

Supporting Information

Cu(II)-mediated aerobic oxidative synthesis of sulfonated chromeno[4,3-*c*] pyrazol-4(2*H*)-ones

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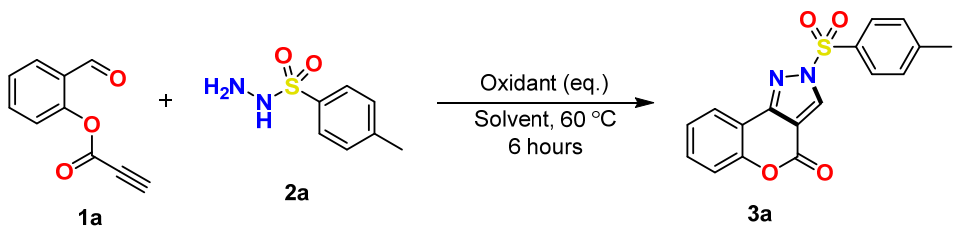
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1. General consideration

Unless otherwise noted, chemicals and materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to the general methods. All ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometer (400/100/376 MHz, respectively). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual in the NMR solvent. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($\text{CDCl}_3 = \delta 77.0$; $\text{DMSO} = \delta 39.5$). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; br, broad. The coupling constants, J , are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI). Products were purified by flash chromatography on 200–300 mesh silica gels, SiO_2 .

2. Further optimization of the reaction conditions

Table S1. Further optimization of the reaction conditions ^a



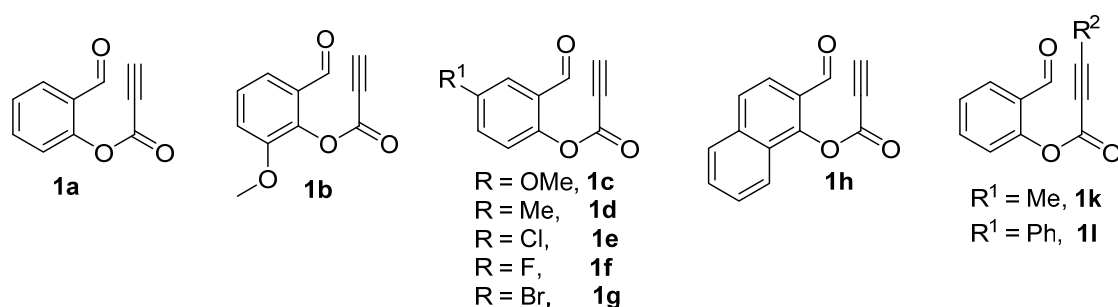
Entry	Oxidant/Lewis acid (eq.)	Solvent	Yield of 3a (%) ^b
1	ZnCl ₂ (1.0)	DCE	trace
2	AlCl ₃ (1.0)	DCE	trace
3	CuCl ₂ (1.0)	DCE	20
4	Cu(OAc) ₂ (1.0)	DCE	74
5	Cu(OAc) ₂ (0.5)	DCE	40
6	Cu(OAc) ₂ (0.2)	DCE	41 ^c
7	Ag ₂ O (1.0)	DCE	20
8	(NH ₄) ₂ Ce(NO ₃) ₆ (1.0)	DCE	15
9	Cu ₂ O (1.0)	DCE	45
10	CuI (1.0)	DCE	30
11	CuSO ₄ (1.0)	DCE	trace
12	Co(OAc) ₂ (1.0)	DCE	trace
13	SeO ₂ (1.0)	DCE	trace
14	^t BuOOH (1.0)	DCE	trace
15	Cu(OAc) ₂ (1.0)	DCE	trace ^d
16	Cu(OAc) ₂ (1.0)	DCE	25 ^e
17	Cu(OAc) ₂ (1.0)	DME	30 ^f
18	Cu(OAc) ₂ (1.0)	DCM	15 ^f
19	Cu(OAc) ₂ (1.0)	DMF	28 ^f
20	Cu(OAc) ₂ (1.0)	DMSO	37 ^f
21	Cu(OAc) ₂ (1.0)	THF	33 ^f
22	Cu(OAc) ₂ (1.0)	DCE	73 ^g (10 ^h)

^aReaction conditions: **1a** (0.30 mmol), **2a** (0.33 mmol), oxidant/Lewis acid (1.00 equiv.), solvent (6.0 mL), 60 °C, 6 h, air. ^bIsolated yield based on **1a**. ^cfor 12 h. ^dat 30 °C. ^eat 90 °C. ^f1,2-Dimethoxy ethane = DME; *N,N*-dimethyl formaldehyde = DMF; dimethylsulfoxide = DMSO; tetrahydrofuran = THF. ^gunder 1 atm O₂. ^hunder Ar.

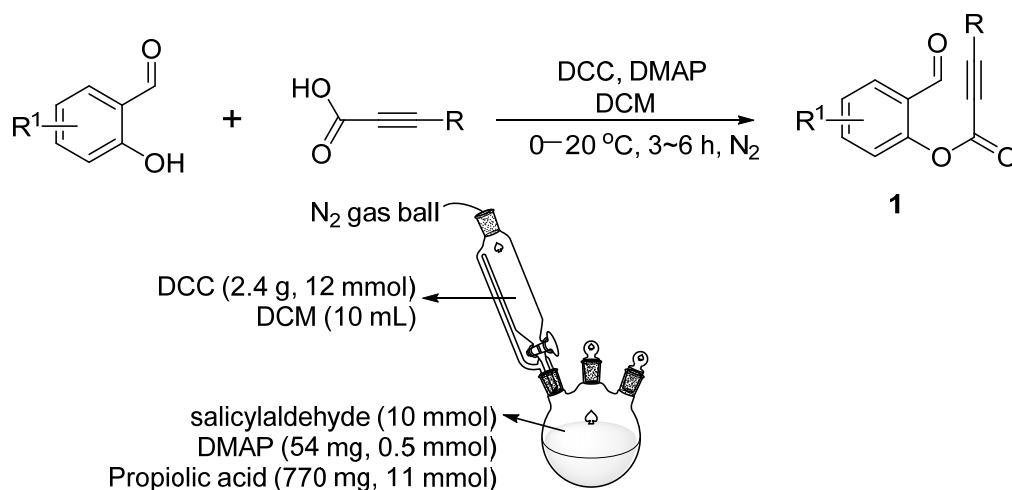
3. Synthesis of substrates 1

3.1 General procedure for the synthesis of substrates (1a–1h, 1k–1l)

The synthesis of the substrates (**1a–1h**, **1k–1l**, shown in the following Scheme S1) was according to reported method (Vagh, S. S.; Hou, B.-J. *Org. Lett.*, **2021**, *23*, 842–846; Chen, Y.-S.; Zheng, Y.; Chen, Z.-J.; Xie, Z.-Z.; He, X.-C.; Xiao, J.-A.; Chen, K.; Xiang, H.-Y.; Yang, H. *Org. Biomol. Chem.*, **2021**, *19*, 7074–7080).

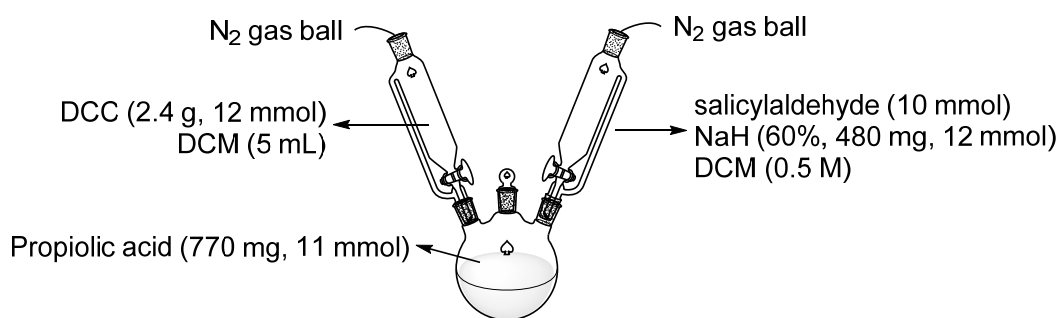


Scheme S1: The structure of substrates



Scheme S2: Apparatus of method **A** for substrate synthesis

The general **method A** for the synthesis of substrates: Into a three-neck round bottle, salicylaldehyde (1.04 mL, 10 mmol, 1.0 equiv.), prop-2-ynoic acid derivative (840 mg, 1.1 equiv.), and DMAP (36.7 mg, 0.03 equiv.) in anhydrous CH_2Cl_2 (10 mL) cooled to 0 °C, and a solution of DCC (2.06 g, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise in 20 min. The reaction mixture was then stirred for 10 minutes at 0 °C and allowed to 30 °C for 1–5 h (monitored by TLC). Precipitated urea was then filtered off and the filtrate was evaporated in vacuum. The crude residue was subjected to flash column chromatography on silica gel to obtain the pure product alkynoate **1**.

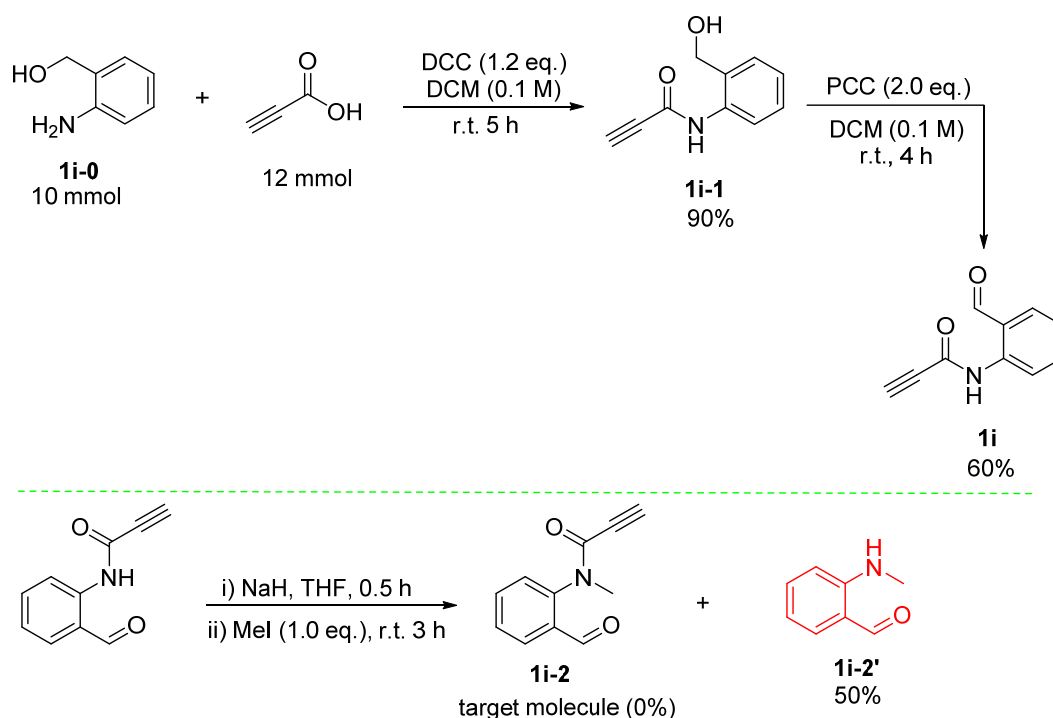


Scheme S3: Apparatus of method **B** for substrate synthesis

The general **method B** for the synthesis of substrates: Under standard Schleck manual, firstly, into one Schlenk tube 1.0 equiv. of NaH was slowly added into substituted salicylaldehyde dichloromethane solution under 0 °C and the mixture was stirred and kept under nitrogen protection. In another three necked round bottle, DCC (1.2 equiv.) in DCM

(0.5 M) were added dropwise into propiolic acid (1.1 equiv.) dichloromethane (0.1 M) solution under 0 °C, after addition, then the deprotonated salicylaldehyde was added into activated propiolic acid ester solution via constant pressure dropping funnel (with PTFE gate), after addition, the solution was warmed to room temperature for another several hours, reaction procession was monitored by TLC.

3.2 General procedure for the synthesis of **1i**

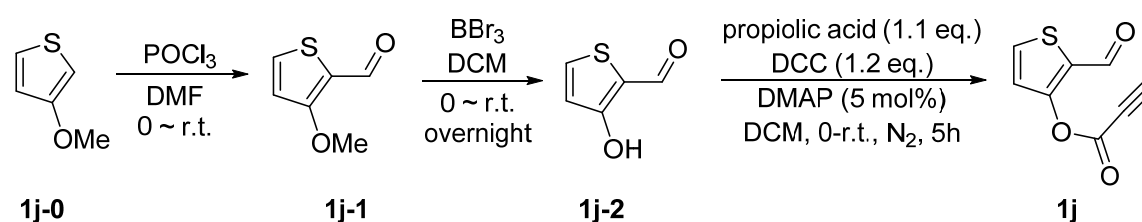


Scheme S4: Synthetic route to **1i**

According to the reported literature (M. Lang and J. Wang, *Org. Chem. Front.*, **2019**, *6*, 1367–1371), **1i** was synthesized by two steps as shown in the Scheme S4. Dicyclohexylmethanediimine (DCC) was used to

promote amidation and pyridinium chlorochromate (PCC) was involved in the oxidation. Furthermore, we have tried to synthesize the **1i-2** to exclude the impact of free hydrogen bonding effect on this oxidative cyclolization, however, no target **1i-2** was obtained, only **1i-2'** was isolated.

3.3 General procedure for the synthesis of **1j**



Scheme S5: Synthetic route to **1j**

Substrate **1j** was synthesized via three steps from commercial available starting material 3-methoxy thiophene as shown in Scheme S5.

(I): DMF as the selective 2-position electrophilic formylation of 3-methoxy thiophene (5 g, 44 mmol) under ice-bath and stirred at room temperature for several hours. After finished, the reaction mixture was poured into ice-water. Precipitation was filtrated, washed with water/petroleum and dried under vaccum (4.5 g, grey solid, 72% yield), which afforded the desired **1j-1**.

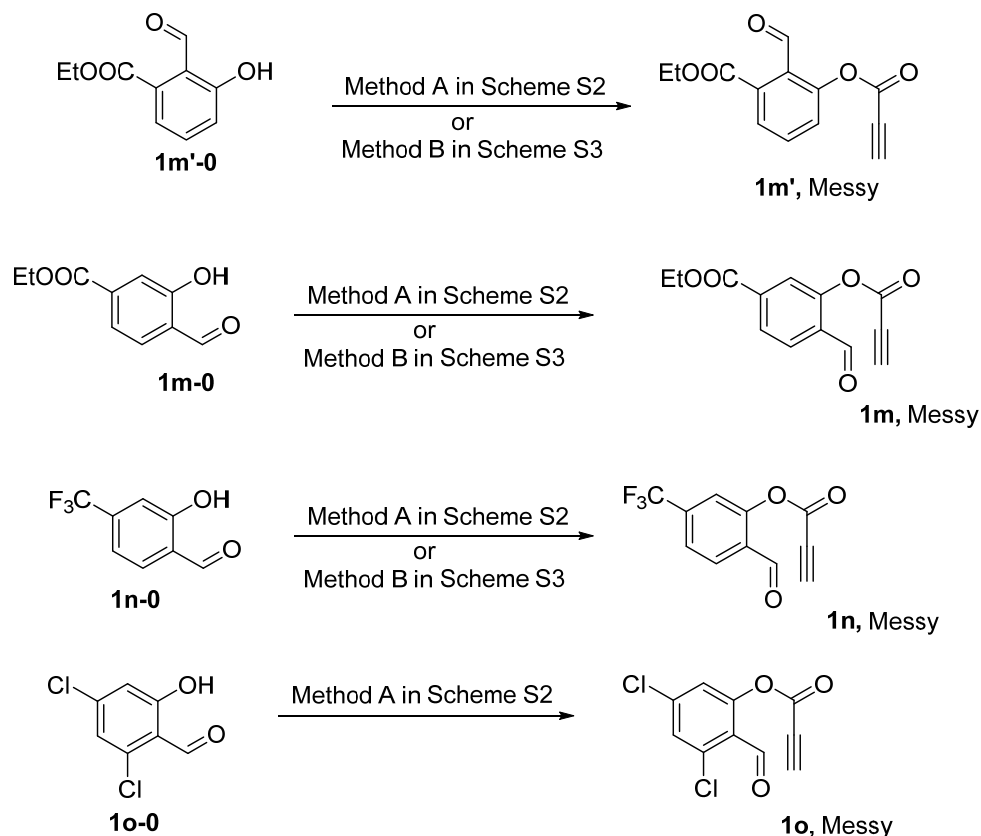
(II): Demethylation: Into an oven-dried, 150 mL three-necked round bottle layered with **1j-1** (2.13 g, 15 mmol), stir bar and anhydrous DCM (50 mL). The mixture was stirred and cooled to 0 °C. BBr₃ (2 M, 10 mL,

1.33 eq.) was added into the mixture via constant pressure dropping funnel (with PTFE gate) under nitrogen gas protected. After addition finished, the mixture was slowly warmed to room temperature (25 centigrade), stirred, and monitored by TLC. Precipitation slowly grew as the reaction proceeded. After nearly 16 hours, the starting material was exhausted. The reaction mixture was quenched with saturated NH_4Cl (10 mL), diluted with DCM (50 mL), washed with brine (20 mL \times 2), dried over anhydrous magnesium sulfate, concentrated under reduced pressure, purified through silica-gel chromatography (PE/EA, 10/1 \sim 4/1), which afforded the desired product **1j-2** in quasi-white solid (1.3 g, 67.6%). (Yuan, Zhao; Younes, Ali H.; Allen, John R.; Davidson, Michael W.; Zhu, Lei, *J. Org. Chem.* **2015**, *80*, 5600–5610).

(III): Into an oven-dried, 100 mL three-necked round bottle layered with **1j-2** (384 mg, 3 mmol), 4-*N*, *N'*-dimethylamino-pyridine (18.3 mg, 0.05 equiv.), propiolic acid (233 mg, 1.1 equiv.), anhydrous dichloromethane (10 mL). The mixture was stirred and cooled under 0 °C cooling bath. Then dicyclohexylmethanediimine (DCC, 730 mg, 1.2 eq.) was dissolved in 10 mL anhydrous dichloromethane and dropped wisely through constant pressure dropping funnel under nitrogen gas protection from moisture. After DCC addition finished, the reaction round bottle was warmed to room temperature, stirred, and monitored by TLC. After nearly 5 hours, **1j-2** was nearly disappeared, then the reaction was

filtrated to remove the urea, concentrated under reduced pressure and purified through silica-gel chromatography (20/1, $R_f = 0.3$), which afforded the desired product **1j** in yellow oil (240 mg, 44%). ^1H NMR (400 MHz, CDCl_3) δ 10.00 (s, 1H), 7.72 (dd, $J = 5.4, 1.0$ Hz, 1H), 7.21 (d, $J = 5.4$ Hz, 1H), 3.25 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 180.6, 151.2, 148.9, 133.9, 128.8, 122.7, 78.8, 73.3. HRMS (ESI) ($[\text{M}+\text{H}]^+$) Calcd. for $[\text{C}_8\text{H}_5\text{O}_3\text{S}]^+$: 180.9954 (100%), Found: 180.9952 (100.0%).

3.4 Unsuccessful synthesis of substrates (**1m**, **1m'**, **1n**, **1o**)



Scheme S6: synthesis attempt for substrates **1m'**, **1m**, **1n**, **1o**

Starting material (salicylaldehyde with various electron-withdrawing

groups or multi-substituents) of **1m'-0**, **1m-0** (BIDE PHARMATECH - CN110407697, 2019, A), **1n-0** (H. LUNDBECK A/S - WO2017/197192, 2017, A1) as shown in Scheme S6, were synthesized according to corresponding reference. While utilizing the various substituted salicylaldehyde en route to salicylaldehyde propiolates, several methods we have tried, however no corresponding substrate was obtained.

4. General procedure for the synthesis of products 3

4.1 Sulfonylated chromeno[4,3-*c*]pyrazol-4(2*H*)-ones

Into a $\phi 20 \times 180$ mm glass tube equipped with a magnetic stirrer bar was charged with salicylaldehyde propiolate (**1a**, 0.30 mmol), sulfonohydrazide (**2**, 0.33 mmol), $\text{Cu}(\text{OAc})_2$ (1.0 equiv.), 1,2-dichloroethane (6.0 mL). The reaction vessel was stirred at 60 °C for 6 h. After completion of the reaction, the mixture was concentrated under reduced pressure. The resulting crude product was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate), which afforded the desired product 2-sulfonylated chromeno[4,3-*c*]pyrazol-4(2*H*)-one (**3a-3h**, **3h-3s**).

4.2 Sulfonylated 2,5-dihydro-4*H*-pyrazolo[4,3-*c*] quinolin-4-ones

Into a $\phi 20 \times 180$ mm glass tube equipped with a magnetic stirrer bar was charged with *N*-(2-formylphenyl)propiolamide (**1i**, 0.30 mmol),

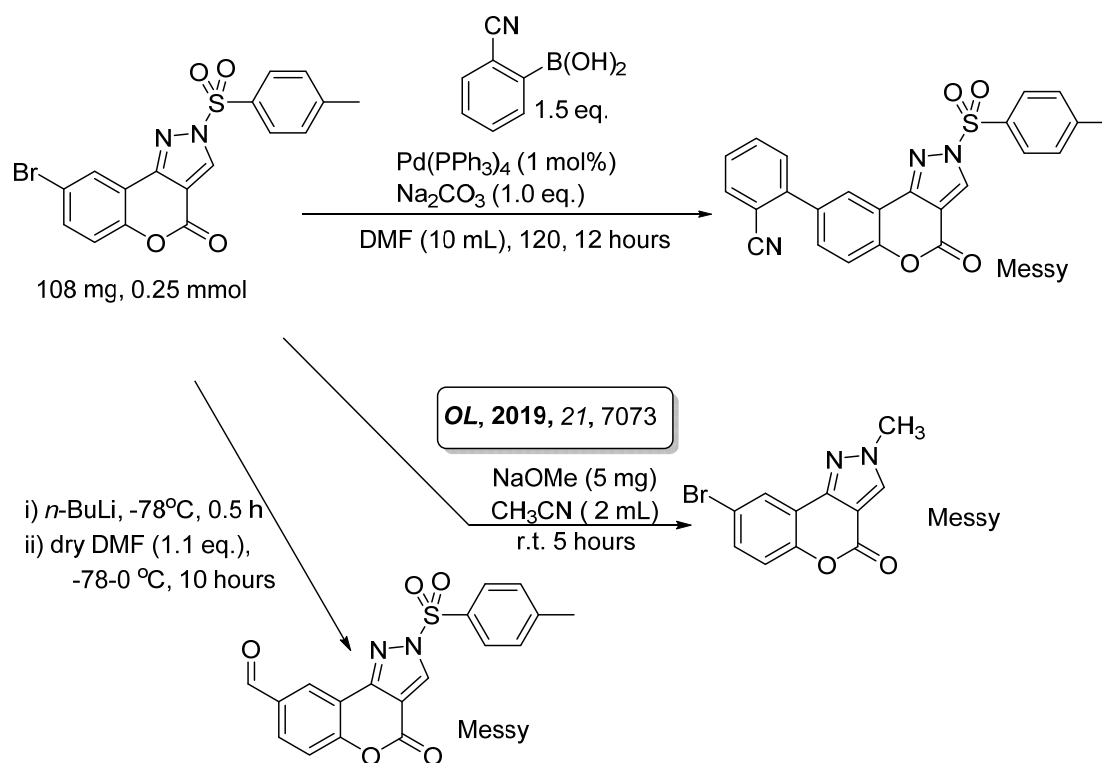
sulfonohydrazide (**2**, 0.33 mmol), Cu(OAc)₂ (1.0 equiv.), 1,2-dichloroethane (6.0 mL), trifluoroacetic acid (15 μ L). The reaction vessel was stirred at 60 °C for 6 h. After completion of the reaction, the mixture was concentrated under reduced pressure. The resulting crude product was further purified by flash chromatography (silica gel, dichloromethane/methanol), which afforded the desired products sulfonfylated 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones (**3ia**, **3ib**).

4.3 General procedure for the synthesis of product **3g** in 4.0 mmol

Into a 100 mL round bottle equipped with a magnetic stirrer bar was charged with 4-bromo-2-formylphenyl propiolate (**1g**, 1.04g, 4.0 mmol), sulfonohydrazide (**2**, 714 mg, 4 mmol), Cu(OAc)₂ (744 mg, 4.0 mmol, 1.0 equiv.), 1,2-dichloroethane (60 mL). The reaction vessel was stirred at 60 °C under air/oxygen for 12 h. TLC monitored, **1g** or Schiff intermediate disappeared, stop reaction, the mixture was filtrated through a short pad of silica gel to remove the undissolved Cu^X salts, washed with ethyl acetate, concentrated the filtrate under reduced pressure. The resulting residue was further purified by flash chromatography (silica gel, dichloromethane/methanol), which afforded the desired product **3g** (415 mg, 25%)/(752 mg, 45%).

4.3 The further late-stage transformations

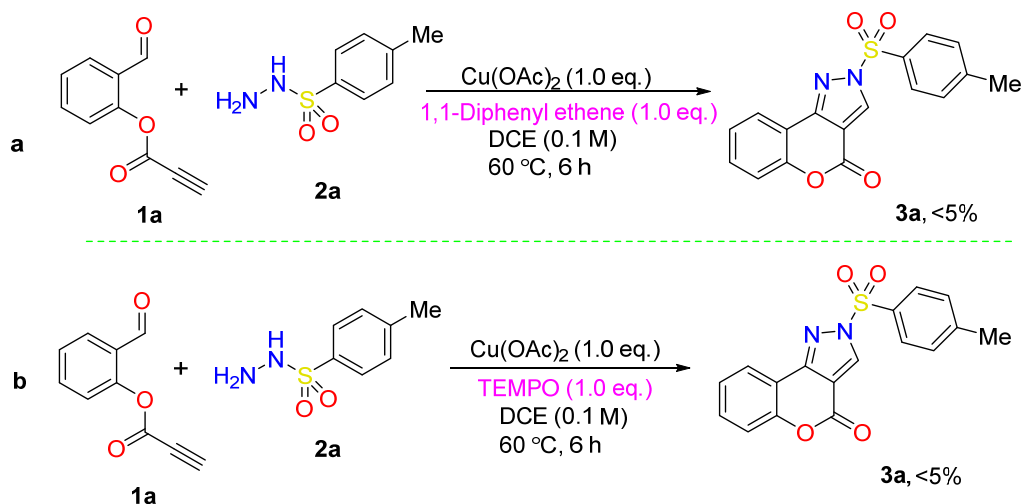
The further late-stage transformations were outlined in Scheme 7. However, no satisfactory results were obtained, shown in the following Scheme 7.



Scheme S7: Attempts of the late stage transformations

5. Mechanism studies

5.1 Free-radical quenching experiments



Scheme S8: Free-radical trapping experiments

Into a 15 mL reaction vessel equipped with a magnetic stirrer bar was charged with salicylaldehyde propiolate (**1a**, 0.30 mmol), sulfonyl hydrazide (**2a**, 0.33 mmol), $\text{Cu}(\text{OAc})_2$ (1.0 equiv.), 1,2-dichloroethane (3.0 mL), radical quenching reagent [0.3 mmol, 1.0 equiv. of 1,1-diphenylethene (54 mg), and 1.0 equiv. of TEMPO (57.5 mg), respectively. The reaction vessel was sealed and stirred at $60\text{ }^\circ\text{C}$ for 6 h. After the reaction stirring for 6 h, the mixture was concentrated under reduced pressure. The resulting crude product was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate), which afforded the desired product. After the radical quenching reagent addition, no target product was observed; the reaction procession was significantly ceased. Furthermore, the reaction solution was applied on HR-MS for *in-situ* detection of intermediate. Satisfying, we had observed the intermediate signal of **3a-TEMPO** (Figure S1).

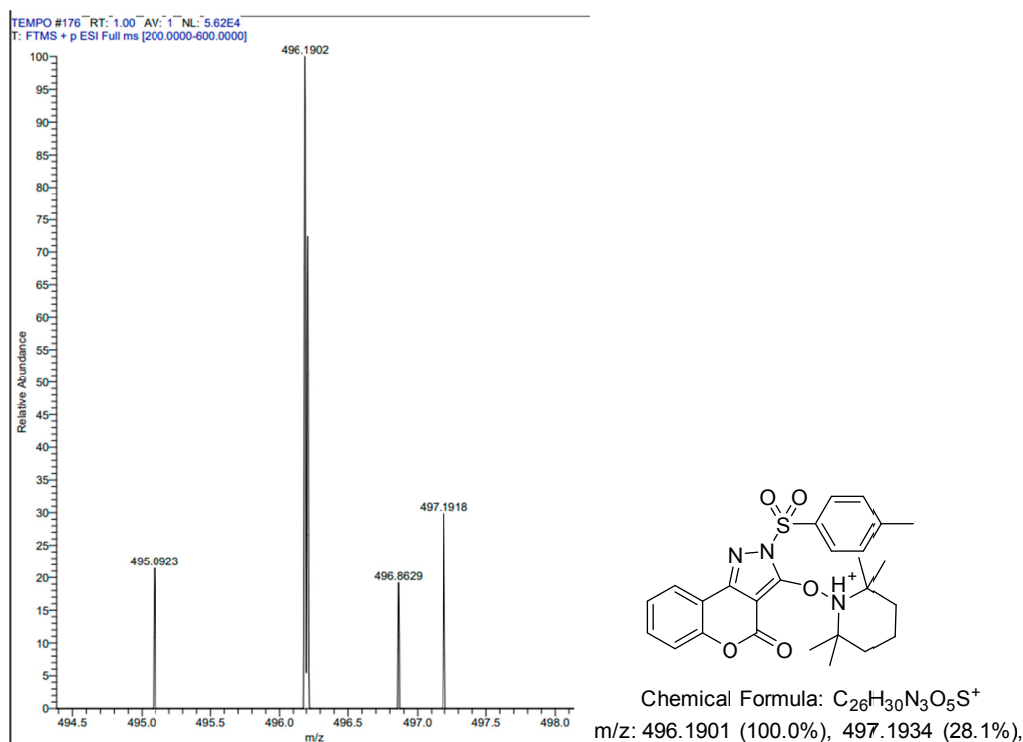
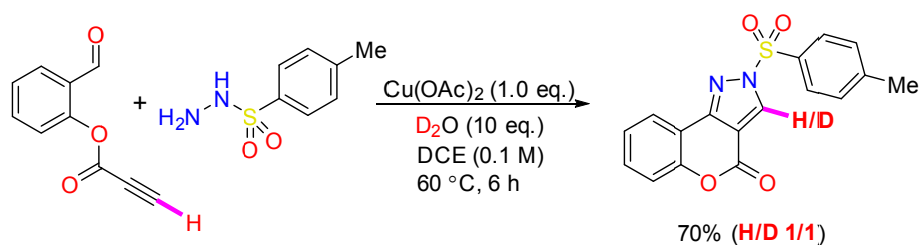


Figure S1: HRMS spectra of m/z for $[(\mathbf{3a-H} + \text{TEMPO}) + \text{H}]^+$

5.2 H/D Isotopic exchange experiment



Scheme S9: H/D exchange experiment

Into a 15 mL reaction vessel equipped with a magnetic stirrer bar was charged with salicylaldehyde propiolate (**1a**, 0.30 mmol), sulfonyl hydrazide (**2a**, 0.33 mmol), Cu(OAc)₂ (1.0 equiv.), 1, 2-dichloroethane (3.0 mL), D₂O (60 mg, 3 mmol, 10 equiv.). The reaction vessel was sealed and stirred at 60 °C for 6 h. After the reaction stirring for 6 hours, the mixture was concentrated under reduced pressure. The resulting crude

product was further purified by flash chromatography (silica gel, PE/EA, 1/10), providing a mixture of **3a** and **3a-D1** in 70% yield. ^1H NMR data analysis found 50% deuterium was obtained (Figure S2), which was confirmed by HRMS (Figure S3).

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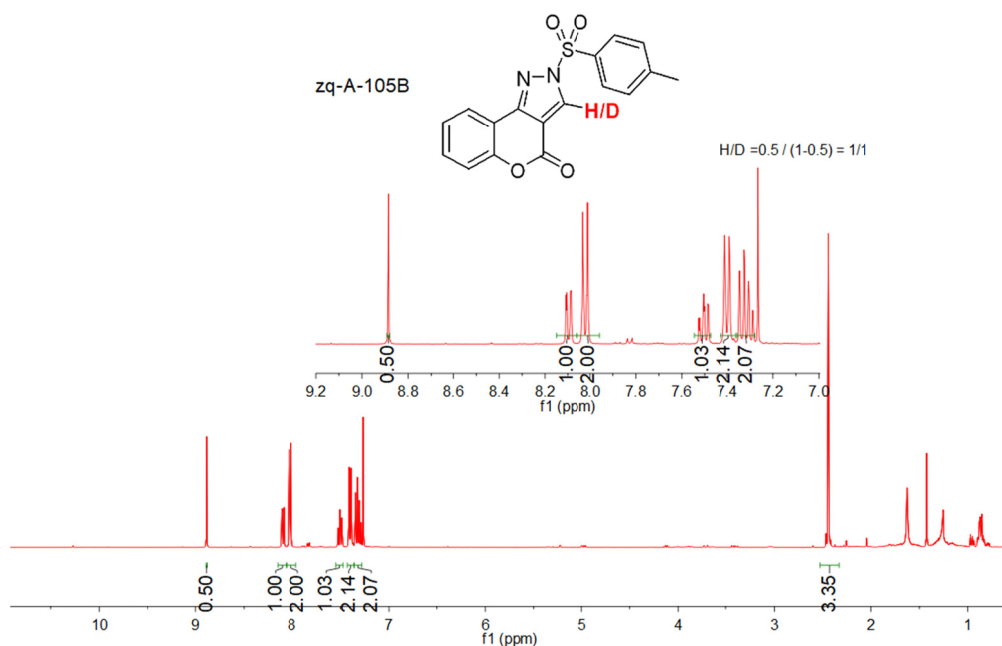


Figure S2: ^1H NMR analysis for the products from H/D isotopic exchange experiment

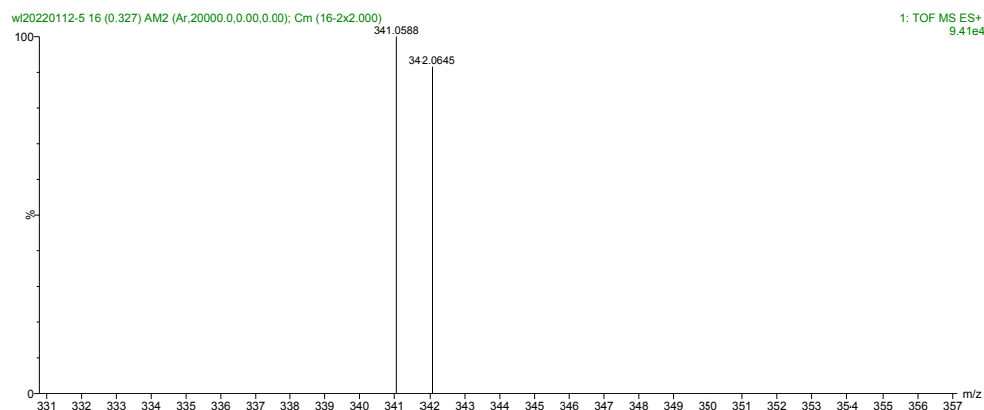
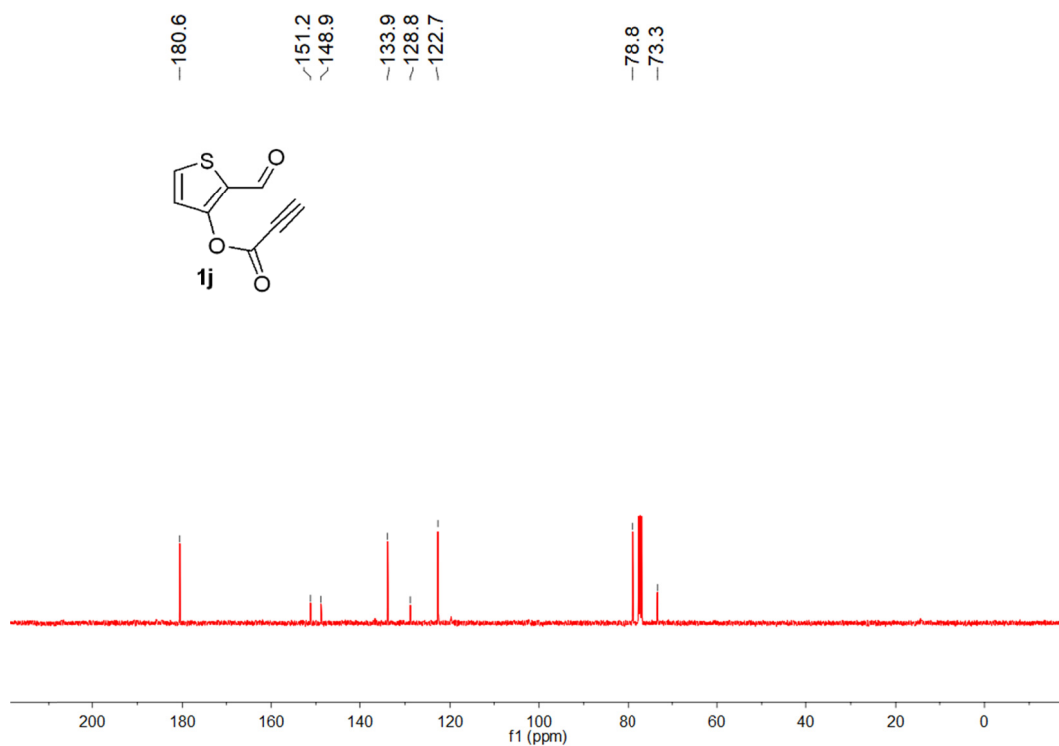
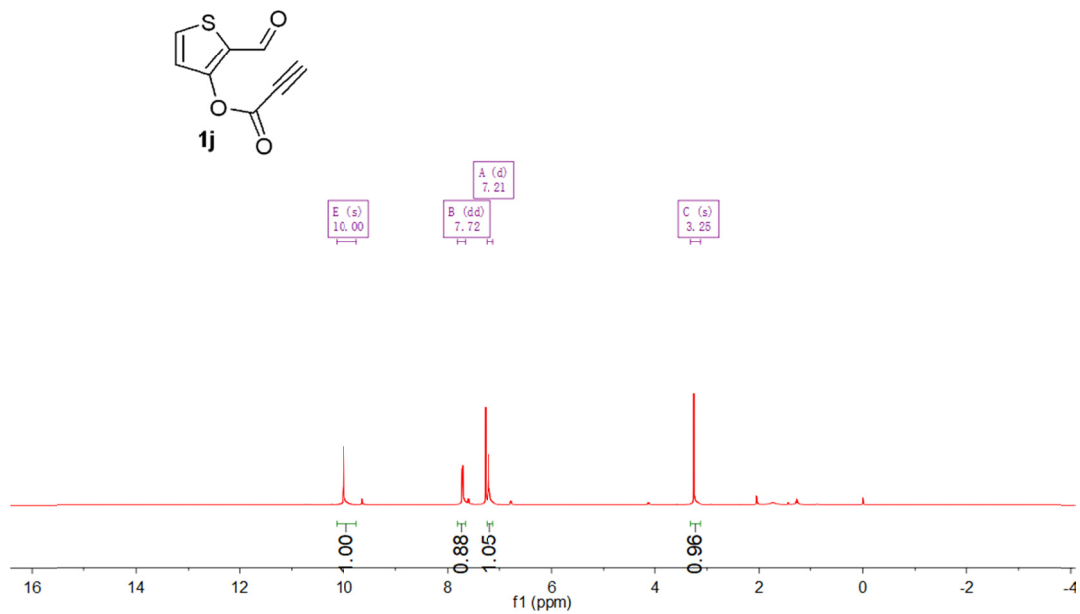
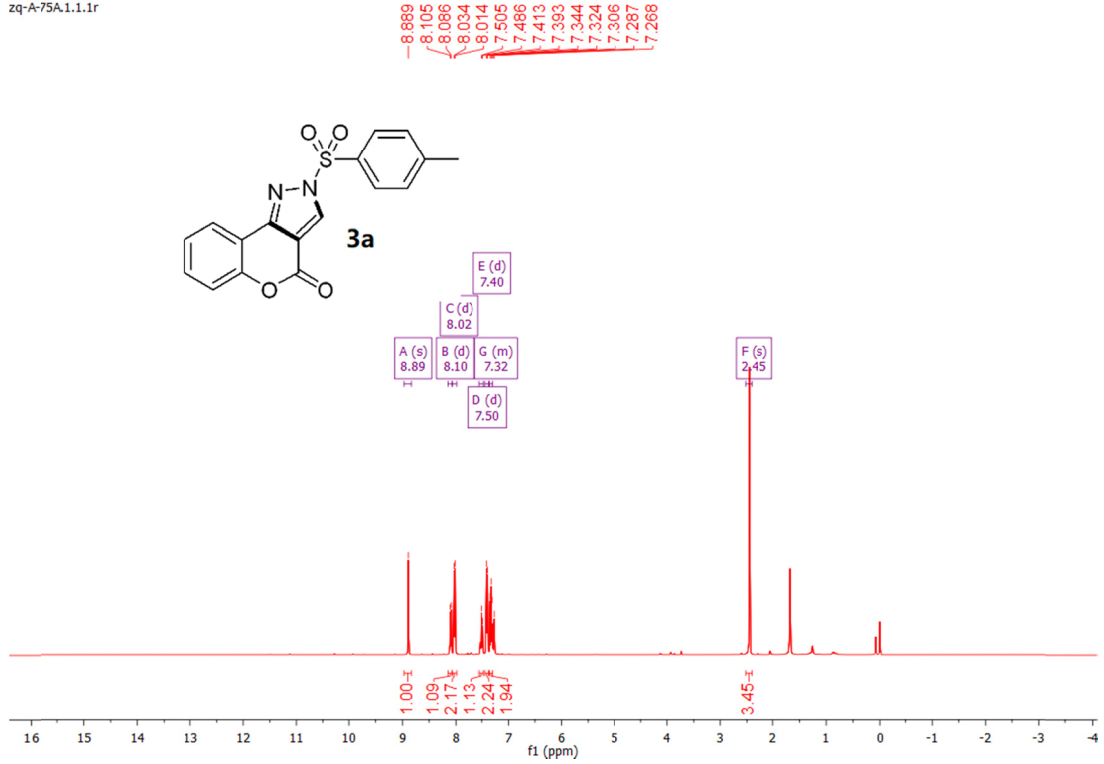


Figure S3: HRMS analysis for $[\text{M} + \text{H}]^+$ of **3a-H** [341.0591 (100.0%)] found 341.0588 & **3a-D₁** [342.0653 (100.0%)] found 342.0645.

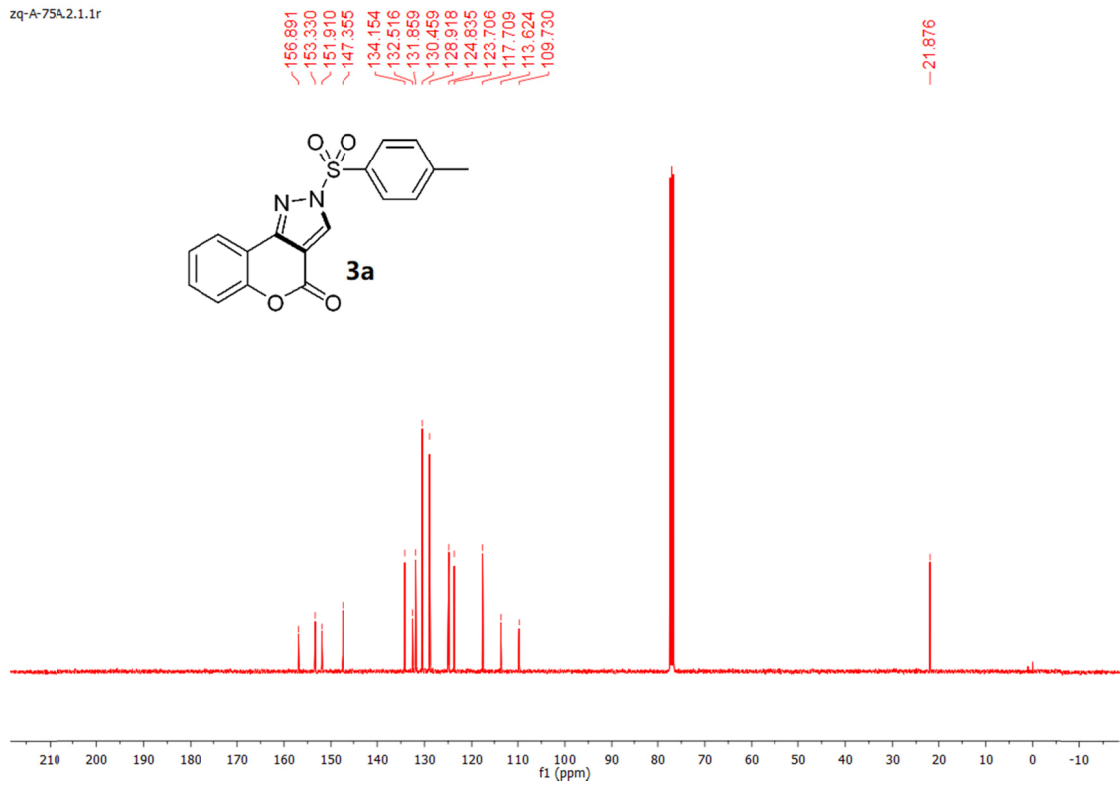
6. Copies NMR spectra of the products

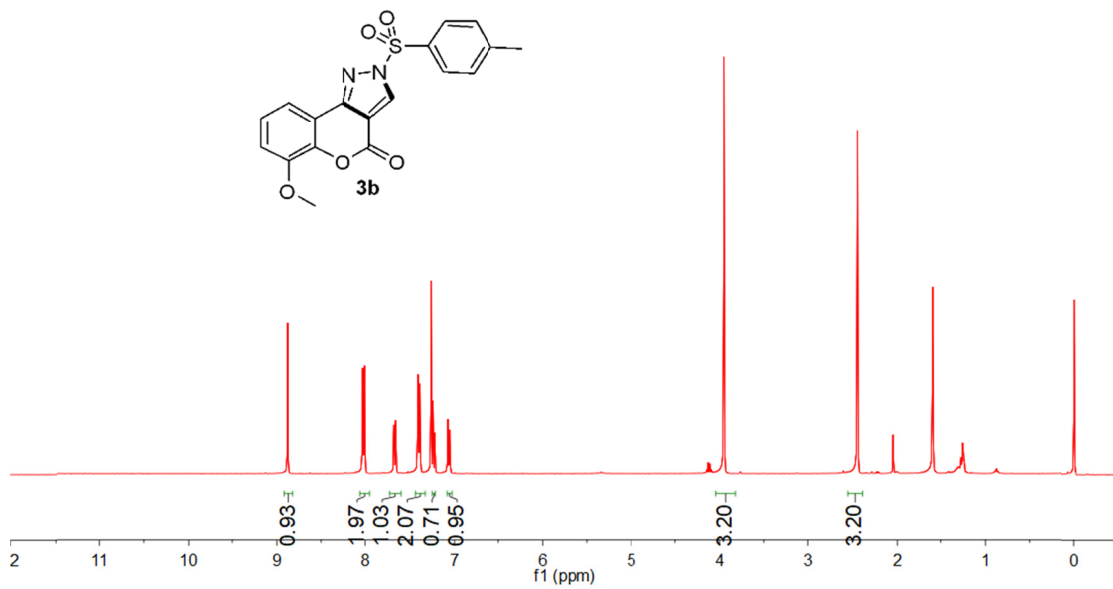


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zq-A-75A.2.1.1r

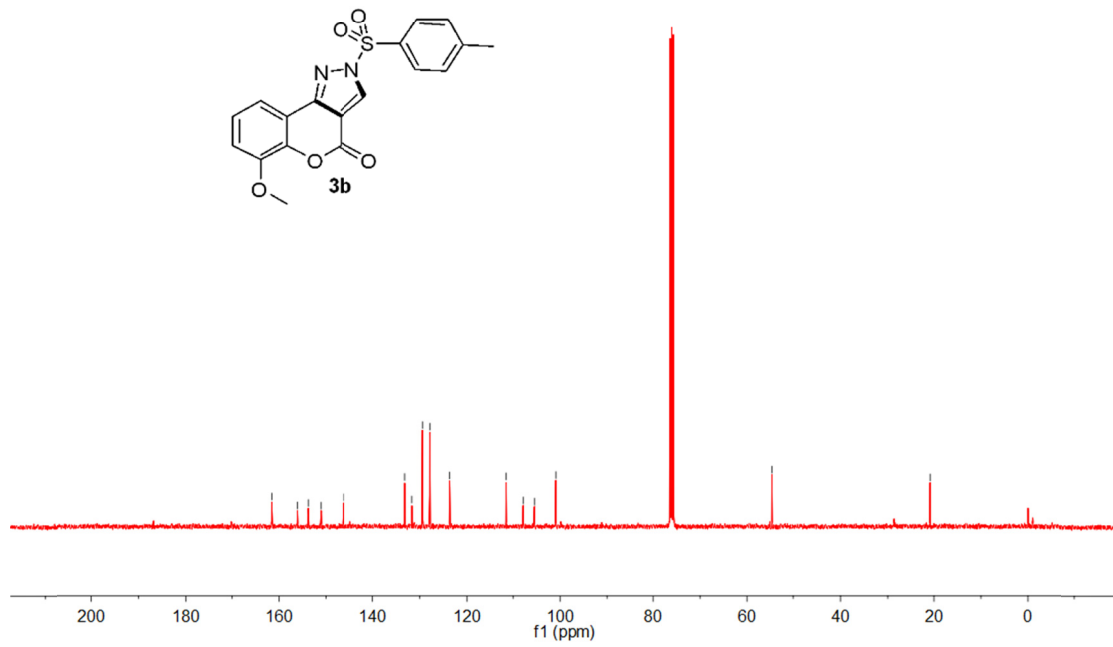


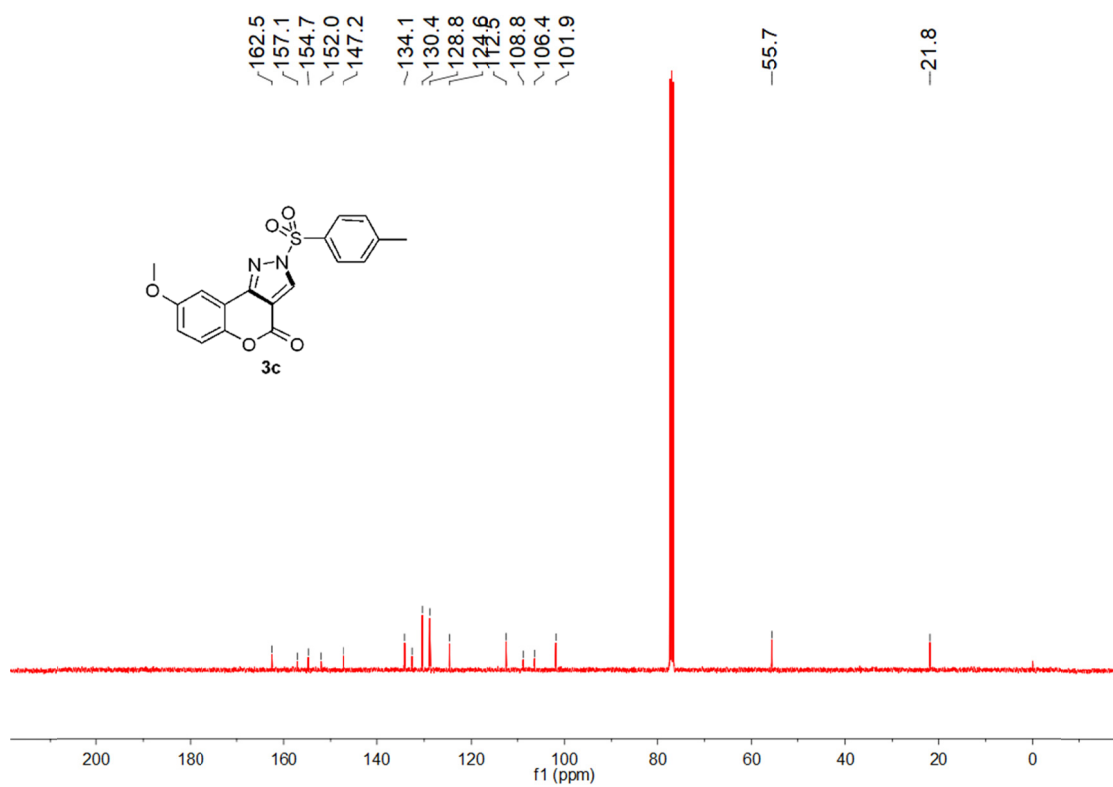
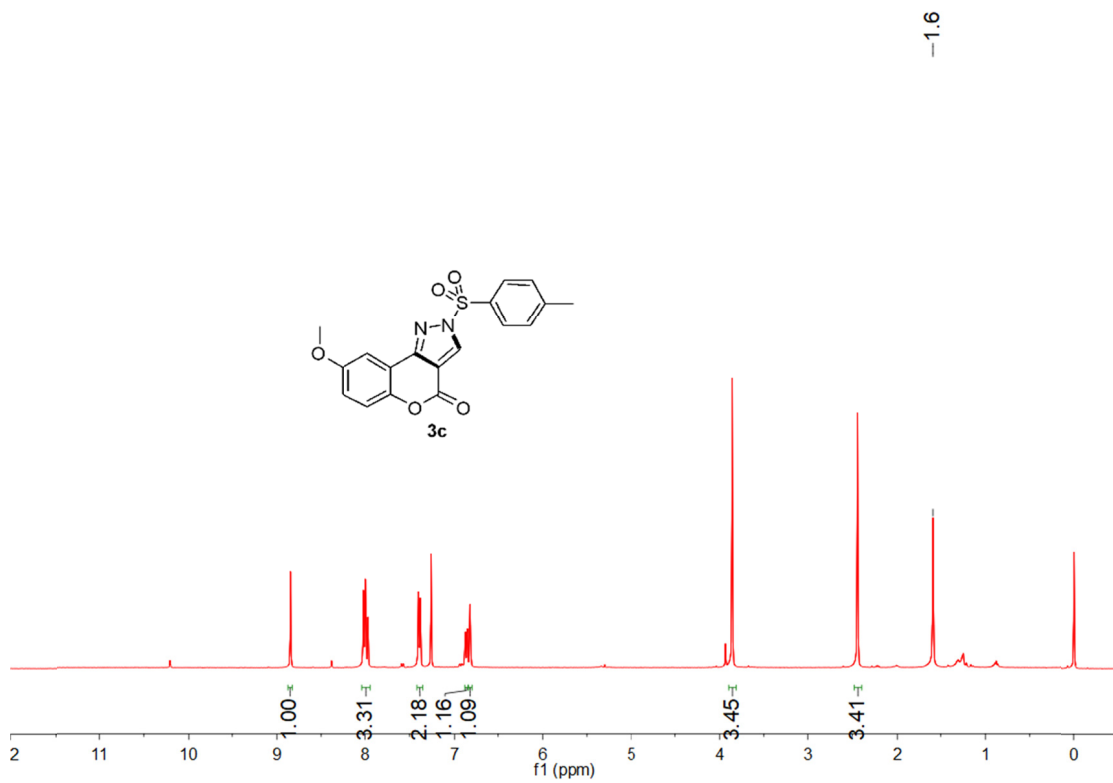


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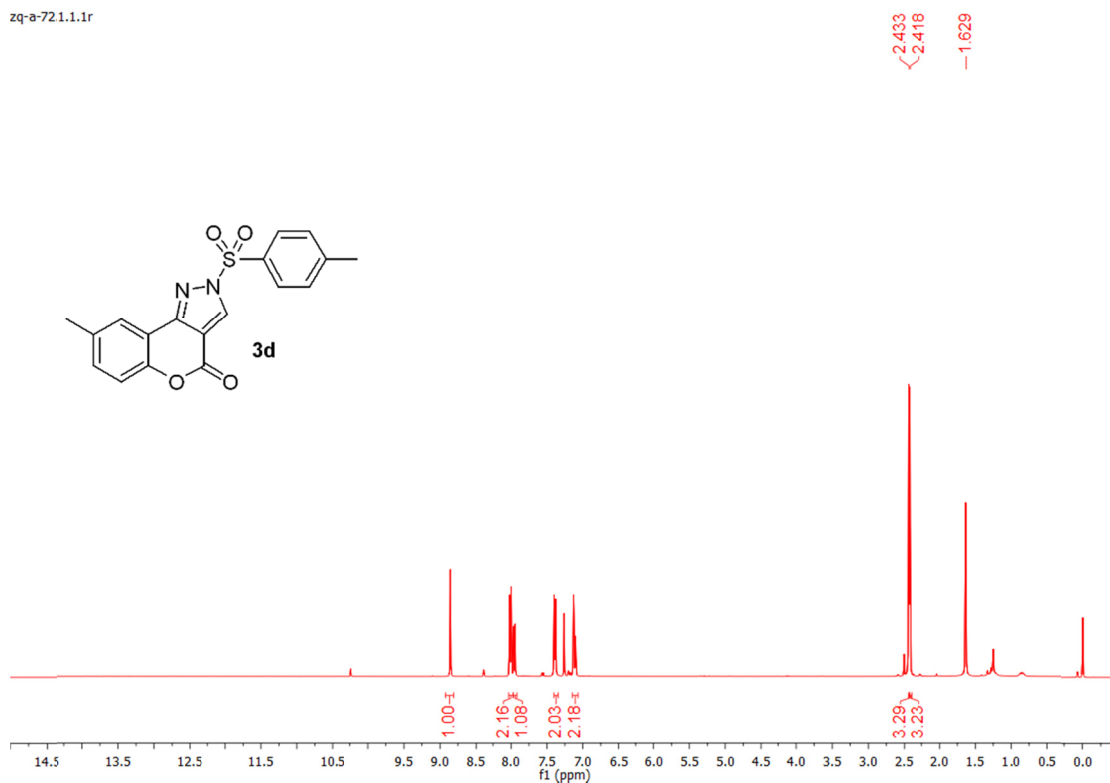
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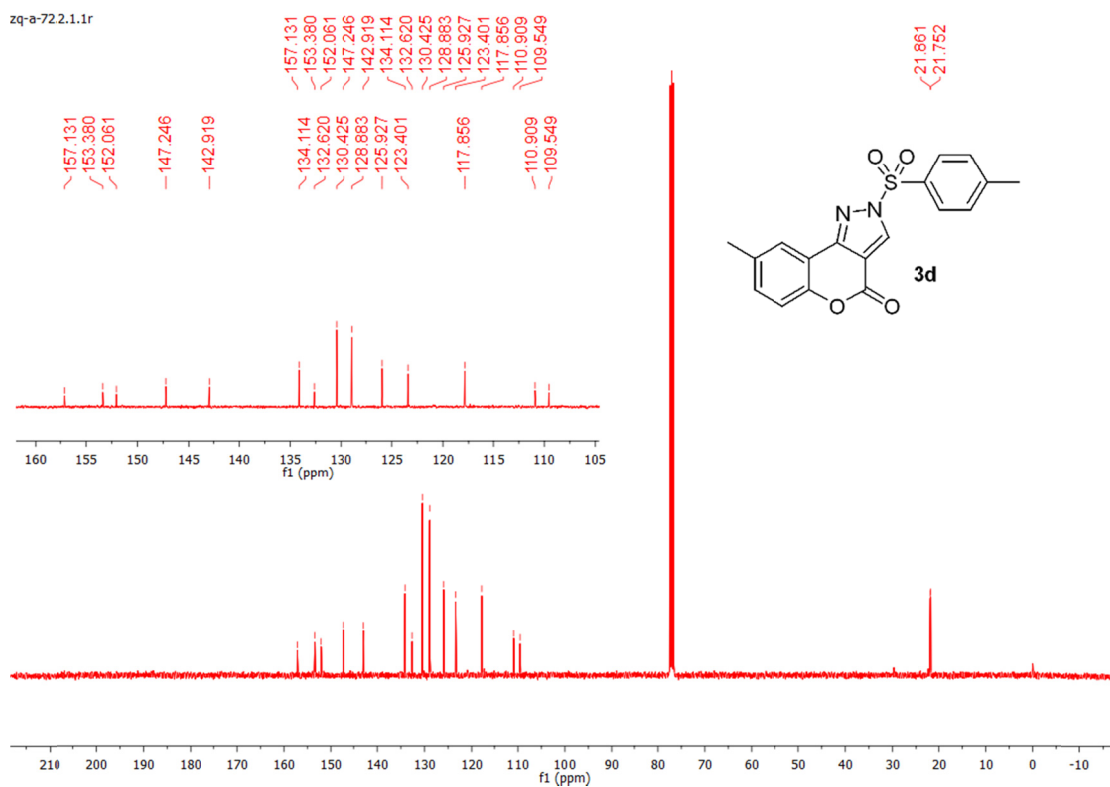


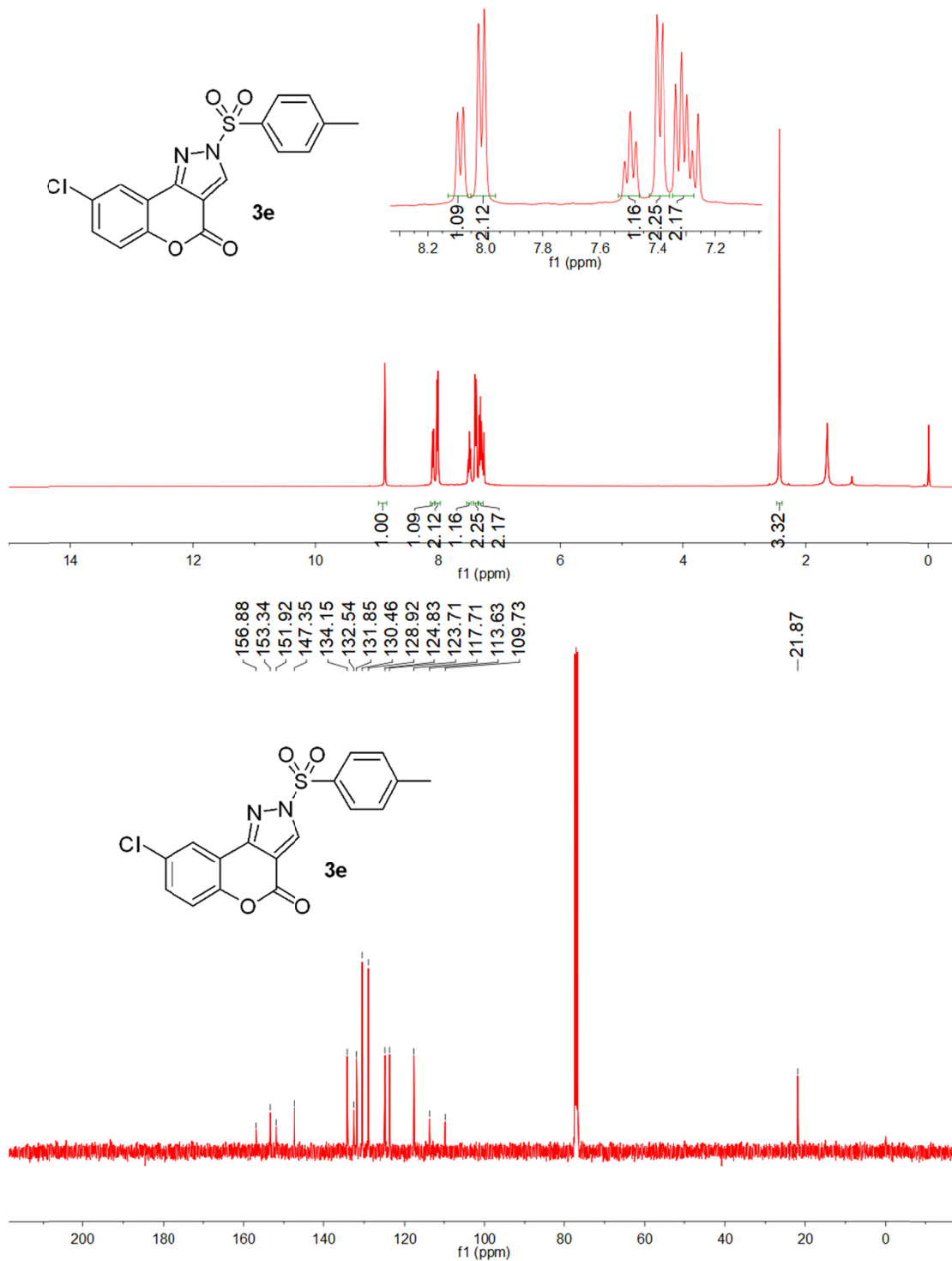


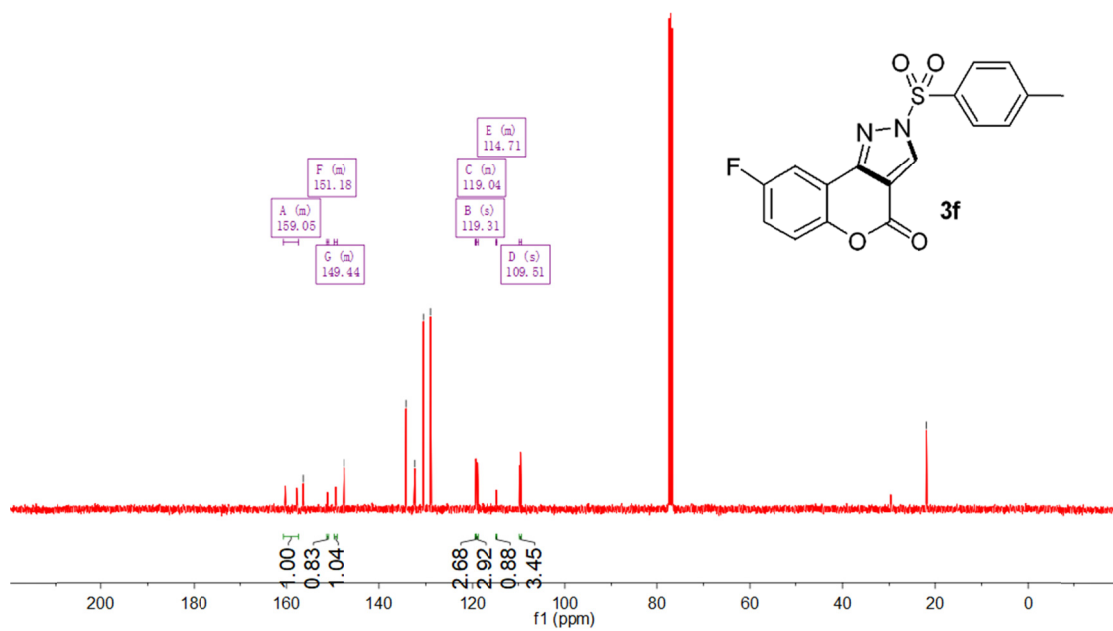
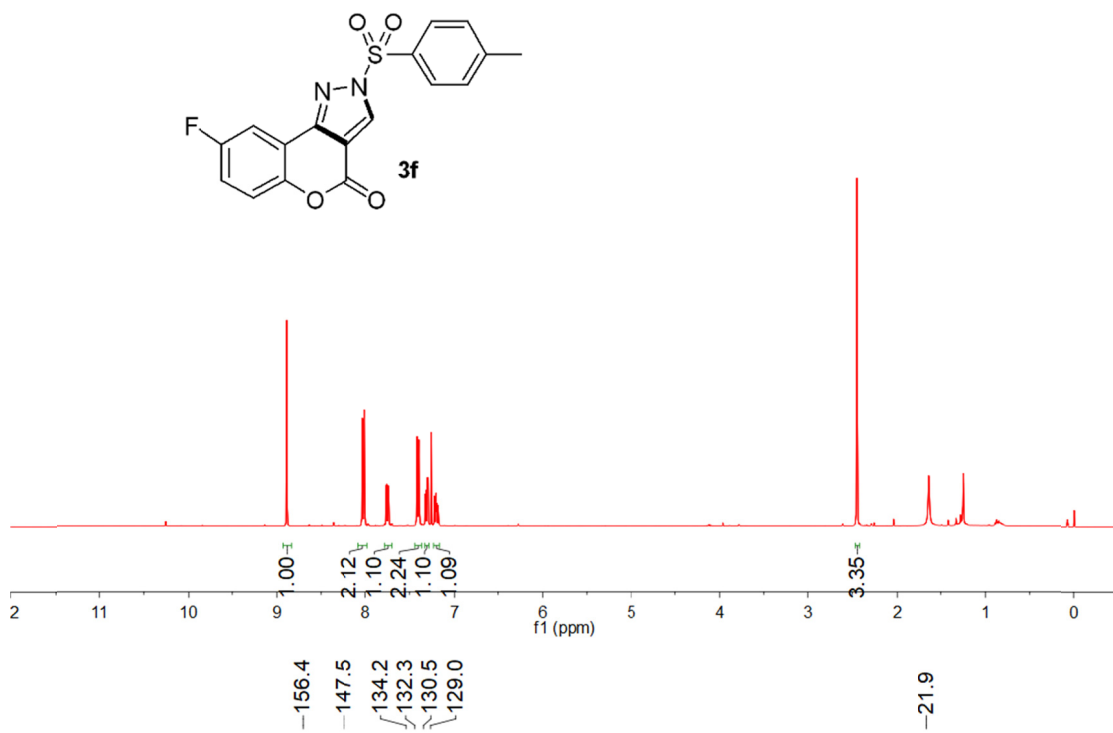
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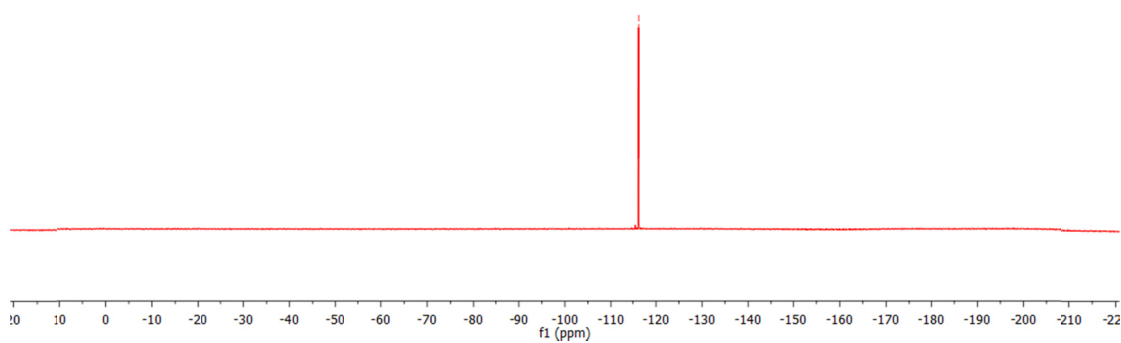
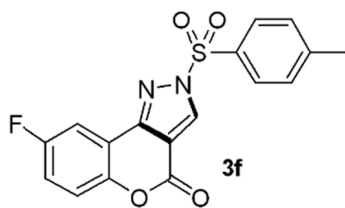


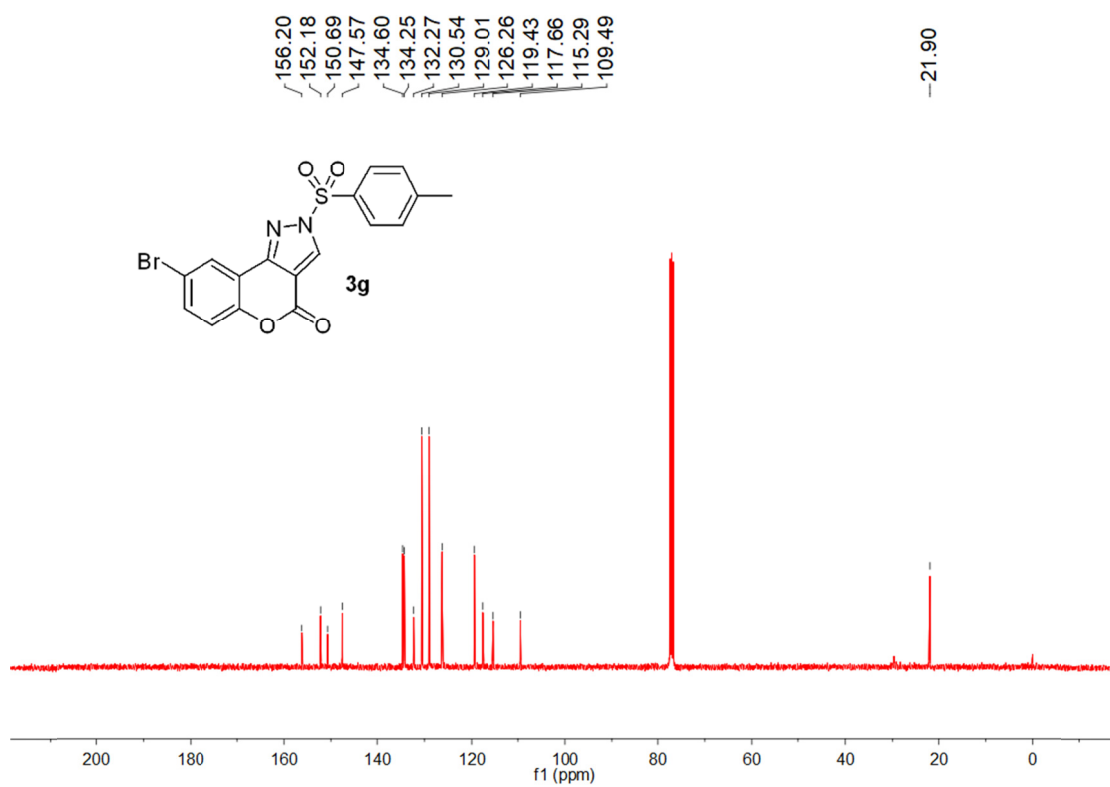
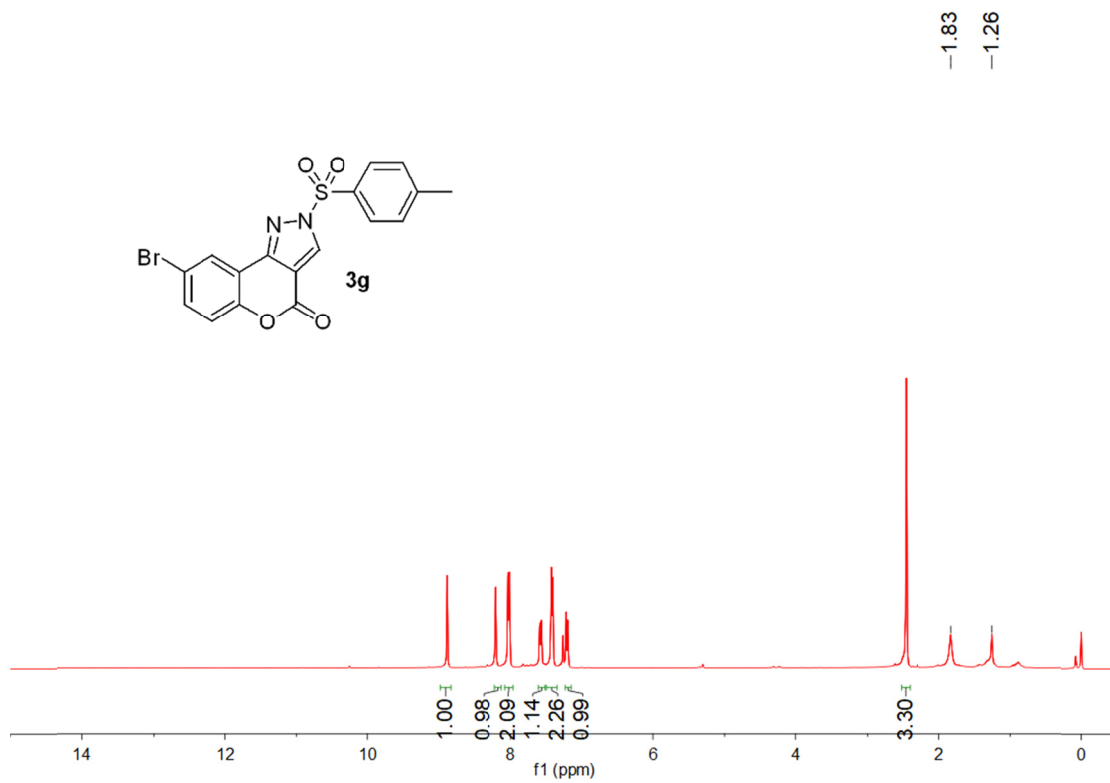


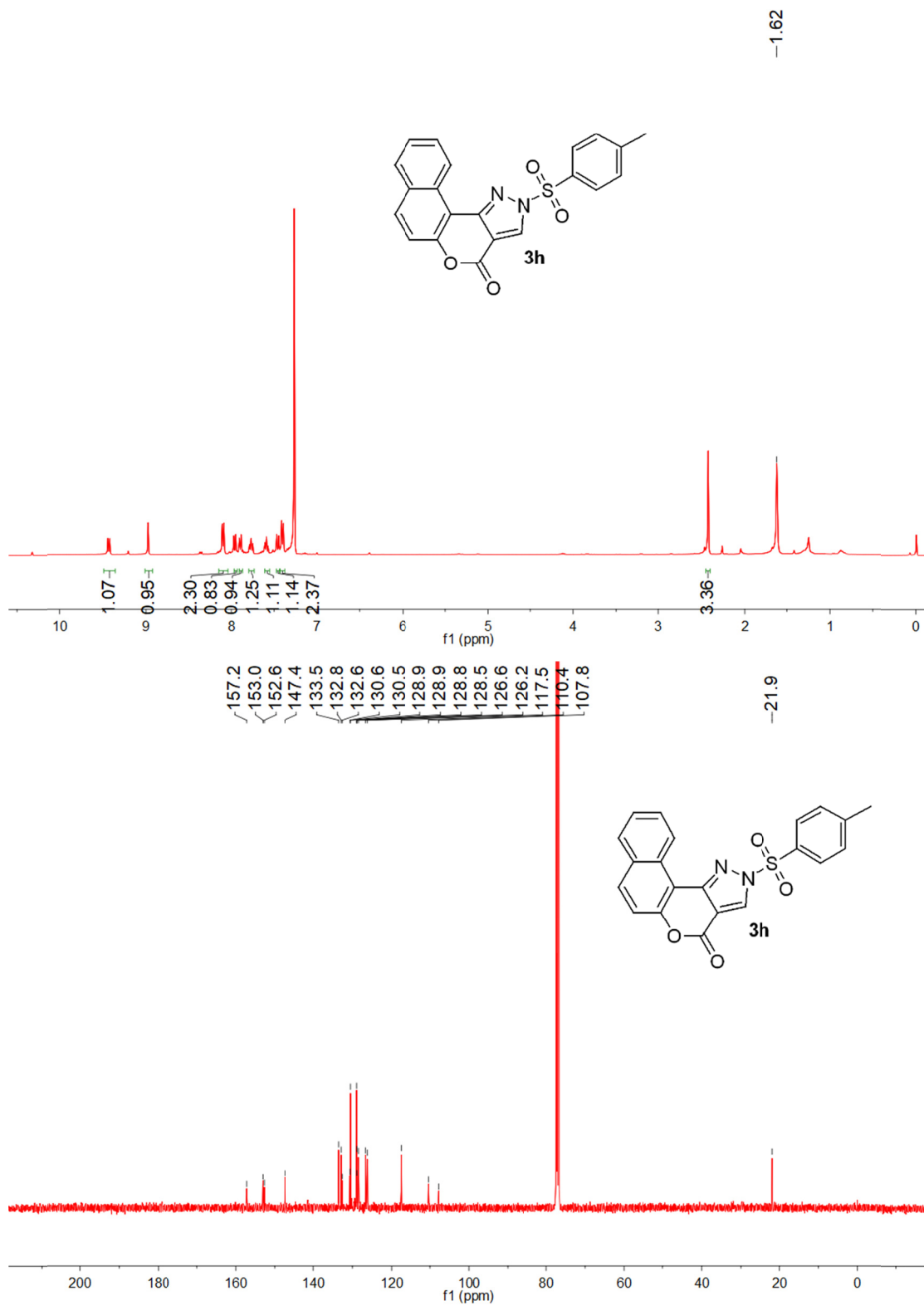


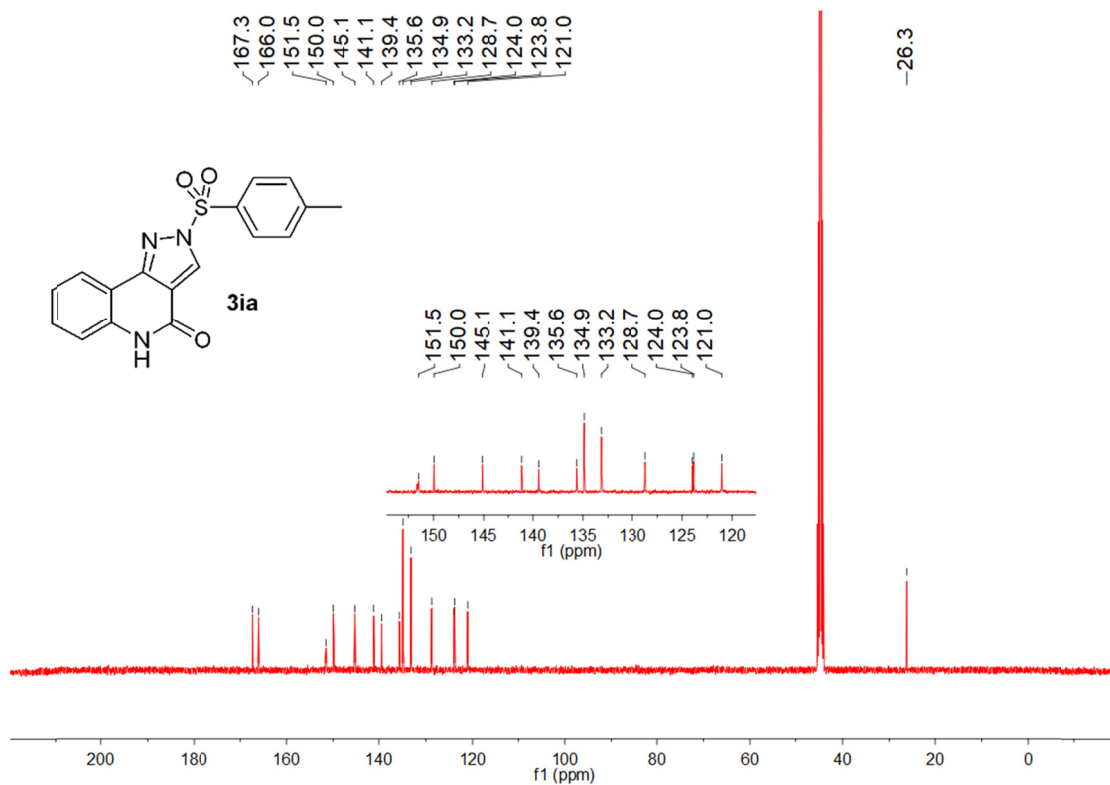
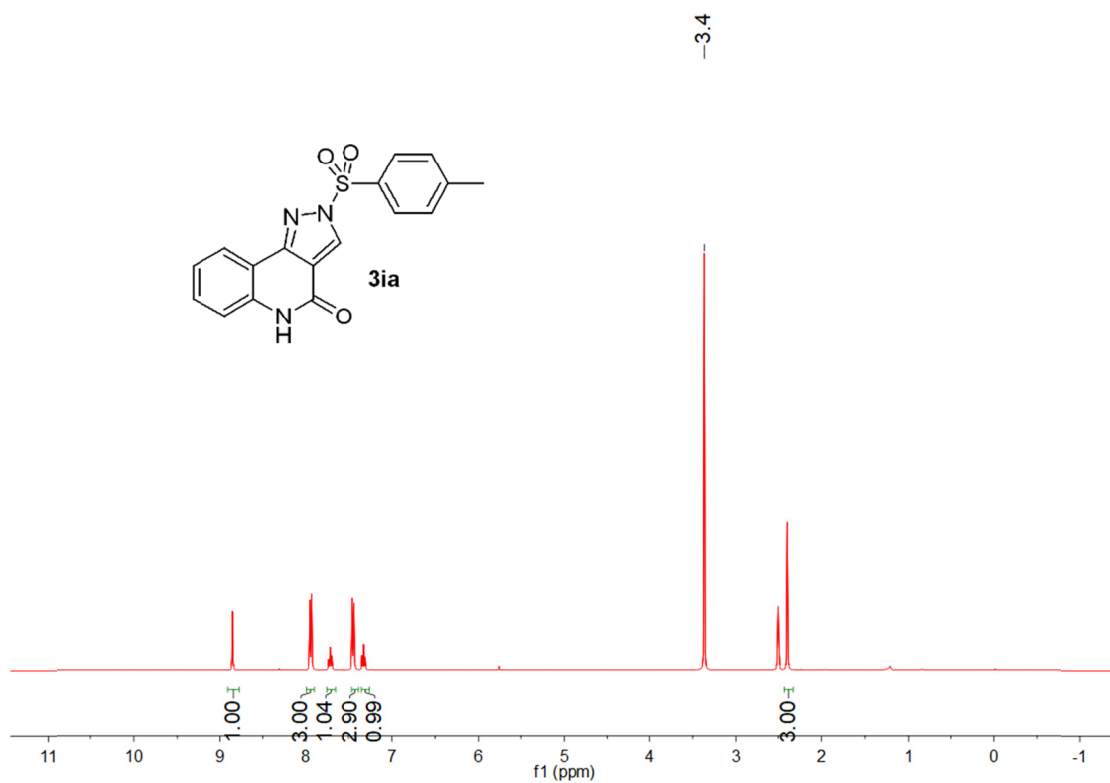
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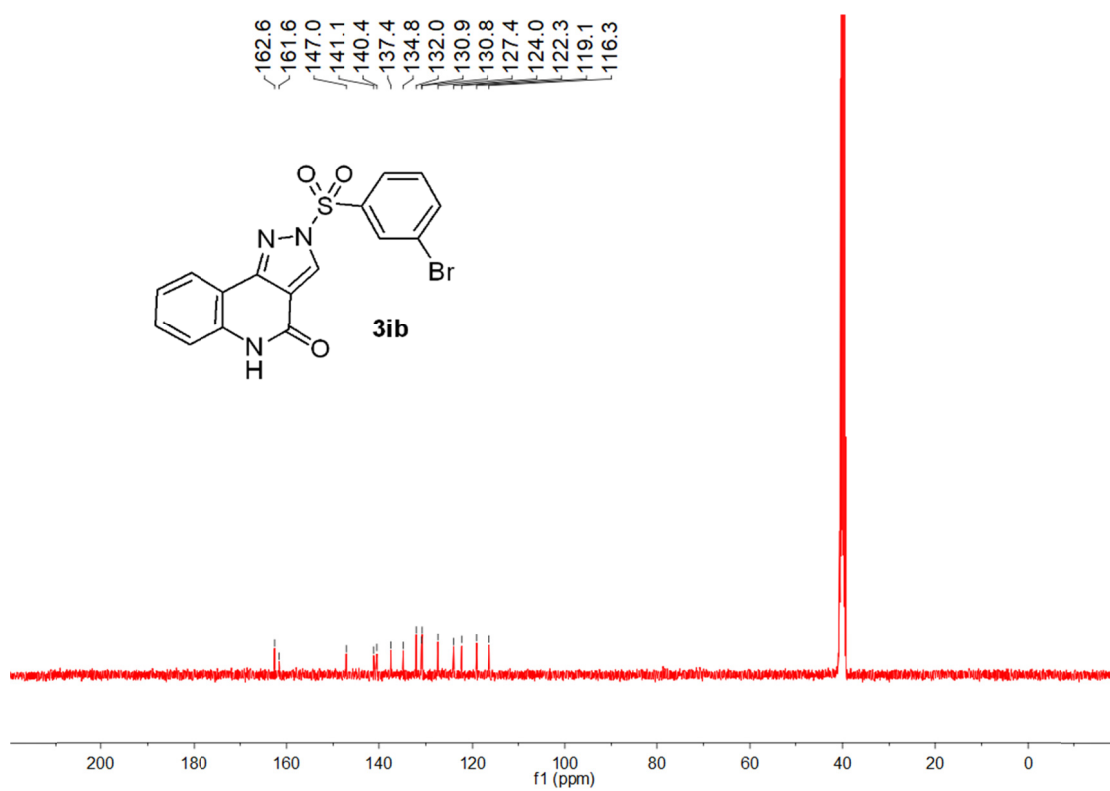
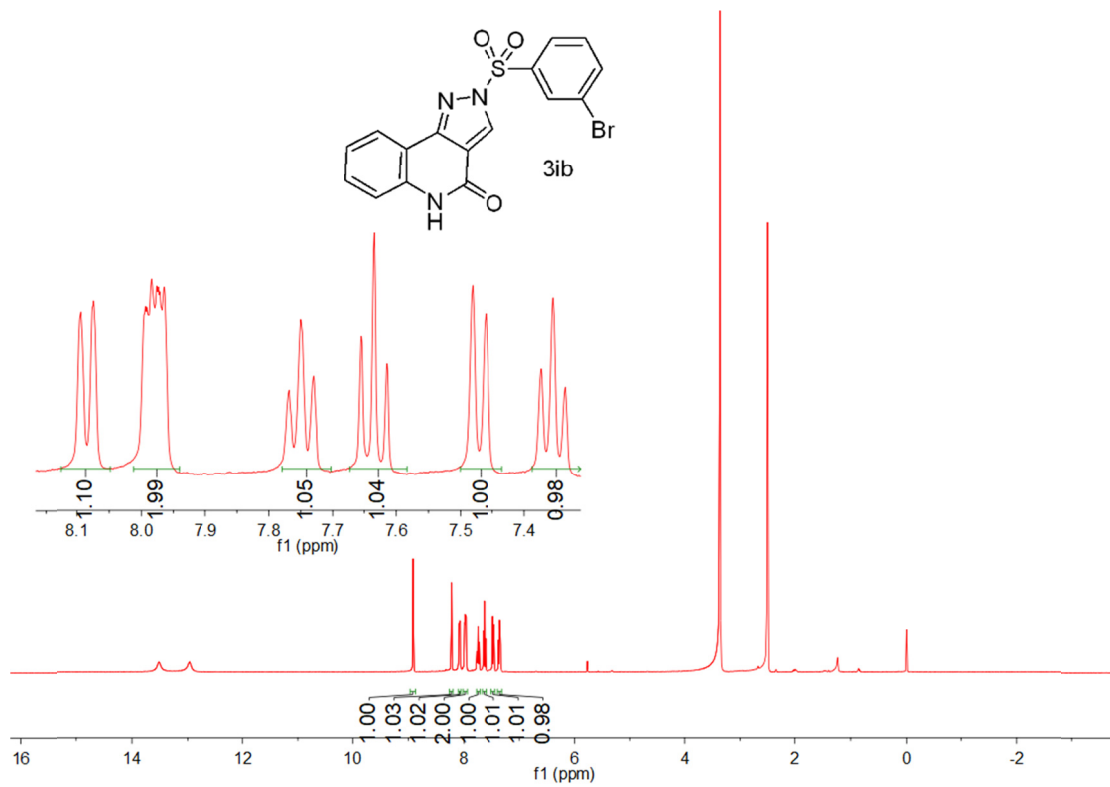
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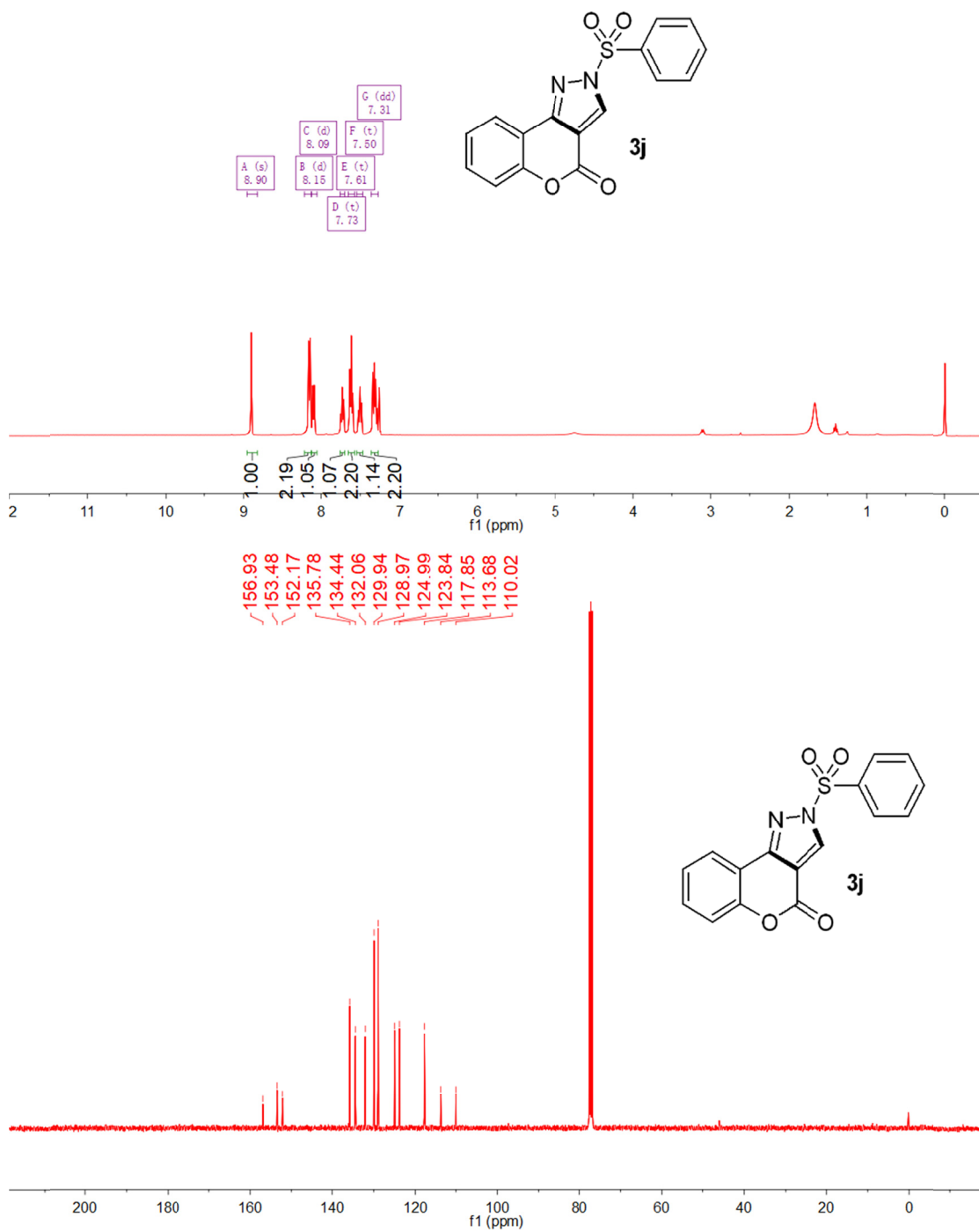






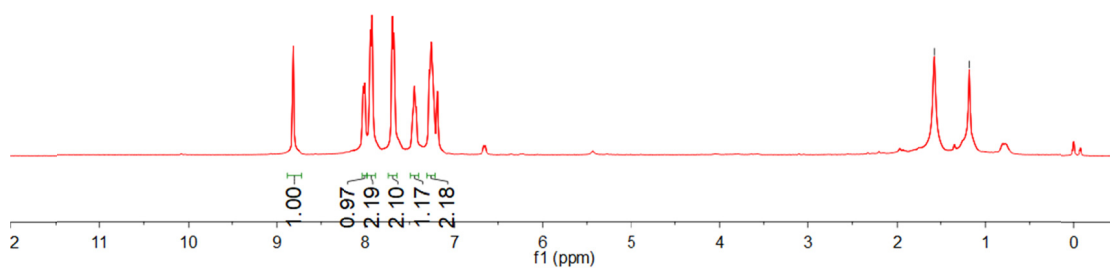
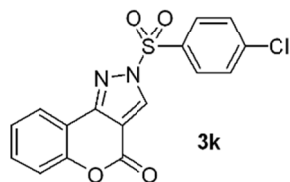






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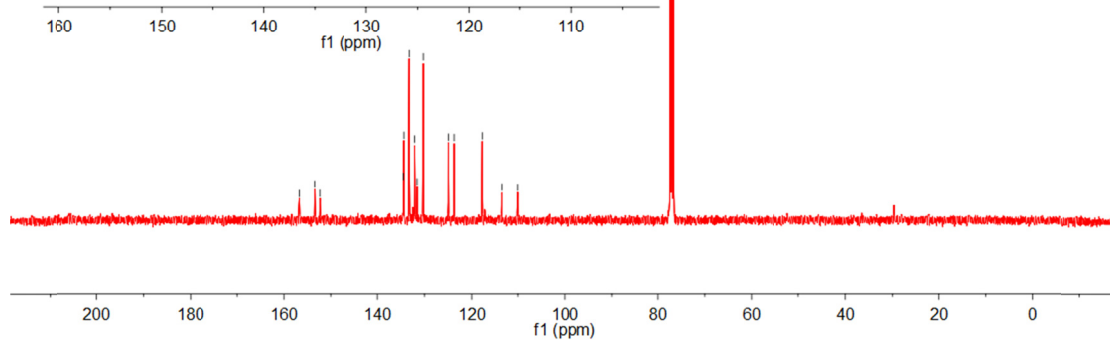
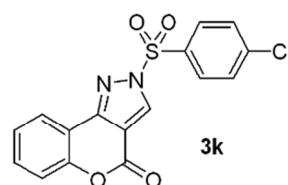
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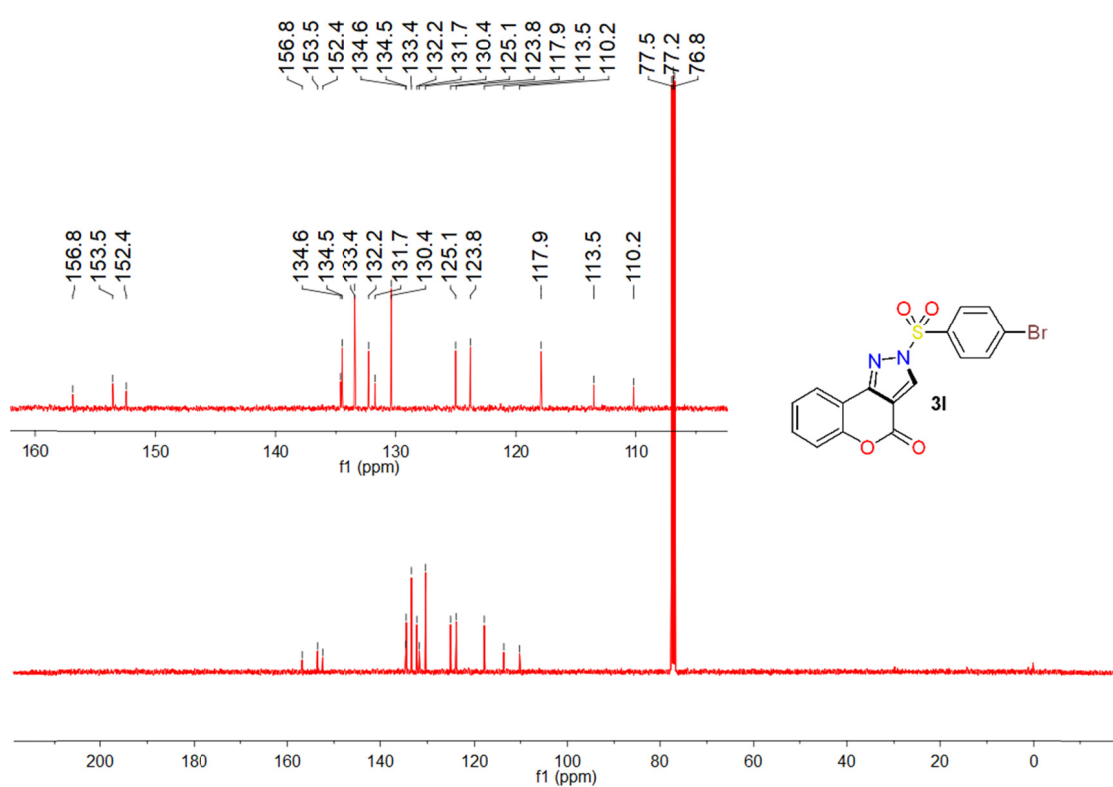
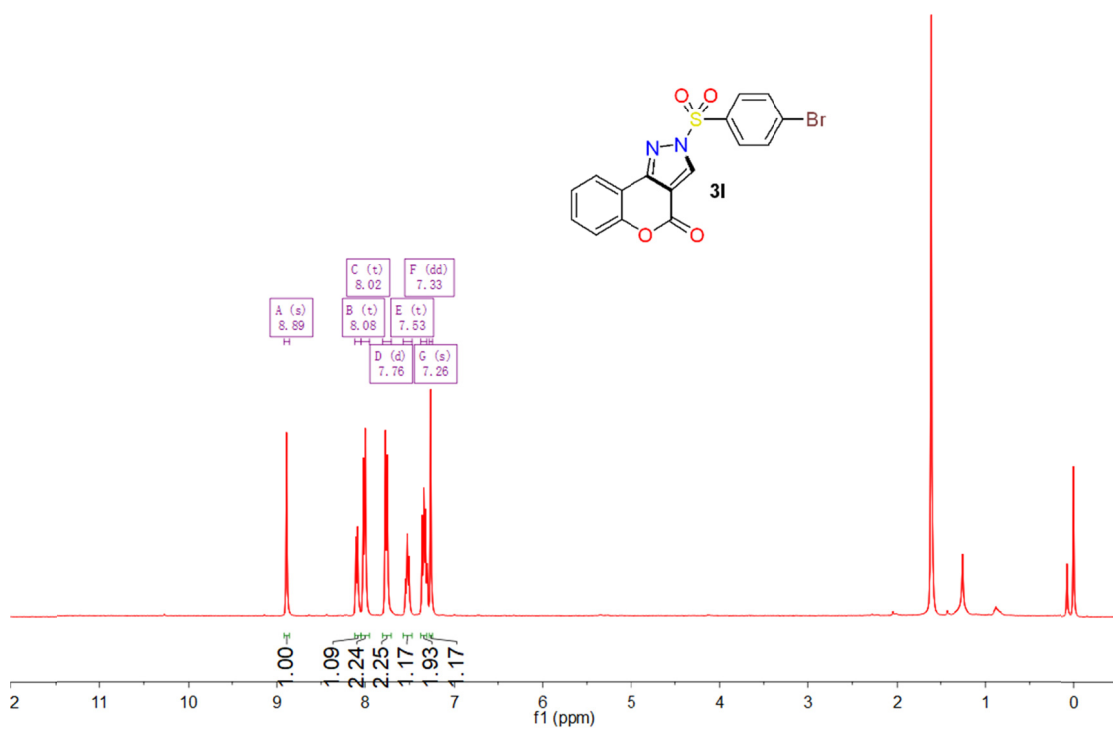


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113.4
110.0

156.7
153.4
152.3

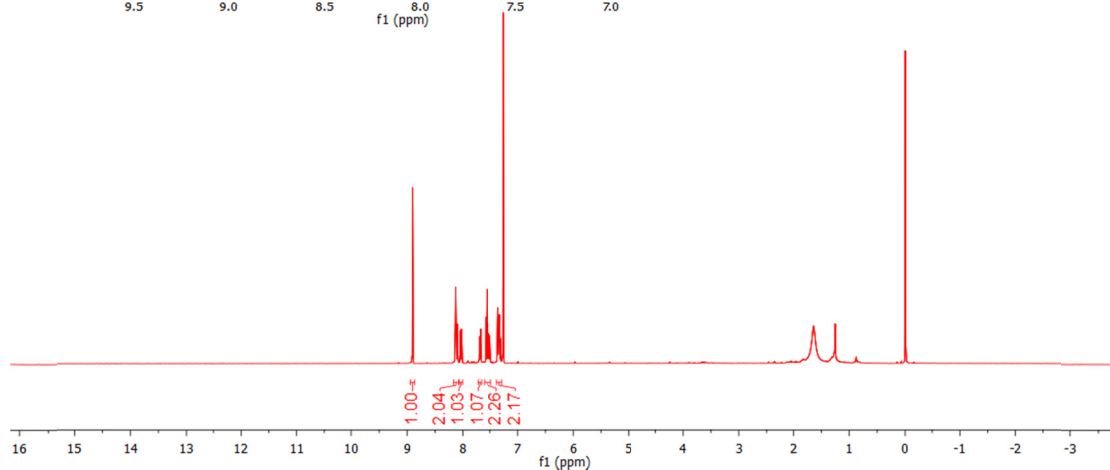
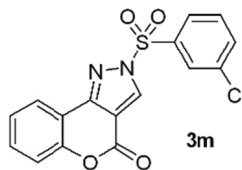
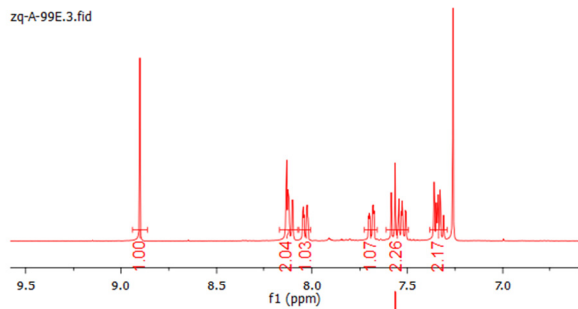
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133.2
132.1
131.6
130.2
124.9
123.7
117.8
113.4
110.0





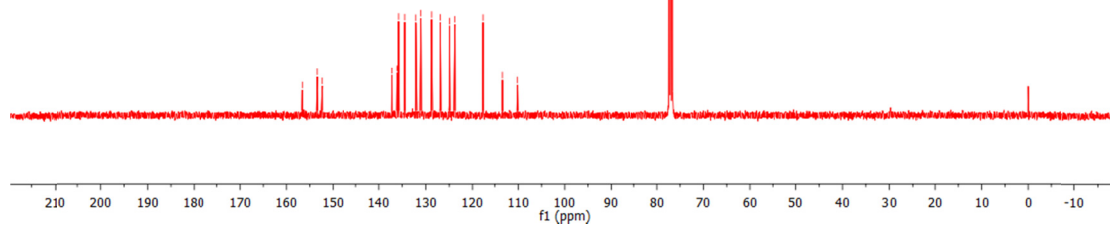
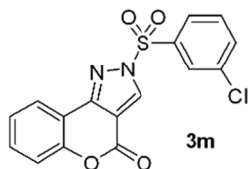
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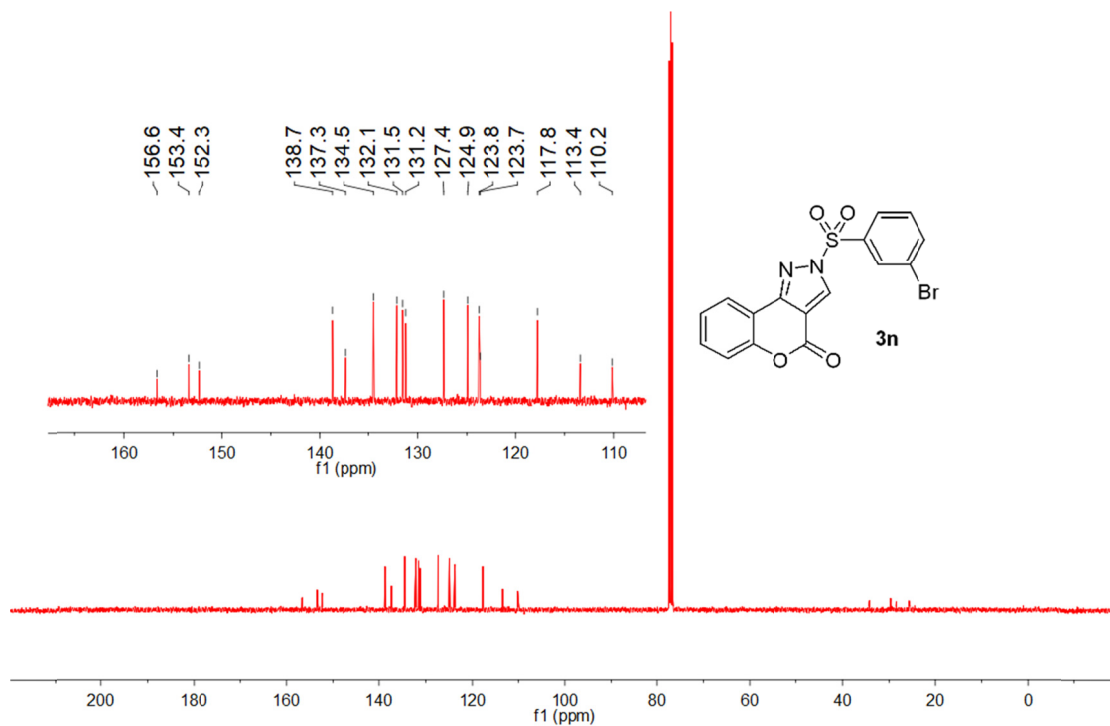
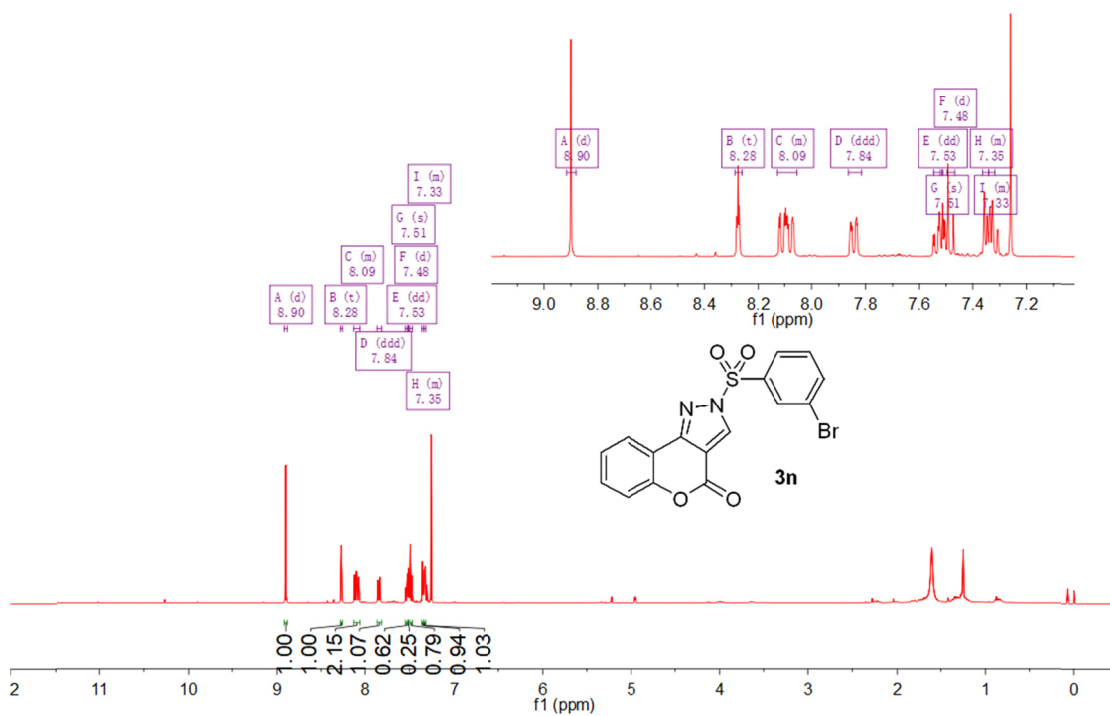
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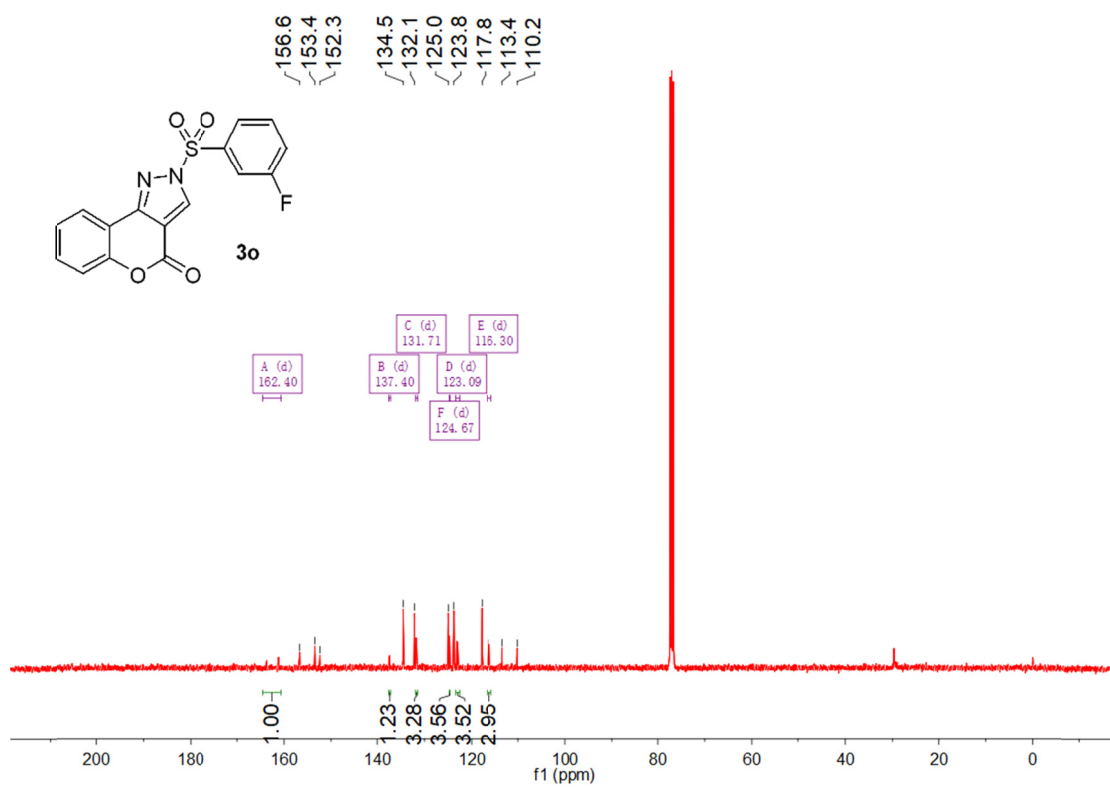
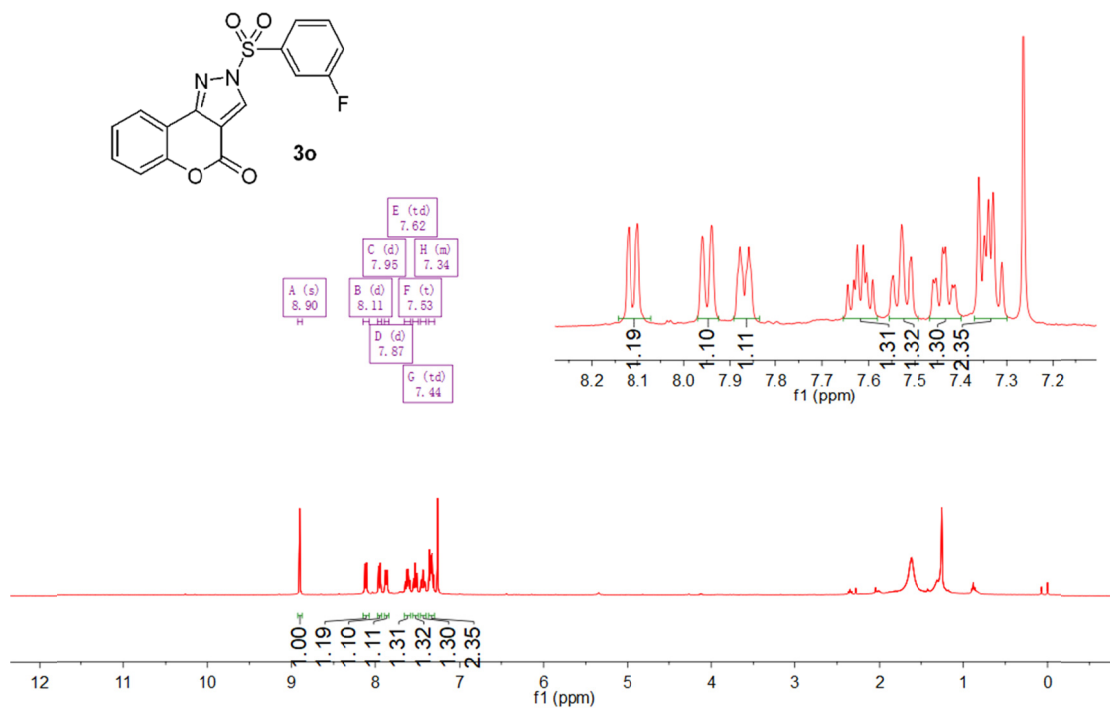


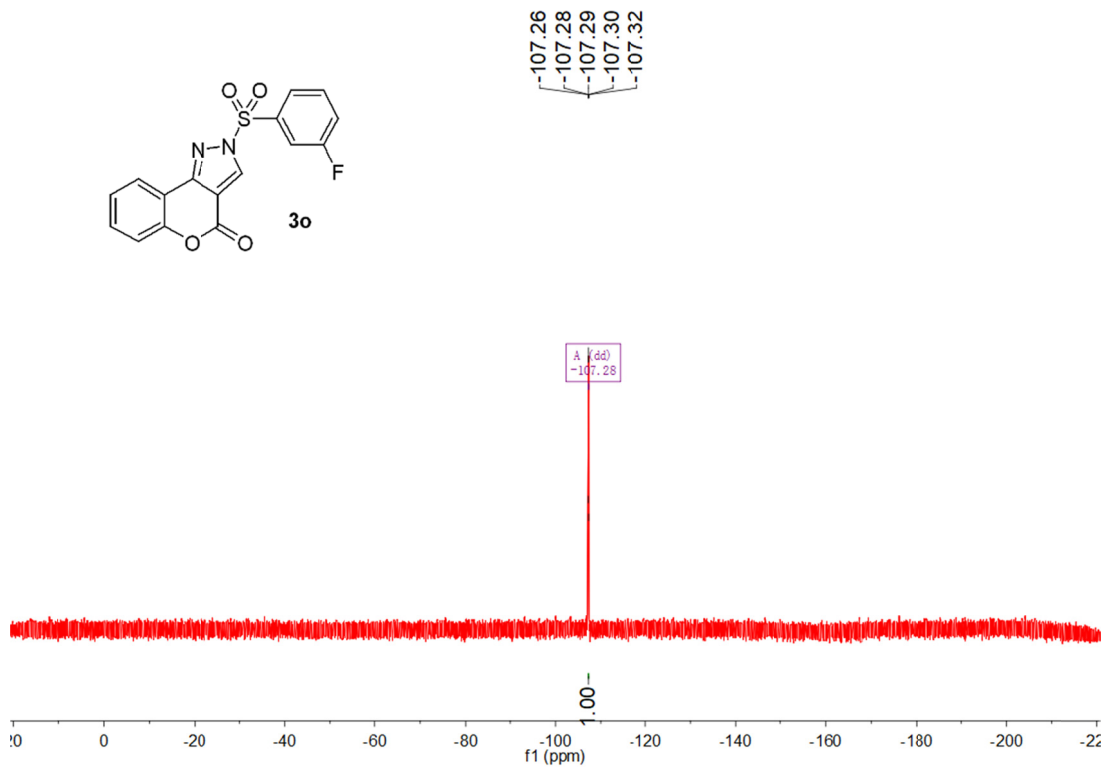
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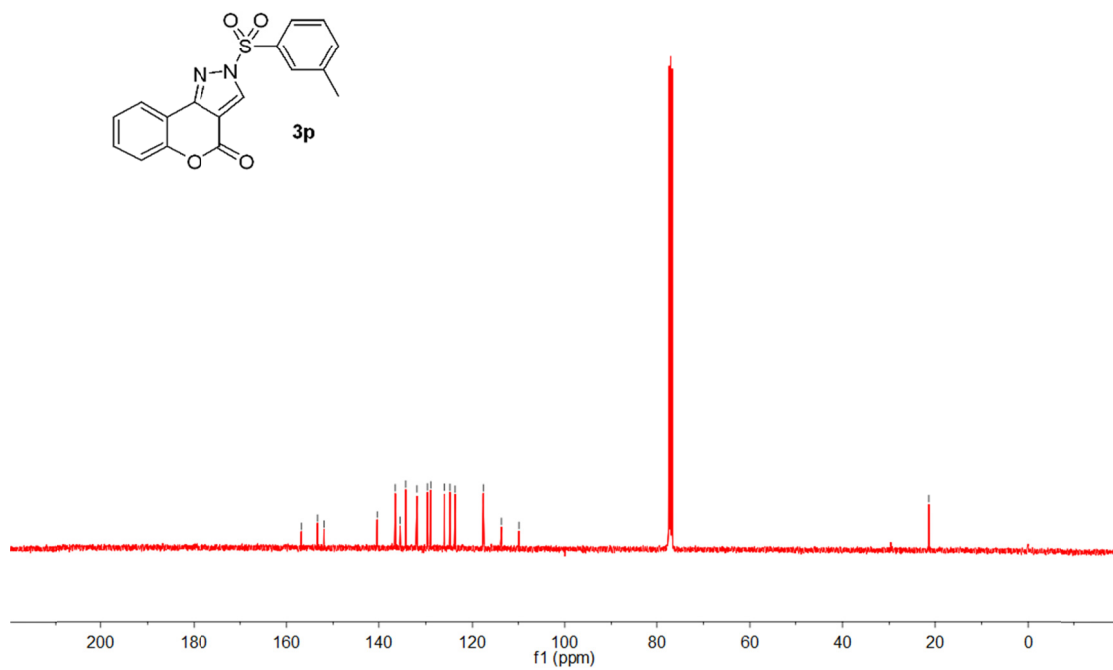
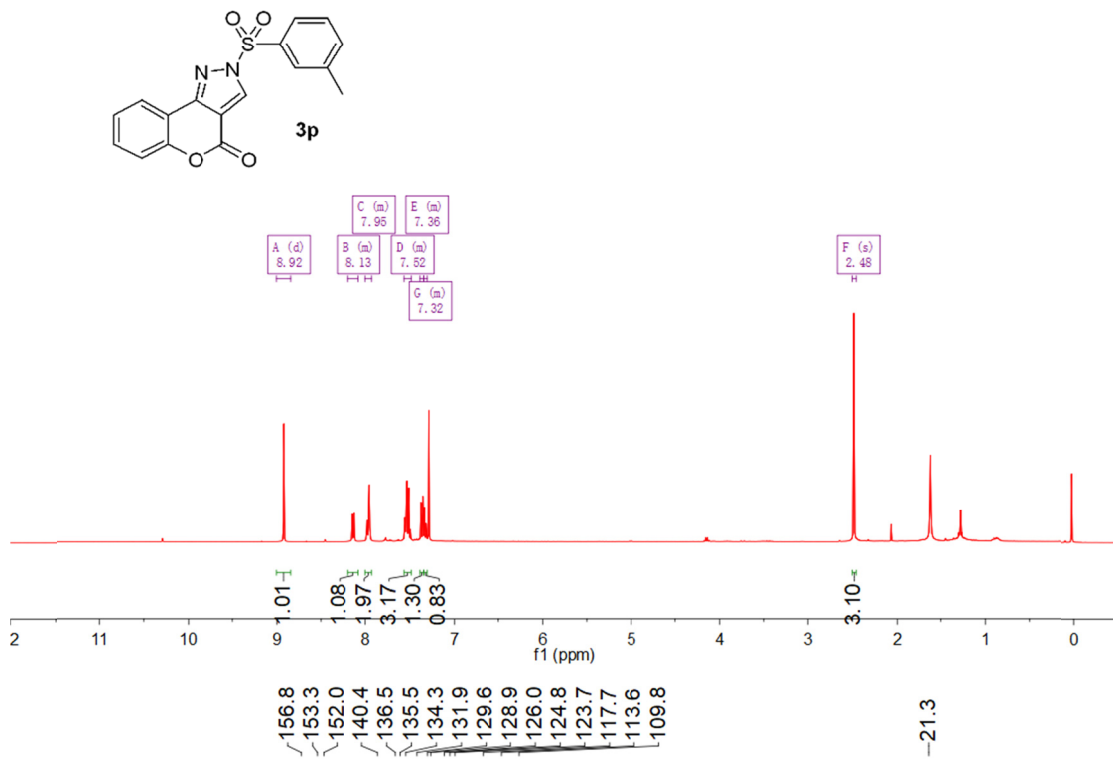
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132.112
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126.911
124.936
123.778
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113.397
110.162

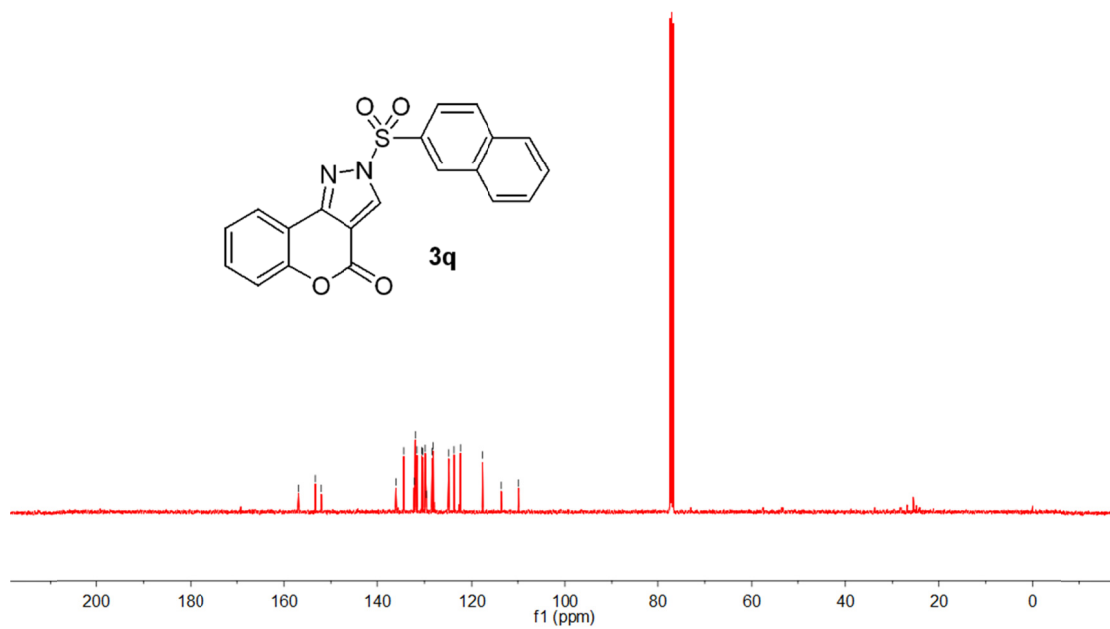
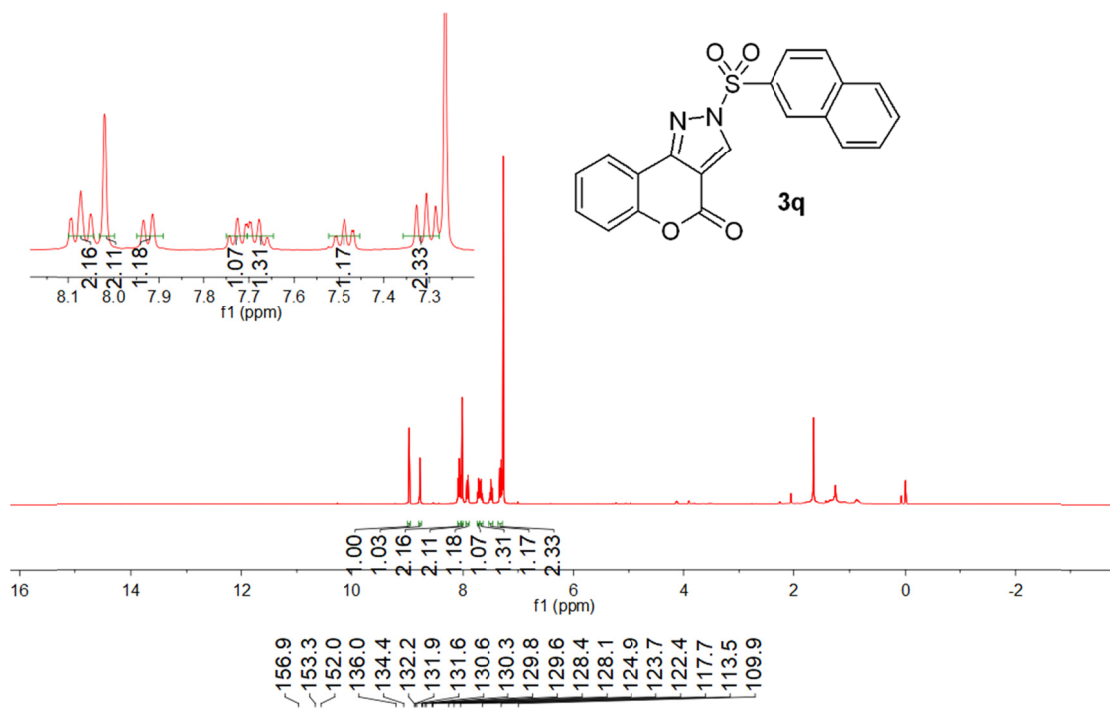


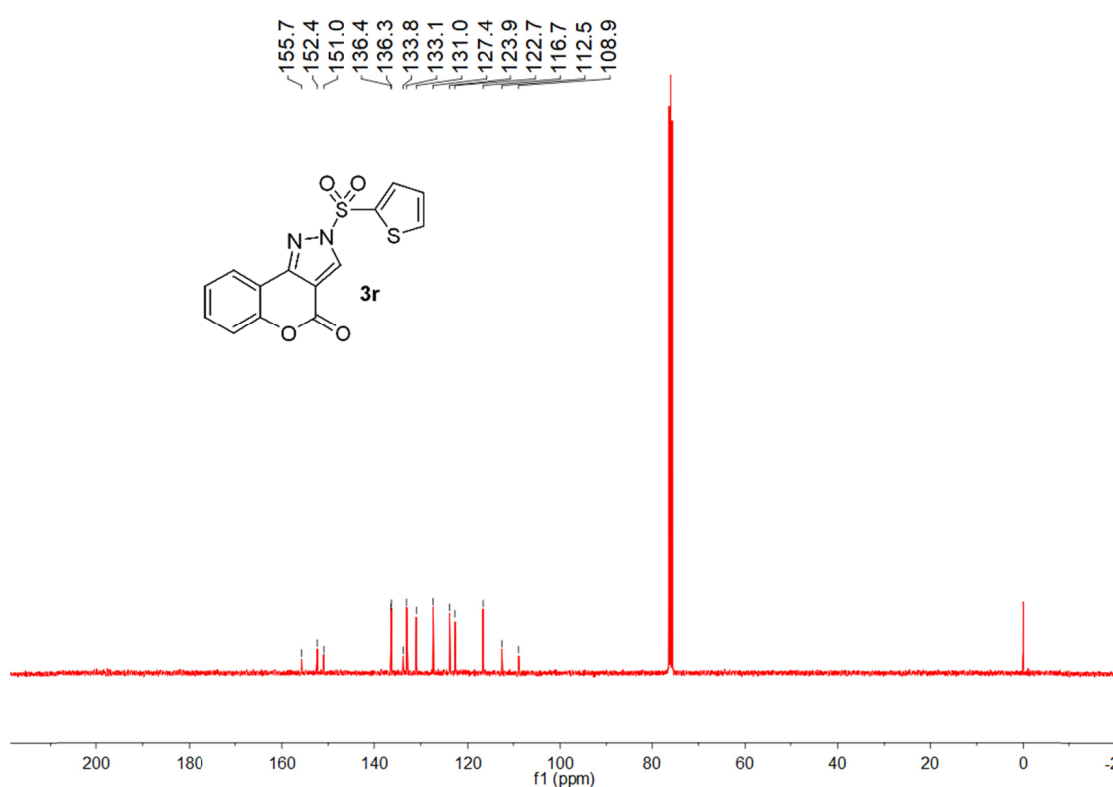
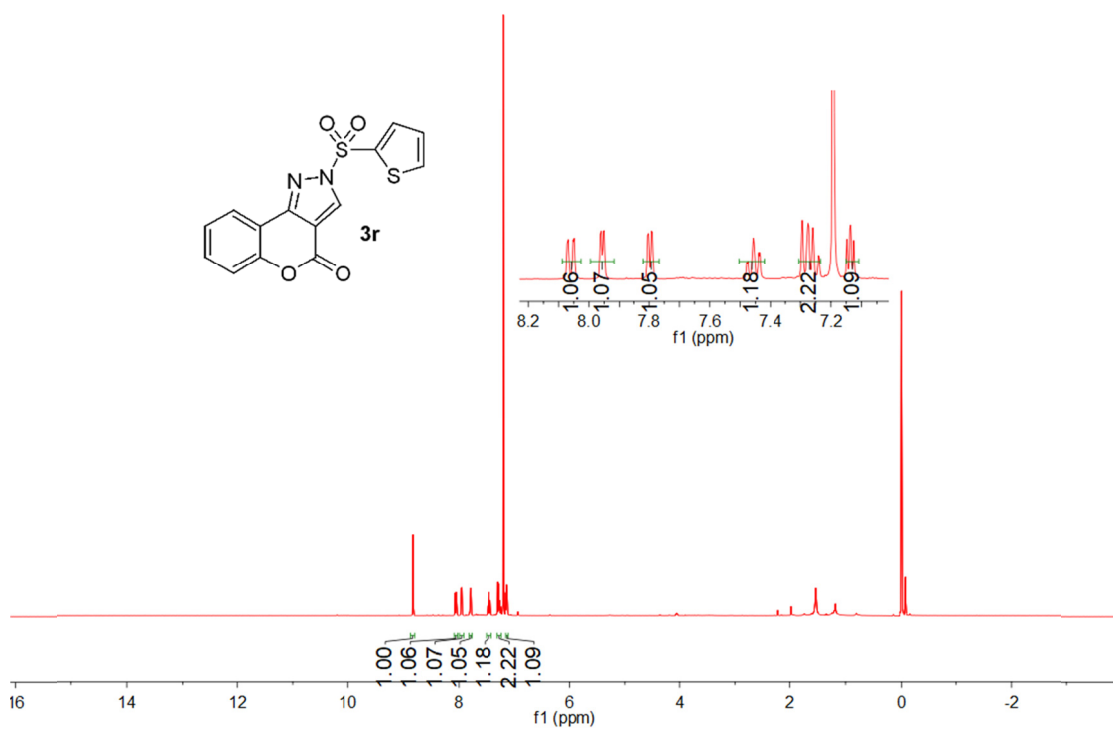


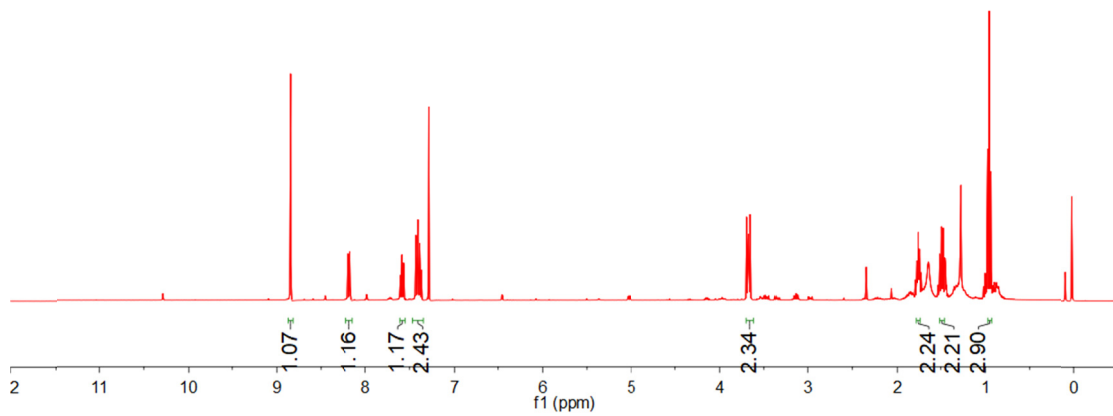
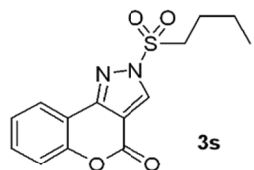












156.7
153.4
152.1
134.8
132.1
125.0
123.7
117.8
113.5
109.6

-53.8

-24.8
-21.1
-13.3

