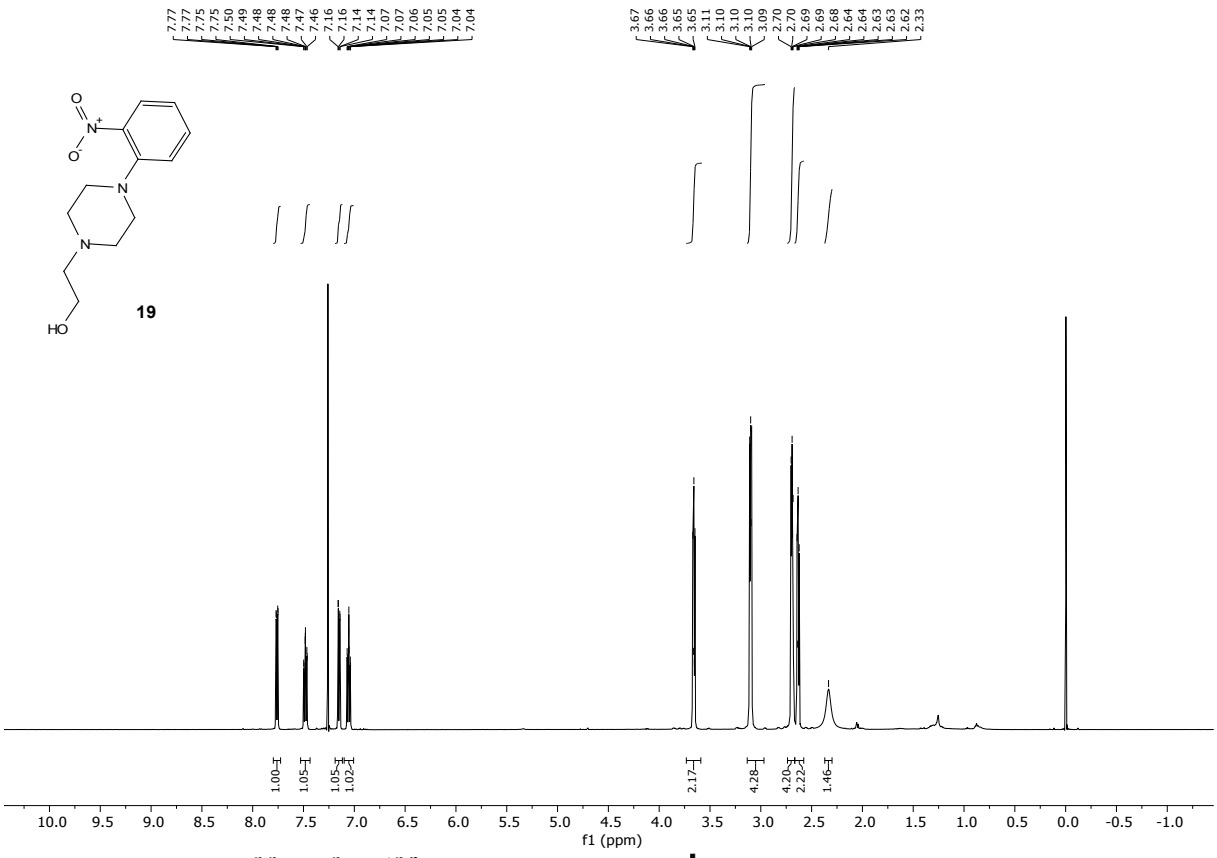
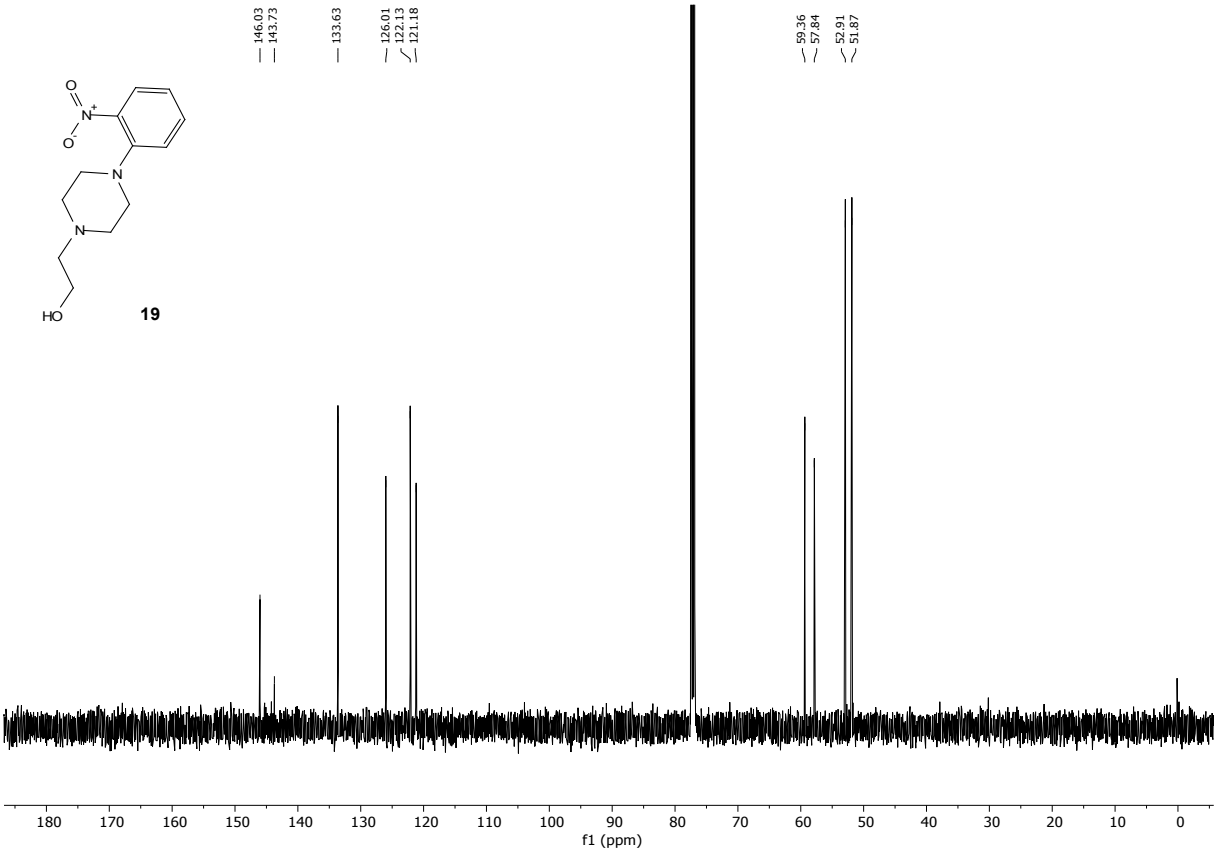
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.20
7.20
7.19
7.18
7.05
7.05
7.04
7.02
7.02
3.43
3.43
3.42
3.42
3.41
3.40
3.40
3.40
3.39
3.00
2.99
2.97
2.97
2.95
2.94
2.76
2.75
2.74
2.74
2.73
2.72
2.72
2.71
2.70
2.02
2.01
2.00
1.99
1.99
1.97
1.96
1.95
1.95
1.94
1.93
1.92
1.92
F
F
F
N
O
N+
O
1.00
5.22
1.05
1.04
2.18
2.21
1.10
4.46
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

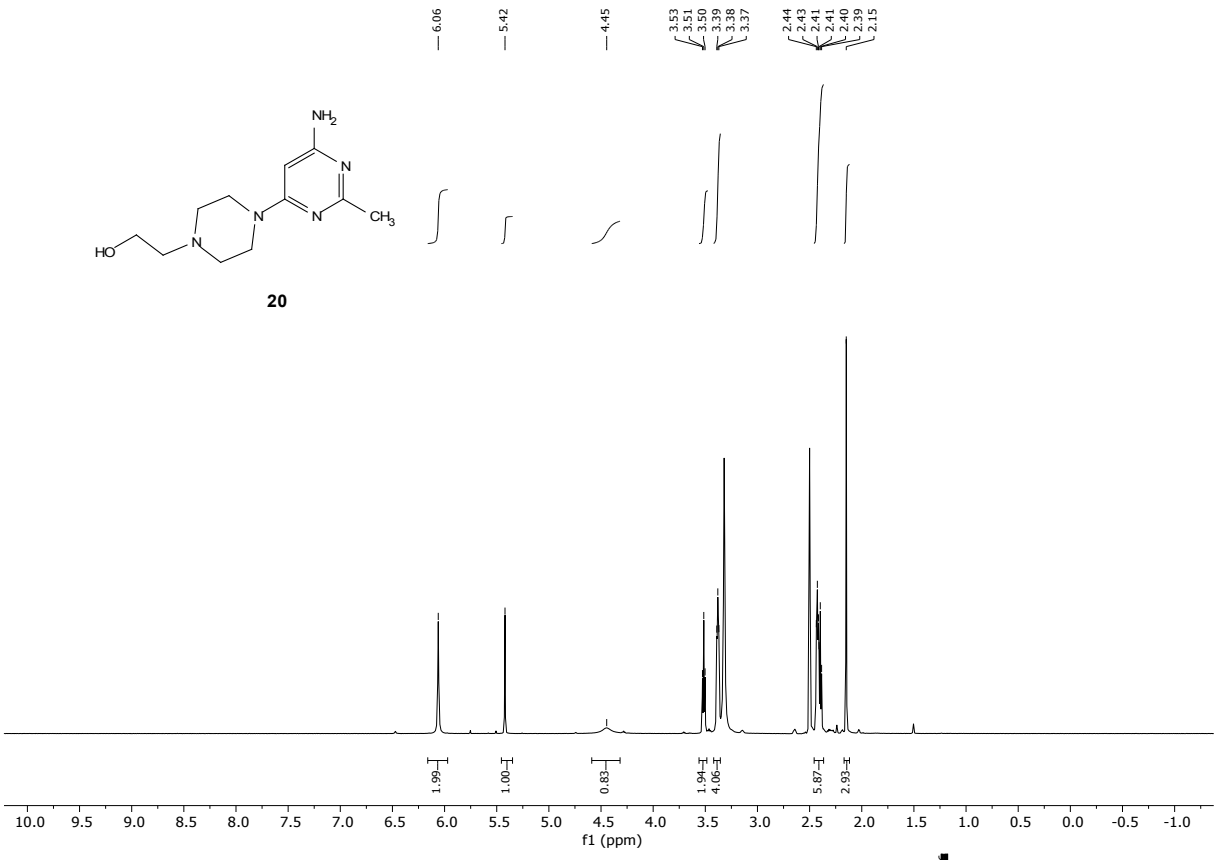
18

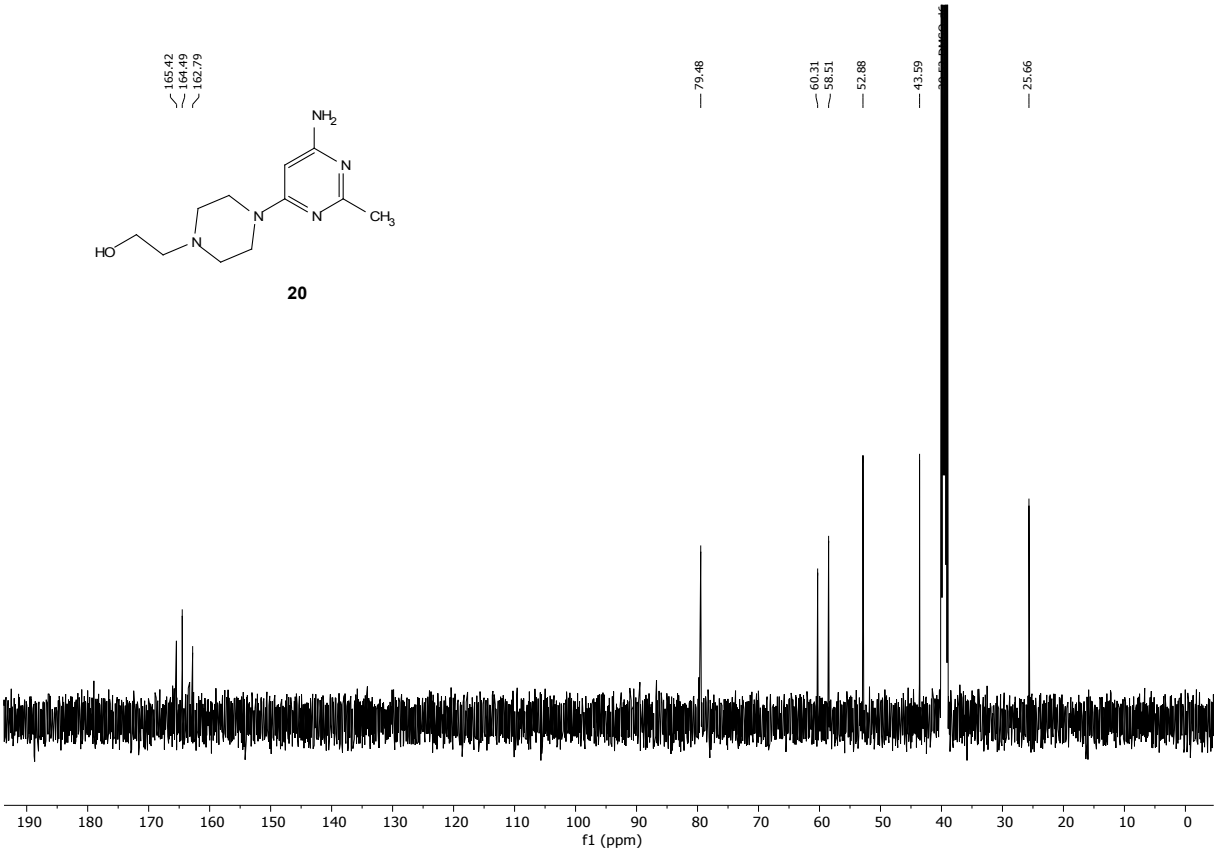

146.70
143.40
133.58
131.33
131.08
130.82
130.57
130.38
129.11
126.13
125.46
123.94
123.91
123.88
123.85
123.46
123.43
123.40
123.37
123.30
121.63
121.38
52.86
42.38
33.44
F F
F
N
O
N+
O-
18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

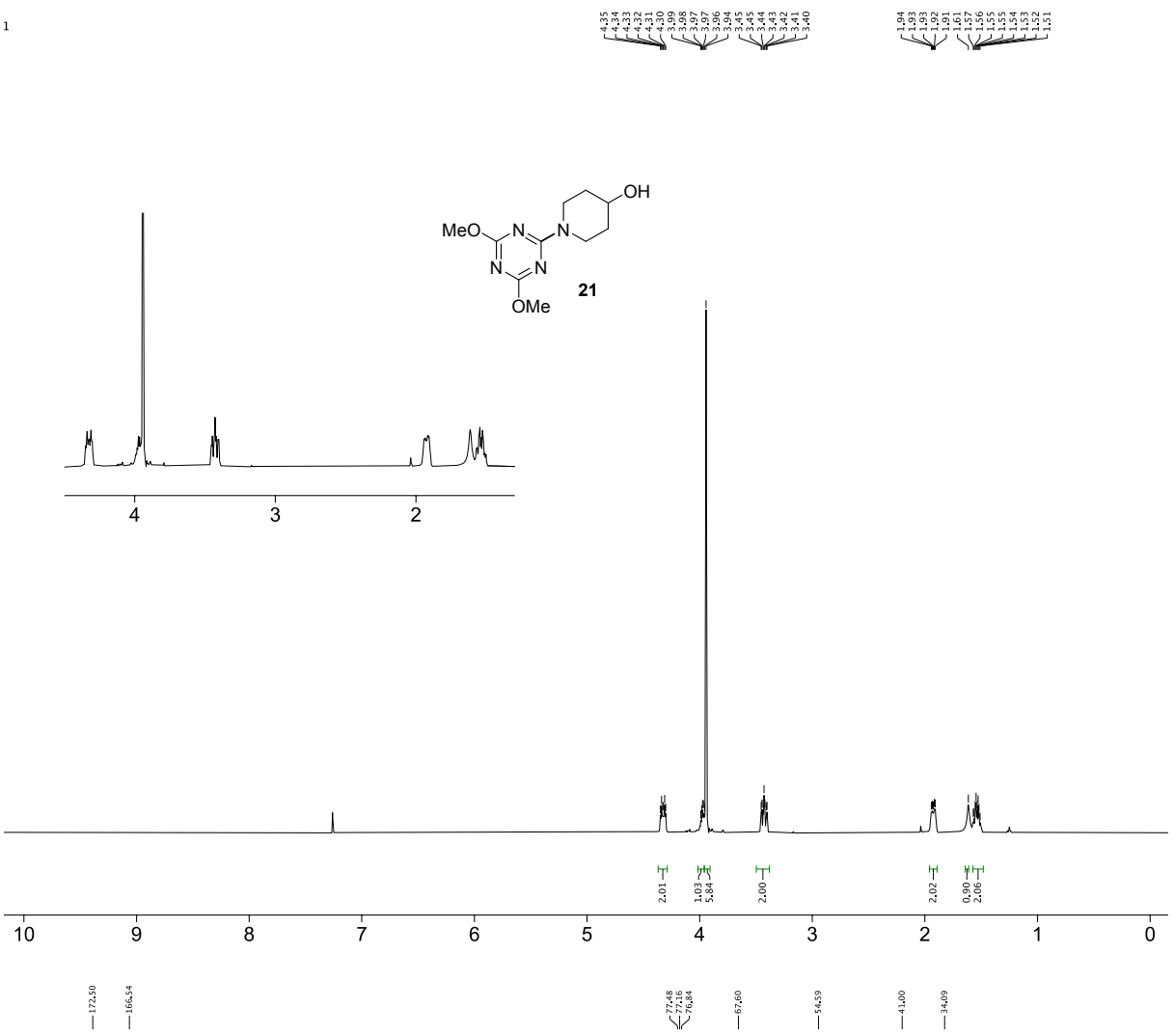

-62.51
F F
F
N
O
N+
O-
18
3.00
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

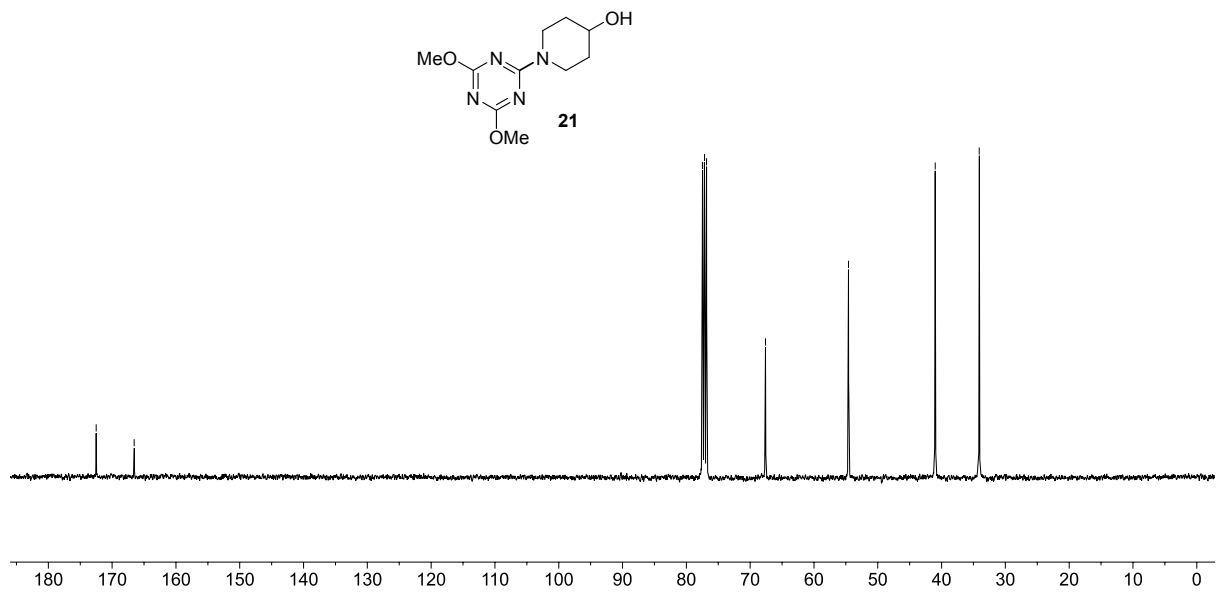

7.77
7.77
7.75
7.75
7.50
7.49
7.48
7.48
7.48
7.47
7.46
7.16
7.16
7.14
7.14
7.07
7.07
7.06
7.05
7.05
7.04
7.04
3.67
3.66
3.66
3.65
3.65
3.11
3.10
3.10
3.10
3.09
2.70
2.70
2.69
2.69
2.68
2.64
2.64
2.63
2.63
2.62
2.33
19
1.00
1.05
1.05
1.02
2.17
4.28
4.20
2.22
1.46
f1 (ppm)

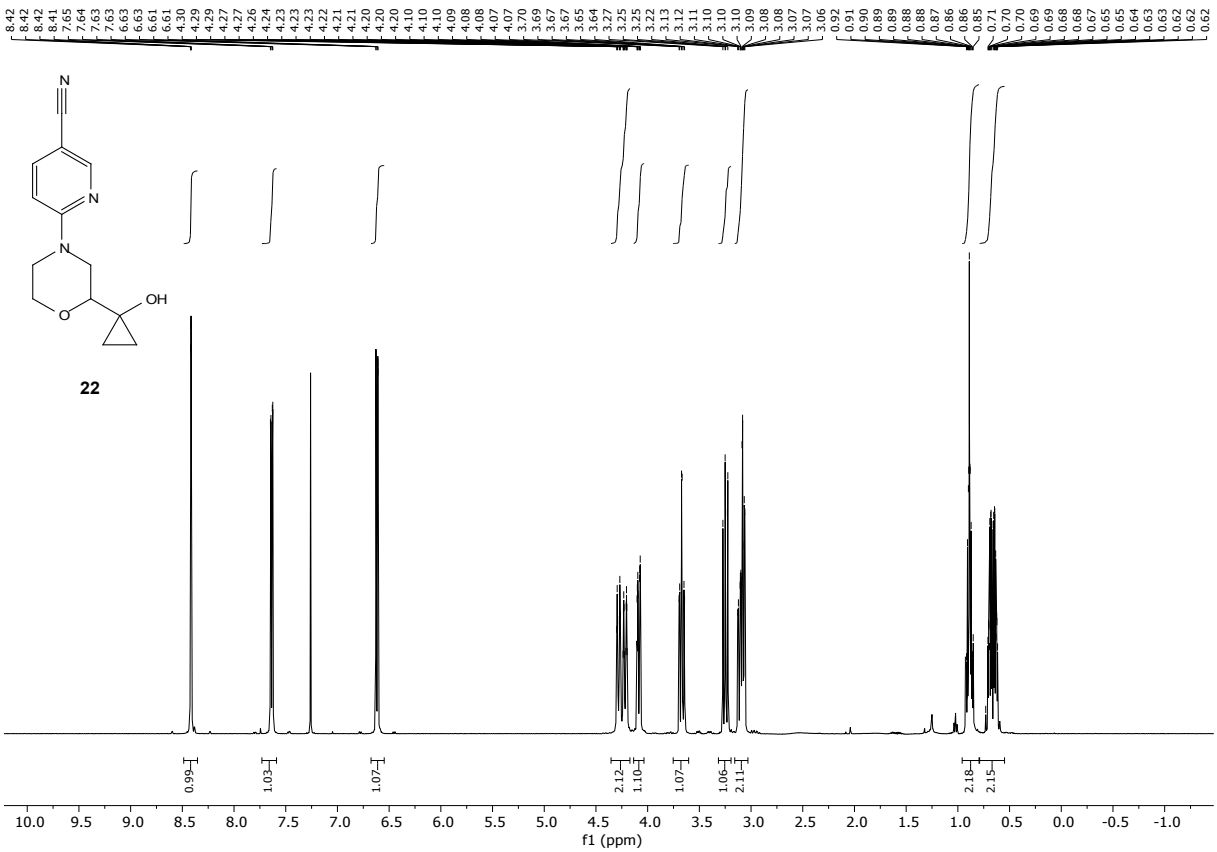

146.03
143.73
133.63
126.01
122.13
121.18
59.36
57.84
52.91
51.87
19
f1 (ppm)

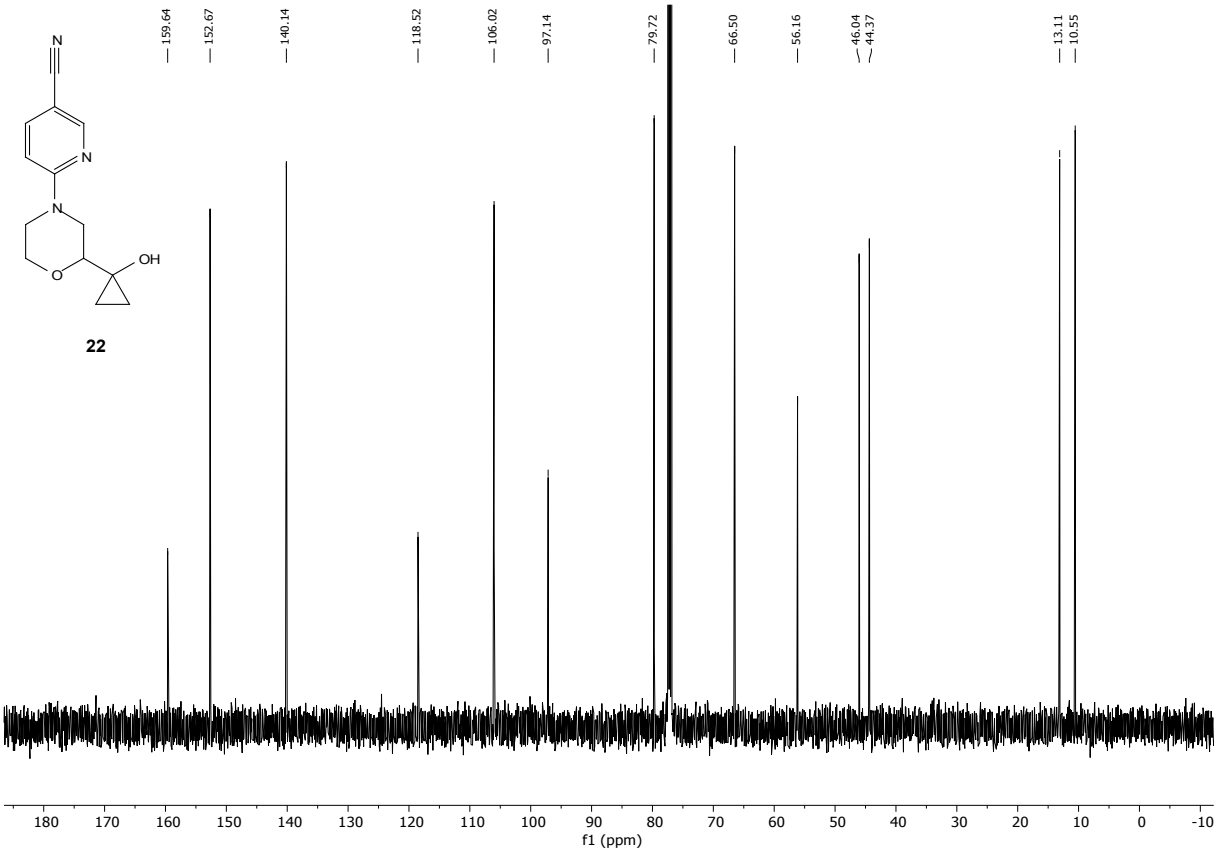

6.06
5.42
4.45
3.53
3.51
3.50
3.39
3.38
3.37
2.44
2.43
2.41
2.41
2.40
2.39
2.15
NH2
N
N
N
CH3
HO
20
1.99
1.00
0.83
1.94
4.06
5.87
2.93
f1 (ppm)

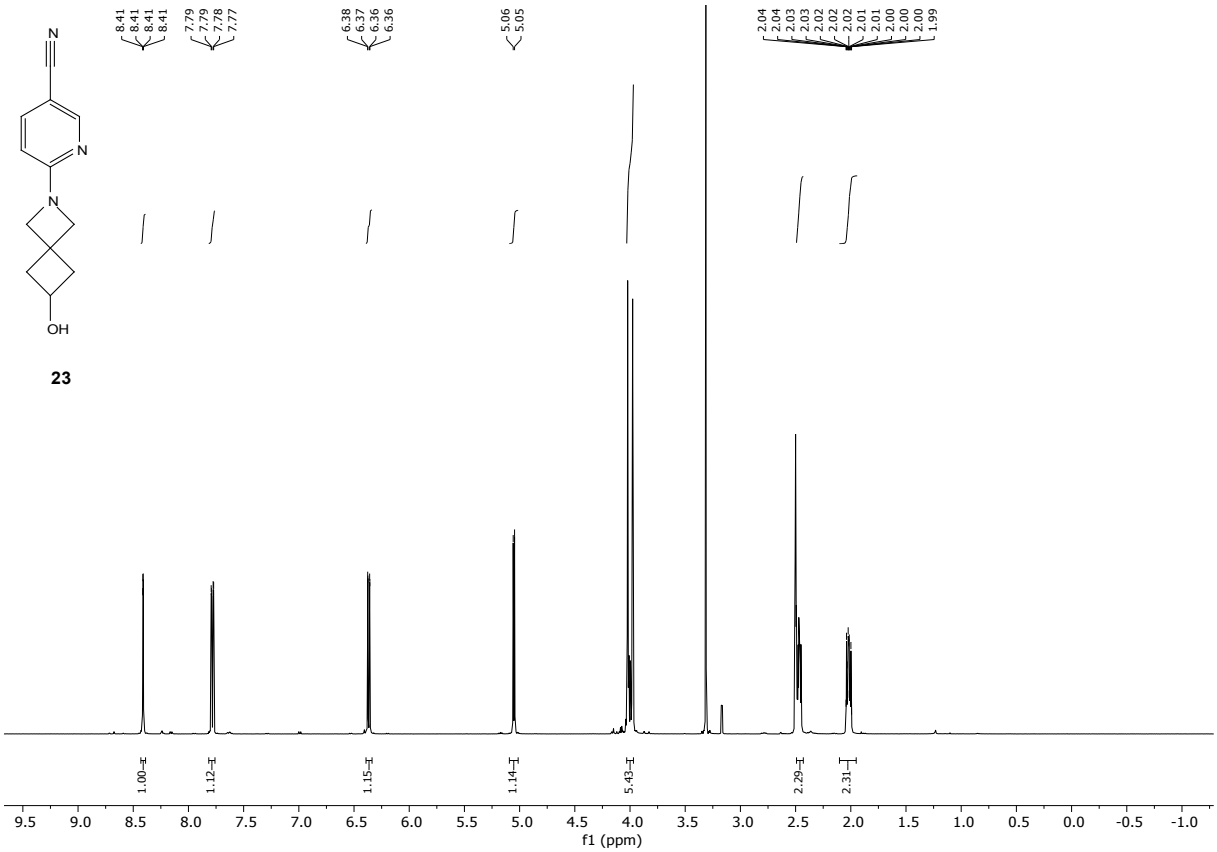

165.42
164.49
162.79
79.48
60.31
58.51
52.88
43.59
25.66
NH2
N
N
N
CH3
HO
20
f1 (ppm)


4.35
4.34
4.33
4.32
4.31
4.30
3.99
3.98
3.97
3.97
3.96
3.94
3.45
3.45
3.44
3.43
3.42
3.41
3.40
1.94
1.93
1.93
1.92
1.91
1.61
1.57
1.56
1.55
1.55
1.54
1.53
1.52
1.51
MeO
N
N
N
N
OH
OMe
21
2.01
1.03
5.84
2.00
2.02
0.90
2.06


172.50
166.54
77.48
77.16
76.84
67.60
54.59
41.00
34.09
MeO
N
N
N
N
OH
OMe
21


N
N
N
O
OH
22
0.99
1.03
1.07
2.12
1.10
1.07
1.05
2.11
2.18
2.15
f1 (ppm)


159.64
152.67
140.14
118.52
106.02
97.14
79.72
66.50
56.16
46.04
44.37
13.11
10.55
N
N
N
O
OH
22
f1 (ppm)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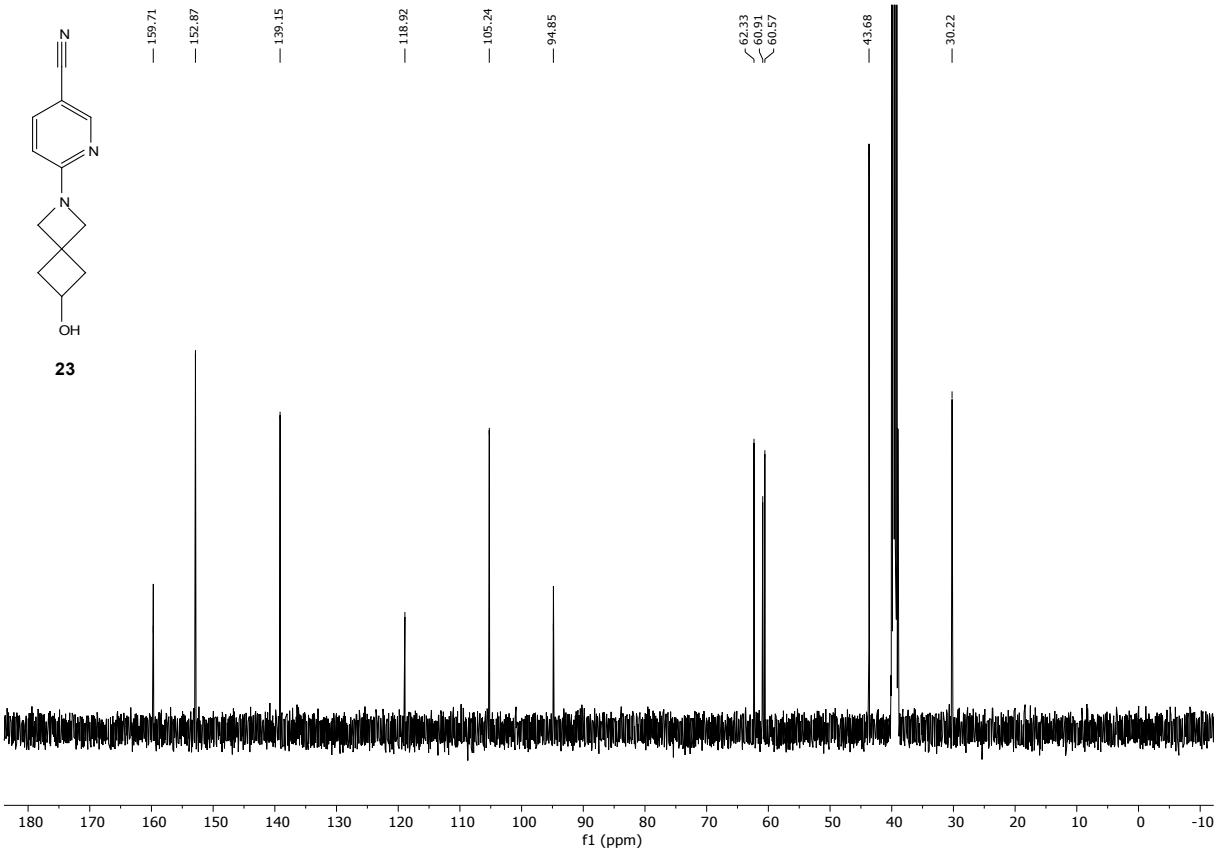
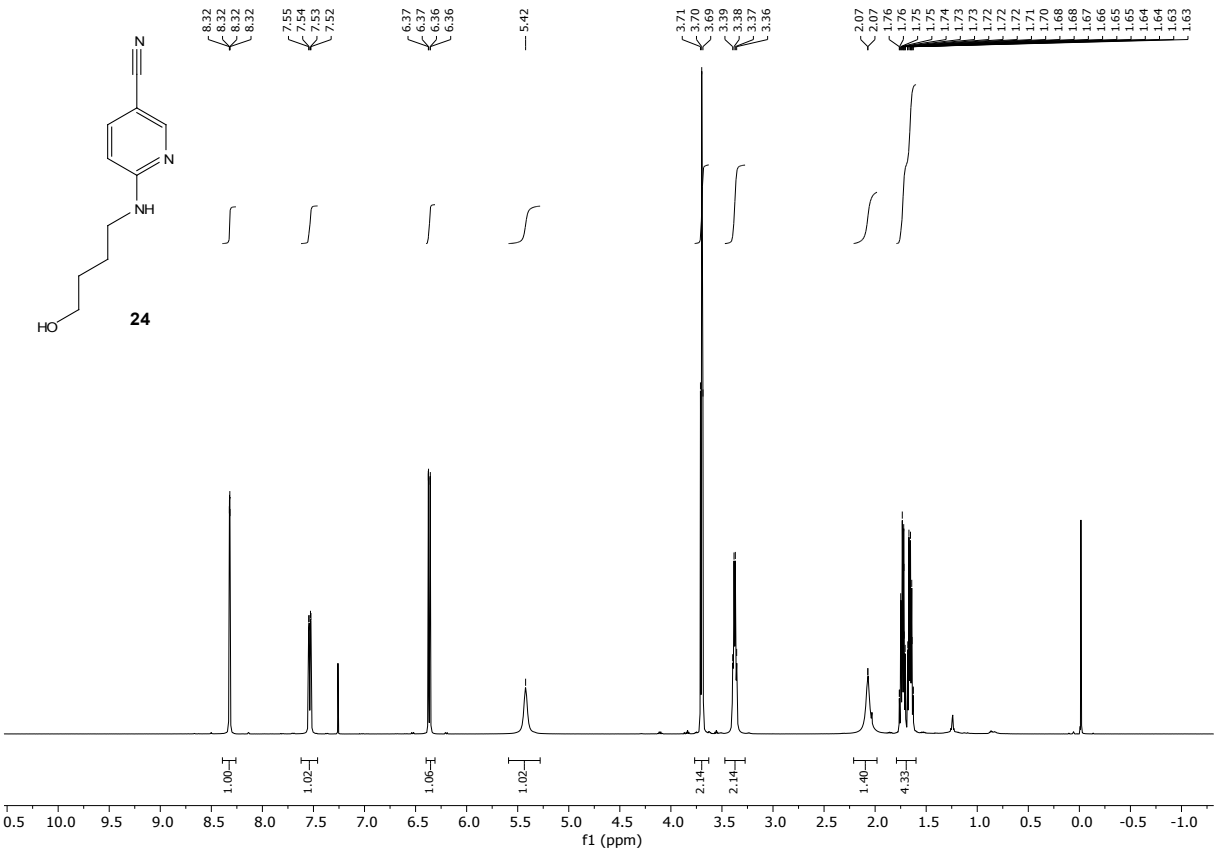
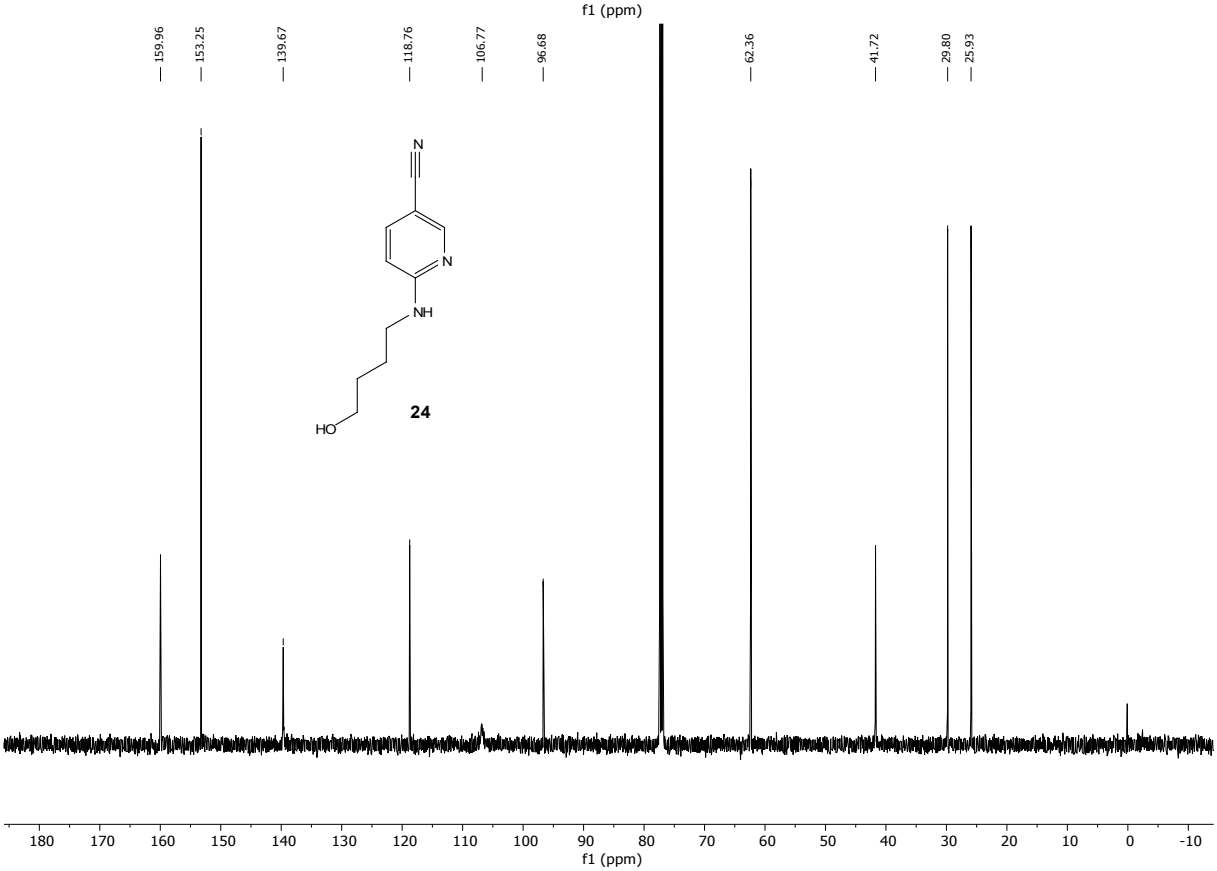
8.41
8.41
7.79
7.79
7.78
7.77
6.38
6.37
6.36
6.36
5.06
5.05
2.04
2.04
2.03
2.03
2.02
2.02
2.02
2.01
2.01
2.00
2.00
2.00
1.99
N
N
N
OH
23
1.00
1.12
1.15
1.14
5.43
2.29
2.31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


159.71
152.87
139.15
118.92
105.24
94.85
62.33
60.91
60.57
43.68
30.22
N
N
N
OH
23
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.32
8.32
8.32
8.32
7.55
7.54
7.53
7.52
6.37
6.37
6.36
6.36
5.42
3.71
3.70
3.69
3.39
3.38
3.37
3.36
2.07
2.07
1.76
1.76
1.75
1.75
1.74
1.73
1.73
1.72
1.72
1.72
1.71
1.70
1.68
1.68
1.67
1.66
1.65
1.65
1.64
1.64
1.63
1.63
N
N
NH
HO
24
1.00
1.02
1.06
1.02
2.14
2.14
1.40
4.33
f1 (ppm)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153.25
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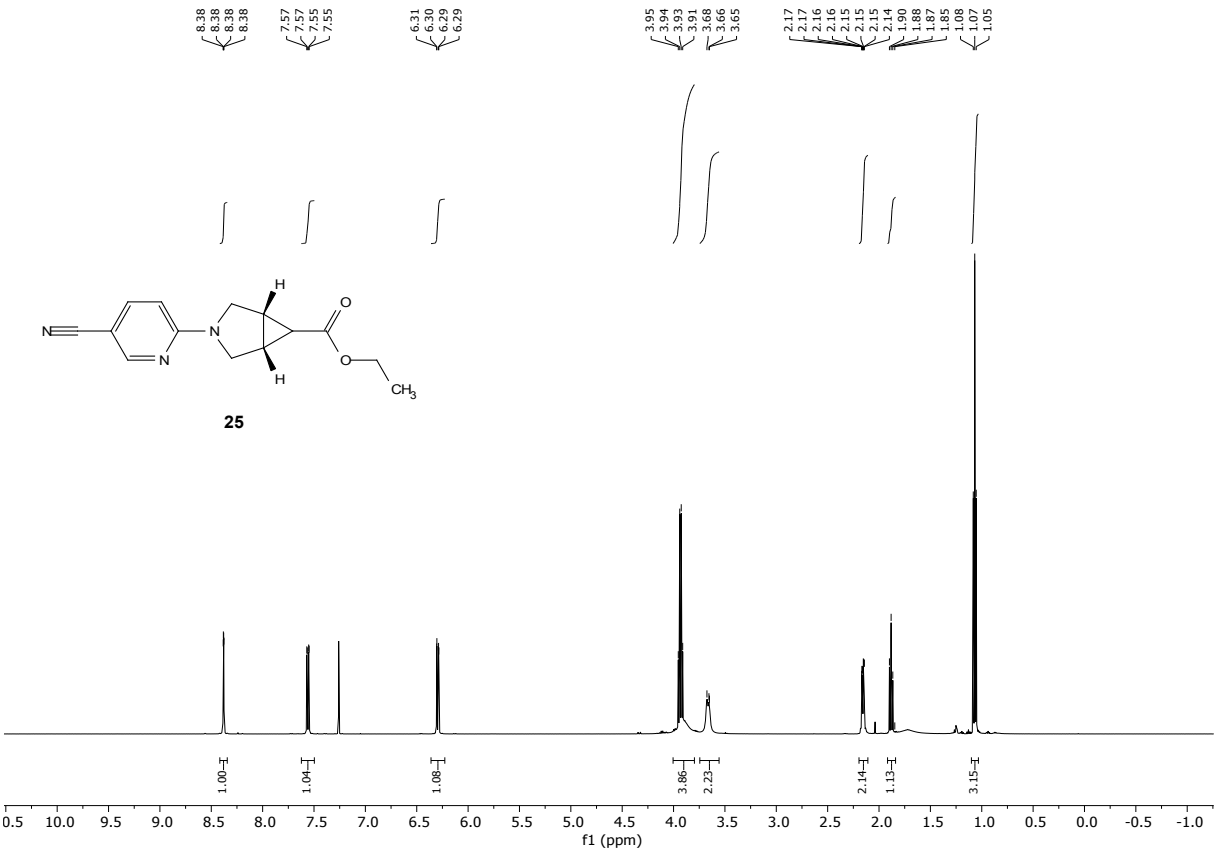
106.77
96.68
62.36
41.72
29.80
25.93
N
N
NH
HO
24
f1 (ppm)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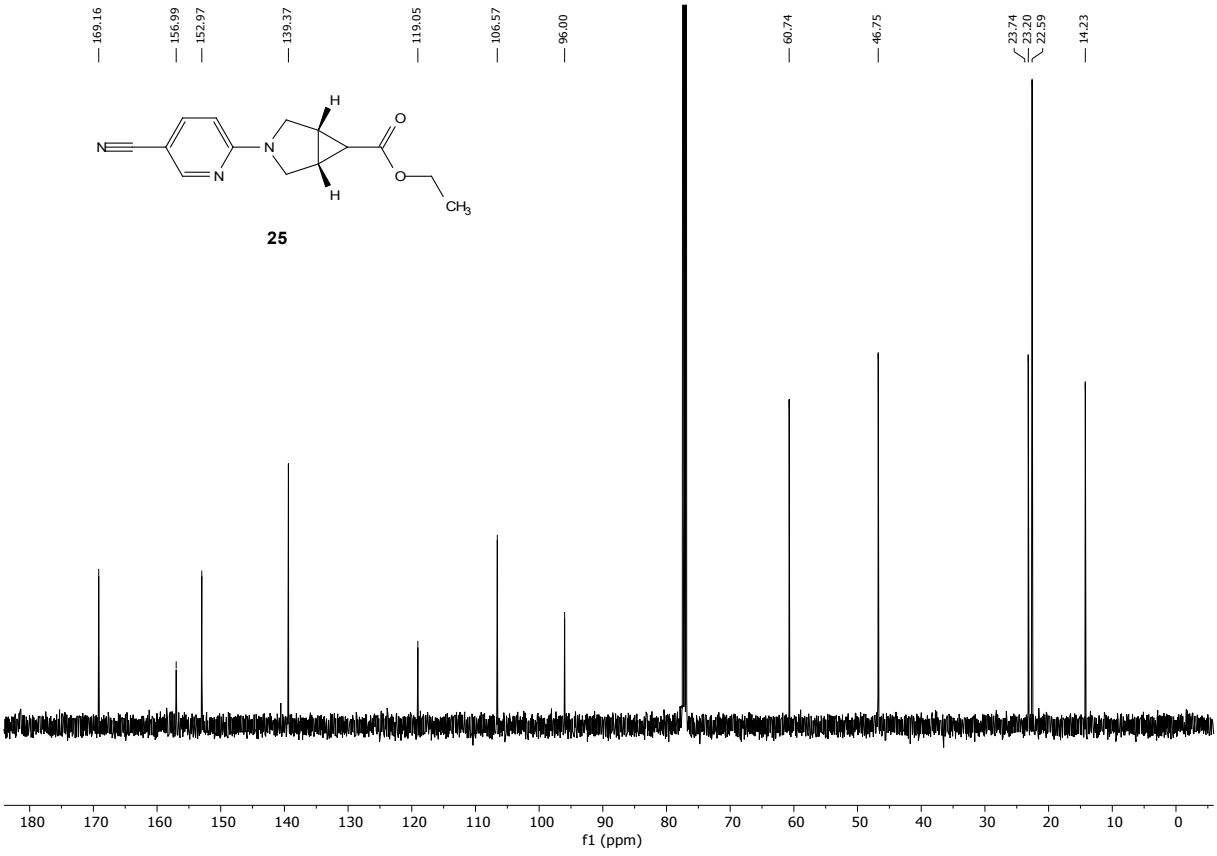
8.38
8.38
8.38
7.57
7.57
7.55
7.55
6.31
6.30
6.29
6.29
3.95
3.94
3.93
3.91
3.68
3.66
3.65
2.17
2.17
2.16
2.16
2.15
2.15
2.15
2.14
1.90
1.88
1.87
1.85
1.08
1.07
1.05
H
O
N
N
O
H
CH3
1.00
1.04
1.08
3.86
2.23
2.14
1.13
3.15
f1 (ppm)

25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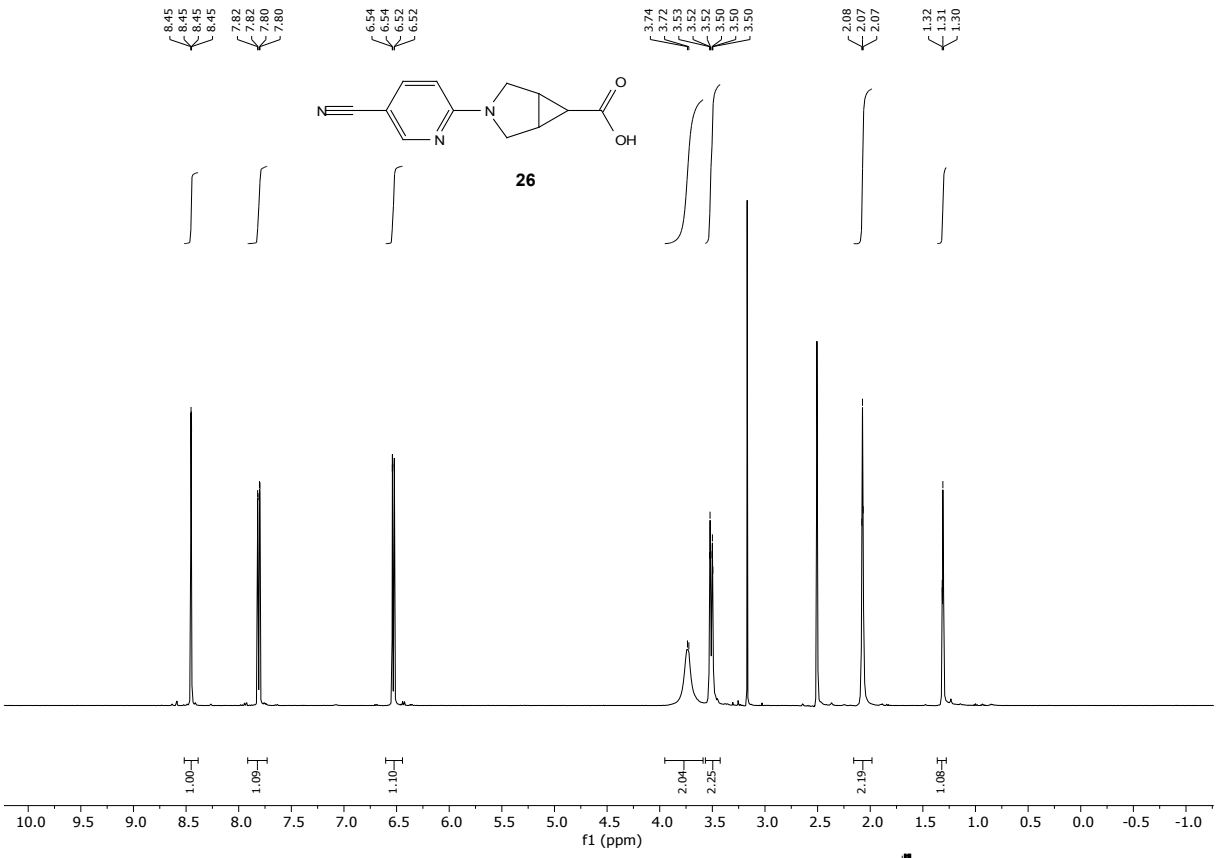
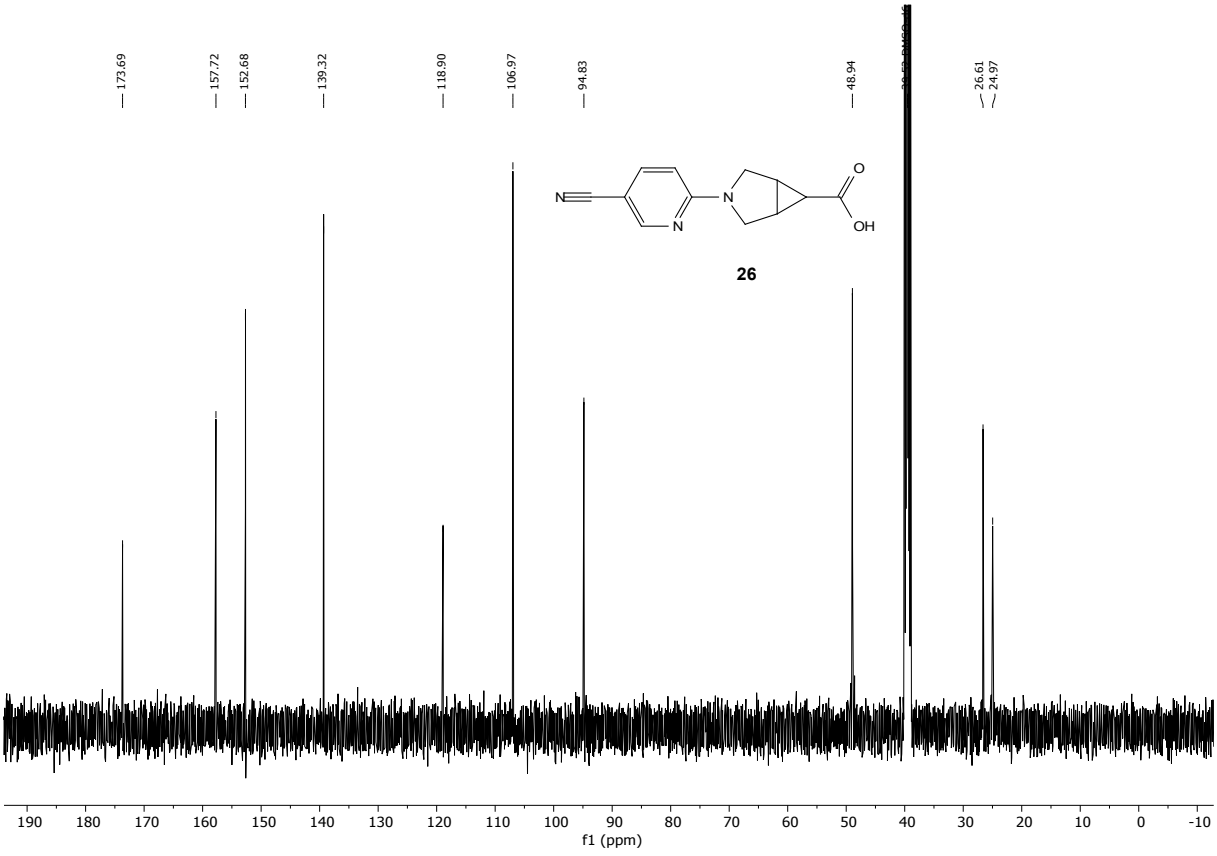
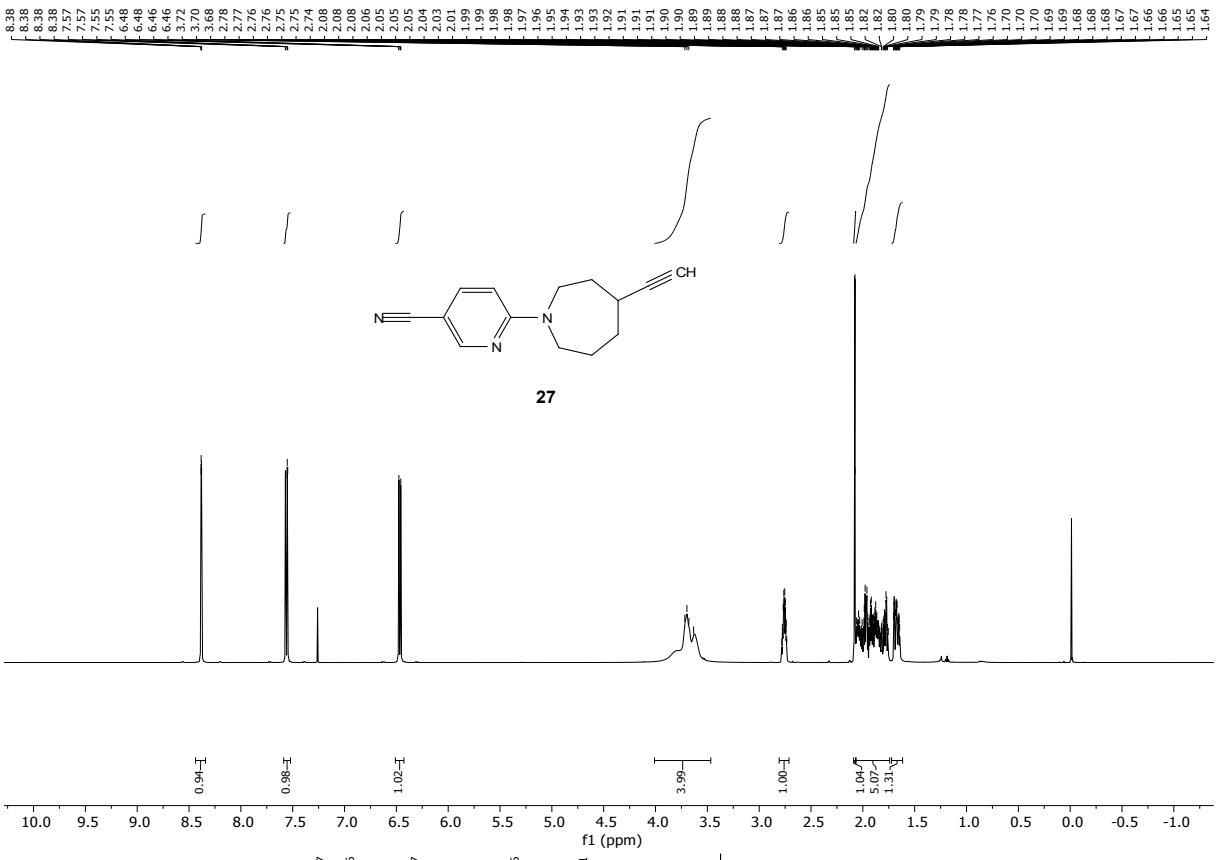
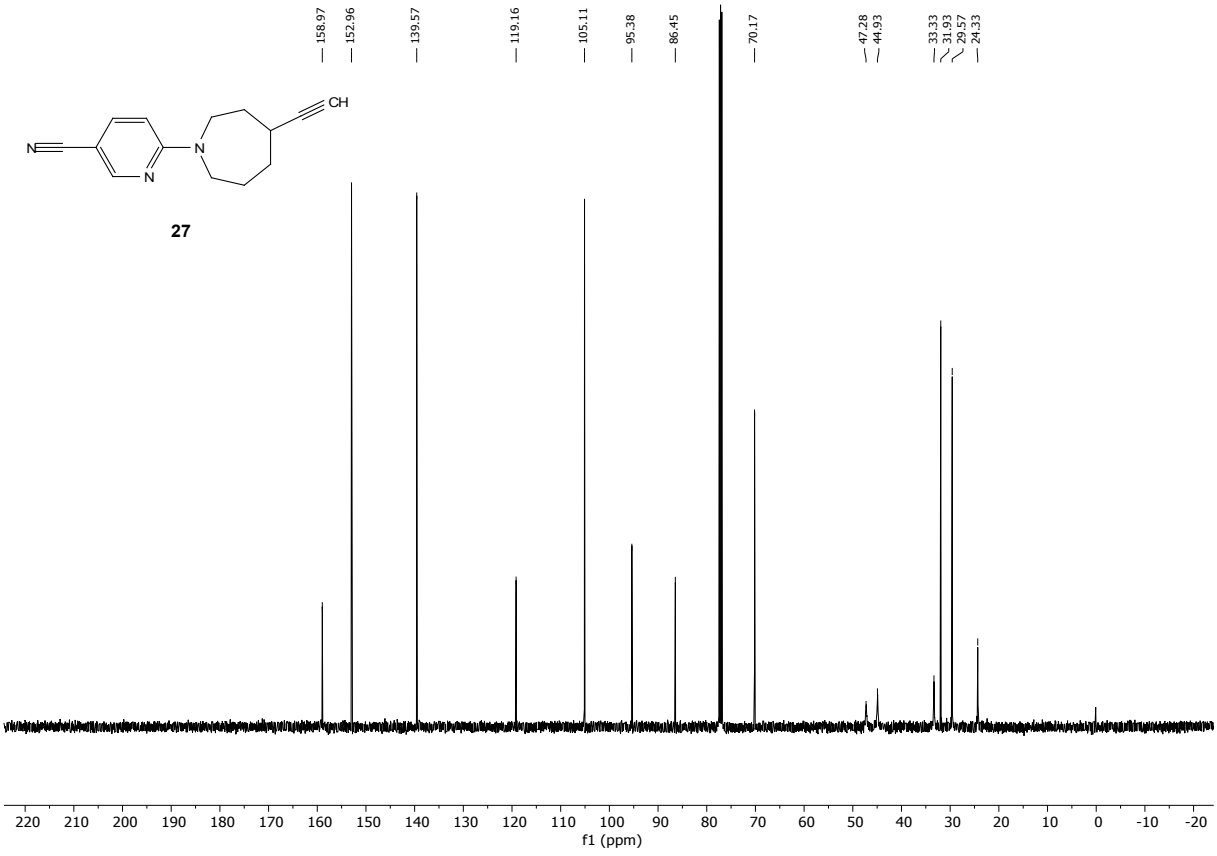
152.97
139.37
119.05
106.57
96.00
60.74
46.75
23.74
23.20
22.59
14.23
H
O
N
N
O
H
CH3
f1 (ppm)

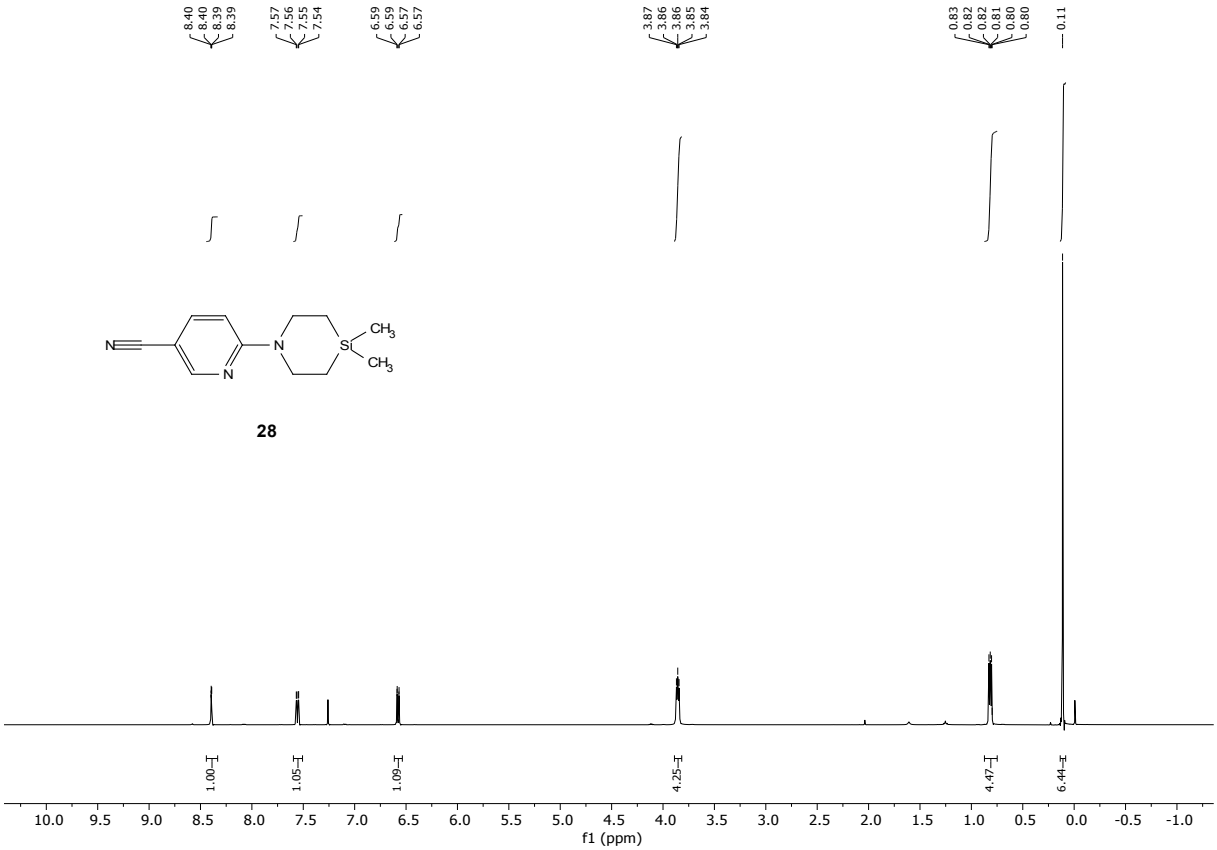
25


8.45
8.45
8.45
8.45
7.82
7.82
7.80
7.80
6.54
6.54
6.52
6.52
3.74
3.72
3.53
3.52
3.52
3.50
3.50
3.50
2.08
2.07
2.07
1.32
1.31
1.30
N
N
O
OH
26
1.00
1.09
1.10
2.04
2.25
2.19
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


173.69
157.72
152.68
139.32
118.90
106.97
94.83
48.94
26.61
24.97
N
N
O
OH
26
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.38 8.38 8.38 8.38 7.57 7.57 7.55 7.55 6.48 6.48 6.46 6.46 3.72 3.70 3.68 2.78 2.77 2.76 2.76 2.75 2.74 2.08 2.08 2.06 2.05 2.05 2.04 2.03 2.01 1.99 1.99 1.98 1.98 1.97 1.96 1.95 1.94 1.93 1.93 1.92 1.91 1.91 1.91 1.90 1.90 1.89 1.89 1.88 1.88 1.87 1.87 1.87 1.86 1.86 1.85 1.85 1.85 1.82 1.82 1.80 1.80 1.79 1.79 1.78 1.78 1.77 1.76 1.70 1.70 1.70 1.69 1.69 1.68 1.68 1.68 1.67 1.67 1.66 1.66 1.65 1.64
CH
N
N
N
27
0.94
0.98
1.02
3.99
1.00
1.04
5.07
1.31
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


158.97
152.96
139.57
119.16
105.11
95.38
86.45
70.17
47.28
44.93
33.33
31.93
29.57
24.33
CH
N
N
N
27
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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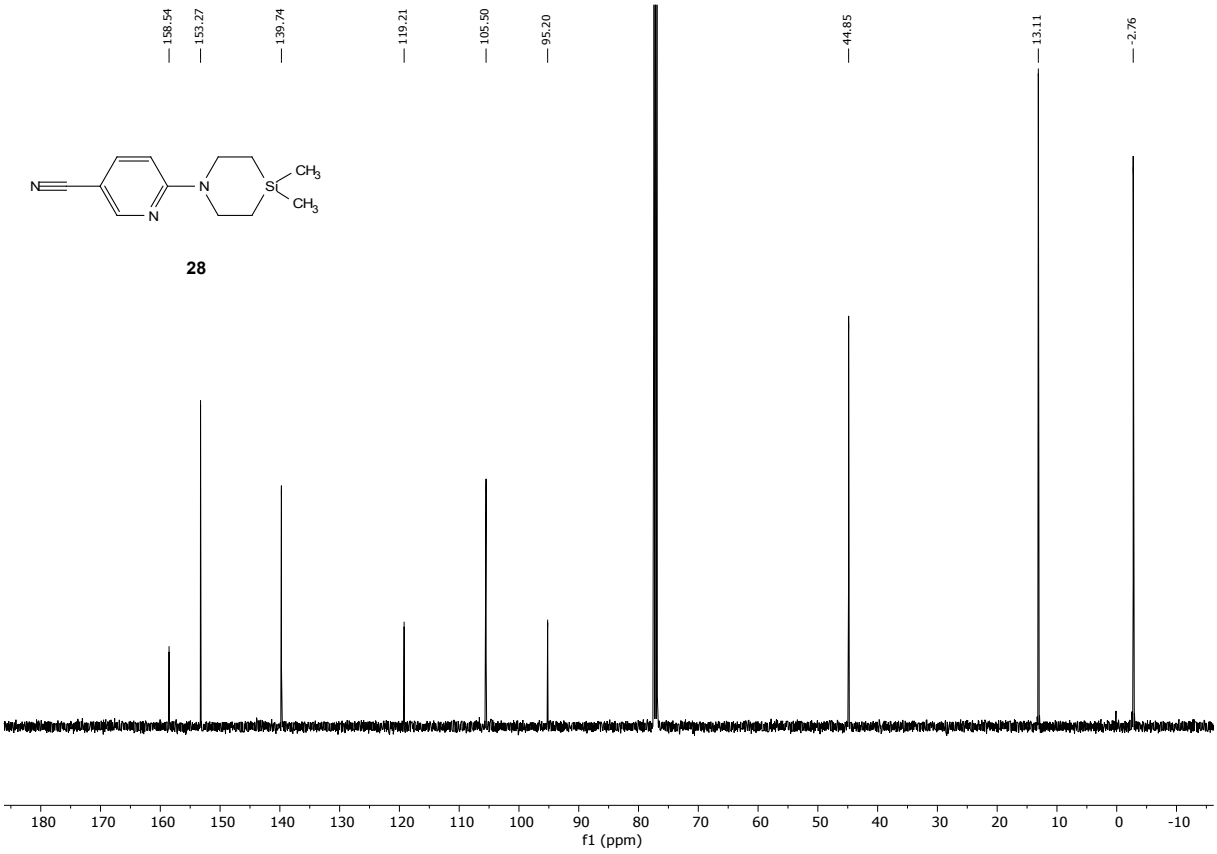
8.40
8.39
8.39
7.57
7.56
7.55
7.54
6.59
6.59
6.57
6.57
3.87
3.86
3.86
3.85
3.84
0.83
0.82
0.82
0.81
0.80
0.80
0.11
N
N
N
Si
CH3
CH3
1.00
1.05
1.09
4.25
4.47
6.44
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

28


158.54
153.27
139.74
119.21
105.50
95.20
44.85
13.11
-2.76
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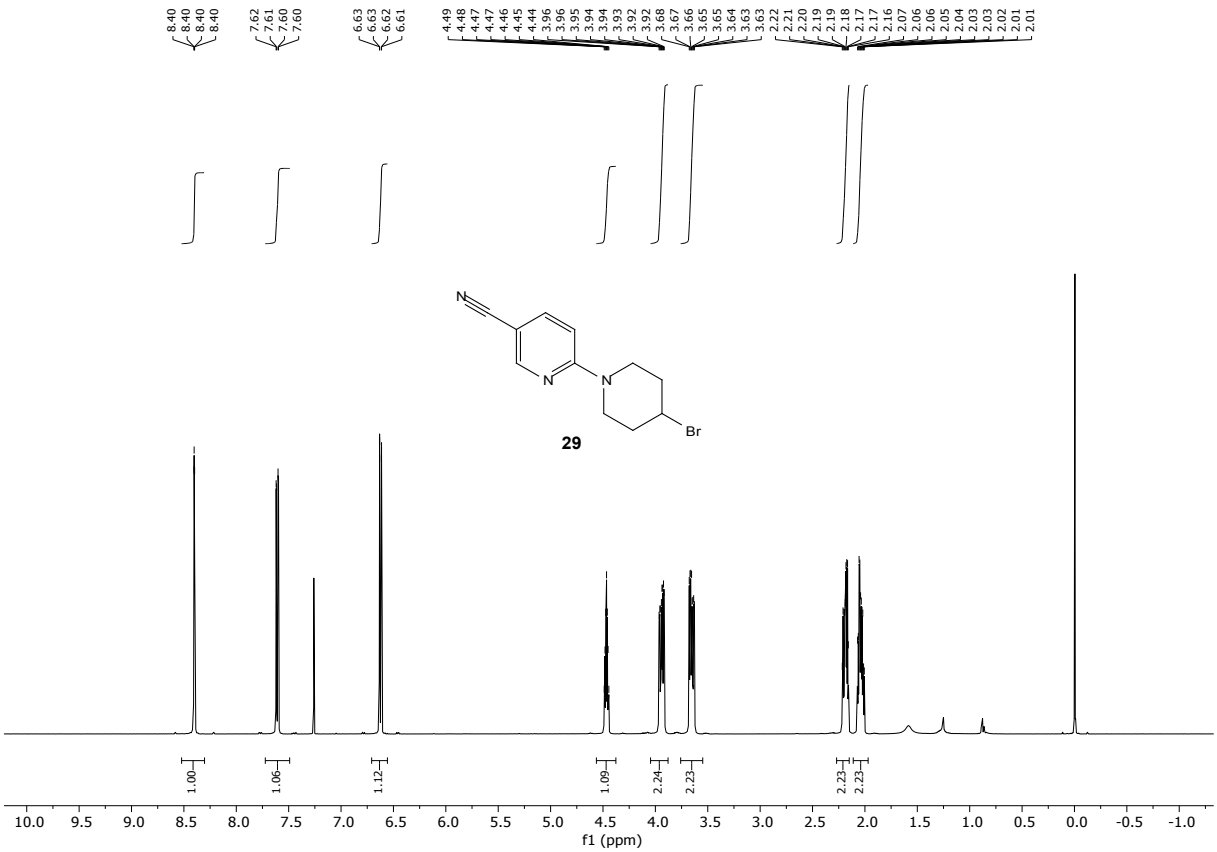
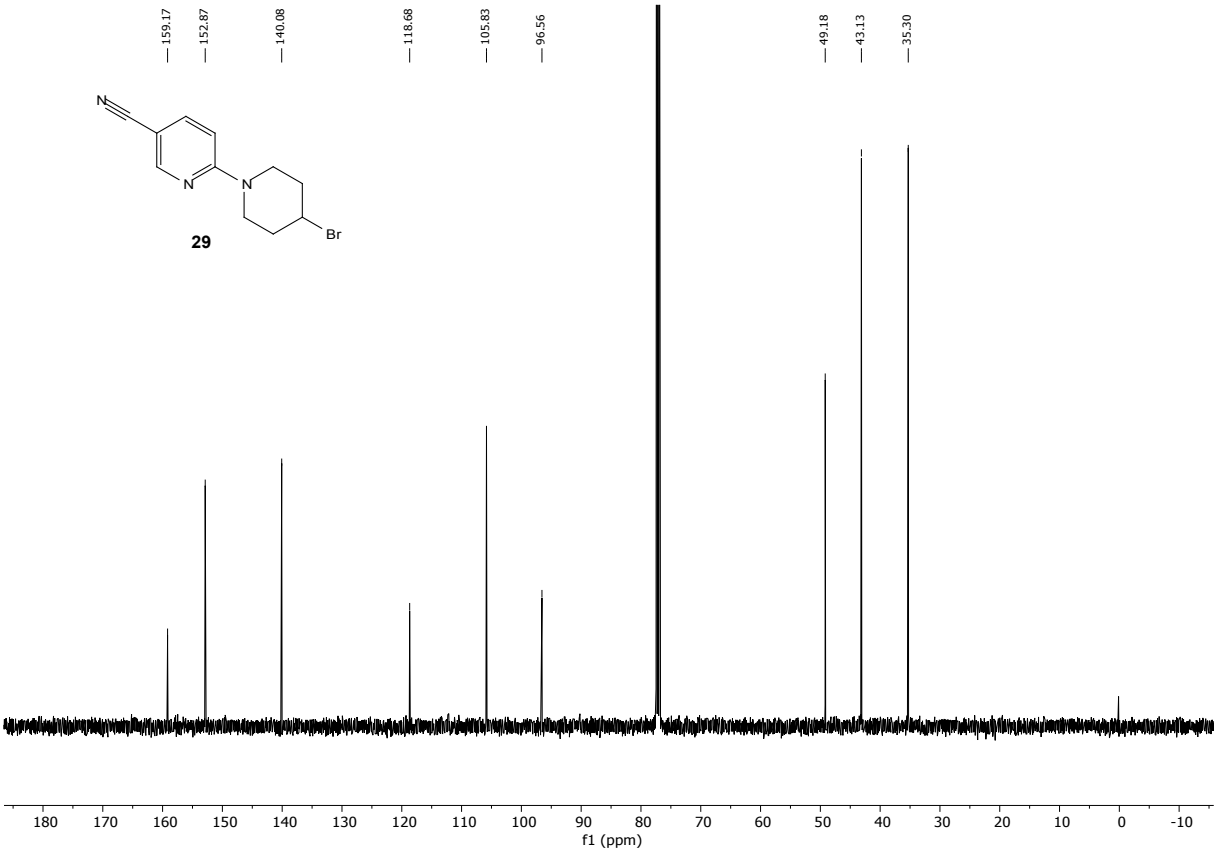
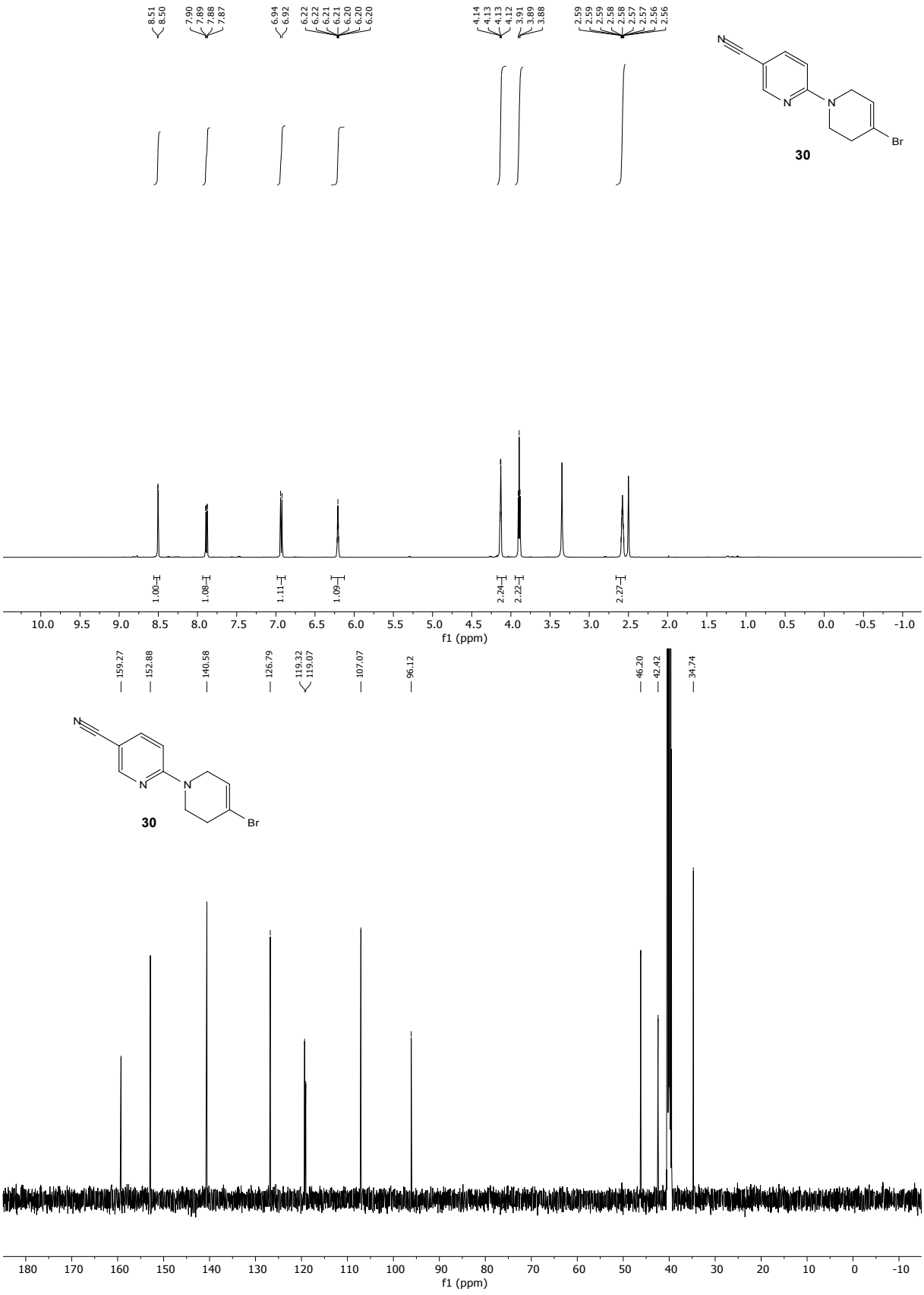
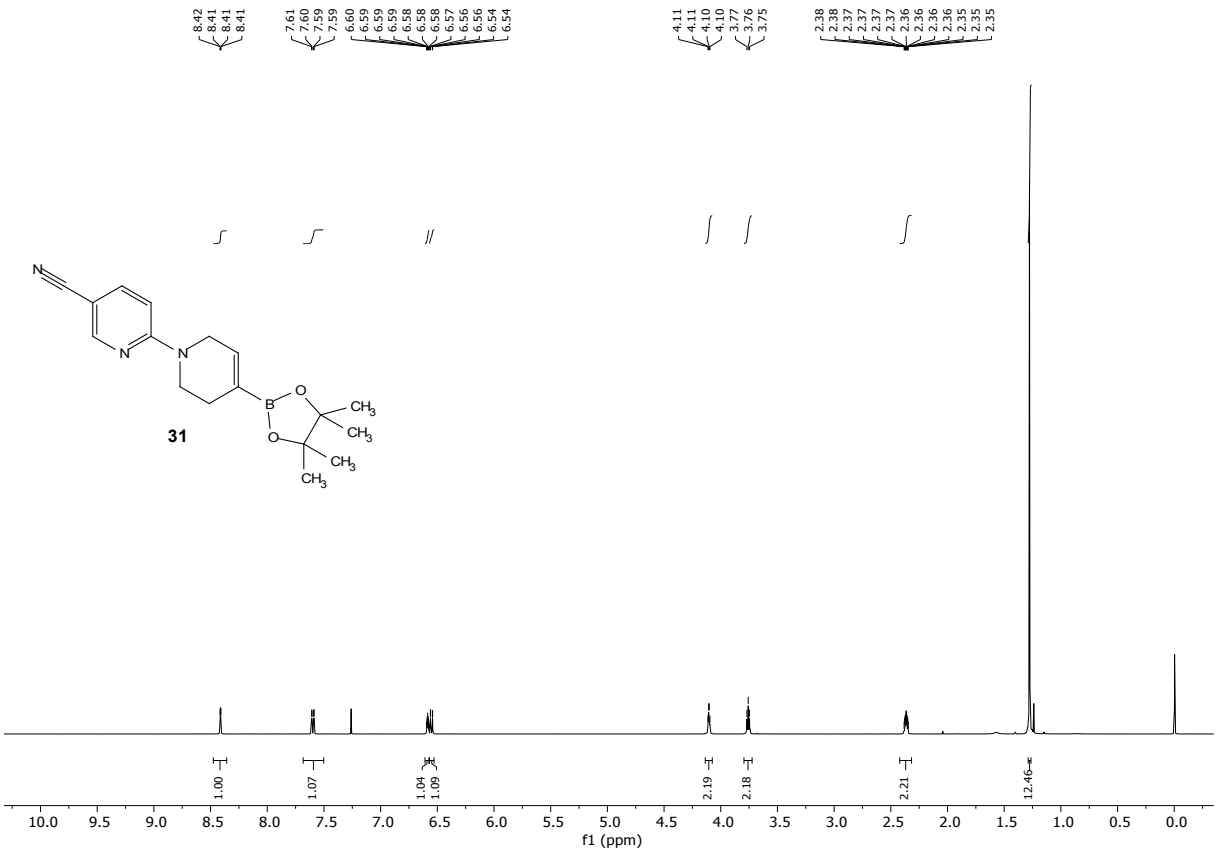
N
N
Si
CH3
CH3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

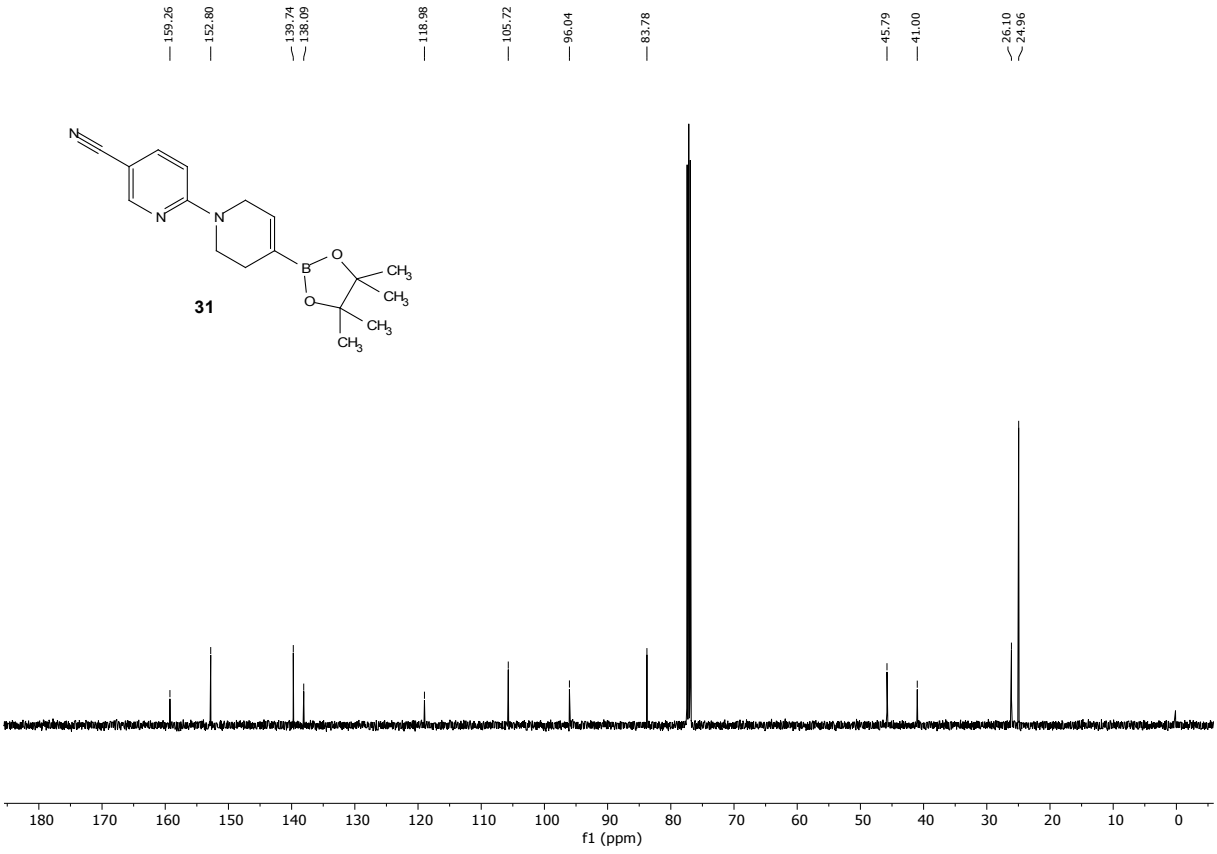
28


8.40 8.40 8.40 8.40
7.62 7.61 7.60 7.60
6.63 6.63 6.62 6.61
4.49 4.48 4.47 4.47 4.46 4.45 4.44 3.96 3.96 3.95 3.94 3.94 3.93 3.92 3.92 3.68 3.67 3.66 3.65 3.65 3.64 3.63 3.63
2.22 2.21 2.20 2.19 2.19 2.18 2.17 2.17 2.16 2.07 2.06 2.06 2.05 2.04 2.03 2.03 2.02 2.01 2.01
N
N
N
Br
29
1.00 1.06 1.12 1.09 2.24 2.23 2.23 2.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


159.17
152.87
140.08
118.68
105.83
96.56
49.18
43.13
35.30
N
N
N
Br
29
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.51
8.50
7.90
7.89
7.88
7.87
6.94
6.92
6.22
6.22
6.21
6.21
6.20
6.20
6.20
4.14
4.13
4.13
4.12
3.91
3.89
3.88
2.59
2.59
2.59
2.58
2.58
2.57
2.57
2.56
2.56
N
N
N
Br
30
1.00
1.08
1.11
1.09
2.24
2.22
2.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
159.27
152.88
140.58
126.79
119.32
119.07
107.07
96.12
46.20
42.42
34.74
N
N
N
Br
30
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.42
8.41
8.41
8.41
7.61
7.60
7.59
7.59
6.60
6.59
6.59
6.59
6.58
6.58
6.57
6.56
6.56
6.54
6.54
4.11
4.11
4.10
4.10
3.77
3.76
3.75
2.38
2.38
2.37
2.37
2.37
2.36
2.36
2.36
2.35
2.35
2.35
N
N
N
B
O
O
CH3
CH3
CH3
CH3
31
1.00
1.07
1.04
1.09
2.19
2.18
2.21
12.46
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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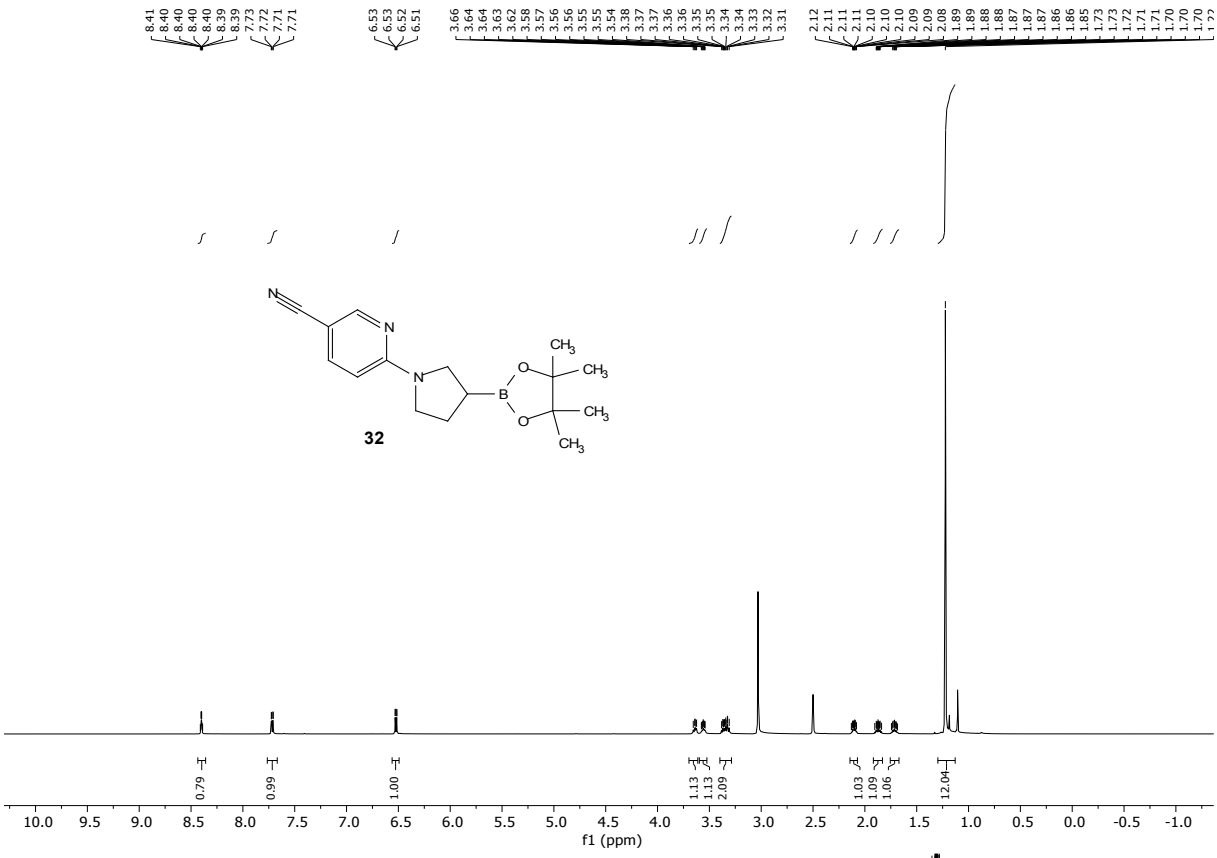
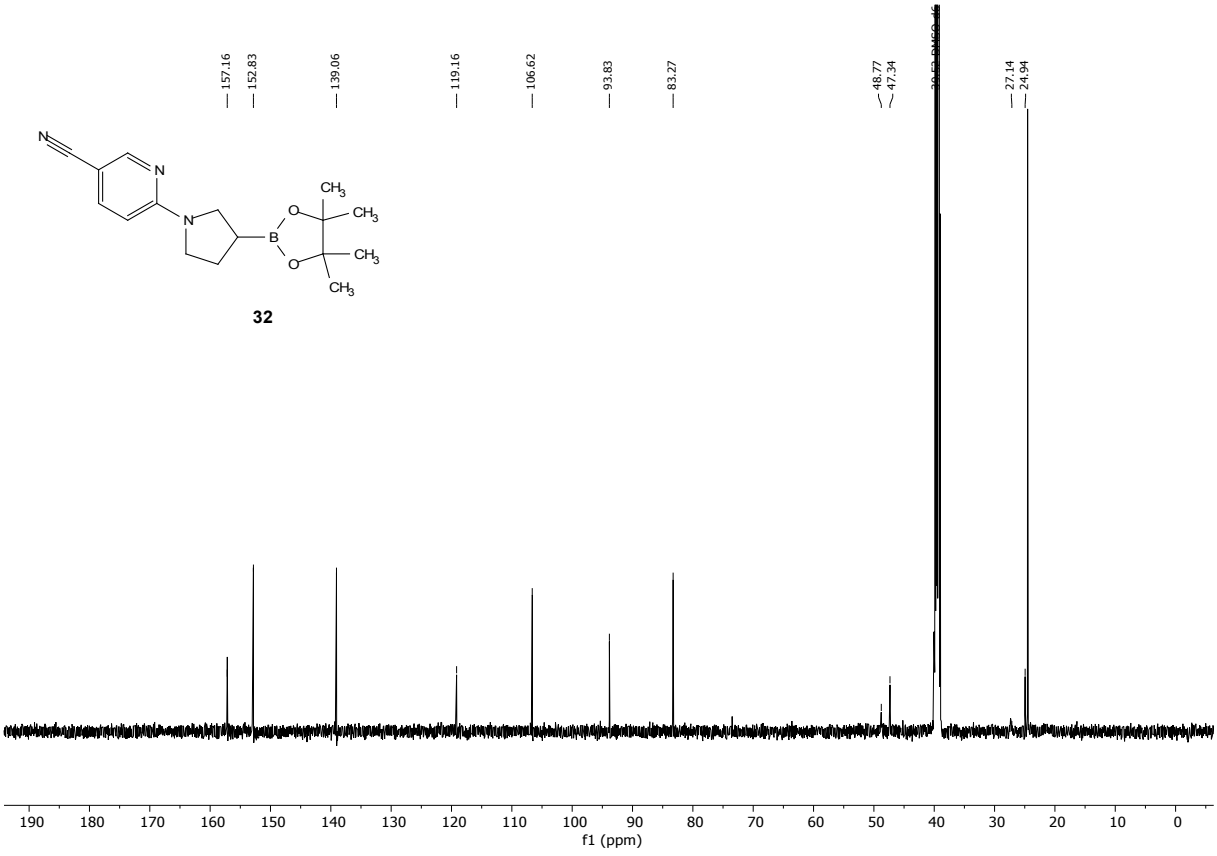
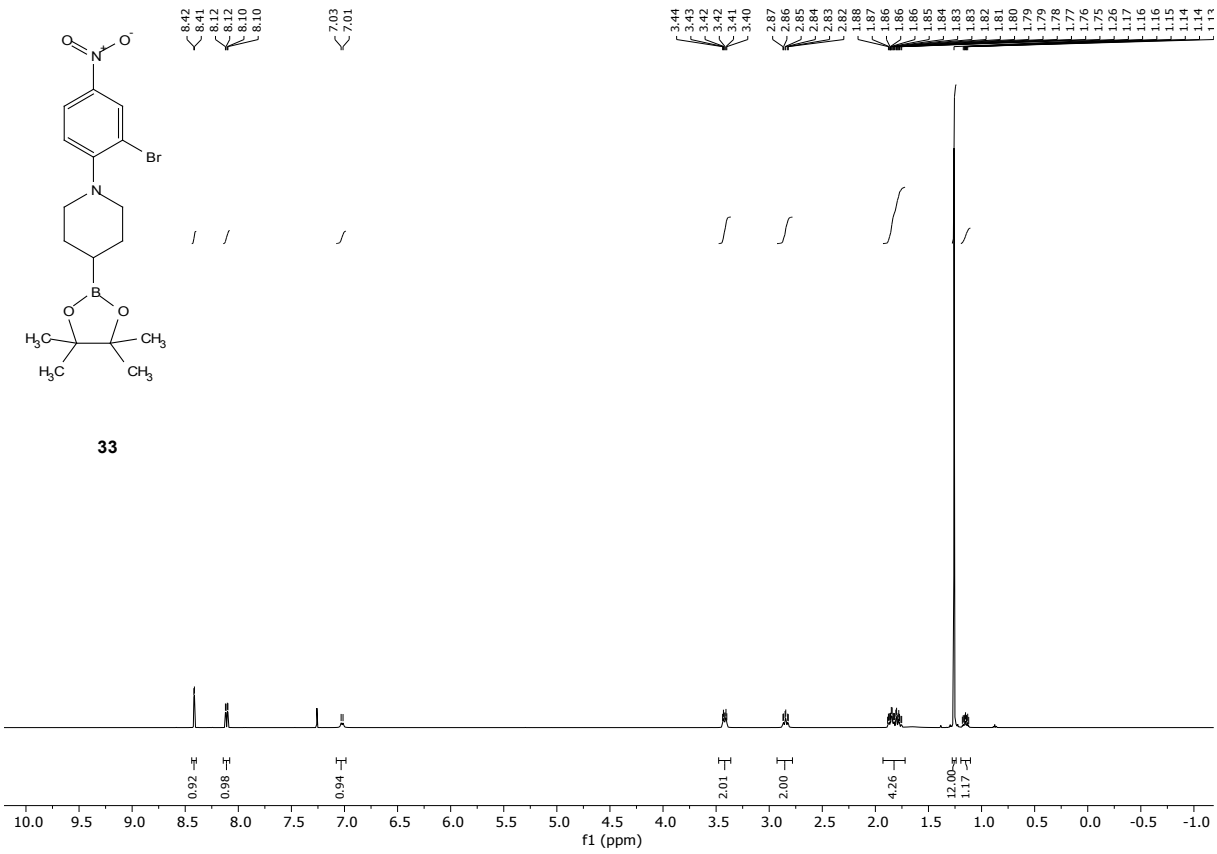
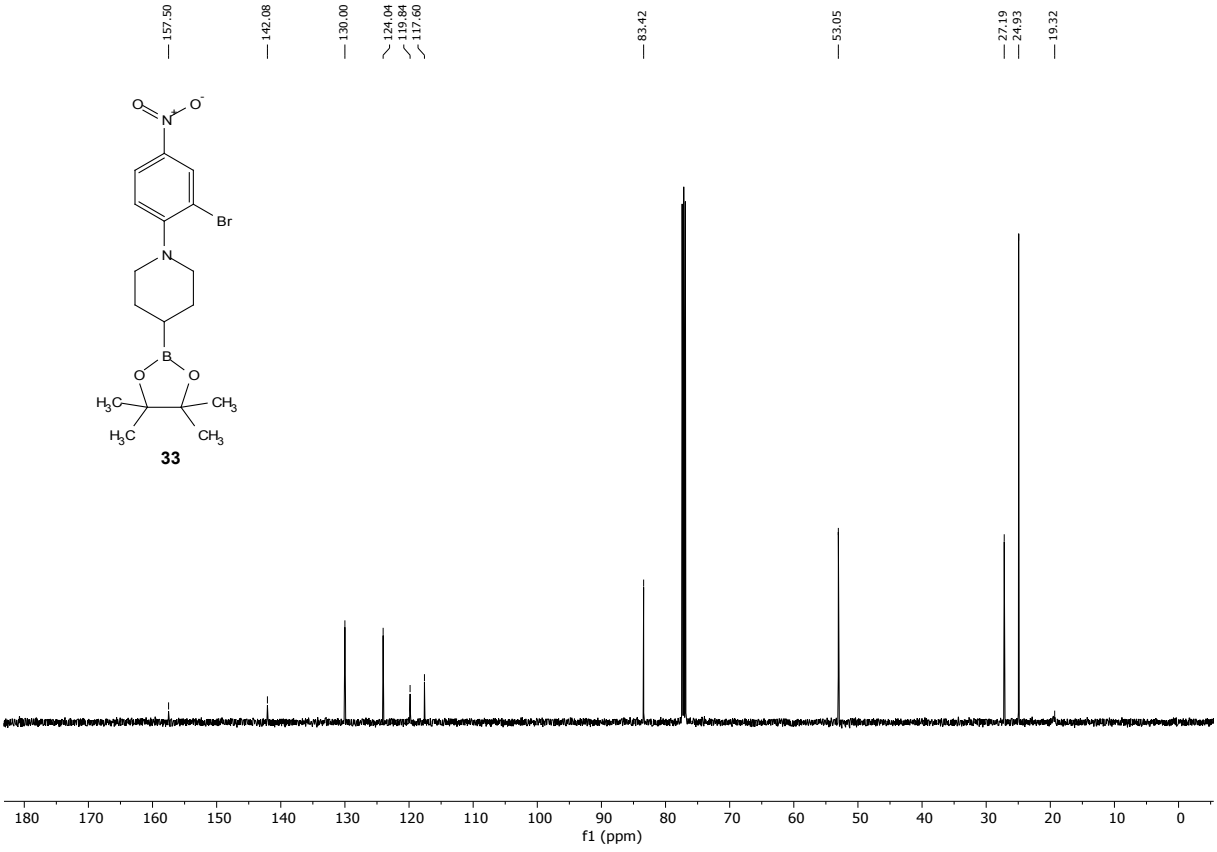
152.80
139.74
138.09
118.98
105.72
96.04
83.78
45.79
41.00
26.10
24.96
N
N
N
B
O
O
CH3
CH3
CH3
CH3
31
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.41
8.40
8.40
8.40
8.40
8.39
8.39
7.73
7.72
7.71
7.71
6.53
6.53
6.52
6.51
3.66
3.64
3.64
3.63
3.62
3.58
3.57
3.56
3.56
3.55
3.55
3.54
3.38
3.37
3.37
3.36
3.36
3.35
3.35
3.34
3.34
3.33
3.32
3.31
2.12
2.11
2.11
2.11
2.10
2.10
2.10
2.09
2.09
2.08
1.89
1.89
1.88
1.88
1.87
1.87
1.87
1.86
1.86
1.85
1.73
1.73
1.72
1.71
1.71
1.70
1.70
1.70
32
0.79
0.99
1.00
1.13
1.13
2.09
1.03
1.09
1.06
12.04
f1 (ppm)

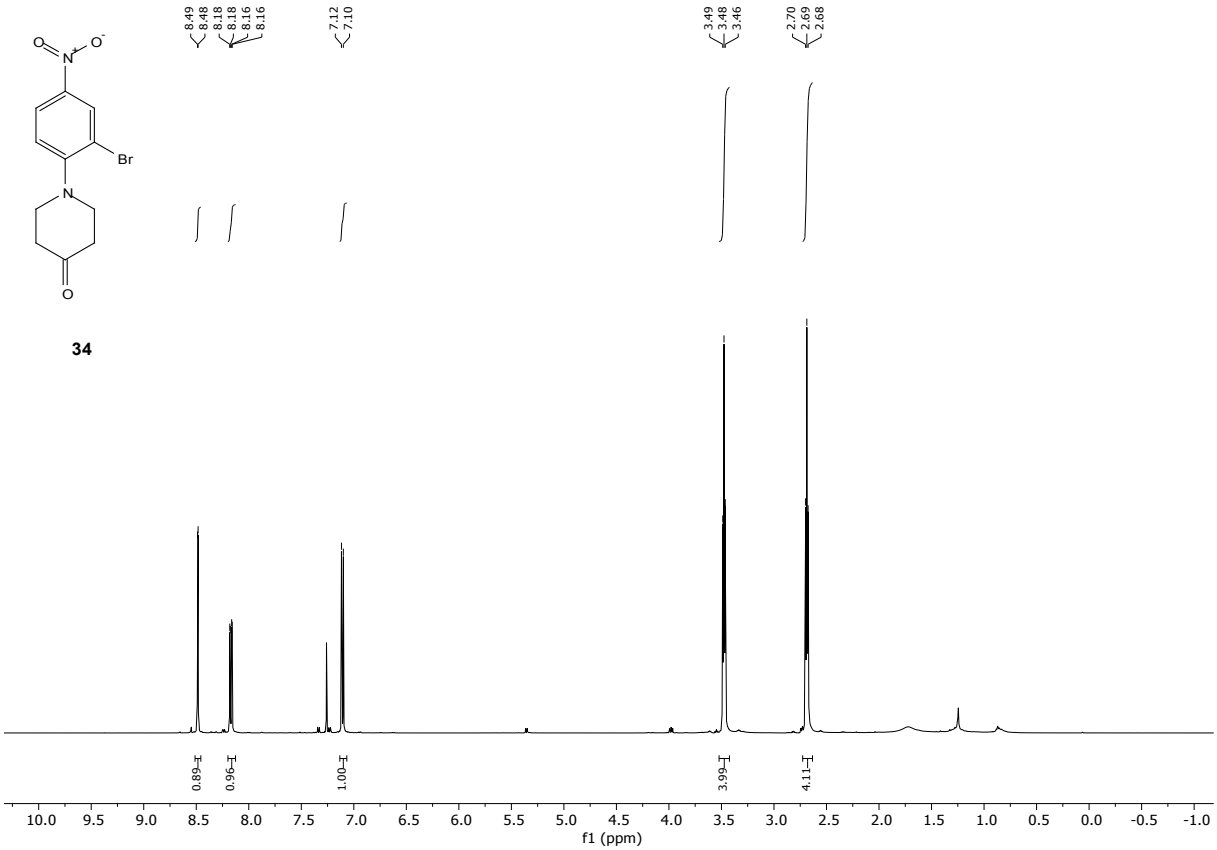

157.16
152.83
139.06
119.16
106.62
93.83
83.27
48.77
47.34
27.14
24.94
32
f1 (ppm)


8.42
8.41
8.12
8.12
8.10
8.10
7.03
7.01
3.44
3.43
3.42
3.42
3.41
3.40
2.87
2.86
2.85
2.84
2.83
2.82
1.88
1.87
1.86
1.86
1.86
1.85
1.84
1.83
1.83
1.82
1.81
1.80
1.79
1.79
1.78
1.77
1.76
1.75
1.26
1.17
1.16
1.16
1.15
1.14
1.14
Br
N
B
O
O
H_3C
CH_3
H_3C
CH_3
0.92
0.98
0.94
2.01
2.00
4.26
12.00
1.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

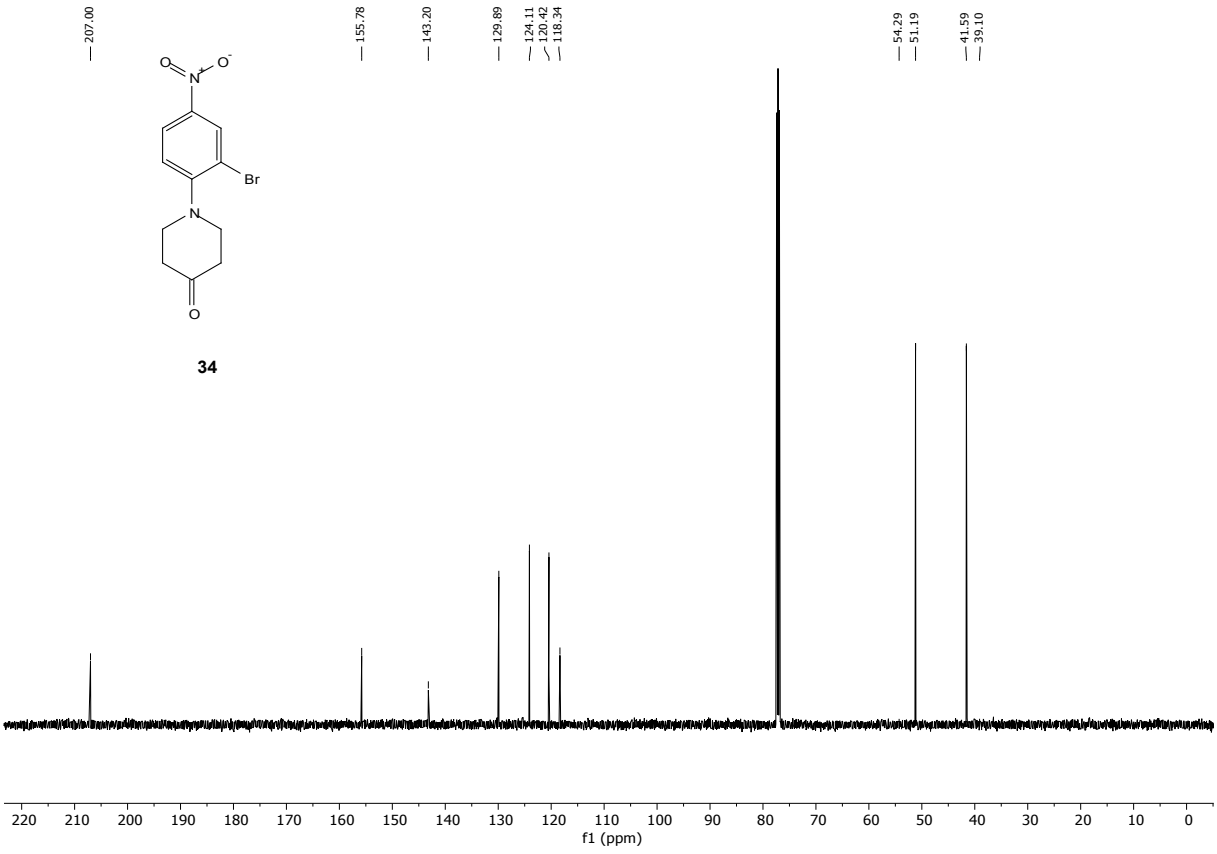
33


157.50
142.08
130.00
124.04
119.84
117.60
83.42
53.05
27.19
24.93
19.32
Br
N
B
O
O
H_3C
CH_3
H_3C
CH_3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

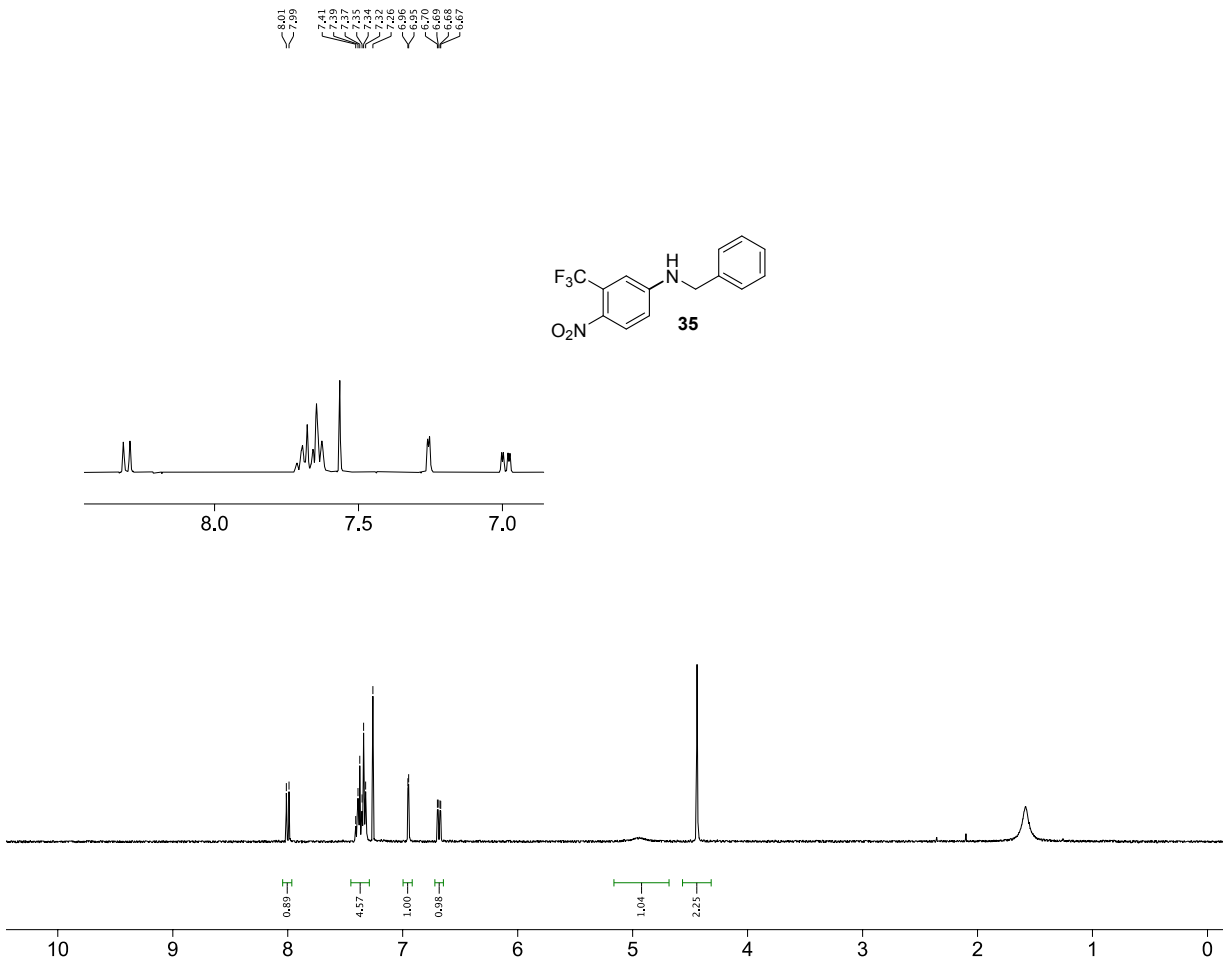
33

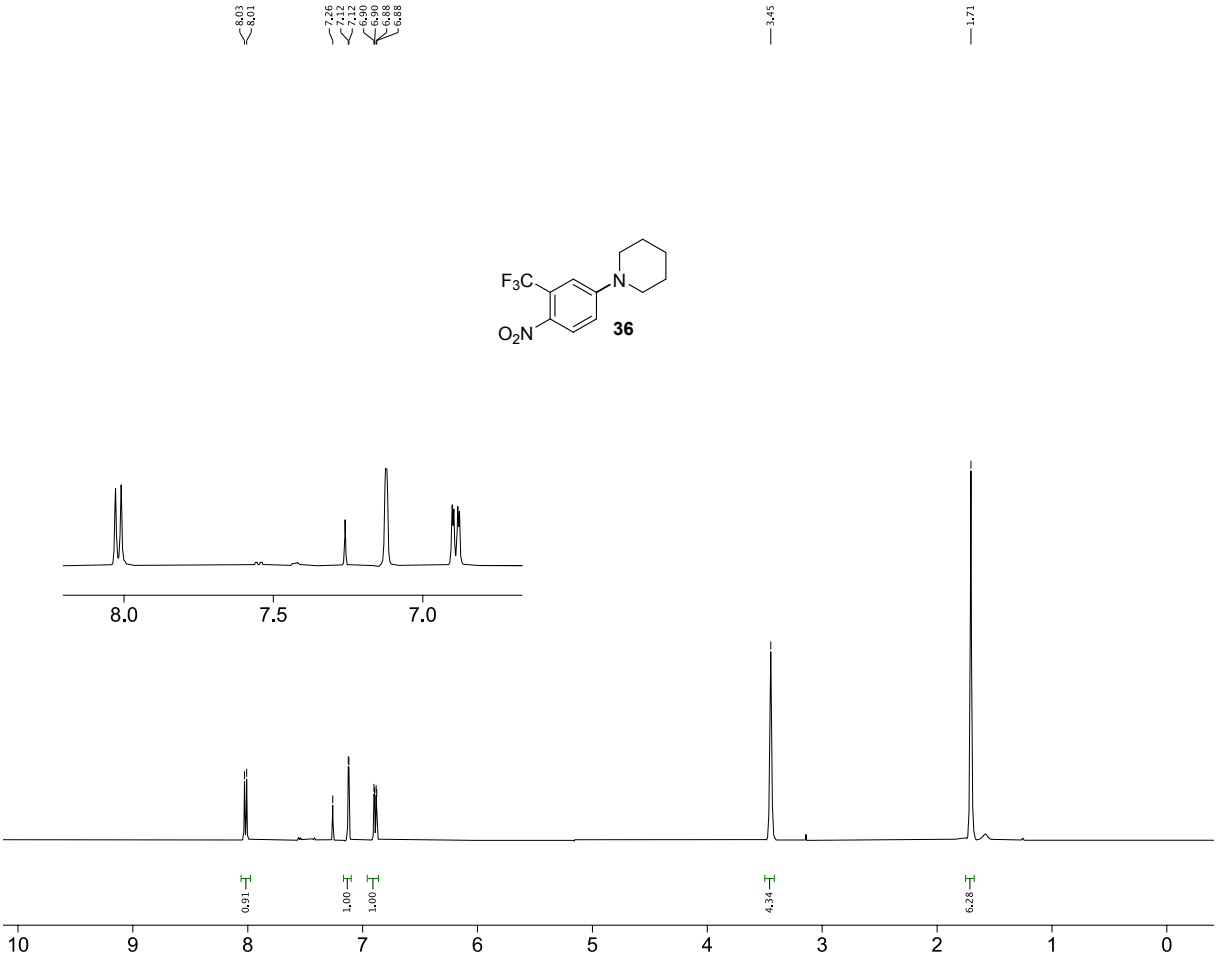

8.49
8.48
8.18
8.18
8.16
8.16
7.12
7.10
3.49
3.48
3.46
2.70
2.69
2.68
Br
N
O
0.89
0.96
1.00
3.99
4.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

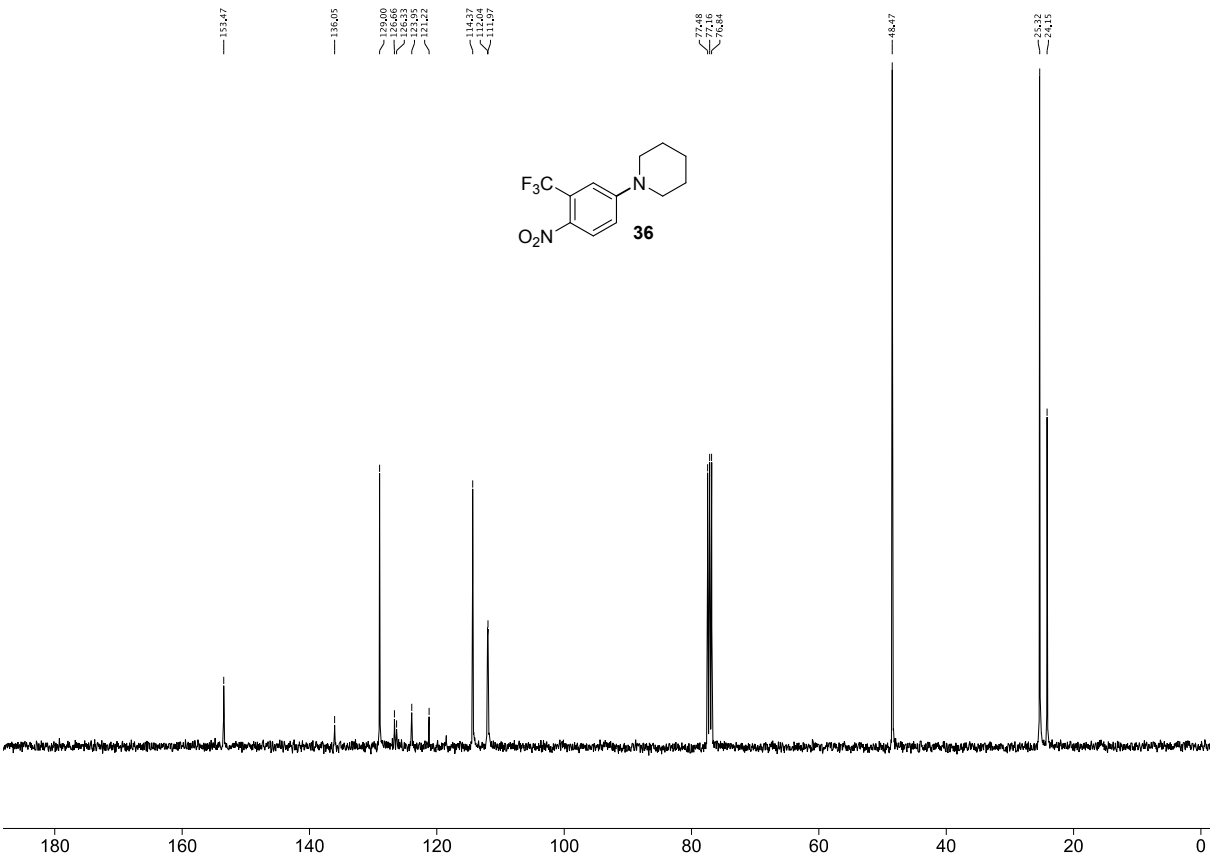
34

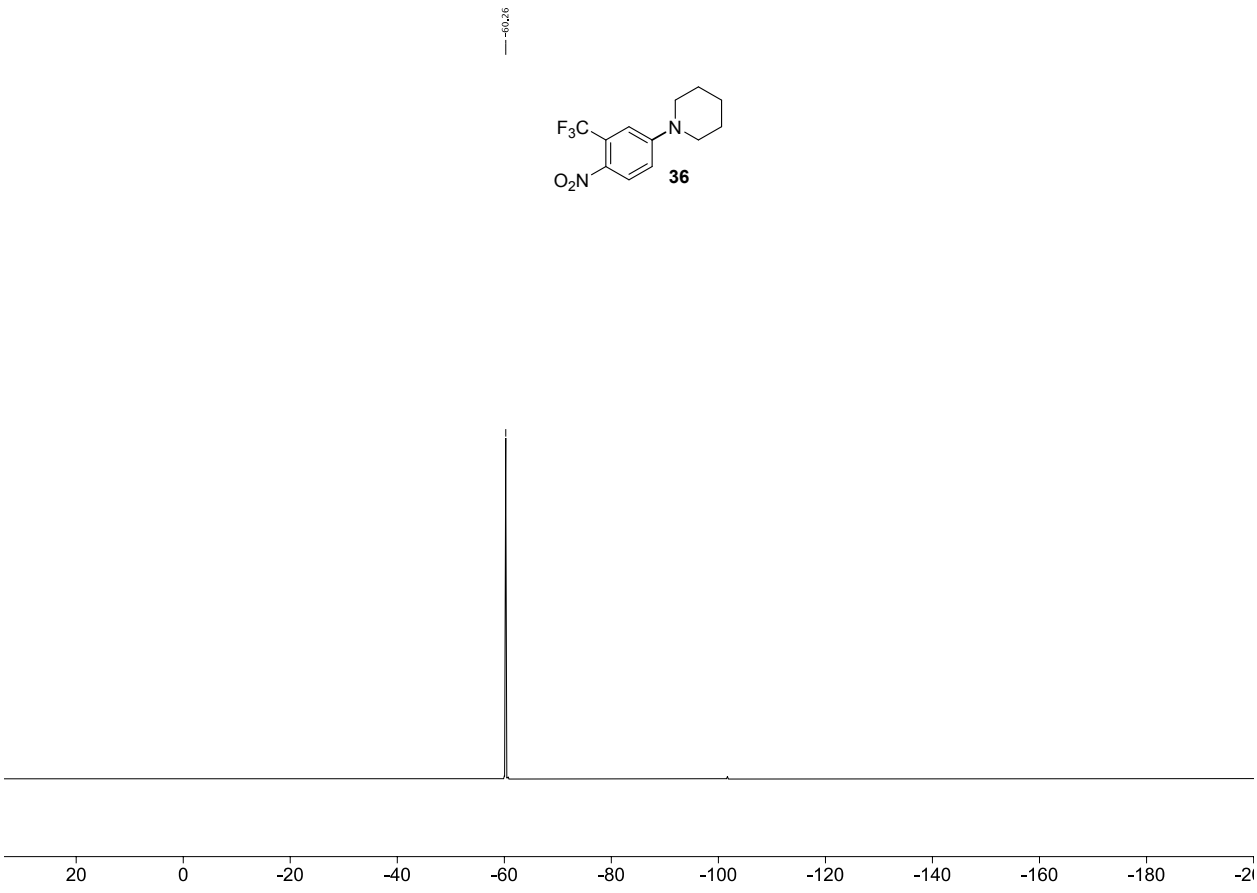

207.00
155.78
143.20
129.89
124.11
120.42
118.34
54.29
51.19
41.59
39.10
Br
N
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

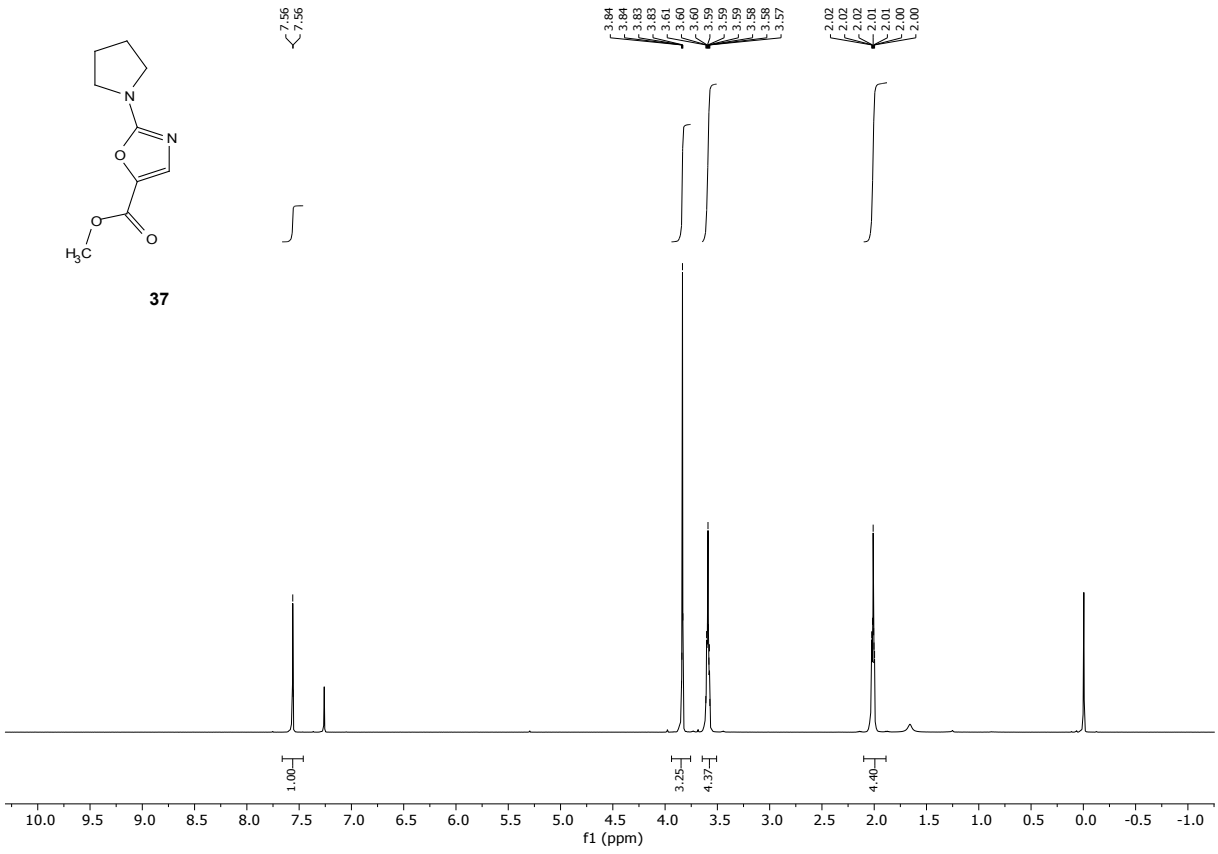
34

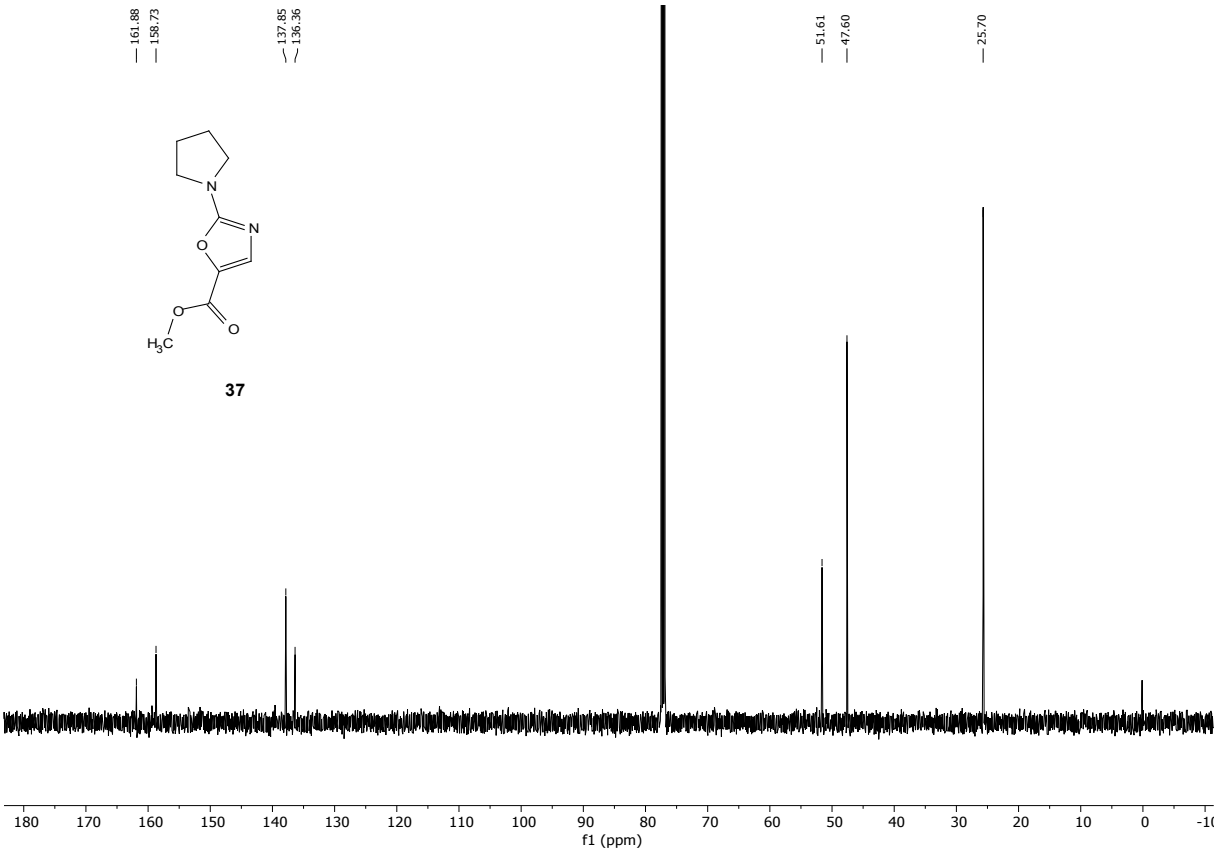

8.01
7.99
7.41
7.39
7.37
7.35
7.34
7.32
7.26
6.96
6.95
6.70
6.69
6.68
6.67
F3C
H
N
O2N
35
8.0
7.5
7.0
0.89
4.57
1.00
0.98
1.04
2.25
10
9
8
7
6
5
4
3
2
1
0


8.03
8.01
7.26
7.12
7.12
6.90
6.90
6.88
6.88
3.45
1.71
F3C
N
O2N
36
8.0
7.5
7.0
0.91
1.00
1.00
4.34
6.28
10
9
8
7
6
5
4
3
2
1
0

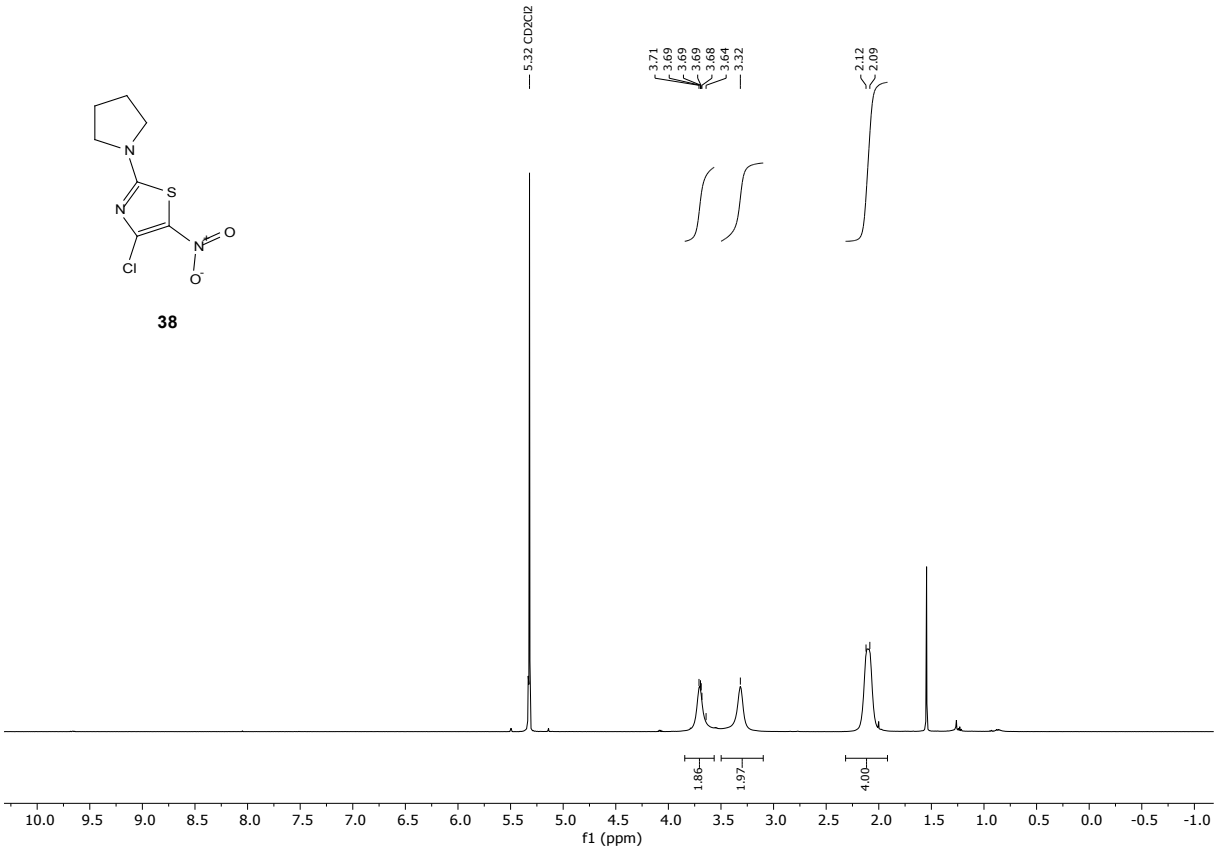

153.47
136.05
129.00
126.66
126.63
123.33
121.22
114.37
112.04
111.97
77.48
77.16
76.84
48.47
25.32
24.15
F3C
N
O2N
36
180
160
140
120
100
80
60
40
20
0


-60.26
F3C
N
O2N
36
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180

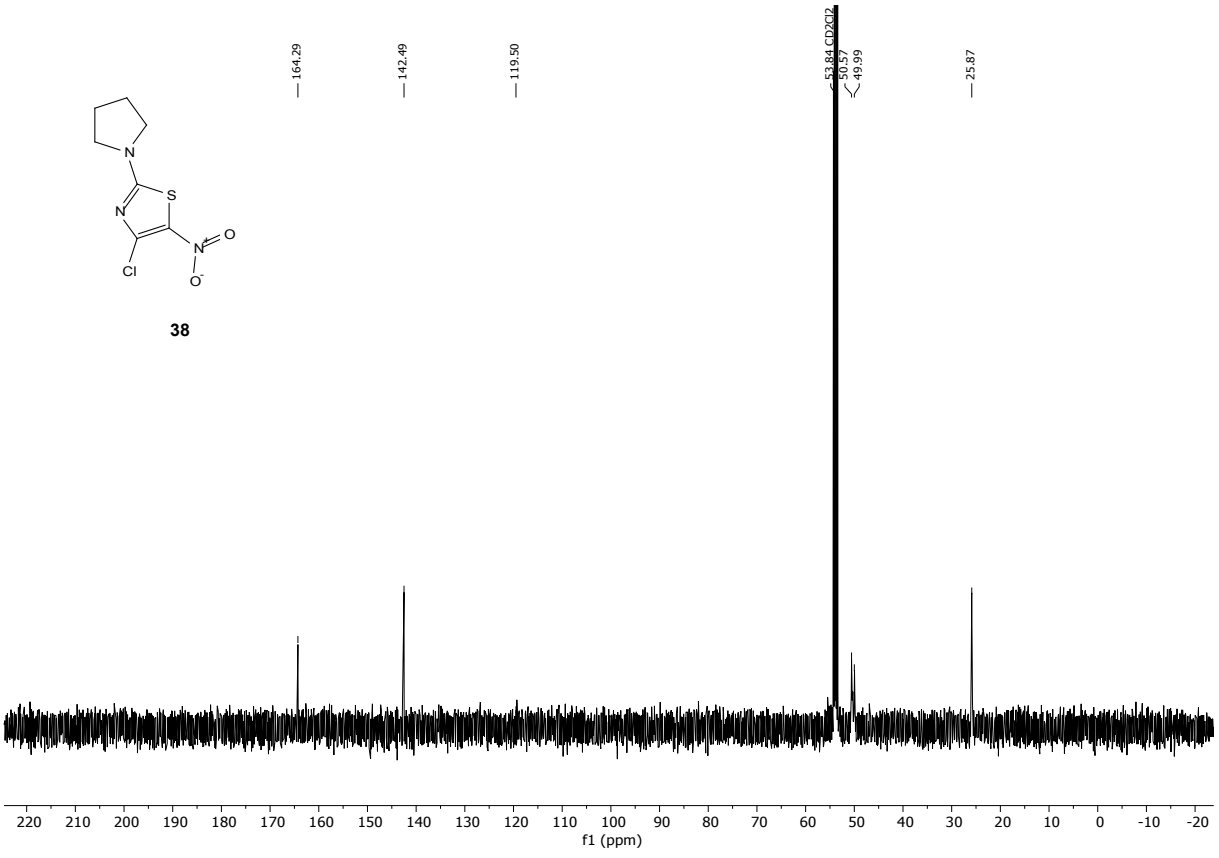

7.56
7.56
3.84
3.84
3.83
3.83
3.61
3.60
3.60
3.59
3.59
3.59
3.58
3.58
3.57
2.02
2.02
2.02
2.01
2.01
2.00
2.00
N
N
O
O
O
H3C
37
1.00
3.25
4.37
4.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

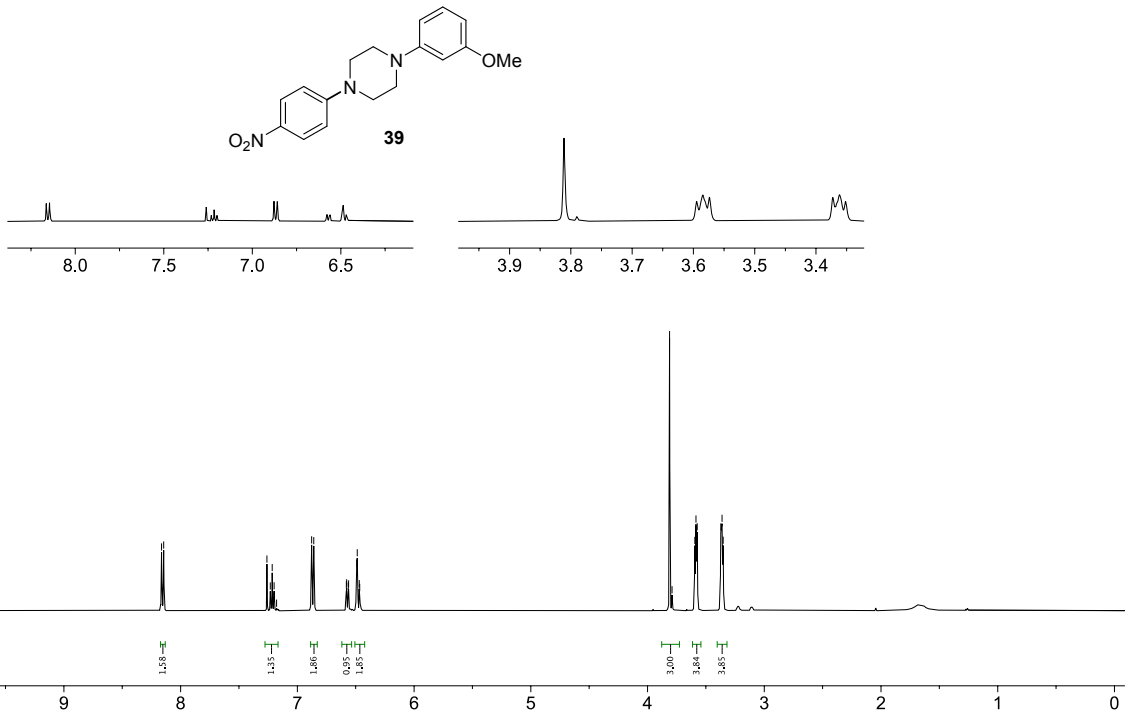

161.88
158.73
137.85
136.36
51.61
47.60
25.70
f1 (ppm)

37

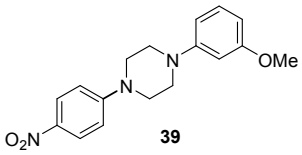

5.32 CD2Cl2
3.71
3.69
3.69
3.69
3.68
3.64
3.32
2.12
2.09
1.86
1.97
4.00
f1 (ppm)

38

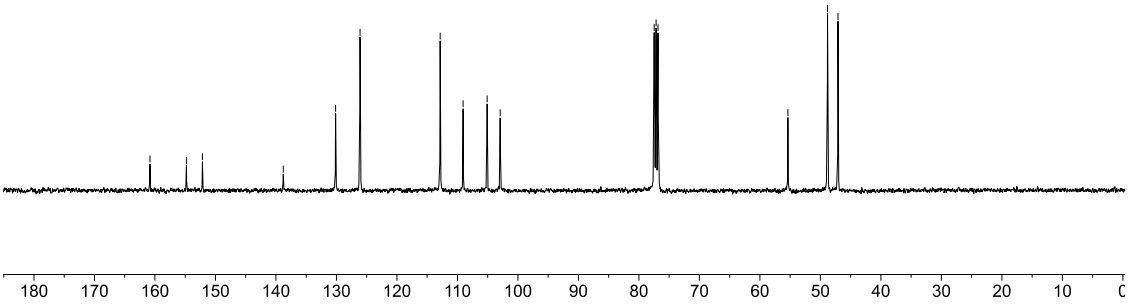

164.29
142.49
119.50
53.84 CDCl3
50.57
49.99
25.87
38
f1 (ppm)


OMe
39

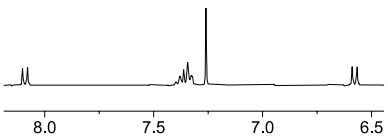

160.83
154.79
152.15
138.79
130.14
126.10
112.85
109.06
105.09
102.93
77.48
77.16
76.84
55.37
48.82
47.09

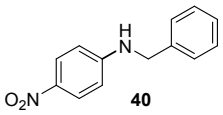

N
N
OMe
O2N

39

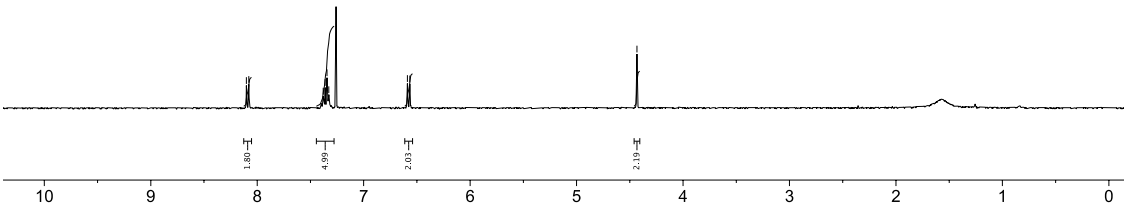

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

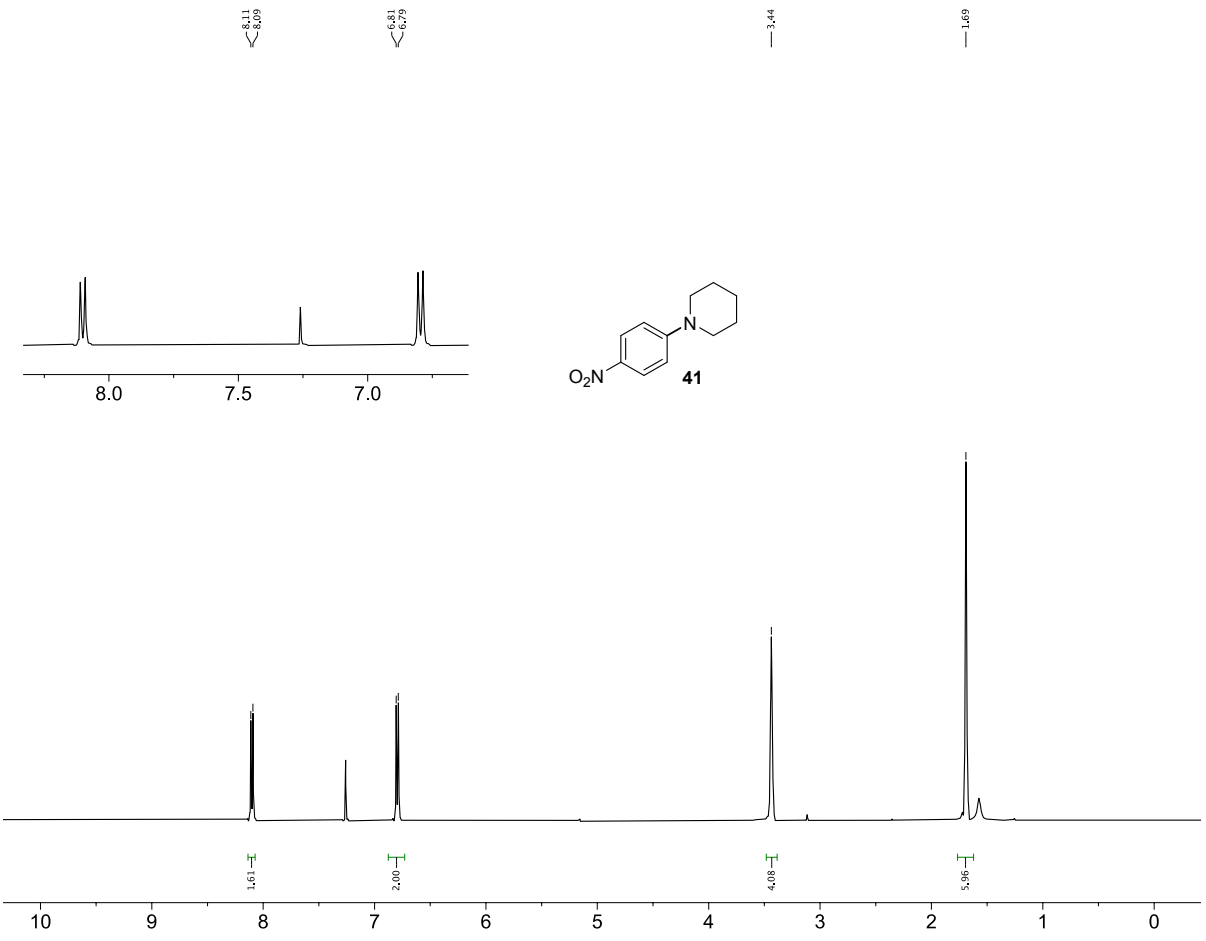

8.10
8.08
7.38
7.36
7.34
7.33
6.59
6.57
4.43


8.0
7.5
7.0
6.5


H
N
O2N

40


1.80
4.99
2.03
2.19
10
9
8
7
6
5
4
3
2
1
0


8.11
8.09
6.81
6.79
3.44
1.69
8.0
7.5
7.0
O2N
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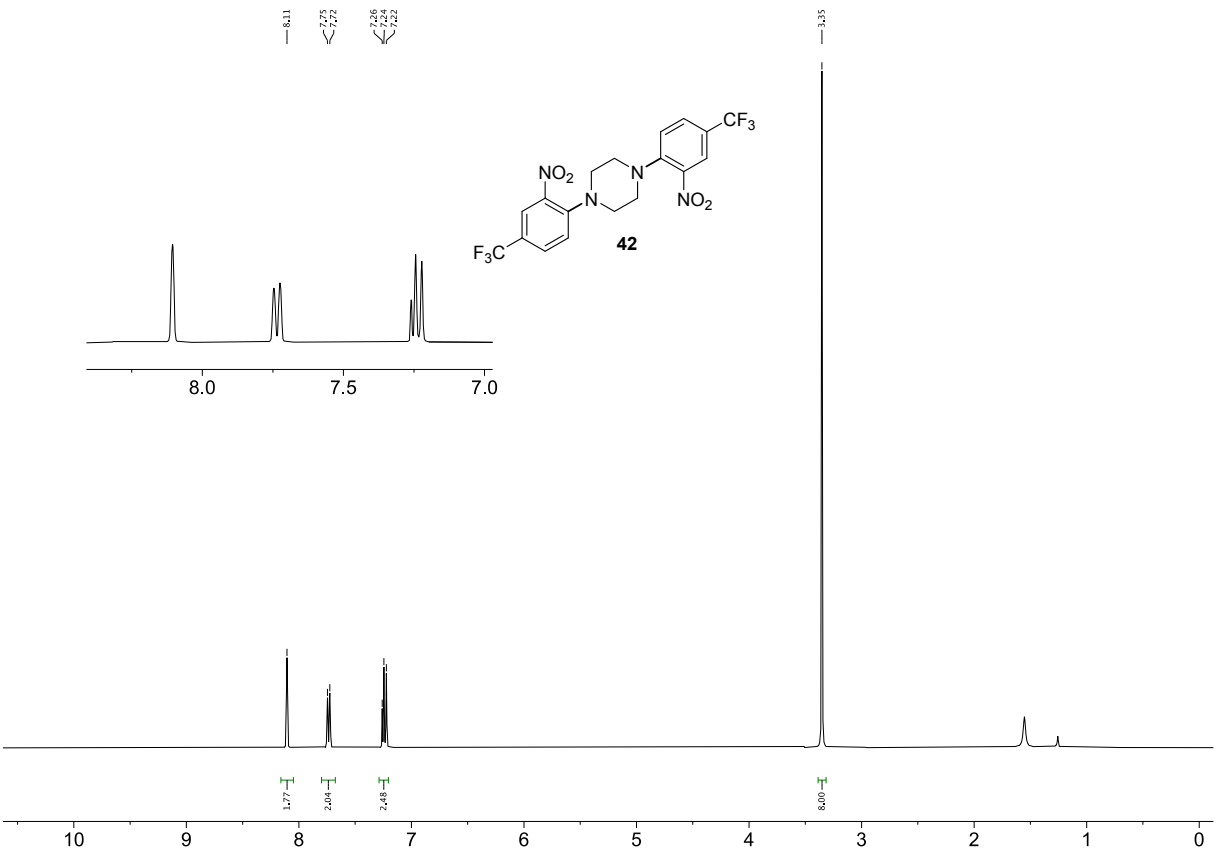
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7.72
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7.24
7.22
3.35
CF3
NO2
N
N
NO2
F3C
42
8.0
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2.04
2.48
8.00
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7
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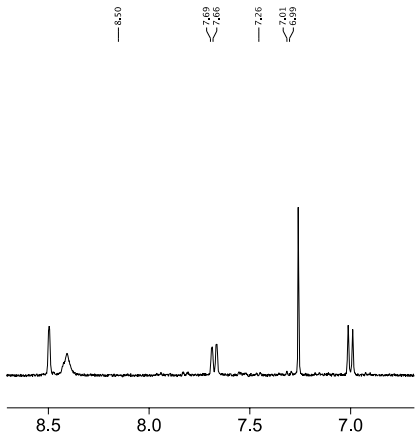
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3.77
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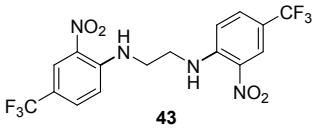
7.5
7.0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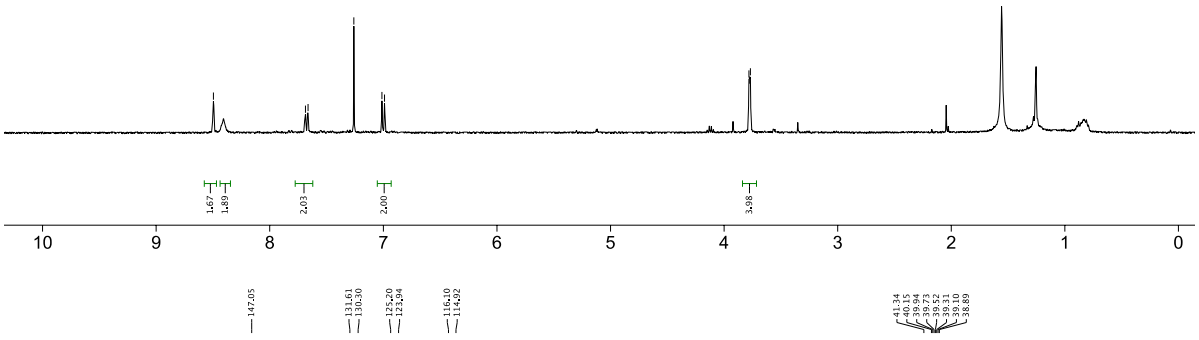
N
H
CF3
NO2
F3C

43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1.89
2.03
2.00
3.98
10
9
8
7
6
5
4
3
2
1
0

147.05
131.61
130.30
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114.92
41.34
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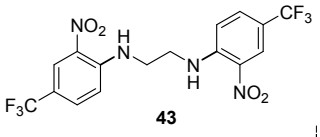
39.94
39.73
39.52
39.31
39.10
38.89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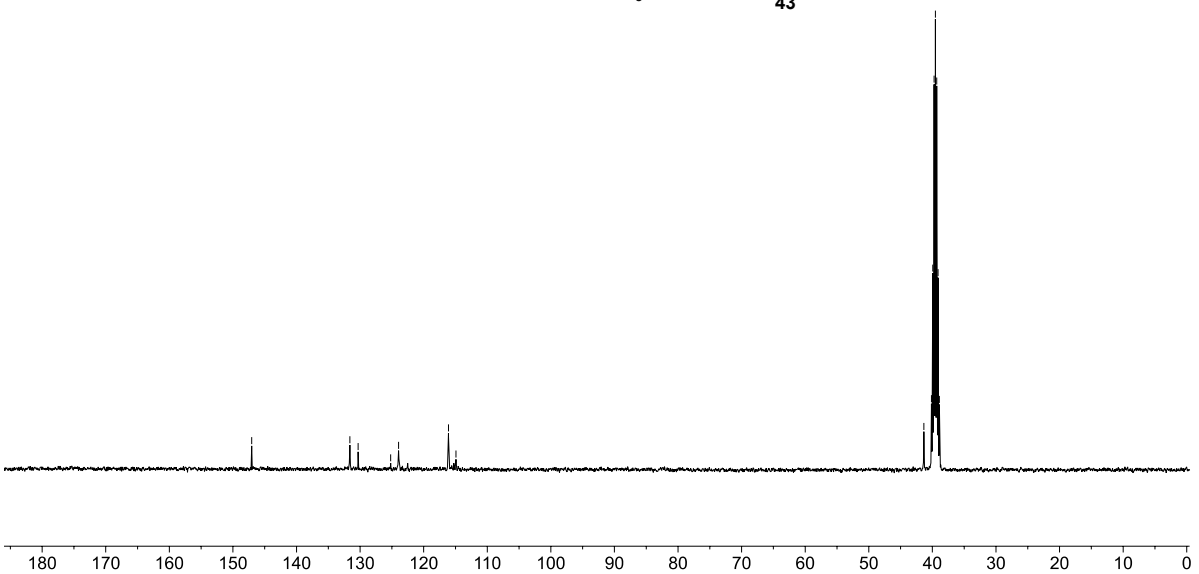
N
N
H
CF3
NO2
F3C

43


180
170
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150
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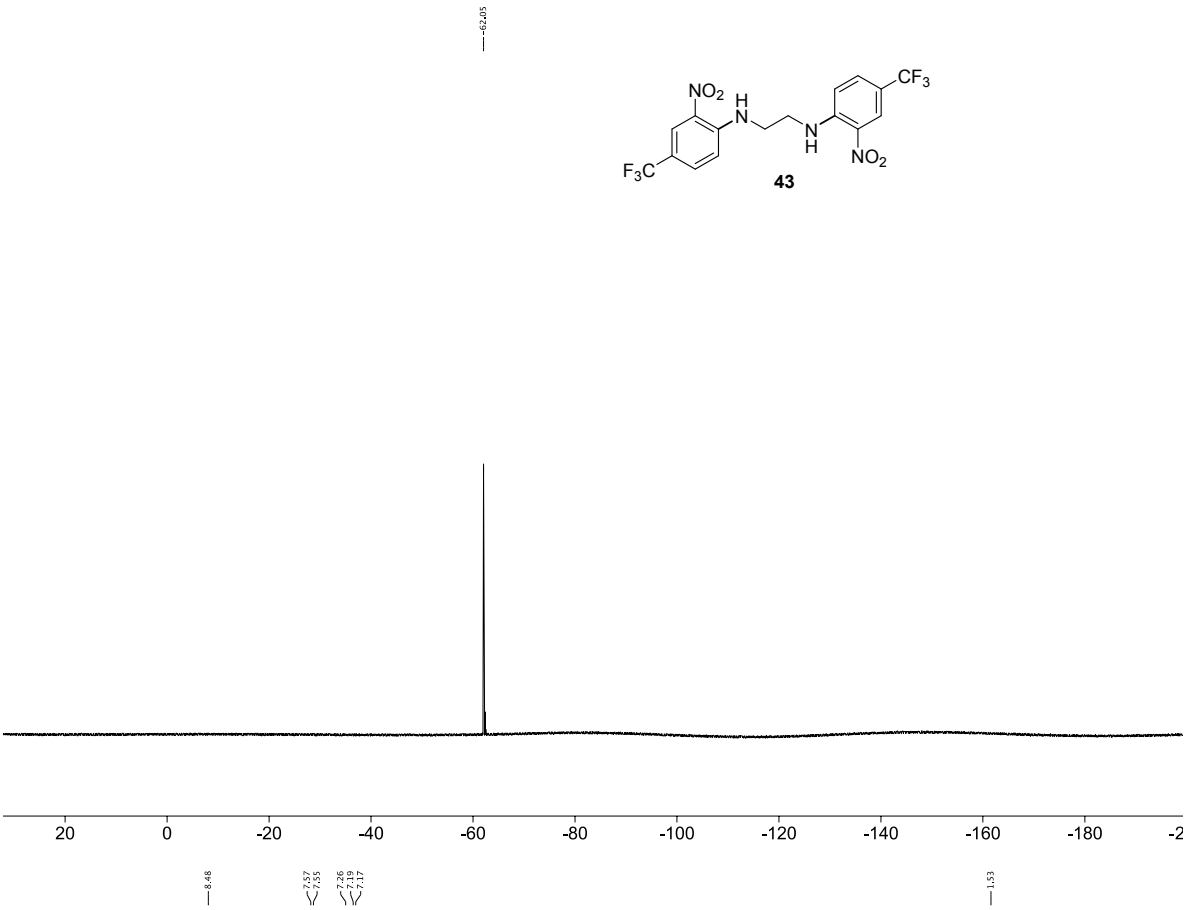
100
90
80
70
60
50
40
30
20
10
0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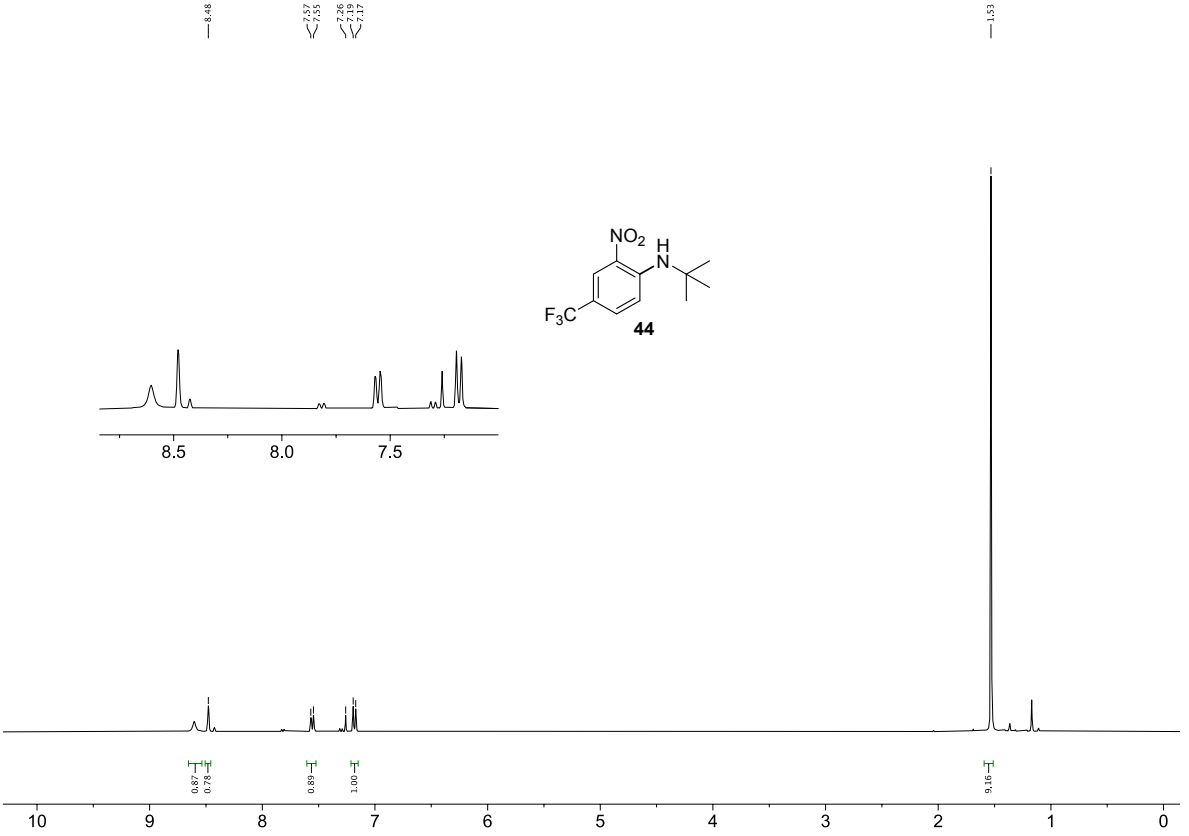
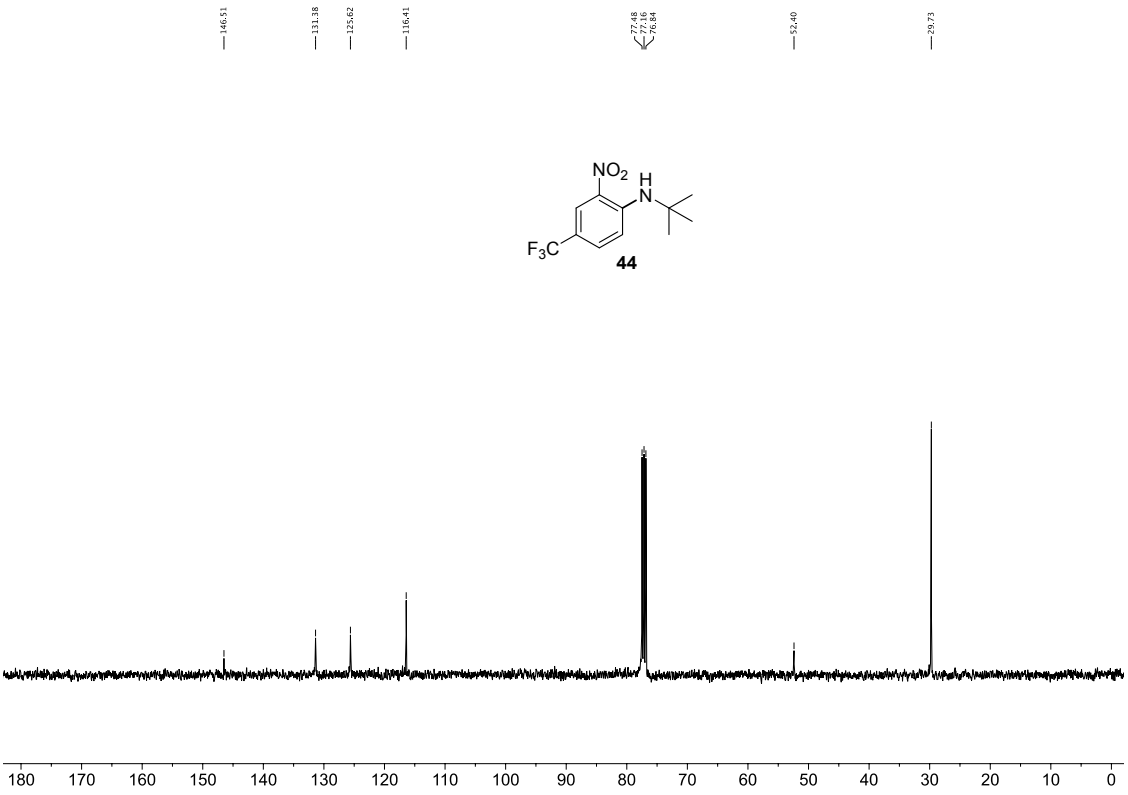
-20
-40
-60
-80
-100
-120
-140
-160
-180
-2

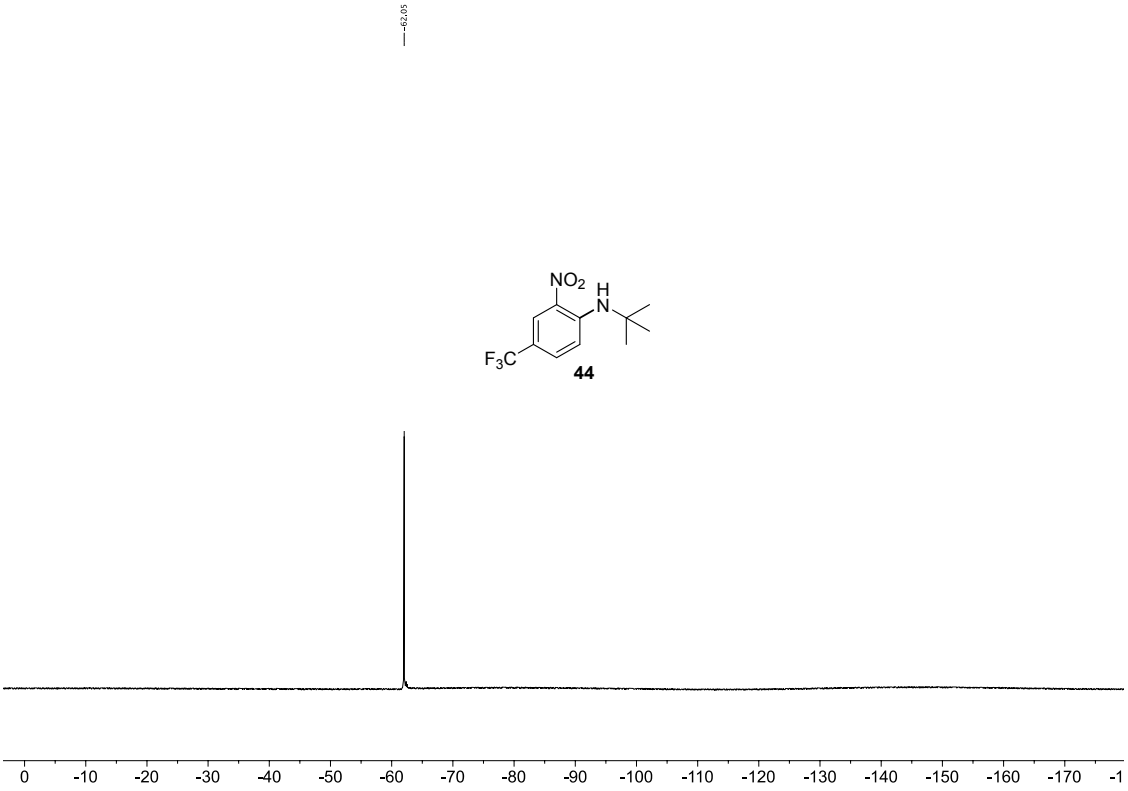
43


8.48
7.57
7.55
7.26
7.19
7.17
1.53
0.87
0.78
0.89
1.00
9.16
10
9
8
7
6
5
4
3
2
1
0

44

8.5
8.0
7.5


146.51
131.38
125.62
116.41
77.48
77.16
76.84
52.40
29.73
NO2
H
N
F3C
44
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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NO2
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N
F3C
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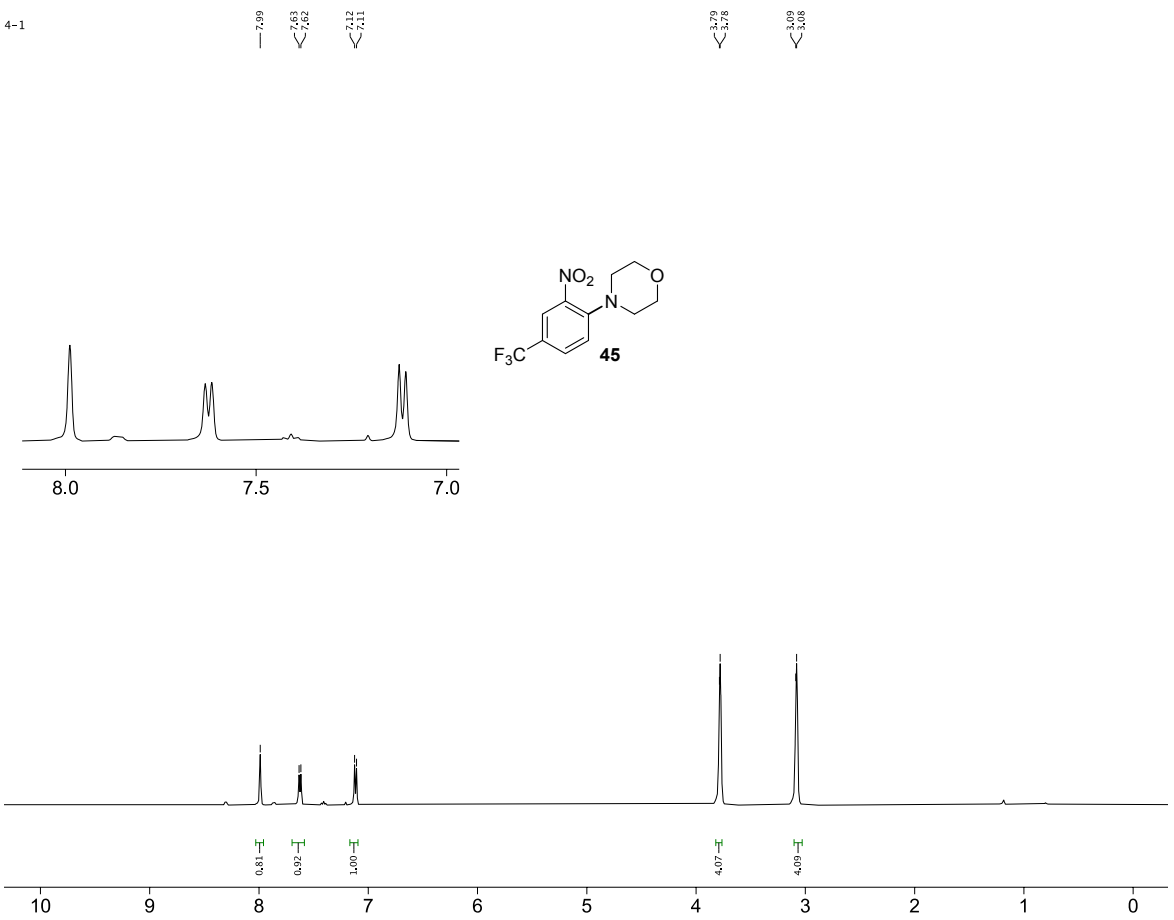
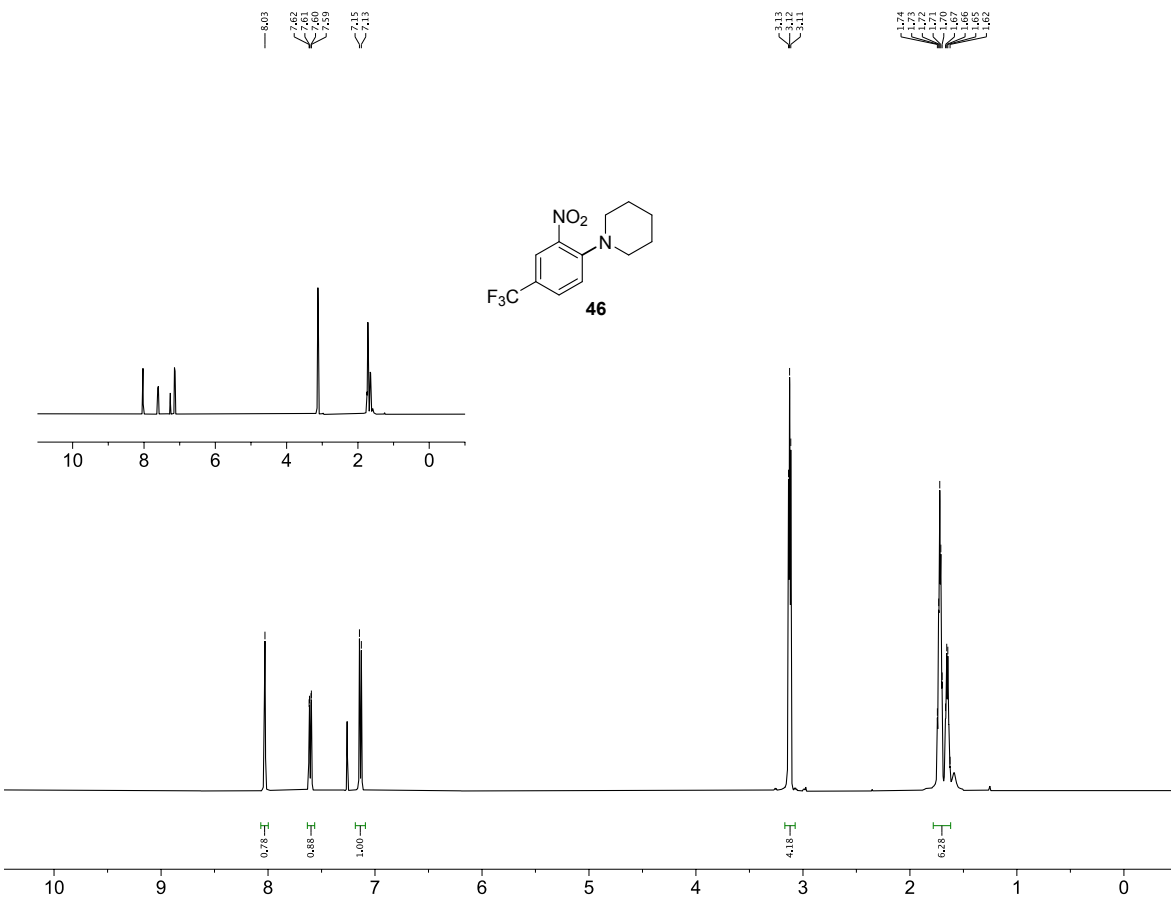
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -1


4-1
7.99
7.63
7.62
7.12
7.11
3.79
3.78
3.09
3.08
NO2
O
N
F3C
45
8.0
7.5
7.0
0.81
0.92
1.00
4.07
4.09
10
9
8
7
6
5
4
3
2
1
0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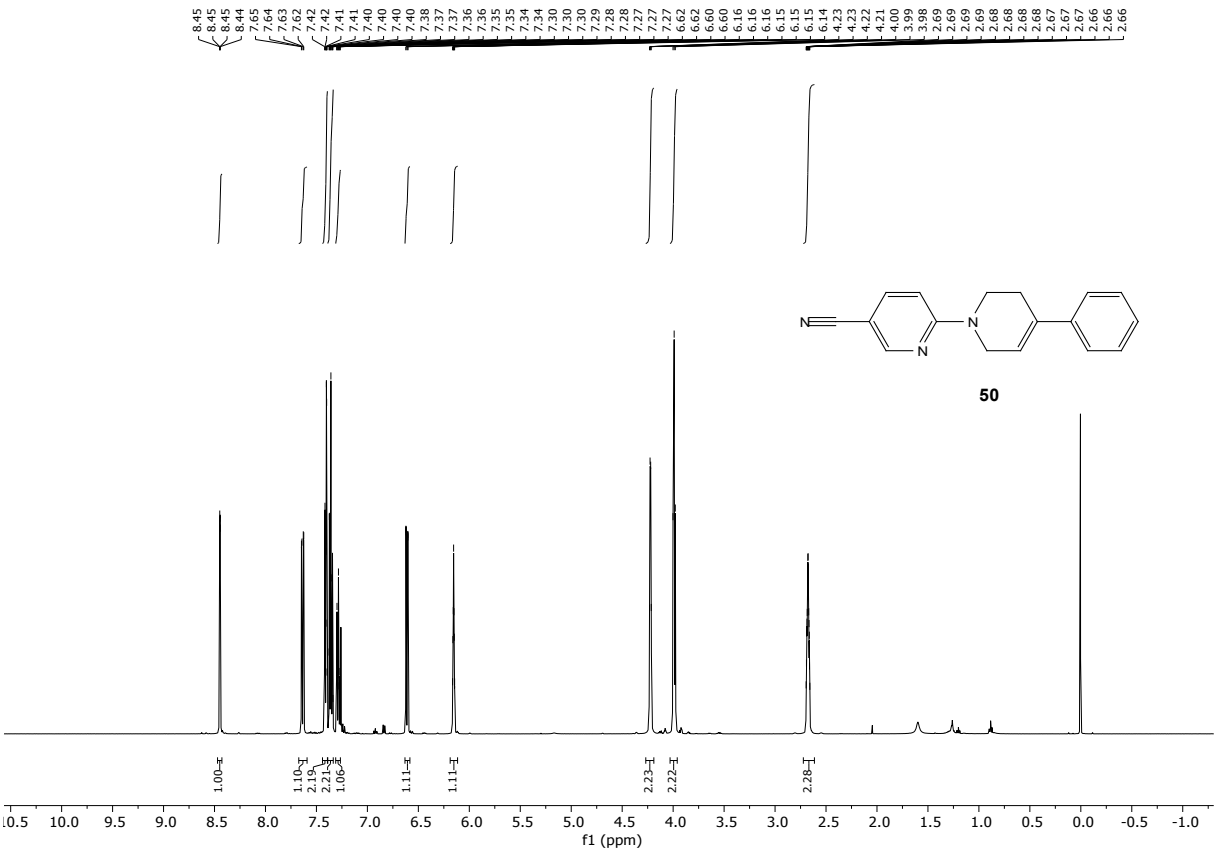
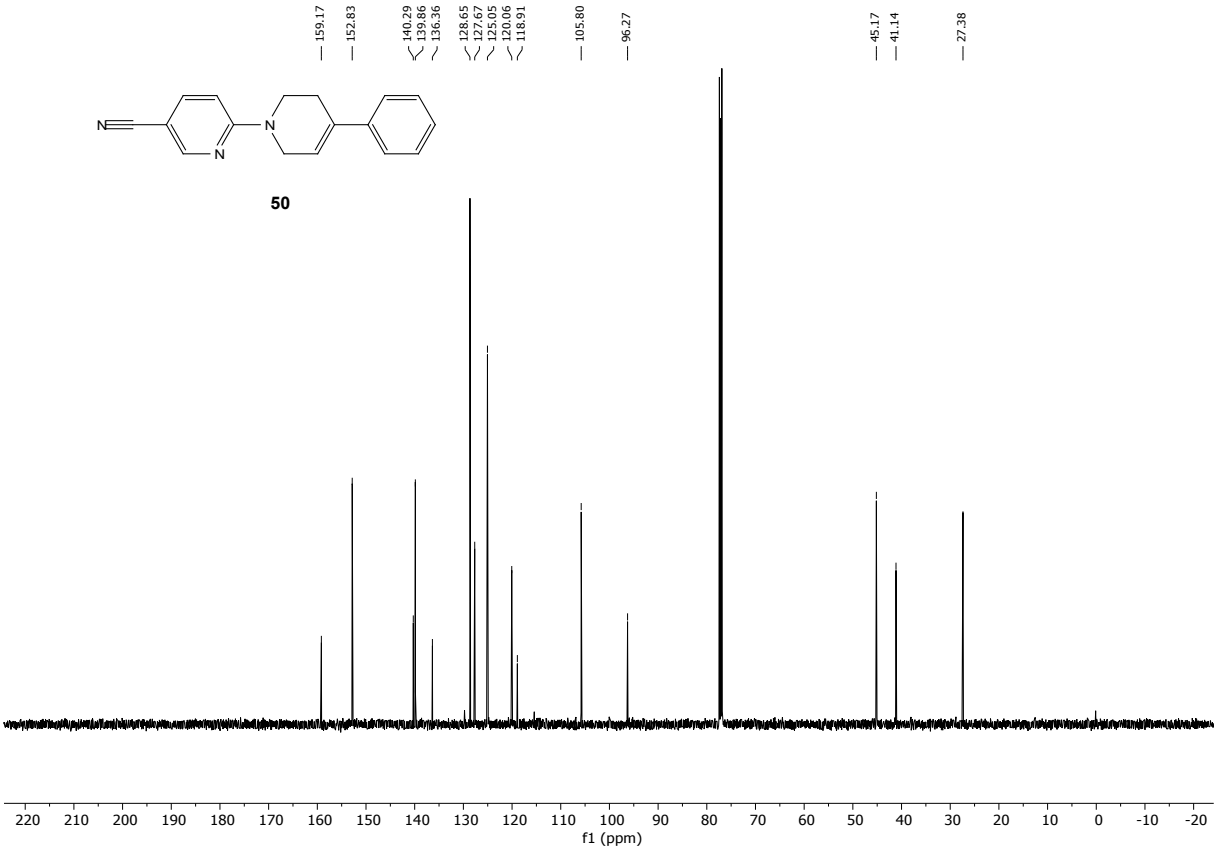
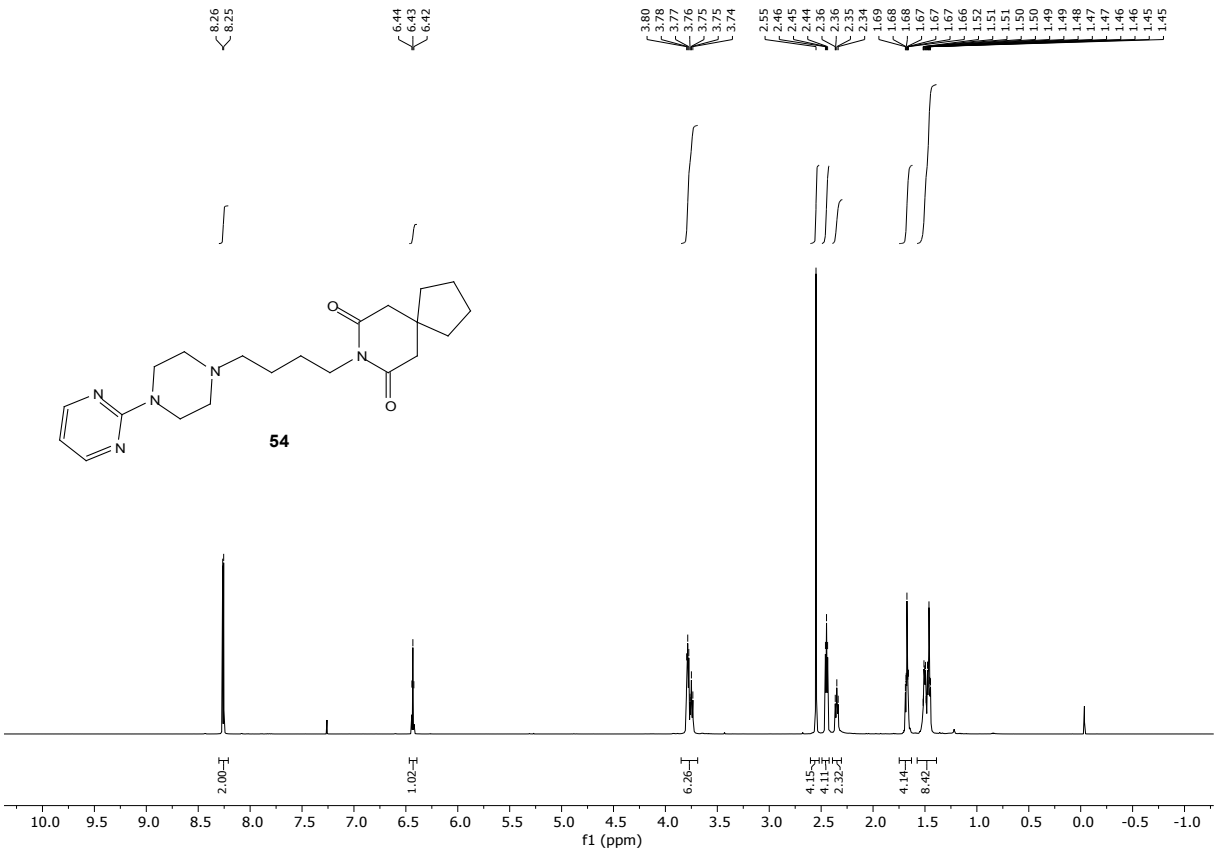
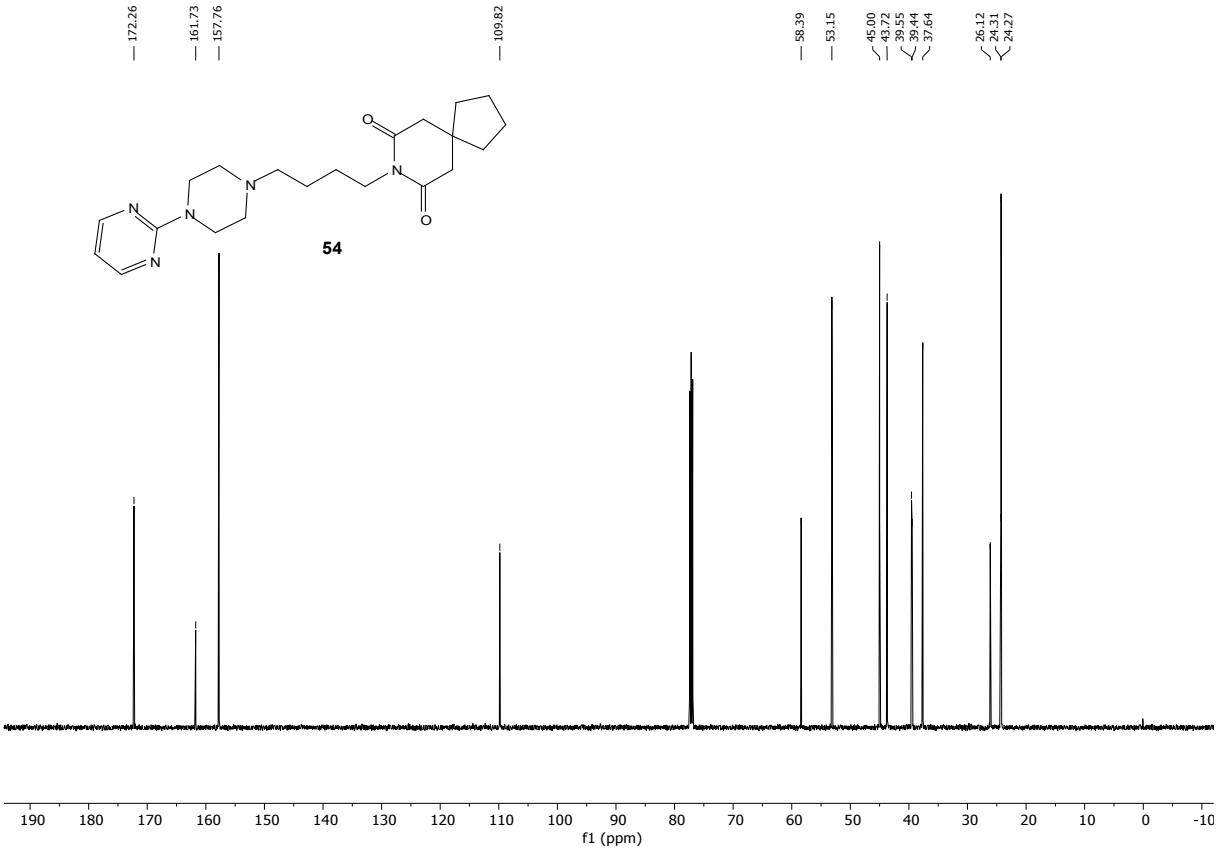
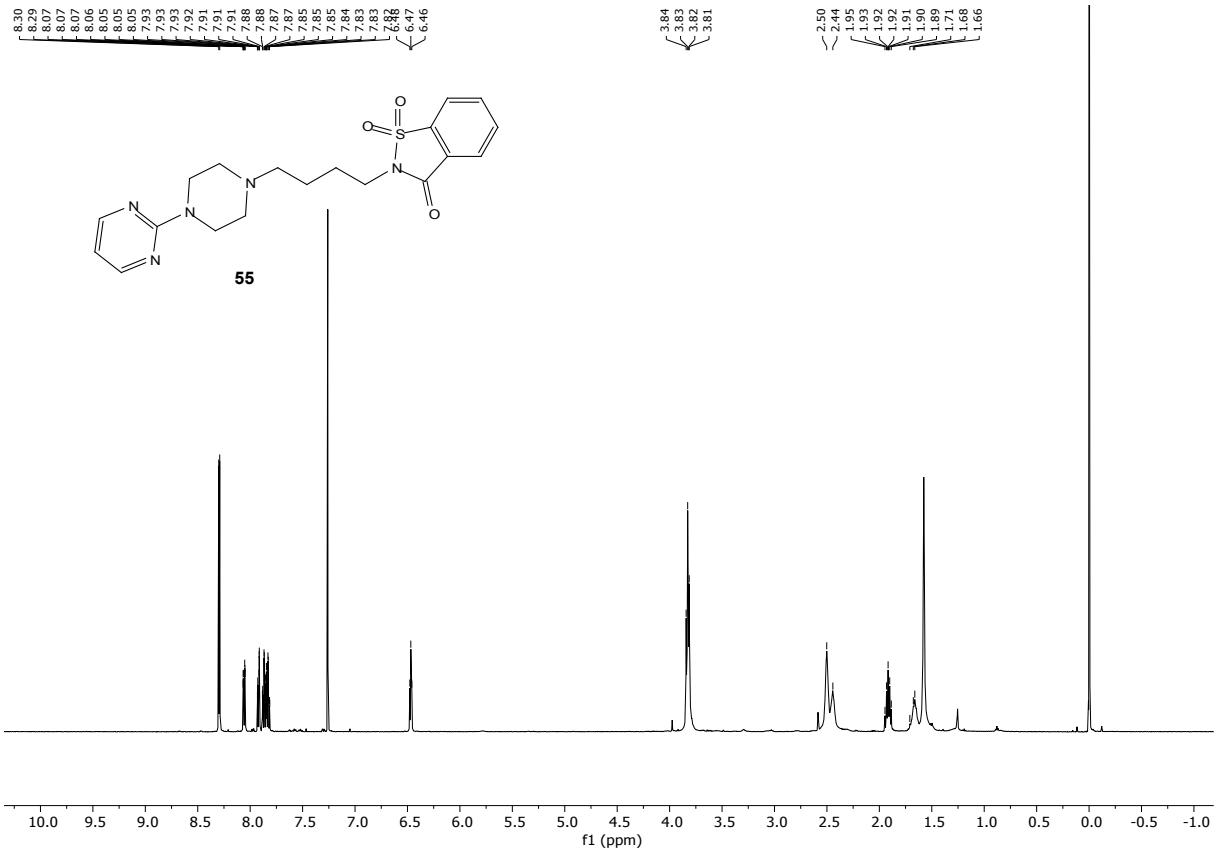
7.62
7.61
7.60
7.59
7.15
7.13
3.13
3.12
3.11
1.74
1.73
1.72
1.71
1.70
1.67
1.66
1.65
1.62
NO2
N
F3C
46
10
8
6
4
2
0
0.78
0.88
1.00
4.18
6.28
10
9
8
7
6
5
4
3
2
1
0

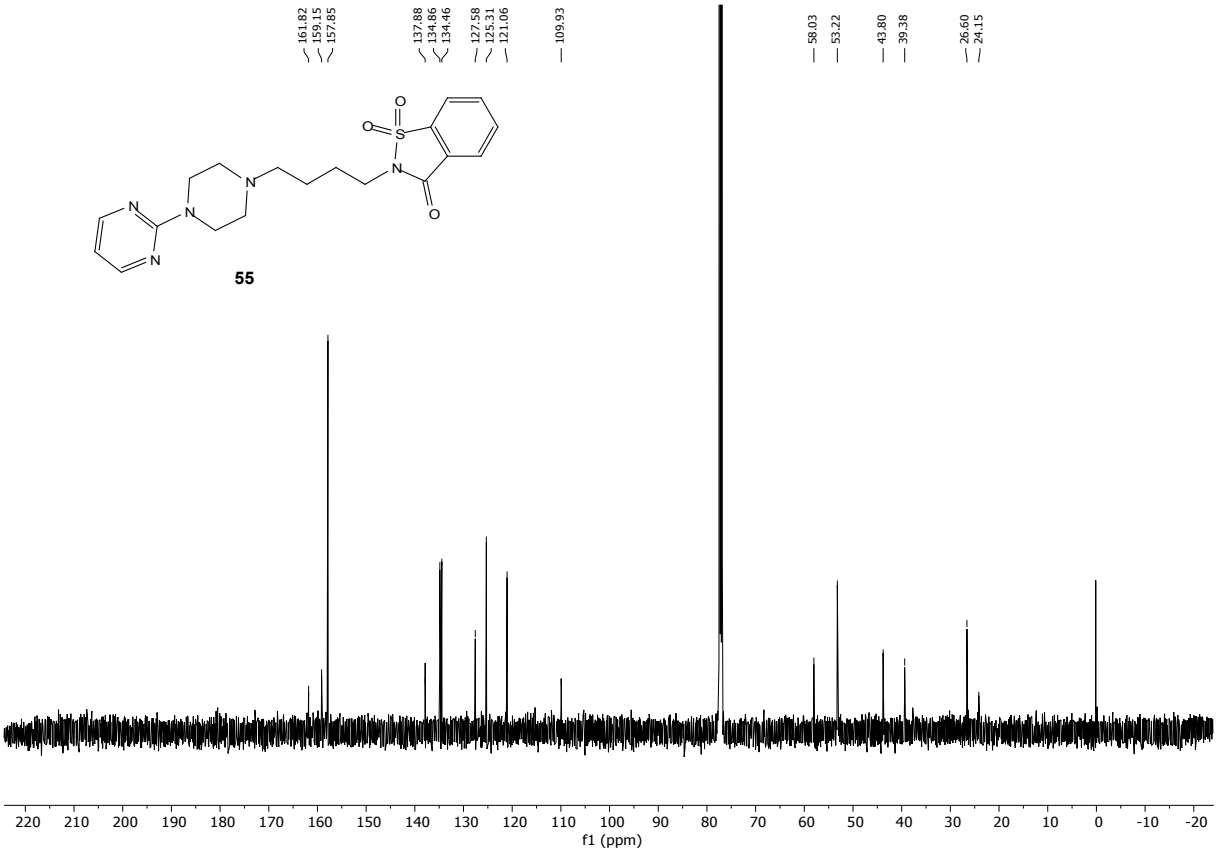

8.45 8.45 8.45 8.44 7.65 7.64 7.63 7.62 7.42 7.42 7.41 7.41 7.40 7.40 7.40 7.40 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.30 7.30 7.29 7.28 7.28 7.27 7.27 6.62 6.62 6.60 6.60 6.16 6.16 6.16 6.15 6.15 6.14 4.23 4.22 4.21 4.00 3.99 3.98 2.69 2.69 2.69 2.68 2.68 2.68 2.67 2.67 2.66 2.66 2.66
N
N
N
50
1.00 1.10 2.19 2.21 1.06 1.11 1.11 2.23 2.22 2.28
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

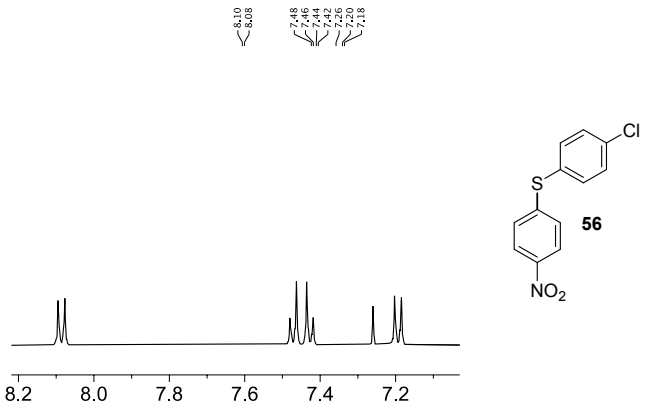

159.17 152.83 140.29 139.86 136.36 128.65 127.67 125.05 120.06 118.91 105.80 96.27 45.17 41.14 27.38
N
N
N
50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


8.26
8.25
6.44
6.43
6.42
3.80
3.78
3.77
3.76
3.75
3.75
3.74
2.55
2.46
2.45
2.44
2.36
2.35
2.34
1.69
1.68
1.68
1.67
1.67
1.67
1.66
1.52
1.51
1.51
1.50
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.46
1.45
1.45
54
2.00
1.02
6.26
4.15
4.11
2.32
4.14
8.42
f1 (ppm)


172.26
161.73
157.76
109.82
58.39
53.15
45.00
43.72
39.55
39.44
37.64
26.12
24.31
24.27
54
f1 (ppm)


8.30
8.29
8.07
8.07
8.07
8.06
8.05
8.05
7.93
7.93
7.92
7.91
7.91
7.88
7.87
7.85
7.85
7.84
7.83
7.83
6.47
6.46
3.84
3.83
3.82
3.81
2.50
2.44
1.95
1.93
1.92
1.91
1.90
1.89
1.71
1.68
1.66
55
f1 (ppm)


161.82
159.15
157.85
137.88
134.86
134.46
127.58
125.31
121.06
109.93
58.03
53.22
43.80
39.38
26.60
24.15
55
f1 (ppm)


8.10
8.08
7.48
7.46
7.44
7.43
7.26
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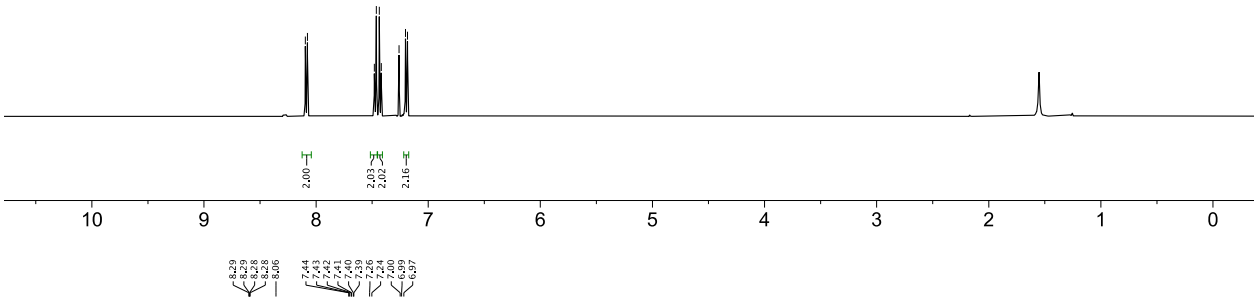
7.18
Cl
S
56
NO2
8.2
8.0
7.8
7.6
7.4
7.2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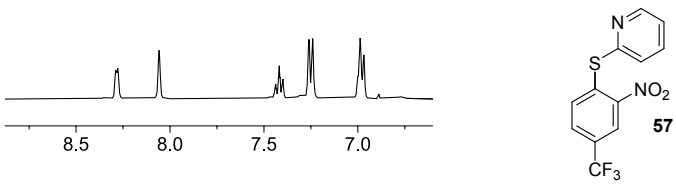
2.03
2.02
2.16
10
9
8
7
6
5
4
3
2
1
0
8.29
8.29
8.28
8.28
8.06
7.44
7.43
7.42
7.41
7.40
7.39
7.26
7.24
7.00
6.99
6.97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7.5
7.0

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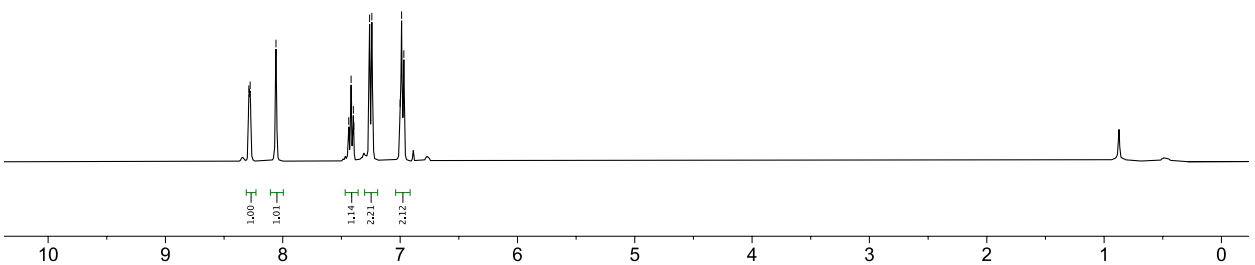
S
NO2
57
CF3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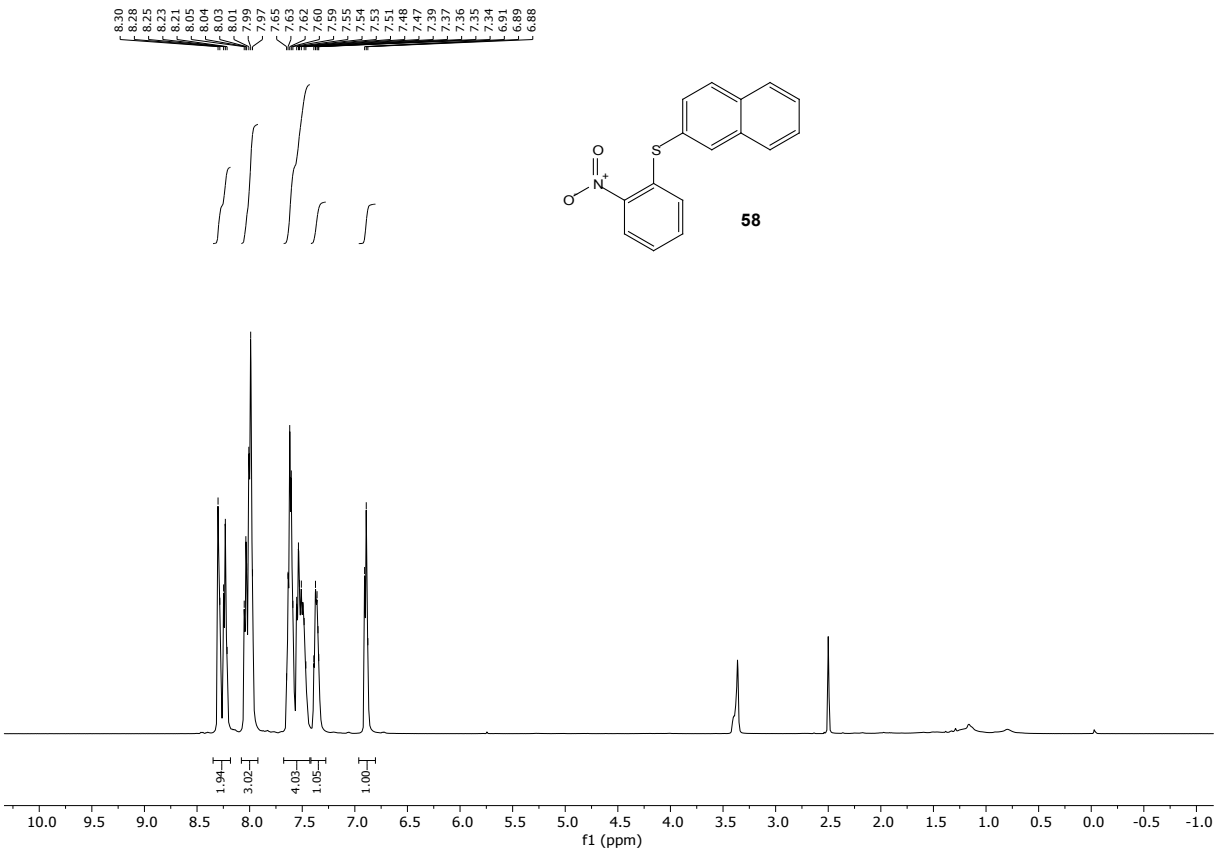
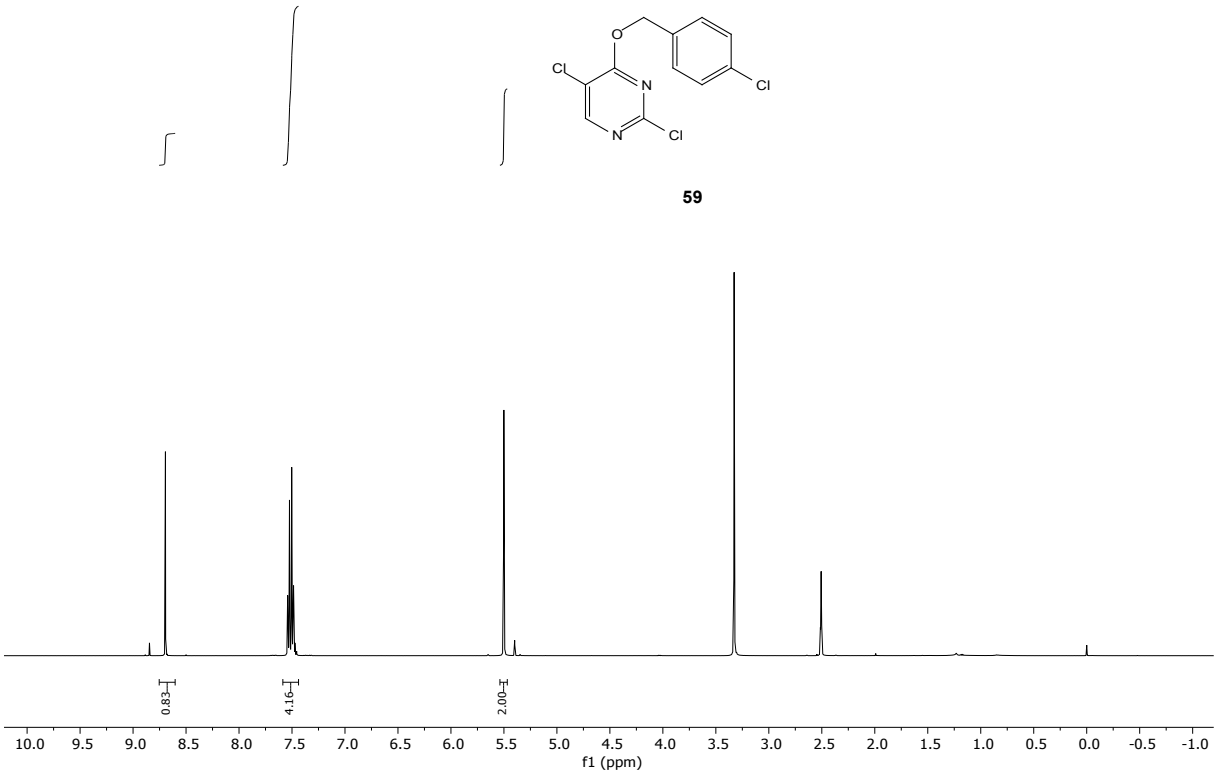
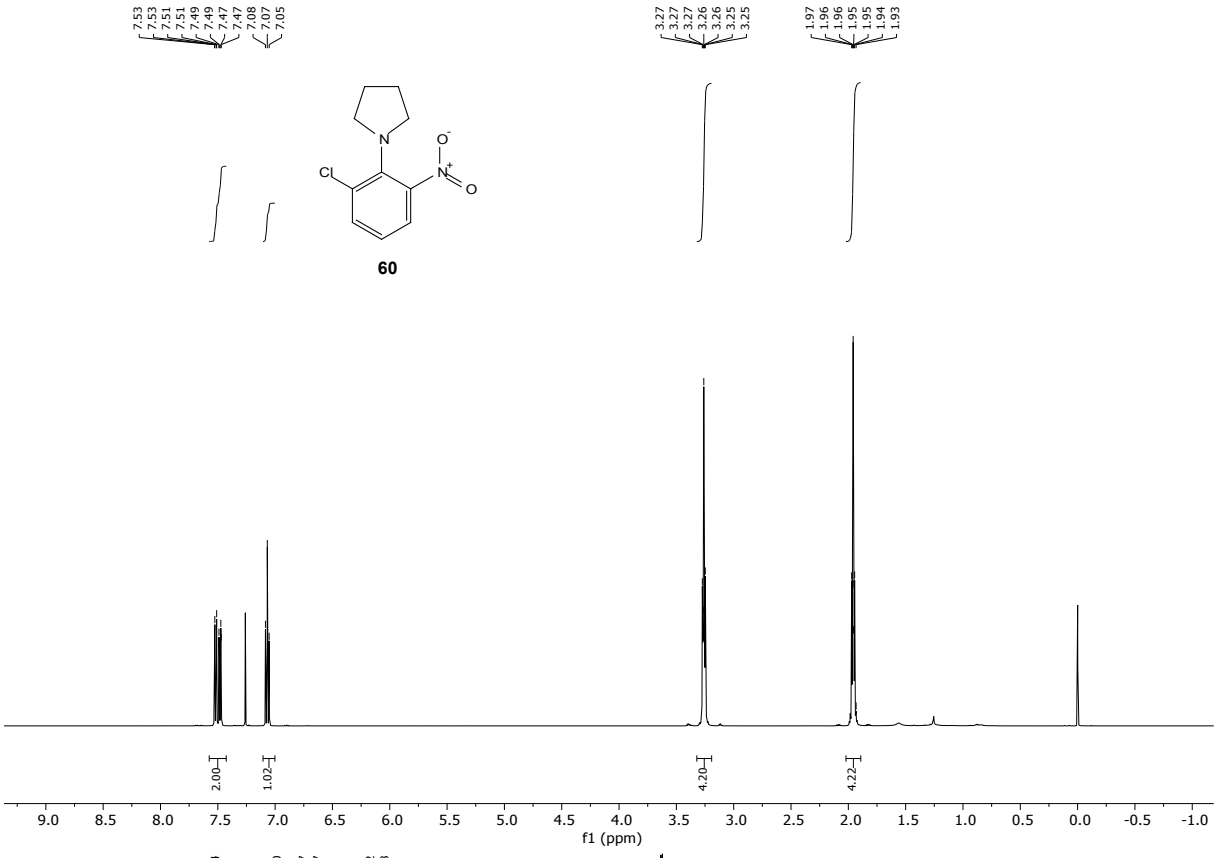
1.01
1.14
2.21
2.12
10
9
8
7
6
5
4
3
2
1
0


8.30
8.28
8.25
8.23
8.21
8.05
8.04
8.03
8.01
7.99
7.97
7.65
7.63
7.62
7.60
7.59
7.55
7.54
7.53
7.51
7.48
7.47
7.39
7.37
7.36
7.35
7.34
6.91
6.89
6.88
O
N+
O-
S
58
1.94
3.02
4.03
1.05
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


O
Cl
N
Cl
N
Cl
59
0.83
4.16
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


7.53
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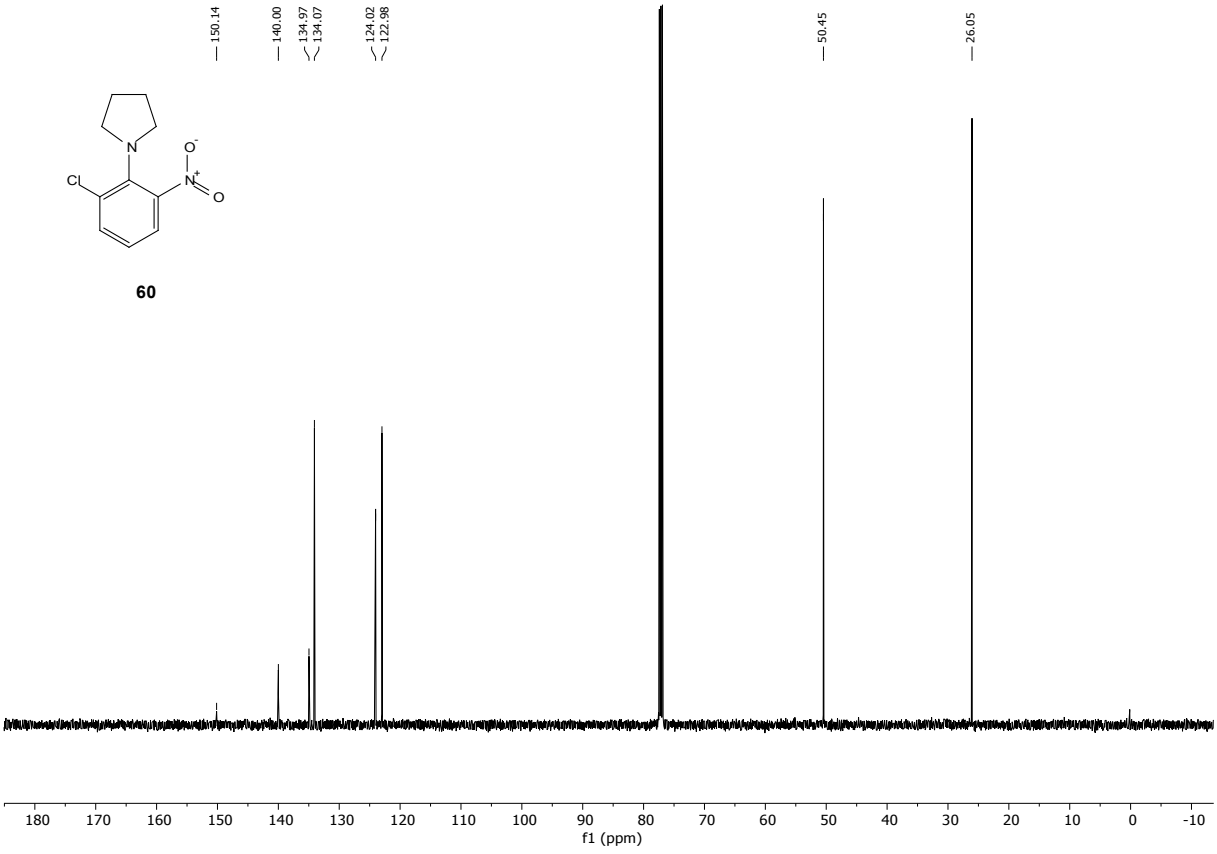
7.51
7.49
7.49
7.47
7.47
7.08
7.07
7.05
3.27
3.27
3.27
3.26
3.26
3.25
3.25
1.97
1.96
1.96
1.95
1.95
1.94
1.93
Cl
N
O
O
60
2.00
1.02
4.20
4.22
f1 (ppm)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134.07
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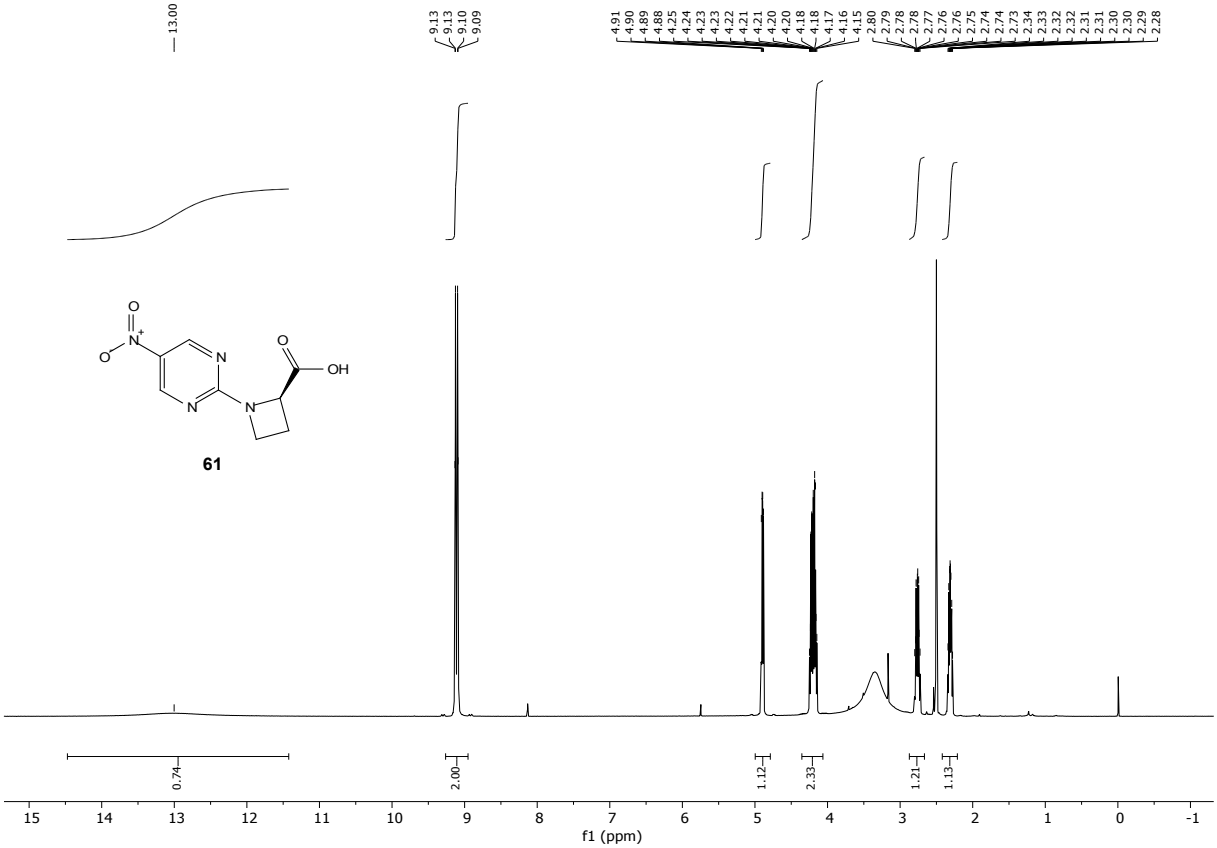
122.98
50.45
26.05
Cl
N
O
O
60
f1 (ppm)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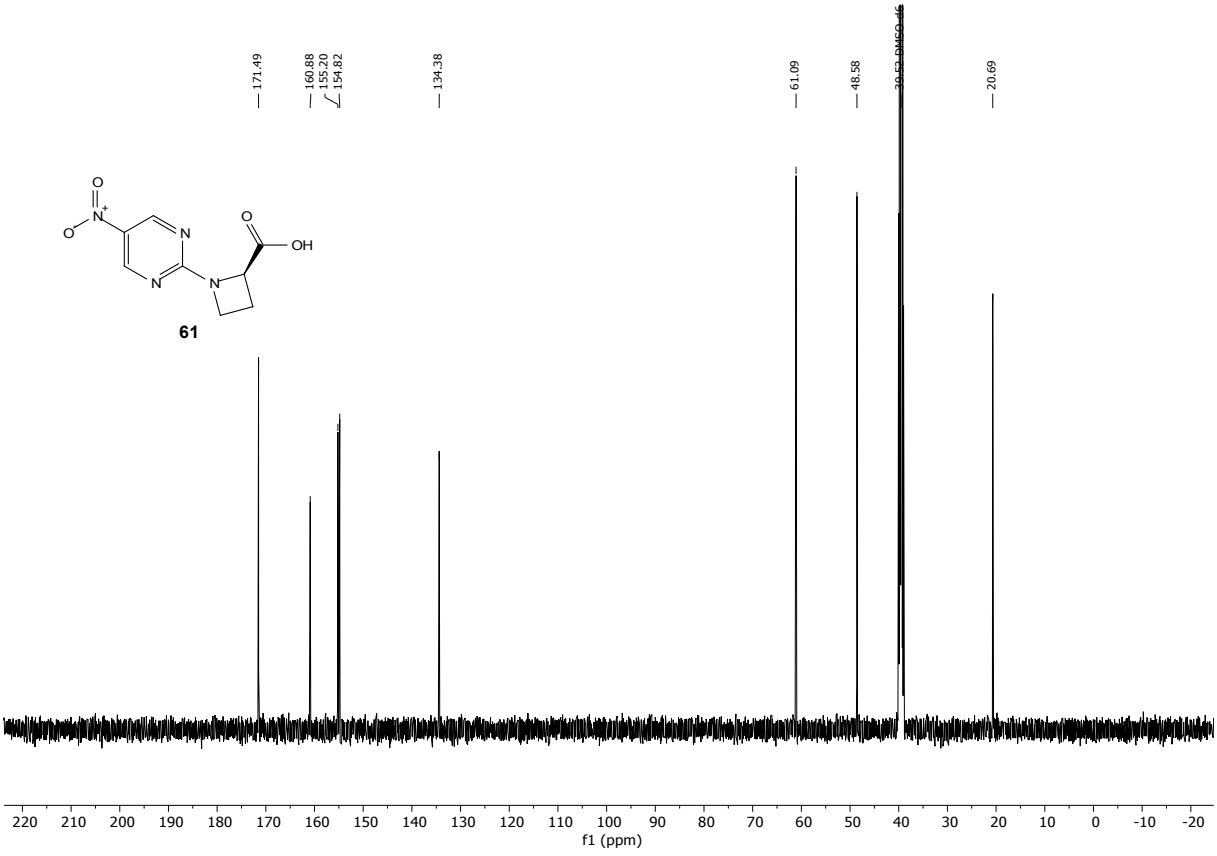
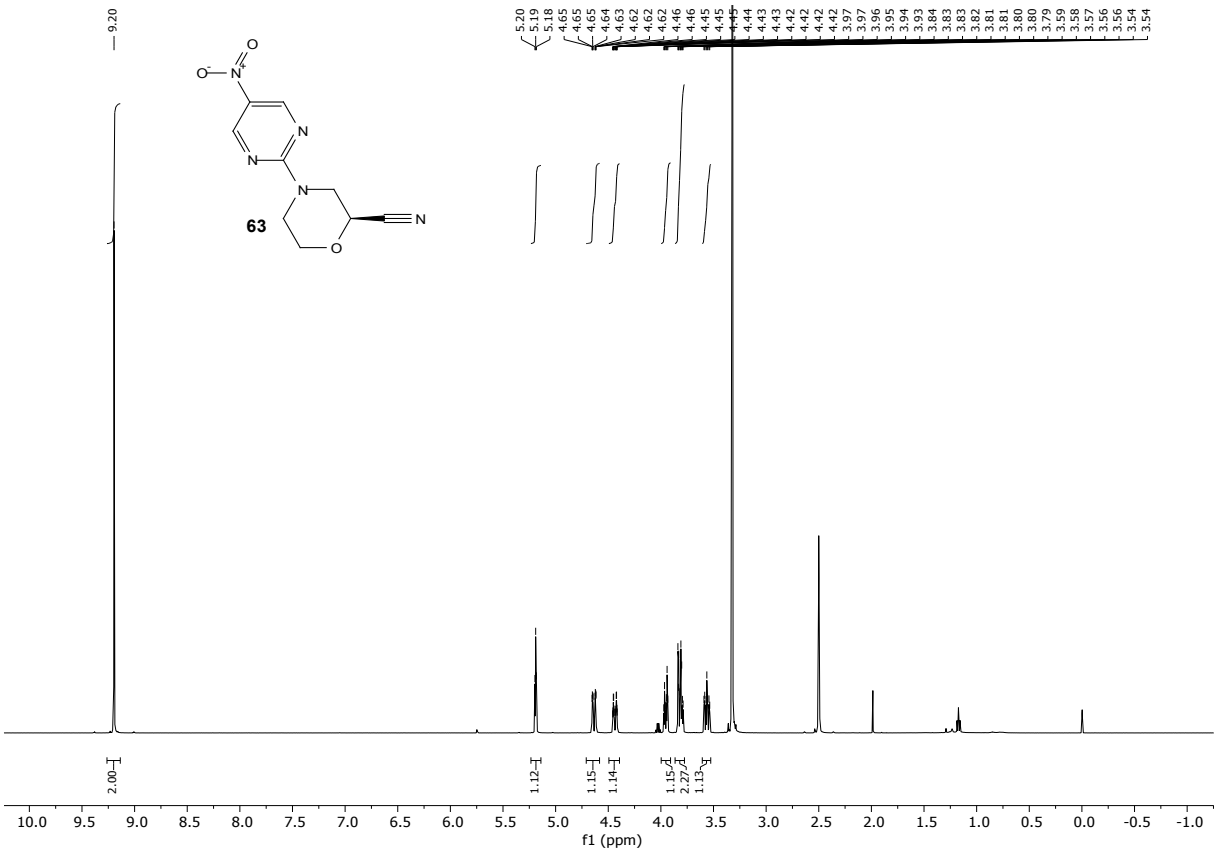
9.13
9.13
9.10
9.09
4.91
4.90
4.89
4.88
4.25
4.24
4.23
4.23
4.22
4.21
4.21
4.20
4.20
4.18
4.18
4.17
4.16
4.15
2.80
2.79
2.78
2.78
2.77
2.76
2.76
2.75
2.74
2.74
2.73
2.34
2.33
2.32
2.32
2.31
2.31
2.30
2.30
2.29
2.28
O
N+
O-
N
N
O
OH
N
61
0.74
2.00
1.12
2.33
1.21
1.13
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


171.49
160.88
155.20
154.82
134.38
61.09
48.58
39.52 DMSO-d6
20.69
O
N+
O-
N
N
O
OH
N
61
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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4.65
4.65
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4.64
4.63
4.62
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4.62
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4.46
4.45
4.45
4.44
4.44
4.43
4.43
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3.82
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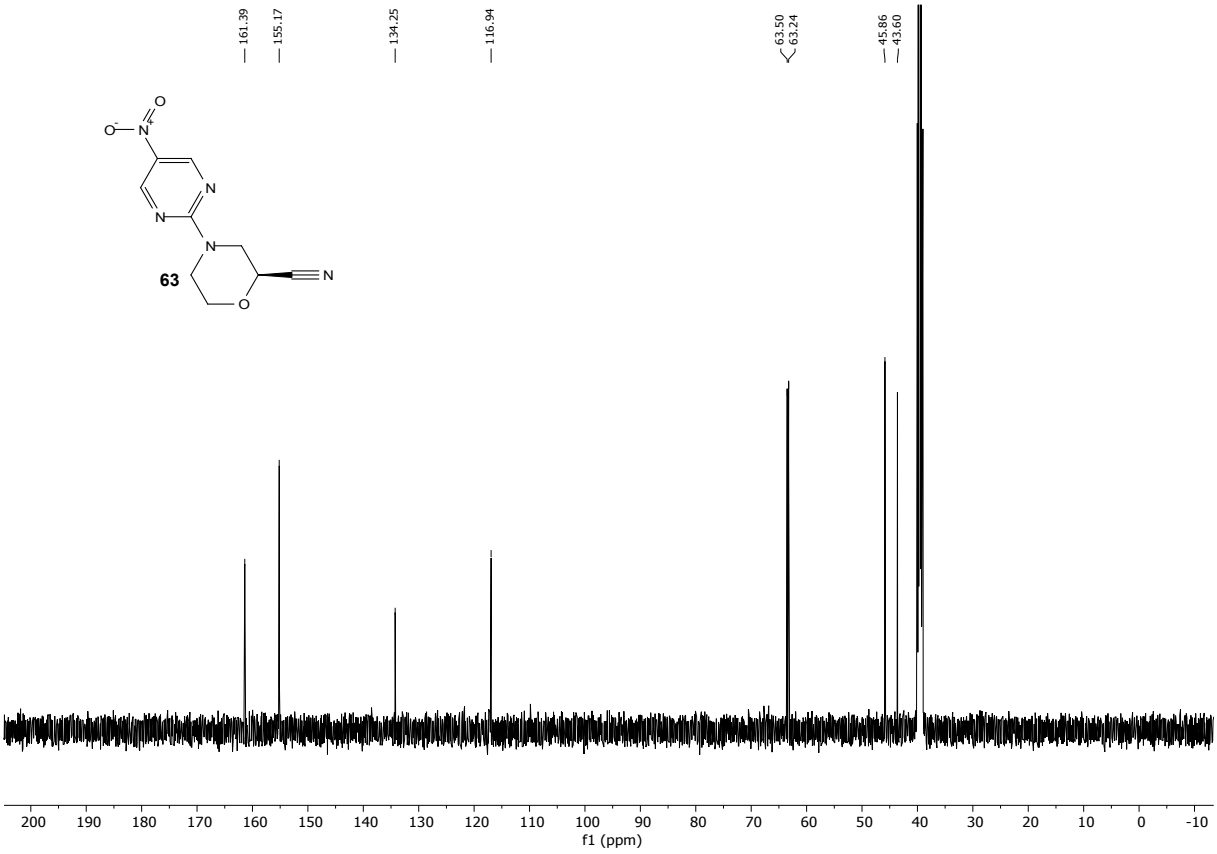
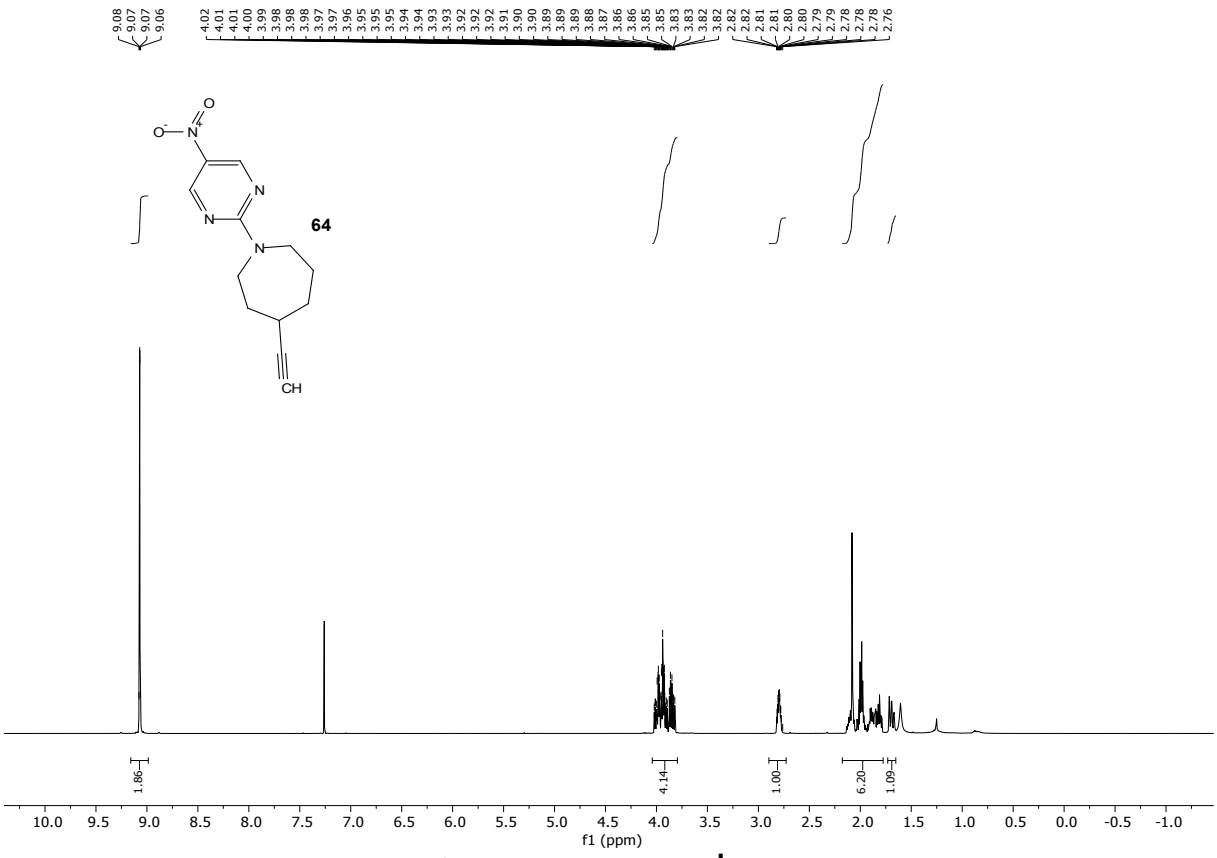
3.58
3.57
3.56
3.56
3.54
3.54
63
2.00
1.12
1.15
1.14
1.15
2.27
1.13
f1 (ppm)


161.39
155.17
134.25
116.94
63.50
63.24
45.86
43.60
63
f1 (ppm)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9.07
9.07
9.06
4.02
4.01
4.01
4.00
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3.98
3.98
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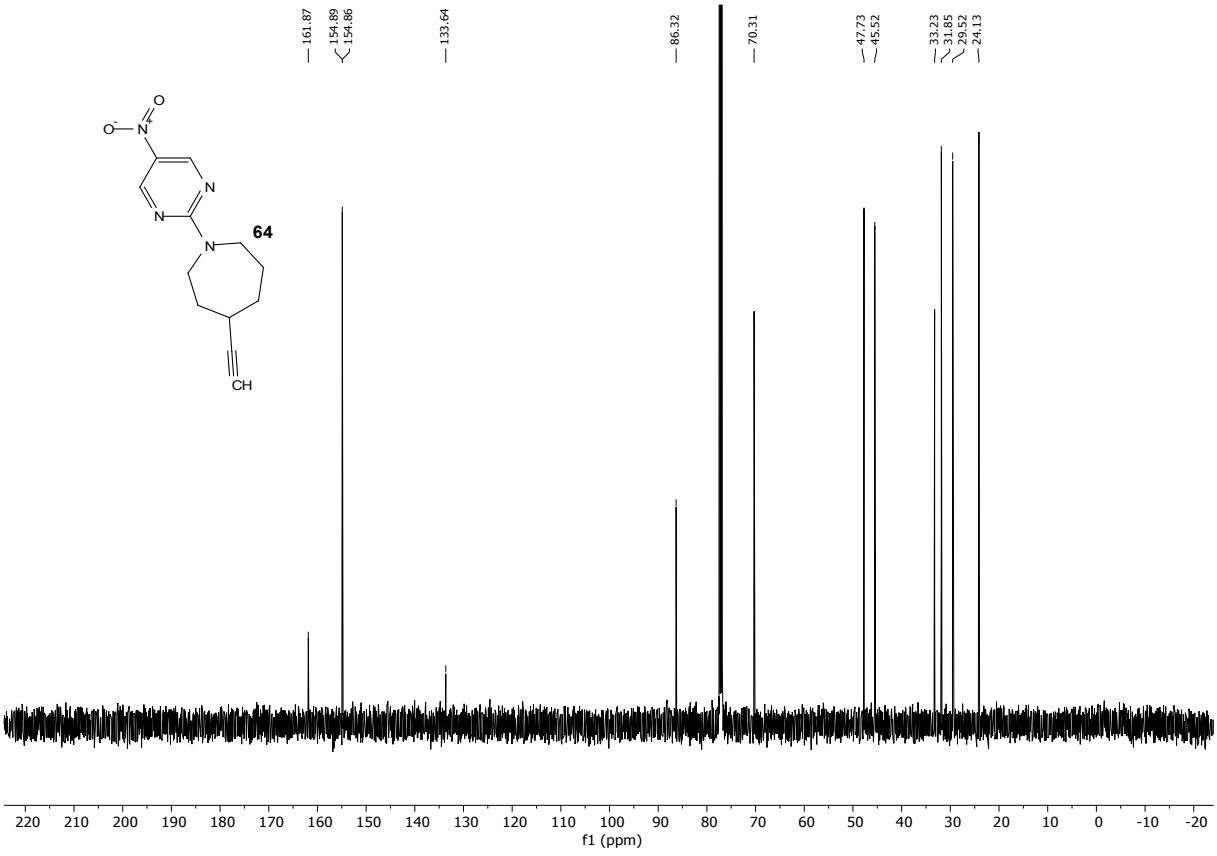
2.82
2.82
2.81
2.81
2.80
2.80
2.79
2.79
2.78
2.78
2.78
2.76
O
O
N
N
N
N
64
CH
1.86
4.14
1.00
6.20
1.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


161.87
154.89
154.86
133.64
86.32
70.31
47.73
45.52
33.23
31.85
29.52
24.13
O
O
N
N
N
N
64
CH
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

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