

Electronic Supplementary Information

Continuous flow synthesis of arylhydrazines via nickel/photoredox coupling of *tert*-butyl carbazate with aryl halides

Alejandro Mata,^{a,b} Duc N. Tran,^c Ulrich Weigl,^d Jason D. Williams^{*a,b}
and C. Oliver Kappe^{*a,b}

^a Center for Continuous Flow Synthesis and Processing (CCFLOW), Research Center
Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, 8010 Graz, Austria

^b Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria

^c Janssen Pharmaceutica N.V., Turnhoutseweg 30, 2340 Beerse, Belgium

^d Cilag AG, Hochstrasse 201, 8200 Schaffhausen, Switzerland

*Email: jason.williams@rcpe.at; oliver.kappe@uni-graz.at

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1. General Information

1.1. Materials and Methods

In all batch and flow experiments, extra dry DMSO (99.7+%, over molecular sieves) was used, purchased from Acros Organics (catalog# 348440010). Photocatalyst [Ir(dtbbpy)(ppy)₂]₂PF₆ was purchased from Synthorix (catalog# B62517). All other reagents were purchased from TCI, Sigma Aldrich or Fluorochem and used without further purification.

NMR spectra: ¹H, ¹⁹F and ¹³C NMR spectra were recorded on a Bruker 300 MHz instrument at 300 MHz, 282 MHz and 75 MHz, respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet, respectively. The prefix br denotes a broad peak.

Infrared spectra: measured on a Bruker alpha p instrument, using attenuated total reflectance (ATR). Spectra were processed using OPUS v6.5 software. The suffixes br, s, m and w denote a broad, strong, medium or weak signal, respectively.

Light source characterization: emission spectra were recorded using a fiber-coupled Avantes Starline AvaSpec-2048 spectrometer and were processed using Avasoft 8.7 software.

Flash column chromatography: automated flash column chromatography was performed on a Biotage Isolera system using columns packed with KP-SIL, 60 Å (32-63 μm particle size) silica.

Melting point: were measured using a Stuart SMP3 melting point apparatus.

High-resolution mass spectrometry (HRMS) measurements were carried out with an Agilent 6230 TOF mass spectrometer, after separation of the compounds with an Agilent 1260 Infinity Series HPLC-system. The injection volume was set to 0.5 μL and the flow rate to 0.3 mL/min of a mixture of 40% H₂O (0.1% 5 M ammonium formate) and 60% MeCN/H₂O (5:1 +0.1% 5 M ammonium formate). The HRMS module comprises an electrospray ionization source (Dual AJS ESI) and uses nitrogen as the nebulizer (15 psig) and the drying gas (5 L/min). ESI experiments were performed using the positive ionization mode (Gas Temp. = 300 °C, Fragmentor = 150 V, Skimmer

= 65 V, OCT 1 RF Vpp = 750 V, Vcap = 1400, Nozzle Voltage = 2000 V, Reference Masses = 121.050873 and 922.009798, Acquisition = 100-1,100 m/z, 1 spectra/s).

1.2. Flow Reactor Setup

The reactions were conducted in a commercial continuous-flow reactor: Corning Advanced-Flow Lab Photo Reactor (Fig. S1).

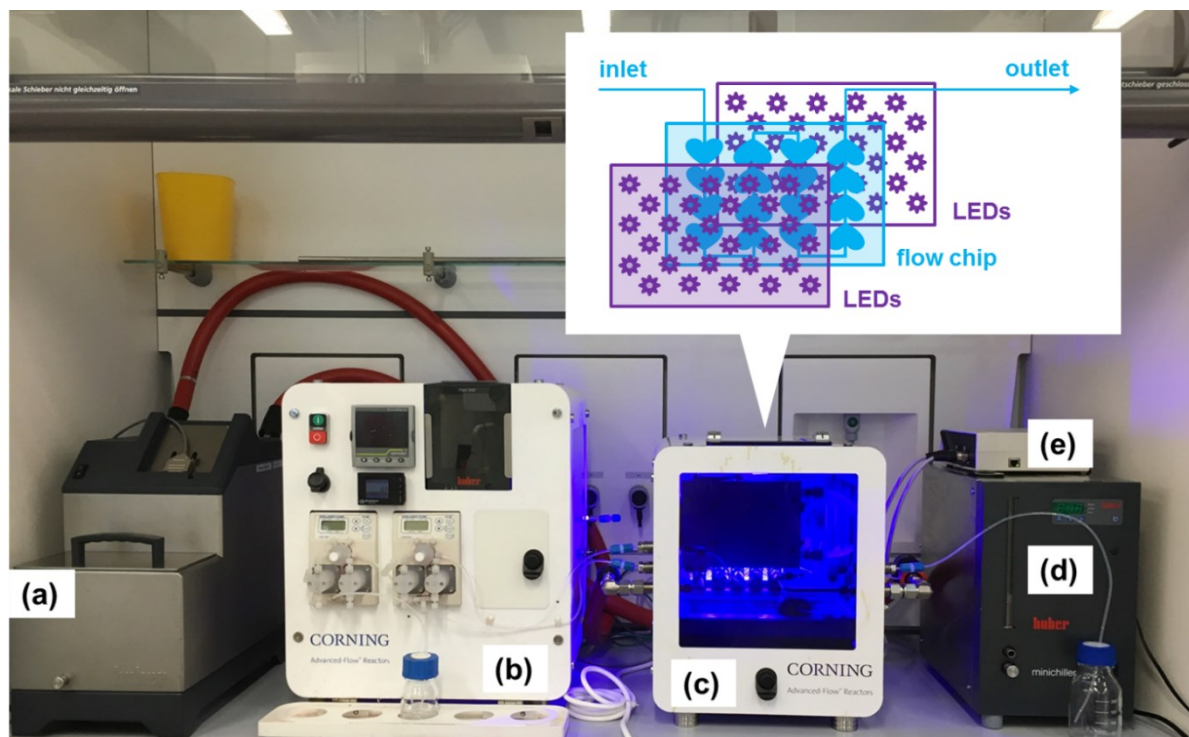


Fig. S1. Photograph of commercial photoreactor setup: a) temperature control for reaction plate; b) control module, containing pumps, mass flow controller, Huber controller and data logger; c) fluidic module housing, with tinted plastic panels for light containment; d) temperature control for LED panels; e) wireless receiver for LED control.

Reactor module (G1LF fluidic module): The flow reactor used in this work consisted of a compact glass fluidic module (155 × 125 × 8 mm size, 0.4 mm channel depth, 2.77 mL internal volume), encased within a high capacity heat exchange channel (20 mL volume).

Light source: LED panels were mounted on both sides of the fluidic module (40 mm from the center of the process stream). Each LED panel was equipped with 20 LEDs of 6 different wavelengths (120 LEDs in total) and a heat exchanger ($T = 15\text{ }^{\circ}\text{C}$). The LED wavelength and intensity was controlled externally using a web-based interface, connected wirelessly to a router. This study utilized 405 nm LEDs; see details on LED power and emission spectra below, Table S1 and Figure S2.

Table S1. Power of LEDs used in flow reactions in this study.

Peak wavelength [nm]	Radiant flux per LED [W]	Total radiant flux (both LED panels) [W]	Photon flux [mmol/h] ^[a]
395	1.34	53.6	635
450	1.19	47.6	650

^[a]Photon flux is calculated based on the radiant flux specified in the respective LED data sheet.

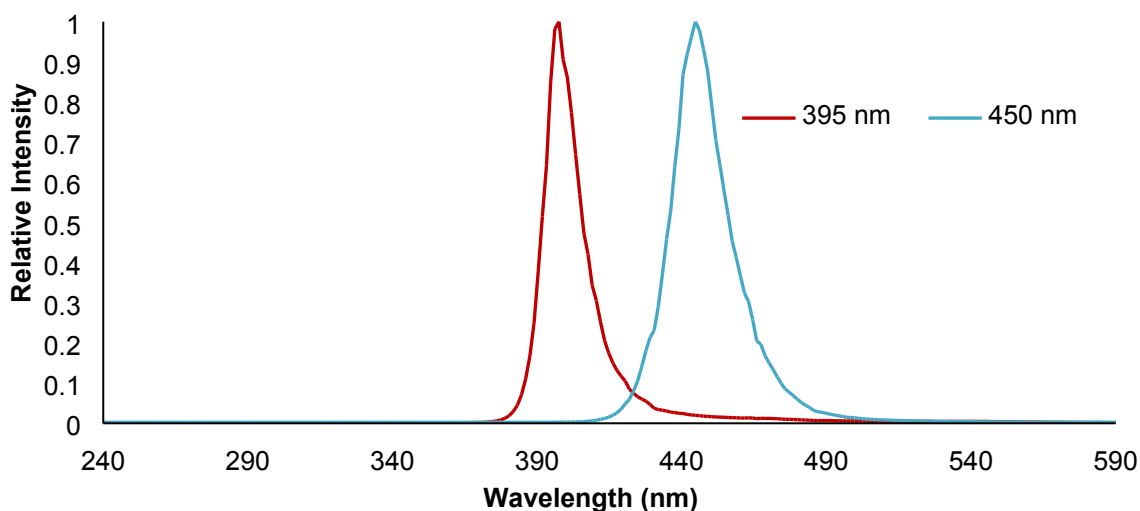


Fig. S2. Emission spectra of LEDs used in this study.

Temperature control: Thermal regulation of the LED panels was carried out using a Huber Minichiller 280 filled with 30% ethylene glycol in water. Thermal regulation of the glass fluidic module was carried out using a Huber Ministat 230 filled with silicon oil (−20 °C to 195 °C).

Pumps: The substrate solution was delivered to the photoreactor using a FLOM UI 22-110DC HPLC pump (0.01-10 mL/min; wetted parts: PTFE, PCTFE, FFKM and ruby).

General connections: Connection between the pumps, fluidic module input and output was achieved using 1/8" (outer diameter, 1.6 mm inner diameter) PFA tubing (Swagelok), using metal-free connectors (Swagelok MS-GC-2 swaging system). Other connections used 1/16" (outer diameter, 0.8 mm inner diameter) PFA tubing, with 1/4" PTFE finger tight fittings.

Sample loop: Optimization experiments were conducted using an Upchurch 6-way switching valve to inject the reaction mixture (part # V-450, <https://www.idex-hs.com/store/injection-valve-2-position-6-port-040-black.html>), with a 10 mL sample loop (made from 1/16" outer diameter, 0.8 mm inner diameter PFA tubing) installed. The sample loop was wrapped in aluminum foil, to shield it from irradiation prior to injection to the reactor.

1.3. General procedure for optimization experiments in batch

A 5 mL microwave vial equipped with a stirring bar was charged with all non-volatile reagents, substrate (90 mg, 0.4 mmol), 4-ethylbiphenyl (internal standard, 7.2 mg, 10 mol%), **photocatalyst**, **catalyst** (5 mol%), **base** (2 equiv.), **ligand**, and *tert*-butyl carbazate (154 mg, 3 equiv.). 1.9 mL of solvent was added and the vial was sealed and degassed for 10 minutes. [Hydrazine monohydrate (60 mg, 3 equiv.) was added at this point for initial experiments.] The reaction mixture was then irradiated with a 50 W LED lamp for 20 h at 5 cm distance, leading to an increased temperature of ~35 °C.

1.4. General procedure for experiments in flow

A 10 mL volumetric flask was charged with [Ir(dtbbpy)(ppy)₂]PF₆ (9.1 mg, 0.01 mmol), NiBr₂·3H₂O (40.8 mg, 0.15 mmol), DBU (365 mg, 2.4 mmol), 4-ethylbiphenyl (internal standard, 36.4 mg, 0.2 mmol) and dry DMSO (5 mL). The mixture was sonicated at 40 °C. Once a red solution was formed, the rest of the components were added: substrate (2 mmol) and *tert*-butyl carbazate (528 mg, 4 mmol). The volume was then corrected to 10 mL with dry DMSO.

The reactor thermostat was set to 129°C (120 °C actual temperature measured in the heat exchange channel – all temperature values used in the manuscript refer to the temperature measured in the heat exchange channel). DMSO was pumped through the system at the desired flow rate for 30 min in order to stabilize the system. The reaction solution was loaded into the sample loop, then injected to the reactor. Collection of the output solution was done at steady state (22 – 42 min for reactions with residence time of 10 min, or 44 – 85 min for reactions with residence time of 20 min)

For product isolation the following steps were taken, using the material collected from the flow reactor:

5 mL of the final solution were taken for work-up. 5 mL of water (brine for heterocycles) and 5% LiCl (5 mL) were added. The mixture was extracted with DCM (3 x 15 mL). The combined organic phases were combined and extracted twice with a mixture of brine (3 mL) and 5% LiCl (3 mL). The organic phase was then dried over Na₂SO₄ and evaporated.

To the resultant solid or oil, HCl in dioxane (4M, 10 mL) was added under inert atmosphere. The mixture was stirred at room temperature for 4 h, then all volatiles were removed under reduced pressure. The resulting material was washed with 3 volumes of solvent (MeCN or Et₂O) to provide the desired product.

2. Additional reaction data

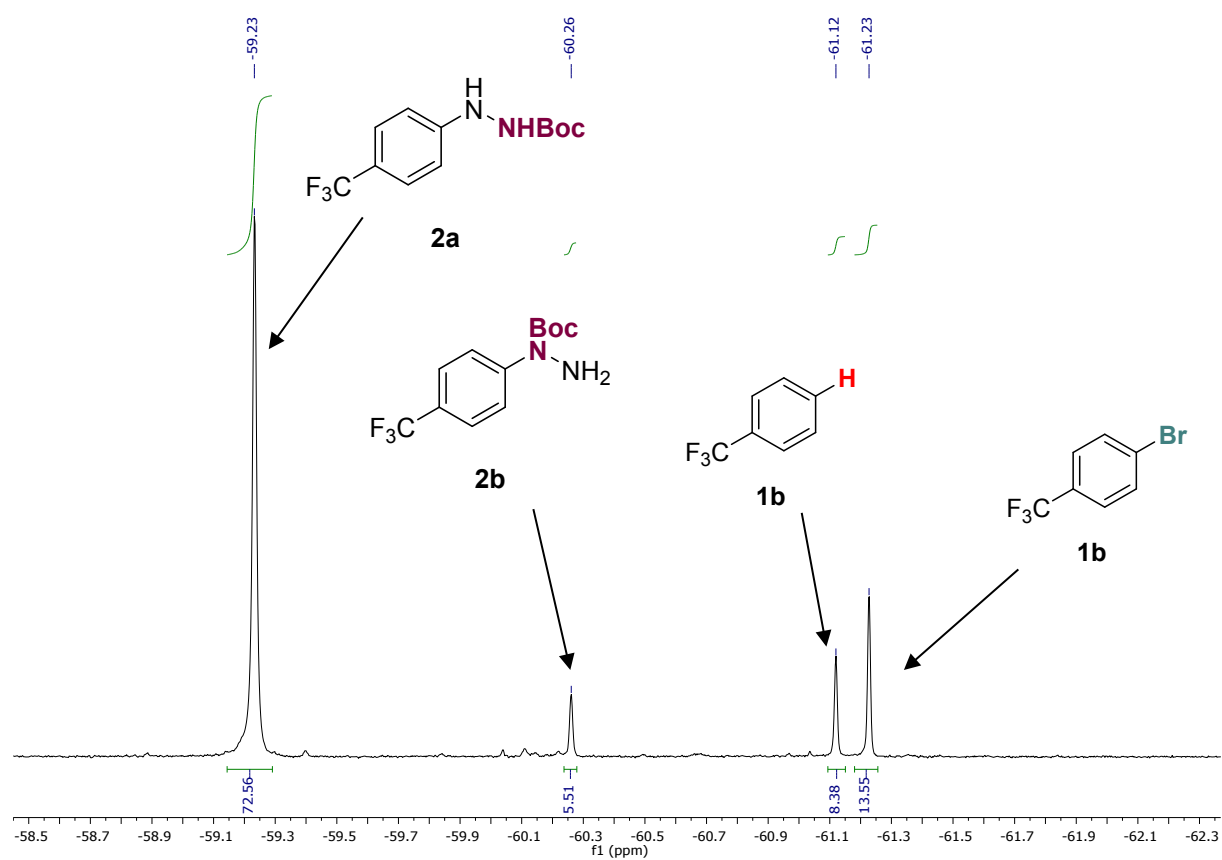


Fig. S3. Example ^{19}F NMR spectrum, showing reaction mixture composition (example taken from scale-out run **a**).

2.1. Initial batch optimization data

2.1.1. Reaction attempts using hydrazine hydrate

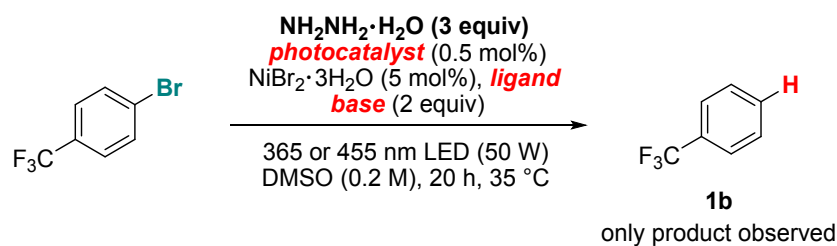
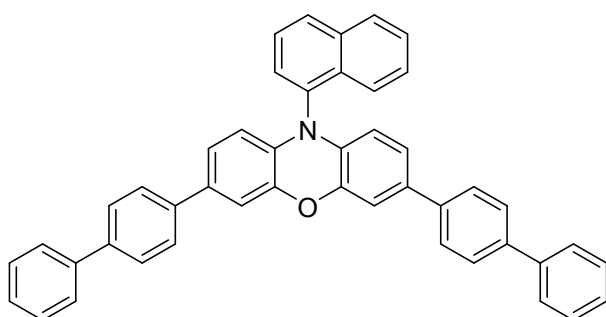


Table S2. Selected results from initial reaction screening in batch using hydrazine hydrate

Entry	Irradiation Wavelength (nm)	Photocatalyst	Base	Ligand (loading)	Conversion (%) ^a
1	365	-	DABCO	-	5
2	365	-	DBU	-	35
3	365	-	2,6-lutidine	-	2
4	455	[Ru(bpy) ₃]Cl ₂	DBU	-	20
5	455	[Ir(dF(CF ₃)ppy) ₂ (dtbpy)]PF ₆	DBU	-	42
6	455	[Ir(dtbbpy)(ppy) ₂]PF ₆	DBU	-	98
7	455	[Ir(dtbbpy)(ppy) ₂]PF ₆	DBU	bpy (5 mol%)	99
8	455	[Ir(dtbbpy)(ppy) ₂]PF ₆	DBU	4,4'-dimethyl bpy (5 mol%)	97
9	455	3,7-di([1,1'-biphenyl]-4-yl)-10-(naphthalen-1-yl)-10H-phenoxazine	DBU	bpy (5 mol%)	99

^aConversion measured by HPLC vs 4-ethylbiphenyl as an internal standard.



3,7-di([1,1'-biphenyl]-4-yl)-10-(naphthalen-1-yl)-10H-phenoxazine

2.1.2. Photocatalyst screening

A screen of photocatalysts identified $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ to be optimal for this reaction. Surprisingly, $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (often used in related CN cross-coupling protocols) showed significantly poorer results, with more dehalogenation.

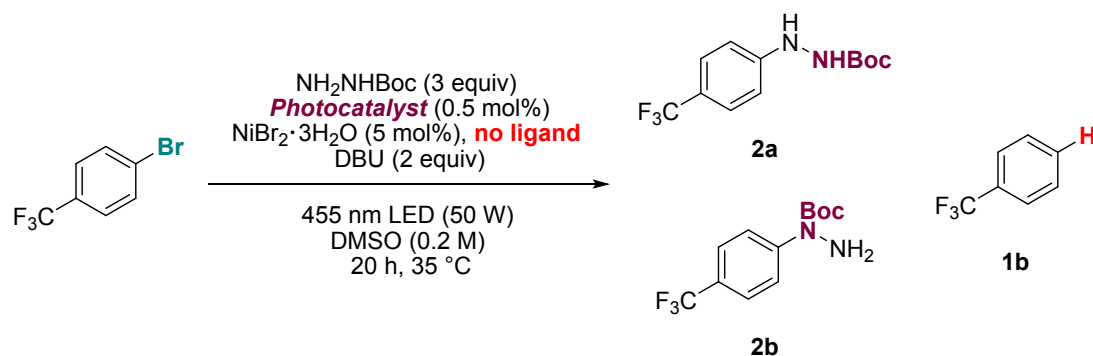
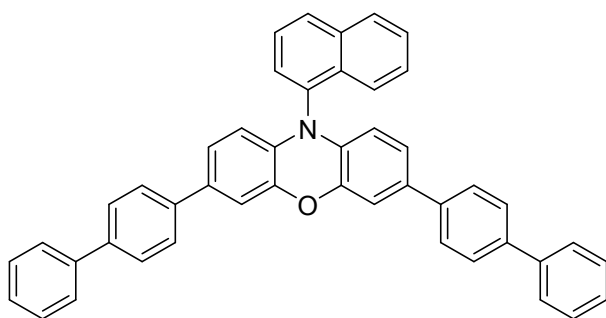


Table S3. Results of photocatalyst screening in batch

Entry	Photocatalyst	Conversion (%) ^a	2a (%) ^b	2b (%) ^b	1b (%) ^b
0	-	<1	-	-	-
1	$[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$	99	82	10	8
2 ^c	$[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$	18	-	-	18
3	3,7-di([1,1'-biphenyl]-4-yl)-10-(naphthalen-1-yl)-10 <i>H</i> -phenoxazine	70	30	3	30
4	$[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$	37	15	2	20
5	$[\text{Ru}(\text{bpy})_3]\text{Cl}_2$	9	4	2	2
6	CN-OA-m (6.66 mg)	70	45	5	12

^aConversion measured by HPLC vs 4-ethylbiphenyl as an internal standard. ^bProduct ratios determined by integration of crude ¹⁹F NMR spectra. ^cReaction was carried out without $\text{NiBr}_2 \cdot 3\text{H}_2\text{O}$ catalyst.



3,7-di([1,1'-biphenyl]-4-yl)-10-(naphthalen-1-yl)-10*H*-phenoxazine

2.1.3. Ligand screening

It appears that the absence of ligand is beneficial for the reaction. All of the examined bipyridine-based ligands favor dehalogenation.

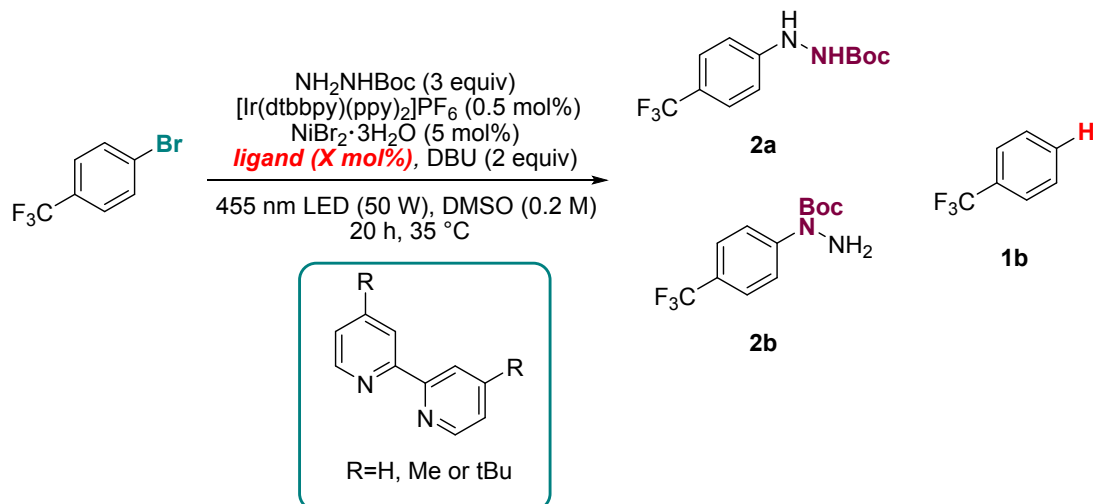


Table S4. Results of ligand screening in batch.

Entry	Ligand (loading)	Conversion (%) ^a	2a (%) ^b	2b (%) ^b	1b (%) ^b
0	-	99	82	10	8
1	bpy, R = H (5 mol%)	99	72	10	18
2	bpy, R = H (10 mol%)	95	58	6	28
3	bpy, R = H (15 mol%)	86	42	4	33
4	R = Me (5 mol%)	99	72	10	18
5	R = Me (10 mol%)	99	62	5	33
6	R = Me (15 mol%)	97	43	2	50
7	dtbpy, R = tBu (5 mol%)	99	67	16	17
8	preformed $[\text{Ni}(\text{bpy})_3]\text{Br}_2$ as catalyst ^{S1}	94	50	6	32

^aConversion measured by HPLC vs 4-ethylbiphenyl as an internal standard. ^bProduct ratios determined by integration of crude ¹⁹F NMR spectra.

2.1.4. Solvent screening

Solvents other than DMSO gave poor reaction performance, with lower conversion and significantly more side product formation. Owing to the unfavorable impurity profiles, the product distribution was not quantified in these cases. Furthermore, precipitate was observed in all three other solvents during the course of the reaction, rendering them unsuitable for flow processing.

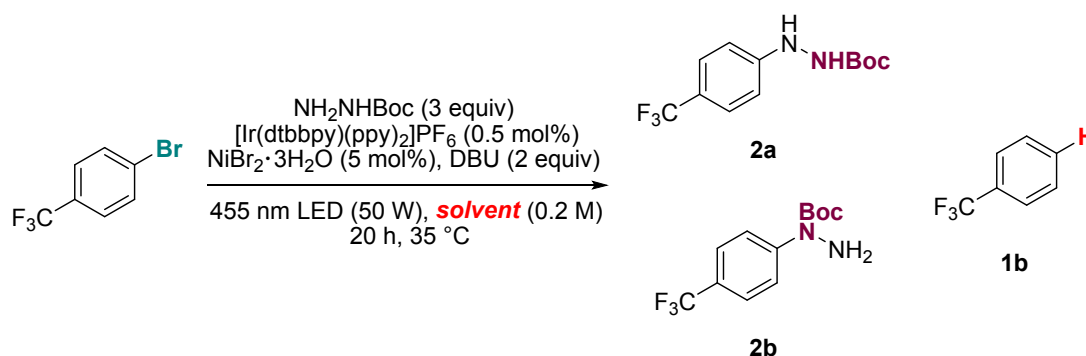


Table S5. Results of solvent screening in batch.

Entry	Solvent	Conversion (%) ^a
1	DMSO	99
2	DMA	55
3	THF	20
4	MeCN	28

^aConversion measured by HPLC vs 4-ethylbiphenyl as an internal standard.

2.2. Additional flow data

2.2.1. Design of Experiments (DoE) optimization

Table S6 Factors varied in DoE study

Name	Abbr.	Units	Type	Settings	Transform	Precision
Photocatalyst Loading	PC	Mol %	Quantitative	0.1 to 0.5	None	0.01
NiBr ₂ Loading	Ni	Mol %	Quantitative	2.5 to 7.5	None	0.125
DBU	DBU	Equivalents	Quantitative	1.5 to 3	None	0.05
SM conc	SMc	M	Quantitative	0.2 to 0.4	None	0.005
NH ₂ NHBoc	Hydra	Equivalents	Quantitative	2 to 4	None	0.1
Temperature	Temp	°C	Quantitative	80 to 120	None	1

Table S7 Responses measured in DoE study

Name	Abbr.	Units	Transform	Type
1	1	%	NegLog: -10Log(100-Y)	Regular
2a	2a	%	Log: 10Log(Y)	Regular
2b	2b	%	Log: 10Log(Y+0.5)	Regular
1b	1b	%	Log: 10Log(Y+3)	Regular
2a+2b	2a+2b	%	Log: 10Log(Y)	Regular
	Double-click here	to add	a new response	

Table S8 All experimental conditions and results for DoE optimization.

Entry	Photocat. Loading (mol%)	NiBr ₂ Loading (mol%)	DBU (equiv)	Conc. (M)	NH ₂ NHBoc (equiv)	Temp. (°C)	1 ^a	2a ^a	2b ^a	1b ^a
1	0.1	2.5	1.5	0.2	2	80	89	8	2	1
2	0.5	2.5	1.5	0.2	4	80	79	16	1	3
3	0.1	7.5	1.5	0.2	4	120	70	22	1	7
4	0.5	7.5	1.5	0.2	2	120	32	56	2	9
5	0.1	2.5	3	0.2	4	120	76	18	1	5
6	0.5	2.5	3	0.2	2	120	45	37	8	10
7	0.1	7.5	3	0.2	2	80	91	6	1	2
8	0.5	7.5	3	0.2	4	80	76	20	1	3
9	0.1	2.5	1.5	0.4	2	120	79	16	1	4
10	0.5	2.5	1.5	0.4	4	120	65	27	1	7
11	0.1	7.5	1.5	0.4	4	80	92	6	0	1
12	0.5	7.5	1.5	0.4	2	80	83	14	1	2
13	0.1	2.5	3	0.4	4	80	92	6	0	2
14	0.5	2.5	3	0.4	2	80	83	11	2	4
15	0.1	7.5	3	0.4	2	120	81	12	0	6
16	0.5	7.5	3	0.4	4	120	64	25	1	9
17	0.3	5	2.25	0.3	3	100	72	22	1	5
18	0.3	5	2.25	0.3	3	100	74	21	1	4
19	0.3	5	2.25	0.3	3	100	75	20	1	4

Highlighted rows show center point conditions. ^aQuantities determined by ¹⁹F NMR integration.

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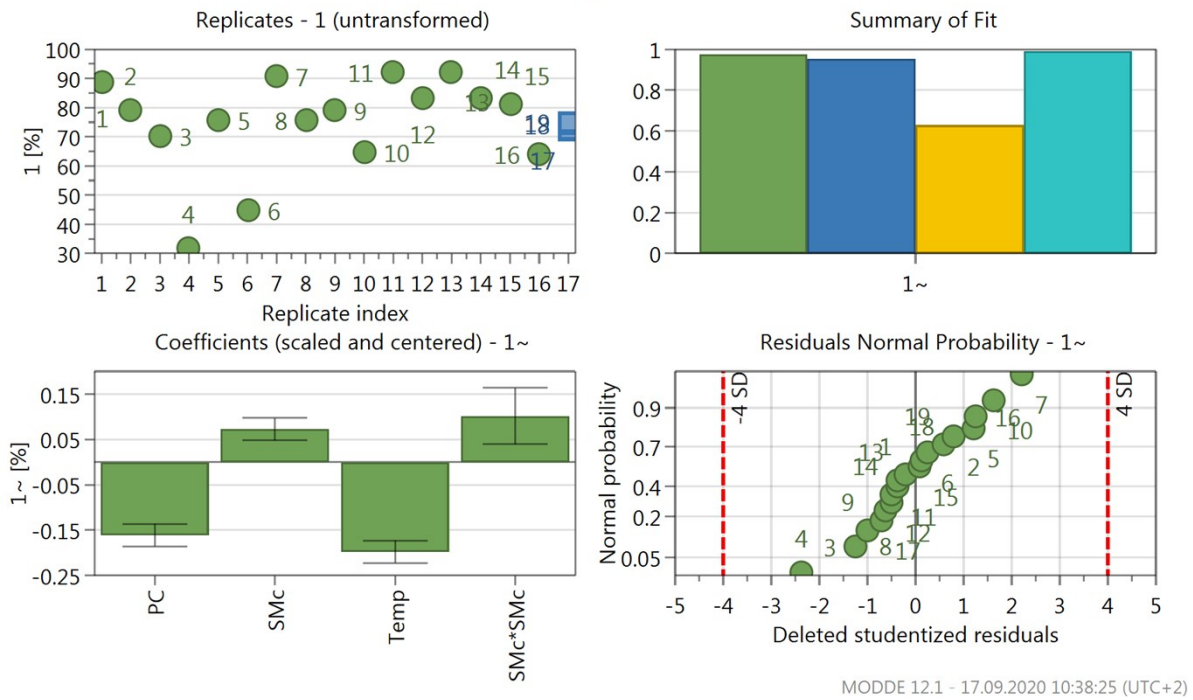


Fig. S4. Summary of DoE model for 1.

Table S9. ANOVA of DoE model for 1.

1~	DF	SS	MS (variance)	F	p	SD
Total	19	35.0216	1.84324			
Constant	1	33.8403	33.8403			
Total corrected	18	1.18136	0.0656313			0.256186
Regression	4	1.15161	0.287902	135.455	0.000	0.536565
Residual	14	0.0297562	0.00212544			0.0461025
Lack of Fit (Model error)	12	0.0285068	0.00237556	3.80253	0.227	0.0487397
Pure error (Replicate error)	2	0.00124946	0.000624731			0.0249946
	N = 19	Q2 =	0.955	Cond. no. =	4.845	
	DF = 14	R2 =	0.975	RSD =	0.0461	
		R2 adj. =	0.968			

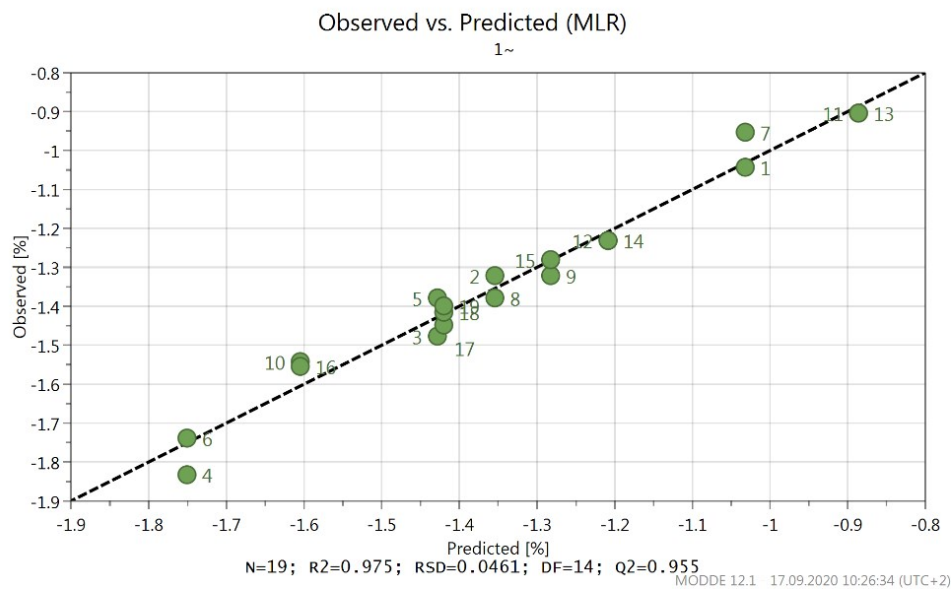


Fig. S5. Predicted vs actual results from DoE model for 1.

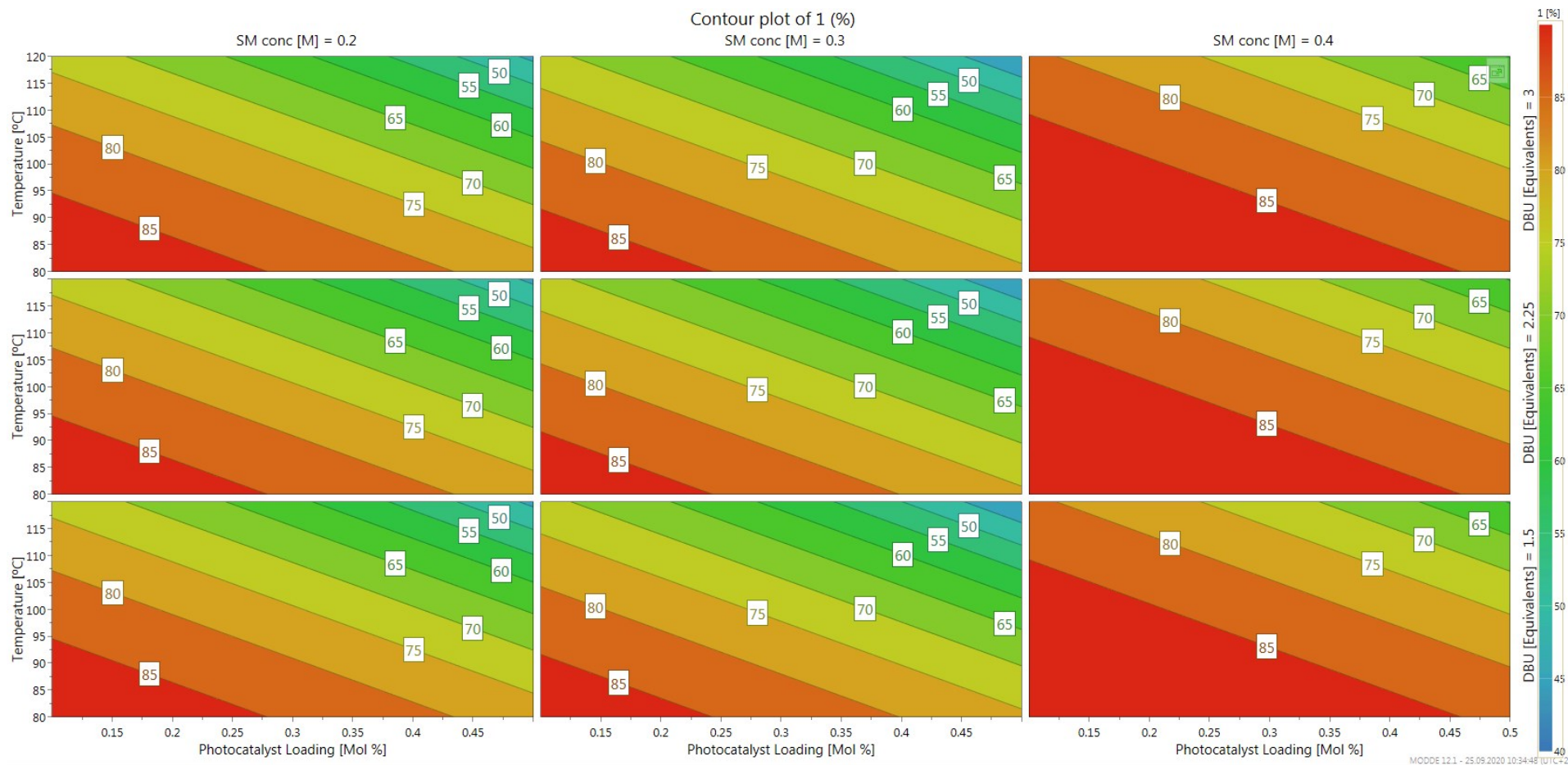


Fig. S6. Contour plot showing results from DoE for 1.

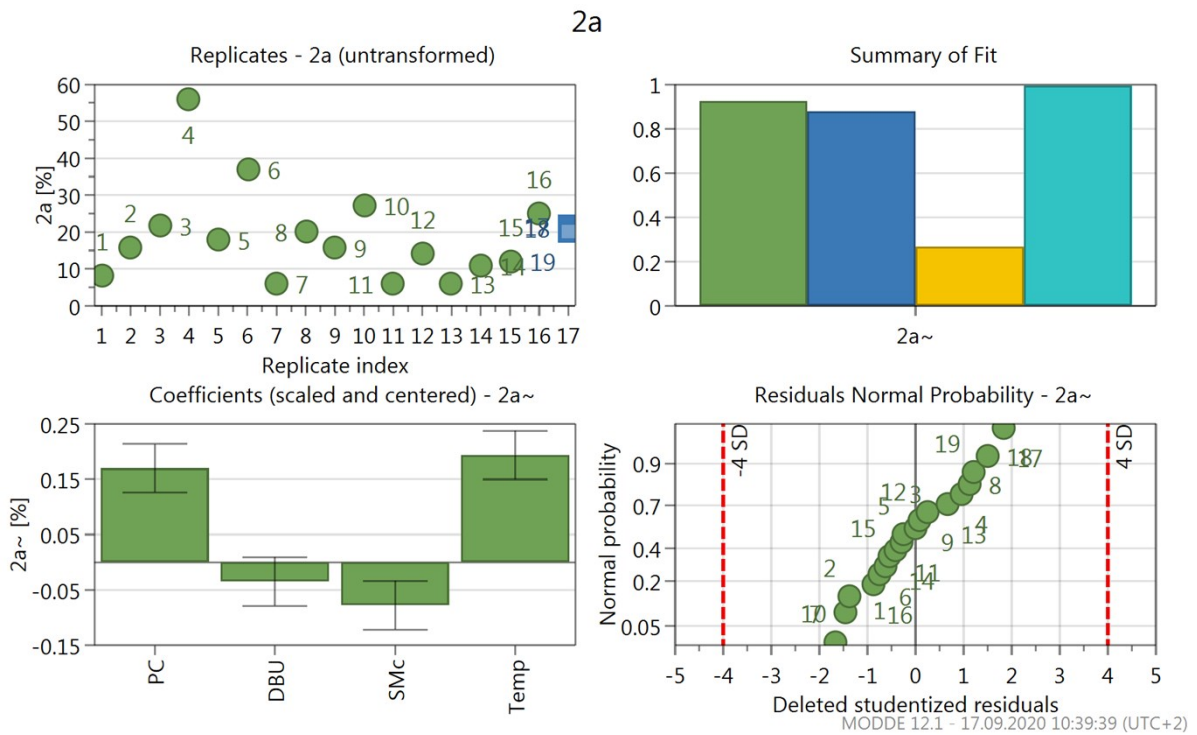


Fig. S7. Summary of DoE model for 2a.

Table S10. ANOVA of DoE model for 2a.

2a~	DF	SS	MS (variance)	F	p	SD
Total	19	28.9267	1.52246			
Constant	1	27.655	27.655			
Total corrected	18	1.27169	0.0706495			0.2658
Regression	4	1.17781	0.294452	43.909	0.000	0.542634
Residual	14	0.0938834	0.00670596			0.0818899
Lack of Fit (Model error)	12	0.0930266	0.00775222	18.0949	0.054	0.0880467
Pure error (Replicate error)	2	0.000856839	0.00042842			0.0206983
	N = 19	Q2 =	0.878	Cond. no. =	1.09	
	DF = 14	R2 =	0.926	RSD =	0.08189	
		R2 adj. =	0.905			

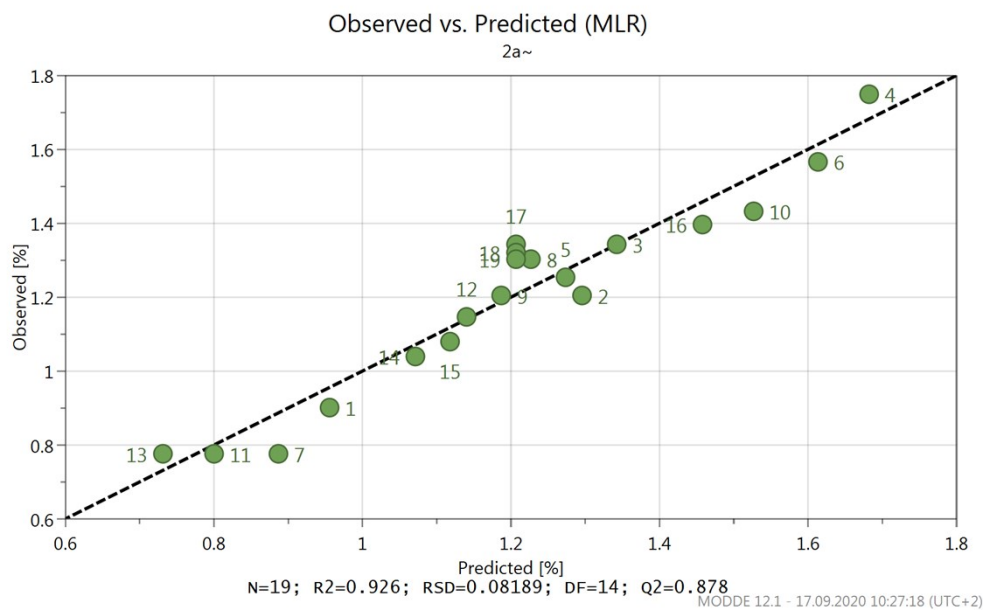


Fig. S8. Predicted vs actual results from DoE model for **2a**.

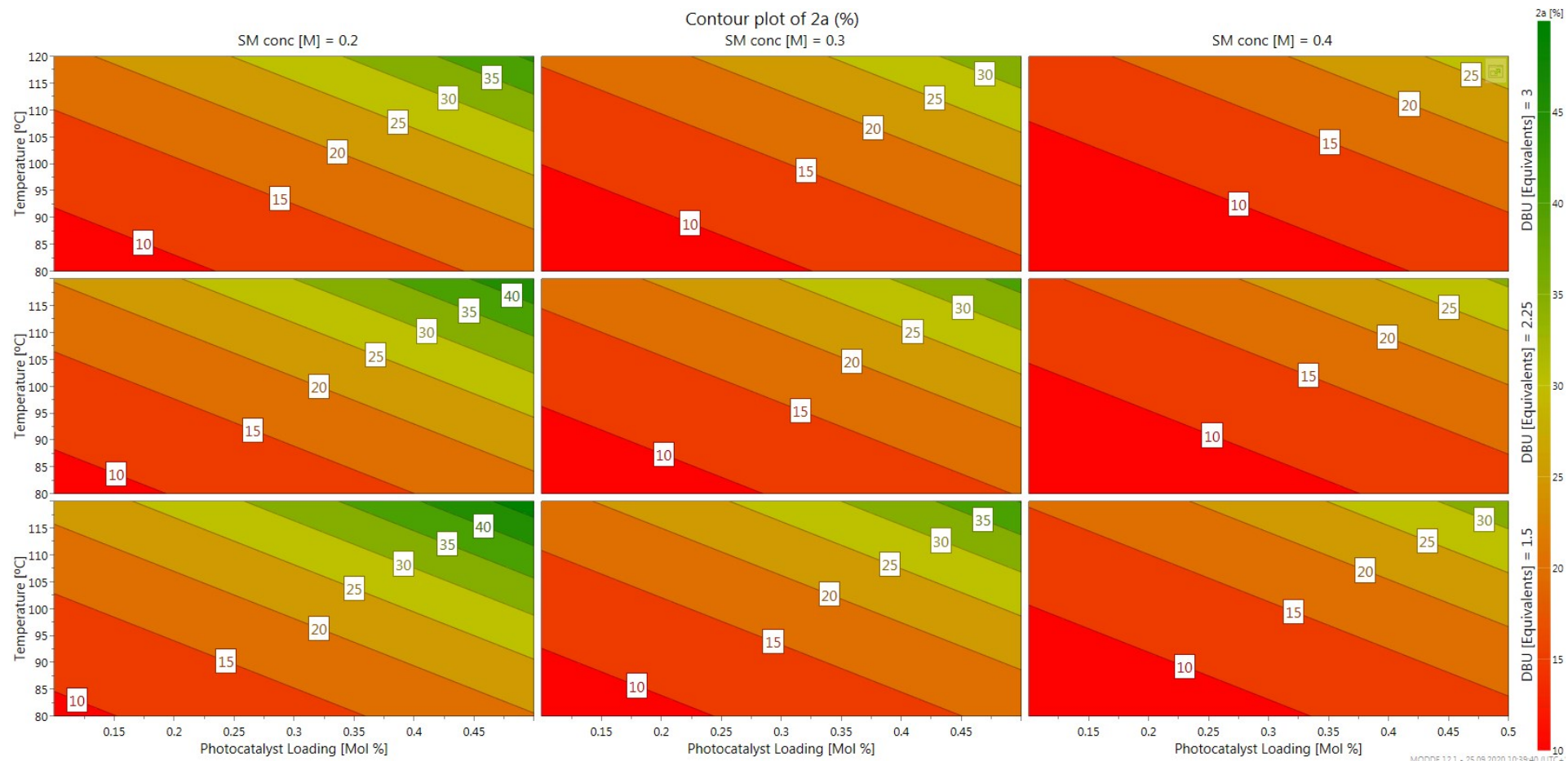


Fig. S9. Contour plot showing results from DoE for **2a**.

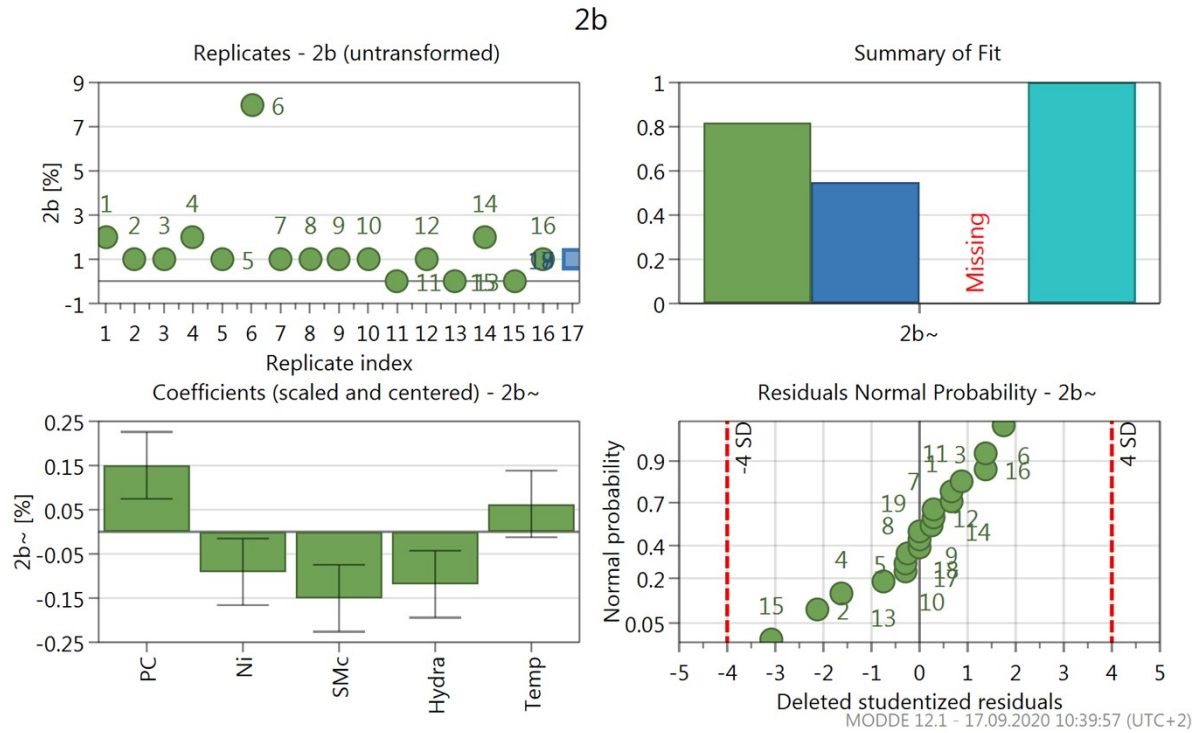


Fig. S10. Summary of DoE model for 2b.

Table S11. ANOVA of DoE model for 2b.

2b~	DF	SS	MS (variance)	F	p	SD
Total	19	1.98284	0.10436			
Constant	1	0.584764	0.584764			
Total corrected	18	1.39808	0.0776711			0.278695
Regression	5	1.14401	0.228801	11.707	0.000	0.478332
Residual	13	0.254072	0.019544			0.1398
Lack of Fit (Model error)	11	0.254072	0.0230975	--	--	0.151978
Pure error (Replicate error)	2	0	0			--
	N = 19	Q2 =	0.549	Cond. no. =	1.09	
	DF = 13	R2 =	0.818	RSD =	0.1398	
		R2 adj. =	0.748			

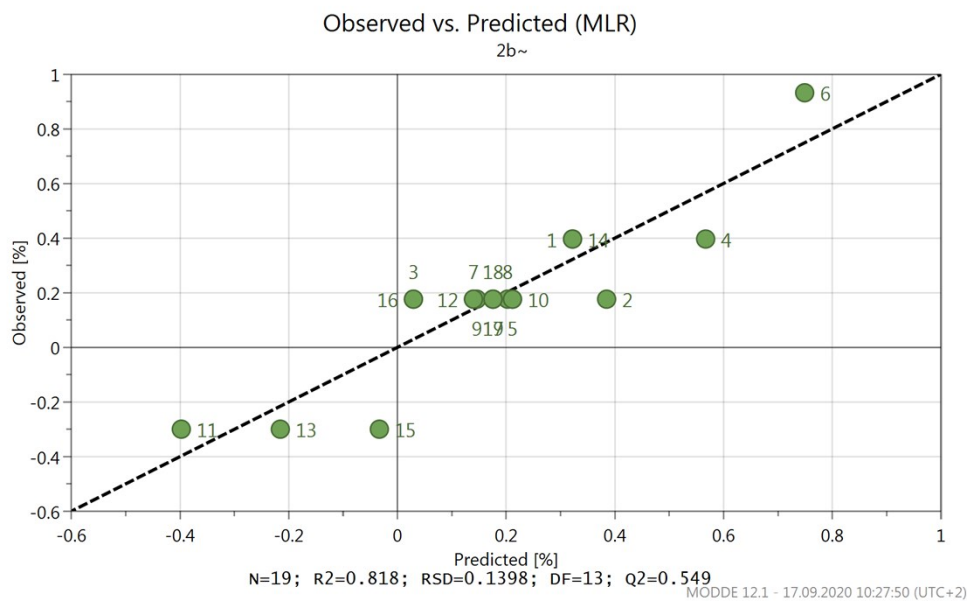


Fig. S11. Predicted vs actual results from DoE model for **2b**.

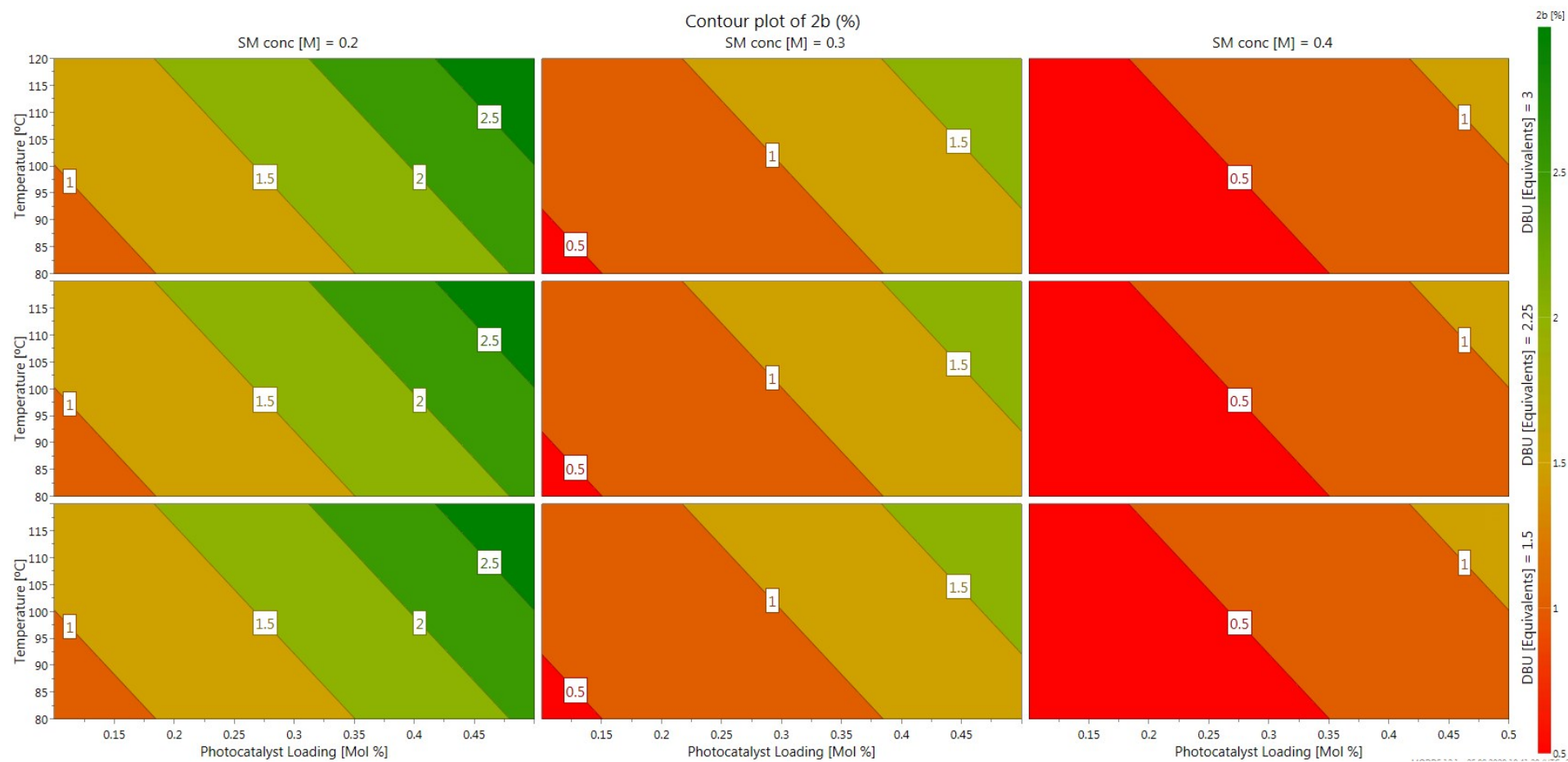


Fig. S12. Contour plot showing results from DoE for **2b**.

1b

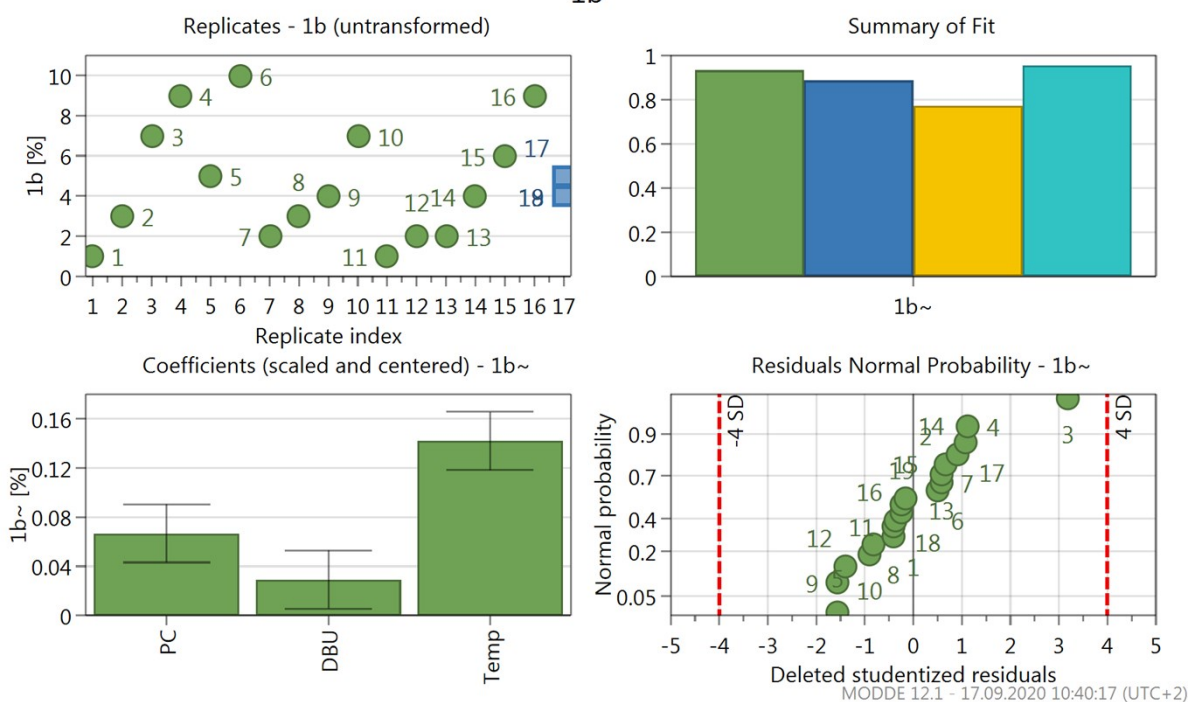


Fig. S13. Summary of DoE model for 1b.

Table S12. ANOVA of DoE model for 1b.

1b~	DF	SS	MS (variance)	F	p	SD
Total	19	14.3703	0.756331			
Constant	1	13.933	13.933			
Total corrected	18	0.437253	0.0242918			0.155858
Regression	3	0.407604	0.135868	68.7379	0.000	0.368603
Residual	15	0.0296492	0.00197661			0.0444591
Lack of Fit (Model error)	13	0.0274071	0.00210824	1.88064	0.400	0.0459156
Pure error (Replicate error)	2	0.00224205	0.00112102			0.0334817
	N = 19	Q2 =	0.886	Cond. no. =	1.09	
	DF = 15	R2 =	0.932	RSD =	0.04446	
		R2 adj. =	0.919			

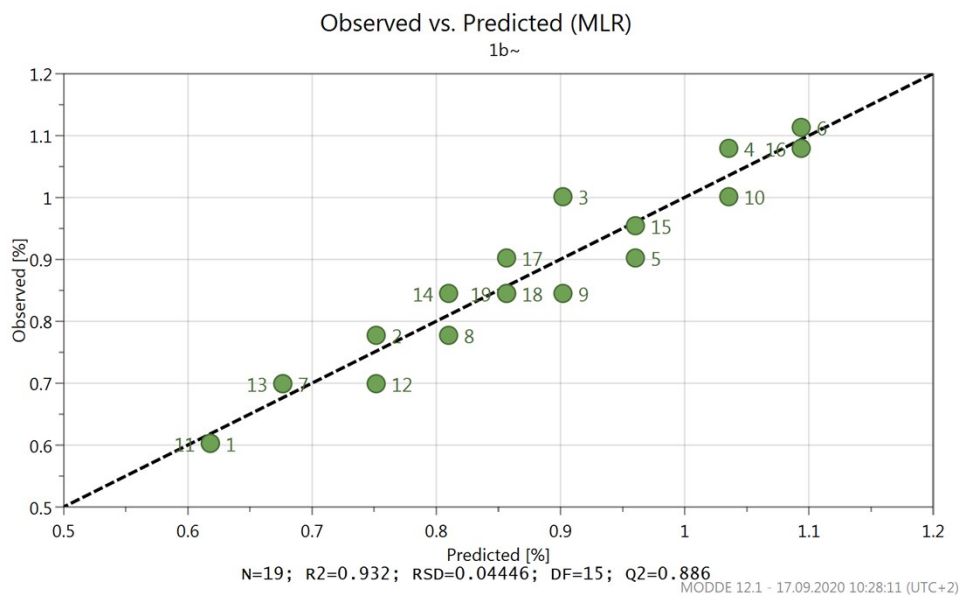


Fig. S14. Predicted vs actual results from DoE model for **1b**.

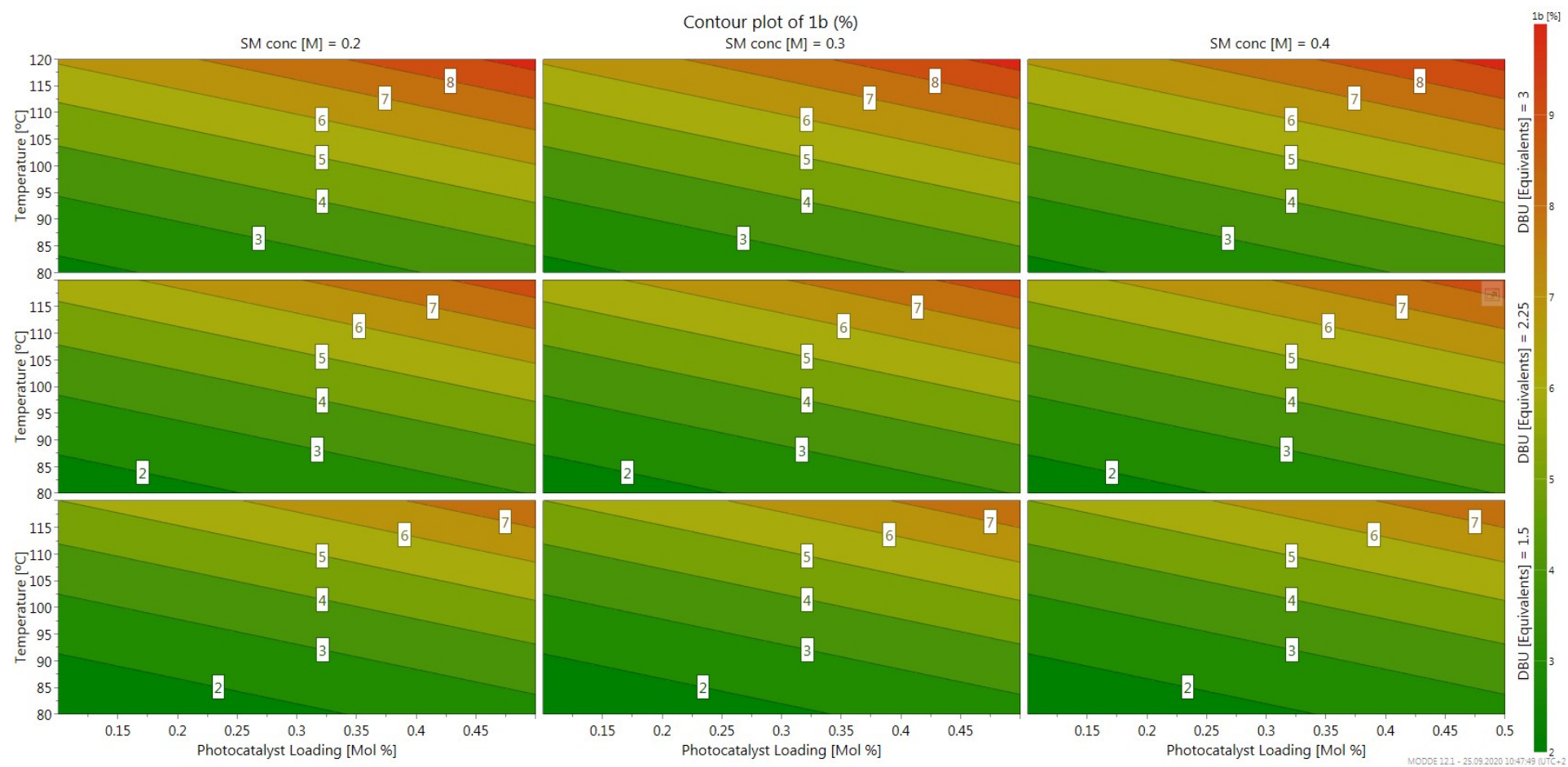


Fig. S15. Contour plot showing results from DoE for **1b**.

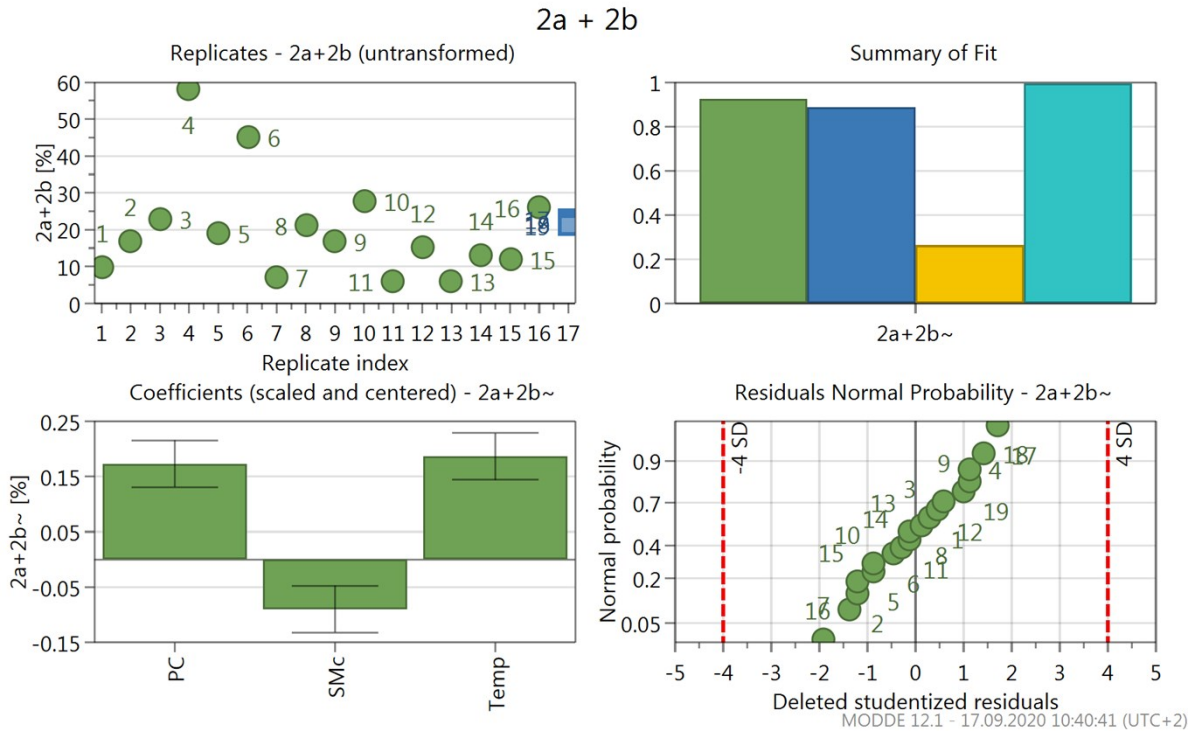


Fig. S16. Summary of DoE model for **2a + 2b**.

Table S13. ANOVA of DoE model for **2a + 2b**.

2a+2b~	DF	SS	MS (variance)	F	p	SD
Total	19	30.3236	1.59598			
Constant	1	29.0642	29.0642			
Total corrected	18	1.25938	0.0699656			0.26451
Regression	3	1.16537	0.388458	61.9824	0.000	0.623264
Residual	15	0.0940083	0.00626722			0.0791658
Lack of Fit (Model error)	13	0.0932278	0.00717137	18.374	0.053	0.0846839
Pure error (Replicate error)	2	0.000780598	0.000390299			0.019756
	N = 19	Q2 =	0.887	Cond. no. =	1.09	
	DF = 15	R2 =	0.925	RSD =	0.07917	
		R2 adj. =	0.910			

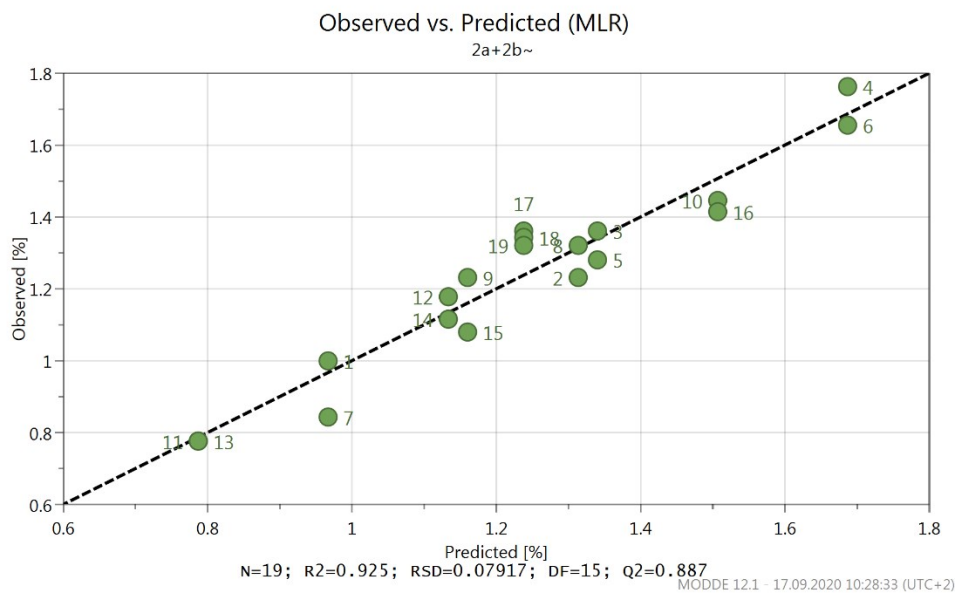


Fig. S17. Predicted vs actual results from DoE model for **2a + 2b**.

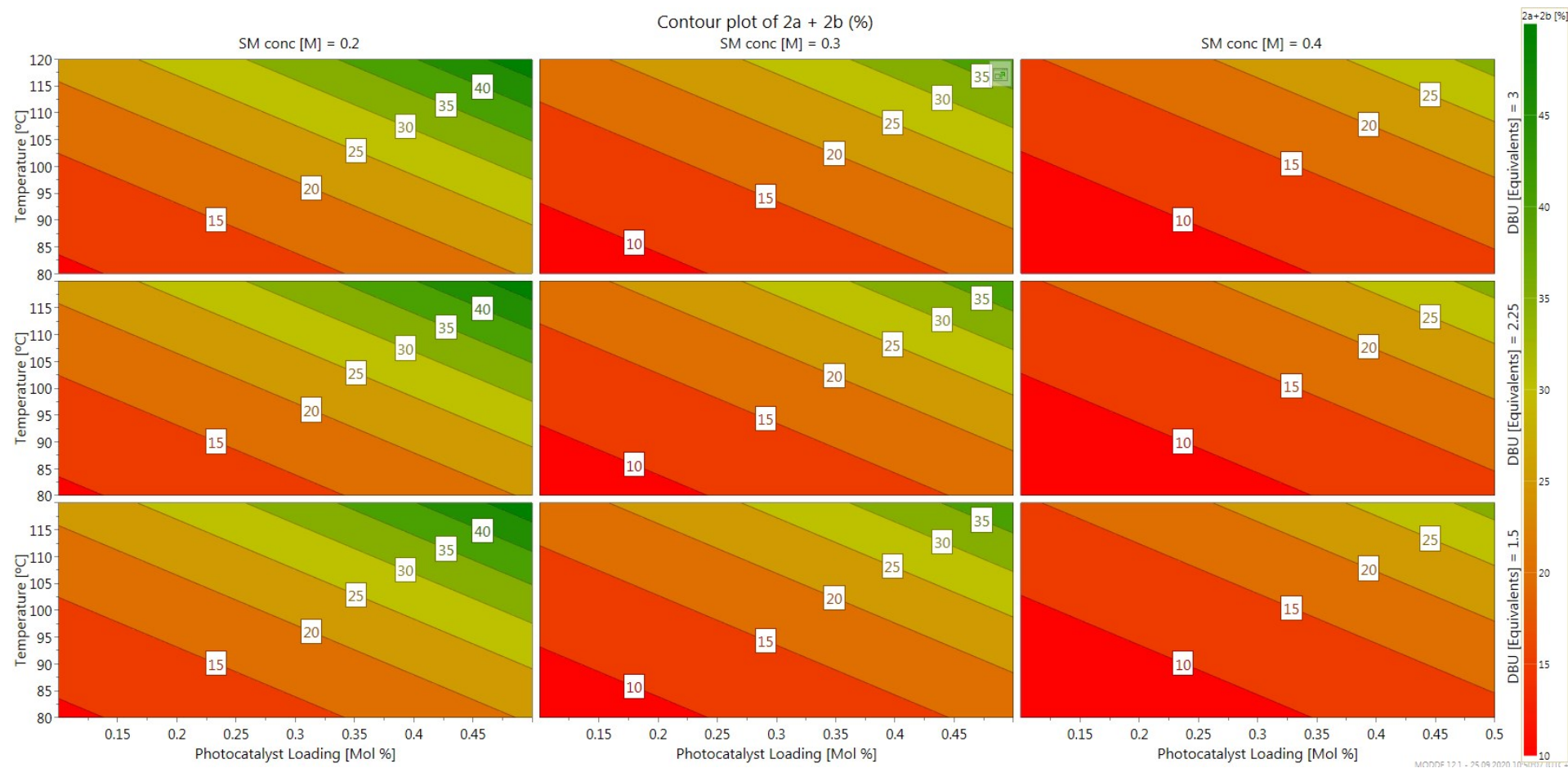
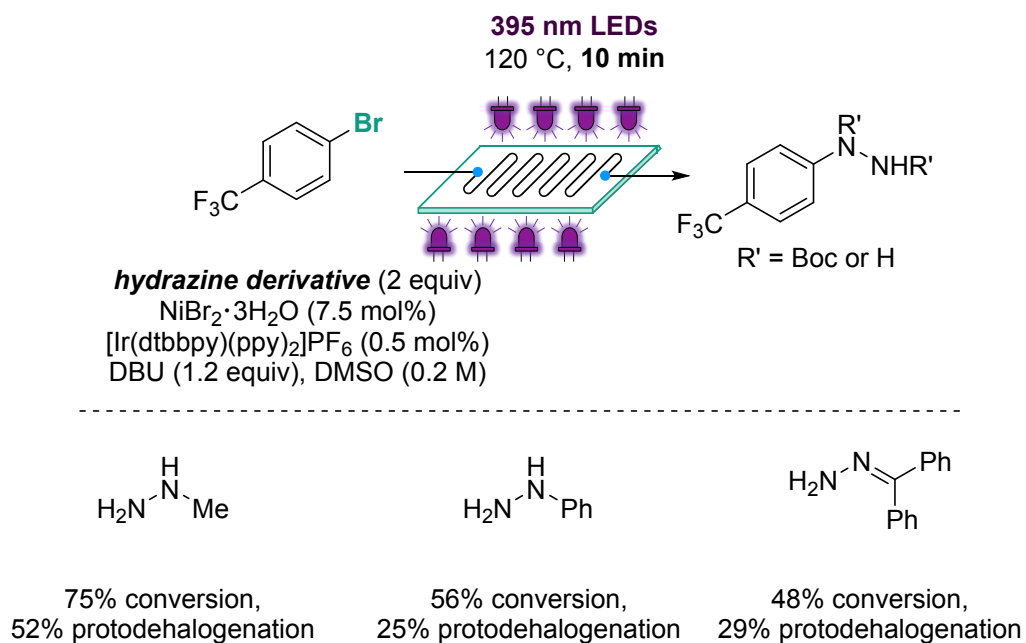
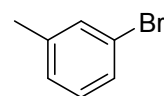
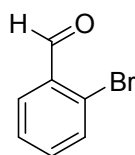
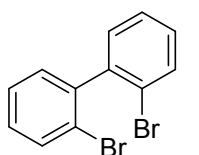
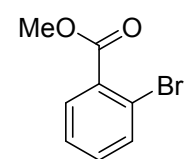
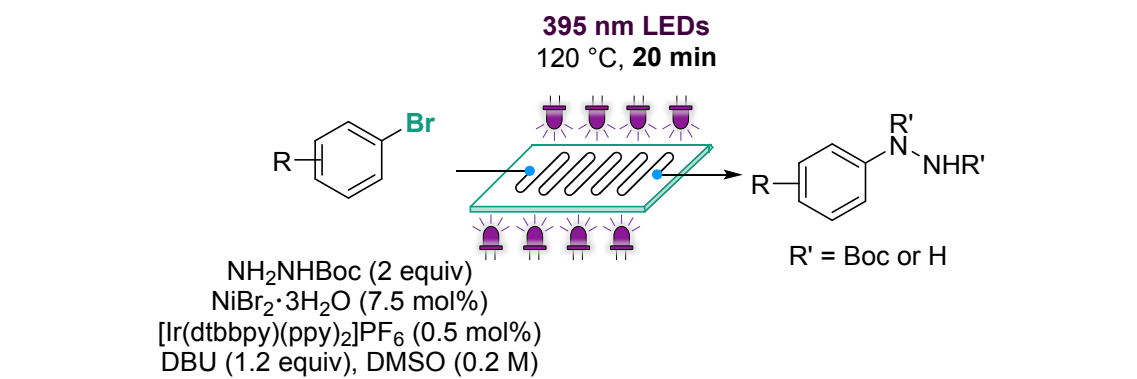


Fig. S18. Contour plot showing results from DoE for **2a + 2b**.

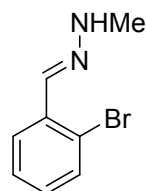
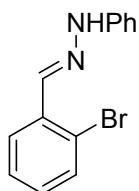
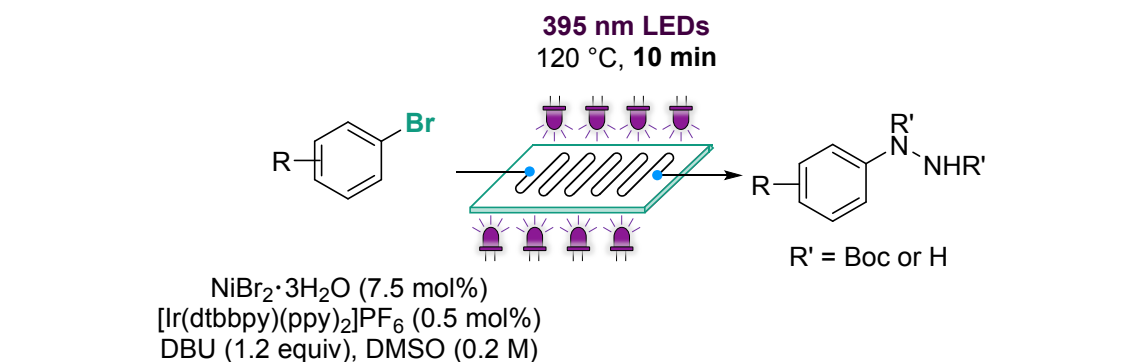
2.2.2. Incompatible reaction substrates



Scheme S1. Hydrazine-derived substrates found to give poor performance using the developed methodology.



Scheme S2. Aryl bromide substrates found to give poor performance using the developed methodology.



Scheme S3. Preformed hydrazone substrates found to give poor performance using the developed methodology.

2.2.3. Reactor fouling observed during scale-out experiments

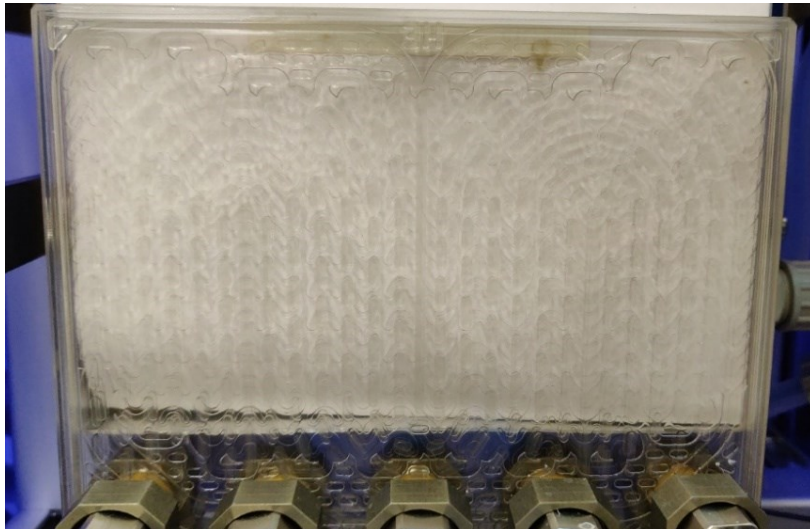


Fig. S19 Photograph of flow reactor prior to fouling

Table S14. Tabulated data from scale-out experiment a (manuscript Fig. 1b).

Time (min)	Conversion (%) ^a	1 (%) ^a	2a + 2b (%) ^a	1b (%) ^a
20	100	0	92	8
40	100	0	92	8
60	100	0	92	8
80	100	0	92	8
100	94	6	86	8
120	86	14	78	8
140	84	16	76	8
160	83	17	75	8
180	81	19	73	8
200	80	20	72	8
220	79	21	71	8
240	78	22	70	8
260	76	24	68	8
280	75	25	67	8
300	75	25	67	8
320	75	25	67	8
340	73	27	65	8

^aProduct ratios determined by integration of crude ¹⁹F NMR spectra.



Fig. S20 Photograph of flow reactor after running scale-out experiment a.

Table S15. Tabulated data from scale-out experiment b (manuscript Fig. 1c).

Time (min)	Conversion (%) ^a	1 (%) ^a	2a + 2b (%) ^a	1b (%) ^a
44	100	0	90	10
64	100	0	89	11
84	100	0	89	11
104	100	0	89	11
124	100	0	89	11
144	100	0	90	10
164	100	0	90	10
184	100	0	90	10
204	100	0	90	10
224	100	0	90	10
244	99	1	90	10
264	99	1	89	10
284	97	3	88	9
304	96	4	87	9
324	96	4	86	10
344	93	7	83	10
364	92	8	82	9

^aProduct ratios determined by integration of crude ¹⁹F NMR spectra.

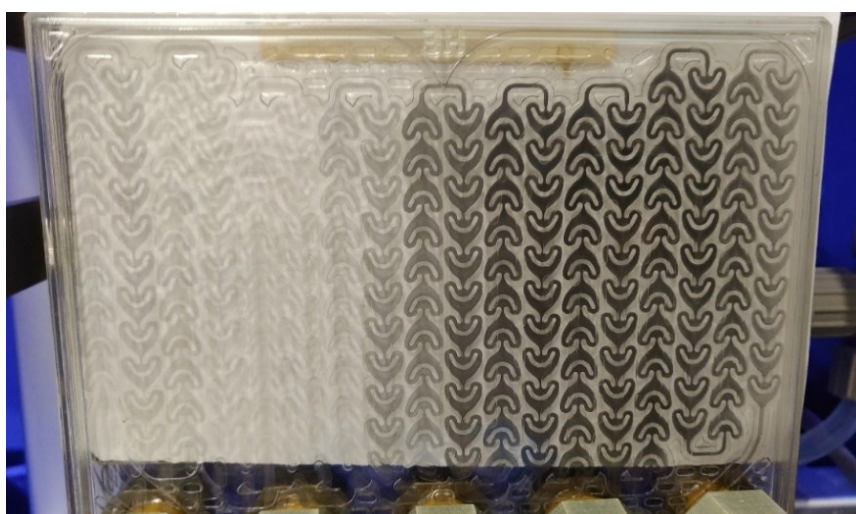
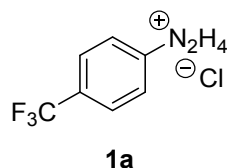


Fig. S21 Photograph of flow reactor after running scale-out experiment b.

3. Compound isolation and characterization

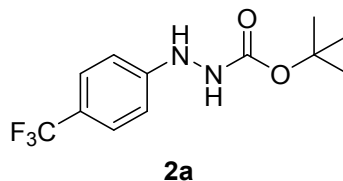
(4-(Trifluoromethyl)phenyl)hydrazine hydrochloride **1a**:^{S2}



The reaction mixture was processed using a residence time of 10 min. The material from Boc deprotection was washed with Et₂O to yield the desired product **1a** (183 mg, 86%) as a beige solid.

¹H NMR (300 MHz, D₂O) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (75 MHz, D₂O) δ 146.9-146.8 (m), 126.8 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 269.0 Hz), 124.1 (q, *J* = 32.7 Hz), 114.2; ¹⁹F NMR (282 MHz, D₂O) -61.7; mp 160 °C (decomp); IR v_{max} (cm⁻¹): 3230 (br, NH), 1619 (m, C=C), 1593 (m, C=C), 1567 (m, C=C), 1537 (m, C=C), 1322 (s, C-N), 1134 (s, C-F), 1112 (s, C-F), 1071 (s, N-N); HRMS (ESI, positive mode) calculated for C₇H₈F₃N₂ (M+H)⁺: 177.0634, found: 177.0643.

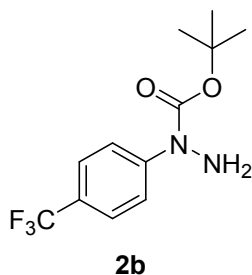
tert-Butyl 2-(4-(trifluoromethyl)phenyl)hydrazine-1-carboxylate **2a**:



The reaction mixture was processed using a residence time of 10 min. The intermediate material (no Boc deprotection carried out) was purified by flash column chromatography, elution gradient 0-25% EtOAc in cyclohexane, to yield the desired products **2a** as a white solid and **2b** as a colorless oil.

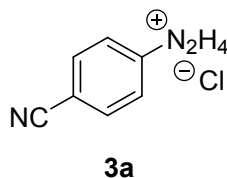
¹H NMR (300 MHz, DMSO) δ 8.95 (br s, 1H), 8.24 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 1.42 (s, 9H); ¹⁹F NMR (282 MHz, DMSO) δ -59.2.

tert-Butyl 1-(4-(trifluoromethyl)phenyl)hydrazine-1-carboxylate 2b:



^1H NMR (300 MHz, DMSO) δ 7.76 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 5.17 (s, 2H), 1.48 (s, 9H); ^{19}F NMR (282 MHz, DMSO) δ -60.3.

4-Hydrazinylbenzonitrile hydrochloride 3a:^{S3}



From aryl bromide, **3**:

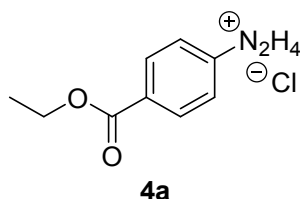
The reaction mixture was processed using a residence time of 10 min. The material from Boc deprotection was washed with MeCN to yield the desired product **3a** (143 mg, 83%) as a beige solid.

From aryl chloride, **3'**:

The reaction mixture was processed using a residence time of 20 min. The material from Boc deprotection was washed with MeCN to yield the desired product **3a** (110 mg, 65%) as a beige solid.

^1H NMR (300 MHz, DMSO) δ 10.77 (s, 3H), 7.69 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.75 (s, 5H); ^{13}C NMR (75 MHz, DMSO) δ 149.5, 133.3, 119.5, 113.9, 102.0; mp 202 °C (decomp), Lit.: 240 °C; IR ν_{max} (cm^{-1}): 3210 (br, N-H), 2236 (w, $\text{C}\equiv\text{N}$), 1613 (m, $\text{C}=\text{C}$), 1586 (m, $\text{C}=\text{C}$), 1088 (s, N-N); HRMS (ESI, positive mode) calculated for $\text{C}_7\text{H}_8\text{N}_3$ ($\text{M}+\text{H}$) $^+$: 134.0711, found: 134.0713.

Ethyl 4-hydrazinylbenzoate hydrochloride **4a**:^{S4}

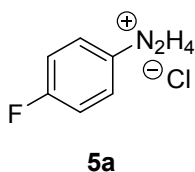


The reaction mixture was processed using a residence time of 10 min. The material from Boc deprotection was washed with Et₂O to yield the desired product **4a** (210 mg, 95%) as a beige solid.

¹H NMR (300 MHz, D₂O) δ 8.01 – 7.94 (m, 2H), 7.04 – 6.94 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, D₂O) δ 168.5, 148.3, 131.2, 123.7, 113.5, 62.0, 13.4; mp 182 °C (decomp), Lit.: 223-226 °C; IR v_{max} (cm⁻¹): 3214 (br, NH), 1711 (s, C=O), 1614 (w, C=C), 1585 (m, C=C), 1275 (s, C-N), 1092 (s, N-N); HRMS (ESI, positive mode) calculated for C₉H₁₃N₂O₂ (M+H)⁺: 181.0972, found: 181.0973.

Note: in the ¹H NMR spectrum, the water signal is thought to overlap with the signal at 7.32, giving the appearance of additional protons.

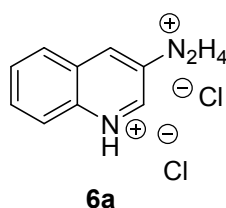
(4-Fluorophenyl)hydrazine hydrochloride **5a**:^{S5}



The reaction mixture was processed using a residence time of 20 min. The material from Boc deprotection was washed with Et₂O to yield the desired product **5a** (100 mg, 62%) as a beige solid.

¹H NMR (300 MHz, DMSO) δ 10.36 (s, 2H), 7.19 (br s, 2H) 7.15 – 7.03 (m, 4H); ¹³C NMR (75 MHz, DMSO) δ 157.36 (d, *J* = 237.1 Hz), 142.08 (d, *J* = 2.1 Hz), 116.49 (d, *J* = 7.9 Hz), 115.45 (d, *J* = 22.6 Hz); ¹⁹F NMR (282 MHz, DMSO) δ -122.7; mp 205 °C (decomp); IR v_{max} (cm⁻¹): 3207 (m, N-H), 1615 (m, C=C), 1590 (m, C=C), 1517 (m, C=C), 1497 (m, C=C), 1248 (m, C-F), 1095 (m, N-N); HRMS (ESI, positive mode) calculated for C₆H₈FN₂ (M+H)⁺: 127.0666, found: 127.0668.

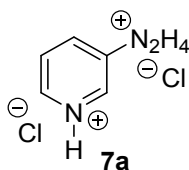
3-Hydrazinylquinoline dihydrochloride **6a**:



The reaction mixture was processed using a residence time of 20 min. Prior to Boc deprotection, the intermediate material was purified by flash column chromatography, elution gradient 0-10% MeOH in DCM. The material from Boc deprotection was washed with MeCN to yield the desired product **6a** (81 mg, 36%) as a beige solid.

^1H NMR (300 MHz, D_2O) δ 8.94 (d, $J = 2.7$ Hz, 1H), 8.53 (d, $J = 2.7$ Hz, 1H), 8.14 (dd, $J = 13.8$, 8.2 Hz, 2H), 8.00 – 7.93 (m, 1H), 7.92 – 7.84 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 138.6, 135.0, 133.9, 133.0, 130.8, 129.2, 128.0, 126.7, 120.0; HRMS (ESI, positive mode) calculated for $\text{C}_9\text{H}_{10}\text{N}_3$ ($\text{M}+\text{H}$) $^+$: 160.0869, found: 160.0872.

3-Hydrazinylpyridine dihydrochloride **7a**:^{S6}

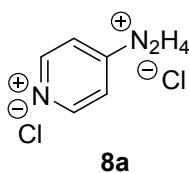


The reaction mixture was processed using a residence time of 20 min. The material from Boc deprotection was washed with MeCN to yield the desired product **7a** (128 mg, 70%) as a beige solid.

^1H NMR (300 MHz, DMSO) δ 9.74 (s, 1H), 8.52 (d, $J = 2.2$ Hz, 1H), 8.43 (d, $J = 5.3$ Hz, 1H), 8.10 (d, $J = 8.6$ Hz, 1H), 7.96 – 7.91 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 145.0, 133.4, 129.2, 127.1, 126.7; mp 187 °C (decomp), Lit.: 181-183 °C; IR ν_{max} (cm^{-1}): 3396 (br, N-H), 3193 (br, N-H), 1633 (m, C=N), 1556 (m, C=C), 1477 (m, C=C), 1454 (m, C=C), 1342 (m, C-N), 1170 (m, N-N); HRMS (ESI, positive mode) calculated for $\text{C}_5\text{H}_8\text{N}_3$ ($\text{M}+\text{H}$) $^+$: 110.0713, found: 110.0714.

Note: multiple exchangeable H signals were not observed in ^1H NMR spectrum.

4-Hydrazinylpyridine dihydrochloride **8a**:



From aryl bromide, **8**:

The reaction mixture was processed using a residence time of 10 min. The material from Boc deprotection was washed with MeCN to yield the desired product **8a** (140 mg, 77%) as a white solid.

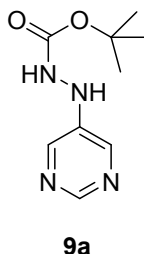
From aryl chloride, **8'**:

The reaction mixture was processed using a residence time of 20 min. The material from Boc deprotection was washed with MeCN to yield the desired product **8a** (120 mg, 66%) as a pale yellow solid.

^1H NMR (300 MHz, D_2O) δ 8.28 (d, $J = 7.5$ Hz, 2H), 7.12 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, D_2O) δ 156.9, 140.6, 107.2; mp 235 °C (decomp); IR ν_{max} (cm^{-1}): 3213 (br, N-N), 1632 (s, C=N), 1600 (m, C=C), 1530 (m, C=C), 1341 (m, C-N), 1086 (s, N-N); HRMS (ESI, positive mode) calculated for $\text{C}_5\text{H}_8\text{N}_3$ ($\text{M}+\text{H}$) $^+$: 110.0713, found: 110.0713.

Note: multiple exchangeable H signals were not observed in the ^1H NMR spectrum.

tert-Butyl 2-(pyrimidin-5-yl)hydrazine-1-carboxylate **9a**:



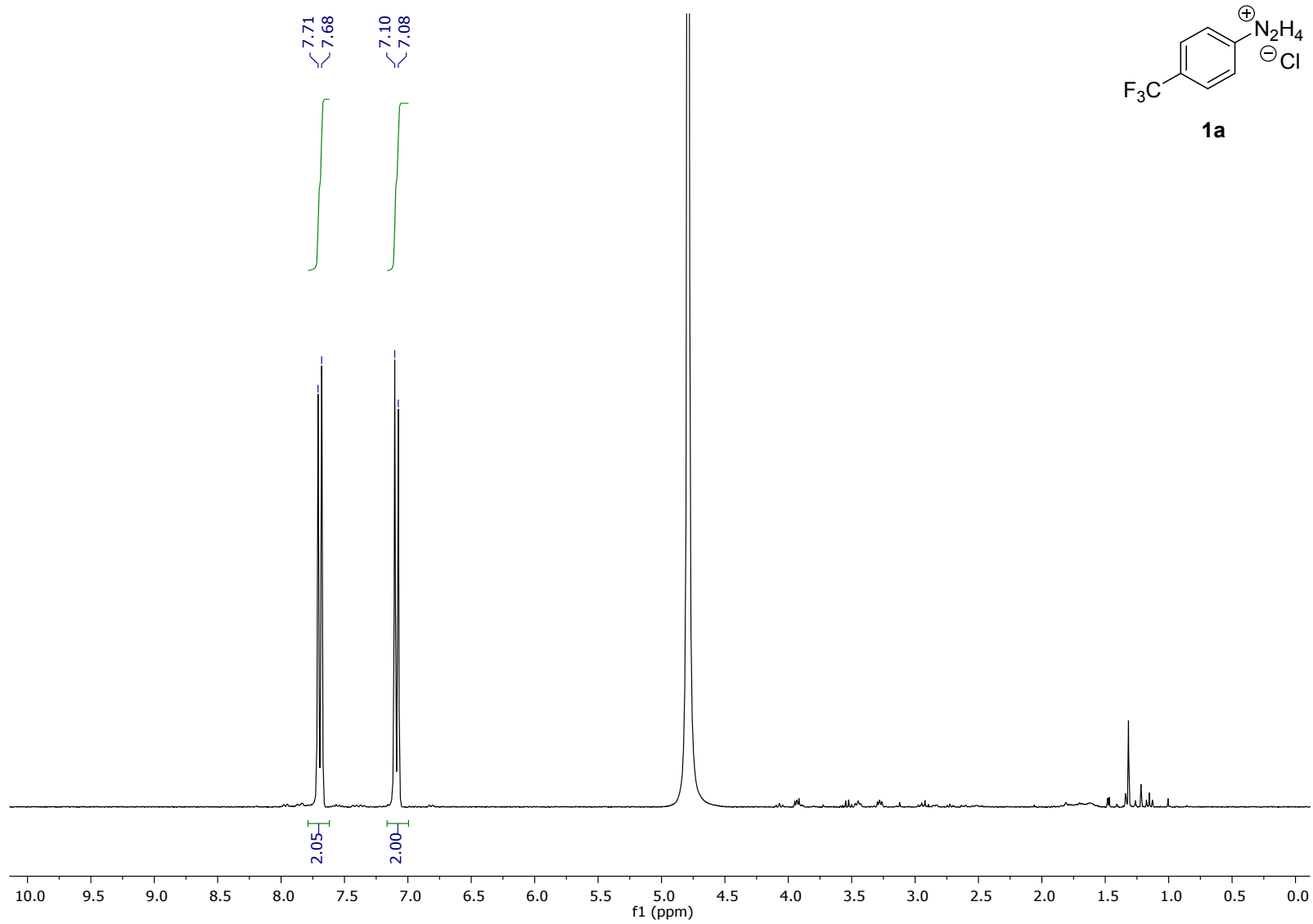
The reaction mixture was processed using a residence time of 20 min. The Boc deprotected product was found to be unstable, so the intermediate material was purified by flash column chromatography, elution gradient 0-10% MeOH in DCM, to yield the desired product **9a** (50 mg, 25%) as a red oil.

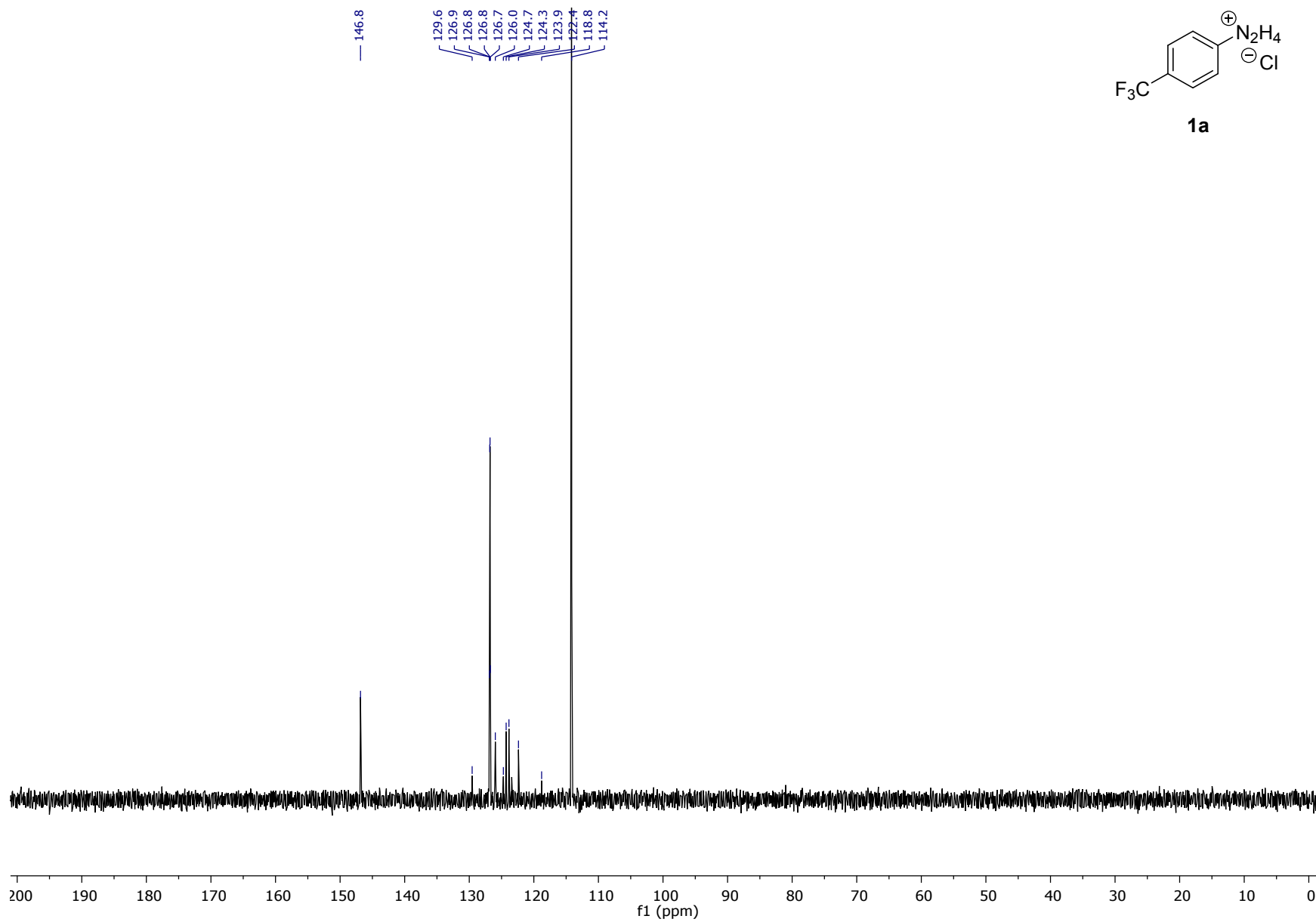
^1H NMR (300 MHz, DMSO) δ 9.00 (s, 1H), 8.55 (s, 1H), 8.18-8.10 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, DMSO) δ 155.8, 149.1, 143.3, 140.2, 79.5, 28.0; HRMS (ESI, positive mode) calculated for $\text{C}_9\text{H}_{15}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 211.1190, found: 211.1193.

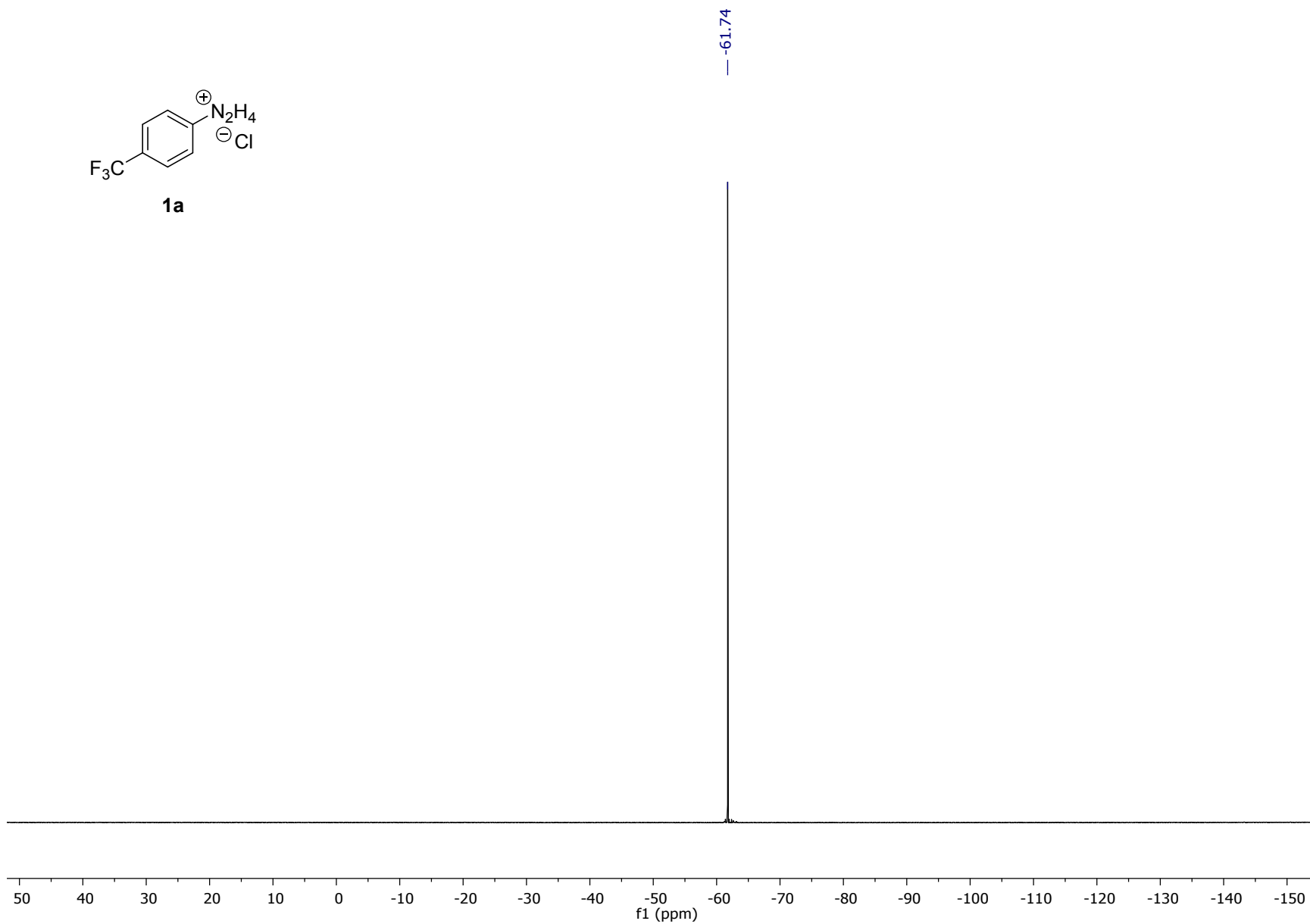
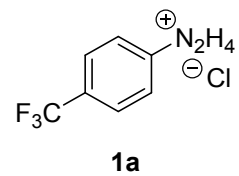
4. References

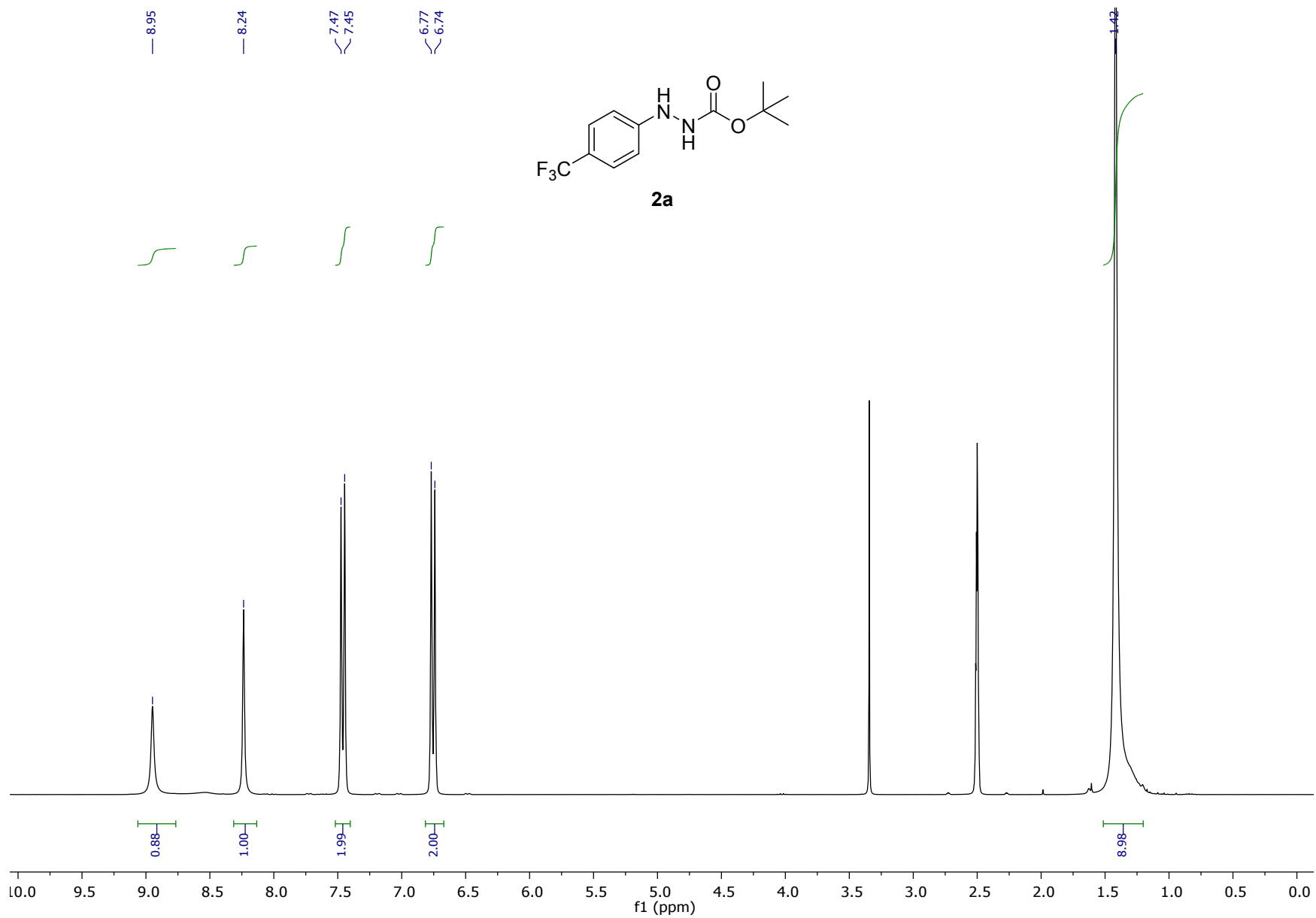
- S1 This nickel species was synthesized as per the following report: Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. Degruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minter and P. S. Baran, *J. Am. Chem. Soc.*, 2019, **141**, 6392–6402.
- S2 K. Muralirajan, R. Haridharan, S. Prakash and C. H. Cheng, *Adv. Synth. Catal.*, 2015, **357**, 761–766.
- S3 N. M. Gallagher, J. J. Bauer, M. Pink, S. Rajca and A. Rajca, *J. Am. Chem. Soc.*, 2016, **138**, 9377–9380.
- S4 J. Restrepo, C. Glidewell, N. Cubillán, Y. Alvarado, N. Dege and M. Morales-Toyo, *J. Mol. Struct.*, 2019, **1177**, 363–370.
- S5 W. Wu, X. H. Fan, L. P. Zhang and L. M. Yang, *RSC Adv.*, 2014, **4**, 3364–3367.
- S6 B. J. Simmons, M. Hoffmann, P. A. Champagne, E. Picazo, K. Yamakawa, L. A. Morrill, K. N. Houk and N. K. Garg, *J. Am. Chem. Soc.*, 2017, **139**, 14833–14836.

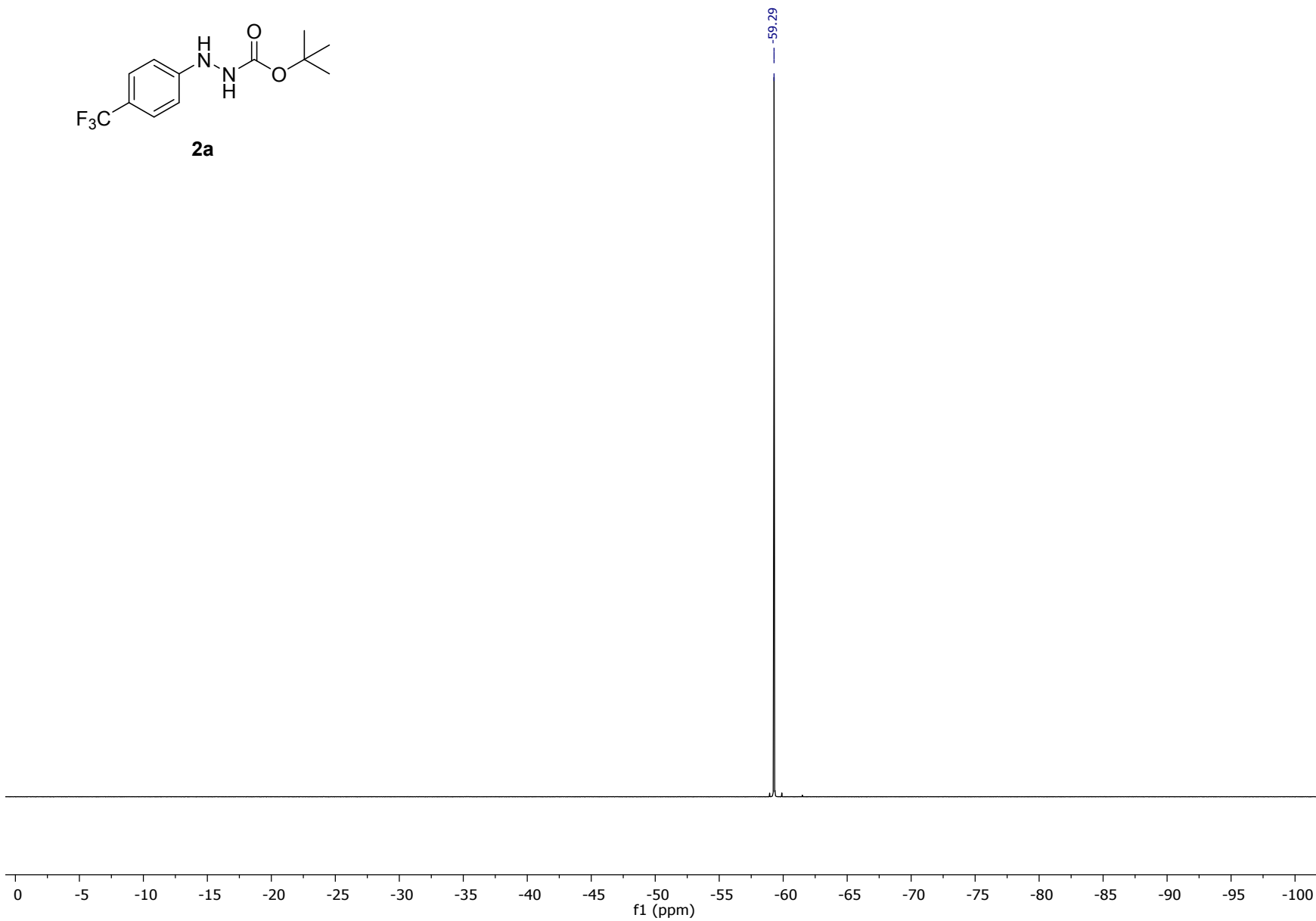
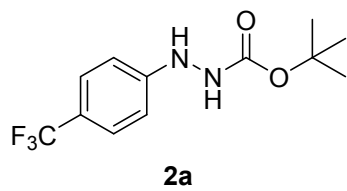
5. NMR Spectra

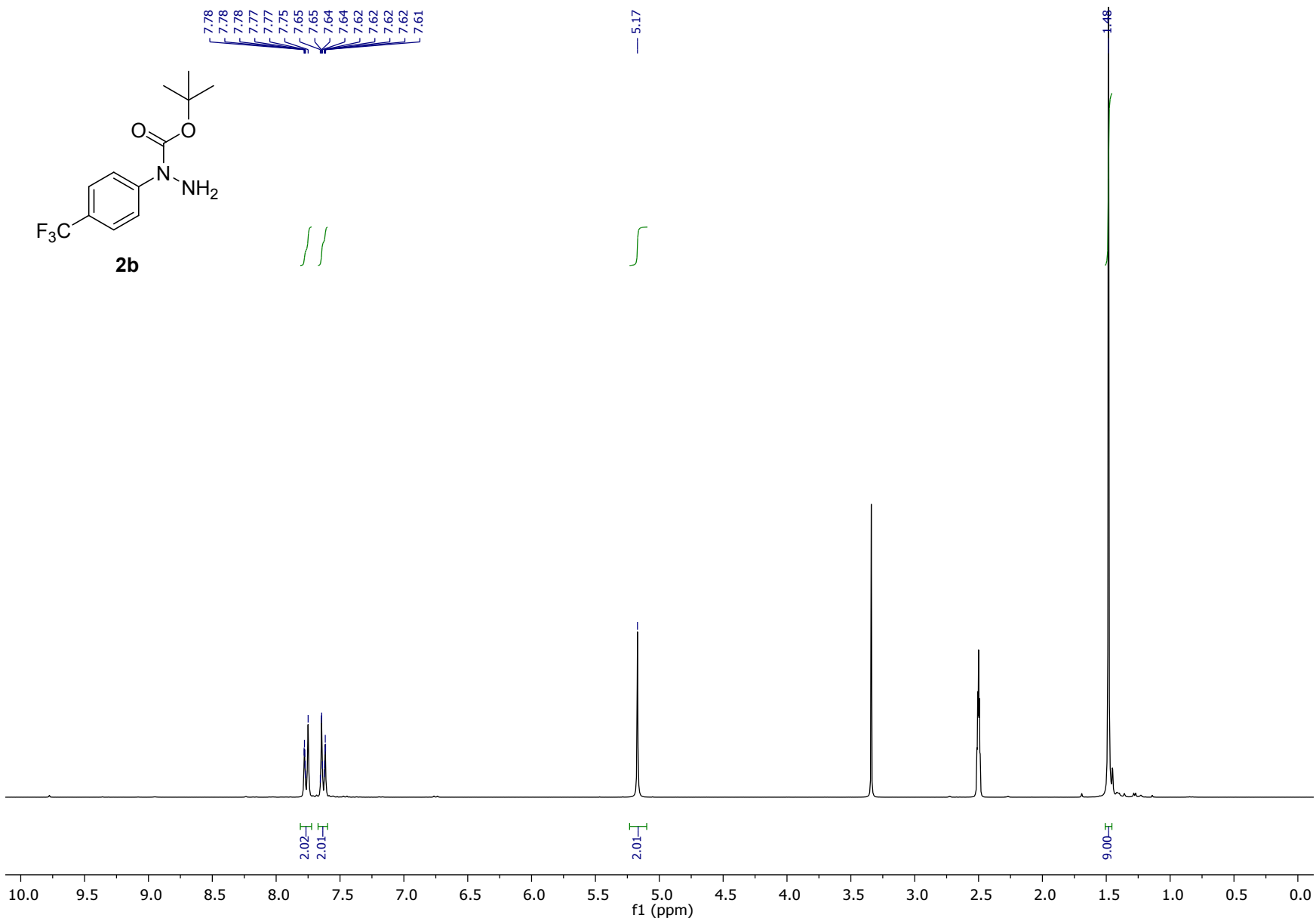


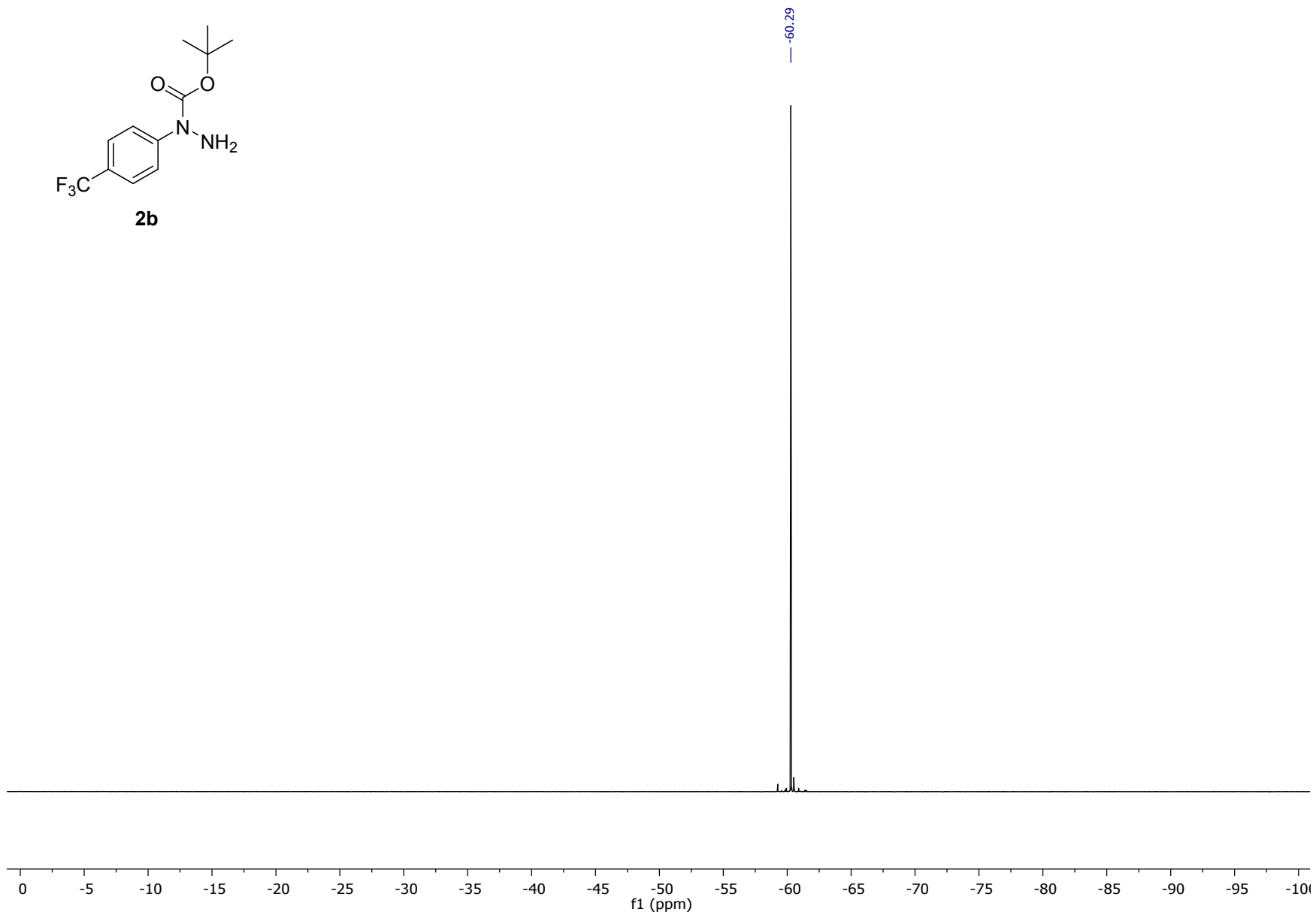
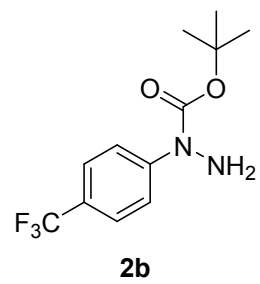


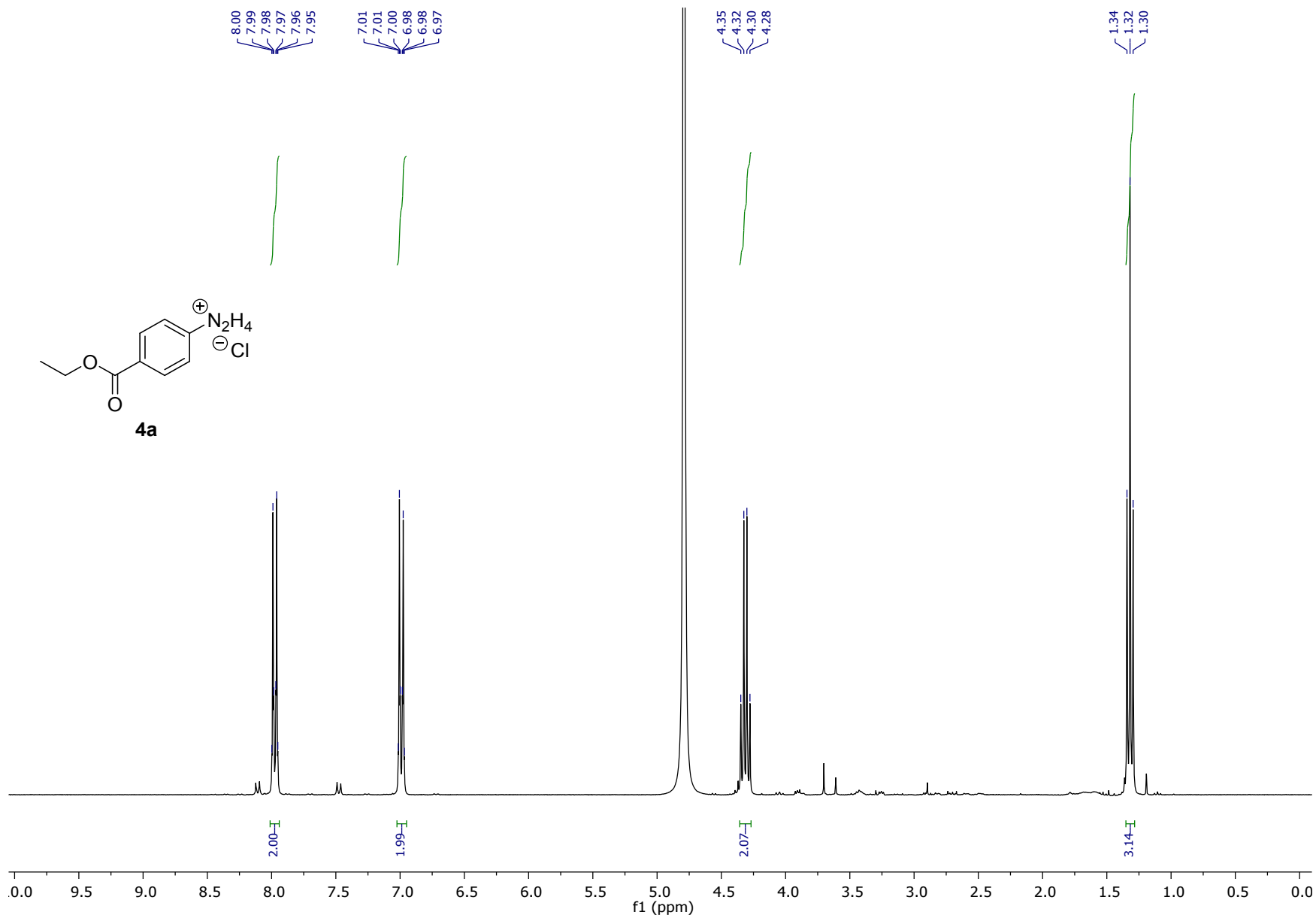


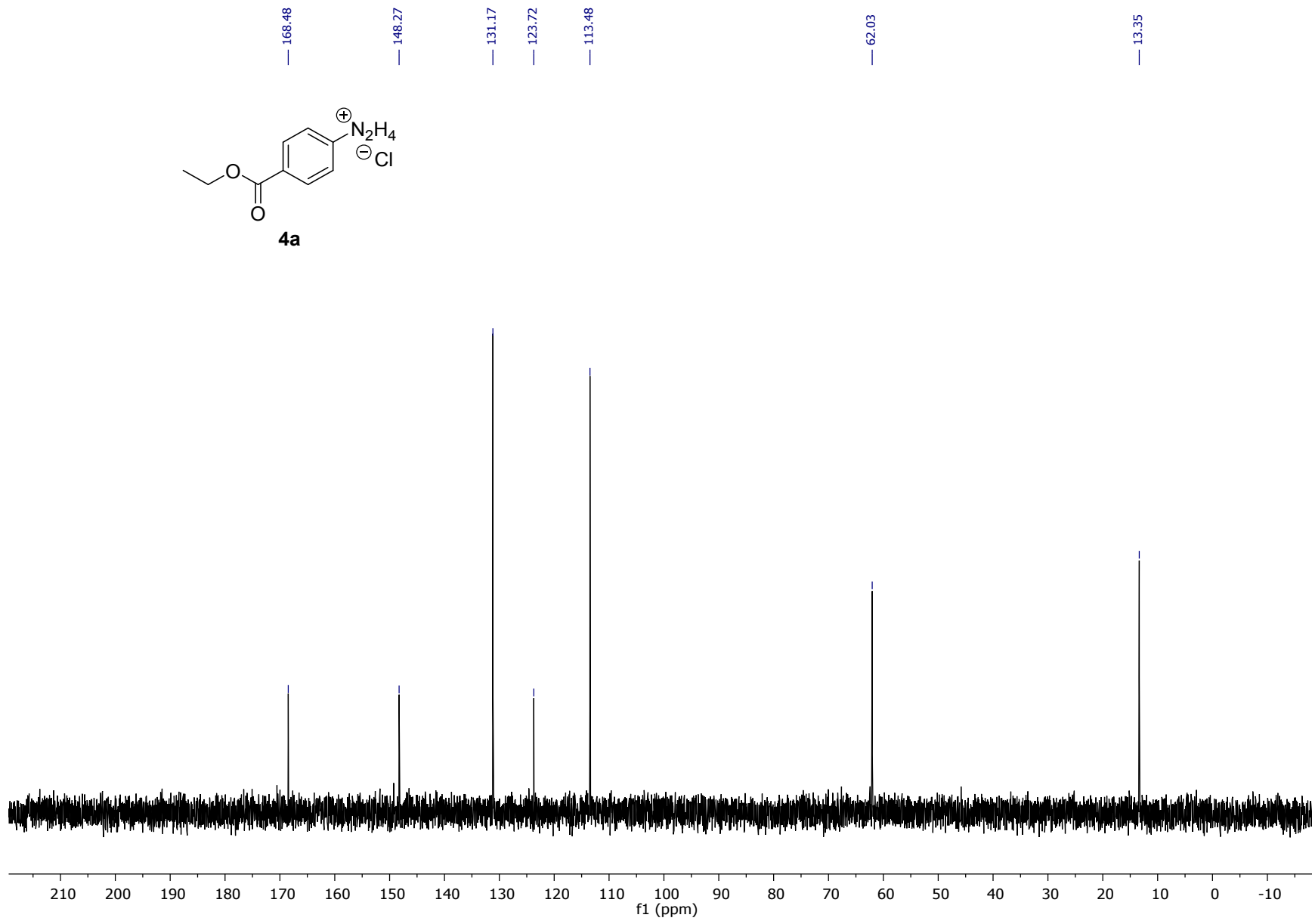
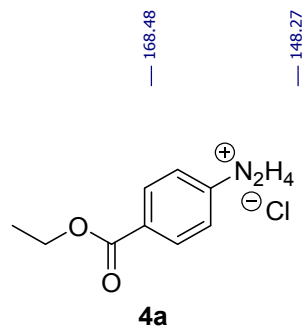


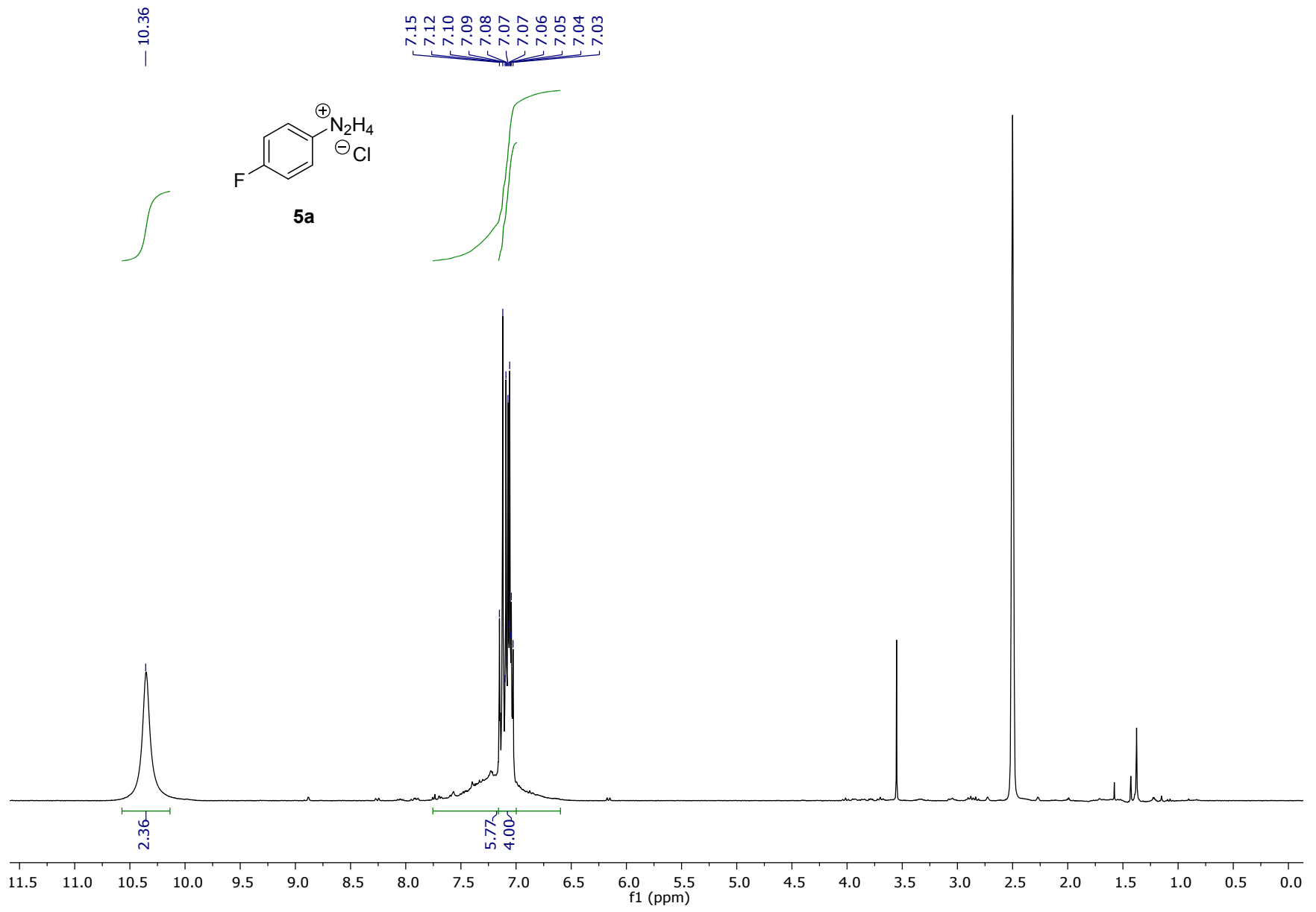


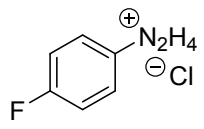




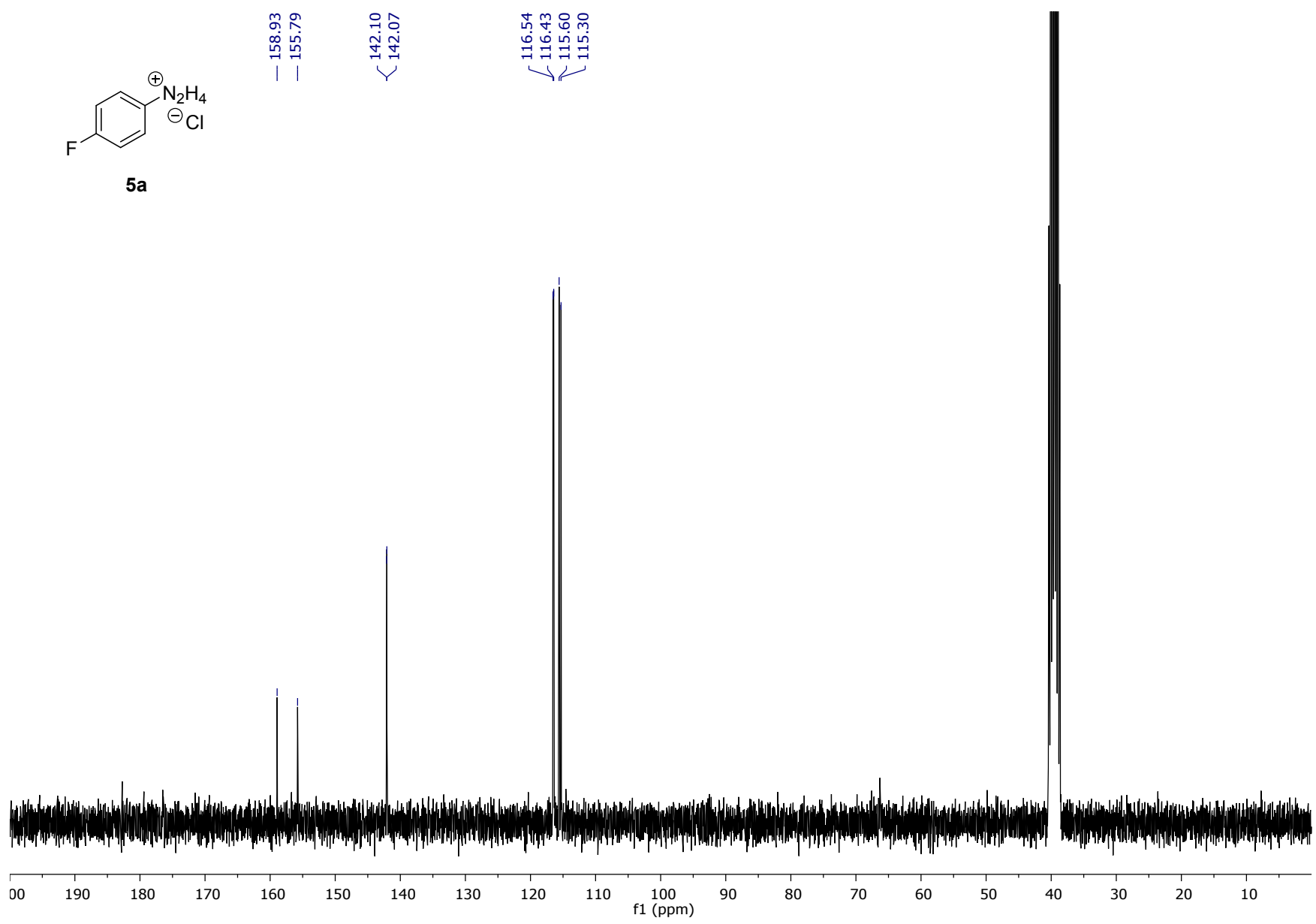


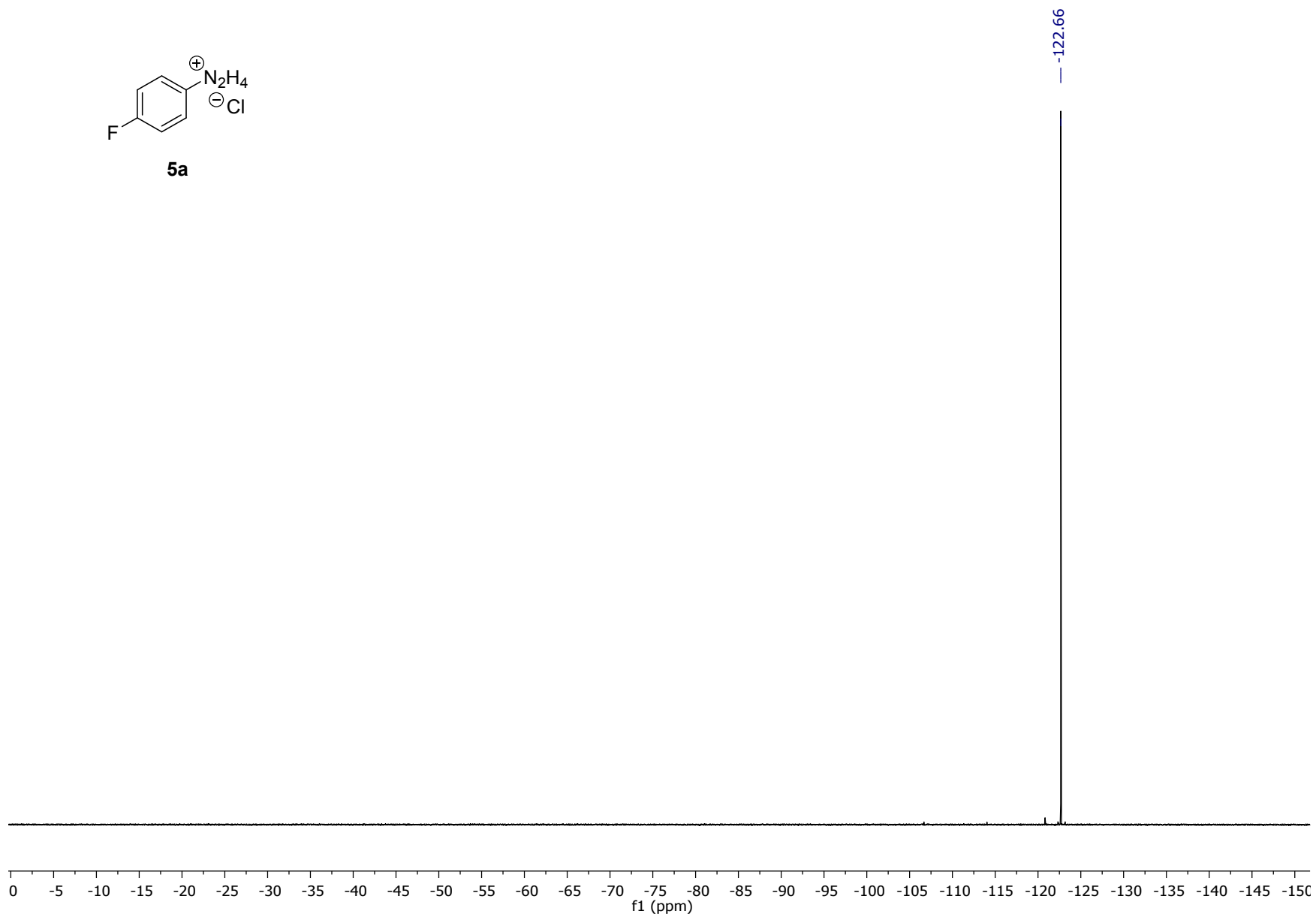
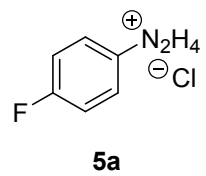


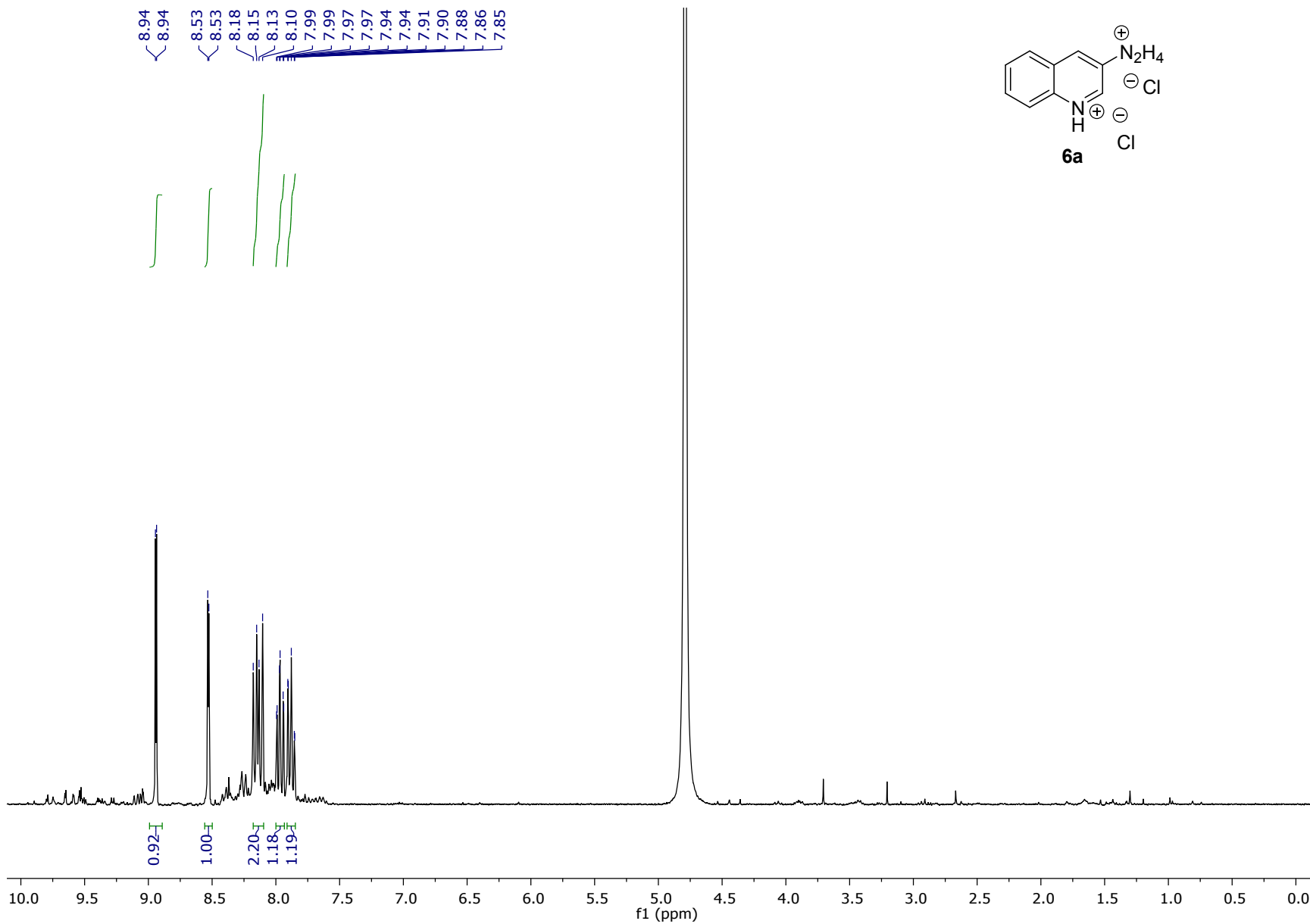




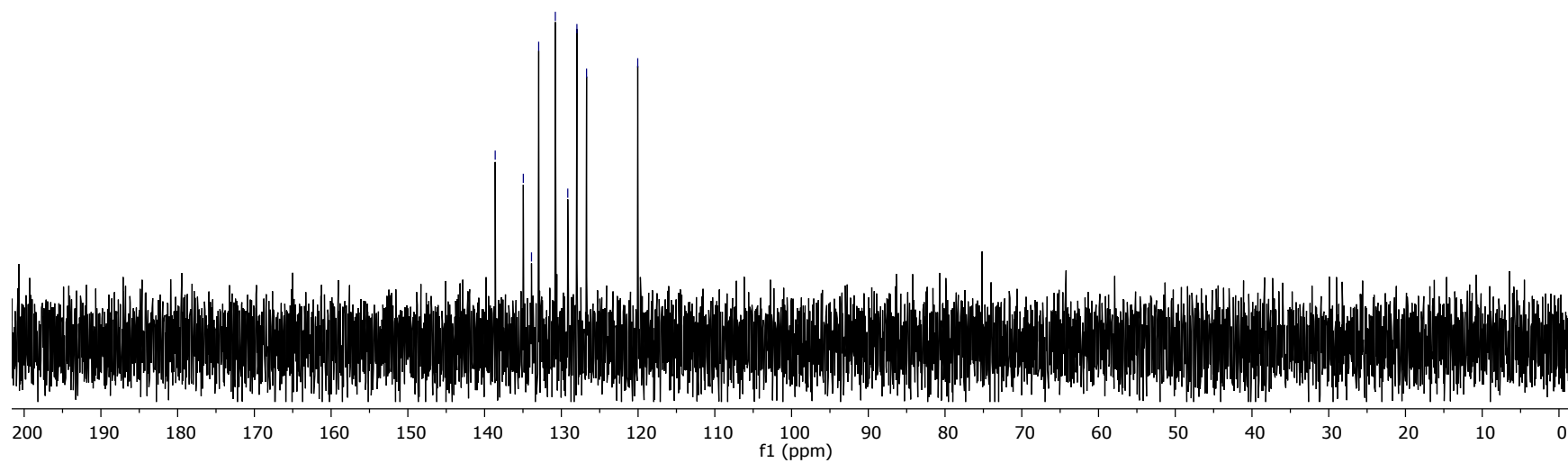
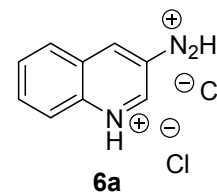
5a

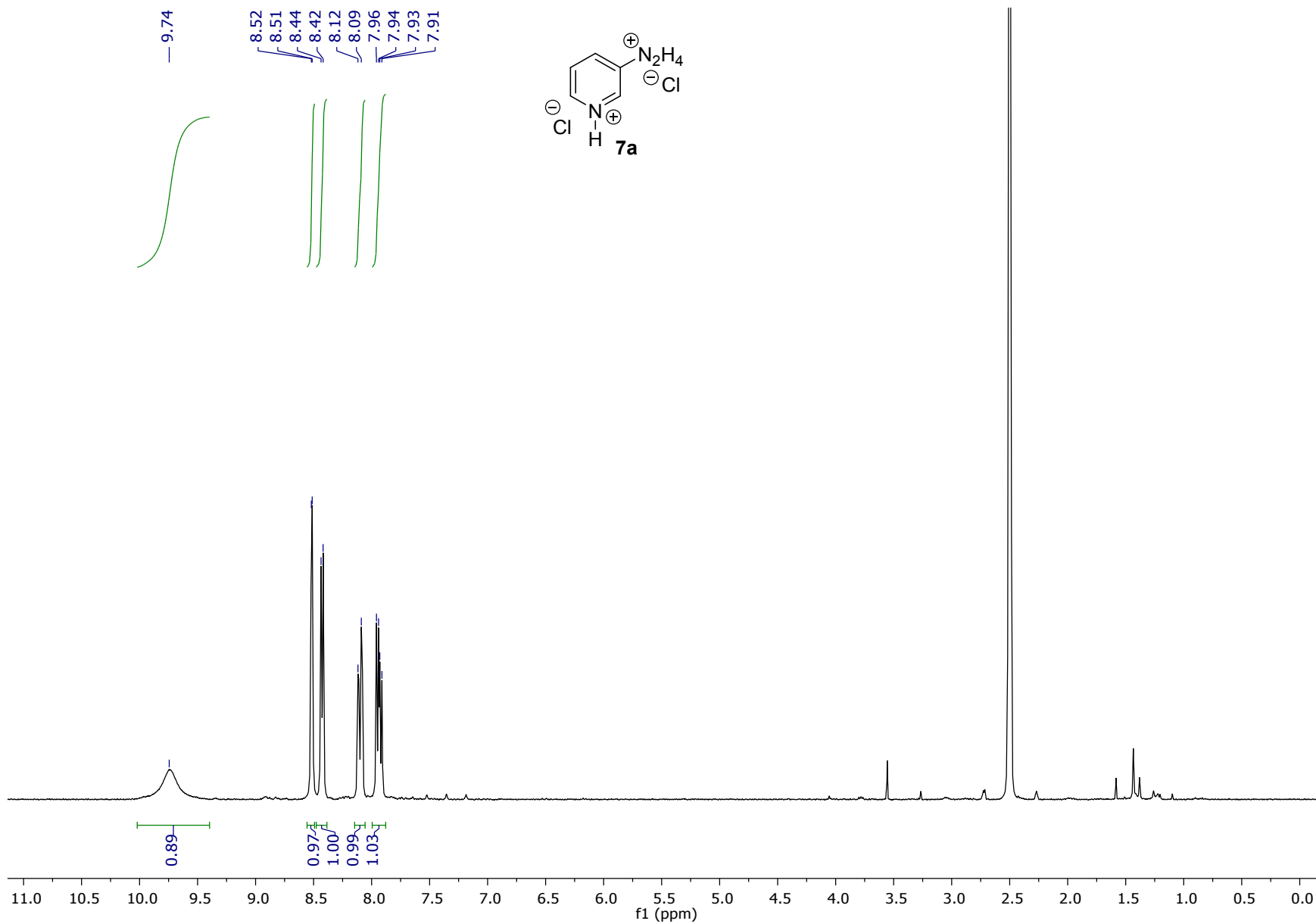


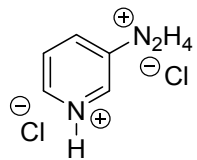




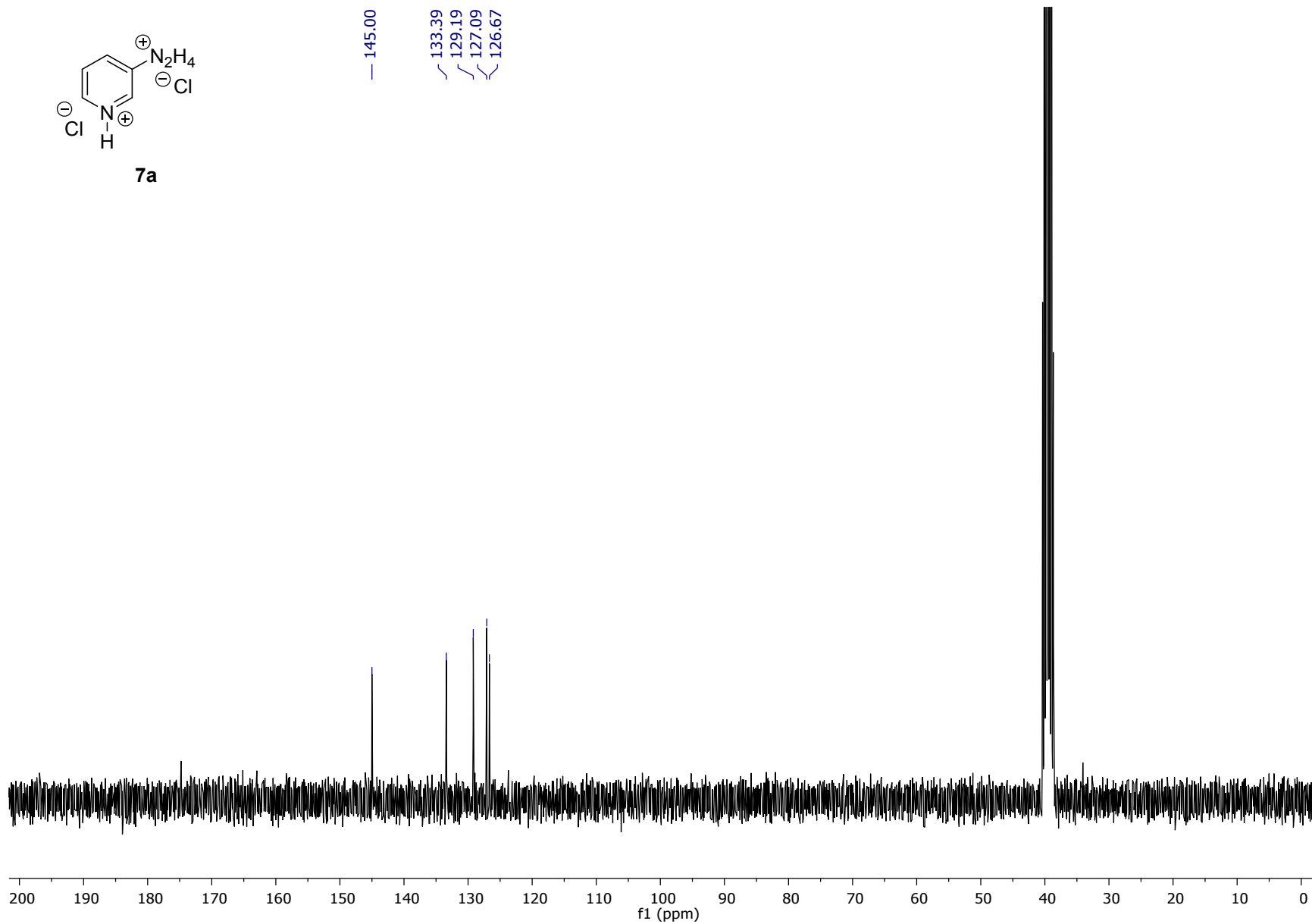
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133.89
132.95
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129.16
127.97
126.71
120.04

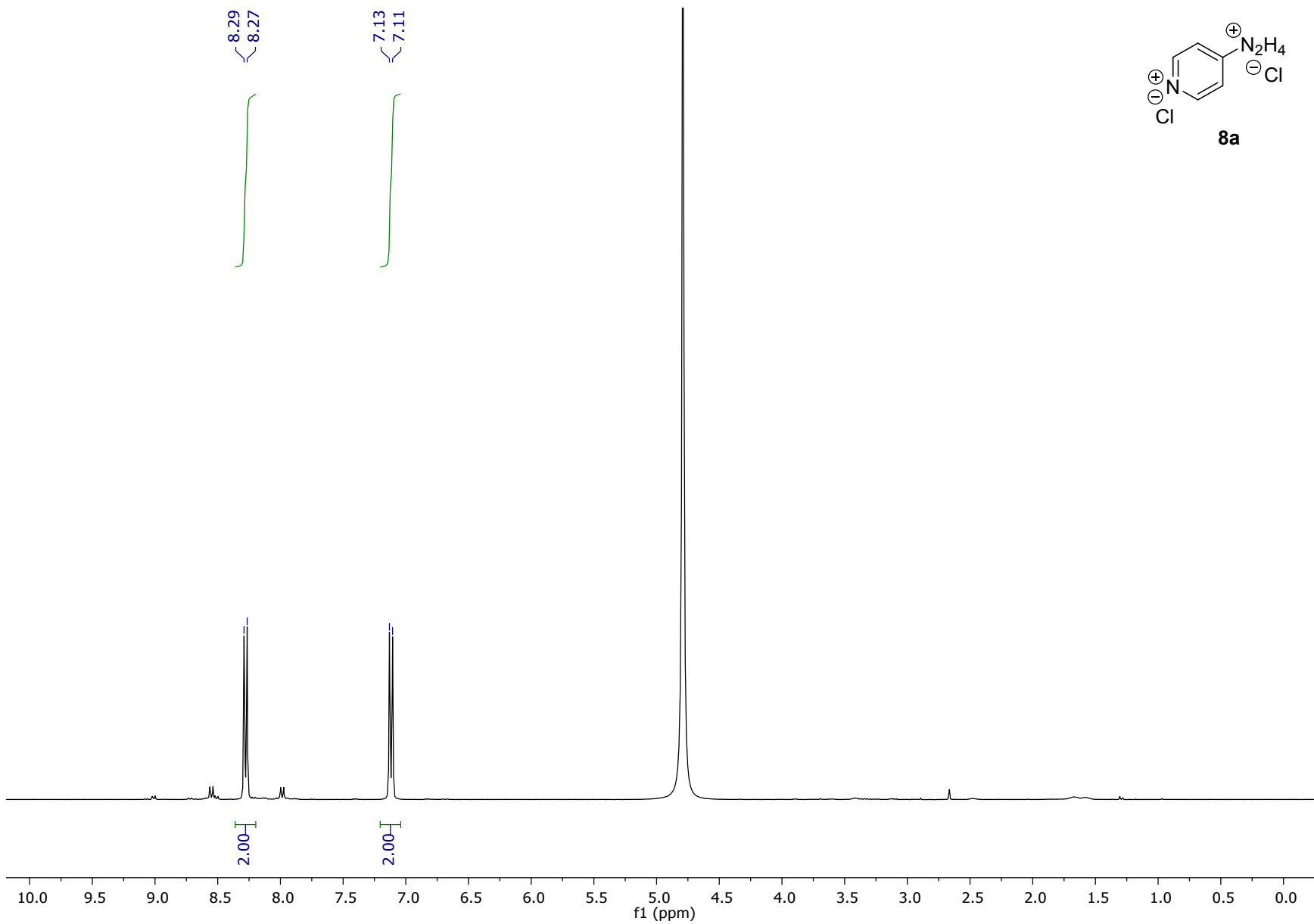


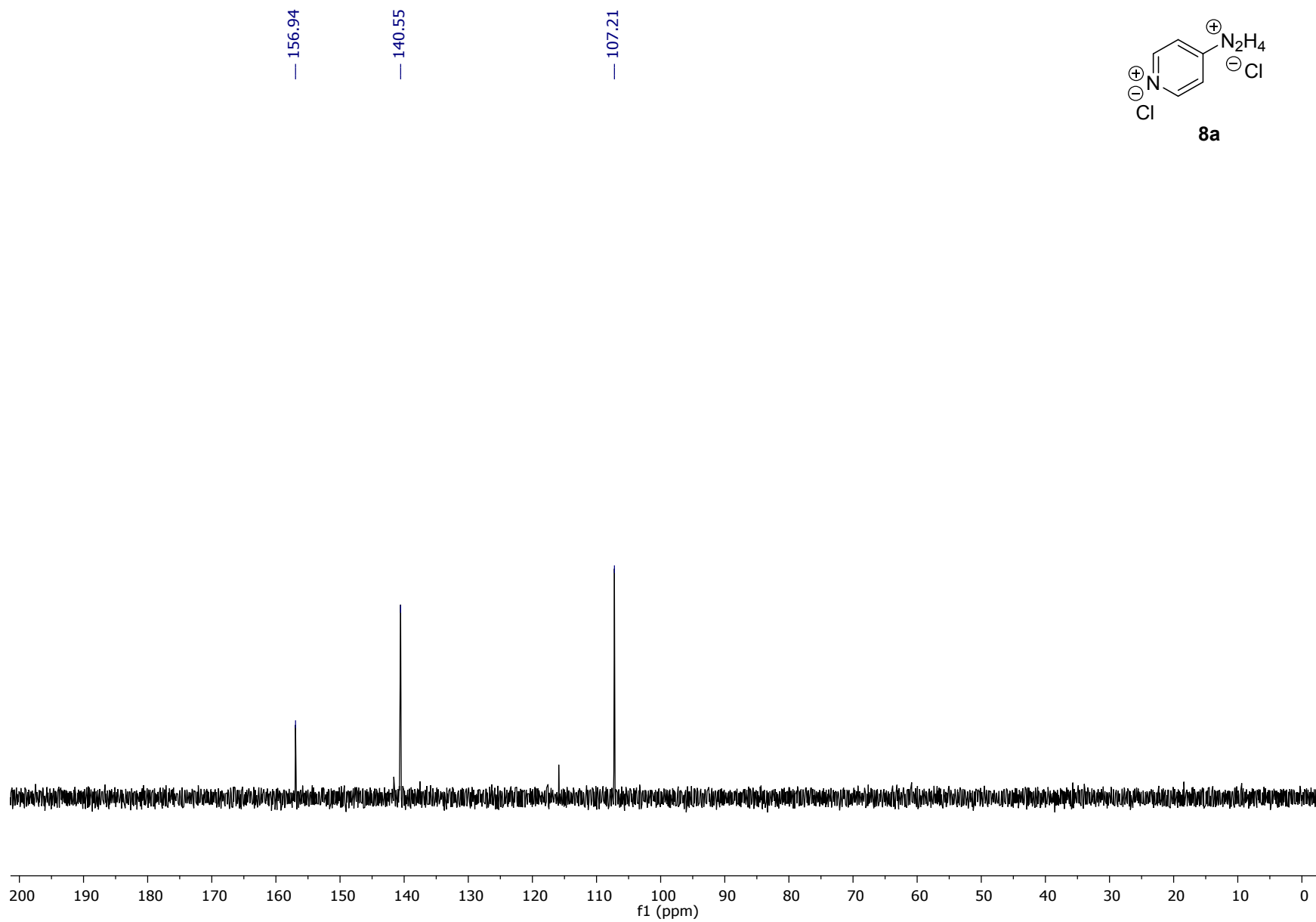


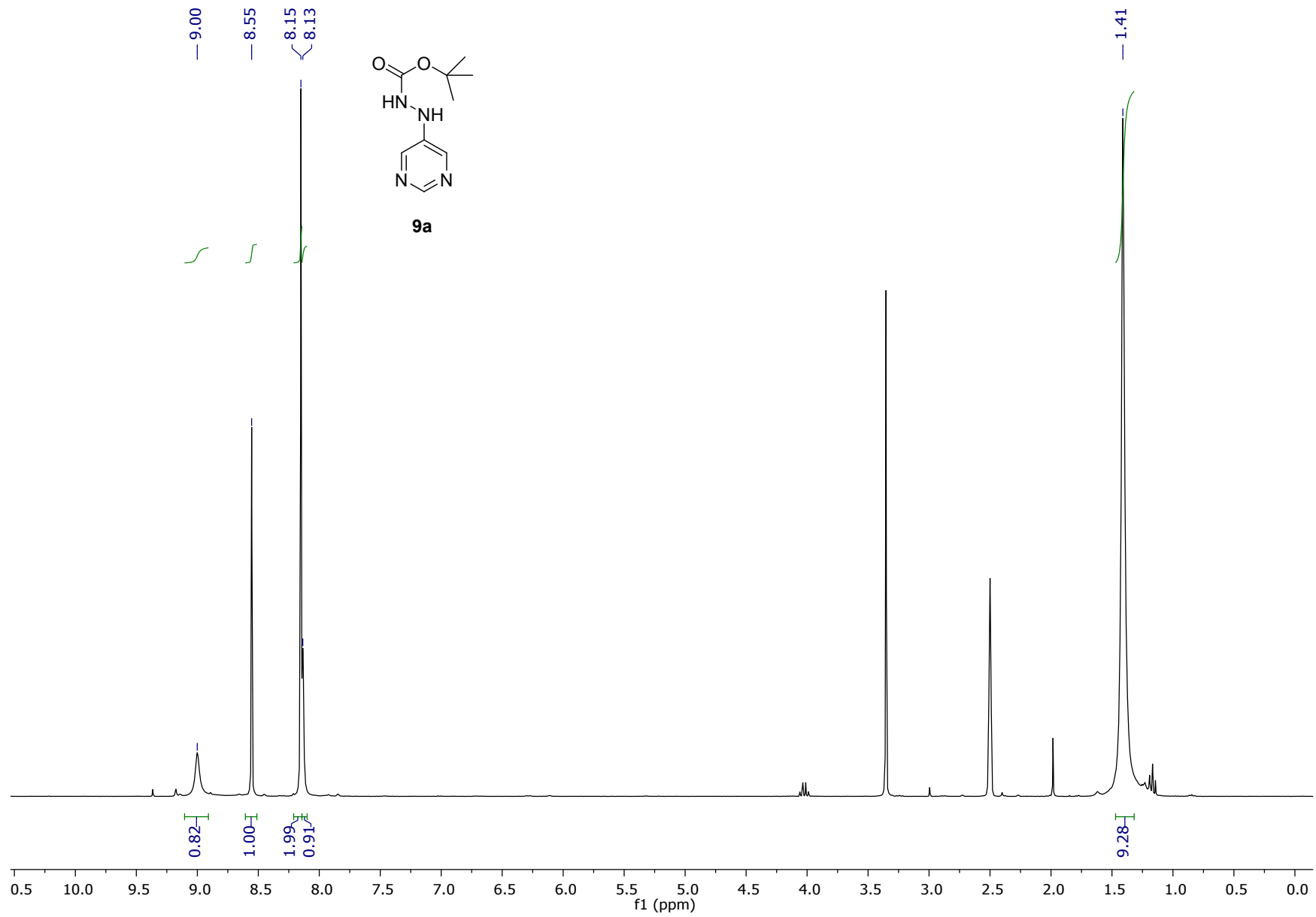


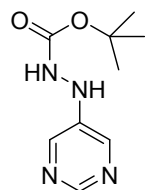
7a











9a

