Supporting Information

Efficient solvent-free synthesis of quaternary α-hydroxy α-trifluoromethyldiazenes: Key step of a nucleophilic formylation strategy

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1. General Information.

Spectra were recorded at [^{1}H NMR (300 or 500 MHz); ^{13}C NMR (75.5 MHz); ^{19}F NMR (470.6 MHz)] with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminum backed plates (1.5 × 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light or by dipping the plates in solutions of $KMnO_4$, vainilline or phosphomolibdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. Formaldehyde hydrazones **2**-**4**[1] and not commercially available trifluoromethylketones **1**[2] were synthesized according to literature procedures.

[1] J.-S. M. Lehn, S. Javed, D. M. Hoffman, Inorg. Chem. 2007, 46, 993.

[2] Trifluormethyl ketones **1** were prepared by Grignard reagent addition to 2,2,2-ethyltrifluoroacetate: a) For catacterization of trifluoromethyl ketone **1g** see K. Fuchibe, H. Jyono, M. Fujiwara, T. Kudo, M. Yokota, and J. Ichiwaka, *Chem. Eur. J.* 2011, **17**, 12175. For catacterization of trifluoromethyl ketone **1i** see E. Massolo, M. Benaglia, M. Orlandini, S. Rossi, and G. Celentano, *Chem. Eur. J.* 2015, **21**, 3589.

2. Optimization of the reaction conditions.

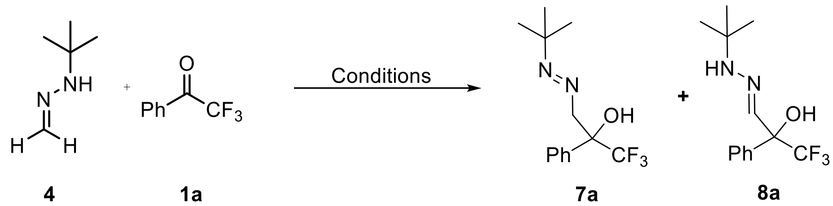


Table 1. Results obtained.

Method	Entry	Solvent	t	**7a:8a**	Yield (%)	*E*-factor	*E-factor* (global process)
A	1	CH_2Cl_2	9 h	10:0	83	12.06	2193
	2	$CHCl_3$	7 h	8:2	70	16.29	2602
	3	*n*-hexane	31 h	10:0	80	6.48	2269
	4	toluene	31 h	10:0	81	8.26	2243
	5	Et_2O	31 h	10:0	74	7.62	2454
	6	CH_3CN	6 h	10:0	90	6.68	2018
B	7	H_2O	45 min	10:0	90	1.31	43
C	8	--	20 min	10:0	>99	0.18	0,18

Method A

Freshly distilled formaldehyde *tert*-butylhydrazone **4** (79 µL, 0.75 mmol) was added to a solution of 2,2,2-trifluoro-1-phenylethan-1-one (**1a**) (70 µL, 0.5 mmol) in the corresponding organic solvent (1 mL) at room temperature. The mixture was stirred for the time specified in each solvent (**Table 1**, tlc monitoring). After completion of the reaction, the solvent was removed under reduced pressure and the crude was purified by flash chromatography (hexane/CH_2Cl_2, 1/1) to afford the pure diazene **7a**.

Method B

Freshly distilled formaldehyde *tert*-butylhydrazone **4** (79 µL, 0.75 mmol) was added to a emulsion of 2,2,2-trifluoro-1-phenylethan-1-one (**1a**) (70 µL, 0.5 mmol) in water (1 mL) at room temperature. The mixture was stirred for 45 minutes (tlc monitoring). The organic phase was extracted with Et_2O (2x3 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the pure diazene **7a** (123 mg, 90%).

Method C

Freshly distilled formaldehyde *tert*-butylhydrazone **4** (79 µL, 0.75 mmol was added to 2,2,2-trifluoro-1-phenylethan-1-one (**1a**) (70 µL, 0.5 mmol) at room temperature. The mixture was stirred for 20 minutes (tlc monitoring) and the hydrazone excess was removed under reduced pressure to afford the pure diazene **7a** (135 mg, 99%).

3. *E-factor* calculation.

The E-factor is the measure of the amount of a waste generated while making a product. The simple ratio of units of waste divided by units of product tells us that the lower the E-factor, the less waste is produced. In this case, for the model reaction *E-factor* was calculated as follow:

$$E_{factor} = \frac{Amount\ of\ waste}{Amount\ of\ final\ product} = \frac{Amount\ of\ all\ reactants - Amount\ of\ final\ product}{Amount\ of\ final\ product} =$$

$$= \frac{(Amount\ of\ hydrazone\ \mathbf{4} + Amount\ of\ ketone\ \mathbf{1a} + Amount\ of\ solvent) - Amount\ of\ diazene\ \mathbf{7a}}{Amount\ of\ diazene\ \mathbf{7a}}$$

Entry	Hydrazone **1a** (mg)	Ketone **3a** (mg)	**1a/3a** ratio	Solvent (mL)	Density solvent (mg/mL)	Solvent (mg)	Diazene **4a**	***E-factor***	Solvent elaboration (mg)[a]	***E-factor* (global process)**
1 (CH_2Cl_2)	75	87	1.5/1	1	1,33E+03	1,33E+03	114	12,08	2,48E+05	2193
2 ($CHCl_3$)	75	87	1.5/1	1	1,50E+03	1,50E+03	96	16,31	2,48E+05	2602
3 (*n*-hexane)	75	87	1.5/1	1	6,59E+02	6,59E+02	110	6,49	2,48E+05	2269
4 (toluene)	75	87	1.5/1	1	8,67E+02	8,67E+02	111	8,27	2,48E+05	2243
5 (Et_2O)	75	87	1.5/1	1	7,13E+02	7,13E+02	101	7,63	2,48E+05	2454
6 (CH_3CN)	75	87	1.5/1	1	7,86E+02	7,86E+02	123	6,69	2,48E+05	2018
7 (H_2O)	75	87	1.5/1	1	9,98E+02	9,98E+02	123	8,41	2,14E+04	43
8 (no solvent)	75	87	1.5/1	-	-	-	137	0,18	-	0,18
9 (no solvent)	75	87	1.5/1	-	-	-	137	0,18	-	0,18
10 (no solvent)	601	1,04E+03	1/1	-	-	-	1,64E+03	0,0004	-	0,0004

[a]*E-factor* (global process) was calculated considering the volume of solvent spent during the purification or extraction process. *Organic solvents (**1**-**6**)*: Chromatography column was performed employing 250 mL of a mixture hexane/CH_2Cl_2 1/1. *Water (**7**)*: Extraction requires 6 mL of Et_2O.

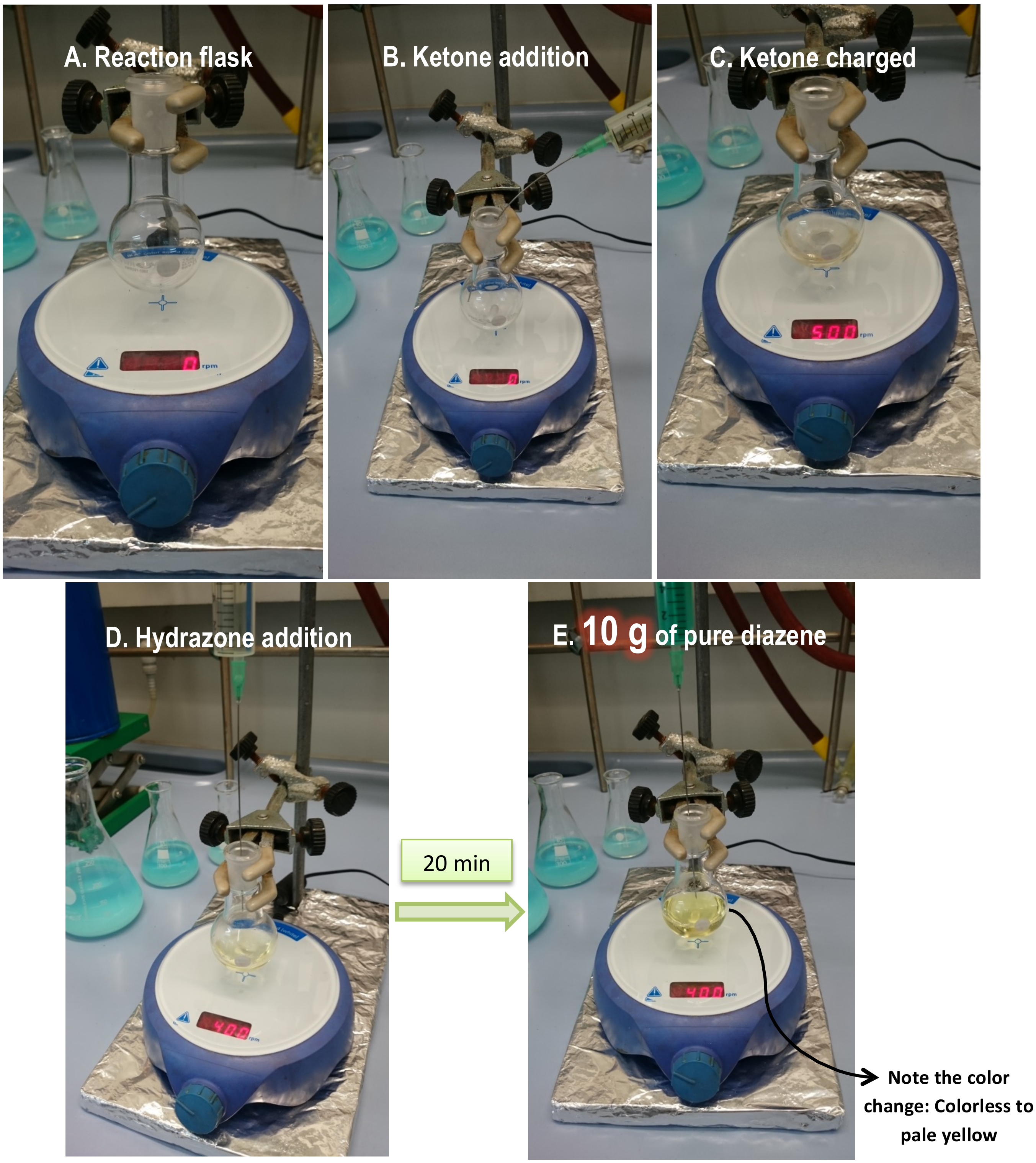
Molecular weights:

- Formaldehyde *tert*-butylhydrazone (**4**): 100.17 g/mol
- Trifluoromethyl ketone **1a**: 174.12 g/mol
- Diazene **7a**: 274.29 g/mol

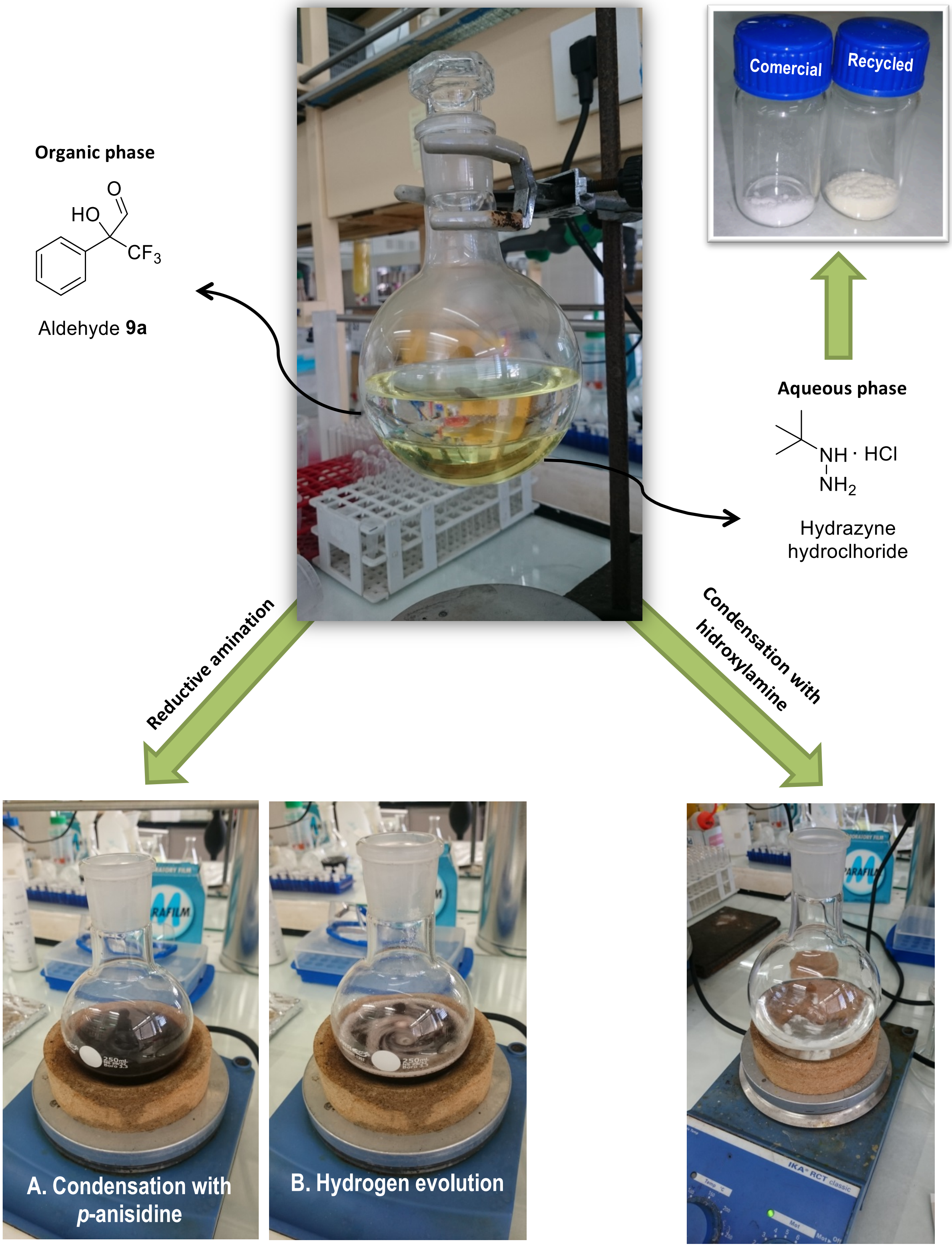
4. Scaling-up of the model reaction.

In this section some pictures of the scaling-up are shown. Hydrolysis, reductive amination and condensation with hydroxylamine are also included.

Addition of formaldehyde tert-butilhydrazone **4** *to trifluoromethylketone* ***1a***

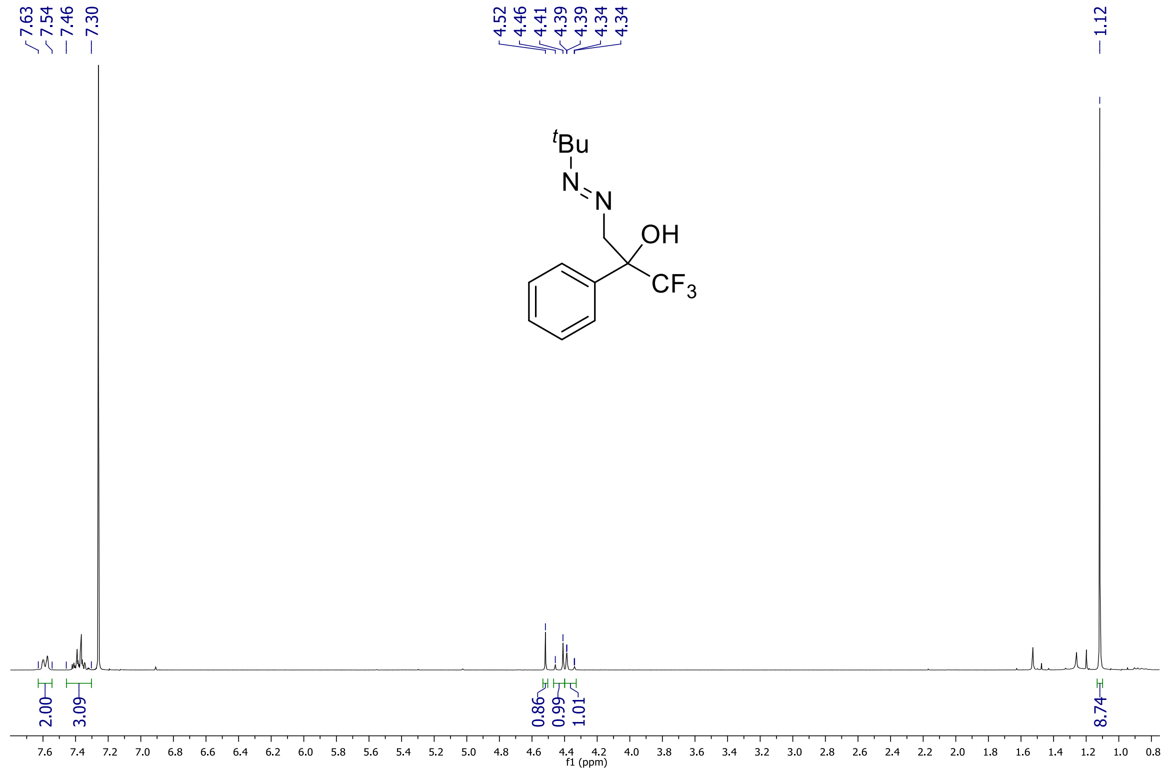


*Hydrolysis of diazene **7a** to afford α-hydroxyaldehyde **9a** in one-pot fashion and some of its transformations*

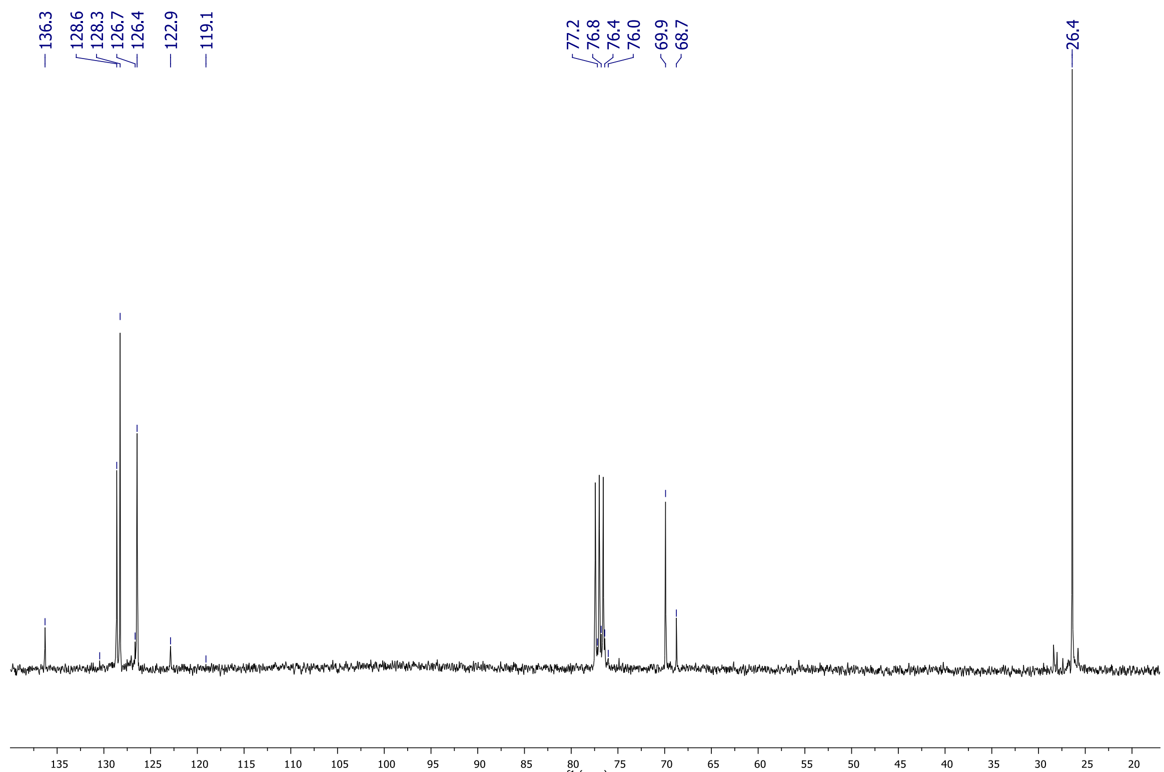


5. NMR spectra for new compounds

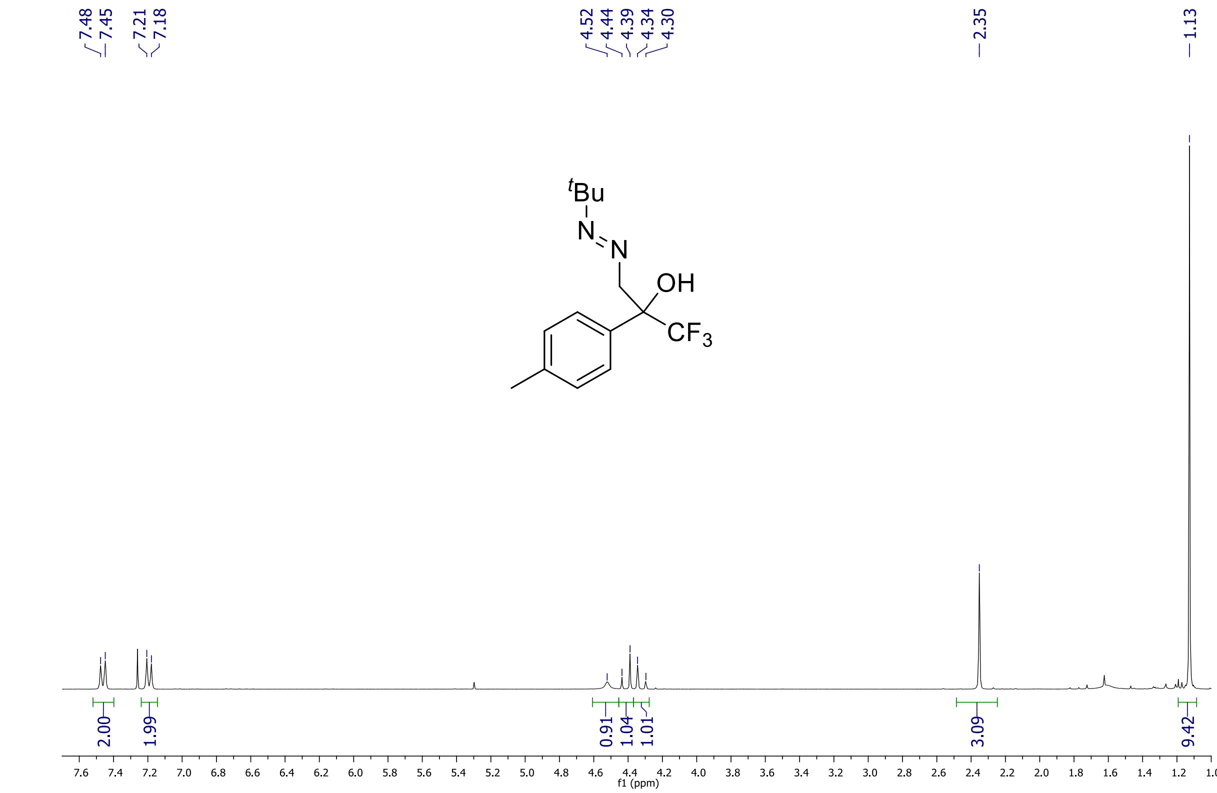
^{1}H NMR ($CDCl_3$, 300 MHz) of **7a**



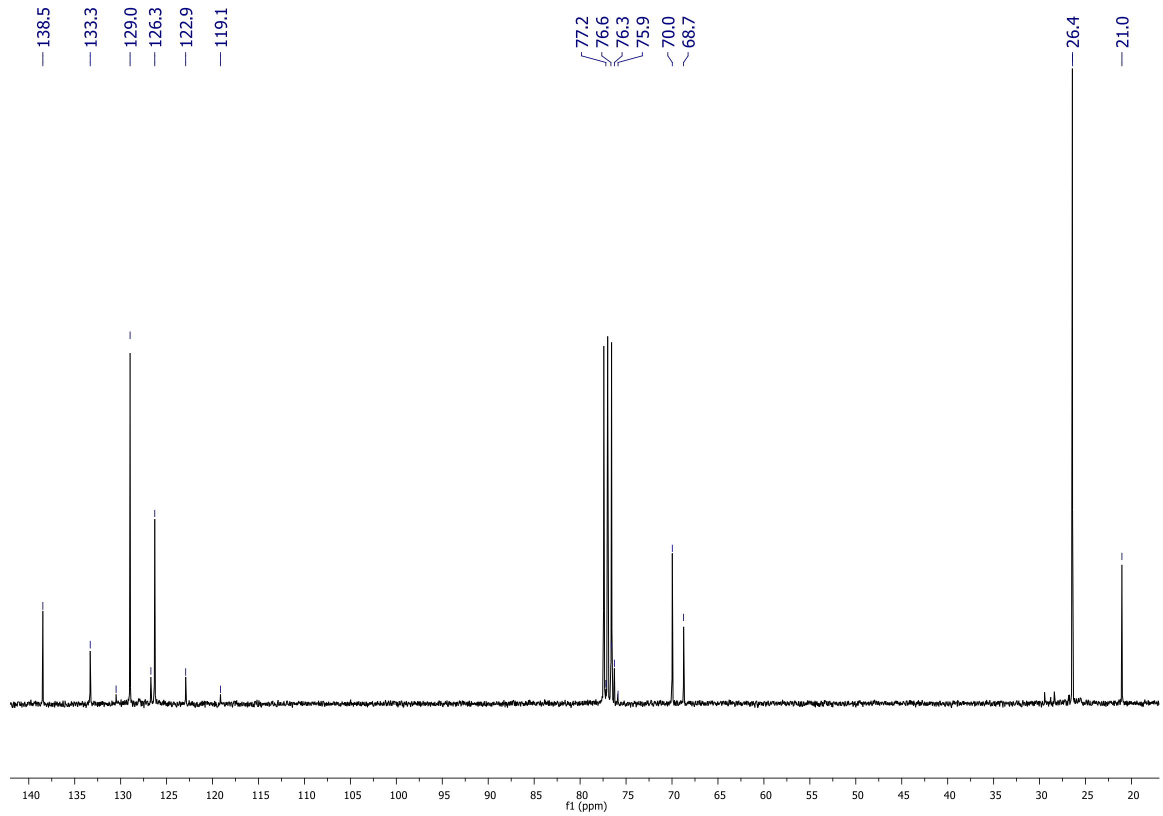
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7a**



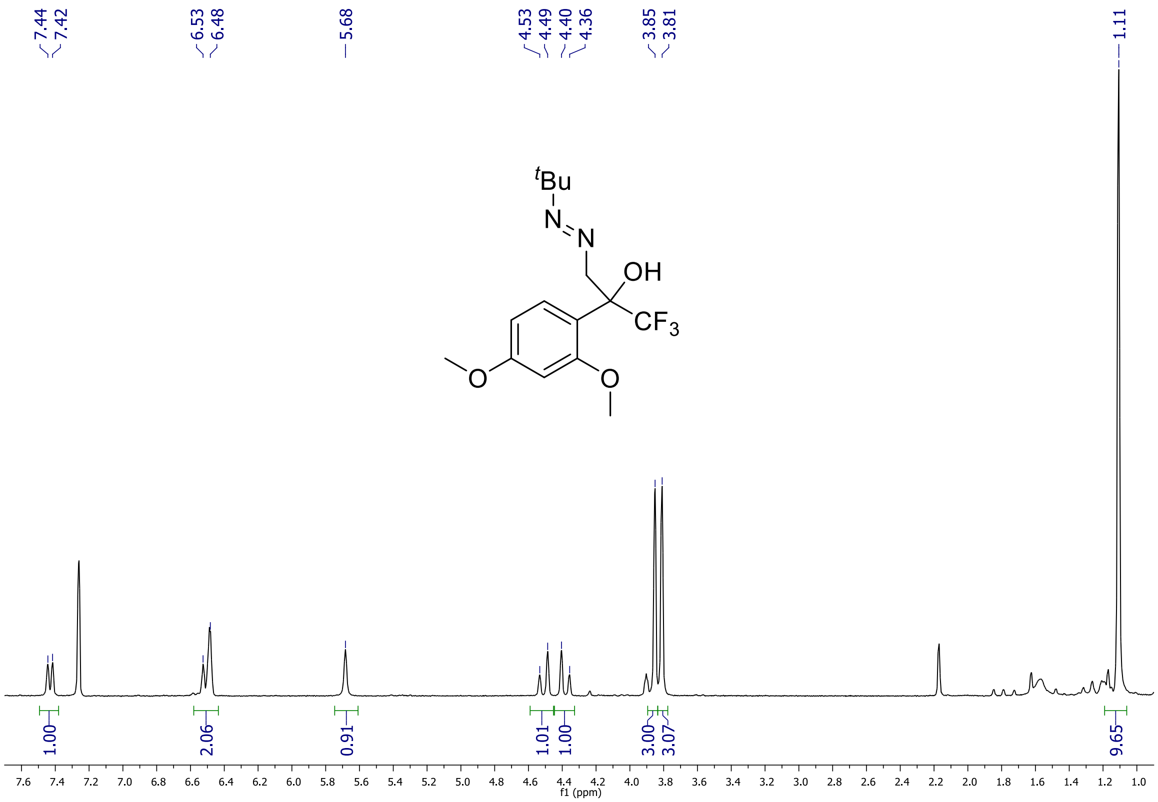
^{1}H NMR ($CDCl_3$, 300 MHz) of **7b**



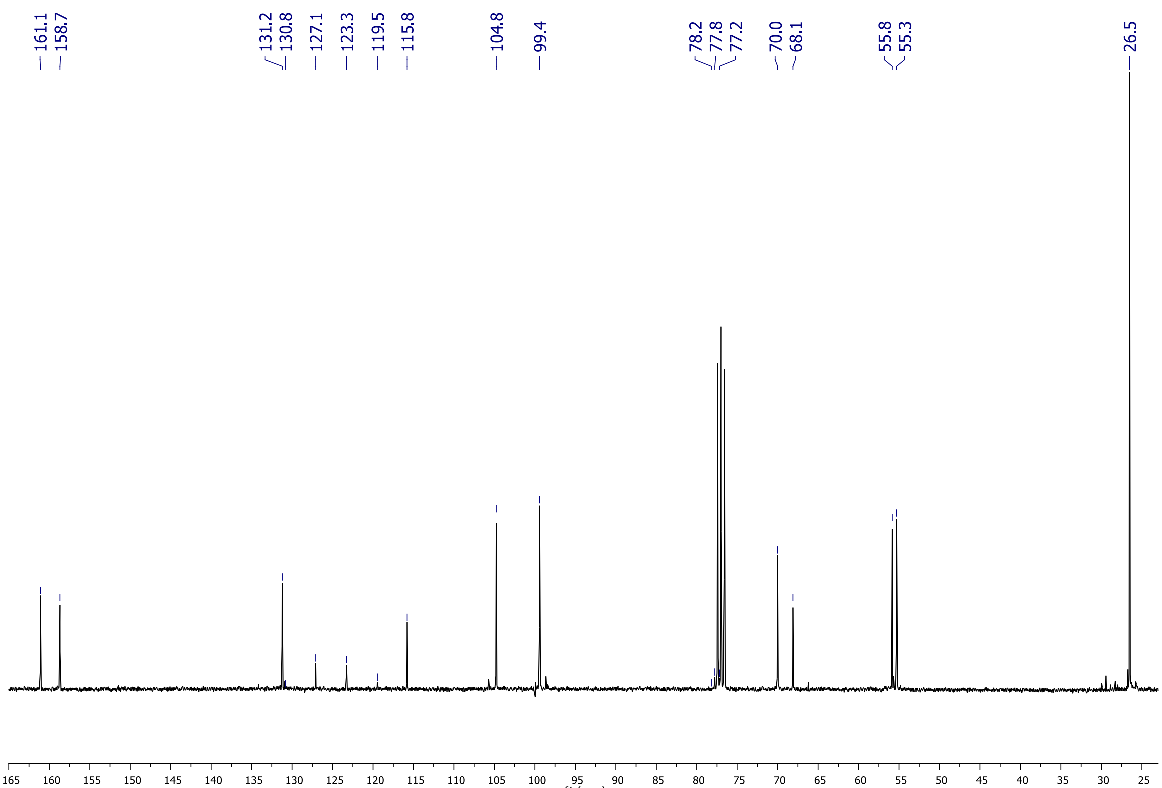
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7b**



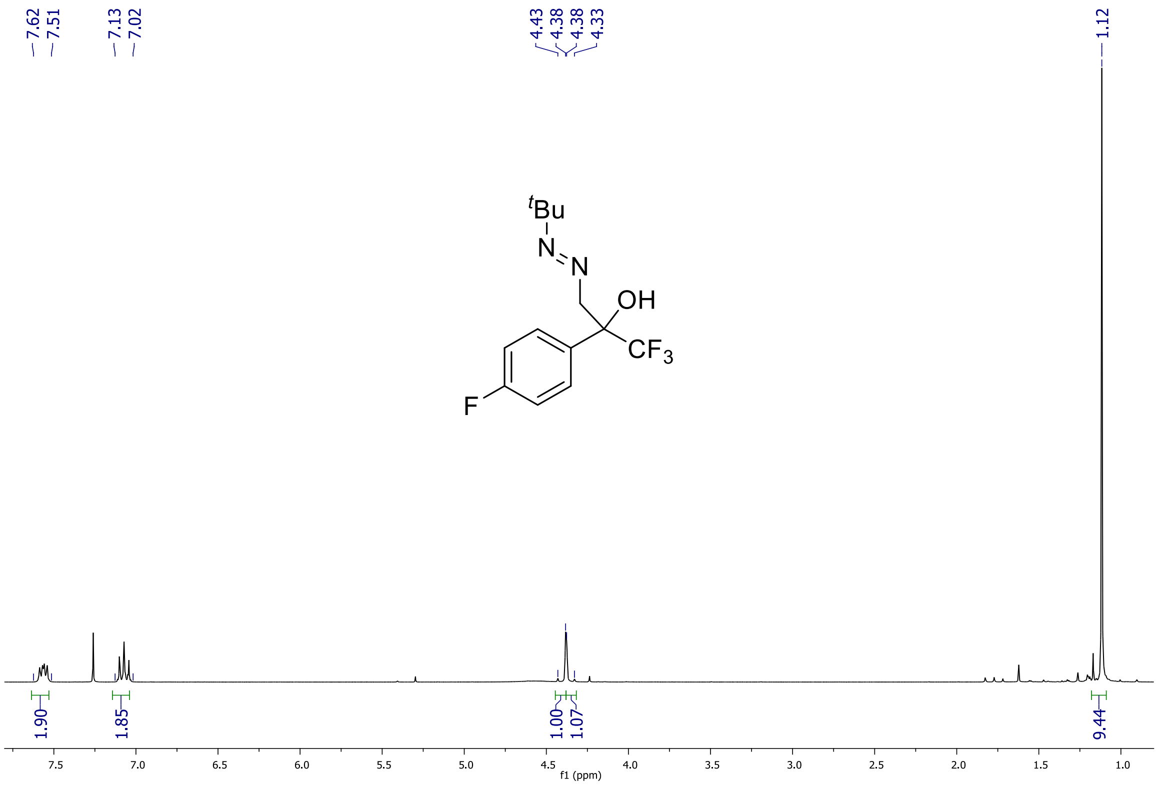
[1]H NMR ($CDCl_3$, 300 MHz) of **7c**



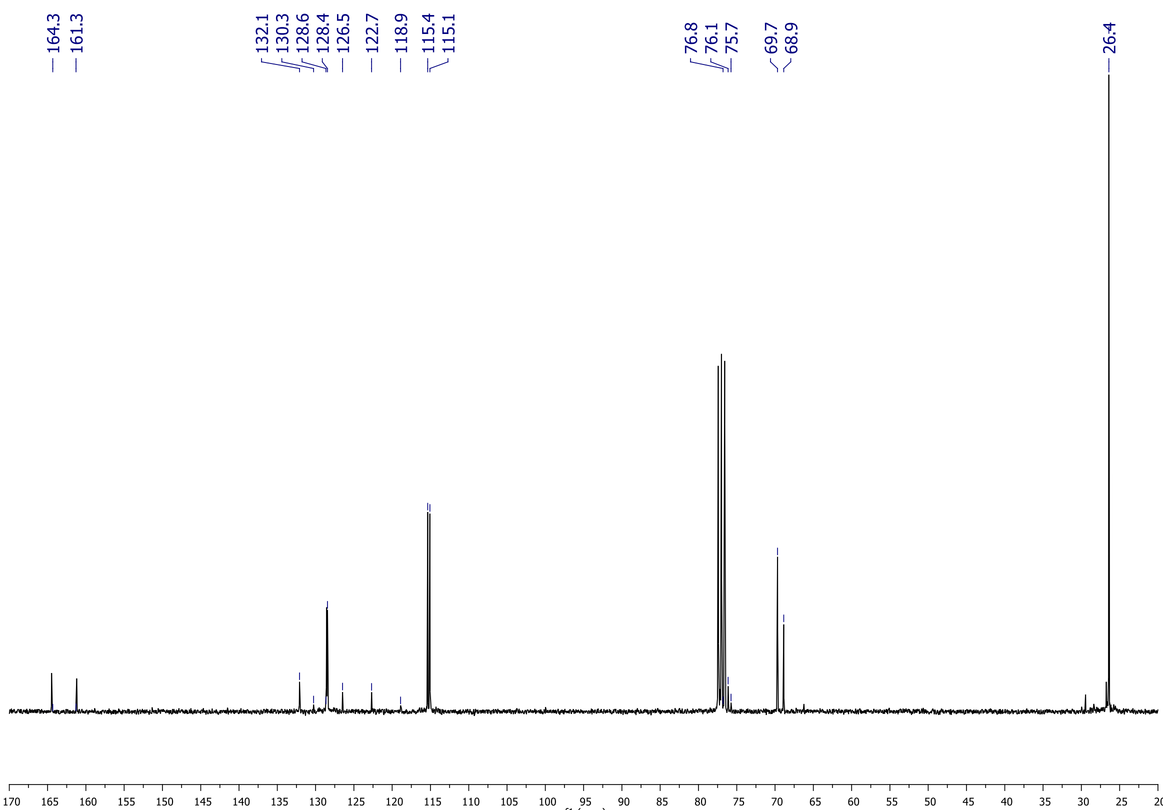
[13]C NMR ($CDCl_3$, 75.5 MHz) of **7c**



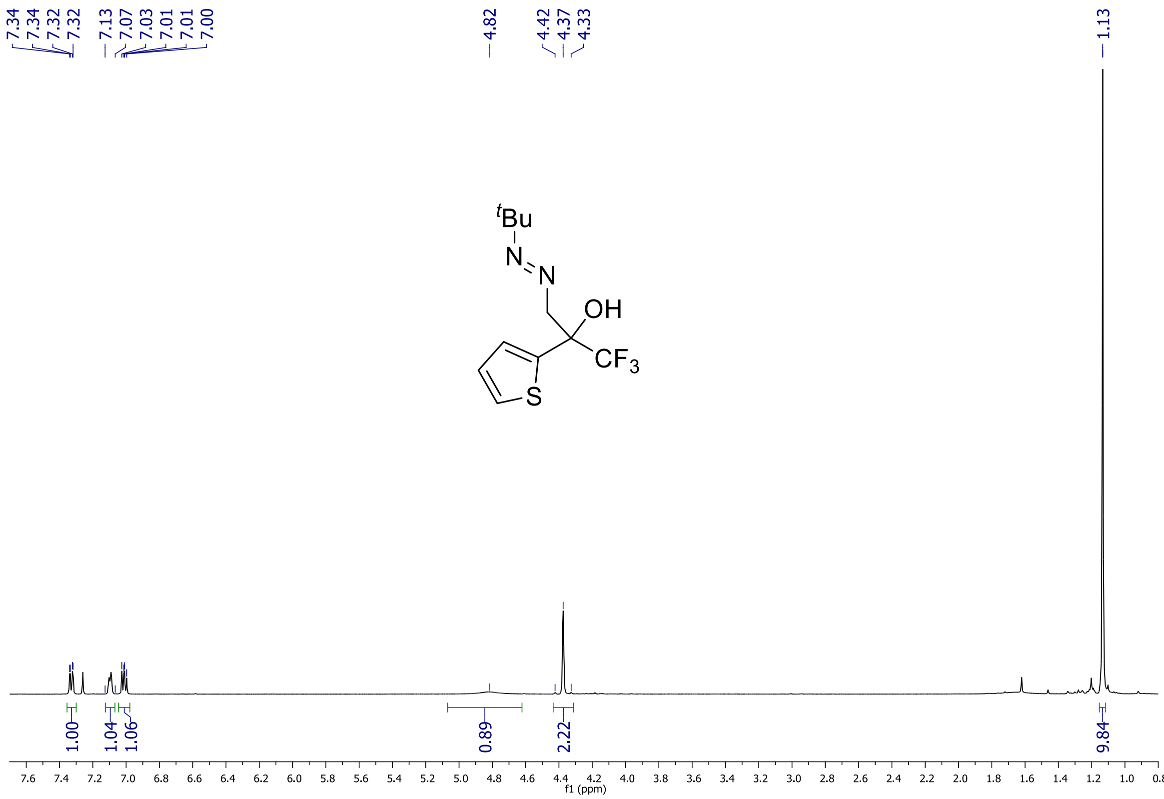
^{1}H NMR ($CDCl_3$, 300 MHz) of **7d**



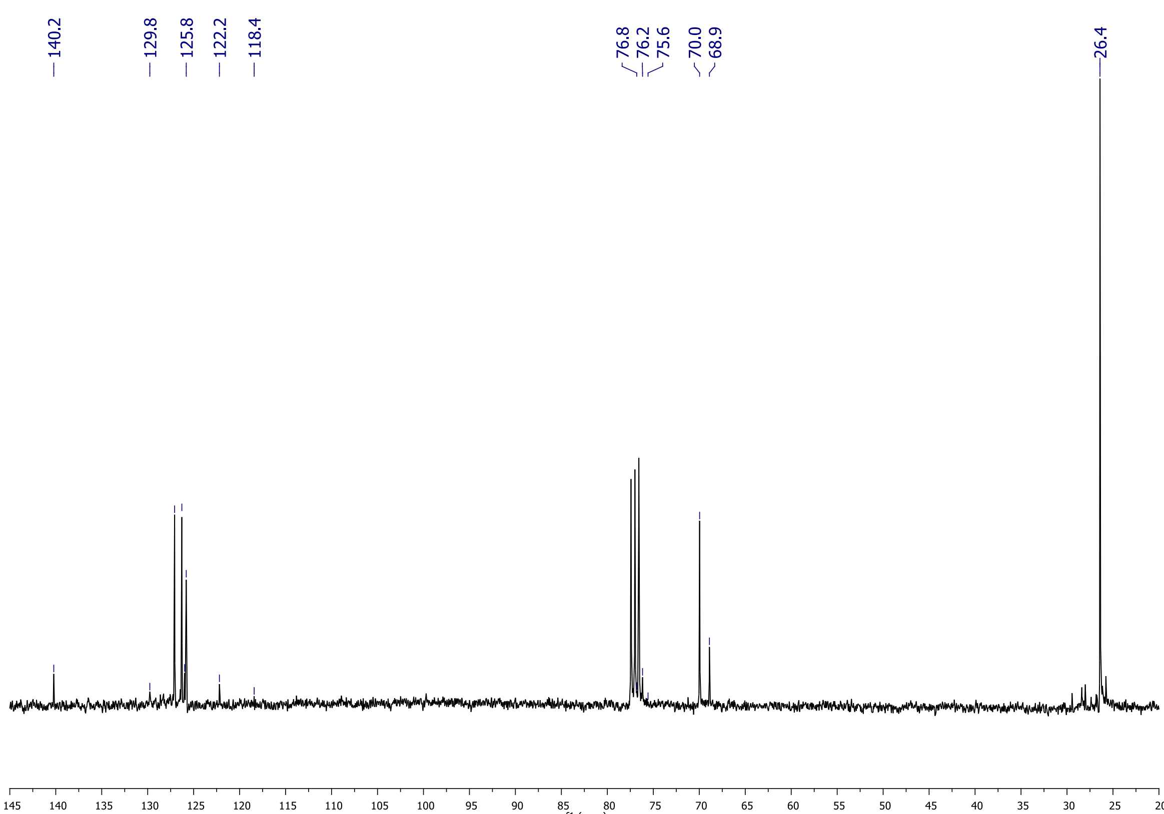
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7d**



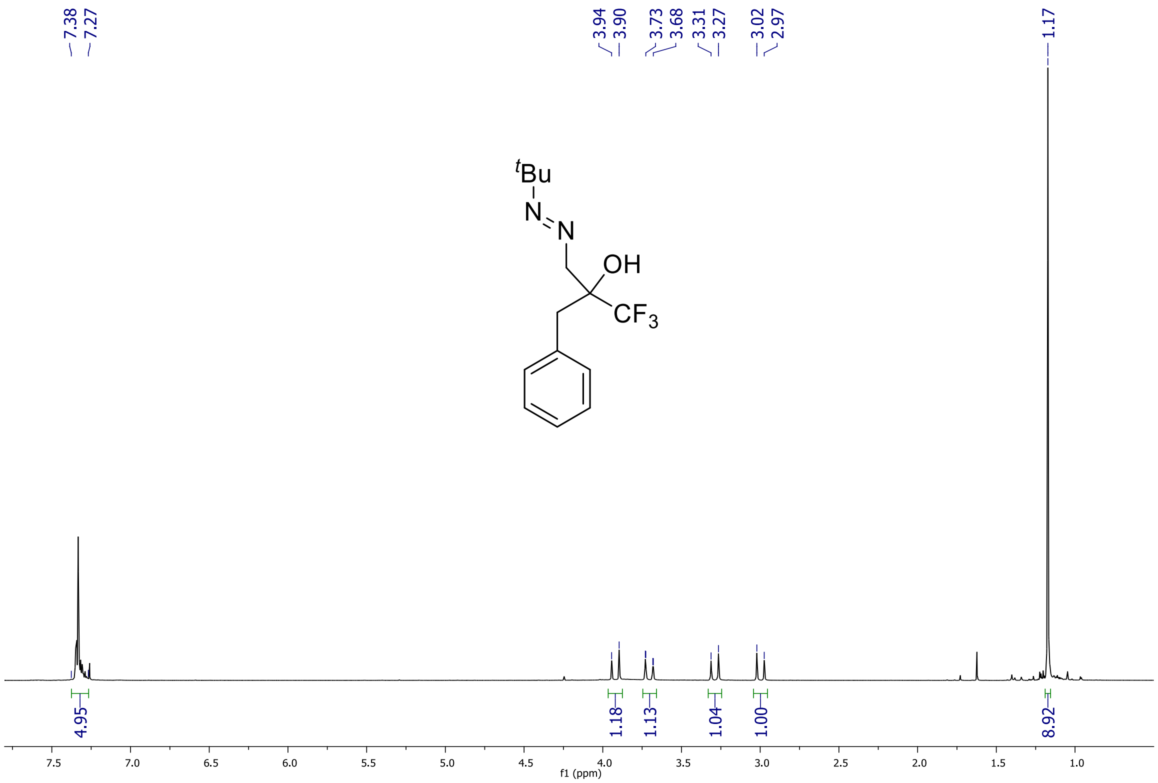
^{1}H NMR ($CDCl_3$, 300 MHz) of **7e**



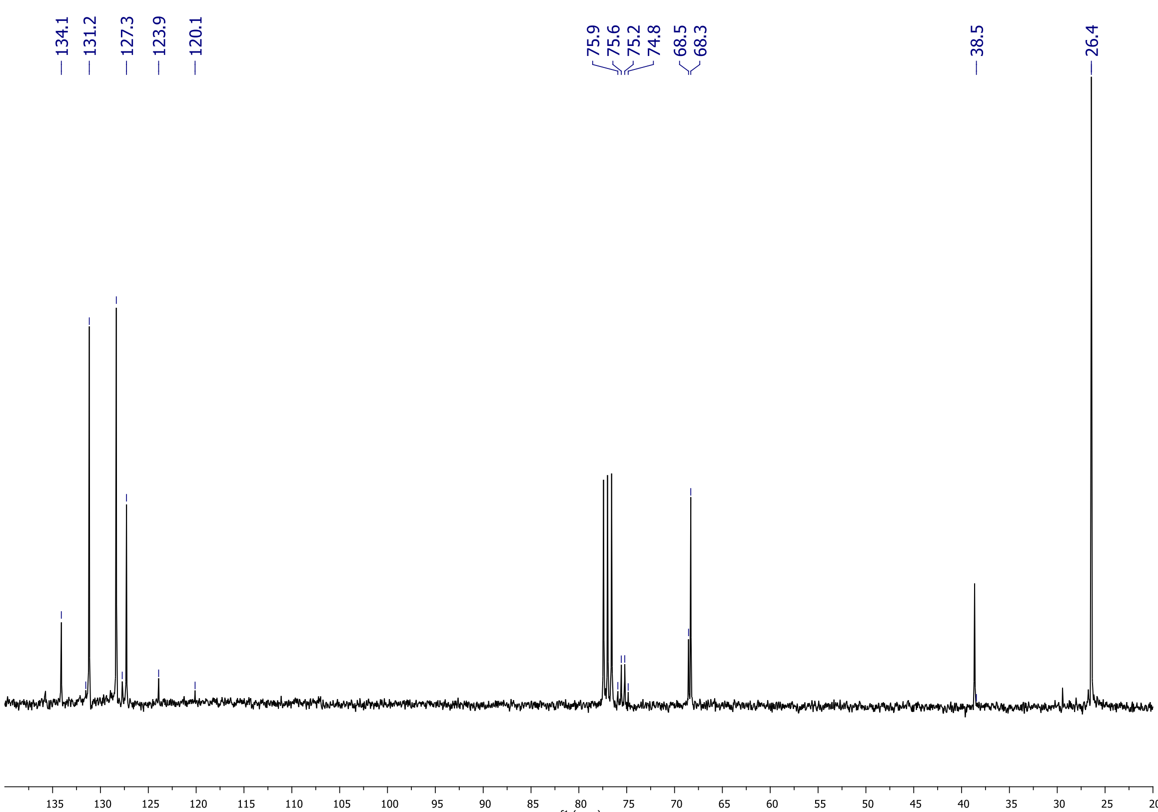
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7e**



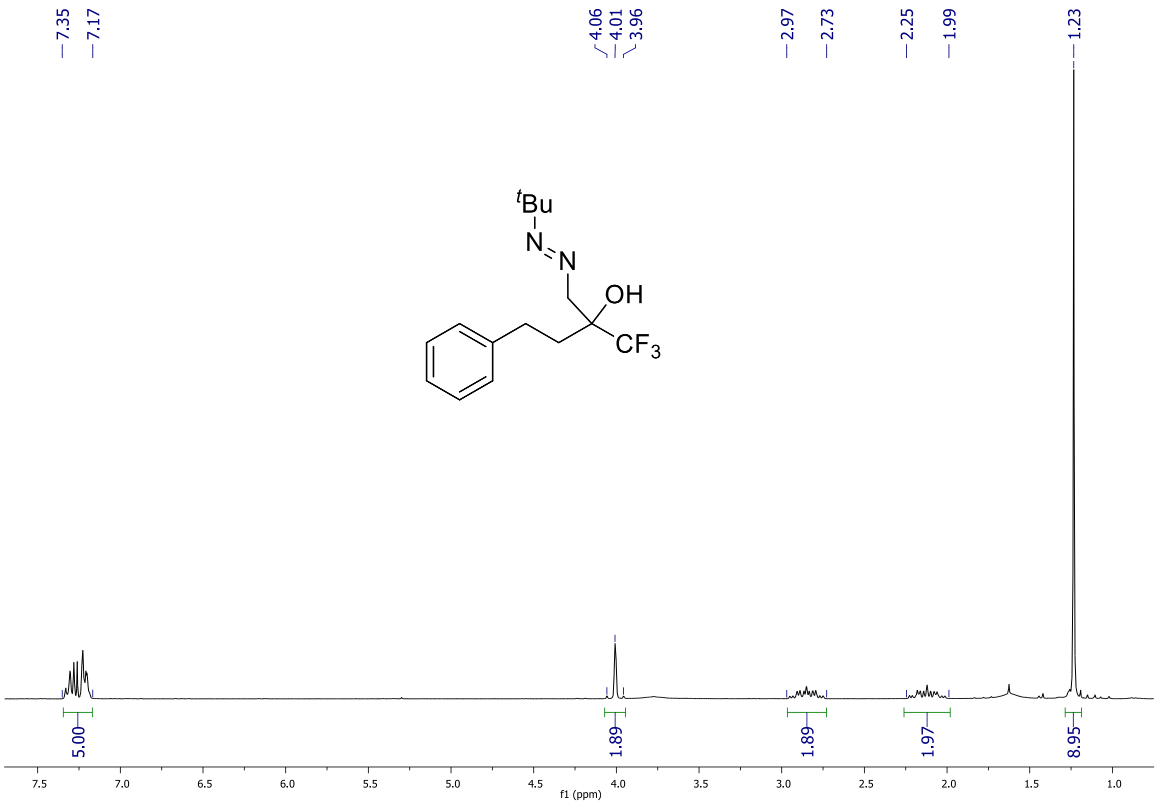
^{1}H NMR ($CDCl_3$, 300 MHz) of **7f**



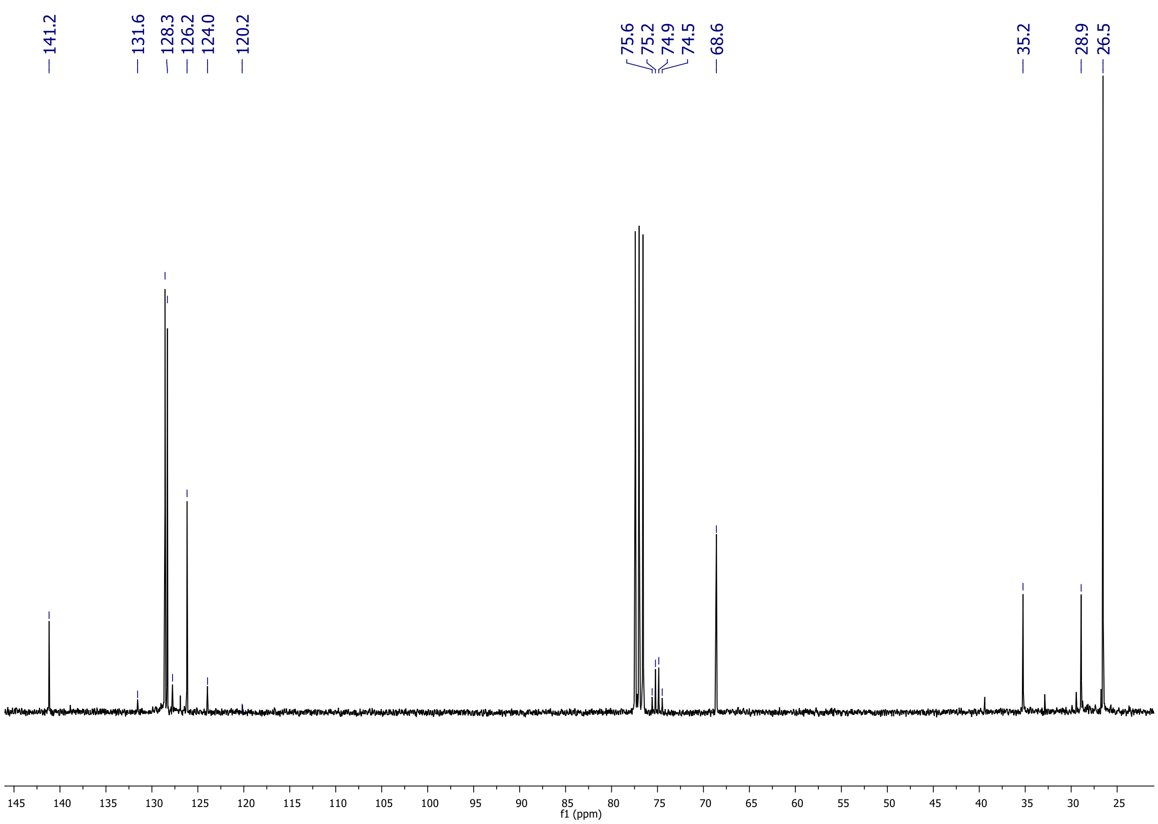
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7f**



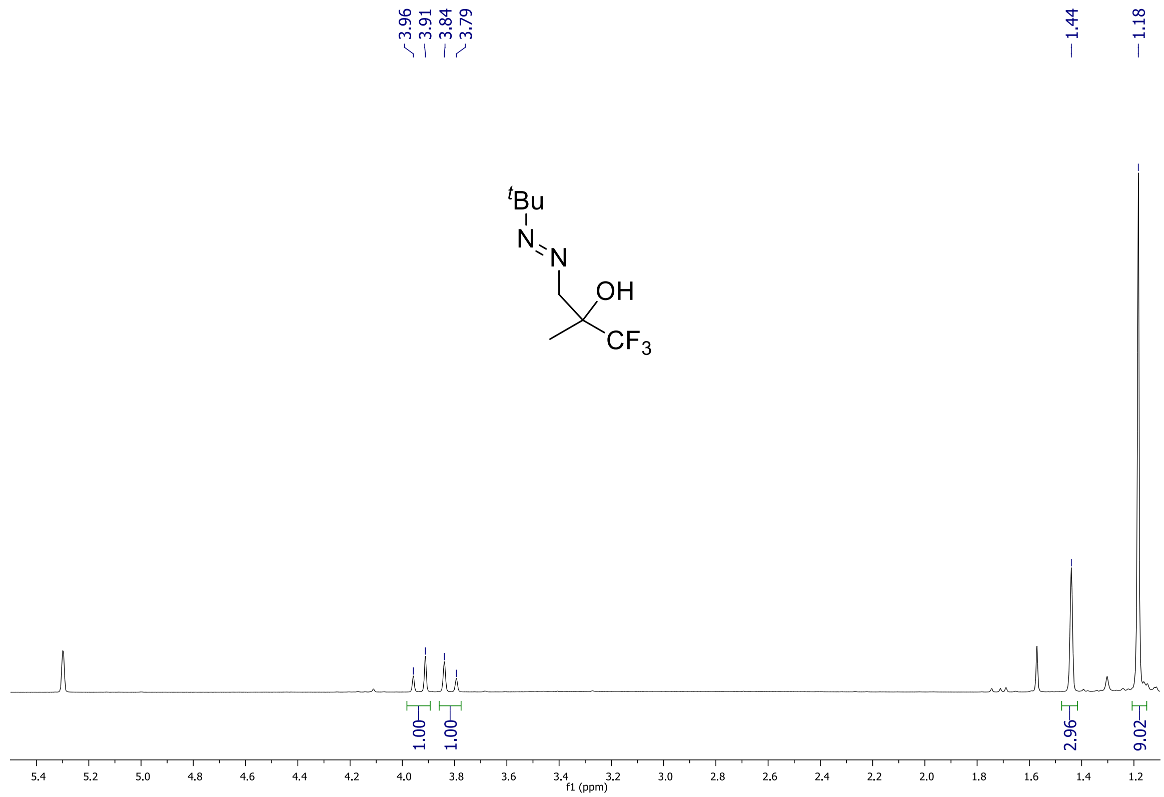
^{1}H NMR ($CDCl_3$, 300 MHz) of **7g**



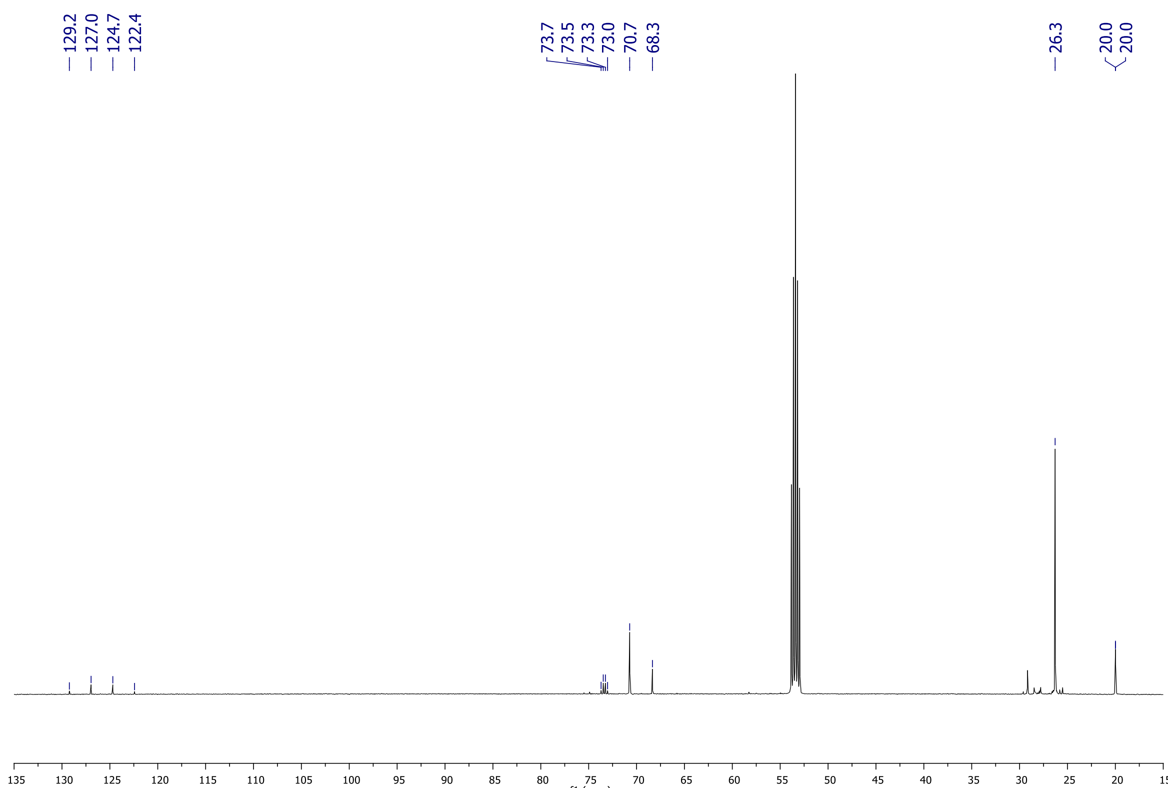
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7g**



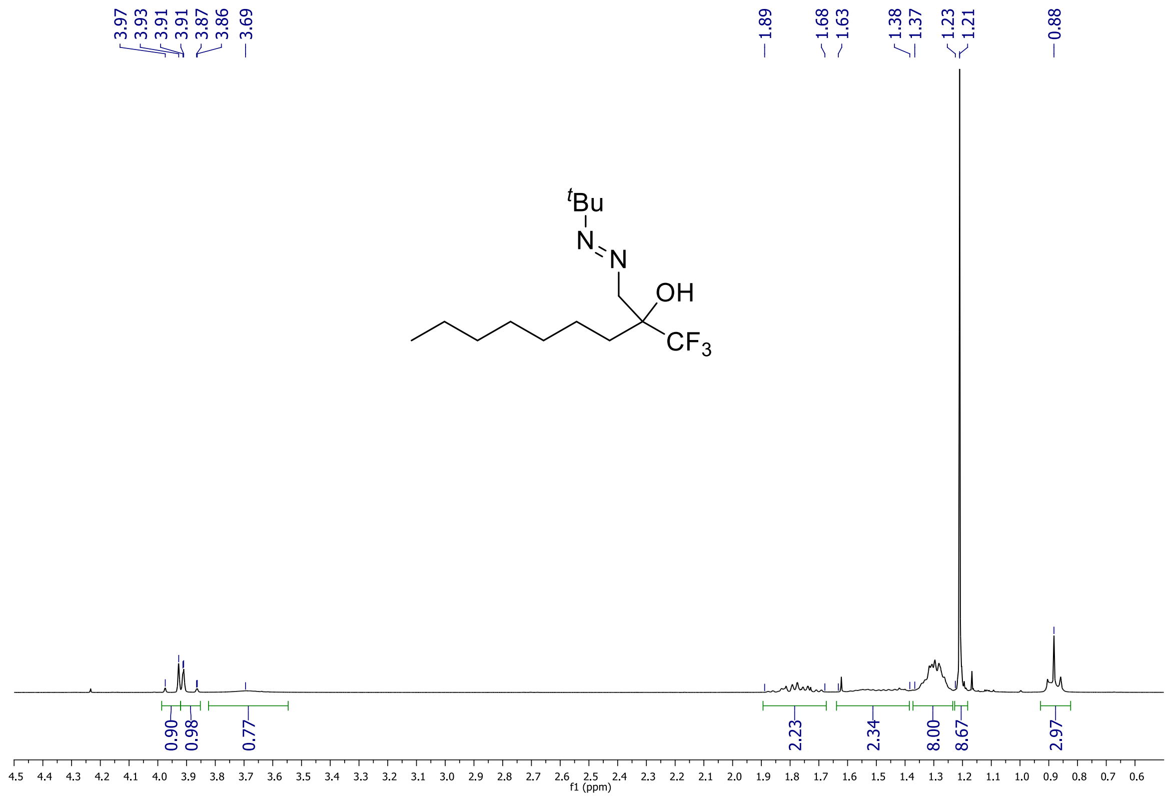
^{1}H NMR (CD_2Cl_2, 300 MHz) of **7h**



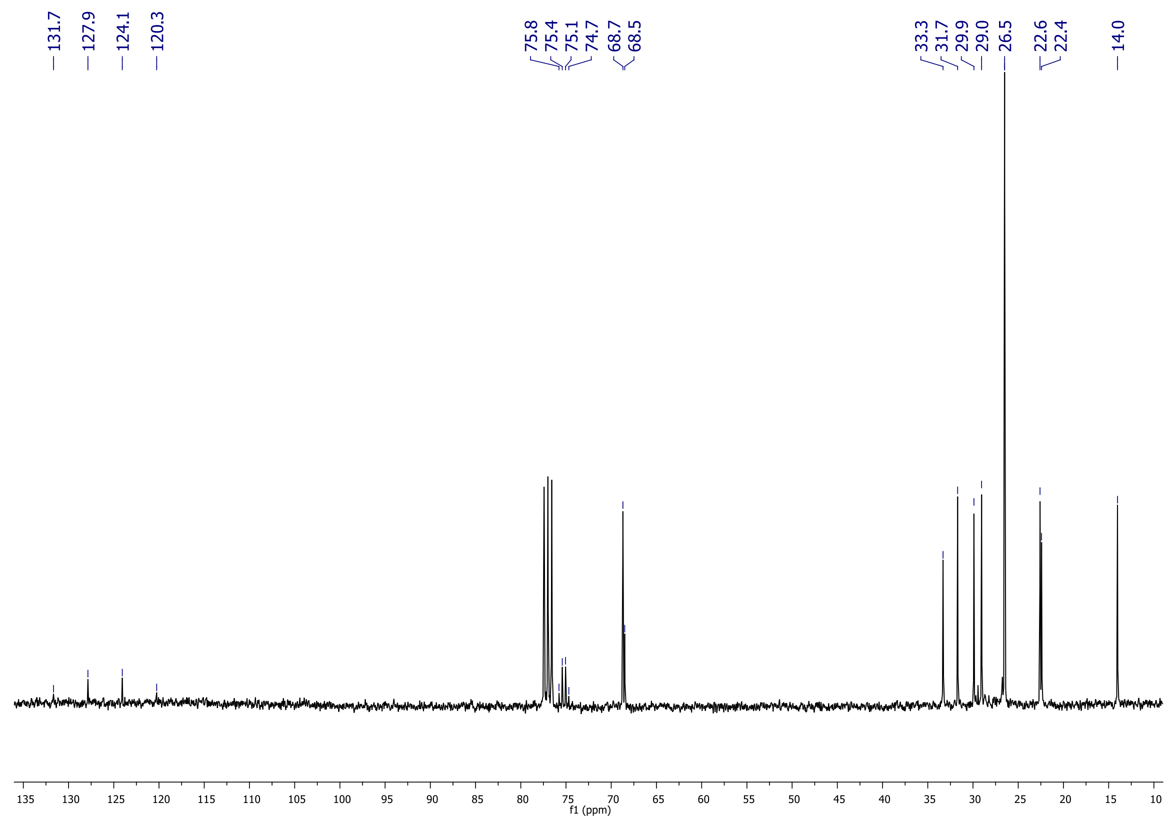
^{13}C NMR (CD_2Cl_2, 125 MHz) of **7h**



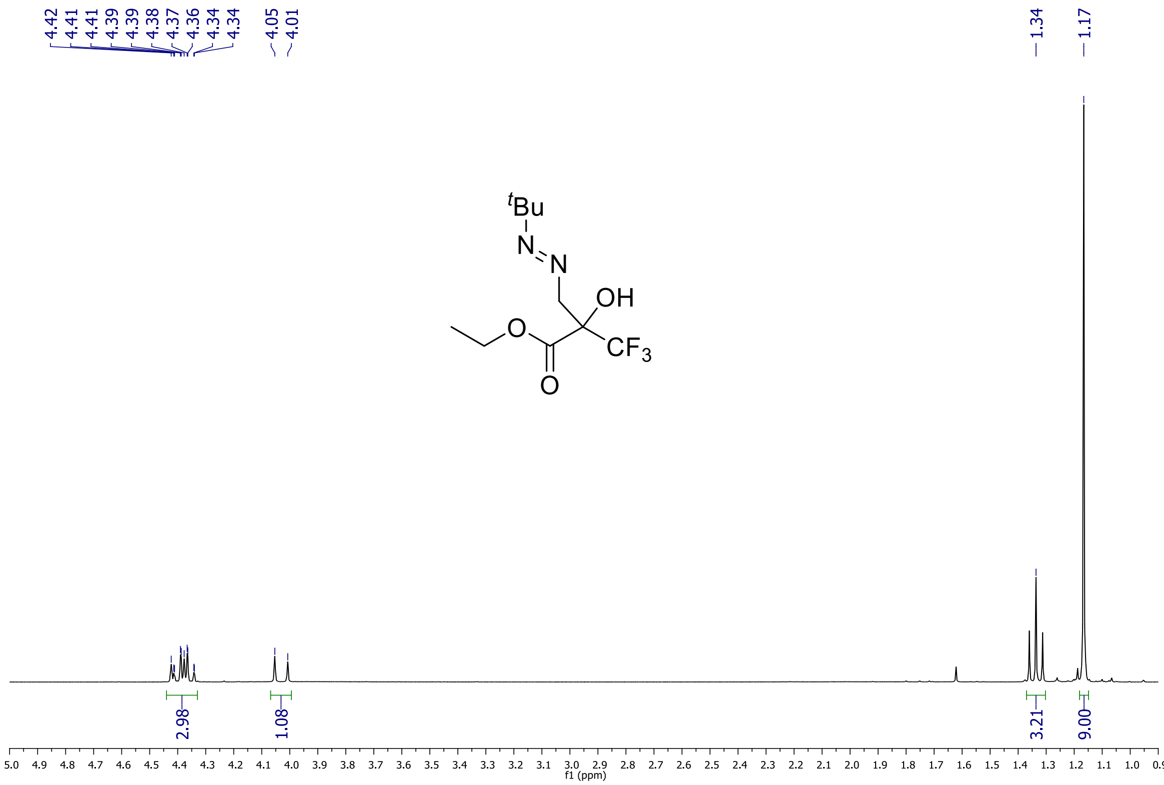
^{1}H NMR ($CDCl_3$, 300 MHz) of **7i**



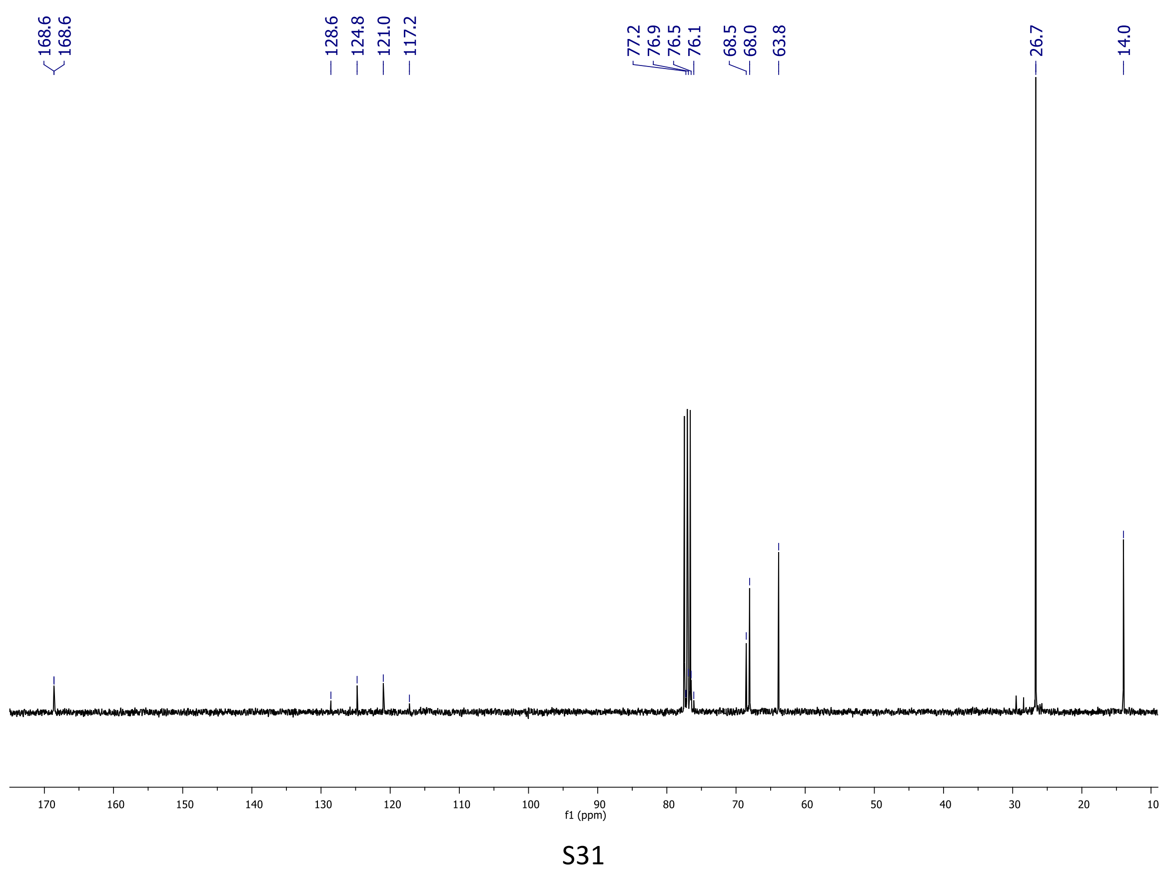
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7i**



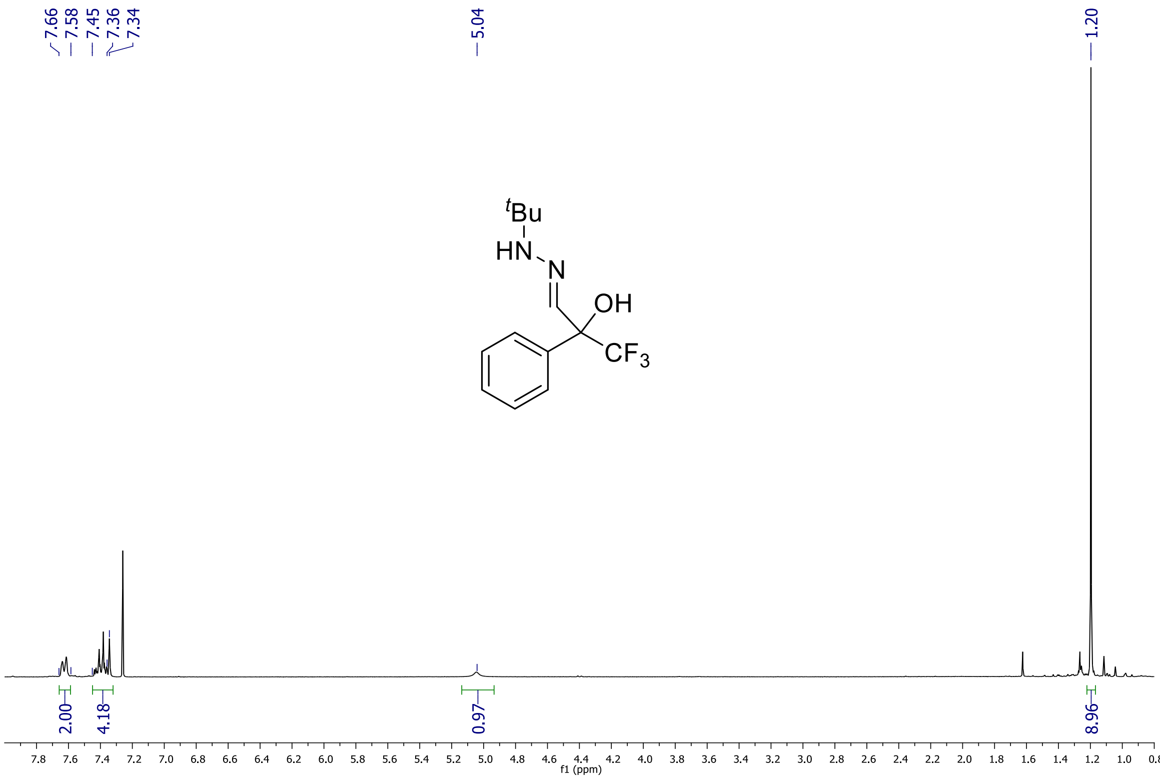
^{1}H NMR ($CDCl_3$, 300 MHz) of **7j**



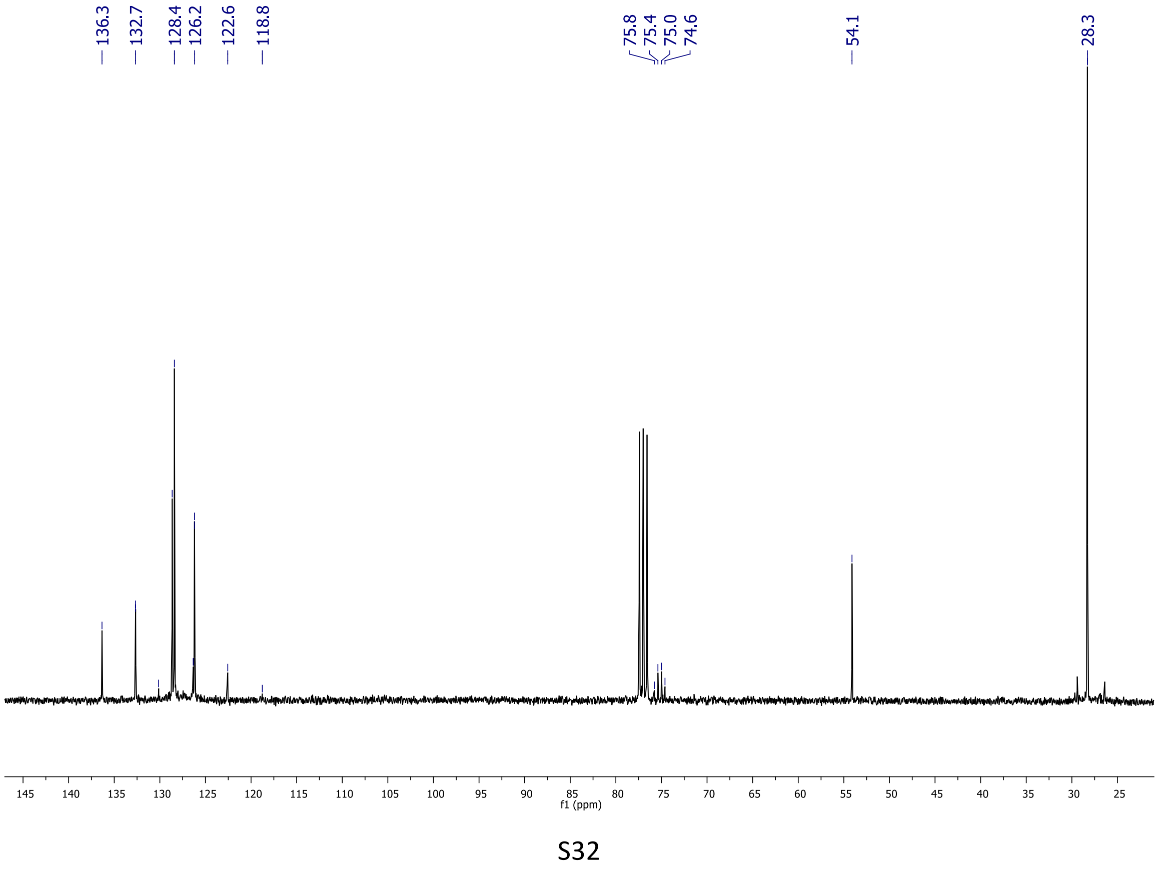
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **7j**



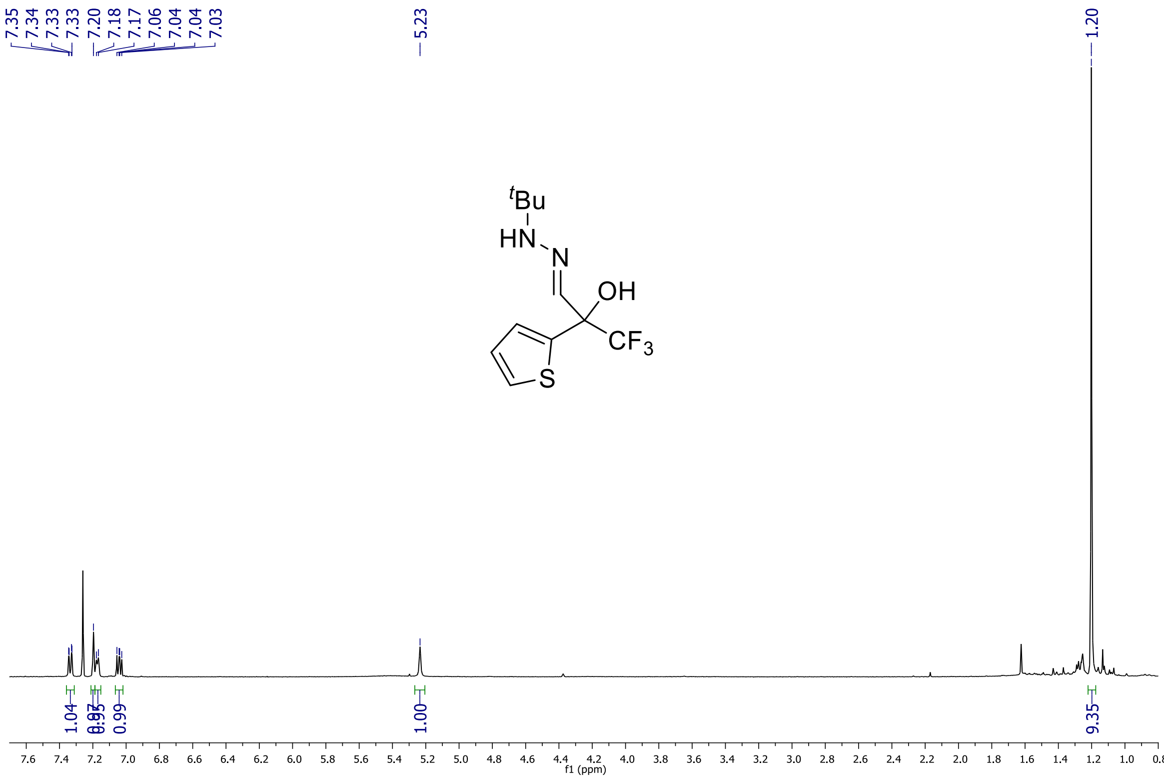
^{1}H NMR ($CDCl_3$, 300 MHz) of **8a**



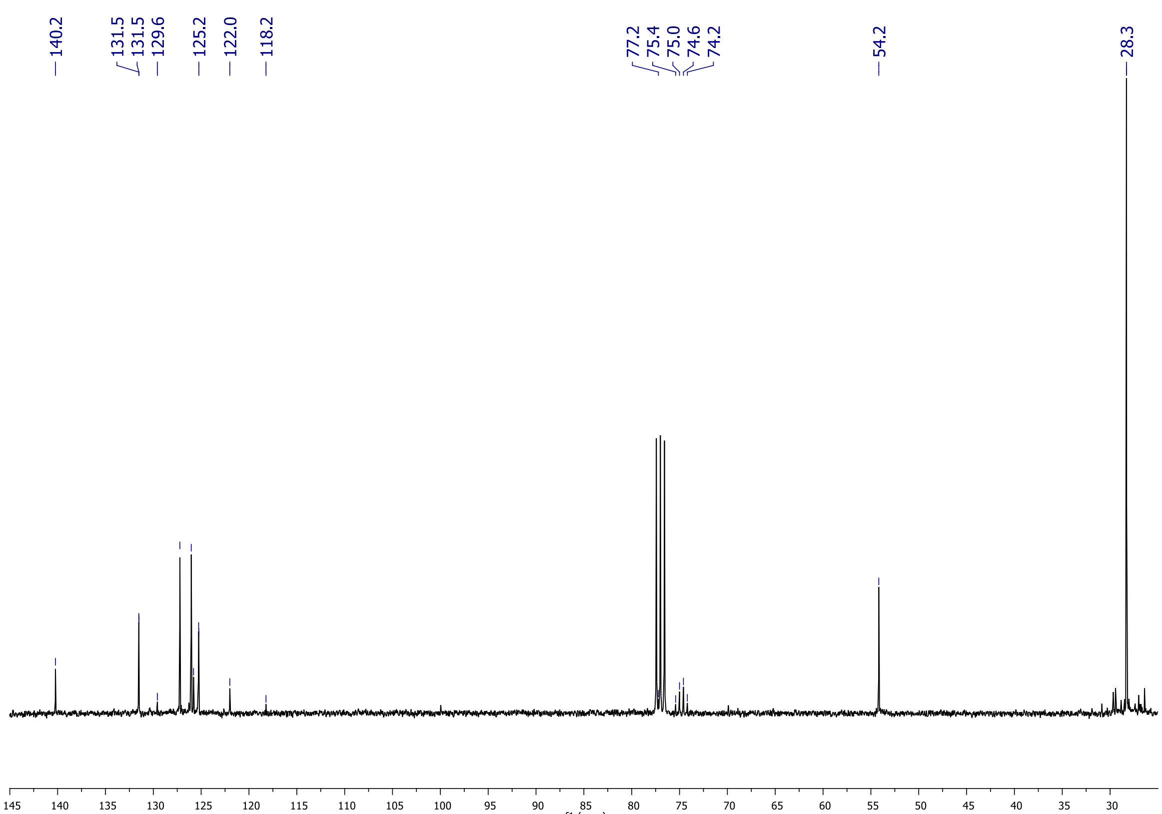
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **8a**



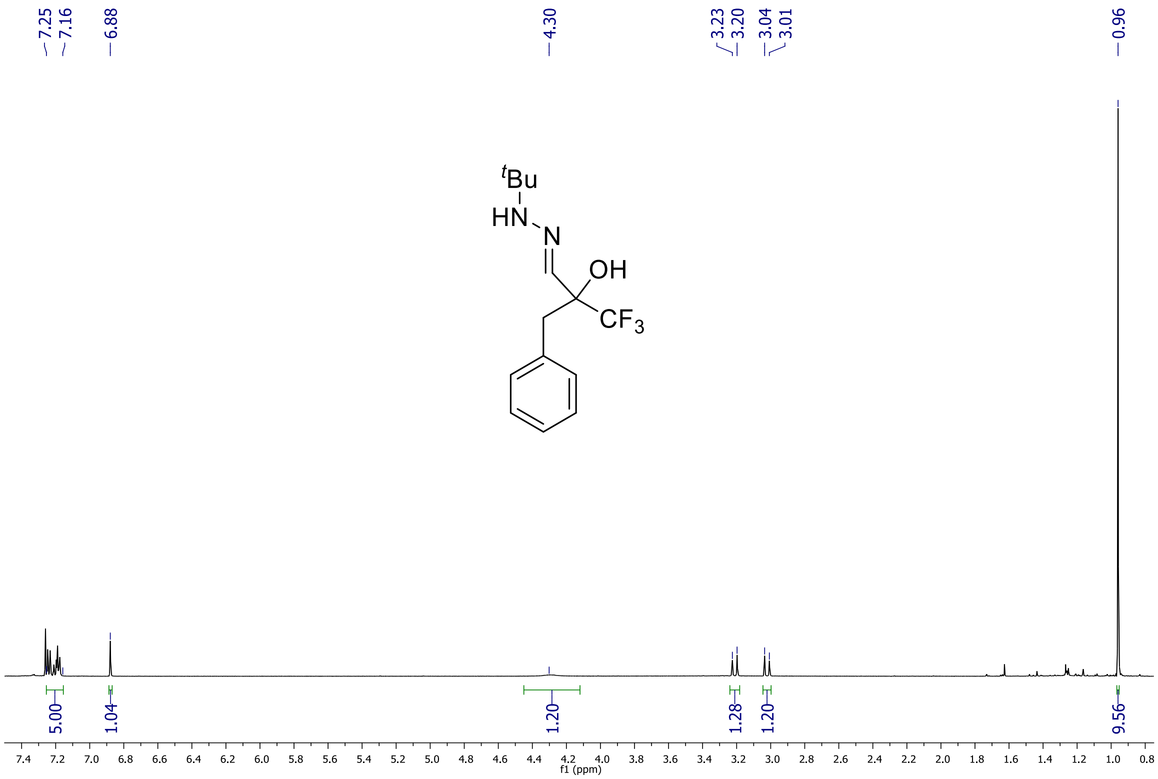
^{1}H NMR ($CDCl_3$, 300 MHz) of **8e**



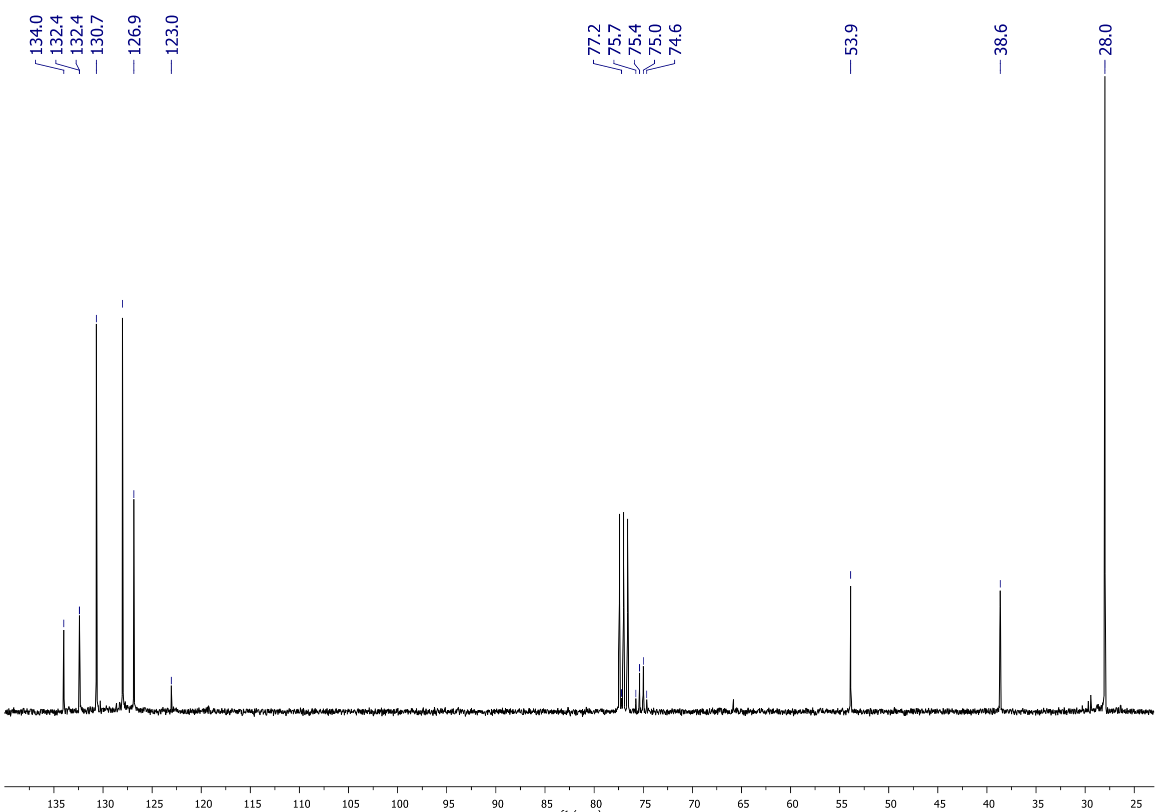
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **8e**



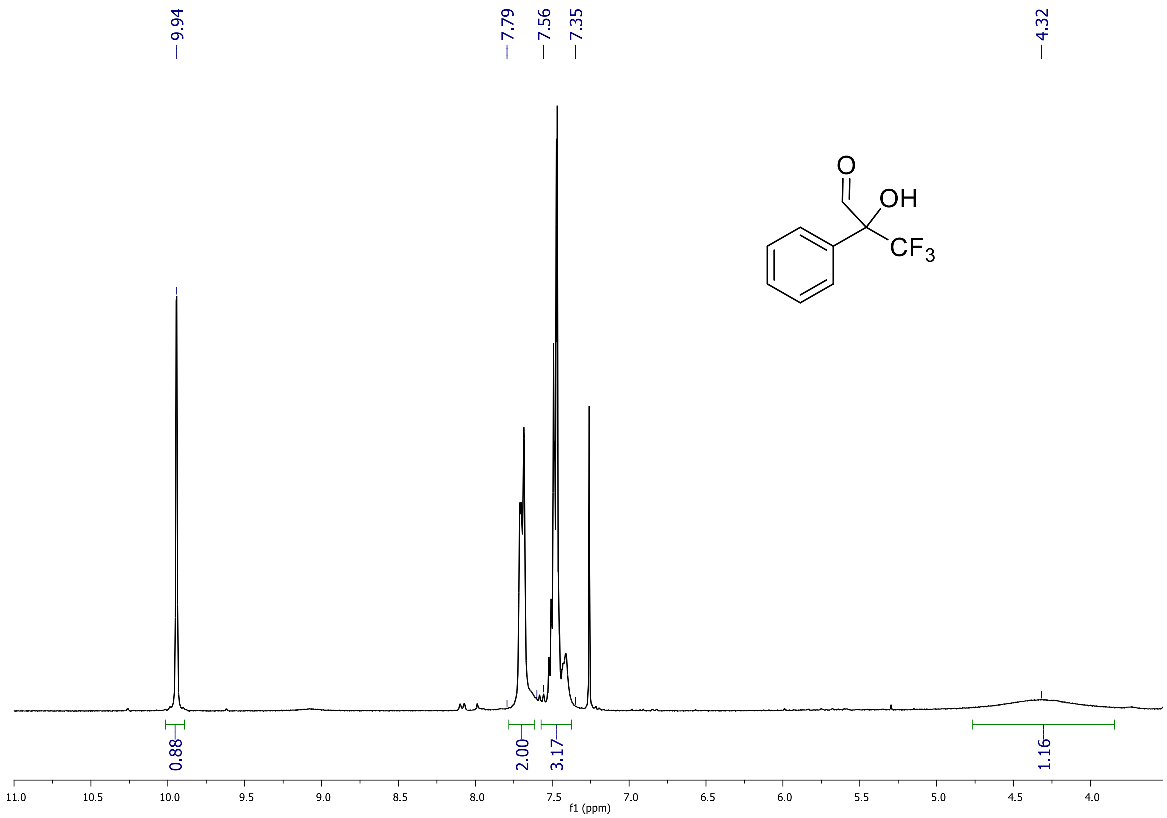
^{1}H NMR ($CDCl_3$, 500 MHz) of **8f**



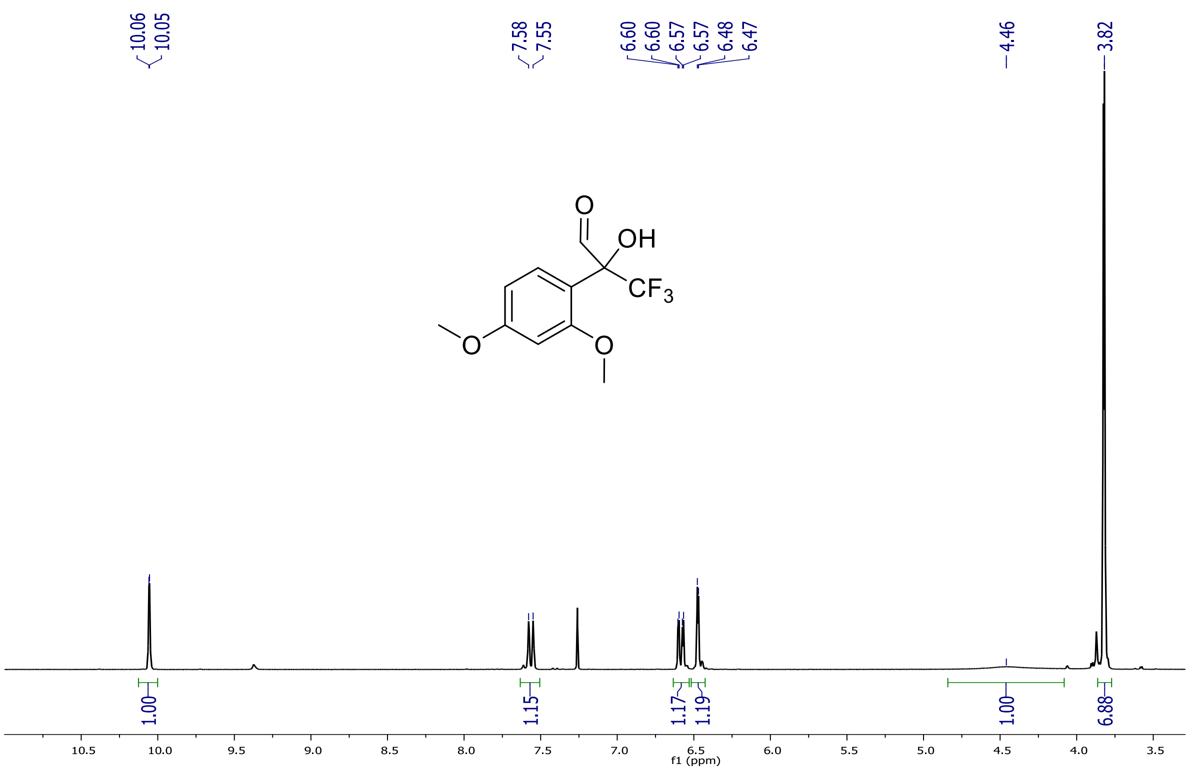
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **8f**



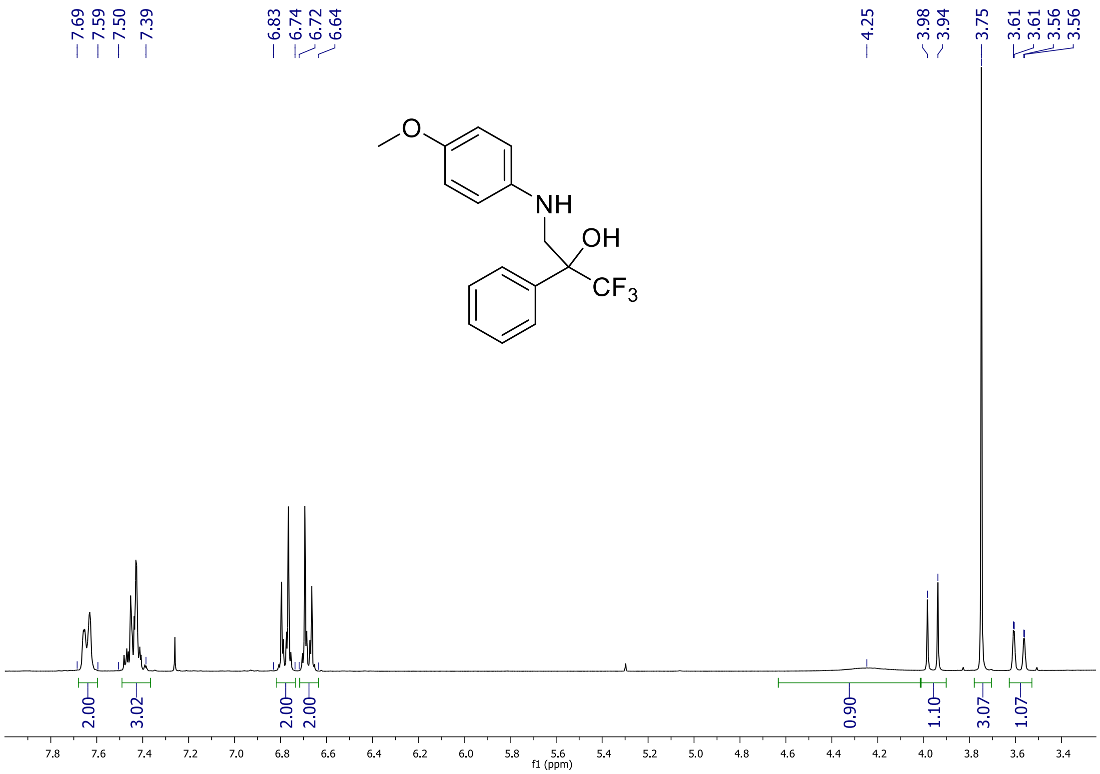
^{1}H NMR ($CDCl_3$, 300 MHz) of **9a**



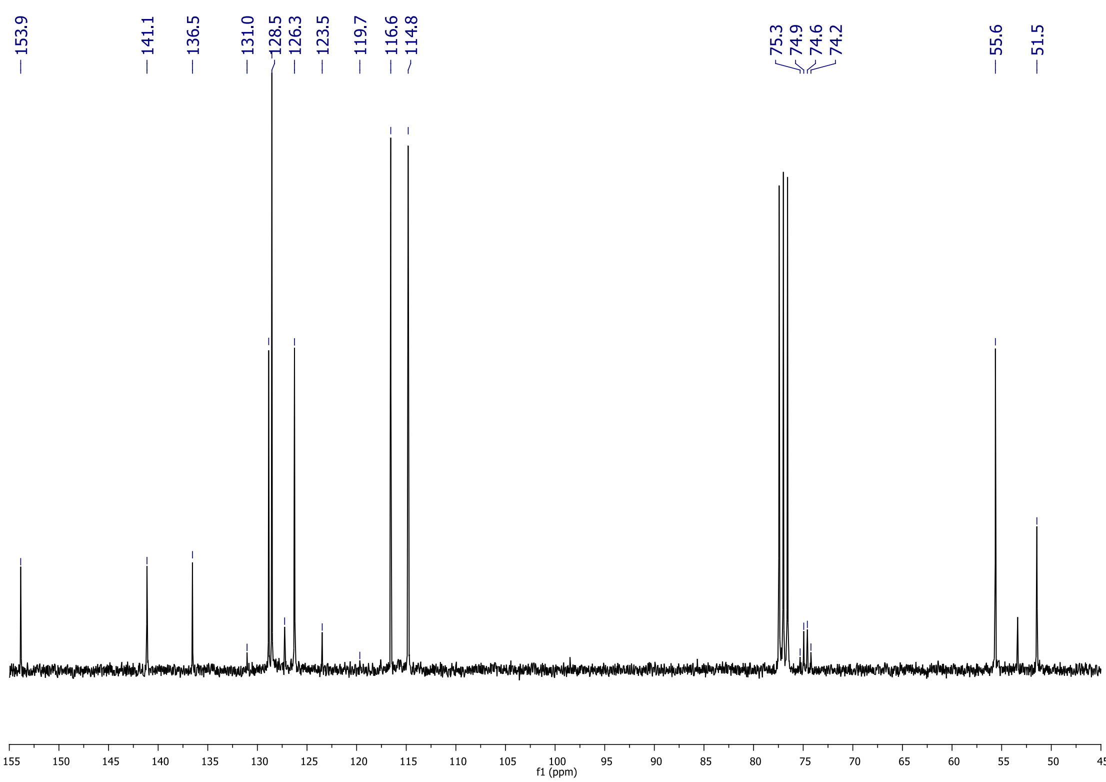
^{1}H NMR ($CDCl_3$, 300 MHz) of **9c**



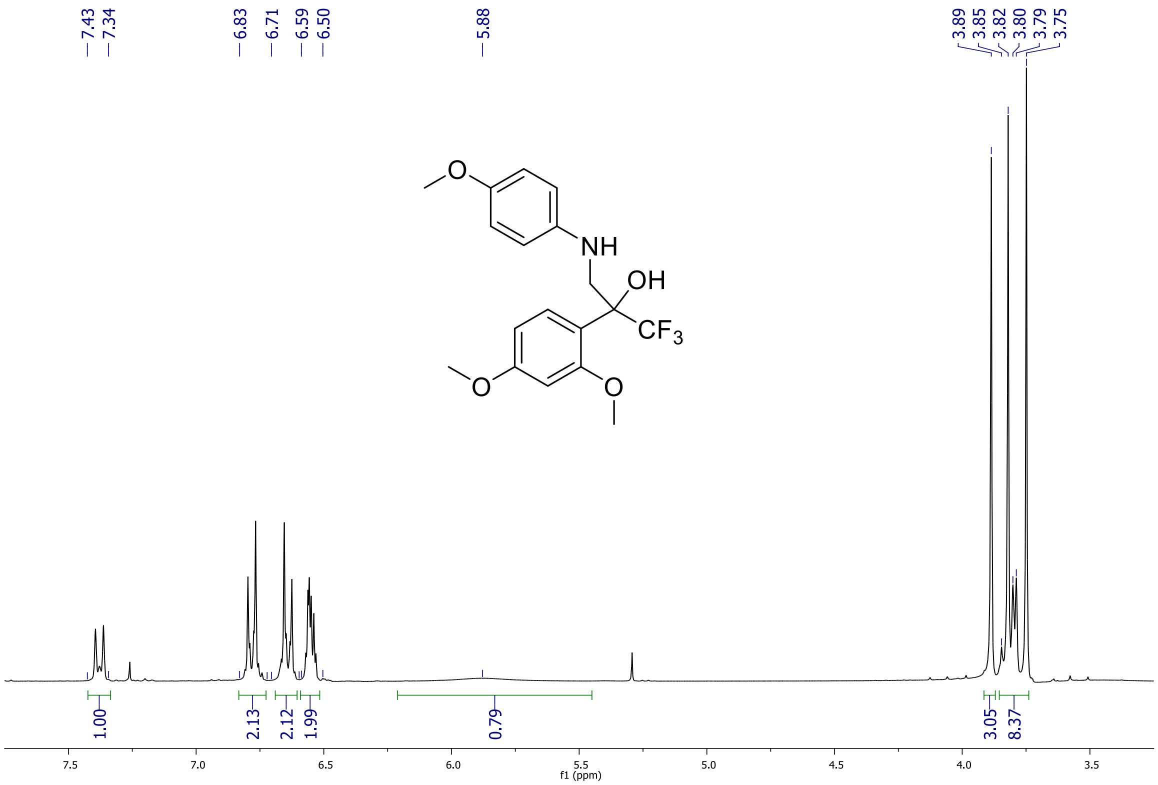
^1H NMR ($CDCl_3$, 300 MHz) of **10a**



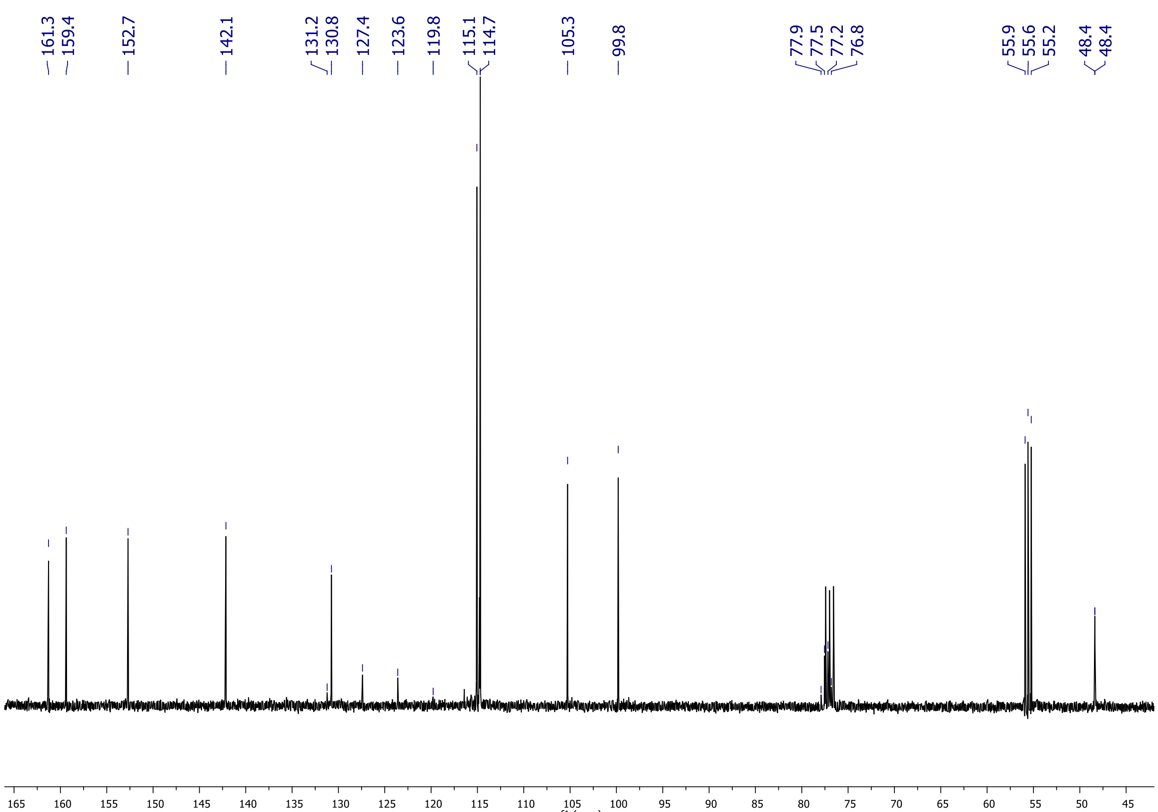
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **10a**



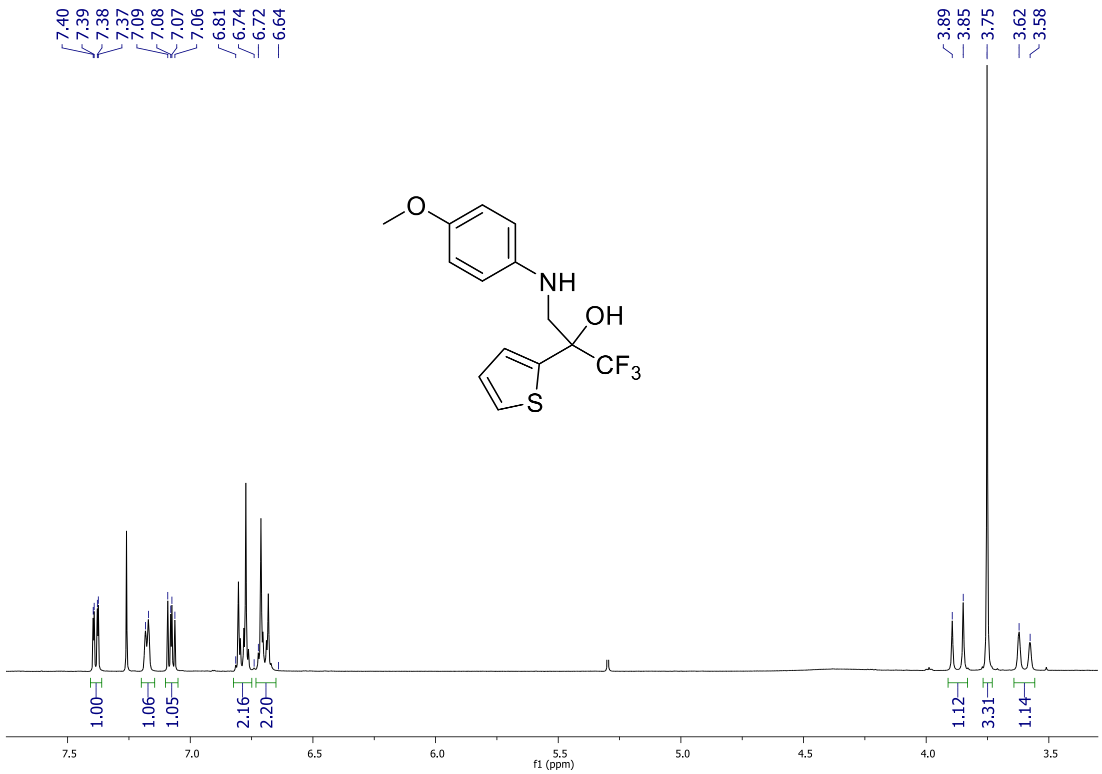
^{1}H NMR ($CDCl_3$, 300 MHz) of **10c**



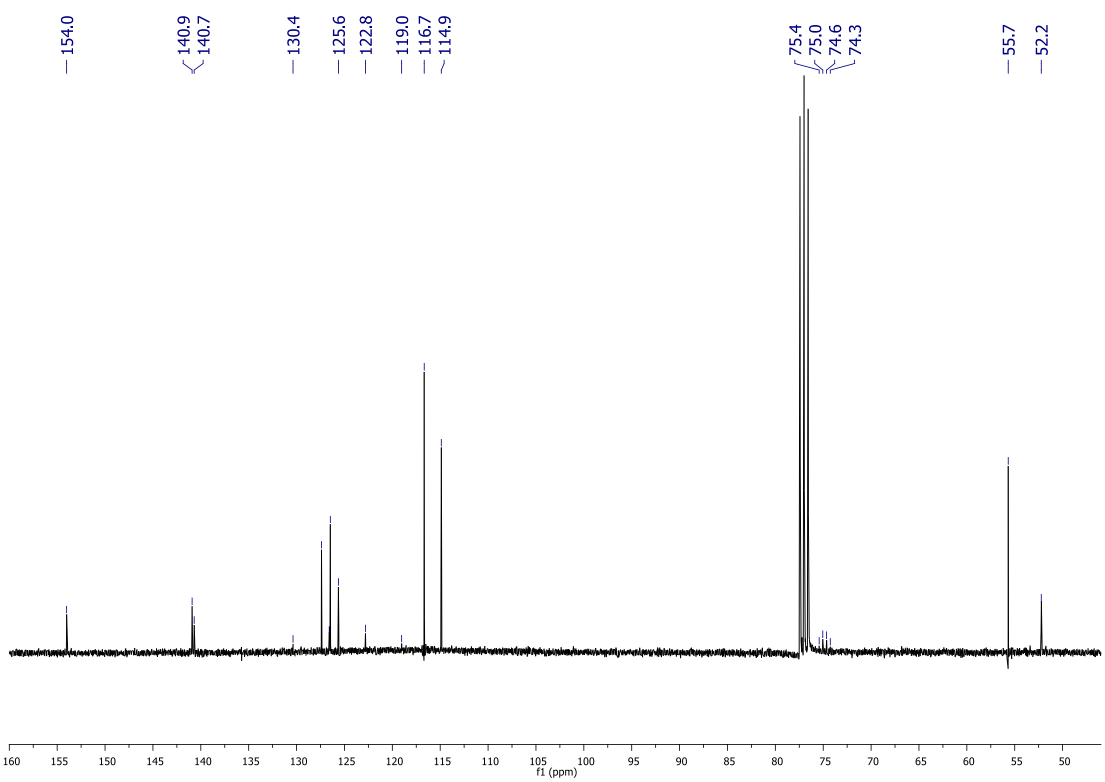
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **10c**



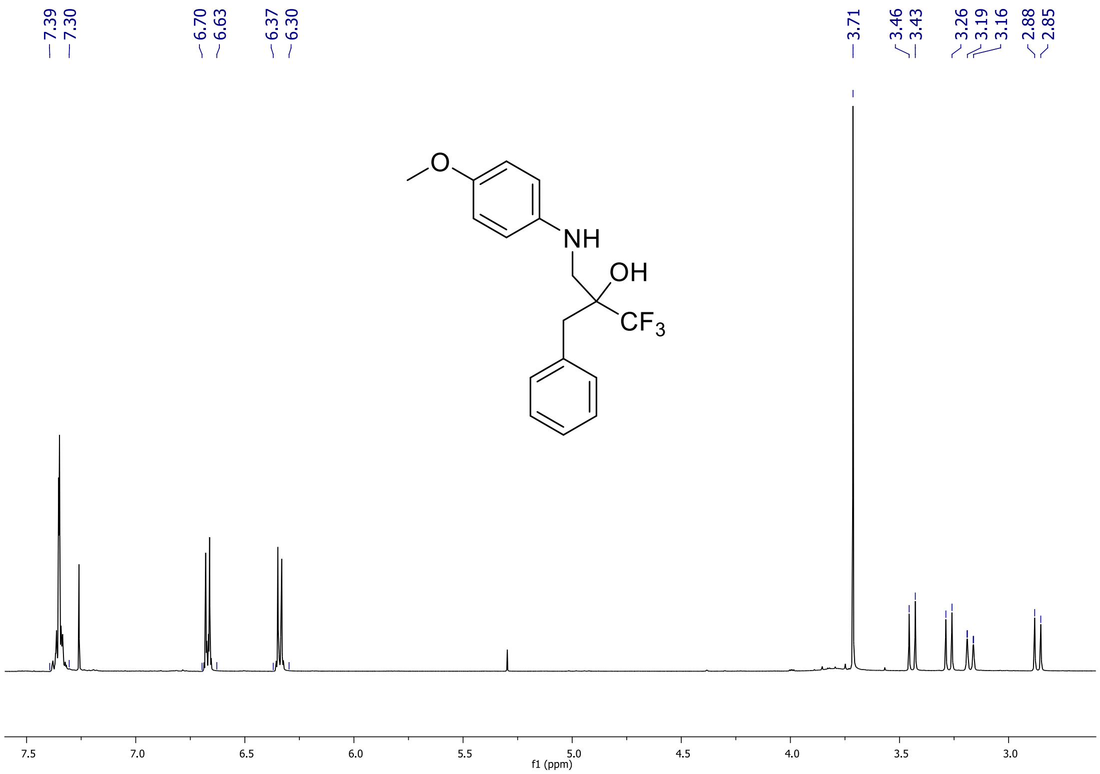
^{1}H NMR ($CDCl_3$, 300 MHz) of **10e**



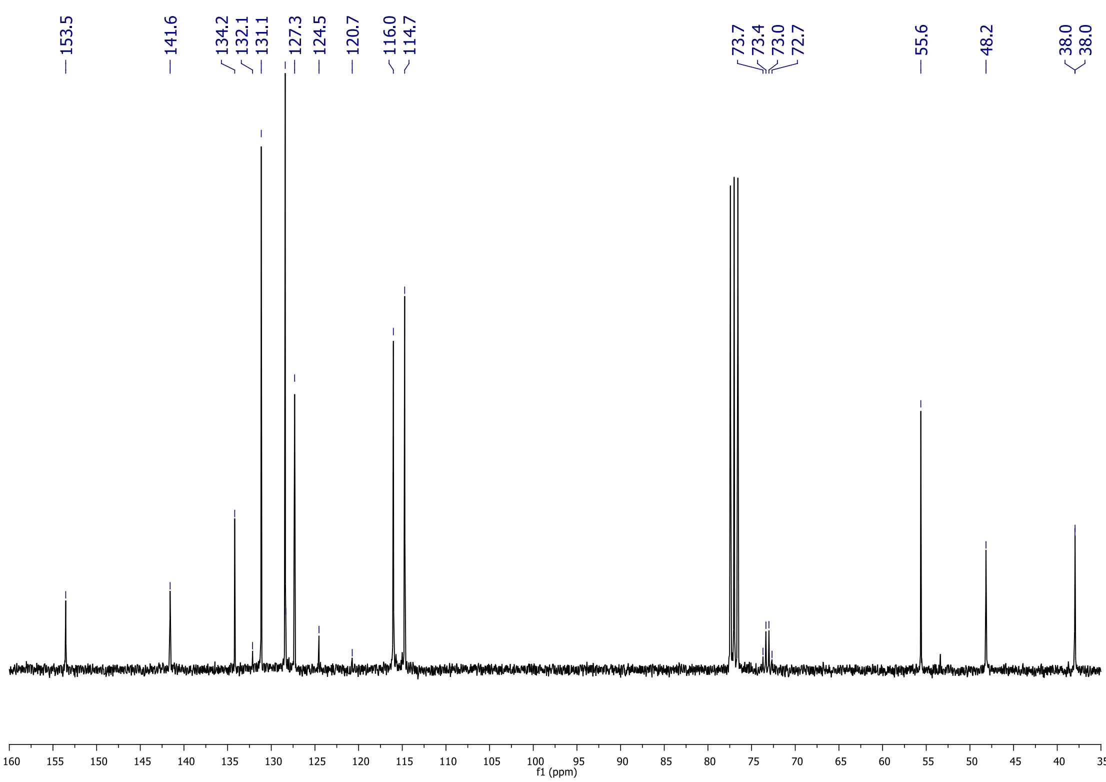
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **10e**



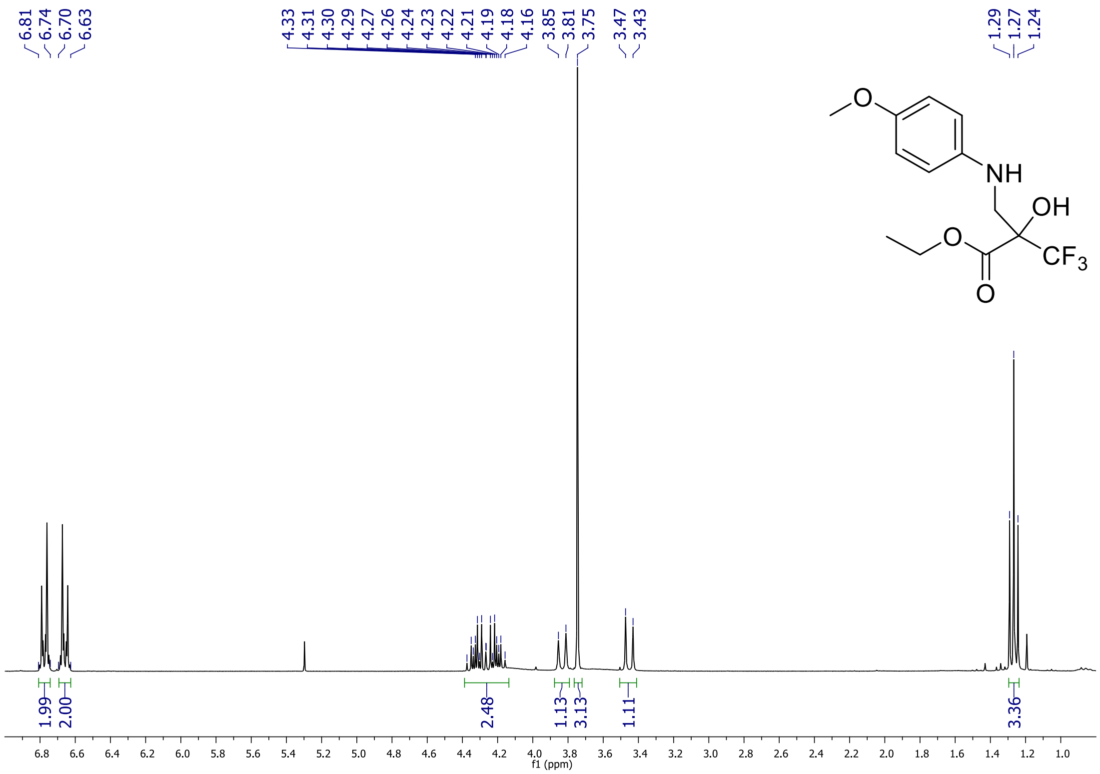
^{1}H NMR ($CDCl_3$, 500 MHz) of **10f**



^{13}C NMR ($CDCl_3$, 75.5 MHz) of **10f**



^{1}H NMR ($CDCl_3$, 300 MHz) of **10j**



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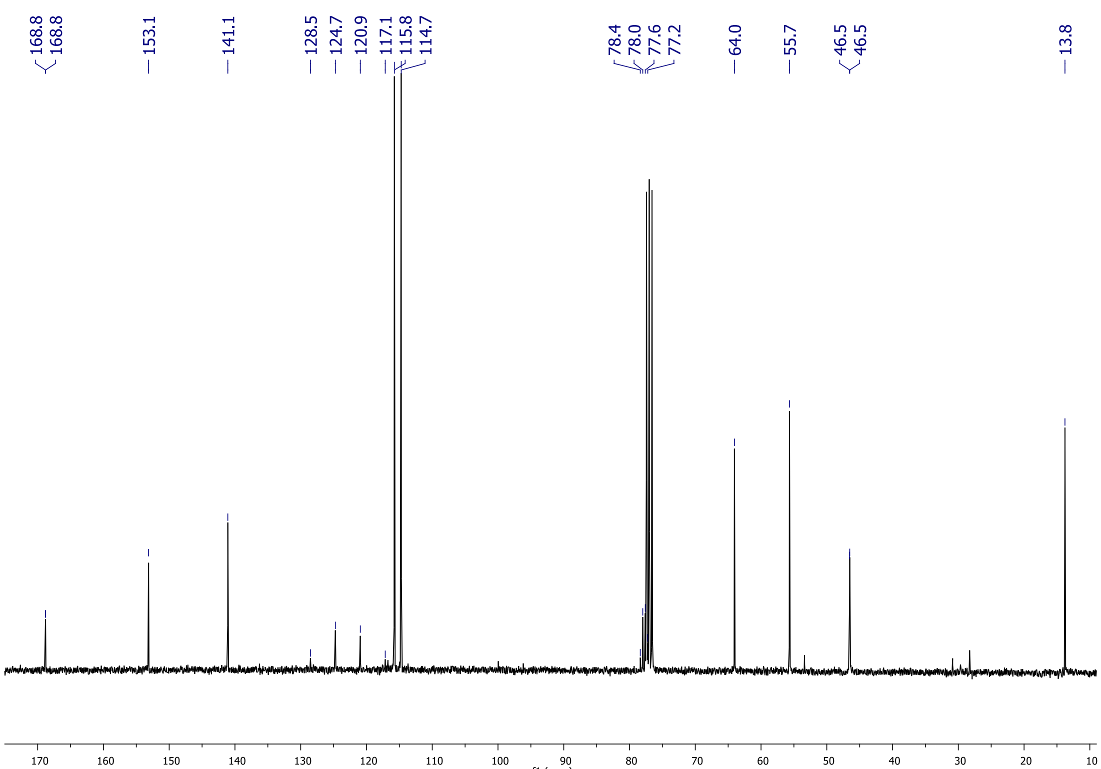
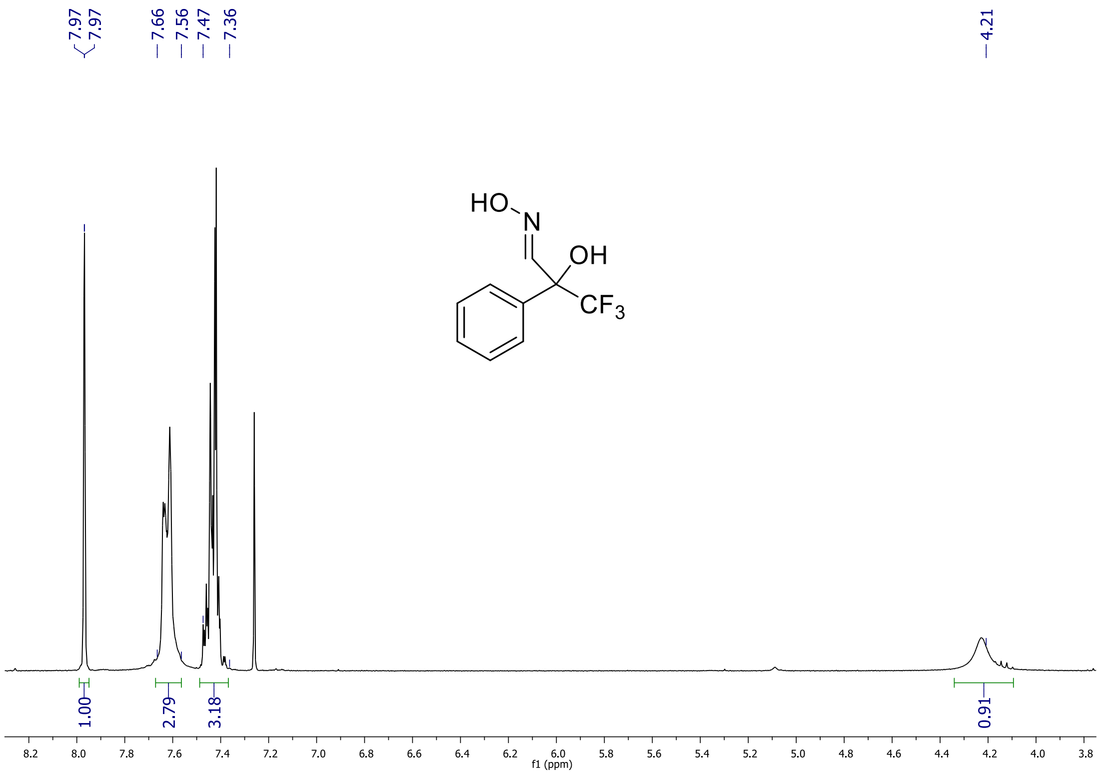
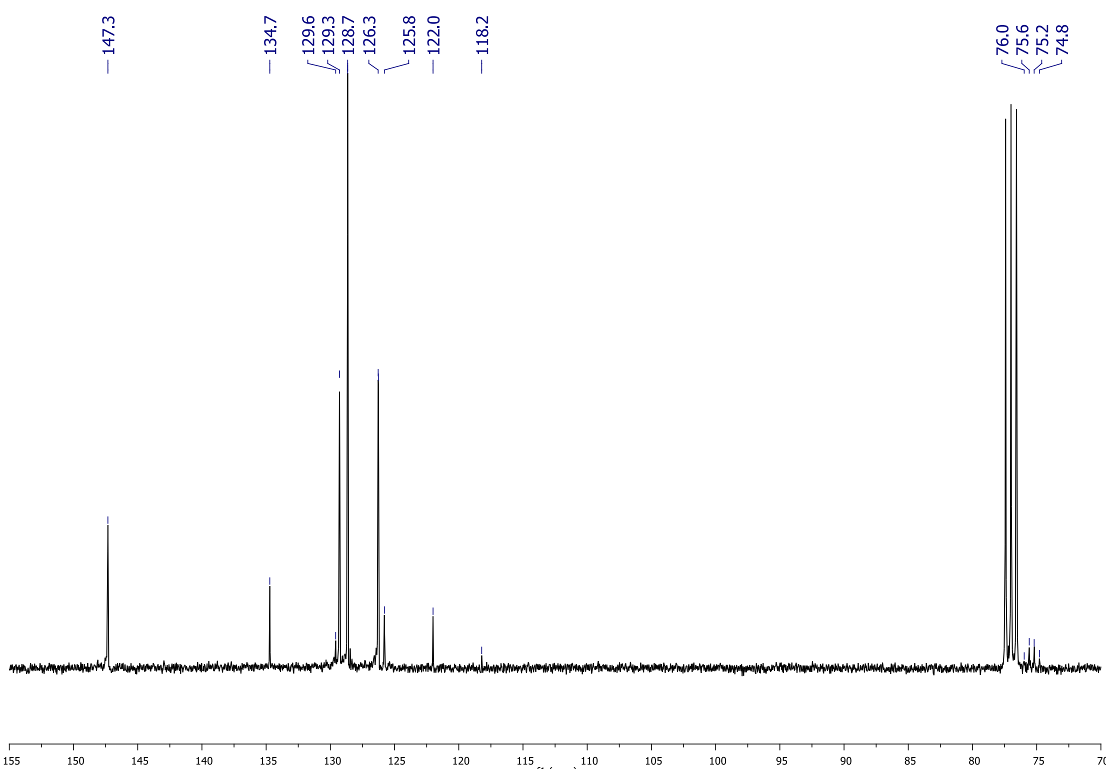


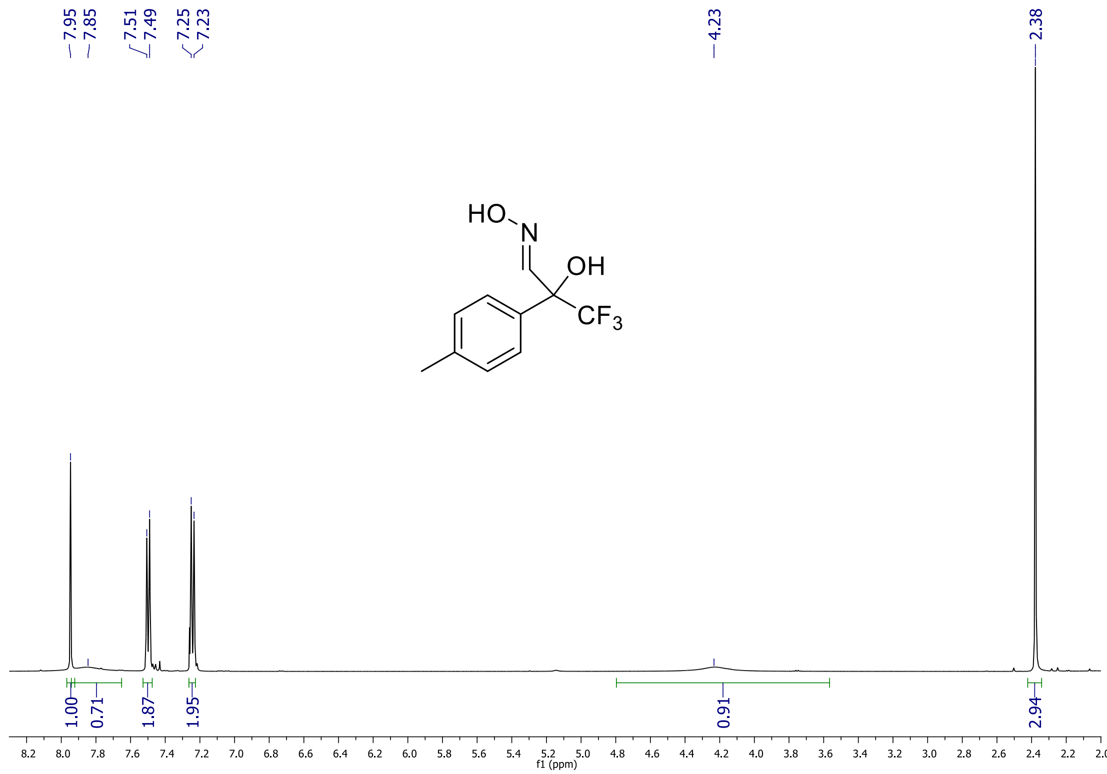
^{1}H NMR ($CDCl_3$, 300 MHz) of **11a**



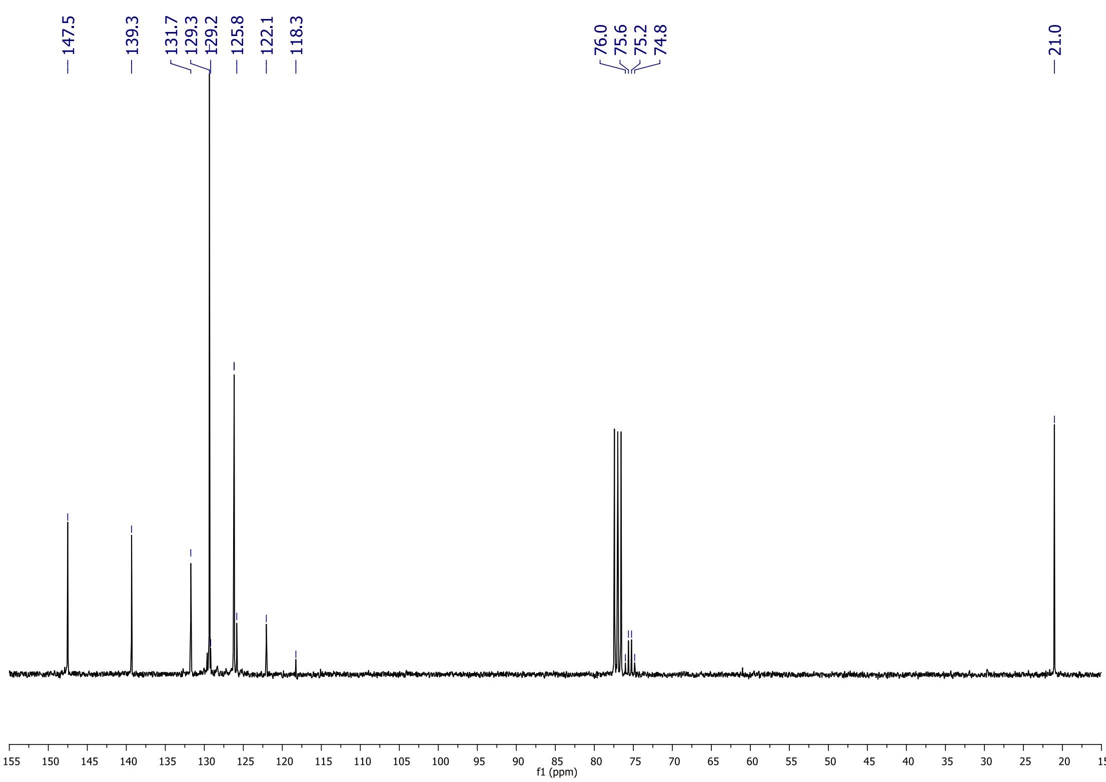
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **11a**



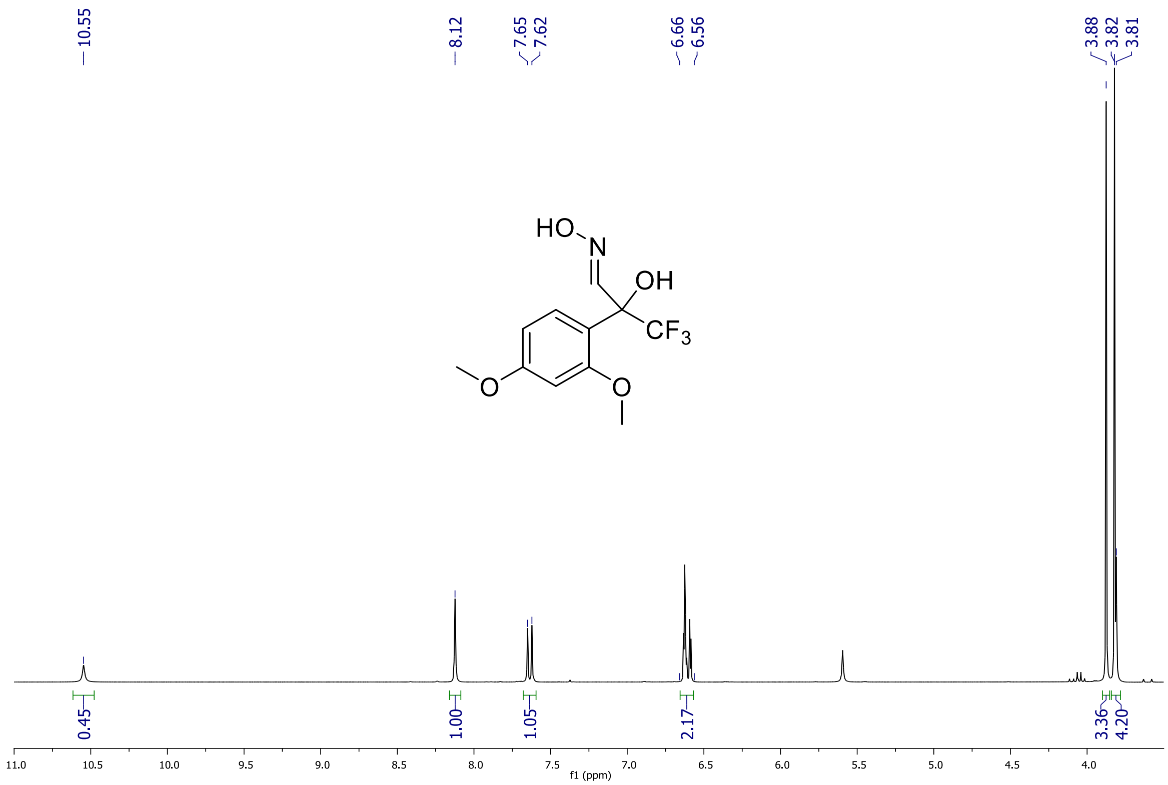
^{1}H NMR ($CDCl_3$, 500 MHz) of **11b**



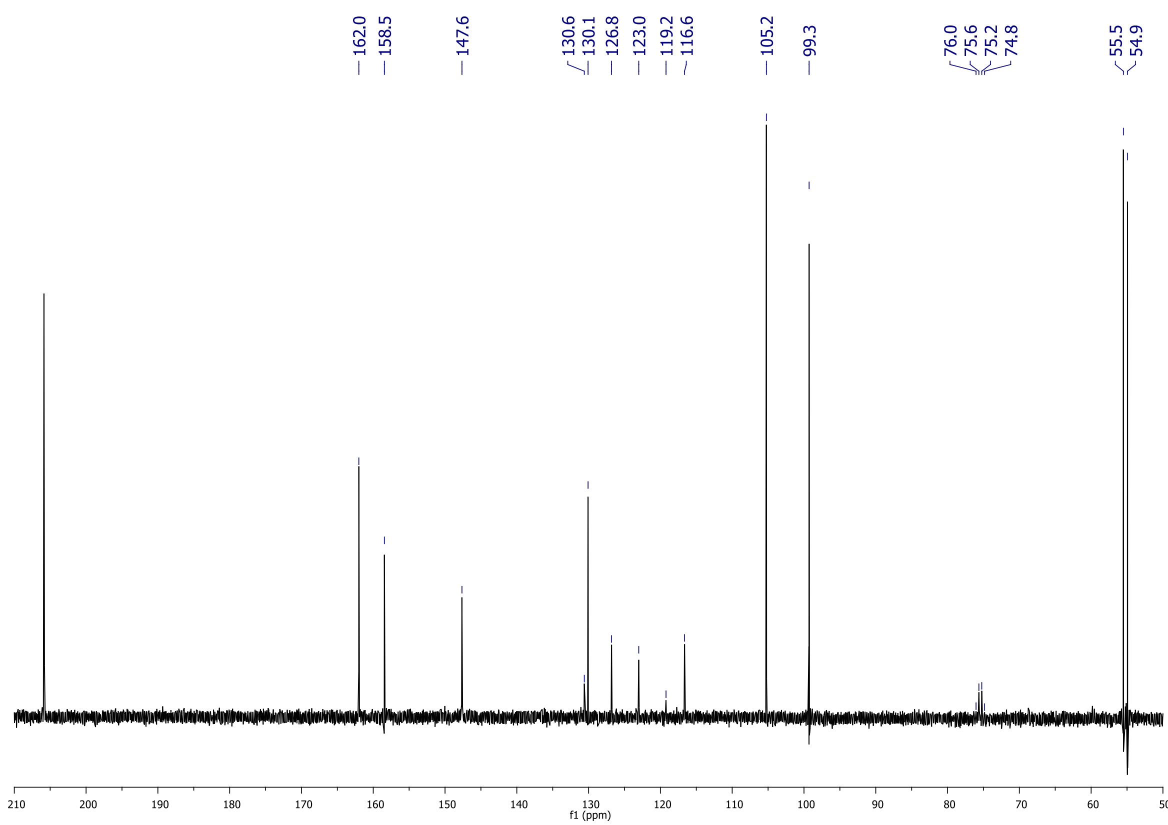
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **11b**



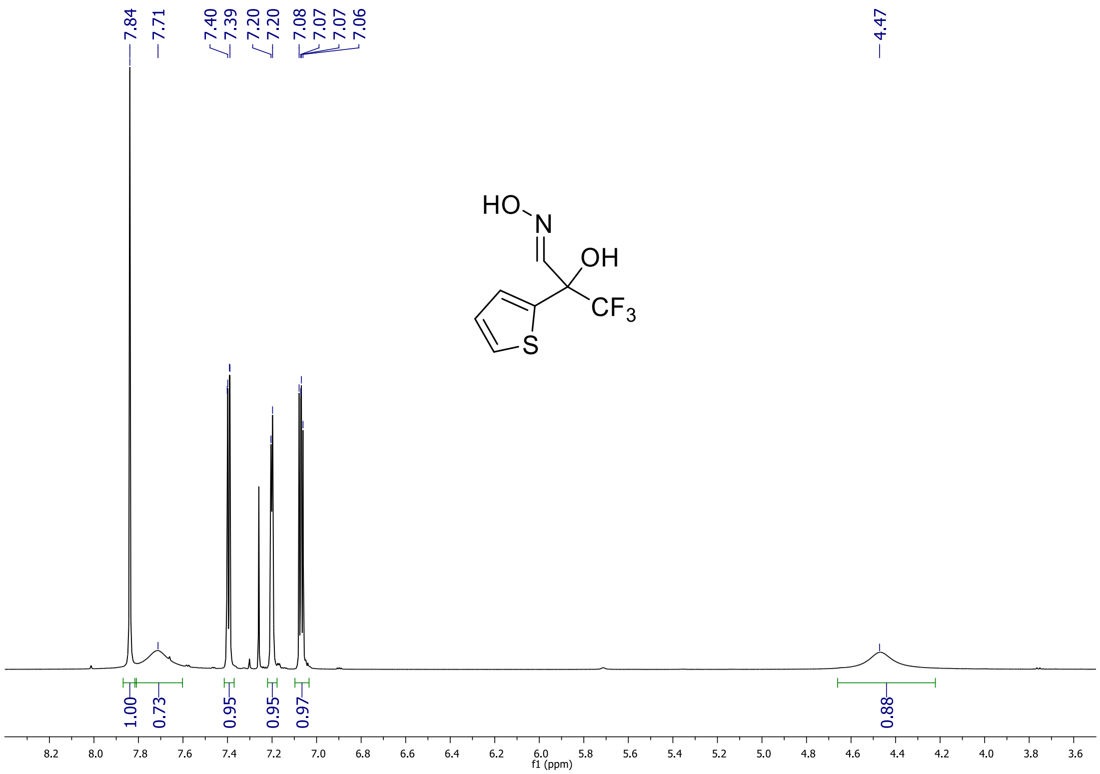
^{1}H NMR ($CO(CD_3)_2$), 300 MHz) of **11c**



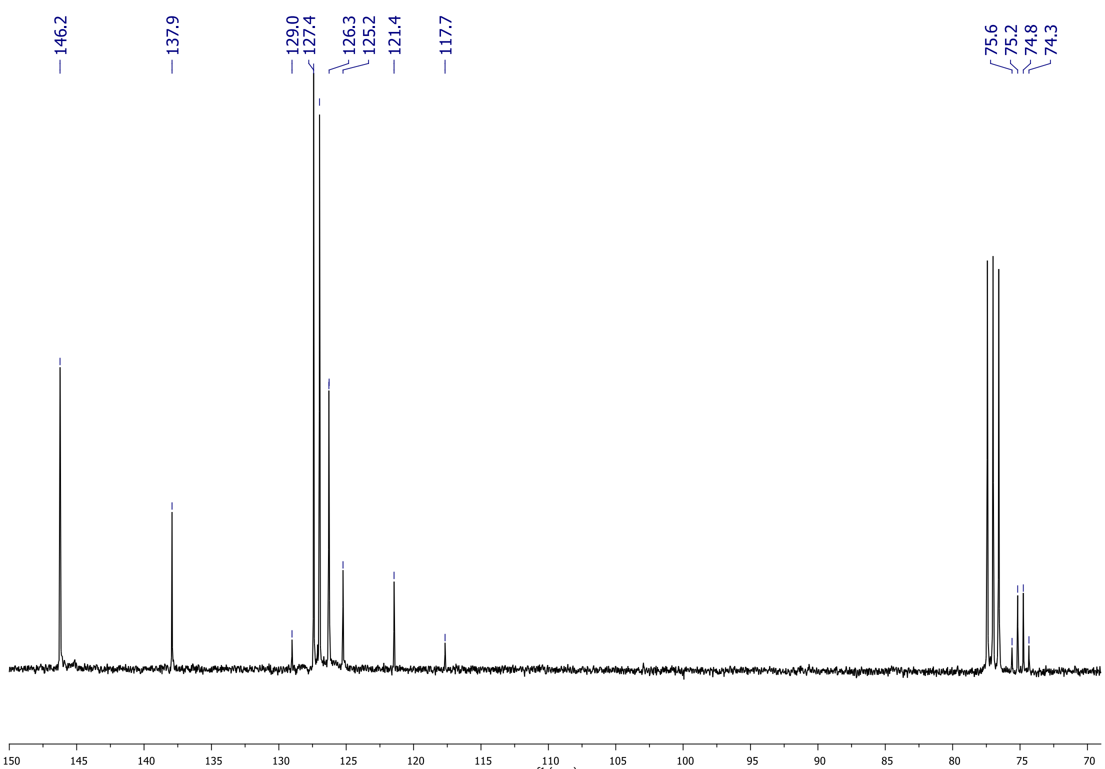
^{13}C NMR ($CO(CD_3)_2$), 75.5 MHz) of **11c**



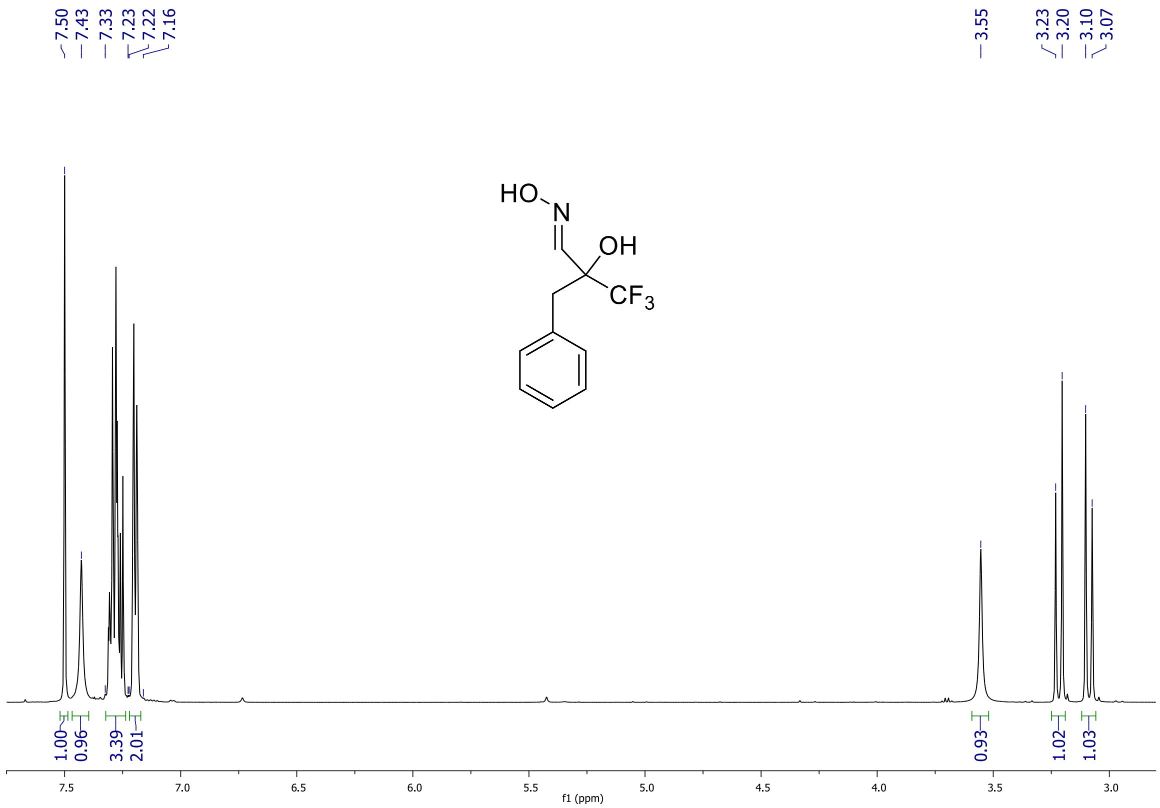
^{1}H NMR ($CDCl_3$, 500 MHz) of **11e**



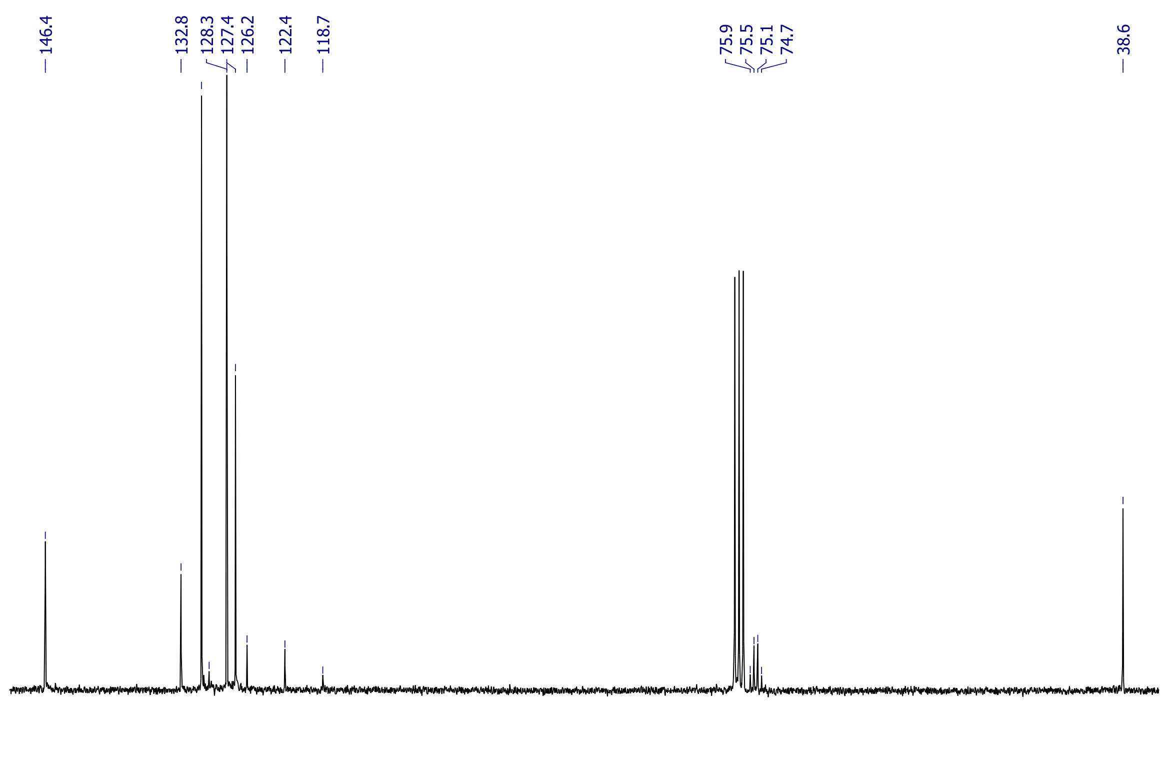
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **11e**



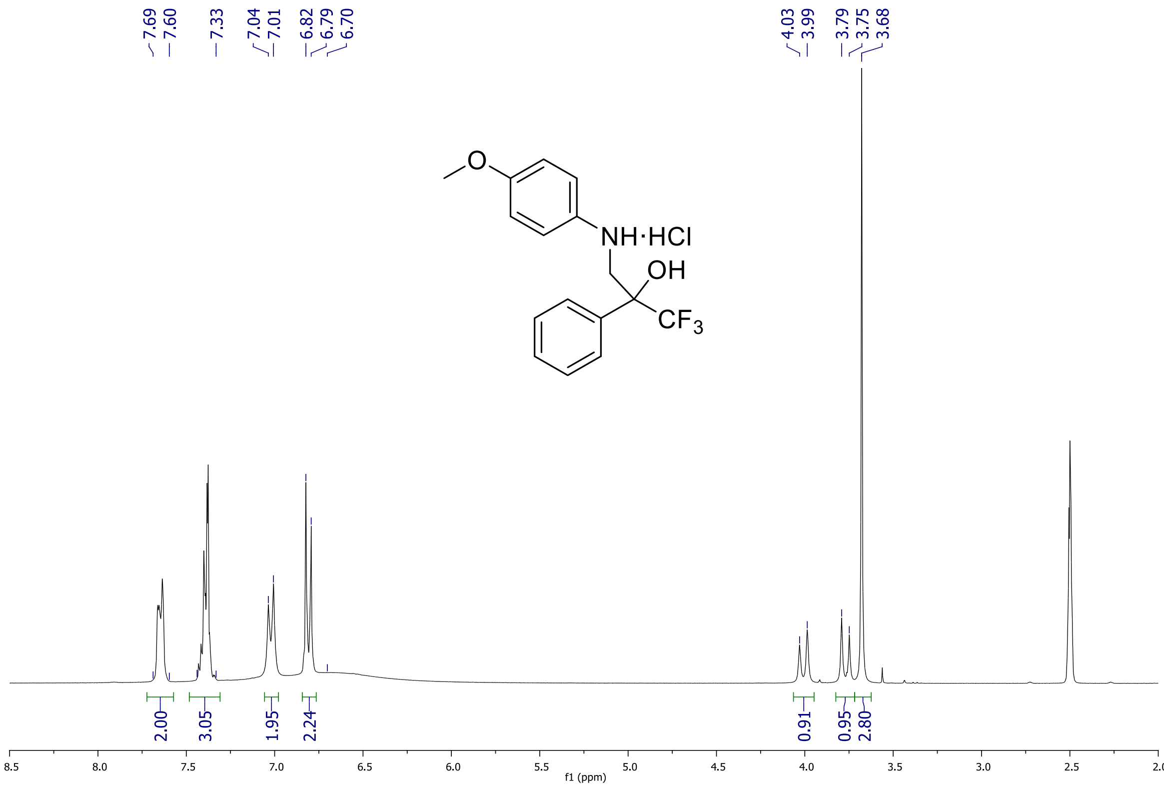
^{1}H NMR ($CDCl_3$, 500 MHz) of **11f**



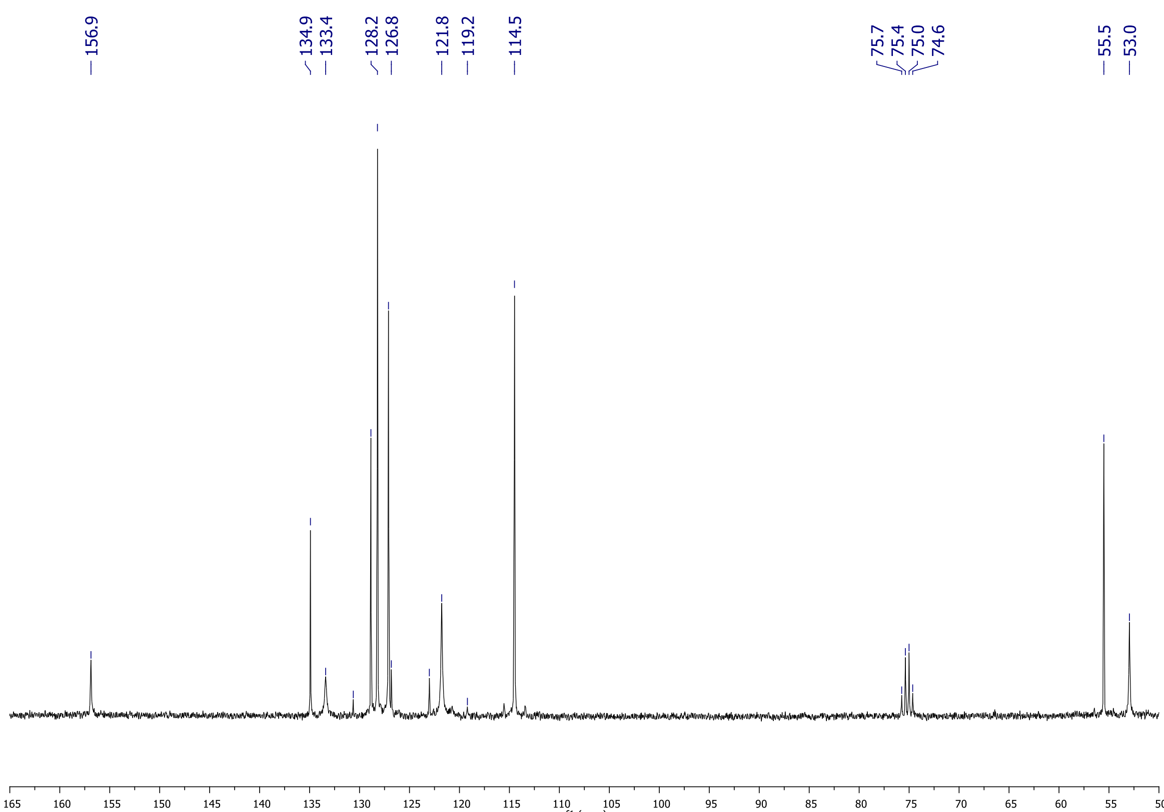
^{13}C NMR ($CDCl_3$, 75.5 MHz) of **11f**



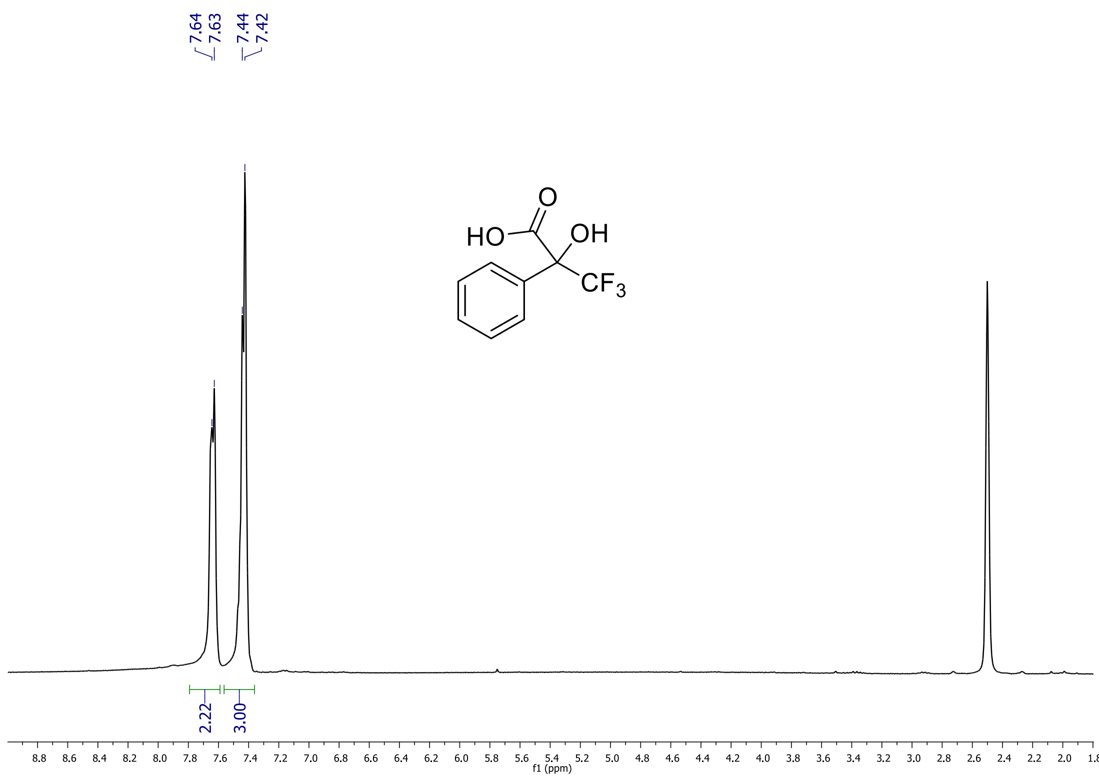
^{1}H NMR (DMSO-d^6, 300 MHz) of **10a-HCl**



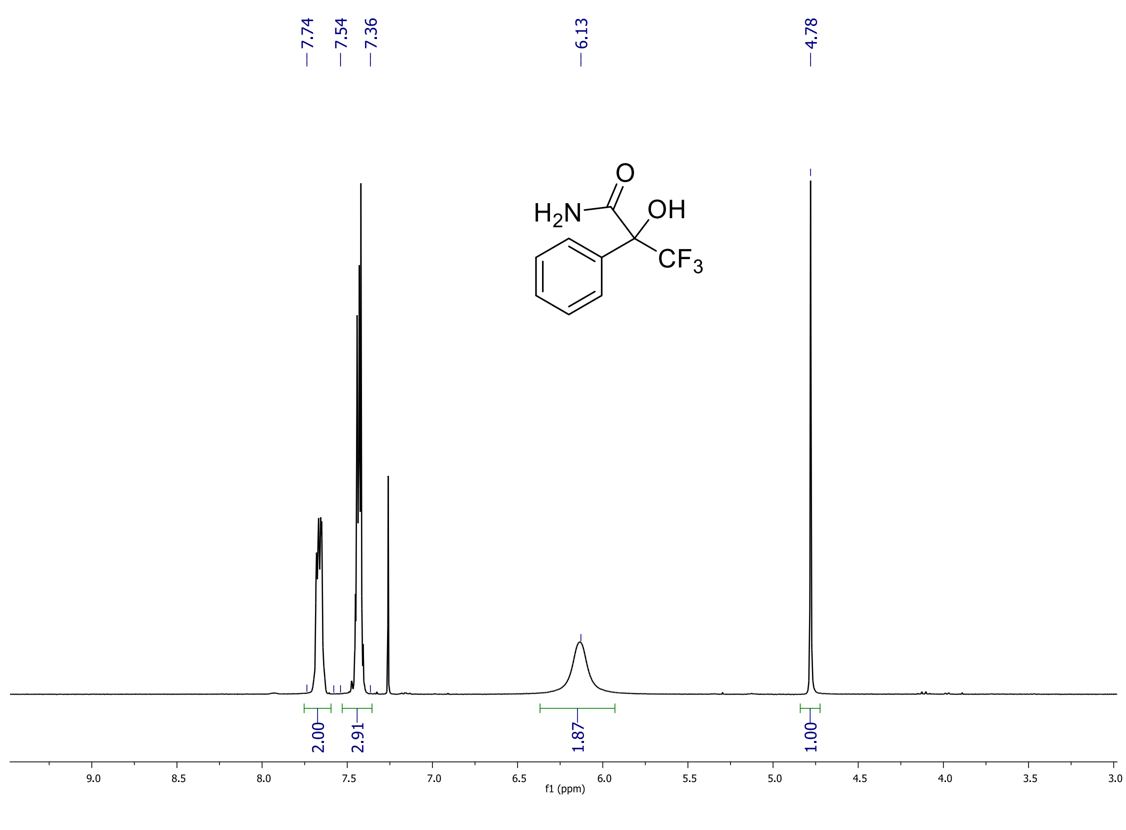
^{13}C NMR (DMSO-d^6, 75.5 MHz) of **10a-HCl**



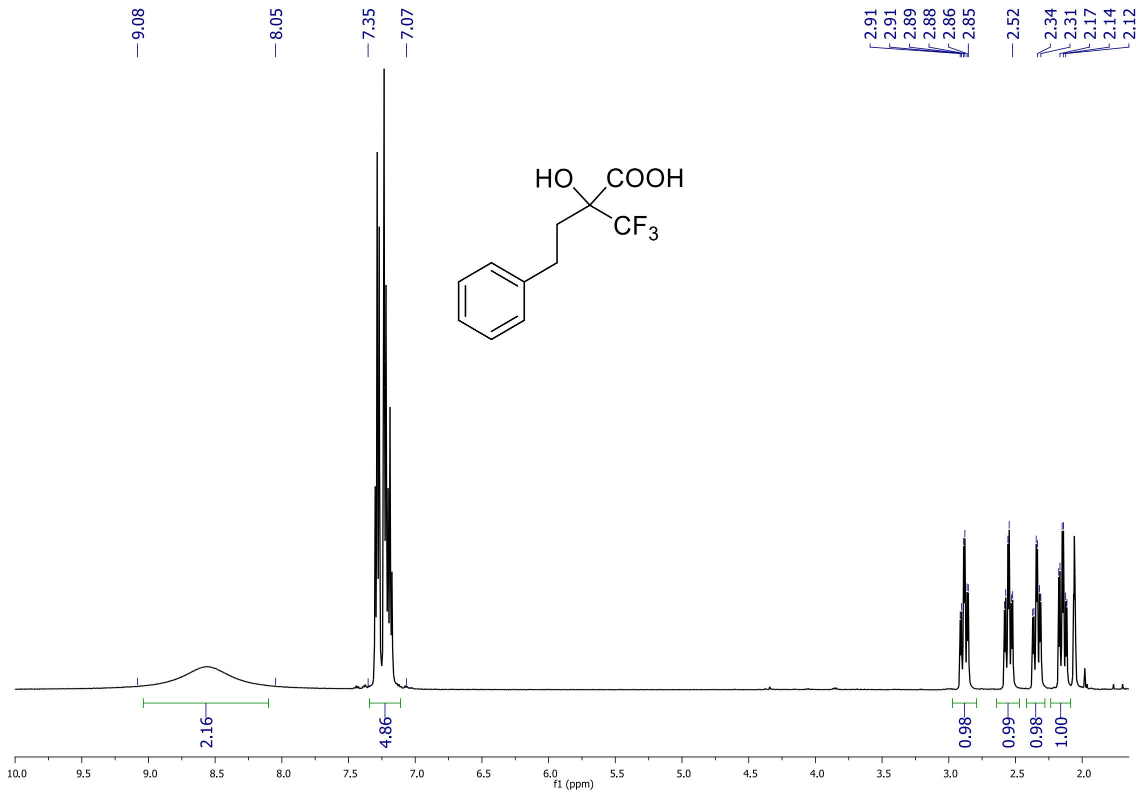
^{1}H NMR (DMSO-d^{6}, 300 MHz) of **12a**



^{1}H NMR ($CDCl_3$, 300 MHz) of **III**



^{1}H NMR (Acetone-d^{6}, 500 MHz) of **12g**



^{13}C NMR (Acetone-d^{6}, 125 MHz) of **12g**