Supplementary Information

Direct Remote Csp^2–H Transformation of Aromatic Amines Enabled by Organophotoredox Catalysis

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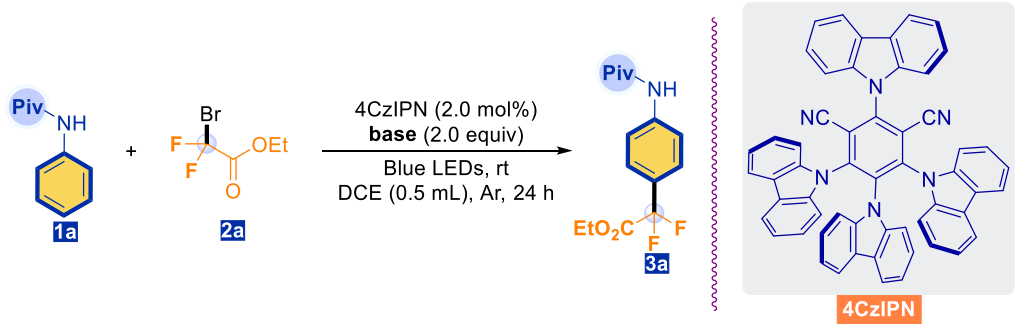
1. General information

Unless otherwise noted, solvents were distilled with a proper drying reagent and stored in a molecular sieve. 4CzIPN were obtained from the commercial vendor Bidepharm® and used without further purification. Dioxane (Water ≤ 50 ppm (by K.F.) 99.7% SafeDry with molecular sieves, stabilized with BHT.) was purchased from the commercial vendor Adamas beta®. Other catalysts and reagents were purchased from commercial vendors and used directly without further purification. Photochemical reactions were carried out with 30 W blue LEDs (460 nm, Jia Deng®). The fluorescence quenching experiments were carried out on a Hitachi F-2500 fluorescence spectrophotometer. The computations for the Gibbs free energy were performed by Gaussian 09 Program. The UV-experiments were measured on a U-3010 spectrophotometer (Hitachi, Japan). Column chromatography purifications performed by using 200～300 mesh silica gel. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on 400, 500 and 600 MHz instruments (Bruker ADVANCE III). Chemical shifts were reported relative to the residual solvent peak ($CHCl_3$ in $CDCl_3$). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) were reported in the Hertz unit (Hz). High resolution mass spectra (HRMS) were obtained by the ESI model from an ab sciex 500R QTOF instrument and Waters Xevo G2-S QTOF instrument.

2. Optimization of reaction conditions

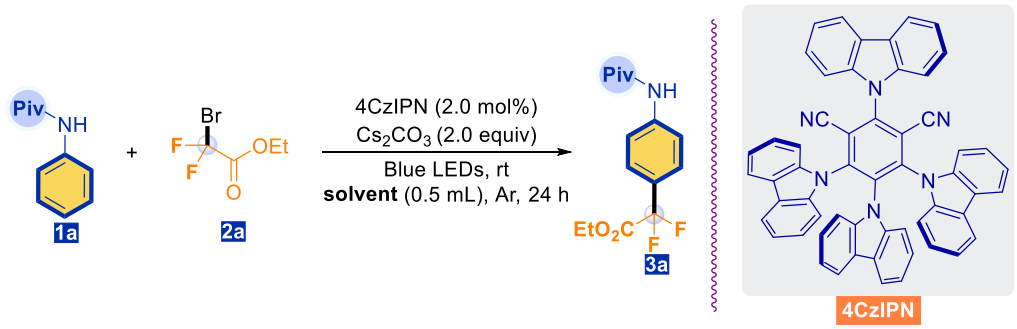
Table S1. Screening of bases[a]



Entry	Bases	Yields[b]
1	NMM	30%
2	DBU	22%
3	TEA	18%
4	DIPEA	trace
5	TMG	50%
6	K_2CO_3	56%
7	Li_2CO_3	41%
8	$NaHCO_3$	51%
9	NaSCN	nr
10	NaOAc	58%
11	$KHCO_3$	51%
12	CsOAc	54%
13	**Cs_2CO_3**	**60%**

[a]Reaction conducted using **1a** (0.2 mmol), **2a** (2.0 equiv), 4CzIPN (2 mol%) and base (2.0 equiv) in DCE (0.5 mL) setup under Ar and irradiated with blue LEDs at RT for 24 h. [b]Isolated yields. nr = no reaction.

Table S2. Screening of solvents[a]

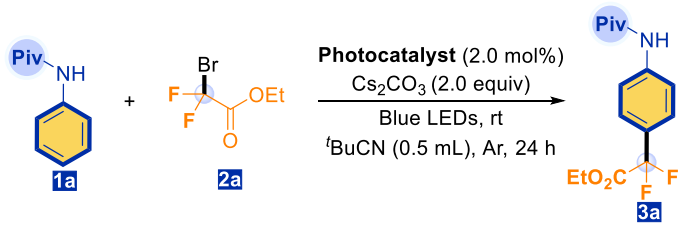


Entry	Solvent	Yields[b]

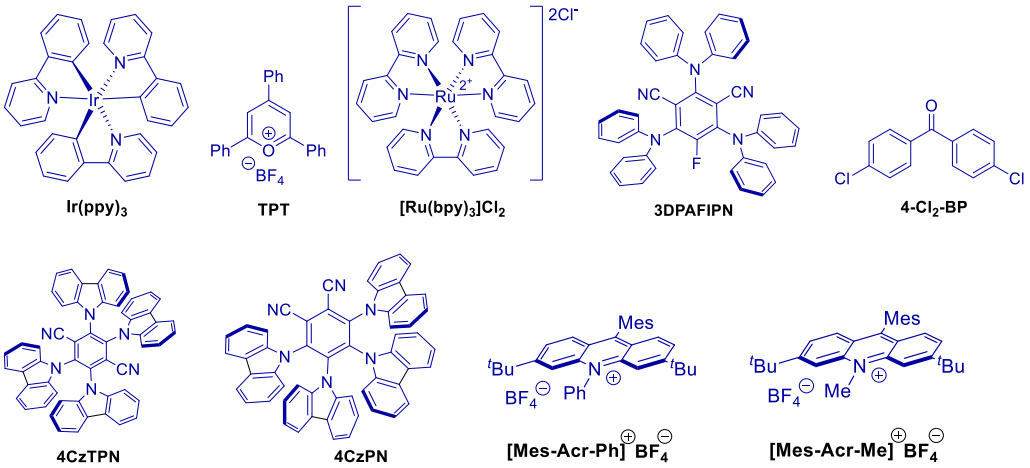
1	DCM	52%
2	Acetone	43%
3	DMF	35%
4	Dioxane	56%
5	DMAc	36%
6	MeCN	58%
7	DMSO	nr
8	THF	19%
9	$PhCF_3$	32%
10	EtOH	65%
11	*n*-Hexane	67%
12	**^{t}BuCN**	**70%**
13	H_2O	nr
14	^{t}BuOH	trace
15	DEDM	40%
16	Ethyl acetate	20%

[a]Reaction conducted using **1a** (0.2 mmol), **2a** (2.0 equiv), 4CzIPN (2 mol%) and Cs_2CO_3 (2.0 equiv) in solvent (0.5 mL) setup under Ar and irradiated with blue LEDs at RT for 24 h. [b]Isolated yields. nr = no reaction.

Table S3. Screening of photocatalysts[a]

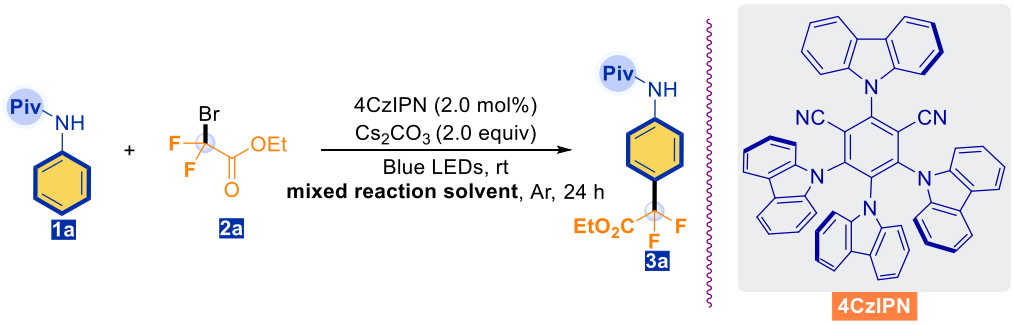


Entry	Photocatalysts	Yields[b]
1	$Ir(ppy)_3$	42%
2	$[Ru(bpy)_3Cl_2]$	nr
3	TPT	nr
4	3DPAFIPN	50%
5	4CzTPN	trace
6	Eosin Y	35%
7	4-Cl_2-BP	trace
8	Fluorescein	trace
9	Fluorescein sodium	18%
10	Rhodamine B	trace
11	$[Acr\text{-}Mes\text{-}Me]^+(BF_4)^-$	trace
12	$[Acr\text{-}Mes\text{-}Ph]^+(BF_4)^-$	17%
13	4CzPN	25%



[a]Reaction conducted using **1a** (0.2 mmol), **2a** (2.0 equiv), Photocatalyst (2 mol%) and Cs_2CO_3 (2.0 equiv) in ^{t}BuCN (0.5 mL) setup under Ar and irradiated with blue LEDs at RT for 24 h. [b]Isolated yields. nr = no reaction.

Table S4. Optimization of mixed reaction solvents[a]

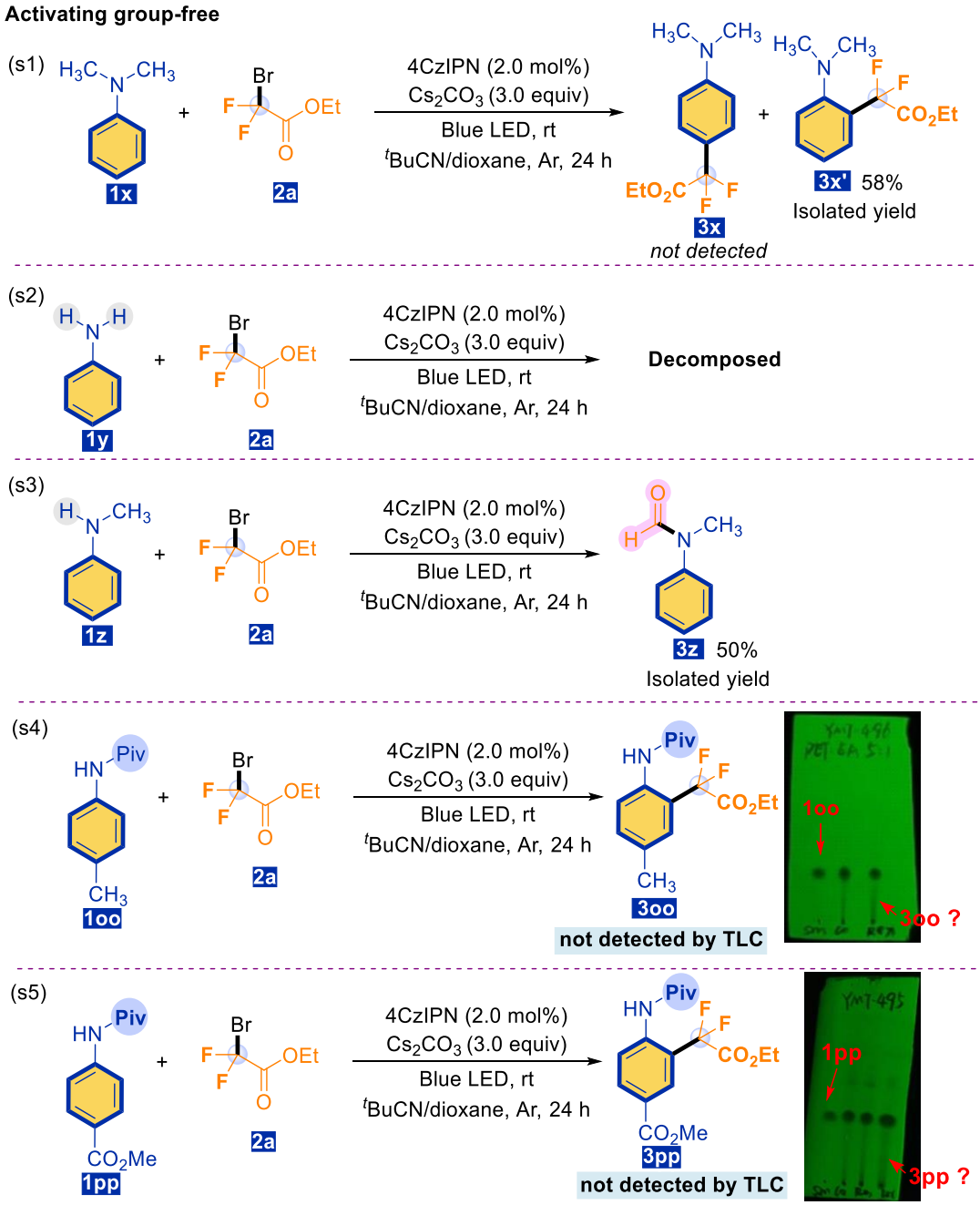


Entry	Mixed reaction solvents	Yields[b]
1	^{t}BuCN/DCM (2.5/1)	63%
2	^{t}BuCN/Dioxane (2.5/1)	75%
3	^{t}BuCN/MeCN (2.5/1)	62%
4	^{t}BuCN/$PhCF_3$ (2.5/1)	58%
5	^{t}BuCN/EtOH (2.5/1)	25%
6	^{t}BuCN/DEDM (2.5/1)	70%
7	^{t}BuCN/*n*-Hexane (2.5/1)	47%
8	^{t}BuCN/Dioxane (5/1)	65%
8[c]	^{t}BuCN/Dioxane (2.5/1)	74%
9[c,d]	^{t}BuCN/Dioxane (2.5/1)	78%

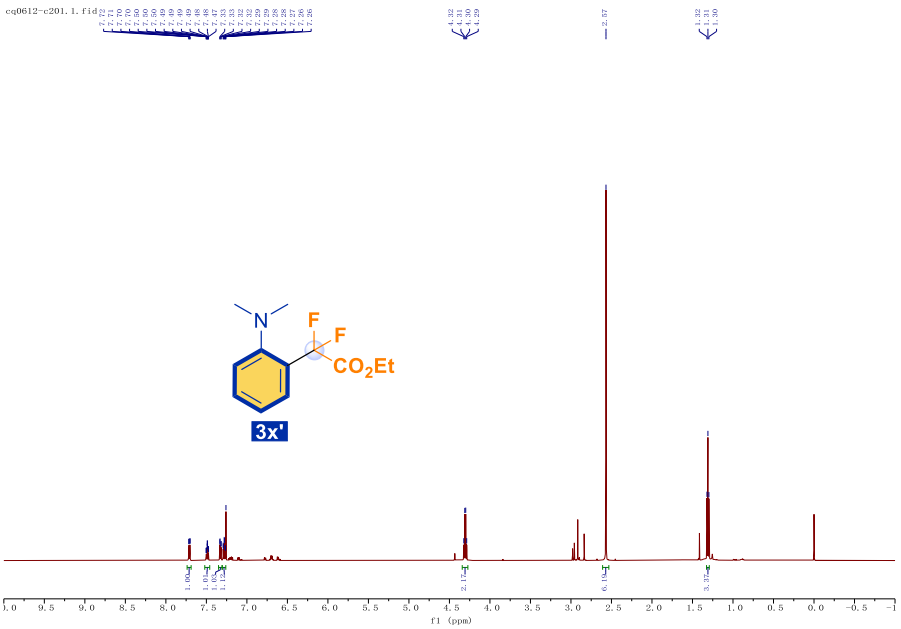
[a]Reaction conducted using **1a** (0.2 mmol), **2a** (2.0 equiv), 4CzIPN (2 mol%) and Cs_2CO_3 (2.0 equiv) in ^{t}BuCN/dioxane (2.5/1 (volt-BuCN /voldioxane), 0.7 mL) setup under Ar and irradiated with blue LEDs at RT for 24 h. [b]Isolated yields. [c]^{t}BuCN/dioxane (2.5/1 ($vol_{t\text{-BuCN}}$ /$vol_{dioxane}$), 1.4 mL). [d]Cs_2CO_3 (3.0 equiv). nr = no reaction. DEDM = Diethylene glycol dimethyl ether.

3. Mechanistic studies

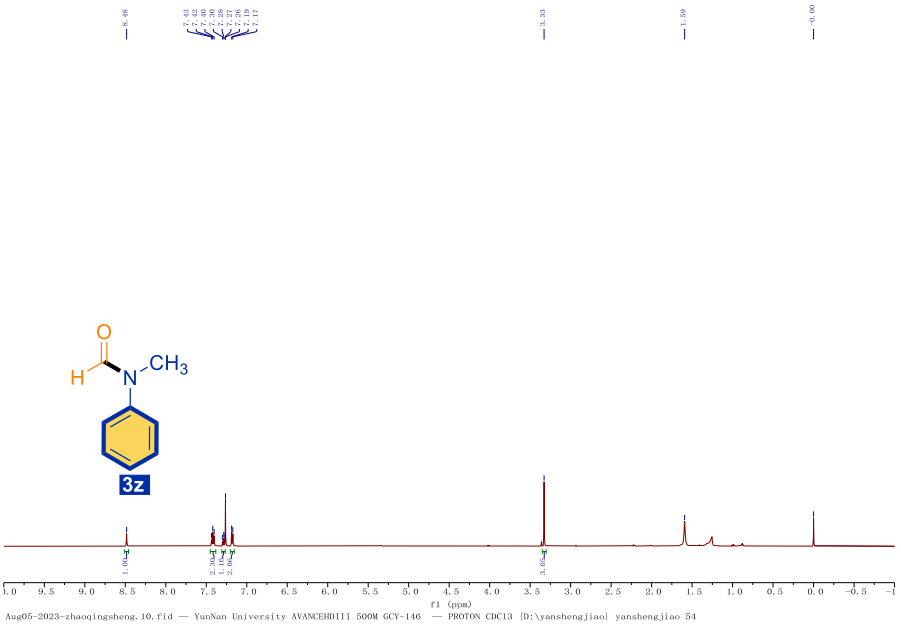
3.1 Comparative experiments



(Eq. s1): ethyl 2-(2-(dimethylamino)phenyl)-2,2-difluoroacetate (3x'): ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.71 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.33 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.28 (td, *J* = 7.6, 1.2 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.57 (s, 6H), 1.31 (t, *J* = 7.2 Hz, 3H). The ^{1}H NMR data of the compound **3x'** were in accordance with the previously reported literature.[1a]

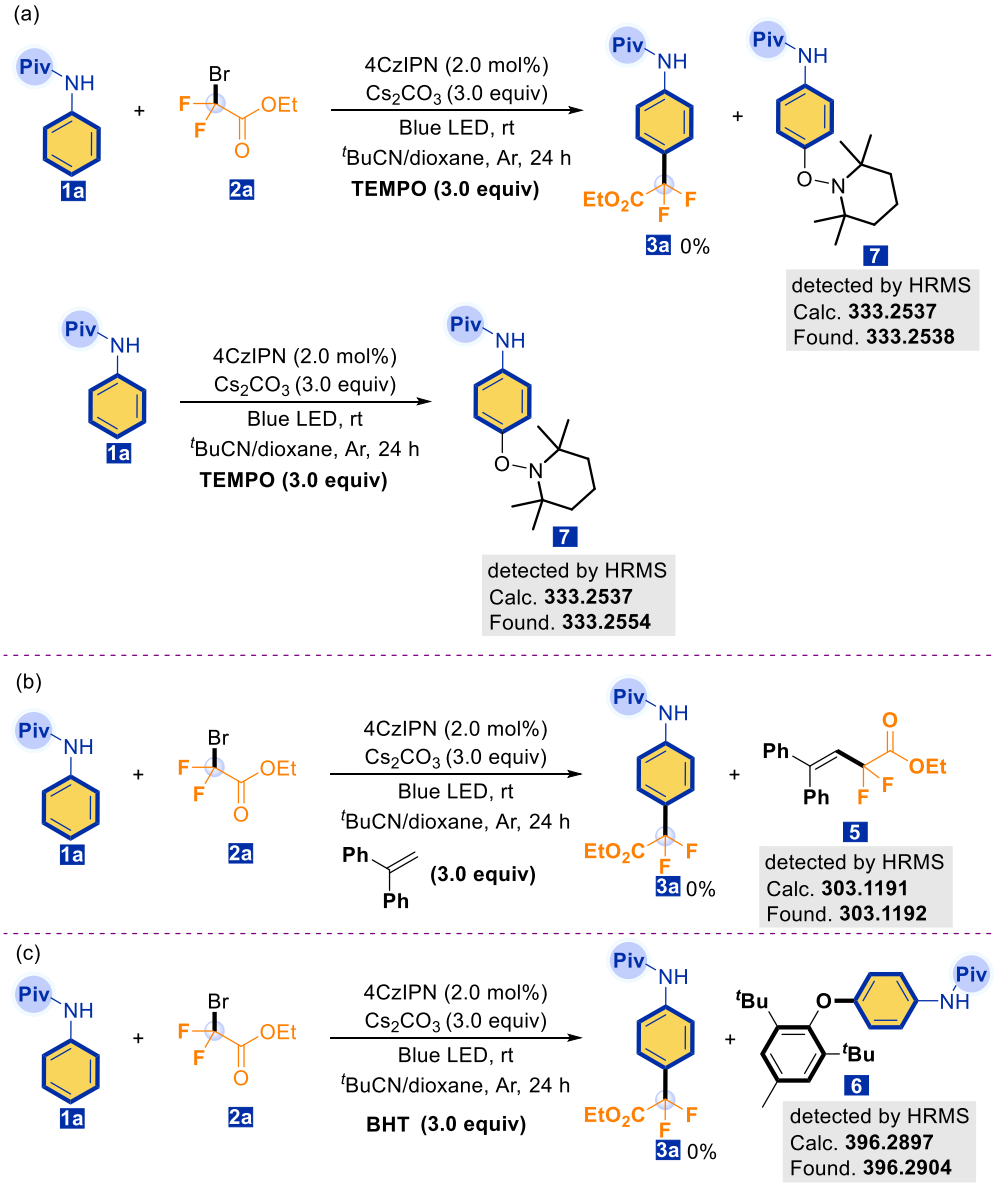


(Eq. s3) ***N*-methyl-*N*-phenylformamide (3z):** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 7.45 – 7.38 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 2H), 3.33 (s, 3H). The ^{1}H NMR data of the compound **3z** were in accordance with the previously reported literature.[1b]



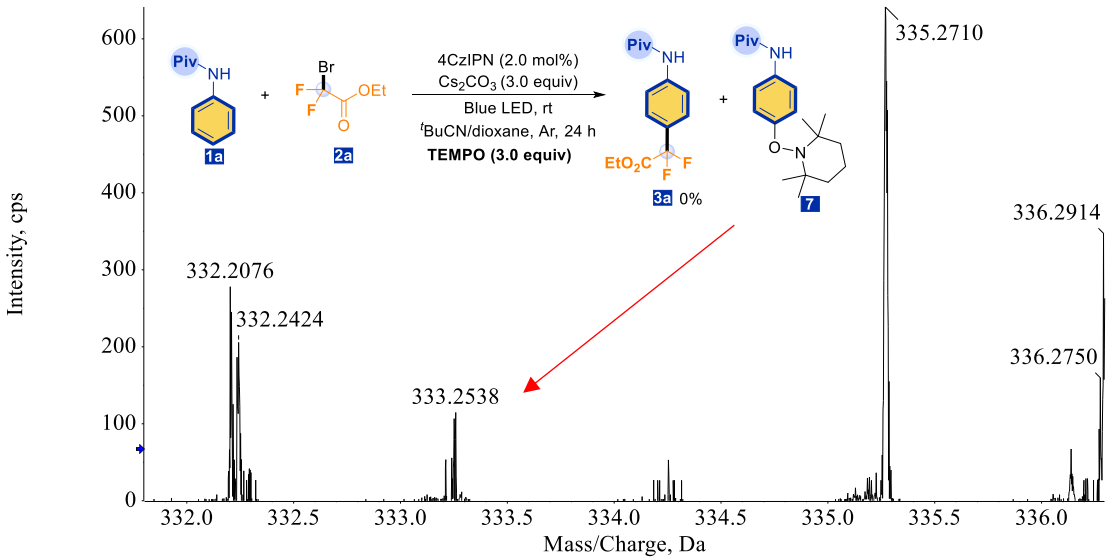
Inference: The carbonyl group as an activating group plays a significant role in regioselective control.

3.2 Radical traping experiments



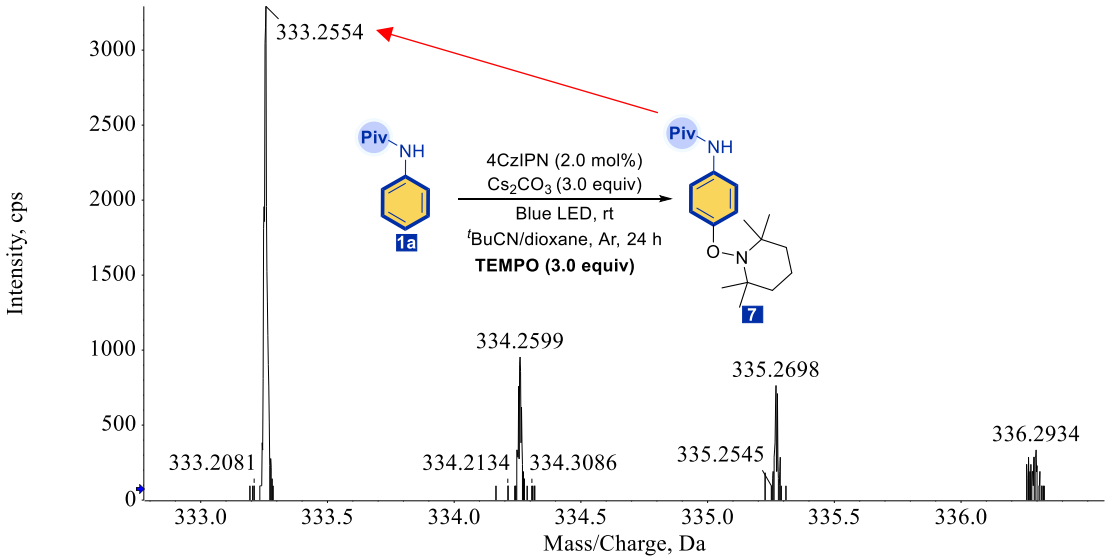
HRMS of Eq. a:

Spectrum from mass20240124.wiff2 (sample 4) - YMT500, Experiment 1, +IDA TOF MS (50 - 1000) from 0.009 to 0.147 min



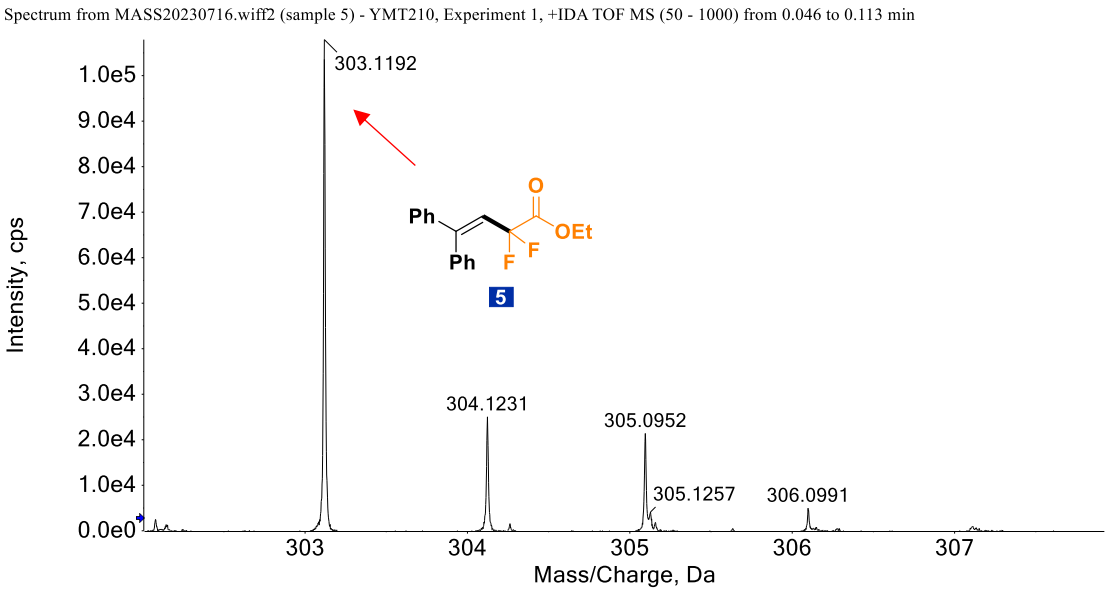
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C20H32N2O2	333.2537	6.0	0.7	1			NA/NA

Spectrum from mass20240124.wiff2 (sample 5) - YMT501, Experiment 1, +IDA TOF MS...le 5) - YMT501, Experiment 1, +IDA TOF MS (50 - 1000) from 0.440 to 0.541 min]



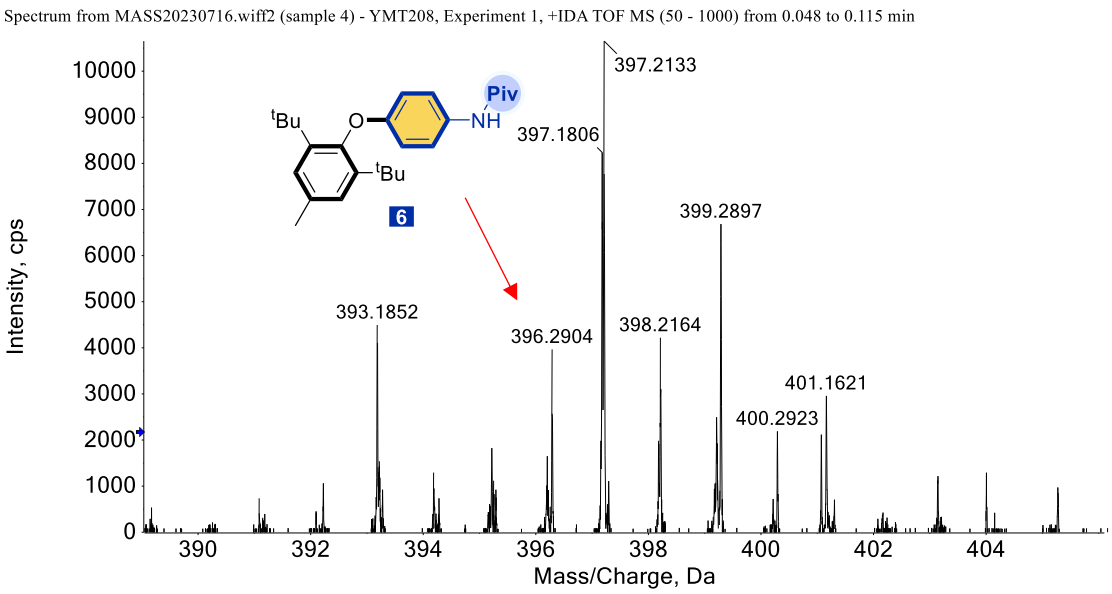
Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C20H32N2O2	333.2537	6.0	5.2	1			NA/NA

HRMS of Eq. b:



Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C18H16F2O2	303.1191	10.0	0.3	1			NA/NA

HRMS of Eq. c:



Hit	Formula	m/z	RDB	ppm	MS Rank	MSMS ppm	MSMS Rank	Found
1	C26H37NO2	396.2897	9.0	1.8	1			NA/NA

Inference: Based on the above experimental data, the experimental results strongly indicate that the alkoxycarbonyldifluoromethylation reaction undergoes a free radical reaction pathway. The success of the reaction is achieved through radical-radical coupling. This result suggests that the alkoxycarbonyldifluoromethylation reaction proceed well due to the generation of radical •CF_2CO_2Et (Eq. b). This experiment indicates that the excited state 4CzIPN can oxidize aromatic amine to offer the corresponding arene radical cation (Eq. a, c). Meanwhile, this experiment also rules out the possibility of radical addition to aromatics.

3.3 UV/vis-experiments

UV/vis absorption spectra were recorded on a U-3010 spectrophotometer (Hitachi, Japan).

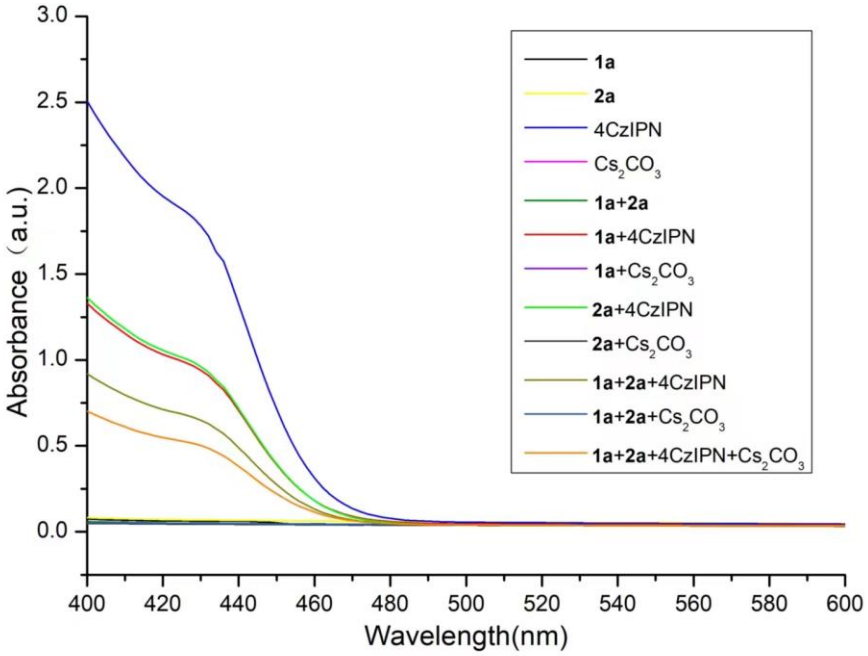


Figure S1. The separate UV Spectra of **1a** (0.6 mmol), **2a** (1.2 mmol), 4CzIPN (0.012 mmol), Cs_2CO_3 (1.8 mmol), **1a** (0.6 mmol) + **2a** (1.2 mmol), **1a** (0.6 mmol) + 4CzIPN (0.012 mmol), **1a** (0.6 mmol) + Cs_2CO_3 (1.8 mmol), **2a** (1.2 mmol) + 4CzIPN (0.012 mmol), **2a** (1.2 mmol) + Cs_2CO_3 (1.8 mmol), **1a** (0.6 mmol) + **2a** (1.2 mmol) + 4CzIPN (0.012 mmol), **1a** (0.6 mmol) + **2a** (1.2 mmol) + Cs_2CO_3 (1.8 mmol) and **1a** (0.6 mmol) + **2a** (1.2 mmol) + 4CzIPN (0.012 mmol) + Cs_2CO_3 (1.8 mmol) in ^{t}BuCN (3 mL) + H_2O (0.5 mL)

Inference: From **Figure S1**, it is not visible that a new peak was generated when **1a** combined with 4CzIPN, indicating that the weak interaction between substrate **1a** and 4CzIPN may not exist.

3.4 Stern-Volmer emission quenching

The fluorescence quenching experiments were taken using an F-2500 spectrophotometer (Hitachi, Japan). The experiments were carried out in $2*10^{-5}$ mol/L of 4CzIPN in ^{t}BuCN at 25 °C. The excitation wavelength was 445 nm and the emission intensity at 576 nm was observed. The following parameters were employed: Ex Slit = 10 nm, scan speed = 3000 nm/min, response = 8 s. I^0 and I are respective fluorescence intensities in the absence and presence of the indicated concentrations of the quenchers.[6]

4CzIPN：3.16 mg dissolved in 50 mL ^{t}BuCN (0.00008 M).

1a: 17.7 mg dissolved in 25 mL ^{t}BuCN (0.004 M).

2a: 20.2 mg dissolved in 25 mL ^{t}BuCN (0.004 M).

Entry	4CzIPN	1a	^{t}BuCN	Total volume	phosphorescence intensity		
					No. 1	*No.* 2	*No.* 3
1	1mL	0mL	3mL	4mL	4575	4714	4798
2	1mL	0.25mL	2.75mL	4mL	4196	4171	4166
3	1mL	0.5mL	2.5mL	4mL	3857	3823	3785
4	1mL	0.75mL	2.25mL	4mL	3422	3332	3309
5	1mL	1mL	2mL	4mL	3018	2931	2970

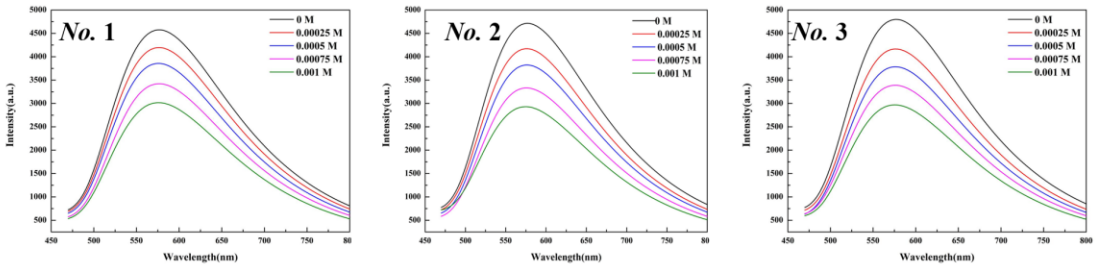


Figure S2. Fluorescence quenching experiments with **1a**

Entry	4CzIPN	2a	^{t}BuCN	Total volume	phosphorescence intensity		
					No. 1	*No.* 2	*No.* 3
1	1mL	0mL	3mL	4mL	4575	4714	4798
2	1mL	0.25mL	2.75mL	4mL	4353	4425	4375
3	1mL	0.5mL	2.5mL	4mL	4137	4199	4150
4	1mL	0.75mL	2.25mL	4mL	3958	3985	3960
5	1mL	1mL	2mL	4mL	3730	3790	3754

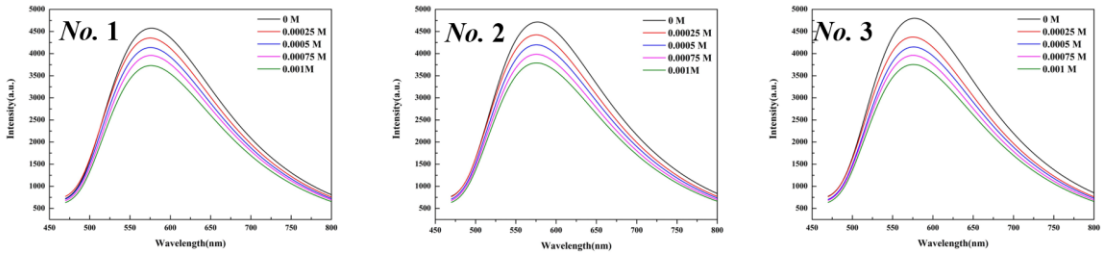


Figure S3. Fluorescence quenching experiments with **2a**

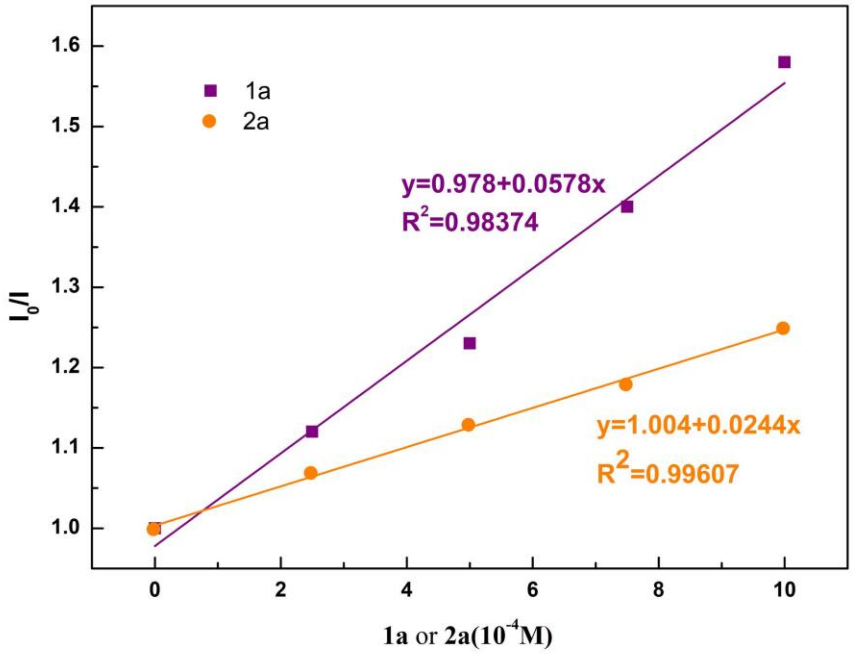


Figure S4. Stern-Volmer plots in comparison

Inference: Based on Stern-Volmer emission quenching studies, the reductive quenching by **1a** ran at a higher rate than its oxidative quenching of 4CzIPN* by **2a**, suggesting that photo-excited 4CzIPN is quenched by **1a** as the initial step, and also suggest that a reductive quenching pathway is operative in the reaction. (Note: Cs_2CO_3 was insoluble in ^{t}BuCN even at low concentrates and was therefore omitted from the emission quenching experiments.)

3.5 Light/dark experiments

The reaction was sequentially irradiated with blue light and in the absence of light (scale based on 0.8 mmol **1a**). 0.5 mL of the reaction solution was withdrawn via a syringe and analyzed by ^{1}H NMR spectroscopy every 4 hours. After a total of 24 h, these determined yields were plotted against the reaction time (Figure S5).

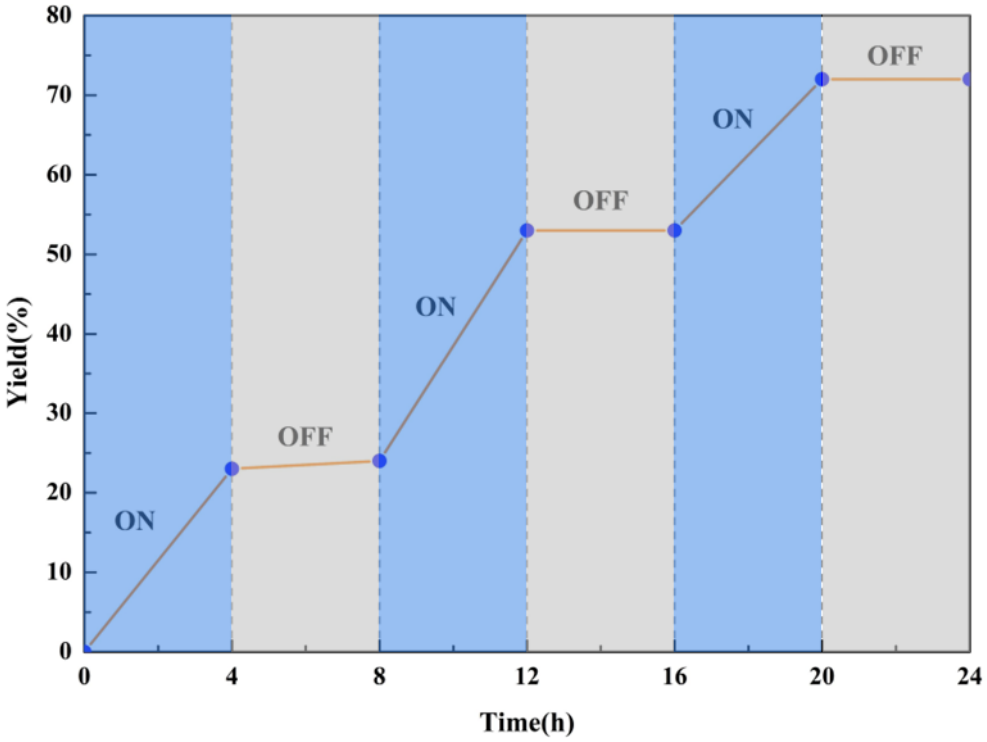


Figure S5. Effect of visible light irradiation

Inference: As shown in Figure S5, product **3a** was produced only under visible light irradiation, which unambiguously disproves the possibility of a radical chain process.

3.6 Computational studies

All calculations have been carried out using the DMol3 program[7,8] based on density functional theory (DFT) within GGA-PBE schame [9] for exchange and correlation potential. We used DFT semicore pseudopotential with double numerical basis set plus polarization functions (DNP). Convergence in energy, force, and displacement was set as 10-5 Ha, 0.001 Ha/Å, and 0.005 Å, respectively. The core treatment was set to effective core potentials (ECP). The space cutoff radius maintained at 4.4 Å. The DFT-D2 Van der Walls correction by Grimmie[10,11] was also considered in all calculations. The SMD continuum solvation model was used to describe bulk water solvation effects. The complete LST/QST method was used for the transition state calculation, in which a single linear synchronous transit (LST) maximization bracketing the maximum between the reactants and product was performed firstly, followed by

repeated conjugate gradient minimizations and quadratic synchronous transit (QST) maximizations until a transition state has been located (Figure S6).

Table S5 The calculated reaction energy barriers

	1a+**2a**→**3a** (Ha)	ΔG(kcal/mol)	**1a**+**2a**→**3a'** (Ha)	ΔG(kcal/mol)
Init	-1076.3796515	0	-1076.3842859	0
TS	-1076.2896375	56.484	-1076.2747979	68.705
Final	-1076.4039638	-15.256	-1076.3998316	-9.755

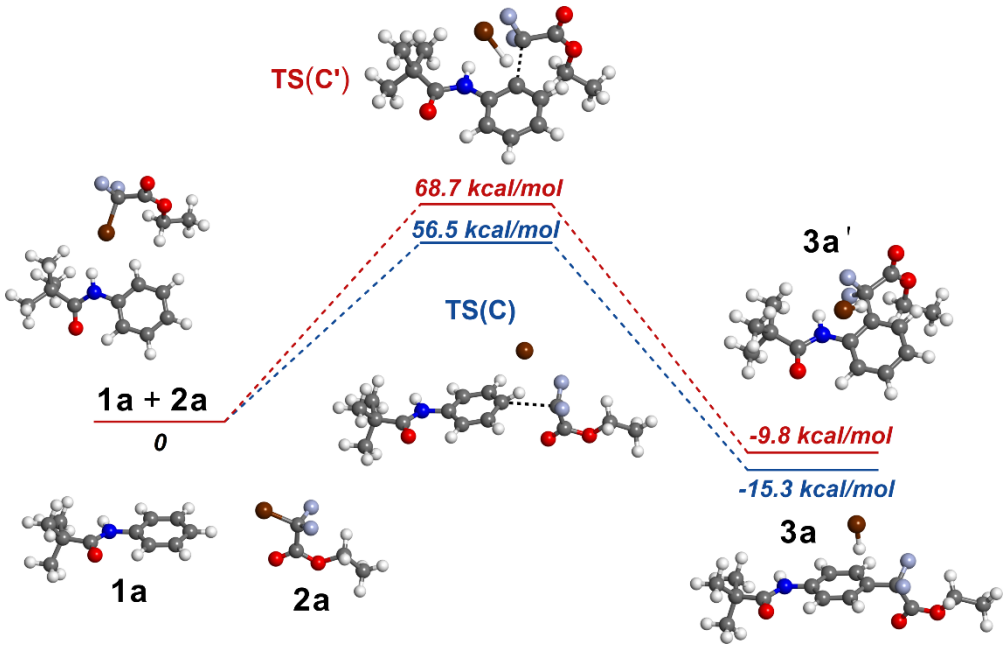


Figure S6 The calculated reaction energy barriers of **1a**+**2a**→**3a** and **1a**+**2a**→**3a'**

Cartesian Coordinates:

1a+2a→3a

Init

C	-0.873500	1.418800	0.651800
C	0.513800	1.325300	0.768800
C	1.157100	0.099000	0.558700
C	0.394100	-1.026800	0.234200
C	-0.997600	-0.948000	0.114600
C	-1.639200	0.285900	0.318900
H	-1.377200	2.374200	0.815700

H	1.092400	2.214700	1.025200
H	0.883900	-1.988500	0.071800
H	-1.588600	-1.823000	-0.139300
N	-3.033100	0.472400	0.209900
H	-3.340000	1.428000	0.373800
C	-4.017800	-0.431100	-0.094300
C	-5.459200	0.112700	-0.146100
C	-5.597400	1.608900	0.161200
H	-5.049800	2.228700	-0.566100
H	-6.659500	1.887000	0.097300
H	-5.254600	1.850300	1.180200
C	-6.277500	-0.690400	0.882900
H	-7.332600	-0.382400	0.825400
H	-6.206000	-1.766600	0.675100
H	-5.914300	-0.499800	1.903900
C	-6.002400	-0.164400	-1.560600
H	-7.067800	0.108200	-1.593300
H	-5.465700	0.436400	-2.310200
H	-5.894700	-1.228700	-1.810500
O	-3.792200	-1.634300	-0.319900
C	10.327600	0.545400	-1.328200
H	10.308700	1.629500	-1.503300
H	11.304400	0.276100	-0.900400
H	10.206700	0.018100	-2.285200
C	9.255800	0.135600	-0.348900
H	9.259800	-0.943300	-0.160200
H	9.337300	0.685100	0.594400
O	7.952100	0.461900	-0.987600
C	6.771600	0.484000	-0.364600

C	6.755900	0.238800	1.179900
O	5.744400	0.719700	-0.976100
F	7.434900	1.255800	1.798700
F	7.391000	-0.929500	1.493700
H	2.243600	0.025200	0.635700
Br	4.940300	0.175400	1.919700

TS

C	-0.796300	1.411100	0.578300
C	0.546400	1.262200	0.876700
C	1.143300	-0.013200	0.874200
C	0.420700	-1.099100	0.342700
C	-0.925100	-0.986200	0.035500
C	-1.565100	0.257300	0.254400
H	-1.277700	2.388600	0.606600
H	1.151700	2.123100	1.184700
H	0.926000	-2.064400	0.242400
H	-1.499200	-1.831700	-0.335000
N	-2.938900	0.449300	0.184500
H	-3.245100	1.389500	0.451000
C	-3.952500	-0.460600	-0.106600
C	-5.372200	0.094600	-0.141500
C	-5.495600	1.573300	0.255000
H	-4.920600	2.229800	-0.419000
H	-6.552500	1.866700	0.175800
H	-5.179200	1.748500	1.295900
C	-6.232400	-0.764100	0.801000
H	-7.279200	-0.436900	0.720700

H	-6.165700	-1.823600	0.518600
H	-5.908400	-0.649100	1.846900
C	-5.864400	-0.081100	-1.591600
H	-6.915500	0.235400	-1.641600
H	-5.276400	0.536200	-2.288300
H	-5.792600	-1.134300	-1.896400
O	-3.707000	-1.653900	-0.358600
C	8.113500	0.085200	-0.716500
H	8.217700	1.179200	-0.784200
H	8.906200	-0.305500	-0.061700
H	8.229400	-0.362100	-1.716200
C	6.769100	-0.279500	-0.130200
H	6.622200	-1.362000	-0.055600
H	6.602300	0.201800	0.838500
O	5.736600	0.220200	-1.076600
C	4.447700	0.385900	-0.748500
C	4.041000	-0.028500	0.660500
O	3.636500	0.849400	-1.537100
F	4.262700	0.834100	1.631600
F	4.227500	-1.278800	1.035300
H	2.043600	-0.193200	1.470600
Br	2.262600	-0.741100	4.074100

Final

C	-0.698700	1.327300	0.666300
C	0.684100	1.232200	0.736200
C	1.314100	-0.005400	0.519200
C	0.536600	-1.129900	0.205900

C	-0.852500	-1.040300	0.133000
C	-1.482200	0.198300	0.353100
H	-1.187800	2.287100	0.840400
H	1.278800	2.114700	0.971700
H	1.018700	-2.091400	0.033400
H	-1.451500	-1.916100	-0.098000
N	-2.866500	0.396200	0.282400
H	-3.163000	1.348400	0.482800
C	-3.864400	-0.480100	-0.083900
C	-5.290200	0.097700	-0.141700
C	-5.408500	1.564600	0.293600
H	-4.816900	2.233700	-0.352300
H	-6.460700	1.872600	0.208300
H	-5.105400	1.705700	1.342600
C	-6.177000	-0.776000	0.764700
H	-7.220700	-0.437700	0.679900
H	-6.117000	-1.829500	0.459400
H	-5.867000	-0.688900	1.817200
C	-5.765000	-0.036500	-1.602300
H	-6.809900	0.302700	-1.668700
H	-5.150700	0.582700	-2.274100
H	-5.709400	-1.084300	-1.929000
O	-3.646800	-1.667600	-0.370700
C	7.113100	-0.098500	-0.466500
H	7.280600	0.986500	-0.497000
H	7.829900	-0.543300	0.239100
H	7.298600	-0.523000	-1.462800
C	5.713400	-0.421800	0.000500
H	5.527500	-1.501100	0.020400

H	5.499900	0.013700	0.982100
O	4.792400	0.169600	-0.998500
C	3.478800	0.339100	-0.811700
C	2.812600	-0.089800	0.531600
O	2.797800	0.856500	-1.686600
F	3.330000	0.753800	1.520900
F	3.217500	-1.378600	0.856700
Br	0.923000	-0.863700	3.974200
H	1.004700	-0.498500	2.567800

1a+2a→3a'

Init

C	-0.363900	1.323800	1.361200
C	-1.501500	2.133400	1.373100
C	-1.697300	3.087900	0.368400
C	-0.736800	3.231300	-0.638900
C	0.408500	2.429700	-0.658000
C	0.592800	1.463800	0.342900
H	-2.235000	2.013600	2.171900
H	-0.872400	3.982200	-1.419100
H	1.156900	2.553100	-1.436000
N	1.732800	0.625700	0.391700
H	1.966800	0.266000	1.313100
C	2.462200	0.147400	-0.669300
C	3.554100	-0.889600	-0.334100
C	2.949500	-2.273800	-0.647100
H	2.594800	-2.311000	-1.688400
H	3.718900	-3.047700	-0.507300
H	2.105200	-2.501100	0.021300

C	4.036800	-0.850400	1.124100
H	4.870600	-1.559300	1.235600
H	4.398200	0.151800	1.401600
H	3.261600	-1.167500	1.840700
C	4.752300	-0.640200	-1.262700
H	5.522600	-1.399700	-1.064900
H	4.445400	-0.704500	-2.315000
H	5.184600	0.354900	-1.083100
O	2.230300	0.483500	-1.843100
O	-0.624000	-1.414600	6.050000
C	-0.897200	-2.068100	5.056700
O	-2.122600	-2.056100	4.538400
H	-2.585800	3.720100	0.373400
C	0.215000	-2.945700	4.411700
F	-0.160400	-4.255300	4.338000
F	1.335000	-2.890500	5.163800
C	-2.548100	-2.726000	3.283900
H	-2.311200	-2.029600	2.469800
H	-1.993900	-3.659700	3.147900
C	-4.031400	-2.975700	3.410400
H	-4.383900	-3.426300	2.471700
H	-4.242600	-3.668100	4.235500
H	-4.573000	-2.032700	3.571900
Br	0.669000	-2.289300	2.587300
H	-0.209300	0.577700	2.143000

TS

C	-0.756200	0.833100	0.575800

C	-1.773300	1.794600	0.706600
C	-1.631900	3.081800	0.191000
C	-0.423900	3.432400	-0.411600
C	0.588400	2.488900	-0.575000
C	0.444300	1.175800	-0.102600
H	-2.679900	1.579700	1.276400
H	-0.283400	4.437900	-0.810200
H	1.471200	2.749400	-1.149600
N	1.508100	0.267600	-0.173000
H	1.291200	-0.650400	0.184200
C	2.827200	0.406400	-0.508400
C	3.775400	-0.786300	-0.332500
C	3.137300	-2.179300	-0.249400
H	2.524400	-2.378400	-1.141200
H	3.918700	-2.952900	-0.200800
H	2.550700	-2.315900	0.670900
C	4.591100	-0.548100	0.949000
H	5.354100	-1.333400	1.052800
H	5.100400	0.425900	0.910300
H	3.944200	-0.574200	1.839200
C	4.720600	-0.777600	-1.549600
H	5.474200	-1.572000	-1.441800
H	4.145800	-0.944900	-2.473600
H	5.263000	0.175300	-1.634200
O	3.227900	1.525800	-0.857700
O	-2.716900	-1.384300	3.229000
C	-2.542800	-1.414700	2.022800
O	-3.562800	-1.454000	1.169100
H	-2.421400	3.820700	0.324500

C	-1.099700	-1.458200	1.473800
F	-0.987100	-2.560300	0.625200
F	-0.245300	-1.770800	2.515700
C	-3.471100	-1.526000	-0.307200
H	-2.738500	-0.796400	-0.666400
H	-3.149800	-2.536800	-0.582900
C	-4.859600	-1.223700	-0.818000
H	-4.855300	-1.291800	-1.916200
H	-5.586300	-1.944600	-0.421700
H	-5.160500	-0.205400	-0.533900
Br	1.357300	0.702500	3.522300
H	0.122700	1.285000	2.365700

Final

C	-0.938800	0.639200	0.215800
C	-1.967900	1.575100	0.404900
C	-1.779000	2.928400	0.136700
C	-0.539300	3.354100	-0.344700
C	0.505700	2.448900	-0.526700
C	0.337900	1.084800	-0.236500
H	-2.939100	1.241400	0.774400
H	-0.373700	4.403900	-0.589600
H	1.472000	2.786500	-0.888000
N	1.394600	0.170900	-0.334000
H	1.157600	-0.801000	-0.170400
C	2.750500	0.415200	-0.440500
C	3.668800	-0.811700	-0.289900
C	2.938800	-2.145700	-0.073300

H	2.285400	-2.395900	-0.924100
H	3.686400	-2.947000	0.012900
H	2.350100	-2.148700	0.857000
C	4.575500	-0.521900	0.922400
H	5.284900	-1.352200	1.049900
H	5.135000	0.411500	0.760900
H	3.973600	-0.425400	1.839500
C	4.529500	-0.907900	-1.564000
H	5.252000	-1.729600	-1.449300
H	3.899300	-1.115000	-2.444100
H	5.077800	0.030200	-1.734900
O	3.225000	1.544100	-0.626500
O	-2.974700	-1.429200	2.041200
C	-2.674300	-1.172200	0.886000
O	-3.603800	-1.185100	-0.074400
H	-2.594800	3.632300	0.294800
C	-1.205200	-0.808100	0.525200
F	-0.812900	-1.646000	-0.533100
F	-0.410000	-1.216000	1.596700
C	-3.353200	-0.896400	-1.507200
H	-2.559200	-0.149200	-1.605000
H	-3.030600	-1.839800	-1.964300
C	-4.660900	-0.392800	-2.071700
H	-4.540000	-0.223900	-3.152700
H	-5.462800	-1.126600	-1.918300
H	-4.939300	0.560500	-1.600000
Br	1.081600	1.574800	3.152600
H	-0.056900	1.134900	2.377100

3.7 Quantum yield determination

The procedure described by previous reports[12] was followed to determine the photon flux of the apparatus used in these experiments. The actinometry data we obtained is presented below.

Preparation of Potassium Ferrioxalate Solution:

$K_3Fe(C_2O_4)_3 \cdot 3H_2O$ (118 mg) and 98% H_2SO_4 (56 μL) were added to a 20 mL volumetric flask and filled to the mark with distilled water.

Buffer solution:

Sodium acetate (0.988 g) and 98% H_2SO_4 (0.2 mL) were added to a 20 mL volumetric flask and filled to the mark with distilled water.

The actinometry measurements:

(a) 1 mL of the actinometer solution was taken in a quartz cuvette (l = 1 cm). The cuvettes of actinometer solution were placed at a distance of 5 cm away from a 20 W blue LED (λmax = 455 nm) and irradiated for 30 s. The same process was repeated for different time intervals: 60 s and 90 s.

(b) After irradiation, the actinometer solution was transferred to a 10 mL volumetric flask containing 1.0 mg of 1,10-phenanthroline in 2 mL of buffer solution. The flask was filled to the mark with distilled water. In a similar manner, a blank solution (10 mL) was also prepared using the actinometer solution stored in dark.

(c) Absorbance of the actinometer solution after complexation with 1,10-phenanthroline at λ = 510 nm was measured by UV/Vis spectrophotometry.

(d) According to Beer's law, the number of moles of Fe^{2+} formed (x) for each sample was determined by equation S6:

$$n_{Fe(2+)} = \frac{V1*V3*\Delta A_{510nm}}{1000*V2*l*\varepsilon} \quad \text{(S6)}$$

Where:

V1 = Irradiated volume (1 mL).

V2 = The aliquot of the irradiated solution taken for the estimation of Fe^{3+} ions (1 mL).

V3 = Final volume of the solution after complexation with 1,10-phenanthroline (10 mL).

ε(510nm) = Molar extinction coefficient of $[Fe(Phen)_3]^{2+}$complex (11100 L $mol^{-1}cm^{-1}$).

l = Optical path-length of the cuvette (1 cm).

Δ A(510 nm) = Difference in absorbance between the irradiated solution and the solution stored in dark (blank).

Sample calculation:

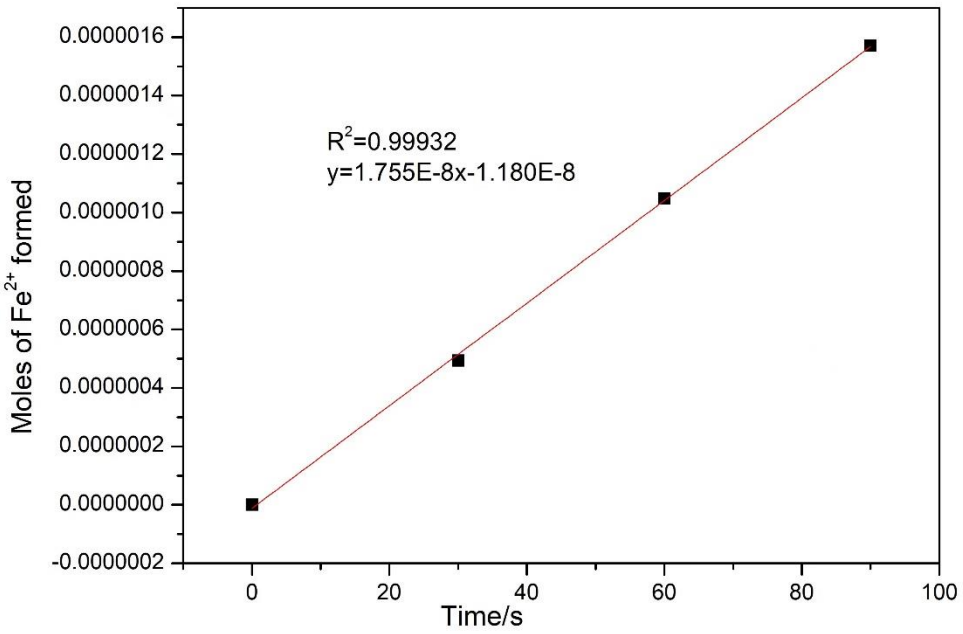
$A^0 = 0.103$, $A^1_{30s} = 0.651$, $A^1_{60s} = 1.266$, $A^1_{90s} = 1.846$

$\Delta A^1_{30s} = 0.548$, $\Delta A^1_{60s} = 1.163$, $\Delta A^1_{90s} = 1.743$

$n(Fe^{2+})_{30s}$ = (1mL x 10 mL x 0.548)/(1000 x 1mL x 1mL x 1110L mol^{-1} cm^{-1}) = 4.937 x 10^{-7} mol

$n(Fe^{2+})_{60s}$ = (1mL x 10 mL x 1.163)/(1000 x 1mL x 1mL x 1110L mol^{-1} cm^{-1}) = 1.048 x 10^{-6} mol

$n(Fe^{2+})_{90s}$ = (1mL x 10 mL x 1.743)/(1000 x 1mL x 1mL x 1110L mol^{-1} cm^{-1}) = 1.570 x 10^{-6} mol



(e) The number of moles of Fe^{2+} formed (x) was plotted as a function of time (t). The

slope (dx/dt) of the line is equal to the number of moles of Fe^{2+} formed per unit time (dx/dt = 1.755 x10^{-8}).

(f) This slope (dx/dt) was correlated to the number of moles of incident photons per unit time (ϕq = photon flux) by using following equation S7:

$$\emptyset_q = \frac{dx/dt}{\emptyset_F.(1-10^{-A_{455nm}})} \qquad \text{(S7)}$$

Where:

Φ_F is the quantum yield of the ferrioxalate actinometer (0.9 at λ = 450 nm).[12e]

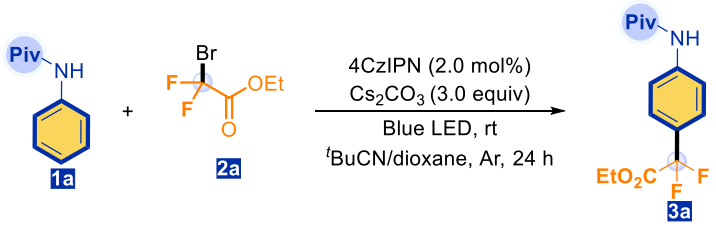
The fraction of light absorbed at λ = 455 nm by the actinometer (f) is calculated by using equation S8.

A_{455nm} is the absorbance of the ferrioxalate solution at λ = 455 nm (A_{455nm} = 1.919).

$$f = 1 - 10^{-A_{450nm}} \qquad \text{(S8)}$$

The photon flux Φ_q was therefore calculated to be 1.974*10^{-8} einstein s^{-1} as an average of three experiments.

Determination of the quantum yield of the reaction:



To a 4 mL quartz cuvette with two sides taped over with electrical tape was charged with **1a** (35.4 mg, 0.20 mmol), 4CzIPN (3.2 mg, 0.004 mmol), **2a** (81.2 mg, 0.4 mmol, 2.0 equiv), Cs_2CO_3 (195.5 mg, 0.60 mmol, 3.0 equiv) in ^{t}BuCN/dioxane (2.5/1, 1.4 mL) under an air atmosphere. Then the cuvette was evacuated and filled with Ar (1 atm), and stirred at rt for proper mixing of the reactants. Then the mixture was irradiated for 3h at λ_{max} = 455 nm with 20 W blue LEDs at rt. After irradiation, the yield of product **3a** was determined to be 20.8% by ^{19}F NMR with 2,2,2-trifluoroacetophenone as internal standard. The reaction quantum yield (ϕ) was determined using equation S9, where the photon flux is 1.974*10^{-8} einstein s^{-1} (determined by actinometry as mentioned above), t is the reaction time (3 h) and f_R is the fraction of incident light

absorbed by the reaction mixture, determined using equation S8. An absorption spectrum of the reaction mixture gave an absorbance value of 3.393 at 455 nm leading to a f_R value of 0.99 indicating that essentially almost all incident light is absorbed by the photocatalyst.

$$\emptyset = \frac{mol\ product}{\emptyset_q \cdot t \cdot f_R} \qquad \text{(S9)}$$

Thus, the reaction quantum yield (Φ) was determined to be ϕ = 0.197.

3.8 Cyclic voltammetry experiments

All voltammograms were taken at room temperature using a saturated calomel (SCE) reference electrode, a mesh platinum (Pt) counter electrode, and a glassy carbon working electrode.[12c] The conditions of the experiments were the following: The sample in 5 mL of 0.001 M tetrabutylammonium tetrafluoroborate (n-Bu_4NBF_4) in dry and degassed MeCN. A scan rate of 0.1 V/s was used, and a negative initial scan direction. The reported potentials were averages over segments, and were taken at half-height of the cathodic peaks (Ep/2).

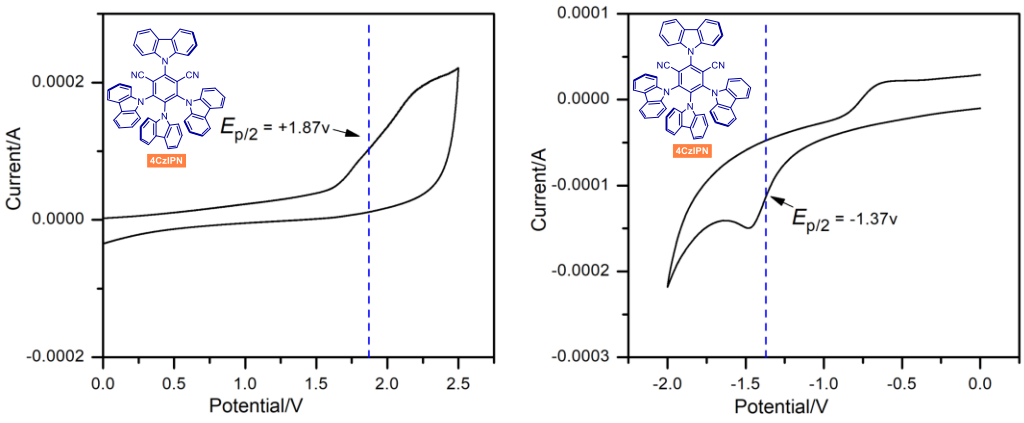


Figure S7. Cyclic voltammogram of **4CzIPN**

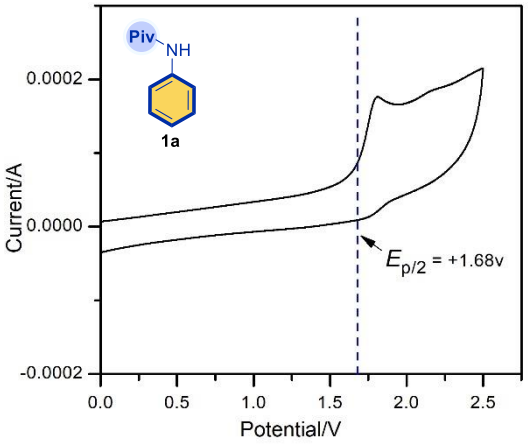


Figure S8. Cyclic voltammogram of **1a**

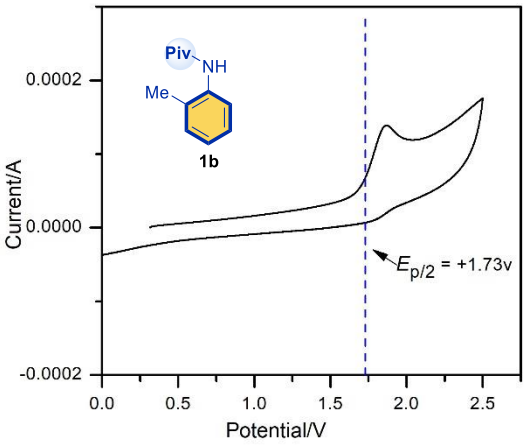


Figure S9. Cyclic voltammogram of **1b**

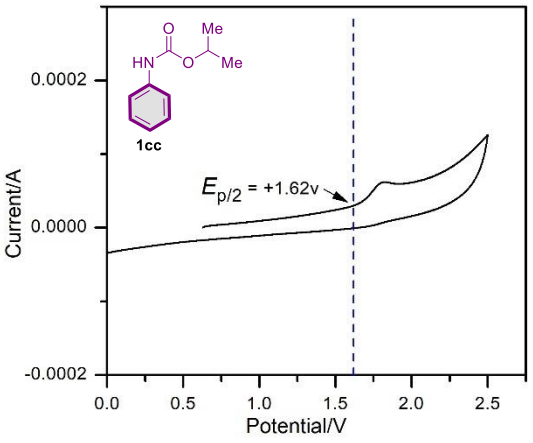


Figure S10. Cyclic voltammogram of **1cc**

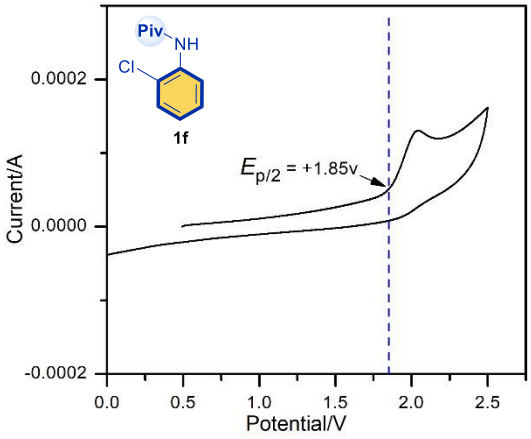


Figure S11. Cyclic voltammogram of **1f**

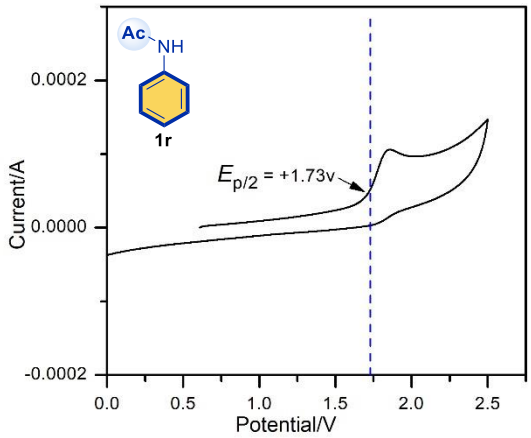


Figure S12. Cyclic voltammogram of **1r**

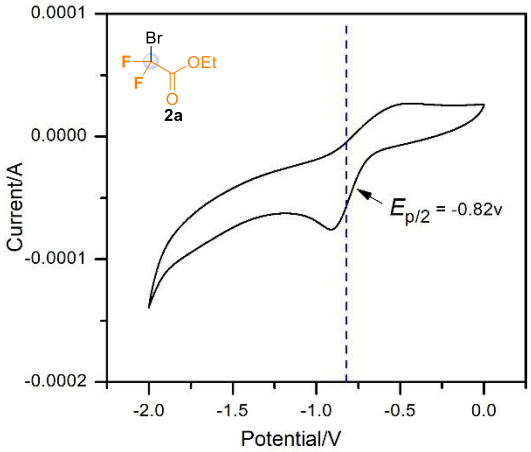


Figure S13. Cyclic voltammogram of **2a**

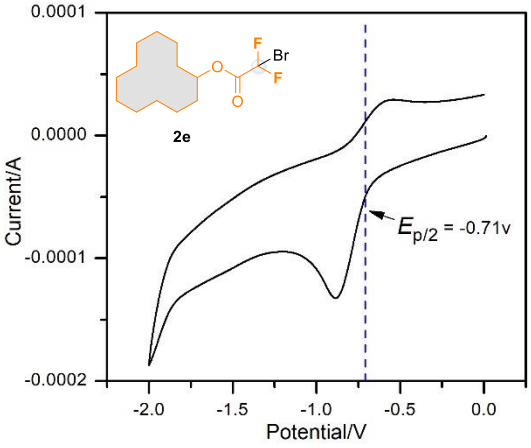


Figure S14. Cyclic voltammogram of **2e**

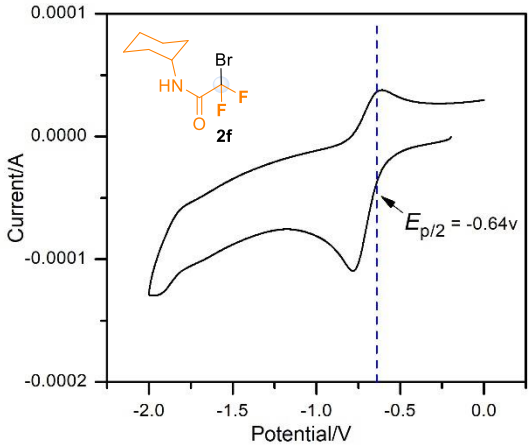


Figure S15. Cyclic voltammogram of **2f**

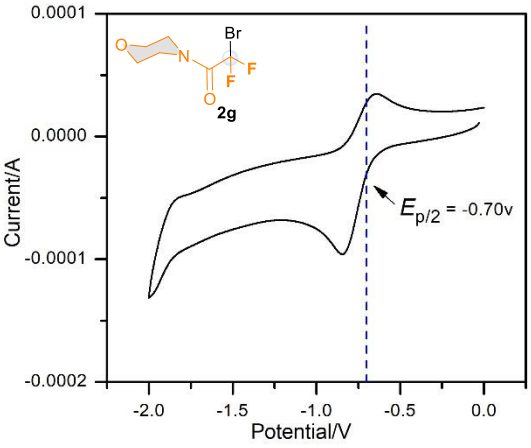


Figure S16. Cyclic voltammogram of **2g**

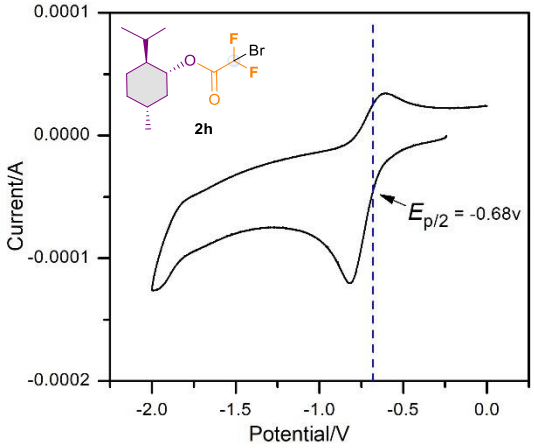
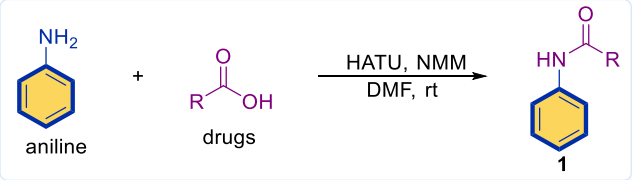


Figure S17. Cyclic voltammogram of **2h**

4. Preparation of starting materials

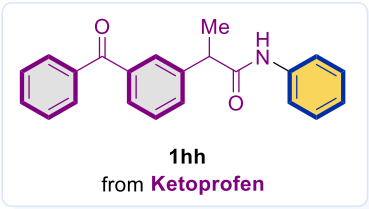
Preparation of the derivatives of aromatic amine:

All of the derivatives of aromatic amine were synthesized according to the previous reports. [2] Other compounds such as **1hh**, **1ii**, **1jj**, **1kk**,**1ll** were prepared according to the following method A.



Method A: To 100 mL round-bottom flask was charged with drugs (1 equiv), aniline (1.1 equiv), HATU (1.2 equiv), NMM (1.5 equiv), in DMF (0.25 M). Then, the mixture was stirred at rt for 24h. After that, the mixture was diluted with ethyl acetate, washed by water and brine, dried with anhydrous sodium sulfate, and concentrated to give the residues. Subsequently, the crude product was separated by column chromatography on silica gel (elution solvent: EtOAc/petroleum ether = 1/20 to 1/3) to afford the amidated compounds **1**.

2-(3-benzoylphenyl)-*N*-phenylpropanamide (1hh): (known compound, CAS: 59512-28-6).

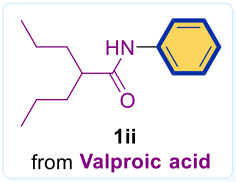


To 100 mL round-bottom flask was charged with ketoprofen (1.1 g, 4.3 mmol), aniline (437 mg, 4.7 mmol), HATU (2.0 g, 5.2 mmol), NMM (656 mg, 6.5 mmol), in DMF (0.25 M). The residue obtained through method A was purified by column chromatograph (silica gel, petroleum ether: AcOEt = 5:1) to give the **1hh** as a white solid (68%, 962 mg, m.p. 102.2–104.0 °C).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.86 – 7.74 (m, 3H), 7.71 – 7.55 (m, 4H), 7.46 (dq, *J* = 8.0, 3.6, 2.8 Hz, 5H), 7.30 – 7.23 (m, 2H), 7.06 (t, *J* = 7.2 Hz, 1H), 3.77 (q, *J* = 7.1 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 196.8, 171.9, 171.9, 141.7, 138.1, 137.9, 137.3, 132.7, 131.5, 130.1, 129.4, 129.2, 129.0, 128.4, 124.4, 119.9, 47.9, 18.8.

***N*-phenyl-2-propylpentanamide (1ii):** (known compound, CAS: 2936-09-6).

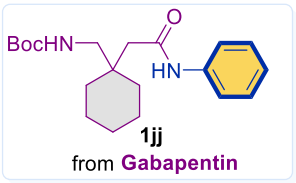


To 100 mL round-bottom flask was charged with valproic acid (0.6 g, 4.2 mmol), aniline (438 mg, 4.6 mmol), HATU (1.9 g, 5.0 mmol), NMM (636 mg, 6.3 mmol), in DMF (0.25 M). The residue obtained through method A was purified by column chromatograph (silica gel, petroleum ether: AcOEt = 15:1) to give the **1ii** as a white solid (81%, 745 mg, m.p. 104.9–105.5 °C).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.50 (m, 2H), 7.35 (s, 1H), 7.33 – 7.27 (m, 2H), 7.12 – 7.06 (m, 1H), 2.27 – 2.14 (m, 1H), 1.74 – 1.63 (m, 2H), 1.50 – 1.28 (m, 6H), 0.91 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.7, 138.0, 128.9, 124.2, 120.0, 48.8, 35.4, 20.9, 14.2.

***tert*-butyl ((1-(2-oxo-2-(phenylamino)ethyl)cyclohexyl)methyl)carbamate (1jj):**



To 100 mL round-bottom flask was charged with Boc-protected gabapentin (1.3 g, 4.8 mmol), aniline (491 mg, 5.3 mmol), HATU (2.2 g 5.8 mmol), NMM (979.7 mg, 9.7 mmol), in DMF (0.25 M). The residue obtained through method A was purified by

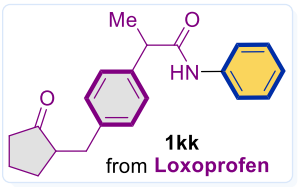
column chromatograph (silica gel, petroleum ether: AcOEt = 10:1) to give the **1jj** as a white solid (70%, 1.1 g, m.p. 154.2–155.1 ºC).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 7.74 – 7.62 (m, 2H), 7.34 – 7.27 (m, 2H), 7.09 – 7.03 (m, 1H), 4.99 (t, *J* = 7.1 Hz, 1H), 3.19 (d, *J* = 7.2 Hz, 2H), 2.28 (s, 2H), 1.67 – 1.57 (m, 2H), 1.49 (s, 14H), 1.41 – 1.31 (m, 1H), 1.29 – 1.17 (m, 2H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.6, 157.9, 139.1, 128.8, 123.6, 119.6, 80.3, 47.5, 43.1, 37.7, 34.2, 28.4, 26.0, 21.4.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{30}N_2O_3Na$ 369.2149; found: 369.2150.

2-(4-((2-oxocyclopentyl)methyl)phenyl)-*N*-phenylpropanamide (1kk): (known compound, CAS: 2644046-40-0).

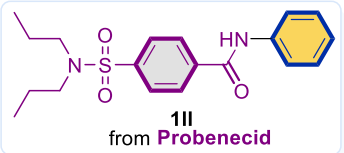


To 100 mL round-bottom flask was charged with Loxoprofen (763 mg, 3.1 mmol), aniline (317 mg, 3.4 mmol), HATU (1.4 g, 3.7 mmol), NMM (464.6 mg, 4.6 mmol), in DMF (0.25 M). The residue obtained through method A was purified by column chromatograph (silica gel, petroleum ether: AcOEt = 10:1) to give the **1kk** as a colorless oil (60%, 597 mg).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.24 (m, 5H), 7.22 – 7.15 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 3.68 (q, *J* = 7.1 Hz, 1H), 3.14 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.54 (dd, *J* = 14.0, 9.4 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.16 – 2.07 (m, 2H), 2.00 – 1.92 (m, 1H), 1.79 – 1.72 (m, 1H), 1.61 – 1.51 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 220.2, 172.4, 139.4, 138.8, 138.7, 137.9, 129.7, 129.6, 128.9, 127.8, 124.2, 119.7, 51.0, 47.8, 38.2, 35.2, 29.3, 20.5, 18.6.

4-(*N*, *N*-dipropylsulfamoyl)-*N*-phenylbenzamide (1ll): (known compound, CAS: 313515-83-2).

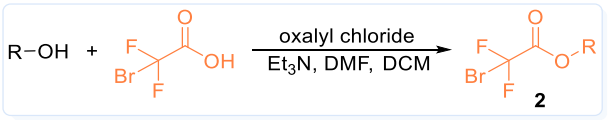


To 100 mL round-bottom flask was charged with probenecid (1.0 g, 3.5 mmol), aniline (358 mg, 3.85 mmol), HATU (1.6 g, 4.2 mmol), NMM (535 mg, 5.3 mmol), in DMF (0.25 M). The residue obtained through method A was purified by column chromatograph (silica gel, petroleum ether: AcOEt = 3:1) to give the **1ll** as a white solid (730 mg, m.p. 125.9–126.9 °C).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.94 (td, *J* = 8.9, 8.3, 4.9 Hz, 2H), 7.86 – 7.76 (m, 2H), 7.68 (t, *J* = 8.1 Hz, 2H), 7.39 (td, *J* = 8.0, 3.6 Hz, 2H), 7.18 (tdd, *J* = 7.4, 3.5, 1.4 Hz, 1H), 3.09 (ddd, *J* = 9.2, 7.4, 5.4 Hz, 4H), 1.55 (ddd, *J* = 12.0, 8.5, 5.9 Hz, 4H), 0.87 (td, *J* = 7.4, 3.4 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.8, 142.7, 138.7, 137.8, 129.1, 128.0, 127.3, 124.9, 120.3, 50.0, 22.0, 11.2.

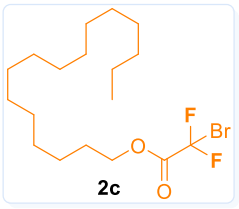
Preparation of bromodifluoroacetic acid ester:



Method B: According to the reported method,[3] to a stirred solution of 2-bromo-2,2 difluoroacetic acid (875 mg, 5.0 mmol) and oxalyl chloride (0.46 mL, 1.1 equiv.) in 10 mL of CH_2Cl_2, was added 2 drops of DMF at room temperature under an argon atmosphere. The mixture was allowed to stir for 2 h before it was cooled to 0 °C and a solution of alcohol (1.05 equiv.) and Et_3N (0.76 mL, 1.1 equiv.) in 10 mL CH_2Cl_2 was added dropwise. The resulting reaction mixture was stirred at room temperature until completion as monitored by TLC. The reaction was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and dried over Na_2SO_4 and the solvent was removed. The crude

was purified with silica gel chromatography (elution solvent: petroleum ether) to give the product (**2c**, **2d**, **2e**, **2h**, **2i** or **2j**).

hexadecyl 2-bromo-2,2-difluoroacetate (2c): (known compound, CAS: 2241635-54-9). (Colorless oil, 73%, 1.5 g).

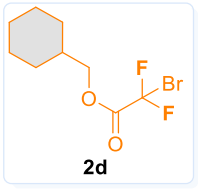


^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.35 (t, *J* = 6.7 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.44 – 1.35 (m, 2H), 1.26 (s, 24H), 0.92 – 0.84 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.7, 108.8 (t, $J_{C\text{-}F}$ = 315.12 Hz), 68.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.1, 28.1, 25.5, 22.7, 14.1.

^{19}F NMR (377 MHz, Chloroform-*d*) δ -60.67.

cyclohexylmethyl 2-bromo-2,2-difluoroacetate (2d): (Colorless oil, 77%, 1.0 g).

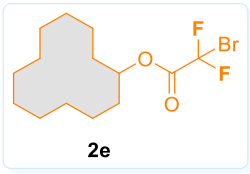


^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.16 (d, *J* = 6.2 Hz, 2H), 1.81 – 1.73 (m, 5H), 1.72 – 1.67 (m, 1H), 1.32 – 1.24 (m, 2H), 1.22 – 1.14 (m, 1H), 1.09 – 0.97 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.7 (t, $J_{C\text{-}F}$ = 31.71 Hz), 108.8 (t, $J_{C\text{-}F}$ = 314.08 Hz), 73.1, 36.9, 29.2, 26.1, 25.5.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -60.55.

cyclododecyl 2-bromo-2,2-difluoroacetate (2e): (known compound, CAS: 2608047-42-1). (Light yellow oil, 70%, 1.2 g).

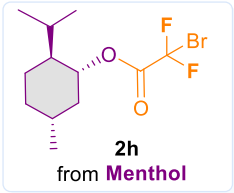


2e

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.22 – 5.10 (m, 1H), 1.91 – 1.77(m, 2H), 1.68 – 1.56 (m, 2H), 1.47 – 1.28 (m, 18H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.3 (t, $J_{C\text{-}F}$ = 30.30 Hz), 109.1 (t, $J_{C\text{-}F}$ = 316.13 Hz), 78.0, 28.6, 24.0, 23.9, 23.3, 23.1, 20.6.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2,2-difluoroacetate (2h): (known compound, CAS: 1037299-19-6). (Light yellow oil, 80%, 1.3 g).

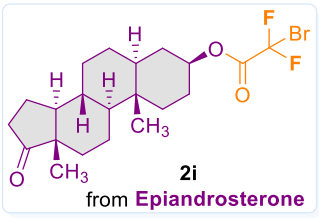


2h
from Menthol

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.84 (td, J = 11.0, 4.5 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.98 – 1.86 (m, 1H), 1.79 – 1.68 (m, 2H), 1.60 – 1.49 (m, 2H), 1.20 – 1.03 (m, 2H), 0.98 – 0.85 (m, 7H), 0.79 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.3 (t, $J_{C\text{-}F}$ = 30.30 Hz), 108.9 (t, $J_{C\text{-}F}$ = 316.13 Hz), 79.5, 46.8, 39.9, 33.9, 31.4, 26.2, 23.3, 21.9, 20.6, 16.1.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2-bromo-2,2-difluoroacetate (2i): (known compound, CAS: 2730126-31-3). (White solid, 58%, 1.3 g, m.p. 169.3–169.5 °C).



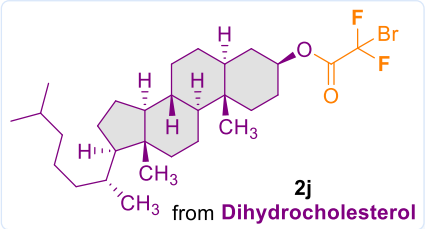
2i
from Epiandrosterone

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.89 (tt, J = 11.5, 5.0 Hz, 1H), 2.44 (ddd, J = 19.1, 8.9, 1.1 Hz, 1H), 2.13 – 2.00 (m, 1H), 1.98 – 1.89 (m, 2H), 1.85 – 1.78 (m, 3H),

1.76 – 1.46 (m, 6H), 1.40 – 1.19 (m, 6H), 1.13 – 0.94 (m, 2H), 0.89 (s, 3H), 0.86 (s, 3H), 0.78 – 0.68 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 221.1, 159.1 (t, $J_{C\text{-}F}$ = 30.30 Hz), 109.0 (t, $J_{C\text{-}F}$ = 315.12 Hz), 78.5, 54.2, 51.3, 47.8, 44.6, 36.5, 35.8, 35.6, 35.0, 33.1, 31.5, 30.7, 28.2, 26.8, 21.8, 20.5, 13.8, 12.2.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[a]phenanthren-3-yl 2-bromo-2,2-difluoroacetate (2j): (White solid, 56%, 1.5 g, m.p. 107.6–108.2 ºC).

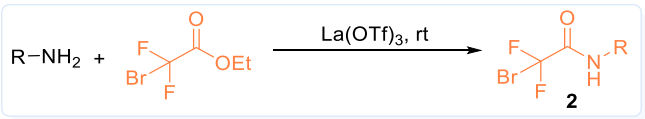


^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.88 (tt, *J* = 11.5, 5.0 Hz, 1H), 1.97 (dt, *J* = 12.6, 3.4 Hz, 1H), 1.94 – 1.87 (m, 1H), 1.85 – 1.76 (m, 2H), 1.72 – 1.62 (m, 3H), 1.61 – 1.43 (m, 5H), 1.40 – 1.24 (m, 8H), 1.23 – 0.96 (m, 10H), 0.92 – 0.83 (m, 12H), 0.72 – 0.60 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.2 (t, $J_{C\text{-}F}$ = 30.30 Hz), 109.1 (t, $J_{C\text{-}F}$ = 315.12 Hz), 78.9, 56.4, 56.3, 54.1, 44.6, 42.6, 39.9, 39.5, 36.5, 36.2, 35.8, 35.4, 33.2, 31.9, 28.5, 28.2, 28.0, 26.8, 24.2, 23.8, 22.8, 22.6, 21.2, 18.7, 12.2, 12.1.

^{19}F NMR (377 MHz, Chloroform-*d*) δ -60.88.

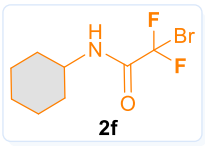
Preparation of bromodifluoroacetamides:[4]



Method C: To a round-bottom flask equipped with stir bar was added amine (2.0 mmol) under argon, then ethyl bromodifluoroacetate (1.2 equiv) was added with lanthanum

trifluoromethanesulfonate (5 mol %). The mixture was stirred at the room temperature and monitored by TLC. After the amine was exhausted, the mixture was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel to give the corresponding amide **2f**, **2g**.

2-bromo-*N*-cyclohexyl-2,2-difluoroacetamide (2f): (known compound, CAS: 1254884-88-2). The reaction was performed following the method C. The residue was purified by flash column chromatography (silica gel, petroleum ether: AcOEt = 10:1) to give the desired product **2f** as a white solid (85%,433 mg, m.p. 100.6–101.6 ºC).

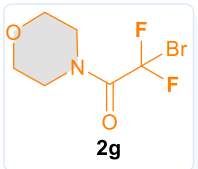


2f

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.18 (s, 1H), 3.87 – 3.69 (m, 1H), 2.01 – 1.91 (m, 2H), 1.80 – 1.71 (m, 2H), 1.69 – 1.59 (m, 1H), 1.45 – 1.31 (m, 2H), 1.30 – 1.12 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.1 (t, $J_{C\text{-}F}$ = 27.27 Hz), 112.0 (t, $J_{C\text{-}F}$ = 317.14 Hz), 49.5, 32.3, 25.2, 24.6.

2-bromo-2,2-difluoro-1-morpholinoethan-1-one (2g): (known compound, CAS: 149229-27-6). The reaction was performed following the method C. The residue was purified by flash column chromatography (silica gel, petroleum ether: AcOEt = 8:1) to give the desired product **2g** as a light-yellow oil (90%,437 mg).



2g

^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.76 (q, J = 6.1, 5.5 Hz, 4H), 3.71 (dt, J = 9.9, 4.9 Hz, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.9 (t, $J_{C\text{-}F}$ = 27.18 Hz), 110.5 (t, $J_{C\text{-}F}$ = 315.59 Hz), 66.5, 66.1, 47.3 (t, $J_{C\text{-}F}$ = 3.02 Hz), 43.9.

5. General procedure for the synthesis of difluoromethylated products

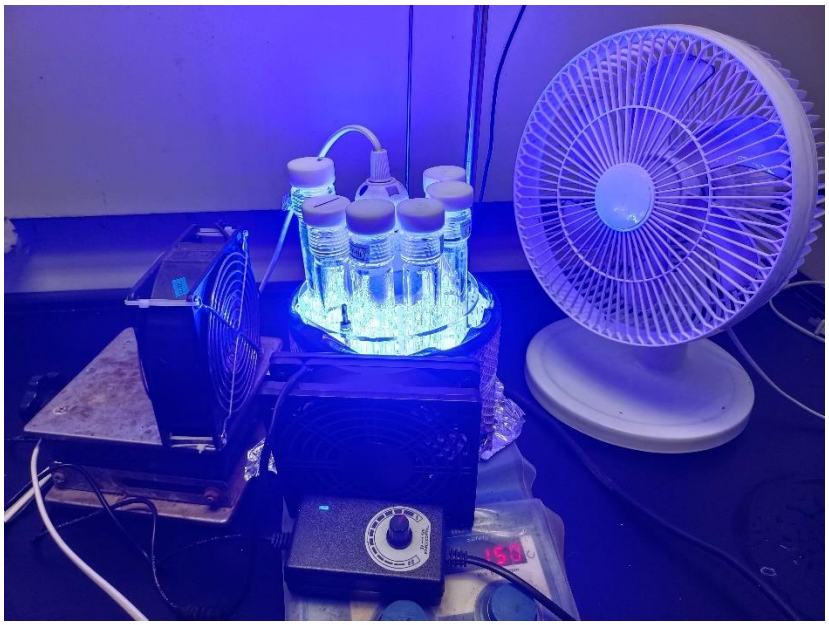
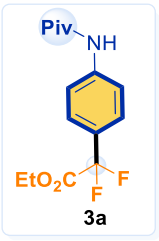


Figure S18. Blue LED photoreactor

To a 15 mL Schlenk tube was charged with **1** (0.20 mmol), 4CzIPN (3.2 mg, 0.004 mmol), **2** (0.4 mmol, 2.0 equiv), Cs_2CO_3 (195.5 mg, 0.60 mmol, 3.0 equiv) in ^{t}BuCN/dioxane (2.5/1, 1.4 mL) under an air atmosphere. Then the tube was evacuated and filled with Ar (1 atm), and stirred at rt for proper mixing of the reactants. Then the mixture was irradiated with 30 W blue LEDs at rt and stirred vigorously for 24 h (Figure S18). After that, the reaction mixture was diluted with ethyl acetate, filtered through diatomite, and concentrated in vacuo to give the residue. The crude product was separated by column chromatography on silica gel (elution solvent: EtOAc/petroleum ether) to afford the title compounds **3** or **4**.

6. Spectroscopic data of the difluoromethylated compounds

ethyl 2,2-difluoro-2-(4-pivalamidophenyl)acetate (3a):



3a

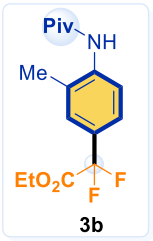
The title compound **3a** was prepared according to the general procedure as a light yellow solid, 46.6 mg, 78% yield, m.p. 101.8–103.2 °C, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.41 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.32 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.8, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 140.5, 128.2 (t, $J_{C\text{-}F}$ = 25.67 Hz), 126.4 (t, $J_{C\text{-}F}$ = 6.04 Hz), 119.6, 113.3 (t, $J_{C\text{-}F}$ = 252.17 Hz), 63.1, 39.8, 27.6, 13.9.

The spectral data of the title compound **3a** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(3-methyl-4-pivalamidophenyl)acetate (3b):



3b

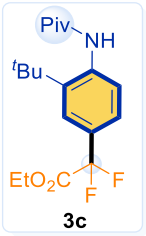
The title compound **3b** was prepared according to the general procedure as a white solid, 45.0 mg, 72% yield, m.p. 75.7–76.8 °C, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.33 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.35 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.6, 164.3 (t, $J_{C\text{-}F}$ = 42.28 Hz), 138.5, 128.5, 127.9, 127.4 (t, $J_{C\text{-}F}$ = 6.04 Hz), 124.3 (t, $J_{C\text{-}F}$ = 6.04 Hz), 121.9, 113.3 (t, $J_{C\text{-}F}$ = 252.17 Hz), 63.1, 40.0, 27.7, 17.6, 13.9.

The spectral data of the title compound **3b** were in accordance with the previously reported literature.[2]

ethyl 2-(3-(*tert*-butyl)-4-pivalamidophenyl)-2,2-difluoroacetate (3c):



3c

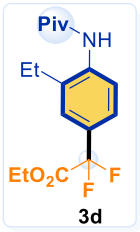
The title compound **3c** was prepared according to the general procedure as a white solid, 53.2 mg, 75% yield, m.p. 105.9–106.0 °C, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.56 (s, 1H), 7.46 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.45 (s, 9H), 1.36 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.3, 164.3, 141.2, 138.3, 129.1, 126.4, 124.2 (t, $J_{C\text{-}F}$ = 6.04 Hz), 123.7 (t, $J_{C\text{-}F}$ = 6.04 Hz), 113.5, 63.1, 39.7, 34.6, 30.4, 27.6, 13.9.

The spectral data of the title compound **3c** were in accordance with the reported literature.[2]

ethyl 2-(3-ethyl-4-pivalamidophenyl)-2,2-difluoroacetate (3d):



3d

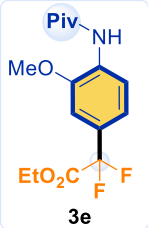
The title compound **3d** was prepared according to the general procedure as a white solid, 53.6 mg, 82% yield, m.p. 79.7–81.4 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.41 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.35 (s, 9H), 1.32 – 1.26 (m, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.6, 164.3 (t, $J_{C\text{-}F}$ = 34.73 Hz), 137.8, 133.6, 128.7 (t, $J_{C\text{-}F}$ = 24.16 Hz), 125.6 (t, $J_{C\text{-}F}$ = 6.04 Hz), 124.3 (t, $J_{C\text{-}F}$ = 6.04 Hz), 122.3, 113.4 (t, $J_{C\text{-}F}$ = 250.66 Hz), 63.1, 40.0, 27.6, 24.4, 13.9, 13.5.

The spectral data of the title compound **3d** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(3-methoxy-4-pivalamidophenyl)acetate (3e):



3e

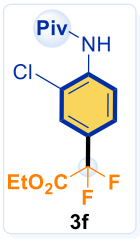
The title compound **3e** was prepared according to the general procedure as a light yellow solid, 49.3 mg, 75% yield, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 8.5 Hz, 1H), 8.19 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.10 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 1.32 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.8, 164.3 (t, $J_{C\text{-}F}$ = 36.24 Hz), 147.8, 130.3, 127.4 (t, $J_{C\text{-}F}$ = 25.67 Hz), 119.1, 118.7 (t, $J_{C\text{-}F}$ = 6.04 Hz), 113.3 (t, $J_{C\text{-}F}$ = 253.68 Hz), 106.8 (t, $J_{C\text{-}F}$ = 6.04 Hz), 63.1, 56.1, 40.2, 27.6, 13.9.

The spectral data of the title compound **3e** were in accordance with the previously reported literature.[5]

ethyl 2-(3-chloro-4-pivalamidophenyl)-2,2-difluoroacetate (3f):



3f

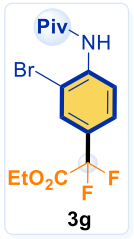
The title compound **3f** was prepared according to the general procedure as a light yellow oil, 36.6 mg, 55% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 8.7 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.35 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.9, 163.8 (t, $J_{C\text{-}F}$ = 34.73 Hz), 137.2, 128.5 (t, $J_{C\text{-}F}$ = 27.18 Hz), 126.2 (t, $J_{C\text{-}F}$ = 6.04 Hz), 125.3 (t, $J_{C\text{-}F}$ = 6.04 Hz), 122.8, 120.9, 112.5 (t, $J_{C\text{-}F}$ = 253.68 Hz), 63.4, 40.4, 27.5, 13.9.

The spectral data of the title compound **3f** were in accordance with the previously reported literature.[2]

ethyl 2-(3-bromo-4-pivalamidophenyl)-2,2-difluoroacetate (3g):



3g

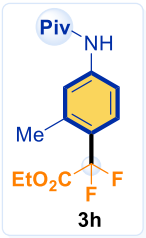
The title compound **3g** was prepared according to the general procedure as a colorless oil, 24.1 mg, 32% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 8.7 Hz, 1H), 8.13 (s, 1H), 7.80 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.36 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.9, 163.8 (t, $J_{C\text{-}F}$ = 34.73 Hz), 138.3, 129.4 (t, $J_{C\text{-}F}$ = 6.04 Hz), 128.9 (t, $J_{C\text{-}F}$ = 27.18 Hz), 125.9 (t, $J_{C\text{-}F}$ = 6.04 Hz), 121.0, 113.2, 112.4 (t, $J_{C\text{-}F}$ = 253.68 Hz), 63.4, 40.4, 27.5, 13.9.

The spectral data of the title compound **3g** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(2-methyl-4-pivalamidophenyl)acetate (3h):



3h

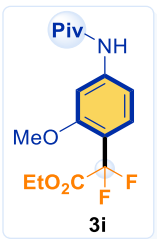
The title compound **3h** was prepared according to the general procedure as a white solid, 38.7 mg, 62% yield, m.p. = 117.8–118.1 °C, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.36 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.32 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.8, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 140.1, 137.7, 127.2 (t, $J_{C\text{-}F}$ = 9.06 Hz), 126.7 (t, $J_{C\text{-}F}$ = 22.65 Hz), 122.6, 116.8, 114.1 (t, $J_{C\text{-}F}$ = 252.17 Hz), 63.1, 39.8, 27.6, 19.8, 13.9.

The spectral data of the title compound **3h** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(2-methoxy-4-pivalamidophenyl)acetate (3i):



3i

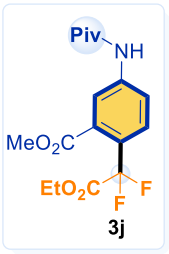
The title compound **3i** was prepared according to the general procedure as a light yellow solid, 46.6 mg, 71% yield, m.p. 85.2–85.5 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.78 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.45 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.33 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.0, 164.1 (t, $J_{C\text{-}F}$ = 34.73 Hz), 157.5, 142.0, 126.7 (t, $J_{C\text{-}F}$ = 6.04 Hz), 117.3 (t, $J_{C\text{-}F}$ = 25.67 Hz), 112.2 (t, $J_{C\text{-}F}$ = 247.64 Hz), 110.7, 103.2, 62.7, 55.8, 39.9, 27.6, 14.0.

The spectral data of the title compound **3i** were in accordance with the previously reported literature.[2]

methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-5-pivalamidobenzoate (3j):



3j

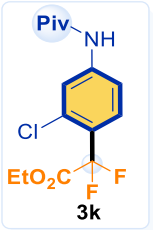
The title compound **3j** was prepared according to the general procedure as a white solid, 40.0 mg, 56% yield, m.p. 83.4–84.7 ºC, EtOAc/petroleum ether = 1:8 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 2.3 Hz, 1H), 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.51 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.34 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.0, 166.1, 163.4 (t, $J_{C\text{-}F}$ = 34.73 Hz), 140.2, 129.6, 128.8 (t, $J_{C\text{-}F}$ = 25.67 Hz), 128.0 (t, $J_{C\text{-}F}$ = 9.06 Hz), 122.6, 121.8, 113.1 (t, $J_{C\text{-}F}$ = 244.62 Hz), 62.7, 52.5, 39.9, 27.5, 13.9.

The spectral data of the title compound **3j** were in accordance with the previously reported literature.[2]

ethyl 2-(2-chloro-4-pivalamidophenyl)-2,2-difluoroacetate (3k):



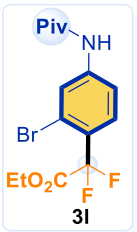
The title compound **3k** was prepared according to the general procedure as a white solid, 30.6 mg, 46% yield, m.p. 107.0–107.6 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.38 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.33 – 1.28 (m, 12H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.9, 163.2 (t, $J_{C\text{-}F}$ = 34.73 Hz), 141.2, 132.7 (t, $J_{C\text{-}F}$ = 4.53 Hz), 127.9 (t, $J_{C\text{-}F}$ = 9.06 Hz), 126.4 (t, $J_{C\text{-}F}$ = 24.16 Hz), 121.3, 117.4, 112.2 (t, $J_{C\text{-}F}$ = 250.66 Hz), 63.3, 39.9, 27.5, 13.8.

The spectral data of the title compound **3k** were in accordance with the previously reported literature.[2]

ethyl 2-(2-bromo-4-pivalamidophenyl)-2,2-difluoroacetate (3l):



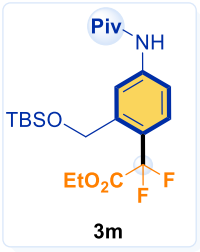
The title compound **3l** was prepared according to the general procedure as a white solid, 35.4 mg, 47% yield, m.p. 89.8–90.7 ºC. EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.43 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.34 – 1.30 (m, 12H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.9, 163.1 (t, J_{C-F} = 34.73 Hz), 141.1, 128.2 (t, J_{C-F} = 7.55 Hz), 128.1 (t, J_{C-F} = 24.16 Hz), 124.6, 120.8 (t, J_{C-F} = 4.53 Hz), 118.0, 112.7 (t, J_{C-F} = 250.66 Hz), 63.4, 39.9, 27.5, 13.8.

The spectral data of the title compound **3l** were in accordance with the previously reported literature.[2]

ethyl 2-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-pivalamidophenyl)-2,2-difluoroacetate (3m):



3m

The title compound **3m** was prepared according to the general procedure as a light yellow solid, 24.8 mg, 28% yield, m.p. 90.8–91.6 ºC, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

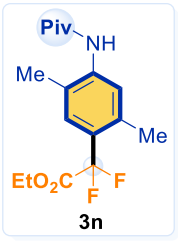
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.25 (s, 1H), 4.76 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.19 (s, 9H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.84 (s, 9H), -0.00 (s, 3H), -0.13 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.7, 164.0 (t, J_{C-F} = 34.73 Hz), 141.4, 140.5, 127.5 (t, J_{C-F} = 9.06 Hz), 124.1 (t, J_{C-F} = 25.67 Hz), 117.9, 117.8, 114.3 (t, J_{C-F} = 255.19 Hz), 63.2, 61.3 (t, J_{C-F} = 6.04 Hz), 39.8, 27.6, 26.0, 18.5, 13.9, -5.4.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -99.87.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{36}F_2NO_4Si$ 444.2376, found: 444.2373.

ethyl 2-(2,5-dimethyl-4-pivalamidophenyl)-2,2-difluoroacetate (3n):



3n

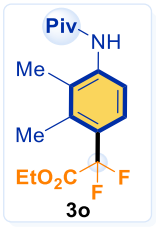
The title compound **3n** was prepared according to the general procedure as a light yellow solid, 54.3 mg, 83% yield, m.p. 105.0–106.9 °C, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 4.29 (q, J = 7.3 Hz, 2H), 2.37 (s, 3H), 2.26 (s, 3H), 1.34 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.6, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 138.0, 135.4, 128.1 (t, $J_{C\text{-}F}$ = 9.06 Hz), 126.8 (t, $J_{C\text{-}F}$ = 22.65 Hz), 124.9, 124.8, 114.1 (t, $J_{C\text{-}F}$ = 252.17 Hz), 63.1, 40.0, 27.7, 19.4, 17.1, 13.9.

The spectral data of the title compound **3n** were in accordance with the previously reported literature.[2]

ethyl 2-(2,3-dimethyl-4-pivalamidophenyl)-2,2-difluoroacetate (3o):



3o

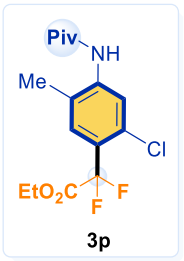
The title compound **3o** was prepared according to the general procedure as a white solid, 53.0 mg, 81% yield, m.p. 98.8–99.8 °C, EtOAc/petroleum ether = 1:15 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.71 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.30 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 1.35 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.7, 164.4 (t, $J_{C\text{-}F}$ = 34.73 Hz), 137.9, 135.8 (t, $J_{C\text{-}F}$ = 3.02 Hz), 129.8, 128.3 (t, $J_{C\text{-}F}$ = 22.65 Hz), 124.3 (t, $J_{C\text{-}F}$ = 9.06 Hz), 121.0, 114.2 (t, $J_{C\text{-}F}$ = 250.66 Hz), 63.1, 39.8, 27.7, 16.5 (t, $J_{C\text{-}F}$ = 3.02 Hz), 13.9, 13.8.

The spectral data of the title compound **3o** were in accordance with the previously reported literature.[5]

ethyl 2-(2-chloro-5-methyl-4-pivalamidophenyl)-2,2-difluoroacetate (3p):



3p

The title compound **3p** was prepared according to the general procedure as a white solid, 26.3 mg, 38% yield, m.p. 77.3–78.5 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

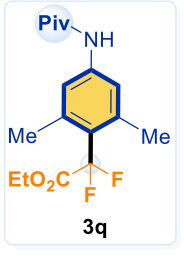
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (s, 1H), 7.53 (s, 1H), 7.35 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.35 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.6, 163.2 (t, $J_{C\text{-}F}$ = 34.73 Hz), 139.1, 130.3 (t, $J_{C\text{-}F}$ = 4.53 Hz), 128.7 (t, $J_{C\text{-}F}$ = 7.55 Hz), 126.3 (t, $J_{C\text{-}F}$ = 24.16 Hz), 125.3, 122.8, 112.2 (t, $J_{C\text{-}F}$ = 253.68 Hz), 63.3, 40.1, 27.6, 17.2, 13.8.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -101.75.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{21}ClF_2NO_3$ 348.1173; found: 348.1165.

ethyl 2-(2,6-dimethyl-4-pivalamidophenyl)-2,2-difluoroacetate (3q):



3q

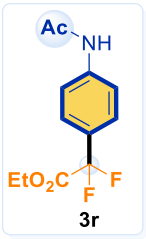
The title compound **3q** was prepared according to the general procedure as a yellow solid, 40.0 mg, 61% yield, m.p. 104.4–104.7 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (s, 2H), 7.26 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 4.2 Hz, 6H), 1.33 – 1.28 (m, 12H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 176.8, 164.4 (t, $J_{C\text{-}F}$ = 34.73 Hz), 139.1, 139.0 (t, $J_{C\text{-}F}$ = 3.02 Hz), 125.4 (t, $J_{C\text{-}F}$ = 22.65 Hz), 120.9, 116.0 (t, $J_{C\text{-}F}$ = 253.68 Hz), 63.0, 39.7, 27.6, 21.8 (t, $J_{C\text{-}F}$ = 6.04 Hz), 13.9.

The spectral data of the title compound **3q** were in accordance with the previously reported literature.[2]

ethyl 2-(4-acetamidophenyl)-2,2-difluoroacetate (3r):



3r

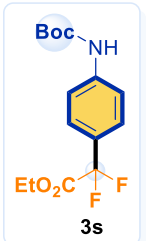
The title compound **3r** was prepared according to the general procedure as a yellow solid, 30.8 mg, 60% yield, m.p. 71.2–72.2 ºC, EtOAc/petroleum ether = 1 : 10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.39 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.5, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 140.3, 128.3, 126.5 (t, $J_{C\text{-}F}$ = 6.04 Hz), 119.4, 113.2 (t, $J_{C\text{-}F}$ = 253.68 Hz), 63.2, 24.7, 13.9.

The spectral data of the title compound **3r** were in accordance with the previously reported literature.[2]

ethyl 2-(4-((*tert*-butoxycarbonyl)amino)phenyl)-2,2-difluoroacetate (3s):



3s

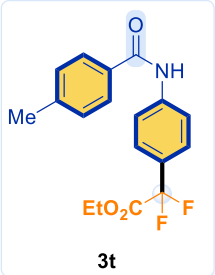
The title compound **3s** was prepared according to the general procedure as a yellow oil, 53.6 mg, 85% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.62 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.52 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.3 (t, $J_{C\text{-}F}$ = 36.24 Hz), 152.4, 140.9, 127.0, 126.5 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.0, 113.4 (t, $J_{C\text{-}F}$ = 252.17 Hz), 81.2, 63.1, 28.3, 13.9.

The spectral data of the title compound **3s** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(4-(4-methylbenzamido)phenyl)acetate (3t):



3t

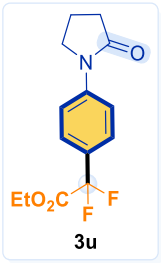
The title compound **3t** was prepared according to the general procedure as a white solid, 30.0 mg, 45% yield, m.p. 83.3–84.0 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.7, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 142.9, 140.5, 131.6, 129.6, 128.4 (t, $J_{C\text{-}F}$ = 22.65 Hz), 127.1, 126.6 (t, $J_{C\text{-}F}$ = 6.04 Hz), 119.8, 113.3 (t, $J_{C\text{-}F}$ = 249.15 Hz), 63.2, 21.5, 13.9.

The spectral data of the title compound **3t** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(4-(2-oxopyrrolidin-1-yl)phenyl)acetate (3u):



3u

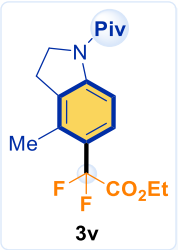
The title compound **3u** was prepared according to the general procedure as a yellow solid, 40.7 mg, 72% yield, m.p. 56.6–58.2 ºC, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 9.0 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.88 (t, *J* = 7.0 Hz, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.25 – 2.15 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.6, 164.2 (t, $J_{C\text{-}F}$ = 36.24 Hz), 141.7, 128.3 (t, $J_{C\text{-}F}$ = 25.67 Hz), 126.2 (t, $J_{C\text{-}F}$ = 6.04 Hz), 119.4, 113.3 (t, $J_{C\text{-}F}$ = 244.62 Hz), 63.1, 48.5, 32.8, 17.9, 13.9.

The spectral data of the title compound **3u** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(4-methyl-1-pivaloylindolin-5-yl)acetate (3v):



3v

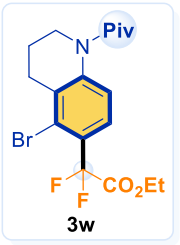
The title compound **3v** was prepared according to the general procedure as a white solid, 20.2 mg, 30% yield, m.p. 80.4–81.2 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 4.35 – 4.24 (m, 4H), 3.08 (t, *J* = 8.2 Hz, 2H), 2.29 (s, 3H), 1.37 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.0, 164.5 (t, J_{C-F} = 36.24 Hz), 146.6, 132.1, 131.4, 126.4 (t, J_{C-F} = 9.06 Hz), 126.2 (t, J_{C-F} = 22.65 Hz), 115.3, 114.4 (t, J_{C-F} = 252.17 Hz), 63.0, 49.5, 40.4, 28.3, 27.7, 15.8 (t, J_{C-F} = 3.02 Hz), 13.9.

The spectral data of the title compound **3v** were in accordance with the previously reported literature.[2]

ethyl 2-(5-bromo-1-pivaloyl-1,2,3,4-tetrahydroquinolin-6-yl)-2,2-difluoroacetate (3w):



3w

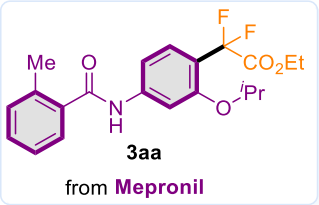
The title compound **3w** was prepared according to the general procedure as a yellow solid, 20.8 mg, 25% yield, m.p. 85.7–87.7 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 (d, J = 1.1 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 3.86 – 3.76 (m, 2H), 2.85 (t, J = 7.1 Hz, 2H), 2.09 – 1.98 (m, 2H), 1.37 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 178.5, 163.4 (t, J_{C-F} = 33.22 Hz), 144.0, 131.1, 129.2 (t, J_{C-F} = 19.63 Hz), 125.2, 124.2 (t, J_{C-F} = 9.06 Hz), 123.3, 112.9 (t, J_{C-F} = 250.66 Hz), 63.3, 44.9, 40.3, 28.6, 28.1, 23.9, 13.8.

The spectral data of the title compound **3w** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(2-isopropoxy-4-(2-methylbenzamido)phenyl)acetate (3aa):



3aa

from **Mepronil**

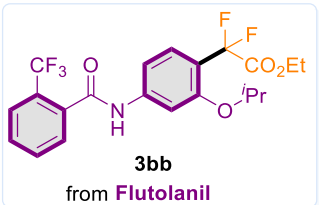
The title compound **3aa** was prepared according to the general procedure as a colorless oil, 57.0 mg, 73% yield, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.63 – 7.55 (m, 2H), 7.47 (d, *J* = 10 Hz, 1H), 7.38 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.30 – 7.24 (m, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.73 – 4.63 (m, 1H), 4.30 (qd, *J* = 7.2, 1.3 Hz, 2H), 2.50 (s, 3H), 1.34 – 1.28 (m, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.2, 164.2 (t, $J_{C\text{-}F}$ = 34.73 Hz), 155.9, 141.7, 136.6, 136.0, 131.4, 130.6, 126.9 (t, $J_{C\text{-}F}$ = 7.55 Hz), 126.6, 126.0, 118.5 (t, $J_{C\text{-}F}$ = 24.16 Hz), 112.2 (t, $J_{C\text{-}F}$ = 247.64 Hz), 110.5, 104.5, 71.1, 62.6, 21.6, 19.8, 14.0.

The spectral data of the title compound **3aa** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(2-isopropoxy-4-(2-(trifluoromethyl)benzamido)phenyl)acetate (3bb):



3bb

from **Flutolanil**

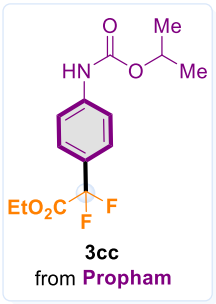
The title compound **3bb** was prepared according to the general procedure as a brown solid, 70.3 mg, 79% yield, m.p. 153.1–154.0 °C, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.78 – 7.74 (m, 1H), 7.71 (s, 1H), 7.68 – 7.56 (m, 5H), 6.86 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.68 (p, *J* = 6.1 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 6.2 Hz, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.8, 164.1 (t, J_{C-F} = 33.22 Hz), 155.9, 141.1, 135.4, 132.3, 130.5, 128.5, 127.4 (q, J_{C-F} = 31.71 Hz), 127.0 (q, J_{C-F} = 7.55 Hz), 126.6 (q, J_{C-F} = 6.04 Hz), 123.5 (q, J_{C-F} = 273.31 Hz), 119.0 (t, J_{C-F} = 24.16 Hz), 112.2 (t, J_{C-F} = 247.64 Hz), 110.7, 104.9, 71.2, 62.7, 21.6, 14.0.

The spectral data of the title compound **3bb** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (3cc):



The title compound **3cc** was prepared according to the general procedure as a colorless oil, 57.2 mg, 95% yield, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

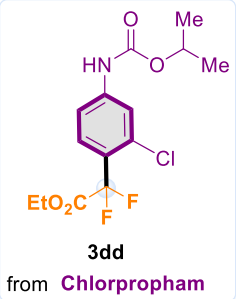
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 5.08 – 4.98 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.32 – 1.27 (m, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.3 (t, J_{C-F} = 36.24 Hz), 152.9, 140.7, 127.2 (t, J_{C-F} = 25.67 Hz), 126.5 (t, J_{C-F} = 6.04 Hz), 118.1, 113.3 (t, J_{C-F} = 252.17 Hz), 69.2, 63.1, 22.0, 13.9.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.22.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{17}F_2NO_4Na$ 324.1018, found: 324.1004.

ethyl 2-(2-chloro-4-((isopropoxycarbonyl)amino)phenyl)-2,2-difluoroacetate (3dd):



3dd

from **Chlorpropham**

The title compound **3dd**was prepared according to the general procedure as a light yellow oil, 54.3 mg, 81% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

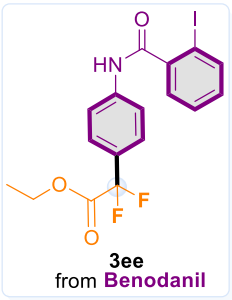
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.66 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 6.70 (s, 1H), 5.08 – 4.97 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.34 – 1.29 (m, 9H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.5 (t, $J_{C\text{-}F}$ = 34.73 Hz), 152.6, 141.4, 132.8, 128.0 (t, $J_{C\text{-}F}$ = 7.55 Hz), 125.5 (t, $J_{C\text{-}F}$ = 25.67 Hz), 119.8, 116.0, 112.2 (t, $J_{C\text{-}F}$ = 250.66 Hz), 69.6, 63.3, 22.0, 13.8.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -101.53.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{16}ClF_2NO_4Na$ 358.0628; found: 358.0630.

ethyl 2,2-difluoro-2-(4-(2-iodobenzamido)phenyl)acetate (3ee):



3ee

from **Benodanil**

The title compound **3ee** was prepared according to the general procedure as a white solid, 36.5 mg, 41%yield, m.p. 97.6–98.2 ºC, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

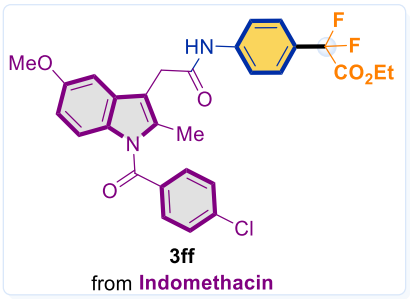
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.56 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.18 (td, *J* = 7.7, 1.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.3, 164.2 (t, J_{C-F} = 33.22 Hz), 141.7, 140.2, 139.9, 131.9, 129.0, 128.7, 128.5, 126.7 (t, J_{C-F} = 7.55 Hz), 119.8, 113.2 (t, J_{C-F} = 255.19 Hz), 92.2, 63.2, 13.9.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.46.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{15}F_2INO_3$ 446.0059, found: 446.0055.

ethyl 2-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)phenyl)-2,2-difluoroacetate (3ff):



3ff
from **Indomethacin**

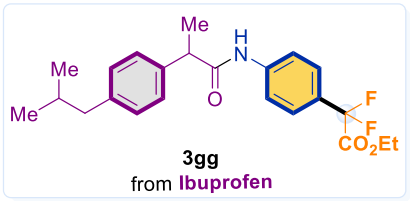
The title compound **3ff** was prepared according to the general procedure as a white solid, 51.0 mg, 46% yield, m.p. 224.7–225.6 ºC, EtOAc/petroleum ether = 1:2 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.30 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.25 (s, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.99 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.86 – 3.77 (m, 5H), 2.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.1, 167.8, 164.3, 164.1, 153.5, 140.2, 138.3, 137.2, 133.0, 132.0, 131.3, 130.1, 129.4, 129.1, 124.8, 120.1, 112.7 (t, J_{C-F} = 9.06 Hz), 112.3, 112.2, 110.7, 99.9, 62.7, 56.2, 33.3, 14.0, 13.5.

The spectral data of the title compound **3ff** were in accordance with the previously reported literature.[2]

ethyl 2,2-difluoro-2-(4-(2-(4-isobutylphenyl)propanamido)phenyl)acetate (3gg):



3gg
from **Ibuprofen**

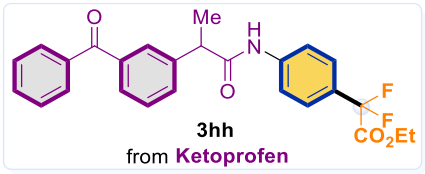
The title compound **3gg** was prepared according to the general procedure as a light yellow oil, 52.4 mg, 65% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 – 7.48 (m, 4H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.14 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 1.86 (hept, *J* = 6.8 Hz, 1H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.8, 164.2 (t, J_{C-F} = 36.24 Hz), 141.4, 140.3, 137.7, 130.0, 128.2 (t, J_{C-F} = 25.67 Hz), 127.4, 126.4 (t, J_{C-F} = 6.04 Hz), 119.3, 113.2 (t, J_{C-F} = 252.17 Hz), 63.1, 47.9, 45.0, 30.2, 22.4, 18.4, 13.9.

The spectral data of the title compound **3gg** were in accordance with the previously reported literature.[2]

ethyl 2-(4-(2-(3-benzoylphenyl)propanamido)phenyl)-2,2-difluoroacetate (3hh):



3hh
from **Ketoprofen**

The title compound **3hh** was prepared according to the general procedure as a colorless oil, 37.9 mg, 42% yield, m.p. 102.2–104.0 ºC, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.82 (t, *J* = 1.8 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.72 – 7.69 (m, 1H), 7.64 – 7.58 (m, 2H), 7.54 (t, *J* = 8.2 Hz, 4H), 7.51 – 7.46 (m, 3H),

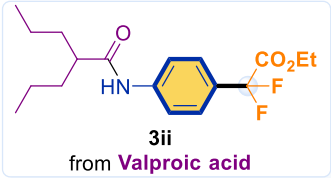
7.24 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.79 (q, J = 7.1 Hz, 1H), 1.63 (d, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 196.4, 171.8, 164.2 (t, J_{C-F} = 34.73 Hz), 141.2, 140.1, 138.4, 137.3, 132.8, 131.4, 130.1, 129.6, 129.1, 128.4, 126.5 (t, J_{C-F} = 6.04 Hz), 119.4, 113.2 (t, J_{C-F} = 253.68 Hz), 63.1, 48.1, 18.8, 13.9

^{19}F NMR (565 MHz, Chloroform-*d*) δ -98.70, -103.49.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}F_2NO_4$ 452.1668, found: 452.1670.

ethyl 2,2-difluoro-2-(4-(2-propylpentanamido)phenyl)acetate (3ii):



3ii
from **Valproic acid**

The title compound **3ii** was prepared according to the general procedure as a white solid, 32.7 mg, 48% yield, m.p. 63.7–65.2 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

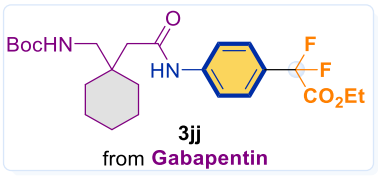
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.64 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.28 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.21 (tt, J = 9.4, 5.1 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.51 – 1.44 (m, 2H), 1.40 – 1.32 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.3 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.8, 164.2 (t, J_{C-F} = 36.24 Hz), 140.3, 128.2 (t, J_{C-F} = 27.18 Hz), 126.5 (t, J_{C-F} = 6.04 Hz), 119.5, 113.3 (t, J_{C-F} = 252.17 Hz), 63.1, 48.9, 35.3, 20.9, 14.1, 13.9.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.43.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{26}F_2NO_3$ 342.1875, found: 342.1866.

Ethyl 2-(4-(2-(1-(((*tert*-butoxycarbonyl)amino)methyl)cyclohexyl)acetamido)phenyl)-2,2-difluoroacetate (3jj):



The title compound **3jj** was prepared according to the general procedure as a light yellow solid, 66.4 mg, 71% yield, m.p. 94.7–95.7 °C, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

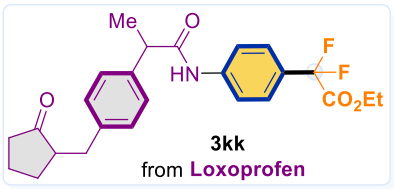
^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.40 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 4.92 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.17 (d, *J* = 7.3 Hz, 2H), 2.29 (s, 2H), 1.67 – 1.58 (m, 5H), 1.55 – 1.45 (m, 14H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.8, 164.4 (t, $J_{C\text{-}F}$ = 36.24 Hz), 158.2, 141.6, 127.3 (t, $J_{C\text{-}F}$ = 27.18 Hz), 126.2 (t, $J_{C\text{-}F}$ = 6.04 Hz), 119.2, 113.5 (t, $J_{C\text{-}F}$ = 250.66 Hz), 80.7, 63.0, 47.7, 42.7, 37.7, 34.2, 28.4, 26.0, 21.4, 13.9.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.29.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{35}F_2N_2O_5$ 469.2509, found: 469.2519.

ethyl 2,2-difluoro-2-(4-(2-(4-((2-oxocyclopentyl)methyl)phenyl)propanamido)phenyl)acetate (3kk):



The title compound **3kk** was prepared according to the general procedure as a colorless oil, 57.6 mg, 65% yield, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

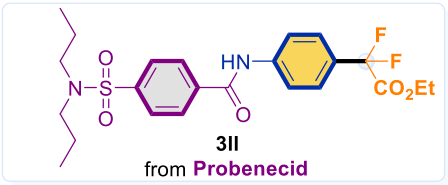
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.52 (s, 4H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.13 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.69 (q, *J* = 7.1 Hz, 1H), 3.17 – 3.10 (m, 1H), 2.55 (ddd, *J* = 14.1, 9.3, 1.4 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.16 – 2.08 (m, 2H), 2.01 – 1.93 (m, 1H), 1.79 – 1.71 (m, 1H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.57 – 1.52 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 220.1, 172.6, 164.2, 140.3, 139.7, 138.4, 129.8, 127.7, 126.4 (t, J_{C-F} = 6.04 Hz), 119.3, 113.2, 63.1, 50.9, 47.9, 38.1, 35.2, 29.3, 20.5, 18.5, 13.9.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.46.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{28}F_2NO_4$ 444.1981, found: 444.1971.

ethyl 2-(4-(4-(*N*,*N*-dipropylsulfamoyl)benzamido)phenyl)-2,2-difluoroacetate (3ll):



3ll
from **Probenecid**

The title compound **3ll** was prepared according to the general procedure as a white solid, 56.0 mg, 58% yield, m.p. 110.0–110.4 °C, EtOAc/petroleum ether = 1:3 (v/v) as eluents for column chromatography.

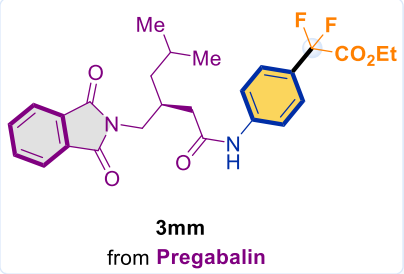
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.13 – 3.07 (m, 4H), 1.57 – 1.52 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.7, 164.2, 143.3, 140.1, 138.2, 129.0 (t, J_{C-F} = 27.18 Hz), 127.9, 127.5, 126.7 (t, J_{C-F} = 6.04 Hz), 120.0, 113.2 (t, J_{C-F} = 252.17 Hz), 63.2, 50.0, 21.9, 13.9, 11.2.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.45.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{29}F_2N_2O_5S$ 483.1760, found: 483.1750.

ethyl (*S*)-2-(4-(3-((1,3-dioxoisoindolin-2-yl)methyl)-5-methylhexanamido)phenyl)-2,2-difluoroacetate (3mm):



3mm
from **Pregabalin**

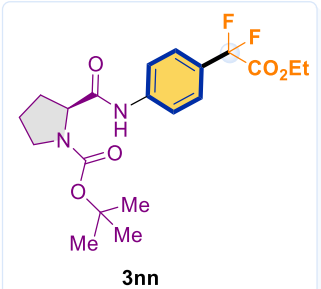
The title compound **3mm** was prepared according to the general procedure as a light yellow oil, 58.3 mg, 60% yield, EtOAc/petroleum ether = 1:8 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.77 – 3.69 (m, 2H), 2.49 (tt, *J* = 7.8, 4.0 Hz, 1H), 2.39 (dd, *J* = 14.2, 3.6 Hz, 1H), 2.28 (dd, *J* = 14.2, 8.6 Hz, 1H), 1.84 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.32 – 1.26 (m, 5H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.0, 169.4, 164.3, 140.7, 134.3, 131.7, 127.8, 126.3 (t, $J_{C\text{-}F}$ = 6.04 Hz), 123.4, 119.1, 113.3, 63.1, 41.8, 41.3, 40.6, 34.0, 25.2, 22.7, 22.5, 13.9.

The spectral data of the title compound **3mm** were in accordance with the previously reported literature.[2]

***tert*-butyl (*S*)-2-((4-(2-ethoxy-1,1-difluoro-2-oxoethyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (3nn):**



3nn
from L-(-)-**Proline**

The title compound **3nn** was prepared according to the general procedure as a light yellow solid, 43.6 mg, 53% yield, m.p. 113.2–114.2 ºC, EtOAc/petroleum ether = 1:5

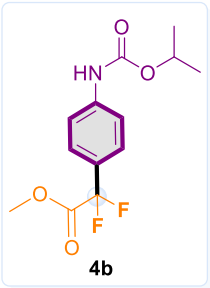
(v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 4.52 – 4.42 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.48 – 3.32 (m, 2H), 2.57 – 2.48 (m, 1H), 2.02 – 1.86 (m, 3H), 1.50 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.1, 164.3 (t, $J_{C\text{-}F}$ = 36.24 Hz), 156.9, 140.9, 126.4, 119.4, 113.3 (t, $J_{C\text{-}F}$ = 252.17 Hz), 81.2, 63.1, 60.5, 47.3, 28.4, 26.8, 24.6, 13.9.

The spectral data of the title compound **3nn** were in accordance with the previously reported literature.[2]

methyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4b):



4b

The title compound **4b** was prepared according to the general procedure as a colorless oil, 47.0 mg, 82%yield, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

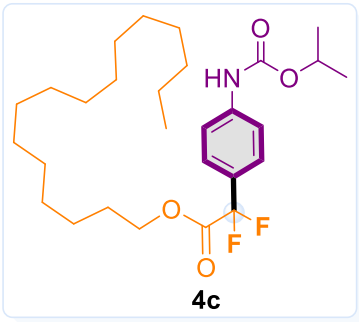
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.65 (s, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 3.84 (s, 3H), 1.31 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 165.0 (t, $J_{C\text{-}F}$ = 36.24 Hz), 152.9, 140.7, 127.1 (t, $J_{C\text{-}F}$ = 25.67 Hz), 126.6 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.2, 113.4 (t, $J_{C\text{-}F}$ = 252.17 Hz), 69.3, 53.6, 22.0.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.09.

HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{15}F_2NO_4Na$ 310.0861, found: 310.0870.

hexadecyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4c):



4c

The title compound **4c** was prepared according to the general procedure as a light yellow oil, 79.5 mg, 80% yield, EtOAc/petroleum ether = 1 : 10 (v/v) as eluents for column chromatography.

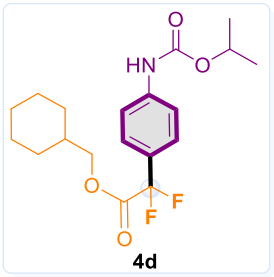
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.66 (s, 1H), 5.03 (p, *J* = 6.3 Hz, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 1.67 – 1.62 (m, 2H), 1.31 (d, *J* = 6.3 Hz, 6H), 1.30 – 1.20 (m, 28H), 0.88 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.4, 152.8, 140.6, 129.0, 127.3, 126.6 (t, J_{C-F} = 6.04 Hz), 118.1, 69.2, 67.1, 31.9, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 29.1, 28.2, 25.6, 22.7, 22.0, 14.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.30.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{46}F_2NO_4$ 498.3389, found: 498.3391.

cyclohexylmethyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4d):



4d

The title compound **4d** was prepared according to the general procedure as a light yellow oil, 52.3 mg, 71% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 5.03 (p, *J* = 6.3 Hz, 1H), 4.03 (d, *J* = 6.1 Hz, 2H), 1.73 – 1.64 (m,

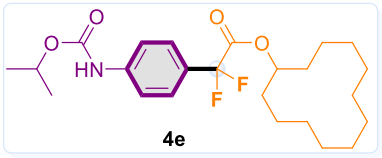
6H), 1.31 (d, J = 6.2 Hz, 6H), 1.25 – 1.17 (m, 2H), 1.18 – 1.1 (m, 1H), 0.96 – 0.88 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.4, 152.9, 140.6, 127.4, 126.6 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.0, 113.4, 71.9, 69.2, 36.9, 29.3, 26.2, 25.5, 22.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.22.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}F_2NO_4$ 370.1824, found: 370.1827.

cyclododecyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4e):



4e

The title compound **4e** was prepared according to the general procedure as a light yellow oil, 68.5 mg, 78% yield, EtOAc/petroleum ether = 1:20 (v/v) as eluents for column chromatography.

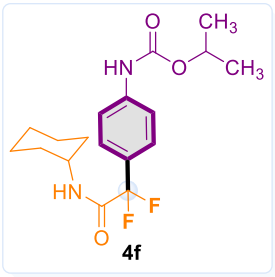
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.66 (s, 1H), 5.09 (tt, J = 7.2, 4.6 Hz, 1H), 5.03 (p, J = 6.3 Hz, 1H), 1.770 – 1.69 (m, 2H), 1.54 – 1.47 (m, 2H), 1.38 – 1.27 (m, 24H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 164.0 (t, $J_{C\text{-}F}$ = 36.24 Hz), 152.9, 140.5, 127.5, 126.5 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.0, 113.4 (t, $J_{C\text{-}F}$ = 252.17 Hz), 76.0, 69.2, 28.7, 24.0, 23.9, 23.2, 23.1, 22.1, 20.6.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.37.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{36}F_2NO_4$ 440.2607, found: 440.2621.

isopropyl (4-(2-(cyclohexylamino)-1,1-difluoro-2-oxoethyl)phenyl)carbamate (4f):



4f

The title compound **4f** was prepared according to the general procedure as a yellow solid, 43.9 mg, 62%yield, m.p. 198.6–198.9 ºC, EtOAc/petroleum ether = 1:5 (v/v) as eluents for column chromatography.

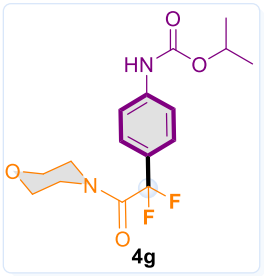
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 6.27 (s, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.84 – 3.74 (m, 1H), 1.98 – 1.89 (m, 2H), 1.76 – 1.68 (m, 2H), 1.66 – 1.59 (m, 1H), 1.43 – 1.28 (m, 8H), 1.26 – 1.16 (m, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.1 (t, $J_{C\text{-}F}$ = 31.71 Hz), 152.9, 140.5, 127.6 (t, $J_{C\text{-}F}$ = 28.69 Hz), 126.6 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.0, 114.8, 69.2, 48.7, 32.7, 25.3, 24.7, 22.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -101.64.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}F_2N_2O_3$ 355.1828, found: 355.1824.

isopropyl (4-(1,1-difluoro-2-morpholino-2-oxoethyl)phenyl)carbamate (4g):



4g

The title compound **4g** was prepared according to the general procedure as a white oil, 47.2 mg, 69%yield, EtOAc/petroleum ether = 1:3 (v/v) as eluents for column chromatography.

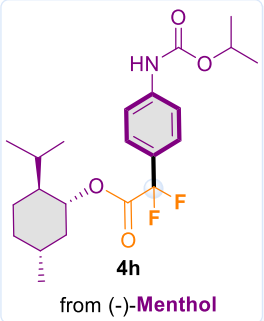
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 – 7.43 (m, 4H), 6.75 (s, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 3.74 – 3.65 (m, 4H), 3.52 – 3.40 (m, 4H), 1.31 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.2 (t, $J_{C\text{-}F}$ = 30.2 Hz), 152.9, 140.7, 127.8 (t, $J_{C\text{-}F}$ = 24.16 Hz), 126.3 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.2, 115.5 (t, $J_{C\text{-}F}$ = 250.66 Hz), 69.3, 66.7, 66.4, 46.7, 43.5, 22.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -93.65.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}F_2N_2O_4$ 343.1464, found: 343.1466.

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4h):



The title compound **4h** was prepared according to the general procedure as a light yellow oil, 61.6 mg, 75% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

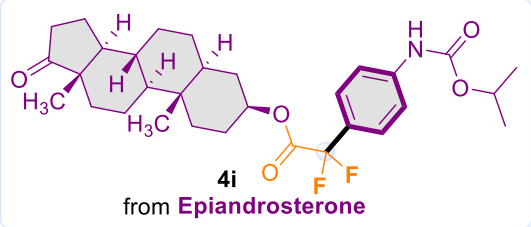
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 5.03 (p, *J* = 6.3 Hz, 1H), 4.76 (td, *J* = 11.0, 4.4 Hz, 1H), 1.96 – 1.91 (m, 1H), 1.69 – 1.63 (m, 3H), 1.50 – 1.41 (m, 2H), 1.31 (d, *J* = 6.3 Hz, 6H), 1.07 – 0.96 (m, 2H), 0.92 (dd, *J* = 9.5, 6.8 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.9 (t, $J_{C\text{-}F}$ = 34.73 Hz), 152.9, 140.5, 127.4 (t, $J_{C\text{-}F}$ = 27.18 Hz), 126.5 (t, $J_{C\text{-}F}$ = 6.04 Hz), 117.9, 113.4 (t, $J_{C\text{-}F}$ = 253.68 Hz), 77.7, 69.2, 46.8, 40.1, 34.0, 31.4, 26.1, 23.3, 22.1, 21.9, 20.6, 16.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -102.39, -102.83, -103.90, -104.34.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{32}F_2NO_4$ 412.2294, found: 412.2305.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[a]phenanthren-3-yl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4i):



The title compound **4i** was prepared according to the general procedure as a white solid, 76.3 mg, 70% yield, m.p. 186.2–186.5 ºC, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

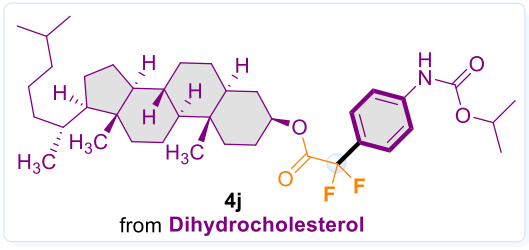
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.76 (s, 1H), 5.03 (p, *J* = 6.3 Hz, 1H), 4.80 (tt, *J* = 11.4, 4.9 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.10 – 2.01 (m, 1H), 1.96 – 1.89 (m, 1H), 1.82 – 1.73 (m, 4H), 1.64 – 1.60 (m, 2H), 1.57 – 1.40 (m, 4H), 1.33 – 1.28 (m, 8H), 1.28 – 1.15 (m, 4H), 1.05 – 0.93 (m, 2H), 0.85 (d, *J* = 2.7 Hz, 6H), 0.74 – 0.66(m, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 221.2, 163.8 (t, $J_{C\text{-}F}$ = 36.24 Hz), 152.9, 140.6, 129.5, 127.3 (t, $J_{C\text{-}F}$ = 27.18 Hz), 126.5 (t, $J_{C\text{-}F}$ = 4.53 Hz), 118.0, 113.3 (t, $J_{C\text{-}F}$ = 252.17 Hz), 69.2, 54.2, 51.3, 47.8, 44.6, 36.5, 35.8, 35.6, 35.0, 33.4, 31.5, 30.7, 28.2, 27.0, 22.1, 21.8, 20.5, 13.8, 12.2.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.15.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{31}H_{42}F_2NO_5$ 546.3026, found: 546.3034.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2,2-difluoro-2-(4-((isopropoxycarbonyl)amino)phenyl)acetate (4j):



The title compound **4j** was prepared according to the general procedure as a light yellow oil, 95.2 mg, 74% yield, EtOAc/petroleum ether = 1:10 (v/v) as eluents for column chromatography.

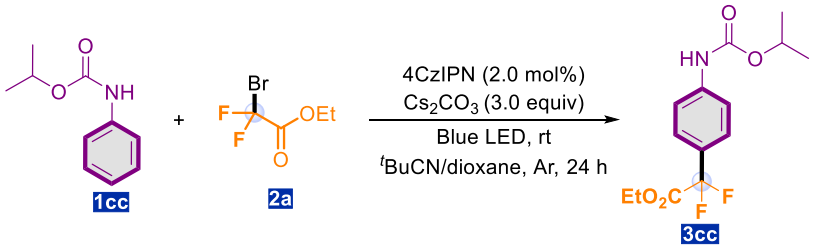
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.67 (s, 1H), 5.03 (h, *J* = 6.3 Hz, 1H), 4.80 (tt, *J* = 11.4, 5.0 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.83 – 1.77 (m, 2H), 1.76 – 1.70 (m, 1H), 1.67 – 1.62 (m, 1H), 1.60 – 1.49 (m, 5H), 1.47 – 1.39 (m, 2H), 1.34 – 1.28 (m, 9H), 1.28 – 1.18 (m, 5H), 1.18 – 1.03 (m, 7H), 1.02 – 0.94 (m, 4H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 2.8 Hz, 6H), 0.81 (s, 3H), 0.64 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.8 (t, $J_{C\text{-}F}$ = 34.73 Hz), 152.9, 140.5, 127.4, 126.5 (t, $J_{C\text{-}F}$ = 6.04 Hz), 118.0, 113.3 (t, $J_{C\text{-}F}$ = 252.17 Hz), 69.2, 56.4, 56.3, 54.1, 44.6, 42.6, 39.9, 39.5, 36.6, 36.2, 35.8, 35.4, 33.5, 31.9, 28.5, 28.2, 28.0, 27.1, 24.2, 23.8, 22.8, 22.6, 22.1, 21.2, 18.7, 12.2, 12.1.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -103.15.

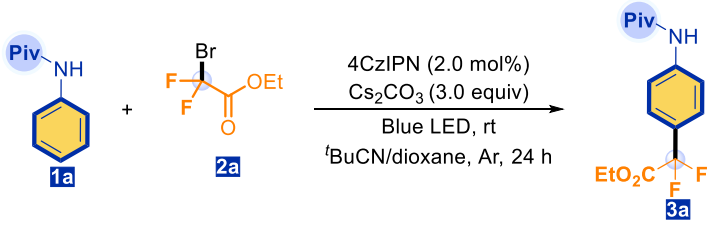
HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{39}H_{59}F_2NO_4Na$ 666.4304, found: 666.4284.

7. Gram-scale synthesis



To a 150 mL Schlenk tube was charged with **1cc** (1.1 g, 6.1 mmol), 4CzIPN (96.2 mg, 0.122 mmol), **2a** (2.5 g, 12.2 mmol), Cs_2CO_3 (6.0 g, 18.3 mmol) in tBuCN/dioxane (2.5/1, 43 mL) under an air atmosphere. Then the tube was evacuated and filled with Ar (1 atm) and stirred at rt for proper mixing of the reactants. Then the mixture was irradiated with 30 W blue LEDs at rt and stirred vigorously for 24 h. After that, the reaction mixture was diluted with 20 mL ethyl acetate, filtered through diatomite, and concentrated in vacuo to give the residue. The crude product was separated by column chromatography on silica gel (elution solvent: EtOAc/petroleum ether = 1/10) to afford the title compounds **3cc** (78%, 1.4 g).

8. Green chemistry metrics



Standard reaction conducted using **1a** (0.2 mmol), **2a** (0.4 mmol), 4CzIPN (2 mol%), and Cs_2CO_3 (0.6 mmol) in ^{t}BuCN/dioxane (2.5/1, 1.4 mL) set up under Ar and irradiated with blue LEDs at RT for 24 h. Isolation product **3a**: 46.3 mg, Filtered insoluble residues (not dried): 193.0 mg, Crude product before purification: 65.2 mg.

(1) **Atom economy** (AE) calculation: $\mathrm{AE} = \frac{\text{m.w.}\mathbf{3a}}{\text{m.w.}\mathbf{1a}+\text{m.w.}\mathbf{2a}} = \frac{299.1}{177.1+201.9} = 0.79$

(2) **Environmental factor** (EF) calculation: $\mathrm{EF} = \frac{(193.0\ \text{mg}+(65.2\ \text{mg}-46.3\ \text{mg}))}{46.3\ \text{mg}} = 4.6$

(Note: All solvents were recycled and reused with a recovery unit. Therefore, solvents are not counted as waste).

9. References

[1]. (a) M. Ke and Q. Song, Copper/B_2pin_2-catalyzed C–H difluoroacetylation–cycloamidation of anilines leading to the formation of 3,3-difluoro-2-oxindoles. *Chem. Commun.* 2017, **53**, 2222; (b) X. Ma, S. Deng and Q. Song, Halodifluoroacetates as formylation reagents for various amines via unprecedented quadruple cleavage. *Org. Chem. Front.* 2018, **5**, 3505.

[2]. Q. Gou, Q. Chen, Q. Tan, M. Zhu, H. Huang, M. Deng, W. Yi and S. He, Divergent Regioselective Csp^2–H Difluoromethylation of Aromatic Amines Enabled by Nickel Catalysis. *Org. Lett.* 2022, **24**, 3549.

[3]. X. Geng, Z. Xu, Y. Cai and L. Wang, Visible-Light-Driven Multicomponent Cyclization by Trapping a 1,3-Vinylimine Ion Intermediate: A Direct Approach to Pyrimido[1,2-*b*]indazole Derivatives. *Org. Lett.* 2021, **23**, 8343.

[4]. C. Yu, F. Ke, J. Su, X. Ma, X. Li and Q. Song, Cu-Catalyzed Three-Component Cascade Synthesis of 1,3-Benzothiazines from *ortho*-Aminohydrazones and Bromodifluoroacetamides. *Org. Lett.* 2022, **24**, 7861.

[5]. C. Yuan, L. Zhu, C. Chen, X. Chen, Y. Yang, Y. Lan and Y. Zhao, Ruthenium(II)-enabled para-selective C–H difluoromethylation of anilides and their derivatives. *Nat. Commun.* 2018, **9**, 1189.

[6]. A. S. Gentleman, T. Lawson, M. G. Ellis, M. Davis, J. Turner-Dore, A. Ryder, M. Frosz, M. Ciaccia, E. Reisner, A. Cresswell and T. G. Euser, Stern–Volmer analysis of photocatalyst fluorescence quenching within hollow-core photonic crystal fibre microreactors. *Chem. Commun.* 2022, **58**, 10548.

[7]. B. Delley, An all-electron numerical method for solving the local density functional for polyatomic molecules. *J. Chem. Phys.* 1990, **92**, 508.

[8]. B. Delley, From molecules to solids with the DMol3 Approach. *J. Chem. Phys.* 2000, **113**, 7756.

[9]. J. P. Perdew, K. Burke and M. Ernzerhof, Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* 1996, **77**, 3865.

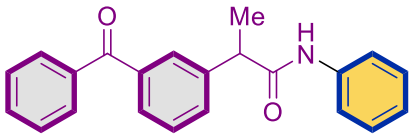
[10]. S. Grimme, Semiempirical GGA-type density functional constructed with a long-range dispersion correction. *Comput. Chem.* 2006, **27**, 1787–1799.

[11]. S. Grimme, J. Antony, S. Ehrlich and H. Krieg, A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* 2010, **132**, 154104.

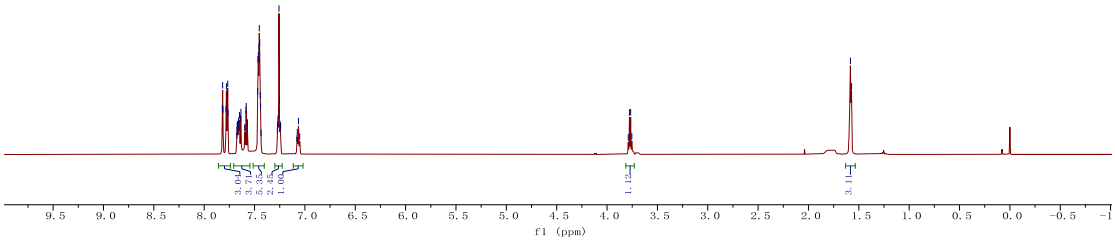
[12]. (a) R. S. A. E. Ali, Y. Zhou, K. Gong and X. Jiang, Parallel photoreactor development with enhanced photon efficiency and reproducibility based on laws of optics. *Green Synth. Catal.* 2023, **4**, 169; (b) R. S. A. E. Ali, J. Meng and X. Jiang, Multimode Photo-CSTR (Continuous Stirred Tank Reactor) Setup for Heterogeneous Photocatalytic Processes. *Org. Process Res. Dev.* 2023. DOI: 10.1021/acs.oprd.3c00328; (c) Y. Sun, X. Wu, Z. Cao and C. Zhu, Multipurpose sulfoximine-mediated radical γ-heteroarylation of unactivated C(sp^3)-H bonds. *Sci. China Chem.* 2023, **66**, 1435; (d) M. Chen, Y. Cui, X. Chen, R. Shang and X. Zhang, C−F bond activation enables synthesis of aryl difluoromethyl bicyclopentanes as benzophenone-type bioisosteres, *Nat. Commun.* 2024, **15**, 419; (e) Y. Xu, H.-X. Gao, C. Pan, Y. Shi, C. Zhang, G. Huang and C. Feng, Stereoselective Photoredox Catalyzed (3+3) Dipolar Cycloaddition of Nitrone with Aryl Cyclopropane. *Angew. Chem. Int. Ed.* 2023, **62**, e202310671.

10. ^{1}H, ^{13}C, ^{19}F NMR spectra

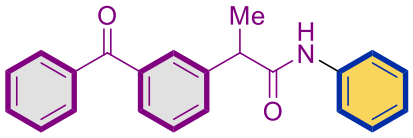
600 MHz ^{1}H NMR spectra of **1hh** in $CDCl_3$.



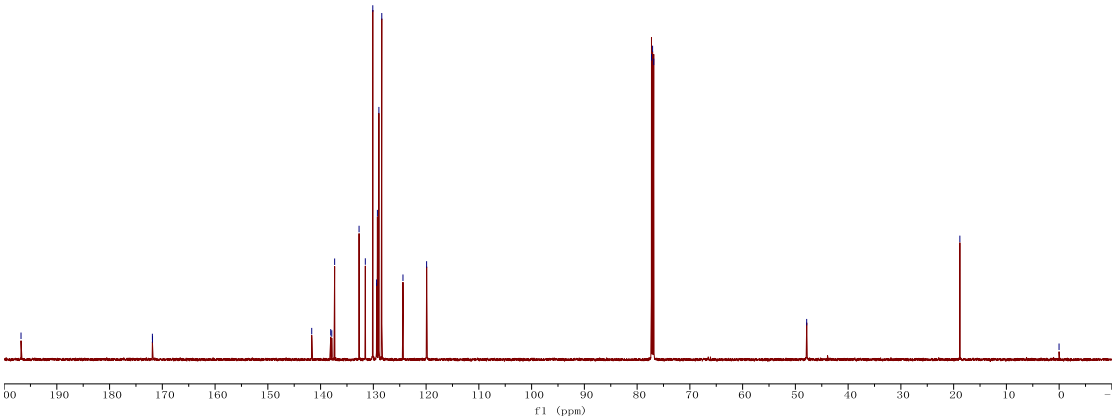
1hh
from **Ketoprofen**



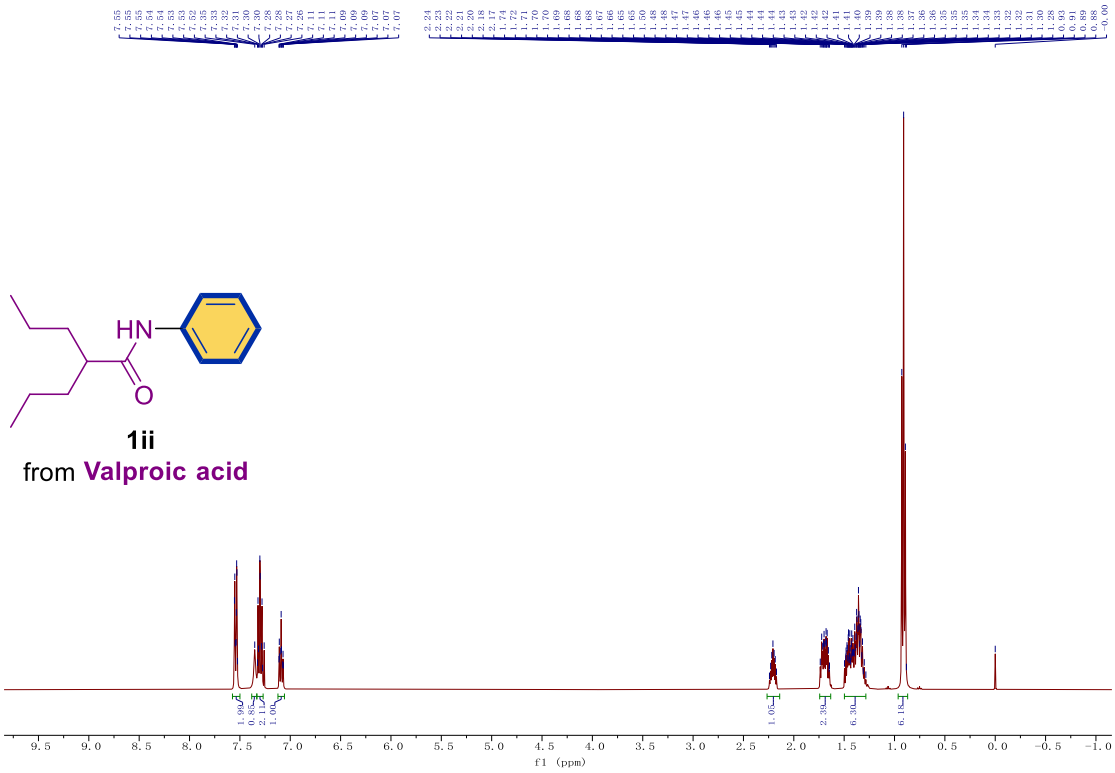
151 MHz ^{13}C NMR spectra of **1hh** in $CDCl_3$.



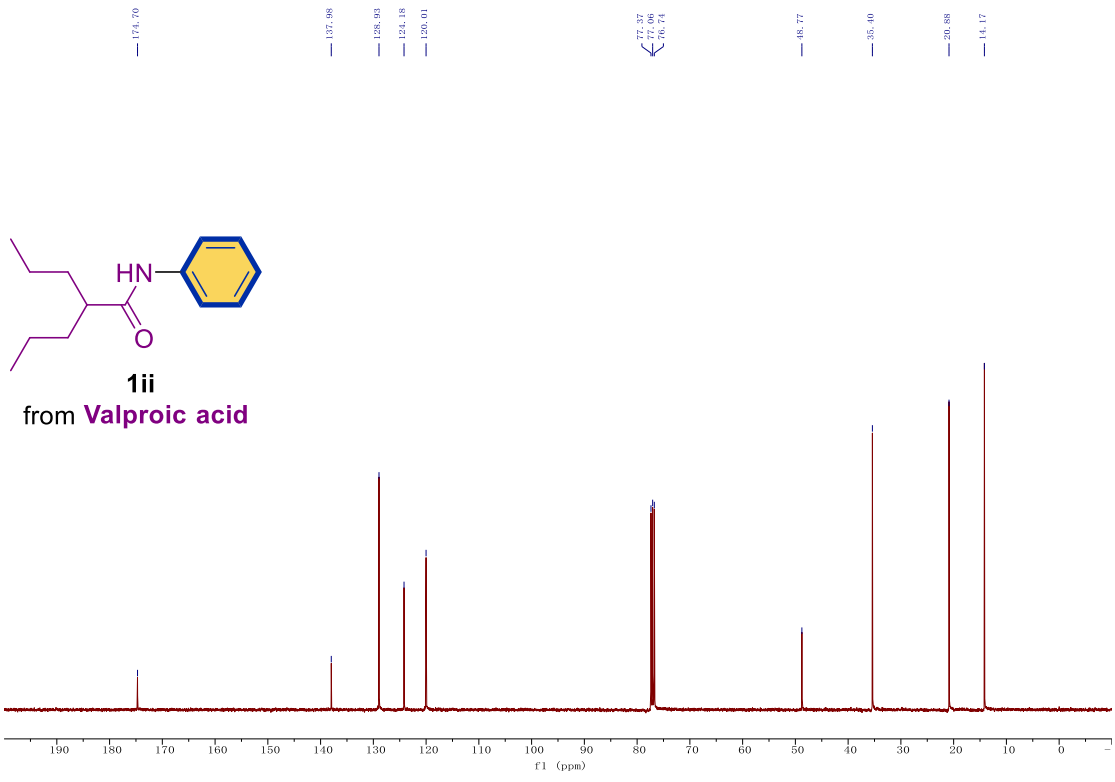
1hh
from **Ketoprofen**



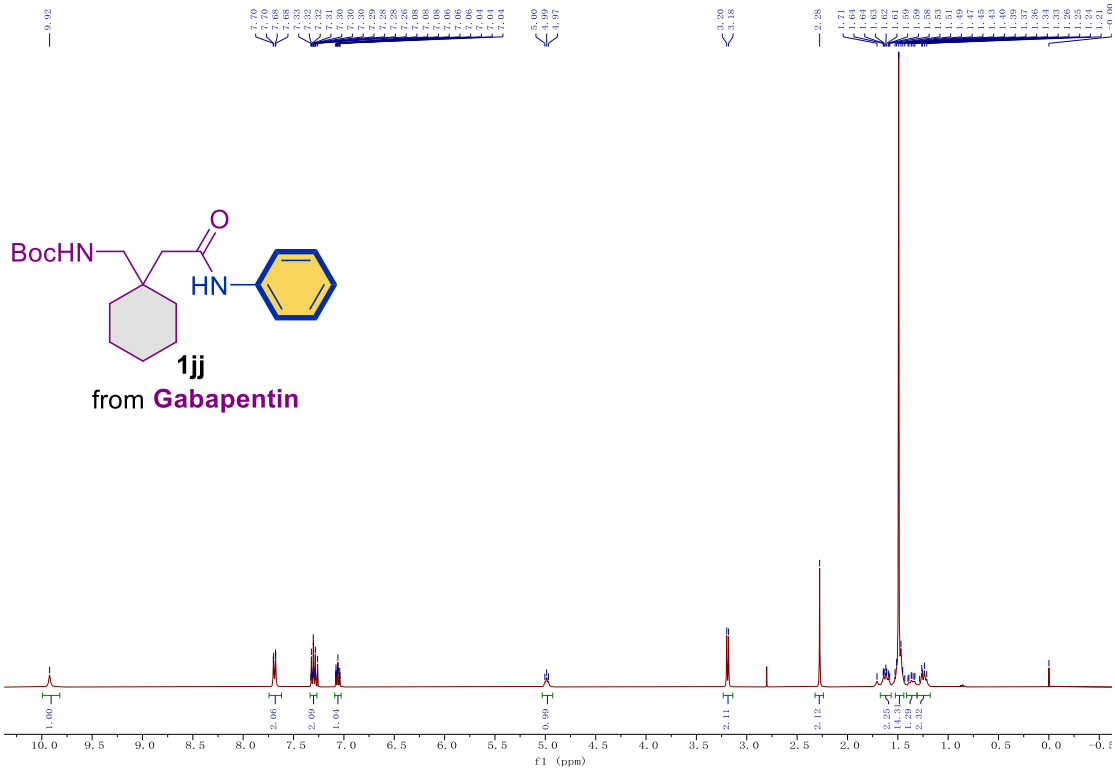
400 MHz ^{1}H NMR spectra of **1ii** in $CDCl_3$.



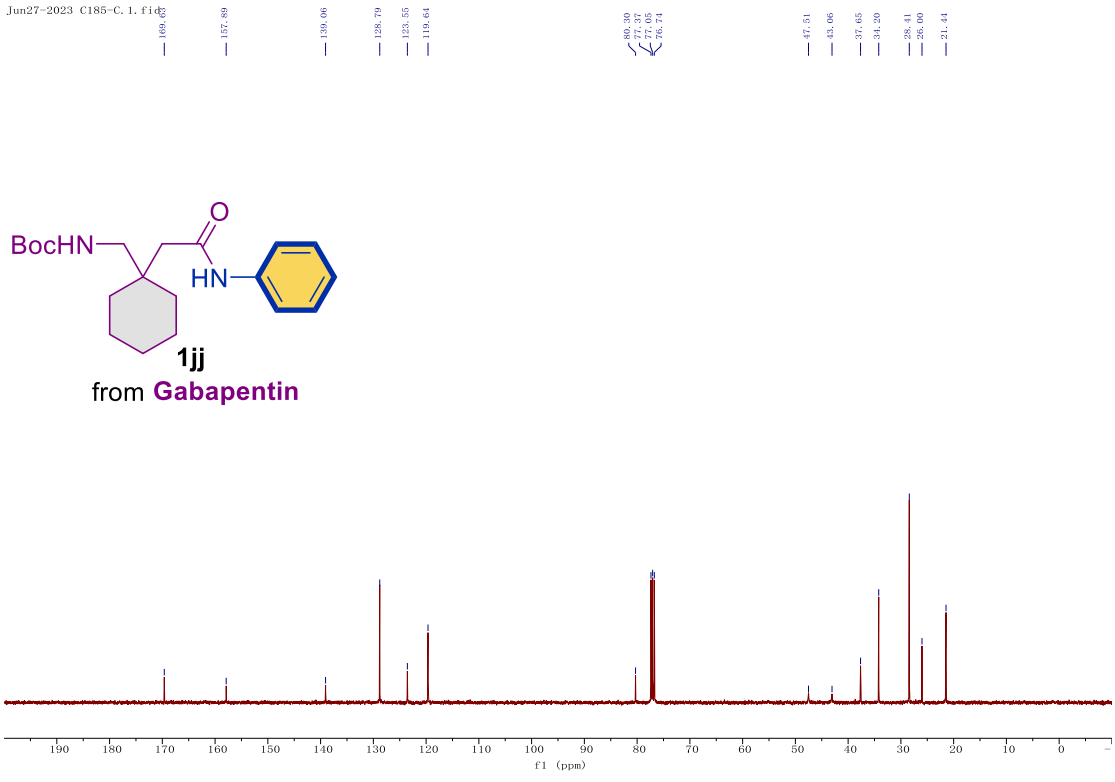
101 MHz ^{13}C NMR spectra of **1ii** in $CDCl_3$.



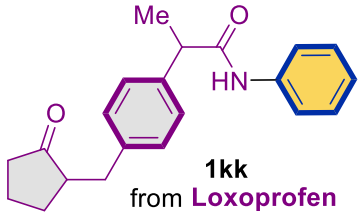
400 MHz ^{1}H NMR spectra of **1jj** in $CDCl_3$.

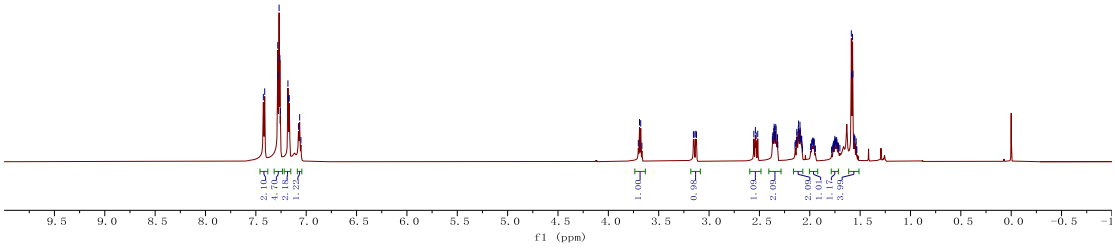


101 MHz ^{13}C NMR spectra of **1jj** in $CDCl_3$.

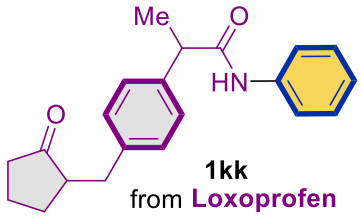


600 MHz ^{1}H NMR spectra of **1kk** in $CDCl_3$.

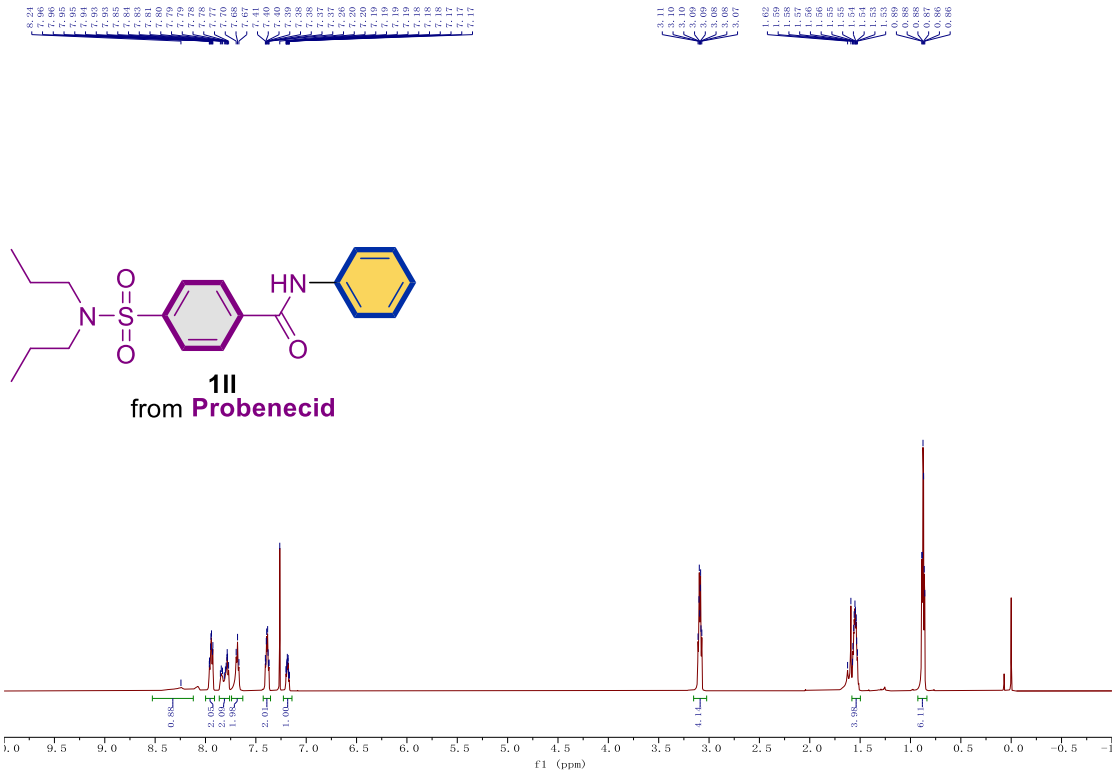




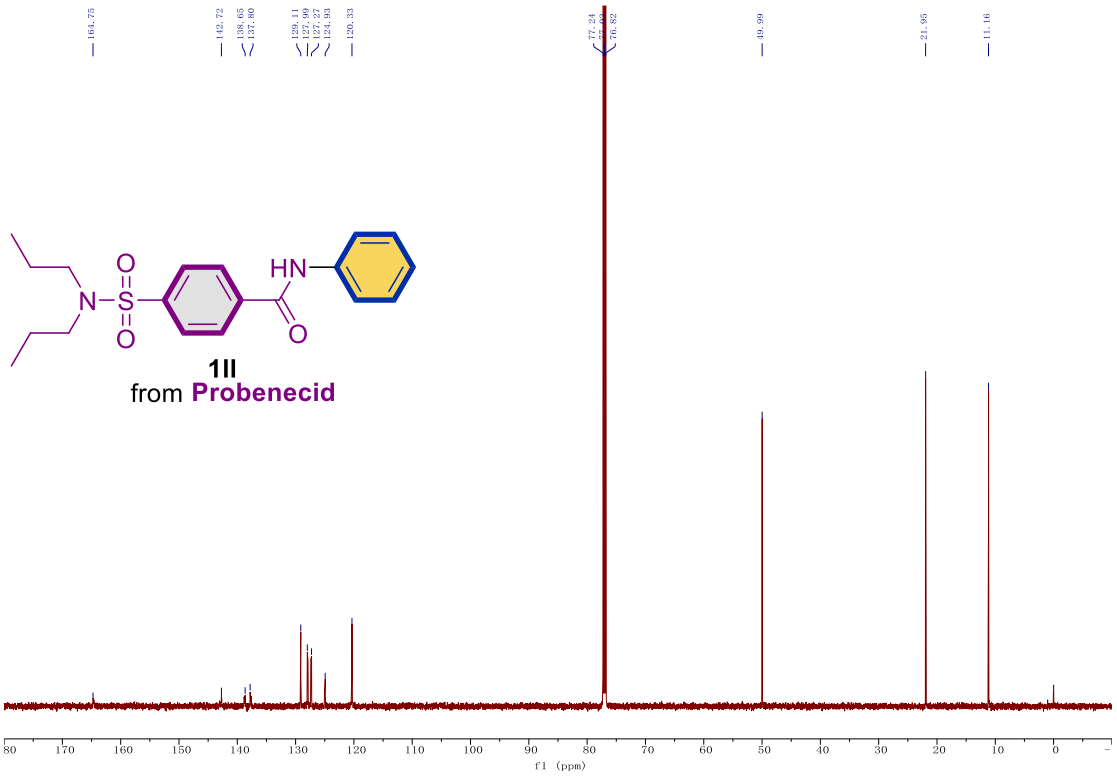
151 MHz ^{13}C NMR spectra of **1kk** in $CDCl_3$.



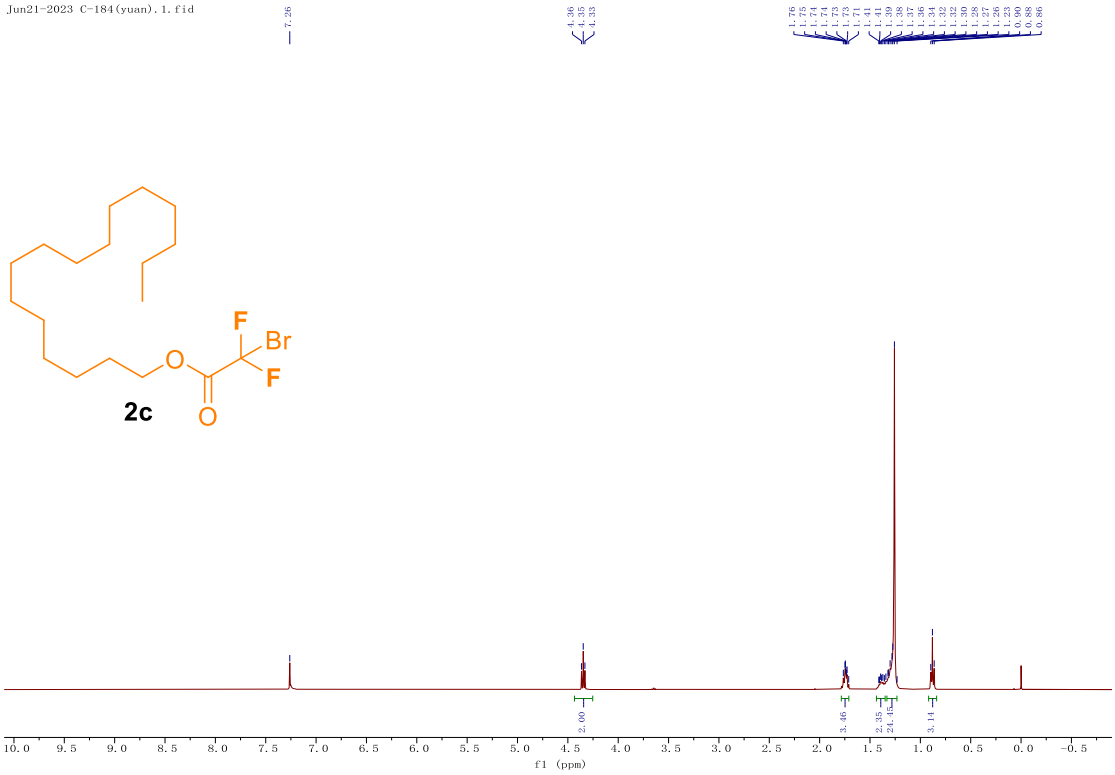
600 MHz ^{1}H NMR spectra of **1ll** in $CDCl_3$.



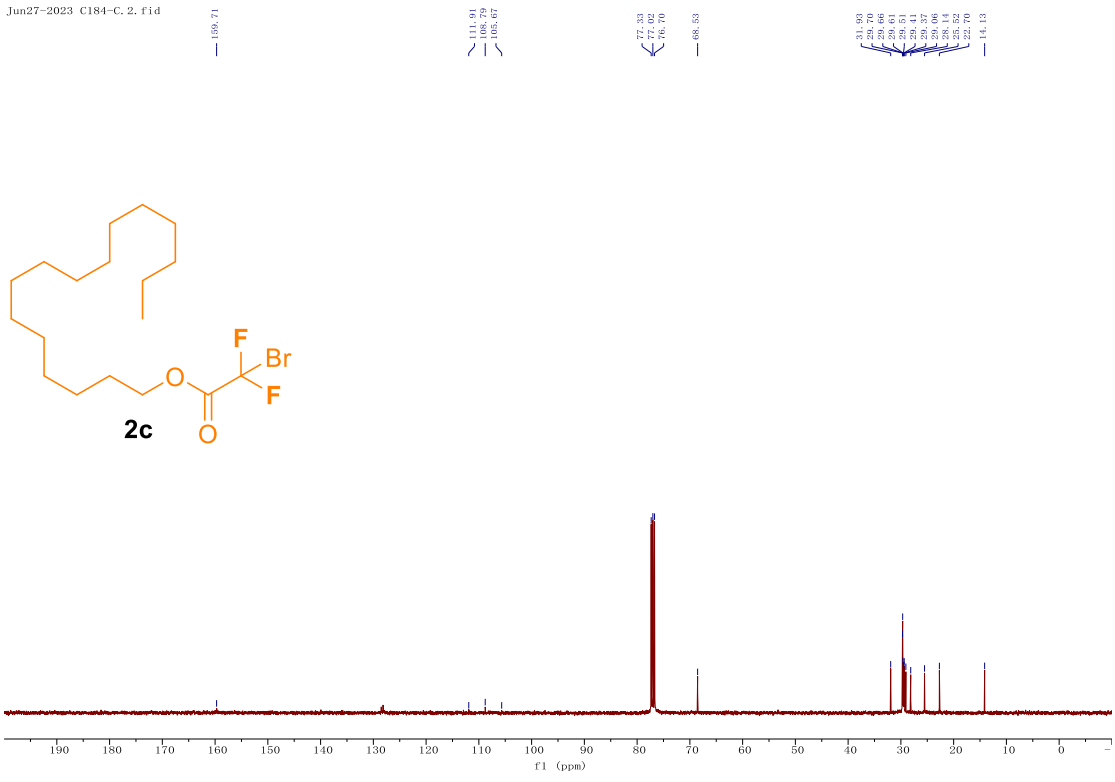
151 MHz ^{13}C NMR spectra of **1ll** in $CDCl_3$.



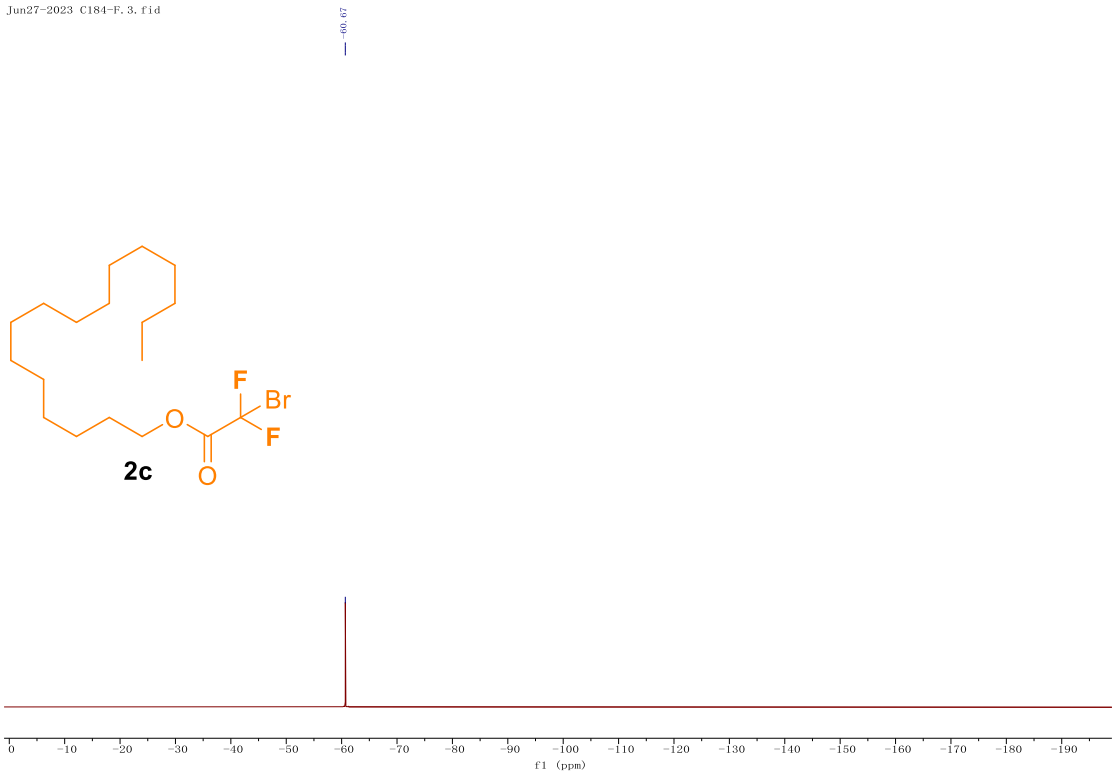
400 MHz ^{1}H NMR spectra of **2c** in $CDCl_3$.



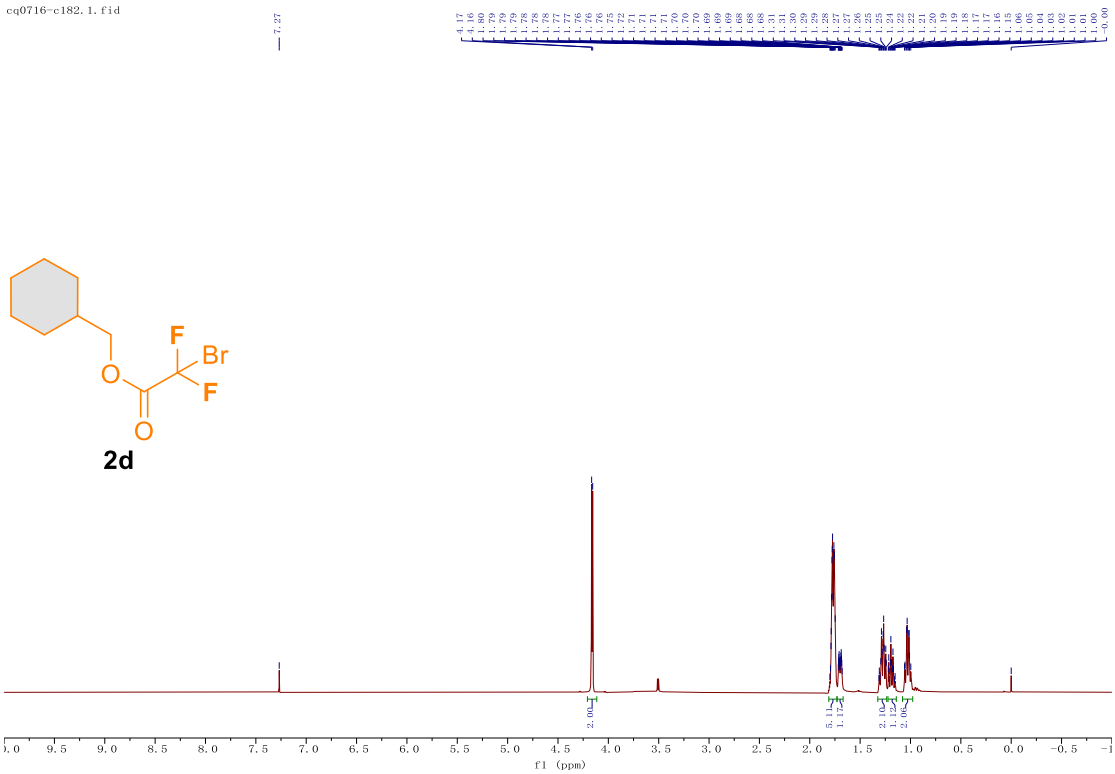
101 MHz ^{13}C NMR spectra of **2c** in $CDCl_3$.



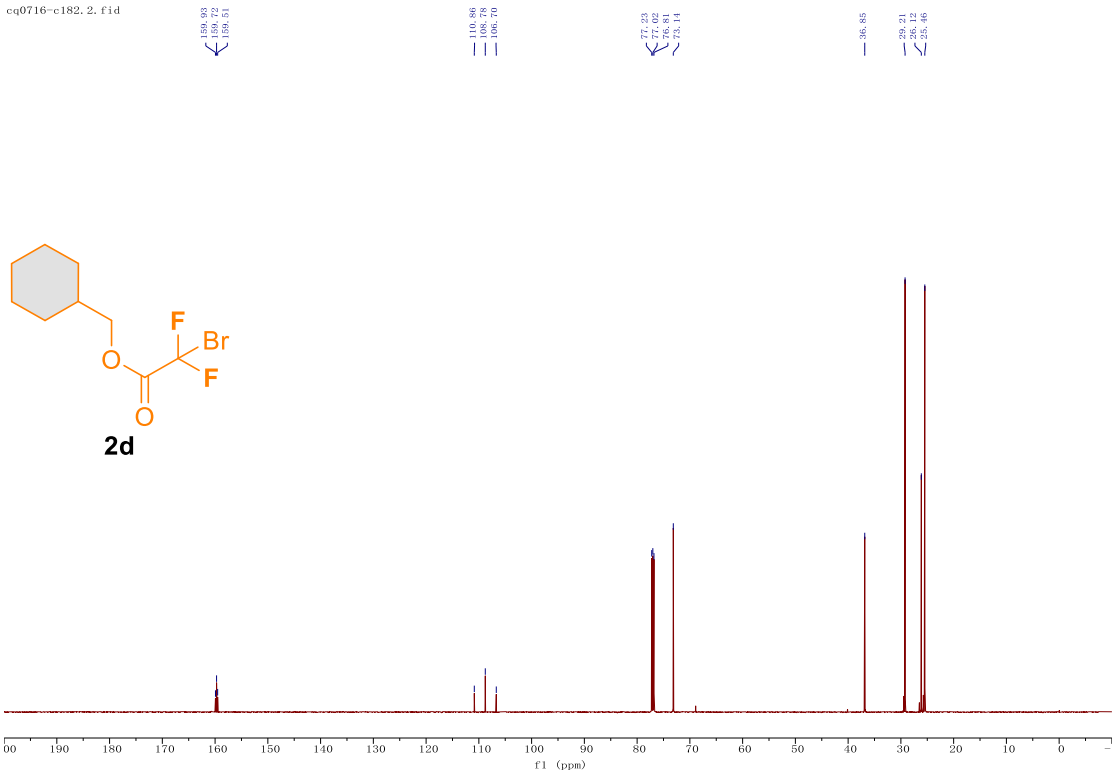
377 MHz ^{19}F NMR spectra of **2c** in $CDCl_3$.



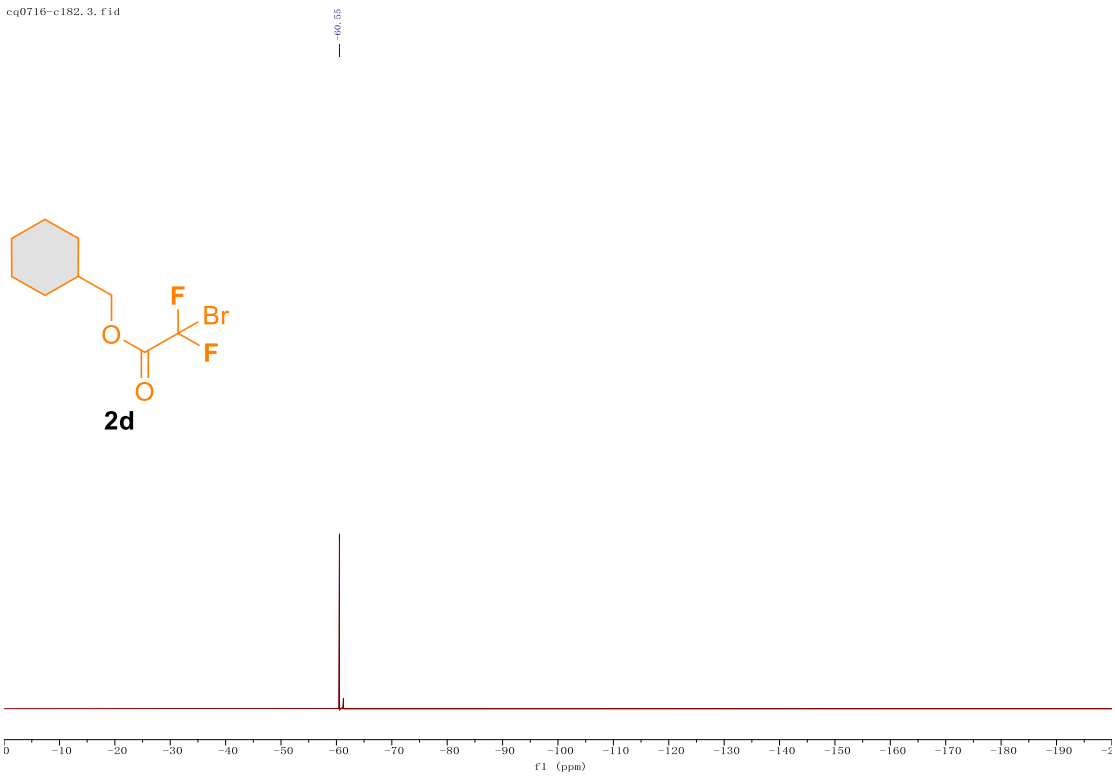
600 MHz ^{1}H NMR spectra of **2d** in $CDCl_3$.



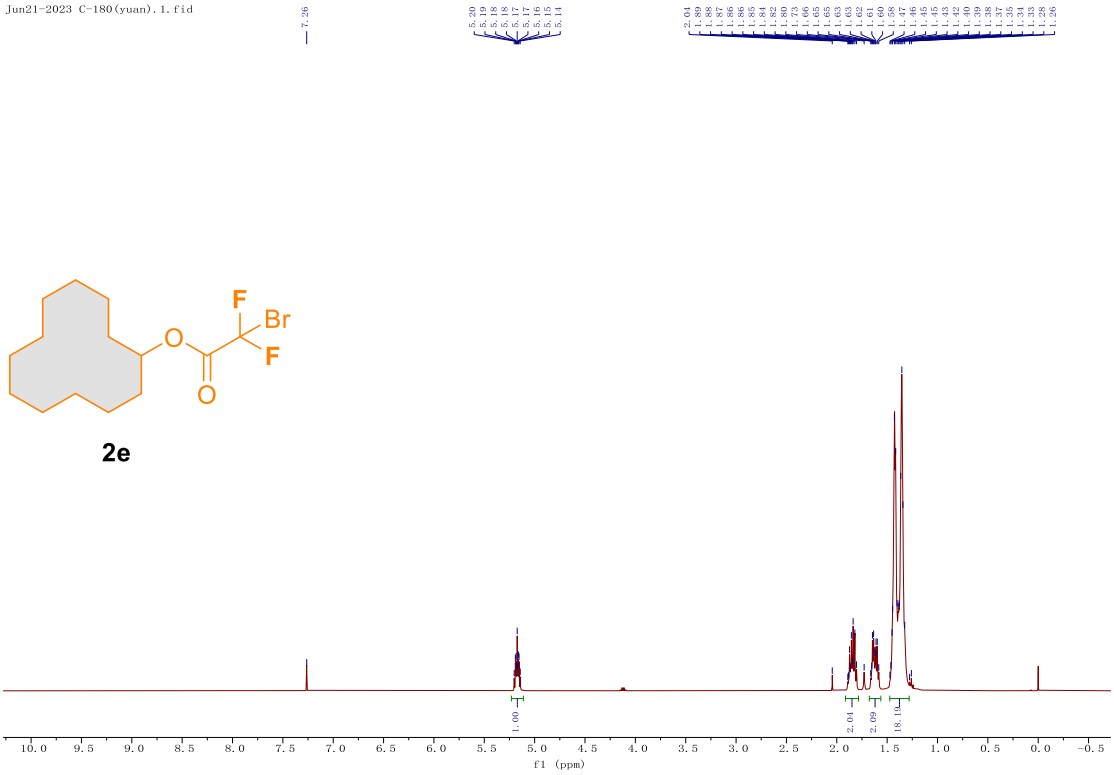
151 MHz ^{13}C NMR spectra of **2d** in $CDCl_3$.



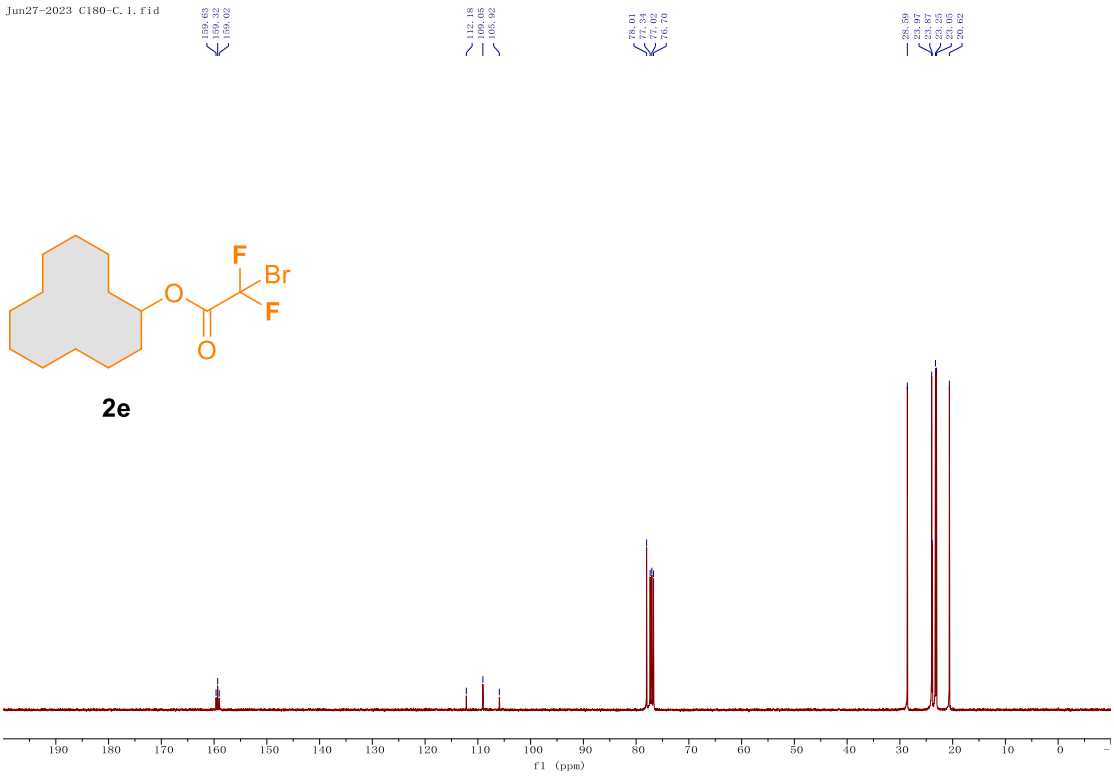
565 MHz ^{19}F NMR spectra of **2d** in $CDCl_3$.



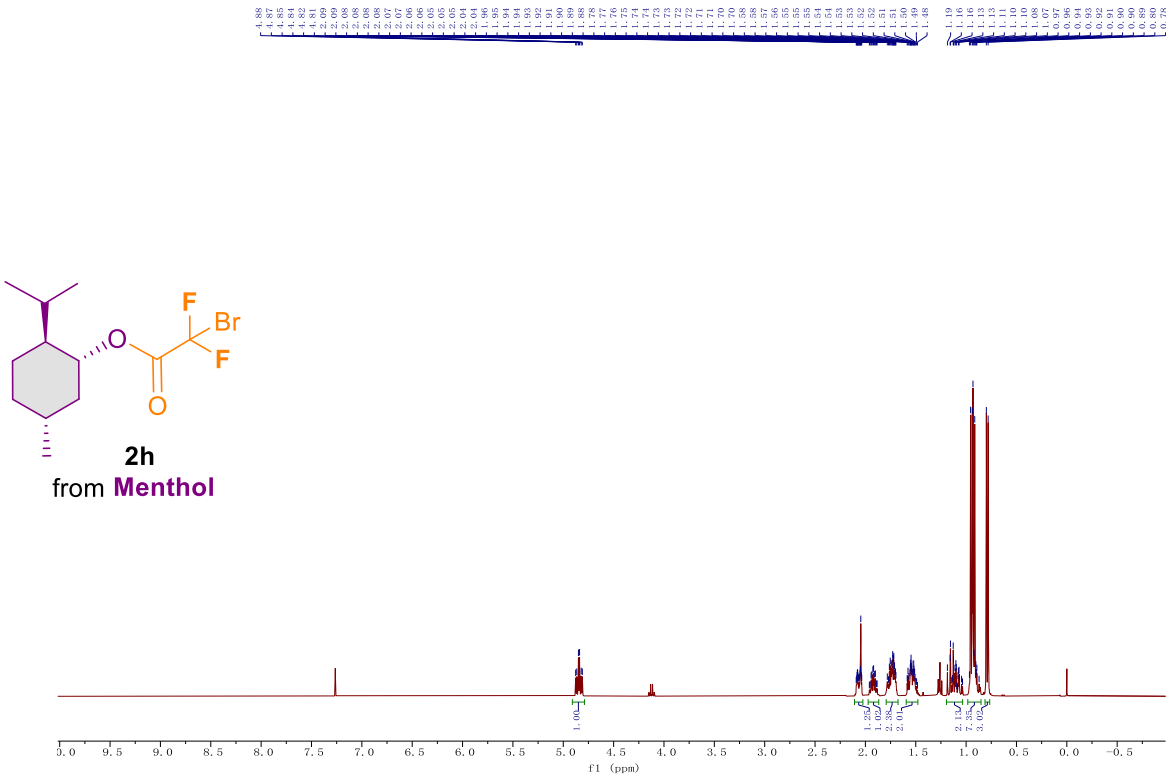
400 MHz ^{1}H NMR spectra of **2e** in $CDCl_3$.



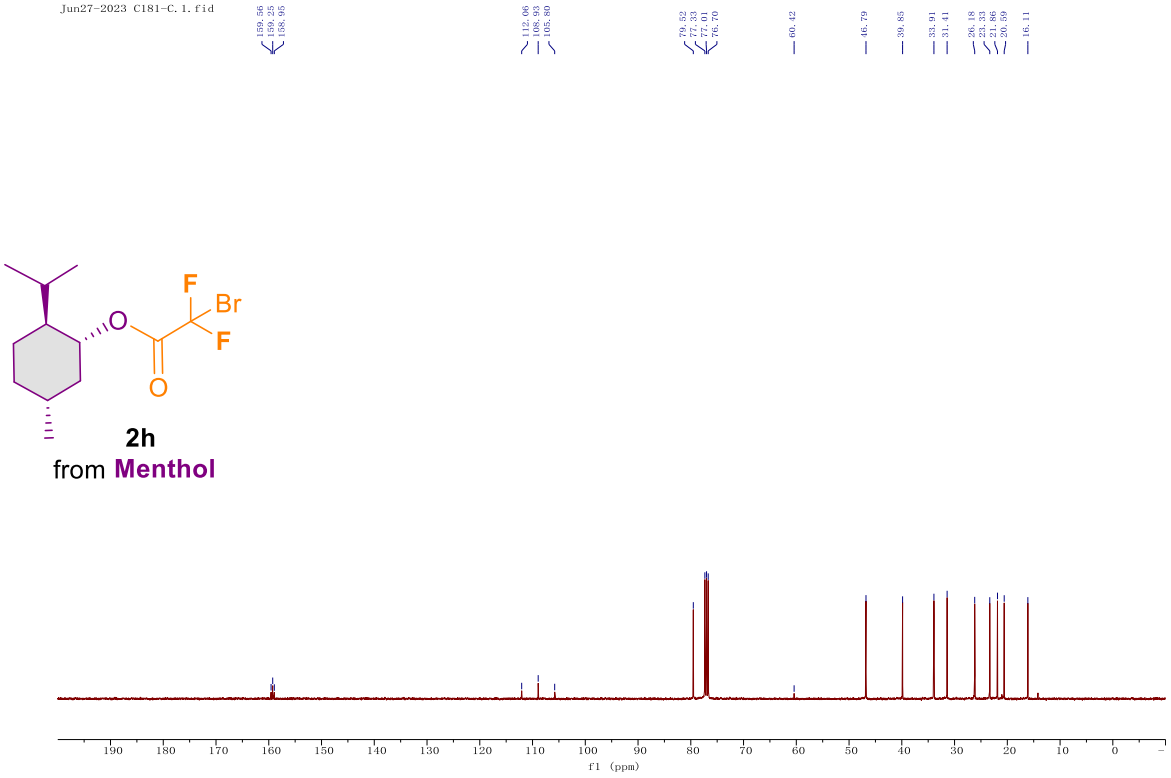
101 MHz ^{13}C NMR spectra of **2e** in $CDCl_3$.



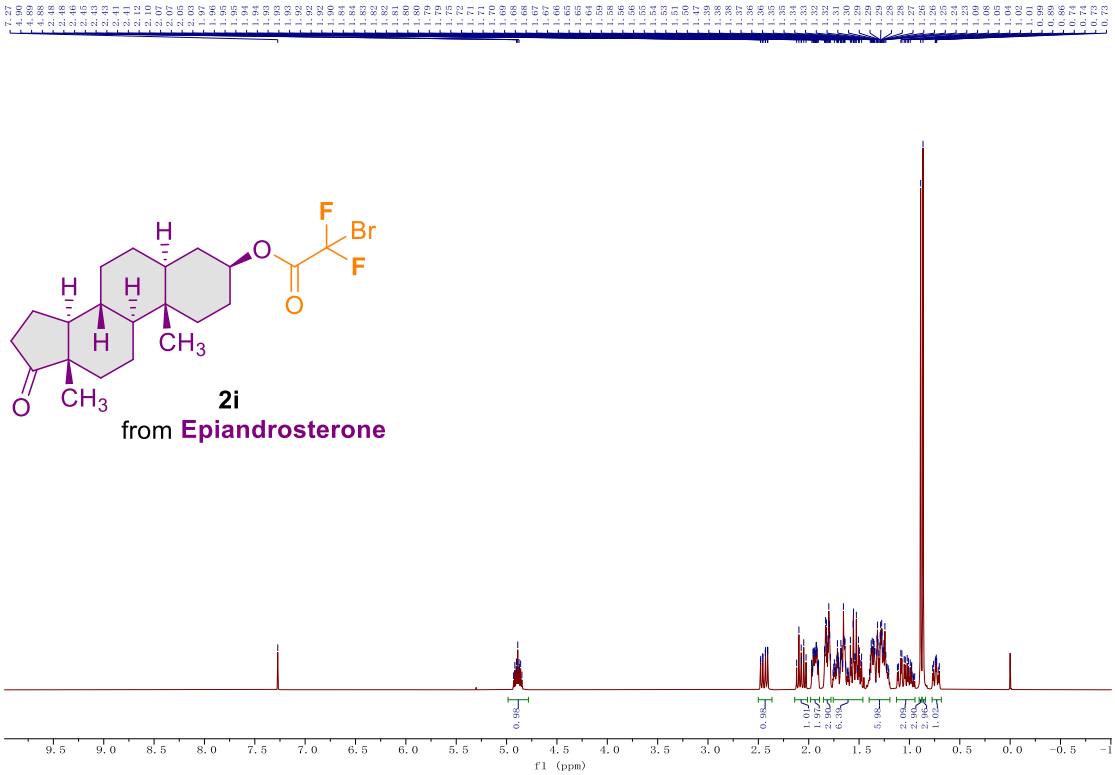
400 MHz ^{1}H NMR spectra of **2h** in $CDCl_3$.



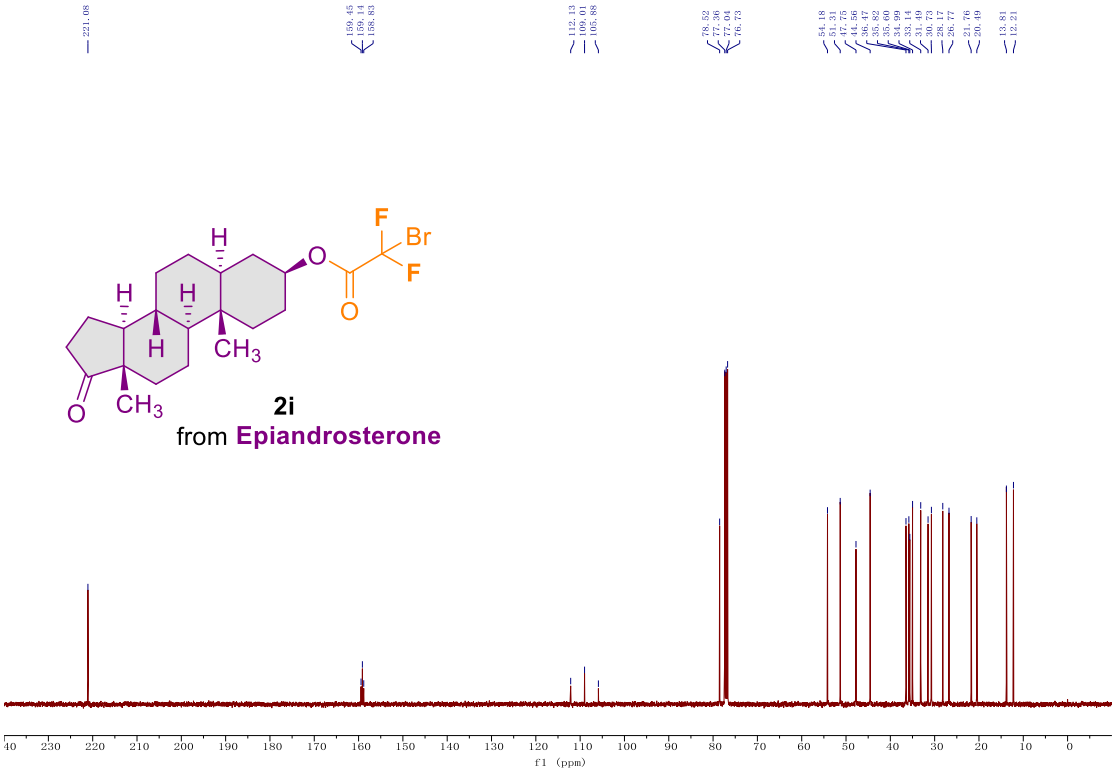
101 MHz ^{13}C NMR spectra of **2h** in $CDCl_3$.



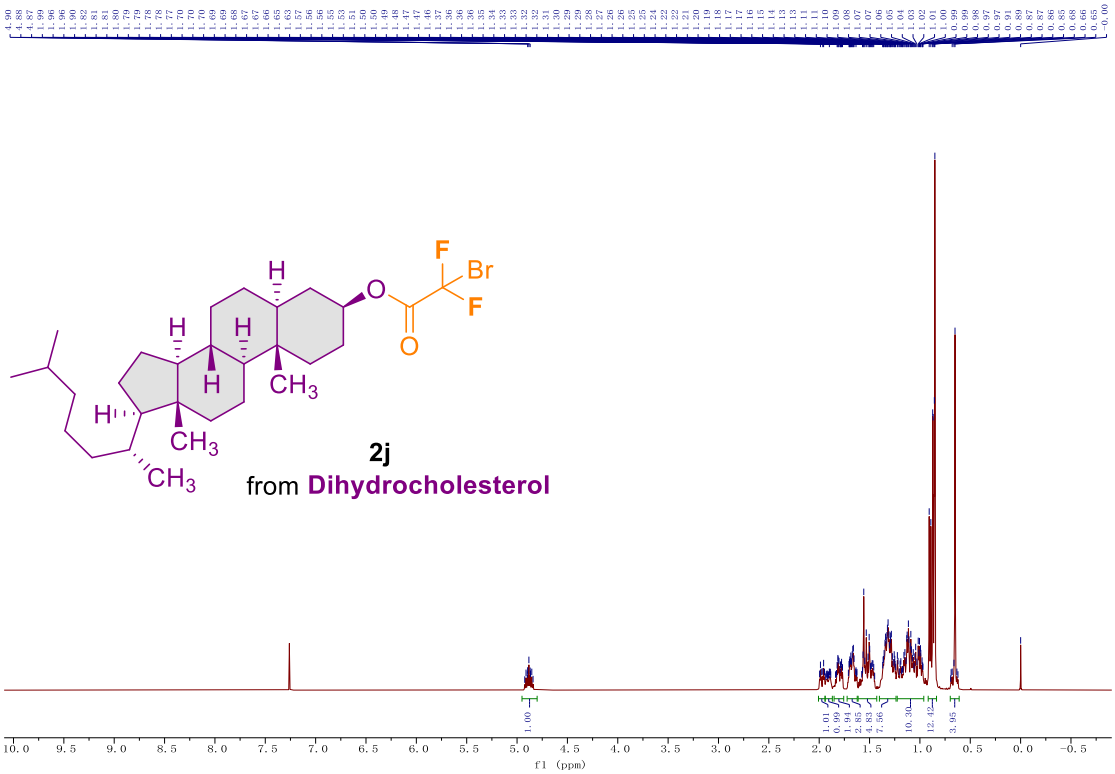
400 MHz ^{1}H NMR spectra of **2i** in $CDCl_3$.



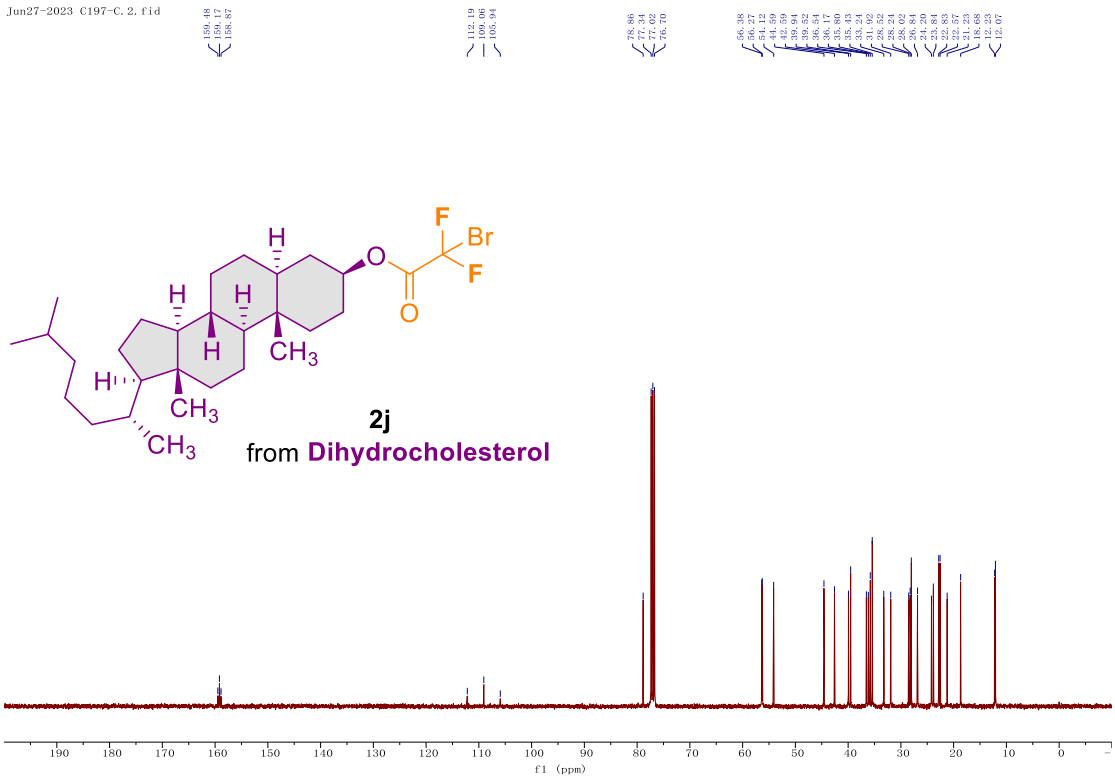
101 MHz ^{13}C NMR spectra of **2i** in $CDCl_3$.



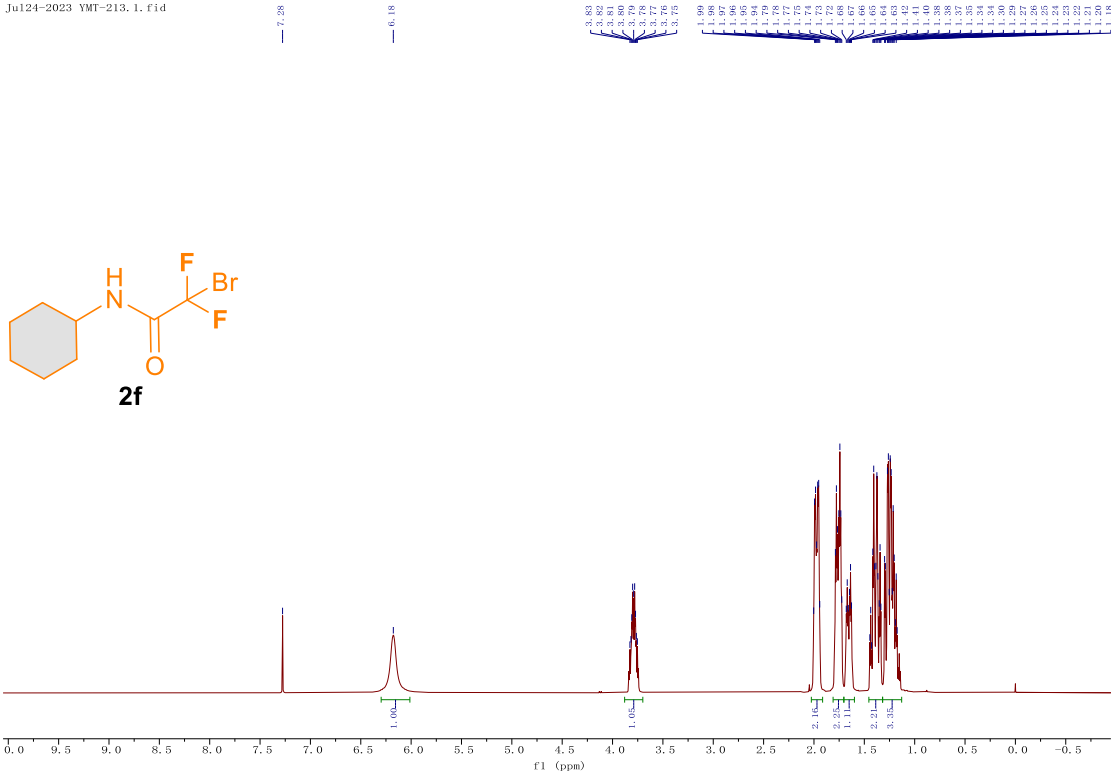
400 MHz ^{1}H NMR spectra of **2j** in $CDCl_3$.



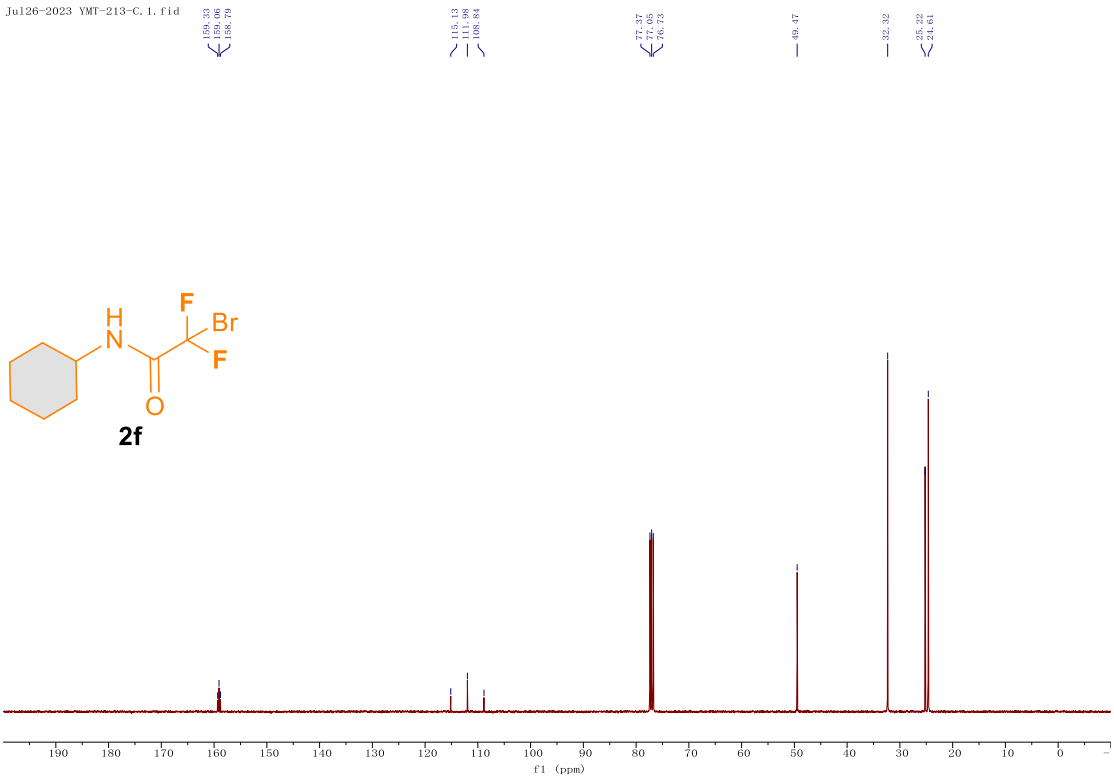
101 MHz ^{13}C NMR spectra of **2j** in $CDCl_3$.



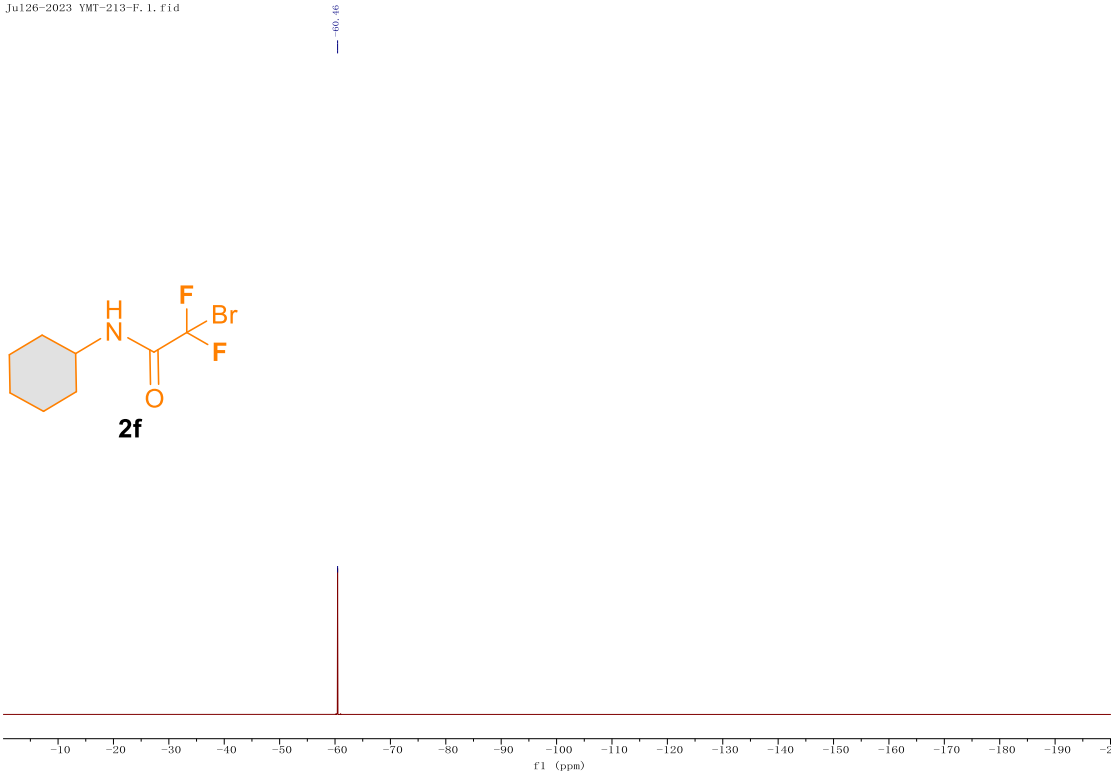
400 MHz ^{1}H NMR spectra of **2f** in $CDCl_3$.



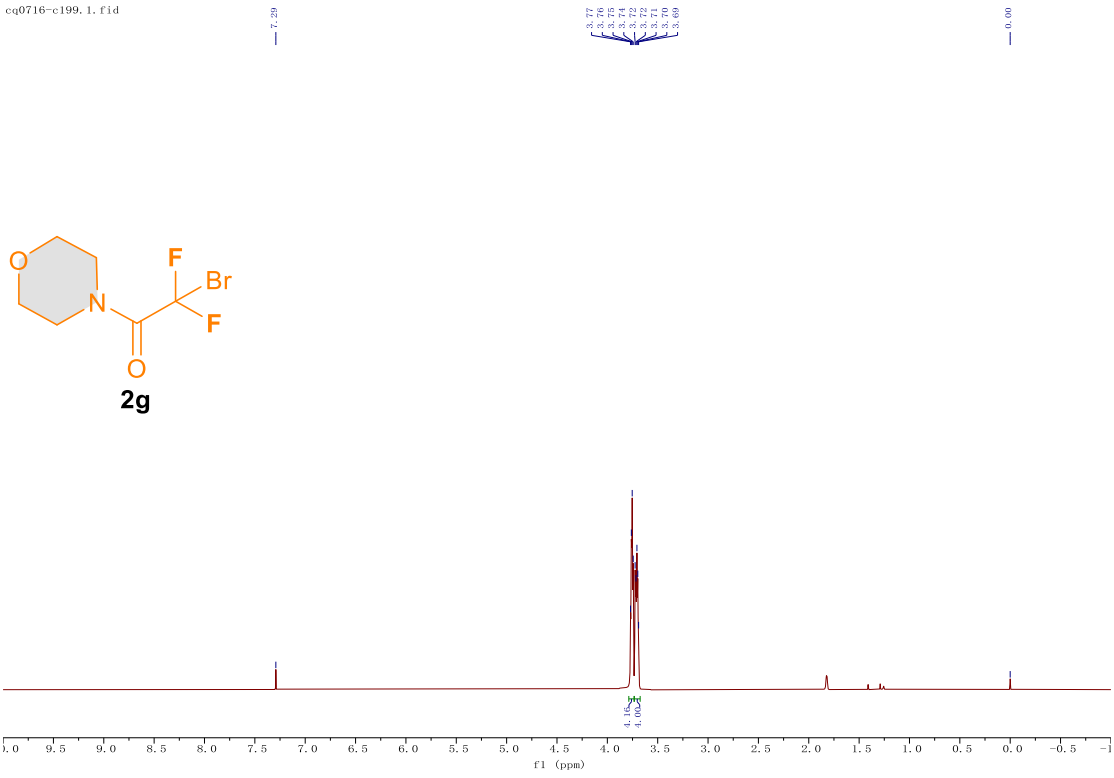
101 MHz ^{13}C NMR spectra of **2f** in $CDCl_3$.



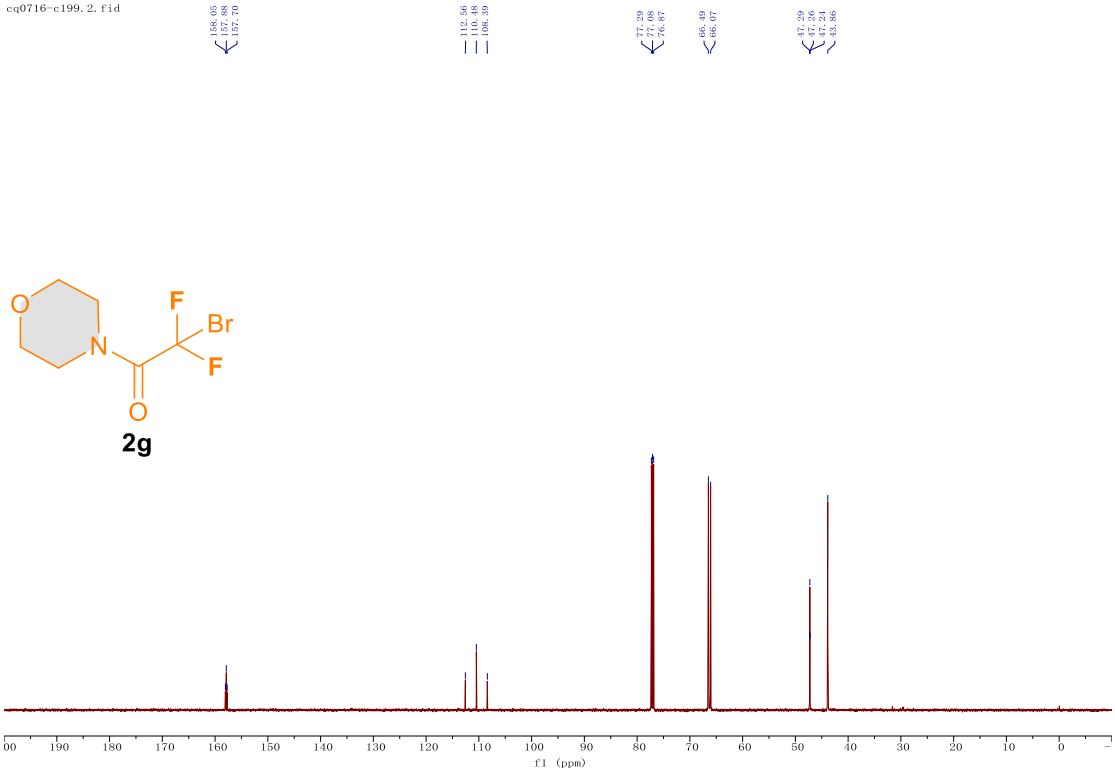
377 MHz ^{19}F NMR spectra of **2f** in $CDCl_3$.



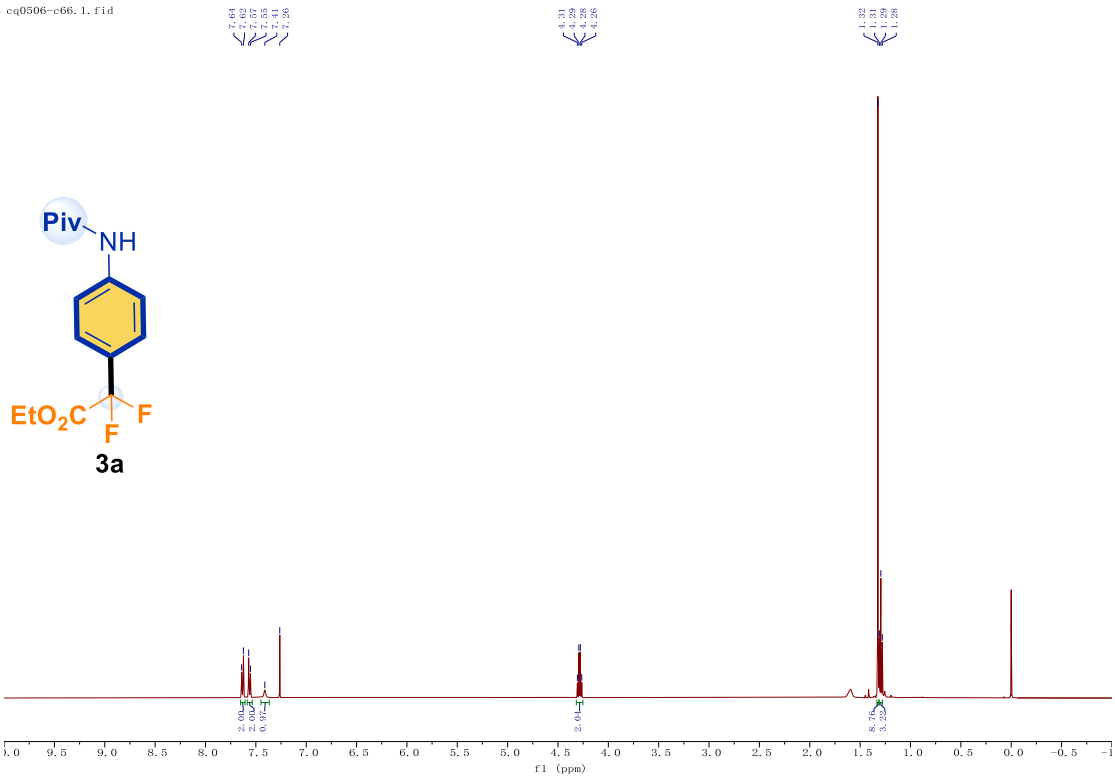
600 MHz ^{1}H NMR spectra of **2g** in $CDCl_3$.



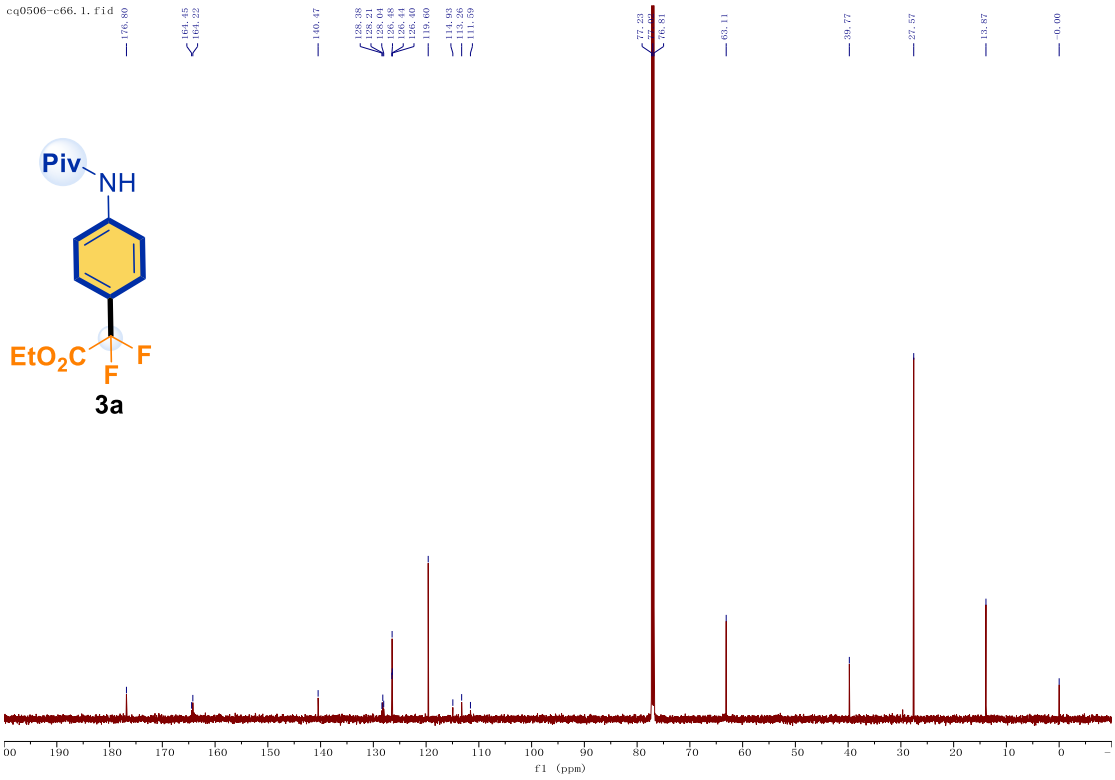
151 MHz ^{13}C NMR spectra of **2g** in $CDCl_3$.



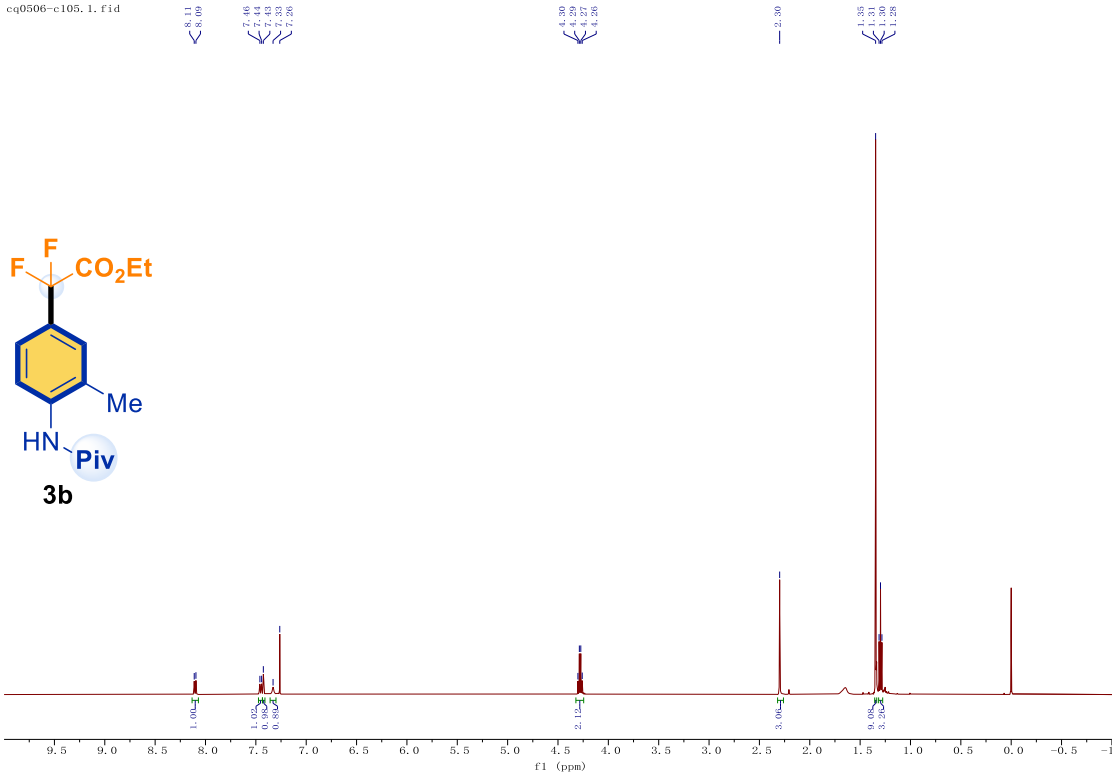
500 MHz ^{1}H NMR spectra of **3a** in $CDCl_3$.



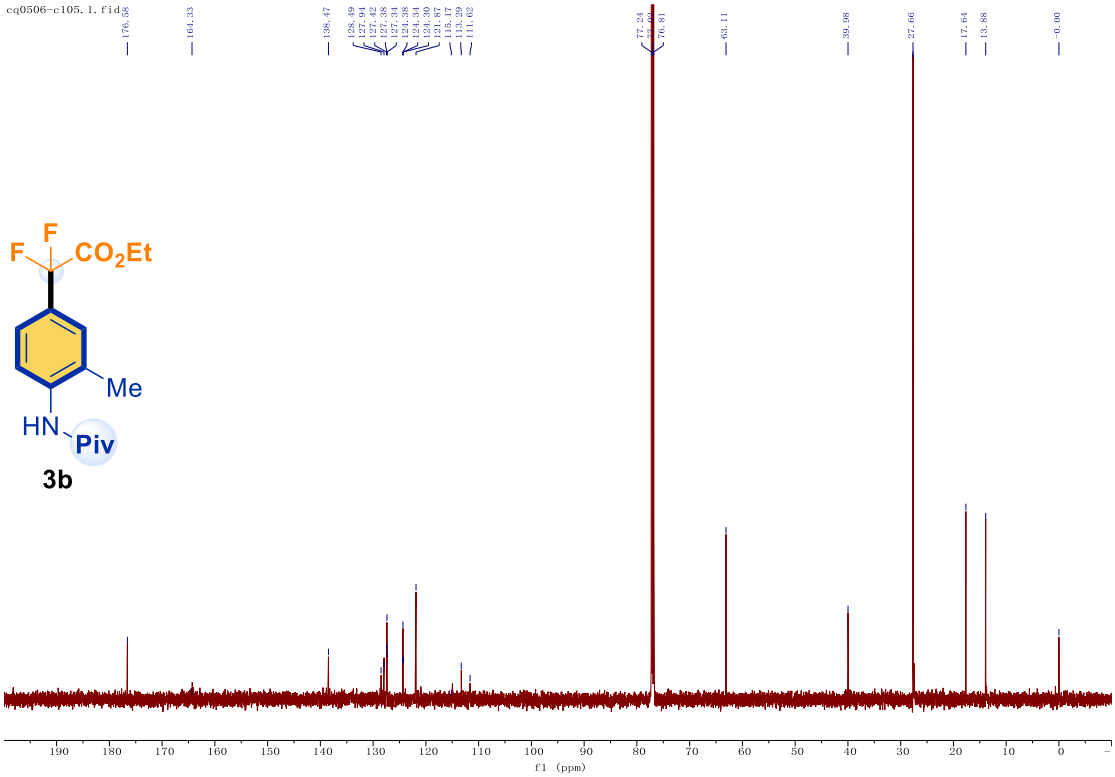
151 MHz ^{13}C NMR spectra of **3a** in $CDCl_3$.



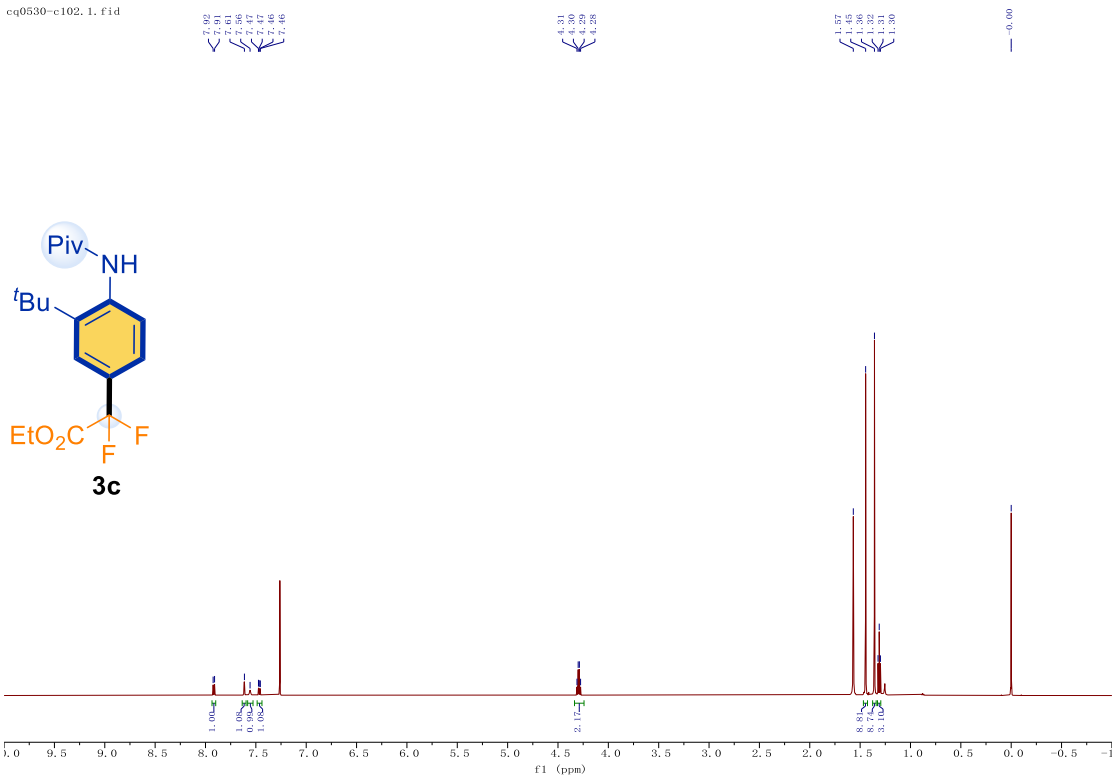
500 MHz ^{1}H NMR spectra of **3b** in $CDCl_3$.



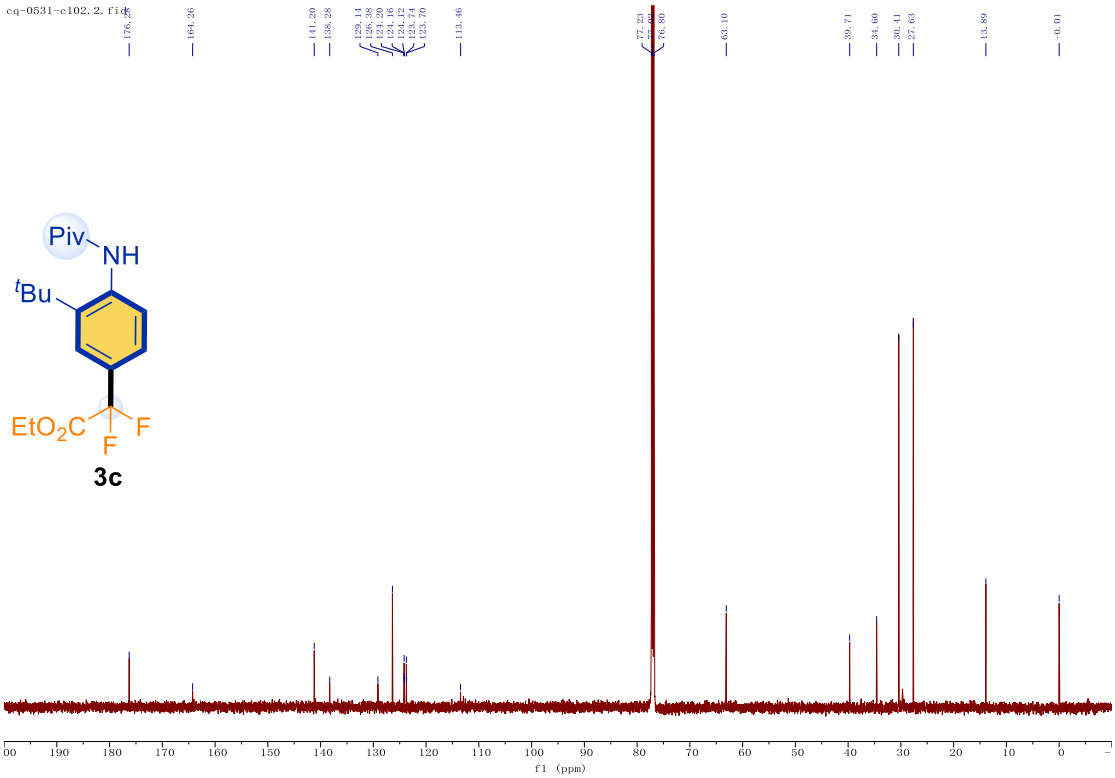
151 MHz ^{13}C NMR spectra of **3b** in $CDCl_3$.



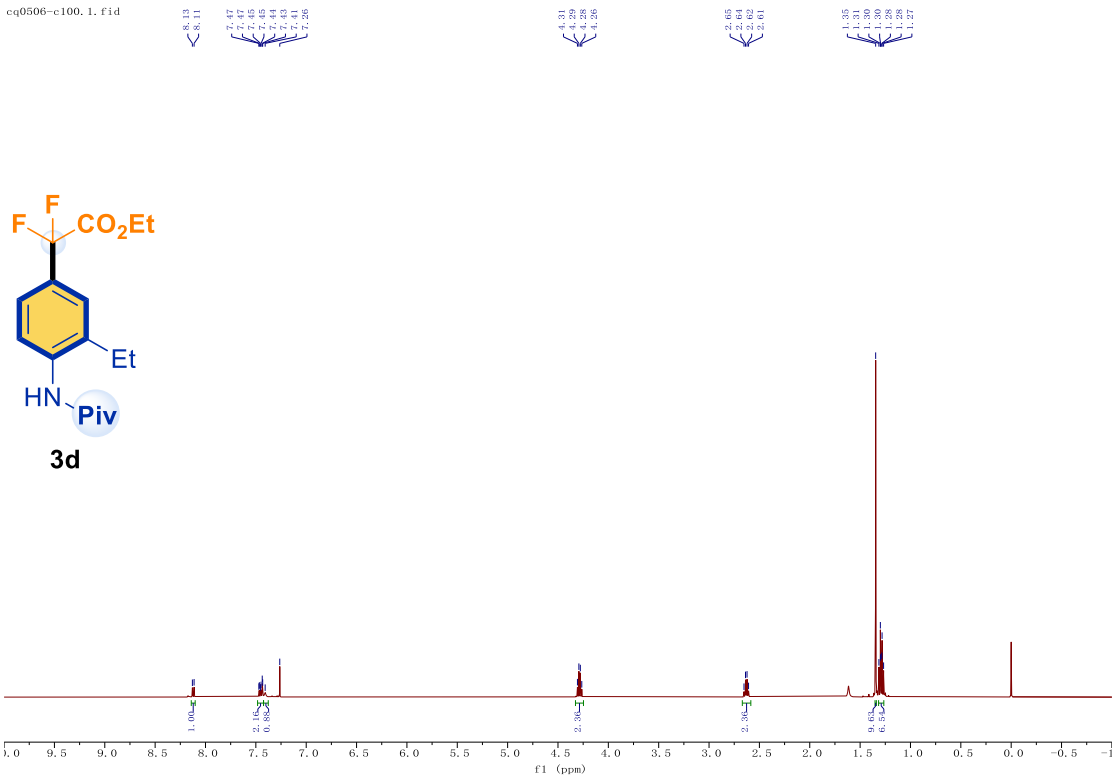
600 MHz ^{1}H NMR spectra of **3c** in $CDCl_3$.



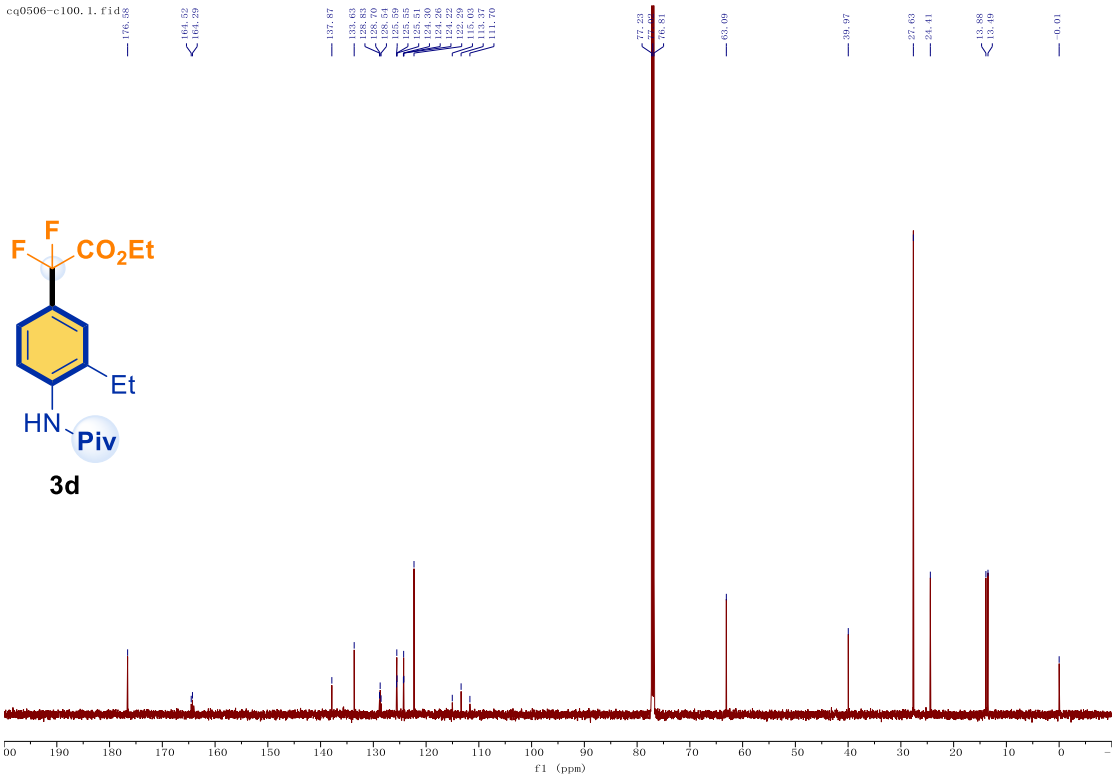
151 MHz ^{13}C NMR spectra of **3c** in $CDCl_3$.



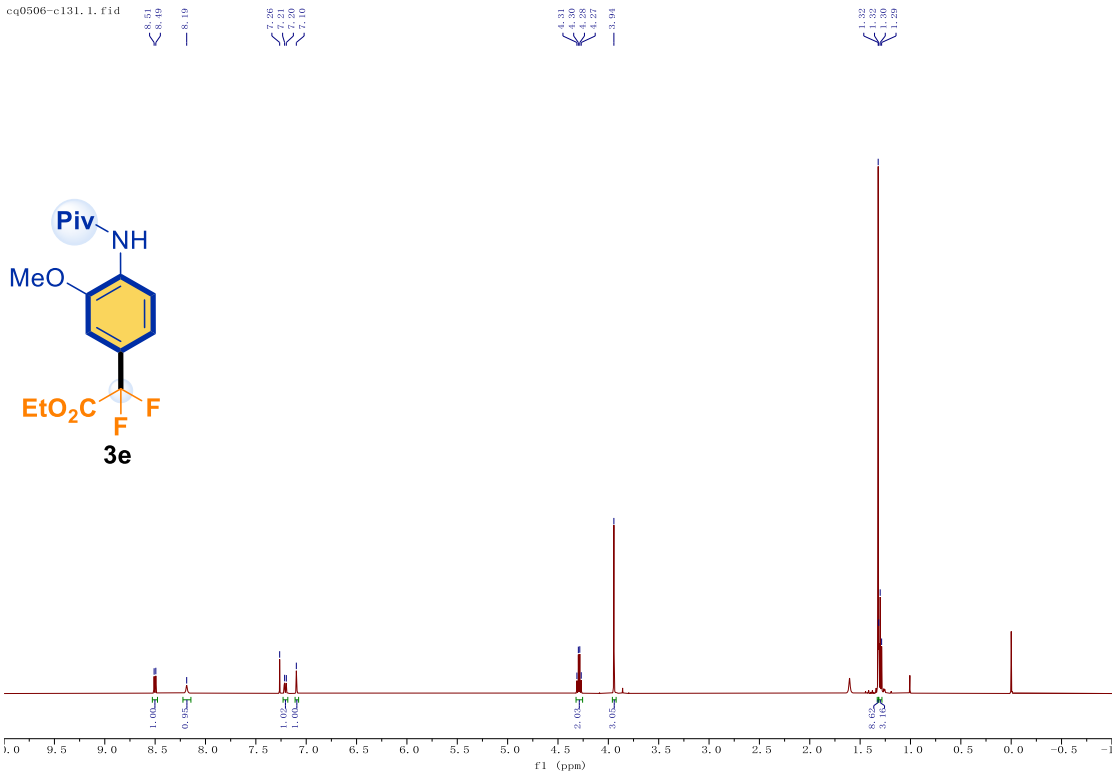
500 MHz ^{1}H NMR spectra of **3d** in $CDCl_3$.



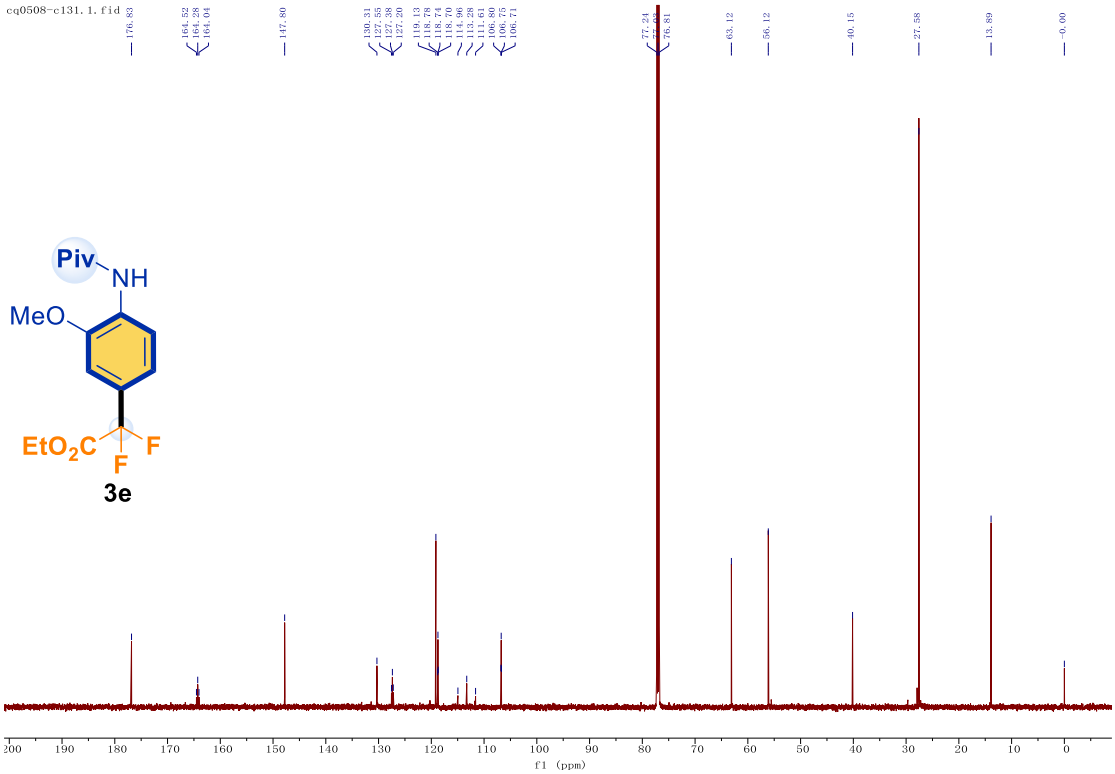
151 MHz ^{13}C NMR spectra of **3d** in $CDCl_3$.



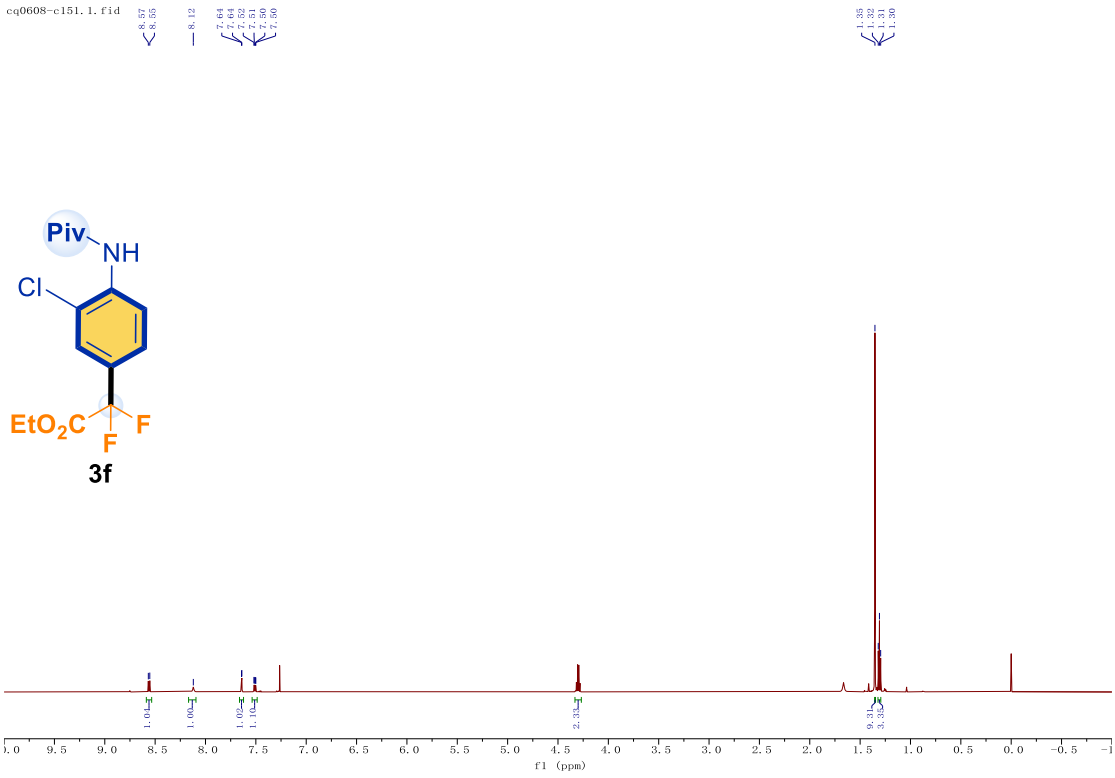
500 MHz ^{1}H NMR spectra of **3e** in $CDCl_3$.



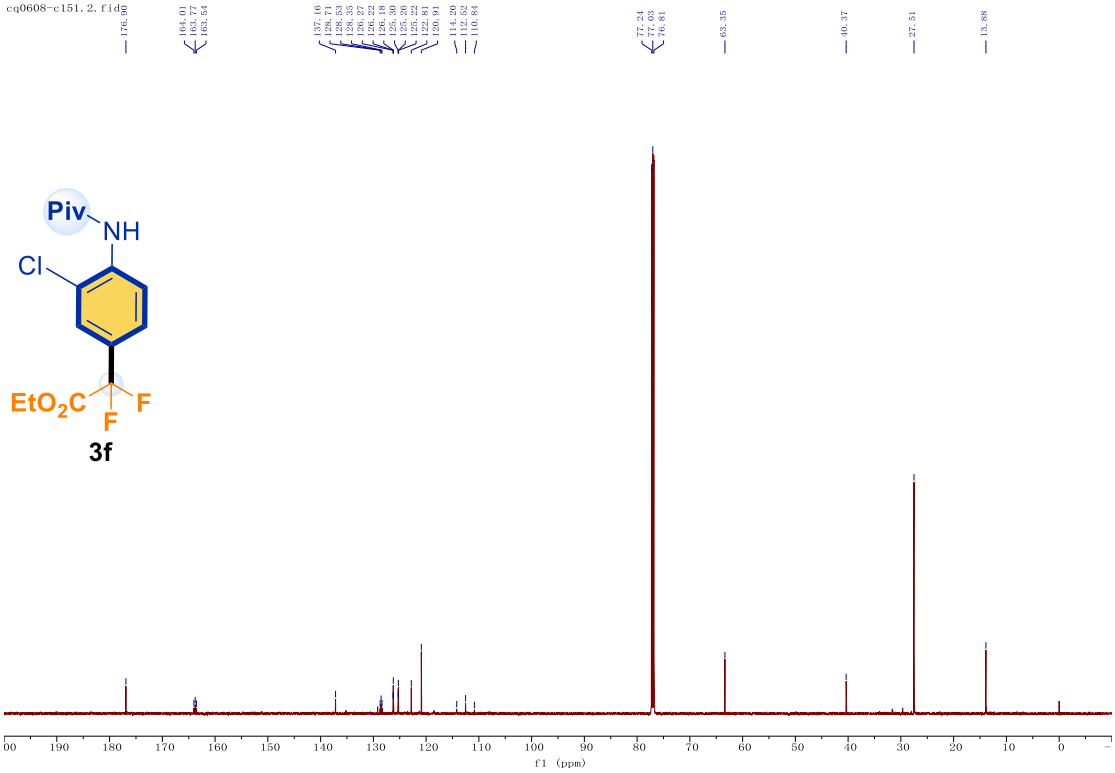
151 MHz ^{13}C NMR spectra of **3e** in $CDCl_3$.



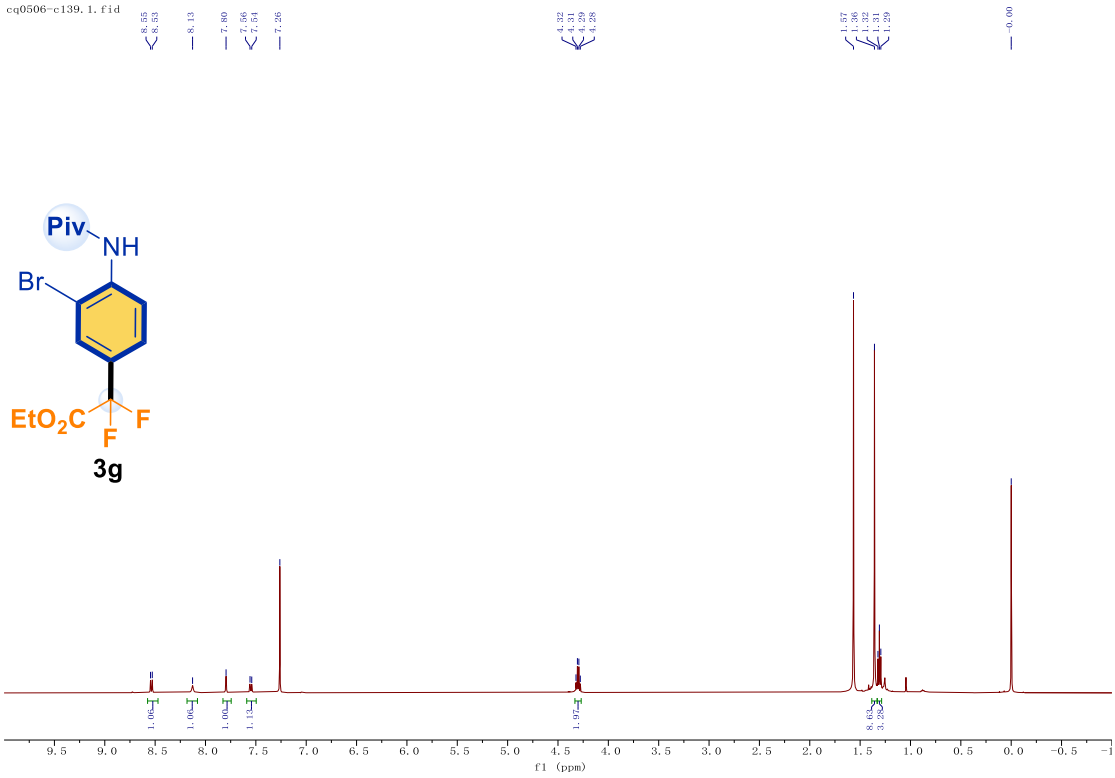
600 MHz ^{1}H NMR spectra of **3f** in $CDCl_3$.



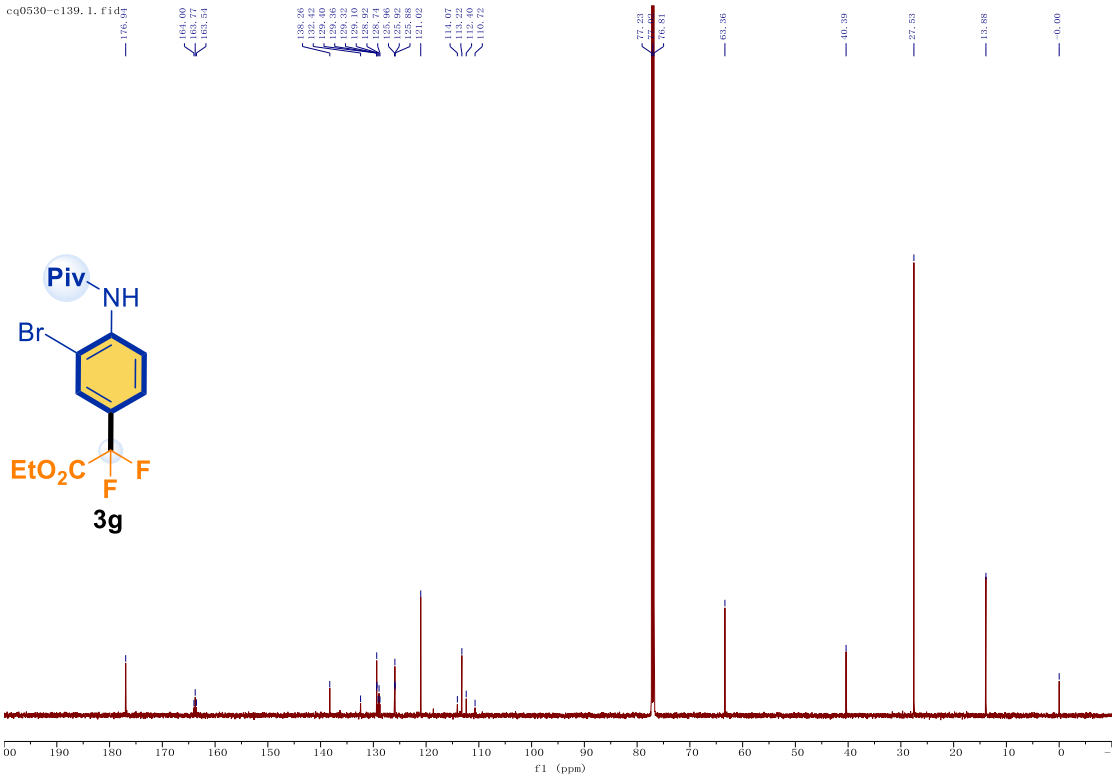
151 MHz ^{13}C NMR spectra of **3f** in $CDCl_3$.



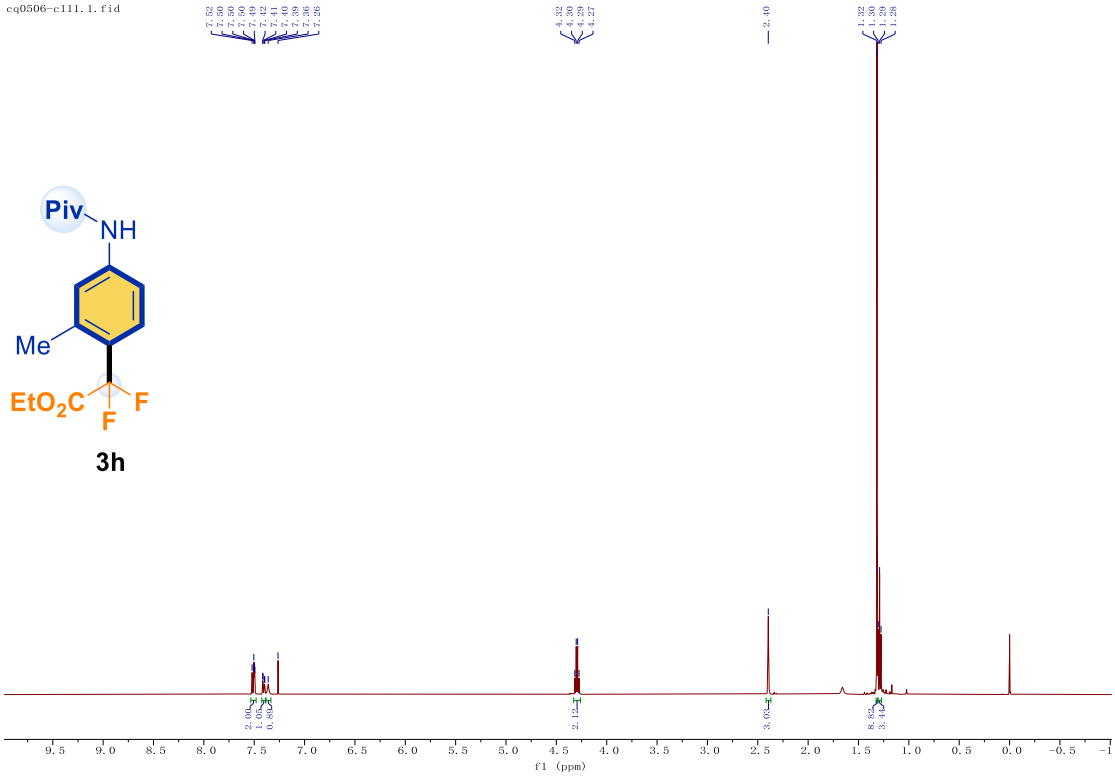
500 MHz ^{1}H NMR spectra of **3g** in $CDCl_3$.



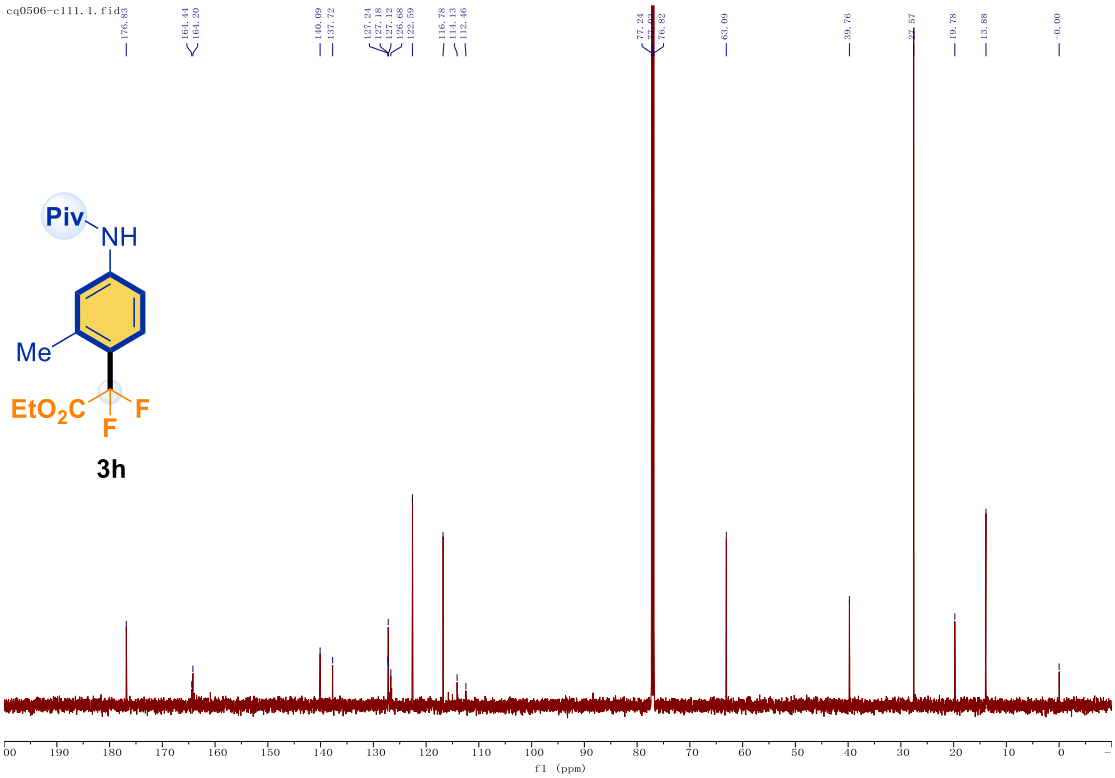
151 MHz ^{13}C NMR spectra of **3g** in $CDCl_3$.



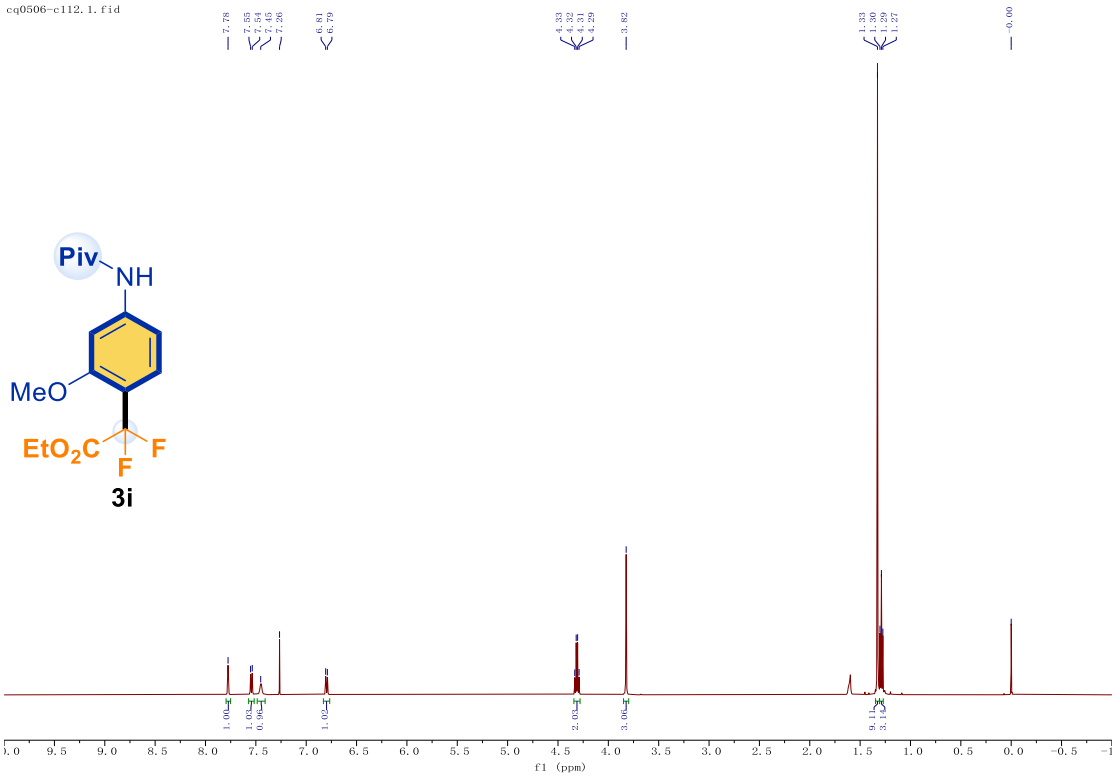
500 MHz ^{1}H NMR spectra of **3h** in $CDCl_3$.



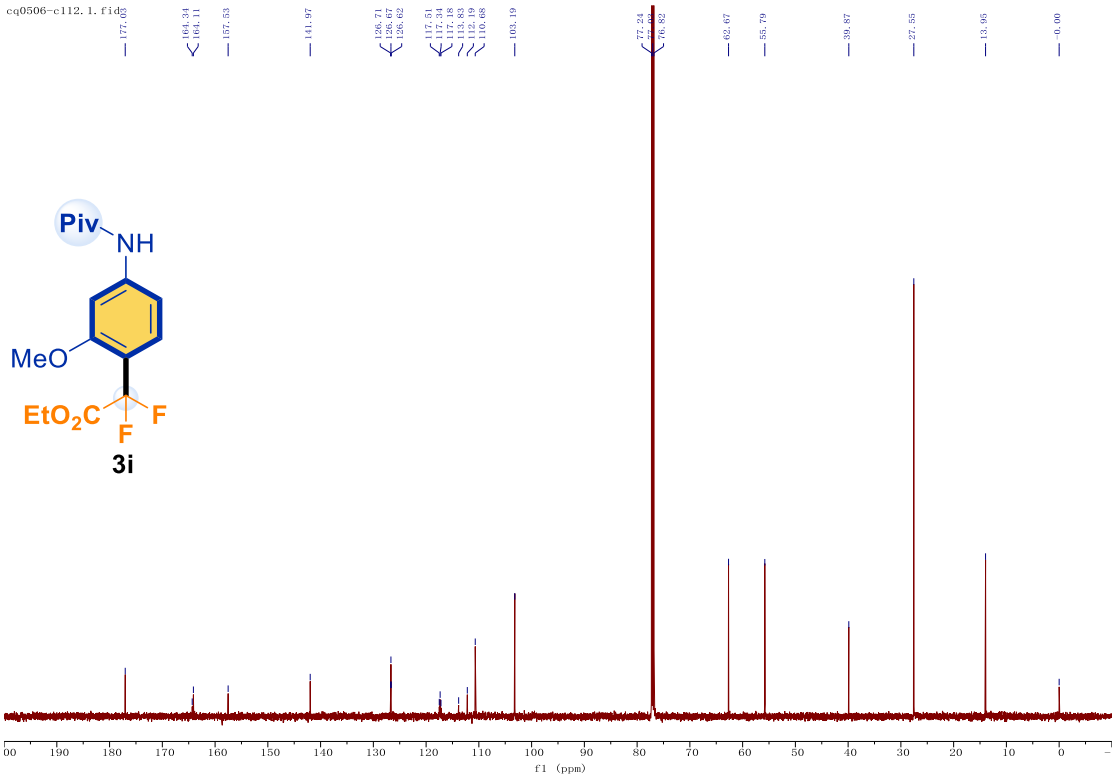
151 MHz ^{13}C NMR spectra of **3h** in $CDCl_3$.



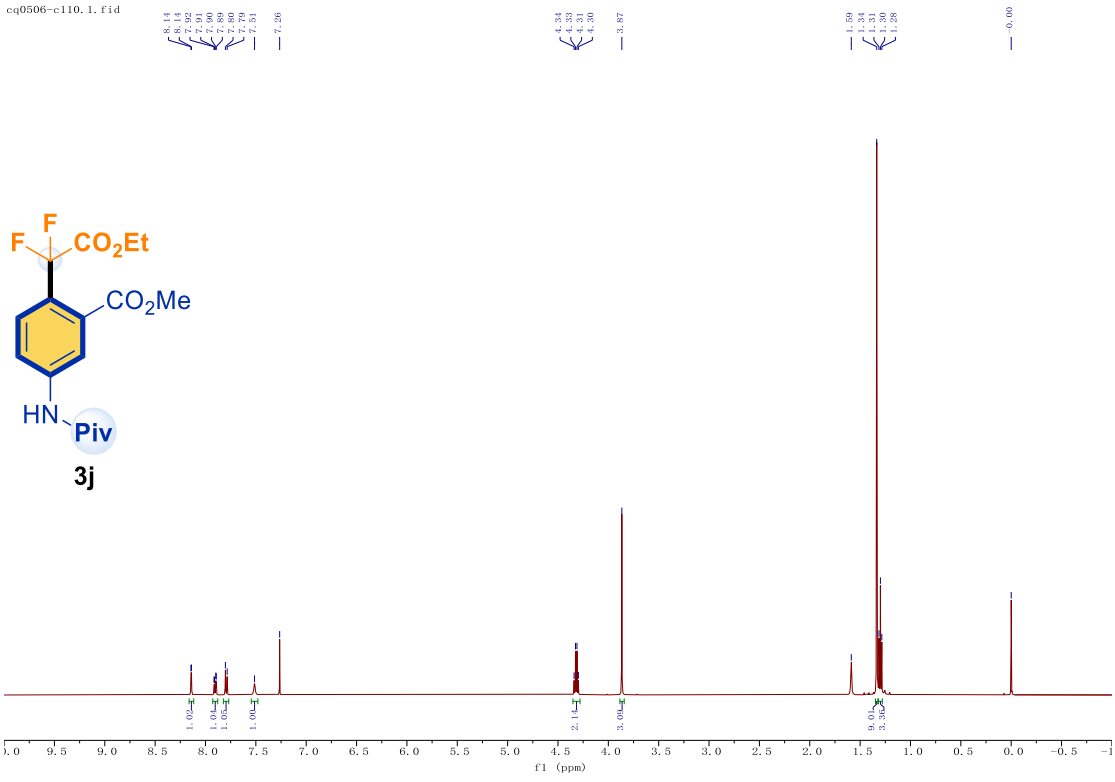
500 MHz ^{1}H NMR spectra of **3i** in $CDCl_3$.



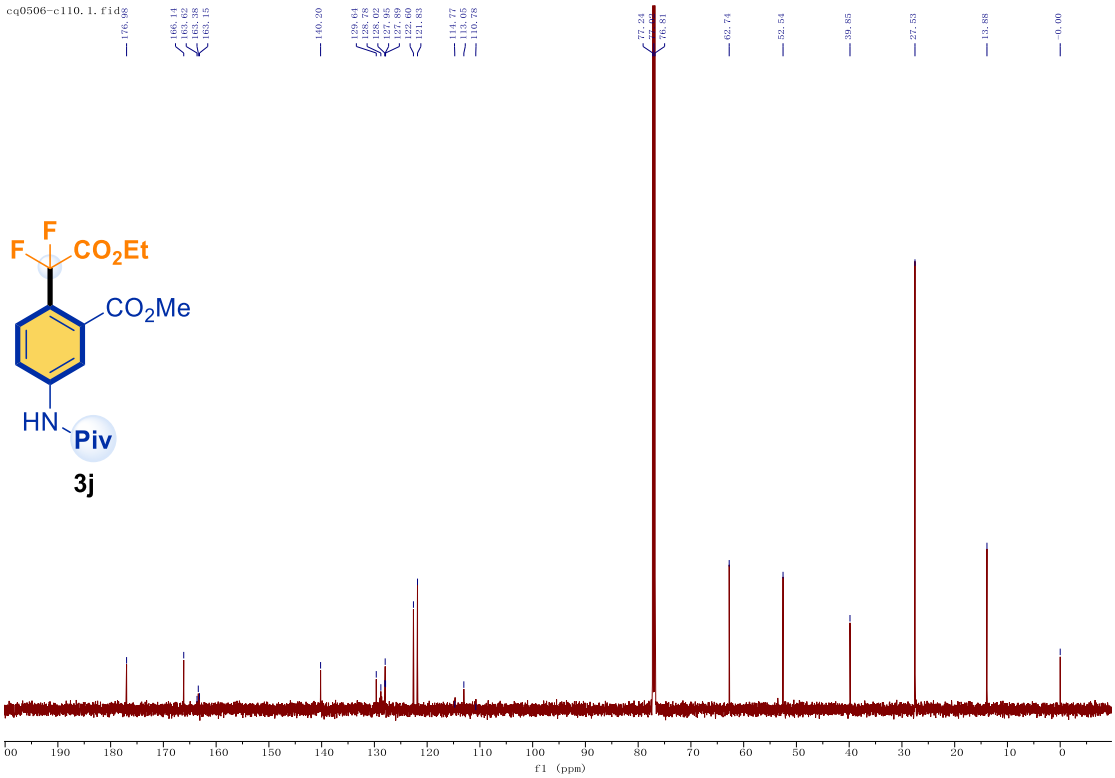
151 MHz ^{13}C NMR spectra of **3i** in $CDCl_3$.



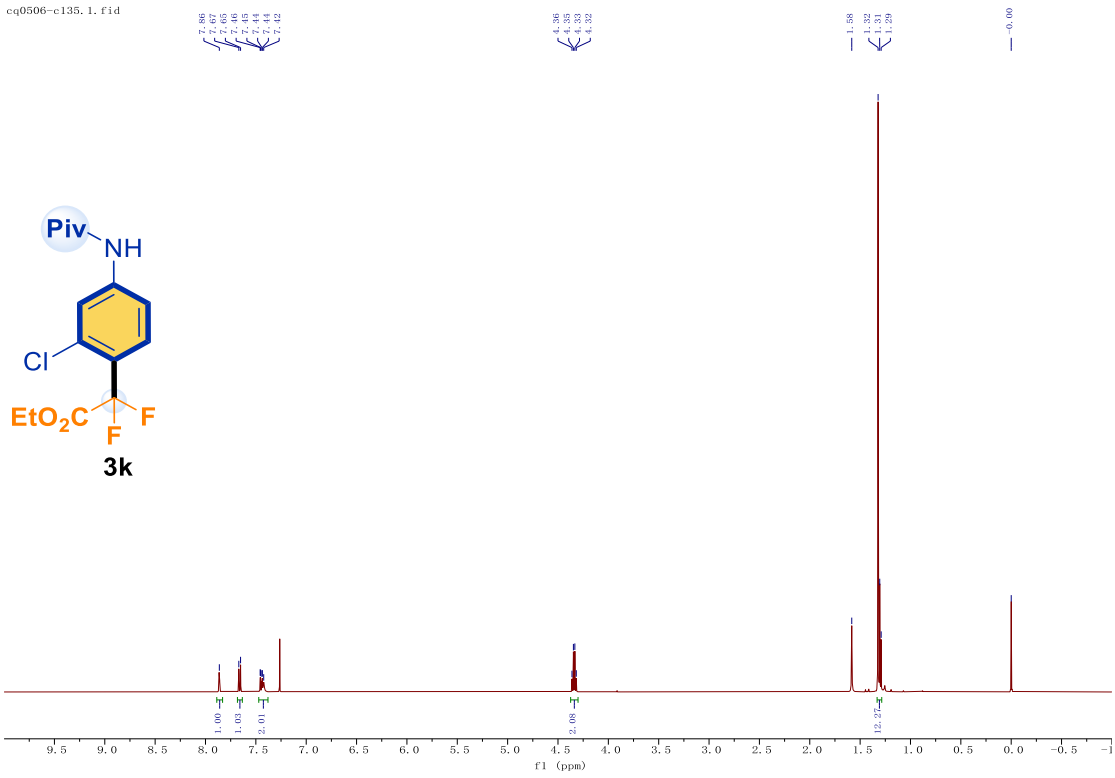
500 MHz ^{1}H NMR spectra of **3j** in $CDCl_3$.



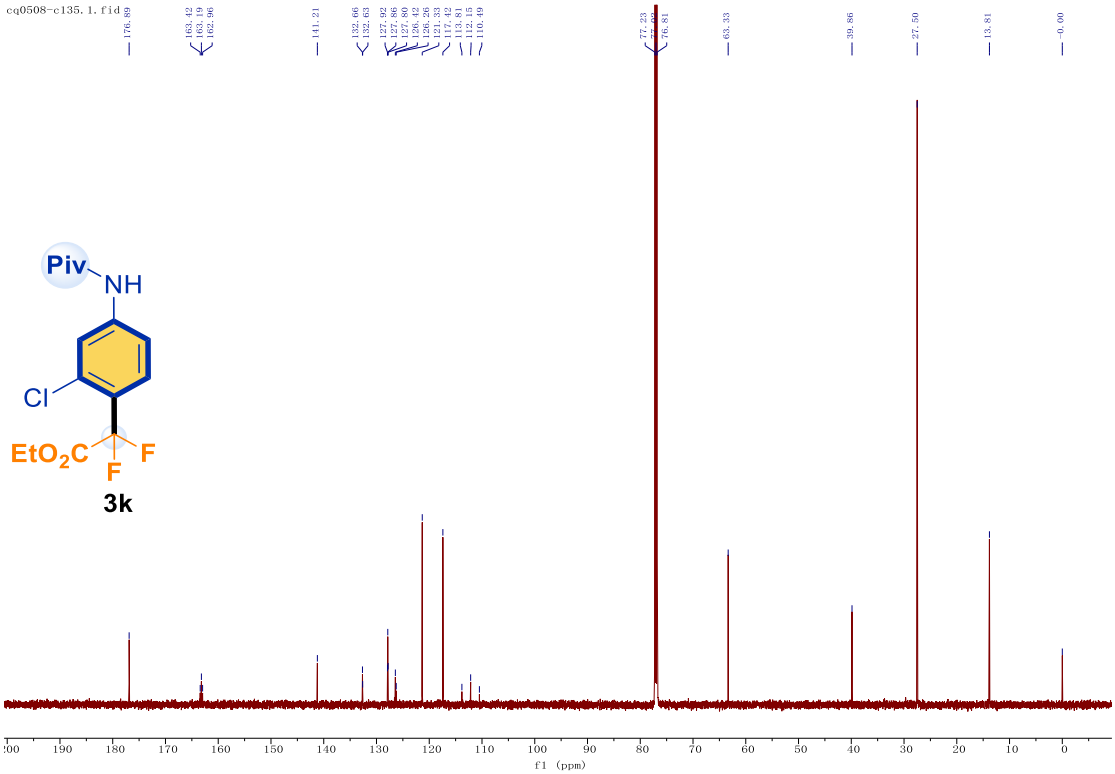
151 MHz ^{13}C NMR spectra of **3j** in $CDCl_3$.



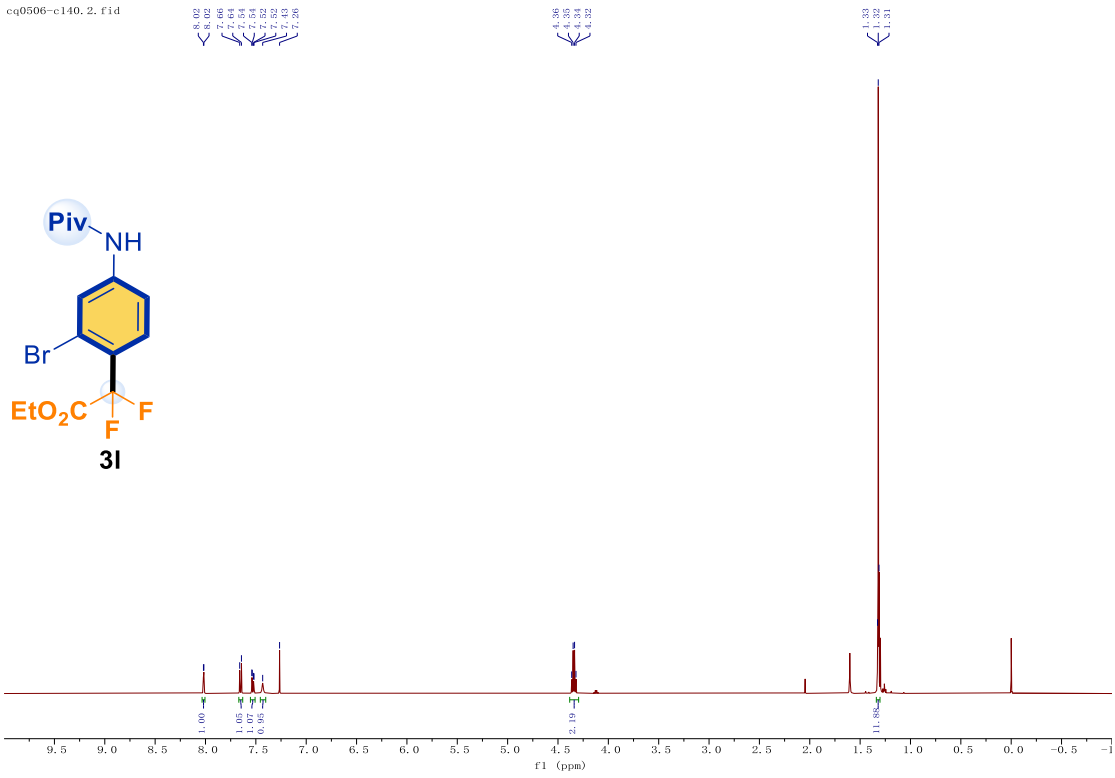
500 MHz ^{1}H NMR spectra of **3k** in $CDCl_3$.



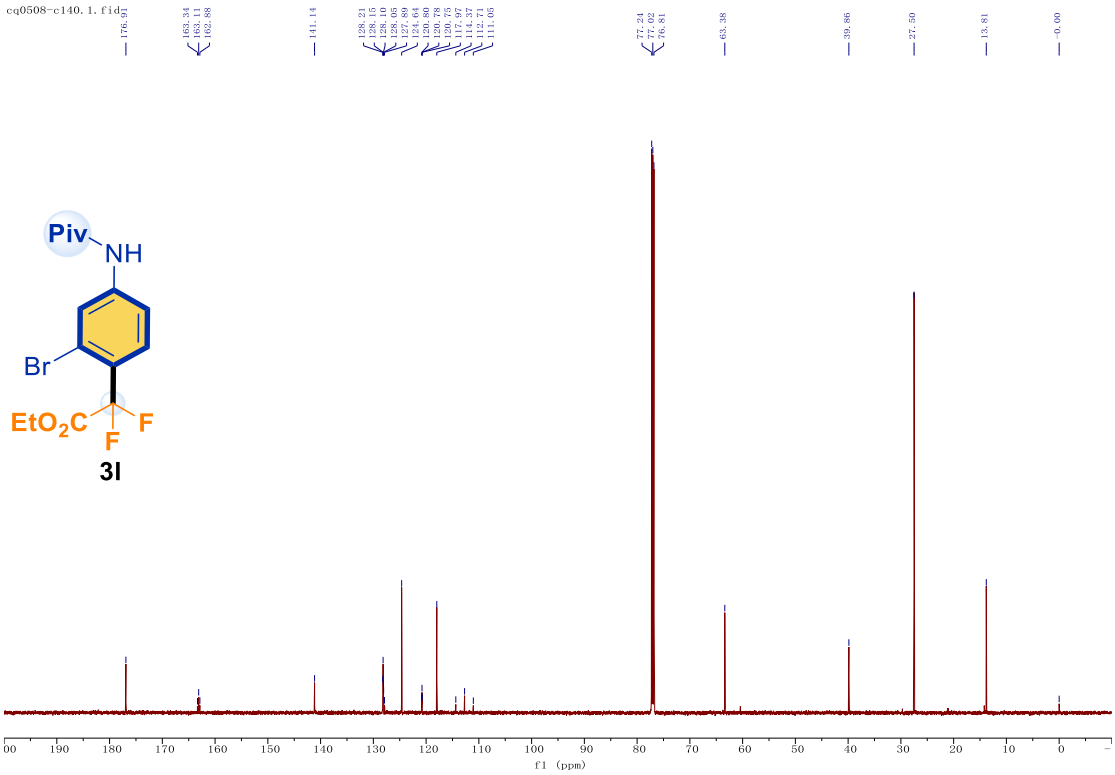
151 MHz ^{13}C NMR spectra of **3k** in $CDCl_3$.



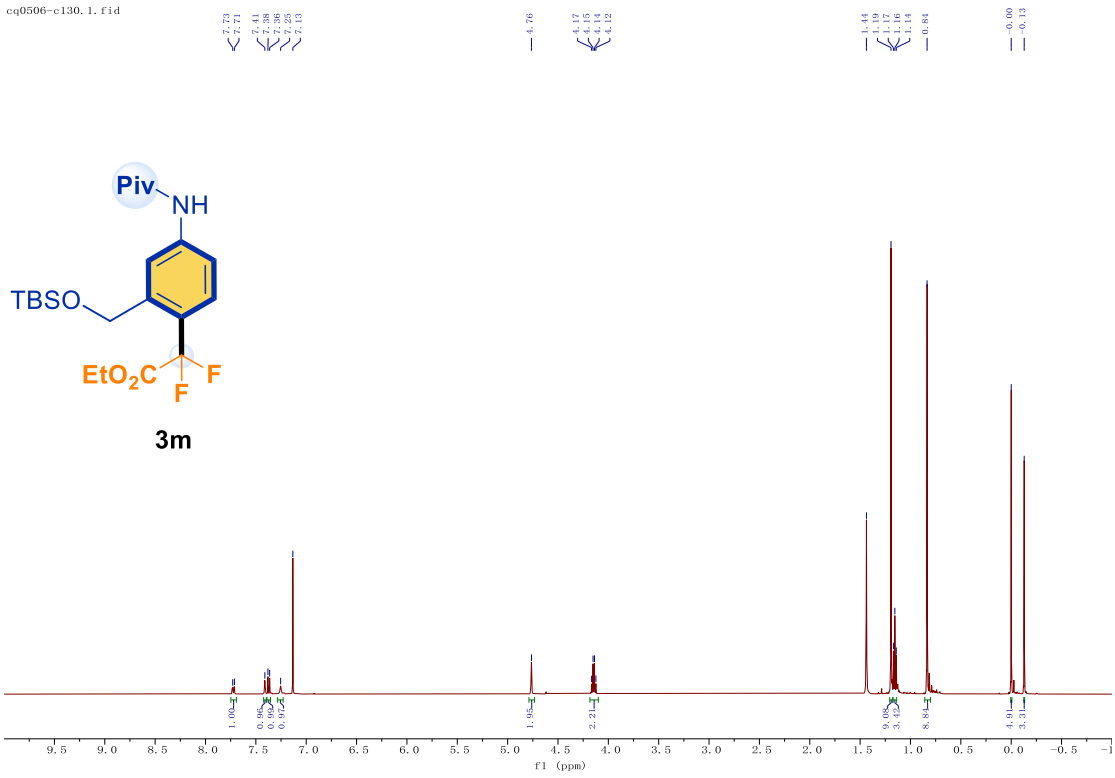
500 MHz ^{1}H NMR spectra of **3l** in $CDCl_3$.



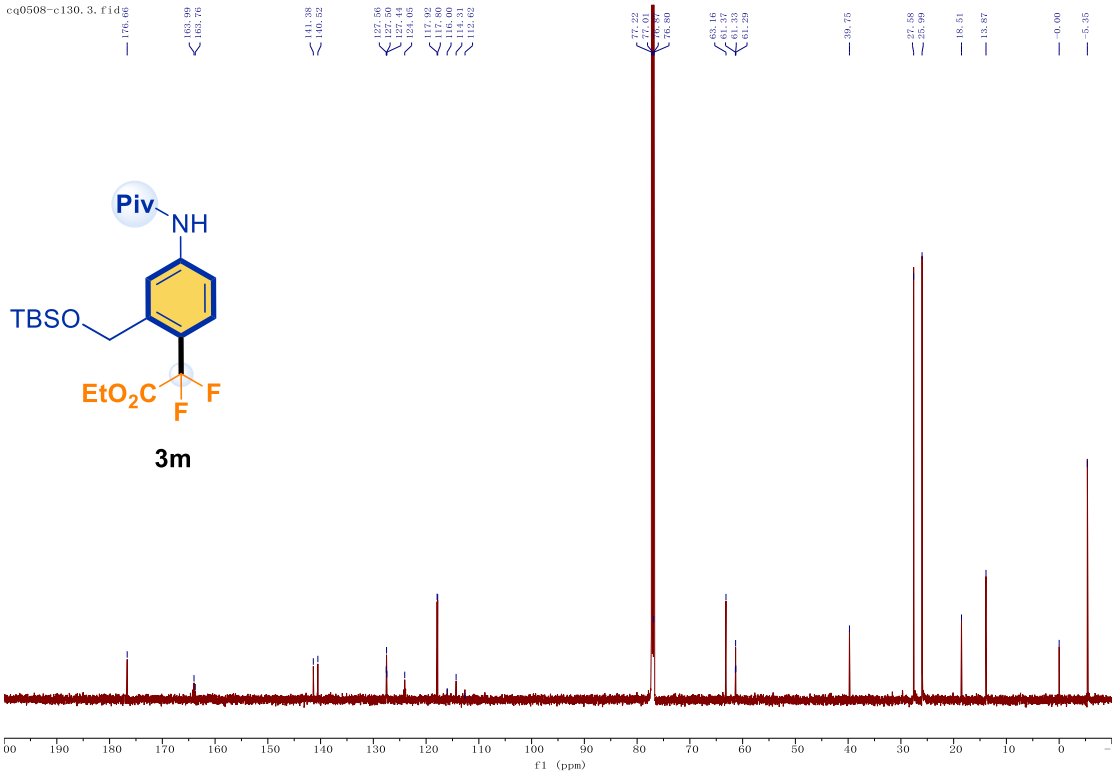
151 MHz ^{13}C NMR spectra of **3l** in $CDCl_3$.



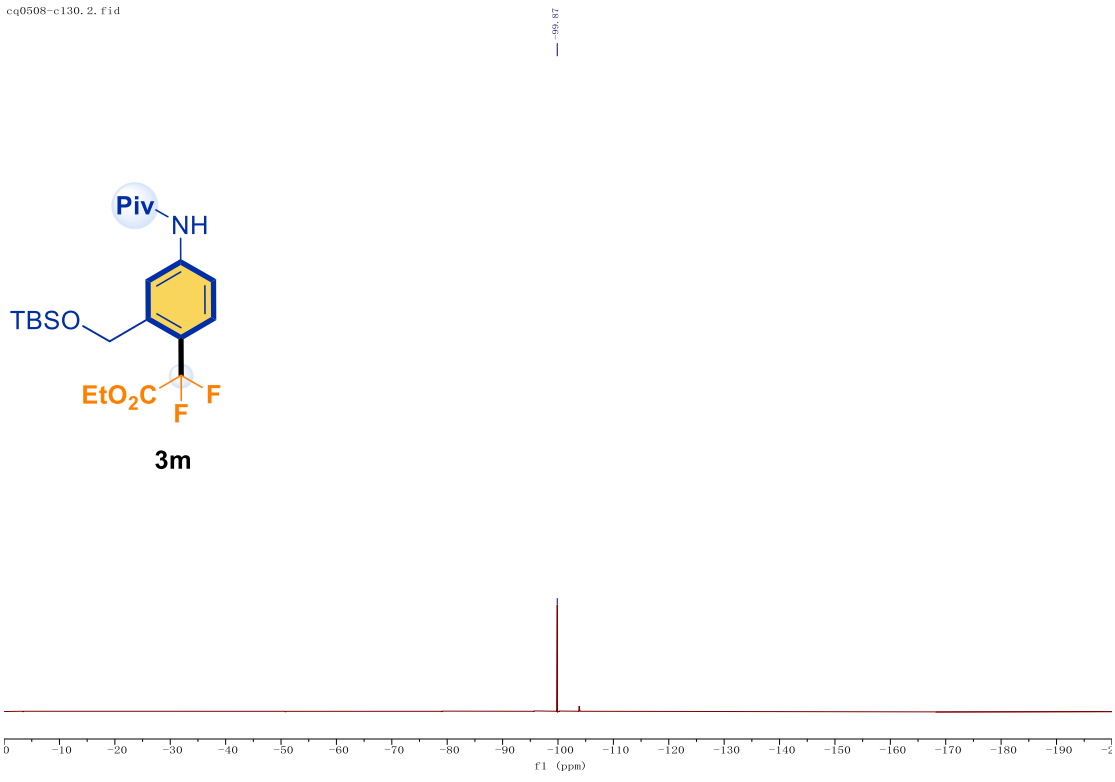
500 MHz ^{1}H NMR spectra of **3m** in $CDCl_3$.



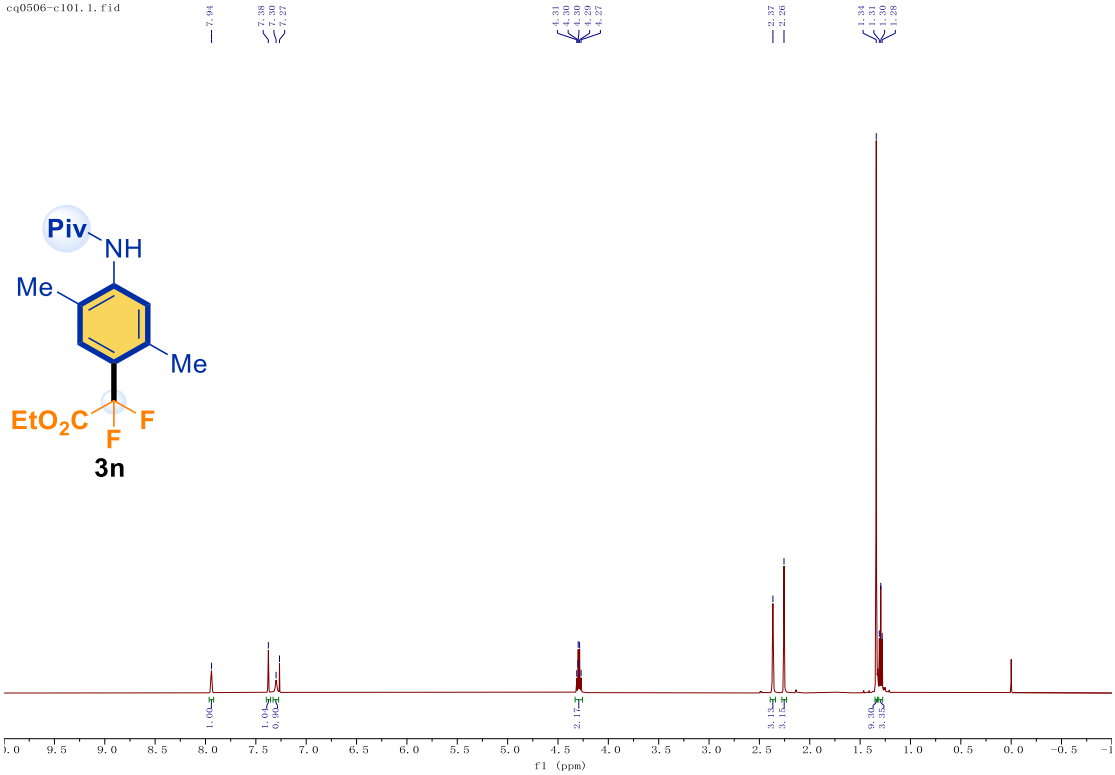
151 MHz ^{13}C NMR spectra of **3m** in $CDCl_3$.



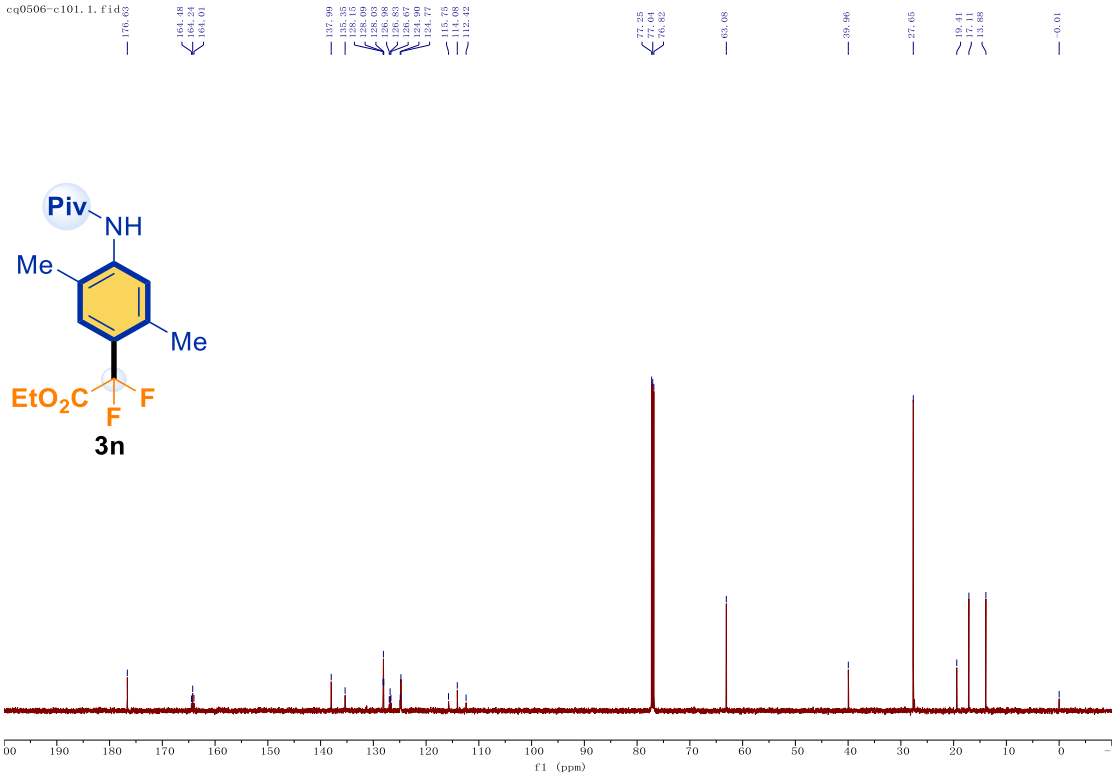
565 MHz ^{19}F NMR spectra of **3m** in $CDCl_3$.



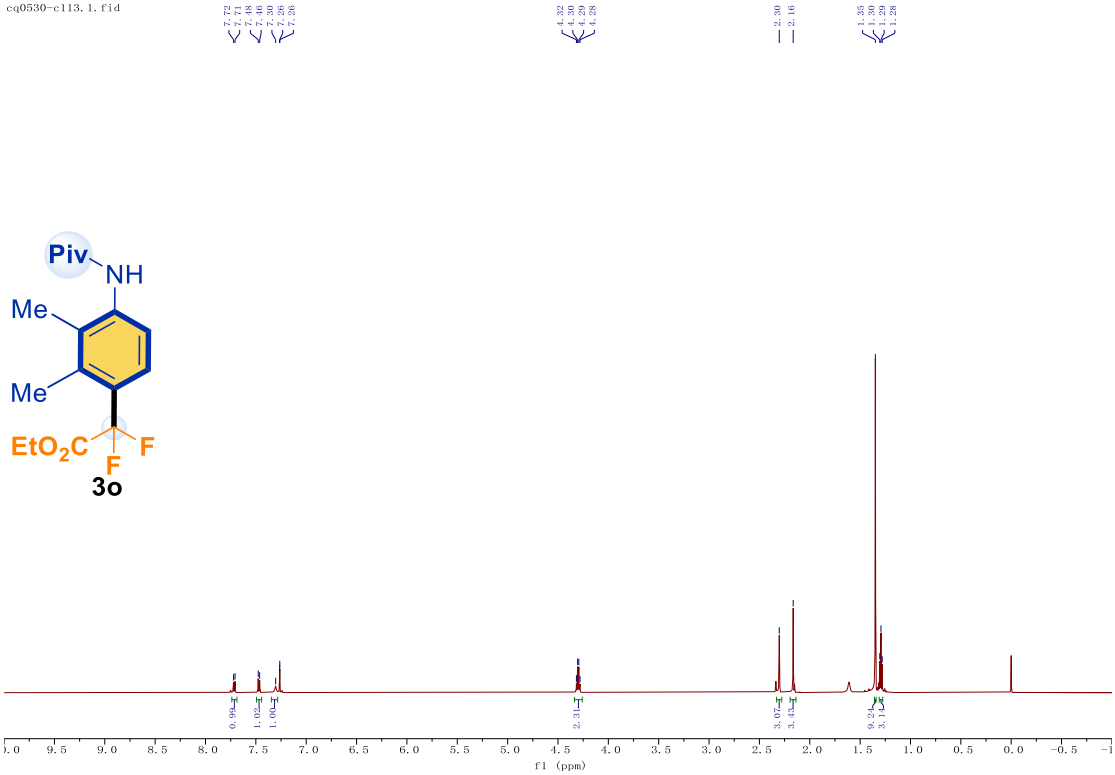
500 MHz ^{1}H NMR spectra of **3n** in $CDCl_3$.



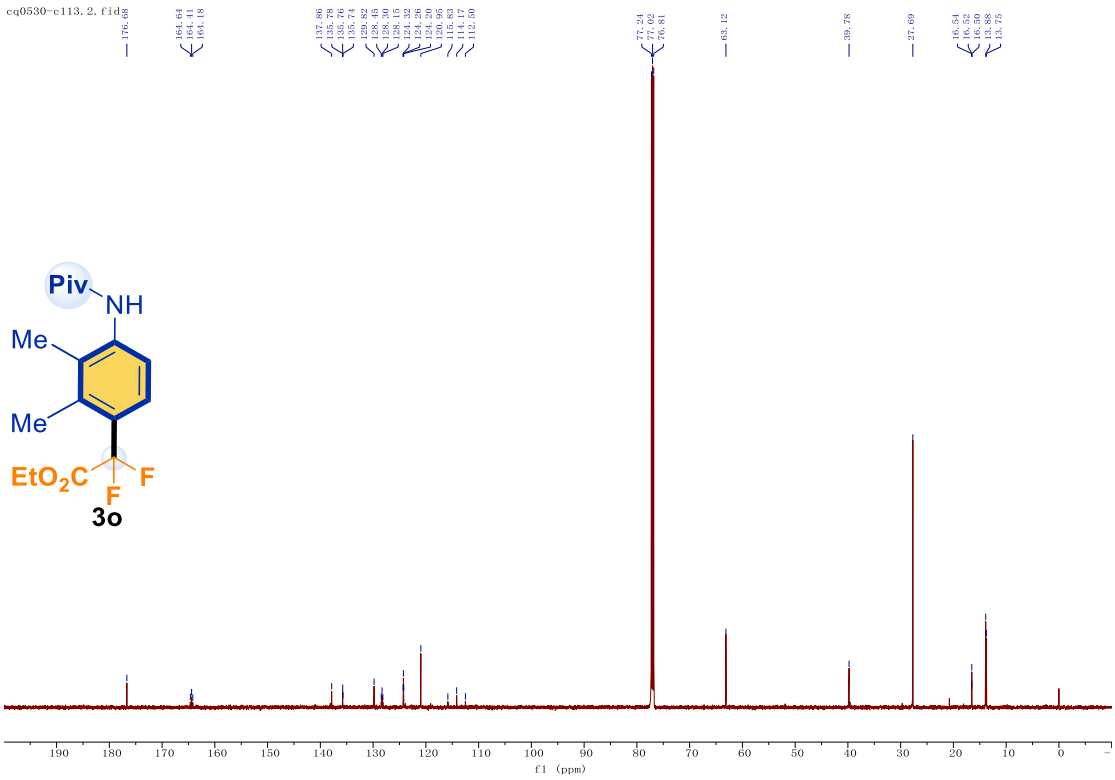
151 MHz ^{13}C NMR spectra of **3n** in $CDCl_3$.



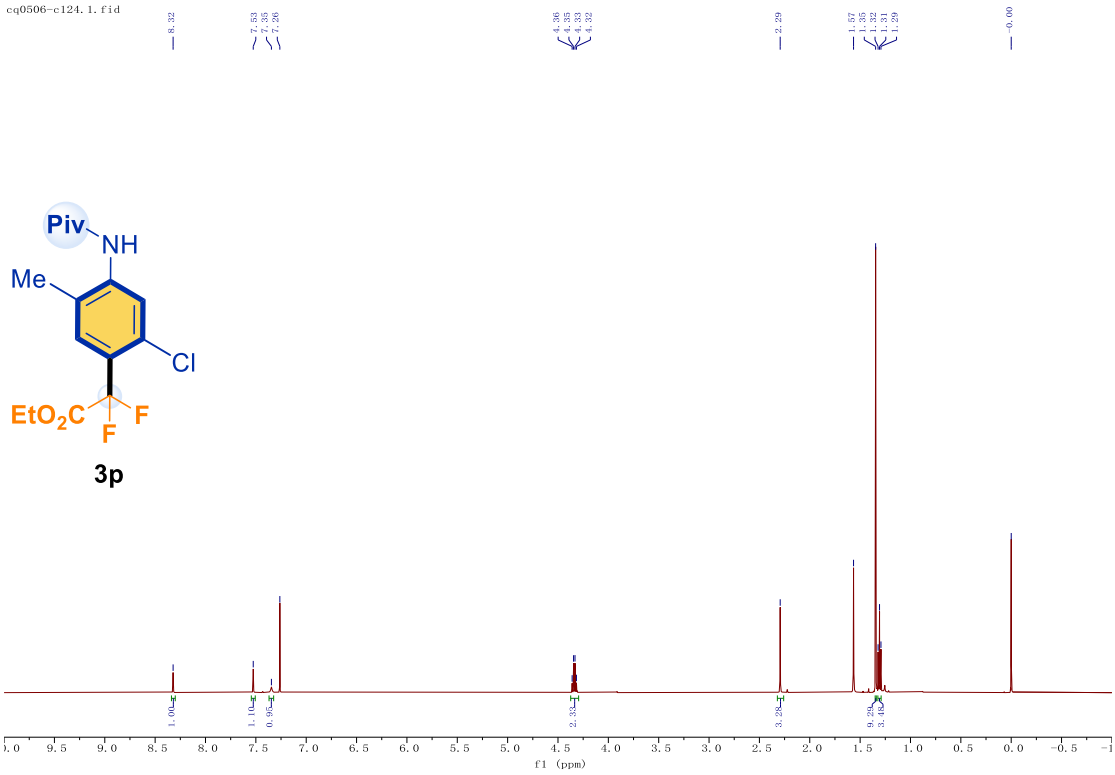
600 MHz ^{1}H NMR spectra of **3o** in $CDCl_3$.



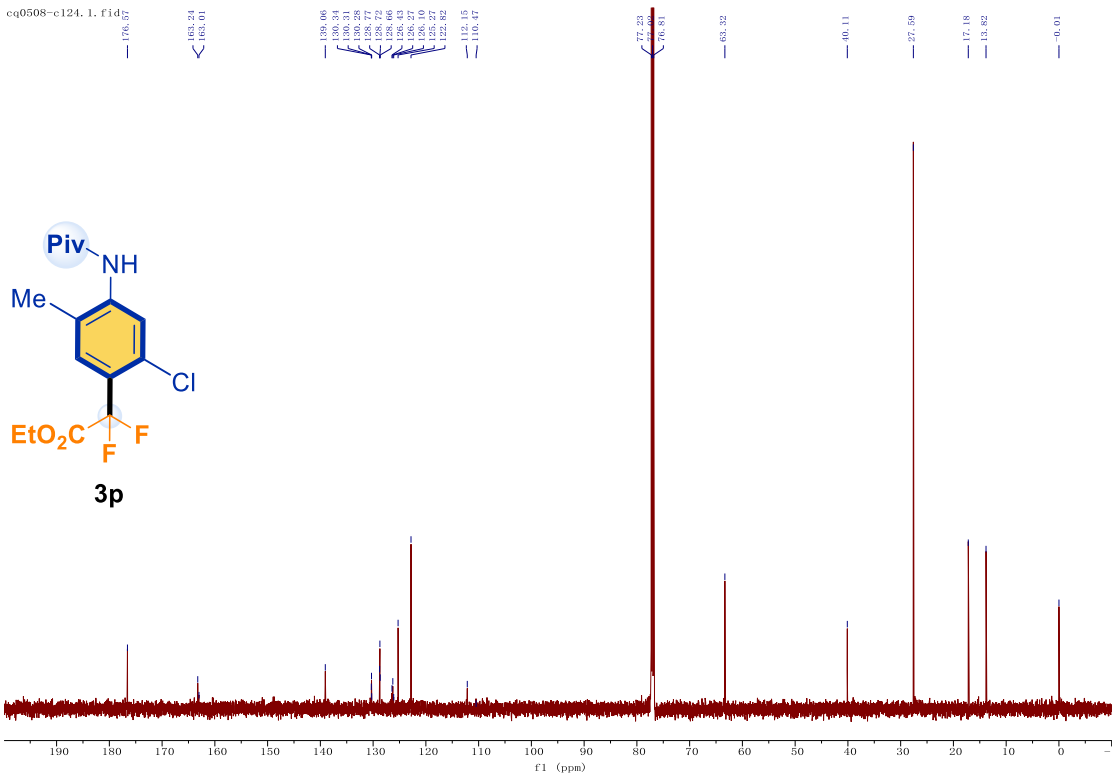
151 MHz ^{13}C NMR spectra of **3o** in $CDCl_3$.



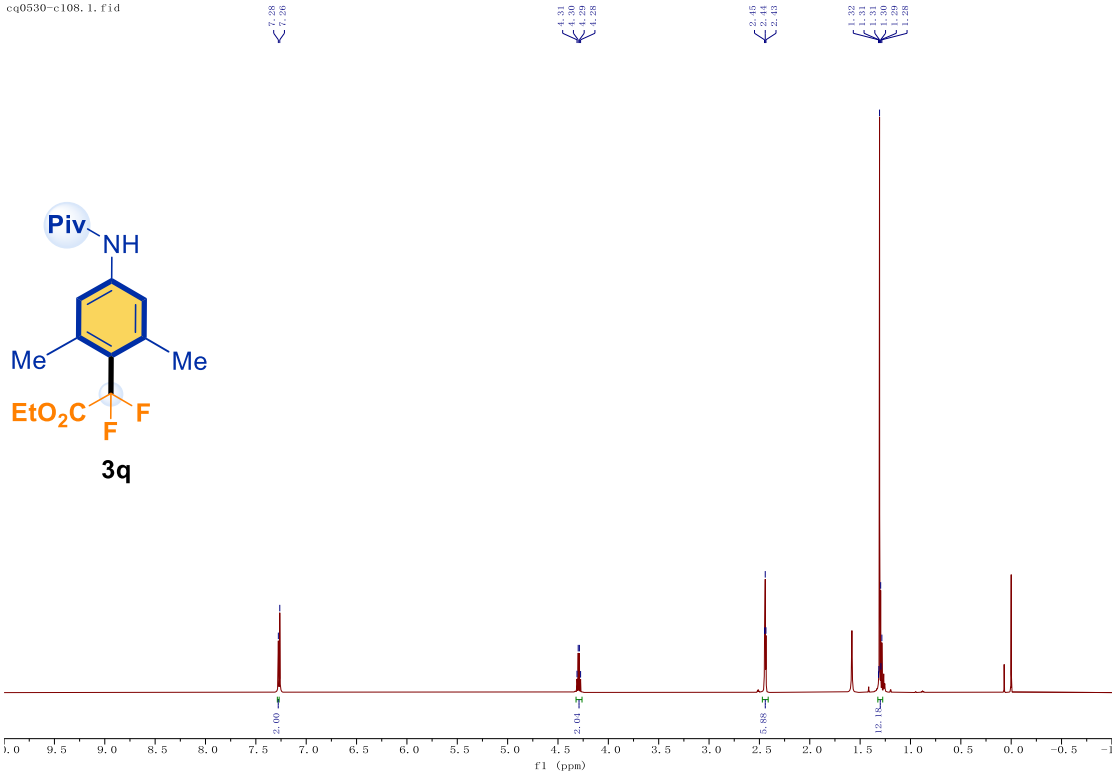
500 MHz ^{1}H NMR spectra of **3p** in $CDCl_3$.



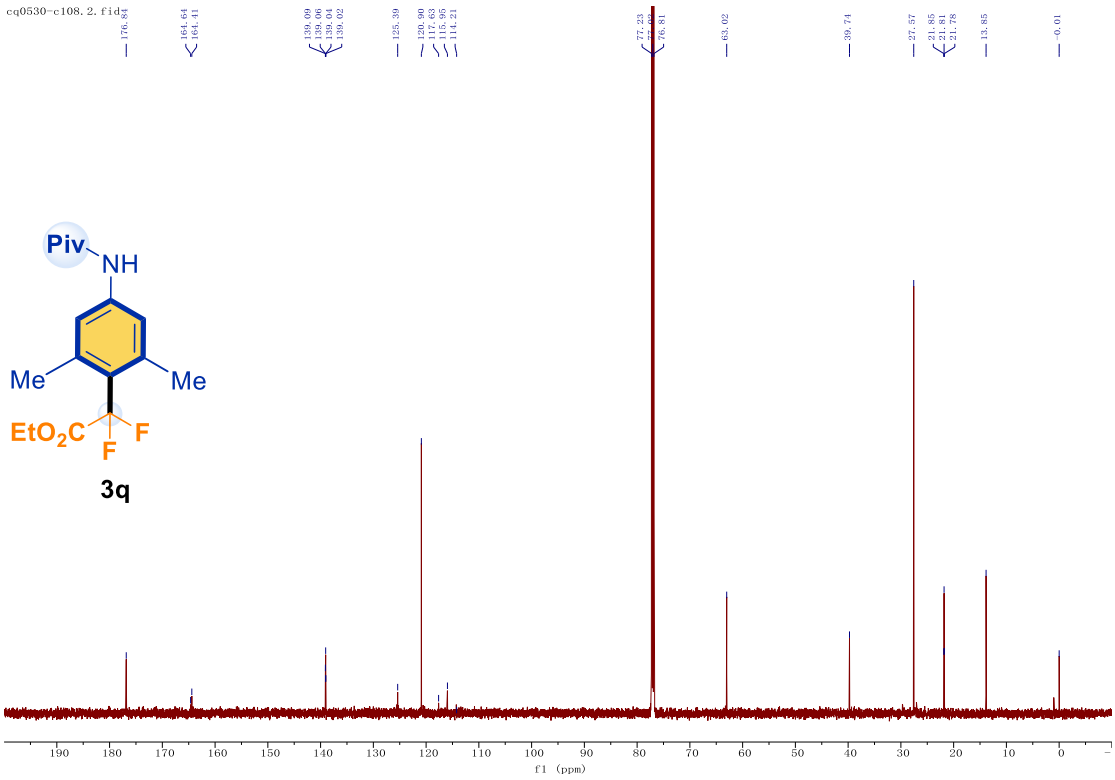
151 MHz ^{13}C NMR spectra of **3p** in $CDCl_3$.



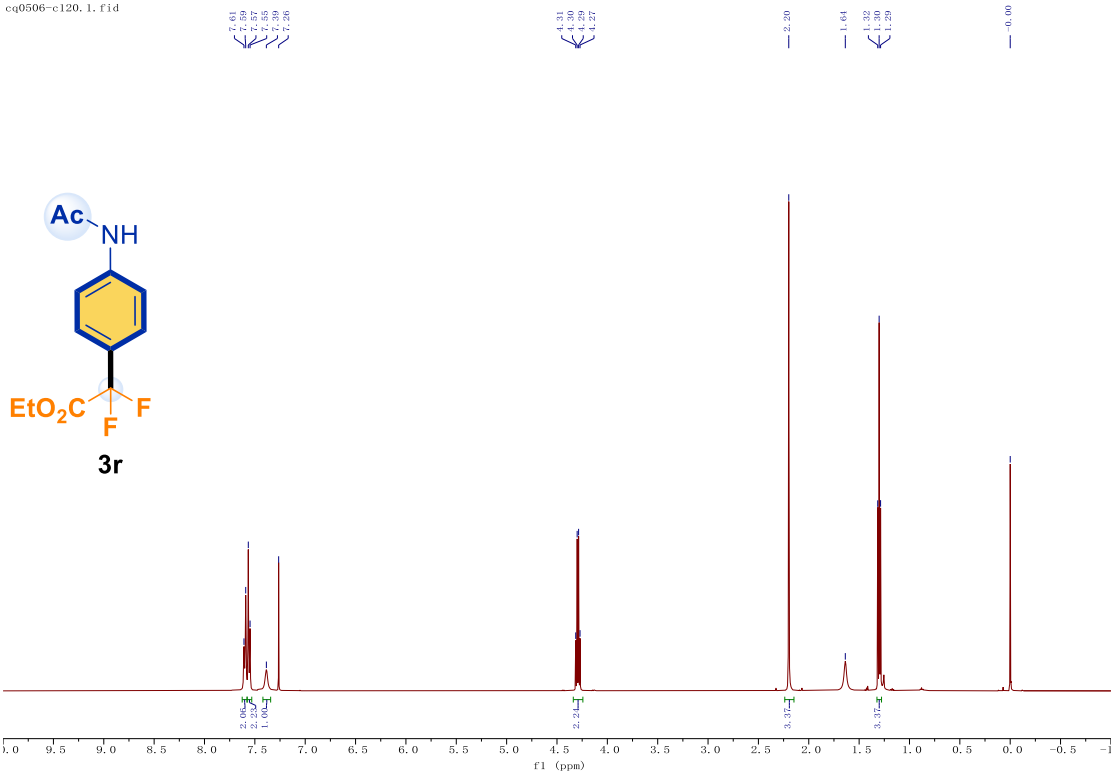
600 MHz ^{1}H NMR spectra of **3q** in $CDCl_3$.



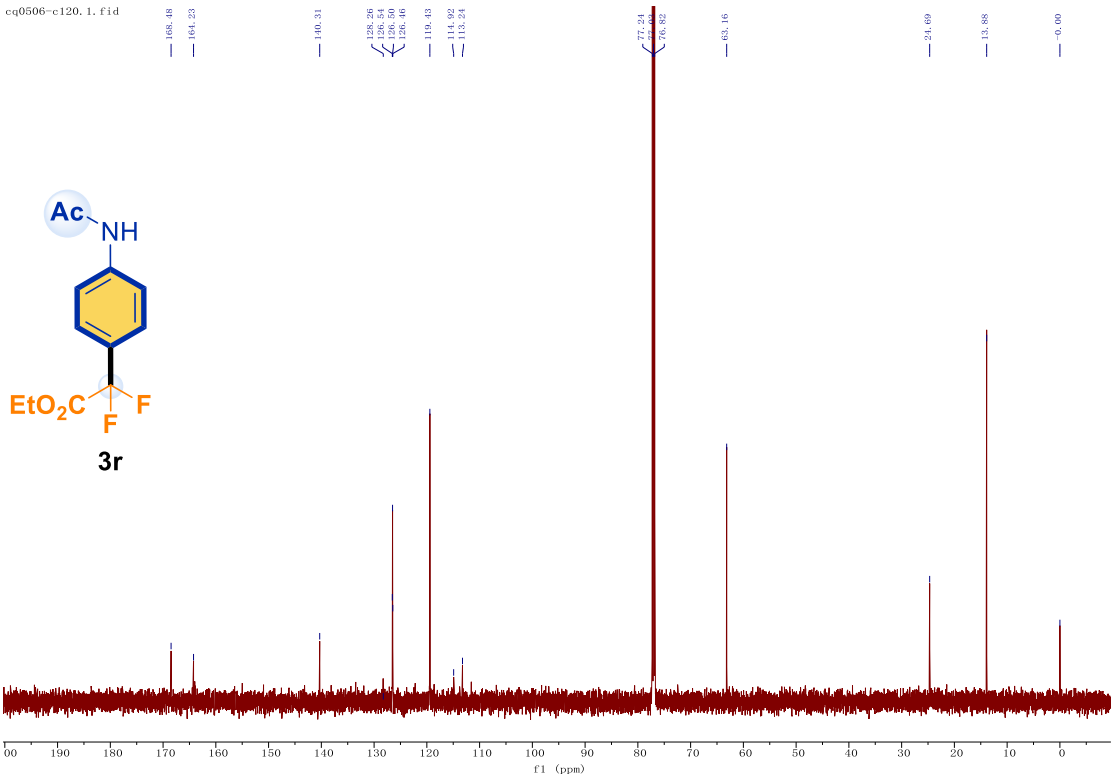
151 MHz ^{13}C NMR spectra of **3q** in $CDCl_3$.



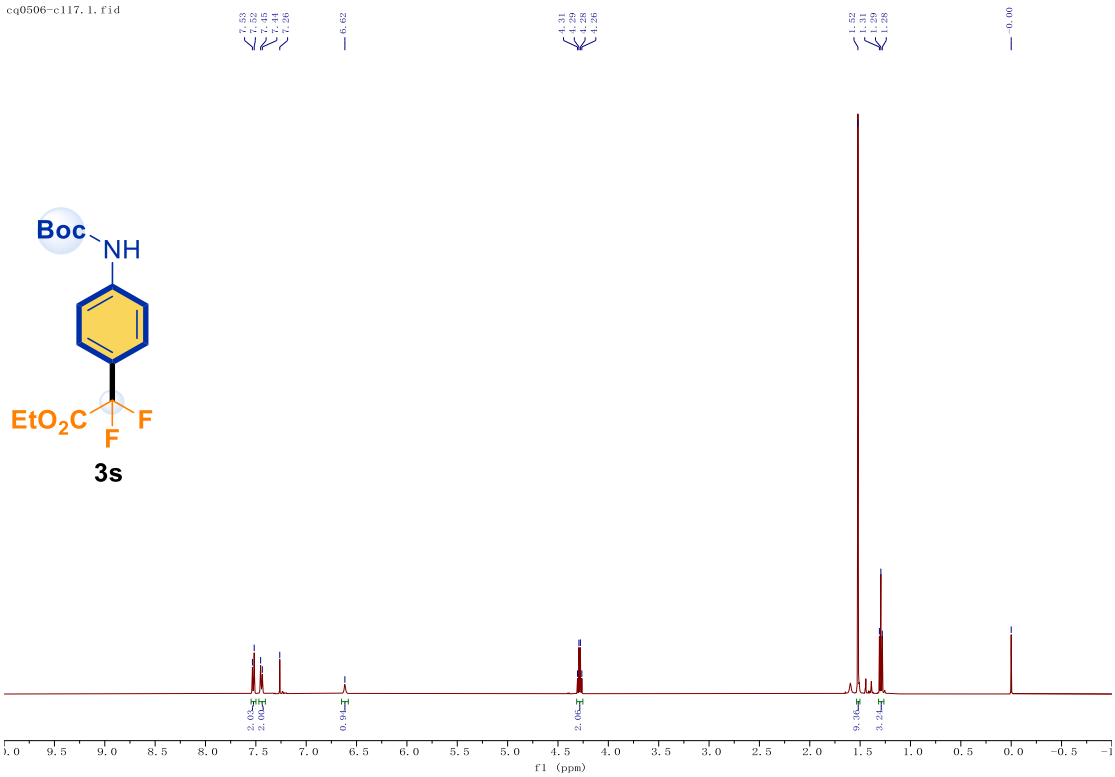
500 MHz ^{1}H NMR spectra of **3r** in $CDCl_3$.



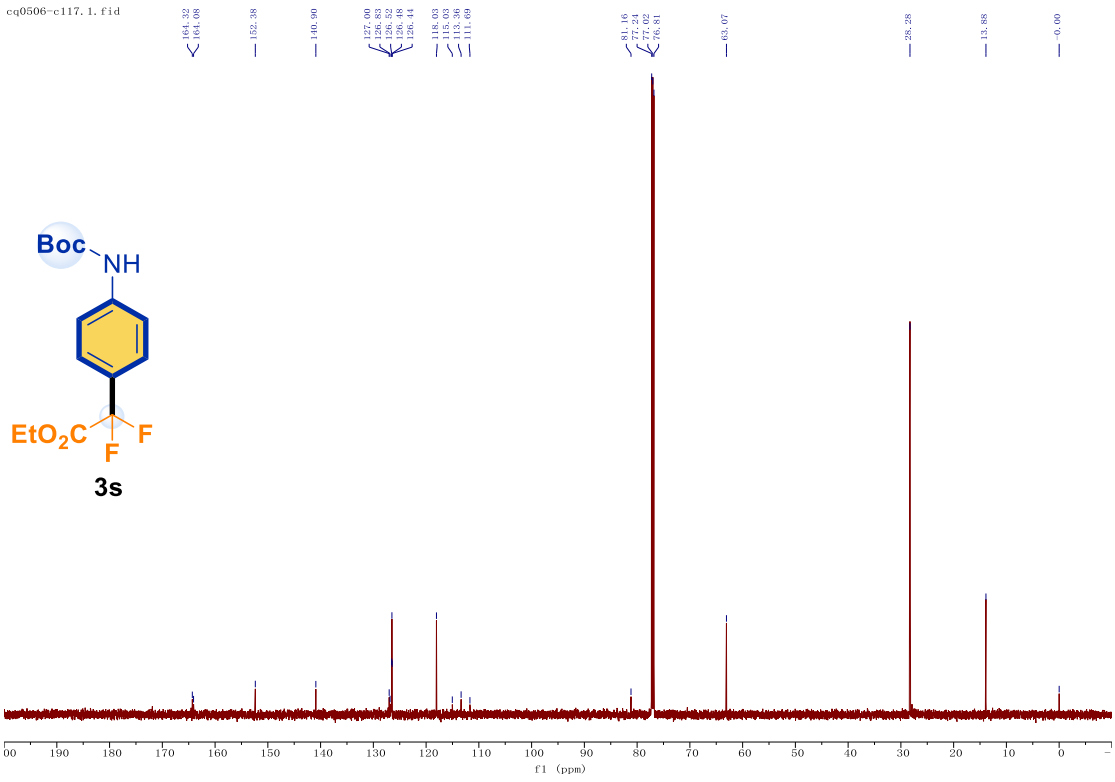
151 MHz ^{13}C NMR spectra of **3r** in $CDCl_3$.



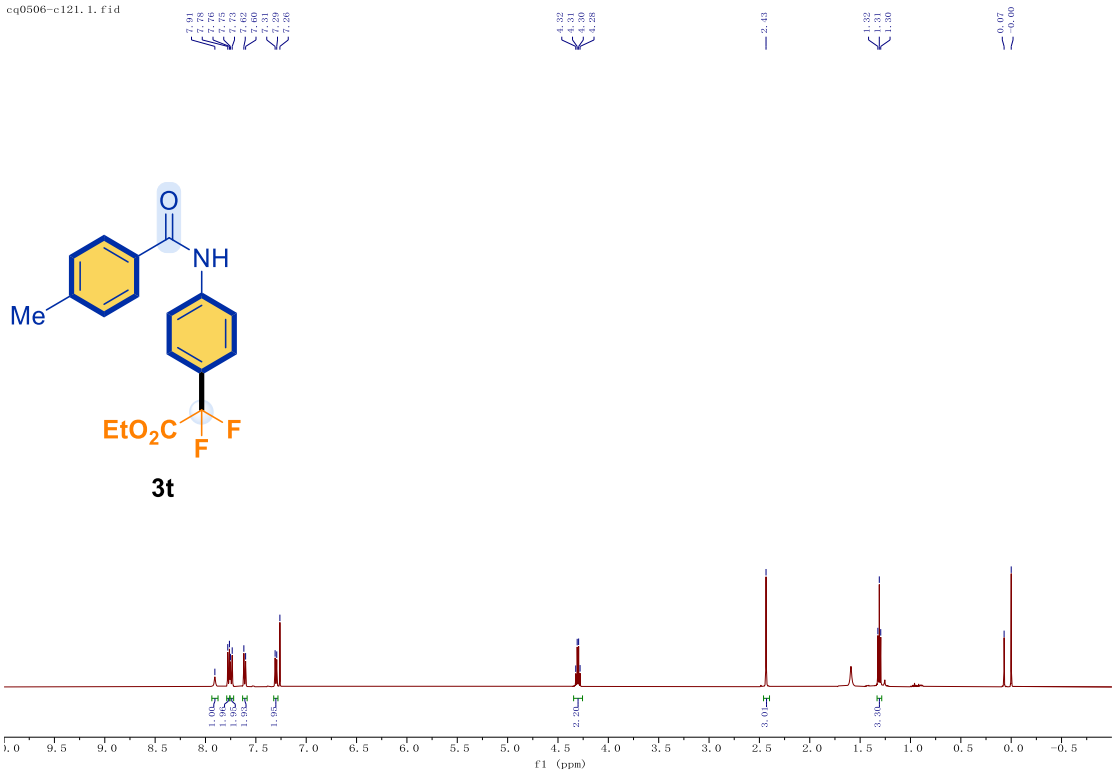
500 MHz ^{1}H NMR spectra of **3s** in $CDCl_3$.



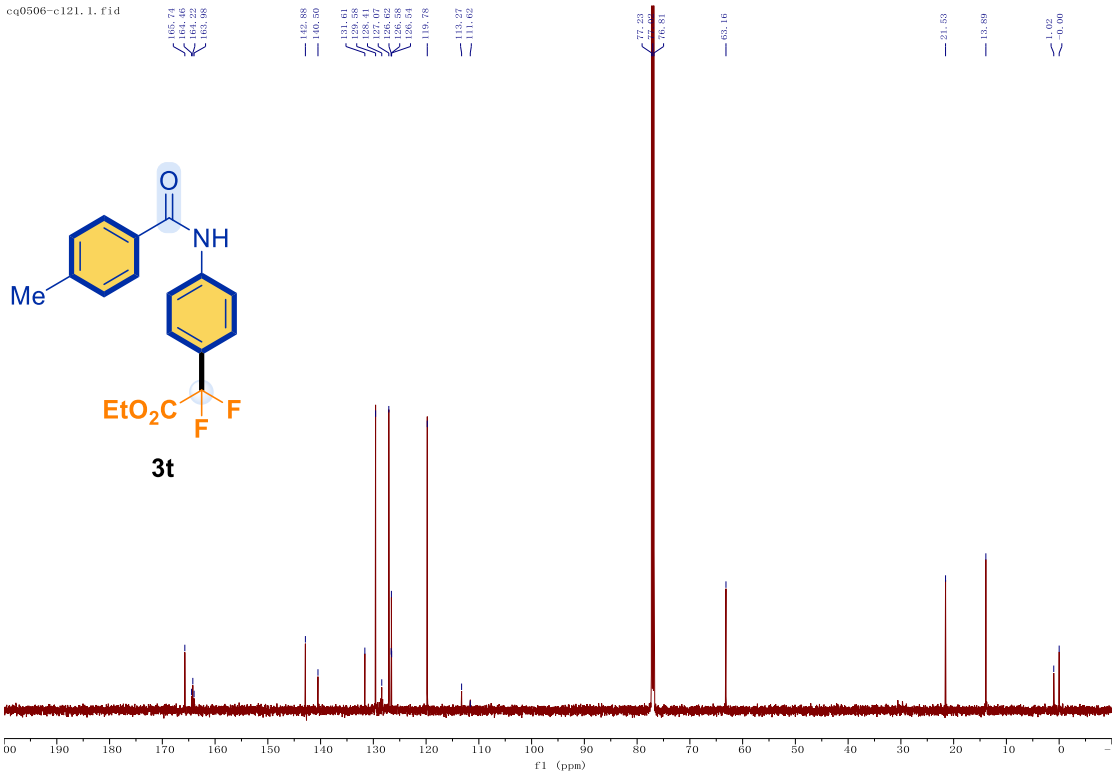
151 MHz ^{13}C NMR spectra of **3s** in $CDCl_3$.



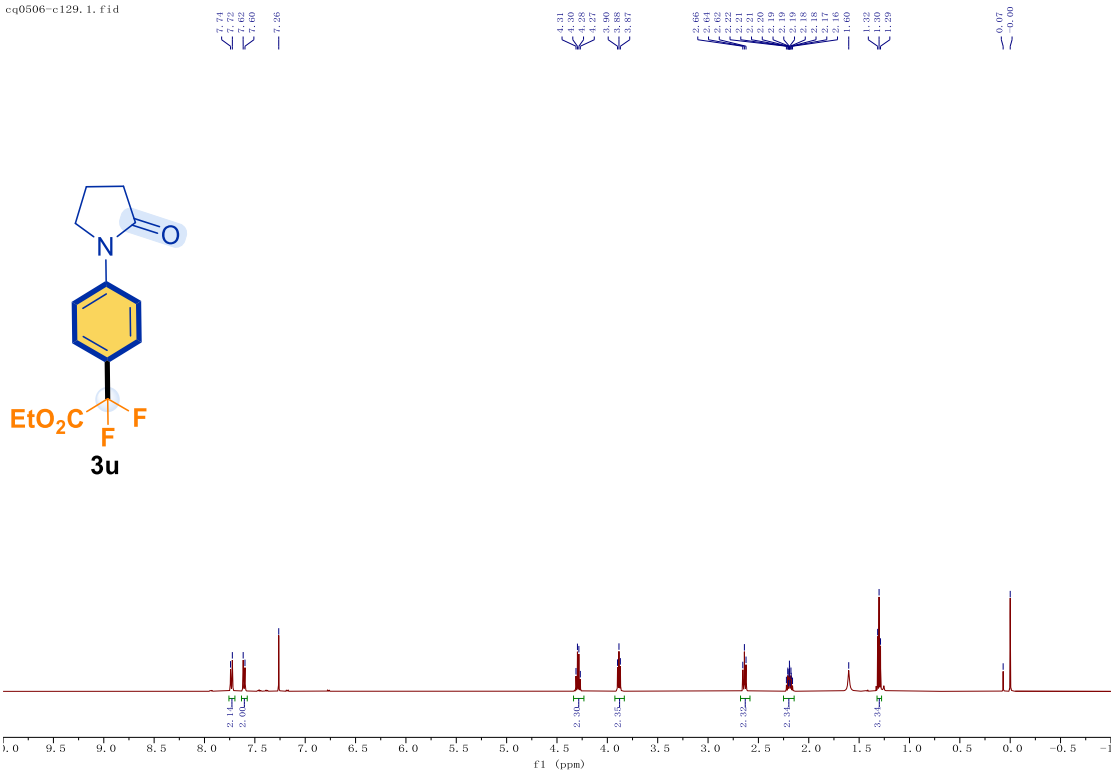
500 MHz ^{1}H NMR spectra of **3t** in $CDCl_3$.



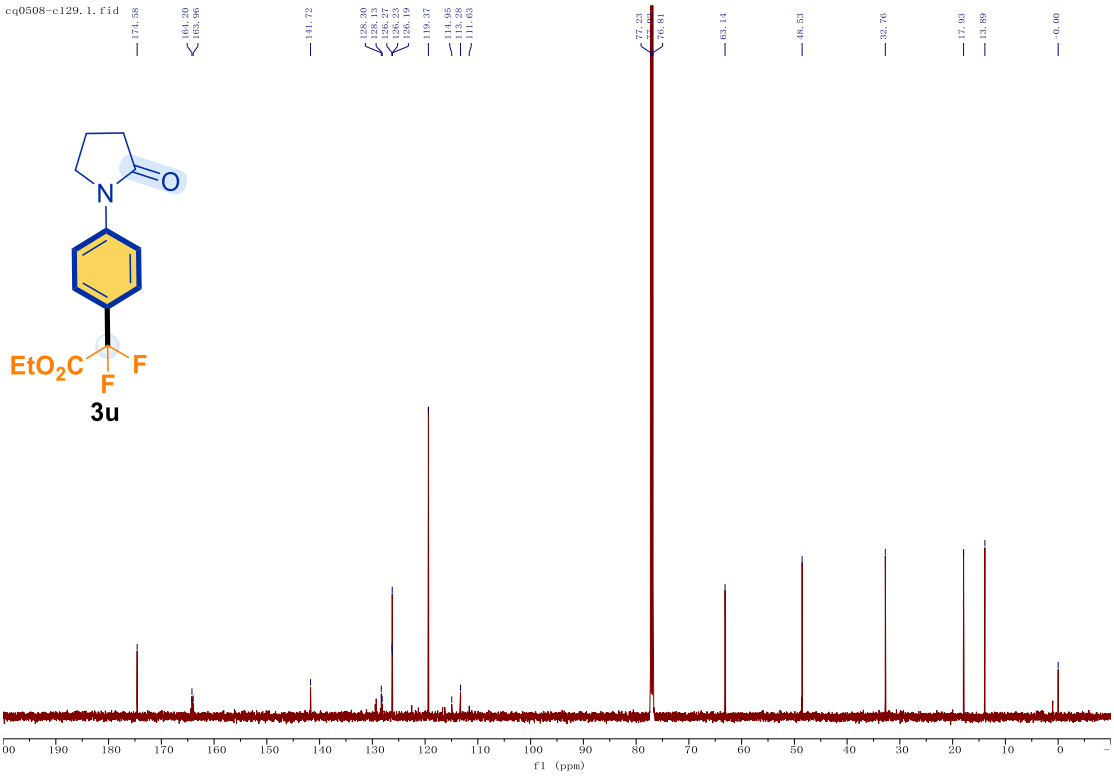
151 MHz ^{13}C NMR spectra of **3t** in $CDCl_3$.



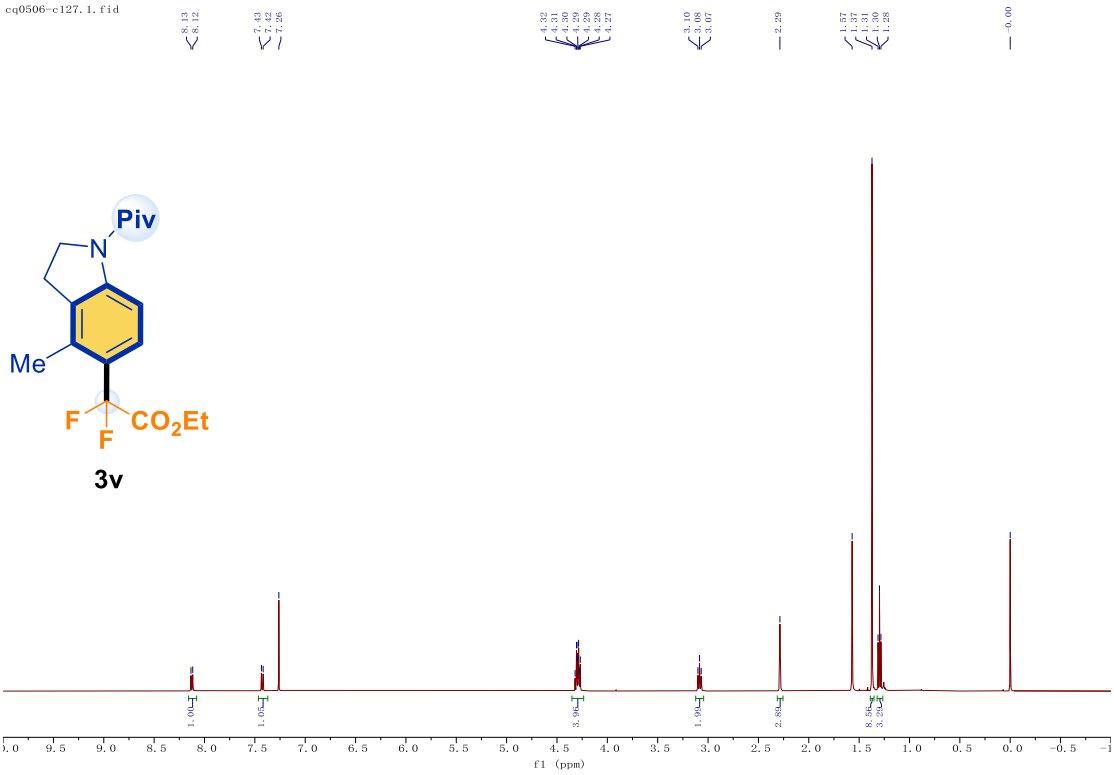
500 MHz ^{1}H NMR spectra of **3u** in $CDCl_3$.



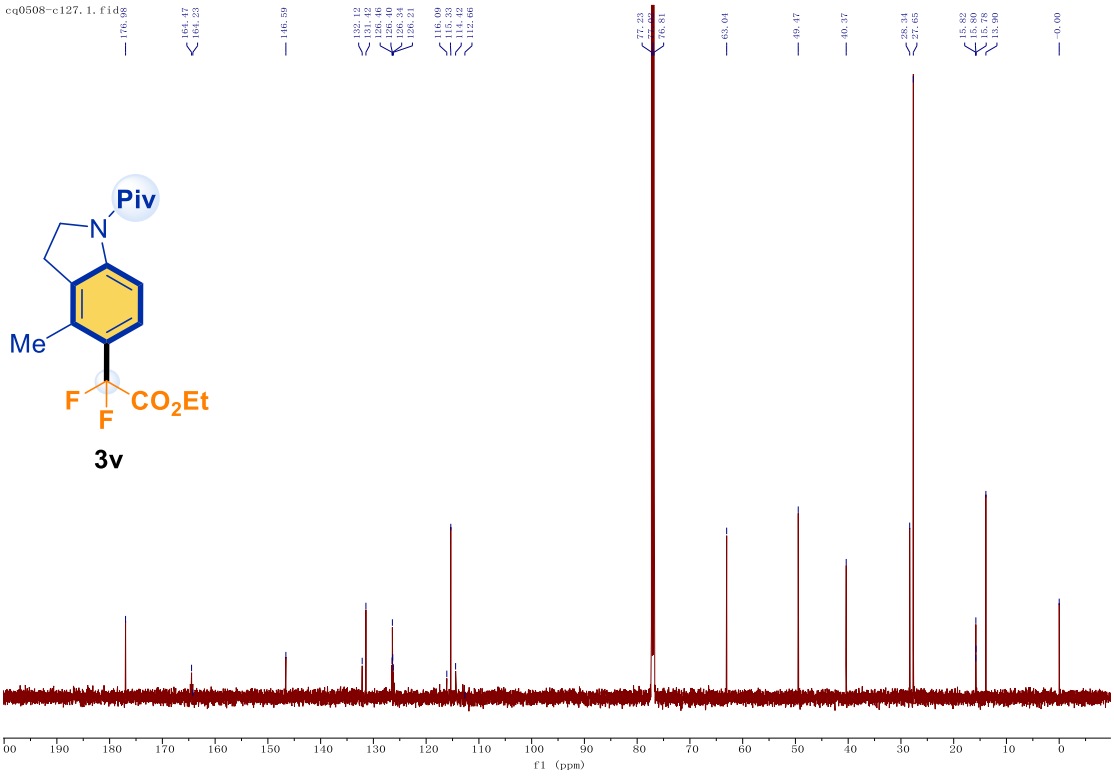
151 MHz ^{13}C NMR spectra of **3u** in $CDCl_3$.



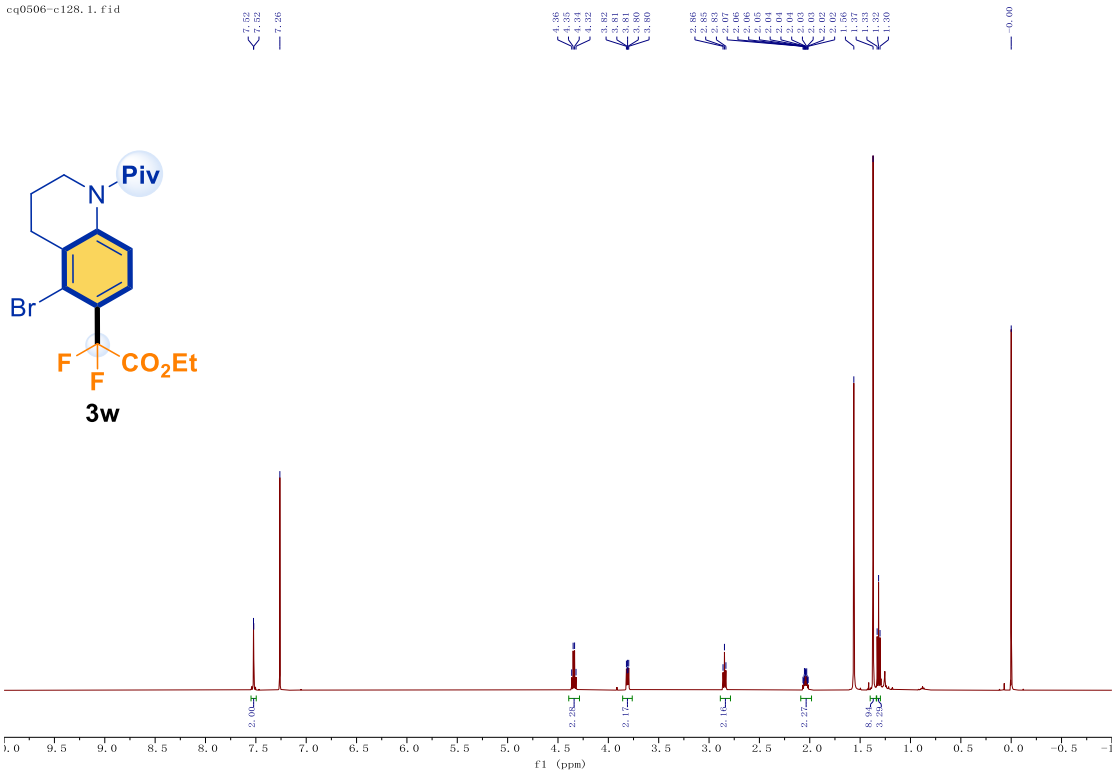
500 MHz ^{1}H NMR spectra of **3v** in $CDCl_3$.



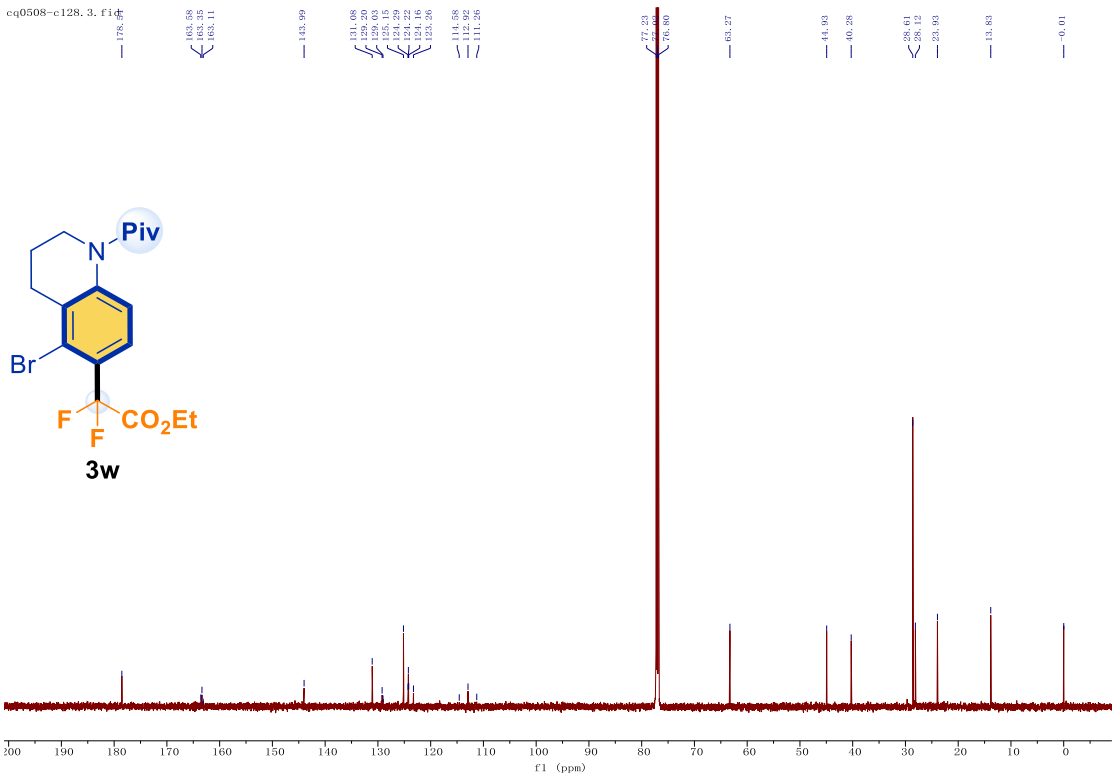
151 MHz ^{13}C NMR spectra of **3v** in $CDCl_3$.



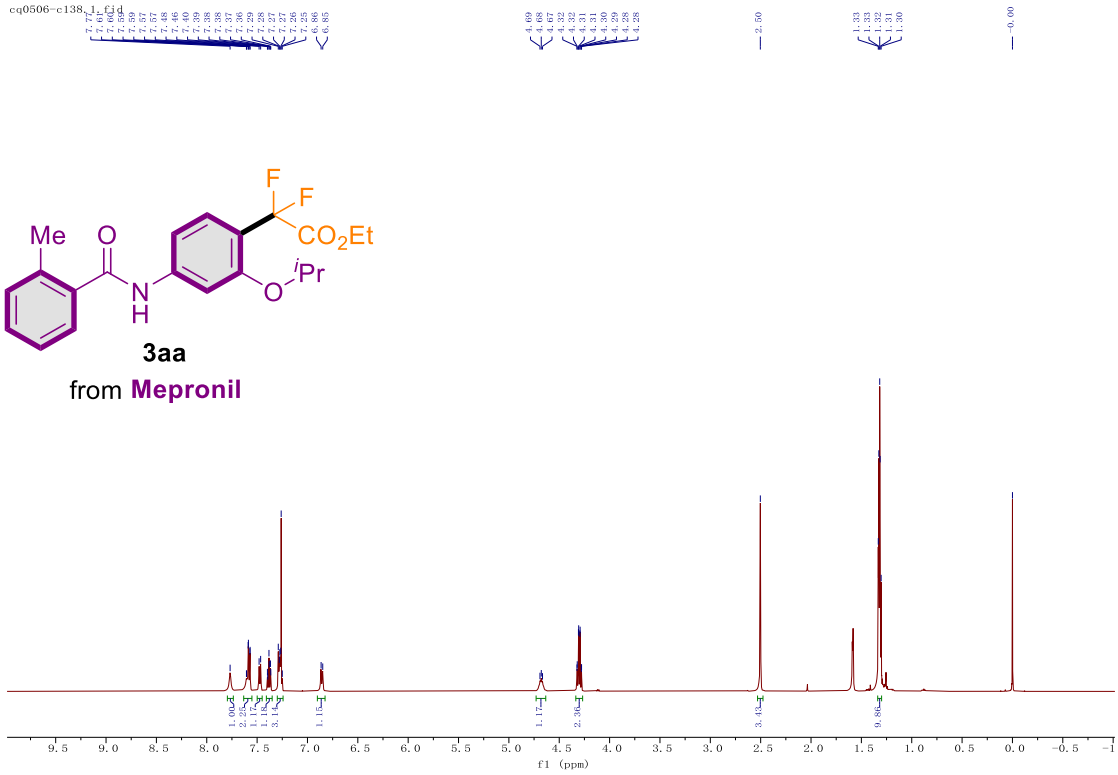
500 MHz ^{1}H NMR spectra of **3w** in $CDCl_3$.



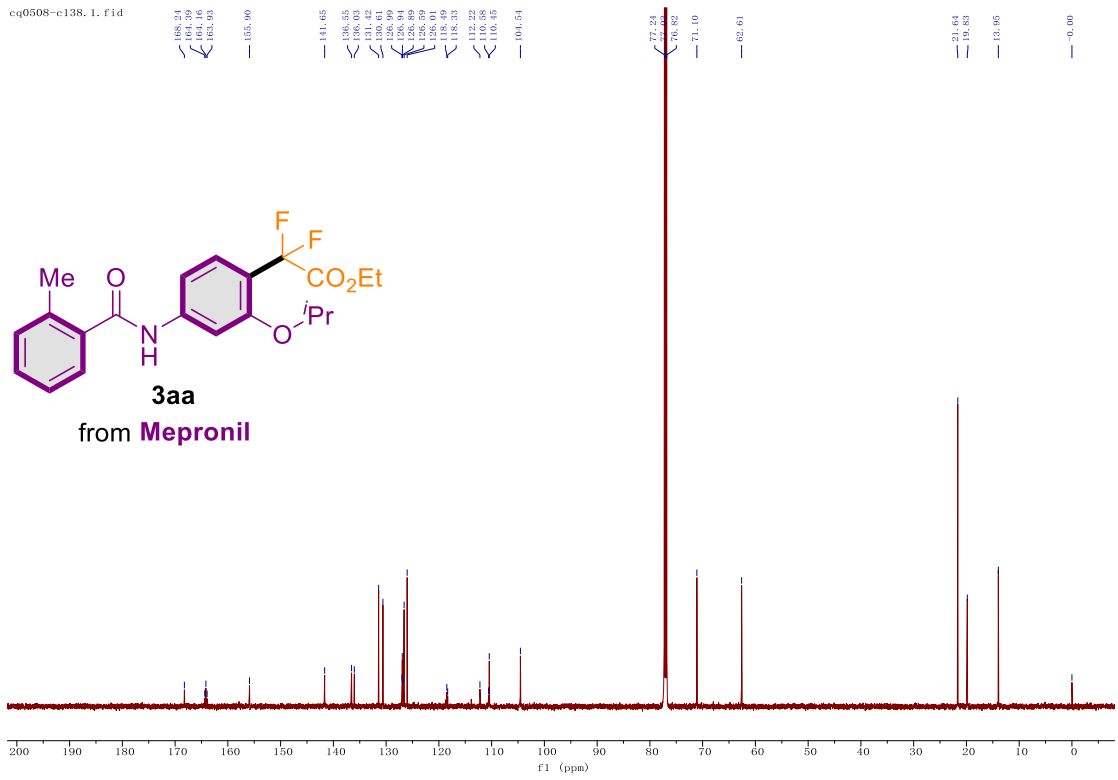
151 MHz ^{13}C NMR spectra of **3w** in $CDCl_3$.



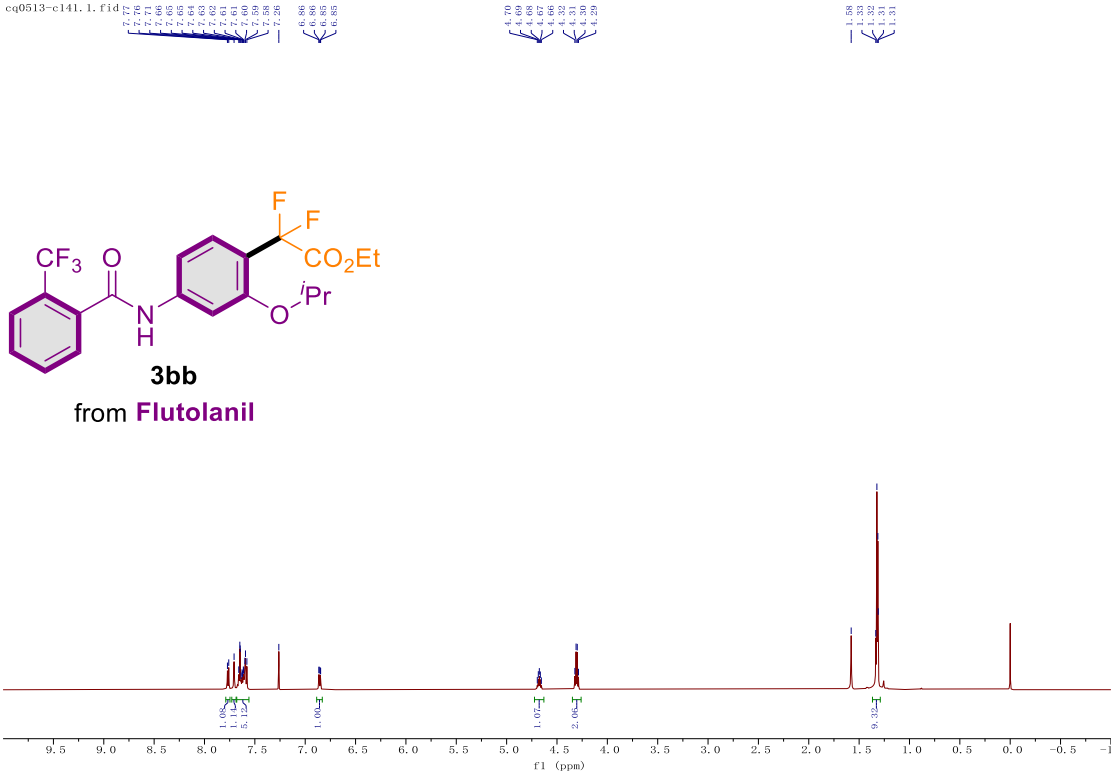
500 MHz ^{1}H NMR spectra of **3aa** in $CDCl_3$.



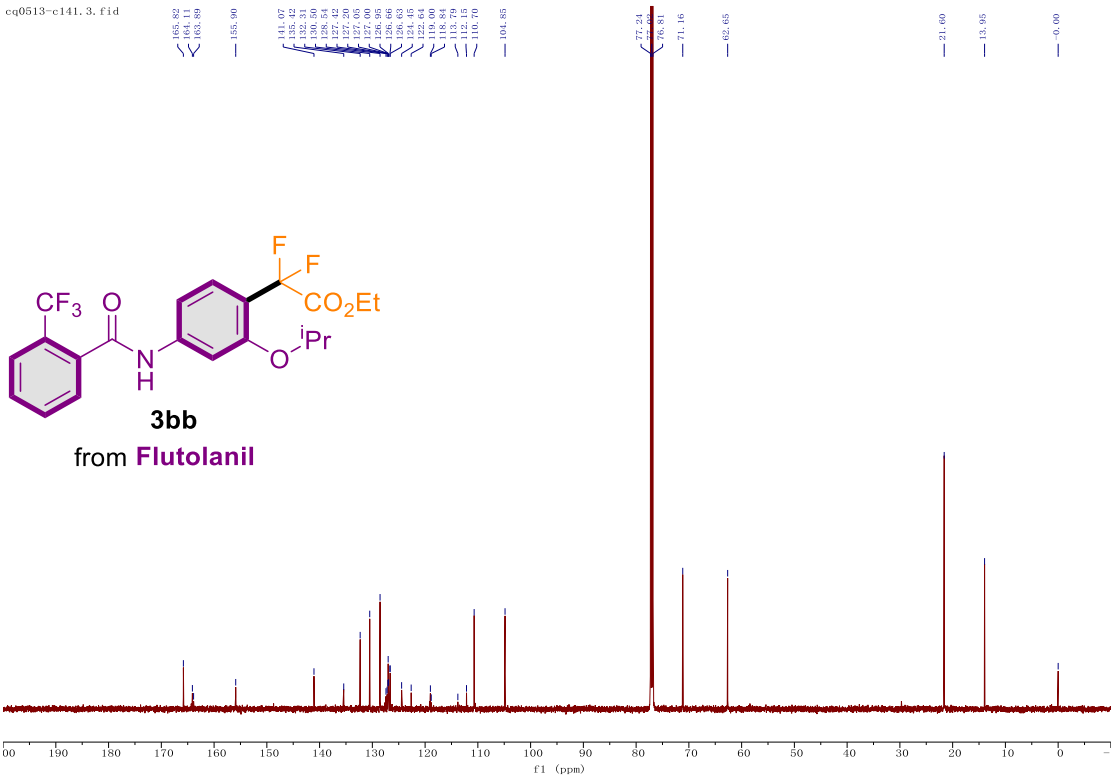
151 MHz ^{13}C NMR spectra of **3aa** in $CDCl_3$.



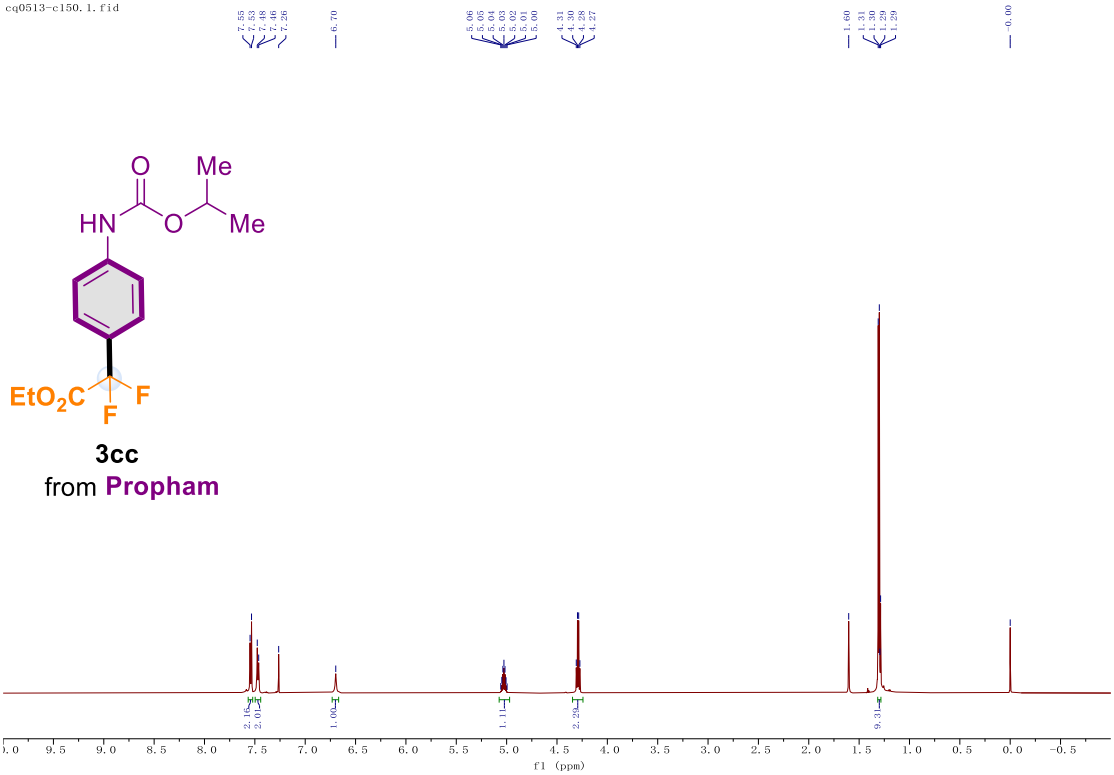
600 MHz ^{1}H NMR spectra of **3bb** in $CDCl_3$.



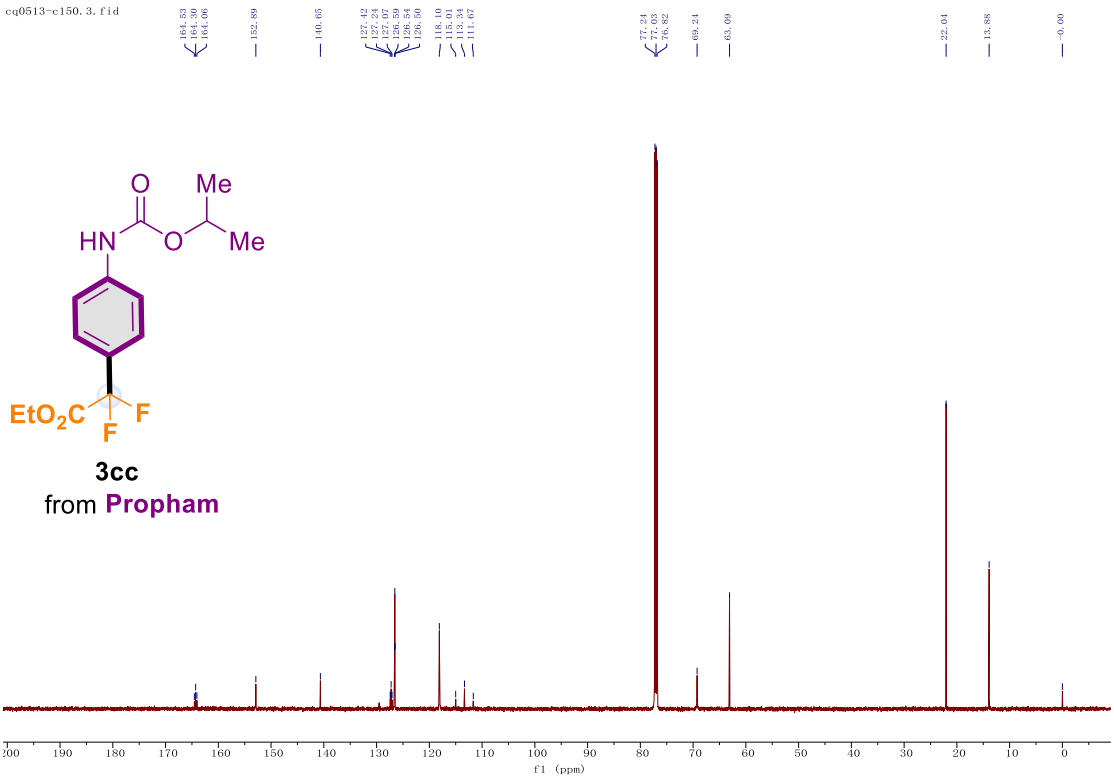
151 MHz ^{13}C NMR spectra of **3bb** in $CDCl_3$.



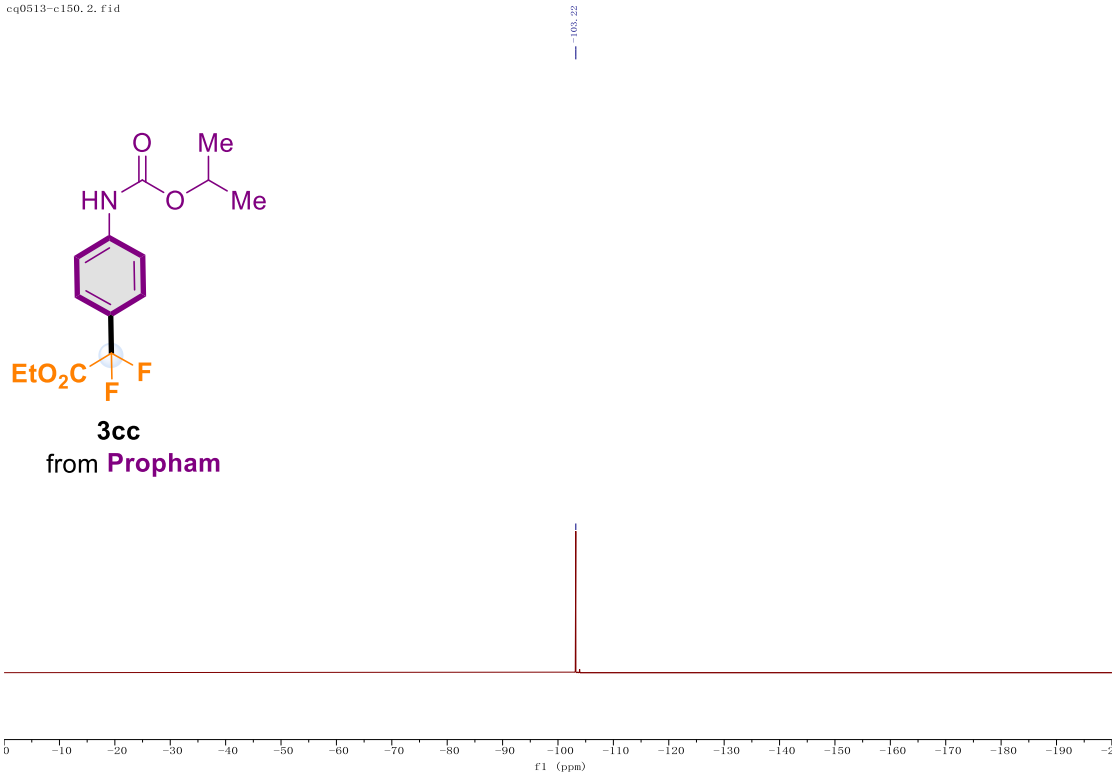
600 MHz ^{1}H NMR spectra of **3cc** in $CDCl_3$.



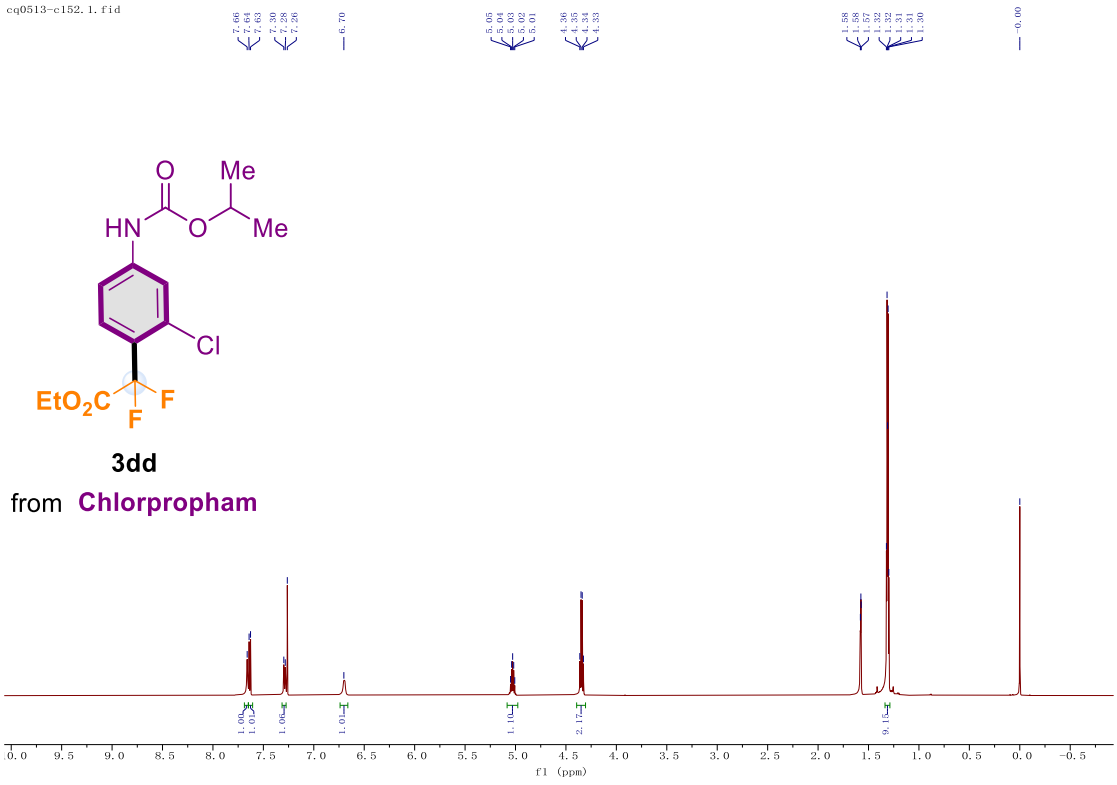
151 MHz ^{13}C NMR spectra of **3cc** in $CDCl_3$.



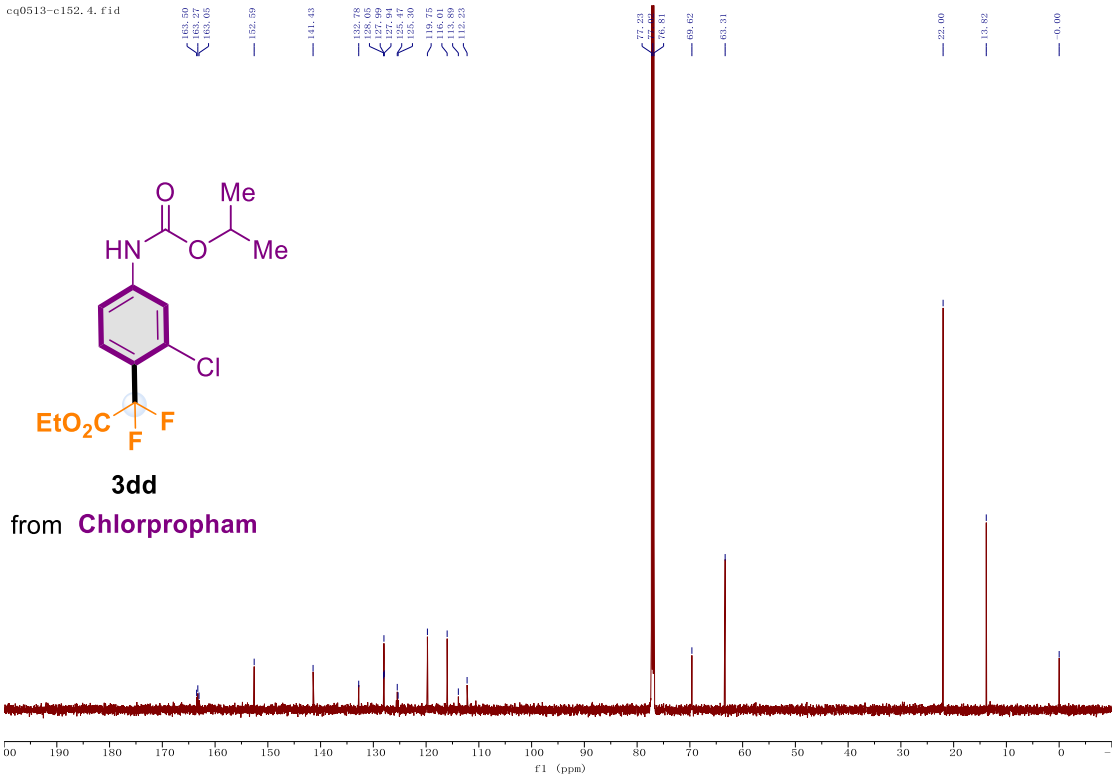
565 MHz ^{19}F NMR spectra of **3cc** in $CDCl_3$.



600 MHz ^{1}H NMR spectra of **3dd** in $CDCl_3$.

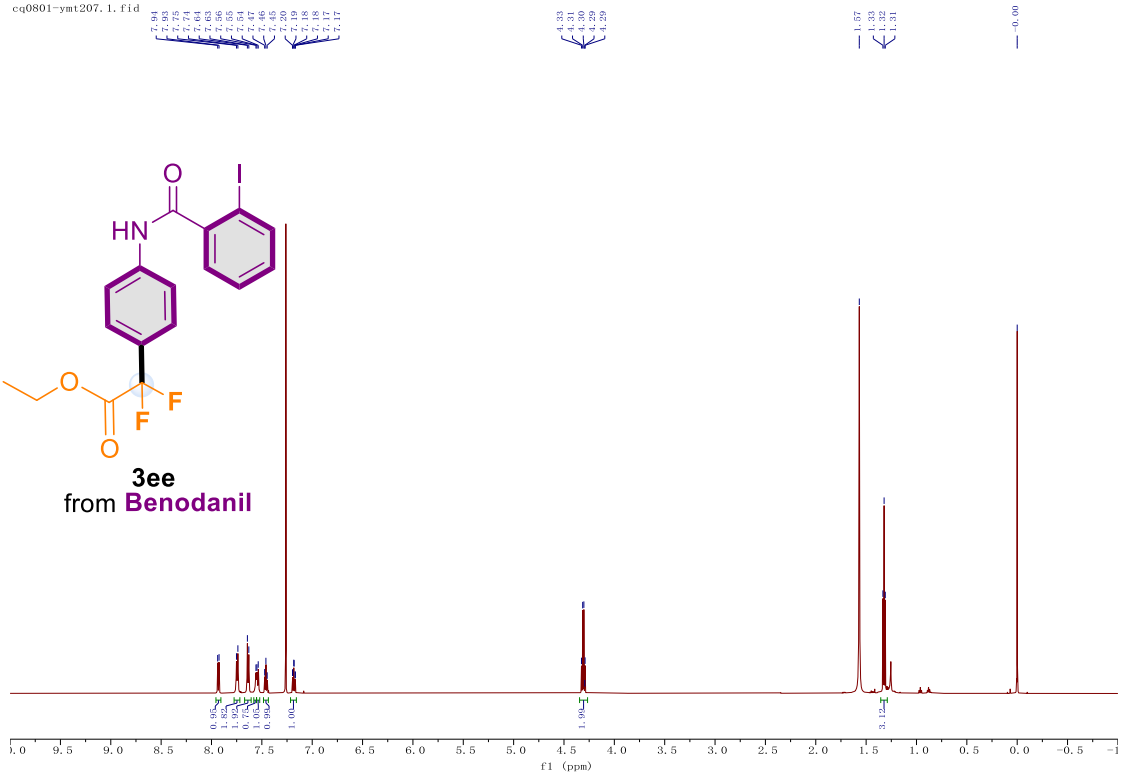


151 MHz ^{13}C NMR spectra of **3dd** in $CDCl_3$.

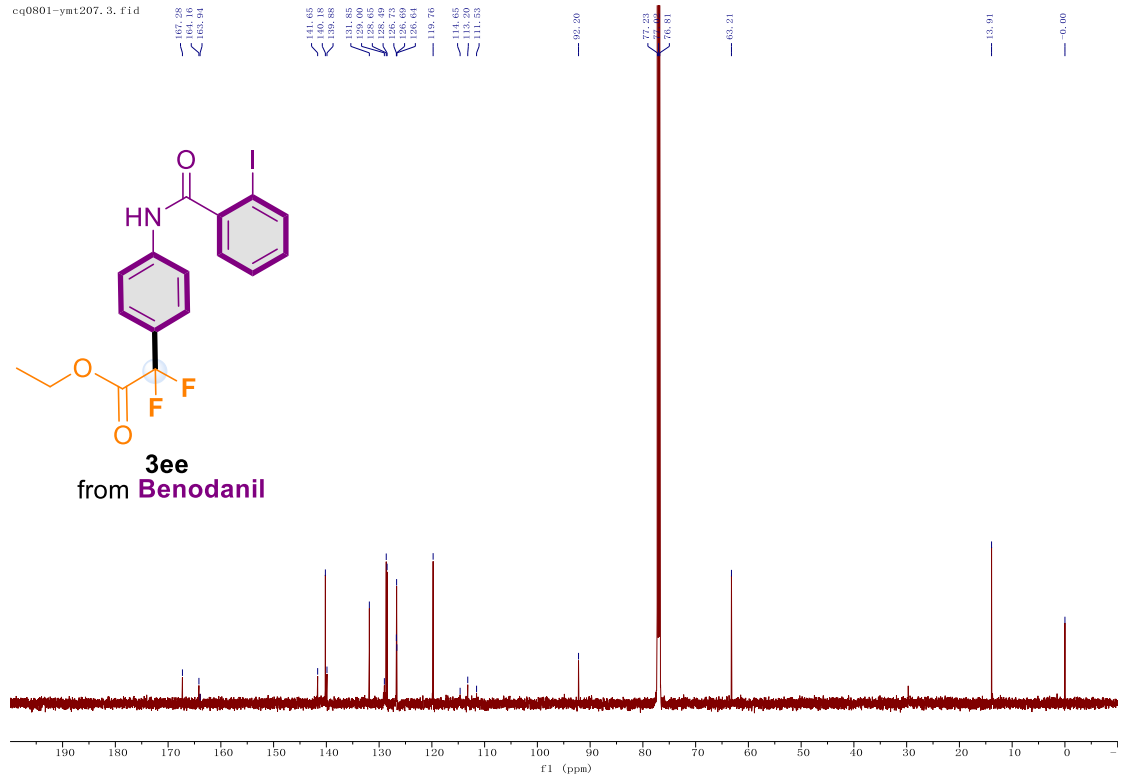


565 MHz ^{19}F NMR spectra of **3dd** in $CDCl_3$.

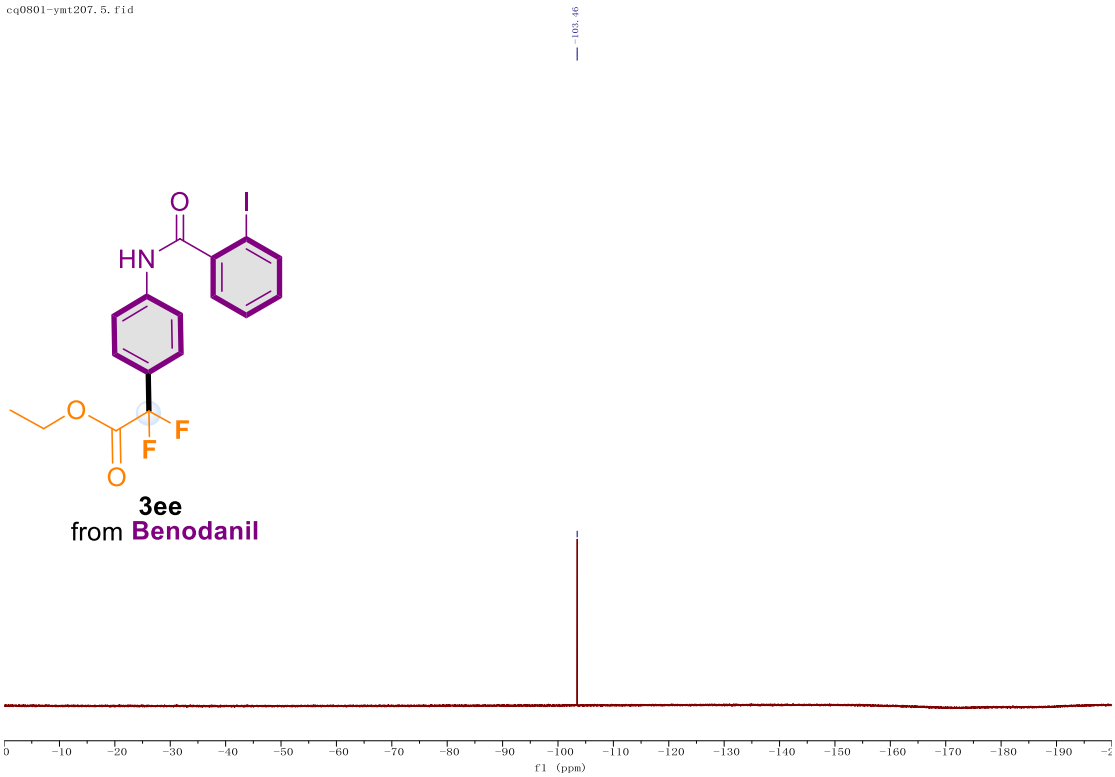
600 MHz ^{1}H NMR spectra of **3ee** in $CDCl_3$.



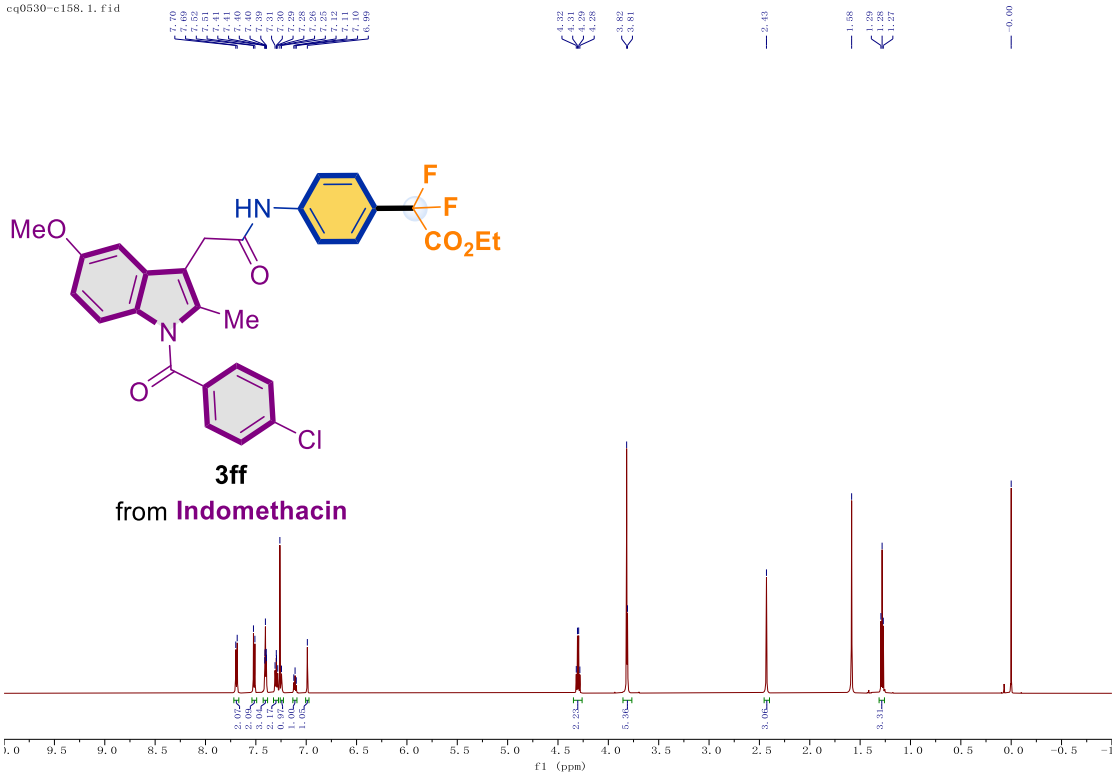
151 MHz ^{13}C NMR spectra of **3ee** in $CDCl_3$.



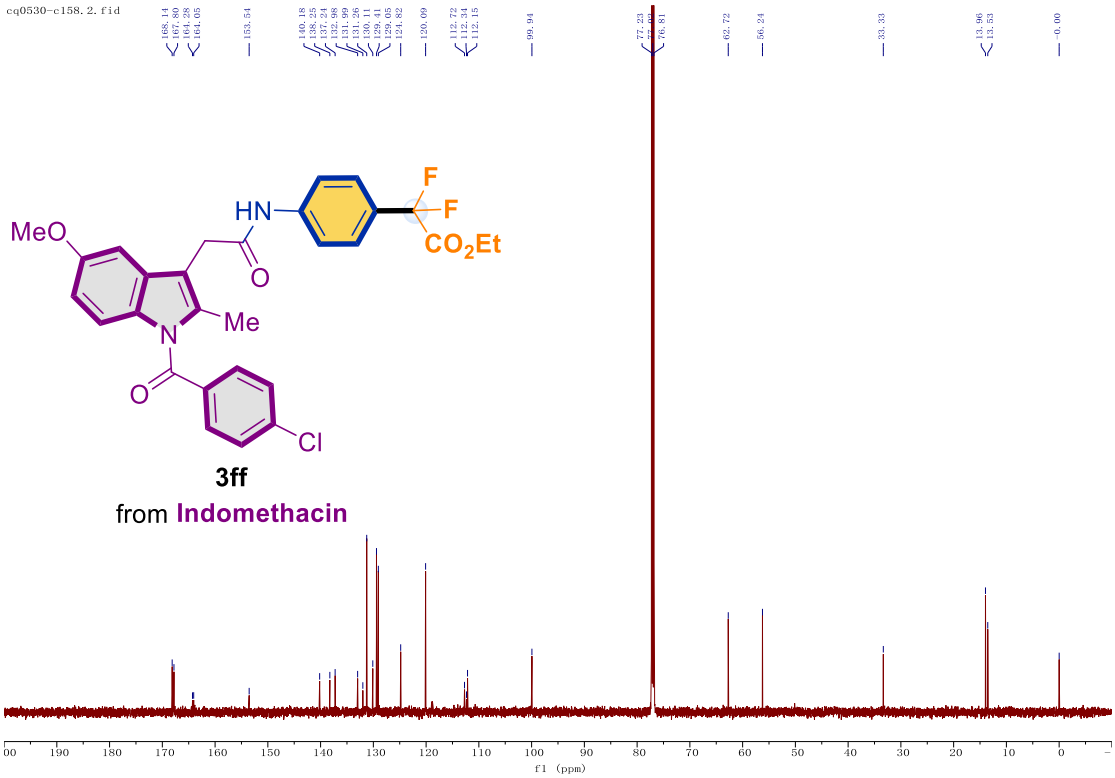
565 MHz ^{19}F NMR spectra of **3ee** in $CDCl_3$.



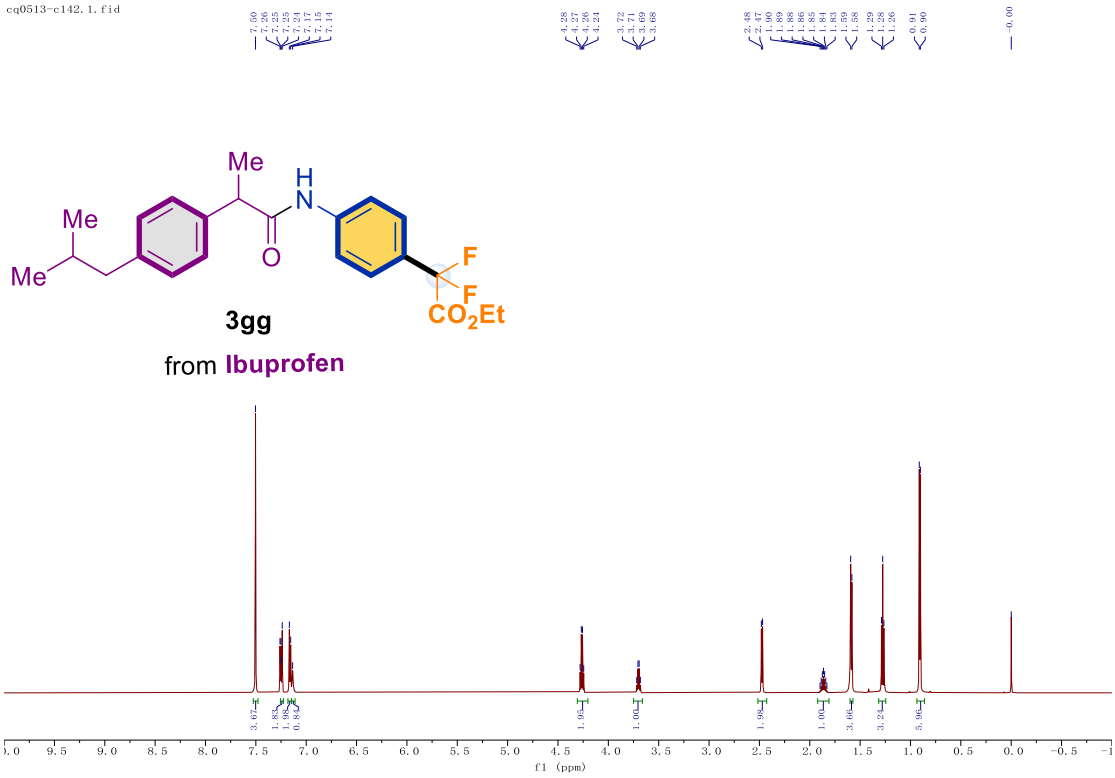
600 MHz ^{1}H NMR spectra of **3ff** in $CDCl_3$.



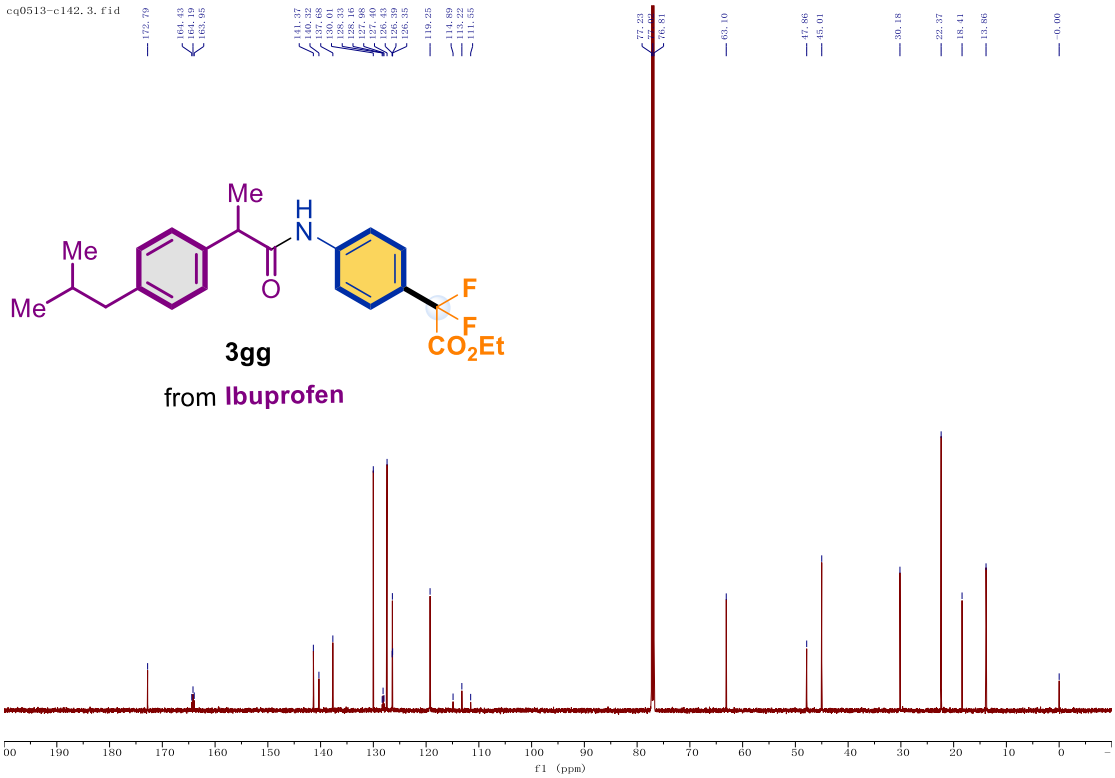
151 MHz ^{13}C NMR spectra of **3ff** in $CDCl_3$.



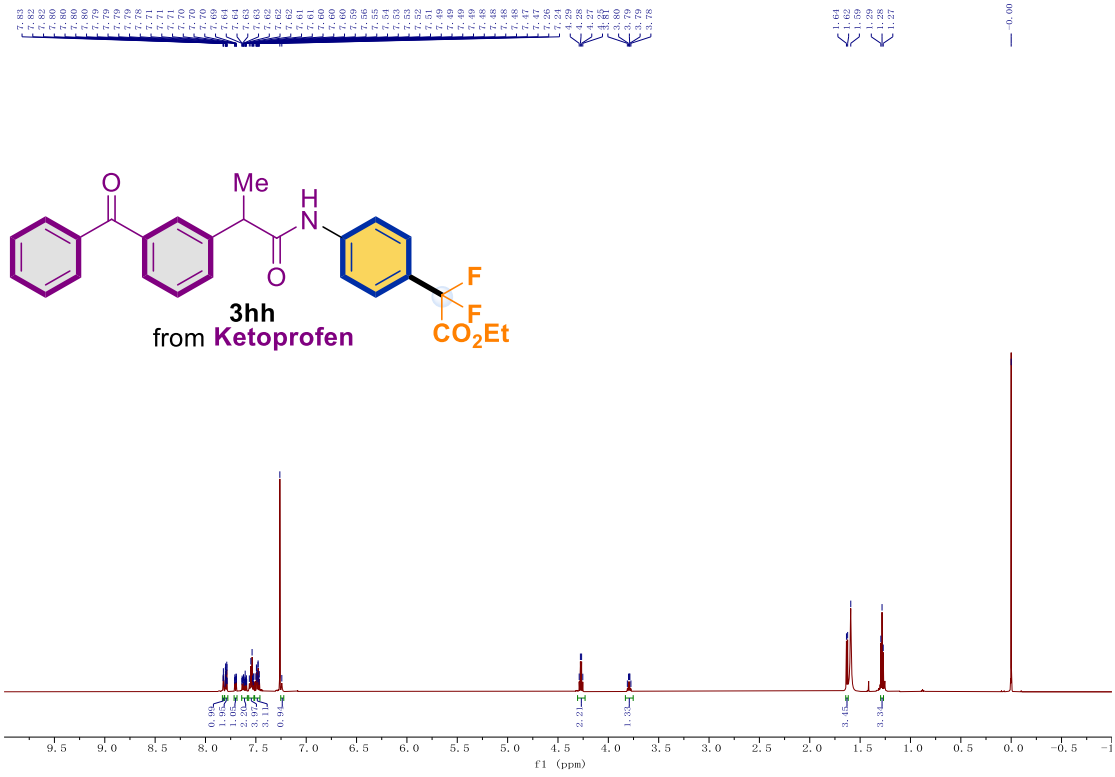
600 MHz ^{1}H NMR spectra of **3gg** in $CDCl_3$.



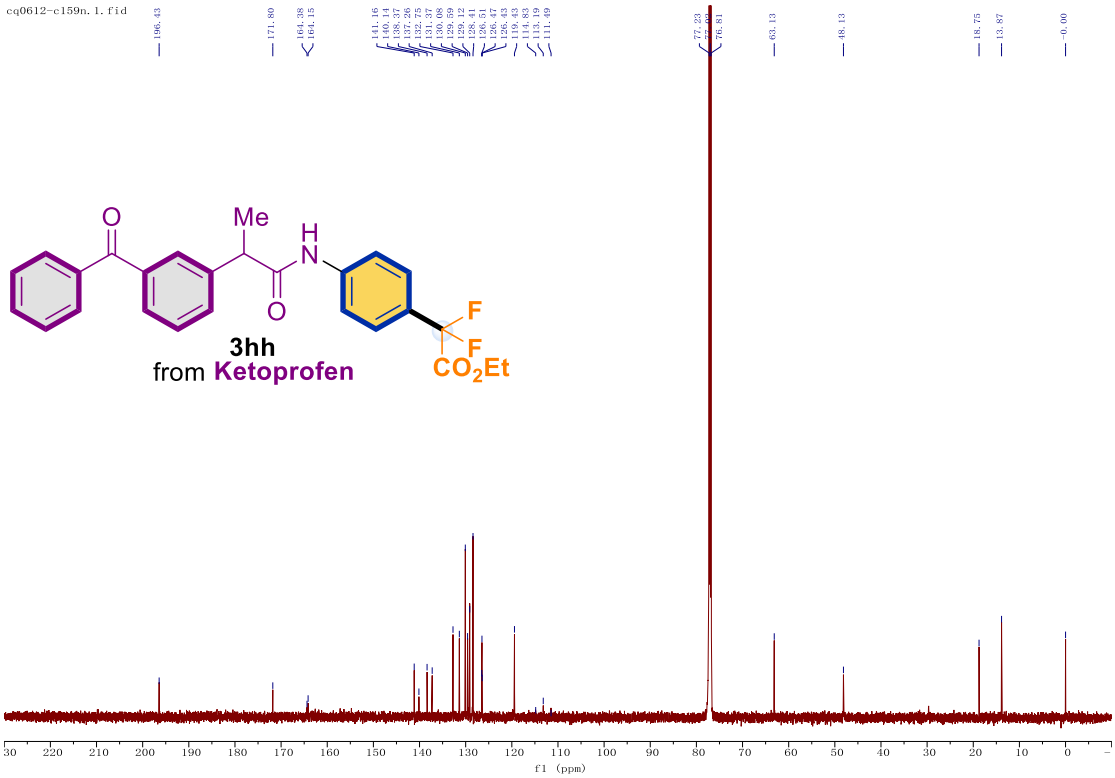
151 MHz ^{13}C NMR spectra of **3gg** in $CDCl_3$.



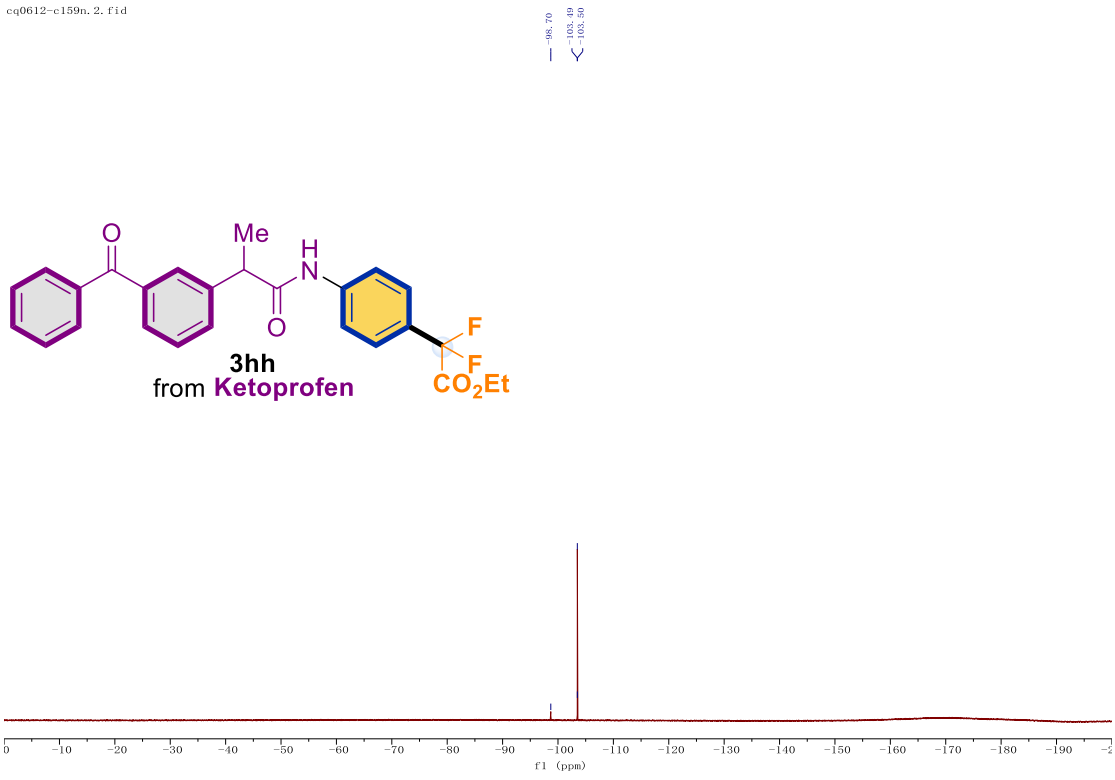
600 MHz ^{1}H NMR spectra of **3hh** in $CDCl_3$.



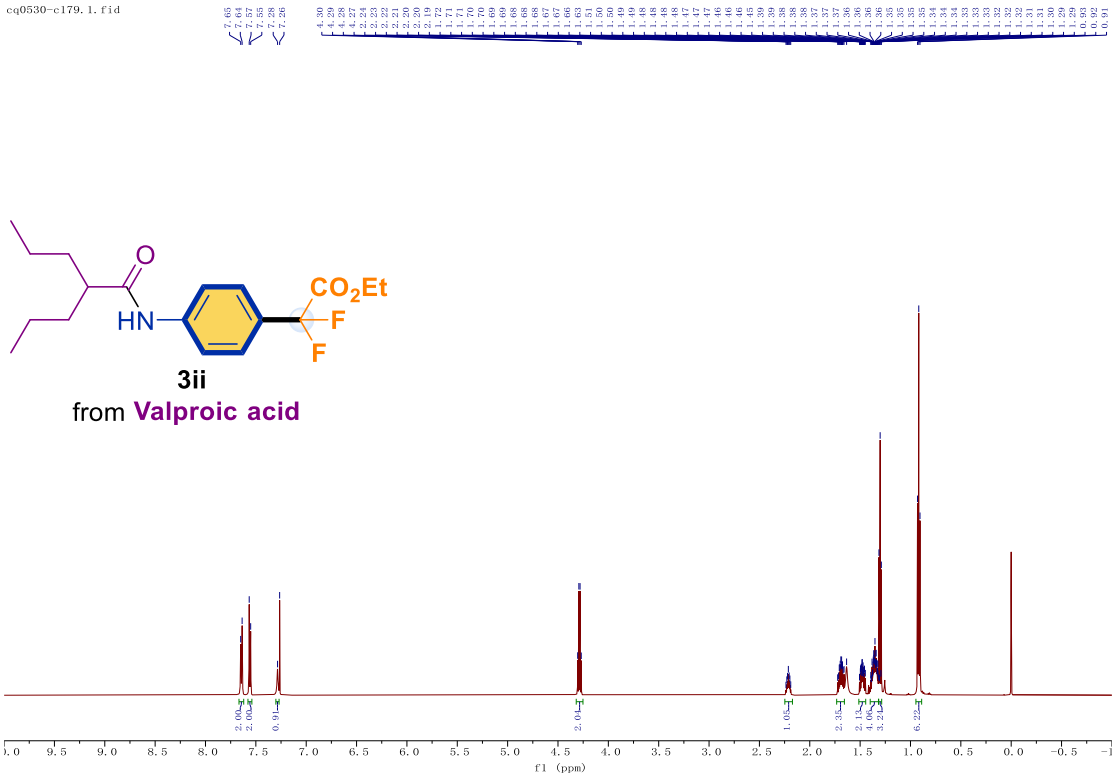
151 MHz ^{13}C NMR spectra of **3hh** in $CDCl_3$.



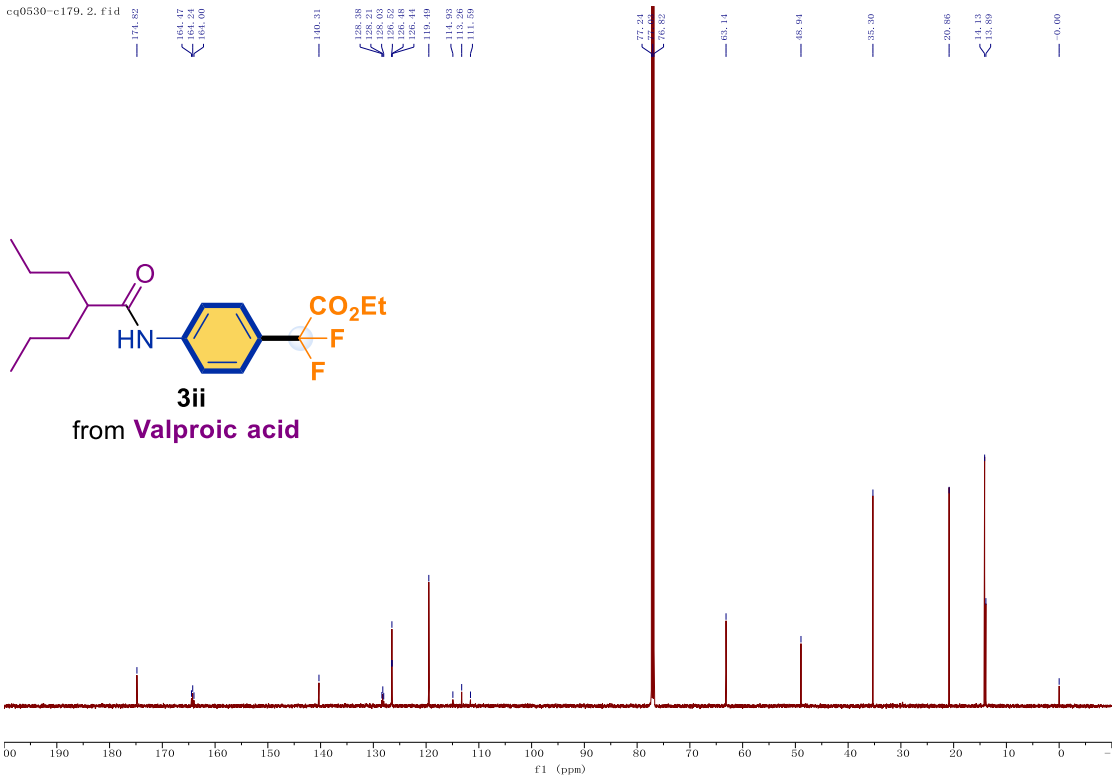
565 MHz ^{1}H NMR spectra of **3hh** in $CDCl_3$.



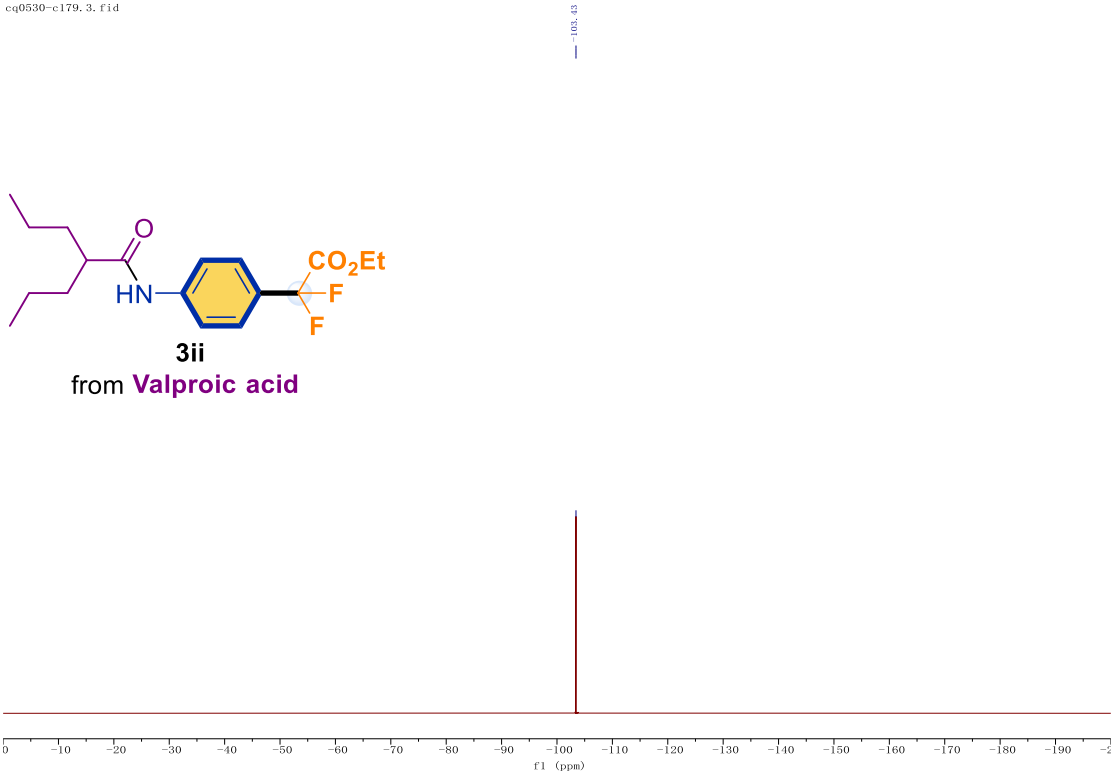
600 MHz ^{1}H NMR spectra of **3ii** in $CDCl_3$.



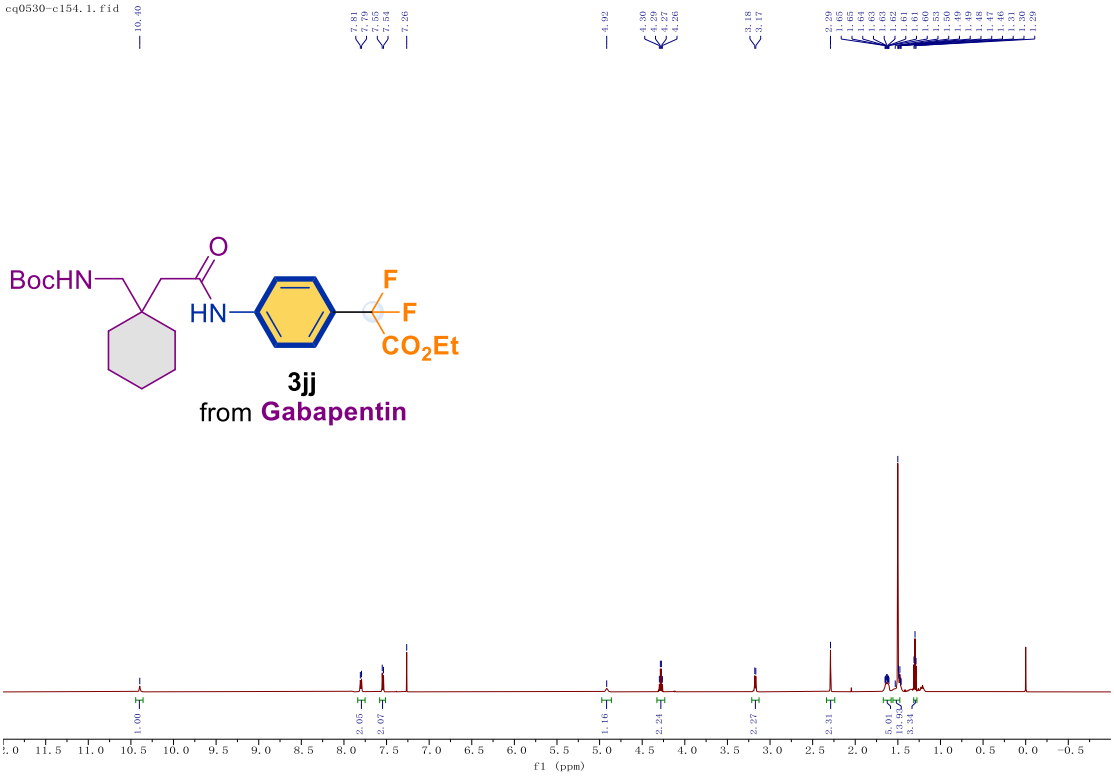
151 MHz ^{13}C NMR spectra of **3ii** in $CDCl_3$.



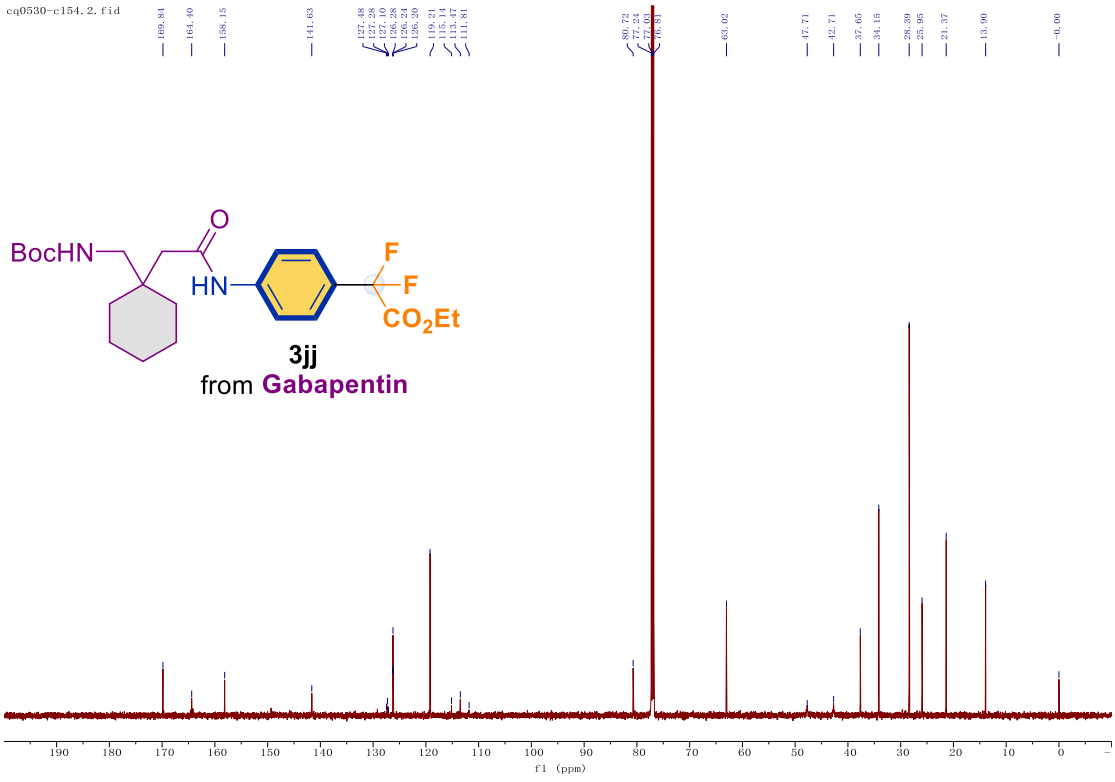
565MHz ^{19}F NMR spectra of **3ii** in $CDCl_3$.



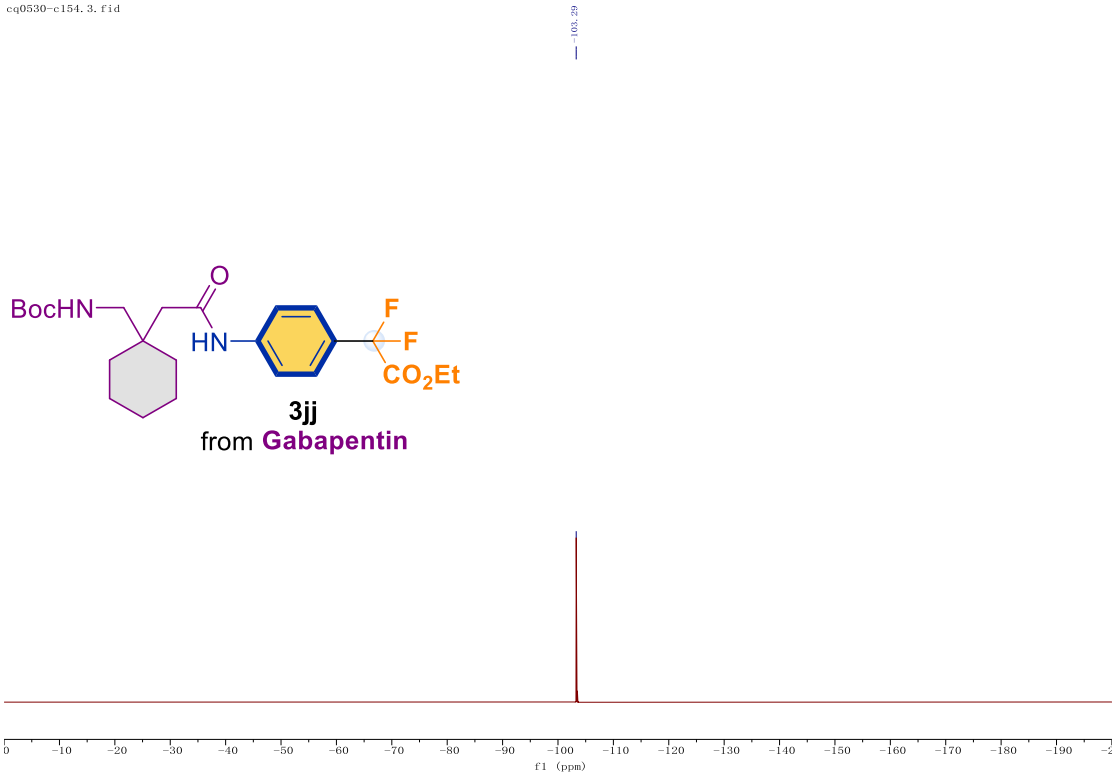
600 MHz ^{1}H NMR spectra of **3jj** in $CDCl_3$.



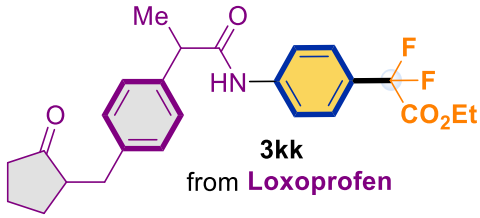
151 MHz ^{13}C NMR spectra of **3jj** in $CDCl_3$.

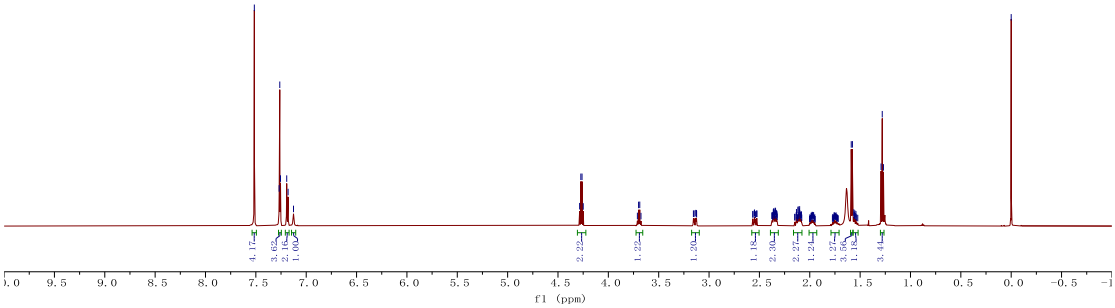


565 MHz ^{19}F NMR spectra of **3jj** in $CDCl_3$.

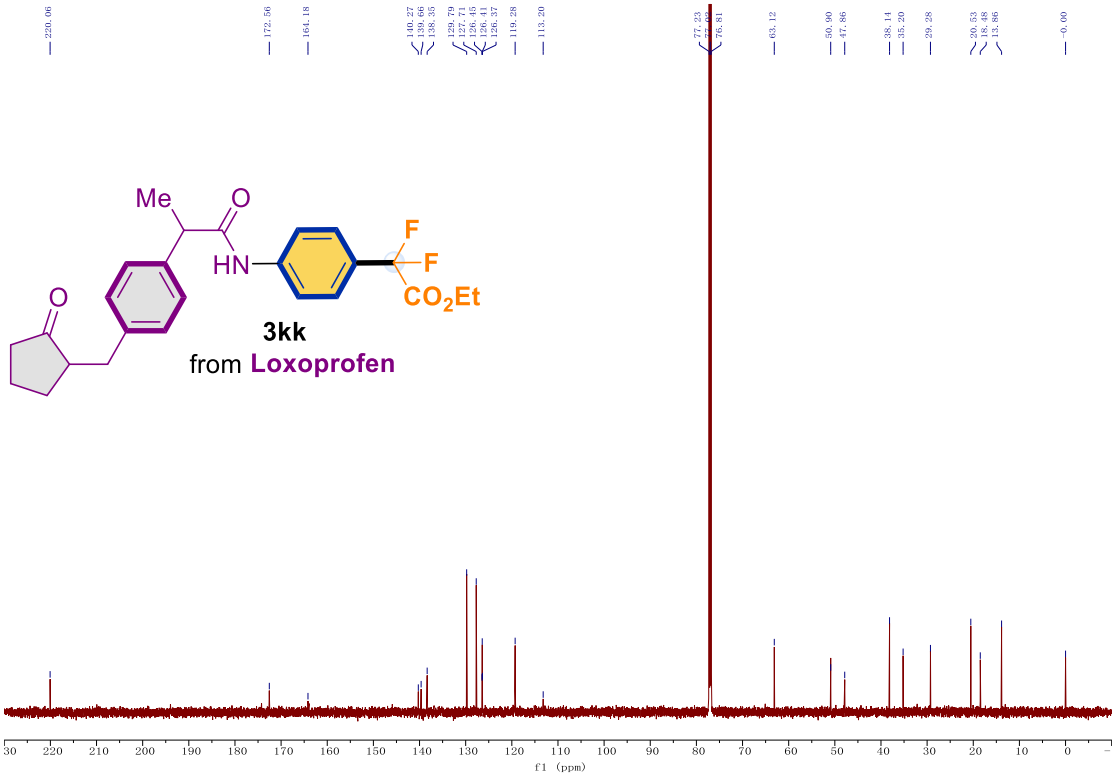


600 MHz ^{1}H NMR spectra of **3kk** in $CDCl_3$.

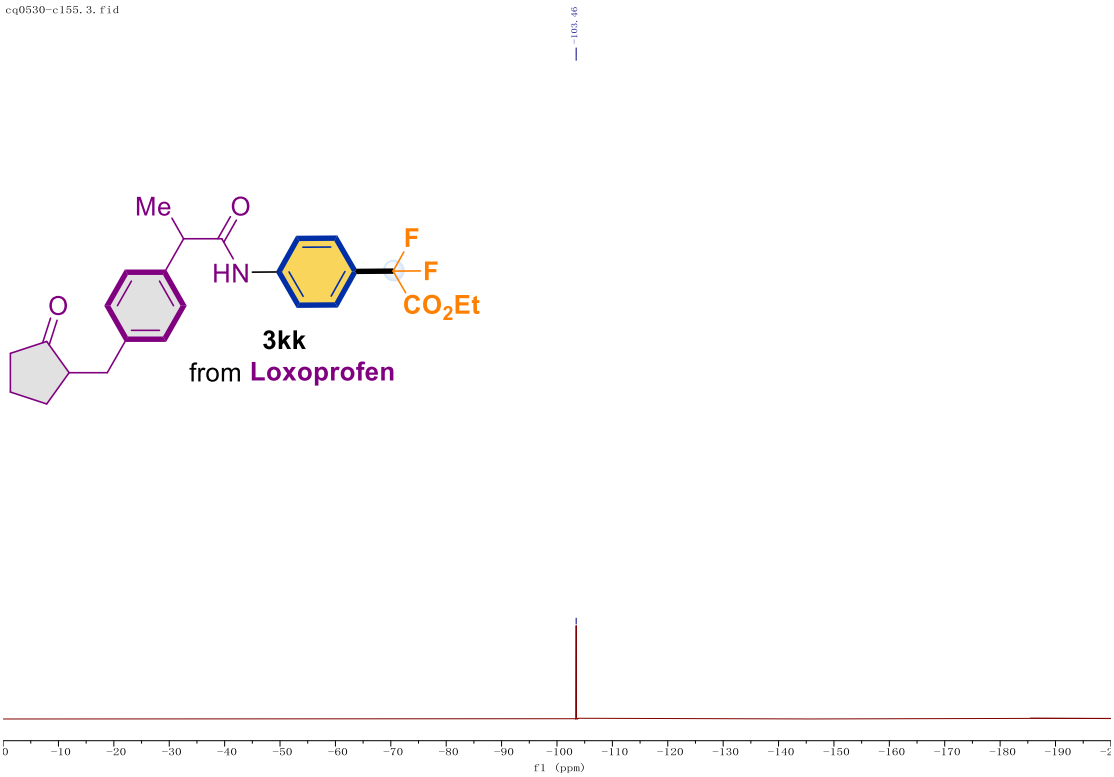




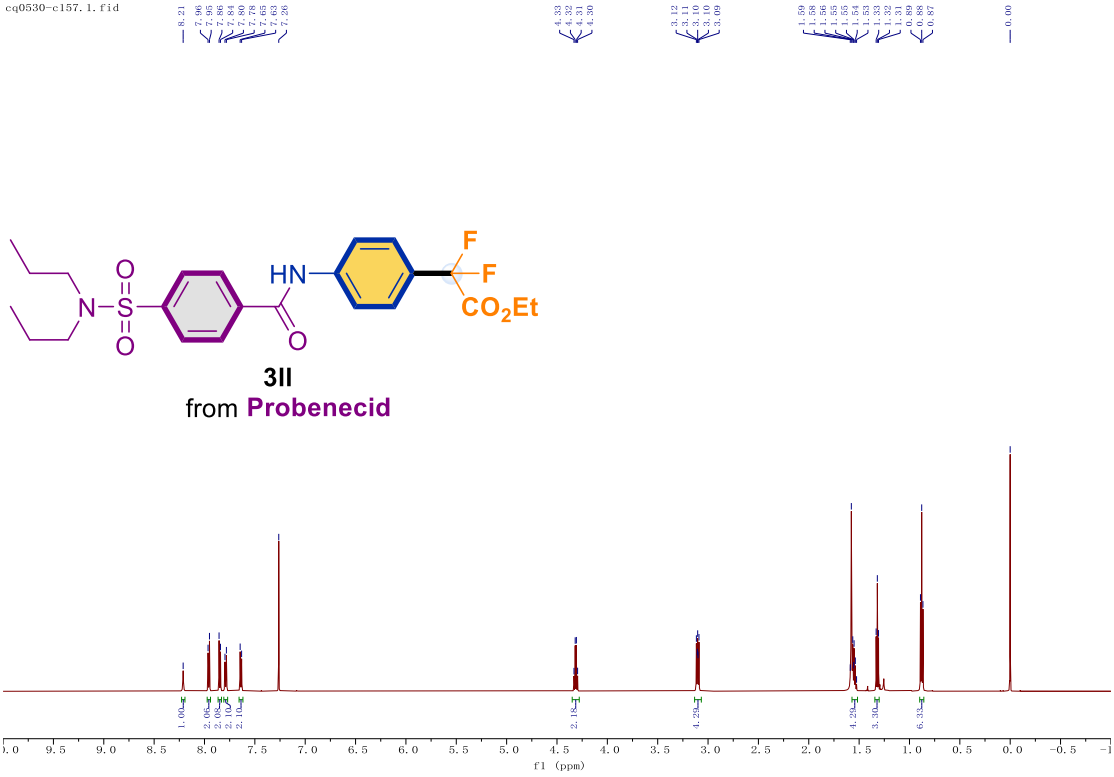
151 MHz ^{13}C NMR spectra of **3kk** in $CDCl_3$.



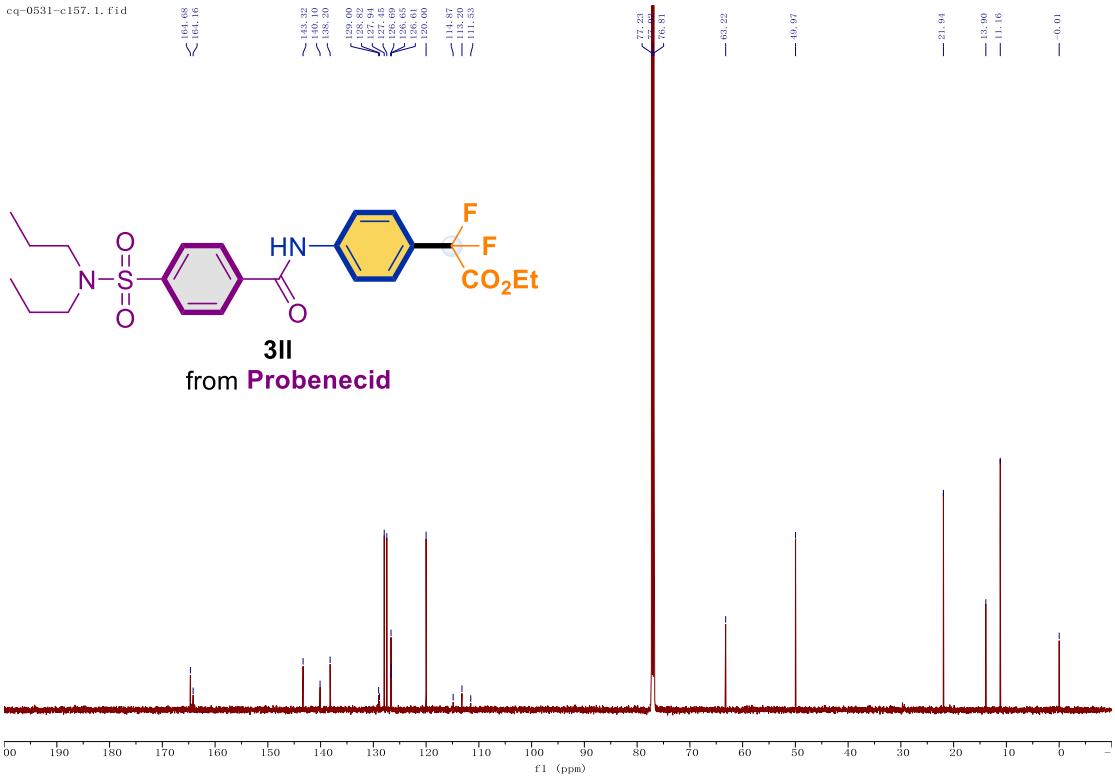
565 MHz ^{19}F NMR spectra of **3kk** in $CDCl_3$.



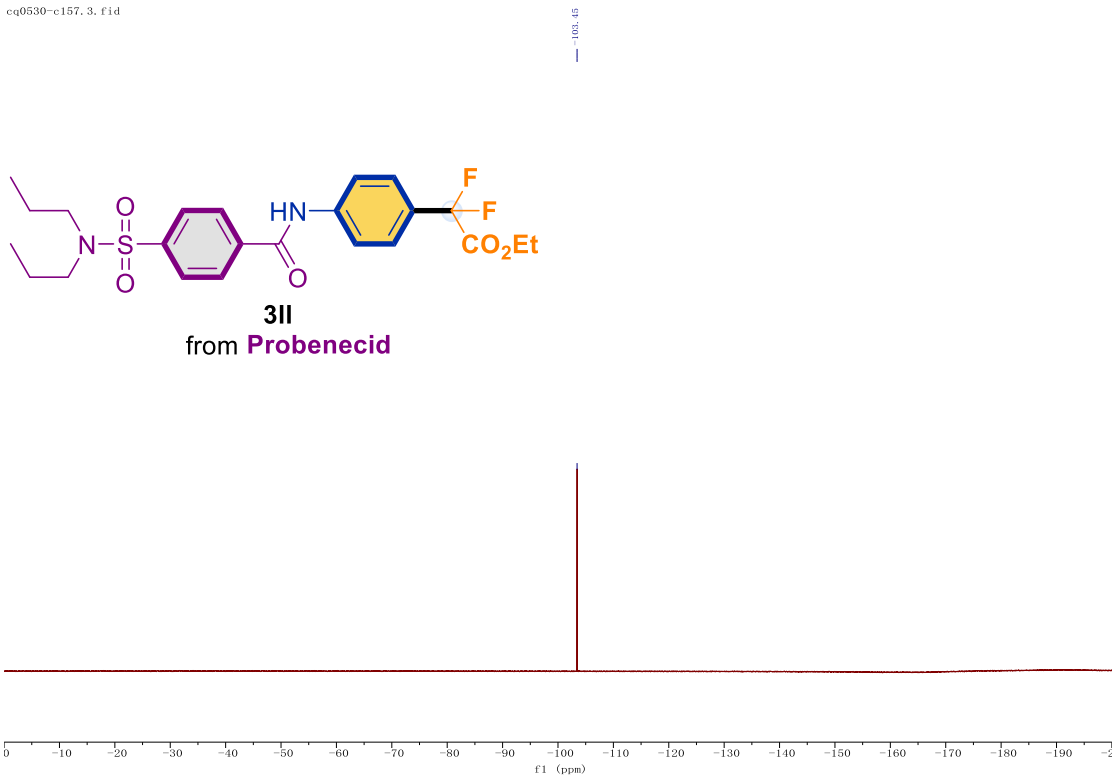
600 MHz ^{1}H NMR spectra of **3ll** in $CDCl_3$.



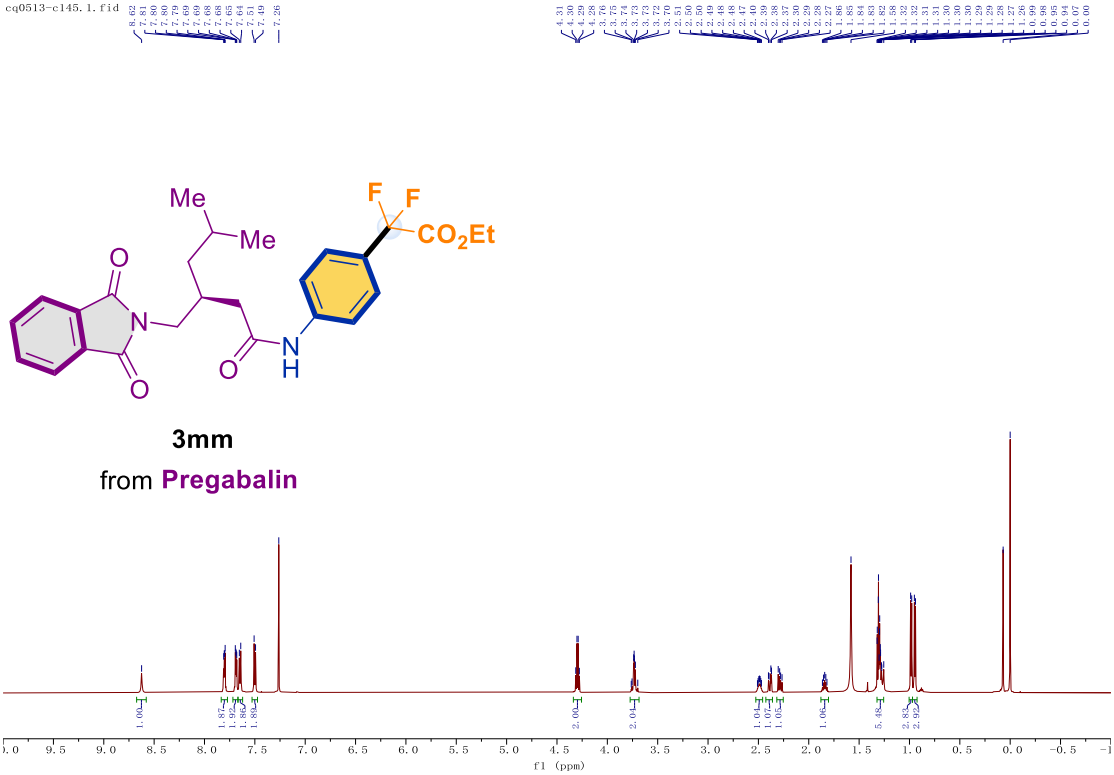
151 MHz ^{13}C NMR spectra of **3ll** in $CDCl_3$.



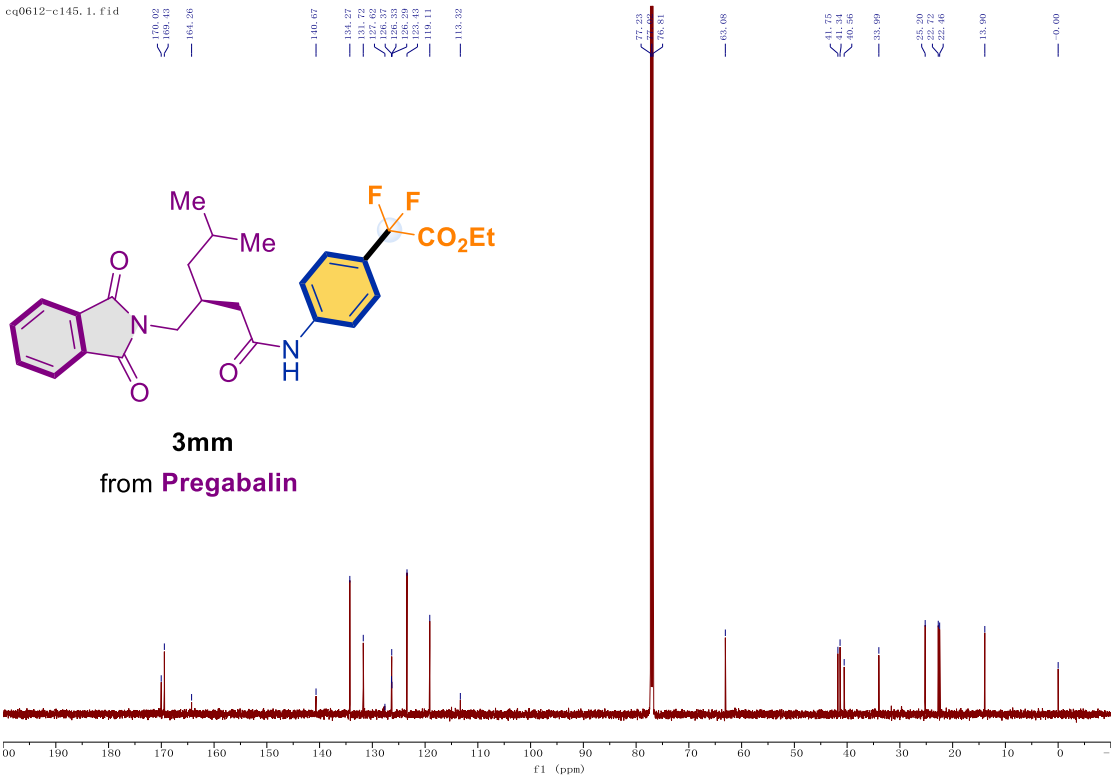
565 MHz ^{19}F NMR spectra of **3ll** in $CDCl_3$.



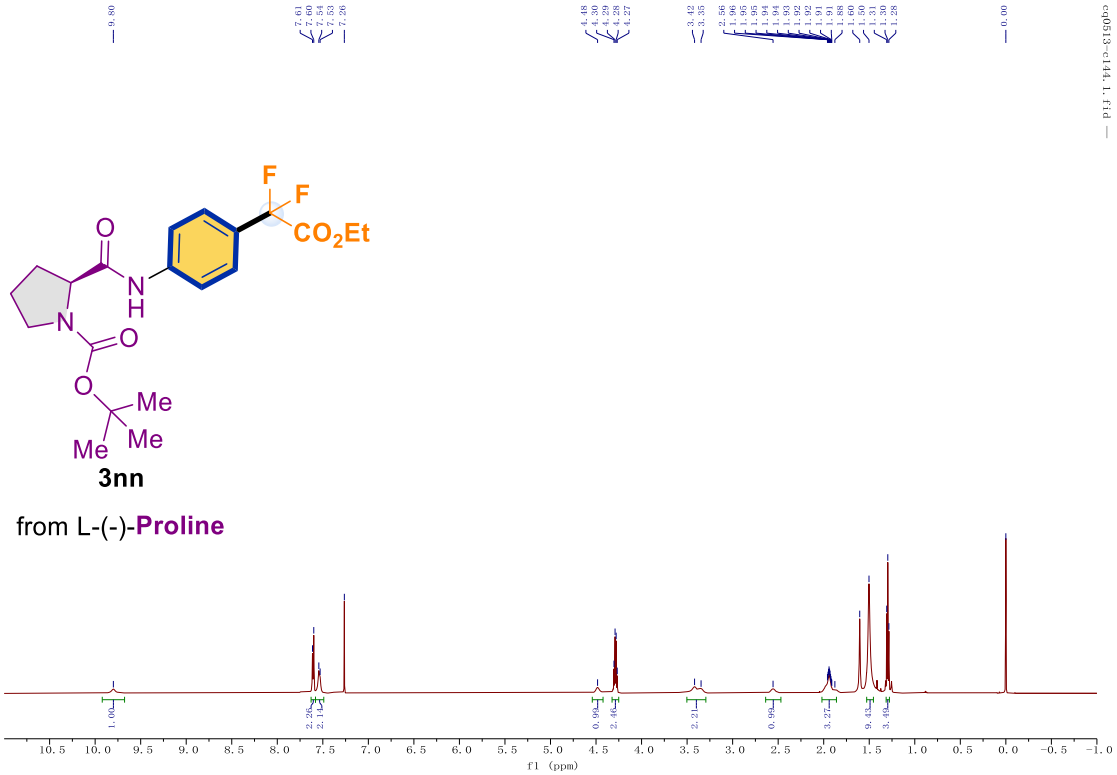
600 MHz ^{1}H NMR spectra of **3mm** in $CDCl_3$.



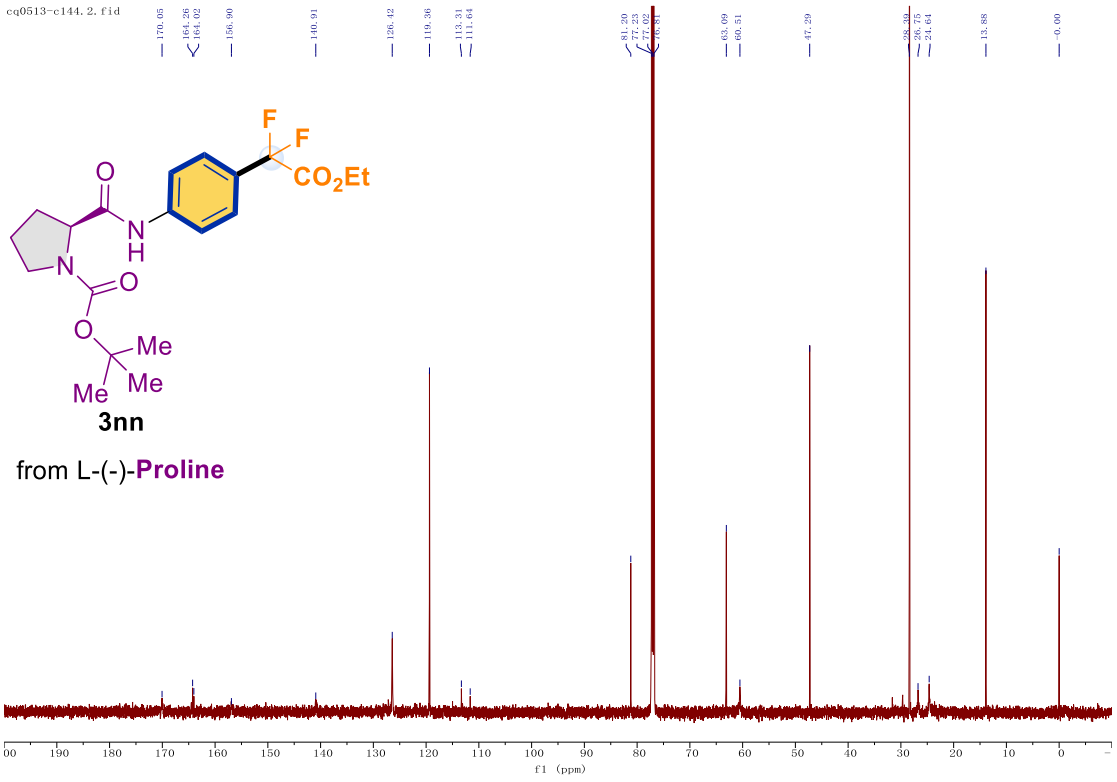
151 MHz ^{13}C NMR spectra of **3mm** in $CDCl_3$.



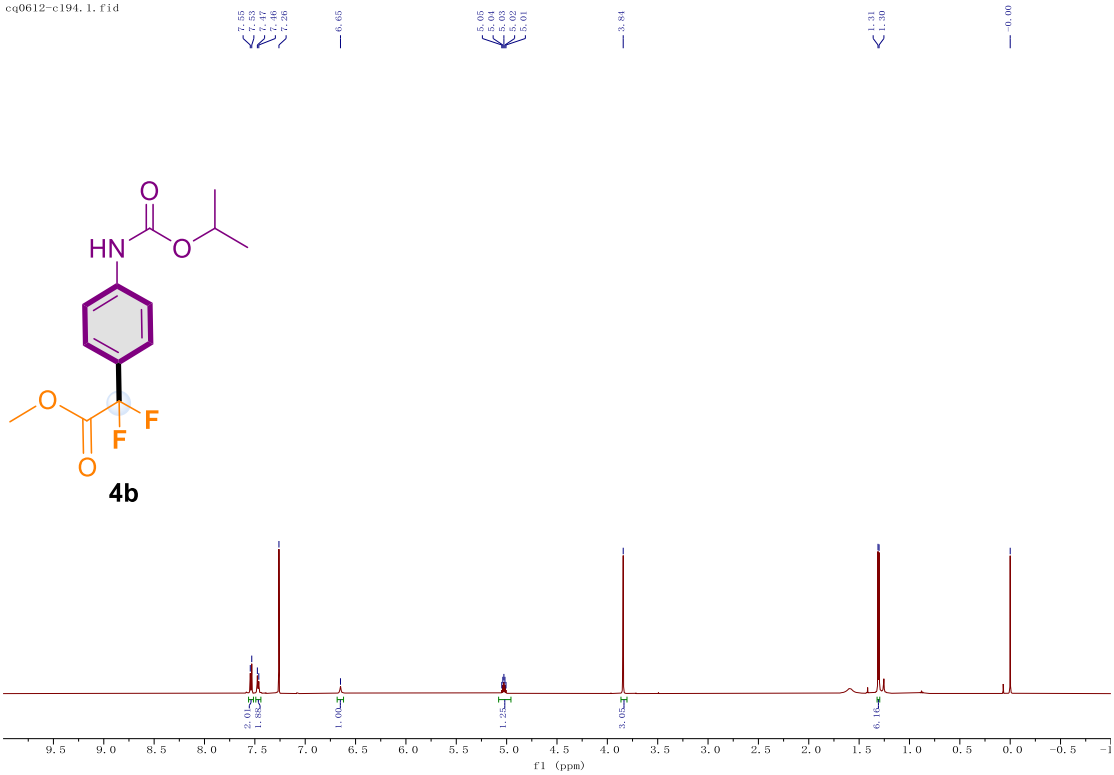
600 MHz ^{1}H NMR spectra of **3nn** in $CDCl_3$.



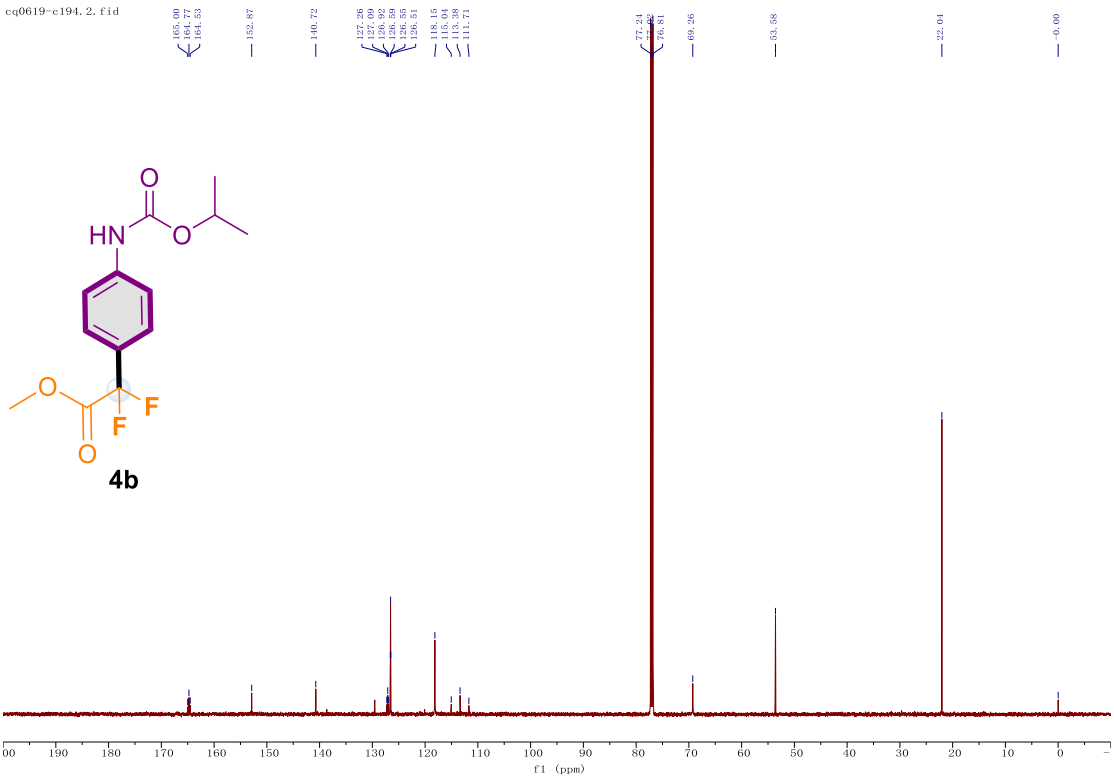
151 MHz ^{13}C NMR spectra of **3nn** in $CDCl_3$.



600 MHz ^{1}H NMR spectra of **4b** in $CDCl_3$.

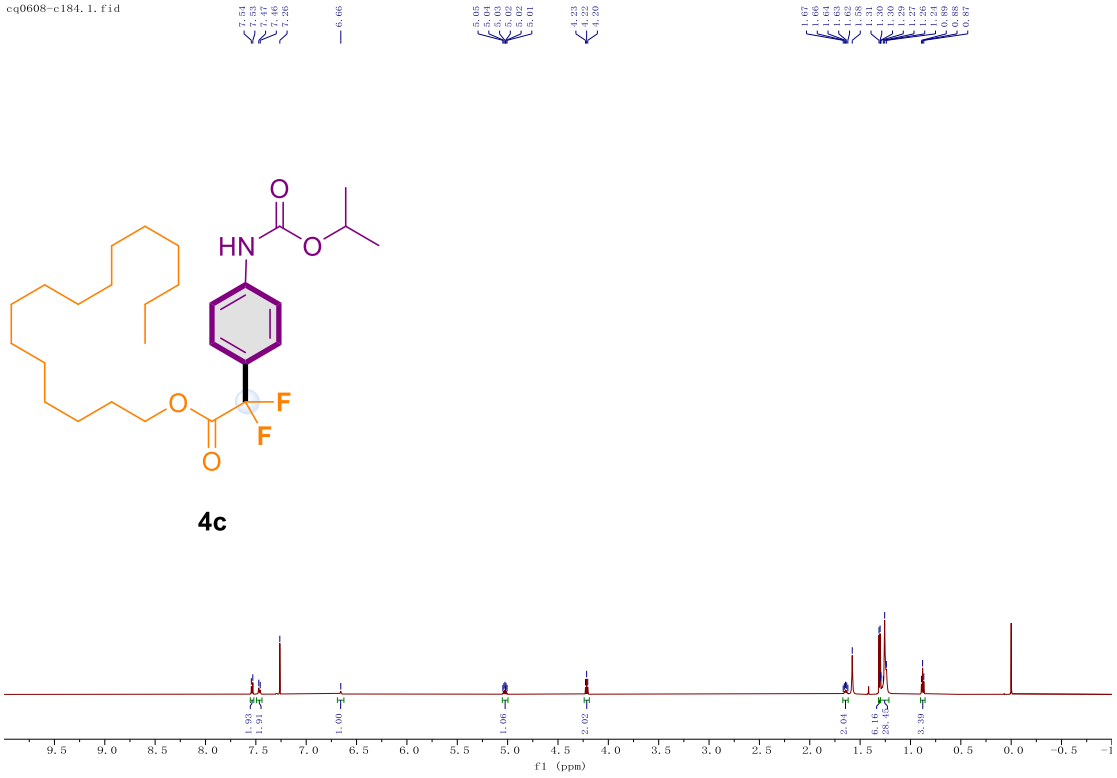


151 MHz ^{13}C NMR spectra of **4b** in $CDCl_3$.

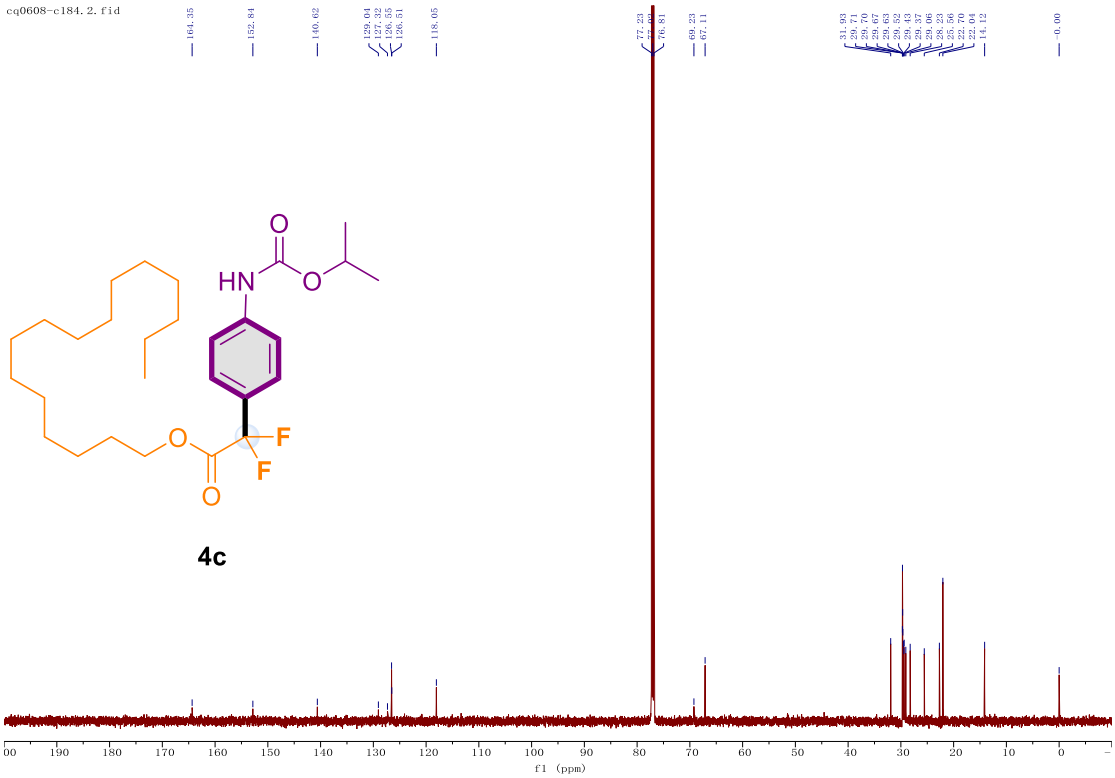


565 MHz ^{19}F NMR spectra of **4b** in $CDCl_3$.

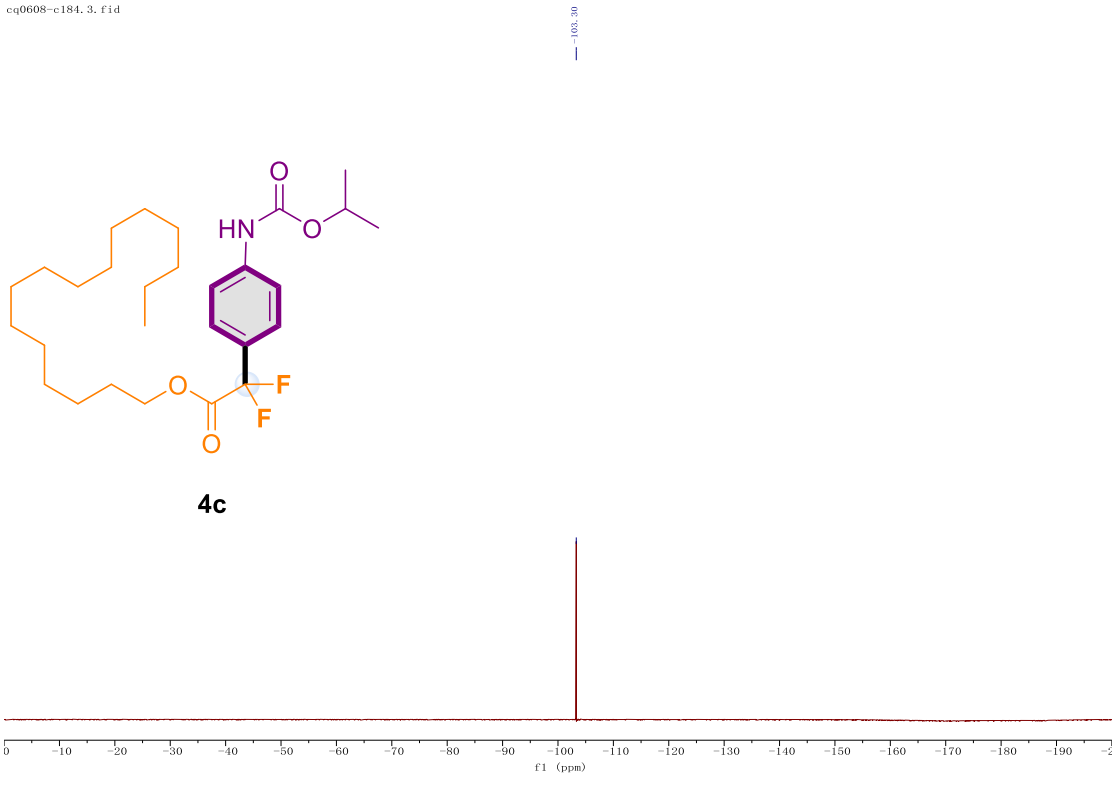
600 MHz ^{1}H NMR spectra of **4c** in $CDCl_3$.



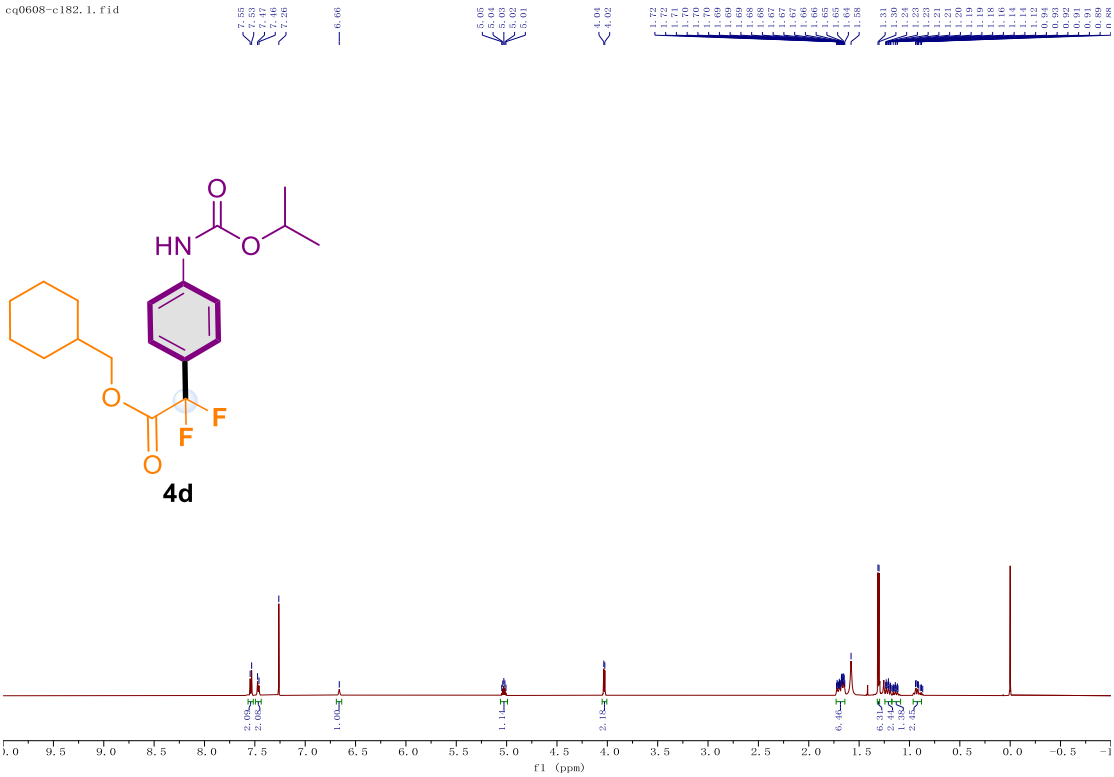
151 MHz ^{13}C NMR spectra of **4c** in $CDCl_3$.



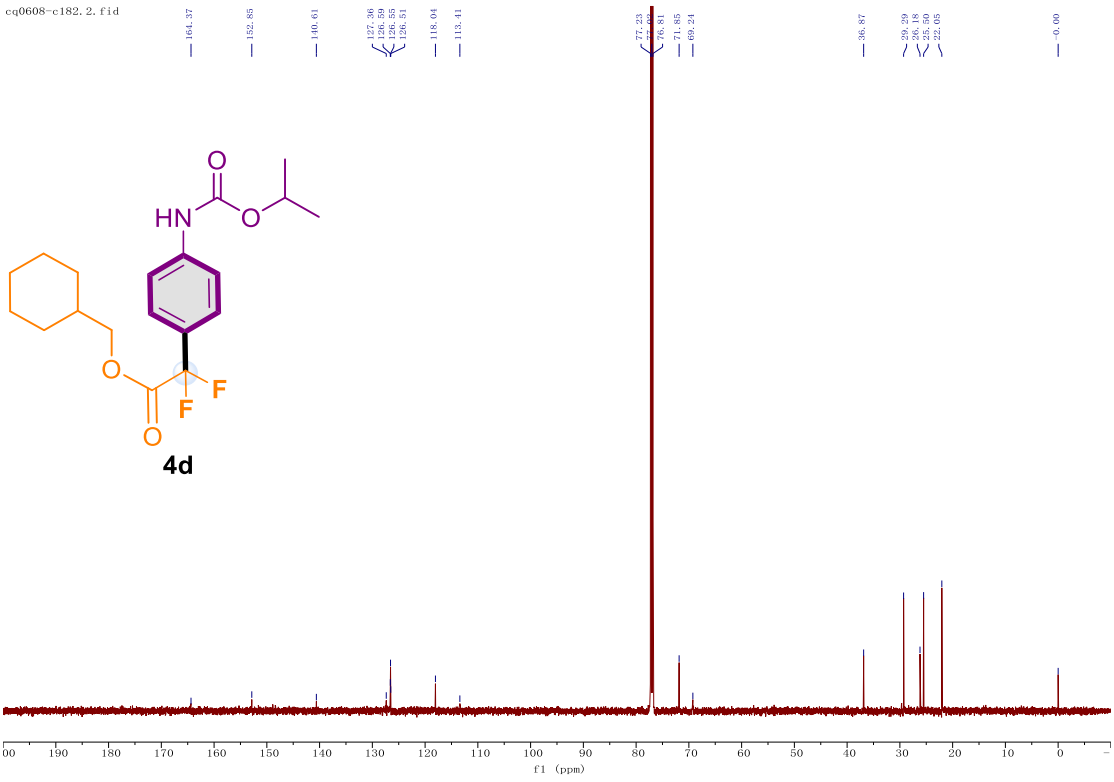
565 MHz ^{19}F NMR spectra of **4c** in $CDCl_3$.



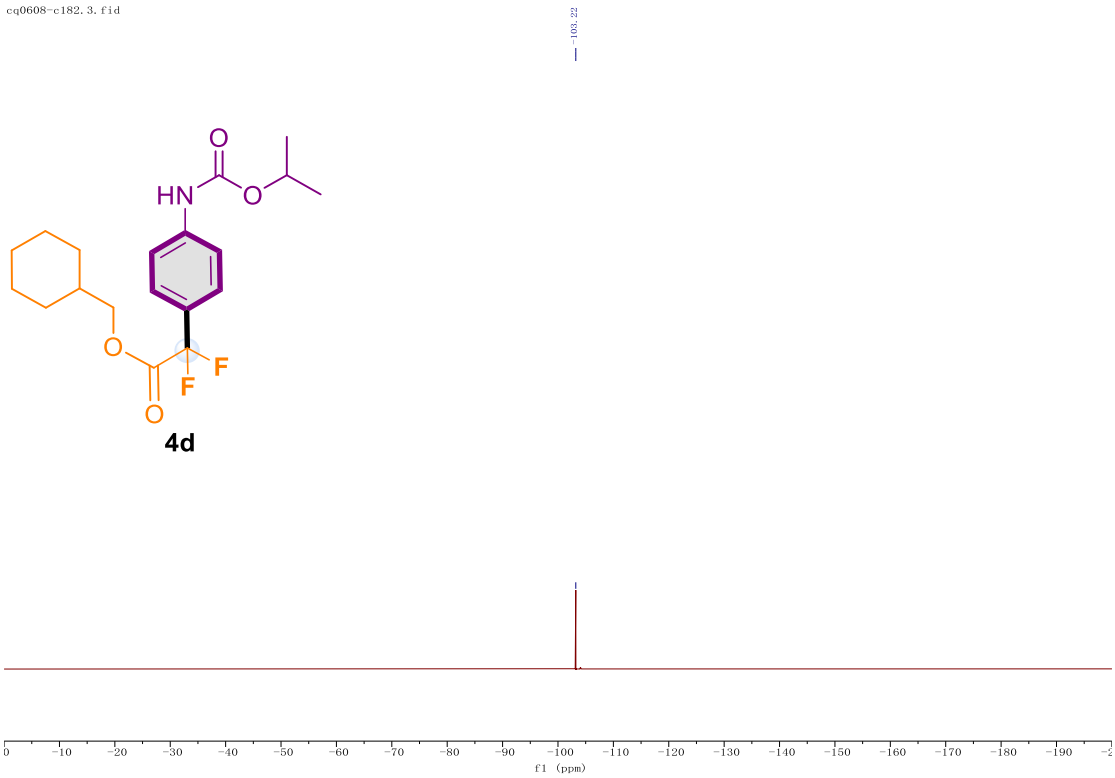
600 MHz ^{1}H NMR spectra of **4d** in $CDCl_3$.



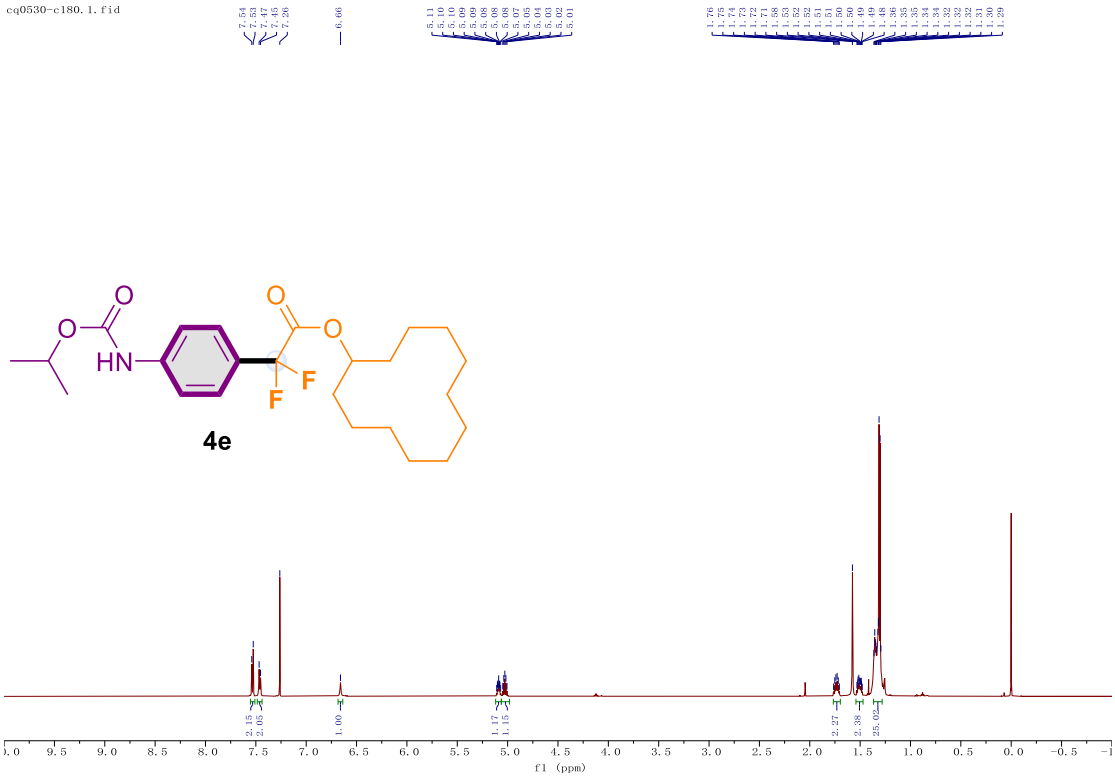
151 MHz ^{13}C NMR spectra of **4d** in $CDCl_3$.



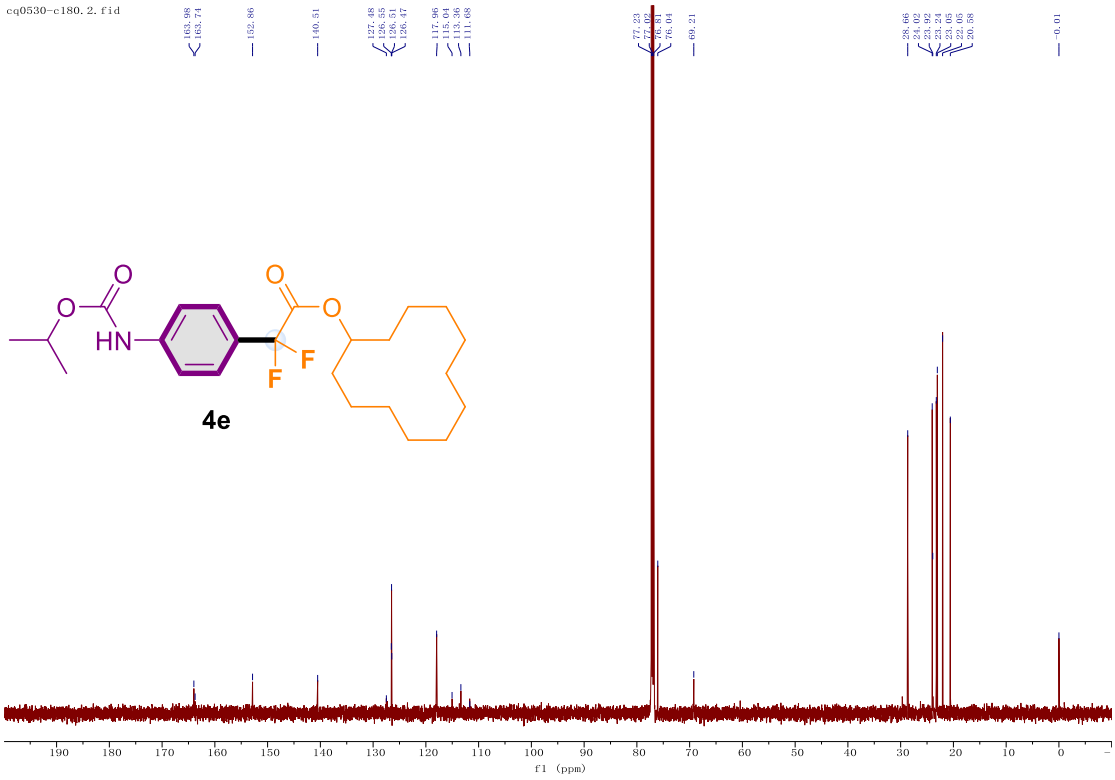
565 MHz ^{19}F NMR spectra of **4d** in $CDCl_3$.



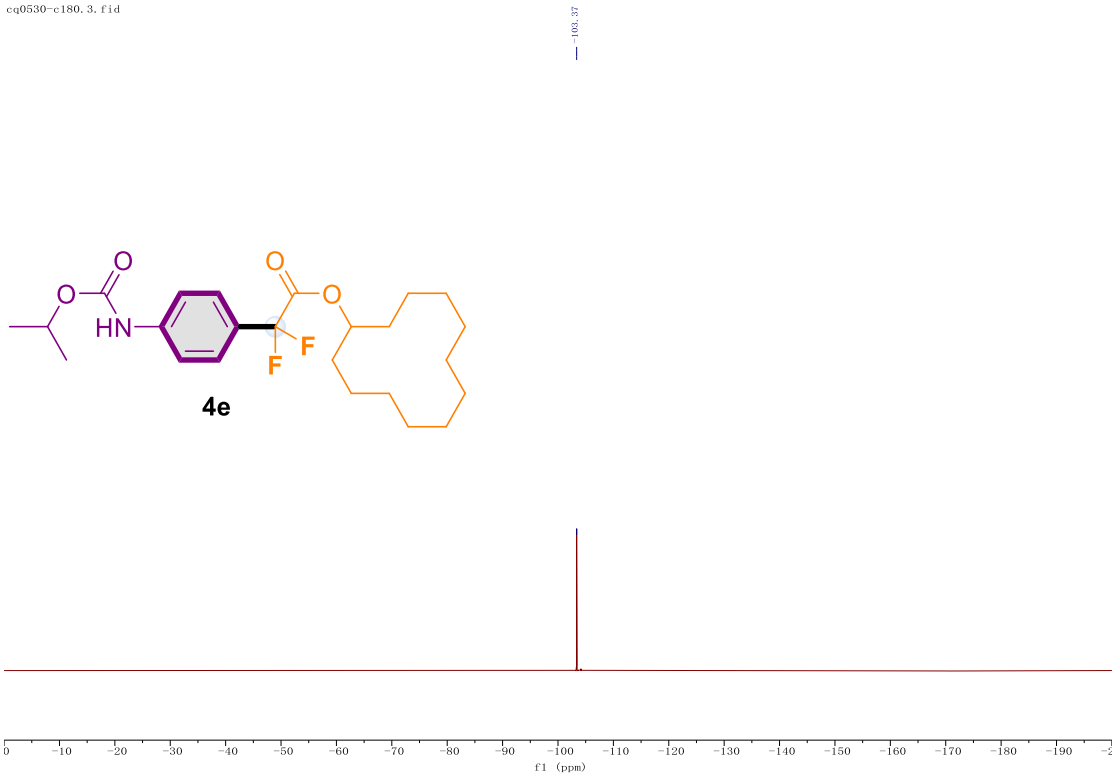
600 MHz ^{1}H NMR spectra of **4e** in $CDCl_3$.



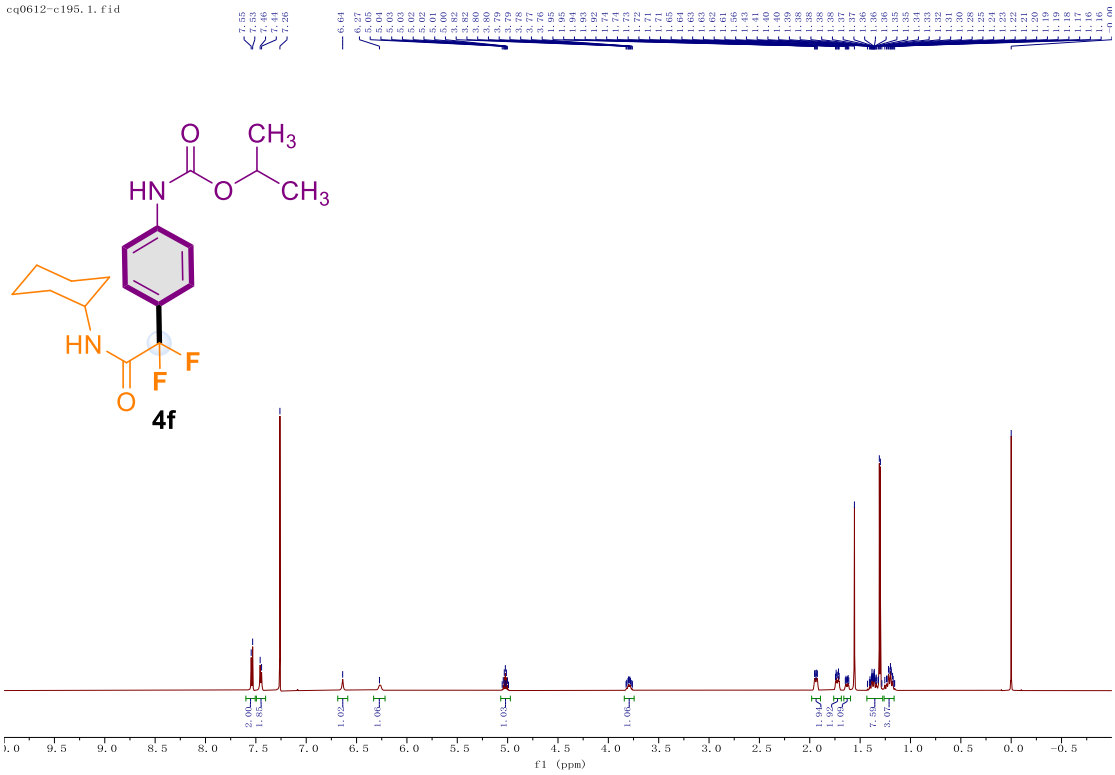
151 MHz ^{13}C NMR spectra of **4e** in $CDCl_3$.



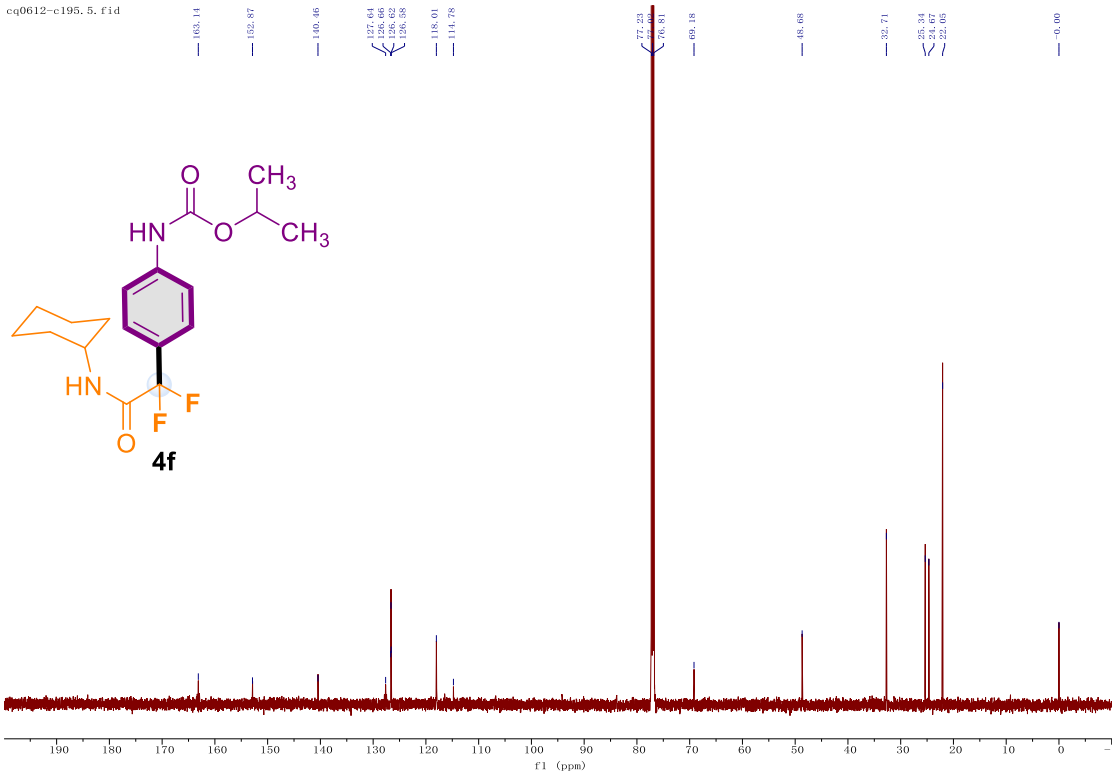
565 MHz ^{19}F NMR spectra of **4e** in $CDCl_3$.



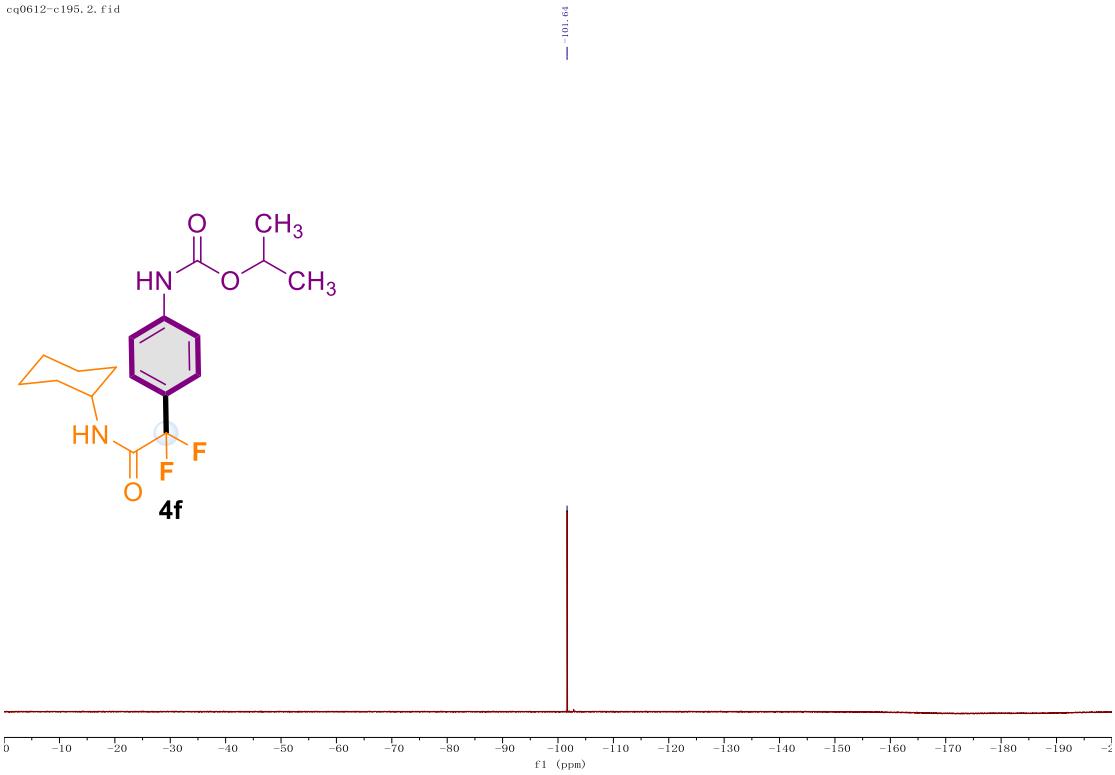
600 MHz ^{1}H NMR spectra of **4f** in $CDCl_3$.



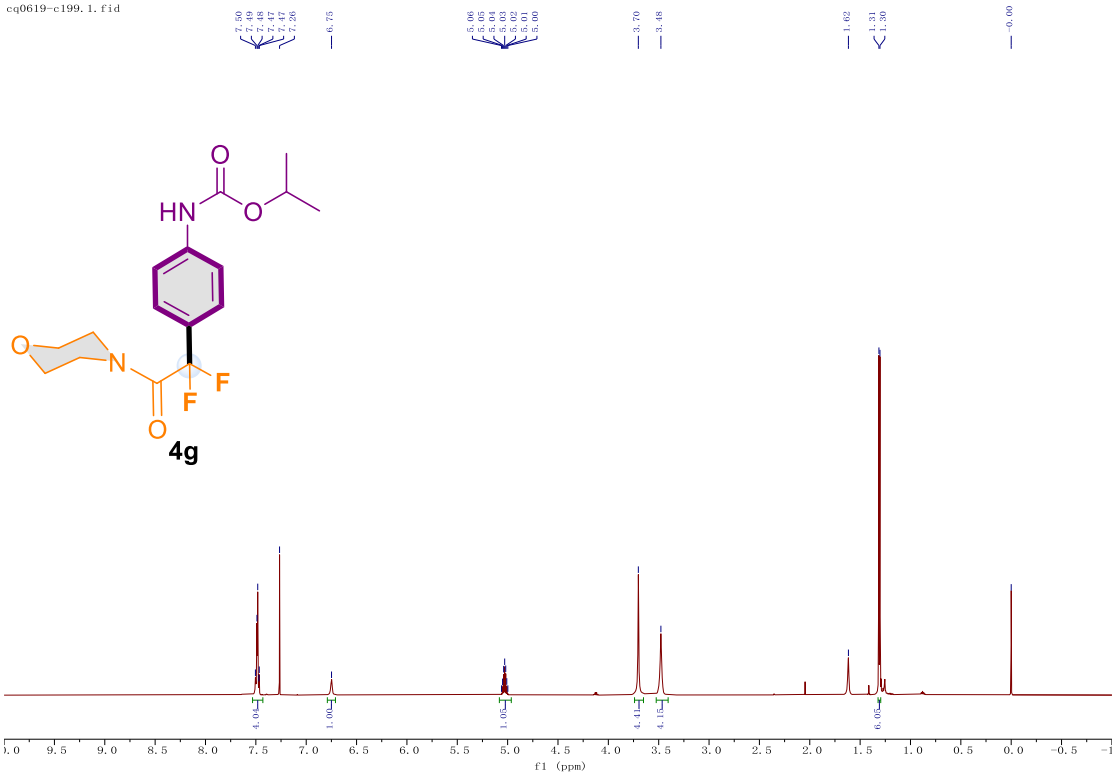
151 MHz ^{13}C NMR spectra of **4f** in $CDCl_3$.



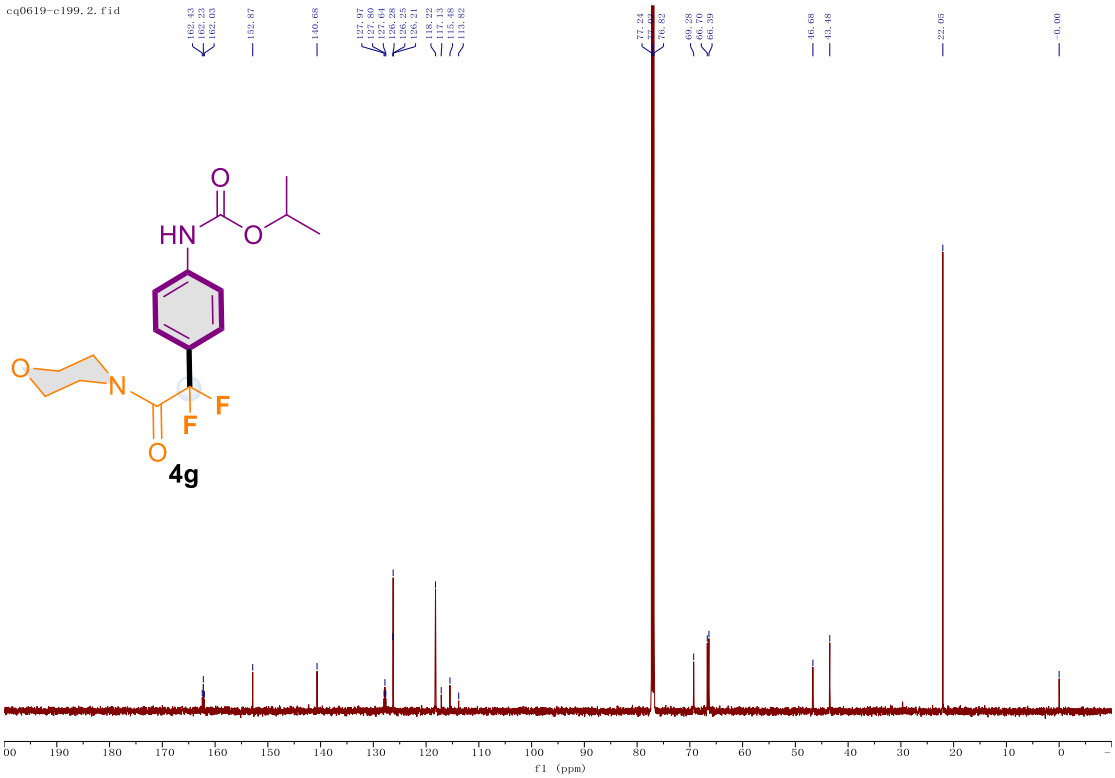
565 MHz ^{19}F NMR spectra of **4f** in $CDCl_3$.



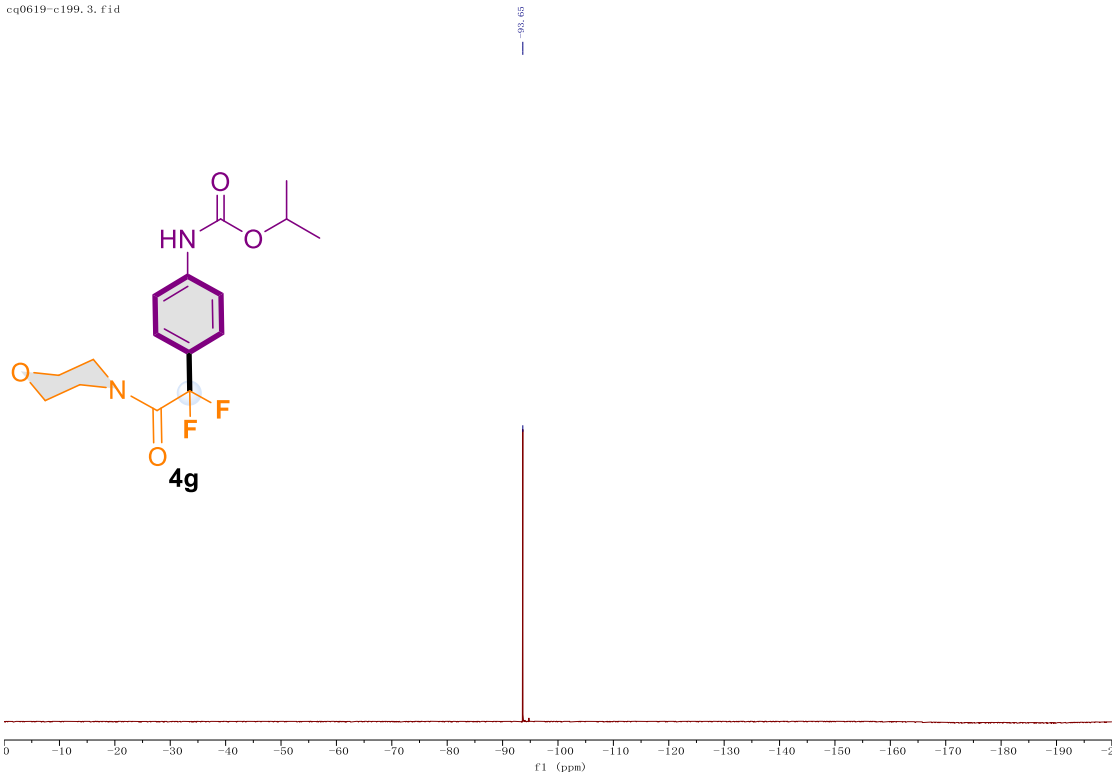
600 MHz ^{1}H NMR spectra of **4g** in $CDCl_3$.



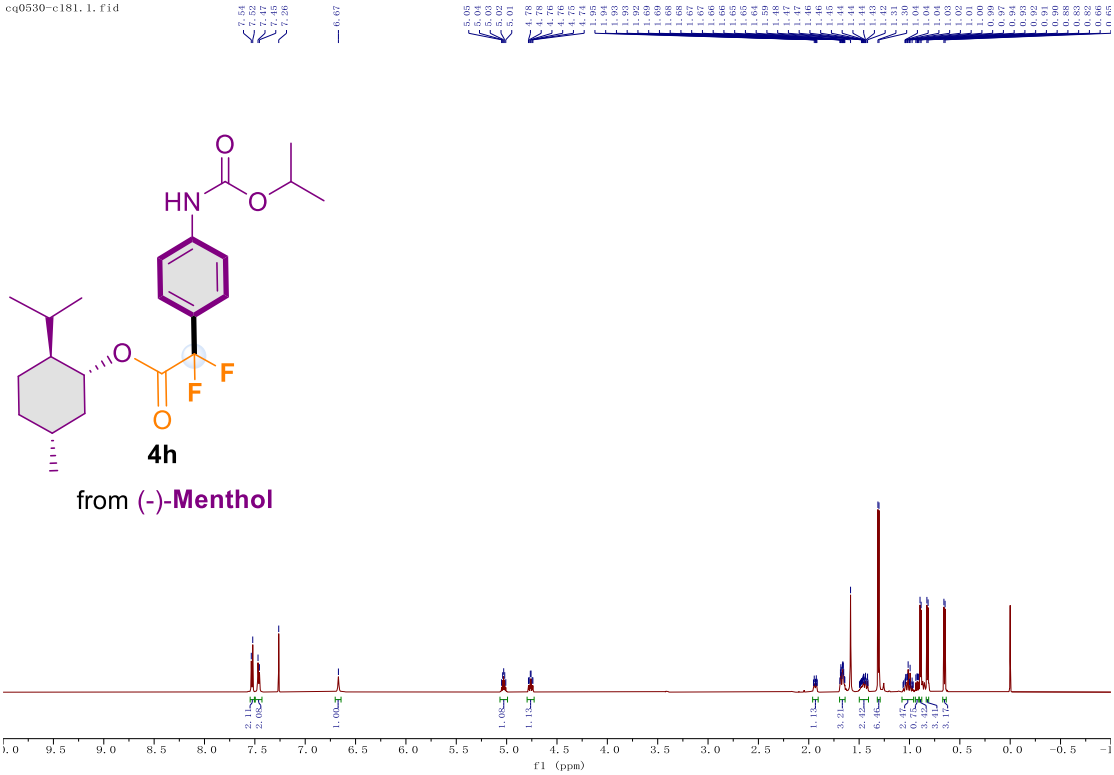
151 MHz ^{13}C NMR spectra of **4g** in $CDCl_3$.



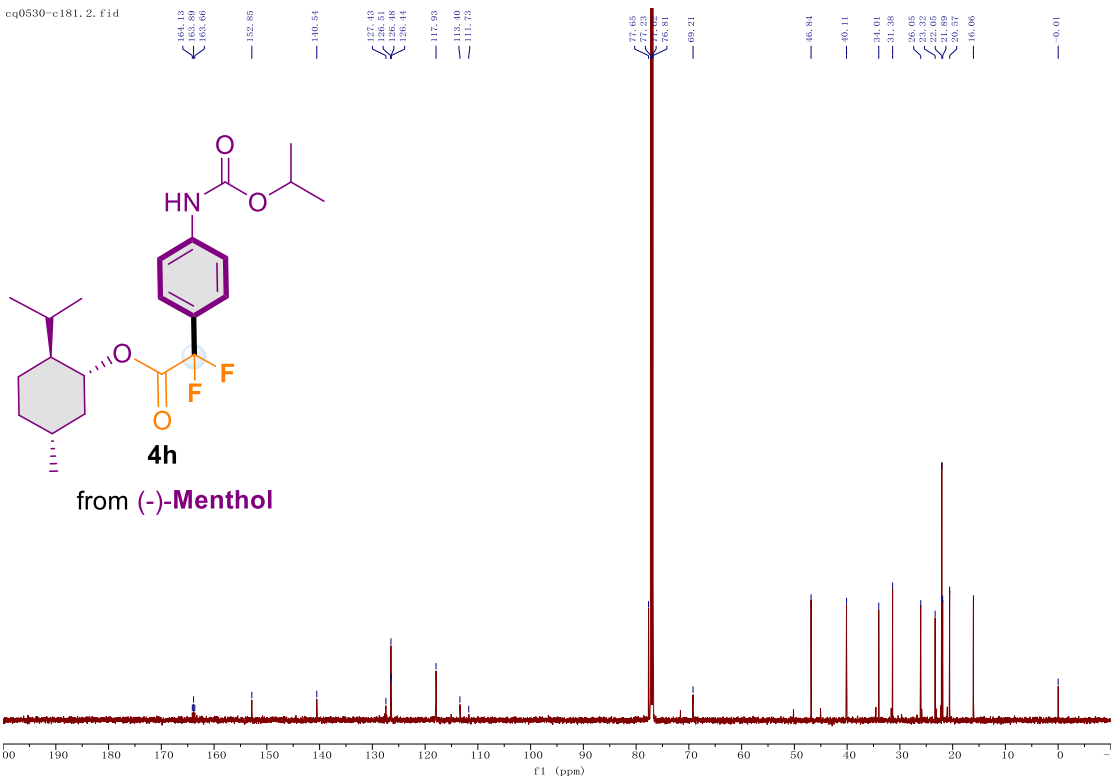
565 MHz ^{19}F NMR spectra of **4g** in $CDCl_3$.



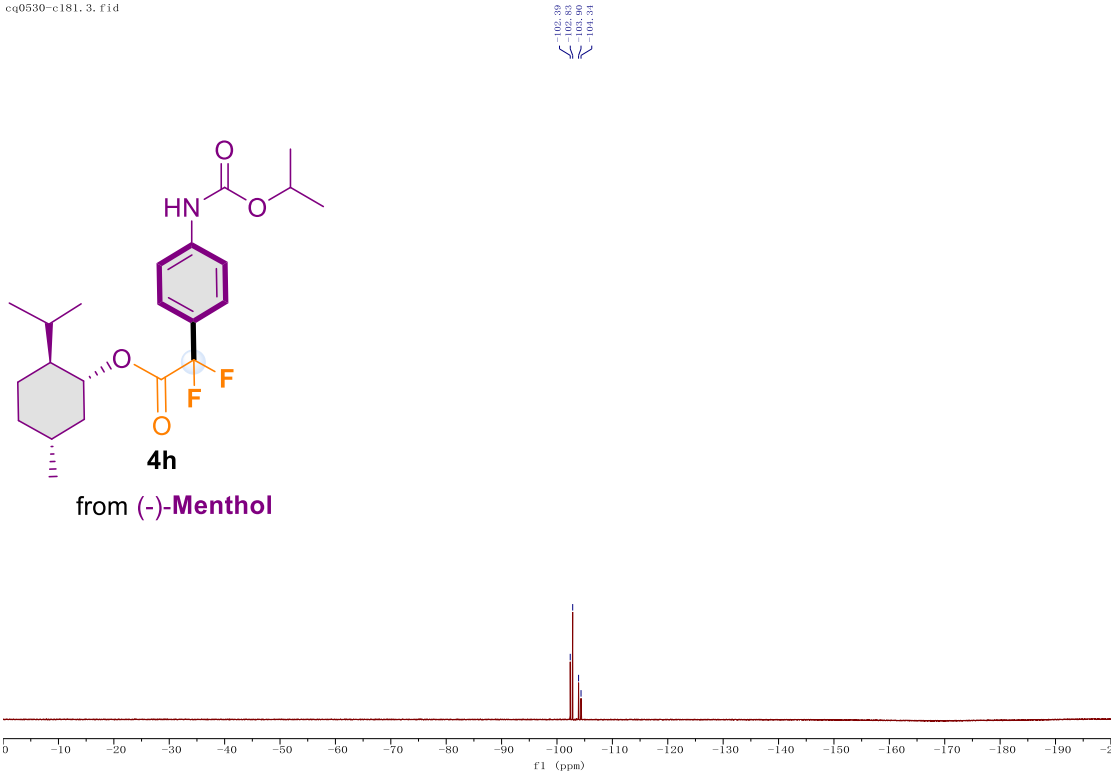
600 MHz ^{1}H NMR spectra of **4h** in $CDCl_3$.



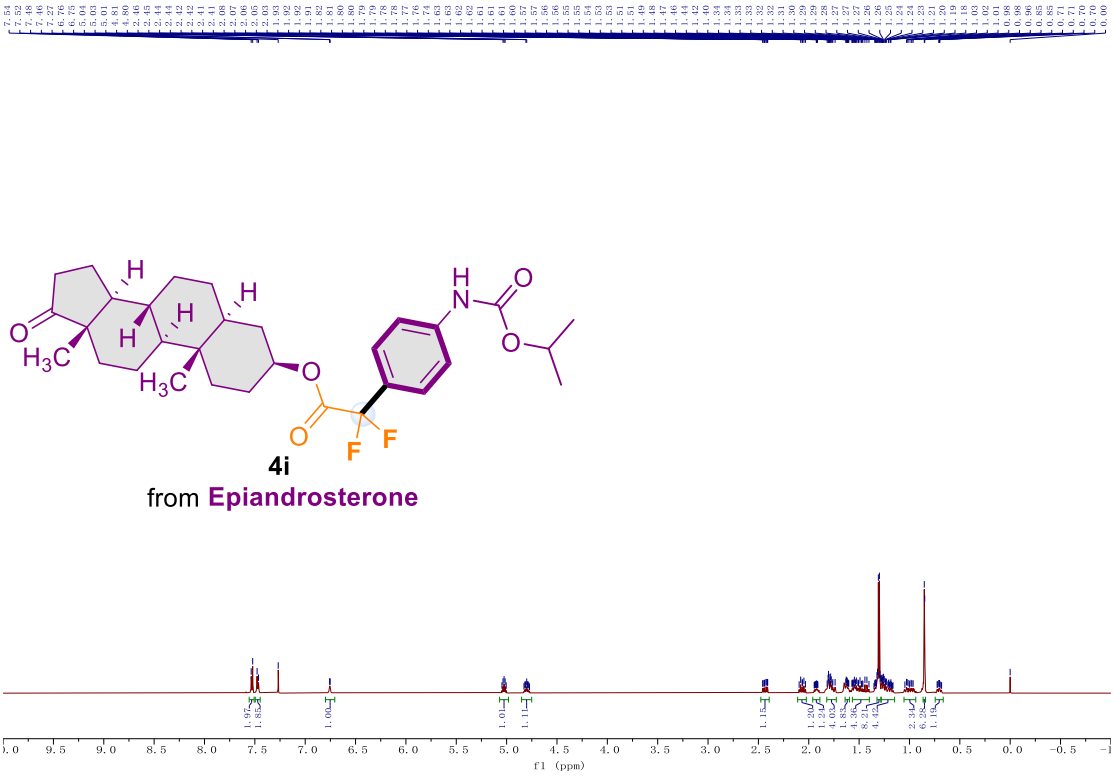
151 MHz ^{13}C NMR spectra of **4h** in $CDCl_3$.



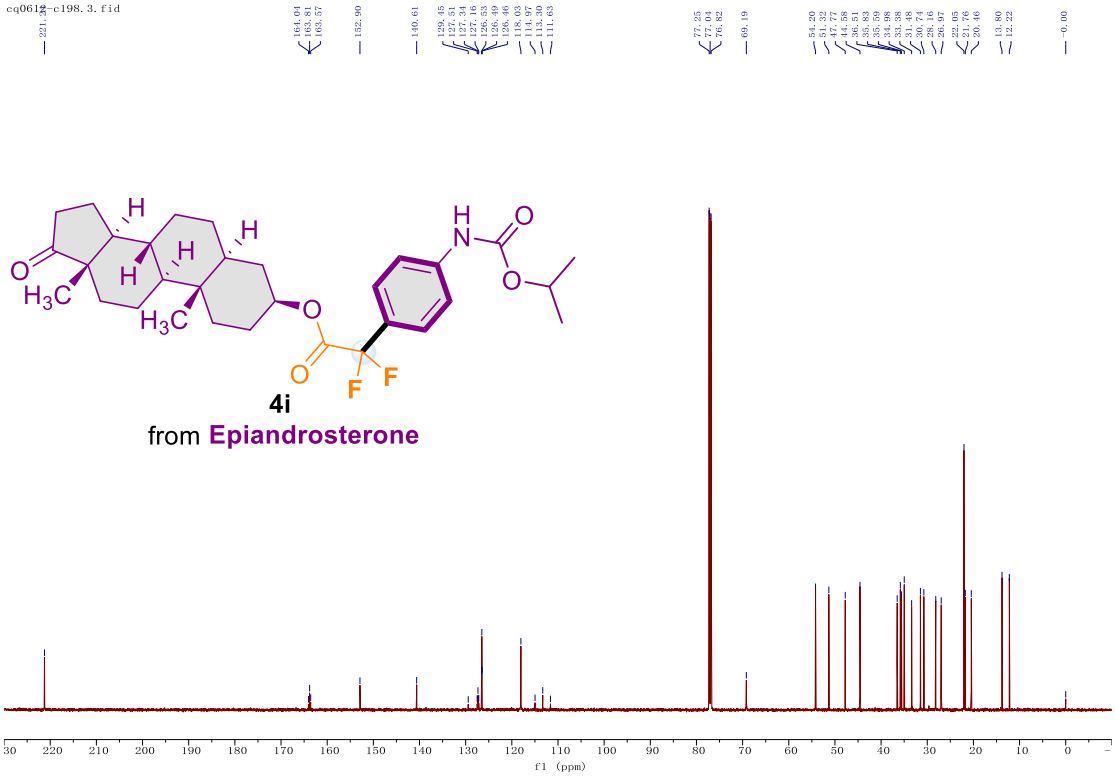
565 MHz ^{19}F NMR spectra of **4h** in $CDCl_3$.



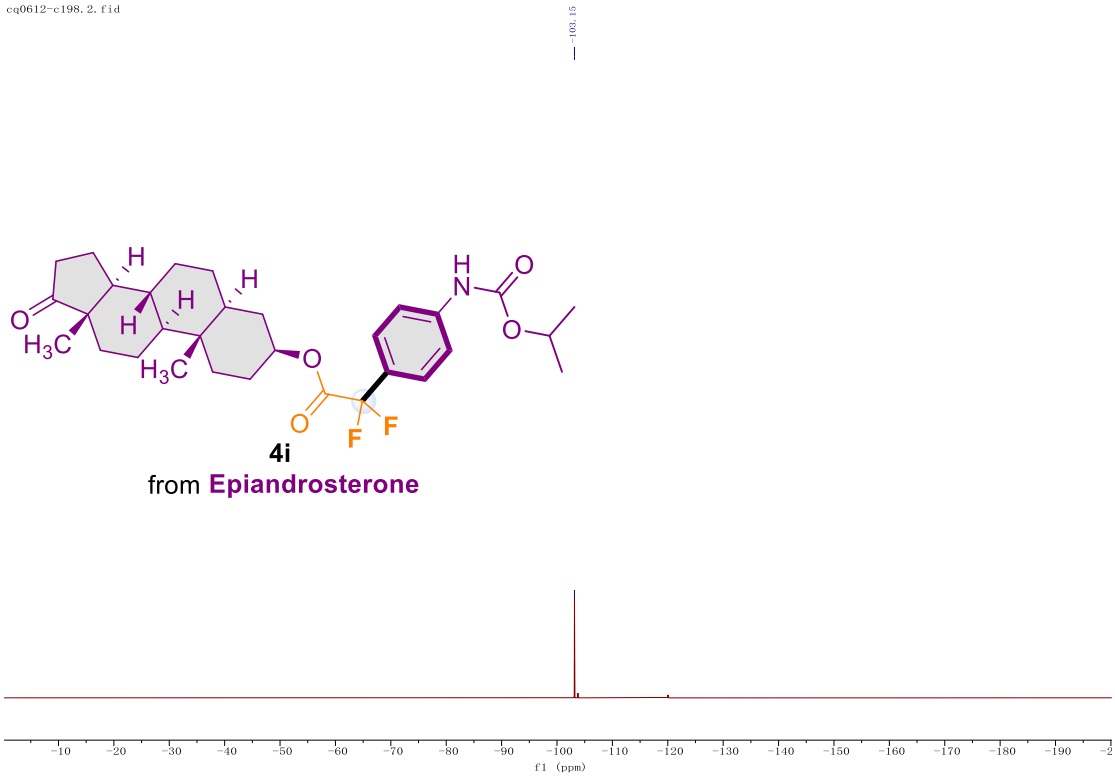
600 MHz ^{1}H NMR spectra of **4i** in $CDCl_3$.



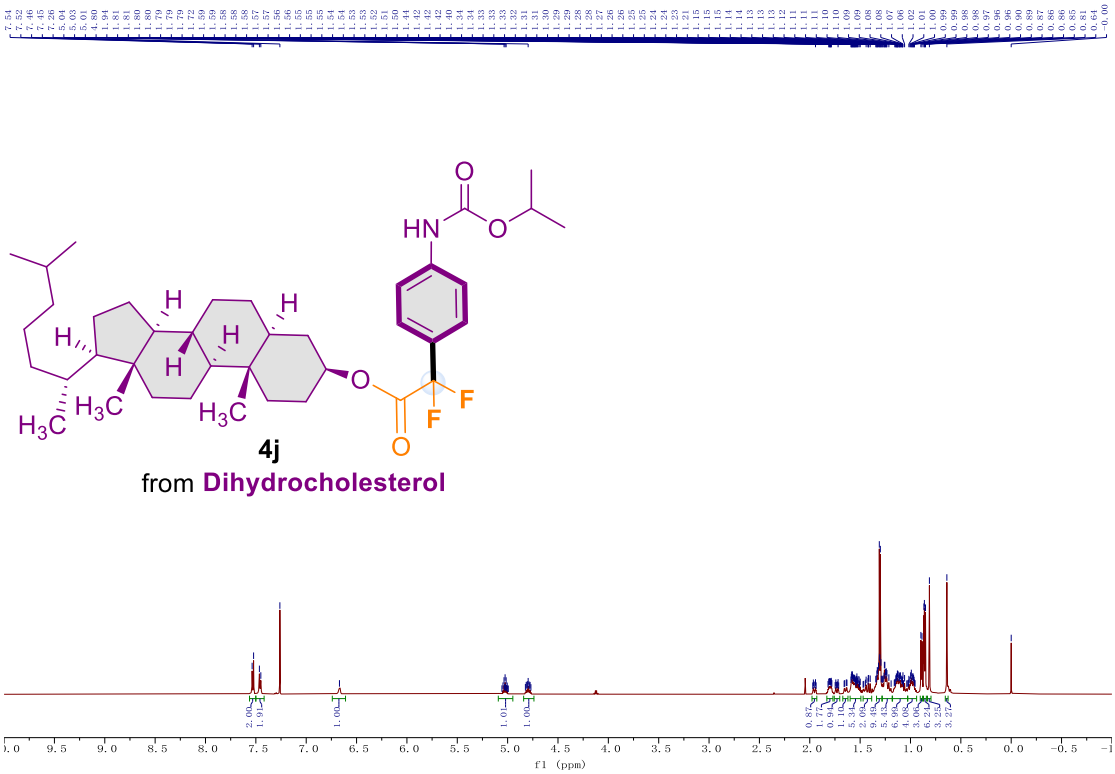
151 MHz ^{13}C NMR spectra of **4i** in $CDCl_3$.



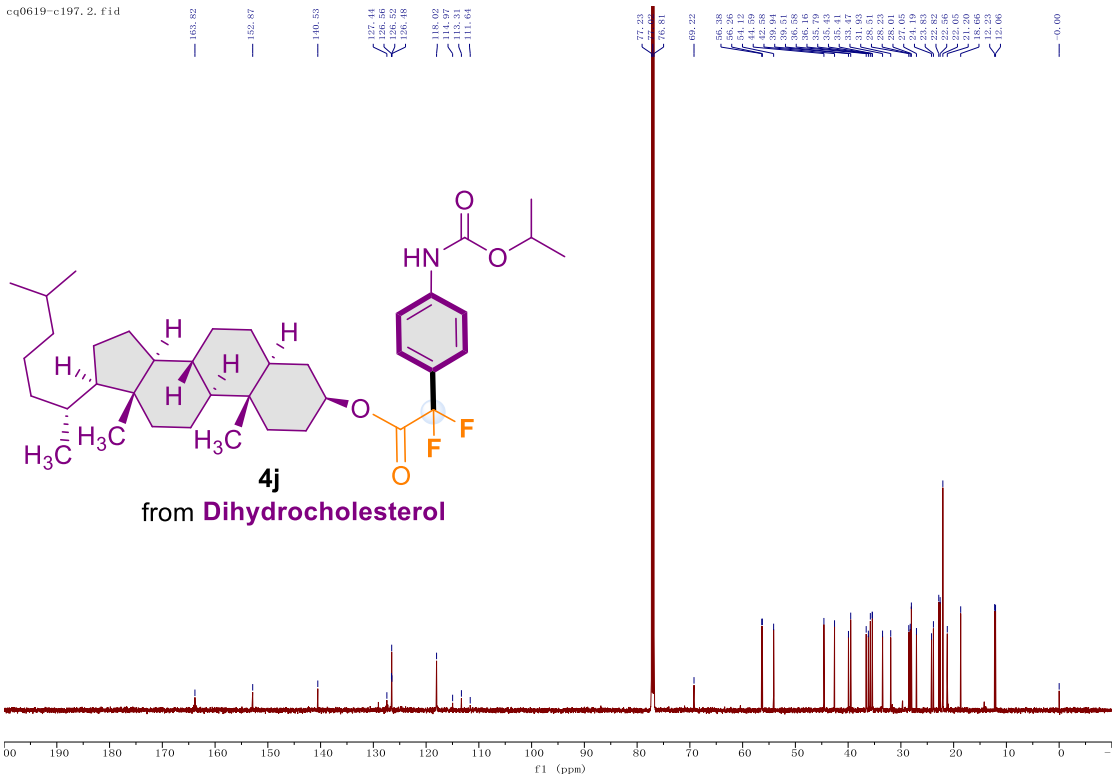
565 MHz ^{19}F NMR spectra of **4i** in $CDCl_3$.



600 MHz ^{1}H NMR spectra of **4j** in $CDCl_3$.



151 MHz ^{13}C NMR spectra of **4j** in $CDCl_3$.



565 MHz ^{19}F NMR spectra of **4j** in $CDCl_3$.