**Supporting information**

**Design and synthesis of selective Fms-like tyrosine kinase 3 inhibitors via exploration of back pocket II**

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**List of Contents**

[1. Representative off-target/selective ligands 1](#_Toc120033985)

[2. Chemistry 1](#_Toc120033986)

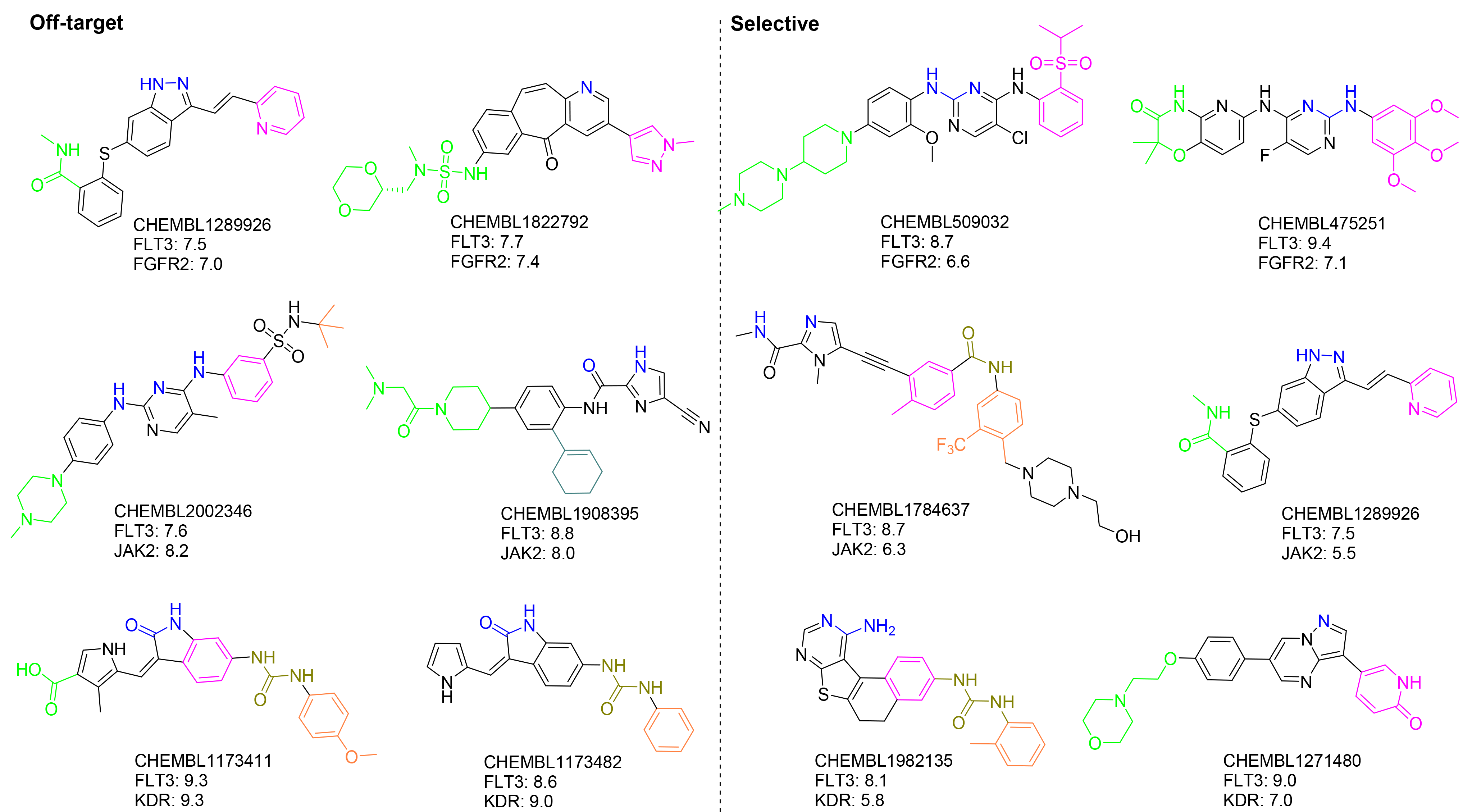
[3. Compounds Information 2](#_Toc120033987)

[3.1 Side chains 2](#_Toc120033988)

[2.2 Target compounds 2](#_Toc120033989)

[4. 1H NMR and 13C NMR Spectra of Title Compounds 8](#_Toc120033990)

## 1. Representative off-target/selective ligands



**Fig. 1.** Representative off-target/selective FLT3-FGFR2, FLT3-JAK2, and FLT3-KDR ligands.

## 2. Chemistry

**General Considerations**:Unless otherwise mentioned, all the reagents and solvents in the synthesis procedure were purchased from commercial sources and used as received. Air/moist sensitive reactions were performed under a nitrogen atmosphere using dried solvents which were transferred via syringes or stainless-steel cannulas. All the reaction was monitored by thin-layer chromatography (TLC) using Yantai silica gel pre-coated F254 plates (0.15–0.20 mm) and were visualized by ultraviolet (UV) light. Column chromatography was performed using silica gel (200-300 mesh) purchased from Qingdao Marine Chemical Plant with. Melting points (Mp.) were measured using a WRS-1B apparatus and were left uncorrected. 1H and 13C NMR spectra were obtained on a Bruker AV-500 spectrometer (500 MHz and 126MHz, respectively). NMR chemical shifts (δ ppm) were recorded with ppm and DMSO-*d6* with tetramethylsilane (TMS) as reference. Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constant (*J*) are provided in herz. ESI-MS spectra were recorded on a Waters Synapt HDMS spectrometer.

**Commonly Used Abbreviations**: **DMF**: *N*, *N*-dimethylformamide; **EtOAc**: ethyl acetate; **Na2SO4**: Sodium sulphate; **PE**: petroleum ether; **DIPEA**: **HATU**: N, N-Diisopropylethylamine; 2-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate; **DCM**: dichloromethane; **MeOH**: methanol

## 3. Compounds Information

### 3.1 Side chains



**20**, coulorless solid, yield76 %, white solid. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 12.15 (s, 1H), 4.21 (d, *J* = 13.1 Hz, 1H), 3.77 (d, *J* = 13.6 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.74 – 2.65 (m, 1H), 2.50 – 2.45 (m, 1H), 2.30 (q, *J* = 7.5 Hz, 2H), 1.81 (t, *J* = 14.0 Hz, 2H), 1.46 (m, *J* = 12.2, 4.0 Hz, 1H), 1.34 (qd, *J* = 12.2, 4.0 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H).



**23**, coulorless solid, yield76 %. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 12.66 (s, 1H), 10.24 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 2.08 (s, 3H).



**24**, coulorless solid, yield76 %. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 12.54 (s, 1H), 10.15 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 2.36 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H).

### 2.2 Target compounds



**10**, yellow solid, yield 44%. Mp: 237°C ~ 239°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.48 (s, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 3.5 Hz, 1H), 7.22 (s, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 5.51 (s, 2H), 2.60 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.85, 160.72, 158.43, 155.69, 149.53, 147.25, 140.11, 130.90, 129.66, 126.16, 120.89, 119.58, 118.03, 114.87, 102.58, 24.52. HRMS (ESI) calcd. for C18H14BrN4O3 [M+H]+:413.0249, found 413.0256.



**32**, yellow solid, yield 37%. Mp: 268°C ~ 270°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.46 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 3H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 3.4 Hz, 1H), 7.22 (s, 1H), 6.74 (dd, *J* = 3.2, 1.5 Hz, 1H), 5.51 (s, 2H), 2.60 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.85, 160.71, 158.44, 156.80, 147.76, 147.31, 146.44, 140.36, 130.70, 129.63, 120.79, 119.58, 115.64, 112.74, 102.58, 24.52. HRMS (ESI) calcd. for C18H15N4O3 [M+H]+:335.1144, found 335.1163.



**33**, yellow solid, yield 42%. Mp: 263°C ~ 265°C. .1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.22 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.18 (s, 1H), 5.47 (s, 2H), 4.43 (d, *J* = 13.0 Hz, 1H), 3.89 (d, *J* = 13.5 Hz, 1H), 3.09 (t, *J* = 11.9 Hz, 1H), 2.69 – 2.60 (m, 2H), 2.60 (d, *J* = 6.9 Hz, 3H), 2.02 (s, 3H), 1.83 (t, *J* = 12.1 Hz, 2H), 1.62 (dd, *J* = 24.6, 12.3 Hz, 1H), 1.45 (dd, *J* = 22.5, 10.3 Hz, 1H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 173.79, 169.85, 168.50, 160.69, 158.40, 147.37, 140.98, 130.11, 129.67, 119.74, 119.48, 102.55, 45.66, 43.21, 40.75, 29.17, 28.58, 24.52, 21.78. HRMS (ESI) calcd. for C21H24N5O3 [M+H]+:394.1879, found 394.1887.



**34**, yellow solid, yield 50%. Mp: 227°C ~ 229°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.21 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.18 (s, 1H), 5.47 (s, 2H), 4.45 (d, *J* = 12.9 Hz, 1H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.06 (t, *J* = 12.1 Hz, 1H), 2.68 – 2.60 (m, 2H), 2.59 (s, 3H), 2.41 – 2.23 (m, 2H), 1.84 (t, *J* = 9.5 Hz, 2H), 1.59 (qd, *J* = 12.6, 3.6 Hz, 1H), 1.45 (qd, *J* = 12.5, 3.9 Hz, 1H), 1.00 (t, *J* = 7.4 Hz, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 173.80, 171.59, 169.84, 160.69, 158.40, 147.37, 140.98, 130.09, 129.68, 119.72, 119.49, 102.54, 44.70, 43.31, 40.98, 29.21, 28.64, 26.04, 24.51, 9.98. HRMS (ESI) calcd. for C22H26N5O3 [M+H]+:408.2036, found 408.2047.



**35**, coulorless solid, yield 46 %. Mp: 208°C ~ 209°C. 1H NMR (500 MHz, CDCl3) *δ* (ppm): 9.27 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.02 (s, 1H), 4.25 (s, 2H), 3.90 – 3.72 (m, 4H), 3.20 (s, 2H), 2.69 (s, 3H), 2.68 – 2.61 (m, 4H). 13C NMR (126 MHz, CDCl3) *δ* (ppm): 170.09, 168.34, 161.21, 146.53, 138.88, 131.34, 129.32, 119.92, 119.11, 67.03, 62.47, 53.85, 24.70. HRMS (ESI) calcd. for C19H22N5O3 [M+H]+:368.1723, found 368.1733.



**36**, coulorless solid, yield 45 %. Mp: 228°C ~ 231°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.00 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.18 (s, 1H), 5.47 (s, 2H), 3.28 (p, *J* = 8.4 Hz, 1H), 2.59 (s, 3H), 2.25 (dq, *J* = 11.2, 9.1 Hz, 2H), 2.18 – 2.10 (m, 2H), 2.04 – 1.91 (m, 2H), 1.88 – 1.77 (m, 2H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 173.72, 169.86, 160.69, 158.42, 147.42, 141.11, 129.94, 129.66, 119.69, 119.50, 102.55, 25.07, 24.52, 18.20. HRMS (ESI) calcd. for C19H21N4O2 [M+H]+:337.1665, found 337.1674.



**37**, yellow solid, yield 47 %. Mp: 288°C ~ 290°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.36 (s, 1H), 10.25 (s, 1H), 7.98 (dd, *J* = 25.7, 8.6 Hz, 4H), 7.68 (dd, *J* = 62.1, 8.6 Hz, 4H), 7.22 (s, 1H), 5.47 (s, 2H), 2.61 (s, 3H), 2.10 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.87, 169.26, 165.67, 160.72, 158.41, 147.39, 142.92, 141.11, 130.45, 129.55, 129.28, 129.16, 120.76, 119.54, 118.62, 102.59, 24.61, 24.53. HRMS (ESI) calcd. for C22H20N5O3 [M+H]+:402.1566, found 402.1579.



**38**, yellow solid, yield 51%. Mp: 293°C ~ 295°C. . 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.36 (s, 1H), 10.18 (s, 1H), 7.99 (dd, *J* = 24.6, 8.5 Hz, 4H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.22 (s, 1H), 5.47 (s, 2H), 2.61 (s, 3H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.5 Hz, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 172.93, 169.87, 165.65, 160.72, 158.41, 147.39, 143.00, 141.11, 130.45, 129.55, 129.16, 120.77, 119.54, 118.65, 102.59, 30.06, 24.52, 9.95. HRMS (ESI) calcd. for C23H22N5O3 [M+H]+:416.1723, found 416.1734.



**39**, coulorless solid, yield 59 %. Mp: 209°C ~ 211°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.42 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 5.48 (s, 2H), 2.61 (s, 3H), 2.41 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.86, 166.11, 160.72, 158.42, 147.38, 142.30, 141.05, 132.35, 130.52, 129.57, 129.44, 128.23, 120.79, 119.55, 102.59, 24.53, 21.51. HRMS (ESI) calcd. for C21H19N4O2 [M+H]+:359.1508, found 359.1516.



**40**, coulorless solid, yield 38 %. Mp: 209°C ~ 211°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.47 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.95 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.22 (s, 1H), 5.48 (s, 1H), 2.61 (s, 1H), 2.34 (s, 1H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.86, 165.33, 160.74, 158.42, 147.35, 140.90, 131.98, 131.93, 131.37, 131.34, 130.67, 129.60, 128.24, 128.16, 125.05, 124.91, 120.81, 119.57, 115.60, 115.41, 102.60, 24.53, 14.68, 14.65. HRMS (ESI) calcd. for C21H18FN4O2 [M+H]+:377.1414, found 377.1422.



**41**, coulorless solid, yield 57 %. Mp: 233°C ~ 235°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.49 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 14.2, 6.7 Hz, 1H), 7.30 – 7.09 (m, 3H), 5.47 (s, 2H), 3.80 (s, 2H), 2.59 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.85, 168.88, 162.12, 160.70, 160.17, 158.40, 147.33, 140.84, 132.48, 132.45, 130.28, 129.75, 129.37, 129.30, 124.74, 124.71, 123.32, 123.20, 119.72, 119.52, 115.59, 115.42, 102.56, 36.92, 24.51. HRMS (ESI) calcd. for C21H18FN4O2 [M+H]+:377.1414, found 377.1418.



**42**, coulorless solid, yield 57 %. Mp: 188°C ~ 190°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.46 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 14.5, 7.4 Hz, 1H), 7.29 – 7.16 (m, 3H), 7.10 (t, *J* = 8.8 Hz, 1H), 5.46 (s, 2H), 3.74 (s, 2H), 2.59 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.85, 169.38, 160.70, 158.39, 147.31, 140.78, 138.98, 130.67, 130.61, 130.35, 129.73, 125.80, 119.77, 119.51, 116.52, 116.35, 113.98, 113.82, 102.55, 43.35, 24.51. HRMS (ESI) calcd. for C21H18FN4O2 [M+H]+:377.1414, found 377.1419.



**43**, coulorless solid, yield 49 %. Mp: 246°C ~ 249°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.44 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.27 (dd, *J* = 8.0, 4.1 Hz, 1H), 7.23 – 7.13 (m, 4H), 5.48 (s, 2H), 3.74 (s, 2H), 2.59 (s, 3H), 2.32 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.87, 169.85, 160.69, 158.42, 147.35, 140.93, 137.14, 134.95, 130.44, 130.37, 130.20, 129.74, 127.21, 126.25, 119.71, 119.52, 102.54, 41.52, 24.52, 19.87. HRMS (ESI) calcd. for C22H21N4O2 [M+H]+:373.1665, found 373.1674.



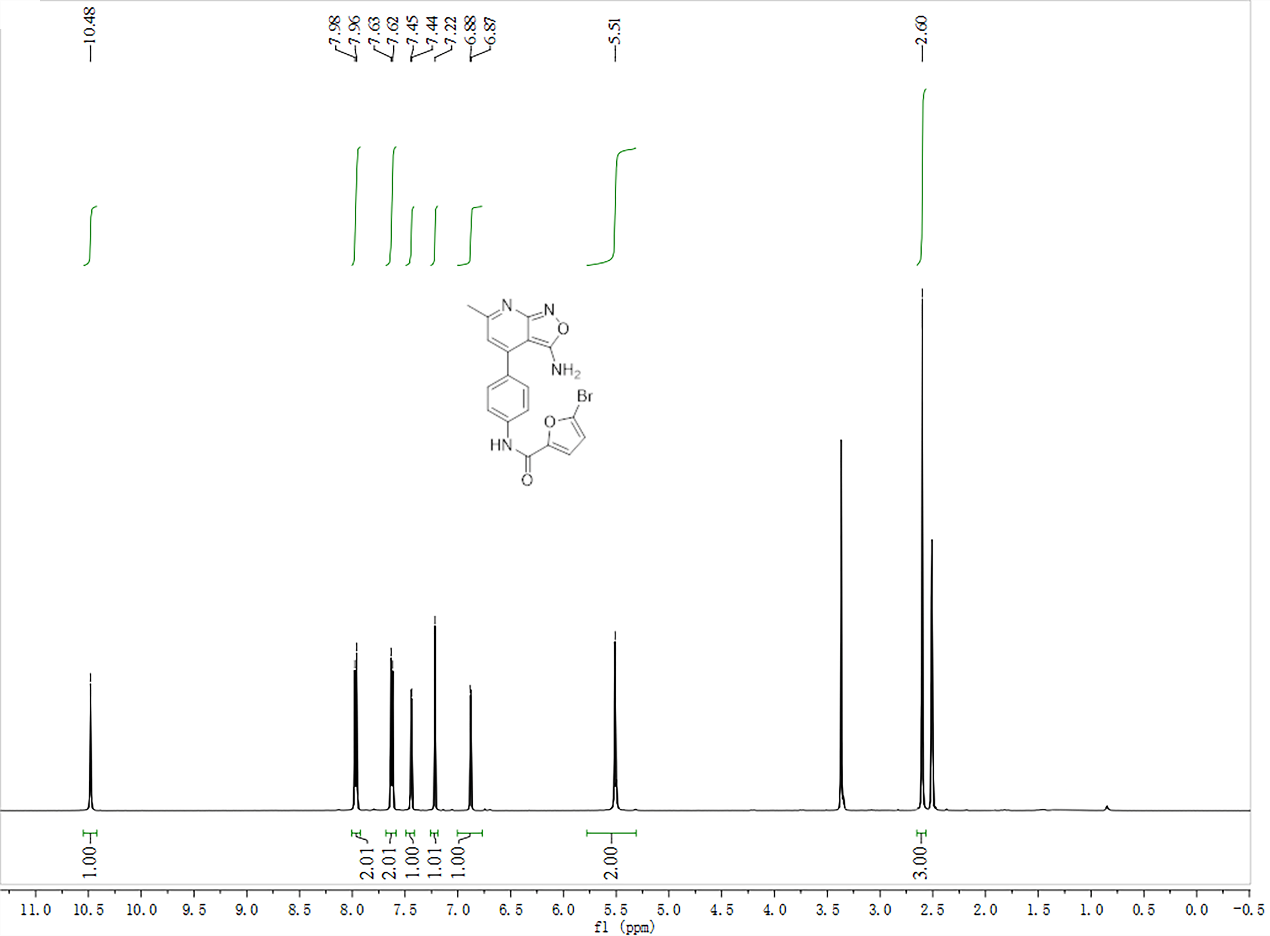
**44**, coulorless solid, yield 56 %. Mp: 203°C ~ 205°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.41 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.13 (m, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.45 (s, 2H), 3.65 (s, 2H), 2.59 (s, 3H), 2.31 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.97, 169.85, 160.69, 158.39, 147.33, 140.92, 137.85, 136.16, 130.24, 130.18, 129.71, 128.71, 127.69, 126.61, 119.73, 119.50, 102.55, 43.86, 24.51, 21.47. HRMS (ESI) calcd. for C22H21N4O2 [M+H]+:373.1665, found 373.1677.



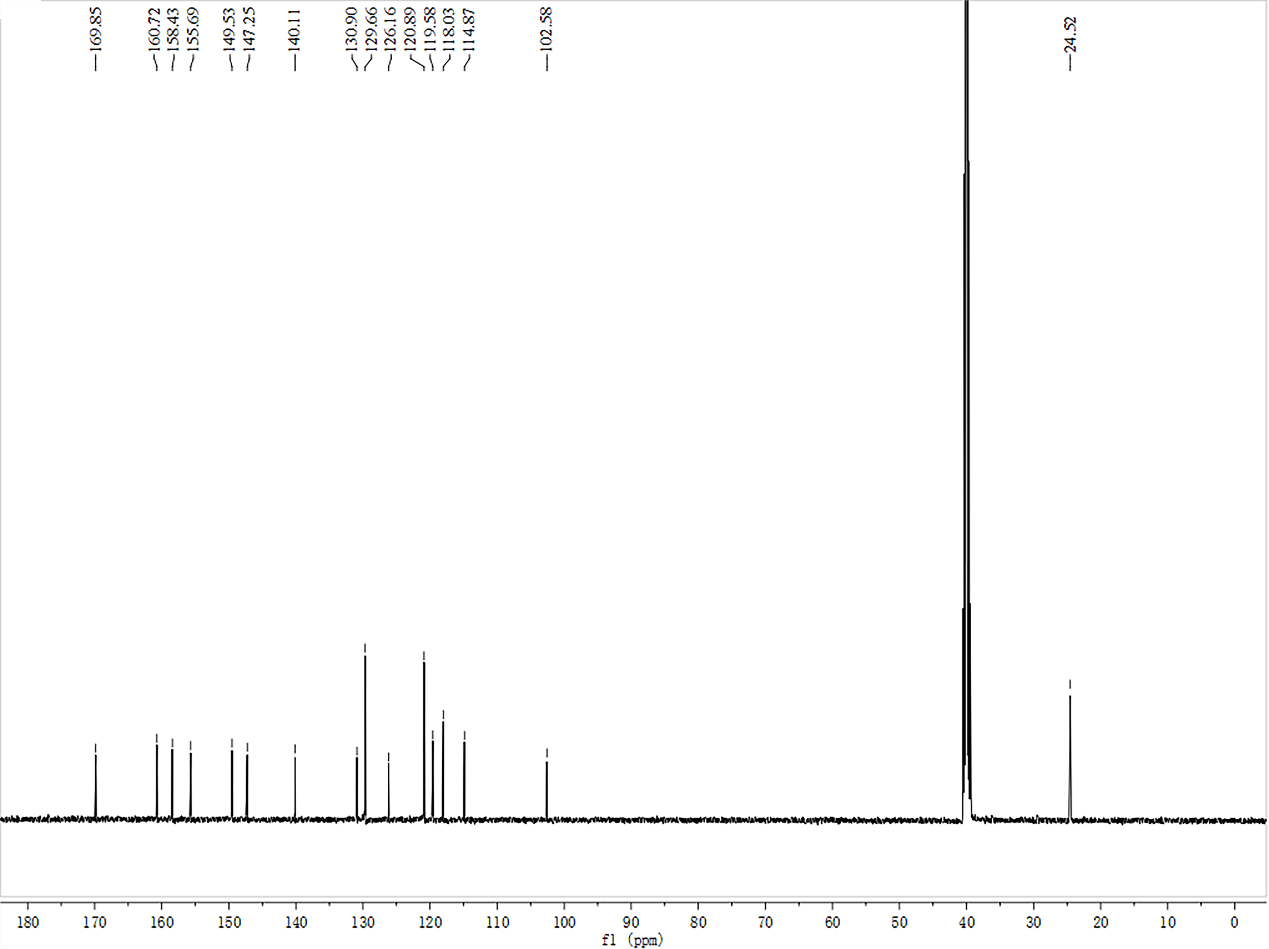
**45**, coulorless solid, yield 64 %. Mp: 207°C ~ 209°C. 1H NMR (500 MHz, DMSO-*d*6) *δ* (ppm): 10.42 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.18 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.46 (s, 2H), 3.76 (s, 3H), 3.66 (s, 2H), 2.59 (s, 3H). 13C NMR (126 MHz, DMSO-*d*6) *δ* (ppm): 169.84, 169.80, 160.70, 159.68, 158.41, 147.33, 140.89, 137.70, 130.25, 129.83, 129.74, 121.77, 119.72, 119.51, 115.38, 112.41, 102.53, 55.45, 43.93, 24.51. HRMS (ESI) calcd. for C22H21N4O3 [M+H]+:389.1614, found 389.1622.

## 4. 1H NMR and 13C NMR Spectra of Title Compounds

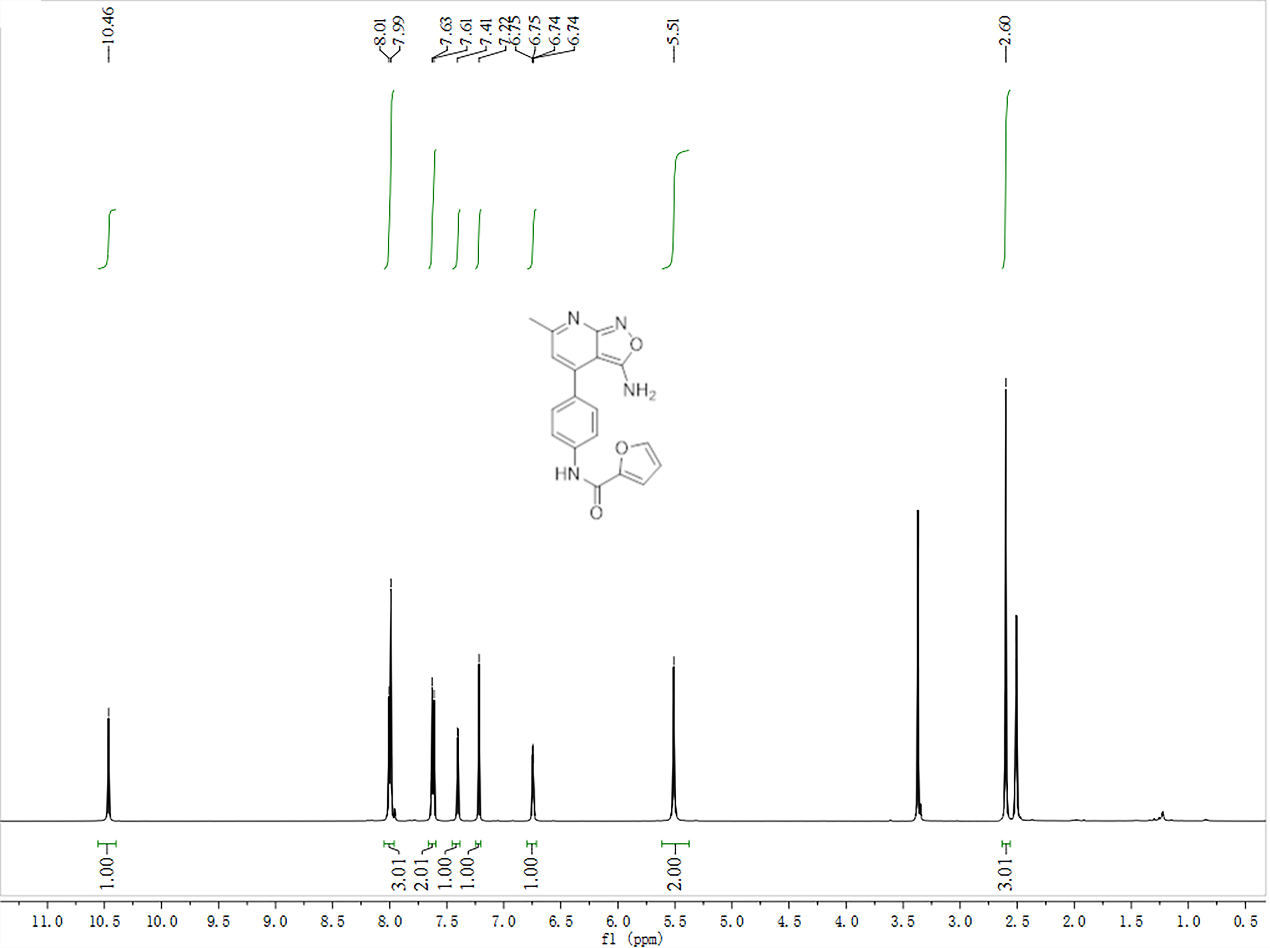
**1H NMR spectrum of compound 10**



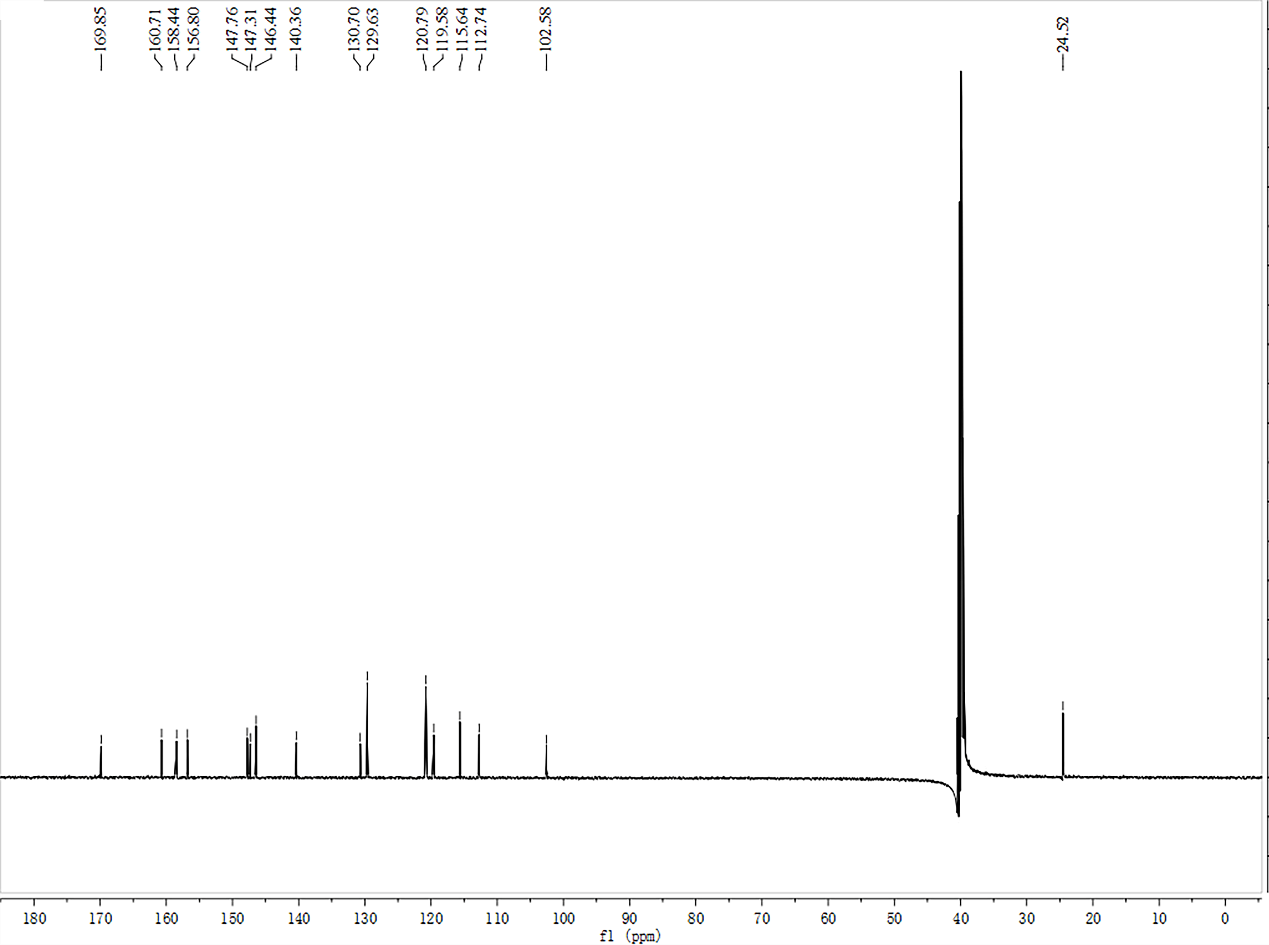
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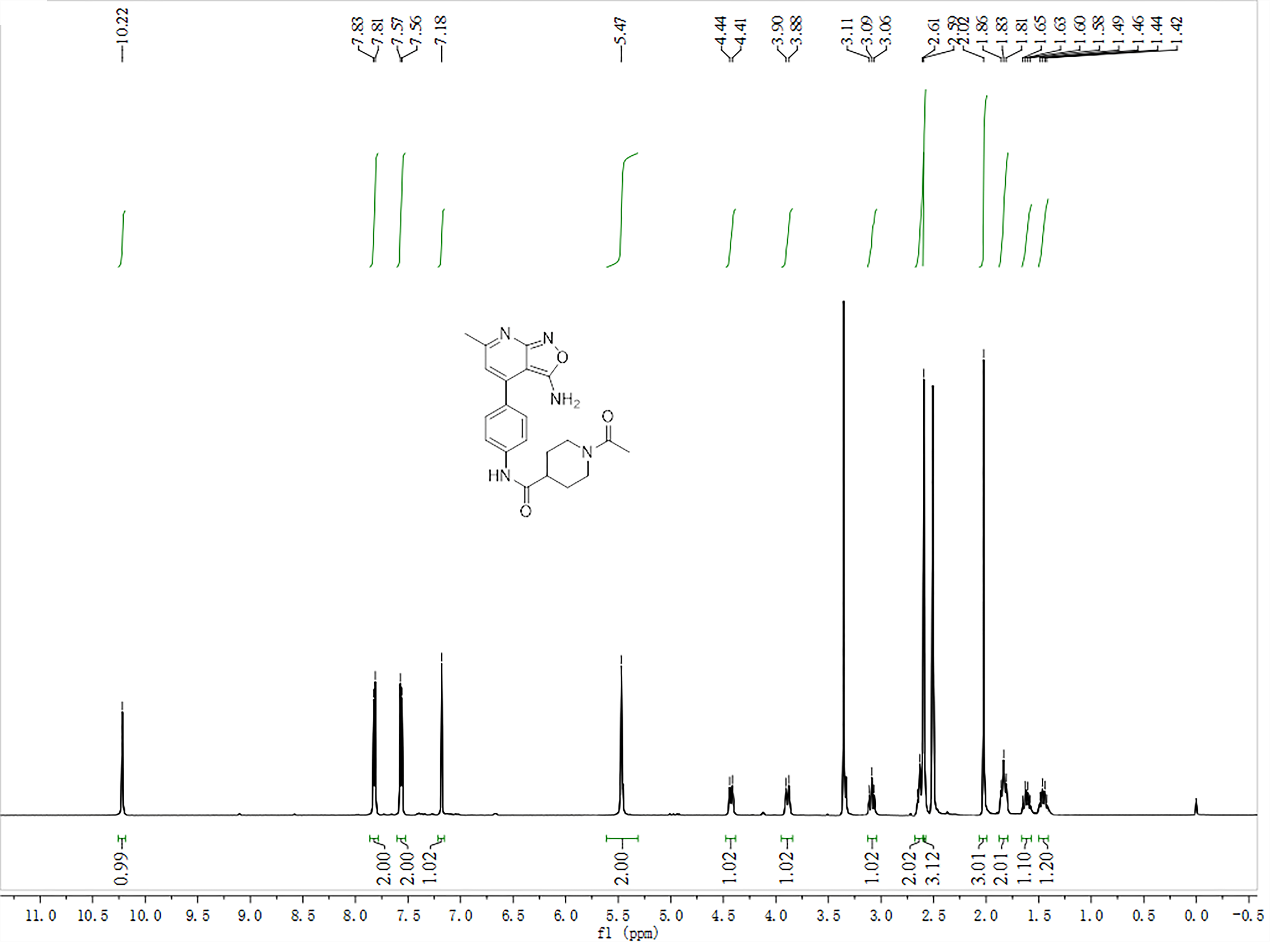
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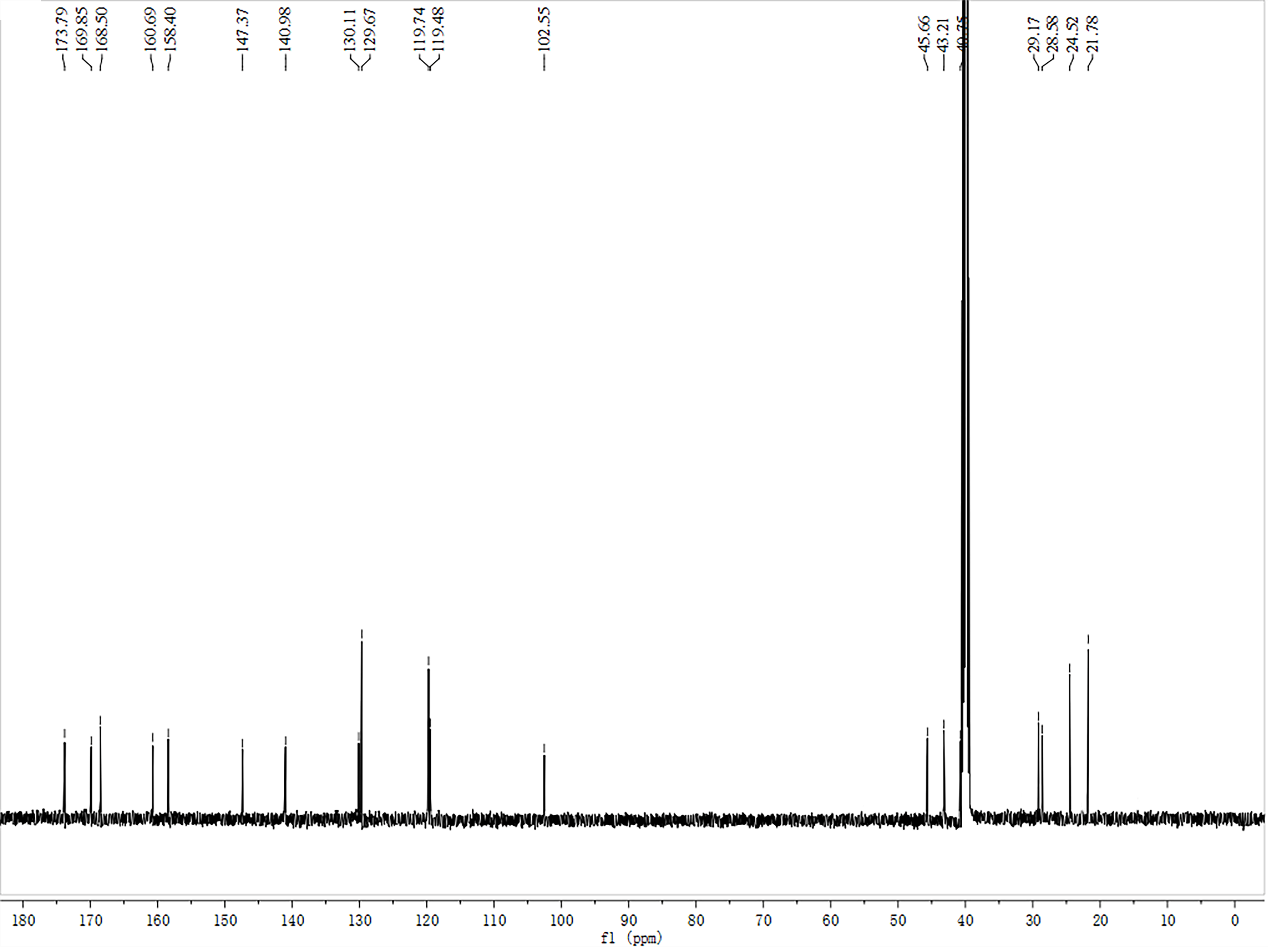
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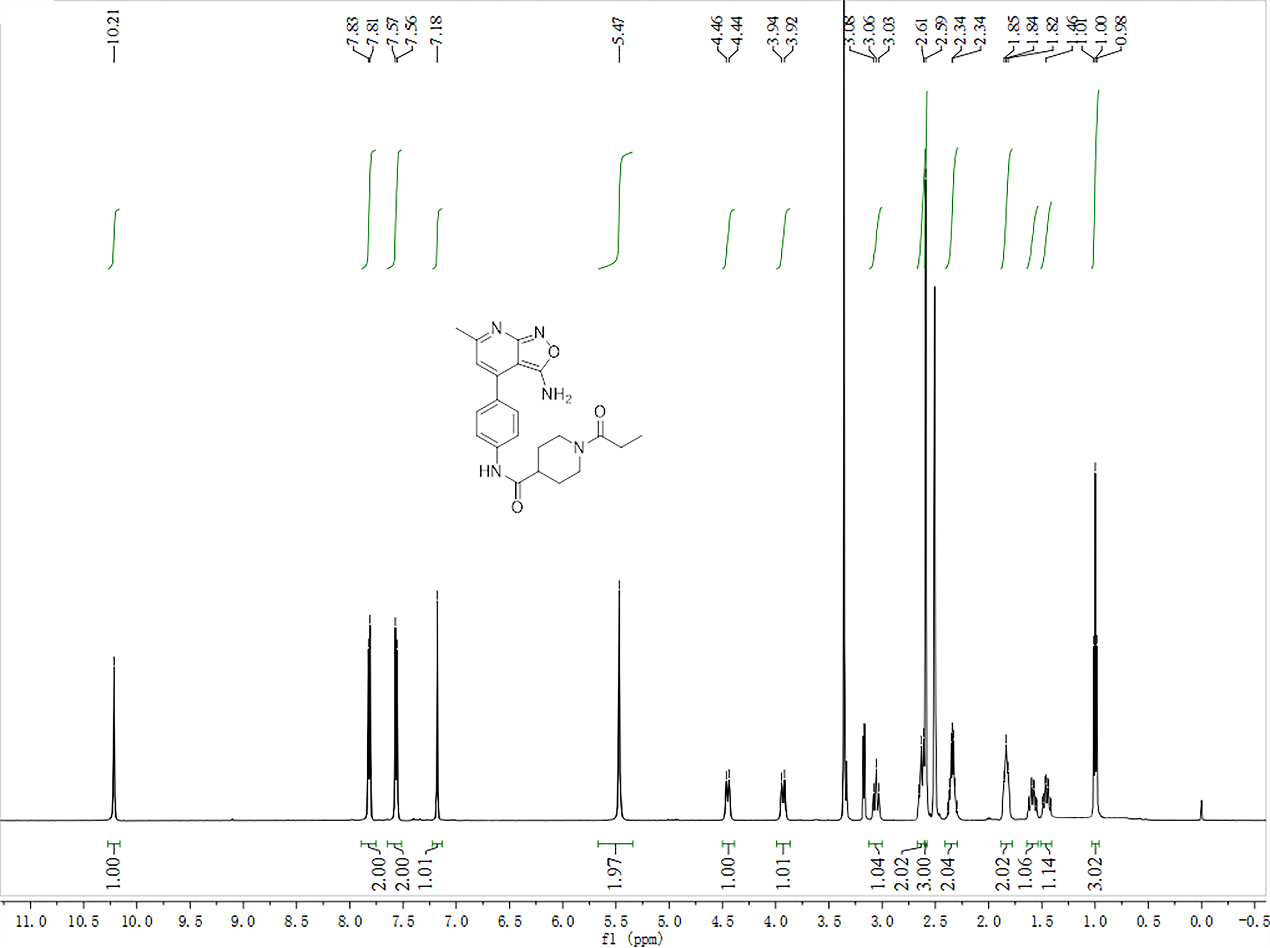
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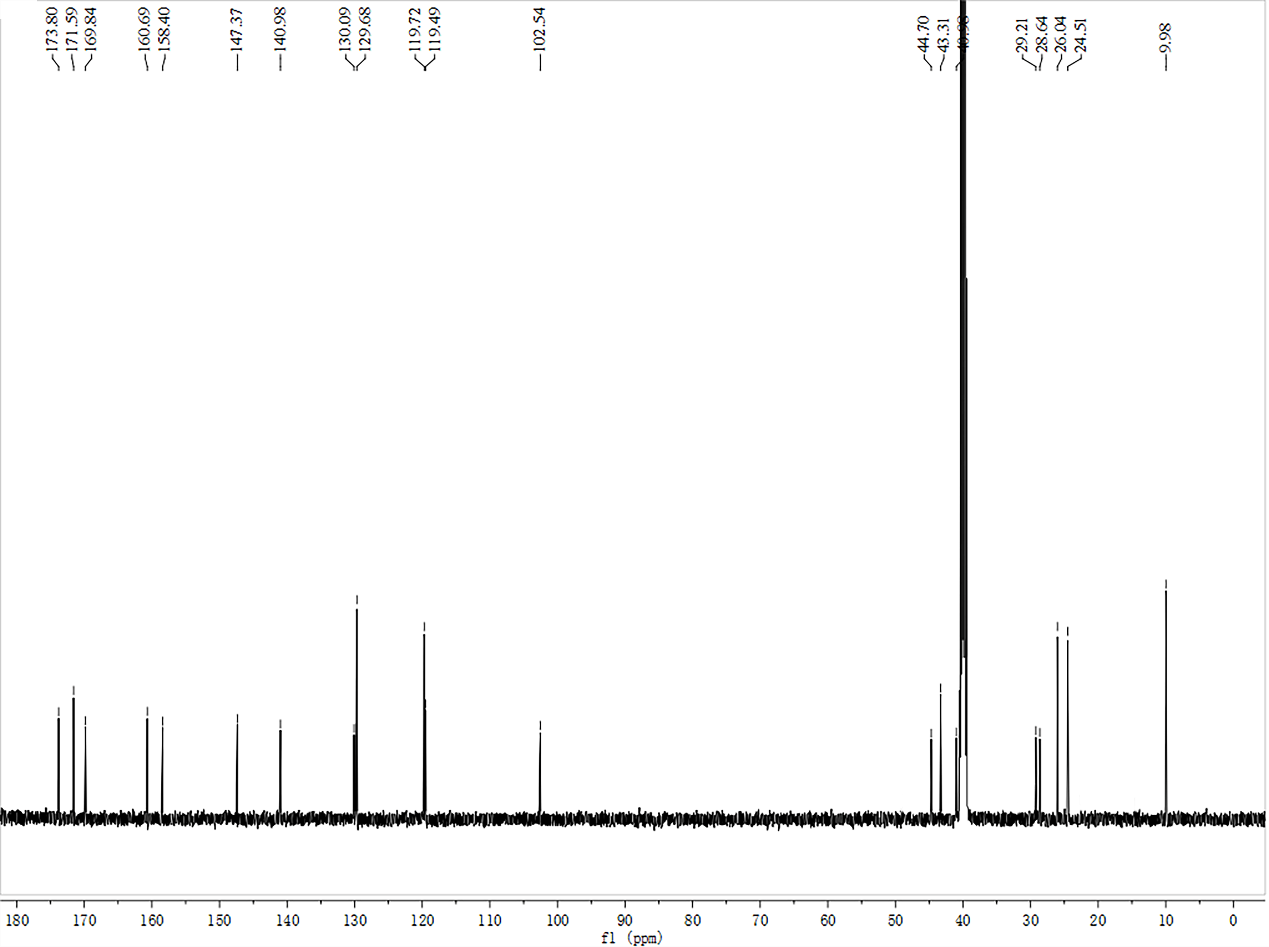
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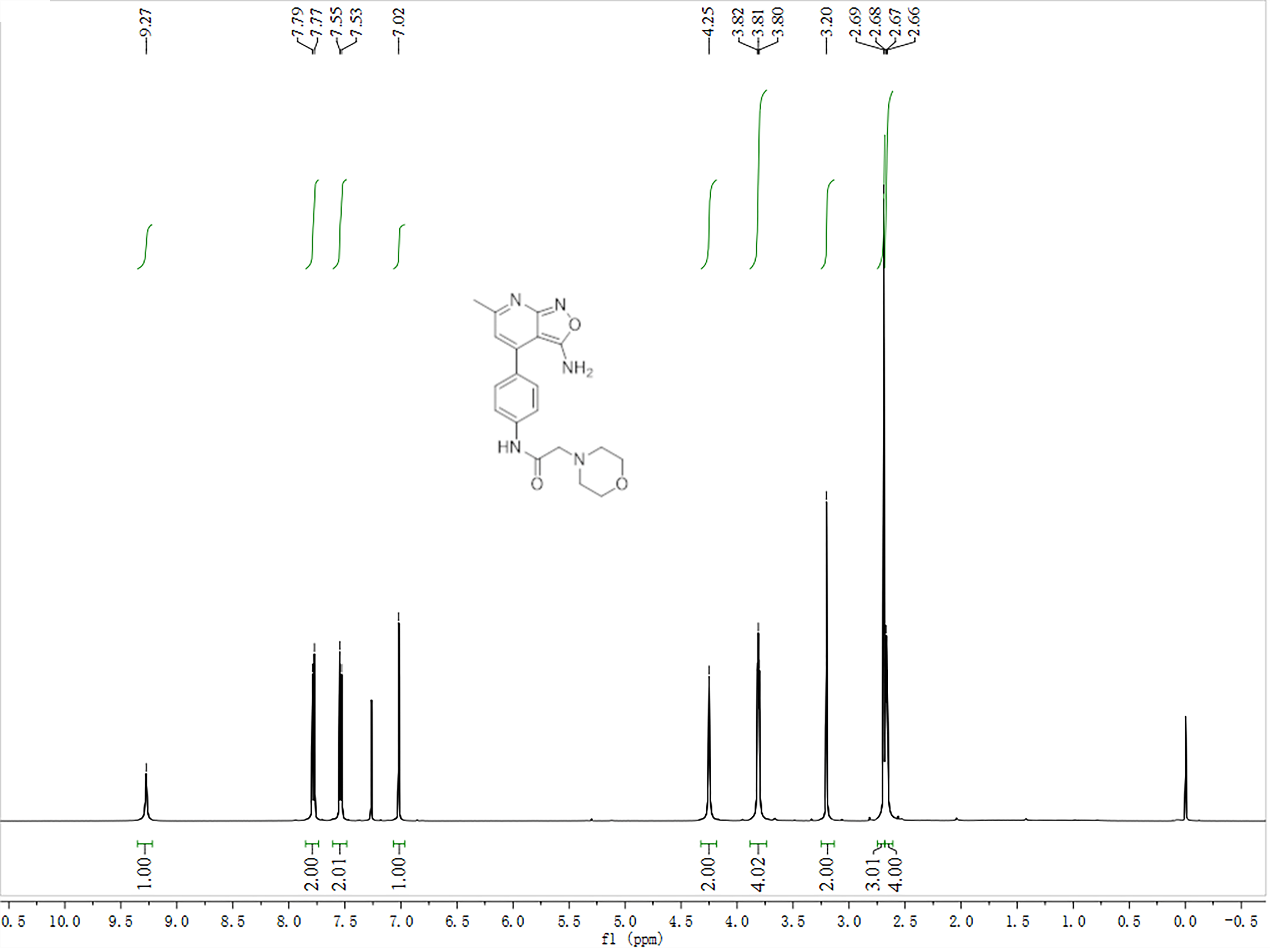
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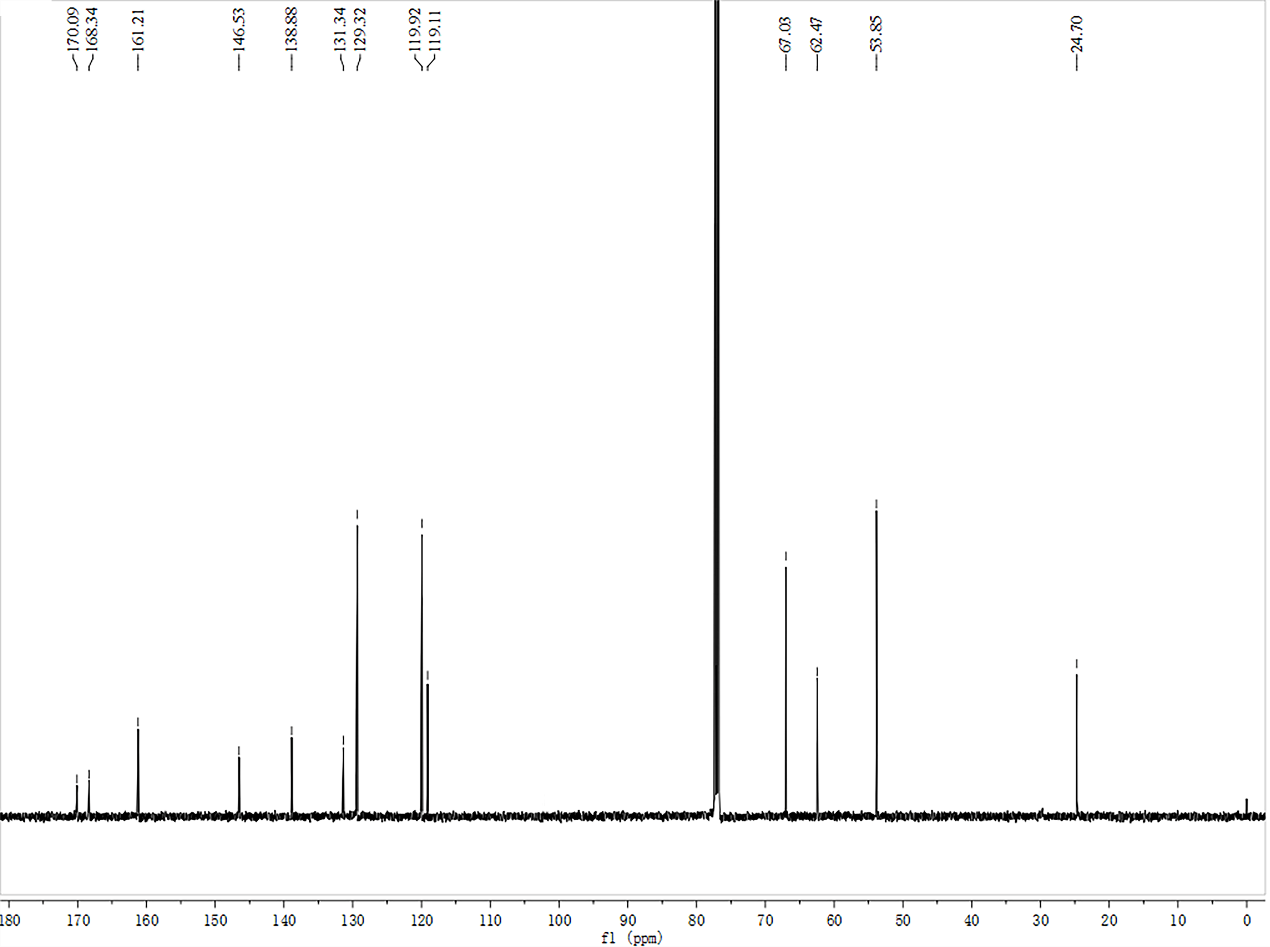
**13C NMR spectrum of compound 34**



**1H NMR spectrum of compound 35**

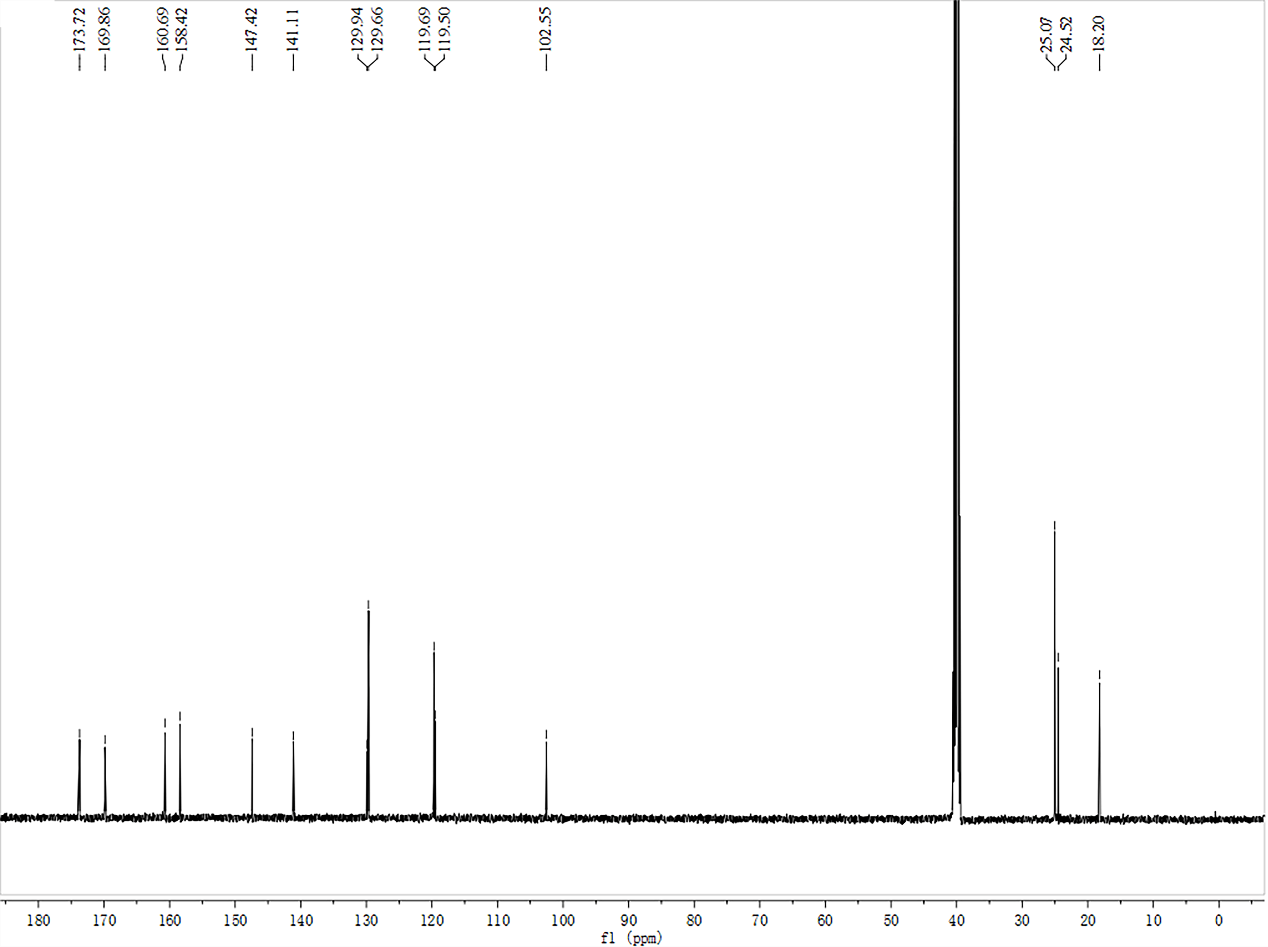
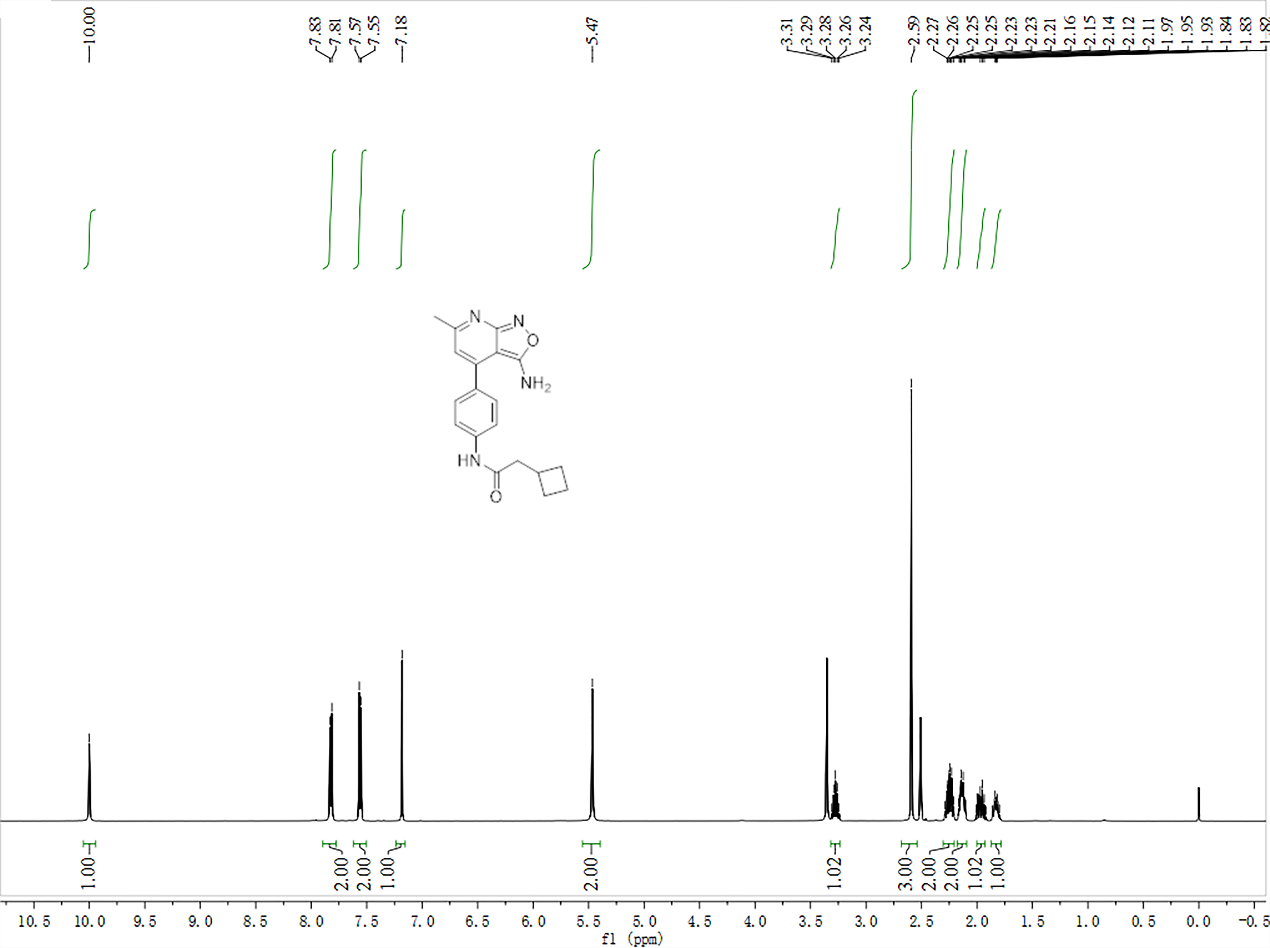


**13C NMR spectrum of compound 35**

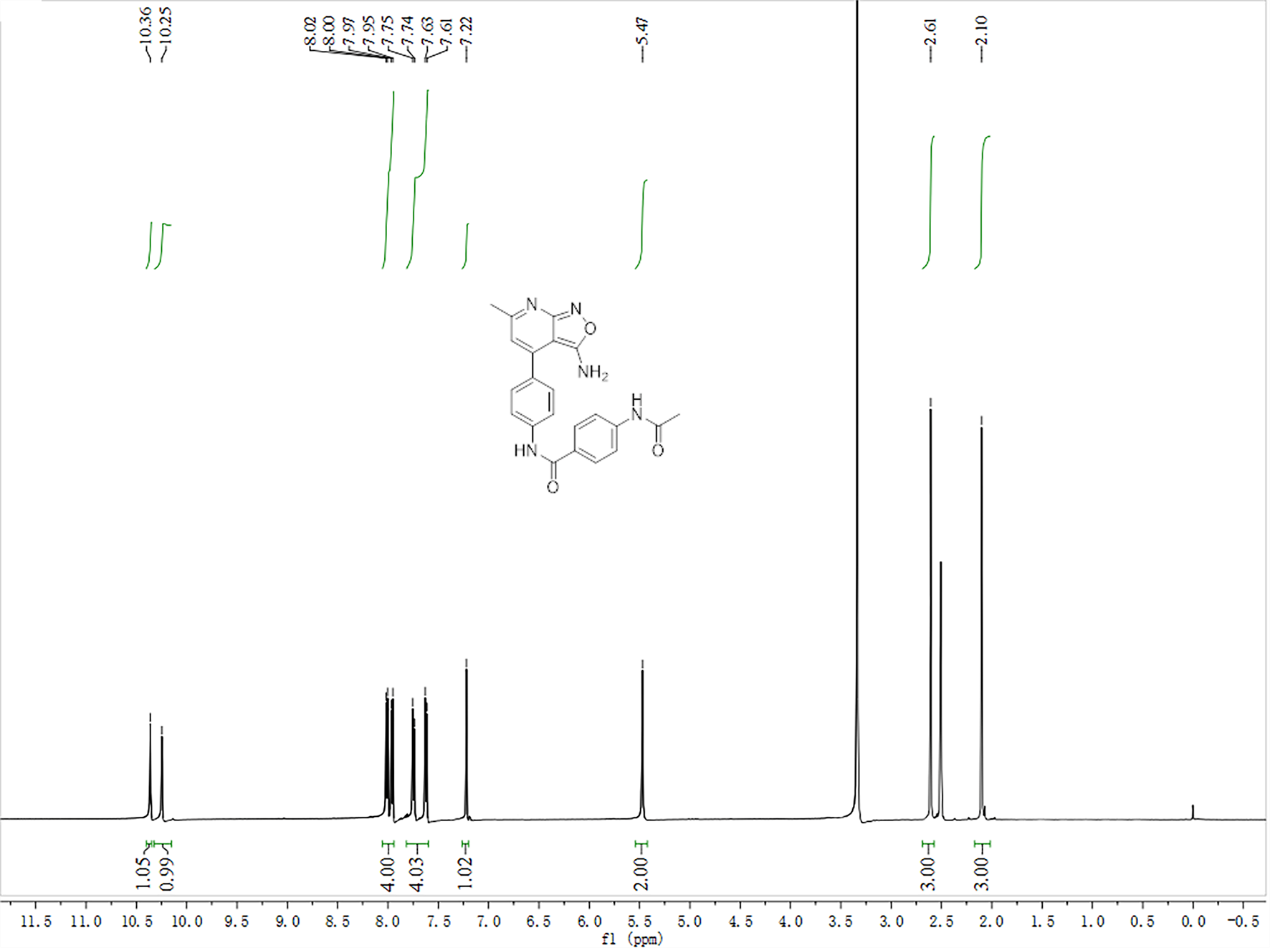


**1H NMR spectrum of compound 36**

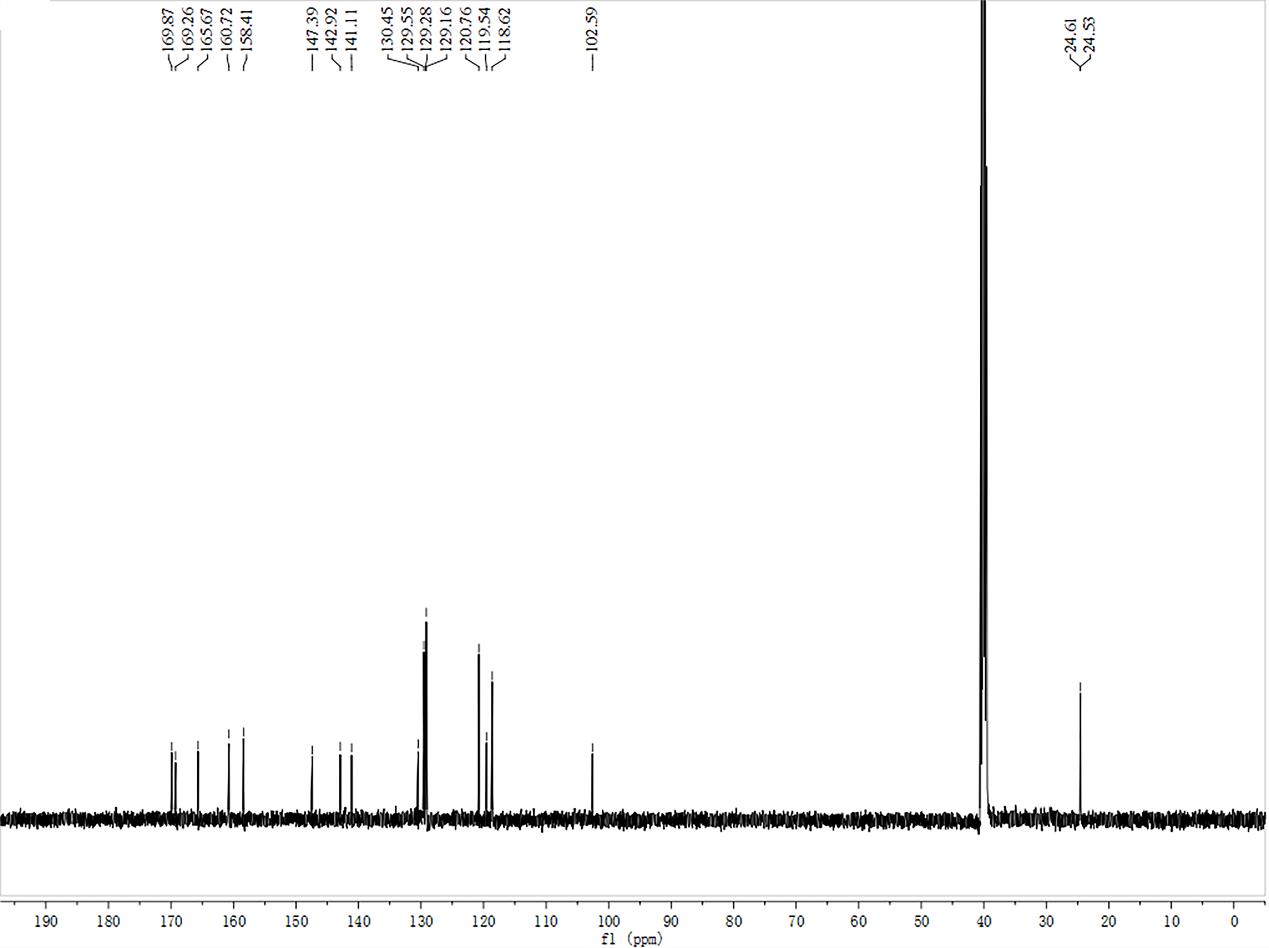
**13C NMR spectrum of compound 36**



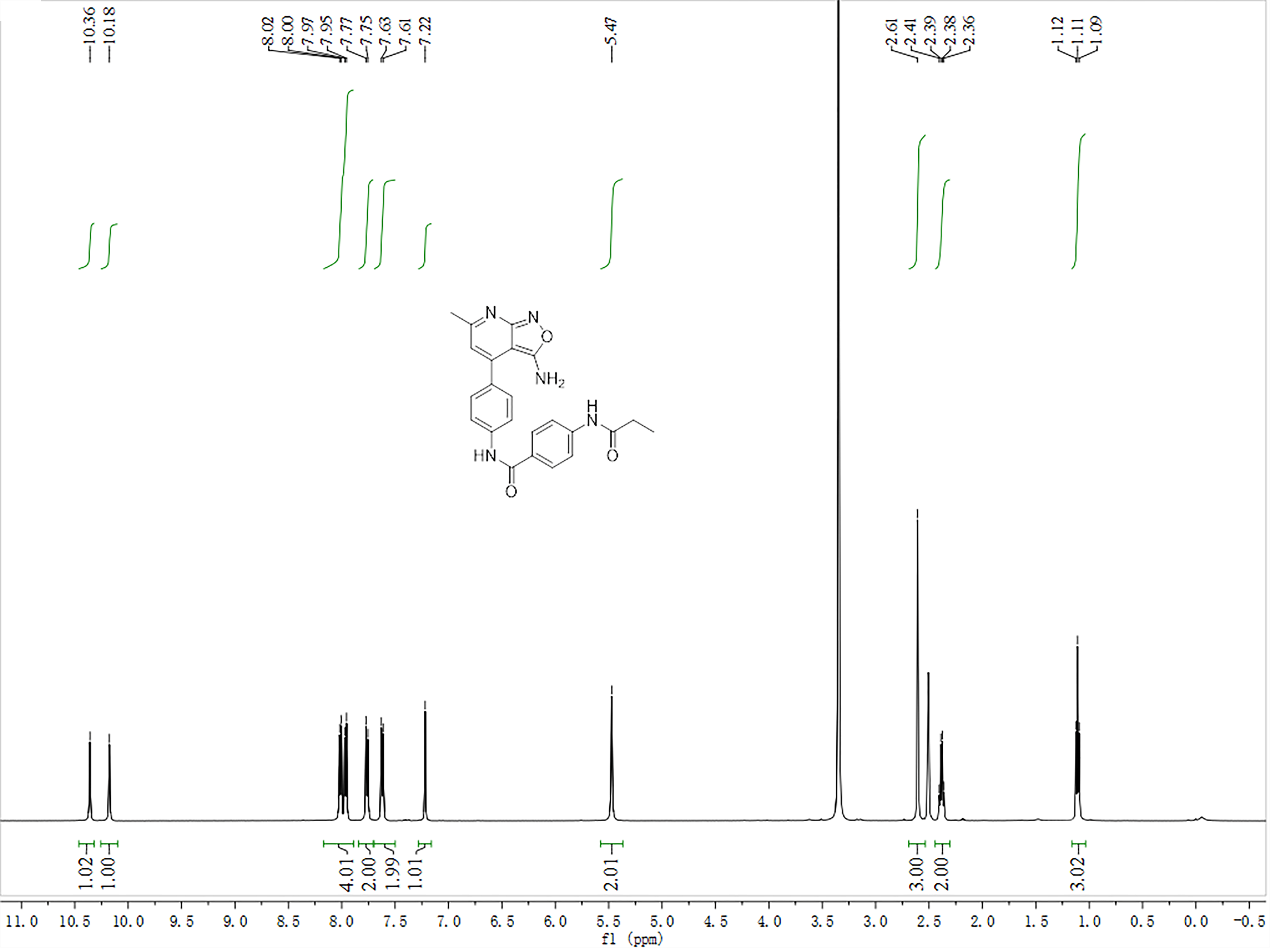
**1H NMR spectrum of compound 37**



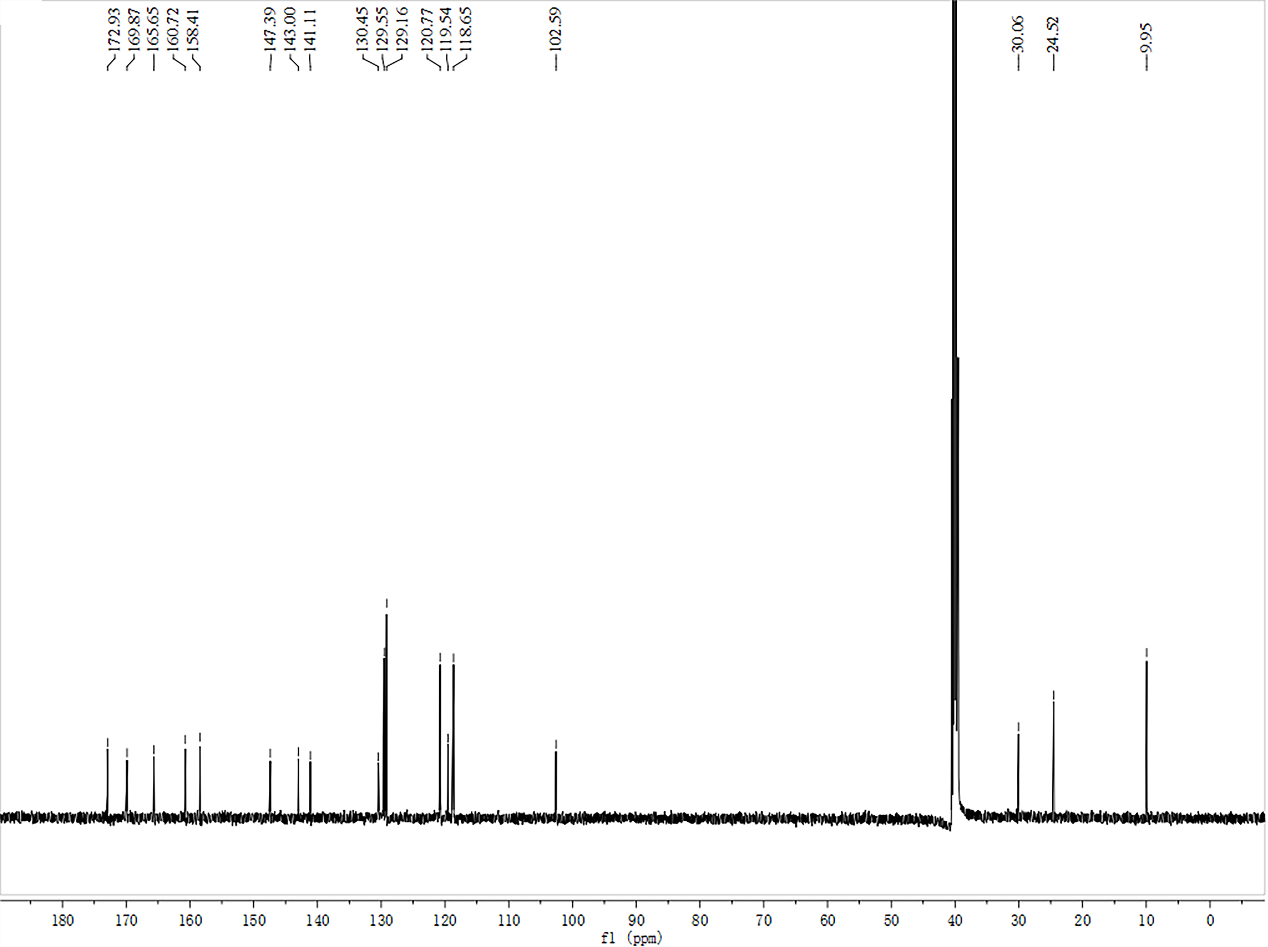
**13C NMR spectrum of compound 37**



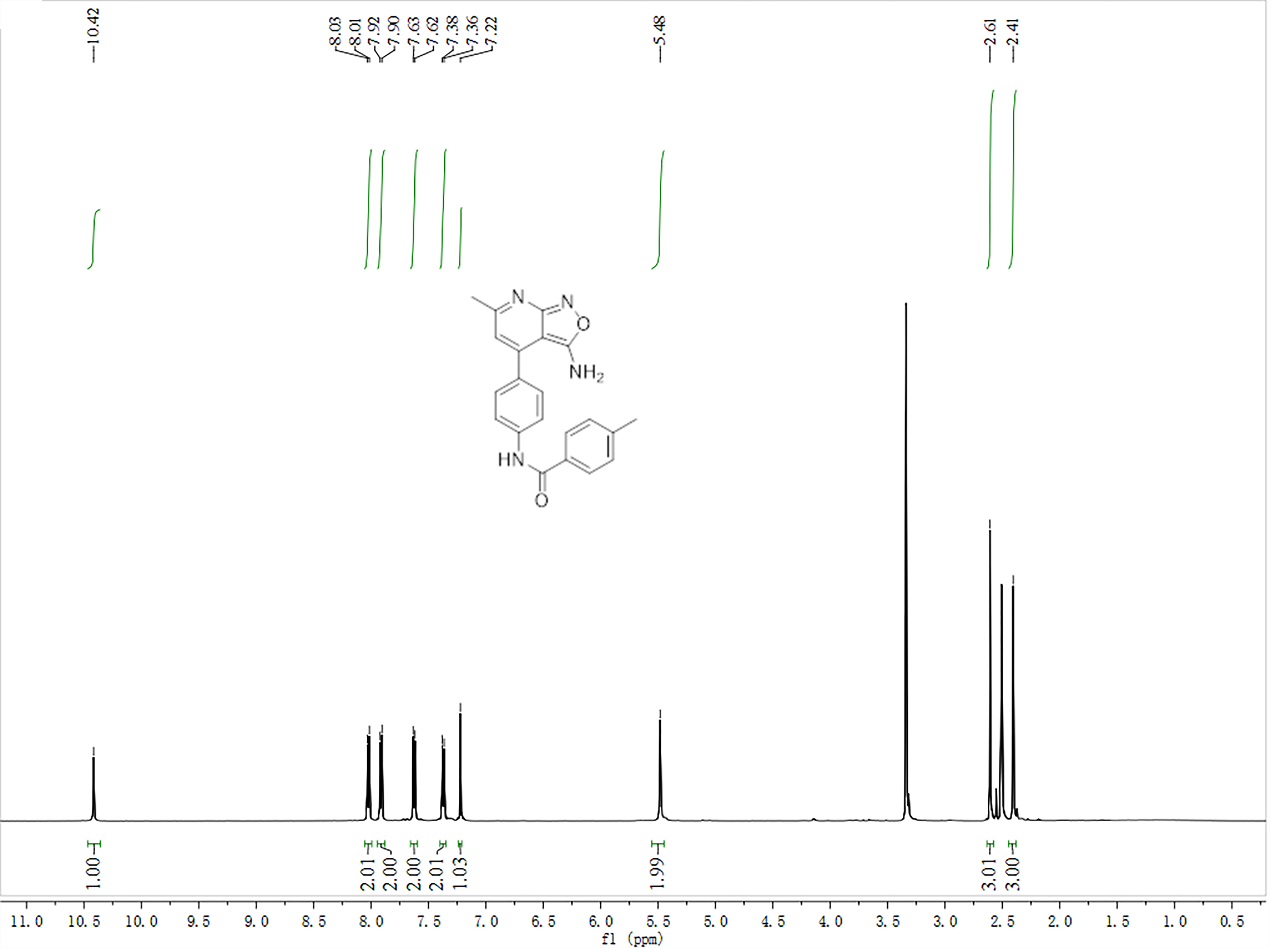
**1H NMR spectrum of compound 38**



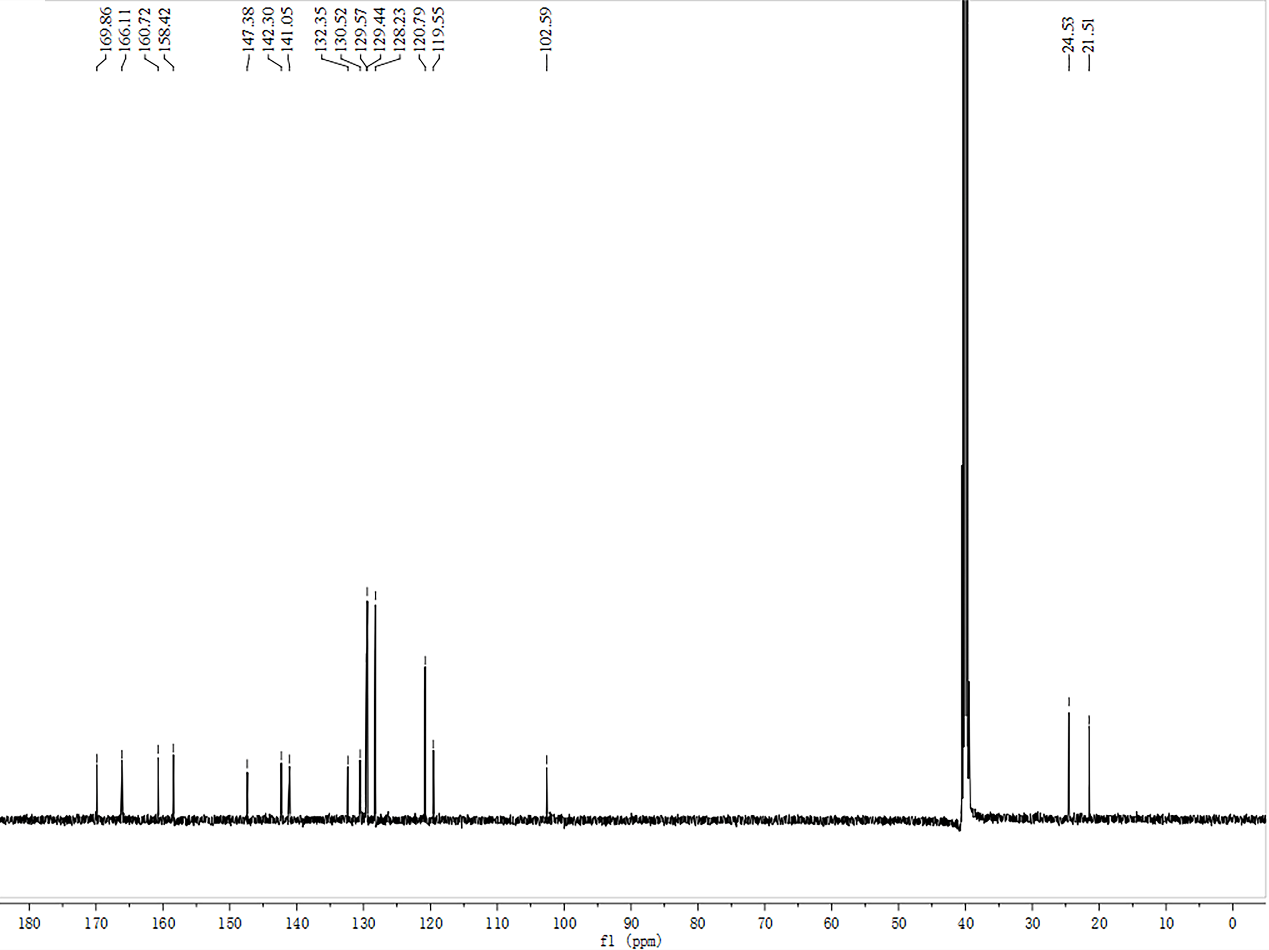
**13C NMR spectrum of compound 38**



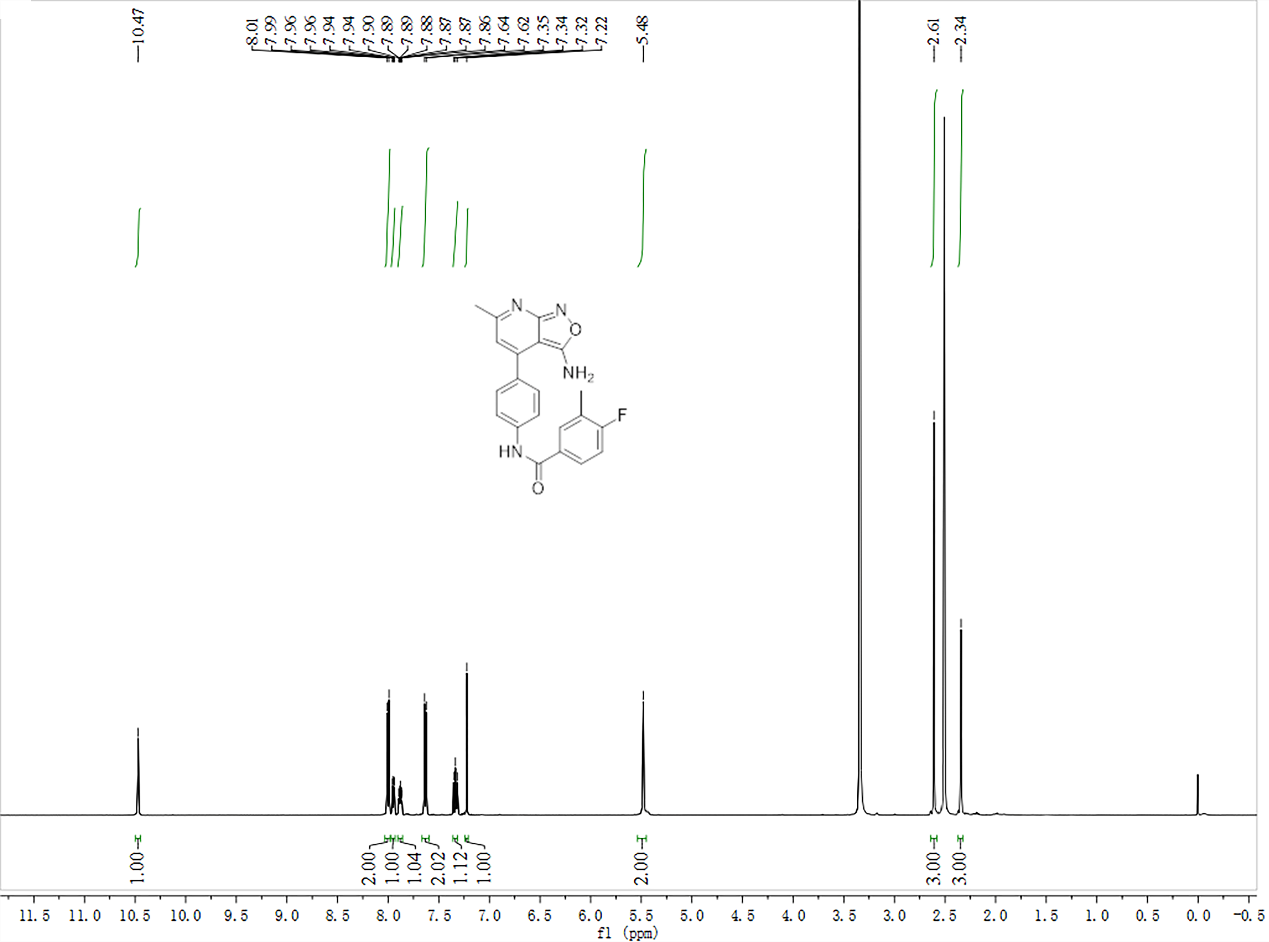
**1H NMR spectrum of compound 39**



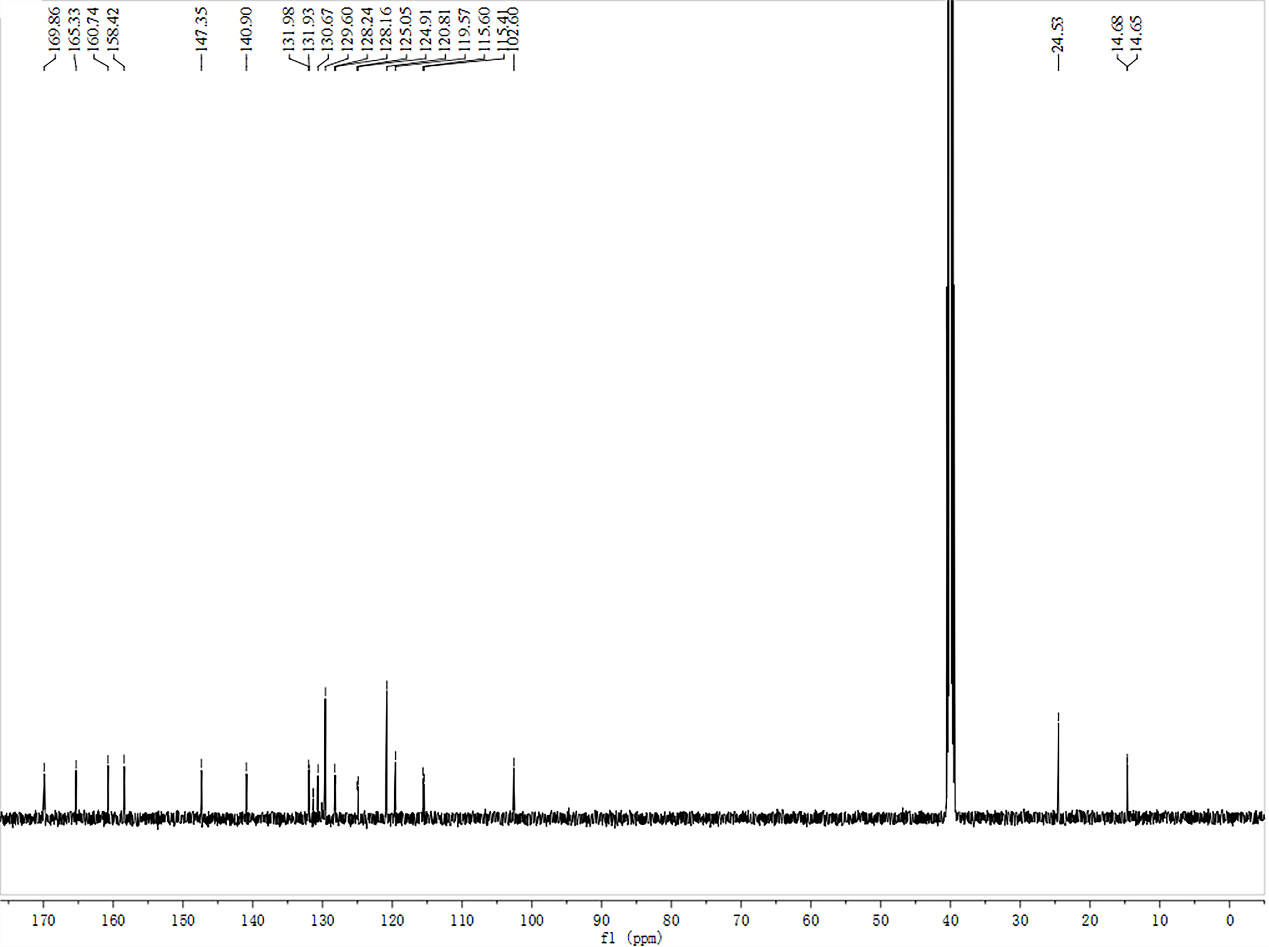
**13C NMR spectrum of compound 39**



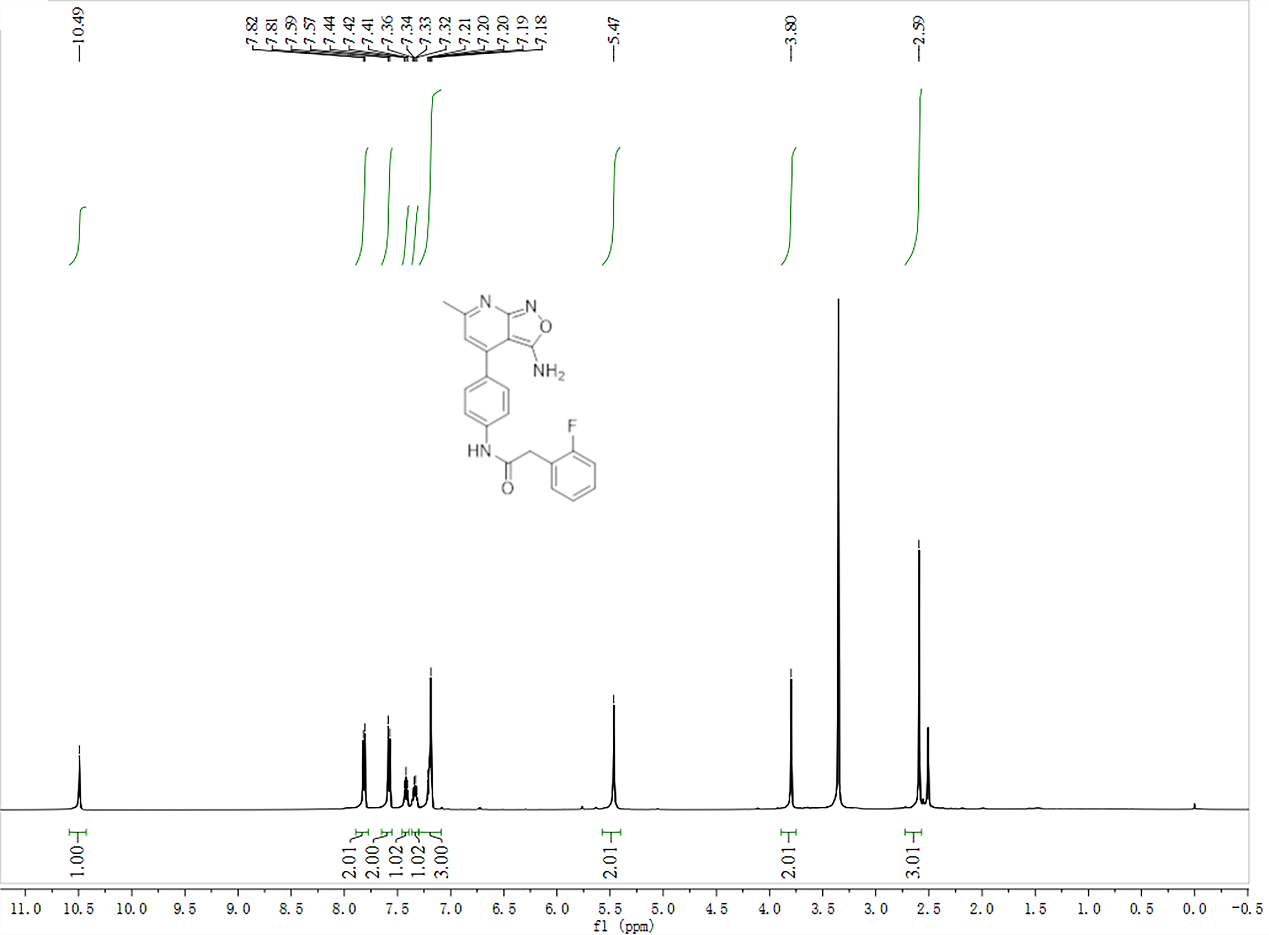
**1H NMR spectrum of compound 40**



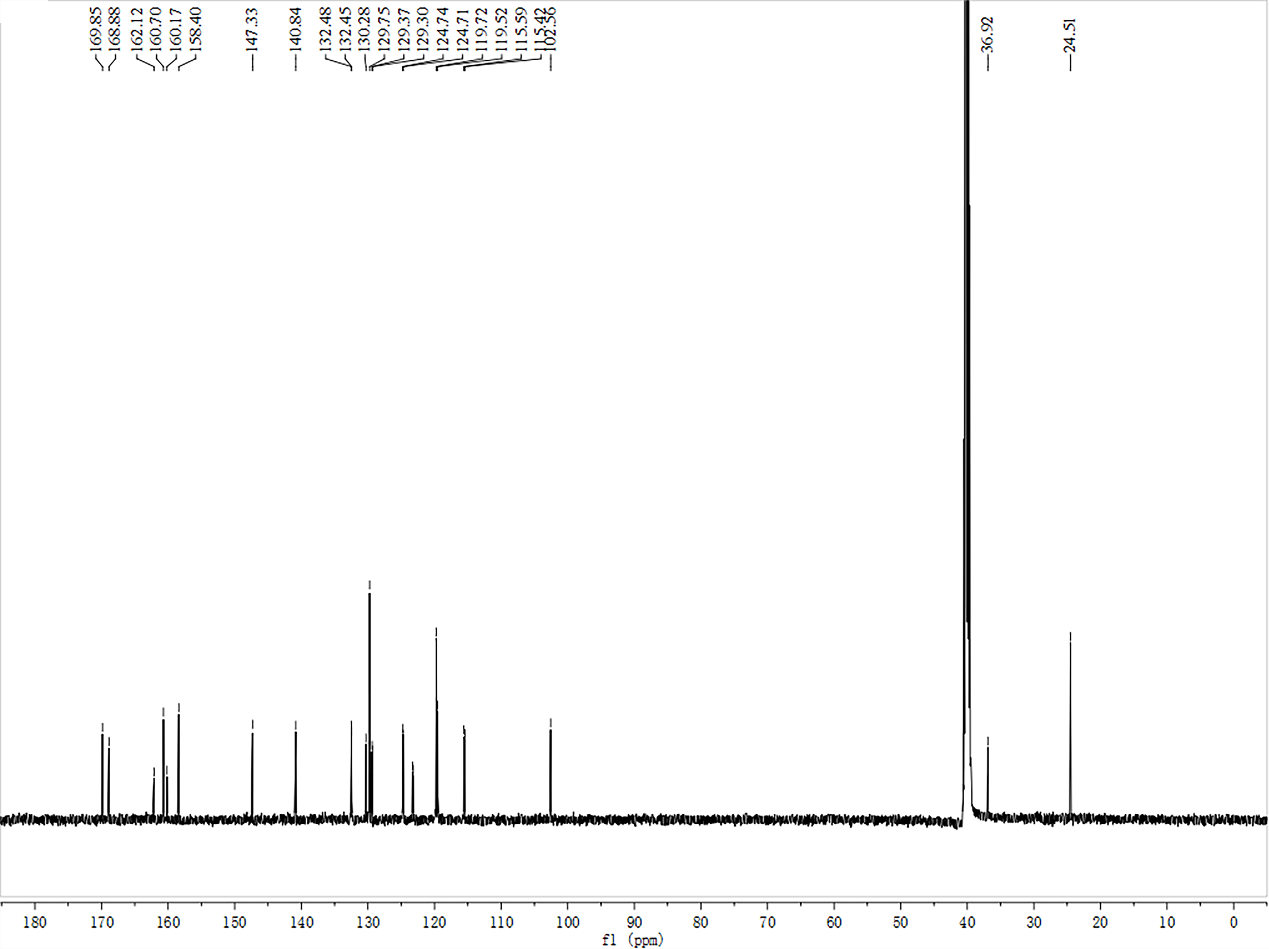
**13C NMR spectrum of compound 40**



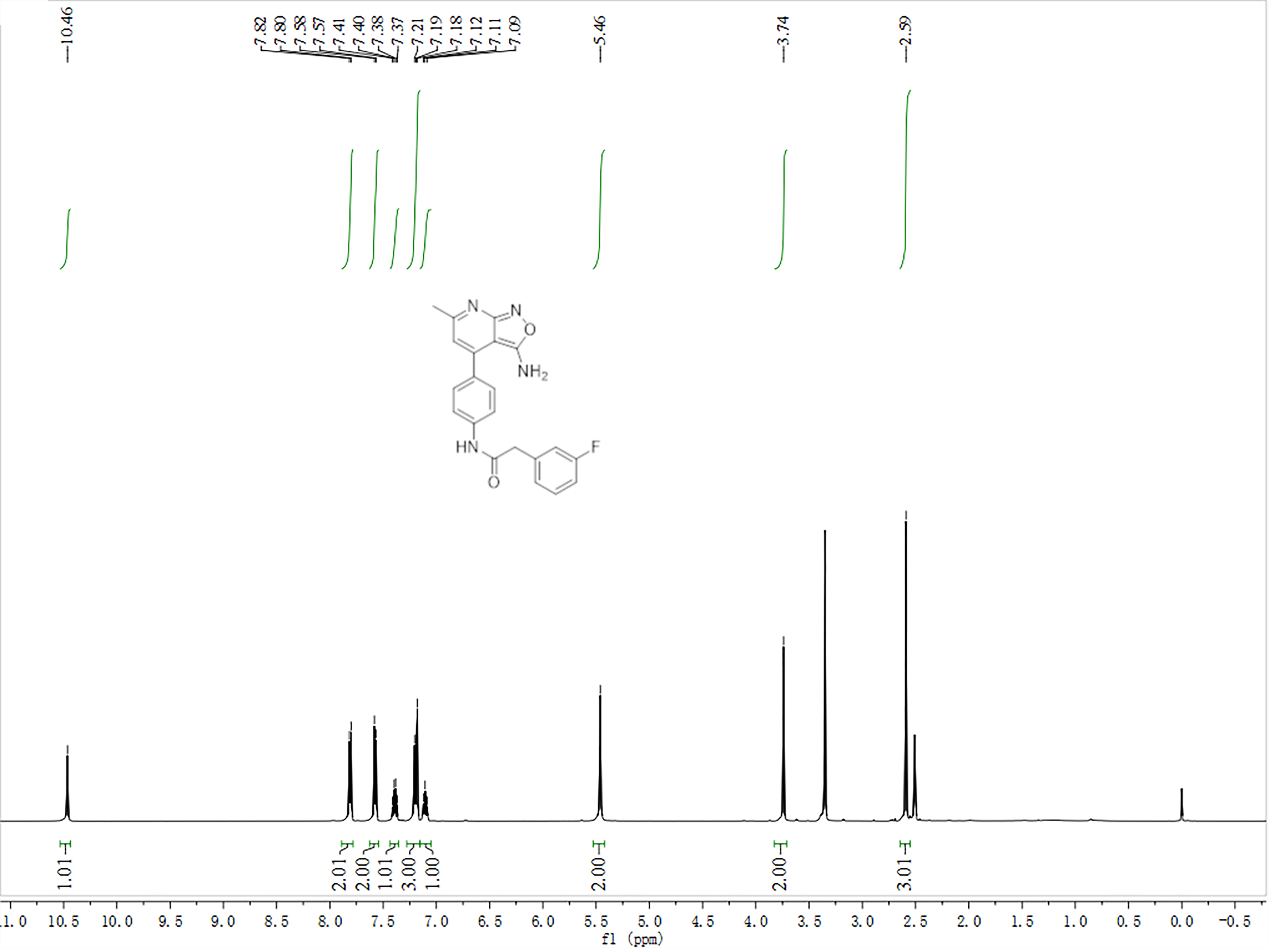
**1H NMR spectrum of compound 41**



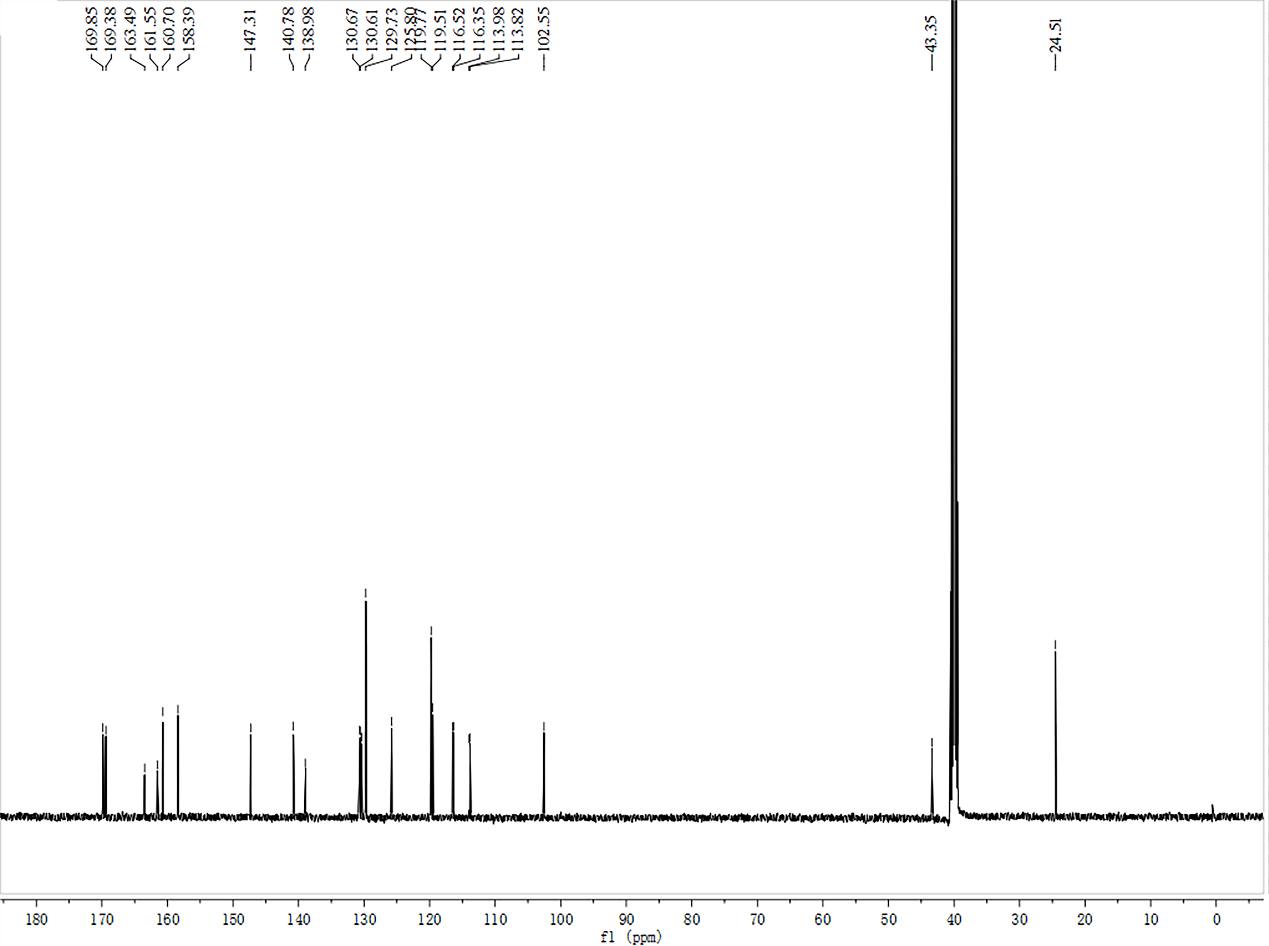
**13C NMR spectrum of compound 41**



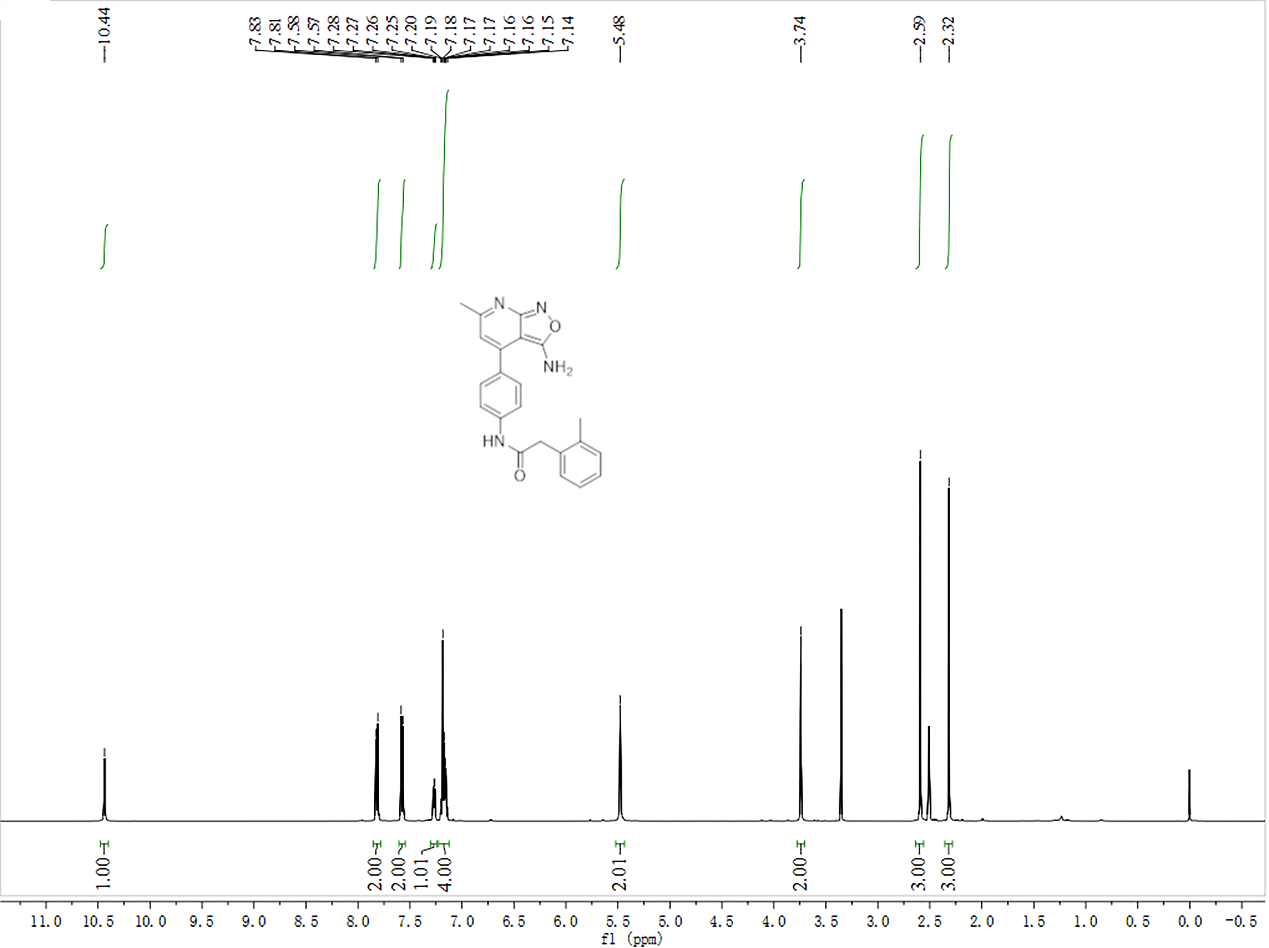
**1H NMR spectrum of compound 42**



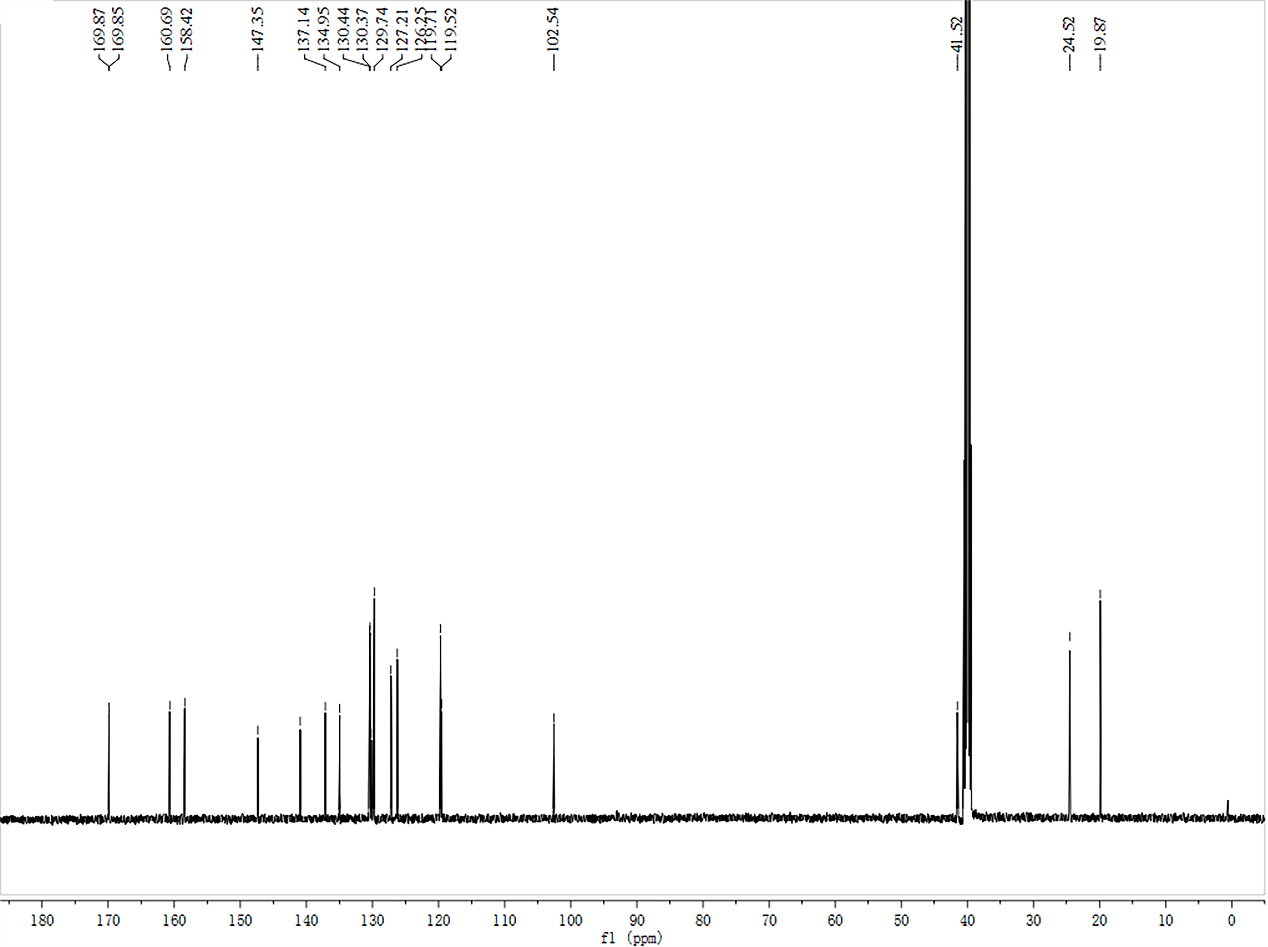
**13C NMR spectrum of compound 42**



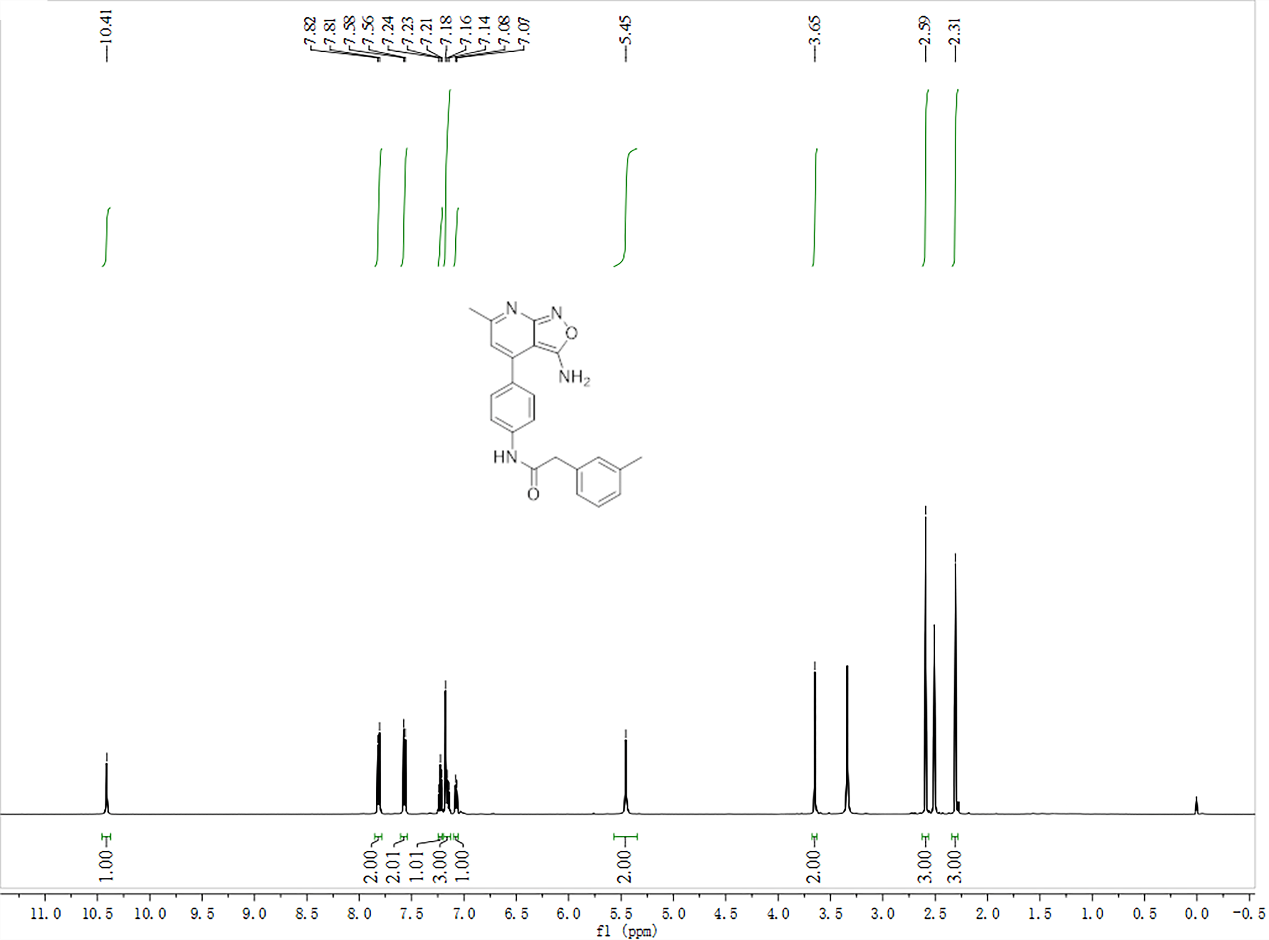
**1H NMR spectrum of compound 43**



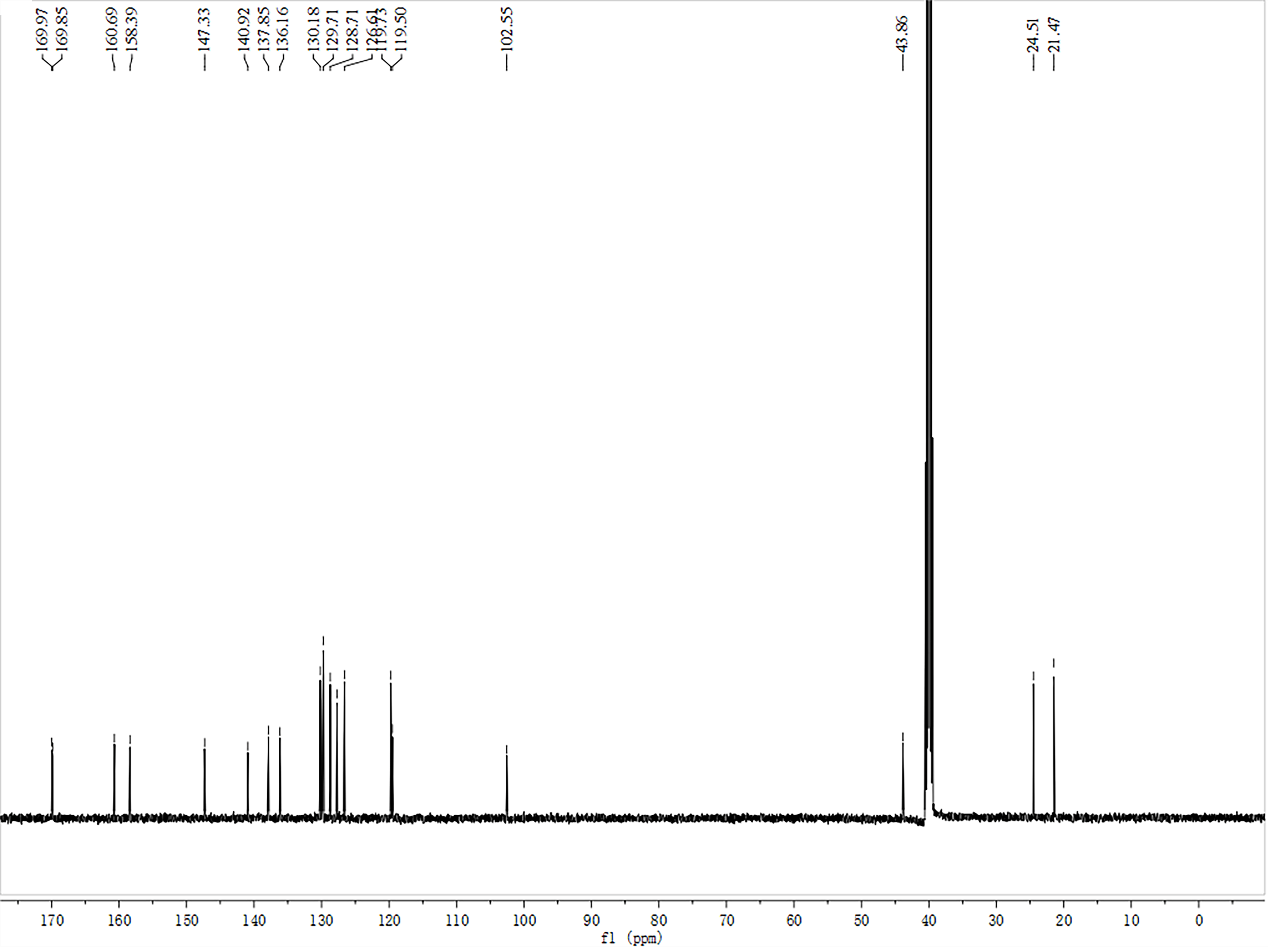
**13C NMR spectrum of compound 43**



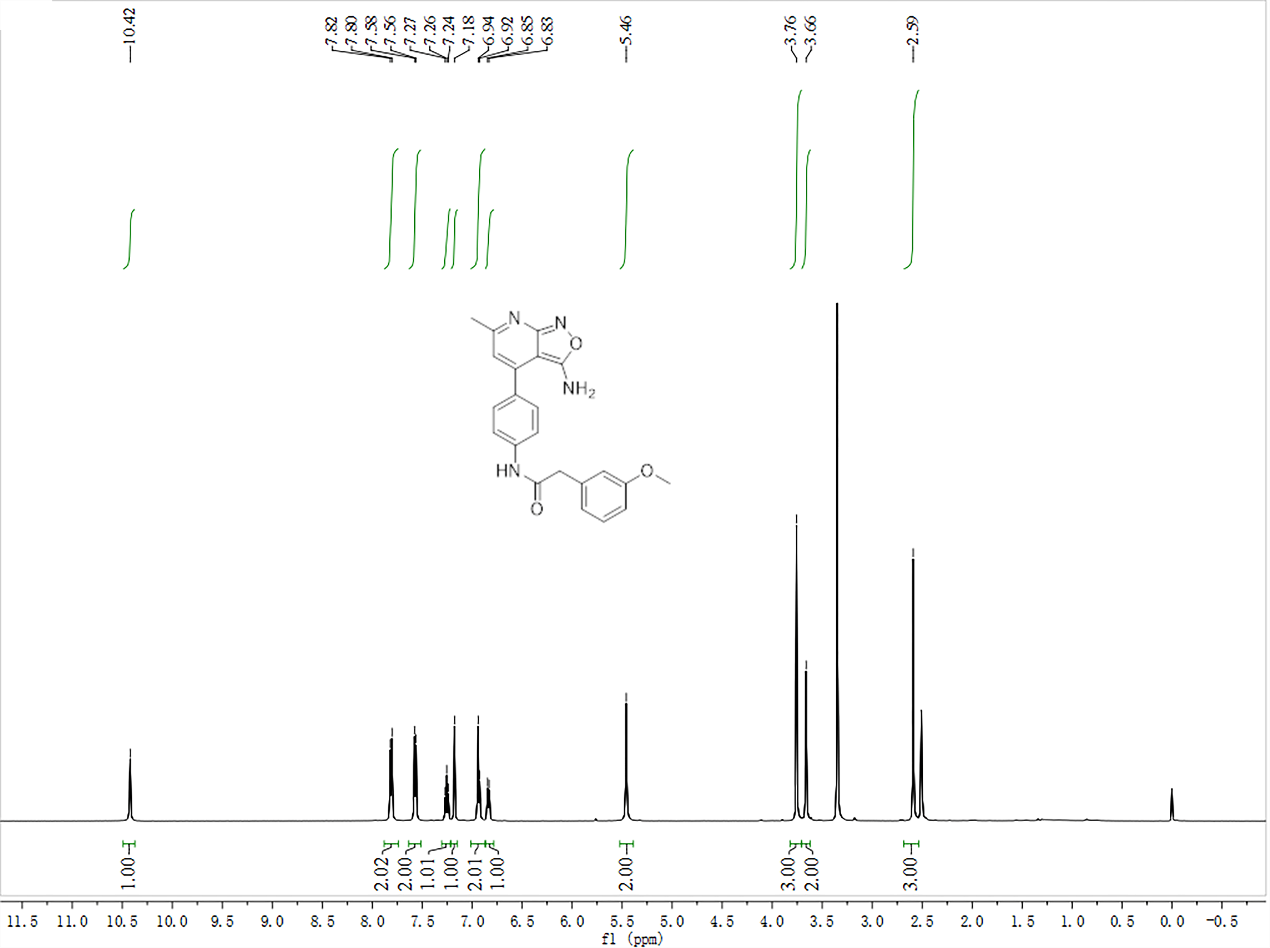
**1H NMR spectrum of compound 44**



**13C NMR spectrum of compound 44**



**1H NMR spectrum of compound 45**



**13C NMR spectrum of compound 45**

