Photo-induced Defluorination Acyl Fluoride Exchange as a Fluorogenic Photo-click Reaction for Photo-affinity labeling

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1. General information

1.1 General information for chemical synthesis

Unless otherwise indicated, all solvents and starting materials were purchased from commercial sources and used directly without further purification. Flash column chromatography was performed by using 200-300 mesh silica gel. Anhydrous solvents, purchased from Acros Organics (dioxane, DMF, and THF), commercially available chemicals were obtained from Adamas, Acros Organics, Aldrich Chemical Co., Alfa, Aesar and TCI. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Brüker Avance 400 or 600 or 800 spectrometer (^{1}H: 400 or 600 or 800 MHz, ^{13}C: 101 or 150 or 201 MHz, ^{19}F: 376 MHz). Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra are given in ppm relative to TMS. The residue solvent signals were used as references for ^{1}H and ^{13}C NMR spectra and the chemical shifts converted to the TMS scale ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; CD_3CN, 1.94 ppm for ^{1}H NMR; CF_3COOD, 11.50 ppm for ^{1}H NMR and 164.2 ppm, 116.6 ppm for ^{13}C NMR; DMSO-d_6, 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). Shifts multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs. = broad.

Abbreviations used: Et_3N = triethylamine; EtOAc = ethyl acetate; PE = petroleum ether; DMF = dimethylformamide; THF = tetrahydrofuran; TLC = thin layer chromatography; HPLC = High Performance Liquid Chromatography; ACN = Acetonitrile; ABC = ammonium bicarbonate; PBS = phosphate buffer solution; FA = formic acid; DTT = dithiothreitol; IAA = Iodoacetamide; TFA = trifluoroacetic acid.

1.2 General information–spectra acquisition

UV-Vis absorption spectra were recorded by using 1.0 cm quartz cuvettes on a Thermo NANODROP 2000C Spectrophotometer. Exact ESI mass spectra were recorded on a SHIMADZU LCMS-IT-TOF, flow rate = 1.0 mL /min. LC-ESI-MS were obtained on a Thermo LTQ-XL mass spectrometer.

The cell imaging experiments were carried out on an Olympus IX83 living cell fluorescence microscope. The cells were stained with a commercially available NucBlue™ Live Ready Probe™ Reagent for cell nucleus fluorescent imaging and identification.

The kinetic data for the amidation reaction between benzoyl fluoride (**5c**) and benzylamine (**2a**) were recorded in real-time by a HORIBA Fluoromax-4 Spectrofluorometer Detector, and deuterium arc & halide lamps were used as the light source (Purchased from Shanghai Wenyi Photoelectric Technology Co., Ltd. China). The absorbance data of photo-switching kinetic and photo-antifatigue performance were recorded on an in-house assembled instrument based on a fast-response modular spectrometer.

1.3 General information–light sources

A 311 nm UV lamp (2.9 mW cm^{-2}, single wavelength output after an optical filter) for the determination of photo-quantum yields and UV-Vis spectra.

A 311 nm UV lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) for HPLC analysis and peptides/protein modification.

A 311 nm UV lamp (21.2 mW cm^{-2}) for the amplified photoreaction.

The photo-irradiation power density of various light sources in photochemical transformation experiments were measured by an optical power meter produced by Thorlabs.

1.4 General CuAAC conjugation procedure

Tris(2-carboxyethyl)phosphine (TCEP) and the CuAAC click chemistry ligand 3,3′,3″-(4,4′,4″-(Nitrilotris(methylene))tris(*1H*-1,2,3-triazole-4,1-diyl))tris(propan-1-ol) (THPTA) were purchased from

Admas, and azide-Alexa-647 was purchased from Beyotime Biotechnology.

Stock solution: 2.0 mM of azide-Alexa-647 in DMSO; 20 mM of THPTA in DMSO; 200 mM of TCEP in water; 200 mM of $CuSO_4$ in water;

1.0 μL of azide-Alexa-647 stock solution, 4.0 μL of THPTA stock solution, 4.0 μL of TCEP stock solution, 4.0 μL of $CuSO_4$ stock solution, and 16 μL water were mixed as working solution. Incubate the 20 μL sample mixture and 2.0 μL working solution for 1.5 h with gentle mixing before subjecting to SDS-PAGE analysis.

2. Supplemental figures and tables

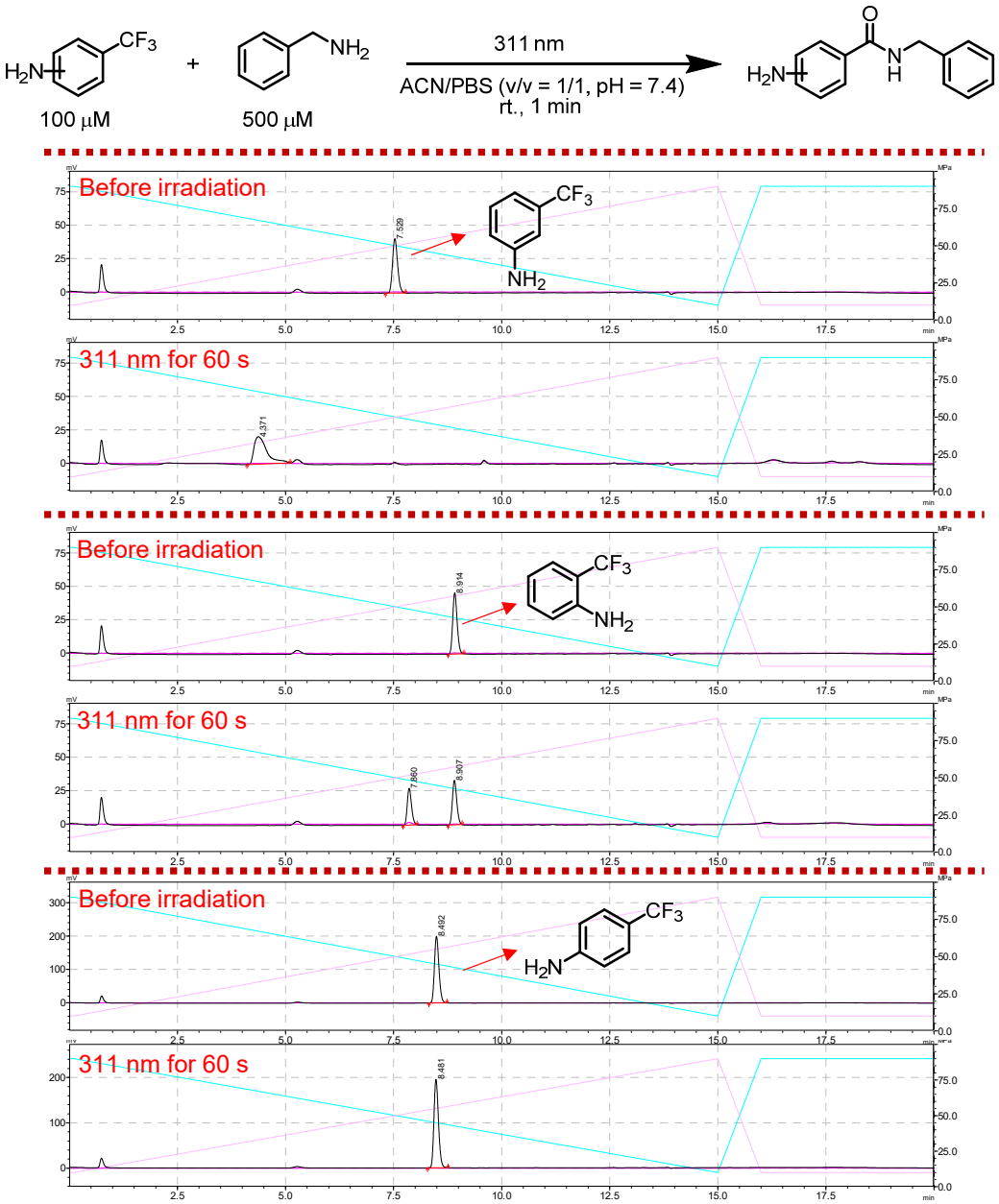
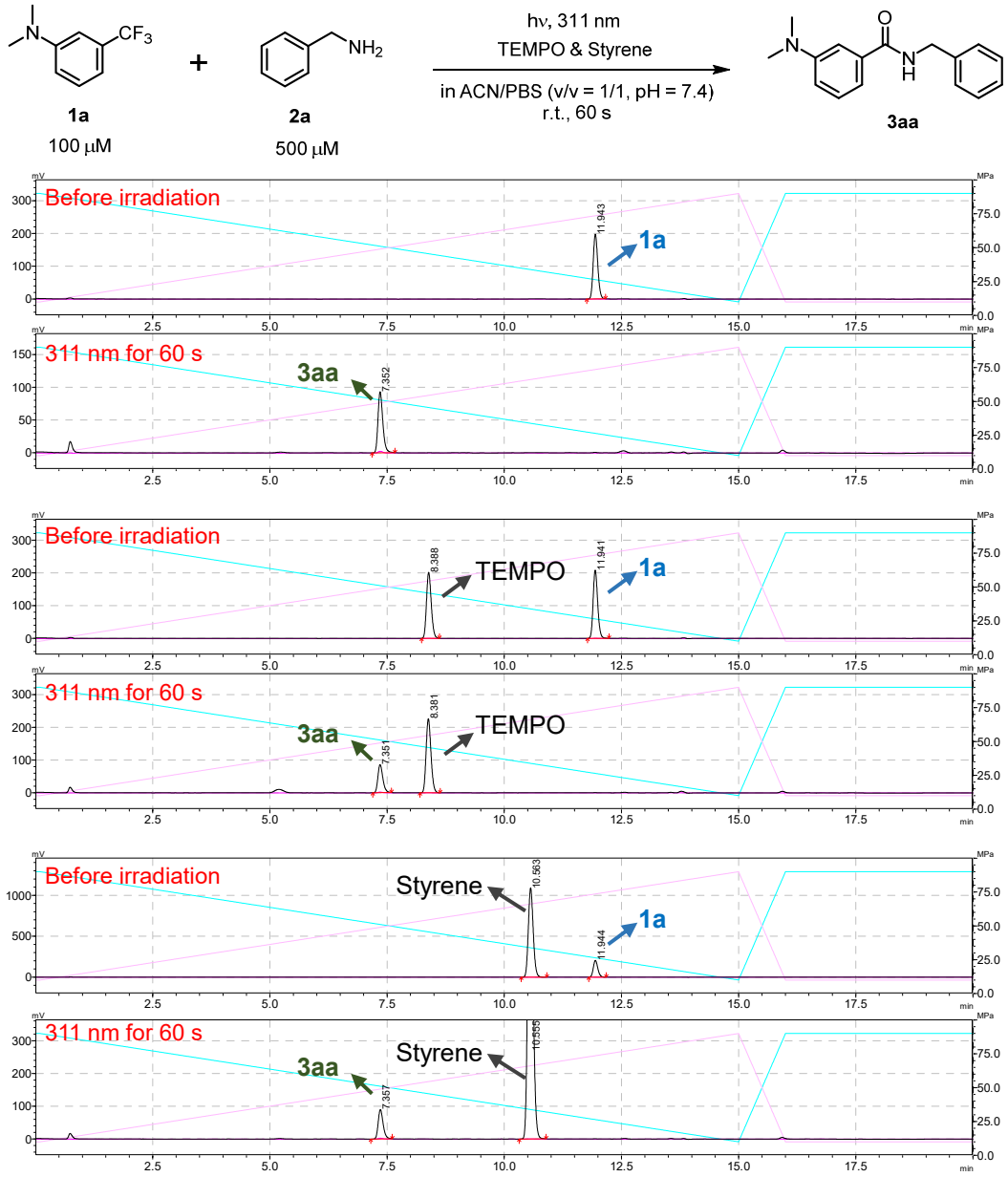


Figure S1. Efficiency evaluation of the photo-click reaction for meta-/ortho-/para-trifluoromethylaniline (100 μM) toward benzylamine (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4).



	Peak	Retention Time	Integrated Area
Control	**1a**	11.943	1342105
	3aa	7.352	665559
TEMPO (750 μM)	**1a**	11.941	1393514
	3aa	7.351	629036
Styrene (750 μM)	**1a**	11.944	1359646
	3aa	7.357	652326

Figure S2. Radical quenching tests toward the photo-DAFEx reactions. Reaction condition: **1a** (100 μM) and **2a** (500 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) with or without TEMPO/Styrene (750 μM) were irradiated with a 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) for 60 s, and the resulting samples were analysed by HPLC.

Note S1. Determination of the photoreaction quantum yields (Φ_R) for the photo-defluorination of **1a-1h**.

The photo-defluorination quantum yields of **1a-1h** were determined by using potassium ferrioxalate-based chemical actinometer [1]. In brief, a 250 μL fresh solution of 6 mM potassium ferrioxalate in 0.1 N H_2SO_4 aqueous solution was irradiated with the 311 nm lamp (2.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz cuvette (0.2 cm × 1.0 cm optical path) for specified times before quenching by addition of 4.75 mL of NaOAc/HOAc buffer (pH = 4.3) and 5.0 mL of 0.1% 1,10-phenanthroline solution in water to develop the characteristic colour at 510 nm. The mixture was stirred for 30 min before UV-Vis measurement. All the works were carried out in the dark and the samples were also protected from light with aluminium foil during handling. All the operating procedures were the same for both the chemical actinometer and tested samples (direct measurement without developing process), including light sources, experimental setup, volume of the solution, and the cuvette. The quantum yield for a test compound was calculated based on the following equations:

The incident monochromic photon flux I_0:

$$I_0 = \frac{d[\mathrm{Act}]}{dt} \times [1/(1-10^{-\mathrm{Abs_c}})]/\Phi_c = \frac{d[\mathrm{photo-DAFEx}]}{dt} \times [1/(1-10^{-\mathrm{Abs_t}})]/\Phi_t \quad ^{2\text{-}3}$$

Because at the initial photo-conversion stage: $\frac{d[Act]}{dt} = \frac{dAbs_{product}}{dt}(\frac{1}{\varepsilon_{product}})$, therefore:

$$I_0 = (40 \times k_c/\varepsilon_{510} l) \times [1/(1-10^{-\mathrm{Abs_c}})]/\Phi_c = (k_t/\Delta\varepsilon_p l) \times [1/(1-10^{-\mathrm{Abs_t}})/\Phi_t$$

The subscript "***c***" represents to the parameters of the chemical actinometer;

The subscript "***t***" represents to the parameters of the tested compound **1a-1h**, and "***p***" for the corresponding acyl fluorides. Therefore:

$$\Phi_{reac.} = \Phi_t = [(1-10^{-\varepsilon_c c_c l})]/(1-10^{-\varepsilon_t c_t l})] \times [k_t/(40 \times k_c)] \times (\varepsilon_{510}/\Delta\varepsilon_p) \times \Phi_c$$

where ε_c and ε_t were extinction coefficients of the standard chemical actinometer and test samples (**1a-1h** at 311 nm), respectively. l = 1.0 cm;

k_t and k_c were the slopes of the linear fitting line of product formation in plots of absorbance changes versus time at the observing wavelength for the tested compound and the standard chemical actinometer, respectively. The zeroth-order photo-conversion rate (k_t and k_c) could be only applied at very low conversion (as low as possible for the initial conversion rate) of the starting materials because the absorption of light by the products formed under such conditions is minimal at the initial stage. Noteworthy, the addition of the buffer solution and the developer during the colour readout of the actinometer conversion resulted in a 40-fold dilution, therefore the k_c need to be multiplied by 40 during the calculation;

c_c and c_t were the concentrations of the standard actinometer and the test compound, respectively;

ε_{510} [4] and $\triangle\varepsilon_p$ were the extinction coefficients of the Fe^{2+}-(1,10-phenanthroline)$_3$ complex at 510 nm for the actinometer and the difference in extinction coefficients of the acyl fluorides compared with the starting sample, **1a-1h**, at the monitoring wavelength, respectively. The photoreaction quantum yields of **1a-1h** in ACN/H_2O (v/v = 1/1) with 311 nm irradiation were then obtained.

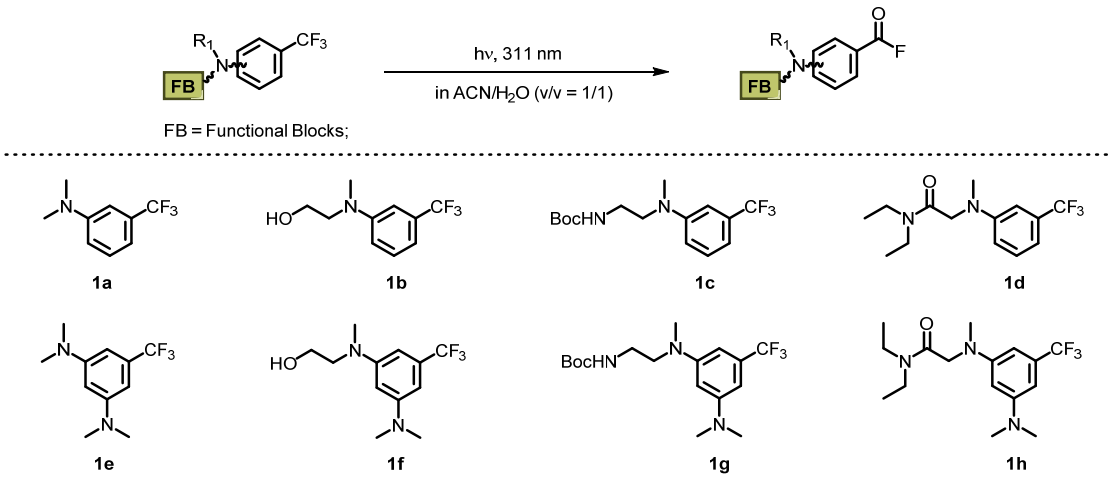
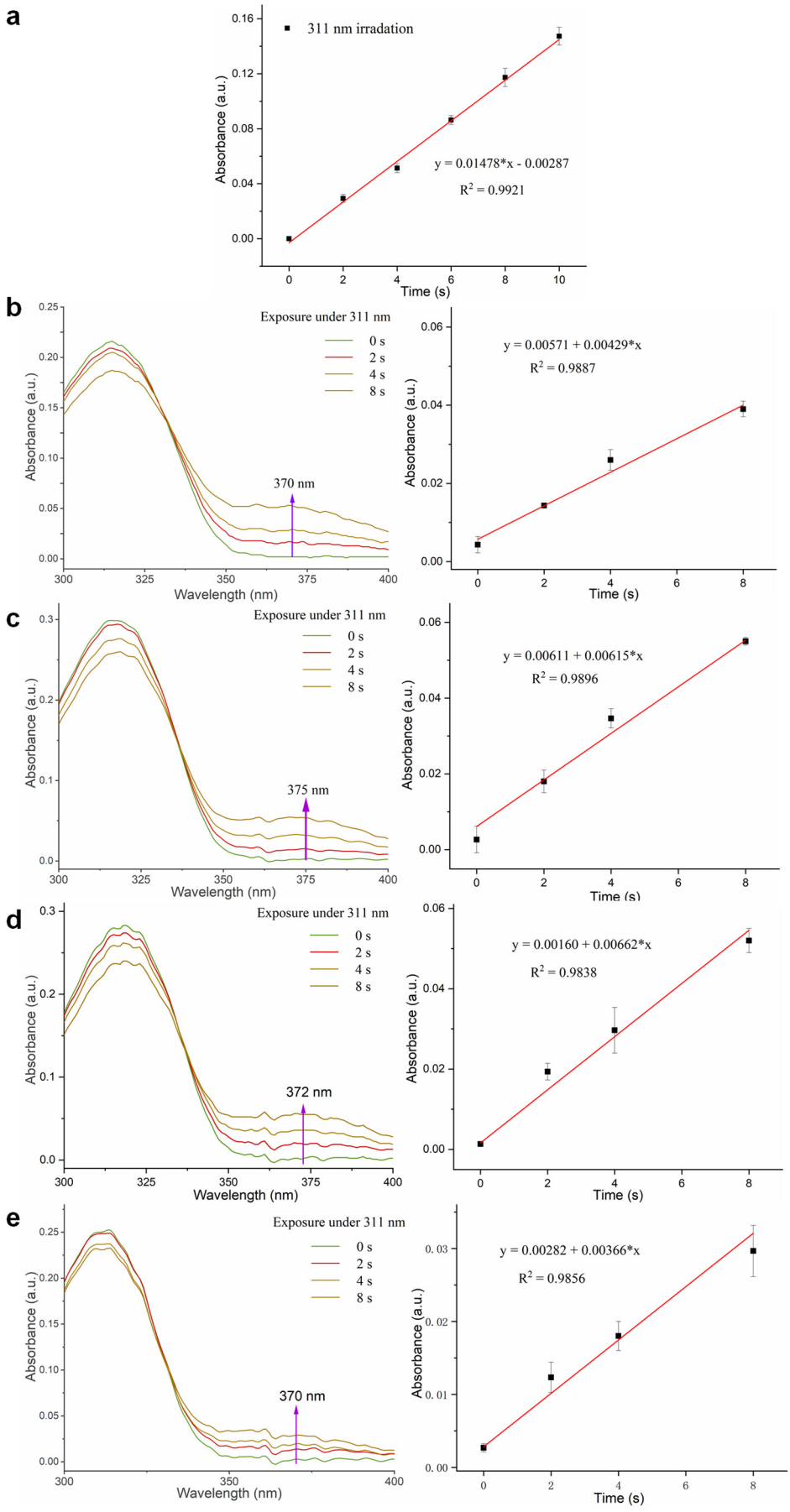


Table S1. The result of photochemical quantum yields (Φ_R) for the photo-defluorination of **1a-1h**.

	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
Φ_R	0.17	0.14	0.16	0.15	0.13	0.16	0.12	0.12


a
311 nm irradation
Absorbance (a.u.)
Time (s)
y = 0.01478*x - 0.00287
R2 = 0.9921
b
Exposure under 311 nm
0 s
2 s
4 s
8 s
370 nm
Wavelength (nm)
Absorbance (a.u.)
y = 0.00571 + 0.00429*x
R2 = 0.9887
Time (s)
c
Exposure under 311 nm
0 s
2 s
4 s
8 s
375 nm
Wavelength (nm)
Absorbance (a.u.)
y = 0.00611 + 0.00615*x
R2 = 0.9896
Time (s)
d
Exposure under 311 nm
0 s
2 s
4 s
8 s
372 nm
Wavelength (nm)
Absorbance (a.u.)
y = 0.00160 + 0.00662*x
R2 = 0.9838
Time (s)
e
Exposure under 311 nm
0 s
2 s
4 s
8 s
370 nm
Wavelength (nm)
Absorbance (a.u.)
y = 0.00282 + 0.00366*x
R2 = 0.9856
Time (s)

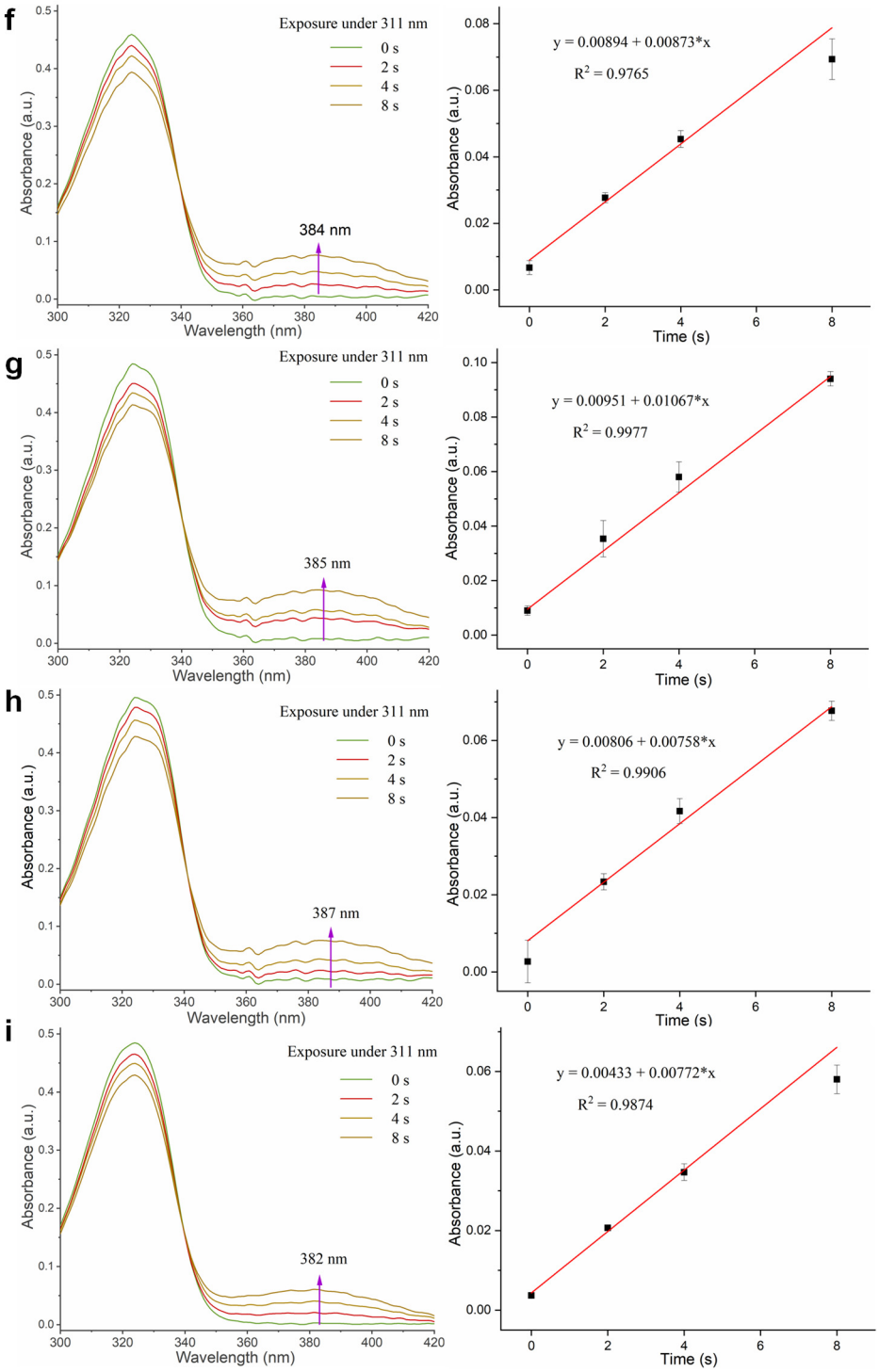


Figure S3. Determination of the photo-defluorination quantum yields by using a potassium ferrioxalate-based chemical actinometer. **a)** Time-course of absorbance changing for observing the formation of Fe^{2+}-(1,10-phenanthroline)$_3$ complex at 510 nm with a linear fitting curve, which was induced by the 311 nm irradiation from the lamp to the actinometer. **b-i)** Time-course of absorbance changing for the photo-defluorination of the trifluoromethylaniline derivatives (**1a-1h**) to corresponding acyl fluorides under 311 nm irradiation with a linear fitting curve (monitored at the labelled wavelength for absorbance tracking).

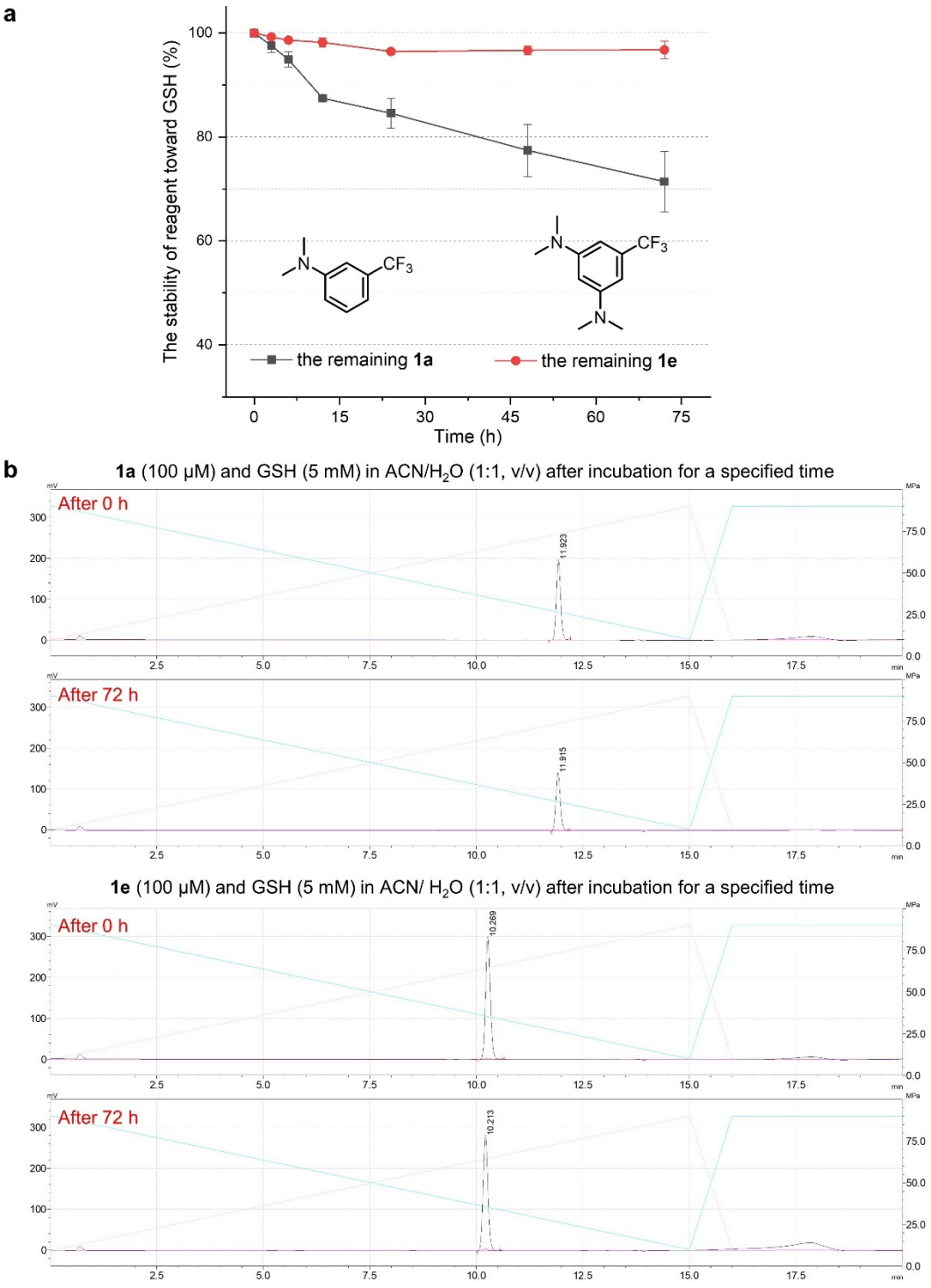
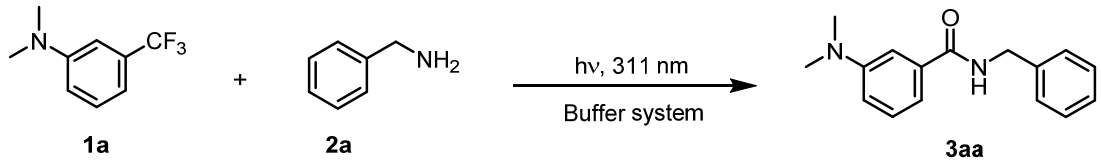


Figure S4. The stability test against thiol addition. a) The stability testing results for **1a**/**1e** (100 μM) toward GSH (5.0 mM) in ACN/H_2O (v/v = 1/1) after incubation for a specific time analysed by quantitative HPLC. The stability of the reagents was determined by the ratio of integrated peak areas of the **1a**/**1e** left at the designated time point in each HPLC trace to the original samples without incubation. b) The HPLC traces for the reaction between **1a**/**1e** (100 μM) and GSH (5.0 mM) in ACN/H_2O (v/v = 1/1) before and after 72 h incubation in dark.



1a + **2a** → **3aa**

Table S2. Optimization on the buffer system for the photo-DAFEx reaction.

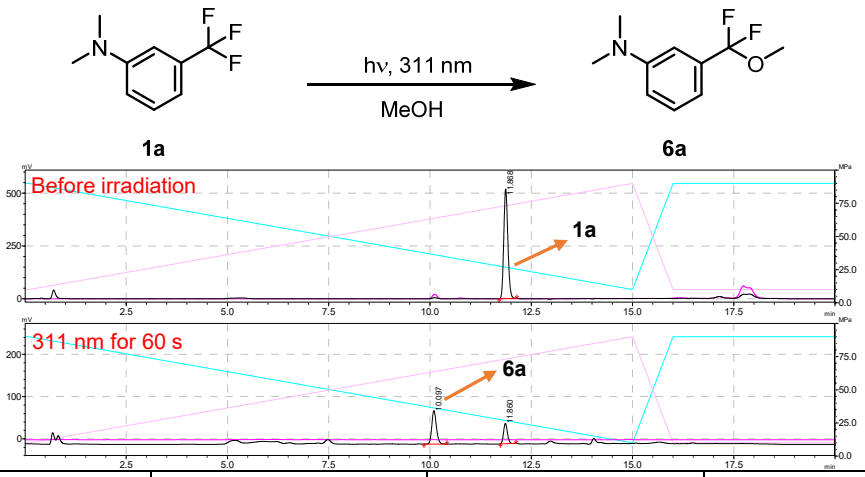
Entry	Buffer System	Yield of 3aa
1	ACN/PBS (v/v = 1/1, pH = 7.4)	93.6%[#]; 83.1%[&]
2	ACN/NaOAc-HOAc (v/v = 1/1, pH = 4.1)	54.4%[#]
3	ACN/$NaHCO_3$-Na_2CO_3 (v/v = 1/1, pH = 11.2)	73.1%[#]
4	ACN/H_2O (v/v = 1/1)	85.9%[#]
5	MeOH/PBS (v/v = 1/1, pH = 7.4)	24.9%[#]
6	DCM/PBS (v/v = 1/1, pH = 7.4)	N.D.[&]
7	Dioxane/PBS (v/v = 1/1, pH = 7.4)	85.3%[&]
8	DMF/PBS (v/v = 1/1, pH = 7.4)	80.6%[&]
9	DMSO/PBS (v/v = 1/1, pH = 7.4)	79.1%[&]

Reaction condition: the reaction was conducted with **1a** (100 μM) and **2a** (500 μM) in 1.0 mL of the buffer system, and irradiated with a 311 nm lamp (5.9 mW cm^{-2}) for 1 min. [#]HPLC yields were determined by external standards.

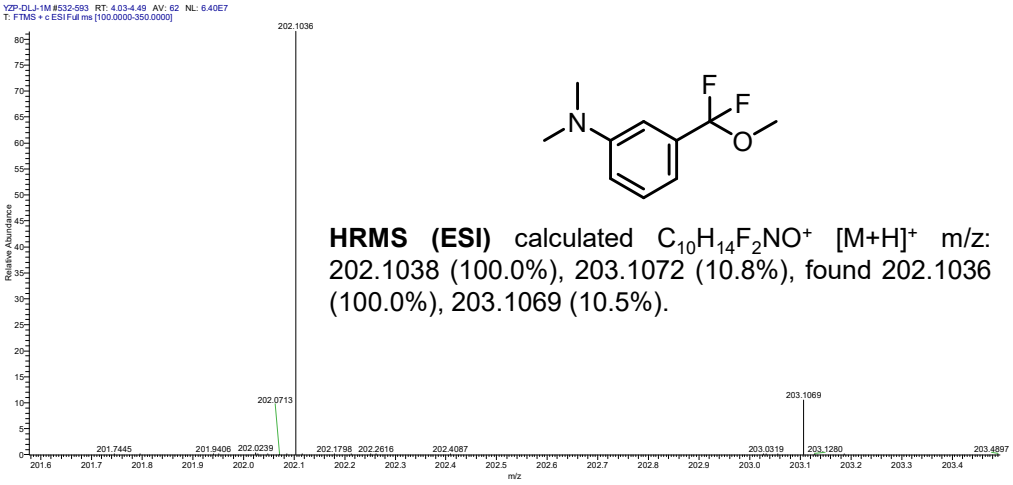
& Reaction conditions: the reaction was conducted with **1a** (20 mg, 0.11 mmol) and **2a** (58 mg, 0.55 mmol) in 200 mL of buffer system, and irradiated with 311 nm lamp (21.2 mW cm^{-2}) for 1.0 h.

[&]Isolated yields of desired products were given.

N.D. = not detected



	Peak	Retention Time	Integrated Area
Before irradiation	**1a**	11.868	3643358
311 nm for 60 s	**1a**	10.097	623774
	3aa	11.868	318728
HPLC yield		17%	



HRMS (ESI) calculated $C_{10}H_{14}F_2NO^+$ $[M+H]^+$ m/z: 202.1038 (100.0%), 203.1072 (10.8%), found 202.1036 (100.0%), 203.1069 (10.5%).

Figure S5. Photo-induced defluorination reaction of **1a** in anhydrous MeOH as both the solvent and the reactant. Reaction condition: the reaction was conducted with **1a** (100 μM) in 1.0 mL of absolute MeOH, and irradiated with a 311 nm lamp (5.9 mW cm^{-2}) for 1.0 min.

Note S2. Determination of the half-life ($t_{1/2}$) of benzoyl fluoride **5a** in ACN/PBS (v/v = 1:1, pH = 7.4).

The hydrolysis of benzoyl fluoride (**5a**) in ACN/PBS (v/v = 1:1, pH = 7.4) at room temperature can be regarded as a *pseudo*-first-order reaction because the concentration of water is almost constant in the buffer and in great excess. In brief, 100 μM of **5a** in ACN/PBS (v/v = 1:1, pH = 7.4) was placed in a sealed sample vial at room temperature for incubation. After incubation for a specific time, the concentration of **5a** was analysis *via* HPLC to determine the remaining **5a** in the sealed vial, $n = 3$.

The *pseudo*-first-order reaction rate constant k was calculated based on the following equations:

$$\ln\left(\frac{a}{c}\right) = kt$$

a represents to the initial concentration of **5a**; ***c*** represents to the concentration of **5a** at the specific time. Therefore:

$$t_{1/2} = \frac{ln2}{k}$$

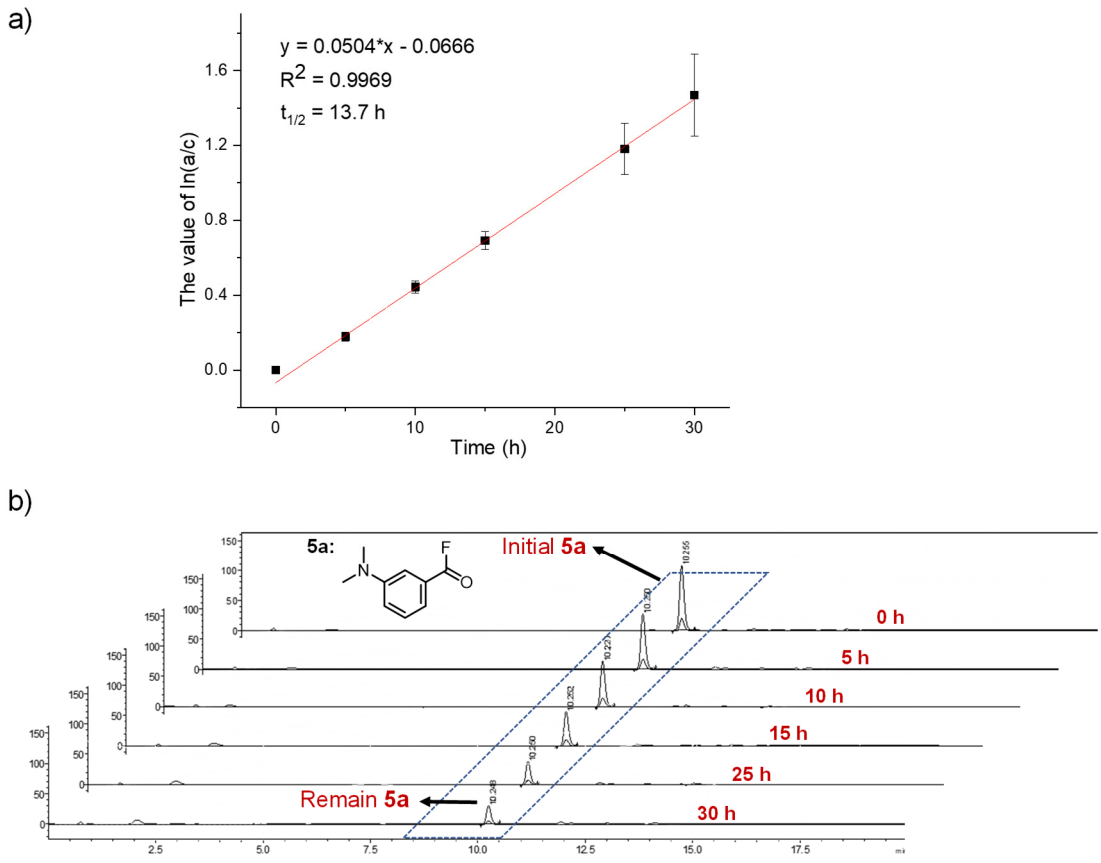


Figure S6. a) Time-course tracking of the decaying of **5a** in aqueous to determine the value of $\ln\left(\frac{a}{c}\right)$ with a linear fitting curve; b) HPLC traces of **5a** after incubation for a specific time.

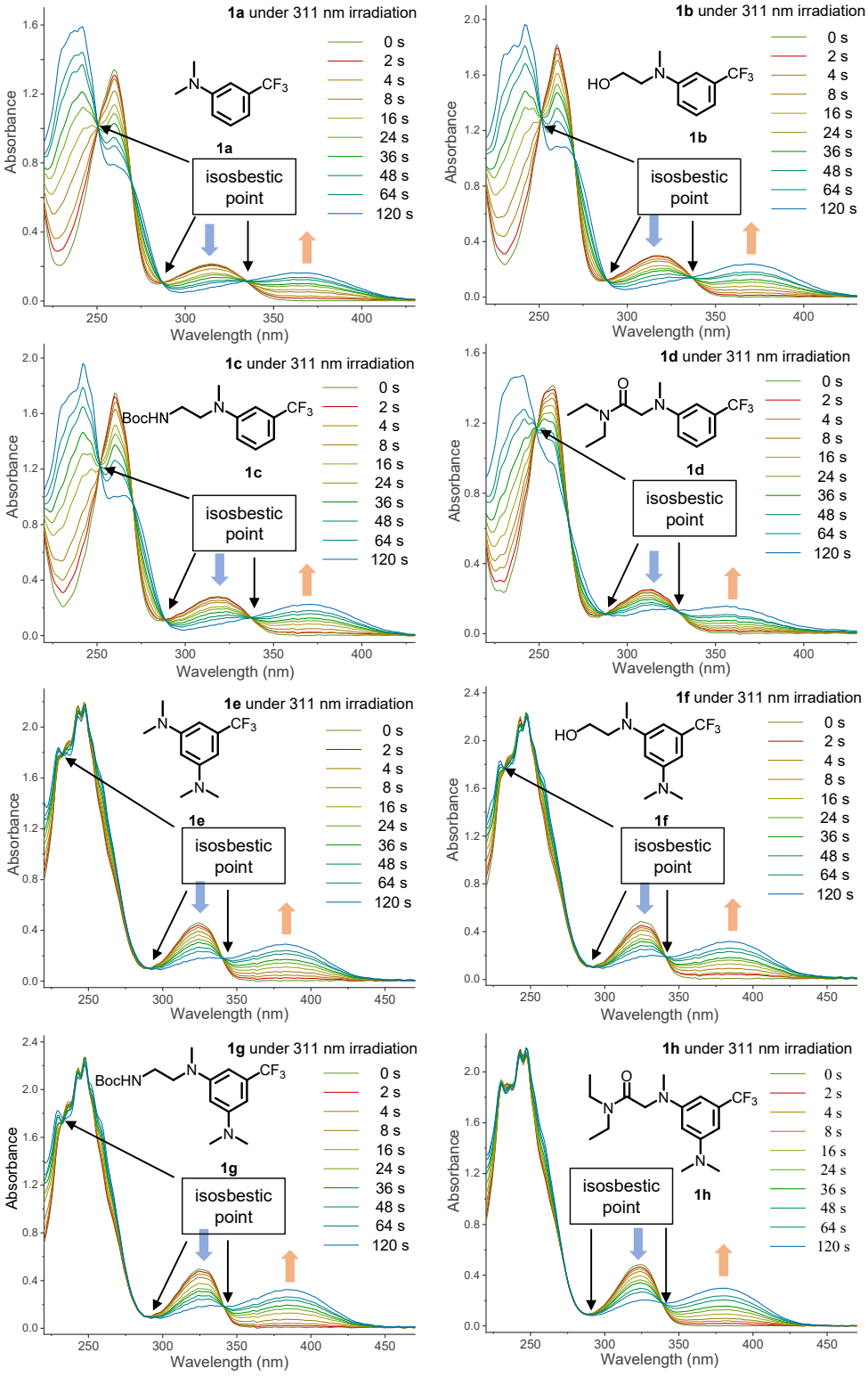


Figure S7. The absorption spectra evolution for tracking the photo-defluorination process from **1a-1e** to corresponding acyl fluorides. In detail, **1a-1e** (100 μM) in ACN/H_2O (v/v = 1/1) were irradiated with a 311 nm lamp (2.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz cuvette (0.2 cm × 1.0 cm optical path) for a specified time, and the spectra were readout by UV-Vis spectrophotometer. l = 1.0 cm for absorbance detection and l = 0.2 cm for irradiation at 311 nm.

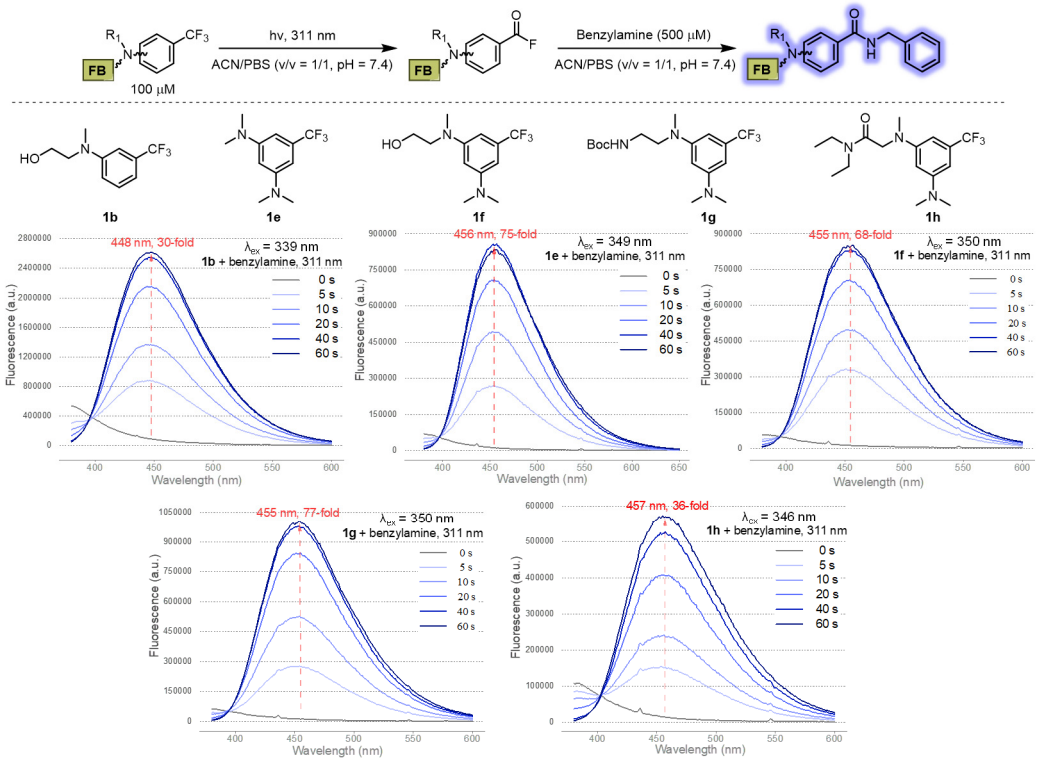


Figure S8. Time-resolved evolution in fluorescence emission intensity for the photo-DAFEx reaction with benzylamine upon irradtion with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter).

Table S3. The photophysical data of the fluorescence emission for the photo-DAFEx products, **3aa-3ca**

Products	**3aa**				**3ba**	**3ca**
$\lambda_{ex.}$	338 nm				339 nm	345 nm
Solvent	ACN/PBS*	MeOH	DMSO	DCM	ACN/PBS*	ACN/PBS*
Ɛ		32.7	46.7	8.96		
Φ_F	0.25	0.22	0.75	0.59	0.22	0.45

Note: * represent a mixed solvent of ACN/PBS (v/v = 1/1, pH = 7.4). Ɛ is the dielectric constant of the solvent medium.

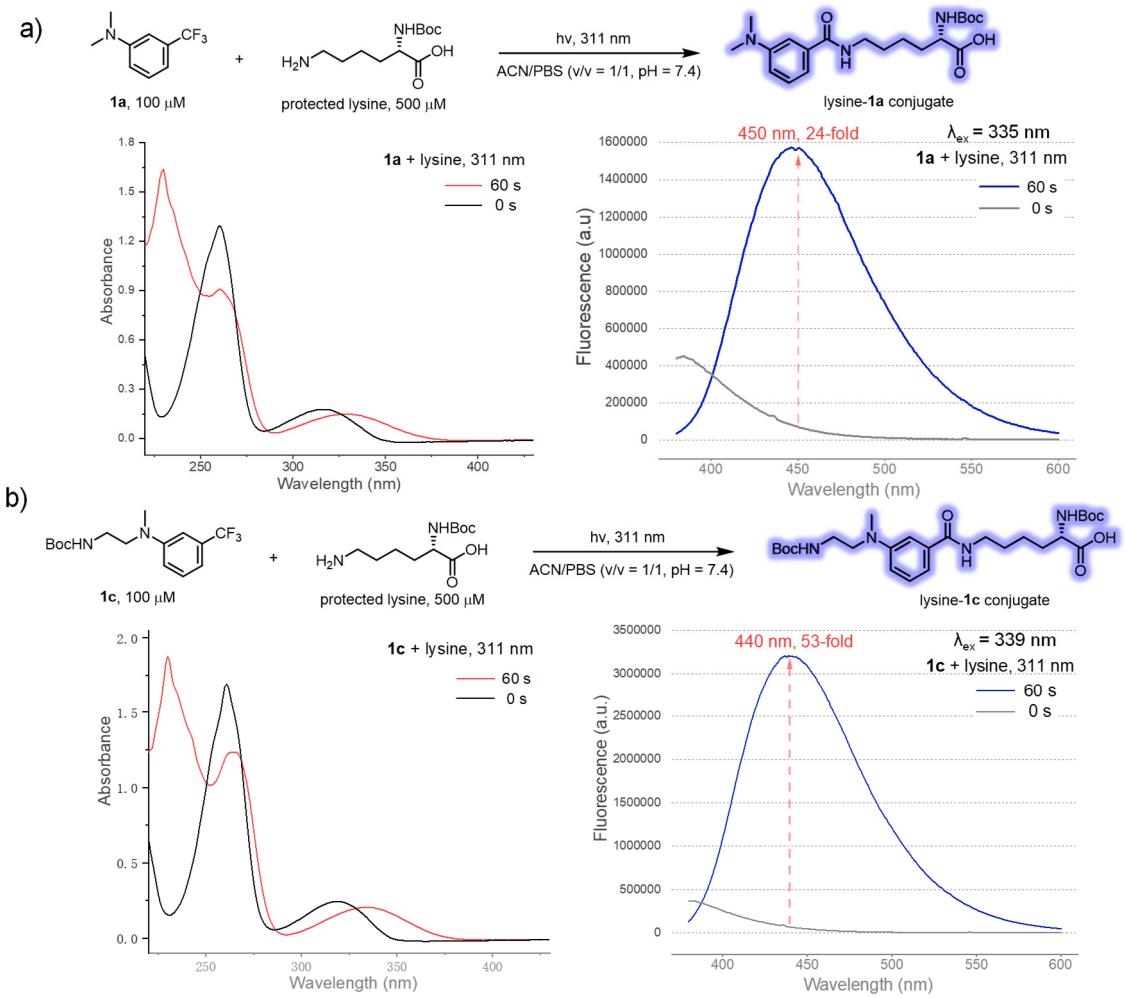


Figure S9. Spectral characters in both the absorbance and the fluorescence emission intensity before and after the photo-DAFEx. a) **1a** (100 μM) and b) **1c** (100 μM) in presence of *N*-Boc protected lysine (500 μM) upon the 311 nm lamp irradiation (5.9 mW cm^{-2}, single wavelength output after an optical filter) irradiation for 60 s.

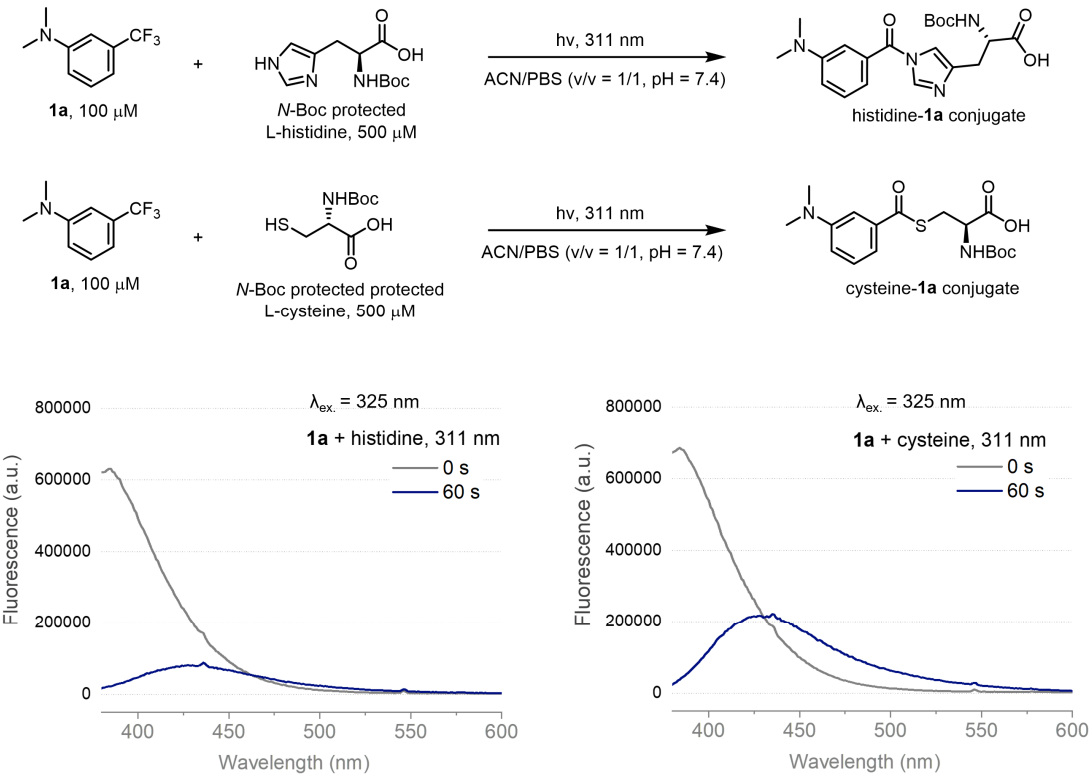
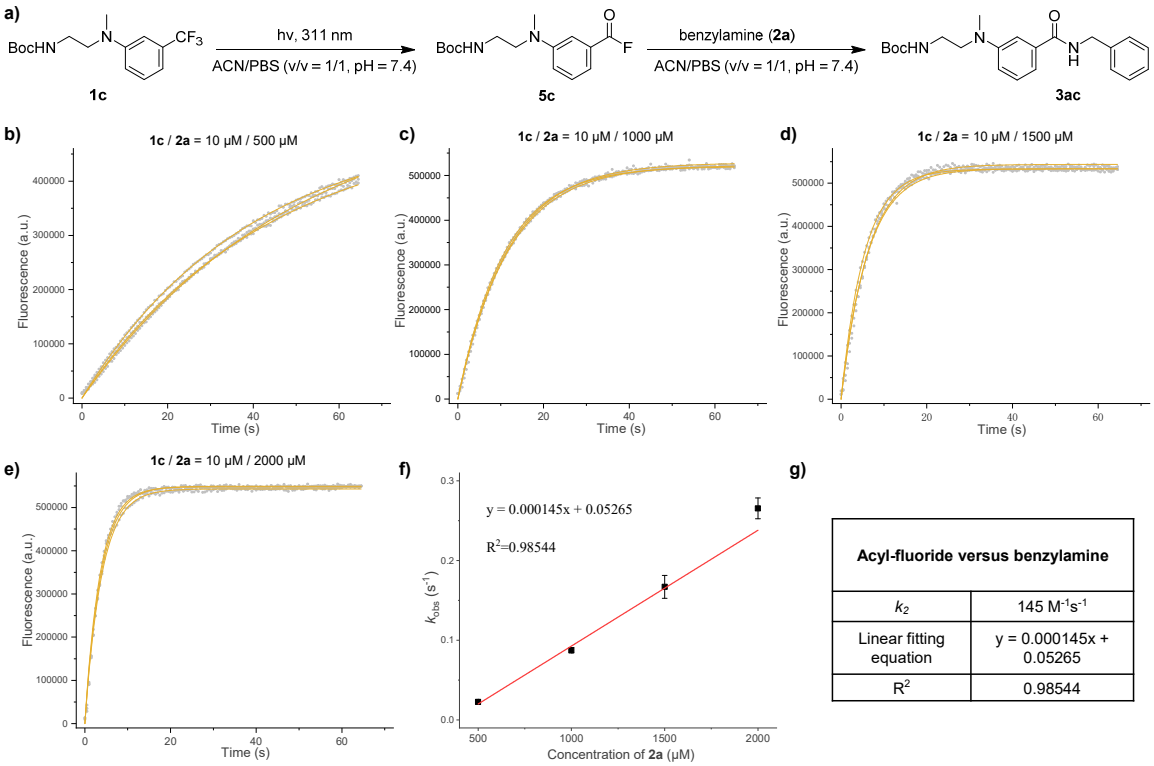


Figure S10. Spectral characters in the fluorescence emission intensity for **1a** (100 μM) in presence of *N*-Boc protected histidine/cysteine (500 μM) before and after photo-DAFEx with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) for 60 s.

Note S3. Kinetic studies on the photo-DAFEx reaction between the benzoyl fluoride intermediate generated from *m*-trifluoromethylaniline derivative **1c** and benzylamine **2a**.

The second-order rate constants k_2 for the reaction between acyl fluoride intermediate from **1c** (10 μM) versus 500 μM, 1000 μM, 1500 μM, and 2000 μM (50-fold to 200-fold excess) of **2a** in ACN/PBS (v/v = 1/1, pH = 7.4) were measured under the *pseudo*-first-order conditions, and the amidation process were monitored by real-time tracking of the fluorescence intensity evolution at 445 nm.[5] Signals were read out by monitoring the fluorescence signal appearance of the desired benzamide product. Kinetic runs were recorded by using the following instrumental parameters: monitoring wavelength, $\lambda_{ex.}$ = 345 nm; $\lambda_{em.}$ = 455 nm; 2 data points per second over the recorded time range (0-65 s). The data sets were averaged out of at least three replicates, which were recorded and analysed with the commercial software, GraphPad Prism 7.



Acyl-fluoride versus benzylamine	
k_2	145 $M^{-1}s^{-1}$
Linear fitting equation	y = 0.000145x + 0.05265
R^2	0.98544

Figure S11. Kinetic study on the photo-DAFEx reaction. a) The schematic diagram of the reaction between the acyl fluoride intermediate from trifluoromethylaniline derivative **1c** versus **2a**. b-e) Plots for the fluorogenic conjugation between acyl fluoride **5c** and **2a** in a time-dependent manner. f) Plot of the apparent rate constant (k_{obs}) versus the concentration of **2a** with the data fitted into a linear equation. g) Derived second-order rate constants k_2 for the photo-DAFEx reaction between **5c** and **2a** at 298 K. Values were determined from three independent measurements. Error bars denote standard deviation from three experimental replicates (n = 3).

Note S4. Sequence coverage based on the spliced peptide fragments from the LC-MS/MS analysis, for identification of the photo-labeling sites on proteins (The green highlight is the covered peptide sequence, and the potential labeling sites are marked in red colour).

Lysozyme: 78%

MRSLLILVLC FLPLAALGKV FGRCELAAAM KRHGLDNYRG YSLGNWVCAA KFESNFNTQA TNRNTDGSTD YGILQINSRW WCNDGRTPGS RNLCNIPCSA LLSSDITASV NCAKKIVSDG NGMNAWVAWR NRCKGTDVQA WIRGCRL

sfGFP: 73%

MSKGEELFTG VVPILVELDG DVNGHKFSVR GEGEGDATNG KLTLKFICTT GKLPVPWPTL VTTLTYGVQC FSRYPDHMKR HDFFKSAMPE GYVQERTISF KDDGNYKTRA EVKFEGDTLV NRIELKGIDF KEDGNILGHK LEYNYNSHNV YITADKQKNG IKVNFKIRHN IEDGSVQLAD HYQQNTPIGD GPVLLPDNHY LSTQSALSKD PNEKRDHMVL LEFVTAAGIT HGMDELYKE HHHHHH

BSA: 80%

MKWVTFISLL LLFSSAYSRG VFRRDTHKSE IAHRFKDLGE EHFKGLVLIA FSQYLQQCPF DEHVKLVNEL TEFAKTCVAD ESHAGCEKSL HTLFGDELCK VASLRETYGD MADCCEKQEP ERNECFLSHK DDSPDLPKLK PDPNTLCDEF KADEKKFWGK YLYEIARRHP YFYAPELLYY ANKYNGVFQE CCQAEDKGAC LLPKIETMRE KVLASSARQR LRCASIQKFG ERALKAWSVA RLSQKFPKAE FVEVTKLVTD LTKVHKECCH GDLLECADDR ADLAKYICDN QDTISSKLKE CCDKPLLEKS HCIAEVEKDA IPENLPPLTA DFAEDKDVCK NYQEAKDAFL GSFLYEYSRR HPEYAVSVLL RLAKEYEATL EECCAKDDPH ACYSTVFDKL KHLVDEPQNL IKQNCDQFEK LGEYGFQNAL IVRYTRKVPQ VSTPTLVEVS RSLGKVGTRC CTKPESERMP CTEDYLSLIL NRLCVLHEKT PVSEKVTKCC TESLVNRRPC FSALTPDETY VPKAFDEKLF TFHADICTLP DTEKQIKKQT ALVELLKHKP KATEEQLKTV MENFVAFVDK CCAADDKEAC FAVEGPKLVV STQTALA

#1	b^+	b^{2+}	b^{3+}	Seq.	y^+	y^{2+}	y^{3+}	#2
1	161.03793	81.02260	54.35083	C-Carbamidomethyl				11
2	436.20130	218.60429	146.07195	K-C9H9NO	1320.70590	660.85659	440.90682	10
3	493.22277	247.11502	165.07911	G	1045.54252	523.27490	349.18569	9
4	594.27044	297.63886	198.76167	T	988.52106	494.76417	330.17854	8
5	709.29739	355.15233	237.10398	D	887.47338	444.24033	296.49598	7
6	808.36580	404.68654	270.12678	V	772.44643	386.72686	258.15366	6
7	936.42438	468.71583	312.81298	Q	673.37802	337.19265	225.13086	5
8	1007.46149	504.23438	336.49202	A	545.31944	273.16336	182.44467	4
9	1193.54081	597.27404	398.51845	W	474.28233	237.64480	158.76563	3
10	1306.62487	653.81607	436.21314	I	288.20302	144.60515	96.73919	2
11				R	175.11895	88.06311	59.04450	1

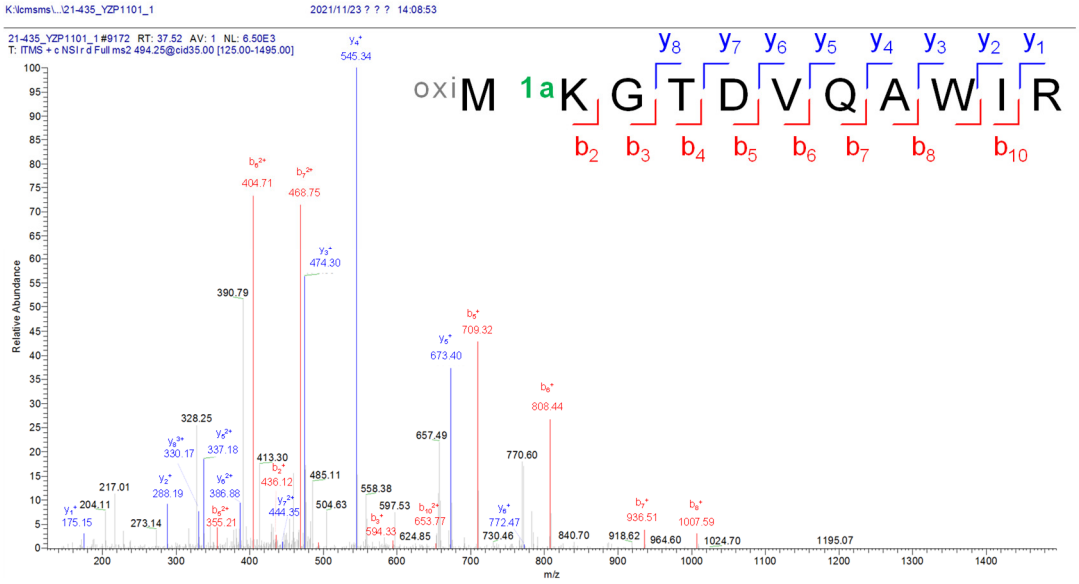


Figure S12. The LC-MS/MS spectrum and the ion peak analysis (b and y ions) for the key peptide fragment from lysozyme. Identification of the photo-labelled moiety at **K134** residue in the peptide fragment with the sequence displayed.

#1	b^+	b^{2+}	Seq.	y^+	y^{2+}	#2
1	116.03422	58.52075	D			8
2	231.06116	116.03422	D	1000.48467	500.74597	7
3	288.08263	144.54495	G	885.45773	443.23250	6
4	402.12555	201.56642	N	828.43626	414.72177	5
5	565.18888	283.09808	Y	714.39334	357.70031	4
6	840.35226	420.67977	K-C9H9NO	551.33001	276.16864	3
7	941.39994	471.20361	T	276.16663	138.58695	2
8			R	175.11895	88.06311	1

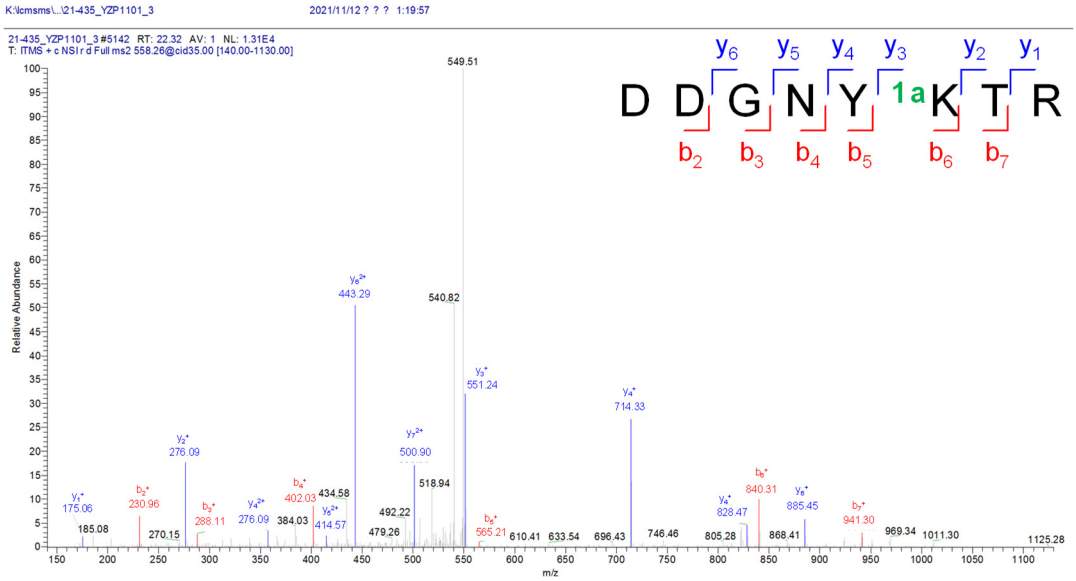


Figure S13. The LC-MS/MS spectrum and the ion peak analysis (b and y ions) for the key peptide fragment from sfGFP. Identification of the photo-labelled moiety at **K107** residue in the peptide fragment with the sequence displayed.

#1	b^+	b^{2+}	Seq.	y^+	y^{2+}	#2
1	72.04439	36.52583	A	1077.62038	539.31383	9
2	185.12845	93.06787	L	964.53631	482.77179	8
3	460.29183	230.64955	K-C9H9NO	964.53631	345.19011	7
4	531.32895	266.16811	A	689.37293	345.19011	6
5	717.40826	359.20777	W	618.33582	309.67155	5
6	804.44029	402.72378	S	432.25651	216.63189	4
7	903.50870	452.25799	V	345.22448	171.11588	3
8	974.54581	487.77655	A	246.15607	123.58167	2
9			R	175.11895	88.06311	1

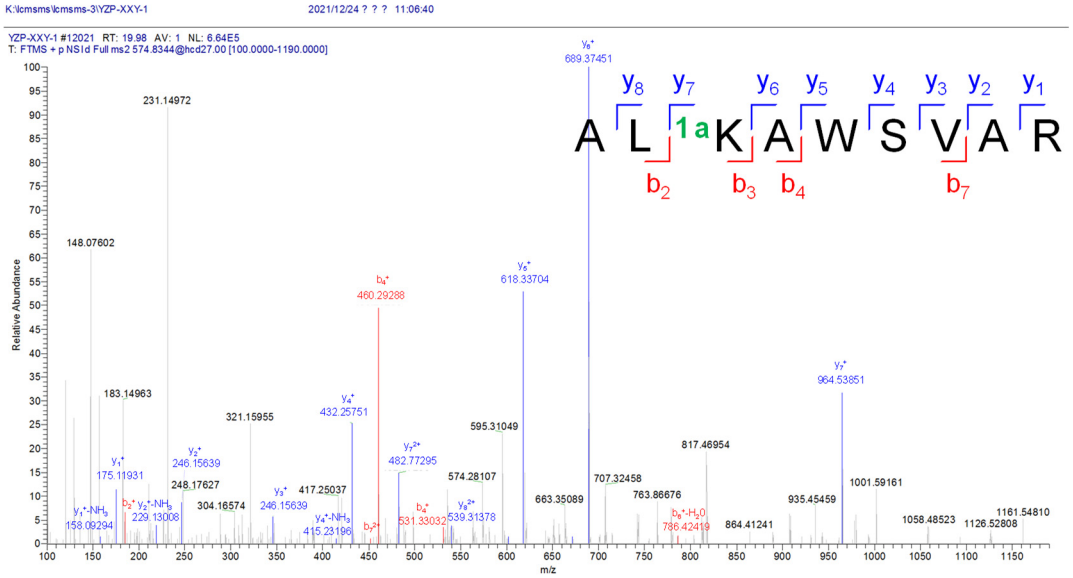


Figure S14. The LC-MS/MS spectrum and the ion peak analysis (b and y ions) for the key peptide fragment from BSA. Identification of the photo-labelled moiety at **K235** residue in the peptide fragment with the sequence displayed.

#1	b^{+}	b^{2+}	Seq.	y^{+}	y^{2+}	#2
1	114.09134	57.54931	L			7
2	201.12337	101.06532	S	881.48796	441.24762	6
3	329.18195	165.09461	Q	794.45994	397.73161	5
4	604.34532	302.67630	K-C9H9NO	666.39736	333.70232	4
5	751.41374	376.21051	F	391.23398	196.12063	3
6	848.46650	424.73689	P	244.16557	122.58642	2
7			K	147.11280	74.06004	1

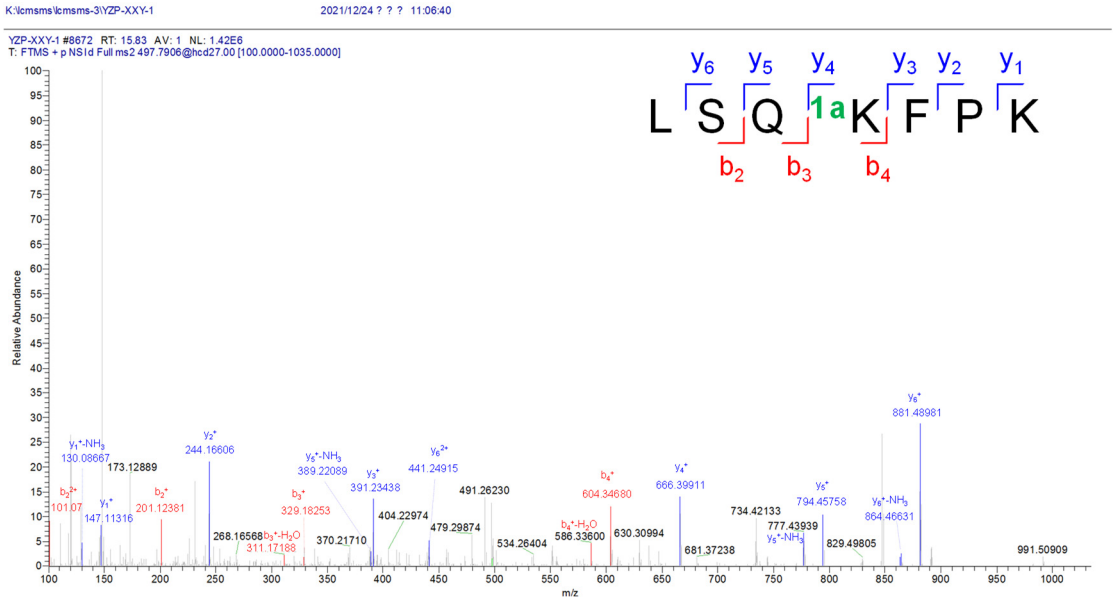


Figure S15. The LC-MS/MS spectrum and the ion peak analysis (b and y ions) for the key peptide fragment from BSA. Identification of the photo-labelled moiety at **K245** residue in the peptide fragment with the sequence displayed

#1	b^+	b^{2+}	Seq.	y^+	y^{2+}	#2
1	276.17065	138.58897	K-C9H9NO			10
2	404.22923	202.61825	Q	1014.61937	507.81332	9
3	505.27691	253.14209	T	886.56080	443.78404	8
4	576.31402	288.66065	A	785.51312	393.26020	7
5	689.39809	345.20268	L	714.47600	357.74164	6
6	788.46650	394.73689	V	601.39194	301.19961	5
7	917.50909	459.25819	E	502.32353	251.66540	4
8	1030.59316	515.80022	L	373.28093	187.14410	3
9	1143.67722	572.34225	L	260.19687	130.60207	2
10			K	147.11280	74.06004	1

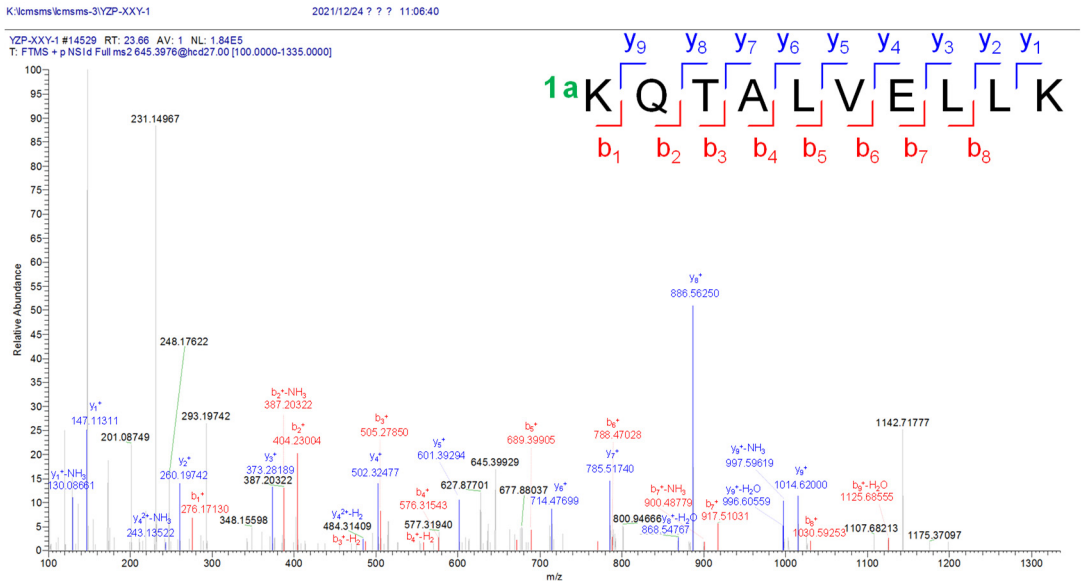
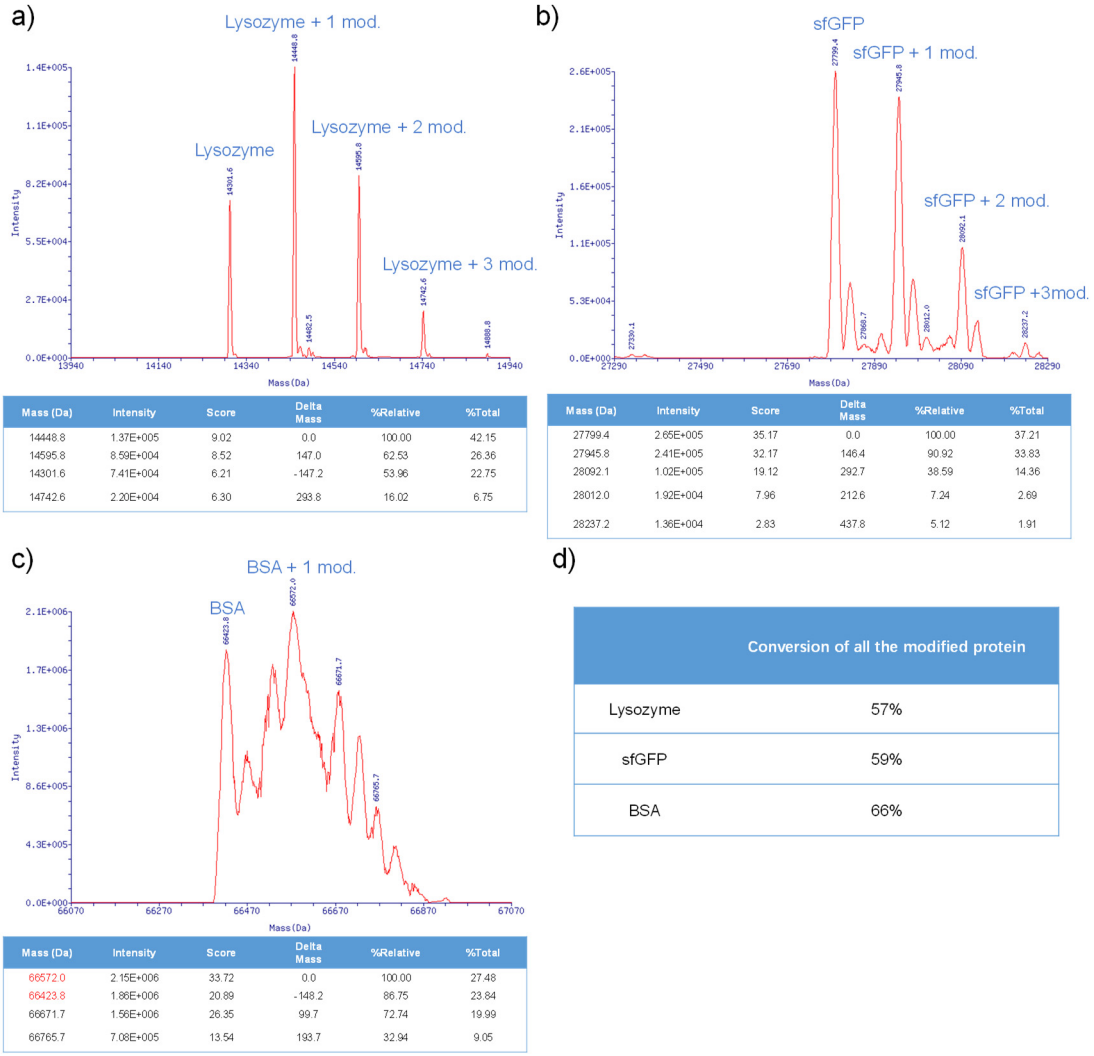


Figure S16. The LC-MS/MS spectrum and the ion peak analysis (b and y ions) for the key peptide fragment from BSA. Identification of the photo-labelled moiety at **K548** residue in the peptide fragment with the sequence displayed.



Mass (Da)	Intensity	Score	Delta Mass	%Relative	%Total
14448.8	1.37E+005	9.02	0.0	100.00	42.15
14595.8	8.59E+004	8.52	147.0	62.53	26.36
14301.6	7.41E+004	6.21	-147.2	53.96	22.75
14742.6	2.20E+004	6.30	293.8	16.02	6.75

Mass (Da)	Intensity	Score	Delta Mass	%Relative	%Total
27799.4	2.65E+005	35.17	0.0	100.00	37.21
27945.8	2.41E+005	32.17	146.4	90.92	33.83
28092.1	1.02E+005	19.12	292.7	38.59	14.36
28012.0	1.92E+004	7.96	212.6	7.24	2.69
28237.2	1.36E+004	2.83	437.8	5.12	1.91

Mass (Da)	Intensity	Score	Delta Mass	%Relative	%Total
66572.0	2.15E+006	33.72	0.0	100.00	27.48
66423.8	1.86E+006	20.89	-148.2	86.75	23.84
66671.7	1.56E+006	26.35	99.7	72.74	19.99
66765.7	7.08E+005	13.54	193.7	32.94	9.05

	Conversion of all the modified protein
Lysozyme	57%
sfGFP	59%
BSA	66%

Figure S17. The deconvolution mass spectra of the photo-labelled protein (20 μM) *via* the photo-DAFEx reaction with **1a** (50 μM). a) lysozyme; b) sfGFP; c) BSA. d) The result of the photo-labeling conversion was determined by the ratio of the modified proteins in the deconvolution mass spectrum.

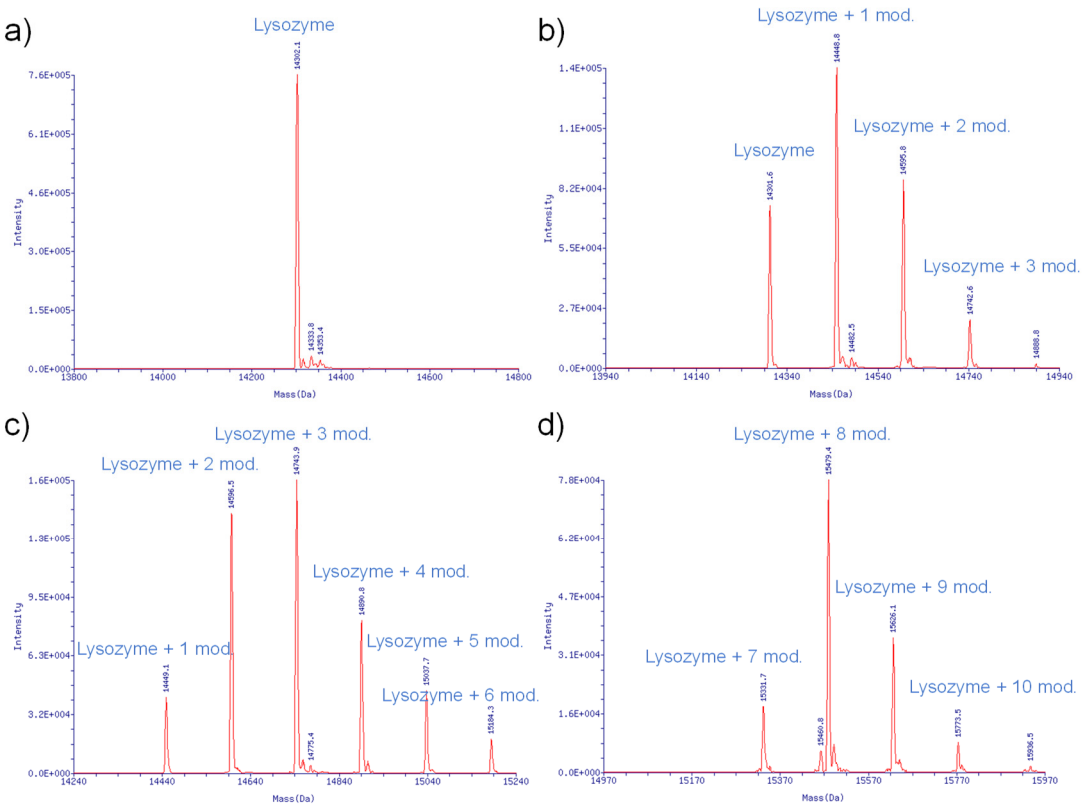


Figure S18. The deconvolution mass spectra for the multiple photo-labelled lysozyme (7.0 μM, 1.0 mg/mL) by the photo-DAFEx reactions with **1a** at various concentration: a) 0 μM, b) 20 μM, c) 50 μM, d) 100 μM.

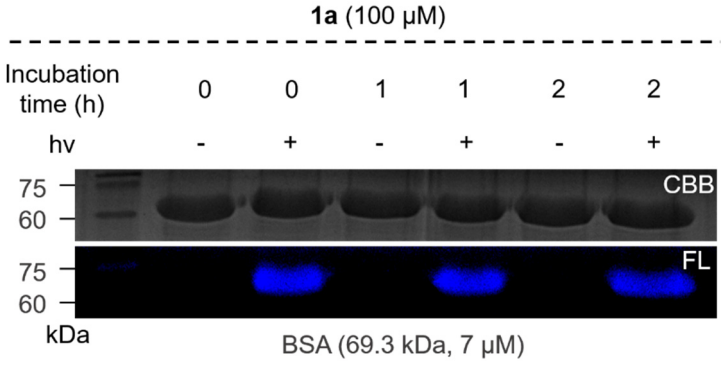


Figure S19. Fluorogenic protein decoration via photo-DAFEx visualized by in-gel fluorescence imaging and a time-course of incubation time. Reaction conditions: proteins (4.0 mg mL^{-1}) and *m*-trifluoro-methylaniline reagents in PBS were treated with/without 311 nm light (5.9 mW cm^{-2}) for 60 s, then resolved by SDS-PAGE for imaging. CBB = Coomassie brilliant blue; FL = in-gel blue fluorescence channel.

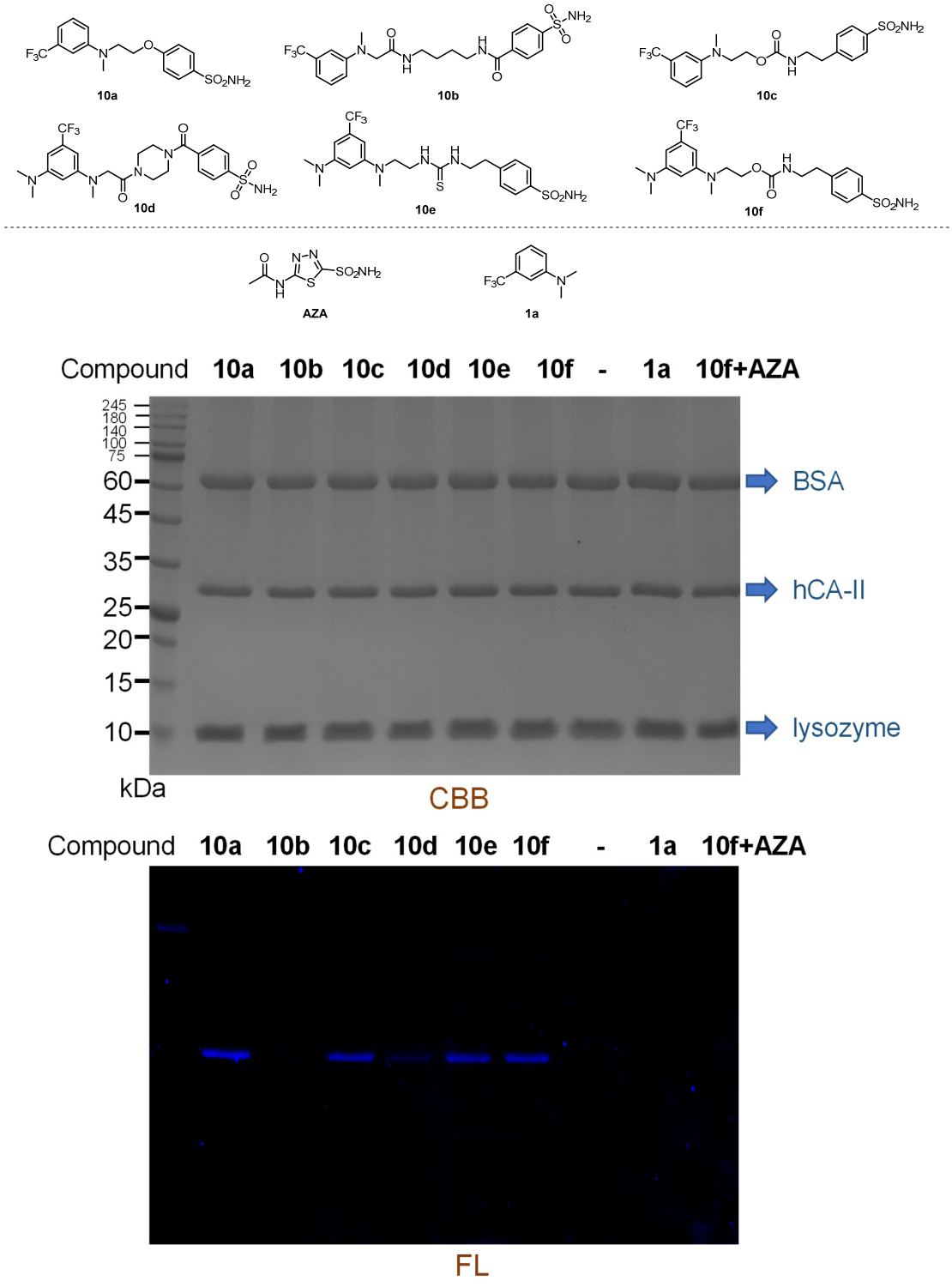


Figure S20. SDS-PAGE analysis of the protein mixture (including lysozyme (4.0 mg/mL, 28 μM), hCA-II (4.0 mg/mL, 15 μM) and BSA (4.0 mg/mL, 7 μM)) after the photo-labelling with **10a-10f** (20 μM) *via* the photo-DAFEx chemistry in PBS (pH = 7.4). CBB: Coomassie brilliant blue staining; FL: in-gel blue fluorescence channel.

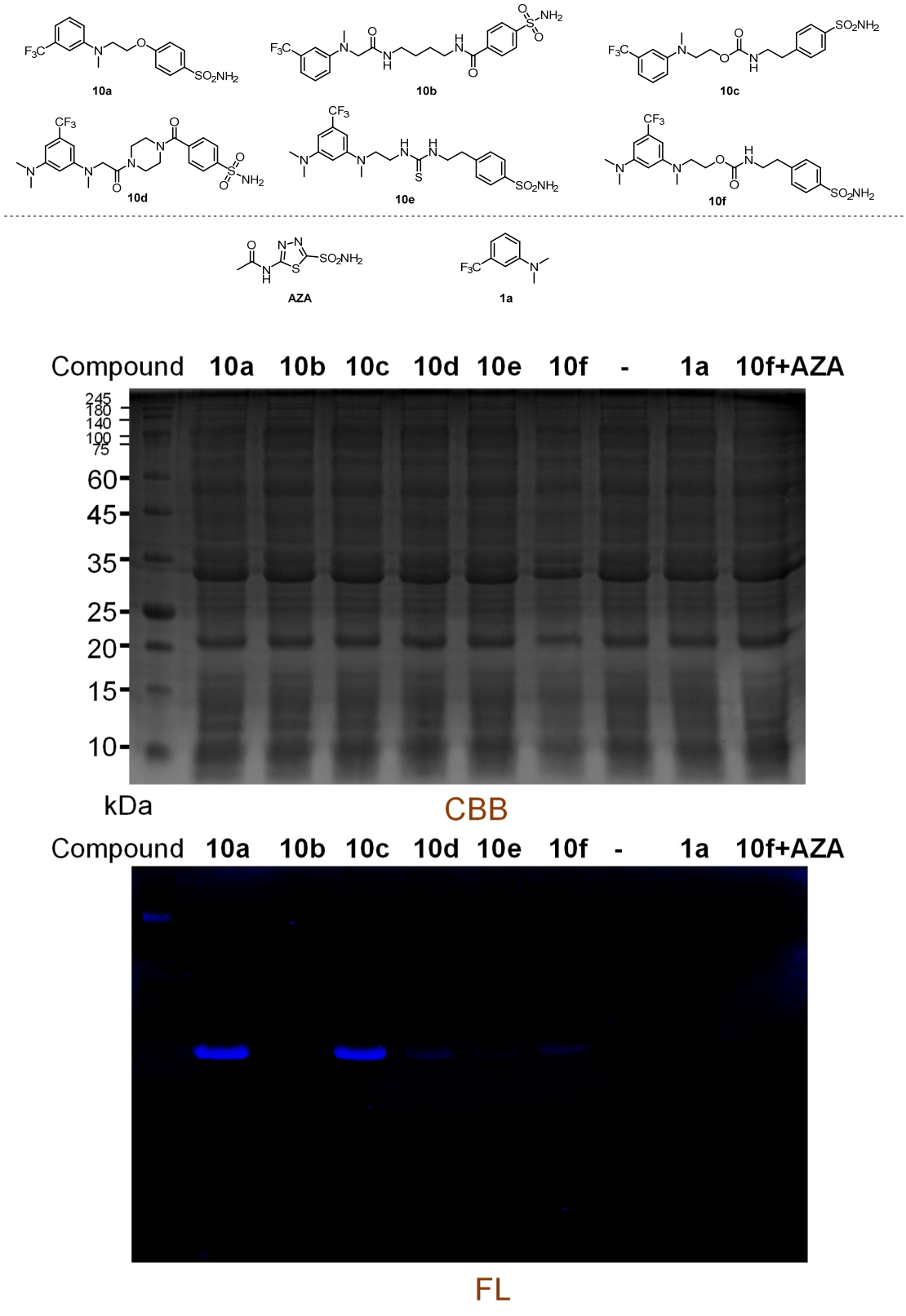


Figure S21. SDS-PAGE analysis of the *E. Coli* cell lysates after the photo-labelling with **10a-10f** (20 μM) *via* the photo-DAFEx chemistry. CBB: Coomassie brilliant blue staining; FL: in-gel blue fluorescence channel.

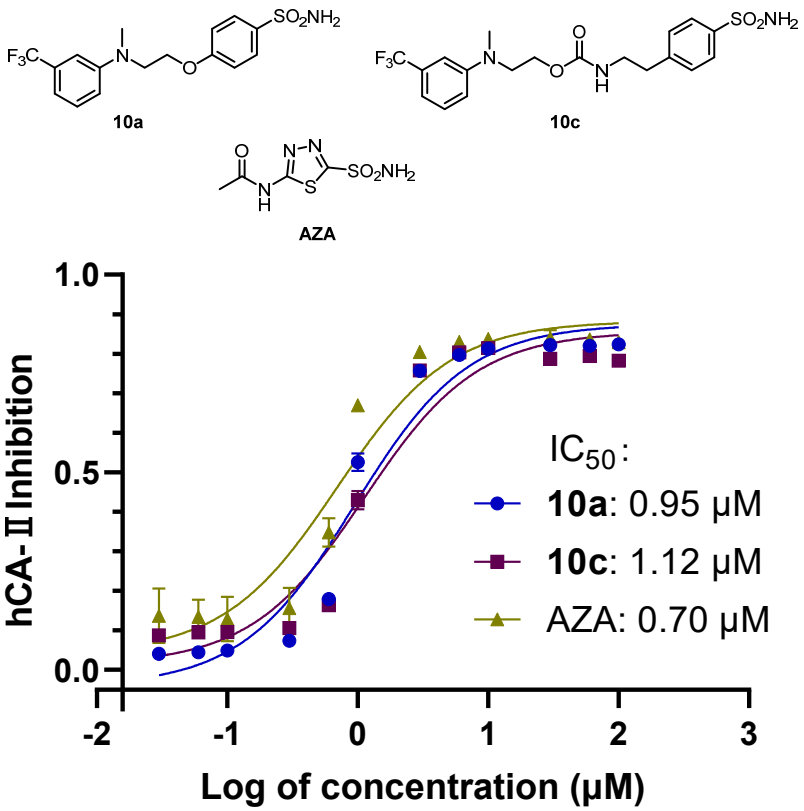


Figure S22. Plot of the enzymatic inhibition of hCA-II to catalyse the hydrolysis of *p*-nitrophenyl acetate *vs*. inhibitor concentration, with the IC_{50} shown. Error bars indicate SD, $n = 3$.

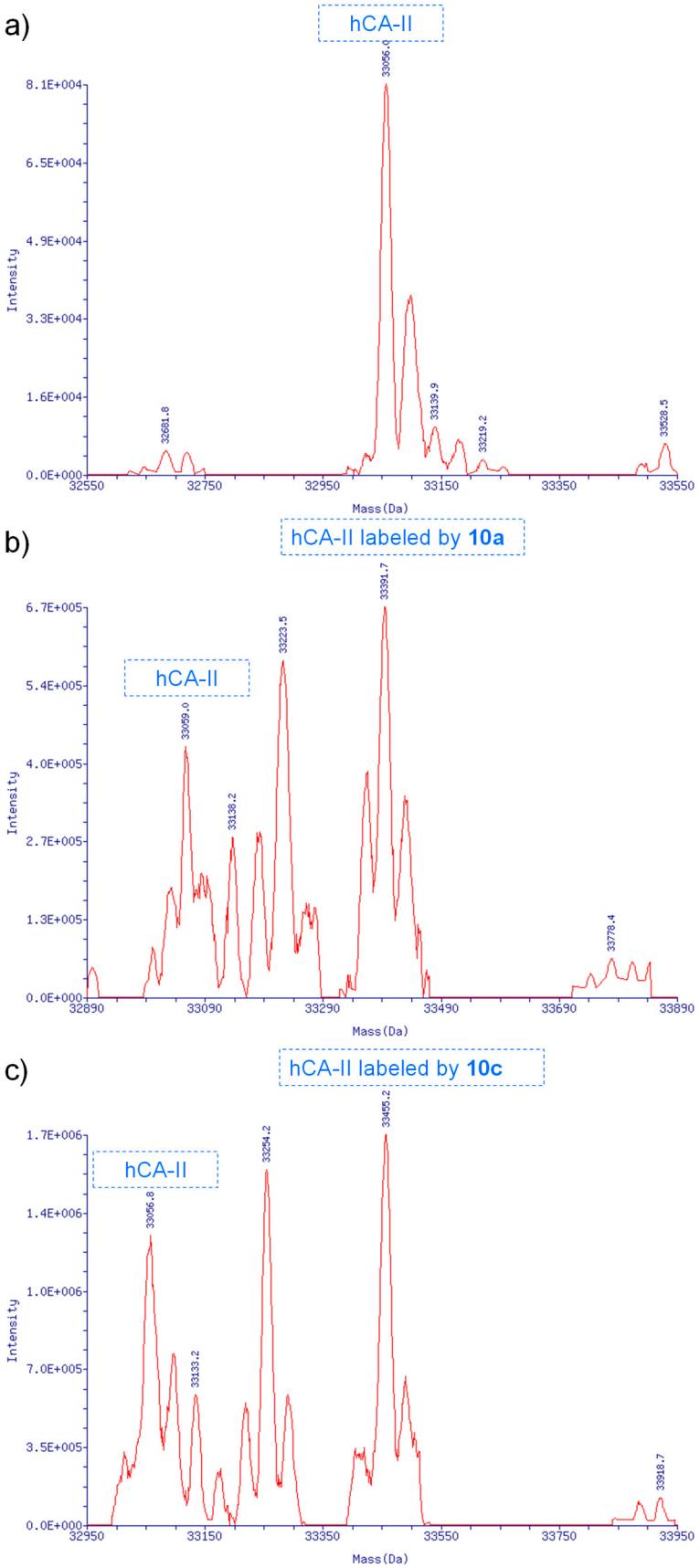


Figure S23. The deconvolution MS spectra for the affinity-based labelling of hCA-II (30 μM) in PBS (pH = 7.4) by the photo-DAFEx reagent: a) blank, b) **10a** (50 μM), c) **10c** (50 μM).

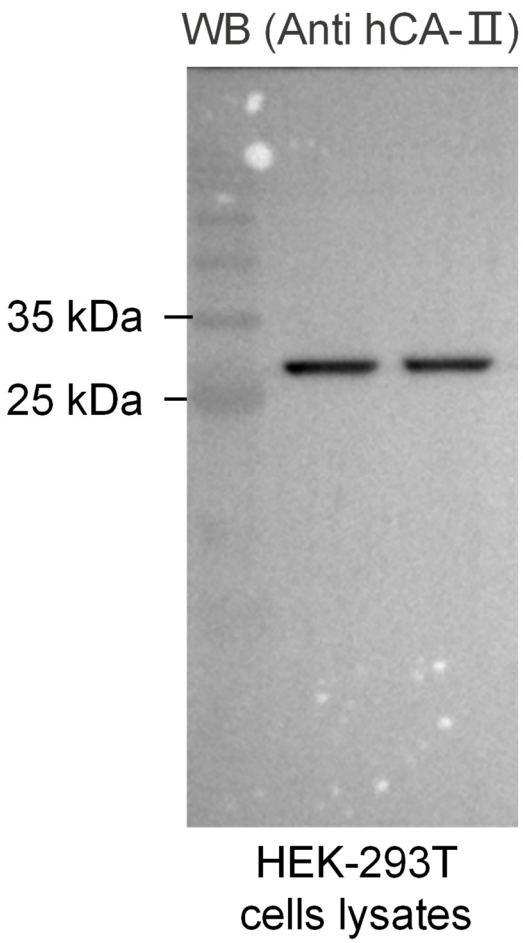


Figure S24. Western blot (WB) analysis targeting endogenous hCA-II in living HEK-293T cells lysates, $n = 2$.

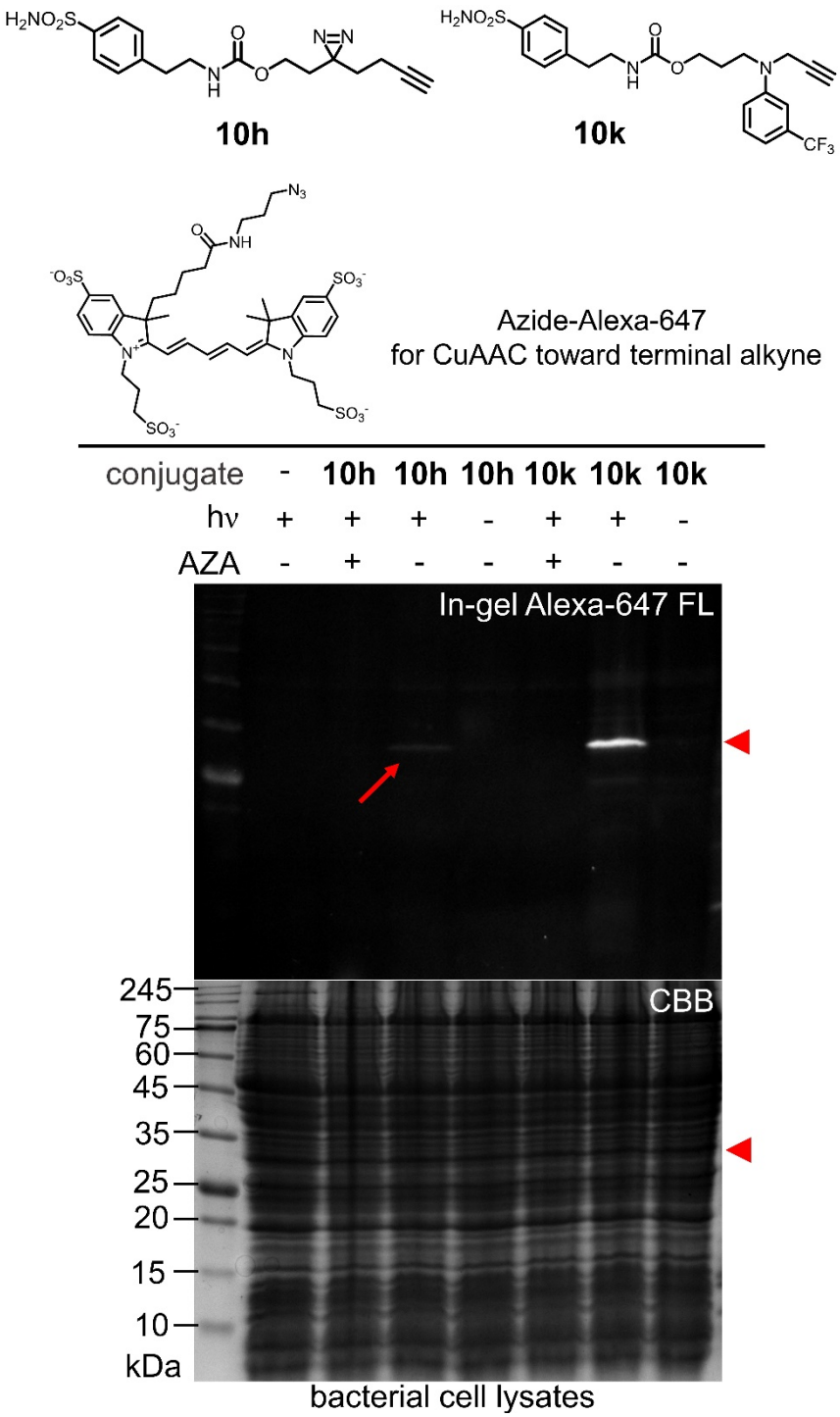


Figure S25. Fluorescent photo-labeling of the recombinant hCA-II in *E. coli* lysate via the photo-DAFEx by probe **10h** *vs*. **10k** (10 μM) in the presence/absence of the competitive inhibitor AZA (1.0 mM). In-gel fluorescence imaging was achieved via CuAAC toward the terminal alkyne attached on the hCA-II after PAL with an azide-Alexa-647 conjugate. **10h** in lysate mixture was irradiated with the 365 nm lamp (68 mW cm^{-2}) for 180 s; **10k** in lysate mixture was irradiated with the 311 nm lamp (10.8 mW cm^{-2}) for 30 s; the groups without irradiation as the negative control were also shown. The red triangles are showing the position for the hCA-II in the resolved SDS-PAGE, and the red arrow represents the fluorescence band for the hCA-II after PAL with the alkyl diazirine probe, **10h**.

Note S5. Sequence coverage based on the spliced peptide fragments from the LC-MS/MS analysis, for identification of the PAL sites on proteins by reagent **10a** (The green highlight is the covered peptide sequence, and the potential labeling sites are marked in red colour).

hCA-II: 88%

MSHHWGYGKH NGPEHWHKDF PIAKGERQSP VDIDTHTAKY DPSLKPLSVS YDQATSLRIL NNGHAFNVEF DDSQDKAVLK GGPLDGTYRL IQFHFHWGSL DGQGSEHTVD KKKYAAELHL VHWNTKYGDF GKAVQQPDGL AVLGIFLKVG SAKPGLQKVV DVLDSIKTKG KSADFTNFDP RGLLPESLDY WTYPGSLTTP PLLECVTWIV LKEPISVSSE QVLKFRKLNF NGEGEPEELM VDNWRPAQPL KNRQIKASFK LEHHHHHH

Table S4. The ion peak analysis based on the LC-MS/MS spectrum for identification of the PAL sites from the digested hCA-II peptide fragment 1.

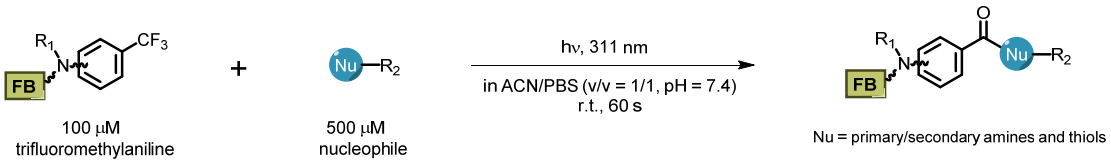
#1	b^+	b^{2+}	Seq.	y^+	y^{2+}	#2
1	138.06619	69.53673	H			15
2	252.10912	126.55820	N	2007.91703	1004.46215	14
3	309.13058	155.06893	G	1893.87410	947.44069	13
4	406.18334	203.59531	P	1836.85264	918.92996	12
5	535.22594	268.11661	E	1739.79987	870.40357	11
6	672.28485	336.64606	H	1610.75728	805.88228	10
7	858.36416	429.68572	W	1473.69837	737.35282	9
8	995.42307	498.21517	H	1287.61906	644.31317	8
9	1455.60111	728.30420	**K-10a**	1150.56014	575.78371	7
10	1570.62806	785.81767	D	690.28210	345.69469	6
11	1717.69647	859.35187	F	575.35516	288.18122	5
12	1814.74923	907.87826	P	428.28675	214.64701	4
13	1927.83330	964.42029	I	331.23398	166.12063	3
14	1998.87041	999.93884	A	218.14992	109.57860	2
15			K	147.11280	74.06004	1

Table S5. The ion peak analysis based on the LC-MS/MS spectrum for identification of the PAL sites from the digested hCA-II peptide fragment 2.

#1	b^+	b^{2+}	Seq.	y^+	y^{2+}	#2
1	100.07569	50.54148	V			11
2	199.14410	100.07569	V	1449.72939	725.36834	10
3	314.17105	157.58916	D	1350.66098	675.83413	9
4	413.23946	207.12337	V	1235.63404	618.32066	8
5	526.32353	263.66540	L	1136.56562	568.78645	7
6	641.35047	321.17887	D	1023.48156	512.24442	6
7	728.38250	364.69489	S	908.45462	454.73095	5
8	841.46656	421.23692	I	821.42259	411.21493	4
9	1301.64460	651.32594	**K-10a**	708.33852	354.67290	3
10	1402.69228	701.84978	T	248.16048	124.58388	2
11			K	147.11280	74.06004	1

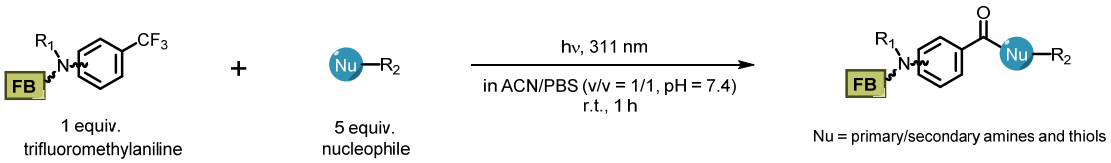
3. HPLC-MS analysis and Preparation & Characterizations for the organic compounds

General procedure I



Trifluoromethylaniline derivatives (100 μM) and the nucleophile (100 μM) were mixed in a total volume of 1.0 mL in ACN/PBS (v/v = 1/1, pH = 7.4) solvent, followed by irradiation with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. After further incubation, the samples were collected and analysed by HPLC-MS, and the yields were obtained by external standard calibration.

General procedure II



For isolation of the photo-DAFEx products, starting the photo-reaction by dissolving the trifluoromethylaniline derivative (1.0 equiv.) and the nucleophile (5.0 equiv.) in a total volume of 200 mL in ACN/PBS (v/v = 1/1, pH = 7.4) solvent, followed by irradiation with the 311 nm lamp (21.2 mW cm^{-2}) in a quartz flask for 1.0 h. The organic solvent was removed under reduced pressure, the aqueous was extracted with DCM for three times. The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude was purified by flash chromatography to give the desired products, **3aa-3qa**, **3ab-3as**, **4aa-4ai** and **5aa-5ae**.

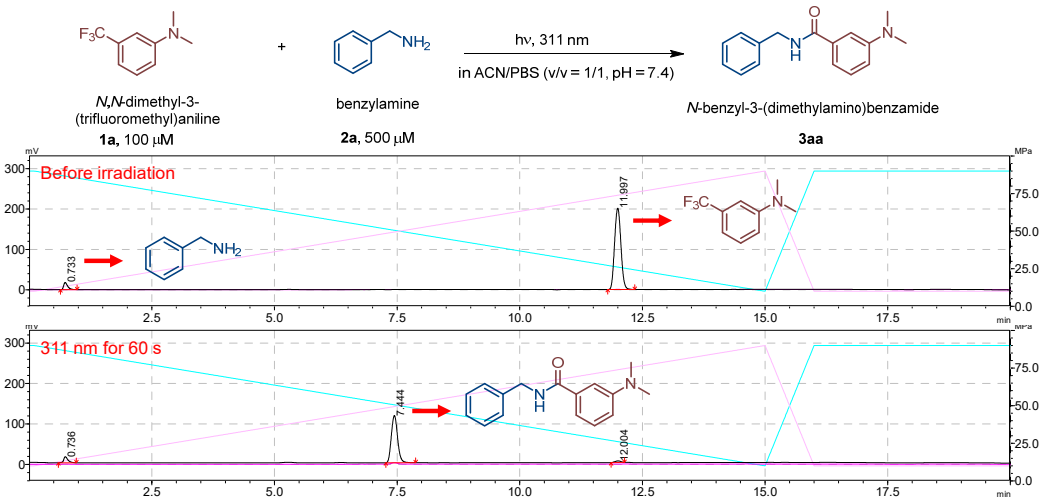


Figure S26. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(dimethylamino)benzamide **(3aa)**

Preparation: 1a (26.3 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and product **3aa** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (25.3 mg, 83%).

^{1}H NMR (400 MHz, CDCl$_3$) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.21 (m, 7H), 6.98 (ddd, J = 7.6, 1.6, 0.9 Hz, 1H), 6.83 (ddd, J = 8.3, 2.7, 0.8 Hz, 1H), 6.43 (s, 1H), 4.64 (d, J = 5.7 Hz, 2H), 2.98 (s, 6H).

^{13}C NMR (101 MHz, CDCl$_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.05, 151.72, 138.56, 136.23, 128.73, 127.88, 127.47, 100.59, 99.74, 77.24, 44.05, 40.84.

HRMS (ESI) calculated $C_{16}H_{19}N_2O^+$ $[M+H]^+$ m/z 255.1492, found 255.1495.

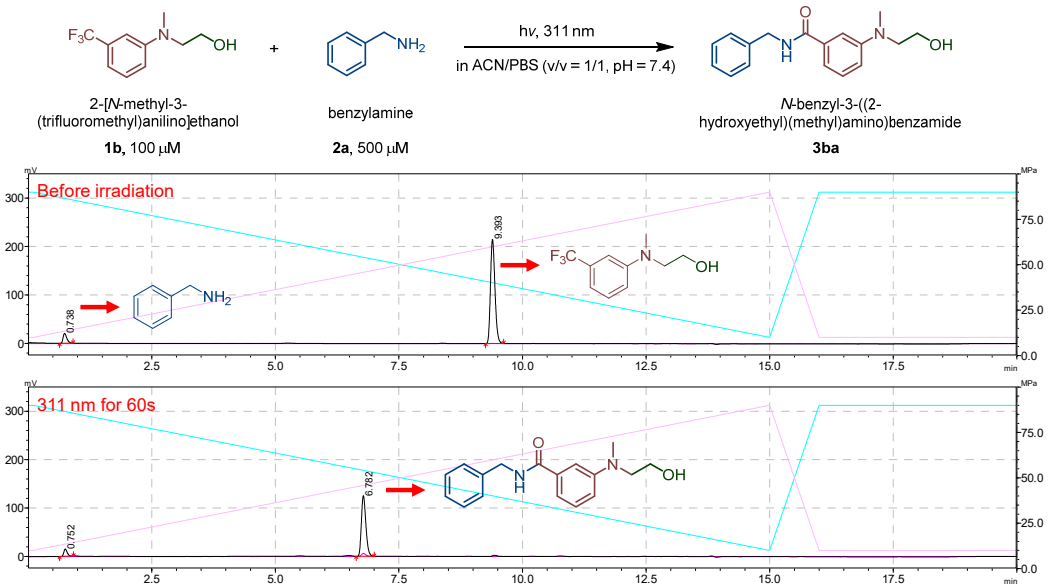


Figure S27. HPLC-MS analysis of the photo-DAFEx reaction between **1b** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-((2-hydroxyethyl)(methyl)amino)benzamide **(3ba).**

Preparation: 1b (26.3 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ba** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (29.6 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 5H), 7.20 (dd, J = 2.6, 1.6 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.05 (t, J = 5.8 Hz, 1H), 6.98 (dt, J = 7.8, 1.1 Hz, 1H), 6.78 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 4.51 (d, J = 5.8 Hz, 2H), 3.66 (t, J = 6.0 Hz, 2H), 3.39 (t, J = 6.0 Hz, 2H), 2.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.55, 149.90, 138.47, 135.11, 129.29, 128.67, 127.77, 127.41, 115.31, 114.31, 111.30, 59.60, 54.74, 43.96, 38.70.

HRMS (ESI) calculated $C_{17}H_{21}N_2O_2^+$ $[M+H]^+$ m/z 285.1598, found 285.1598.

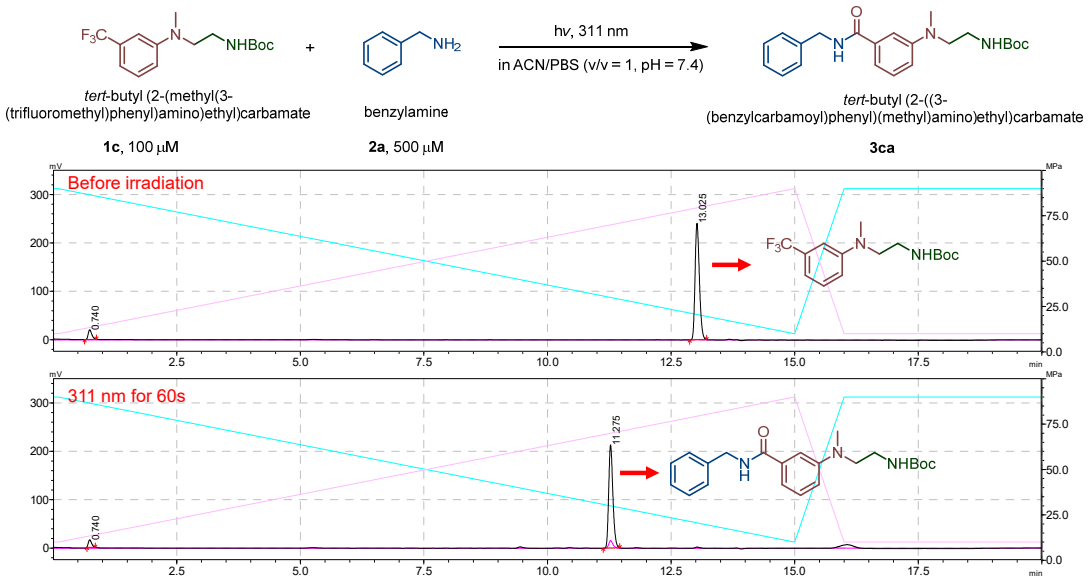


Figure S28. HPLC-MS analysis of the photo-DAFEx reaction between **1c** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

tert-butyl (2-((3-(benzylcarbamoyl)phenyl)(methyl)amino)ethyl)carbamate **(3ca).**

Preparation: 1c (38.2 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ca** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (36.5 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.38 – 7.29 (m, 4H), 7.28 – 7.21 (m, 2H), 7.15 (d, J = 7.6 Hz, 2H), 6.82 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 4.80 (d, J = 6.4 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 3.46 (dd, J = 8.2, 6.0 Hz, 2H), 3.27 (dt, J = 8.8, 6.2 Hz, 2H), 2.99 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.98, 156.25, 149.00, 138.79, 135.21, 129.42, 128.60, 127.70, 127.27, 114.99, 114.90, 110.76, 79.61, 52.07, 43.89, 38.80, 37.37, 28.35.

HRMS (ESI) calculated $C_{22}H_{30}N_3O_3^+$ $[M+H]^+$ m/z 384.2282, found 384.2276.

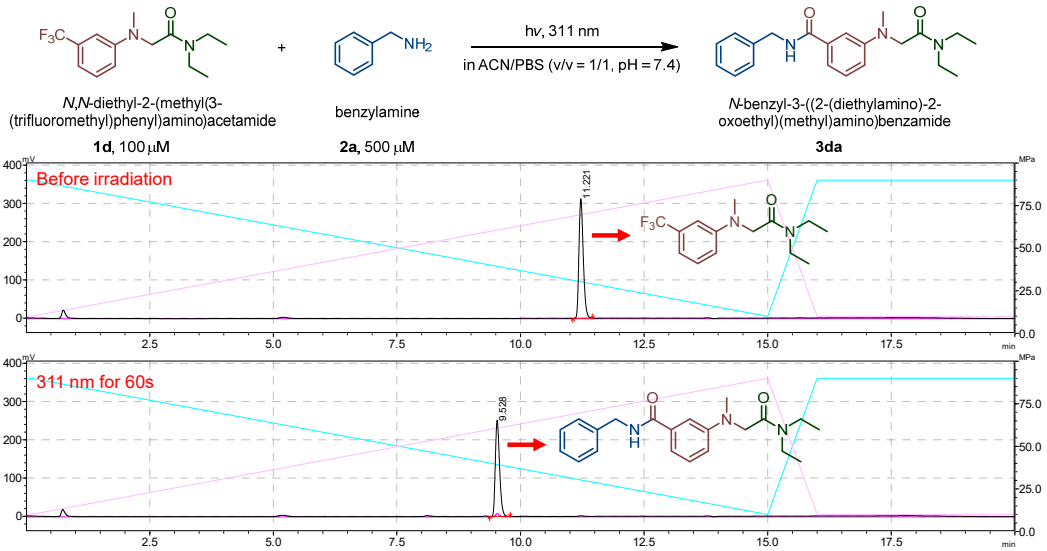


Figure S29. HPLC-MS analysis of the photo-DAFEx reaction between **1d** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-((2-(diethylamino)-2-oxoethyl)(methyl)amino)benzamide **(3da).**

Preparation: 1d (34.6 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3da** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a white solid (34.7 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 4.4 Hz, 4H), 7.29 – 7.24 (m, 1H), 7.22 – 7.16 (m, 2H), 6.98 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 6.75 (ddd, J = 8.3, 2.8, 0.9 Hz, 1H), 6.61 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 5.7 Hz, 2H), 4.11 (s, 2H), 3.33 (dq, J = 18.2, 7.1 Hz, 4H), 3.05 (s, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.20, 168.15, 149.79, 138.47, 135.32, 129.25, 128.70, 127.85, 127.45, 115.13, 114.50, 111.39, 53.93, 44.00, 41.20, 40.40, 39.70, 14.35, 13.05.

HRMS (ESI) calculated $C_{21}H_{28}N_3O_2^+$ $[M+H]^+$ m/z 354.2176, found 354.2170.

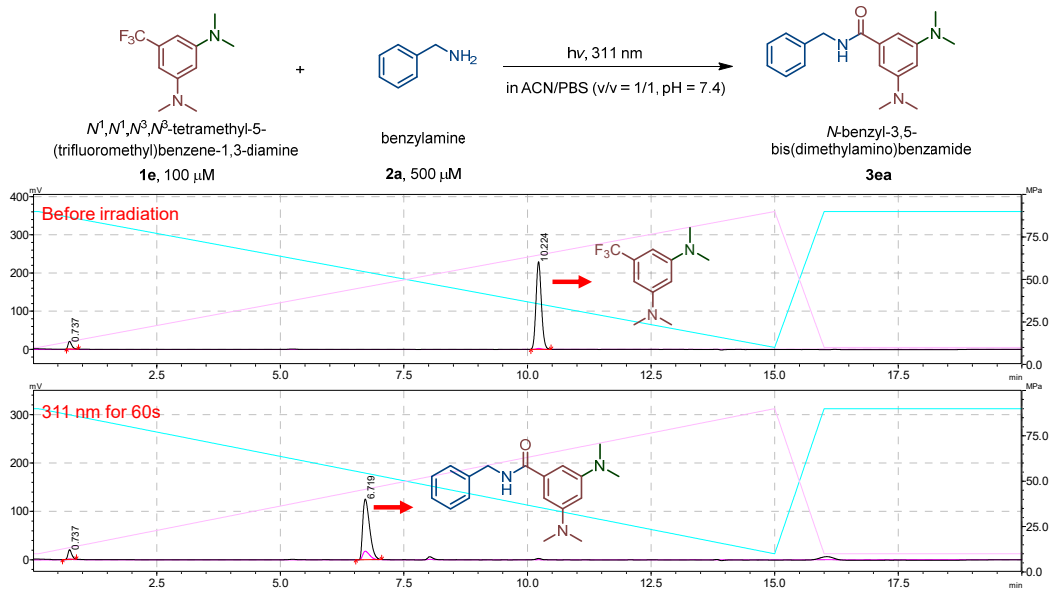


Figure S30. HPLC-MS analysis of the photo-DAFEx reaction between **1e** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3,5-bis(dimethylamino)benzamide **(3ea).**

Preparation: 1e (27.9 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ea** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (29.2 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 6.53 (d, J = 2.2 Hz, 2H), 6.39 (s, 1H), 6.16 (t, J = 2.3 Hz, 1H), 4.65 (d, J = 5.7 Hz, 2H), 2.97 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.06, 151.74, 138.57, 136.24, 128.74, 127.89, 127.48, 100.60, 99.74, 44.04, 40.84.

HRMS (ESI) calculated $C_{18}H_{24}N_3O^+$ $[M+H]^+$ m/z 298.1914, found 298.1911.

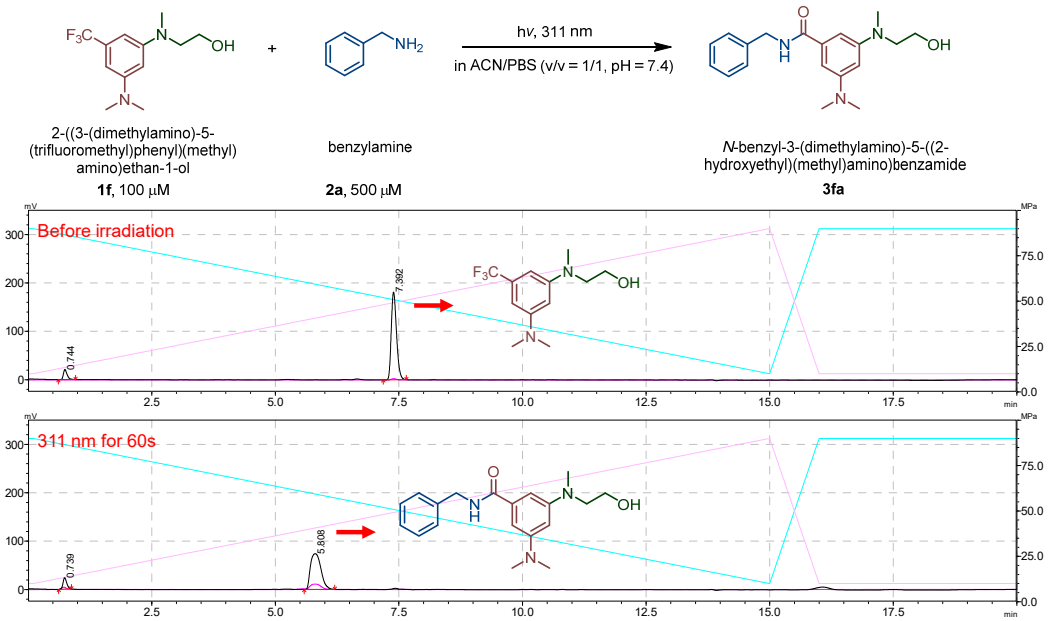


Figure S31. HPLC-MS analysis of the photo-DAFEx reaction between **1f** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(dimethylamino)-5-((2-hydroxyethyl)(methyl)amino)benzamide **(3fa).**

Preparation: 1f (31.5 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3fa** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (29.7 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.26 – 7.20 (m, 1H), 6.80 (t, J = 5.8 Hz, 1H), 6.59 (dd, J = 2.2, 1.4 Hz, 1H), 6.53 (dd, J = 2.2, 1.2 Hz, 1H), 6.16 (t, J = 2.2 Hz, 1H), 4.56 (d, J = 5.8 Hz, 2H), 3.72 (t, J = 5.8 Hz, 2H), 3.42 (t, J = 5.8 Hz, 2H), 2.92 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.16, 151.79, 151.08, 138.59, 136.06, 128.66, 127.80, 127.37, 100.85, 100.83, 99.94, 59.89, 55.30, 43.96, 40.79, 38.88.

HRMS (ESI) calculated $C_{19}H_{26}N_3O_2^+$ $[M+H]^+$ m/z 328.2020, found 328.2015.

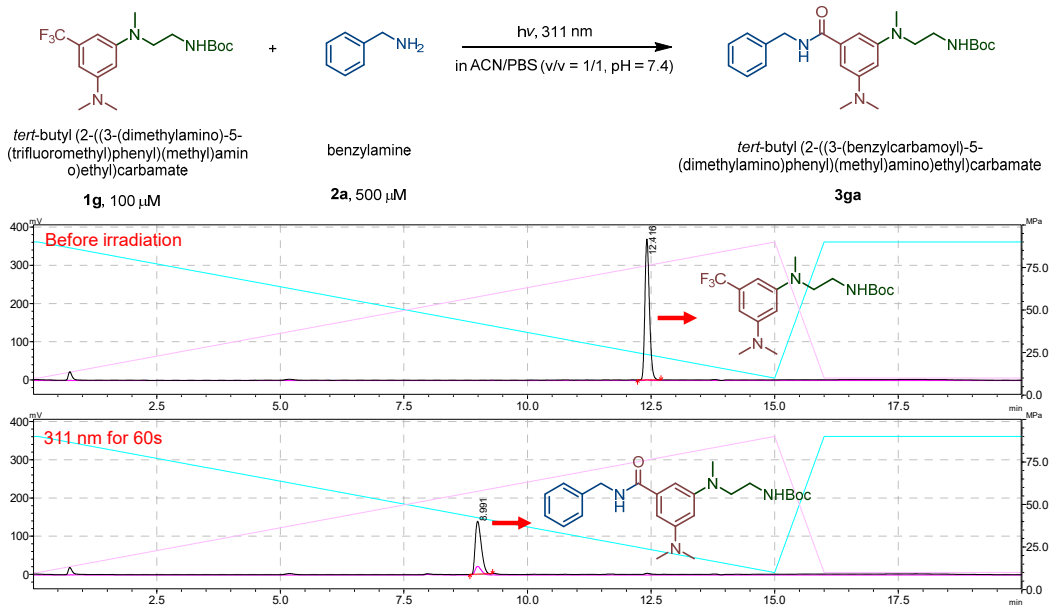


Figure S32. HPLC-MS analysis of the photo-DAFEx reaction between **1g** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

tert-butyl (2-((3-(benzylcarbamoyl)-5-(dimethylamino)phenyl)(methyl)amino)ethyl)carbamate **(3ga).**

Preparation: 1g (43.3 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ga** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (39.6 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.28 (m, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.17 (s, 1H), 6.80 (s, 1H), 6.69 (s, 1H), 6.15 (t, J = 2.3 Hz, 1H), 4.65 (d, J = 5.9 Hz, 2H), 3.43 (dd, J = 8.3, 5.9 Hz, 2H), 3.28 (dt, J = 8.9, 6.2 Hz, 2H), 2.98 (s, 3H), 2.97 (s, 6H), 1.38 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.74, 156.21, 151.93, 149.95, 138.99, 135.95, 128.55, 127.69, 127.16, 101.24, 100.20, 99.37, 79.55, 52.51, 43.85, 40.83, 38.98, 29.71, 28.34.

HRMS (ESI) calculated $C_{24}H_{35}N_4O_3^+$ $[M+H]^+$ m/z 427.2704, found 427.2700.

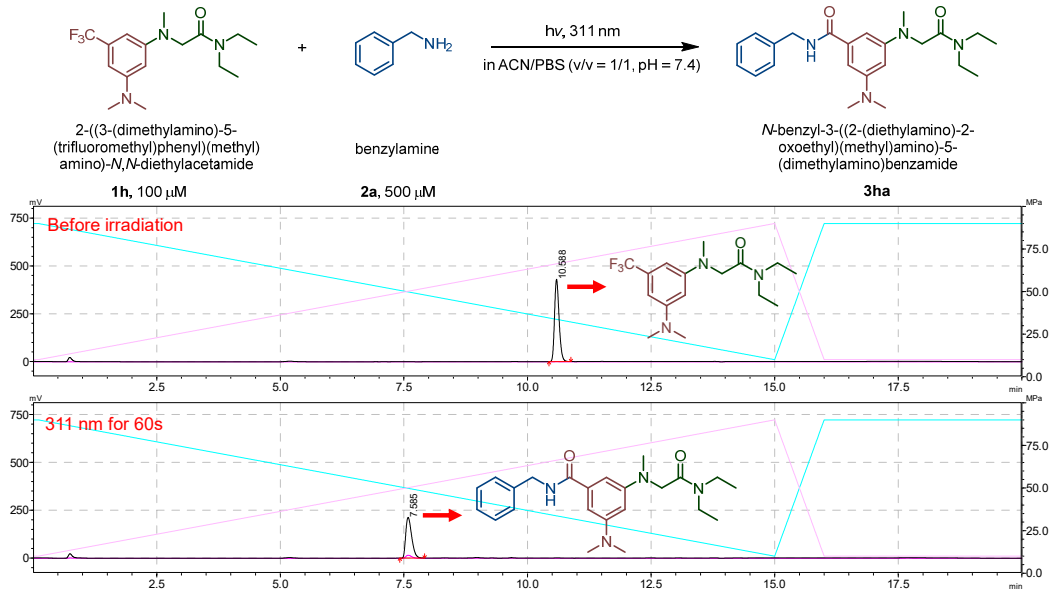


Figure S33. HPLC-MS analysis of the photo-DAFEx reaction between **1h** (100 μM) and **2a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

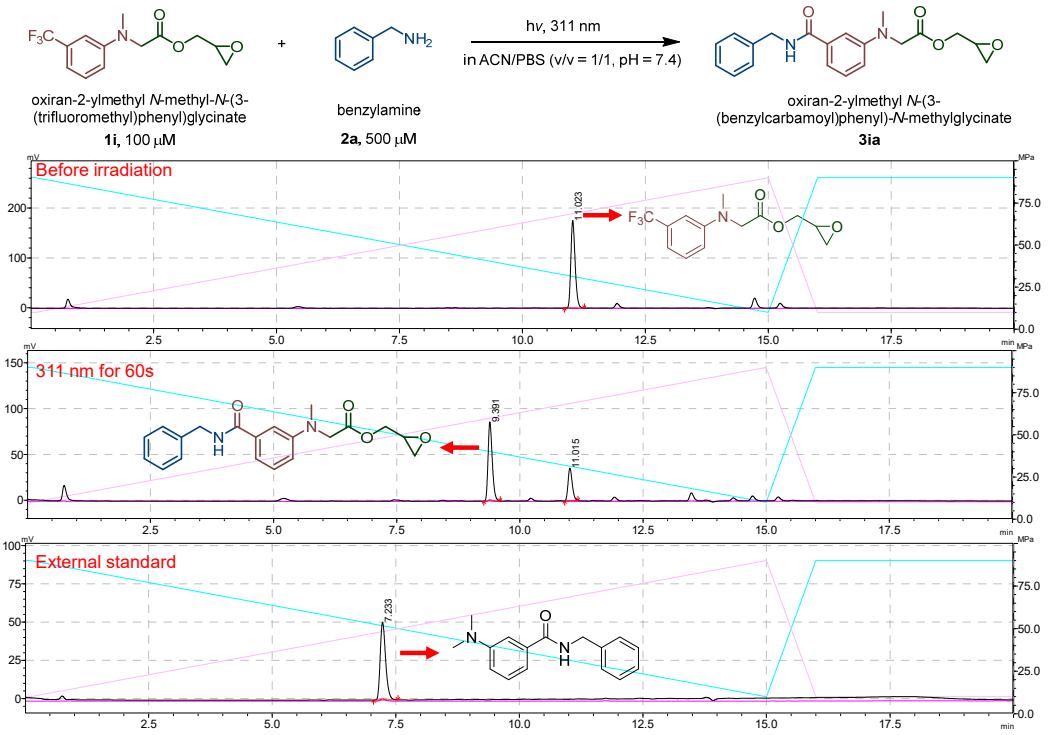
N-benzyl-3-((2-(diethylamino)-2-oxoethyl)(methyl)amino)-5-(dimethylamino)benzamide **(3ha).**

Preparation: 1h (39.7 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ha** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a white solid (38.5 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 4.4 Hz, 4H), 7.30 – 7.26 (m, 1H), 6.51 (dd, J = 2.2, 1.2 Hz, 1H), 6.48 – 6.41 (m, 2H), 6.09 (t, J = 2.2 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H), 4.09 (s, 2H), 3.33 (dq, J = 14.4, 7.2 Hz, 4H), 3.06 (s, 3H), 2.93 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.13, 168.64, 151.77, 150.61, 138.54, 136.24, 128.69, 127.87, 127.43, 101.02, 100.52, 99.72, 54.69, 44.02, 41.32, 40.77, 40.48, 39.94, 14.36, 13.07.

HRMS (ESI) calculated $C_{23}H_{33}N_4O_2^+$ $[M+H]^+$ m/z 397.2598, found 397.2594.



Item	Peak No.	Retention Time (min)	Area
Before irradiation	1	11.023	1061360
311 nm for 60 s	2	9.391	510942
	3	11.015	208757
External standard	4	7.233	385476
HPLC Yield		66%	

Figure S34. HPLC-MS analysis of the photo-DAFEx reaction between **1c** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I** and the HPLC yield of **3ia** was determined by external standard of *N*-benzyl-3-(dimethylamino)benzamide (**3aa**, 50 μM).

Preparation and characterization

oxiran-2-ylmethyl *N*-(3-(benzylcarbamoyl)phenyl)-*N*-methylglycinate **(3ia).**

In attempting to isolate the **3ia**, we found that concentration procedure would lead to ring-opening of the epoxy moiety and even ring-opening substitution reaction with benzylamine, resulting in a messy mixture. Therefore, we were unable to obtain a purely isolated **3ia** for characterization via ^{1}H and ^{13}C NMR.

HRMS (ESI) calculated $C_{20}H_{22}N_2O_4^+$ $[M+H]^+$ m/z 354.1580, found 354.1586.

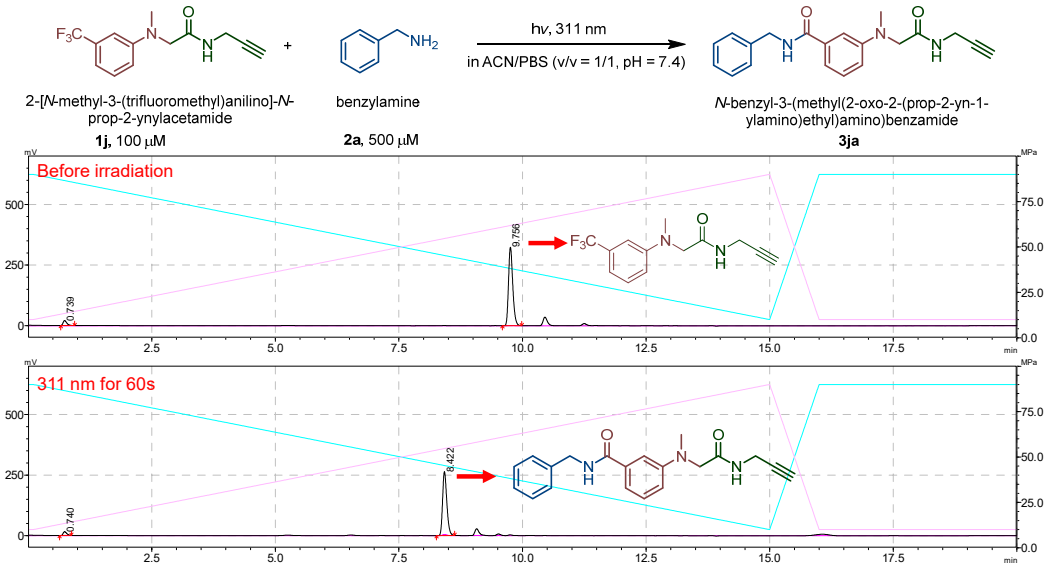


Figure S35. HPLC-MS analysis of the photo-DAFEx reaction between **1j** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(methyl(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)amino)benzamide **(3ja).**

Preparation: **1j** (32.4 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ja** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (29.8 mg, 70%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (t, J = 6.2 Hz, 1H), 8.38 (t, J = 5.6 Hz, 1H), 7.32 (d, J = 5.8 Hz, 4H), 7.24 (dq, J = 8.4, 2.8 Hz, 2H), 7.20 (dd, J = 7.2, 1.6 Hz, 2H), 6.79 – 6.73 (m, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.98 (s, 2H), 3.87 (dd, J = 5.6, 2.6 Hz, 2H), 3.07 (t, J = 2.4 Hz, 1H), 3.01 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 169.95, 167.21, 149.65, 140.34, 135.51, 129.24, 128.73, 127.60, 127.15, 115.58, 115.01, 111.29, 81.63, 73.29, 55.83, 43.03, 39.74, 28.34.

HRMS (ESI) calculated $C_{20}H_{22}N_3O_2^+$ $[M+H]^+$ m/z 336.1707, found 336.1700.

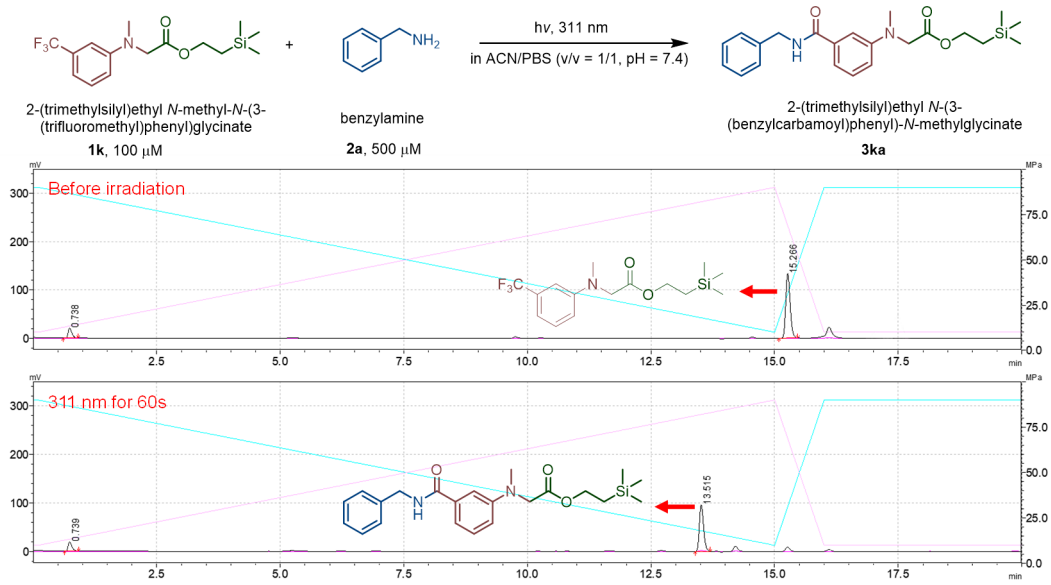


Figure S36. HPLC-MS analysis of the photo-DAFEx reaction between **1k** (100 μM) and **2a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

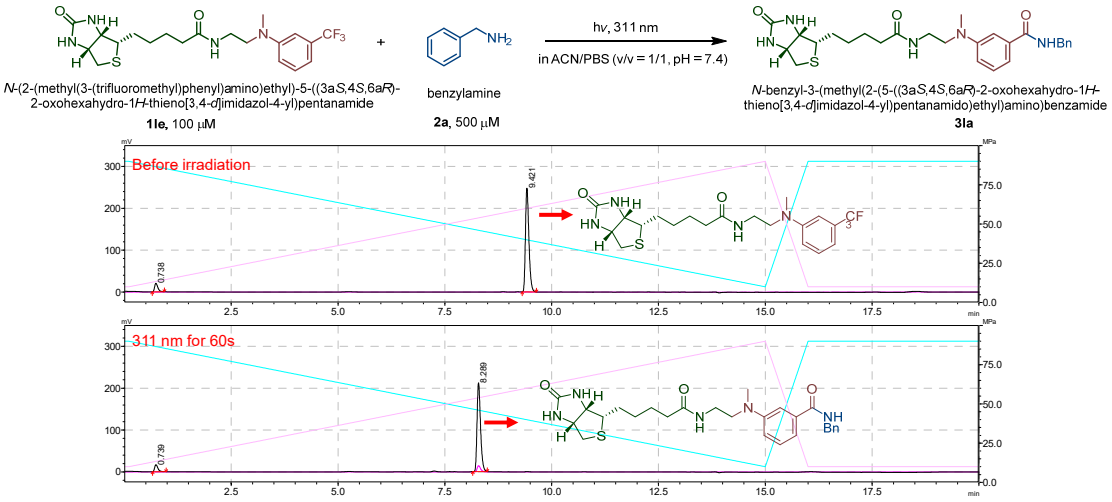
2-(trimethylsilyl)ethyl *N*-(3-(benzylcarbamoyl)phenyl)-*N*-methylglycinate **(3ka).**

Preparation: 1k (40.0 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ka** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (35.4 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 4.4 Hz, 4H), 7.32 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 7.01 (d, J = 8.2 Hz, 1H), 6.78 (dd, J = 8.2, 2.8 Hz, 1H), 6.41 (d, J = 6.0 Hz, 1H), 4.63 (d, J = 5.6 Hz, 2H), 4.24 – 4.16 (m, 2H), 4.08 (s, 2H), 3.09 (s, 3H), 1.02 – 0.94 (m, 2H), 0.02 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.27, 169.50, 150.78, 139.86, 136.96, 130.81, 130.29, 129.41, 129.08, 116.60, 116.25, 112.94, 64.92, 55.88, 45.63, 41.07, 18.96, 0.00.

HRMS (ESI) calculated $C_{22}H_{31}N_2O_3Si^+$ $[M+H]^+$ m/z 399.2098, found 399.2089.



N-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide
1le, 100 μM

N-benzyl-3-(methyl(2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)ethyl)amino)benzamide
3la

Figure S37. HPLC-MS analysis of the photo-DAFEx reaction between **1l** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

2-(trimethylsilyl)ethyl *N*-(3-(benzylcarbamoyl)phenyl)-*N*-methylglycinate **(3la).**

Preparation: 1l (53.3 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3la** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow solid (50.2 mg, 82%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.93 (t, *J* = 6.1 Hz, 1H), 7.92 (t, *J* = 5.8 Hz, 1H), 7.35 – 7.29 (m, 4H), 7.26 – 7.21 (m, 3H), 7.13 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.39 (dt, *J* = 22.2, 1.7 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.29 (ddt, *J* = 6.4, 5.3, 1.1 Hz, 1H), 4.10 (ddd, *J* = 7.8, 4.4, 1.9 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.21 (q, *J* = 6.4 Hz, 2H), 3.06 (ddd, *J* = 8.6, 6.1, 4.3 Hz, 1H), 2.93 (s, 3H), 2.81 (dd, *J* = 12.4, 5.1 Hz, 1H), 2.57 (d, *J* = 12.4 Hz, 1H), 2.02 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.38 (m, 4H), 1.32 – 1.23 (m, 2H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 172.87, 167.30, 163.20, 149.32, 140.35, 135.59, 129.36, 128.72, 128.15, 127.64, 114.97, 114.88, 110.83, 61.50, 59.67, 55.86, 51.36, 43.05, 40.31, 38.61, 36.28, 35.68, 28.68, 28.49, 25.58.

HRMS (ESI) calculated $C_{27}H_{36}N_5O_3S^+$ $[M+H]^+$ m/z 510.2533, found 510.2528.

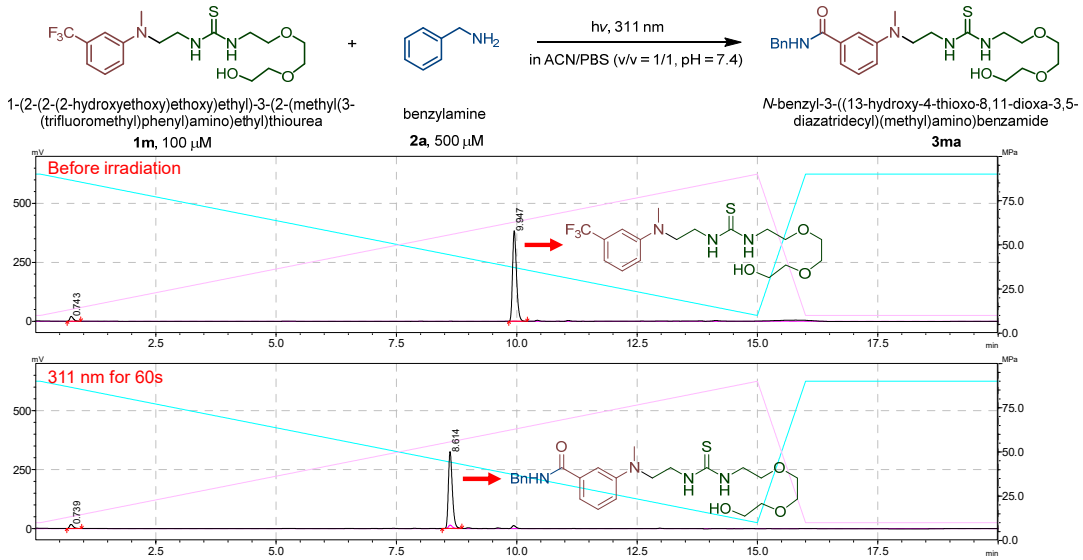


Figure S38. HPLC-MS analysis of the photo-DAFEx reaction between **1m** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-((13-hydroxy-4-thioxo-8,11-dioxa-3,5-diazatridecyl)(methyl)amino)benzamide **(3ma).**

Preparation: 1m (49.1 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ma** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow oil (46.0 mg, 81%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (t, J = 6.2 Hz, 1H), 7.59 (s, 1H), 7.56 – 7.49 (m, 1H), 7.35 – 7.29 (m, 4H), 7.26 – 7.19 (m, 3H), 7.13 (dt, J = 7.6, 1.2 Hz, 1H), 6.96 (dd, J = 8.2, 2.6 Hz, 1H), 4.60 (t, J = 5.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.55 – 3.45 (m, 12H), 3.41 (dd, J = 5.4, 4.4 Hz, 2H), 2.95 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 167.32, 149.43, 140.34, 135.65, 129.35, 128.72, 127.64, 127.13, 115.05, 110.81, 72.81, 70.18, 70.11, 69.38, 60.68, 51.08, 43.03, 38.56.

HRMS (ESI) calculated $C_{24}H_{35}N_4O_4S^+$ $[M+H]^+$ m/z 475.2374, found 475.2369.

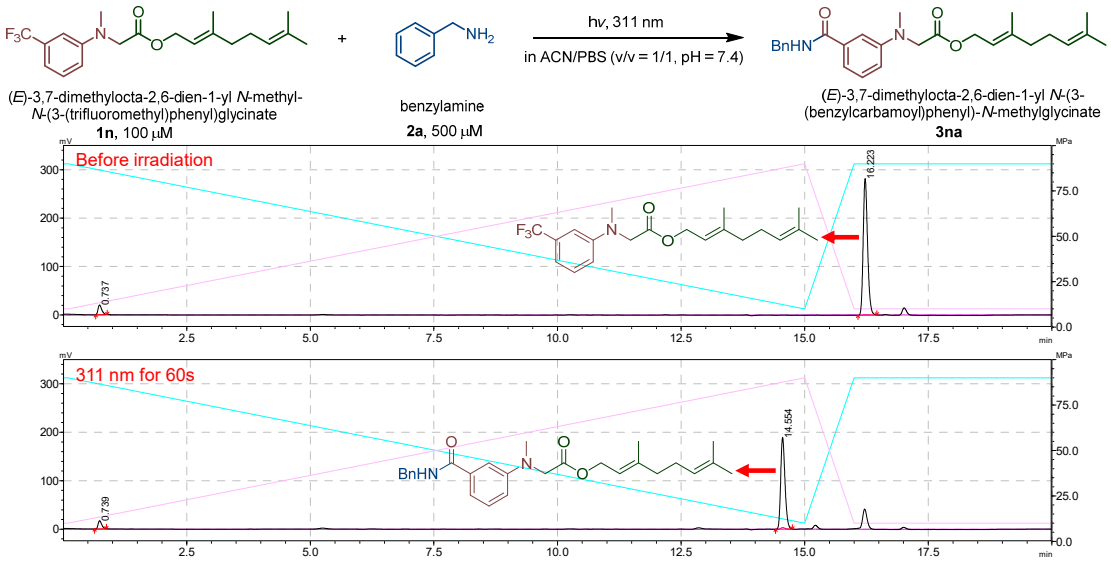


Figure S39. HPLC-MS analysis of the photo-DAFEx reaction between **1n** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

(*E*)-3,7-dimethylocta-2,6-dien-1-yl *N*-(3-(benzylcarbamoyl)phenyl)-*N*-methylglycinate **(3na).**

Preparation: 1n (44.3 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3na** was isolated by flash chromatography (PE : EtOH = 2 : 1) as a yellow oil (47.0 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 4.4 Hz, 4H), 7.31 – 7.27 (m, 1H), 7.25 – 7.20 (m, 2H), 7.02 (dt, J = 7.8, 1.2 Hz, 1H), 6.78 (ddd, J = 8.2, 2.8, 0.8 Hz, 1H), 6.47 (t, J = 5.8 Hz, 1H), 5.31 (ddq, J = 7.0, 5.6, 1.3 Hz, 1H), 5.07 (tdd, J = 6.6, 3.0, 1.4 Hz, 1H), 4.63 (d, J = 2.0 Hz, 2H), 4.62 (s, 2H), 4.10 (s, 2H), 3.08 (s, 3H), 2.14 – 1.95 (m, 4H), 1.67 (dd, J = 7.4, 1.4 Hz, 6H), 1.60 (d, J = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.58, 167.98, 149.25, 142.94, 138.38, 135.45, 131.87, 129.27, 128.75, 127.88, 127.53, 123.72, 117.87, 115.11, 114.81, 111.49, 61.86, 54.26, 44.09, 39.54, 39.51, 26.29, 25.71, 17.73, 16.50.

HRMS (ESI) calculated $C_{27}H_{35}N_2O_3^+$ $[M+H]^+$ m/z 435.2642, found 435.2646.

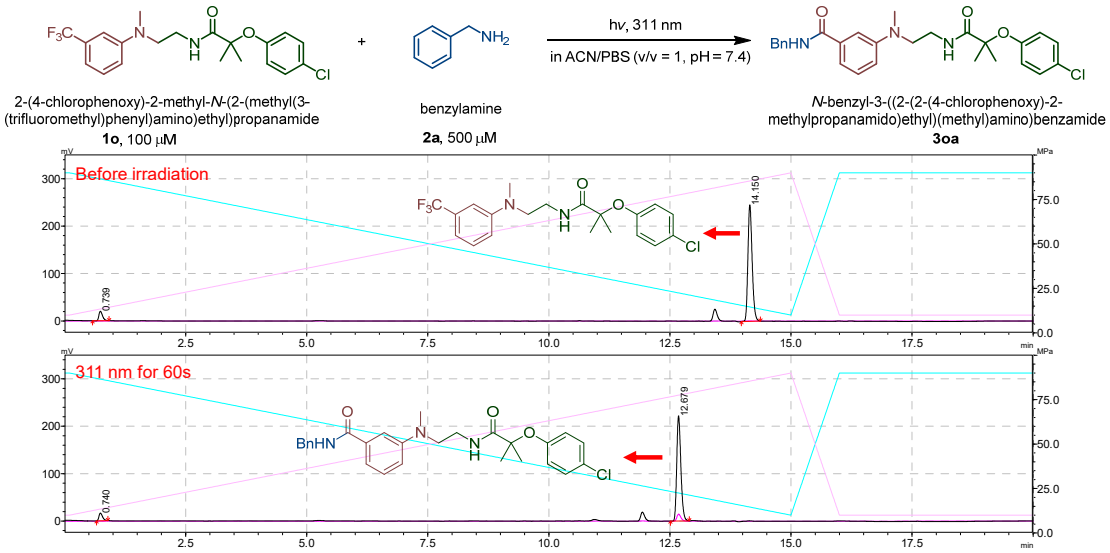


Figure S40. HPLC-MS analysis of the photo-DAFEx reaction between **1o** (100 μM) and **2a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-((2-(2-(4-chlorophenoxy)-2-methylpropanamido)ethyl)(methyl)amino)benzamide **(3oa)**

Preparation: 1o (49.7 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3oa** was isolated by flash chromatography (PE : EtOH = 2 : 1) as a yellow oil (46.4 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 2.6, 1.6 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.32 (ddd, J = 7.8, 6.8, 0.8 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.20 (d, J = 2.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.14 (ddd, J = 7.4, 1.6, 0.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.93 (d, J = 6.4 Hz, 1H), 6.83 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 2.2 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 3.54 – 3.46 (m, 4H), 2.99 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.07, 167.79, 152.56, 149.02, 138.71, 135.32, 129.47, 129.26, 128.73, 128.63, 127.94, 127.37, 122.87, 115.03, 114.96, 110.99, 81.89, 51.40, 44.05, 38.63, 36.54, 24.83.

HRMS (ESI) calculated $C_{27}H_{31}ClN_3O_3^+$ $[M+H]^+$ m/z 480.2048, found 480.2046.

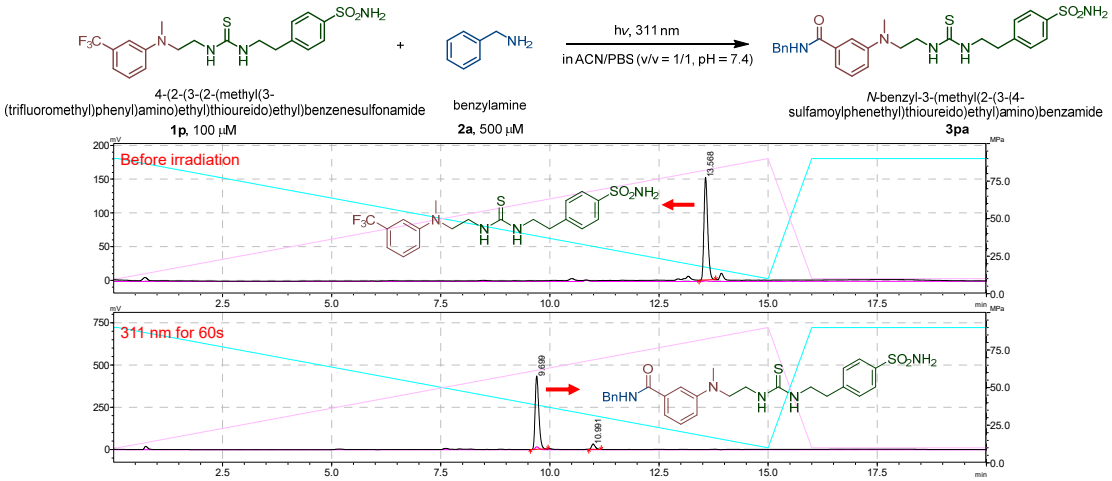


Figure S41. HPLC-MS analysis of the photo-DAFEx reaction between **1p** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(methyl(2-(3-(4-sulfamoylphenethyl)thioureido)ethyl)amino)benzamide **(3pa).**

Preparation: 1p (55.2 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3pa** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow solid (53.3 mg, 85%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.88 (t, J = 6.2 Hz, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.53 (d, J = 14.2 Hz, 2H), 7.41 (d, J = 1.8 Hz, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.34 – 7.28 (m, 6H), 7.27 – 7.19 (m, 3H), 7.14 (dt, J = 7.6, 1.2 Hz, 1H), 7.03 – 6.93 (m, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.72 – 3.42 (m, 6H), 2.95 (s, 3H), 2.87 (t, J = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.35, 149.42, 144.04, 142.55, 140.33, 135.67, 129.59, 129.36, 128.73, 127.63, 127.14, 126.18, 115.03, 110.81, 51.05, 43.04, 38.57, 34.99, 29.49, 22.57.

HRMS (ESI) calculated $C_{26}H_{32}N_5O_3S_2^+$ $[M+H]^+$ m/z 526.1941, found 526.1938.

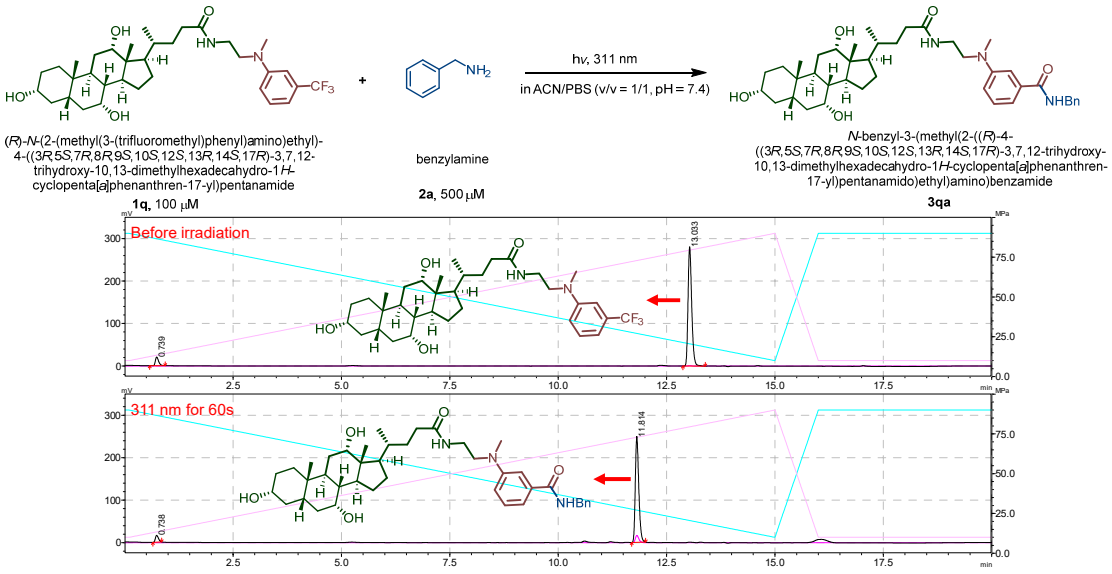


Figure S42. HPLC-MS analysis of the photo-DAFEx reaction between **1q** (100 μM) and **2a** (500μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(methyl(2-((*S*)-4-((3*S*,5*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,14*R*,17*S*)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanamido)ethyl)amino)benzamide **(3qa)**.

Preparation: **1q** (73.0 mg, 0.12 mmol) and **2a** (66 μL, 0.60 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3qa** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a wight solid (49.8 mg, 62%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, J = 6.1 Hz, 1H), 7.90 (t, J = 5.8 Hz, 1H), 7.35 – 7.29 (m, 4H), 7.26 – 7.19 (m, 3H), 7.13 (dt, J = 7.6, 1.1 Hz, 1H), 6.87 (dd, J = 8.1, 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 4.33 (d, J = 4.3 Hz, 1H), 4.09 (d, J = 3.6 Hz, 1H), 4.00 (d, J = 3.4 Hz, 1H), 3.77 (q, J = 3.1 Hz, 1H), 3.61 (t, J = 3.3 Hz, 1H), 3.40 (d, J = 6.9 Hz, 2H), 3.20 (q, J = 5.2, 4.2 Hz, 3H), 2.93 (s, 3H), 2.28 – 1.86 (m, 4H), 1.83 – 1.55 (m, 4H), 1.49 – 1.08 (m, 8H), 1.02 – 0.78 (m, 7H), 0.57 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 173.51, 167.29, 149.27, 140.34, 135.59, 129.35, 128.72, 127.64, 127.13, 114.96, 114.86, 110.80, 71.48, 70.92, 66.72, 51.39, 46.56, 46.20, 43.05, 41.99, 41.83, 38.69, 36.30, 35.78, 35.60, 35.36, 34.86, 32.96, 32.04, 30.87, 29.03, 27.74, 26.68, 23.28, 23.10, 17.58, 12.82.

HRMS (ESI) calculated $C_{41}H_{60}N_3O_5^+$ $[M+H]^+$ m/z 674.4527, found 674.4517.

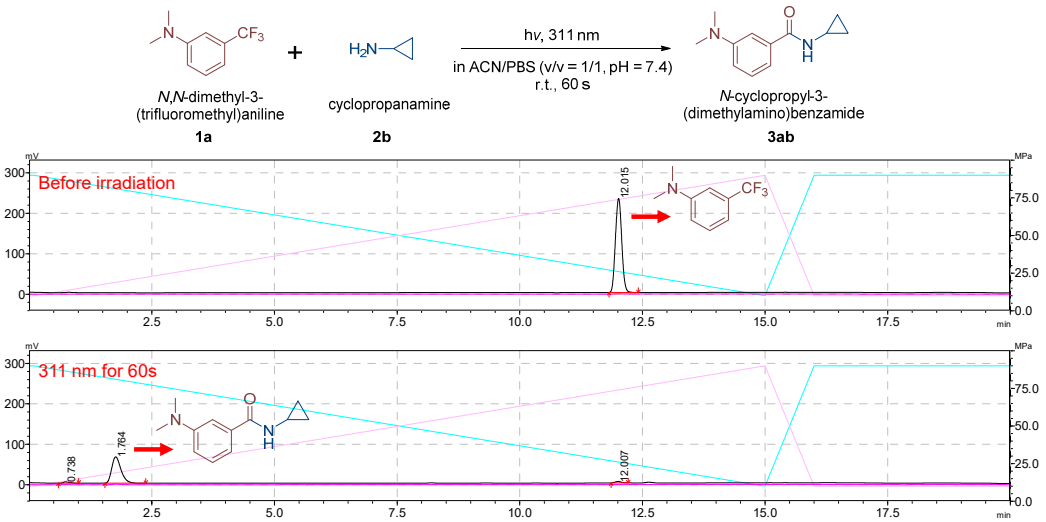


Figure S43. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2b** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-cyclopropyl-3-(dimethylamino)benzamide **(3ab)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2b** (46.8 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ab** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a white solid (27.5 mg, 82%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 1H), 7.17 (dd, J = 2.8, 1.6 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.80 (dd, J = 8.2, 2.6 Hz, 1H), 6.38 (s, 1H), 2.96 (s, 6H), 2.88 (m, 1H), 0.83 (m, 2H), 0.63 – 0.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.77, 150.70, 135.32, 129.05, 115.18, 113.90, 111.26, 77.39, 77.08, 76.76, 40.49, 23.13, 6.74.

HRMS (ESI) calculated $C_{12}H_{17}N_2O^+$ $[M+H]^+$ m/z 205.1335, found 205.1333.

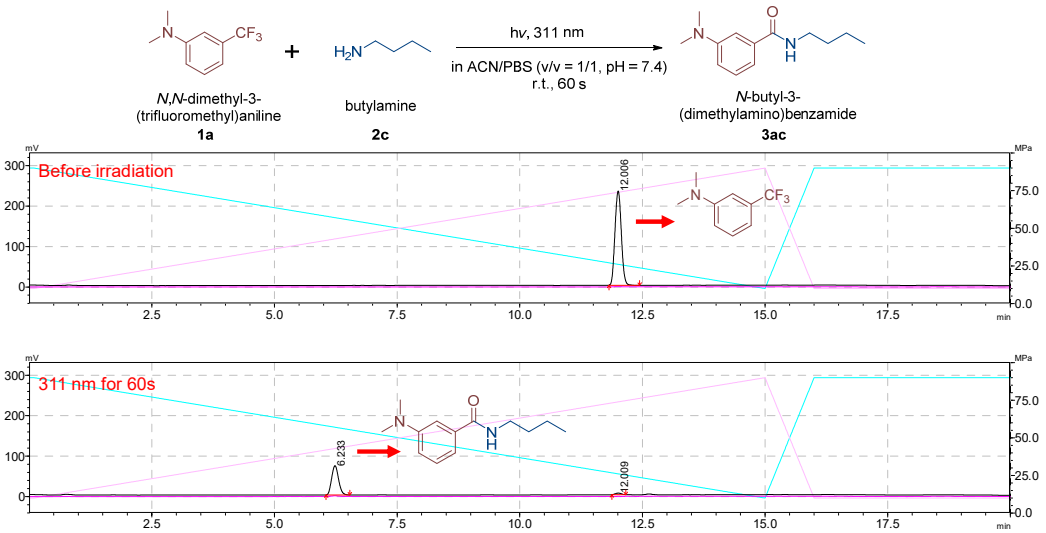


Figure S44. HPLC-MS analysis of the photo-DAFEx reaction between **1a** and **2c** in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-butyl-3-(dimethylamino)benzamide **(3ac)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2c** (60.0 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ac** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (31.8 mg, 88%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.8 Hz, 1H), 7.19 (dd, J = 2.8, 1.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 8.2, 2.6 Hz, 1H), 6.22 (s, 1H), 3.43 (td, J = 7.2, 5.6 Hz, 2H), 2.97 (s, 6H), 1.64 – 1.50 (m, 2H), 1.48 – 1.30 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.35, 150.73, 135.81, 129.05, 115.03, 113.82, 111.35, 40.50, 39.77, 31.80, 20.18, 13.82.

HRMS (ESI) calculated $C_{13}H_{21}N_2O^+$ $[M+H]^+$ m/z 221.1648, found 221.1646.

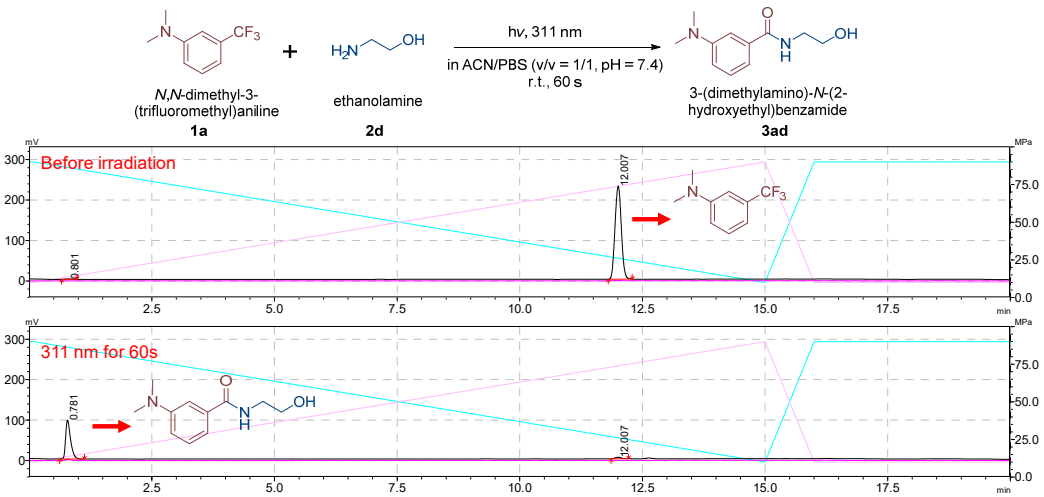


Figure S45. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2d** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-(2-hydroxyethyl)benzamide **(3ad)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2d** (50.1 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ad** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow oil (26.2 mg, 77%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 1H), 7.16 (dd, J = 2.6, 1.6 Hz, 1H), 7.02 – 6.92 (m, 2H), 6.80 (dd, J = 8.2, 2.2 Hz, 1H), 3.76 (t, J = 5.0 Hz, 2H), 3.55 (q, J = 5.6 Hz, 2H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.62, 150.67, 134.98, 129.14, 115.37, 114.21, 111.26, 62.20, 42.93, 40.47.

HRMS (ESI) calculated $C_{11}H_{17}N_2O_2^+$ $[M+H]^+$ m/z 209.1285, found 209.1283.

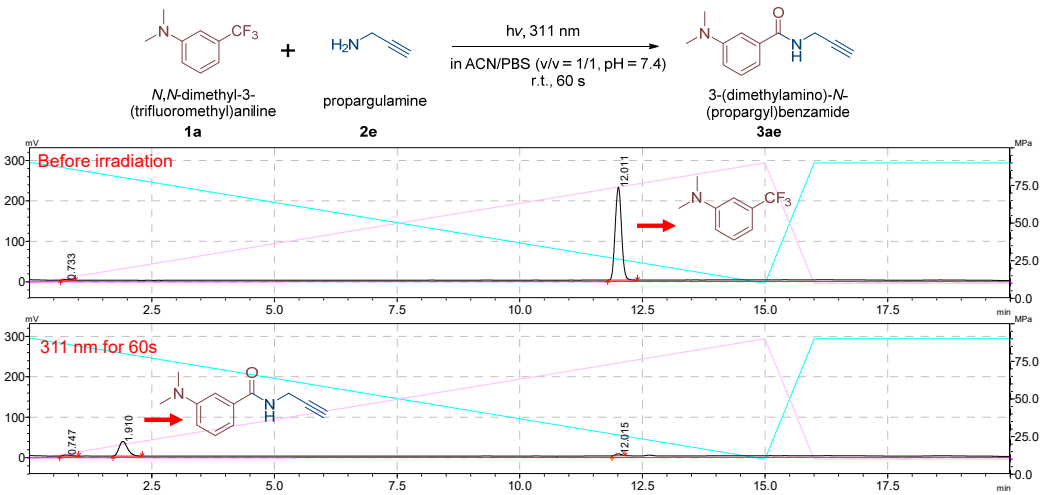


Figure S46. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2e** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-(prop-2-yn-1-yl)benzamide **(3ae)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2e** (45.2 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ae** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow solid (23.2 mg, 70%);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.2, 7.6 Hz, 1H), 7.19 (dd, J = 2.6, 1.6 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 7.8, 2.6 Hz, 1H), 6.40 (s, 1H), 4.23 (dd, J = 5.2, 2.6 Hz, 2H), 2.97 (s, 6H), 2.26 (t, J = 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.98, 150.72, 134.64, 129.18, 115.45, 114.00, 111.33, 79.71, 71.73, 40.48, 29.75.

HRMS (ESI) calculated $C_{12}H_{15}N_2O^+$ $[M+H]^+$ m/z 203.1179, found 203.1176.

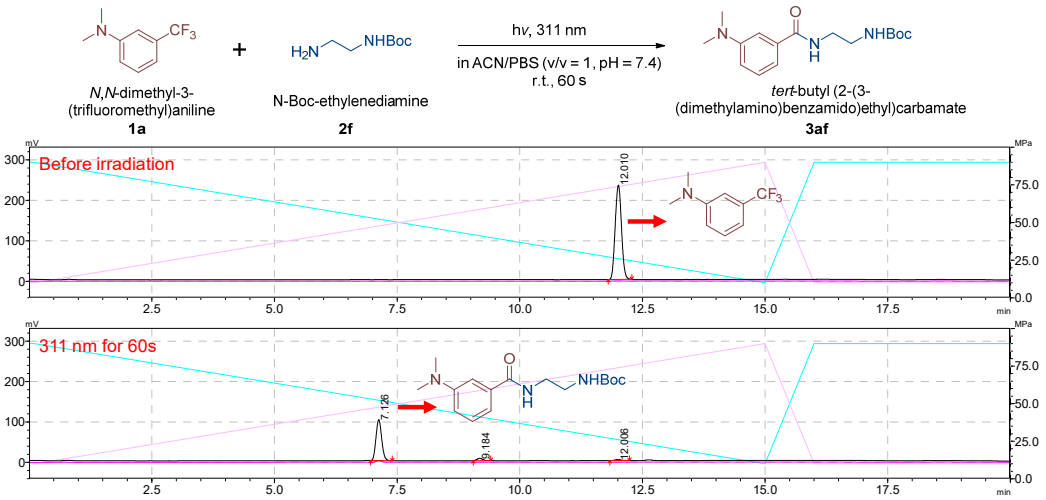


Figure S47. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2f** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

tert-butyl (2-(3-(dimethylamino)benzamido)ethyl)carbamate **(3af)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2f** (131.4 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3af** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (45.4 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.14 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.82 (dd, J = 8.2, 2.2 Hz, 1H), 5.11 (s, 1H), 3.53 (q, J = 5.4 Hz, 2H), 3.37 (q, J = 5.8 Hz, 2H), 2.97 (s, 6H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.69, 157.31, 150.67, 134.99, 129.08, 115.29, 114.41, 111.31, 79.79, 41.68, 40.53, 40.22, 28.37.

HRMS (ESI) calculated $C_{16}H_{26}N_3O_3^+$ $[M+H]^+$ m/z 308.1969, found 308.1964.

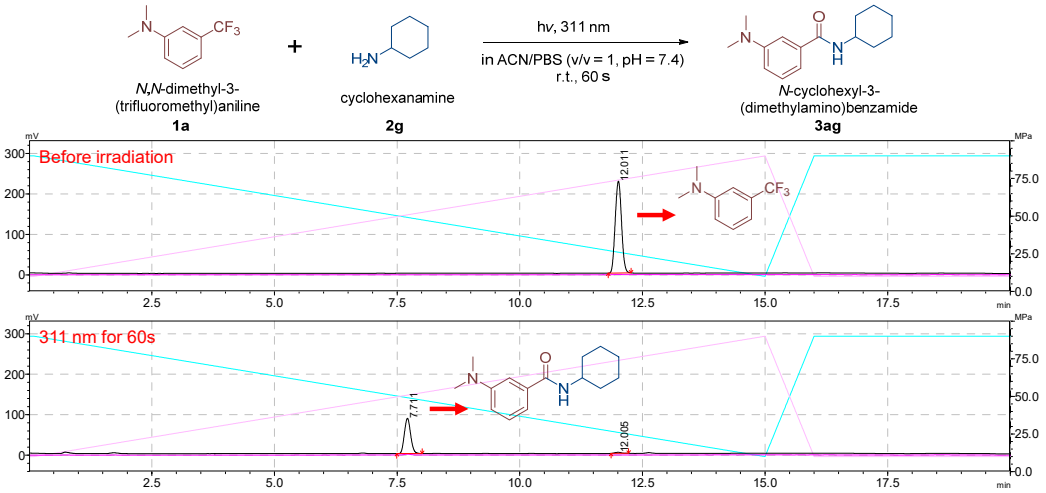


Figure S48. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2g** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-cyclohexyl-3-(dimethylamino)benzamide **(3ag)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2g** (81.3 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ag** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (33.4 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 1H), 7.19 (dd, J = 2.8, 1.6 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.81 (dd, J = 8.3, 1.8 Hz, 1H), 5.97 (d, J = 7.4 Hz, 1H), 3.97 (dddd, J = 14.7, 10.6, 8.0, 3.8 Hz, 1H), 2.98 (s, 6H), 2.02 (dt, J = 12.0, 3.2 Hz, 2H), 1.79 – 1.59 (m, 3H), 1.53 – 1.34 (m, 2H), 1.30 – 1.15 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.46, 150.76, 136.09, 129.03, 115.00, 113.74, 111.39, 48.58, 40.53, 33.25, 25.63, 24.93.

HRMS (ESI) calculated $C_{15}H_{23}N_2O^+$ $[M+H]^+$ m/z 247.1805, found 247.1803.

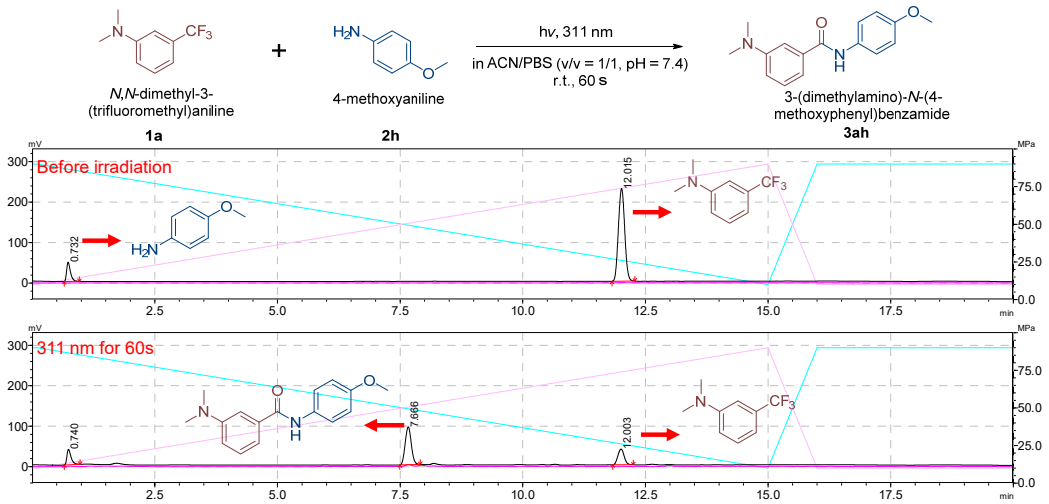


Figure S49. HPLC-MS analysis of the photo-DAFEx reaction between **1q** (100 μM) and **2h** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-(4-methoxyphenyl)benzamide **(3ah)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2h** (101.0 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ah** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (24.1 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H), 7.32 – 7.24 (m, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.92 – 6.83 (m, 3H), 3.80 (s, 3H), 2.99 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.48, 156.48, 150.81, 135.98, 131.29, 129.28, 121.98, 115.38, 114.21, 113.83, 111.35, 55.52, 40.49.

HRMS (ESI) calculated $C_{16}H_{19}N_2O_2^+$ $[M+H]^+$ m/z 271.1441, found 271.1438.

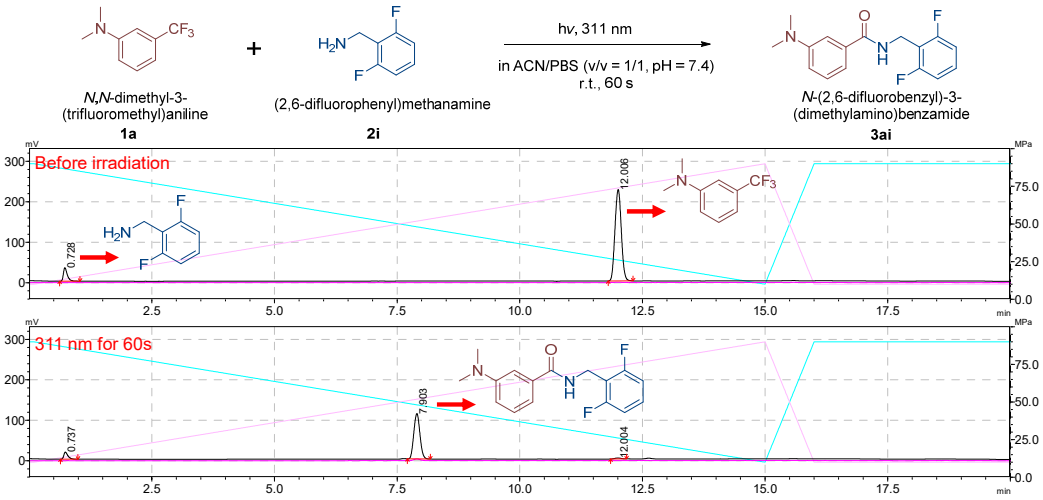


Figure S50. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2i** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-(2,6-difluorobenzyl)-3-(dimethylamino)benzamide **(3ai)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2i** (117.4 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ai** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (42.7 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 3H), 6.96 – 6.88 (m, 3H), 6.82 (ddd, J = 8.4, 2.8, 0.8 Hz, 1H), 6.46 (s, 1H), 4.74 (dd, J = 5.8, 1.2 Hz, 2H), 2.97 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.85, 162.87 (d, J = 7.6 Hz), 160.39 (d, J = 8.0 Hz), 150.74, 135.05, 129.51 (t, J = 10.5 Hz), 129.08, 115.28, 114.11 (d, J = 18.9 Hz), 113.81, 111.56 (d, J = 7.9 Hz), 111.51, 111.38 (d, J = 6.5 Hz), 40.48, 32.02 (t, J = 3.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.73.

HRMS (ESI) calculated $C_{16}H_{17}F_2N_2O^+$ $[M+H]^+$ m/z 291.1303, found 291.1299.

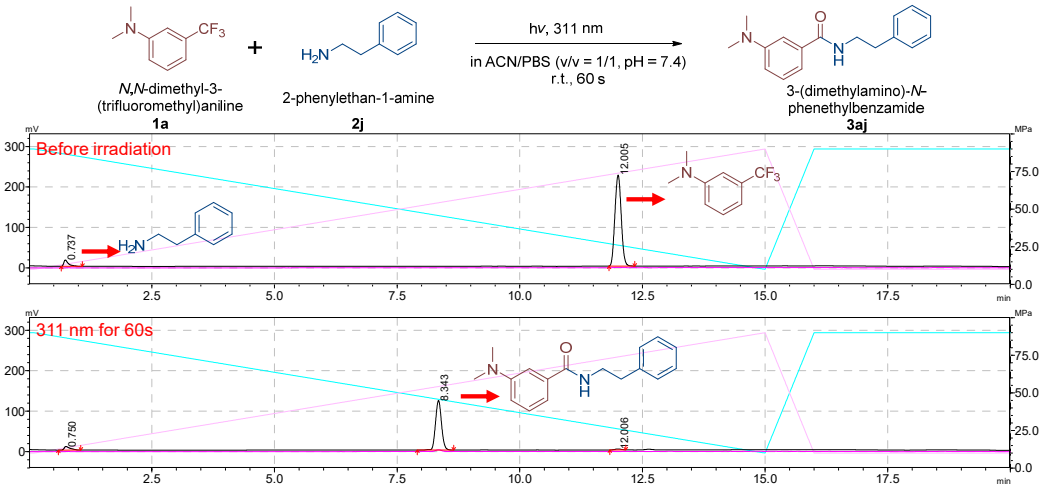


Figure S51. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2j** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

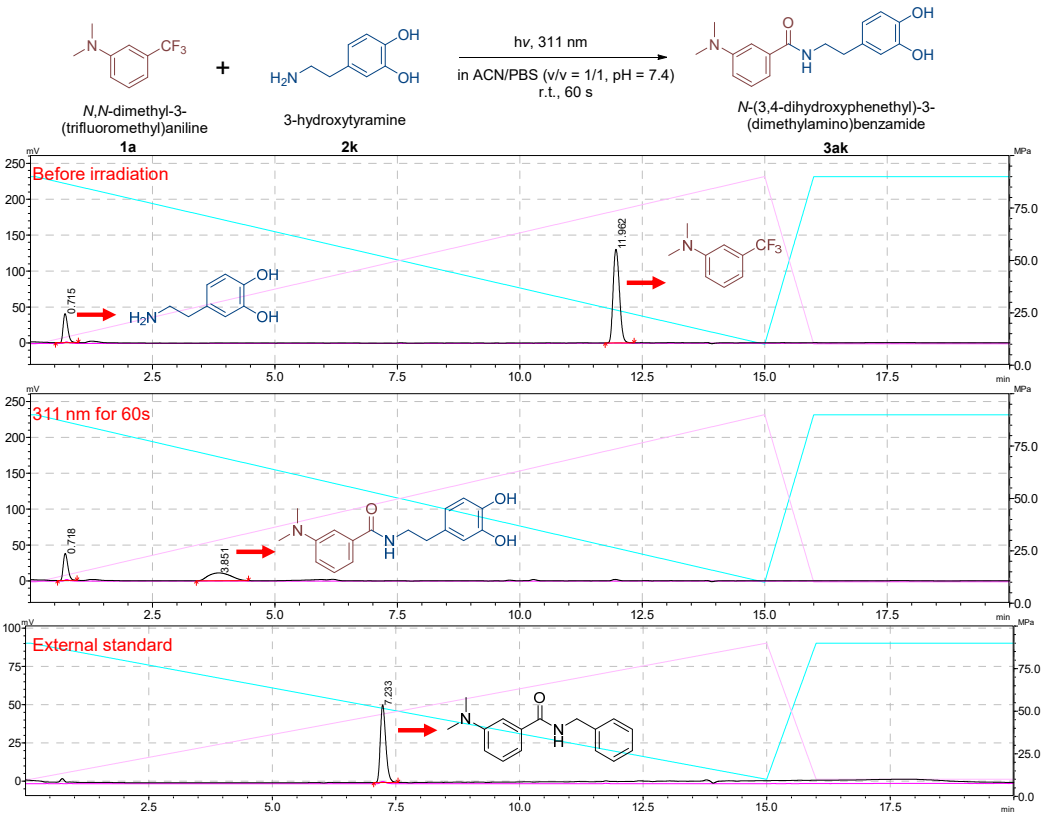
3-(dimethylamino)-*N*-phenethylbenzamide **(3aj)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2j** (99.4 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3aj** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (38.1 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.33 – 7.27 (m, 4H), 7.20 (dd, J = 2.8, 1.6 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.87 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 6.29 (s, 1H), 3.76 (td, J = 6.8, 5.8 Hz, 2H), 3.02 (s, 6H), 2.98 (t, J = 6.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.34, 150.69, 139.08, 135.60, 129.13, 128.89, 128.70, 126.56, 115.13, 113.90, 111.22, 41.14, 40.48, 35.77.

HRMS (ESI) calculated $C_{17}H_{21}N_2O^+$ $[M+H]^+$ m/z 269.1648, found 269.1644.



Item	Peak No.	Retention Time (min)	Area
Before irradiation	1	0.715	259714
	2	11.962	1164239
311 nm for 60 s	3	0.718	245016
	4	3.851	344354
External standard	5	7.233	385476
HPLC yield	45%		

Figure S52. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2k** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**. and the HPLC yield of **3ak** was determined by external standard *N*-benzyl-3-(dimethylamino)benzamide (**3aa**, 50 μM).

Preparation and characterization

N-(3,4-dihydroxyphenethyl)-3-(dimethylamino)benzamide **(3ak)**

In attempting to isolate the **3ak**, we found that both the starting material, dopamine, and the related conjugate **3ak** are sensitive to photo-irradiation, which resulted in their photo-decomposition under continuous irradiation for 1 h, and consequently led to a messy mixture. Therefore, we were unable to obtain a purely isolated **3ak** for characterization via ^{1}H and ^{13}C NMR.

HRMS (ESI) calculated $C_{17}H_{21}N_2O_3^+$ $[M+H]^+$ m/z 301.1547, found 301.1544.

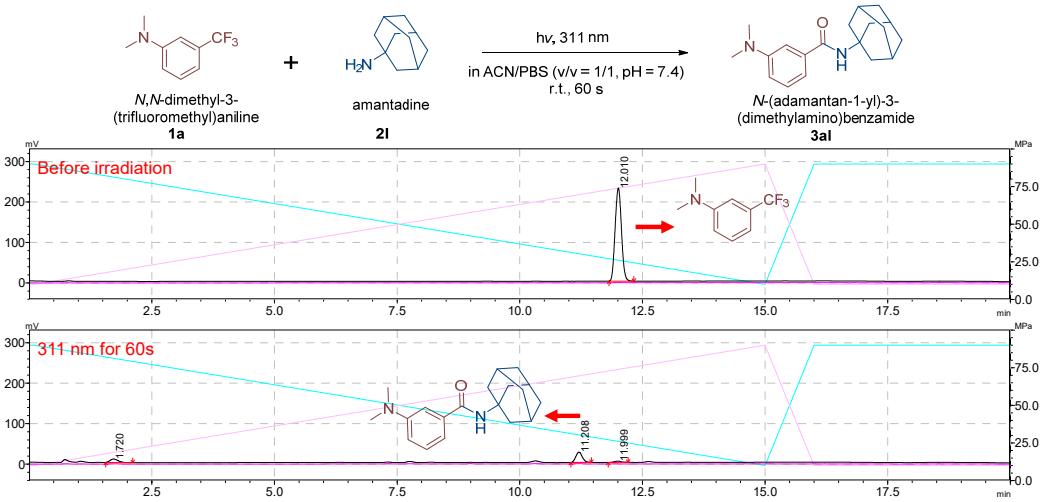


Figure S53. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2l** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-(adamantan-1-yl)-3-(dimethylamino)benzamide **(3al)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2l** (124.0 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3al** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (37.6 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 8.2, 7.6 Hz, 1H), 7.19 (dd, J = 2.8, 1.6 Hz, 1H), 6.89 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 6.80 (ddd, J = 8.3, 2.8, 0.8 Hz, 1H), 5.81 (s, 1H), 2.98 (s, 6H), 2.12 (s, 9H), 1.72 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.41, 150.78, 136.91, 128.93, 114.85, 113.63, 111.40, 52.15, 41.70, 40.53, 36.44, 29.54.

HRMS (ESI) calculated $C_{19}H_{27}N_2O^+$ $[M+H]^+$ m/z 299.2118, found 299.2120.

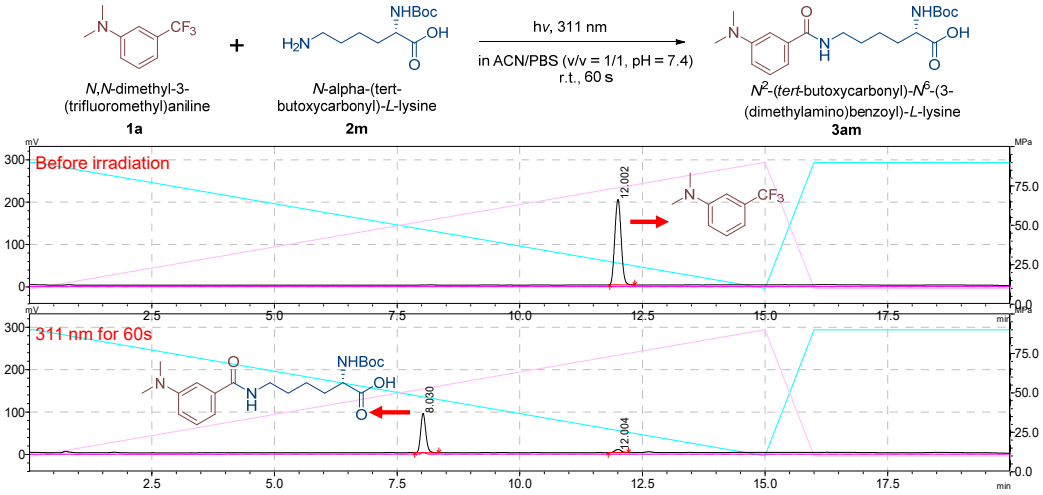


Figure S54. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2m** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

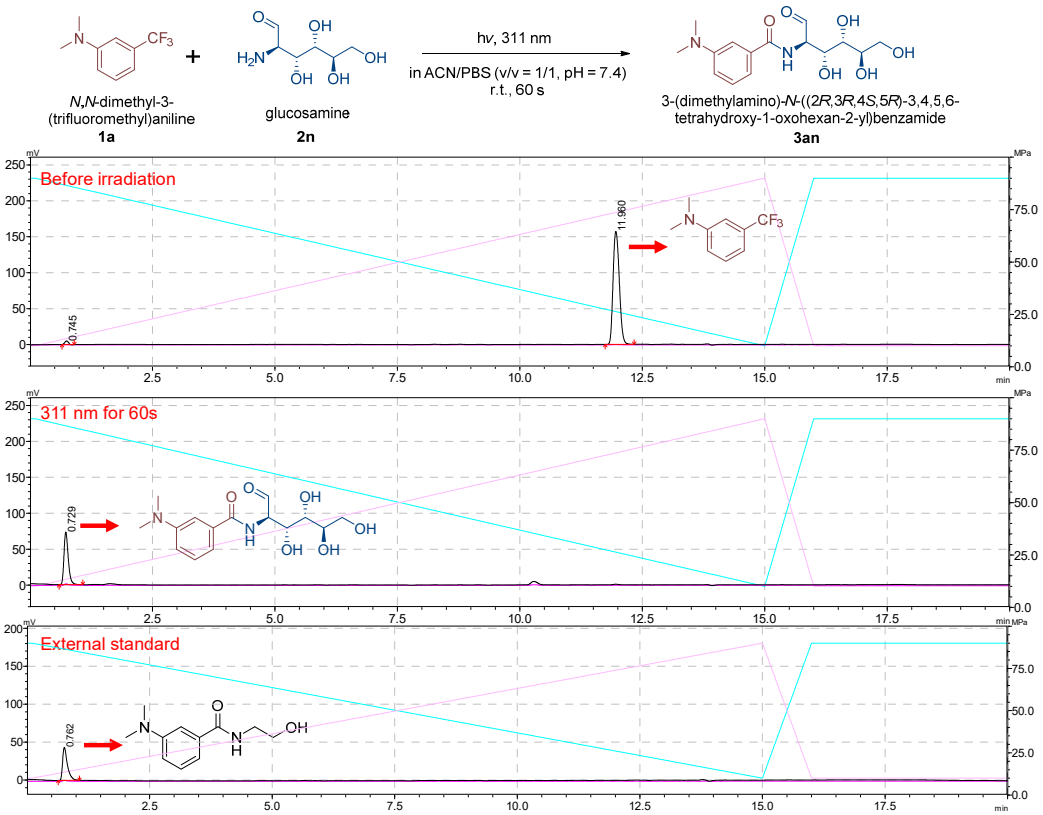
N^2-(tert-butoxycarbonyl)-N^6-(3-(dimethylamino)benzoyl)-L-lysine **(3am)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2m** (201.9 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3am** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (52.2 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.25 – 7.17 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 6.82 (dd, J = 8.2, 2.6 Hz, 1H), 6.74 (s, 1H), 5.33 (d, J = 7.8 Hz, 1H), 4.26 (d, J = 6.8 Hz, 1H), 3.37 (q, J = 6.6 Hz, 2H), 2.93 (s, 6H), 1.92 – 1.51 (m, 4H), 1.46 – 1.33 (m, 11H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.48, 169.03, 150.51, 135.24, 129.16, 115.72, 114.92, 111.87, 79.93, 53.27, 40.71, 39.84, 32.17, 28.97, 28.32, 22.56.

HRMS (ESI) calculated $C_{20}H_{32}N_3O_5^+$ $[M+H]^+$ m/z 394.2336, found 394.2330.



Item	Peak No.	Retention Time (min)	Area
Before irradiation	1	0.745	25190
	2	11.960	1391940
311 nm for 60 s	3	0.729	444535
External standard	4	0.762	297489
HPLC yield	75%		

Figure S55. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2n** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**, and the yield of **3an** was determined by external standard 3-(dimethylamino)-*N*-(2-hydroxyethyl)benzamide (**3ad**, 50 μM).

Preparation and characterization

3-(dimethylamino)-*N*-((2R,3R,4S,5R)-3,4,5,6-tetrahydroxy-1-oxohexan-2-yl)benzamide **(3an)**

In attempting to isolate the **3an**, we found that the desired conjugate **3an** is very soluble in water containing solvent system, which resulted in difficulty in the separation against the starting material, glucosamine. Therefore, we were unable to obtain a purely isolated **3an** for characterization via ^{1}H and ^{13}C NMR.

HRMS (ESI) calculated $C_{15}H_{23}N_2O_6^+$ $[M+H]^+$ m/z 327.1551, found 327.1546.

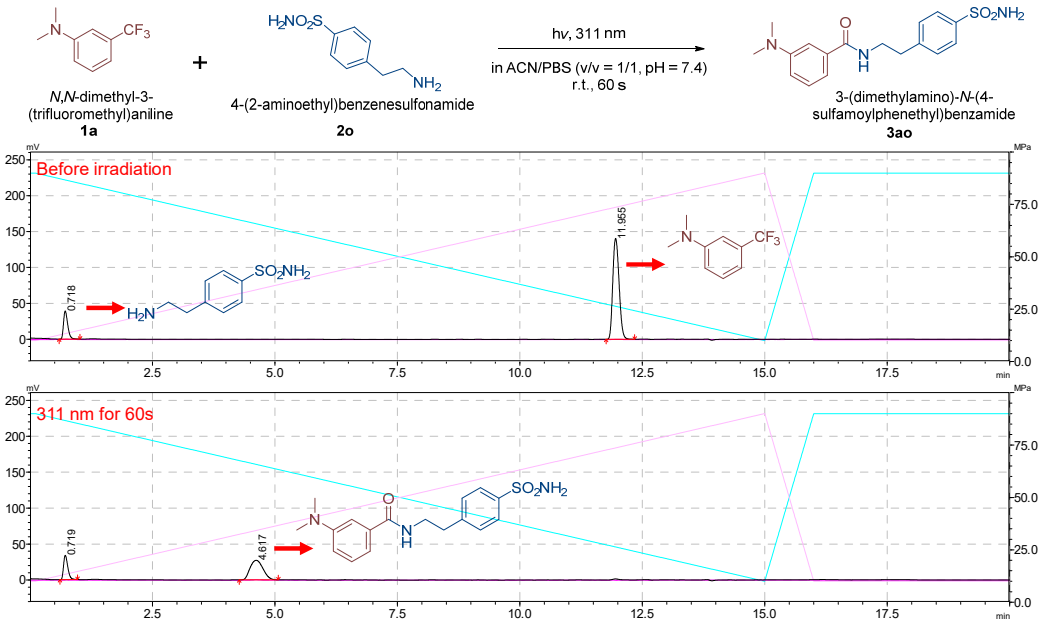


Figure S56. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2o** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-(4-sulfamoylphenethyl)benzamide **(3ao)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2o** (164.2 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II** and **3ao** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow solid (49.2 mg, 86%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (t, J = 5.6 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.28 (s, 2H), 7.23 (t, J = 7.8 Hz, 1H), 7.11 (dd, J = 2.6, 1.6 Hz, 1H), 7.08 (dt, J = 7.8, 1.2 Hz, 1H), 6.85 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 3.53 – 3.45 (m, 2H), 2.96 – 2.88 (m, 8H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 167.41, 150.70, 144.34, 142.51, 135.77, 129.64, 129.25, 126.17, 115.34, 115.29, 111.41, 40.90, 35.28, 29.49.

HRMS (ESI) calculated $C_{17}H_{22}N_3O_3S^+$ $[M+H]^+$ m/z 348.1376, found 348.1371.

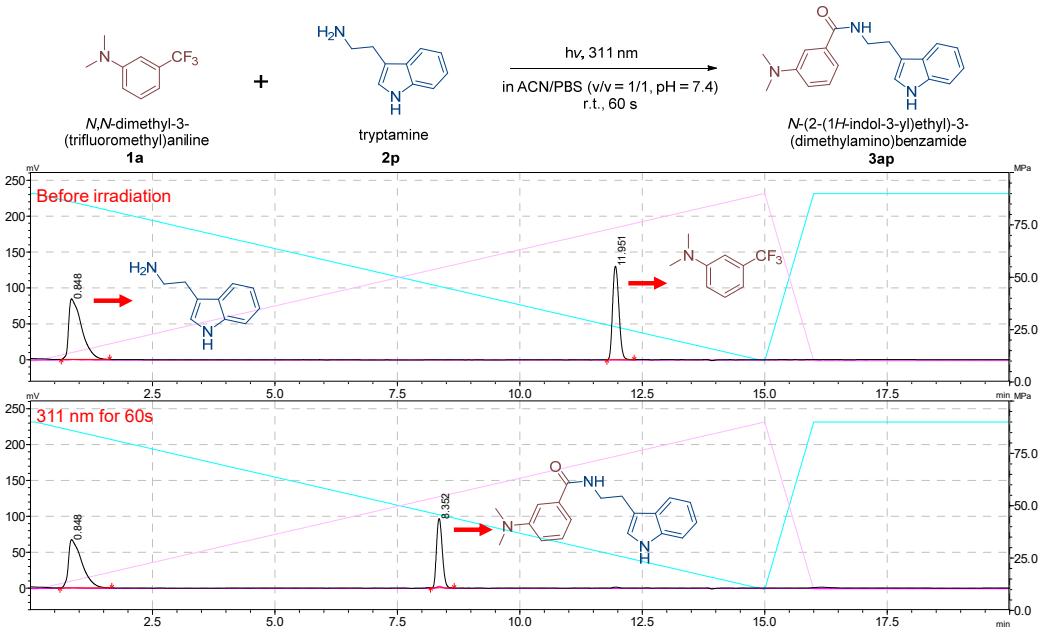


Figure S57. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2p** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-(2-(1*H*-indol-3-yl)ethyl)-3-(dimethylamino)benzamide **(3ap)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2p** (131.38 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ap** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (39 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.64 (dd, J = 7.8, 1.2 Hz, 1H), 7.35 (dt, J = 8.2, 1.0 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.17 (dq, J = 5.2, 1.2 Hz, 2H), 7.11 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.93 (ddd, J = 7.8, 1.8, 0.8 Hz, 1H), 6.80 (ddd, J = 8.4, 2.8, 0.8 Hz, 1H), 6.56 (t, J = 5.8 Hz, 1H), 3.77 (td, J = 6.8, 5.6 Hz, 2H), 3.09 – 3.05 (m, 2H), 2.90 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.67, 150.63, 136.61, 135.59, 129.19, 127.40, 122.52, 121.94, 119.29, 118.65, 115.29, 112.59, 111.57, 111.29, 40.55, 40.50, 25.32.

HRMS (ESI) calculated $C_{19}H_{22}N_3O^+$ $[M+H]^+$ m/z 308.1757, found 308.1751.

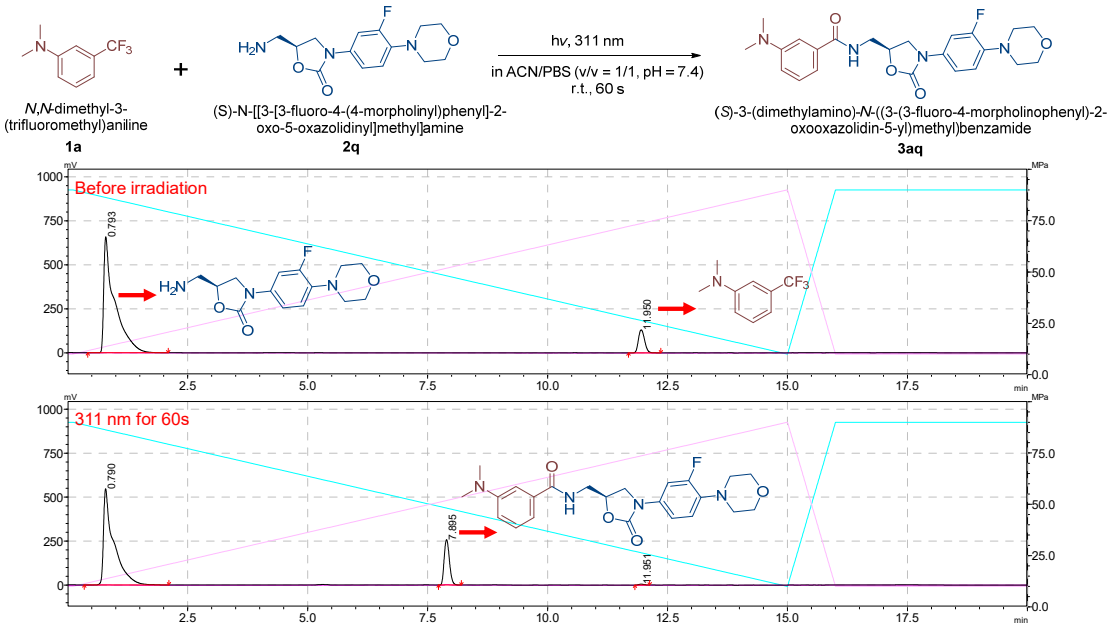


Figure S58. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2q** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

(*S*)-3-(dimethylamino)-*N*-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)benzamide **(3aq)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2q** (242.15 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3aq** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (59.1 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 14.4, 2.6 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.12 (dd, J = 2.6, 1.6 Hz, 1H), 7.01 (ddt, J = 7.6, 4.8, 1.2 Hz, 2H), 6.83 (t, J = 9.2 Hz, 1H), 6.78 (ddd, J = 8.4, 2.8, 0.8 Hz, 1H), 4.87 – 4.76 (m, 1H), 3.99 (t, J = 9.0 Hz, 1H), 3.85 – 3.72 (m, 7H), 3.01 – 2.96 (m, 4H), 2.91 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.37, 155.40 (d, J = 246.3 Hz), 154.56, 150.62, 136.41 (d, J = 8.7 Hz), 134.47, 133.01 (d, J = 10.7 Hz), 129.23, 118.79 (d, J = 4.2 Hz), 115.57, 114.40, 114.05 (d, J = 3.0 Hz), 111.11, 107.53 (d, J = 26.2 Hz), 72.17, 66.92, 50.96 (d, J = 2.9 Hz), 47.88, 42.55, 40.41.

HRMS (ESI) calculated $C_{23}H_{28}FN_4O_4^+$ $[M+H]^+$ m/z 443.2089, found 443.2085.

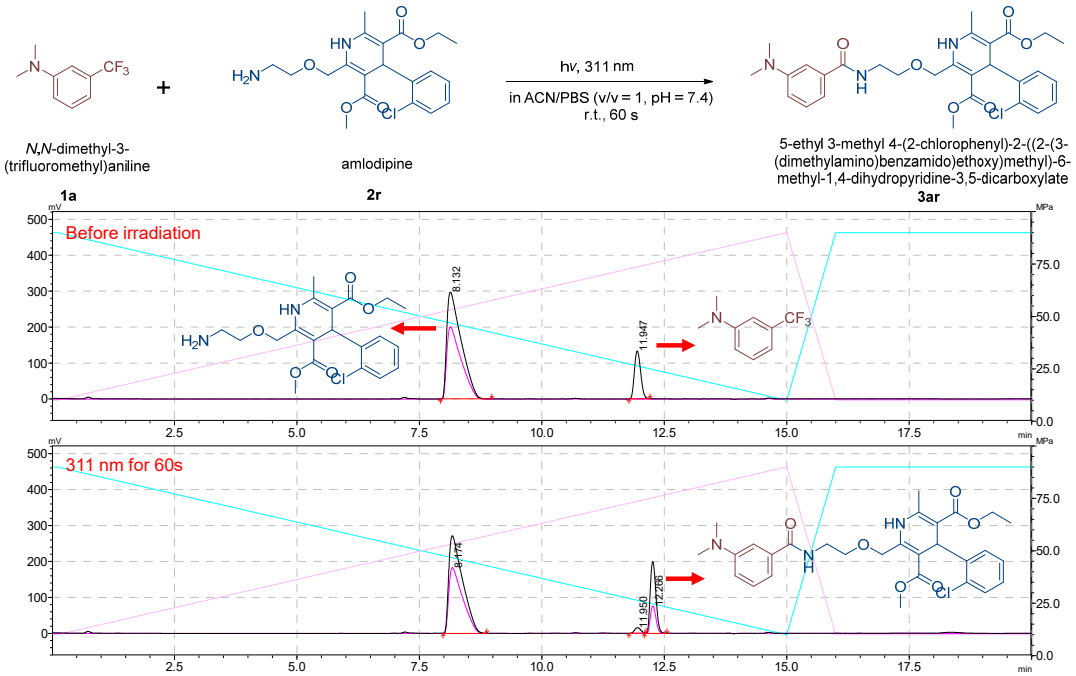


Figure S59. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **2r** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

5-ethyl 3-methyl 4-(2-chlorophenyl)-2-((2-(3-(dimethylamino)benzamido)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate **(3ar)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **2r** (335.28 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **3ar** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow solid (79.1 mg, 87%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.51 (t, J = 5.6 Hz, 1H), 8.47 (s, 1H), 7.35 – 7.06 (m, 7H), 6.86 (dd, J = 8.2, 2.8 Hz, 1H), 5.29 (s, 1H), 4.62 (q, J = 14.2 Hz, 2H), 3.96 (qq, J = 6.8, 3.8 Hz, 2H), 3.61 (t, J = 5.6 Hz, 2H), 3.50 (d, J = 7.8 Hz, 5H), 2.92 (s, 6H), 2.24 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 167.76, 167.57, 166.74, 150.75, 146.34, 145.84, 145.55, 135.55, 131.55, 131.45, 129.40, 129.22, 128.21, 127.87, 115.42, 115.31, 111.45, 102.79, 102.30, 79.65, 69.98, 66.94, 59.82, 50.94, 40.55, 37.13, 18.59, 14.53.

HRMS (ESI) calculated $C_{29}H_{34}ClKN_3O_6^+$ $[M+K]^+$ m/z 594.1768, found 594.1764.

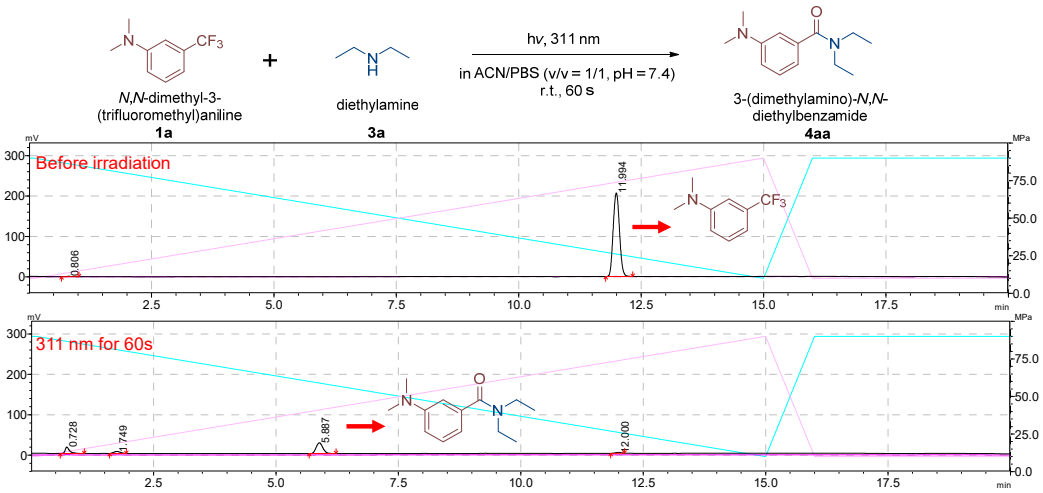


Figure S60. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N,N*-diethylbenzamide **(4aa)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3a** (60.0 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4aa** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a white solid (32.2 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, J = 7.8 Hz, 1H), 6.76 – 6.62 (m, 3H), 3.52 (s, 2H), 3.26 (s, 2H), 2.94 (s, 6H), 1.23 (d, J = 8.6 Hz, 3H), 1.11 (d, J = 10.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.08, 150.49, 138.05, 129.01, 114.00, 113.02, 110.15, 43.24, 40.49, 39.08, 14.32, 12.92.

HRMS (ESI) calculated $C_{13}H_{21}N_2O^+$ $[M+H]^+$ m/z 221.1648, found 221.1641.

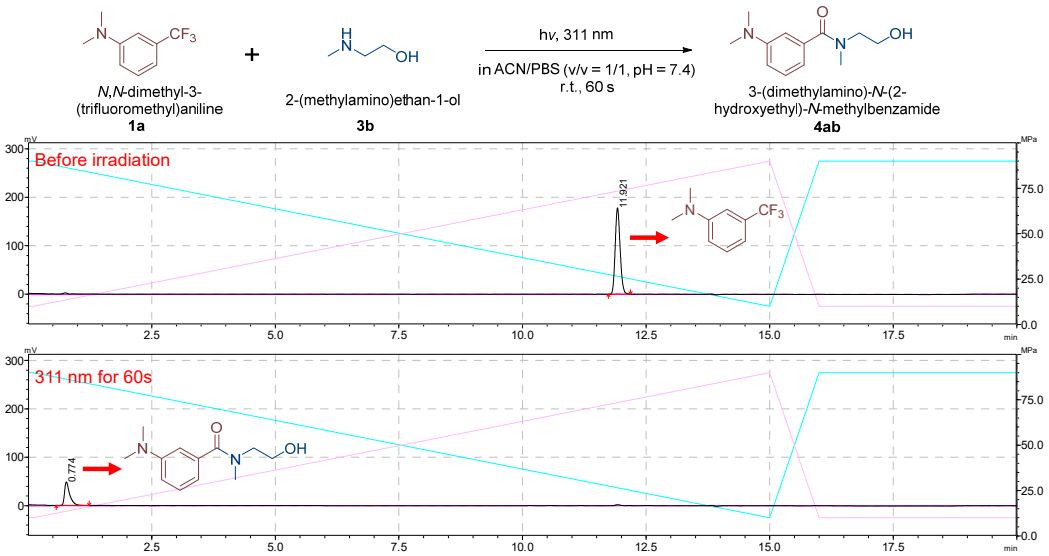


Figure S61. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3b** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-(2-hydroxyethyl)-*N*-methylbenzamide **(4ab)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3b** (61.6 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ab** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (31.5 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 9.8, 7.2 Hz, 1H), 6.77 – 6.66 (m, 3H), 3.90 – 3.61 (m, 4H), 3.11 – 2.99 (m, 3H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.28, 150.51, 136.54, 129.00, 114.70, 113.72, 110.91, 61.21, 51.14, 40.47, 38.77.

HRMS (ESI) calculated $C_{12}H_{19}N_2O_2^+$ $[M+H]^+$ m/z 223.1441, found 223.1440.

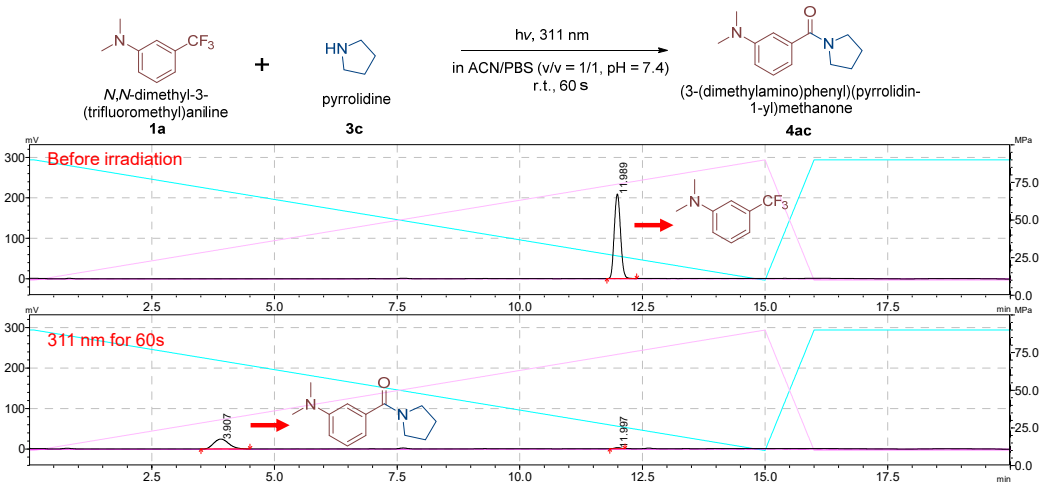


Figure S62. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3c** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

(3-(dimethylamino)phenyl)(pyrrolidin-1-yl)methanone **(4ac)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3c** (58.3mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ac** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (30.1mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 8.4, 7.4 Hz, 1H), 6.78 (dd, J = 2.8, 1.6 Hz, 1H), 6.75 – 6.70 (m, 2H), 3.92 (s, 2H), 3.67 (s, 4H), 3.45 (s, 2H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.62, 150.43, 136.98, 129.16, 114.76, 113.45, 110.92, 61.08, 60.79, 53.49, 49.75, 40.48.

HRMS (ESI) calculated $C_{13}H_{19}N_2O^+$ $[M+H]^+$ m/z 219.1492, found 219.1490.

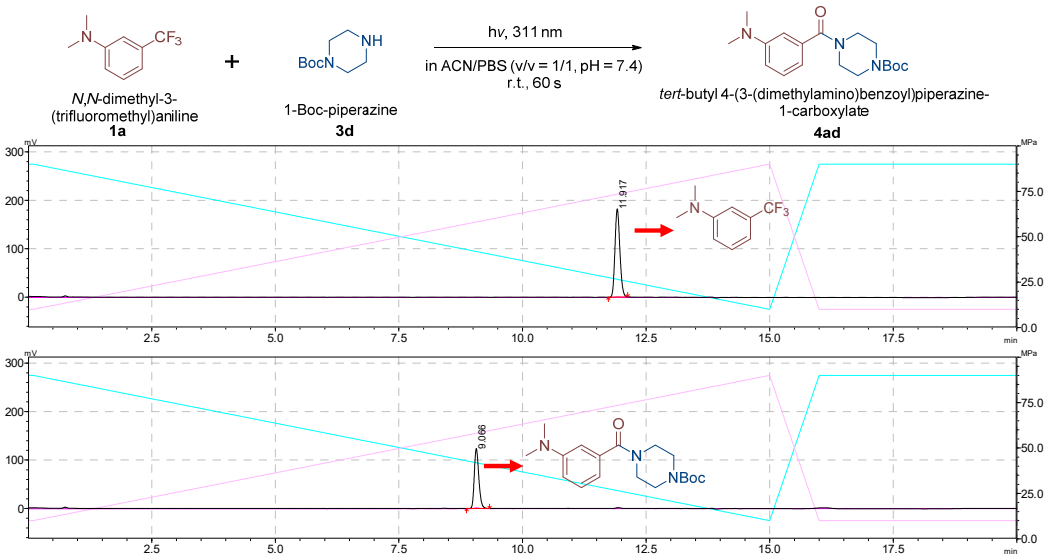


Figure S63. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3d** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

tert-butyl 4-(3-(dimethylamino)benzoyl)piperazine-1-carboxylate **(4ad)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3d** (152.7mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ad** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (44.3 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 8.4, 7.4 Hz, 1H), 6.75 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 6.71 (dd, J = 2.8, 1.4 Hz, 1H), 6.65 (dt, J = 7.4, 1.2 Hz, 1H), 3.72 (s, 2H), 3.57 – 3.27 (m, 6H), 2.95 (s, 6H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.41, 154.62, 150.61, 136.30, 129.15, 114.38, 113.60, 110.65, 80.29, 40.42, 28.38.

HRMS (ESI) calculated $C_{18}H_{28}N_3O_3^+$ $[M+H]^+$ m/z 334.2125, found 334.2123.

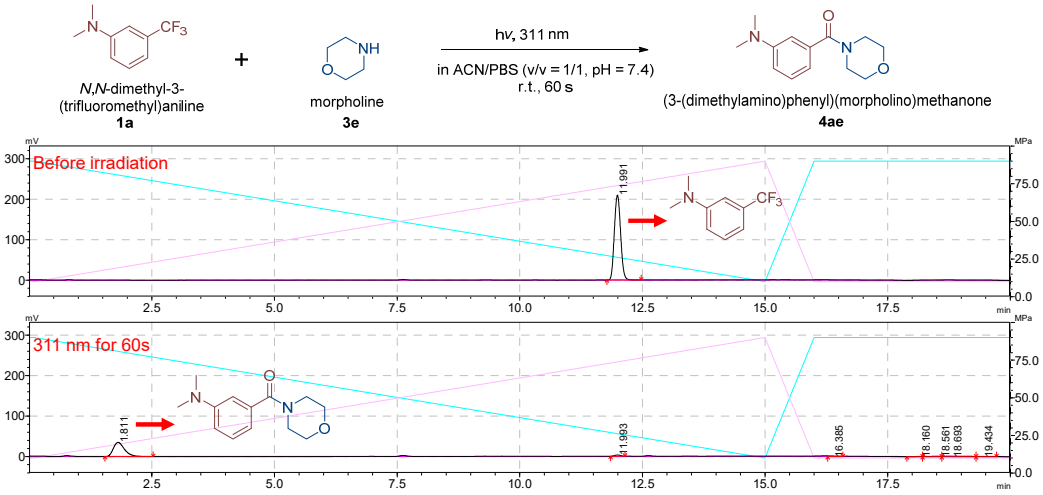


Figure S64. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3e** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

(3-(dimethylamino)phenyl)(morpholino)methanone **(4ae)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3e** (71.4mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ae** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (31.1 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, J = 8.2, 7.4, 0.8 Hz, 1H), 6.77 – 6.71 (m, 2H), 6.66 (dt, J = 7.6, 1.2 Hz, 1H), 3.87 – 3.36 (m, 8H), 2.96 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.23, 150.63, 136.18, 129.10, 114.46, 113.58, 110.77, 66.99, 40.44.

HRMS (ESI) calculated $C_{13}H_{19}N_2O_2^+$ $[M+H]^+$ m/z 235.1441, found 235.1439.

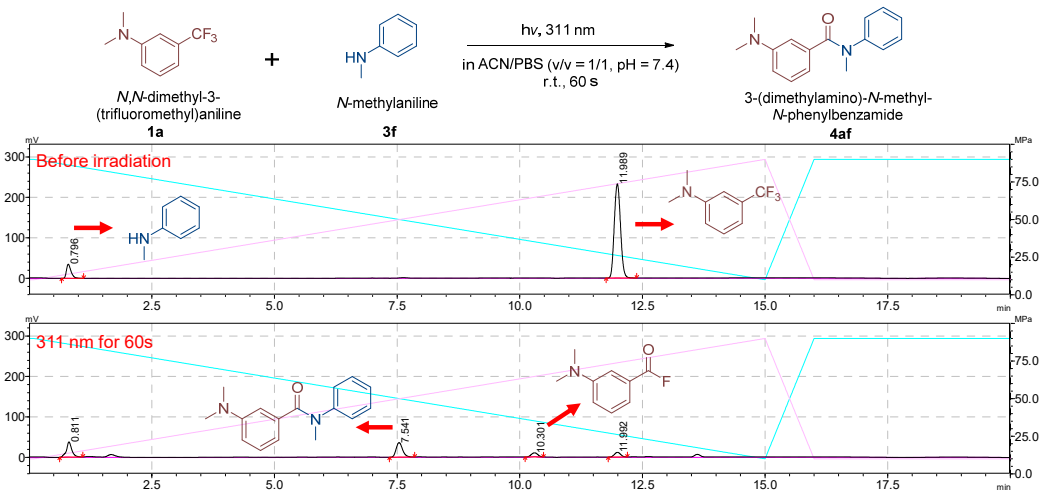


Figure S65. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3f** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-(dimethylamino)-*N*-methyl-*N*-phenylbenzamide **(4af)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3f** (87.9 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4af** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (33.2 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.16 – 7.10 (m, 1H), 7.06 (dd, J = 8.6, 1.4 Hz, 2H), 6.99 (t, J = 7.8 Hz, 1H), 6.69 (dd, J = 2.6, 1.4 Hz, 1H), 6.60 (dt, J = 8.2, 2.2 Hz, 2H), 3.49 (s, 3H), 2.80 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.31, 149.89, 145.32, 136.38, 129.05, 128.30, 126.74, 126.24, 117.18, 113.76, 113.24, 40.45, 38.43.

HRMS (ESI) calculated $C_{16}H_{19}N_2O^+$ $[M+H]^+$ m/z 255.1492, found 255.1489.

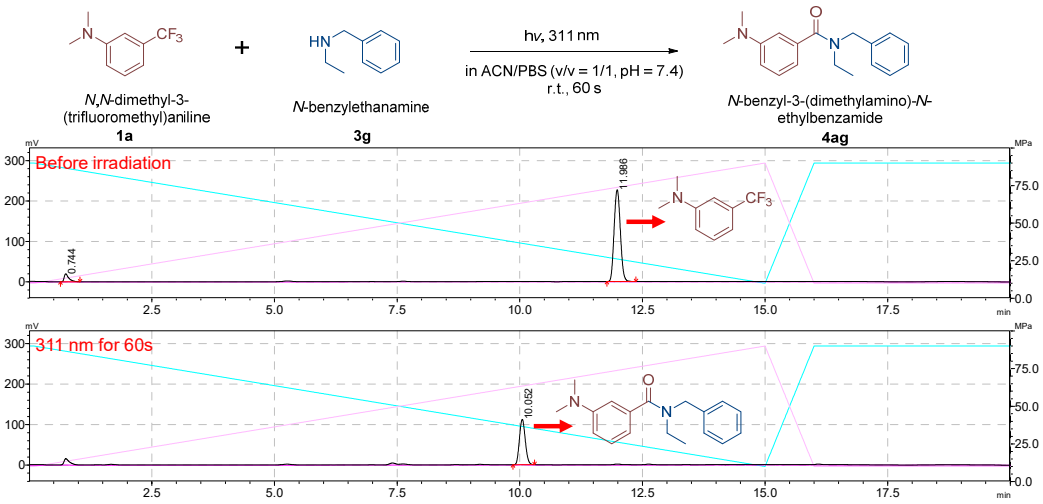


Figure S66. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3g** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-benzyl-3-(dimethylamino)-N-ethylbenzamide **(4ag)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3g** (110.9 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ag** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (38.7 mg, 84%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.35 (d, J = 6.4 Hz, 3H), 7.31 – 7.17 (m, 3H), 6.75 (s, 1H), 6.68 – 6.61 (m, 2H), 4.57 (d, J = 82.0 Hz, 2H), 3.25 (d, J = 86.2 Hz, 2H), 2.97 – 2.67 (m, 6H), 1.15 – 0.93 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 173.08, 150.47, 136.87, 129.20, 128.80, 128.71, 128.44, 128.21, 127.48, 127.00, 114.41, 113.54, 110.46, 53.16, 51.54, 46.93, 40.37.

HRMS (ESI) calculated $C_{18}H_{23}N_2O^+$ $[M+H]^+$ m/z 283.1805, found 283.1803.

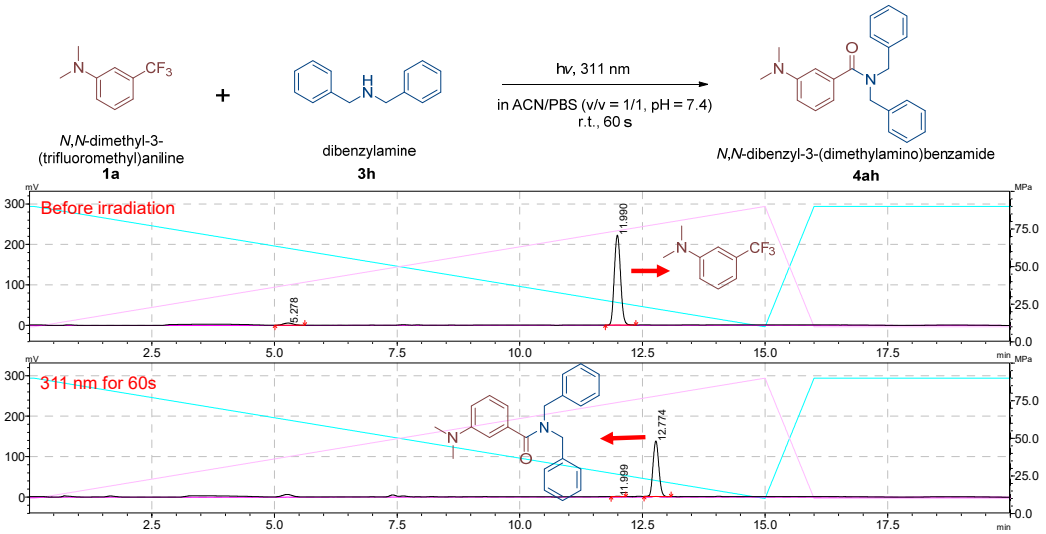


Figure S67. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3h** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N,N-dibenzyl-3-(dimethylamino)benzamide **(4ah)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3h** (161.8 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4ah** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (48.5 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.12 (m, 11H), 6.83 – 6.77 (m, 2H), 6.69 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 4.71 (s, 2H), 4.42 (s, 2H), 2.82 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.10, 150.47, 136.90, 129.26, 128.85, 128.76, 128.50, 128.47, 128.25, 127.54, 127.06, 127.04, 114.41, 113.58, 110.46, 51.60, 47.01, 40.38.

HRMS (ESI) calculated $C_{23}H_{25}N_2O^+$ $[M+H]^+$ m/z 345.1961, found 345.1962.

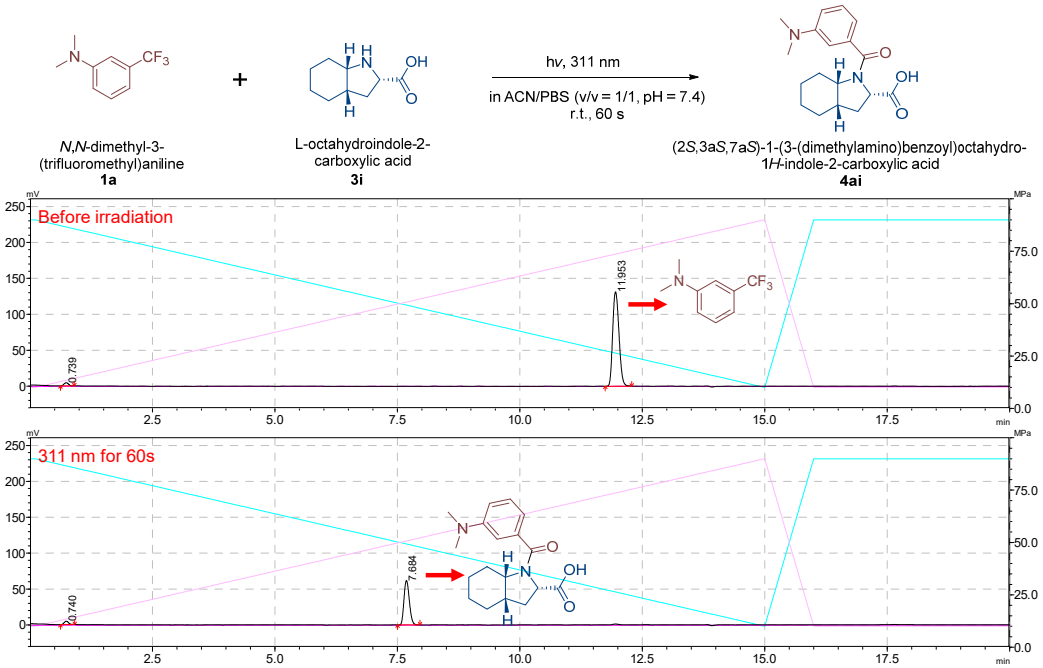


Figure S68. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **3i** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

(2*S*,3a*S*,7a*S*)-1-(3-(dimethylamino)benzoyl)octahydro-1*H*-indole-2-carboxylic acid **(4hi)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **3i** (138.8 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **4hi** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a white solid (40.4 mg, 78%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.21 (t, J = 7.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.62 (dd, J = 4.6, 3.2 Hz, 2H), 4.41 (dd, J = 9.8, 8.4 Hz, 1H), 3.55 (s, 1H), 2.90 (s, 6H), 2.33 (dt, J = 13.4, 6.6 Hz, 1H), 2.27 – 2.12 (m, 1H), 1.93 (td, J = 12.6, 9.8 Hz, 1H), 1.74 – 1.42 (m, 5H), 1.40 – 1.11 (m, 2H), 0.88 (q, J = 13.4, 12.7 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 174.04, 169.78, 150.39, 138.43, 129.28, 114.03, 113.37, 109.99, 59.33, 58.68, 40.47, 37.35, 30.58, 28.55, 25.59, 23.86, 20.05.

HRMS (ESI) calculated $C_{18}H_{25}N_2O_3^+$ $[M+H]^+$ m/z 317.1860, found 317.1857.

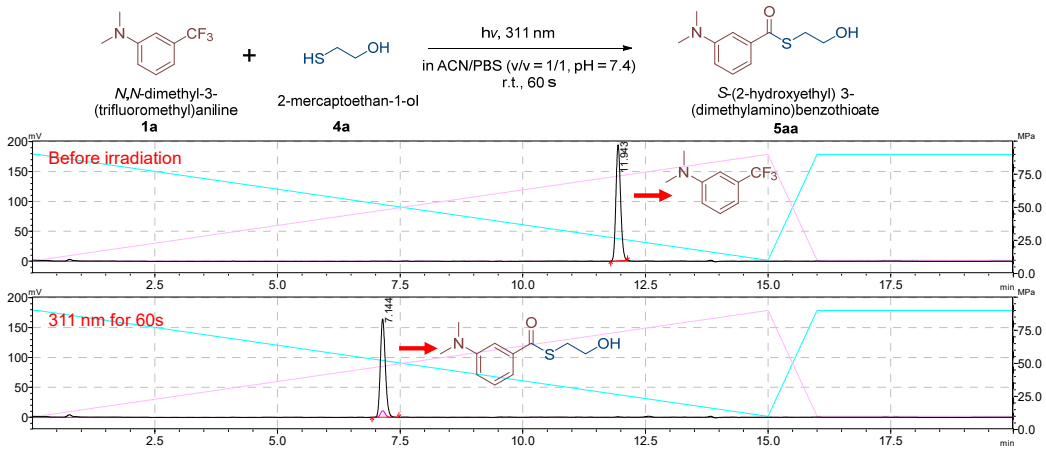


Figure S69. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **4a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

S-(2-hydroxyethyl) 3-(dimethylamino)benzothioate **(5aa)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **4a** (64.1 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **5aa** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow oil (31.1 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 3H), 6.92 (ddd, J = 7.8, 2.8, 1.2 Hz, 1H), 3.85 (t, J = 6.0 Hz, 2H), 3.26 (t, J = 6.2 Hz, 2H), 2.99 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.07, 150.53, 137.61, 129.28, 117.35, 115.53, 110.36, 61.96, 40.48, 31.96.

HRMS (ESI) calculated $C_{11}H_{16}NO_2S^+$ $[M+H]^+$ m/z 226.0896, found 226.0895.

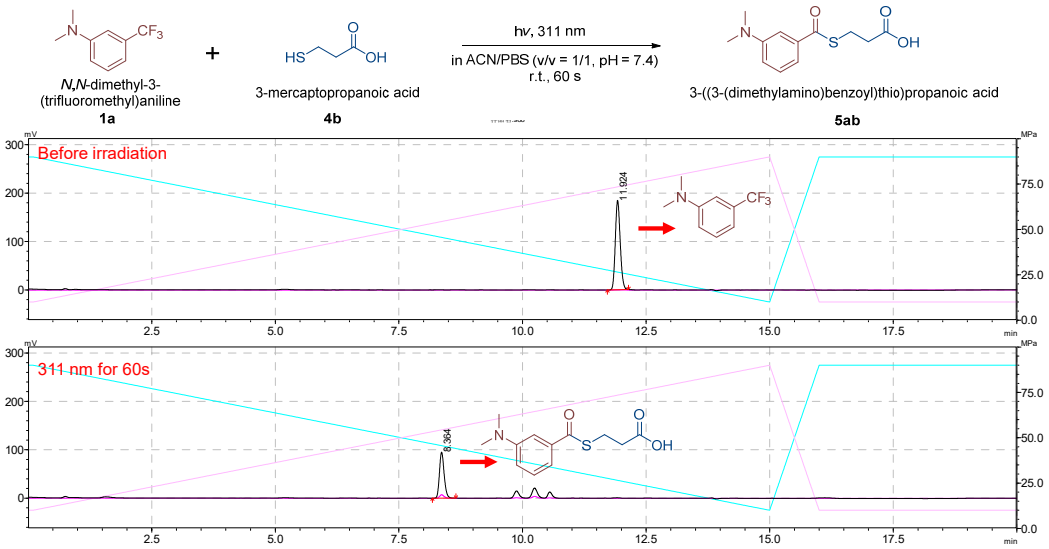


Figure S70. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **4b** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

3-((3-(dimethylamino)benzoyl)thio)propanoic acid **(5ab)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **4b** (87.0 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **5ab** was isolated by flash chromatography (DCM : MeOH = 10 : 1) as a yellow solid (27.1 mg, 65%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 – 7.30 (m, 1H), 7.19 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 7.11 (dd, J = 2.6, 1.6 Hz, 1H), 7.02 (ddd, J = 8.4, 2.8, 0.8 Hz, 1H), 3.18 (t, J = 6.8 Hz, 2H), 2.95 (s, 6H), 2.60 (t, J = 6.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.13, 173.44, 150.88, 137.68, 130.03, 117.83, 114.86, 109.57, 34.53, 24.46.

HRMS (ESI) calculated $C_{12}H_{16}NO_3S^+$ $[M+H]^+$ m/z 254.0845, found 254.0845.

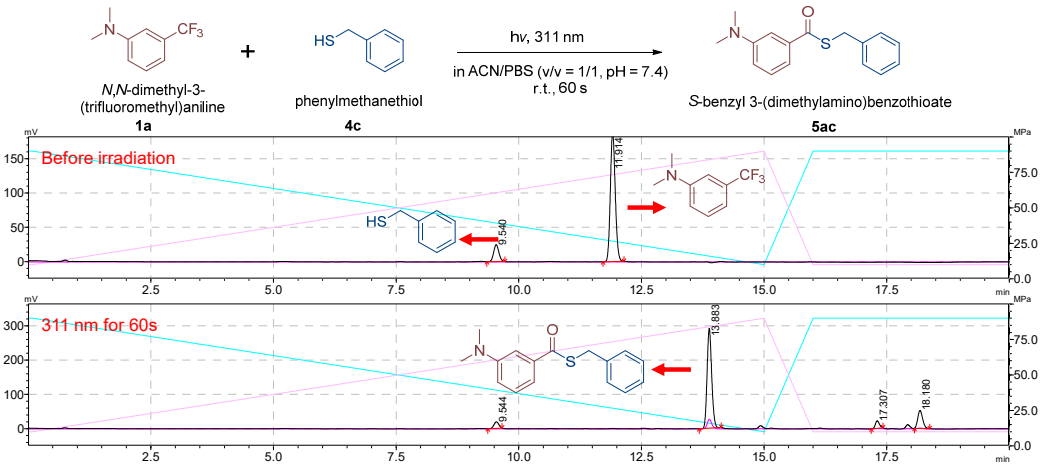


Figure S71. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **4c** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

S-benzyl 3-(dimethylamino)benzothioate **(5ac)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **4c** (101.8 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **5ac** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (27.1 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.32 – 7.27 (m, 3H), 7.27 – 7.20 (m, 3H), 6.89 (ddd, J = 7.8, 2.8, 1.3 Hz, 1H), 4.29 (s, 2H), 2.97 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.16, 150.56, 137.70, 137.63, 129.25, 129.01, 128.63, 127.26, 117.18, 115.46, 110.38, 40.48, 33.41.

HRMS (ESI) calculated $C_{16}H_{17}KNOS^+$ $[M+K]^+$ m/z 310.0662, found 310.0670.

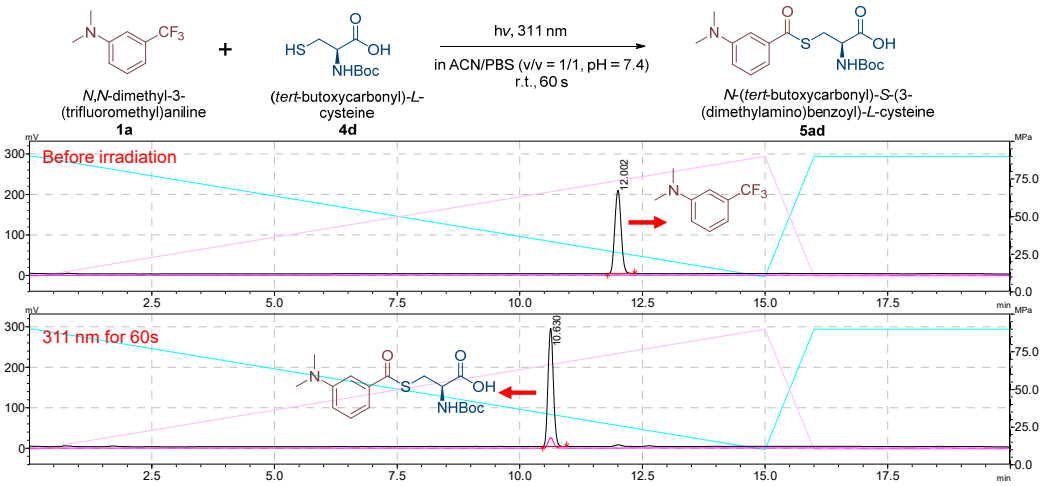


Figure S72. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **4d** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

N-(tert-butoxycarbonyl)-*S*-(3-(dimethylamino)benzoyl)-L-cysteine **(5ad)**

Preparation: 1a (31.0 mg, 0.16 mmol) and **4d** (181.4 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **5ad** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (49.8 mg, 83%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (s, 1H), 7.33 (dt, J = 7.8, 1.4 Hz, 1H), 7.29 (d, J = 7.8 Hz, 2H), 6.98 – 6.92 (m, 1H), 4.67 – 4.54 (m, 1H), 3.62 (dd, J = 14.2, 4.5 Hz, 1H), 3.49 (dd, J = 14.4, 6.8 Hz, 1H), 2.98 (s, 6H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 192.13, 174.12, 155.78, 150.35, 137.35, 129.36, 117.94, 116.23, 110.95, 80.55, 53.60, 40.75, 30.75, 28.28.

HRMS (ESI) calculated $C_{17}H_{25}N_2O_5S^+$ $[M+H]^+$ m/z 369.1479, found 369.1477.

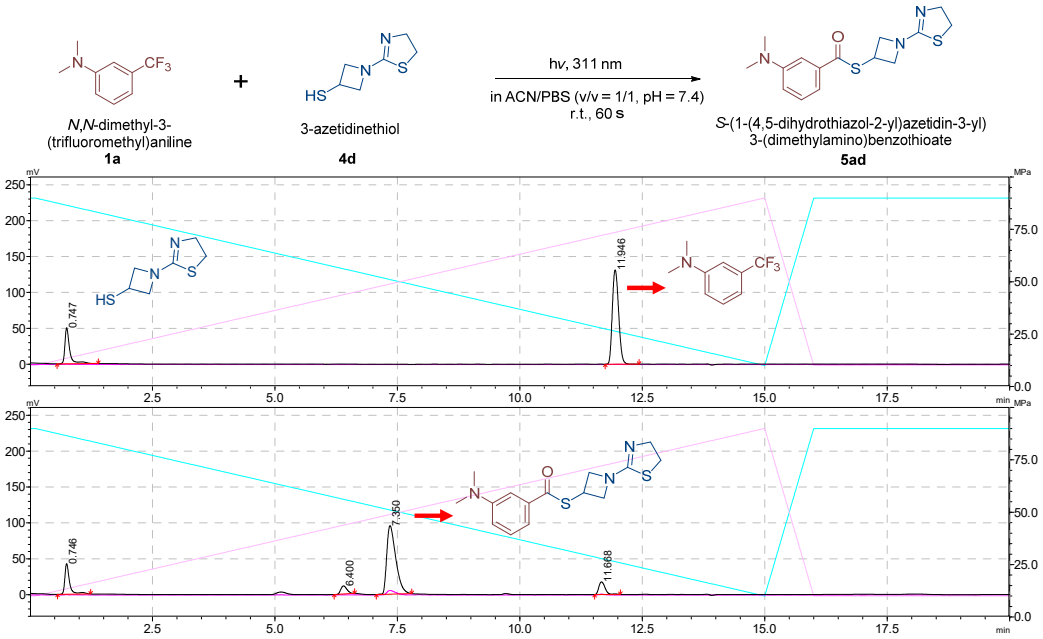


Figure S73. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and **4e** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I**.

Preparation and characterization

S-(1-(4,5-dihydrothiazol-2-yl)azetidin-3-yl) 3-(dimethylamino)benzothioate **(5ae)**

Preparation: 1a (31.0 mg, 0.16mmol) and **4e** (142.9 mg, 0.82 mmol) in 200 mL mixture of ACN/PBS (v/v = 1/1, pH = 7.4) were performed for the **general procedure II**, and **5ae** was isolated by flash chromatography (PE : EtOAc = 2 : 1) as a yellow oil (29.3 mg, 56%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.38 – 7.29 (m, 1H), 7.17 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 7.08 (dd, J = 2.6, 1.6 Hz, 1H), 7.03 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 4.49 – 4.33 (m, 3H), 3.88 (t, J = 7.6 Hz, 2H), 3.86 – 3.81 (m, 2H), 3.34 (d, J = 7.5 Hz, 2H), 2.94 (s, 6H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 191.60, 163.13, 150.91, 137.18, 130.15, 118.12, 114.91, 109.56, 61.17, 58.72, 40.38, 36.27, 32.21.

HRMS (ESI) calculated $C_{15}H_{20}N_3OS_2^+$ $[M+H]^+$ m/z 322.1042, found 322.1040.

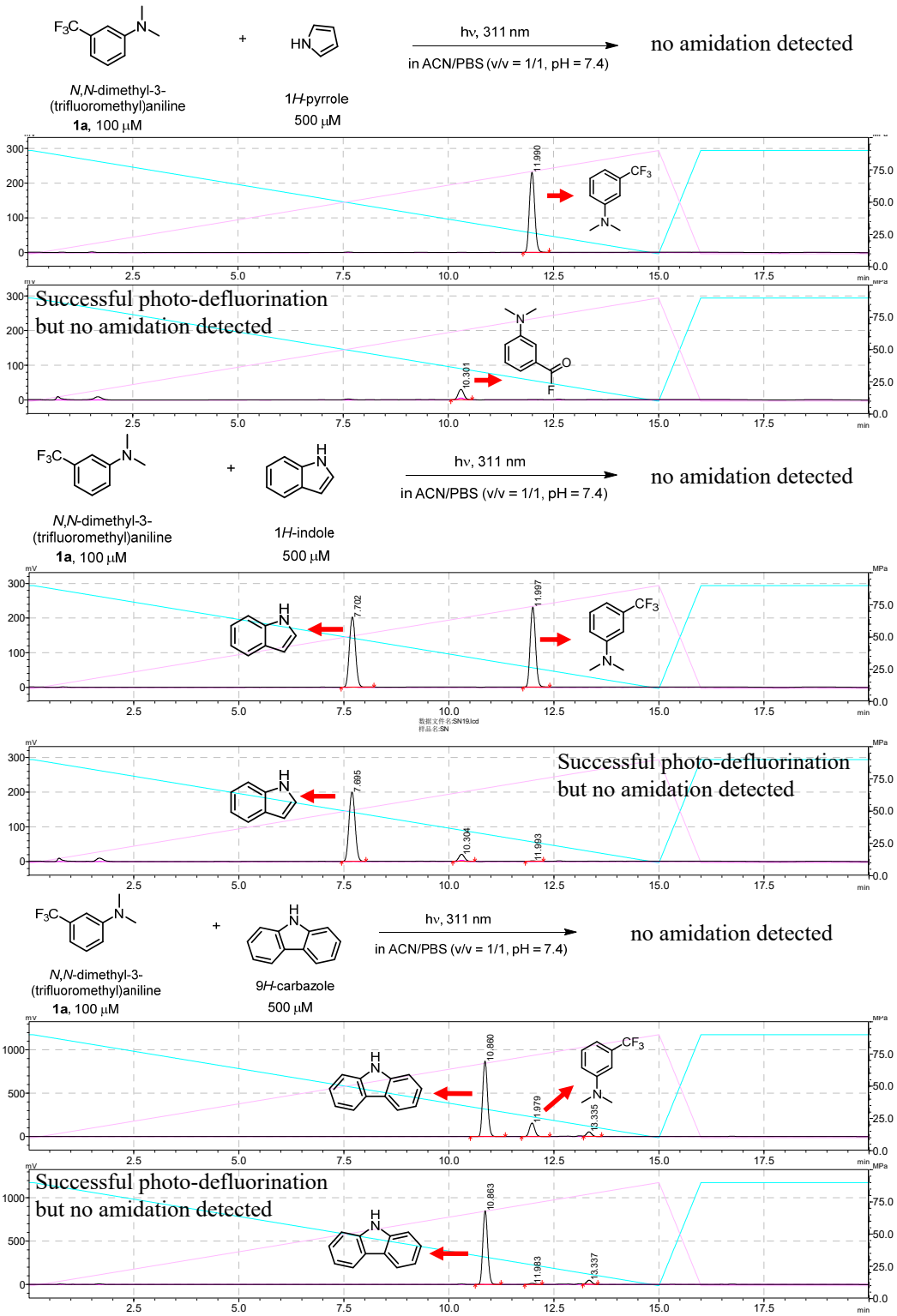


Figure S74. HPLC-MS analysis of the photo-DAFEx reaction between **1a** (100 μM) and pyrrole/indole/carbazole (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) upon 311 nm irradiation according to the **general procedure I.**

4. Peptide cyclization and modification via the photo-DAFEx reactions

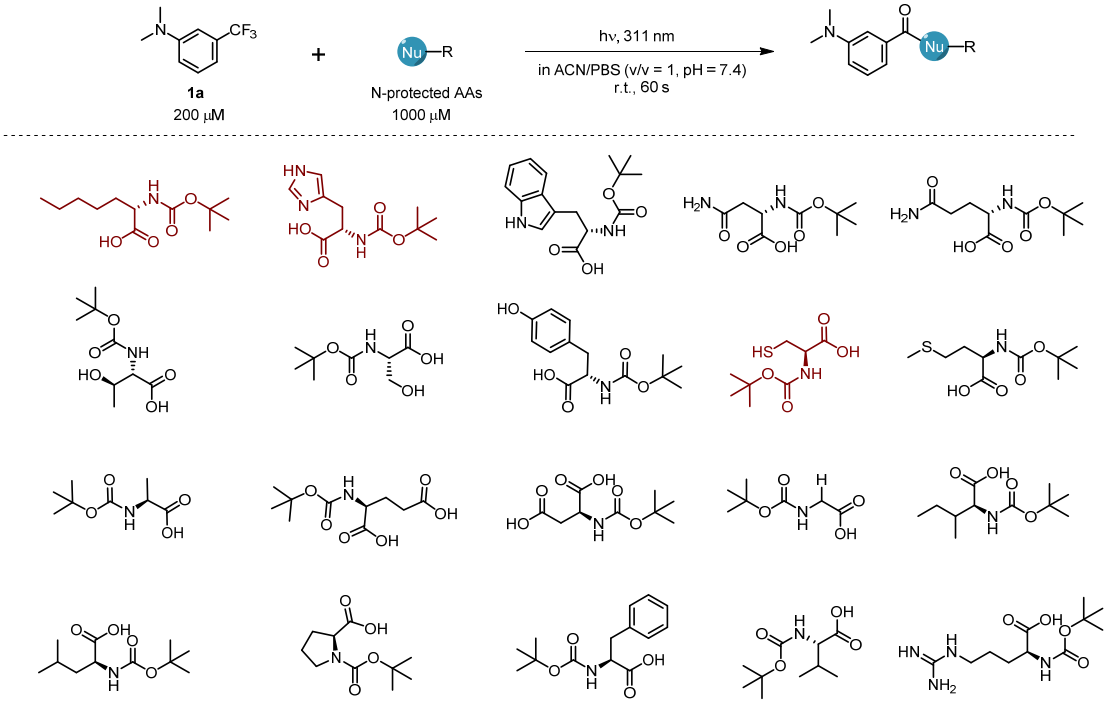
4.1 Studies on the chemical selectivity of the photo-DAFEx reaction toward natural amino acids (NAAs)

Stock solution:

- ✓ *N*-Boc protected NAAs in PBS (5.0 mM for each one);
- ✓ **1a** (1.0 mM) in ACN/PBS (v/v = 1/1, pH = 7.4).

100 μL of **1a** stock solution, 100 μL of *N*-Boc protected NAAs stock solutions and 800 μL ACN/PBS (v/v = 1/1, pH = 7.4) were mixed and irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected and was subjected to HPLC-MS analysis, and the yields were determined by external standard calibration.

Table S6. The reactivity screening for the photo-DAFEx chemistry (**5a**) towards natural amino acid residues based on HPLC-MS analysis.



Note: **1a** (100 μM) and one selected natural amino acid (500 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. Then the sample was collected for HPLC-MS analysis.

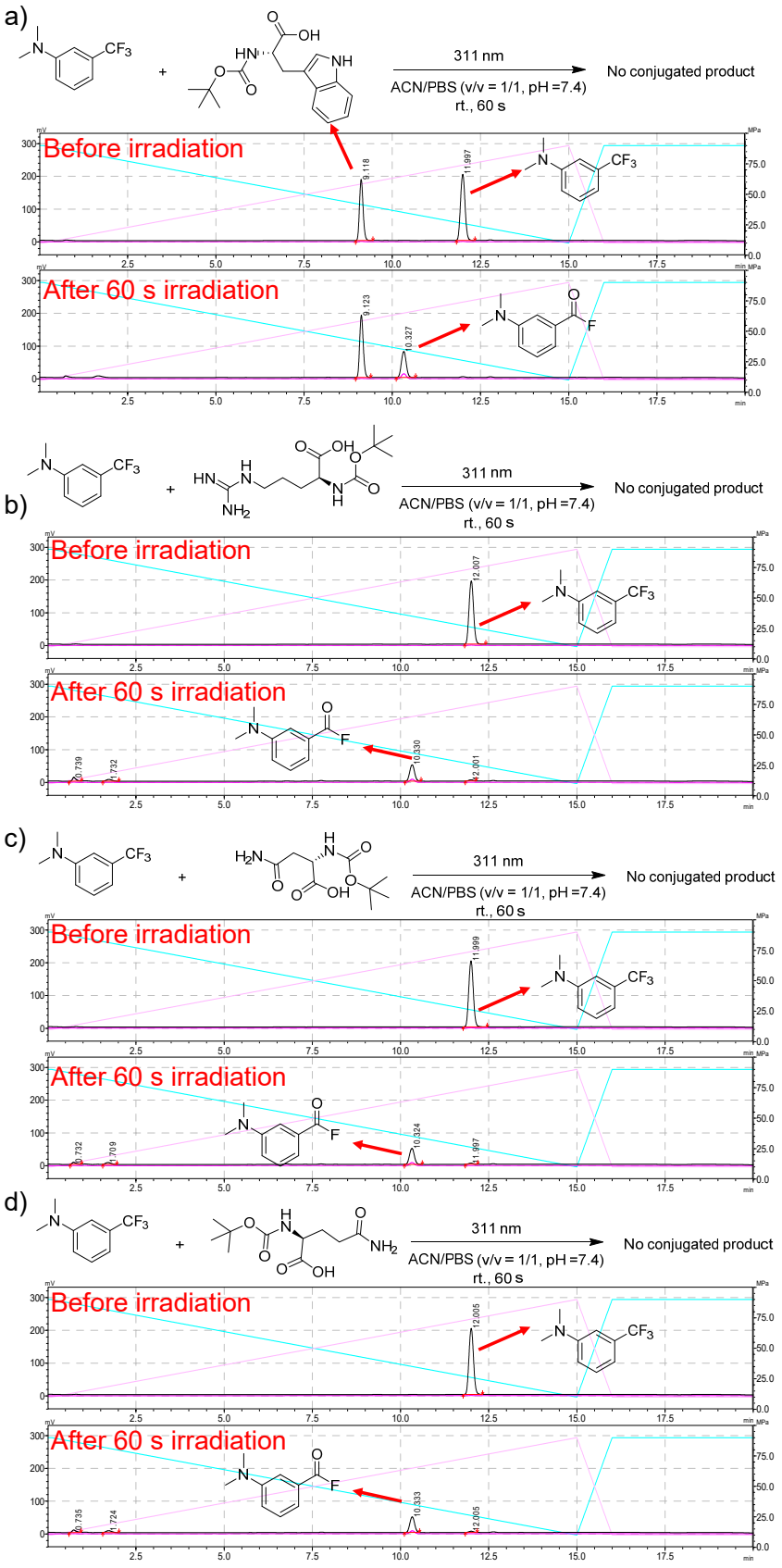
4.2 Competitive reactions among the preferred NAAs

NAAs stock solution:

- ✓ *N*-terminal Boc protected L-histidine, L-cysteine and L-lysine in PBS (5.0 mM for each one);
- ✓ *N*-terminal Boc protected L-cysteine and L-lysine in PBS (5.0 mM for each one);
- ✓ *N*-terminal Boc protected L-histidine and L-lysine in PBS (5.0 mM for each one);
- ✓ *N*-terminal Boc protected L-histidine and L-cysteine in PBS (5.0 mM for each one).

Reactant stock solution: **1a** (1.0 mM) in ACN/PBS (v/v = 1/1, pH = 7.4).

100 μL of **1a** stock solution, 100 μL of AAs stock solutions and 800 μL ACN/PBS (v/v = 1/1, pH = 7.4) were mixed and irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yields were determined by external calibration.


a)
311 nm
ACN/PBS (v/v = 1/1, pH =7.4)
rt., 60 s
No conjugated product
Before irradiation
After 60 s irradiation
b)
311 nm
ACN/PBS (v/v = 1/1, pH =7.4)
rt., 60 s
No conjugated product
Before irradiation
After 60 s irradiation
c)
311 nm
ACN/PBS (v/v = 1/1, pH =7.4)
rt., 60 s
No conjugated product
Before irradiation
After 60 s irradiation
d)
311 nm
ACN/PBS (v/v = 1/1, pH =7.4)
rt., 60 s
No conjugated product
Before irradiation
After 60 s irradiation

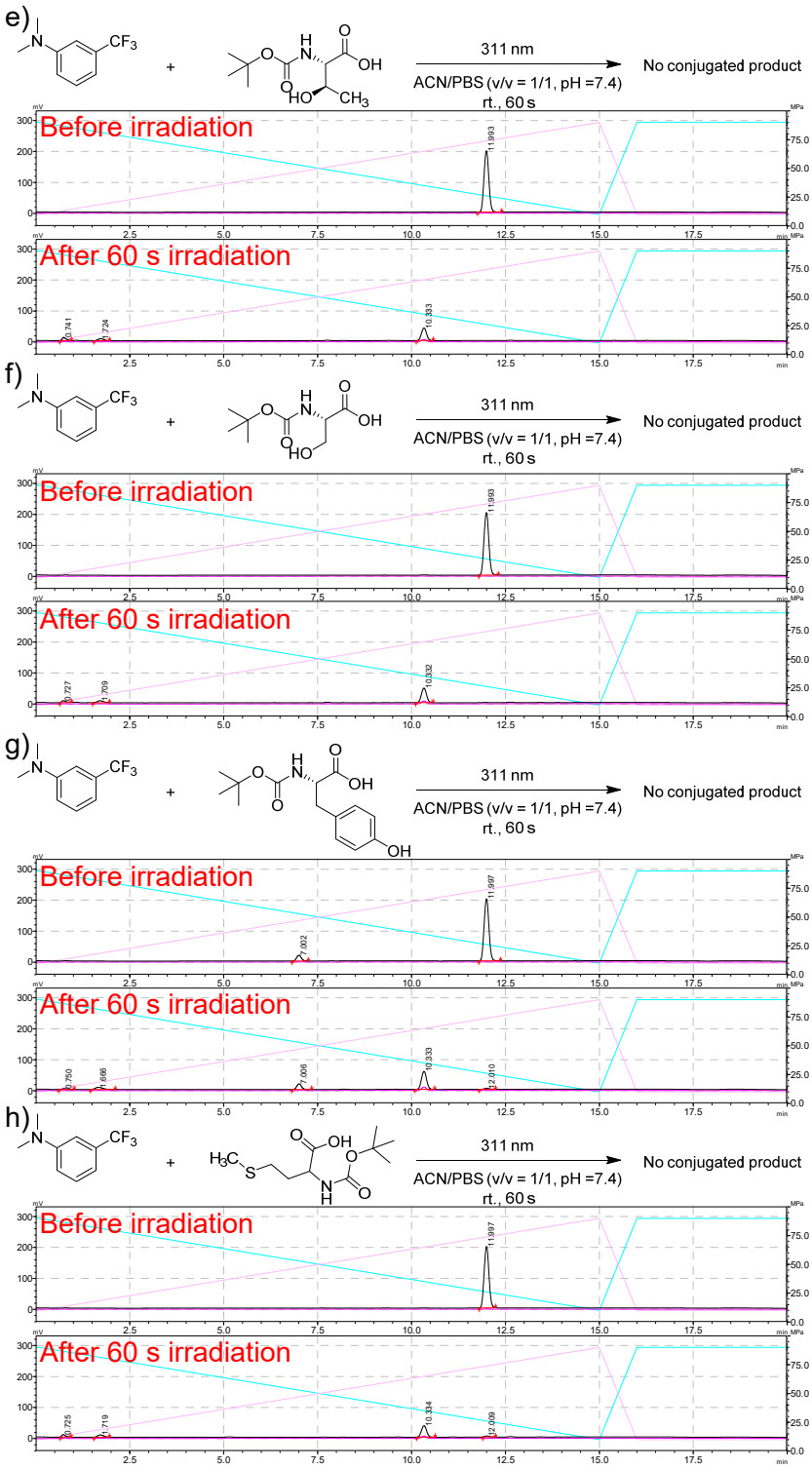
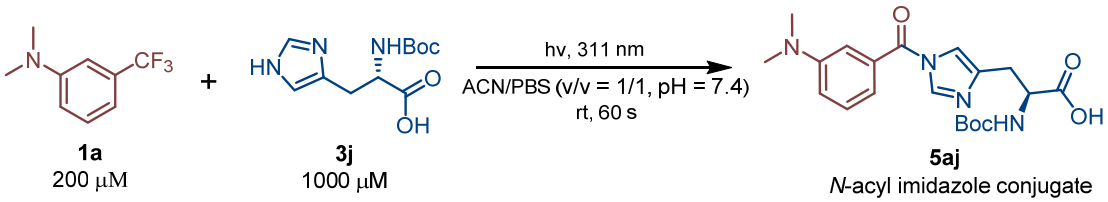
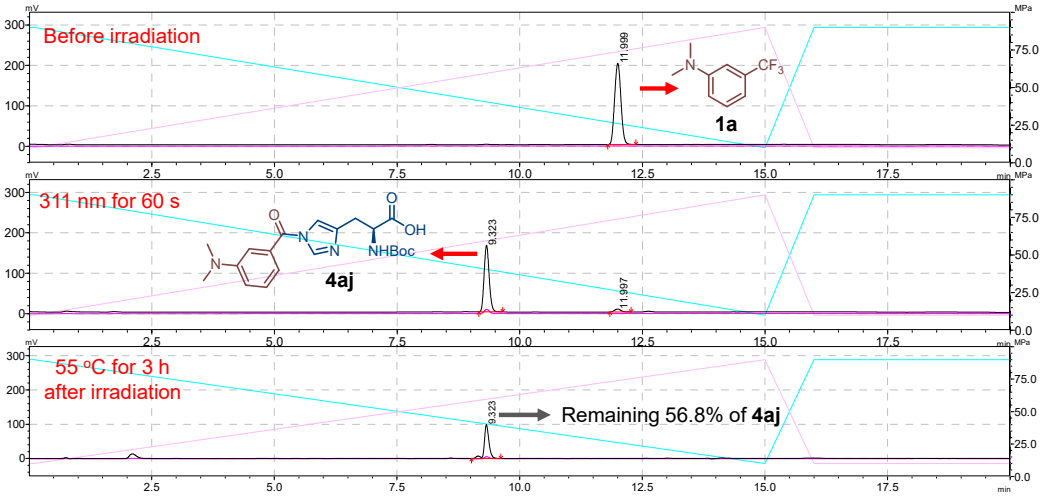


Figure S75. HPLC-MS results for screening the photo-DAFEx reaction between **1a** (100 μM) and the *N*-terminal Boc protected NAAs in ACN/PBS (v/v = 1/1, pH = 7.4).





Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	1	11.999	1797506
311 nm for 60 s	2	9.323	1175588
	3	11.997	65071
55 °C for 3 h after irradiation	4	9.323	668035

Figure S76. HPLC-MS results for the photo-DAFEx reaction between **1a** (200 μM) and *N*-terminal Boc protected histidine (1000 μM) in ACN/PBS (v/v = 1/1, pH = 7.4), and subsequent stability test under 55 °C incubation for 3 h in ACN/PBS (v/v = 1/1, pH = 7.4). The stability test was started after the complete formation of **4aj** via the photo-DAFEx from 1a.

In attempting to isolate the **4aj**, we found that the desired conjugate **4aj** is hydrolysed in water containing solvent system during the concentration procedure. After trying for several time, we were unable to obtain an isolated **4aj** as a pure compound for characterization via ^{1}H and ^{13}C NMR.

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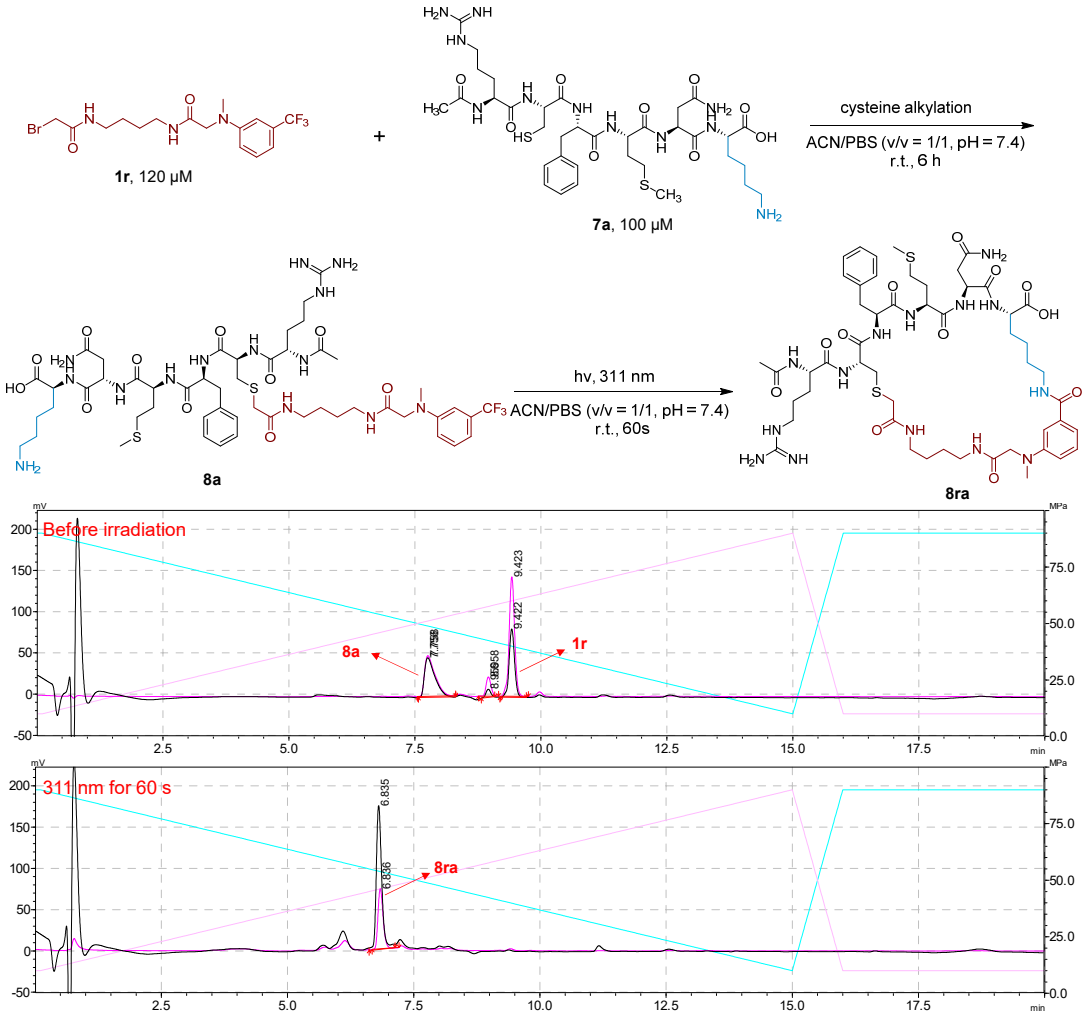
4.3 Peptide cyclization via intramolecular photo-DAFEx reactions



Item	Peak No.	Time (min)	Area (under 254 nm detecting)
Before irradiation	1	7.758	712067
	2	9.423	1105858
311 nm for 60 s	3	6.836	524145
Conversion		74 %	

Figure S77. Schematic illustration of peptide, Ac-RCFMNK-COOH, cyclization and corresponding HPLC traces for determination of the conversion. Reaction conditions: **1r** (120 μM) and **7a** (100 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were incubated at 37 °C to alkylate the cysteine residue on the peptide. After incubation for 6 h, the mixture was irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The resulting sample was collected for HPLC-MS analysis, and the conversion was determined by the integrated area ratio between **8a** and **8ra** in the HPLC traces.

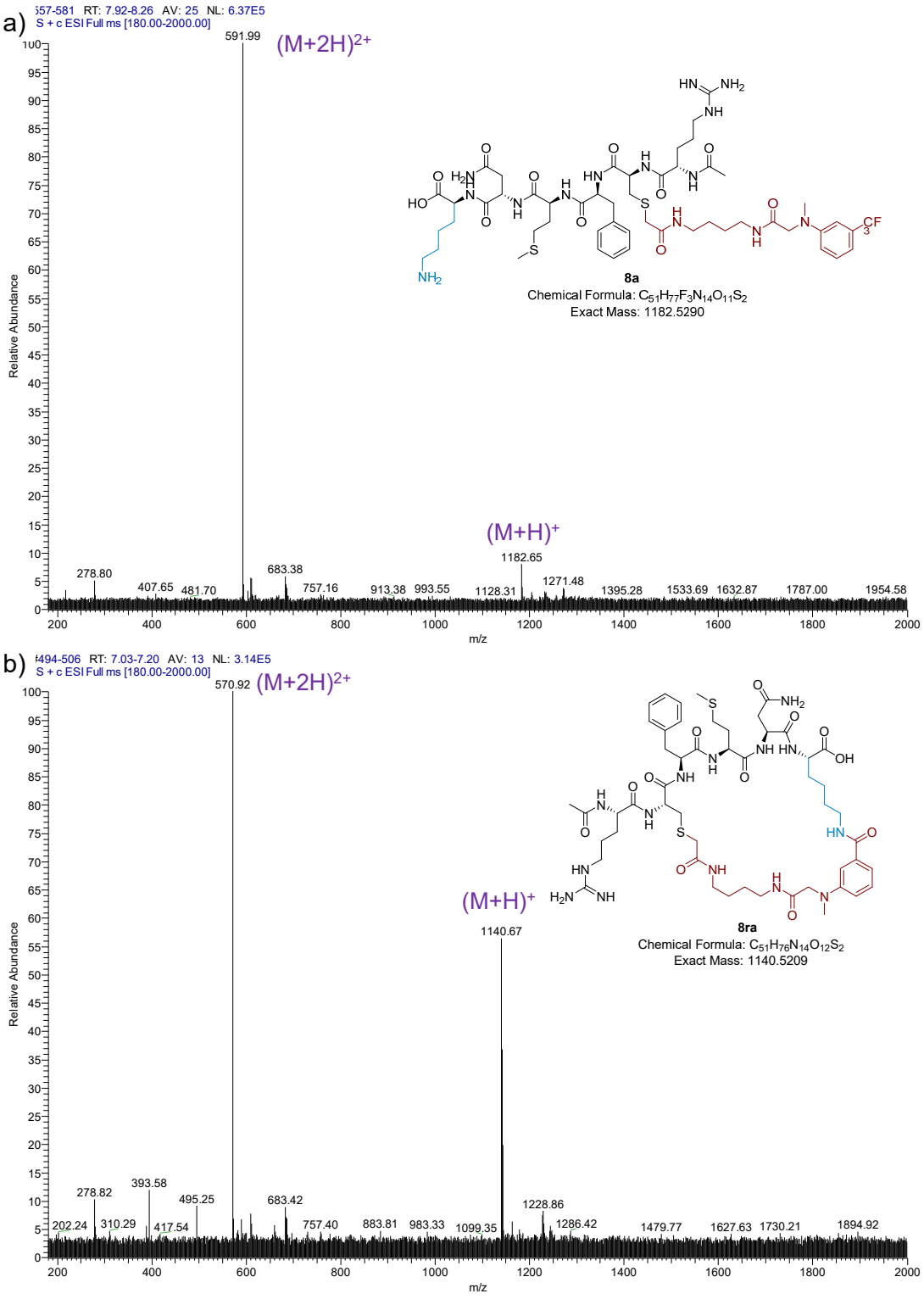
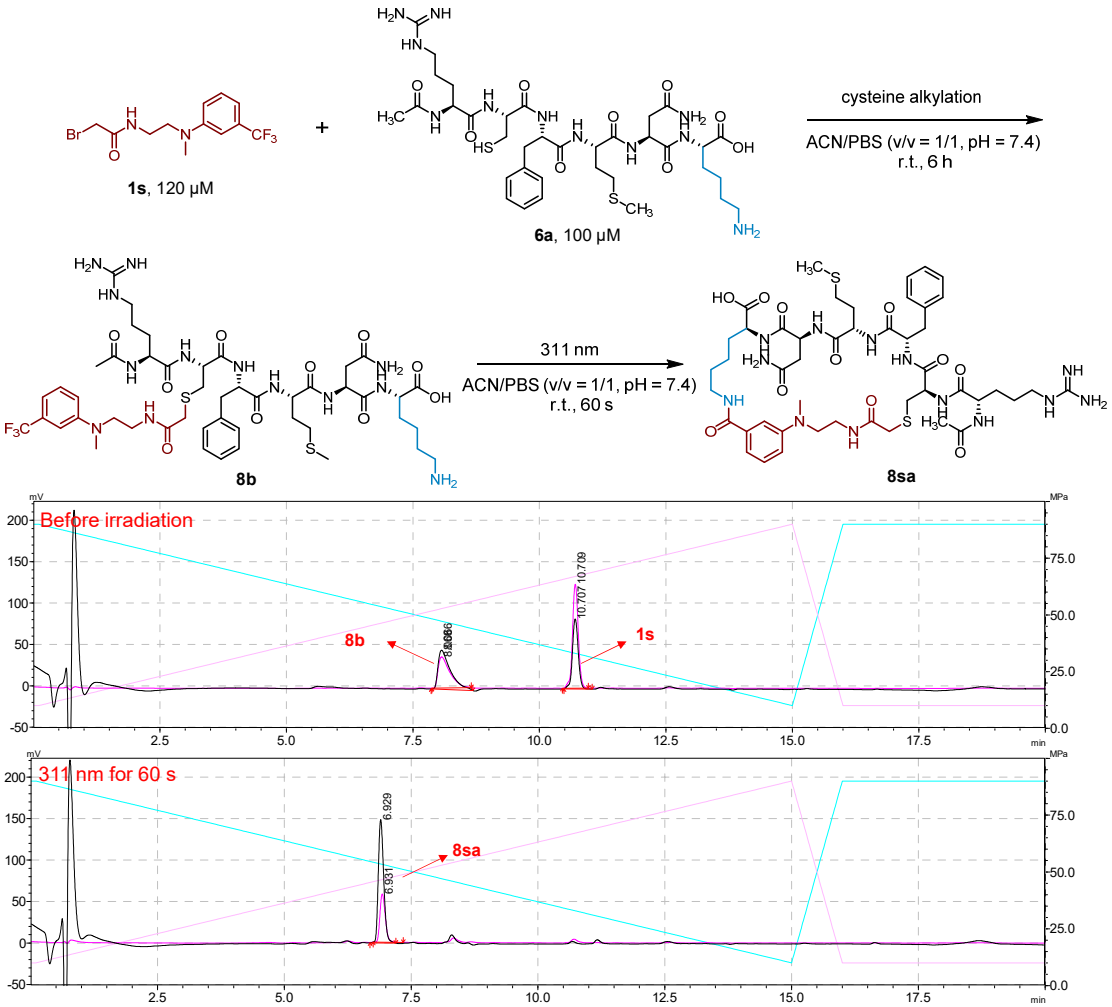


Figure S78. The mass spectra for identification of corresponding peptides: a) **8a**; b) **8ra**.



Item	Peak No.	Time (min)	Area (under 254 nm detecting)
Before irradiation	1	8.068	608970
	2	10.709	1008329
311 nm for 60 s	3	6.931	431223
Conversion	71 %		

Figure S79. Schematic illustration of peptide, Ac-RCFMNK-COOH, cyclization and corresponding HPLC traces for analysis of the conversion. Reaction conditions: **1s** (120 μM) and **7a** (100 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were incubated at 37 °C to alkylate the cysteine residue on the peptide. After incubation for 6 h, the mixture was irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the conversion was determined by the integrated area ratio between **8b** and **8sa** in the HPLC traces.

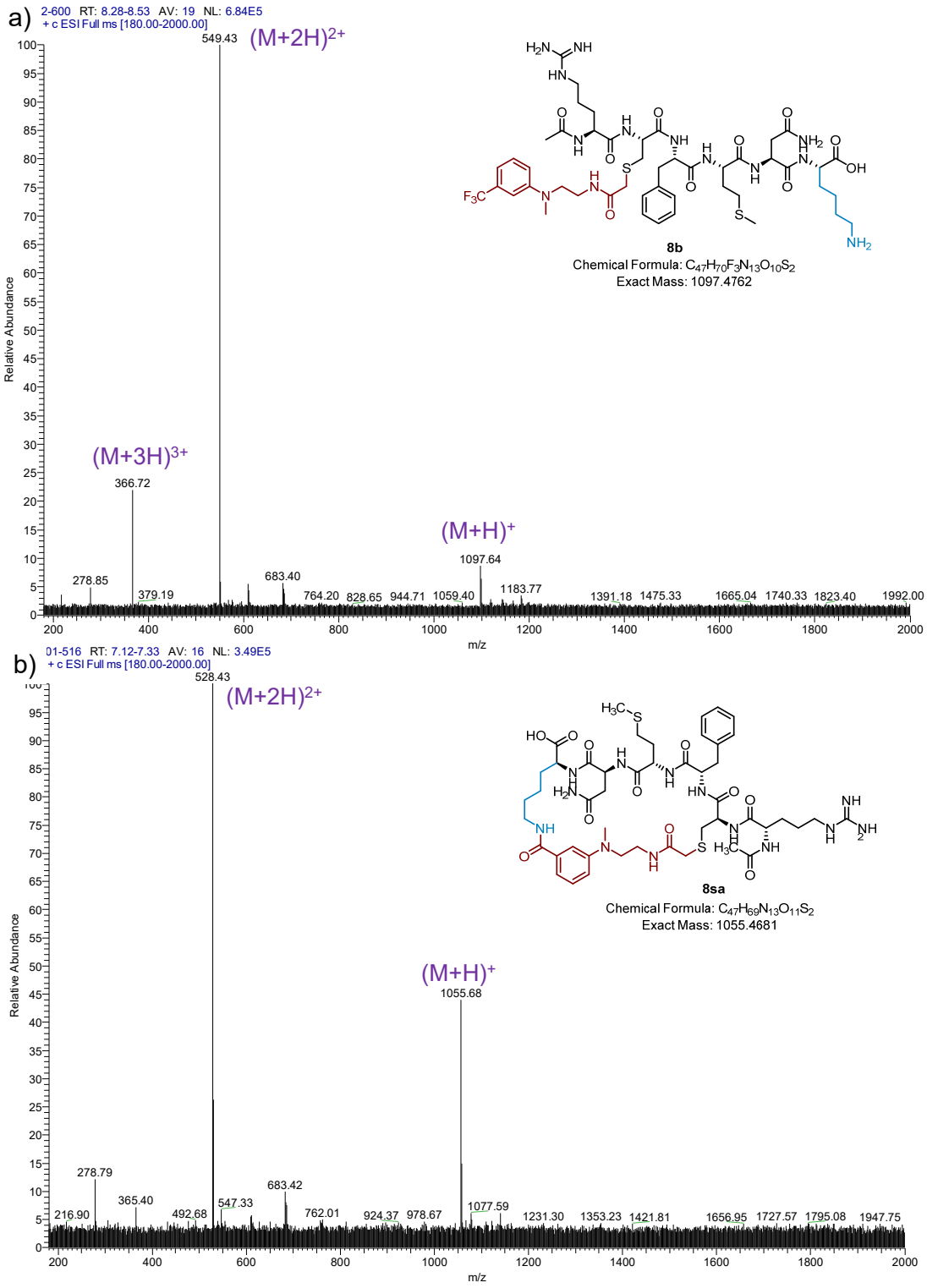
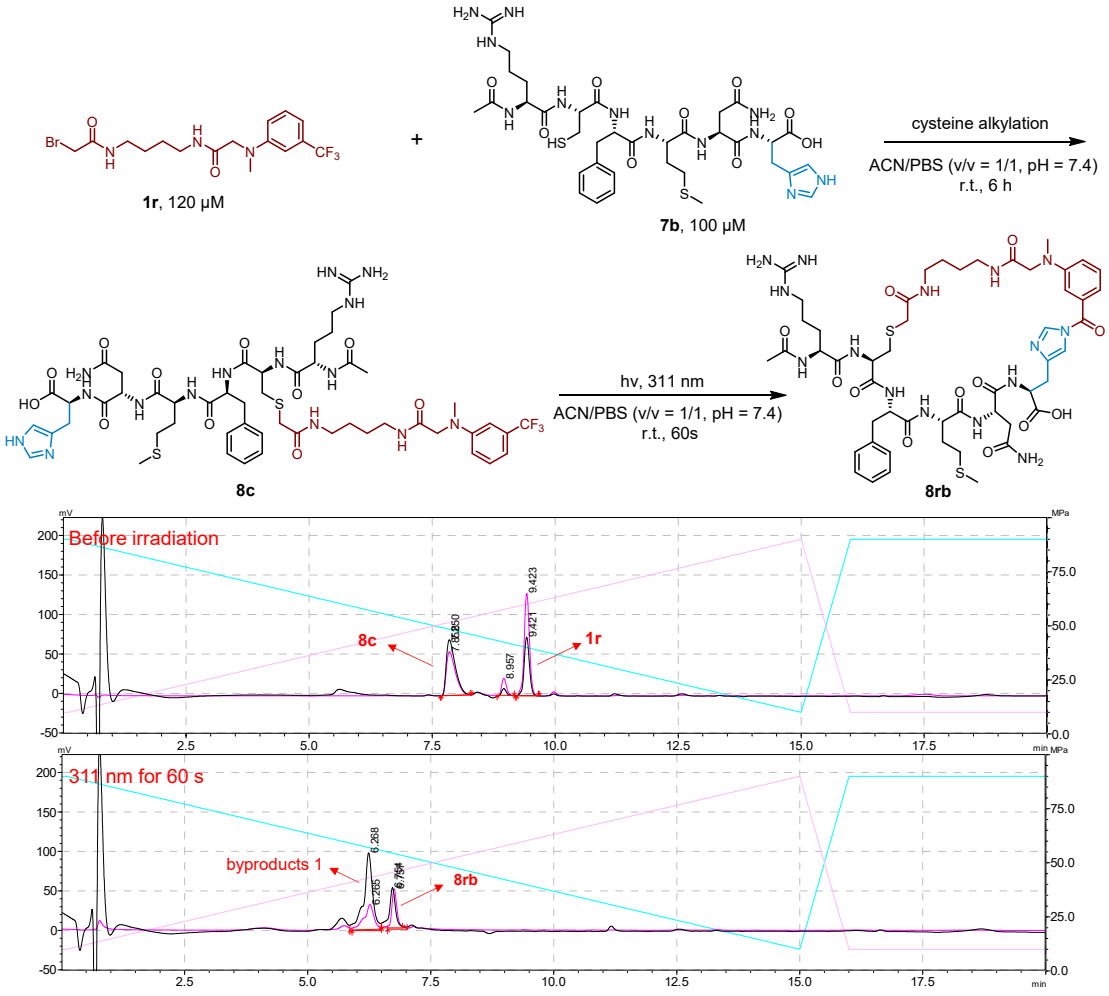
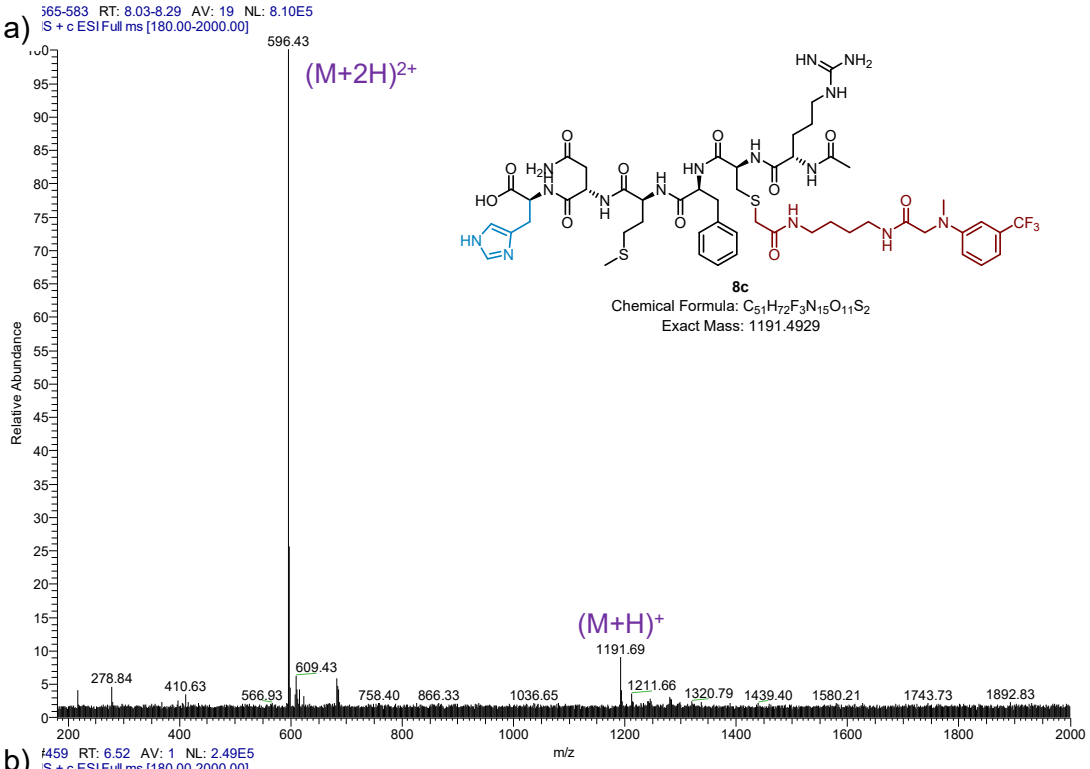


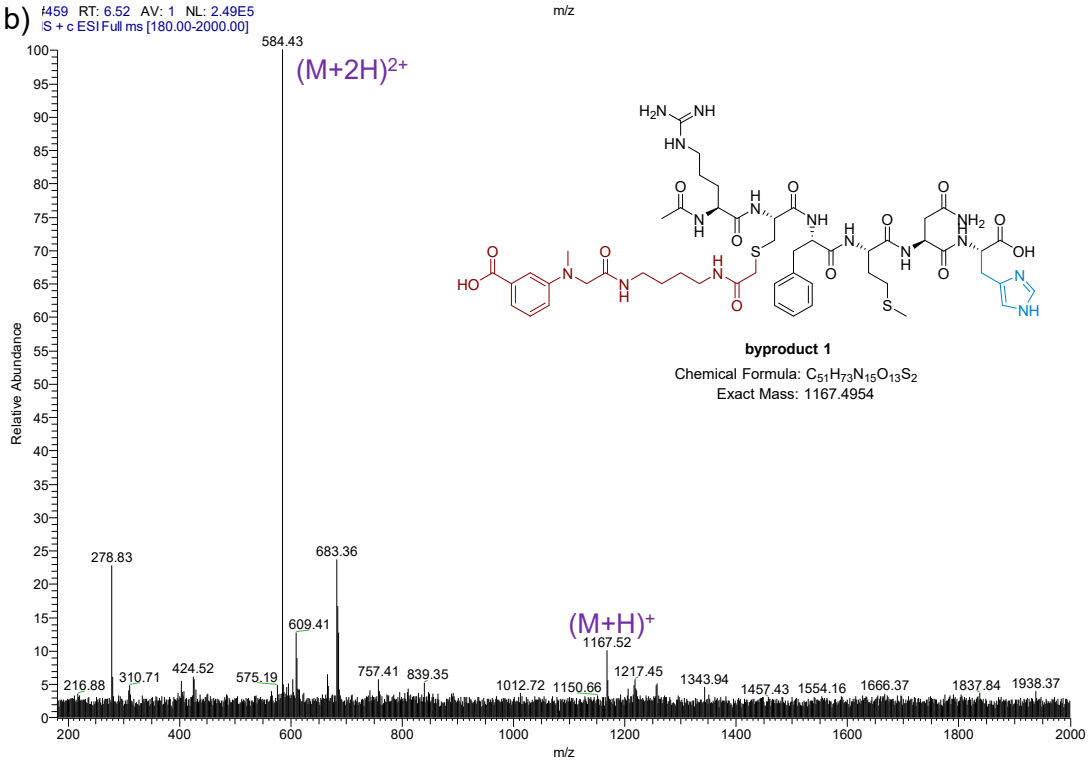
Figure S80. The mass spectra for identification of corresponding peptides: a) **8b**; b) **8sa**.



Item	Peak No.	Time (min)	Area (under 220 nm detecting)
Before irradiation	1	7.85	903592
	2	9.421	555768
311 nm for 60 s	3	6.268	1221125
	4	6.754	450934
Conversion	50 %		

Figure S81. Schematic illustration of peptide, Ac-RCFMNH-COOH, cyclization and corresponding HPLC traces for analysis of the conversion. Reaction conditions: **1r** (120 μM) and **7b** (100 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were incubated at 37 °C to alkylate the cysteine residue on the peptide. After incubation for 6 h, the mixture was irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the conversion was determined by the integrated area ratio between **8c** and **8rb** in the HPLC traces.


a)
565-583 RT: 8.03-8.29 AV: 19 NL: 8.10E5
S + c ESI Full ms [180.00-2000.00]
596.43
(M+2H)2+
(M+H)+
1191.69
609.43
278.84
410.63
566.93
758.40
866.33
1036.65
1211.66
1320.79
1439.40
1580.21
1743.73
1892.83
Relative Abundance
m/z
8c
Chemical Formula: C51H72F3N15O11S2
Exact Mass: 1191.4929


b)
459 RT: 6.52 AV: 1 NL: 2.49E5
S + c ESI Full ms [180.00-2000.00]
584.43
(M+2H)2+
(M+H)+
1167.52
683.36
609.41
278.83
216.88
310.71
424.52
575.19
757.41
839.35
1012.72
1150.66
1217.45
1343.94
1457.43
1554.16
1666.37
1837.84
1938.37
Relative Abundance
m/z
byproduct 1
Chemical Formula: C51H73N15O13S2
Exact Mass: 1167.4954

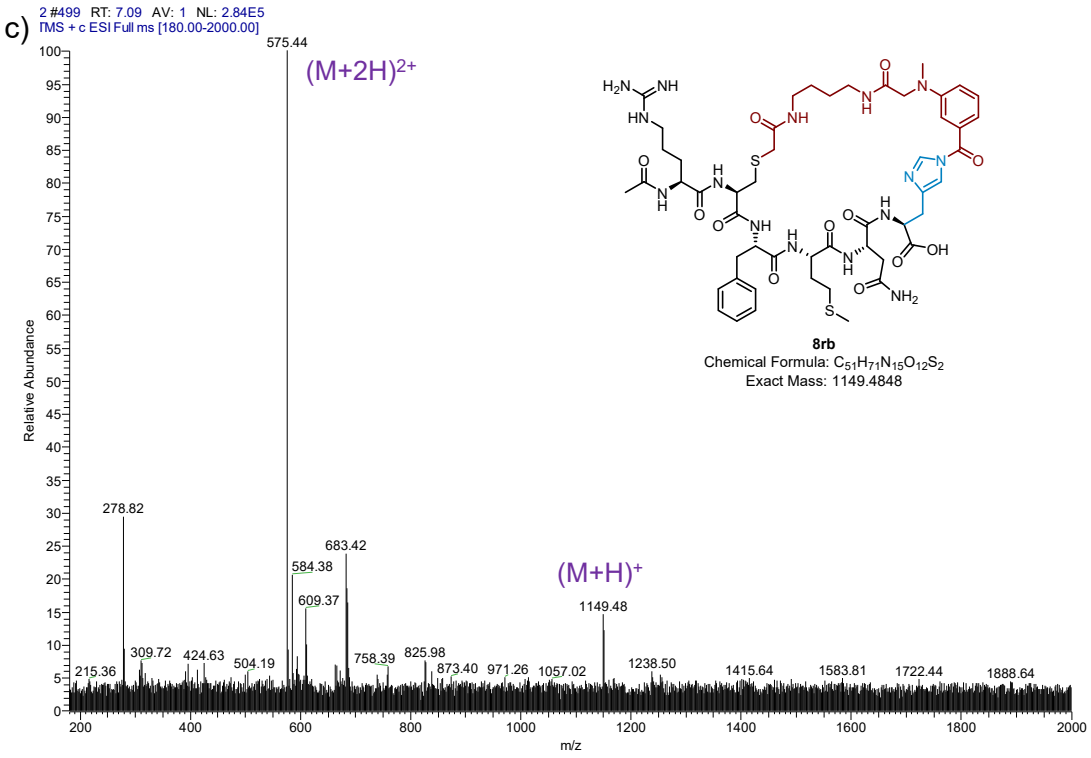
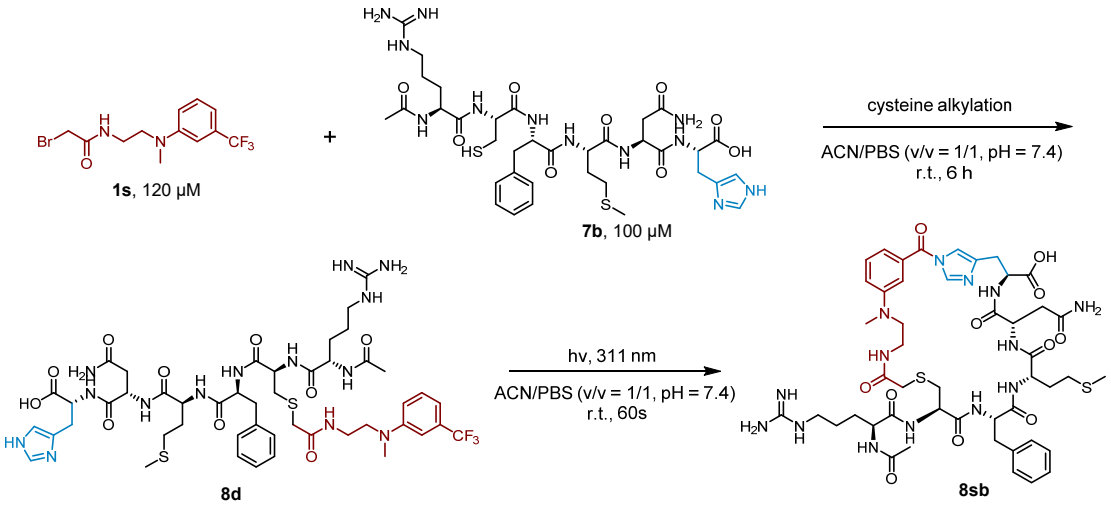
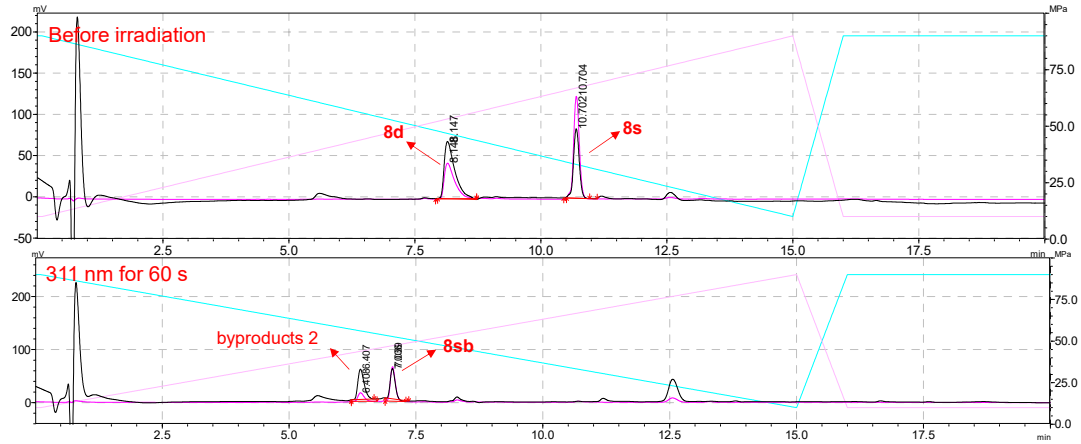


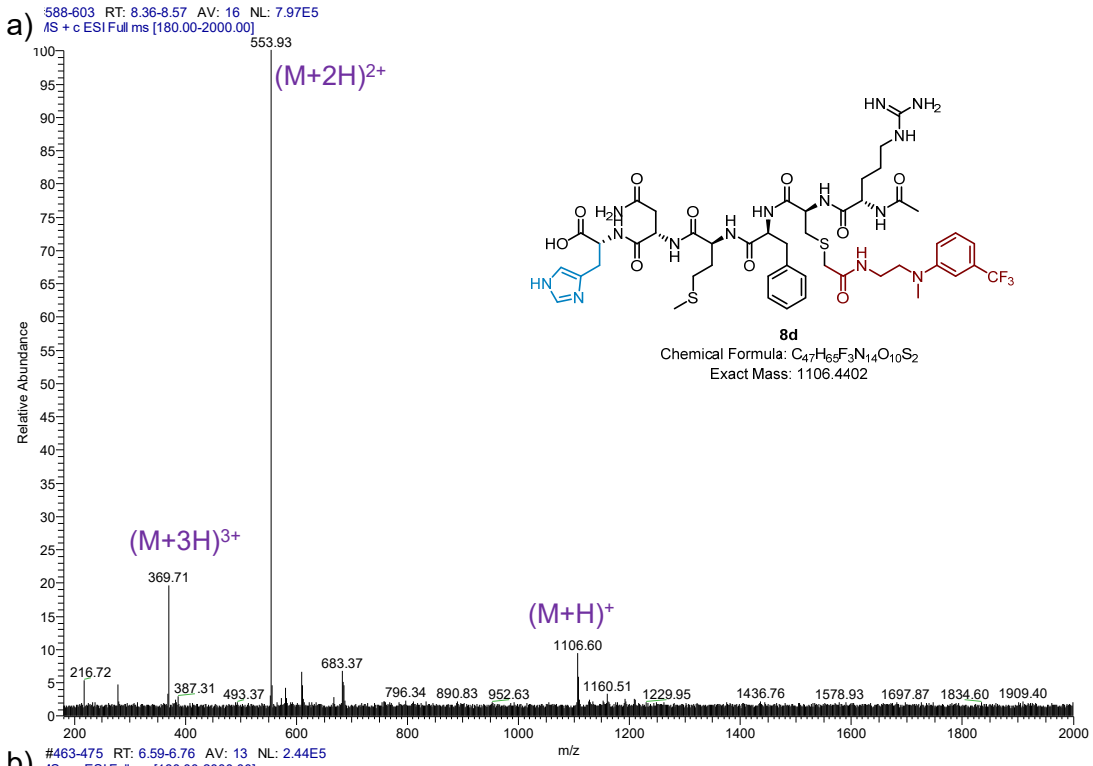
Figure S82. The mass spectra for identification of corresponding peptides: a) **8c**; b) the hydrolysis by-product-1; c) **8rb.**

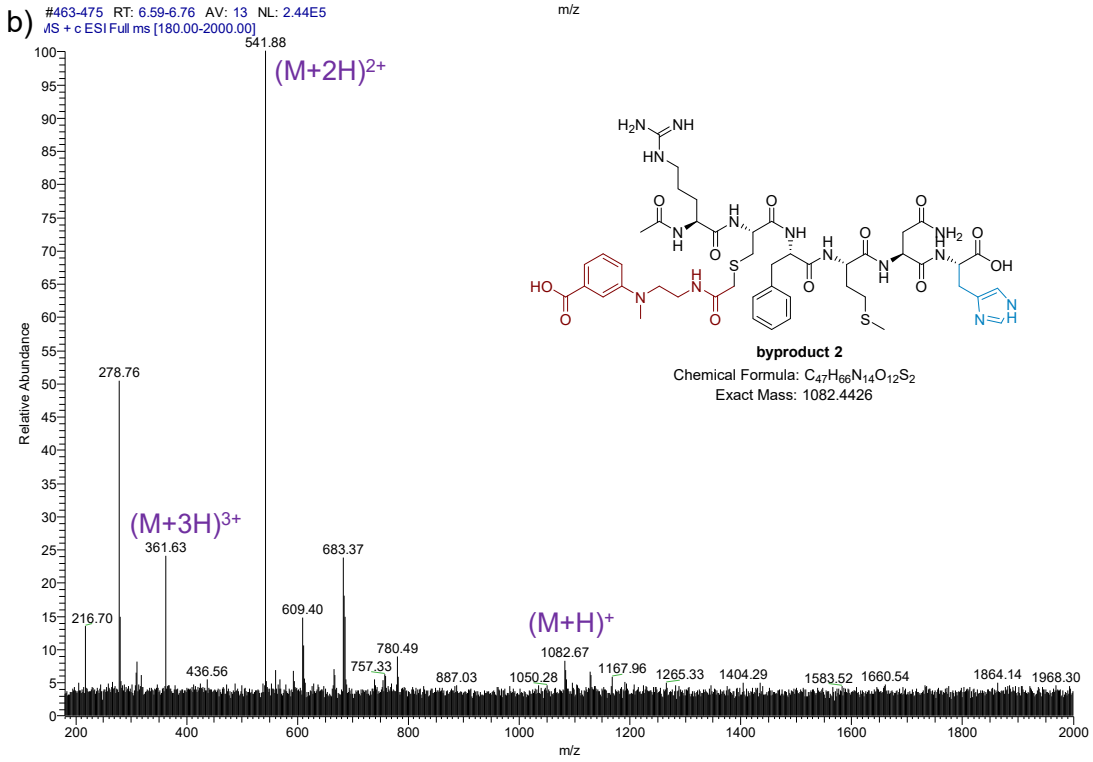




Item	Peak No.	Time (min)	Area (under 220 nm detecting)
Before irradiation	1	8.147	1034934
	2	10.702	670572
311 nm for 60 s	3	6.407	492305
	4	7.036	372731
Conversion	36 %		

Figure S83. Schematic illustration of peptide, Ac-RCFMNH-COOH, cyclization and corresponding HPLC traces for analysis of the conversion. Reaction conditions: **1s** (120 μM) and **7b** (100 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were incubated at 37 °C to alkylate the cysteine residue on the peptide. After incubation for 6 h, the mixture was irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the conversion was determined by the integrated area ratio between **8d** and **8sb** in the HPLC traces.


a)
588-603 RT: 8.36-8.57 AV: 16 NL: 7.97E5
/IS + c ESI Full ms [180.00-2000.00]
553.93
(M+2H)2+
(M+3H)3+
369.71
(M+H)+
1106.60
683.37
216.72
387.31
493.37
796.34
890.83
952.63
1160.51
1229.95
1436.76
1578.93
1697.87
1834.60
1909.40
Relative Abundance
m/z
8d
Chemical Formula: C47H65F3N14O10S2
Exact Mass: 1106.4402


b)
#463-475 RT: 6.59-6.76 AV: 13 NL: 2.44E5
/IS + c ESI Full ms [180.00-2000.00]
541.88
(M+2H)2+
278.76
(M+3H)3+
361.63
683.37
609.40
(M+H)+
1082.67
216.70
436.56
780.49
757.33
887.03
1050.28
1167.96
1265.33
1404.29
1583.52
1660.54
1864.14
1968.30
Relative Abundance
m/z
byproduct 2
Chemical Formula: C47H66N14O12S2
Exact Mass: 1082.4426

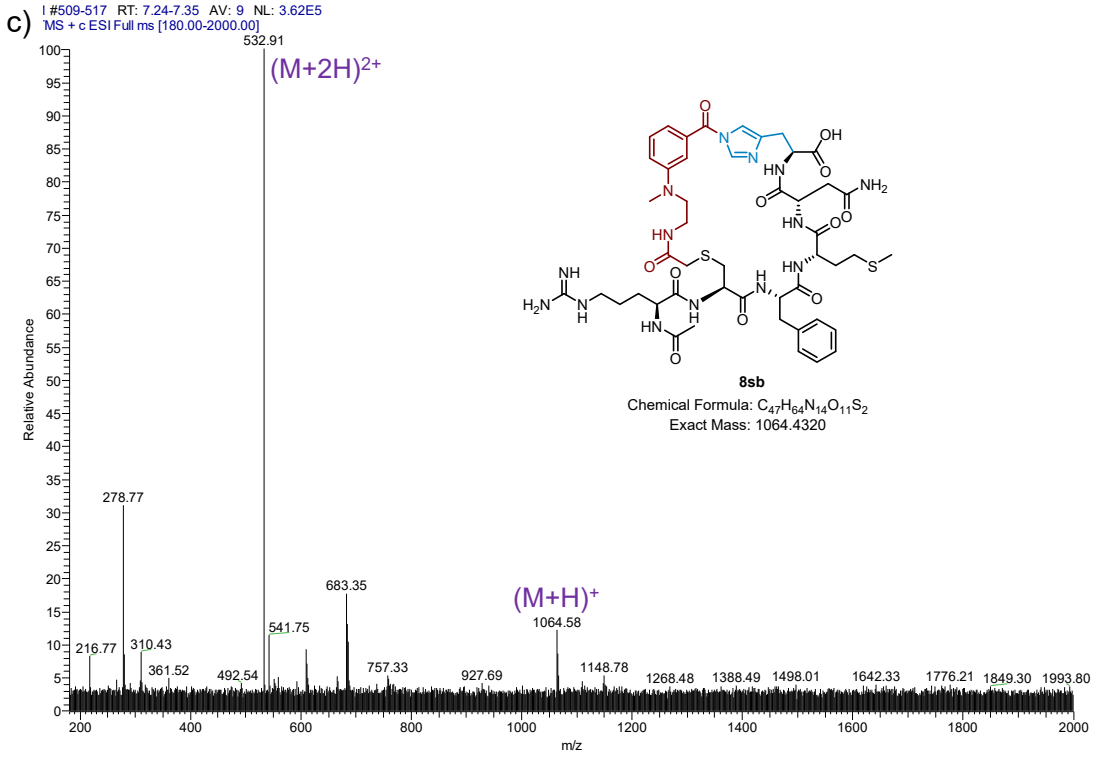
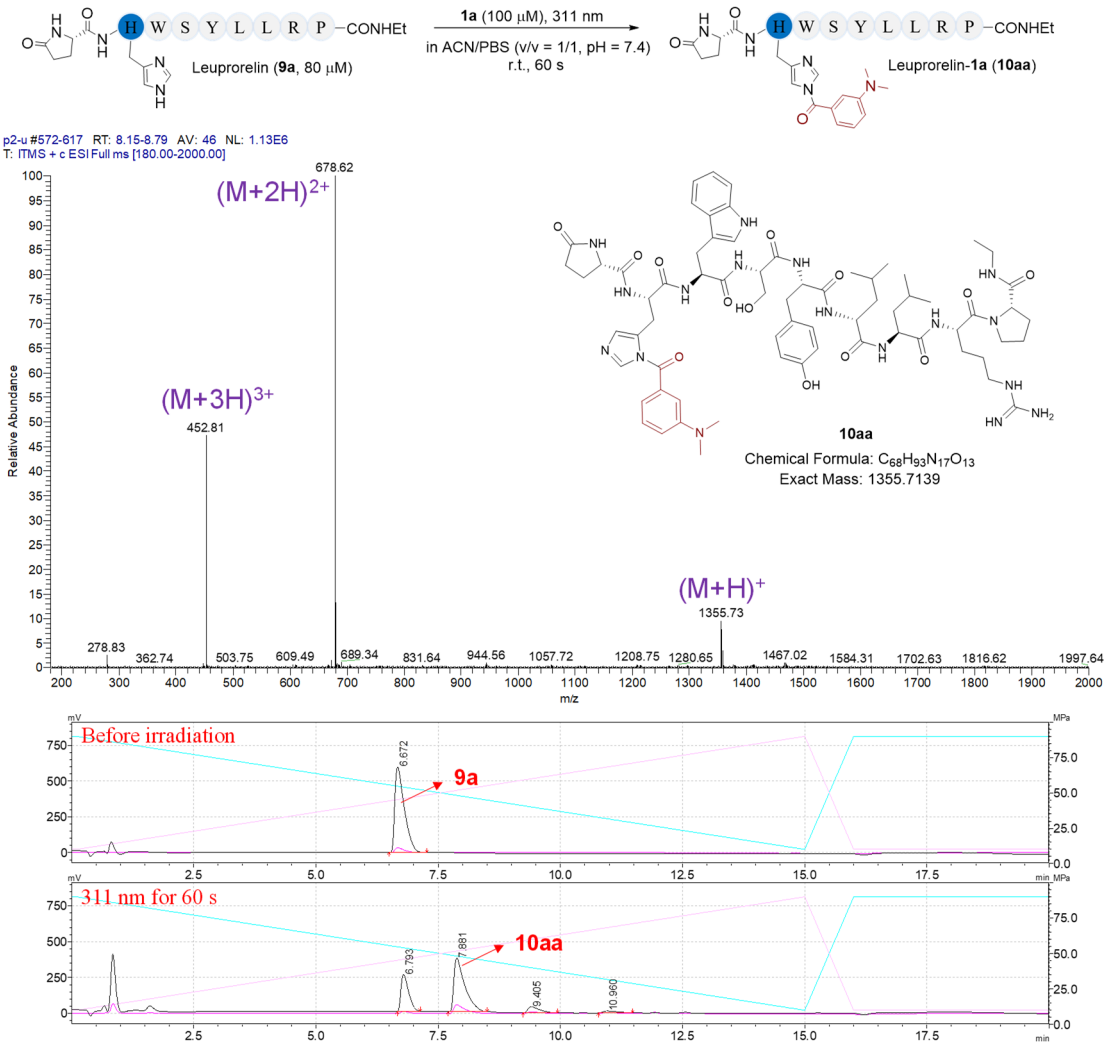


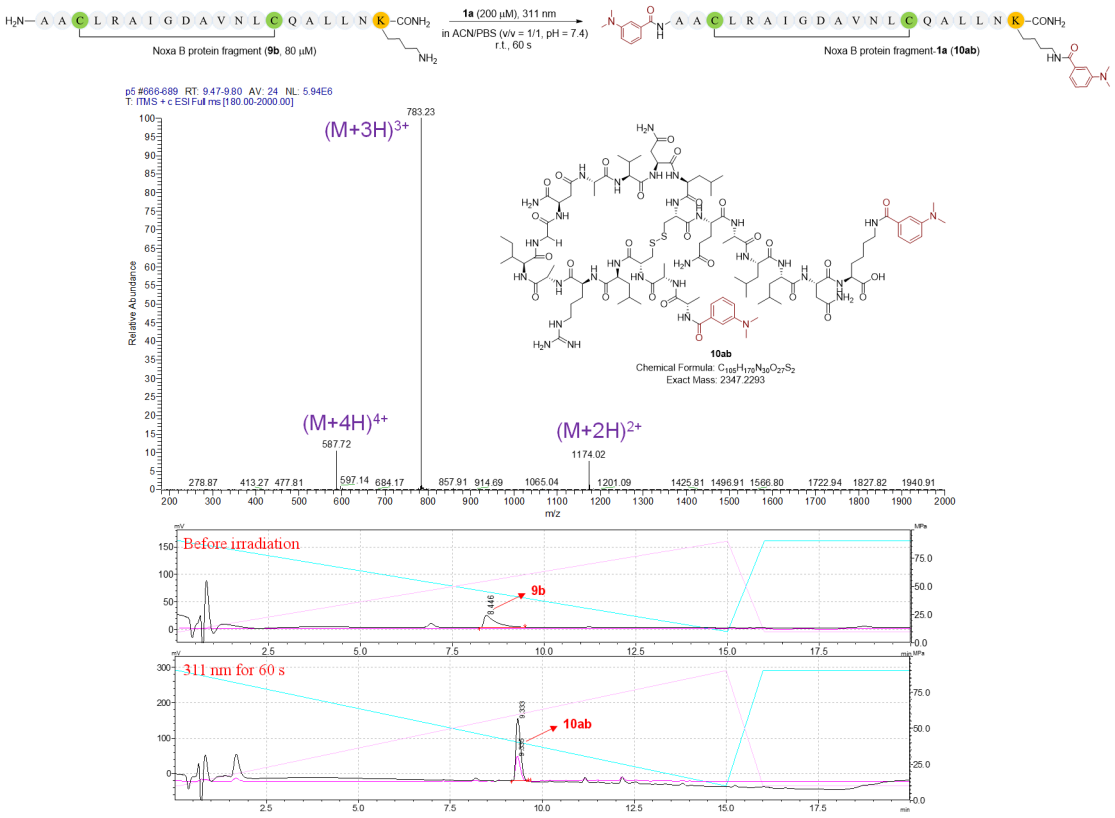
Figure S84. The mass spectra for identification of corresponding peptides: a) **8d**; b) the hydrolysis by-product-2; c) **8sb**.

4.4 Peptide modification via the photo-DAFEx reactions



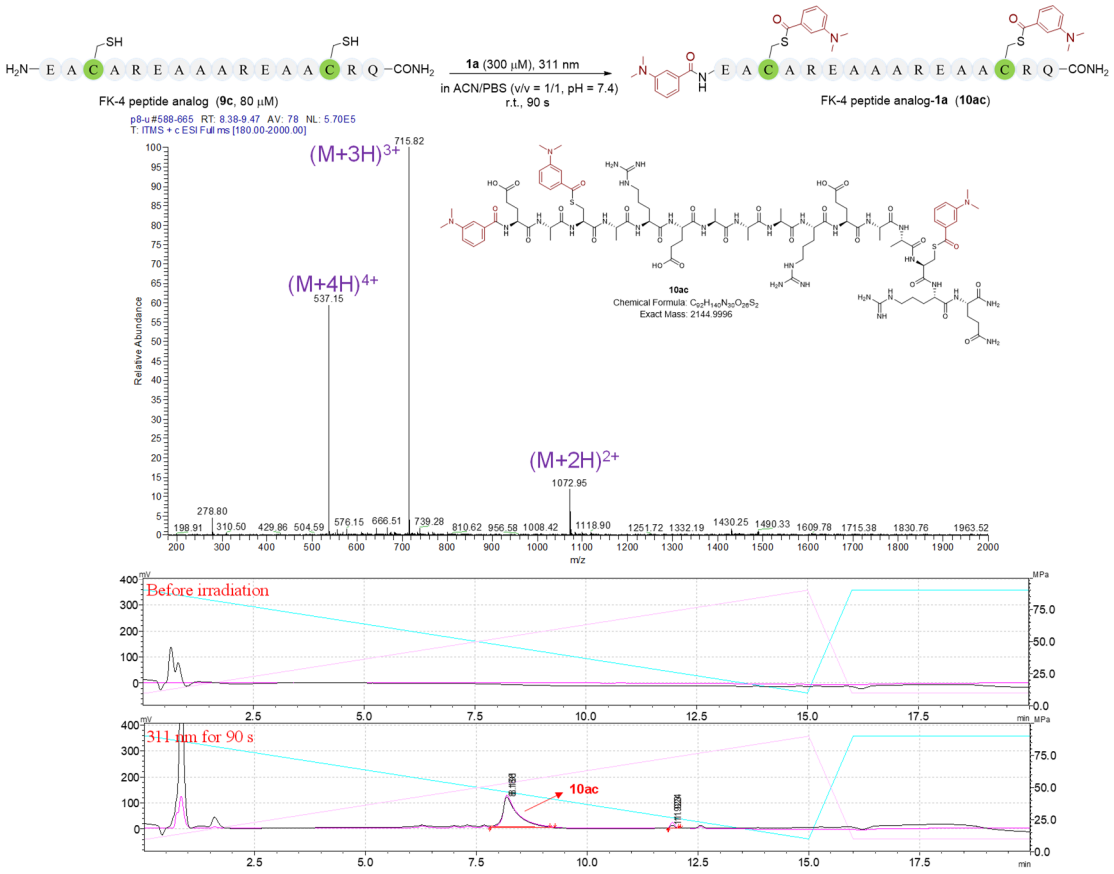
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	1	6.672	8070548
311 nm for 60 s	2	6.793	2784166
	3	7.881	5796087
	4	9.405	695458
	5	10.960	267900
HPLC yield	56%		

Figure S85. 1a (100 μM) and **9a** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yield was determined by the integrated area ratio between **10aa** and **9a** in the HPLC traces.



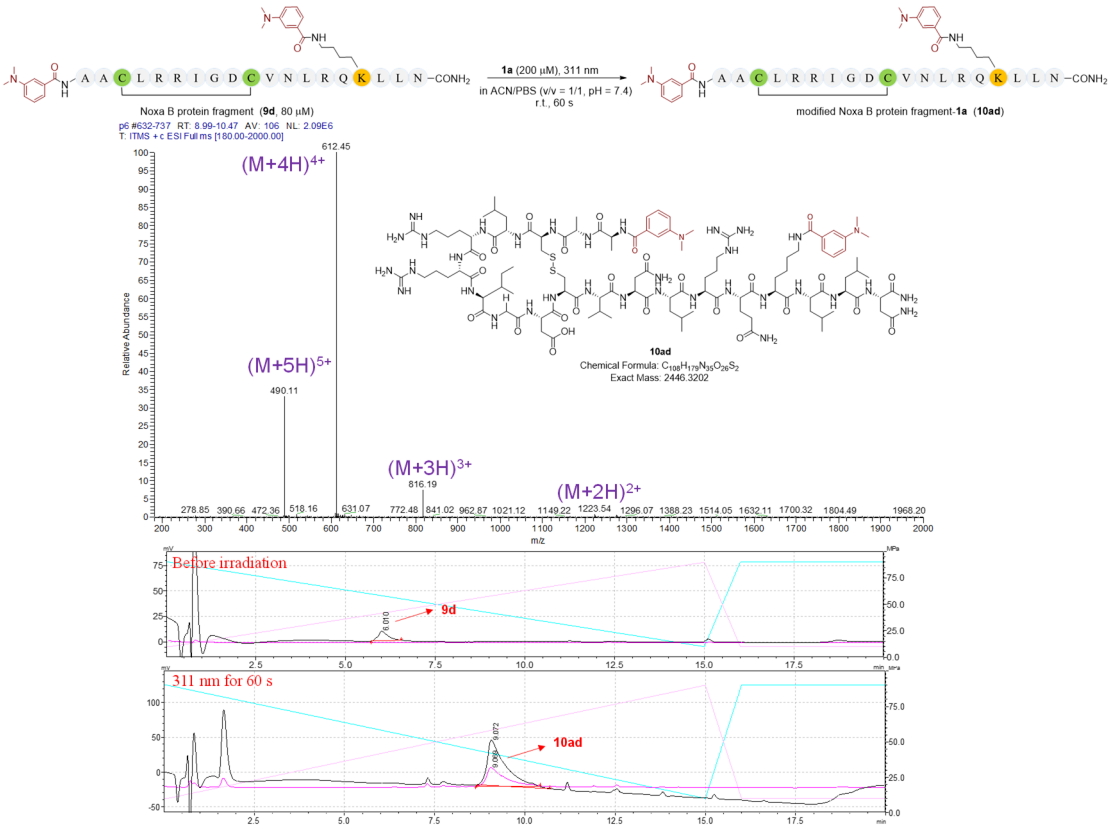
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	1	8.446	474439
311 nm for 60 s	2	9.333	1553386
HPLC yield	53%		

Figure S86. 1a (200 μM) and **9b** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



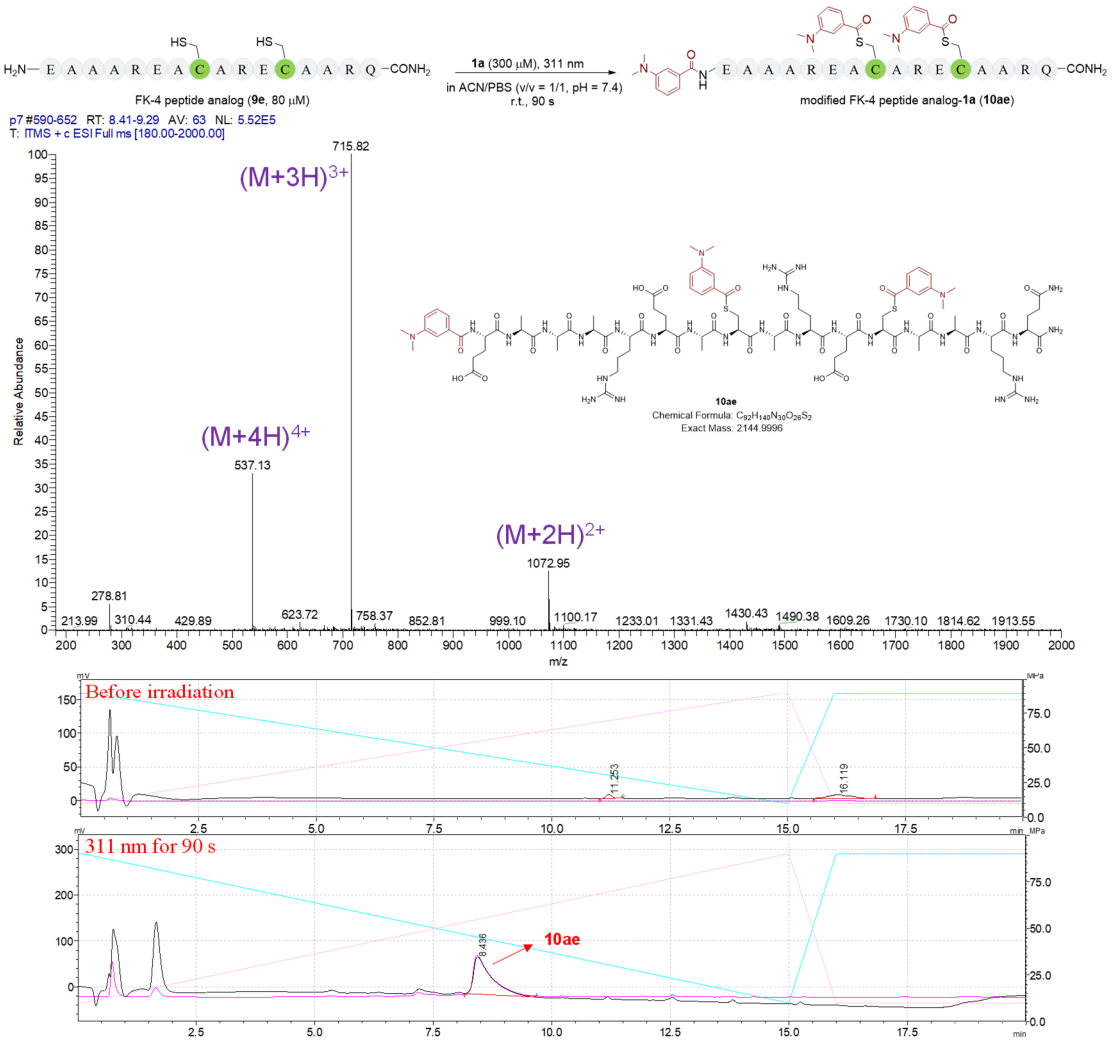
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	/	/	/
311 nm for 90 s	1	8.272	2729799
	2	11.924	272667
HPLC yield	74%		

Figure S87. 1a (300 μM) and **9c** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 90 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



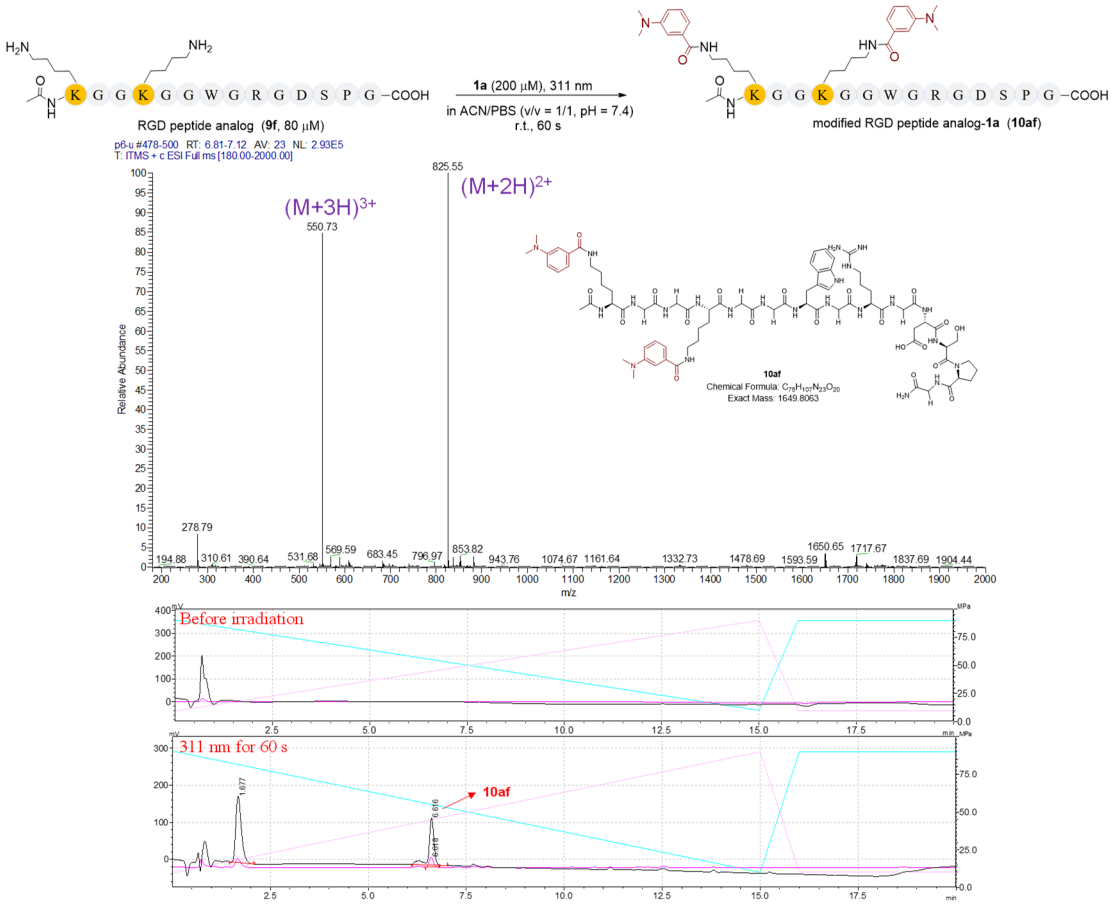
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	1	6.010	178493
311 nm for 90 s	2	9.072	2156563
HPLC yield	78%		

Figure S88. 1a (200 μM) and **9d** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



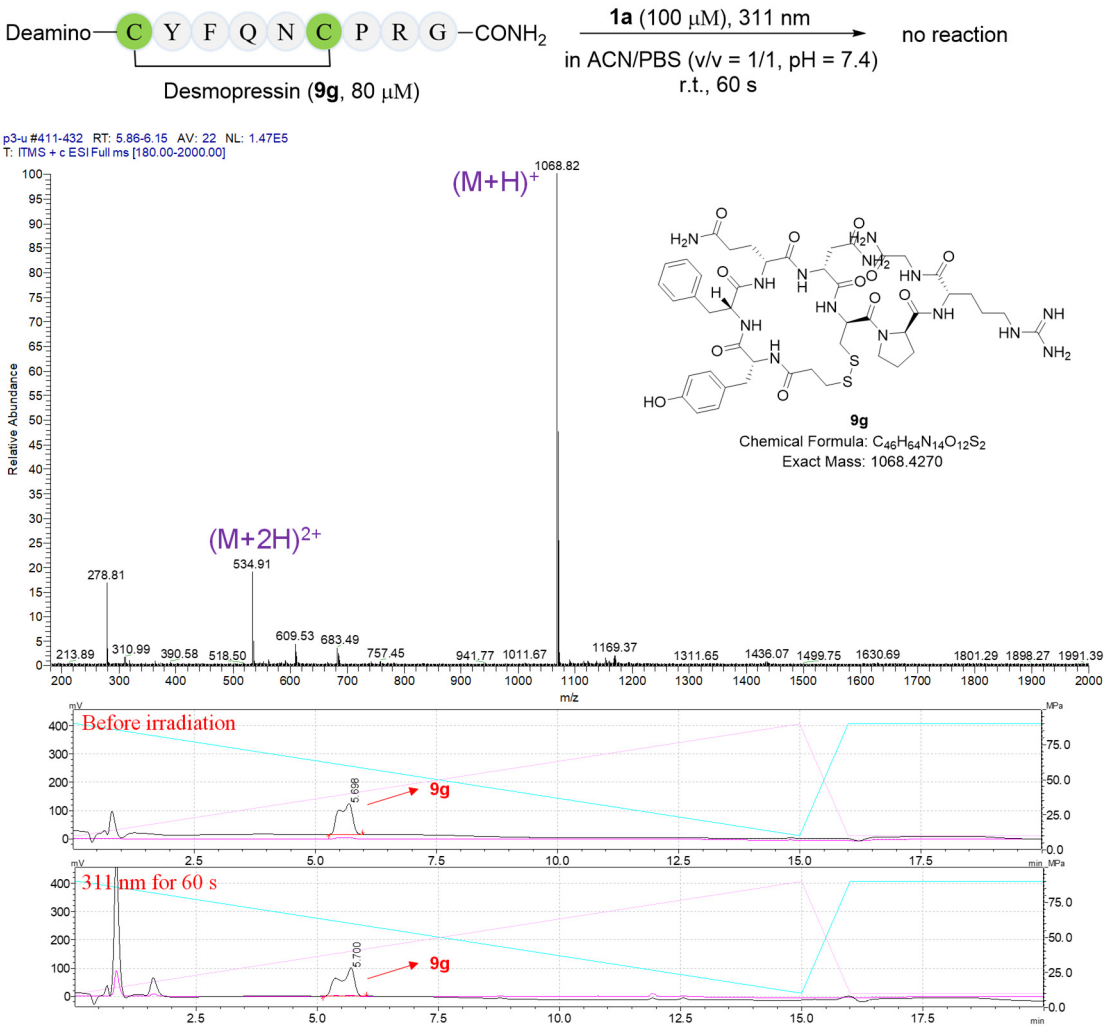
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	/	/	/
311 nm for 90 s	1	8.436	2156563
HPLC yield	60%		

Figure S89. 1a (300 μM) and **9e** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 90 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



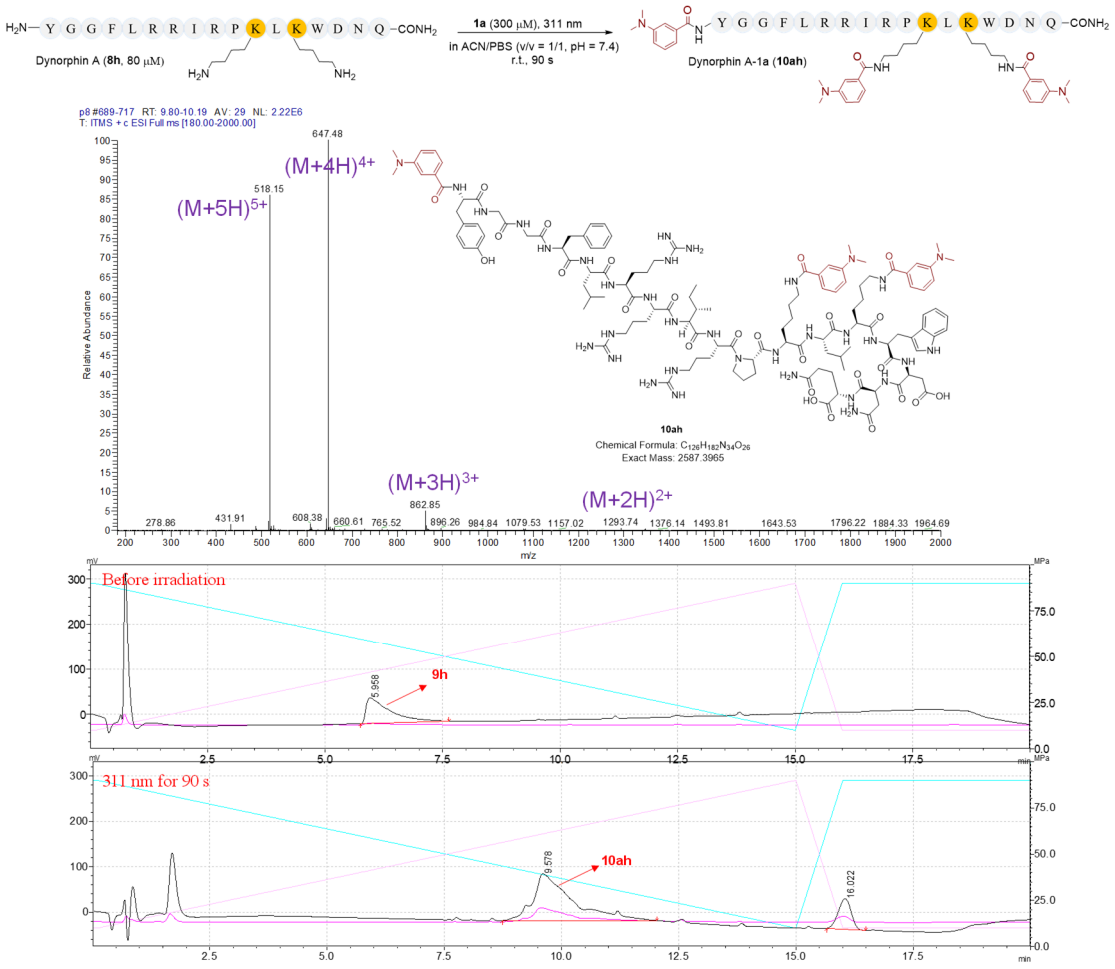
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	/	/	/
311 nm for 60 s	1	1.677	1765453
	2	6.616	1125022
HPLC yield	40%		

Figure S90. 1a (200 μM) and **9f** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



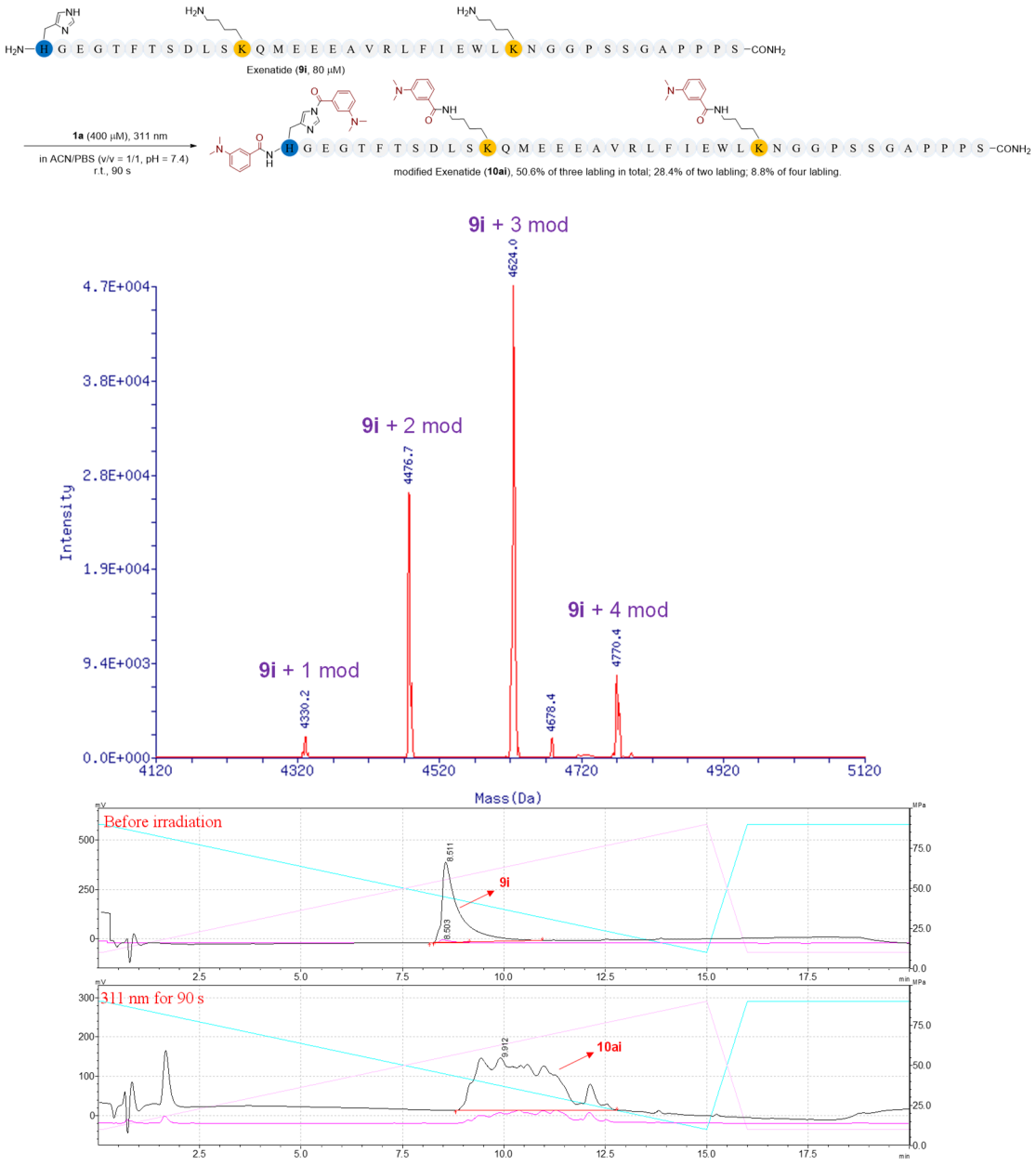
Item	Peak No.	Retention Time (min)	Integrated Area
Before irradiation	1	5.698	2121756
311 nm for 90 s	2	5.700	2172692
HPLC yield	No reaction		

Figure S91. 1a (100 μM) and **9g** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 60 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



Item	Peak No.	Retention Time (min)	Integrated Area at 254 nm
Before irradiation	/	/	/
311 nm for 90 s	1	9.578	1358301
HPLC yield	73%		

Figure S92. 1a (300 μM) and **9h** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 90 s. The sample was collected for HPLC-MS analysis, and the yield was determined by external standards.



	Item	Mass data (Da)	Content in total
Deconvoluted mass spectra	**9i** + 1 mod.	4330.2	2%
	9i + 2 mod.	4476.7	28%
	9i + 3 mod.	4624.0	51%
	9i + 4 mod.	4770.4	9%

Figure S93. 1a (400 μM) and **9i** (80 μM) in 1.0 mL of ACN/PBS (v/v = 1/1, pH = 7.4) solution were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 0.8 cm, l = 8.0 cm optical path) for 90 s. The sample was collected for HPLC-MS analysis, and the contents of each type of modified peptide were determined by deconvoluting the charge ladder. mod. = the photo-DAFEx modification.

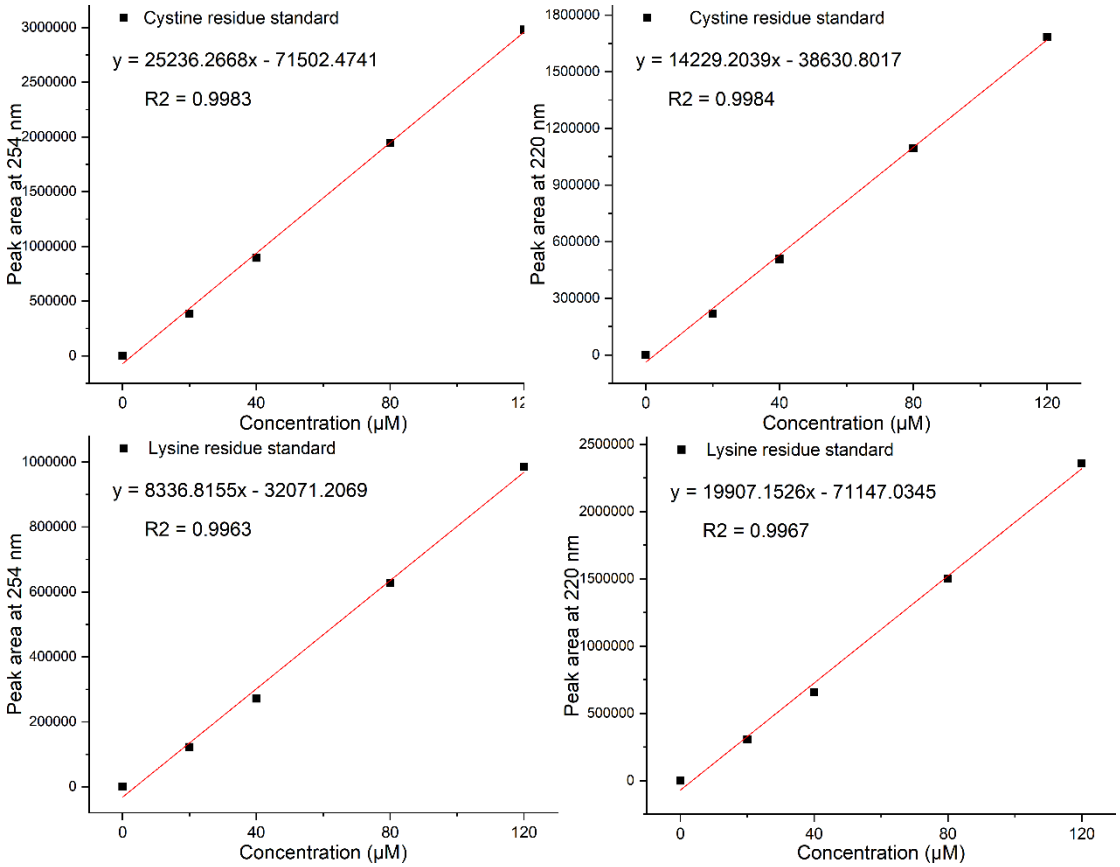


Figure S94. The calibration curves for determination of the photo-DAFEx reaction yields between **1a** and *N*-terminal Boc protected L-cystine/ L-lysine residues.

5. Methods

5.1 Expression and purification of sfGFP

Escherichia coli BL21 (DE3) strain harboring the sfGFP expression plasmid (pET-sfGFP-His6) were grown in 5.0 mL LB broth supplemented with ampicillin (100 μg/mL) overnight at 37 °C. An aliquot of this culture was then used to inoculate a fresh culture (1:100 dilution). When the culture grew to an OD of 0.5, protein production was induced with 1.0 mM IPTG. After further incubation for 8 h, the cells were pelletized in 50 mL conical centrifuge tubes by centrifugation at 4000 g for 30 min at 4 °C and the pellet was resuspended in a fresh 3.0 mL of lysis buffer (50 mM NaH_2PO_4, 300 mM NaCl, 10 mM imidazole, pH = 8.0). The resuspension was further treated with ultrasonication in an ice/water bath to lysis the cells. Following a high-speed centrifugation at 10000g at 4 °C, the supernatants were incubated with 200 μL Ni-NTA resin (Thermo HisPur) at 4 °C for 2 h with gentle shaking. The resin was centrifuged briefly and washed three times with washing buffer. Finally, the protein was eluted with elution buffer. The eluted fractions were collected, concentrated and subjected to buffer exchange to PBS buffer (pH = 7.4) using an Amicon Ultra-15 Centrifugal Filter (10k MWCO, Millipore). The protein purity was analysed by SDS-PAGE and LC/ESI-MS, and the original protein mass was obtained by deconvoluting the charge ladder.

5.2 LC-MS/MS analysis for protein photo-labeling

Protein stock solutions: lysozyme (200 μM) in PBS (pH = 7.4) buffer; sfGFP (200 μM) in PBS (pH = 7.4) buffer; BSA (200 μM) in PBS (pH = 7.4) buffer.
Reactant stock solution: **1a** (500 μM) in ACN/PBS (v/v = 1/1, pH = 7.4) solution.

20 μL of the protein stock solution, 20 μL of **1a** stock solution and 160 μL of PBS (pH = 7.4) buffer were mixed, and irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 30 s. After 30 min incubation, each specimen was divided into two equal portions. One for LC/ESI-MS analysis and the conversion was determined by deconvoluting the charge ladder. The other portion was collected and subjected to SDS-PAGE resolving and in-gel staining with Coomassie Brilliant Blue (CBB). After gel-cutting and destaining with acetonitrile, the in-gel identified protein samples were treated with 10 mM DTT in 25 mM ABC solution at 56 °C for 1 h. The supernatants were removed, and the gel samples were alkylated with 55 mM IAA (in 25 mM ABC solution) in dark for 45 min at RT. After centrifugation, the supernatants were removed, and the gel samples were washed again with ACN. MS grade trypsin (1.0 μg, trypsin:protein = 1:50, w/w) was added to the gel samples with the target protein in 50 mM ABC buffer, and the digestion reaction was incubated for 16 h at 37 °C. A final concentration of 5% acetic acid was added to the suspension to terminate the reaction, and supernatant was discarded to collect the gel pellet, after centrifugation. The in-gel treated and identified proteins were then extracted with 50 μL 50%ACN/5%TFA in water, and the obtained peptides were desalted with a Millipore ZipTip® pipette tip and dried in a speedvac. The desalted peptides were resuspended in 15 μL of 0.1% (v/v) formic acid, and 5.0 μL of samples were subjected to LC−MS/MS analysis (with a Q Exactive plus mass spectrometer, Thermo). The mass spectroscopic raw data were searched and spliced by using the Mascot software.

5.3 In-gel fluorescence imaging for protein photo-labeling

Protein stock solutions: lysozyme (280 μM, 4.0 mg/mL) in PBS (pH = 7.4) buffer; sfGFP (150 μM, 4.0 mg/mL) in PBS (pH = 7.4) buffer; BSA (70 μM, 4.0 mg/mL) in PBS (pH = 7.4) buffer.

Reactant stock solutions: **1a** in ACN/PBS (v/v = 1/1, pH = 7.4) given in three concentrations as stock solution: 100 μM, 500 μM and1000 μM; **1l** in ACN/PBS (v/v = 1/1, pH = 7.4) as a 1000 μM stock solution; **1m** in ACN/PBS (v/v = 1/1, pH = 7.4) as a 1000 μM stock solution.

20 μL of the protein stock solution, 20 μL of reactant stock solution and 160 μL of PBS (pH = 7.4) buffer were mixed, and irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 60 s. After 30 min incubation, specimens were collected and analysed by SDS-PAGE. The labelled proteins were visualized by illumination with 365 nm UV on a gel imager (ChampChemi^{TM} 610Plus, SAGECREATION).

5.4 Mass analysis for multi-labeling lysozyme

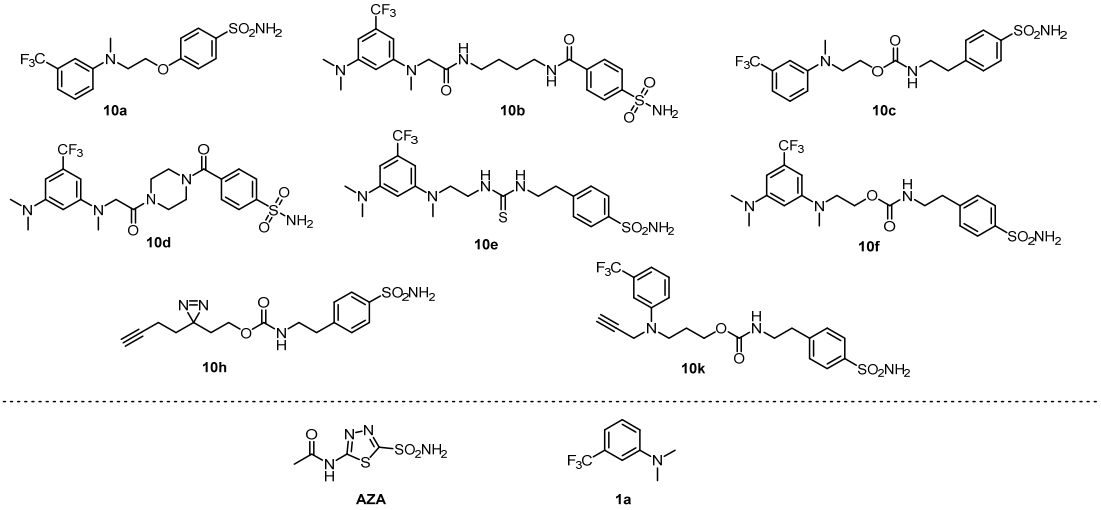
Protein stock solution: lysozyme (70 μM, 1 mg/mL) in PBS (pH = 7.4) buffer.
Reactant stock solutions: **1a** in ACN/PBS (v/v = 1/1, pH = 7.4) given in three concentrations as stock solution: 100 μM, 500 μM and 1000 μM;

20 μL of the protein stock solution, 20 μL of reactant stock solution and 160 μL of PBS (pH = 7.4) buffer were mixed, and irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 60 s. After 30 min incubation, specimens were collected and analysed by LC/ESI-MS. The protein mass was obtained by deconvoluting the charge ladder.

5.5 Expression and purification of the recombinant hCA-II

Escherichia coli BL21(DE3) strain harbouring the hCA-II expression plasmid (pET-hCA-II-His6) were grown in 5.0 mL LB broth supplemented with ampicillin (100 μg/mL) overnight at 37 °C. An aliquot of this culture was then used to inoculate a fresh culture (1:100 dilution). When the culture grew to an OD of 0.5, the culture mixture was supplemented with 50 μM $ZnSO_4$, and protein expression was induced with 1.0 mM IPTG. After further incubation for 8 h, the cells were pelletized in 50 mL conical centrifuge tubes by centrifugation at 4000 g for 30 min at 4 °C and the pellet was resuspended in a fresh 3.0 mL of lysis buffer (50 mM NaH_2PO_4, 300 mM NaCl, 10 mM imidazole, pH = 8.0). The resuspension was further treated with ultrasonication in an ice/water bath to lysis the cells. Following a high-speed centrifugation at 10000g at 4 °C, the supernatants were incubated with 200 μL Ni-NTA resin (Thermo HisPur) at 4 °C for 2 h with gentle shaking. The resin was centrifuged briefly and washed three times with washing buffer. Finally, the protein was eluted with elution buffer. The eluted fractions were collected, concentrated and subjected to buffer exchange to PBS buffer (pH = 7.4) using an Amicon Ultra-15 Centrifugal Filter (10k MWCO, Millipore). The protein purity was analysed by SDS-PAGE and LC/ESI-MS, and the original protein mass was obtained by deconvoluting the charge ladder.

Table S7. The synthesized photo-affinity labeling probes



5.6 Inhibitor screening conditions and procedure

Protein mixtures: lysozyme (280 μM, 4 mg/mL), hCA-II (130 μM, 4 mg/mL) and BSA (70 μM, 4 mg/mL) were mixed in PBS (pH = 7.4) buffer.

Inhibitor stock solutions: **10a-10f** (200 μM for each inhibitor) in DMSO.

Control stock solutions: **1a** (200 μM) in DMSO; AZA (10 mM) in DMSO.

20 μL of the protein mixture, 20 μL of the inhibitor stock solution (**10a-10f**) and 160 μL of PBS buffer (pH = 7.4) were mixed as test groups. 20 μL of the protein mixture, 20 μL of **1a** stock solution and 160 μL of PBS buffer (pH = 7.4) buffer were mixed as the control group; 20 μL of the protein mixture, 20 μL of **10f** stock solution, 20 μL of AZA stock solution and 140 μL of PBS buffer (pH = 7.4) buffer were mixed as the control group. Following, all groups were incubated under darkness for 30 min at room temperature, and treated with a 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 30 s at room temperature. After 30 min incubation, specimens were collected and analysed by SDS-PAGE. The labelled proteins were visualized by illumination with 365 nm UV on a gel imager (ChampChemi^{TM} 610Plus, SAGECREATION).

5.7 In-gel fluorescence analysis for screening the probe concentration

Protein stock solution: hCA-II (130 μM, 4.0 mg/mL) in PBS buffer (pH = 7.4);

Inhibitor stock solutions: **10a/10c/10h/10k** in DMSO with five concentrations as stock solution: 100 μM, 200 μM, 400 μM, 800 μM, 1200 μM;

20 μL of hCA-II stock solution, 20 μL of the inhibitor stock solution and 160 μL of PBS buffer (pH = 7.4) were mixed, incubated under darkness for 30 min at room temperature, and then treated with a 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 60 s at room temperature. After 30 min incubation, specimens were collected and analyzed by SDS-PAGE. The **10a/10c** labelled hCA-II were directly visualized on a gel imager (ChampChemi^{TM} 610Plus, SAGECREATION), while **10h/10k** labelled hCA-II were treated with azide-Alexa-647 according to the general CuAAC procedure and resolved by SDS-PAGE before visualized on a gel imager (ChampChemi^{TM} 610Plus, SAGECREATION).

5.8 In-gel fluorescence analysis for the irradiation time-course tracking

Protein stock solution: hCA-II (130 μM, 4.0 mg/mL) in PBS buffer (pH = 7.4);
Inhibitor stock solution: **10a/10c** in DMSO with 1200 μM of concentrations;

20 μL of hCA-II stock solution, 20 μL of the inhibitor stock solution and 160 μL of PBS buffer (pH = 7.4) were mixed, incubated under darkness for 30 min at room temperature, and then treated with a 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for different irradiation time at room temperature. After 30 min incubation, specimens were collected and analysed by SDS-PAGE. The labelled proteins were visualized by illumination with 365 nm UV on a gel imager (ChampChemi™ 610Plus, SAGECREATION).

5.9 Enzymatic activity assay of the purified hCA-II

The hCA-II activity can be determined by the catalytic hydrolysis of *p*-nitrophenyl acetate into *p*-nitrophenol, which shows strong absorbance at 405 nm. hCA-II (1 μM) and *p*-nitrophenyl acetate (2.5 mM) were incubated in the presence of the inhibitor at various concentrations in a 96-well plate in PBS buffer of pH = 7.4 (final volume of 100 μL). After incubation at 24 °C for 30 min, the absorbance at 405 nm was measured using a multimode microplate reader (iMark, BIO-RAD). The percentage inhibition was defined relative to the maximal activity which was measured without the inhibitor. The IC_{50} value of **10a**, **10c**, **10h**, **10k**, and **AZA** were obtained from a graph of percent inhibition versus inhibitor concentration and calculated using the Prism GraphPad software.

5.10 PAL Labeling of the recombinant hCA-II in *E. Coli* bacterial lysates

Escherichia coli BL21 (DE3) strain harbouring the hCA-II expression plasmid (pET-hCA-II-His6) were grown in 5.0 mL LB broth supplemented with ampicillin (100 μg/mL) overnight at 37 °C. An aliquot of this culture was then used to inoculate a fresh culture (1 : 100 dilution, 50 mL in total). After further incubation for 8 h, the cells were pelletized in 50 mL conical centrifuge tubes by centrifugation at 4000 g for 30 min at 4 °C and resuspended in a fresh 2 mL of PBS buffer (pH = 7.4). The cells in the buffer were further treated with ultrasonication in an ice/water bath to lysis the cells. Following a high-speed centrifugation at 10000g at 4 ºC, the supernatants were collected as cell lysates for further tests.

20 μL of cell lysate and 20 μL of the inhibitor solution (**10a-10f**, 200 μM) and 160 μL PBS (pH = 7.4) buffer were mixed as the test groups. 20 μL of cell lysate and 20 μL of **1a** stock solution and 160 μL of PBS buffer (pH = 7.4) buffer were mixed as the control group; 20 μL of cell lysate and 20 μL of **10f** stock solution, 20 μL of AZA stock solution, and 140 μL of PBS buffer (pH = 7.4) buffer were mixed as the control group with the AZA competitor. All groups were incubated under darkness for 30 min at room temperature, and irradiated with the 311 nm lamp (10.8 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 30 s at room temperature. After 30 min incubation, specimens were collected and analysed by SDS-PAGE. The labelled proteins were visualized by illumination with 365 nm UV on a gel imager (ChampChemi™ 610Plus, SAGECREATION). The resolved proteins were then transferred to PVDF membranes, and a western blot was performed with anti-CA-II rabbit pAb (ZEN-BIO, #820344, 1:2000) and goat anti-rabbit IgG (ZEN-BIO, #550037, 1:2000).

5.11 Tandem mass analysis of the hCA-II after PAL labeling

20 μL of the hCA-II solution (50 μM, 4 mg/mL) and 20 μL of **10a/10c** solution (200 μM) were mixed

in a total volume of 200 μL solution in PBS buffer, which was incubated under darkness for 30 min at room temperature. The samples were then irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) in a quartz test tube (φ = 1 cm, l = 8.0 cm optical path) for 30 s at room temperature. After another 30 min incubation, the samples were collected and subjected with LC/ESI-MS, and the protein mass was obtained by deconvoluting the charge ladder.

In the LC-MS/MS analysis, the collected protein samples were firstly separated by SDS-PAGE and stained with Coomassie Brilliant Blue. After gel-cutting and destaining with acetonitrile, the in-gel identified protein samples were treated with 10 mM DTT in 25 mM ABC solution at 56 °C for 1 h. The supernatants were removed, and the gel samples were alkylated with 55 mM IAA (in 25 mM ABC solution) in dark for 45 min at RT. After centrifugation, the supernatants were removed, and the gel samples were washed again with ACN. MS grade trypsin (1.0 μg, trypsin:protein = 1:50, w/w) was added to the gel samples with the target protein in 50 mM ABC buffer, and the digestion reaction was incubated for 16 h at 37 °C. A final concentration of 5% acetic acid was added to the suspension to terminate the reaction, and supernatant was discarded to collect the gel pellet, after centrifugation. The in-gel treated and identified proteins were then extracted with 50 μL 50%ACN/5%TFA in water, and the obtained peptides were desalted with a Millipore ZipTip® pipette tip and dried in a speedvac. The desalted peptides were resuspended in 15 μL of 0.1% (v/v) formic acid, and 5.0 μL of samples were subjected to LC−MS/MS analysis (with a Q Exactive plus mass spectrometer, Thermo). The mass spectroscopic raw data were searched and spliced by using the Mascot software.

5.12 PAL Labeling of the overexpressed hCA-II in living bacterial cells

Escherichia coli BL21 (DE3) strain with the hCA-II expression plasmid (pET- hCA-II -His6) were grown in 5.0 mL LB broth supplemented with ampicillin (100 μg/mL) overnight at 37 °C. An aliquot of this culture was then used to inoculate a fresh culture (1 : 100 dilution). When the culture grew to an OD of 0.5, the culture mixture was supplemented with 50 μM $ZnSO_4$, and protein production was induced with 1.0 mM IPTG and 0.2% arabinose. After further incubation for 4 h, the cells were incubated with **10a** (20 μM) in 1.0 mL culture medium for 1.5 h, with or without AZA (400 μM). The supernatant was discarded after centrifugation at 4000 g, and the cells were washed gently twice with PBS buffer to remove the excessive probe. The cell pellets were re-suspended with 1.0 mL PBS, then 10 μL of cell/PBS suspension was pipetted onto a sterilized glass slide and spread evenly. The specimens were irradiated with the 311 nm lamp (5.9 mW cm^{-2}, single wavelength output after an optical filter) for 60 s. Then the specimen was subjected to fluorescence microscopic imaging and the imaging data were collected on an Olympus IX83 live cell fluorescence (100× oil-immersion objective, $\lambda_{ex.}$ = 365 nm, $\lambda_{em.}$ = 420-460 nm).

5.13 Photo-affinity labeling in bacterial lysates with side-by-side comparisons between the photo-DAFEx and the diazirine photolysis

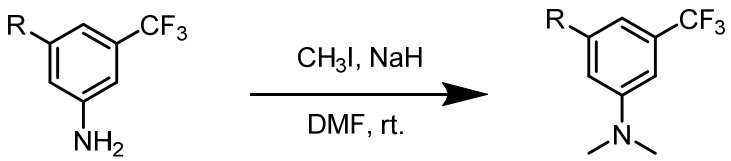
100 μL of *Escherichia coli* BL21 (DE3) lysate (containing about 16 μg of recombinant hCA-II) and 20 μL of the inhibitor solution (**10h/10k**, 20 μM in final) with/without AZA competitor (200 μM in final concentration) in final 200 μL of PBS (pH = 7.4) buffer were incubated under darkness for 30 min at room temperature. Then the **10h** containing samples were treated 365 nm lamp (68 mW cm^{-2}) for 180 s; the **10k** containing samples were treated 311 nm lamp (10.8 mW cm^{-2}) for 30 s at room temperature. After 30 min incubation, specimens were treated with azide-647 according to the general CuAAC procedure before visualized on a gel imager (ChampChemi™ 610Plus, SAGECREATION).

5.14 Photo-affinity labeling of the endogenous CA-II in living mammalian cells

HEK 293T cells were seeded in 6-well plates at 10^5 cells/mL density for 36 h prior to the PAL experimental procedure. Cells were then treated with 1.0 mL of the DMEM containing **10h/10k** (5.0 μM), with or without AZA (25 μM). After 2 h of incubation at 37 °C/5% CO_2, the culture medium was aspirated, and cells were washed gently once with PBS to remove the excessive probe, followed by the irradiation (**10h** treated cell samples were exposed to 365 nm lamp (68 mW cm^{-2}) for 4 min; **10k** treated cell samples were exposed to 311 nm lamp (10.8 mW cm^{-2}) for 1 min in PBS. The cells were lysed in RIPA lysis buffer, and the endogenous proteins were collected and treated with azide-Alexa-647 conjugate according to the general CuAAC procedure, resolved by SDS-PAGE before visualized on a gel imager (ChampChemi^{TM} 610Plus, SAGECREATION). After imaging, the resolved proteins from cell lysate were then transferred to PVDF membranes via electro-transferring, and then a western blot staining was performed with a primary anti-CA-II rabbit pAb (ZEN-BIO, #820344, 1:2000 dilution) and a secondary HRP-labelled Goat Anti-Rabbit IgG (Beyotime, A0208, 1:1000 dilution) for ECL detection.

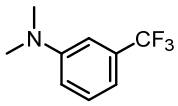
6. Synthetic procedures and compound characterization

6.1 The synthetic method for 1a, 1t, and 1e.



R = H, Br, NH_2

3-aminobenzotrifluoride (1.0 equiv.) or 3-amino-5-bromobenzotrifluoride (1.0 equiv.) 3,5-diaminobenzotrifluoride (1.0 equiv.) and sodium hydride (3.0 equiv.) in anhydrous DMF solvent were added iodomethane (3.0 equiv.) under argon, and the mixture was stirred for 12 h at room temperature. The reaction was quenched with water and extracted with ethyl acetate three times. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 10 : 1) to afford corresponding products.



1a

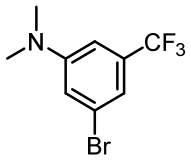
***N,N*-dimethyl-3-(trifluoromethyl)aniline** (**1a**): as a yellow oil (82% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (ddt, J = 8.4, 7.6, 0.6 Hz, 1H), 6.94 (ddd, J = 7.4, 1.6, 0.8 Hz, 1H), 6.89 (d, J = 1.8 Hz, 1H), 6.85 (dd, J = 8.4, 2.6 Hz, 1H), 2.99 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.46, 131.36 (q, J = 31.3 Hz), 129.43, 124.57 (q, J = 272.1 Hz), 115.18, 112.67 (q, J = 4.2 Hz), 108.47 (q, J = 3.8 Hz), 40.37.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.79.

HRMS (ESI) calculated $C_9H_{11}F_3N^+$ $[M+H]^+$ m/z 190.0844, found 190.0836.



1t

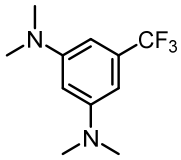
3-bromo-*N,N*-dimethyl-5-(trifluoromethyl)aniline (1t): as a yellow oil (57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (td, J = 1.6, 0.8 Hz, 1H), 6.93 (t, J = 2.2 Hz, 1H), 6.78 (ddd, J = 2.4, 1.6, 0.8 Hz, 1H), 2.99 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.26, 132.64 (q, J = 32.0 Hz), 123.62 (q, J = 273.0 Hz), 123.44, 117.51, 115.28 (q, J = 3.9 Hz), 107.17 (q, J = 3.9 Hz), 40.21.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.97.

HRMS (ESI) calculated $C_9H_{10}BrF_3N^+$ $[M+H]^+$ m/z 267.9943, found 267.9941.



1e

***N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-5-(trifluoromethyl)benzene-1,3-diamine (1e)**: as a white solid (73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, J = 2.2 Hz, 2H), 6.13 (t, J = 2.2 Hz, 1H), 2.99 (s, 12H).

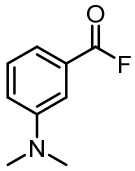
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.62, 131.85 (q, J = 30.8 Hz), 124.89 (q, J = 272.6 Hz), 99.02 (d, J = 1.4 Hz), 98.21 (q, J = 4.0 Hz), 40.60.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.81.

HRMS (ESI) calculated $C_{11}H_{16}F_3N_2^+$ $[M+H]^+$ m/z 233.1260, found 233.1264.

6.2 Isolation of the acyl fluoride

30 mg of *N,N*-dimethyl-3-(trifluoromethyl)aniline (**1a**) was added into a total volume of 100 mL in ACN/H_2O (v/v = 1/1) solution, followed by irradiation with the 311 nm lamp (21.2 mW cm^{-2}) in a quartz test flask for 30 min. After removing ACN in vacuo, the aqueous layer was extracted with DCM three times, dried over $MgSO_4$ and concentrated in vacuo, and given 3-(dimethylamino)benzoyl fluoride (**5a**).



5a

3-(dimethylamino)benzoyl fluoride (5a): as a yellow oil (77% yield).

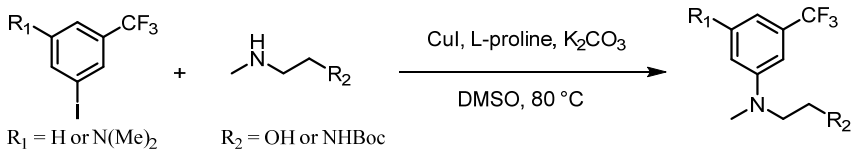
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (ddd, J = 8.5, 7.5, 1.2 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.22 (dd, J = 2.8, 1.7 Hz, 1H), 7.16 (ddd, J = 8.3, 2.8, 0.9 Hz, 1H), 2.97 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 158.12 (d, J = 344.1 Hz), 151.04, 130.45, 124.93 (d, J = 58.9 Hz), 119.72, 118.73 (d, J = 3.4 Hz), 113.77 (d, J = 4.4 Hz), 40.33.

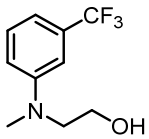
^{19}F NMR (376 MHz, DMSO-d_6) δ 17.66.

HRMS (ESI) calculated $C9H11FNO^+$ $[M+H]^+$ m/z 168.0819, found 168.0818.

6.3 The synthetic method for 1b-1c and 1f-1g.



A mixture of aryl halide (1 equiv.), alkylamine (1.5 equiv.), K_2CO_3 (2 equiv.), CuI (0.1 equiv.) and L-proline (0.2 equiv.) in DMSO was stirred overnight at 80 °C under argon. The reaction was quenched with water and extracted with ethyl acetate three times. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products.



1b

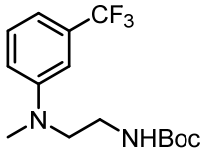
2-(methyl(3-(trifluoromethyl)phenyl)amino)ethan-1-ol (1b): as a yellow oil (78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (td, J = 8.2, 0.8 Hz, 1H), 6.98 – 6.90 (m, 3H), 3.82 (t, J = 5.6 Hz, 2H), 3.51 (t, J = 5.6 Hz, 2H), 3.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.92, 131.50 (q, J = 31.5 Hz), 129.60, 124.47 (q, J = 272.6 Hz), 115.58, 113.22 (q, J = 4.2 Hz), 108.77 (q, J = 3.8 Hz), 60.05, 55.03, 38.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.73.

HRMS (ESI) calculated $C_{10}H_{13}F_3NO^+$ $[M+H]^+$ m/z 220.0944, found 220.0944.



1c

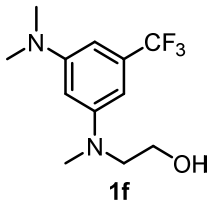
***tert*-butyl (2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)carbamate (1c):** as a yellow solid (58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.91 – 6.85 (m, 2H), 3.49 (t, J = 6.4 Hz, 2H), 3.31 (q, J = 6.4 Hz, 2H), 2.99 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.01, 149.40, 131.52 (q, J = 31.4 Hz), 129.64, 124.49 (q, J = 272.4 Hz), 115.02, 112.82 (q, J = 3.9 Hz), 108.18 (q), 52.01, 38.24 (d, J = 22.7 Hz), 28.33.

^{19}F NMR (376 MHz, $CDCl_3$) δ -61.08.

HRMS (ESI) calculated $C_{15}H_{22}F_3N_2O_2^+$ $[M+H]^+$ m/z 319.1628, found 319.1625.



1f

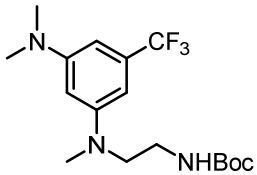
2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)ethan-1-ol (1f): as a yellow oil (60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (t, J = 1.8 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 6.20 (t, J = 2.2 Hz, 1H), 3.81 (t, J = 5.6 Hz, 2H), 3.49 (t, J = 5.6 Hz, 2H), 2.99 (s, 3H), 2.97 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.69, 151.17, 131.99 (q, J = 31.2 Hz), 124.79 (q, J = 273.0 Hz), 99.46, 98.72 (q, J = 4.0 Hz), 98.39 (q, J = 3.8 Hz), 60.16, 55.39, 40.58, 38.90.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.82.

HRMS (ESI) calculated $C_{12}H_{18}F_3N_2O^+$ $[M+H]^+$ m/z 263.1366, found 263.1363.



1g

***tert*-butyl (2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)ethyl)carbamate (1g):** as a yellow oil (78% yield).

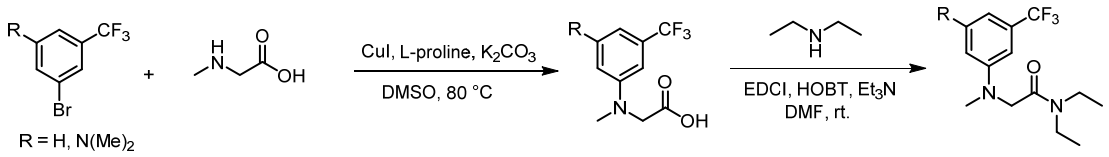
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.89 (t, J = 6.0 Hz, 1H), 6.26 (d, J = 15.4 Hz, 2H), 6.20 (s, 1H), 3.40 – 3.30 (m, 2H), 3.07 (q, J = 6.4 Hz, 2H), 2.92 (s, 6H), 2.91 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 155.97, 151.72, 150.51, 131.86 (q, J = 30.9 Hz), 124.78 (q, J = 272.8 Hz), 98.91, 98.37 (q, J = 4.2 Hz), 97.91 (q, J = 3.6 Hz), 79.44, 52.40, 40.61, 38.58, 38.24, 28.36.

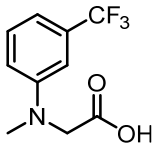
^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -61.23.

HRMS (ESI) calculated $C_{17}H_{27}F_3N_3O_2^+$ $[M+H]^+$ m/z 362.2050, found 362.2045.

6.4 The synthetic method for 1d, 1h and 1u-1v.



A mixture of aryl halide (1 equiv.), sarcosine (1.5 equiv.), K_2CO_3 (2 equiv.), CuI (0.1 equiv.) and L-proline (0.2 equiv.) in DMSO was stirred overnight at 80 °C under argon. The reaction was quenched with water and extracted with ethyl acetate three times. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford corresponding carboxylic acid derivatives.



1u

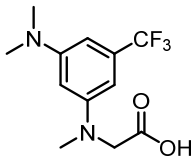
***N*-methyl-*N*-(3-(trifluoromethyl)phenyl)glycine (1u):** as a white solid (84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 8.0 Hz, 1H), 7.05 – 6.97 (m, 1H), 6.89 (t, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.4, 2.8 Hz, 1H), 4.14 (s, 2H), 3.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.39, 148.74, 131.64 (q, J = 31.4 Hz), 129.74, 124.35 (q, J = 272.5 Hz), 115.16, 114.14 (q, J = 3.8 Hz), 108.64 (q, J = 4.0 Hz), 53.85, 39.47.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76.

HRMS (ESI) calculated $C_{10}H_{11}F_3NO_2^+$ $[M+H]^+$ m/z 234.0736, found 234.0731.



1v

***N*-(3-(dimethylamino)-5-(trifluoromethyl)phenyl)-*N*-methylglycine (1v):** as a white solid (78% yield).

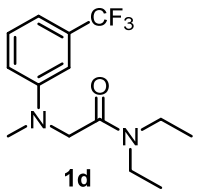
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.27 (t, J = 1.8 Hz, 1H), 6.20 (t, J = 1.9 Hz, 1H), 6.07 (t, J = 2.3 Hz, 1H), 4.12 (s, 2H), 3.00 (s, 3H), 2.91 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.46, 151.90, 150.74, 130.80 (q, J = 30.0 Hz), 125.35 (q, J = 272.6 Hz), 99.00, 97.66 (t, J = 4.1 Hz), 97.11 (q, J = 4.2 Hz), 53.90, 40.51.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.93.

HRMS (ESI) calculated $C_{12}H_{16}F_3N_2O_2^+$ $[M+H]^+$ m/z 277.1158, found 277.1159.

Compound **m2** or **m3** (1.0 equiv.), EDCI (2 equiv.), HOBT (2 equiv.) and triethylamine in DMF were added diethylamine (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford the product.



1d

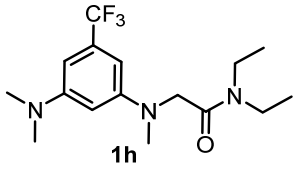
***N,N*-diethyl-2-(methyl(3-(trifluoromethyl)phenyl)amino)acetamide (1d):** as white solid (84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, 1H), 6.93 (ddt, J = 7.7, 1.7, 0.8 Hz, 1H), 6.82 (t, J = 2.2 Hz, 1H), 6.78 (dd, J = 8.4, 2.7 Hz, 1H), 4.13 (s, 2H), 3.46 – 3.27 (m, 4H), 3.10 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.75, 149.56, 131.31 (q, J = 31.5 Hz), 129.54, 124.52 (q, J = 272.4 Hz), 115.06 (d, J = 1.5 Hz), 113.21 (q, J = 3.8 Hz), 108.44 (q, J = 4.1 Hz), 53.81, 41.22, 40.51, 39.79, 14.34, 13.02.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.78.

HRMS (ESI) calculated $C_{14}H_{20}F_3N_{2O}^+$ $[M+H]^+$ m/z 289.1522, found 289.1519.



1h

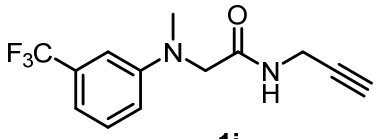
2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)-*N,N*-diethylacetamide (1h): as a white solid (79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (t, J = 1.8 Hz, 1H), 6.25 (t, J = 1.8 Hz, 1H), 6.08 (t, J = 2.3 Hz, 1H), 4.10 (s, 2H), 3.36 (dq, J = 17.6, 7.2 Hz, 4H), 3.09 (s, 3H), 2.95 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.35, 151.54, 150.53, 131.82 (q, J = 30.8 Hz), 124.81 (q, J = 272.6 Hz), 99.23, 98.84 (q, J = 4.0 Hz), 98.19 (q, J = 4.0 Hz), 54.44, 41.34, 40.65, 40.57, 39.95, 14.33, 13.04.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.89.

HRMS (ESI) calculated $C_{16}H_{25}F_3N_3O^+$ $[M+H]^+$ m/z 332.1944, found 332.1941.



1j

Compound **1u** (1.0 equiv.), EDCI (2 equiv.), HOBT (2 equiv.) and triethylamine in DMF were added propargylamine (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford the yellow solid product (71% yield).

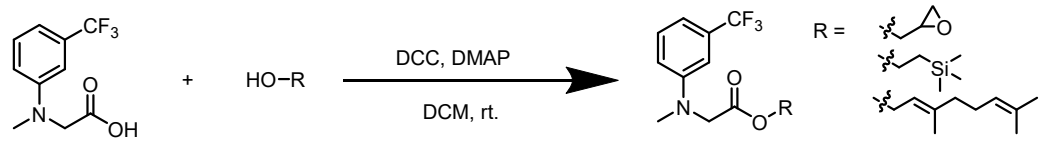
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 8.1 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.93 (t, J = 2.1 Hz, 1H), 6.85 (dd, J = 8.4, 2.8 Hz, 1H), 6.63 (s, 1H), 4.08 (dd, J = 5.6, 2.5 Hz, 2H), 3.92 (s, 2H), 3.07 (s, 3H), 2.20 (t, J = 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.54, 149.36, 131.98, 131.66, 129.96, 125.52, 122.82, 115.30, 115.26, 109.44, 109.40, 79.03, 71.74, 58.45, 39.86, 28.96.

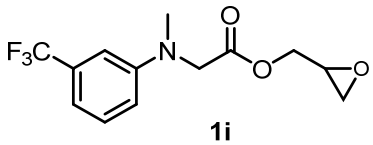
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76.

HRMS (ESI) calculated $C_{13}H_{14}F_3N_2O^+$ $[M+H]^+$ m/z 271.1053, found 271.1051.

6.5 The synthetic method for 1i, 1k and 1n.



Compound **1u** (1.0 equiv.), DCC (2 equiv.) and DMAP (0.1 equiv.) in DCM was added glycidol (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with dichloromethane three times. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products.



1i

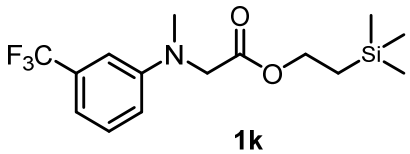
oxiran-2-ylmethyl *N*-methyl-*N*-(3-(trifluoromethyl)phenyl)glycinate (1i): as a yellow oil (69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (td, J = 8.0, 1.0 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.88 (t, J = 2.1 Hz, 1H), 6.82 (dd, J = 8.4, 2.7 Hz, 1H), 4.48 (dd, J = 12.3, 3.0 Hz, 1H), 4.15 (s, 2H), 3.97 (dd, J = 12.3, 6.2 Hz, 1H), 3.17 (ddt, J = 6.3, 4.1, 2.8 Hz, 1H), 3.10 (s, 3H), 2.81 (dd, J = 4.8, 4.1 Hz, 1H), 2.58 (dd, J = 4.9, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 148.88, 131.53 (q, J = 31.3 Hz), 129.68, 124.39 (q, J = 272.2 Hz), 115.19, 113.90 (q, J = 4.0 Hz), 108.60 (q, J = 3.9 Hz), 65.37, 54.03, 49.08, 44.56, 39.52.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.74.

HRMS (ESI) calculated $C_{13}H_{15}F_3NO_3^+$ $[M+H]^+$ m/z 290.0999, found 290.0995.



1k

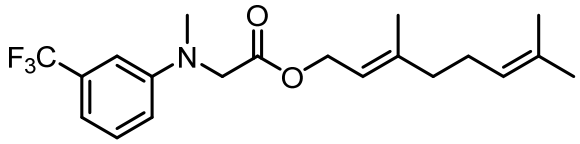
2-(trimethylsilyl)ethyl *N*-methyl-*N*-(3-(trifluoromethyl)phenyl)glycinate (1k): as a yellow oil (51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 8.1 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.4, 2.7 Hz, 1H), 4.30 – 4.18 (m, 2H), 4.07 (s, 2H), 3.10 (s, 3H), 1.07 – 0.91 (m, 2H), 0.03 (d, J = 1.9 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.12, 150.58, 133.05 (q, J = 31.6 Hz), 131.16, 126.00 (q, J = 272.5 Hz), 116.68 (d, J = 1.5 Hz), 115.22 (q, J = 3.9 Hz), 110.13 (q, J = 4.0 Hz), 65.07, 55.97, 41.14, 19.00, 0.00.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.76.

HRMS (ESI) calculated $C_{15}H_{22}F_3NNaO_2Si^+$ $[M+Na]^+$ m/z 356.1264, found 356.1269.



1n

(*E*)-3,7-dimethylocta-2,6-dien-1-yl *N*-methyl-*N*-(3-(trifluoromethyl)phenyl)glycinate (1n): as a yellow oil (69% yield).

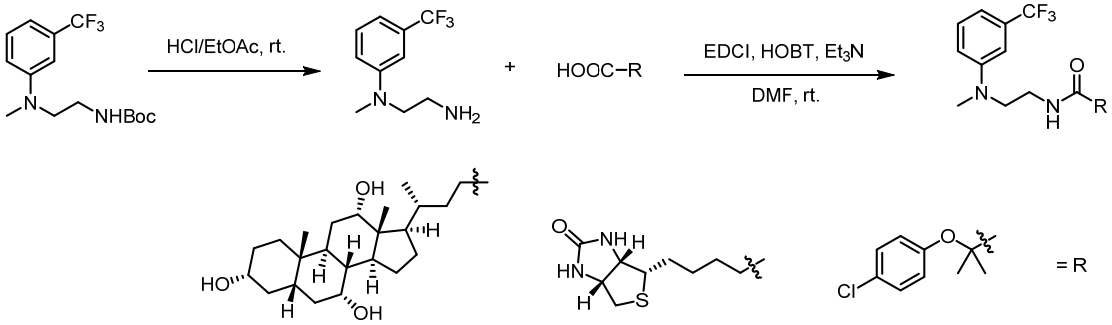
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.81 (dd, J = 8.4, 2.7 Hz, 1H), 5.32 (tq, J = 7.3, 1.4 Hz, 1H), 5.08 (tt, J = 6.7, 1.4 Hz, 1H), 4.65 (d, J = 7.2 Hz, 2H), 4.09 (s, 2H), 3.10 (s, 3H), 2.12 – 1.99 (m, 4H), 1.68 (dd, J = 7.0, 1.5 Hz, 6H), 1.61 (d, J = 1.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.39, 149.01, 143.24, 131.88, 131.48 (q, J = 31.5 Hz), 129.58, 124.43 (q, J = 272.3 Hz), 123.68, 117.71, 115.15, 113.68 (q, J = 3.9 Hz), 108.59 (q, J = 4.0 Hz), 61.91, 54.30, 39.58, 39.49, 26.26, 25.68, 17.67, 16.44.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.74.

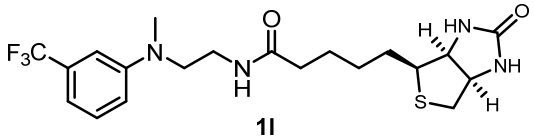
HRMS (ESI) calculated $C_{20}H_{27}F_3NO_2^+$ $[M+H]^+$ m/z 370.1988, found 370.1985.

6.6 The synthetic method for 1l, 1o and 1q.



Compound **1c** (318 mg ,1.0 mmol) was dissolved in EtOAc (4 mL) and was added 4 M HCl/EtOAc (8 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford crude product for the next step without further purification.

D-Biotin (1.0 equiv.), or clofibric acid (1.0 equiv.), or cholic acid (1.0 equiv.), EDCI (2 equiv.), HOBT (2 equiv.) and triethylamine (2 equiv.) in DMF were added crude product from the previous step (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products.



1l

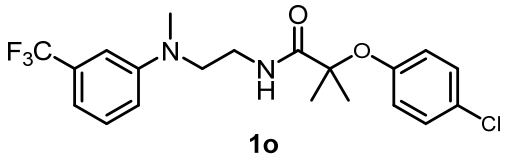
***N*-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanamide (1l):** as a white solid (40% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (t, J = 5.8 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 8.5, 2.6 Hz, 1H), 6.93 – 6.84 (m, 2H), 6.41 (s, 1H), 6.35 (s, 1H), 4.34 – 4.26 (m, 1H), 4.11 (ddd, J = 7.7, 4.4, 1.9 Hz, 1H), 3.41 (t, J = 6.7 Hz, 2H), 3.20 (q, J = 6.4 Hz, 2H), 3.07 (ddd, J = 8.5, 6.2, 4.4 Hz, 1H), 2.94 (s, 3H), 2.81 (dd, J = 12.4, 5.1 Hz, 1H), 2.57 (d, J = 12.4 Hz, 1H), 2.00 (t, J = 7.4 Hz, 2H), 1.66 – 1.37 (m, 4H), 1.33 – 1.20 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.86, 163.20, 149.65, 130.41 (1, J = 30.6 Hz), 130.33, 125.10 (q, J = 272.9 Hz), 111.84 (q, J = 4.3 Hz), 107.63 (q, J = 4.2 Hz), 61.49, 59.67, 55.85, 51.13, 40.31, 38.47, 36.23, 35.67, 28.68, 28.48, 25.55.

^{19}F NMR (376 MHz, DMSO-d_6) δ -61.10.

HRMS (ESI) calculated $C_{20}H_{28}F_3N_4O_2S^+$ $[M+H]^+$ m/z 445.1880, found 445.1876.



1o

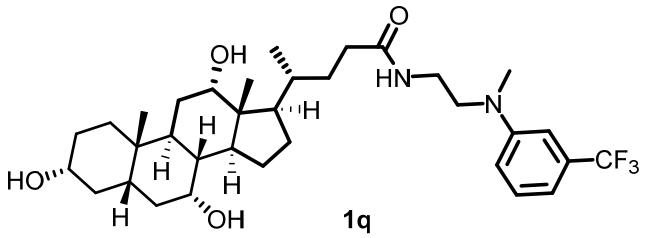
2-(4-chlorophenoxy)-2-methyl-*N*-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)propanamide (1o): as a yellow solid (71% yield).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.33 – 7.24 (m, 1H), 7.23 – 7.16 (m, 2H), 6.97 – 6.86 (m, 4H), 6.80 – 6.72 (m, 2H), 3.56 – 3.49 (m, 4H), 2.97 (s, 3H), 1.42 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-d) δ 174.85, 152.55, 149.38, 131.57 (q, J = 31.5 Hz), 129.73, 129.25, 128.79, 124.45 (q, J = 272.4 Hz), 122.93, 115.19, 113.04 (q, J = 3.7 Hz), 108.30 (q, J = 3.8 Hz), 81.95, 51.40, 38.22, 37.01, 24.80.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.69.

HRMS (ESI) calculated $C_{20}H_{23}ClF_3N_2O_2^+$ $[M+H]^+$ m/z 415.1395, found 415.1391.



1q

(*S*)-*N*-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)-4-((3*S*,5*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,14*R*,17*S*)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pentanamide (1q): as a white solid (57% yield).

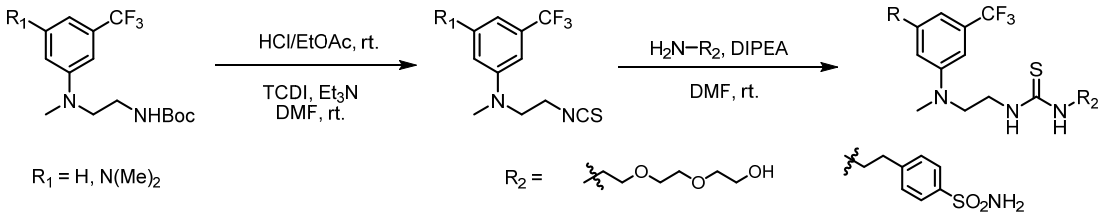
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (t, J = 5.8 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 6.97 (dd, J = 8.5, 2.5 Hz, 1H), 6.92 – 6.83 (m, 2H), 4.05 – 3.68 (m, 4H), 3.61 (q, J = 3.0 Hz, 1H), 3.41 (t, J = 6.6 Hz, 2H), 3.19 (q, J = 6.2 Hz, 3H), 2.93 (s, 3H), 2.30 – 2.10 (m, 2H), 2.07 – 1.85 (m, 3H), 1.81 – 1.55 (m, 6H), 1.51 – 1.06 (m, 12H), 0.99 – 0.78 (m, 8H), 0.56 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 173.47, 149.64, 130.42 (q, J = 31.1 Hz), 125.08 (q, J = 272.5 Hz), 115.56, 111.80 (q, J = 3.8 Hz), 107.60 (q, J = 3.9 Hz), 79.65, 71.48, 70.92, 66.72, 51.15, 46.52, 46.18, 42.00, 41.82, 38.43, 36.28, 35.78, 35.59, 35.36, 34.84, 32.92, 31.99, 30.87, 29.03, 27.71, 26.68, 23.25, 23.06, 17.54, 12.77.

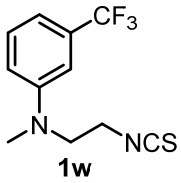
^{19}F NMR (376 MHz, DMSO-d_6) δ -61.15.

HRMS (ESI) calculated $C_{34}H_{52}F_3N_2O_4^+$ $[M+H]^+$ m/z 609.3874, found 609.3865.

6.7 The synthetic method for 1w, 1m and 1p.



Compound **1c** (318 mg, 1.0 mmol) or **1g** (361 mg, 1.0 mmol) was dissolved in EtOAc (4.0 mL) and was added 4 M HCl/EtOAc (8 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford the product for the next step without further purification. The product was dissolved in anhydrous DMF (8 mL), added TCDI (214 mg,1.2 mmol) and triethylamine (202 mg, 2.0 mmol) at room temperature. The reaction mixture was stirred for 6 h and added H_2O and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 10 : 1) to afford corresponding products.



1w

2-(4-chlorophenoxy)-2-methyl-*N*-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)propanamide (1w): as a yellow oil (74% yield).

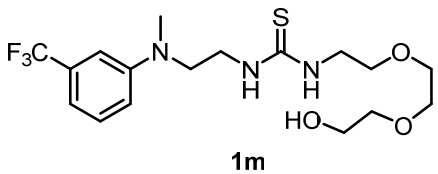
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 1H), 7.00 (ddt, J = 7.6, 1.6, 0.8 Hz, 1H), 6.90 – 6.81 (m, 2H), 3.70 (d, J = 2.0 Hz, 4H), 3.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.17, 131.78 (q, J = 31.9 Hz), 129.90, 124.35 (q, J = 272.4 Hz), 115.15, 113.75 (q, J = 3.9 Hz), 108.41 (q, J = 3.8 Hz), 52.18, 42.62, 39.18.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75.

HRMS (ESI) calculated $C_{11}H_{12}F_3N_2S^+$ $[M+H]^+$ m/z 261.0668, found 261.0662.

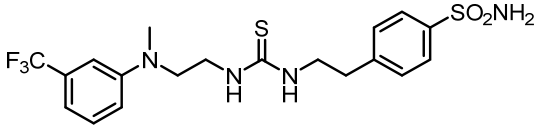
Compound **1w** (1 equiv.) and DIPEA (2 equiv.) were dissolved in DMF and added 2-(2-(2-aminoethoxy)ethoxy)ethan-1-ol (1.2 equiv.) or 4-(2-aminoethyl)benzenesulfonamide (1.2 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 6 h and added H_2O and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford corresponding products.



1m

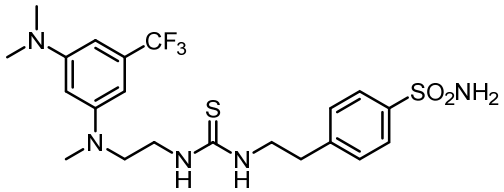
1-(2-(2-(2-hydroxyethoxy)ethoxy)ethyl)-3-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)thiourea (1m): as a yellow oil (95% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (ddt, J = 8.3, 6.5, 0.9 Hz, 1H), 6.98 – 6.89 (m, 3H), 6.84 (s, 1H), 6.75 (s, 1H), 3.76 (q, J = 6.2 Hz, 2H), 3.68 – 3.55 (m, 12H), 3.54 – 3.48 (m, 2H), 2.99 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 183.30, 149.52, 131.48 (q, J = 31.5 Hz), 129.67, 124.49 (q, J = 272.4 Hz), 115.21, 112.78 (d, J = 3.4 Hz), 108.23 (q, J = 3.5 Hz), 77.24, 72.20, 70.00, 69.86, 61.61, 51.31, 44.27, 41.84, 38.25.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.64.
HRMS (ESI) calculated $C_{17}H_{27}F_3N_3O_3S^+$ $[M+H]^+$ m/z 410.1720, found 410.1716.



1p

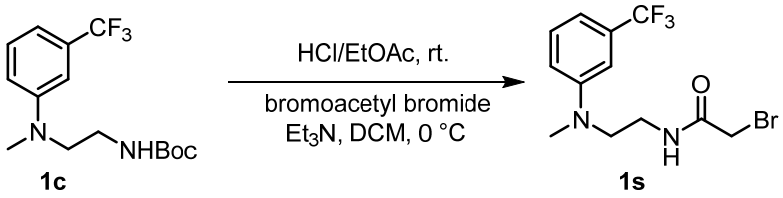
4-(2-(3-(2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl)thioureido)ethyl)benzenesulfonamide (1p): as white solid (93% yield).
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.3 Hz, 2H), 7.57-7.52 (brs., 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.29 (s, 2H), 7.03 (dd, J = 12.0, 3.7 Hz, 1H), 7.00 (s, 1H) 6.88 (d, J = 7.6 Hz, 1H), 3.67 – 3.46 (m, 6H), 2.95 (s, 3H), 2.90 – 2.82 (m, 2H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 162.79, 149.74, 144.04, 142.58, 130.30, 131.04 – 129.90 (q, J = 30.0 Hz), 129.59, 126.20, 125.12 (q, J = 272.5 Hz), 115.61, 111.90 (q, J = 4.5 Hz), 107.80 (1, J = 4.1 Hz), 50.88, 36.25, 34.96, 31.24.
^{19}F NMR (376 MHz, DMSO-d_6) δ -61.05.



10e

HRMS (ESI) calculated $C_{19}H_{24}F_3N_4O_2S_2^+$ $[M+H]^+$ m/z 461.1287, found 461.1283.
4-(2-(3-(2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)ethyl)thioureido)ethyl)benzenesulfonamide (10e) as yellow solid (93% yield).
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.40 (s, 1H), 7.38 (s, 1H), 7.29 (s, 2H), 6.36 (s, 1H), 6.25 (d, J = 9.1 Hz, 2H), 3.68 – 3.45 (m, 6H), 2.93 (s, 9H), 2.85 (t, J = 7.5 Hz, 2H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 151.94, 150.72, 144.03, 142.56, 130.89 (q, J = 29.9 Hz), 129.58, 126.18, 125.41 (q, J = 272.7 Hz), 99.17 – 98.89 (m), 97.50 – 97.16 (m), 51.10, 40.78, 38.42, 35.00.
^{19}F NMR (376 MHz, DMSO-d_6) δ -61.16.
HRMS (ESI) calculated $C_{21}H_{29}F_3N_5O_2S_2^+$ $[M+H]^+$ m/z 504.1709, found 504.1707.

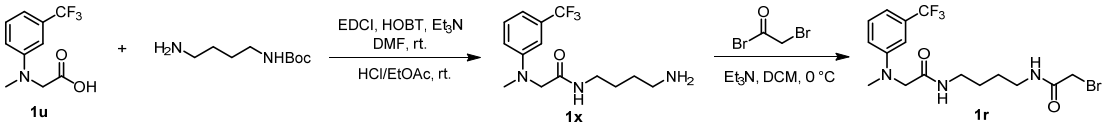
6.8 The synthetic method for 1r and 1s.



1c **1s**

Compound **1c** (318 mg, 1.0 mmol) was dissolved in EtOAc (4.0 mL) and was added 4 M HCl/EtOAc (8.0 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford the product for the next step without further purification. The above product and triethylamine (202 mg, 2.0 mmol) were dissolved in DCM and added bromoacetyl bromide (222 mg, 1.1 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h, added H_2O, and extracted with DCM three times. The organic layer was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford **2-bromo-*N*-(2-(methyl(3-(trifluoromethyl)-phenyl)amino)ethyl)acetamide (1s)** as white solid (79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (tt, J = 7.6, 0.9 Hz, 1H), 6.96 (ddt, J = 7.6, 1.6, 0.8 Hz, 1H), 6.92 (d, J = 8.1 Hz, 2H), 3.82 (s, 2H), 3.59 – 3.46 (m, 4H), 3.01 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.84, 149.21, 131.64 (q, J = 31.8 Hz), 129.79, 124.42 (q, J = 272.5 Hz), 115.29, 113.33 (q, J = 3.65 Hz), 108.49 (q, J = 3.9 Hz), 51.39, 38.58, 37.82, 28.96.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.74.
HRMS (ESI) calculated $C_{12}H_{15}BrF_3N_2O^+$ $[M+H]^+$ m/z 339.0314, found 339.0313.

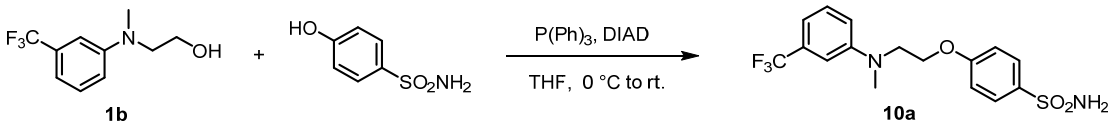


Compound **1u** (1.0 equiv.), EDCI (2 equiv.), HOBT (2 equiv.) and triethylamine (2 equiv.) in DMF was added *tert*-butyl *N*-(4-aminobutyl)carbamate (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products. The obtained product was dissolved in EtOAc (4 mL) and was added 4 M HCl/EtOAc (8 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford the product for the next step without further purification.

Compound **1x** (1.0 equiv.) and triethylamine (2.0 equiv.) were dissolved in DCM and added bromoacetyl bromide (1.2 equiv.) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h, added H_2O, and extracted with DCM three times. The organic layer was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford **2-bromo-*N*-(4-(2-(methyl(3-(trifluoromethyl)phenyl)amino)acetamido)butyl)acetamide (1r)** as a white solid (82% yield).

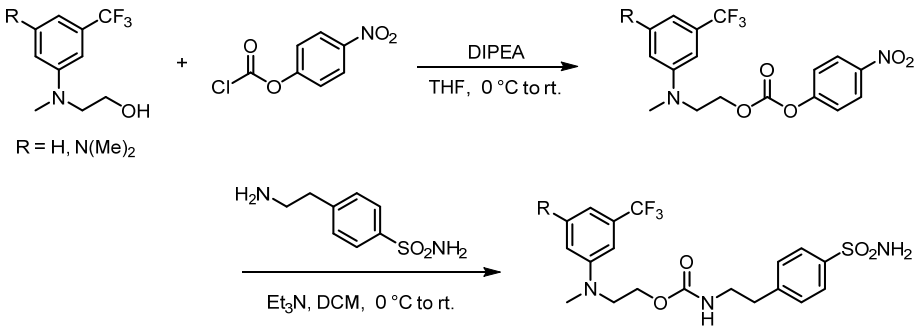
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 8.0 Hz, 1H), 7.07 (ddt, J = 7.6, 1.6, 0.9 Hz, 1H), 6.91 (t, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.4, 2.7 Hz, 1H), 6.64 – 6.49 (m, 2H), 3.90 (s, 2H), 3.83 (s, 2H), 3.32 (q, J = 6.4 Hz, 2H), 3.25 (q, J = 6.6 Hz, 2H), 3.08 (s, 3H), 1.56 – 1.44 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.74, 165.57, 149.26, 131.73 (q, J = 31.7 Hz), 129.92, 124.20 (q, J = 272.2 Hz), 115.94, 114.98 (q, J = 3.7 Hz), 109.21 (q, J = 3.8 Hz), 58.44, 39.95, 39.63, 38.68, 29.16, 26.87, 26.45.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.73.
HRMS (ESI) calculated $C_{16}H_{22}BrF_3N_3O_2^+$ $[M+H]^+$ m/z 424.0842, found 424.0838.

6.9 The synthetic method for 10a-10f.



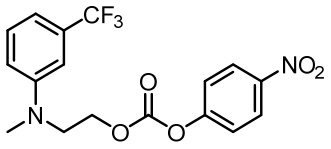
Compound **1b** (1 equiv.), 4-hydroxybenzenesulfonamide (1.0 equiv.), and triphenylphosphine (1.1 equiv.) were dissolved in dry THF and added DIAD (1.1 equiv.) at 0 °C under argon. The reaction mixture was stirred at room temperature for 8 h, added H_2O, and extracted with ethyl acetate three times. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford **4-(2-(methyl(3-(trifluoro-methyl)phenyl)amino)ethoxy)benzenesulfonamide (10a)** as a white solid (56% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 – 7.71 (m, 2H), 7.37 (ddd, J = 8.6, 7.6, 1.0 Hz, 1H), 7.20 (s, 2H), 7.05 (dq, J = 8.6, 2.6, 2.2 Hz, 3H), 6.97 (d, J = 2.3 Hz, 1H), 6.95 – 6.89 (m, 1H), 4.22 (t, J = 5.5 Hz, 2H), 3.82 (t, J = 5.5 Hz, 2H), 3.03 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 161.17, 149.65, 136.85, 130.41 (q, J = 30.8 Hz), 130.38, 128.16, 125.06 (q, J = 272.5 Hz), 116.00, 114.88, 112.27 (q, J = 3.8 Hz), 108.10 (q, J = 4.1 Hz), 66.25, 51.14, 38.98.
^{19}F NMR (376 MHz, DMSO-d_6) δ -61.11.
HRMS (ESI) calculated $C_{16}H_{18}F_3N_2O_3S^+$ $[M+H]^+$ m/z 375.0985, found 375.0982.



Compound **1b/1f** (1 equiv.) and 4-nitrophenyl chloroformate (1.5 equiv.) were dissolved in dry THF and added DIPEA (1.1 equiv.) at 0 °C under argon. The reaction mixture was stirred at room temperature for 6 h, added H_2O, and extracted with ethyl acetate three times. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products.

Then the obtained product (1.0 equiv.) and 4-(2-aminoethyl)benzenesulfonamide (1.2 equiv.) was dissolved in DCM and added triethylamine (2.0 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 8 h, added H_2O, and extracted with DCM three times. The organic layer was dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford corresponding products.



1y

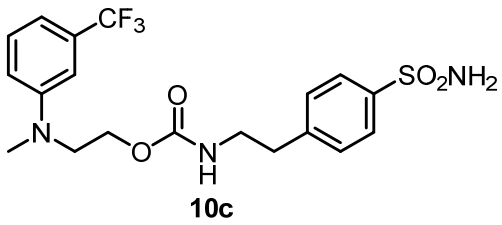
2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl (4-nitrophenyl) carbonate (1y) as a yellow oil (97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 2.2 Hz, 1H), 7.33 (ddt, J = 8.4, 7.6, 0.8 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 6.98 (ddt, J = 7.7, 1.6, 0.8 Hz, 1H), 6.96 – 6.90 (m, 2H), 4.48 (t, J = 5.7 Hz, 2H), 3.76 (t, J = 5.7 Hz, 2H), 3.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.36, 152.52, 148.91, 145.49, 131.65 (q, J = 31.7 Hz), 129.78, 125.31, 124.43 (q, J = 272.5 Hz), 121.77, 115.10, 113.35 (q, J = 4.0 Hz), 108.40 (q, J = 4.1 Hz), 66.17, 50.81, 38.57.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72.

HRMS (ESI) calculated $C_{17}H_{16}F_3N_2O_5^+$ $[M+H]^+$ m/z 385.1006, found 385.1002.



10c

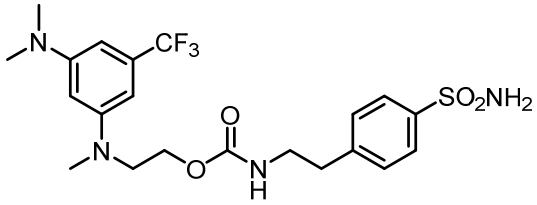
2-(methyl(3-(trifluoromethyl)phenyl)amino)ethyl (4-sulfamoylphenethyl)carbamate (10c) as a white solid (76% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.2 Hz, 1H), 7.42 – 7.21 (m, 3H), 7.02 – 6.96 (m, 1H), 6.90 (d, J = 7.0 Hz, 1H), 4.09 (t, J = 5.8 Hz, 1H), 3.58 (t, J = 5.9 Hz, 1H), 3.21 (q, J = 6.8 Hz, 1H), 2.94 (s, 1H), 2.76 (t, J = 7.3 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.52, 149.53, 143.99, 142.52, 130.44 (q, J = 30.9 Hz), 130.39, 129.57, 125.06 (q, J = 272.6 Hz), 115.82, 112.12 (d, J = 4.0 Hz), 107.72 (q, J = 5.5, 3.9 Hz), 61.19, 51.03, 41.87, 38.82, 35.52.

^{19}F NMR (376 MHz, DMSO-d_6) δ -61.12.

HRMS (ESI) calculated $C_{19}H_{23}F_3N_3O_4S^+$ $[M+H]^+$ m/z 446.1356, found 446.1353.



10f

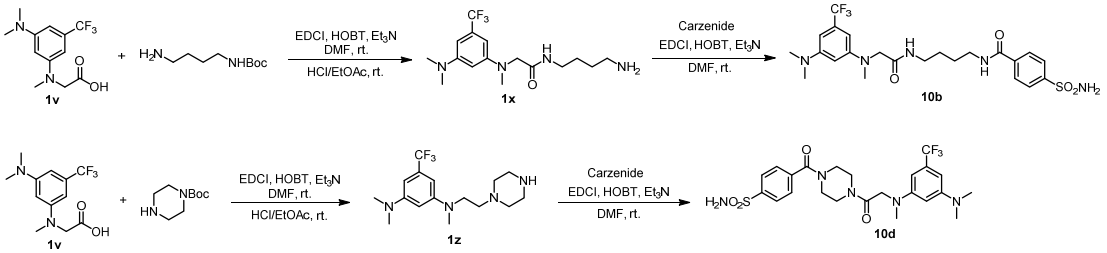
2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)ethyl (4-sulfamoylphenethyl)carbamate (10f) as a white solid (47% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.37 – 6.30 (m, 2H), 6.13 (t, J = 2.3 Hz, 1H), 5.03 (s, 2H), 4.72 (t, J = 6.9 Hz, 1H), 4.22 (t, J = 5.9 Hz, 2H), 3.55 (t, J = 5.9 Hz, 2H), 3.47 – 3.26 (m, 2H), 2.96 (d, J = 3.8 Hz, 9H), 2.83 (t, J = 7.0 Hz, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.22, 151.72, 150.37, 144.24, 140.28, 131.71 (d, J = 31.1 Hz), 129.52, 126.71, 123.36 (d, J = 272.8 Hz), 98.82, 98.28 (q, J = 4.0 Hz), 98.00 (q, J = 3.7 Hz), 62.07, 51.58, 41.78, 40.62, 38.51, 36.01.

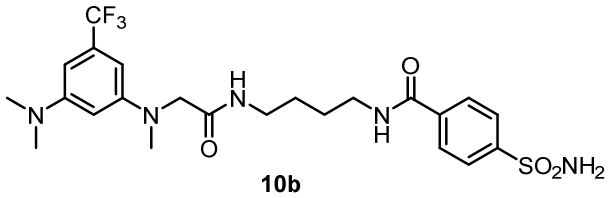
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75.

HRMS (ESI) calculated $C_{21}H_{28}F_3N_4O_4S^+$ $[M+H]^+$ m/z 489.1778, found 489.1776.



Compound **1v** (1.0 equiv.), EDCI (2.0 equiv.), HOBT (2.0 equiv.) and triethylamine (2.0 equiv.) in DMF were added *tert*-butyl 1-piperazinecarboxylate (1.2 equiv.) or *tert*-butyl *N*-(4-aminobutyl)-carbamate (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (PE : EtOAc = 2 : 1) to afford corresponding products. The obtained product was dissolved in EtOAc (4.0 mL) and was added 4 M HCl/EtOAc (8.0 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford the product for the next step without further purification.

Compound **1x** or **1z** (1.0 equiv.), EDCI (2.0 equiv.), HOBT (2.0 equiv.) and triethylamine (2.0 equiv.) in DMF were added *tert*-butyl 1-piperazinecarboxylate (1.2 equiv.), and then the mixture was stirred at room temperature overnight. The mixture was added H_2O and extracted with ethyl acetate. The organic layer was washed with saturated H_2O, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford corresponding products. The obtained product was dissolved in EtOAc (4 mL) and was added 4 M HCl/EtOAc (8 mL). The reaction mixture was stirred at room temperature for 6 h and concentrated to afford products **10b** and **10d**.



10b

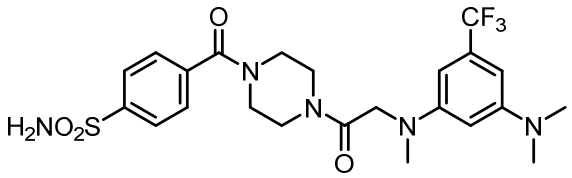
***N*-(4-(2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)acetamido)butyl)-4-sulfamoylbenzamide (10b)** as a white solid (56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (t, J = 5.6 Hz, 1H), 8.01 – 7.92 (m, 3H), 7.92 – 7.85 (m, 2H), 7.47 (s, 2H), 6.26 (t, J = 1.8 Hz, 1H), 6.19 (t, J = 1.8 Hz, 1H), 6.02 (t, J = 2.2 Hz, 1H), 3.90 (s, 2H), 3.25 (q, J = 6.3 Hz, 2H), 3.10 (q, J = 6.4 Hz, 2H), 3.02 (s, 3H), 2.88 (s, 6H), 1.55 – 1.39 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.60, 170.30, 156.60, 155.58, 151.36, 142.77, 135.50 (q, J = 30.1 Hz), 133.01, 130.80, 130.12 (q, J = 273.0 Hz), 103.78, 102.37 (q, J = 4.2 Hz), 102.00 (q, J = 4.0 Hz), 61.07, 45.26, 44.95, 43.32, 31.93, 31.58.

^{19}F NMR (376 MHz, $CDCl_3$) δ -56.51.

HRMS (ESI) calculated $C_{23}H_{31}F_3N_5O_4S^+$ $[M+H]^+$ m/z 530.2043, found 530.2042.



10d

4-(4-(2-((3-(dimethylamino)-5-(trifluoromethyl)phenyl)(methyl)amino)ethyl)piperazine-1-carbonyl)benzenesulfonamide (10d) as yellow solid (47% yield).

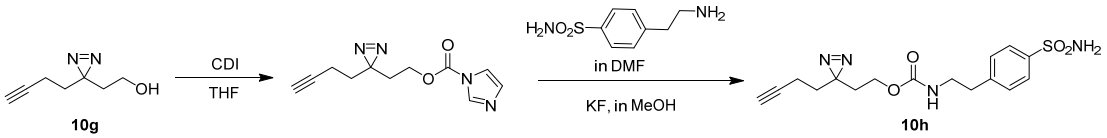
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 7.48 (s, 2H), 6.24 (t, J = 1.7 Hz, 1H), 6.22 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 4.35 (d, J = 23.5 Hz, 2H), 3.77 – 3.40 (m, 6H), 3.32 – 3.19 (m, 2H), 2.97 (s, 3H), 2.91 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 168.52, 168.06, 151.83, 151.17, 145.39, 139.33, 130.65 (d, J = 30.0 Hz), 128.10, 126.33, 125.42 (d, J = 272.3 Hz), 99.90 – 98.68 (m), 97.41 (q, J = 3.4 Hz), 53.36, 40.57.

^{19}F NMR (376 MHz, $CDCl_3$) δ -56.37.

HRMS (ESI) calculated $C_{23}H_{29}F_3N_5O_4S^+$ $[M+H]^+$ m/z 528.1887, found 528.1887.

6.10 The synthetic method for the conjugate probes, 10g and 10k.

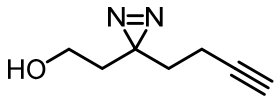


10g **10h**

The synthesis method of compound **10g** can be found in previous literature[6].

Compound **10g** (1.0 equiv.) and CDI (3.0 equiv.) were dissolved in dry THF, and the reaction mixture was stirred at room temperature for 6 h, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo without purification. Then the obtained product (1.0 equiv.) and 4-(2-aminoethyl)benzenesulfonamide (1.5 equiv.) was dissolved in DMF and added DBU (2.0 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 8 h, added H_2O, and extracted with EA three times. The organic layer was dried over Na_2SO_4 and then concentrated

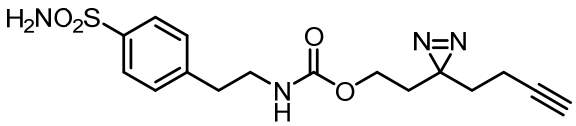
in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford the desired products **10h**.



10g

2-(3-(But-3-ynyl)-3*H*-diazirin-3-yl)ethanol (10g): as a yellow oil (56 % yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (t, J = 6.2 Hz, 2H), 2.08-1.95 (m, 3H), 1.74-1.63 (m, 5H).



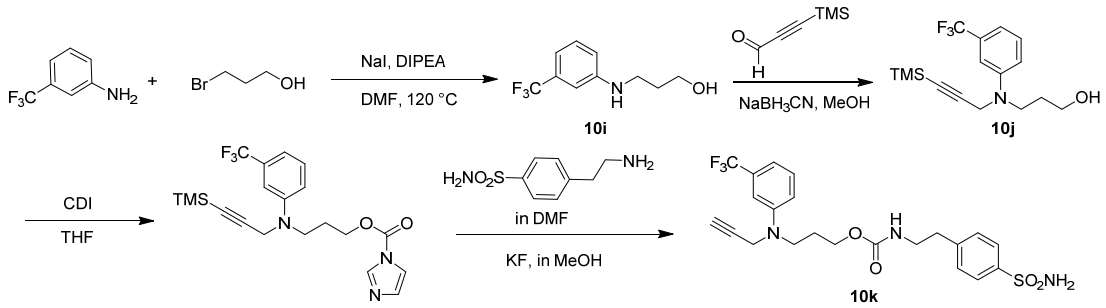
10h

2-(3-(but-3-yn-1-yl)-3*H*-diazirin-3-yl)ethyl (4-sulfamoylphenethyl)carbamate (10h): as a yellow solid (82 % yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 2H), 7.37-7.27 (m, 2H), 5.49 (s, 2H), 3.90 (t, J = 6.2 Hz, 2H), 3.47-3.35 (m, 2H), 2.91-2.78 (m, 2H), 2.03-1.93 (m, 2H), 1.73-1.51 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.18, 144.19, 140.37, 129.57, 126.64, 82.75, 69.47, 59.64, 41.81, 35.98, 32.51, 32.15, 26.52, 13.23.

HRMS (ESI) calculated $C_{16}H_{21}N_4O_4S^+$ $[M+H]^+$ m/z 365.1278, found 365.1271.

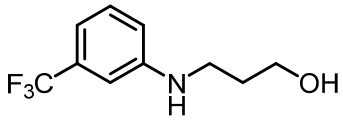


3-aminobenzotrifluoride (1.0 equiv.), 3-bromo-1-propanol (1.5 equiv.), sodium iodide (1.0 equiv.), and DIPEA (3.0 equiv.) in DMF was stirred at 120 °C overnight. The reaction was quenched by water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo without purification. The residue was further purified by silica chromatography (PE : EA = 2 : 1) to afford corresponding product, **10i**.

Compound **10i** (1.0 equiv.), 3-(trimethylsilyl)-2-propynal (2.0 equiv.), and a few drops of acetic acid were dissolved in MeOH. After 6 h reaction, the mixture was concentrated in vacuo and purified by silica chromatography (PE : EA = 2 : 1) to afford corresponding product, **10j**.

Compound **10j** (1.0 equiv.) and CDI (3.0 equiv.) were dissolved in dry THF, and the reaction mixture was stirred at room temperature for 6 h, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo without purification. Then the obtained product (1.0 equiv.) and 4-(2-aminoethyl)benzenesulfonamide (1.5 equiv.) was dissolved in DMF and added DBU (2.0 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 8 h, added H_2O, and extracted with EA three times. The organic layer was dried over Na_2SO_4 and then concentrated

in vacuo. The residue was purified by silica chromatography (DCM : MeOH = 10 : 1) to afford product **10k**.



10i

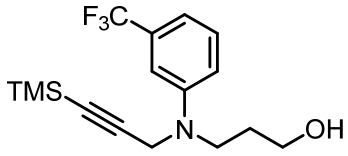
3-((3-(trifluoromethyl)phenyl)amino)propan-1-ol (10i): as a yellow oil (50 % yield)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.24 (t, J = 7.8 Hz, 1H), 6.89-6.71 (m, 3H), 6.08 (t, J = 5.5 Hz, 1H), 4.55 (t, J = 5.1 Hz, 1H), 3.56-3.50 (m, 2H), 3.19-3.04 (m, 2H), 1.72 (p, J = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 149.93, 130.62 (q, J = 30.7 Hz), 130.16, 125.06 (q, J = 272.2 Hz), 115.59, 111.53 (q, J = 4.0 Hz), 107.98 (q, J = 4.0 Hz), 58.97, 40.04, 32.18.

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -61.53.

HRMS (ESI) calculated $C_{10}H_{13}F_3NO^+$ $[M+H]^+$ m/z 220.0944, found 220.0942.



10j

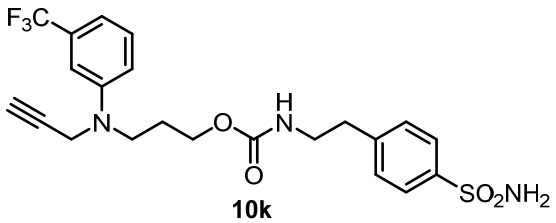
3-((3-(trifluoromethyl)phenyl)(3-(trimethylsilyl)prop-2-yn-1-yl)amino)propan-1-ol (10j): as a white solid (88 % yield)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.42-7.30 (m, 1H), 7.08-7.00 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 4.66 (t, J = 4.9 Hz, 1H), 4.17 (s, 2H), 3.48-3.42 (m, 4H), 1.76-1.64 (m, 2H), 0.07 (s, 9H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 147.69, 129.55, 129.51 (q, J = 30.8 Hz), 124.31 (q, J = 272.4 Hz), 116.23, 112.14 (d, J = 4.0 Hz), 108.46 (t, J = 4.1 Hz), 102.74, 87.87, 57.81, 47.54, 40.15, 29.49, -0.50.

^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -61.52.

HRMS (ESI) calculated $C_{16}H_{23}F_3NOSi^+$ $[M+H]^+$ m/z 330.1496, found 330.1496.



10k

3-(prop-2-yn-1-yl(3-(trifluoromethyl)phenyl)amino)propyl (4-sulfamoylphenethyl)carbamate (10k): as a white solid (53 % yield)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.78-7.66 (m, 2H), 7.43-7.34 (m, 3H), 7.29 (s, 3H), 7.06 (dd, J = 8.5, 2.6 Hz, 1H), 7.02-6.93 (m, 2H), 4.17 (d, J = 2.4 Hz, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.45 (t, J = 7.2 Hz, 2H), 3.29-3.21 (m, 2H), 3.16 (t, J = 2.3 Hz, 1H), 2.80 (t, J = 7.2 Hz, 2H), 1.93-1.77 (m, 2H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 156.67, 148.26, 144.05, 142.54, 130.46, 130.39 (q, J = 30.7 Hz), 129.60, 126.17, 124.98 (q, J = 272.3 Hz), 117.05, 113.29 (q, J = 4.1 Hz), 109.16 (q, J = 3.7 Hz), 80.69, 75.03, 61.92, 47.87, 41.90, 35.60, 26.88.

^{19}F NMR (376 MHz, DMSO-d_6) δ -61.14.

HRMS (ESI) calculated $C_{22}H_{25}F_3N_3O_4S^+$ $[M+H]^+$ m/z 484.1512, found 484.1508.

7. Computational details

DFT calculations were performed using Gaussian 09 program package.[7] All structures were optimized at the M06-2X(D3) level of theory[8] in experimental solvents ACN/H_2O (v/v = 1/1) with the 6-31+G** basis set,[9-10] and structures in triplet state were optimized by using UDFT method at the same level of theory. Vibrational frequencies were calculated at the same level of theory to evaluate zero-point vibrational energy and thermal correction at 298.15 K. The self-consistent reaction field (SCRF) method based on the universal solvation model SMD was adopted to evaluate the effect of solvent.[11] All single-point energies were computed using the same function with the ma-TZVP basis set (**Table S8**),[12] zero-point energy frequency correction factor is 0.967.[13] The intrinsic reaction coordinate (IRC) path was traced to check the energy profiles connecting each transition state to two associated minima of the proposed mechanism.[14] For TD-DFT calculation, the excitation energy from S_0 to S_1 was computed at M06-2X(D3)/ma-TZVP level in the same solvent model. The 3D diagrams of molecules were generated using CYLView20.[15]

Table S8. Electronic energies (E_e), correct enthalpies (H) and Gibbs free energies (G) for all stationary points (in Hartree), obtained at the M06-2X(D3)/6-31+G** theoretical level. The imaginary frequencies (in cm^{-1}) for all transition states were listed.

Structures	[a]*ZPE*	E_e	[b]E_e	[c]H_c	*H*	[d]G_c	*G*	[e]*G*	Imaginary Frequency
1a	0.17970	-703.03684	-703.29052	0.19275	-702.84409	0.14030	-702.89654	-703.15615	-
IM1	0.20327	-779.44914	-779.73362	0.22013	-779.22900	0.15910	-779.29004	-779.58123	-
TS1	0.20015	-779.36501	-779.65183	0.21667	-779.14835	0.15594	-779.20907	-779.50249	88.22
IM2	0.20429	-779.46134	-779.74378	0.21993	-779.24141	0.16167	-779.29968	-779.58886	-
IM3	0.19197	-679.03073	-679.27273	0.20522	-678.82551	0.15309	-678.87765	-679.12598	-
IM4	0.21582	-755.45180	-755.72308	0.23232	-755.21947	0.17215	-755.27965	-755.55806	-
TS2	0.21355	-755.41937	-755.68967	0.22906	-755.19031	0.17139	-755.24797	-755.52532	583.56
5a	0.17669	-578.60678	-578.80761	0.18892	-578.41786	0.13876	-578.46802	-578.67468	-
IM1-T_1	0.19826	-779.33660	-779.61993	0.21601	-779.12059	0.15237	-779.18423	-779.47410	-
TS3-T_1	0.19871	-779.33115	-779.61413	0.21557	-779.11558	0.15412	-779.17703	-779.46657	370.55
IM5-T_1	0.19825	-779.34565	-779.63032	0.21573	-779.12992	0.15244	-779.19321	-779.48442	-
TS4-T_1	0.19716	-779.32520	-779.60778	0.21305	-779.11215	0.15330	-779.17190	-779.46099	500.22
IM6-T_1	0.19913	-779.34490	-779.62717	0.21574	-779.12917	0.15369	-779.19121	-779.48004	-
H_2O	0.02131	-76.40975	-76.44080	0.02509	-76.38466	0.00365	-76.40610	-76.43785	-
HF	0.00918	-100.42098	-100.46240	0.01248	-100.40850	-0.00725	-100.42823	-100.46995	-
1a-T_1	0.17498	-702.92194	-703.17514	0.18884	-702.73309	0.13395	-702.78798	-703.04696	-

[a] Zero-point correction energy;

[b] Electronic energy obtained at the M06-2X(D3)/ma-TZVP/SMD (ACN/H_2O = 1:1, v/v) // M06-2X(D3)/6-31+G**/ SMD (ACN/H_2O = 1:1, v/v) theoretical level;

[c] Thermal correction to enthalpy;

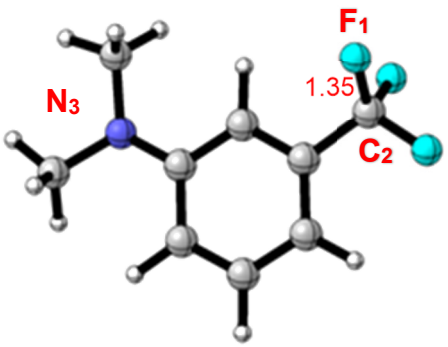
[d] Thermal correction to Gibbs free energy;

[e] Gibbs free energy obtained at the M06-2X(D3)/ma-TZVP/SMD (ACN/H_2O = 1:1, v/v) // M06-2X(D3)/6-31+G**/SMD (ACN/H_2O = 1/1, v/v) theoretical level.

Cartesian coordinates of all stationary points in this work.

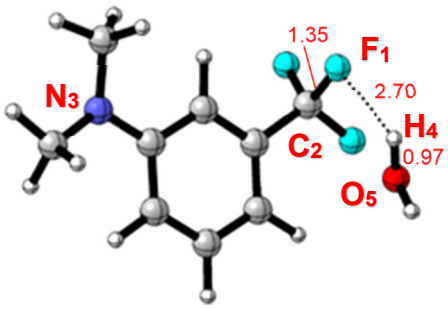
1a

	X	Y	Z
C	-0.969453	0.348148	-0.012864
C	-0.932693	1.737857	0.033444
C	0.321932	2.348856	0.024627
C	1.491119	1.601800	-0.035917
C	0.186405	-0.427839	-0.072084
C	1.453961	0.188389	-0.103588
C	-2.281522	-0.378703	0.008258
H	-1.842935	2.324361	0.081538
H	0.392016	3.431617	0.072252
H	2.440135	2.124248	-0.031826
H	0.092266	-1.507638	-0.097529
N	2.611734	-0.559981	-0.209208
F	-2.453665	-1.155480	-1.084330
F	-3.340425	0.448328	0.059849
F	-2.390346	-1.209025	1.069593
C	3.878802	0.088868	0.097615
C	2.530405	-1.985050	0.076717
H	2.175017	-2.185018	1.099016
H	3.521343	-2.423820	-0.040738
H	4.067398	0.918735	-0.588513
H	4.682733	-0.635832	-0.033540
H	3.914059	0.471394	1.128856
H	1.862025	-2.486541	-0.628317



IM1

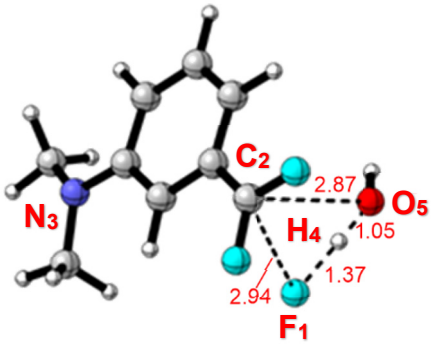
	X	Y	Z
H	-2.815560	2.403762	2.385360
O	-2.765261	1.559496	1.918171
H	-2.529657	0.914074	2.597593
C	-0.698056	0.052381	-0.451921
C	-0.769095	1.383787	-0.847412
C	0.425585	2.102721	-0.905382
C	1.642173	1.512514	-0.587734
C	0.507317	-0.566042	-0.126758
C	1.717739	0.152337	-0.204510
C	-1.944252	-0.775551	-0.338017
H	-1.717810	1.850851	-1.085988



H	0.409303	3.148580	-1.197726
H	2.540267	2.115958	-0.640637
H	0.496166	-1.604683	0.182935
N	2.930736	-0.454352	0.069572
F	-1.871879	-1.908877	-1.073263
F	-3.048631	-0.127401	-0.745005
F	-2.178664	-1.179191	0.931336
C	4.075421	0.403971	0.343013
C	2.910186	-1.734791	0.762004
H	2.421067	-1.669883	1.746025
H	3.937174	-2.072167	0.904150
H	4.324537	1.013550	-0.529223
H	4.938458	-0.225023	0.562657
H	3.899827	1.072324	1.199521
H	2.393617	-2.491598	0.165659

TS1

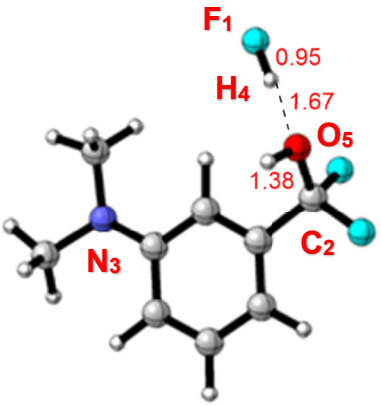
	X	Y	Z
H	-2.534095	0.718982	2.336076
O	-3.002771	0.123933	1.738453
H	-2.422413	-0.742021	1.662351
C	-0.707852	0.477342	-0.532048
C	-0.711506	1.847973	-0.186780
C	0.499841	2.400774	0.182680
C	1.662574	1.629554	0.200757
C	0.456087	-0.323120	-0.515833
C	1.683518	0.255699	-0.165511
C	-1.914152	-0.115392	-0.900931
H	-1.627304	2.427778	-0.199747
H	0.556464	3.444565	0.471728
H	2.583220	2.111993	0.509321
H	0.376087	-1.371757	-0.772846
N	2.848949	-0.465036	-0.171888
F	-2.033449	-1.338417	-1.233449
F	-3.008573	0.526087	-1.027275
F	-1.693188	-1.876796	1.441972
C	4.022235	0.087733	0.492785
C	2.759715	-1.913042	-0.294757
H	2.179200	-2.360861	0.524956
H	3.767130	-2.327733	-0.279852
H	4.339565	1.019013	0.015204
H	4.839527	-0.626922	0.401237



H	3.839921	0.280811	1.559354
H	2.296333	-2.193041	-1.245601

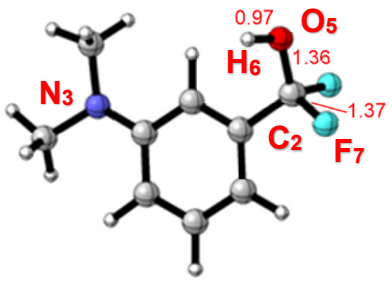
IM2

	X	Y	Z
H	2.053218	0.448646	1.725203
O	2.425622	0.651043	0.849257
H	2.115409	2.238041	0.432044
C	0.690141	-0.827809	-0.014528
C	0.400758	-2.182243	0.120438
C	-0.943620	-2.555847	0.157909
C	-1.960634	-1.615600	0.053533
C	-0.311027	0.136120	-0.120196
C	-1.669263	-0.240216	-0.107897
C	2.115516	-0.340790	-0.052781
H	1.190428	-2.919422	0.207846
H	-1.206184	-3.602849	0.279221
H	-2.988156	-1.955690	0.098411
H	-0.024022	1.177198	-0.215997
N	-2.674541	0.698183	-0.258728
F	2.419796	0.190979	-1.269457
F	2.991032	-1.372287	0.115543
F	1.959618	3.147612	0.209527
C	-4.028765	0.313759	0.114808
C	-2.330943	2.100575	-0.072232
H	-1.913296	2.298380	0.926850
H	-3.232115	2.701070	-0.198883
H	-4.384286	-0.513567	-0.504954
H	-4.691879	1.161928	-0.056926
H	-4.102696	0.016869	1.172060
H	-1.606601	2.429342	-0.822670



IM3

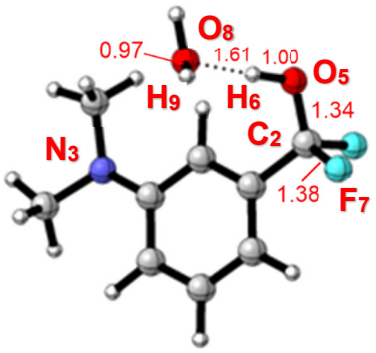
	X	Y	Z
C	-1.463075	0.190524	0.109009
C	-1.487775	1.601494	0.038081
C	-0.308763	2.334481	-0.041994
C	0.935876	1.707990	-0.072242
C	0.964657	0.315340	-0.028175
C	-0.201693	-0.440224	0.059169



H	-2.430401	2.135348	0.046940
H	-0.366540	3.418179	-0.090162
H	1.851806	2.284262	-0.139388
H	-0.121189	-1.520143	0.091112
N	-2.629094	-0.548961	0.236281
C	-2.561501	-1.971987	-0.066178
H	-1.880666	-2.483867	0.618324
H	-3.551813	-2.407087	0.070232
H	-2.232737	-2.163559	-1.099236
C	-3.886576	0.106074	-0.099175
H	-3.909599	0.456644	-1.142241
H	-4.700397	-0.604822	0.048200
H	-4.071974	0.957730	0.559971
C	2.287834	-0.411246	-0.014585
F	3.259462	0.368249	-0.595911
F	2.719716	-0.587293	1.271599
O	2.308598	-1.650976	-0.571156
H	1.861877	-1.645423	-1.433125

IM4

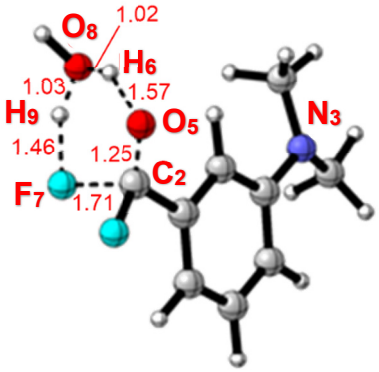
	X	Y	Z
C	-1.589781	-0.367221	-0.152482
C	-1.686727	-1.643369	0.445818
C	-0.544782	-2.372915	0.760800
C	0.730576	-1.869118	0.512777
C	0.832746	-0.602568	-0.061998
C	-0.295756	0.141585	-0.393367
H	-2.655558	-2.074041	0.668287
H	-0.657754	-3.351599	1.218587
H	1.616232	-2.439880	0.768712
H	-0.161798	1.119450	-0.840047
N	-2.717619	0.359132	-0.502926
C	-2.555010	1.789606	-0.727029
H	-1.909944	1.981746	-1.588362
H	-3.531600	2.222873	-0.944508
H	-2.128999	2.301879	0.149532
C	-3.991388	-0.049132	0.072777
H	-3.985850	-0.008537	1.173011
H	-4.771082	0.617100	-0.297539
H	-4.250717	-1.064707	-0.236428
C	2.191660	-0.030432	-0.396036
F	3.143017	-0.577269	0.446680



F	2.581415	-0.459288	-1.643923
O	2.306529	1.308552	-0.402613
H	1.839919	1.724891	0.382660
O	1.064484	2.458592	1.591936
H	1.127050	3.421025	1.507502
H	1.456215	2.249127	2.452124

TS2

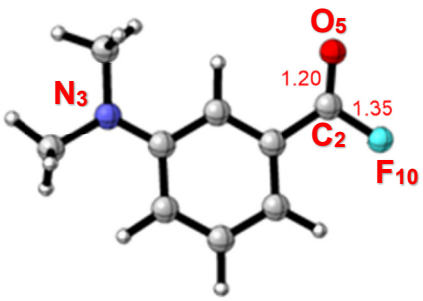
	X	Y	Z
C	-1.697808	-0.247726	-0.148345
C	-1.905962	-1.592931	0.231187
C	-0.835931	-2.472064	0.364668
C	0.476616	-2.057362	0.147192
C	0.689363	-0.728540	-0.217408
C	-0.366878	0.167658	-0.360144
H	-2.906957	-1.961371	0.420918
H	-1.035620	-3.500718	0.651712
H	1.306710	-2.745269	0.263458
H	-0.139656	1.189353	-0.641117
N	-2.758869	0.628824	-0.320826
C	-2.460480	2.054261	-0.345745
H	-1.822568	2.304745	-1.197274
H	-3.394292	2.605408	-0.461394
H	-1.962492	2.393257	0.576034
C	-4.039880	0.260553	0.266280
H	-3.971943	0.106455	1.354244
H	-4.756469	1.058803	0.071997
H	-4.431999	-0.652083	-0.190040
C	2.076205	-0.196929	-0.436021
F	2.501549	0.147860	1.180151
F	2.980257	-1.210715	-0.606607
O	2.308755	0.834617	-1.097340
H	2.077067	2.106598	-0.199788
O	2.000828	2.464606	0.756328
H	2.670121	3.153967	0.915969
H	2.255779	1.589483	1.237279



5a

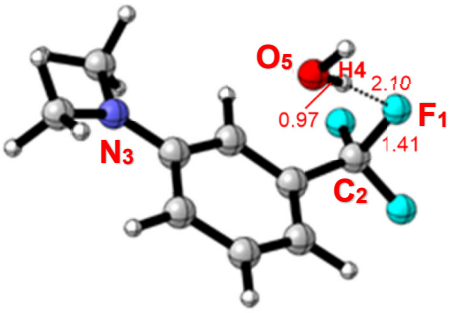
	X	Y	Z
C	1.168758	0.173984	-0.108792

C	1.095881	1.586286	-0.047858
C	-0.126248	2.246700	0.008517
C	-1.328371	1.544028	0.021353
C	-1.262953	0.149300	-0.016838
C	-0.046732	-0.535803	-0.072922
H	2.002862	2.178740	-0.047931
H	-0.135503	3.331745	0.049487
H	-2.279384	2.061127	0.069089
H	-0.066049	-1.618665	-0.090481
N	2.382656	-0.480673	-0.211453
C	2.410800	-1.909382	0.068438
H	1.777742	-2.456705	-0.634853
H	3.431634	-2.270535	-0.058229
H	2.078889	-2.140458	1.092186
C	3.588404	0.262007	0.130249
H	3.568630	0.635862	1.165078
H	4.448414	-0.397931	0.014333
H	3.729038	1.110113	-0.544623
C	-2.487609	-0.666850	0.010974
F	-3.618225	0.077049	0.060729
O	-2.592801	-1.857954	-0.004896



IM1-T_1

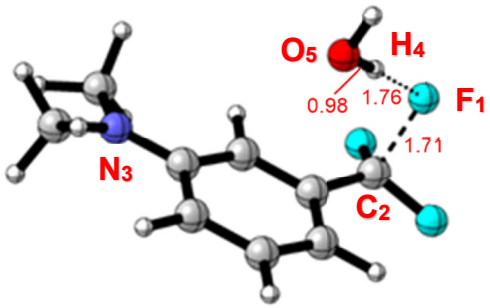
	X	Y	Z
H	-0.436855	1.280621	3.386153
O	-0.170521	0.964566	2.512706
H	-0.963021	0.551291	2.140680
C	-0.969972	0.111905	-0.575827
C	-0.897828	1.558658	-0.785802
C	0.311385	2.205434	-0.826645
C	1.528586	1.516952	-0.619348
C	0.236828	-0.590870	-0.309042
C	1.468311	0.078662	-0.341487
C	-2.236330	-0.486653	-0.206255
H	-1.817499	2.118558	-0.931697
H	0.339959	3.271069	-1.034786
H	2.476167	2.014566	-0.768613
H	0.195877	-1.637160	-0.028811
N	2.627587	-0.588899	-0.131262
F	-2.284142	-1.830211	-0.381272
F	-3.307434	0.040068	-0.852837
F	-2.594691	-0.335909	1.150391



C	3.901441	0.071034	0.142932
C	2.671495	-2.045763	-0.084892
H	2.383914	-2.400740	0.911683
H	3.694308	-2.362136	-0.291542
H	3.750296	1.079088	0.519139
H	4.514783	0.090030	-0.764163
H	4.422247	-0.511647	0.905694
H	2.003805	-2.469463	-0.834881

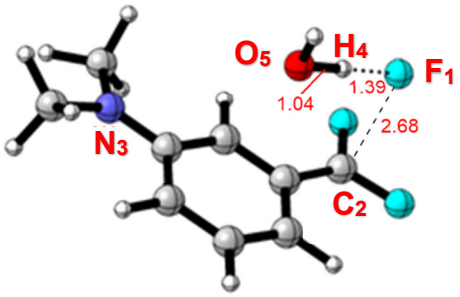
TS3-T_1

	X	Y	Z
H	-0.926394	0.976376	3.435427
O	-0.645840	0.792984	2.529812
H	-1.409676	0.357918	2.101364
C	-0.905870	0.152001	-0.578587
C	-0.827820	1.589290	-0.764765
C	0.393297	2.236527	-0.727932
C	1.584358	1.550681	-0.483953
C	0.293812	-0.564617	-0.330300
C	1.529353	0.117268	-0.284874
C	-2.145674	-0.476895	-0.422947
H	-1.737915	2.153520	-0.941385
H	0.429061	3.308187	-0.898701
H	2.531365	2.070849	-0.510910
H	0.247113	-1.625783	-0.120282
N	2.672885	-0.563792	-0.059735
F	-2.213684	-1.802794	-0.570416
F	-3.226174	0.095973	-0.961142
F	-2.696180	-0.436771	1.200191
C	3.942205	0.098462	0.236012
C	2.721110	-2.023995	-0.077065
H	2.433306	-2.416411	0.904563
H	3.745843	-2.324432	-0.294581
H	3.779388	1.038492	0.758165
H	4.495638	0.269715	-0.693757
H	4.524777	-0.565928	0.874874
H	2.059727	-2.419835	-0.846352



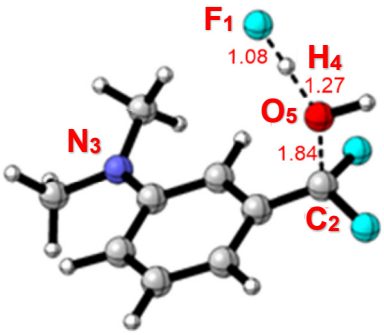
IM5-T_1

	X	Y	Z
H	-0.443563	0.929705	3.340179
O	-0.404544	0.634211	2.422474
H	-1.345149	0.248014	2.200427
C	-0.917237	0.158454	-0.709723
C	-0.859928	1.582873	-0.839974
C	0.360212	2.242373	-0.719859
C	1.534461	1.557446	-0.461881
C	0.267281	-0.565645	-0.468812
C	1.500945	0.128463	-0.336131
C	-2.131238	-0.504803	-0.758609
H	-1.770112	2.141638	-1.027342
H	0.390305	3.321084	-0.832058
H	2.472298	2.092609	-0.399588
H	0.218160	-1.637441	-0.327160
N	2.629412	-0.560500	-0.082251
F	-2.264095	-1.806847	-0.629348
F	-3.285434	0.091046	-0.961825
F	-2.591897	-0.279805	1.872555
C	3.877597	0.104214	0.291095
C	2.681169	-2.020984	-0.153336
H	2.322354	-2.445474	0.790485
H	3.719001	-2.313567	-0.305956
H	3.677823	0.992160	0.887560
H	4.434939	0.371118	-0.613530
H	4.467724	-0.598387	0.878734
H	2.079955	-2.385537	-0.984835



TS4-T_1

	X	Y	Z
H	-3.716676	-0.829485	0.700629
O	-2.820314	-0.544260	0.939060
H	-2.122032	-1.565319	1.240926
C	-0.765016	0.677573	-0.274293
C	-0.568733	1.978427	0.332364
C	0.698351	2.397467	0.701194
C	1.821886	1.594050	0.517492
C	0.357383	-0.174443	-0.425357
C	1.643274	0.274453	-0.046638
C	-2.053654	0.212861	-0.548988



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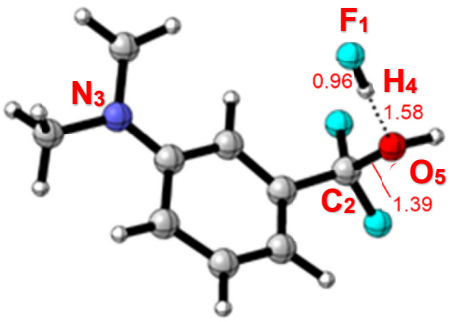
H	0.820453	3.377058	1.153046
H	2.793314	1.926478	0.855700
H	0.227772	-1.151164	-0.873984
N	2.712290	-0.535123	-0.200009
F	-2.199910	-0.830386	-1.376027
F	-3.027140	1.105565	-0.770159
F	-1.506462	-2.410188	1.498963
C	4.086270	-0.063335	-0.033294
C	2.562379	-1.946377	-0.548962
H	1.716770	-2.380565	-0.016220
H	3.475375	-2.466199	-0.261882
H	4.181678	0.969851	-0.360429
H	4.732737	-0.692352	-0.644848
H	4.384401	-0.157136	1.016701
H	2.414689	-2.048288	-1.629821

IM6-T_1

	X	Y	Z
H	-3.624587	-0.776859	0.544383
O	-2.720502	-0.438625	0.683457
H	-1.820604	-1.338326	1.626598
C	-0.817127	0.574112	-0.356510
C	-0.707603	1.828583	0.393872
C	0.518548	2.329457	0.749891
C	1.716847	1.644395	0.434106
C	0.344230	-0.228442	-0.477053
C	1.597625	0.285819	-0.121758
C	-2.146974	-0.020753	-0.515587
H	-1.612757	2.370246	0.656704
H	0.577983	3.272460	1.285735
H	2.667760	2.017023	0.786830
H	0.265253	-1.223317	-0.899651
N	2.719904	-0.466618	-0.237659
F	-2.135163	-1.094044	-1.369666
F	-3.056259	0.861325	-1.074342
F	-1.276091	-1.869438	2.211821
C	4.074280	0.073717	-0.162678
C	2.640746	-1.894073	-0.522428
H	1.845154	-2.352061	0.067195
H	3.594497	-2.351409	-0.259401
H	4.083118	1.144279	-0.347957



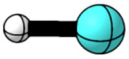
H	4.672809	-0.417842	-0.933271
H	4.513070	-0.147735	0.816235
H	2.447174	-2.058620	-1.588880

H_2O

	X	Y	Z
O	0.000000	0.000000	0.117581
H	0.000000	0.766463	-0.470323
H	0.000000	-0.766463	-0.470323

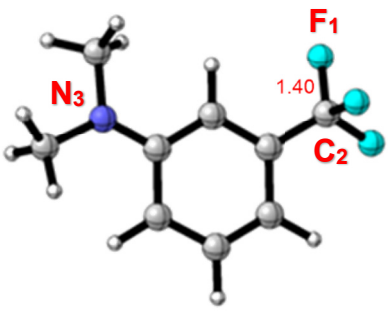
HF

	X	Y	Z
F	0.000000	0.000000	0.093149
H	0.000000	0.000000	-0.838341



1a-T_1

	X	Y	Z
C	-0.993683	0.273620	-0.189443
C	-0.918060	1.732076	-0.087446
C	0.294210	2.372391	-0.063447
C	1.513379	1.653707	-0.082385
C	0.211039	-0.470387	-0.085748
C	1.448668	0.187162	-0.052646
C	-2.272154	-0.385485	0.008352
H	-1.837421	2.310357	-0.055208
H	0.325331	3.457951	-0.044411
H	2.455681	2.167581	-0.205760
H	0.167814	-1.550233	-0.006249
N	2.605865	-0.516922	-0.014500
F	-2.296596	-1.668584	-0.434893
F	-3.313990	0.257582	-0.590057
F	-2.697643	-0.494155	1.332988
C	3.907592	0.064351	0.300031
C	2.612961	-1.962887	-0.206504
H	2.265446	-2.467338	0.702519
H	3.635100	-2.275886	-0.417878
H	3.806842	1.052862	0.737501
H	4.521042	0.106209	-0.605874



H	4.399818	-0.589912	1.024588
H	1.969639	-2.234010	-1.044647

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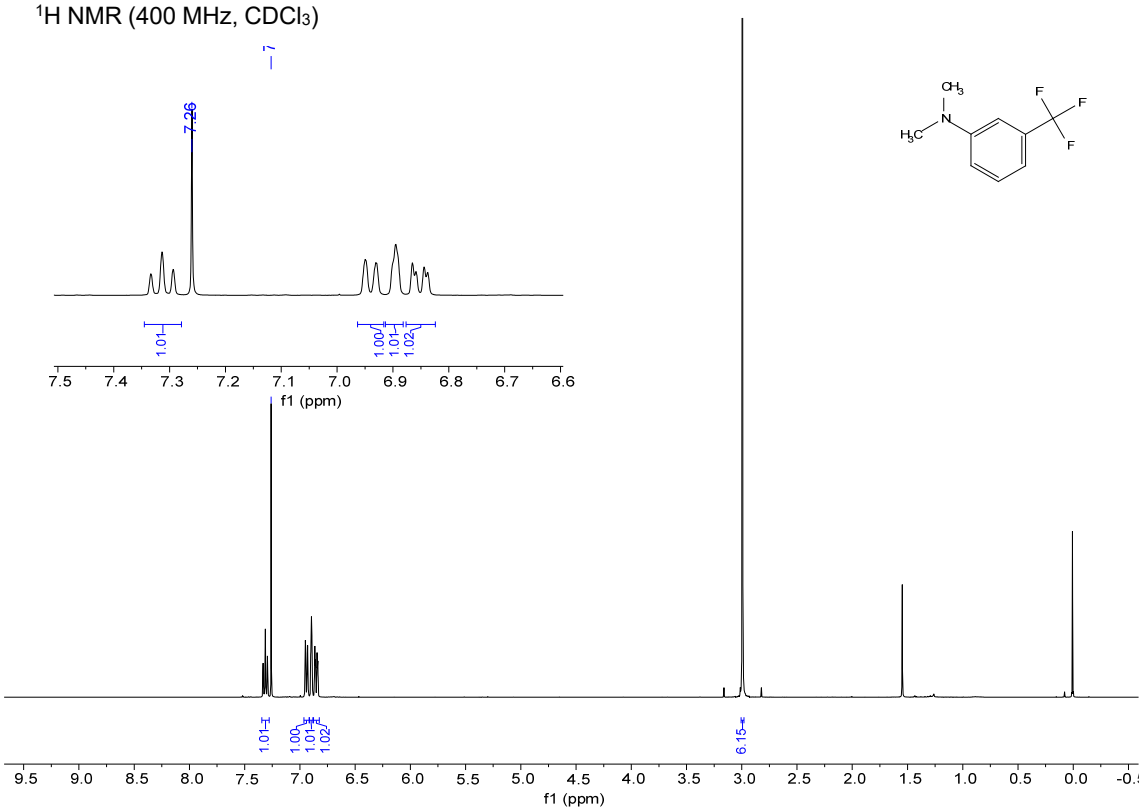
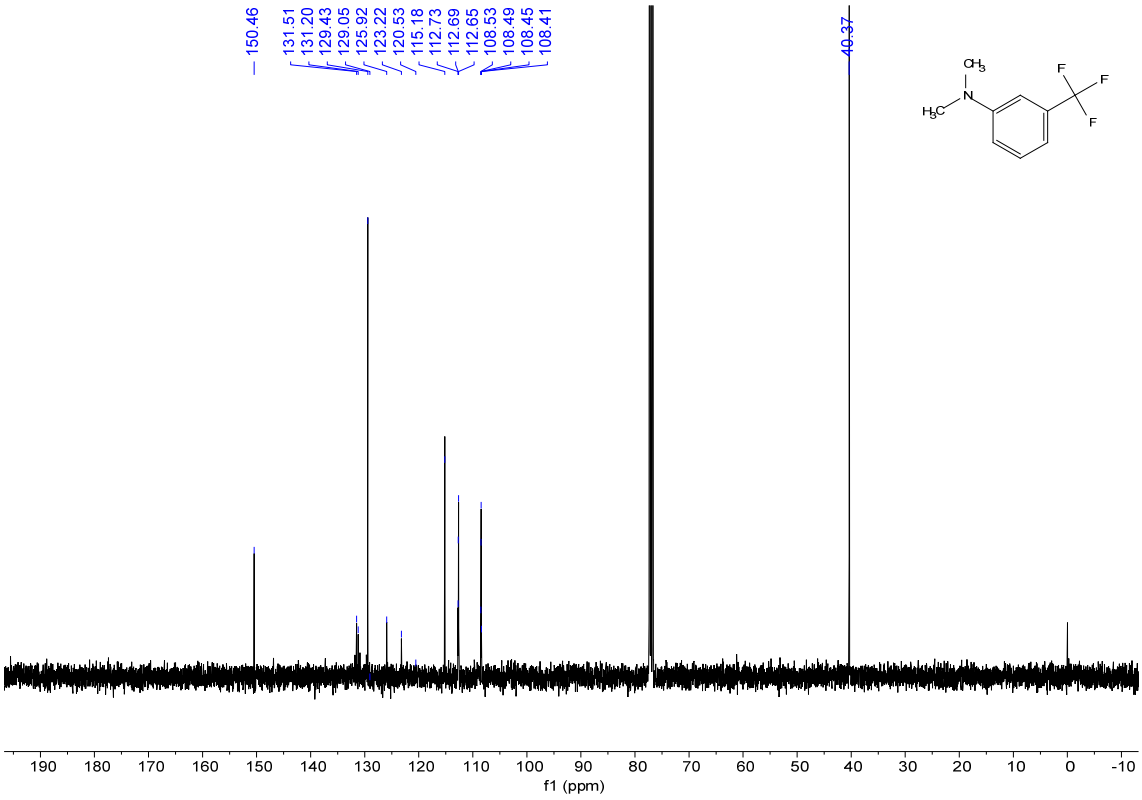
9. NMR spectra

^{1}H NMR (400 MHz, $CDCl_3$)



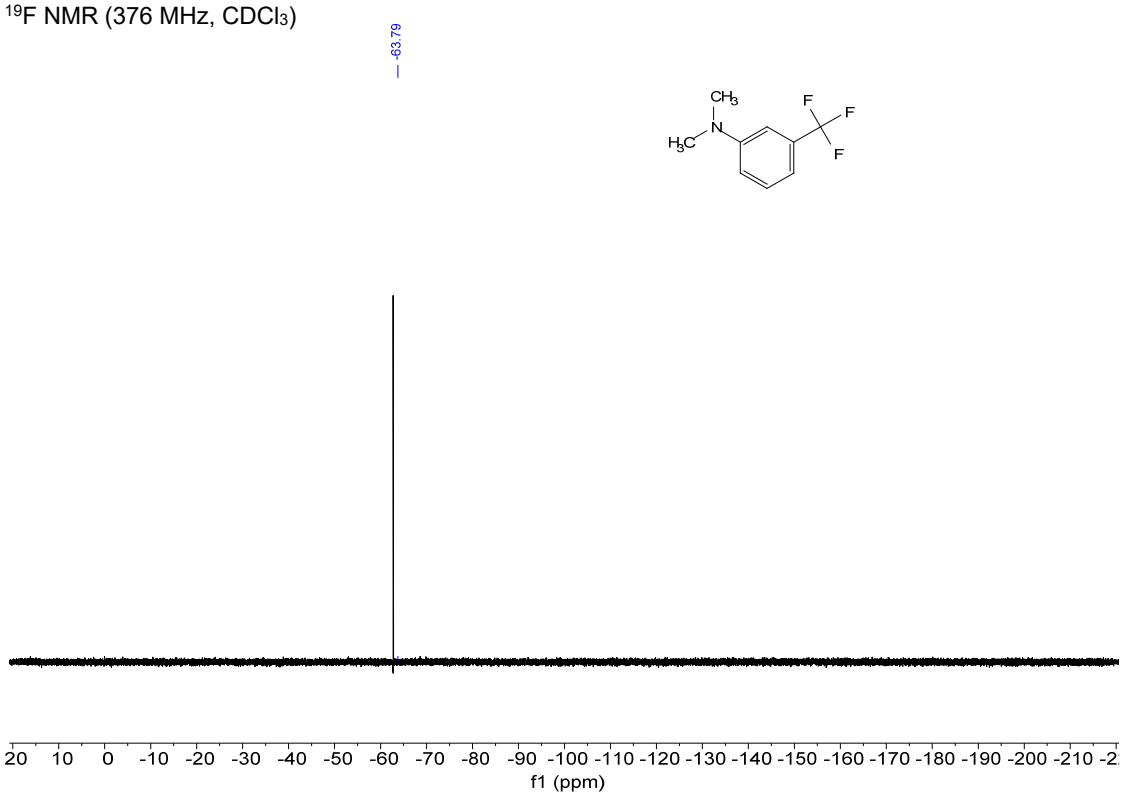
^{1}H NMR spectrum of **1a**

^{13}C NMR (101 MHz, $CDCl_3$)



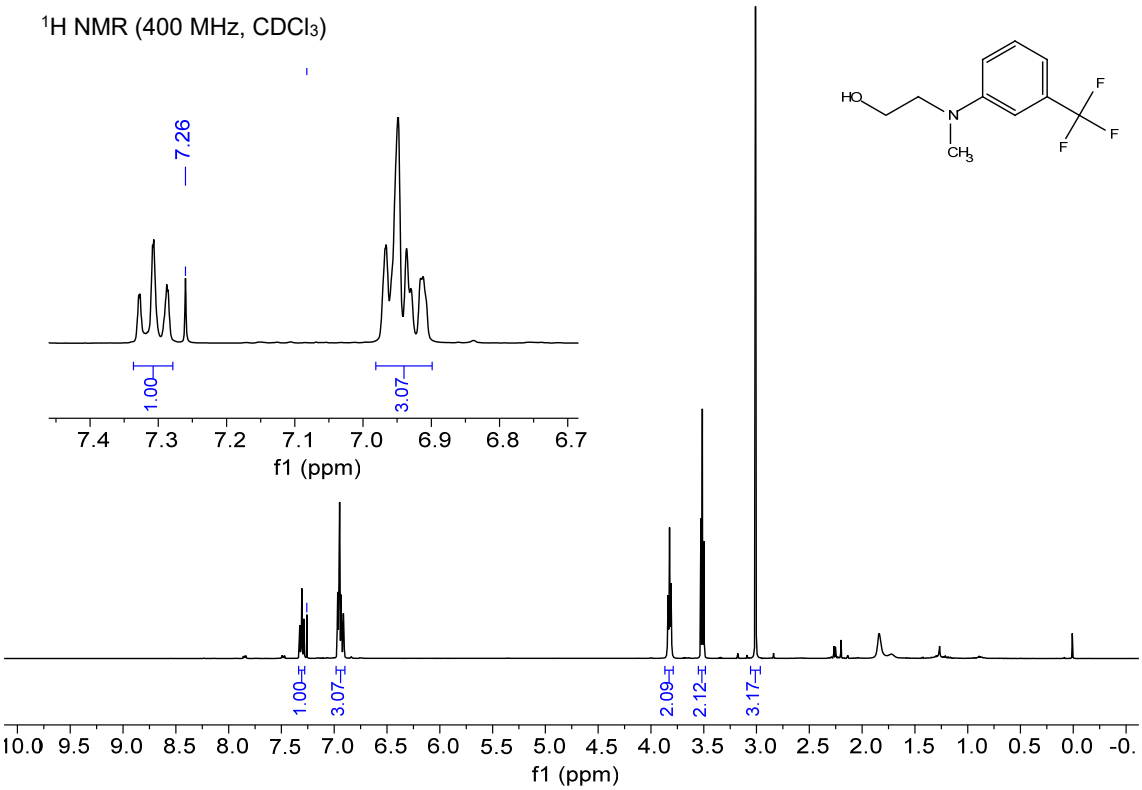
^{13}C NMR spectrum of **1a**

^{19}F NMR (376 MHz, $CDCl_3$)



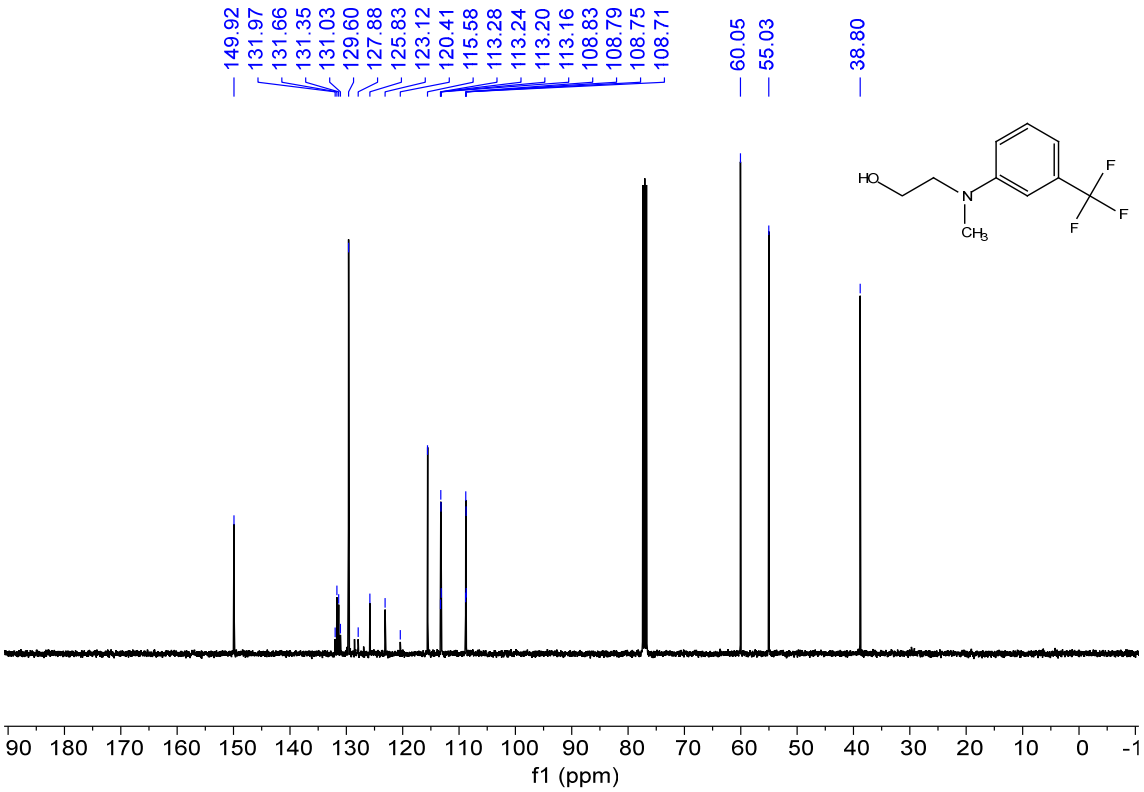
^{19}F NMR spectrum of **1a**

^{1}H NMR (400 MHz, $CDCl_3$)



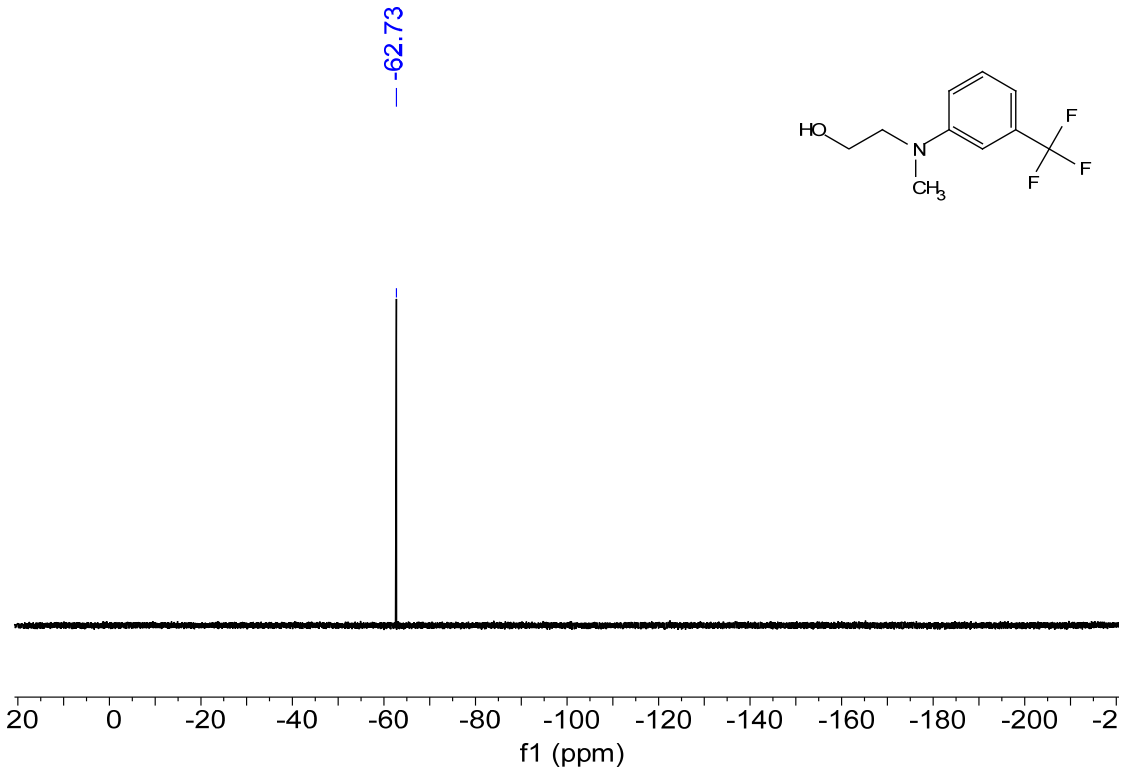
^{1}H NMR spectrum of **1b**

^{13}C NMR (101 MHz, $CDCl_3$)

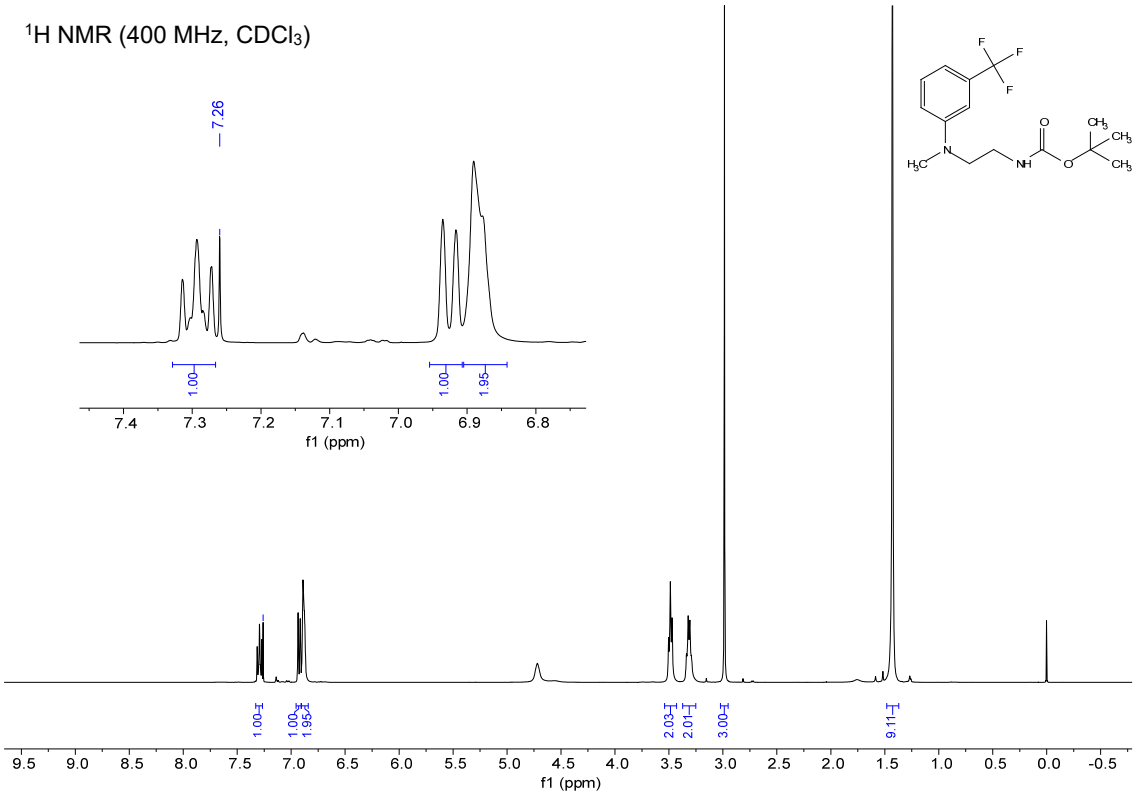


^{13}C NMR spectrum of **1b**

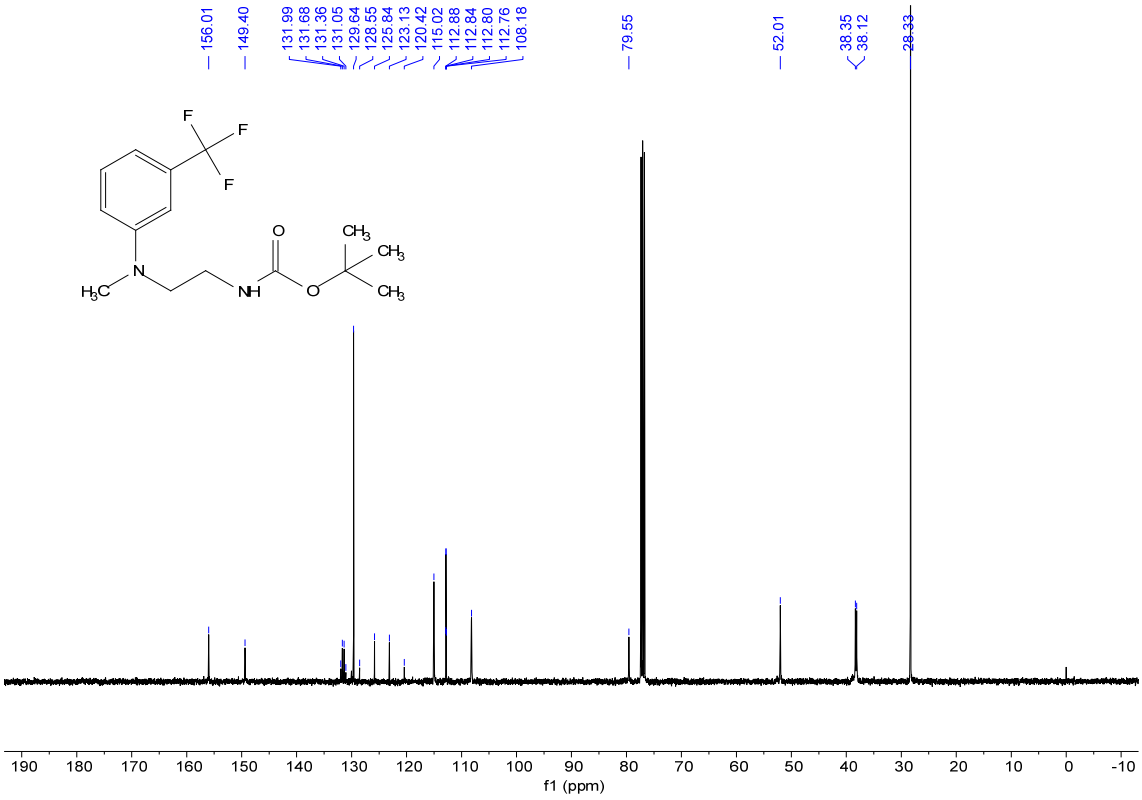
^{19}F NMR (376 MHz, $CDCl_3$)



^{19}F NMR spectrum of **1b**

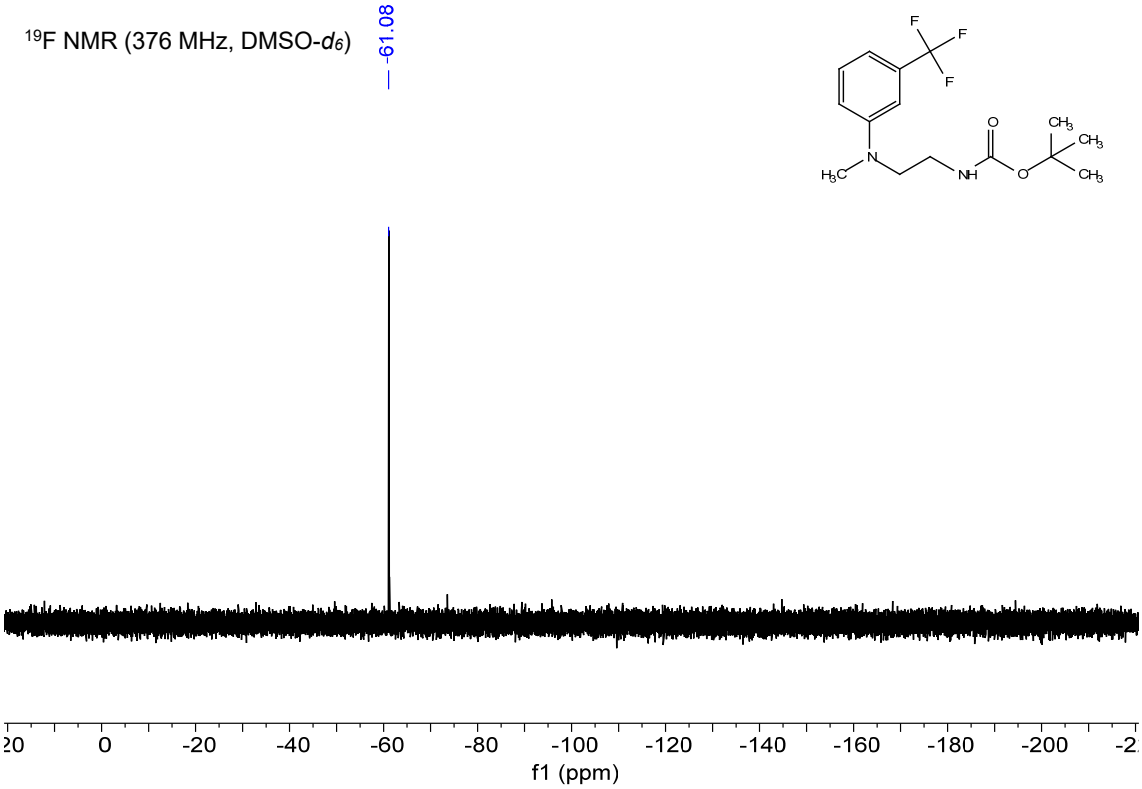


^{1}H NMR spectrum of **1c**



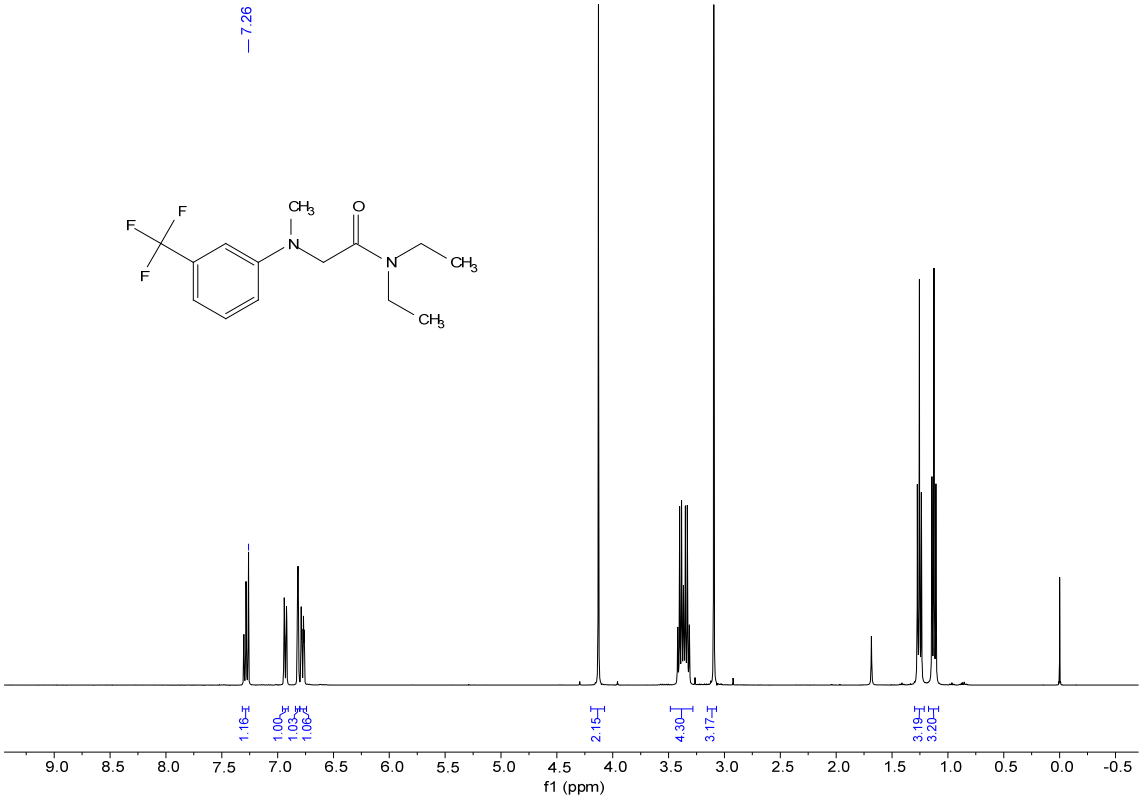
^{13}C NMR spectrum of **1c**

^{19}F NMR (376 MHz, DMSO-d_6)



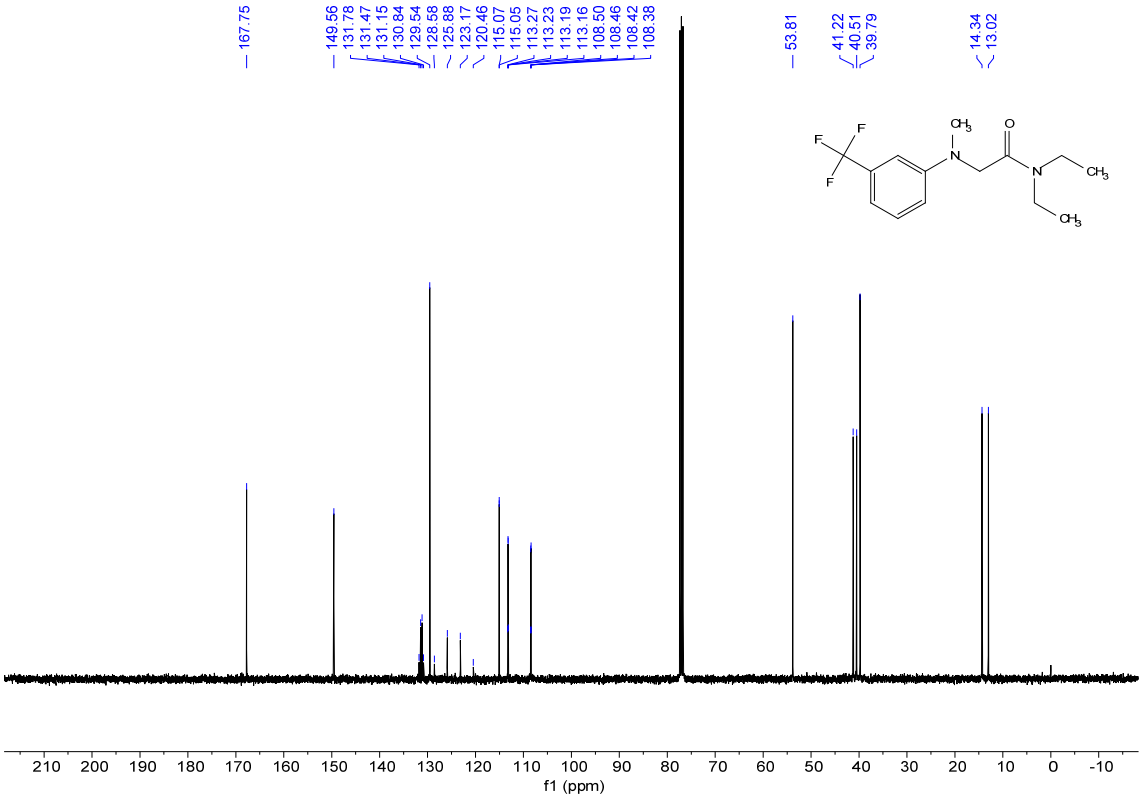
^{19}F NMR spectrum of **1c**

^{1}H NMR (400 MHz, $CDCl_3$)



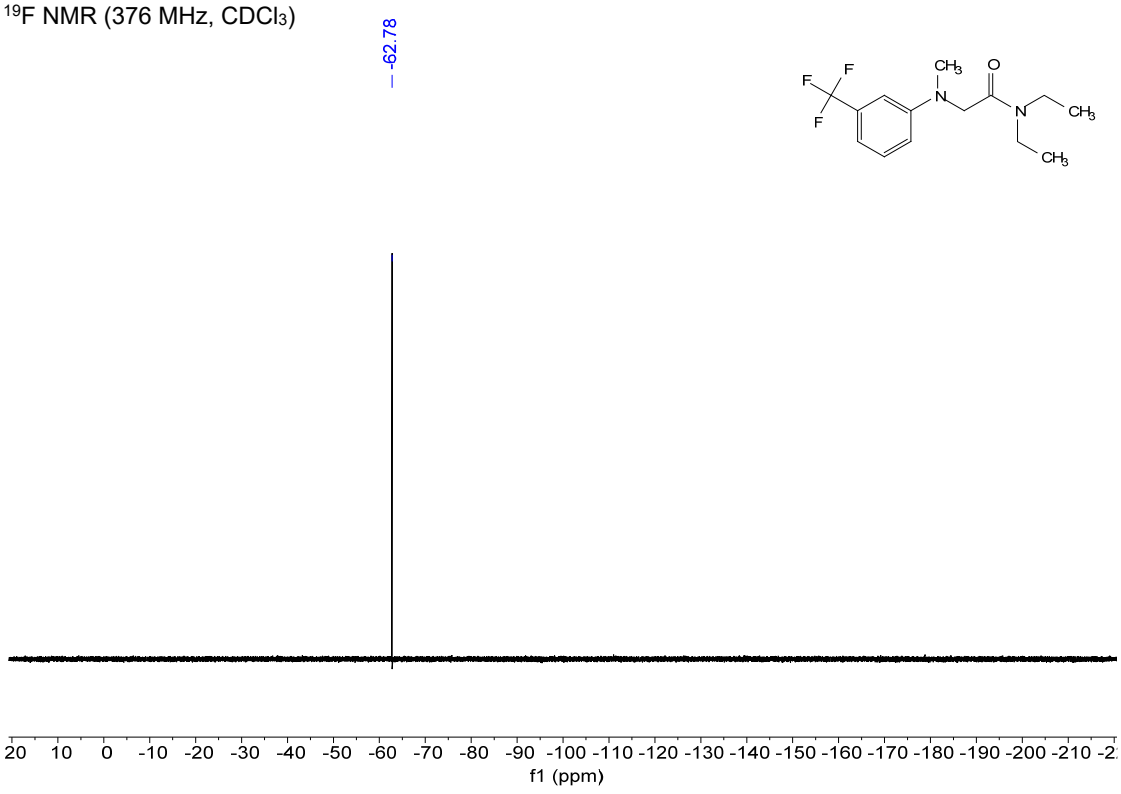
^{1}H NMR spectrum of **1d**

^{13}C NMR (101 MHz, $CDCl_3$)



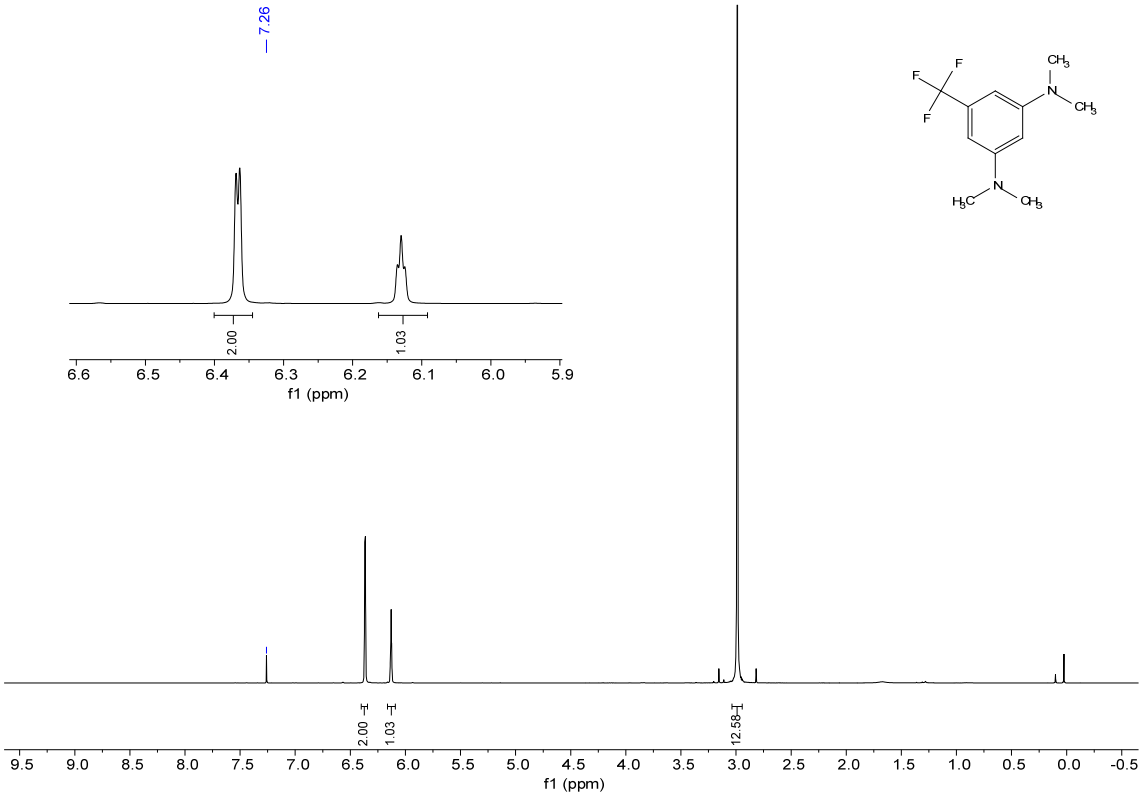
^{13}C NMR spectrum of **1d**

^{19}F NMR (376 MHz, $CDCl_3$)



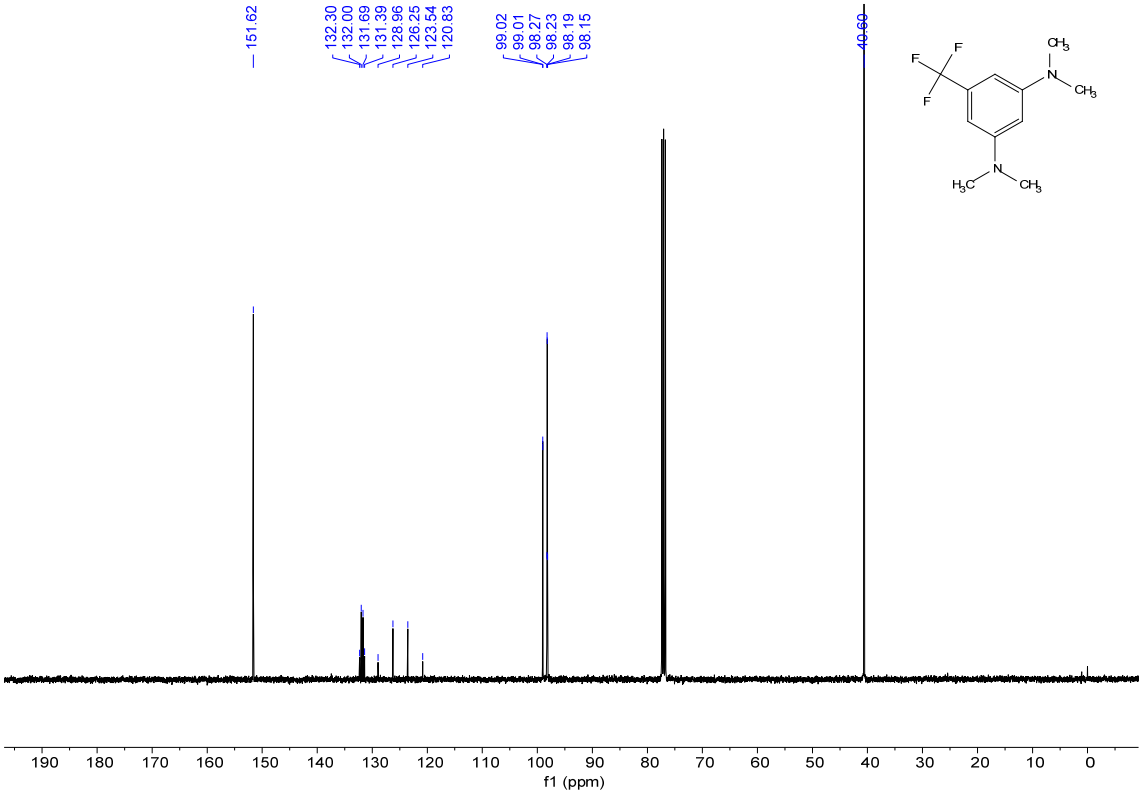
^{19}F NMR spectrum of **1d**

^{1}H NMR (400 MHz, $CDCl_3$)



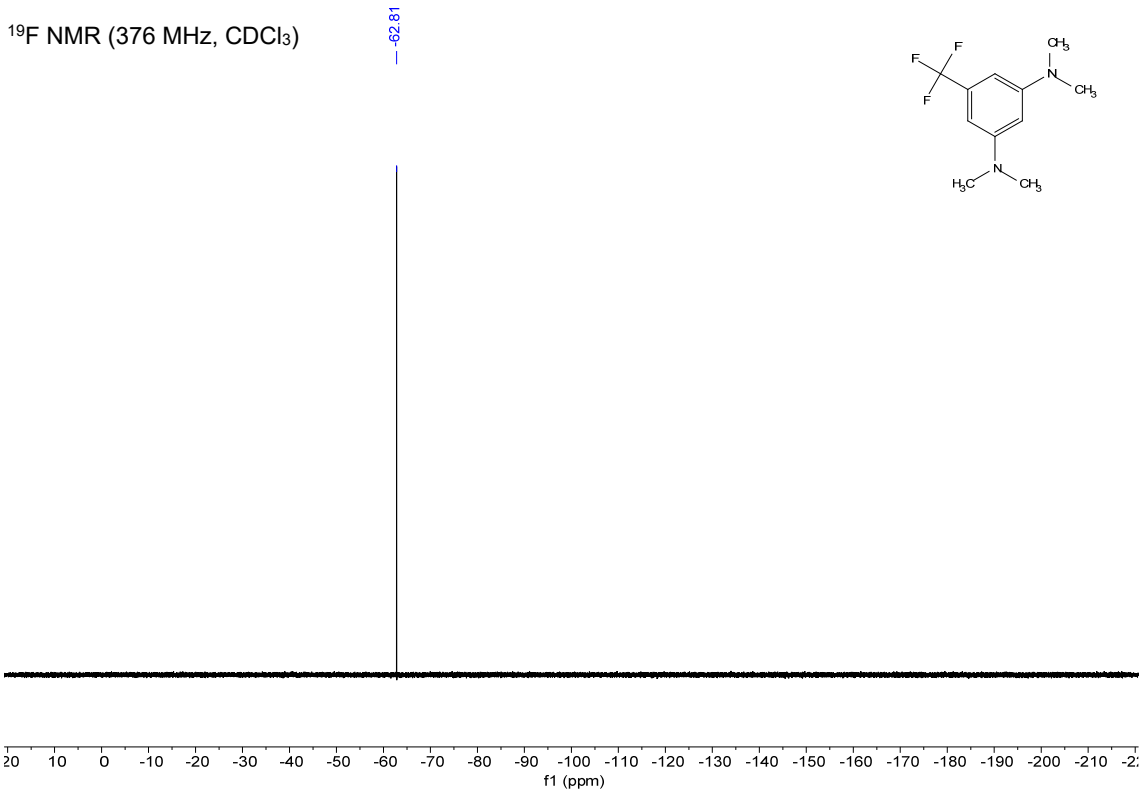
^{1}H NMR spectrum of **1e**

^{13}C NMR (101 MHz, $CDCl_3$)



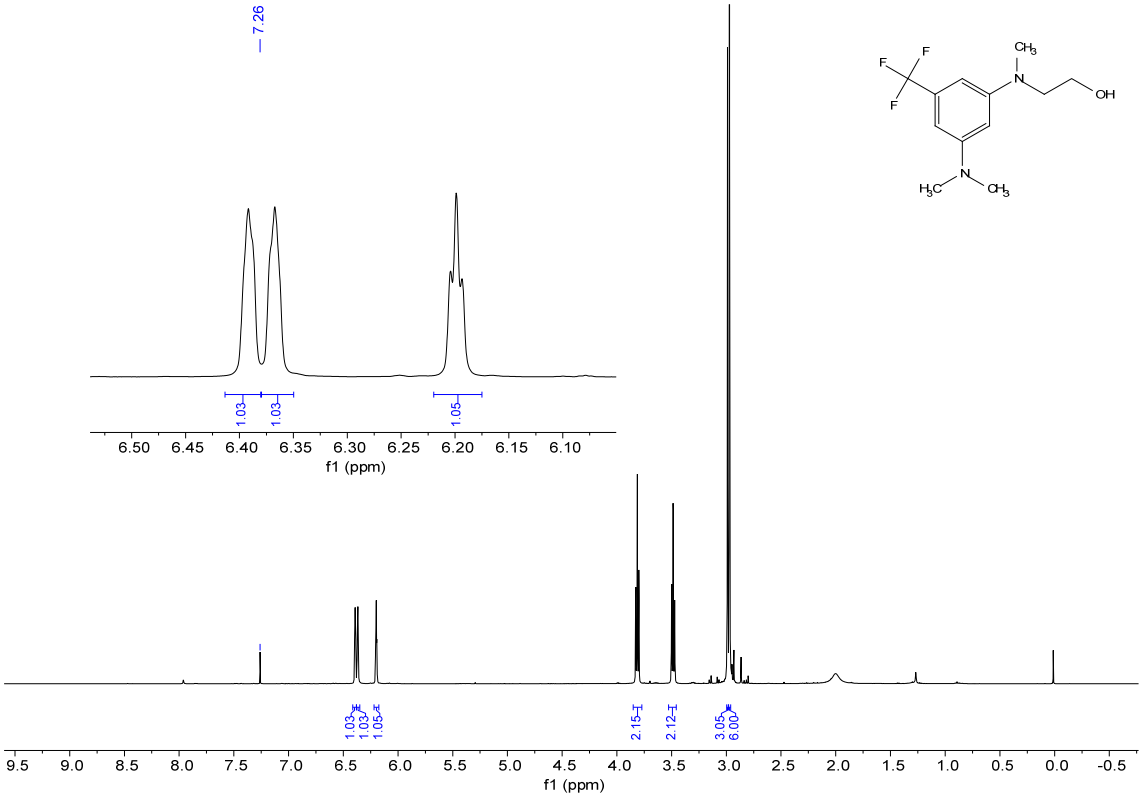
^{13}C NMR spectrum of **1e**

^{19}F NMR (376 MHz, $CDCl_3$)



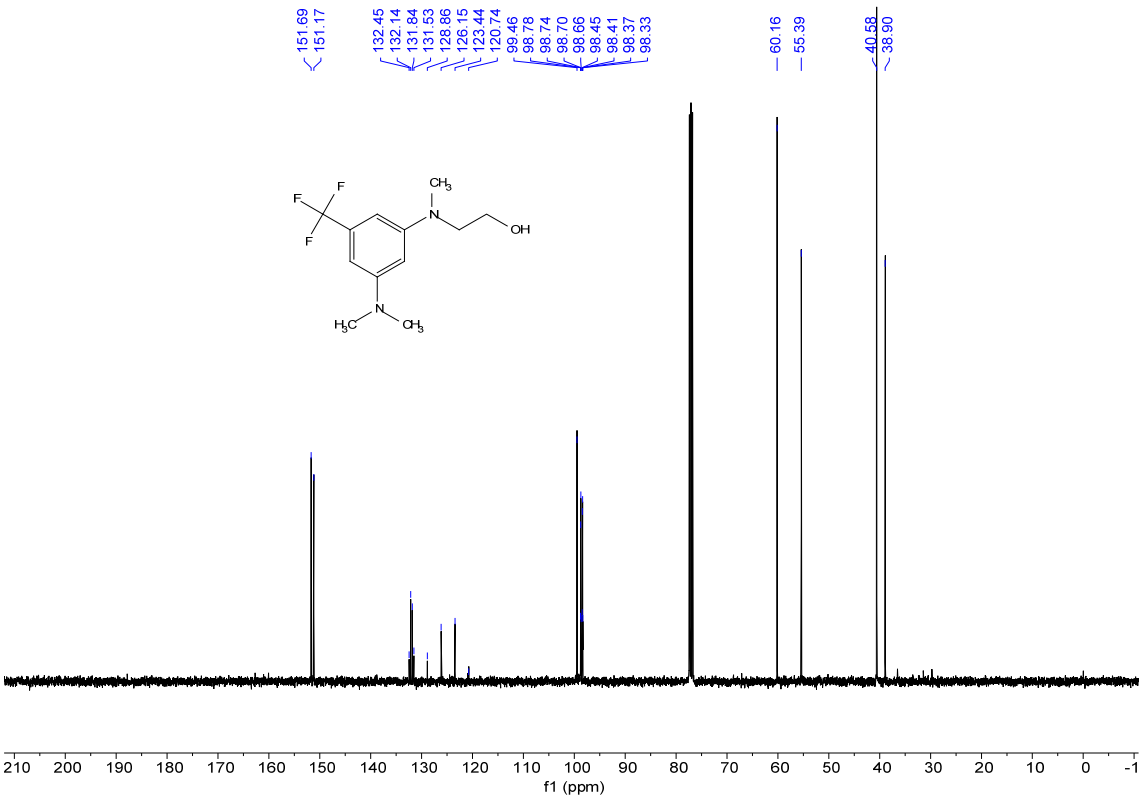
^{19}F NMR spectrum of **1e**

^{1}H NMR (400 MHz, $CDCl_3$)



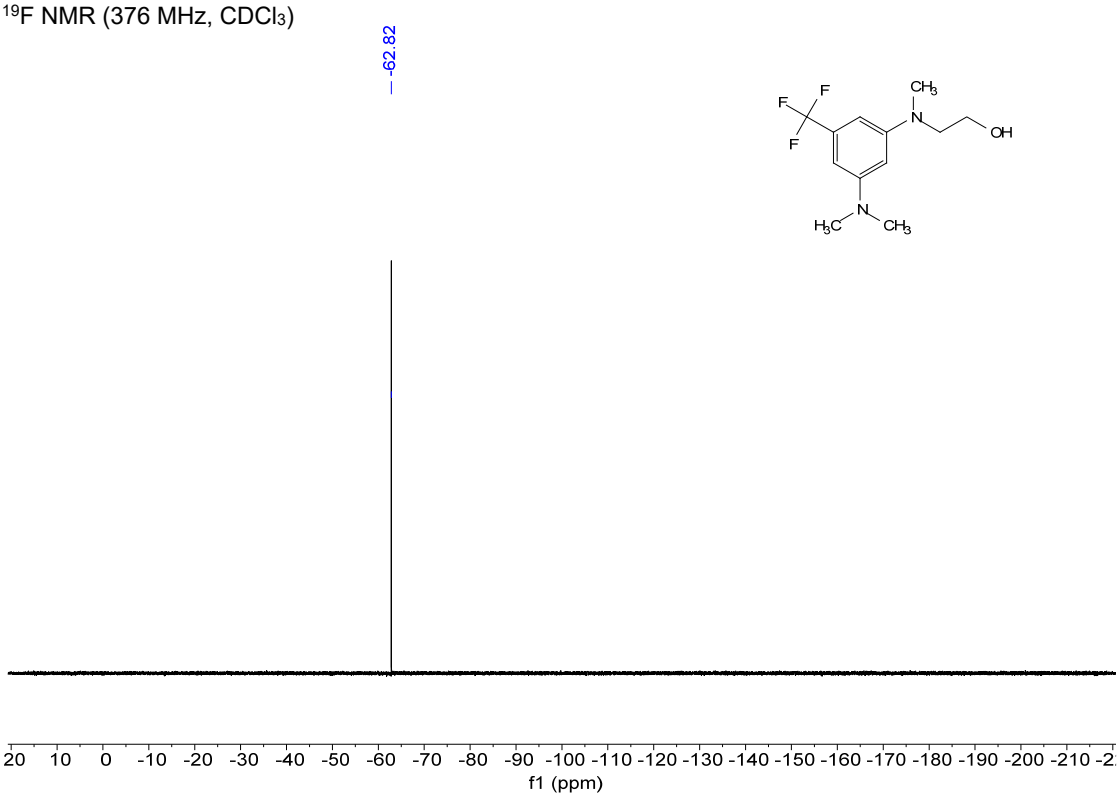
^{1}H NMR spectrum of **1f**

^{13}C NMR (101 MHz, $CDCl_3$)

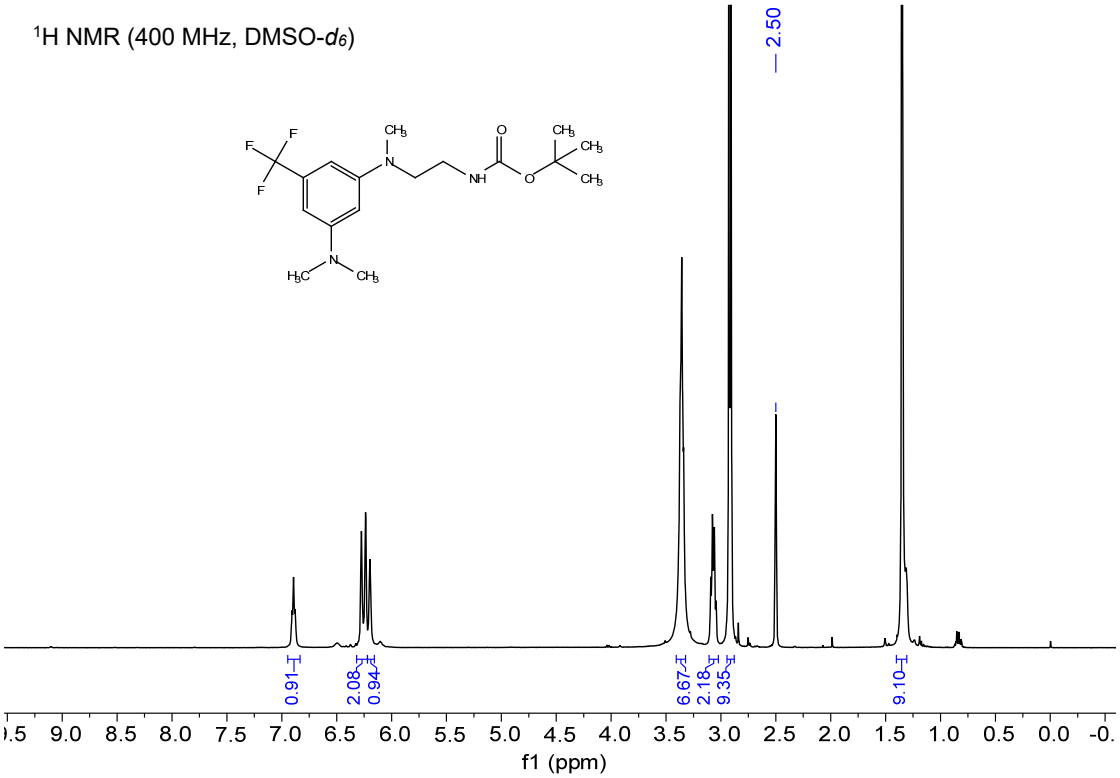


^{13}C NMR spectrum of **1f**

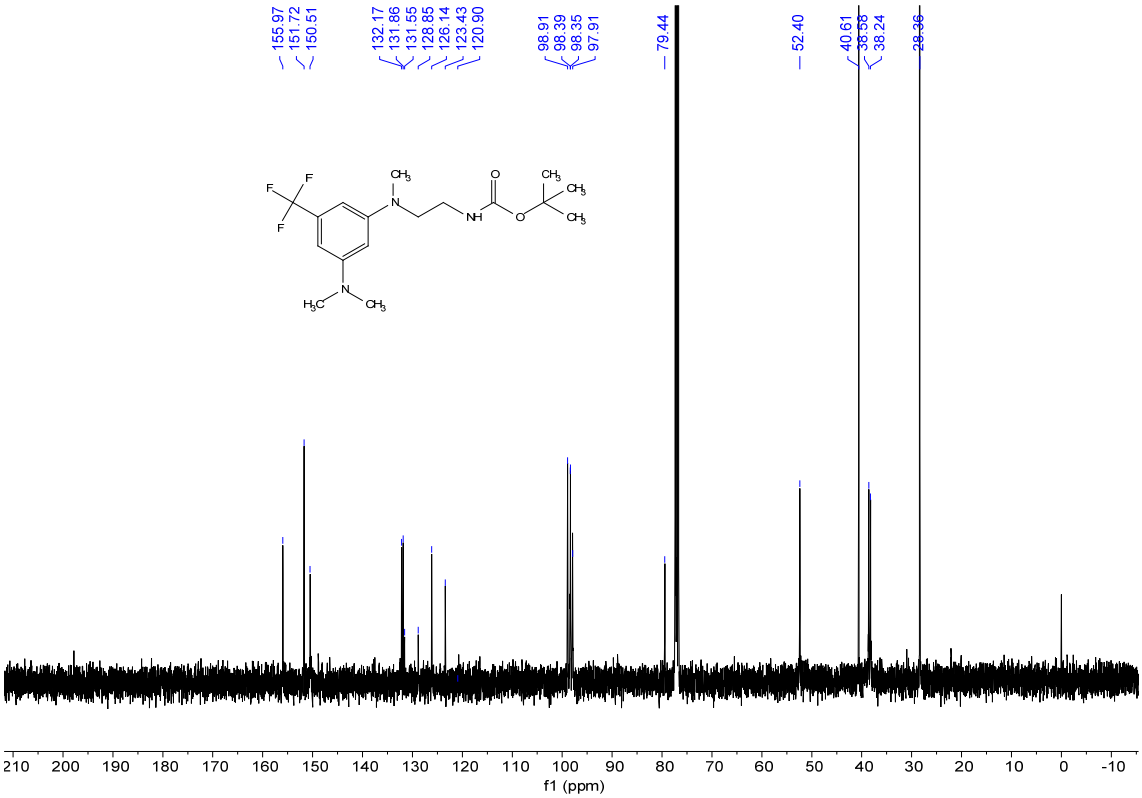
^{19}F NMR (376 MHz, $CDCl_3$)



^{19}F NMR spectrum of **1f**

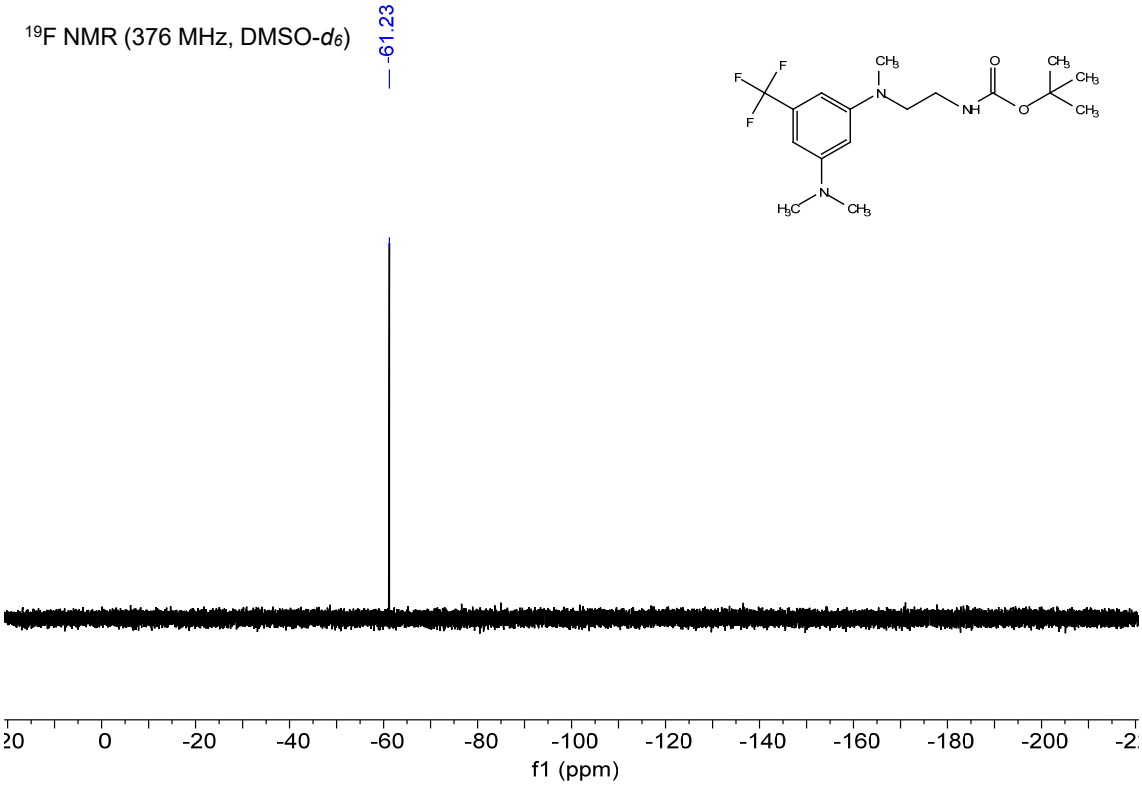


^{1}H NMR spectrum of **1g**



^{13}C NMR spectrum of **1g**

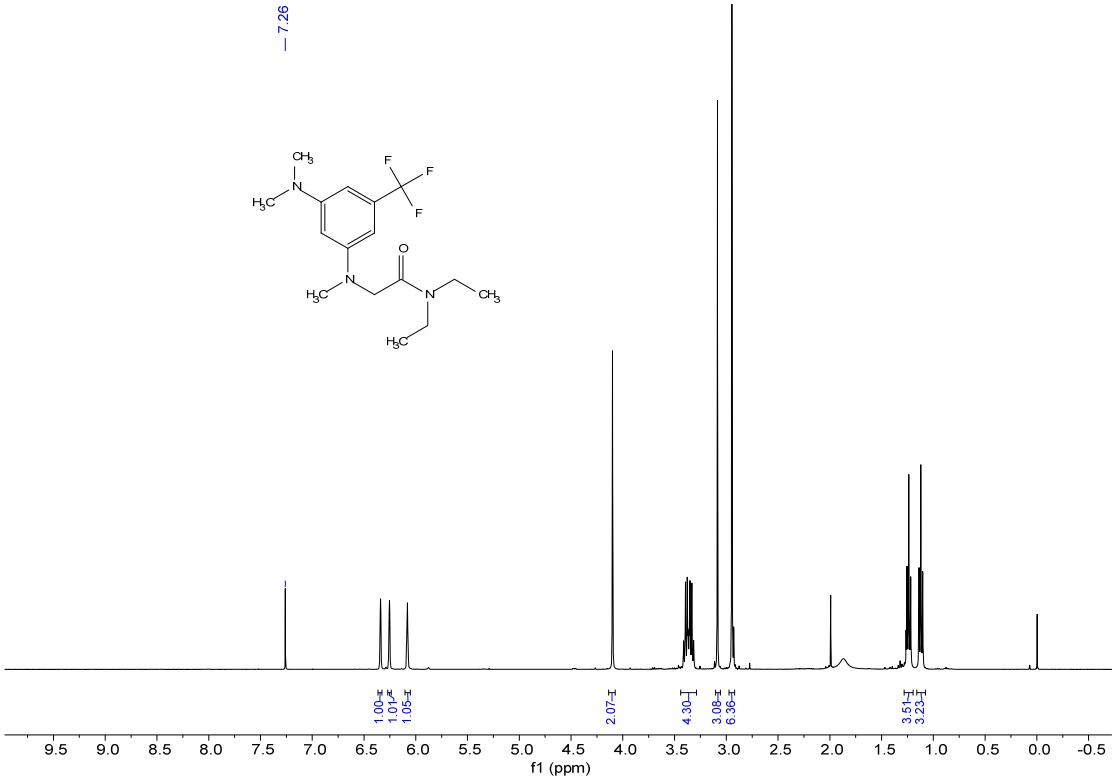
^{19}F NMR (376 MHz, DMSO-d_6)



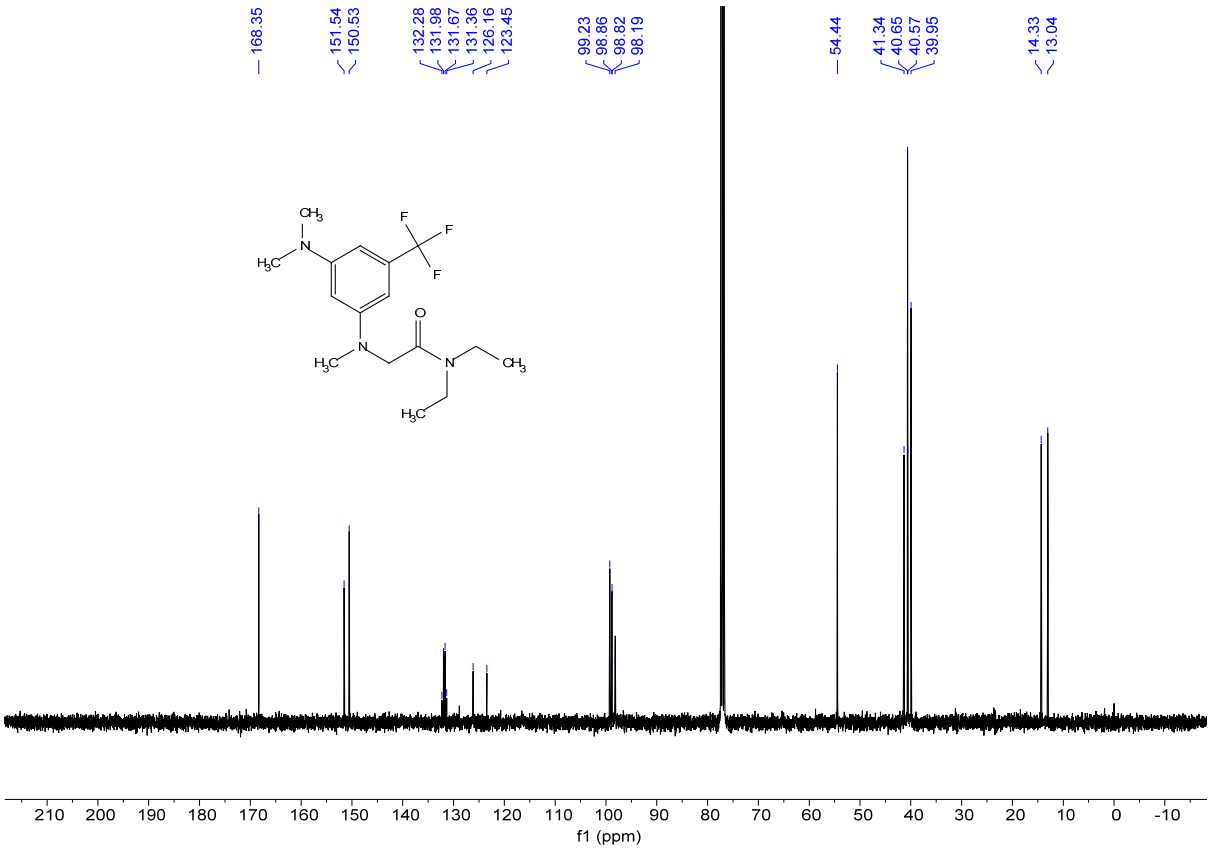
^{19}F NMR spectrum of **1g**

^{1}H NMR (400 MHz, $CDCl_3$)

^{1}H NMR spectrum of **1h**

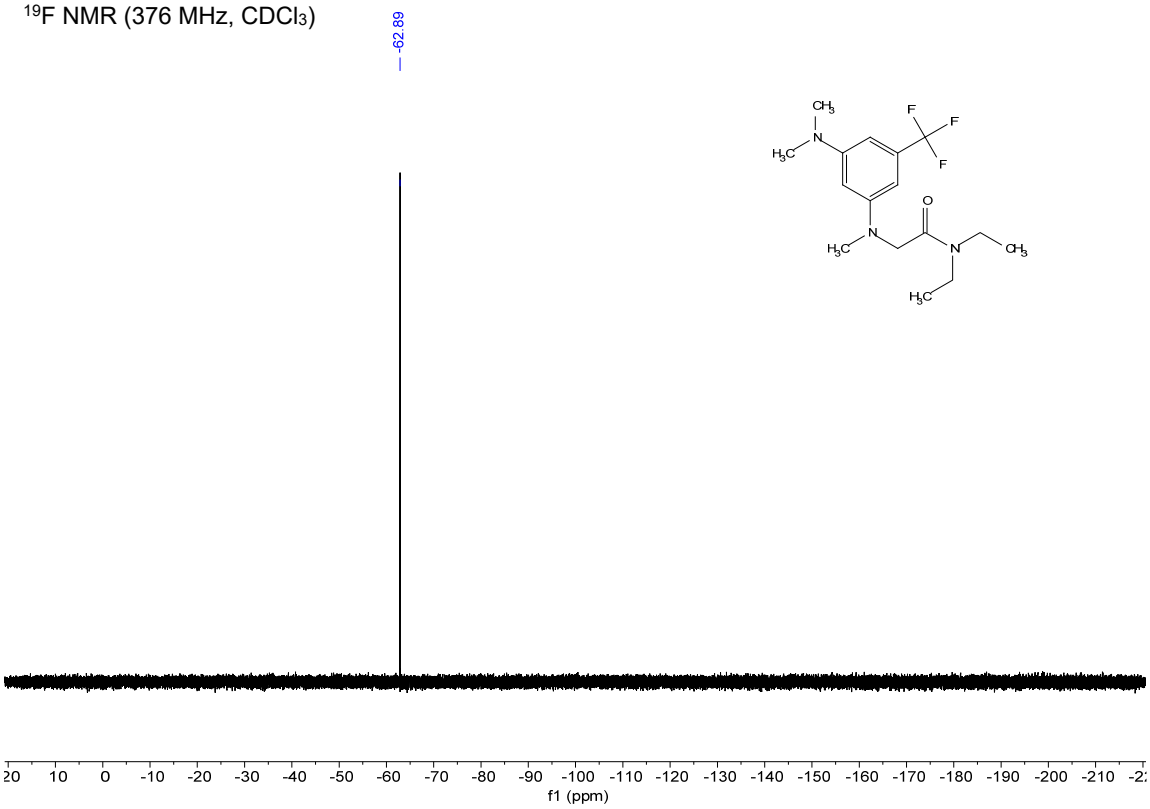


^{13}C NMR (101 MHz, $CDCl_3$)



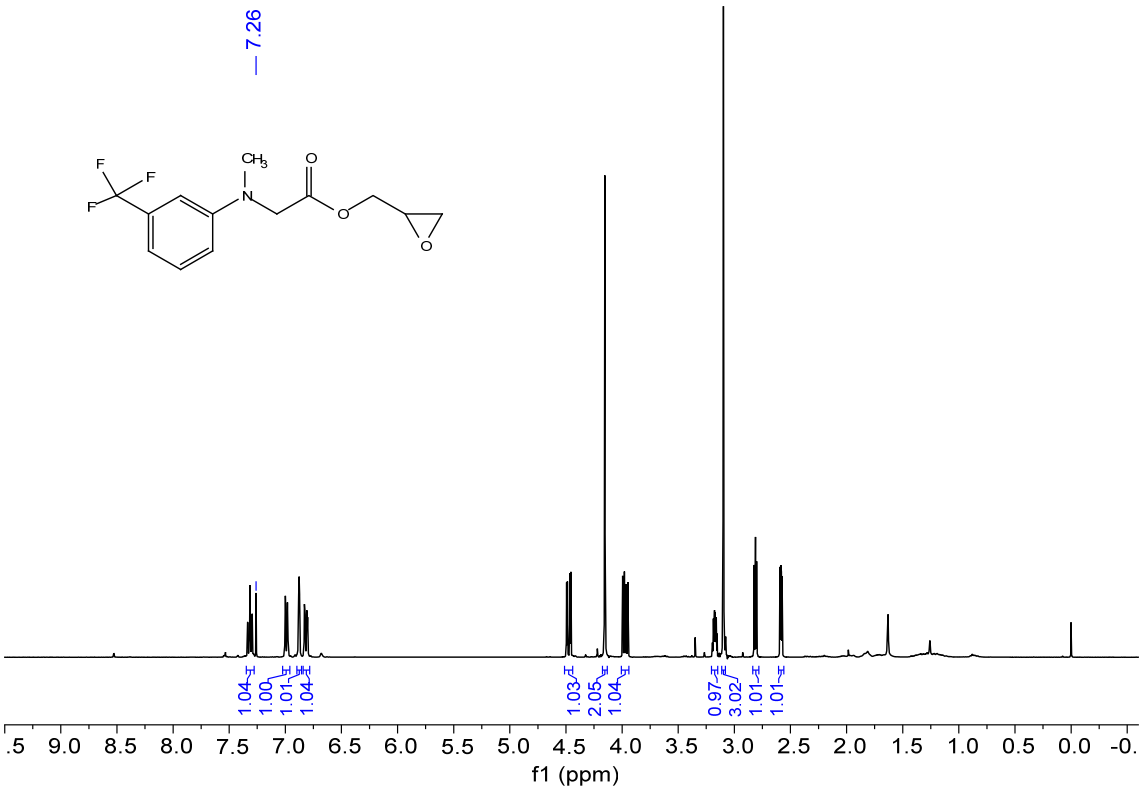
^{13}C NMR spectrum of **1h**

^{19}F NMR (376 MHz, $CDCl_3$)



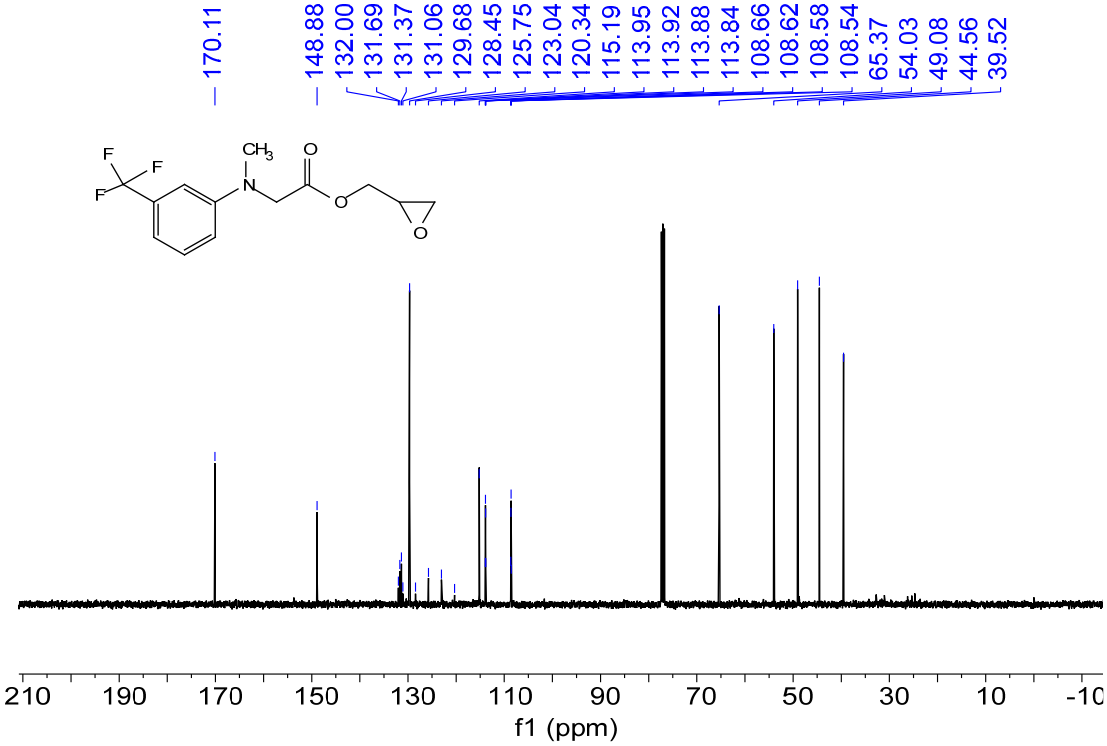
^{19}F NMR spectrum of **1 h**

^{1}H NMR (400 MHz, $CDCl_3$)



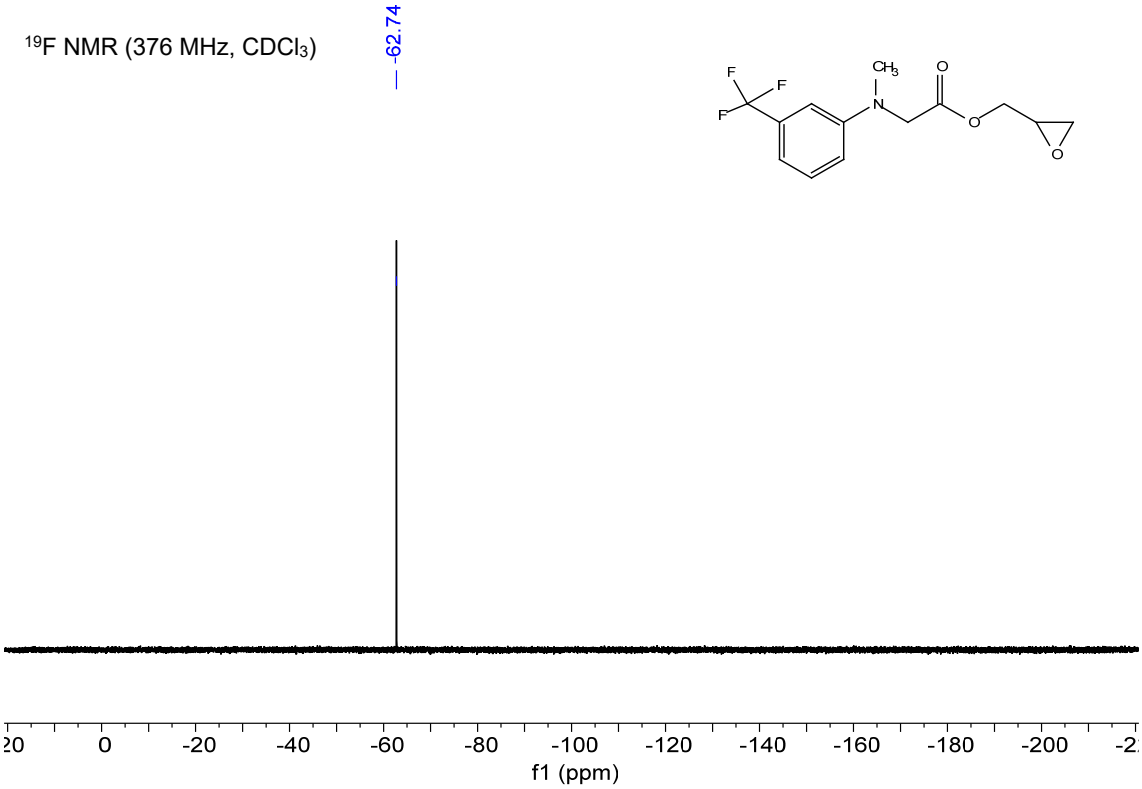
^{1}H NMR spectrum of **1i**

^{13}C NMR (101 MHz, $CDCl_3$)



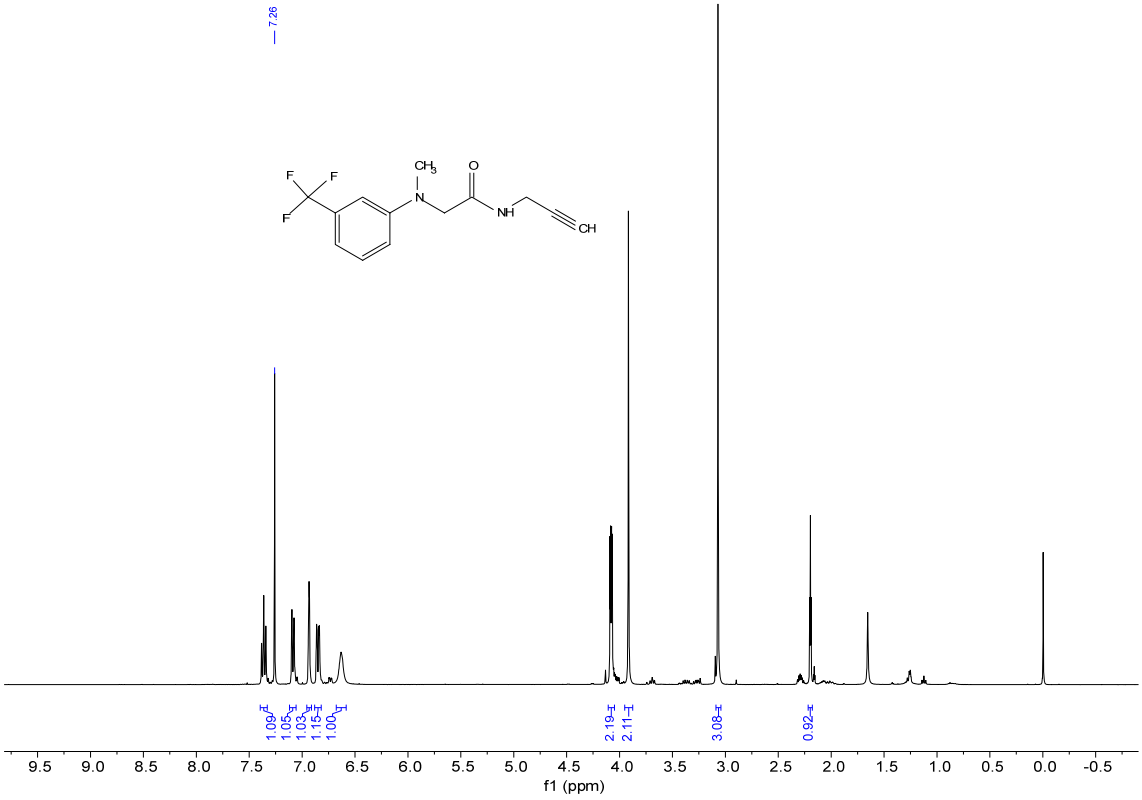
^{13}C NMR spectrum of **1i**

^{19}F NMR (376 MHz, $CDCl_3$)



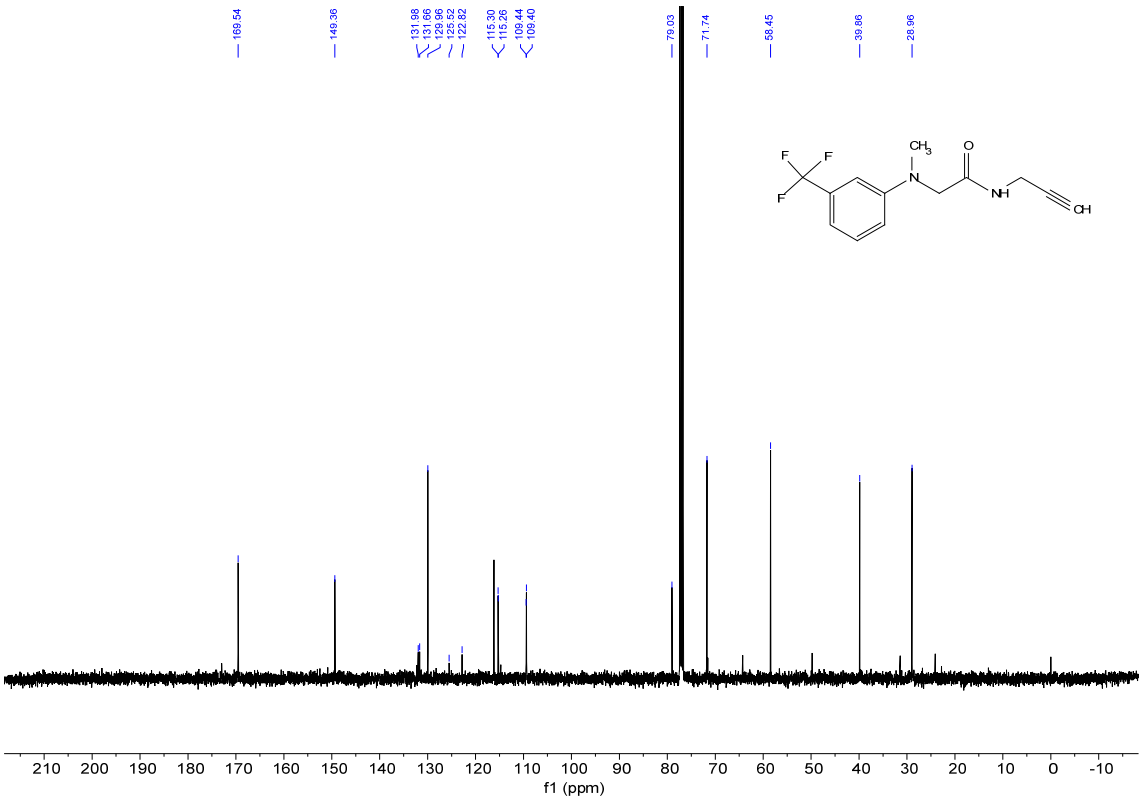
^{19}F NMR spectrum of **1i**

^{1}H NMR (400 MHz, $CDCl_3$)



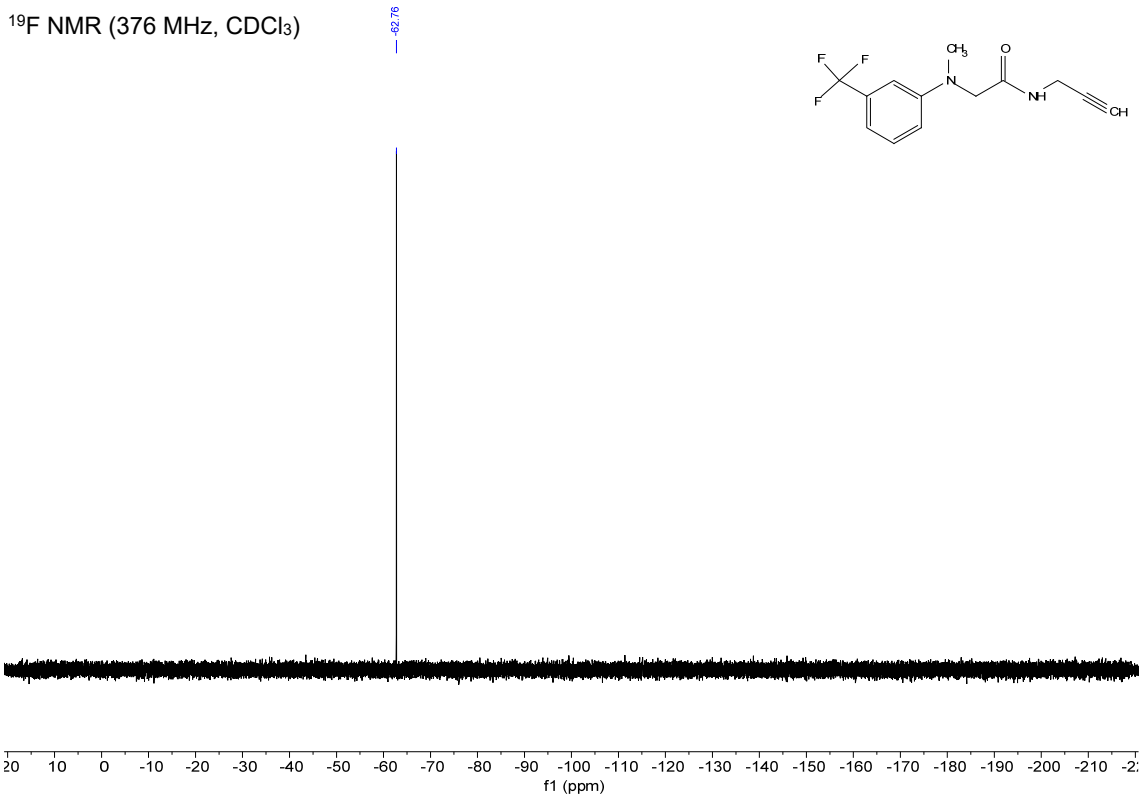
^{1}H NMR spectrum of **1j**

^{13}C NMR (101 MHz, $CDCl_3$)



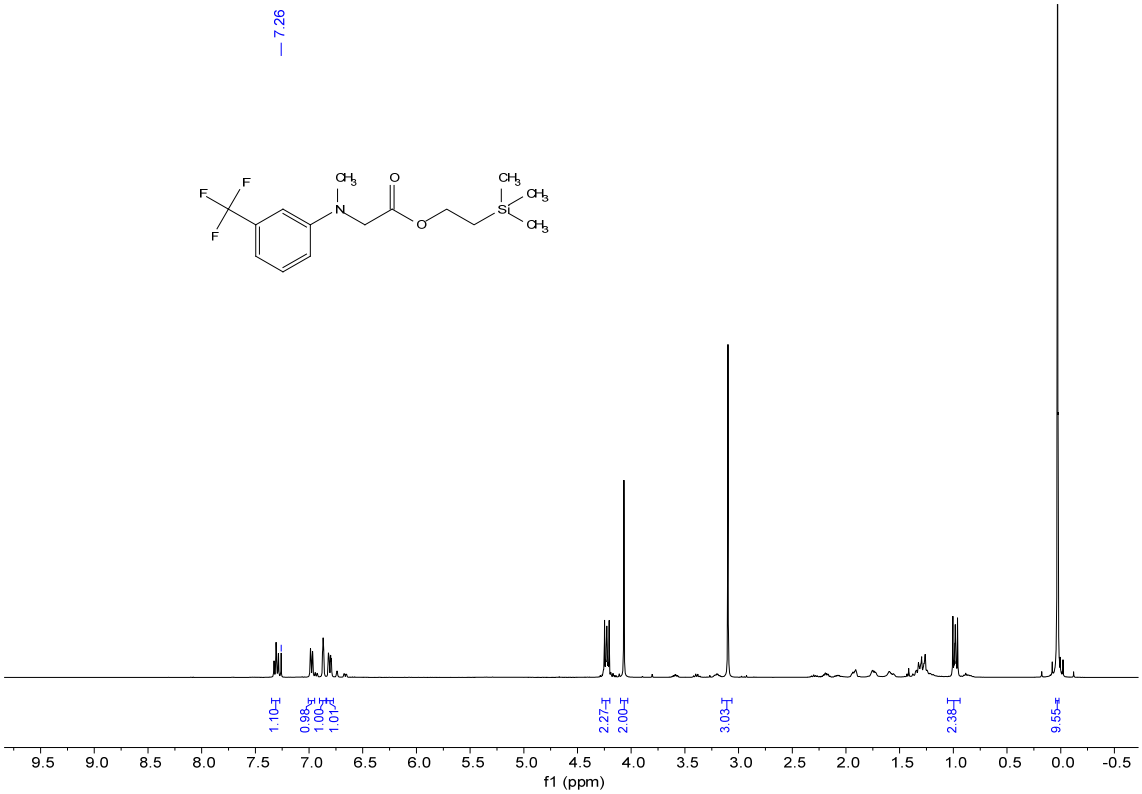
^{13}C NMR spectrum of **1j**

^{19}F NMR (376 MHz, $CDCl_3$)



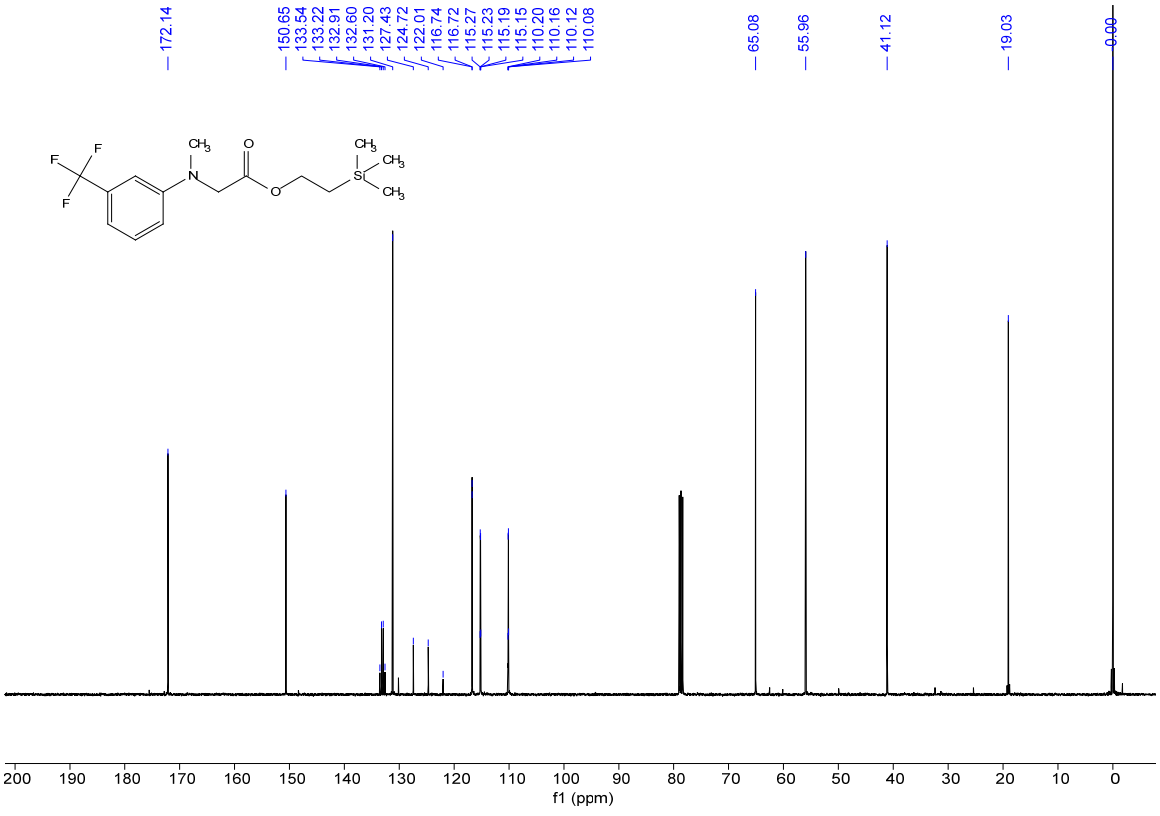
^{19}F NMR spectrum of **1j**

^{1}H NMR (400 MHz, $CDCl_3$)



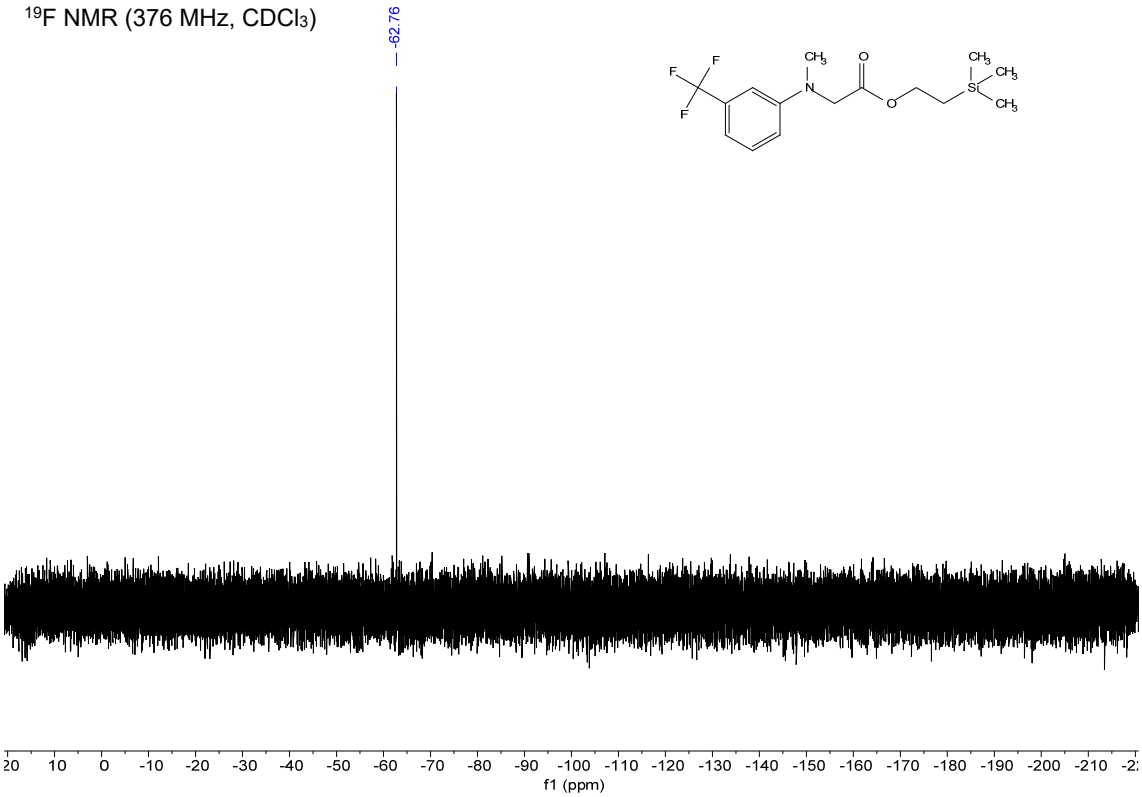
^{1}H NMR spectrum of **1k**

^{13}C NMR (101 MHz, $CDCl_3$)



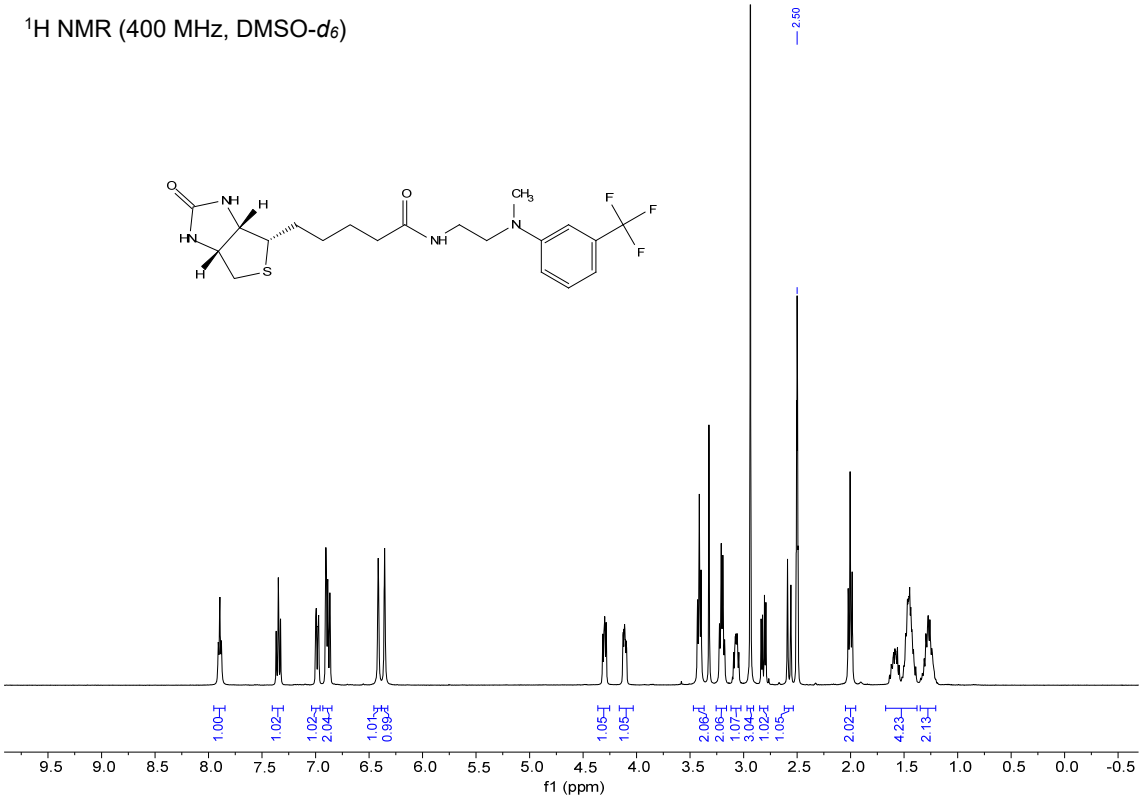
^{13}C NMR spectrum of **1k**

^{19}F NMR (376 MHz, $CDCl_3$)



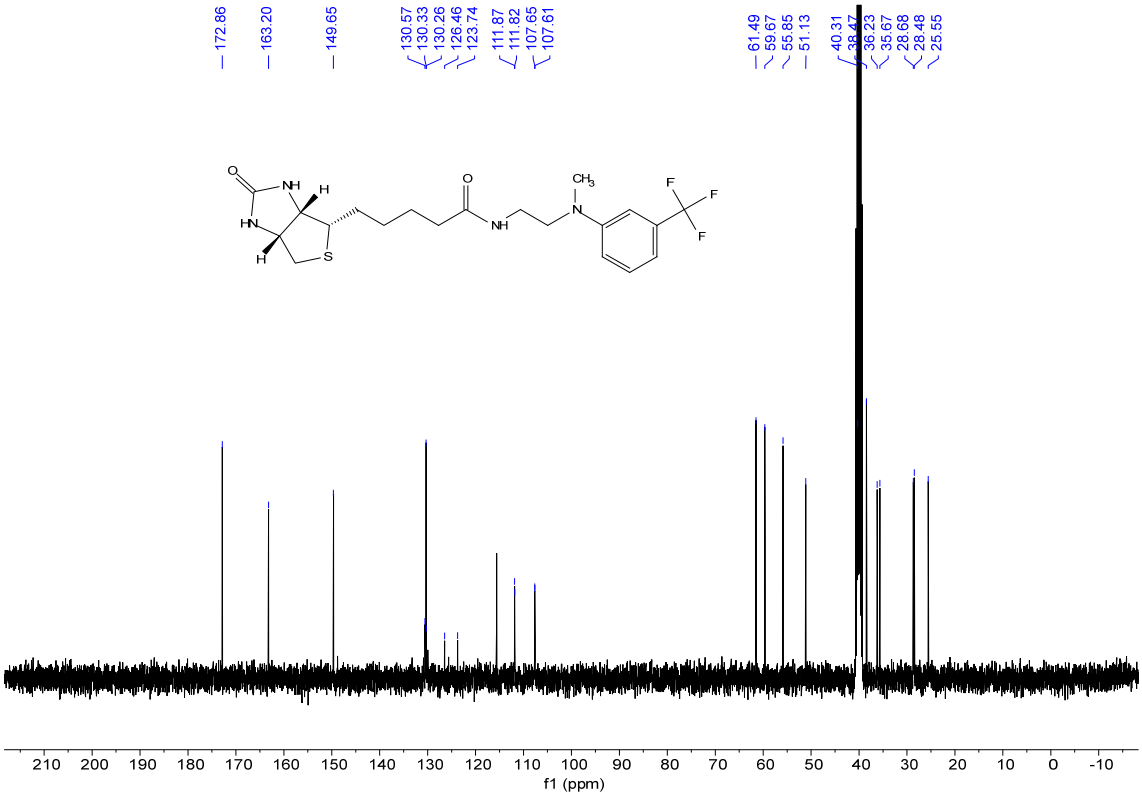
^{19}F NMR spectrum of **1k**

^{1}H NMR (400 MHz, DMSO-d_6)



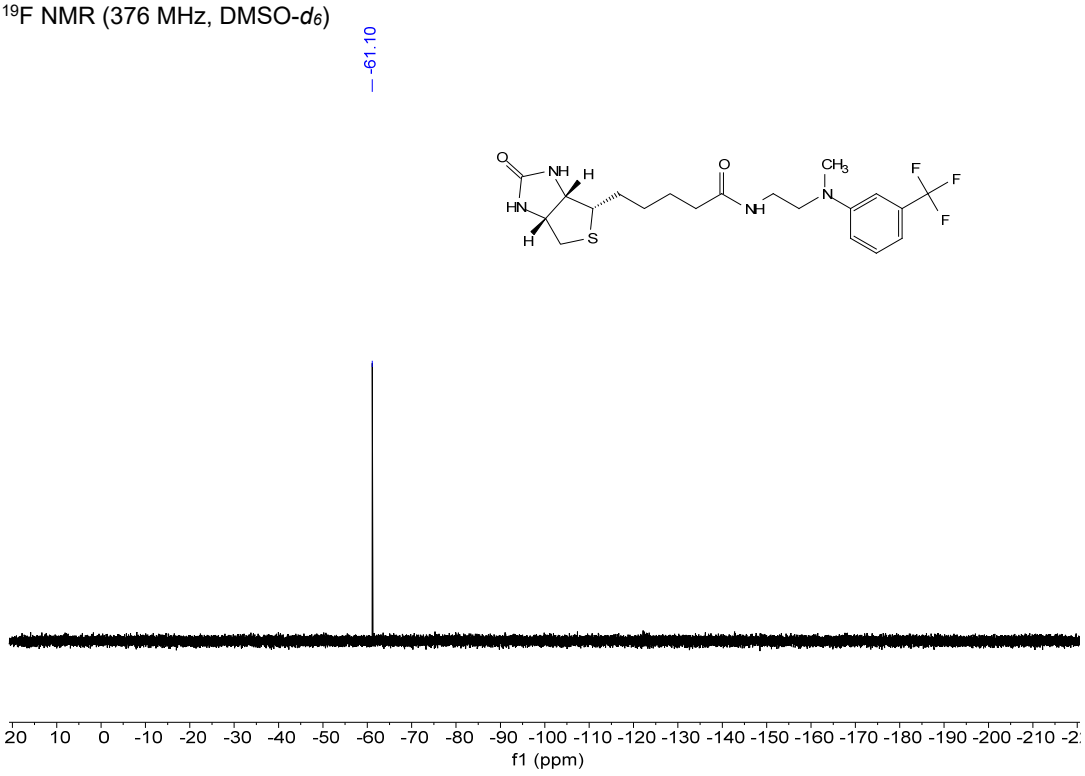
^{1}H NMR spectrum of **1l**

^{13}C NMR (101 MHz, DMSO-d_6)



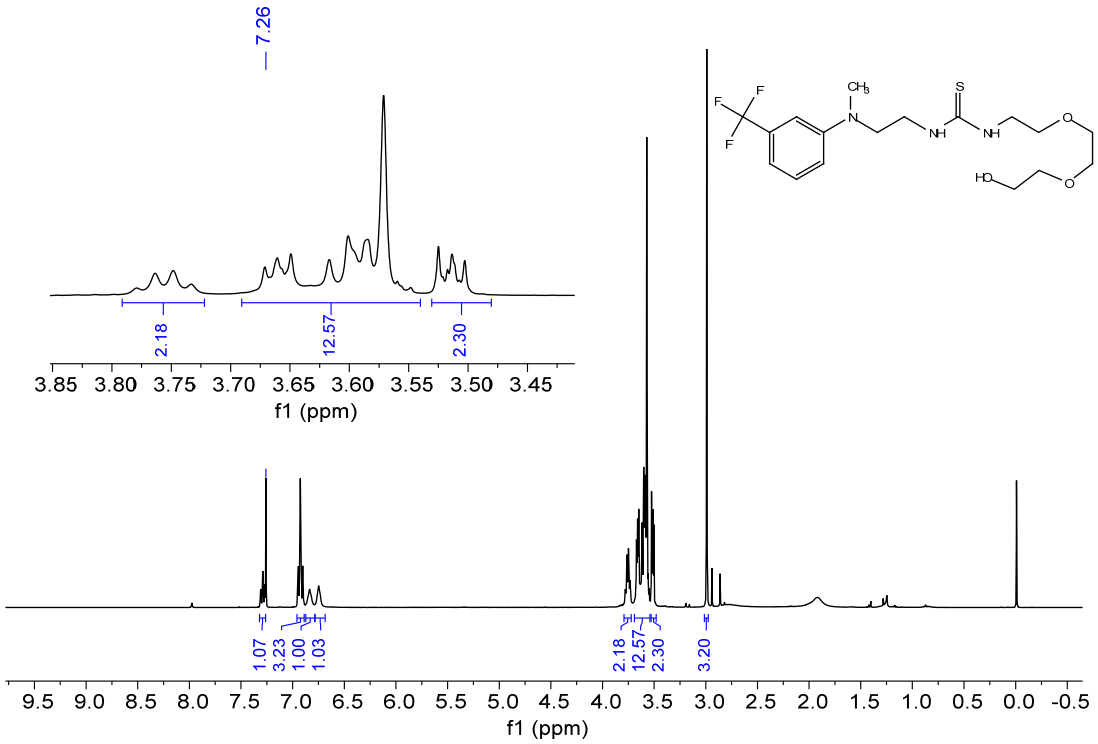
^{13}C NMR spectrum of **1l**

^{19}F NMR (376 MHz, DMSO-d_6)



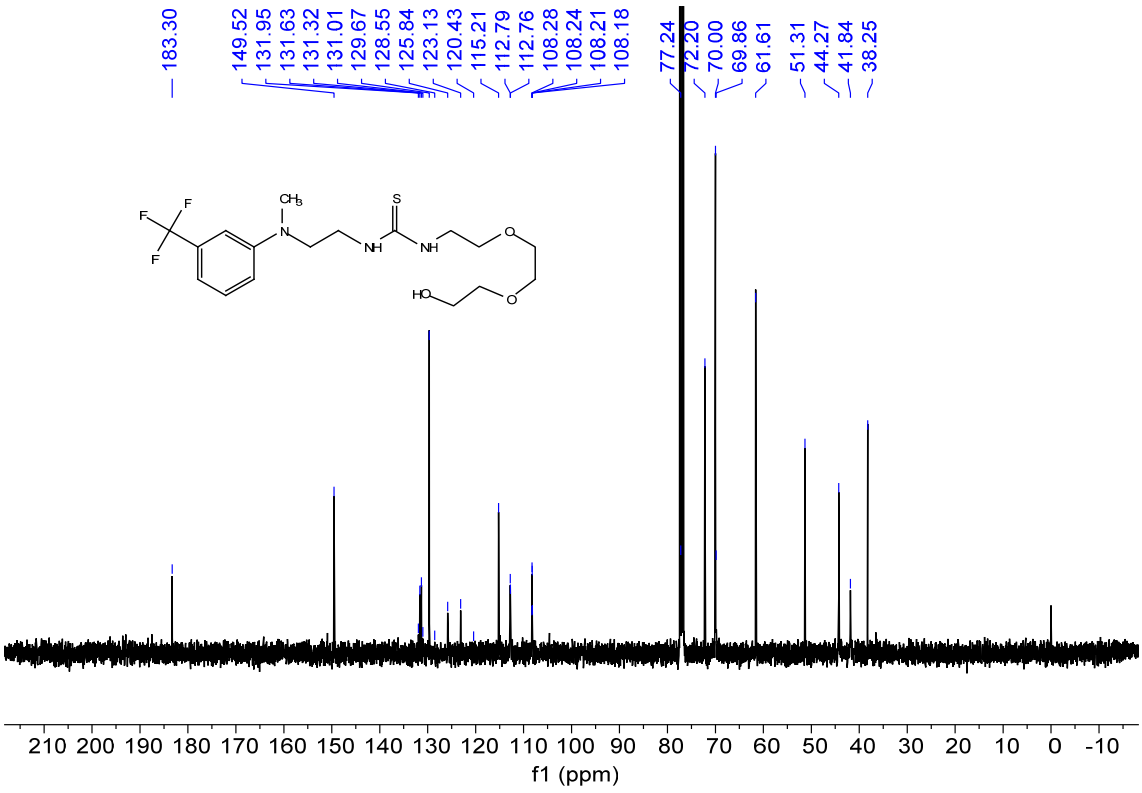
^{19}F NMR spectrum of **1l**

^{1}H NMR (400 MHz, $CDCl_3$)



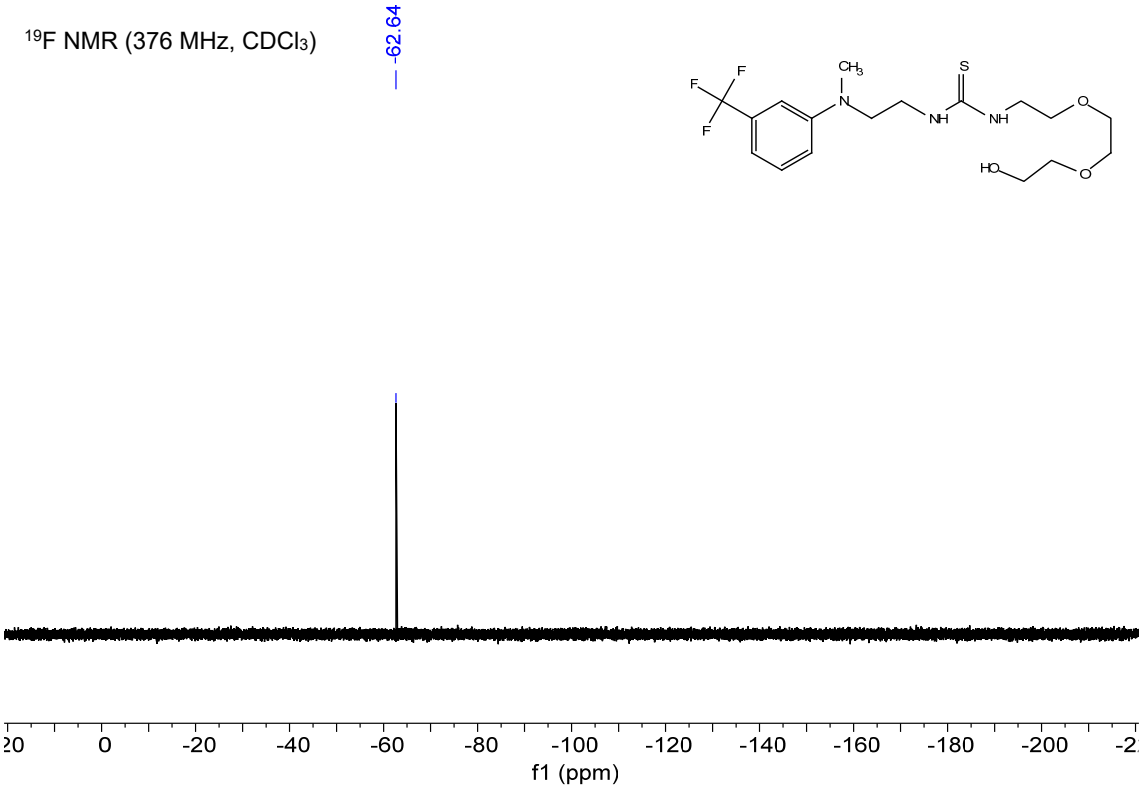
^{1}H NMR spectrum of **1m**

^{13}C NMR (101 MHz, $CDCl_3$)



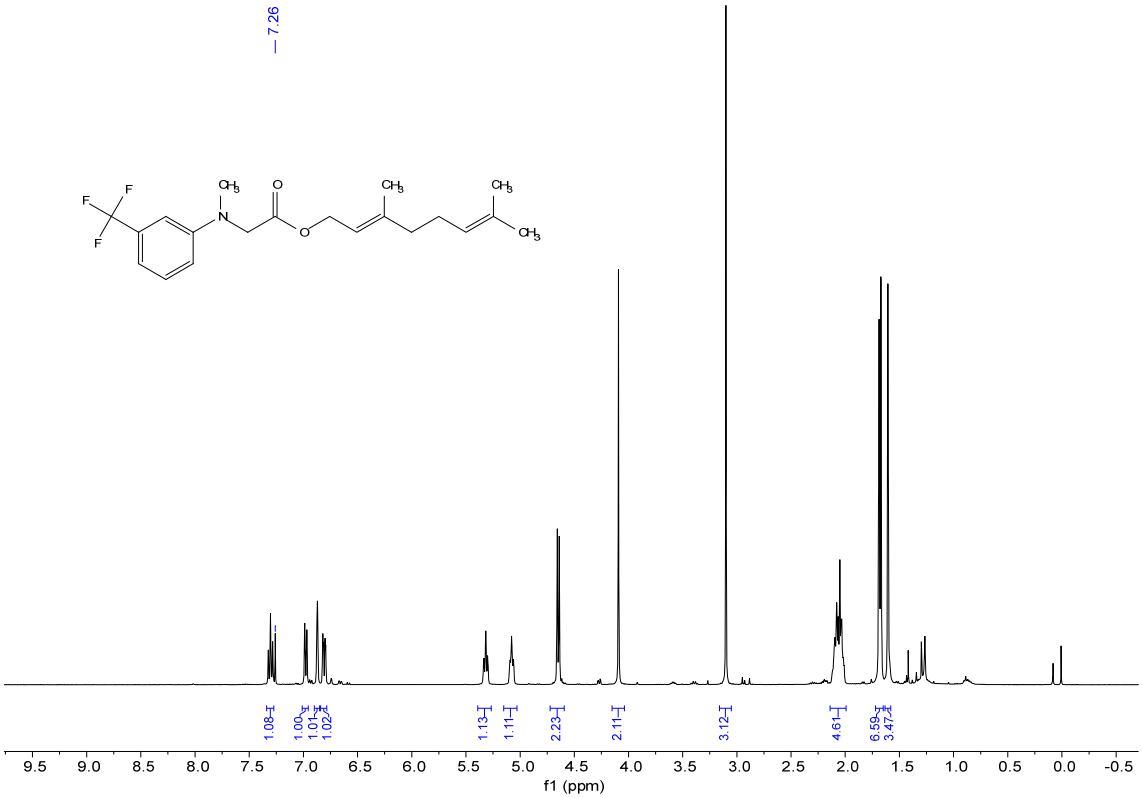
^{13}C NMR spectrum of **1m**

^{19}F NMR (376 MHz, $CDCl_3$)



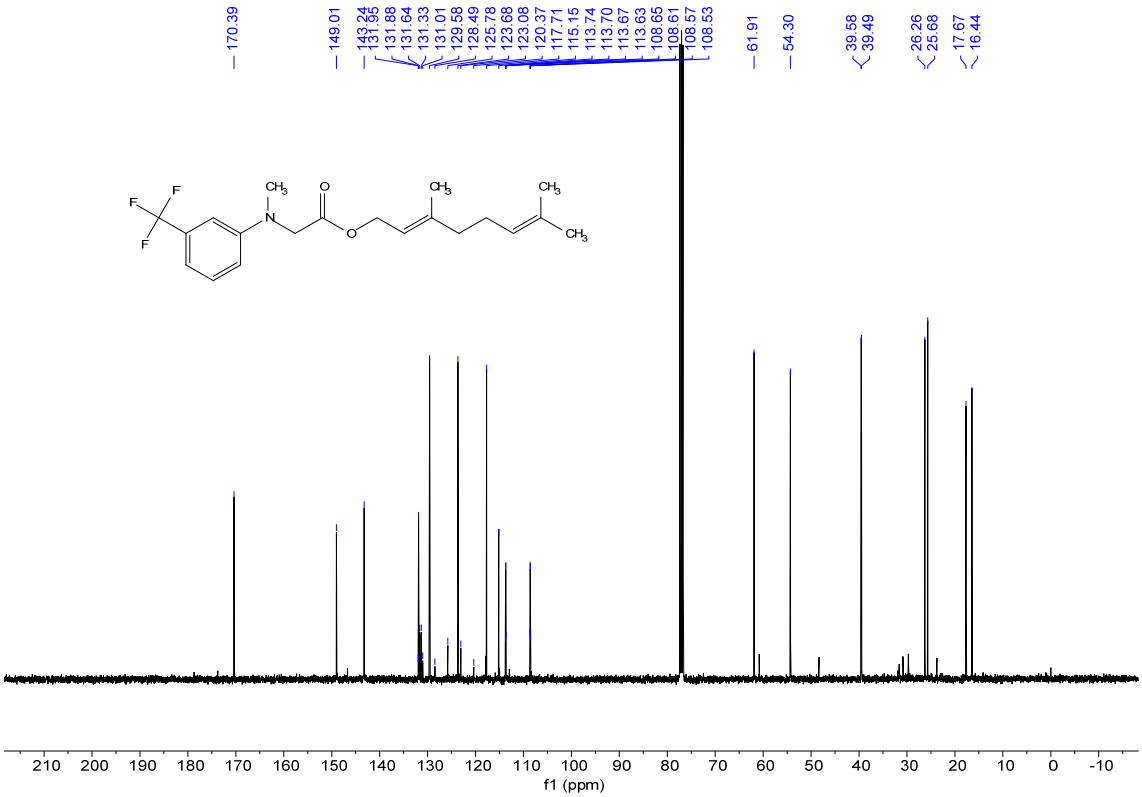
^{19}F NMR spectrum of **1m**

^{1}H NMR (400 MHz, $CDCl_3$)



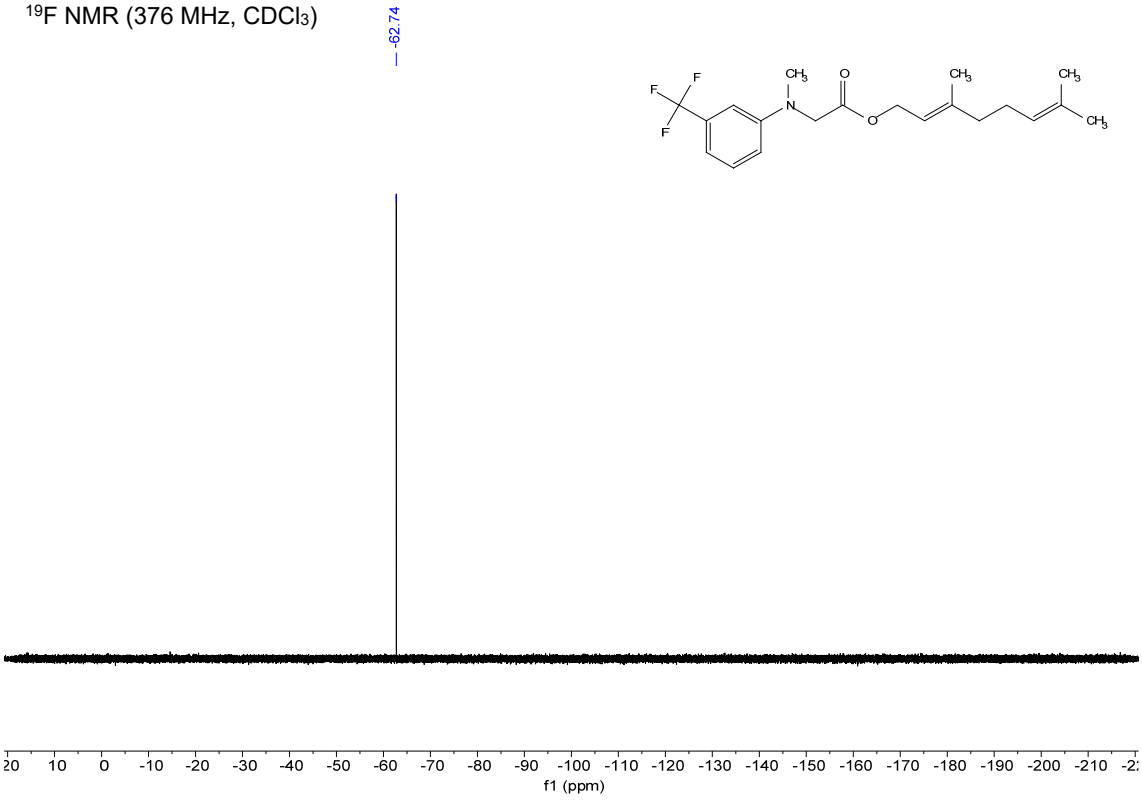
^{1}H NMR spectrum of **1n**

^{13}C NMR (101 MHz, $CDCl_3$)



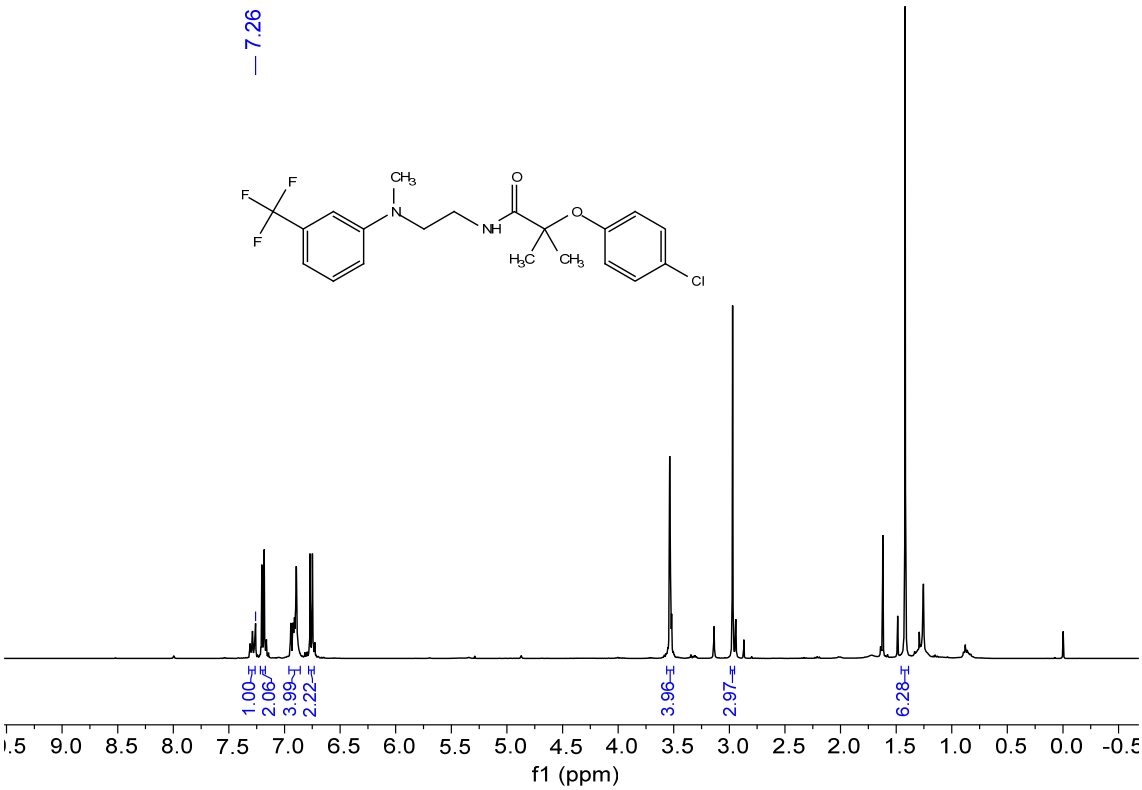
^{13}C NMR spectrum of **1n**

^{19}F NMR (376 MHz, $CDCl_3$)



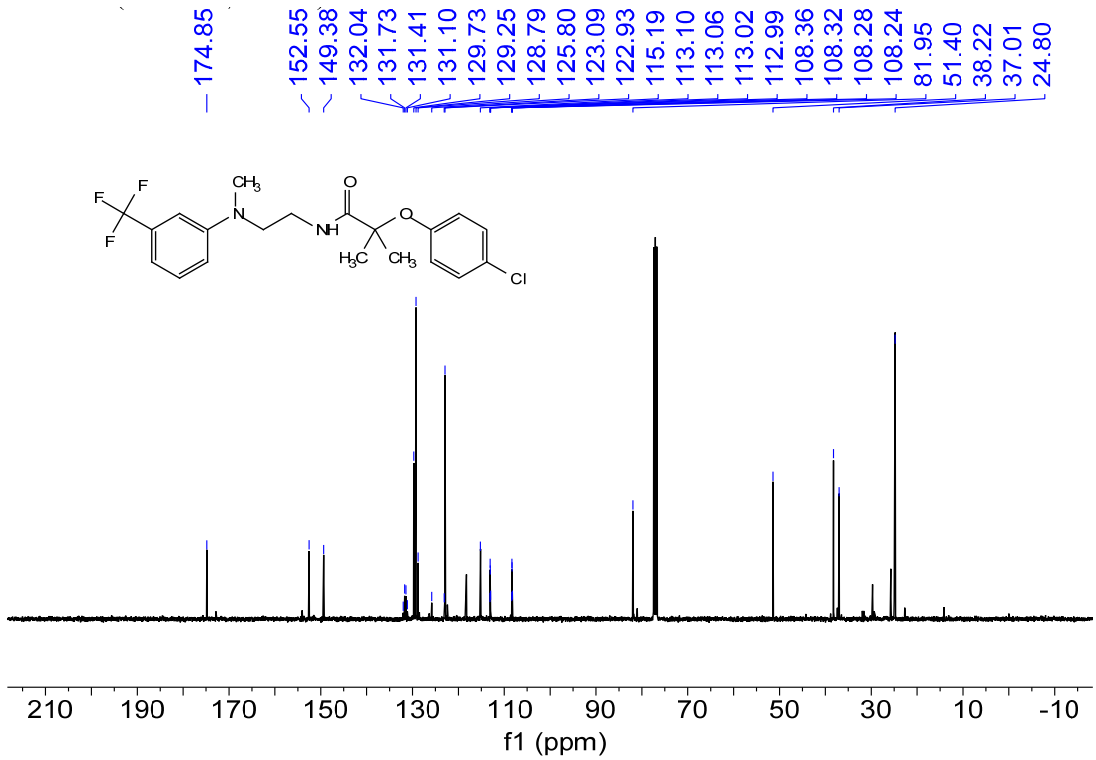
^{19}F NMR spectrum of **1n**

^{1}H NMR (400 MHz, $CDCl_3$)



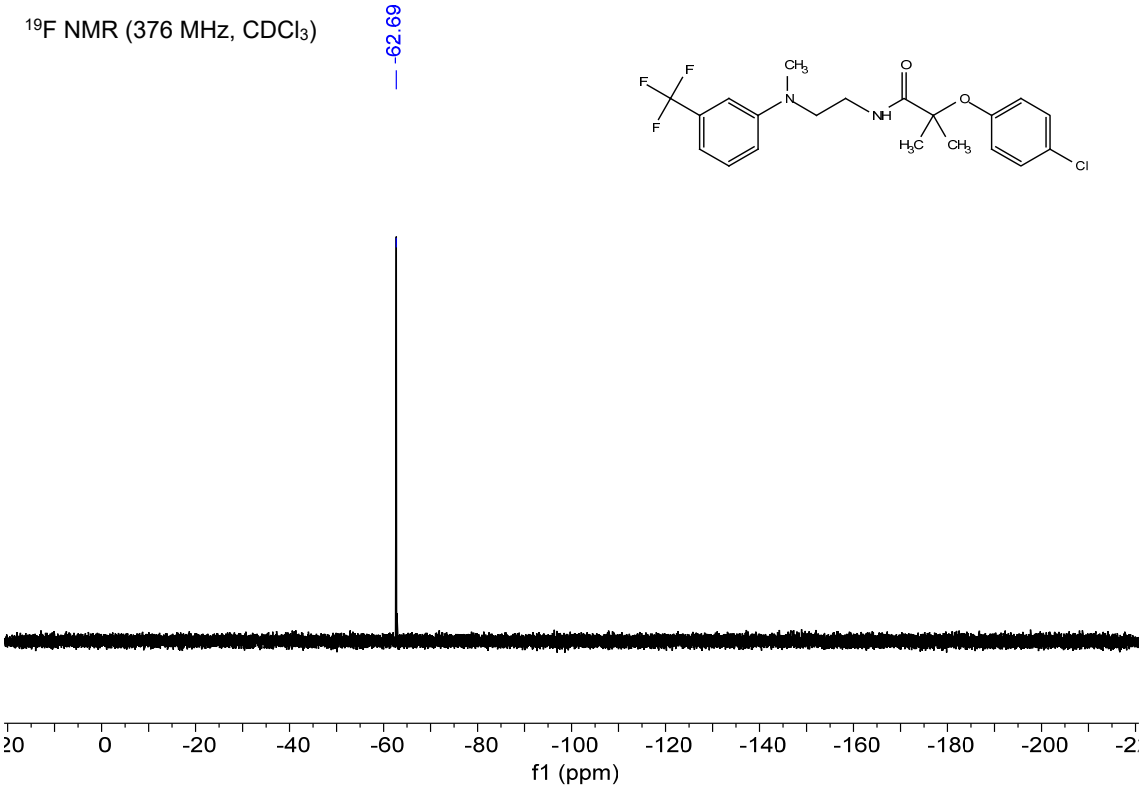
^{1}H NMR spectrum of **1o**

^{13}C NMR (101 MHz, $CDCl_3$)



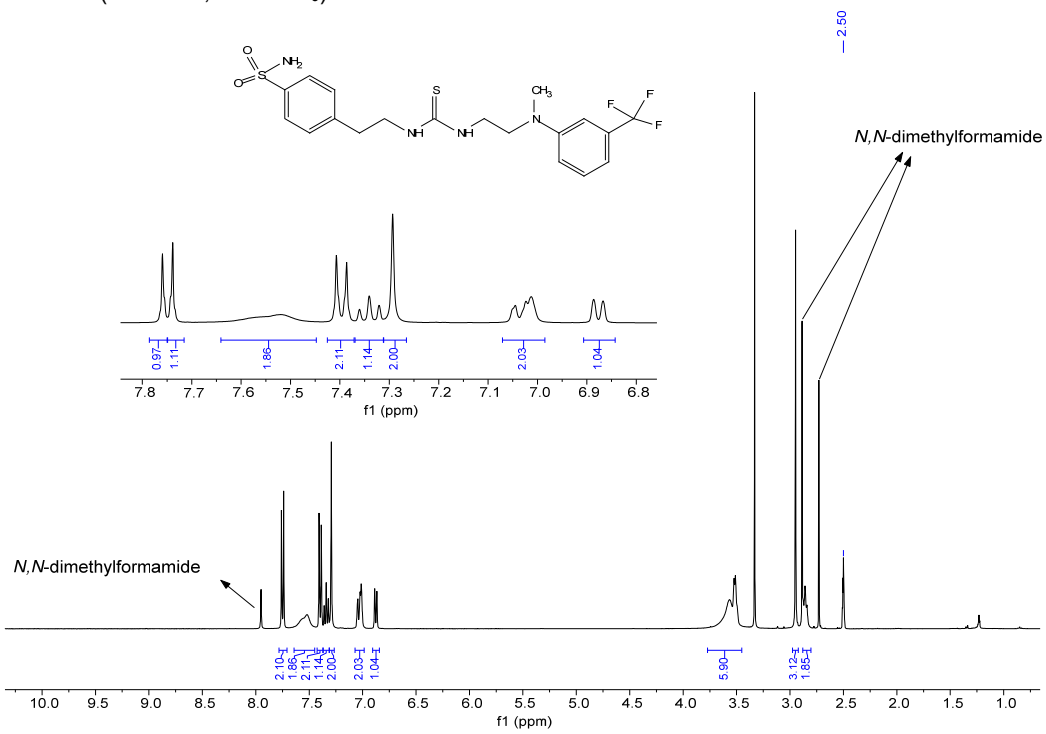
^{13}C NMR spectrum of **1o**

^{19}F NMR (376 MHz, $CDCl_3$)



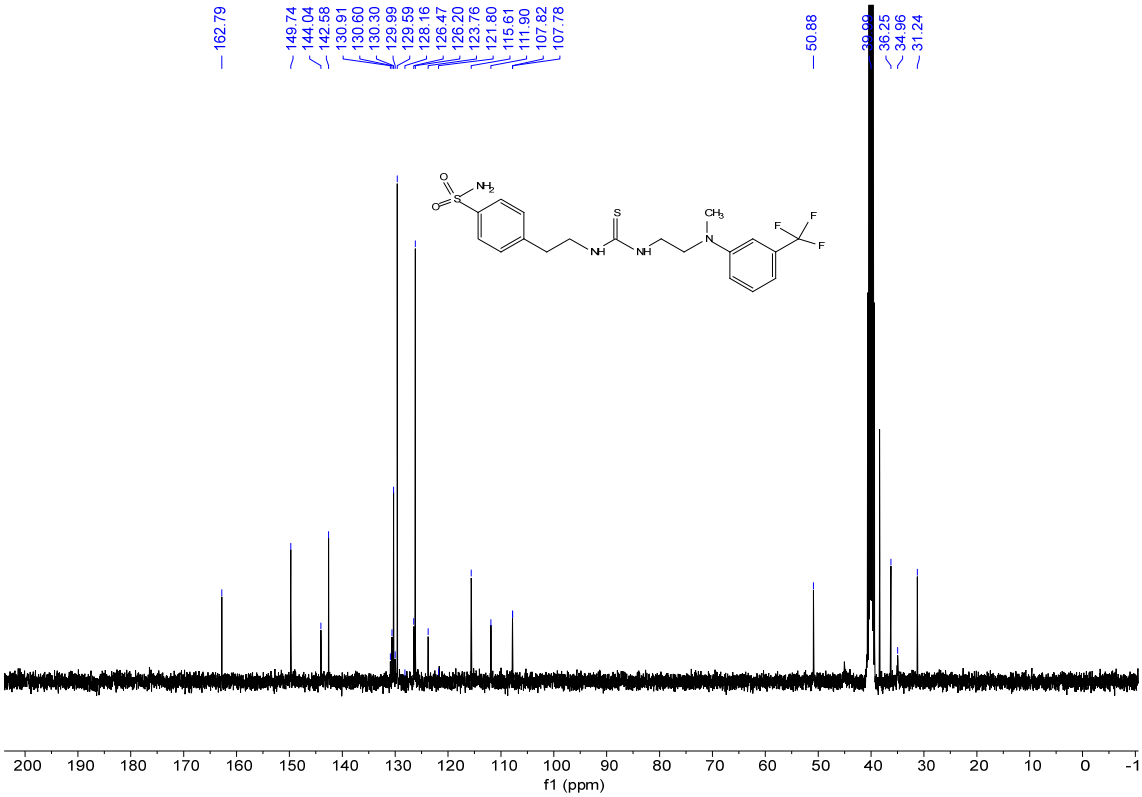
^{19}F NMR spectrum of **1o**

^{1}H NMR (400 MHz, DMSO-d_6)



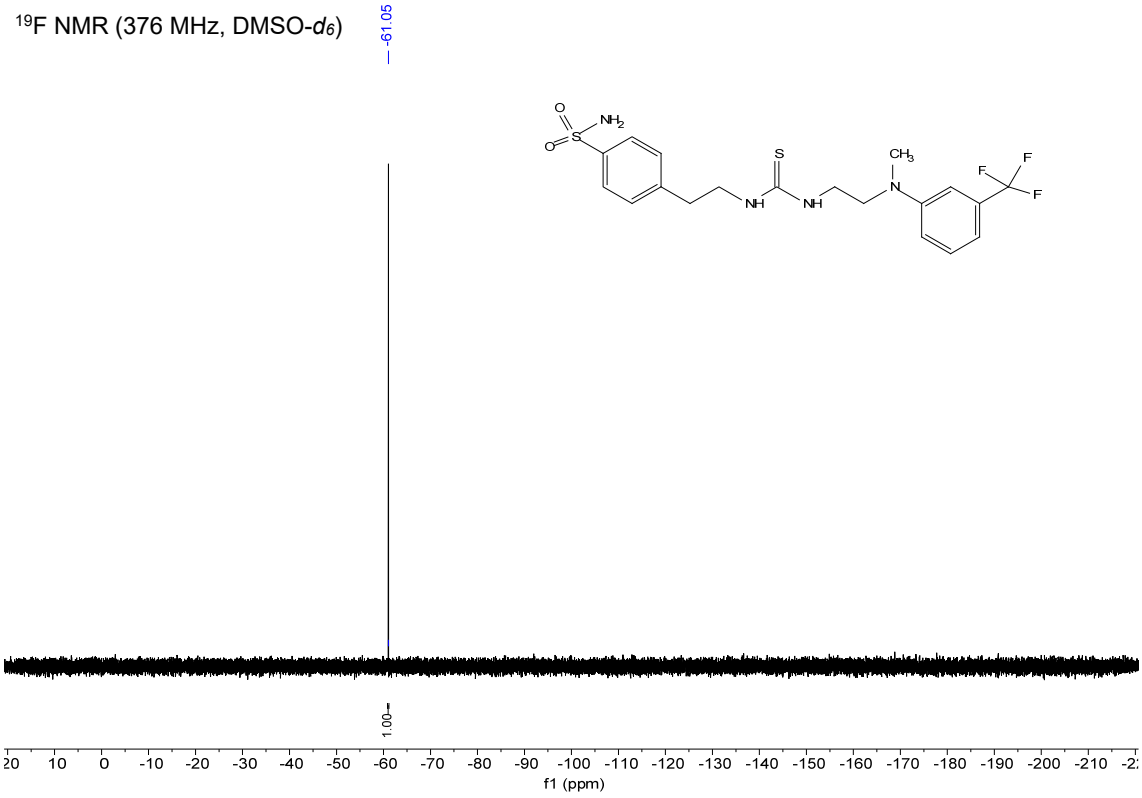
^{1}H NMR spectrum of **1p**

^{13}C NMR (101 MHz, DMSO-d_6)

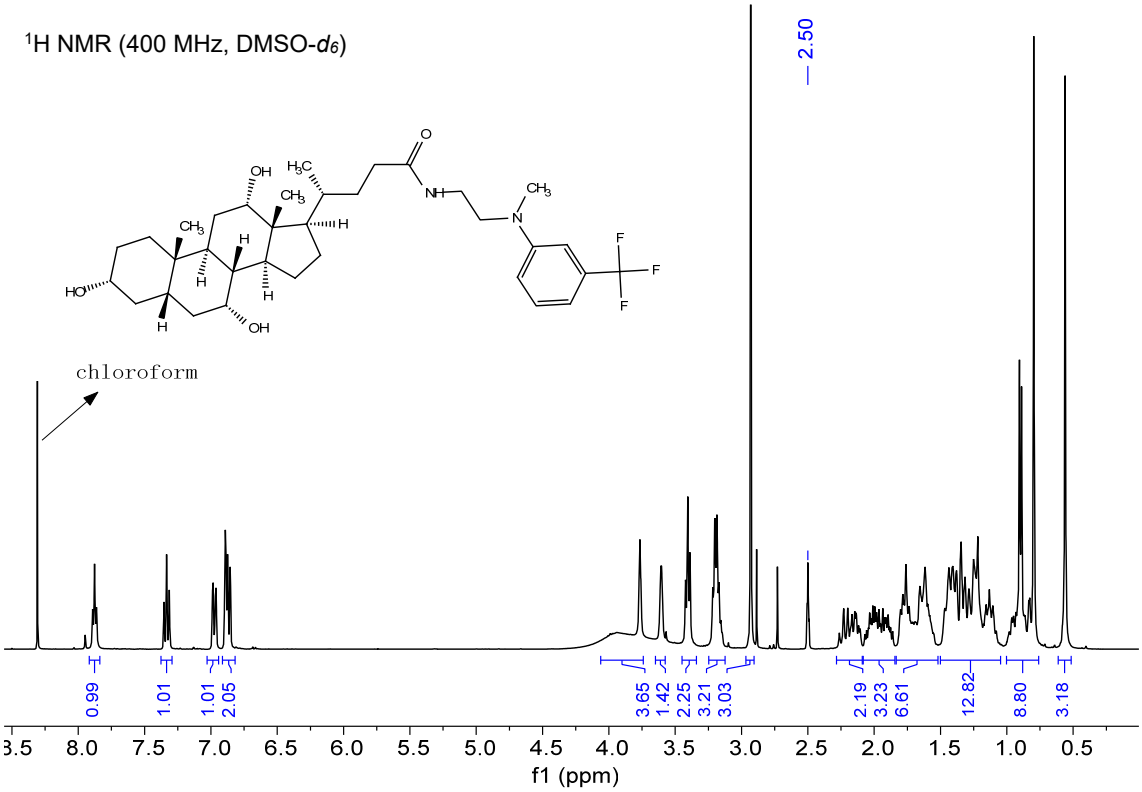


^{13}C NMR spectrum of **1p**

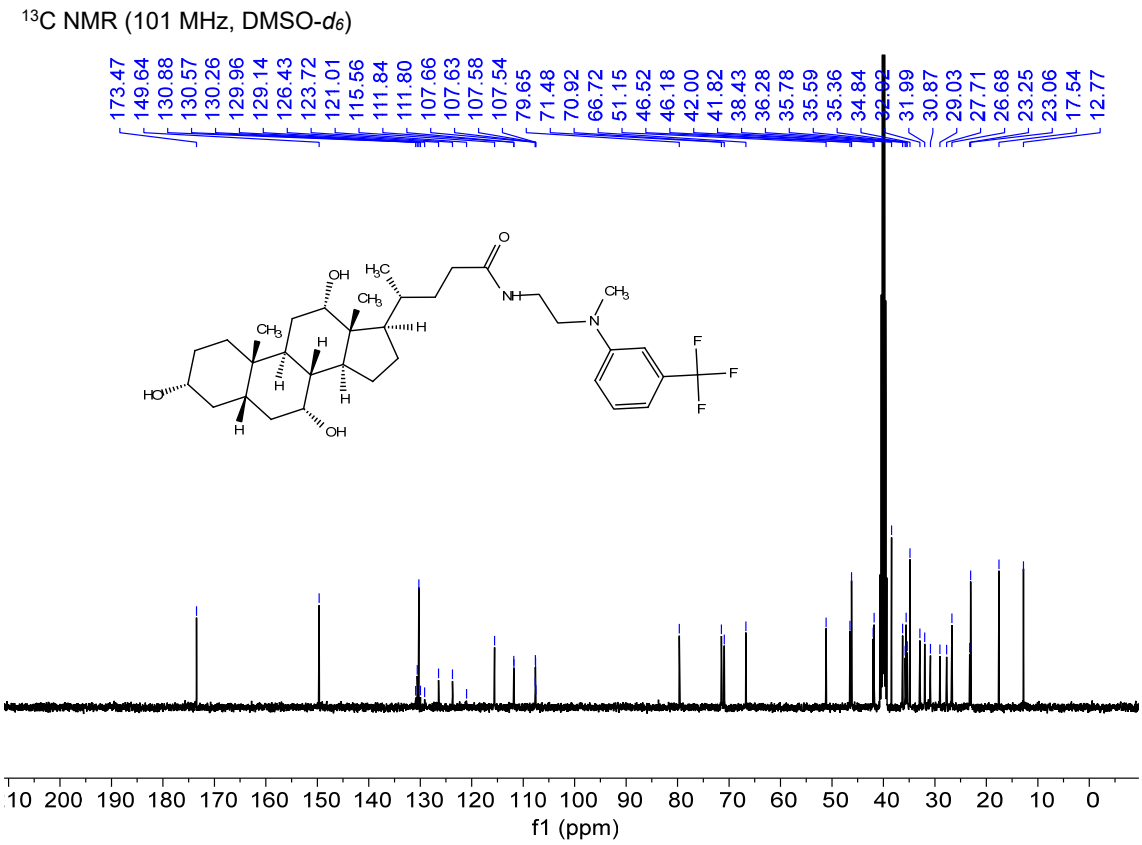
^{19}F NMR (376 MHz, DMSO-d_6)



^{19}F NMR spectrum of **1p**

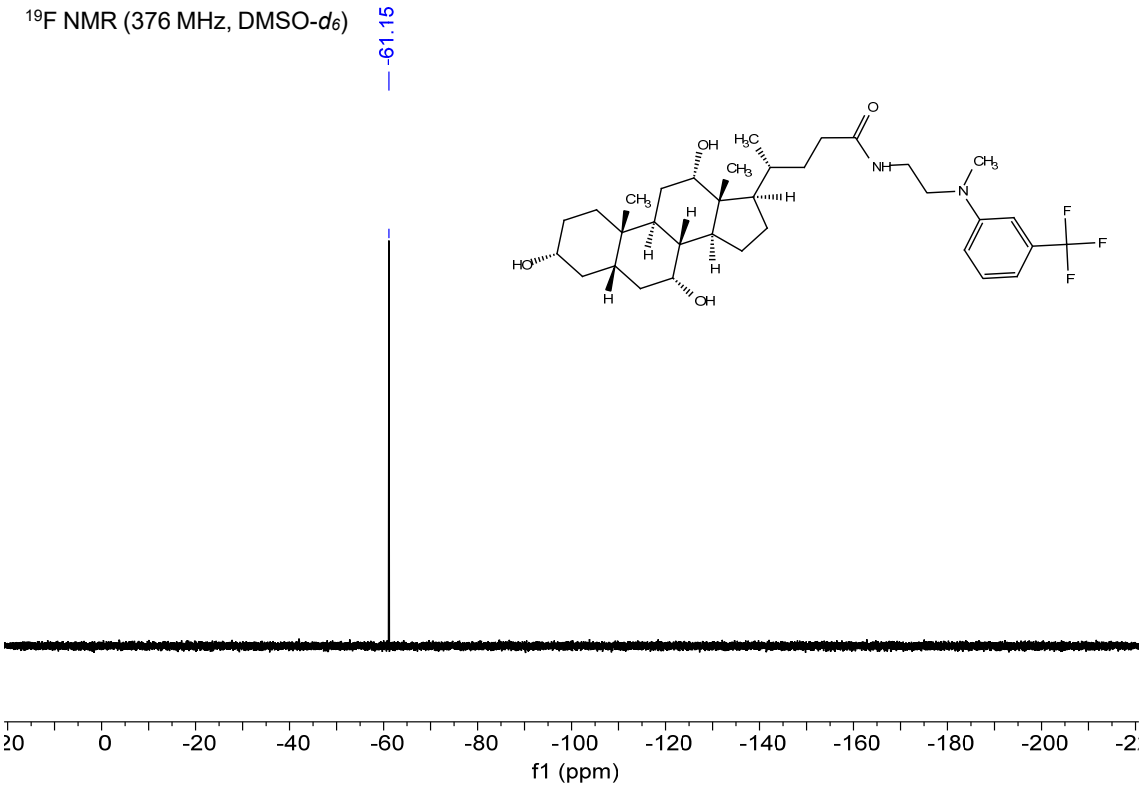


^{1}H NMR spectrum of **1q**



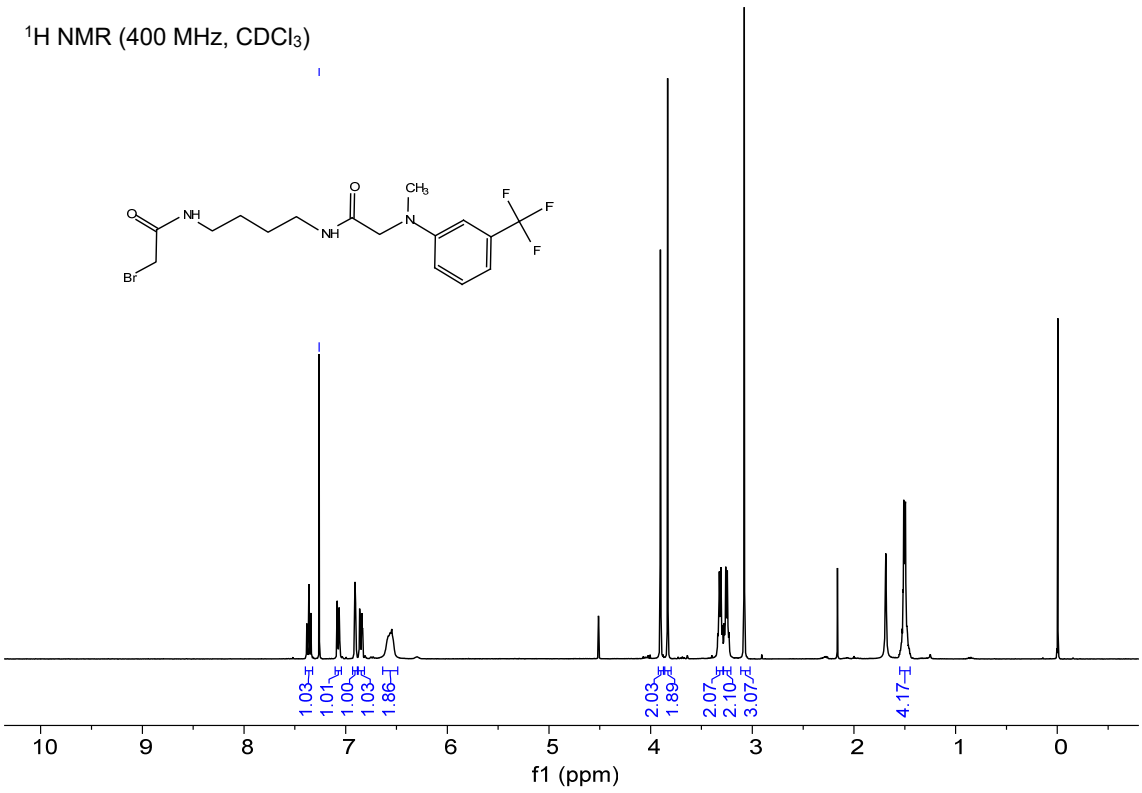
^{13}C NMR spectrum of **1q**

^{19}F NMR (376 MHz, DMSO-d_6)



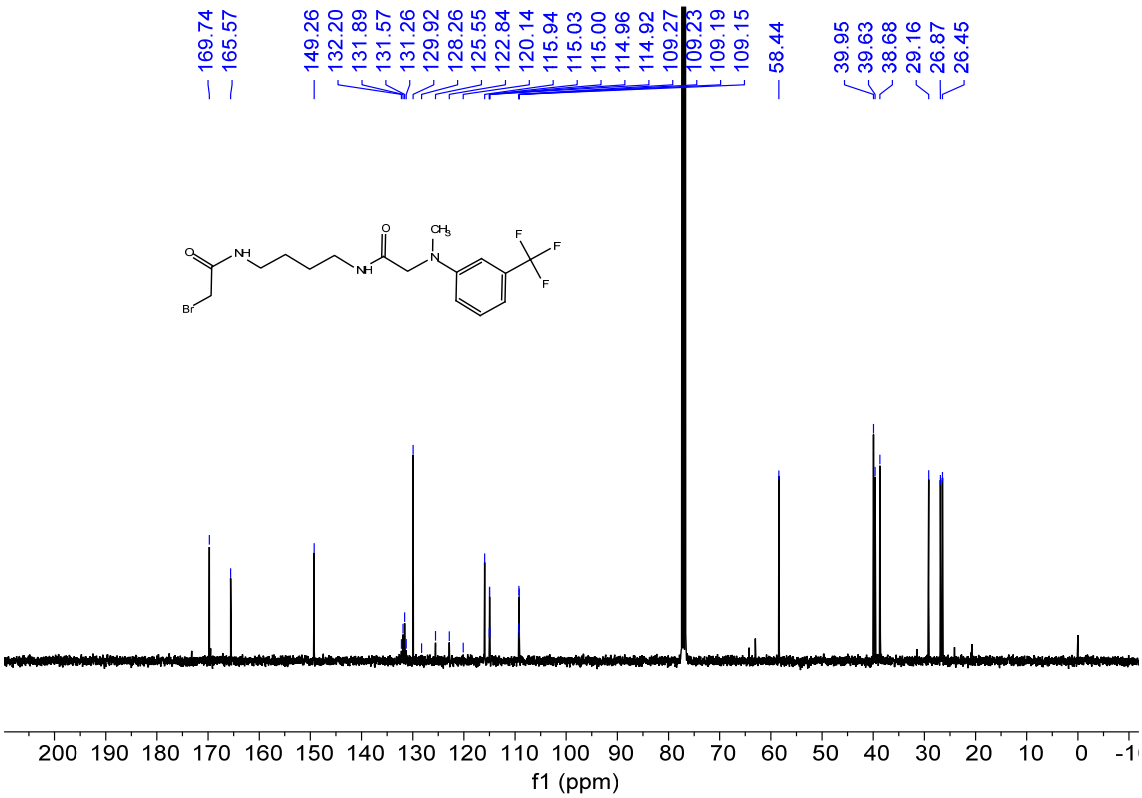
^{19}F NMR spectrum of **1q**

^{1}H NMR (400 MHz, $CDCl_3$)



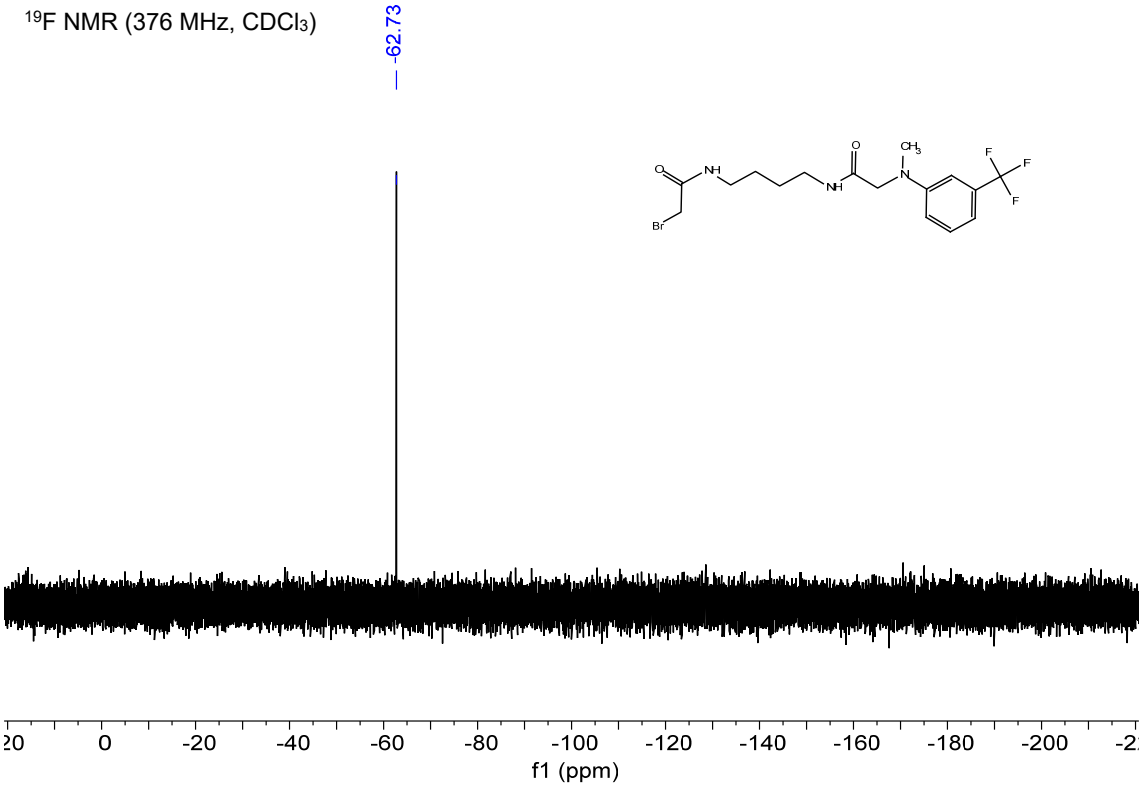
^{1}H NMR spectrum of **1r**

^{13}C NMR (101 MHz, $CDCl_3$)



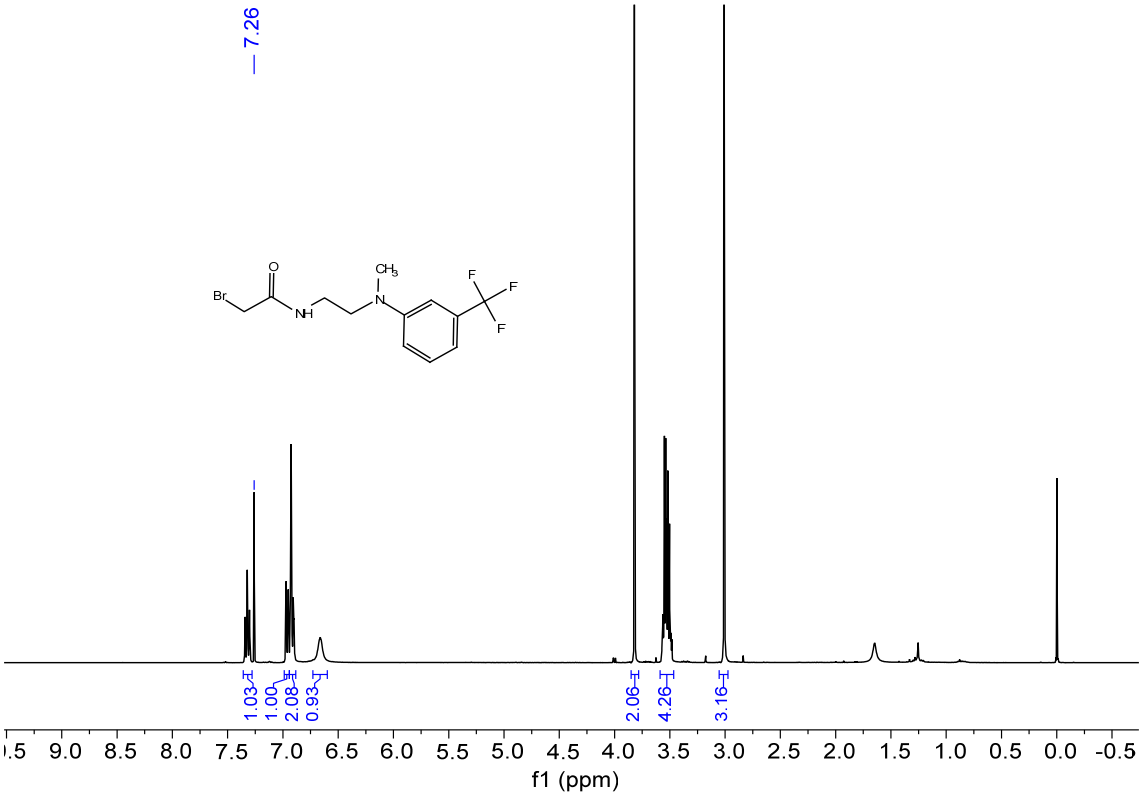
^{13}C NMR spectrum of **1r**

^{19}F NMR (376 MHz, $CDCl_3$)



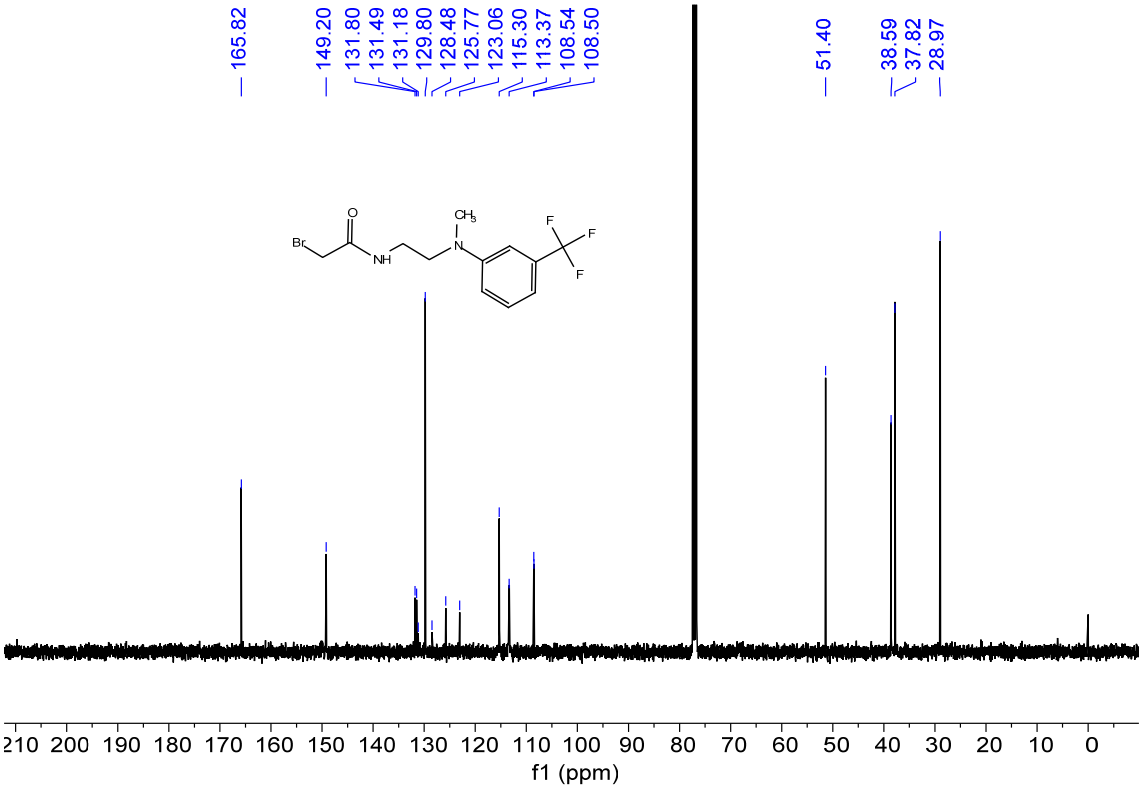
^{19}F NMR spectrum of **1r**

^{1}H NMR (400 MHz, $CDCl_3$)



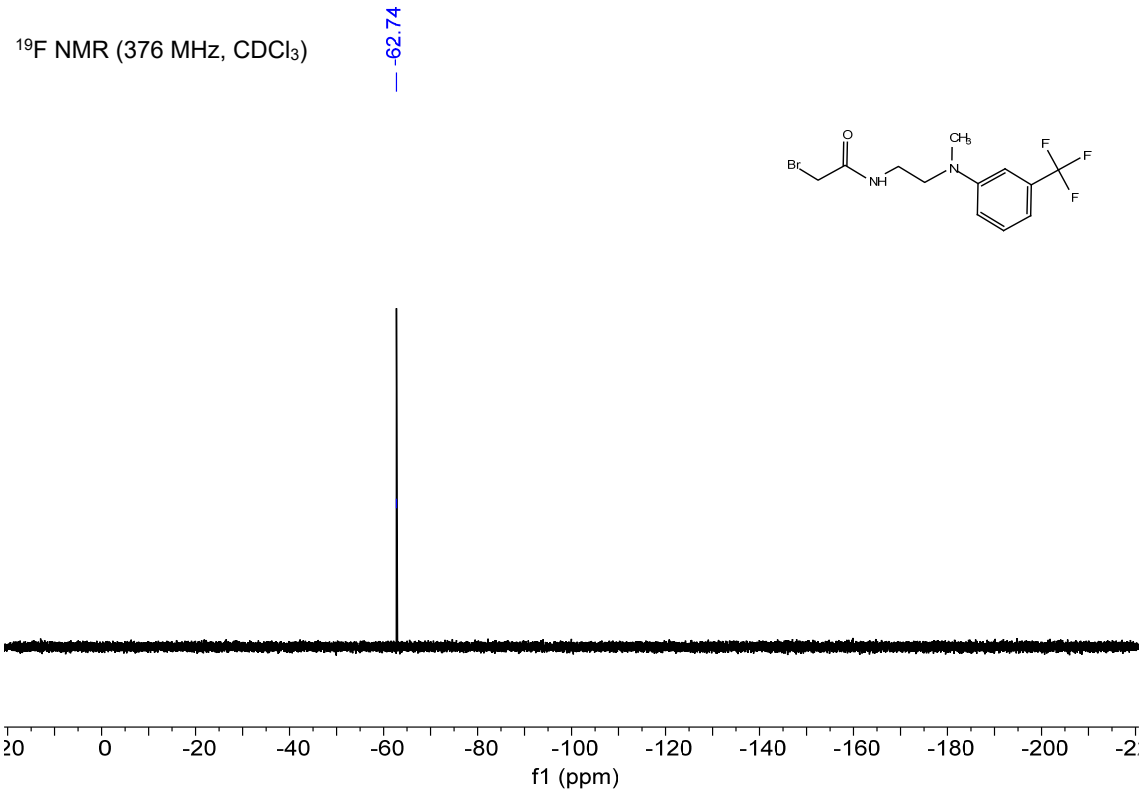
^{1}H NMR spectrum of **1s**

^{13}C NMR (101 MHz, $CDCl_3$)



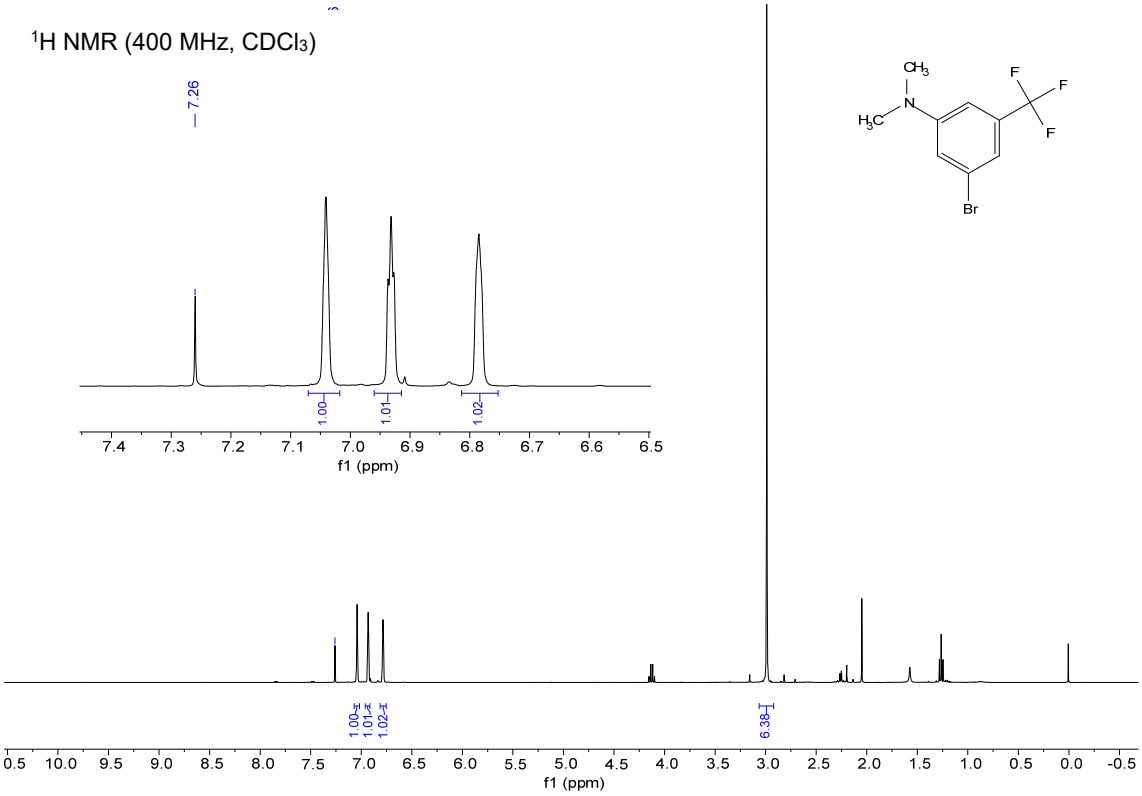
^{13}C NMR spectrum of **1s**

^{19}F NMR (376 MHz, $CDCl_3$)



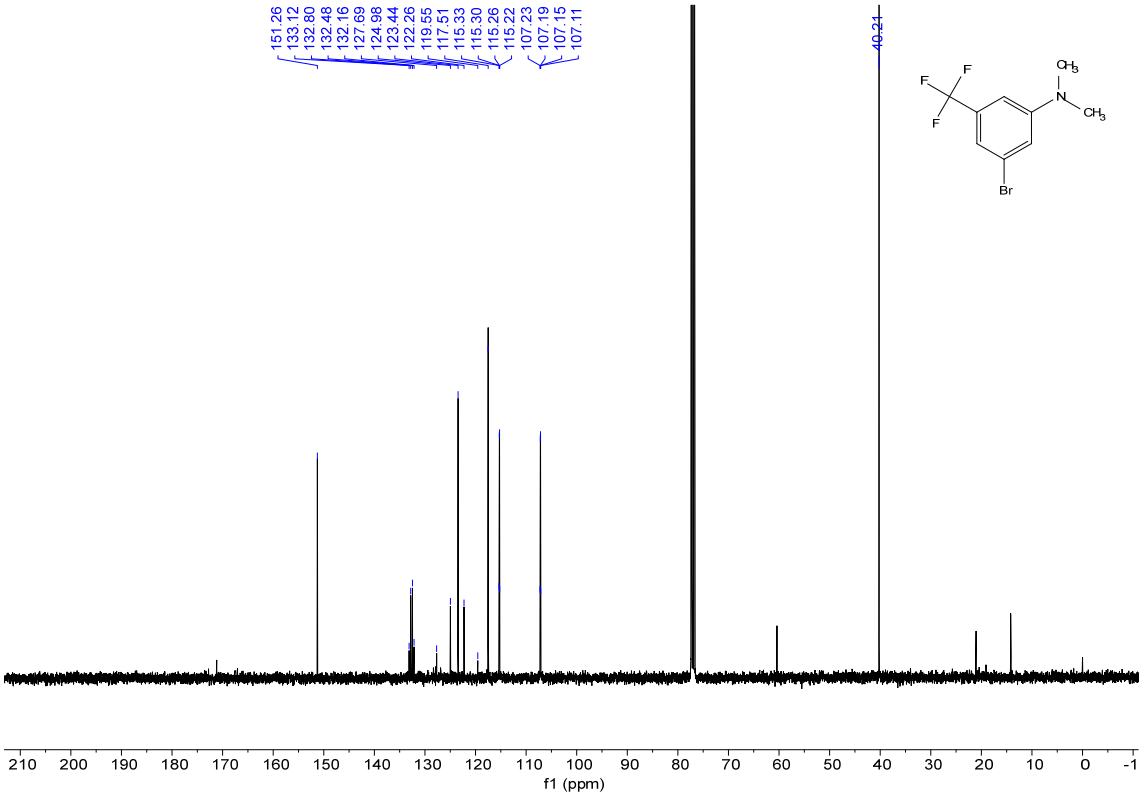
^{19}F NMR spectrum of **1s**

^{1}H NMR (400 MHz, $CDCl_3$)



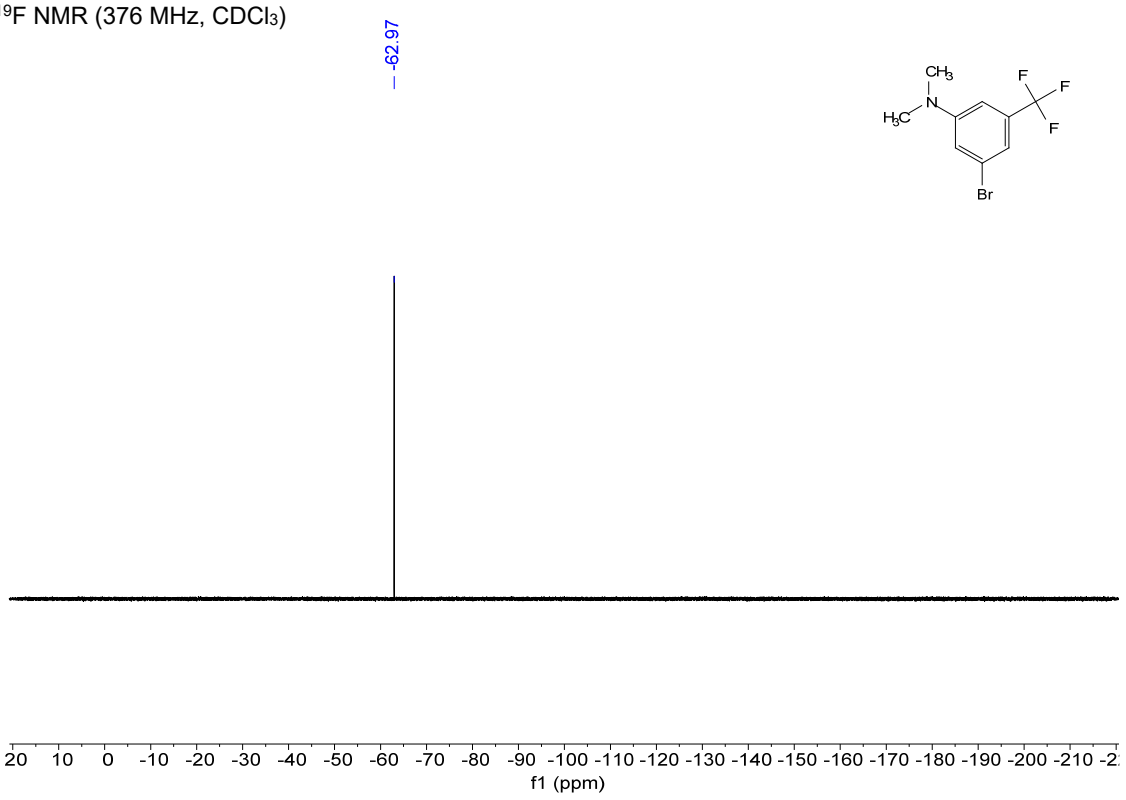
^{1}H NMR spectrum of **1t**

^{13}C NMR (101 MHz, $CDCl_3$)



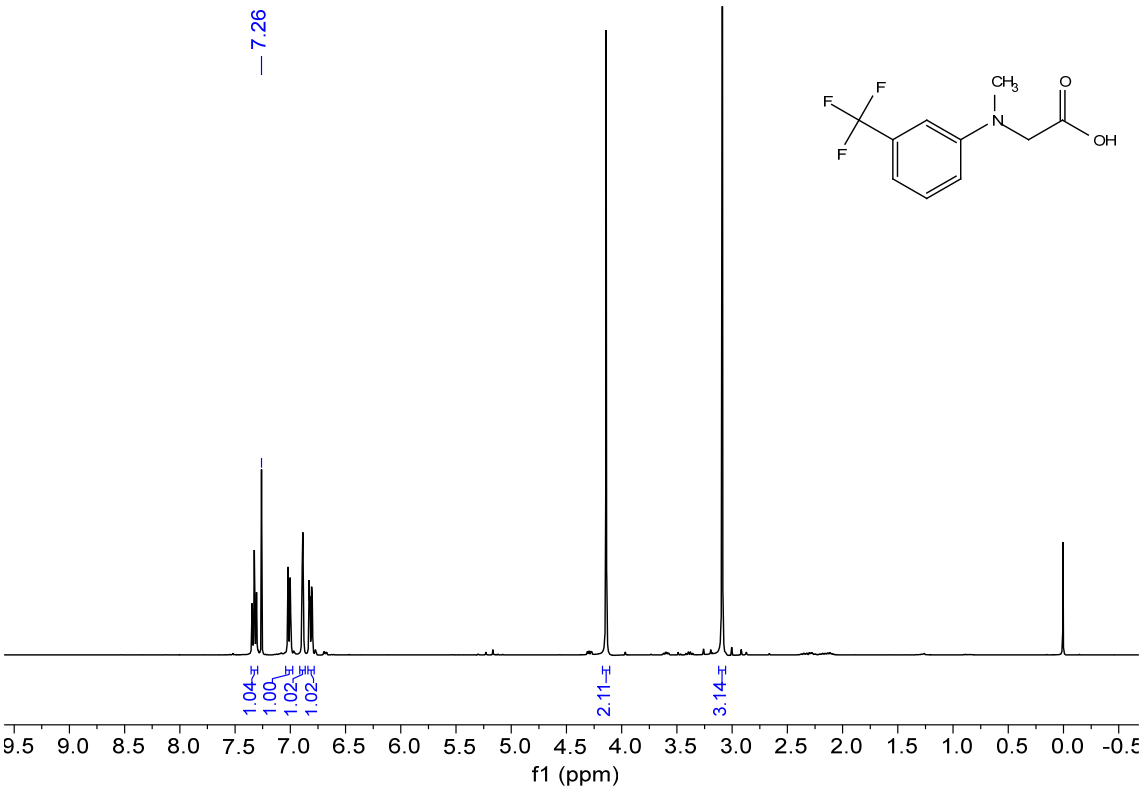
^{13}C NMR spectrum of **1t**

^{19}F NMR (376 MHz, $CDCl_3$)



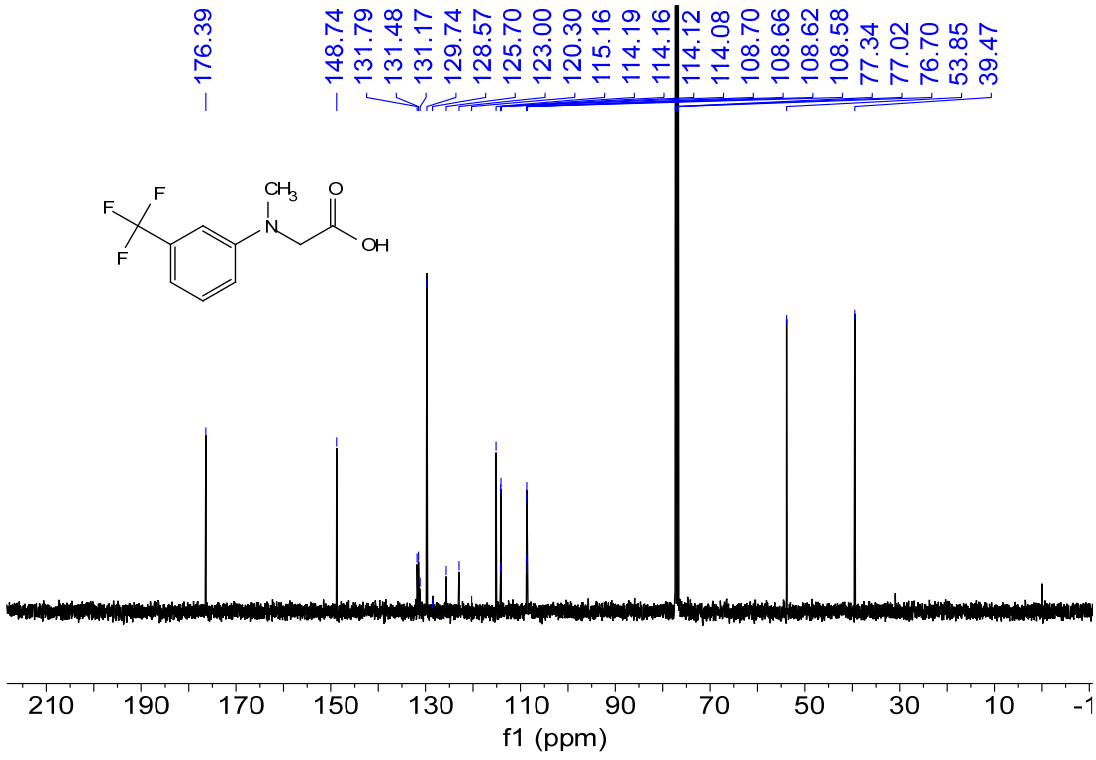
^{19}F NMR spectrum of **1t**

^{1}H NMR (400 MHz, $CDCl_3$)

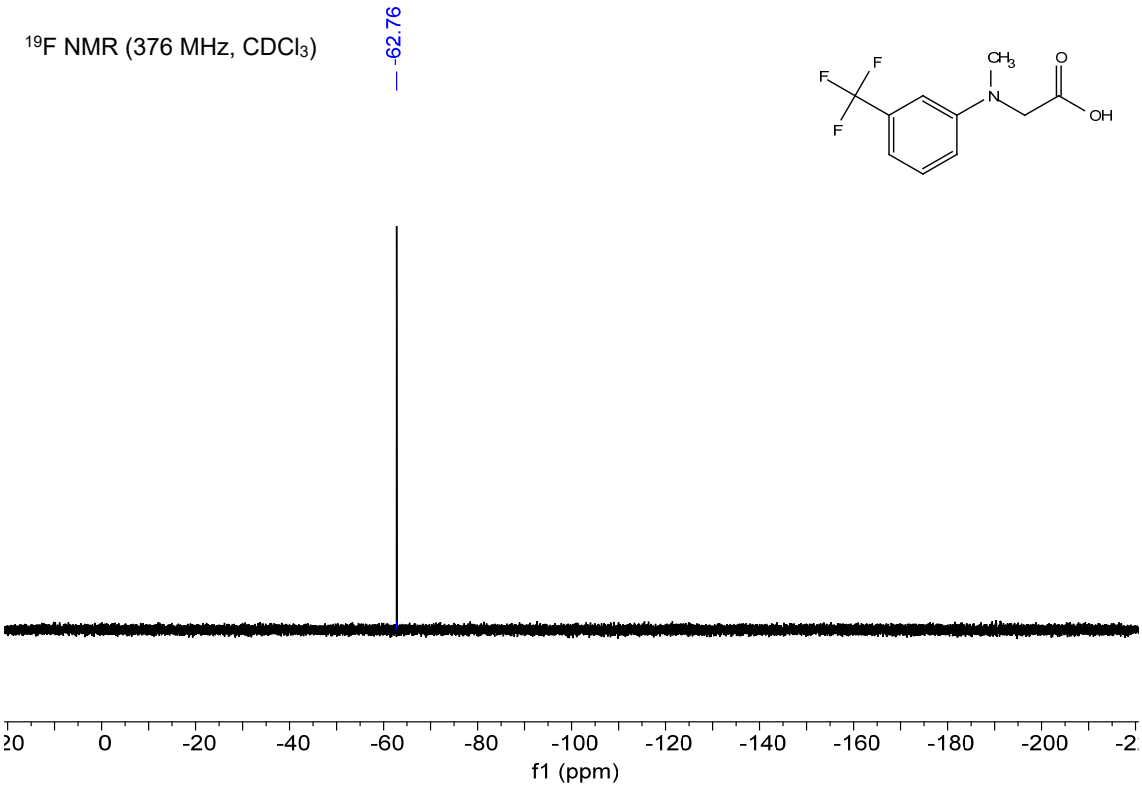


^{1}H NMR spectrum of **1u**

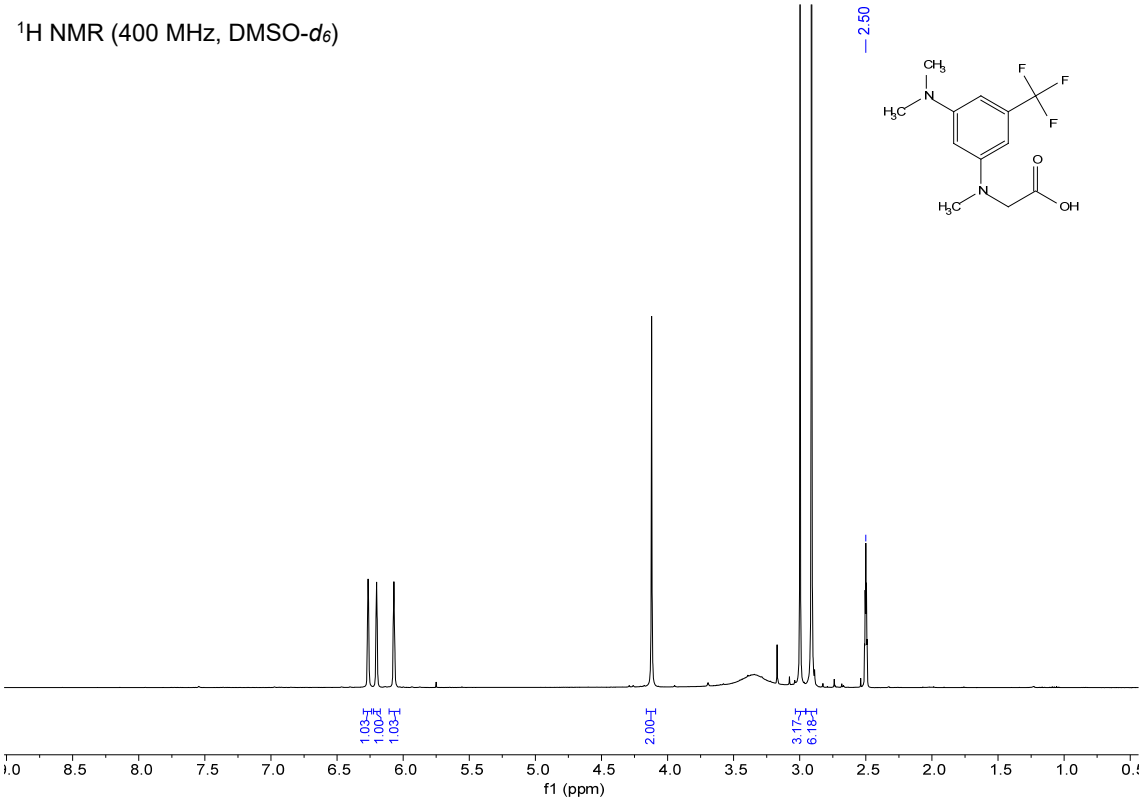
^{13}C NMR (101 MHz, $CDCl_3$)



^{13}C NMR spectrum of **1u**

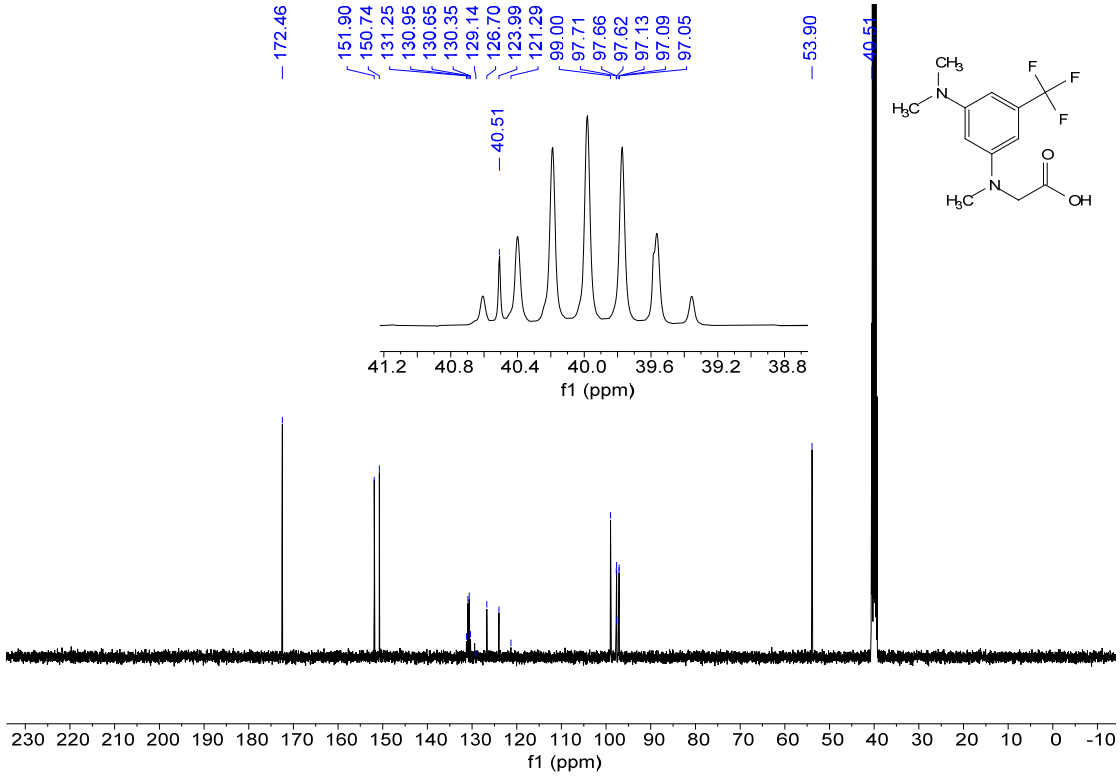


^{19}F NMR spectrum of **1u**



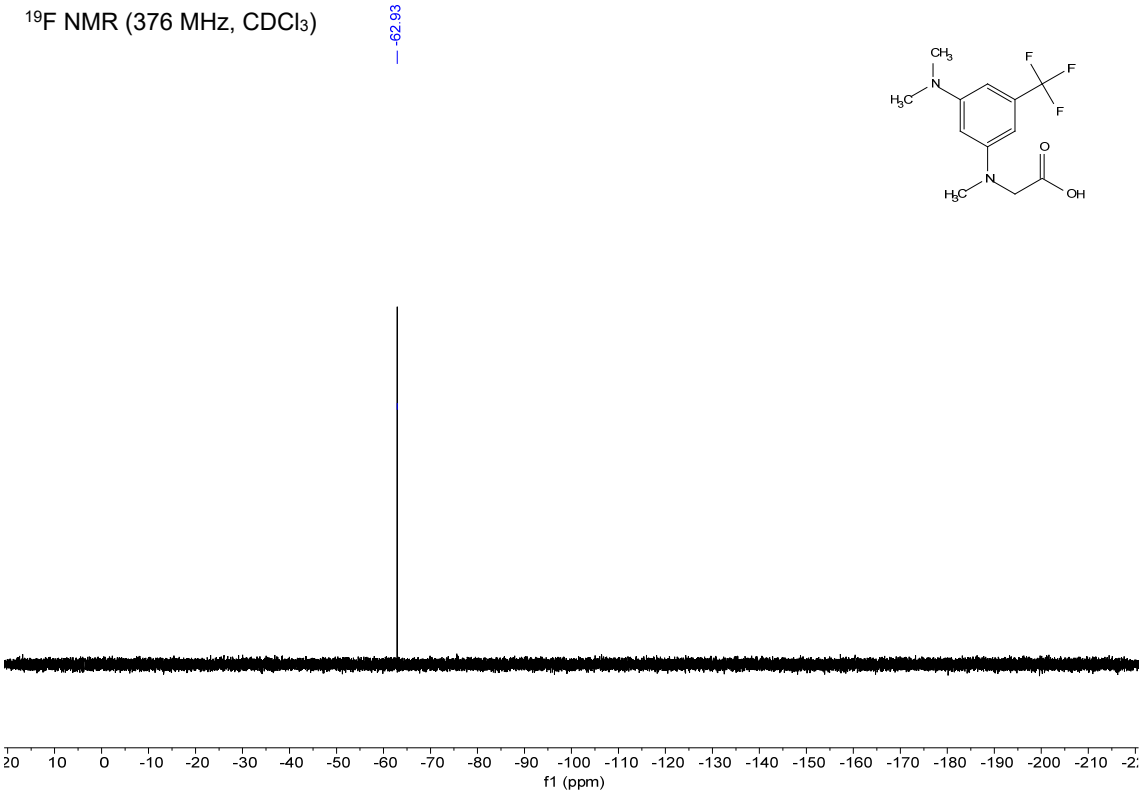
^{1}H NMR spectrum of **1v**

^{13}C NMR (101 MHz, DMSO-d_6)



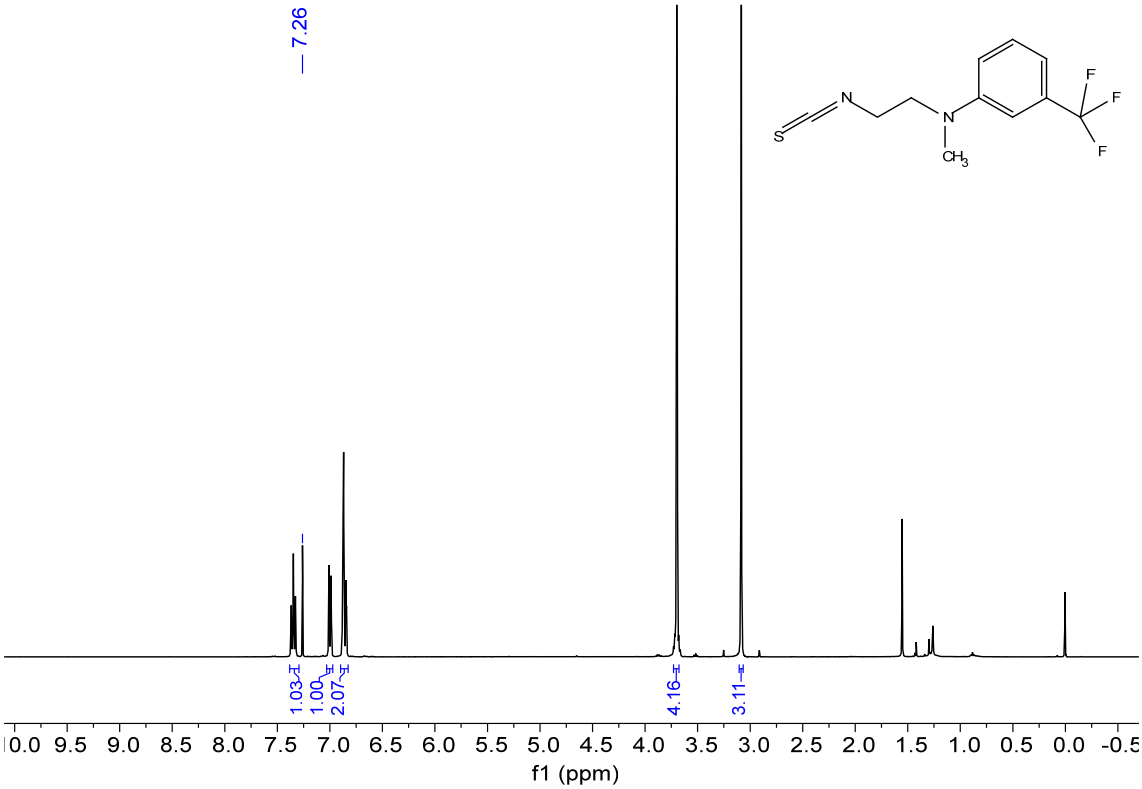
^{13}C NMR spectrum of **1v**

^{19}F NMR (376 MHz, $CDCl_3$)



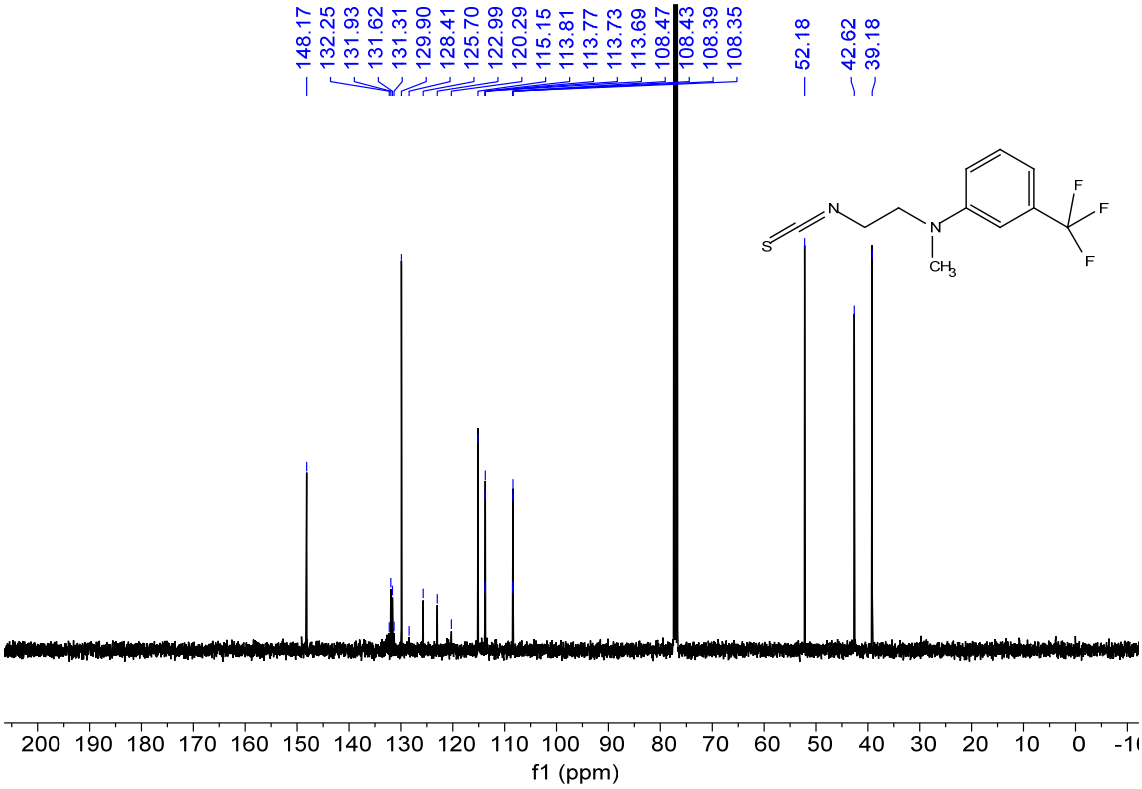
^{19}F NMR spectrum of **1v**

^{1}H NMR (400 MHz, $CDCl_3$)



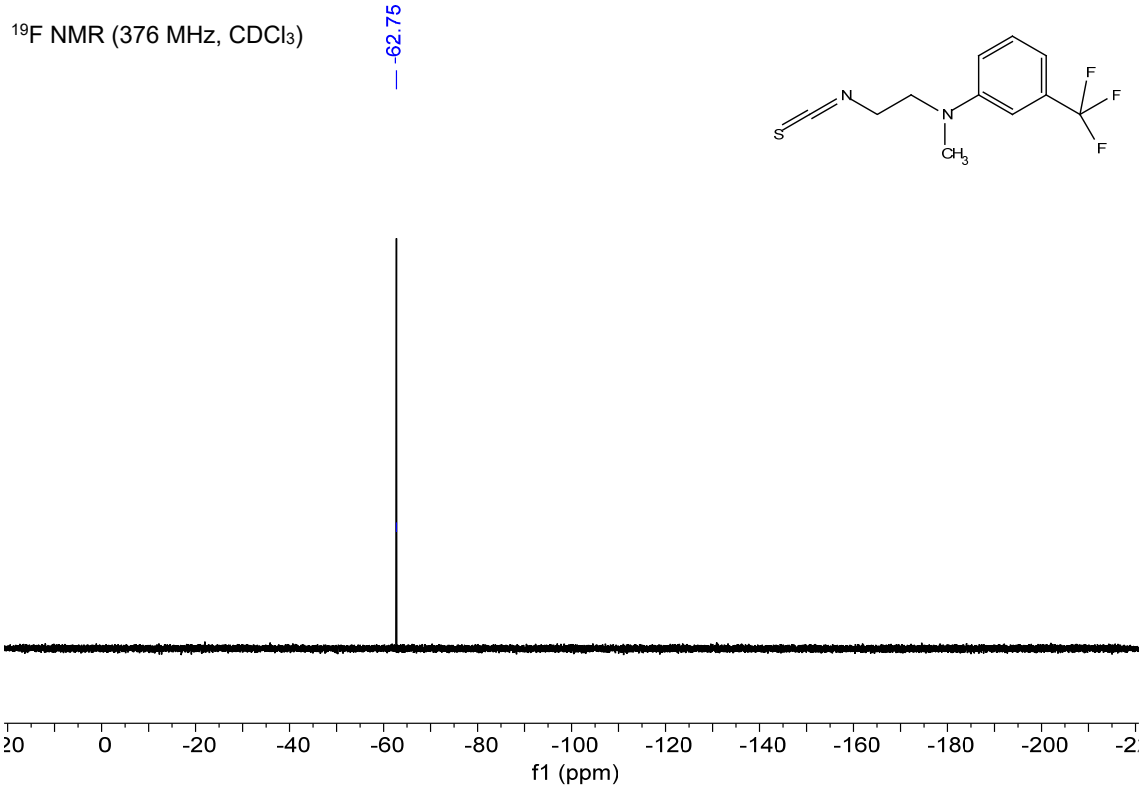
^{1}H NMR spectrum of **1w**

^{13}C NMR (101 MHz, $CDCl_3$)



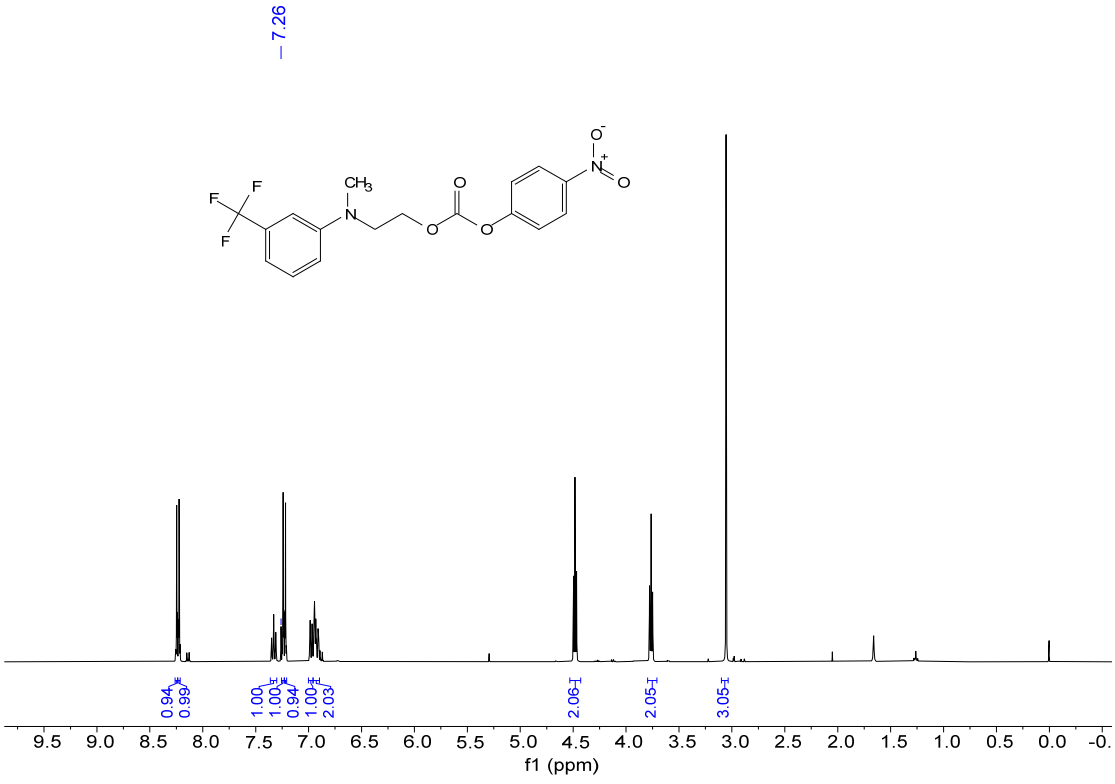
^{13}C NMR spectrum of **1w**

^{19}F NMR (376 MHz, $CDCl_3$)



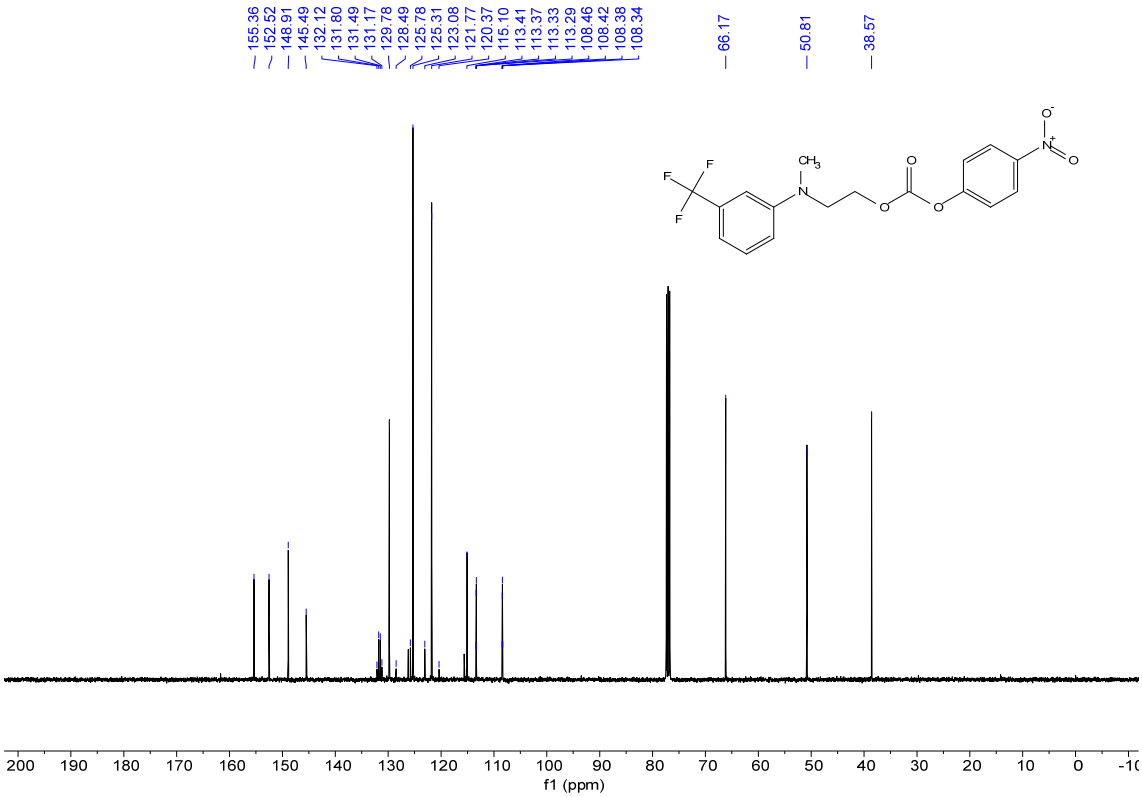
^{19}F NMR spectrum of **1w**

^{1}H NMR (400 MHz, $CDCl_3$)



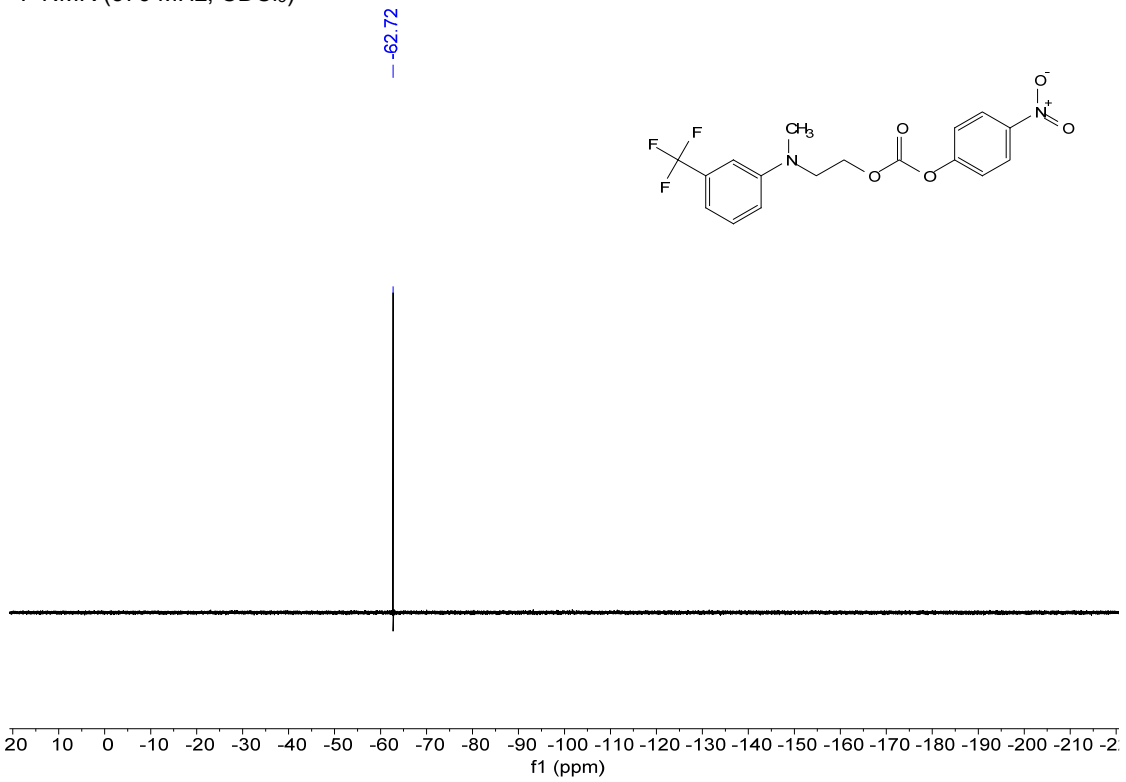
^{1}H NMR spectrum of **1y**

^{13}C NMR (101 MHz, $CDCl_3$)



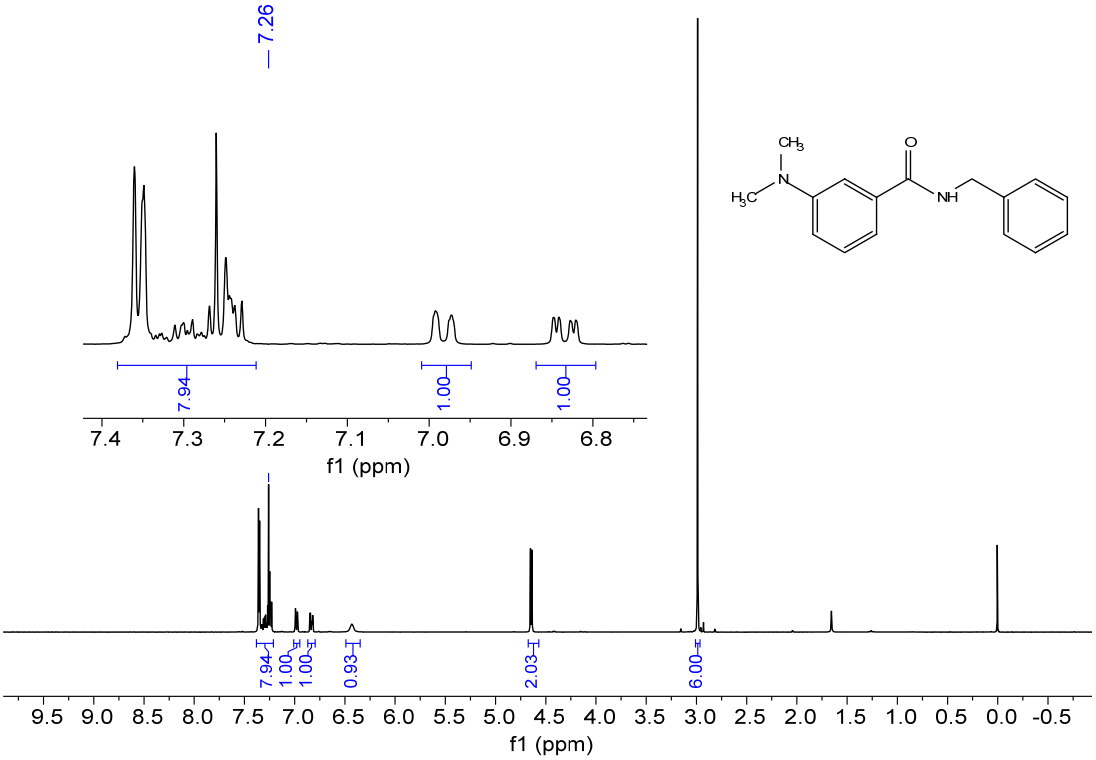
^{13}C NMR spectrum of **1y**

^{19}F NMR (376 MHz, $CDCl_3$)



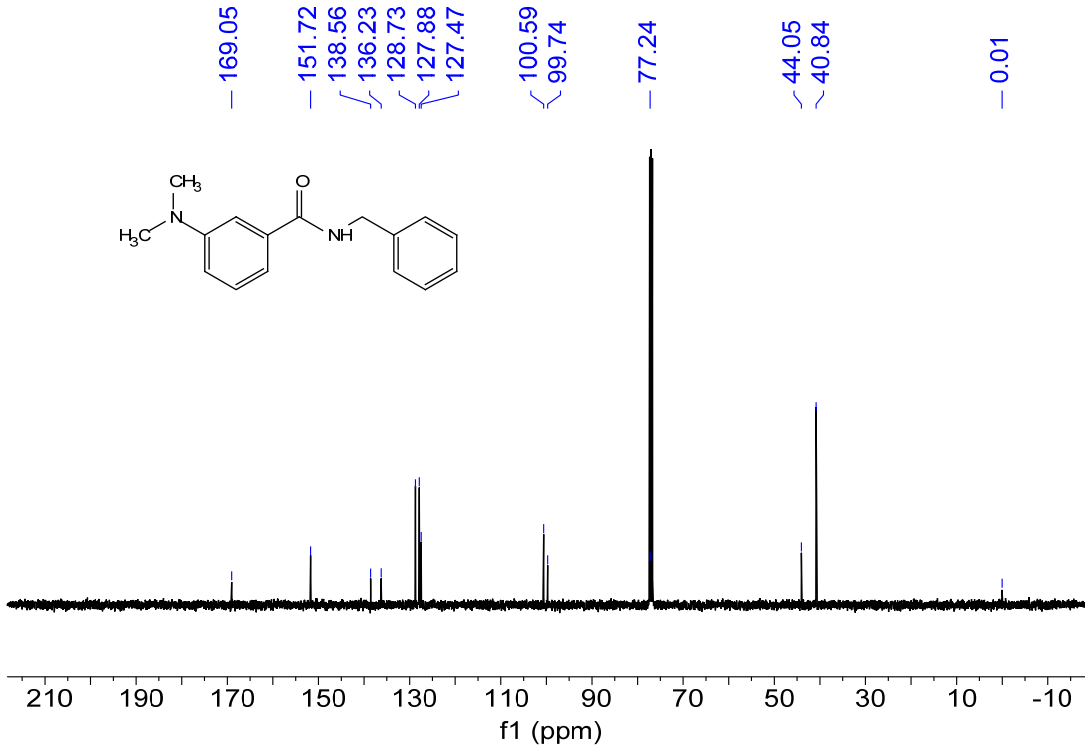
^{19}F NMR spectrum of **1y**

^{1}H NMR (400 MHz, $CDCl_3$)



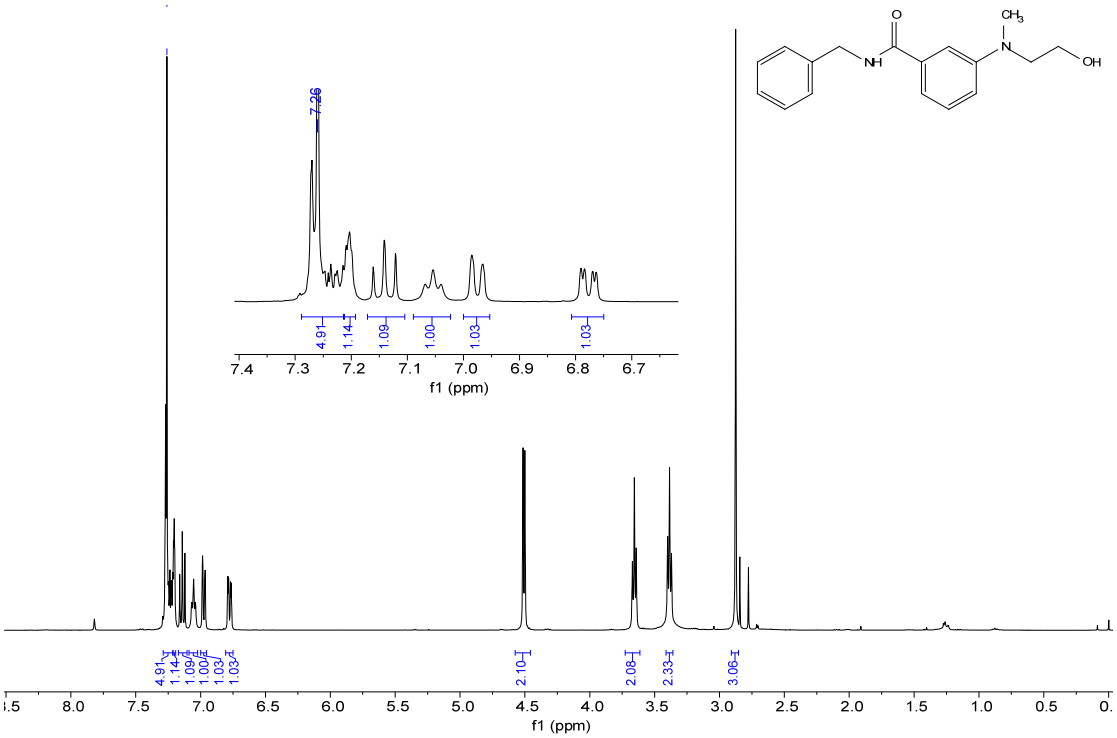
^{1}H NMR spectrum of **3aa**

^{13}C NMR (101 MHz, $CDCl_3$)

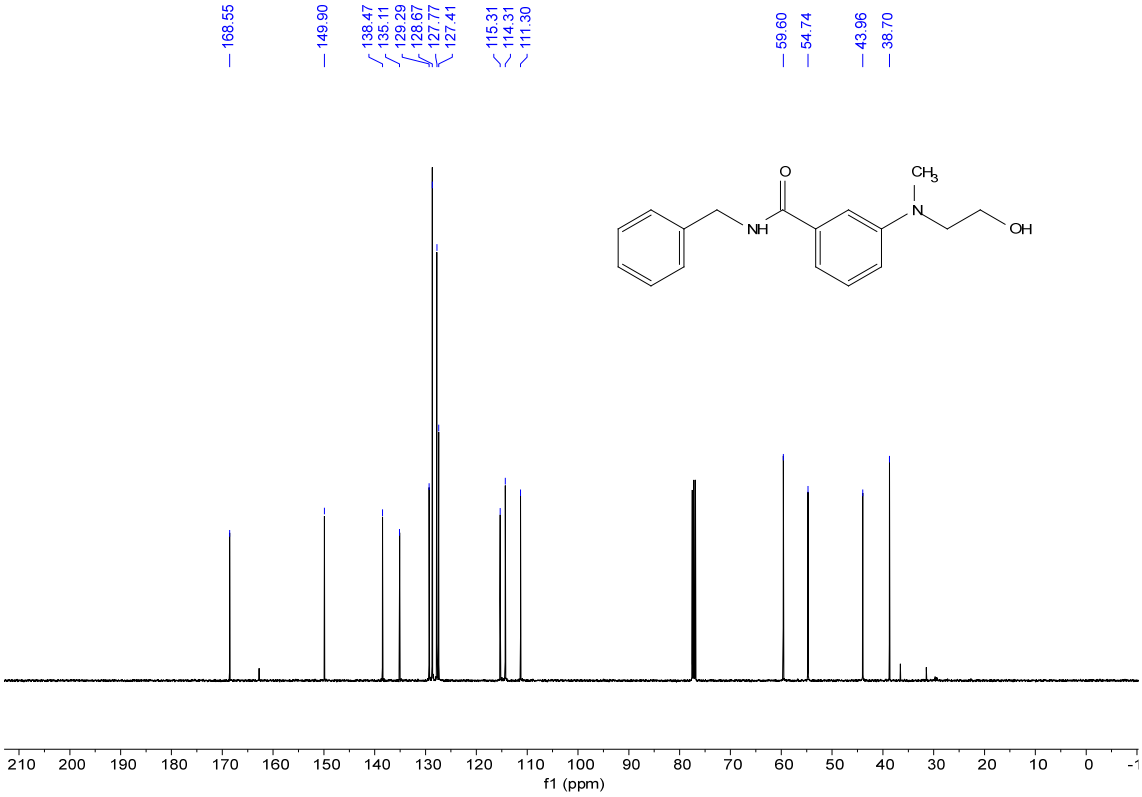


^{13}C NMR spectrum of **3aa**

^{1}H NMR (400 MHz, $CDCl_3$)

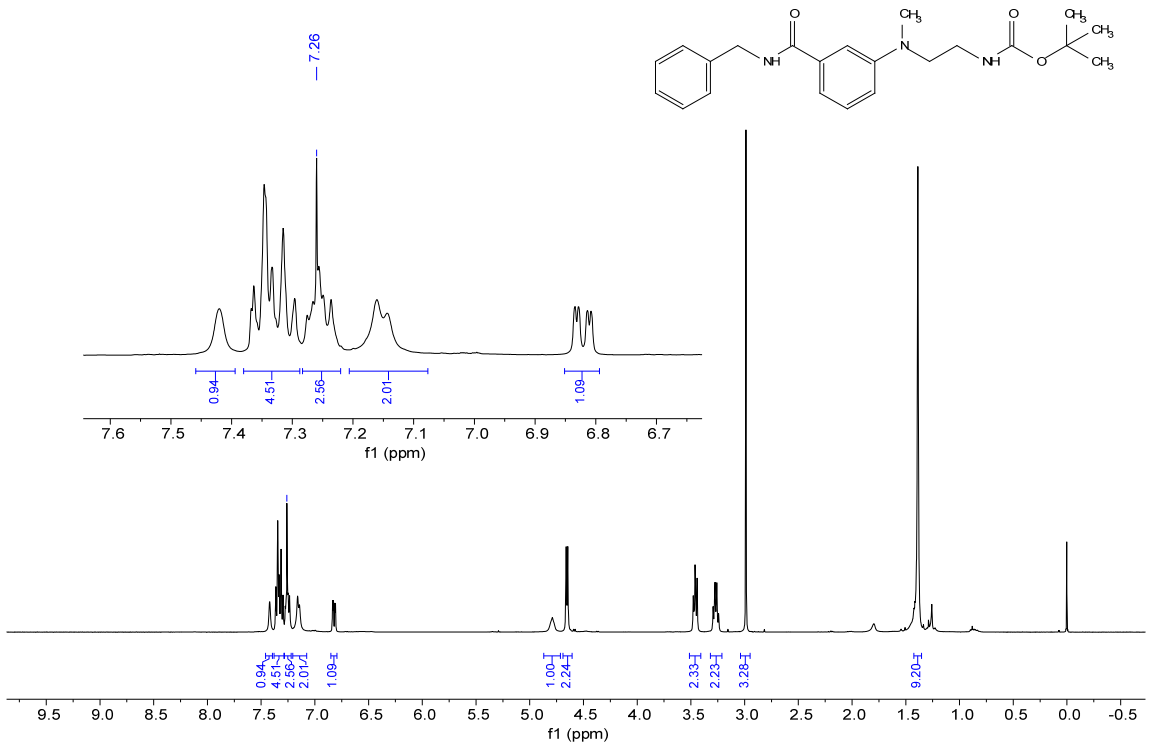


^{13}C NMR (101 MHz, $CDCl_3$)

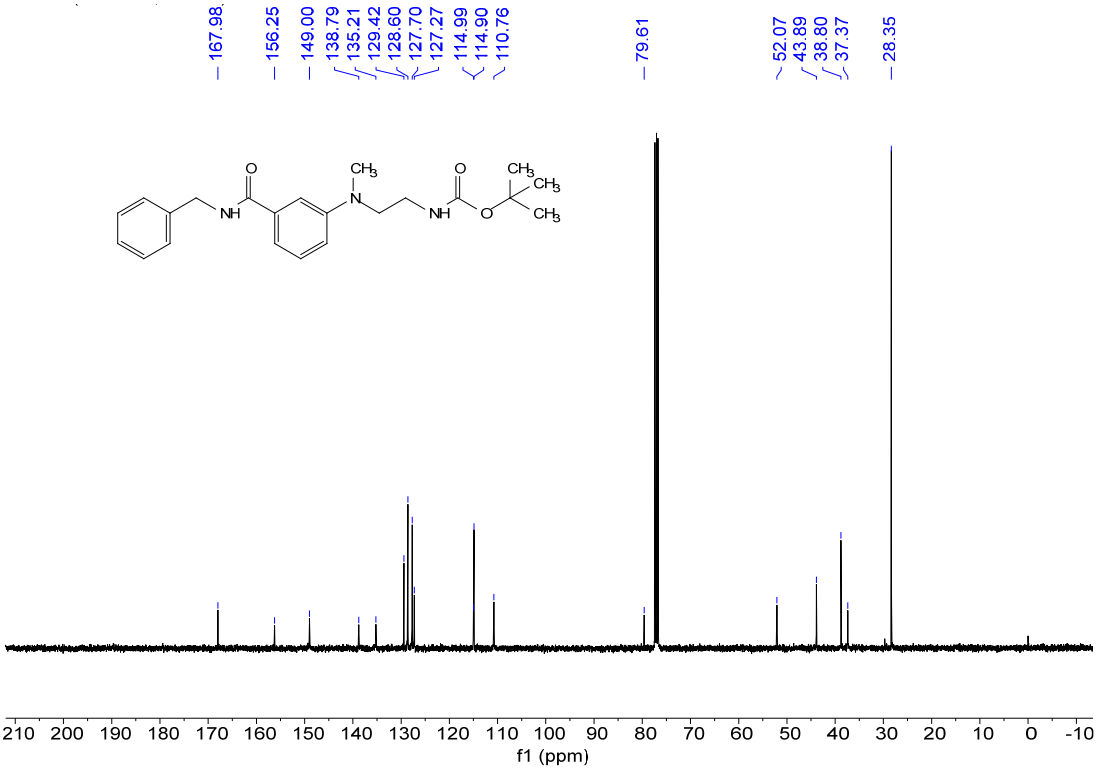


^{1}H NMR and ^{13}C NMR spectrum of **3ba**

^{1}H NMR (400 MHz, $CDCl_3$)

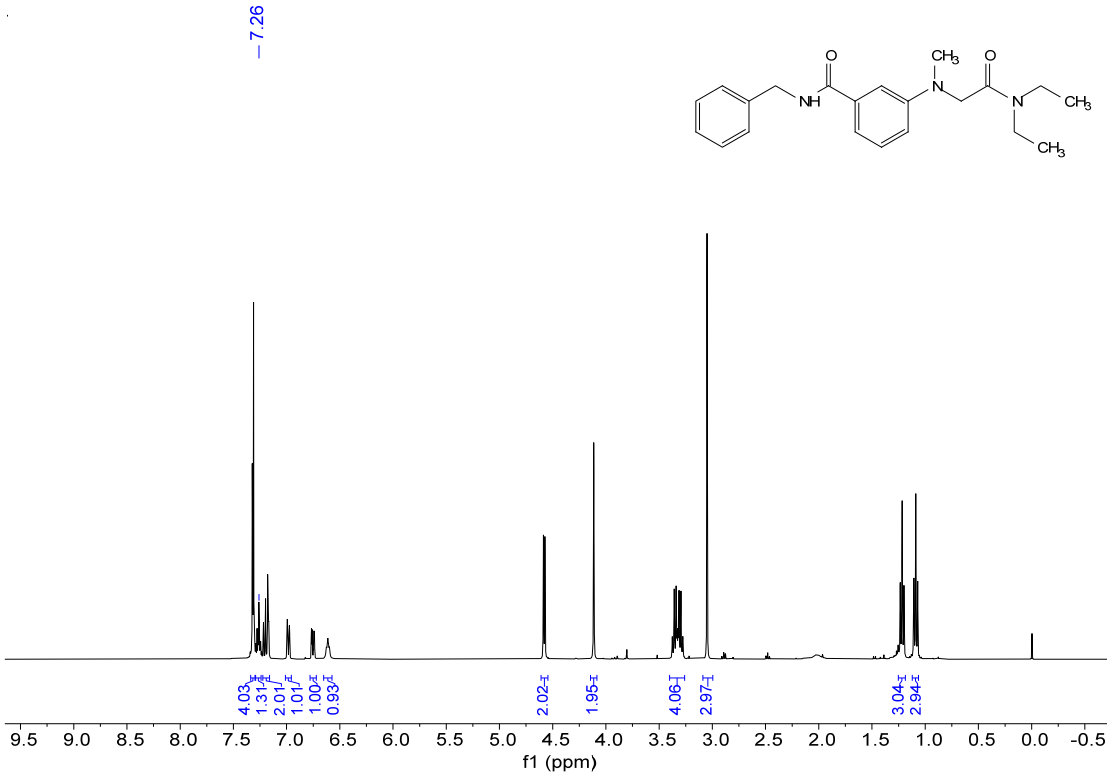


^{13}C NMR (101 MHz, $CDCl_3$)

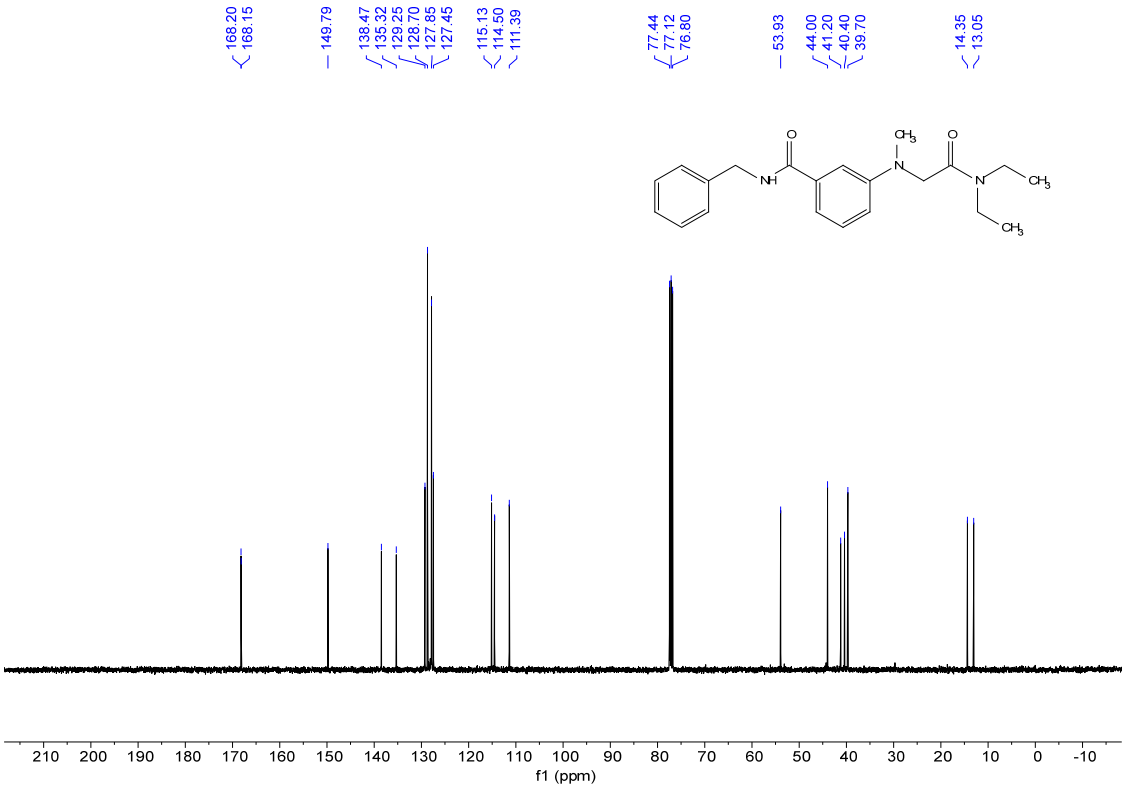


^{1}H NMR and ^{13}C NMR spectrum of **3ca**

^{1}H NMR (400 MHz, $CDCl_3$)

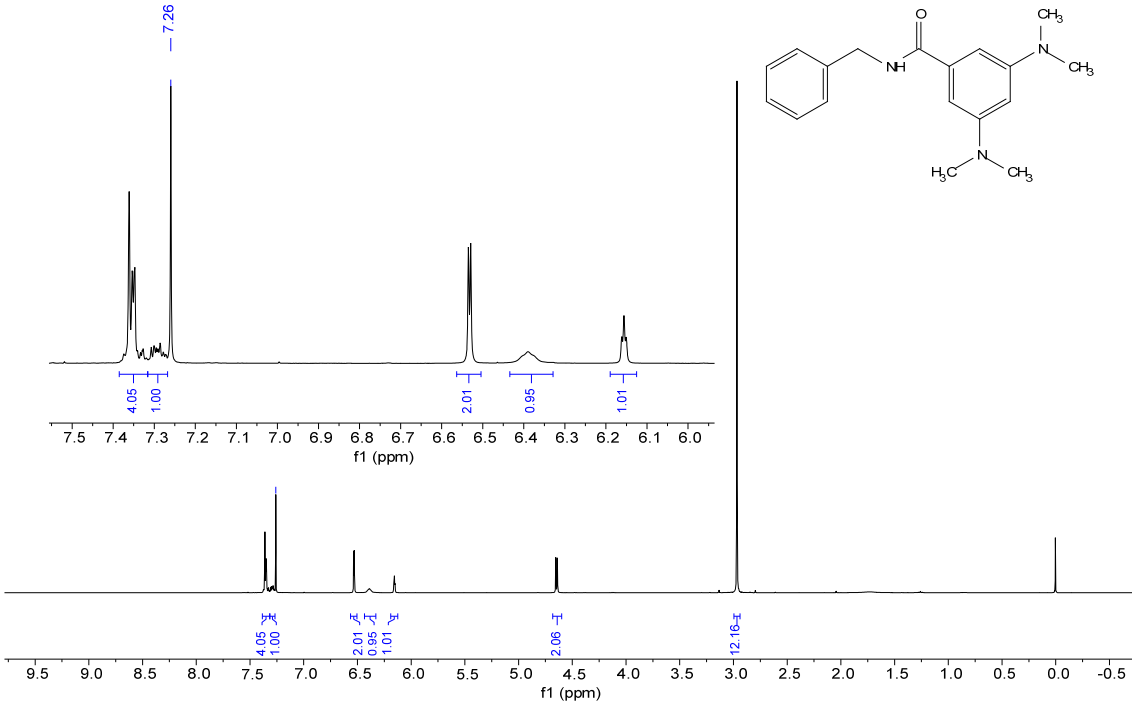


^{13}C NMR (101 MHz, $CDCl_3$)

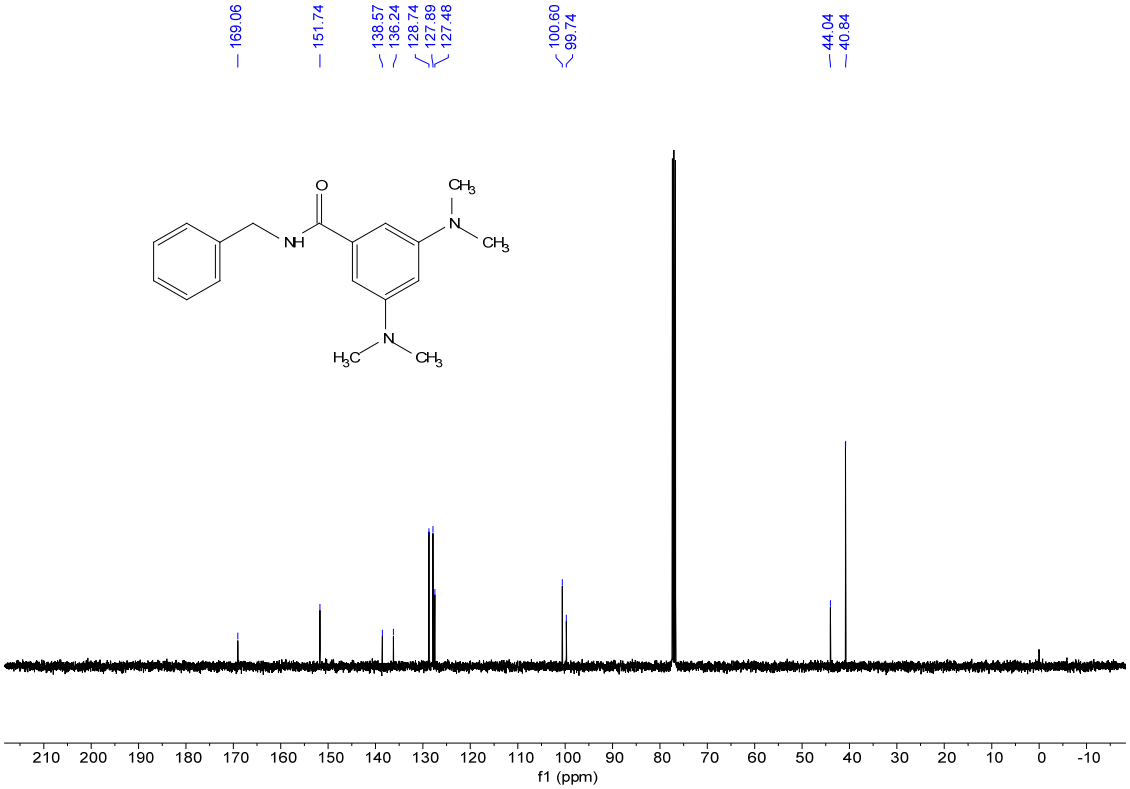


^{1}H NMR and ^{13}C NMR spectrum of **3da**

^{1}H NMR (400 MHz, $CDCl_3$)

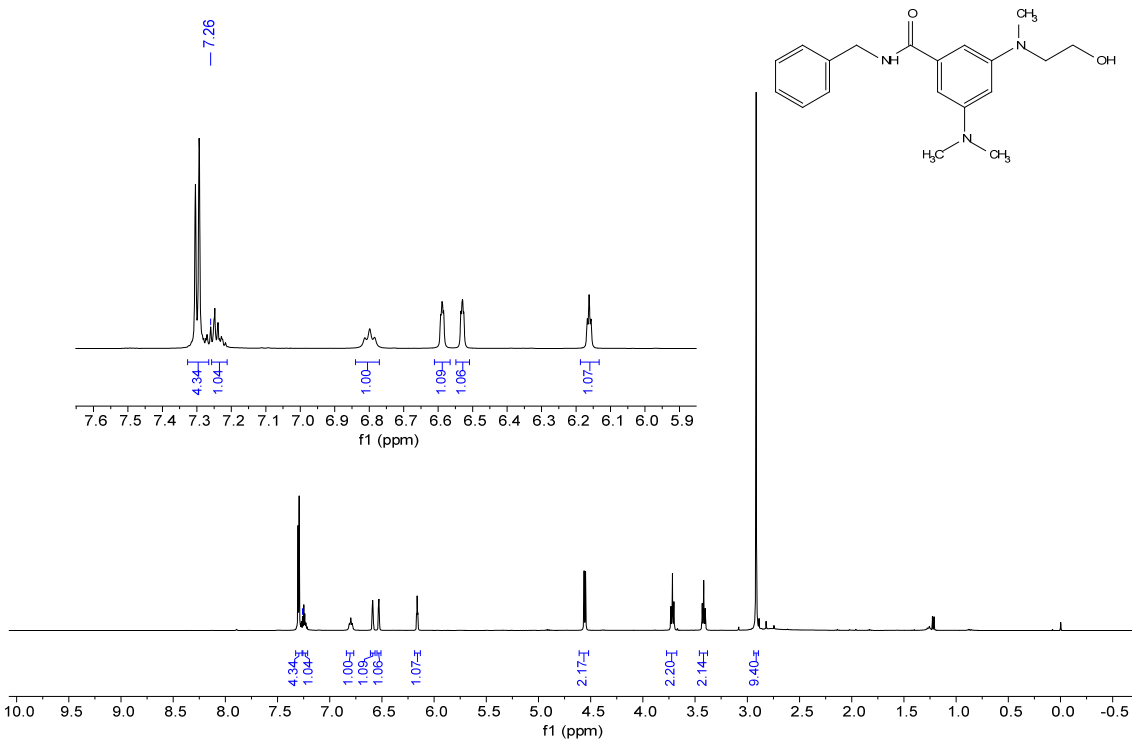


^{13}C NMR (101 MHz, $CDCl_3$)

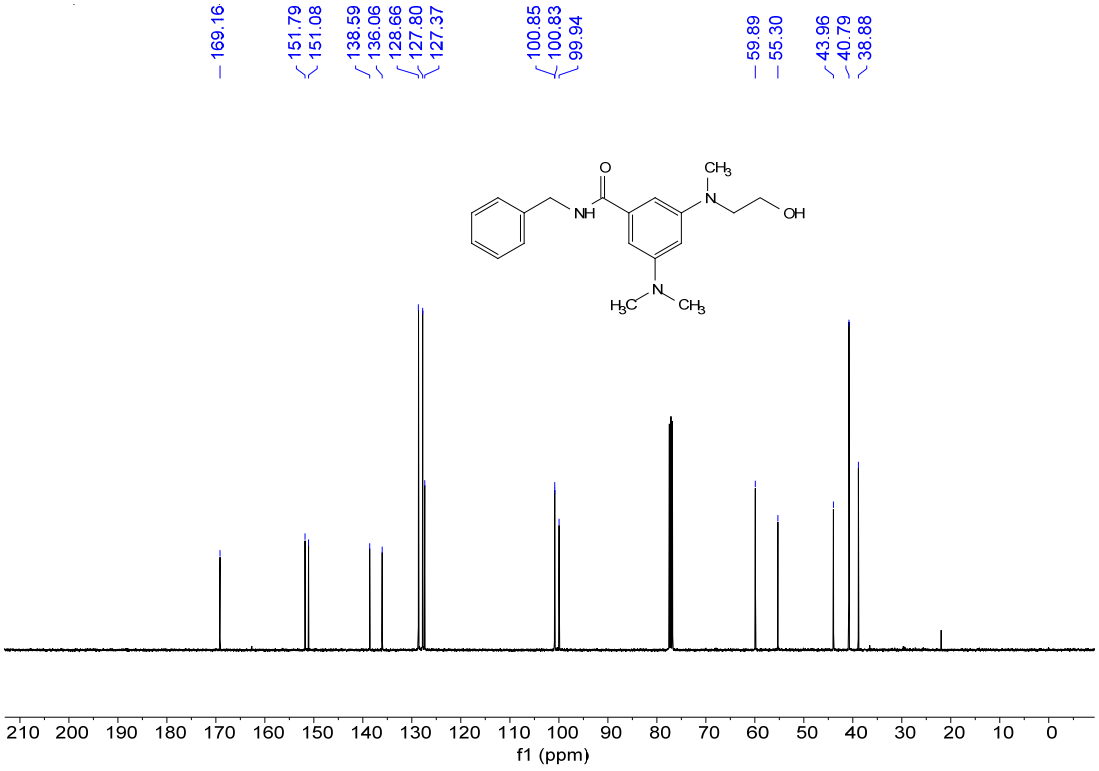


^{1}H NMR and ^{13}C NMR spectrum of **3ea**

^{1}H NMR (400 MHz, $CDCl_3$)

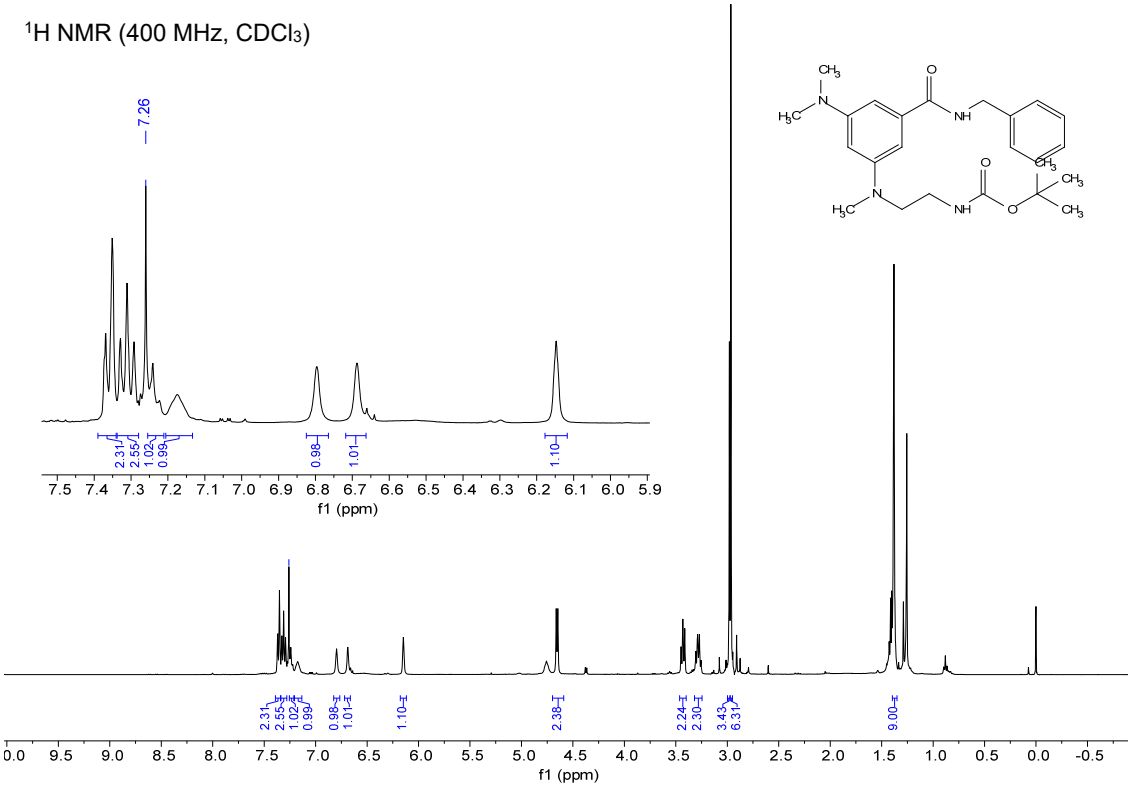


^{13}C NMR (101 MHz, $CDCl_3$)

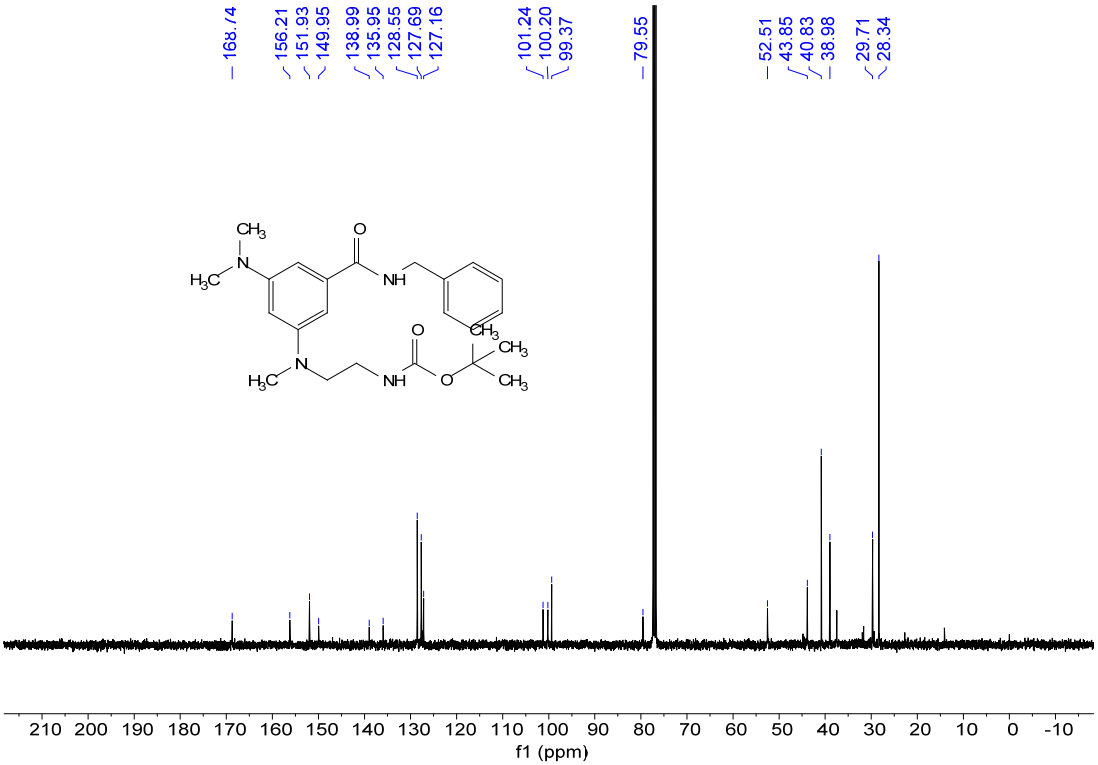


^{1}H NMR and ^{13}C NMR spectrum of **3fa**

^{1}H NMR (400 MHz, $CDCl_3$)

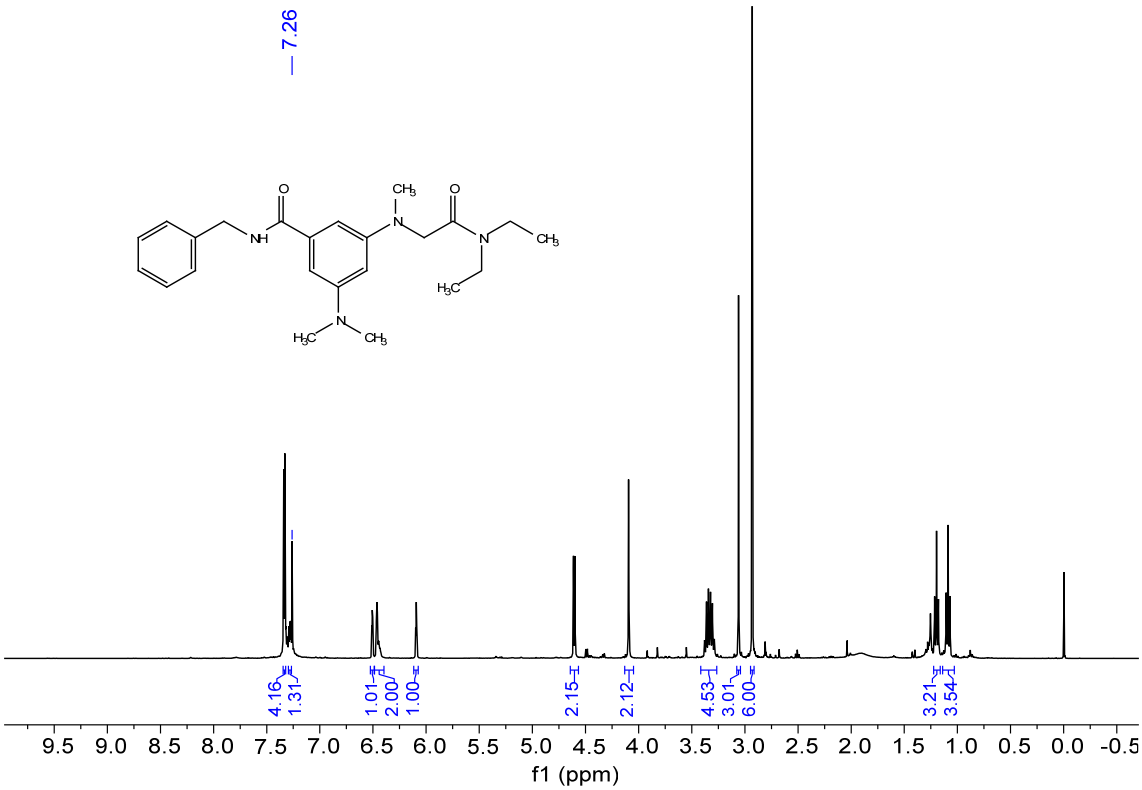


^{13}C NMR (101 MHz, $CDCl_3$)

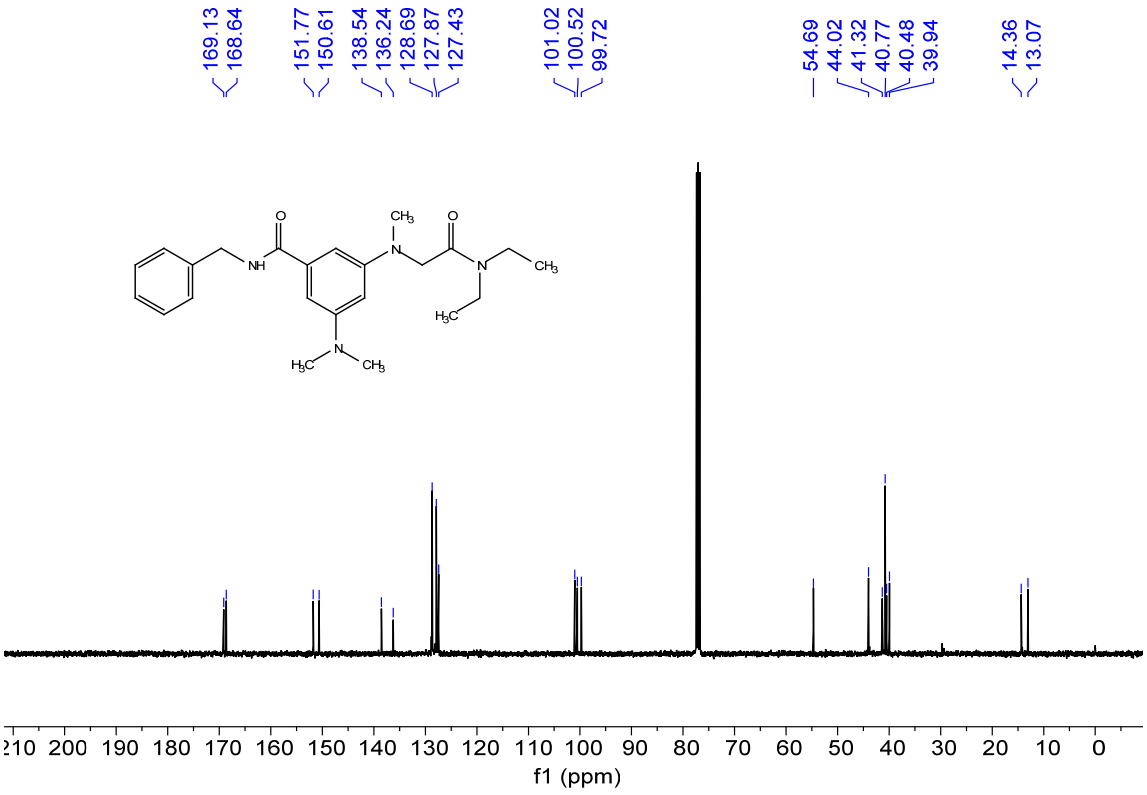


^{1}H NMR and ^{13}C NMR spectrum of **3ga**

^{1}H NMR (400 MHz, $CDCl_3$)

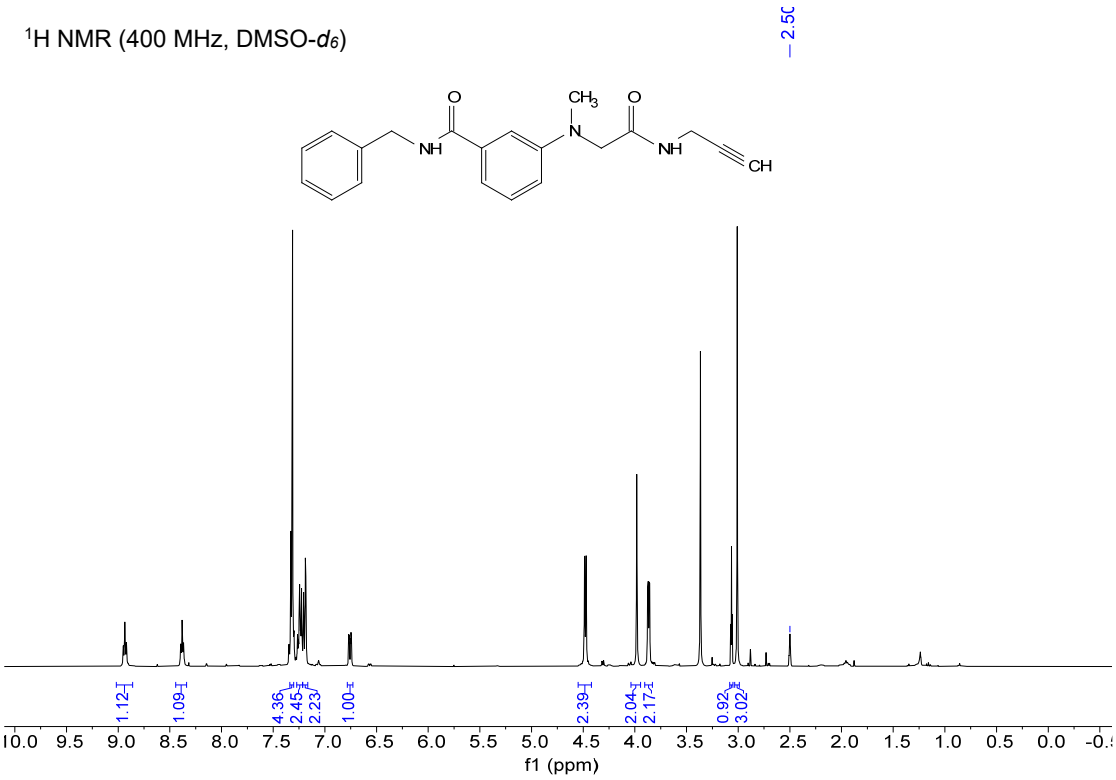


^{13}C NMR (101 MHz, $CDCl_3$)

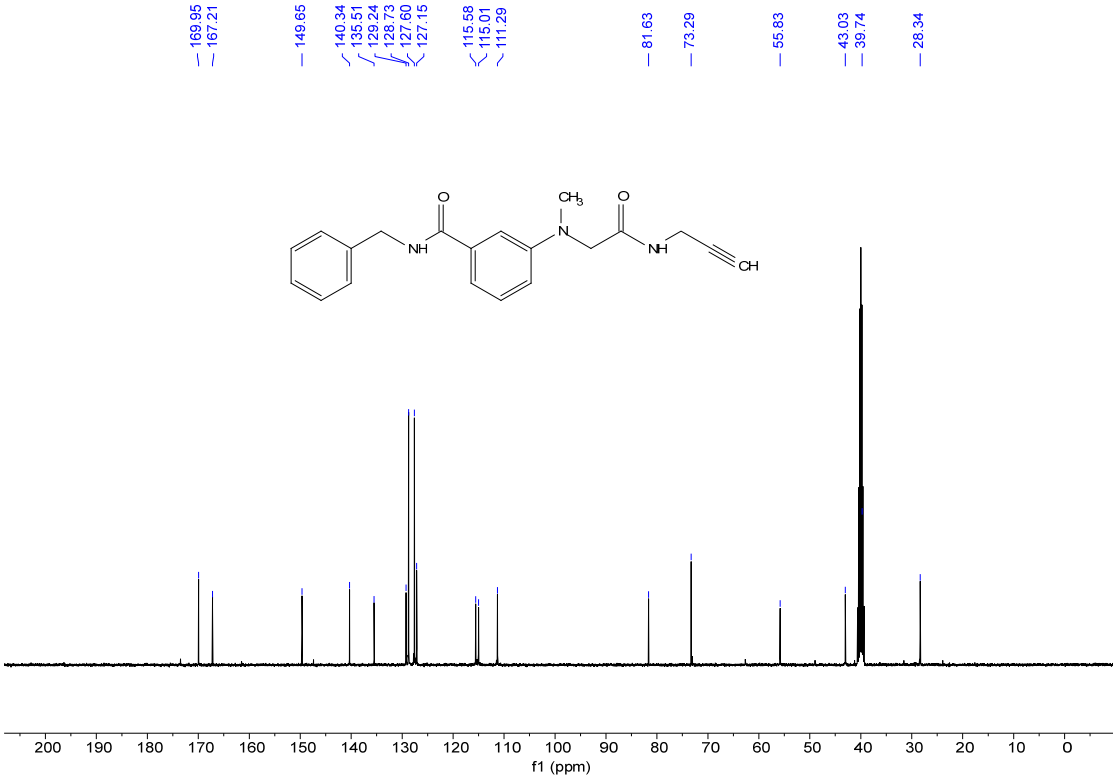


^{1}H NMR and ^{13}C NMR spectrum of **3ha**

^{1}H NMR (400 MHz, DMSO-d_6)

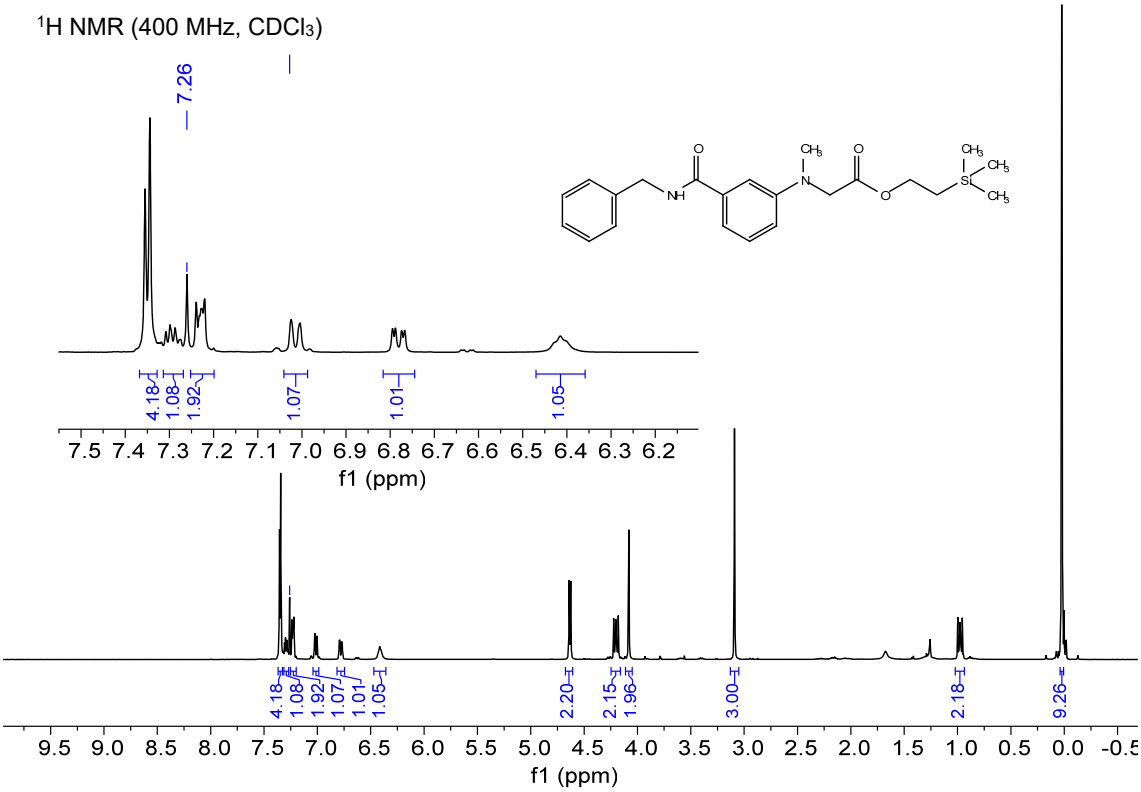


^{13}C NMR (101 MHz, DMSO-d_6)

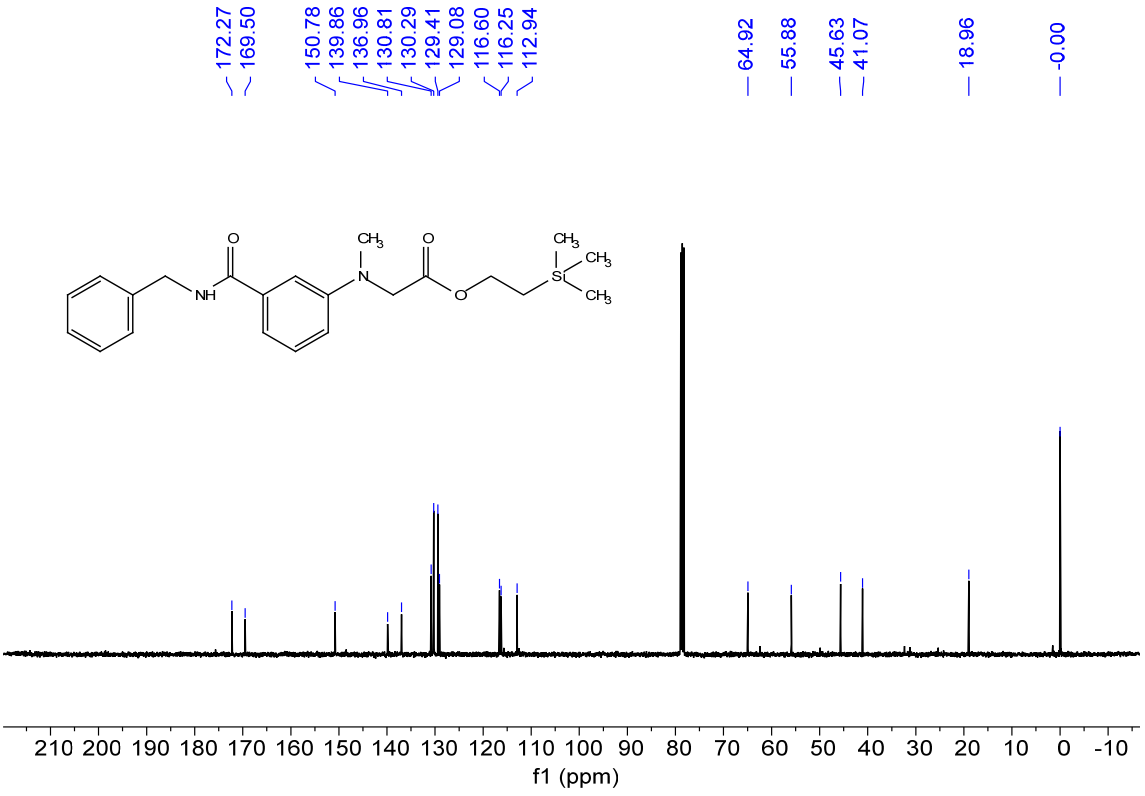


^{1}H NMR and ^{13}C NMR spectrum of **3ja**

^{1}H NMR (400 MHz, $CDCl_3$)

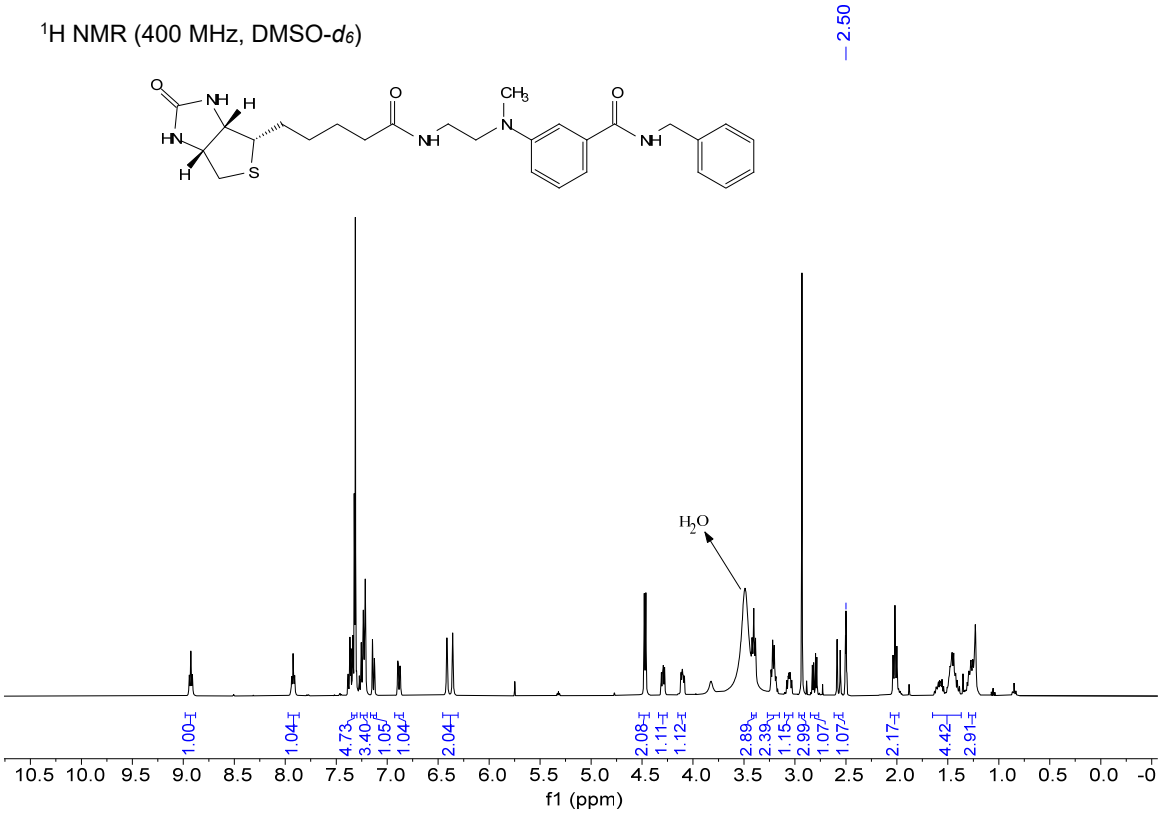


^{13}C NMR (101 MHz, $CDCl_3$)

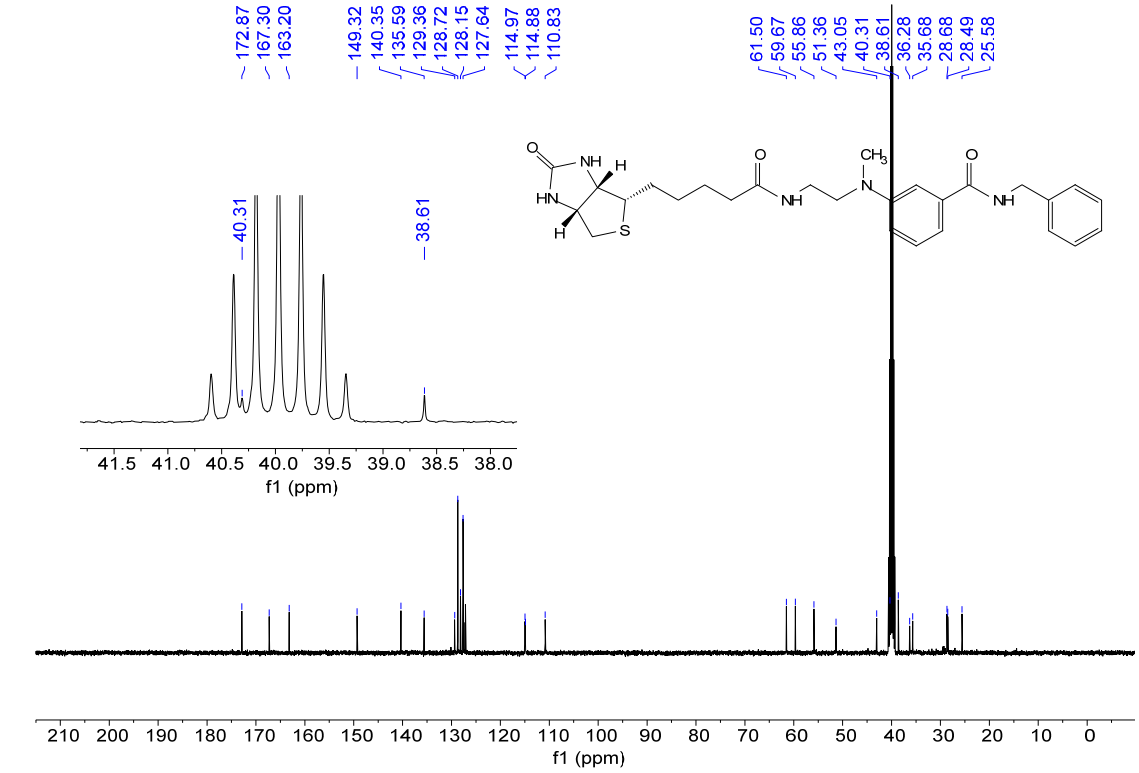


^{1}H NMR and ^{13}C NMR spectrum of **3ka**

^{1}H NMR (400 MHz, DMSO-d_6)

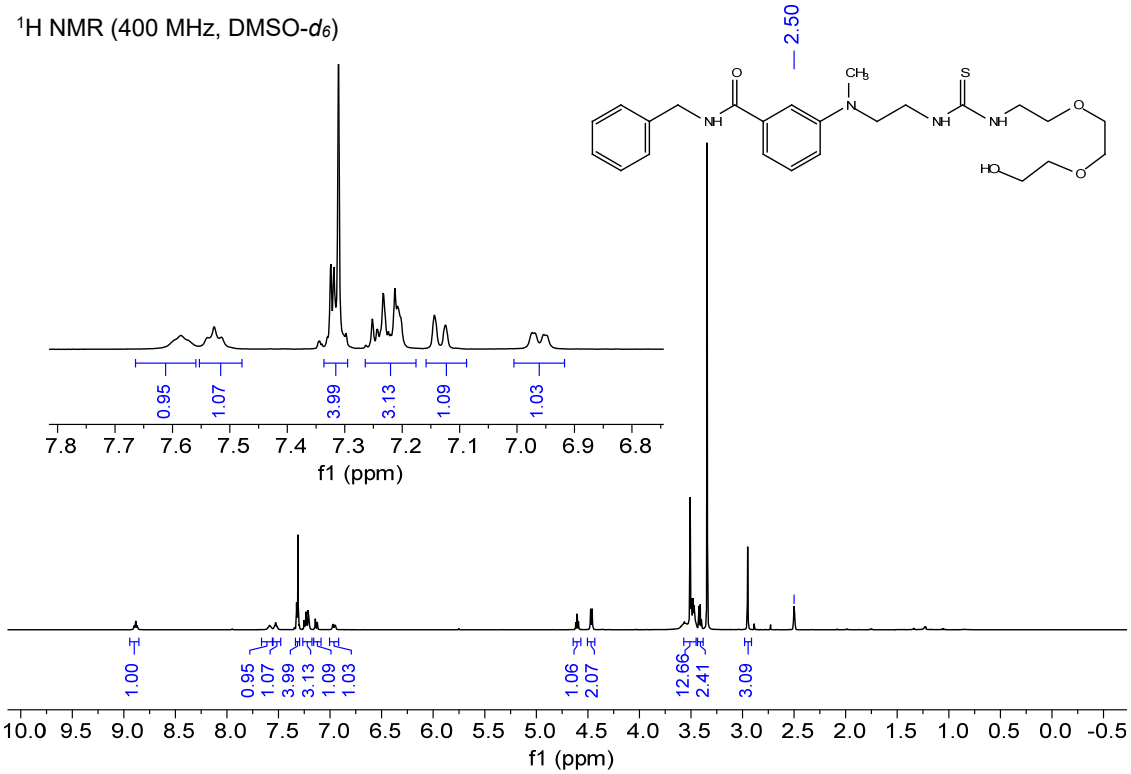


^{13}C NMR (101 MHz, DMSO-d_6)

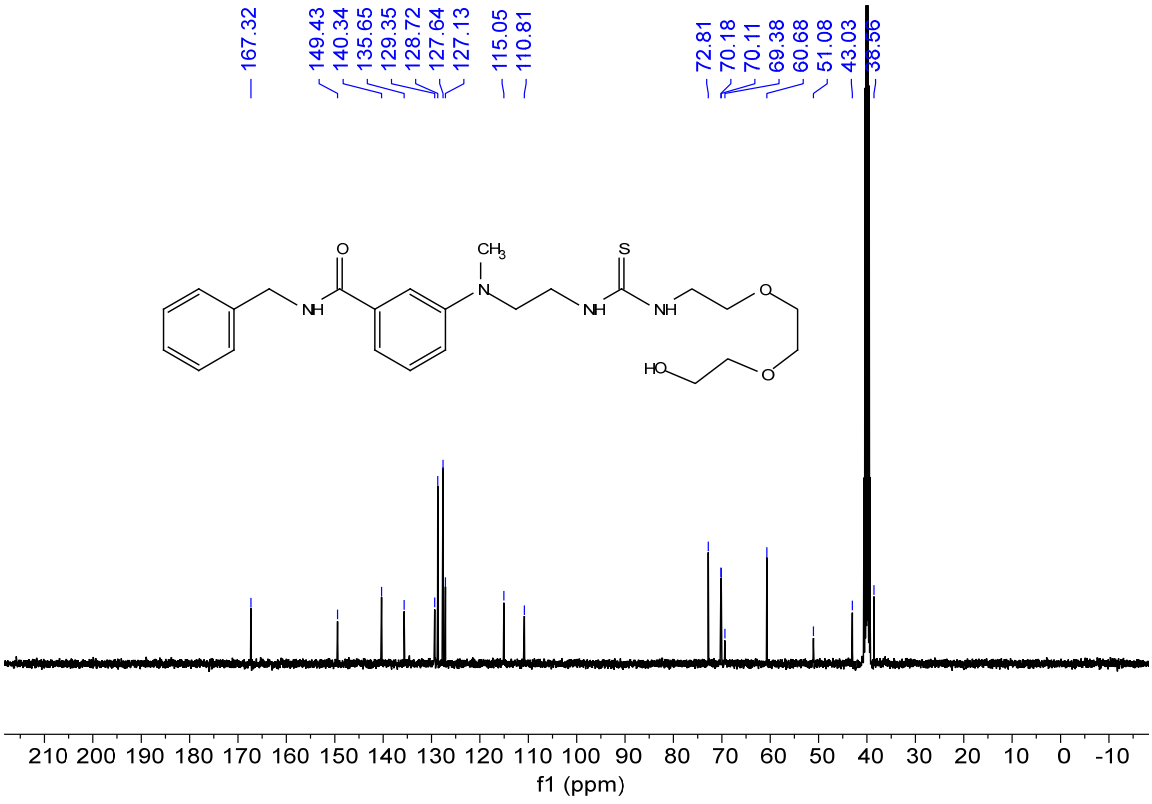


H NMR and ^{13}C NMR spectrum of **3la**

^{1}H NMR (400 MHz, DMSO-d_6)

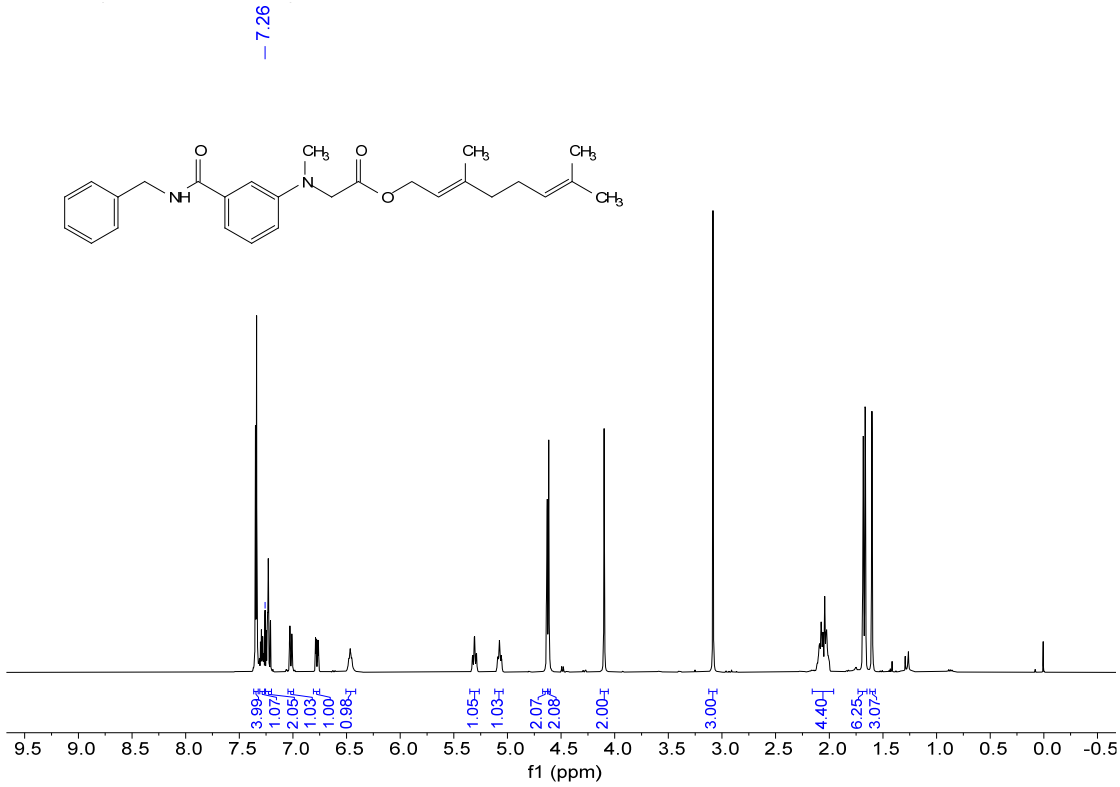


^{13}C NMR (101 MHz, DMSO-d_6)

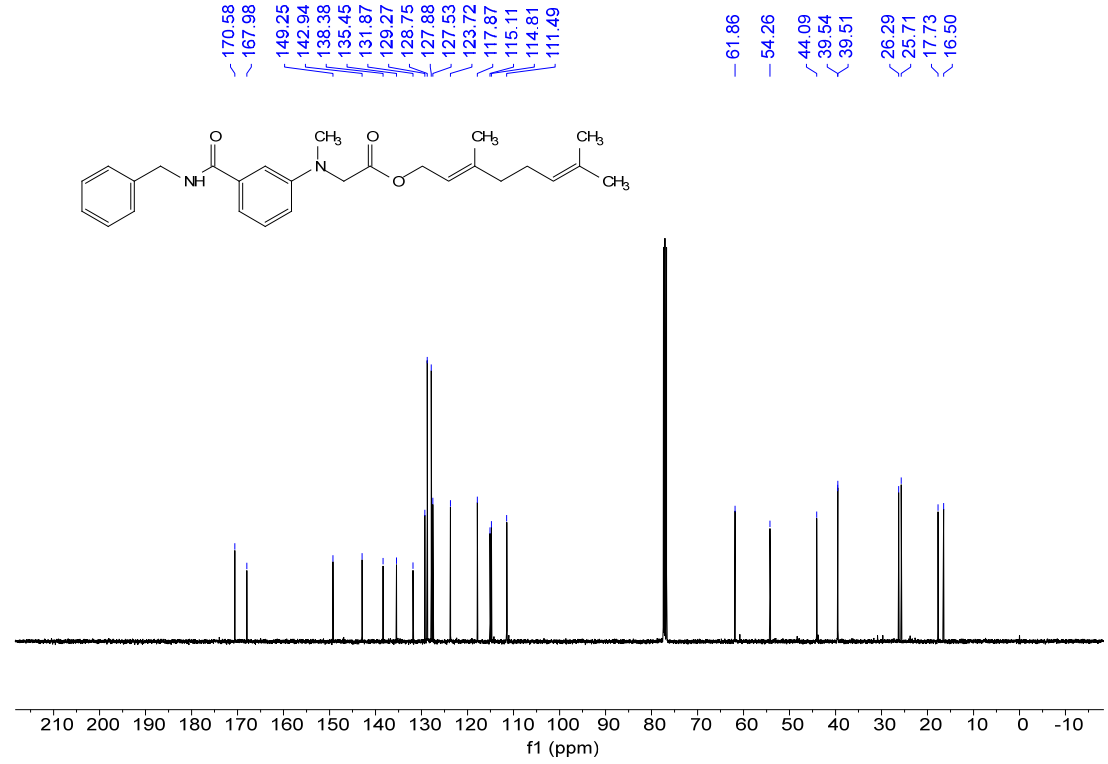


^{1}H NMR and ^{13}C NMR spectrum of **3ma**

^{1}H NMR (400 MHz, $CDCl_3$)

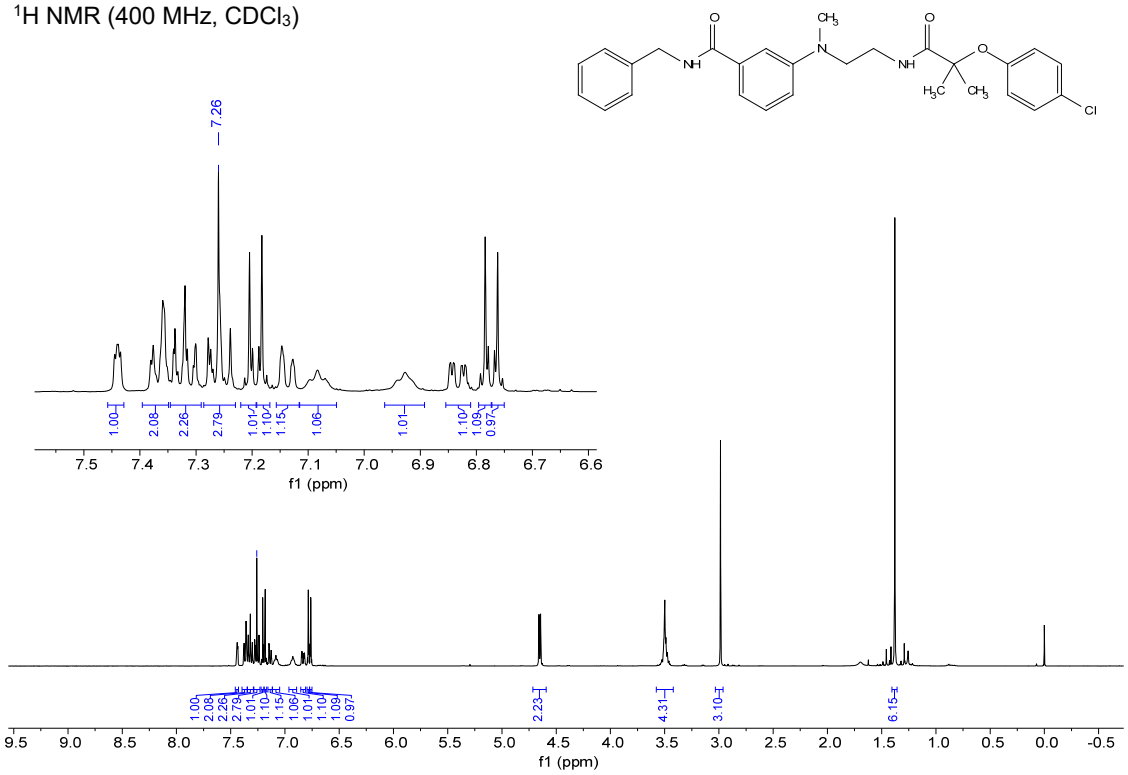


^{13}C NMR (101 MHz, $CDCl_3$)

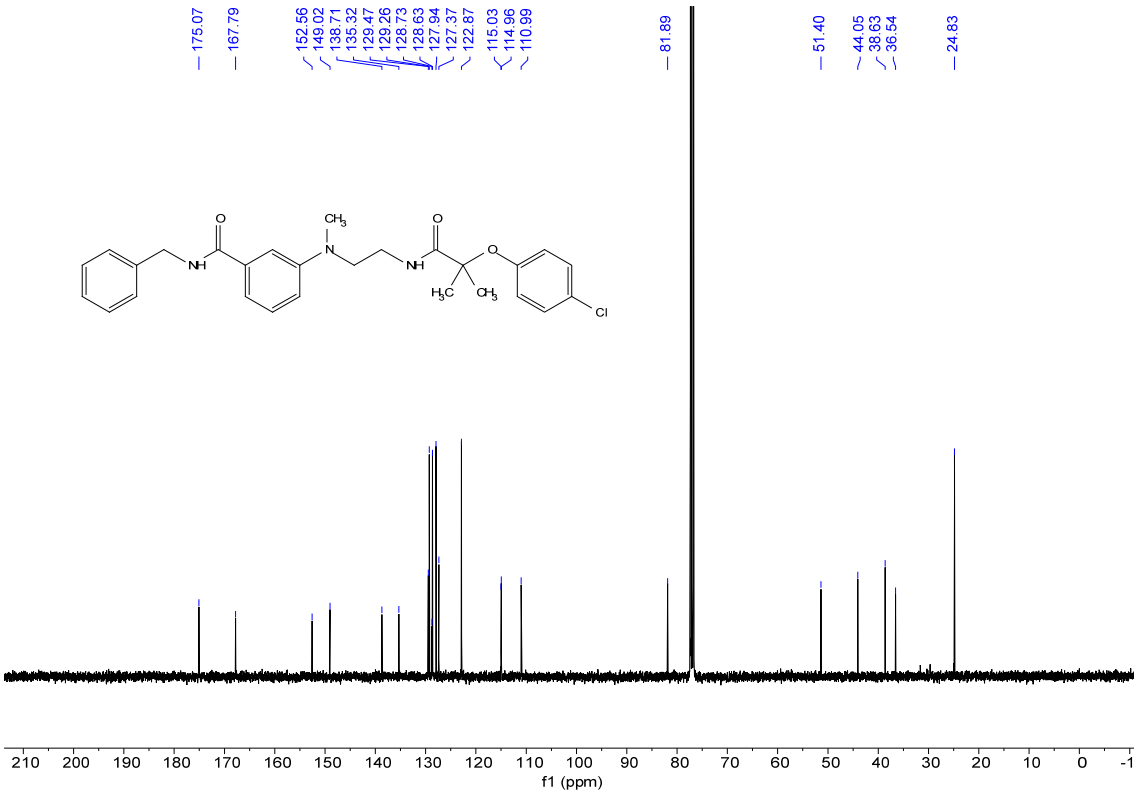


^{1}H NMR and ^{13}C NMR spectrum of **3na**

^{1}H NMR (400 MHz, $CDCl_3$)

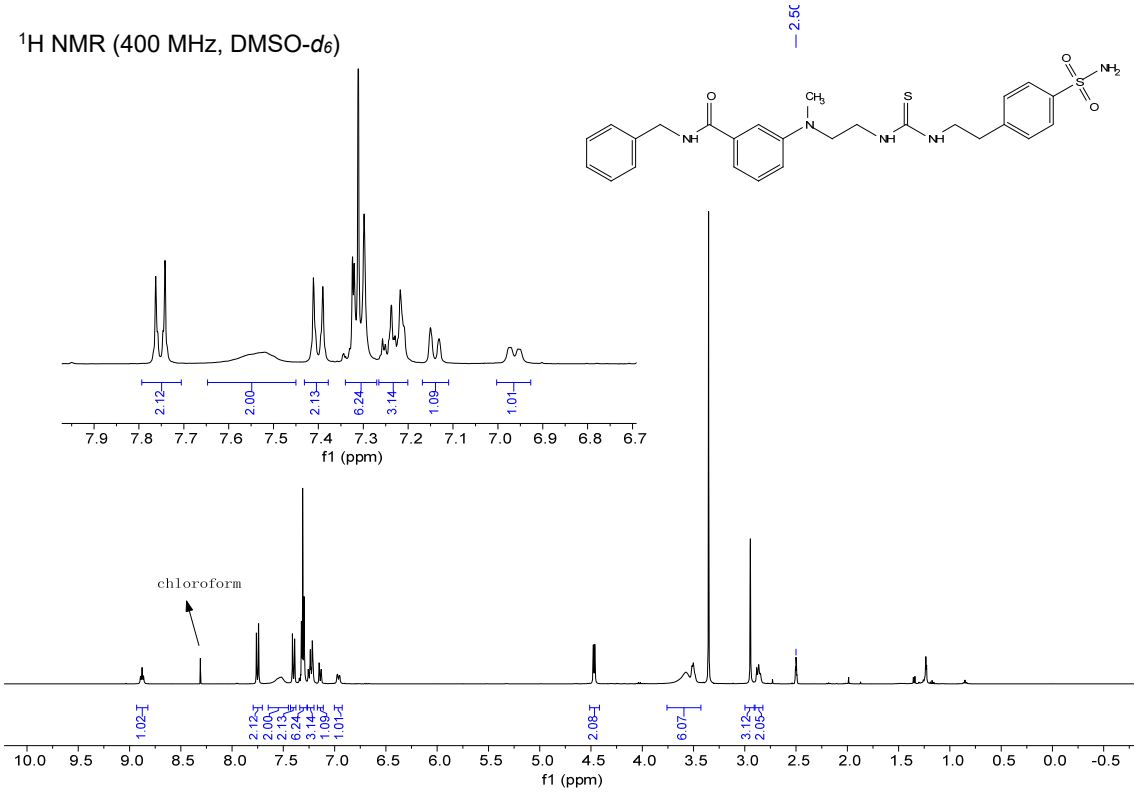


^{13}C NMR (101 MHz, $CDCl_3$)

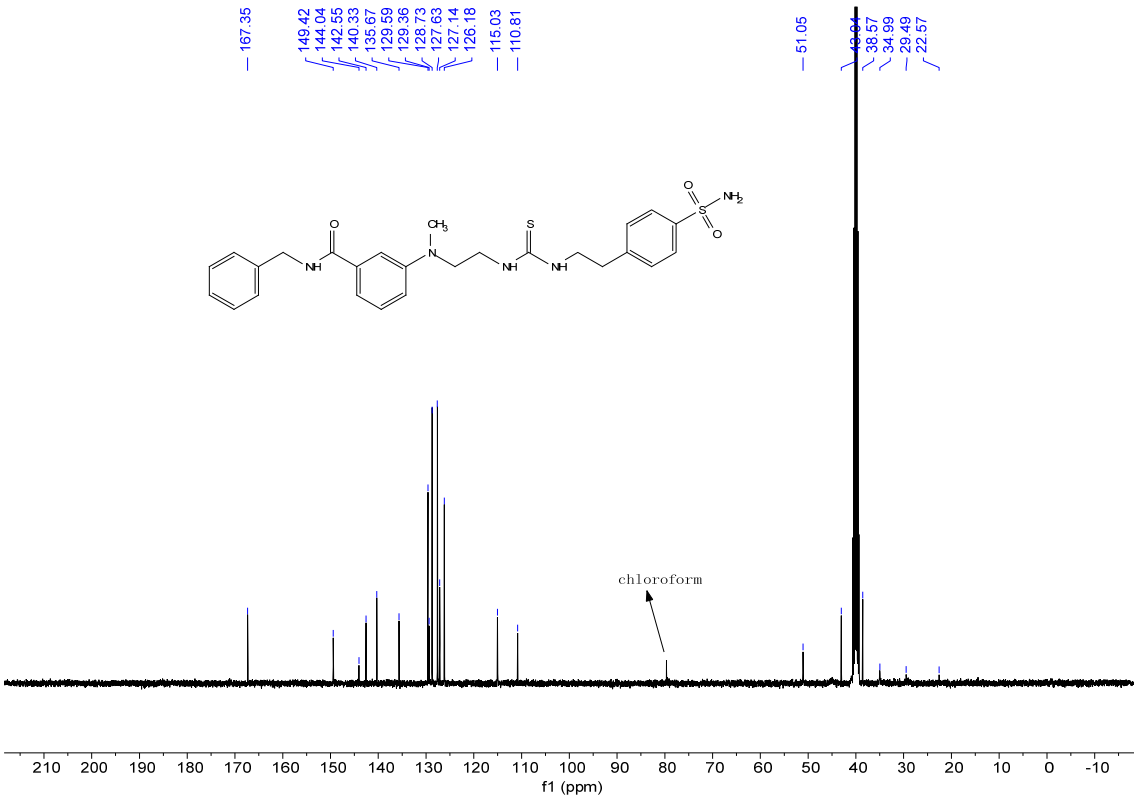


^{1}H NMR and ^{13}C NMR spectrum of **3oa**

^{1}H NMR (400 MHz, DMSO-d_6)

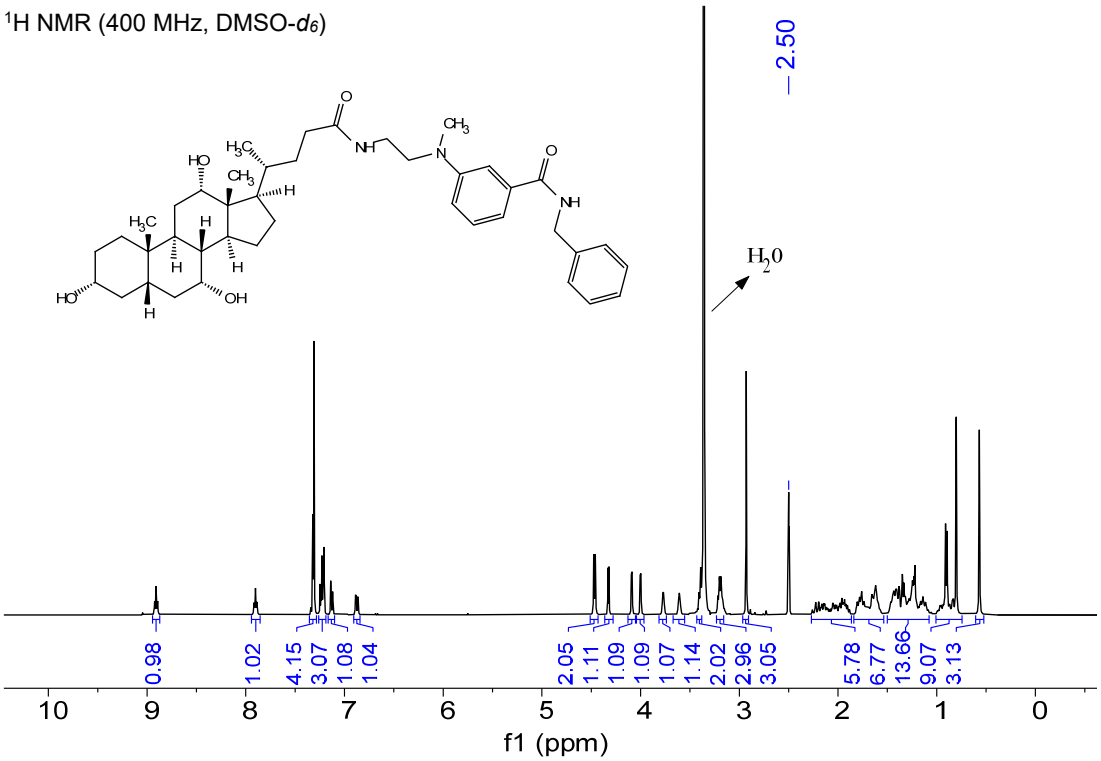


^{13}C NMR (101 MHz, DMSO-d_6)

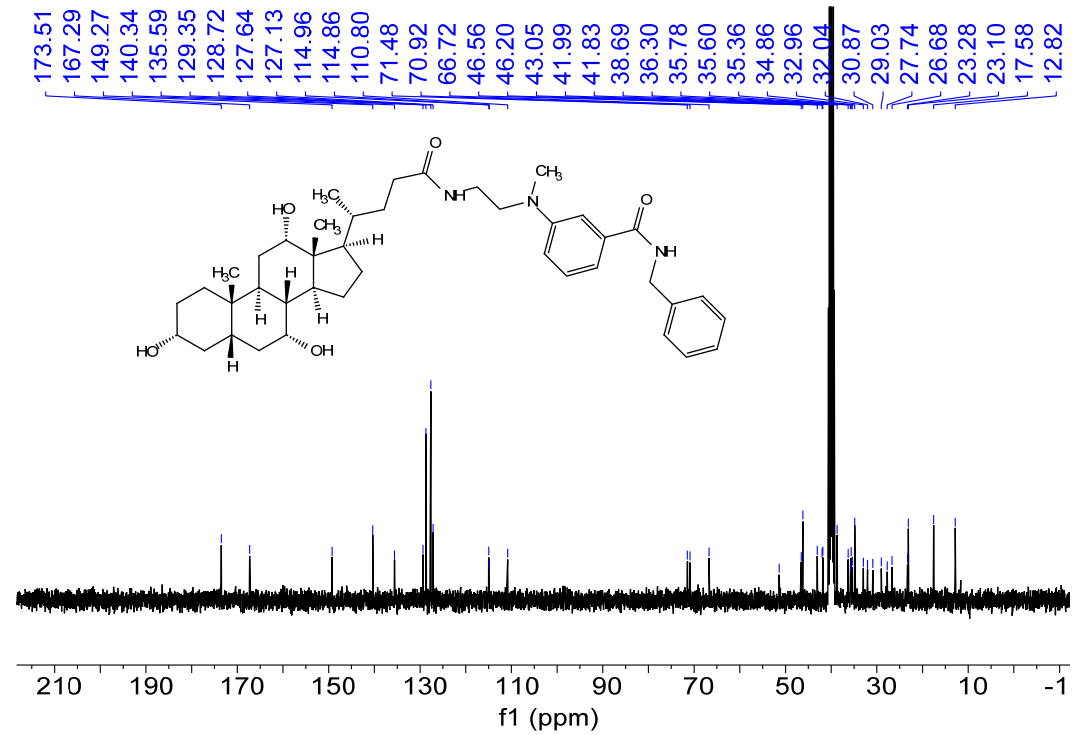


^{1}H NMR and ^{13}C NMR spectrum of **3pa**

^{1}H NMR (400 MHz, DMSO-*d*$_6$)

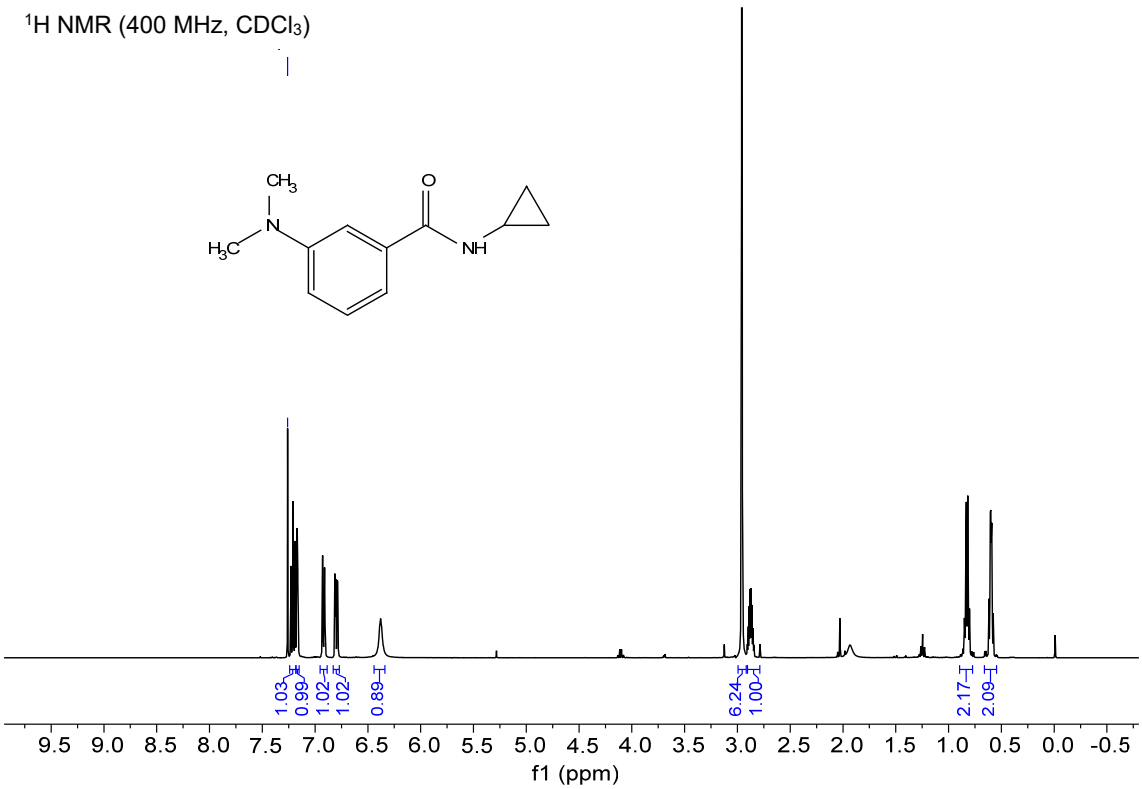


^{13}C NMR (101 MHz, DMSO-*d*$_6$)

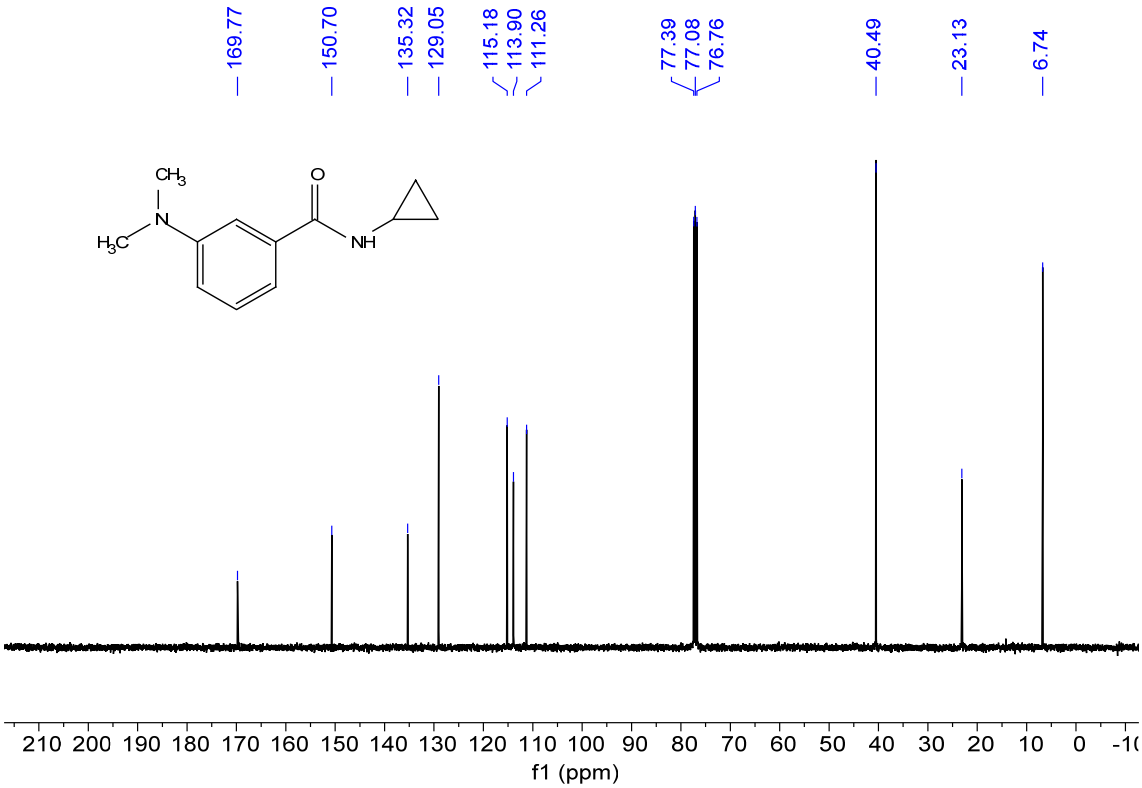


^{1}H NMR and ^{13}C NMR spectrum of **3qa**

^{1}H NMR (400 MHz, $CDCl_3$)

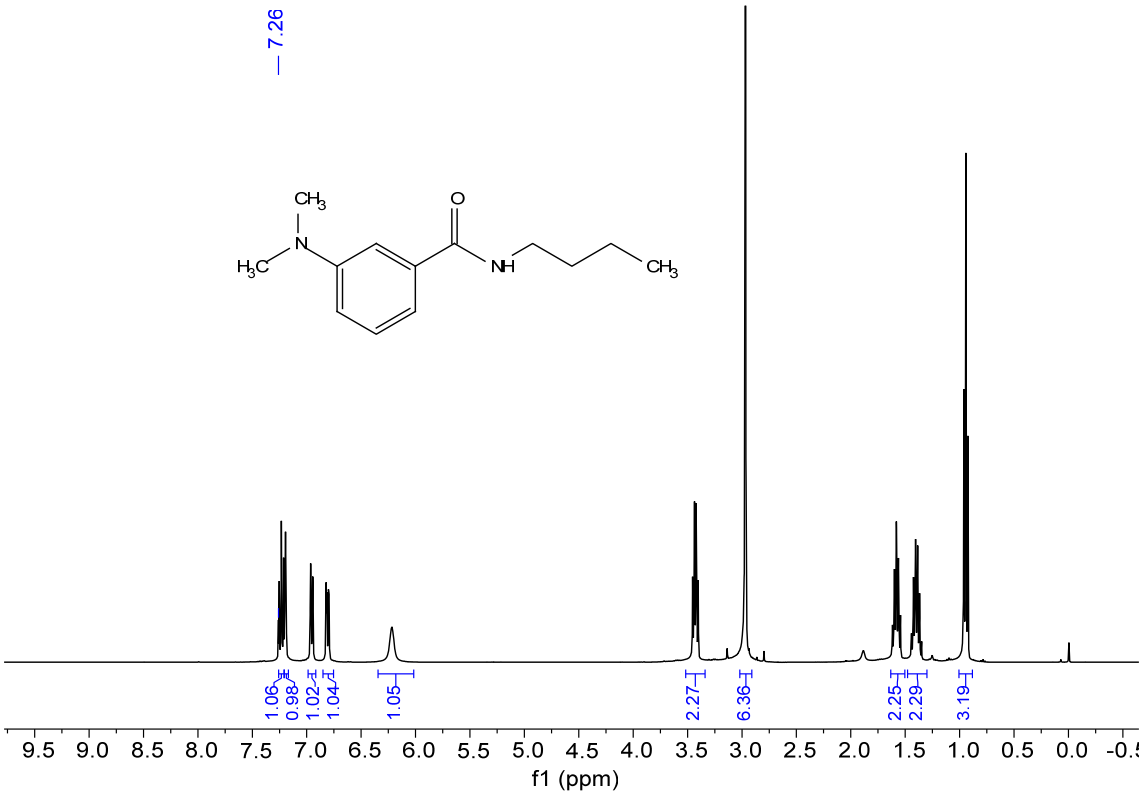


^{13}C NMR (101 MHz, $CDCl_3$)

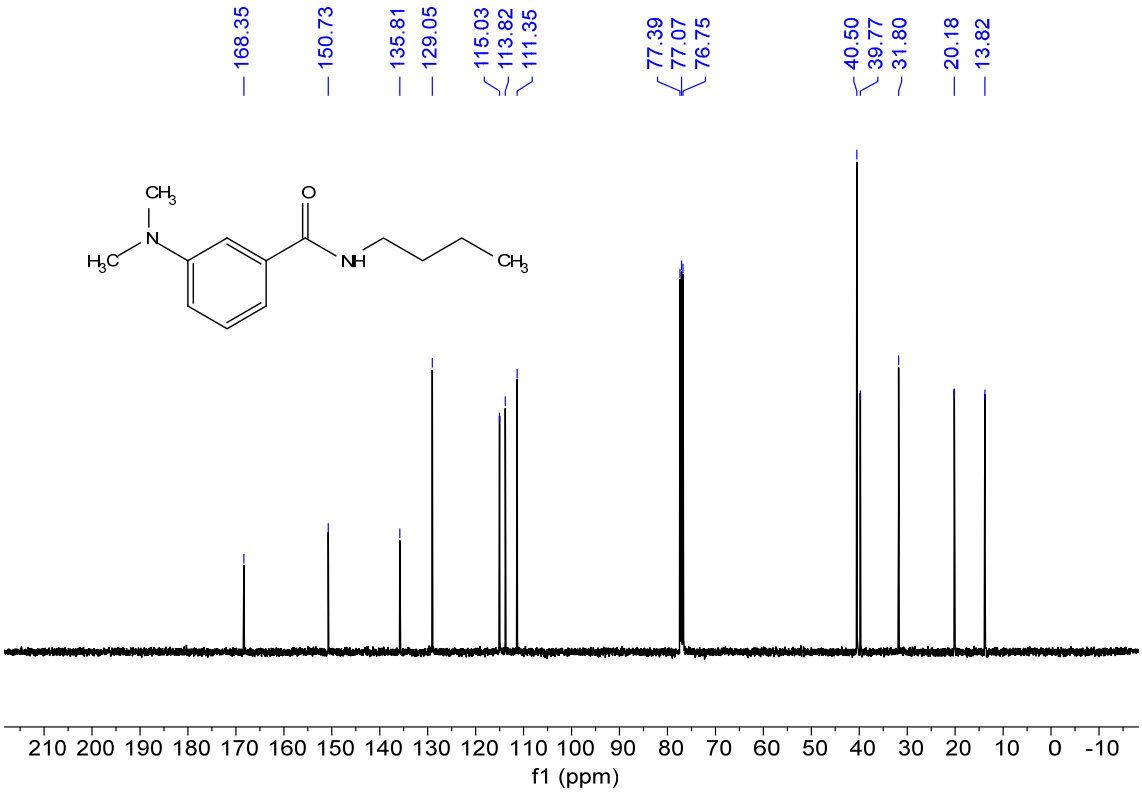


^{1}H NMR and ^{13}C NMR spectrum of **3ab**

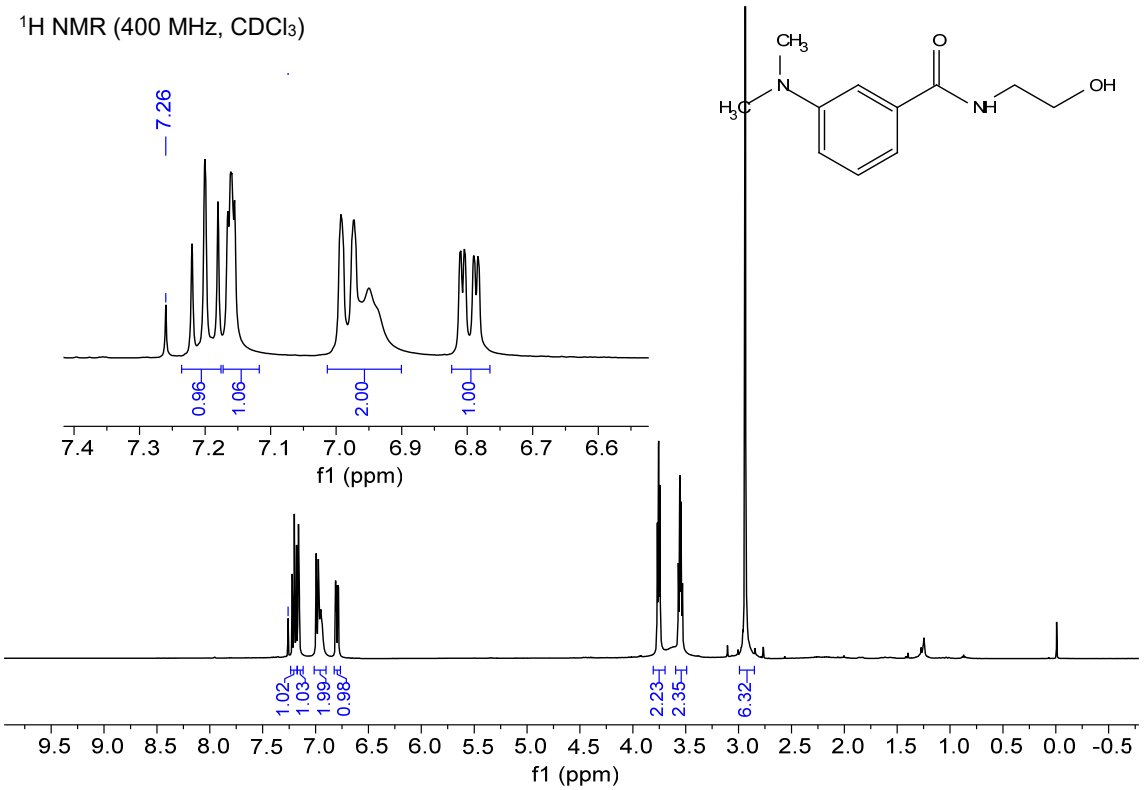
^{1}H NMR (400 MHz, $CDCl_3$)

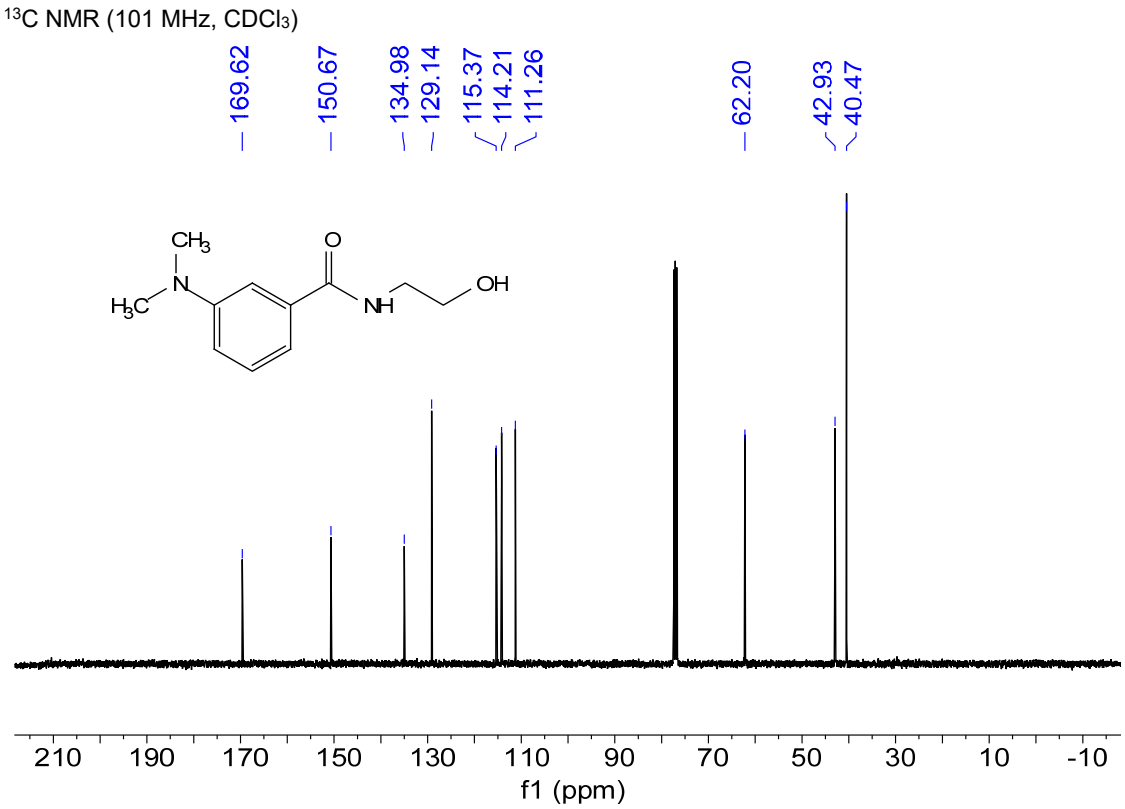


^{13}C NMR (101 MHz, $CDCl_3$)

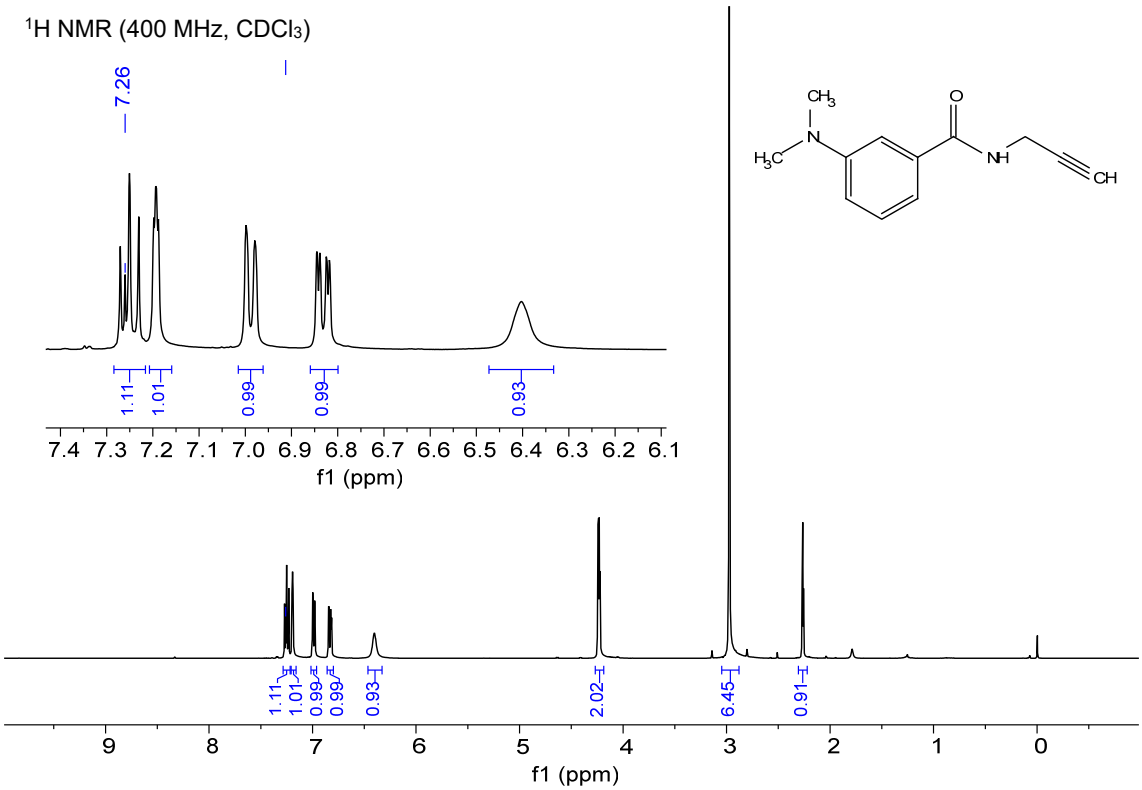


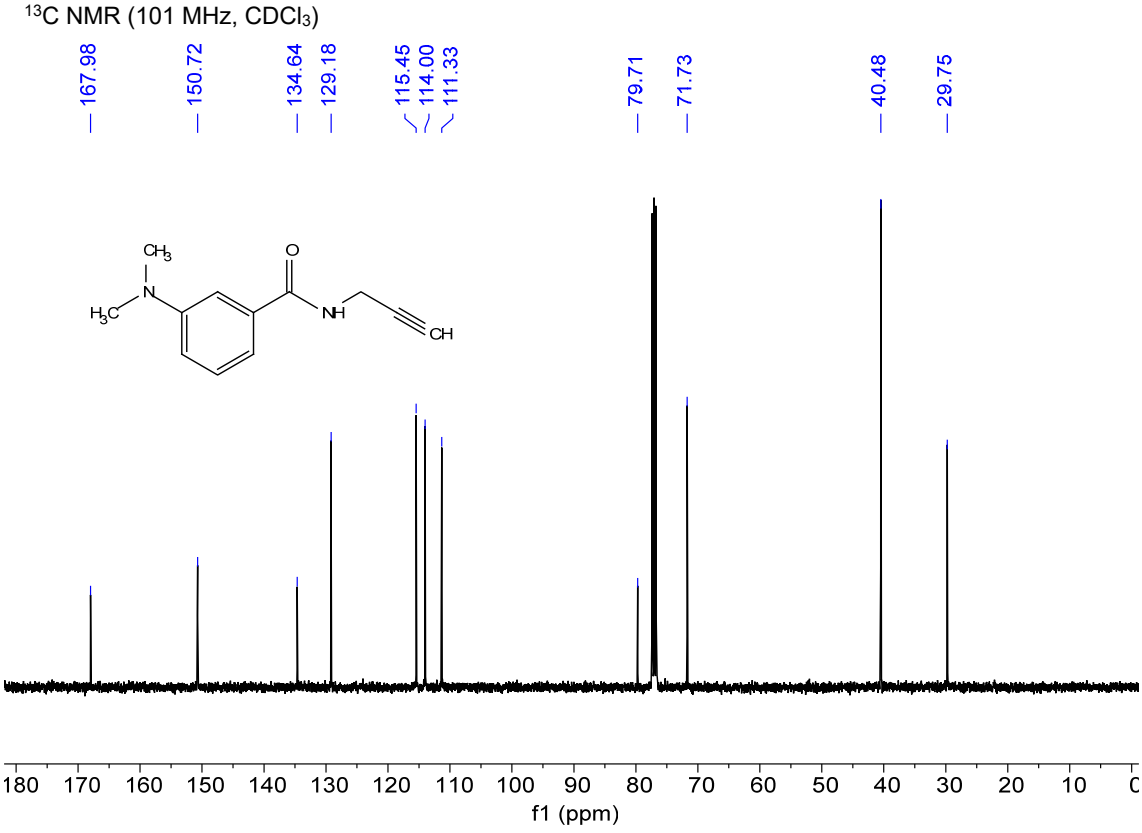
^{1}H NMR and ^{13}C NMR spectrum of **3ac**



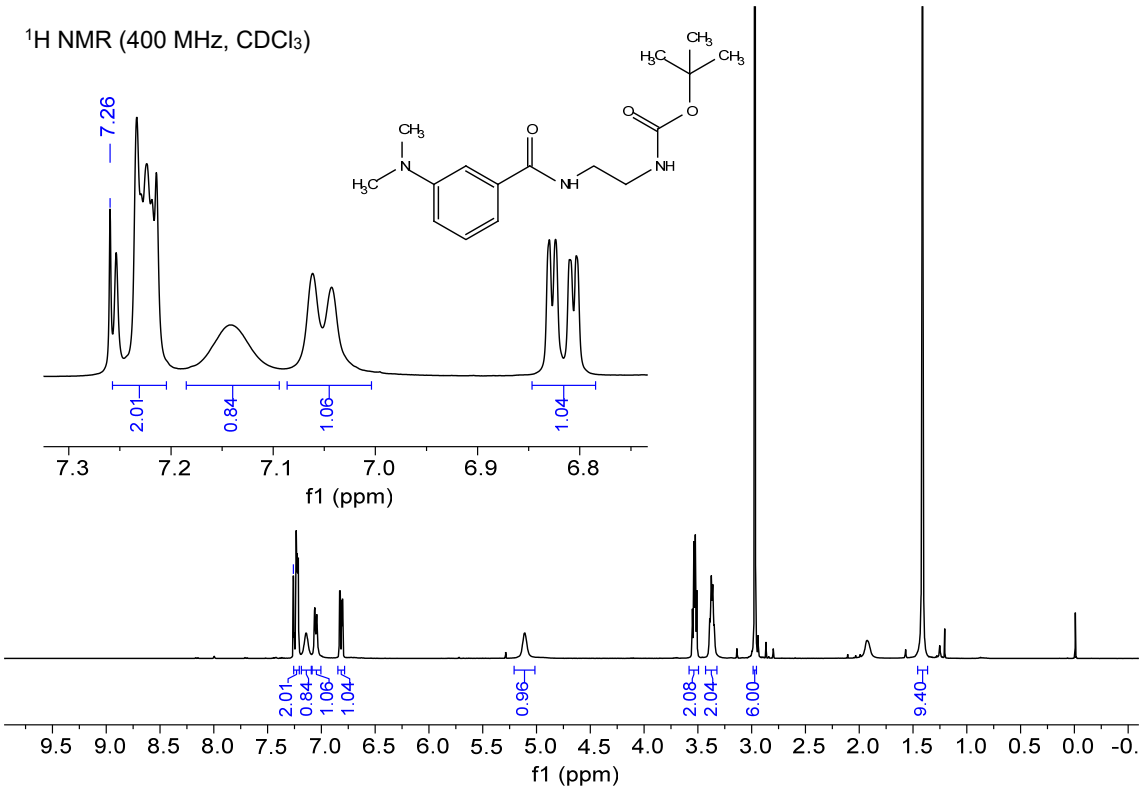


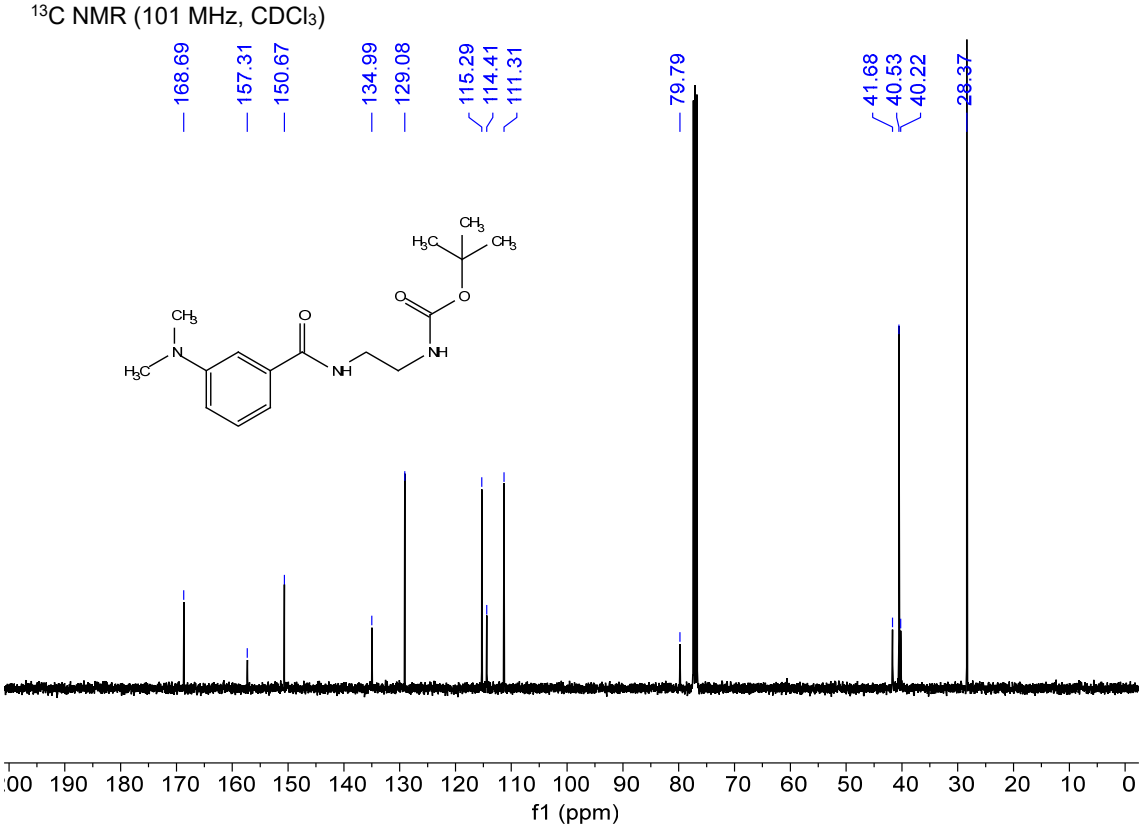
^{1}H NMR and ^{13}C NMR spectrum of **3ad**





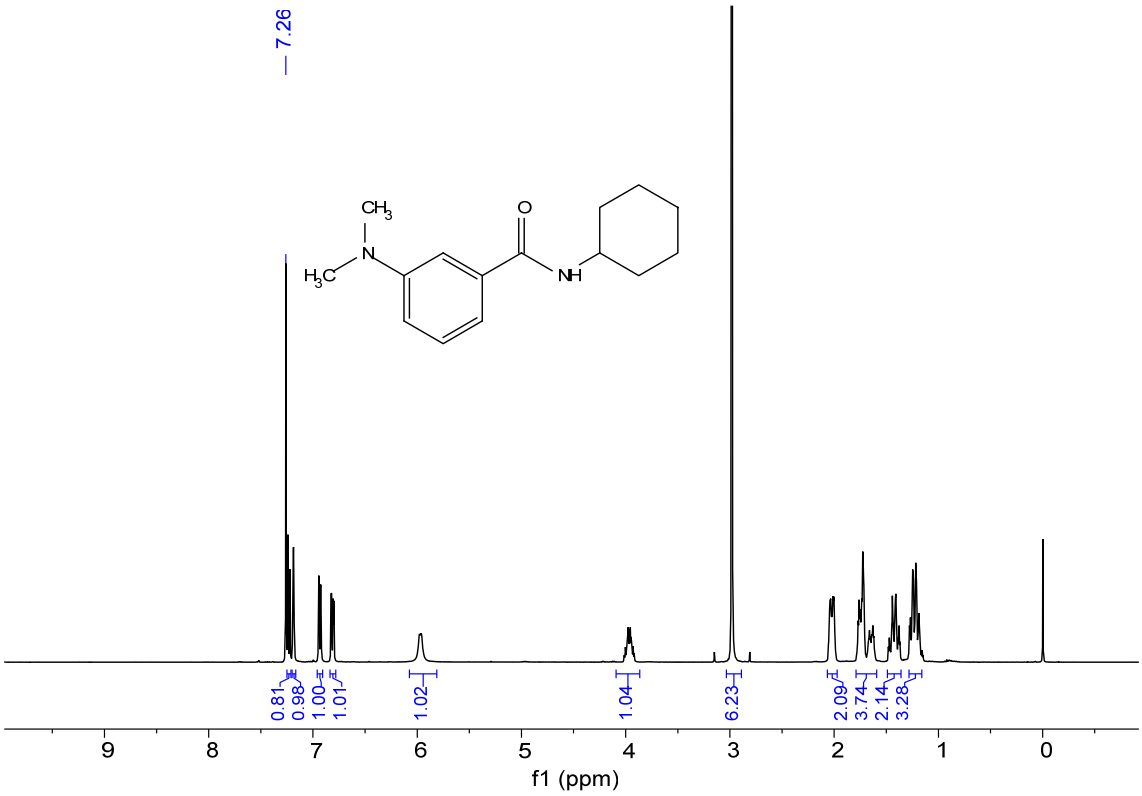
^{1}H NMR and ^{13}C NMR spectrum of **3ae**



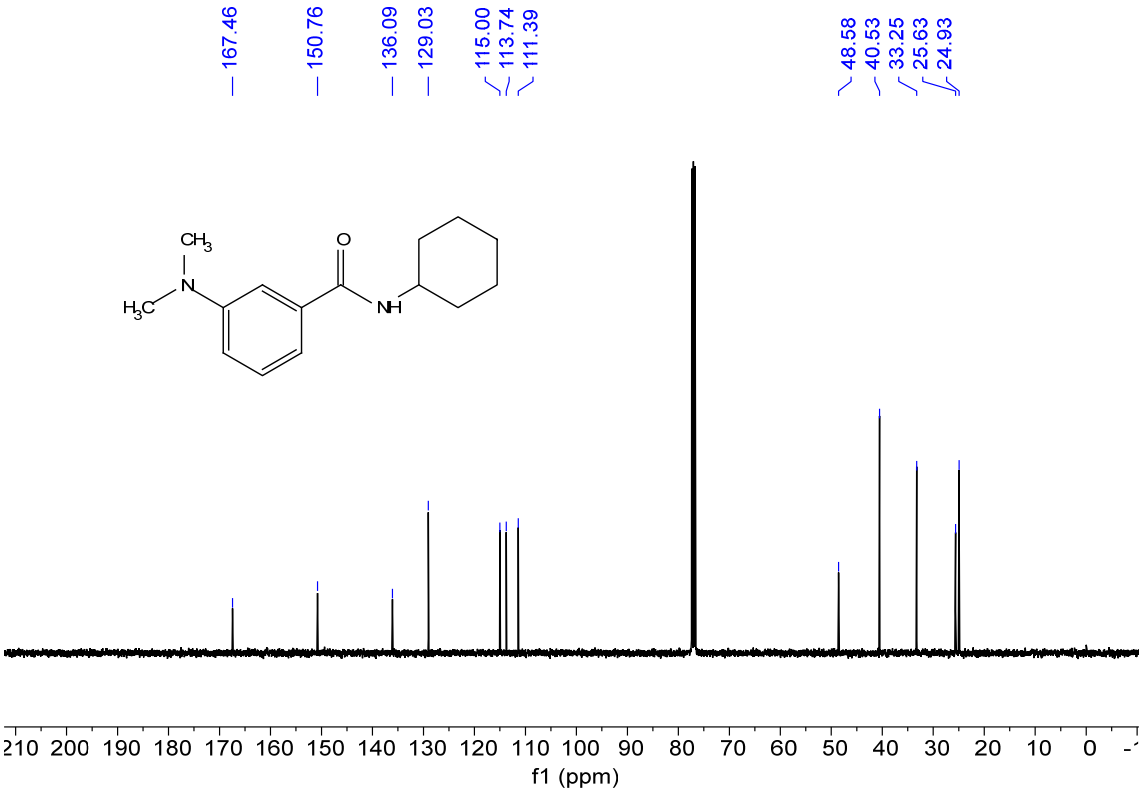


^{1}H NMR and ^{13}C NMR spectrum of **3af**

^{1}H NMR (400 MHz, $CDCl_3$)

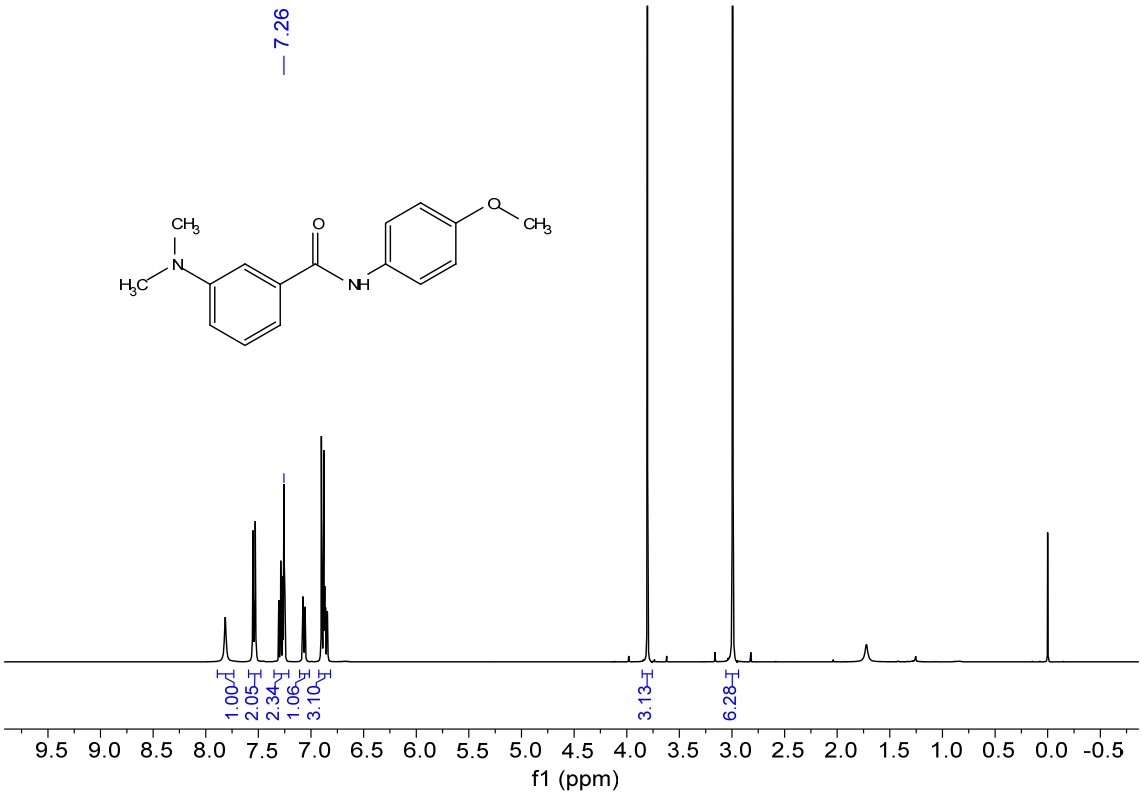


^{13}C NMR (101 MHz, $CDCl_3$)

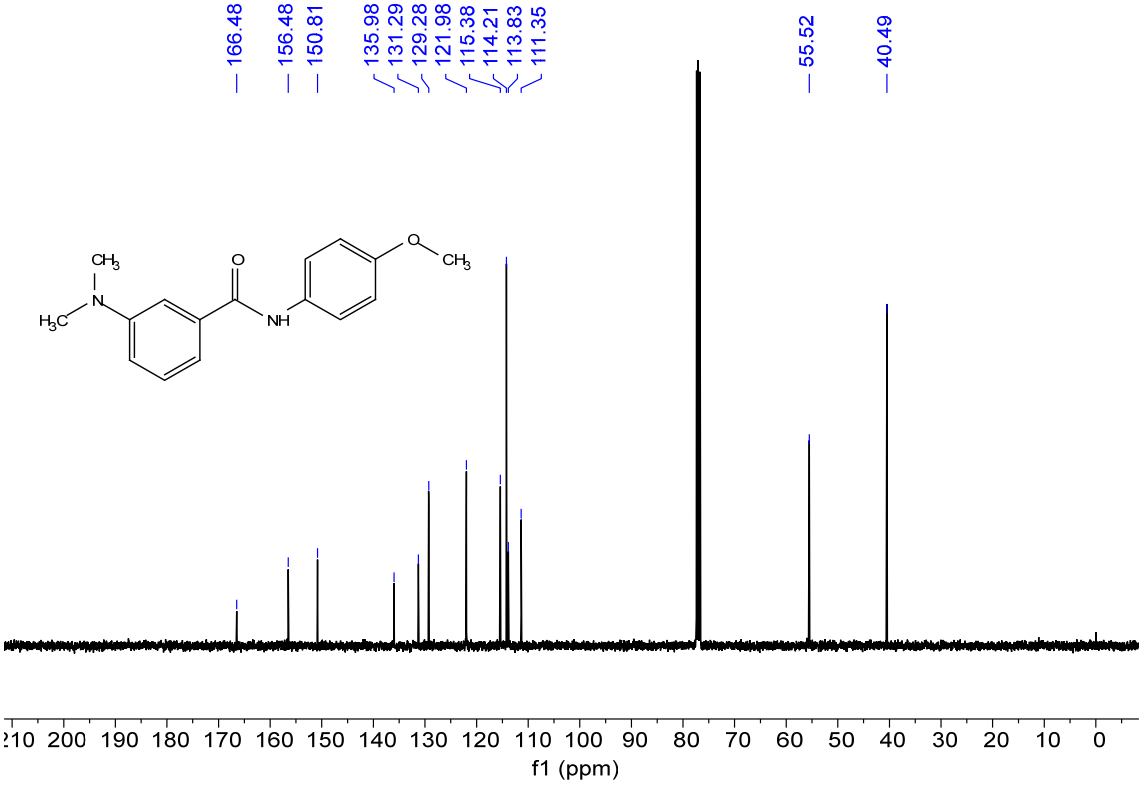


^{1}H NMR and ^{13}C NMR spectrum of **3ag**

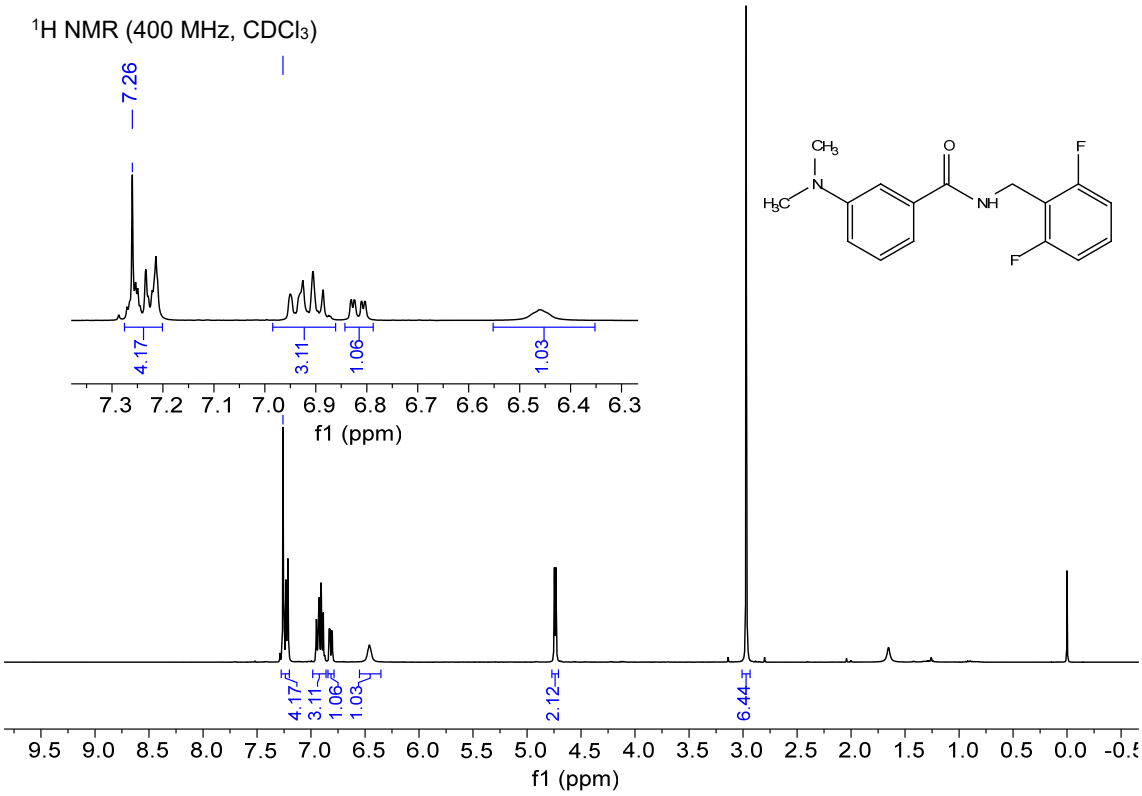
^{1}H NMR (400 MHz, $CDCl_3$)

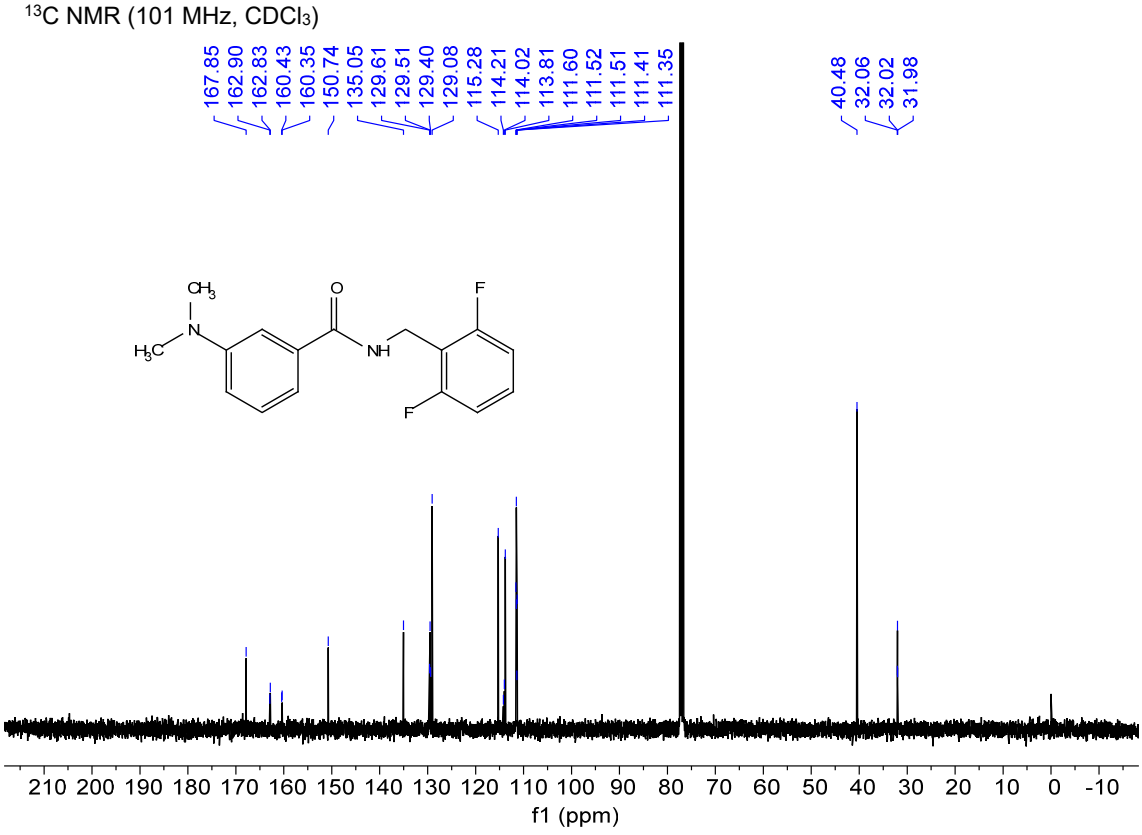


^{13}C NMR (101 MHz, $CDCl_3$)



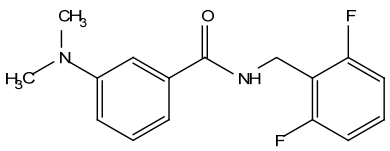
^{1}H NMR and ^{13}C NMR spectrum of **3ah**





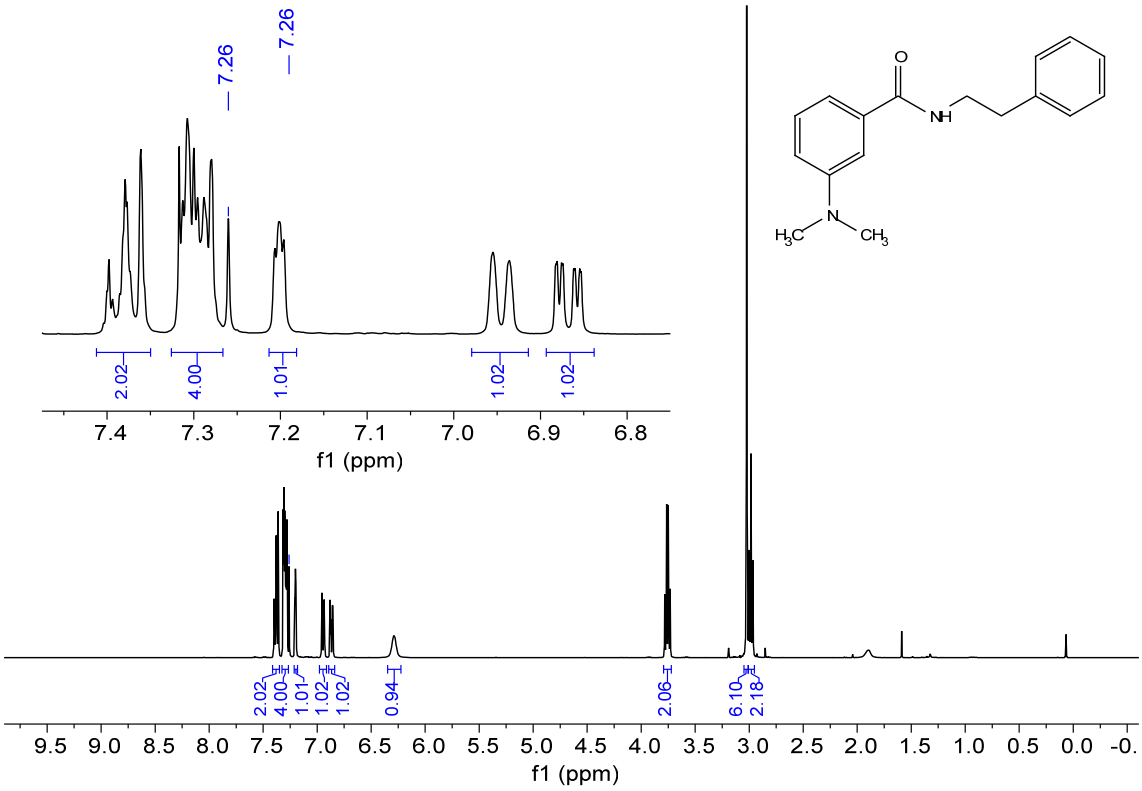
^{1}H NMR and ^{13}C NMR spectrum of **3ai**

^{19}F NMR (376 MHz, $CDCl_3$)

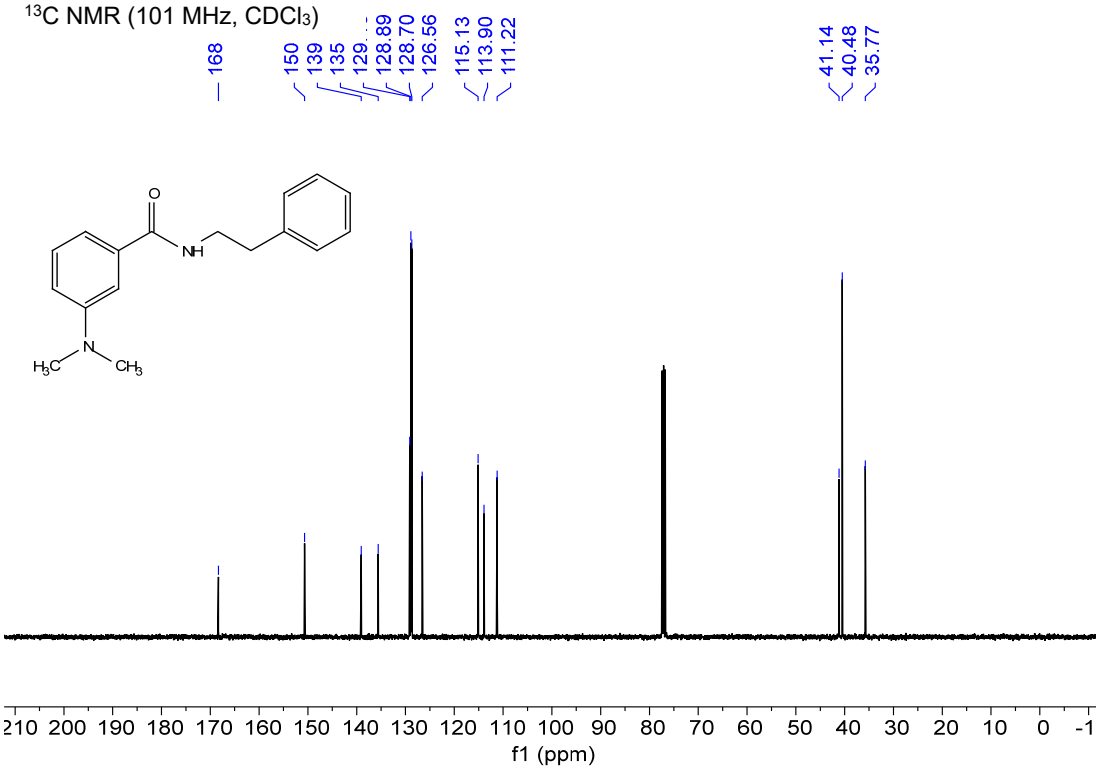


^{19}F NMR spectrum of **3ai**

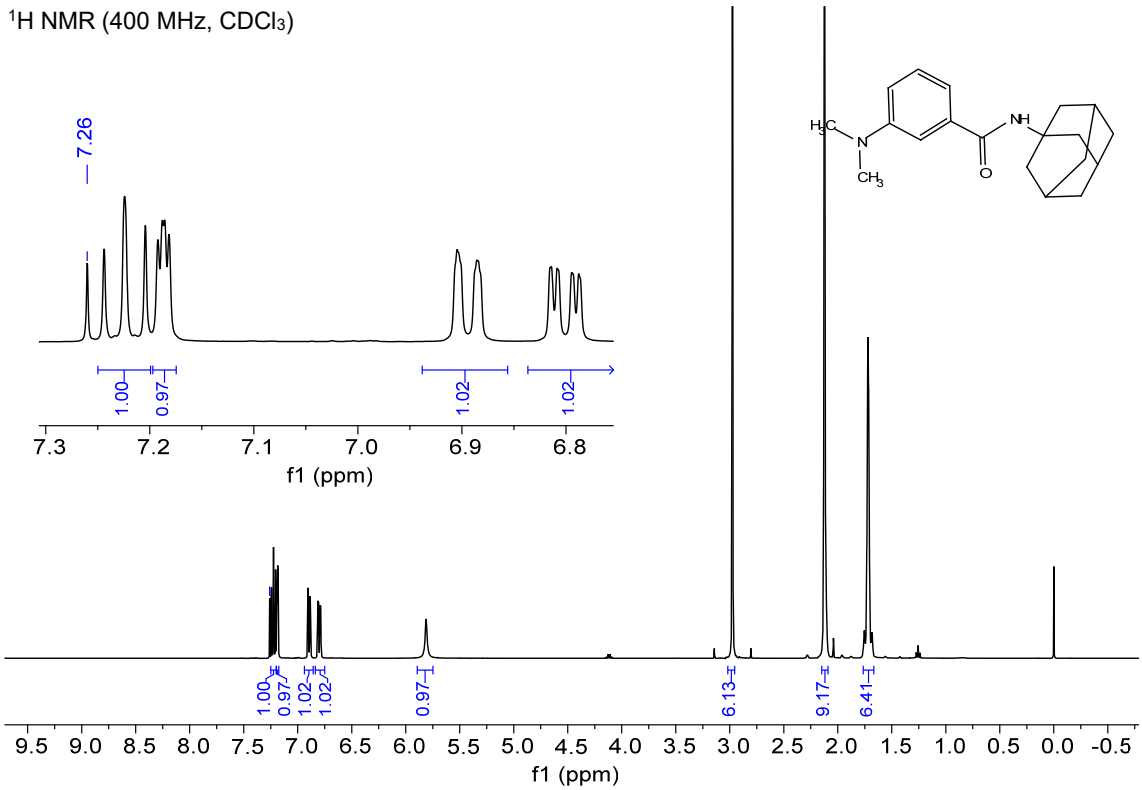
^{1}H NMR (400 MHz, $CDCl_3$)

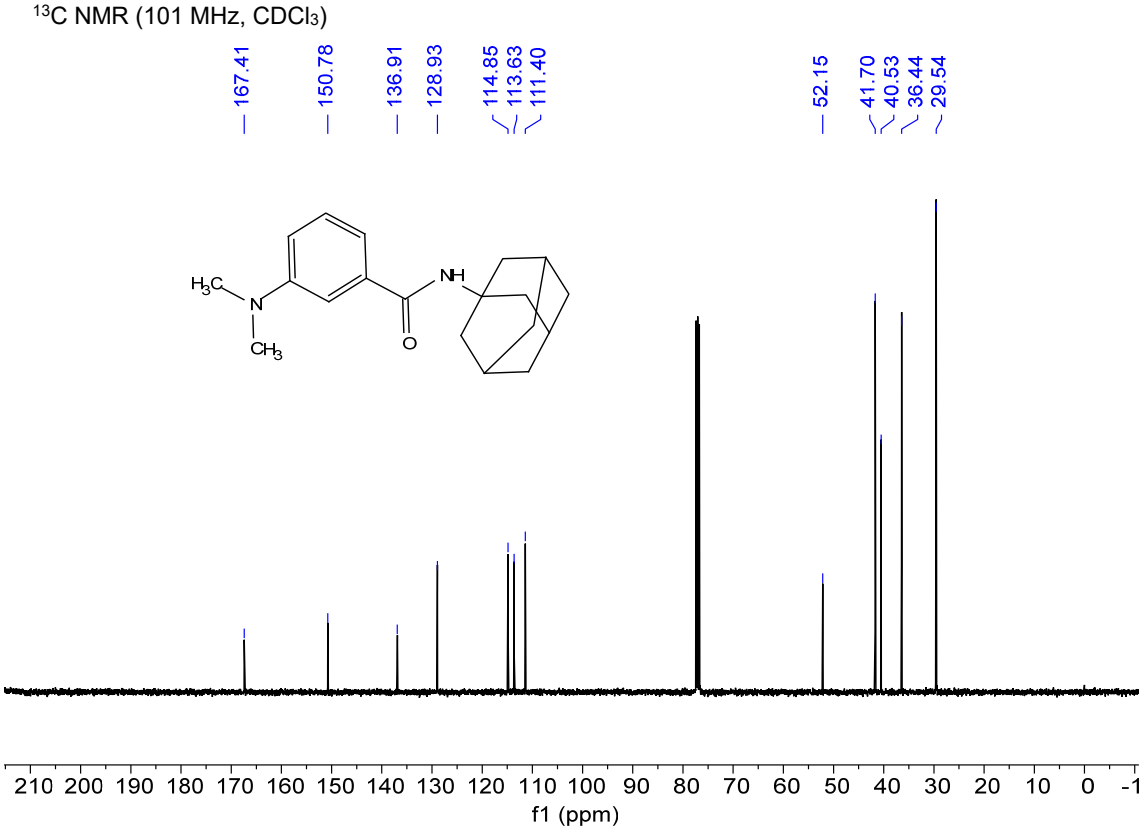


^{13}C NMR (101 MHz, $CDCl_3$)

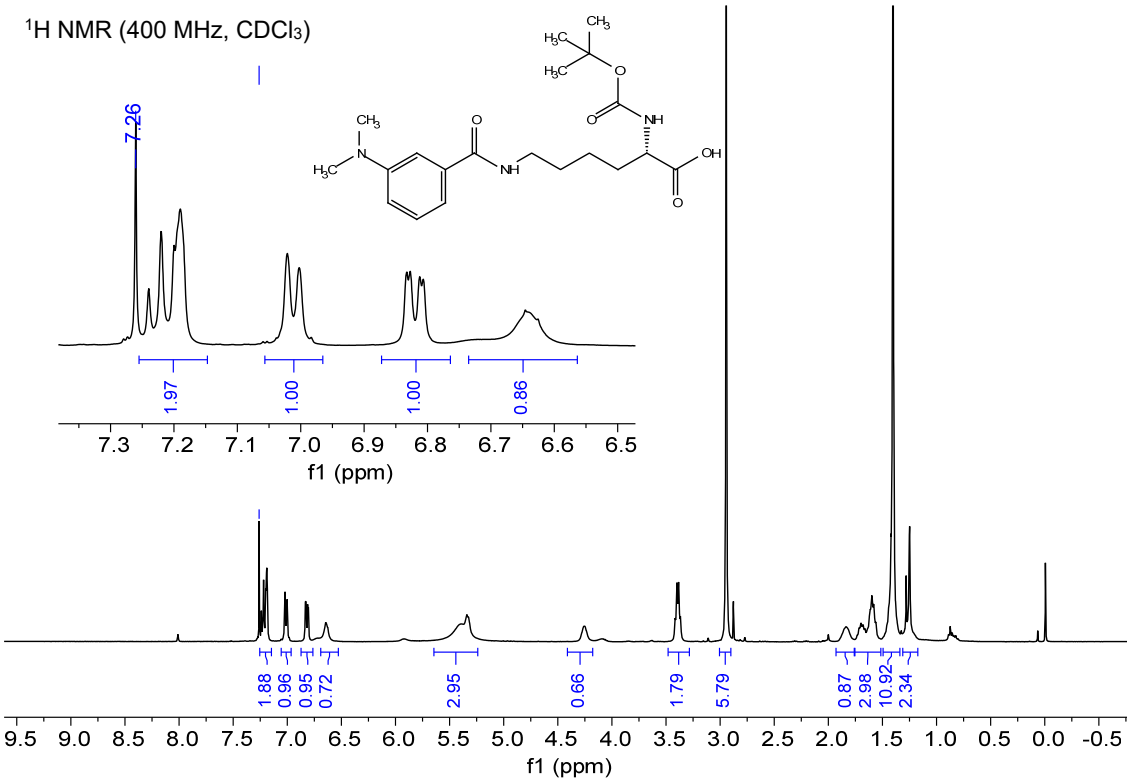


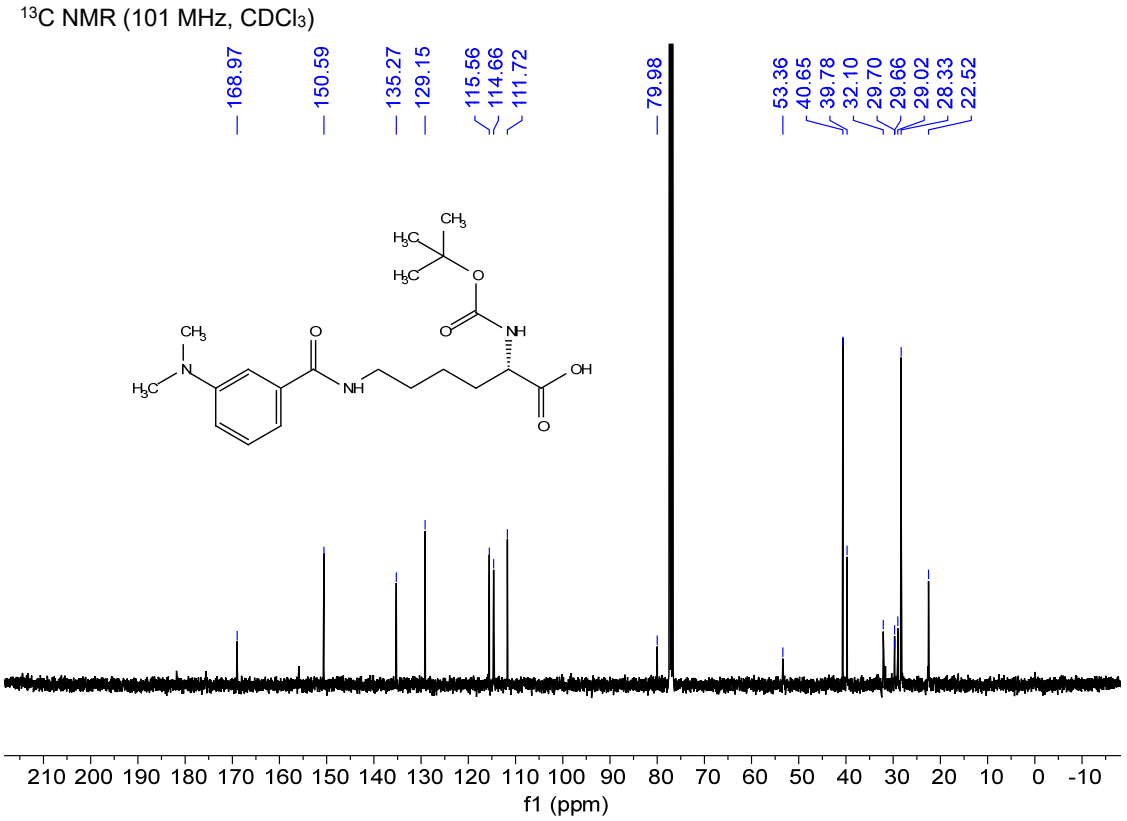
^{1}H NMR and ^{13}C NMR spectrum of **3aj**



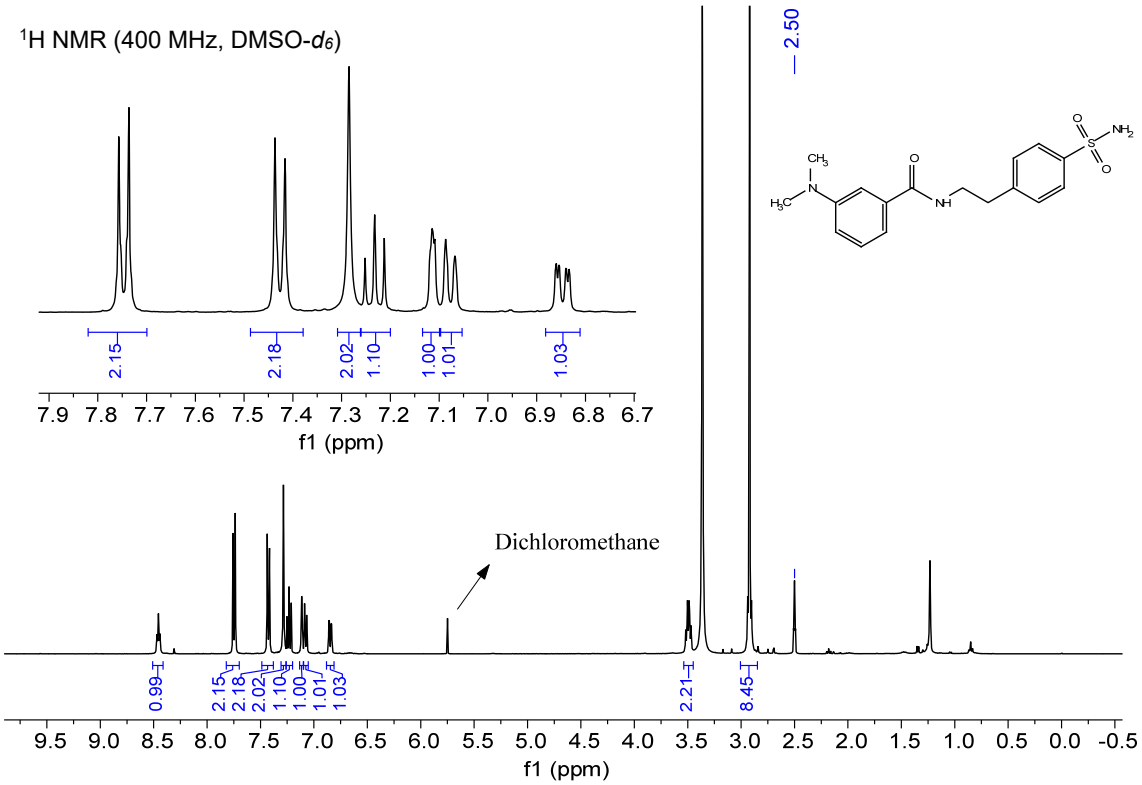


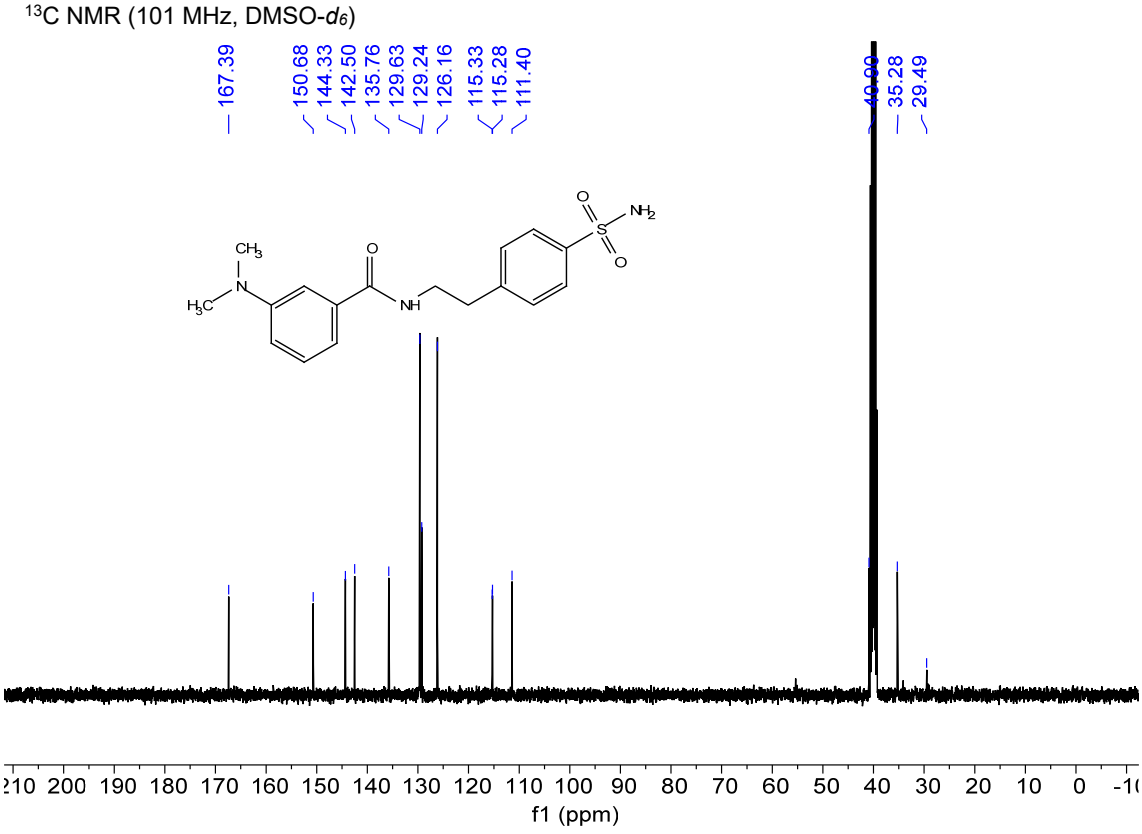
^{1}H NMR and ^{13}C NMR spectrum of **3al**



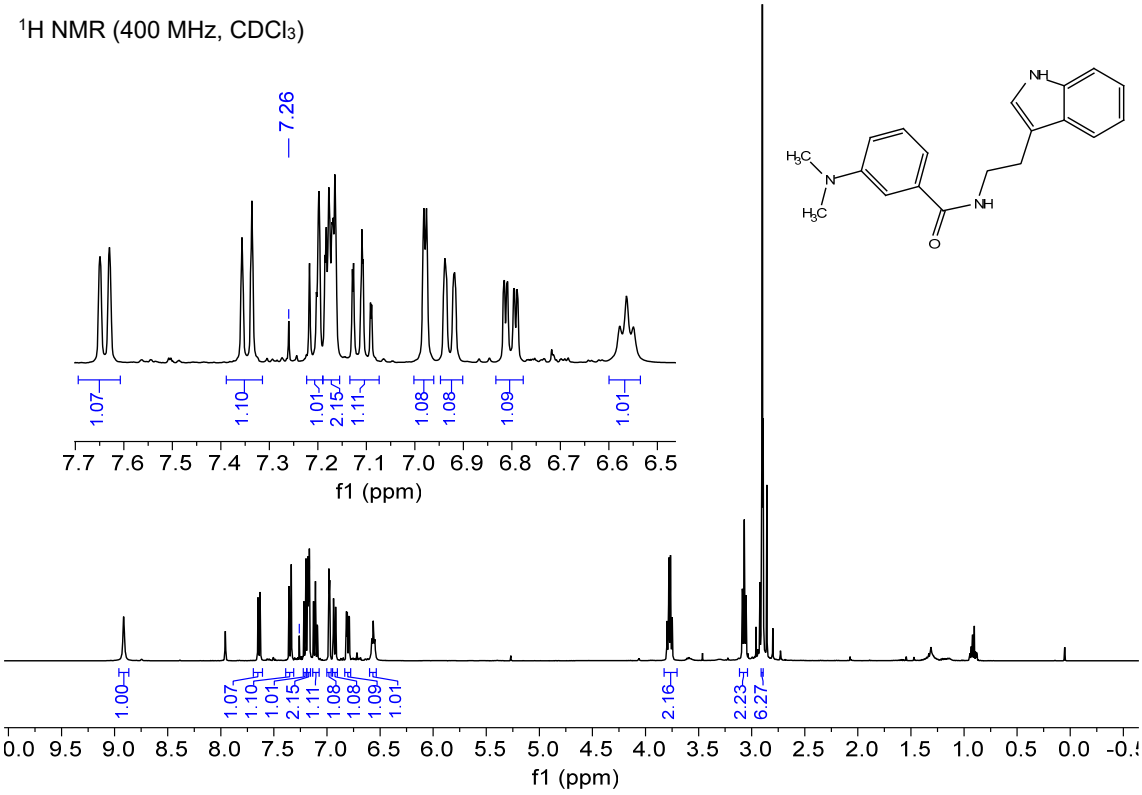


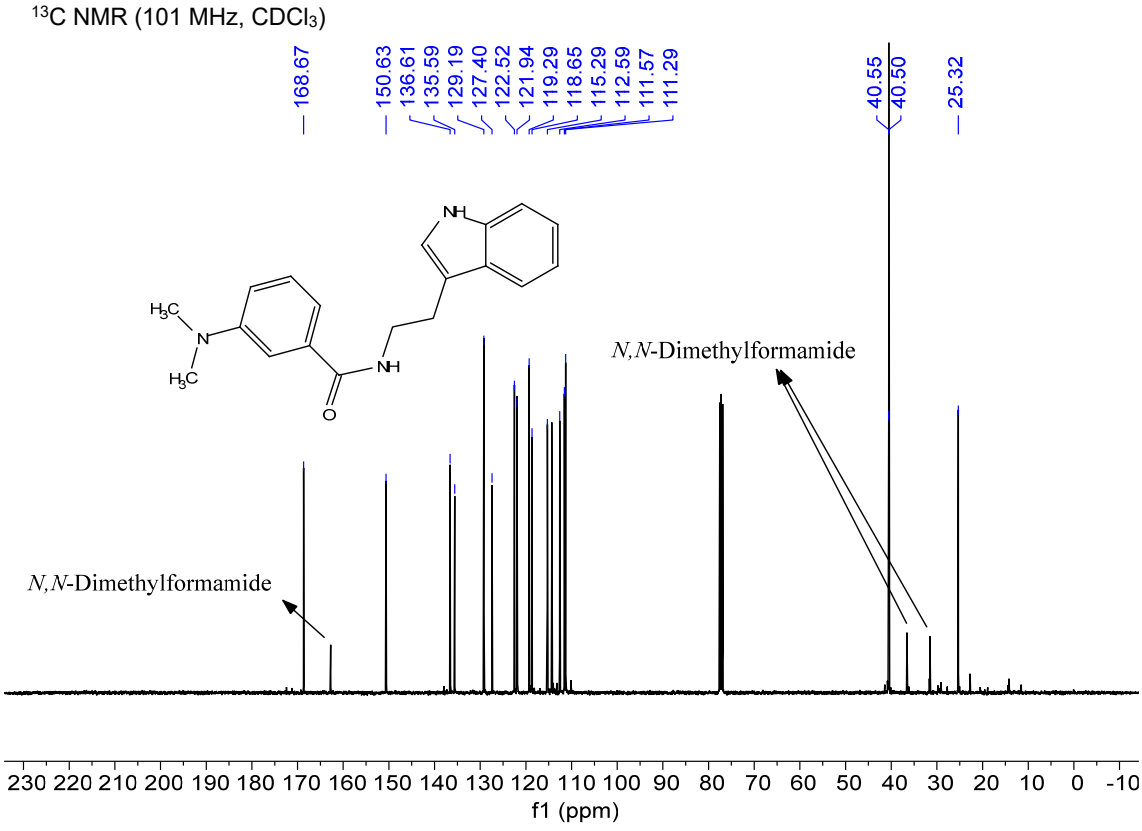
^{1}H NMR and ^{13}C NMR spectrum of **3am**



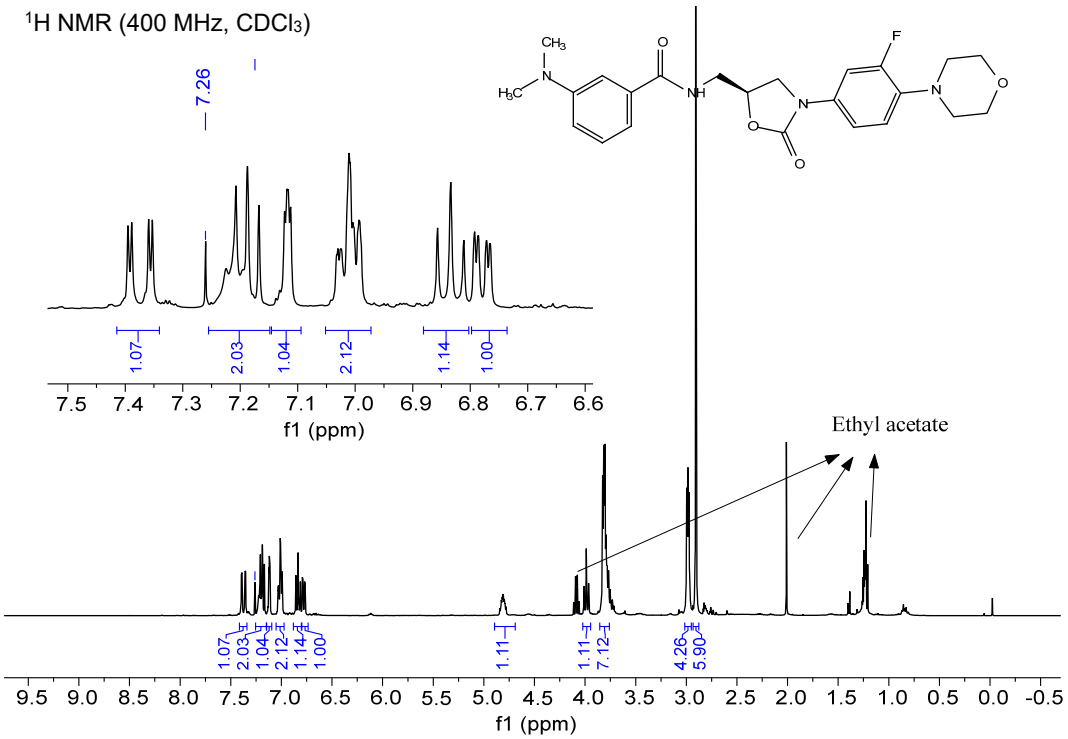


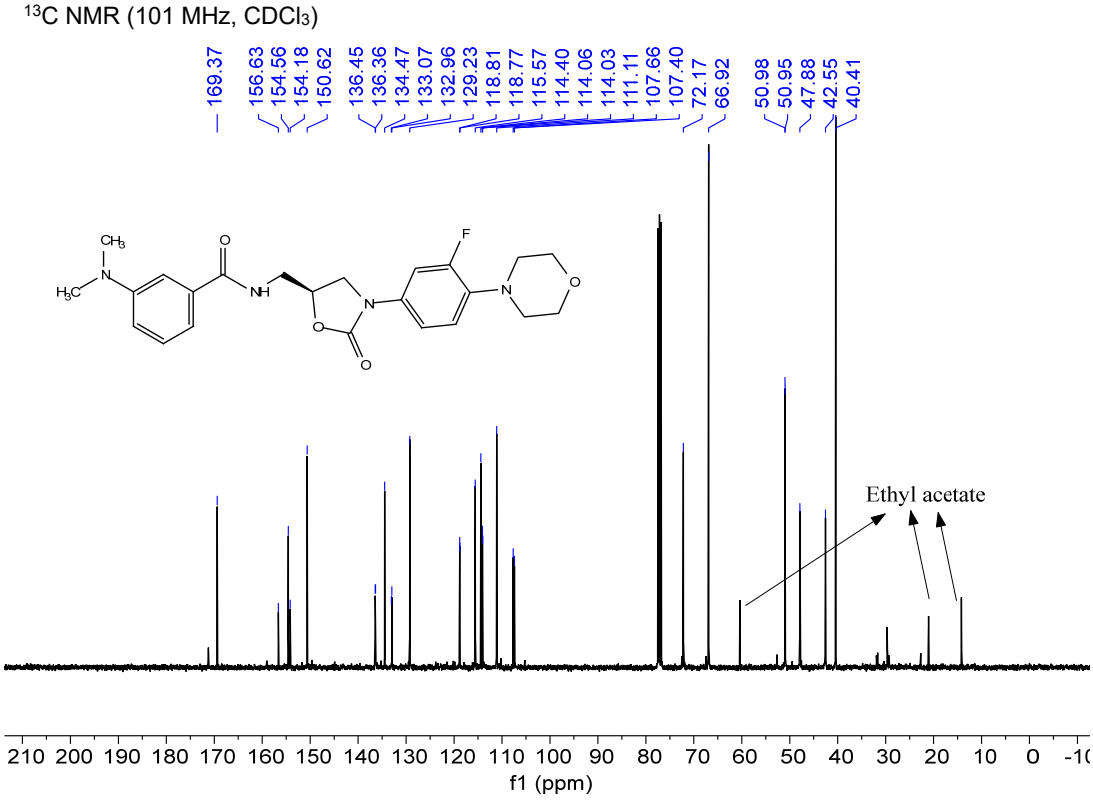
^{1}H NMR and ^{13}C NMR spectrum of **3an**



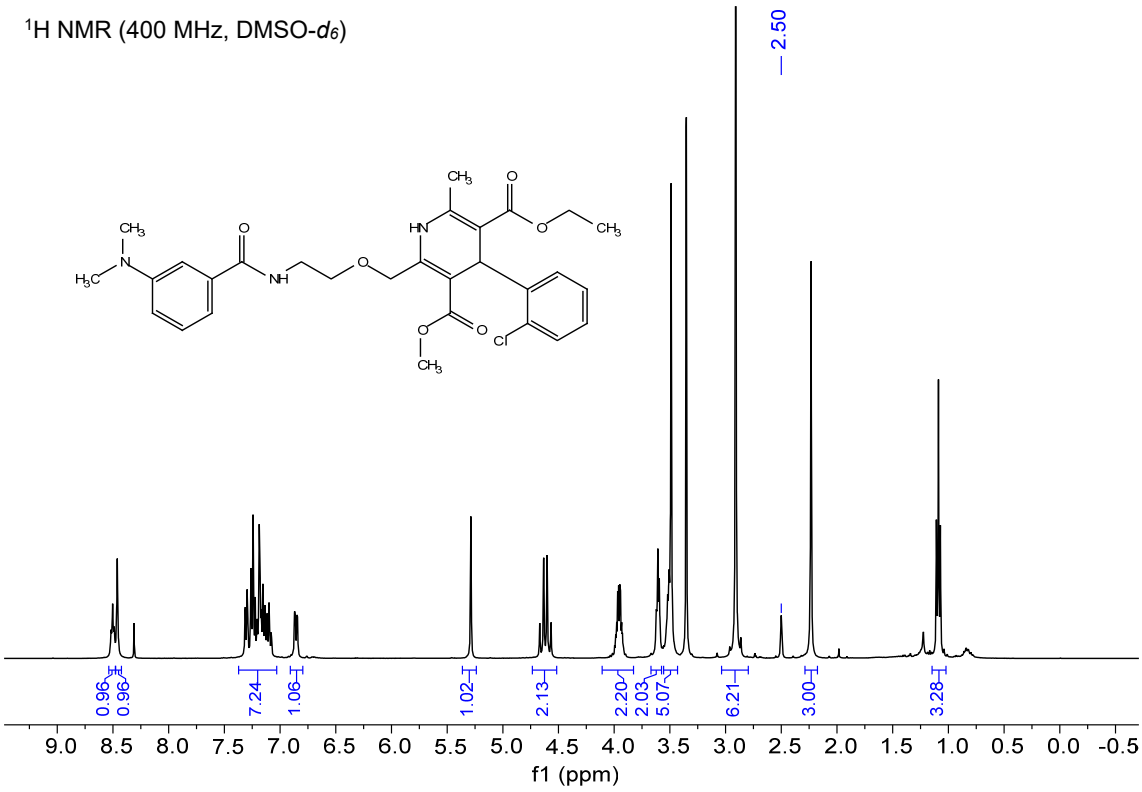


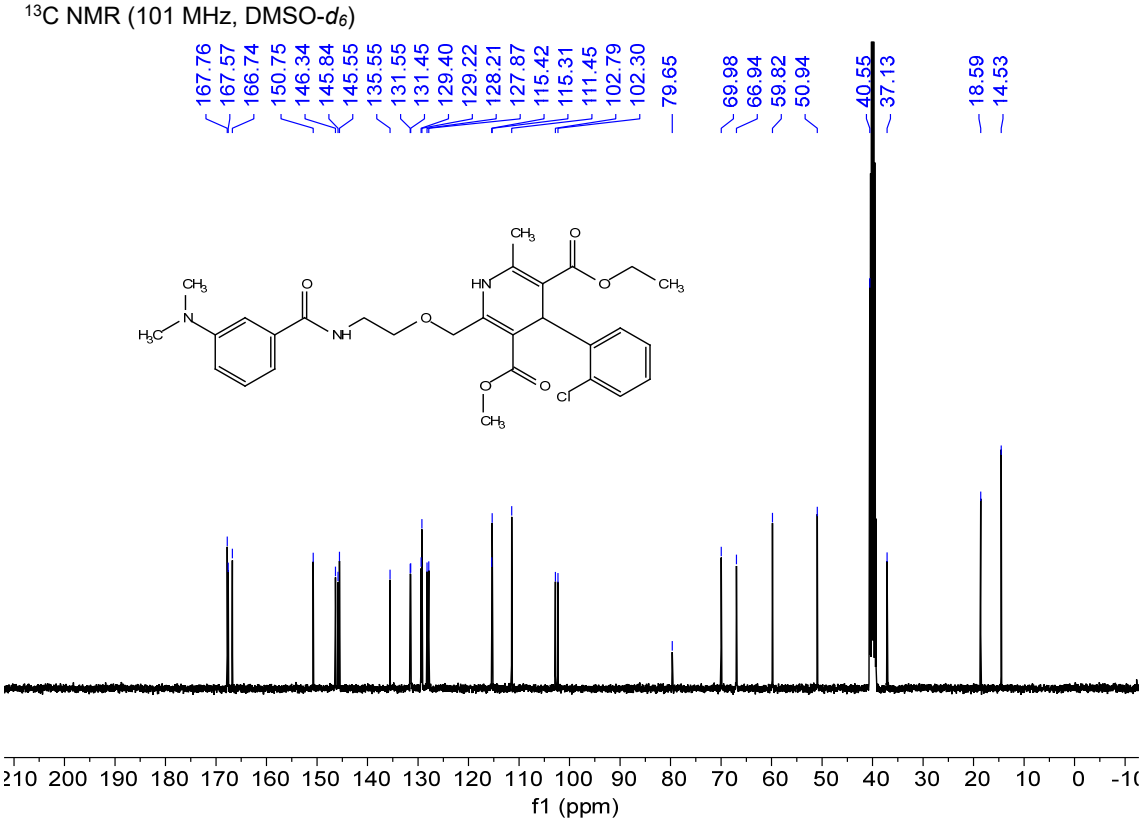
^{1}H NMR and ^{13}C NMR spectrum of **3ao**



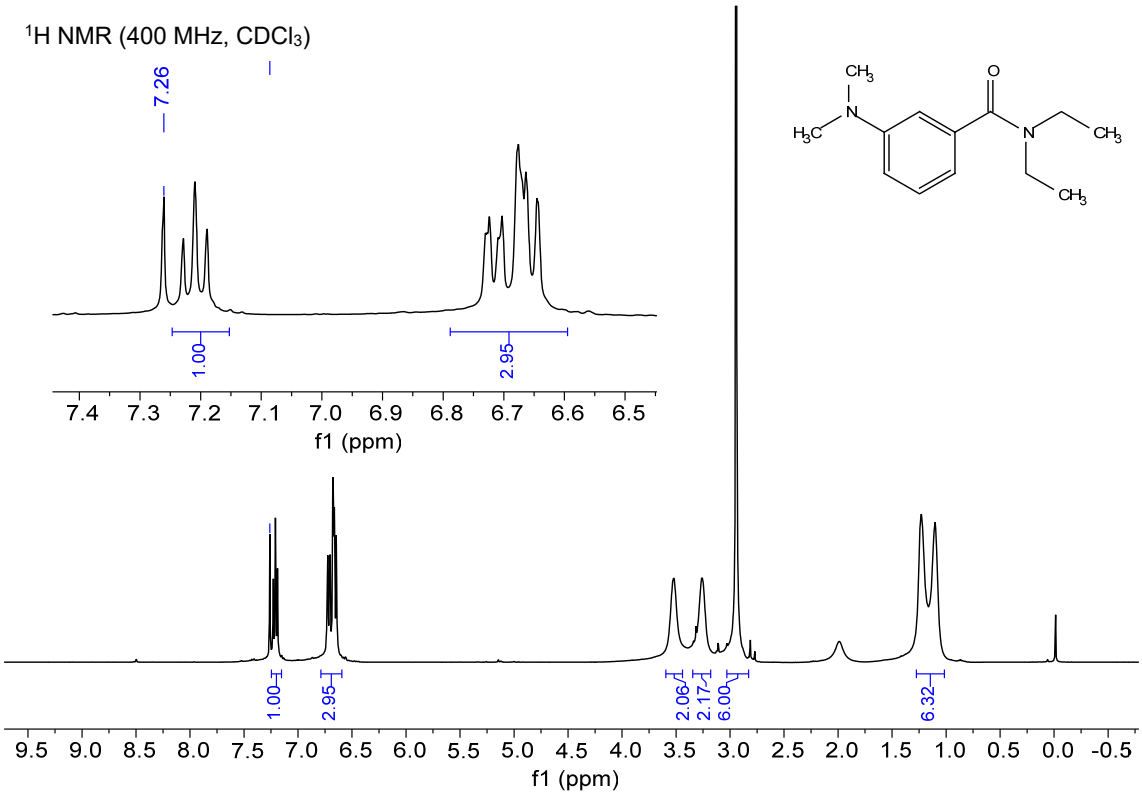


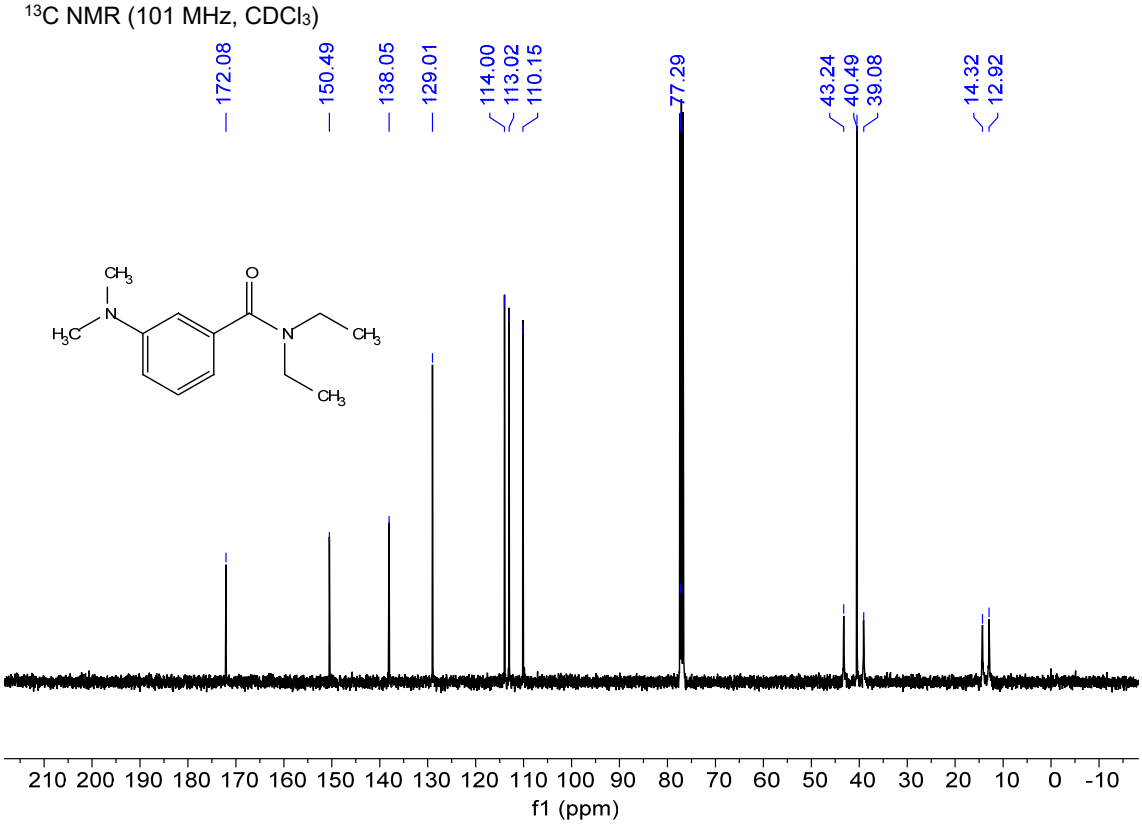
^{1}H NMR and ^{13}C NMR spectrum of **3ap**





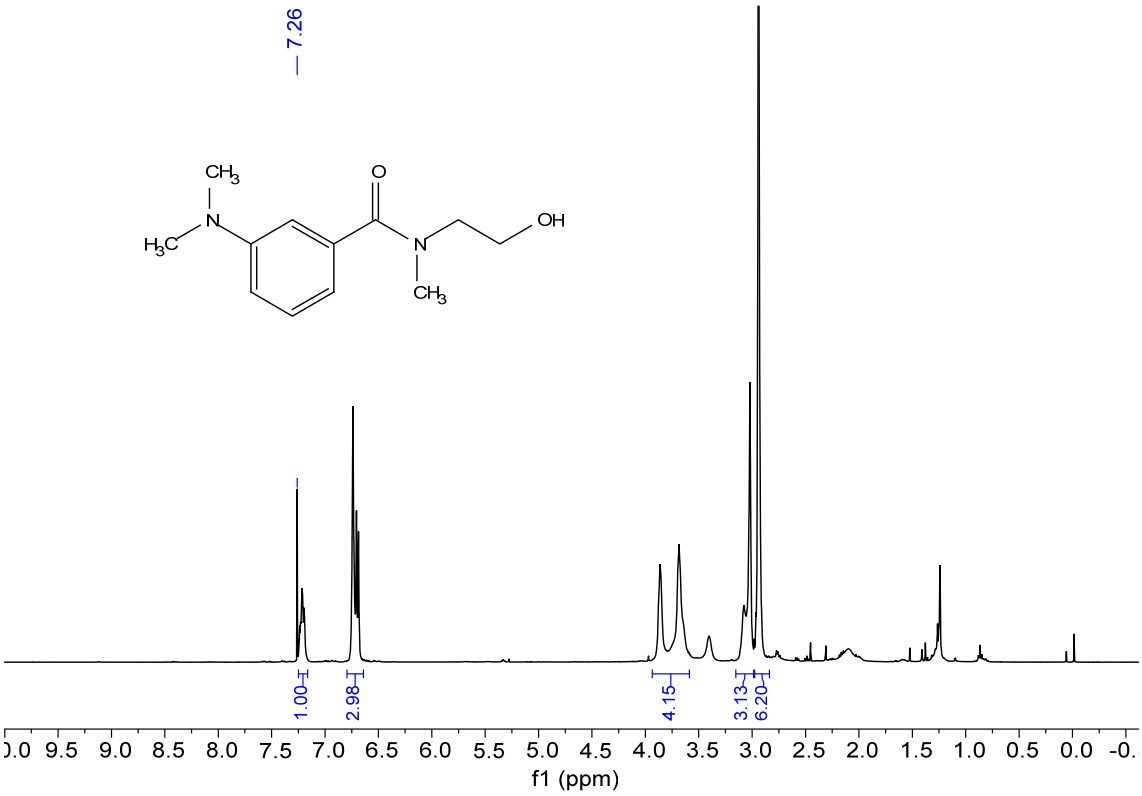
^{1}H NMR and ^{13}C NMR spectrum of **3aq**



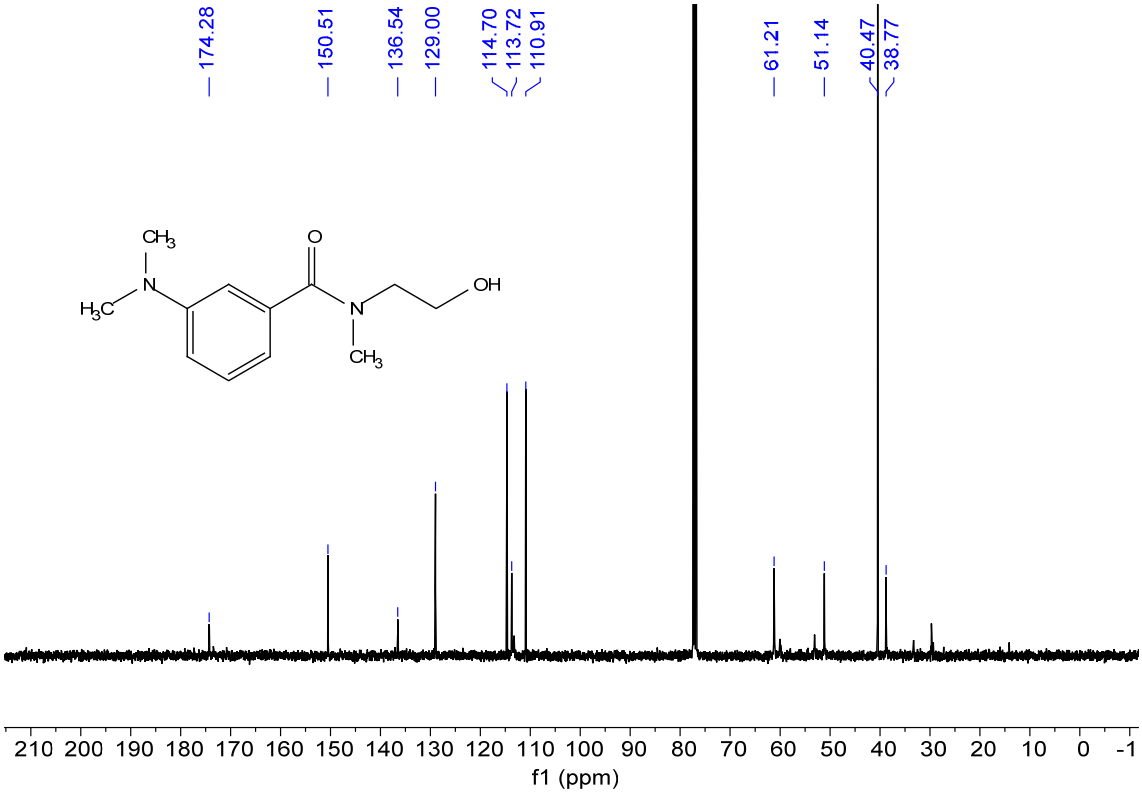


^{1}H NMR and ^{13}C NMR spectrum of **4aa**

^{1}H NMR (400 MHz, $CDCl_3$)

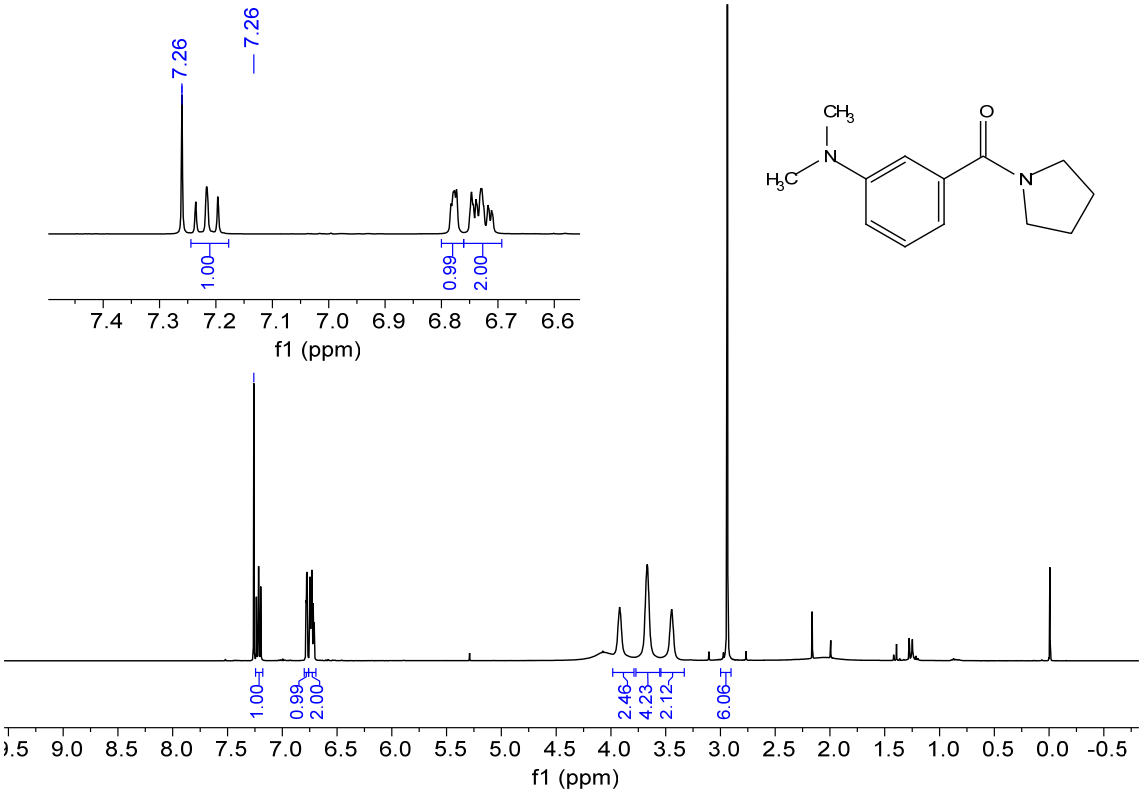


^{13}C NMR (101 MHz, $CDCl_3$)

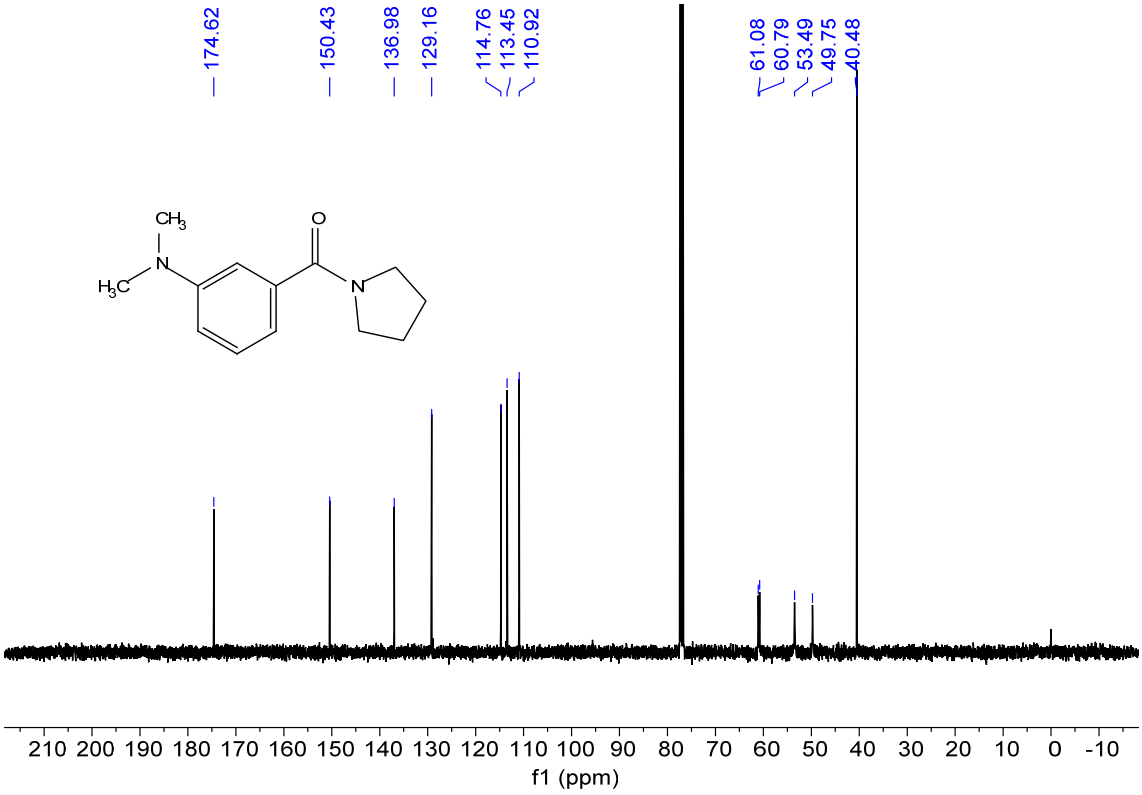


^{1}H NMR and ^{13}C NMR spectrum of **4ab**

^{1}H NMR (400 MHz, $CDCl_3$)

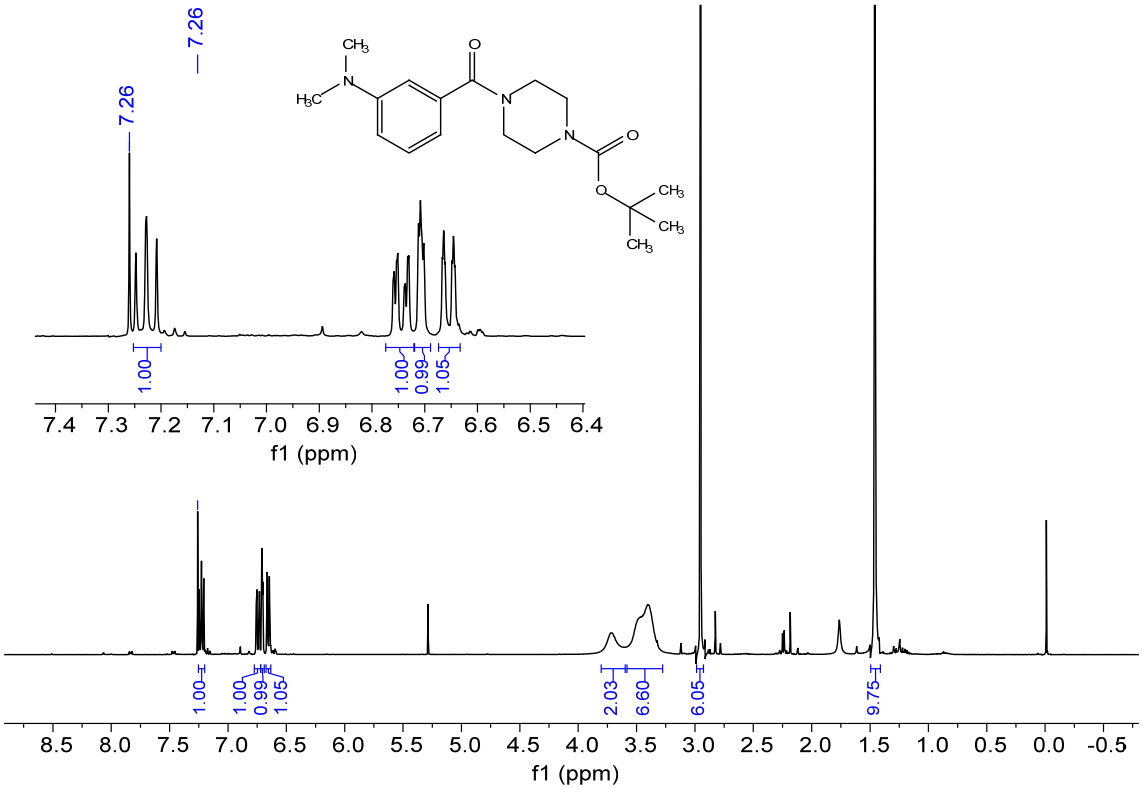


^{13}C NMR (101 MHz, $CDCl_3$)

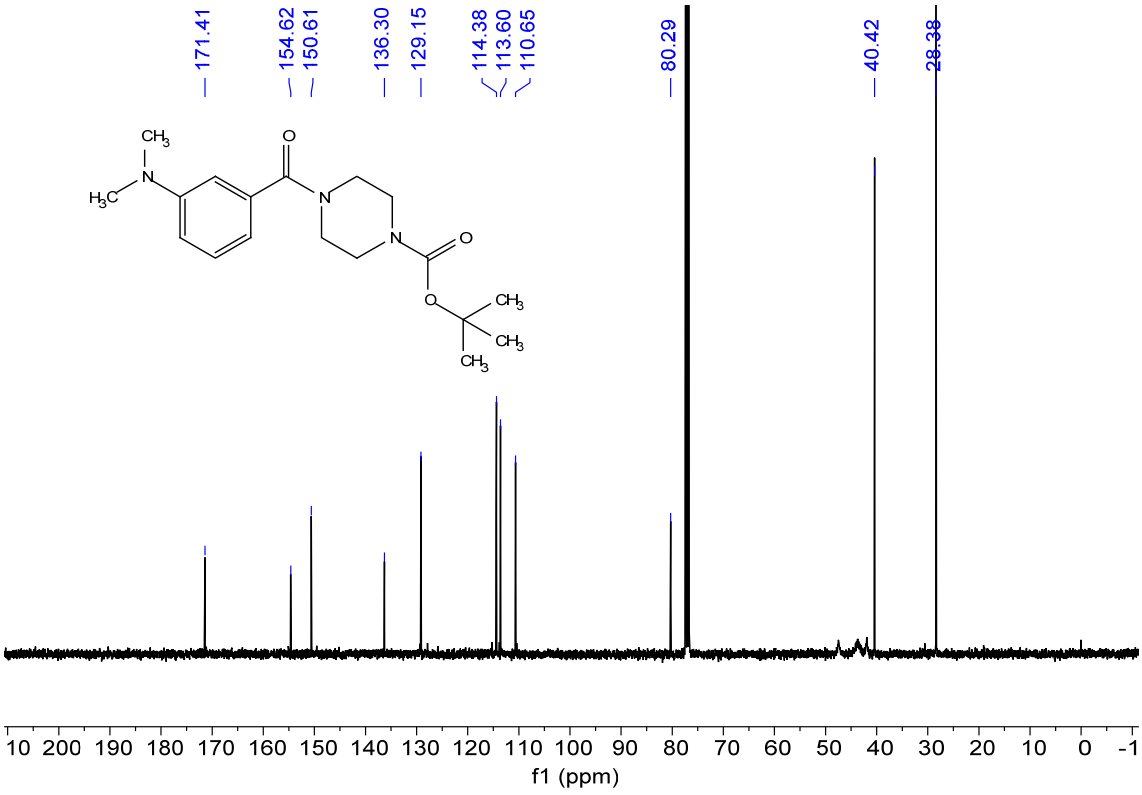


^{1}H NMR and ^{13}C NMR spectrum of **4ac**

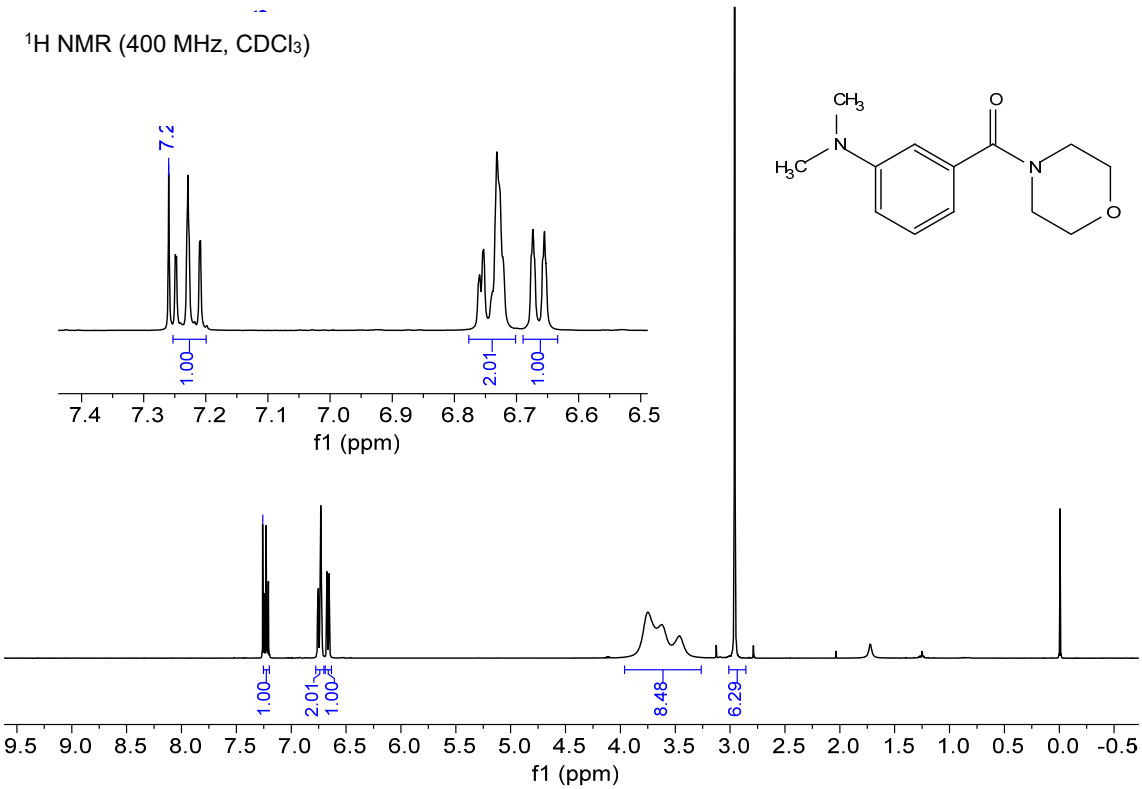
^{1}H NMR (400 MHz, $CDCl_3$)

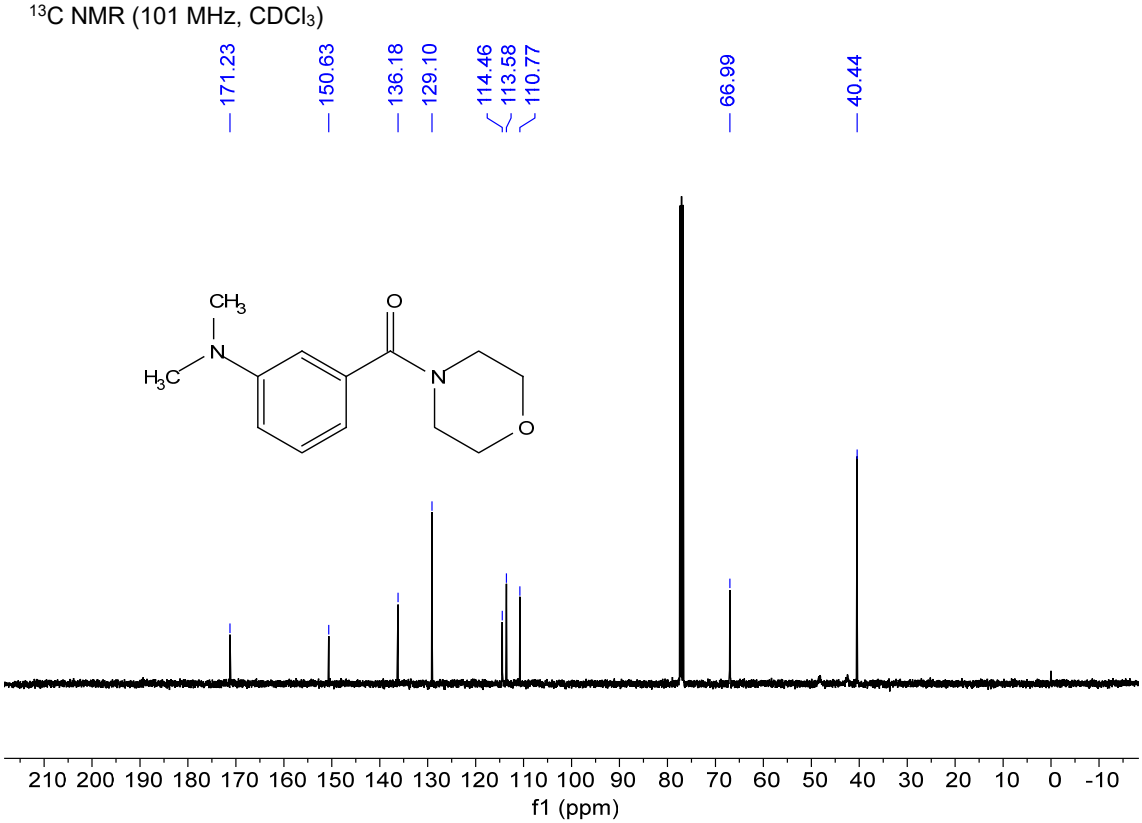


^{13}C NMR (101 MHz, $CDCl_3$)



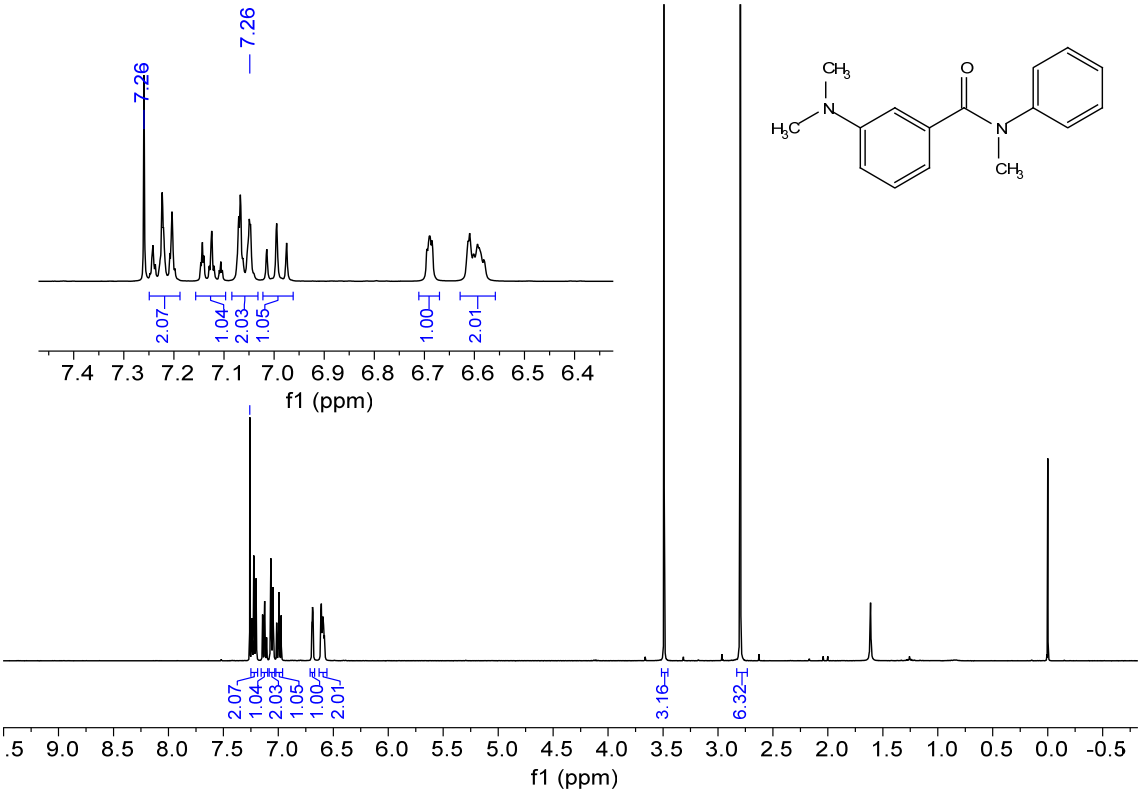
^{1}H NMR and ^{13}C NMR spectrum of **4ad**



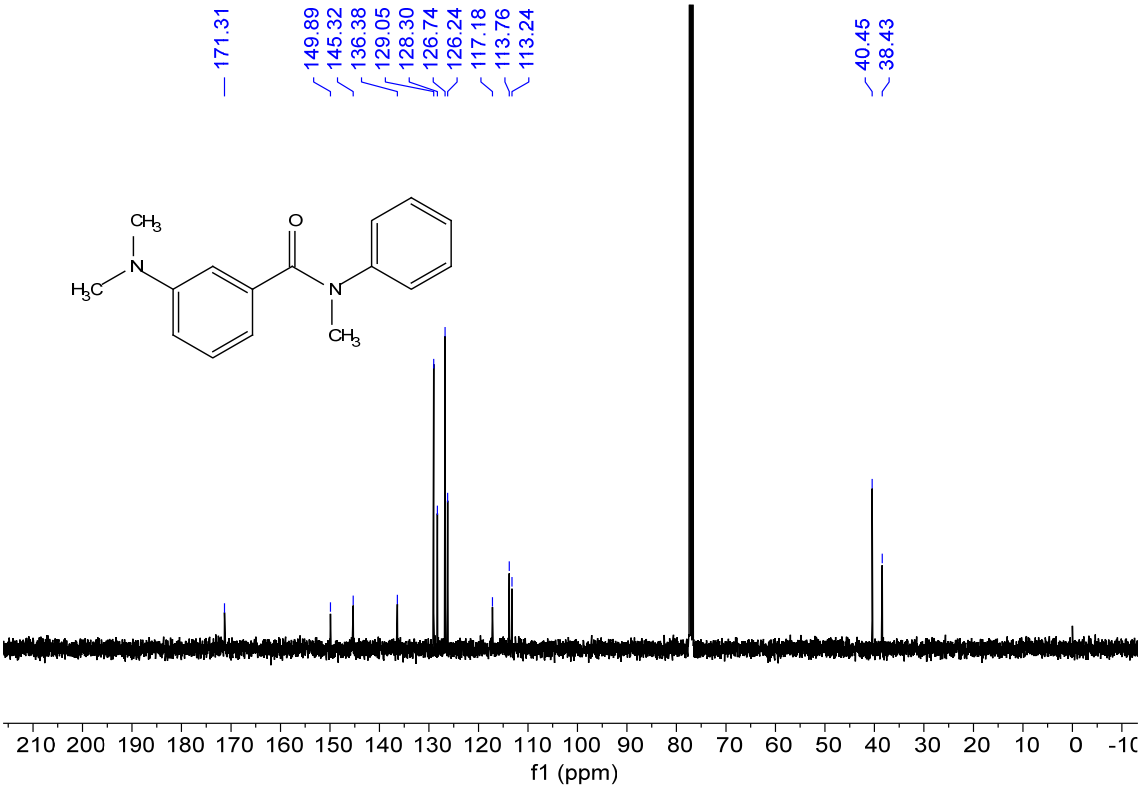


^{1}H NMR and ^{13}C NMR spectrum of **4ae**

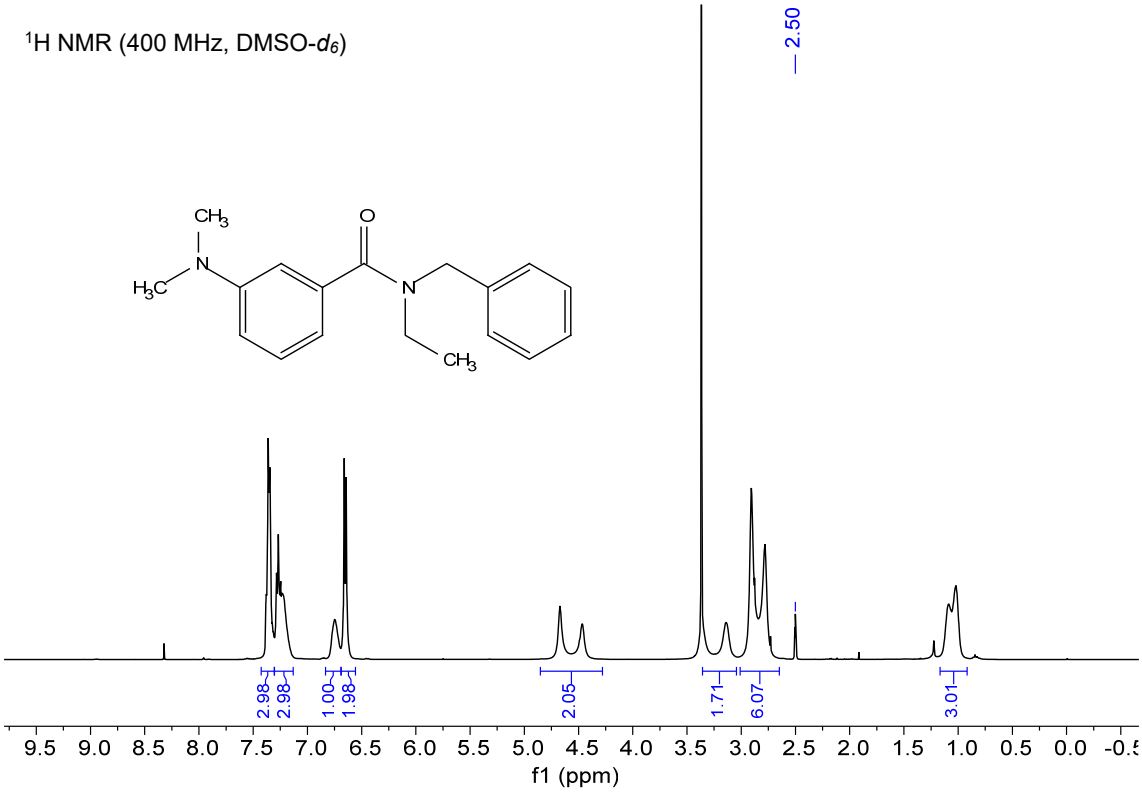
^{1}H NMR (400 MHz, $CDCl_3$)

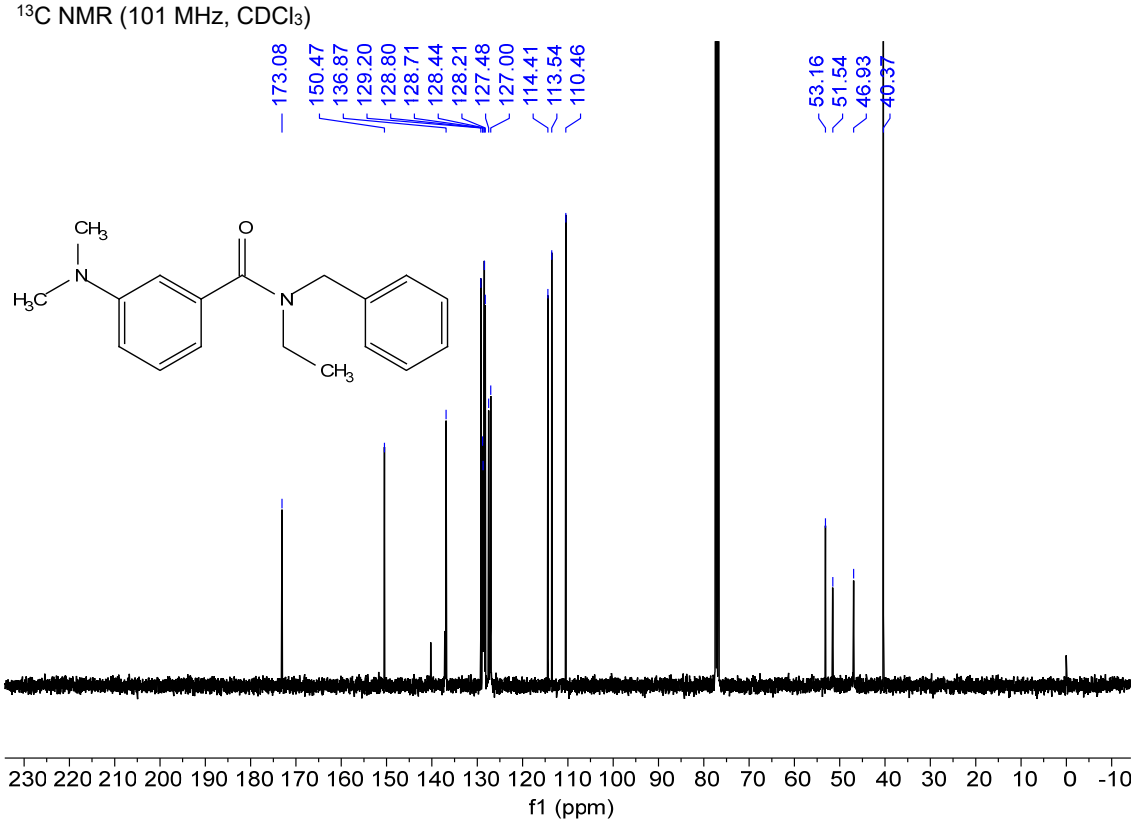


^{13}C NMR (101 MHz, $CDCl_3$)



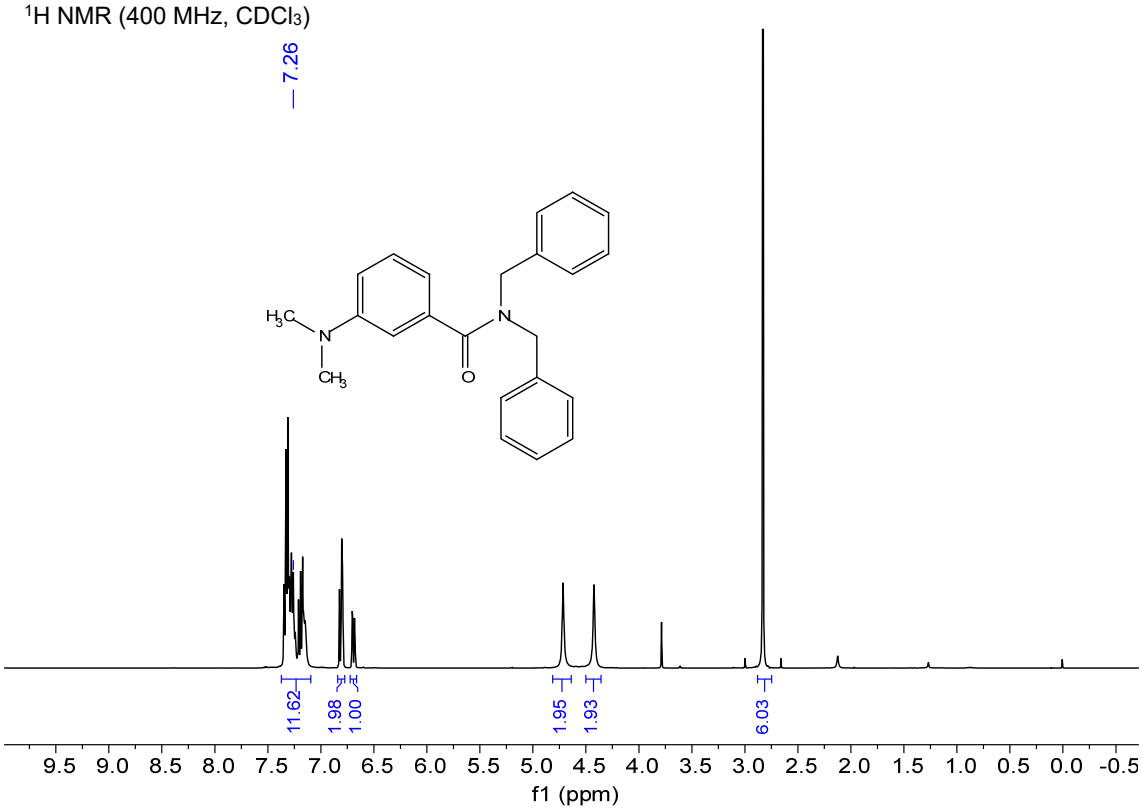
^{1}H NMR and ^{13}C NMR spectrum of **4af**



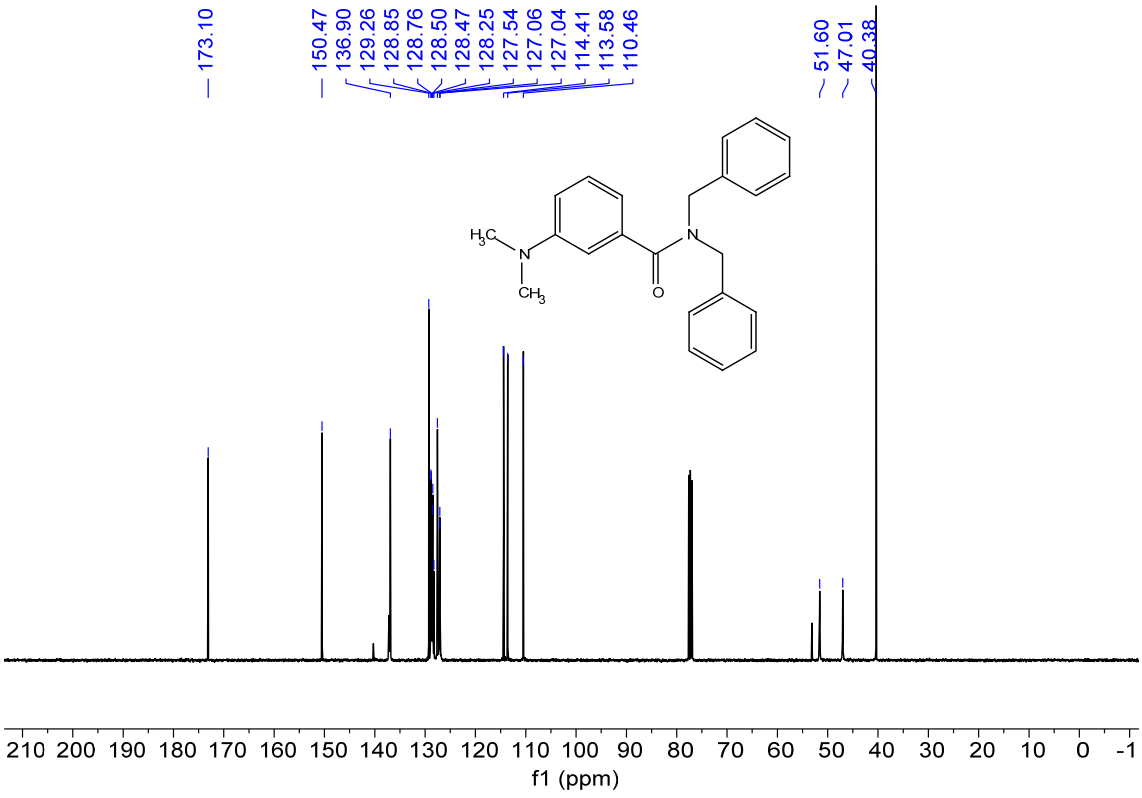


^{1}H NMR and ^{13}C NMR spectrum of **4ag**

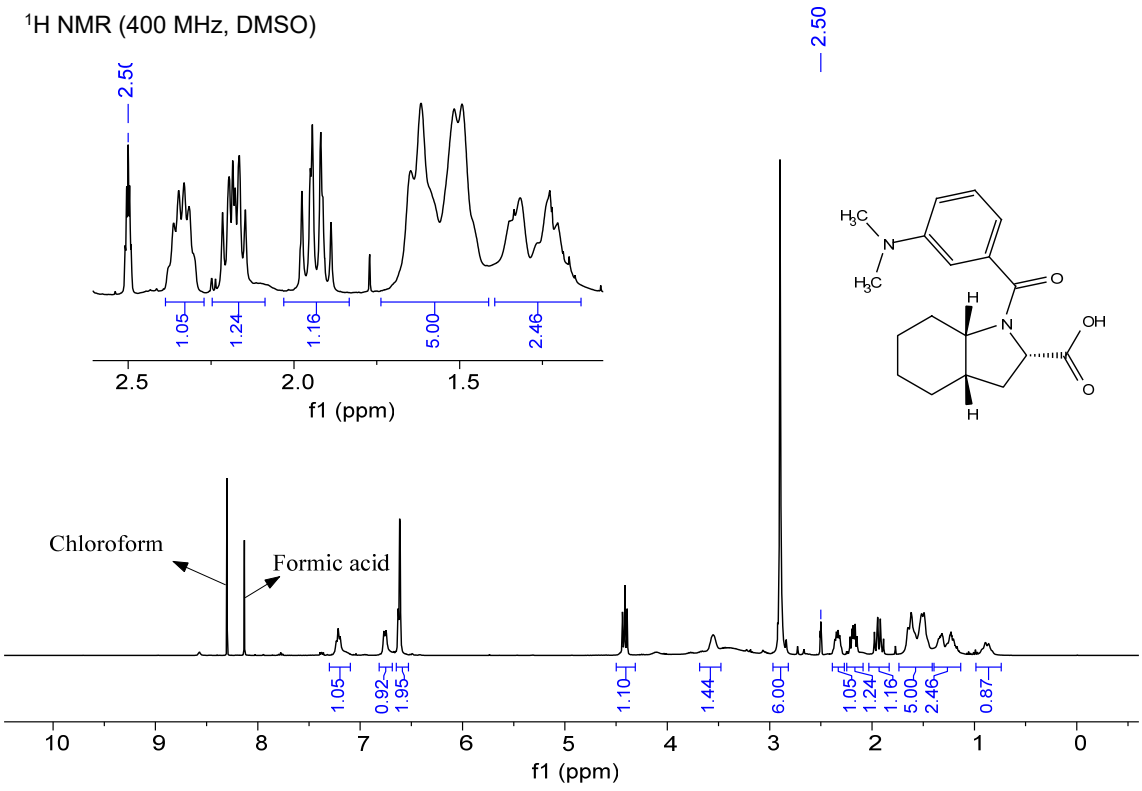
^{1}H NMR (400 MHz, $CDCl_3$)

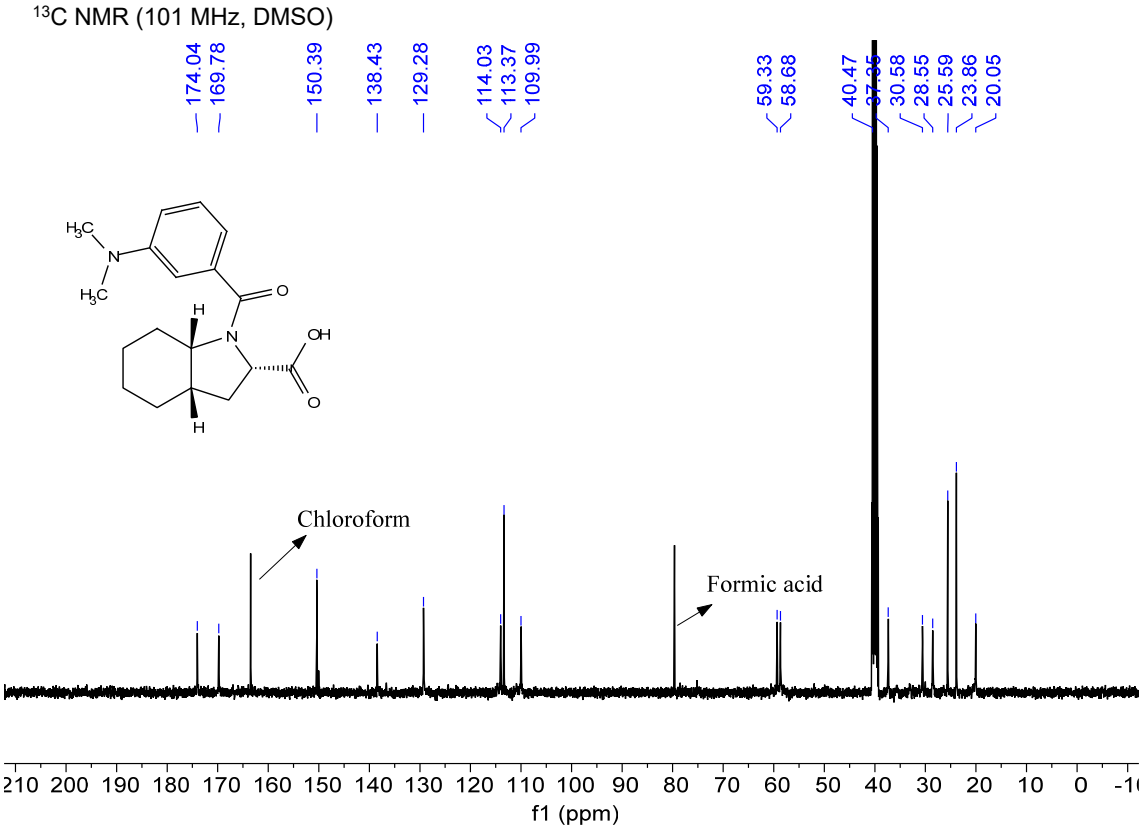


^{13}C NMR (101 MHz, $CDCl_3$)

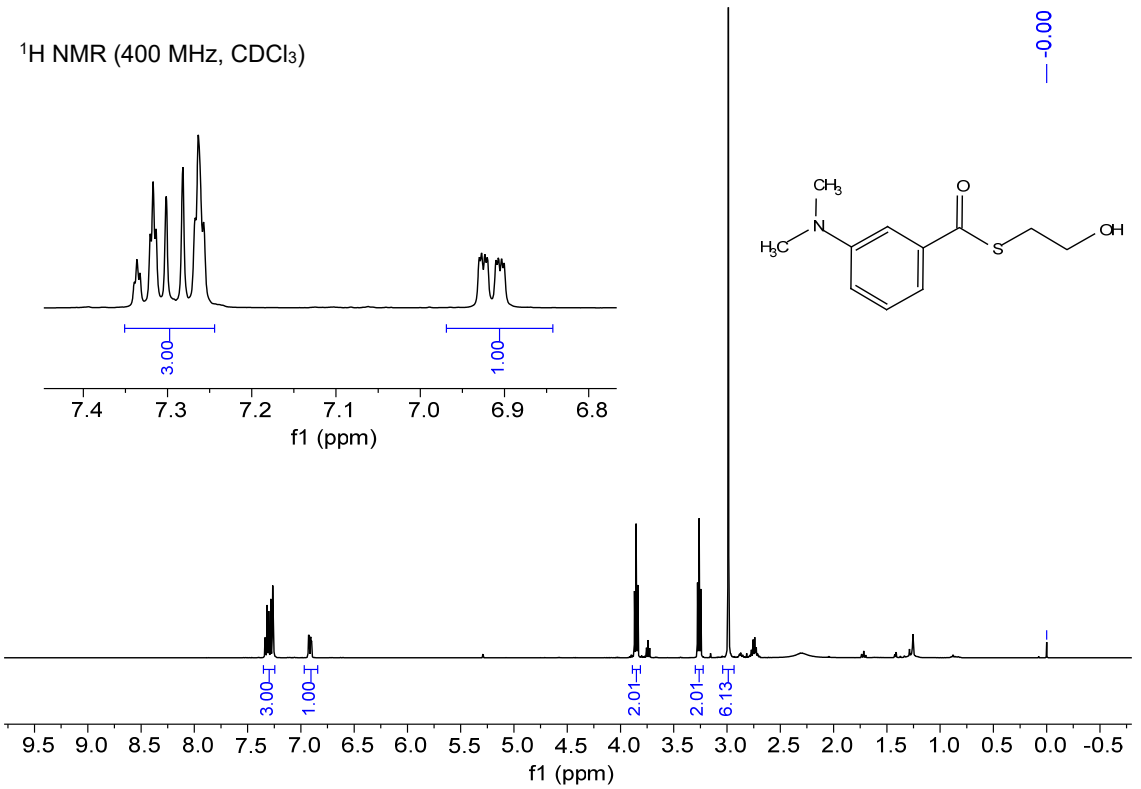


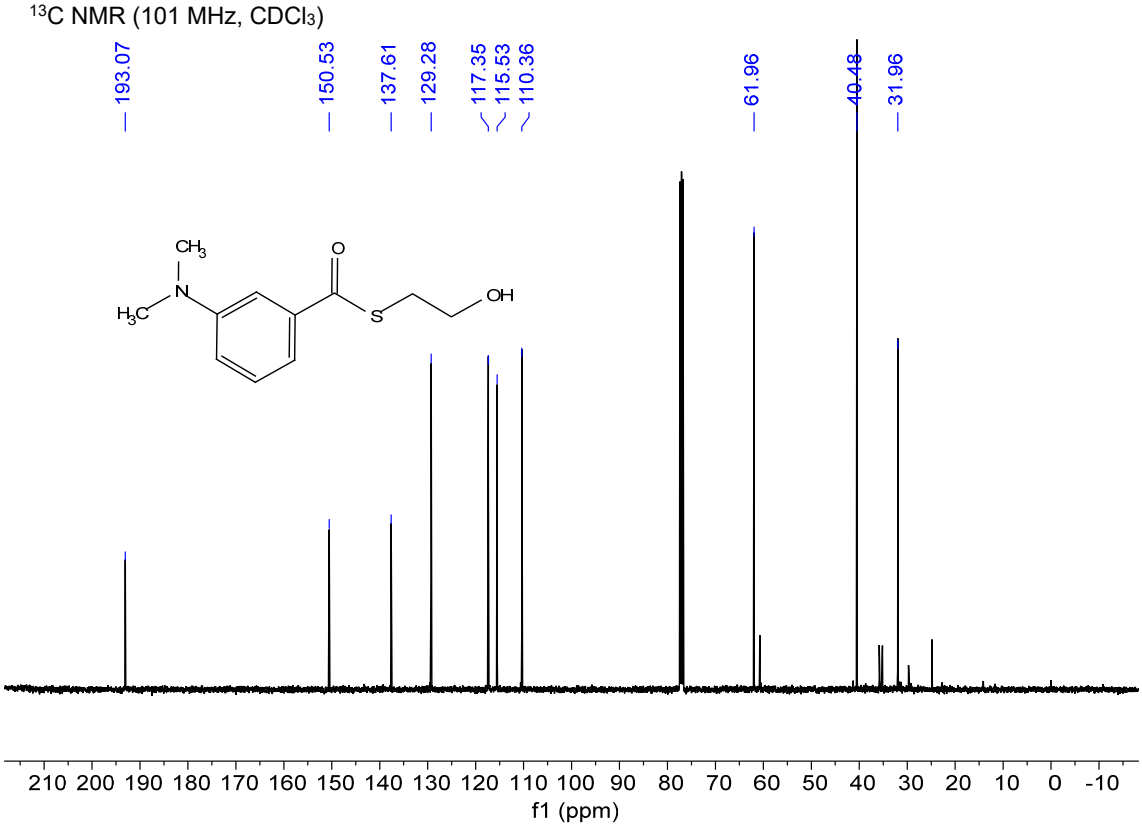
^{1}H NMR and ^{13}C NMR spectrum of **4ah**



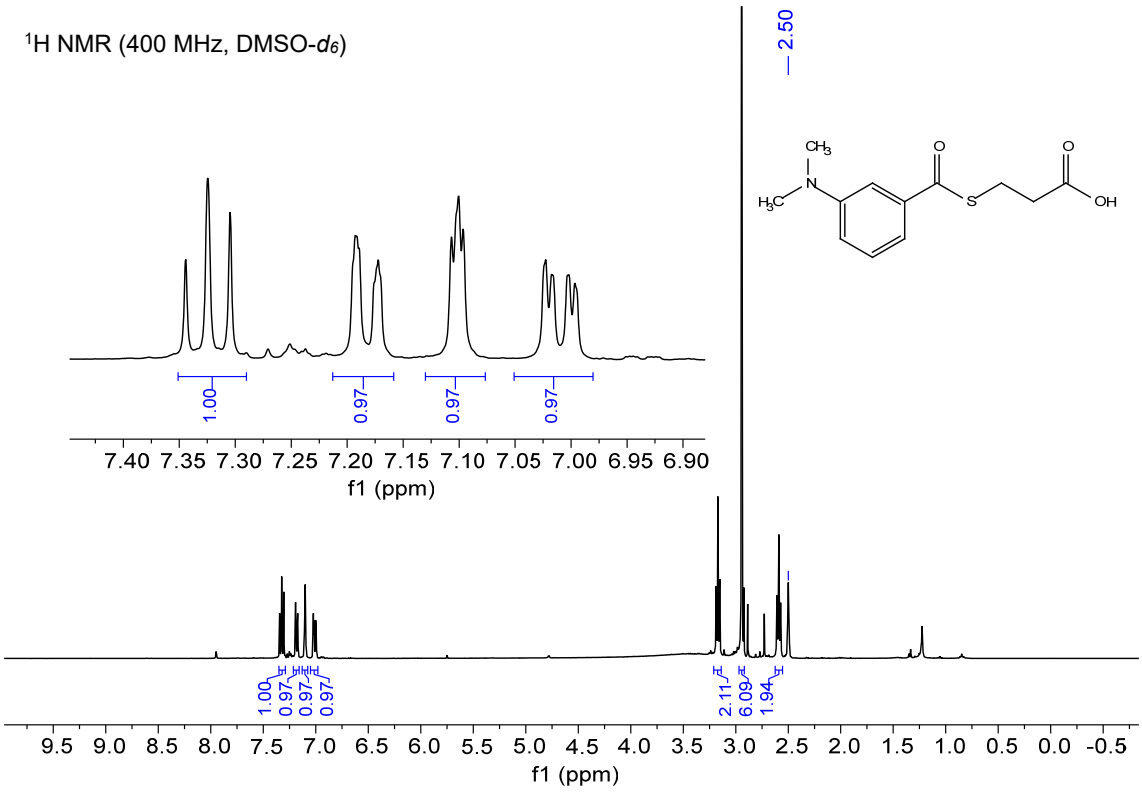


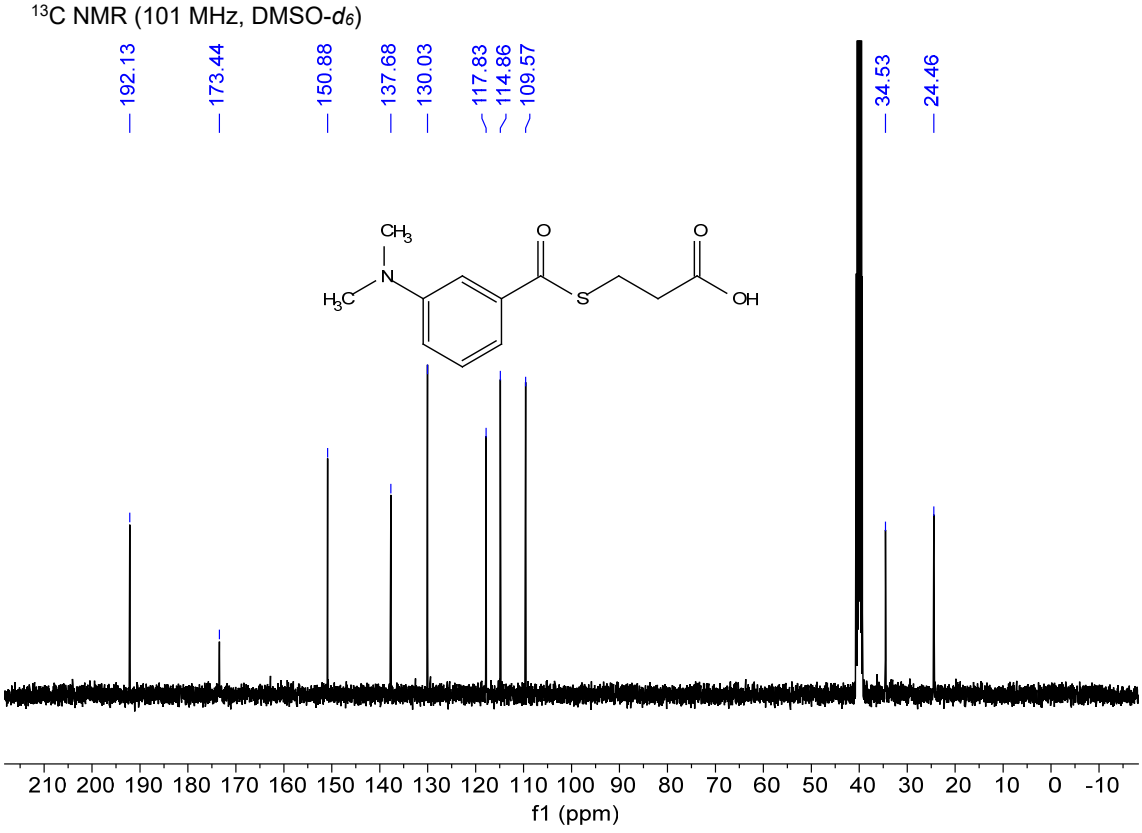
^{1}H NMR and ^{13}C NMR spectrum of **4ai**





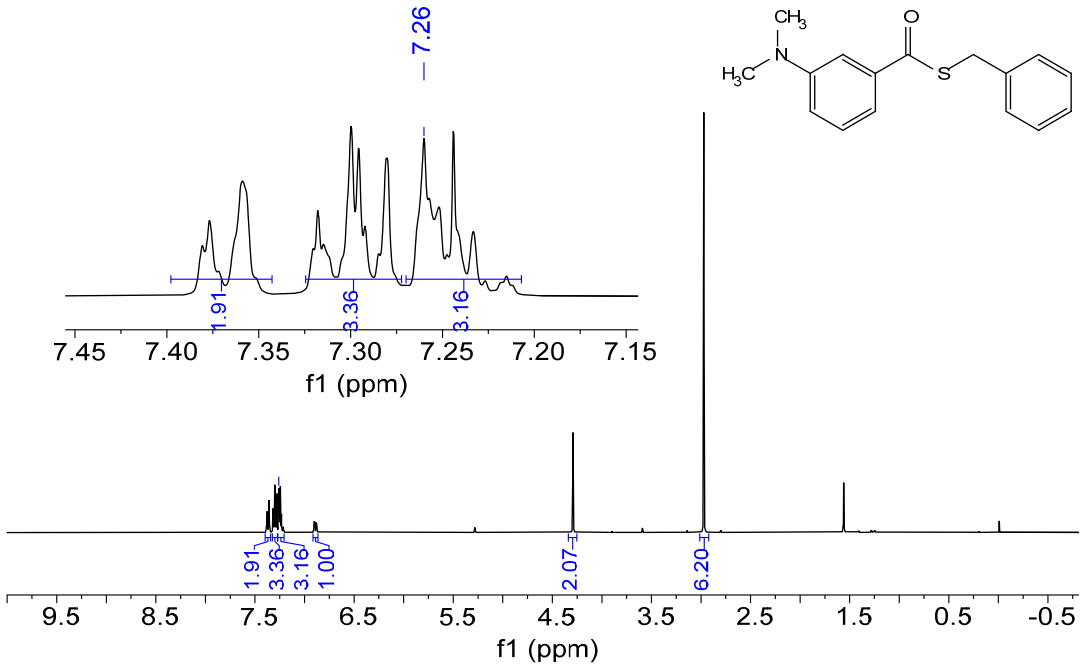
^{1}H NMR and ^{13}C NMR spectrum of **5aa**



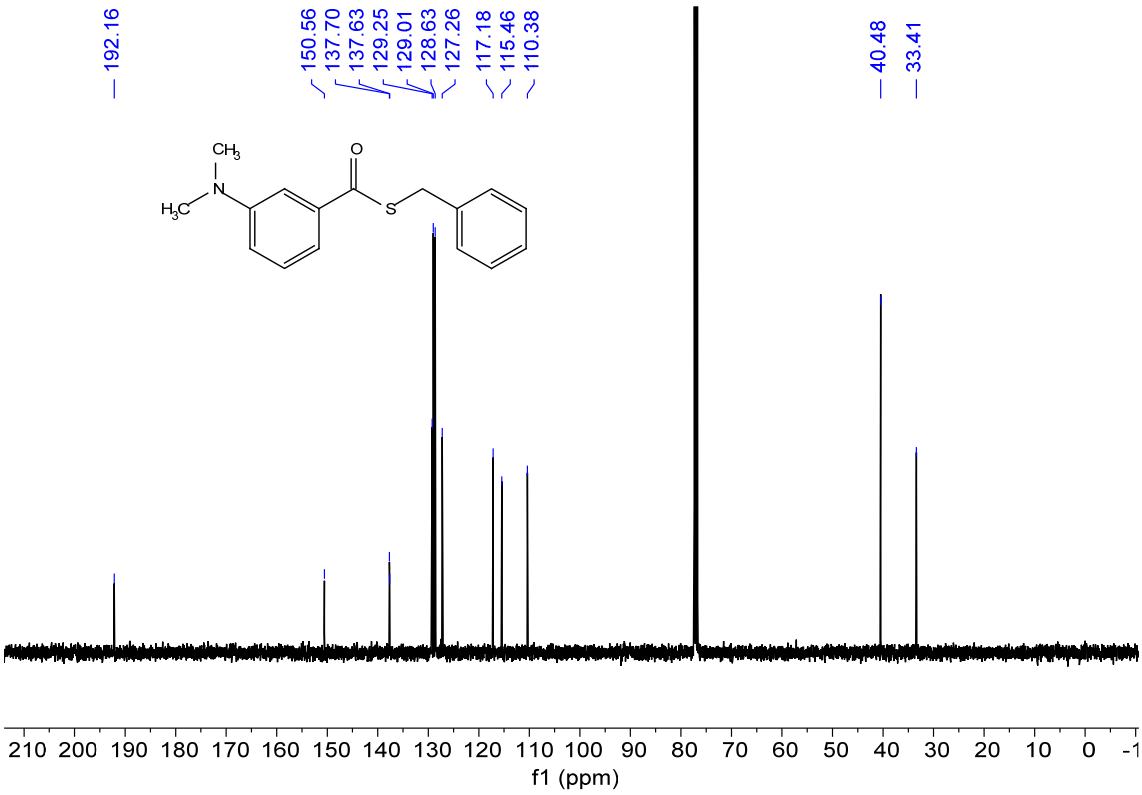


^{1}H NMR and ^{13}C NMR spectrum of **5ab**

^{1}H NMR (400 MHz, $CDCl_3$)

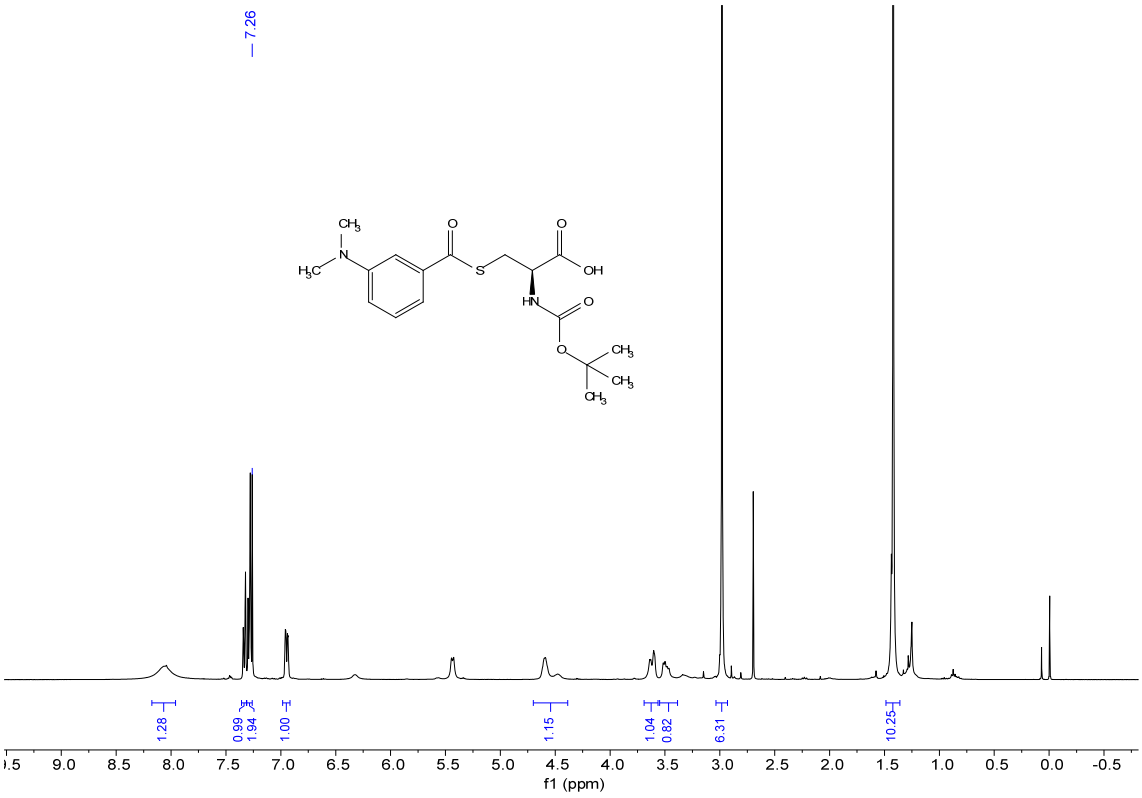


^{13}C NMR (101 MHz, $CDCl_3$)

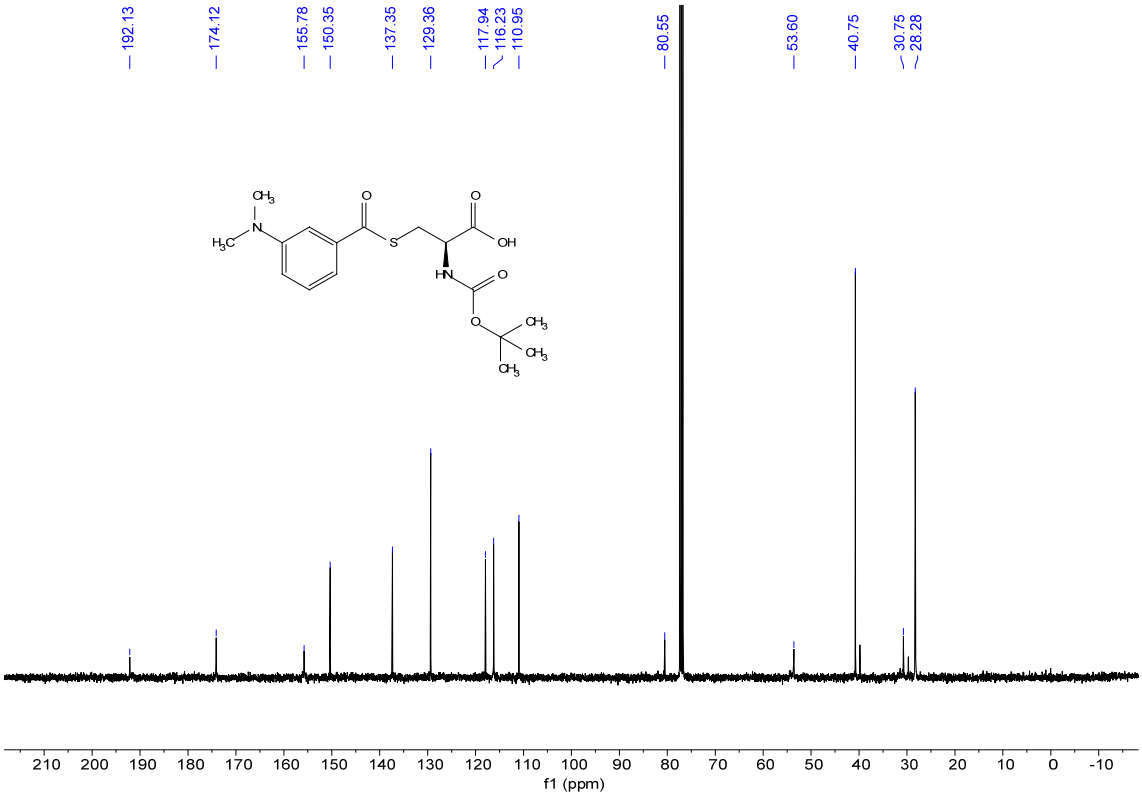


^{1}H NMR and ^{13}C NMR spectrum of **5ac**

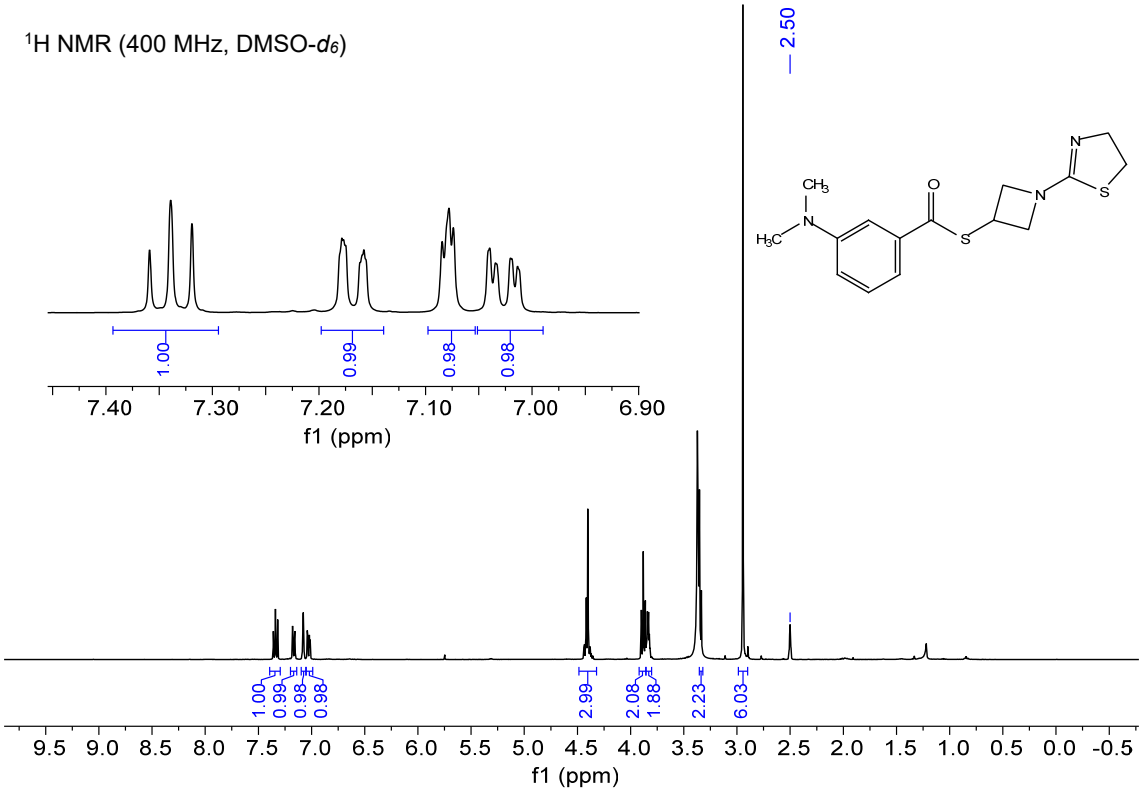
^{1}H NMR (400 MHz, $CDCl_3$)

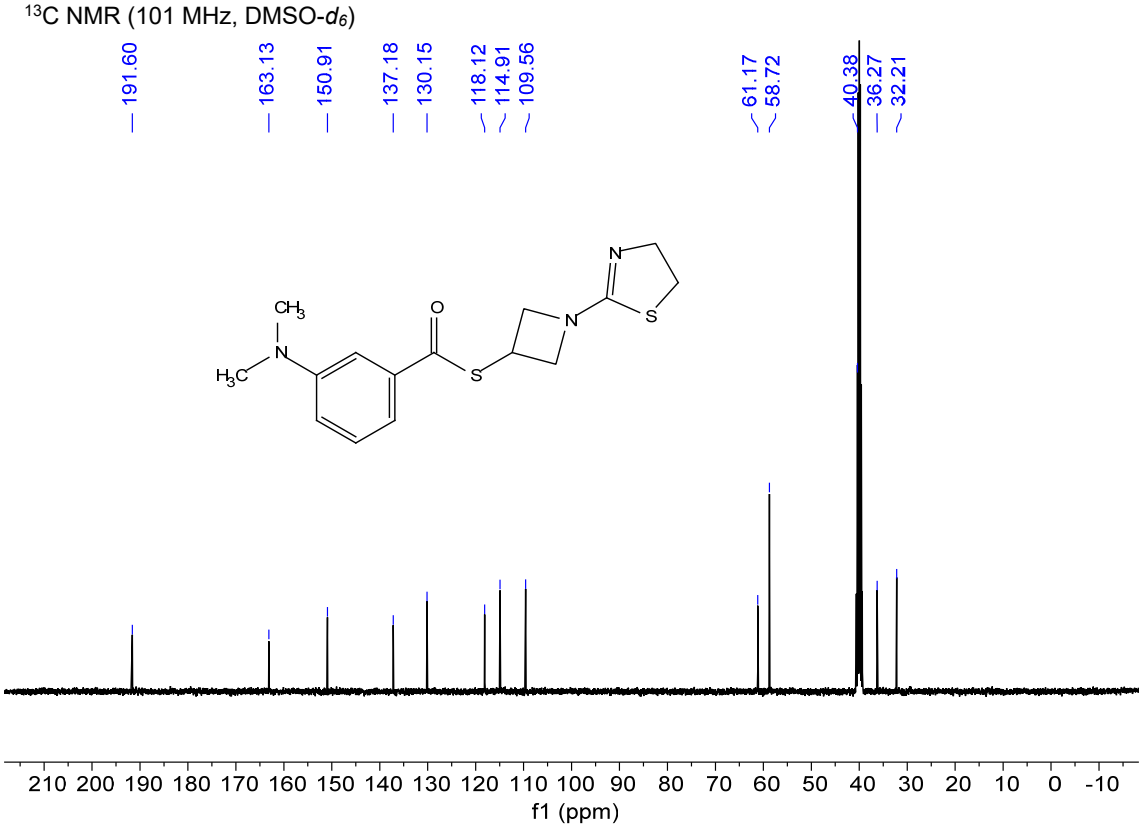


^{13}C NMR (101 MHz, $CDCl_3$)



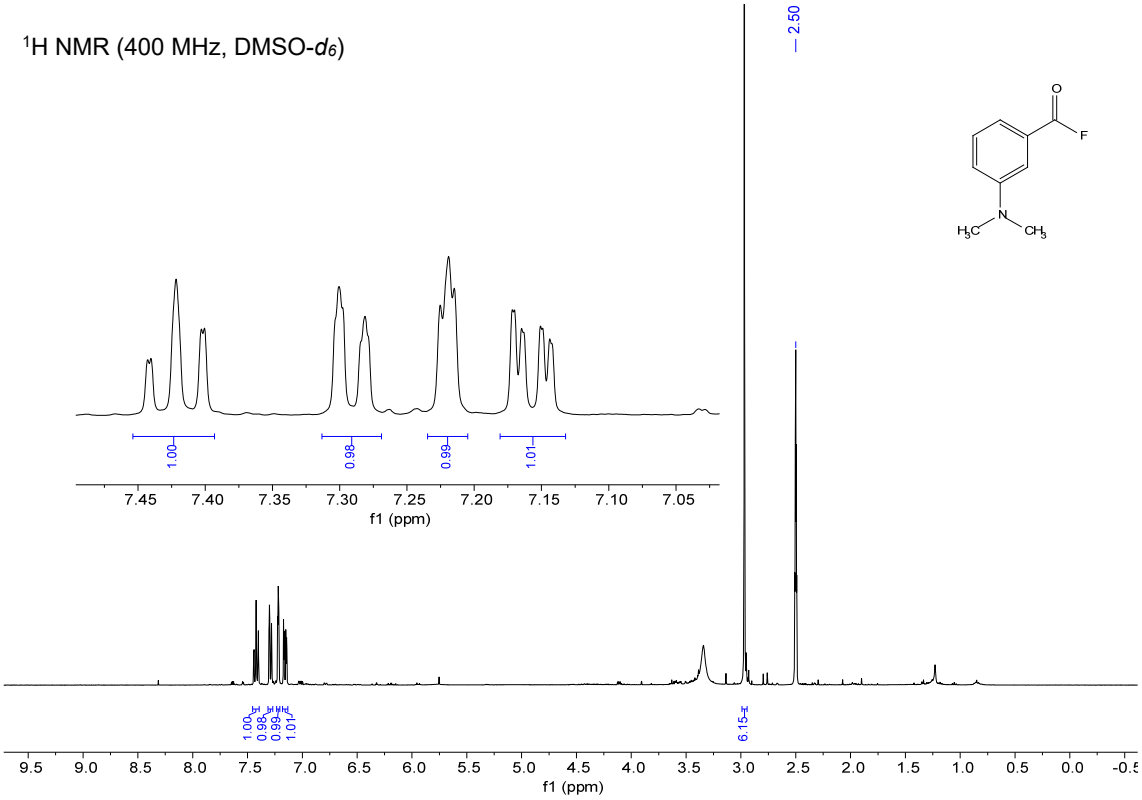
^{1}H NMR and ^{13}C NMR spectrum of **5ad**





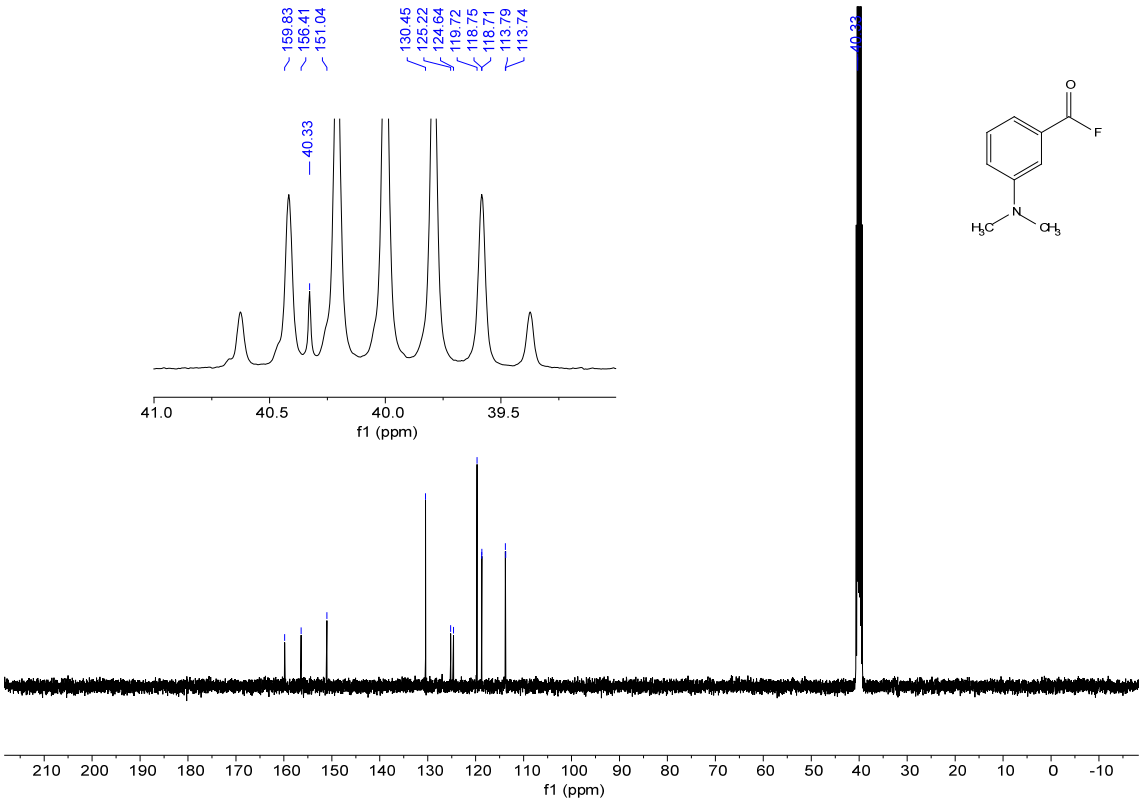
^{1}H NMR and ^{13}C NMR spectrum of **5ae**

^{1}H NMR (400 MHz, DMSO-d_6)

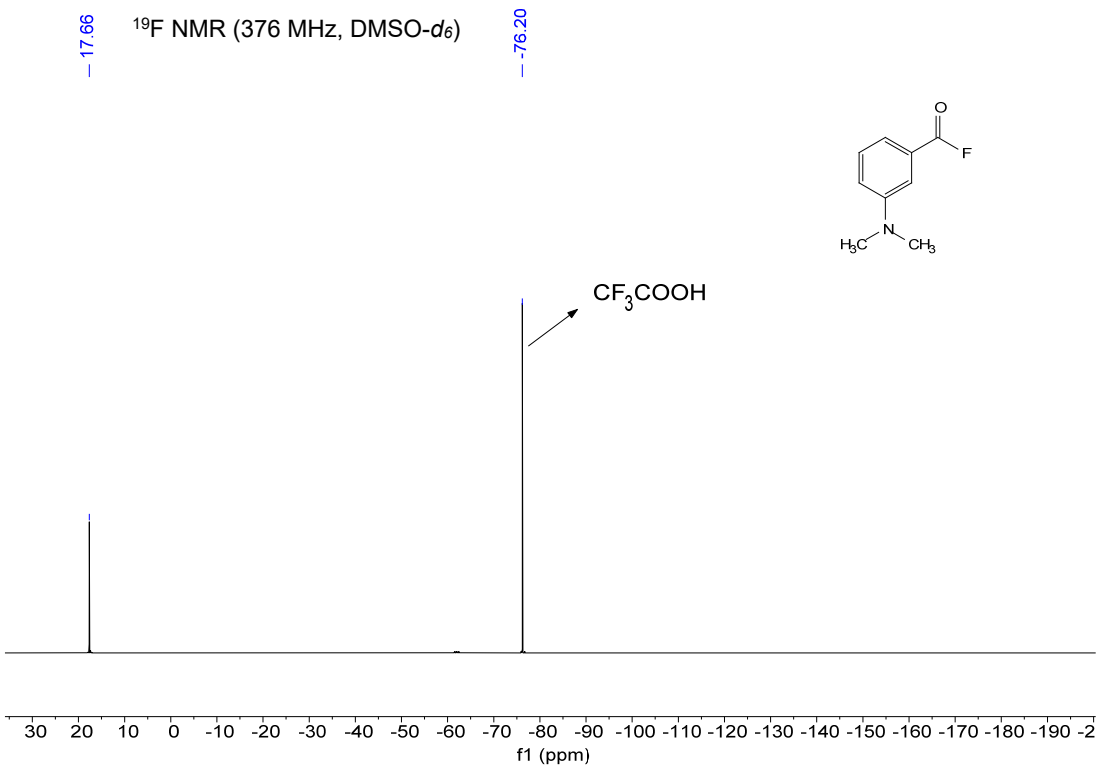


^{1}H NMR spectrum of **5a**

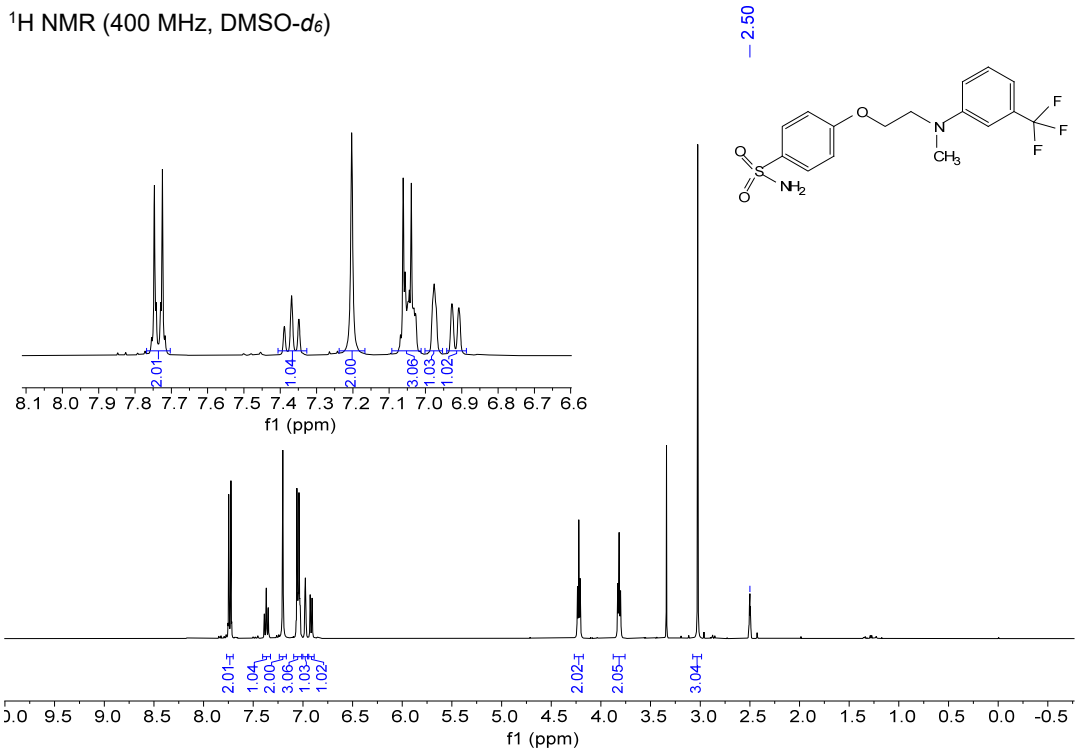
^{13}C NMR (101 MHz, DMSO-d_6)



^{13}C NMR spectrum of **5a**

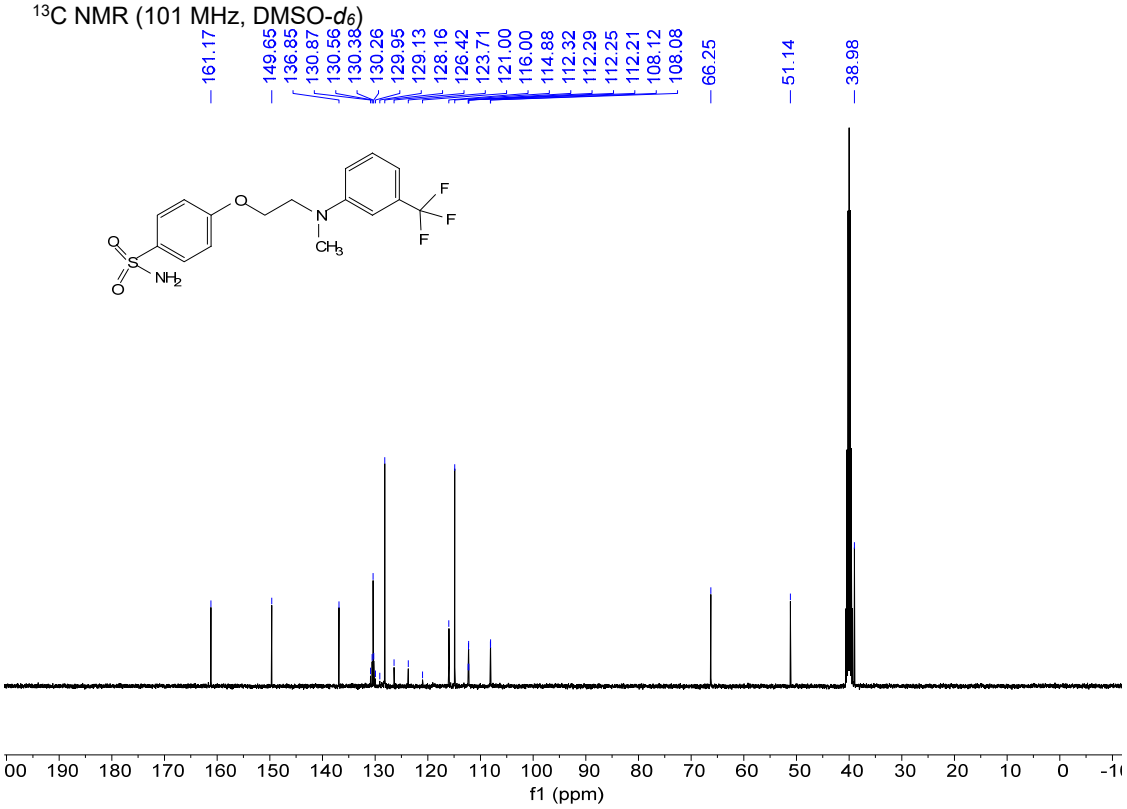


^{19}F NMR spectrum of **5a**



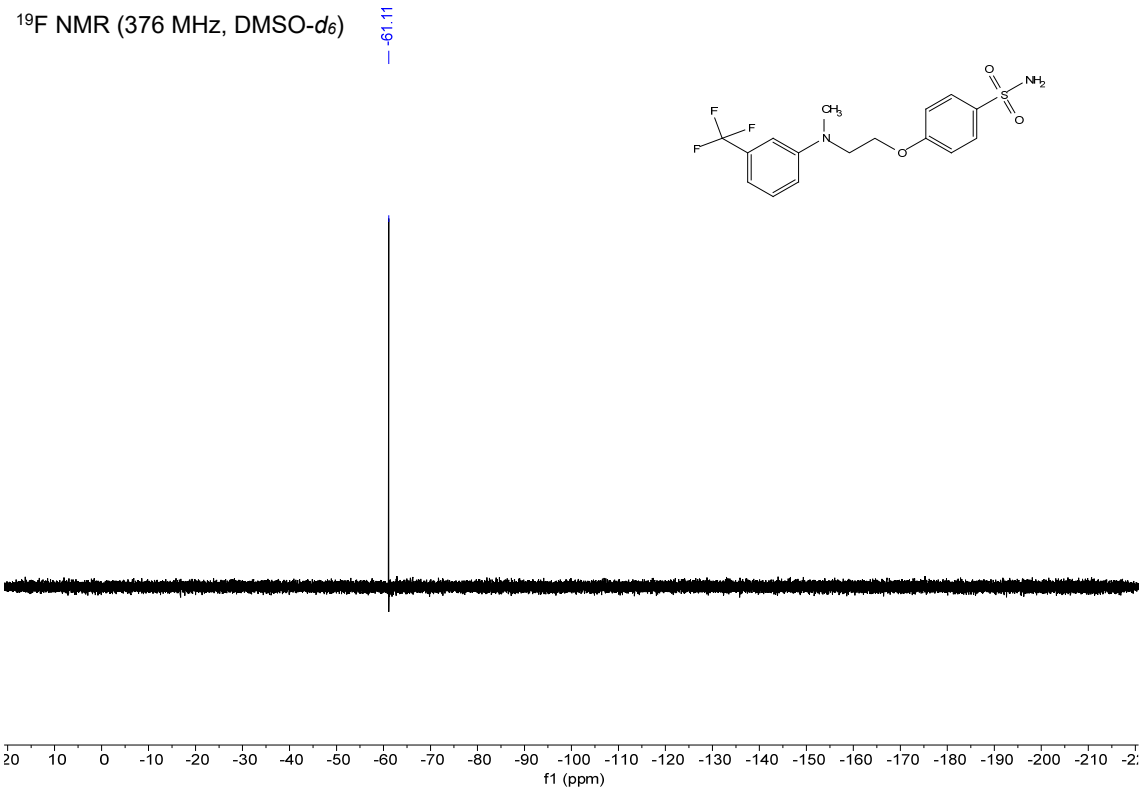
^{1}H NMR spectrum of **10a**

^{13}C NMR (101 MHz, DMSO-*d*$_6$)

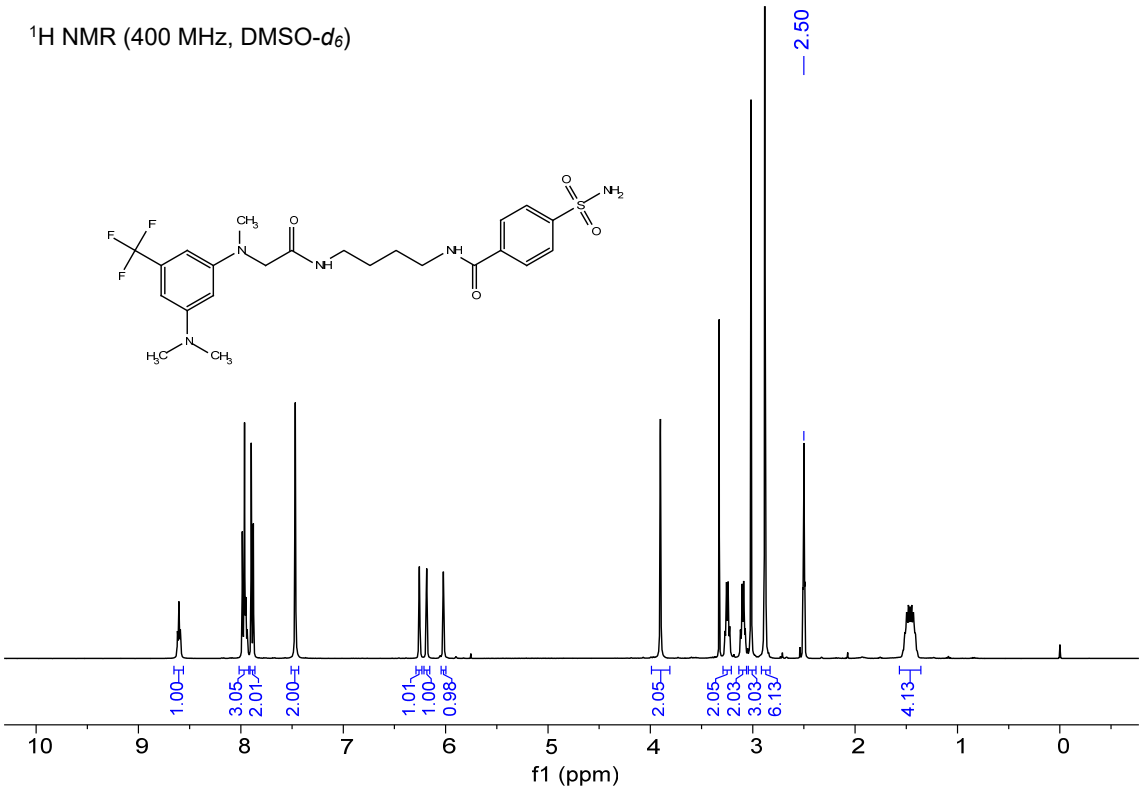


^{13}C NMR spectrum of **10a**

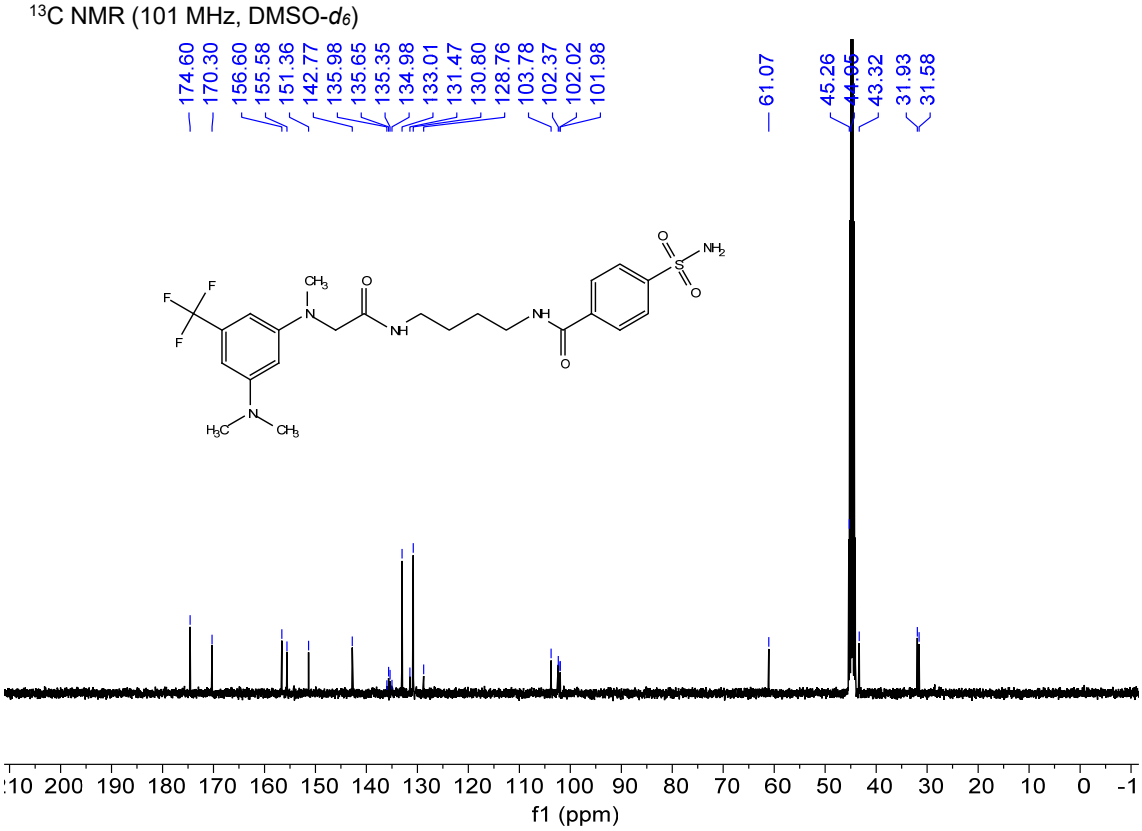
^{19}F NMR (376 MHz, DMSO-*d*$_6$)



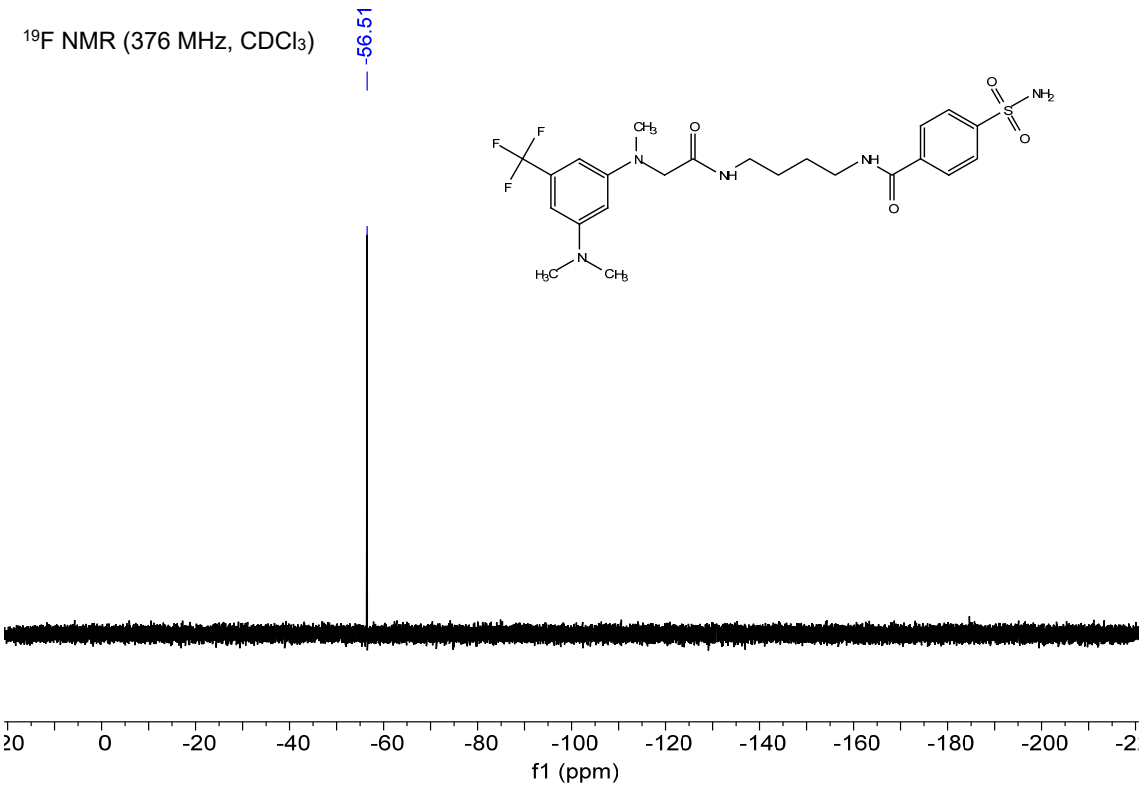
^{19}F NMR spectrum of **10a**



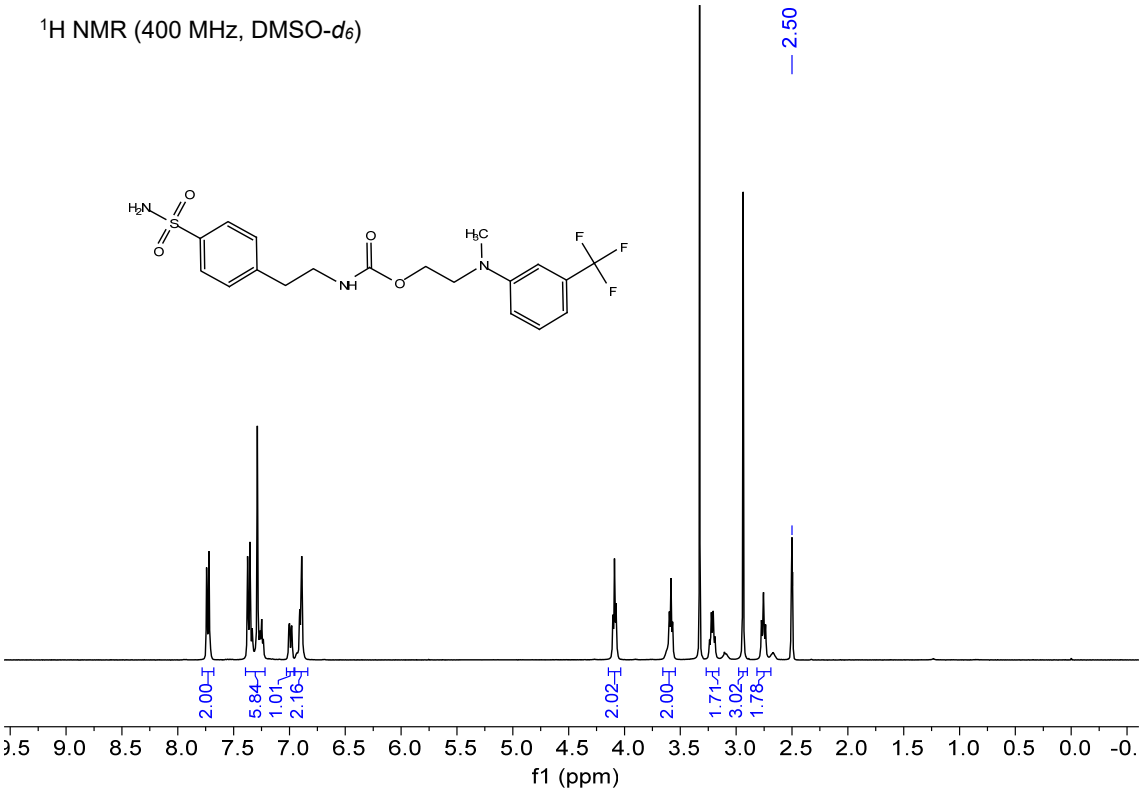
^{1}H NMR spectrum of **10b**



^{13}C NMR spectrum of **10b**

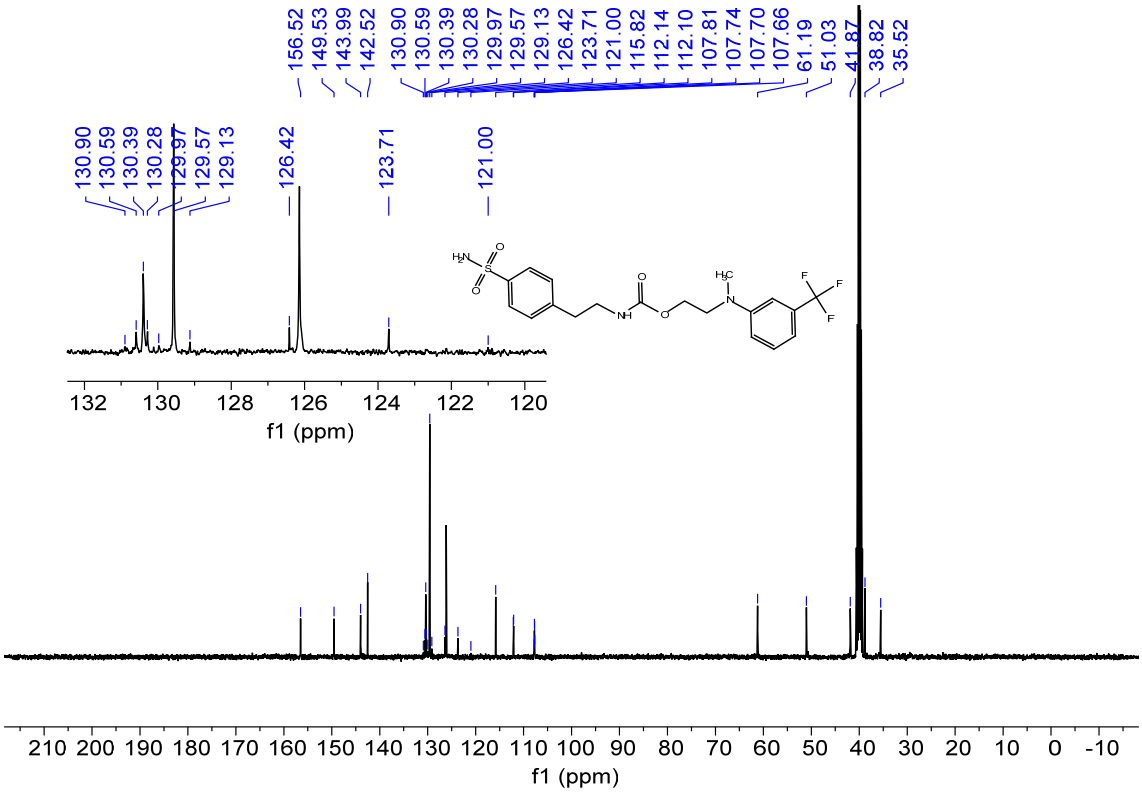


^{19}F NMR spectrum of **10b**



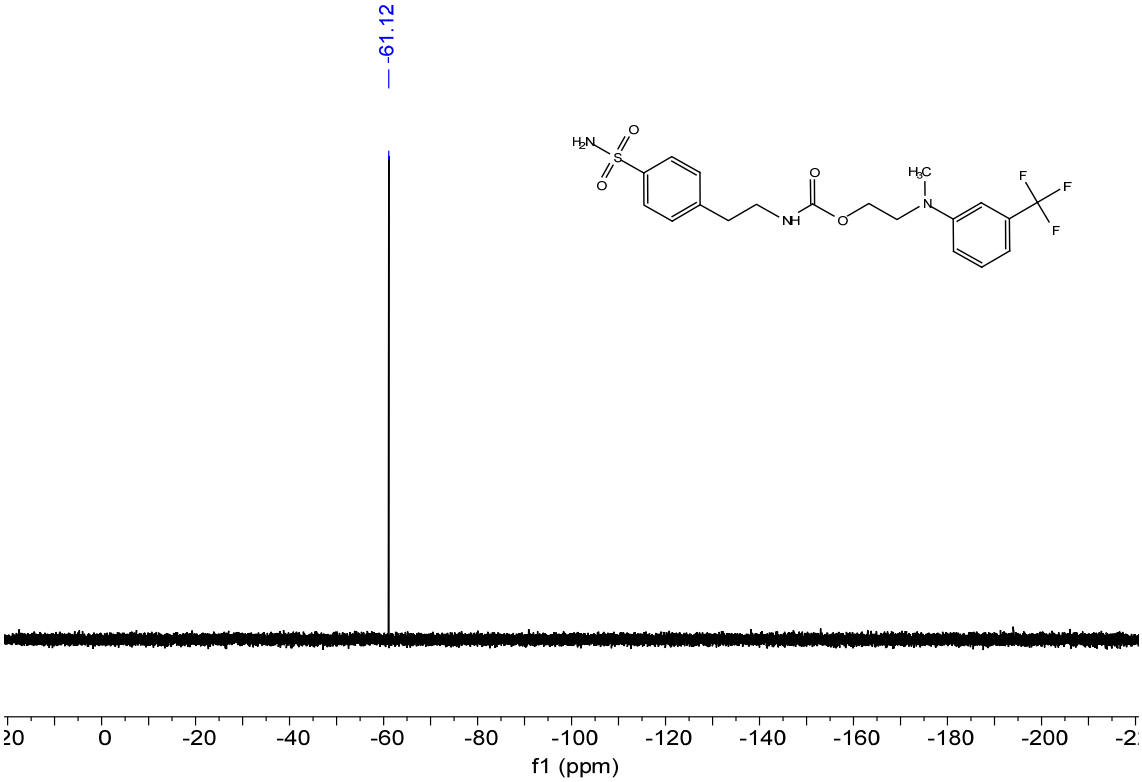
^{1}H NMR spectrum of **10c**

^{13}C NMR (101 MHz, DMSO-d_6)

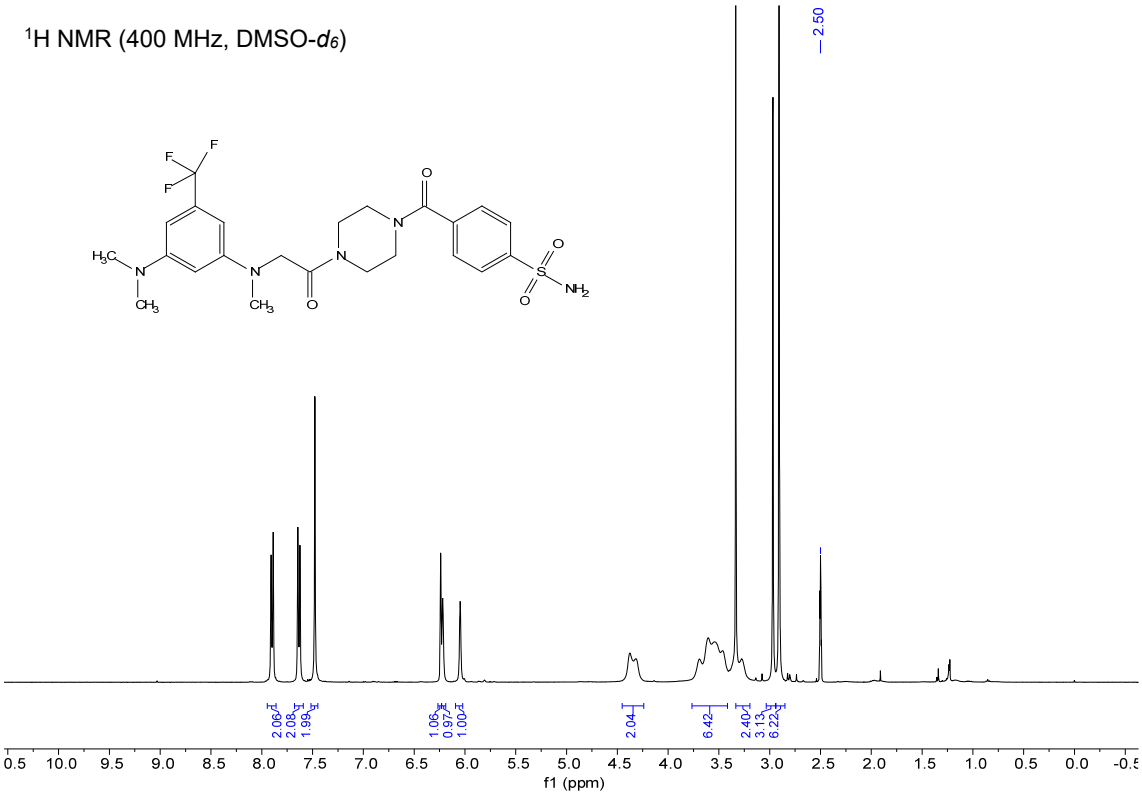


^{13}C NMR spectrum of **10c**

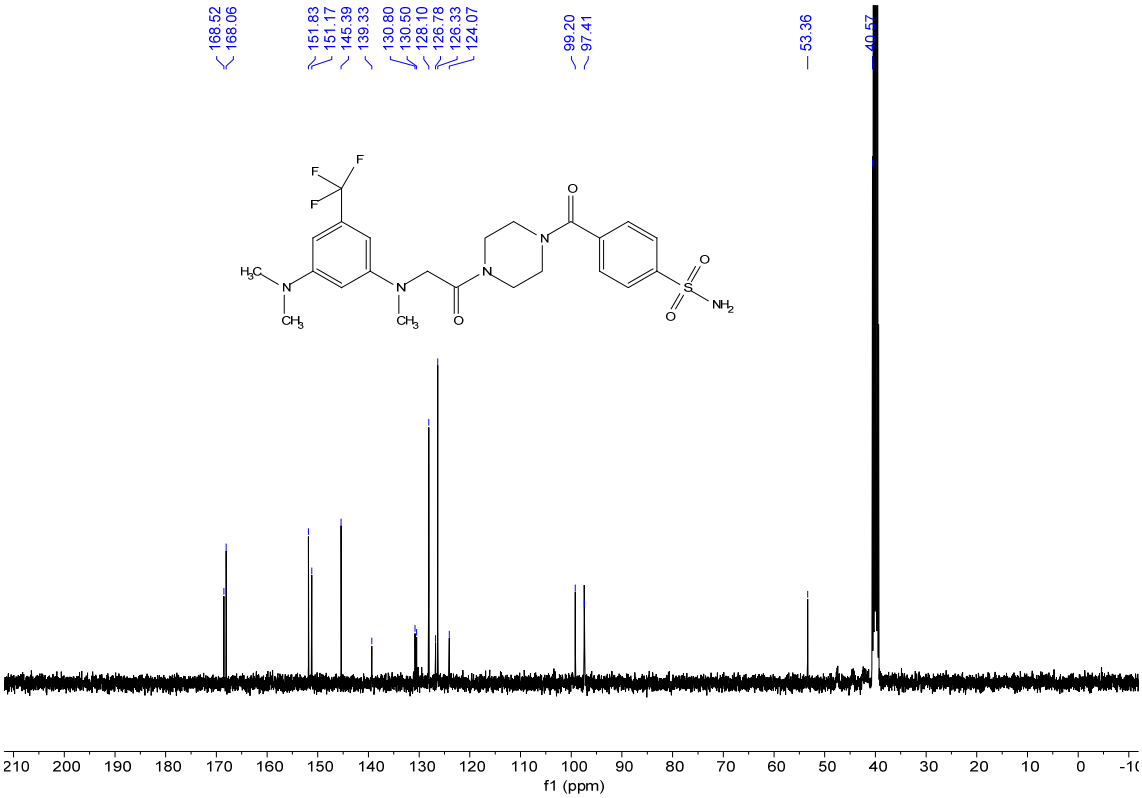
^{19}F NMR (376 MHz, DMSO-d_6)



^{19}F NMR spectrum of **10c**

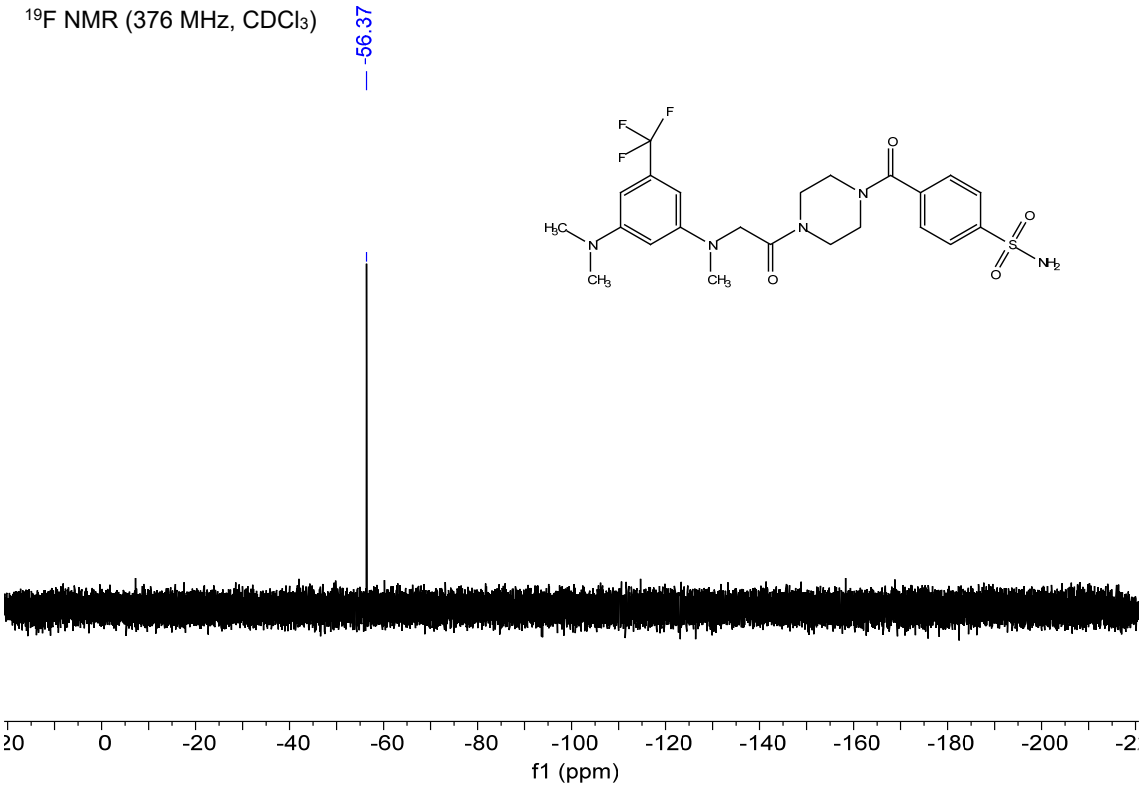


^{1}H NMR spectrum of **10d**



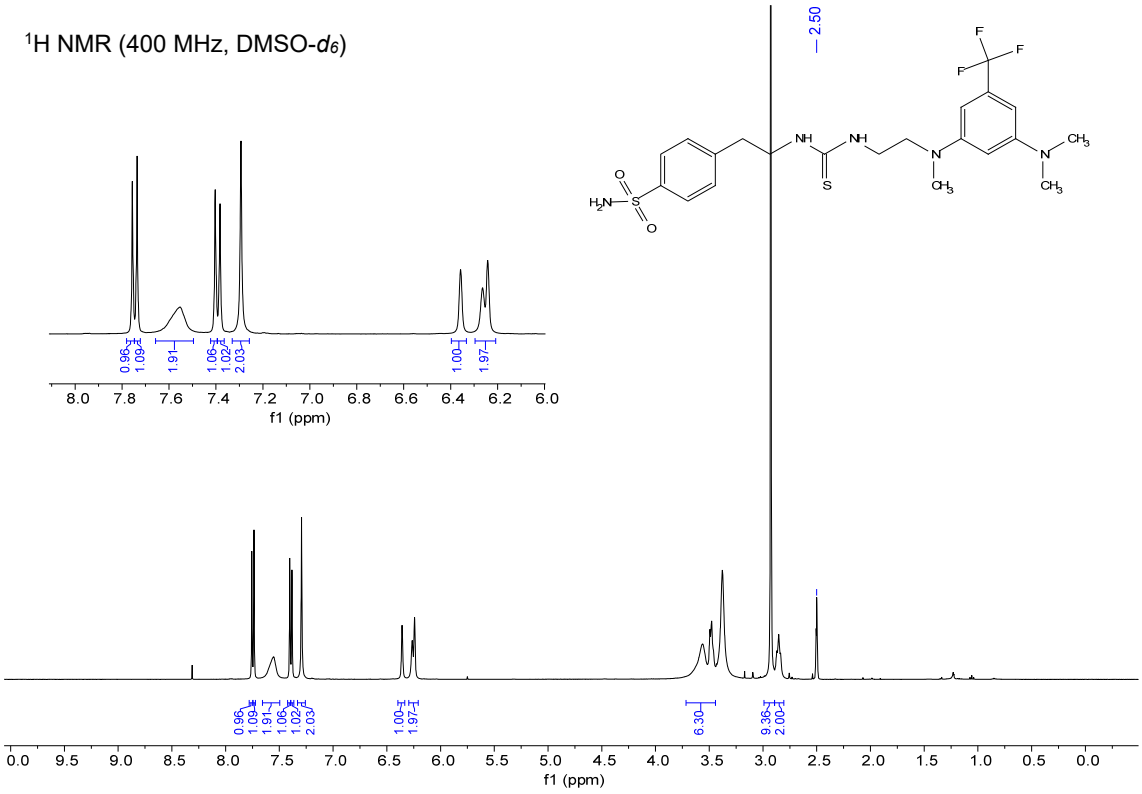
^{13}C NMR spectrum of **10d**

^{19}F NMR (376 MHz, $CDCl_3$)



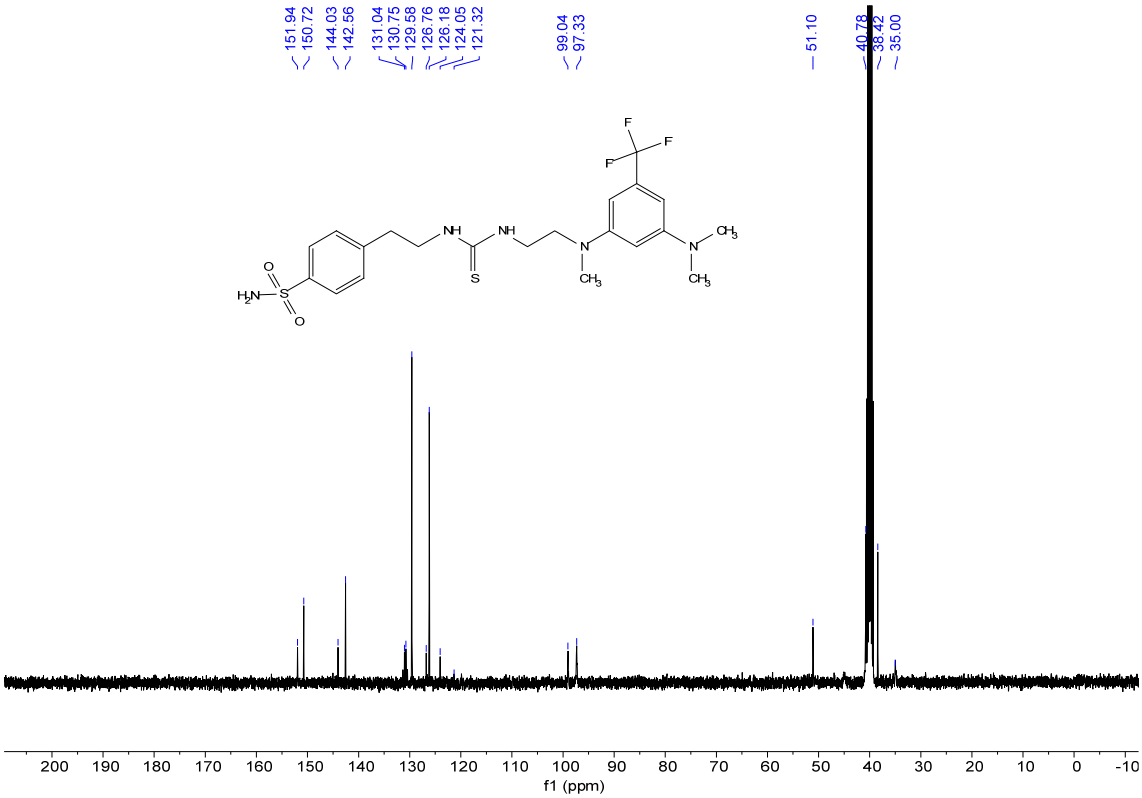
^{19}F NMR spectrum of **10d**

^{1}H NMR (400 MHz, DMSO-d_6)



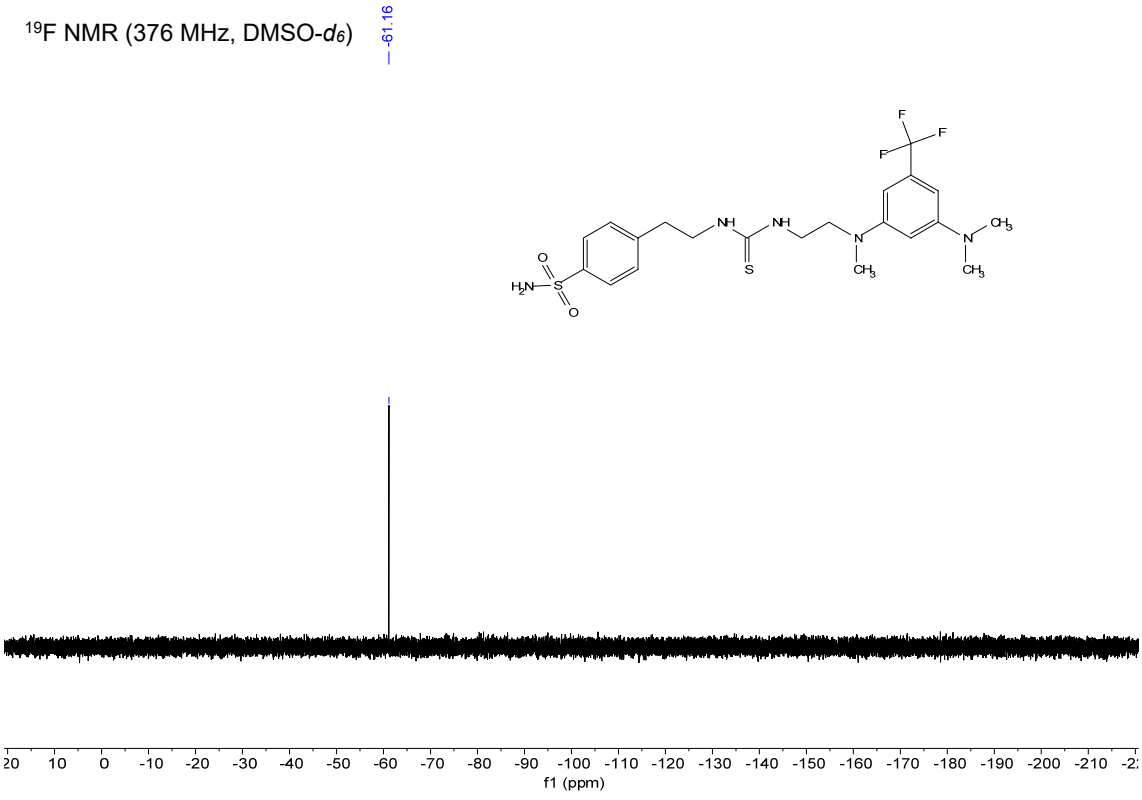
^{1}H NMR spectrum of **10e**

^{13}C NMR (101 MHz, DMSO-d_6)



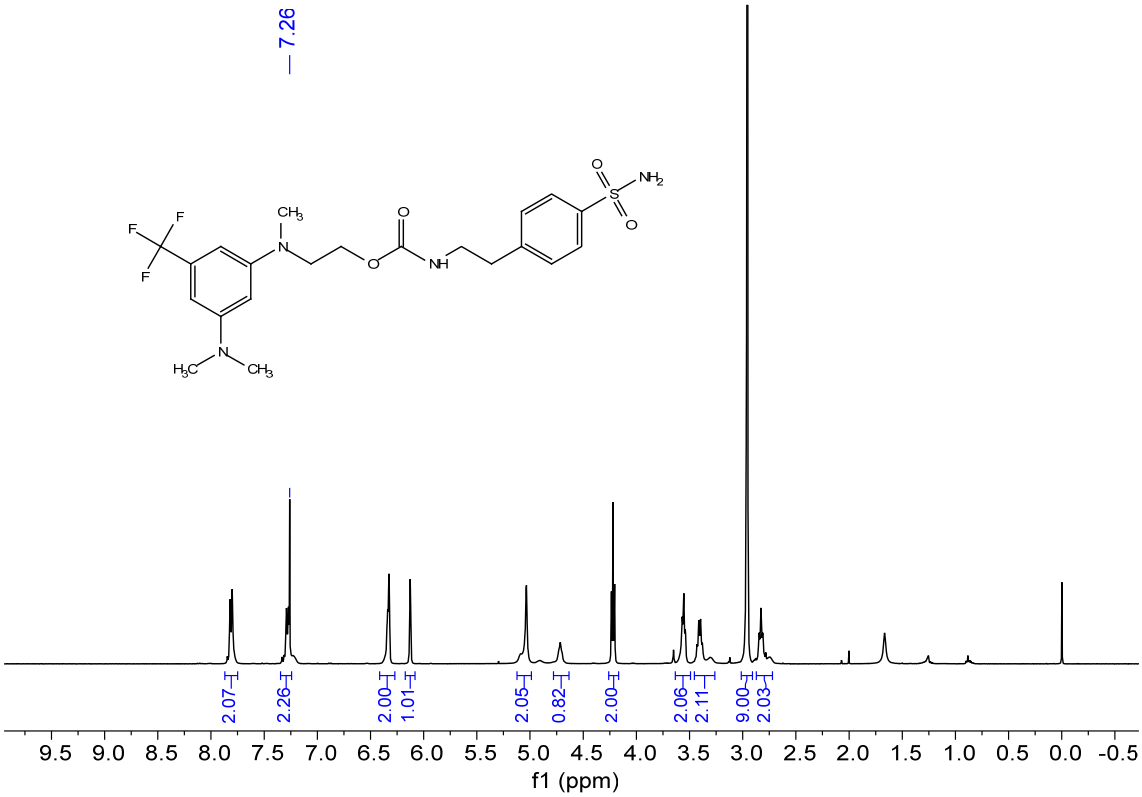
^{13}C NMR spectrum of **10e**

^{19}F NMR (376 MHz, DMSO-d_6)



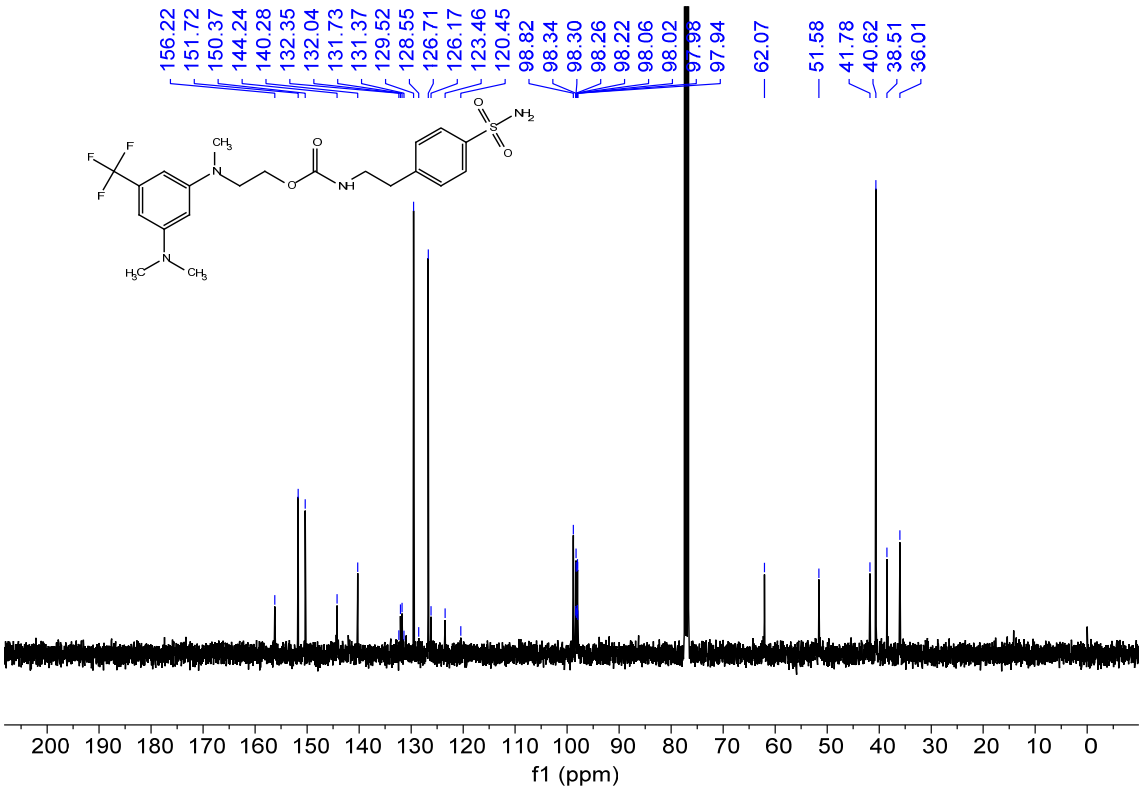
^{19}F NMR spectrum of 10**e**

^{1}H NMR (400 MHz, $CDCl_3$)



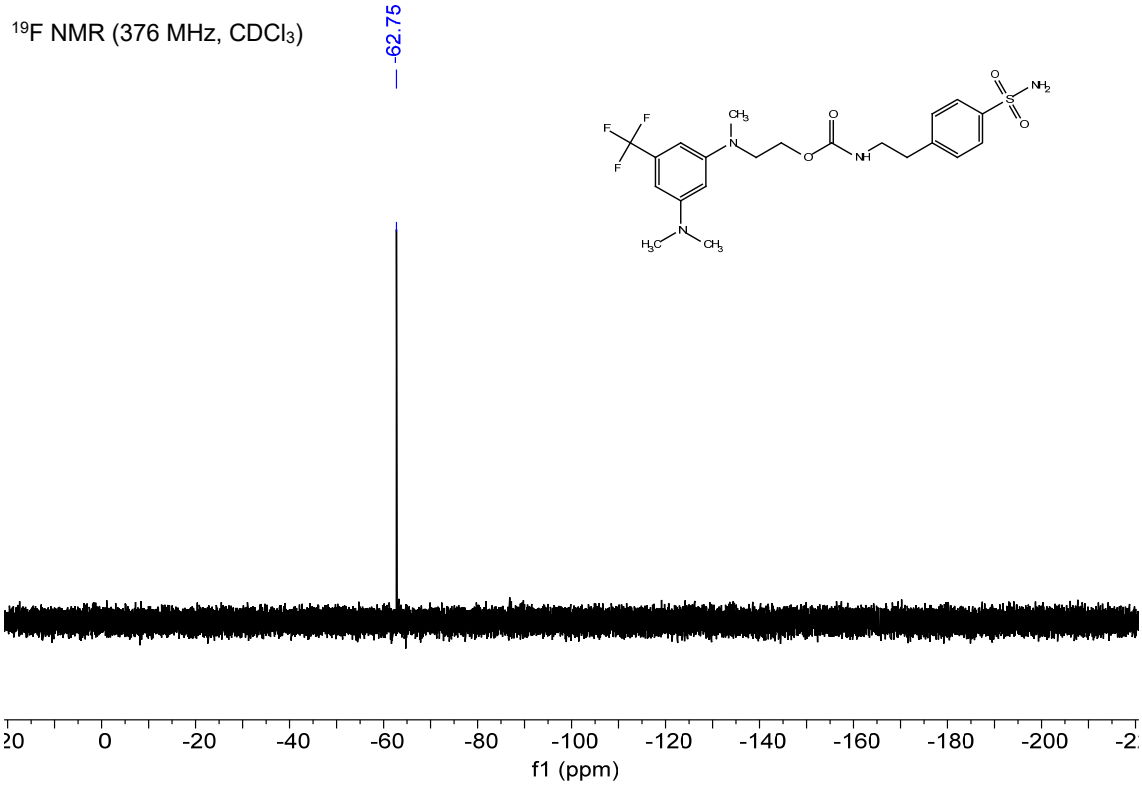
^{1}H NMR spectrum of **10f**

^{13}C NMR (101 MHz, $CDCl_3$)



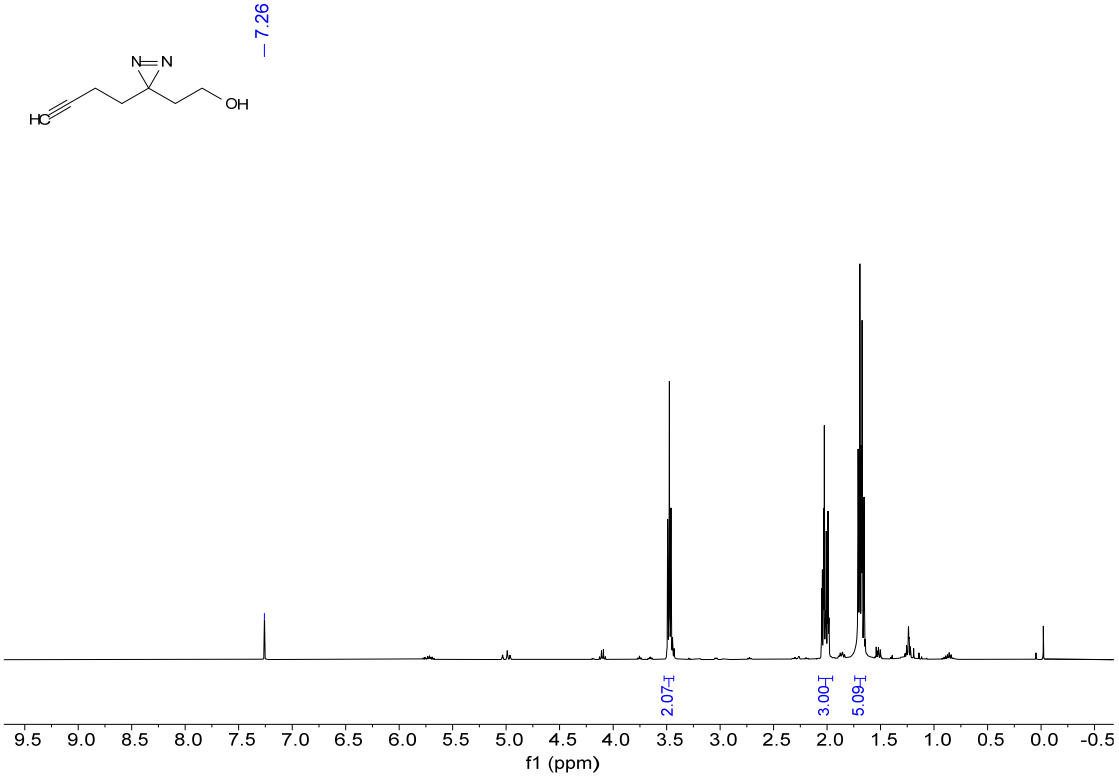
^{13}C NMR spectrum of **10f**

^{19}F NMR (376 MHz, $CDCl_3$)



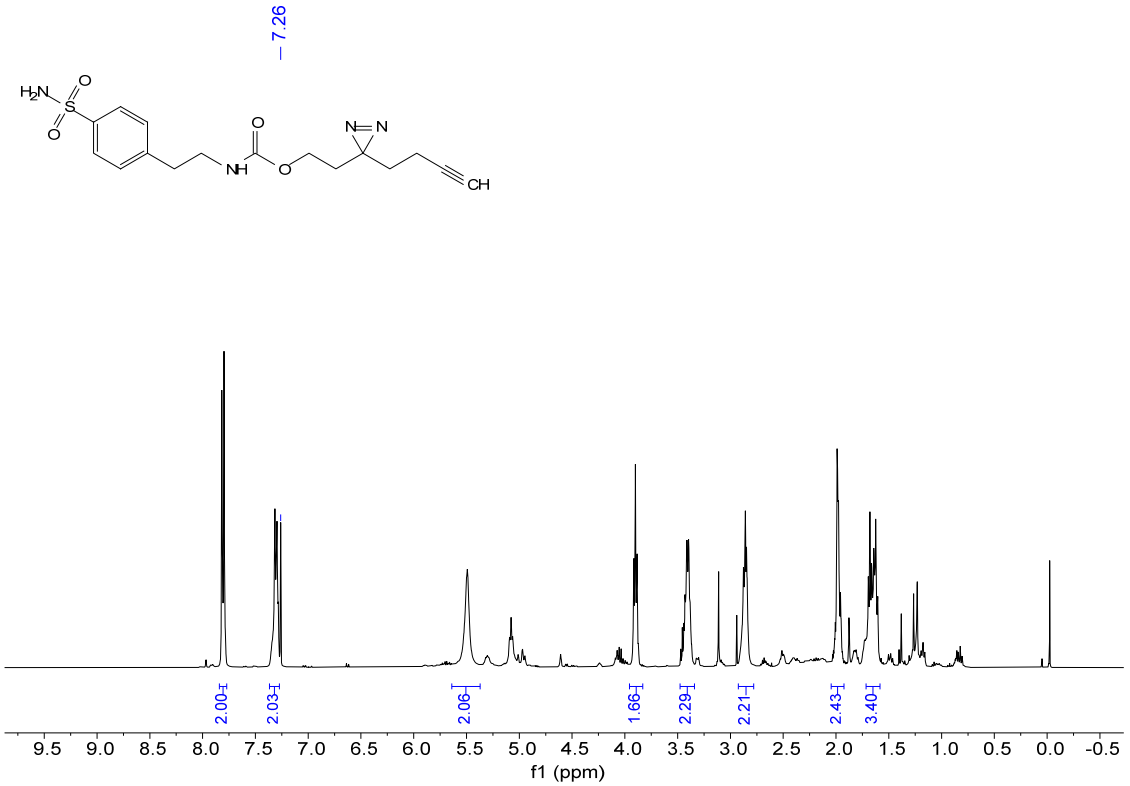
^{19}F NMR spectrum of **10f**

^{19}H NMR (400 MHz, $CDCl_3$)



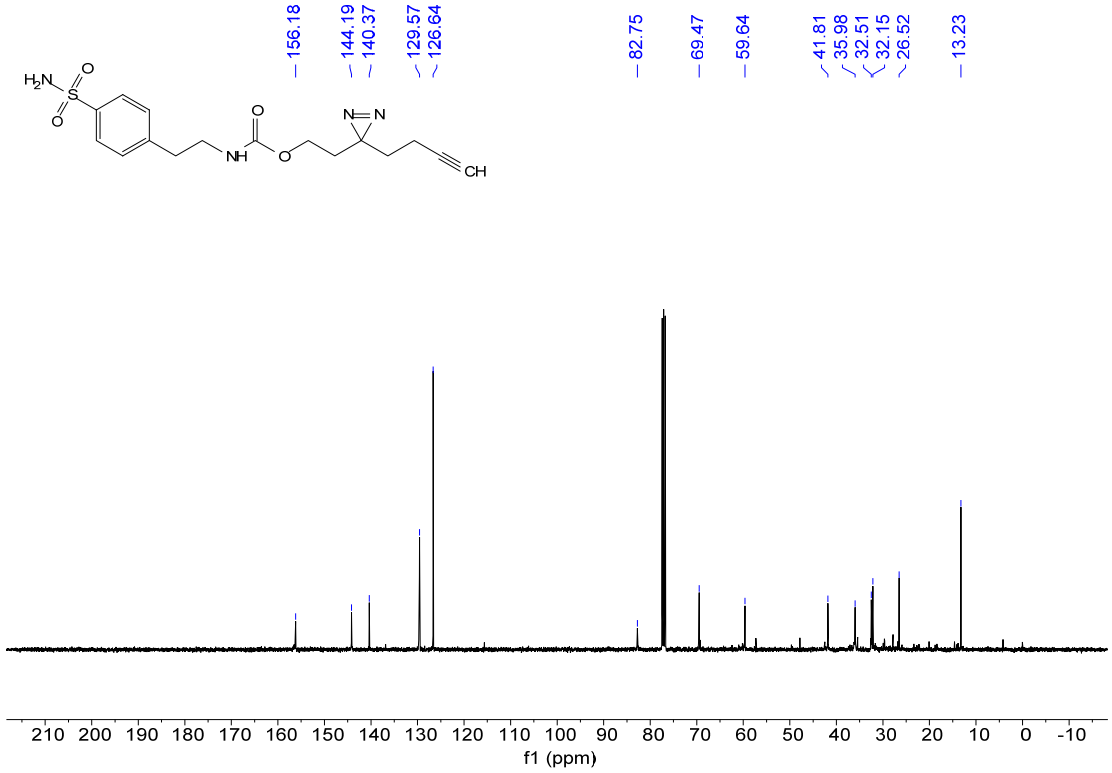
^{19}H NMR spectrum of **10g**

^{19}H NMR (400 MHz, $CDCl_3$)



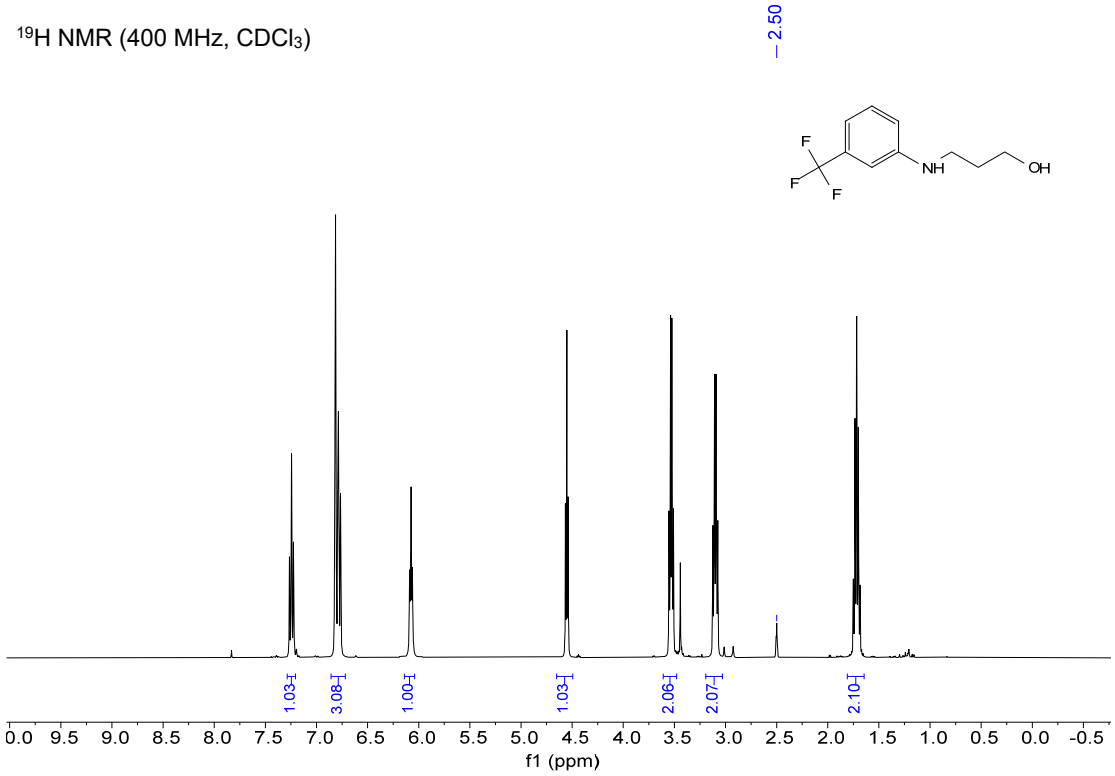
^{19}H NMR spectrum of **10h**

^{13}C NMR (101 MHz, $CDCl_3$)



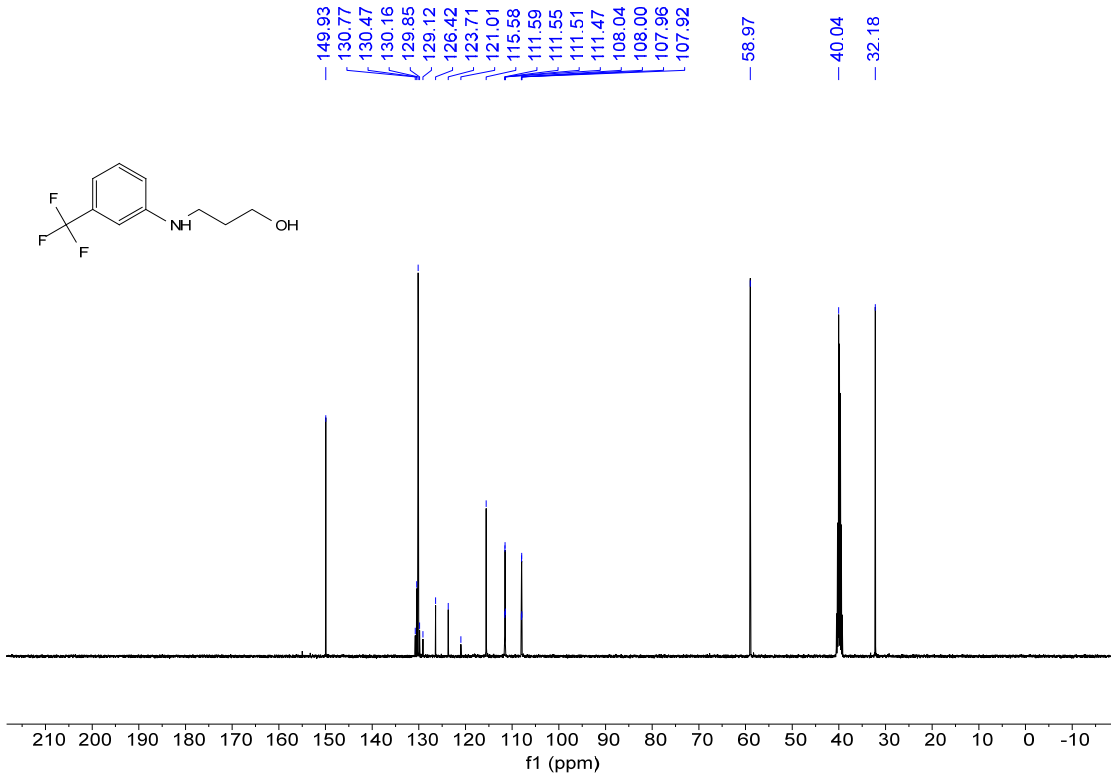
^{13}C NMR spectrum of **10h**

^{19}H NMR (400 MHz, $CDCl_3$)



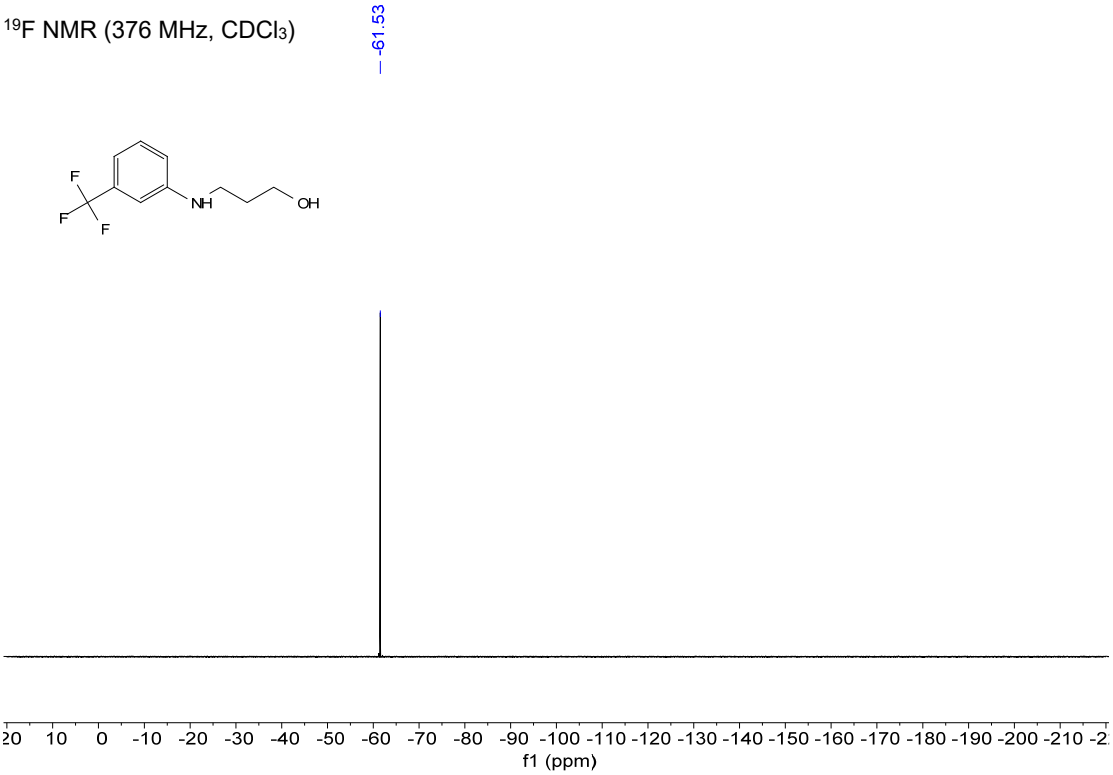
^{19}H NMR spectrum of **10i**

^{13}C NMR (101 MHz, $CDCl_3$)



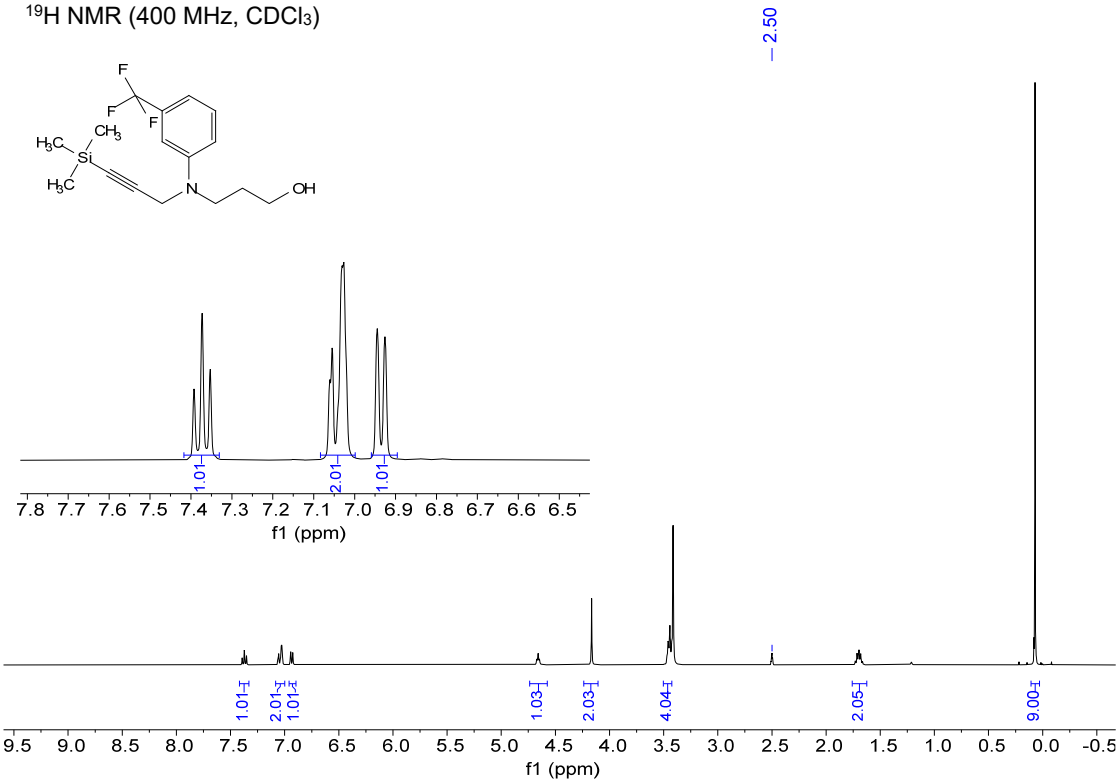
^{13}C NMR spectrum of **10i**

^{19}F NMR (376 MHz, $CDCl_3$)

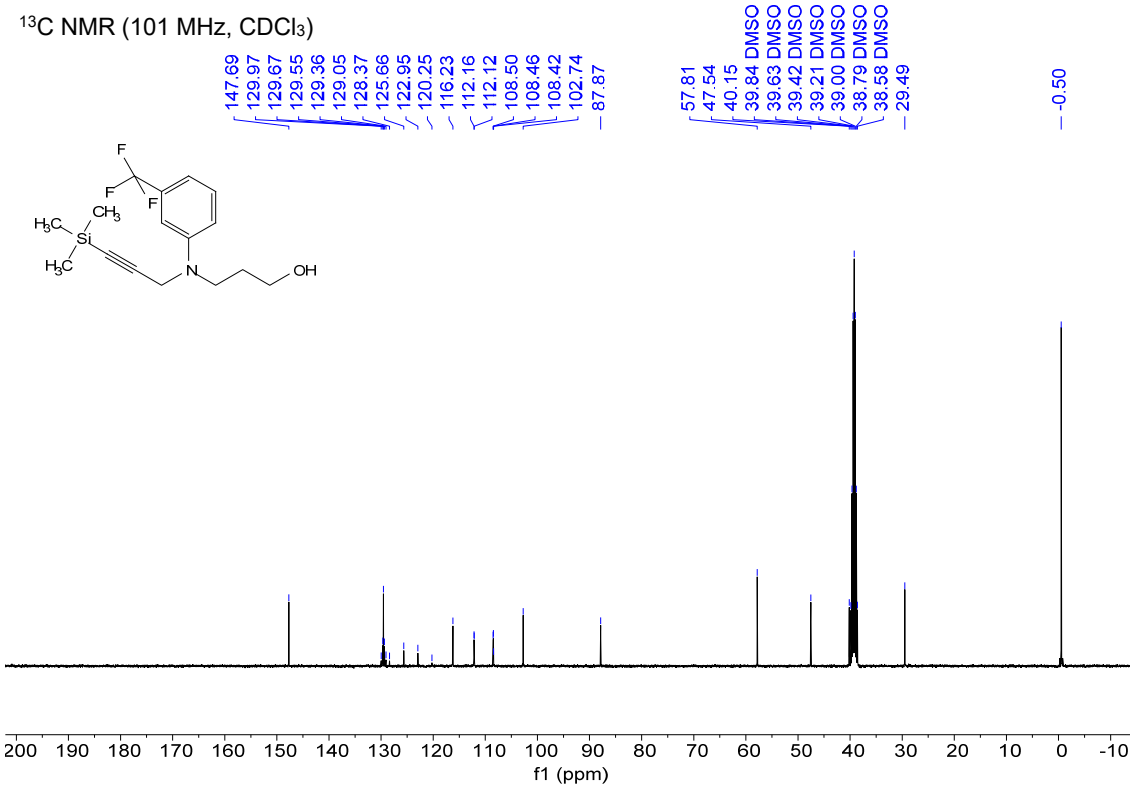


^{19}F NMR spectrum of **10i**

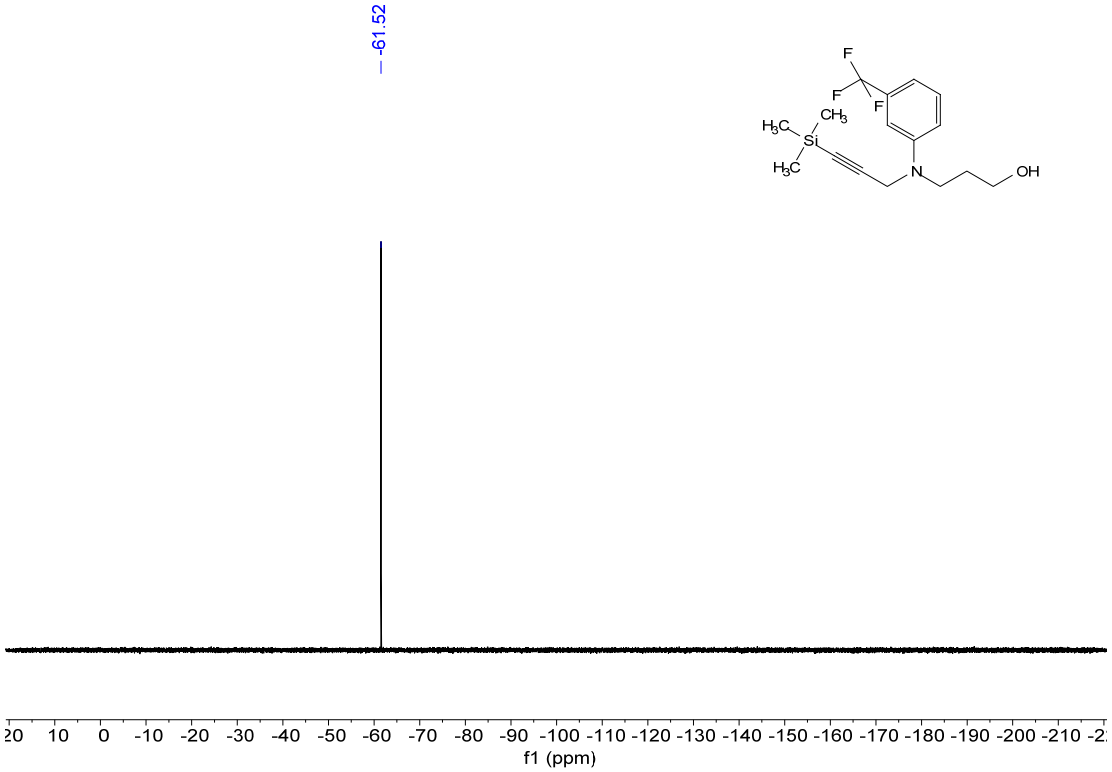
^{19}H NMR (400 MHz, $CDCl_3$)



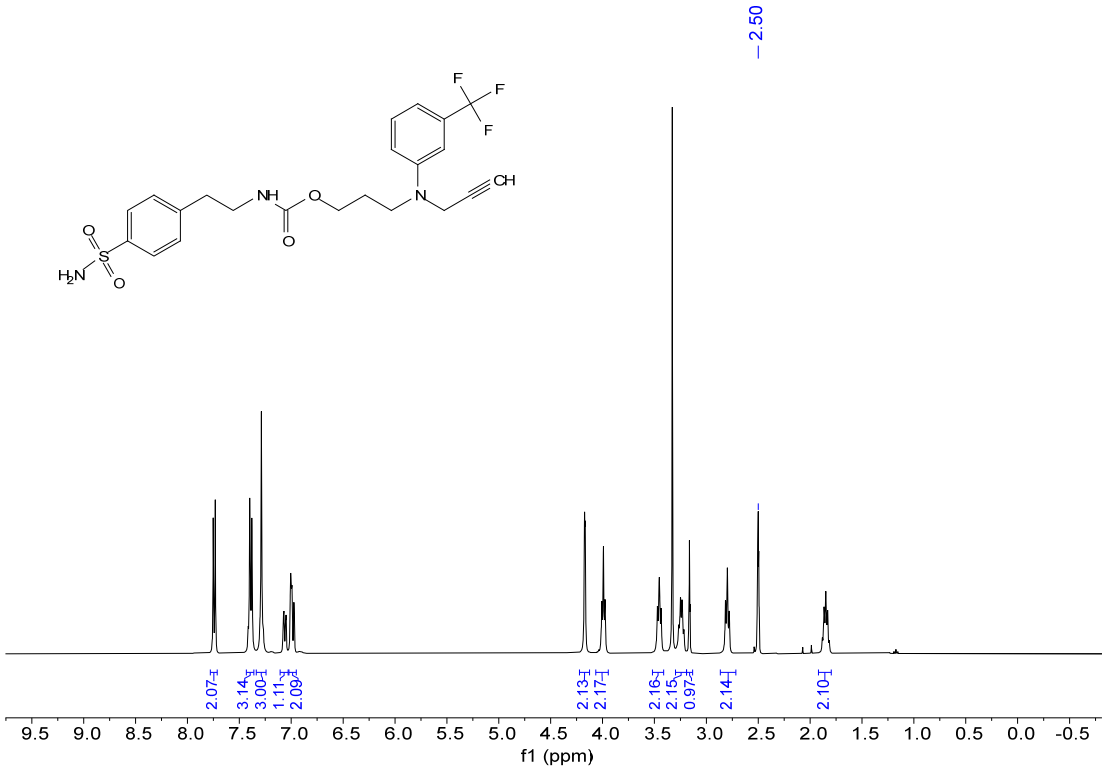
^{19}H NMR spectrum of **10j**



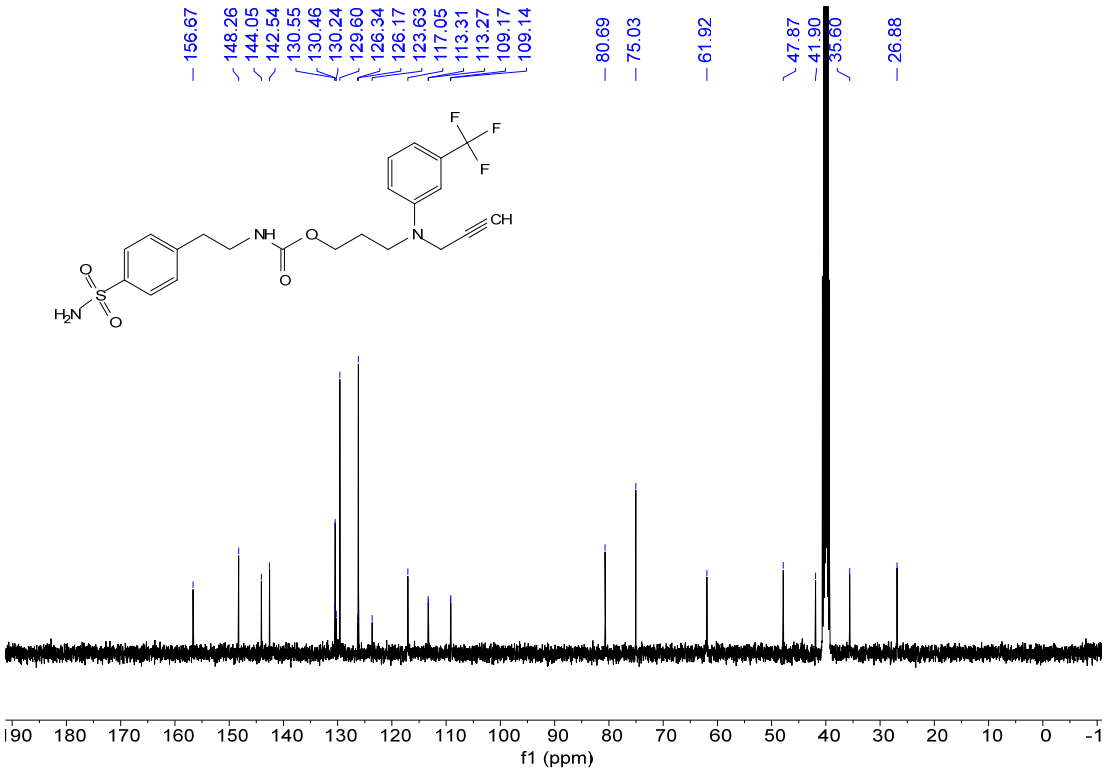
^{13}C NMR spectrum of **10j**



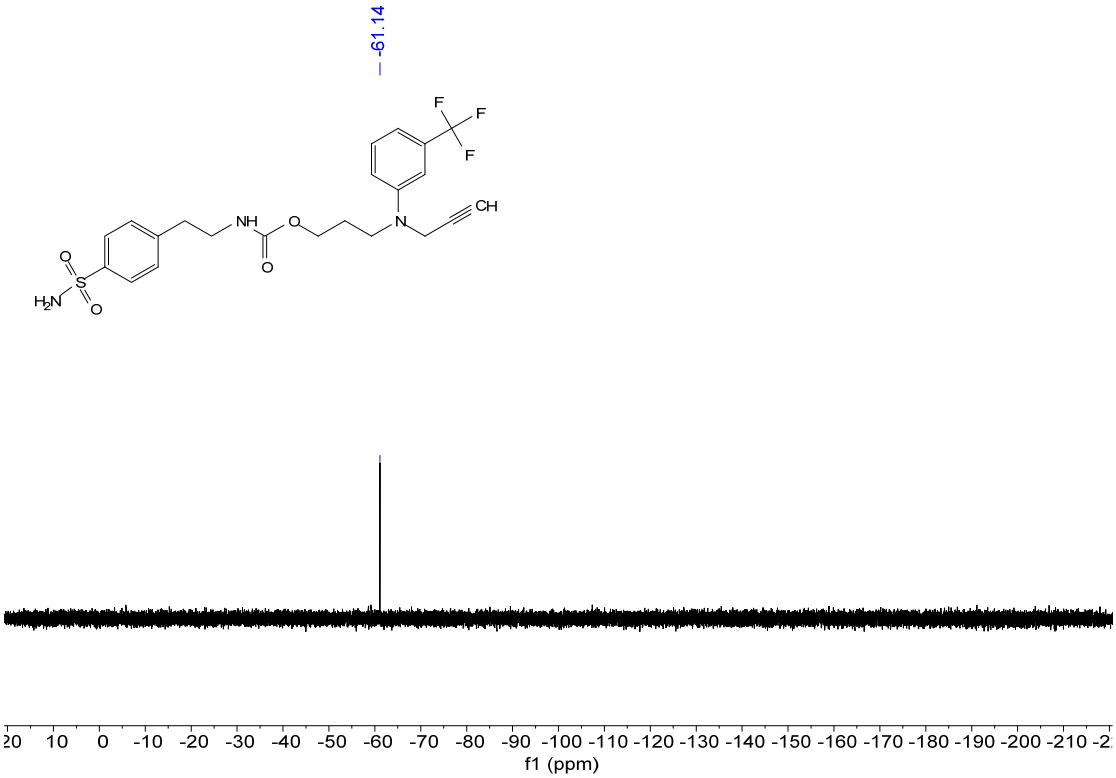
^{19}F NMR spectrum of **10j**



^{19}H NMR spectrum of **10k**



^{13}C NMR spectrum of **10k**



^{19}F NMR spectrum of **10k**