Supporting Information for

Synthesis of ^{18}F-Labelled Aryl Trifluoromethyl Ketones with Improved Molar Activity

Lukas Veth,* Albert D. Windhorst, Danielle J. Vugts

Amsterdam UMC location Vrije Universiteit Amsterdam, dept Radiology & Nuclear Medicine, De Boelelaan 1117, Amsterdam, The Netherlands

* E-mail: l.r.veth@amsterdamumc.nl

Table of contents

1. Supplementary methods

Unless stated otherwise, all non-radioactive reactions and manipulations were conducted on the laboratory bench or in a well-ventilated fume hood with reagent grade solvents. All reagents and solvents were purchased from commercial suppliers and used without further purification, except when noted in the experimental. For experiments under inert gas atmosphere, dried and degassed solvents were purchased from commercial suppliers and used as received. Column chromatography was carried out with Merck silica gel (pore size 60 Å, 230-400 mesh particle size) and TLC on Merck TLC Silica gel 60 F_{254} plates. TLC visualization was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. NMR spectra were acquired on a Bruker Avance 500 or 300 instrument. Chemical shifts are reported in parts per million (ppm) and referenced to residual solvent peaks. Coupling constants are reported in hertz (Hz). NMR spectra were processed using MestReNova 14.2 software.

All radioactive reactions were performed manually. If desired, a previously published protocol can be utilized for automated synthesis of [^{18}F]fluoroform.[1] Analysis of radioactive reactions and products was carried out with high-performance liquid chromatography (HPLC). HPLC analysis was obtained on a Shimadzu system, consisting of a LC-20AT liquid chromatography module, SIL-20A HT auto sampler, SPD-20A UV/VIS detector, CTO-20A column oven, DGU-20A5R degassing unit, CBM-20A communication bus module, a Elysia Raytest GABI Nova radio detector, and using LabSolutions 5.85 software. Analysis was performed using an Alltima C18 column (5 μm 4.6x250mm) (VWR), MeCN/water/TFA (mixture as indicated) as eluent and a flow of 1 mL/min. Radioactive products were identified by comparison with the unlabelled reference compounds.

2. Radiochemistry

2.1 Synthesis of [^{18}F]Fluoroform

The procedure was adapted from a literature report.[2] [^{18}F]fluoride (2-4 GBq) was eluted from a PS-HCO_3^- cartridge with potassium sulfate solution (500 µL, 0.1M in H_2O) into a 3 mL V-Vial containing DMF (850 µL). The mixture was heated to 40 °C and *N*,*N*-bis(trifluoromethylsulfonyl)aniline (150 µL, 0.1M in DMF) was added. Immediately after, the product [^{18}F]triflyl fluoride was distilled with a stream of helium (10 mL/min), passed over a calcium chloride column, and trapped in a V-vial containing a mixture of MeCN (890 µL) and a K_2CO_3/Kryptofix[2.2.2] (10 µL, 0.15 mM K_2CO_3 and 0.35 mM Kryptofix[2.2.2] in MeCN/H_2O (9/1)) at -40 ºC for 3 min. The trapping vessel was then heated to 80 °C and subsequently, difluoroiodomethane (100 µL, 0.01M in MeCN) was added and left to react for 5 minutes at the same temperature. After cooling down to 20 °C, the formed [^{18}F]fluoroform was purged out of the reaction mixture with a stream of helium (10 mL/min), led over a silica plus cartridge and trapped in another V-Vial containing DMF (1 mL) at -60 °C.

2.2 Synthesis of ^{18}F-labelled aryl trifluoromethyl ketones

An aliquot of [^{18}F]fluoroform DMF (100 µL, ca. 25-50 MBq) was added to a vial containing the respective Weinreb amide precursor (50 µmol) and potassium hexamethyldisilazide (KHMDS, 50 µmol, 50 µL 1M in THF) in DMF (500 µL). After allowing to stir (500 rpm) at 20 °C for 5 min, HCl (conc., 100 µL) was added and the resulting mixture was allowed to stir for 1 min at 20 °C. An aliquot of the reaction mixture was subjected to HPLC analysis to determine the radiochemical conversion (RCC) by analyzing the relative ratio of all radioactive compounds in the reaction mixture. The identity of the obtained product was confirmed by co-injection of non-radioactive reference.

2.3 Synthesis of TFMK [^{18}F]2l with a full batch of [^{18}F]fluoroform

[^{18}F]Fluoroform was synthesized as described in section 2.1 and trapped in a V-vial containing Weinreb amide **1l-a** (9.9 mg, 30 µmol) and KHMDS (1M in THF, 30 µL, 30 µmol) in DMF (620 µL) or methyl ester **1l-b** (15.0 mg, 50 µmol) and KHMDS (1M in THF, 50 µL, 50 µmol) in DMF (600 µL) at -60 °C. The resulting reaction mixture was then warmed up to 20 °C and allowed to stir at this temperature for 5 min. Subsequently, HCl (conc., 100 µL) was added and the resulting mixture was allowed to stir for 1 min at 20 °C. The mixture was then diluted with mobile phase (MeCN/H_2O/TFA, 40/60/0.1, 3 mL) and purified by semi-preparative HPLC (Alltima C18 5u 250x10 mm, MeCN/H_2O/TFA, 40/60/0.1, 5 mL/min). The product fraction was collected and an aliquot (1 mL) was taken. After determining the activity, the

aliquot was analysed by analytical HPLC (20 µL injection volume, Luna 5 µm C18(2) 100A 250x4.6 mm, MeCN/H_2O/TFA, 50/50/0.1, 1 mL/min) and the UV-peak area (UV: 254 nm) was determined. Based on this analysis, the molar activity of **[^{18}F]2l** was determined using a calibration curve of the non-radioactive reference compound.

2.4 Calibration curve for determination of molar activity

The calibration curve was obtained in the following way: samples of different concentrations of **2l** (1 mL sample volume) were measured by analytical HPLC using the conditions indicated in the procedure in 2.3 (20 µL injection volume) and UV-peak areas (UV: 254 nm) were determined. The amount of product in the sample was then plotted against the determined peak area (Figure S1). The amount of reference compound in the analyzed sample from 2.3 was determined by the inserting the UV-peak area determined in the analysis in 2.3 (20 µL injection volume) in the equation of the linear trendlines in Figure S1. The molar activity was then calculated according to

$$A_m = \text{activity of HPLC sample/amount of reference compound}$$

with the amount of activity of the HPLC sample determined in 2.3 and the amount of reference compound calculated above. Shown below is the calibration curve and equation of the linear trendline.

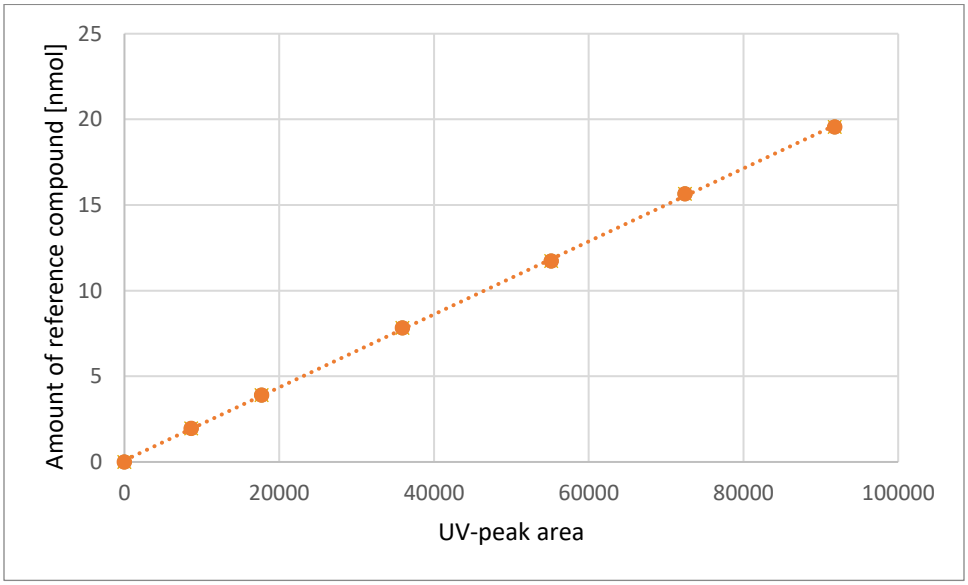


Figure S1: Calibration curve of **2l**; HPLC conditions: Luna 5 µm C18(2) 100A 250x4.6 mm, MeCN/H_2O/TFA, 50/50/0.1, 1 mL/min, UV: 254 nm.

The equation of the linear trendline was determined to be:

Amount of reference compound [nmol] = (0.0002130309 * area + 0.0921857181) [nmol]

2.5 Summary of experiments using full batches of [^{18}F]fluoroform

Table S1. Detailed overview of activities, molar activities, and total synthesis time for [^{18}F]2l.

	[^{18}F]F$^-$ (GBq)	*[^{18}F]HCF$_3$* (GBq)	***[^{18}F]2l** (GBq)*	*RCY from [^{18}F]F$^-$*	*AY from [^{18}F]F$^-$*	*RCY from [^{18}F]HCF$_3$*	*AY from [^{18}F]HCF$_3$*	*RCP (%)*	*A_m* [GBq/µmol]*
*[^{18}F]**2l-1** from **1l-a***	6.77	1.81	1.19	27%	18%	93%	66%	100	22.7
*[^{18}F]**2l-2** from **1l-a***	10.98	2.65	1.68	24%	15%	89%	63%	100	26.1
*[^{18}F]**2l-3** from **1l-b***	4.72	1.39	0.456	15%	10%	46%	33%	100	12.4
*[^{18}F]**2l-4** from **1l-b***	5.13	1.64	0.626	19%	12%	54%	38%	100	13.2

*: A_m determined at end of synthesis, synthesis time for all reactions 69-71 minutes.

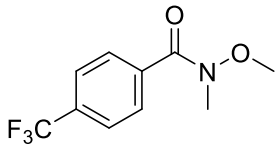
3. Synthesis of starting materials

1a was obtained from a commercial source and used as received.

General procedure 1: Synthesis of Weinreb amides from the corresponding carboxylic acids

This procedure was adapted from a literature report.[3] To a solution of the corresponding carboxylic acid in DCM (1M) was added 1,1-carbonyldiimidazole (1.1 equiv.). After allowing to stir at room temperature for 2h, *N,O*-dimethylhydroxylamine hydrochloride (1.2 equiv.) was added. After allowing to stir for another 2 h, more DCM (20 mL) was added and the mixture was washed with brine (3 x 25 mL). The organic layer was then dried over Na_2SO_4, filtered, and volatiles were removed under reduced pressure.

***N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide 1b**

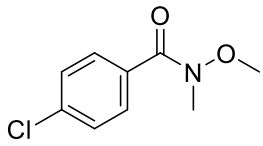


The title compound was prepared according to general procedure 1 using 4-(trifluoromethyl)benzoic acid (475 mg, 2.50 mmol) as starting material. After work-up, the title compound (468 mg, 2.01 mmol, 80%) was obtained as light yellow oil. The NMR data match previously reported data for the title product.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 3.53 (s, 3H), 3.38 (s, 3H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -63.0 (s).

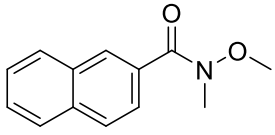
4-chloro-*N*-methoxy-*N*-methylbenzamide 1c



The title compound was prepared according to general procedure 1 using 4-chloro benzoic acid (391 mg, 2.50 mmol) as starting material. After work-up, the title compound (406 mg, 2.03 mmol, 81%) was obtained as light yellow oil. The NMR data match previously reported data for the title product.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 3.53 (s, 3H), 3.36 (s, 3H).

***N*-methoxy-*N*-methyl-2-naphthamide 1d**

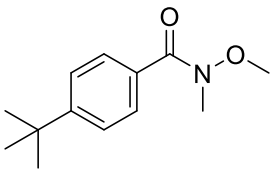


The title compound was prepared according to general procedure 1 using 2-naphthoic acid (431 mg, 2.50 mmol) as starting material. After work-up, the title

compound (446 mg, 2.07 mmol, 83%) was obtained as light yellow oil. The NMR data match previously reported data for the title product.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.20 (m, 1H), 7.93 – 7.82 (m, 3H), 7.75 (dd, J = 8.6, 1.7 Hz, 1H), 7.59 – 7.48 (m, 2H), 3.57 (s, 3H), 3.42 (s, 3H).

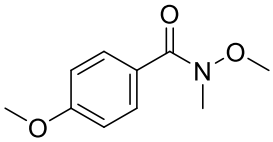
4-(*tert*-butyl)-*N*-methoxy-*N*-methylbenzamide 1e



The title compound was prepared according to general procedure 1 using 4-*tert*-butylbenzoic acid (446 mg, 2.50 mmol) as starting material. After work-up, the title compound (472 mg, 2.13 mmol, 85%) was obtained as white solid. The NMR data match previously reported data for the title product.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 3.58 (s, 3H), 3.35 (s, 3H), 1.33 (s, 9H).

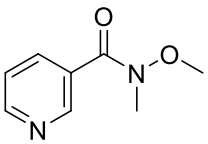
***N*,4-dimethoxy-*N*-methylbenzamide 1f**



The title compound was prepared according to general procedure 1 using 4-methoxybenzoic acid (380 mg, 2.50 mmol) as starting material. After work-up, the title compound (417 mg, 2.14 mmol, 85%) was obtained as colorless oil. The NMR data match previously reported data for the title product.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.84 (s, 3H), 3.55 (s, 3H), 3.35 (s, 3H).

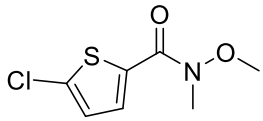
***N*-methoxy-*N*-methylnicotinamide 1g**



The title compound was prepared according to general procedure 1 using nicotinic acid (308 mg, 2.50 mmol) as starting material. After work-up, the title compound (358 mg, 2.16 mmol, 86%) was obtained as light yellow oil. The NMR data match previously reported data for the title product.[6]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 – 8.92 (m, 1H), 8.68 (dd, *J* = 5.0, 1.7 Hz, 1H), 8.05 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.37 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 3.55 (s, 3H), 3.39 (s, 3H).

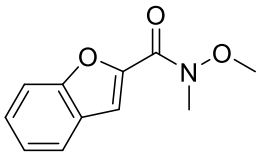
5-chloro-*N*-methoxy-*N*-methylthiophene-2-carboxamide 1h



The title compound was prepared according to general procedure 1 using 5-chlorothiophene-2-carboxylic acid (407 mg, 2.50 mmol) as starting material. After work-up, the title compound (106 mg, 517 µmol, 21%) was obtained as a light yellow oil. The NMR data match previously reported data for the title product.[7]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 4.2 Hz, 1H), 6.95 (d, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H).

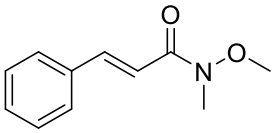
***N*-methoxy-*N*-methylbenzofuran-2-carboxamide 1i**



The title compound was prepared according to general procedure 1 using benzofuran-2-carboxylic acid (405 mg, 2.50 mmol) as starting material. After work-up, the title compound (434 mg, 2.12 mmol, 85%) was obtained as yellow oil. The NMR data match previously reported data for the title product.[8]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 1H), 7.63 – 7.57 (m, 1H), 7.52 – 7.48 (m, 1H), 7.46 – 7.39 (m, 1H), 7.33 – 7.26 (m, 1H), 3.83 (s, 3H), 3.42 (s, 3H).

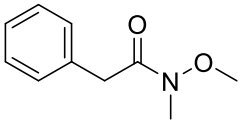
***N*-methoxy-*N*-methylcinnamamide 1j**



The procedure was adapted from a literature report.[9] Under a nitrogen atmosphere, triethylamine (522 µL, 380 mg, 3.75 mmol, 1.5 equiv.) was added to a mixture of *trans*-cinnamic acid (370 mg, 2.5 mmol, 1.0 equiv.), DMAP (61.1 mg, 500 µmol, 0.2 equiv.), *N*,*O*-dimethylhydroxylamine hydrochloride (366 mg, 3.75 mmol, 1.5 equiv.), and EDC (719 mg, 3.75 mmol, 1.5 equiv.) in DCM (5 mL) at 0 °C. The resulting reaction mixture was allowed to stir at room temperature for 3h. HCl (aq. 1M, 10 mL) was added and the resulting mixture was washed with diethyl ether (3 x 30 mL). The combined organic layers were then washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL) and dried over Na_2SO_4. After filtration, volatiles were removed under reduced pressure and the resulting residue was subjected to column chromatography (silica gel, 20% EtOAc in hexane) to give the title product (387 mg, 2.02 mmol, 81%) as light yellow oil. The NMR data match previously reported data for the title product.[9]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 15.8 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.38 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.04 (d, *J* = 15.8 Hz, 1H), 3.77 (s, 3H), 3.31 (s, 3H).

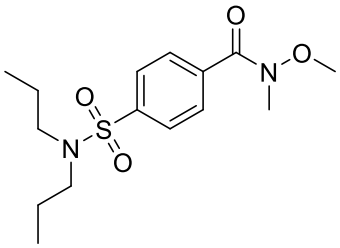
***N*-methoxy-*N*-methyl-2-phenylacetamide 1k**



The title compound was prepared according to general procedure 1 using phenylacetic acid (340 mg, 2.50 mmol) as starting material. After work-up, the title compound (329 mg, 1.83 mmol, 73%) was obtained as light yellow oil. The NMR data match previously reported data for the title product.[10]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 5H), 3.77 (s, 2H), 3.60 (s, 3H), 3.19 (s, 3H).

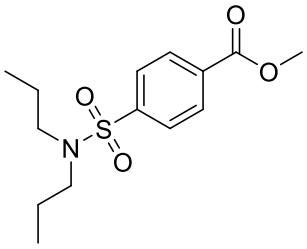
4-(*N*,*N*-dipropylsulfamoyl)-*N*-methoxy-*N*-methylbenzamide 1l-a



The title compound was prepared according to general procedure 1 using probenecid (713 mg, 2.50 mmol) as starting material. After work-up, the title compound (724 mg, 2.21 mmol, 88%) was obtained as colorless oil. The NMR data match previously reported data for the title product.[11]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 3.51 (s, 3H), 3.37 (s, 3H), 3.12 – 3.05 (m, 4H), 1.64 – 1.45 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6H).

methyl 4-(*N*,*N*-dipropylsulfamoyl)benzoate 1l-b



The procedure was adapted from a literature report.[12] Under a nitrogen atmosphere, methanol (400 µL) and *N*,*N*'-diisopropylccarbodiimide (DIC, 172 µL, 1.10 mmol, 1.1 equiv.) were added to a mixture of probenecid (285 mg, 1.0 mmol, 1.0 equiv.) and DMAP (36.7 mg, 300 µmol, 0.3 equiv.) in DCM (10 mL). The resulting reaction mixture was allowed to stir at room temperature for 18h. Then, the volatiles were removed under reduced pressure and the resulting residue was subjected to column chromatography (silica gel, 0-10% EtOAc in pentane) to give the title product (219 mg, 733 µmol, 73%) as a colourless oil. The NMR data match previously reported data for the title product.[12]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 3.95 (s, 3H), 3.16 – 3.01 (m, 4H), 1.62 – 1.45 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 6H).

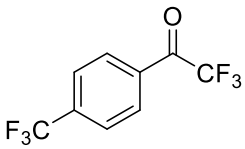
4. Synthesis of non-radioactive reference compounds

2a, **2g**, **2h,** and **2k** were obtained from commercial sources and used as received.

General procedure 2: Synthesis of trifluoromethyl ketones from Weinreb amides

The procedure was adapted from a literature report.[13] To a screw-cap vial with cesium fluoride (0.2 equiv.) under a nitrogen atmosphere were added toluene (0.4M) and the corresponding Weinreb amide (1.0 equiv.). After cooling to 0 °C, Ruppert-Prakash reagent (2.0 equiv.) was added and the reaction mixture was allowed to stir at room temperature. After full conversion of the Weinreb amide as indicated by TLC analysis, a 1:1 mixture of TBAF (1M in THF, 1.0 equiv.) and H_2O were added. The resulting reaction mixture was allowed to stir at 50 °C for 1 h. After cooling down to room temperature, diethyl ether (30 mL) was added and the solution was washed with brine (30 mL) and dried over Na_2SO_4. After filtration, volatiles were removed under reduced pressure and the resulting residue was subjected to column chromatography to give the corresponding product.

2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one 2b

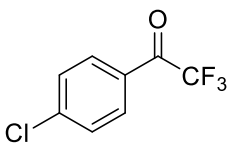


The title compound was prepared according to general procedure 2 using *N*-methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (117 mg, 500 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 20% EtOAc in hexane) to give the title product (34.6 mg, 143 µmol, 36%) as a light yellow liquid. The NMR data match previously reported data for the title product.[14] [NOTE: The title compound is volatile and vacuum should be applied carefully when removing volatiles.]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -63.6 (s), -71.8 (s).

1-(4-chlorophenyl)-2,2,2-trifluoroethan-1-one 2c

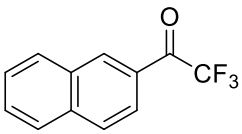


The title compound was prepared according to general procedure 2 using 4-chloro-*N*-methoxy-*N*-methylbenzamide (79.9 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 10% EtOAc in pentane) to give the title product (47.6 mg, 228 µmol, 57%) as a red oil. The NMR data match previously reported data for the title product.[14]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -71.5 (s).

2,2,2-trifluoro-1-(naphthalen-2-yl)ethan-1-one 2d

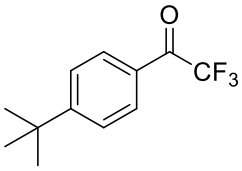


The title compound was prepared according to general procedure 2 using *N*-methoxy-*N*-methyl-2-naphthamide (86.1 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 10% EtOAc in pentane) to give the title product (71.3 mg, 318 µmol, 80%) as an orange oil. The NMR data match previously reported data for the title product.[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.16 – 7.91 (m, 4H), 7.66 (dddd, *J* = 23.3, 8.2, 6.9, 1.4 Hz, 2H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -70.7 (s).

1-(4-(*tert*-butyl)phenyl)-2,2,2-trifluoroethan-1-one 2e

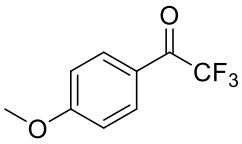


The title compound was prepared according to general procedure 2 using 4-(*tert*-butyl)-*N*-methoxy-*N*-methylbenzamide (88.5 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 10% EtOAc in pentane) to give the title product (62.2 mg, 270 µmol, 68%) as an orange oil. The NMR data match previously reported data for the title product.[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 1.36 (s, 9H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -71.3 (s).

2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one 2f

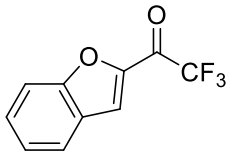


The title compound was prepared according to general procedure 2 using *N*,4-dimethoxy-*N*-methylbenzamide (78.1 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 10% EtOAc in hexane) to give the title product (46.1 mg, 226 µmol, 57%) as a yellow oil. The NMR data match previously reported data for the title product.[14]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 2H), 7.03 – 6.97 (m, 2H), 3.92 (s, 3H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -71.0 (s).

1-(benzofuran-2-yl)-2,2,2-trifluoroethan-1-one 2i

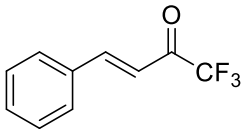


The title compound was prepared according to general procedure 2 using *N*-methoxy-*N*-methylbenzofuran-2-carboxamide (82.1 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 10% EtOAc in pentane) to give the title product (78.9 mg, 368 µmol, 92%) as yellow solid. The NMR data match previously reported data for the title product.[16]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.84 (m, 1H), 7.83 – 7.76 (m, 1H), 7.68 – 7.54 (m, 2H), 7.43 – 7.34 (m, 1H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -73.1 (s).

(*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one 2j

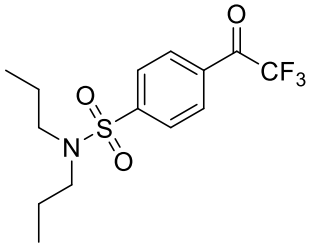


The procedure was adapted from a literature report.[17] Under a nitrogen atmosphere, TBAF (1M in THF, 10 µL, 10 µmol, 2.5 mol%) was added to a mixture of Ruppert-Prakash reagent (73.8 µL, 71.1 mg, 500 µmol, 1.25 equiv.) and methyl cinnamate (64.9 mg, 400 µmol, 1.0 equiv.) in *n*-hexane (1 mL) at 0 °C. The resulting reaction mixture was allowed to stir at room temperature for 24h. Then, the volatiles were removed under reduced pressure and THF (600 µL) and HCl (aq. 4M, 500 µL) were added. After allowing to stir for another 24h at room temperature, diethyl ether (30 mL) and brine (30 mL) were added. The layers were separated and the organic layer was dried over Na_2SO_4. After filtration, volatiles were removed under reduced pressure and the resulting residue was subjected to column chromatography (silica gel, 0-5% EtOAc in pentane) to give the title product (42.6 mg, 213 µmol, 53%) as a yellow oil. The NMR data match previously reported data for the title product.[17]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 15.9 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.53 – 7.43 (m, 3H), 7.02 (dd, *J* = 16.0, 0.9 Hz, 1H);

^{19}F NMR (471 MHz, $CDCl_3$) δ -77.6 (s).

***N*,*N*-dipropyl-4-(2,2,2-trifluoroacetyl)benzenesulfonamide 2l**



The title compound was prepared according to general procedure 2 using 4-(*N*,*N*-dipropylsulfamoyl)-*N*-methoxy-*N*-methylbenzamide (131 mg, 400 µmol) as starting material. The residue obtained after work-up was subjected to column chromatography (silica gel, 30% EtOAc in pentane) to give the title product (118 mg, 350 µmol, 87%) as a yellow solid. The NMR data match previously reported data for the title product.[16]

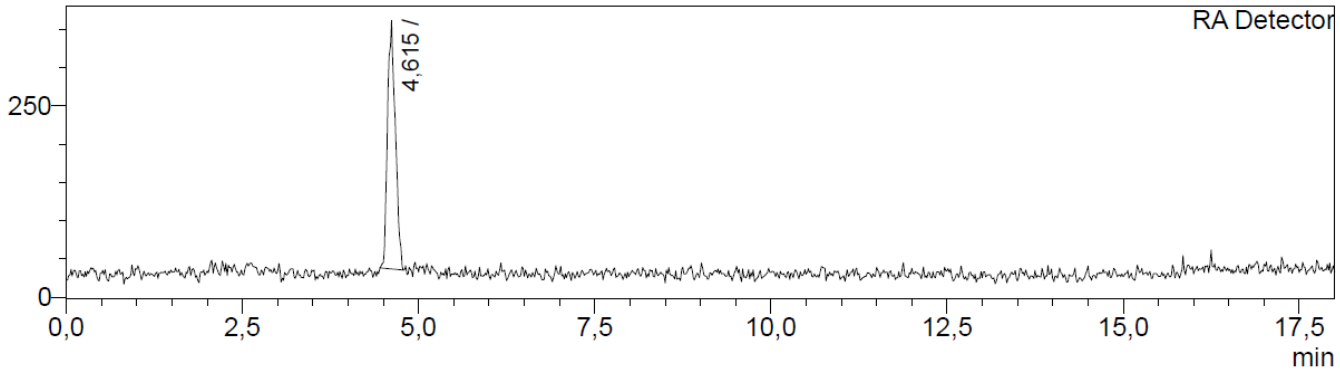
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.10 (m, 2H), 8.03 – 7.92 (m, 2H), 3.25 – 3.03 (m, 4H), 1.64 – 1.47 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 6H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -71.7 (s).

5. HPLC analysis

5.1 HPLC chromatograms of [^{18}F]fluoroform

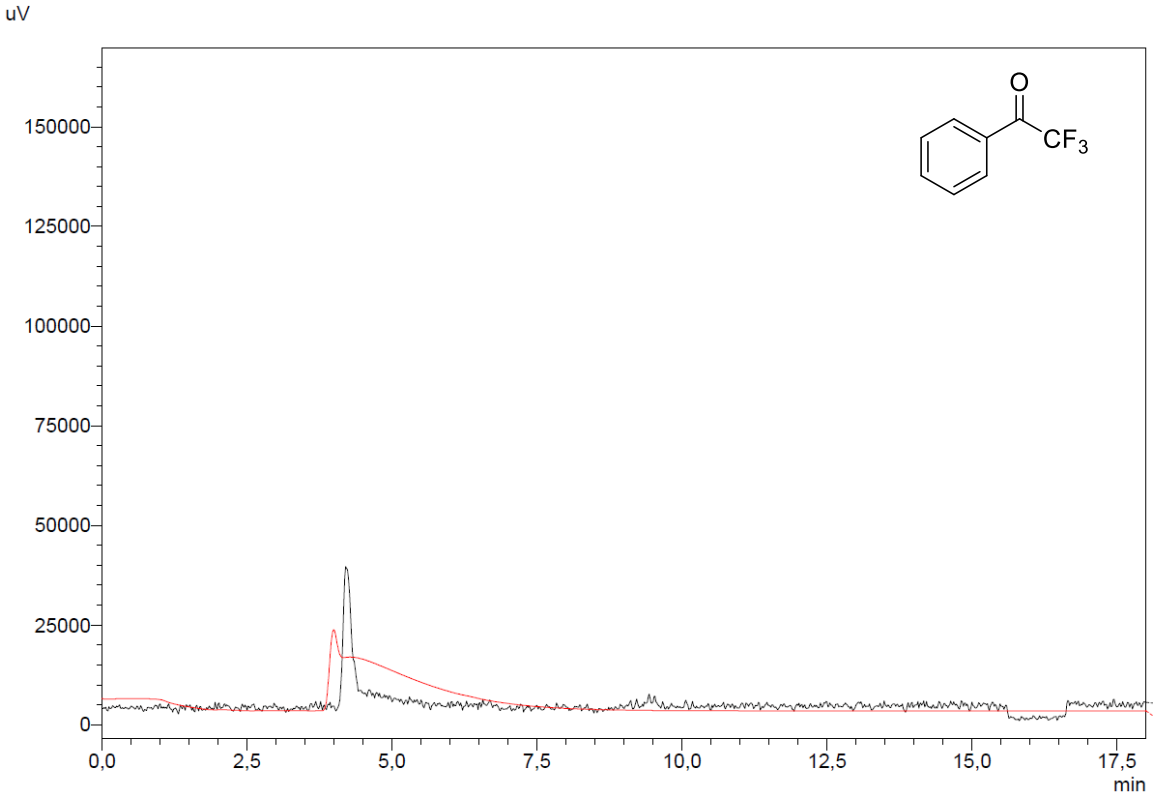
Shown below is the radio-HPLC analysis of [^{18}F]fluoroform using the eluent system used for the analysis of crude reaction mixtures.



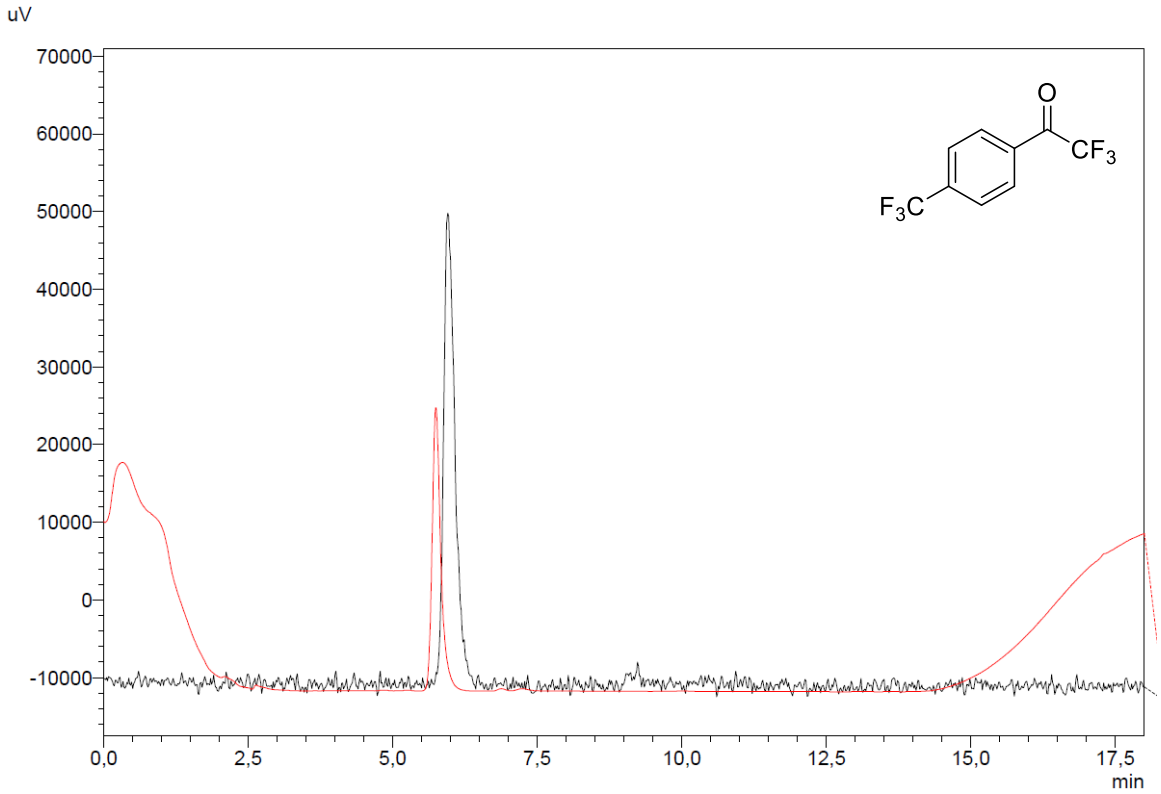
HPLC chromatogram of [^{18}F]fluoroform; eluent: MeCN/water/TFA 60:40:0.1.

5.2 HPLC chromatograms of crude reaction mixtures

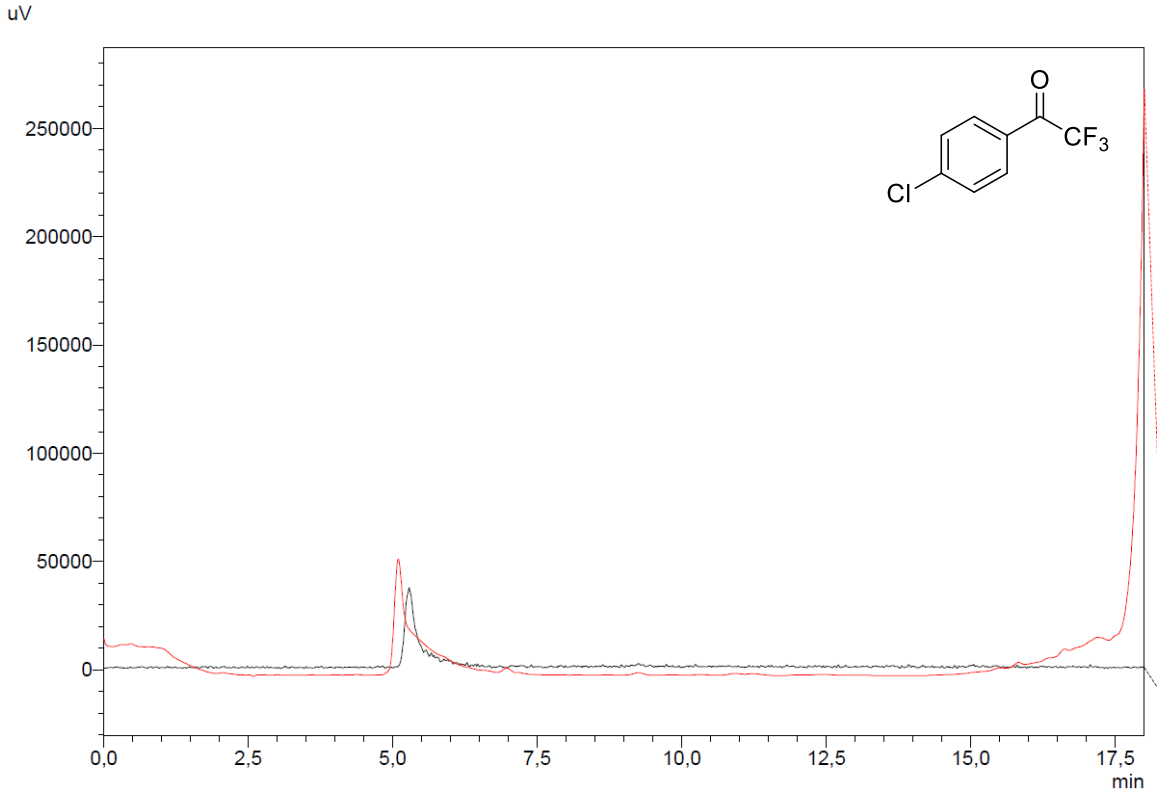
Shown below are radio-HPLC traces of crude mixtures for successful substrates overlaid with authentic UV references. The black line indicated the crude radio-HPLC and the red line is the UV trace (254 nm) for the non-radioactive reference compound. Some compounds show extensive tailing which could not be prevented.



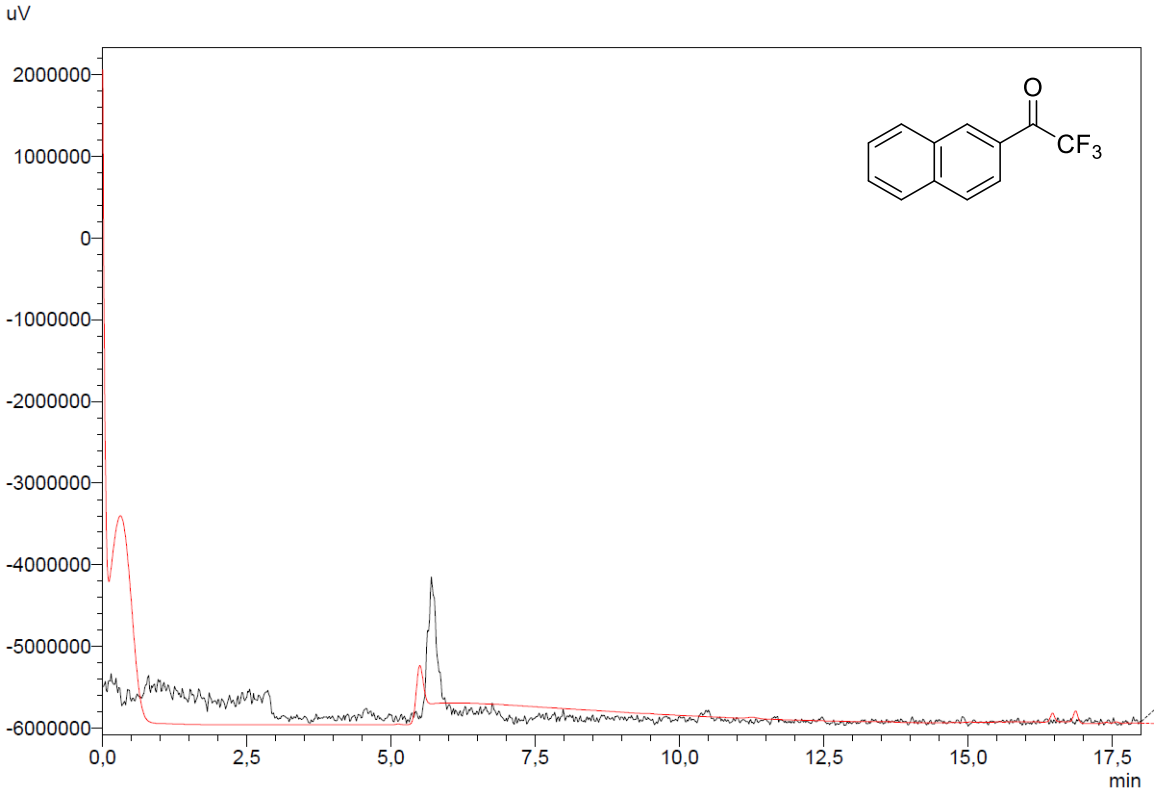
HPLC chromatograms for **[^{18}F]2a**/**2a**; eluent: MeCN/water/TFA 60:40:0.1.



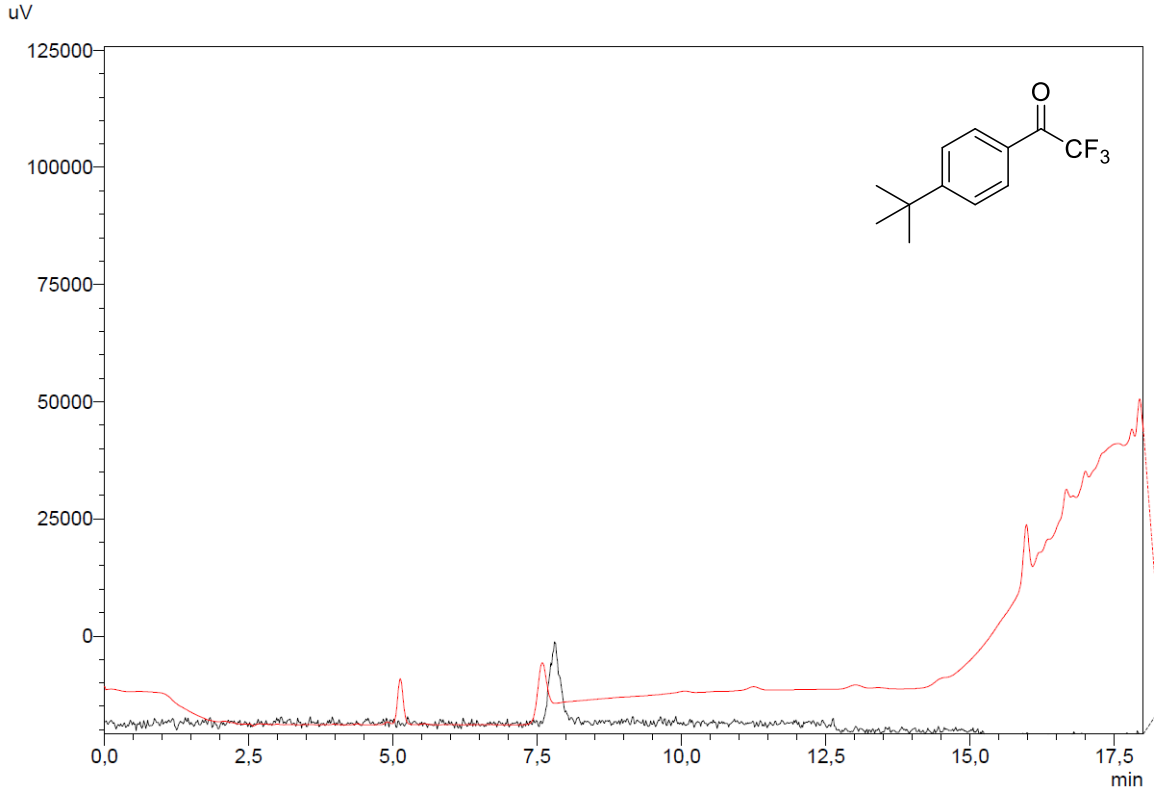
HPLC chromatograms for **[^{18}F]2b**/**2b**; eluent: MeCN/water/TFA 60:40:0.1.



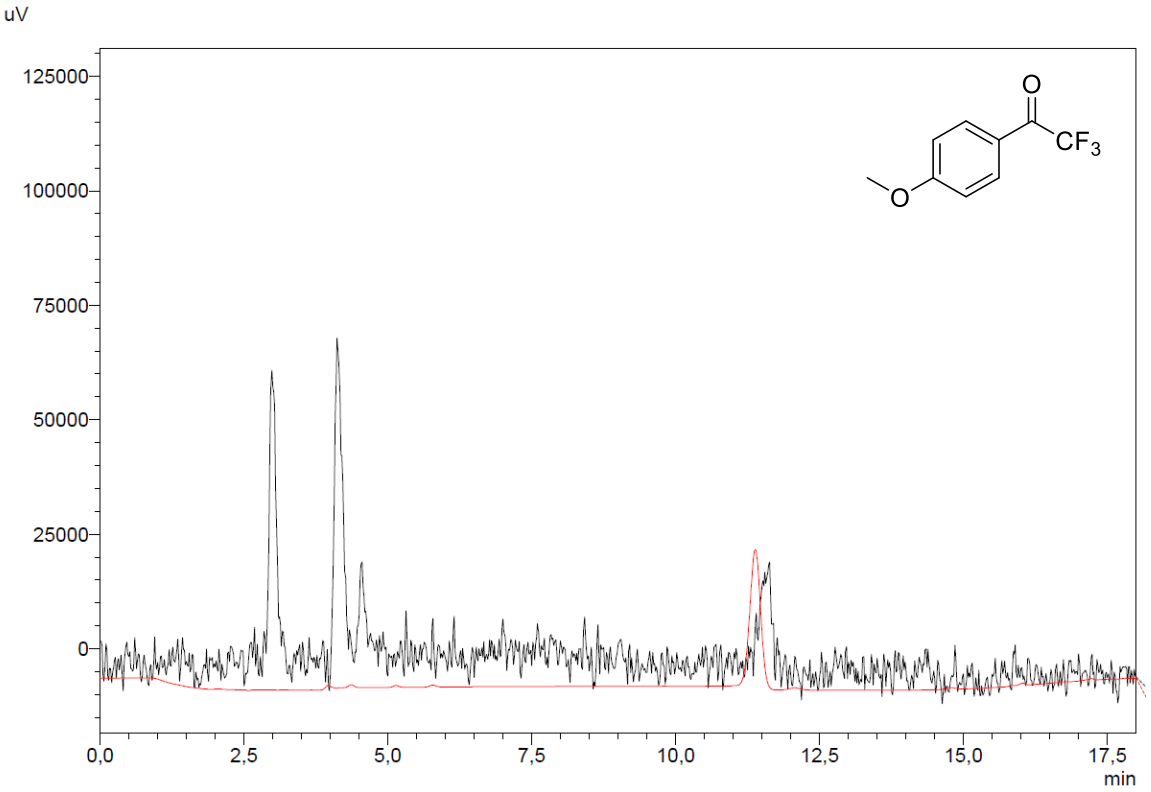
HPLC chromatograms for **[^{18}F]2c**/**2c**; eluent: MeCN/water/TFA 60:40:0.1.



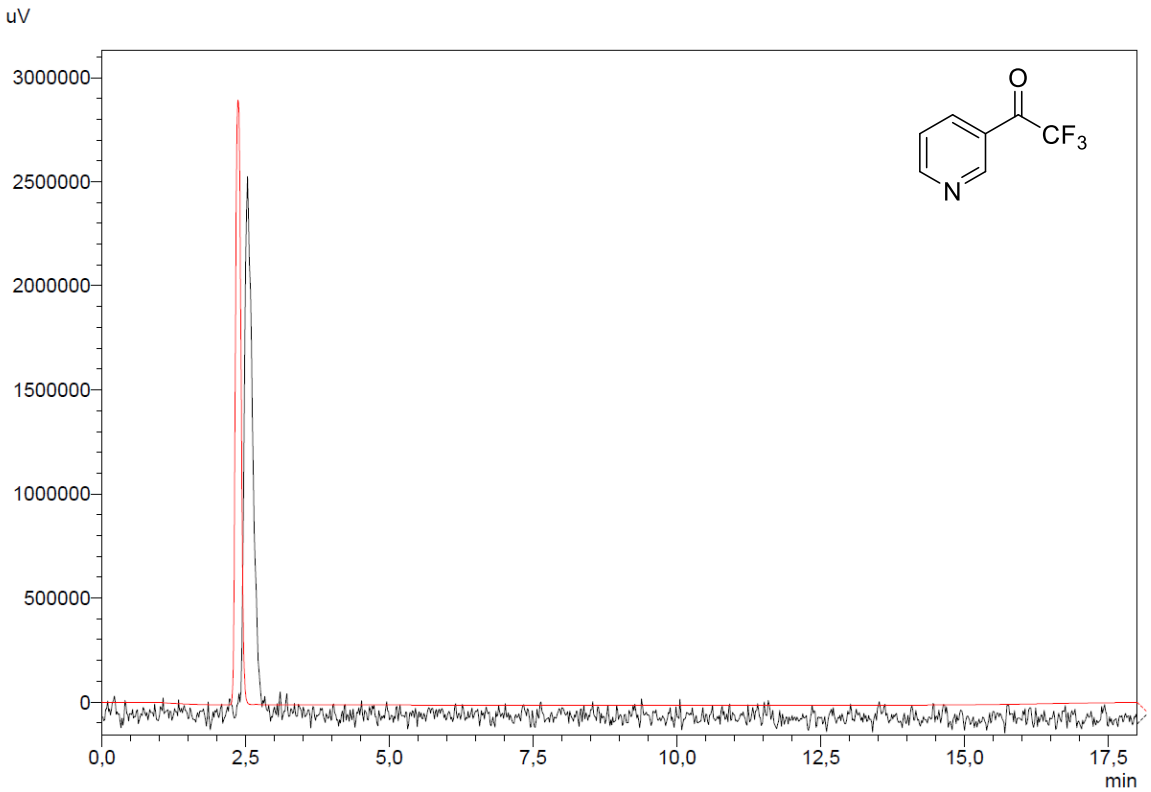
HPLC chromatograms for **[^{18}F]2d**/**2d**; eluent: MeCN/water/TFA 60:40:0.1.



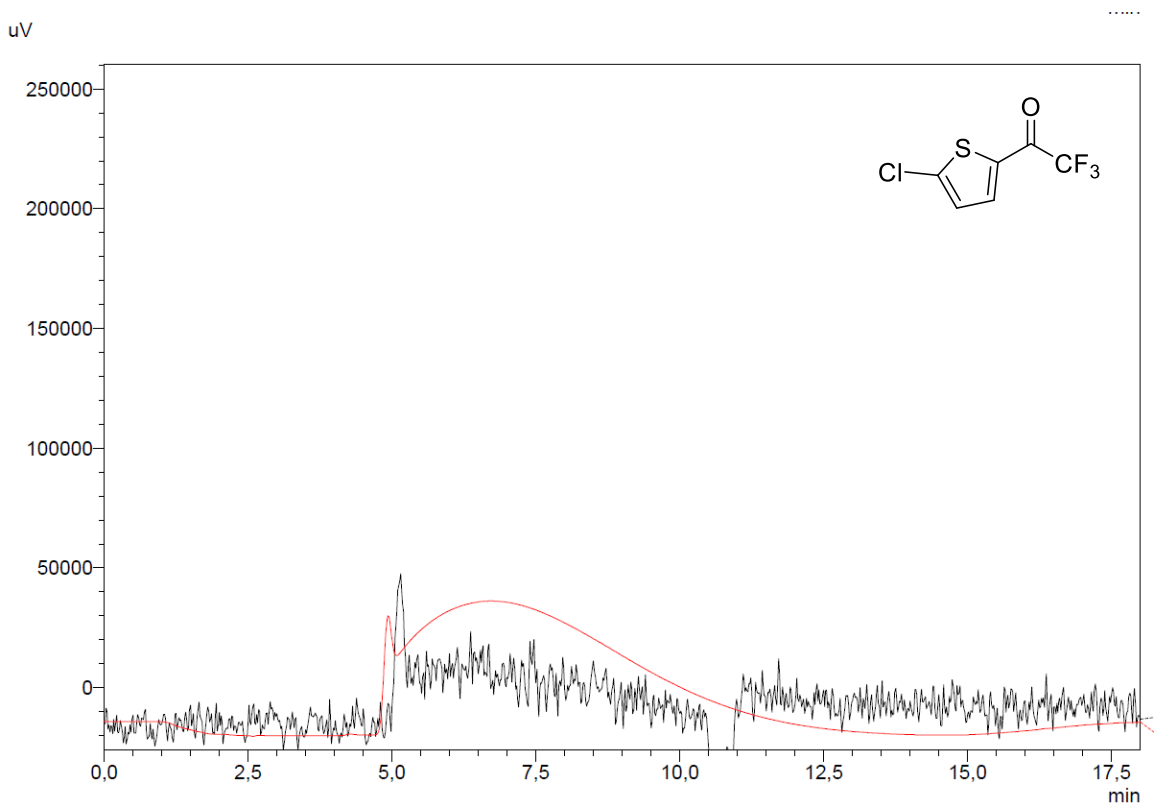
HPLC chromatograms for **[^{18}F]2e**/**2e**; eluent: MeCN/water/TFA 60:40:0.1.



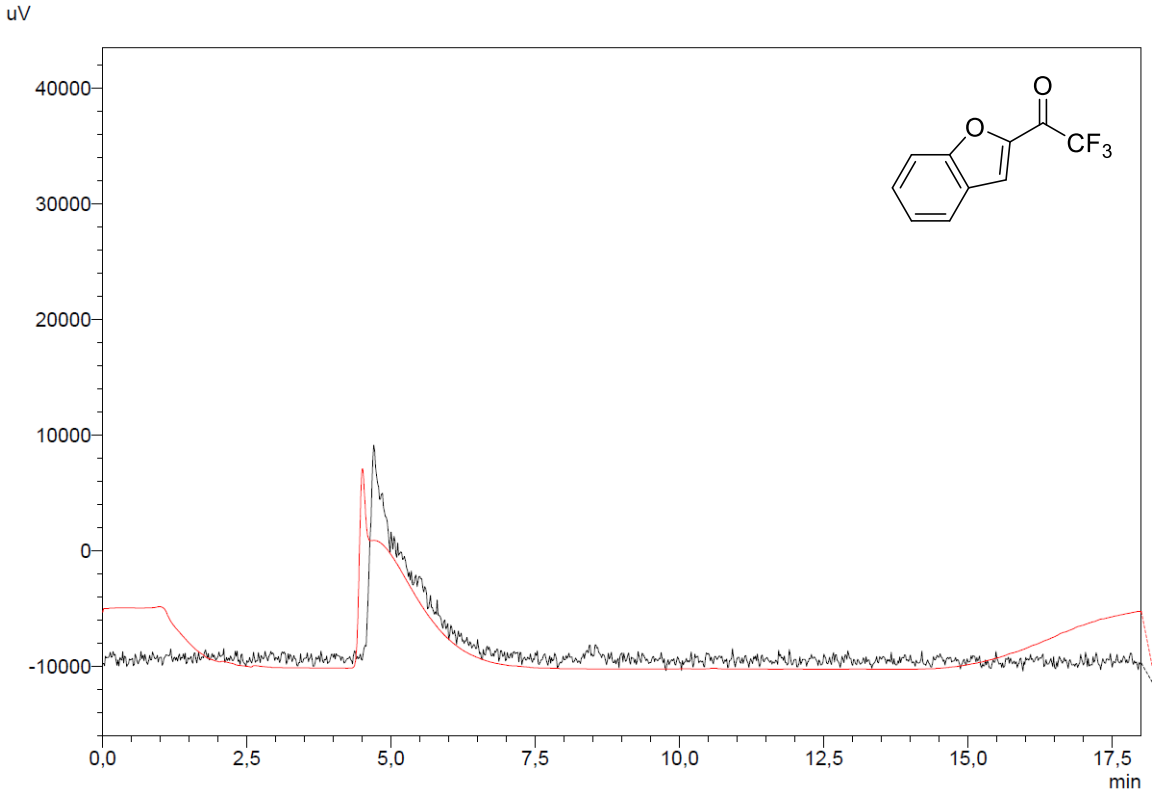
HPLC chromatograms for **[^{18}F]2f**/**2f**; eluent: MeCN/water/TFA 60:40:0.1.



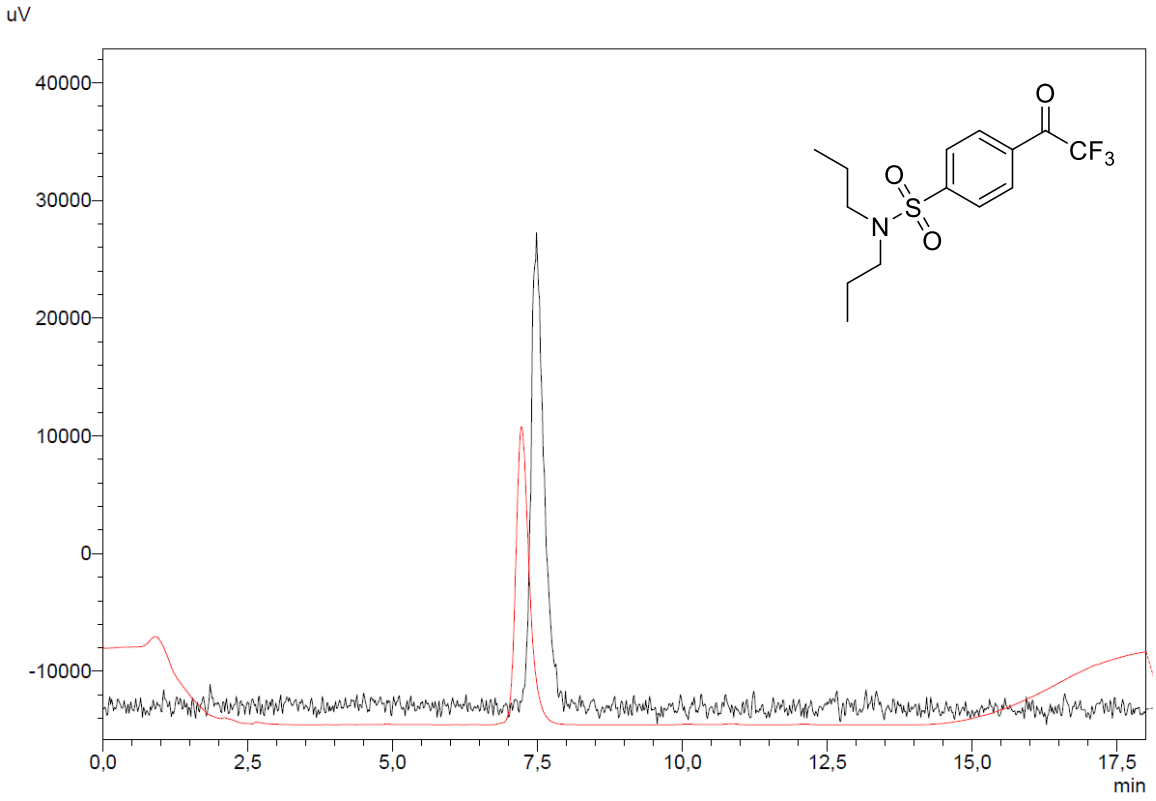
HPLC chromatograms for **[^{18}F]2g**/**2g**; eluent: MeCN/water/TFA 60:40:0.1.



HPLC chromatograms for **[^{18}F]2h**/**2h**; eluent: MeCN/water/TFA 60:40:0.1.



HPLC chromatograms for **[^{18}F]2i**/**2i**; eluent: MeCN/water/TFA 60:40:0.1.

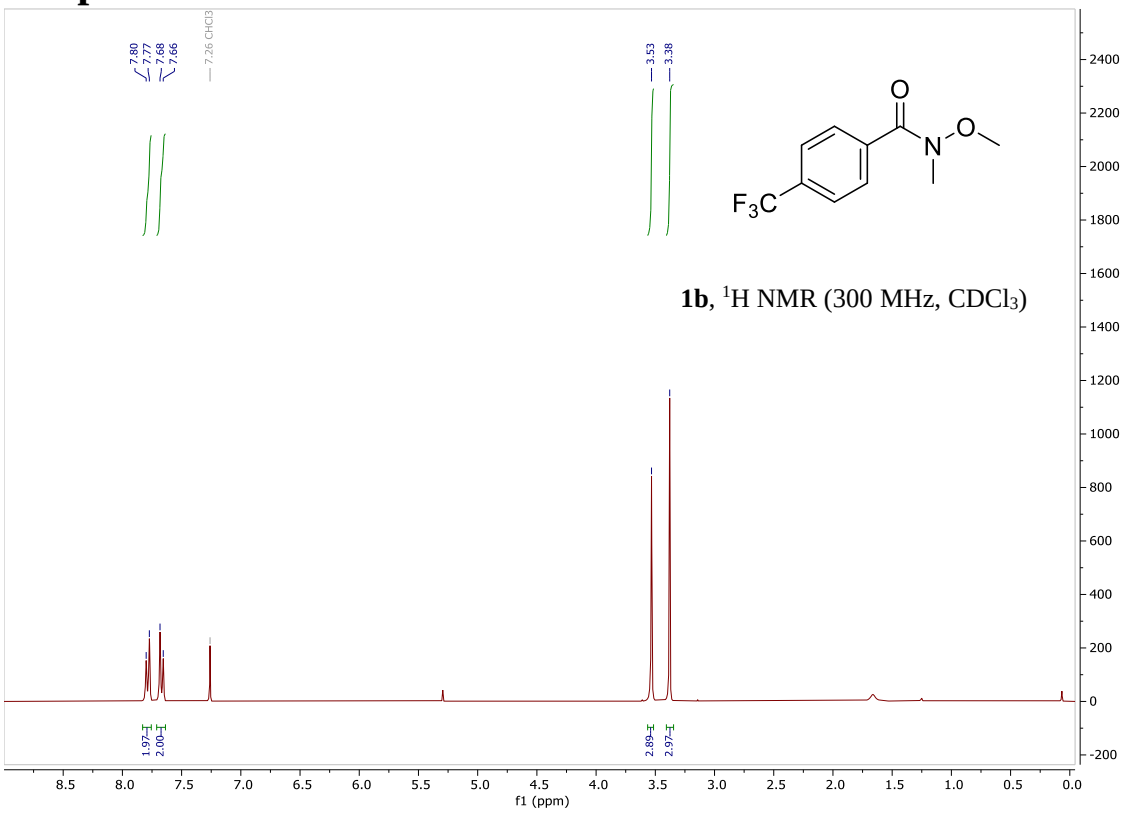


HPLC chromatograms for **[^{18}F]2l/2l** from **1l-a**; eluent: MeCN/water/TFA 60:40:0.1.

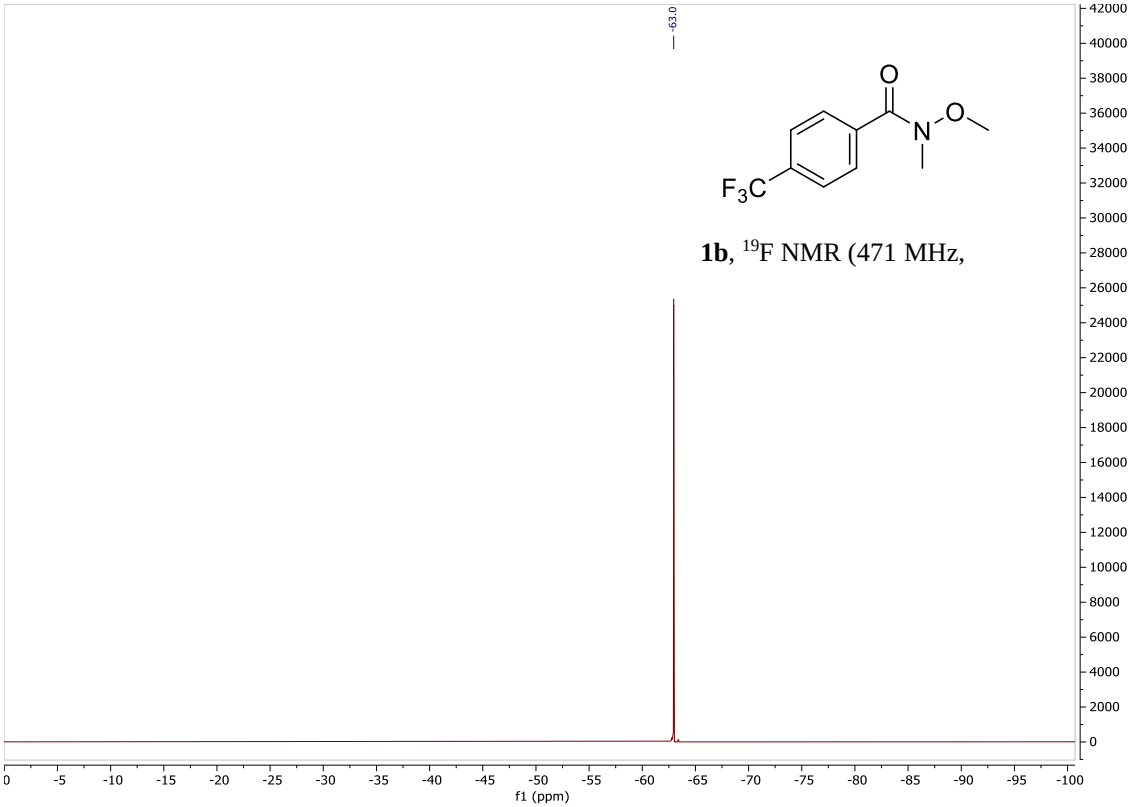
6. References

1 A. Pees, A. D. Windhorst, M. J. W. D. Vosjan, V. Tadino and D. J. Vugts, *Eur. J. Org. Chem.*, 2020, **2020**, 1177–1185.
2 A. Pees, M. J. W. D. Vosjan, N. Vasdev, A. D. Windhorst and D. J. Vugts, *Chem. Commun.*, 2021, **57**, 5286–5289.
3 A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem. Int. Ed.*, 2020, **59**, 20515–20521.
4 N. Radhoff, C. G. Daniliuc and A. Studer, *Angew. Chem. Int. Ed.*, 2023, **62**, e202304771.
5 D. N. Primer and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 9847–9850.
6 Y. Yang, J. Liu, F. S. Kamounah, G. Ciancaleoni and J.-W. Lee, *J. Org. Chem.*, 2021, **86**, 16867–16881.
7 C. Lamberth, S. Trah, S. Wendeborn, R. Dumeunier, M. Courbot, J. Godwin and P. Schneiter, *Bioorg. Med. Chem.*, 2012, **20**, 2803–2810.
8 R. Krishnamoorthy, S. Q. Lam, C. M. Manley and R. J. Herr, *J. Org. Chem.*, 2010, **75**, 1251–1258.
9 N. Salaverri, B. Carli, S. Díaz-Tendero, L. Marzo and J. Alemán, *Org. Lett.*, 2022, **24**, 3123–3127.
10 S. Plöger and A. Studer, *Org. Lett.*, 2022, **24**, 8568–8572.
11 D. Chen, L. Xu, B. Ren, Z. Wang and C. Liu, *Org. Lett.*, 2023, **25**, 4571–4575.
12 J.-L. Tu, A.-M. Hu, L. Guo and W. Xia, *J. Am. Chem. Soc.*, 2023, **145**, 7600–7611.
13 D. M. Rudzinski, C. B. Kelly and N. E. Leadbeater, *Chem. Commun.*, 2012, **48**, 9610.
14 M. S. Said, N. S. Khonde, P. Kumar and J. M. Gajbhiye, *Org. Lett.*, 2023, **25**, 1094–1098.
15 J. Huang, X. Yan and Y. Xia, *Angew. Chem. Int. Ed.*, 2022, **61**, e202211080.
16 X. Liu, L. Liu, T. Huang, J. Zhang, Z. Tang, C. Li and T. Chen, *Org. Lett.*, 2021, **23**, 4930–4934.
17 A. Sanz-Marco, G. Blay, M. C. Muñoz and J. R. Pedro, *Chem. Commun.*, 2015, **51**, 8958–8961.

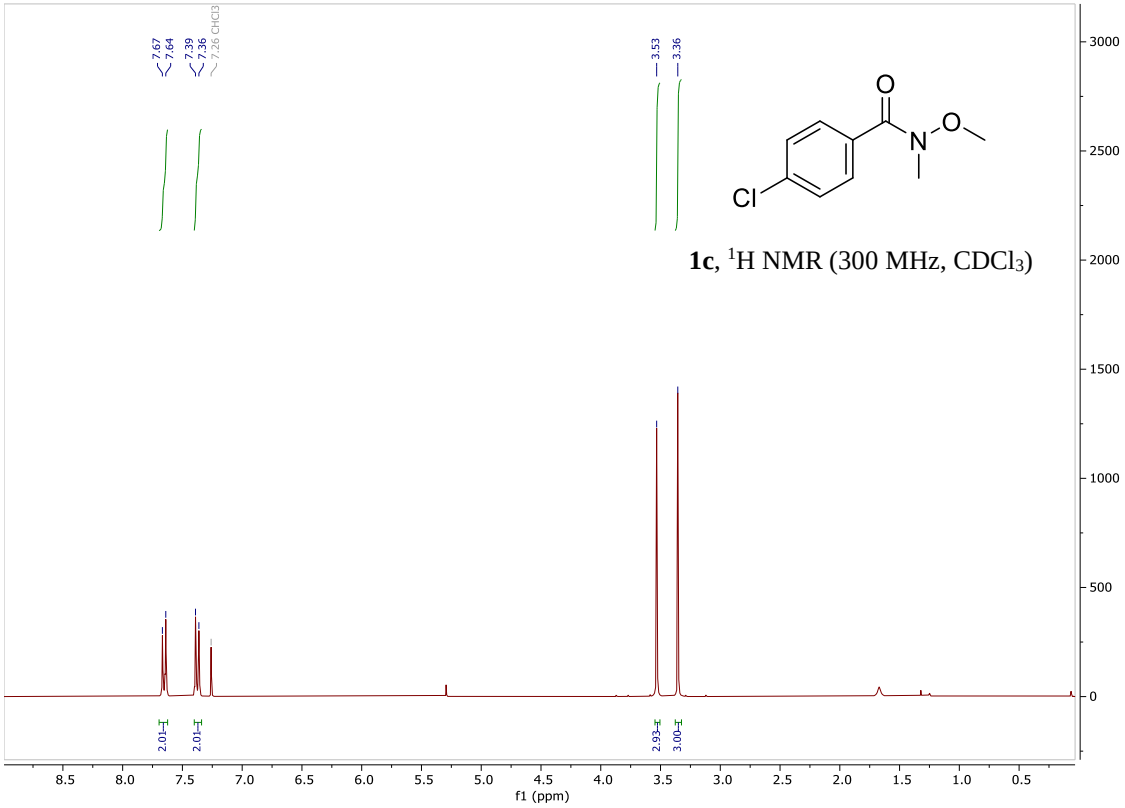
7. NMR spectra



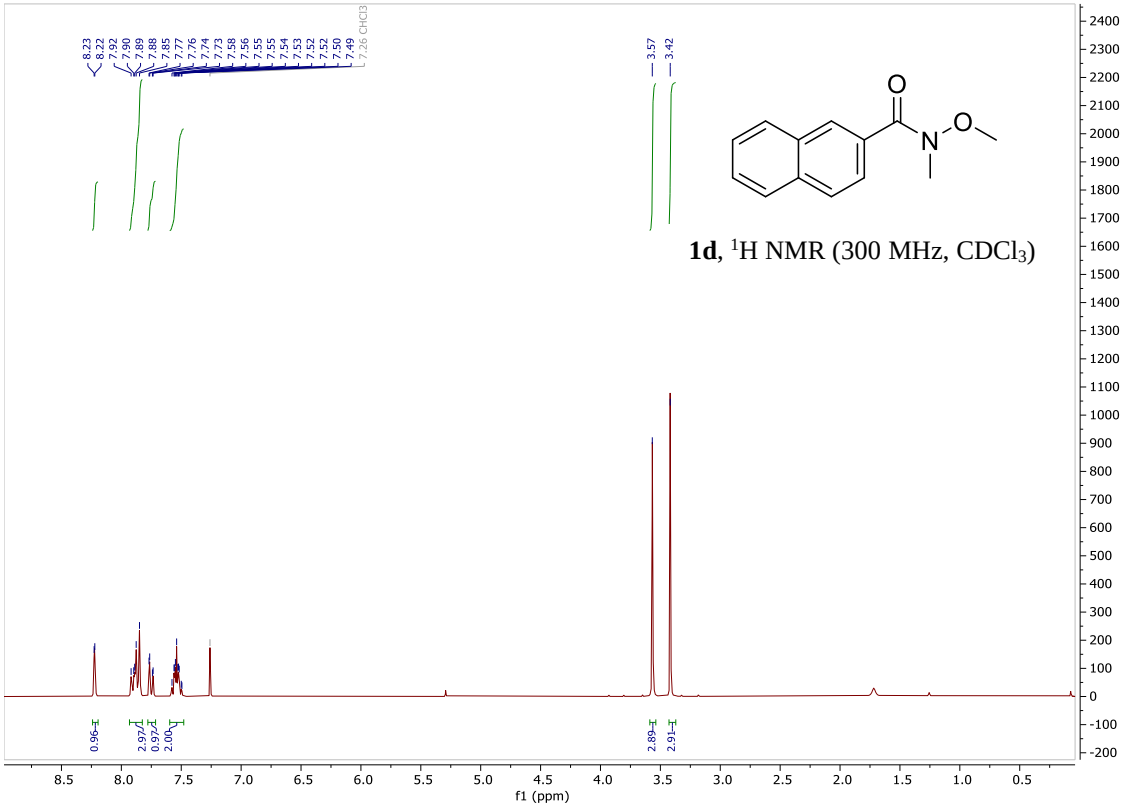
1b, ^{1}H NMR (300 MHz, $CDCl_3$)



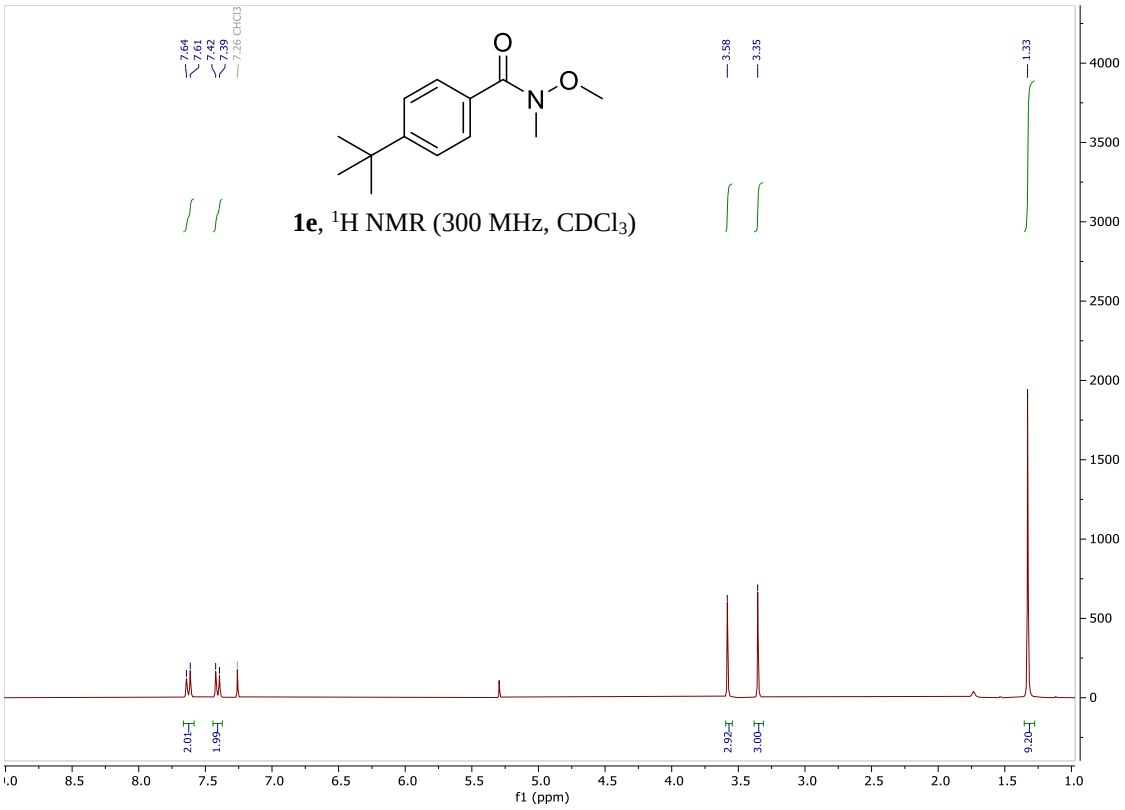
1b, ^{19}F NMR (471 MHz,



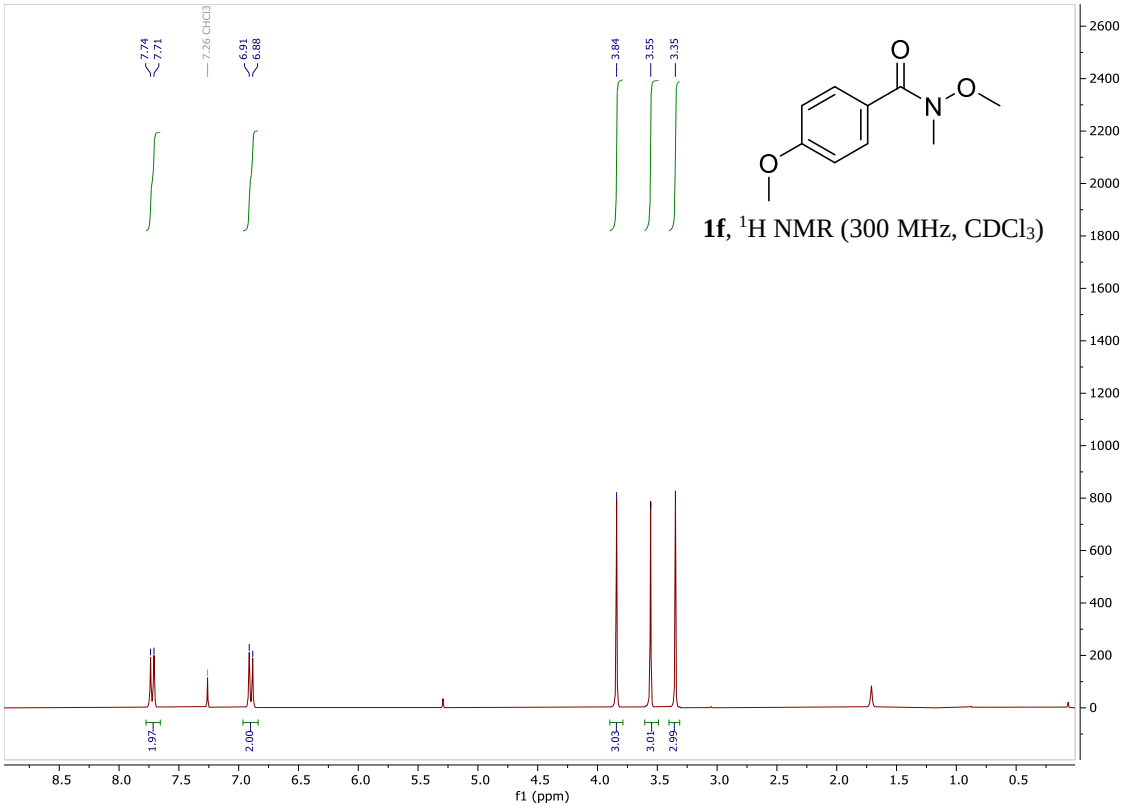
1c, ^{1}H NMR (300 MHz, $CDCl_3$)



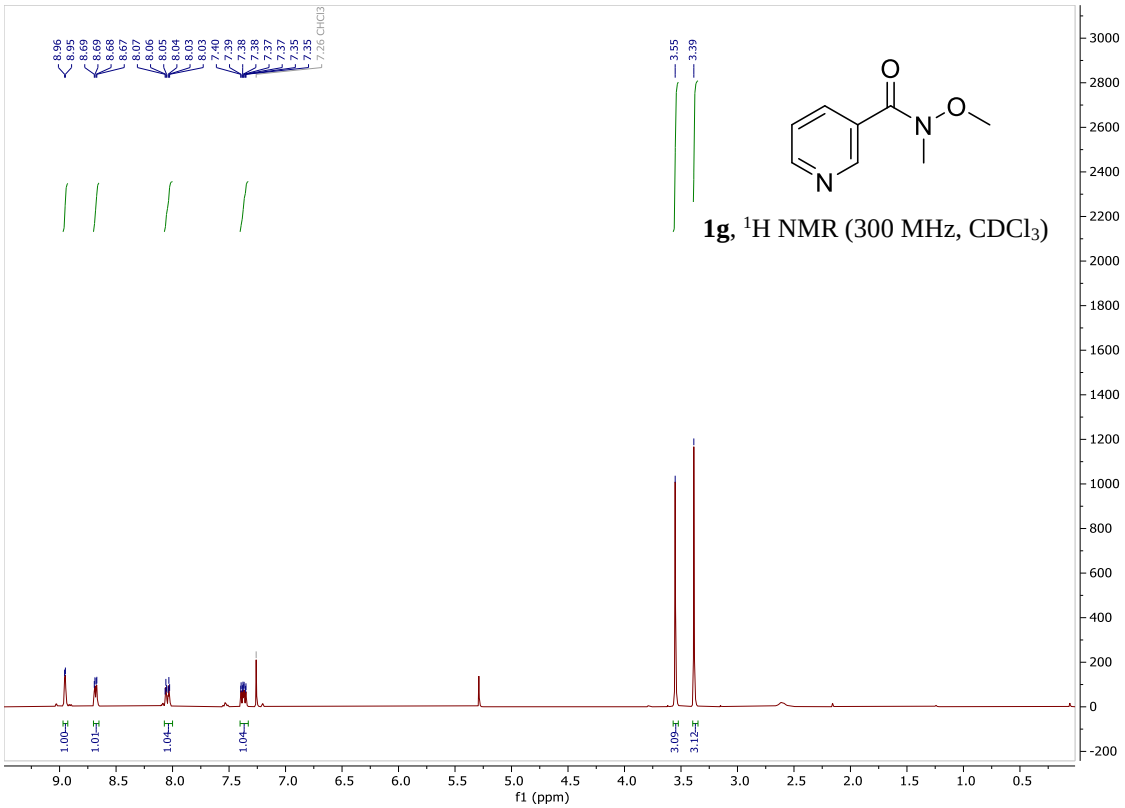
1d, ^{1}H NMR (300 MHz, $CDCl_3$)



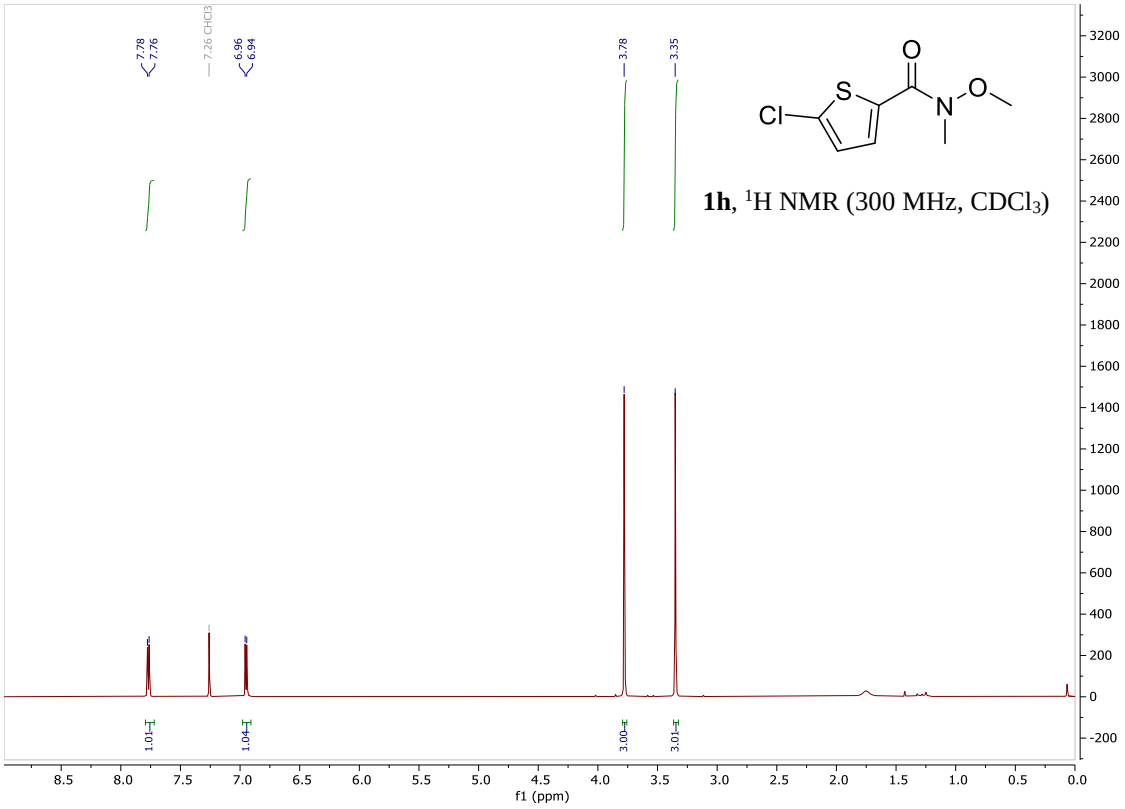
1e, ^{1}H NMR (300 MHz, $CDCl_3$)



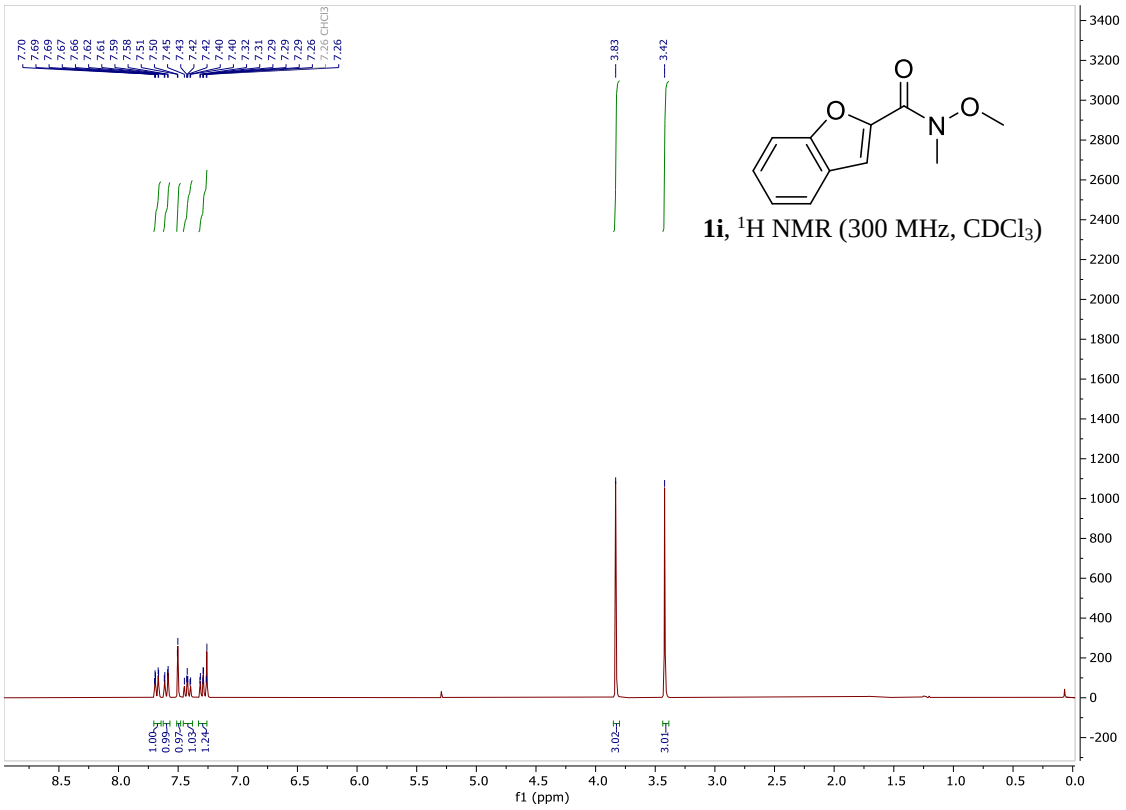
1f, ^{1}H NMR (300 MHz, $CDCl_3$)



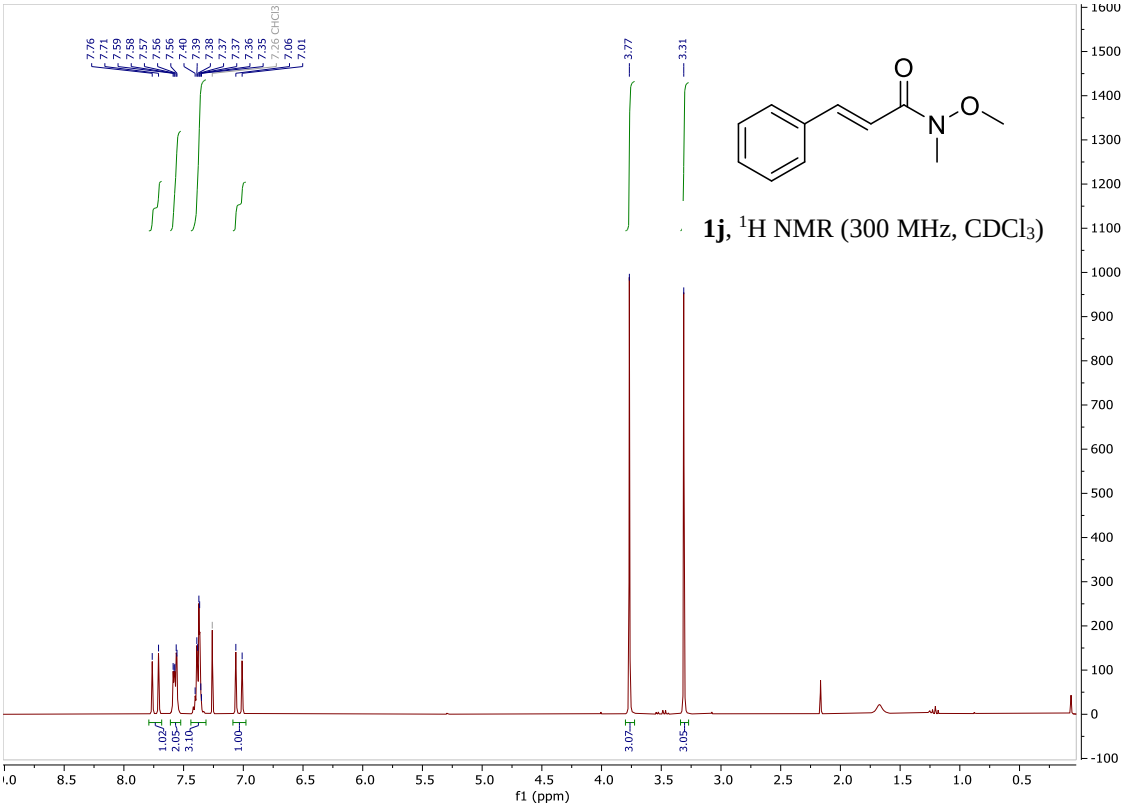
1g, ^{1}H NMR (300 MHz, $CDCl_3$)



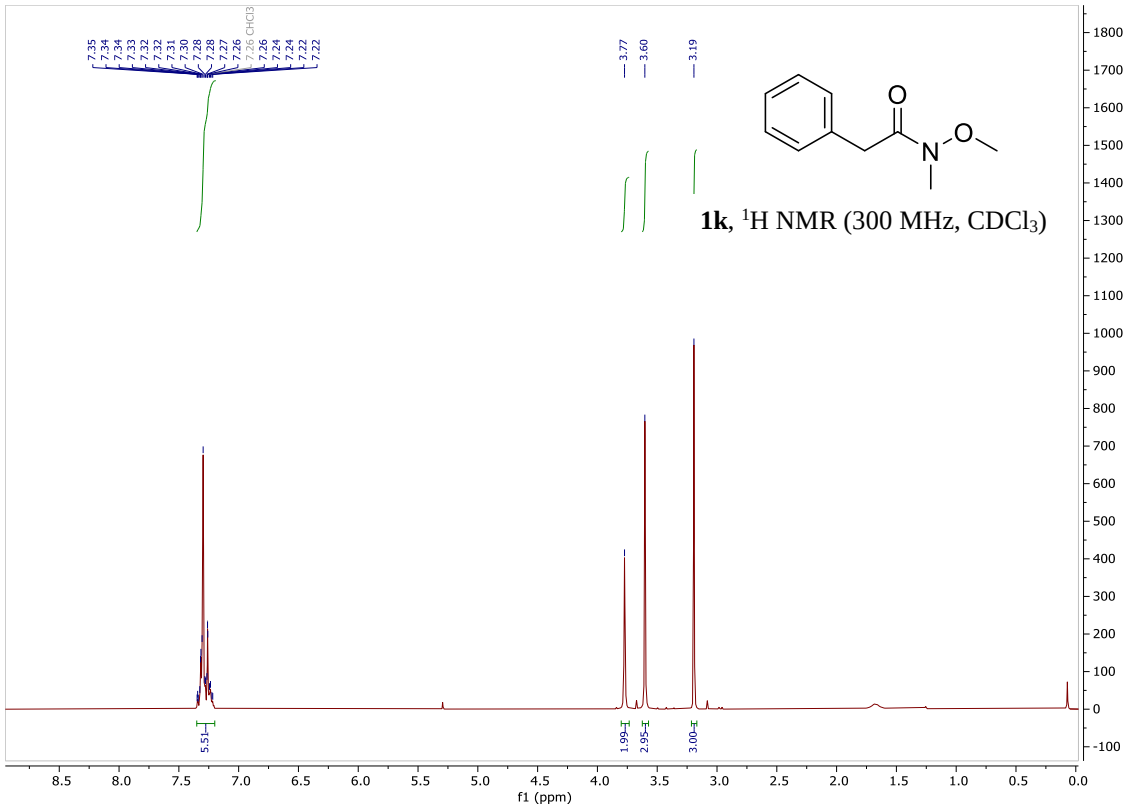
1h, ^{1}H NMR (300 MHz, $CDCl_3$)



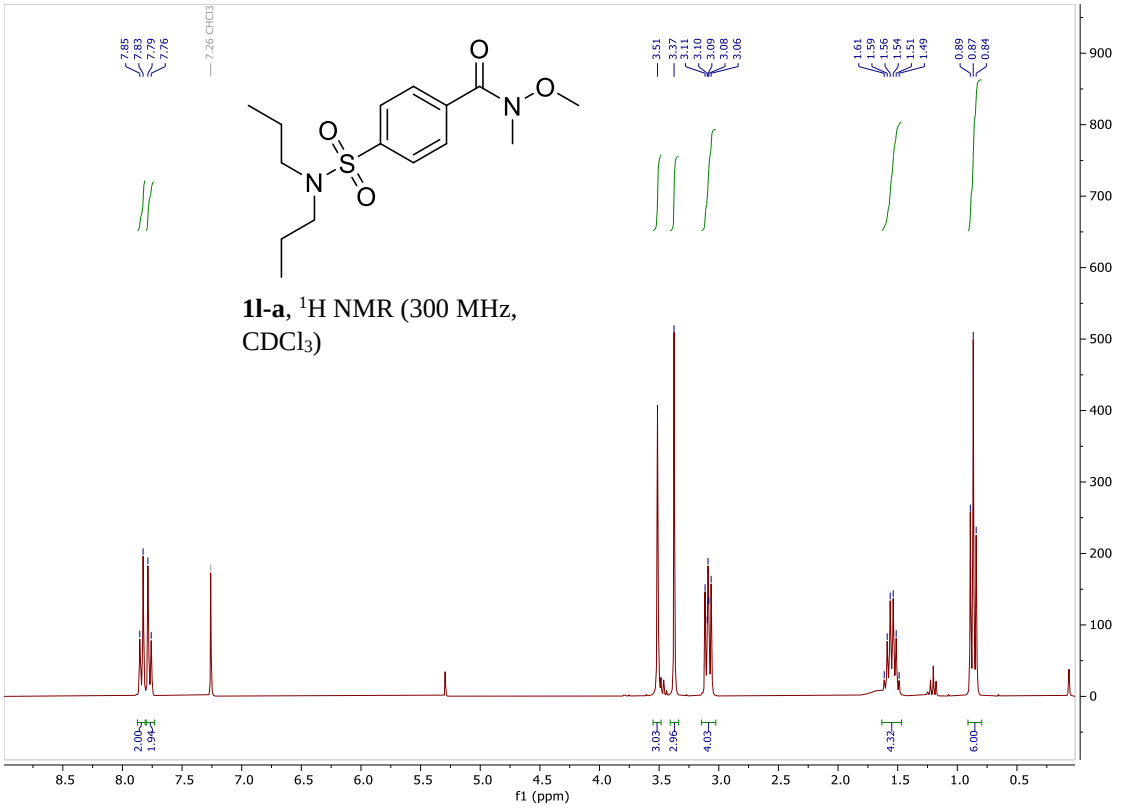
1i, ^{1}H NMR (300 MHz, $CDCl_3$)



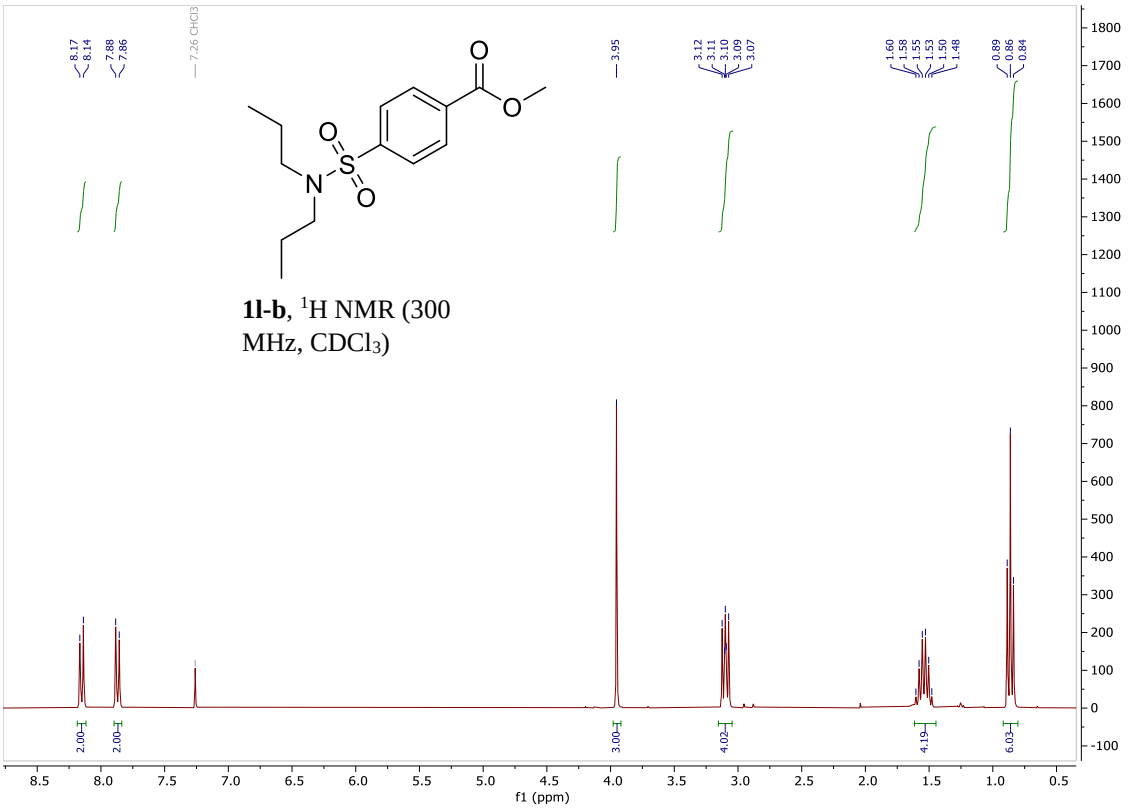
1j, ^{1}H NMR (300 MHz, $CDCl_3$)



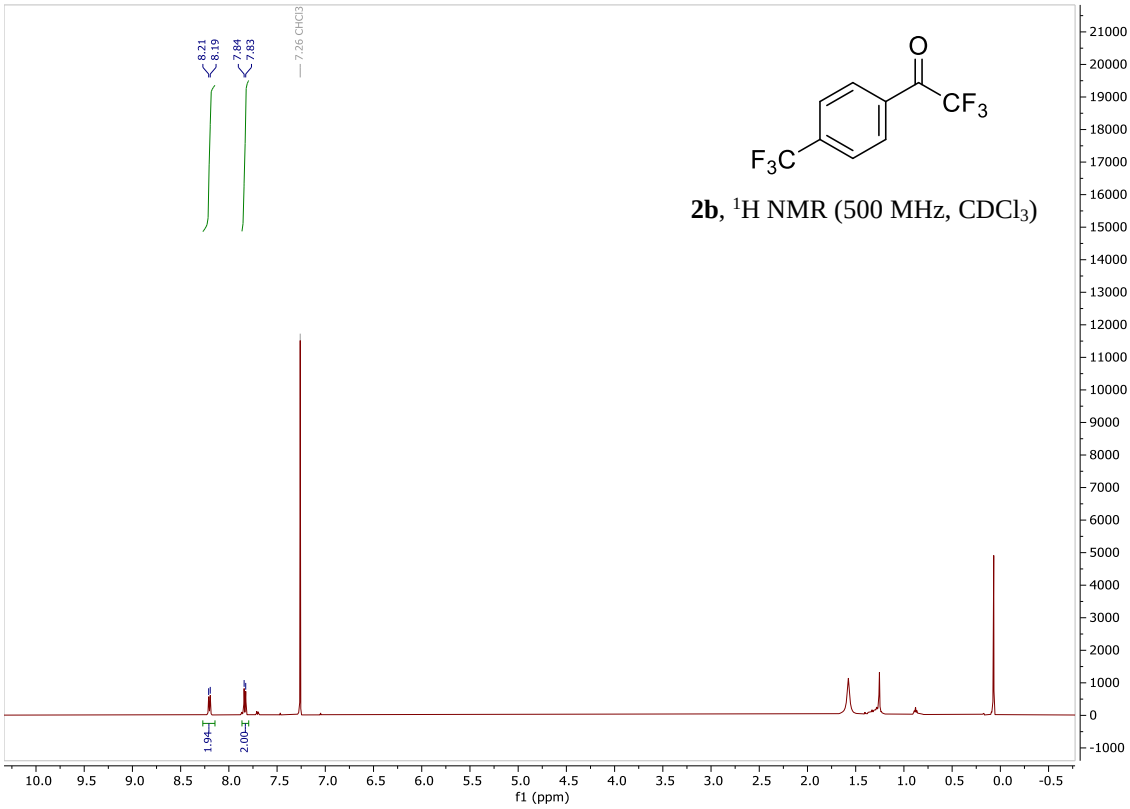
1k, ^{1}H NMR (300 MHz, $CDCl_3$)



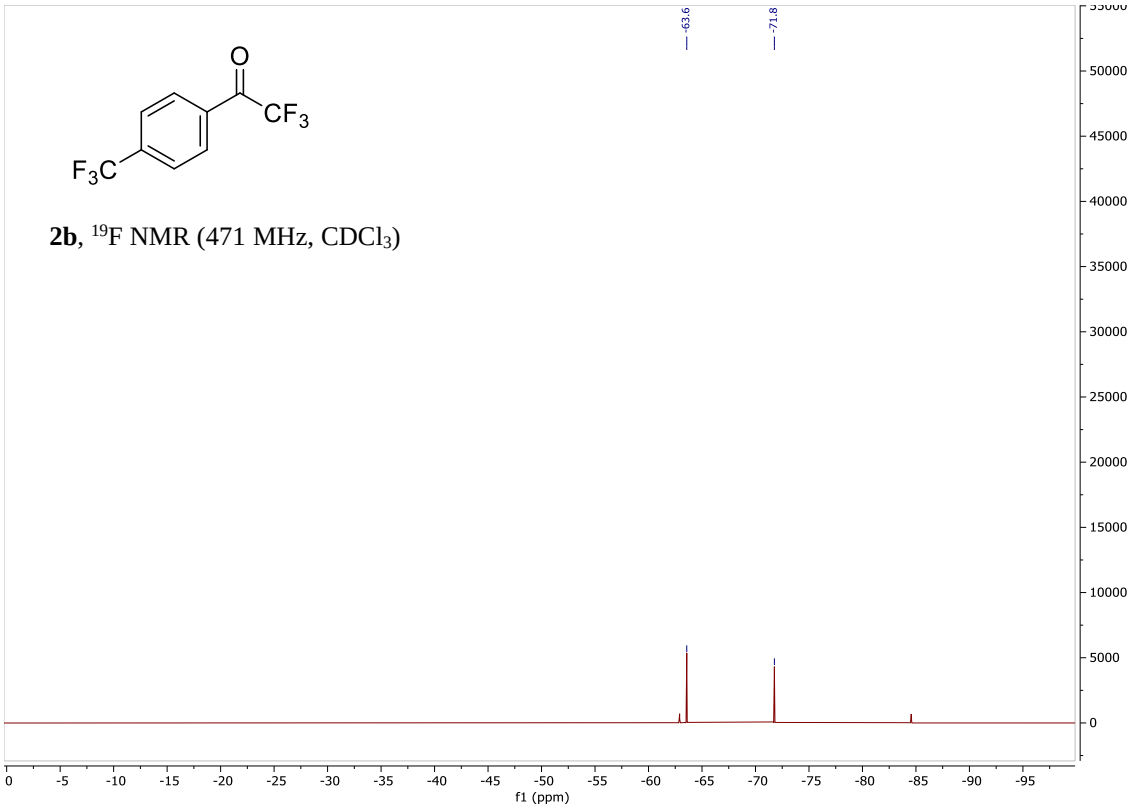
1l-a, ^{1}H NMR (300 MHz, $CDCl_3$)



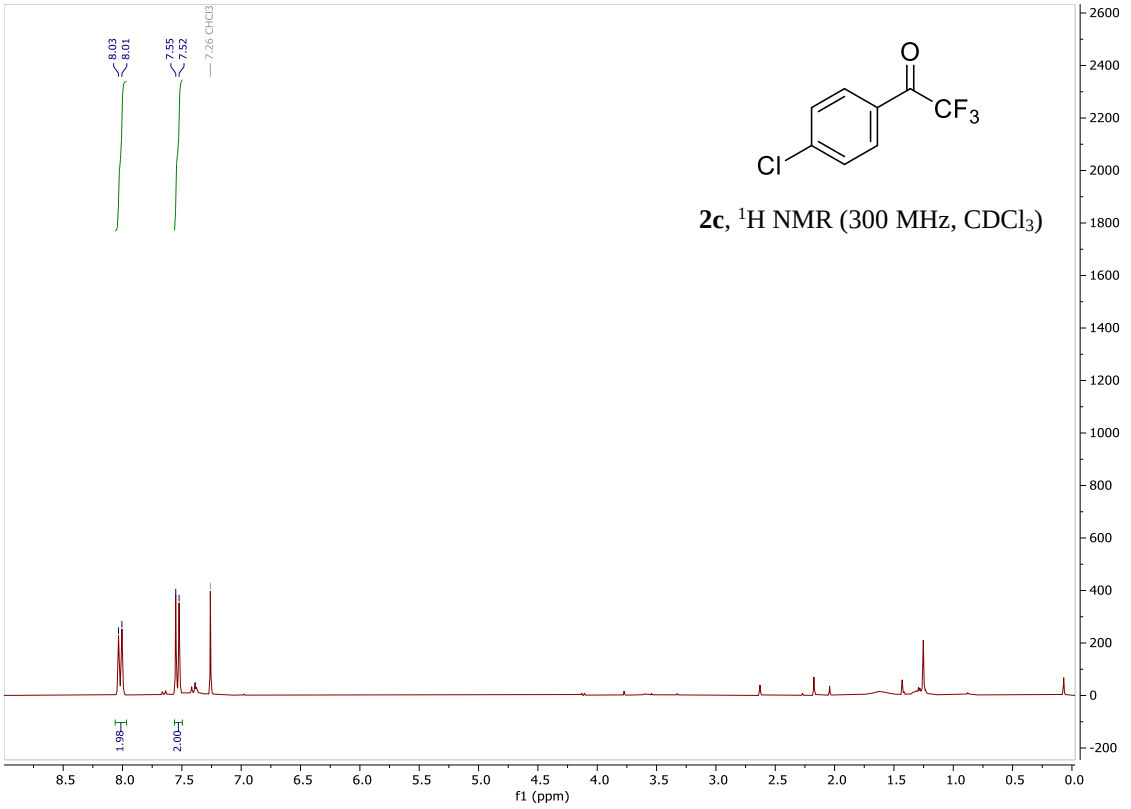
1l-b, ^{1}H NMR (300 MHz, $CDCl_3$)



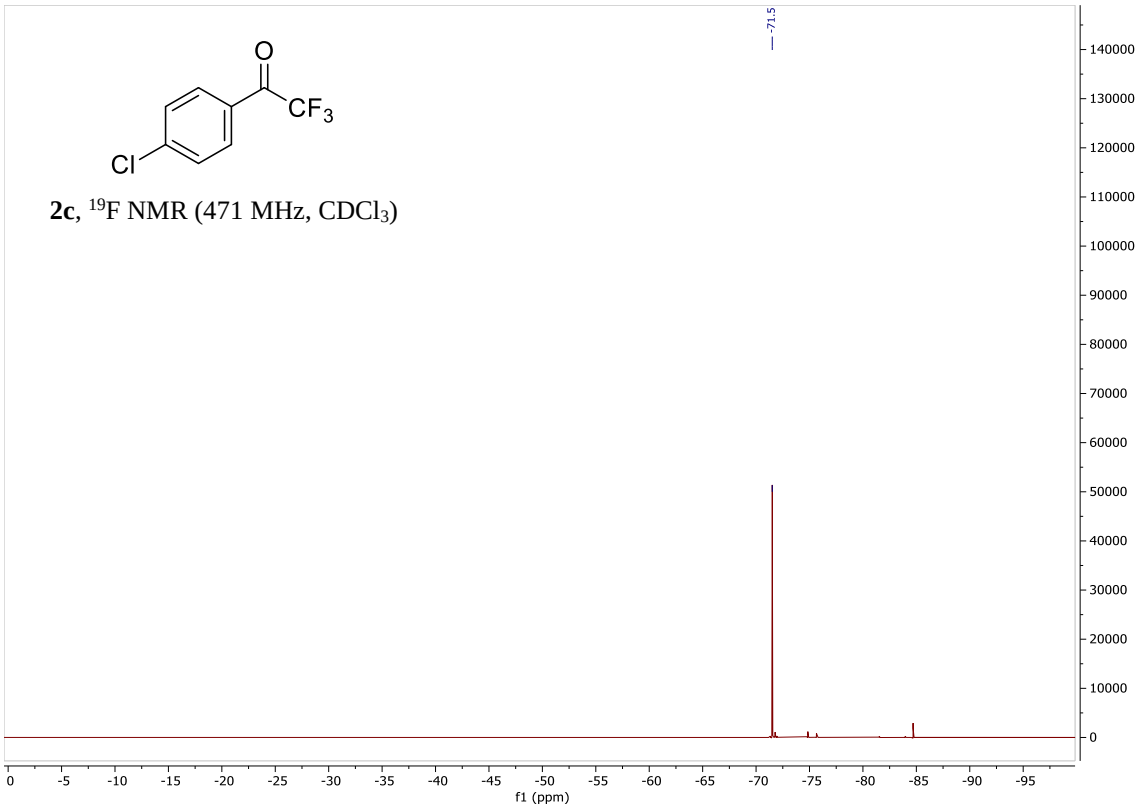
2b, ^{1}H NMR (500 MHz, $CDCl_3$)



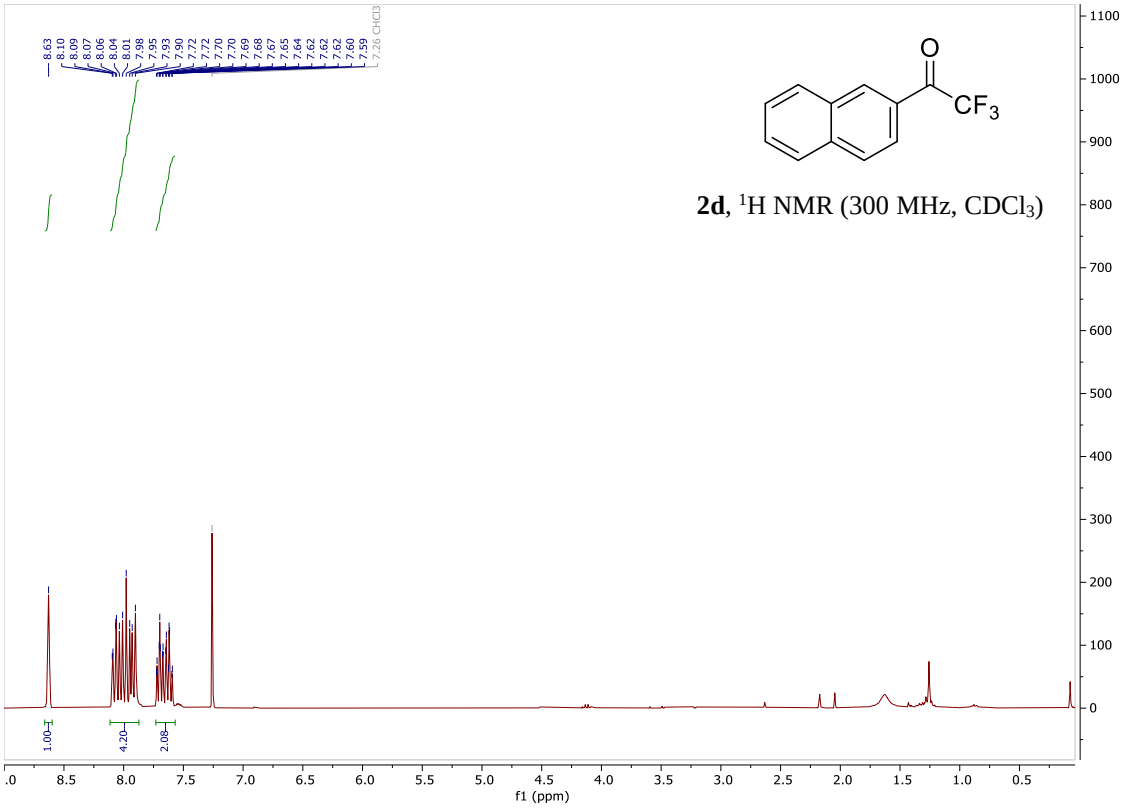
2b, ^{19}F NMR (471 MHz, $CDCl_3$)



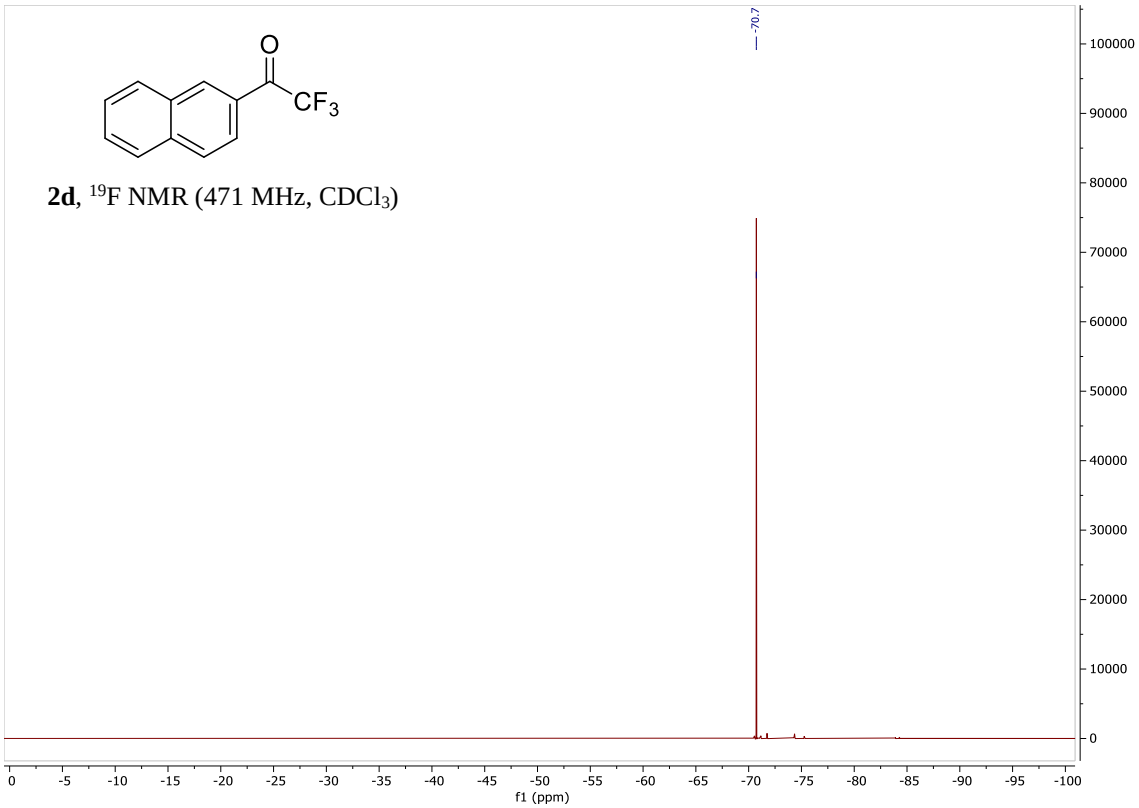
2c, ^{1}H NMR (300 MHz, $CDCl_3$)



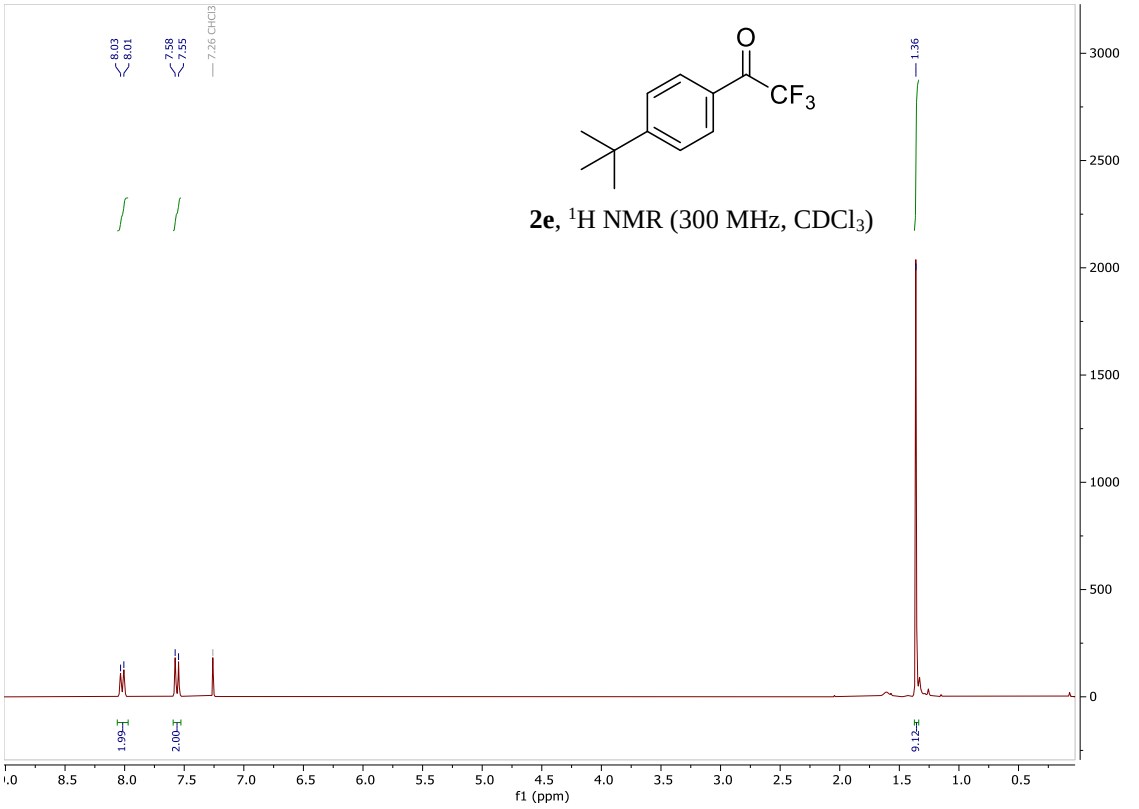
2c, ^{19}F NMR (471 MHz, $CDCl_3$)



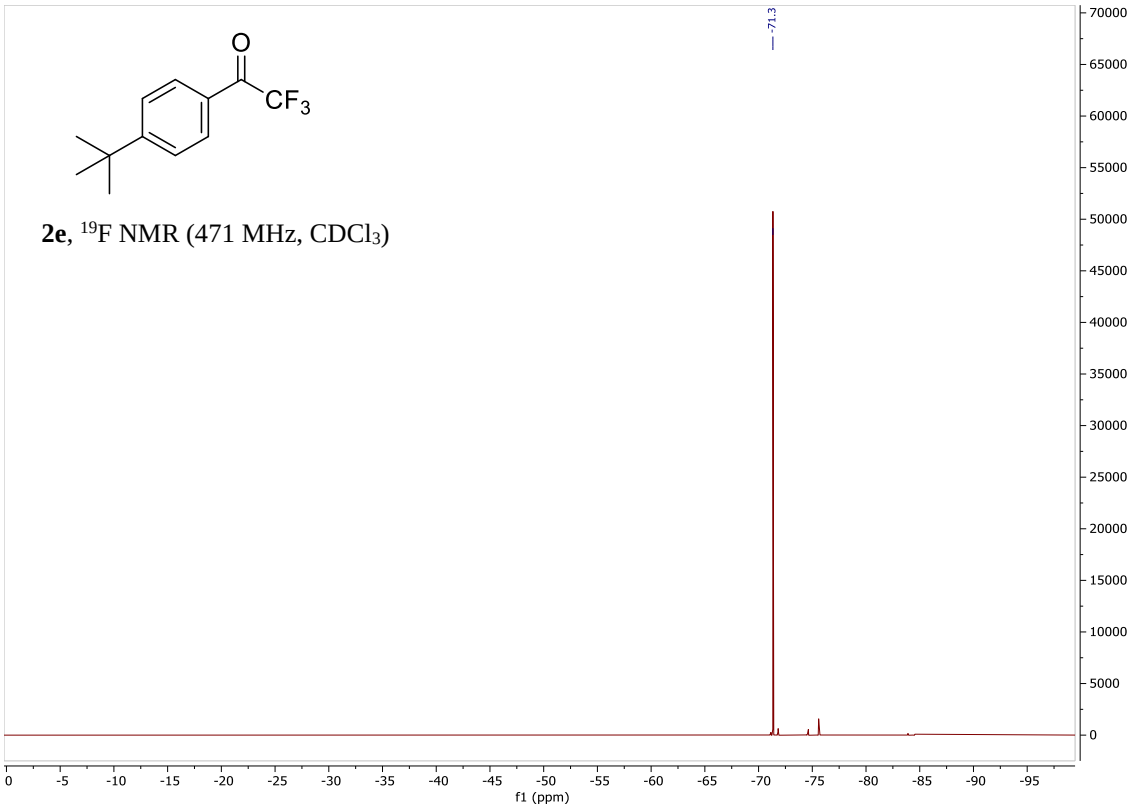
2d, ^{1}H NMR (300 MHz, $CDCl_3$)



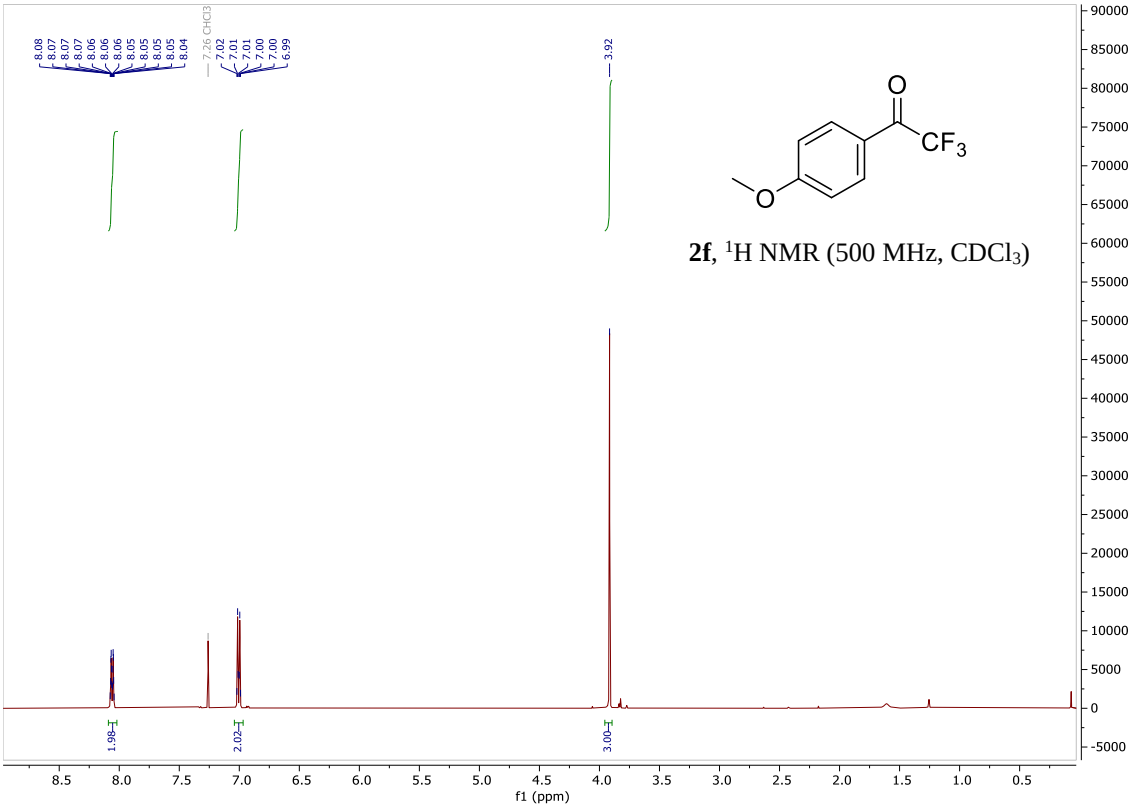
2d, ^{19}F NMR (471 MHz, $CDCl_3$)



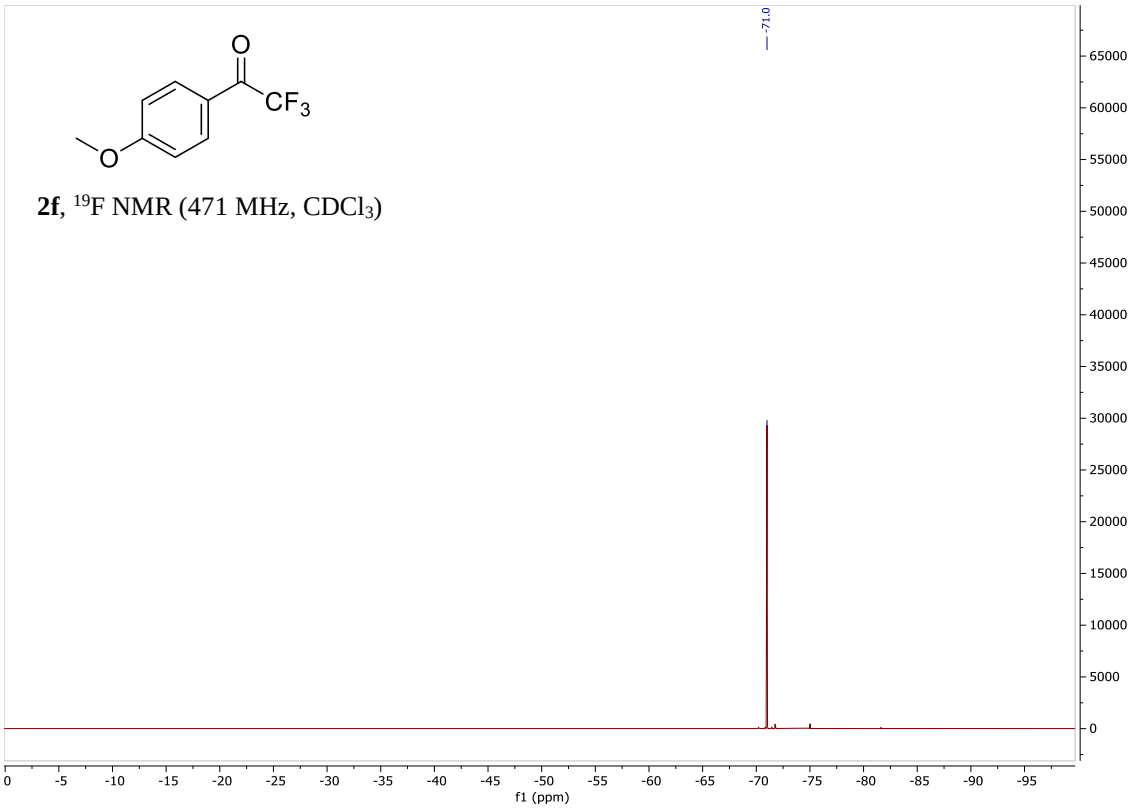
2e, ^{1}H NMR (300 MHz, $CDCl_3$)



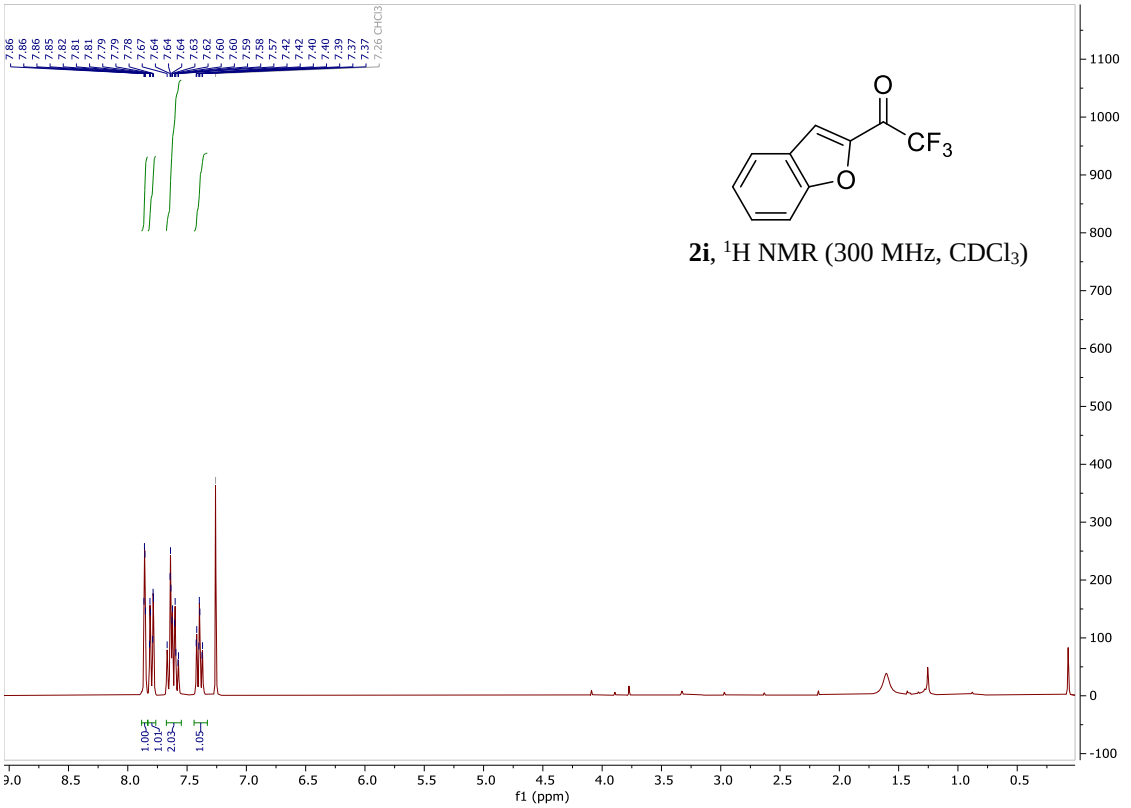
2e, ^{19}F NMR (471 MHz, $CDCl_3$)



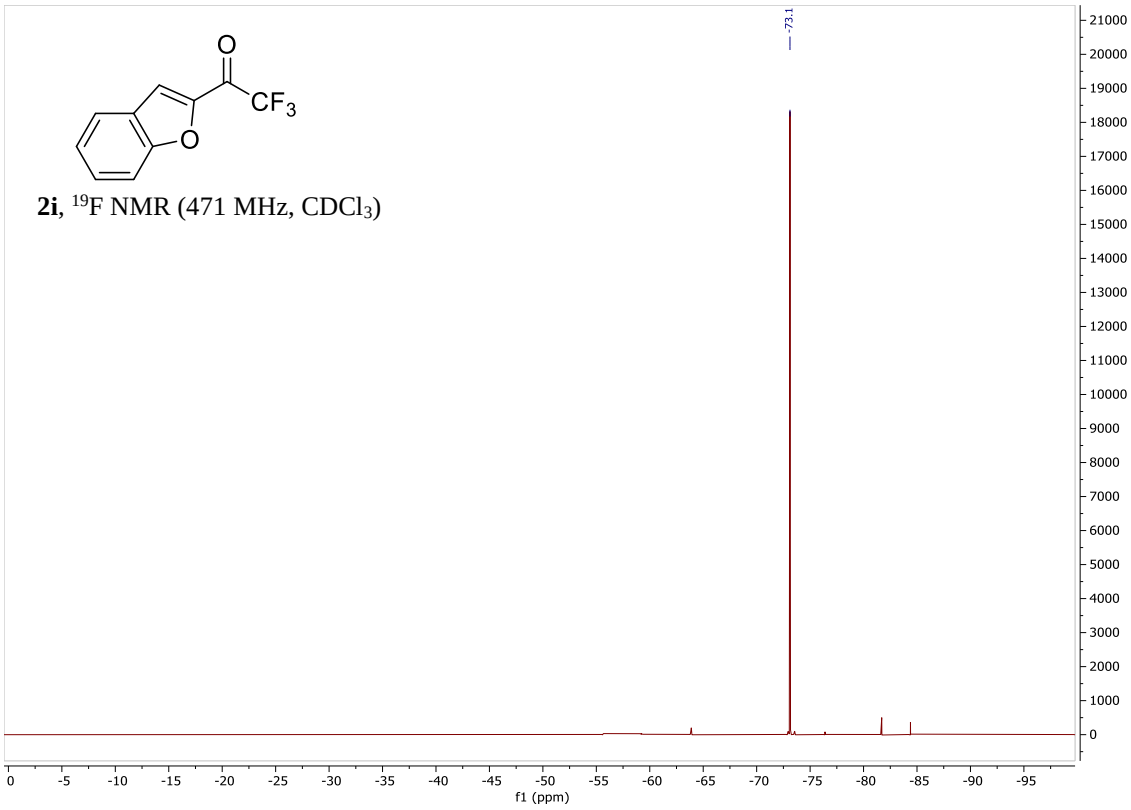
2f, ^{1}H NMR (500 MHz, $CDCl_3$)



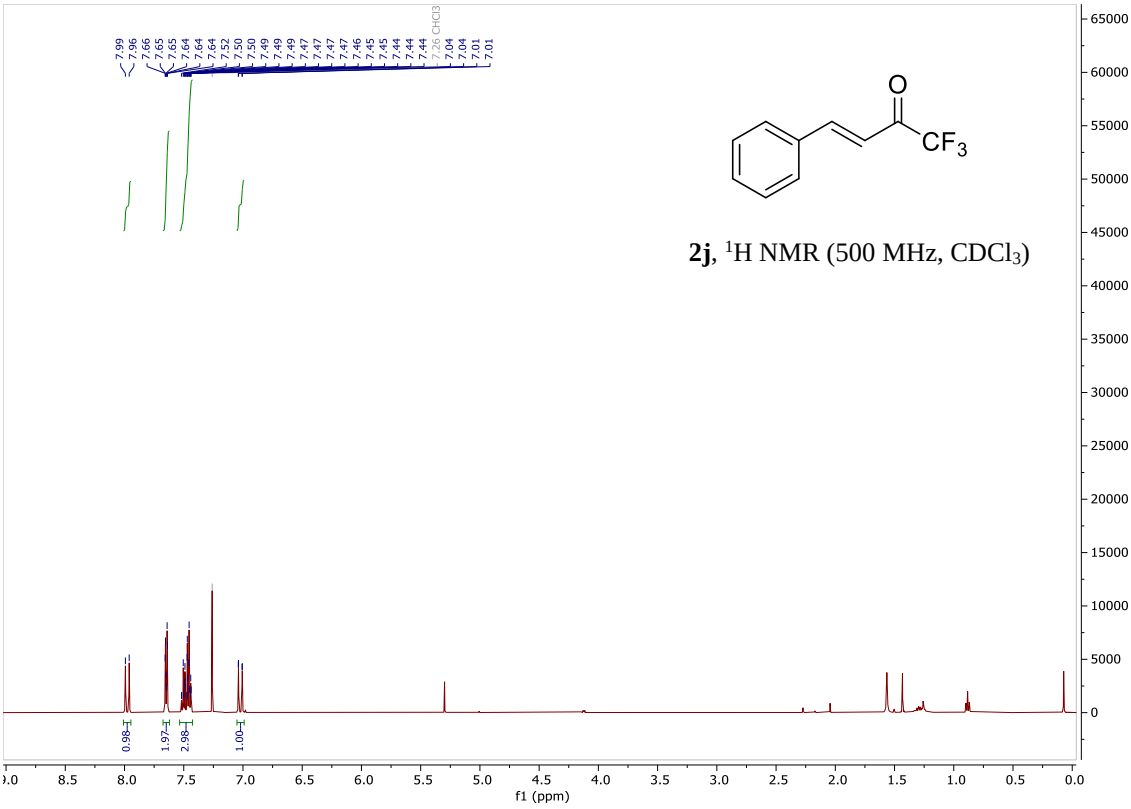
2f, ^{19}F NMR (471 MHz, $CDCl_3$)



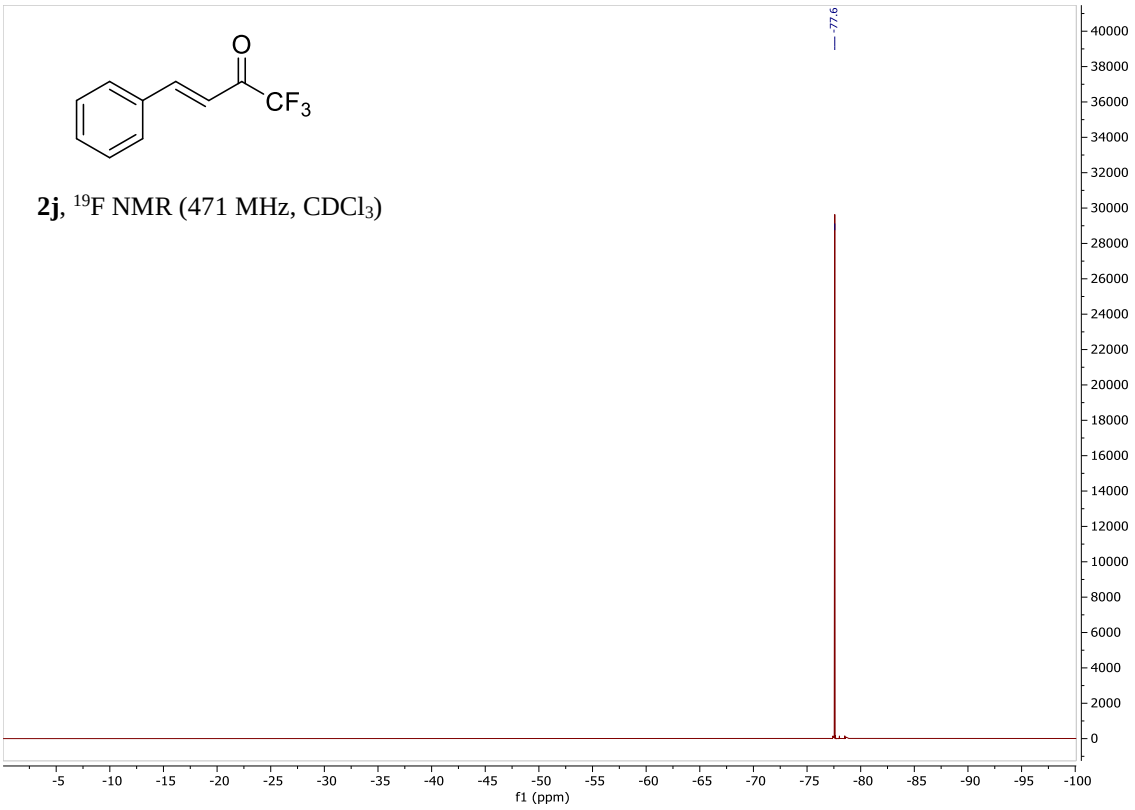
2i, ^{1}H NMR (300 MHz, $CDCl_3$)



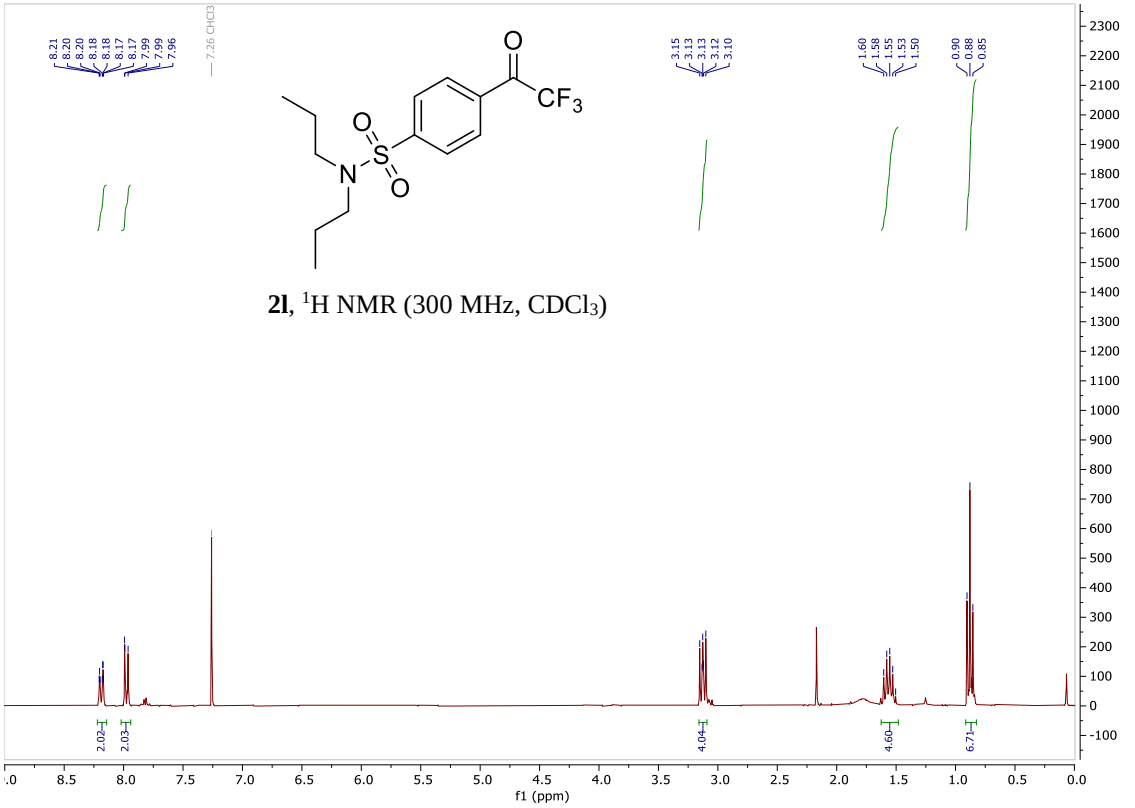
2i, ^{19}F NMR (471 MHz, $CDCl_3$)



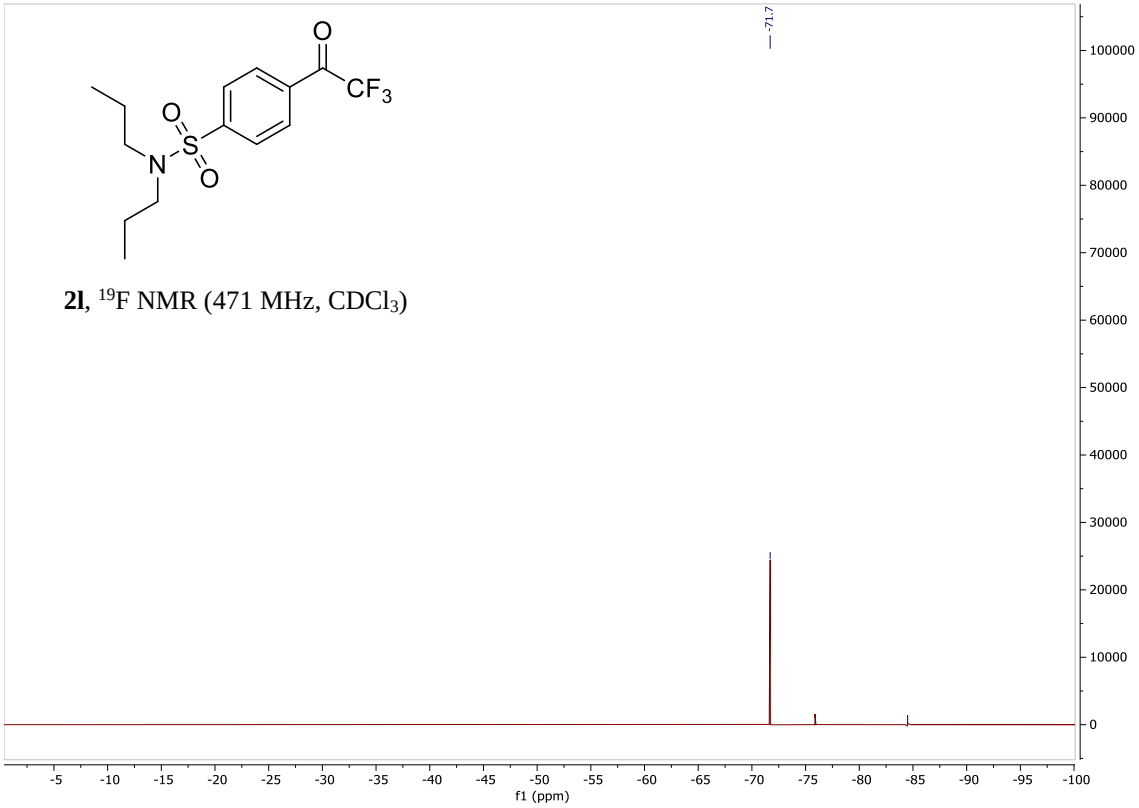
2j, ^{1}H NMR (500 MHz, $CDCl_3$)



2j, ^{19}F NMR (471 MHz, $CDCl_3$)



2l, ^{1}H NMR (300 MHz, $CDCl_3$)



2l, ^{19}F NMR (471 MHz, $CDCl_3$)