

Supporting Information

Photocatalytically switchable chemoselective difluoramidation of olefins for the synthesis of diversified difluoro- γ -lactams

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1. General information

Materials and General Experimental: Ethyl bromodifluoroacetate was purchased from Shanghai Shaoyuan Co. Sodium iodide and ammonium bromide were purchased from Maclean's. *fac*-Ir(ppy)₃ was purchased from Bidepharm. Unless otherwise stated, commercially available solvents and reagents were obtained from commercial suppliers without further purification. In addition, petroleum ether (b.p. 60-90 °C) used for column chromatography was distilled before use. Non-commercial starting materials were prepared as described below or according to literature procedures. Analytical thin layer chromatography (TLC) was performed using precoated silica gel HF254 glass plates. Column chromatography was performed using silica gel (200-300 mesh).

Instrumentation: Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Advance 400 MHz and 500 MHz spectrometer at ambient temperature using the non or partly deuterated solvent as internal standard (¹H: δ 7.26 ppm and ¹³C{¹H}: δ 77.0 ppm for CDCl₃, ¹H: δ 2.50 ppm and ¹³C{¹H}: δ 40.0 ppm for DMSO-*d*₆). Chemical shifts (δ) are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). The coupling constants (*J*) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or combinations thereof. High resolution mass spectra were obtained on Thermo Scientific Q-Exactive (ESI mode, Q-Exactive Orbitrap MS system). Melting points were determined using SGW X-4 apparatus and not corrected. The X-ray diffraction data for the crystallized compound were collected on a Bruker Smart APEX CCD area detector diffractometer (graphite monochromator, Mo Kα radiation, λ = 0.71073 Å) at 296(2) K.

2. Experimental Procedures

2.1 General procedure for the catalytic process

2.1.1 General synthesis steps for product series 2. (2a as an example)

The following ingredients should be added to the 25 mL Schlenk tube: Na₂CO₃ (63.6 mg, 0.6 mmol, 3.0 equiv), NaI (89.9 mg, 0.6 mmol, 3.0 equiv), and *fac*-Ir(ppy)₃ (1.2 mg, 0.002 mmol, 1% mmol). After vacuuming and backfilling three times with argon, DMSO (2.0 mL) was added through a 5 mL syringe. Through a 100 μL microinjector, *N*-vinyl bromodifluoroacetamide (57.6 mg, 0.2 mmol, 1.0 equiv) was added to the reaction mixture. Under the irradiation of a 460 nm 30 W blue LED, the mixture was stirred at room temperature for 24 hours. After the reaction was complete (TLC monitoring), 50 mL water was added and then extracted three times with 3×50 mL ethyl acetate. The organic phase was dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel 200-300 mesh, petroleum ether/ethyl acetate = 10:1-5:1) led to the corresponding product **2a** being obtained.

2.1.2 General synthesis steps for product series 3. (3a as an example)

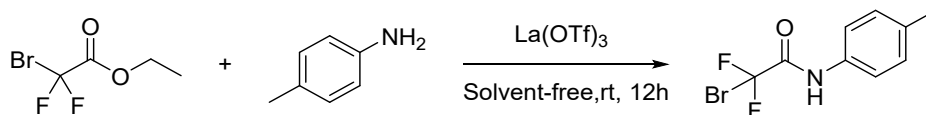
The following ingredients should be added to the 25 mL Schlenk tube: 4DPAIPN (1.6 mg, 0.002 mmol, 1% mmol). After vacuuming and backfilling three times with argon, THF (2.0 mL) was added through a 5mL syringe. Through a 100 μ L microinjector, *N*-vinyl bromodifluoroacetamide (57.6 mg, 0.2 mmol, 1.0 equiv.) was added to the reaction mixture. Under the irradiation of a 460 nm 30 W blue LED, the mixture was stirred at room temperature for 24 hours. After the reaction was complete (TLC monitoring), 50 mL water was added and then extracted three times with 3 $\times$ 50 mL ethyl acetate. The organic phase was dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel 200-300 mesh, petroleum ether/ethyl acetate = 10:1-5:1) led to the corresponding product **3a** being obtained.

2.1.3 General synthesis steps for product series 4 and 5. (4a as an example)

The following ingredients should be added to the 25 mL Schlenk tube: NaI (74.9 mg, 0.5 mmol, 2.5 equiv) and *fac*-Ir(ppy)₃ (1.2 mg, 0.002 mmol, 1% mmol). After vacuuming and backfilling three times with argon, MeCN (2.0 mL) was added through a 5mL syringe. Through a 100 μ L microinjector, *N*-vinyl bromodifluoroacetamide (57.6 mg, 0.2 mmol, 1.0 equivalent) was added to the reaction mixture. Under the irradiation of a 460 nm 30 W blue LED, the mixture was stirred at room temperature for 24 hours. After the reaction was complete (TLC monitoring), 50 mL water was added and then extracted three times with 3 $\times$ 50 mL ethyl acetate. The organic phase was dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel 200-300 mesh, petroleum ether/ethyl acetate = 10:1-5:1) led to the corresponding product **4a** being obtained.

2.2 Synthesis of starting materials

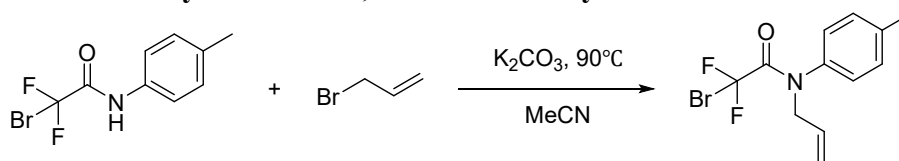
Preparation of the *N*-substituted-2-bromo-2,2-difluoroacetamide



Ethyl dibromodifluoroacetate (1212 mg, 6.0 mmol, 1.2 equiv), lanthanum trifluoromethanate La(OTf)₃ (147mg, 0.25mmol, 5mol%), and p-toluidine (535mg, 5.0 mmol, 1.0 equiv) were dissolved in 25 mL dry Schlenk tubes. Vacuum backfill with argon three times. The mixture was stirred at room temperature and monitored by thin layer chromatography. After the amine was consumed, 50 mL of water is added and the ethyl acetate is extracted three times. The organic phase is dried by anhydrous Na₂SO₄, filtered and condensed under reduced pressure. The crude product was purified by

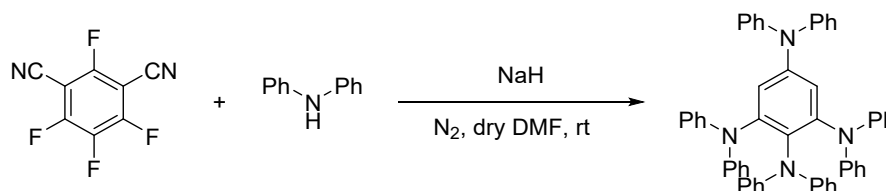
column chromatography (silica gel 200-300 mesh, petroleum ether/ethyl acetate = 10:1) to obtain the corresponding product.¹

Preparation of *N*-allyl-2-bromo-2,2-difluoro-*N*-arylacetamide



To a solution of 2-bromo-2, 2-difluoro-*N*-phenylacetamide (1.25 g, 5.0 mmol, 1.0 equiv) in CH₃CN, K₂CO₃ (2.07 g, 15 mmol, 3.0 equiv) and 3-bromopropene (1.21 g, 10 mmol, 2.0 equiv) were added. The reaction was stirred at 90°C for 12h. Extraction was carried out with ethyl acetate/water after the reaction. The organic phase was dried by anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. In order to obtain the corresponding product, the crude product was purified by column chromatography (silica gel 200-300 mesh, petroleum ether/ethyl acetate = 25:1).²

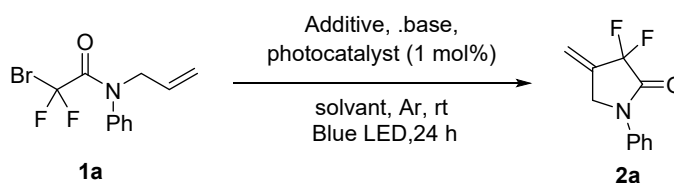
Synthesis of 2,4,5,6-tetrakis(diphenylamino)-isophthalonitrile (4DPAIPN)



Under Nitrogen atmosphere, a 25 mL heat-gun dried two-necked round-bottom flask was filled with dry DMF (5 mL) and diphenylamine (2.8 mmol, 474 mg, 6.0 equiv.) under inert atmosphere. NaH (60% suspension in mineral oil, 3.75 mmol, 150 mg, 8.0 eq.) was slowly added and the mixture was stirred at 60 °C for 5 hours. 2,4,5,6-tetrafluoroisophthalonitrile (0.45 mmol, 93.5 mg, 1 equiv.) was added and the reaction mixture was stirred at 90 °C for 8 hours. After that, the solution was cooled to 0°C and water (3 mL) was slowly added to quench the reaction. A yellow precipitate appeared upon addition of MeOH (10 mL) and was collected by filtration. The solid was redissolved in DCM (10 mL) and reprecipitated by the addition of MeOH (10 mL) to afford the desired clean product.³

2.3 Reaction Optimization

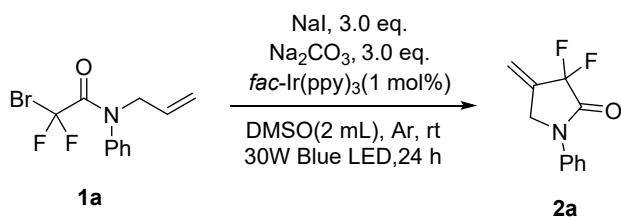
Table S1 Optimization of reaction conditions for preparation 2a^{a, b}



Entry	Photocatalysts	Blue LED	Solvent	Base	Atmosphere	Additive	Yield 2a
1	<i>fac</i>-Ir(ppy)₃	30W	DMSO	Na₂CO₃	Ar	NaI	78%
2	4CziPN	30W	DMSO	Na ₂ CO ₃	Ar	NaI	48%
3	[Acr ⁺ -Mes][ClO ₄ ⁻]	30W	DMSO	Na ₂ CO ₃	Ar	NaI	NR
4	Eosion Y	30W	DMSO	Na ₂ CO ₃	Ar	NaI	53%
5	Rh-6G	30W	DMSO	Na ₂ CO ₃	Ar	NaI	NR
6	methylene blue	30W	DMSO	Na ₂ CO ₃	Ar	NaI	NR
7	<i>fac</i> -Ir(ppy) ₃	6W	DMSO	Na ₂ CO ₃	Ar	NaI	62%
8	<i>fac</i> -Ir(ppy) ₃	8W	DMSO	Na ₂ CO ₃	Ar	NaI	70%
7	<i>fac</i> -Ir(ppy) ₃	30W	DMAC	Na ₂ CO ₃	Ar	NaI	46%
9	<i>fac</i> -Ir(ppy) ₃	30W	DCE	Na ₂ CO ₃	Ar	NaI	trace
10	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	Na ₂ CO ₃	Ar	NaI	N.D.
11	<i>fac</i> -Ir(ppy) ₃	30W	1,4-Dioxane	Na ₂ CO ₃	Ar	NaI	N.D.
12	<i>fac</i> -Ir(ppy) ₃	30W	THF	Na ₂ CO ₃	Ar	NaI	N.D.
13	<i>fac</i> -Ir(ppy) ₃	30W	DCM	Na ₂ CO ₃	Ar	NaI	N.D.
14	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Et ₃ N	Ar	NaI	45%
15	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	DIPEA	Ar	NaI	60%
16	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	PMDET A	Ar	NaI	48%
17	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	NaHCO ₃	Ar	NaI	53%
18	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	K ₂ CO ₃	Ar	NaI	70%
19	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	K ₃ PO ₄	Ar	NaI	43%
20	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Na ₂ CO ₃	Ar	TBAI	53%
21	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Na ₂ CO ₃	Ar	KI	29%
22	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Na ₂ CO ₃	Ar	NH ₄ I	20%
23	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Na ₂ CO ₃	Ar	NIS	NR
24	<i>fac</i> -Ir(ppy) ₃	30W	DMSO	Na ₂ CO ₃	O ₂	NaI	13%

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), additive (0.6 mmol, 3.0 equiv.), base (0.6 mmol, 3.0 equiv.), Photocatalysts (1 mol%), solvent (2.0 mL), room temperature, blue LEDs, 24 h. ^b Isolated yields. Et₃N: triethylamine; DIPEA: *N,N*-diisopropylethylamine; PMDETA: *N,N,N',N',N''*-pentamethyldiethylenetriamine. N.D.: Not Detected.

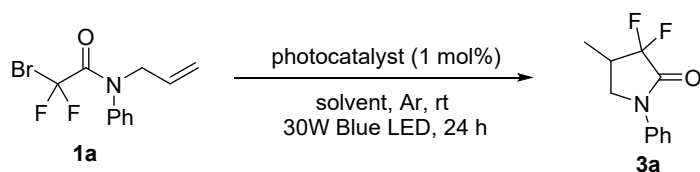
Table S2 Control experiments ^{a, b}



Entry	[Ir]	NaI	Na ₂ CO ₃	Ar	light	Yield 2a
1	-	+	+	+	+	NR
2	+	-	+	+	+	NR
3	+	+	-	+	+	NR
4	+	+	+	-	+	23%
5	+	+	+	+	-	NR

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), NaI (0.6 mmol, 3.0 equiv.), Na₂CO₃ (0.6 mmol, 3.0 equiv.), *fac*-Ir(ppy)₃ (1 mol%), DMSO (2.0 mL), room temperature, argon atmosphere, blue LEDs 30W, 24 h. ^b Isolated yields.

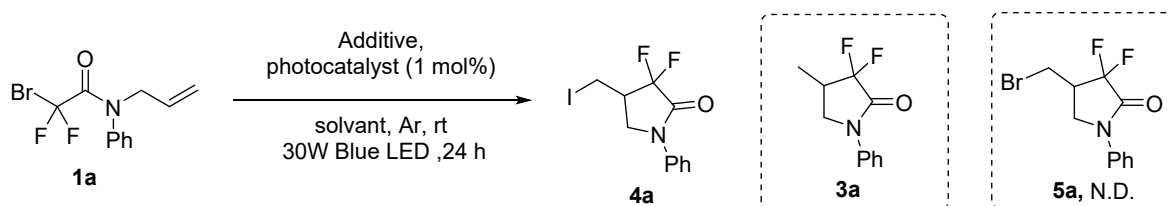
Table S3 Optimization of reaction conditions for preparation **3a^{a, b}**



Entry	Photocatalysts	Solvent	Yield 3a (%)
1	<i>fac</i> -Ir(ppy) ₃	MeCN:H ₂ O=2:1	46
2	<i>fac</i> -Ir(ppy) ₃	MeCN:H ₂ O=1:1	23
4	<i>fac</i> -Ir(ppy) ₃	THF	80
5	<i>fac</i> -Ir(ppy) ₃	Isopropanol	35
6	<i>fac</i> -Ir(ppy) ₃	EtOH	N.D.
7	Eosin Y	THF	65
8	Na ₂ Eosin Y	THF	71
9	Rh-6G	THF	80
10	4DPAIPN	THF	85
11	DCQ	THF	57
12	<i>fac</i> -Ir(ppy) ₃	THF	80
13	4CziPN	THF	71
14	[Acr ⁺ -Mes][ClO ₄ ⁻]	THF	59

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.). Photocatalysts (1 mol %), solvent (2.0 mL), room temperature, argon atmosphere, blue LEDs 30W, 24 h. ^b Isolated yields. N.D.: Not Detected.

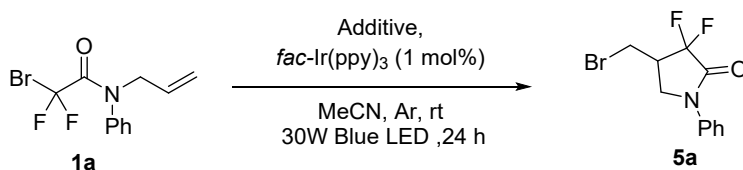
Table S4 Optimization of reaction conditions for preparation **4a^{a, b}**



Entry	Photocatalysts (1%)	Solvent (0.1M)	Additive (2.5 eq)	Yield 3a (%)	Yield 4a (%)
1	<i>fac</i> -Ir(ppy) ₃	DMSO	NaI	N.D.	65
2	Eosin Y	DMSO	NaI	N.D.	N.D.
3	4CziPN	DMSO	NaI	N.D.	25
4	[Ir{dFCF ₃ ppy} ₂ (bpy)]PF ₆	DMSO	NaI	N.D.	N.D.
5	EosinY Na	DMSO	NaI	N.D.	N.D.
6	Rh-6G	DMSO	NaI	N.D.	N.D.
7	Methylene Blue	DMSO	NaI	N.D.	N.D.
8	Mes-Acr+ClO ₄ ⁻	DMSO	NaI	N.D.	N.D.
7	<i>fac</i> -Ir(ppy) ₃	DMSO	KI	N.D.	60
9	<i>fac</i> -Ir(ppy) ₃	DMSO	NH ₄ I	N.D.	17
10	<i>fac</i> -Ir(ppy) ₃	DMSO	TBAI	N.D.	20
11	<i>fac</i> -Ir(ppy) ₃	DMSO	NIS	N.D.	N.D.
12	<i>fac</i> -Ir(ppy) ₃	DMSO	NaI	N.D.	65
13	<i>fac</i> -Ir(ppy) ₃	DMSO	NaI	N.D.	65%
14	<i>fac</i> -Ir(ppy) ₃	DMF	NaI	17%	53%
15	<i>fac</i>-Ir(ppy)₃	MeCN	NaI	N.D.	72%
16	<i>fac</i> -Ir(ppy) ₃	MeOH	NaI	N.D.	30%
17	<i>fac</i> -Ir(ppy) ₃	DCM	NaI	16%	25%
18	<i>fac</i> -Ir(ppy) ₃	MeCN ^c	NaI	N.D.	40
19	<i>fac</i> -Ir(ppy) ₃	MeCN ^d	NaI	N.D.	58
20	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI ^e	N.D.	72
21	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI ^f	N.D.	67
22	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI ^g	N.D.	69
23 ^h	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI	47%	N.D.
24 ⁱ	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI	55%	N.D.
25 ^j	<i>fac</i> -Ir(ppy) ₃	MeCN	NaI	42%	trace

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), additive (0.5 mmol, 2.5 equiv.), Photocatalysts (1 mol %), solvent (2.0 mL), room temperature, argon atmosphere, blue LEDs 30W, 24 h. ^b Isolated yields. ^c solvent 3.0 mL. ^d solvent 4.0 mL. ^e additive (3.0 equiv.), ^f additive (3.5 equiv.), ^g additive (4.0 equiv.), ^h *N,N,N',N'*-Tetramethylethylenediamine with 1.0 eq added, ⁱ Pentamethyldiethylenetriamine with 1.0 eq added, ^j DBU with 1.0 eq added. N.D.: Not Detected.

Table S5 Optimization of reaction conditions for preparation 5a^{a, b}



Entry	Photocatalysts	Blue LED	Solvent	Additive	Yield 5a (%)
1	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	NaBr	63
2	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	LiBr	46
3	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	KBr	29
4	<i>fac</i>-Ir(ppy)₃	30W	MeCN	NH₄Br	73
5	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	TBAB	40
6	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	NBS	N.D.
7	<i>fac</i> -Ir(ppy) ₃	30W	MeCN	-	45

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv.), additive (0.5 mmol, 2.5 equiv.), *fac*-Ir(ppy)₃ (1 mol %), MeCN (2.0 mL), room temperature, argon atmosphere, blue LEDs 30W, 24 h. ^b Isolated yields. N.D.: Not Detected.

3. X-Ray Crystal Structure and Crystallographic Data

The purified compound **2d** is dissolved in dichloromethane and petroleum ether, and placed in a dark cabinet to slowly evaporate. After several days, a yellow bulk crystal is obtained. The X-ray crystal-structure determinations were obtained on a Bruker Smart APEX CCD area detector diffractometer at 296(2) K.

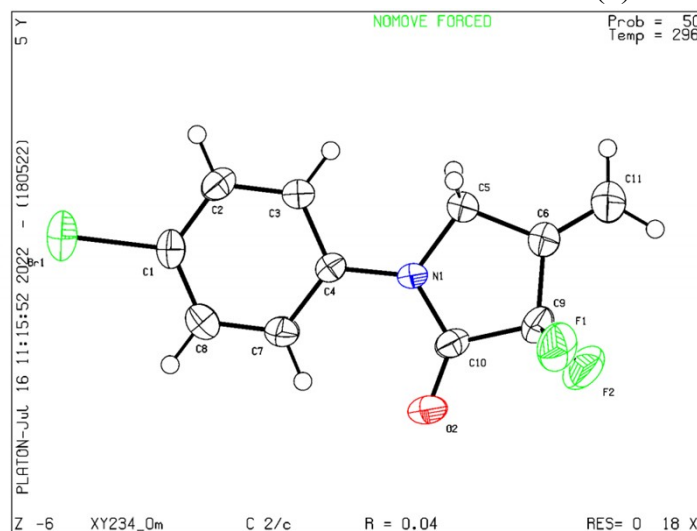


Table S6. Crystal data and structure refinement for compound 2d.

Identification code	CCDC: 2412290
Empirical formula	C ₁₁ H ₈ BrF ₂ NO
Formula weight	286.97
Temperature/K	296 (2)
Crystal system	monoclinic
Space group	C2/c
a/Å	23.396(10)
b/Å	6.177(3)
c/Å	16.234(7)
α /°	90
β /°	111.845(6)
γ /°	90
Mr	288.08
Volume/Å ³	2177.6(17)
Z	8
Dx,g /cm ³	1.758
Mu/mm ⁻¹	3.779
F (000)	1136.0
F000'	1134.37
h,k,lmax	30,8,21
Nref	2509
Tmin,Tmax	0.493,0.546
Tmin'	0.483
Data completeness	0.992
Theta(max)	27.556
R(reflections)	0.0442(1787)
wR2(reflections)	0.1137(2490)
S	1.091
Npar	145

4. Emission quenching experiments (Stern-Volmer Studies)

All fluorescence measurements were recorded using a Hitachi FL-7000 Fluorometer. All fluorescein solution were irradiated 282nm approximately and the emission intensity from 350 nm to 650 nm was recorded by F-7000 FL Spectrophotometer. In this section, a 4 mL solution of *fac*-Ir(ppy)₃ in DMSO (0.002 mmol/mL) was added **1a** (0.04 mmol, 0.08 mmol, 0.16 mmol,

0.32 mmol in turn) 、NaI (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn) 、 Na_2CO_3 (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn). Then the emission intensity was collected and the results were presented in Figure S1-S4

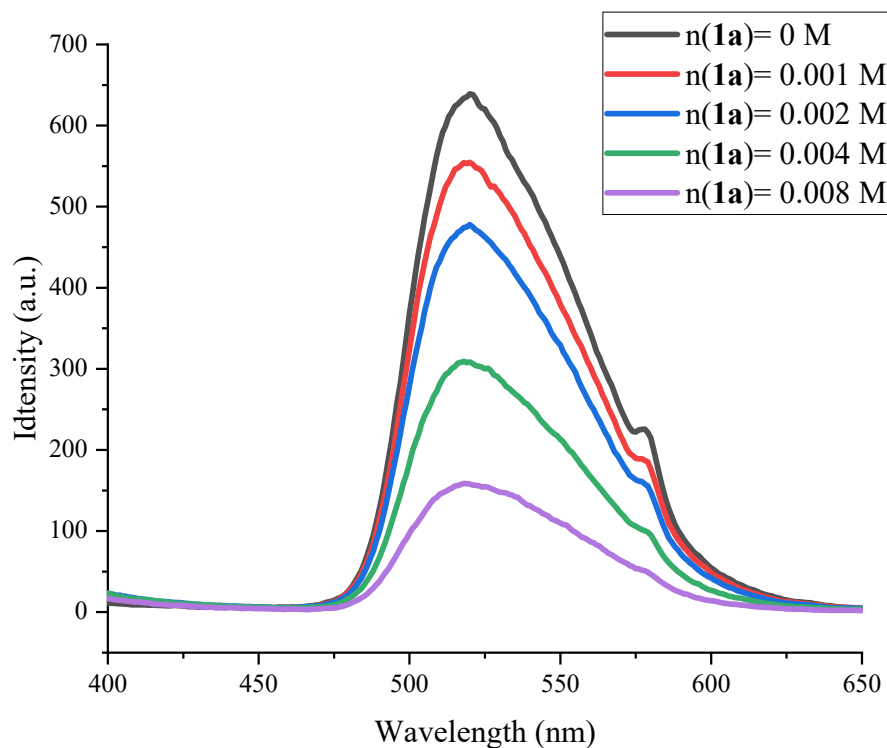


Figure S1: Fluorescence quenching of *fac*-Ir(ppy)₃ in DMSO by **1a**

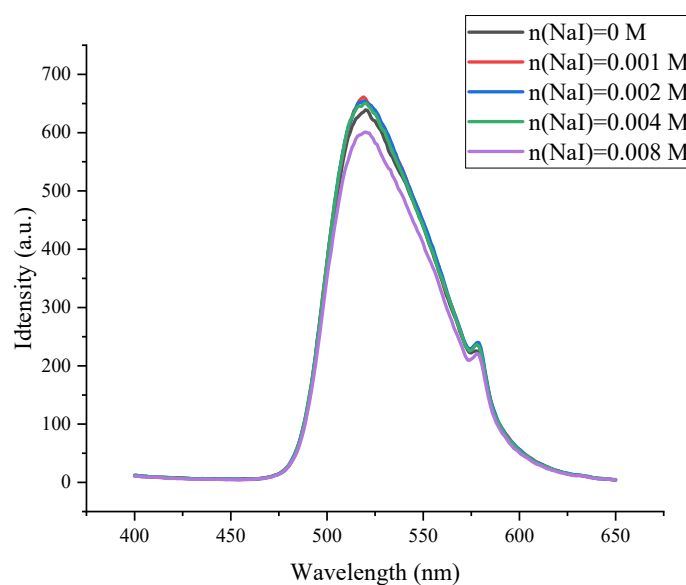


Figure S2: Fluorescence quenching of *fac*-Ir(ppy)₃ in DMSO by NaI

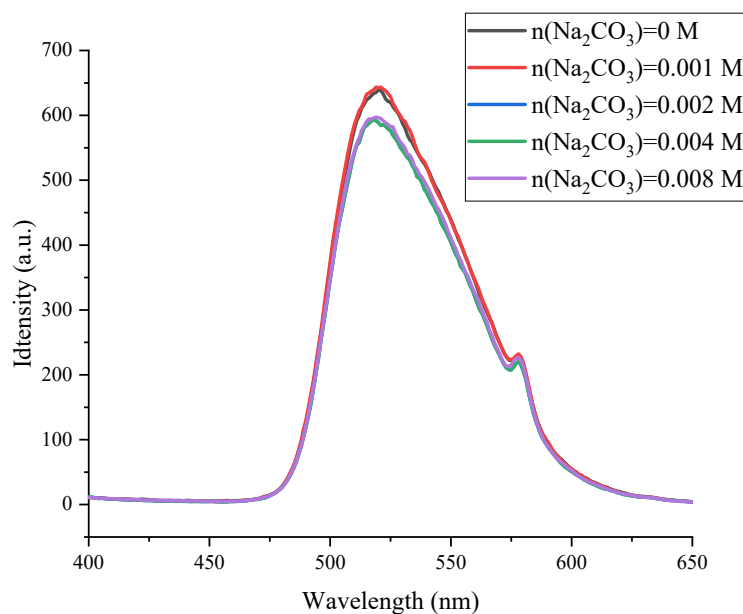


Figure S3: Fluorescence quenching of *fac*-Ir(ppy)₃ in DMSO by Na₂CO₃

An indeed fluorescence quenching phenomenon of fluorescein under various concentrations of **1a** or NaI or Na₂CO₃ was demonstrated in a curve of [I₀/I] vs [Concentration], as shown in Figure S4.

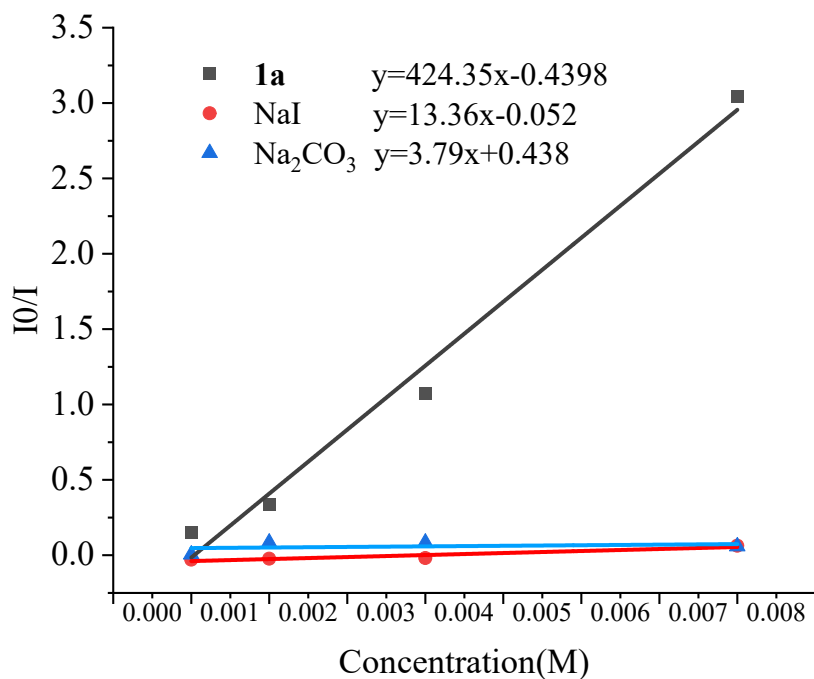


Figure S4: Stern-Volmer plot of Fluorescein in DMSO by **1a**, NaI or Na₂CO₃

In this section, a 4 mL solution of *fac*-Ir(ppy)₃ in MeCN (0.002 mmol/mL) was added **1a** (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn) · NaI (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn) · NH₄Br (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn). Then the emission

intensity was collected and the results were presented in Figure S5-S8

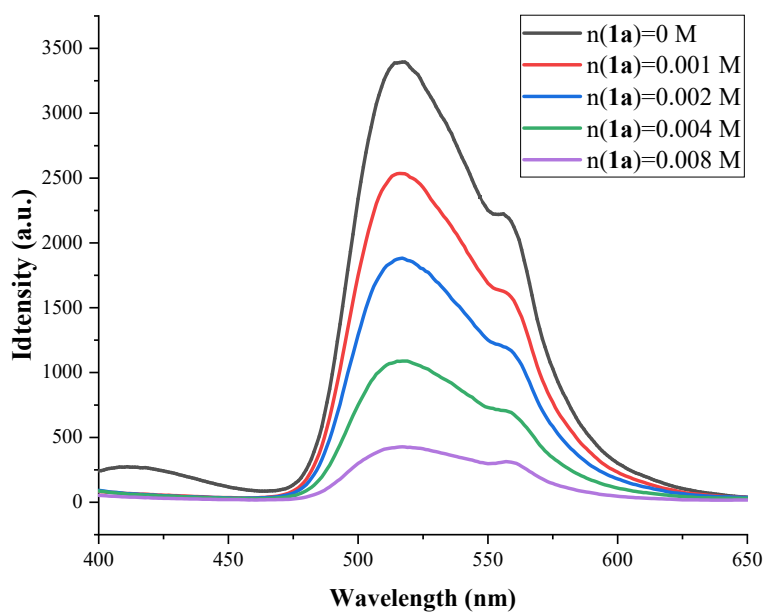


Figure S5: Fluorescence quenching of *fac*-Ir(ppy)₃ in MeCN by **1a**

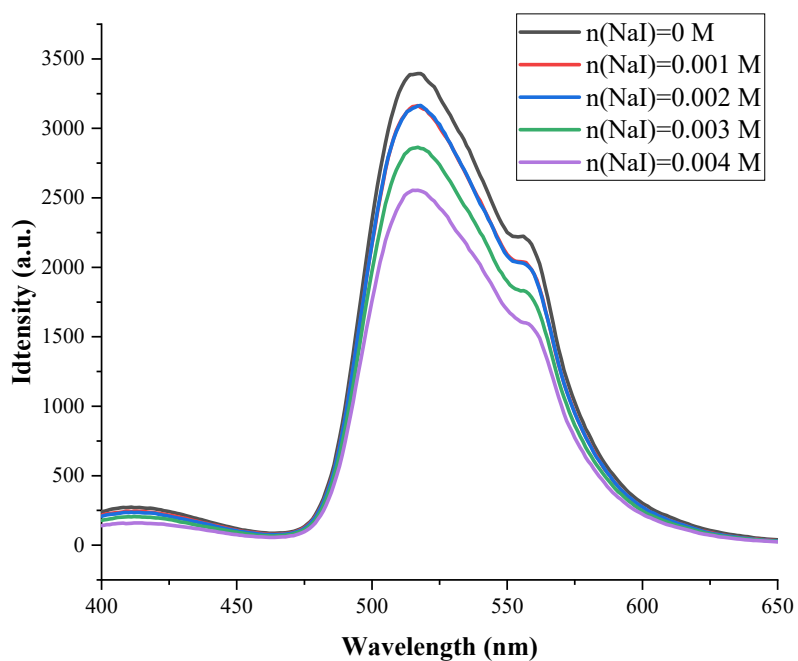


Figure S6: Fluorescence quenching of *fac*-Ir(ppy)₃ in MeCN by NaI

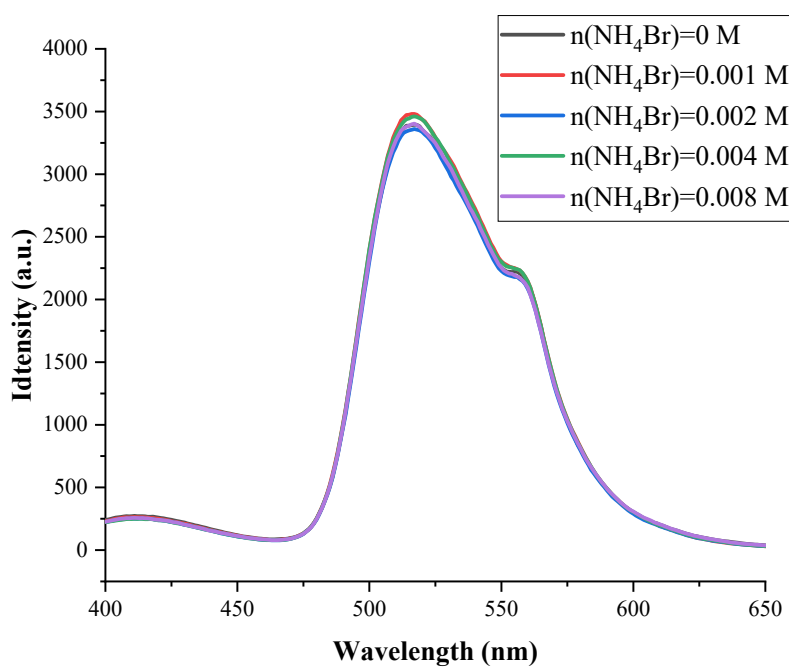


Figure S7: Fluorescence quenching of *fac*-Ir(ppy)₃ in MeCN by NH₄Br

An indeed fluorescence quenching phenomenon of fluorescein under various concentrations of **1a** or NaI or NH₄Br was demonstrated in a curve of [I₀/I] vs [Concentration], as shown in Figure S8.

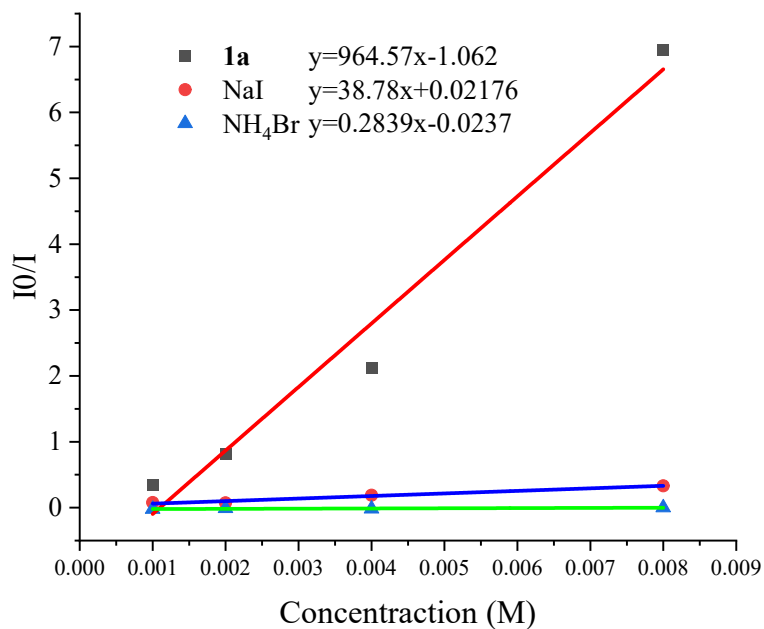


Figure S8: Stern-Volmer plot of Fluorescein in MeCN by **1a**, NaI or NH₄Br

In this section, a 4 mL solution of 4DPAIPN in THF (0.002 mmol/mL) was added **1a** (0.04 mmol, 0.08 mmol, 0.16 mmol, 0.32 mmol in turn). Then the emission intensity was collected and

the results were presented in Figure S9-S10

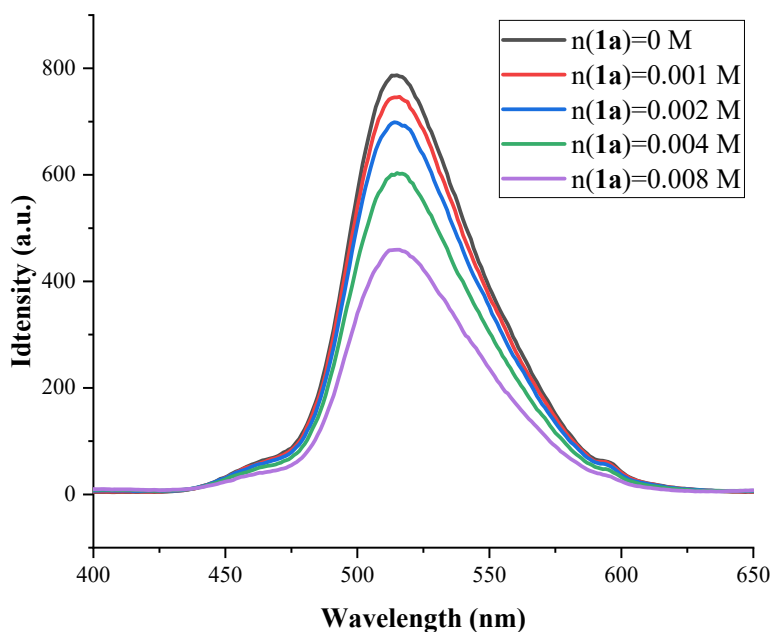


Figure S9: Fluorescence quenching of 4DPAIPN in THF by **1a**

An indeed fluorescence quenching phenomenon of fluorescein under various concentrations of **1a** was demonstrated in a curve of $[I_0/I]$ vs [Concentration], as shown in Figure S10.

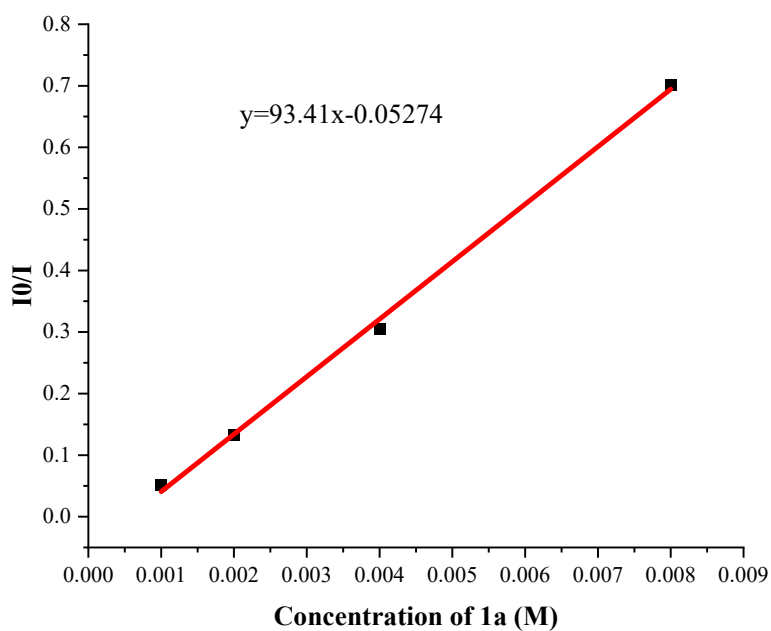


Figure S10: Stern-Volmer plot of Fluorescein in THF by **1a**

5. Cyclic Voltametric experiments

Cyclic Voltametric experiments were conducted on a “IKA ElectraSyn 2.0 pro Package” in a three-electrode cell at room temperature ($25 \pm 2^\circ\text{C}$) using Glassy carbon electrode working electrode, Ag/AgCl electrode (3M KCl) as reference electrode, a platinum electrode as the counter electrode. Prior to the measurement, the solution was purged with Ar, and the glassy carbon electrode was rotated to homogenize the probe solution. The testing solution was prepared by dissolving the sample (**1a**, 0.05 mmol) into MeCN (5 mL) with 0.1 M tetrabutylammonium hexafluorophosphate (TBAPF₆) for CV study. The potential was scanned back and forward linearly between -2.5 and 2.5 V at a 100 mV/s scan rate. Throughout the measurement process, the solution was shielded by a positive N₂ stream⁴. The CV experiments of all the forms of the substrates were carried out following the aforementioned procedure and the diagrams are depicted as follows:

Cyclic voltammetry studies showed that the reduction of *N*-allyl difluorobromoacetamide **1a** occurs at -1.40 V with a significant peak current. The above experimental data show that the excited photocatalysts *Ir(III) ($E^*_{\text{red}} = -1.73$ V, VS. SCE) and *4DPAIPN ($E^*_{\text{red}} = -1.52$ V, vs. SCE) can undergo a single electron transfer process with reactant **1a** ($E^*_{\text{red}} = -1.40$ V vs. SCE in MeCN).

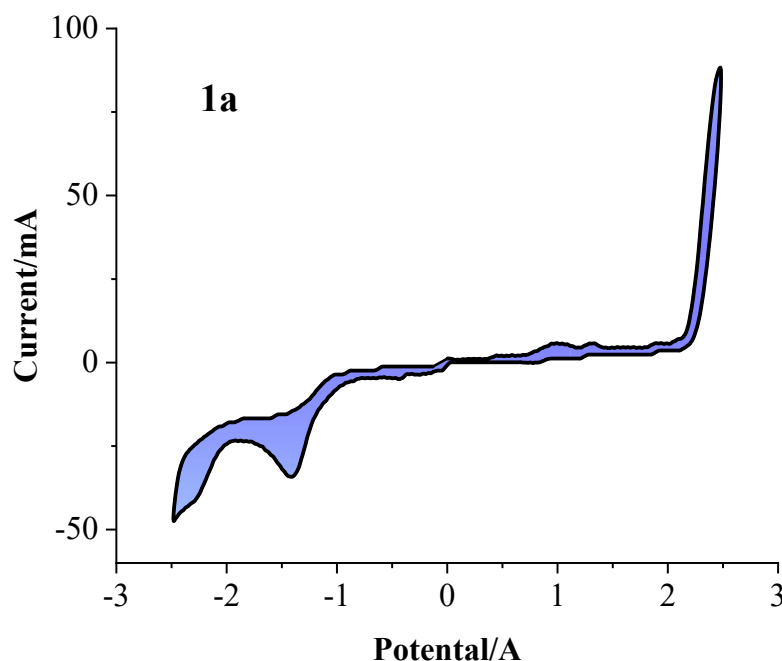
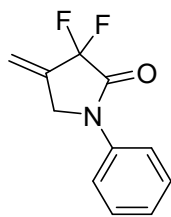


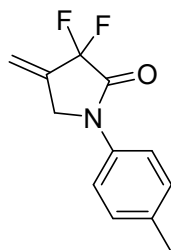
Figure S11. Cyclic voltammogram of **1a** (0.1 mmol vs Ag/AgNO₃), scan rate 100 mV/s.

6. Characterization of Products



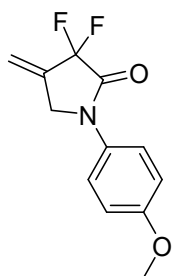
2a

3,3-Difluoro-4-methylene-1-phenylpyrrolidin-2-one (2a), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 36mg 78%, white solid, m.p.: 120-121 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.72 – 7.69 (m, 2H), 7.46 – 7.41 (m, 2H), 7.29 – 7.24 (m, 1H), 6.08 – 6.04 (m, 1H), 5.78 – 5.75 (m, 1H), 4.50 (t, $J = 2.1$ Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.94 (t, $J = 30.5$ Hz), 137.54, 132.65 (t, $J = 19.9$ Hz), 129.29, 126.42, 120.08, 118.27, 110.80 (t, $J = 246.6$ Hz), 48.37. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_9\text{F}_2\text{NNaO}$:232.0544; found:232.0540.



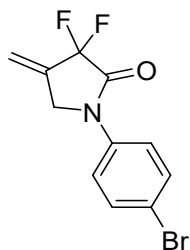
2b

3,3-Difluoro-4-methylene-1-(p-tolyl)pyrrolidin-2-one (2b), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 36mg 73%, white solid, m.p.: 128-129 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.63 – 7.54 (m, 3H), 7.26 – 7.20 (m, 4H), 6.05 (ddd, $J = 4.4, 2.1, 1.0$ Hz, 1H), 5.77 – 5.72 (m, 1H), 4.47 (t, $J = 2.1$ Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.77 (t, $J = 30.8$ Hz), 136.34, 135.03, 132.80 (t, $J = 19.9$ Hz), 129.79, 120.07, 118.13, 110.87 (t, $J = 246.2$ Hz), 48.46, 20.94. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{F}_2\text{NNaO}$:246.0701; found: 246.0697.



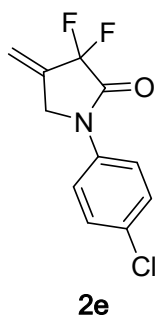
2c

3,3-Difluoro-1-(4-methoxyphenyl)-4-methylenepyrrolidin-2-one (2c), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 38 mg, 72%, white solid, m.p.: 122.5-123.7 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (d, J = 9.1 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 6.05 (s, 1H), 5.74 (s, 1H), 4.45 (t, J = 2.0 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.63 (t, J = 30.7 Hz), 157.82, 132.83 (t, J = 20.1 Hz), 130.58, 121.85, 118.08 (t, J = 2.3 Hz), 114.41, 110.89 (t, J = 246.3 Hz), 55.49, 48.72. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{F}_2\text{NNaO}_2$: 262.0650; found: 262.0645.

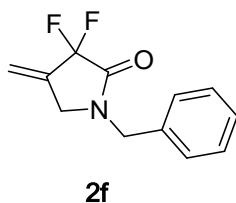


2d

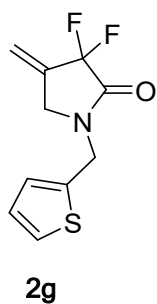
1-(4-Bromophenyl)-3,3-difluoro-4-methylenepyrrolidin-2-one (2d), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 42mg 68%, white solid, m.p.: 147-149 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.60 (m, 2H), 7.57 – 7.53 (m, 2H), 6.10 – 6.06 (m, 1H), 5.80 – 5.76 (m, 1H), 4.47 (t, J = 2.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.95 (t, J = 31.3 Hz), 136.60, 132.32, 121.40, 119.51, 118.65 (t, J = 3.2 Hz), 110.61 (t, J = 246.3 Hz), 48.21. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_8\text{BrF}_2\text{NNaO}$ calcd for: 309.9650; found: 309.9644.



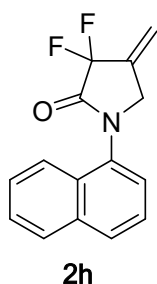
1-(4-Chlorophenyl)-3,3-difluoro-4-methylenepyrrolidin-2-one (2e), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 37mg 70%, white solid, m.p. : 143-145 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.70 – 7.66 (m, 2H), 7.43 – 7.38 (m, 2H), 6.09 – 6.06 (m, 1H), 5.80 – 5.77 (m, 1H), 4.48 (t, J = 2.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.94 (t, J = 31.0 Hz), 136.10, 132.23 (t, J = 20.2 Hz), 131.72, 129.36, 121.14, 118.62, 110.62 (t, J = 246.7 Hz), 48.29 (t, J = 2.8 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_8\text{ClF}_2\text{NNaO}$ calcd for: 266.0155; found: 266.0148.



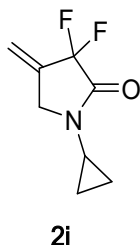
1-Benzyl-3,3-difluoro-4-methylenepyrrolidin-2-one (2f), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 26mg 52%, white solid, m.p.: 127-126 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.31 (m, 3H), 7.25 (d, J = 7.0 Hz, 2H), 5.97 – 5.90 (m, 1H), 5.60 – 5.54 (m, 1H), 4.59 (s, 2H), 3.88 (t, J = 2.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.99 (t, J = 30.3 Hz), 134.13, 133.36 (t, J = 20.2 Hz), 129.04, 128.38, 117.94, 111.05 (t, J = 247.3 Hz), 47.11, 46.51. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{11}\text{F}_2\text{NNaO}$ calcd for: 246.0701; found: 246.0694



3,3-Difluoro-4-methylene-1-(thiophen-2-ylmethyl)pyrrolidin-2-one (2g), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 28mg 55%, white solid, m.p.: 80-82 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.29 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.03 (d, *J* = 3.3 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.96 (s, 1H), 5.60 (s, 1H), 4.76 (s, 2H), 3.97 (t, *J* = 2.1 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 162.59 (t, *J* = 30.3 Hz), 135.93, 133.29 (t, *J* = 20.2 Hz), 127.92, 127.24, 126.48, 118.10 (t, *J* = 2.6 Hz), 110.94 (t, *J* = 247.4 Hz), 46.38, 41.37. HRMS (ESI): *m/z* [M+Na]⁺ C₁₀H₉F₂NNaOS calcd for: 252.0265; found: 252.0257

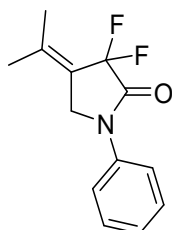


3,3-Difluoro-4-methylene-1-(naphthalen-1-yl)pyrrolidin-2-one (2h), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 20mg 40%, yellow solid, m.p.: 133-134 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.12 (dd, *J* = 14.6, 7.8 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 6.01 – 5.93 (m, 1H), 5.31 (d, *J* = 2.5 Hz, 1H), 5.28 (d, *J* = 2.6 Hz, 1H), 4.88 (d, *J* = 5.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 160.26 – 159.90 (m), 132.73, 131.83 (t, *J* = 2.6 Hz), 130.91, 127.03 (t, *J* = 2.6 Hz), 126.84, 126.14 (t), 124.08, 117.78, 112.35, 45.04. HRMS (ESI): *m/z* [M+H]⁺ C₁₅H₁₂F₂NO calcd for: 260.0881; found: 260.0676



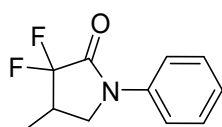
1-Cyclopropyl-3,3-difluoro-4-methylenepyrrolidin-2-one (2i), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 24mg 62%, Light yellow oil, ¹H NMR (500 MHz, CDCl₃) δ 5.95 – 5.92 (m, 1H), 5.63 – 5.59 (m, 1H),

3.95 (t, $J = 2.1$ Hz, 2H), 2.82 – 2.76 (m, 1H), 0.91 – 0.86 (m, 2H), 0.85 – 0.80 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.94 (t, $J = 30.1$ Hz), 133.59 (t, $J = 20.1$ Hz), 117.72 (t, $J = 2.6$ Hz), 111.20 (t, $J = 246.8$ Hz), 47.50 (t, $J = 2.0$ Hz), 26.00, 5.03. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_8\text{H}_9\text{F}_2\text{NNaO}$ calcd for: 196.0544; found: 196.0542



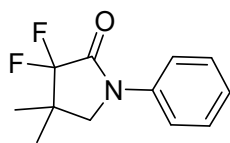
2j

3,3-Difluoro-1-phenyl-4-(propan-2-ylidene)pyrrolidin-2-one (2j), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 32mg 62%, white solid, m.p.: 142-145 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, $J = 7.8$ Hz, 2H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 9.1$ Hz, 1H), 4.39 (s, 2H), 2.10 (s, 3H), 1.87 (t, $J = 4.0$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.84 (t, $J = 31.4$ Hz), 143.58, 137.77, 129.21, 126.24, 120.22, 116.91 (t, $J = 18.5$ Hz), 112.56 (t, $J = 243.7$ Hz), 47.79, 21.23, 20.57. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{13}\text{F}_2\text{NNaO}$ calcd for: 260.0857; found: 260.0853



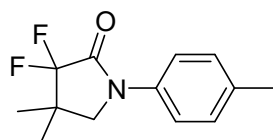
3a

3,3-Difluoro-4-methyl-1-phenylpyrrolidin-2-one (3a), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 40 mg 85%, white solid, m.p.: 86-87 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 7.9$ Hz, 2H), 7.42 (t, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 7.4$ Hz, 1H), 3.95 (t, $J = 8.8$ Hz, 1H), 3.50 (t, $J = 8.7$ Hz, 1H), 2.80 – 2.69 (m, 1H), 1.32 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.54 (t, $J = 31.7$ Hz), 138.01, 129.17, 126.07, 119.85, 119.73 – 115.46 (m), 49.83 (d, $J = 6.4$ Hz), 34.74 (t, $J = 21.9$ Hz), 10.00 (d, $J = 8.2$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{11}\text{F}_2\text{NNaO}$ calcd for: 234.0701 found: 234.0695.



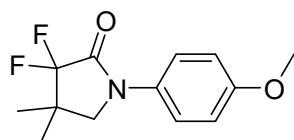
3b

3,3-Difluoro-4,4-dimethyl-1-phenylpyrrolidin-2-one (3b), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 40mg 80%, white solid, m.p.: 52-54 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.66 – 7.61 (m, 2H), 7.45 – 7.39 (m, 2H), 7.26 – 7.21 (m, 1H), 3.59 (t, J = 0.9 Hz, 2H), 1.30 (t, J = 1.2 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.52 (t, J = 31.9 Hz), 138.14, 129.11, 125.90, 119.73, 118.47 (t, J = 254.6 Hz), 56.58, 38.28 (t, J = 19.9 Hz), 19.62 (t, J = 4.5 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{13}\text{F}_2\text{NNaO}$ calcd for: 248.0857, found: 248.0852.



3c

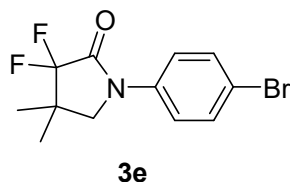
3,3-Difluoro-4,4-dimethyl-1-(p-tolyl)pyrrolidin-2-one (3c), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 38mg 72%, white solid, m.p.: 49-51 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 3.56 (s, 2H), 2.35 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.38 (t, J = 31.7 Hz), 135.82, 135.70, 129.66, 119.78, 118.54 (t, J = 254.4 Hz), 56.79, 38.36 (t, J = 20.0 Hz), 20.89, 19.72 (t, J = 4.6 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{F}_2\text{NNaO}$ calcd for: 262.1014 found: 262.1011.



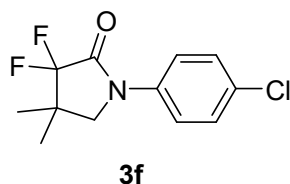
3d

3,3-Difluoro-1-(4-methoxyphenyl)-4,4-dimethylpyrrolidin-2-one (3d), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 40mg 73%,

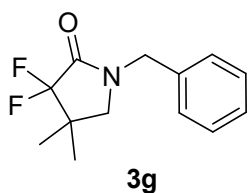
yellow solid, m.p.: 45-46 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.60 – 7.47 (m, 2H), 7.02 – 6.87 (m, 2H), 3.82 (s, 3H), 3.55 (s, 2H), 1.29 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.26 (t, $J = 31.5$ Hz), 157.55, 131.31, 121.53, 118.58 (t, $J = 253.26$ Hz), 114.34, 57.12, 55.51, 38.45 (t, $J = 20.2$ Hz), 19.78 (t, $J = 4.6$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{F}_2\text{NNaO}_2$ calcd for: 278.0963, found: 278.0960.



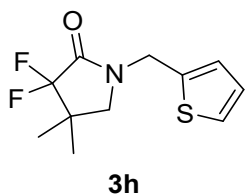
1-(4-Bromophenyl)-3,3-difluoro-4,4-dimethylpyrrolidin-2-one (3e), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 52mg 81%, white solid, m.p.: 60-61 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (dd, $J = 8.7, 3.8$ Hz, 4H), 3.56 (s, 2H), 1.29 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.59 (t, $J = 32.0$ Hz), 137.25, 132.19, 121.12, 118.97, 118.27 (t, $J = 254.7$ Hz), 56.50, 38.31 (t, $J = 19.8$ Hz), 19.69 (t, $J = 4.3$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{12}\text{BrF}_2\text{NNaO}$ calcd for: 325.9963, found: 325.9959.



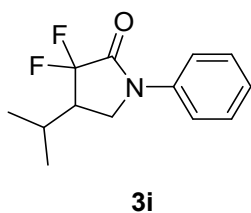
1-(4-Chlorophenyl)-3,3-difluoro-4,4-dimethylpyrrolidin-2-one (3f), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 44mg 79%, white solid, m.p.: 73-76 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (d, $J = 8.9$ Hz, 2H), 7.37 (d, $J = 8.9$ Hz, 2H), 3.56 (s, 2H), 1.29 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.58 (t, $J = 32.0$ Hz), 136.75, 131.23, 129.23, 120.84, 118.28 (t, $J = 254.7$ Hz), 56.58, 38.33 (t, $J = 19.9$ Hz), 19.69 (t, $J = 4.5$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{12}\text{ClF}_2\text{NNaO}$ calcd for: 282.0468 found: 282.0461.



1-Benzyl-3,3-difluoro-4,4-dimethylpyrrolidin-2-one (3g), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 39mg 75%, yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.30 (m, 3H), 7.23 (d, J = 7.8 Hz, 2H), 4.51 (s, 2H), 2.97 (s, 2H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.70 (t, J = 31.5 Hz), 134.65, 128.95, 128.33, 128.19, 118.92 (t, J = 255.1 Hz), 54.99, 47.18, 38.62 (t, J = 20.2 Hz), 19.71 (t, J = 4.6 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{F}_2\text{NNaO}$ calcd for: 262.1014, found: 262.1007.

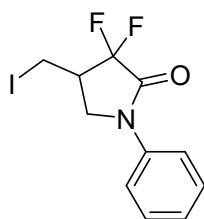


3,3-Difluoro-4,4-dimethyl-1-(thiophen-2-ylmethyl)pyrrolidin-2-one (3h), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 22mg 42%, white solid, m.p.: 63-66 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.28 (d, J = 4.9 Hz, 1H), 6.97 (dd, J = 8.7, 3.7 Hz, 2H), 4.69 (s, 2H), 3.05 (s, 2H), 1.13 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.28 (t, J = 31.2 Hz), 136.53, 127.61, 127.09, 126.27, 118.80 (t, J = 255.5 Hz), 54.70, 41.49, 38.70 (t, J = 20.1 Hz), 19.62 (t, J = 4.7 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{13}\text{F}_2\text{NNa}$ calcd for: 268.0578, found: 268.0572



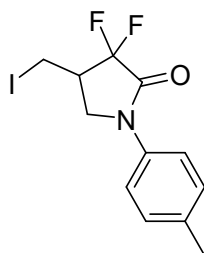
3,3-Difluoro-4,4-dimethyl-1-phenylpyrrolidin-2-one (3i), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 36mg 65%, white solid, m.p.: 119-121 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, J = 8.5 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.31 – 7.21 (m, 1H), 3.88 (t, J = 9.0 Hz, 1H), 3.57 (t, J = 9.2 Hz, 1H), 2.35 – 2.21

(m, 1H), 2.16 – 2.05 (m, 1H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.83 (t $J = 31.5$ Hz), 137.97, 129.15, 126.09, 119.96, 117.67 (dd, $J = 254.6, 249.1$ Hz), 47.78 (d, $J = 7.4$ Hz), 46.67 – 45.73 (m), 26.17 (d, $J = 5.5$ Hz), 20.64, 20.04. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{F}_2\text{NNa}$ calcd for: 262.1014, found: 262.1009.



4a

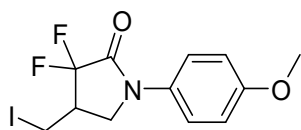
3,3-Difluoro-4-(iodomethyl)-1-phenylpyrrolidin-2-one (4a), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 50mg 70%, yellow solid, m.p.: 86-88 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, $J = 9.8$ Hz, 2H), 7.44 (t, $J = 8.1$ Hz, 2H), 7.27 (t, $J = 7.5$ Hz, 1H), 4.09 (t, $J = 9.0$ Hz, 1H), 3.61 (t, $J = 7.7$ Hz, 1H), 3.51 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.23 (t, $J = 10.7$ Hz, 1H), 3.14 – 2.97 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.71 (t, $J = 31.3$ Hz), 137.54, 129.26, 126.46, 120.06, 116.06 (dd, $J = 256.5, 250.9$ Hz), 50.28, 42.71 (t, $J = 21.1$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$: $\text{C}_{11}\text{H}_{10}\text{F}_2\text{INNaO}$ calcd for: 359.9667; found: 359.9663.



4b

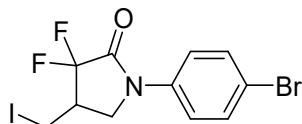
3,3-Difluoro-4-(iodomethyl)-1-(p-tolyl)pyrrolidin-2-one (4b), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 48mg 65%, yellow solid, m.p.: 123-124 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.52 (d, $J = 8.5$ Hz, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 4.10 – 4.02 (m, 1H), 3.59 (t, $J = 7.7$ Hz, 1H), 3.50 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.23 (t, $J = 10.6$ Hz, 1H), 3.12 – 2.99 (m, 1H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.57 (t, $J = 30.8$ Hz), 136.39, 135.05, 129.81, 120.05, 116.14 (dd, J

= 256.5, 250.9 Hz), 50.41 (d, $J = 5.5$ Hz), 42.74 (t, $J = 21.1$ Hz), 29.68, 20.95. HRMS (ESI): m/z $[M+Na]^+$ $C_{12}H_{12}F_2INNaO$ calcd for: 373.9824; found: 373.9816.



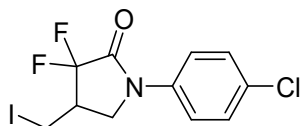
4c

3,3-Difluoro-4-(iodomethyl)-1-(4-methoxyphenyl)pyrrolidin-2-one (4c), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 50mg 64%, white solid, m.p.: 94-96 °C. 1H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 2H), 6.98 – 6.91 (m, 2H), 4.04 (t, $J = 9.8$ Hz, 1H), 3.82 (s, 3H), 3.57 (t, $J = 7.7$ Hz, 1H), 3.50 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.22 (t, $J = 10.7$ Hz, 1H), 3.13 – 2.98 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.45 (t, $J = 30.24$ Hz), 157.86, 130.58, 121.81, 116.19 (dd, $J = 256.5, 250.9$ Hz), 114.40, 55.50, 50.69 (d, $J = 5.5$ Hz), 42.76 (t, $J = 21.1$ Hz). HRMS (ESI): m/z $[M+Na]^+$ $C_{12}H_{12}F_2INO_2$ calcd for: 389.9773; found: 389.9767.



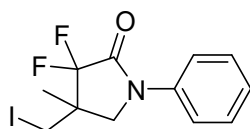
4d

1-(4-Bromophenyl)-3,3-difluoro-4-(iodomethyl)pyrrolidin-2-one (4d), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 62mg 71%, yellow solid, m.p.: 105-109 °C. 1H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 4H), 4.06 (t, $J = 8.9$ Hz, 1H), 3.58 (t, $J = 8.8$ Hz, 1H), 3.50 (dd, $J = 10.4, 4.5$ Hz, 1H), 3.24 (d, $J = 10.7$ Hz, 1H), 3.14 – 2.99 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.73 (t, $J = 30.8$ Hz), 136.58, 132.31, 121.39, 119.57, 115.87 (dd, $J = 256.9, 250.5$ Hz), 50.16 (d, $J = 5.5$ Hz), 42.57 (t, $J = 21.1$ Hz). HRMS (ESI): m/z $[M+Na]^+$ $C_{11}H_9BrF_2INNaO$ calcd for: 437.8722 found: 437.8767.



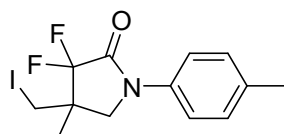
4e

1-(4-Chlorophenyl)-3,3-difluoro-4-(iodomethyl)pyrrolidin-2-one (4e), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1). 58mg 74%, yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.62 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 4.06 (t, J = 9.7 Hz, 1H), 3.58 (t, J = 8.9 Hz, 1H), 3.50 (dd, J = 10.4, 4.6 Hz, 1H), 3.22 (t, J = 10.5 Hz, 1H), 3.15 – 2.95 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.77 (t, J = 31.3 Hz), 136.13, 131.82, 129.38, 121.18, 115.94 (dd, J = 256.9, 250.5 Hz), 50.29, 42.61 (t, J = 21.1 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_9\text{ClF}_2\text{INNaO}$ calcd for: 393.9278 found: 393.9269.



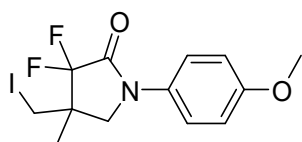
4f

3,3-Difluoro-4-(iodomethyl)-4-methyl-1-phenylpyrrolidin-2-one (4f), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 53mg 72%, yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.61 (m, 2H), 7.46 – 7.40 (m, 2H), 7.29 – 7.24 (m, 1H), 3.82 – 3.78 (m, 1H), 3.58 – 3.50 (m, 2H), 3.31 (d, J = 10.6 Hz, 1H), 1.42 (d, J = 2.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.82 (t, J = 32.76 Hz), 137.69, 129.25, 126.32, 119.96, 116.28 (dd, J = 261.3, 253.1 Hz), 56.63 (d, J = 2.6 Hz), 42.09 (t, J = 18.8 Hz), 19.78 (d, J = 7.9 Hz), 6.90 (d, J = 9.6 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{12}\text{F}_2\text{INNaO}$ calcd for: 373.9824 found: 373.9817.



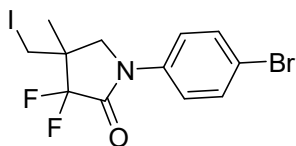
4g

3,3-Difluoro-4-(iodomethyl)-4-methyl-1-(p-tolyl)pyrrolidin-2-one (4g), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 54mg 70%, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 3.77 (d, J = 10.1 Hz, 1H), 3.52 (d, J = 11.9 Hz, 2H), 3.30 (d, J = 10.5 Hz, 1H), 2.36 (s, 3H), 1.41 (d, J = 2.7 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.68 (t, J = 30.24 Hz), 136.26, 135.21, 129.77, 119.98, 116.36 (dd, J = 261.5, 253.2 Hz), 56.76, 42.12 (t, J = 18.4 Hz), 20.93, 19.80 (d, J = 7.4 Hz), 7.02 (d, J = 9.2 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{14}\text{F}_2\text{INNaO}$ calcd for: 387.9980 found: 387.9971.



4h

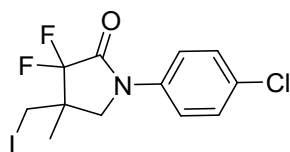
3,3-Difluoro-4-(iodomethyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (4h), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), yellow oil. 56mg 73%, ^1H NMR (500 MHz, CDCl_3) δ 7.52 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H), 3.76 (d, J = 10.0 Hz, 1H), 3.53 – 3.48 (m, 2H), 3.30 (d, J = 10.5 Hz, 1H), 1.41 (d, J = 2.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.55 (t, J = 31.5 Hz), 157.82, 121.75, 118.56 – 116.02 (m), 114.42, 57.09, 55.52, 42.18 (t, J = 18.8 Hz), 19.81 (d, J = 7.4 Hz), 7.07 (d, J = 9.2 Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{14}\text{F}_2\text{INNaO}$ calcd for: 387.9980 found: 387.9971.



4i

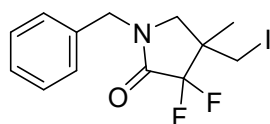
1-(4-Bromophenyl)-3,3-difluoro-4-(iodomethyl)-4-methylpyrrolidin-2-one (4i), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 67mg 75%, white solid, m.p.: 85-89 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.54 (s, 4H), 3.77 (d, J = 9.9 Hz, 1H), 3.54 – 3.50 (m, 2H), 3.30 (d, J = 10.6 Hz, 1H), 1.42 (d, J =

2.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.86 (t, $J = 31.3$ Hz), 136.74, 132.30, 121.31, 119.42, 116.10 (dd, $J = 261.6$, 253.2 Hz), 56.51, 42.05 (t, $J = 18.8$ Hz), 19.76 (d, $J = 6.3$ Hz), 6.68 (d, $J = 9.3$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{11}\text{BrF}_2\text{INNaO}$ calcd for: 451.8929 found: 451.8921.



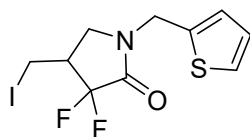
4j

1-(4-Chlorophenyl)-3,3-difluoro-4-(iodomethyl)-4-methylpyrrolidin-2-one (4j), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 61mg 76%, white solid, m.p.: 66-68 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.62 – 7.58 (m, 2H), 7.41 – 7.37 (m, 2H), 3.77 (dd, $J = 9.9$, 1.1 Hz, 1H), 3.55 – 3.49 (m, 2H), 3.30 (d, $J = 10.6$ Hz, 1H), 1.41 (d, $J = 2.6$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.84 (t, $J = 31.6$ Hz), 136.22, 131.64, 129.32, 121.04, 116.11 (dd, $J = 261.4$, 253.2 Hz), 56.56 (d, $J = 2.4$ Hz), 42.05 (t, $J = 18.8$ Hz), 19.75 (d, $J = 6.3$ Hz), 6.68 (d, $J = 9.6$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{12}\text{H}_{11}\text{ClF}_2\text{INNaO}$ calcd for: 407.9434 found: 407.9427.



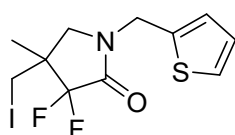
4k

1-Benzyl-3,3-difluoro-4-(iodomethyl)-4-methylpyrrolidin-2-one (4k), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 53mg 69%, white solid, m.p.: 85-86 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.40 – 7.32 (m, 3H), 7.24 (d, $J = 6.6$ Hz, 2H), 4.57 (d, $J = 14.6$ Hz, 1H), 4.47 (d, $J = 14.6$ Hz, 1H), 3.35 (d, $J = 10.3$ Hz, 1H), 3.23 – 3.17 (m, 2H), 2.93 (d, $J = 10.3$ Hz, 1H), 1.24 (d, $J = 2.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 163.06 (t, $J = 30.24$ Hz), 134.29, 129.08, 128.37, 128.30, 116.82 (dd, $J = 262.9$, 253.7 Hz), 54.85, 47.26, 42.48 (t, $J = 18.8$ Hz), 19.69 (d, $J = 7.4$ Hz), 7.19 (d, $J = 10.1$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{13}\text{H}_{14}\text{F}_2\text{INNaO}$ calcd for: 387.9980 found: 387.9971.



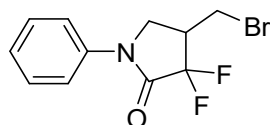
4l

3,3-Difluoro-4-(iodomethyl)-1-(thiophen-2-ylmethyl)pyrrolidin-2-one (4l), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 32mg 43%, yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.30 (dd, $J = 5.0, 1.4$ Hz, 1H), 7.05 – 7.00 (m, 1H), 7.01 – 6.98 (m, 1H), 4.76 – 4.67 (m, 2H), 3.60 – 3.55 (m, 1H), 3.40 (dd, $J = 10.5, 4.7$ Hz, 1H), 3.10 – 3.05 (m, 2H), 2.95 – 2.83 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.56 (t, $J = 30.8$ Hz), 136.01, 127.84, 127.27, 126.49, 116.41 (dd, $J = 256.9, 251.4$ Hz), 48.41 (d, $J = 6.4$ Hz), 43.13 (dd, $J = 22.5, 20.7$ Hz), 41.70. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{10}\text{H}_{10}\text{F}_2\text{INNaOS}$ calcd for: 379.9388 found: 379.9381.



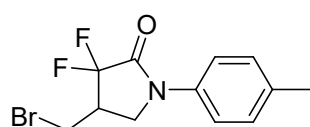
4m

3,3-Difluoro-4-(iodomethyl)-4-methyl-1-(thiophen-2-ylmethyl)pyrrolidin-2-one (4m), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 33mg 43%, yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.28 (m, 1H), 7.03 – 6.96 (m, 2H), 4.82 – 4.59 (m, 2H), 3.31 (dd, $J = 38.9, 10.4$ Hz, 2H), 3.11 (dd, $J = 84.1, 11.4$ Hz, 2H), 1.24 (d, $J = 2.9$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.61 (t, $J = 30.8$ Hz), 136.07, 127.82, 127.18, 126.50, 116.68 (dd, $J = 262.4, 254.2$ Hz), 54.54 (d, $J = 3.7$ Hz), 42.55 (t, $J = 18.8$ Hz), 41.53, 19.54 (d, $J = 7.4$ Hz), 7.13 (d, $J = 10.1$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{11}\text{H}_{12}\text{F}_2\text{INNaOS}$ calcd for: 393.9545 found: 393.9540.



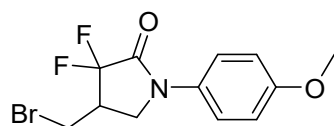
5a

4-(Bromomethyl)-3,3-difluoro-1-phenylpyrrolidin-2-one (5a), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 37mg 65%, yellow solid, m.p.: 56-58 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 4.12 (t, *J* = 9.1 Hz, 1H), 3.79 – 3.70 (m, 2H), 3.50 (t, *J* = 10.5 Hz, 1H), 3.20 – 3.07 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 161.46 (t, *J* = 30.8 Hz), 137.54, 129.28, 126.49, 120.05, 116.24 (dd, *J* = 256.2, 251.2 Hz), 48.43 (d, *J* = 4.6 Hz), 43.74 – 40.71 (m), 25.62 (d, *J* = 9.2 Hz). HRMS (ESI): *m/z* [M+H]⁺ C₁₁H₁₁BrF₂NO calcd for: 289.9987 found: 289.9985.



5b

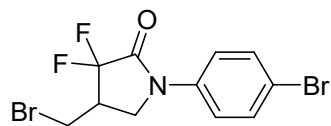
4-(Bromomethyl)-3,3-difluoro-1-(*p*-tolyl)pyrrolidin-2-one (5b), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 37mg 62%, yellow solid, m.p.: 136-137 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 4.08 (t, *J* = 9.1 Hz, 1H), 3.75 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.69 (t, *J* = 8.7 Hz, 1H), 3.49 (t, *J* = 10.5 Hz, 1H), 3.21 – 3.04 (m, 1H), 2.36 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 161.31 (t *J* = 23.94 Hz), 136.42, 135.04, 129.78, 120.03, 116.31 (dd, *J* = 255.6, 250.9 Hz), 48.53 (d, *J* = 5.5 Hz), 42.06 (dd, *J* = 22.5, 19.8 Hz), 25.71 (d, *J* = 10.1 Hz), 20.94. HRMS (ESI): *m/z* [M+H]⁺ C₁₂H₁₃BrF₂NO calcd for: 304.0143 found: 304.0137.



5c

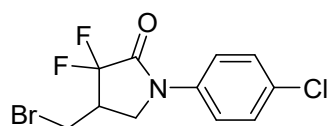
4-(Bromomethyl)-3,3-difluoro-1-(4-methoxyphenyl)pyrrolidin-2-one (5c), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 38mg 60%, yellow solid, m.p.: 94-96 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.59 – 7.50 (m, 2H), 6.98 – 6.91 (m, 2H), 4.10 – 4.03 (m, 1H), 3.82 (s, 3H), 3.76 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.71 – 3.64 (m, 1H), 3.49 (t, *J* = 10.8 Hz, 1H), 3.26 – 3.01 (m, 1H). ¹³C NMR (126

MHz, CDCl₃) δ 161.20 (t, J = 30.24 Hz), 157.89, 130.58, 121.82, 118.83 – 114.29 (m), 114.41, 55.51, 48.82 (d, J = 5.5 Hz), 42.10 (dd, J = 22.5, 19.8 Hz), 25.76 (d, J = 10.1 Hz). HRMS (ESI): m/z [M+H]⁺ C₁₂H₁₃BrF₂NO₂ calcd for: 320.0092 found: 320.0088.



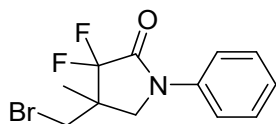
5d

4-(Bromomethyl)-1-(4-bromophenyl)-3,3-difluoropyrrolidin-2-one (5d), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 52mg 71%, white solid, m.p.: 115–117 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.59 – 7.52 (m, 4H), 4.14 – 4.03 (m, 1H), 3.78 – 3.72 (m, 1H), 3.69 (t, J = 7.6 Hz, 1H), 3.49 (t, J = 10.5 Hz, 1H), 3.21 – 3.04 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 161.46 (t, J = 31.3 Hz), 136.58, 132.30, 121.38, 119.59, 116.04 (dd, J = 256.5, 250.9 Hz), 48.27 (d, J = 5.5 Hz), 41.87 (dd, J = 22.1, 19.3 Hz), 25.46 (d, J = 10.1 Hz). HRMS (ESI): m/z [M+H]⁺ C₁₁H₁₀Br₂F₂NO calcd for: 367.0692; found: 367.0688.



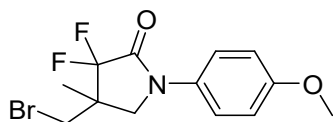
5e

4-(Bromomethyl)-1-(4-chlorophenyl)-3,3-difluoropyrrolidin-2-one (5e), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 48mg 75%, white solid, m.p.: 111–113 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.56 (m, 2H), 7.47 – 7.33 (m, 2H), 4.14 – 4.03 (m, 1H), 3.76 (dd, J = 10.7, 4.7 Hz, 1H), 3.73 – 3.66 (m, 1H), 3.50 (t, J = 10.5 Hz, 1H), 3.23 – 3.04 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 161.48 (t, J = 31.31 Hz), 136.10, 131.85, 129.37, 121.15, 116.06 (dd, J = 256.2, 250.9 Hz), 48.37 (d, J = 5.8 Hz), 41.94 (dd, J = 22.4, 19.5 Hz), 25.49 (d, J = 10.1 Hz). HRMS (ESI): m/z [M+H]⁺ C₁₁H₁₀BrClF₂NO calcd for: 323.9597 found: 323.9588.



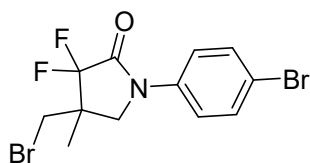
5f

4-(Bromomethyl)-3,3-difluoro-4-methyl-1-phenylpyrrolidin-2-one (5f), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 46mg, 76%, yellow solid, m.p.: 56-58 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 3.90 (d, J = 10.1 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.53 (d, J = 10.8 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.53 (t, J = 30.8 Hz), 137.66, 129.23, 126.32, 119.94, 117.23 (dd, J = 258.8, 255.1 Hz), 54.61, 42.71 (t, J = 18.8 Hz), 33.95 (dd, J = 7.8, 3.2 Hz), 17.69 (dd, J = 6.0, 3.2 Hz). HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ $\text{C}_{12}\text{H}_{13}\text{BrF}_2\text{NO}$ calcd for: 304.0143; found: 304.0140.



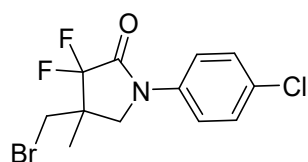
5g

4-(Bromomethyl)-3,3-difluoro-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (5g), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 40mg 60%, yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.48 (m, 2H), 6.98 – 6.89 (m, 2H), 3.86 (d, J = 10.1 Hz, 1H), 3.82 (d, J = 2.3 Hz, 4H), 3.68 (d, J = 10.7 Hz, 1H), 3.57 – 3.52 (m, 2H), 1.44 (d, J = 2.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.28 (t, J = 32.76 Hz), 157.82, 130.73, 121.75, 119.57 – 115.07 (m), 114.41, 55.51, 55.07, 42.85 (t, J = 18.4 Hz), 34.12 (d, J = 8.3 Hz), 17.75 (dd, J = 6.4, 2.8 Hz). HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{15}\text{BrF}_2\text{NO}_2$ calcd for: 334.0249 found: 332.0243.



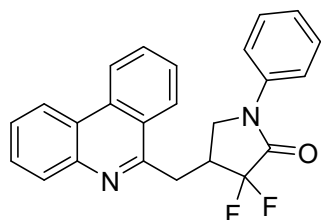
5h

4-(Bromomethyl)-1-(4-bromophenyl)-3,3-difluoro-4-methylpyrrolidin-2-one (5h), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 62mg 77%, white solid, m.p.: 68-73 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 4H), 3.87 (d, *J* = 10.1 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 10.1 Hz, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 1.44 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 161.58 (t, *J* = 31.5 Hz), 136.75, 132.30, 121.30, 119.45, 117.04 (dd, *J* = 259.2, 255.5 Hz), 54.51, 42.71 (t, *J* = 18.8 Hz), 33.86 (dd, *J* = 8.3, 2.8 Hz), 17.72 (dd, *J* = 6.0, 3.2 Hz). HRMS (ESI): *m/z* [M+Na]⁺ C₁₂H₁₁Br₂F₂NNaO calcd for: 403.9068 found: 403.9059.



5i

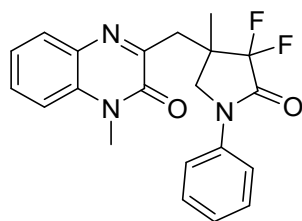
4-(Bromomethyl)-1-(4-chlorophenyl)-3,3-difluoro-4-methylpyrrolidin-2-one (5i), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 53mg 75%, yellow solid, m.p.: 38-40 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 3.87 (d, *J* = 10.1 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.57 (d, *J* = 11.3 Hz, 1H), 3.51 (d, *J* = 10.8 Hz, 1H), 1.44 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 161.57 (t, *J* = 31.3 Hz), 136.24, 131.67, 129.33, 121.05, 117.05 (dd, *J* = 259.2, 255.5 Hz), 54.59, 42.72 (t, *J* = 18.4 Hz), 33.86 (dd, *J* = 8.3, 2.8 Hz), 17.71 (dd, *J* = 6.4, 2.8 Hz). HRMS (ESI): *m/z* [M+Na]⁺ C₁₂H₁₁BrClF₂NNaO calcd for: 359.9573 found: 359.9565.



6a

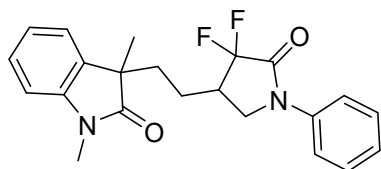
3,3-Difluoro-4-(phenanthridin-6-ylmethyl)-1-phenylpyrrolidin-2-one (6a), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 32mg

40%, white solid, m.p.: 164-166 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.67 (d, $J = 8.2$ Hz, 1H), 8.57 (d, $J = 9.8$ Hz, 1H), 8.26 (d, $J = 8.1$ Hz, 1H), 8.09 (d, $J = 8.1$ Hz, 1H), 7.89 (t, $J = 7.7$ Hz, 1H), 7.78 – 7.65 (m, 5H), 7.43 – 7.38 (m, 2H), 7.23 (t, $J = 7.4$ Hz, 2H), 4.50 (t, $J = 9.6$ Hz, 1H), 4.02 (dd, $J = 16.9, 3.1$ Hz, 1H), 3.90 – 3.79 (m, 1H), 3.74 (t, $J = 8.6$ Hz, 1H), 3.63 (dd, $J = 16.9, 11.1$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.86 – 162.17 (m), 156.38, 143.24, 138.17, 132.69, 130.79, 129.81, 129.11, 127.75, 126.95, 126.00, 125.22, 123.75, 122.63, 122.04, 119.96, 120.75 – 115.98 (m), 49.63 (d, $J = 6.4$ Hz), 39.30 – 35.49 (m), 31.02 (d, $J = 6.4$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{24}\text{H}_{18}\text{F}_2\text{N}_2\text{NaO}$ calcd for: 411.1279; found: 411.1270.



6b

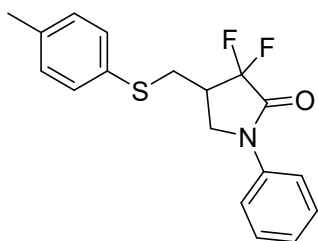
3-((4,4-Difluoro-3-methyl-5-oxo-1-phenylpyrrolidin-3-yl)methyl)-1-methylquinoxalin-2(1H)-one (6b), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 51mg 67%, yellow solid, m.p.: 163-164 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 7.9$ Hz, 1H), 7.63 (d, $J = 7.9$ Hz, 2H), 7.58 (t, $J = 7.8$ Hz, 1H), 7.42 – 7.30 (m, 4H), 7.23 (t, $J = 7.4$ Hz, 1H), 4.29 (d, $J = 10.2$ Hz, 1H), 3.84 (d, $J = 10.2$ Hz, 1H), 3.68 (s, 3H), 3.49 (d, $J = 15.8$ Hz, 1H), 3.30 (d, $J = 15.8$ Hz, 1H), 1.38 (d, $J = 2.3$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.84 – 161.82 (m), 156.62, 155.02, 138.24, 133.06, 132.24, 130.50, 129.98, 129.08, 125.87, 123.84, 119.97, 120.69 – 117.96 (m), 113.71, 55.02, 41.86 (t, $J = 18.8$ Hz), 34.74 (d, $J = 8.4$ Hz), 29.27, 17.92 (d, $J = 7.3$ Hz). HRMS (ESI): m/z $[\text{M}+\text{H}]^+$ $\text{C}_{21}\text{H}_{20}\text{F}_2\text{N}_3\text{O}_2$ calcd for: 384.1518; found: 384.1510.



6c

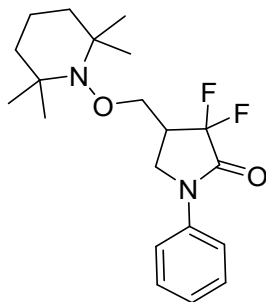
3-(2-(4,4-Difluoro-5-oxo-1-phenylpyrrolidin-3-yl)ethyl)-1,3-dimethylindolin-2-

one (6c), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 47mg 62%, white solid, m.p.: 139-144 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.58 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.12 (t, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.41 (t, *J* = 8.9 Hz, 1H), 3.24 (s, 3H), 2.55 – 2.44 (m, 1H), 2.08 – 1.98 (m, 2H), 1.40 (s, 3H), 1.37 – 1.30 (m, 1H), 1.24 – 1.15 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 180.07, 143.17, 137.80, 132.88, 129.16, 128.14, 126.15, 122.96, 122.52, 119.90, 108.24, 48.45 (d, *J* = 7.2 Hz), 48.33, 40.06 – 39.20 (m), 35.21, 26.23, 24.31, 21.04 (d, *J* = 6.7 Hz). HRMS (ESI): *m/z* [M+H]⁺ C₂₂H₂₃F₂N₂O calcd for: 385.1722; found: 385.1720.



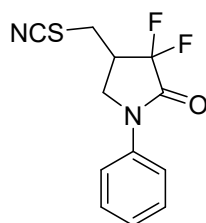
6d

3,3-Difluoro-1-phenyl-4-((p-tolylthio)methyl)pyrrolidin-2-one (6d), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 45mg 68%, yellow solid, m.p.: 99-102 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.63 (d, *J* = 7.7 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.01 – 3.97 (m, 1H), 3.70 (d, *J* = 15.1 Hz, 1H), 3.45 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.95 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.34 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 137.90, 137.81, 131.43, 130.22, 129.77, 129.20, 126.24, 119.90, 119.29 – 114.63 (m), 48.02 (d, *J* = 6.4 Hz), 39.26 (t, *J* = 21.1 Hz), 30.82 (d, *J* = 7.4 Hz), 21.07. HRMS (ESI): *m/z* [M+H]⁺ C₁₈H₁₈F₂NOS calcd for: 334.1072; found: 334.1066.



6e

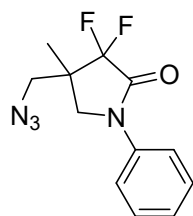
3,3-Difluoro-1-phenyl-4-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)pyrrolidin-2-one (6e), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), yellow solid, m.p.: 120-124 °C. 19mg 25%, ^1H NMR (500 MHz, CDCl_3) δ 7.67 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 7.9 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 4.13 (dd, J = 9.2, 5.4 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.80 (dd, J = 9.3, 6.2 Hz, 1H), 3.01 – 2.88 (m, 1H), 1.54 – 1.41 (m, 5H), 1.32 (d, J = 12.2 Hz, 1H), 1.17 (d, J = 5.3 Hz, 6H), 1.09 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.22 (t, J = 31.2 Hz), 138.00, 129.17, 126.10, 119.94, 118.16 (d, J = 252.3 Hz), 71.72 – 71.48 (m), 60.08, 46.98 – 46.29 (m), 39.64, 39.45 – 38.94 (m), 33.07, 19.94 (d, J = 13.8 Hz), 16.94. HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ $\text{C}_{20}\text{H}_{28}\text{F}_2\text{N}_2\text{NaO}_2$ calcd for: 389.2011; found: 389.2004.



6f

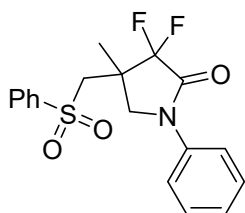
3,3-Difluoro-1-phenyl-4-(thiocyanatomethyl)pyrrolidin-2-one (6f), (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1-5:1), 43mg 75%, white solid, m.p.: 100-102 °C. ^1H NMR (500 MHz, CDCl_3) δ 7.67 – 7.61 (m, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 4.21 – 4.15 (m, 1H), 3.80 – 3.73 (m, 1H), 3.53 – 3.44 (m, 1H), 3.26 – 3.09 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.77 – 160.07 (m), 137.27, 129.34, 126.70, 120.10, 116.14 (dd, J = 257.4, 250.1 Hz), 110.51,

47.34 (d, $J = 5.5$ Hz), 41.85 – 38.81 (m), 29.51 (d, $J = 8.7$ Hz). HRMS (ESI): m/z $[M+Na]^+ C_{12}H_{10}F_2N_2NaOS$ calcd for: 291.0374; found: 291.0372.



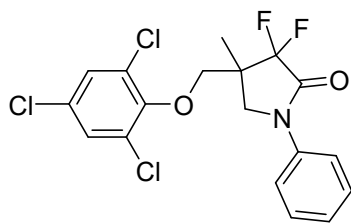
6g

4-(Azidomethyl)-3,3-difluoro-4-methyl-1-phenylpyrrolidin-2-one (6g) (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 10:1, 45mg 85%, yellow oil. 1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, $J = 8.5$ Hz, 2H), 7.43 (t, $J = 8.1$ Hz, 2H), 7.30 – 7.23 (m, 1H), 3.82 (d, $J = 10.2$ Hz, 1H), 3.60 (d, $J = 2.6$ Hz, 2H), 3.56 (d, $J = 10.2$ Hz, 1H), 1.36 (d, $J = 2.6$ Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.56 (t, $J = 31.3$ Hz), 137.75, 129.24, 126.29, 119.91, 119.62 – 115.01 (m), 53.53 (d, $J = 8.7$ Hz), 53.05, 42.38 – 41.99 (m), 16.26 (d, $J = 8.2$ Hz). HRMS (ESI): m/z $[M+H]^+ C_{12}H_{14}F_2N_4O$ calcd for: 267.1052; found: 267.1054.



6h

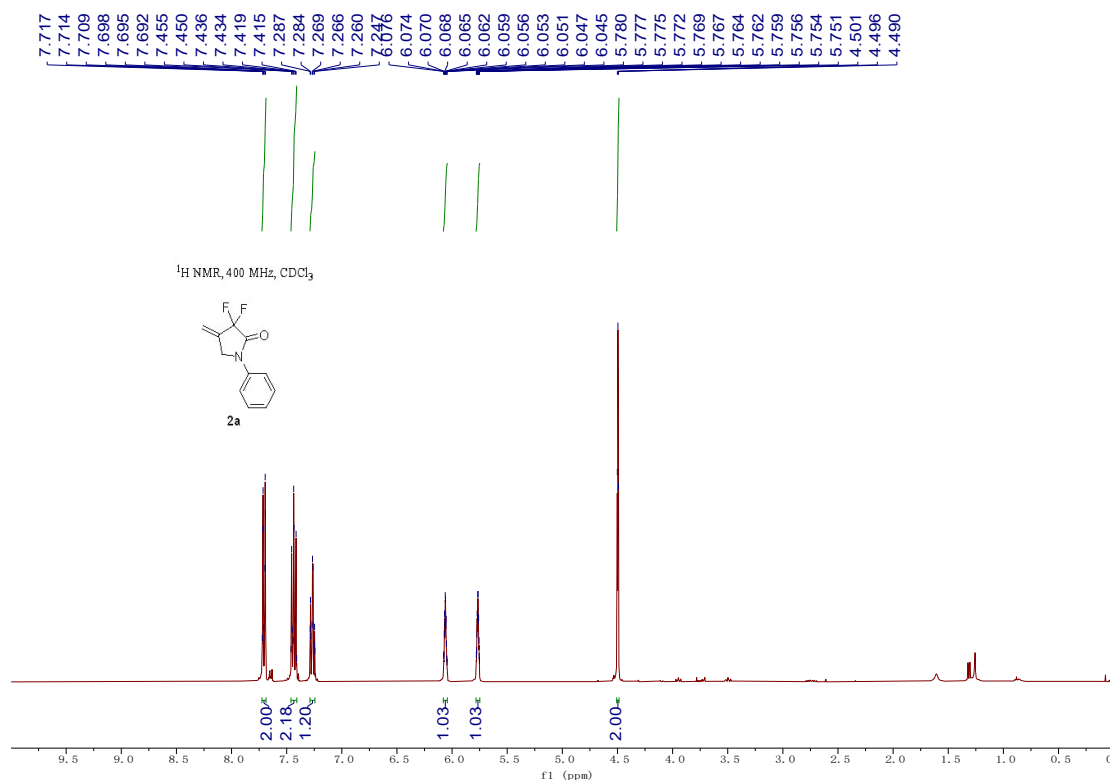
3,3-Difluoro-4-methyl-1-phenyl-4-((2,4,6-trichlorophenoxy)methyl)pyrrolidin-2-one (6h) (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 5:1, 19mg 27%, yellow oil. 1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.0$ Hz, 2H), 7.75 – 7.69 (m, 1H), 7.67 (d, $J = 9.9$ Hz, 2H), 7.63 (d, $J = 8.2$ Hz, 2H), 7.48 – 7.41 (m, 2H), 7.31 – 7.23 (m, 1H), 4.34 (d, $J = 10.7$ Hz, 1H), 4.00 (dd, $J = 10.7, 2.4$ Hz, 1H), 3.60 – 3.33 (m, 2H), 1.64 (d, $J = 2.9$ Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.98 – 159.90 (m), 140.41, 137.67, 134.38, 129.66, 129.27, 127.60, 126.39, 120.02, 119.71 – 115.33 (m), 57.07 (d, $J = 9.2$ Hz), 54.23, 41.23 (t, $J = 18.8$ Hz), 29.67, 18.12 (d, $J = 6.4$ Hz). HRMS (ESI): m/z $[M+H]^+ C_{18}H_{18}F_2NO_3S$ calcd for: 366.0970; found: 366.0977.

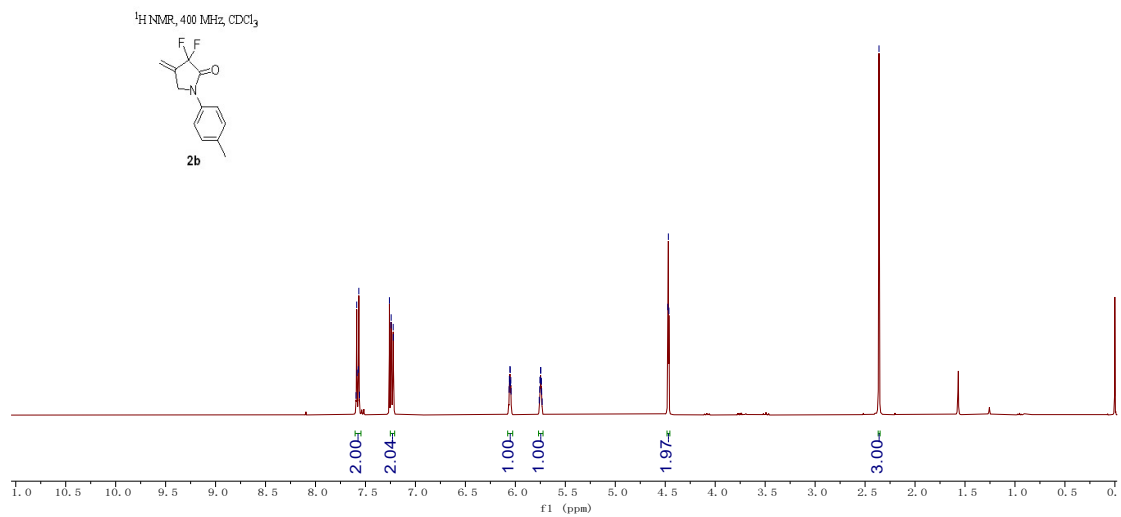
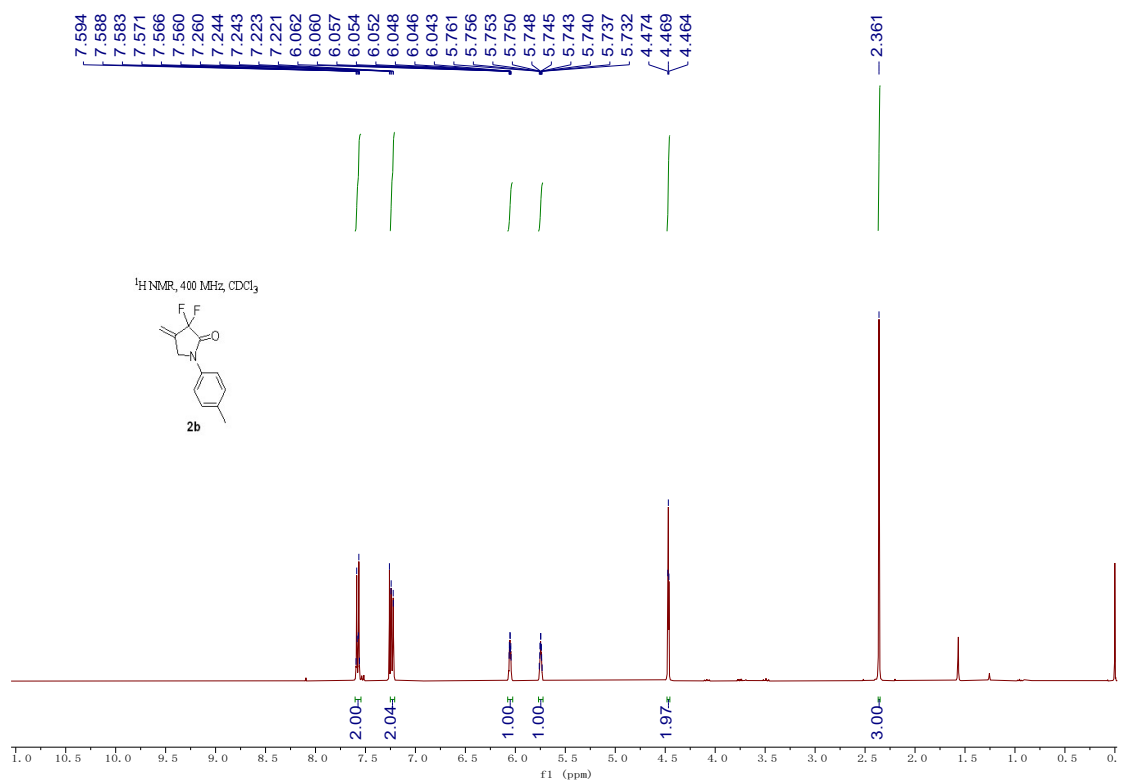
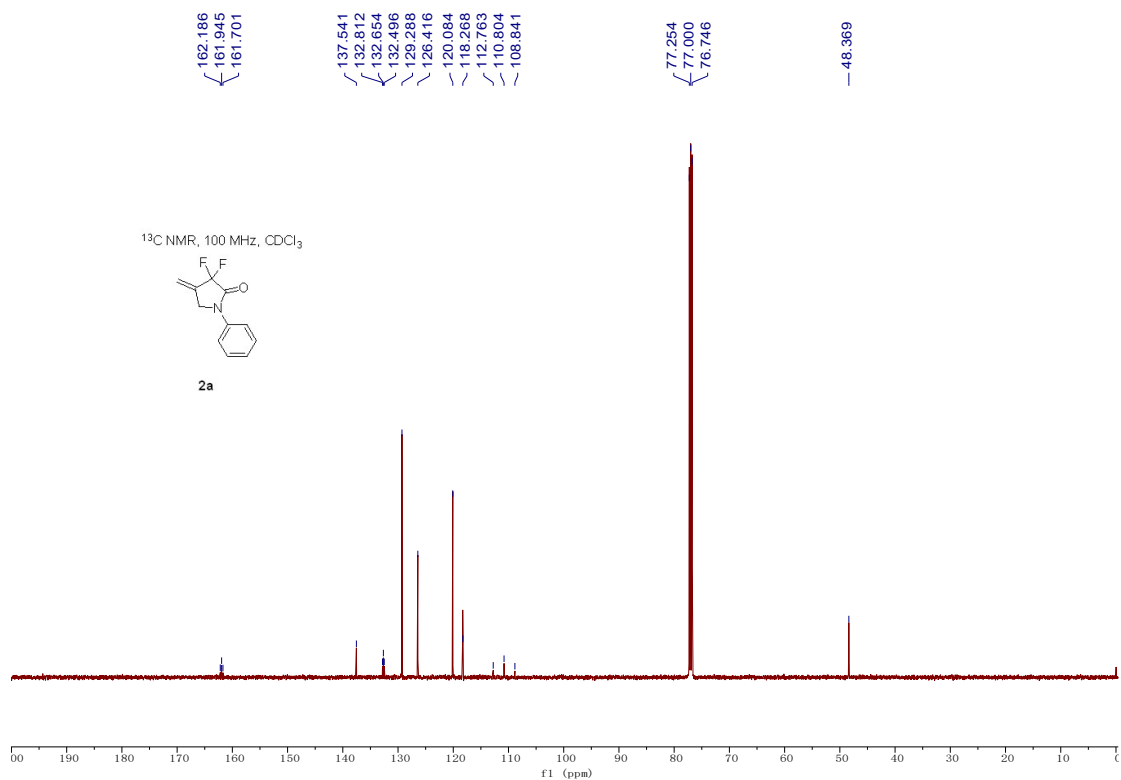


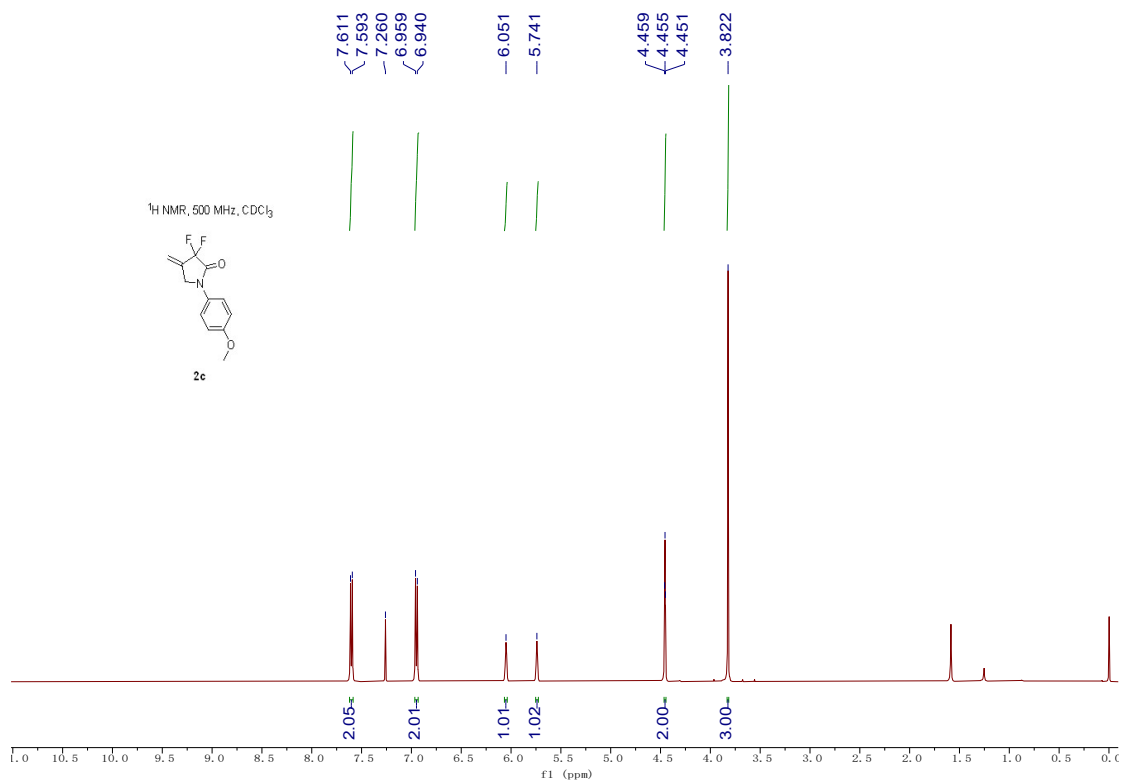
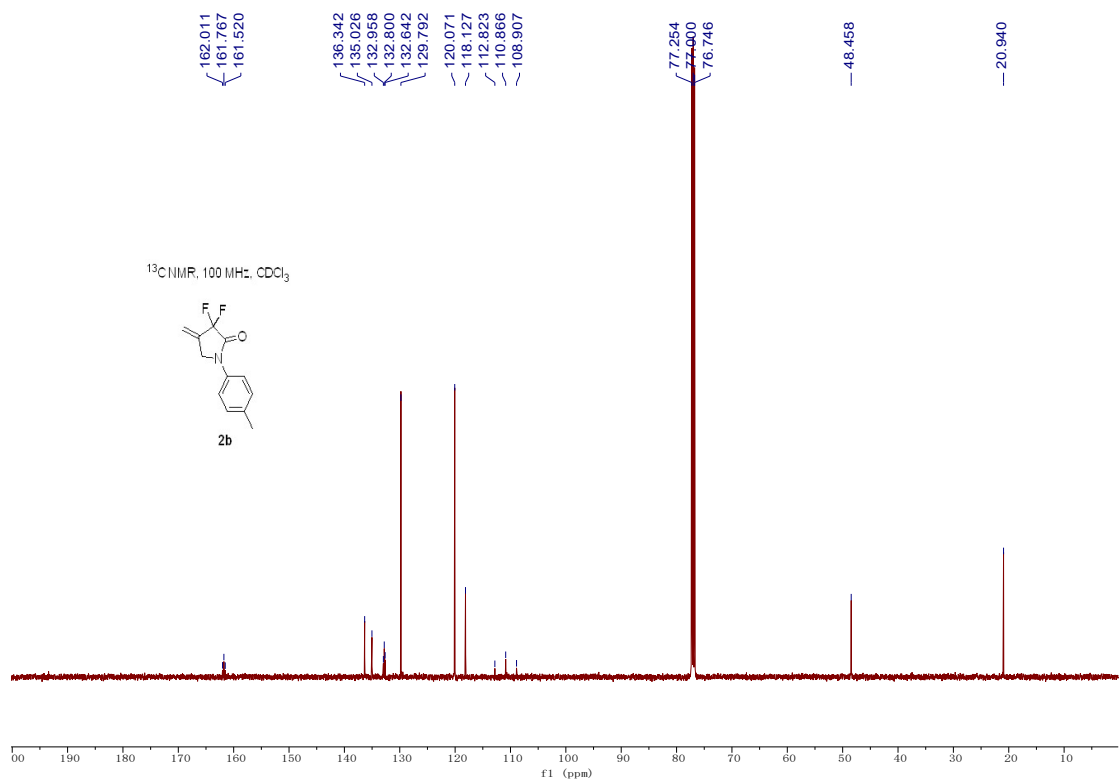
6i

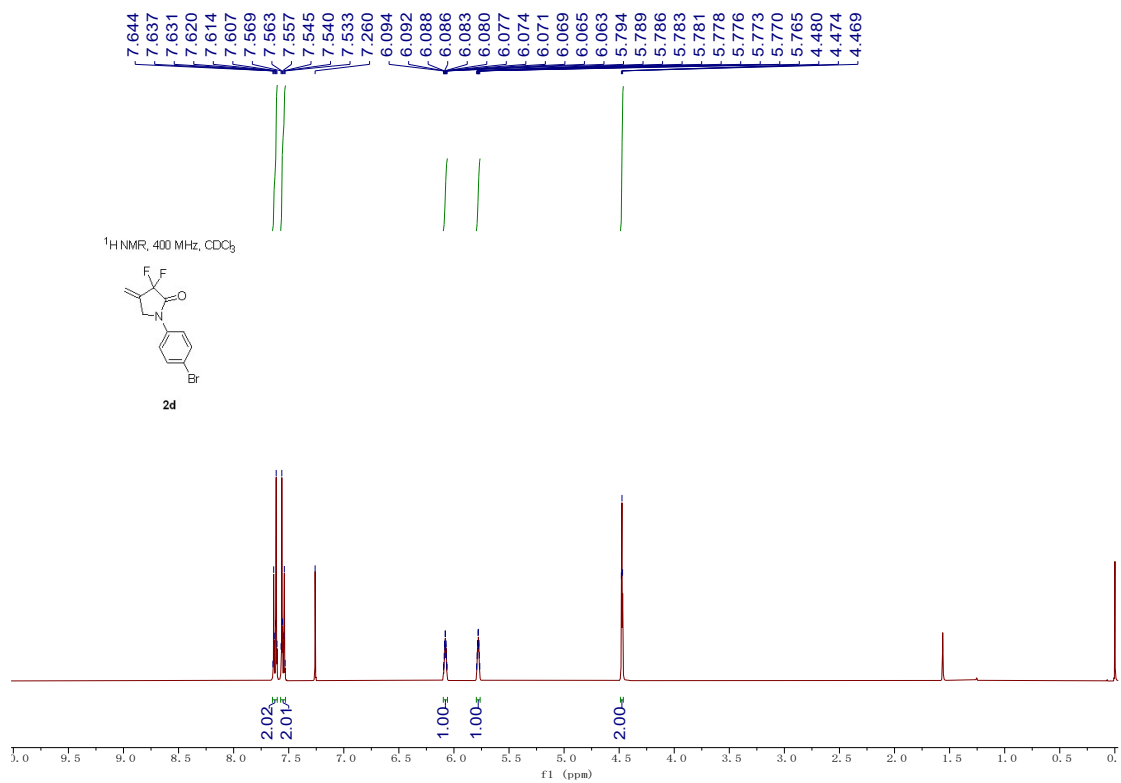
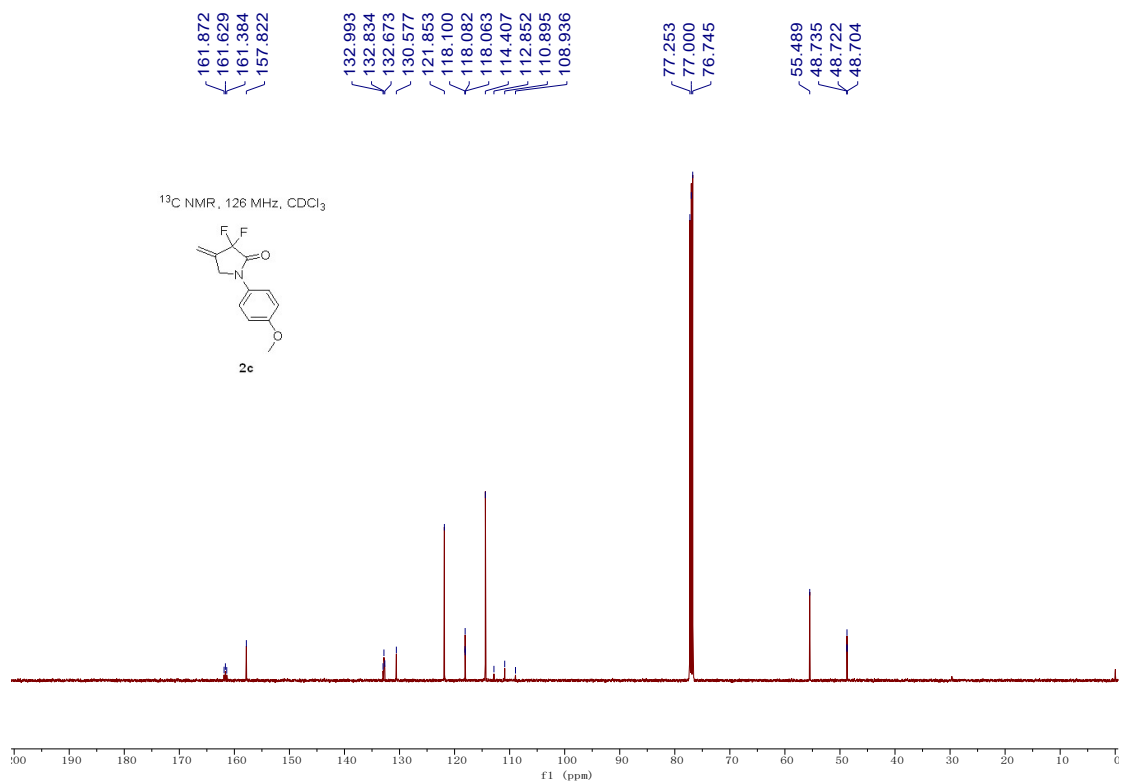
3,3-Difluoro-4-methyl-1-phenyl-4-((2,4,6-trichlorophenoxy)methyl)pyrrolidin-2-one (6i) (silica gel: 200–300 mesh, solvent system: petroleum ether/ethyl acetate = 5:1, 59mg 71%, colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, $J = 8.7$ Hz, 2H), 7.46 – 7.41 (m, 1H), 7.30 (s, 2H), 7.28 – 7.23 (m, 1H), 4.37 (dd, $J = 10.2, 1.5$ Hz, 1H), 4.11 (d, $J = 8.7$ Hz, 1H), 4.04 (d, $J = 8.7$ Hz, 1H), 3.71 (d, $J = 10.6$ Hz, 1H), 1.58 (d, $J = 2.4$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 161.83 (t, $J = 31.3$ Hz), 148.83, 137.93, 130.53, 129.95, 129.21, 128.98, 126.16, 119.95, 117.43 (t, $J = 256.0$ Hz), 72.15 (d, $J = 9.3$ Hz), 52.33 (d, $J = 2.8$ Hz), 42.98 (dd, $J = 20.3, 17.5$ Hz), 15.16 (d, $J = 8.3$ Hz). HRMS (ESI): m/z $[\text{M}+\text{Na}]^+ \text{C}_{18}\text{H}_{15}\text{Cl}_3\text{F}_2\text{NO}_2$ calcd for: 420.0131; found: 420.0130.

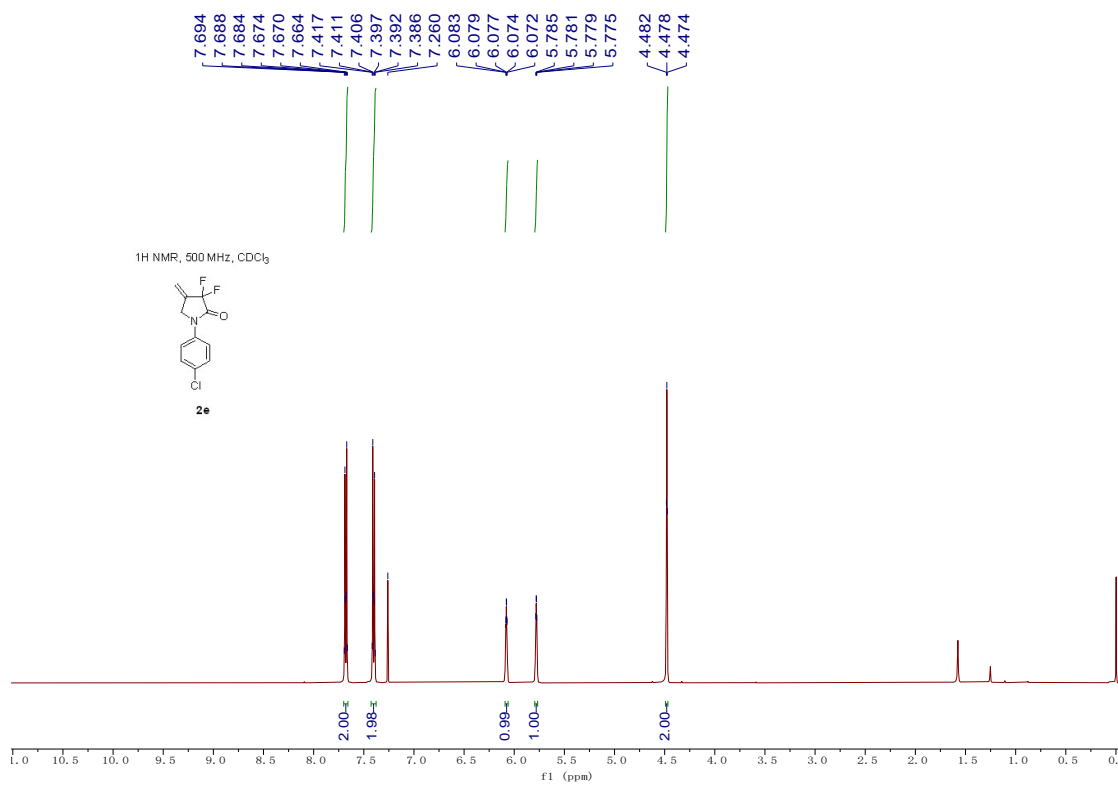
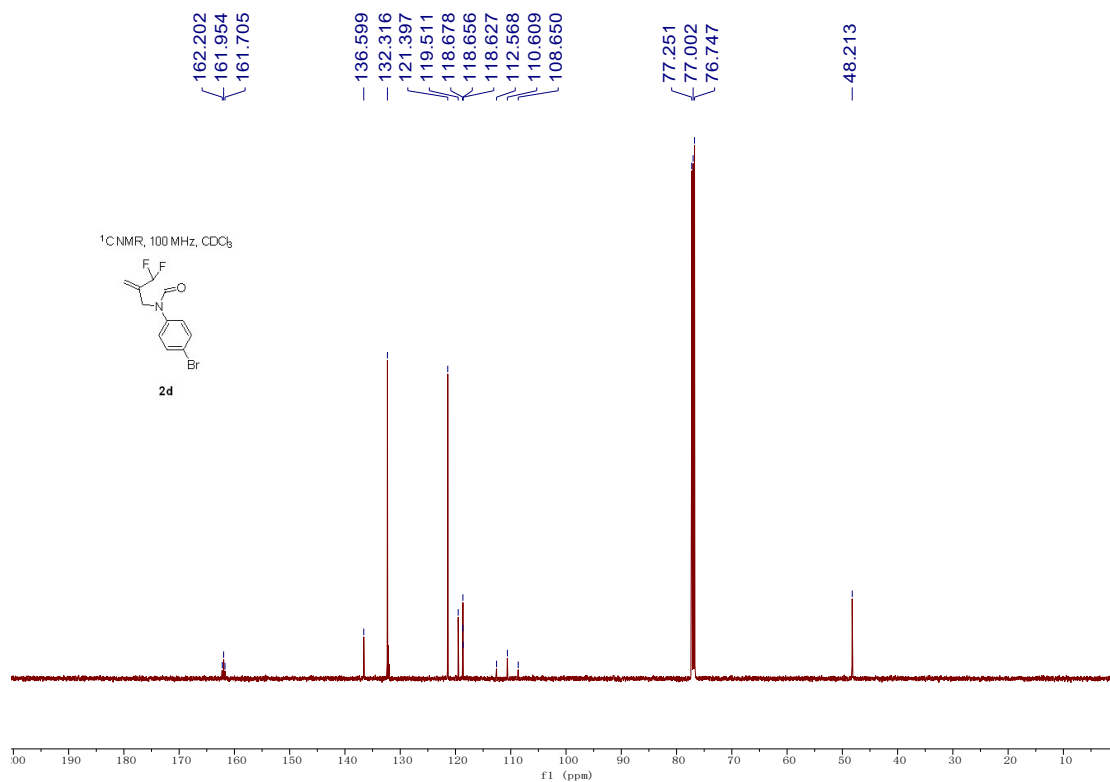
7. ^1H -NMR and ^{13}C -NMR Spectra of Products

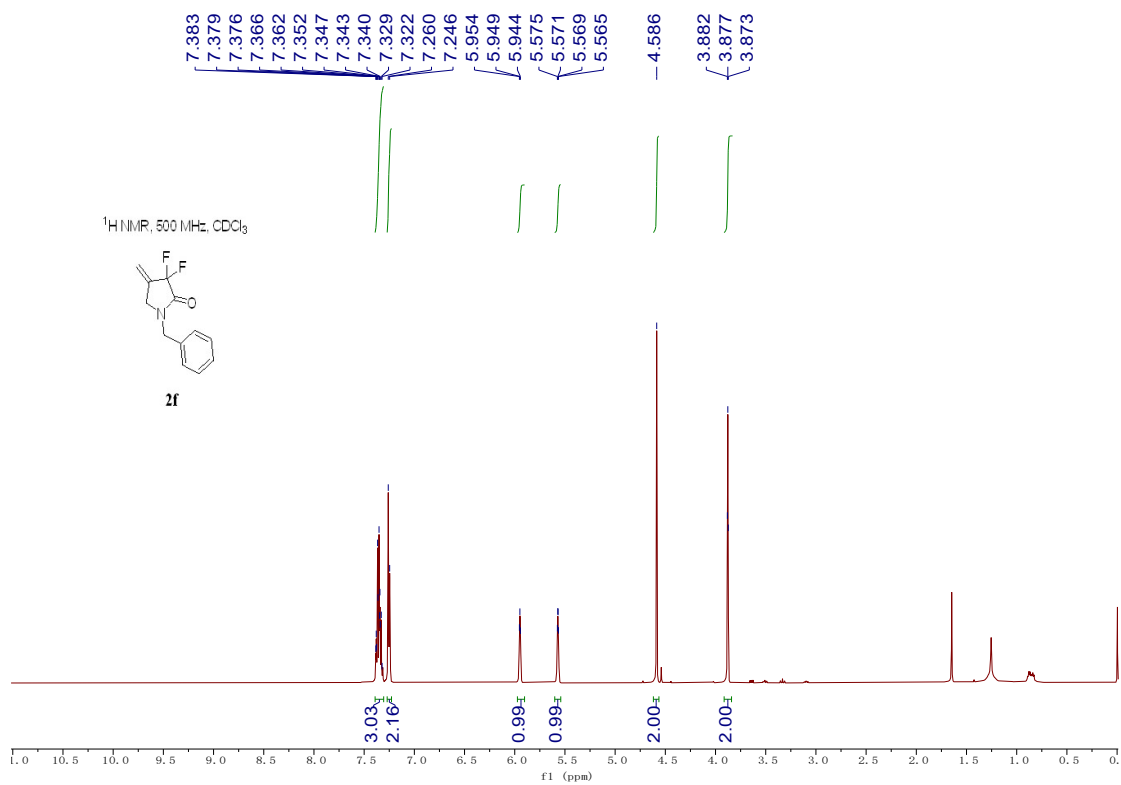
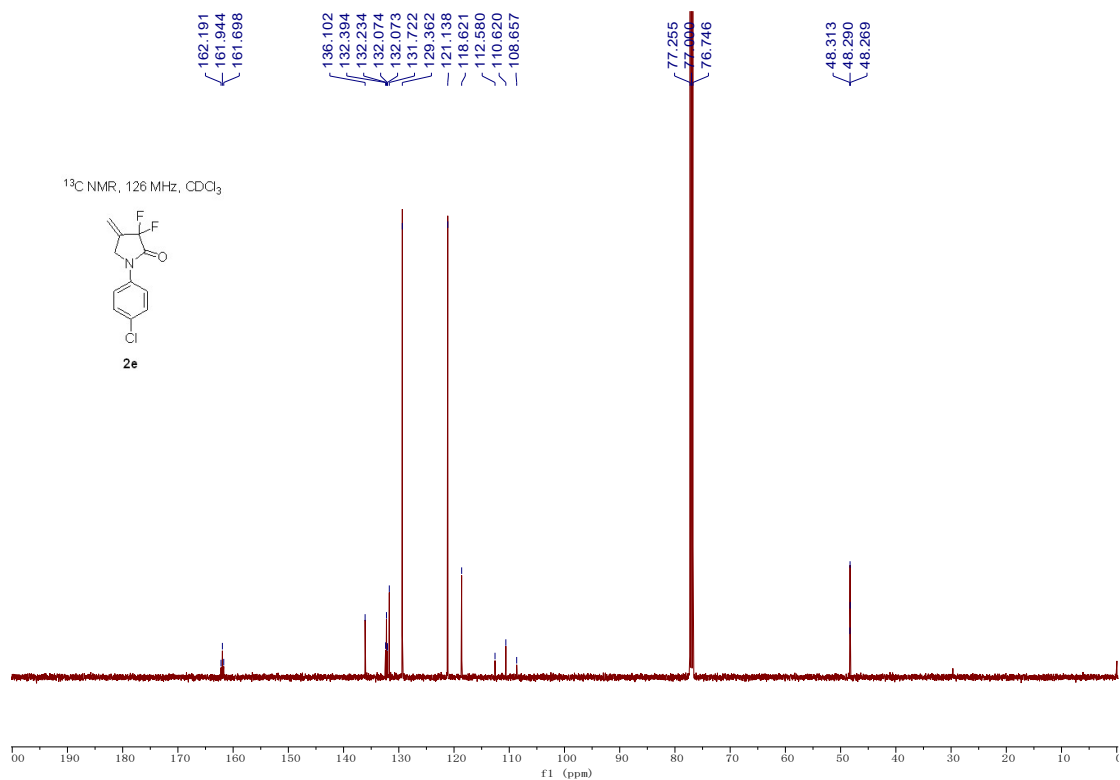


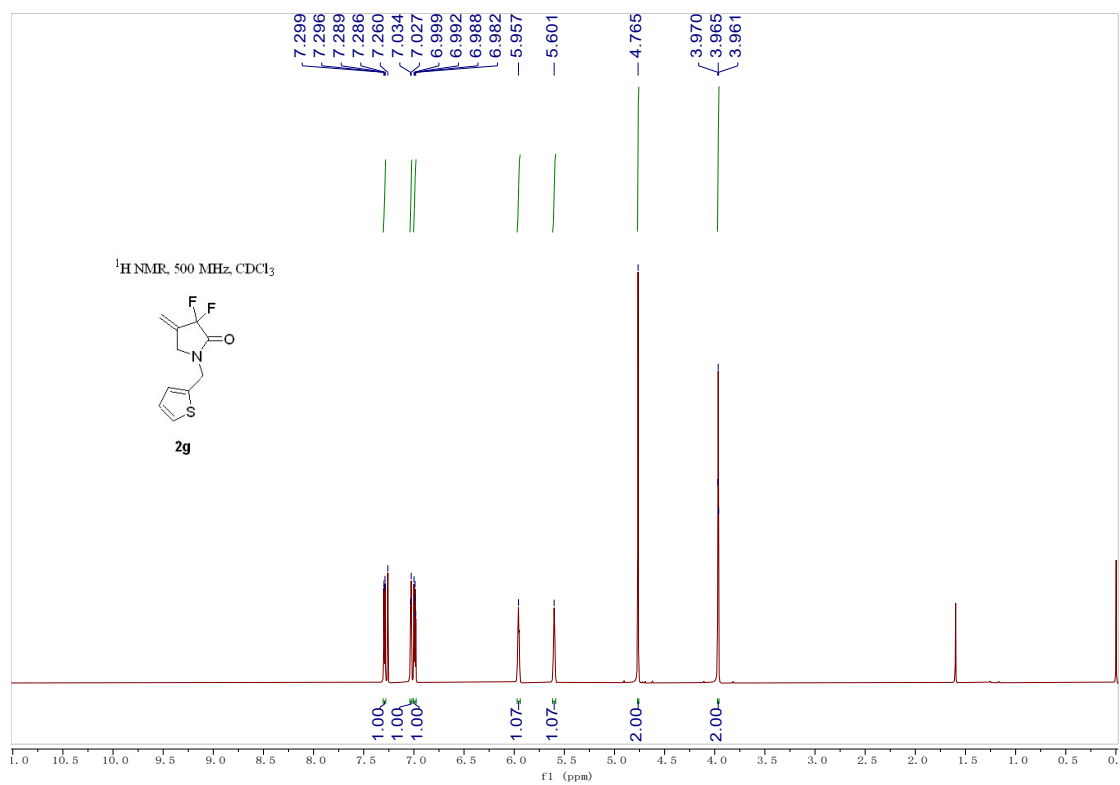
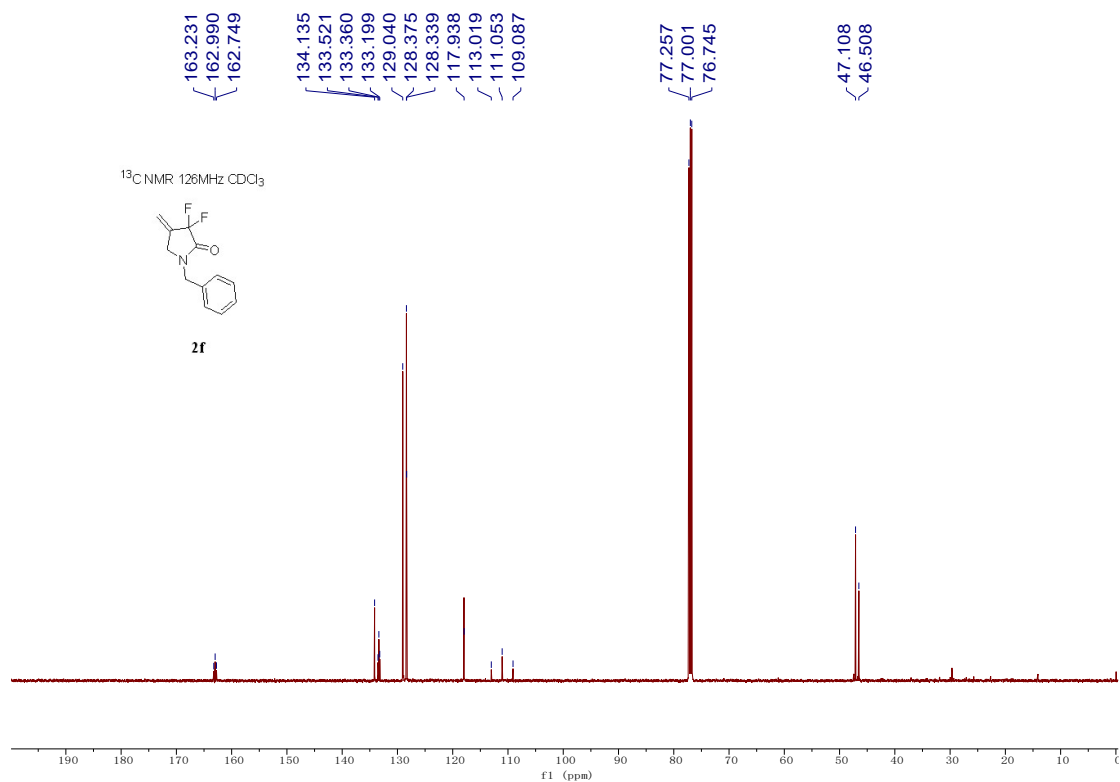


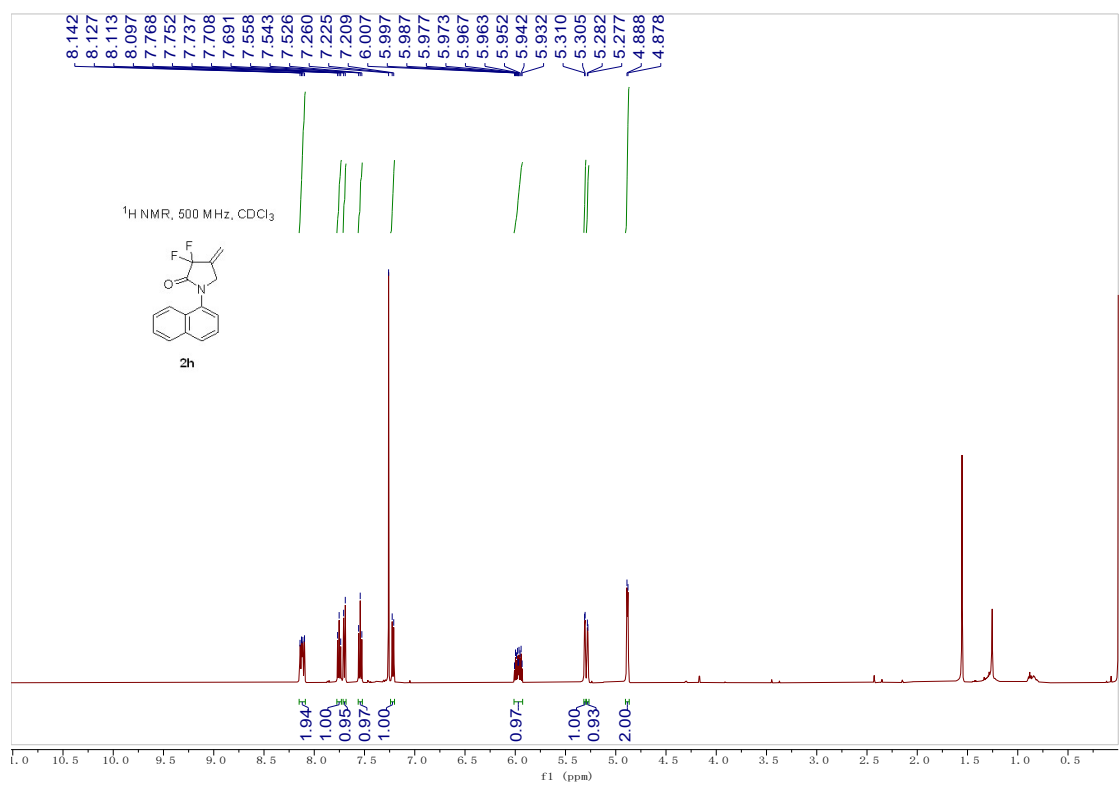
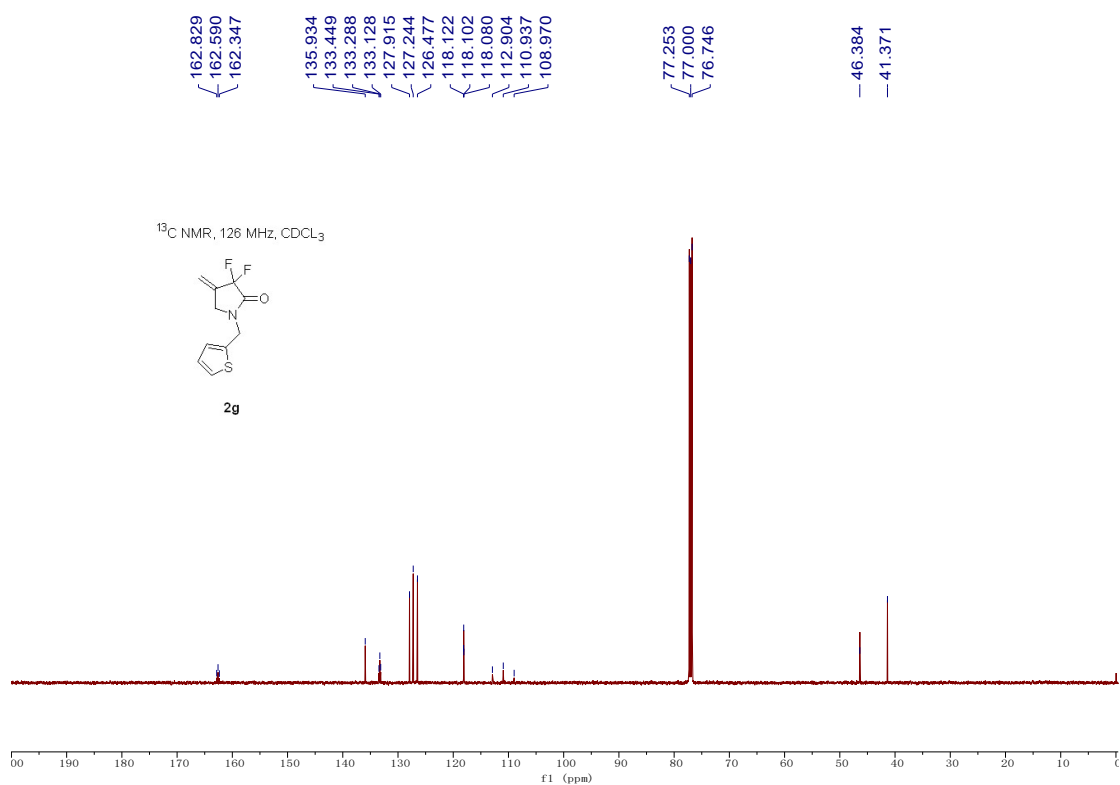


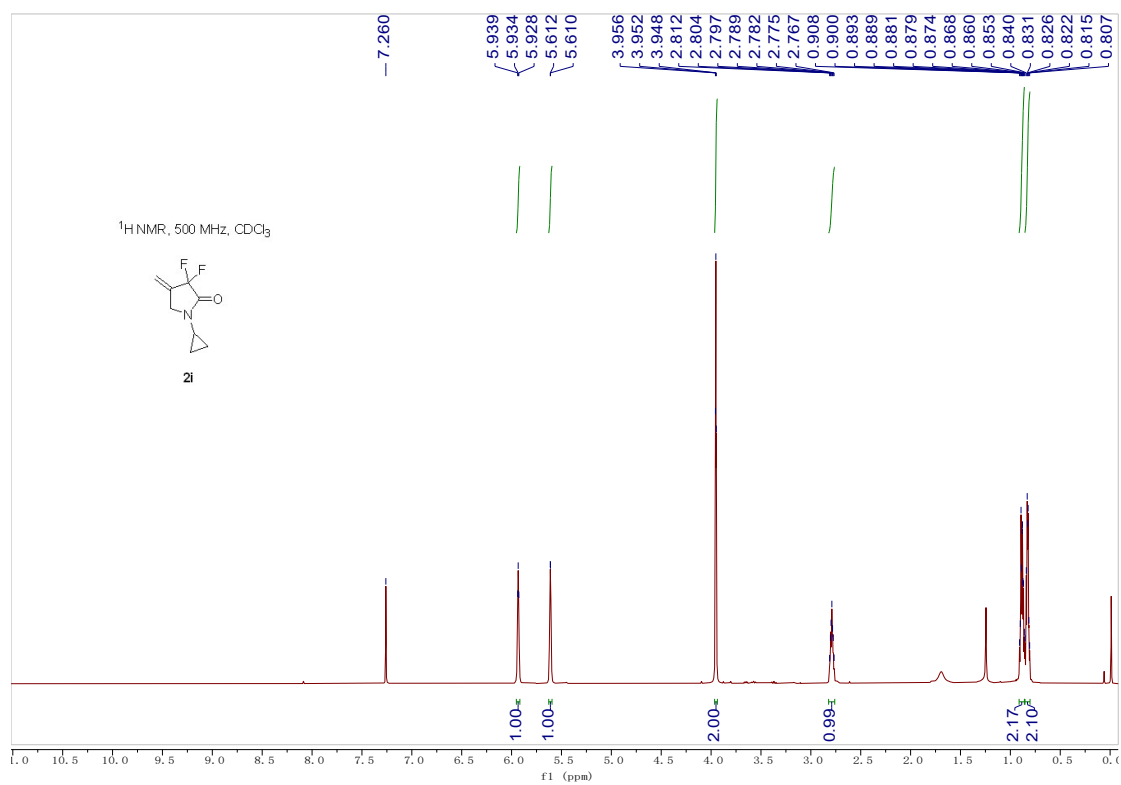
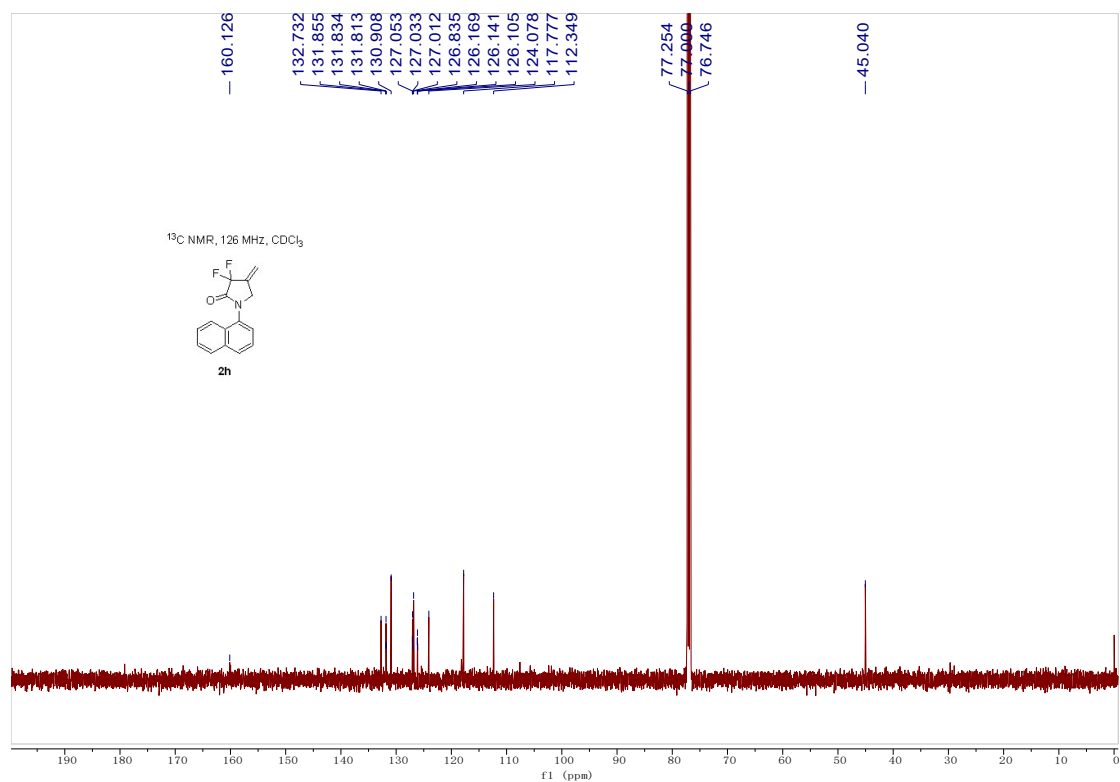


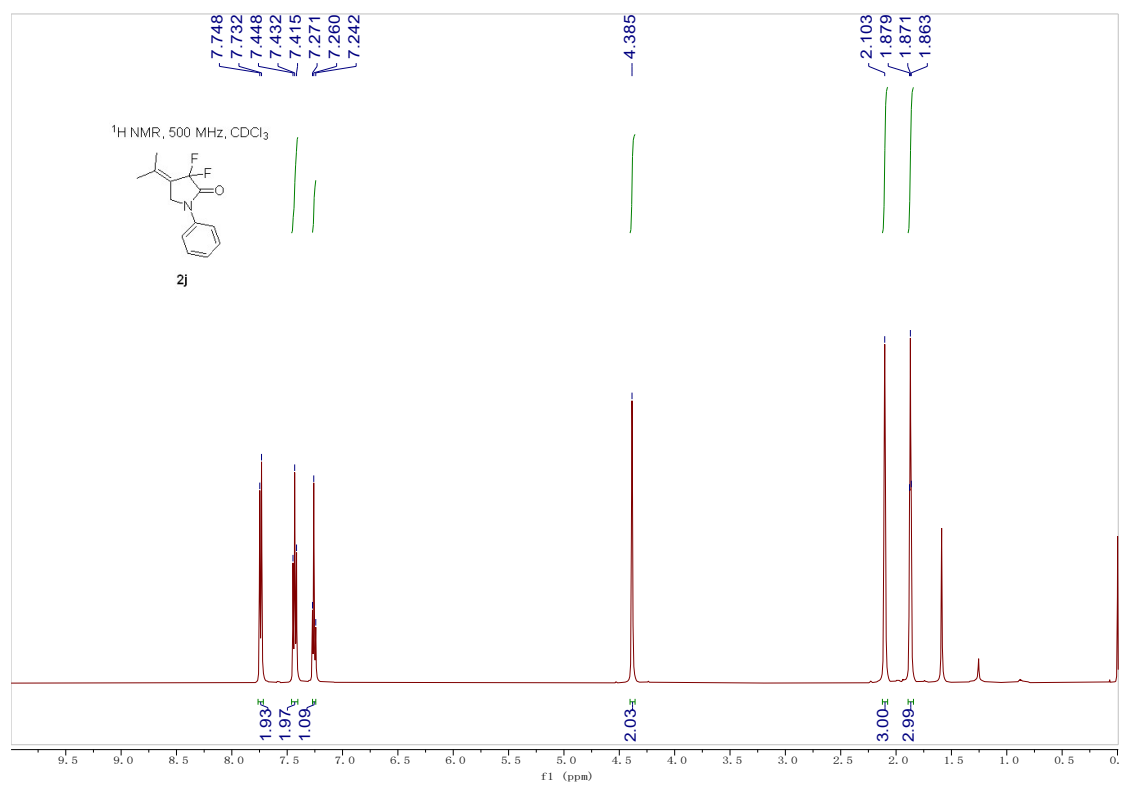
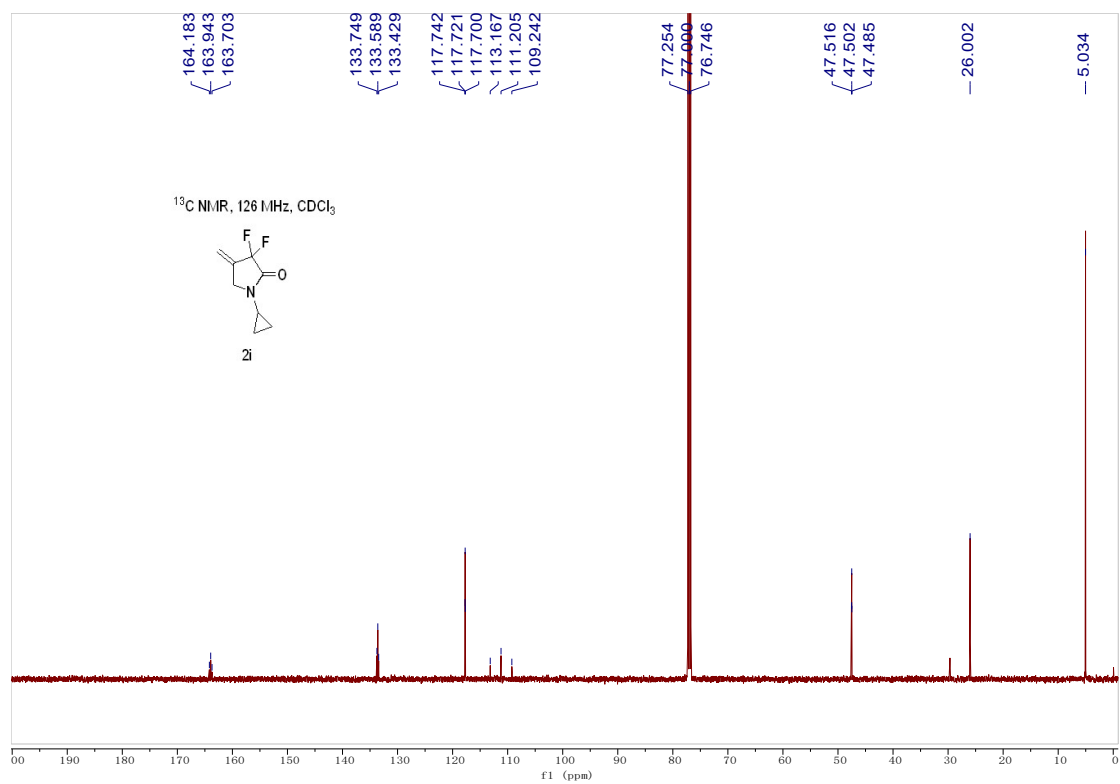


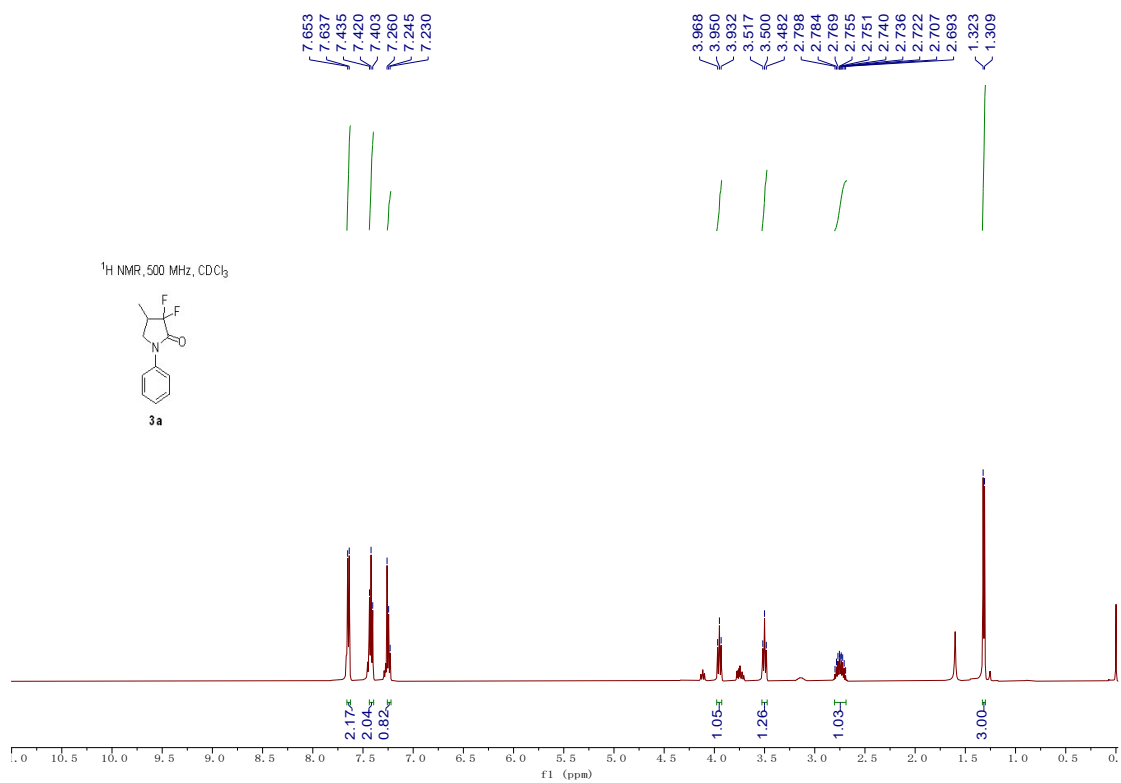
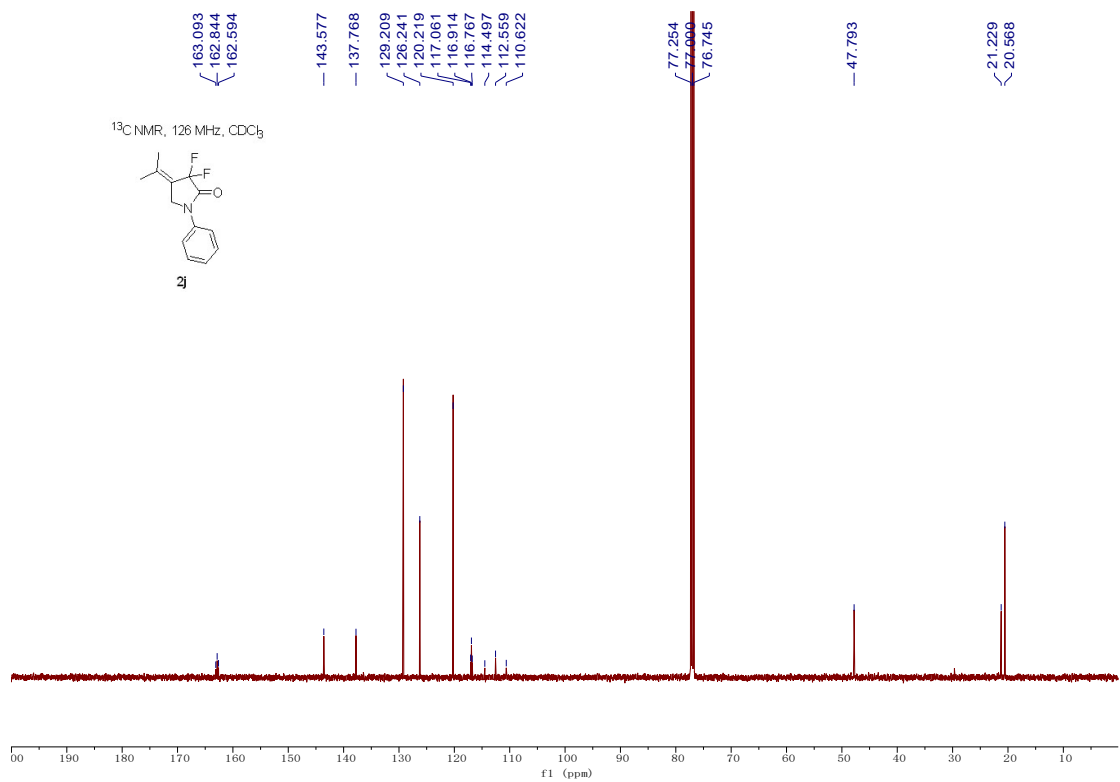


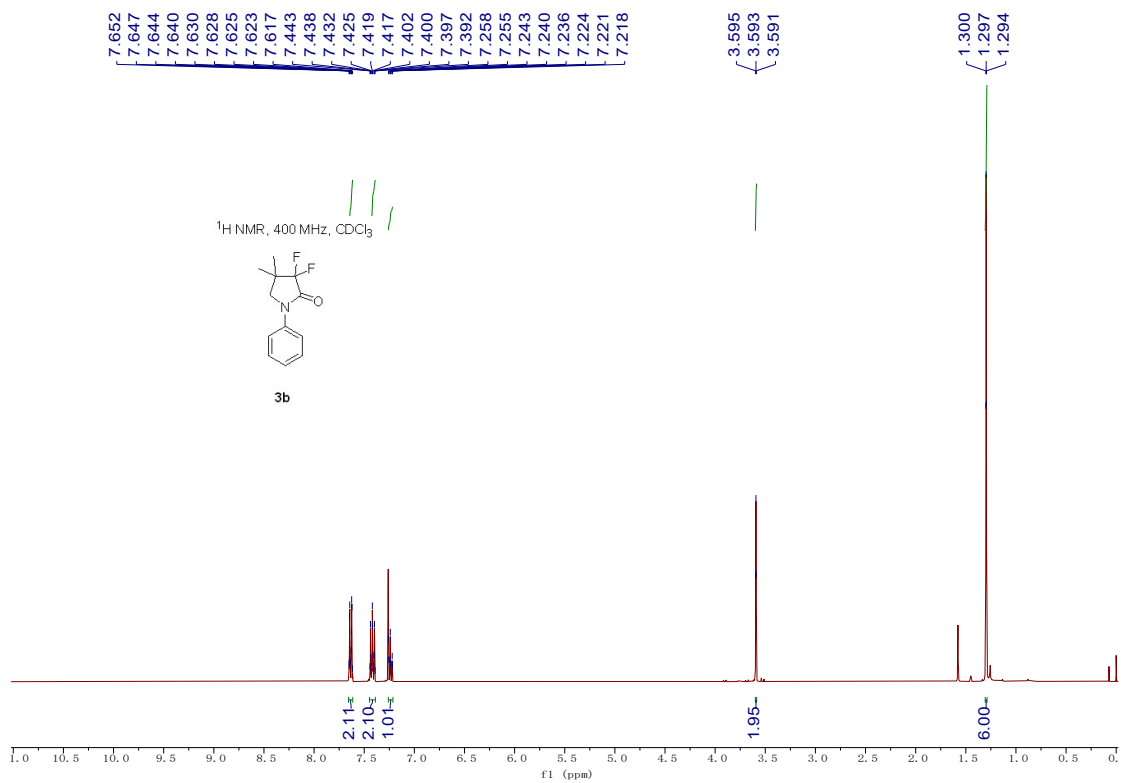
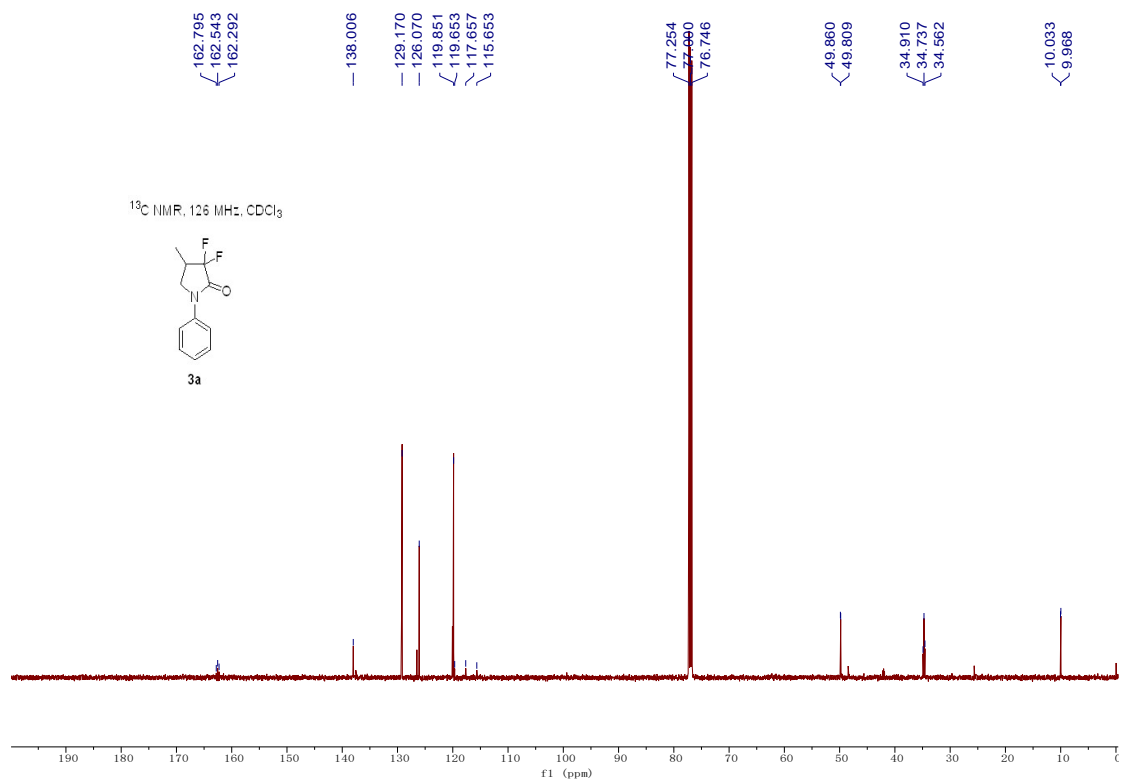


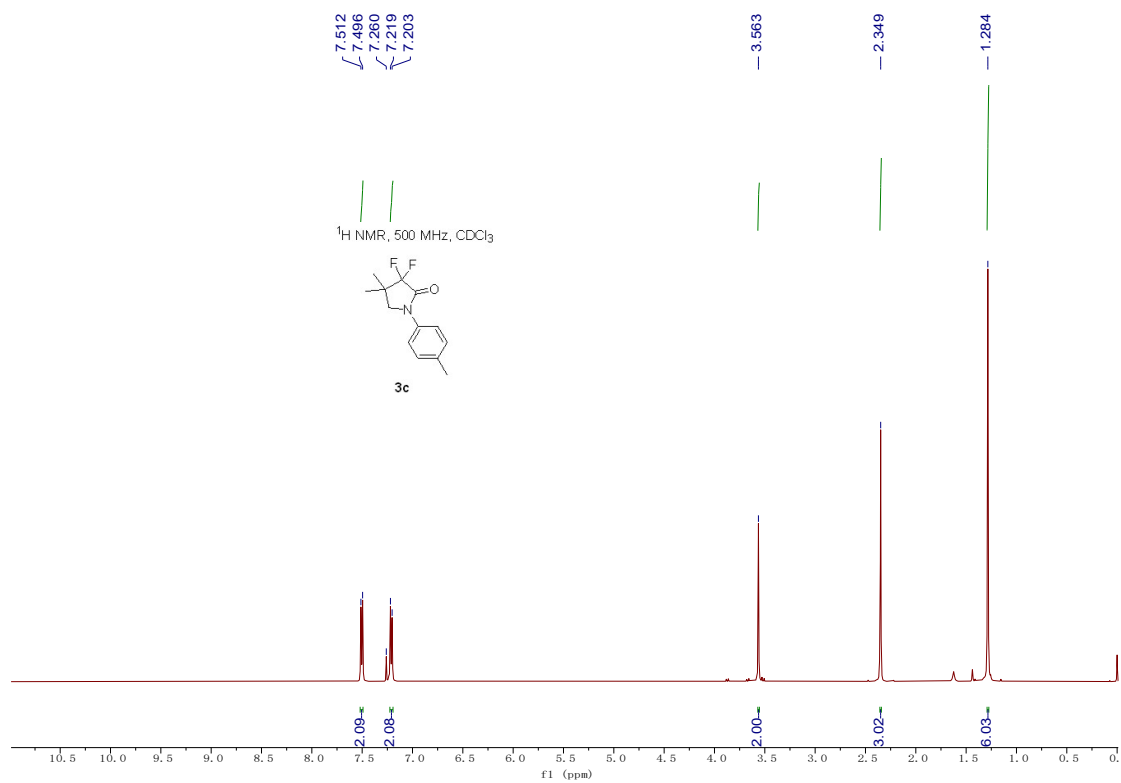
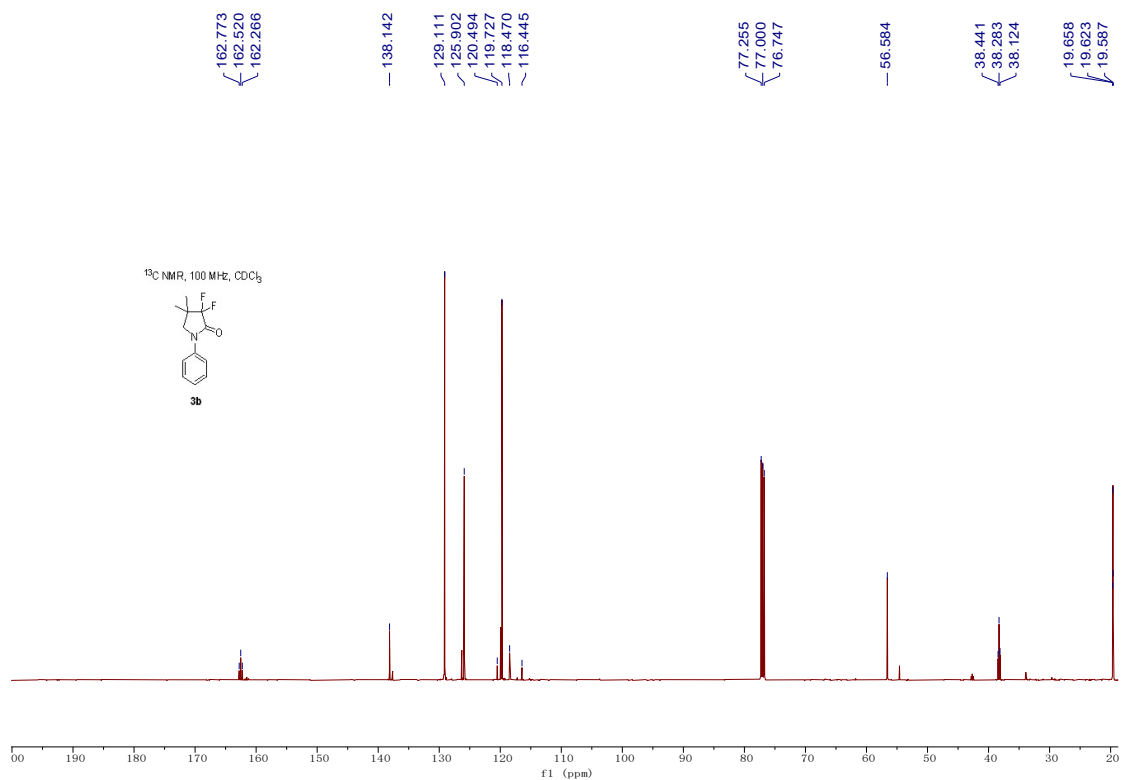


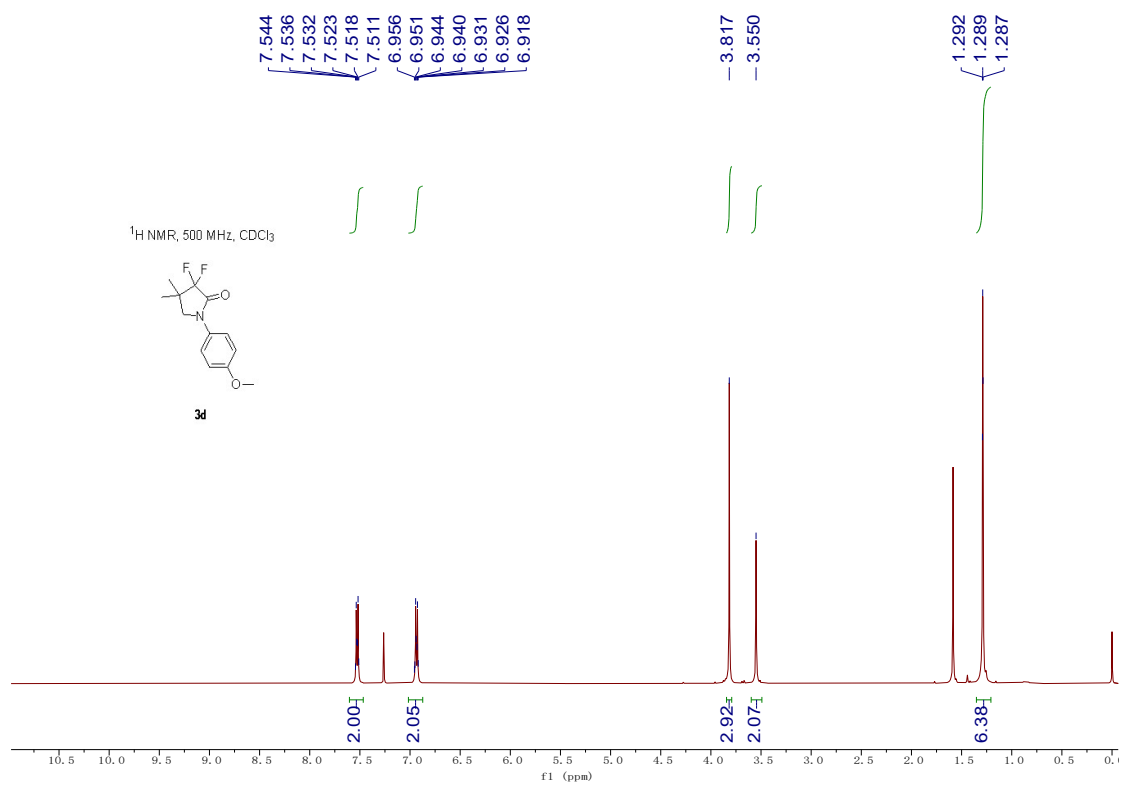
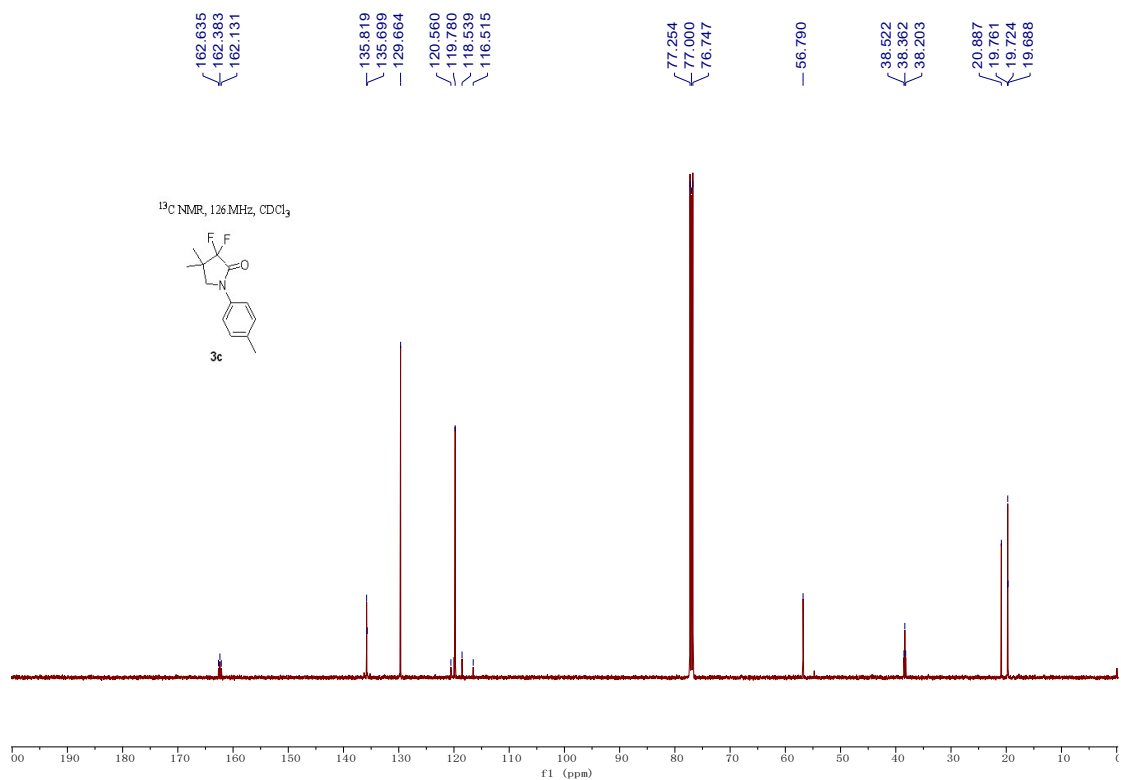


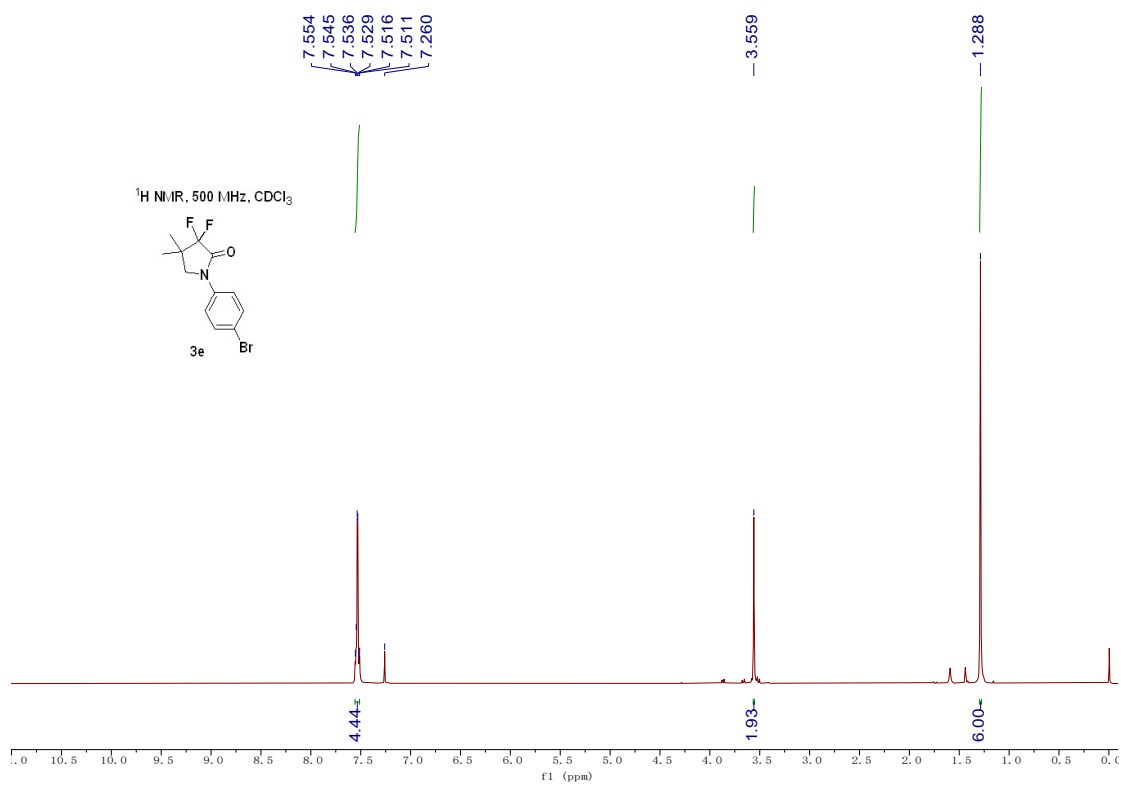
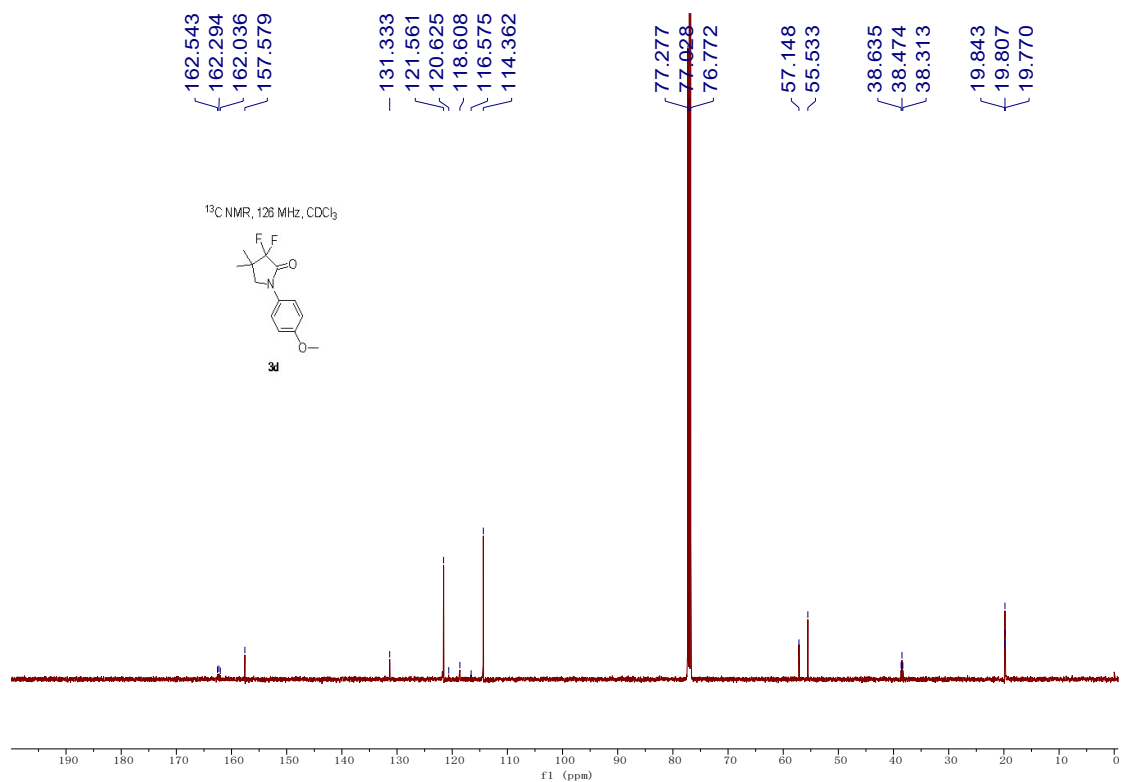


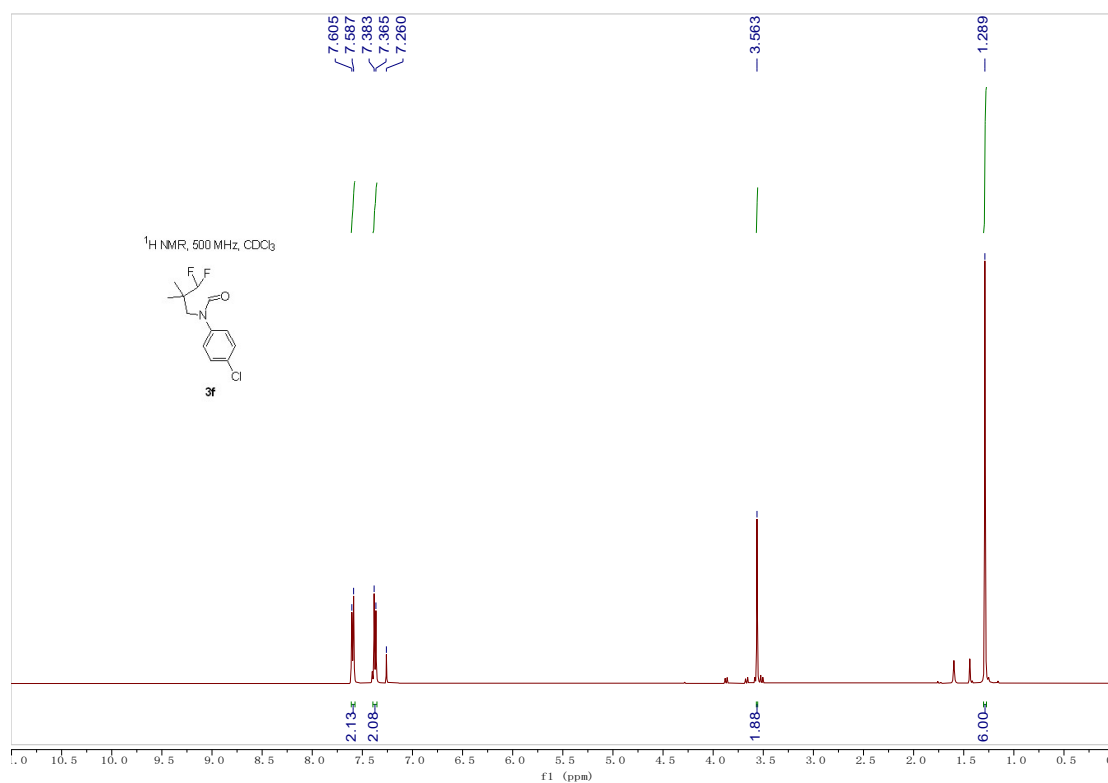
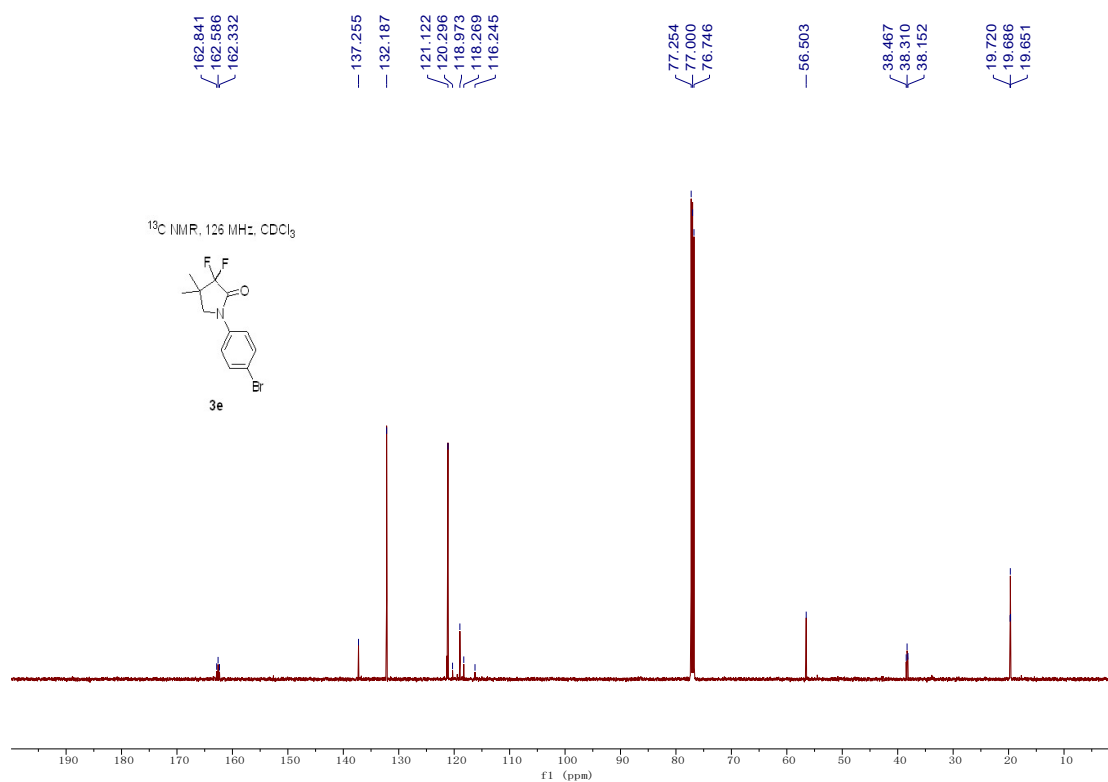


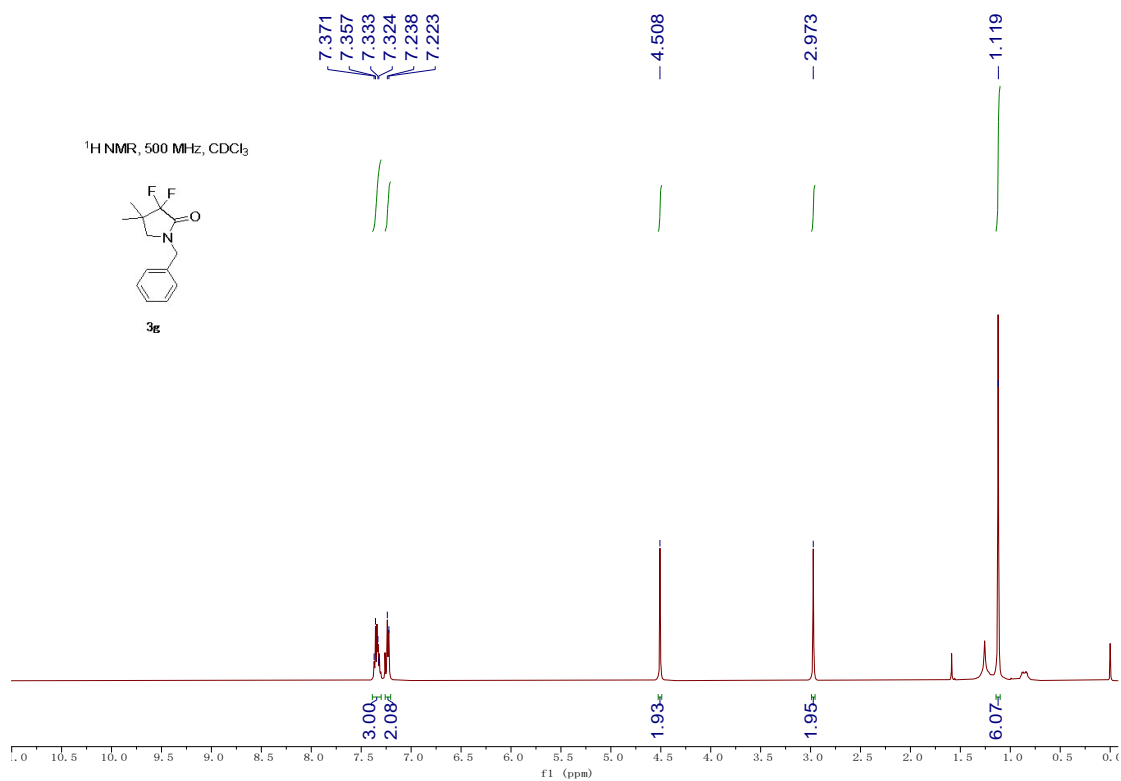
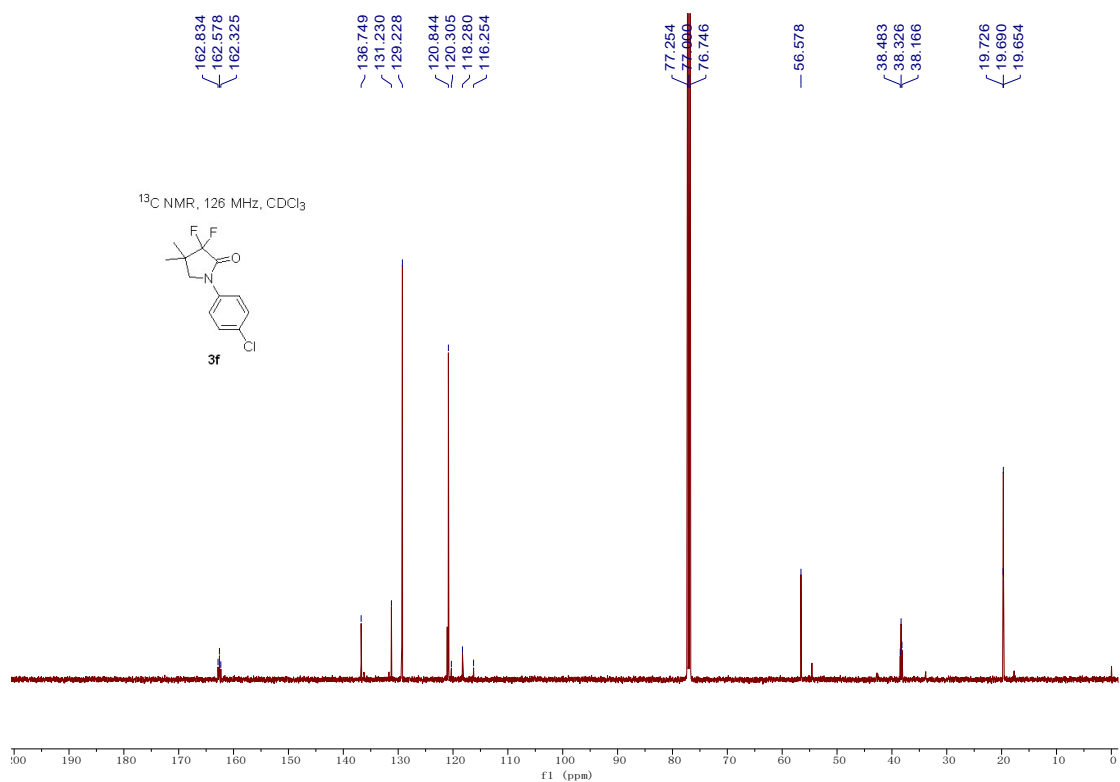


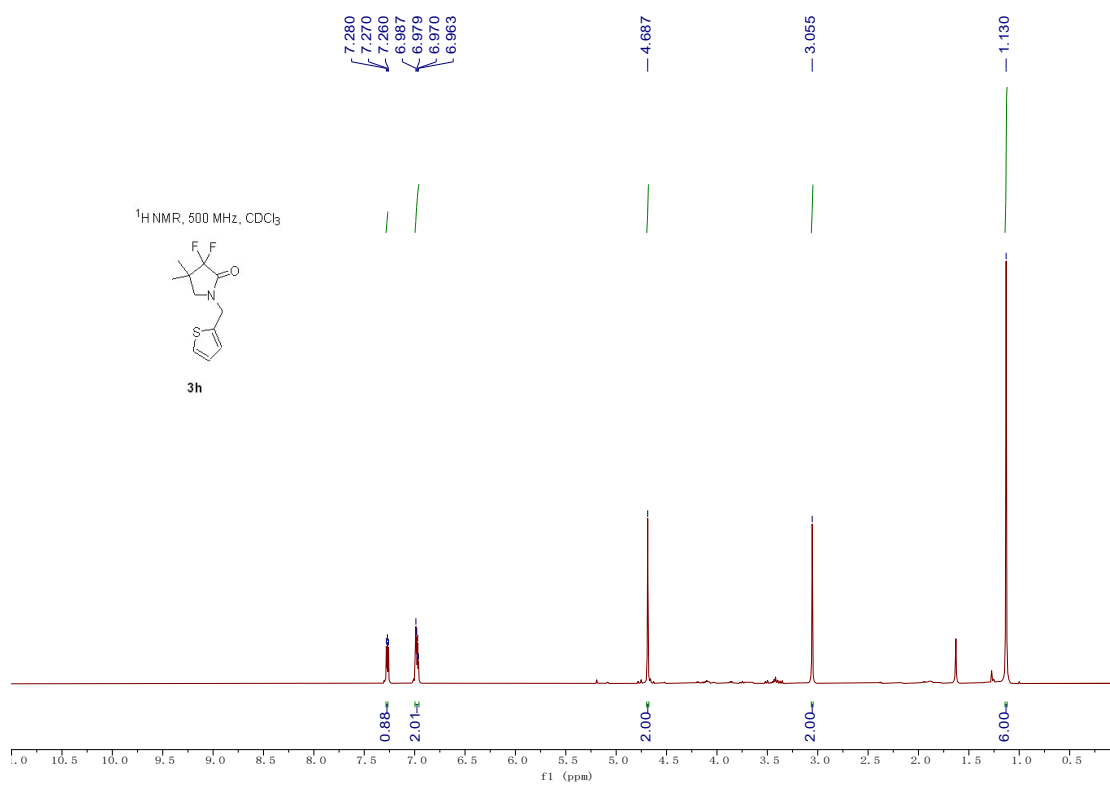
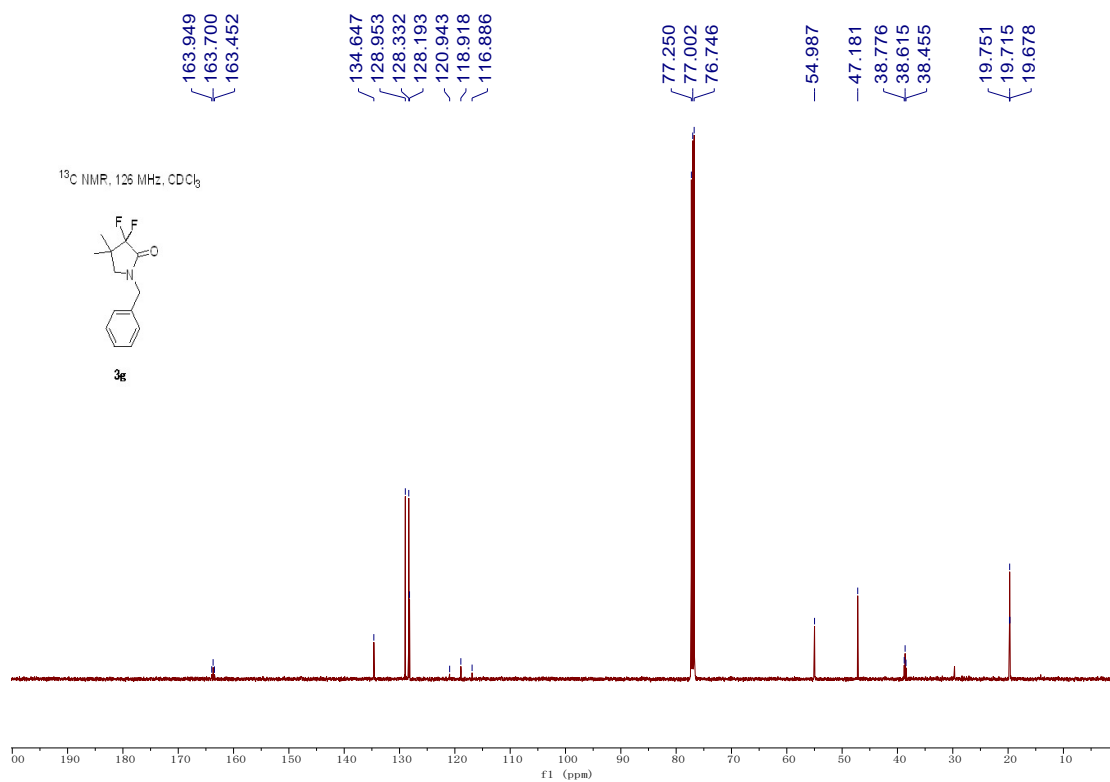


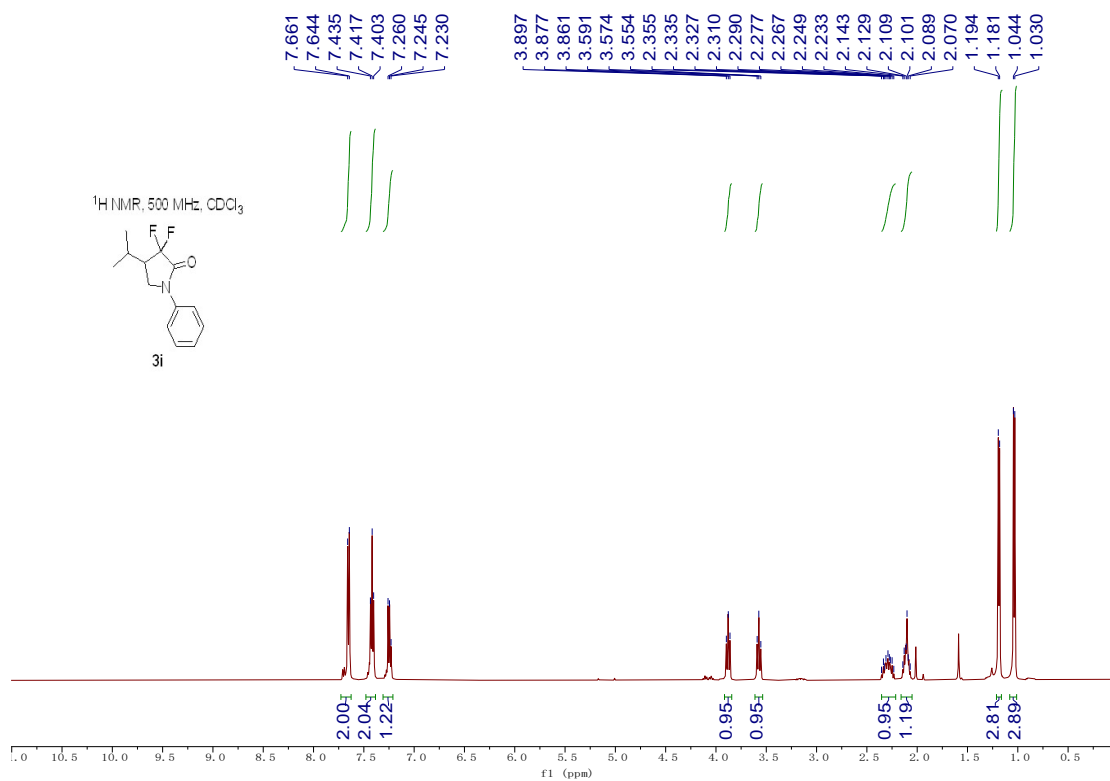
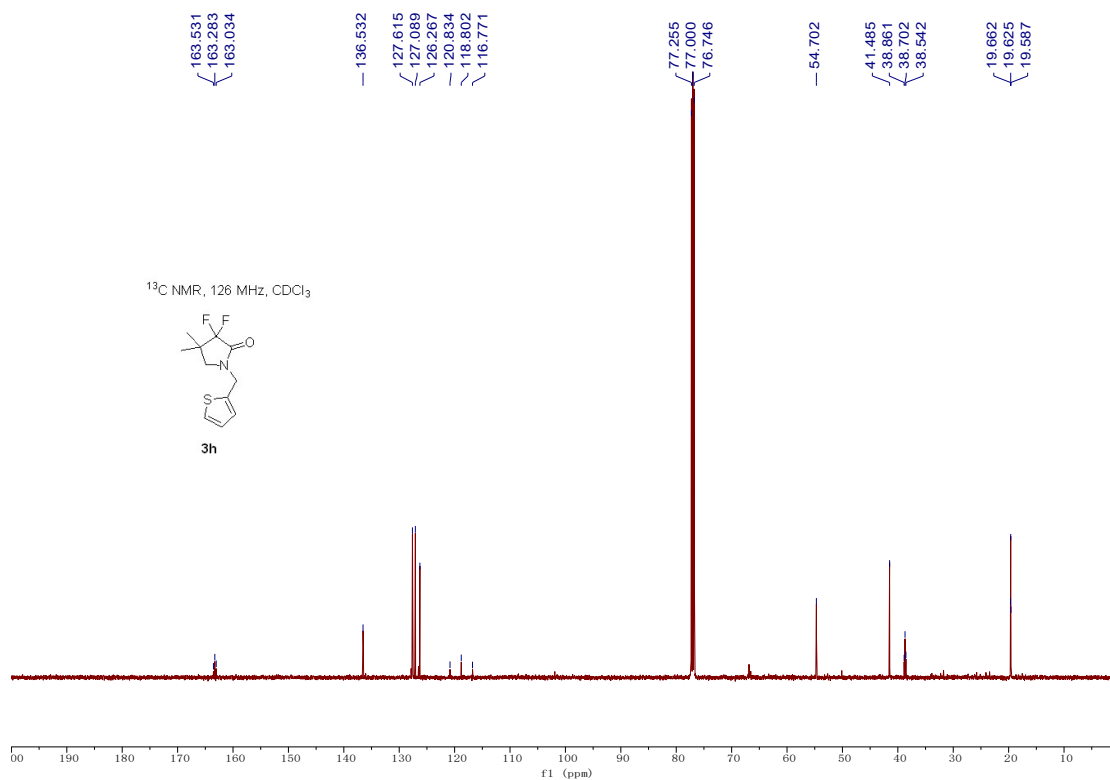


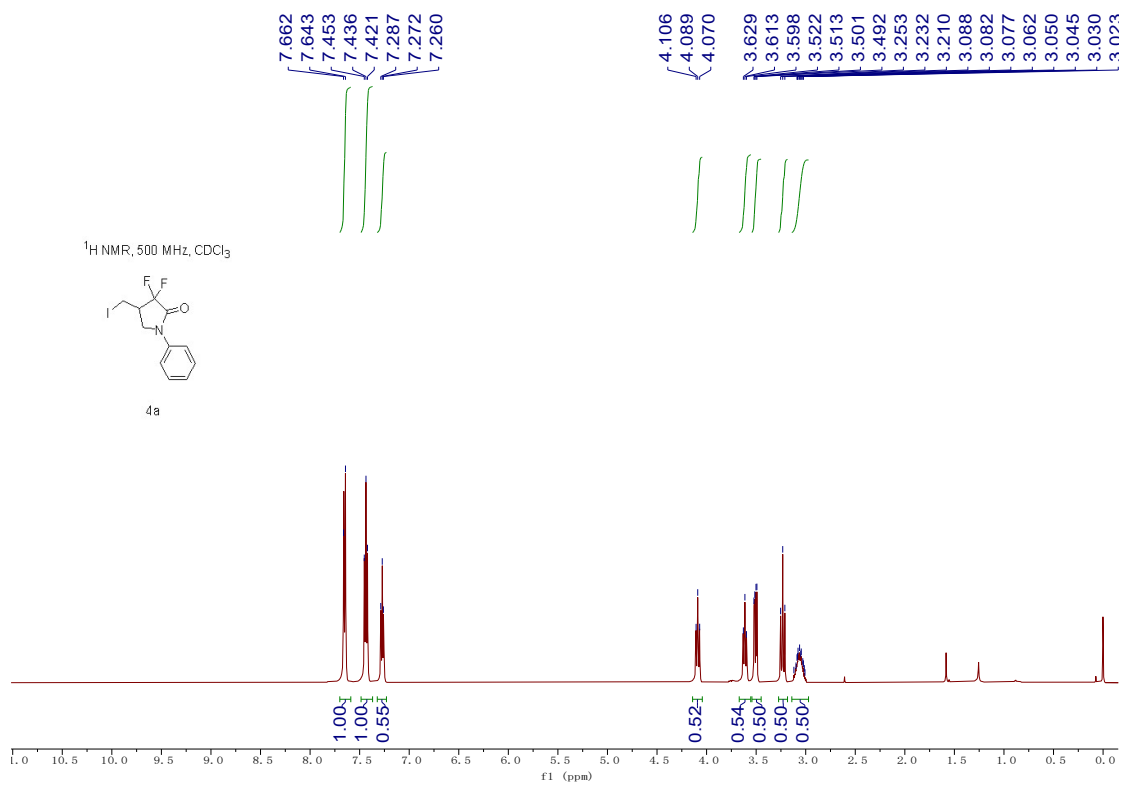
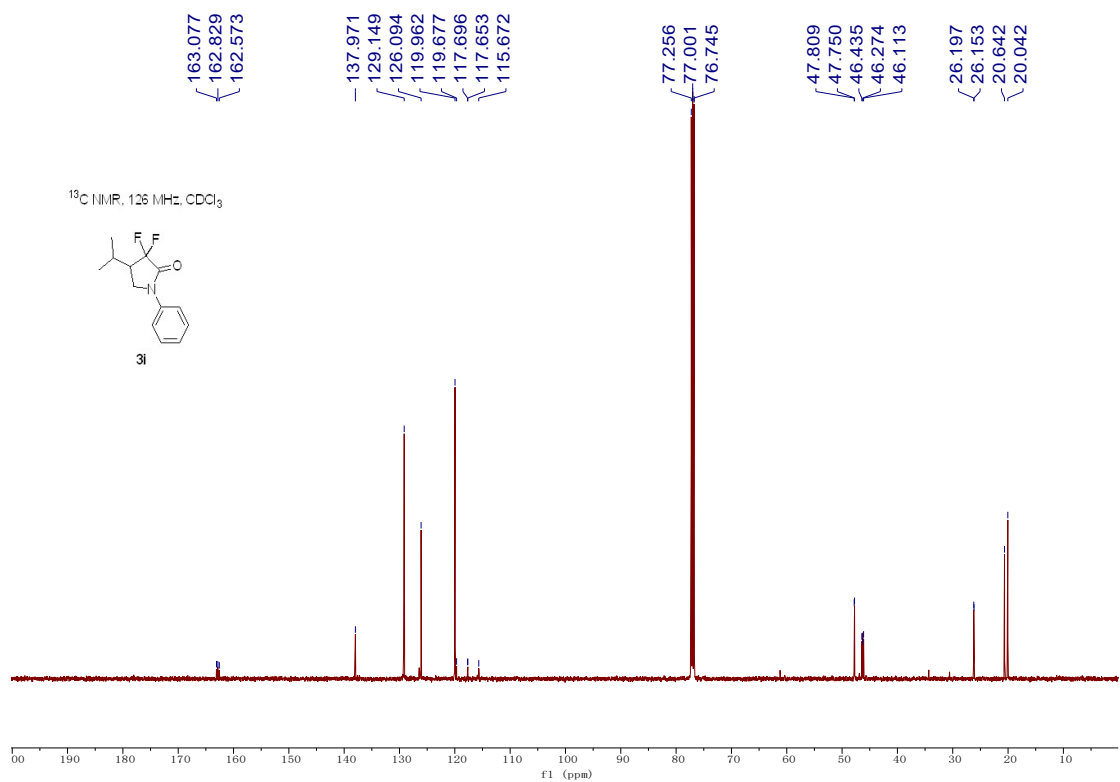


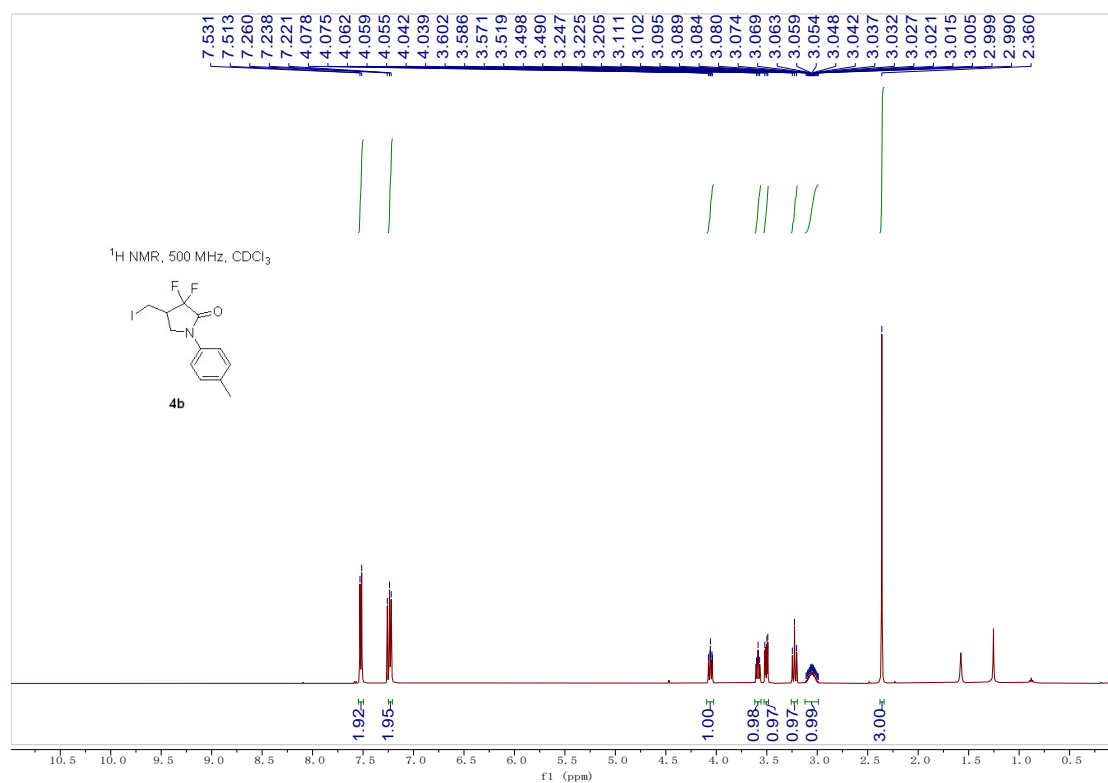
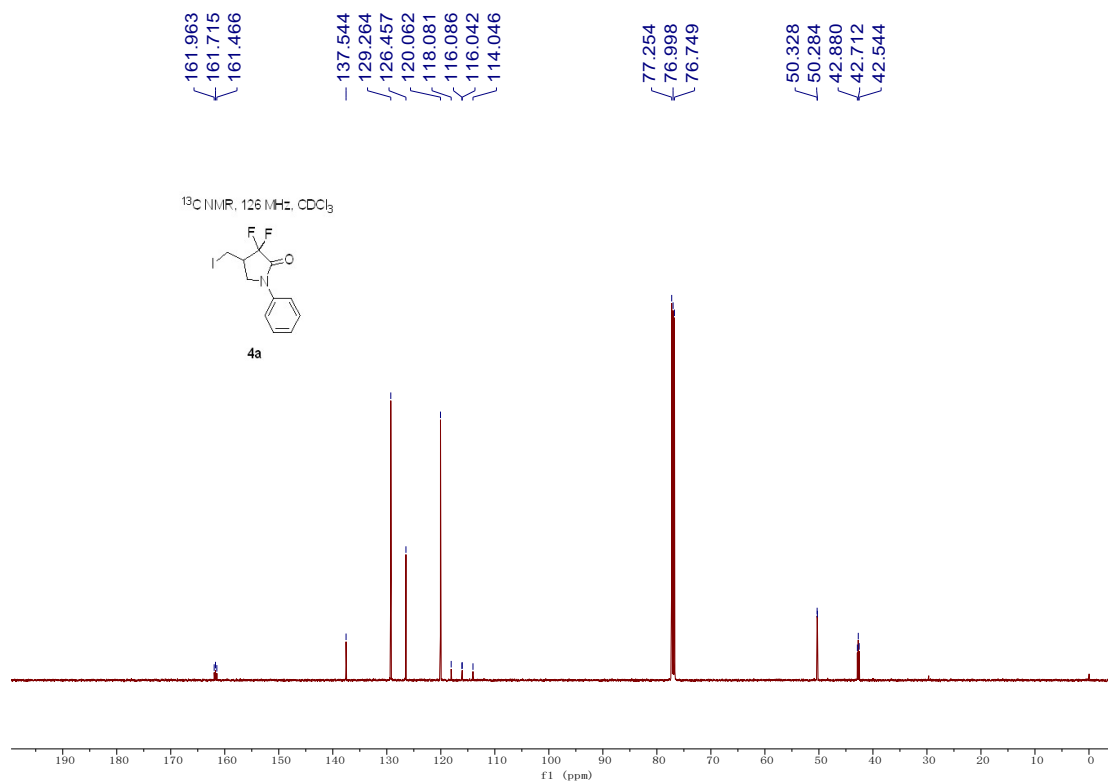


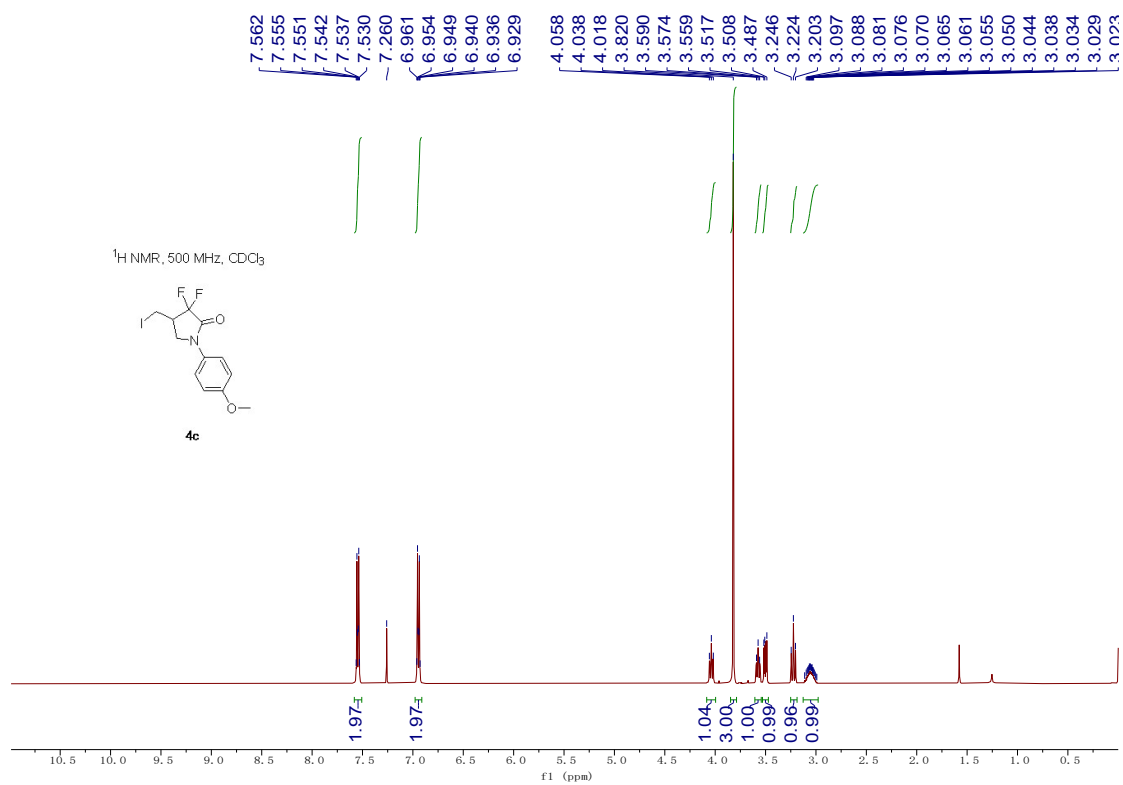
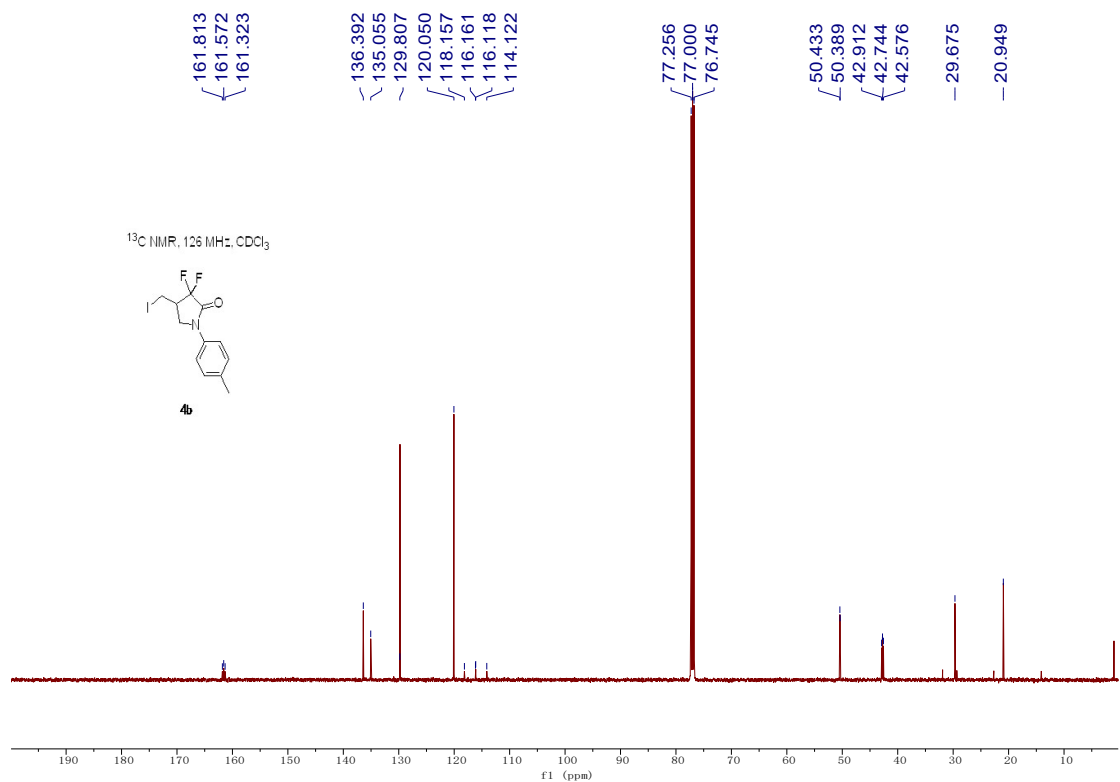


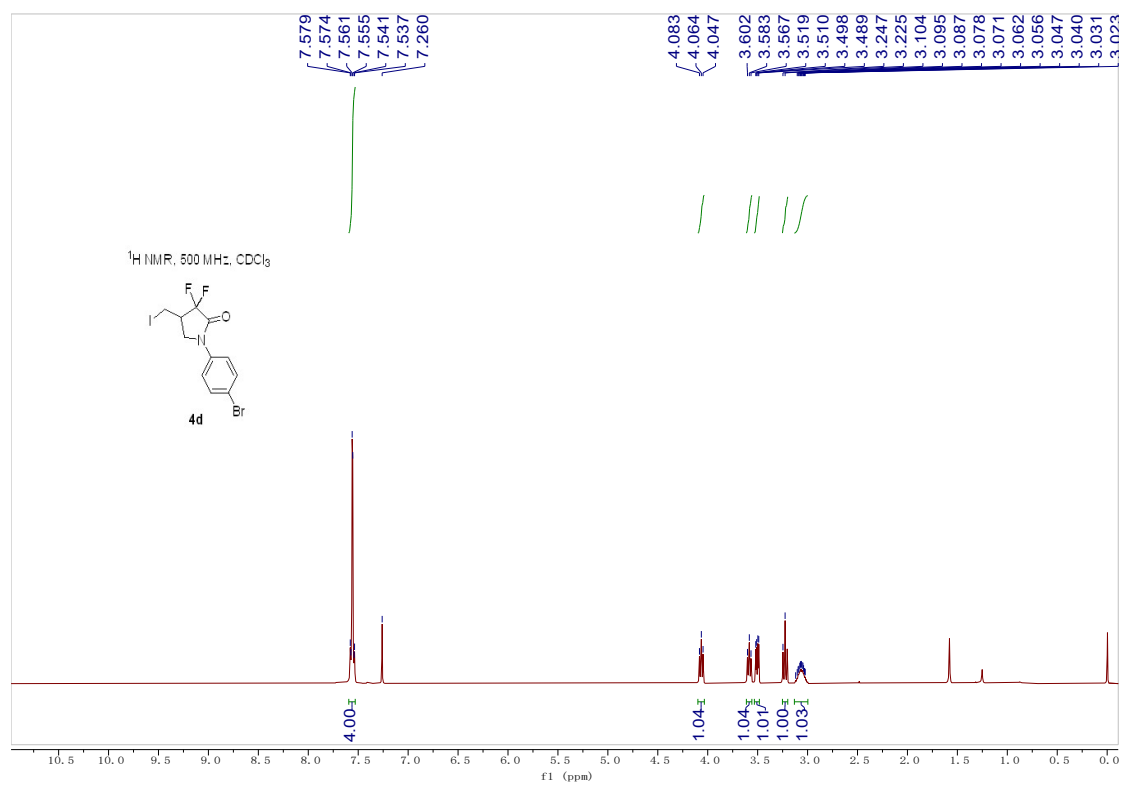
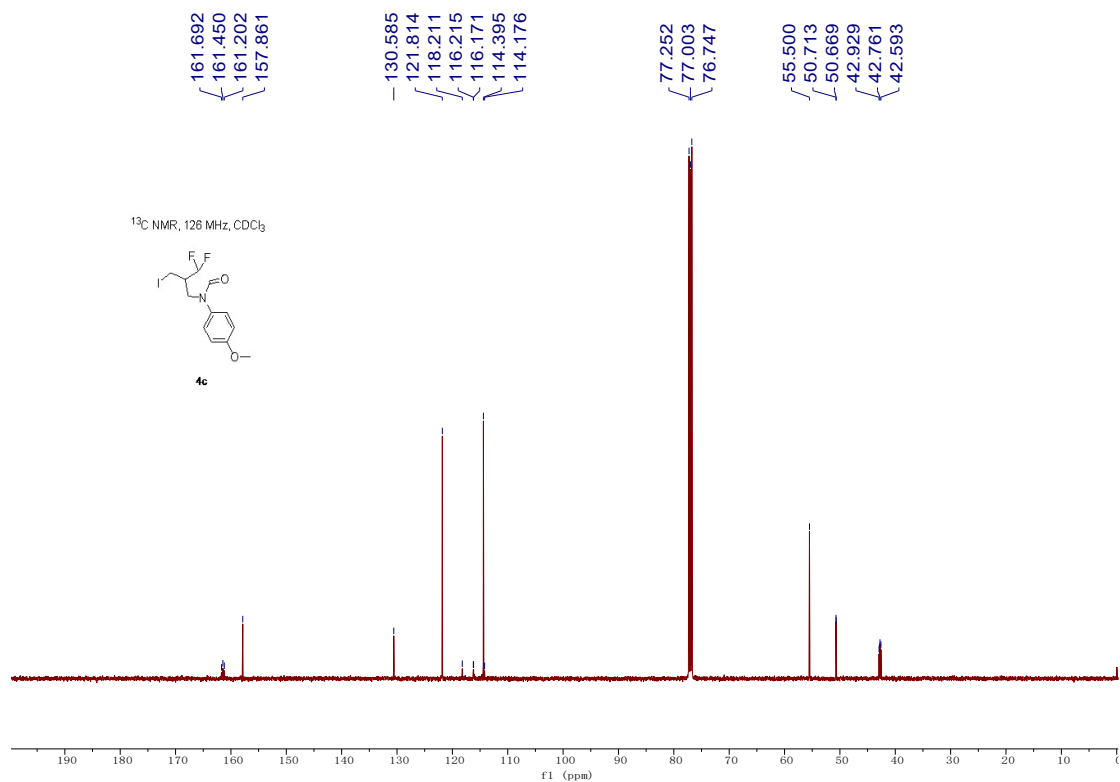


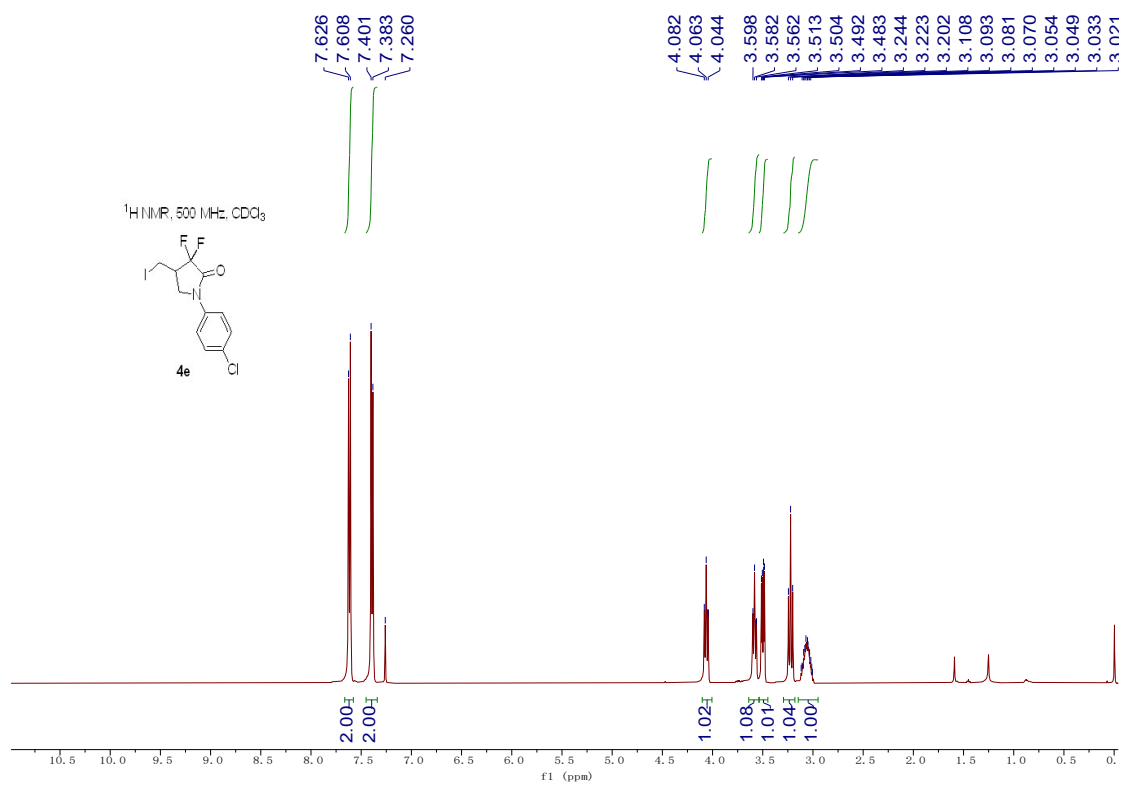
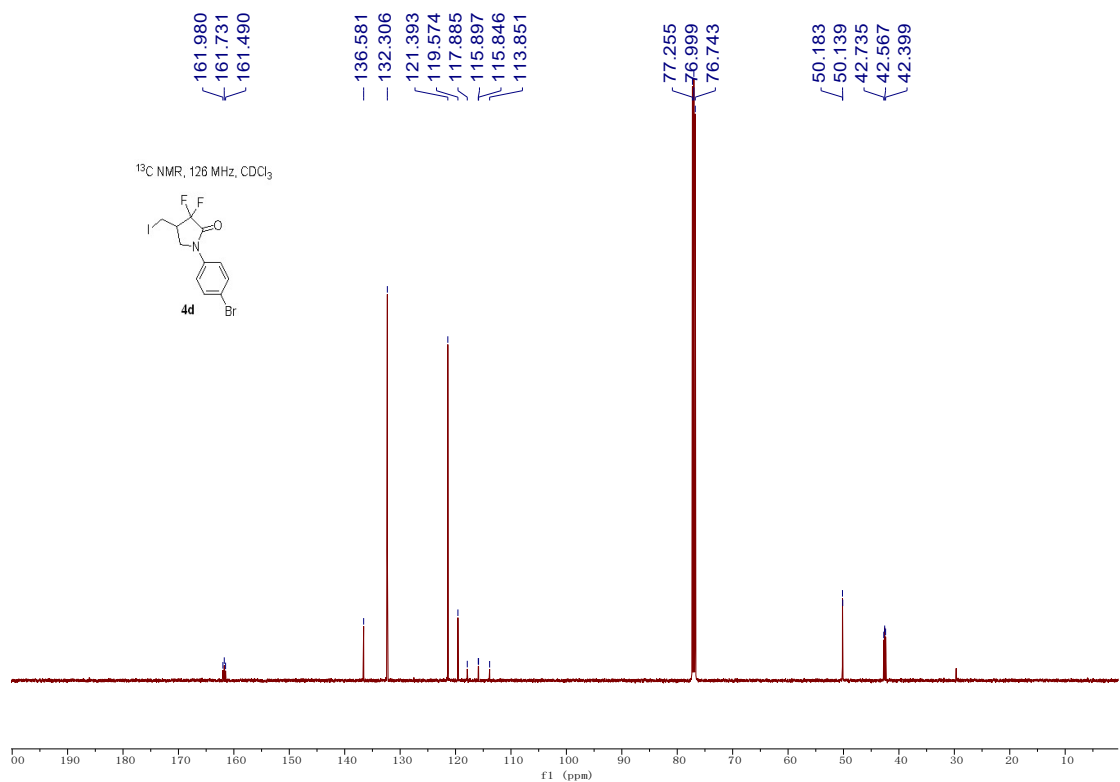


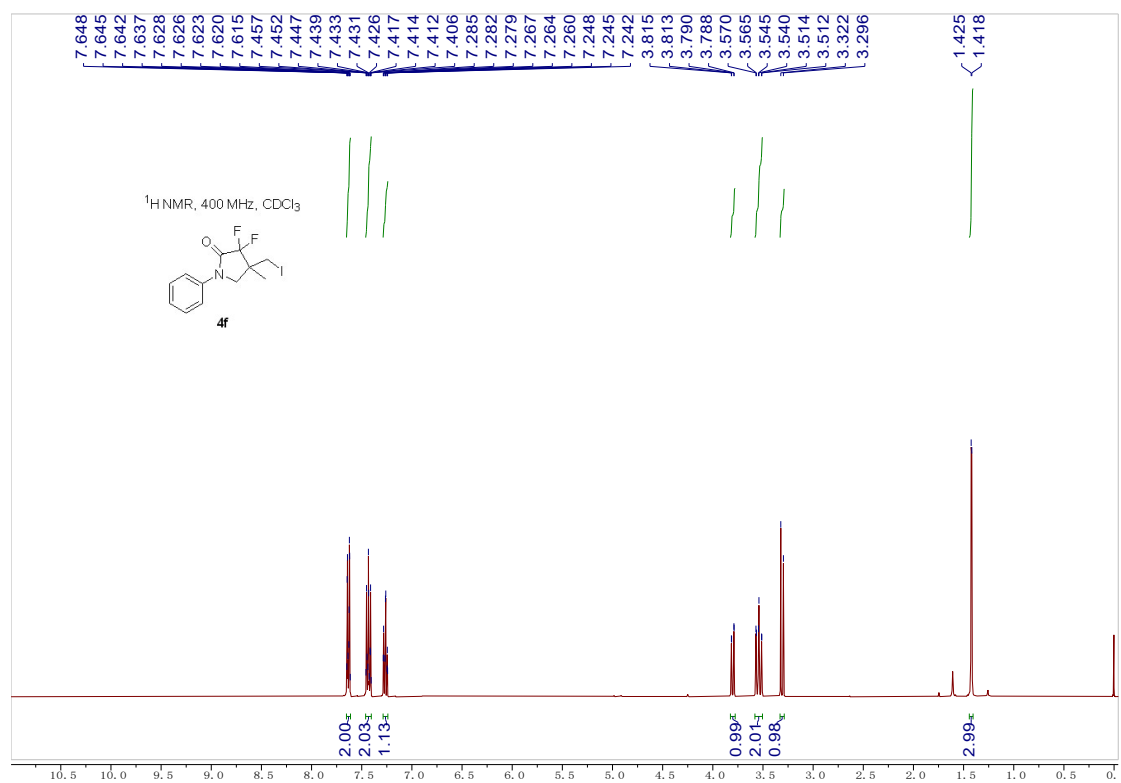
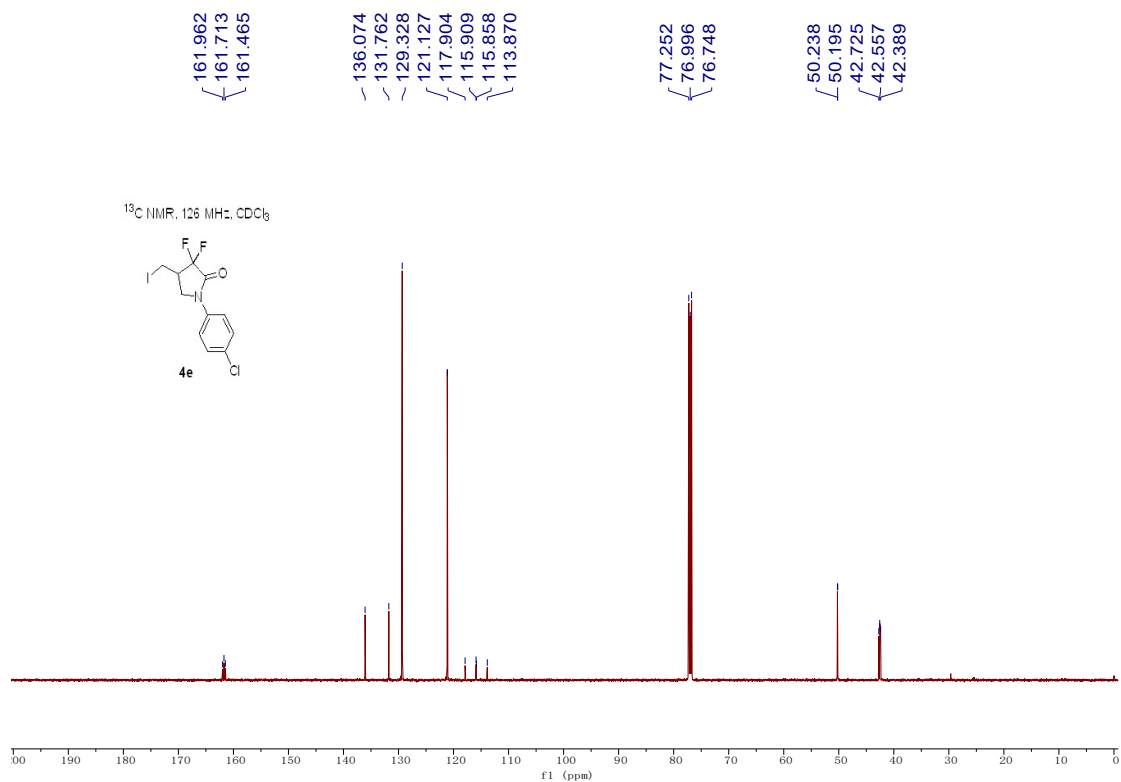


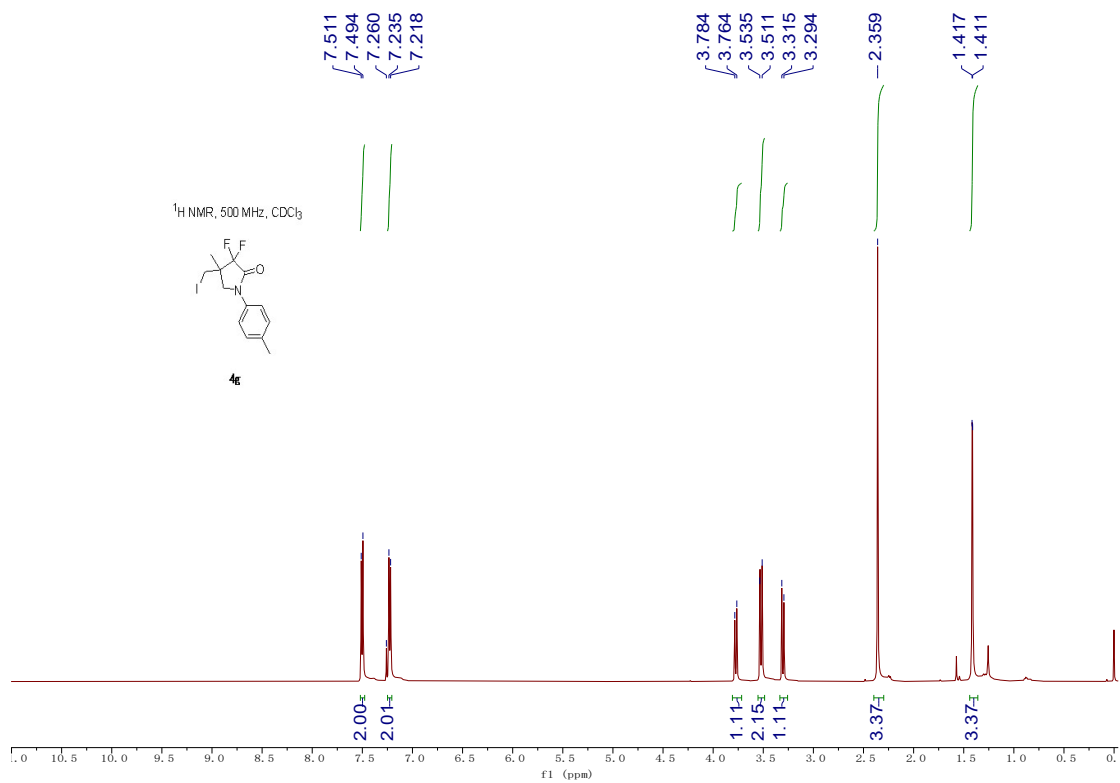
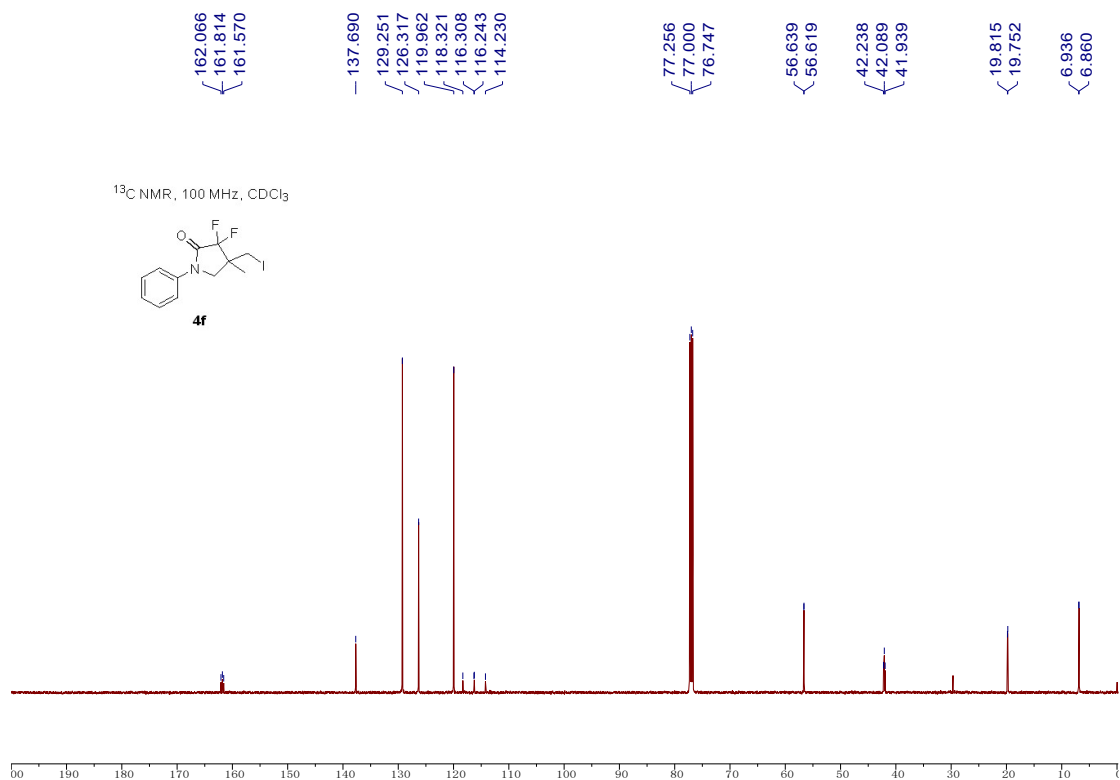


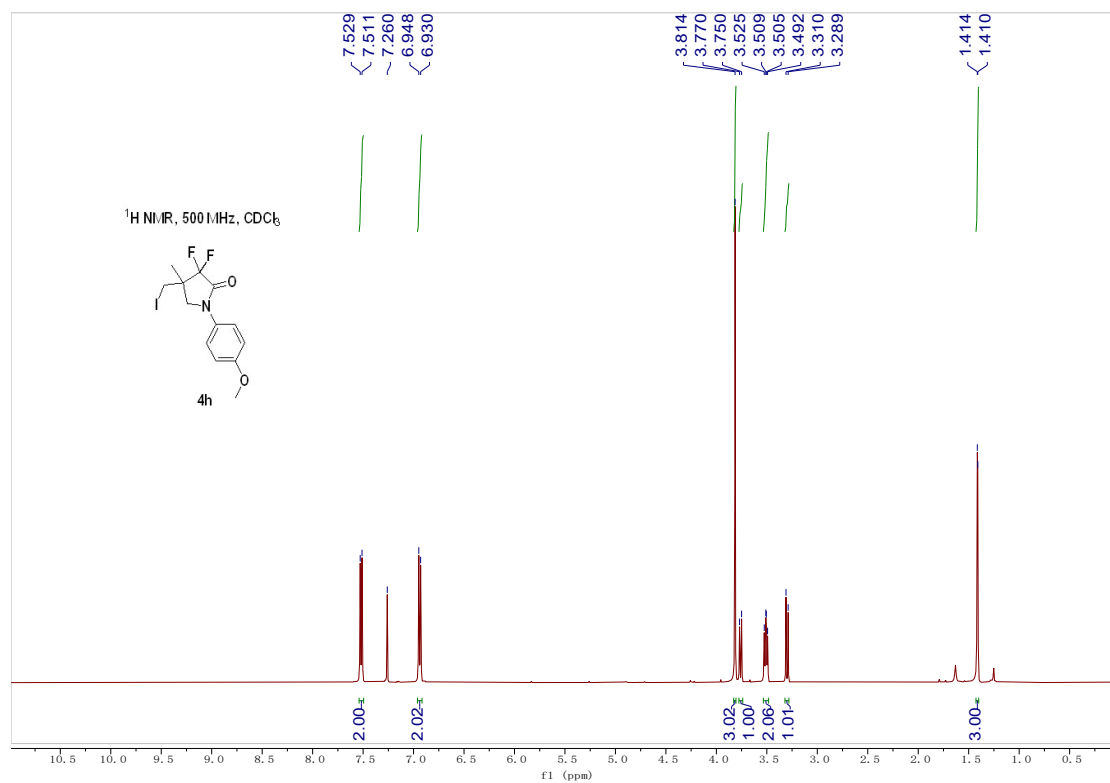
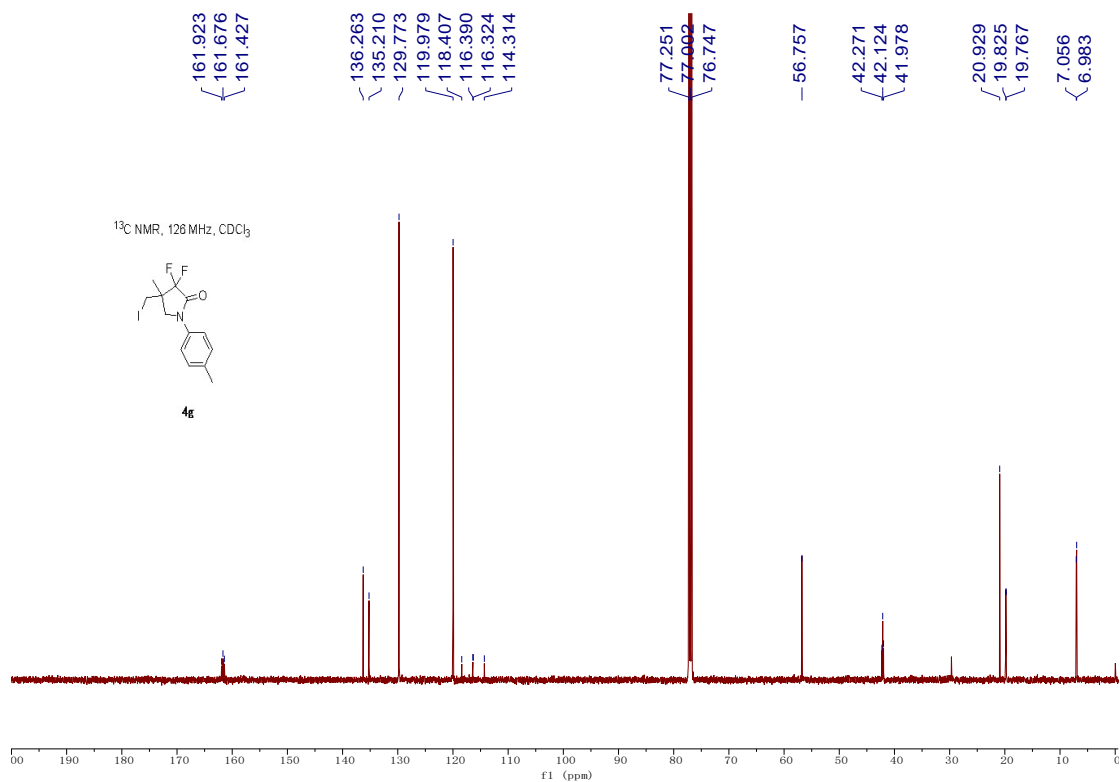


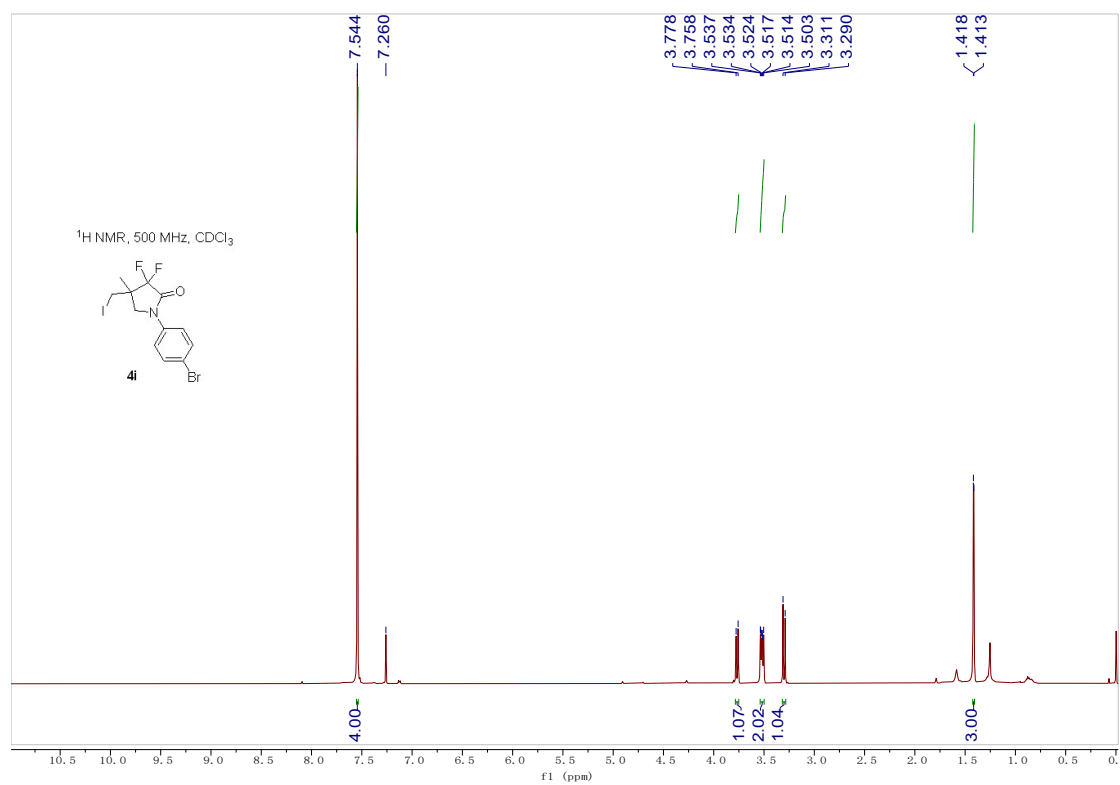
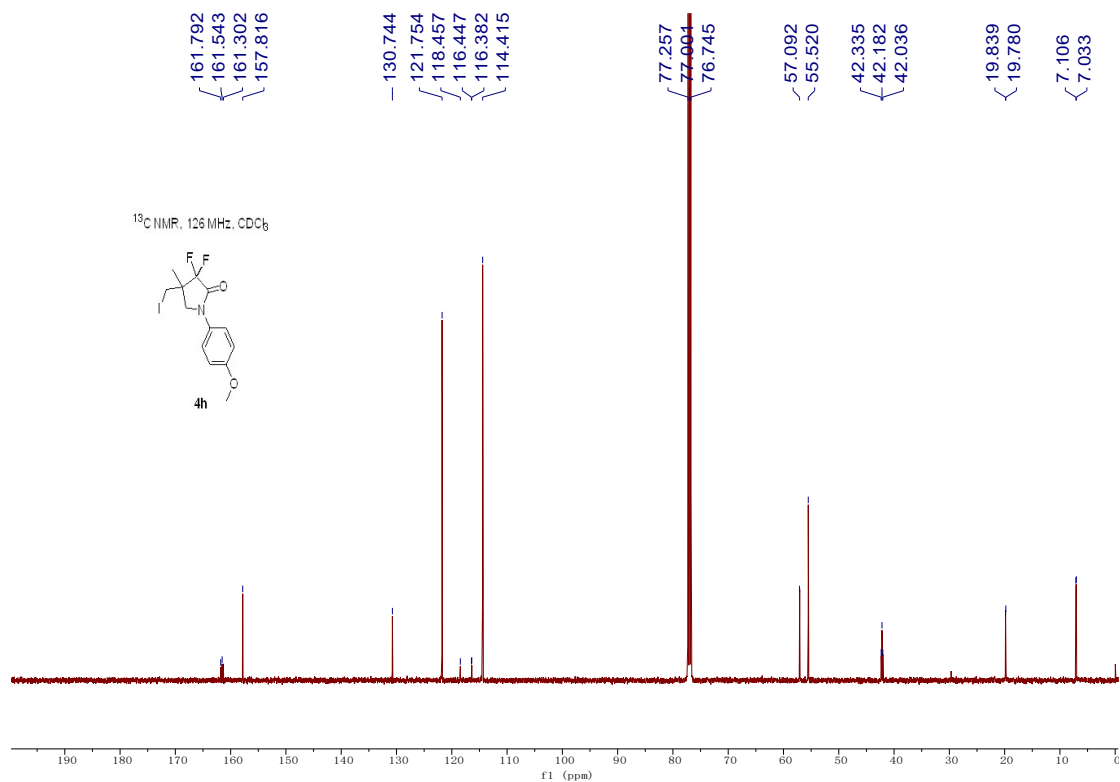


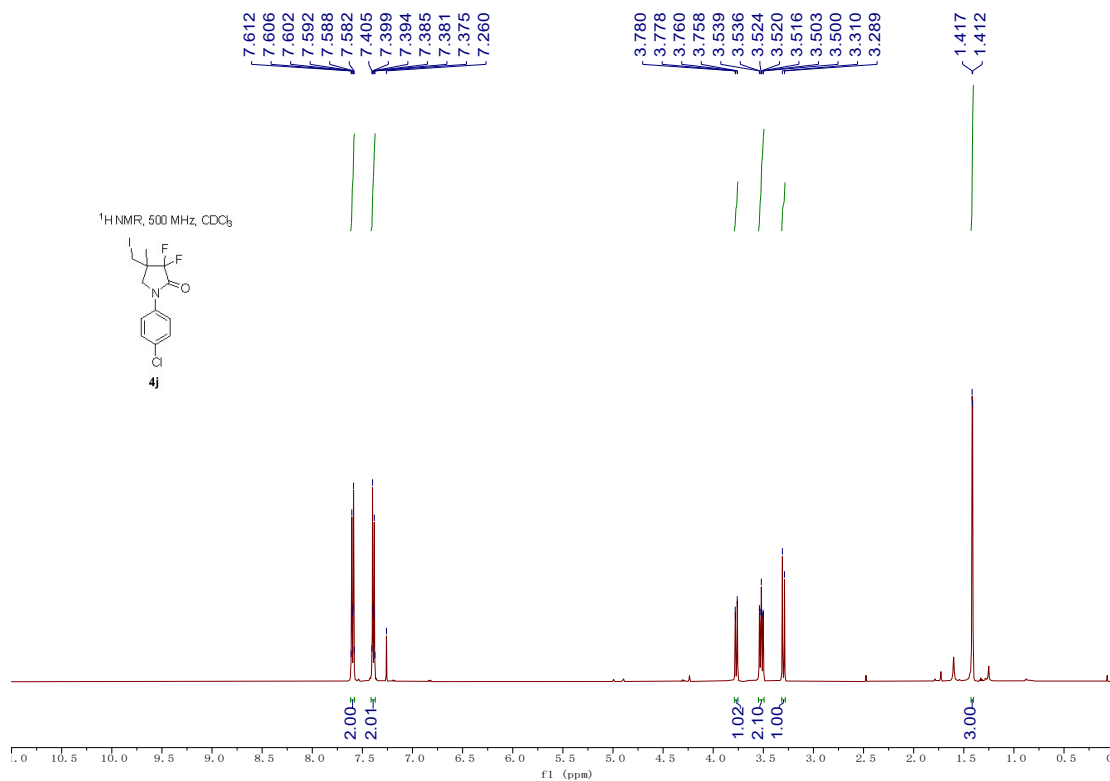
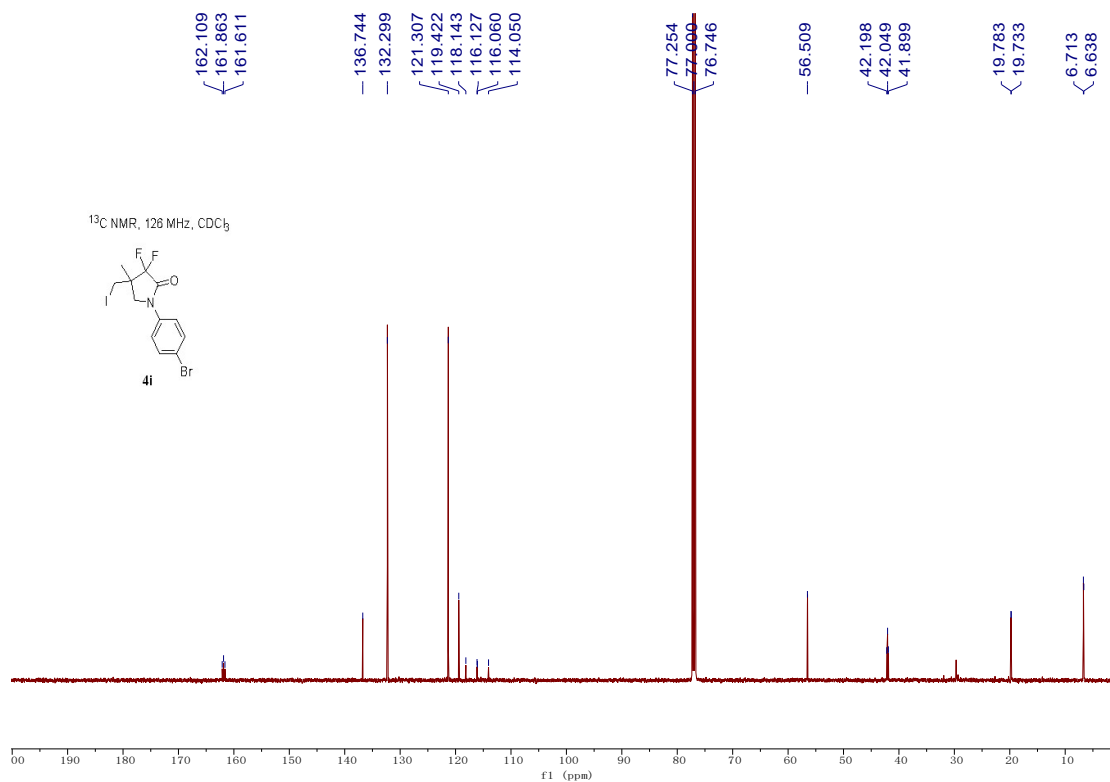


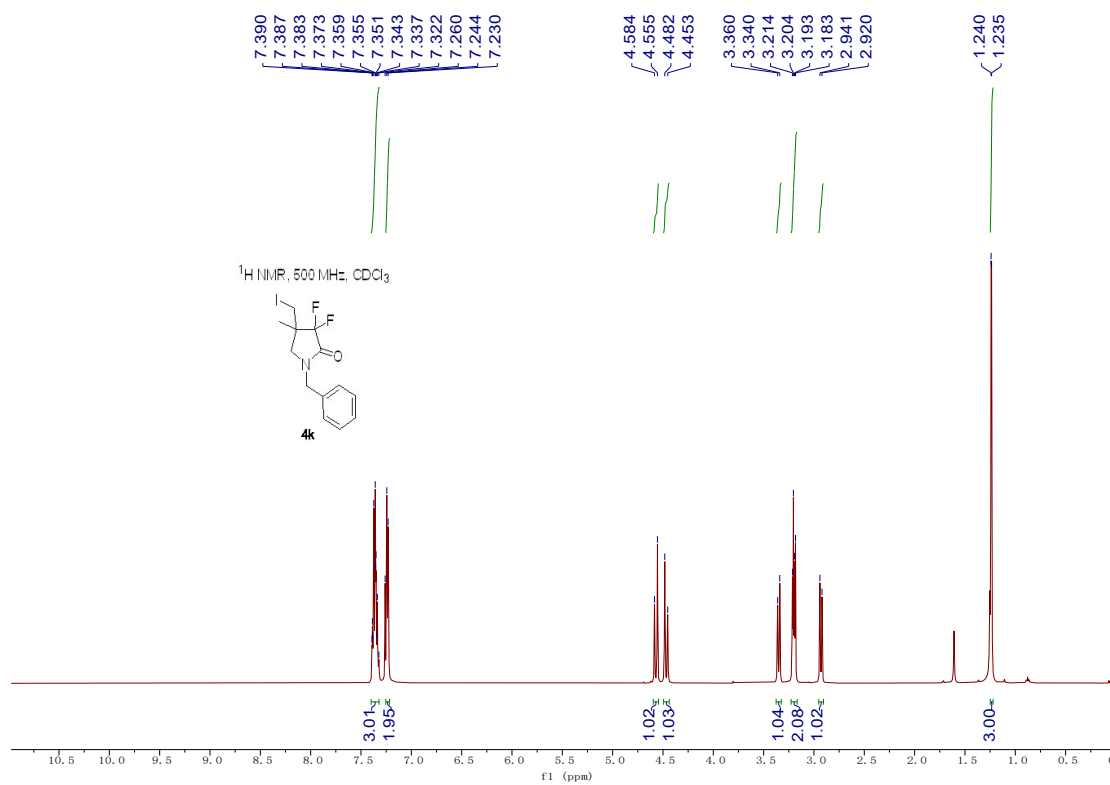
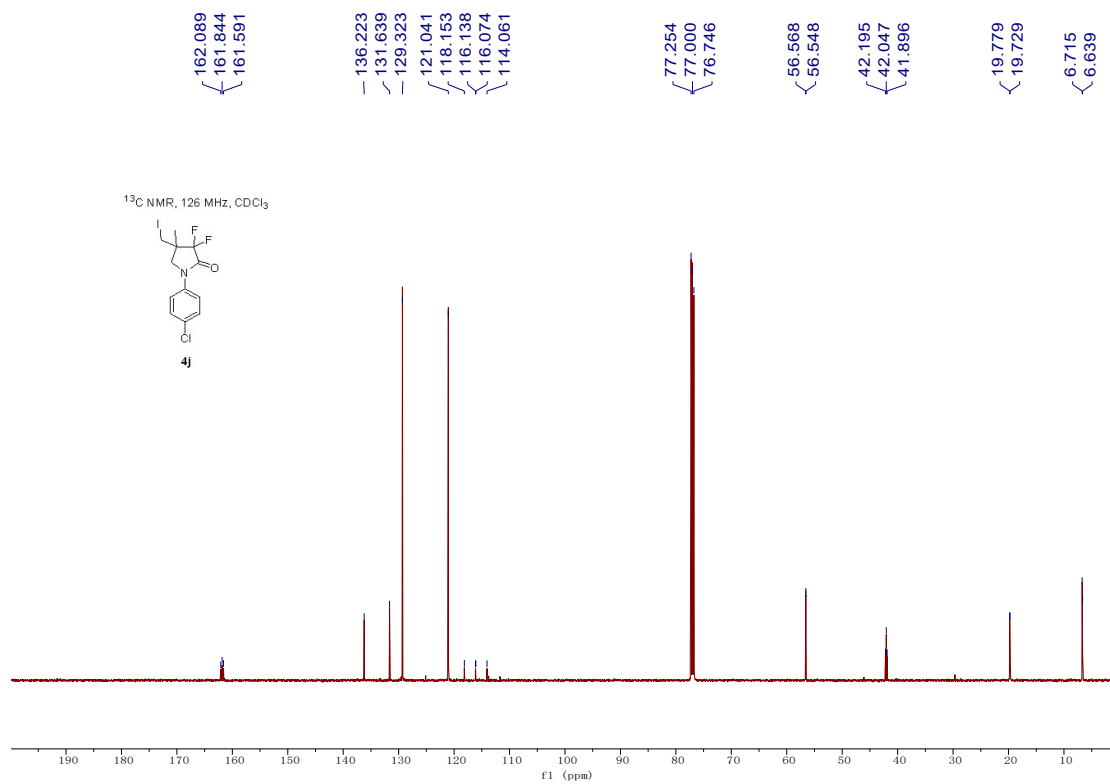


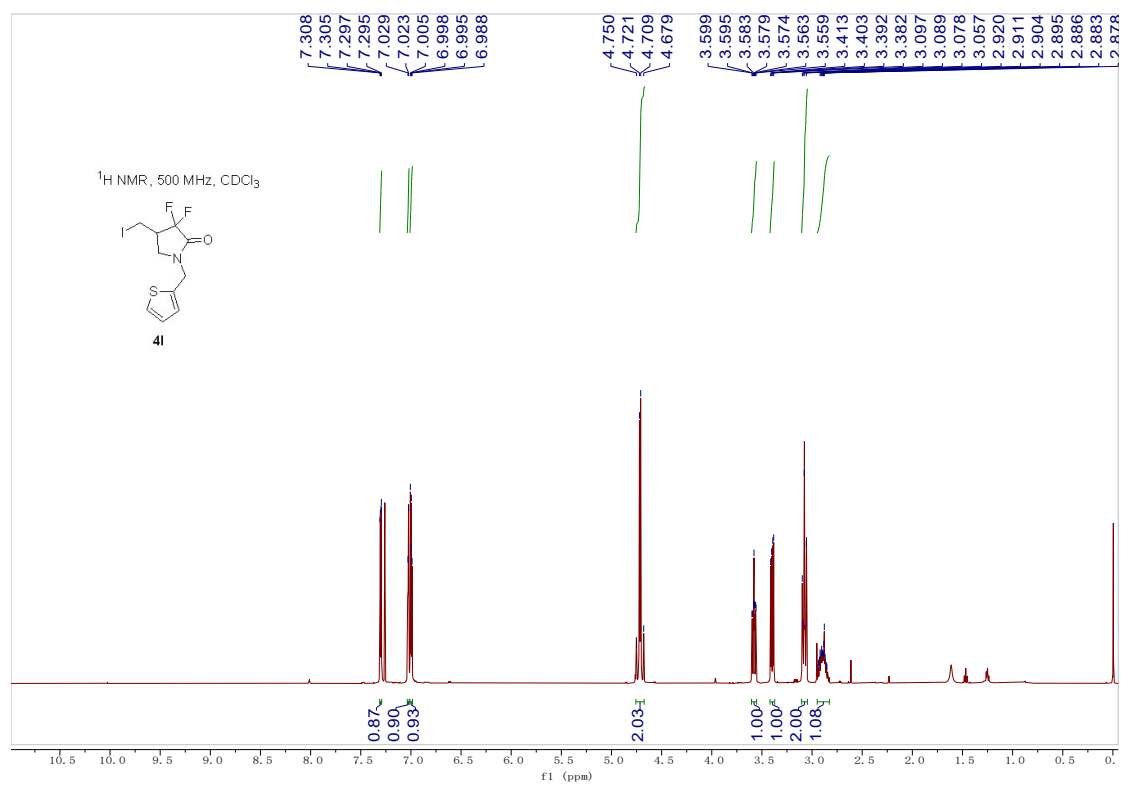
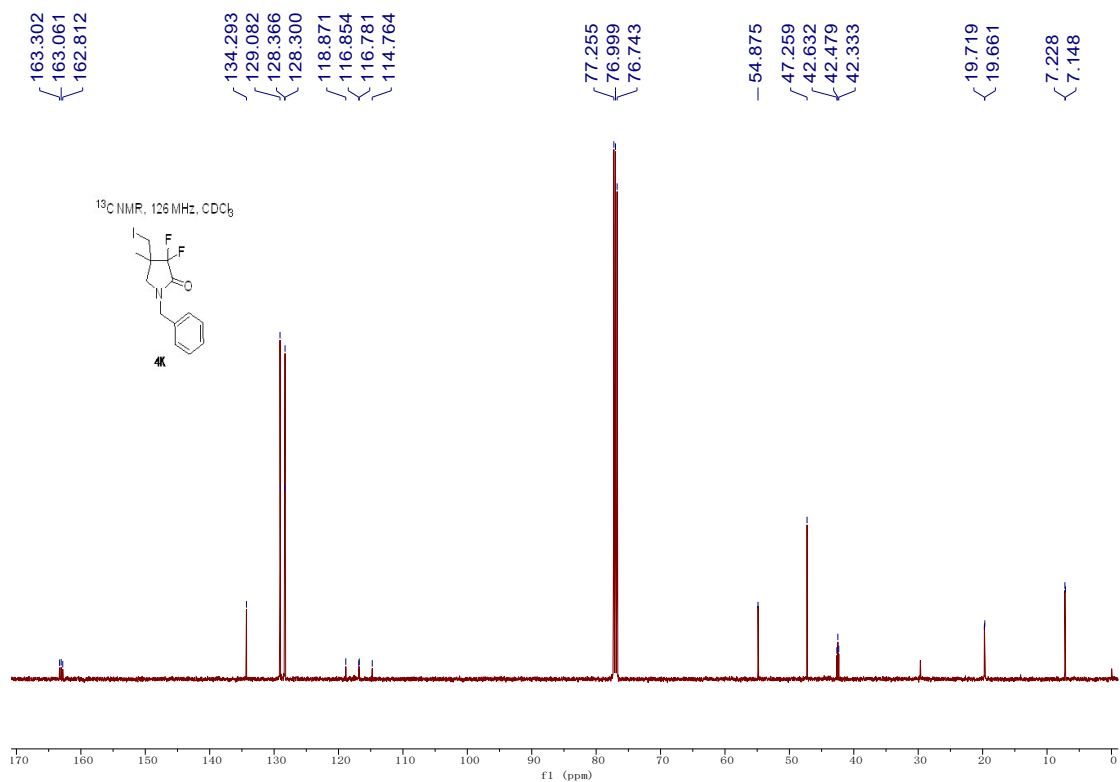


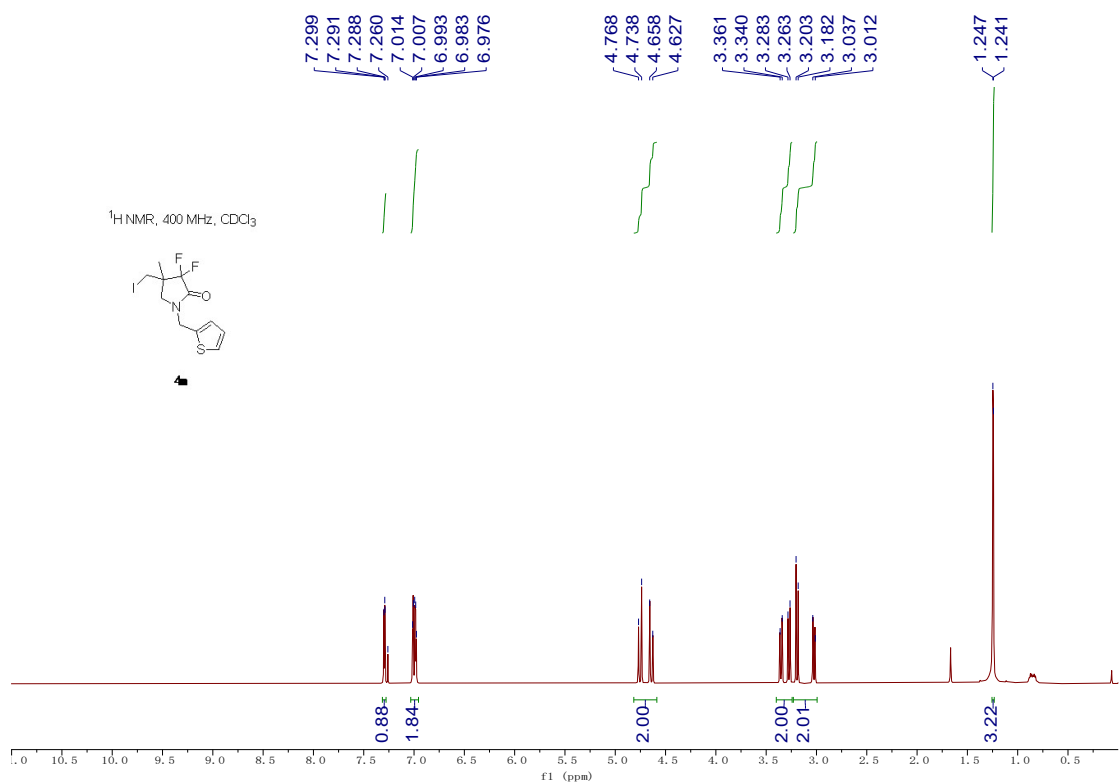
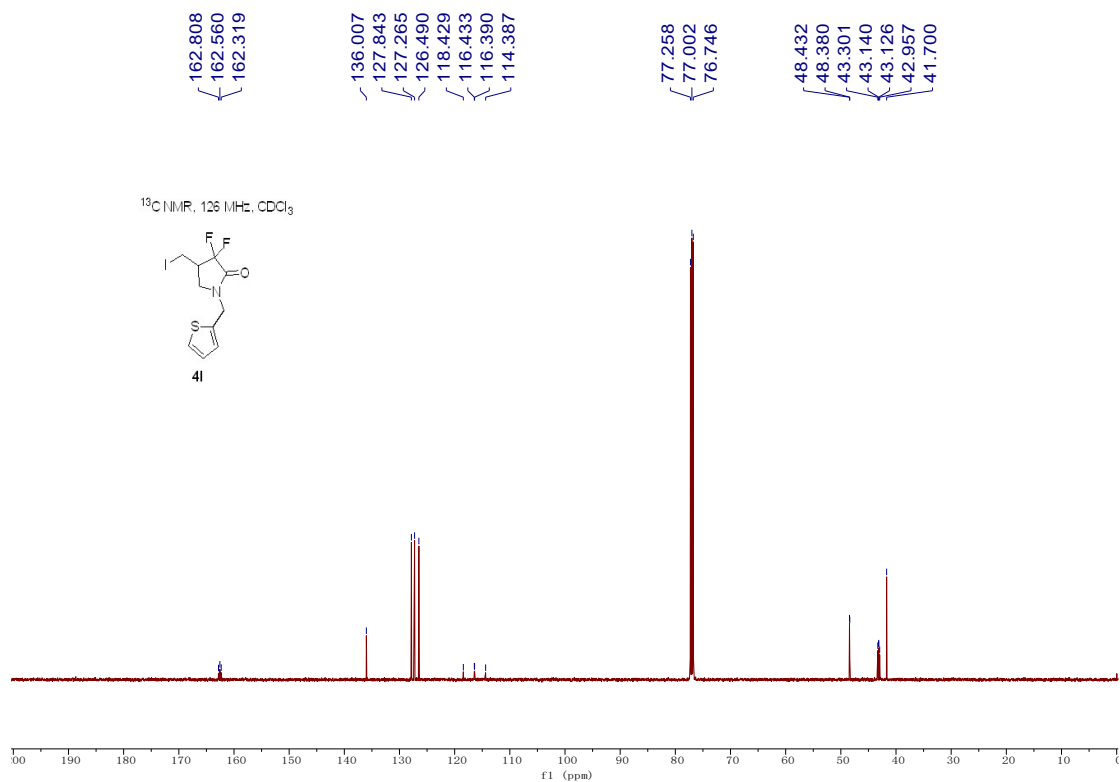


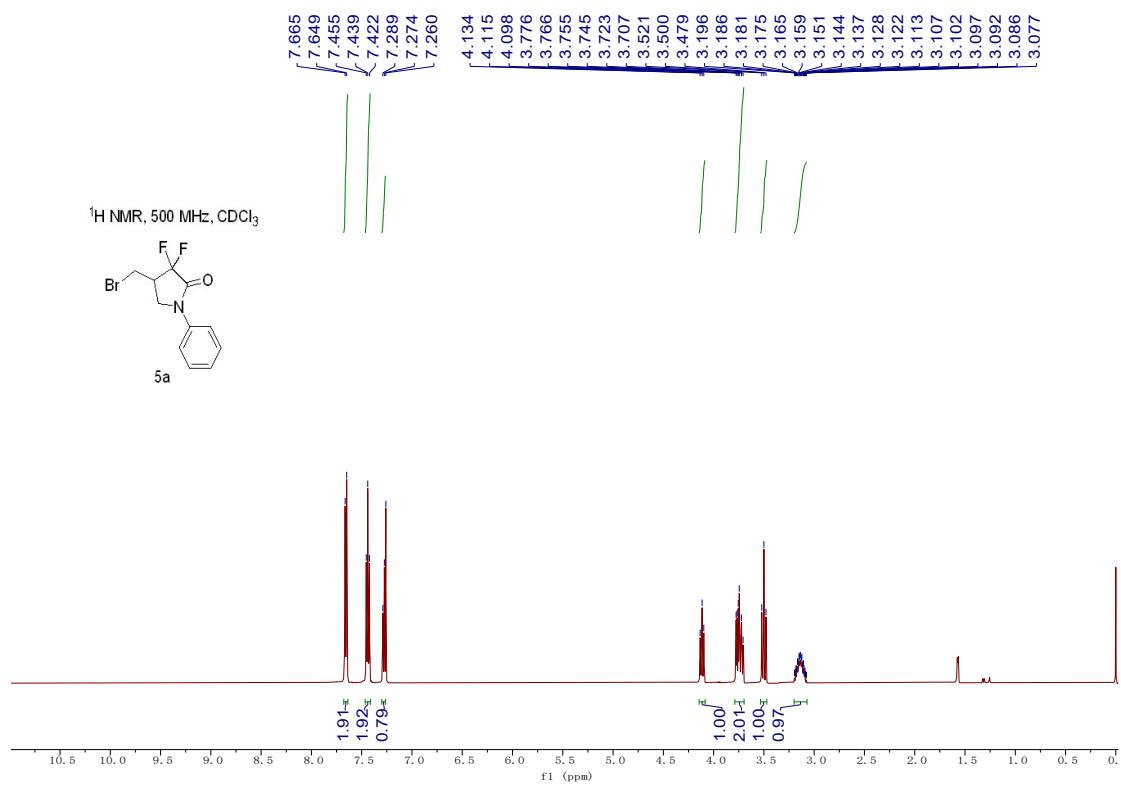
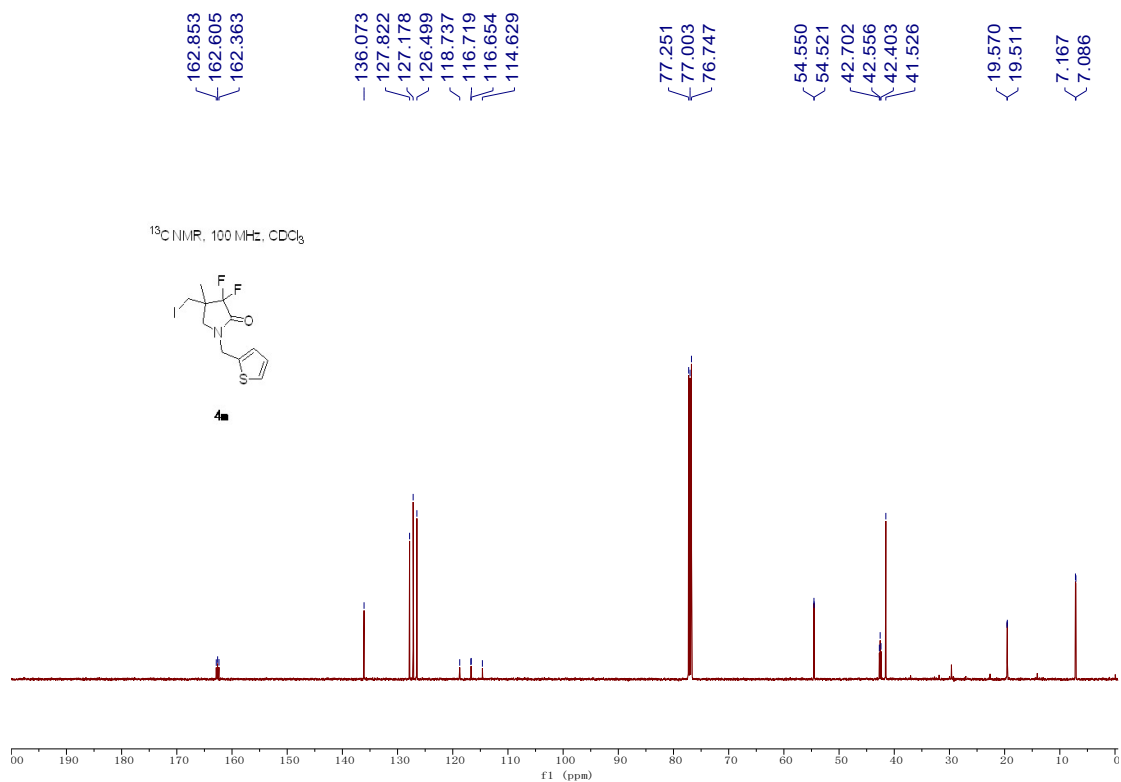


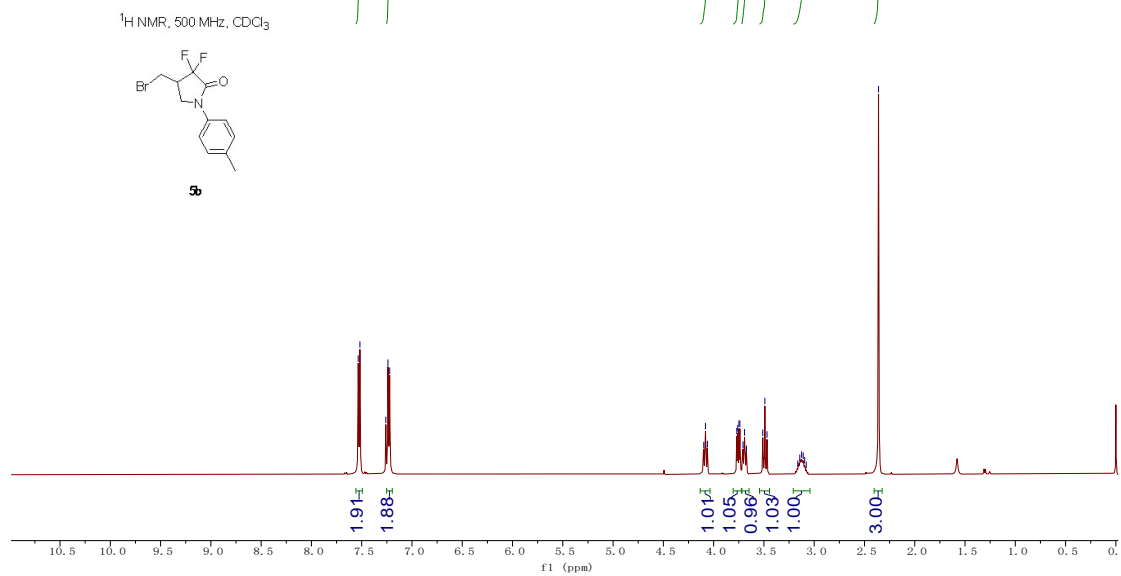
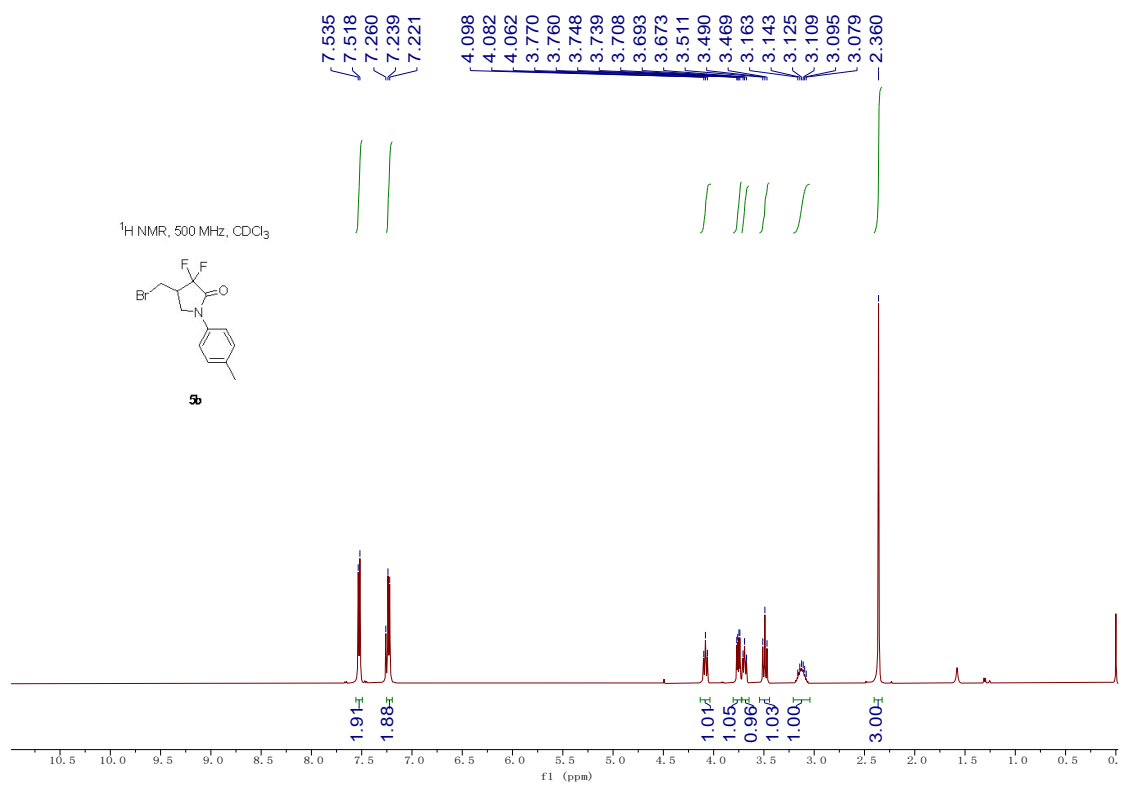
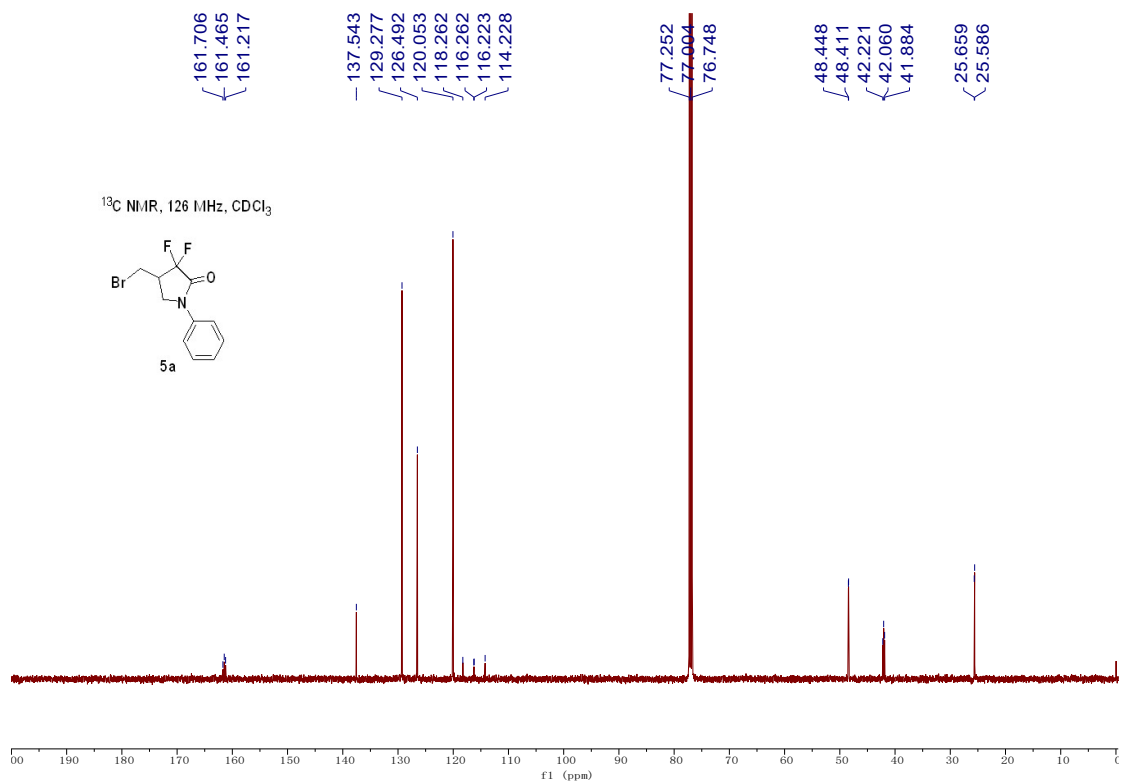


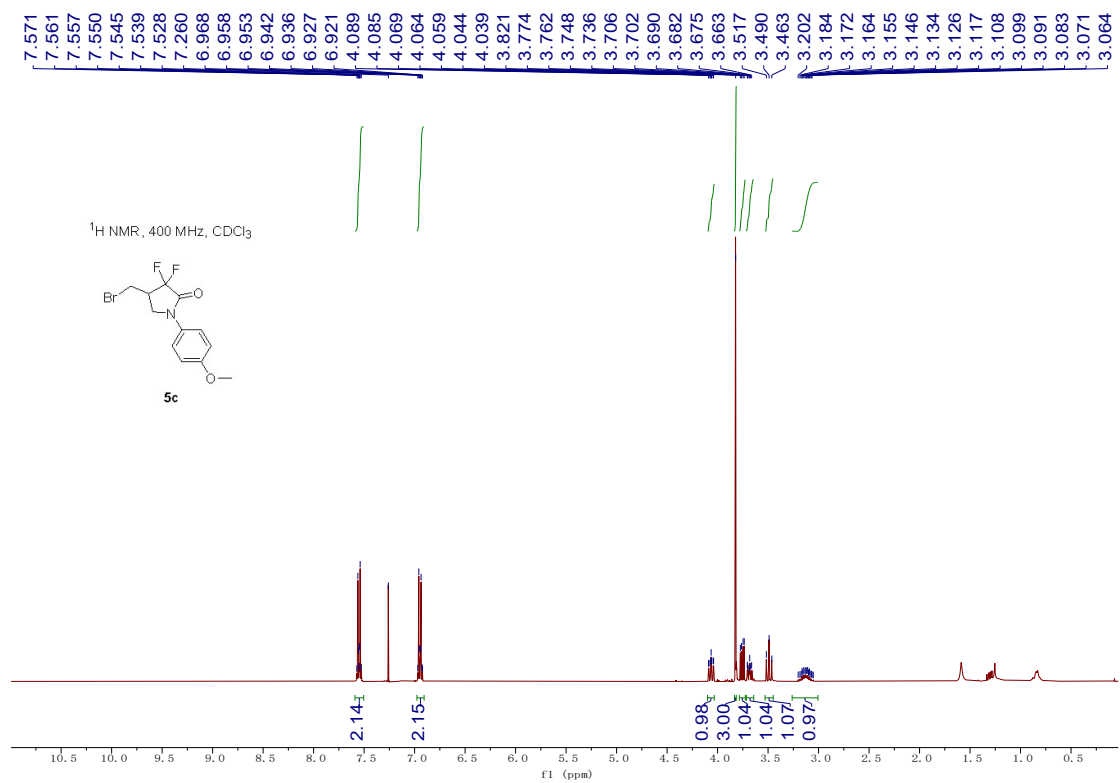
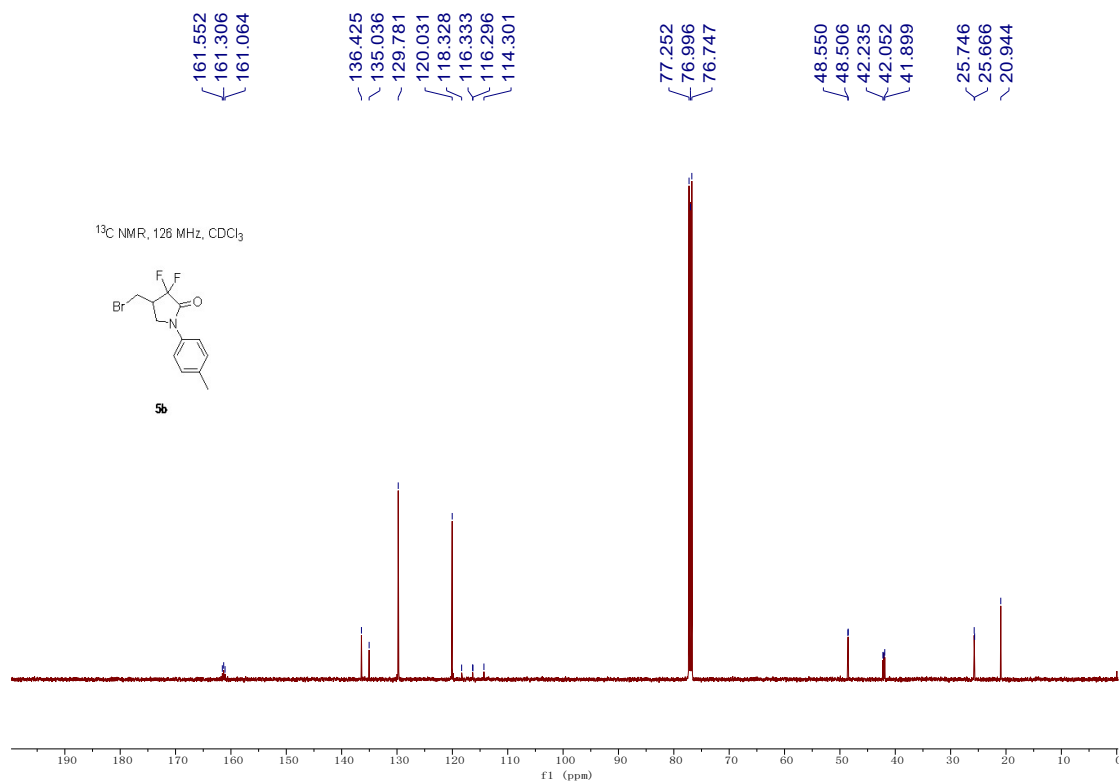


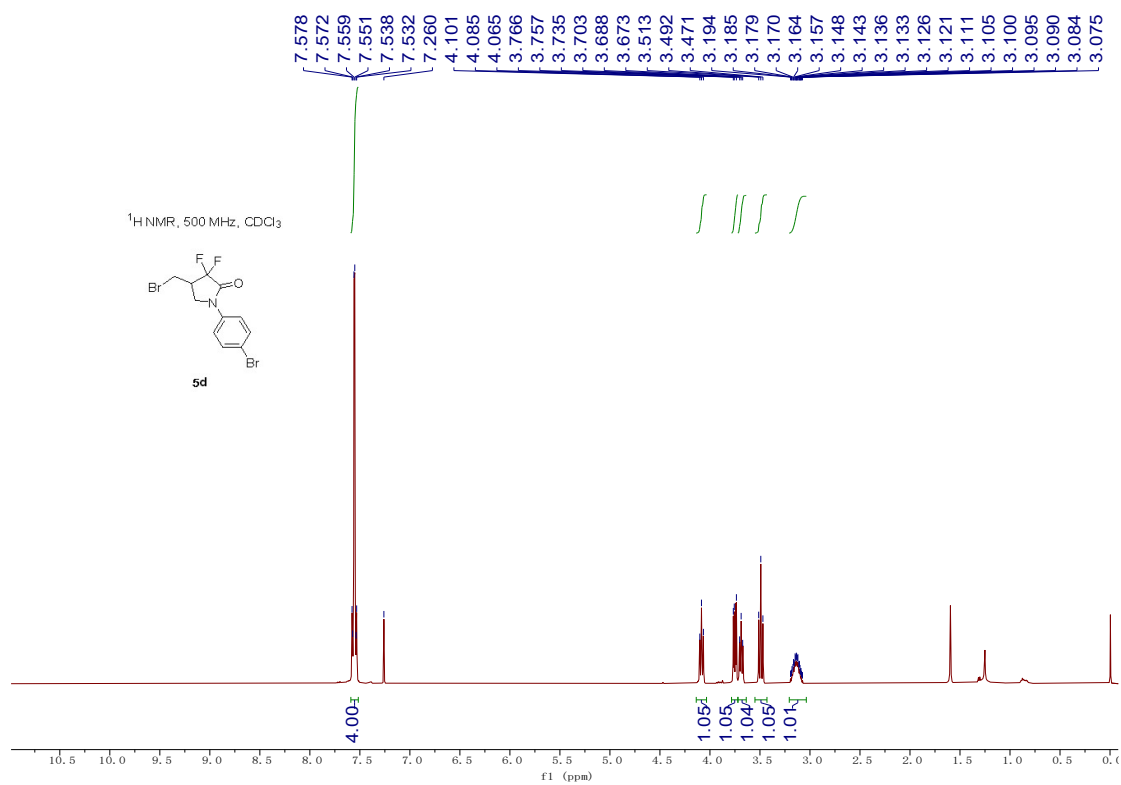
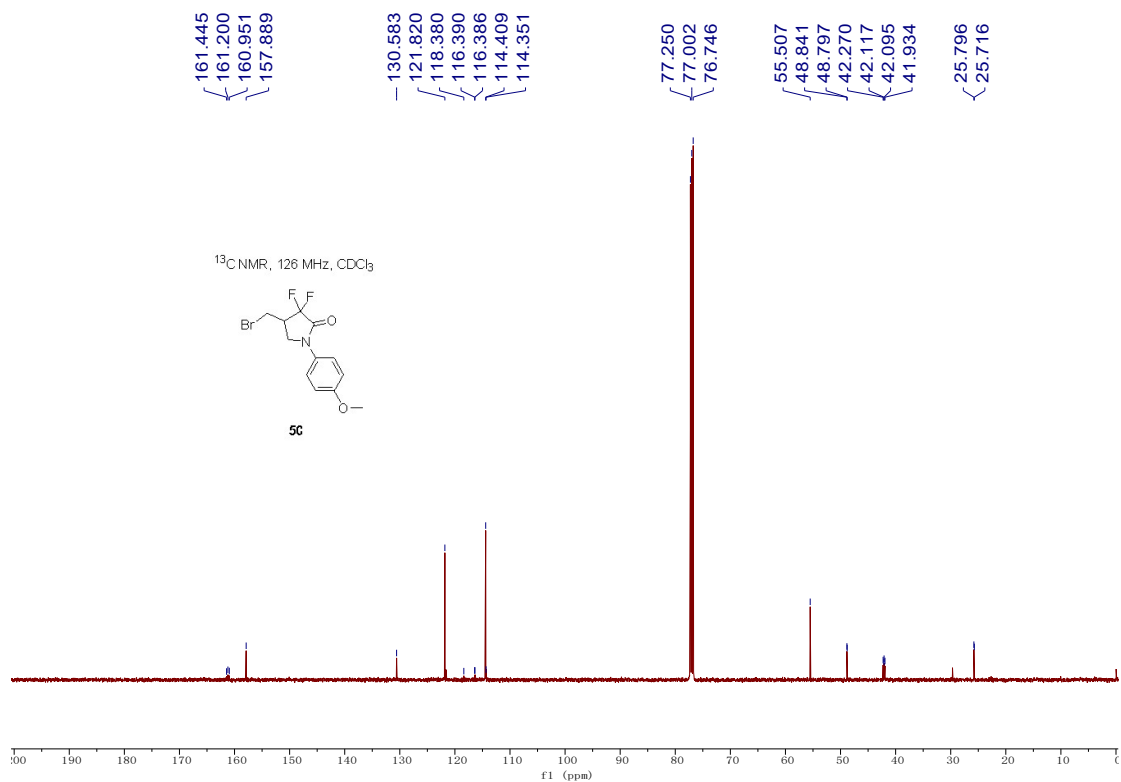


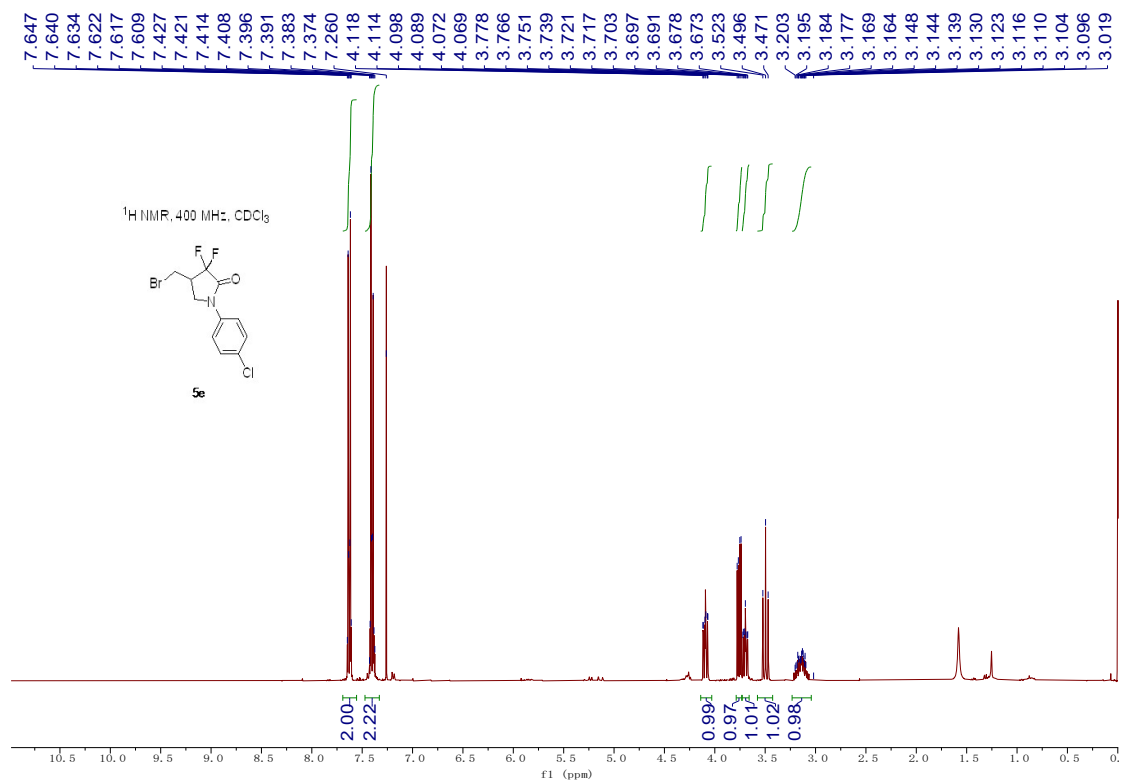
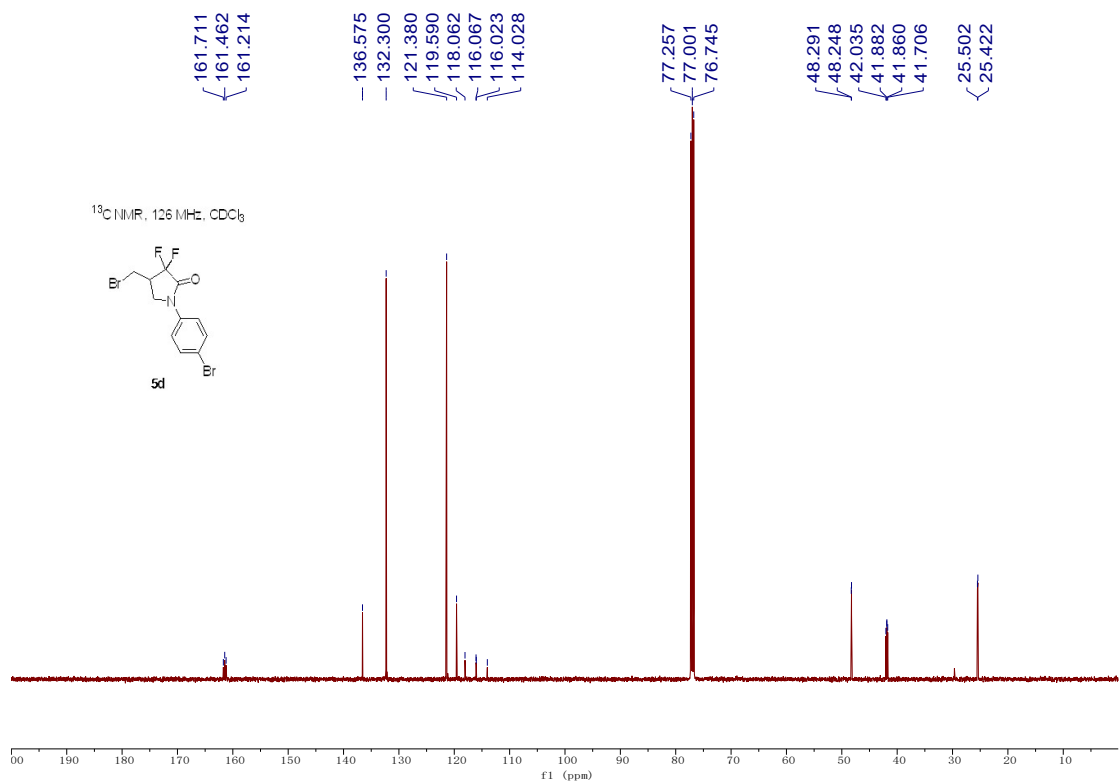


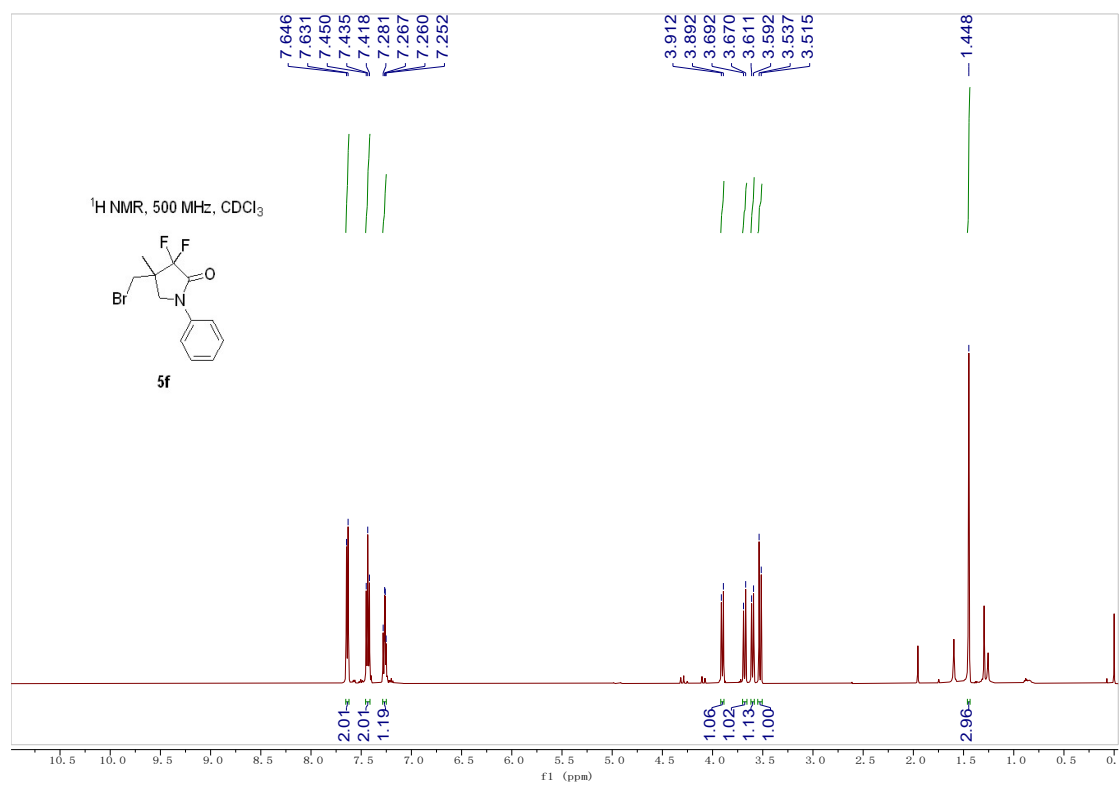
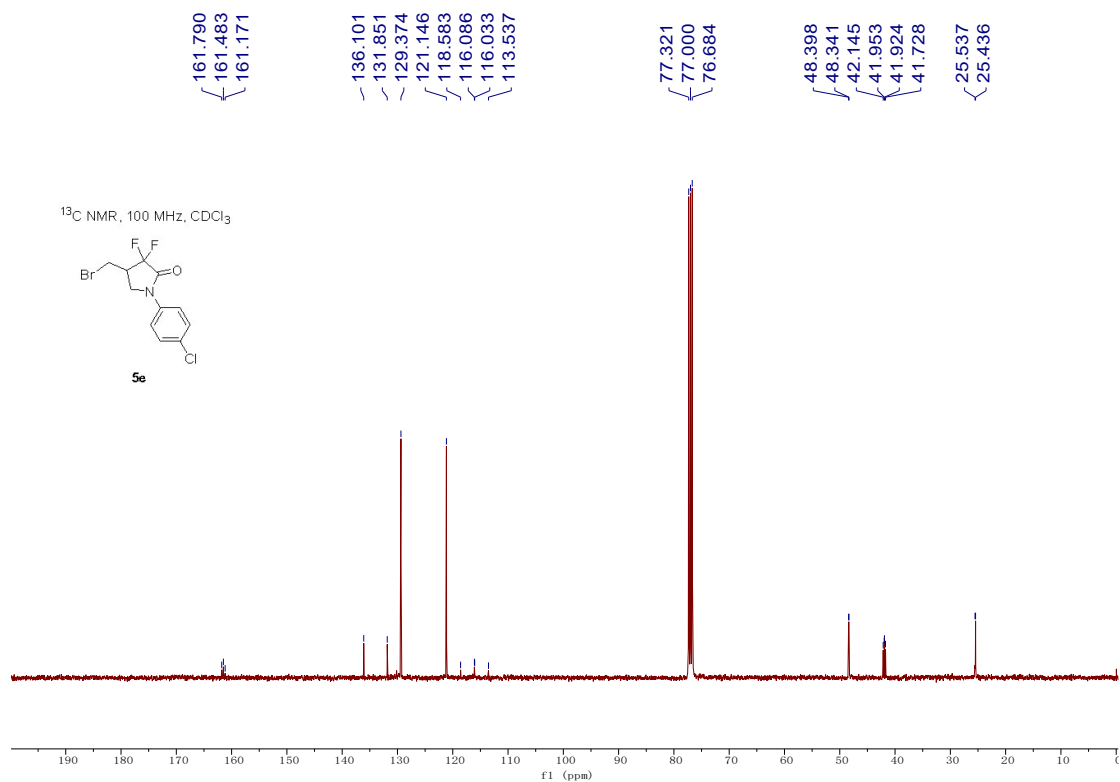


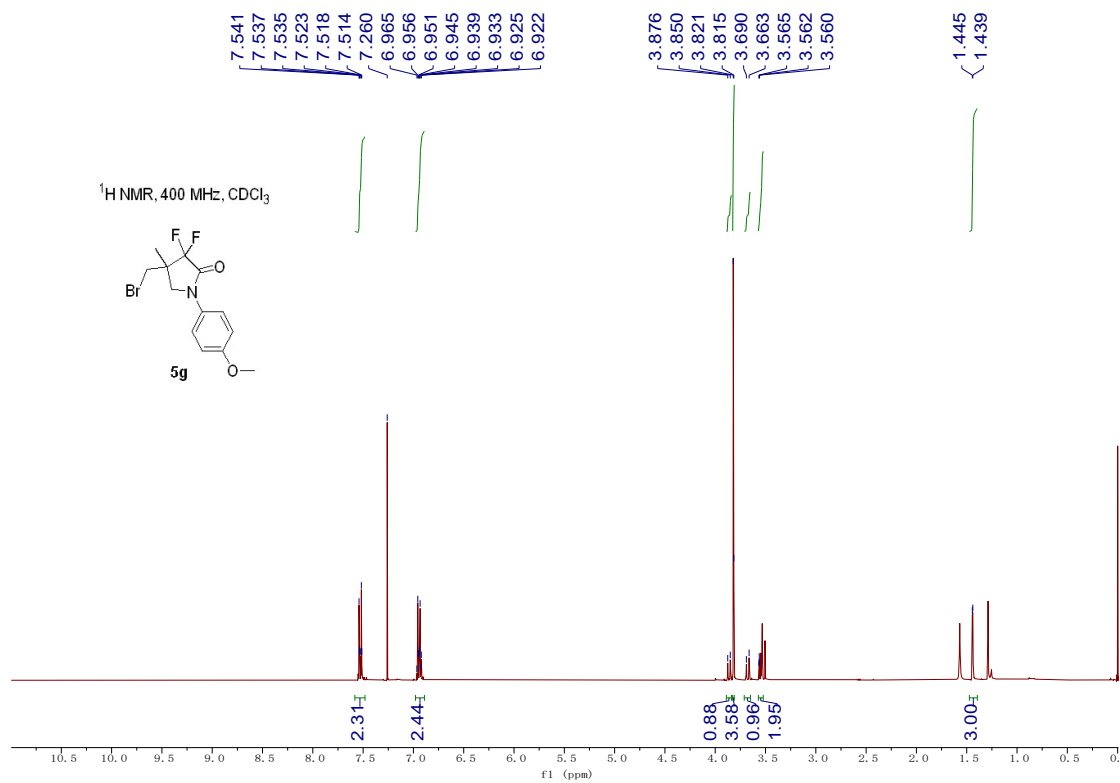
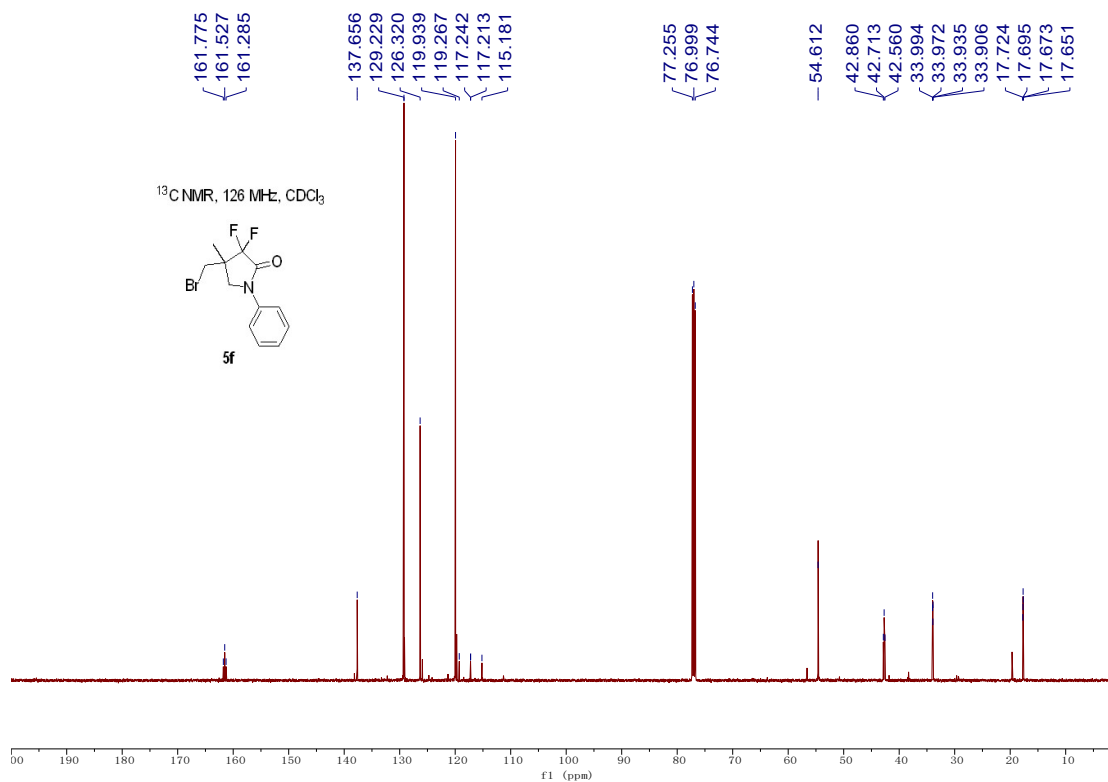


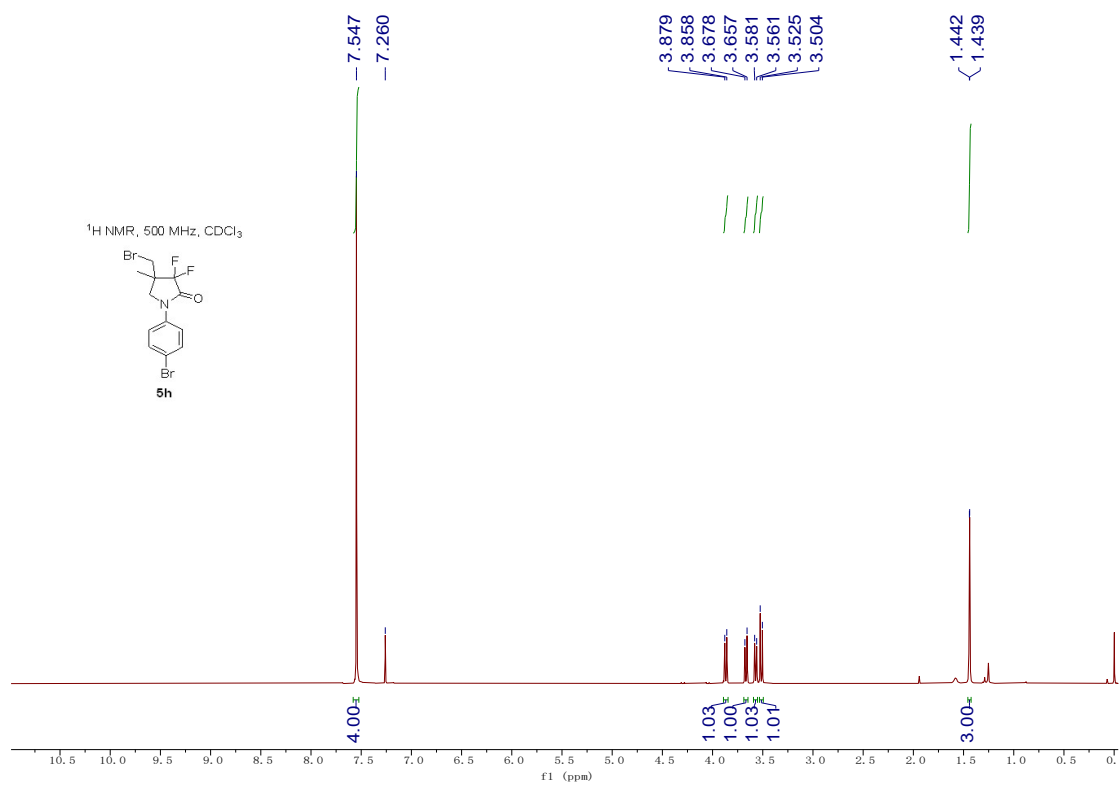
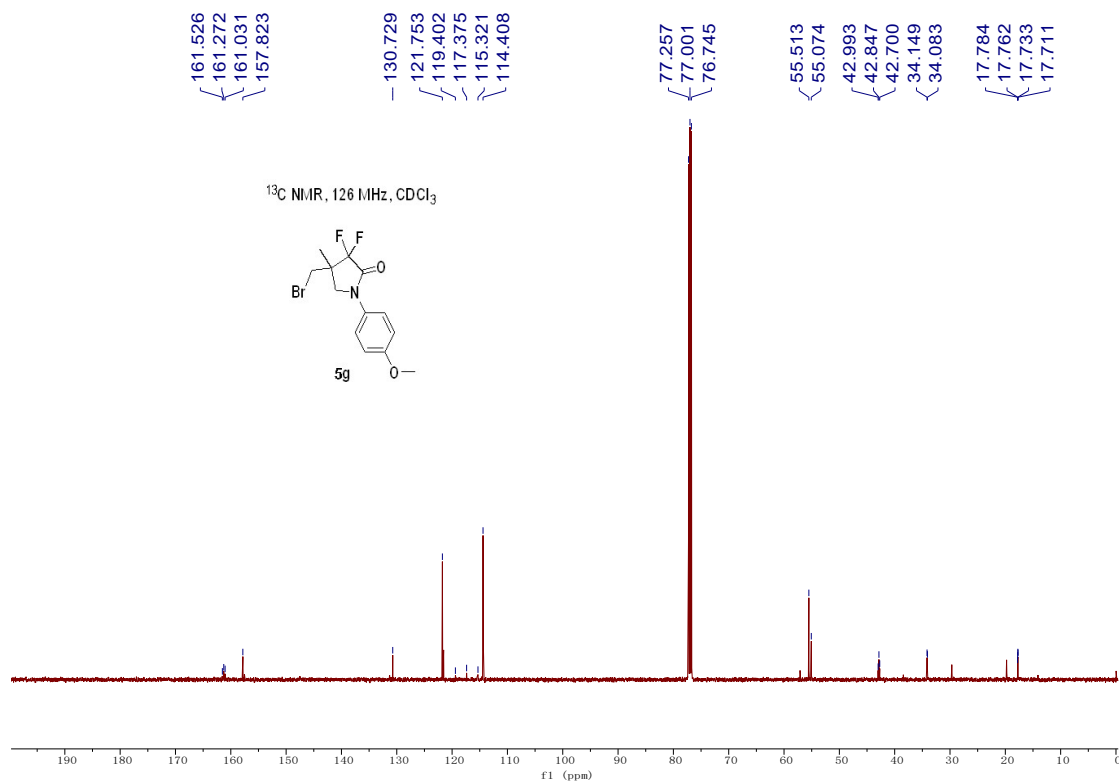


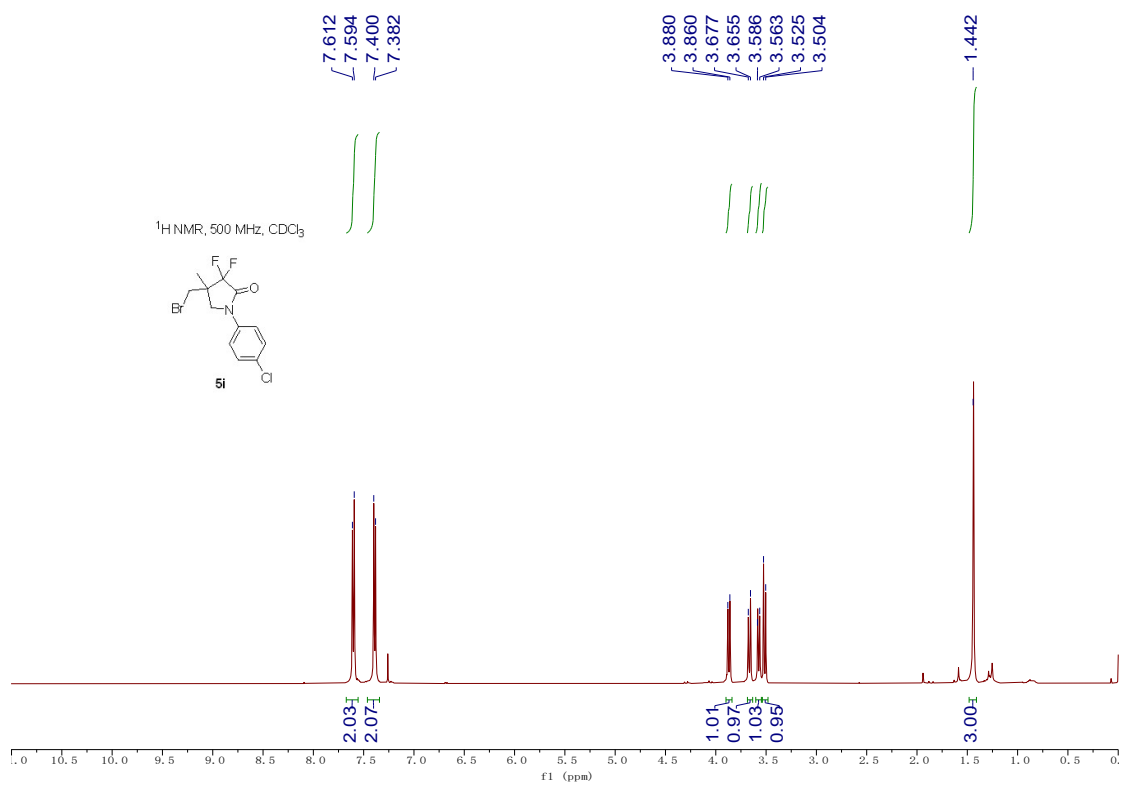
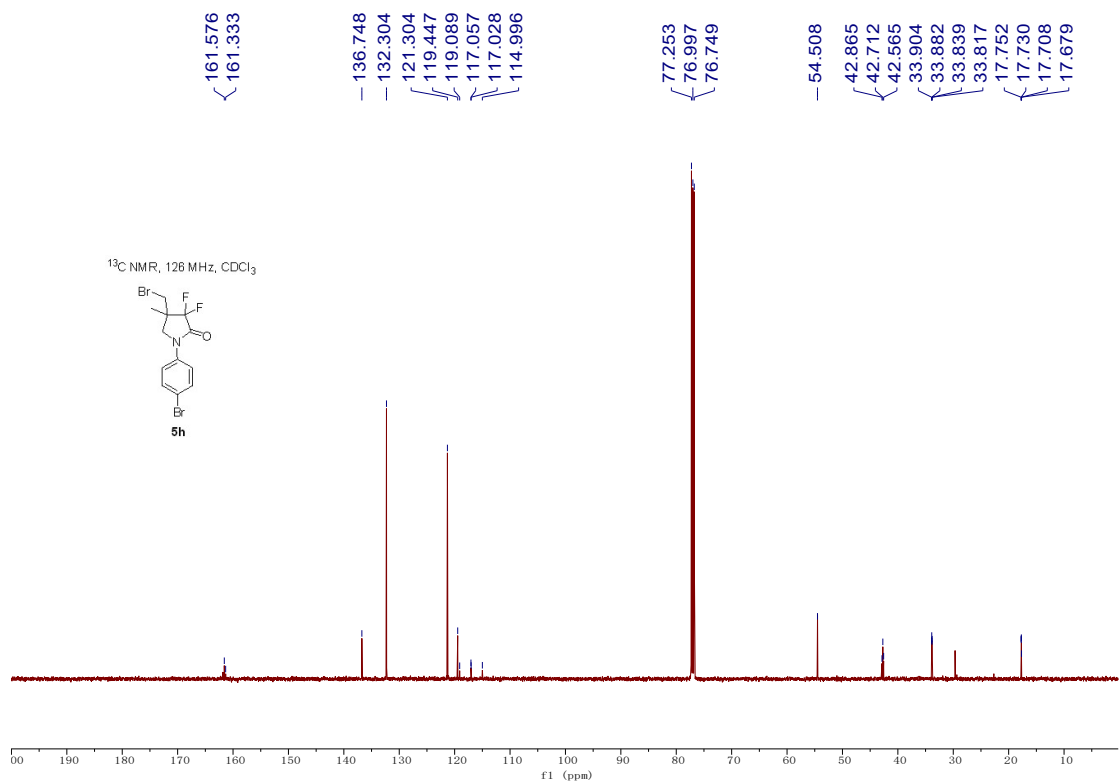


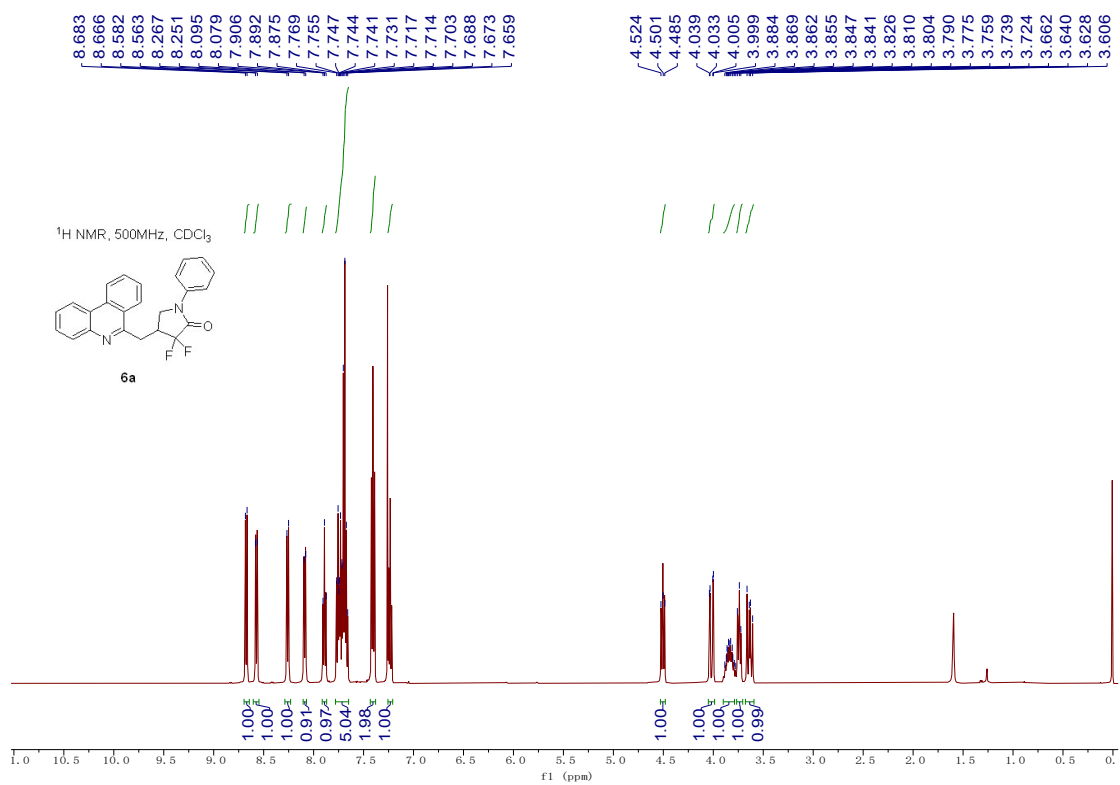
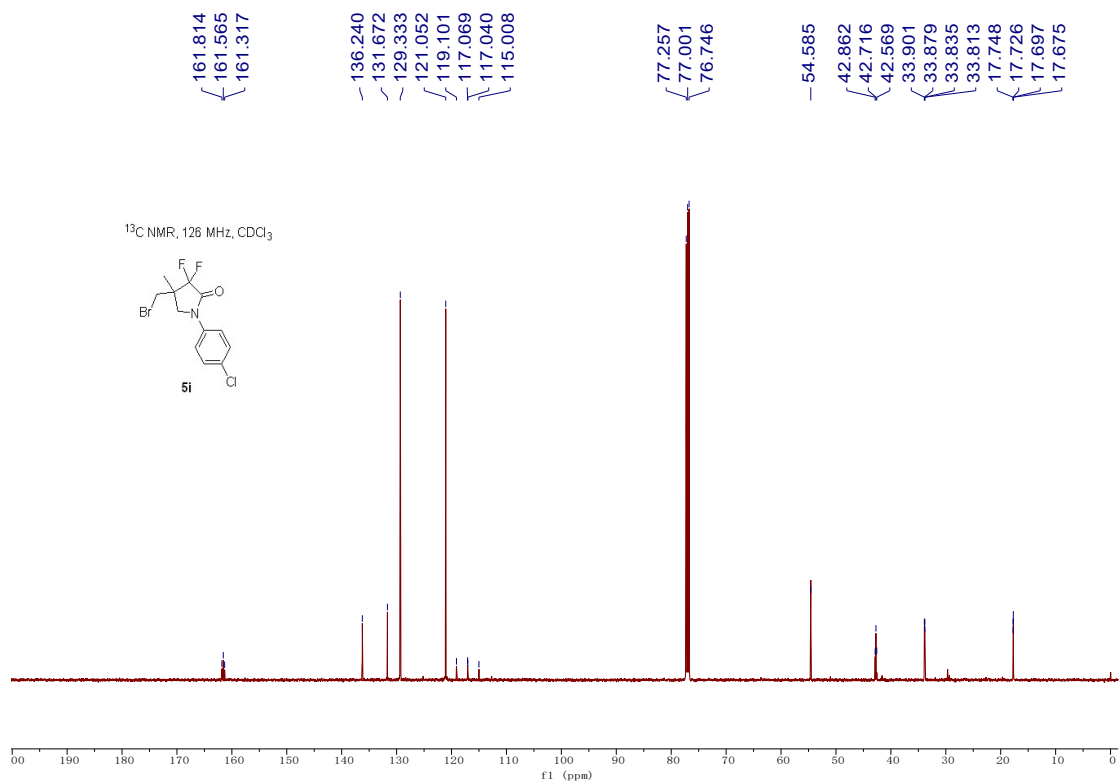


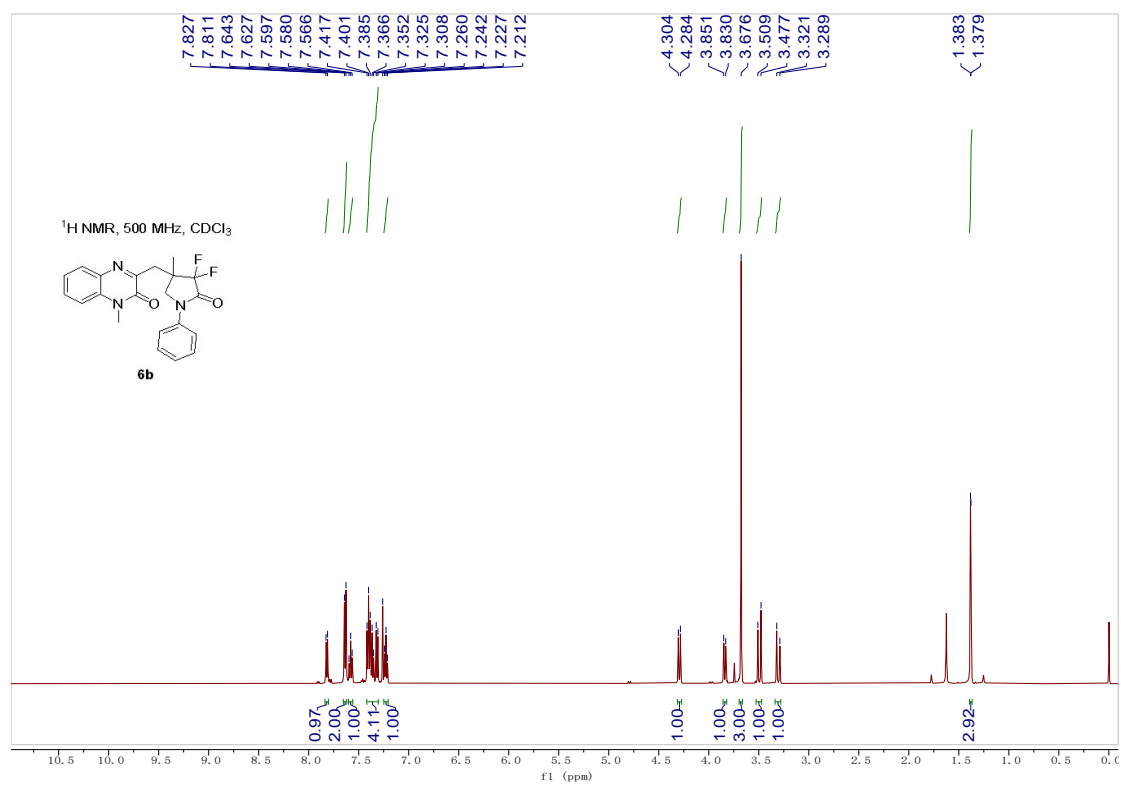
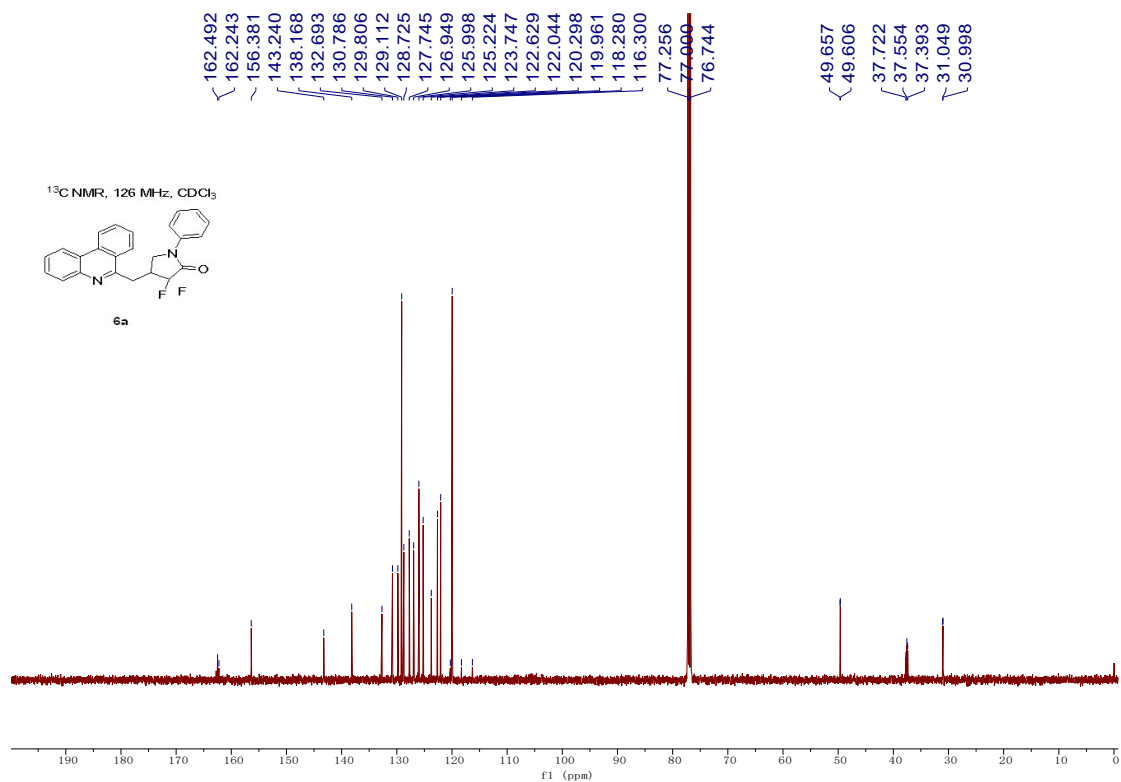


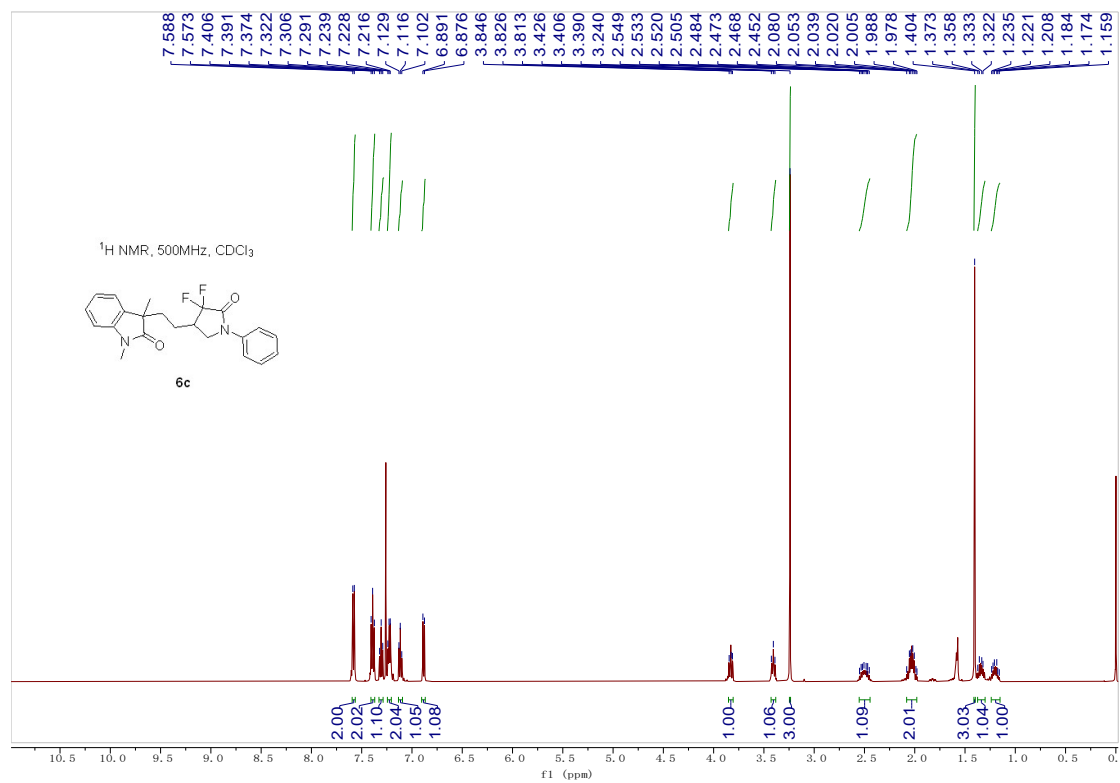
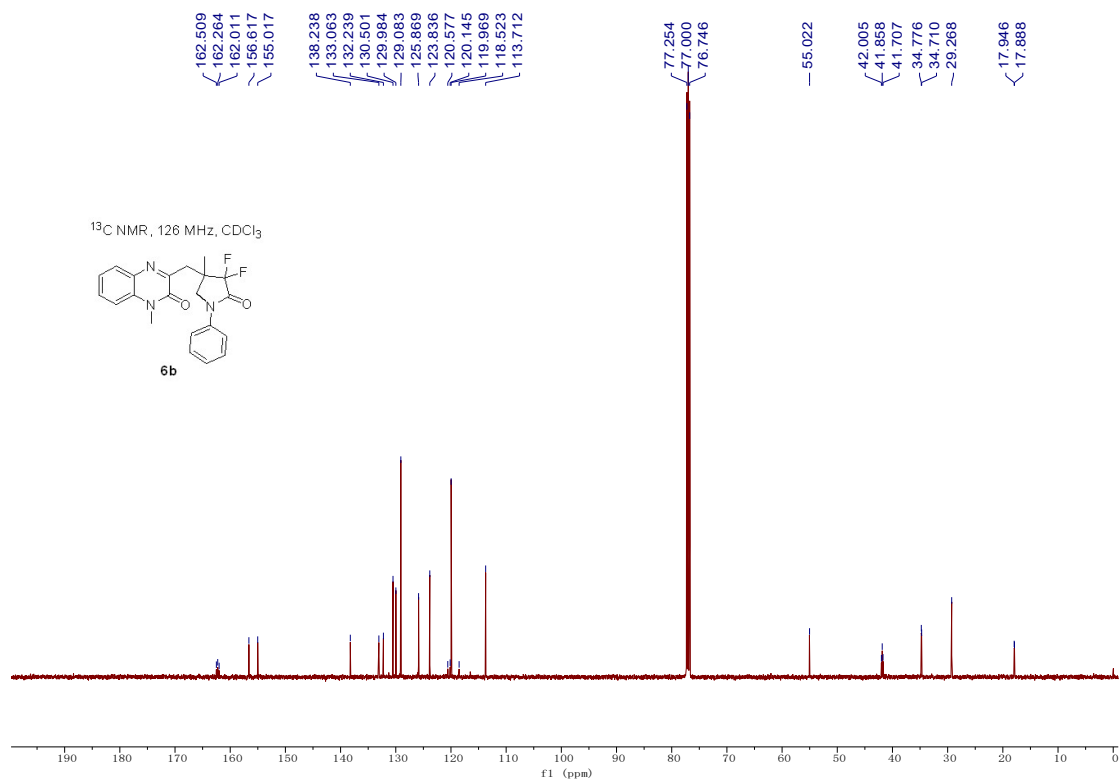


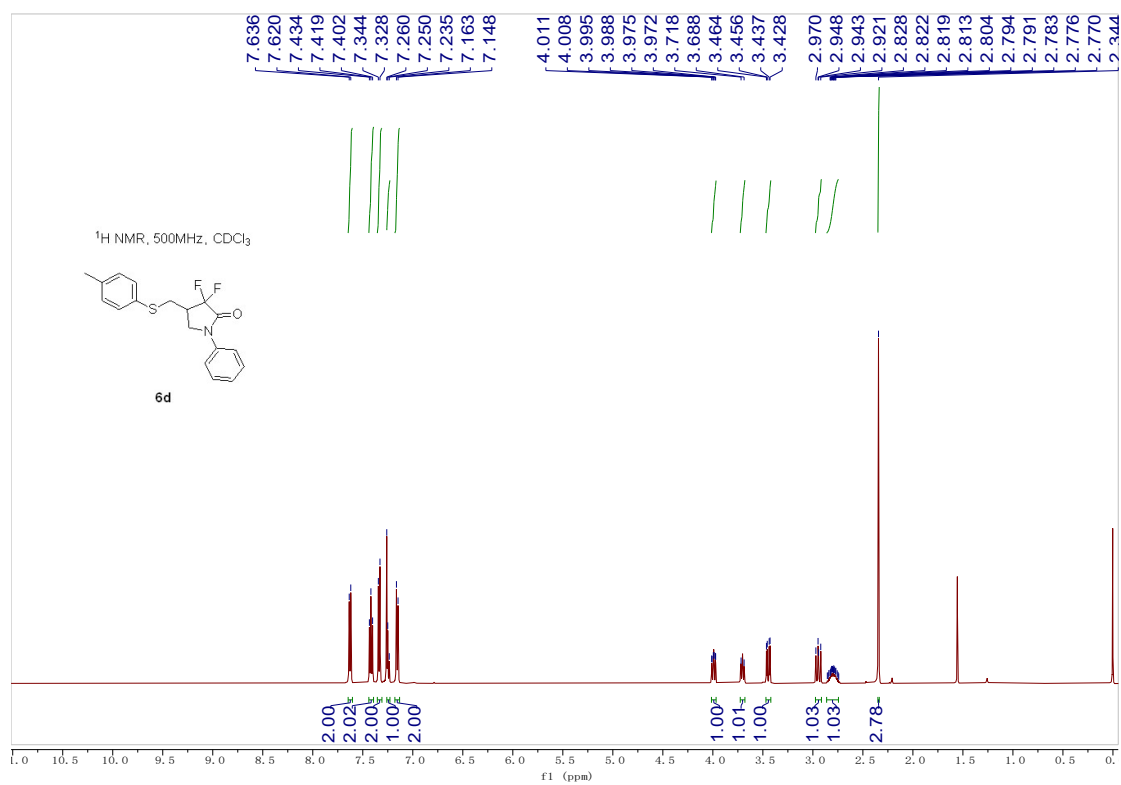
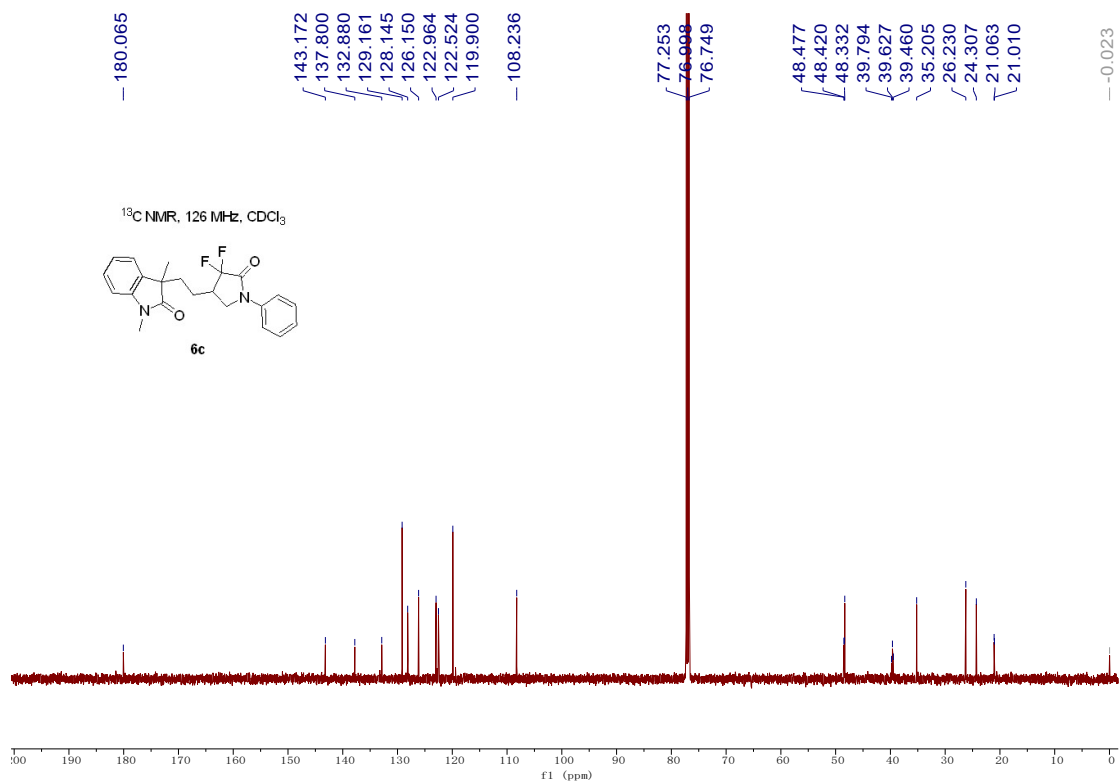


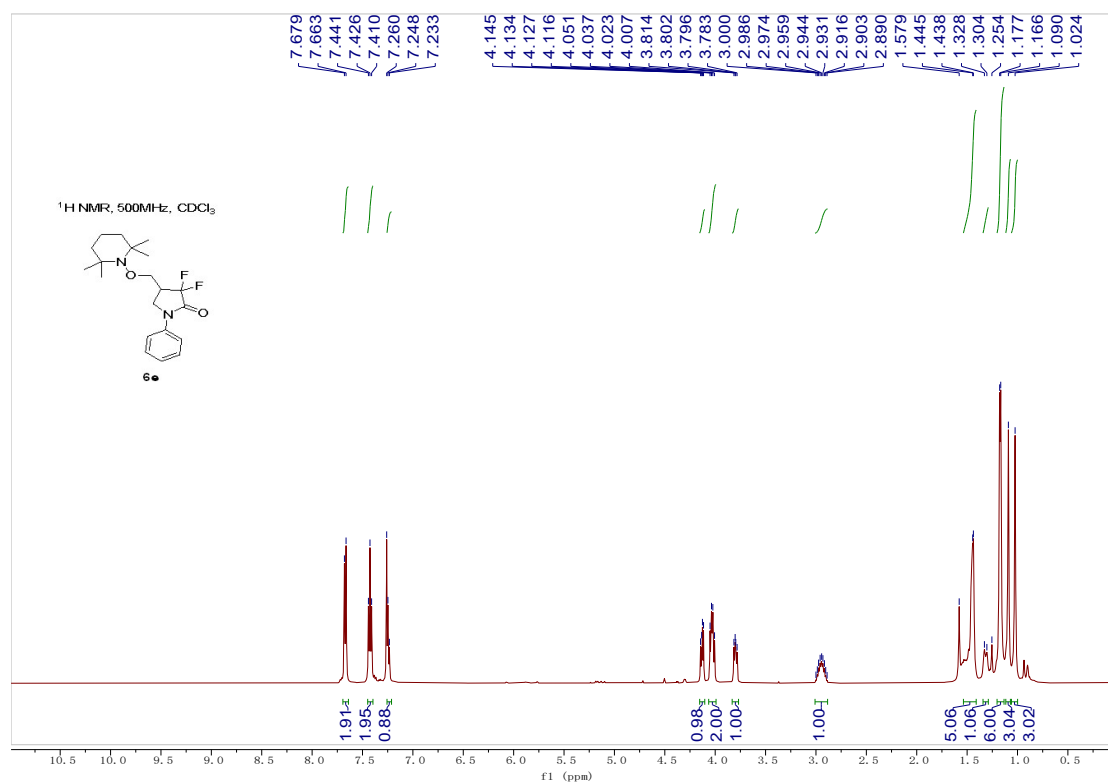
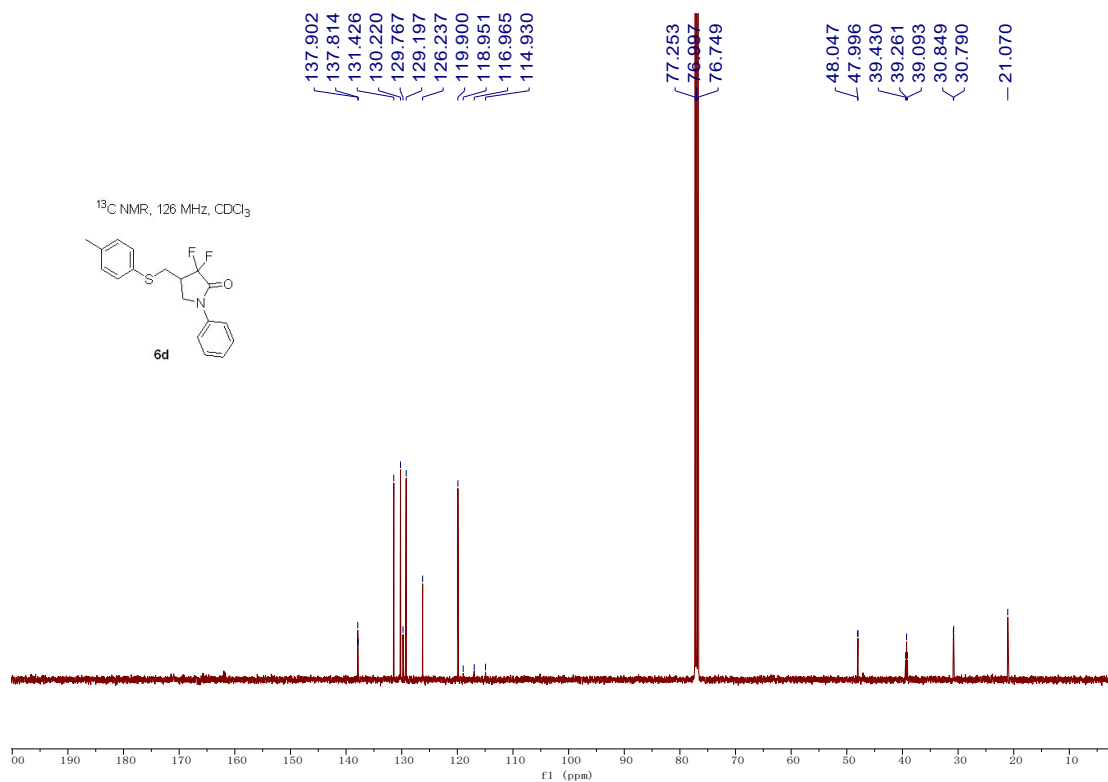


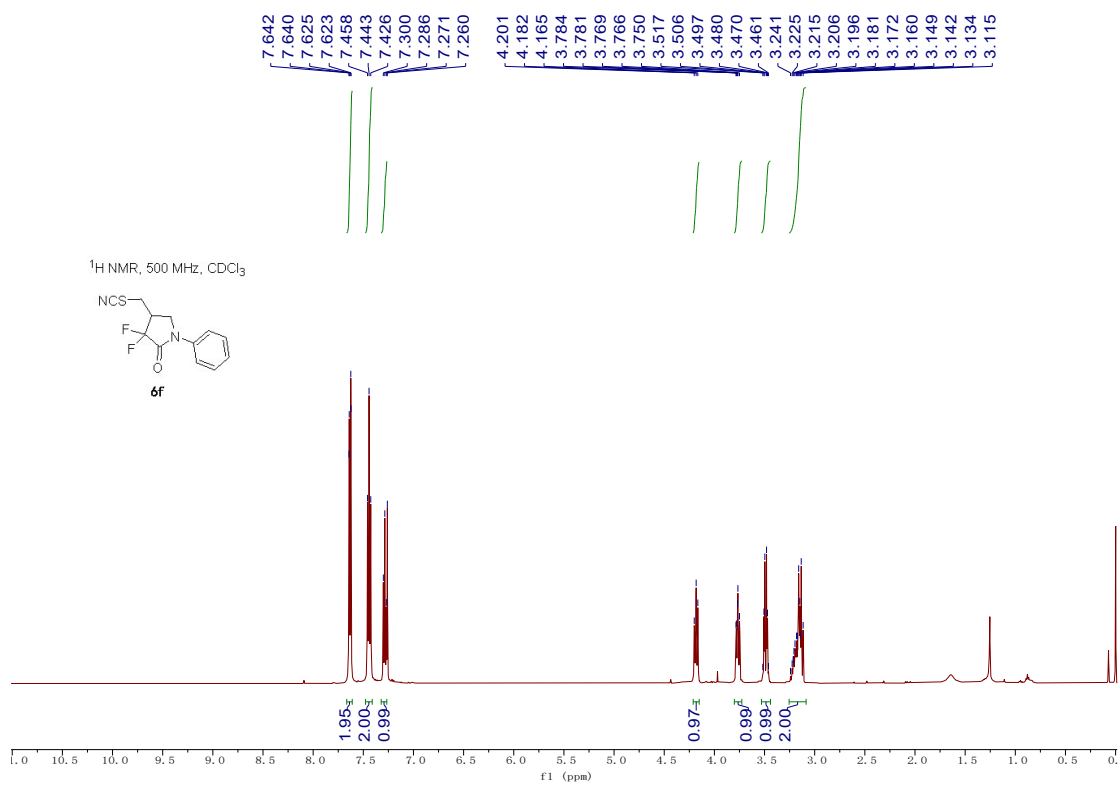
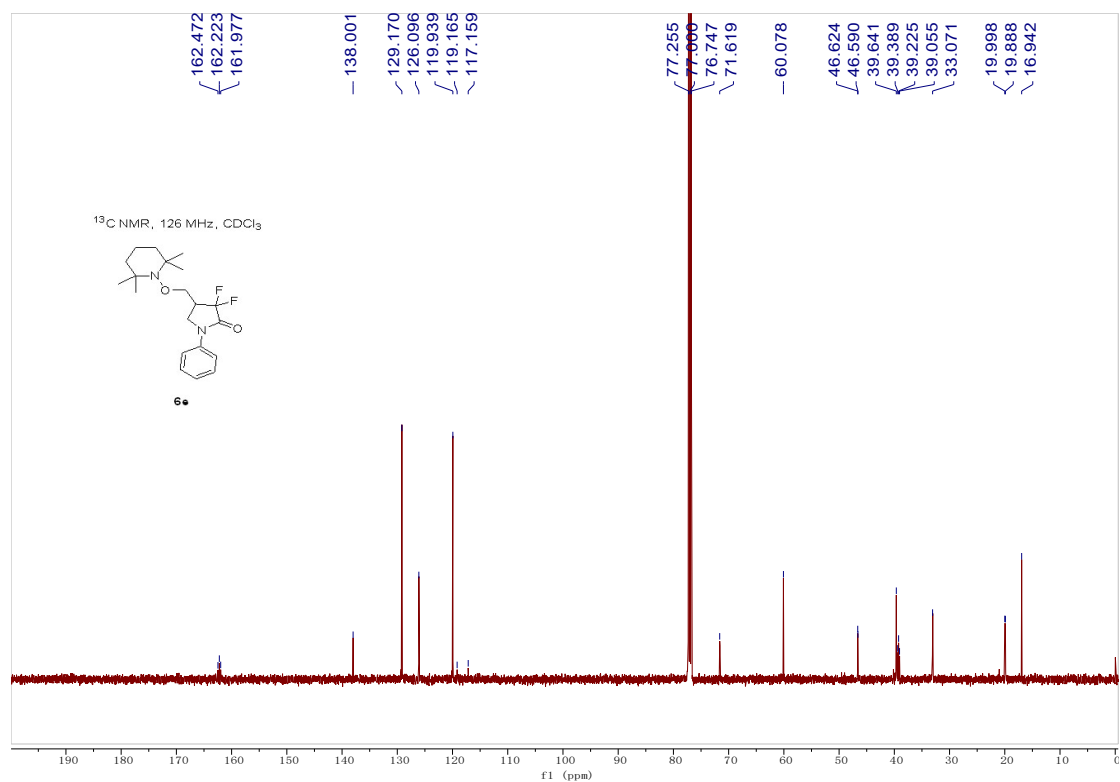


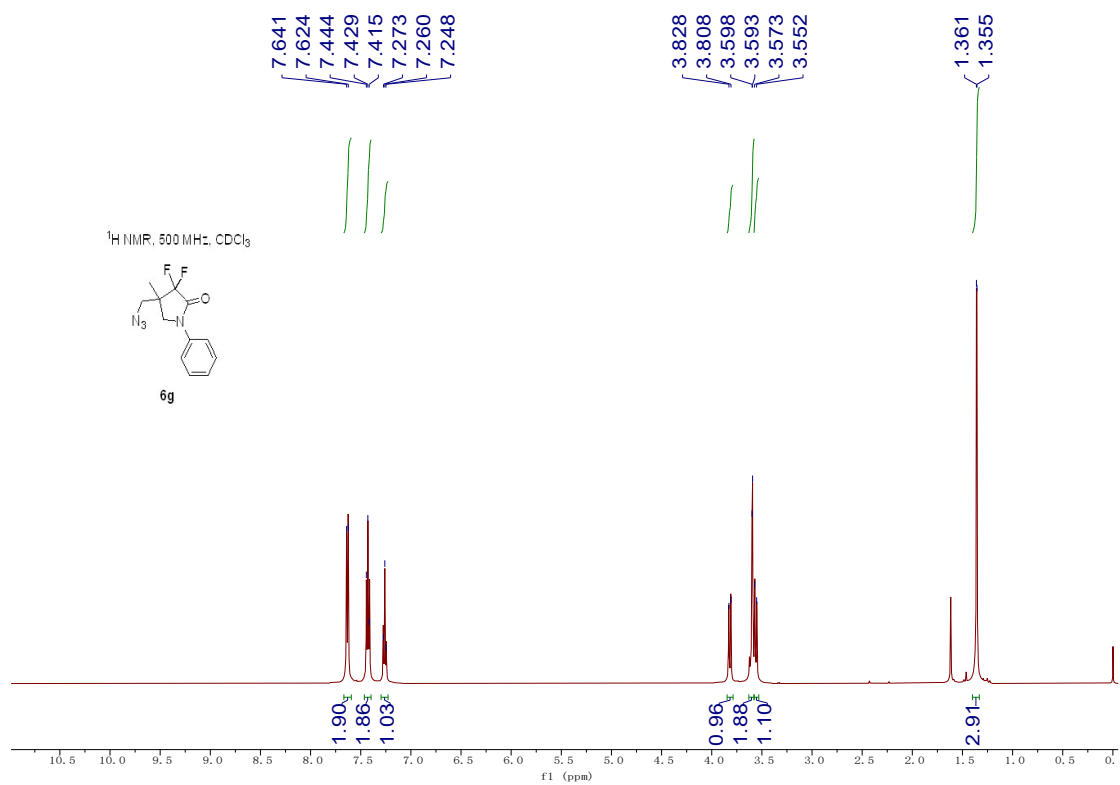
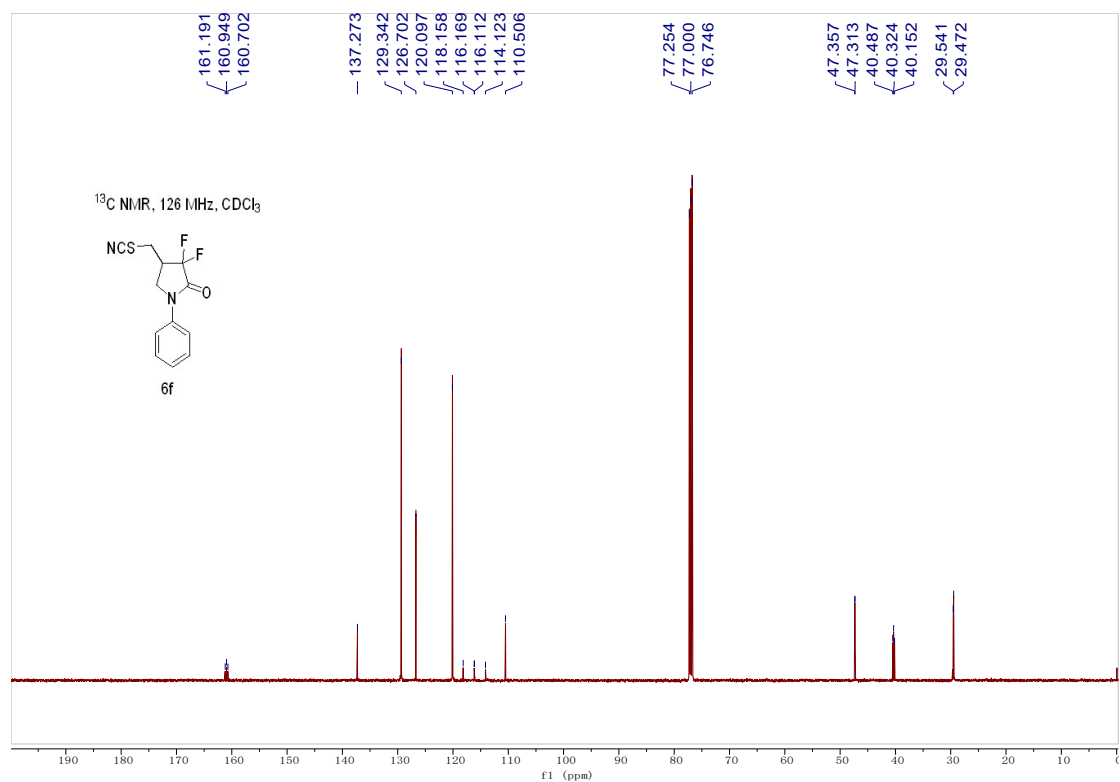


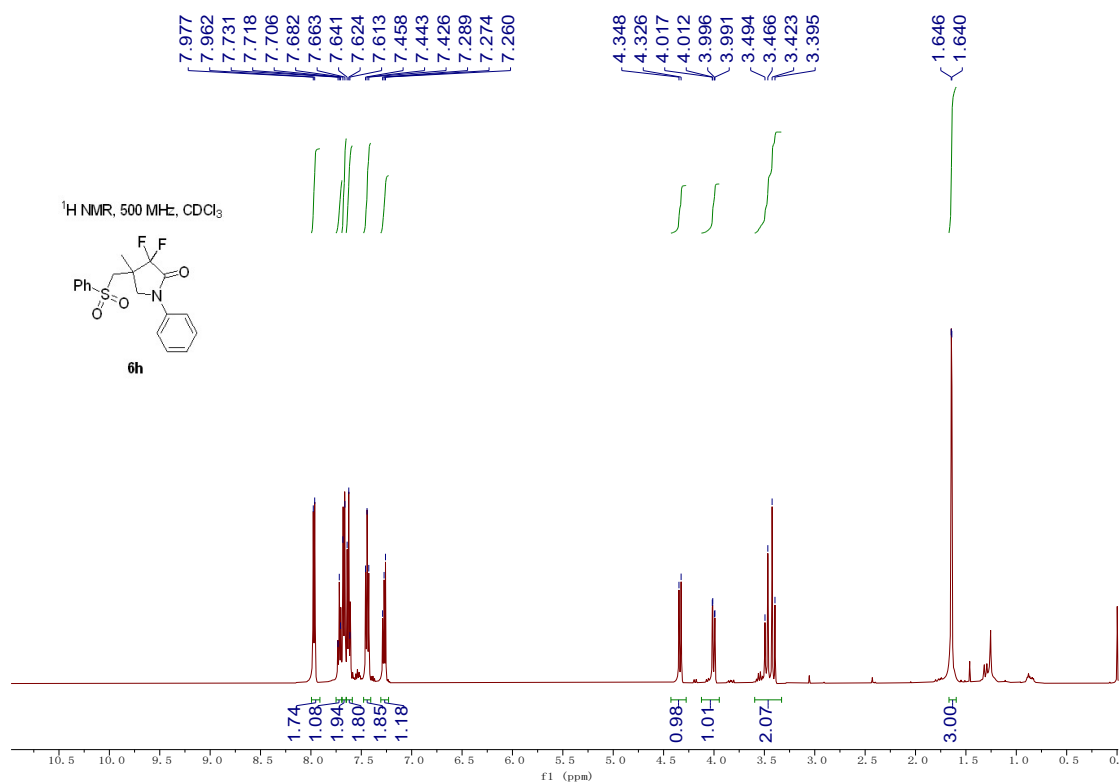
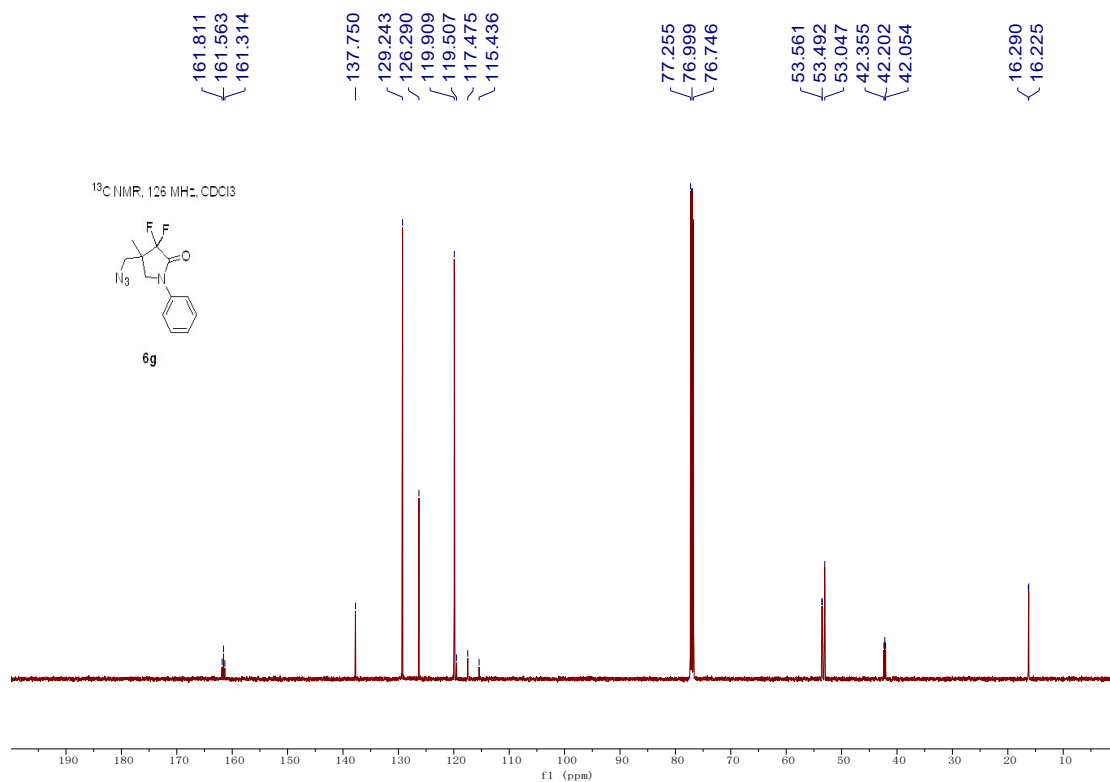


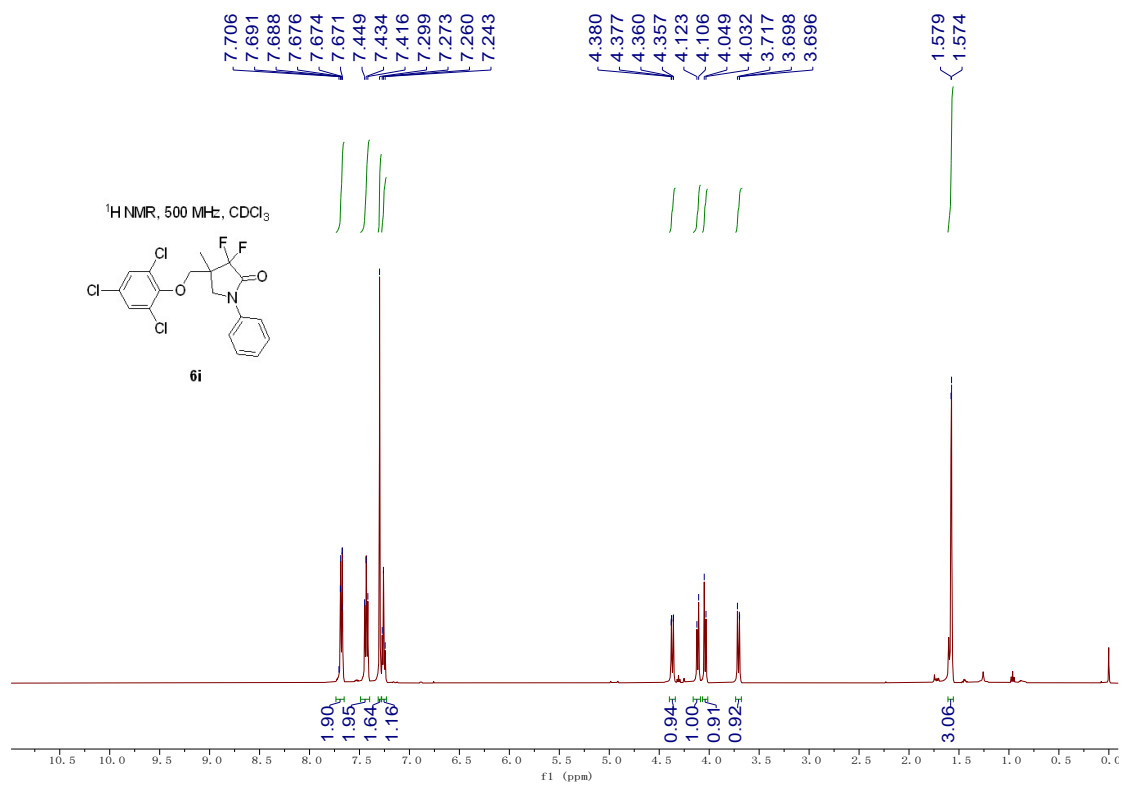
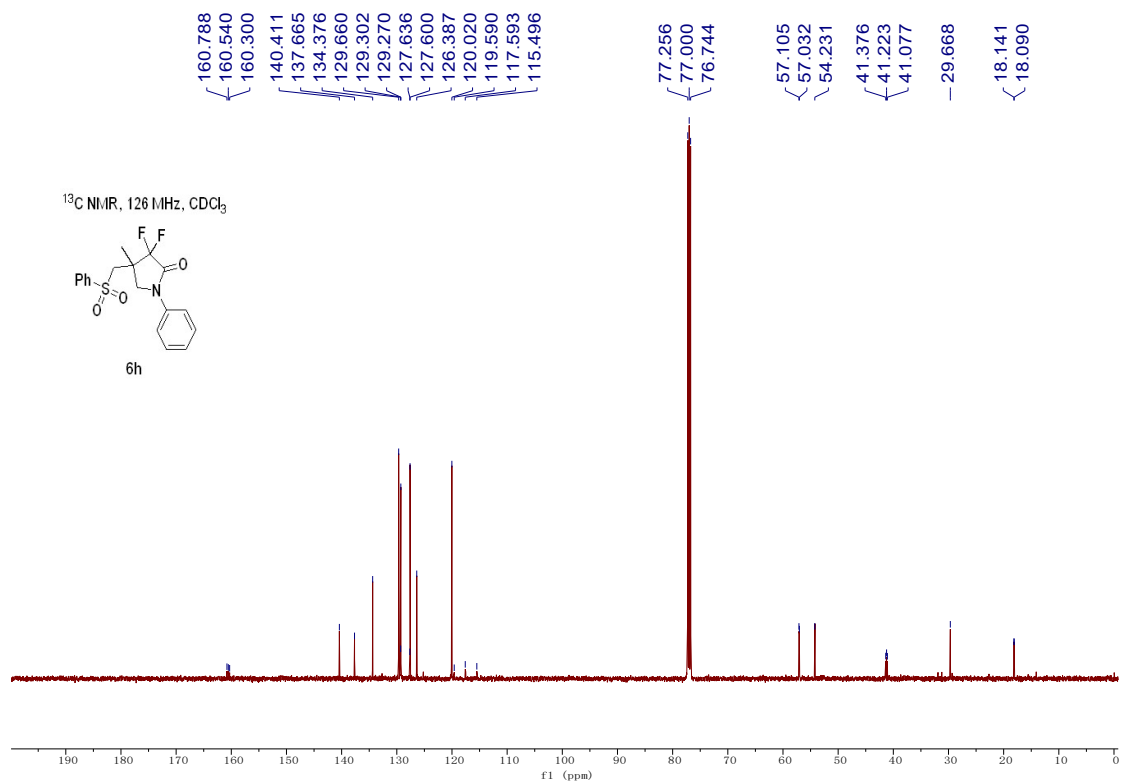


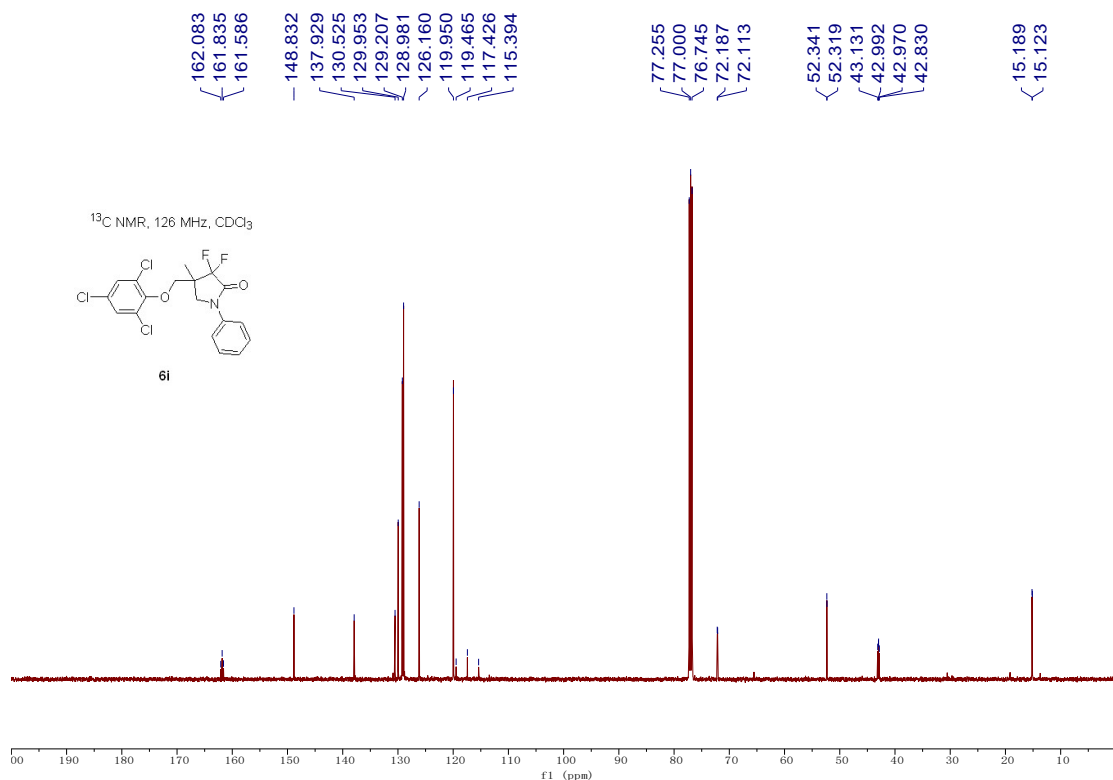












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