Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information for

# $I_2$-promoted [4 + 2] Cycloaddition of in Situ Generated Azoalkenes with Enaminones: Facile and Efficient Synthesis of 1,4-Dihydropyridazines and Pyridazines

JiaJun Feng,[a] Tiantong He,[a] Yuxing Xie,[b] Yang Yu,[c] Jonathan B. Baell,[a,d] Fei Huang*,[a,b]

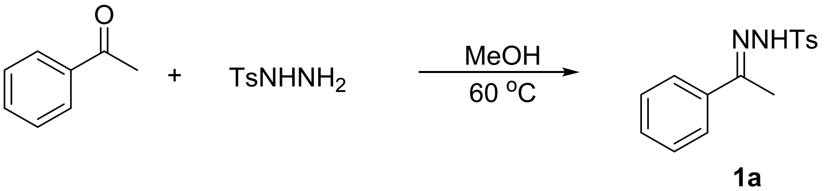
[a]School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing, 211816, P. R. China
[b]School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing, 210023, P. R. China
[c]School of Environmental Science and Engineering, Nanjing Tech University, Nanjing, 211816, P. R. China
[d]Medicinal Chemistry Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia
Email: huangfei0208@yeah.net

## Table of contents

## 1. General information

The solvents were dried and distilled prior to use by the literature methods. Analytical TLC plates, Sigma-Aldrich silica gel 60F200 were viewed by UV light (254 nm). Column chromatographic purifications were performed on SDZF silica gel 160. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker NMR spectrometer at 400 MHz and 100 MHz, respectively, and referenced internally based on the residual solvent signal. The data reporting for $^1$H NMR spectra is as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. The data reporting for $^{13}$C spectra is given as chemical shift (δ, ppm). High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using electrospray ionization-time of flight (ESI-TOF). Melting points were measured with a melting point instrument without correction. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated.

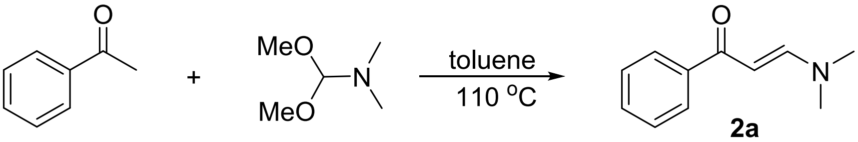
## 2. General procedure for the synthesis of *N*-sulfonylhydrazones (1)



**1a**

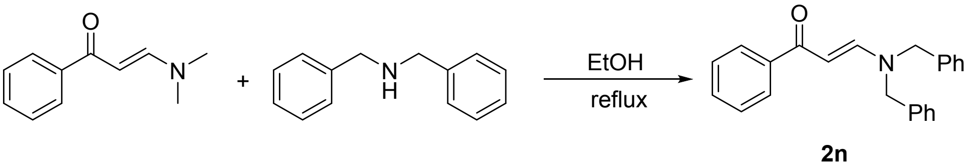
**A typical procedure for the synthesis of *N*-sulfonylhydrazones (1a-1u) –** ***Synthesis of 1a:*** A mixture of acetophenone compounds (5.0 mmol) and *p*-toluenesulfonhydrazide (5.0 mmol) in 7.5 mL of MeOH was stirred at 60 °C for 0.5-3 h to afford the *N*-tosylhydrazone **1a** as a white precipitate. After that, the precipitate was washed and filtered with petroleum ether twice and dried under a vacuum to provide the pure compound **1a** (white solid, 1.37 g, 95%).[1-4]

## 3. General procedure for the synthesis of enaminones (2)



**2a**

**A typical procedure for the synthesis of enaminones (2a-2m, 2o) –** ***Synthesis of 2a:*** To a stirred solution of acetophenone (5.0 mmol, 1.0 eq.) in toluene (5.0 mL), 1,1-dimethoxy-*N, N*-dimethylmethanamine (7.0 mmol, 1.4 eq.) was added and stirred at 110 °C. After completion of the reaction (monitored by TLC), it was quenched with water, extracted with ethyl acetate and dried with anhydrous $Na_2SO_4$. Then the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C)/EtOAc = 1:1, v/v) to give the desired product **2a** (yellow solid, 856 mg, 98%).[2,5]



**2n**

**Procedure for the synthesis of enaminones 2n***:* To a stirred solution of enaminones **2a** (2 mmol, 1.0 eq.) in EtOH (5 mL), dibenzylamine (8 mmol, 4.0 eq.) was added and then heated at reflux for 12h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and concentrated under reduced pressure to get the crude compound. The crude compound was purified by silica gel column chromatography (eluent: petroleum ether (60-90 °C)/EtOAc = 1:1, v/v) to give the desired product **2n** (yellow solid, 345 mg, 53%).[6]

## 4. Supplementary Reference

(1) S. P. Hu, S. Y. Du, Z. G. Yang, L. F. Ni and Z. K. Chen, *Adv. Synth. Catal.* 2019, **361**, 3124.

(2) M. Y. Ni, J. G. Zhang, X. Y. Liang, Y. J. Jiang and T. P. Loh, *Chem. Commun.* 2017, **53**, 12286.

(3) Z. Chen, Q. Yan, Z. Liu, Y. Xu and Y. Zhang, *Angew. Chem., Int. Ed.* 2013, **52**, 13324.

(4) X. L. Yang, X. X. Peng, F. Chen and B. Han. *Org. Lett.* 2016, **18**, 2070.

(5) C. Song, C. Yang, H. Zeng, W. Zhang, S. Guo and J. Zhu, *Org. Lett.* 2018, **20**, 3819.

(6) Y. Gao, Y. Liu, L. Wei, and J. Wan, *Res. Chem. Intermed.* 2017, **43**, 5547.

## 5. X-Ray crystallographic studies

Single crystals for the X–ray diffraction studies for compounds **3e** was carried out on a SMART APEX diffractometer with graphite-monochromated Mo radiation ($\lambda$ = 0.71073 Å). Cell parameters were obtained by global refinement of the positions of all collected reflections. Intensities were corrected for Lorentz and polarization effects and empirical absorption. The structures were solved by direct methods and refined by full-matrix least squares on $F^2$. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in calculated positions. Structure solution and refinement were performed by using the SHELXL-97 package. The X-ray crystallographic files, in CIF format, are available from the Cambridge Crystallographic Data Centre on quoting the deposition numbers CCDC 2014085 for **3e**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www. ccdc.cam.ac.uk).

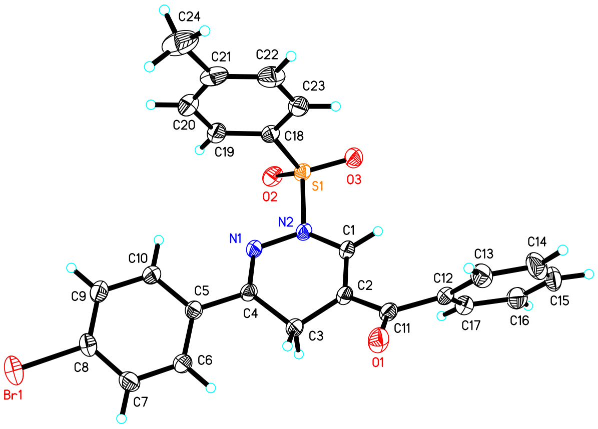


**Figure 1.** Molecular structure of compound **3e**.

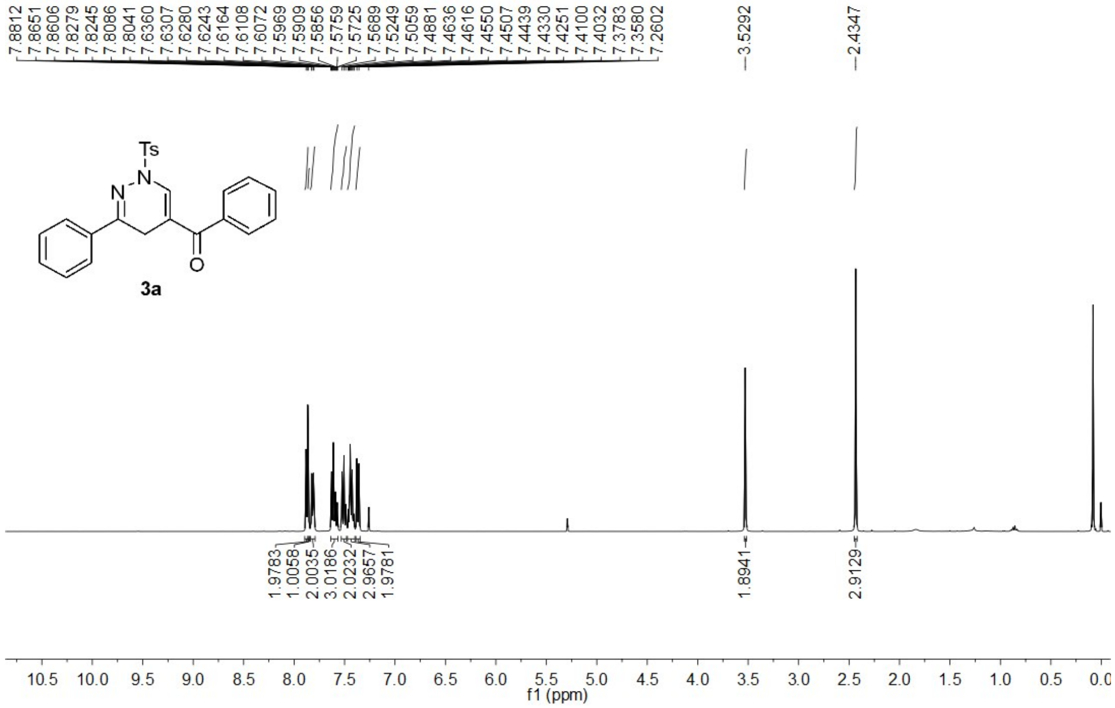
**Table S1.** Crystal data and structure refinement for **3e**.

| | | |
|---|---|---|
| Empirical formula | $C_{24}H_{19}BrN_2O_3S$ | |
| Formula weight | 495.38 | |
| Temperature | 293(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system, space group | Triclinic, P-1 | |
| Unit cell dimensions | a = 8.1722(4) Å | □ a= 80.9050(10)° |

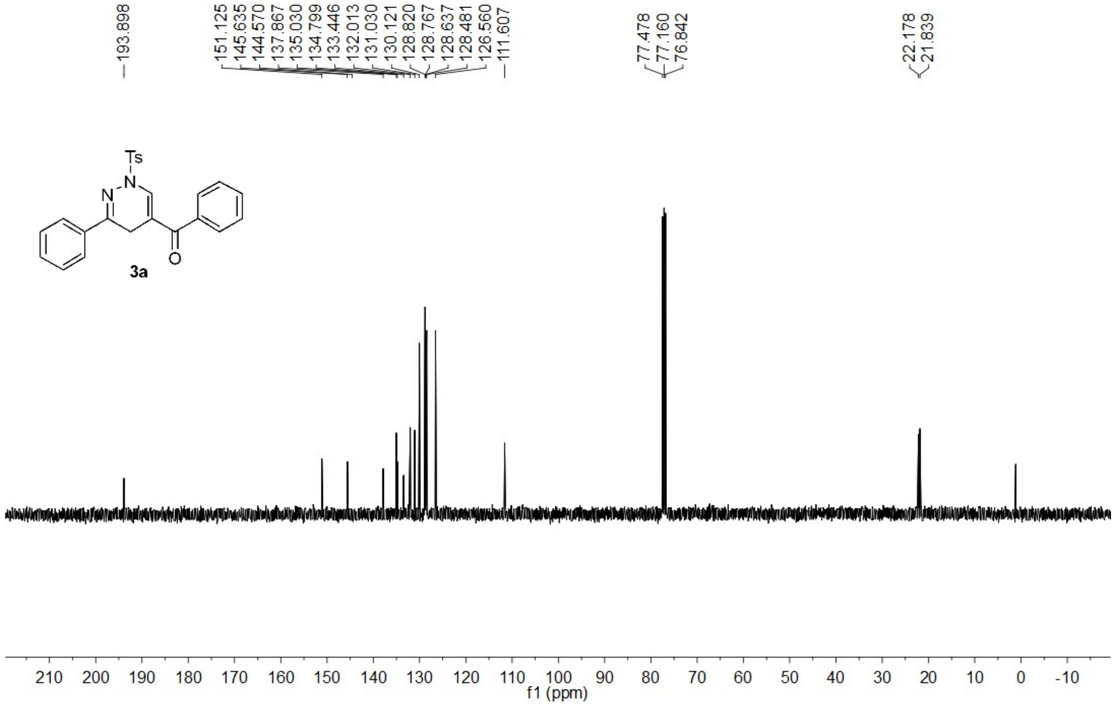
|  |  |  |
|---|---|---|
|  | b = 10.5252(5) Å | b= 79.4010(10)° |
|  | c = 13.3654(6) Å | g = 76.2740(10)° |
| Volume | 1089.82(9) Å$^3$ |  |
| Z, Calculated density | 2, 1.510 Mg/m$^3$ |  |
| Absorption coefficient | 2.011 mm$^{-1}$ |  |
| F(000) | 504 |  |
| Crystal size | 0.170 x 0.140 x 0.120 mm$^3$ |  |
| Theta range for data collection | 2.390 to 25.999° |  |
| Index ranges | -10<=h<=10, -12<=k<=12, -16<=l<=16 |  |
| Reflections collected | 27113 |  |
| Independent reflections | 4245 [R(int) = 0.0458] |  |
| Completeness to theta = 25.242 | 99.2 % |  |
| Absorption correction | Semi-empirical from equivalents |  |
| Max. and min. transmission | 0.7456 and 0.4312 |  |
| Refinement method | Full-matrix least-squares on F$^2$ |  |
| Data/restraints/parameters | 4245 / 0 / 282 |  |
| Goodness-of-fit on F$^2$ | 1.018 |  |
| Final R indices [I > 2 sigma(I)] | R1 = 0.0300, wR2 = 0.0784 |  |
| R indices (all data) | R1 = 0.0352, wR2 = 0.0819 |  |
| Extinction coefficient | 0.062(4) |  |
| Largest diff. peak and hole | 0.241 and -0.242 e.Å$^{-3}$ |  |

## 6. Copies of NMR spectra for compounds

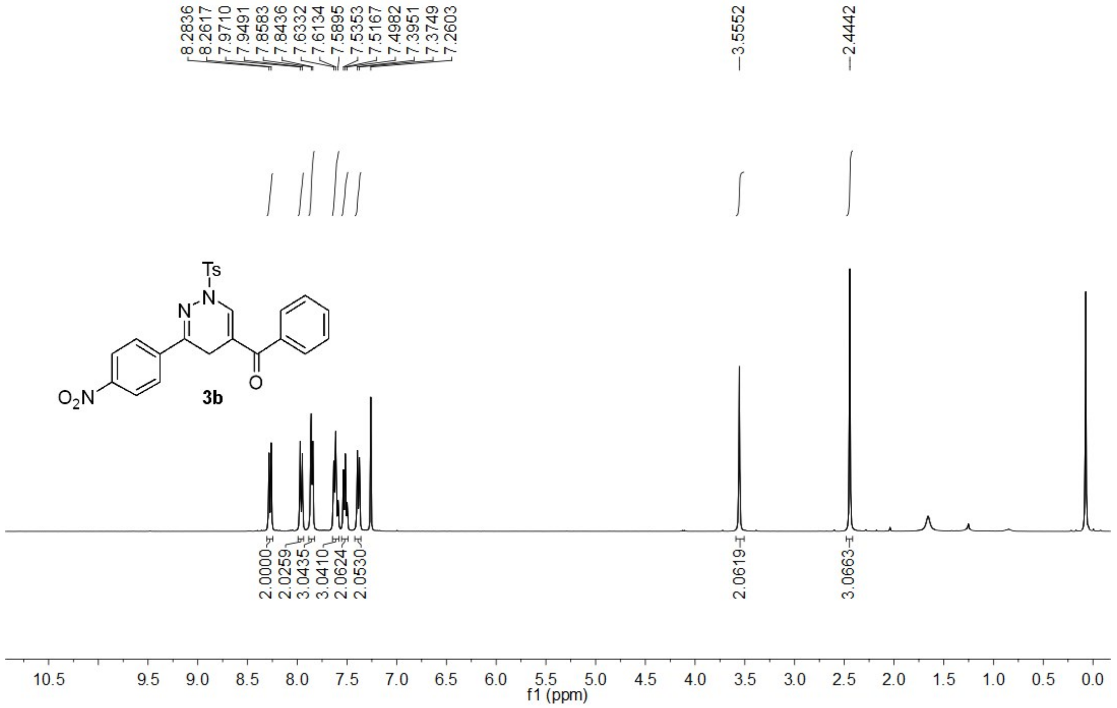
FJJ-151P



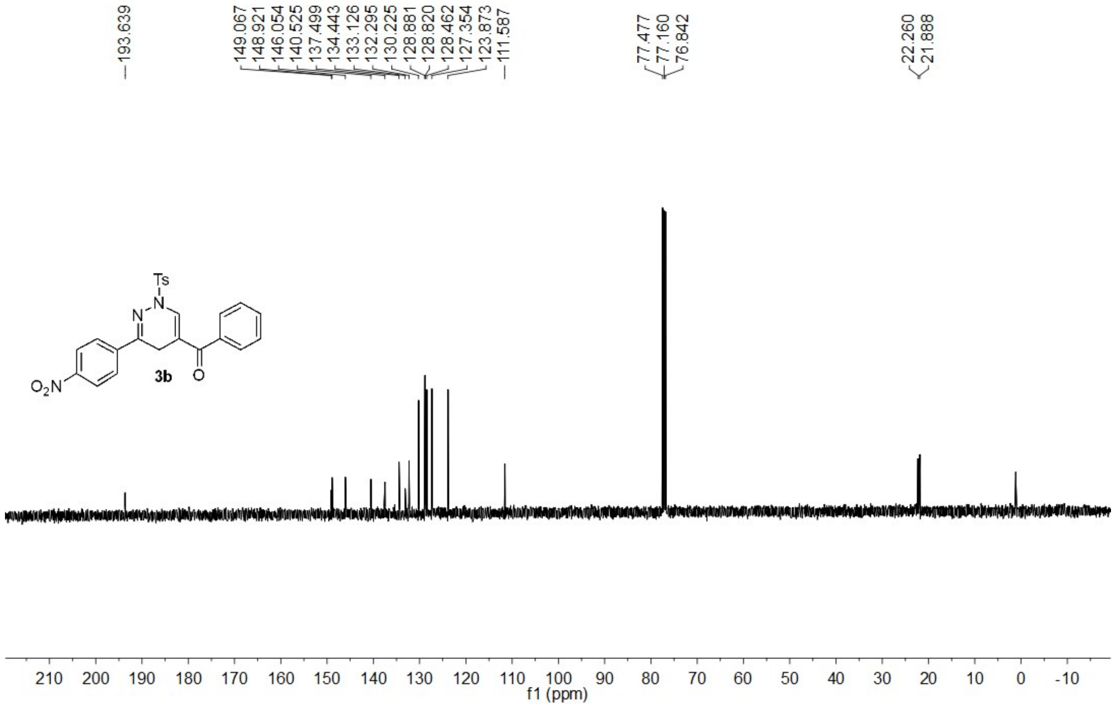
FJJ-151PC



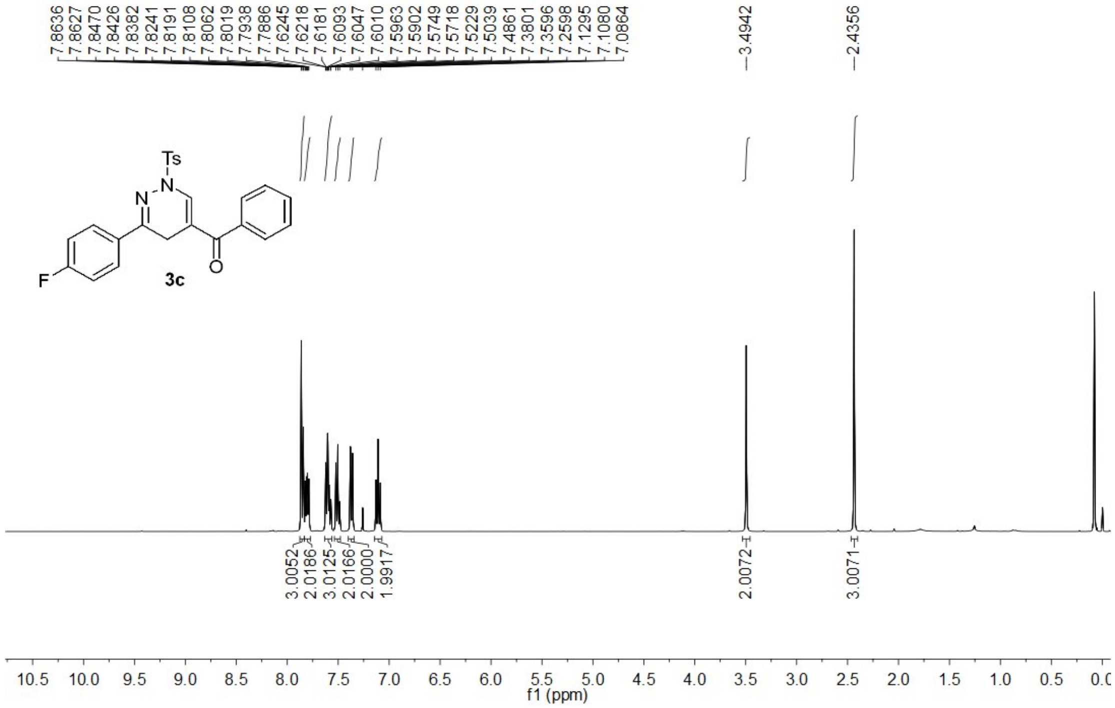
FJJ-254-H



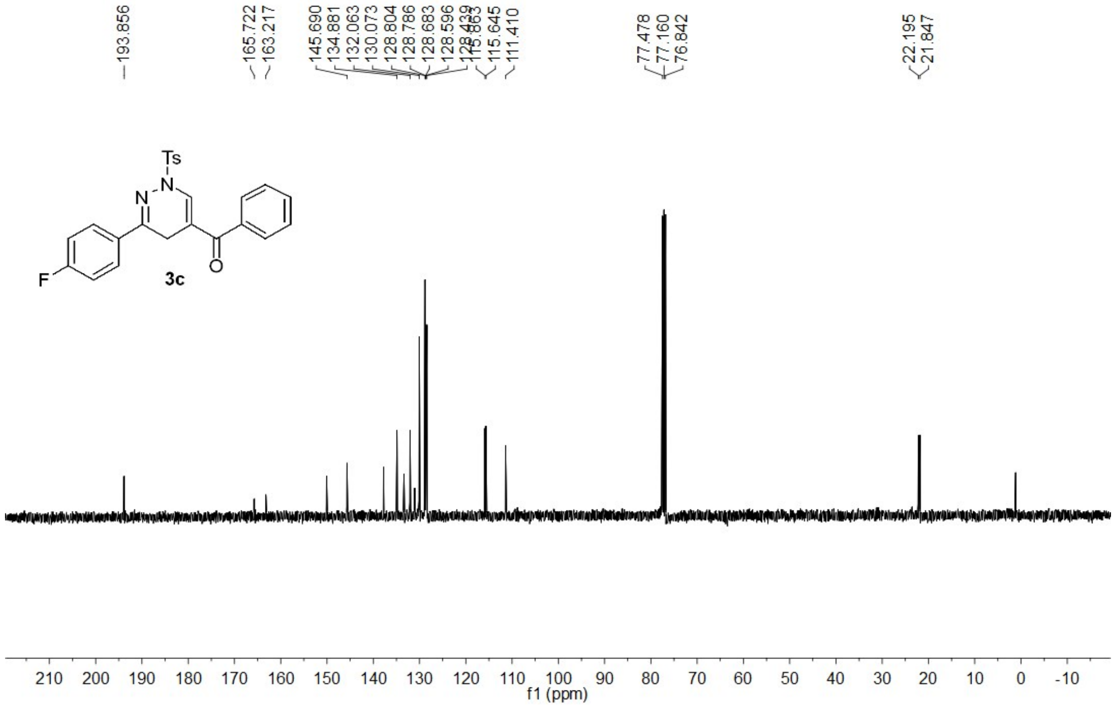
FJJ-R254



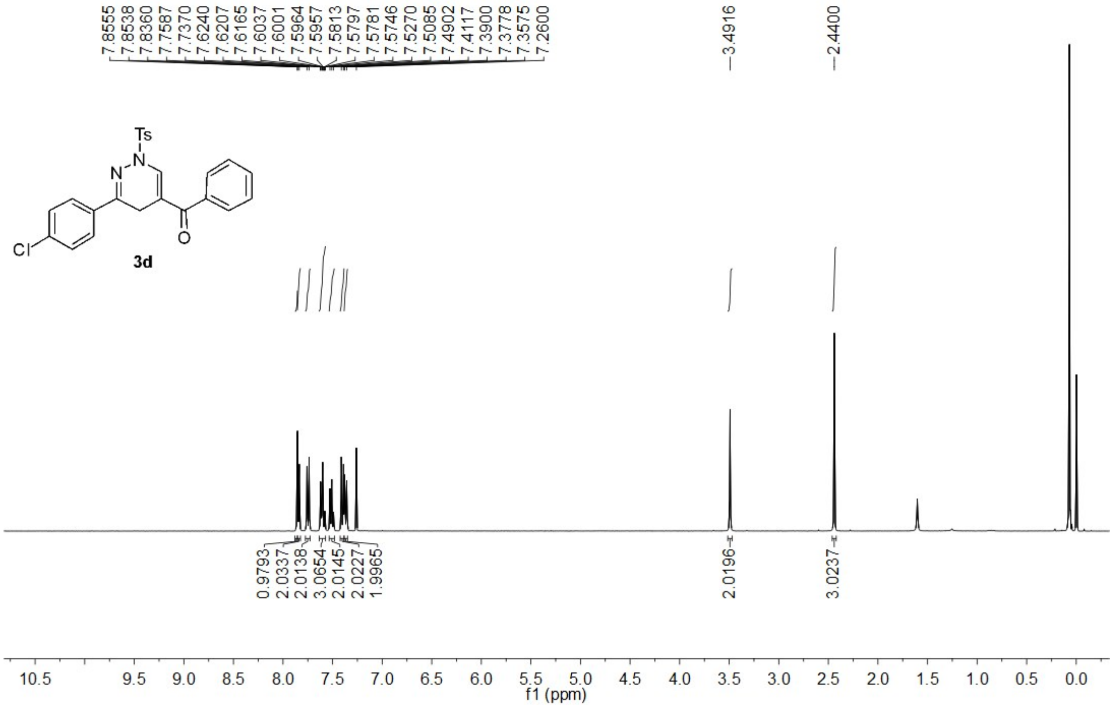
FJJ-R250



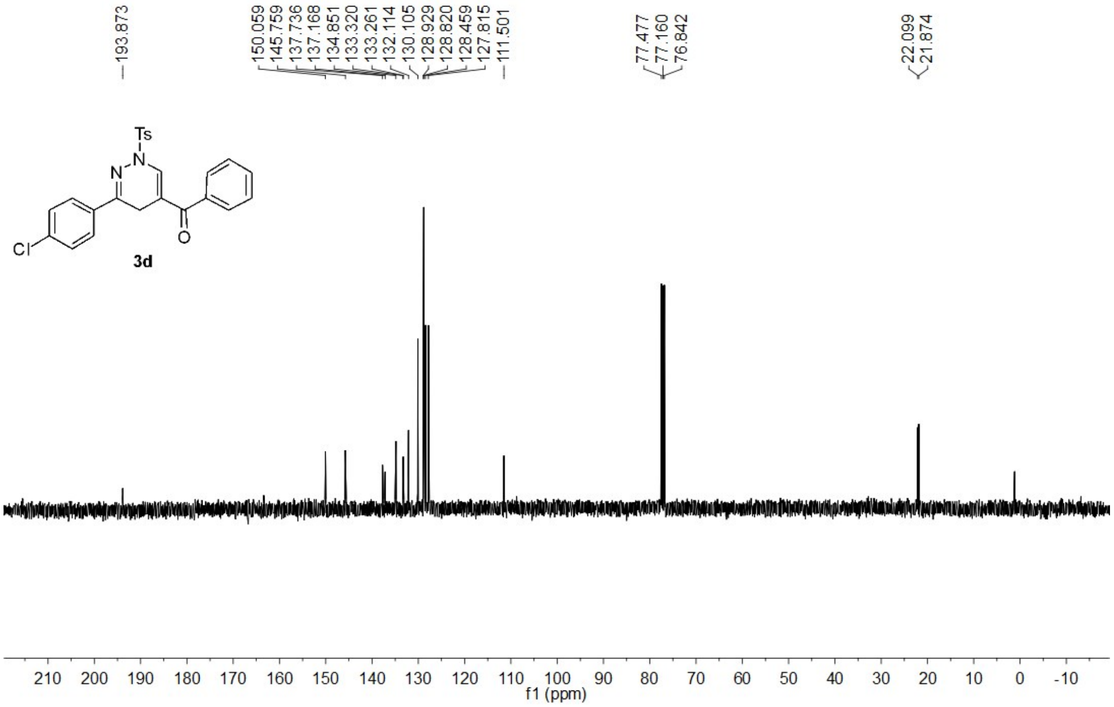
FJJ-R250



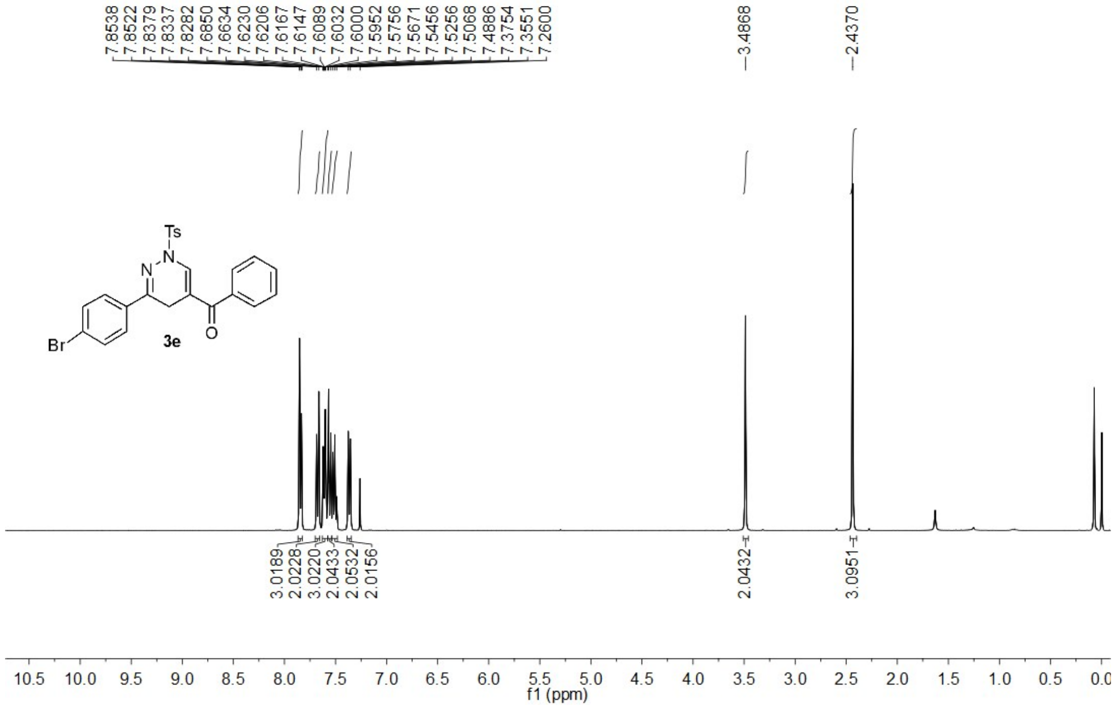
FJJ-R249



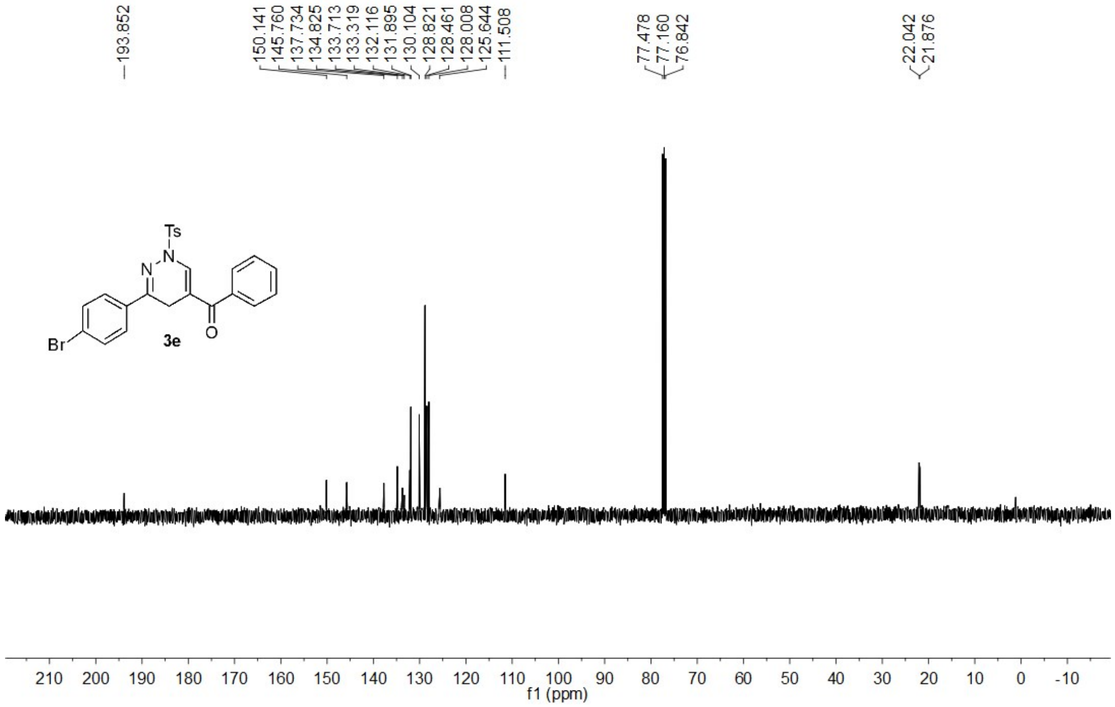
FJJ-R249-13C



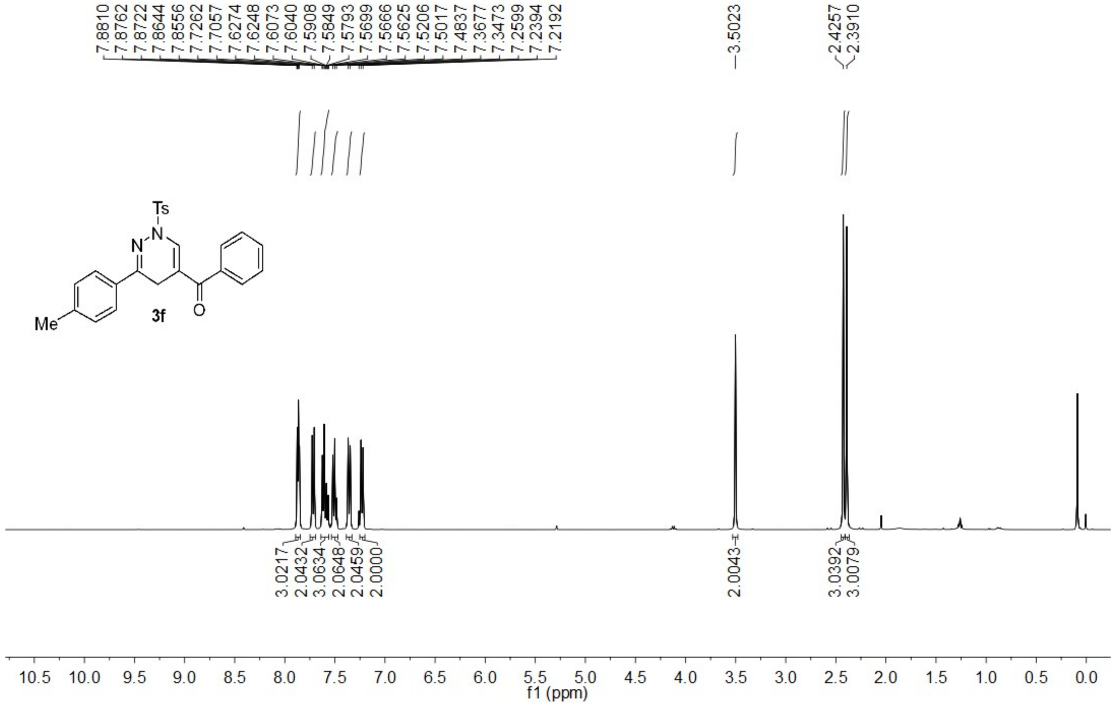
FJJ-R248



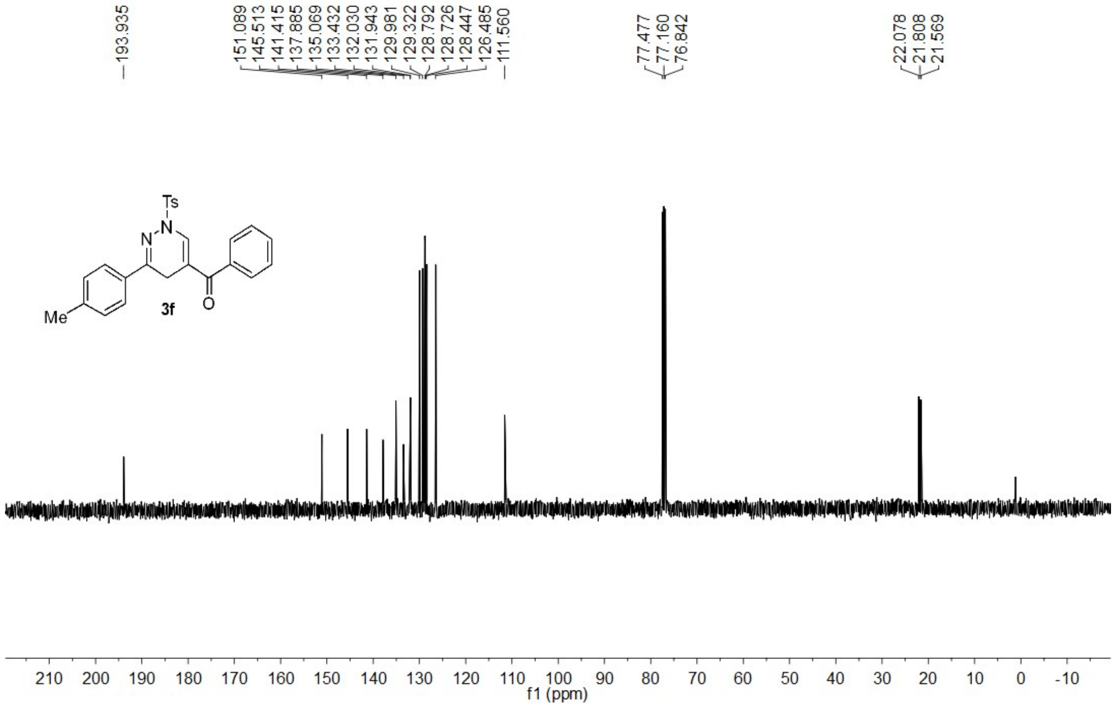
FJJ-R248



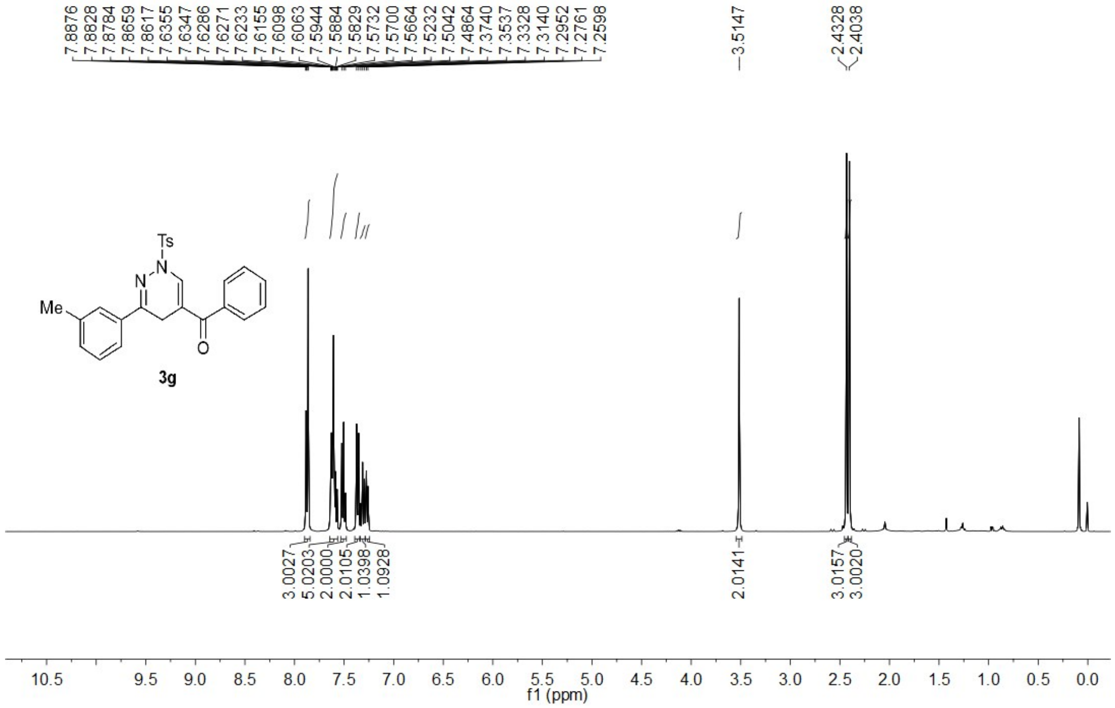
FJJ-R260
hq-4-114



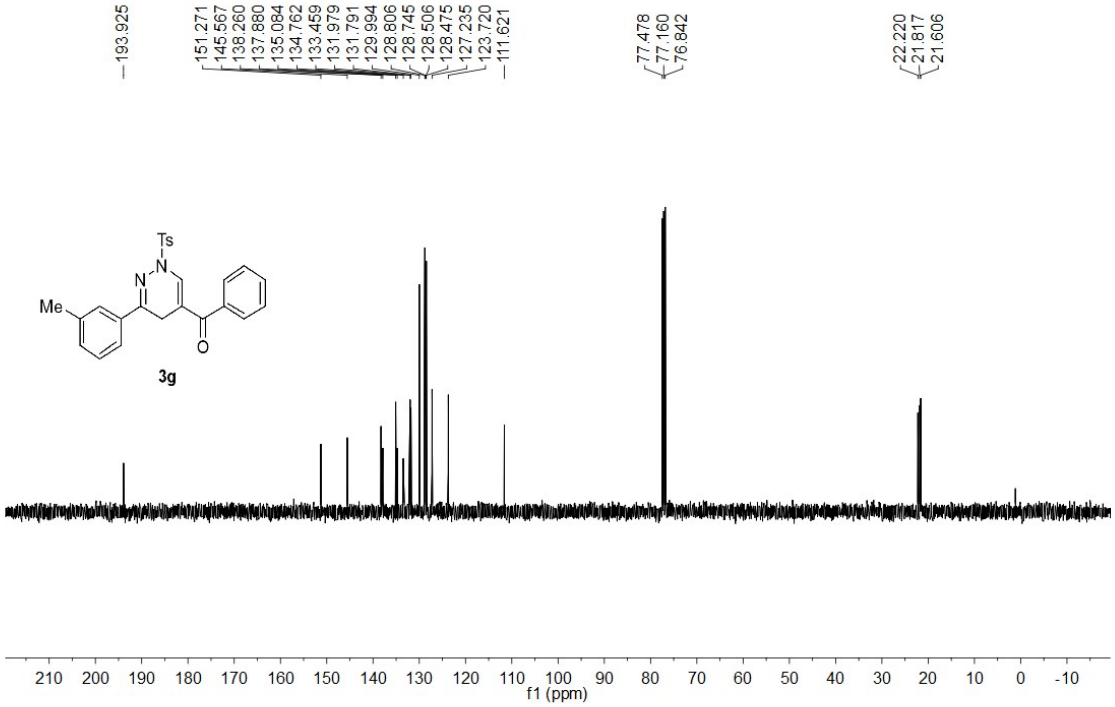
FJJ-R260-CC
hq-4-114



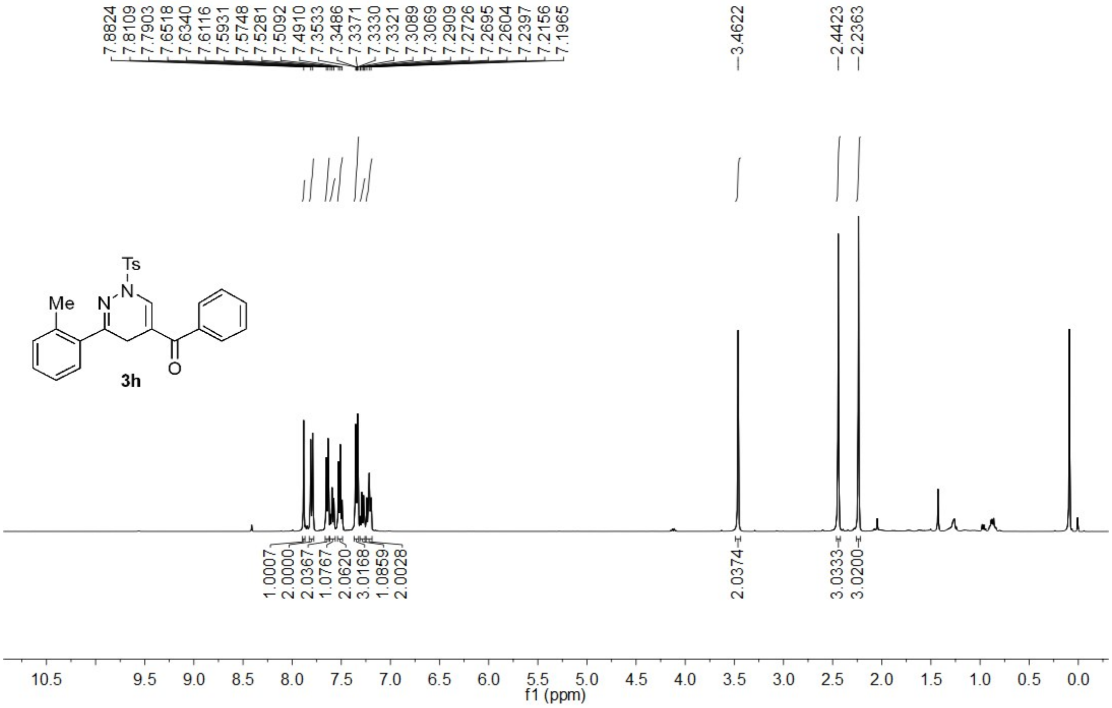
FJJ-R263



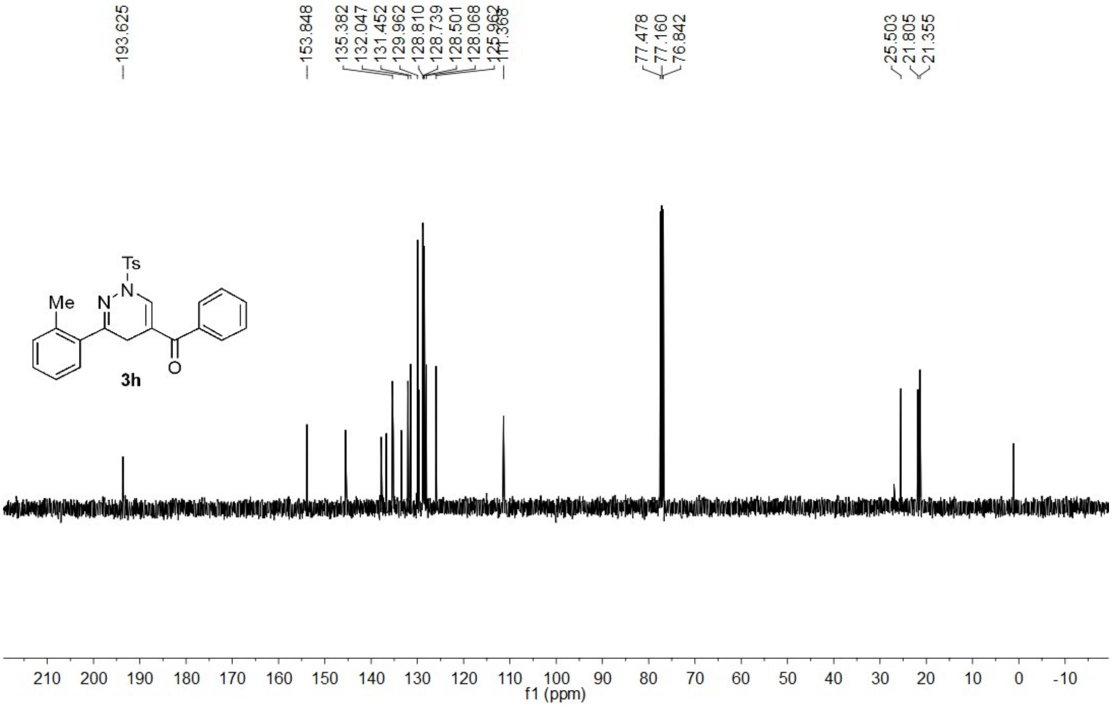
FJJ-R263



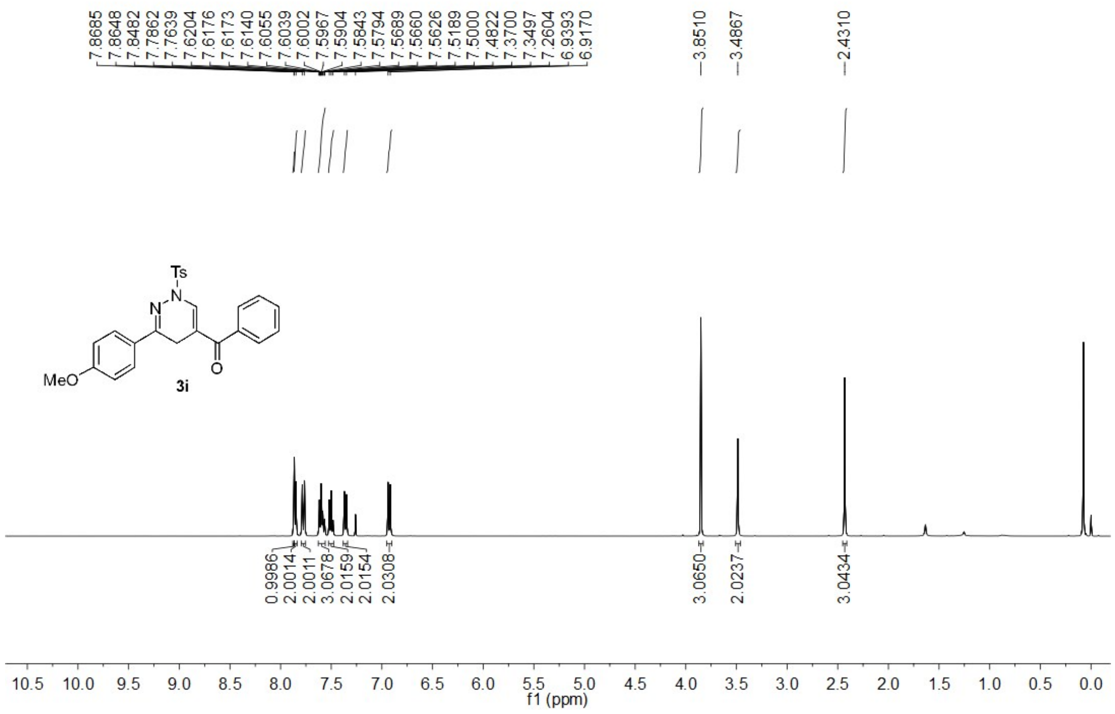
FJJ-R251



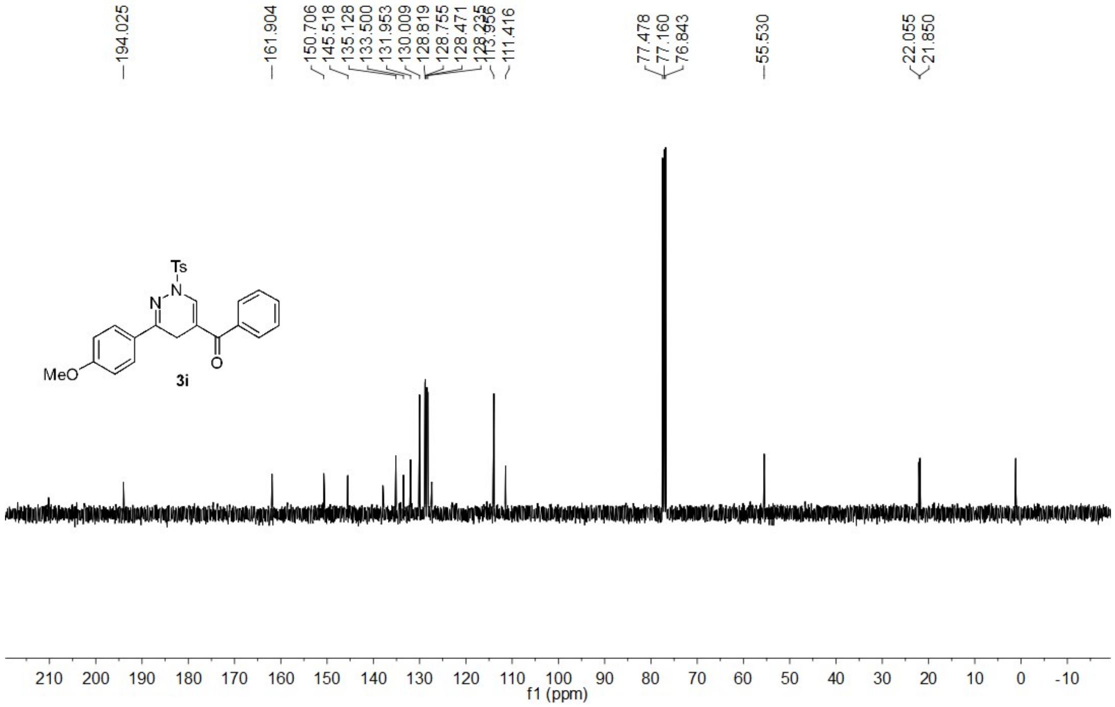
FJJ-R251

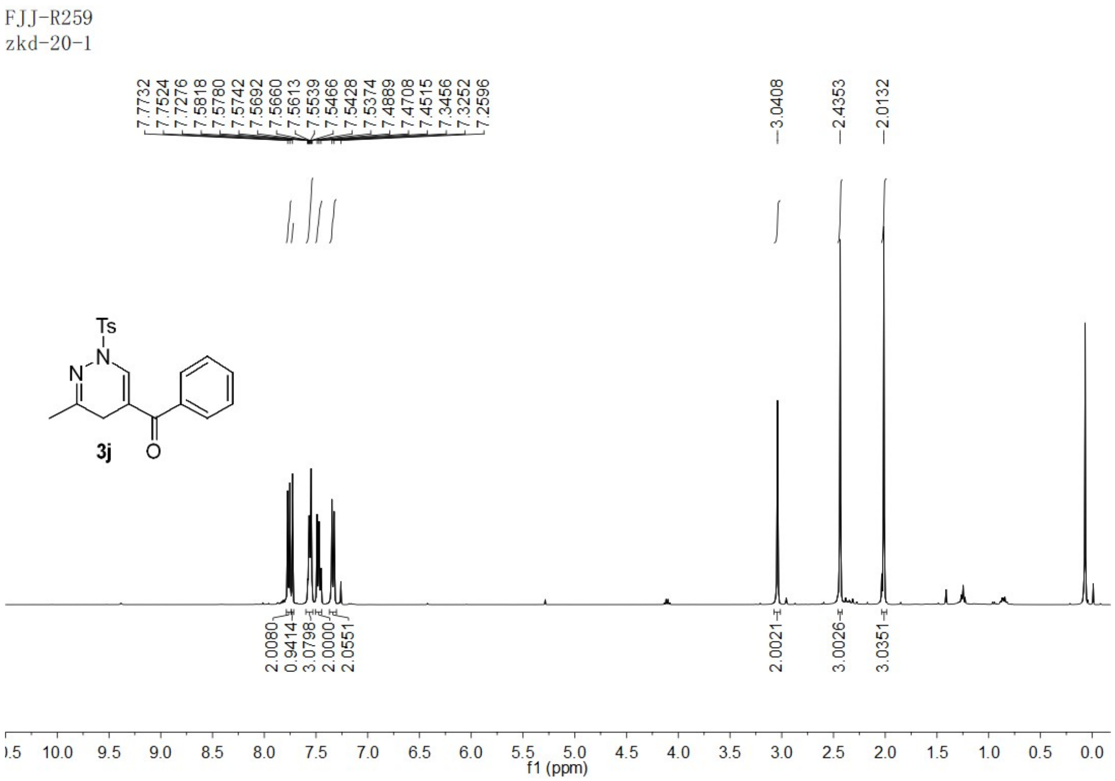


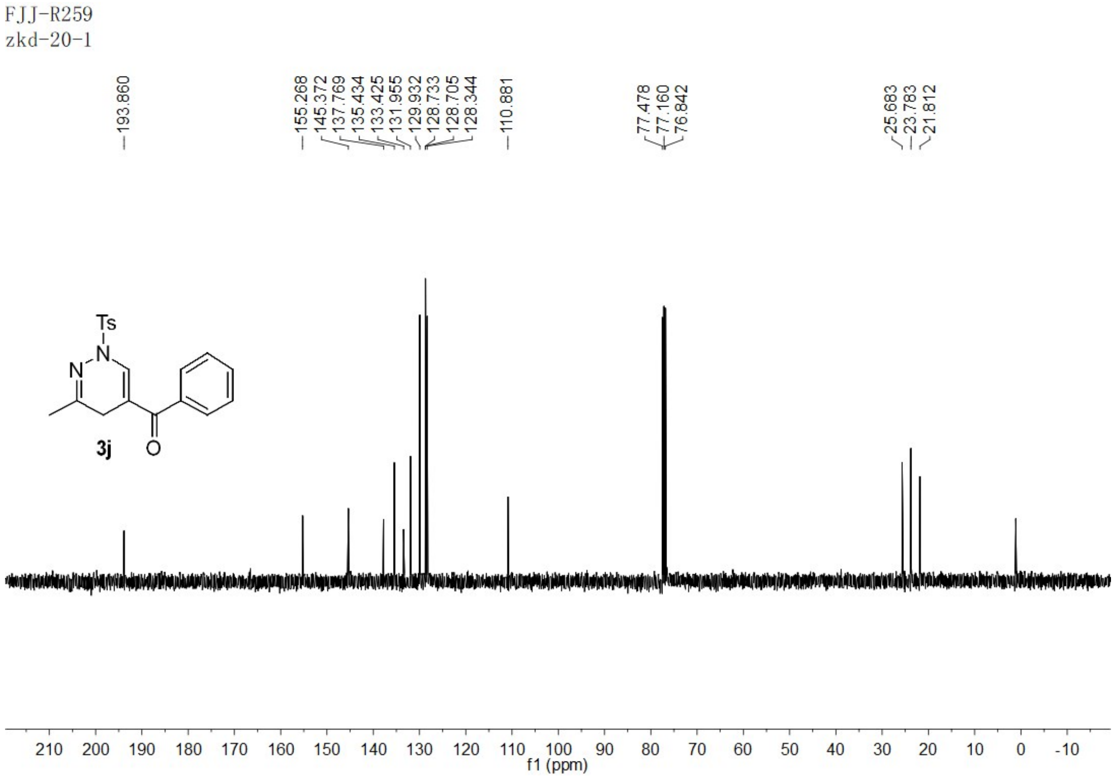
FJJ-R252



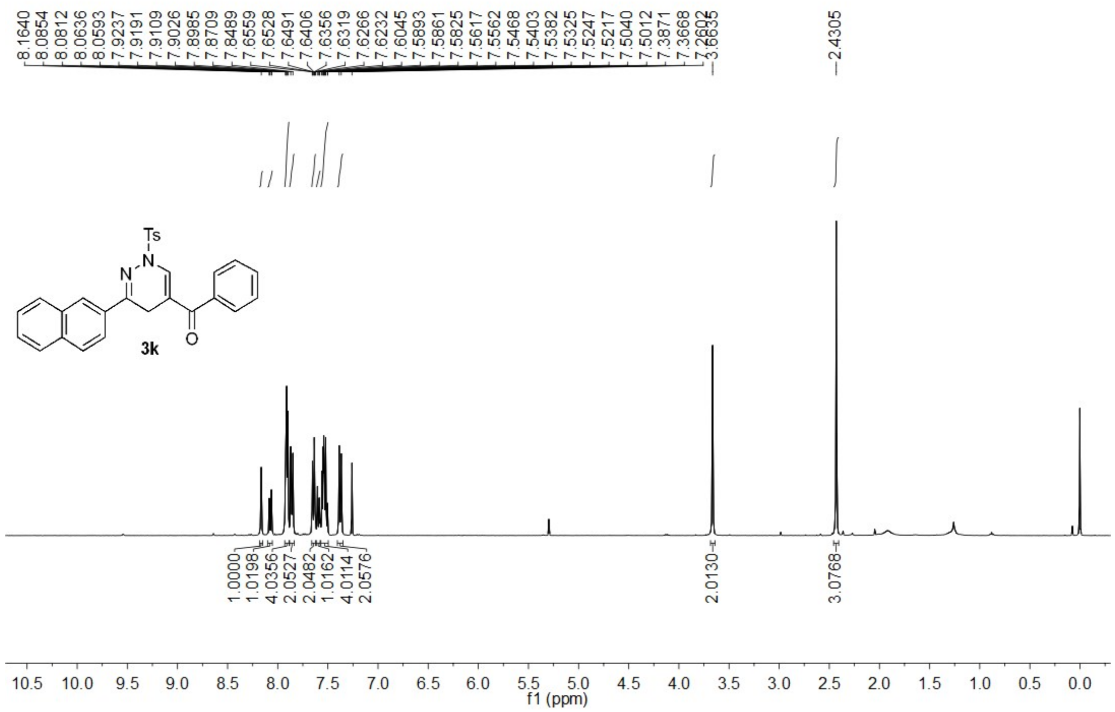
FJJ-R252-C



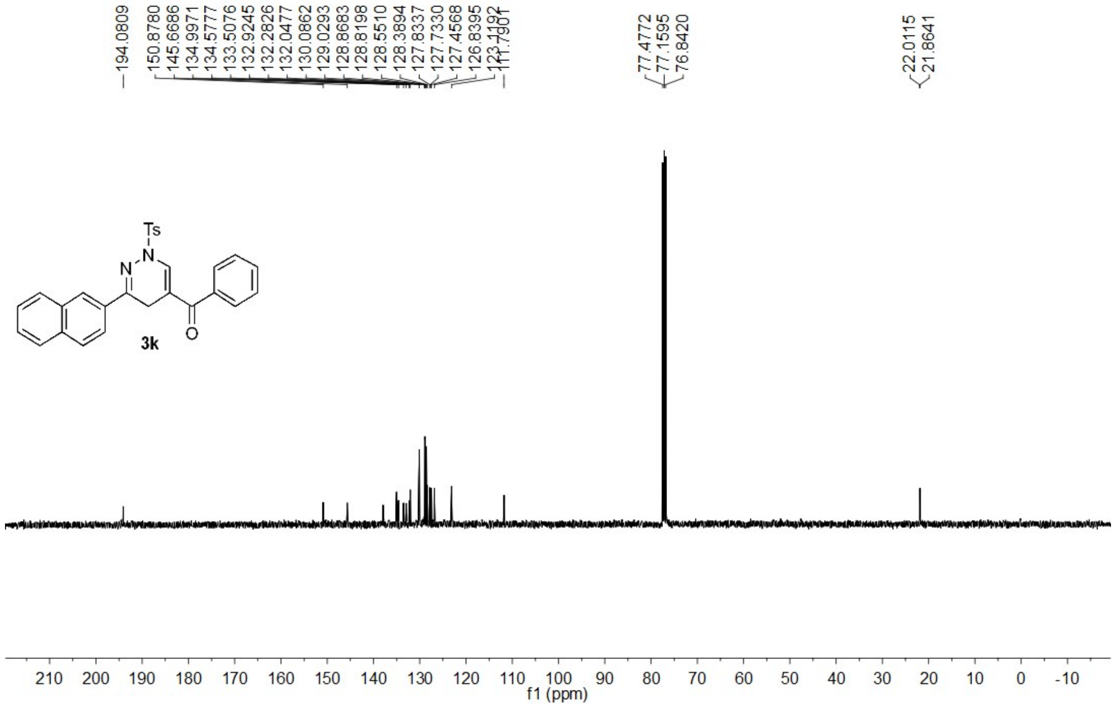

FJJ-R259
zkd-20-1
7.7732
7.7524
7.7276
7.5818
7.5780
7.5742
7.5692
7.5660
7.5613
7.5539
7.5466
7.5428
7.5374
7.4889
7.4708
7.4515
7.3456
7.3252
7.2596
3.0408
2.4353
2.0132
Ts
N
N
3j
O
2.0080
0.9414
3.0798
2.0000
2.0551
2.0021
3.0026
3.0351
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


FJJ-R259
zkd-20-1
193.860
155.268
145.372
137.769
135.434
133.425
131.955
129.932
128.733
128.705
128.344
110.881
77.478
77.160
76.842
25.683
23.783
21.812
Ts
N
N
3j
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

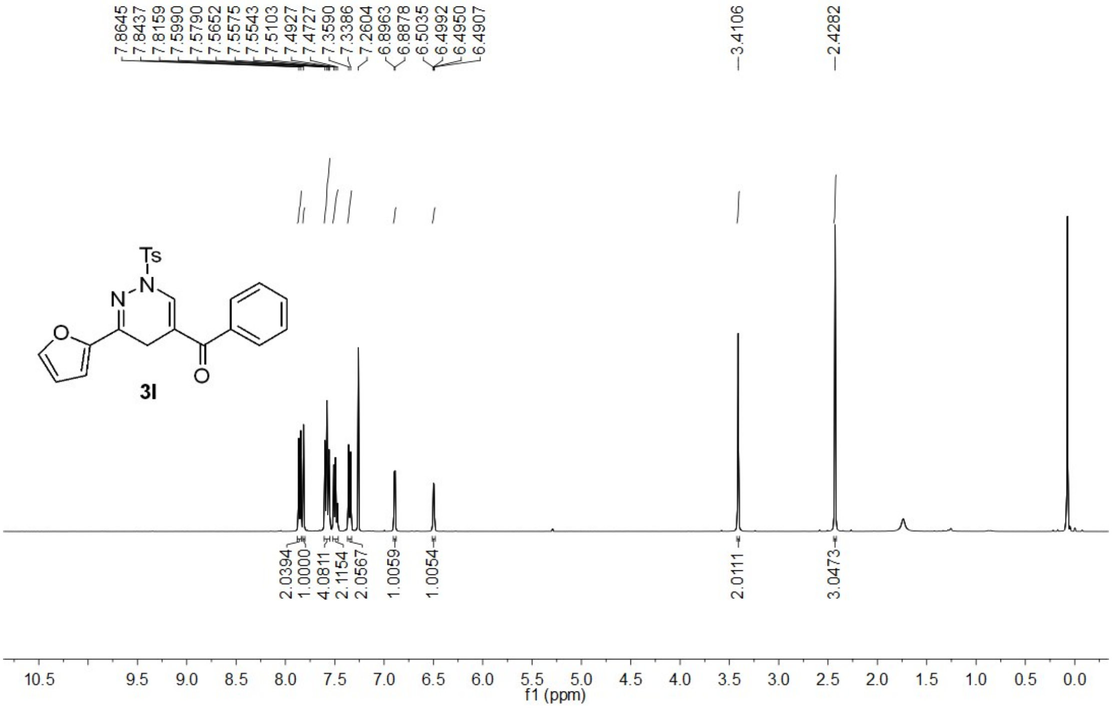
FJJ-R257-2



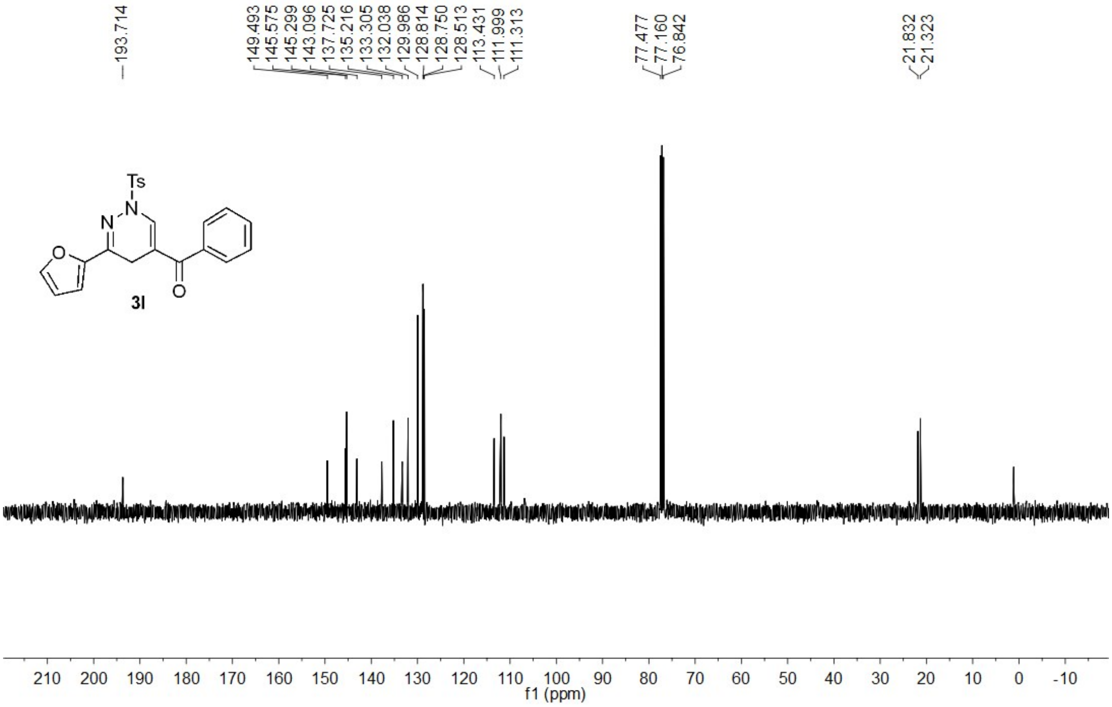
FJJ-R257-2



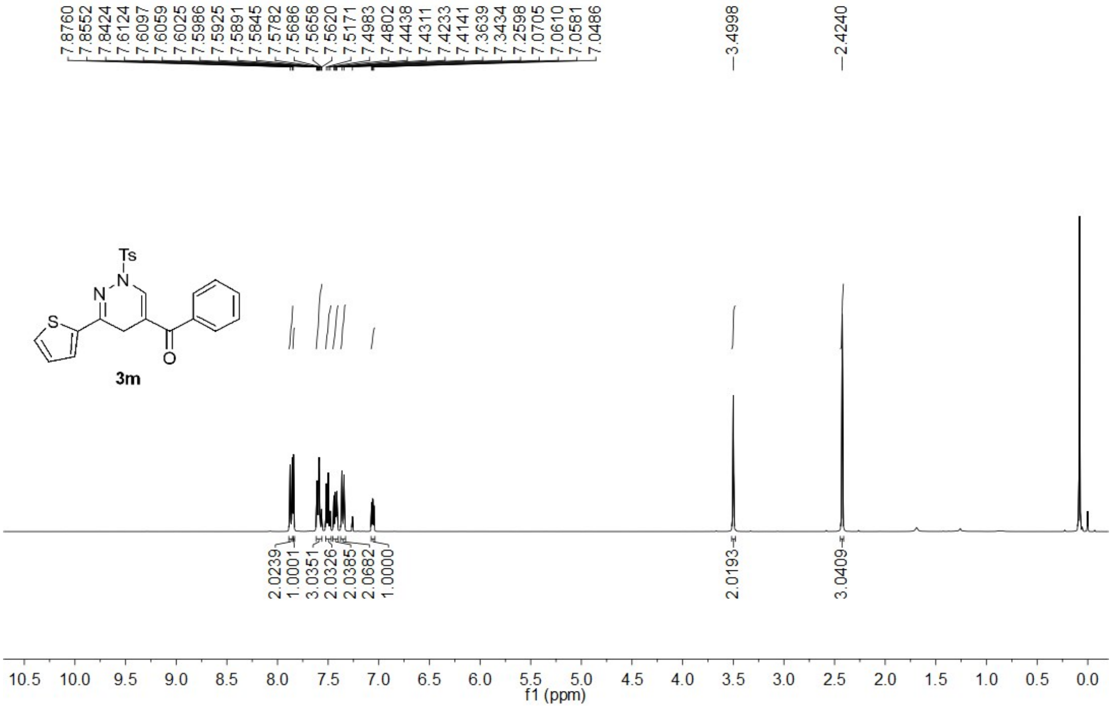
FJJ-258-H



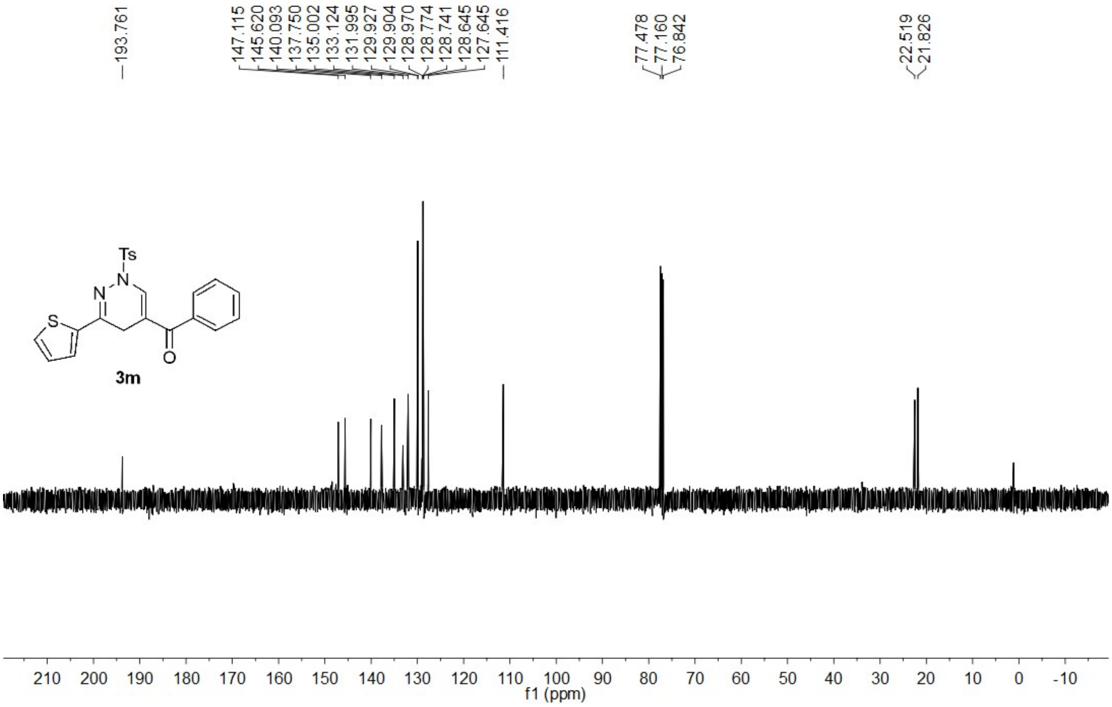
FJJ-R258



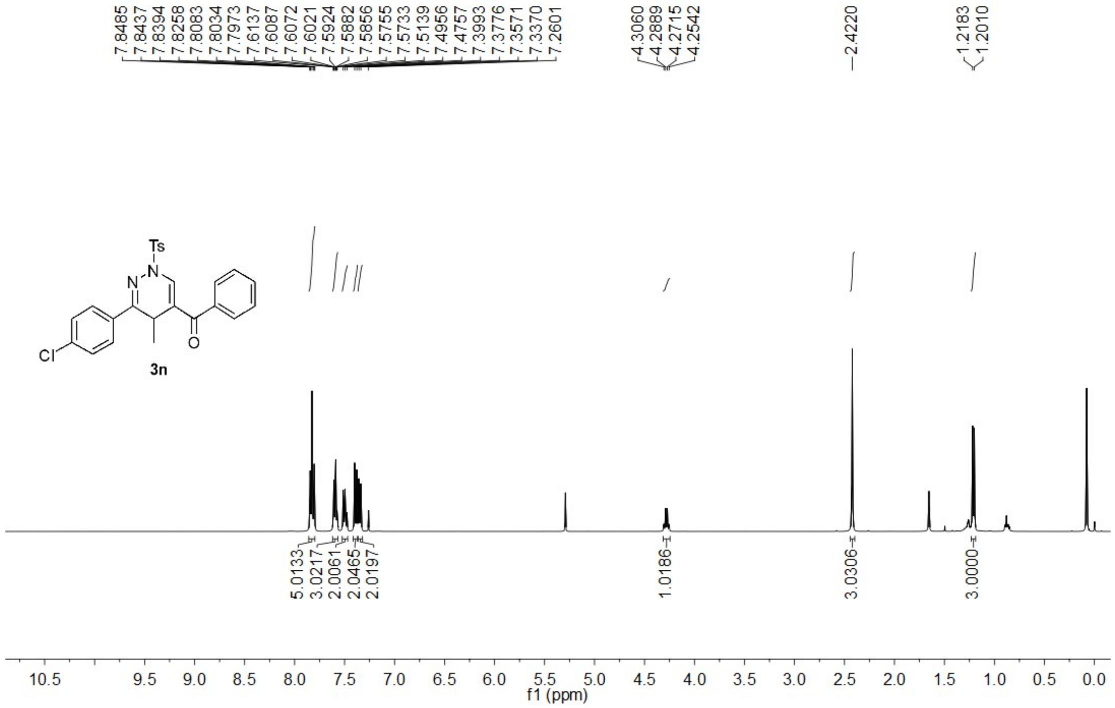
FJJ-R261-H



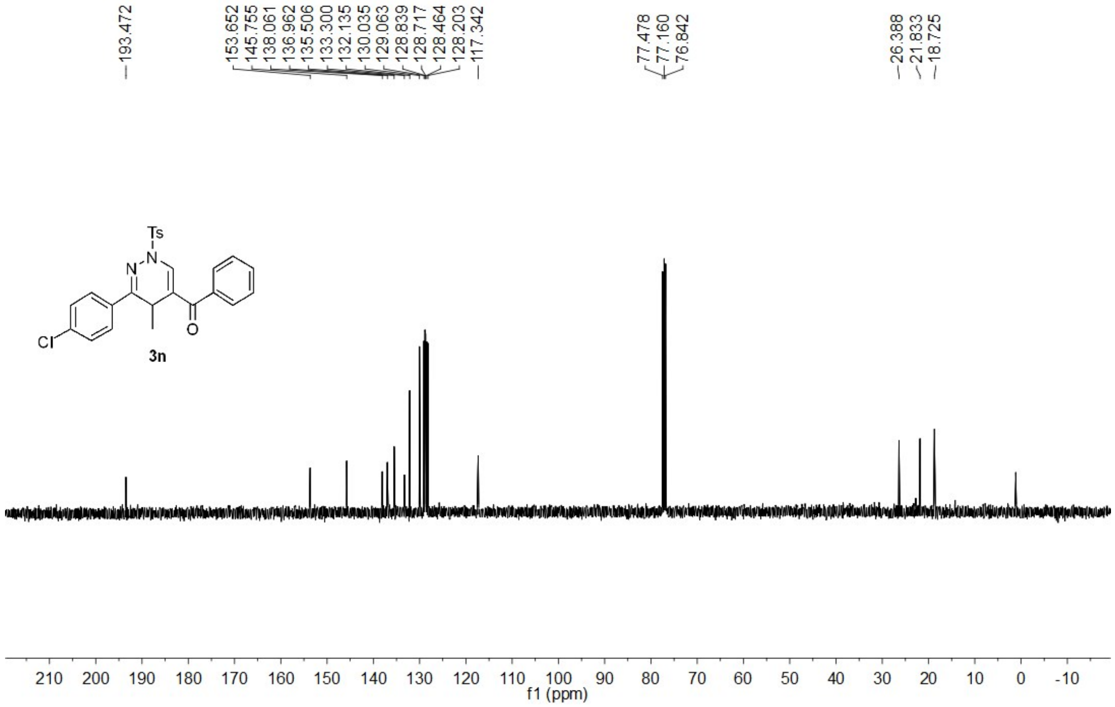
FJJ-R261-2



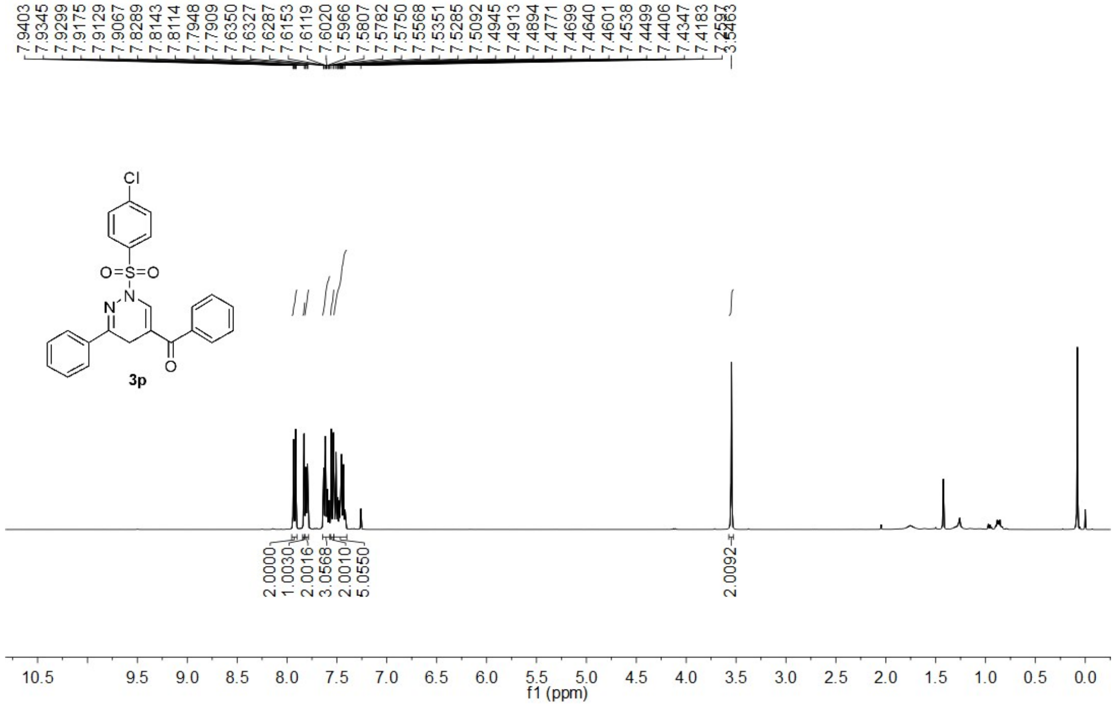
FJJ-R283



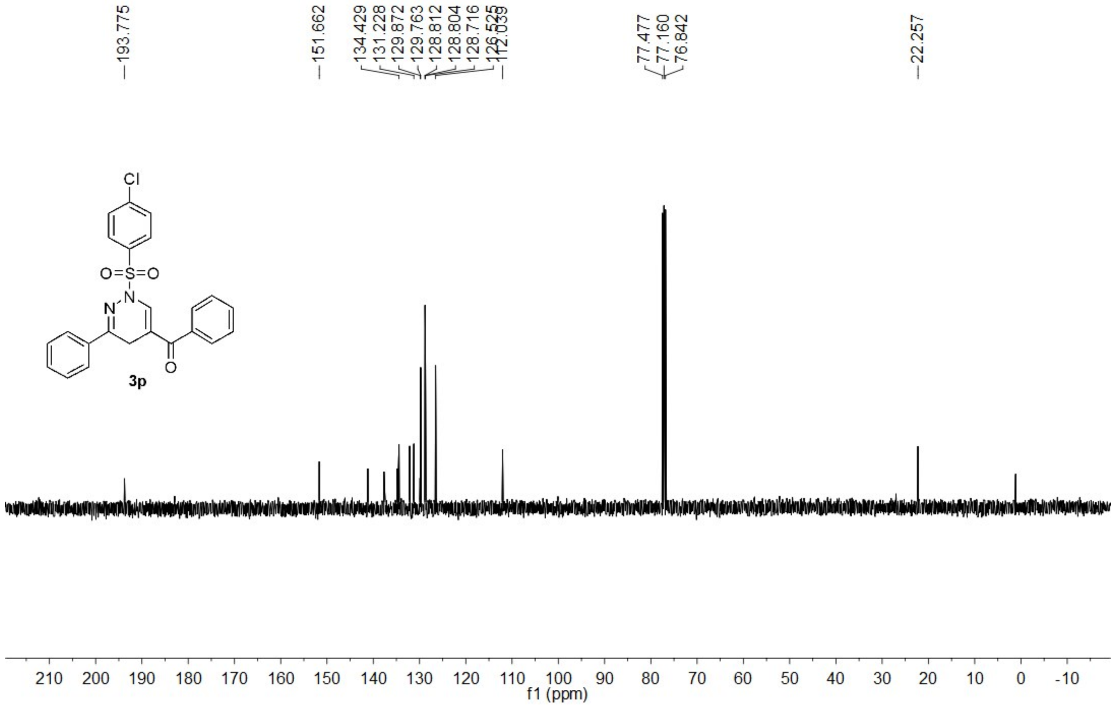
FJJ-R283



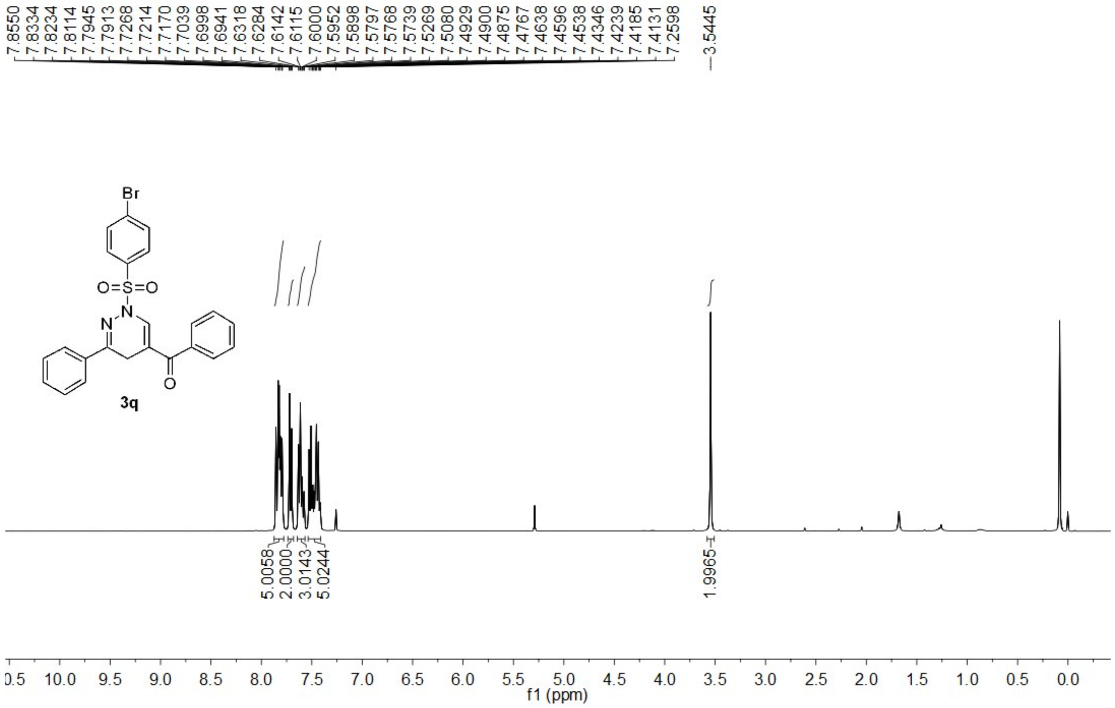
FJJ-R256



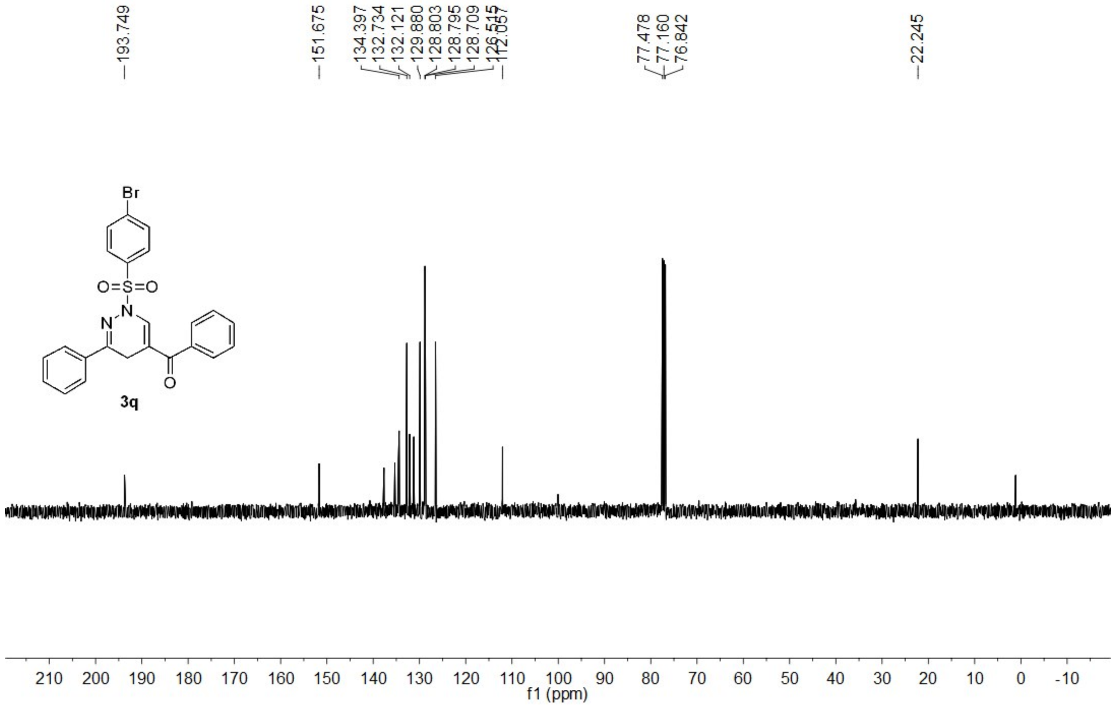
FJJ-R256



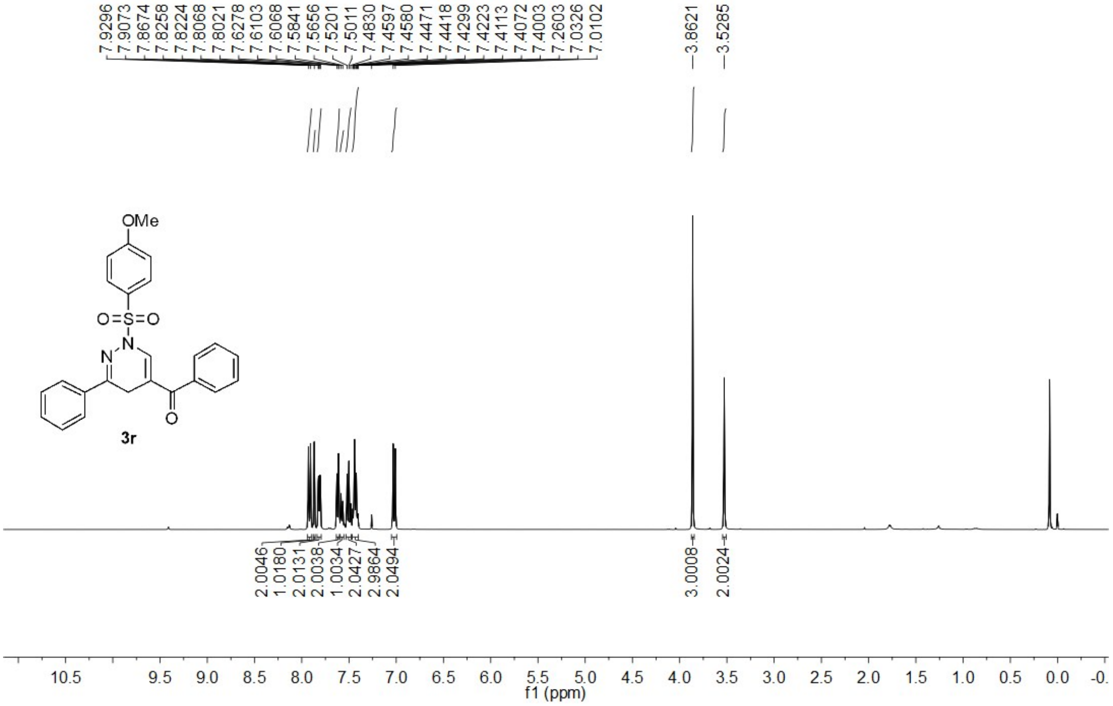
FJJ-R255



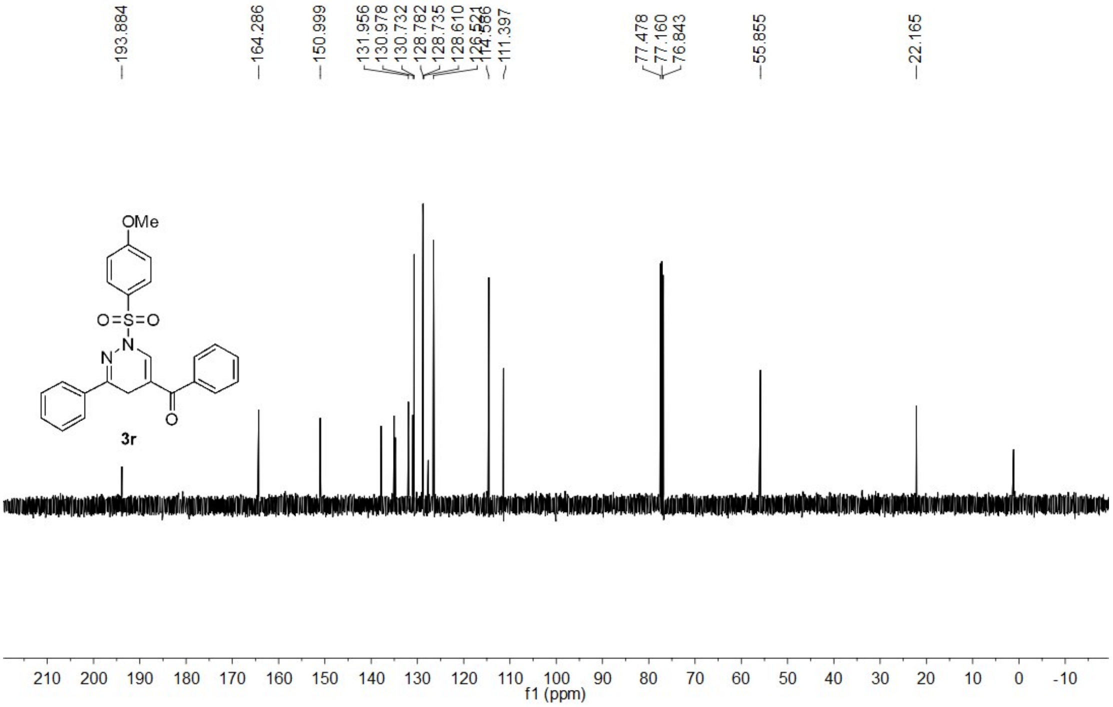
FJJ-R255



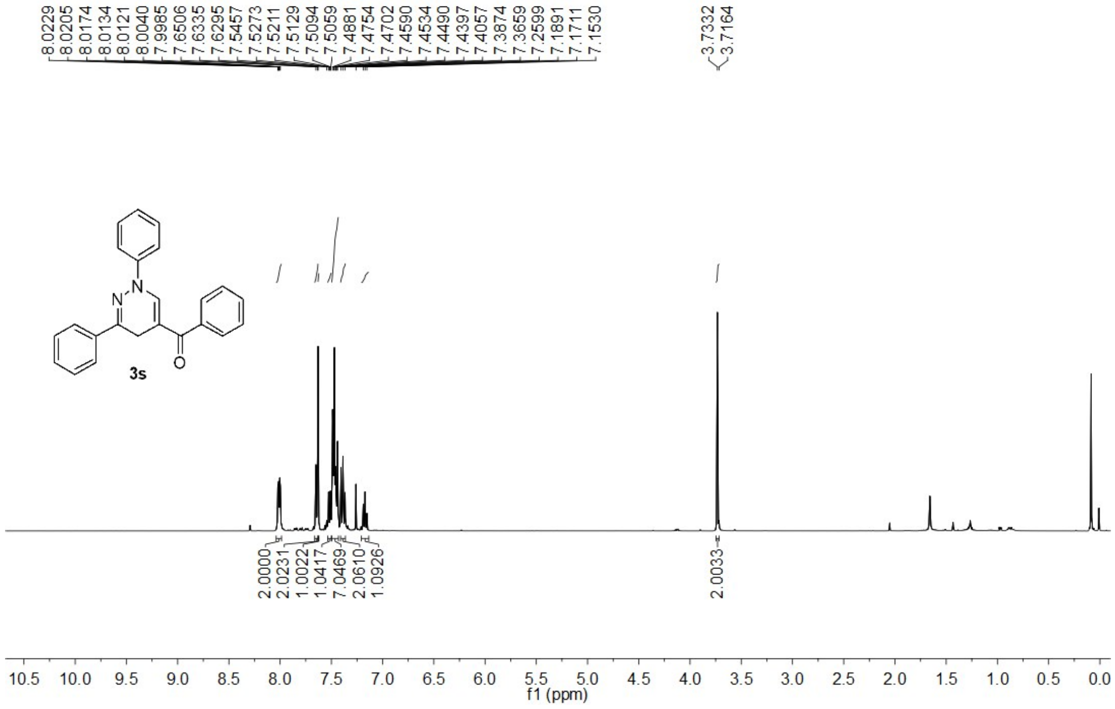
FJJ-R262



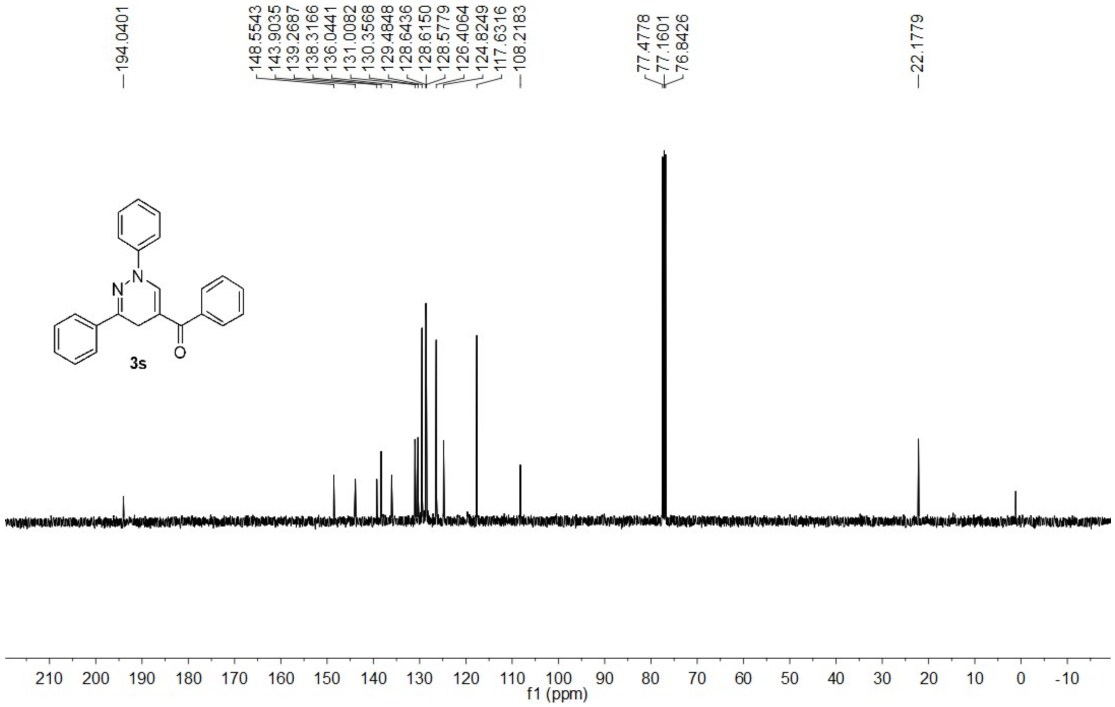
FJJ-R262



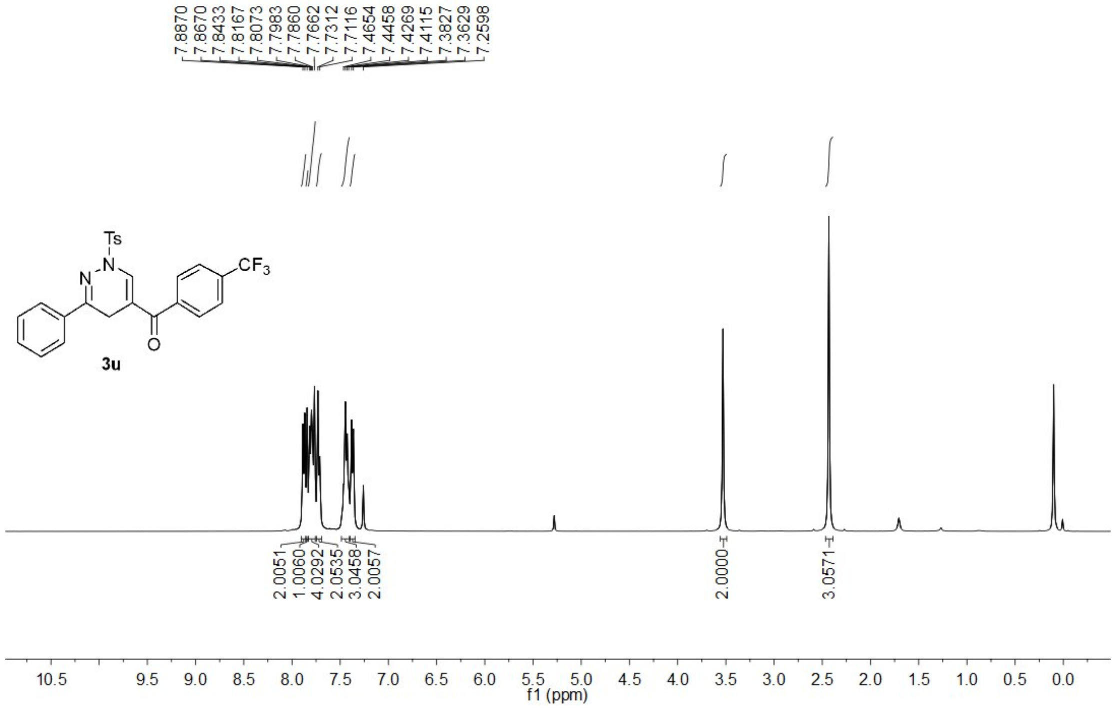
FJJ-R282



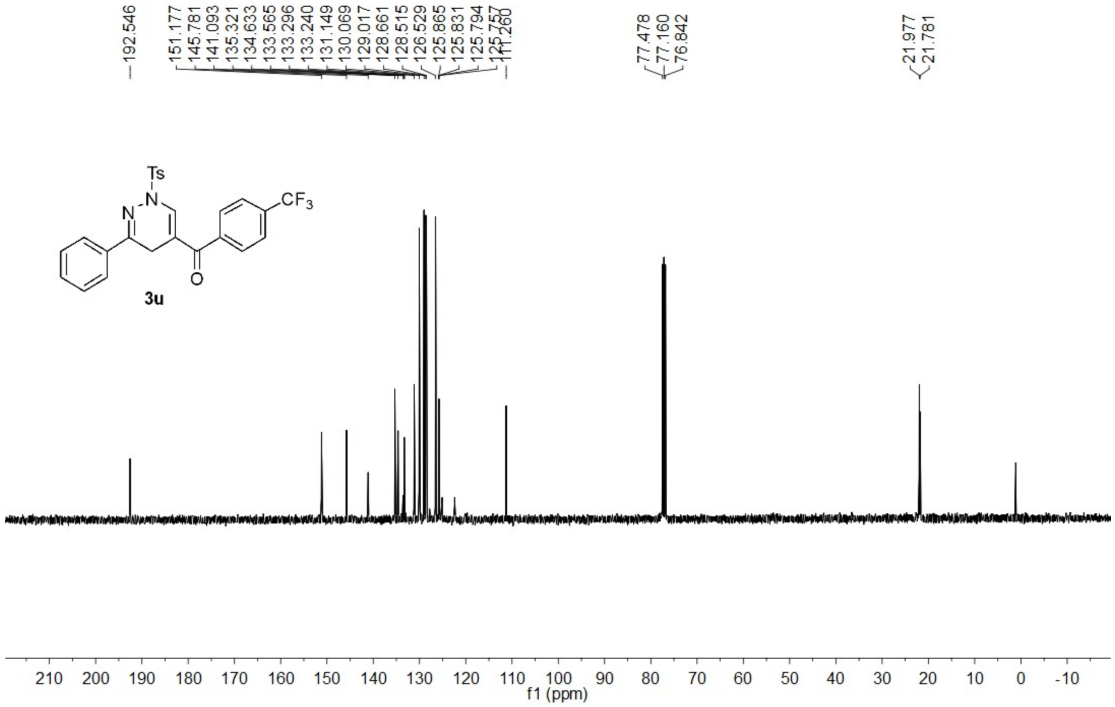
FJJ-R282



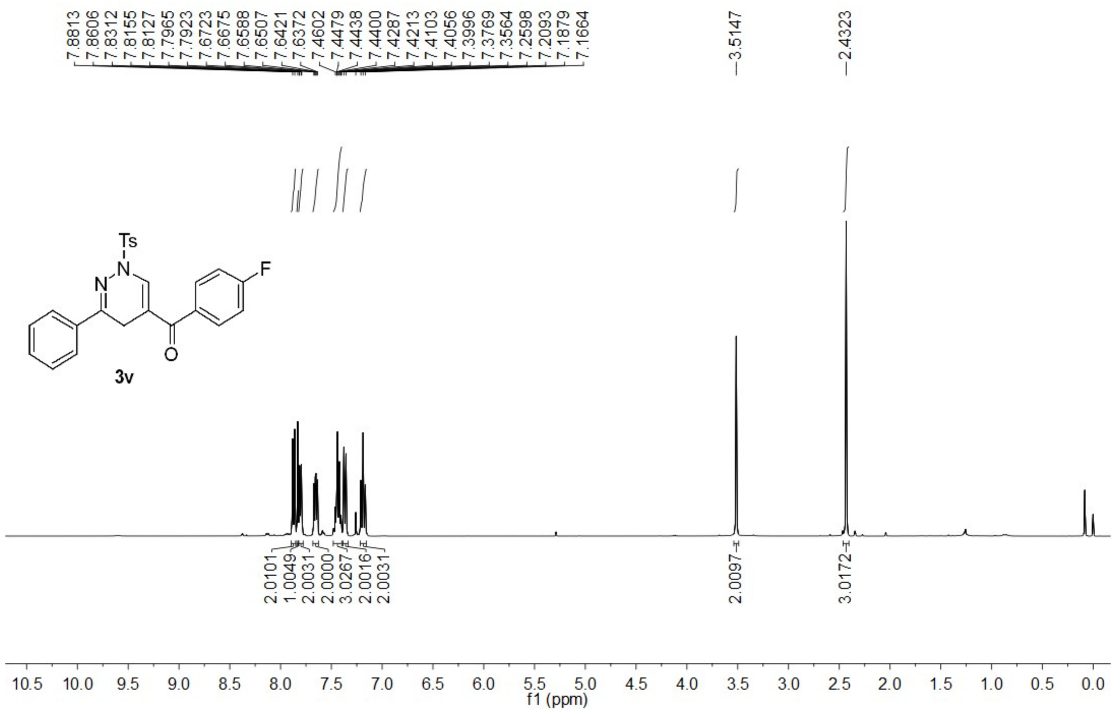
FJJ-R291



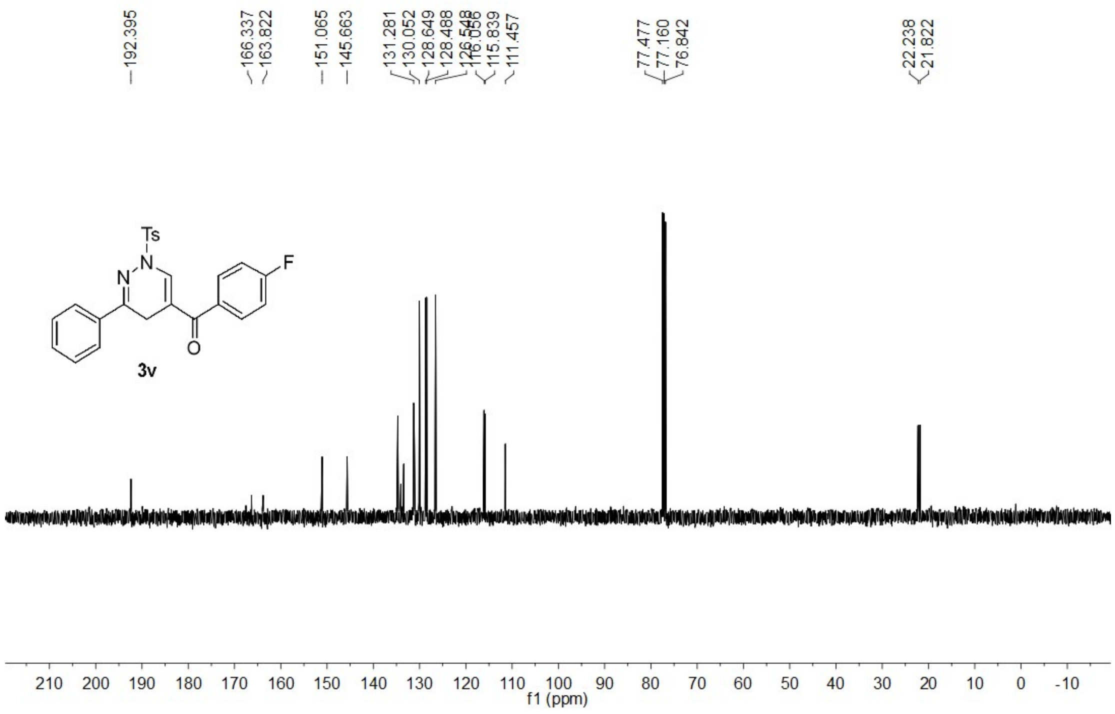
FJJ-R291



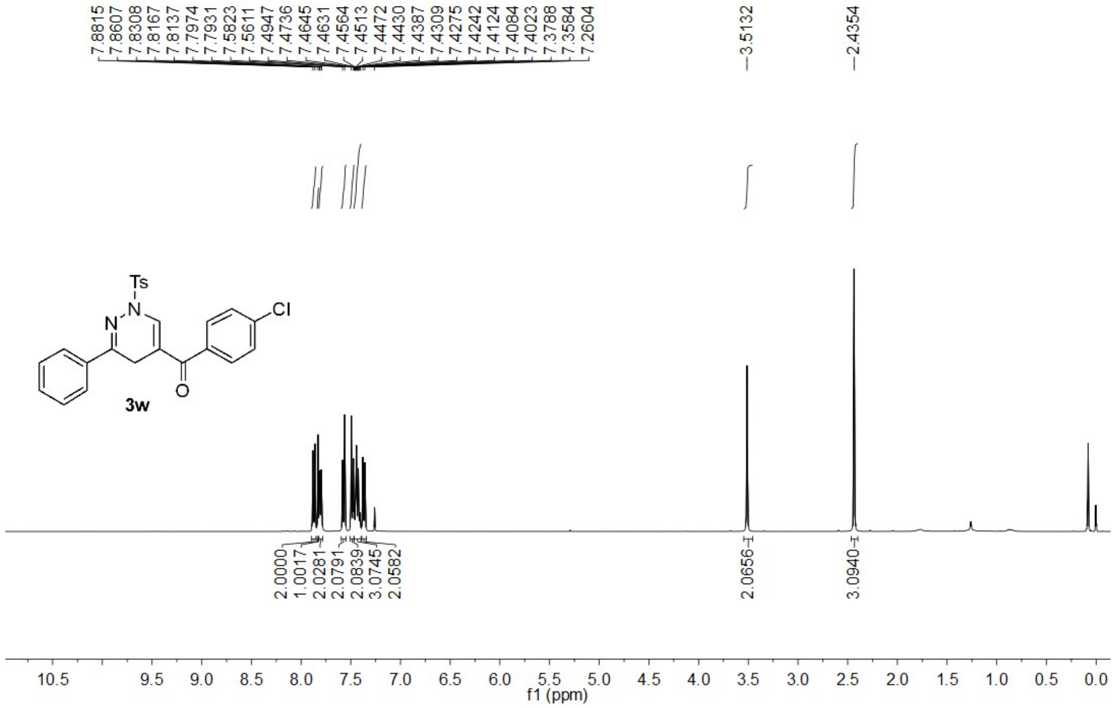
FJJ-R265



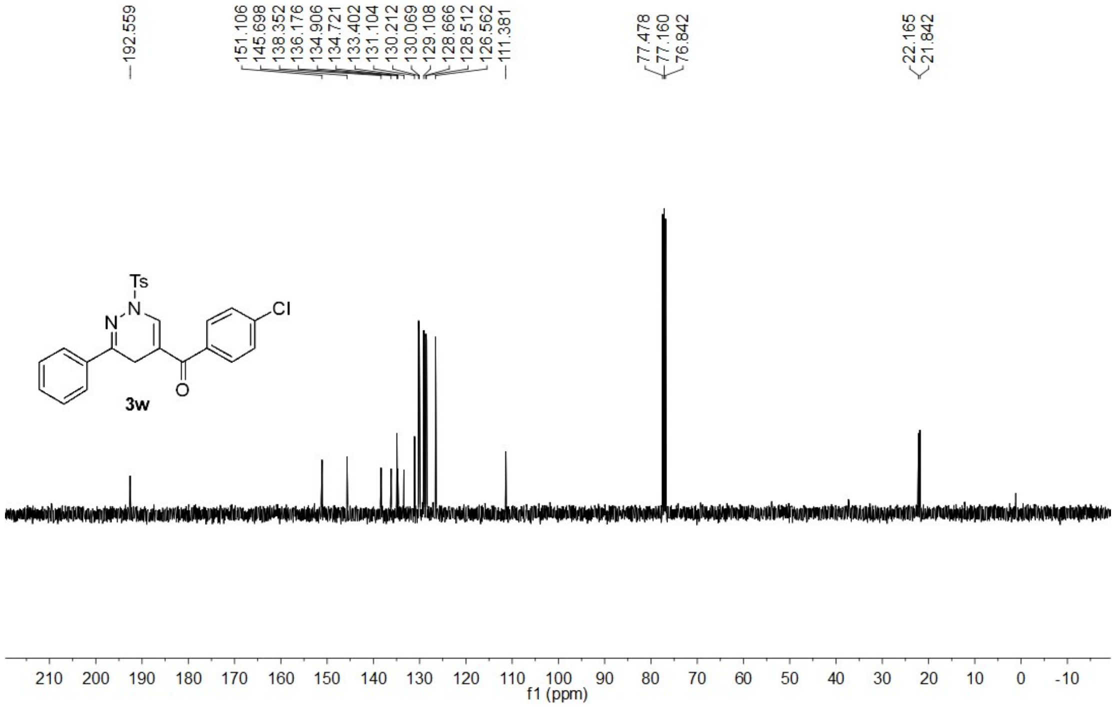
FJJ-R265

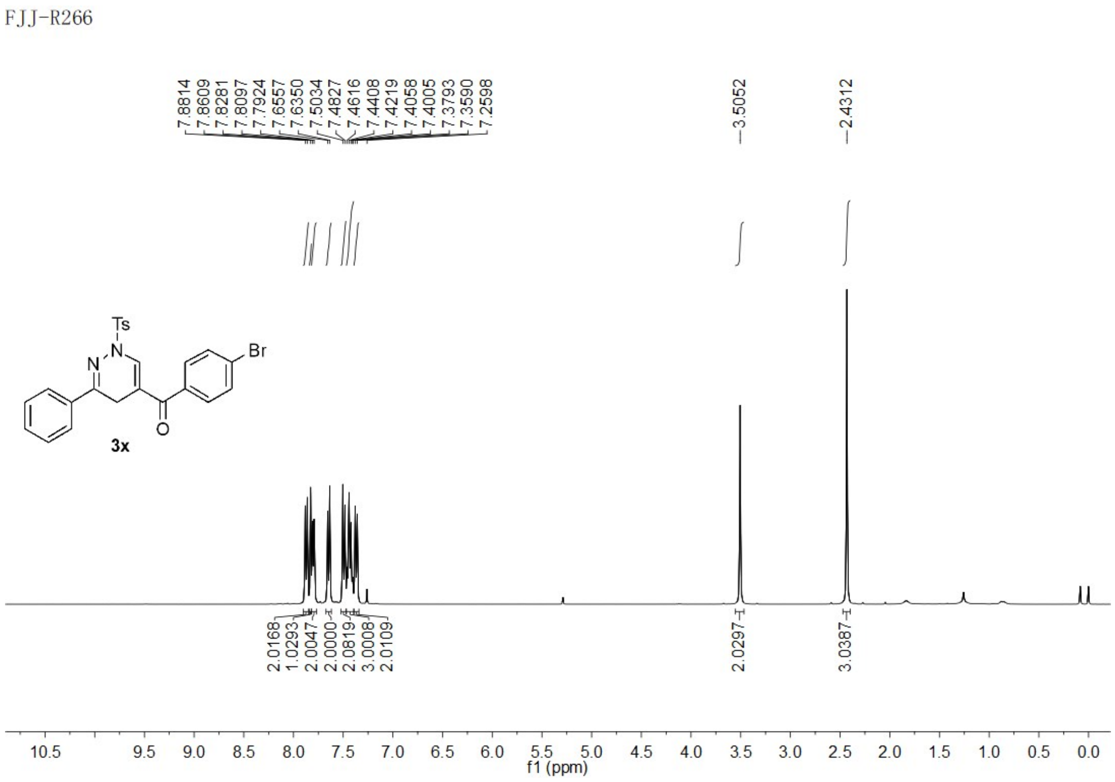


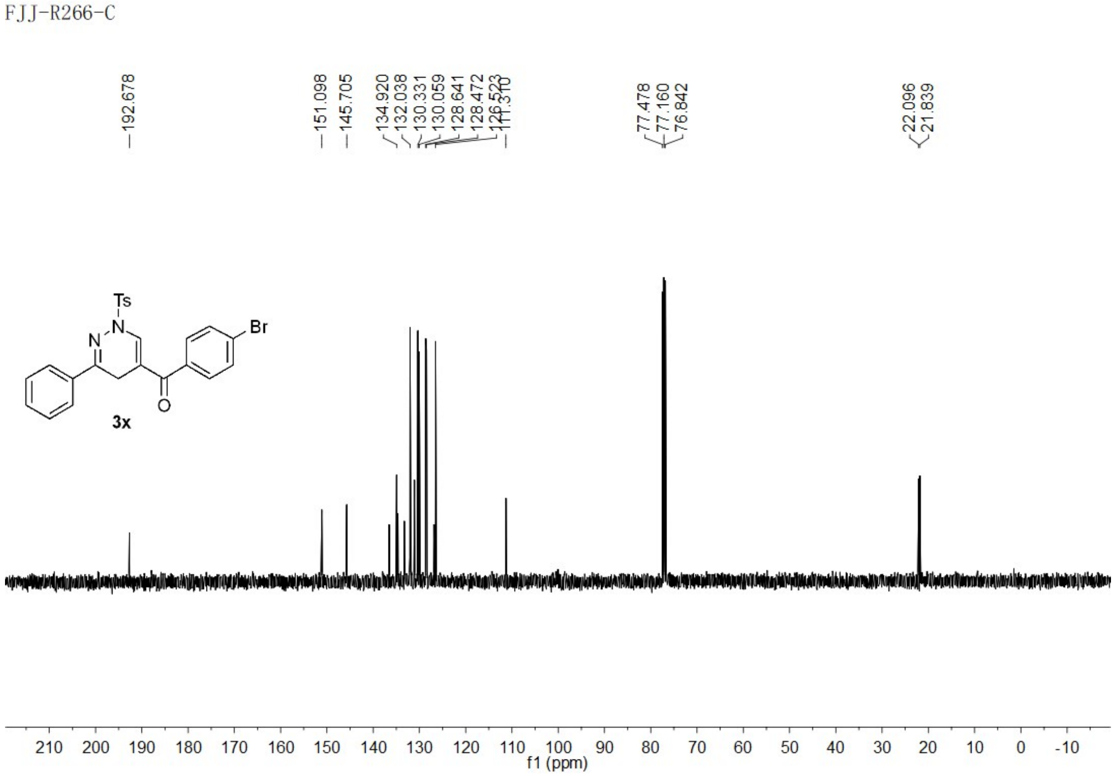
FJJ-R264



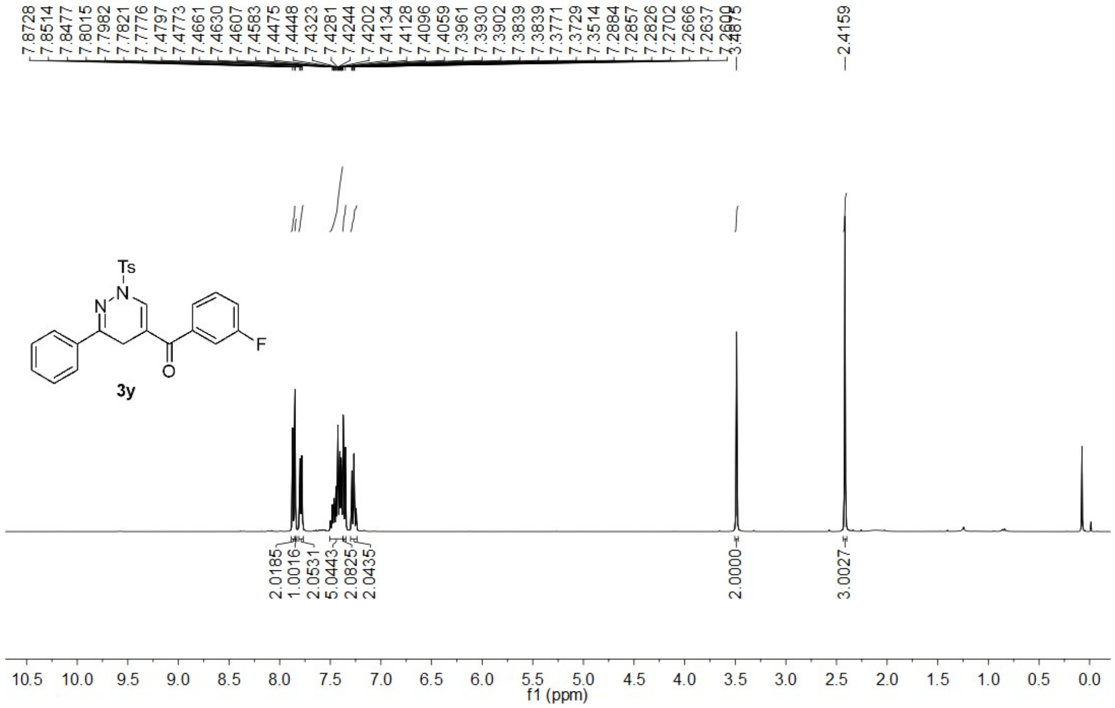
FJJ-R264-C



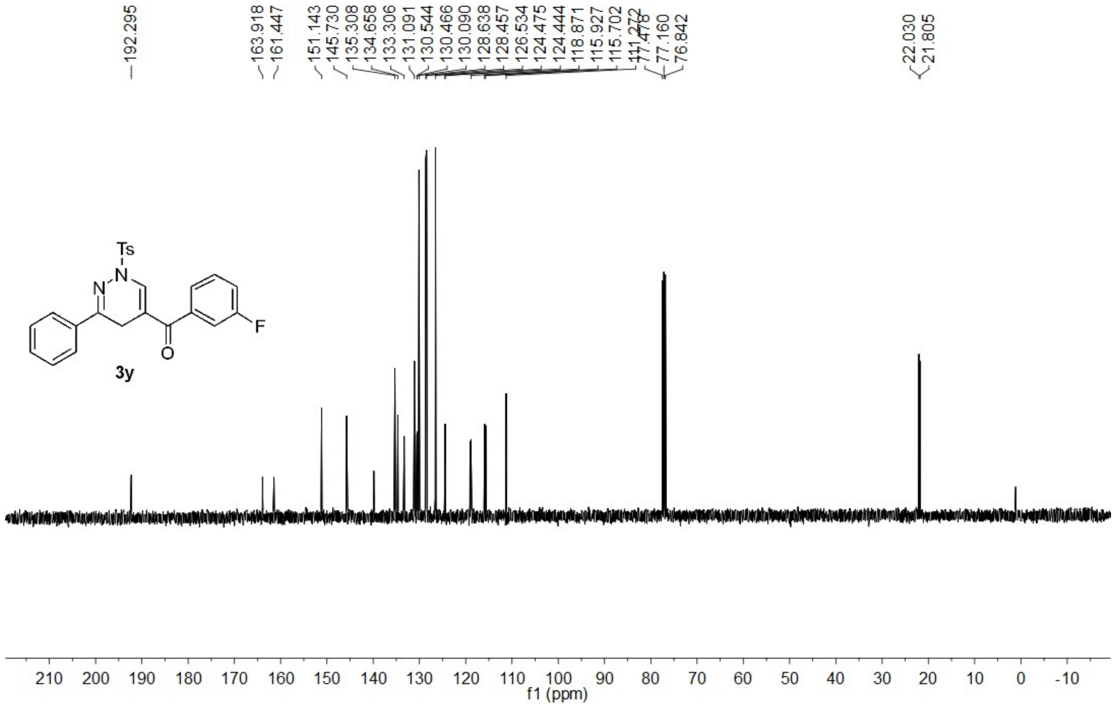

FJJ-R266
7.8814
7.8609
7.8281
7.8097
7.7924
7.6557
7.6350
7.5034
7.4827
7.4616
7.4408
7.4219
7.4058
7.4005
7.3793
7.3590
7.2598
3.5052
2.4312
Ts
N
N
Br
O
3x
2.0168
1.0293
2.0047
2.0000
2.0819
3.0008
2.0109
2.0297
3.0387
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


FJJ-R266-C
192.678
151.098
145.705
134.920
132.038
130.331
130.059
128.641
128.472
126.523
111.310
77.478
77.160
76.842
22.096
21.839
Ts
N
N
Br
O
3x
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

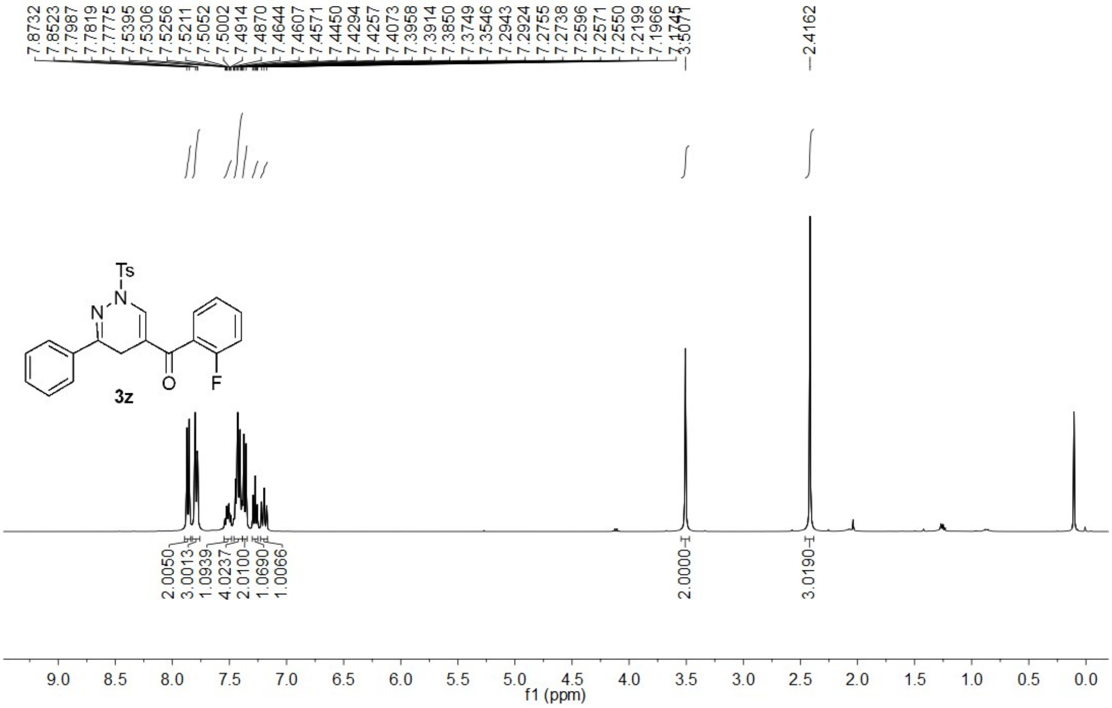
FJJ-R276



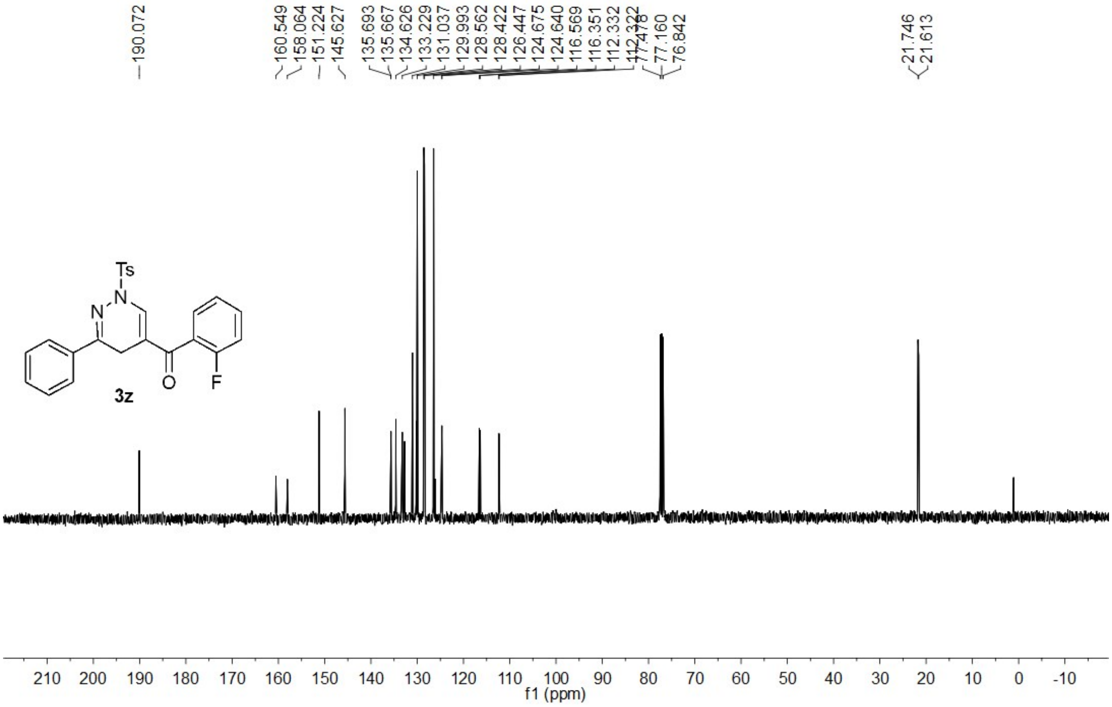
FJJ-R276



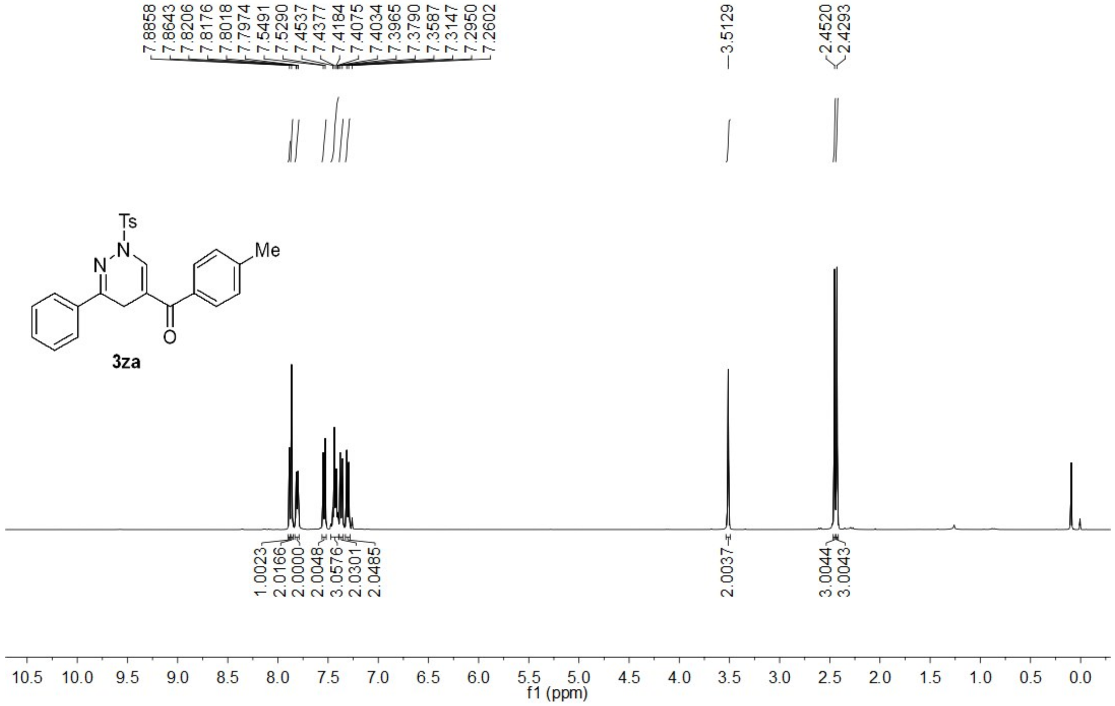
FJJ-R275



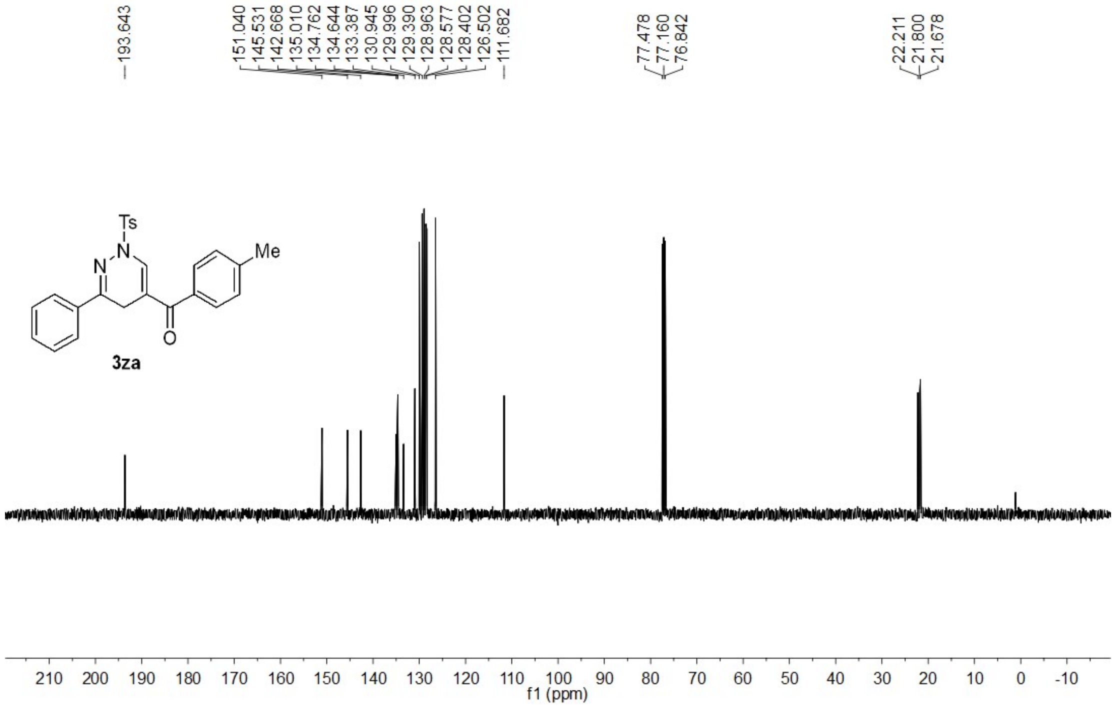
FJJ-R275



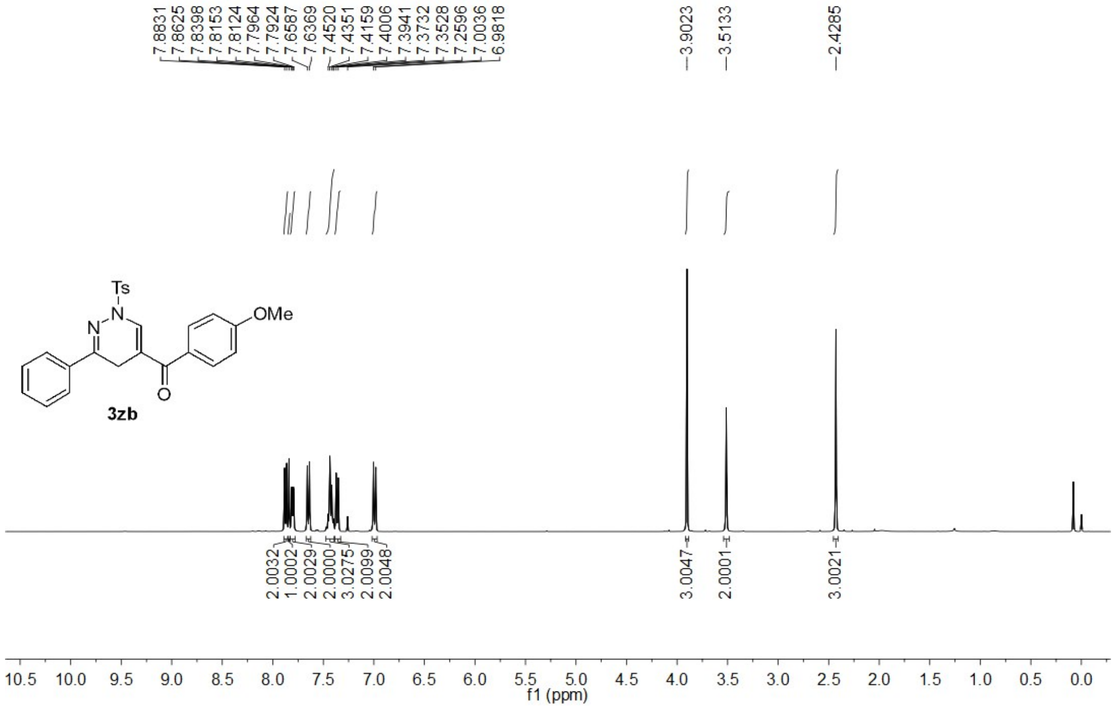
FJJ-R269



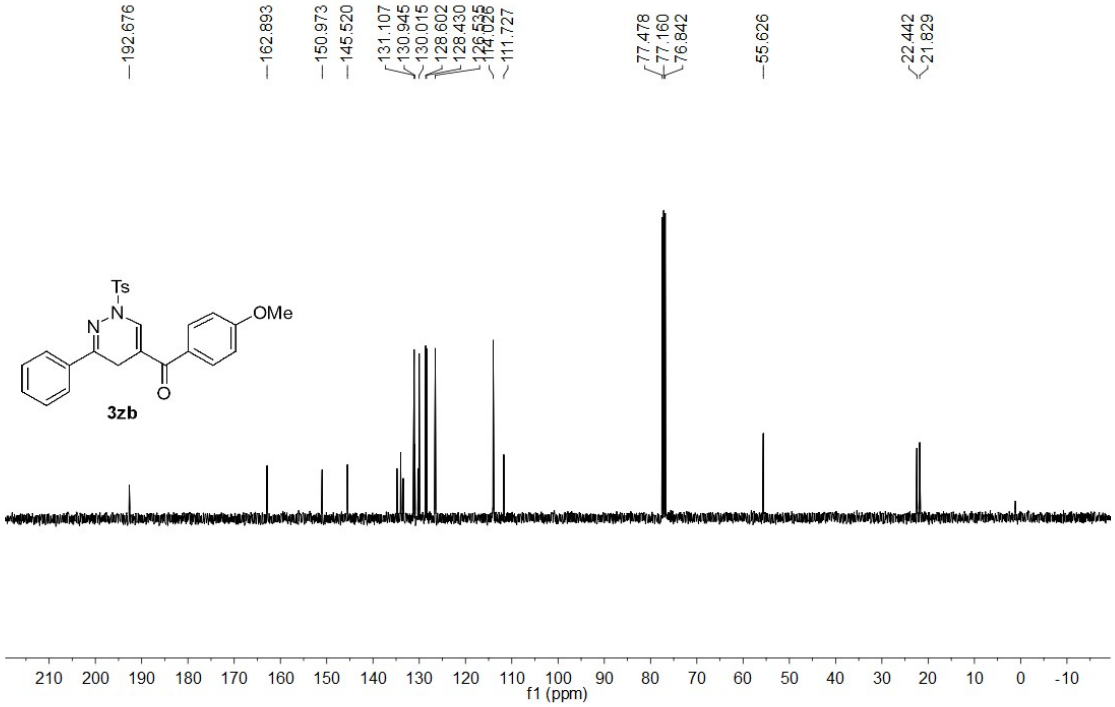
FJJ-R269



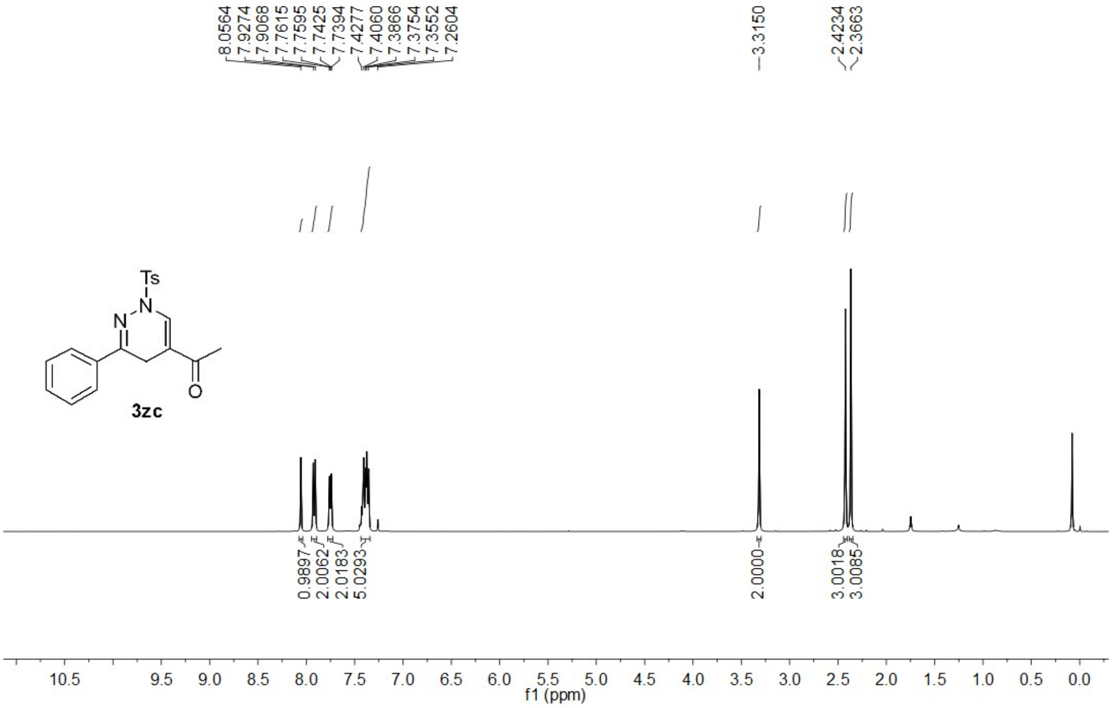
FJJ-R267-



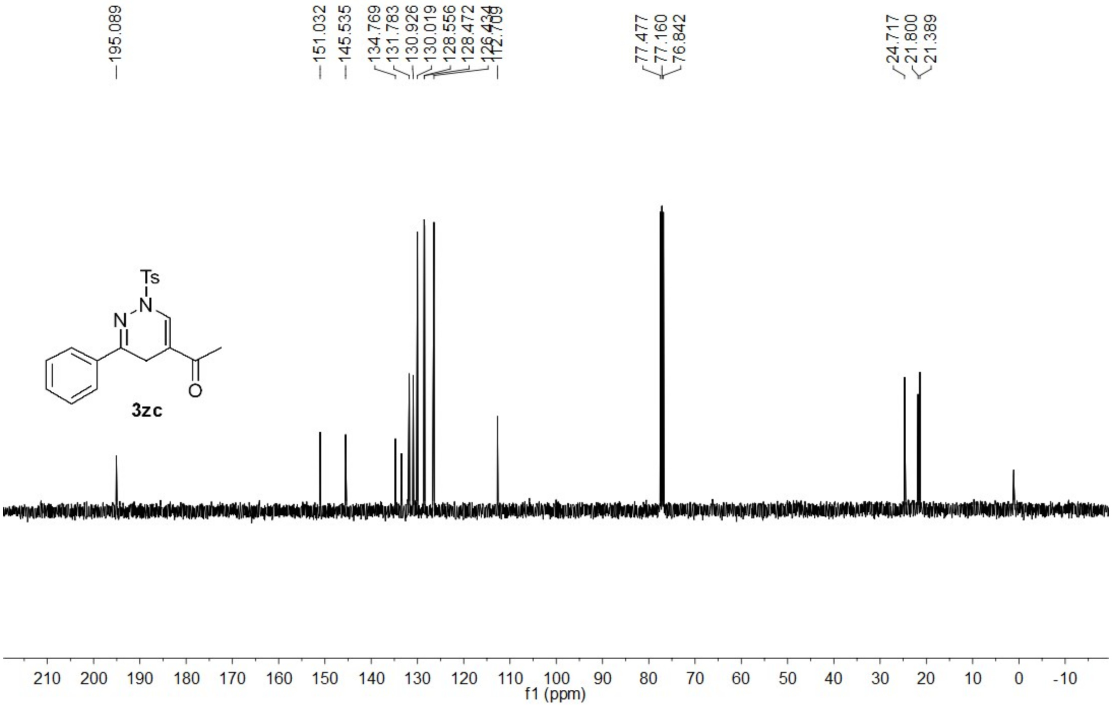
FJJ-R267-

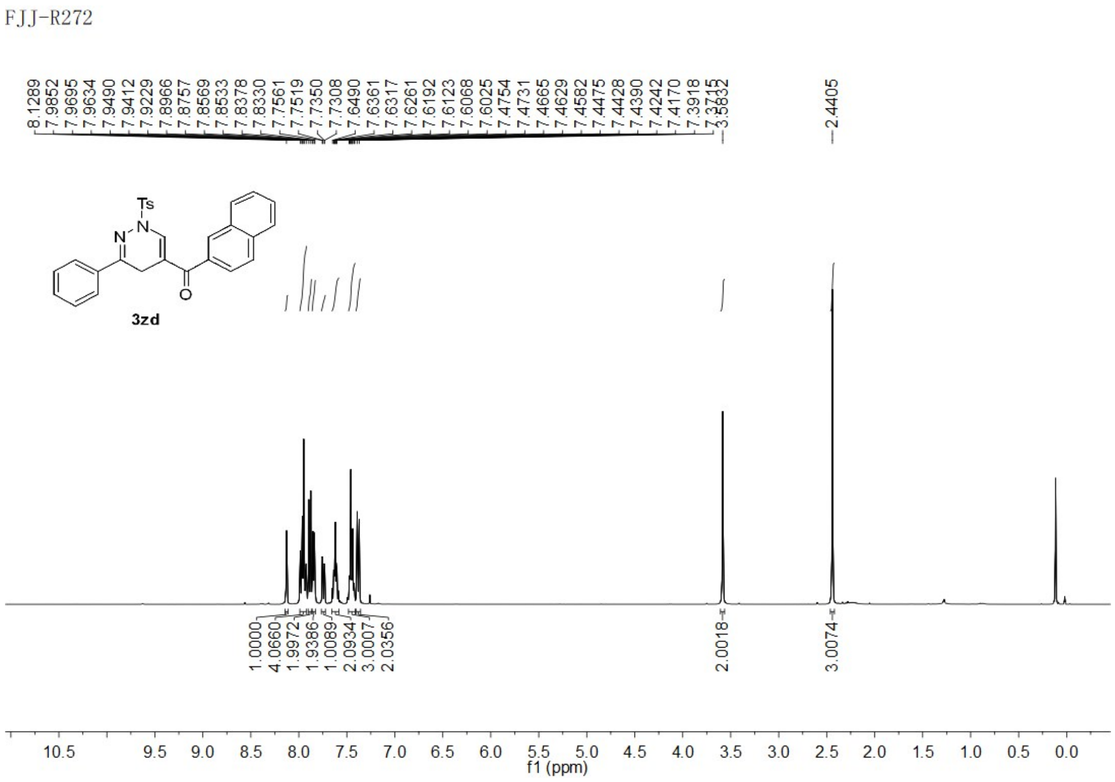


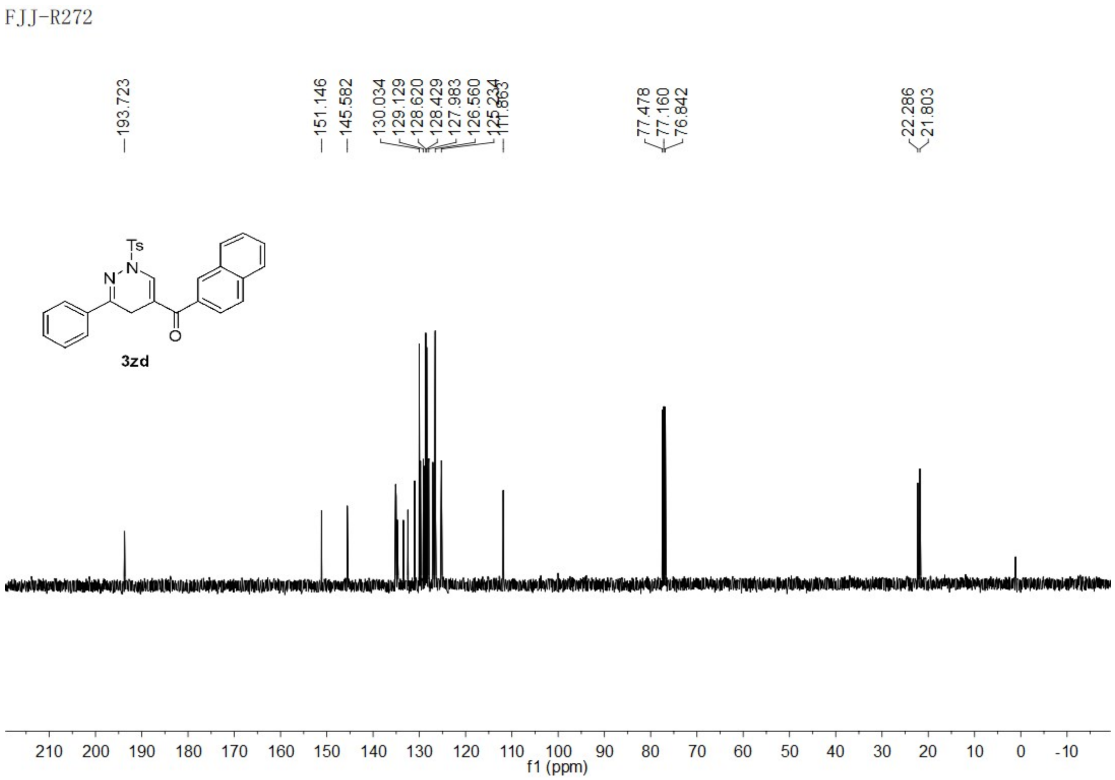
FJJ-R287

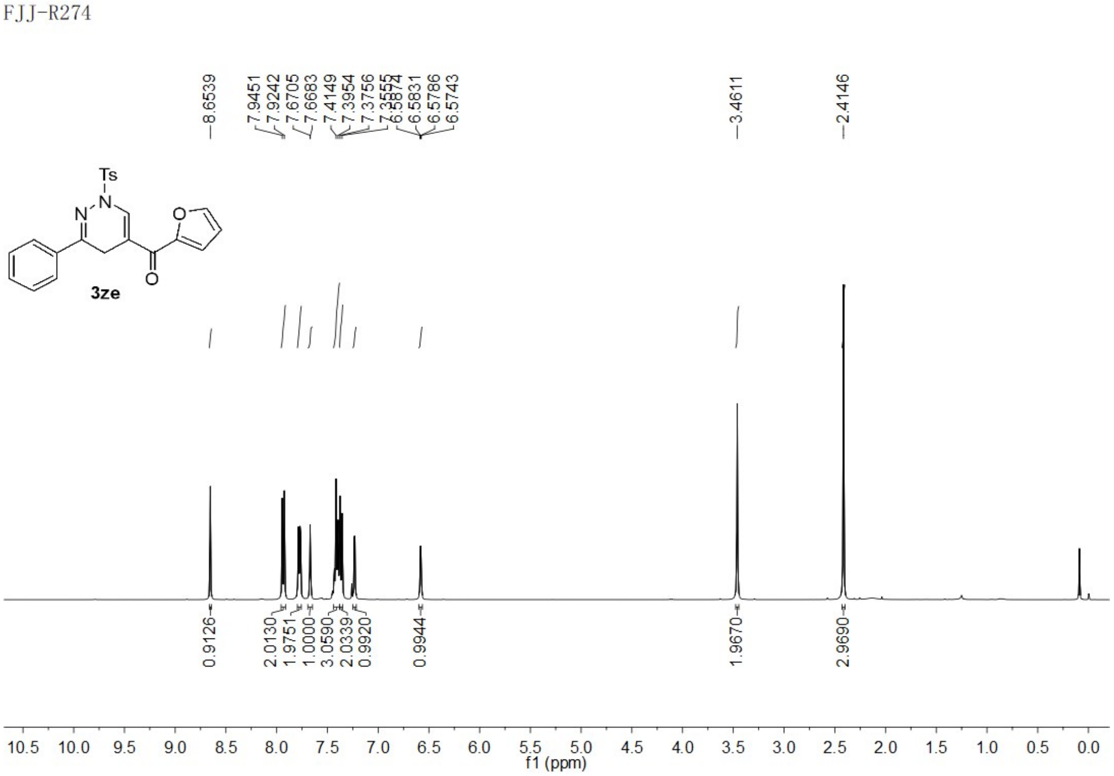


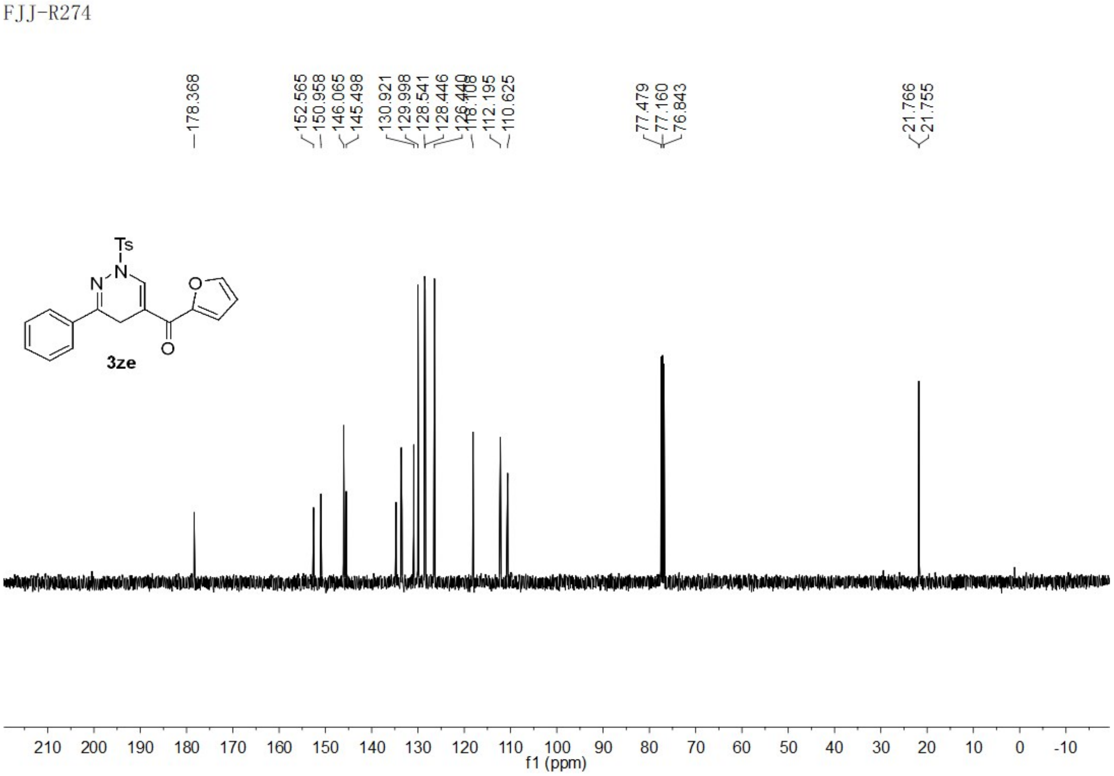
FJJ-R287



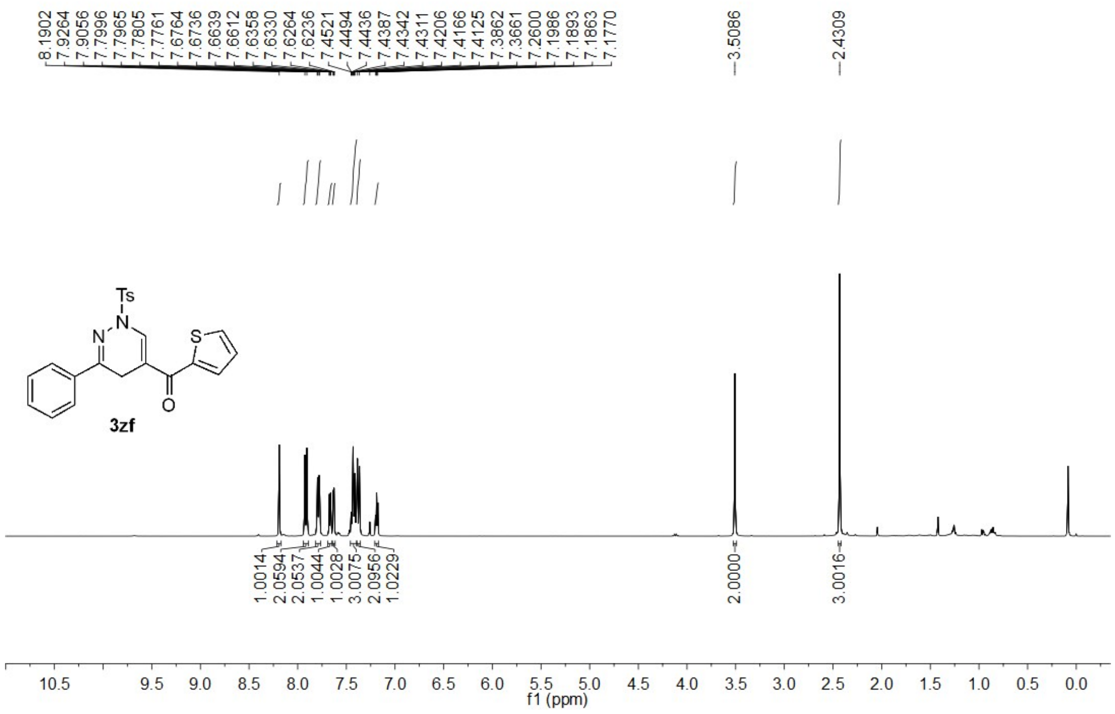

FJJ-R272
8.1289
7.9852
7.9695
7.9634
7.9490
7.9412
7.9229
7.8966
7.8757
7.8569
7.8533
7.8378
7.8330
7.7561
7.7519
7.7350
7.7308
7.6490
7.6361
7.6317
7.6261
7.6192
7.6123
7.6068
7.6025
7.4754
7.4731
7.4665
7.4629
7.4582
7.4475
7.4428
7.4390
7.4242
7.4170
7.3918
7.3715
3.5832
2.4405
Ts
N
N
O
3zd
1.0000
4.0660
1.9972
1.9386
1.0089
2.0934
3.0007
2.0356
2.0018
3.0074
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


FJJ-R272
193.723
151.146
145.582
130.034
129.129
128.620
128.429
127.983
126.560
125.234
111.863
77.478
77.160
76.842
22.286
21.803
Ts
N
N
O
3zd
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

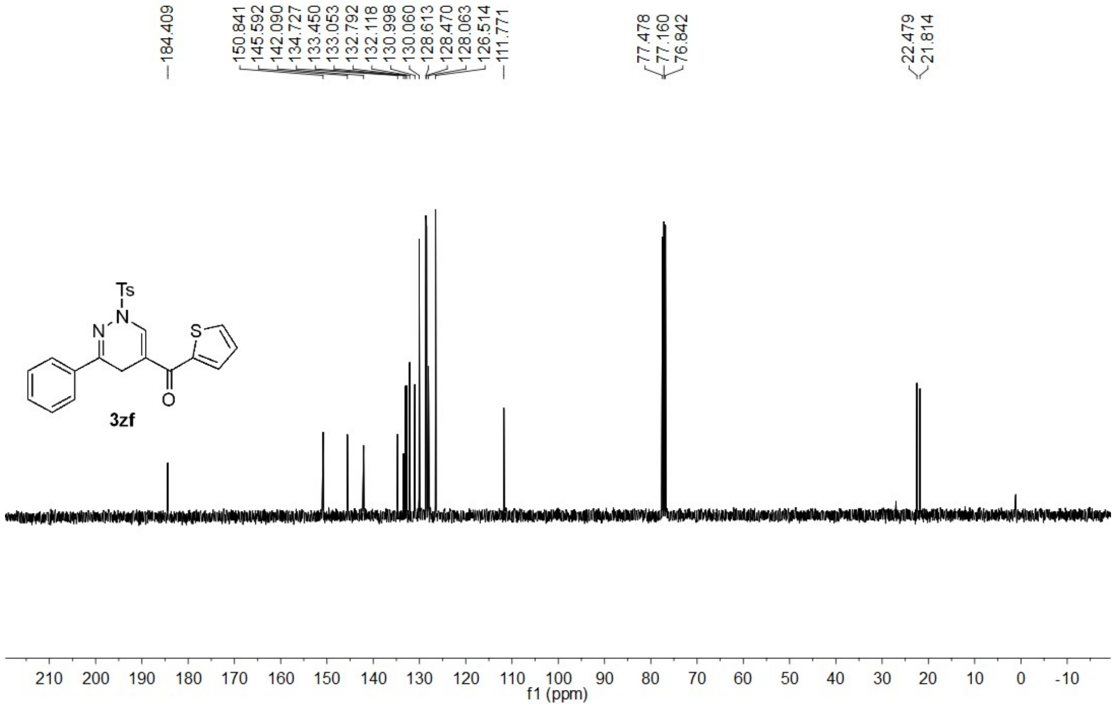

FJJ-R274
8.6539
7.9451
7.9242
7.6705
7.6683
7.4149
7.3954
7.3756
7.3555
6.5874
6.5831
6.5786
6.5743
3.4611
2.4146
Ts
N
N
O
O
3ze
0.9126
2.0130
1.9751
1.0000
3.0590
2.0339
0.9920
0.9944
1.9670
2.9690
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


FJJ-R274
178.368
152.565
150.958
146.065
145.498
130.921
129.998
128.541
128.446
126.440
118.108
112.195
110.625
77.479
77.160
76.843
21.766
21.755
Ts
N
N
O
O
3ze
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

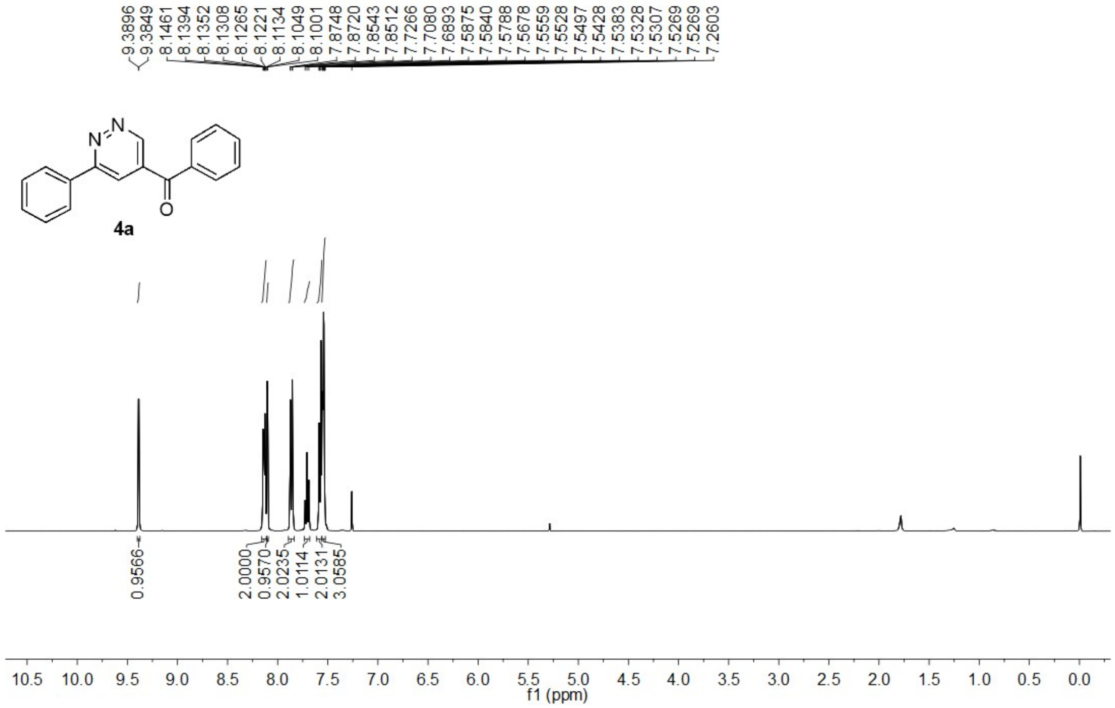
FJJ-R270



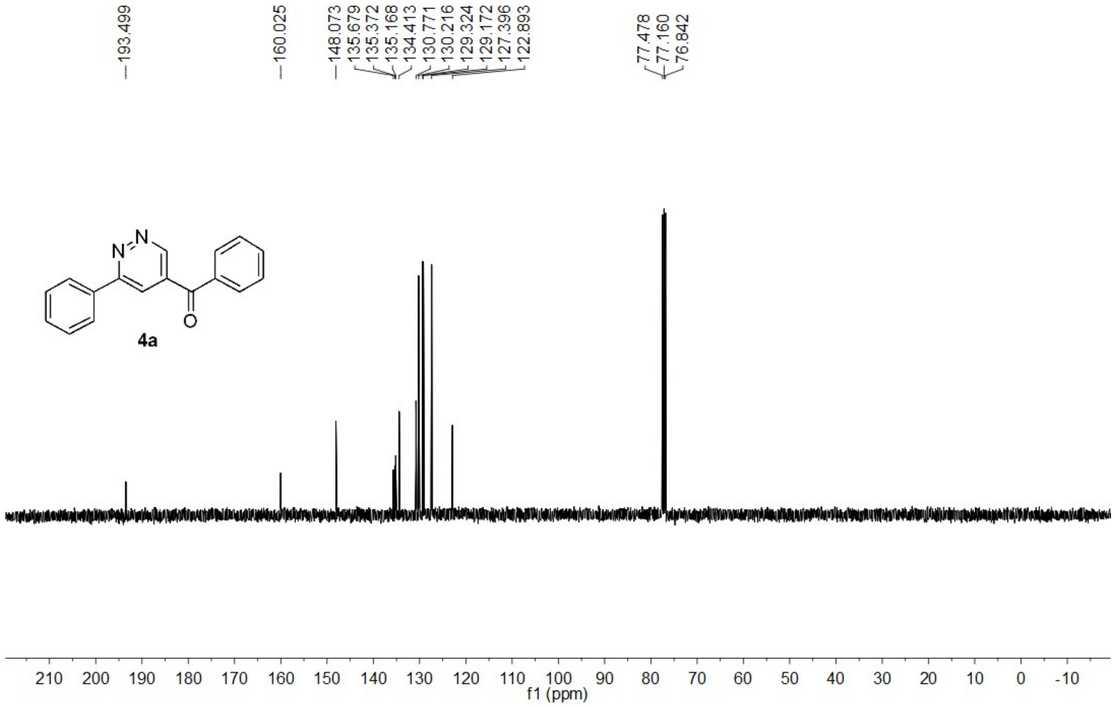
FJJ-R270



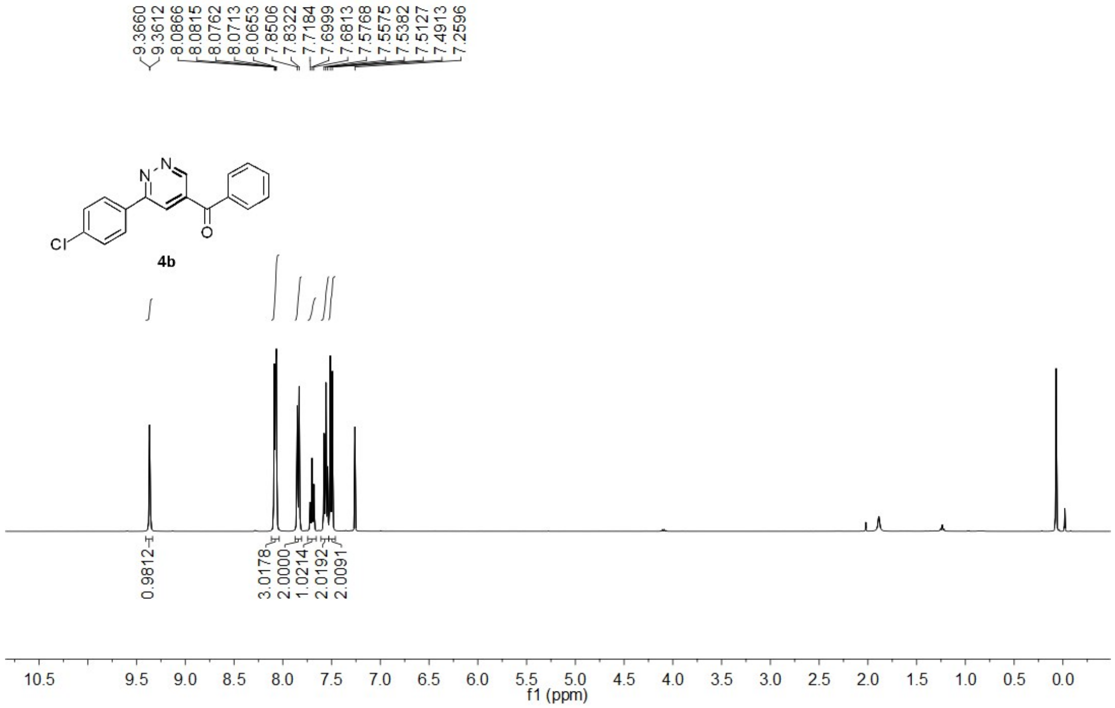
FJJ-R214



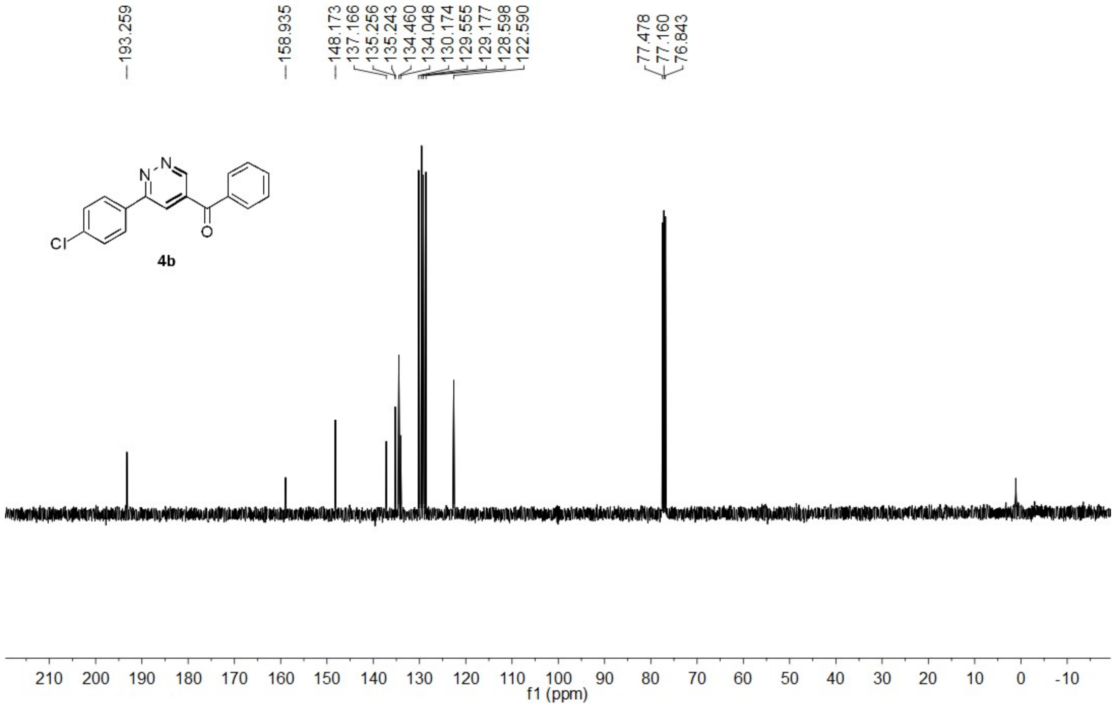
FJJ-R214



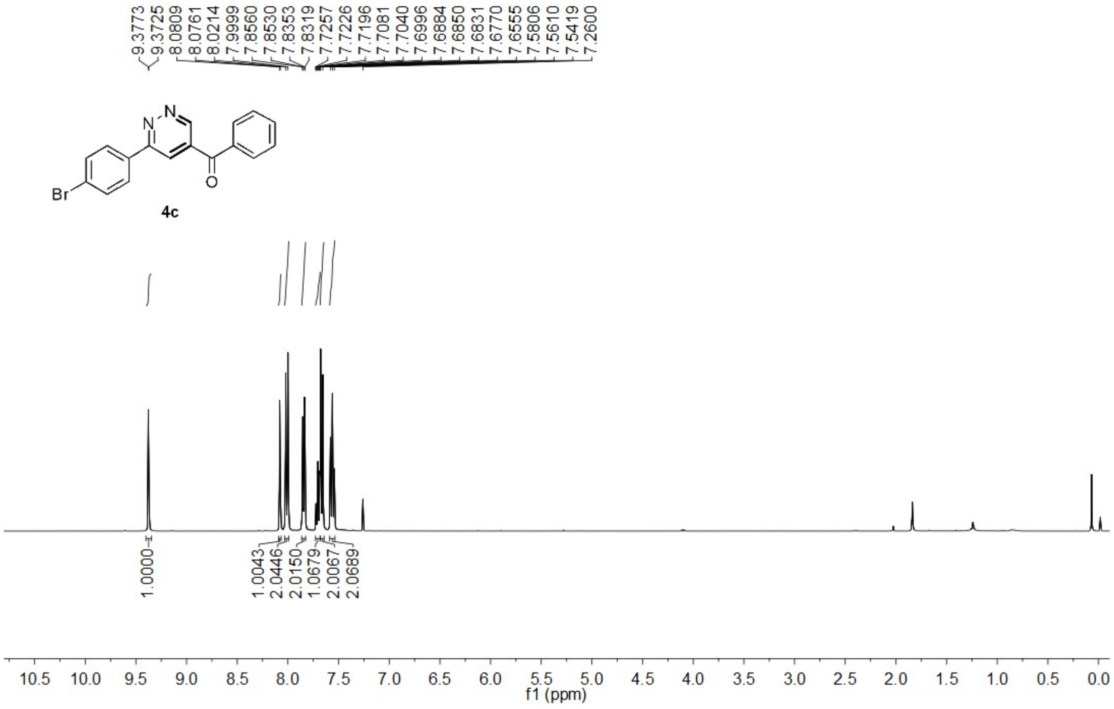
FJJ-OBC-1H,C



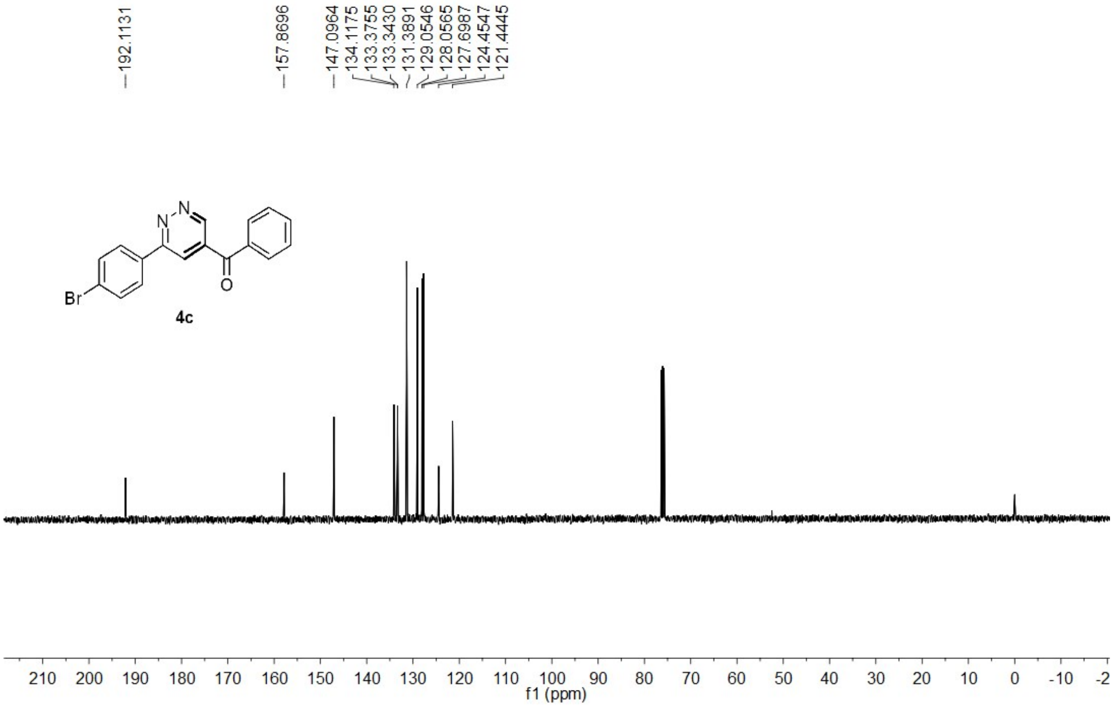
FJJ-OBC-1H,C



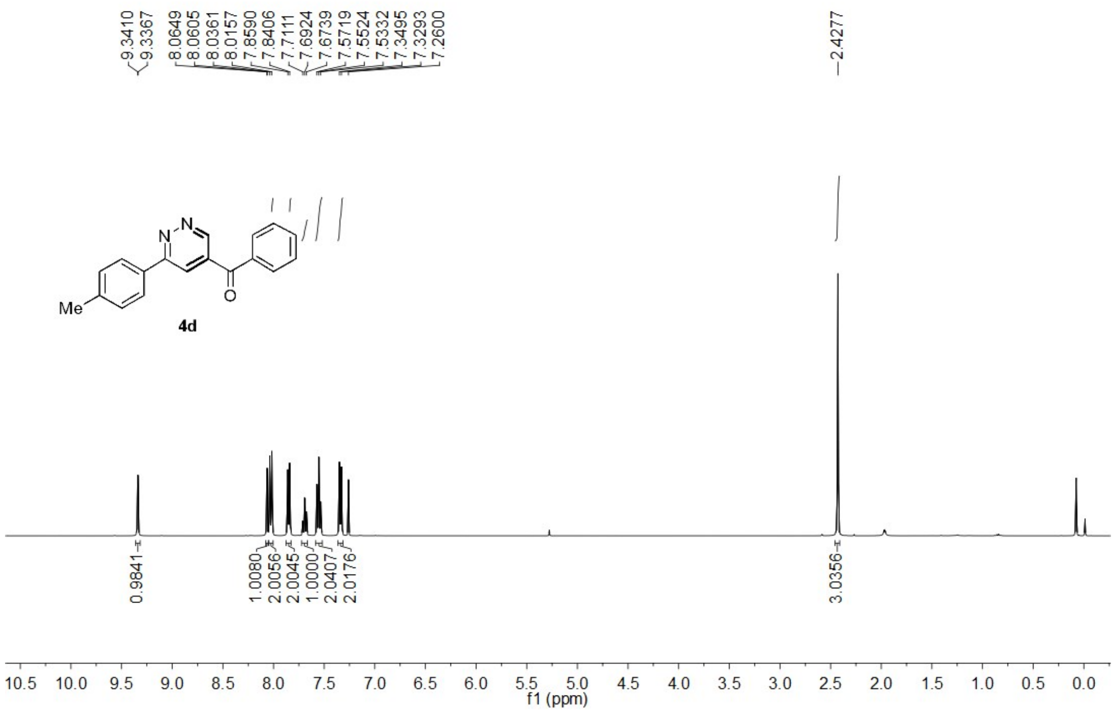
FJJ-R273



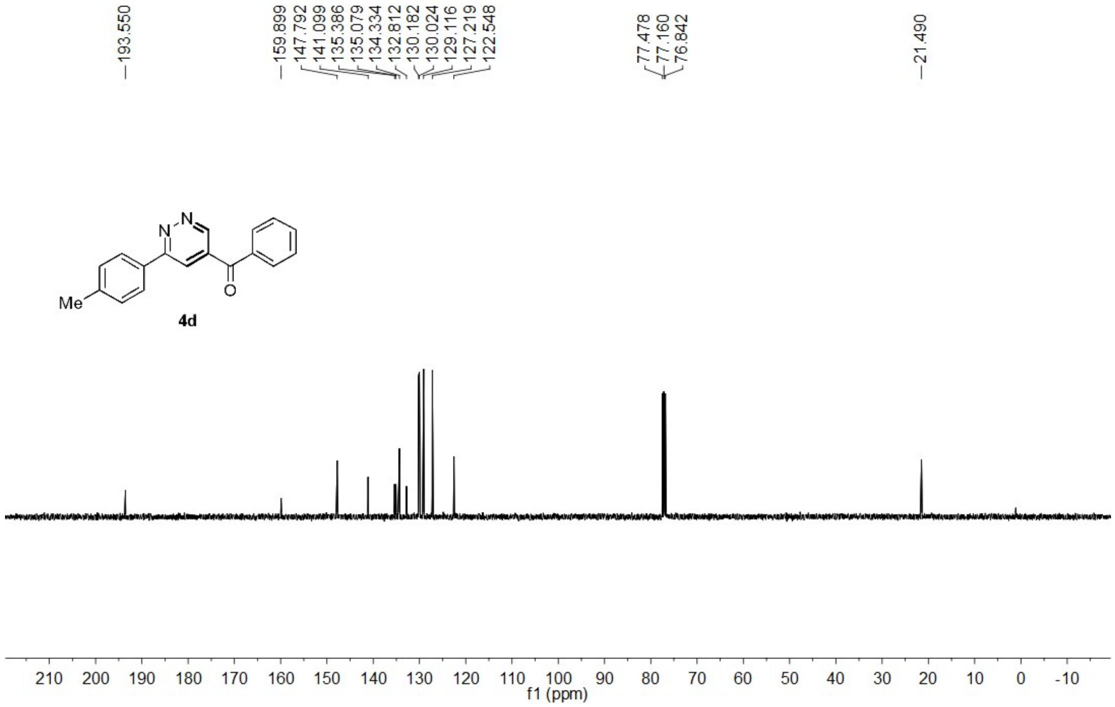
FJJ-R271-2



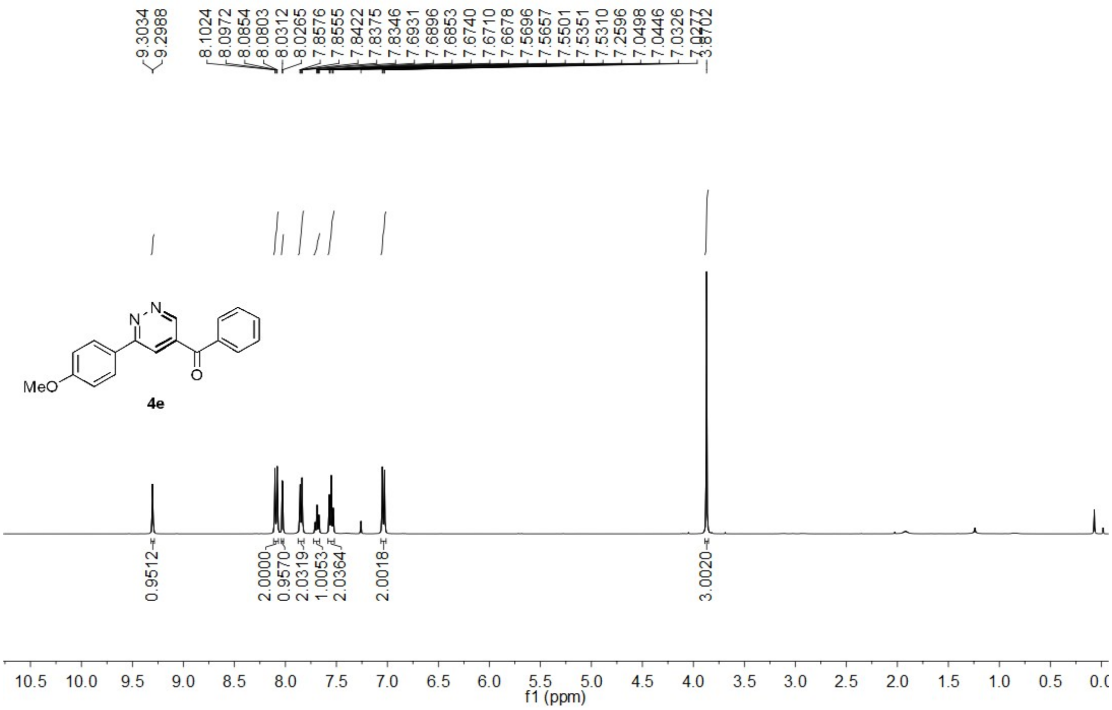
FJJ-OBC-2



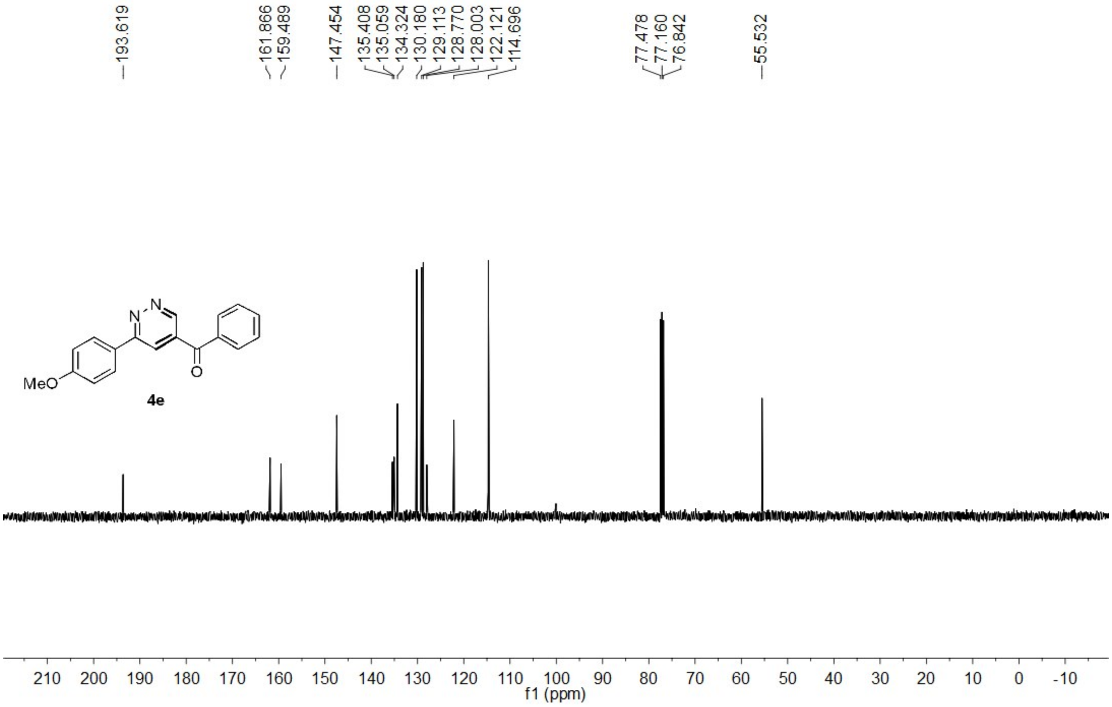
FJJ-OBC-2



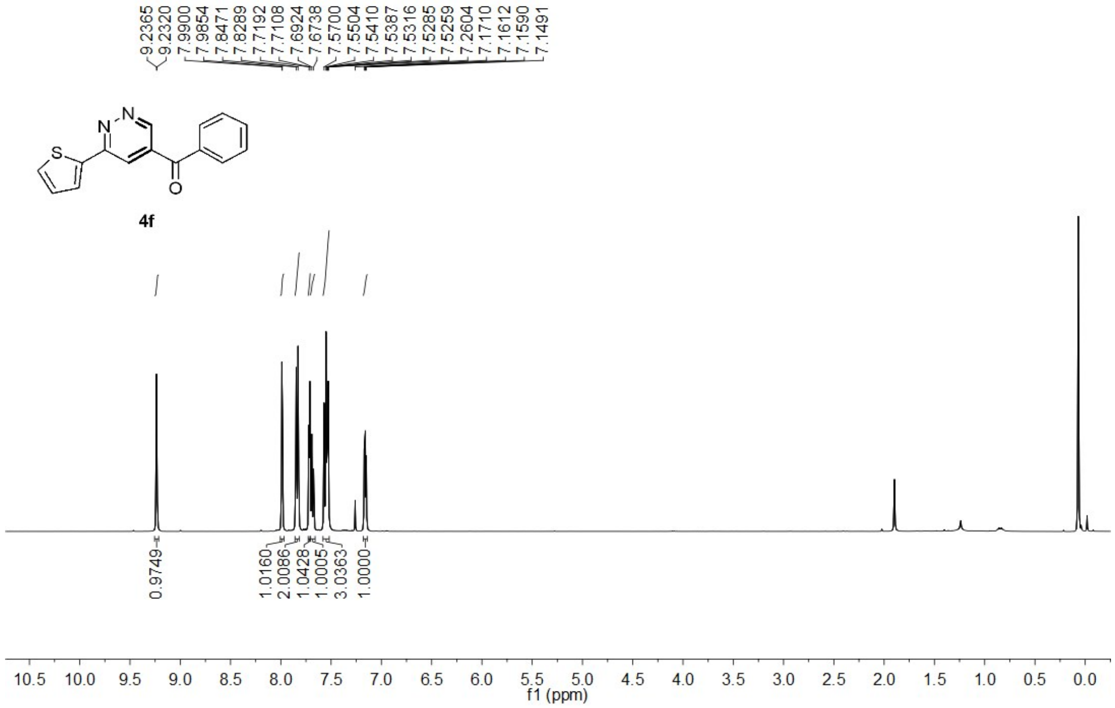
FJJ-R271



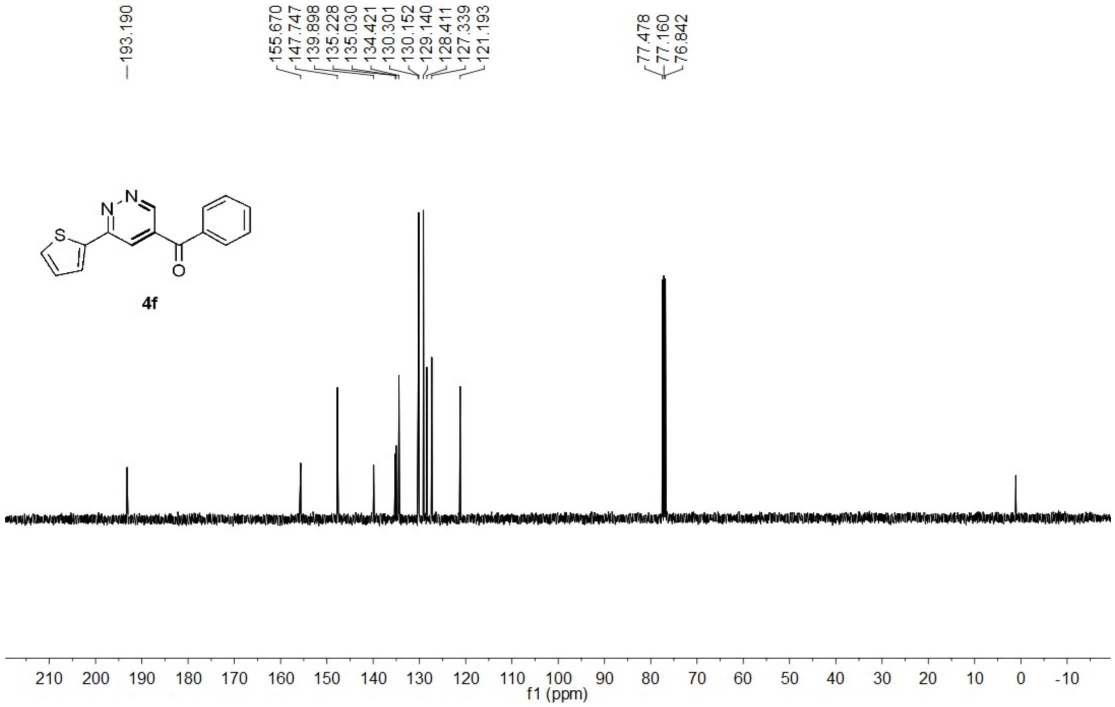
FJJ-R271



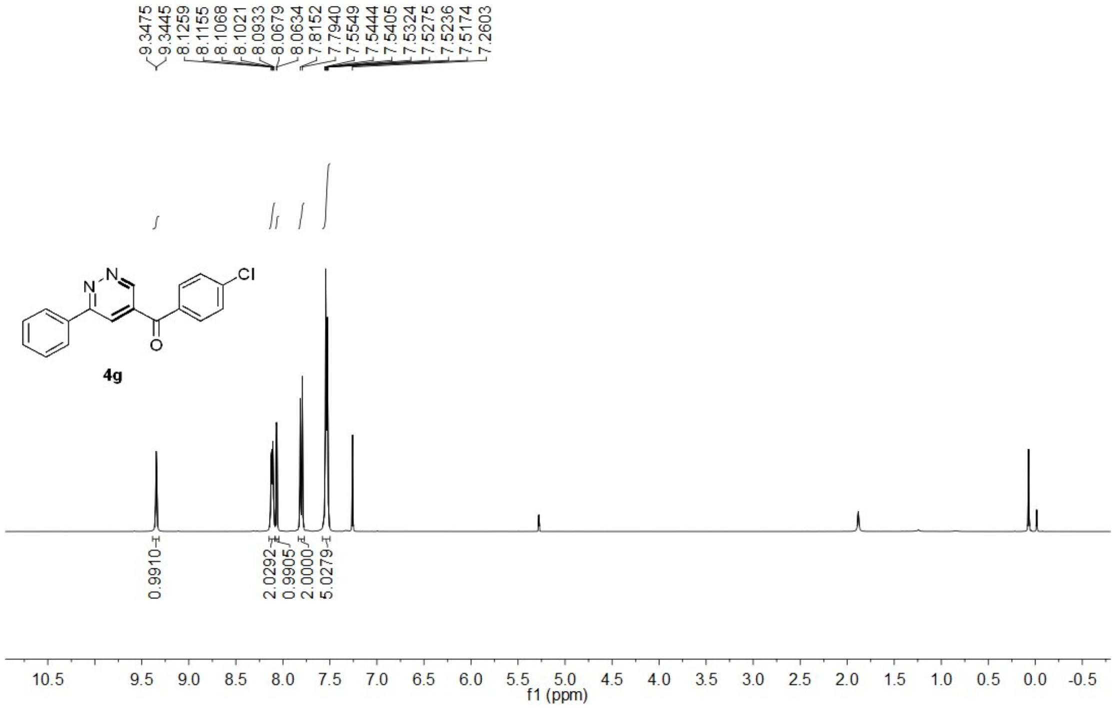
FJJ-R279



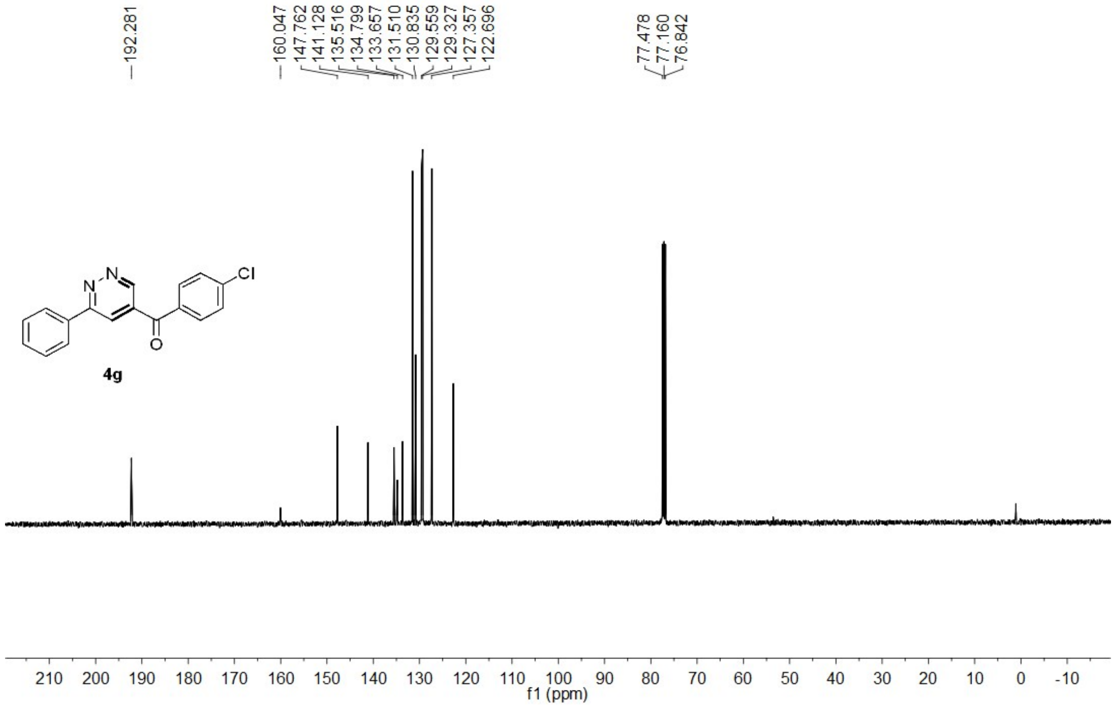
FJJ-R279



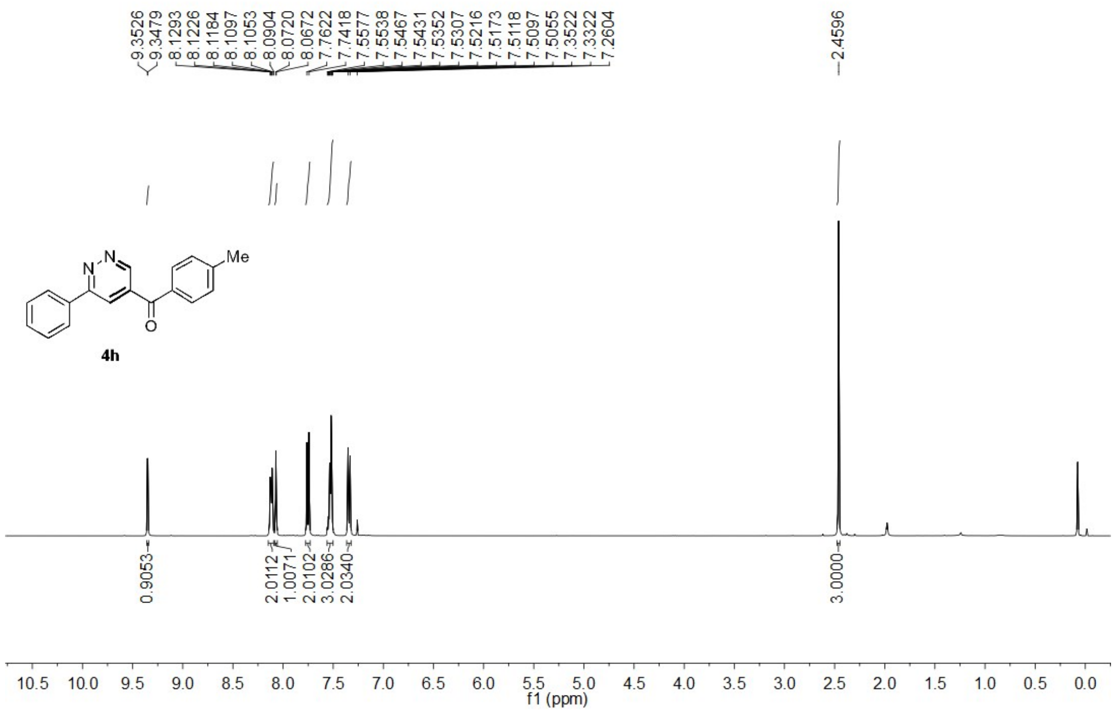
FJJ-OBC-3H,C



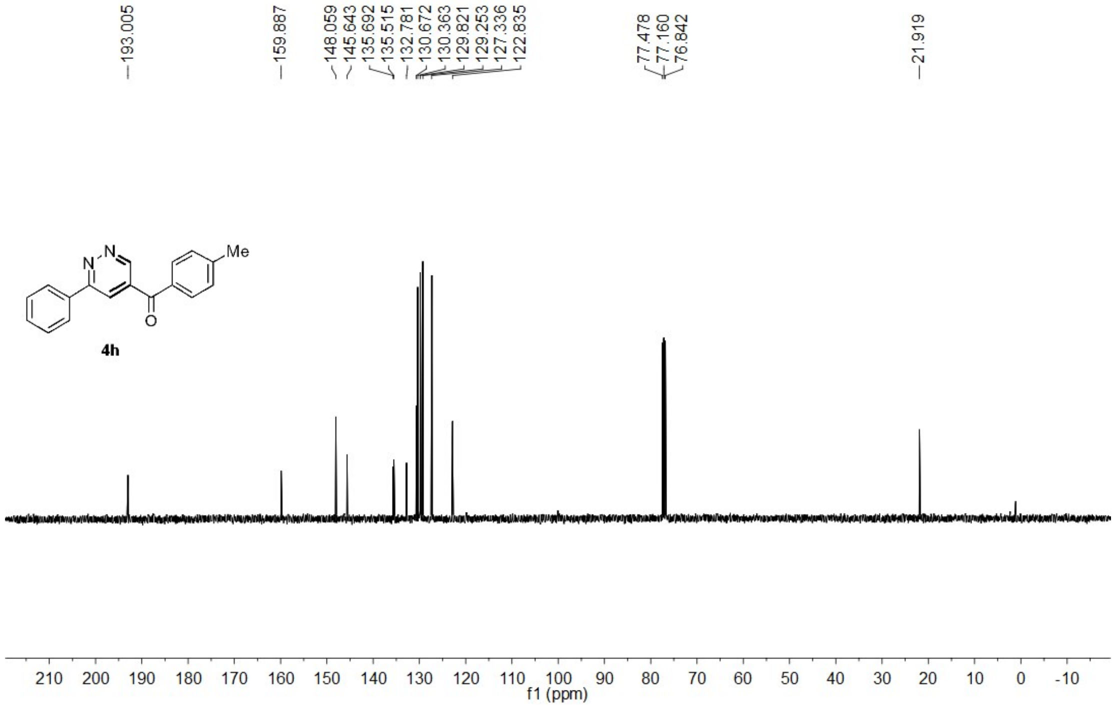
FJJ-OBC-3C

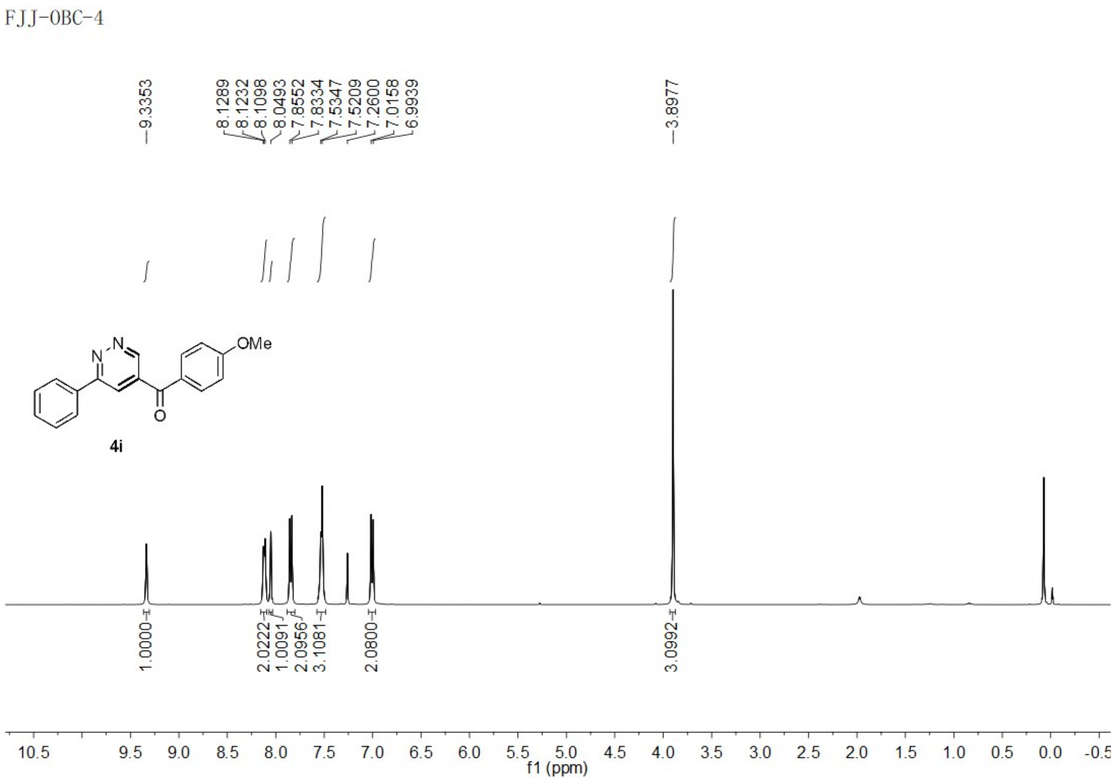


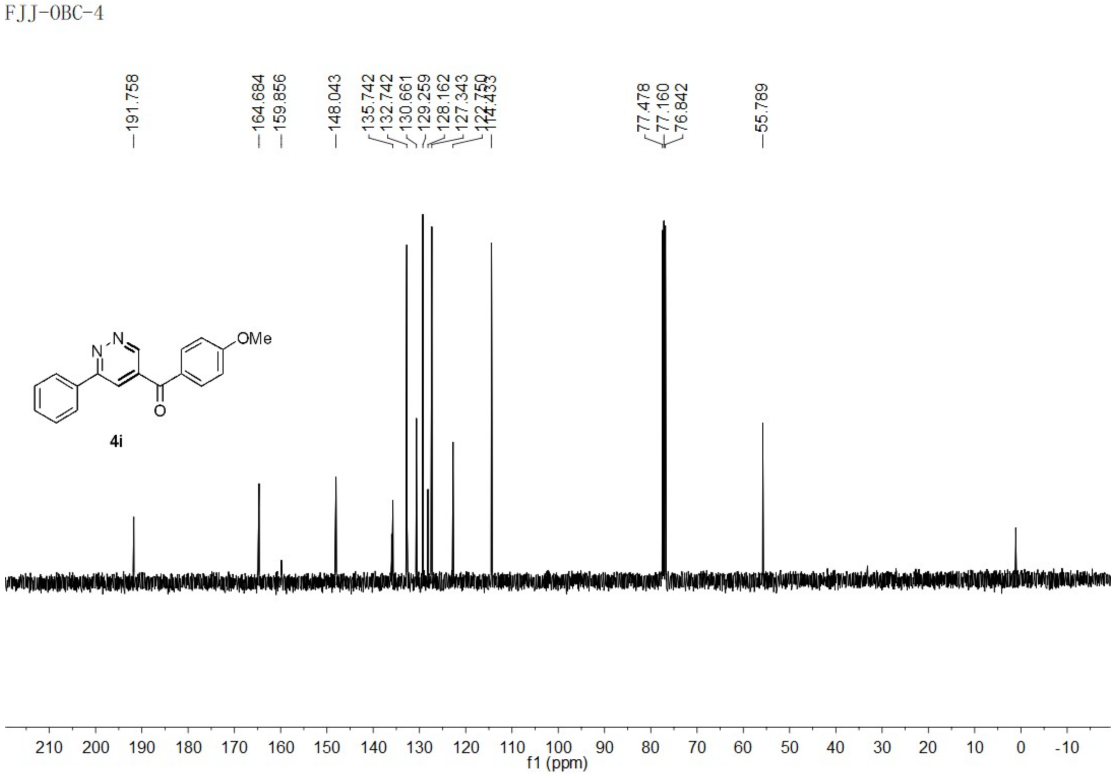
FJJ-R278



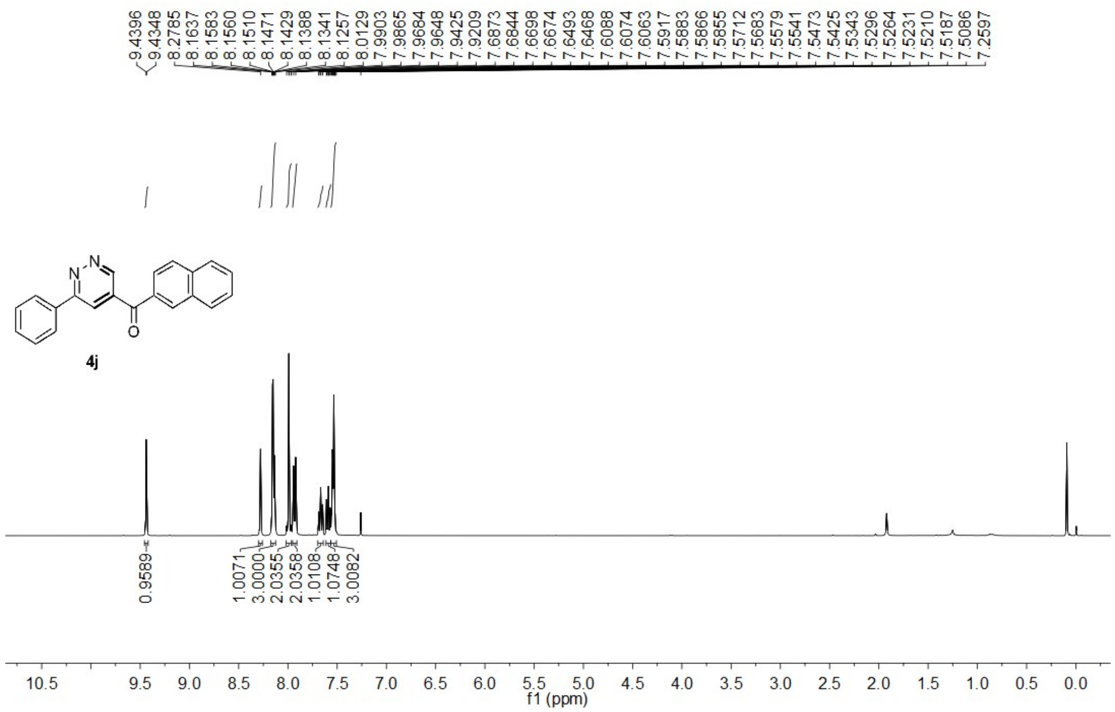
FJJ-R278



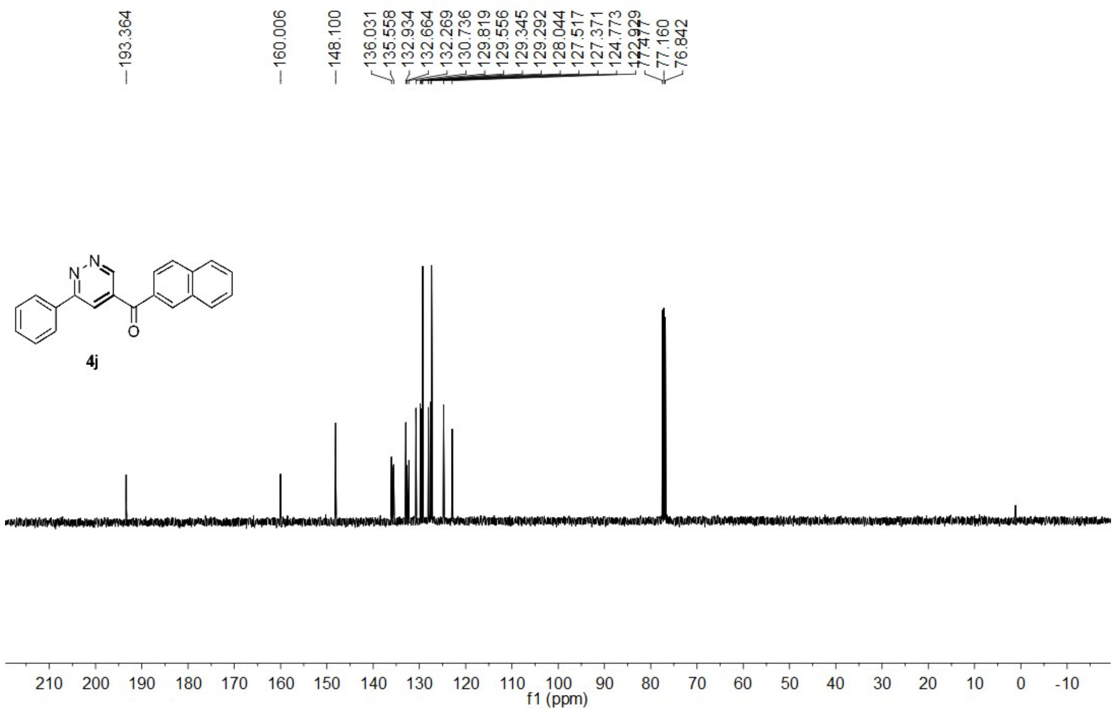

FJJ-OBC-4


FJJ-OBC-4

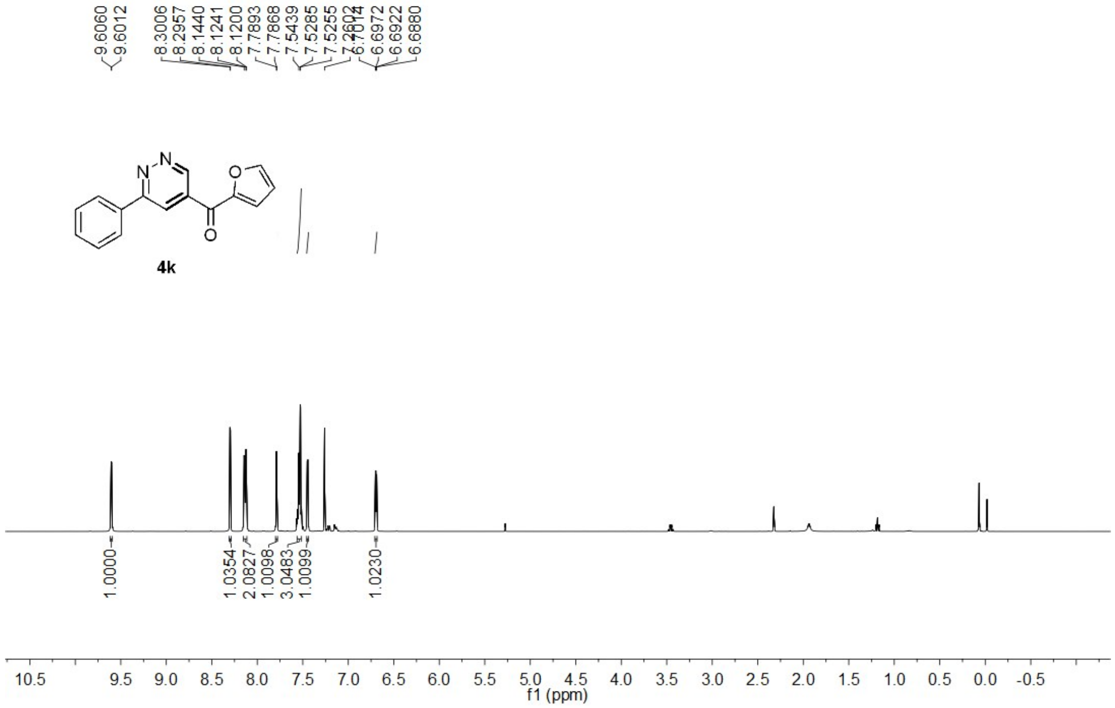
FJJ-R280



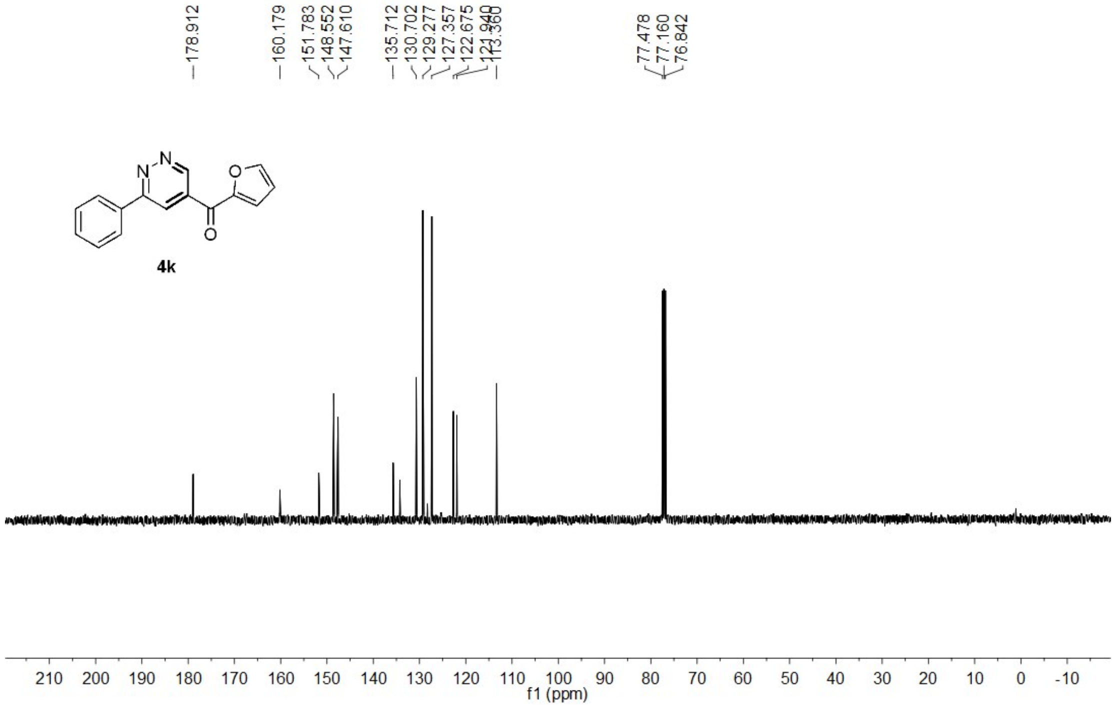
FJJ-R280



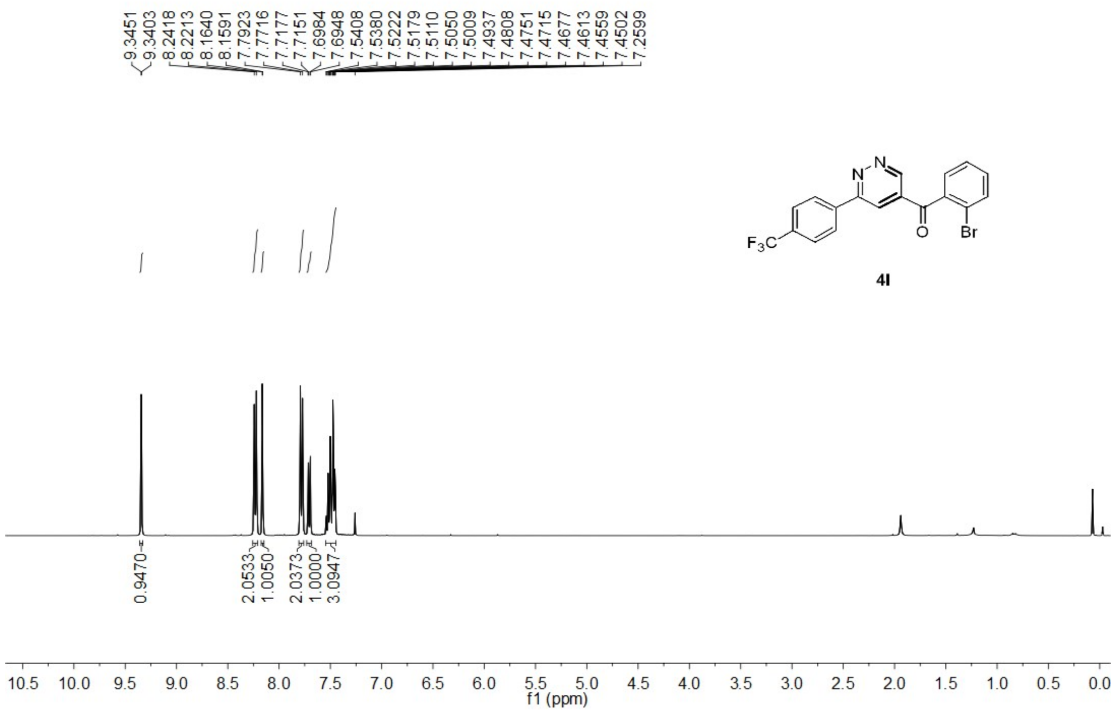
FJJ-R290



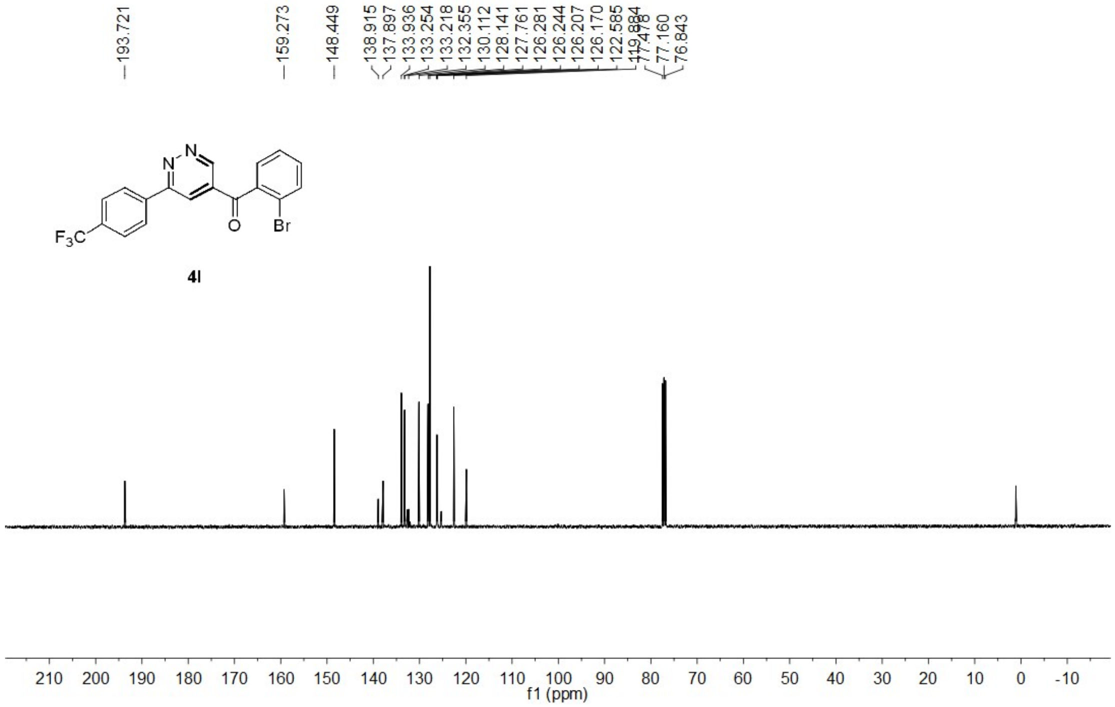
FJJ-R290



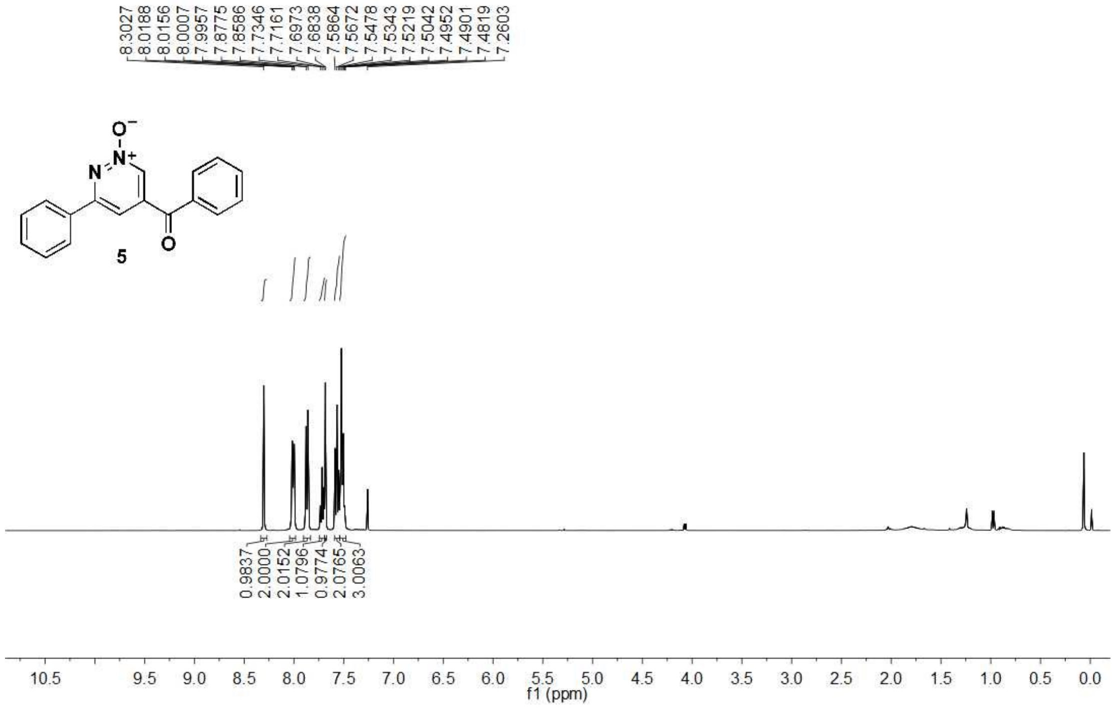
FJJ-R285



FJJ-R285-CF3



FJJ-N0-1



FJJ-N0-1