Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Synthesis of Withasomnine and Pyrazole Derivatives via Intramolecular Dehydrogenative Cyclization, as well as Biological Evaluation of Withasomnine-based Scaffolds

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Supporting Information

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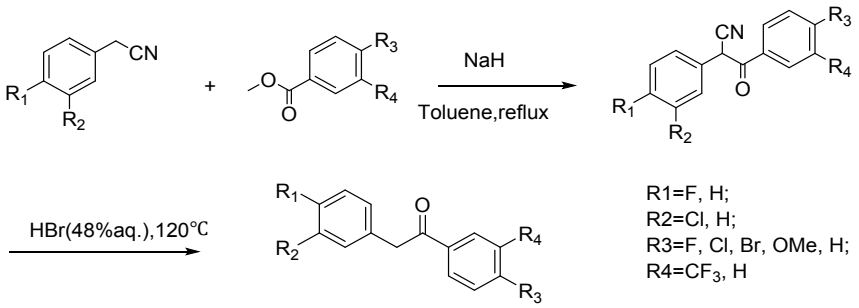
I. General Information

Unless otherwise noted, all reagents were used as received from commercial sources. All Reagents were commercial available from Strem Chemical Co., Aldrich Chemical Co and Beijing Ouhe Technology Co. DMF, dioxane were super dry with molecular sieves purchased from J&K Co. Stored in glovebox. DCM and toluene were collected through solvent system containing a 1 m column of activated alumina under nitrogen.

Ketones was prepared according to the known procedures. All glassware for moisture sensitive reactions was dried at 120°C in oven.

^{1}H NMR spectra were obtained on a 400 MHz spectrometer, chemical shifts were recorded relative to residual protiated solvent. ^{13}C NMR spectra were obtained at 100.6 MHz on a 400 MHz instrument, chemical shifts were recorded relative to the solvent resonance. Both ^{1}H NMR and ^{13}C NMR chemical shifts are reported in parts per million downfield from tetramethylsilane. Chromatographic purifications were peRformed by flash chromatography using silica gel (200-400 mesh). The yields of the products included refer to isolated yields.The melting point of solid compounds was measured by Beijing Taike X-5 Digital Micro Melting Point Instrument.

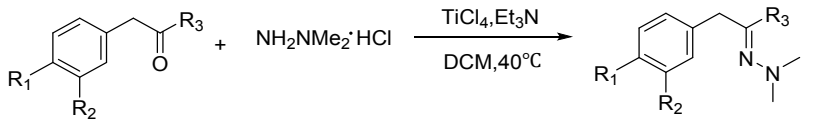
II. General Procedure for the Synthesis of Ketones.



To a solution of the benzeneacetonitrile or benzeneacetonitrile analogues (15 mmol) in toluene (100mL) was slowly added NaH (20 mmol, 60% in mineral oil) and kept stirring for 10 min at room temperature. Then methyl benzoate or 2-phenylacetonitril derivatives (16 mmol) was added. The mixture was heated to 130℃ until TLC indicated the full conversion of the 2-phenylacetonitril derivatives. After cooled to room temperature, water (10 mL) was added, and the mixture was concentrated by rotary evaporation. An additional 20 mL of water was added and extracted (3 × 50 mL)

with CH_2Cl_2. The organic phases were combined and discarded, and the aqueous portion was acidified with 3 M HCl until no more precipitate formed. The aqueous solution was then extracted (3 × 50 mL) with CH_2Cl_2. The combined organic layers were washed (2 × 25 mL) with brine and dried over anhydrous Na_2SO_4. The dichloromethane was then removed by rotary evaporation. The resulting diphenylpropanenitriles were directly used for the next step without further purification. Then added 40 mL aqueous hydrobromic acid (48%) to the diphenylpropanenitriles. The resulting solution was heated to 120℃ for 3h. After TLC indicated the full conversion of the diphenylpropanenitriles, the reaction was then quenched with saturated aqueous $NaHCO_3$. The aqueous solution was then extracted with ethyl acetate (30mL×3). The organic phases were combined. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Pure diphenylethanones were obtained after silica gel chromatography.

III. General Procedure for the Synthesis of Hydrazones

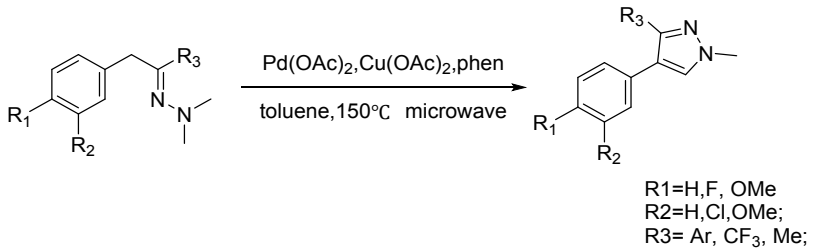


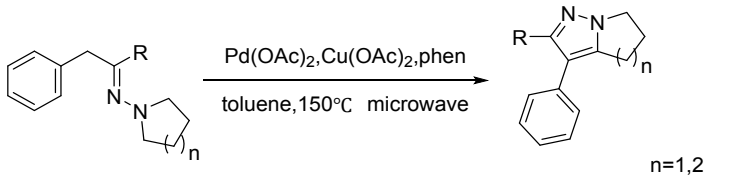
R_1=H,F, OMe
R_2=H,Cl,OMe;
R_3=H, Ar, CF_3, Me;

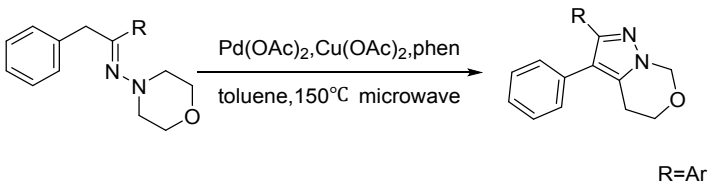
An oven dried 100mL round-bottom flask was charged with ketones or aldehydes (10 mmol), N,N-dimethylhydrazine(11mmol), Et_3N (5mmol) and 40mL DCM. The reaction vessel was sealed. Then $TiCl_4$(0.5mmol) in 10mL dry DCM was slowly injected into the rapidly stirred solution. The flask was transferred to an oil bath and kept stirring for 4 h at 40 ℃. The resulting reaction solution was quenched with saturated aqueous $NaHCO_3$, The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield oils or solids products . Analytically pure sample was obtained after silica gel chromatography.

IV. General Procedure for the Synthesis of Pyrazoles

1. General Procedure for the Synthesis of 1,3,4-trisubstitued pyrazoles and fused bicyclic pyrazoles.

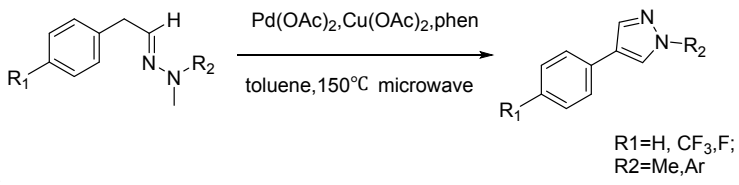






A 5mL microwave vial was charged with hydrazones(0.5 mmol,1 equiv), $Pd(OAc)_2$(0.05 mmol,0.10 equiv),$Cu(OAc)_2$ (1.25 mmol, 2.5 equiv) and phen (0.15 mmol, 0.30 equiv) in toluene (3.0 mL) with no specific order . The reaction mixture was then carried out under microwave irradiation at the temperature of 150℃ for 30min~10h. After the indicated time, the reaction solution was quenched with ammonium hydroxide and extracted with ethyl acetate. The combined organic layers were filtrated through celite, then washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield oils or solids. Pure pyrazole derivertives were obtained after silica gel chromatography.

2. General Procedure for the Synthesis of 1, 4-disubstitued Pyrazoles.



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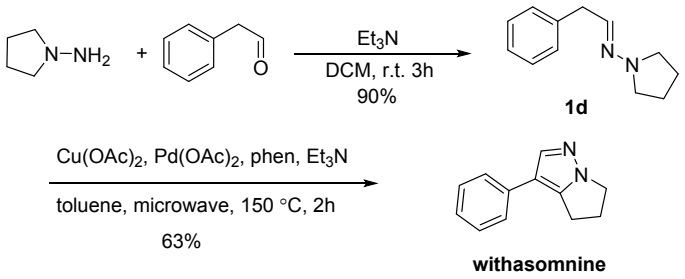
A 50mL microwave vial was charged with hydrazones(0.4 mmol, 1 equiv), $Pd(OAc)_2$ (0.04 mmol,0.1 equiv), $Cu(OAc)_2$ (1.00 mmol, 2.5 equiv) and phen (0.12 mmol, 0.3 equiv) in toluene (16.0 mL) with no specific order . The resulting mixture was then carried out under microwave irradiation at the temperature of 150℃ for 30min. After

the indicated time, the reaction solution was quenched with ammonium hydroxide and extracted with ethyl acetate. The combined organic layers were filtrated through celite, then washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield oils or solids. Pure pyrazole derivertives were obtained after silica gel chromatography.

V. Synthesis of Withasomnine



To a solution of N-aminopyrrolidine (947mg, 11 mmol) in DCM (50 mL) was added Et_3N (2.0g, 20 mmol) and phenylacetaldehyde (1.2g, 10 mmol). The reaction mixture was stirred for 3 h at room temperature. The resulting solution was then extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then evaporated under reduced pressure. The crude product was purified by flash column chromatography (PE:EtOAc:Et_3N/100:10:1) to afford pure product (10.1g, 90%) as yellow liquid.

N-(2-phenylethylidene)pyrrolidin-1-amine(79mg,0.42mmol) ,$Cu(OAc)_2$(182mg,1mmol) ,$Pd(OAc)_2$ (9mg, 0.04mmol) , 1,10-phenanthroline(22mg, 0.12mmol), Et_3N(121mg, 1.2mmol), toluene (16mL) was added to a microwave reaction tube. The resulting mixture was heated to 150℃ and kept for 2 hours in the microwave reactor. The reaction solution was then cooled down to room temperature, the mixture was filtered through celite. The filtrate was poured into saturated ammonia and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by flash column chromatography (PE:EtOAc/3:1) to afford pure product (49mg, 63%) as colorless solid.

VI. Biological Methods and Contents

Method

COX-2 inhibition assay in human whole blood

The production of PGE2 was measured in human blood from healthy volunteers. To determine COX-2 activity, LPS (10μg/ml) (Sigma CAT L2630) was added to the whole blood, and test compound (starting concentration of test compounds 540μM, half log increases, 8 points per Curve) or DMSO was added in triplicate, then the blood was incubated at 37℃ overnight, after which PGE2 production was measured. The samples were centrifuged at 250g for 10 min at 4℃to collect supernatant and PGE2 concentrations were determined in the supernatant using enzyme-linked immunoassays (Cayman, CAT 514010).

CCK8 assay and cell growth curve

The cell proliferation was determined by Cell Counting Kit-8 staining (Solarbio, China) according to the manufacturer's instructions. HCT116 and HT29 cells were seeded at 1×10^3 cells/ml in 96-well plates containing 100 μl of RPMI medium with 10% FBS and incubated overnight. **3l (D007)** was dissolved in DMSO, the cells were pretreated with various concentrations of **3l (D007)** (0-10 μM) for 1, 2, 3, 4, 5, 6 or 7 days, respectively. The cell viability was measured by fluorescence chemistry using CCK8 kit (Solarbio, China) with a spectrophotometer (Thermo, Multisckan GO, USA) at the OD of 450 nm.

Plate Colony formation assay

HCT116 and HT-29 cancer cell lines were planted into 6-well plates at a density of 1×103/well, respectively. After **3l** or control treatment for 10 days, each plate was washed with phosphate buffered saline for three times, and then stained with crystal violet. The number of colonies with more than 50 cells was counted using optical microscope. The experiments were repeated three times.

Wound healing assay

We performed a wound healing assay using the IncuCyte ZOOMTM live cell imaging system (Essen BioScience, MI USA) as instructions suggested. This system measures scratch closure in real time and automatically calculates the relative wound density within the initially-vacant area at each time point. The results were shown in photos clearly.

Contents

Figure S1. CCK8 assay showed that **3l (D007)** treatment decreased the proliferation of HT-29 and HCT116 cells.

Figure S2. 3l (D007) treatment inhibited the colony formation ability of HCT116 and HT-29 cancer cells.

Figure S3. 3l (D007) treatment inhibited scratch-wound healing of A549 cancer cells.

Table S1. IC_{50} of COX-2 inhibitors

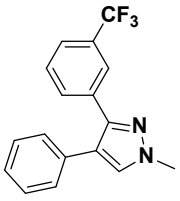
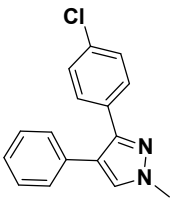
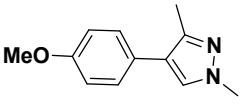
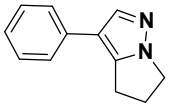
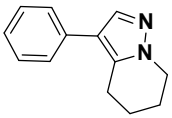
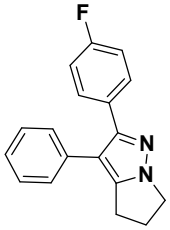
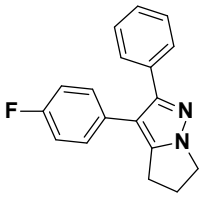
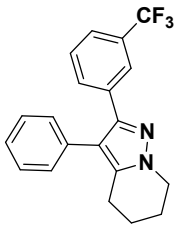
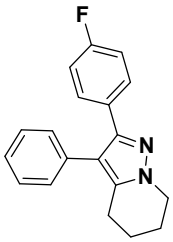
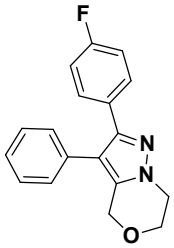
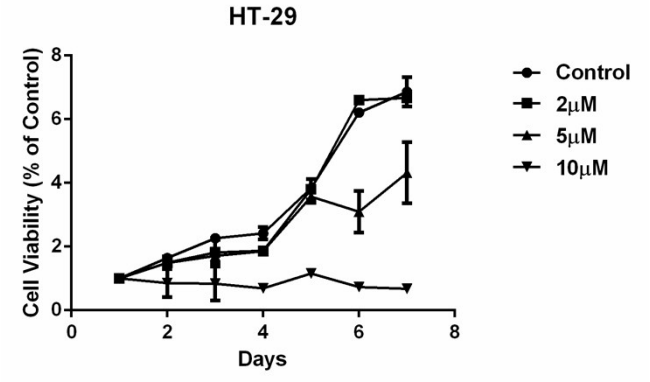
				
3a IC_{50} (63.5μM)	**3d** IC_{50} (145μM)	**3r** IC_{50} (73.7μM)	**withasomnine** IC_{50} (74.7μM)	**2i** IC_{50} (62.2μM)
				
2g IC_{50} (293μM)	**2a** IC_{50} (152μM)	**2k** IC_{50} (66.9μM)	**2j** IC_{50} (42.7μM)	**2l** IC_{50} (51.1μM)

Figure S1. 3l (D007) treatment decreased the proliferation of HT-29 (A) and HCT116 (B) cells as determined by CCK8 assay.



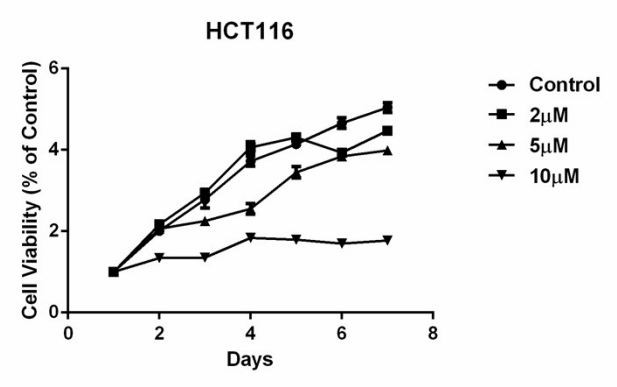


Figure S2. 3l (D007) treatment inhibited the colony formation ability of HCT116 and HT-29 cancer cells. *The representatives of colony formation for D007 treated cancer cells (A HCT116, B HT-29). C The mean colony number was presented.*

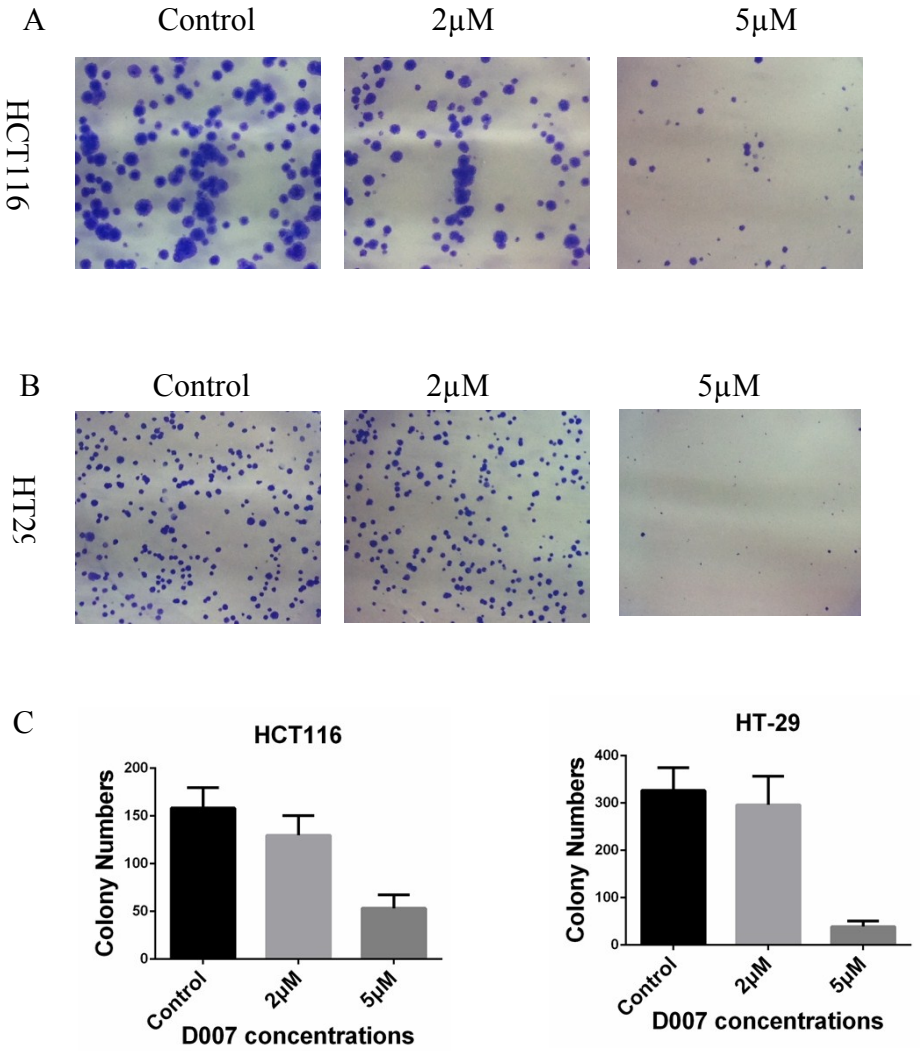
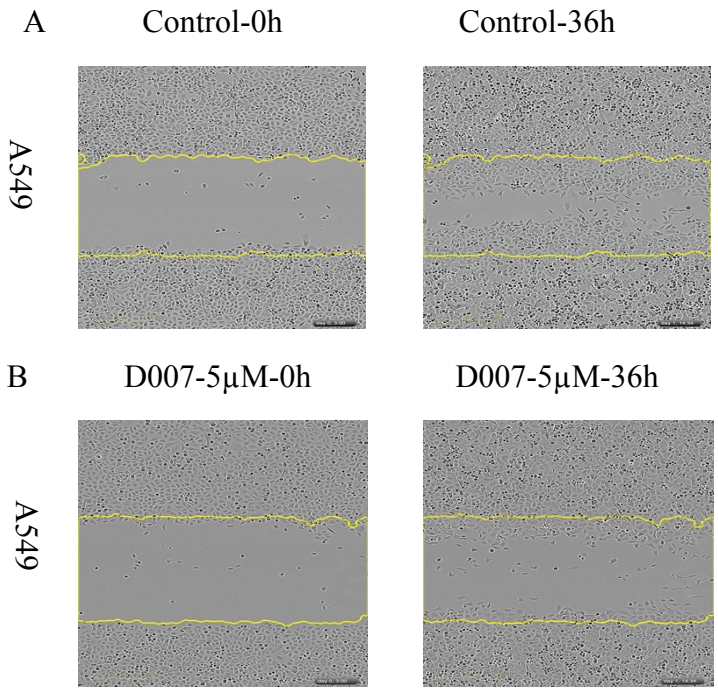
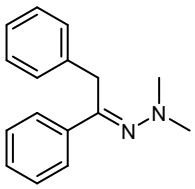


Figure S3. **3l (D007) treatment inhibited scratch-wound healing of A549 cancer cells.** *Representative wound healing assay of A549 cells with or without 5μM D007*

treatment for 36hrs were shown in A and B, respectively.



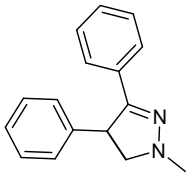
VII. Spectral Data



(E)-2-(1, 2-diphenylethylidene)-1,1-dimethylhydrazine (1a)

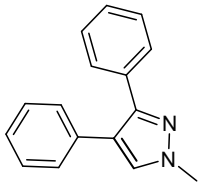
Yellow oil. R_f = 0.8 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.65 (m, 2H), 7.30 (m, 3H), 7.26 – 7.19 (m, 2H), 7.15 (d, J = 6.8 Hz, 3H), 4.36 (s, 2H), 2.61 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.33 (s), 137.88 (s), 137.47(s), 129.44 (s), 128.67 (s), 128.62 (s), 128.34(s), 127.36(s), 126.17(s), 48.01(s), 34.59(s).

MS (ESI^+): m / z calculated for $C_{16}H_{19}N_2$ $(M + H)^+$: 239.1548, found: 239.1546.



1-methyl-3,4-diphenyl-4,5-dihydro-1H-pyrazole (1b)

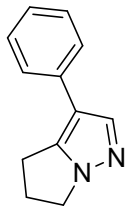
White solid. m.p. 114-116℃. R_f= 0.6 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.35 – 7.22 (m, 8H), 4.56 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.50 – 3.37 (m, 2H), 3.01 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 153.28 (s), 140.49 (s), 132.34 (s), 129.03 (s), 128.45 (s), 128.43 (s), 127.84 (s), 127.17 (s), 126.46 (s), 65.69 (s), 52.74 (s), 43.33 (s).



1-methyl-3,4-diphenyl-1H-pyrazole (1c)

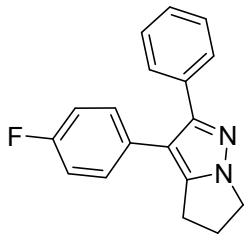
White solid. m.p. 70-72℃ R_f= 0.4 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H), 7.47 (s, 1H), 7.38 – 7.26 (m, 8H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.73 (s), 133.59 (s), 133.32 (s), 130.29 (s), 128.57 (s), 128.45 (s), 128.29 (s), 127.52 (s), 126.53 (s), 120.85 (s), 38.99 (s).

MS (ESI^+): m / z calculated for $C_{16}H_{15}N_2$ $(M + H)^+$: 235.1235, found: 235.1231.



withasomnine

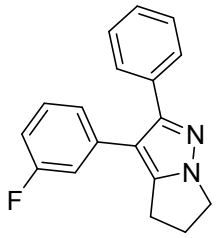
White solid. m.p. 116-117℃. R_f= 0.3 (EA/hexane=1:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.44 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.35 (dd, *J* = 10.6, 4.9 Hz, 2H), 7.22 – 7.15 (m, 1H), 4.18 – 4.09 (m, 2H), 3.11 – 2.97 (m, 2H), 2.63 (dd, *J* = 14.7, 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.56 (s), 140.79 (s), 133.37 (s), 128.76 (s), 125.56 (s), 124.93 (s), 115.19 (s), 47.50 (s), 26.33 (s), 23.79 (s)



3-(4-fluorophenyl)-2-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2a)

Yellow solid. m.p. 116-118℃ R_f = 0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dt, *J* = 4.3, 2.4 Hz, 2H), 7.34 – 7.26 (m, 3H), 7.22 – 7.15 (m, 2H), 6.98 (ddd, *J* = 10.8, 5.9, 2.5 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 2.98 (t, *J* = 7.0 Hz 2H), 2.66 (tt, *J* = 7.0, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.47 (d, *J* = 245.1 Hz), 153.21 (s), 145.22 (s), 134.21 (s), 130.15 (s), 130.07 (s), 128.34 (d, *J* = 11.0 Hz), 127.58 (s), 115.47 (d, *J* = 21.3 Hz), 112.46 (s), 48.08 (s), 26.09 (s), 23.41 (s).

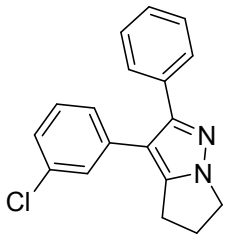
MS (ESI$^+$): m / z calculated for $C_{18}H_{15}FN_2$ $(M + H)^+$: 279.1298, found: 279.1288.



3-(3-fluorophenyl)-2-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2b)

Brown solid. m.p. 113-115℃. R_f = 0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 2H), 7.39 – 7.29 (m, 3H), 7.29 – 7.21 (m, 1H), 7.03 (m, 1H), 6.94 (m, 2H), 4.26 (t, *J* = 7.3 Hz,2H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.69 (tt, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 162.99 (d, J = 245.1 Hz), 153.44 (s), 145.48 (s), 136.36 (d, J = 8.4 Hz), 134.09 (s), 129.92 (d, J = 8.6 Hz), 128.42 (s), 128.41 (s), 127.73 (s), 124.20 (d, J = 2.8 Hz), 115.11 (d, J = 21.7 Hz), 112.89 (d, J = 21.1 Hz), 112.35 (s), 48.08 (s), 26.06 (s), 23.60 (s).

MS (ESI$^+$): m / z calculated for $C_{18}H_{15}FN_2$ $(M + H)^+$: 279.1298, found: 279.1289.

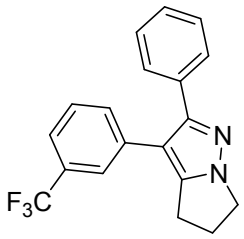


3-(3-chlorophenyl)-2-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2c)

Brown solid. m.p. 121-122℃. R_f = 0.3 (EA/hexane=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.34 – 7.27 (m, 3H), 7.25 – 7.22 (m, 1H), 7.20 – 7.15 (m, 2H), 7.11 – 7.04 (m, 1H), 4.24 (t, *J* = 7.2 Hz,2H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.67 (tt, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.41 (s), 145.53 (s), 136.03 (s), 134.33 (s), 134.00 (s), 129.74 (s), 128.45 (s), 128.35 (s), 128.23 (s), 127.76 (s), 126.82 (s),

126.17 (s), 112.13 (s), 48.10 (s), 26.06 (s), 23.57 (s).

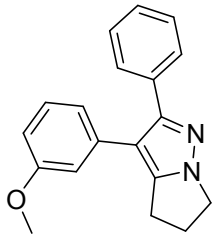
MS (ESI$^+$): m / z calculated for $C_{18}H_{15}ClN_2$ $(M + H)^+$: 295.1002, found: 295.0996.



2-phenyl-3-(3-(trifluoromethyl)phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2d)

Brown solid. m.p. 144-146℃ R_f = 0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.46 (m, 3H), 7.37 (m, 2H), 7.32 (m, 3H), 4.26 (t, *J* = 7.3 Hz, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.69 (tt, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50 (s), 145.56 (s), 135.01 (s), 133.91 (s), 131.75 (s), 130.94 (q, *J* = 32.0 Hz), 128.92 (s), 128.48 (s), 128.36 (s), 127.85 (s), 124.90 (q, *J* = 3.8 Hz), 124.24(q, *J* = 124.24 Hz)122.70 (q, *J* = 3.8 Hz), 112.10 (s), 48.12 (s), 26.06 (s), 23.56 (s).

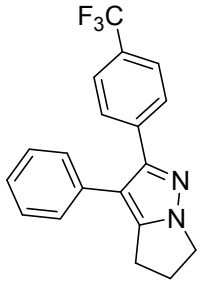
MS (ESI$^+$): m / z calculated for $C_{19}H_{15}F_3N_2$ $(M + H)^+$: 329.1266, found: 329.1256.



3-(3-methoxyphenyl)-2-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2e)

Yellow solid. m.p. 123-125℃. R_f =0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.34 – 7.26 (m, 3H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.76 (m, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 3.68 (s, 3H), 3.07 – 2.98 (t, *J* = 7.2 Hz, 2H), 2.71 – 2.60 (tt, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.65 (s), 153.38 (s), 145.34 (s), 135.42 (s), 134.41 (s), 129.50 (s), 128.48 (s), 128.31 (s), 127.56 (s), 121.00 (s), 113.98 (s), 113.24 (s), 111.79 (s), 55.17 (s), 48.06 (s), 26.10 (s), 23.64 (s).

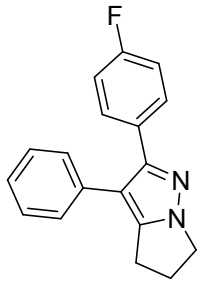
MS (ESI$^+$): m / z calculated for $C_{19}H_{18}N_2O$ $(M + H)^+$: 291.1497, found: 291.1491.



3-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2f)

Yellowish solid. R_f=0.3 (EA/PE=1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 – 7.17 (m, 3H), 4.25 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.66 (tt, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.56 (s), 145.71 (s), 137.99 (s), 133.56 (s), 129.24 (q, *J* = 32.3 Hz), 128.71 (s), 128.66 (s), 128.32 (s), 126.51 (s), 125.25 (q, *J* = 3.7 Hz), 124.43 (q, *J* = 273 Hz), 113.96 (s), 48.15 (s), 26.07 (s), 23.34 (s).

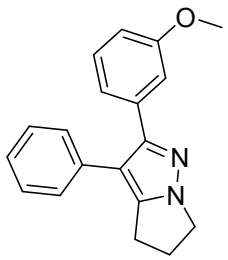
MS (ESI^+): m / z calculated for $C_{19}H_{15}F_3N_2$ $(M + H)^+$: 329.1266, found: 329.1273.



2-(4-fluorophenyl)-3-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2g)

Yellow solid. m.p. 137-139℃. R_f= 0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 2H), 7.29 (dd, *J* = 9.3, 5.5 Hz, 2H), 7.26 – 7.17 (m, 3H), 7.02 – 6.92 (m, 2H), 4.22 (t, *J* = 7.3 Hz, 2H), 3.00 t, *J* = 7.3 Hz, 2H), 265 (tt, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.43 (d, *J* = 246.1 Hz), 152.28 (s), 145.38 (s), 133.85 (s), 130.52 (d, *J* = 3.2 Hz), 130.01 (d, *J* = 8.0 Hz), 128.60 (s), 128.52 (s), 126.21 (s), 115.25 (d, *J* = 21.4 Hz), 113.27 (s), 48.04 (s), 26.07 (s), 23.49 (s).

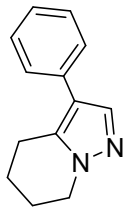
MS (ESI^+): m / z calculated for $C_{18}H_{15}FN_2$ $(M + H)^+$: 279.1298, found: 279.1283.



2-(3-methoxyphenyl)-3-phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole (2h)

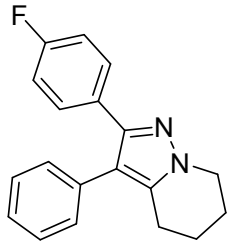
Yellow oil. R_f=0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 4H), 7.23 – 7.14 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.86 – 6.79 (m, 1H), 4.24 (t, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.65 (tt, *J* = 7.2 Hz,2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.54 (s), 153.08 (s), 145.36 (s), 135.68 (s), 134.04 (s), 129.31 (s), 128.71 (s), 128.51 (s), 126.18 (s), 120.87 (s), 114.04 (s), 113.51 (s), 112.98 (s), 55.24 (s), 48.09 (s), 26.11 (s), 23.50 (s).

MS (ESI^+): m / z calculated for $C_{19}H_{18}N_2O$ $(M + H)^+$: 291.1497, found: 291.1495.



3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine (2i)

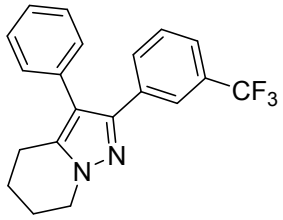
Yellowish solid. m.p. 123-125℃. R_f=0.3 (EA/PE=1:3). ^{1}H NMR (400 MHz, CDCl3) δ 7.68 (s, 1H), 7.43 – 7.34 (m, 4H), 7.25 – 7.19 (m, 1H), 4.21 (t, J = 6.2 Hz, 2H), 2.95 (t, J = 6.4 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.94 – 1.85 (m, 2H).13C NMR (101 MHz, CDCl3) δ 137.36 (s), 135.91 (s), 133.79 (s), 128.74 (s), 126.88 (s), 125.87 (s), 118.60 (s), 48.31 (s), 23.28 (s),23.25 (s), 20.67 (s).



2-(4-fluorophenyl)-3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine (2j)

Brown solid. R_f = 0.2 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.02 – 6.84 (m, 2H), 4.22 (t, *J* = 6.2 Hz, 2H), 2.76 (t, *J* = 6.3 Hz, 2H), 2.16 – 1.99 (m, 2H), 1.93 – 1.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.29 (d, *J* = 246.0 Hz), 147.48 (s), 138.20 (s), 133.61 (s), 129.99 (d, *J* = 3.2 Hz), 129.82-129.74(d, *J* = 6.0 Hz) 129.78 (s),128.47 (s), 126.42 (s), 116.36 (s), 115.11 (d, *J* = 21.4 Hz), 48.08 (s), 23.42 (s), 22.53 (s), 20.44 (s).

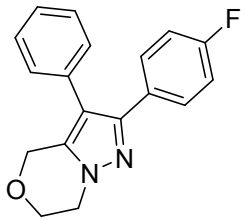
MS (ESI$^+$): m / z calculated for $C_{19}H_{17}FN_2$ $(M + H)^+$: 293.1454 , found: 293.1449.



3-phenyl-2-(3-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine (2k)

Brown solid. R_f = 0.6 (EA/PE=1:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.23 (m, 4H), 7.18 (dd, *J* = 5.2, 3.2 Hz, 2H), 4.26 (t, *J* = 6.2 Hz, 2H), 2.78 (t, *J* = 6.3 Hz, 2H), 2.18 – 2.05 (m, 2H), 1.94 – 1.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.96 (s), 138.51 (s), 134.75 (s), 133.32 (s), 131.29 (s), 130.71 (q, *J* = 32.2 Hz), 129.85 (s), 128.63 (s), 128.58 (s), 126.77 (s), 124.84 (q, *J* = 3.9 Hz), 124.26 (q, *J* =270.7 Hz)), 123.90 (q, *J* = 3.8 Hz), 116.96 (s), 48.27 (s), 23.48 (s), 22.52 (s), 20.46 (s).

MS (ESI$^+$): m / z calculated for $C_{20}H_{17}F_3N_2$ $(M + H)^+$: 343.1422 , found: 343.1414.

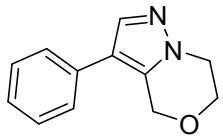


2-(4-fluorophenyl)-3-phenyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine (2l)

Brown solid. R_f =0.2 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.31 (tt, *J* = 8.1, 1.8 Hz, 2H), 7.26 (ddd, *J* = 7.1, 3.7, 1.4 Hz, 1H), 7.15 – 7.08 (m, 2H), 6.96 (ddd, *J* = 10.9, 5.9, 2.5 Hz, 2H), 4.84 (s, 2H), 4.30 – 4.24 (m, 2H), 4.16 (dd, *J* = 6.0, 4.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.52 (d, *J* = 246.5 Hz), 147.91

(s), 135.20 (s), 132.58 (s), 129.93 (d, *J* = 8.1 Hz), 129.47 (d, *J* = 3.2 Hz), 129.34 (s), 128.77 (s), 126.90 (s), 115.33 (d, *J* = 21.5 Hz), 115.13 (s), 64.62 (s), 63.74 (s), 47.07 (s).

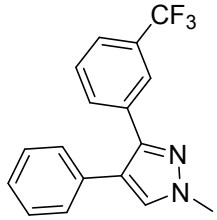
MS (ESI$^+$): m / z calculated for $C_{18}H_{15}FN_2O$ $(M + H)^+$: 295.1247, found:295.1239 .



3-phenyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazine (2m)

Yellow solid. R_f = 0.3 (EA/PE=1:3).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.42 – 7.34 (m, 2H), 7.26 (ddd, *J* = 16.3, 9.2, 4.3 Hz, 4H), 5.02 (s, 2H), 4.25 (d, *J* = 5.5 Hz, 2H), 4.15 (dd, *J* = 5.9, 4.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.49 (s), 132.96 (s), 132.78 (s), 129.04 (s), 126.56 (s), 126.35 (s), 117.69 (s), 64.38 (s), 64.35 (s), 47.33 (s).

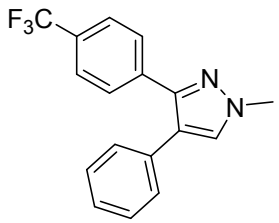
MS (ESI$^+$): m / z calculated for $C_{12}H_{12}N_2O$ $(M + H)^+$: 201.1028, found: 201.103 .



1-methyl-4-phenyl-3-(3-(trifluoromethyl)phenyl)-1H-pyrazole (3a)

Yellow solid. m.p. 72-74℃. R_f = 0.3 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.46 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.27 (d, *J* = 6.6 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.33 (s), 134.48 (s), 132.86 (s), 131.51 (s), 130.85 (q, *J* = 331.9 Hz), 130.65 (s), 128.74 (s), 128.72 (s), 127.04 (s), 125.59 (s), 125.03 (q, *J* = 3.8 Hz), 124.24 (q, *J* = 270.6 Hz),124.21 (q, *J* = 3.8 Hz), 121.38 (s), 39.24 (s).

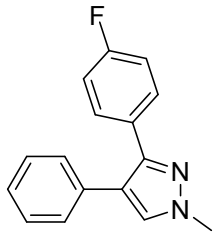
MS (ESI$^+$): m / z calculated for $C_{17}H_{13}F_3N_2$ $(M + H)^+$: 303.1109 found: 303.1104.



1-methyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrazole (3b)

Yellow solid. m.p. 69-71℃ R_f = 0.3 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.47 (s, 1H), 7.36 – 7.21 (m, 5H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.26 (s), 137.29 (s), 132.94 (s), 130.72 (s), 129.40 (q, *J* = 32.3 Hz), 128.79 (s), 128.72 (s), 128.36 (s), 127.01 (s), 125.29 (q, *J* = 3.7 Hz), 124.24(q, *J* = 273 Hz) 121.56 (s), 39.20 (s).

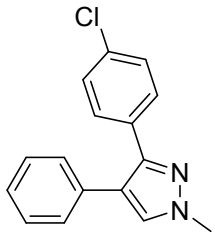
MS (ESI$^+$): m / z calculated for C17H13F3N2 $(M + H)^+$: 303.1109, found: 303.1115.



3-(4-fluorophenyl)-1-methyl-4-phenyl-1H-pyrazole (3c)

Yellow solid. m.p. 68-70℃. R_f = 0.2 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 3H), 7.29 (m, *2*H), 7.24 (m,*3*H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.95 (s, 3H). ^{113}C NMR (101 MHz, $CDCl_3$) δ 162.49 (d, *J* = 246.3 Hz), 147.93 (s), 133.19 (s), 130.39 (s), 130.03 (d, *J* = 8.1 Hz), 129.73 (d, *J* = 3.2 Hz), 128.79 – 128.79 (m), 128.63 (s), 128.61 (s), 126.73 (s), 120.85 (s), 115.42 (s), 115.20 (s), 77.48 (s), 77.16 (s), 76.84 (s), 39.12 (s).

MS (ESI$^+$): m / z calculated for $C_{16}H_{14}N_2F$ $(M + H)^+$: 253.1141 found: 253.1139.

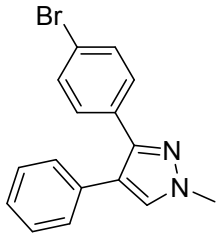


3-(4-chlorophenyl)-1-methyl-4-phenyl-1H-pyrazole (3d)

Yellowish solid. m.p. 110-112℃. R_f=0.5 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 2H), 7.34 – 7.19 (m, 7H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 147.64 (s), 133.45 (s), 133.11 (s), 132.16 (s), 130.52 (s), 129.58 (s), 128.69 (s), 128.65 (s), 128.57 (s), 126.83 (s), 121.08 (s), 39.15 (s).

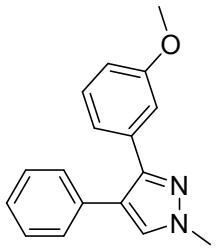
MS (ESI$^+$): m / z calculated for $C_{16}H_{14}N_2Cl$ $(M + H)^+$: 269.0846, found: 269.0840.



3-(4-bromophenyl)-1-methyl-4-phenyl-1H-pyrazole (3e)

White solid. m.p. 119-120℃. R_f = 0.4 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.45 (s, 1H), 7.33 – 7.20 (m, 8H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.87 (s), 133.66 (s), 133.41 (s), 130.35 (s), 128.67 (s), 128.54 (s), 128.37 (s), 127.59 (s), 126.61 (s), 120.97 (s), 39.14 (s).

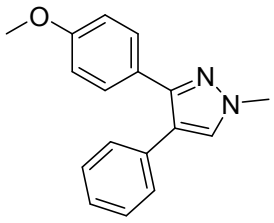
MS (ESI$^+$): m / z calculated for $C_{16}H_{14}N_2Br$ $(M + H)^+$: 313.0340, found: 313.0327.



3-(3-methoxyphenyl)-1-methyl-4-phenyl-1H-pyrazole (3f)

Yellow solid. m.p. 87-89℃. R_f=0.5 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.20 (m, 6H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.25 (s), 148.73 (s), 133.60 (s), 130.28 (s), 129.60 (s), 128.67 (s), 128.55 (s), 126.56 (s), 126.25 (s), 120.61 (s), 113.84 (s), 55.34 (s), 39.11 (s).

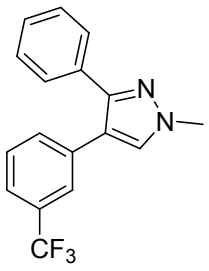
MS (ESI$^+$): m / z calculated for $C_{17}H_{17}N_2O$ $(M + H)^+$: 265.1341 found: 265.1338.



3-(4-methoxyphenyl)-1-methyl-4-phenyl-1H-pyrazole (3g)

Yellow solid. R_f = 0.3 (EA/PE=1:10).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.35 (m, 3H), 7.35 – 7.18 (m, 35H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.25 (s), 148.73 (s), 133.60 (s), 130.28 (s), 129.60 (s), 128.67 (s), 128.55 (s), 126.56 (s), 126.25 (s), 120.61 (s), 113.84 (s), 55.34 (s), 39.11 (s).

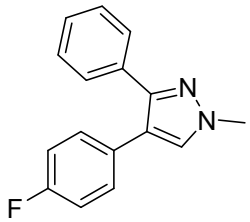
MS (ESI$^+$): m / z calculated for $C_{17}H_{16}N_2O$ $(M + H)^+$: 265.1341, found: 265.1342.



1-methyl-3-phenyl-4-(3-(trifluoromethyl)phenyl)-1H-pyrazole (3h)

Yellow oil. R_f=0.4 (EA/PE=1:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.53 (s, 1H), 7.51 – 7.48 (m, 1H), 7.45 (m, 2H), 7.38 (m, 2H), 7.34 – 7.27 (m, 3H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.10 (s), 134.25 (s), 133.10 (s), 131.88(s), 130.98 (q, *J* = 32.1 Hz), 130.50 (s), 128.96 (s), 128.55 (s), 128.38 (s), 127.97 (s), 125.08 (q, *J* = 3.8 Hz), 124.20 (q, *J* = 272.2 Hz), 123.26 (q, *J* = 3.8 Hz), 119.58 (s), 39.25 (s).

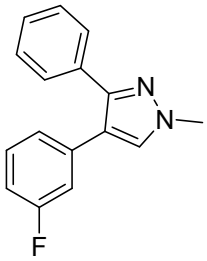
MS (ESI$^+$): m/z calculated for $C_{17}H_{13}F_3N_2$ $(M + H)^+$: 303.1109 , found: 303.1098.



4-(4-fluorophenyl)-1-methyl-3-phenyl-1H-pyrazole (3i)

White solid. m.p. 75-77℃. R_f= 0.5 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.43 (s, 1H), 7.30 (m, 3H), 7.22 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.98 (t, *J* = 8.6 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.83 (d, *J* = 245.5 Hz), 148.76 (s), 133.43 (s), 130.24 (s), 130.16 (s), 129.39 (d, *J* = 3.3 Hz), 128.33 (d, *J* = 13.3 Hz), 127.65 (s), 119.92 (s), 115.41 (d, *J* = 21.4 Hz), 39.07 (s).Two signals combined to a single one.

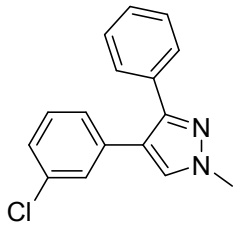
MS (ESI$^+$):m/z calculated for $C_{16}H_{13}FN_2$ $(M + H)^+$: 253.1141, found: 253.1134.



4-(3-fluorophenyl)-1-methyl-3-phenyl-1H-pyrazole (3j)

Brown oil. R_f = 0.2 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 3H), 7.30 (m, 3H), 7.22 (dd, *J* = 13.9, 7.4 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 10.2 Hz, 1H), 6.92 (t, *J* = 8.6 Hz, 1H), 3.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.92 (d, *J* = 245.3 Hz), 149.00 (s), 135.63 (d, *J* = 8.4 Hz), 133.29 (s), 130.43 (s), 129.96 (d, *J* = 8.6 Hz), 128.46 (s), 128.40 (s), 127.83 (s), 124.27 (d, *J* = 2.8 Hz), 119.82 (s), 115.29 (d, *J* = 21.8 Hz), 113.40 (d, *J* = 21.0 Hz), 39.15 (s).

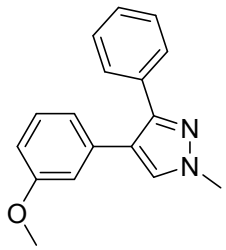
MS (ESI$^+$): m/z calculated for $C_{16}H_{13}FN_2$ $(M + H)^+$: 253.1141 , found: 253.1128.



4-(3-chlorophenyl)-1-methyl-3-phenyl-1H-pyrazole (3k)

Yellow solid. m.p. 74-76℃. R_f = 0.2 (EA/PE=1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.45 (s, 1H), 7.32 (dd, *J* = 11.8, 5.6 Hz, 4H), 7.20 (q, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 6.8 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.93 (s), 135.29 (s), 134.29 (s), 133.22 (s), 130.43 (s), 129.72 (s), 128.46 (s), 128.37 (s), 128.33 (s), 127.82 (s), 126.82 (s), 126.62 (s), 119.57 (s), 39.14 (s).

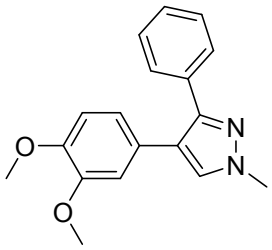
MS (ESI$^+$): m/z calculated for $C_{16}H_{14}N_2Cl$ $(M + H)^+$: 269.0846, found: 269.0839



4-(3-methoxyphenyl)-1-methyl-3-phenyl-1H-pyrazole (3l)

Yellowish solid. R_f=0.3 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.3 Hz, 2H), 7.47 (s, 1H), 7.36 – 7.27 (m, 3H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.84 – 6.77 (m, 2H), 3.96 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.65 (s), 148.92 (s), 134.72 (s), 133.62 (s), 130.32 (s), 129.50 (s), 128.44 (s), 128.32 (s), 127.62 (s), 121.06 (s), 120.79 (s), 114.00 (s), 112.36 (s), 55.17 (s), 39.09 (s).

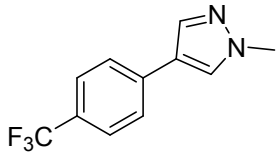
MS (ESI$^+$): m/z calculated for $C_{17}H_{17}N_2O$ $(M + H)^+$: 265.1341, found: 265.1338.



4-(3,4-dimethoxyphenyl)-1-methyl-3-phenyl-1H-pyrazole (**3m**)

Yellowish solid. R_f= 0.2 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.1 Hz, 2H), 7.44 (s, 1H), 7.28 (t, *J* = 8.0 Hz, 3H), 6.87 – 6.79 (m, 2H), 6.75 (s, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.79 (s), 148.74 (s), 147.93 (s), 133.72 (s), 129.99 (s), 128.42 (s), 128.31 (s), 127.58 (s), 126.11 (s), 120.76 (s), 112.26 (s), 111.38 (s), 55.98 (s), 55.77 (s), 39.12 (s).Two signals combined to a single one.

MS (ESI$^+$): m/z calculated for $C_{18}H_{19}N_2O_2$ $(M + H)^+$: 295.1447, found: 295.1442.

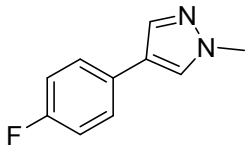


1-methyl-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**3n**)

Brown solid. R_f= 0.5 (EA/PE=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.67 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 3.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.93 (s), 136.22 (s), 128.18 (q, *J* = 32.6 Hz), 127.45 (s), 125.81 (q, *J* = 3.7 Hz), 125.41 (s), 124.278 (q, *J* =270.0 Hz), 121.91 (s), 39.16 (s).

MS (ESI$^+$): m/z calculated for $C_{11}H_9F_3N_2$ $(M + H)^+$: 227.0796, found: 227.0800.

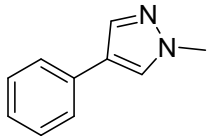


4-(4-fluorophenyl)-1-methyl-1H-pyrazole (3o)

Brown solid. R_f = 0.4 (EA/PE=1:1). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.54 (s, 1H), 7.40 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.04 (t, *J* = 8.7 Hz, 2H), 3.92 (s, 3H).

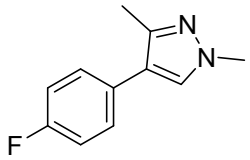
^{13}C NMR(101 MHz, $CDCl_3$) δ 161.66 (d, *J* = 245.0 Hz), 136.69 (s), 128.89 (d, *J* = 3.3 Hz), 127.10 (d, *J* = 7.8 Hz), 126.85 (s), 122.46 (s), 115.78 (d, *J* = 21.5 Hz), 39.15 (s).

MS (ESI^+): m/z calculated for $C_{10}H_9FN_2$ $(M + H)^+$: 177.0828, found: 177.0824



1-methyl-4-phenyl-1H-pyrazole (**3p**)

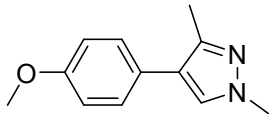
Brown solid. m.p. 91-92℃. R_f = 0.4 (EA/PE=1:1).^{1}H NMR (400 MHz, CDCl3) δ 7.75 (s, 1H), 7.57 (s, 1H), 7.45 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.21 (m, 1H), 3.91 (s, 3H).



4-(4-fluorophenyl)-1,3-dimethyl-1H-pyrazole (3q)

Yellow solid. R_f = 0.4 (EA/PE=1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.30 (m, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.57 (d, *J* = 245.1 Hz), 145.61 (s), 129.76 (d, *J* = 3.2 Hz), 129.10 (d, *J* = 7.8 Hz), 128.88 (s), 120.35 (s), 115.52 (d, *J* = 21.3 Hz), 38.75 (s), 13.05 (s).

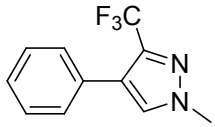
MS (ESI^+): m/z calculated for $C_{11}H_{11}FN_2$ $(M + H)^+$: 191.0979, found: 191.0974.



4-(4-methoxyphenyl)-1,3-dimethyl-1H-pyrazole (3r)

Yellowish solid. m.p. 64-66℃. R_f = 0.2 (EA/PE=1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.23 (s), 145.61 (s), 128.78 (s), 128.67 (s), 126.27 (s), 120.94 (s), 114.17 (s), 55.44 (s), 38.77 (s), 13.15 (s).

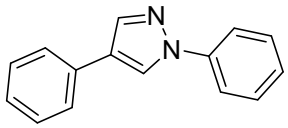
MS (ESI^+): m/z calculated for $C_{12}H_{14}N_2O$ $(M + H)^+$: 203.1184, found: 203.1180.



1-methyl-4-phenyl-3-(trifluoromethyl)-1H-pyrazole (3s)

Yellow solid. R_f=0.4 (EA/PE=1:4).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.45 – 7.30 (m, 5H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.68 (q, J=36 Hz), 130.96 (s), 130.69 (s), 128.74 (s), 128.64 (s), 127.77 (s), 122.66 (s), 121.74 (q, J=268 Hz), 39.68 (s).

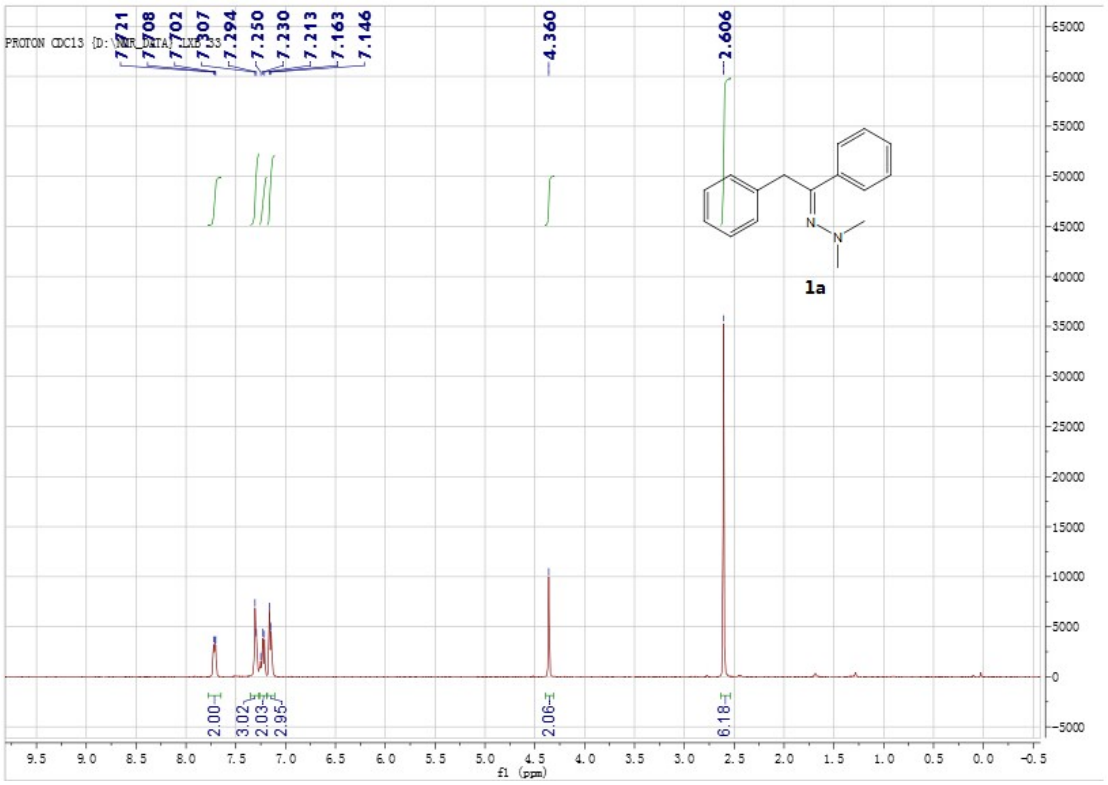
MS (ESI^+): m/z calculated for $C_{11}H_9F_3N_2$ $(M + H)^+$: 227.0796, found: 227.0796



1,4-diphenyl-1H-pyrazole (3t)

Yellowish solid. m.p. 92-94℃. R_f =0.2 (acetone/PE=1:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.01 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.19 (s), 138.92 (s), 132.19 (s), 129.61 (s), 129.08 (s), 126.99 (s), 126.70 (s), 125.85 (s), 125.05 (s), 123.44 (s), 119.19 (s).

MS (ESI^+): m/z calculated for $C_{15}H_{12}N_2$ $(M + H)^+$: 221.1079, found: 221.1078.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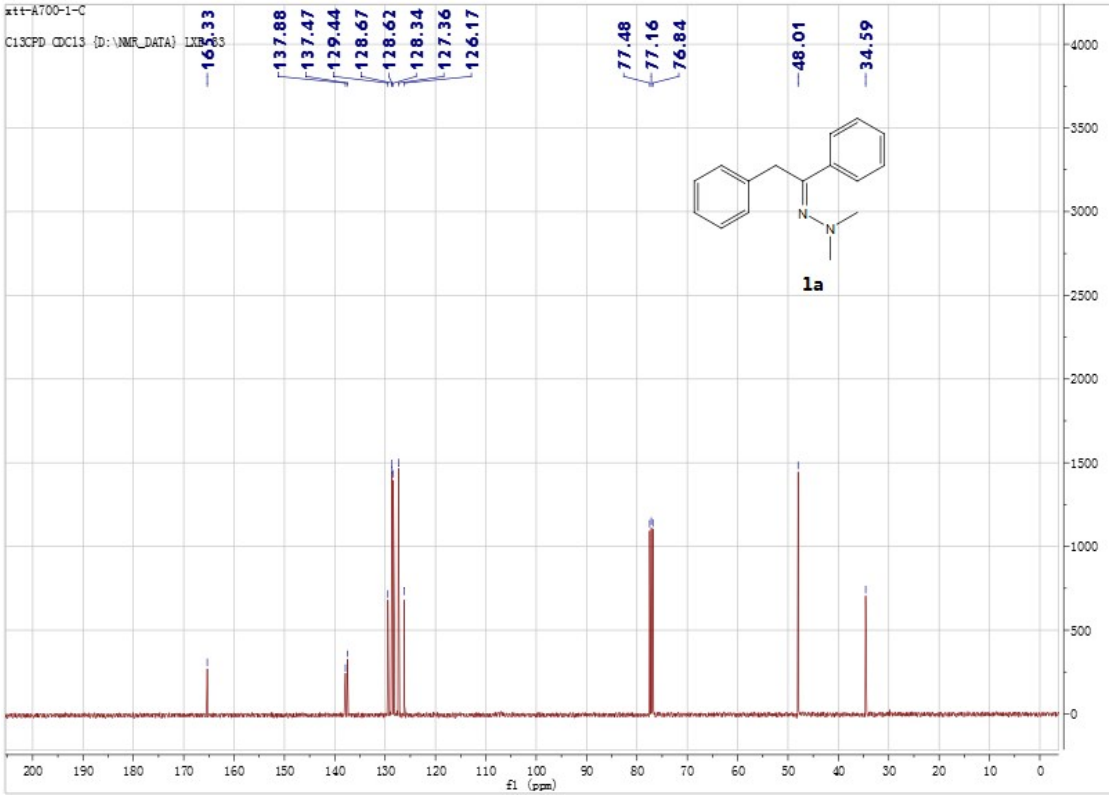
2.03
2.95
2.06
6.18
f1 (ppm)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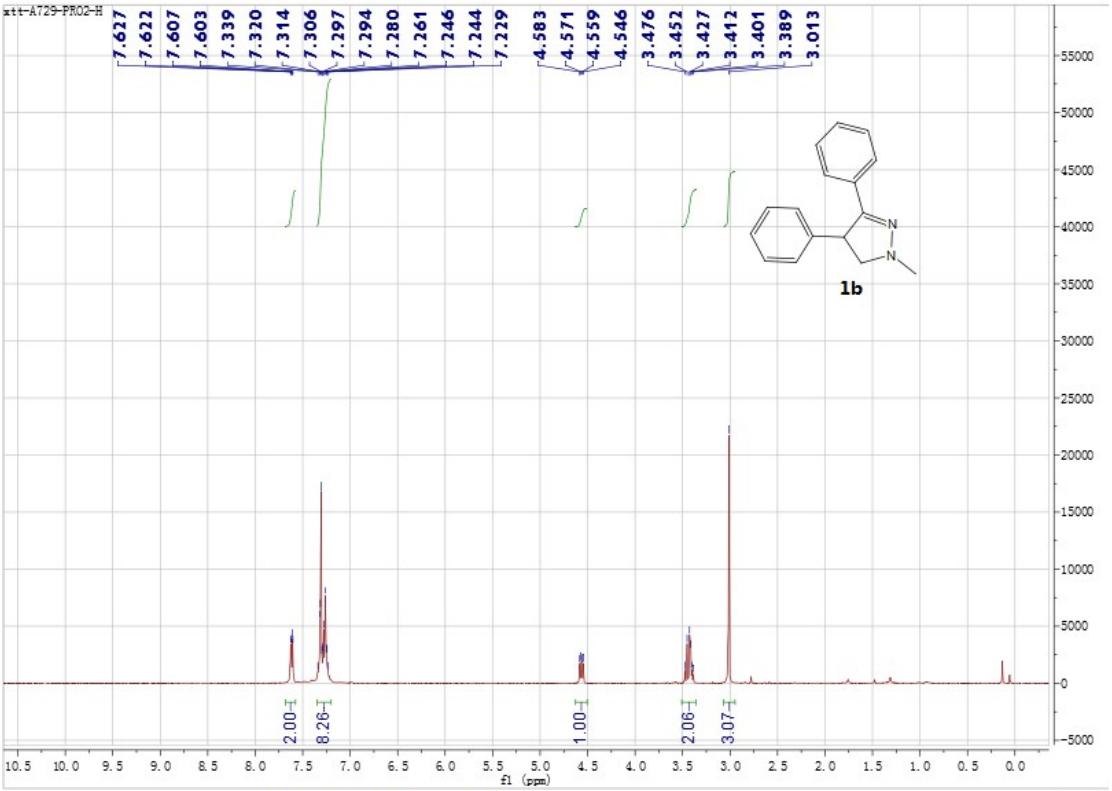
f1 (ppm)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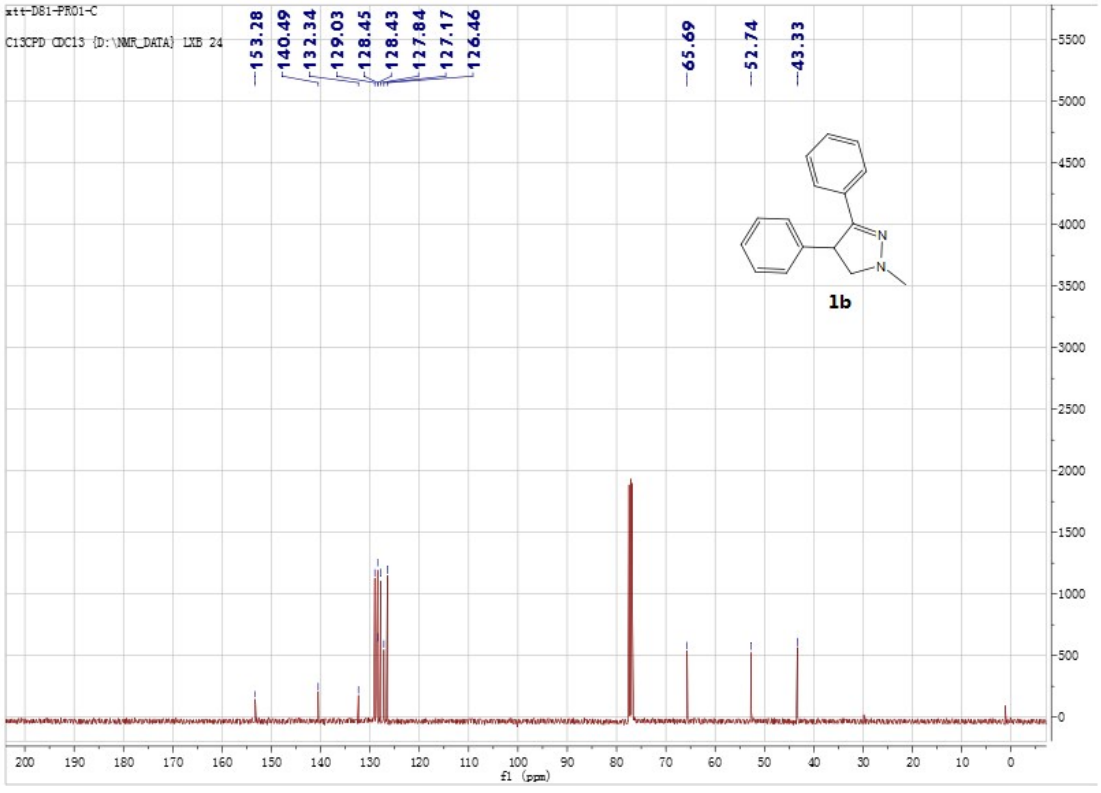
f1 (ppm)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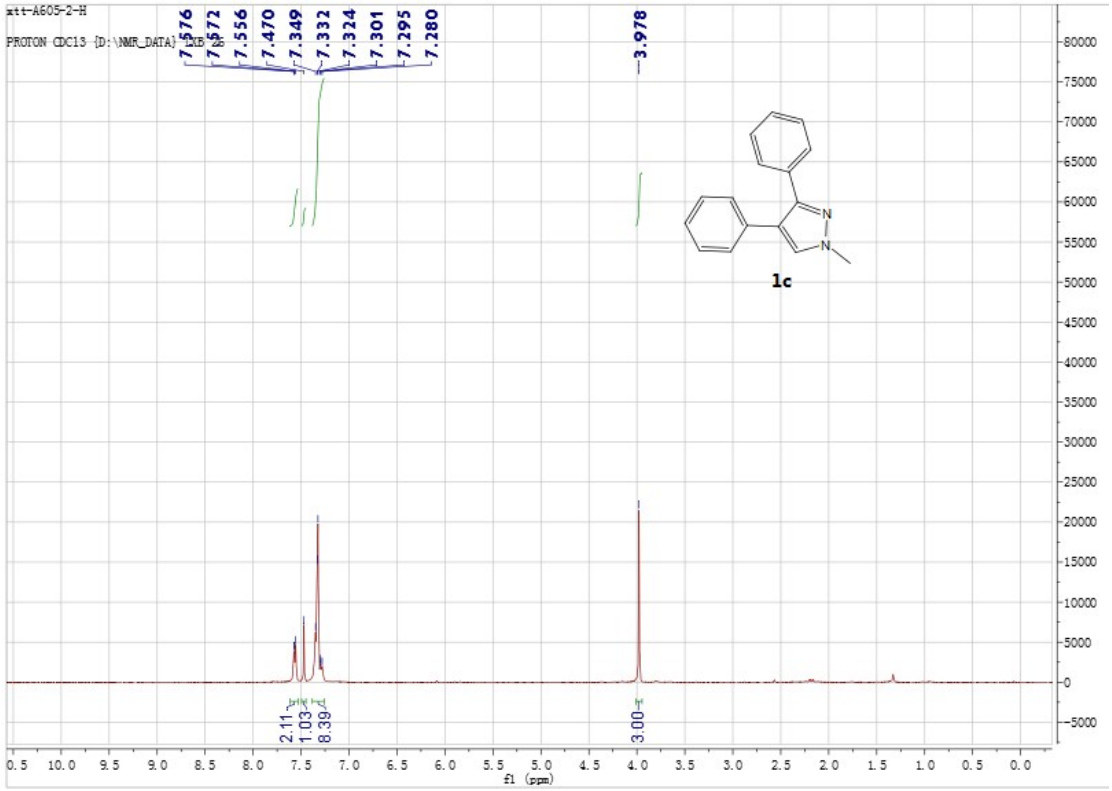
f1 (ppm)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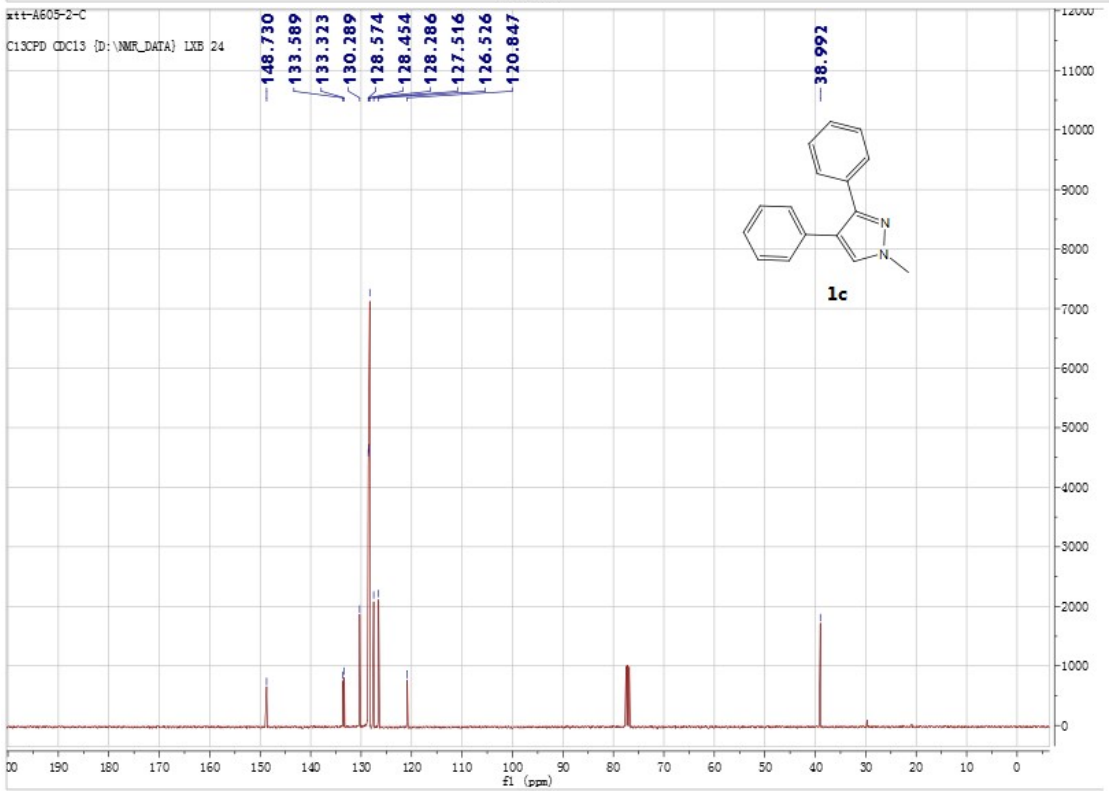
f1 (ppm)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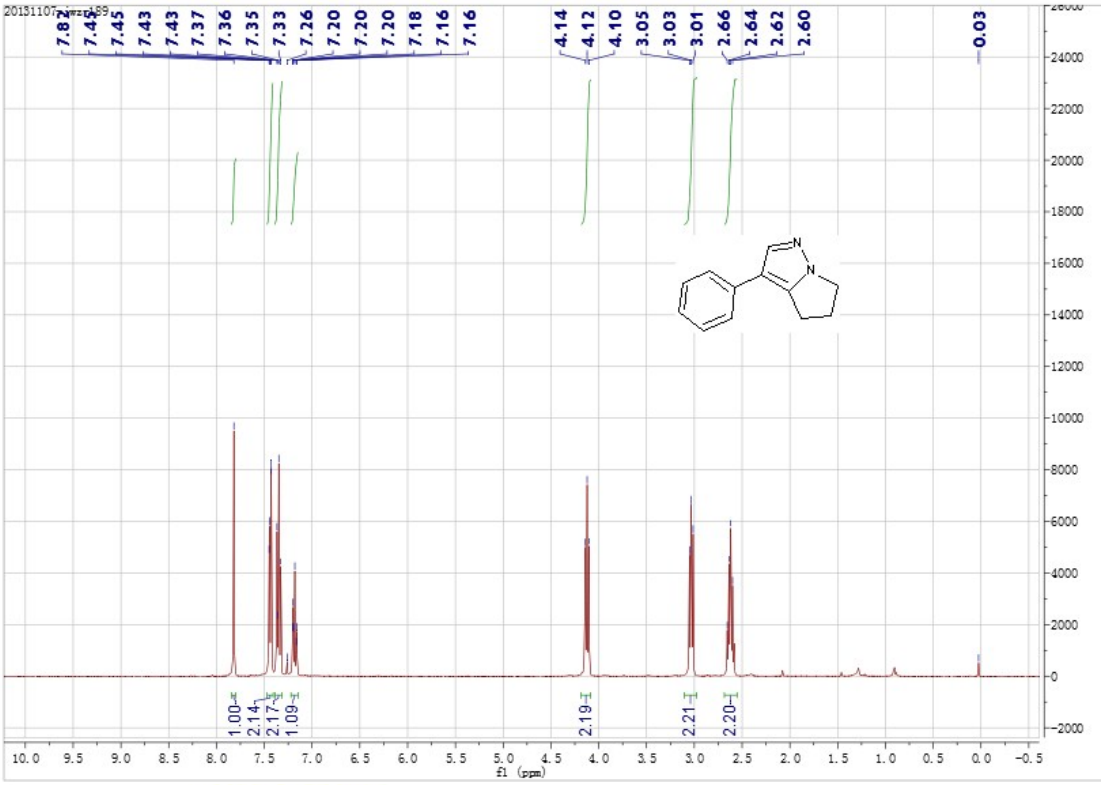
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7.16
4.14
4.12
4.10
3.05
3.03
3.01
2.66
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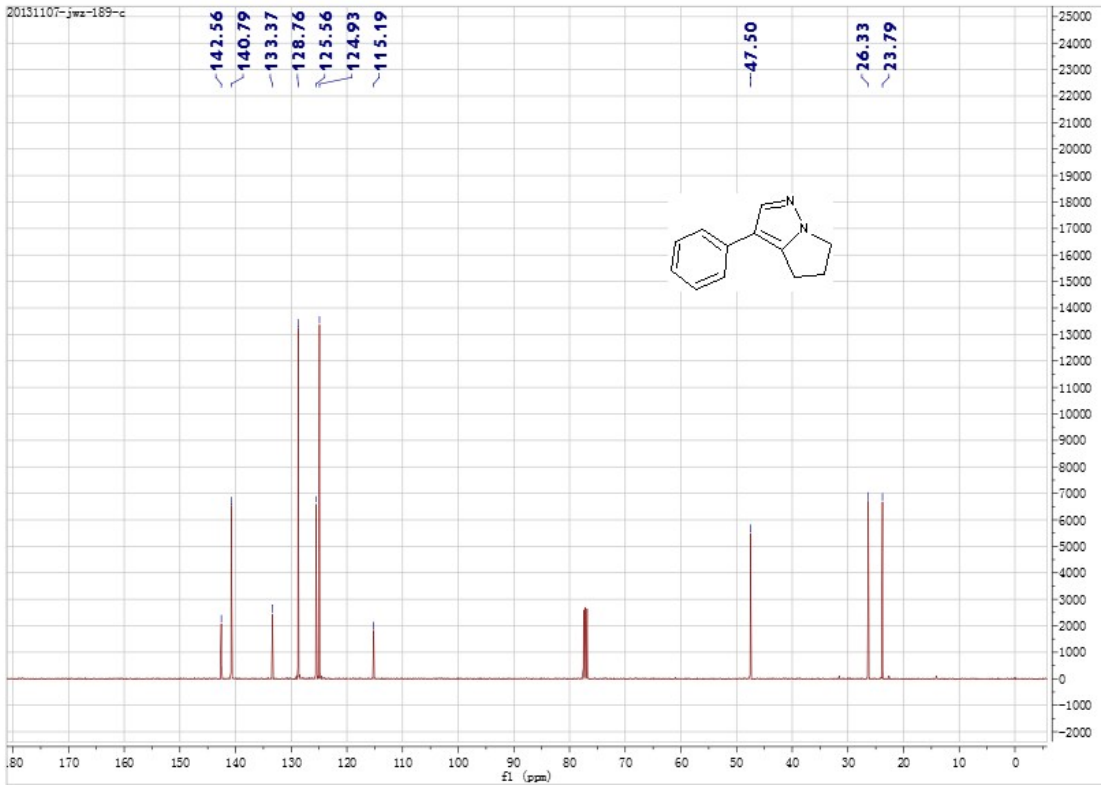
1.00
2.14
2.17
1.09
2.19
2.21
2.20
f1 (ppm)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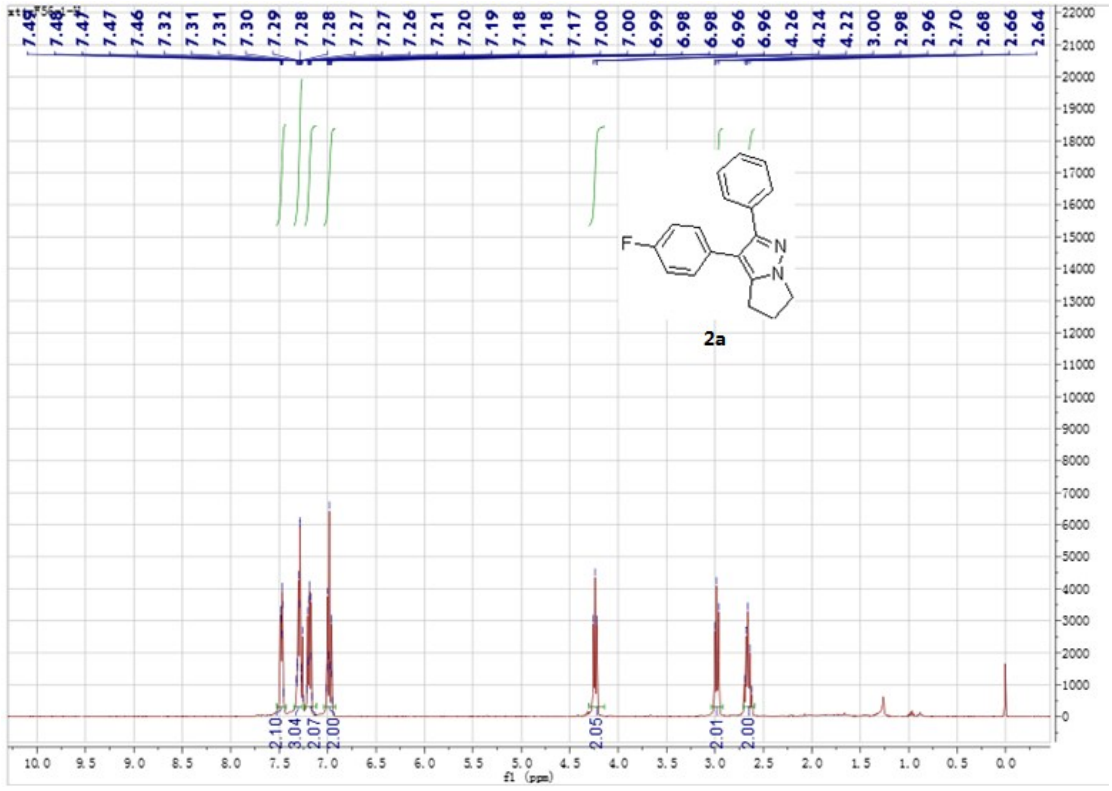
124.93
115.19
47.50
26.33
23.79
f1 (ppm)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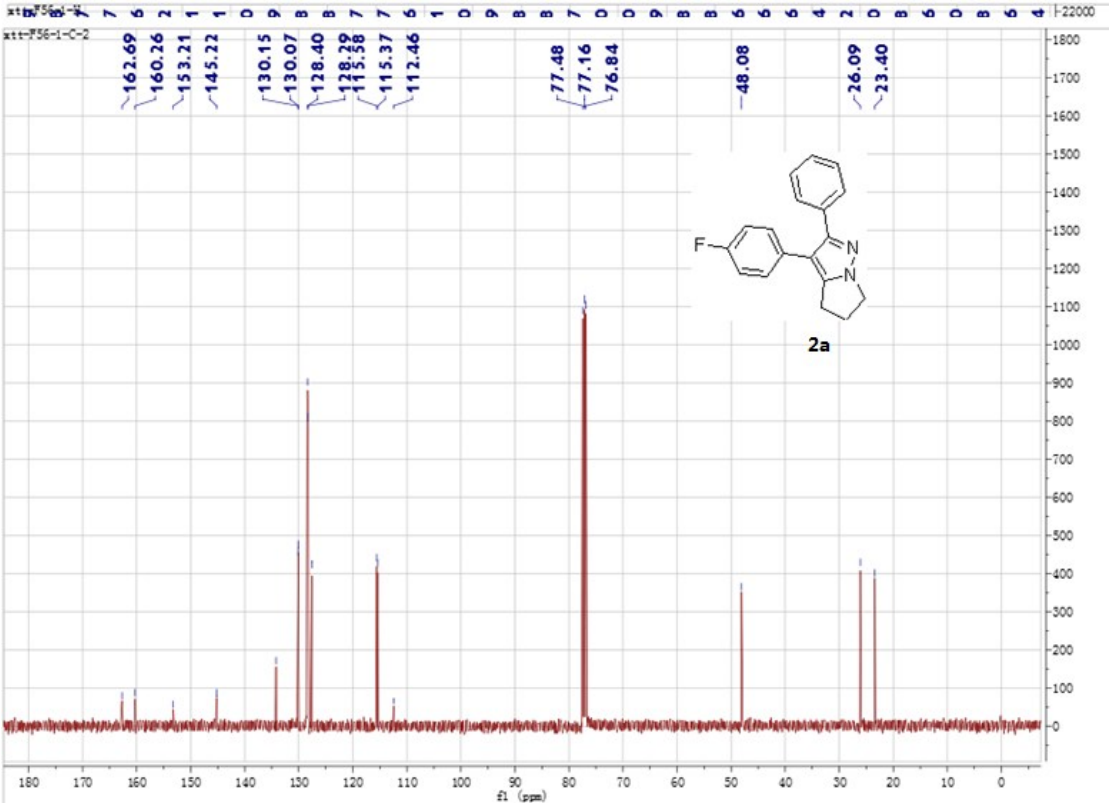
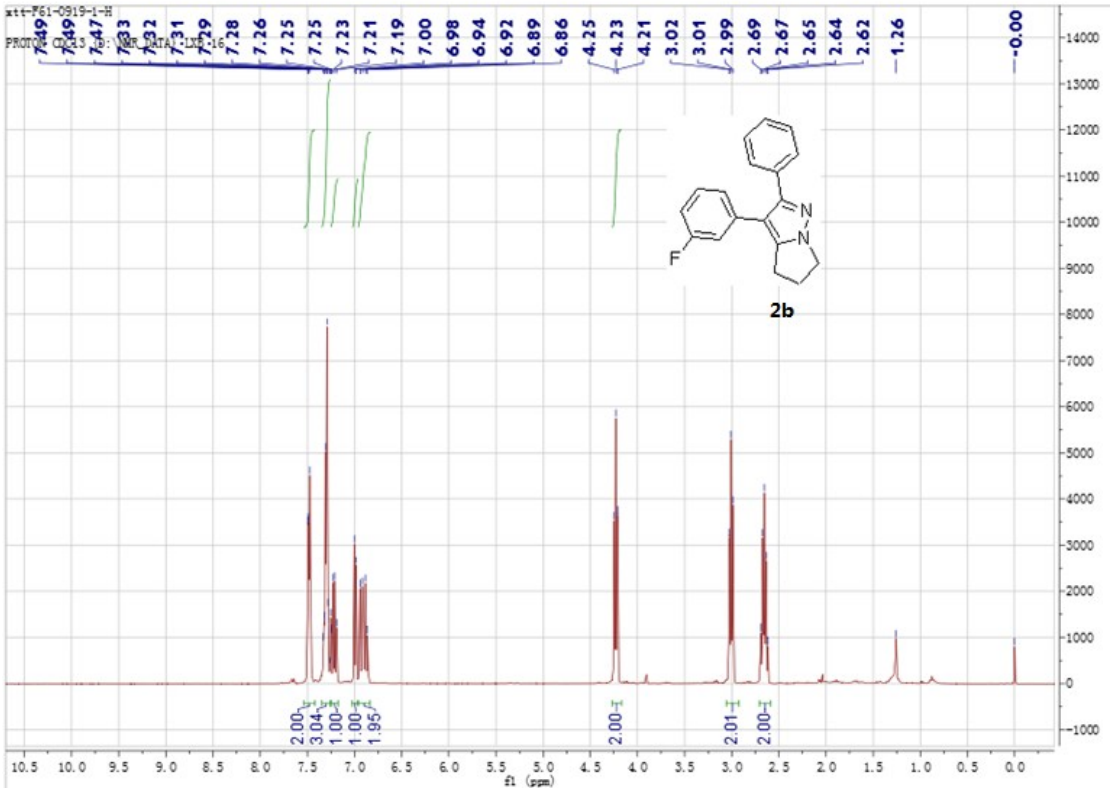
F
N
N
2a
2.10 3.04 2.07 2.00 2.05 2.01 2.00
f1 (ppm)


xtt-F56-1-C-2
162.69 160.26 153.21 145.22 130.15 130.07 128.40 128.29 115.58 115.37 112.46 77.48 77.16 76.84 48.08 26.09 23.40
F
N
N
2a
f1 (ppm)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7.23
7.21
7.19
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6.94
6.92
6.89
6.86
4.25
4.23
4.21
3.02
3.01
2.99
2.69
2.67
2.65
2.64
2.62
1.26
0.00
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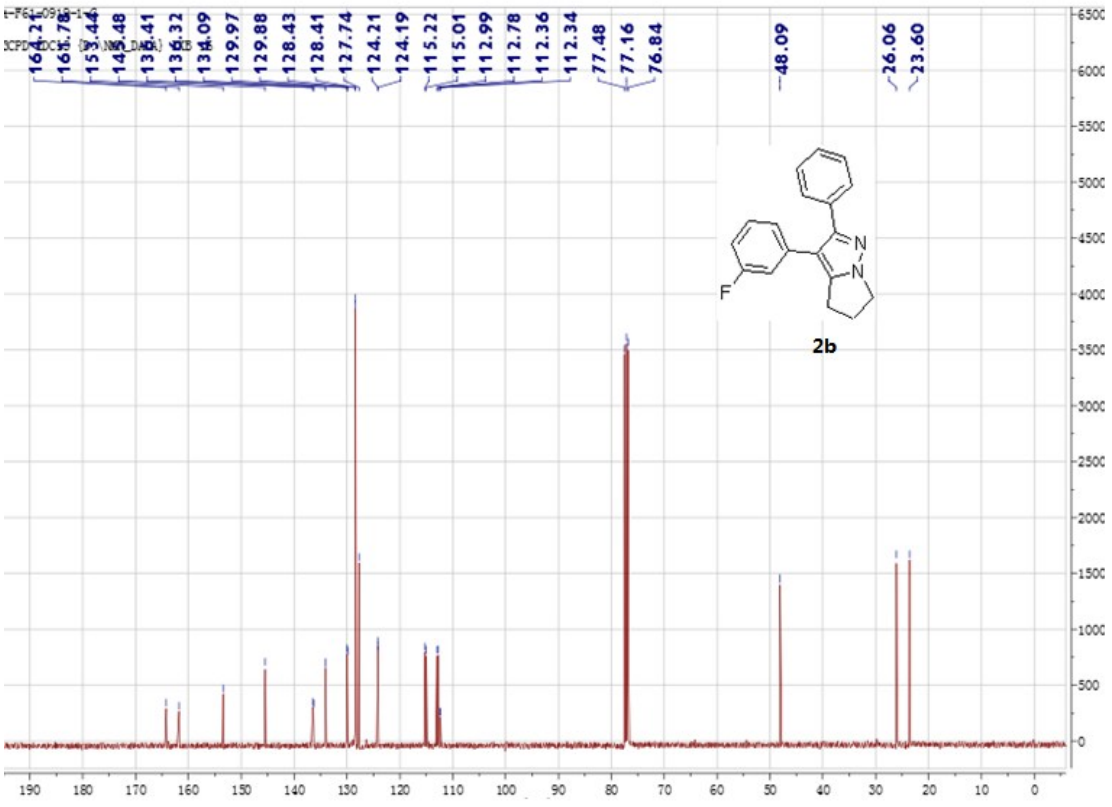
N
N
2b
2.00
3.04
1.00
1.00
1.95
2.00
2.01
2.00
f1 (ppm)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124.21
124.19
115.22
115.01
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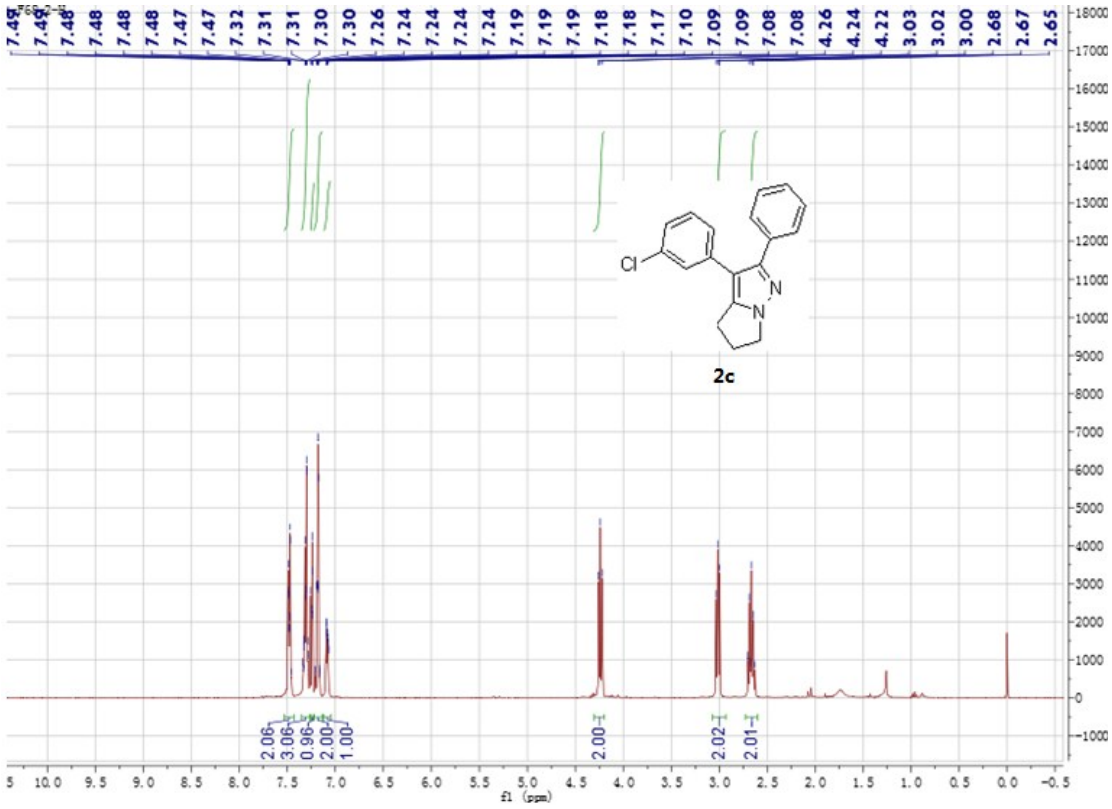
77.16
76.84
48.09
26.06
23.60
F
N
N
2b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7.24
7.24
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7.19
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7.18
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7.17
7.10
7.09
7.09
7.08
7.08
4.26
4.24
4.22
3.03
3.02
3.00
2.68
2.67
2.65
Cl
N
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2c
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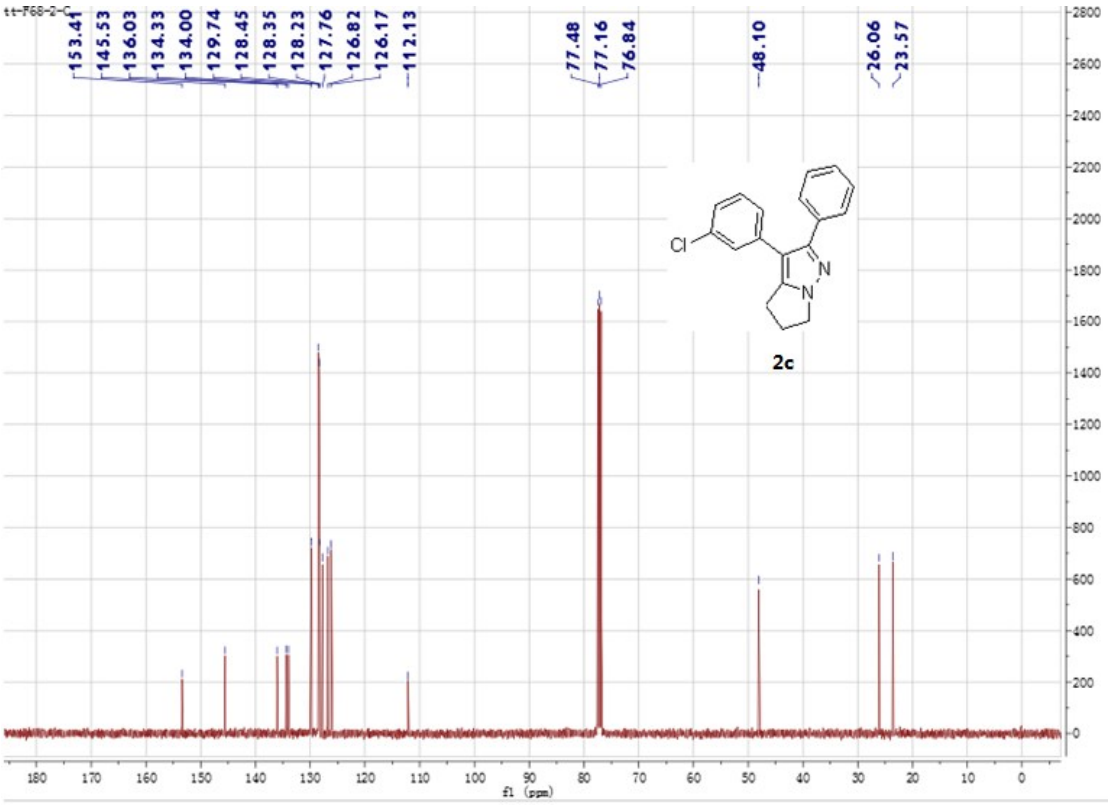
0.96
2.00
1.00
2.00
2.02
2.01
f1 (ppm)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134.33
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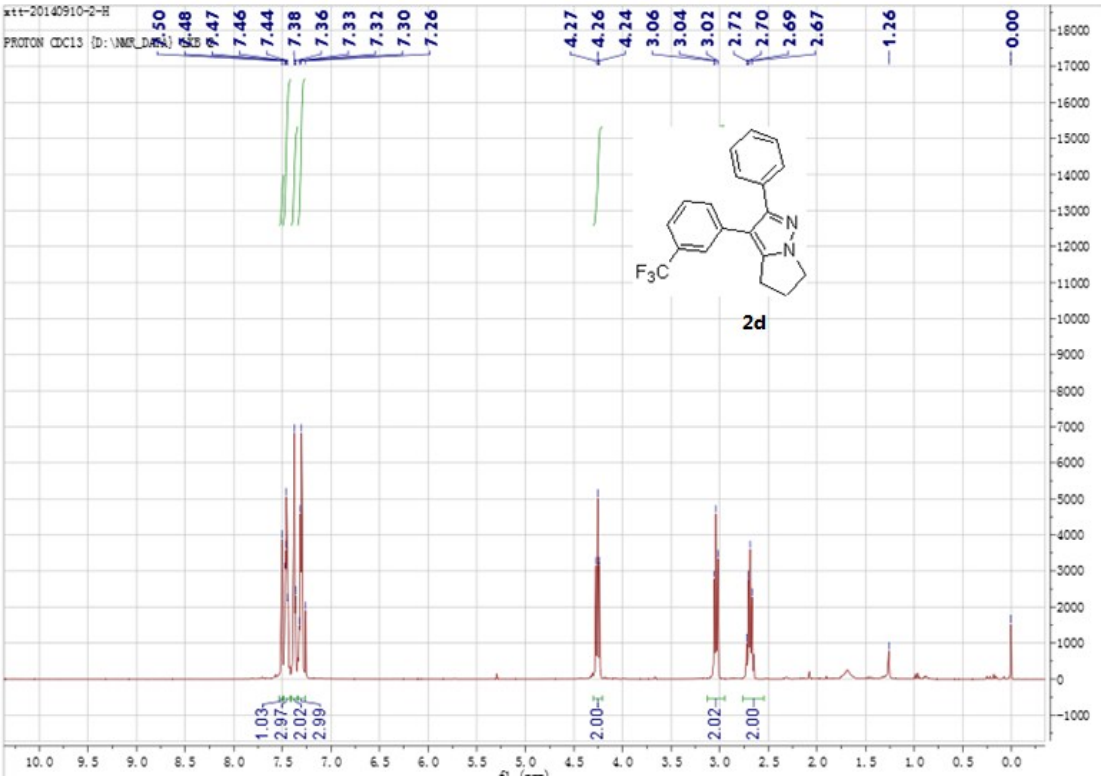
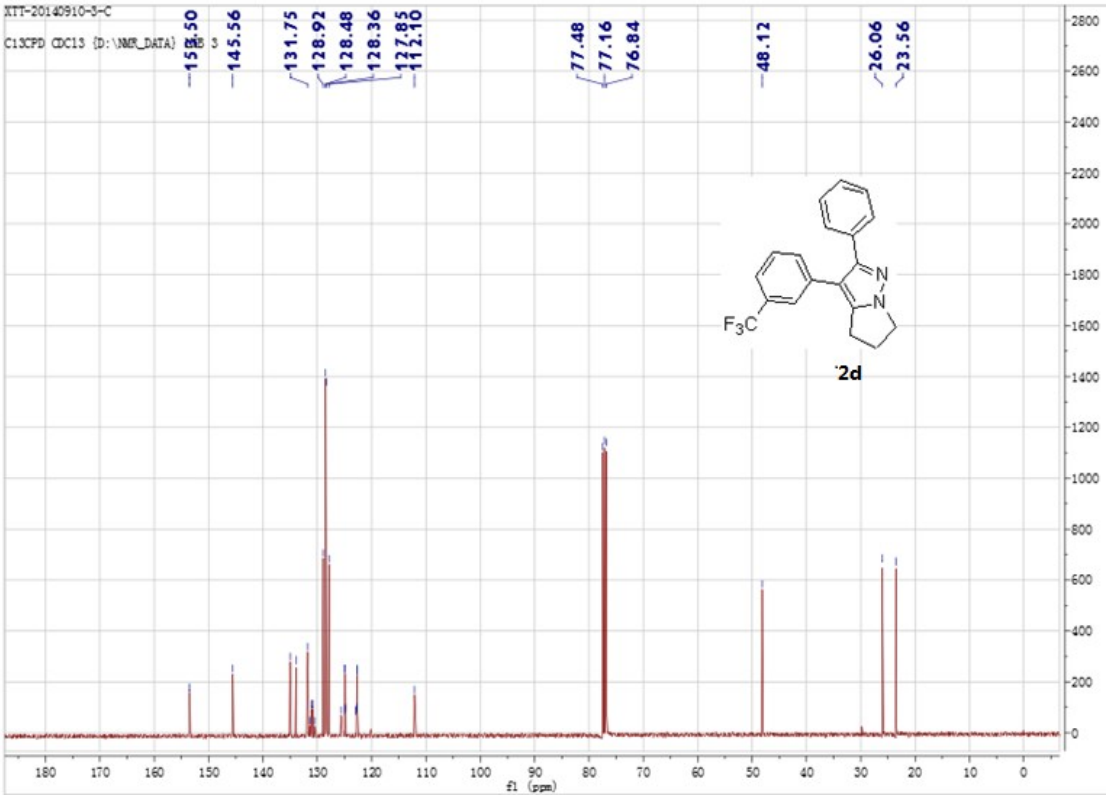
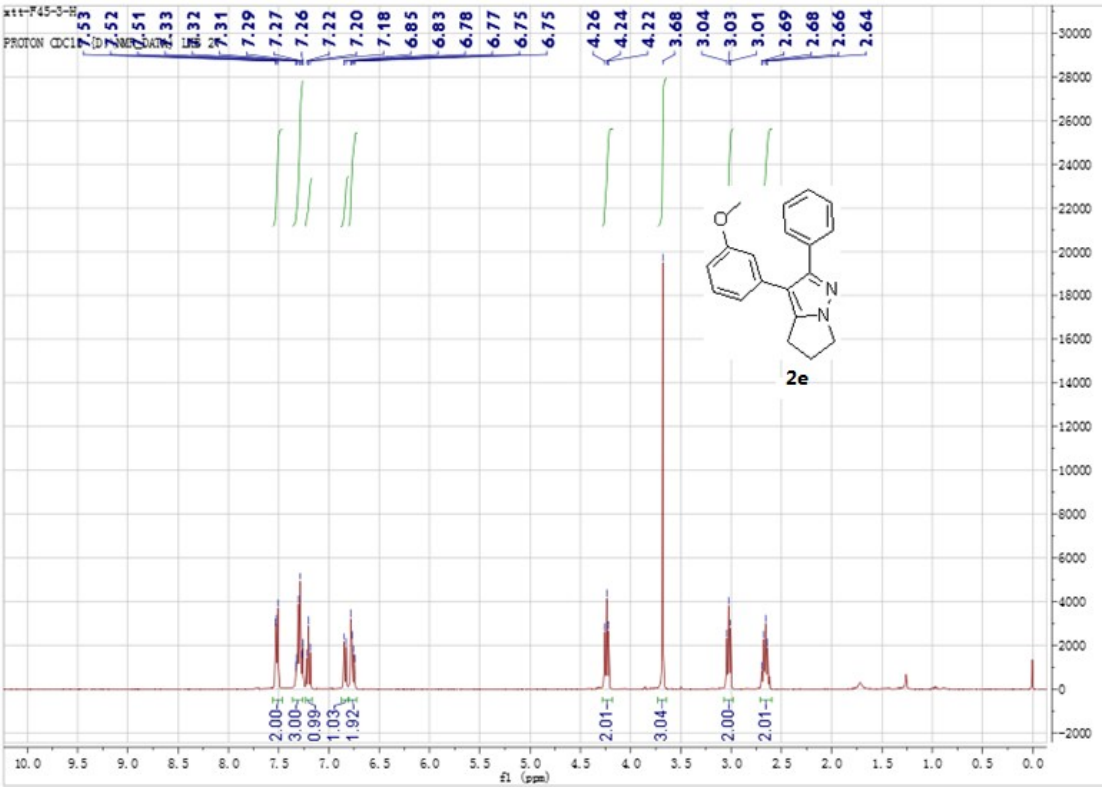
129.74
128.45
128.35
128.23
127.76
126.82
126.17
112.13
77.48
77.16
76.84
48.10
26.06
23.57
Cl
N
N
2c
f1 (ppm)


xtt-20140910-2-H
PROTON CDCl3 (D:\NMR_DATA)
7.50
7.48
7.47
7.46
7.44
7.38
7.36
7.33
7.32
7.30
7.26
4.27
4.26
4.24
3.06
3.04
3.02
2.72
2.70
2.69
2.67
1.26
0.00
1.03
2.97
2.02
2.99
2.00
2.02
2.00
F3C
N
N
2d


XTT-20140910-3-C
C13CPD CDCl3 (D:\NMR_DATA)
150.50
145.56
131.75
128.92
128.48
128.36
127.85
112.10
77.48
77.16
76.84
48.12
26.06
23.56
F3C
N
N
2d
f1 (ppm)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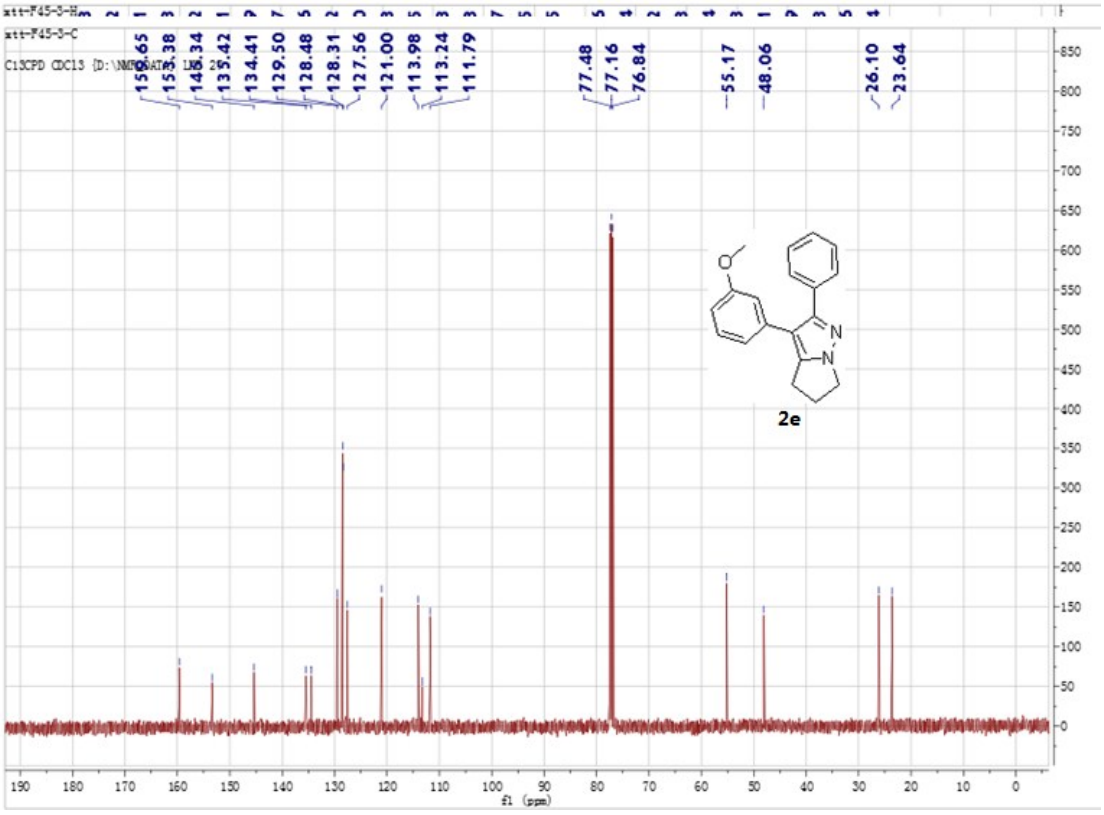
7.52
7.51
7.33
7.32
7.31
7.29
7.27
7.26
7.22
7.20
7.18
6.85
6.83
6.78
6.77
6.75
6.75
4.26
4.24
4.22
3.68
3.04
3.03
3.01
2.69
2.68
2.66
2.64
2.00
3.00
0.99
1.03
1.92
2.01
3.04
2.00
2.01
f1 (ppm)
2e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135.42
134.41
129.50
128.48
128.31
127.56
121.00
113.98
113.24
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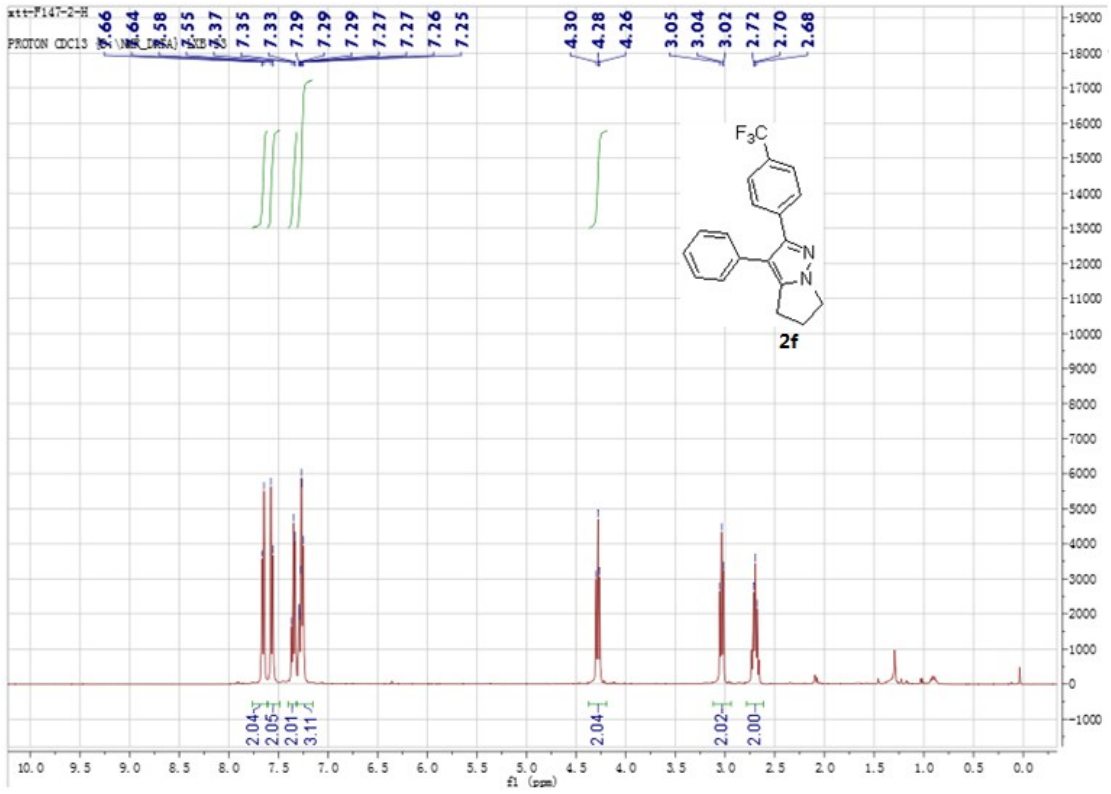
77.48
77.16
76.84
55.17
48.06
26.10
23.64
f1 (ppm)
2e


7.66
7.64
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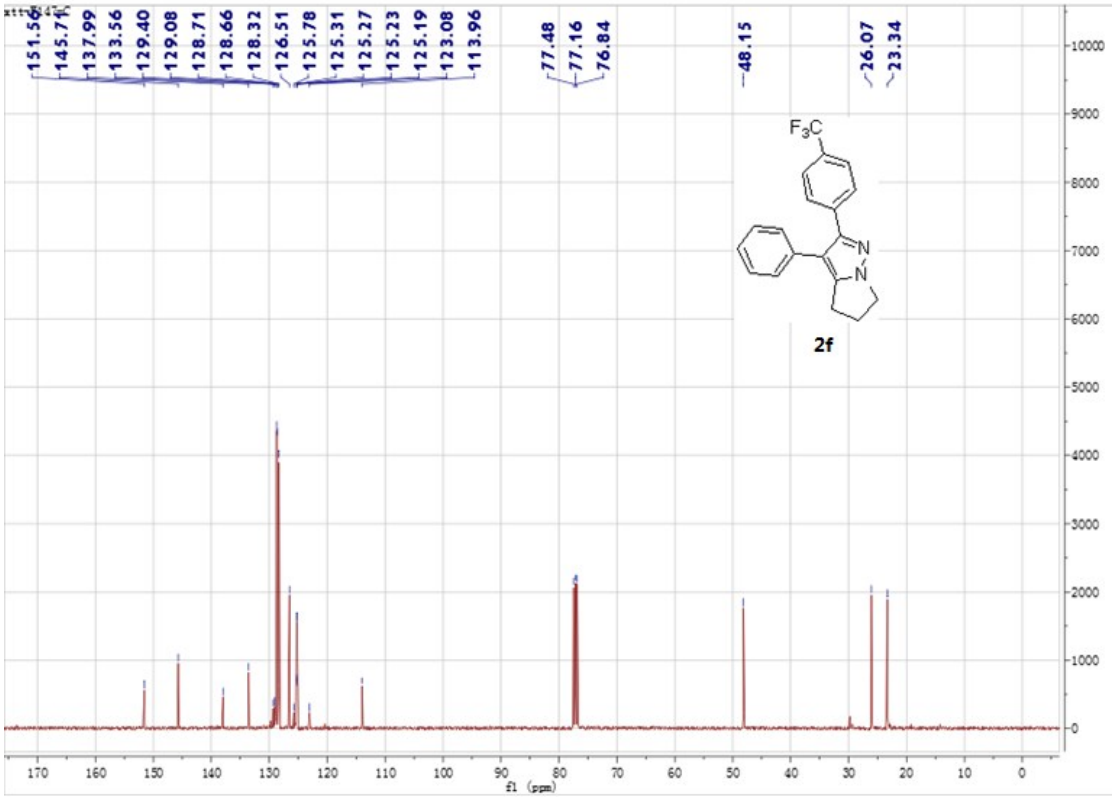
7.35
7.33
7.29
7.29
7.29
7.27
7.27
7.26
7.25
4.30
4.28
4.26
3.05
3.04
3.02
2.72
2.70
2.68
F3C
N
N
2f
2.04
2.05
2.01
3.11
2.04
2.02
2.00
f1 (ppm)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133.56
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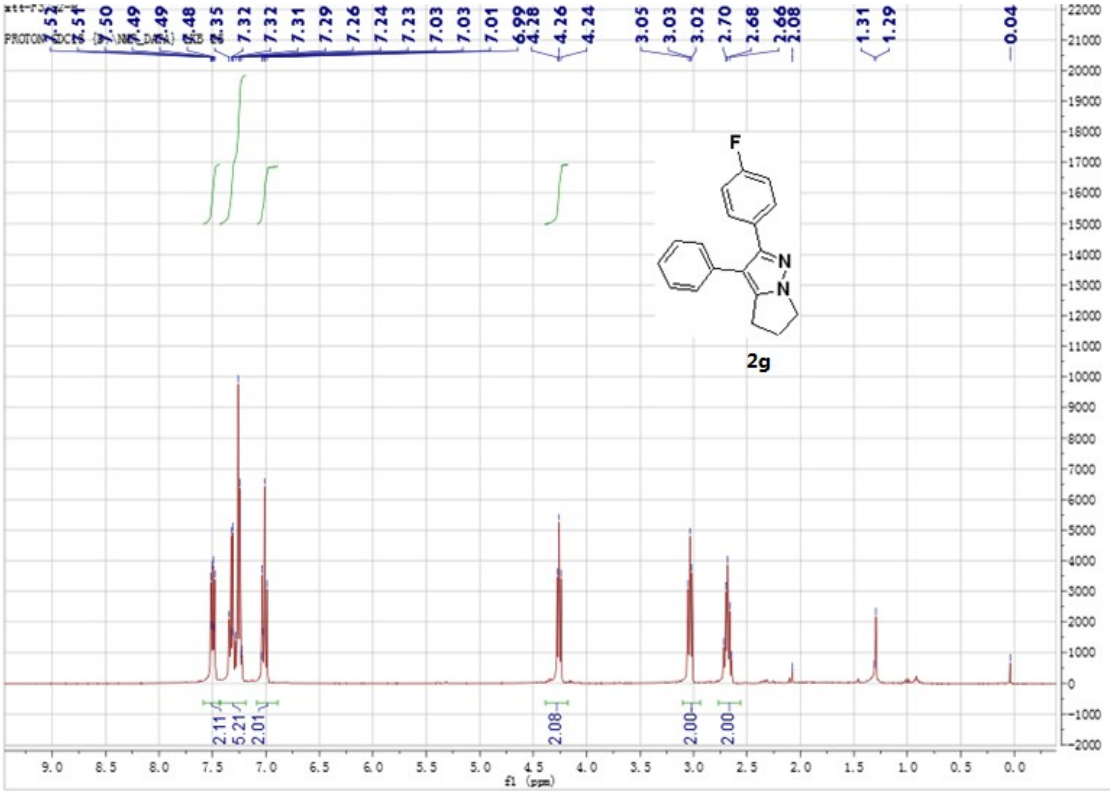
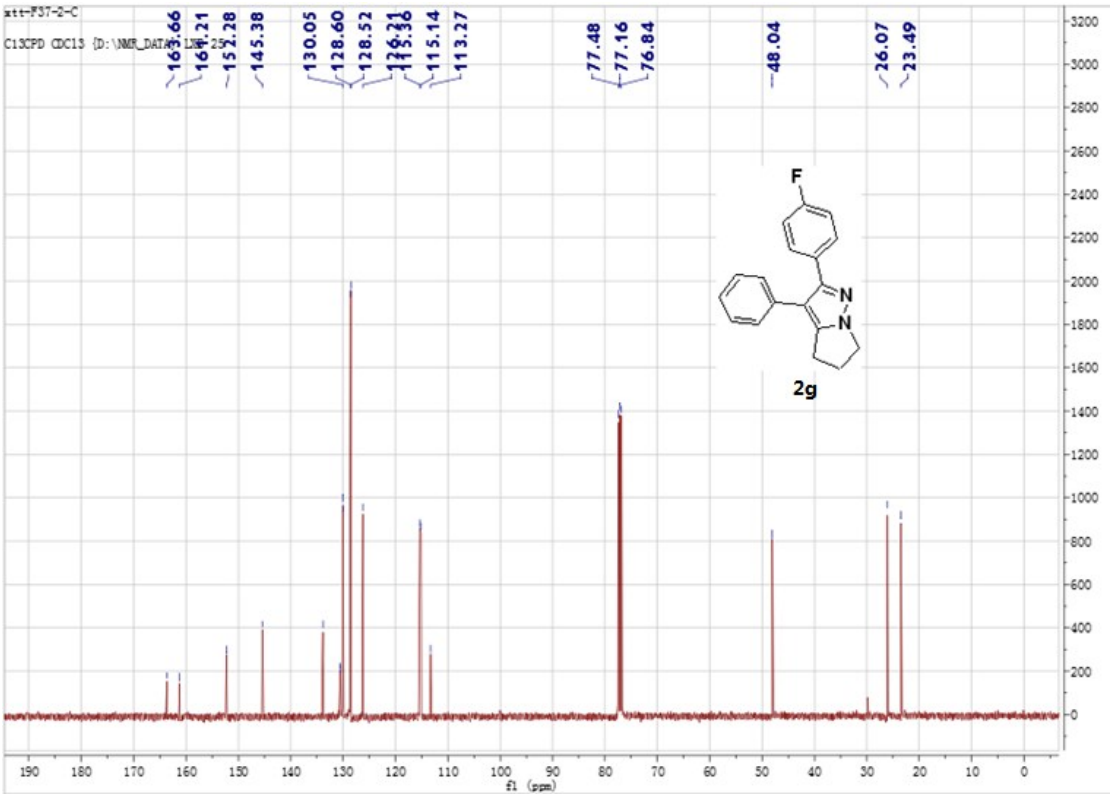
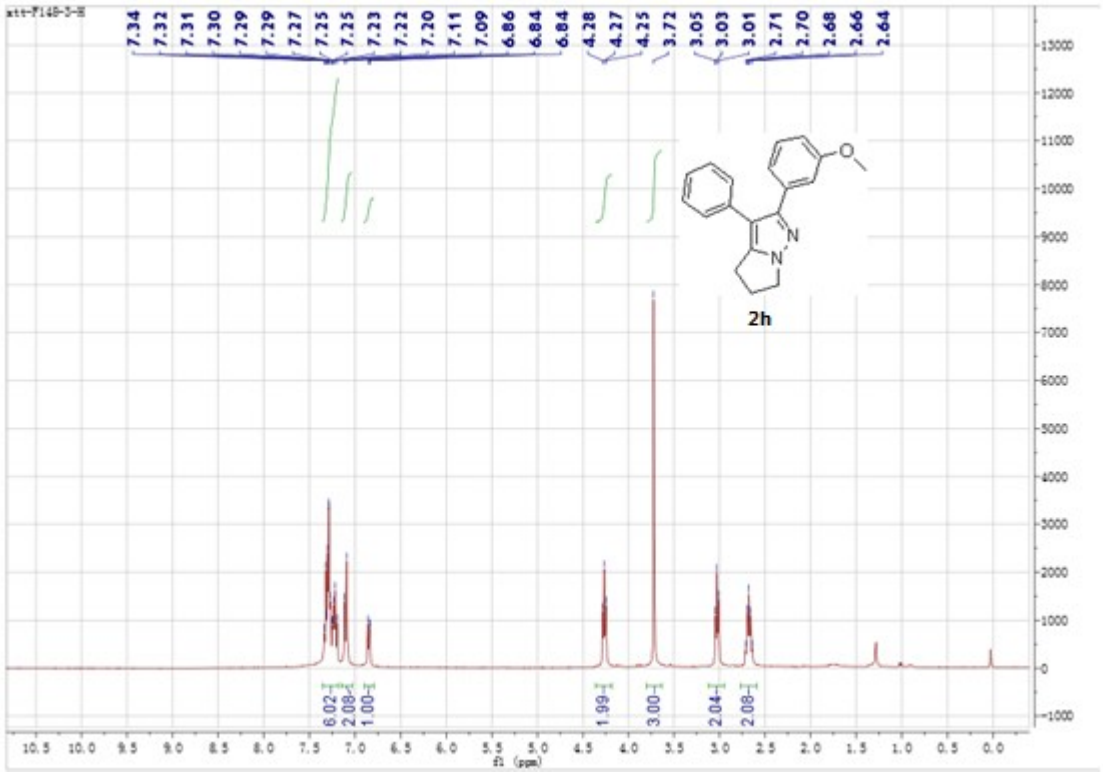
129.08
128.71
128.66
128.32
126.51
125.78
125.31
125.27
125.23
125.19
123.08
113.96
77.48
77.16
76.84
48.15
26.07
23.34
F3C
N
N
2f
f1 (ppm)


F
N
N
2g
f1 (ppm)


F
N
N
2g
f1 (ppm)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7.29
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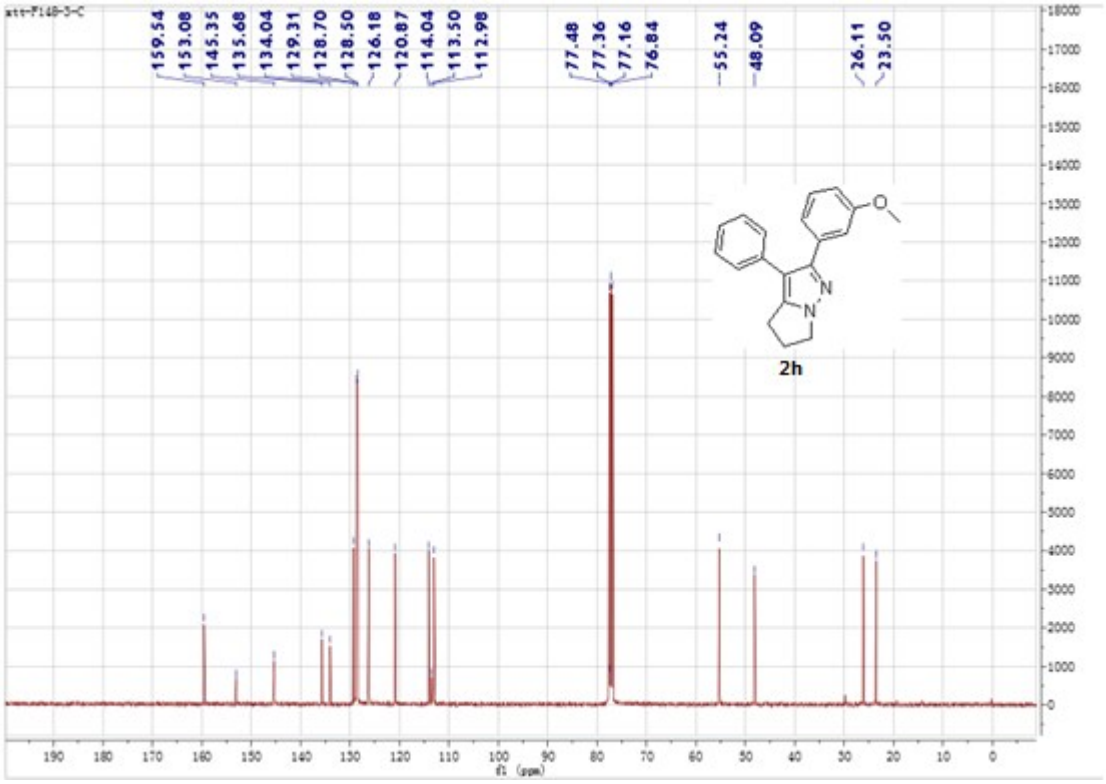
7.27
7.25
7.25
7.23
7.22
7.20
7.11
7.09
6.86
6.84
6.84
4.28
4.27
4.25
3.72
3.05
3.03
3.01
2.71
2.70
2.68
2.66
2.64
6.02
2.08
1.00
1.99
3.00
2.04
2.08
f1 (ppm)
2h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129.31
128.70
128.50
126.18
120.87
114.04
113.50
112.98
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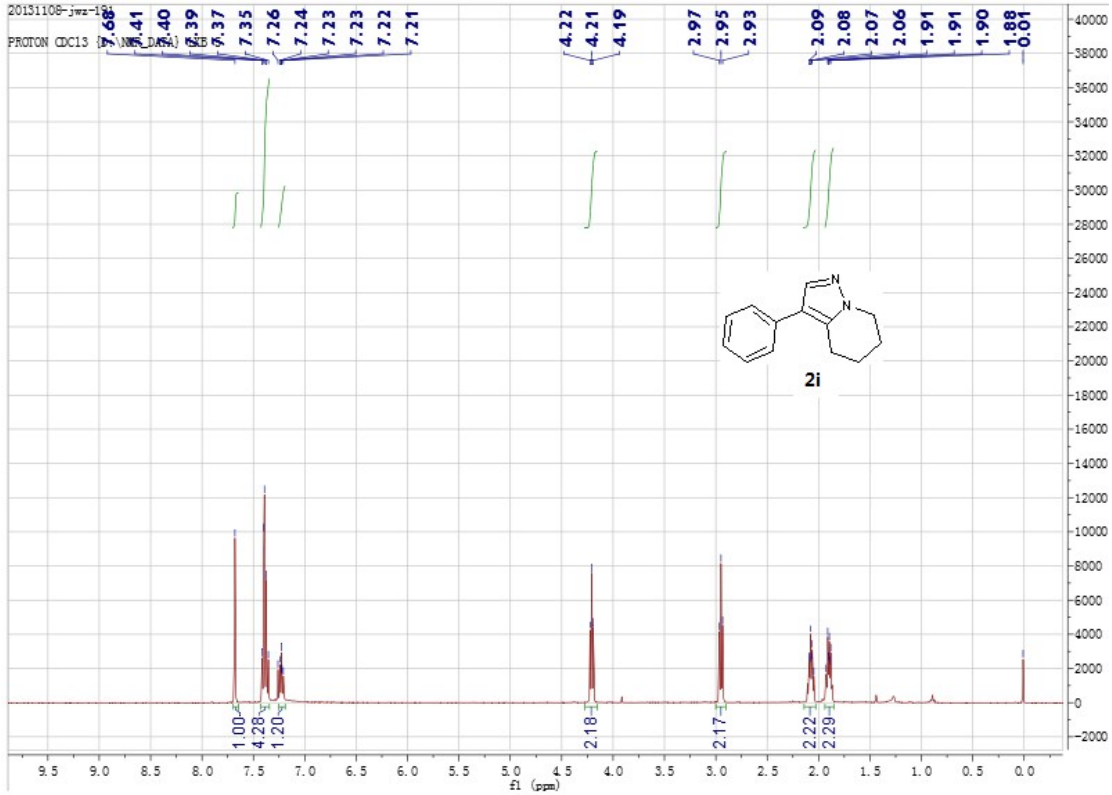
77.36
77.16
76.84
55.24
48.09
26.11
23.50
f1 (ppm)
2h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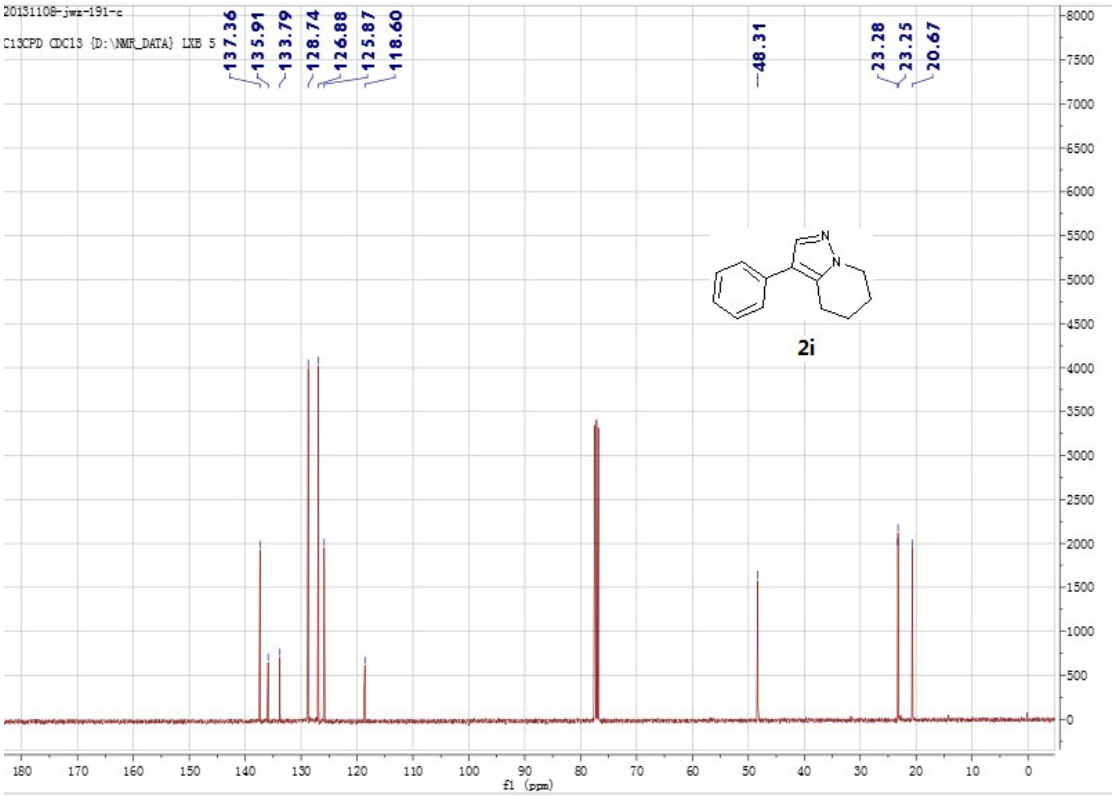
7.24
7.23
7.23
7.22
7.21
4.22
4.21
4.19
2.97
2.95
2.93
2.09
2.08
2.07
2.06
1.91
1.91
1.90
1.88
0.01
1.00
4.28
1.20
2.18
2.17
2.22
2.29
f1 (ppm)
2i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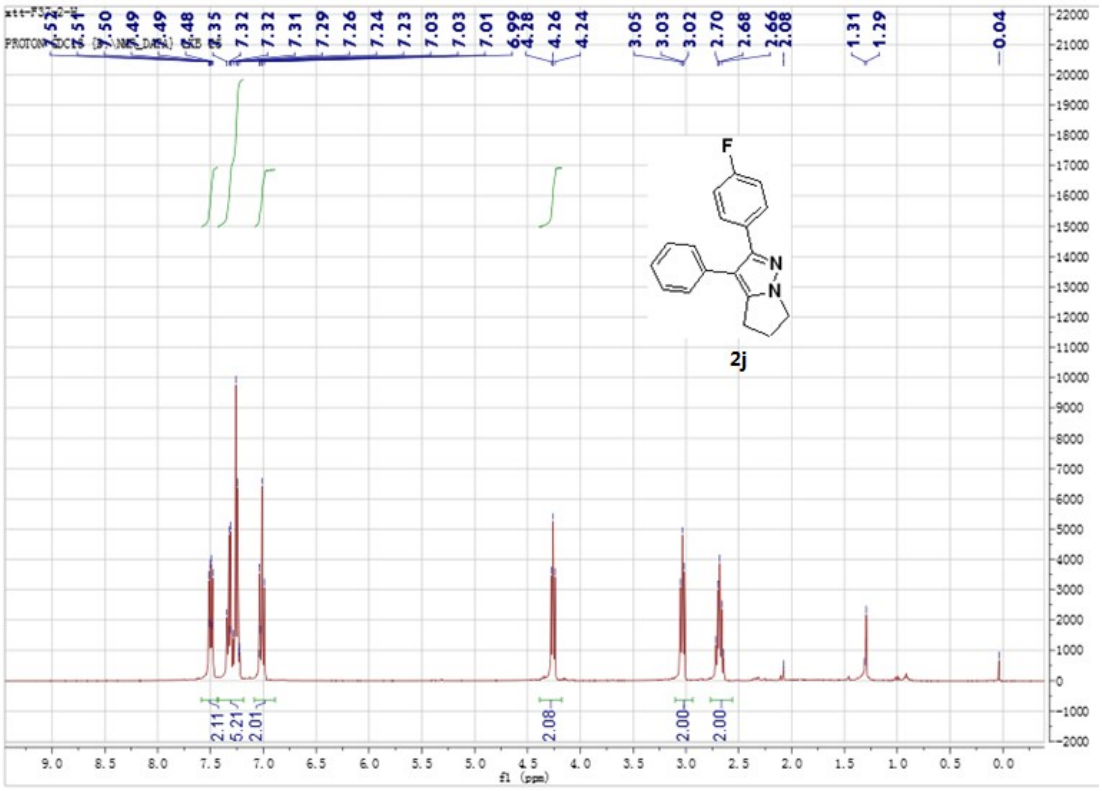
23.28
23.25
20.67
f1 (ppm)
2i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N
2j
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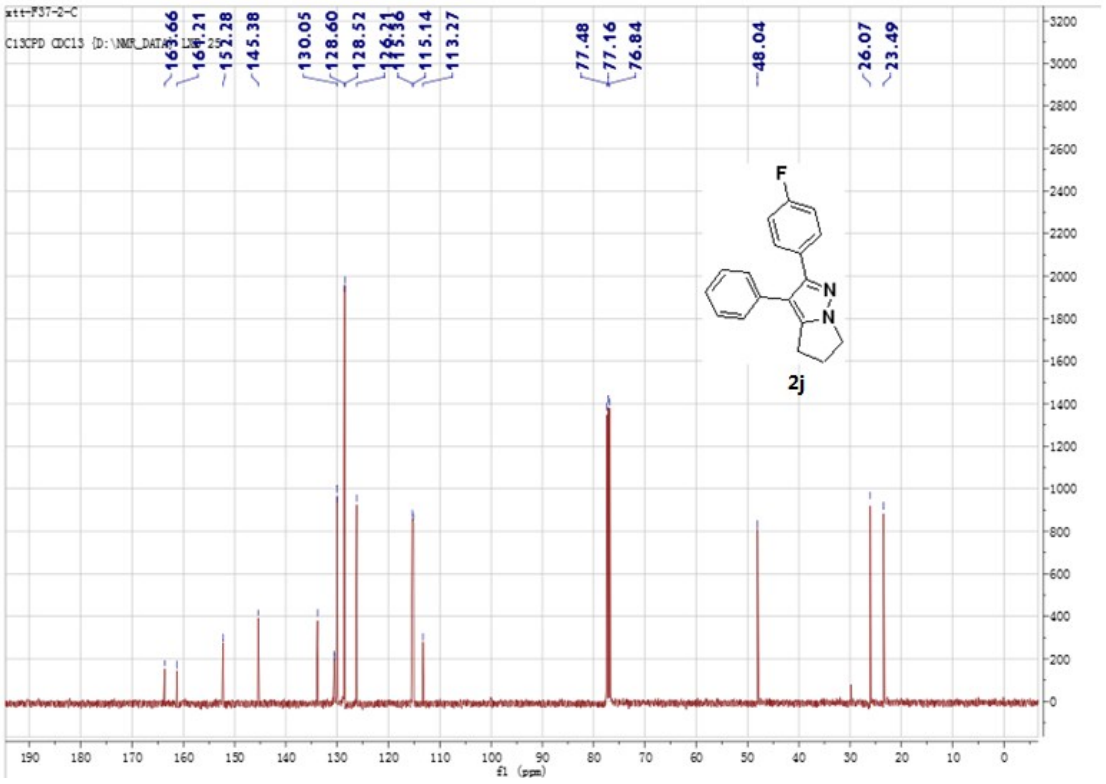
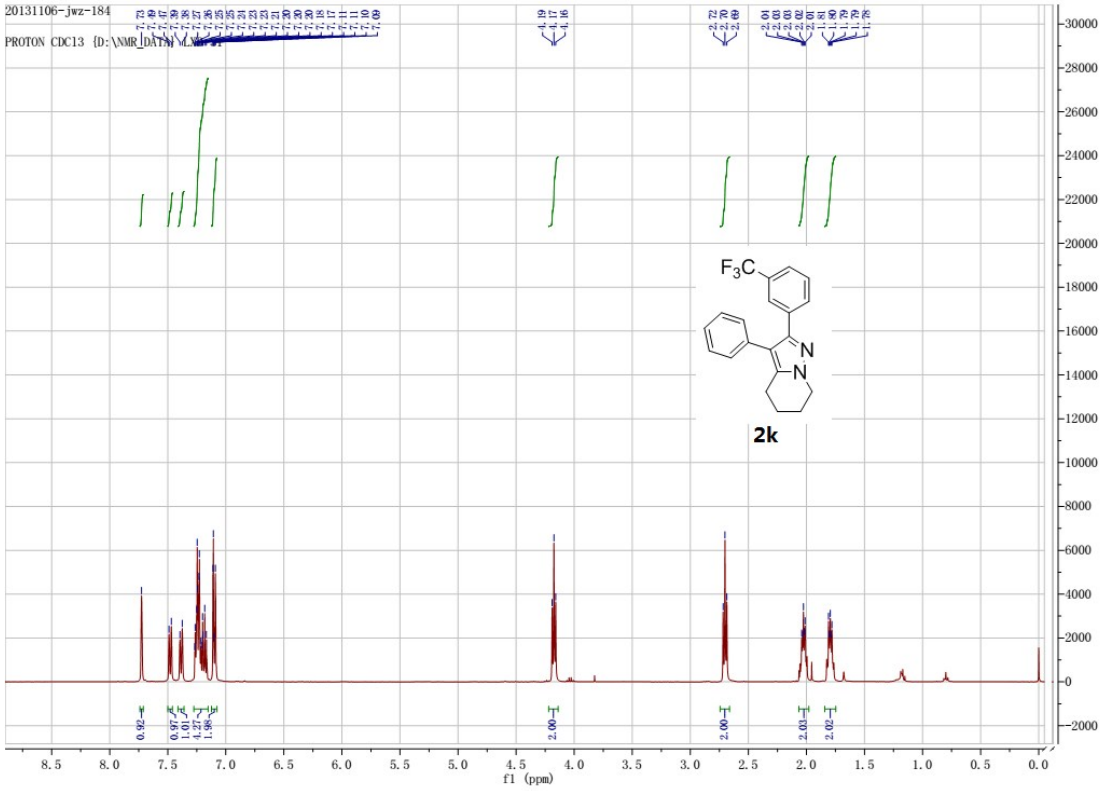
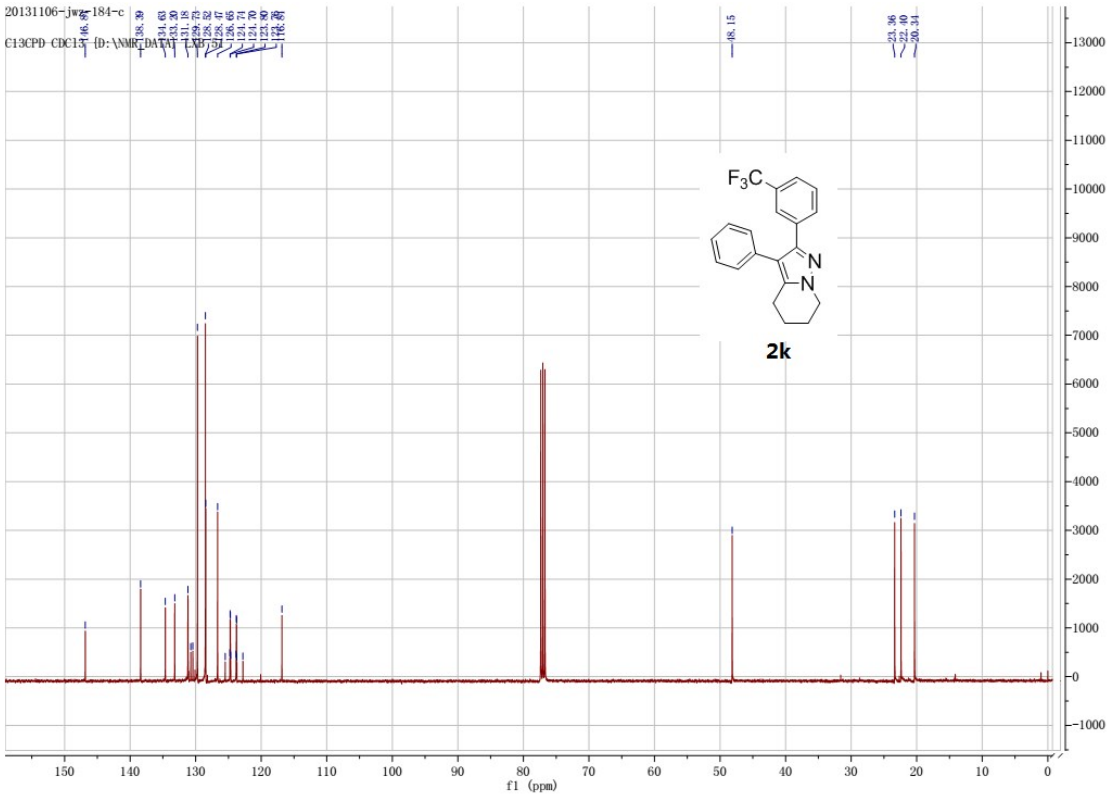
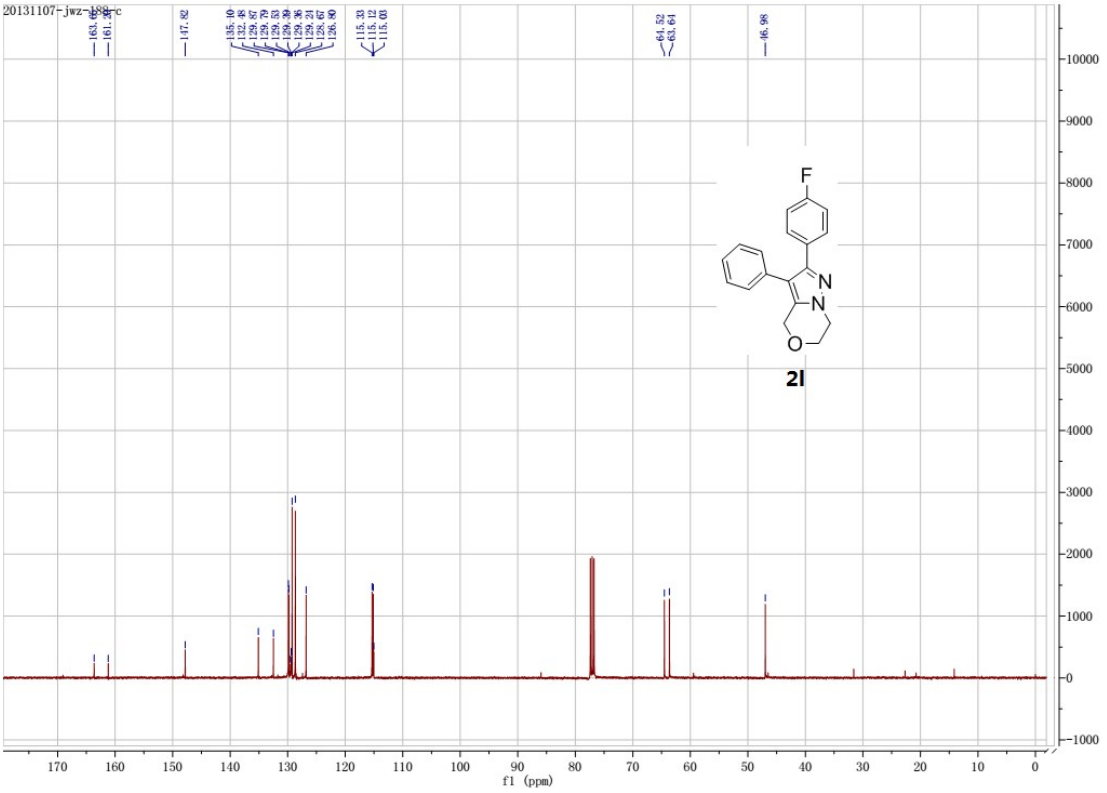
7.49
7.48
7.35
7.32
7.32
7.31
7.29
7.26
7.24
7.23
7.03
7.03
7.01
6.99
4.28
4.26
4.24
3.05
3.03
3.02
2.70
2.68
2.66
2.08
1.31
1.29
0.04
2.11
5.21
2.01
2.08
2.00
2.00
f1 (ppm)


F
N
N
2j
163.66
161.21
152.28
145.38
130.05
128.60
128.52
126.21
125.36
115.14
113.27
77.48
77.16
76.84
48.04
26.07
23.49
f1 (ppm)


20131106-jwz-184
PROTON CDC13
F3C
N
N
2k
f1 (ppm)


20131106-jwz-184-c
C13CPD CDC13
F3C
N
N
2k
f1 (ppm)


20131107-jwz-188-c
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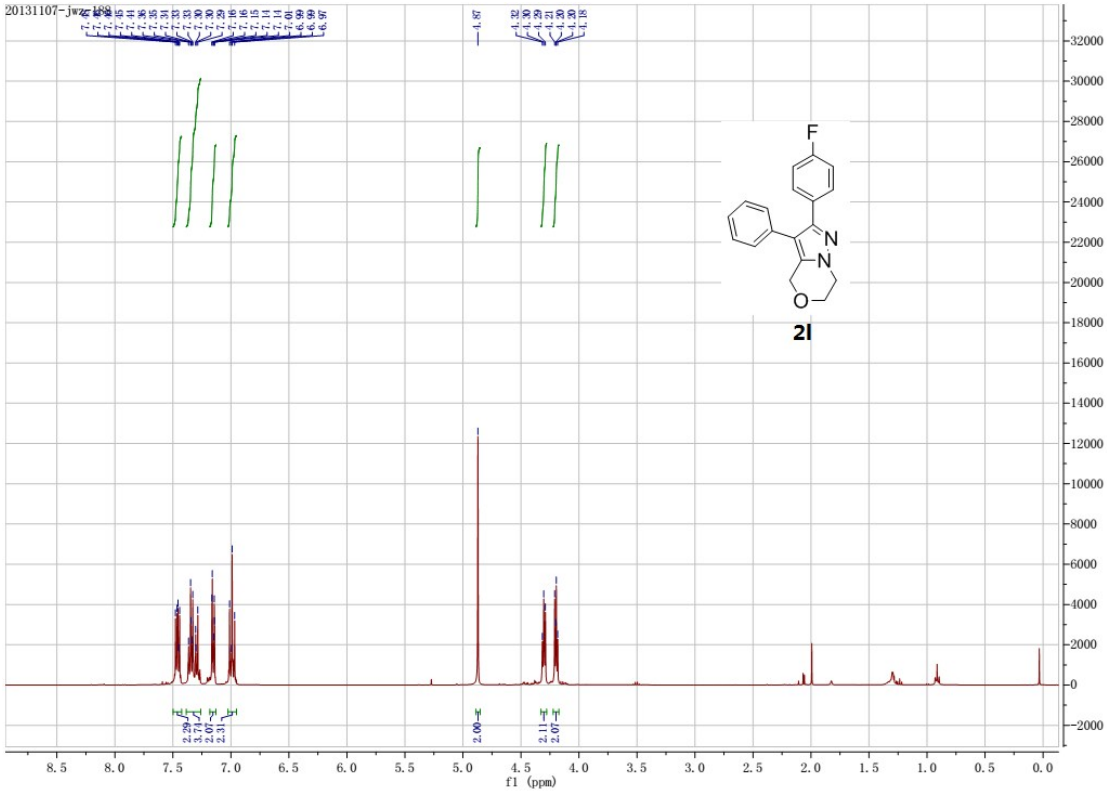
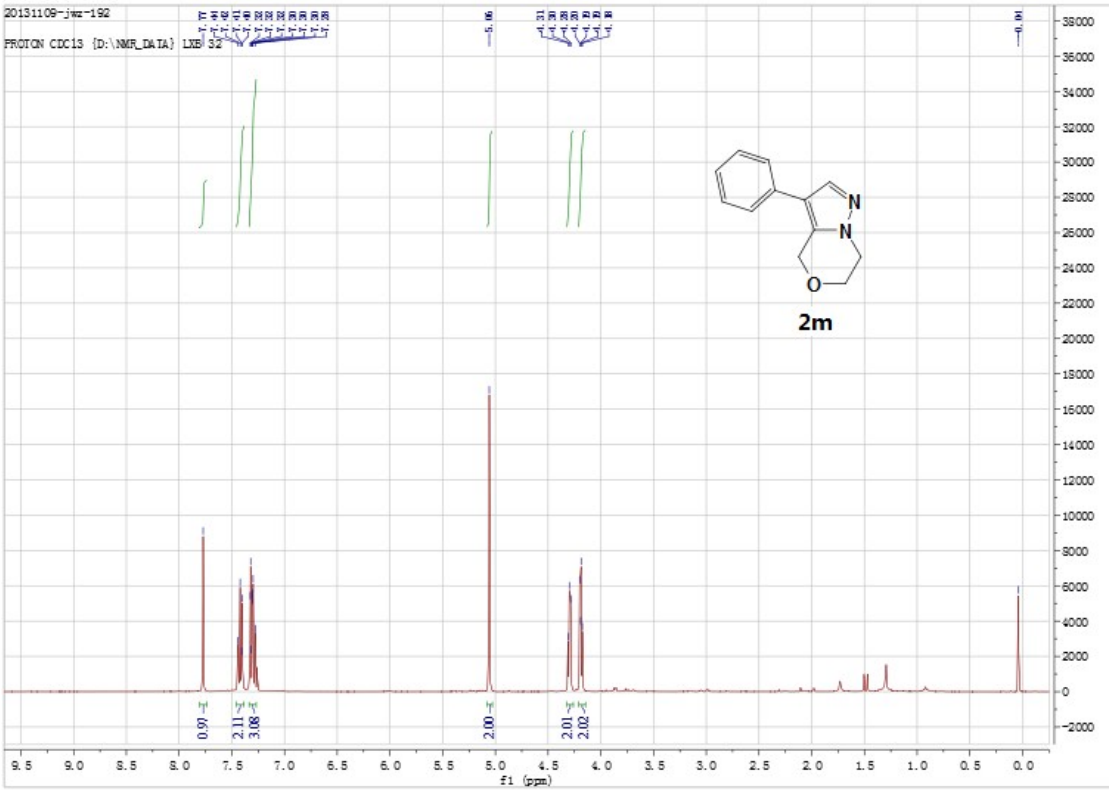
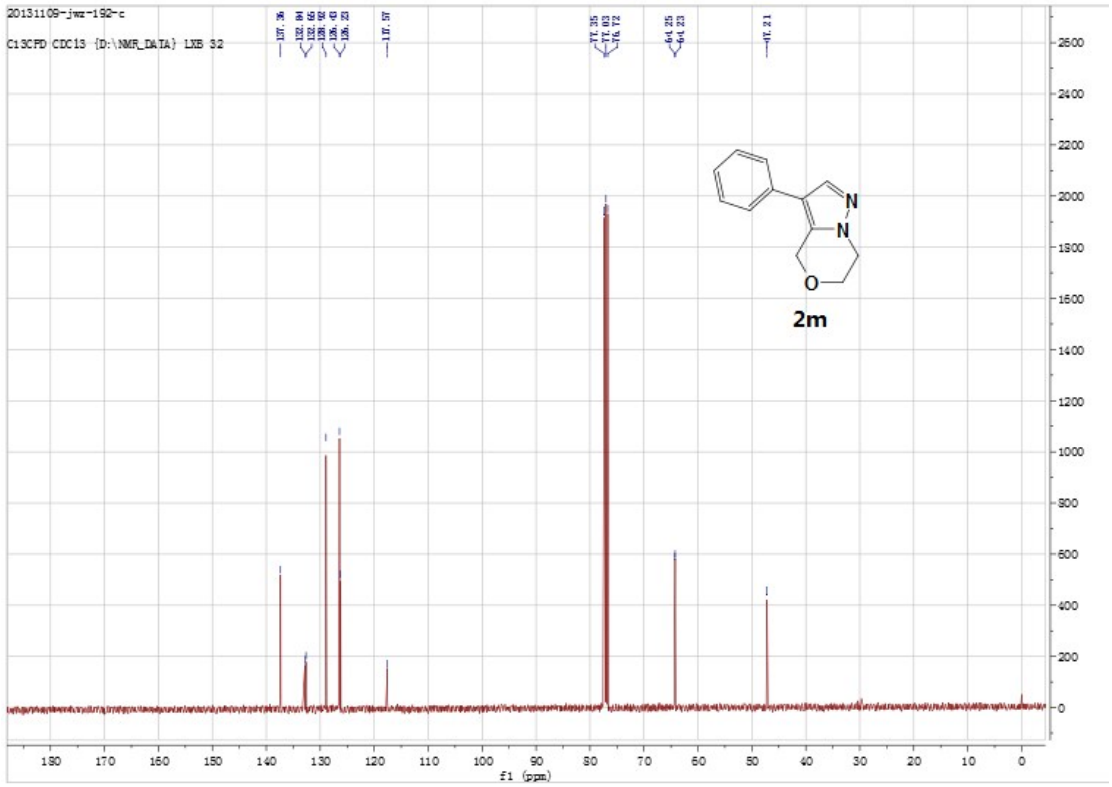
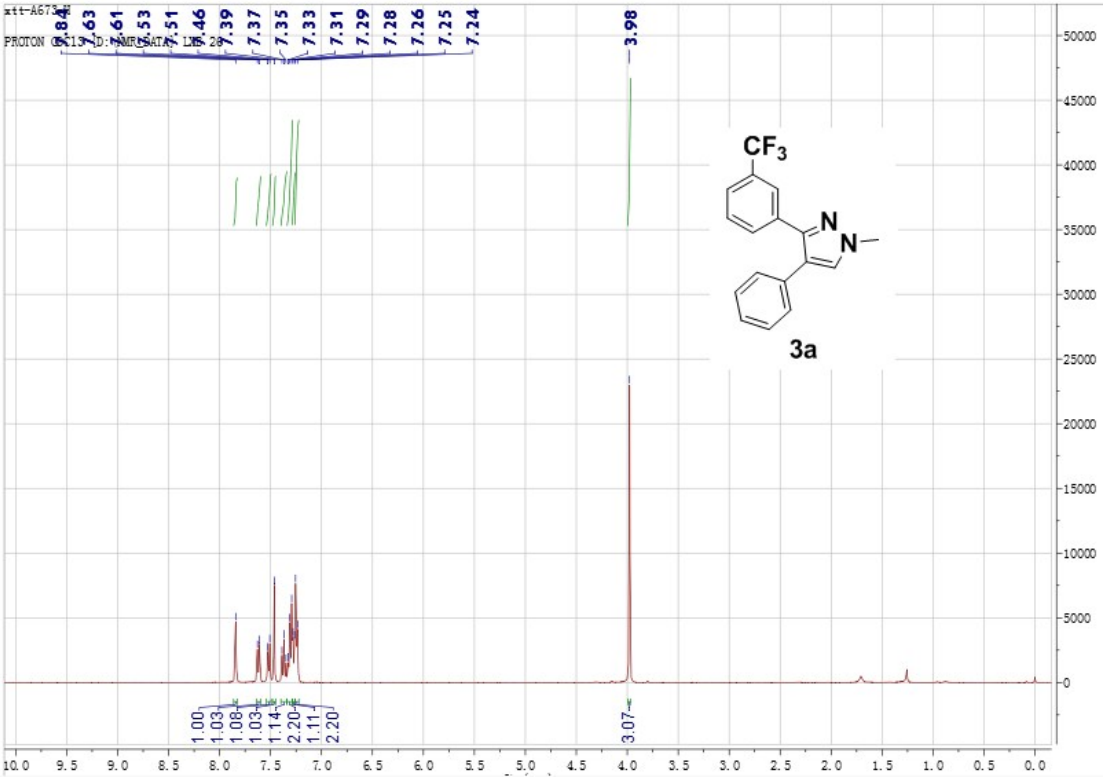
N
N
O
2l
f1 (ppm)


F
N
N
O
2l
f1 (ppm)


20131109-jwz-192
PROTON CDCl3 {D:\NMR_DATA} LXB 32
2m
f1 (ppm)


20131109-jwz-192-c
C13CPD CDCl3 {D:\NMR_DATA} LXB 32
2m
f1 (ppm)


xtt-A673-H
PROTON
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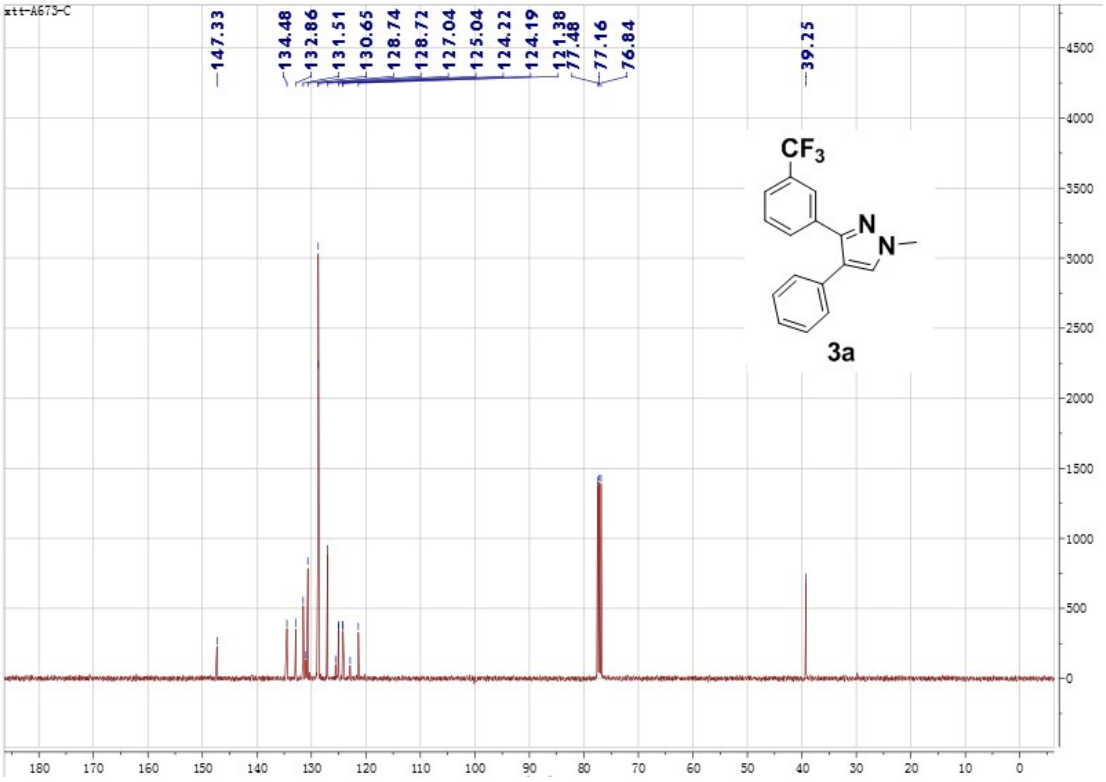
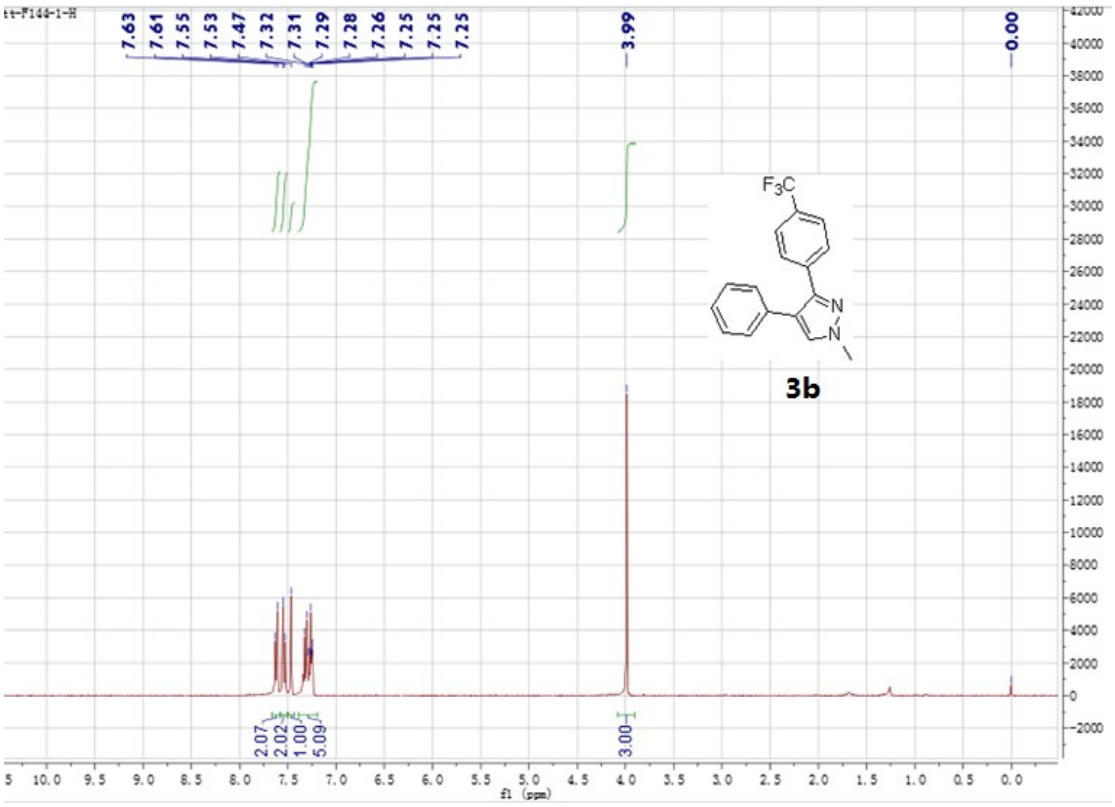
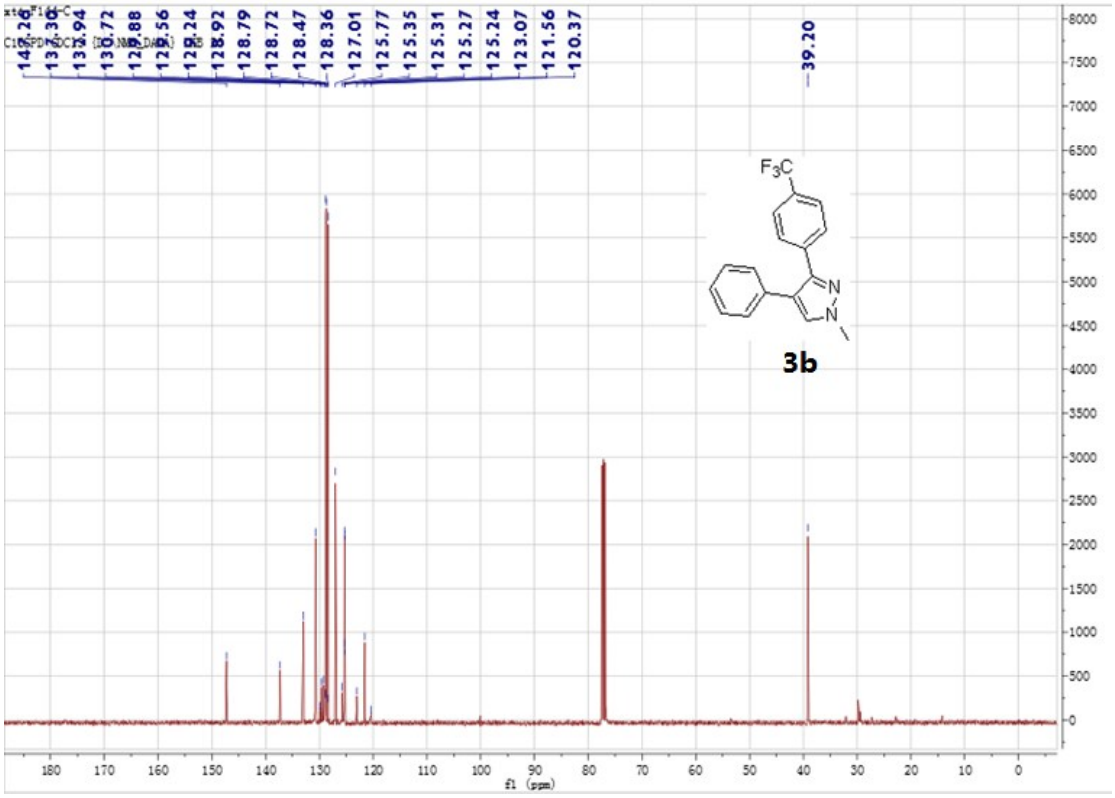
8.63
8.61
8.53
8.51
8.46
7.39
7.37
7.35
7.33
7.31
7.29
7.28
7.26
7.25
7.24
3.98
1.00
1.03
1.08
1.03
1.14
2.20
1.11
2.20
3.07
CF3
N
N
3a


xtt-A673-C
147.33
134.48
132.86
131.51
130.65
128.74
128.72
127.04
125.04
124.22
124.19
121.38
77.48
77.16
76.84
39.25
CF3
N
N
3a


7.63
7.61
7.55
7.53
7.47
7.32
7.31
7.29
7.28
7.26
7.25
7.25
7.25
3.99
0.00
2.07
2.02
1.00
5.09
3.00
F3C
N
N
3b
f1 (ppm)


142.26
131.30
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130.72
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129.24
128.92
128.79
128.72
128.47
128.36
127.01
125.77
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123.07
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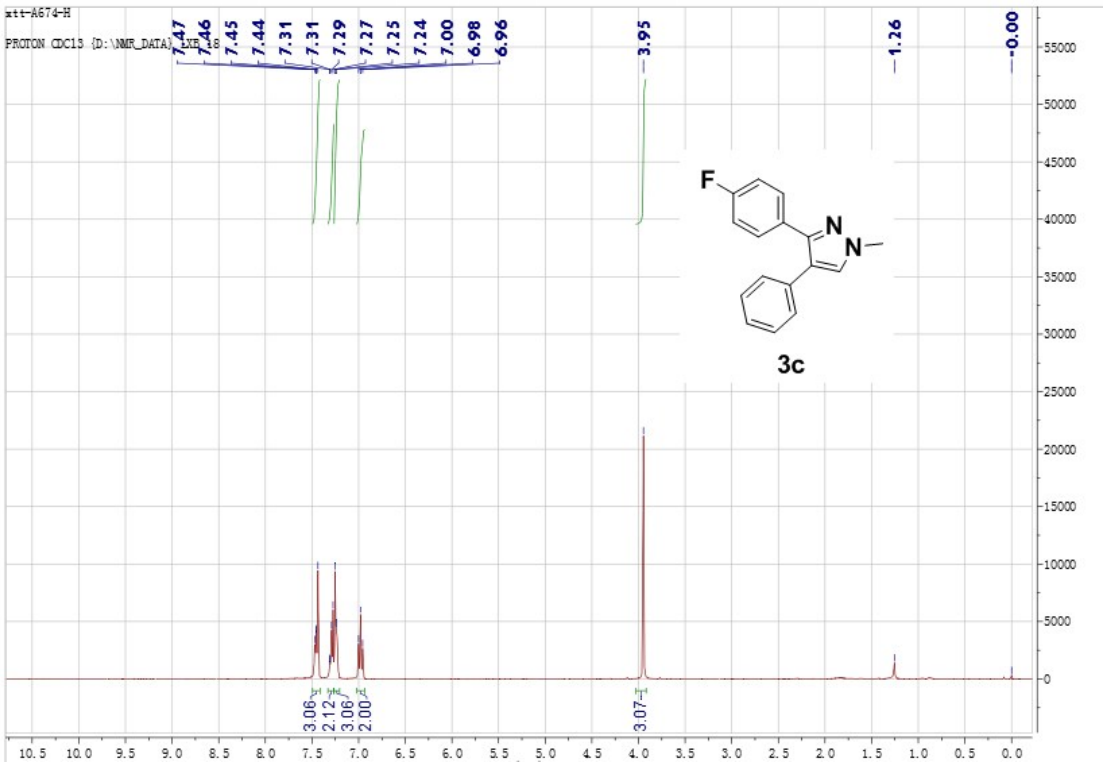
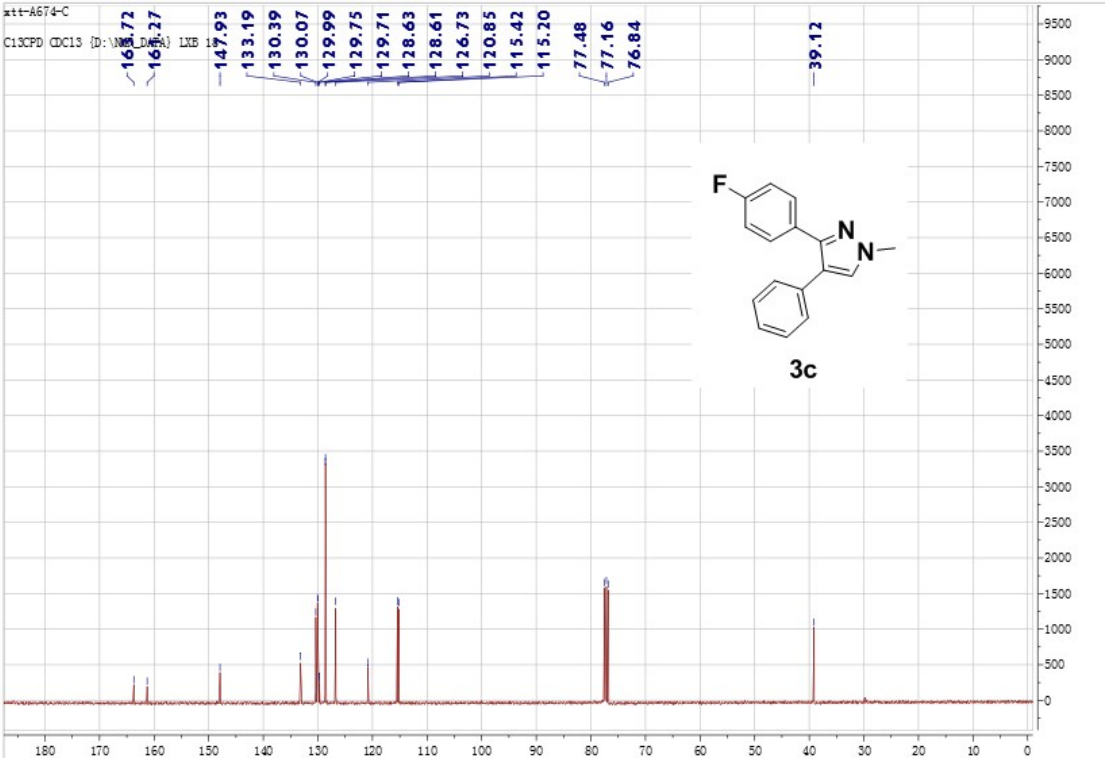
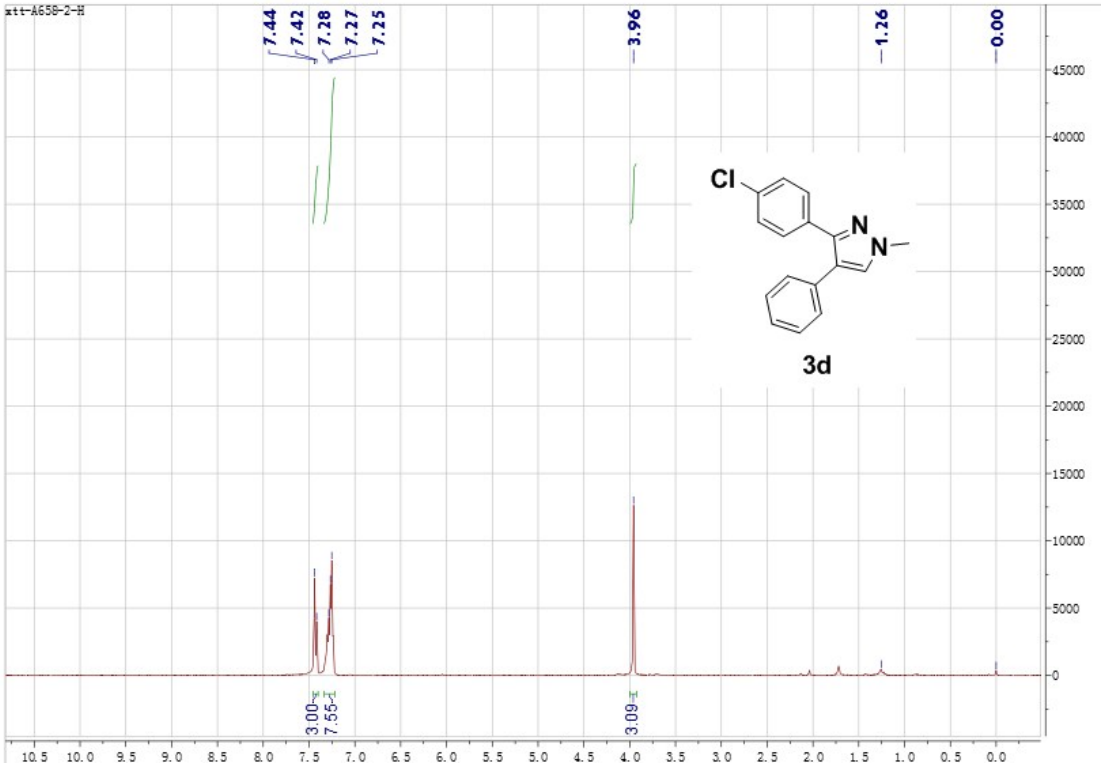
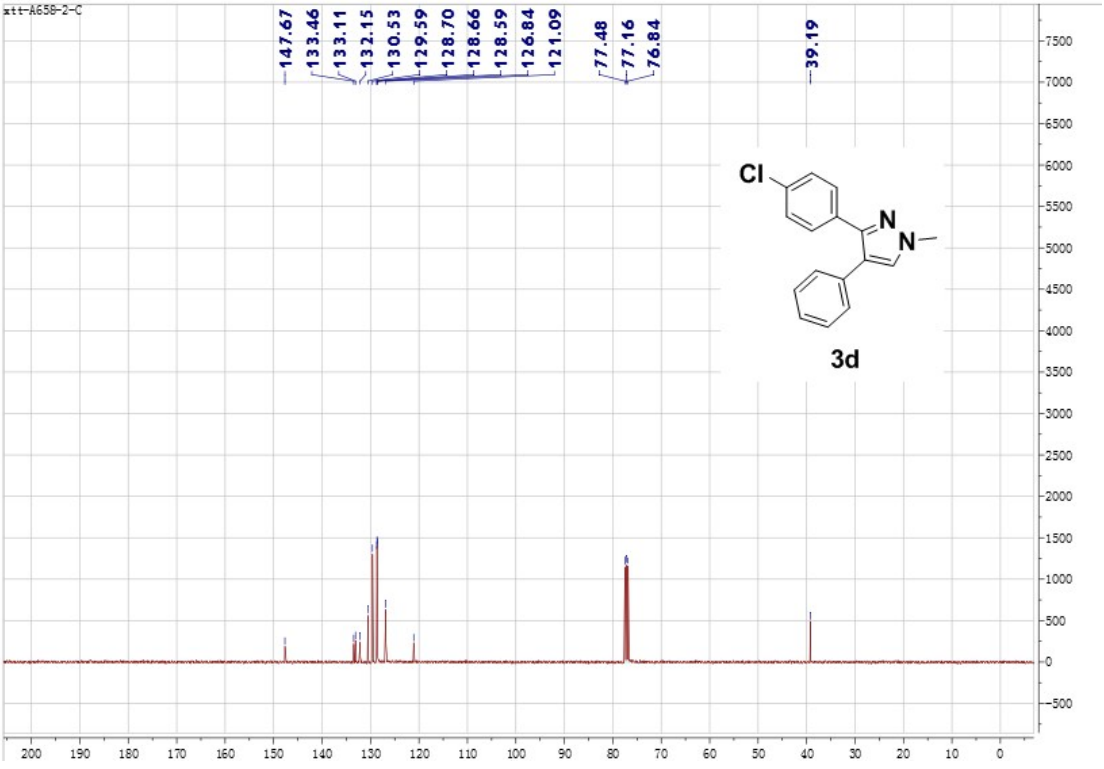
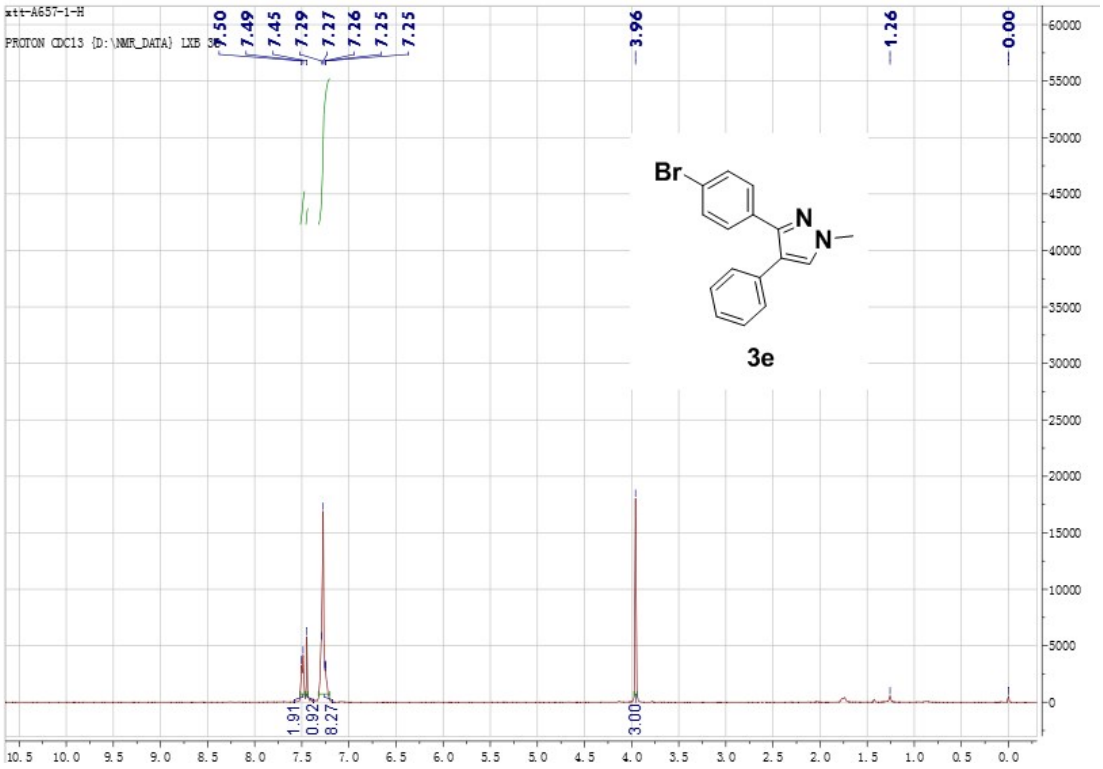
120.37
39.20
F3C
N
N
3b
f1 (ppm)

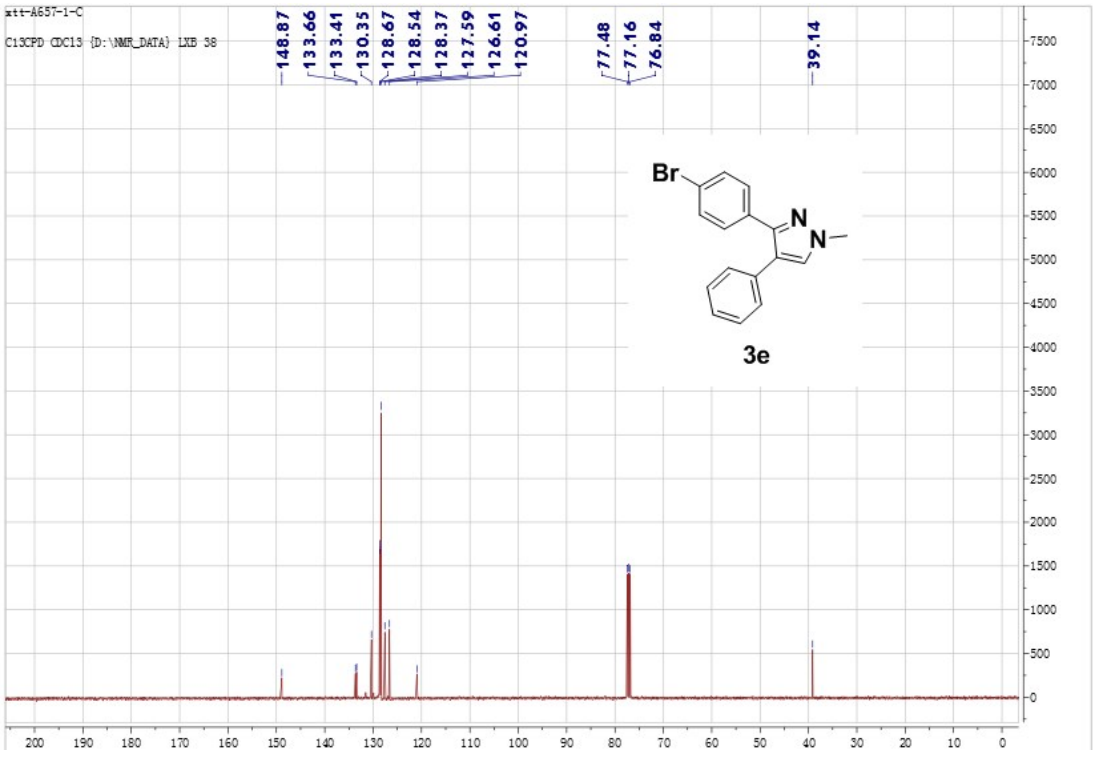

xtt-A674-H
PROTON CDCl3 {D:\NMR_DATA} LXB 18
7.47
7.46
7.45
7.44
7.31
7.31
7.29
7.27
7.25
7.24
7.00
6.98
6.96
3.95
1.26
0.00
F
N
N
3c
3.06
2.12
3.06
2.00
3.07

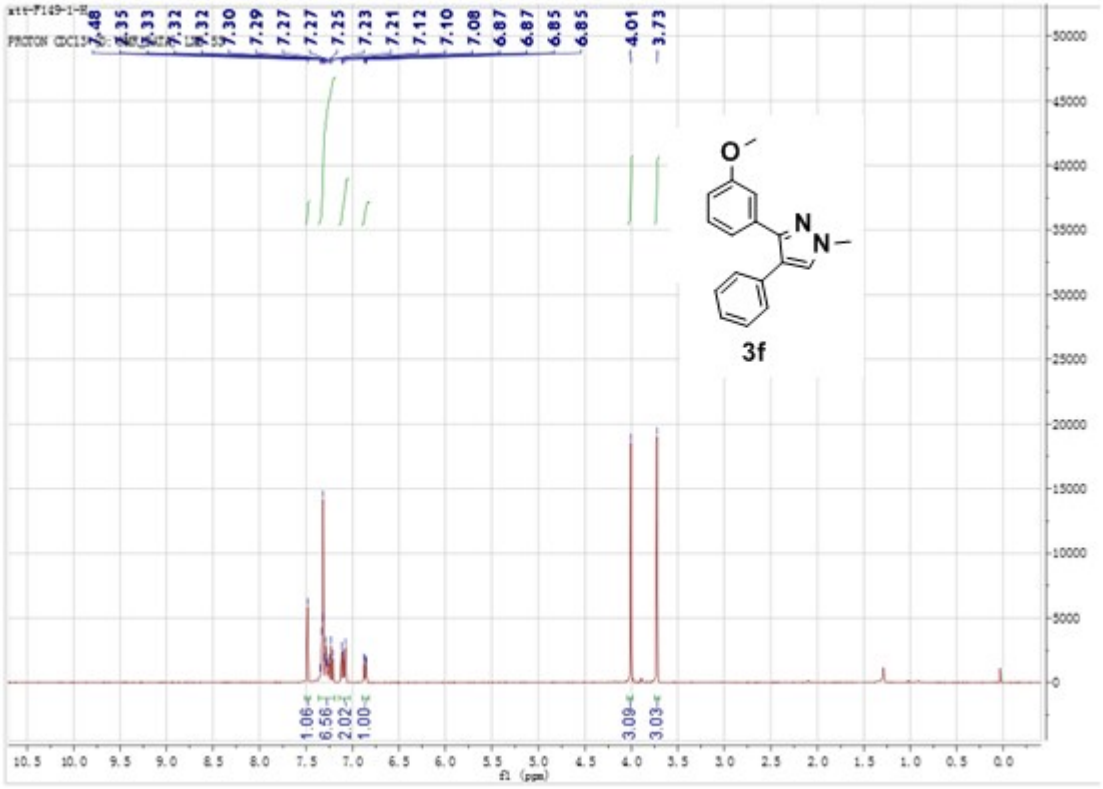

xtt-A674-C
C13CPD CDCl3 {D:\NMR_DATA} LXB 18
147.93
133.19
130.39
130.07
129.99
129.75
129.71
128.63
128.61
126.73
120.85
115.42
115.20
77.48
77.16
76.84
39.12
F
N
N
3c

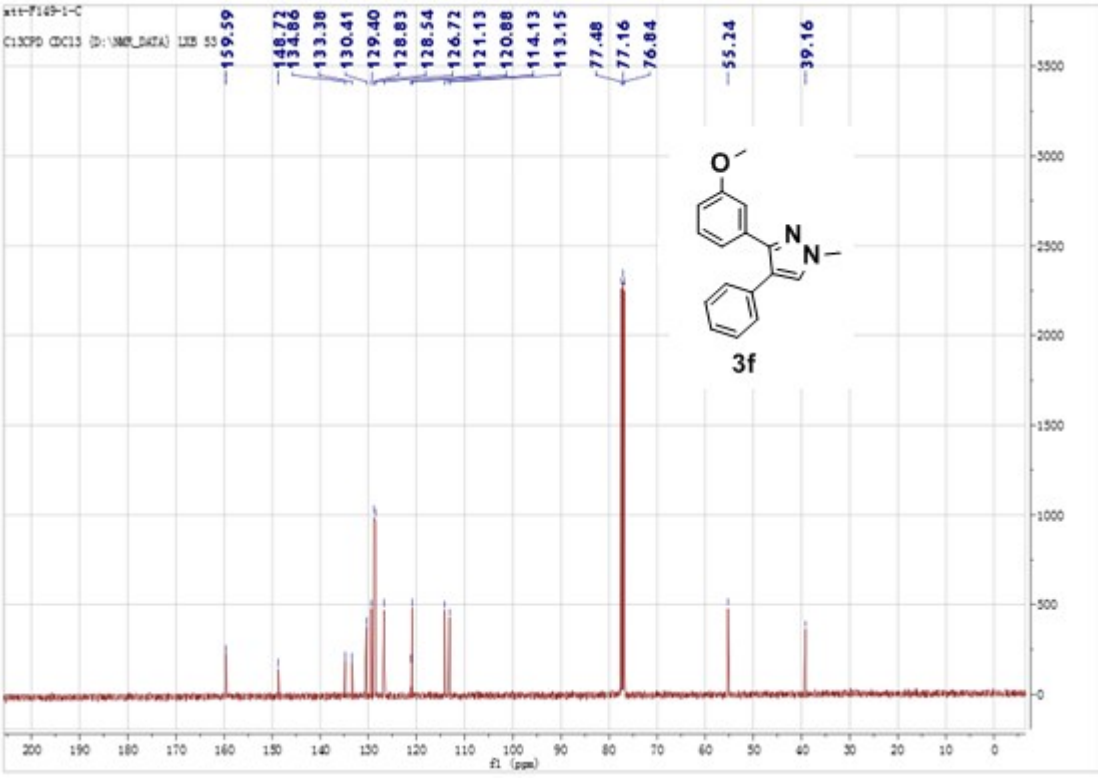

xtt-A658-2-H
7.44
7.42
7.28
7.27
7.25
3.96
1.26
0.00
Cl
N
N
3d
3.00
7.55
3.09

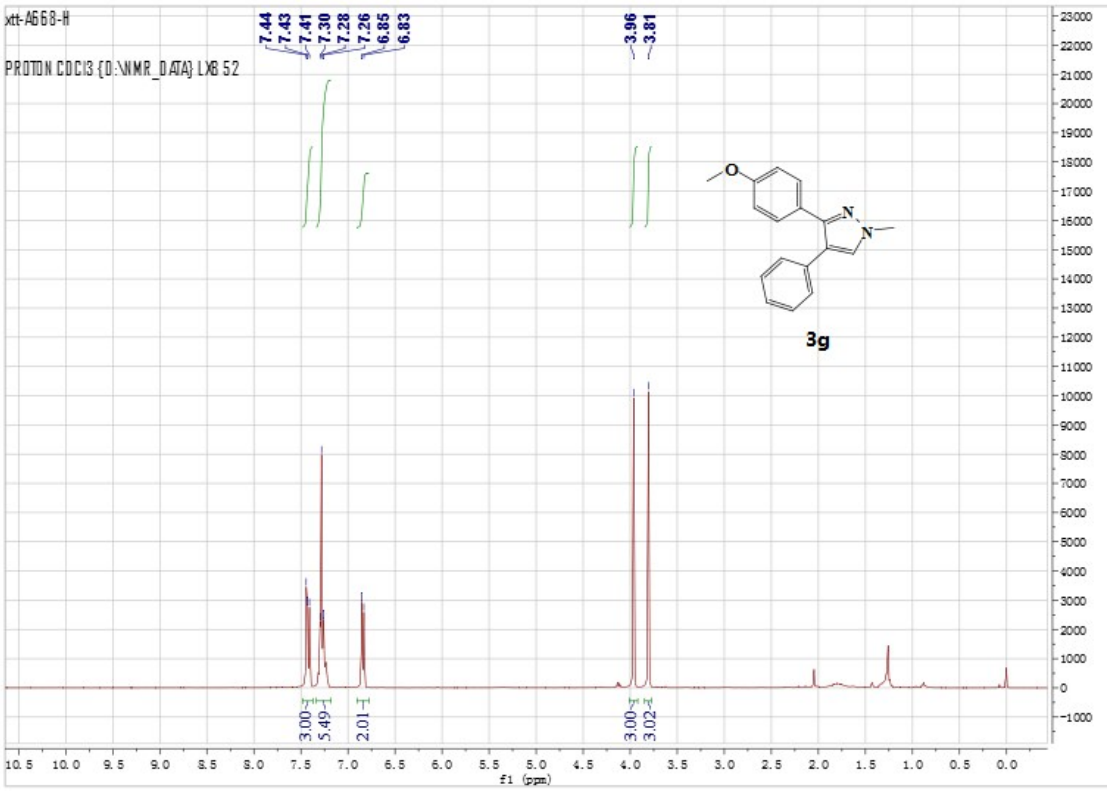

xtt-A658-2-C
147.67
133.46
133.11
132.15
130.53
129.59
128.70
128.66
128.59
126.84
121.09
77.48
77.16
76.84
39.19
Cl
N
N
3d

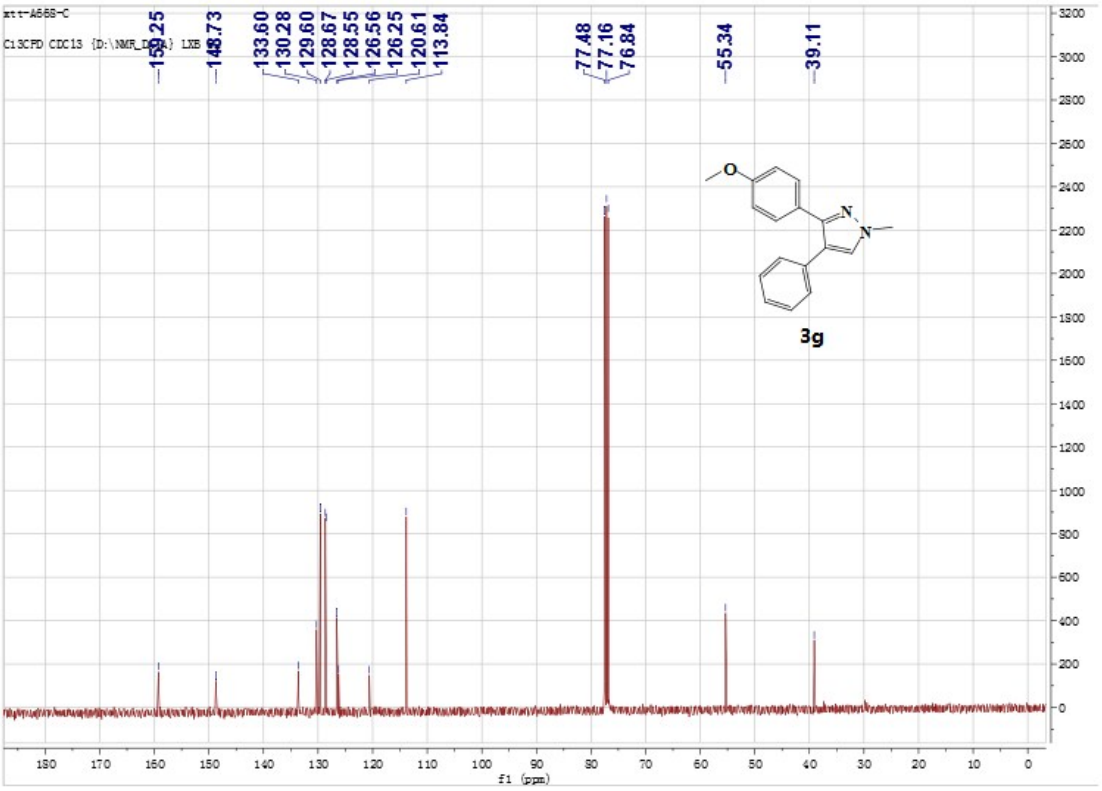

xtt-A657-1-H
PROTON CDC13 {D:\NMR_DATA} LXB 38
7.50
7.49
7.45
7.29
7.27
7.26
7.25
7.25
3.96
1.26
0.00
Br
N
N
3e
1.91
0.92
8.27
3.00

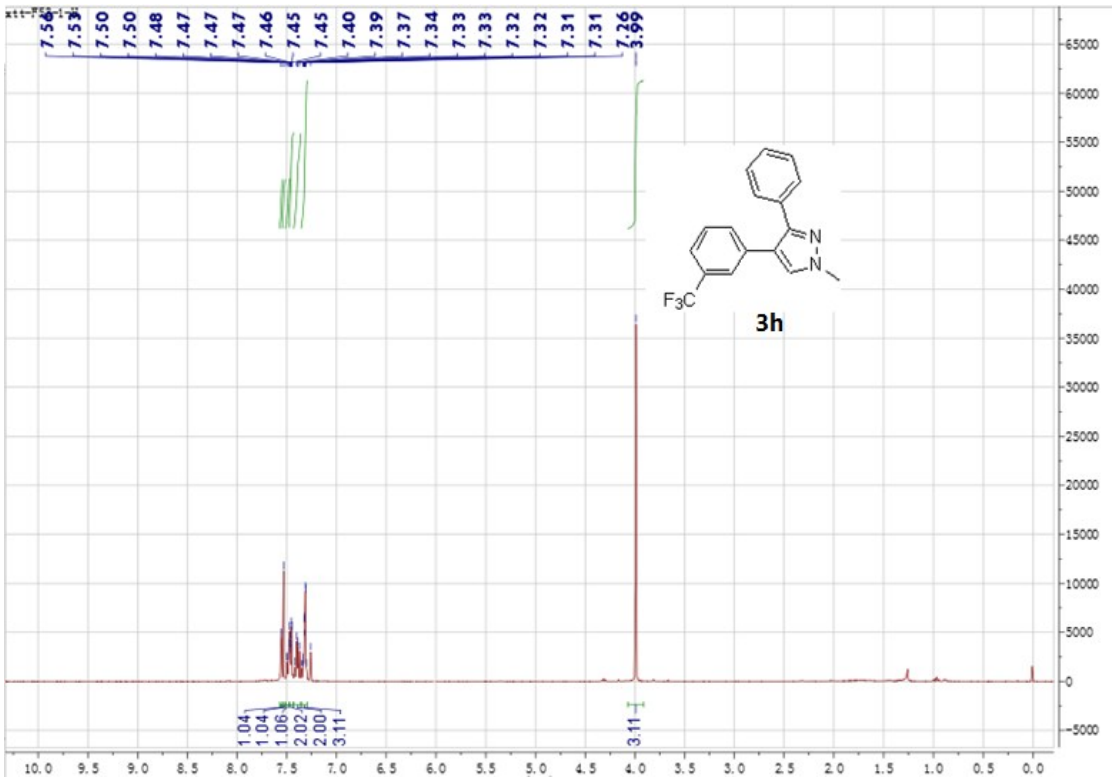

xtt-A657-1-C
C13CPD CDC13 {D:\NMR_DATA} LXB 38
148.87
133.66
133.41
130.35
128.67
128.54
128.37
127.59
126.61
120.97
77.48
77.16
76.84
39.14
Br
N
N
3e

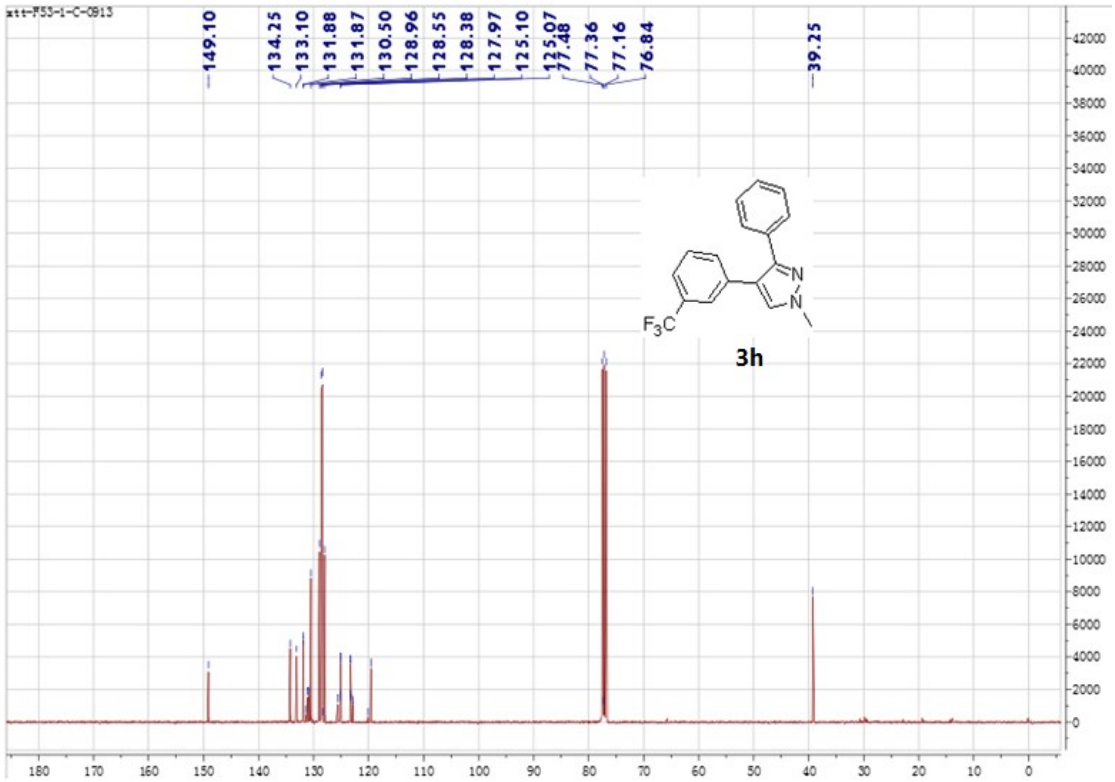

7.48
7.35
7.33
7.32
7.32
7.30
7.29
7.27
7.27
7.25
7.23
7.21
7.12
7.10
7.08
6.87
6.87
6.85
6.85
4.01
3.73
1.06
6.56
2.02
1.00
3.09
3.03
3f
f1 (ppm)

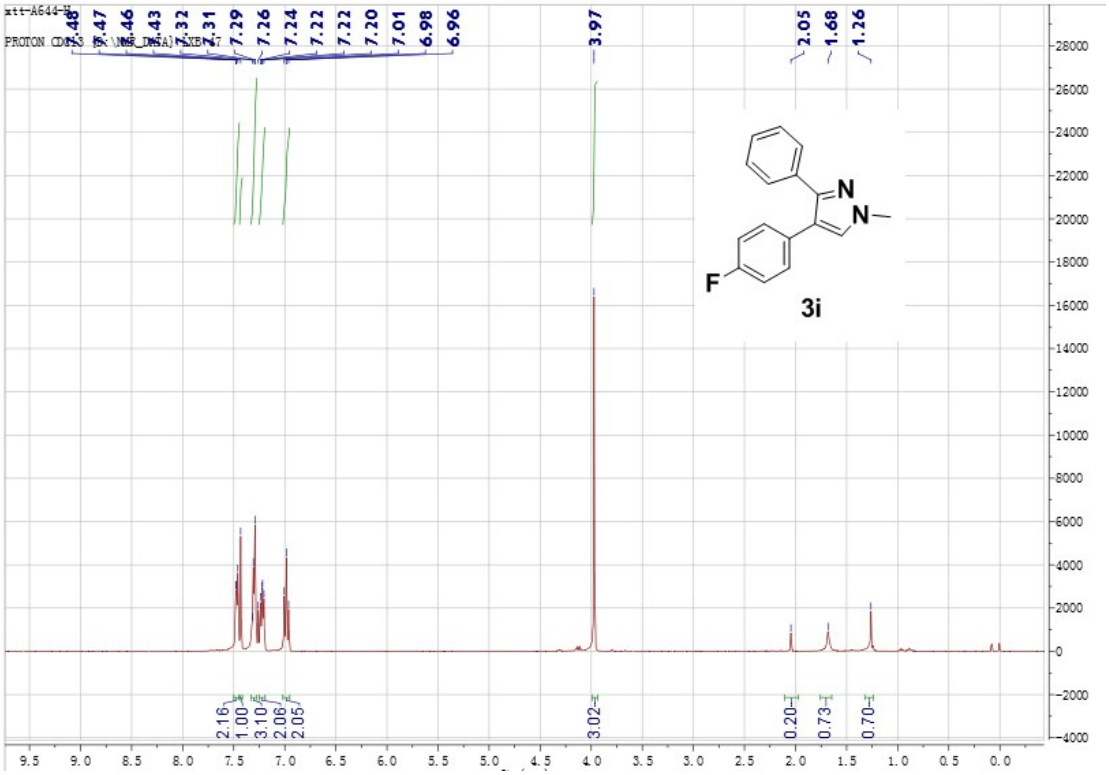

159.59
148.72
134.82
133.38
130.41
129.40
128.83
128.54
126.72
121.13
120.88
114.13
113.15
77.48
77.16
76.84
55.24
39.16
3f
f1 (ppm)

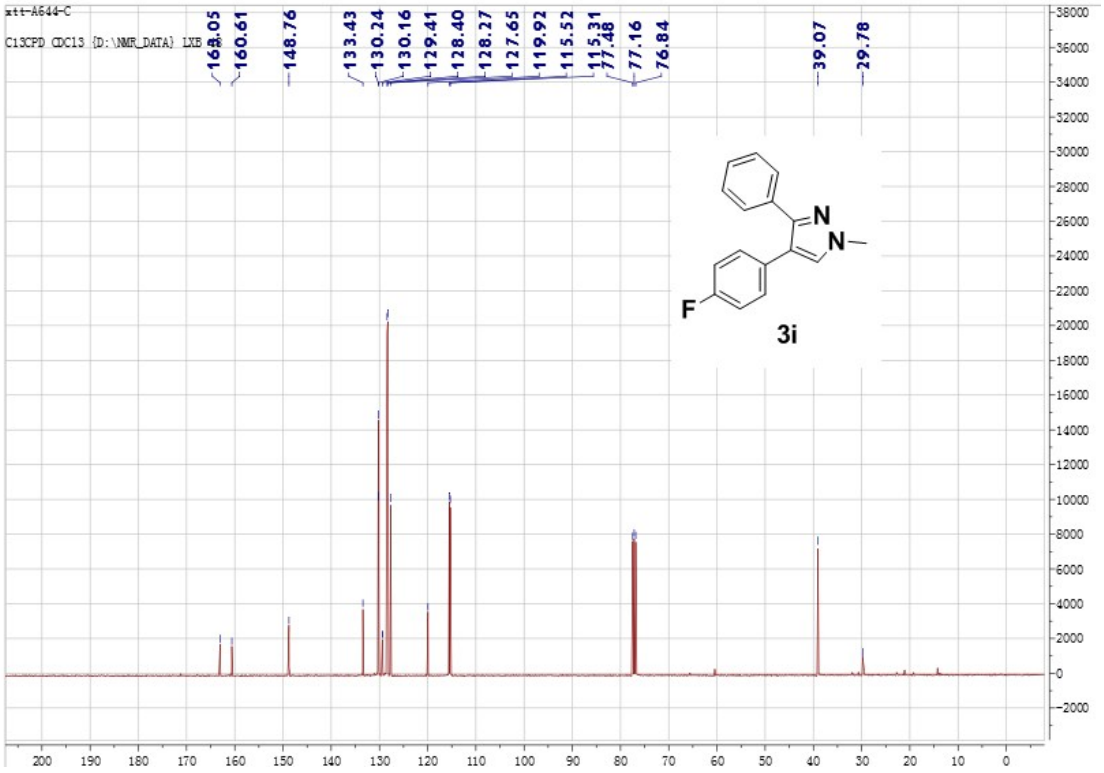

xtt-A668-H
PROTON CDCl3 {D:\NMR_DATA} LXB 52
7.44
7.43
7.41
7.30
7.28
7.26
6.85
6.83
3.96
3.81
3g
3.00
5.49
2.01
3.00
3.02
f1 (ppm)

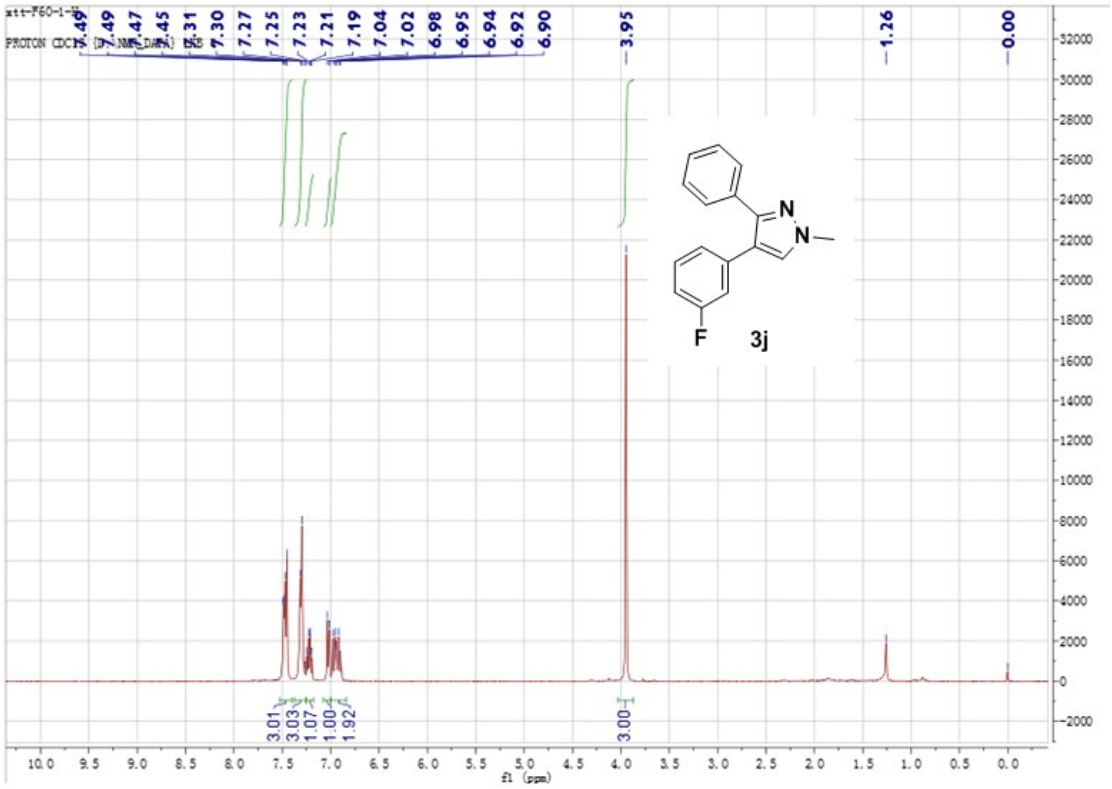

xtt-A668-C
C13CPD CDCl3 {D:\NMR_DATA} LXB
133.60
130.28
129.60
128.67
128.55
126.56
126.25
120.61
113.84
77.48
77.16
76.84
55.34
39.11
3g
f1 (ppm)

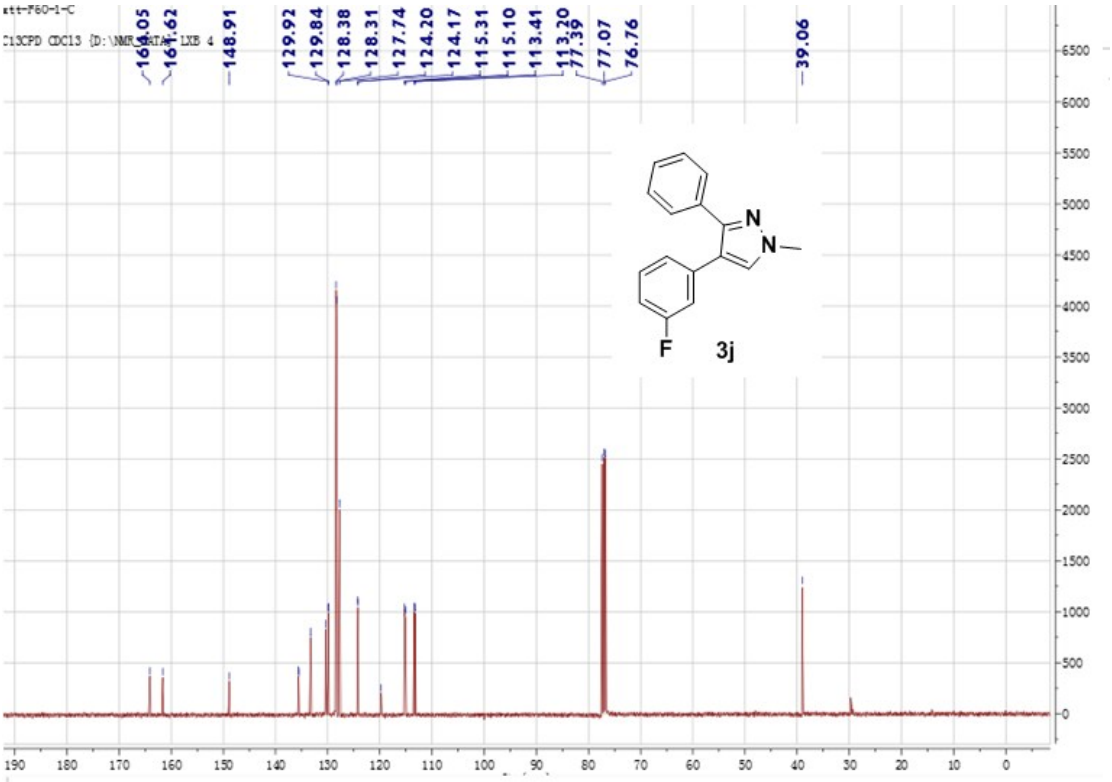

7.56
7.53
7.50
7.50
7.48
7.47
7.47
7.47
7.46
7.45
7.45
7.40
7.39
7.37
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.26
3.99
1.04
1.04
1.06
2.02
2.00
3.11
3.11
F3C
N
N
3h

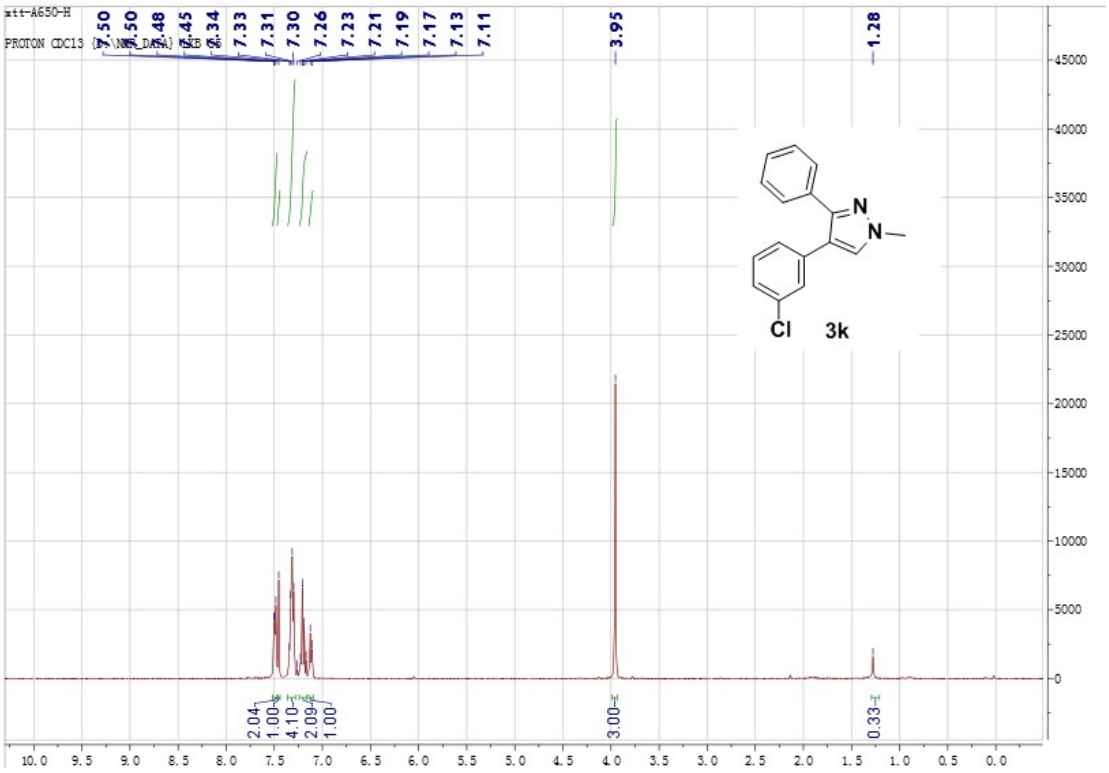

xtt-F53-1-C-0913
149.10
134.25
133.10
131.88
131.87
130.50
128.96
128.55
128.38
127.97
125.10
125.07
77.48
77.36
77.16
76.84
39.25
F3C
N
N
3h

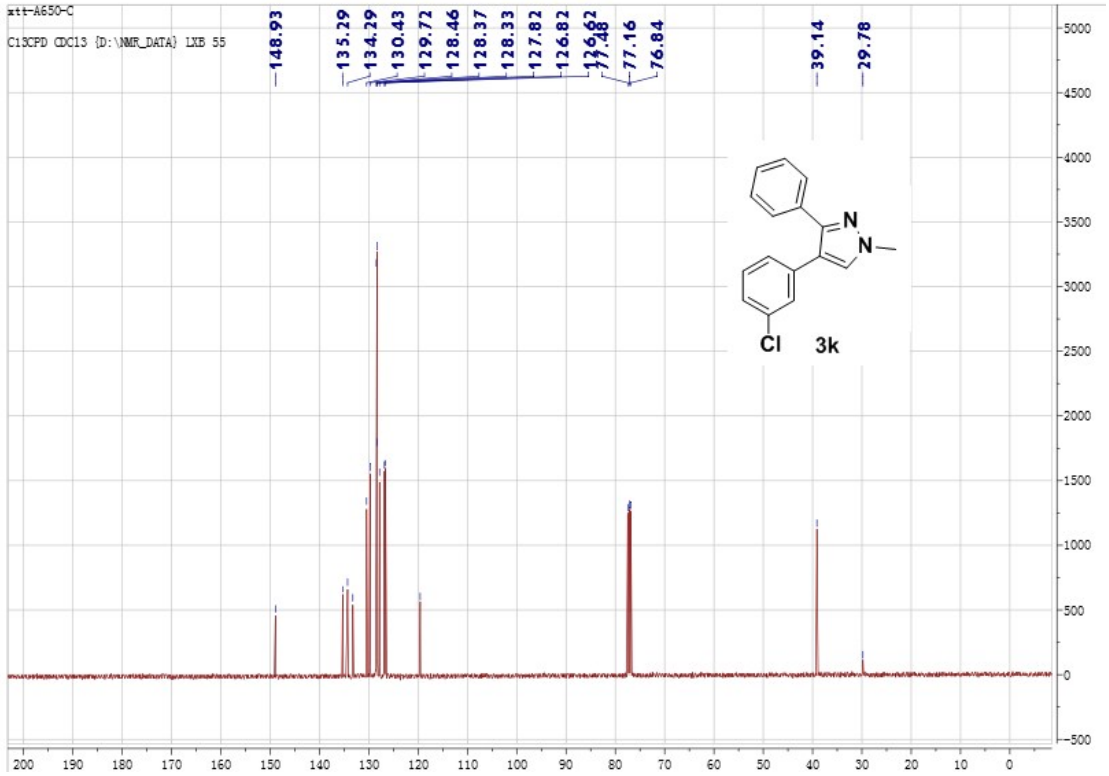

7.48
7.47
7.46
7.43
7.32
7.31
7.29
7.26
7.24
7.22
7.22
7.20
7.01
6.98
6.96
3.97
2.05
1.68
1.26
N
N
F
3i
2.16
1.00
3.10
2.06
2.05
3.02
0.20
0.73
0.70

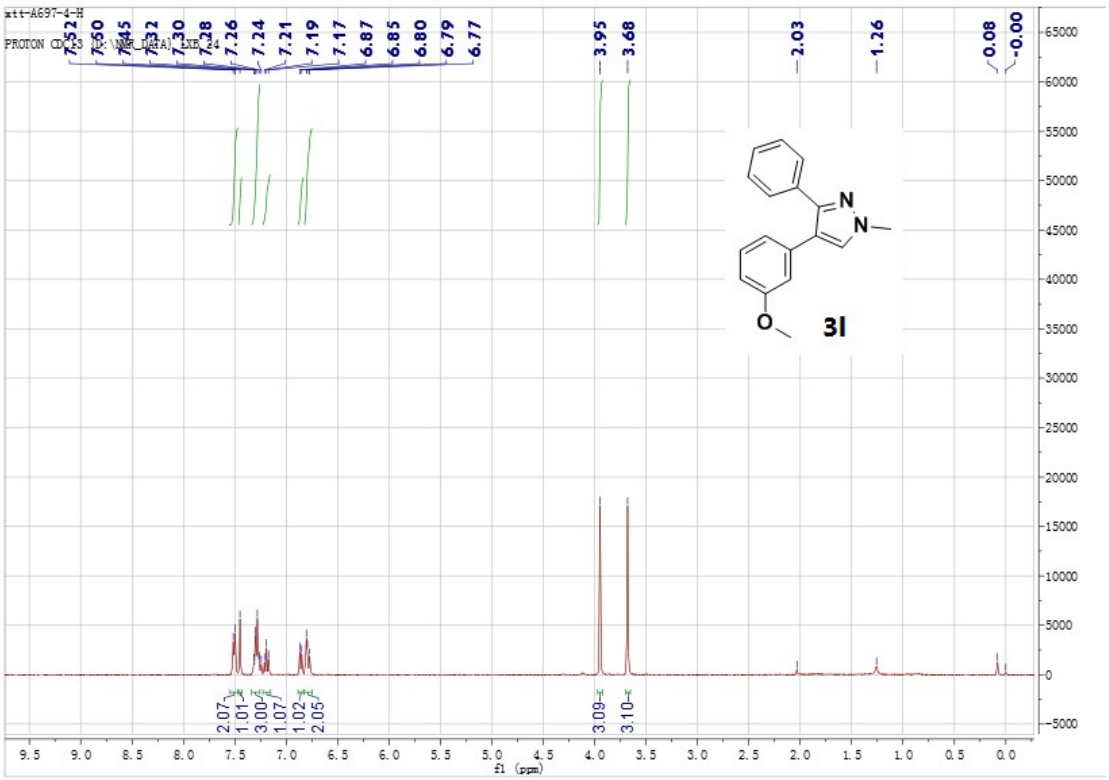

xtt-A644-C
C13CPD CDCl3 (D:\NMR_DATA) LXB
168.05
160.61
148.76
133.43
130.24
130.16
129.41
128.40
128.27
127.65
119.92
115.52
115.31
77.48
77.16
76.84
39.07
29.78
N
N
F
3i

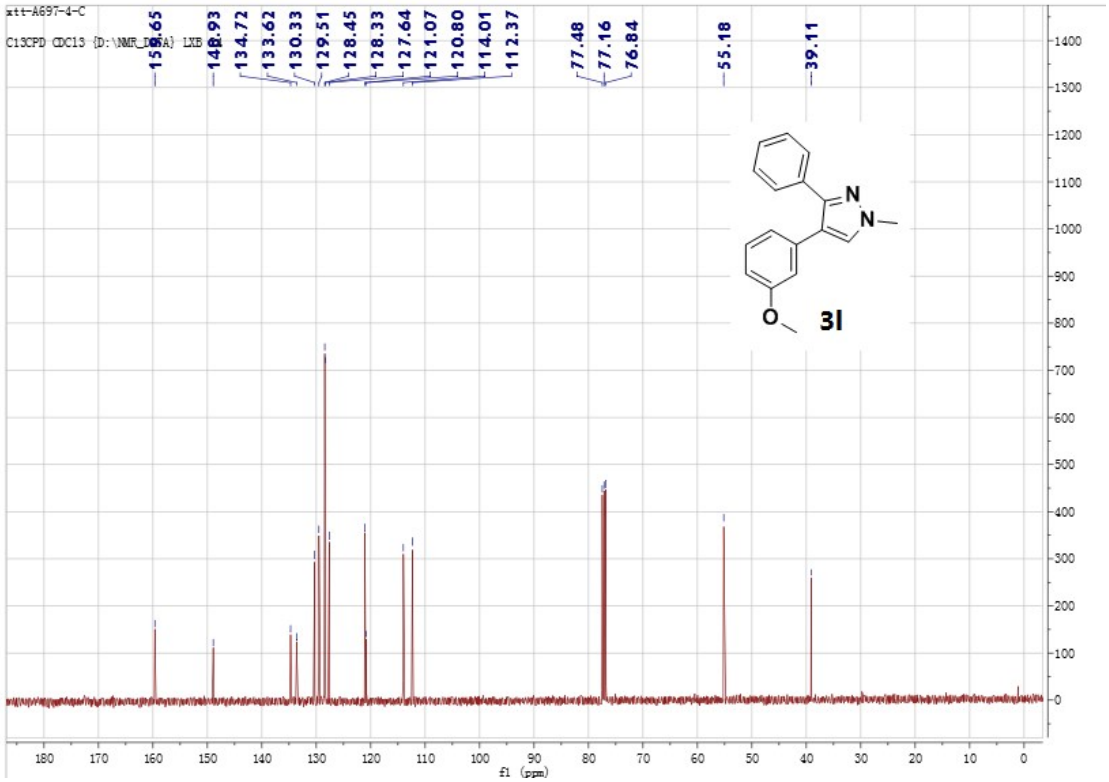

7.49
7.47
7.45
7.31
7.30
7.27
7.25
7.23
7.21
7.19
7.04
7.02
6.98
6.95
6.94
6.92
6.90
3.95
1.26
0.00
3.01
3.03
1.07
1.00
1.92
3.00
f1 (ppm)
N
N
F
3j

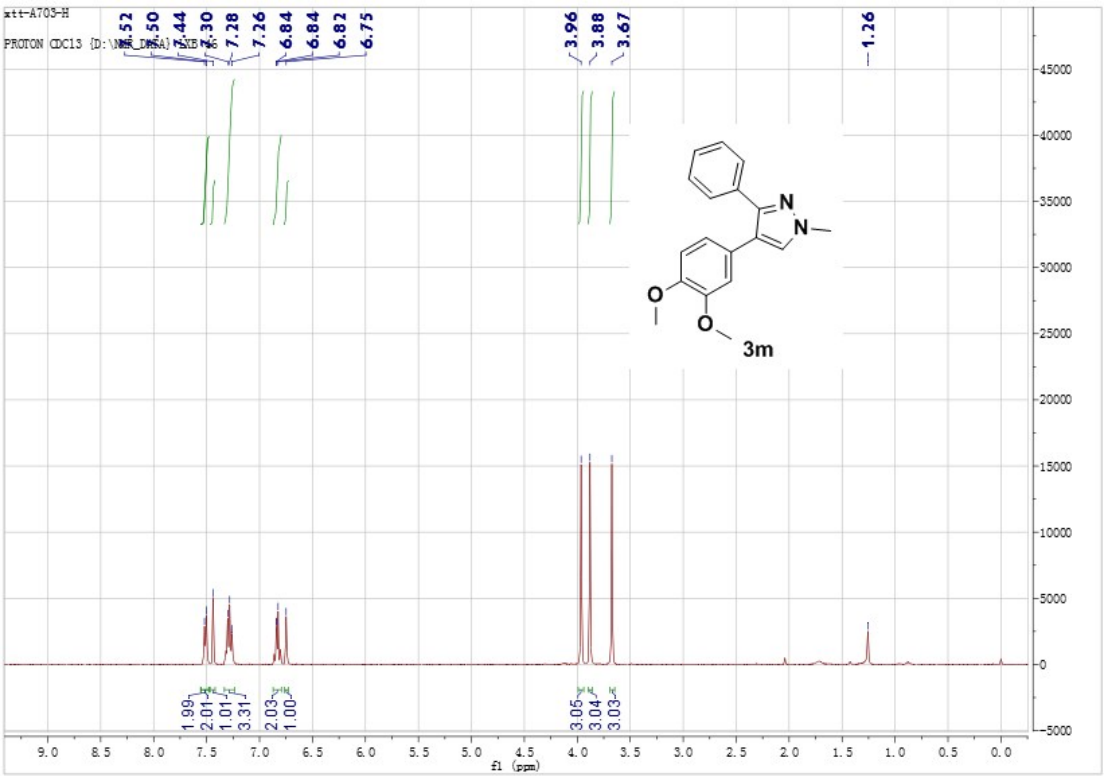

161.05
161.62
148.91
129.92
129.84
128.38
128.31
127.74
124.20
124.17
115.31
115.10
113.41
113.20
77.39
77.07
76.76
39.06
N
N
F
3j

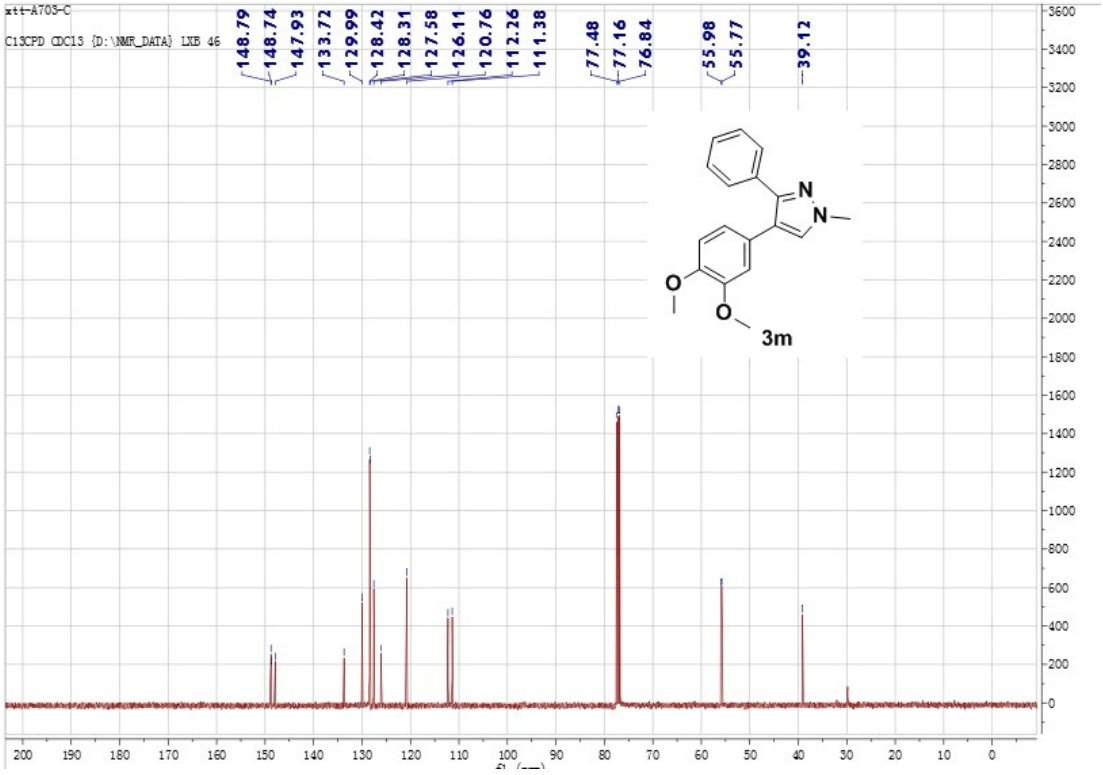

xtt-A650-H
PROTON CDCl3 {D:\NMR_DATA} LXB 55
8.50
8.50
8.48
8.45
8.34
7.33
7.31
7.30
7.26
7.23
7.21
7.19
7.17
7.13
7.11
3.95
1.28
2.04
1.00
4.10
2.09
1.00
3.00
0.33
N
N
Cl
3k

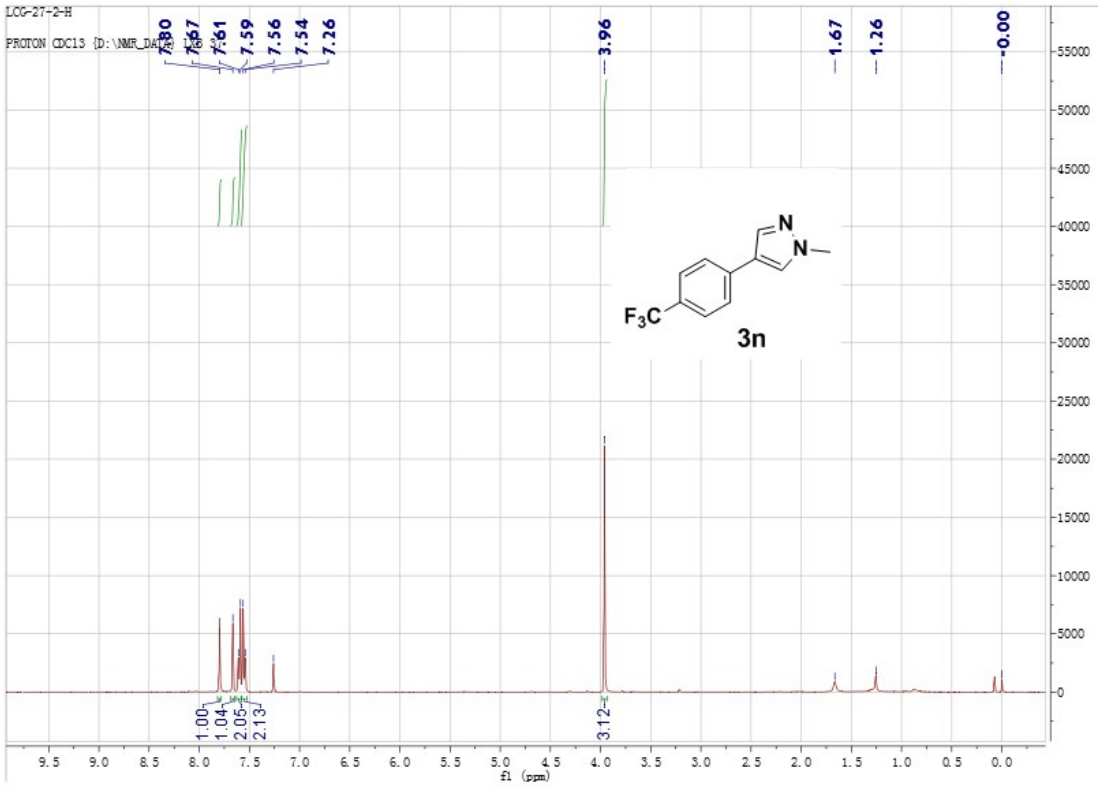

xtt-A650-C
C13CPD CDCl3 {D:\NMR_DATA} LXB 55
148.93
135.29
134.29
130.43
129.72
128.46
128.37
128.33
127.82
126.82
77.48
77.16
76.84
39.14
29.78
N
N
Cl
3k

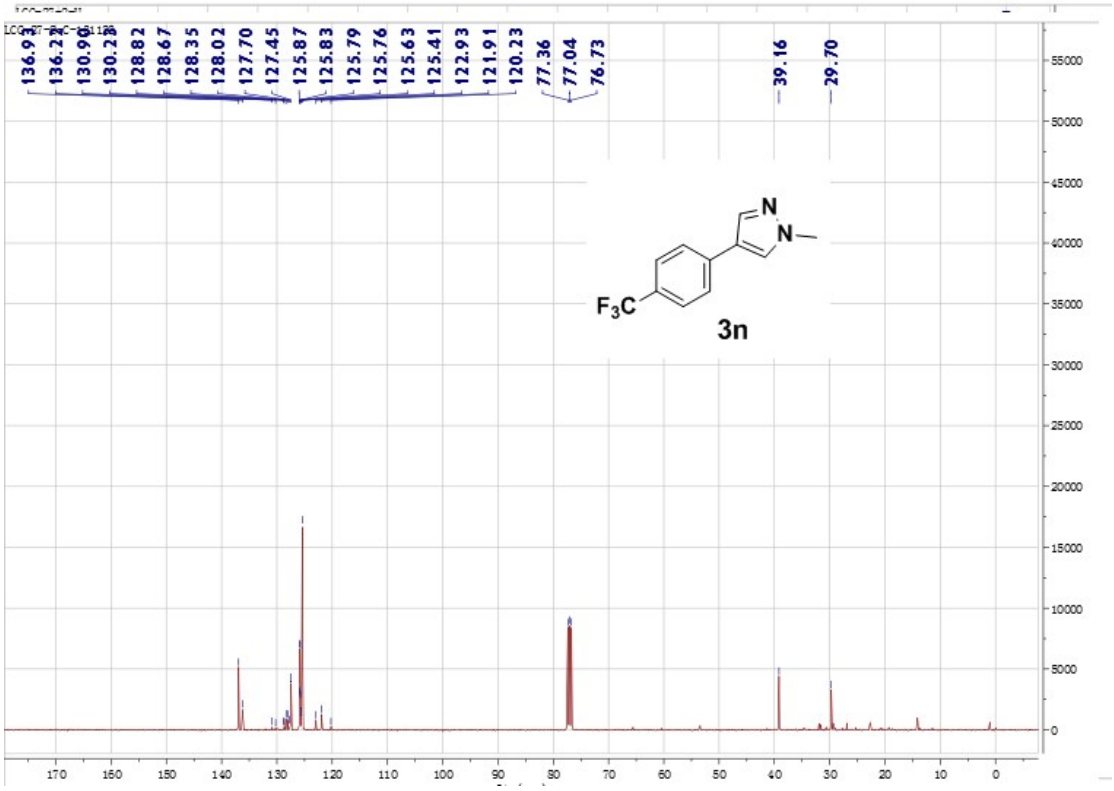

xtt-A697-4-H
7.52
7.50
7.45
7.32
7.30
7.28
7.26
7.24
7.21
7.19
7.17
6.87
6.85
6.80
6.79
6.77
3.95
3.68
2.03
1.26
0.08
-0.00
2.07
1.01
3.00
1.07
1.02
2.05
3.09
3.10
f1 (ppm)
3l

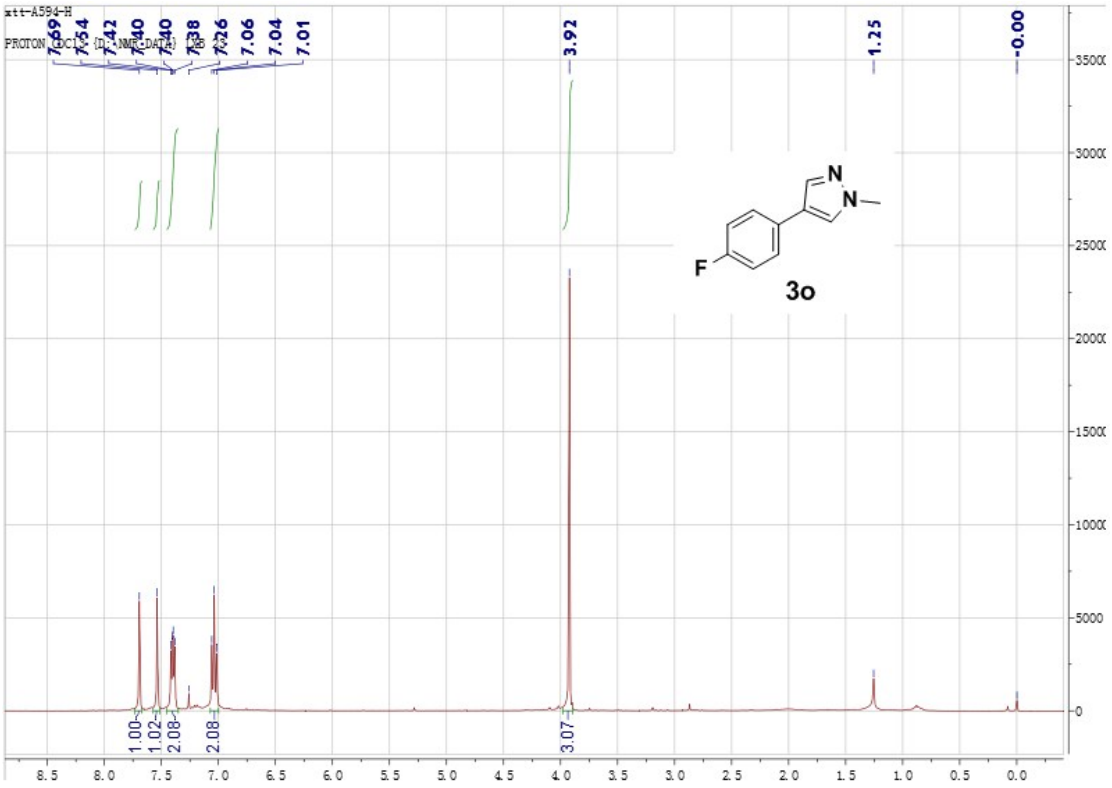

xtt-A697-4-C
159.65
148.93
134.72
133.62
130.33
129.51
128.45
128.33
127.64
121.07
120.80
114.01
112.37
77.48
77.16
76.84
55.18
39.11
f1 (ppm)
3l

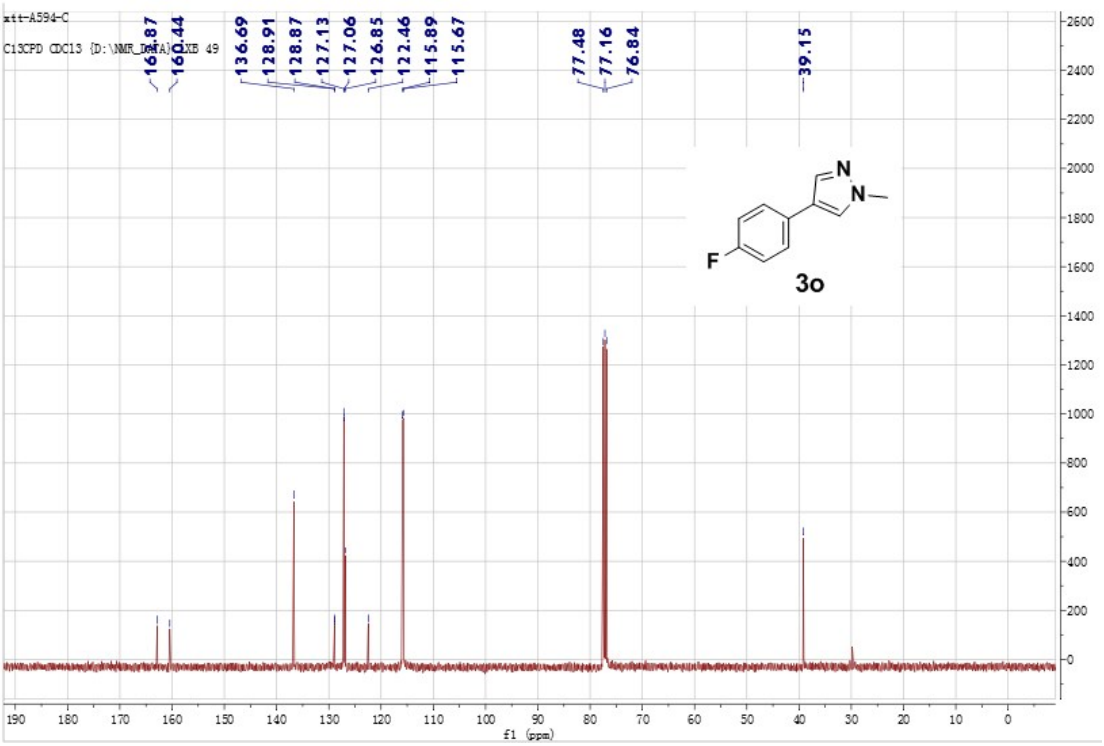

xtt-A703-H
PROTON CDCl3 {D:\NMR_DATA} LXB 46
7.52
7.50
7.44
7.30
7.28
7.26
6.84
6.84
6.82
6.75
3.96
3.88
3.67
1.26
1.99
2.01
1.01
3.31
2.03
1.00
3.05
3.04
3.03
f1 (ppm)
3m

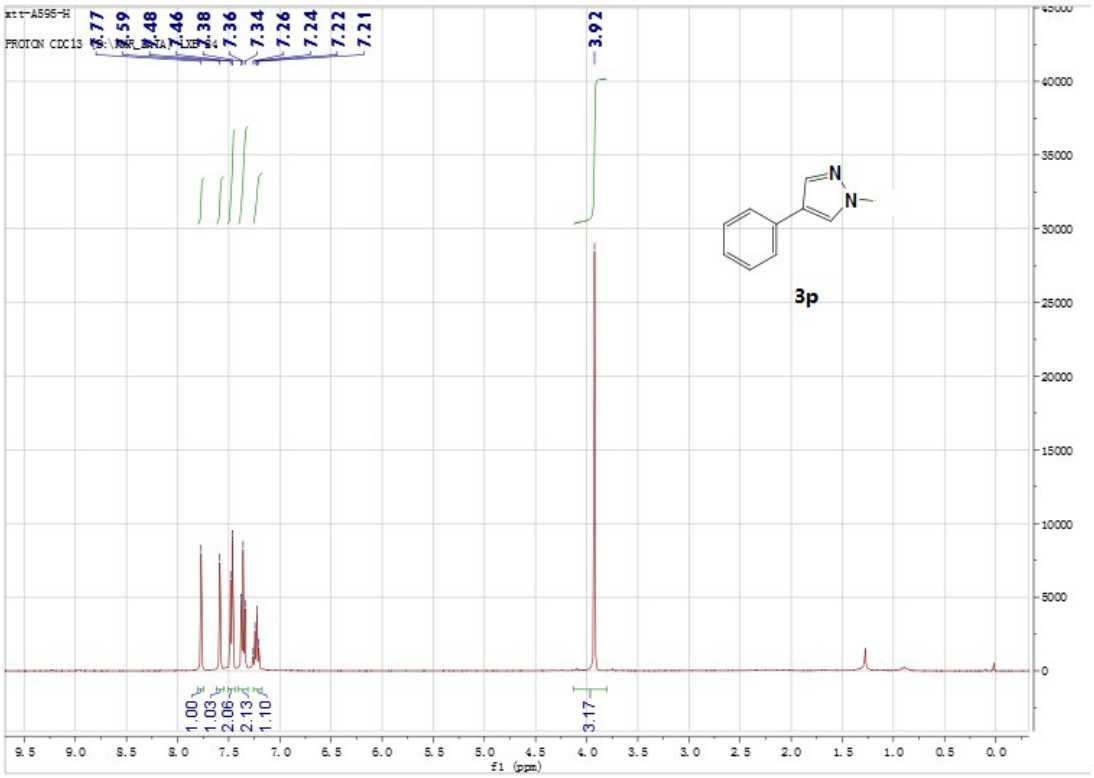

xtt-A703-C
C13CPD CDCl3 {D:\NMR_DATA} LXB 46
148.79
148.74
147.93
133.72
129.99
128.42
128.31
127.58
126.11
120.76
112.26
111.38
77.48
77.16
76.84
55.98
55.77
39.12
f1 (ppm)
3m

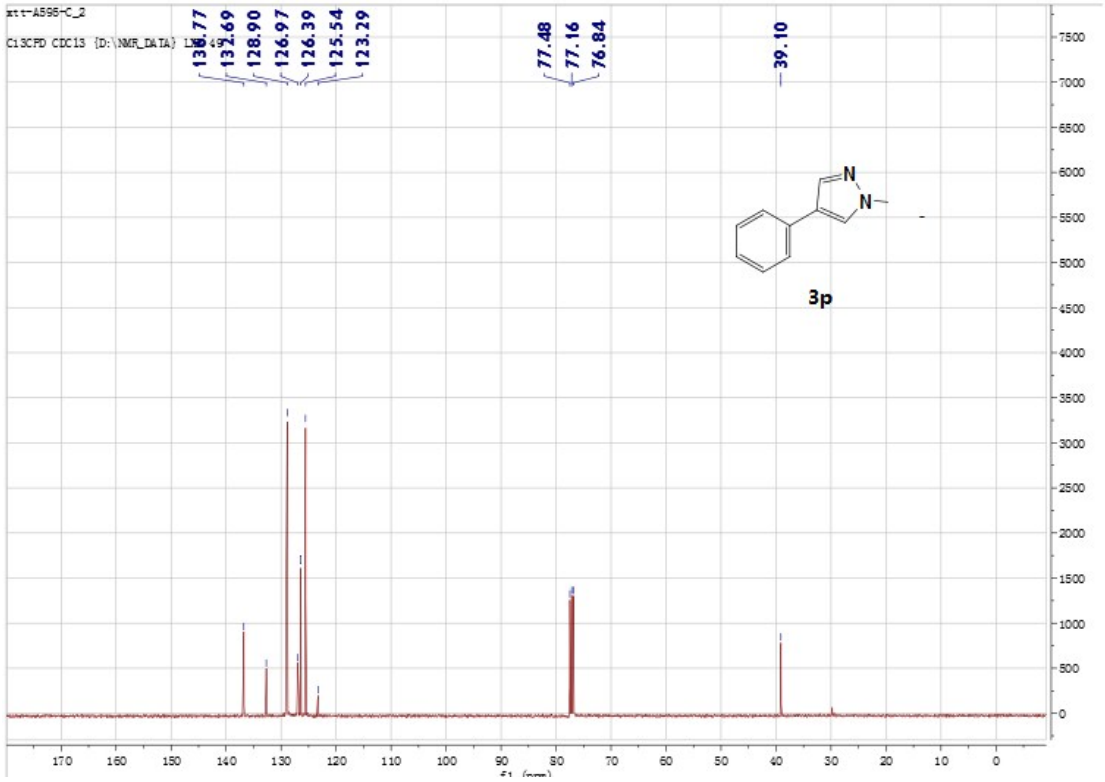

LCG-27-2-H
PROTON CDC13
7.80
7.67
7.61
7.59
7.56
7.54
7.26
3.96
1.67
1.26
0.00
1.00
1.04
2.05
2.13
3.12
f1 (ppm)
F3C
3n

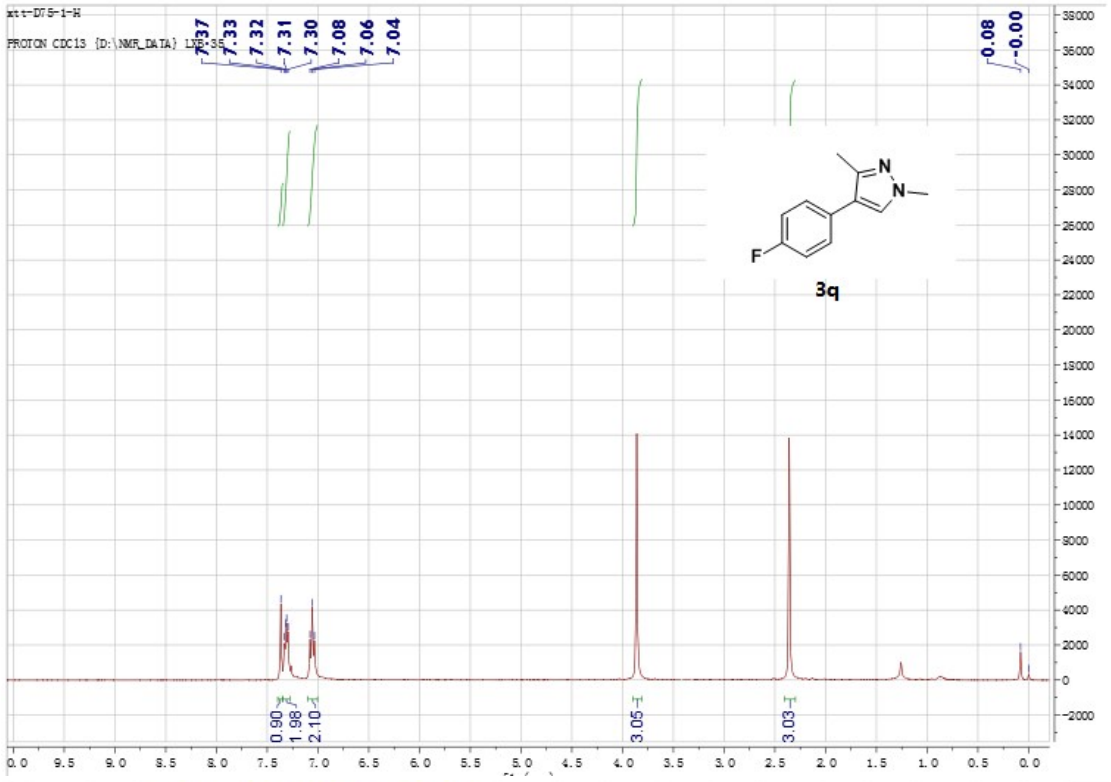

136.91
136.21
130.96
130.28
128.82
128.67
128.35
128.02
127.70
127.45
125.87
125.83
125.79
125.76
125.63
125.41
122.93
121.91
120.23
77.36
77.04
76.73
39.16
29.70
F3C
3n

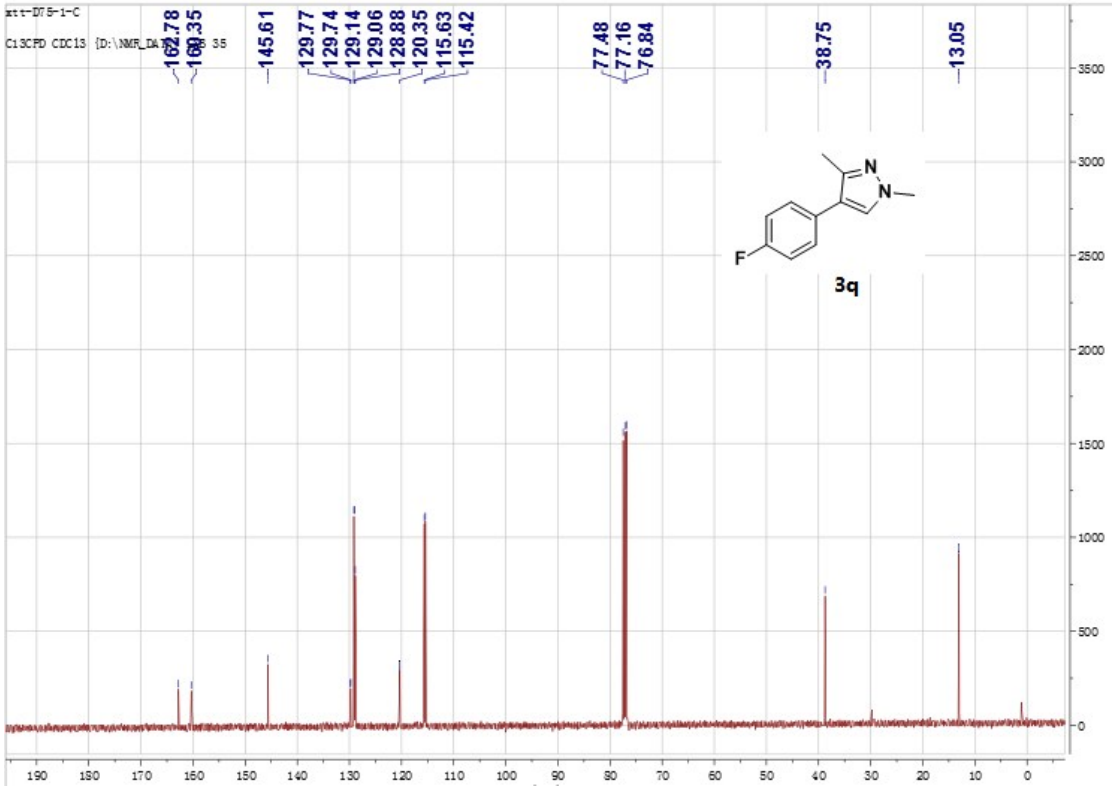

xtt-A594-H
7.69
7.54
7.42
7.40
7.40
7.38
7.26
7.06
7.04
7.01
3.92
1.25
0.00
1.00
1.02
2.08
2.08
3.07
3o

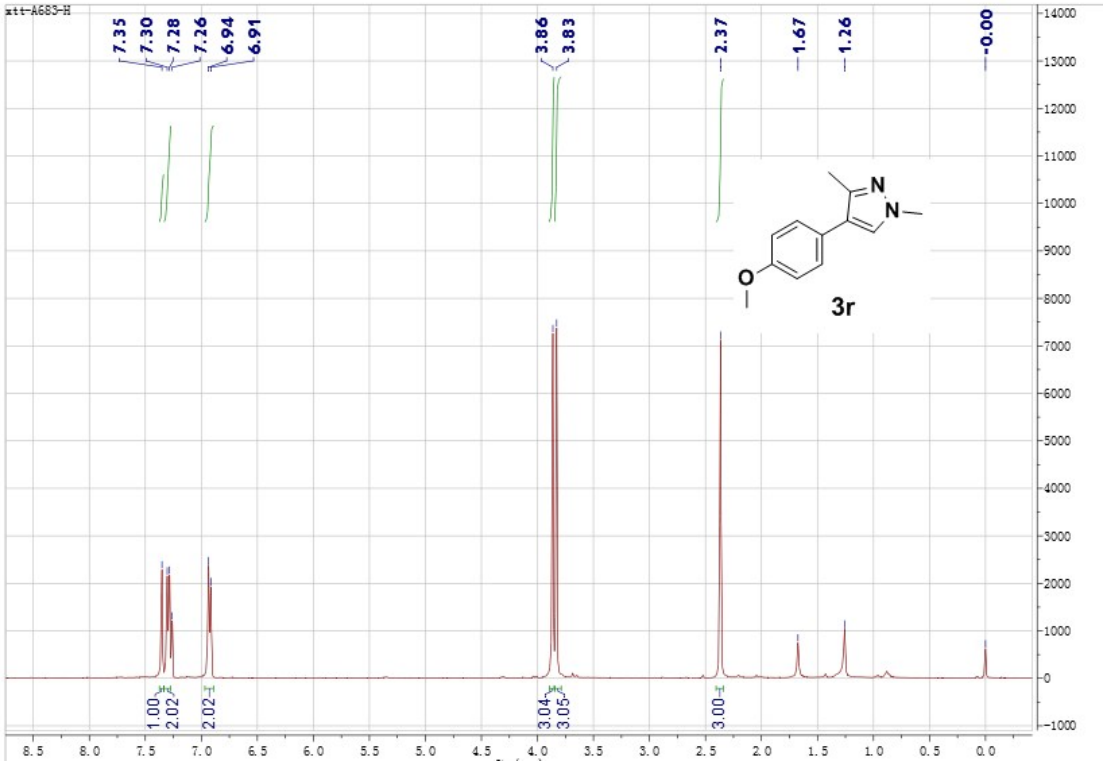

xtt-A594-C
163.87
160.44
136.69
128.91
128.87
127.13
127.06
126.85
122.46
115.89
115.67
77.48
77.16
76.84
39.15
f1 (ppm)
3o

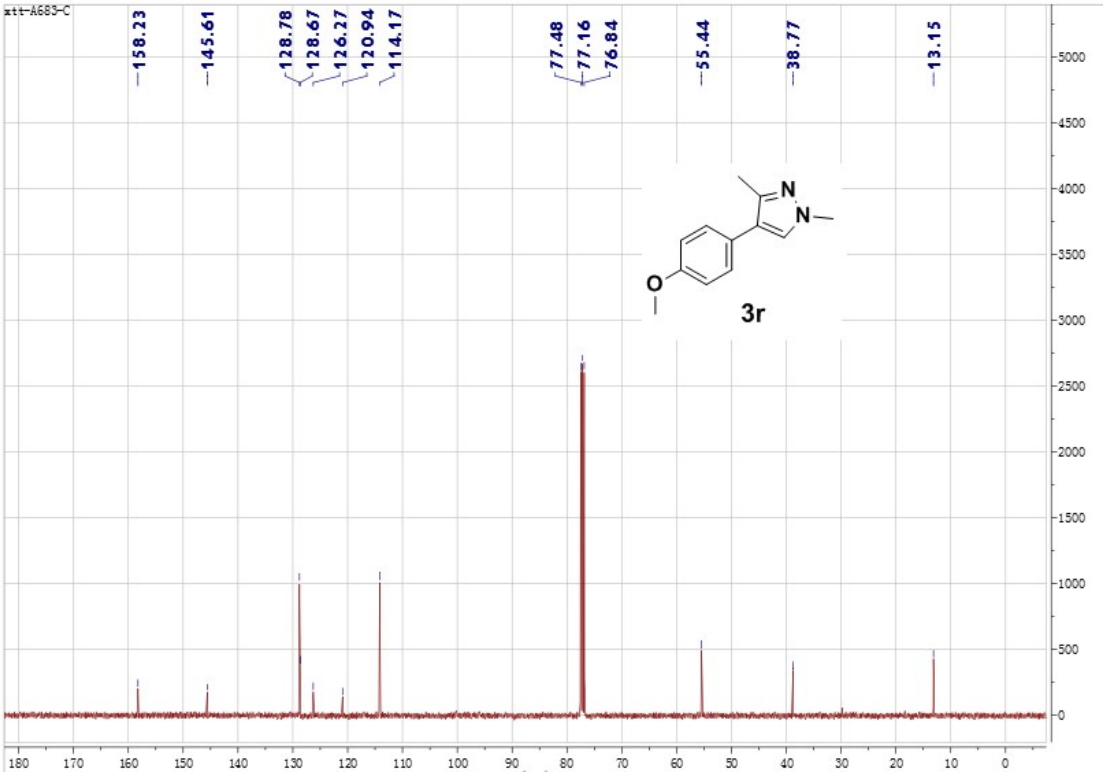

7.77
7.59
7.48
7.46
7.38
7.36
7.34
7.26
7.24
7.22
7.21
3.92
1.00
1.03
2.06
2.13
1.10
3.17
f1 (ppm)
3p

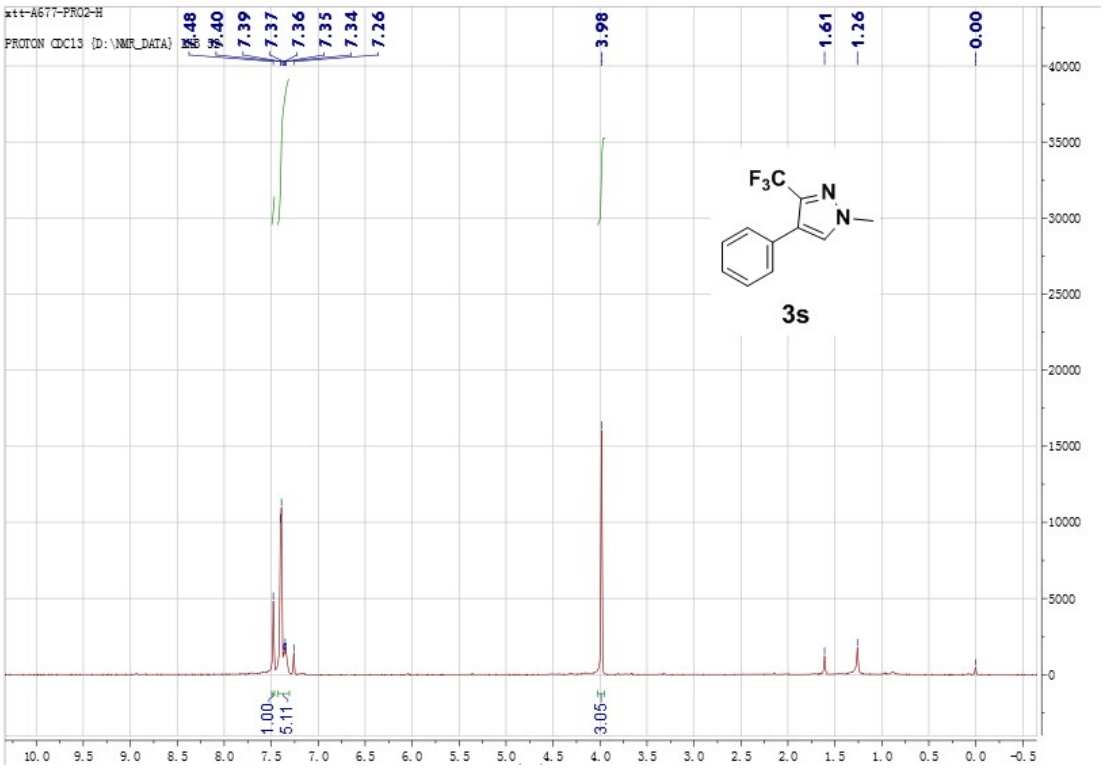

138.77
132.69
128.90
126.97
126.39
125.54
123.29
77.48
77.16
76.84
39.10
f1 (ppm)
3p

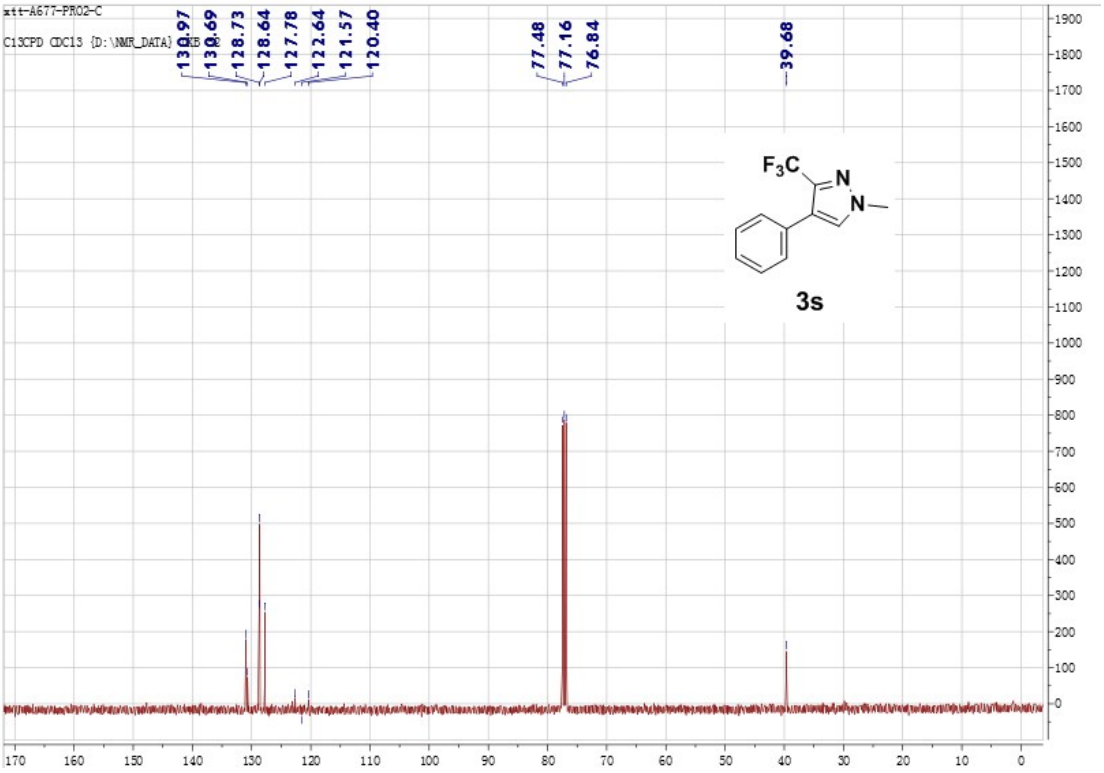

7.37
7.33
7.32
7.31
7.30
7.08
7.06
7.04
0.08
-0.00
0.90
1.98
2.10
3.05
3.03
3q

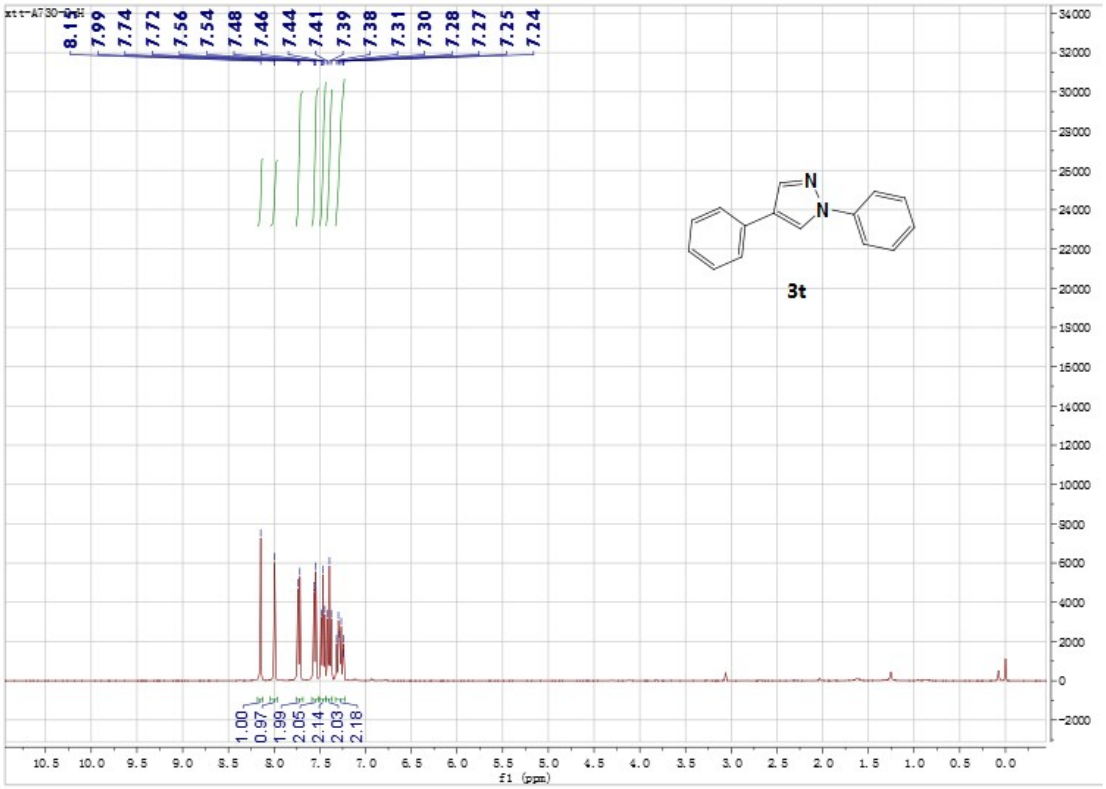

162.78
160.35
145.61
129.77
129.74
129.14
129.06
128.88
120.35
115.63
115.42
77.48
77.16
76.84
38.75
13.05
3q

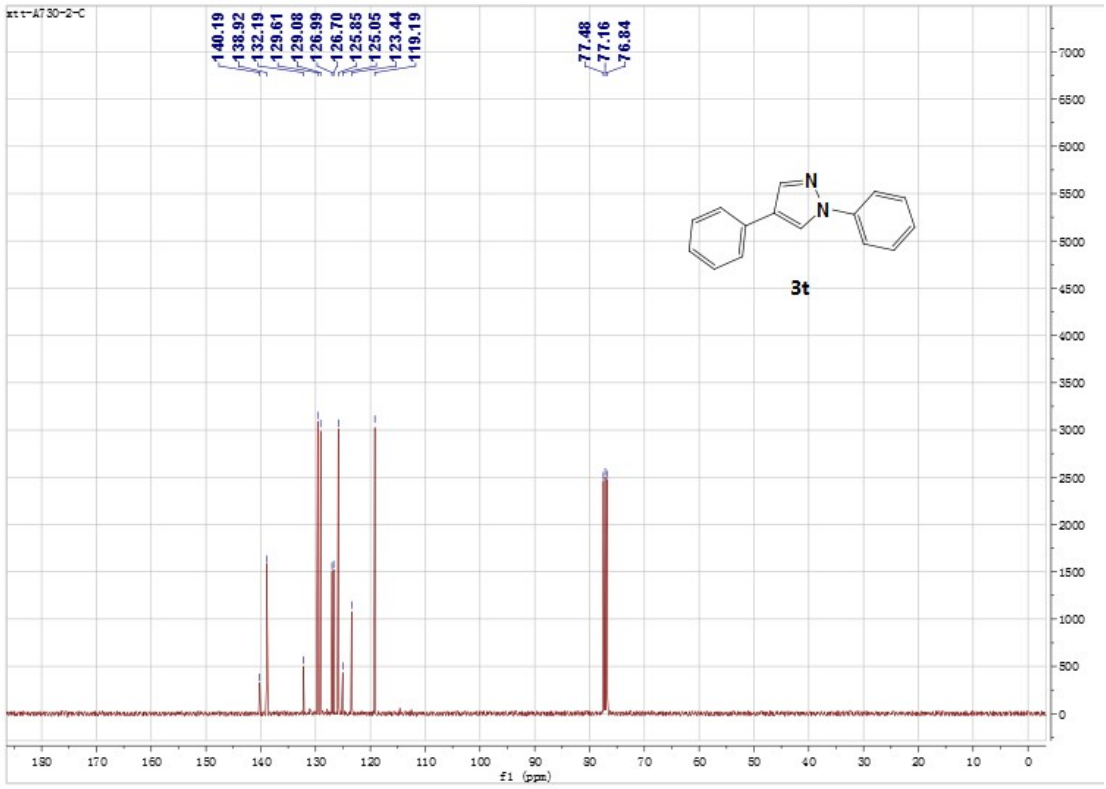

xtt-A683-H
7.35
7.30
7.28
7.26
6.94
6.91
3.86
3.83
2.37
1.67
1.26
0.00
1.00
2.02
2.02
3.04
3.05
3.00
3r


xtt-A683-C
158.23
145.61
128.78
128.67
126.27
120.94
114.17
77.48
77.16
76.84
55.44
38.77
13.15
3r


xtt-A677-PRO2-H
PROTON CDCl3 {D:\NMR_DATA}
7.48
7.40
7.39
7.37
7.36
7.35
7.34
7.26
3.98
1.61
1.26
0.00
1.00
5.11
3.05
3s


xtt-A677-PRO2-C
C13CPD CDCl3 {D:\NMR_DATA}
130.97
130.69
128.73
128.64
127.78
122.64
121.57
120.40
77.48
77.16
76.84
39.68
3s


8.15
7.99
7.74
7.72
7.56
7.54
7.48
7.46
7.44
7.41
7.39
7.38
7.31
7.30
7.28
7.27
7.25
7.24
3t
1.00
0.97
1.99
2.05
2.14
2.03
2.18
f1 (ppm)


140.19
138.92
132.19
129.61
129.08
126.99
126.70
125.85
125.05
123.44
119.19
77.48
77.16
76.84
3t
f1 (ppm)