Supporting Information

Synthesis of pyrazino[1,2-*b*]indazoles *via* cascade cyclization of indazole aldehydes with propargylic amines

Zeng-Hui Wu,[a] Heng-Tong Qu,[a] Ben-Jun Han,[a] Jia-Xin Yang,[a] Xiang-Wei Chang*[a,b] and Cheng-Tao Feng*[a]

[a]School of Pharmacy, Anhui University of Chinese Medicine; Anhui academy of Chinese medicine, Hefei, 230012, China.

[b.]MOE-Anhui Joint Collaborative Innovation Center for Quality Improvement of Anhui Genuine Chinese Medicinal Materials, Hefei, 230012, China.

Contents

1. General Information

All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were performed under an atmosphere of air. Analytical TLC was performed with silica gel GF254 plates. Visualization was accomplished by UV light. Products were purified by flash column chromatography on 200-300 mesh silica gel. Flash chromatography was conducted eluting with PE/EA, and they are listed as volume/volume ratios. ^{1}H and ^{13}C NMR spectra were recorded in Chloroform-d at 600 MHz (^{1}H NMR)/150 MHz (^{13}C NMR) on Bruker spectrometers. Chemical shifts are expressed in parts per million (δ) and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet), and coupling constants (*J*) were given in Hz. Chemical shifts as internal standard are referenced to $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.16 for ^{13}C NMR). High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and the time-of-flight (TOF) mass analyzer, accurate masses are reported for the molecular ion + hydrogen ($[M+H]^+$). Melting points were measured on a capillary melting point apparatus.

2. Structures of starting materials

Figure 1: Structures of aldehyde starting materials (1a-q)

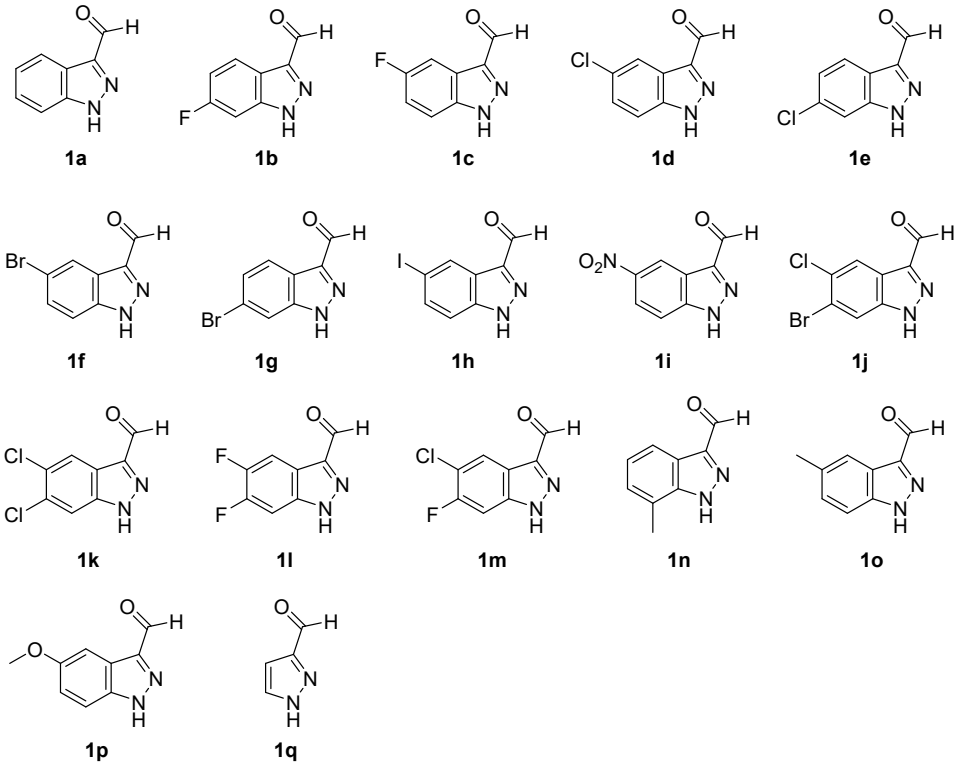
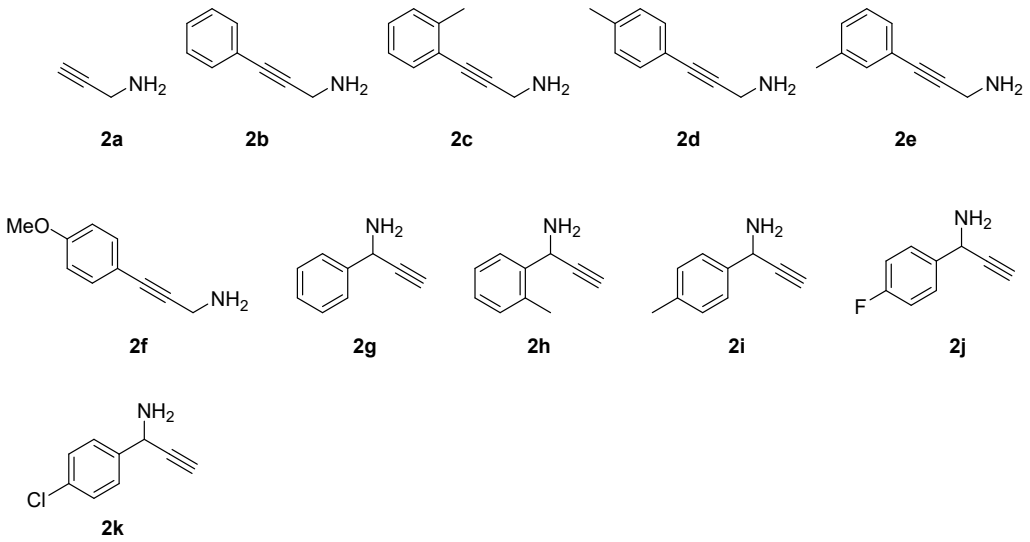


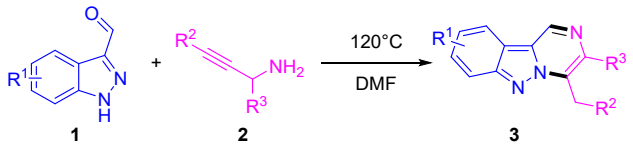
Figure 2: Structures of propargylic amines (2a-k)



Commercially available aldehydes (**1a**, **1d**, **1f**, **1i, 1k** and **1q**) and propargylic amines (**2a**) were used without further purification and the other starting aldehydes (**1b**, **1c**, **1e**, **1f**, **1g**, **1h**, **1j**, **1l**, **1m**, **1n**, **1o** and **1p**) and propargylic amines (**2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j** and **2k**) were synthesized as described below.

3. Experimental Procedures

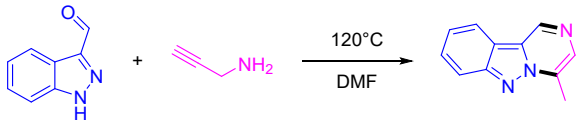
3.1 General procedure for the synthesis of **3**



1 **2** **3**

To a solution of aldehyde (0.4 mmol) in DMF (3 ml) was added amine (0.6 mmol) at room temperature. The reaction mixture was stirred for 10 min at room temperature, followed by 12 h at 120°C. After reaction finished, the mixture was cooled to room temperature, added water (45 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were dried with Na_2SO_4. Then, the solvent was removed under reduced pressure and purified by silica gel column chromatography (petroleum ether/ethyl acetate).

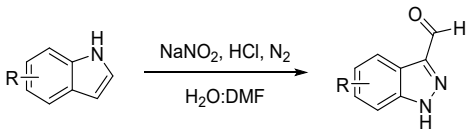
3.2 Scale-up procedure for the synthesis of **3aa**



1a **2a** **3aa**

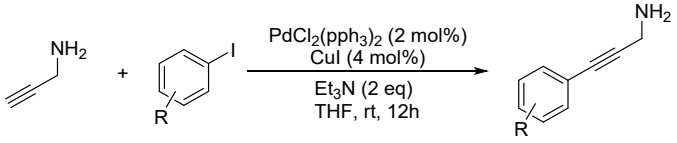
An oven-dried three-necked, round-bottom flask (100 mL), equipped with reflux condenser, was charged with 1H-indazole-3-carbaldehyde **1a** (5 mmol, 731 mg). Subsequently DMF (38 ml), propargylamine **2a** (7.5 mmol, 475ul) were added in order. The reaction was stirred at room temperature for 10 minutes, then further stirred at 120 °C for 12h. After completion of the reaction, the mixture was cooled to room temperature, then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate (P:E = 1:2) as an eluent to afford the pure product **3aa** (613 mg, 67%).

3.3 General procedure for the synthesis of aldehydes **2**



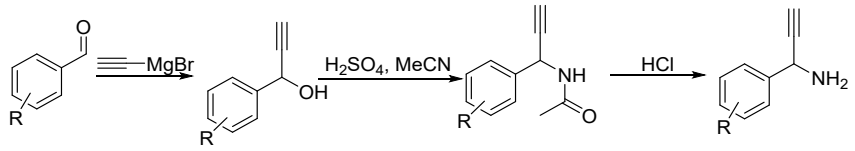
1b, 1c, 1e, 1f, 1g, 1h, 1j, 1l, 1m, 1n, 1o and **1p** were prepared by a literature procedure[1]. General procedure for 1 mmol of indole. To a solution of $NaNO_2$ (550 mg, 8 mmol, 8 equiv.) in 4 mL of deionized water and 3 mL of DMF at 0 °C was added slowly HCl (1.33 mL of 2 mol/L, 2.7 mmol, 2.7 equiv.) and the resulting mixture was kept under argon for 10 min. A solution of indole (1 mmol, 1 equiv.) in DMF (3 mL) was then added at 0 °C over a period of 2 h using a syringe. After reaction finished, added water, and extracted with EtOAc (3×15 mL). The combined organic layers were dried with Na_2SO_4. Then, the solvent was removed under reduced pressure and purified by silica gel column chromatography (petroleum ether/ ethyl acetate).

3.4 General procedure for the synthesis of **2b, 2d, 2e** and **2f**



2b, 2d, 2e and 2f were prepared by a literature procedure[2]. To a degassed solution of aryl iodide (5.5 mmol) and propargylic amine (5.0 mmol) in THF/Et_3N (4:1) under nitrogen, were added CuI (38.1 mg, 0.20 mmol) and $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol) at room temperature. The mixture was stirred overnight, and an aqueous solution of saturated NH_4Cl was added, and the mixture was extracted with EtOAc (3 x30 mL). The combined organic layer was washed with brine (50mL) and dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ ethyl acetate) to give the corresponding propargylic amine derivatives in high yield.

3.4 The synthesis of **2c**, **2g**, **2h**, **2j** and **2k**



2c, 2g, 2h, 2j, 2k

2c, 2g, 2h, 2j and **2k** was prepared by a literature procedure[3].

4. Biological Assay

Fungi.

Rhizoctonia solani (*R.S.*), *Sclerotonia sclerotiorum* (*S.s.*); *Valsa mali* (*V.m.*); *Botryosphaeria dothidea* (*B.d.*); *Alternaria alternata* (*A.a.*) and *Alternaria solani* (*A.s.*) were provided by Anhui University of Science and Technology.

In Vitro Fungicidal Activities[4].

The tested compounds were dissolved in DMSO to give a 10 mg/mL stock solution before mixing with PDA. The media containing compounds at a concentration of 2**5** mg/L were then poured into sterilized Petri dishes for primary screening. After 24-72 h at 28 °C, the colony diameter of each strain was measured. Percentage inhibition rate was calculated as (C-A)/(C-B) × 100%, where A represents the colony diameter in the Petri dishes with tested compounds, B represents the diameter of mycelial disc, and C is the mean colony diameter in control Petri dishes. Fluxapyroxad w**as** selected as positive controls. Each treatment was performed three times. The inhibition rate of the potent compounds was further tested **and t**he complete inhibition rate data is shown in the table **S1** below**.**

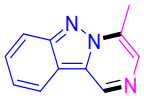
Table S1. Growth inhibition of the mycelium of the pathogenic fungi by pyrazino[1,2 *b*]indazoles.[a]

No	Compd	Mycelium growth inhibition, % (C = 25 mg·L^{-1})					
		R.S.	*S.s.*	*V.m.*	*B.d.*	*A.a.*	*A.s.*
1	**3aa**	46.8 ± 6.0	36.3 ± 1.3	34.4 ± 0.2	44.9 ± 3.0	54.7 ± 3.8	42.2 ± 0.7
2	**3ba**	62.2 ± 1.0	53.2 ± 4.2	32.6 ± 1.1	48.2 ± 1.5	51.6 ± 2.9	36.9 ± 1.0
3	**3ca**	38.8 ±0.5	43.2 ± 0.7	58.7 ± 5.0	45.7 ± 1.8	49.5 ± 1.7	30.3 ± 1.0
4	**3da**	65.9 ± 2.4	63.8 ± 1.1	44.8 ± 0.6	34.2 ± 0.6	55.5 ± 0.6	46.4 ± 0.2
5	**3ea**	65.8 ±0.1	57.3 ± 0.5	47.2 ± 2.9	56.8 ± 2.1	60.4 ± 0.4	52.7 ± 1.2
6	**3fa**	52.3 ±1.3	67.7 ± 1.3	55.4 ± 4.1	50.9 ± 1.4	57.8 ± 0.6	53.4 ± 2.2
7	**3ga**	47.9 ±2.3	46.9 ± 3.1	44.7 ± 1.5	43.8 ± 3.4	49.0 ± 0.9	41.6 ± 5.0
8	**3ha**	58.2 ± 2.5	7.6 ± 0.8	16.4 ± 4.0	5.2 ± 0.3	6.5 ± 1.5	<5
9	**3ia**	<5	28.9 ± 2.4	8.2 ± 2.8	22.4 ± 4.6	30.1 ± 0.3	22.9 ± 0.6
10	**3ja**	15.7 ± 1.8	17.8 ± 0.6	30.1 ± 4.1	9.0 ± 2.3	<5	/
11	**3ka**	26.3 ±2.6	19.8 ± 1.1	61.0 ± 3.1	9.7 ± 2.0	<5	/
12	**3la**	35.0 ± 1.0	23.9 ± 0.5	40.0 ± 5.1	10.6 ± 2.2	11.2 ± 1.6	/
13	**3ma**	63.6 ± 5.9	31.4 ± 0.3	76.5 ± 4.0	33.8 ± 2.8	<5	/
14	**3oa**	41.7 ± 1.9	46.3 ± 2.5	48.0 ± 2.3	41.4 ± 1.9	59.9 ± 5.7	46.1 ± 1.2
15	**3pa**	22.8 ±3.0	44.6 ± 0.5	31.3 ± 2.4	33.2 ± 4.6	51.4 ± 0.7	43.3 ± 1.2
16	**3ab**	41.6 ± 4.0	22.0 ± 1.8	68.1 ± 4.3	26.3 ± 0.8	24.5 ± 1.2	10.2 ± 3.4
17	**3ad**	8.2 ± 0.9	8.1 ± 2.8	18.0 ± 2.5	7.9 ± 1.2	12.3 ± 1.1	14.1 ± 0.4
18	**3af**	29.2 ±3.4	8.1 ± 1.3	36.0 ± 4.2	11.6 ± 2.3	21.5 ± 0.6	12.0 ± 1.6
19	**3ag**	41.9 ± 0.5	14.9 ± 2.2	4.9 ± 1.6	16.8 ± 4.8	13.8 ± 0.8	9.0 ± 0.2
20	**3ai**	37.0 ± 3.0	7.1 ± 0.3	24.6 ± 1.8	15.6 ± 1.7	9.4 ± 1.8	2.4 ± 1.1
21	**3aj**	10.1 ± 3.6	<5	5.2 ± 2.0	8.8 ± 2.6	13.7 ± 0.6	6.5 ± 0.9
22	**3ak**	48.2 ± 0.8	40.8 ± 0.9	39.1 ± 2.3	27.5 ± 2.5	32.0 ± 2.4	50.0 ± 2.2
23	**fluxapyroxad**	88.5±2.7	93.3±3.3	20.2±0.7	35.4±1.1	93.8±1.4	94.2±2.1

[a]Data are given as the mean of triplicate experiments.

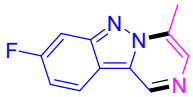
5. Characterization Data of Products

4-methylpyrazino[1,2-*b*]indazole (3aa)



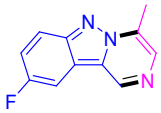
Yield 71%, red solid; mp: 170-172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.16 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.44 – 7.38 (m, 1H), 2.90 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2, 140.7, 133.2, 131.2, 130.5, 129.1, 122.6, 119.7, 116.9, 115.7, 15.5. HRMS (ESI): calculated for $C_{11}H_{10}N_3$ $[M+H]^+$ 184.0869, found 184.0869.

8-fluoro-4-methylpyrazino[1,2-*b*]indazole (3ba)



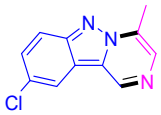
Yield 56%, red solid; mp: 182-185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.16 – 8.10 (m, 2H), 7.56 (dd, J = 9.7, 2.3 Hz, 1H), 7.16 (td, J = 9.0, 2.2 Hz, 1H), 2.87 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{CF}$ = 247.1 Hz), 149.8 (d, J_{CF} = 13.2 Hz), 140.2, 133.1, 131.4, 130.5, 121.4 (d, J_{CF} = 10.9 Hz), 113.2 (d, $^2J_{CF}$ = 27.3 Hz), 112.4, 101.0 (d, $^2J_{CF}$ = 24.1 Hz), 15.4. HRMS (ESI): calculated for $C_{11}H_9FN_3$ $[M+H]^+$ 202.0775 found 202.0775.

9-fluoro-4-methylpyrazino[1,2-*b*]indazole (3ca)



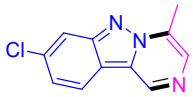
Yield 63%, red solid; mp: 145-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.12 (s, 1H), 7.94 (dd, J = 9.3, 4.4 Hz, 1H), 7.74 (dd, J = 8.3, 2.5 Hz, 1H), 7.40 (td, J = 9.1, 2.5 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8 (d, $^1J_{CF}$ = 242.9 Hz), 146.2, 140.9, 133.2, 131.3, 130.6 (d, J_{CF} = 7.2 Hz), 119.5 (d, $^2J_{CF}$ = 27.4 Hz), 118.7 (d, J_{CF} = 9.1 Hz), 115.3 (d, J_{CF} = 11.9 Hz), 103.4 (d, $^2J_{CF}$ = 25.3 Hz), 15.4. HRMS (ESI): calculated for $C_{11}H_9FN_3$ $[M+H]^+$ 202.0775, found 202.0775.

9-chloro-4-methylpyrazino[1,2-*b*]indazole (3da)



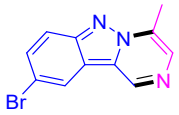
Yield 52%, orange solid; mp: 153-156 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.19 – 8.14 (m, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.58 (dd, J = 9.1, 2.0 Hz, 1H), 2.89 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.5, 140.9, 133.6, 131.4, 130.2, 130.0, 128.2, 118.8, 118.3, 116.2, 15.5. HRMS (ESI): calculated for $C_{11}H_9ClN_3$ $[M+H]^+$ 218.0480, found 218.0479.

8-chloro-4-methylpyrazino[1,2-*b*]indazole (3ea)



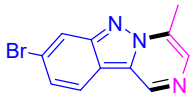
Yield 79%, white solid; mp: 155-158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.16 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.8 Hz, 1H), 2.87 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.5, 140.5, 134.9, 133.5, 131.5, 130.4, 123.7, 120.8, 116.1, 113.9, 15.4. HRMS (ESI): calculated for $C_{11}H_9ClN_3$ $[M+H]^+$ 218.0480, found 218.0480.

9-*b*romo-4-methylpyrazino[1,2-*b*]indazole (3fa）



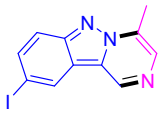
Yield 52%, red solid; mp: 148-151 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.30 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.68 (dd, *J* = 9.0, 1.9 Hz, 1H), 2.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.6, 140.8, 133.7, 132.5, 131.4, 129.7, 122.1, 118.5, 116.9, 115.7, 15.5. HRMS (ESI): calculated for $C_{11}H_9BrN_3$ $[M+H]^+$ 261.9974, found 261.9976.

8-*b*romo-4-methylpyrazino[1,2-*b*]indazole (3ga)



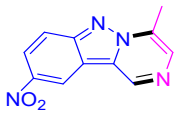
Yield 48%, brown solid; mp: 146-149 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 1.7 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.46 (dd, *J* = 8.7, 1.6 Hz, 1H), 2.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.9, 140.6, 133.7, 131.5, 130.5, 126.1, 123.1, 120.9, 119.4, 114.2, 15.5. HRMS (ESI): calculated for $C_{11}H_9BrN_3$ $[M+H]^+$ 261.9974, found 261.9976.

9-iodo-4-methylpyrazino[1,2-*b*]indazole (3ha)



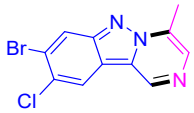
Yield 44%, red solid; mp: 150-153 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.55 (d, *J* = 1.5 Hz, 1H), 8.18 (s, 1H), 7.84 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 2.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.9, 140.8, 137.6, 133.7, 131.4, 129.3, 128.6, 118.7, 117.8, 86.1, 15.5. HRMS (ESI): calculated for $C_{11}H_8IN_3$ $[M]^+$ 309.9763, found 308.9719.

4-methyl-9-nitropyrazino[1,2-*b*]indazole (3ia)



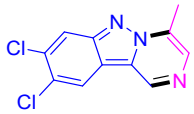
Yield 49%, yellow solid; mp: 225-228 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.61 (s, 1H), 9.24 (s, 1H), 8.54 – 8.29 (m, 2H), 8.04 (s, 1H), 2.96 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.7, 142.8, 140.9, 135.4, 132.5, 132.1, 123.7, 118.2, 117.4, 114.3, 15.4. HRMS (ESI): calculated for $C_{11}H_9N_4O_2$ $[M+H]^+$ 229.0720, found 229.0721.

8-bromo-9-chloro-4-methylpyrazino[1,2-b]indazole (3ja)



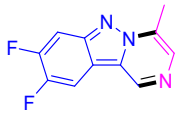
Yield 53%, red solid; mp: 80-83 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.27 (s, 1H), 8.22 (d, *J* = 1.2 Hz, 1H), 8.09 (s, 1H), 2.88 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.4, 140.8, 135.1, 134.2, 131.7, 129.7, 124.3, 117.9, 116.3, 115.3, 15.5. HRMS (ESI): calculated for $C_{11}H_7BrClN_3$ $[M]^+$ 294.9506, found 294.9527.

8,9-dichloro-4-methylpyrazino[1,2-b]indazole (3ka)



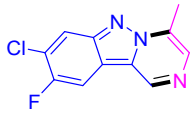
Yield 69%, red solid; mp: 106-109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.29 (s, 1H), 8.22 (d, *J* = 1.1 Hz, 1H), 8.10 (s, 1H), 2.89 (t, *J* = 0.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.9, 140.8, 134.2, 133.7, 131.7, 129.9, 126.9, 120.7, 118.1, 114.7, 15.5. HRMS (ESI): calculated for $C_{11}H_8Cl_2N_3$ $[M+H]^+$ 252.0090, found 252.0087.

8,9-difluoro-4-methylpyrazino[1,2-b]indazole (3la)



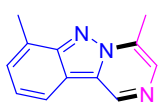
Yield 51%, red solid; mp: 156-159 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.17 (s, 1H), 7.92 (dd, *J* = 9.3, 7.5 Hz, 1H), 7.72 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.89 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.9 (dd, J_{CF} = 16.2, 252.1 Hz), 148.6 (dd, J_{CF} = 16.6, 246.9 Hz), 145.5 (d, J_{CF} = 11.7 Hz), 140.6, 133.1, 131.5, 130.7 (d, J_{CF} = 7.5 Hz), 110.8 (d, J_{CF} = 9.2 Hz), 105.7 (d, J_{CF} = 21.0 Hz), 103.5 (d, J_{CF} = 20.5 Hz), 15.4. HRMS (ESI): calculated for $C_{11}H_8F_2N_3$ $[M+H]^+$ 220.0681, found 220.0680.

8-chloro-9-fluoro-4-methylpyrazino[1,2-b]indazole (3ma)



Yield 45%, red solid; mp: 130-133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.19 (d, *J* = 1.2 Hz, 1H), 8.06 (d, *J* = 6.2 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 2.89 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.1 (d, $^1J_{CF}$ = 245.2 Hz), 145.9, 140.9, 133.7, 131.6, 130.7 (d, J_{CF} = 6.6 Hz), 124.9 (d, J_{CF} = 21 Hz), 118.4, 113.7 (d, J_{CF} = 9.0 Hz), 104.9 (d, J_{CF} = 25.1 Hz), 15.4. HRMS (ESI): calculated for $C_{11}H_8ClFN_3$ $[M+H]^+$ 236.0385, found 236.0385.

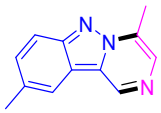
4,7-dimethylpyrazino[1,2-*b*]indazole (3na)



Yield 77%, red solid; mp: 102-105 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.98 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 2.77 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (151 MHz,

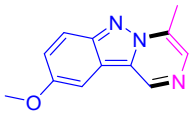
$CDCl_3$) δ 149.2, 140.7, 132.6, 131.3, 130.7, 128.2, 127.2, 122.7, 116.9, 115.4, 17.4, 15.4. HRMS (ESI): calculated for $C_{12}H_{12}N_3$ $[M+H]^+$ 198.1026, found 198.1024.

4,9-dimethylpyrazino[1,2-*b*]indazole (3oa)



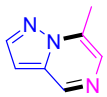
Yield 64%, red solid; mp: 115-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.48 (dd, *J* = 8.7, 1.7 Hz, 1H), 2.87 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.0, 140.7, 132.7, 132.4, 131.6, 131.0, 130.0, 118.3, 116.5, 115.9, 22.0, 15.5. HRMS (ESI): calculated for $C_{12}H_{12}N_3$ $[M+H]^+$ 198.1026, found 198.1024.

9-methoxy-4-methylpyrazino[1,2-*b*]indazole (3pa)



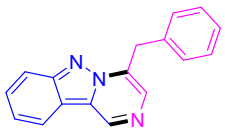
Yield 41%, brown solid; mp: 133-136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.04 (s, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.5 Hz, 1H), 3.95 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.0, 145.4, 140.9, 132.2, 131.1, 130.1, 122.7, 118.3, 115.9, 97.5, 55.8, 15.4. HRMS (ESI): calculated for $C_{12}H_{12}N_3O$ $[M+H]^+$ 214.0975, found 214.0976.

7-methylpyrazolo[1,5-a]pyrazin (3qa)



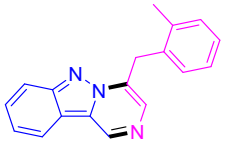
Yield 56%, pale yellow oil; ^{1}H NMR (600 MHz, DMSO-*d6*) δ 9.17 (s, 1H), 8.27 (d, *J* = 6 Hz, 1H), 7.90 (s, 1H), 7.09 (s, *J* = 6 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 142.9, 142.1, 135.6, 131.8, 128.2, 99.7, 14.7. MS (EI): m/z calculated for $C_7H_7N_3$ 133, found 133.

4-*b*enzylpyrazino[1,2-*b*]indazole (3ab)



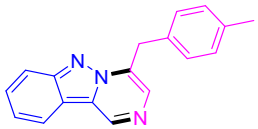
Yield 50%, gray solid; mp: 130-133 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.94 (s, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 4.66 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2, 140.8, 135.4, 134.0, 133.1, 130.6, 129.7, 129.1, 128.9, 127.4, 122.7, 119.6, 117.0, 115.8, 35.2. HRMS (ESI): calculated for $C_{17}H_{14}N_3$ $[M+H]^+$ 260.1182, found 260.1180.

4-(2-methylbenzyl)pyrazino[1,2-*b*]indazole (3ac)



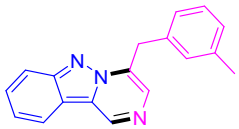
Yield 28%, red solid; mp: 118-121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.71-7.67 (m, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.29-7.21 (m, 4H), 4.66 (s, 2H), 2.32 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 149.3, 140.6, 137.4, 133.3, 132.7, 130.9, 130.6, 130.5, 129.2, 127.9, 126.7, 122.8, 119.7, 117.0, 115.9, 33.1, 19.6. HRMS (ESI): calculated for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1340.

4-(4-methylbenzyl)pyrazino[1,2-*b*]indazole (3ad)



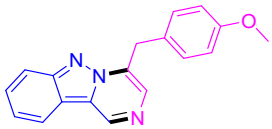
Yield 35%, white solid; mp: 138-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.94 (s, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 4.63 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2, 140.8, 137.1, 134.2, 133.2, 132.3, 130.5, 129.7, 129.6, 129.0, 122.6, 119.6, 117.0, 115.8, 34.8, 21.2 HRMS (ESI): calculated for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1341.

4-(3-methylbenzyl)pyrazino[1,2-*b*] indazole (3ae)



Yield 47%, red solid; mp: 185-188°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.94 (s, 1H), 7.67 (s, 1H), 7.43 (s, 1H), 7.23 (s, 3H), 7.13 (s, 1H), 4.63 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.2, 140.8, 138.6, 135.3, 134.2, 133.2, 130.5, 129.1, 128.8, 128.2, 126.8, 122.7, 119.7, 117.1, 115.8, 35.1, 21.5. HRMS (ESI): calculated for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1337.

4-(4-methoxybenzyl)pyrazino[1,2-*b*]indazole (3af)



Yield 47%, gray solid; mp: 112-115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.92 (s, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 6.93 – 6.88 (m, 2H), 4.59 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 149.2, 140.7, 134.4, 133.0, 130.8, 130.5, 129.0, 127.3, 122.7, 119.6, 117.0, 115.8, 114.4, 55.4, 34.4. HRMS (ESI): calculated for $C_{18}H_{16}N_3O$ $[M+H]^+$ 290.1288, found 290.1296.

4-methyl-3-phenylpyrazino[1,2-*b*]indazole (3ag)

Yield 67%, red solid; mp: 191-194 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.66 (t, *J* = 5.9 Hz, 2H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 2.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6, 143.7, 139.3, 138.2, 130.0, 129.4, 129.0, 128.9, 128.6, 128.5, 122.5, 119.6, 116.7, 115.8, 15.6. HRMS (ESI): calculated for $C_{17}H_{14}N_3$ $[M+H]^+$ 260.1182, found 260.1182.

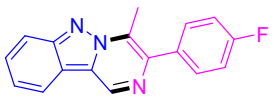
4-methyl-3-(o-tolyl)pyrazino[1,2-*b*]indazole (3ah)

Yield 45%, yellow oil; mp: 100-103 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.41 – 7.29 (m, 4H), 2.78 (s, 3H), 2.19 (s, 3H), 1.32 – 1.24 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.4, 142.7, 138.1, 136.4, 135.7, 129.5, 128.8, 128.5, 128.4, 127.9, 127.8, 124.9, 121.5, 118.5, 115.7, 114.8, 18.7, 13.8. HRMS (ESI): calculated for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1336.

4-methyl-3-(p-tolyl)pyrazino[1,2-*b*]indazole (3ai)

Yield 66%, white solid; mp: 160-163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 3.01 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6, 143.8, 139.3, 138.6, 135.3, 129.9, 129.4, 129.3, 128.9, 128.9, 122.5, 119.6, 116.8, 115.9, 21.5, 15.7. HRMS (ESI): calculated for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1339.

3-(4-fluorophenyl)-4-methylpyrazino[1,2-b]indazole (3aj)



Yield 74%, yellow solid; mp: 191-194 °C^{1}H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.66 (t, *J* = 9.3 Hz, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 2H), 3.00 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{CF}$ = 247.5 Hz), 149.7, 142.7, 139.3, 134.1 (d, J_{CF} = 4.5 Hz), 131.8 (d, J_{CF} = 9.0 Hz), 129.5, 129.0 (d, J_{CF} = 9.0 Hz), 122.7, 119.6, 116.9, 115.9, 115.7, 115.6, 15.6. HRMS (ESI): calculated for $C_{17}H_{13}FN_3$ $[M+H]^+$ 278.1088, found 278.1088.

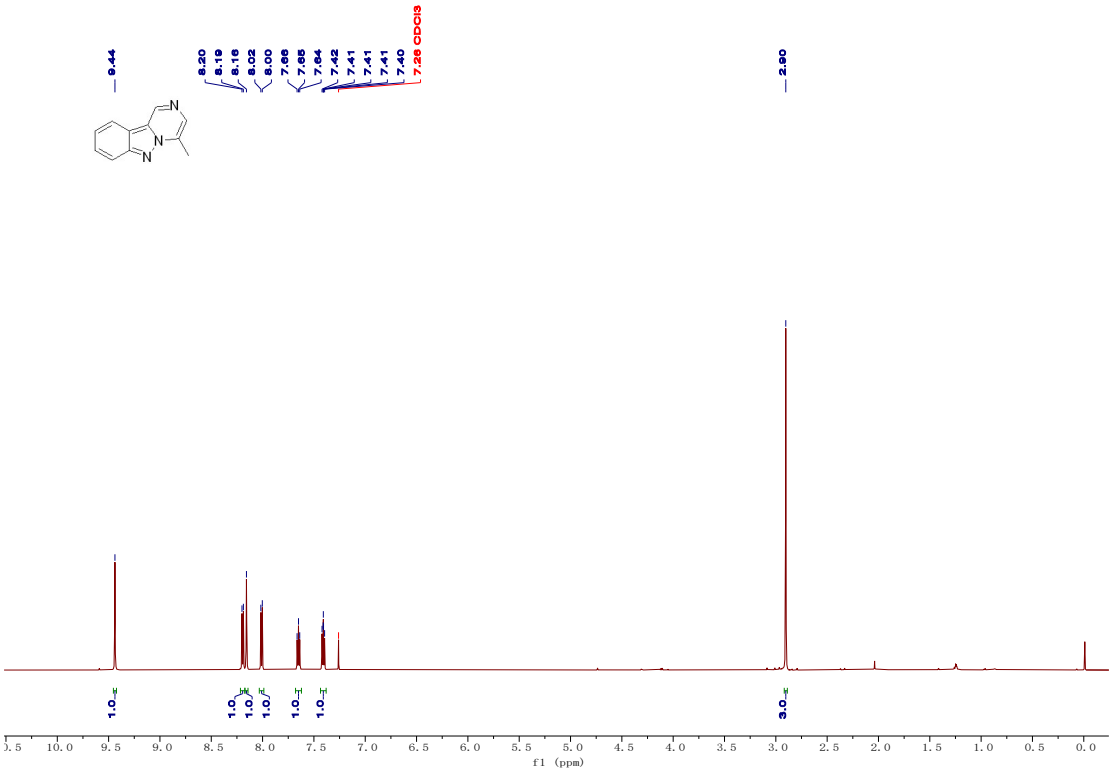
3-(4-chlorophenyl)-4-methylpyrazino[1,2-*b*]indazole (3ak)

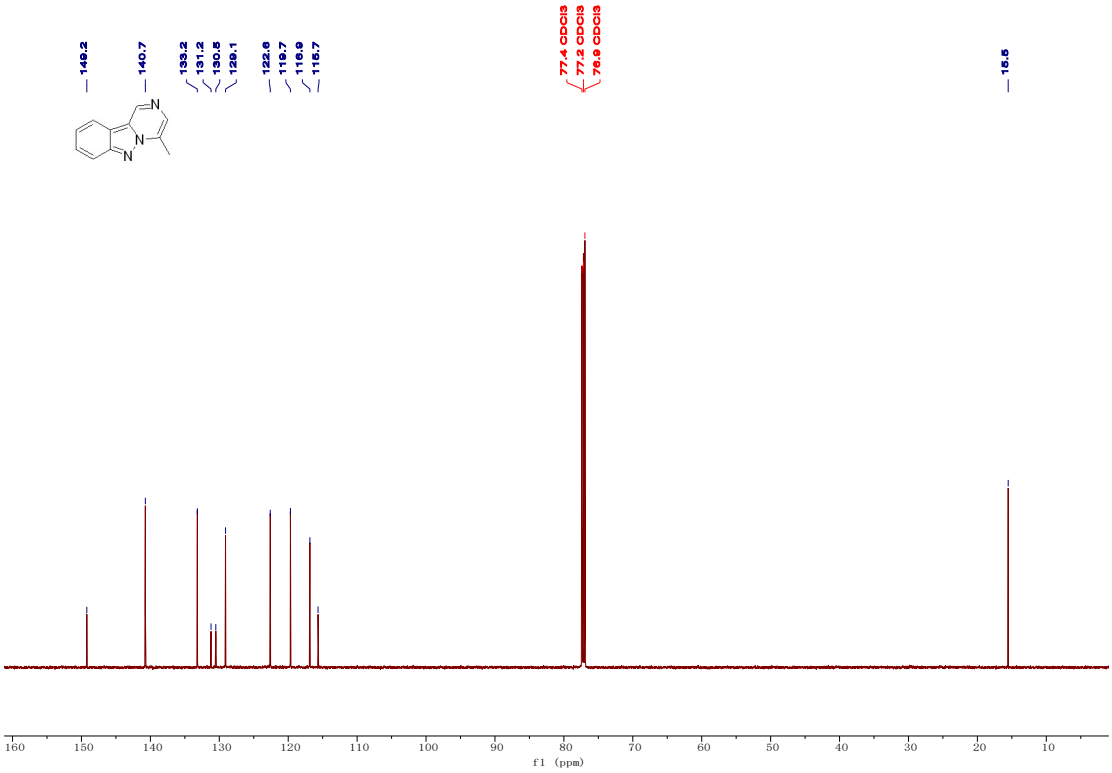
Yield 69%, white solid; mp: 207-210 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 2.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6, 142.5, 139.4, 136.6, 134.8,

131.4, 129.4, 129.1, 128.8, 122.7, 119.6, 116.8, 115.8, 15.6. HRMS (ESI): calculated for $C_{17}H_{13}ClN_3$ $[M+H]^+$ 294.0793, found 294.0792.

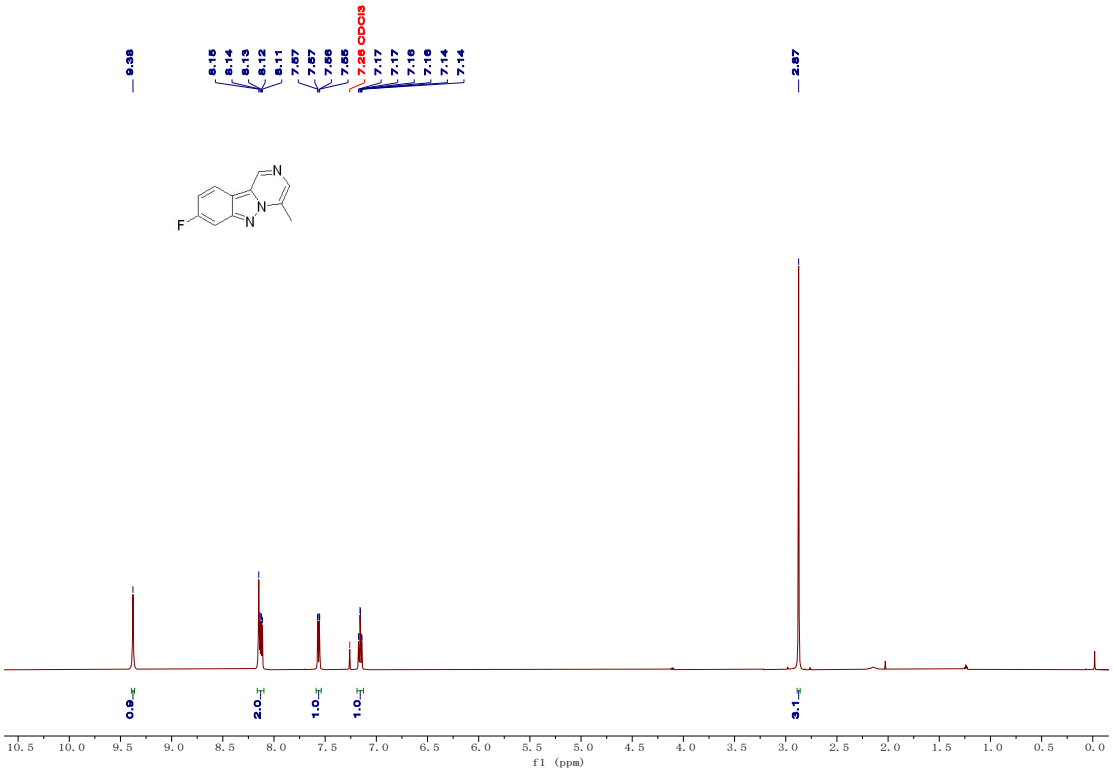
6. ^{1}H NMR and ^{13}C NMR Spectra of products

3aa


9.44
8.20
8.19
8.18
8.02
8.00
7.66
7.65
7.64
7.42
7.41
7.41
7.41
7.40
7.26 CDCl3
2.90
1.0
1.0
1.0
1.0
1.0
3.0
f1 (ppm)


148.2
140.7
133.2
131.2
130.5
129.1
122.6
119.7
116.9
115.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.5
f1 (ppm)

3ba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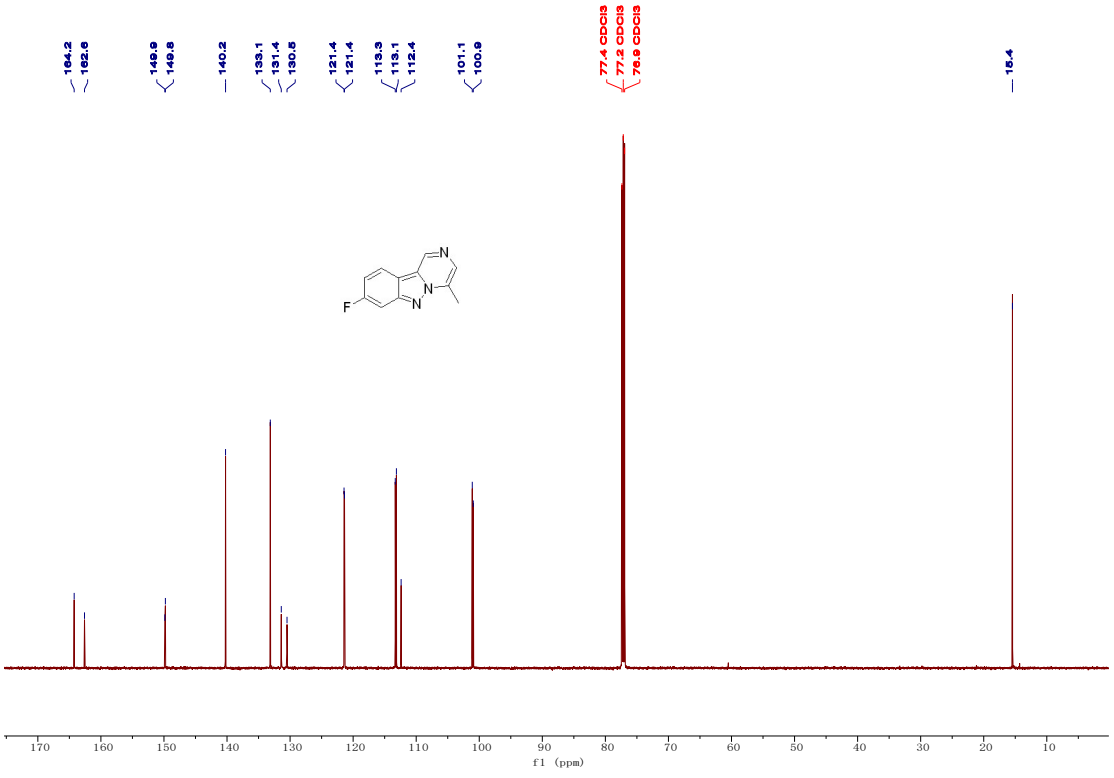
8.15
8.14
8.13
8.12
8.11
7.57
7.57
7.56
7.55
7.26 CDCl3
7.17
7.17
7.16
7.16
7.14
7.14
2.67
F
N
N
N
0.9
2.0
1.0
1.0
3.1
f1 (ppm)


164.2
162.6
149.9
149.8
140.2
133.1
131.4
130.5
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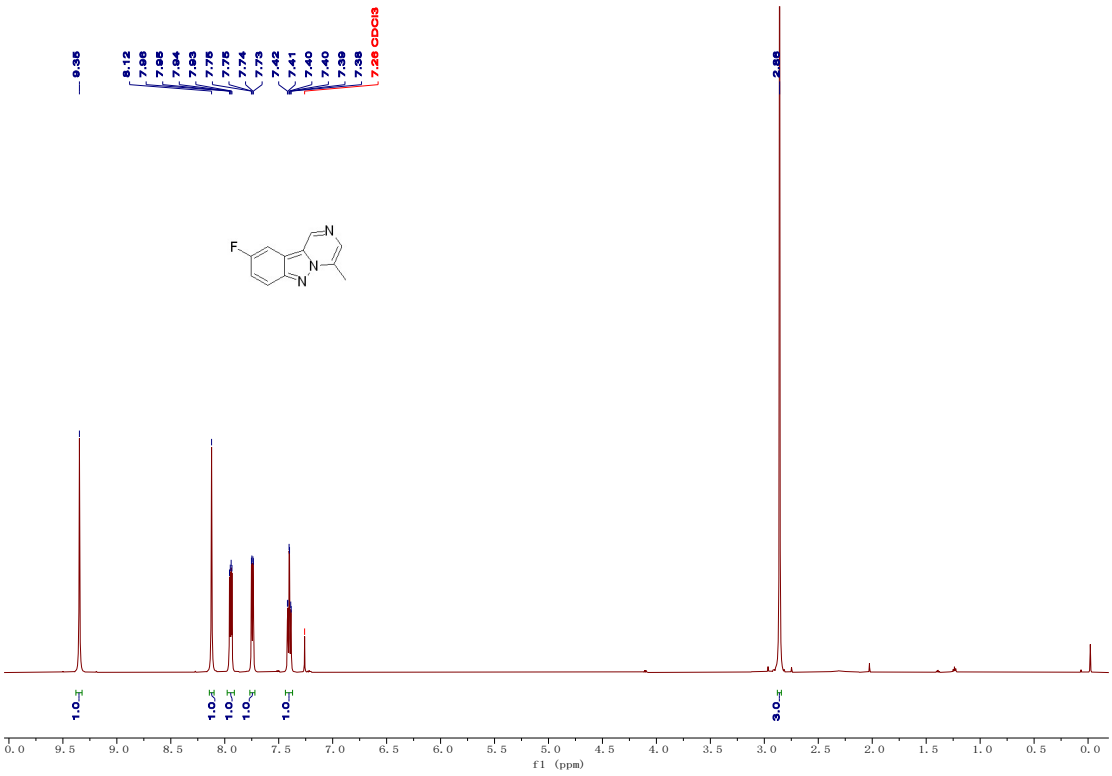
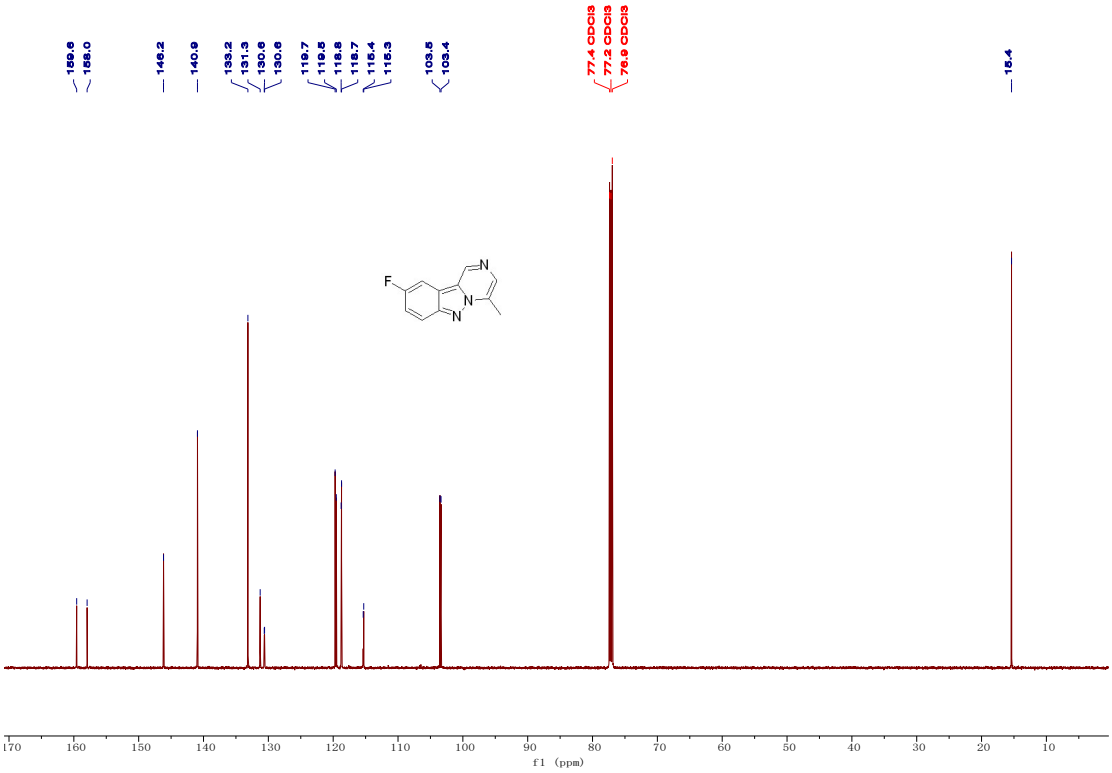
121.4
113.3
113.1
112.4
101.1
100.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.4
F
N
N
N
f1 (ppm)

3ca


9.35
8.12
7.96
7.95
7.94
7.93
7.75
7.75
7.74
7.73
7.42
7.41
7.40
7.40
7.39
7.38
7.26 CDCl3
2.88
F
N
N
N
1.0
1.0
1.0
1.0
3.0
f1 (ppm)


159.6
158.0
146.2
140.9
133.2
131.3
130.6
130.6
119.7
119.5
118.8
118.7
116.4
116.3
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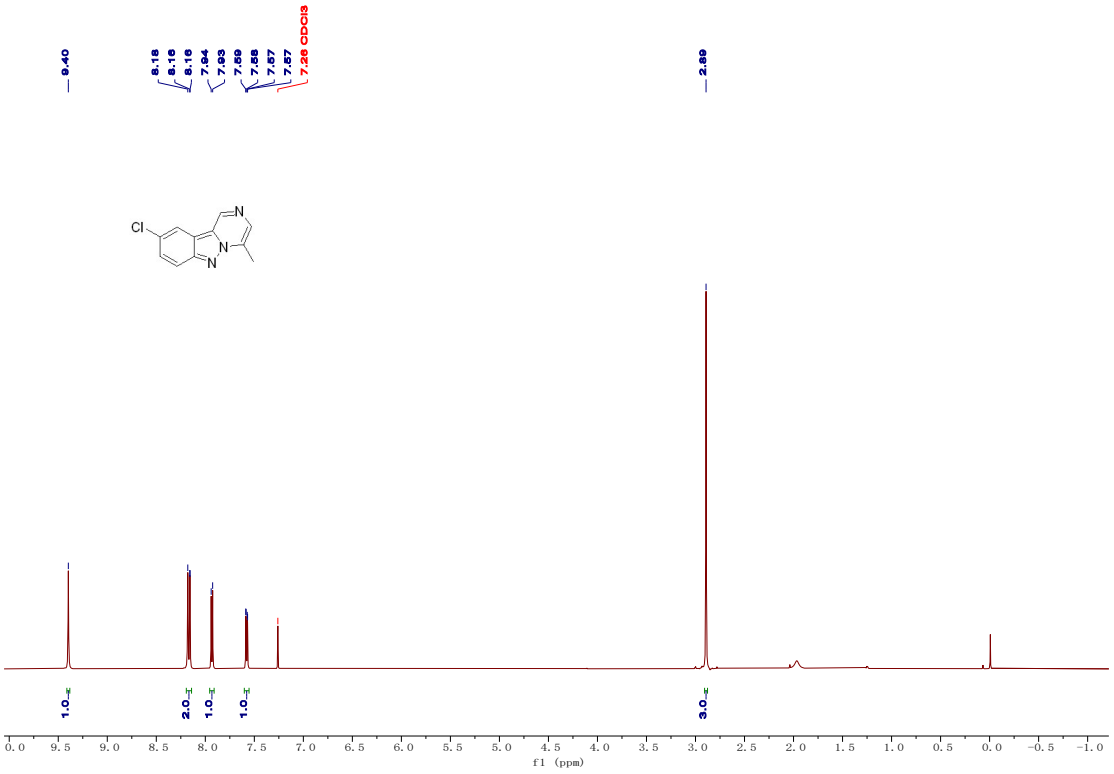
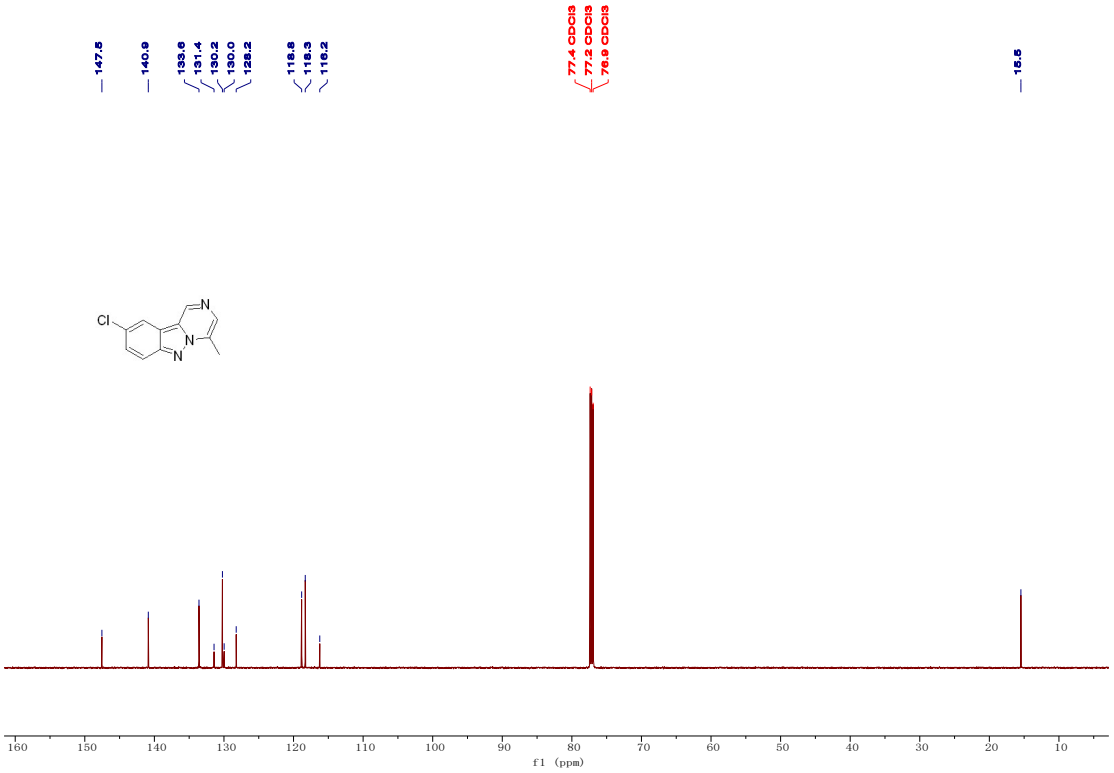
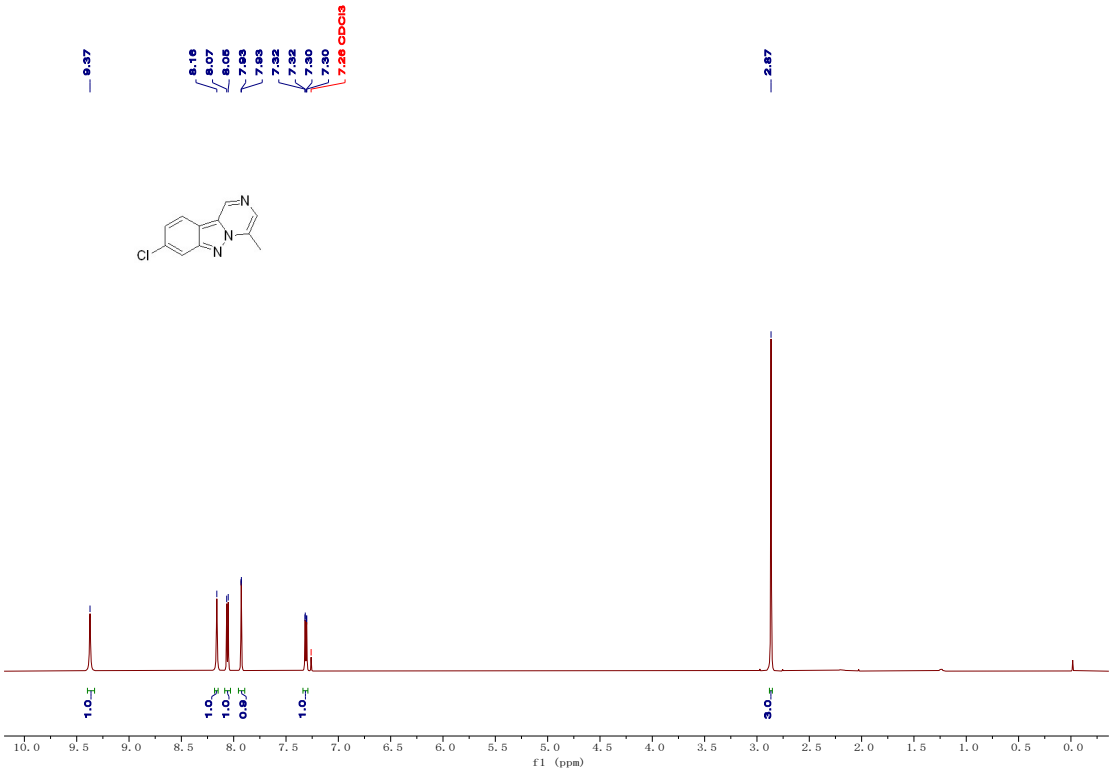
15.4
F
N
N
N
f1 (ppm)

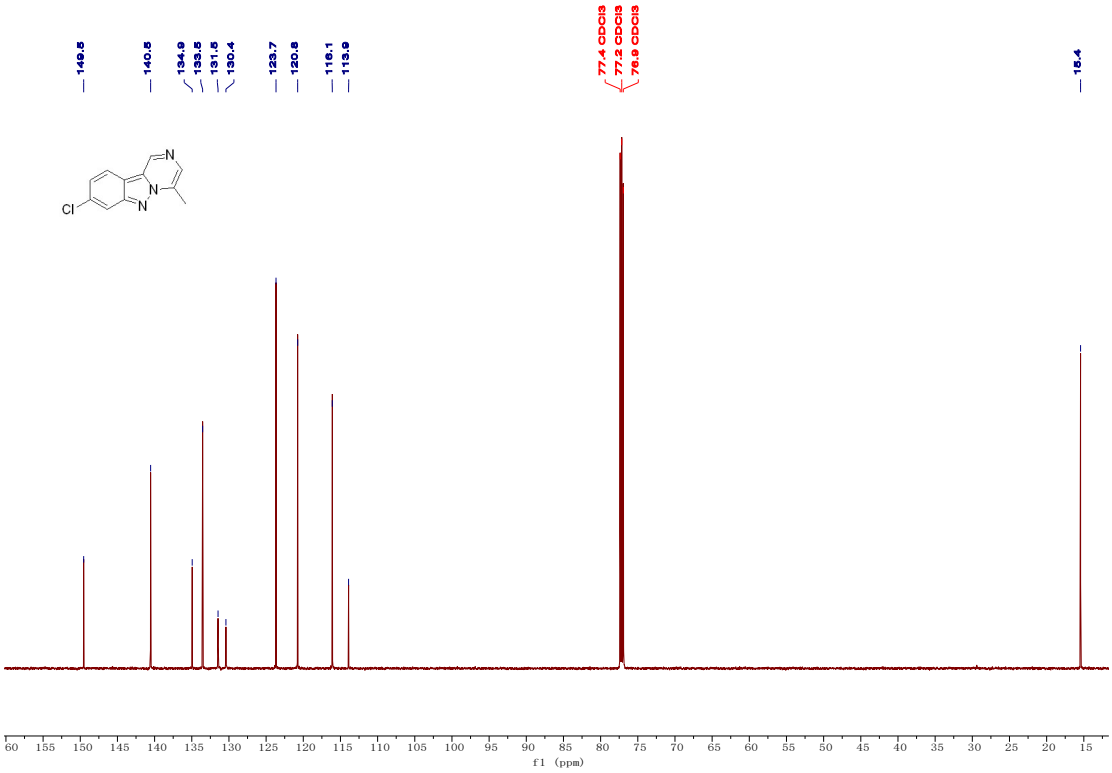
3da


9.40
8.18
8.16
8.16
7.94
7.93
7.59
7.58
7.57
7.57
7.26 CDCl3
2.69
Cl
N
N
N
1.0
2.0
1.0
1.0
3.0
f1 (ppm)

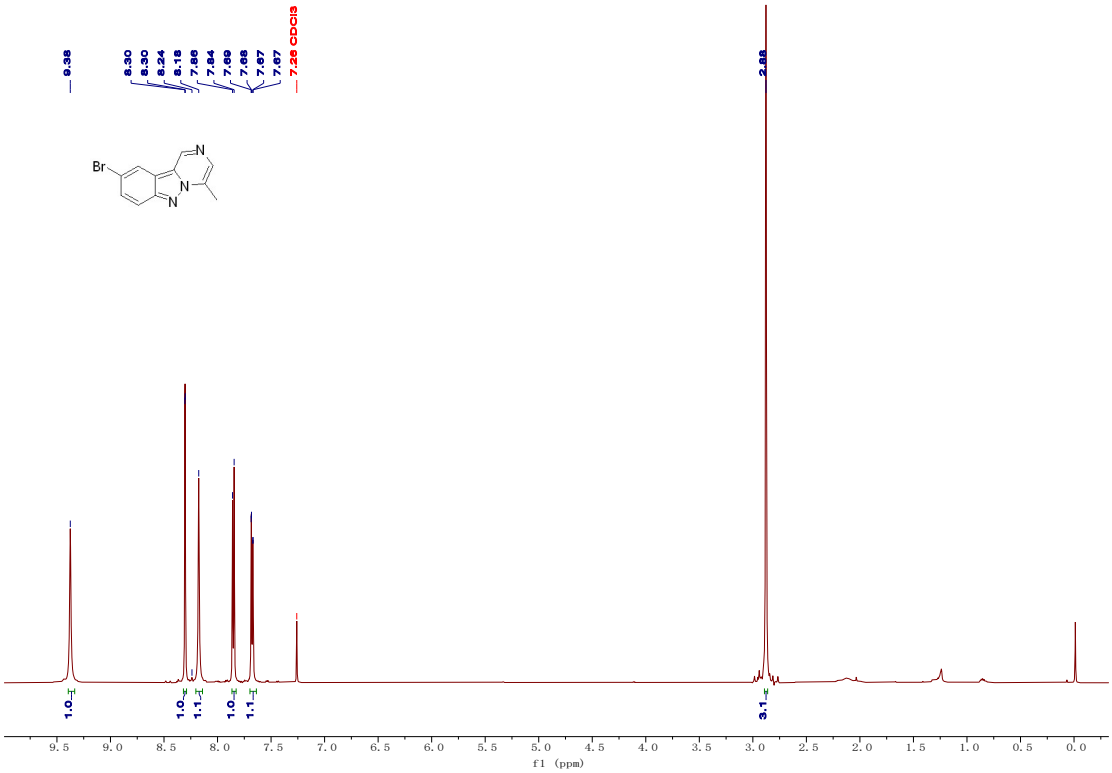

147.5
140.9
133.6
131.4
130.2
130.0
128.2
118.8
118.3
116.2
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.5
Cl
N
N
N
f1 (ppm)

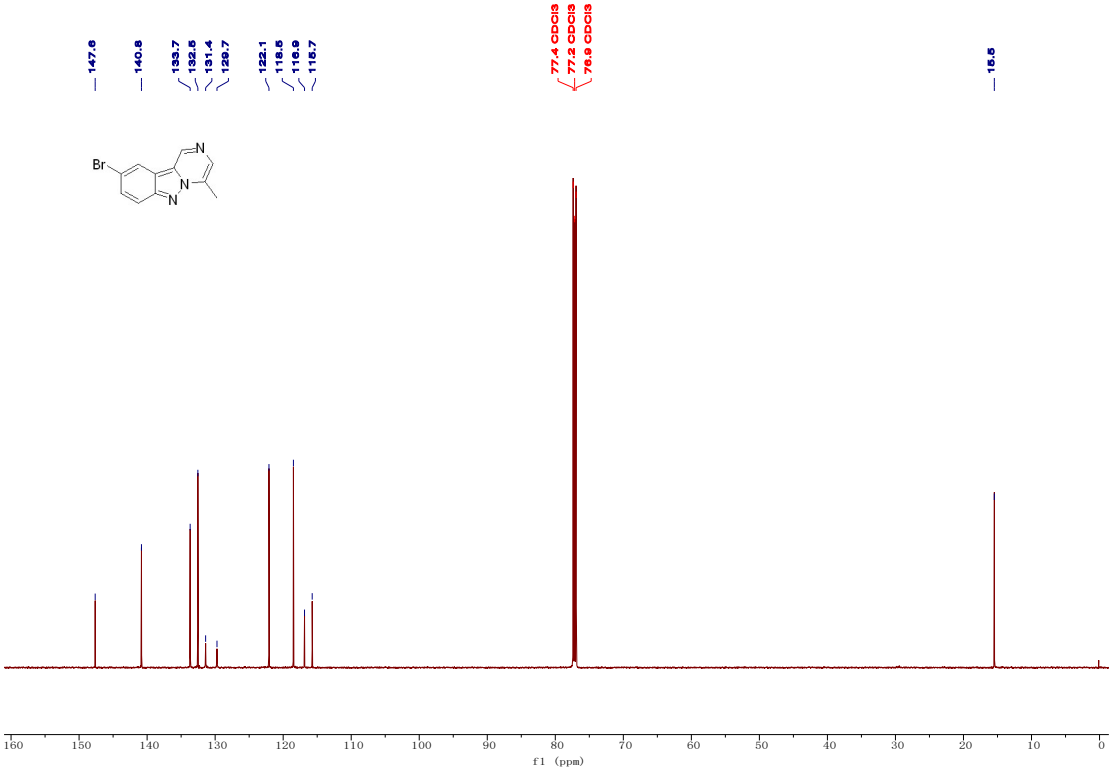
3ea


9.37
8.16
8.07
8.05
7.93
7.93
7.32
7.32
7.30
7.30
7.26 CDCl3
2.67
Cl
N
N
N
1.0
1.0
1.0
0.9
1.0
3.0
f1 (ppm)

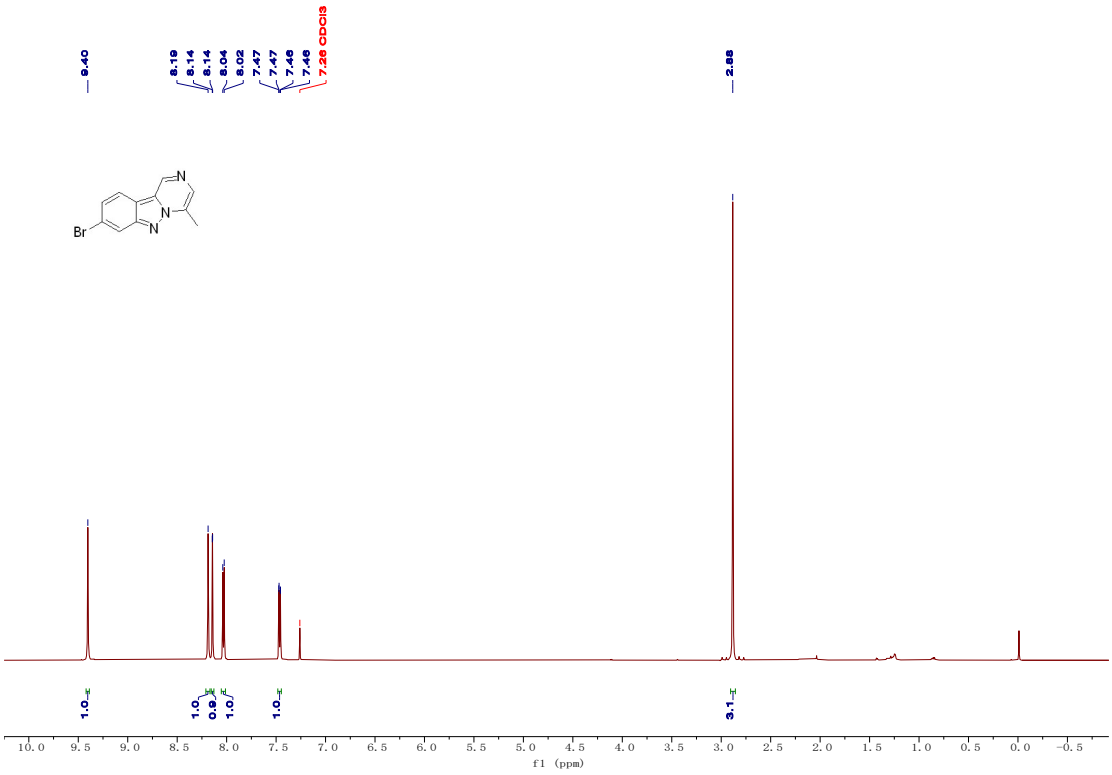

149.5
140.5
134.9
133.5
131.5
130.4
123.7
120.8
116.1
113.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.4
Cl
N
N
N
f1 (ppm)

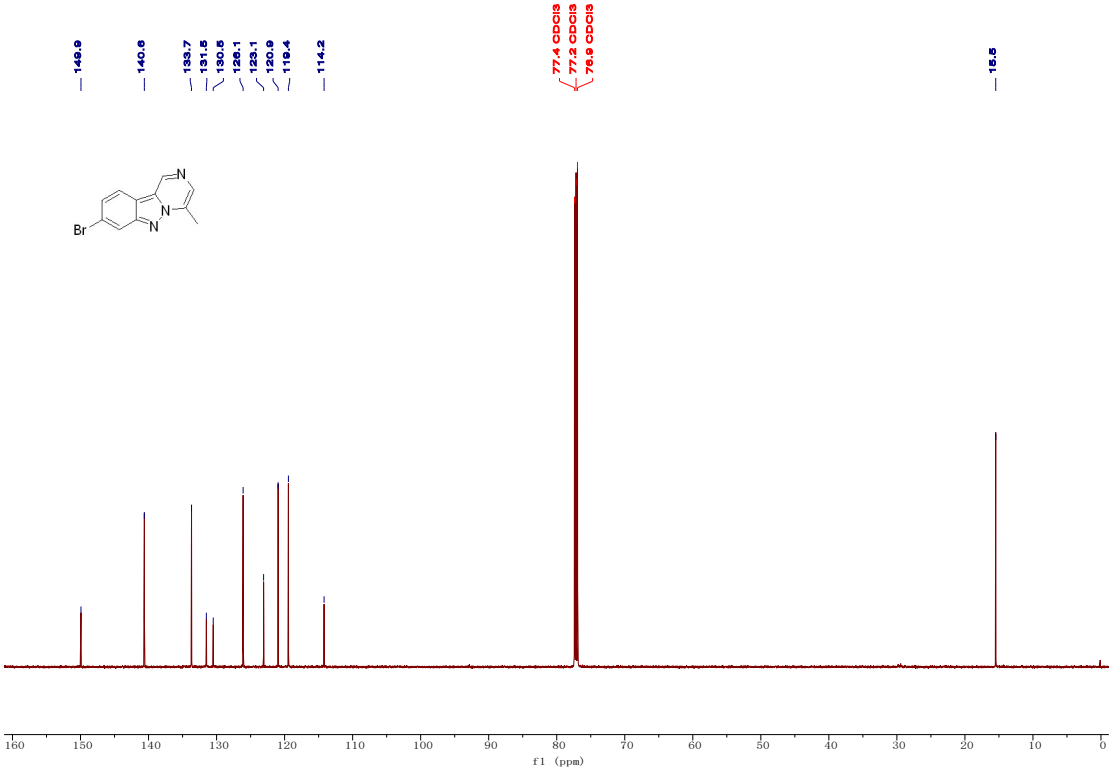
3fa


9.38
8.30
8.30
8.24
8.18
7.86
7.84
7.68
7.67
7.67
7.26 CDCl3
2.68
Br
N
N
N
1.0
1.0
1.1
1.0
1.1
3.1
f1 (ppm)

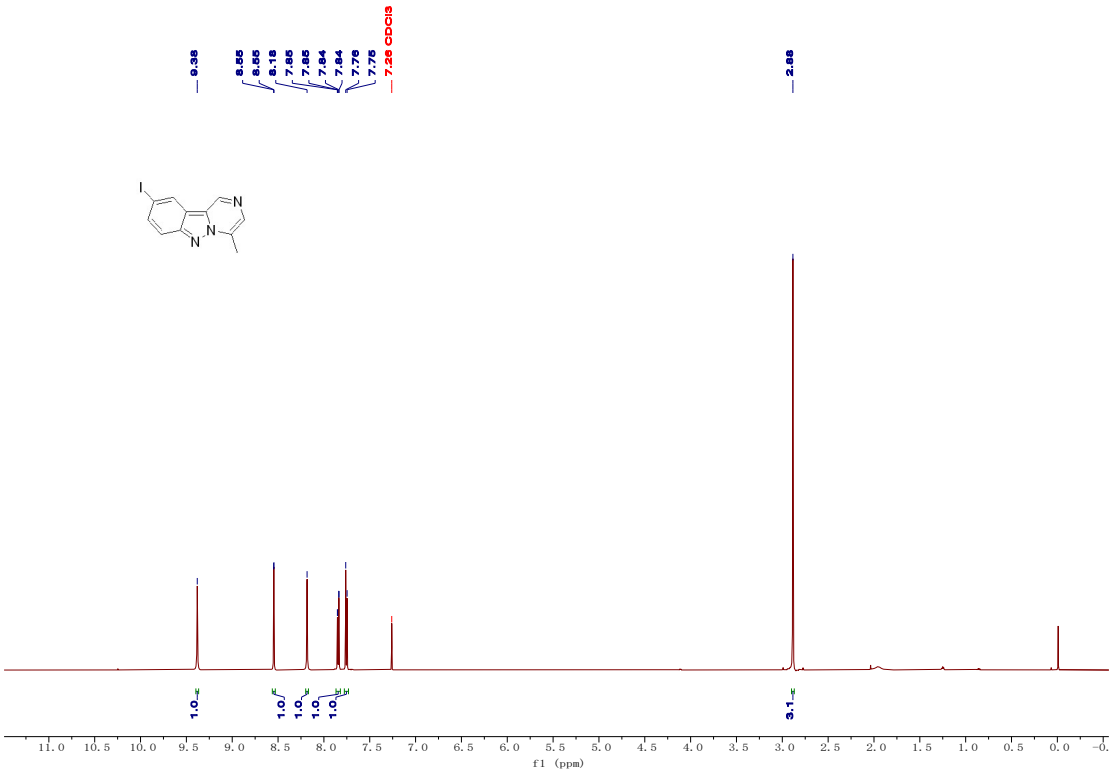

147.6
140.8
133.7
132.5
131.4
129.7
122.1
118.5
116.9
116.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.5
Br
N
N
N
f1 (ppm)

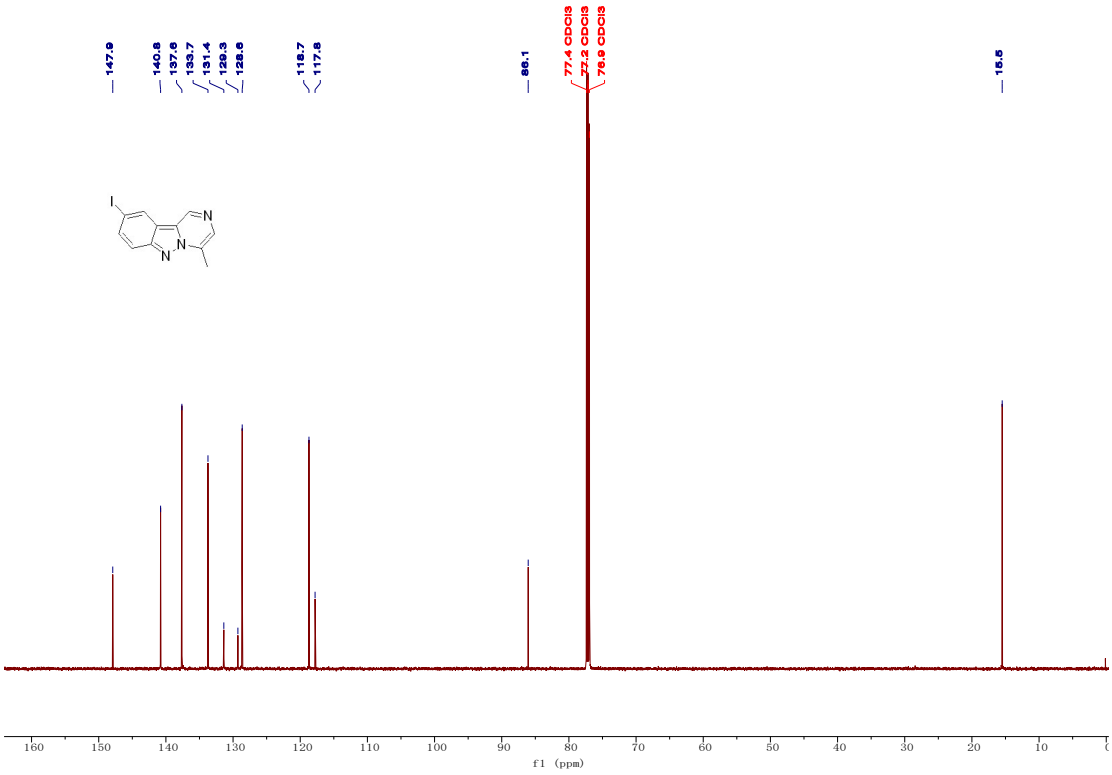
3ga


9.40
8.19
8.14
8.14
8.04
8.02
7.47
7.47
7.46
7.46
7.26 CDCl3
2.68
Br
N
N
N
1.0
1.0
0.9
1.0
1.0
3.1
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 -0.5
f1 (ppm)

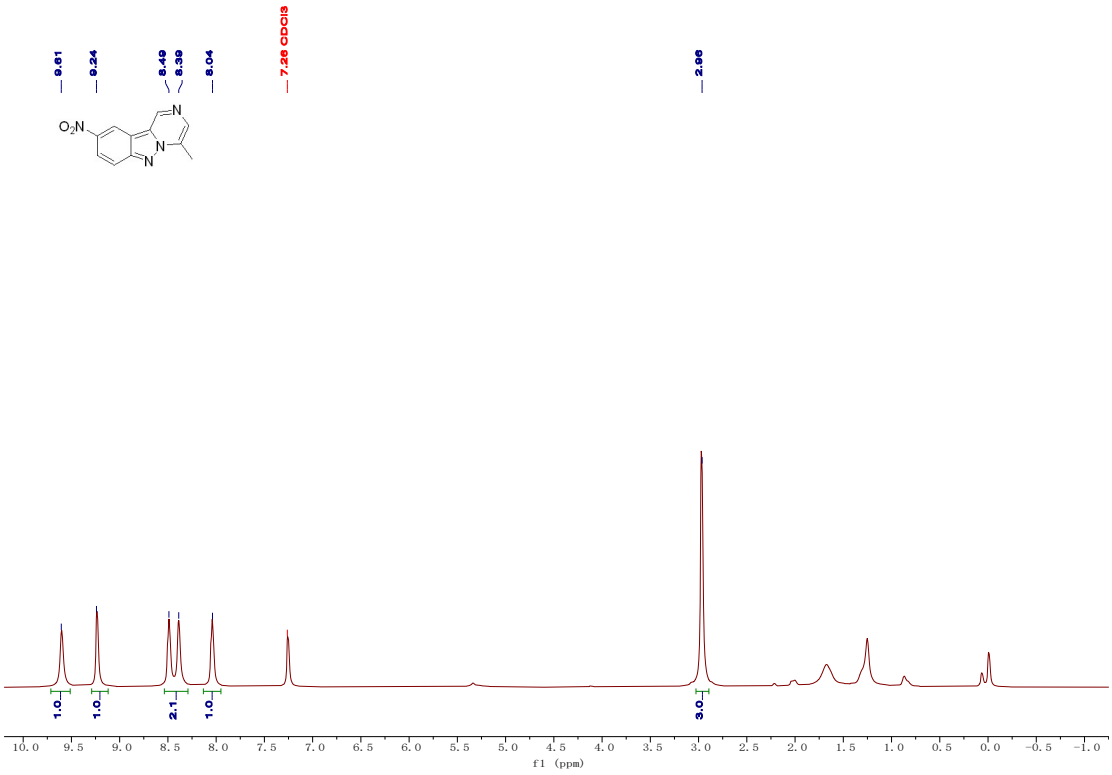

149.9
140.6
133.7
131.5
130.5
128.1
123.1
120.9
119.4
114.2
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.5
Br
N
N
N
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

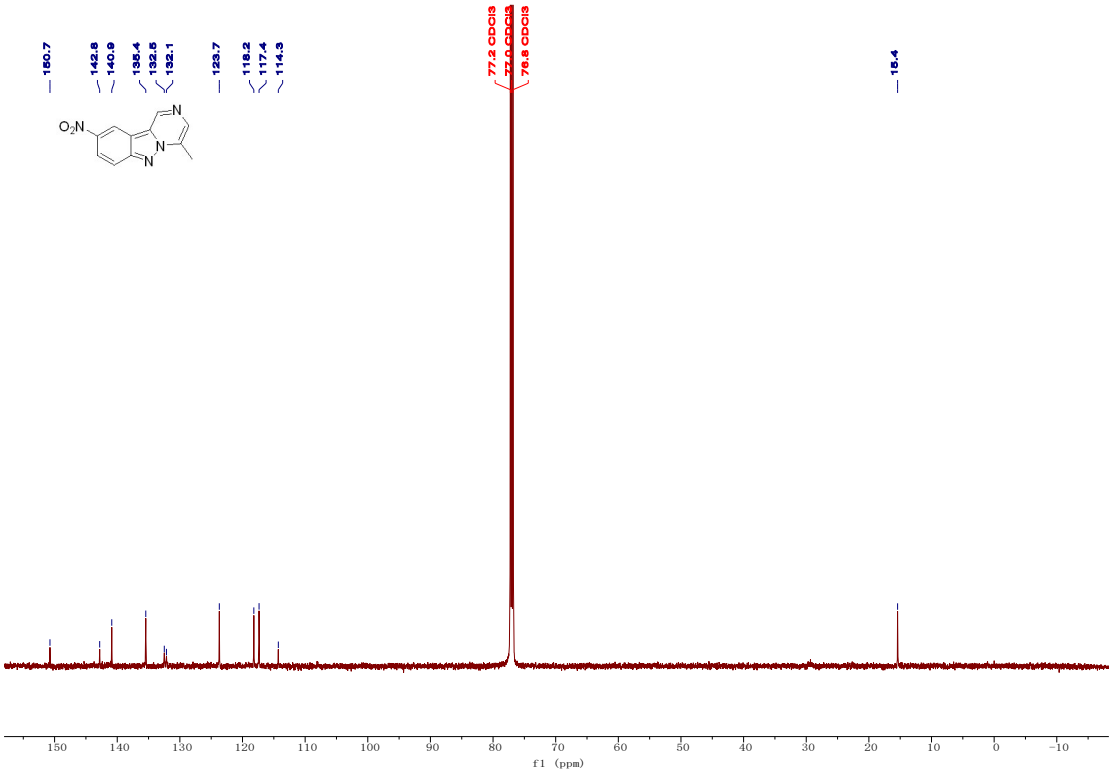
3ha


9.38
8.55
8.55
8.18
7.85
7.85
7.84
7.84
7.76
7.75
7.26 CDCl3
2.68
I
N
N
N
1.0
1.0
1.0
1.0
3.1
f1 (ppm)

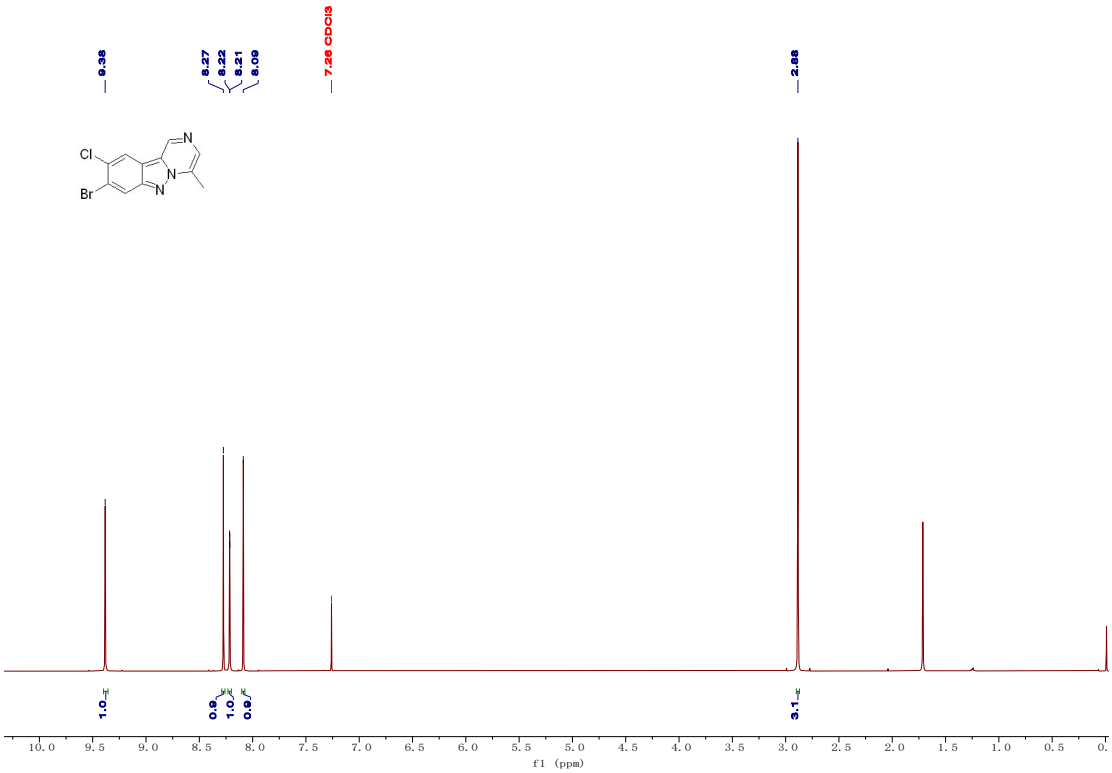

147.9
140.8
137.6
133.7
131.4
129.3
128.6
118.7
117.8
86.1
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
16.8
I
N
N
N
f1 (ppm)

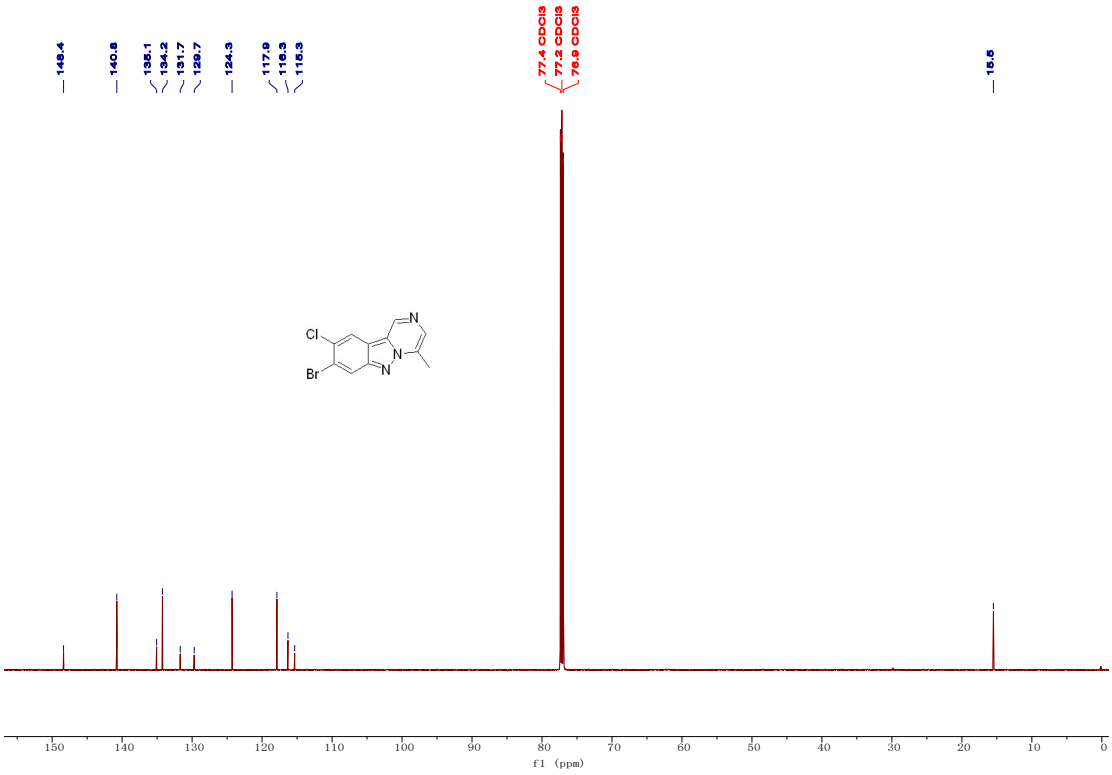
3ia


9.61
9.24
8.40
8.39
8.04
7.26 CDCl3
2.66
O2N
N
N
N
1.0
1.0
2.1
1.0
3.0
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 −0.5 −1.0
f1 (ppm)

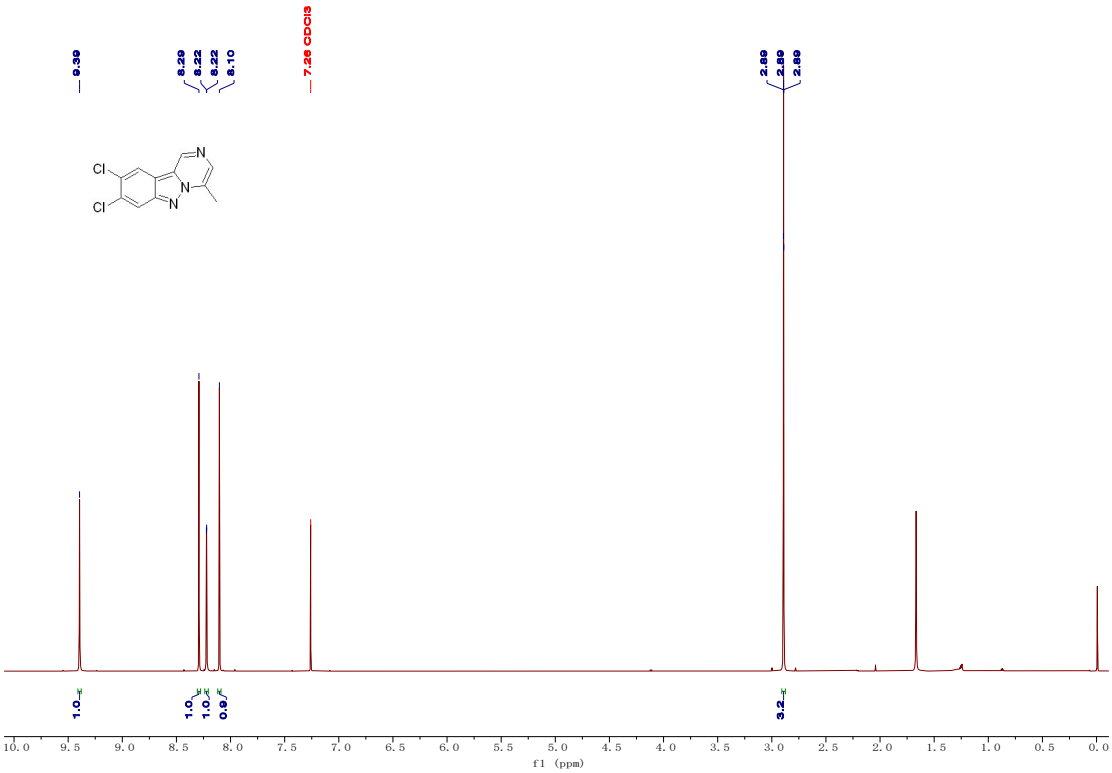

160.7
142.8
140.9
135.4
132.5
132.1
123.7
118.2
117.4
114.3
77.2 CDCl3
76.8 CDCl3
18.4
O2N
N
N
N
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

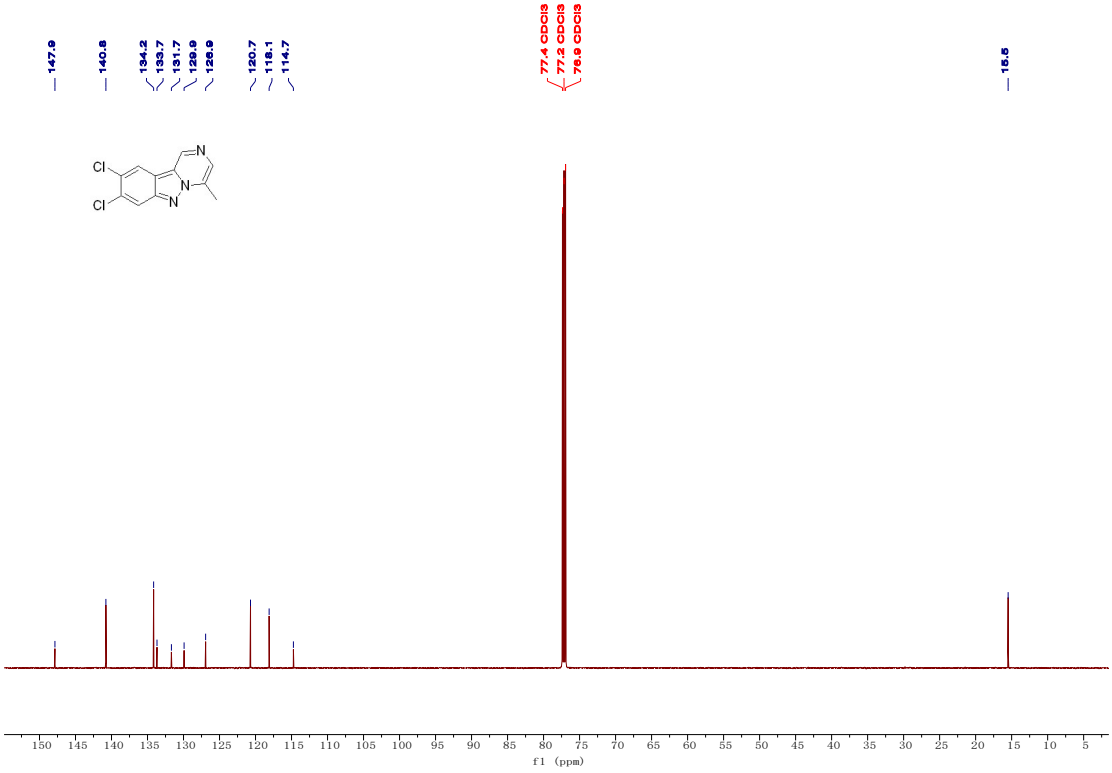
3ja


9.38
8.27
8.22
8.21
8.09
7.26 CDCl3
2.68
Cl
Br
N
N
1.0
0.9
1.0
0.9
3.1
f1 (ppm)

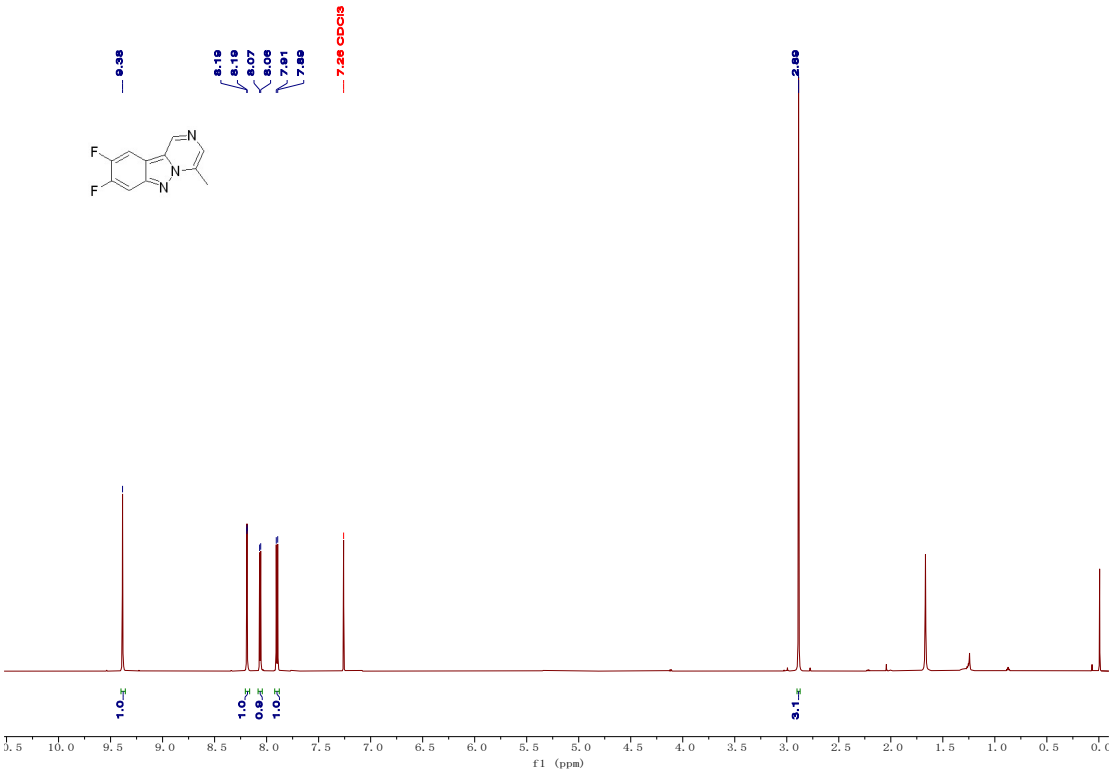

148.4
140.8
135.1
134.2
131.7
129.7
124.3
117.9
116.3
116.3
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
16.5
Cl
Br
N
N
f1 (ppm)

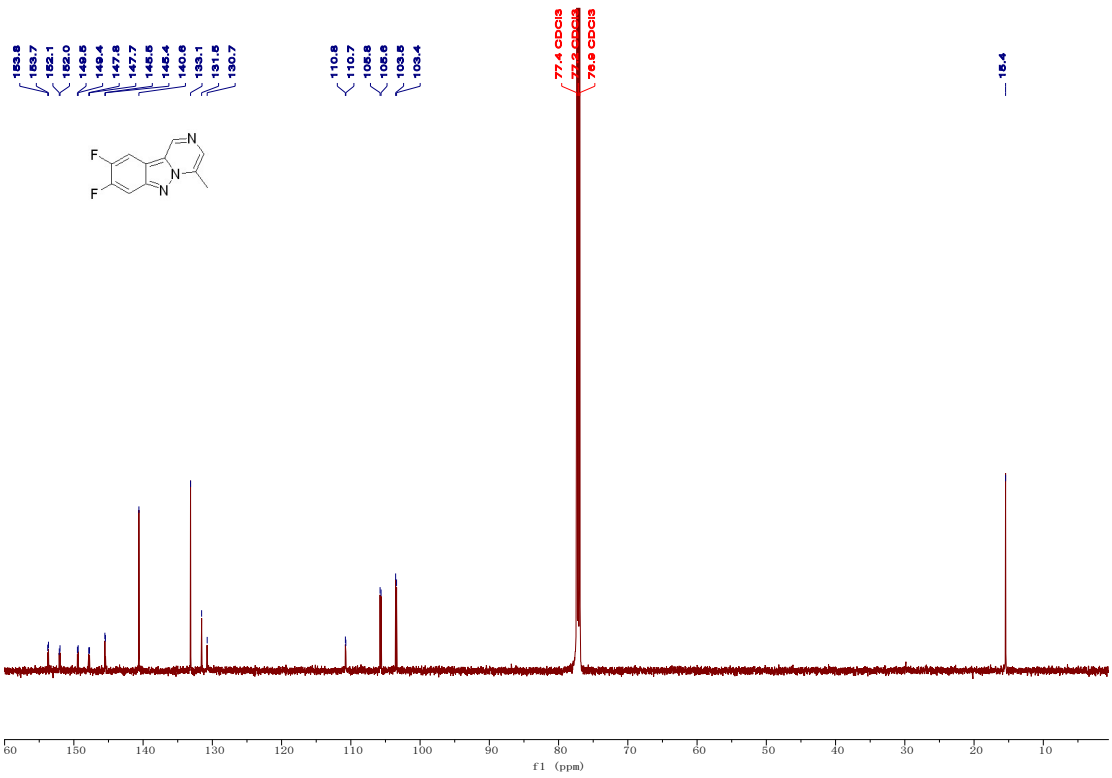
3ka


9.39
8.29
8.22
8.22
8.10
7.26 CDCl3
2.69
2.69
2.69
Cl
Cl
N
N
N
1.0
1.0
1.0
0.9
3.2
f1 (ppm)

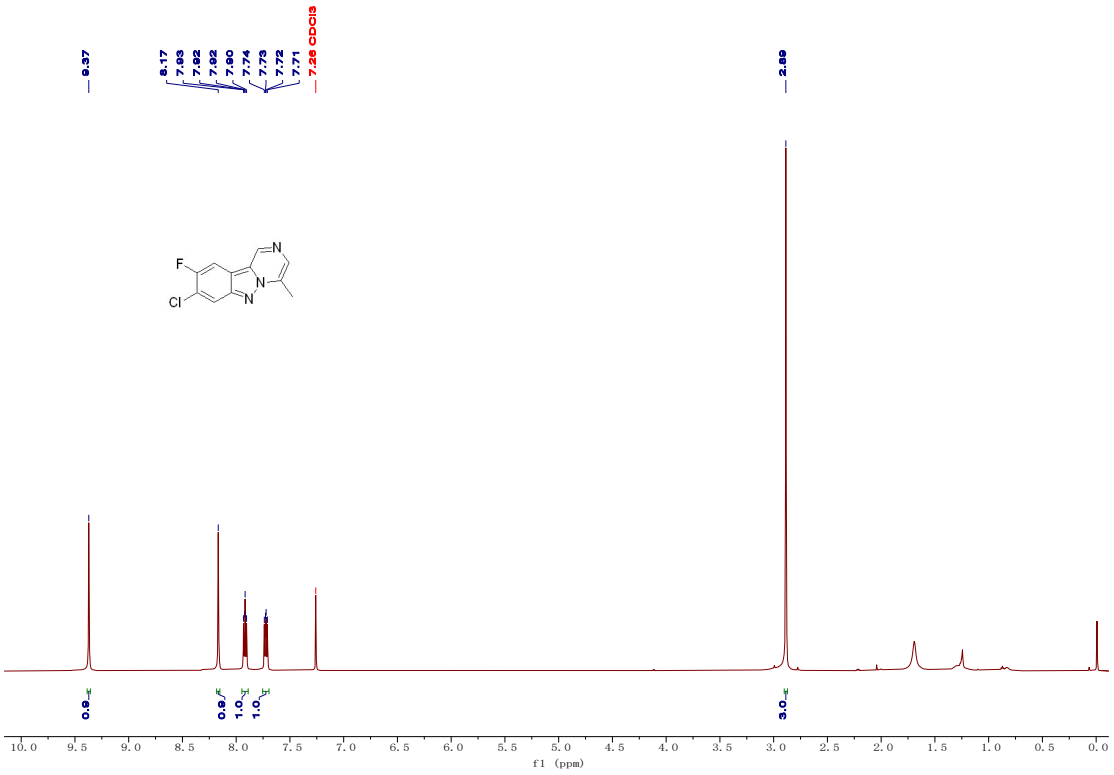

147.9
140.8
134.2
133.7
131.7
129.9
128.9
120.7
118.1
114.7
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.5
Cl
Cl
N
N
N
f1 (ppm)

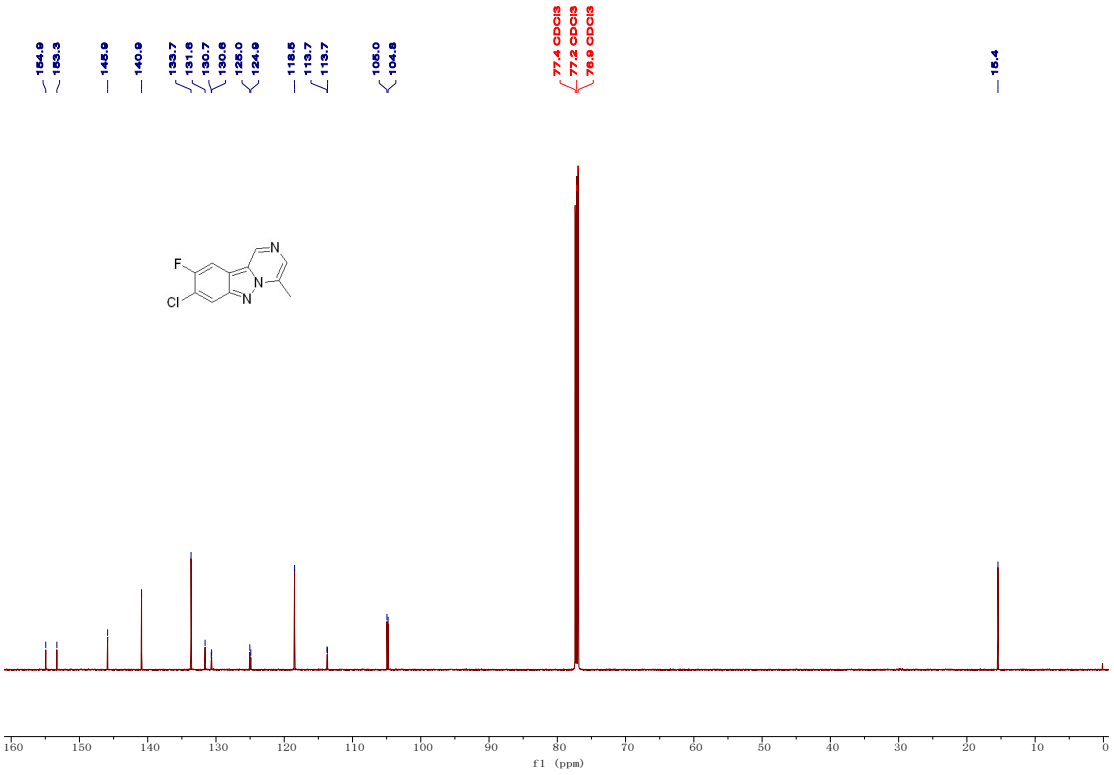
3la


9.38
8.19
8.19
8.07
8.06
7.91
7.89
7.26 CDCl3
2.89
F
F
N
N
1.0
1.0
0.9
1.0
3.1
f1 (ppm)

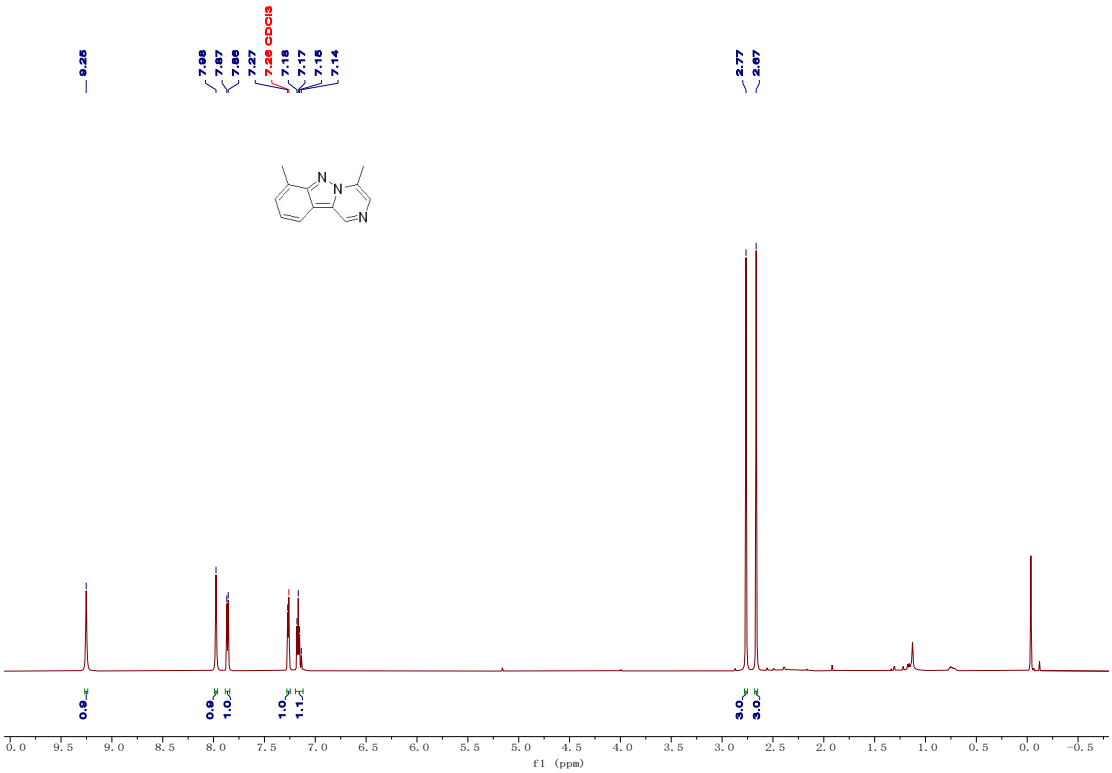

153.8
153.7
152.1
152.0
149.5
149.4
147.8
147.7
145.5
145.4
140.6
133.1
131.5
130.7
110.8
110.7
106.8
106.6
103.5
103.4
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.4
F
F
N
N
f1 (ppm)

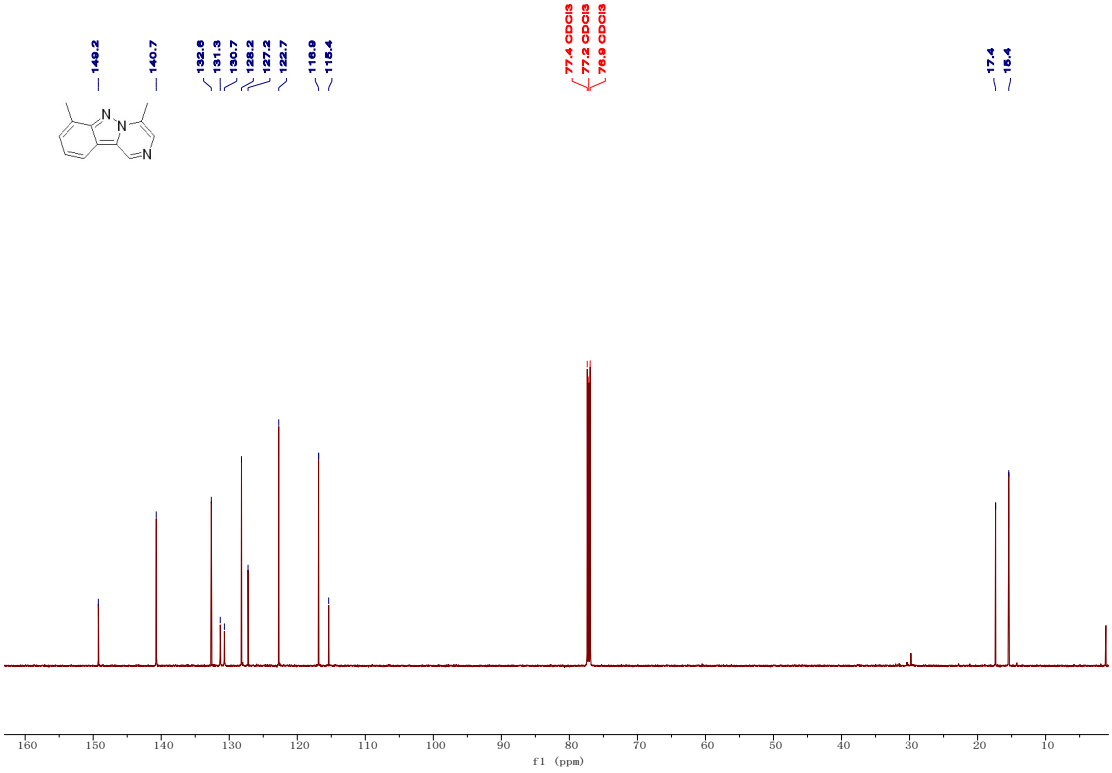
3ma


9.37
8.17
7.93
7.92
7.92
7.90
7.74
7.73
7.72
7.71
7.26 CDCl3
2.89
F
Cl
N
N
N
0.9
0.9
1.0
1.0
3.0
f1 (ppm)

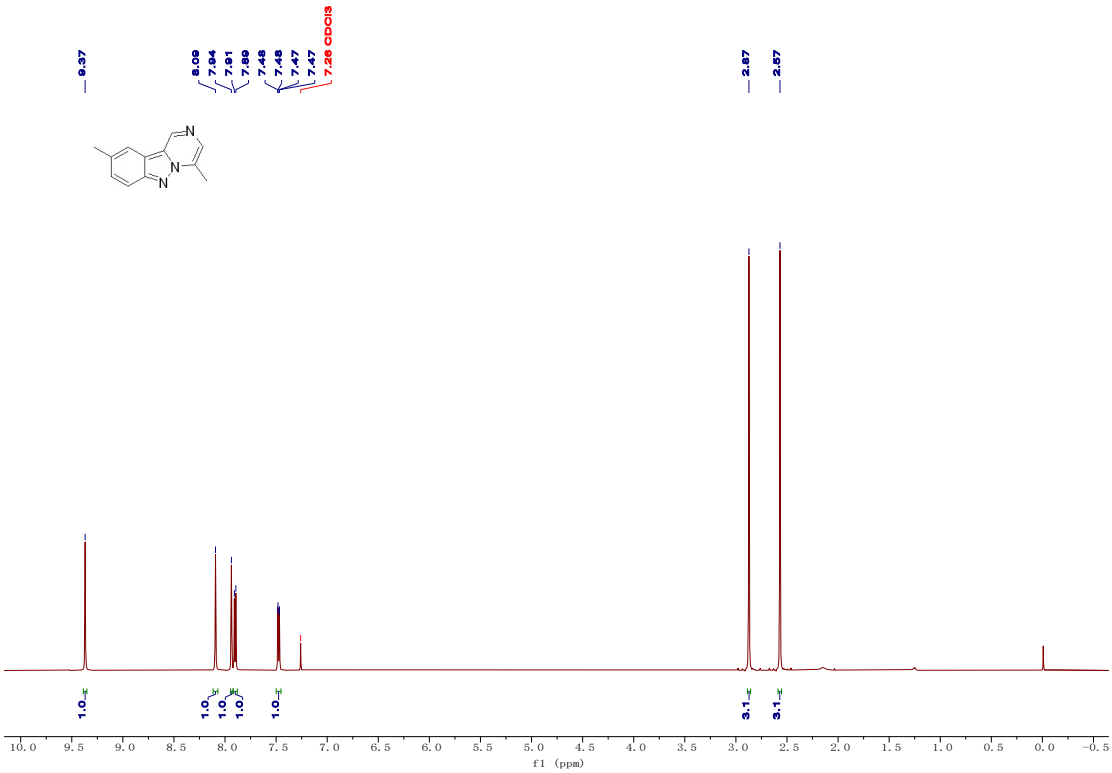

154.9
153.3
145.9
140.9
133.7
131.6
130.7
130.6
125.0
124.9
118.5
113.7
113.7
105.0
104.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.4
F
Cl
N
N
N
f1 (ppm)

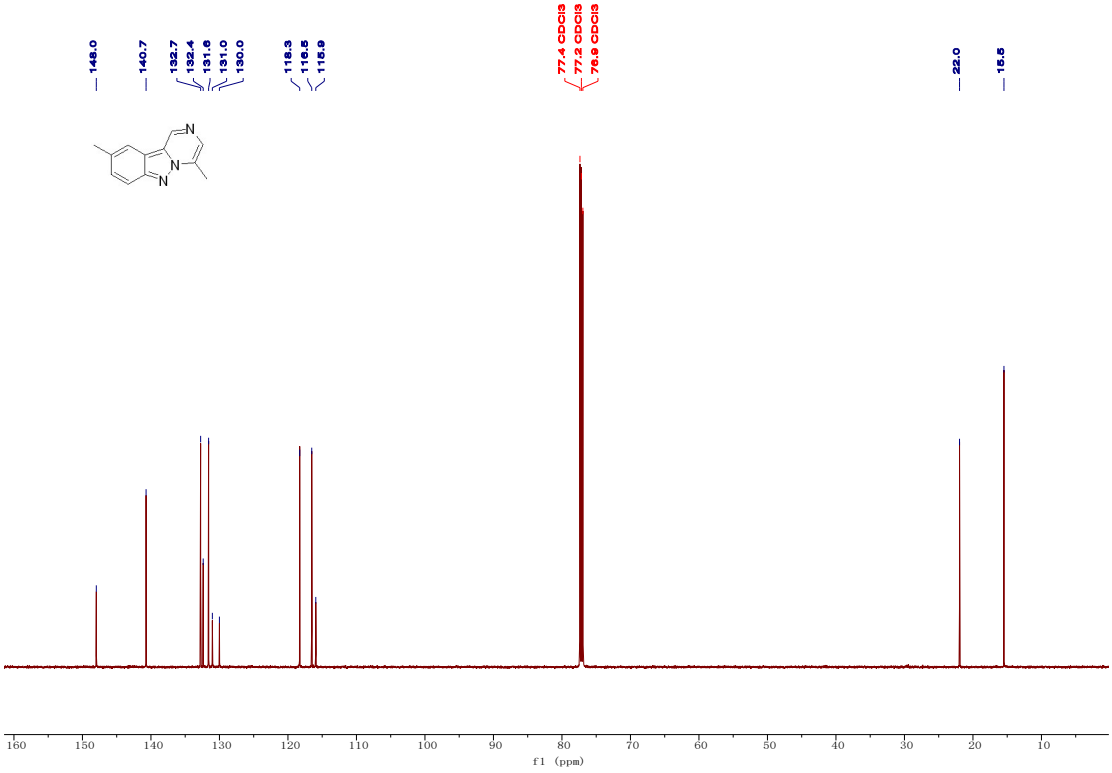
3na


9.25
7.98
7.87
7.86
7.27
7.26 CDCl3
7.18
7.17
7.15
7.14
2.77
2.67
0.9
0.9
1.0
1.0
1.1
3.0
3.0
f1 (ppm)

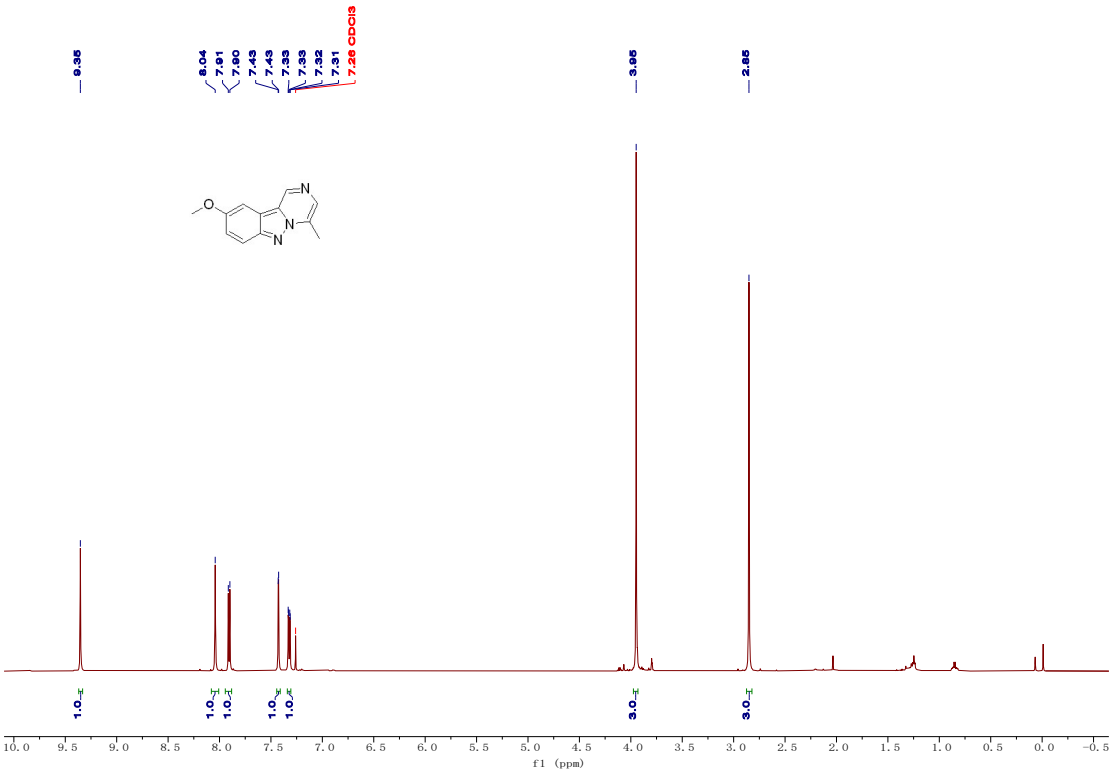

149.2
140.7
132.6
131.3
130.7
128.2
127.2
122.7
116.9
116.4
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
17.4
15.4
f1 (ppm)

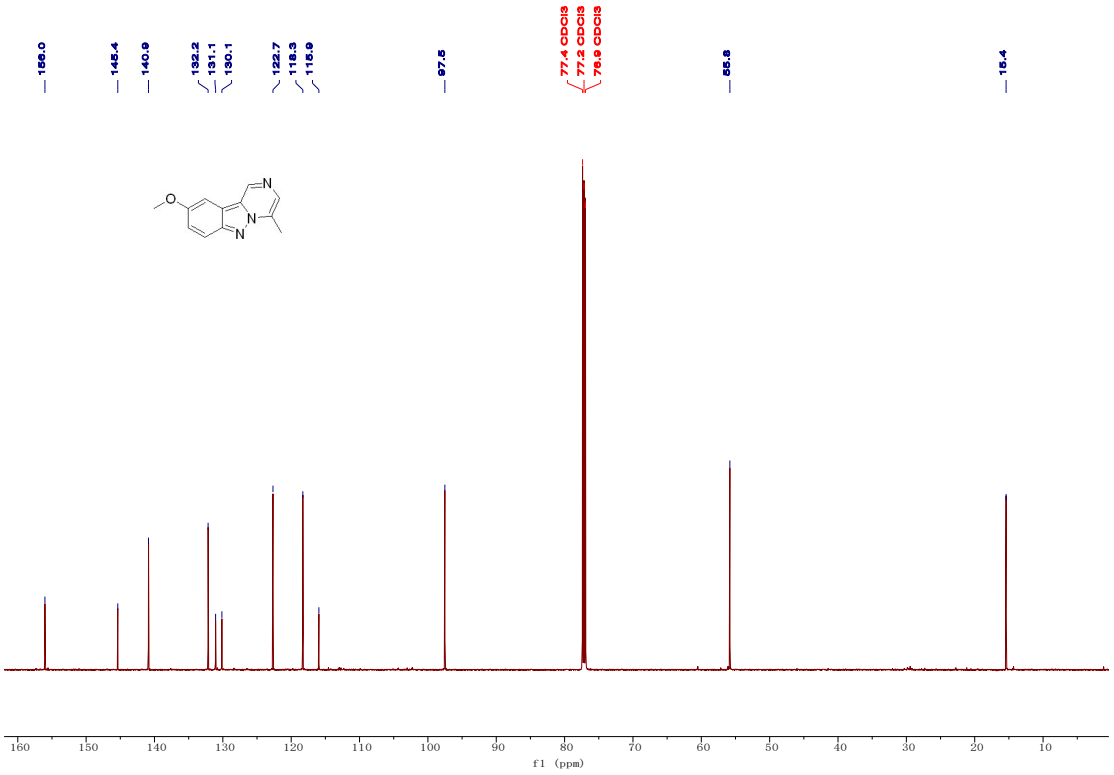
3oa


9.37
8.09
7.94
7.91
7.89
7.48
7.47
7.47
7.26 CDCl3
2.67
2.57
1.0
1.0
1.0
1.0
3.1
3.1
f1 (ppm)

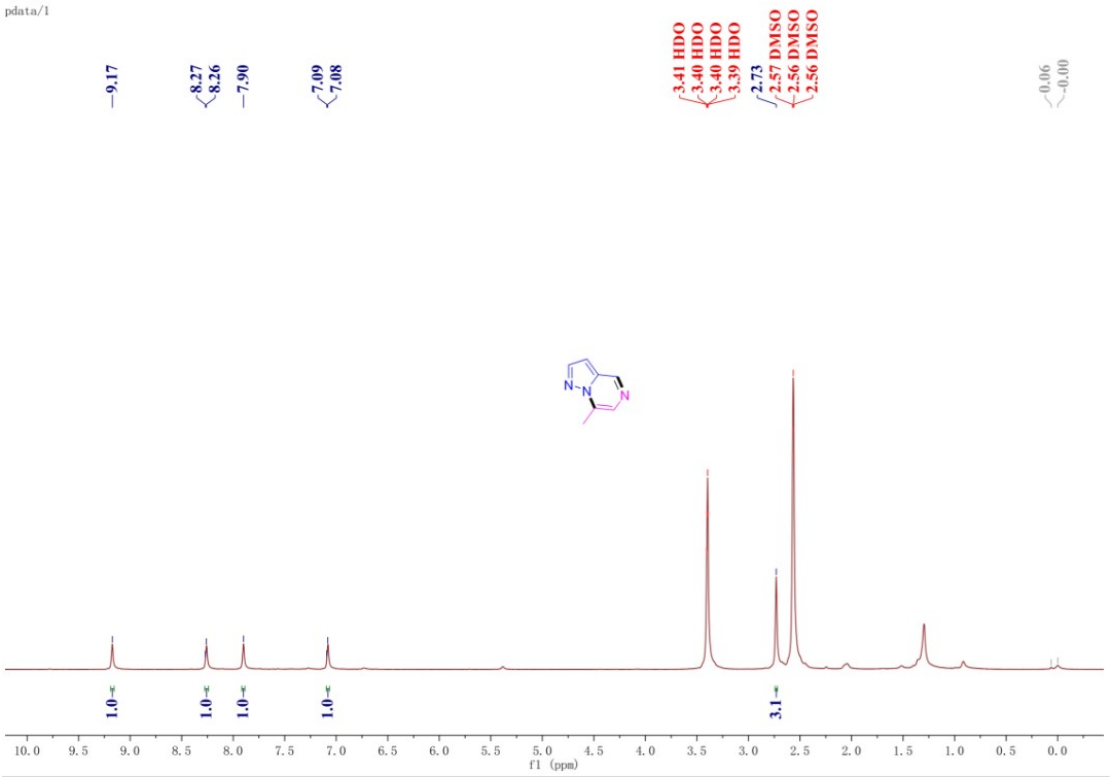

148.0
140.7
132.7
132.4
131.6
131.0
130.0
118.3
116.5
115.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
22.0
15.5
f1 (ppm)

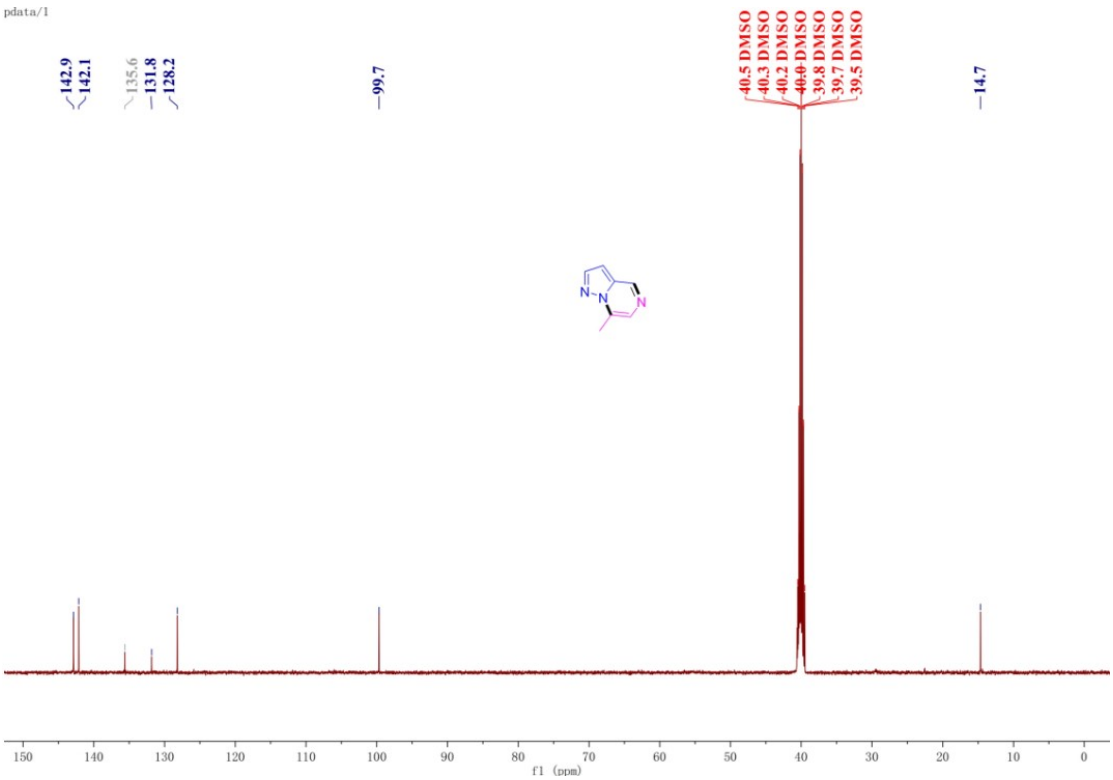
3pa


9.35
8.04
7.91
7.90
7.43
7.43
7.33
7.33
7.32
7.31
7.26 CDCl3
3.95
2.85
1.0
1.0
1.0
1.0
1.0
3.0
3.0
f1 (ppm)

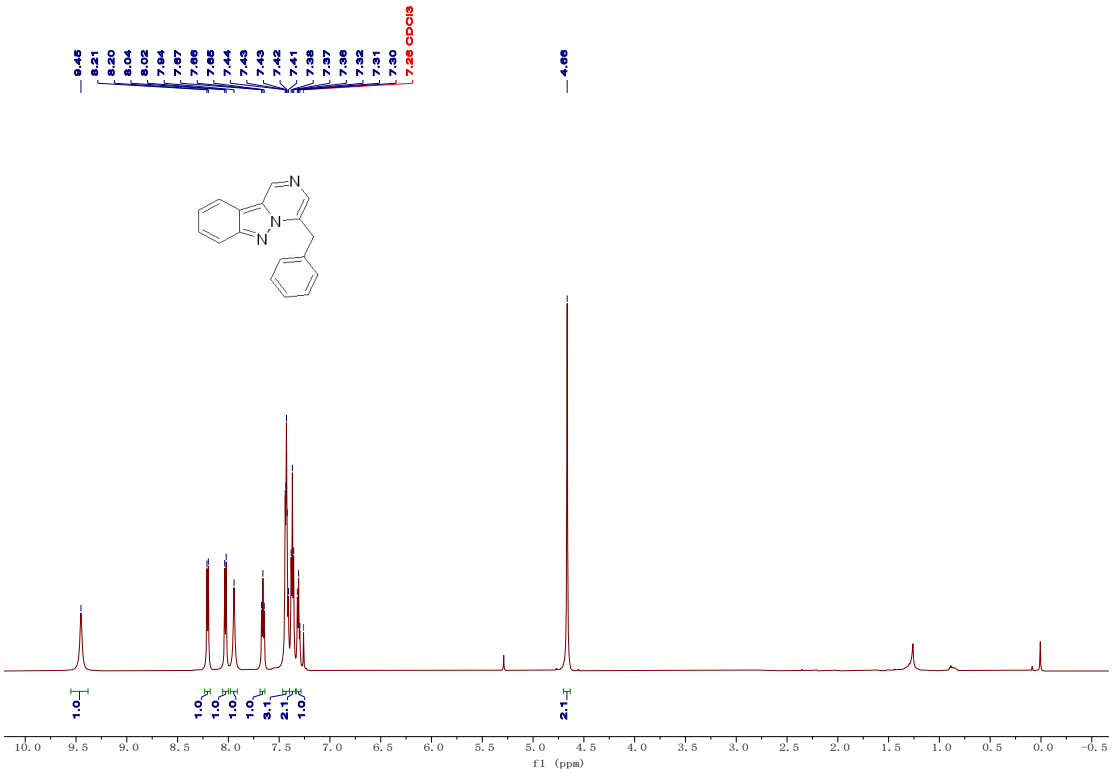

156.0
145.4
140.9
132.2
131.1
130.1
122.7
118.3
115.9
97.5
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
55.8
15.4
f1 (ppm)

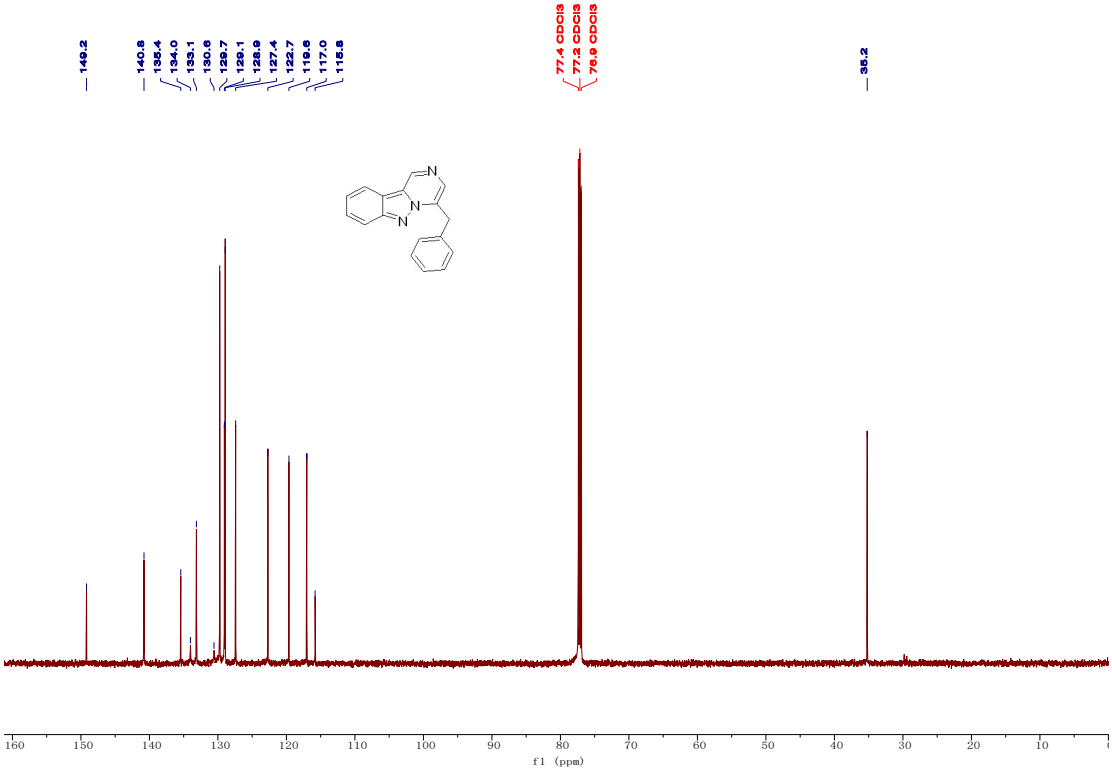
3qa


pdata/1
9.17
8.27
8.26
7.90
7.09
7.08
3.41 HDO
3.40 HDO
3.40 HDO
3.39 HDO
2.73
2.57 DMSO
2.56 DMSO
2.56 DMSO
0.06
0.00
1.0
1.0
1.0
1.0
3.1
f1 (ppm)

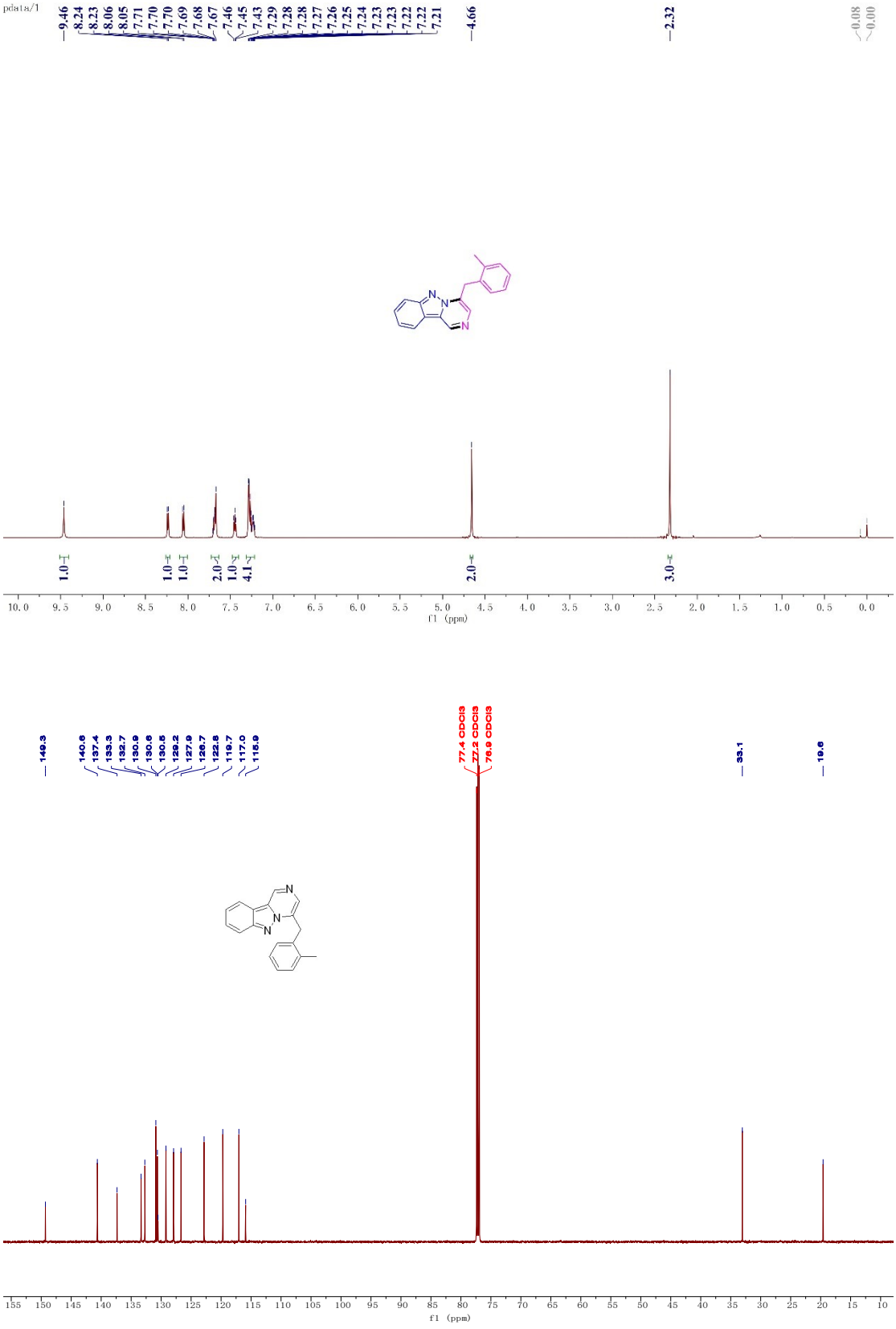

pdata/1
142.9
142.1
135.6
131.8
128.2
99.7
40.5 DMSO
40.3 DMSO
40.2 DMSO
40.0 DMSO
39.8 DMSO
39.7 DMSO
39.5 DMSO
14.7
f1 (ppm)

3ab

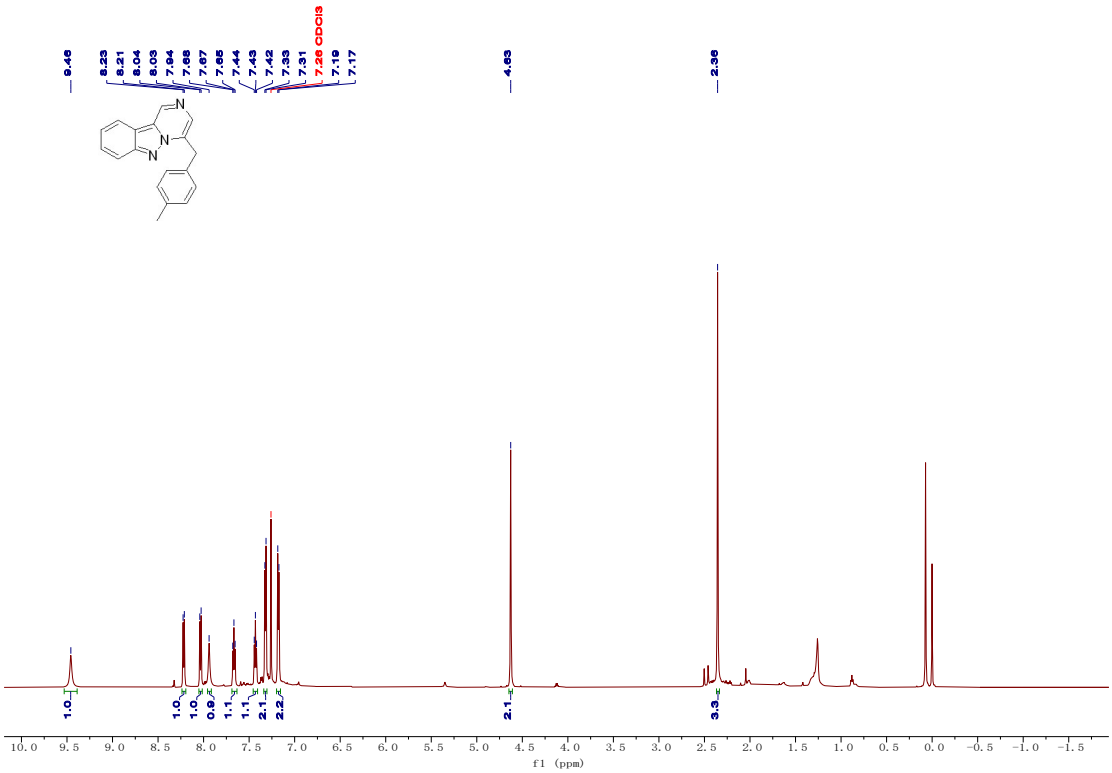

9.45
8.21
8.20
8.04
8.02
7.94
7.67
7.66
7.65
7.44
7.43
7.43
7.42
7.41
7.38
7.37
7.36
7.32
7.31
7.30
7.26 CDCl3
4.66
1.0
1.0
1.0
1.0
1.0
3.1
2.1
1.0
2.1
f1 (ppm)

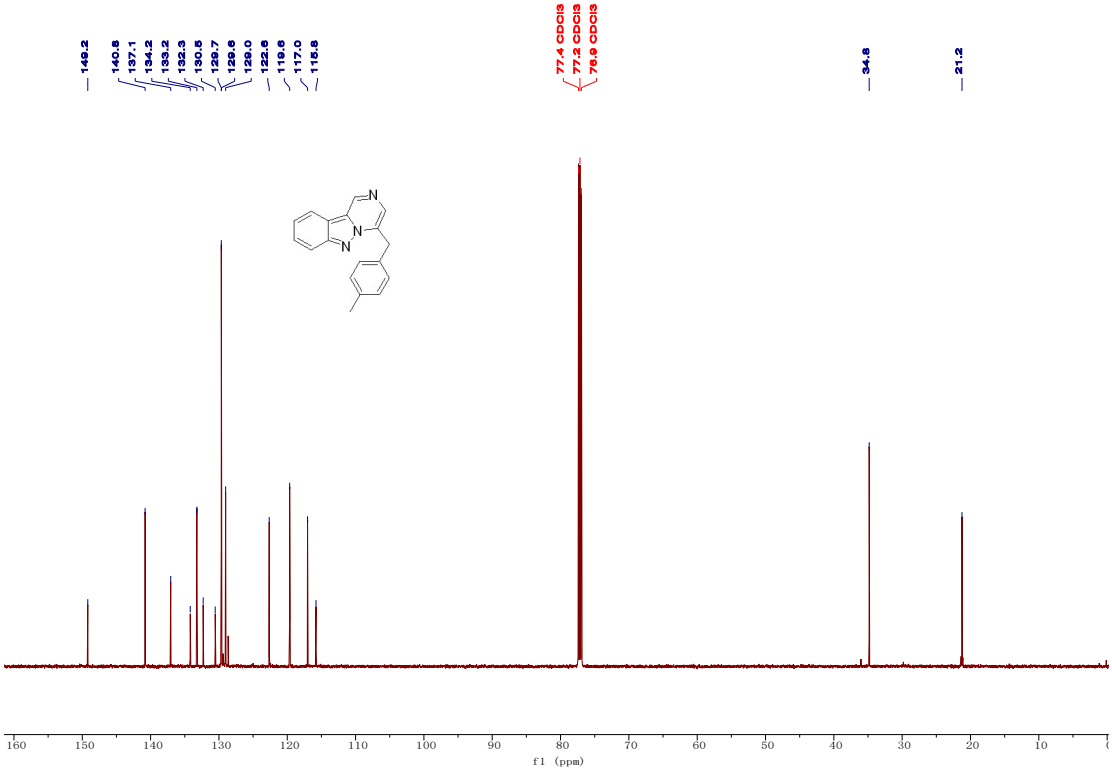

149.2
140.6
138.4
134.0
133.1
130.6
129.7
129.1
128.9
127.4
122.7
119.6
117.0
116.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
35.2
f1 (ppm)

3ac

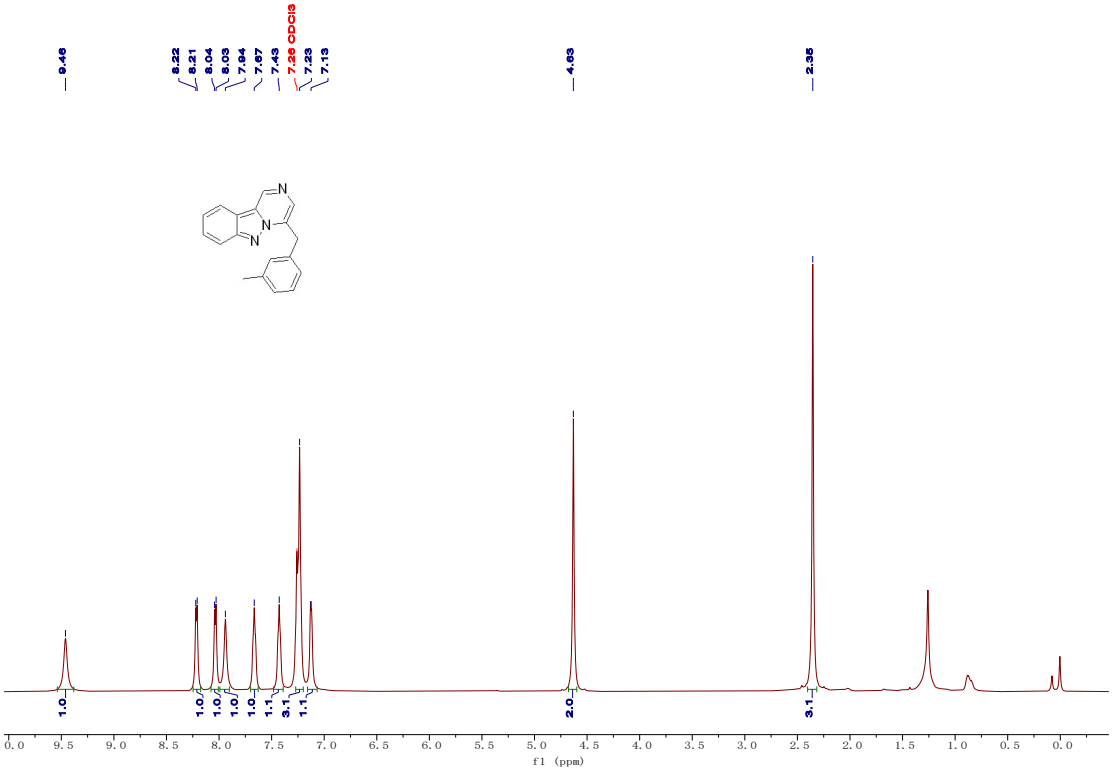

pda1a/1
9.46
8.24
8.23
8.06
8.05
7.71
7.70
7.70
7.69
7.68
7.67
7.46
7.45
7.43
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.23
7.23
7.22
7.22
7.21
4.66
2.32
0.08
0.00
1.0
1.0
1.0
2.0
1.0
4.1
2.0
3.0
f1 (ppm)
149.3
140.8
137.4
133.3
132.7
130.9
130.6
130.5
129.2
127.9
126.7
122.8
119.7
117.0
115.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
33.1
19.6
f1 (ppm)

3ad


9.46
8.23
8.21
8.04
8.03
7.94
7.68
7.67
7.65
7.44
7.43
7.42
7.33
7.31
7.26 CDCl3
7.19
7.17
4.63
2.36
1.0
1.0
1.0
0.9
1.1
1.1
2.1
2.2
2.1
3.3
f1 (ppm)


149.2
140.8
137.1
134.2
133.2
132.3
130.5
129.7
129.6
129.0
122.6
119.6
117.0
115.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
34.8
21.2
f1 (ppm)

3ae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1.0
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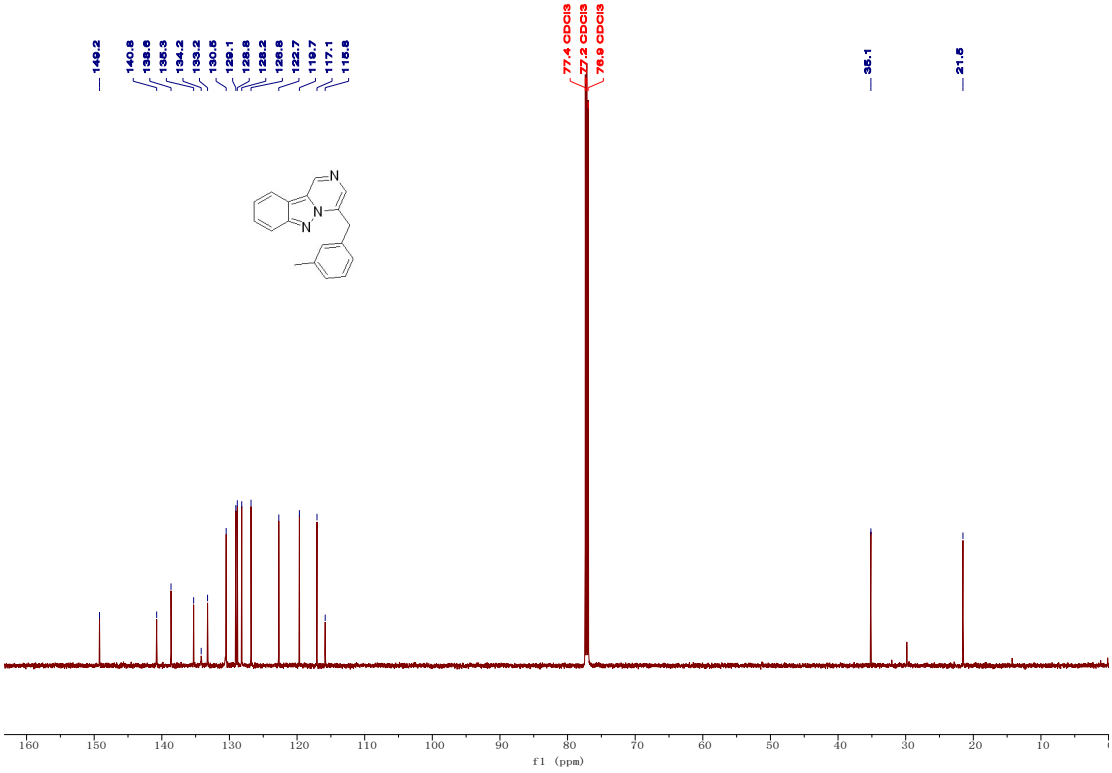
f1 (ppm)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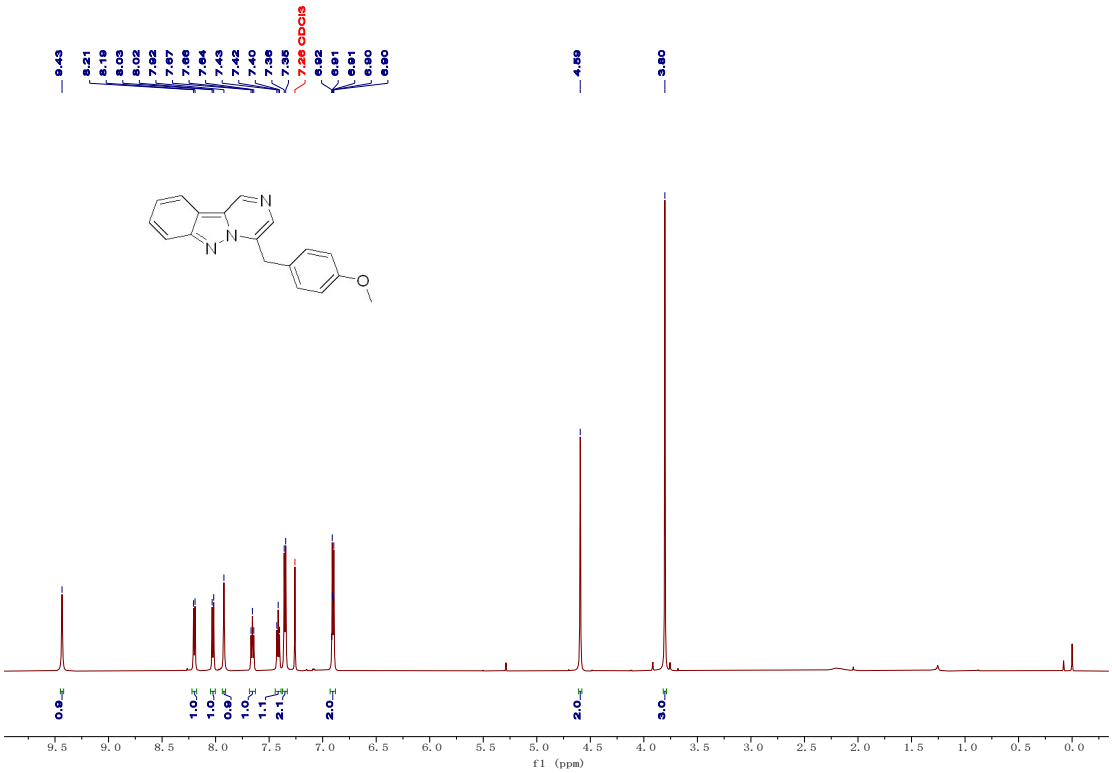
115.8
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
35.1
21.5
f1 (ppm)

3af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7.66
7.64
7.43
7.42
7.40
7.36
7.35
7.26 CDCl3
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6.91
6.91
6.90
6.90
4.56
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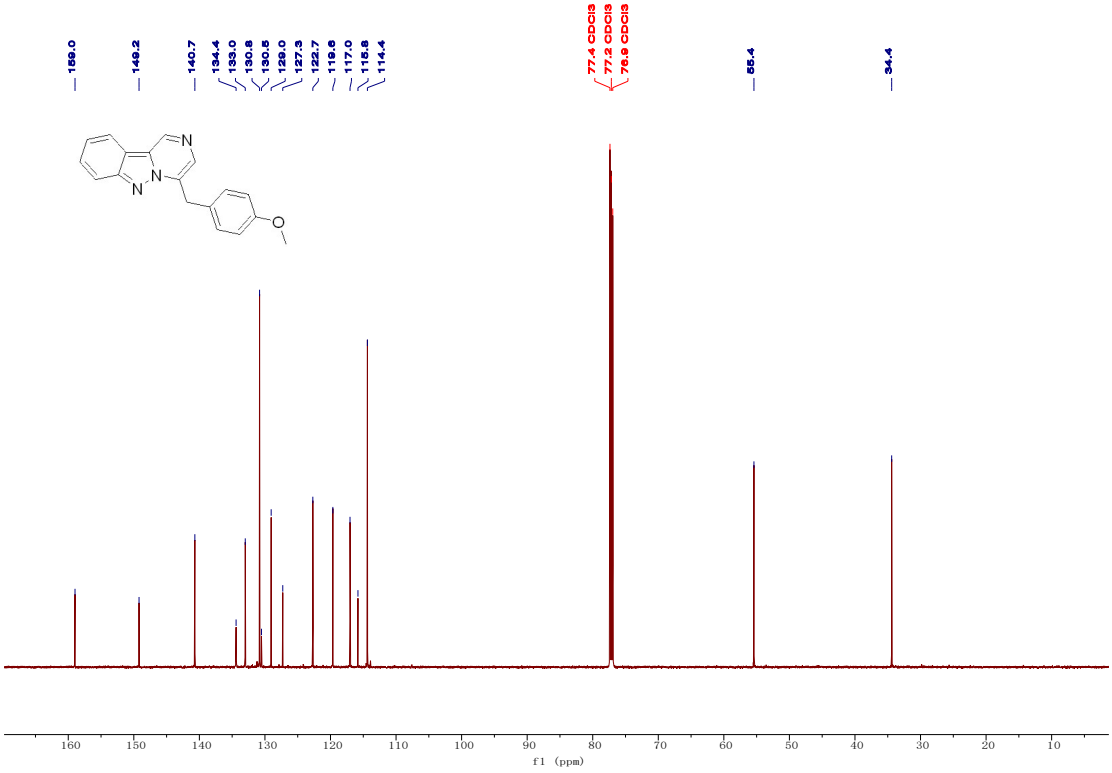
1.0
1.1
2.1
2.0
2.0
3.0
f1 (ppm)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129.0
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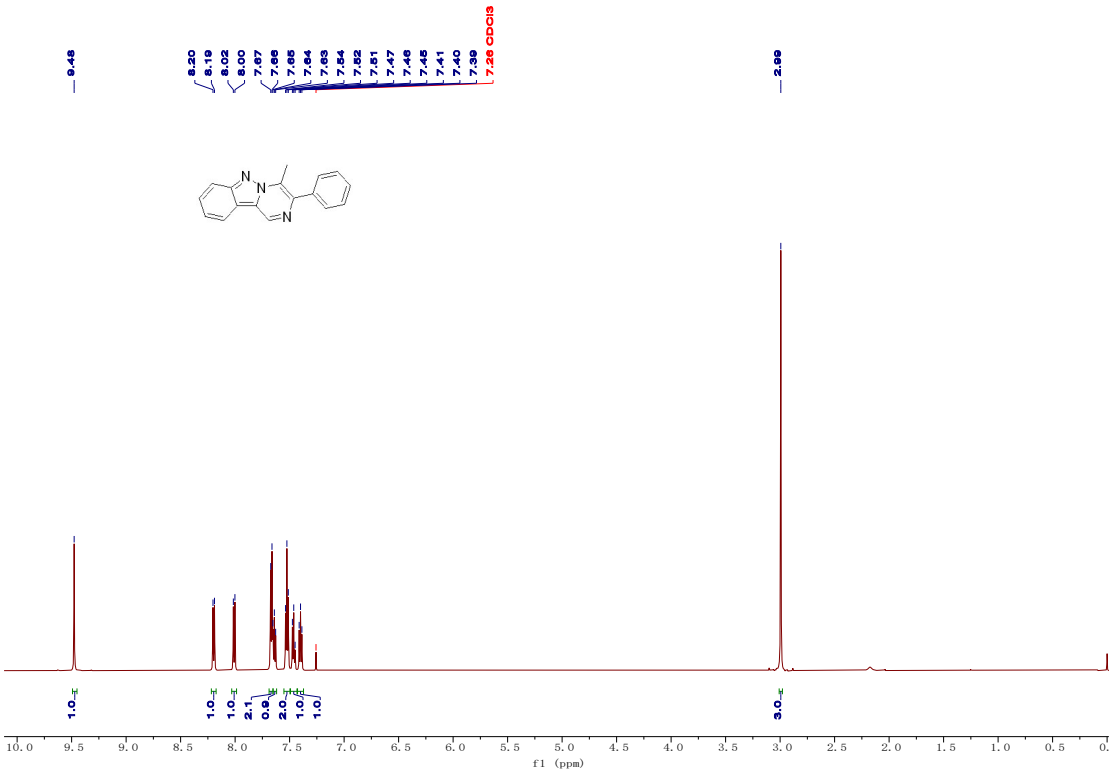
114.4
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
55.4
34.4
f1 (ppm)

3ag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7.52
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7.47
7.46
7.45
7.41
7.40
7.39
7.26 CDCl3
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1.0
1.0
2.1
0.9
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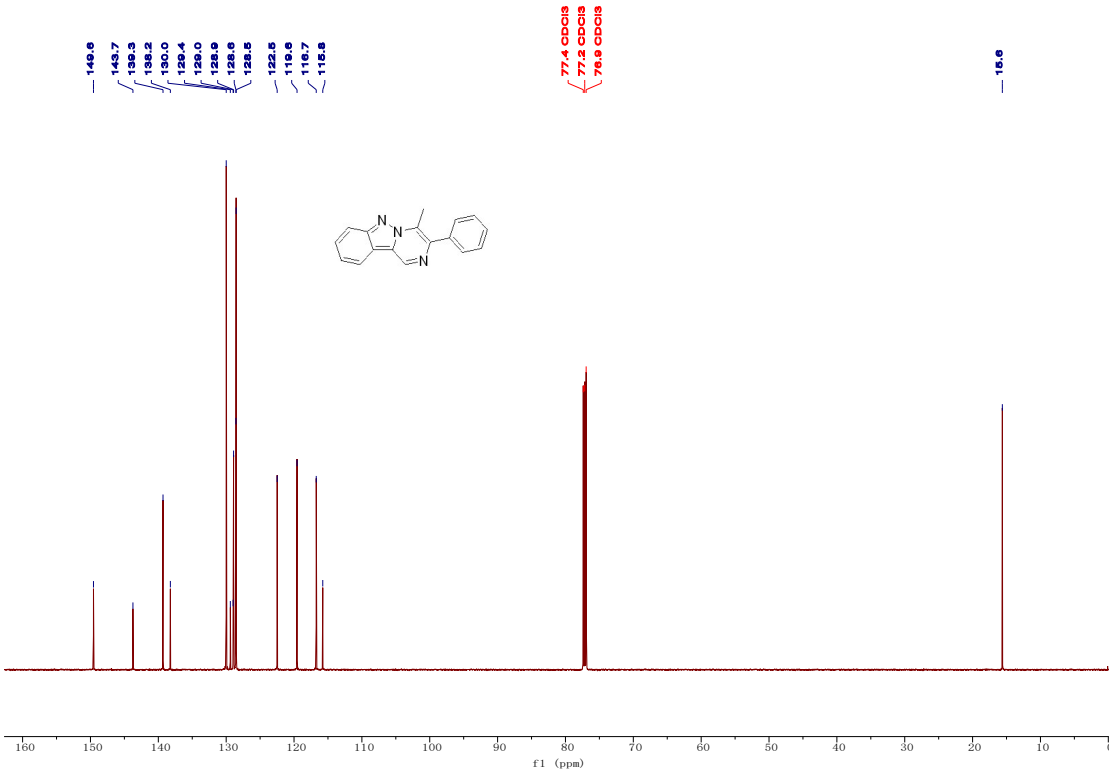
1.0
1.0
3.0
f1 (ppm)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128.9
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128.5
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116.7
115.6
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77.2 CDCl3
76.9 CDCl3
16.6
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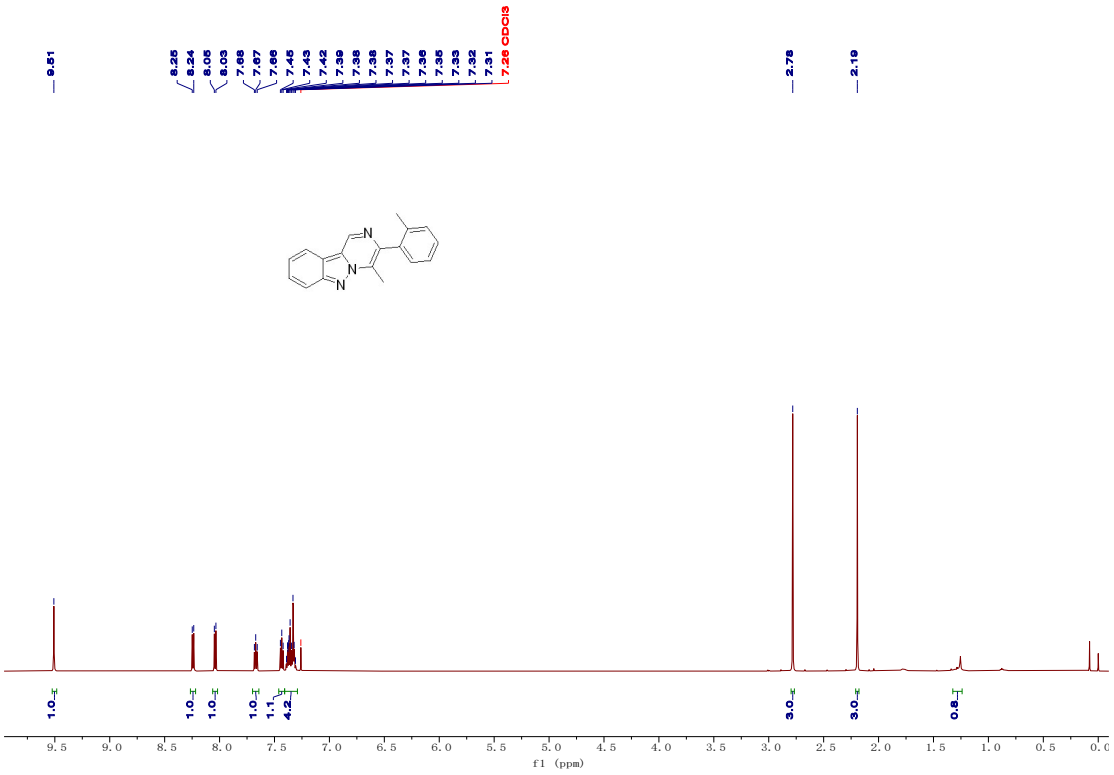
3ah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7.38
7.38
7.37
7.37
7.36
7.35
7.33
7.32
7.31
7.26 CDCl3
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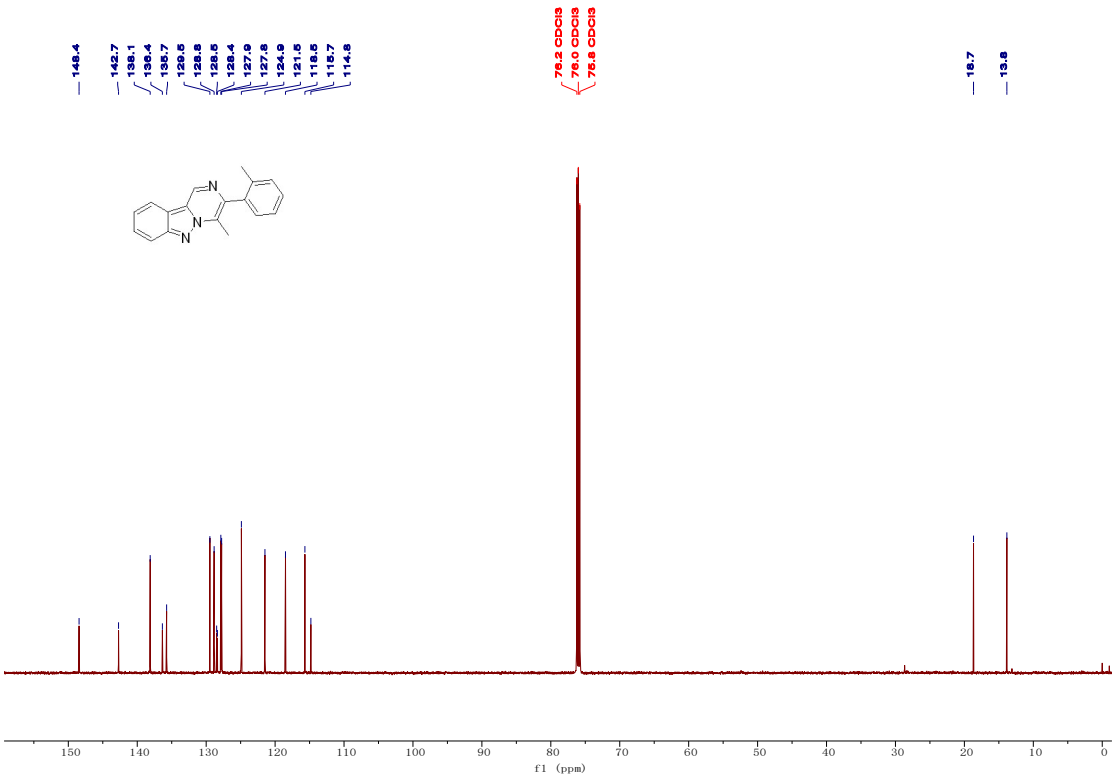
f1 (ppm)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128.8
128.5
128.4
127.9
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124.9
121.5
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114.8
76.2 CDCl3
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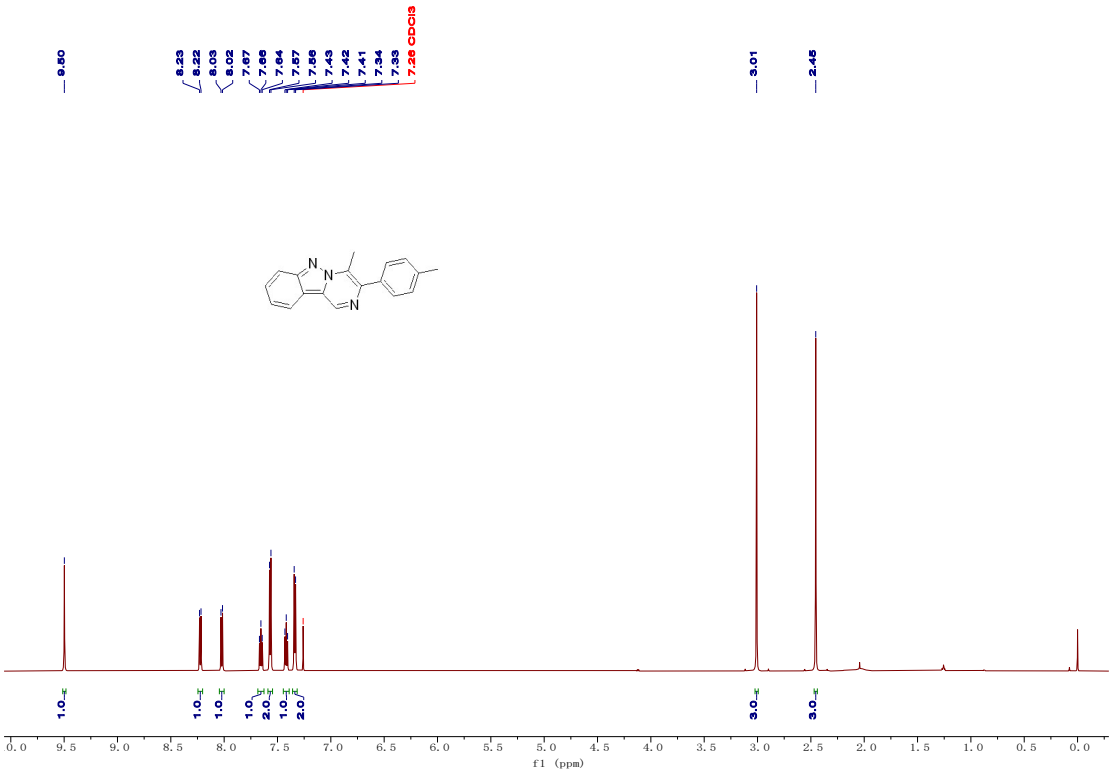
18.7
13.8
f1 (ppm)

3ai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7.33
7.26 CDCl3
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1.0
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1.0
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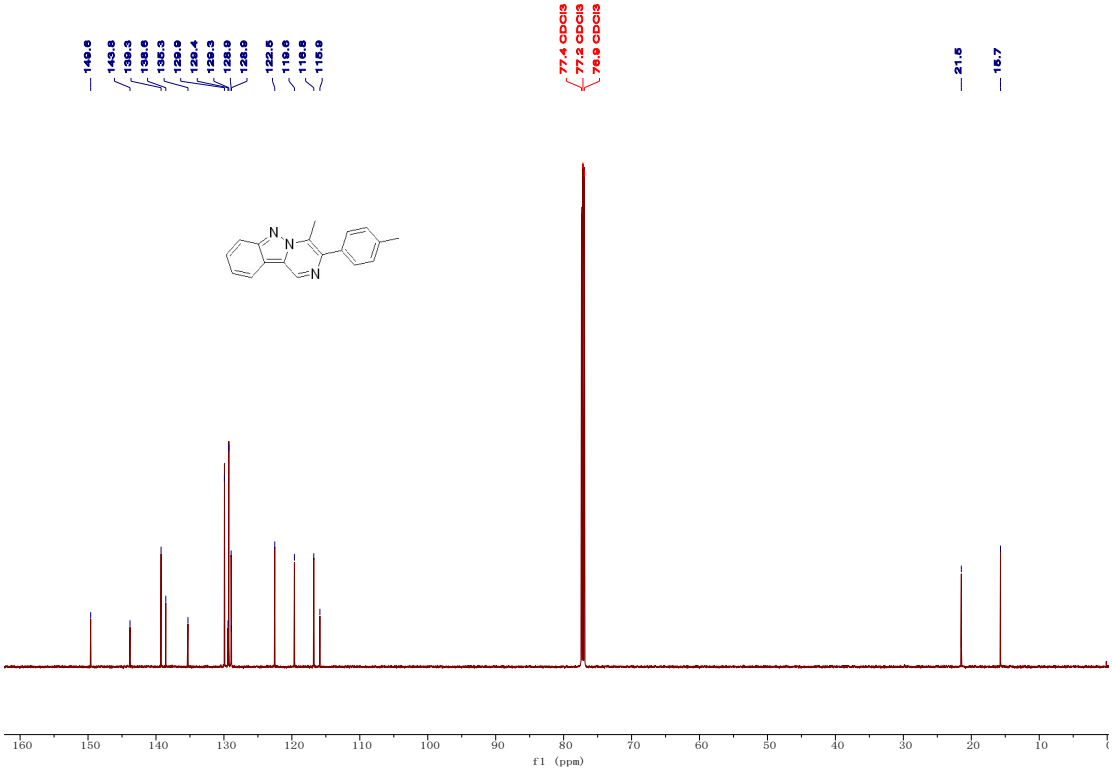
1.0
2.0
3.0
3.0
f1 (ppm)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128.9
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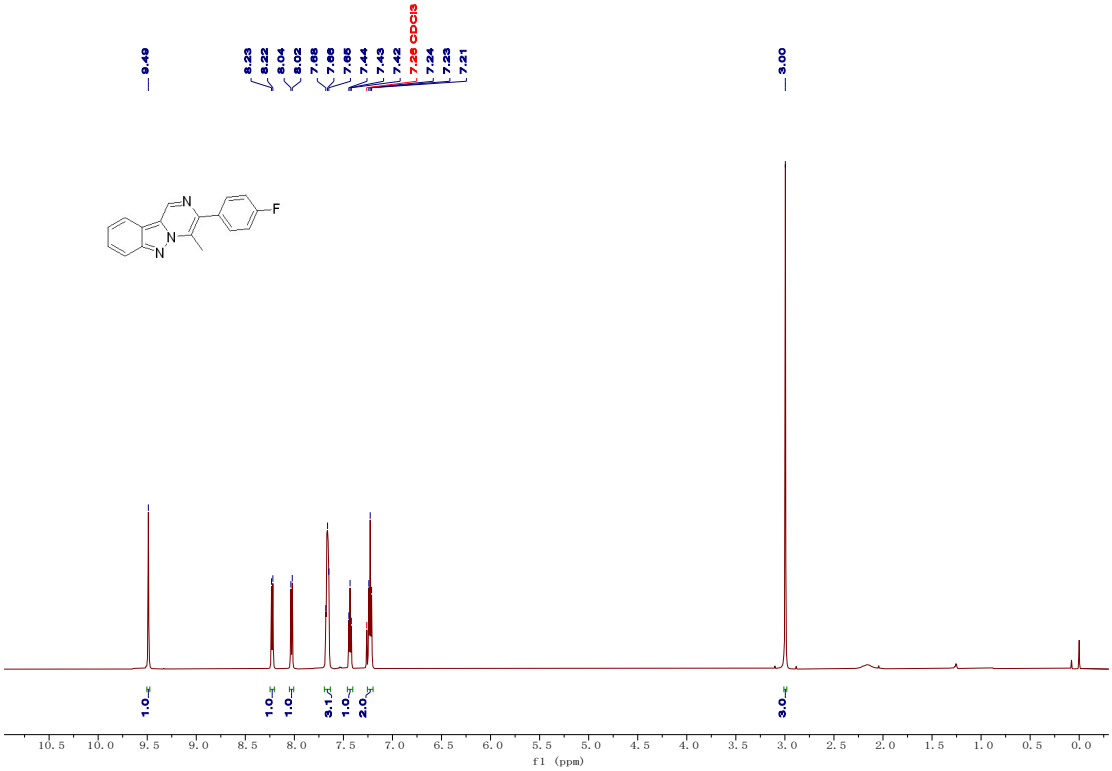
116.8
115.9
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
21.5
15.7
f1 (ppm)

3aj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7.43
7.42
7.26 CDCl3
7.24
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7.21
3.00
F
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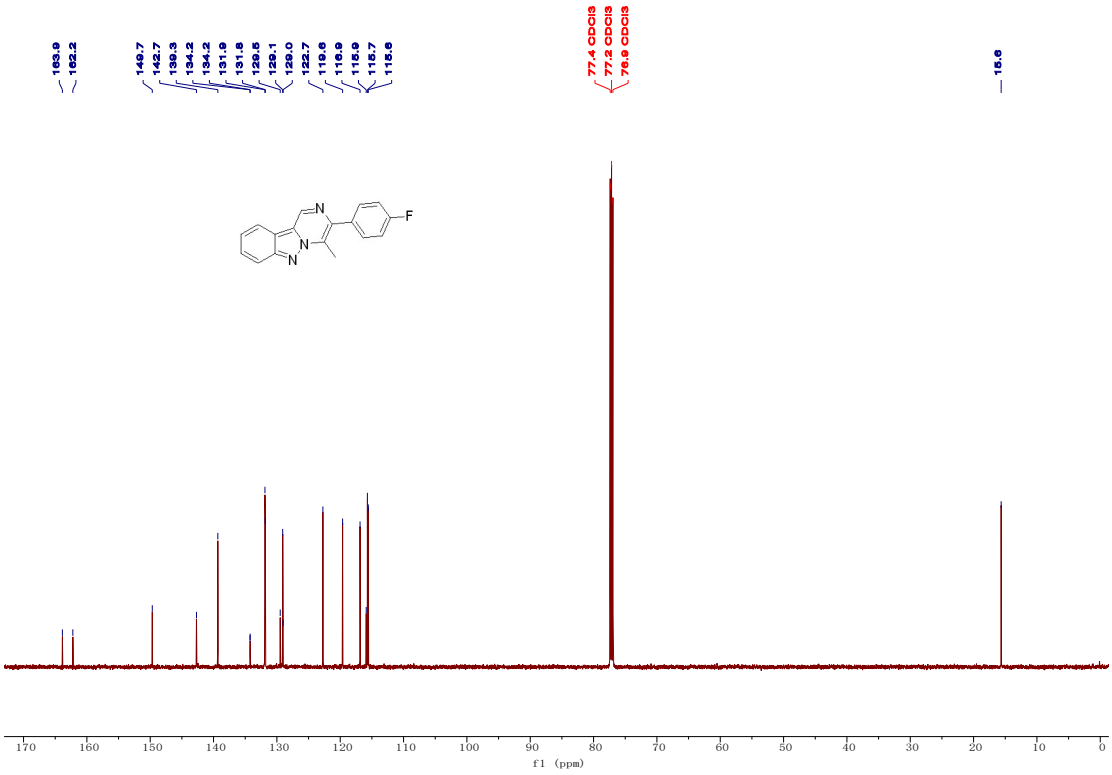
1.0
1.0
3.1
1.0
2.0
3.0
f1 (ppm)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142.7
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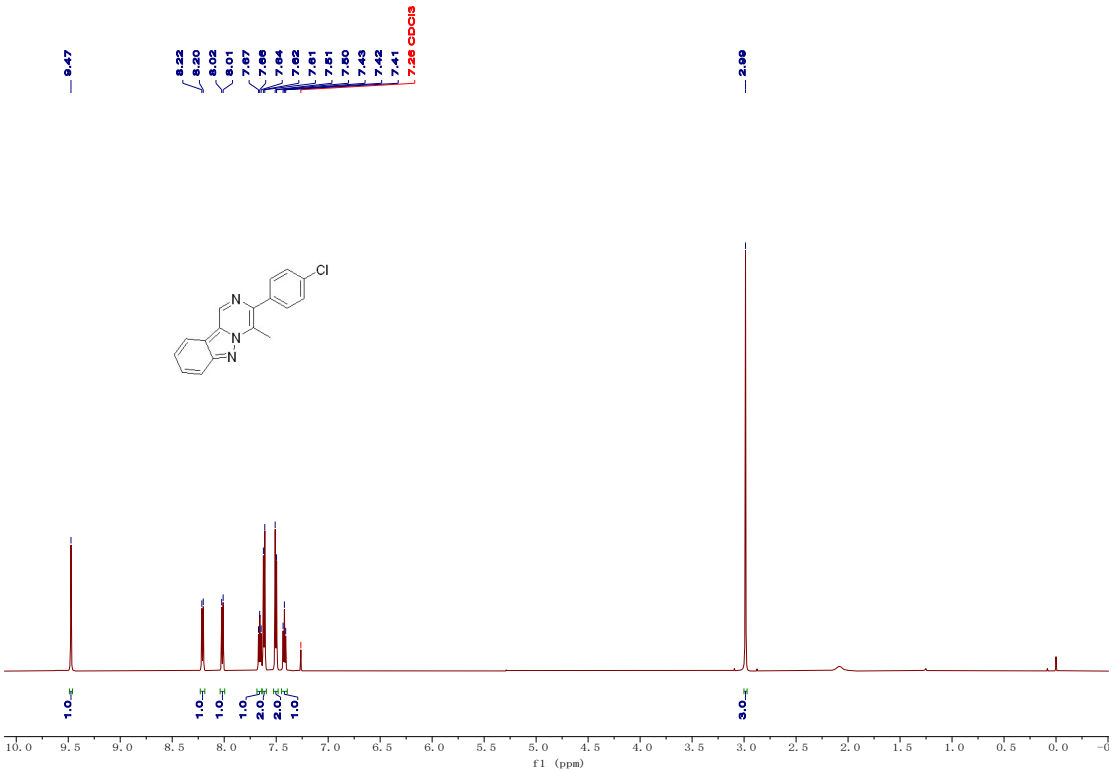
134.2
134.2
131.9
131.8
129.5
129.1
129.0
122.7
119.6
119.6
116.9
116.7
116.6
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
15.6
F
f1 (ppm)

3ak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7.64
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7.61
7.51
7.50
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7.42
7.41
7.26 CDCl3
2.99
Cl
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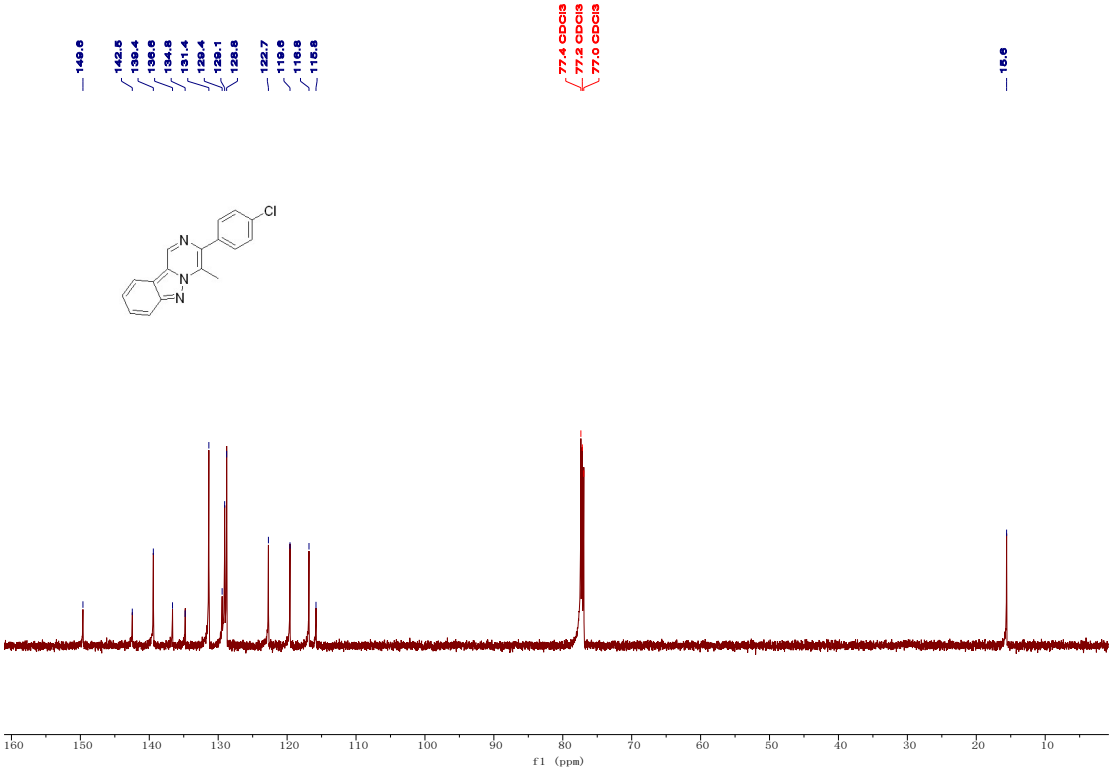
N
N
1.0
1.0
1.0
1.0
2.0
2.0
1.0
3.0
f1 (ppm)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142.5
139.4
138.6
134.8
131.4
129.4
129.1
128.8
122.7
119.6
116.8
116.8
77.4 CDCl3
77.2 CDCl3
77.0 CDCl3
15.6
Cl
N
N
N
f1 (ppm)

7. Single-crystal X-ray Diffraction

Single crystal of **3aa** was grown by slow evaporation of its dichloromethane/methanol/petroleum ether solution.

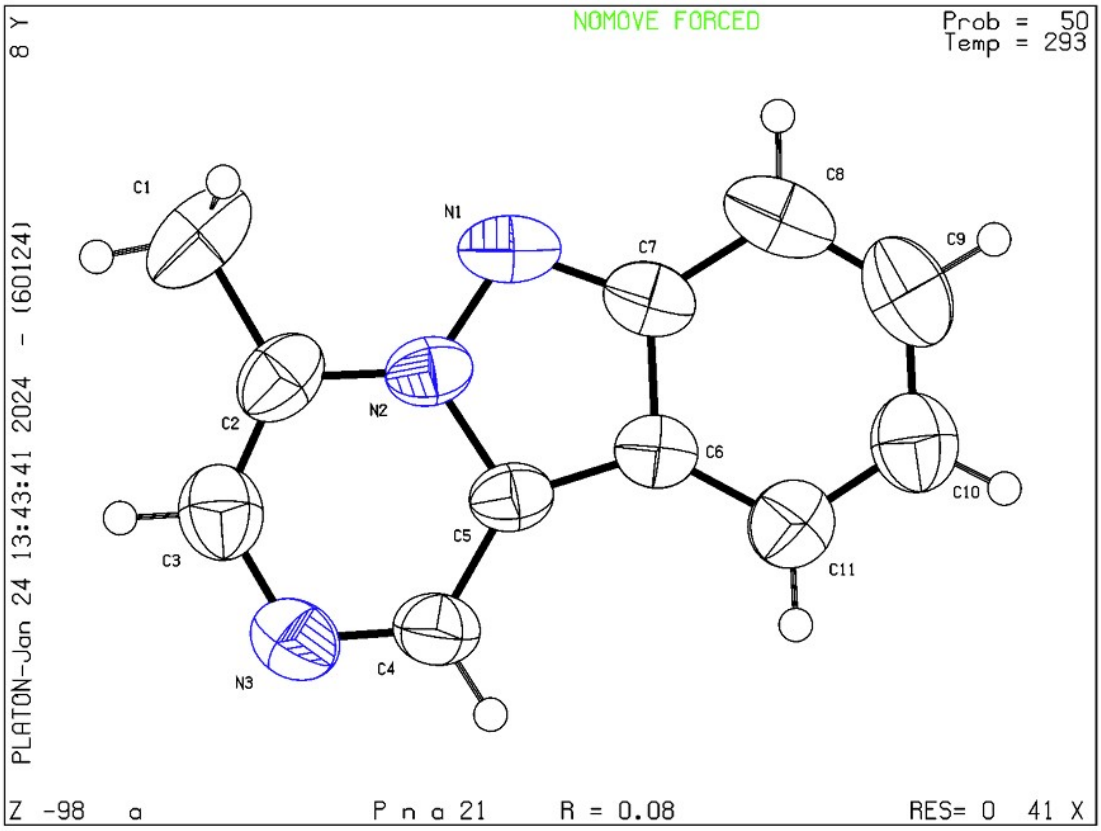

Figure S1. X-ray single crystal structure of **3aa**

Table S2 Crystal data and structure refinement for **3aa**.

Identification code	3aa
Empirical formula	$C_{11}H_9N_3$
Formula weight	183.21
Temperature/K	293.15
Crystal system	orthorhombic
Space group	$Pna2_1$
a/Å	13.009(3)
b/Å	15.324(3)
c/Å	4.6638(9)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	929.7(3)
Z	4
ρ_{calc}g/cm^3	1.309
μ/mm^{-1}	0.082
F(000)	384.0
Crystal size/mm^3	0.19 × 0.18 × 0.18
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	4.108 to 49.996
Index ranges	$-15 \leq h \leq 15$, $-18 \leq k \leq 18$, $-5 \leq l \leq 5$
Reflections collected	6472
Independent reflections	1541 [R_{int} = 0.1180, R_{sigma} = 0.0602]
Data/restraints/parameters	1541/1/128
Goodness-of-fit on F^2	1.053
Final R indexes [I>=2σ (I)]	R_1 = 0.0775, wR_2 = 0.2056
Final R indexes [all data]	R_1 = 0.0792, wR_2 = 0.2102
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.20
Flack parameter	-10.0(10)

8. References

1. A. Chevalier, A. Ouahrouch, A. Arnaud, T. Gallavardin and X. Franck, *RSC Adv*, 2018, **8**, 13121-13128.
2. M. Duan, G. Hou, Y. Zhao, C. Zhu and C. Song, *J Org Chem*, 2022, **87**, 11222-11225.
3. A. Guđmundsson, K. P. J. Gustafson, B. K. Mai, V. Hobiger, F. Himo and J.-E. Bäckvall, *ACS Catalysis*, 2019, **9**, 1733-1737.
4. W. Wang, J. Wang, J. Wu, M. Jin, J. Li, S. Jin, W. Li, D. Xu, X. Liu and G. Xu, *J Agric Food Chem*, 2022, **70**, 7566-7575.