

## **Supplementary Information**

### **Synthesis and structure–activity relationships of pirfenidone derivatives as anti-fibrosis agents in vitro**

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*School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, 450001, China*

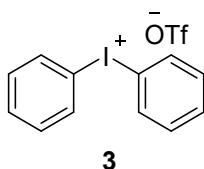
\*Corresponding authors. E-mail address: yxyxianglu@zzu.edu.cn

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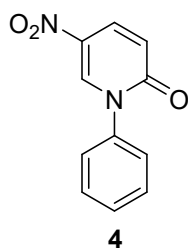
Synthesis of compound <b>3~5</b>	S1~S3
<sup>1</sup> HNMR and <sup>13</sup> CNMR data of target compounds ( <b>YZQ01~18</b> )	S3~S21

## 1. Synthesis of compound 3~5

Most chemicals and solvents were of analytical grade and, when necessary, were purified and dried by standard methods. Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel plates (silica gel GF/UV 254), and spots were visualized under UV light (254 nm). Melting points (uncorrected) were determined on a XT5A melting point apparatus and are uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer at 300 K, using TMS as an internal standard. MS spectra were recorded on a Shimadzu GC-MS 2050 (ESI) or an Agilent 1946A-MSD (ESI) Mass Spectrum. Column chromatography was performed with silica gel (Qingdao Ocean Co., Ltd. 200-300 mesh). Chemical shifts ( $\delta$ ) are expressed in parts per million relatives to tetramethylsilane, which was used as an internal standard, coupling constants ( $J$ ) are in hertz (Hz), and the signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

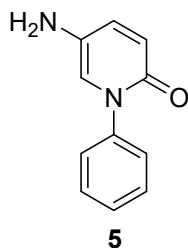


**Diaryliodonium Salt (3).** To a solution of Iodobenzene (**2**) and *m*-CPBA in DCM was added trifluoromethanesulfonic acid dropwise at ice bath and then the mixture was stirred at this temperature for 10 min. After that, the reaction mixture was concentrated in vacuum and redissolved in diethyl ether. Next, the solution was stirred for additional 10 min and stored in a freezer for 0.5 h. Then the precipitate was filtrated, washed with cold diethyl ether and dried in vacuum to afford diaryliodonium Salt (**3**) that was used for next step without further purification.



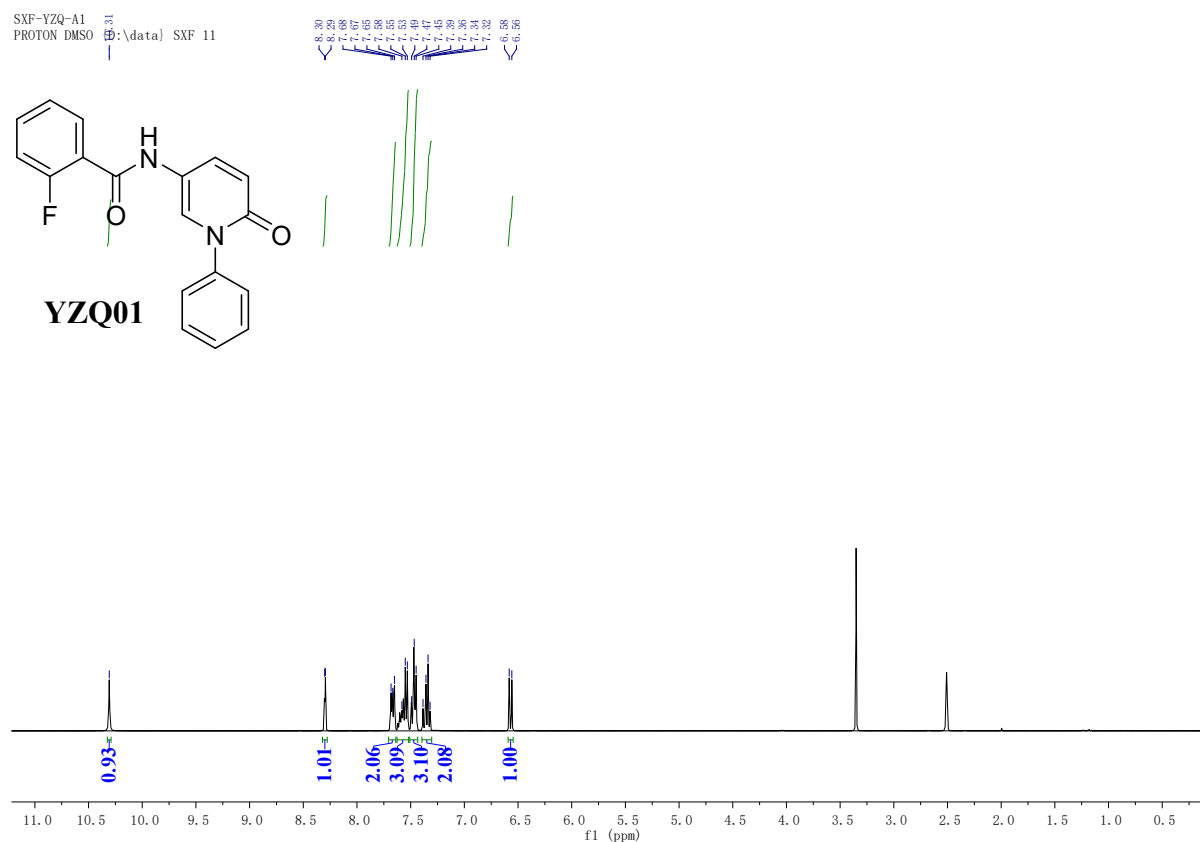
**5-nitro-1-phenylpyridin-2(1H)-one (4).** 2-hydroxy-5-nitropyridine (2.1 g, 14.99 mmol), copper iodide (0.29 g, 1.5 mmol) and **3** (8.3 g, 19.29 mmol) were dissolved in DCM (140 ml) under nitrogen condition. Then, the mixture was stirred at an ice bath for 5 min. After that, triethylamine (4 ml, 28.78 mmol) dissolved in anhydrous DCM (10 ml) was slowly added dropwise into the reaction and next the mixture was stirred at room temperature for additional 10 min. Then, the reaction mixture was evaporated under reduced pressure and re-dissolved in ethyl acetate (200 ml), and the organic phase was washed with water and brine and then concentrated to get crude product in vacuum. The crude product was purified by recrystallization with methanol to obtain compound **4** as a pale-yellow solid (2.7 g, 83%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.93 (d,  $J = 3.1$  Hz, 1H), 8.24 (dd,  $J =$

10.1, 3.1 Hz, 1H), 7.58 – 7.52 (m, 5H), 6.62 (d,  $J = 10.1$  Hz, 1H).

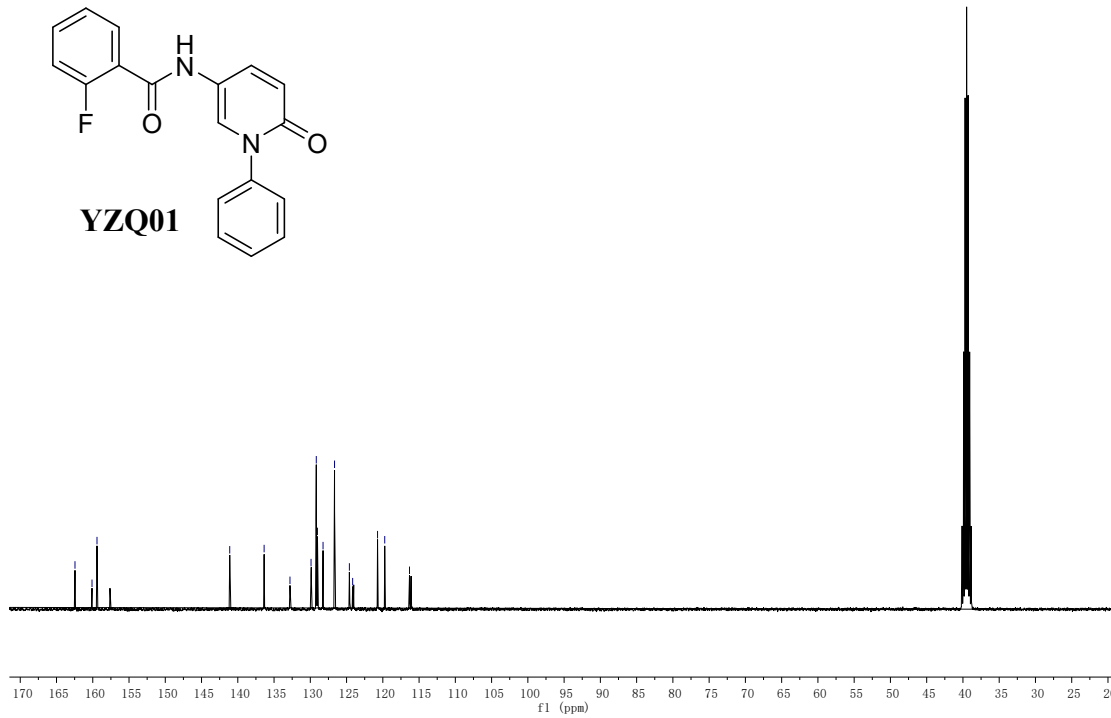
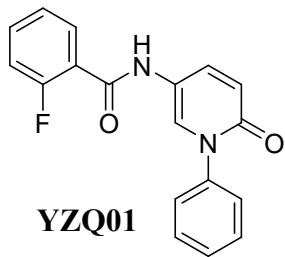


**5-amino-1-phenylpyridin-2(1H)-one (5).** Compound **4** (0.5 g, 2.31 mmol), reduced iron powder (0.5 g, 8.95 mmol) and ammonium chloride (0.19 g, 3.55 mmol) were dissolved in a mixed solvent (ethanol/water =4:1, v/v), and then the mixture was refluxed for 2 h. After completion, the reaction mixture was filtered with diatomite and the filter cake was washed with absolute ethanol, and the titled compound was purified by column chromatography as an atrovirens solid (0.43g, 94%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  7.48 (t,  $J = 7.5$  Hz, 2H), 7.41 – 7.35 (m, 3H), 7.18 (dd,  $J = 9.6, 3.0$  Hz, 1H), 6.82 (d,  $J = 2.9$  Hz, 1H), 6.36 (d,  $J = 9.6$  Hz, 1H), 4.39 (s, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  158.43, 141.63, 135.87, 129.43, 128.90, 127.60, 126.59, 120.83, 118.83.

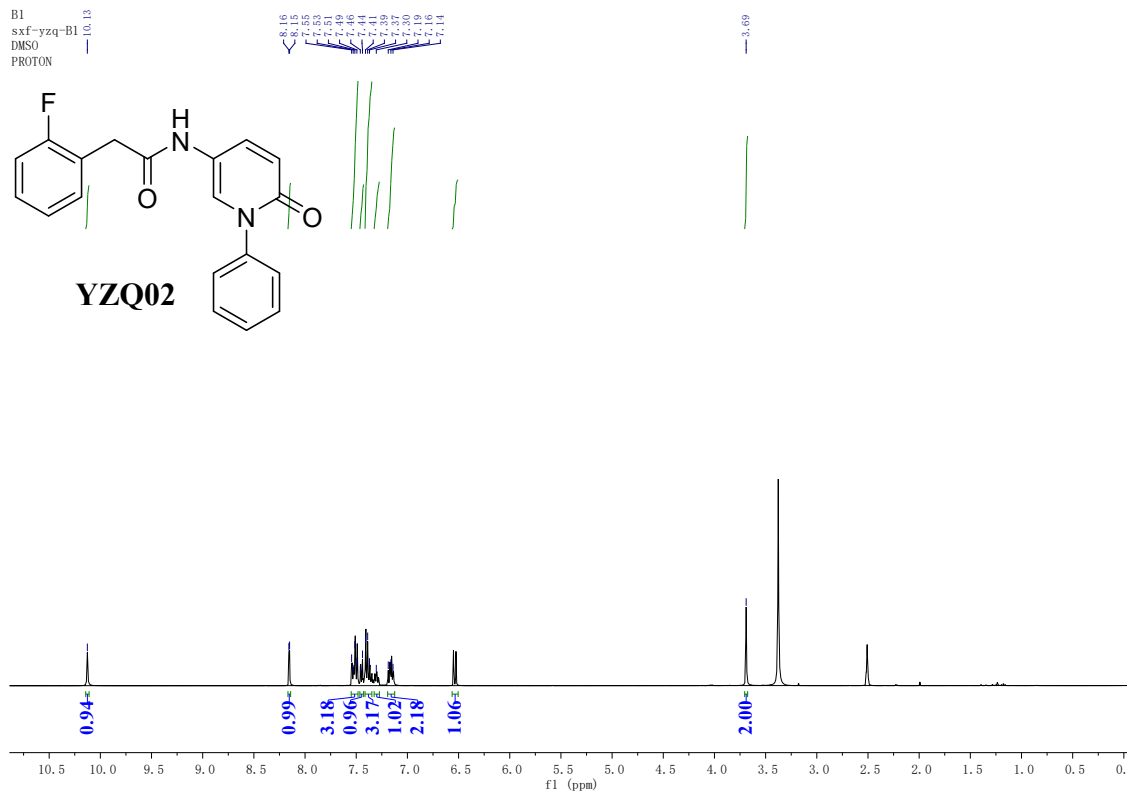
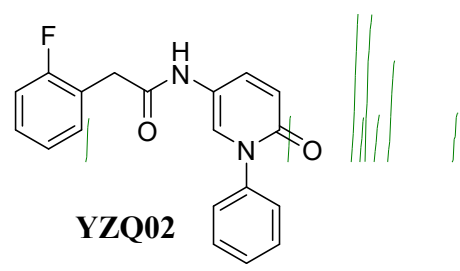
## 2. $^1\text{H}$ NMR and $^{13}\text{C}$ NMR data of target compounds (YZQ01~18)

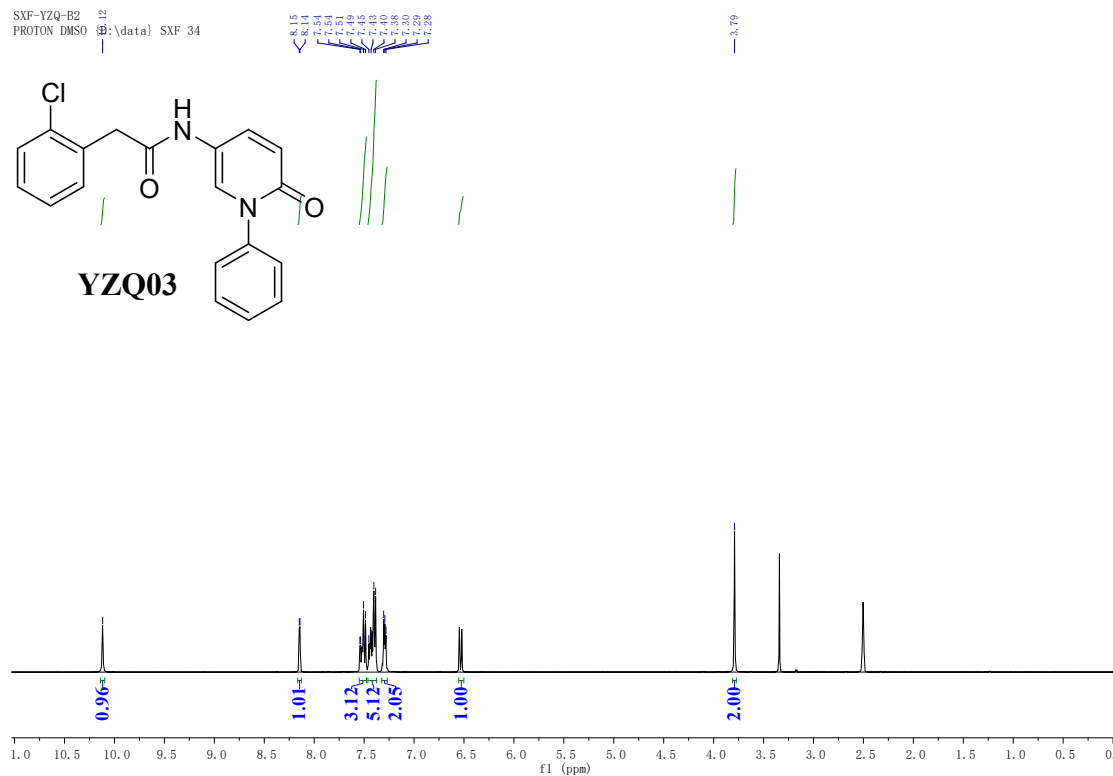
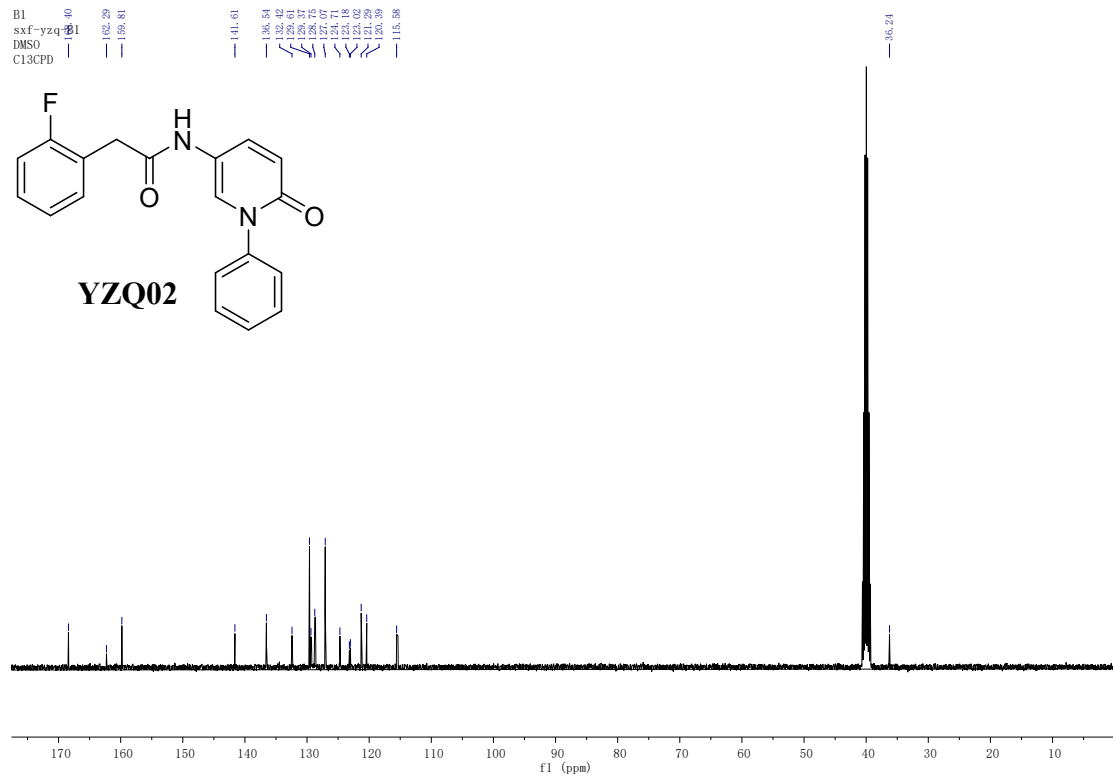


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 C13CPD DMSO-D6 (data) SXF 22

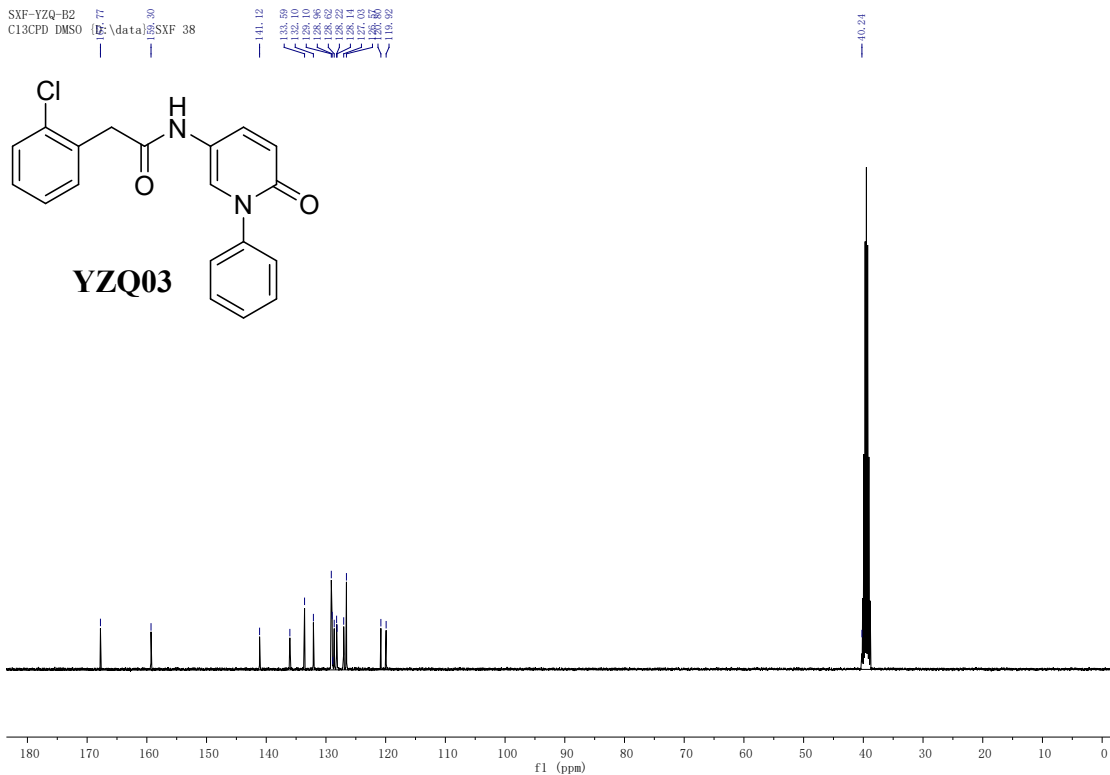
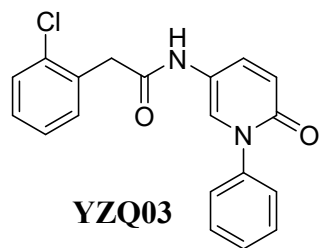


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 sxf-yzq-B1  
 DMSO  
 PROTON

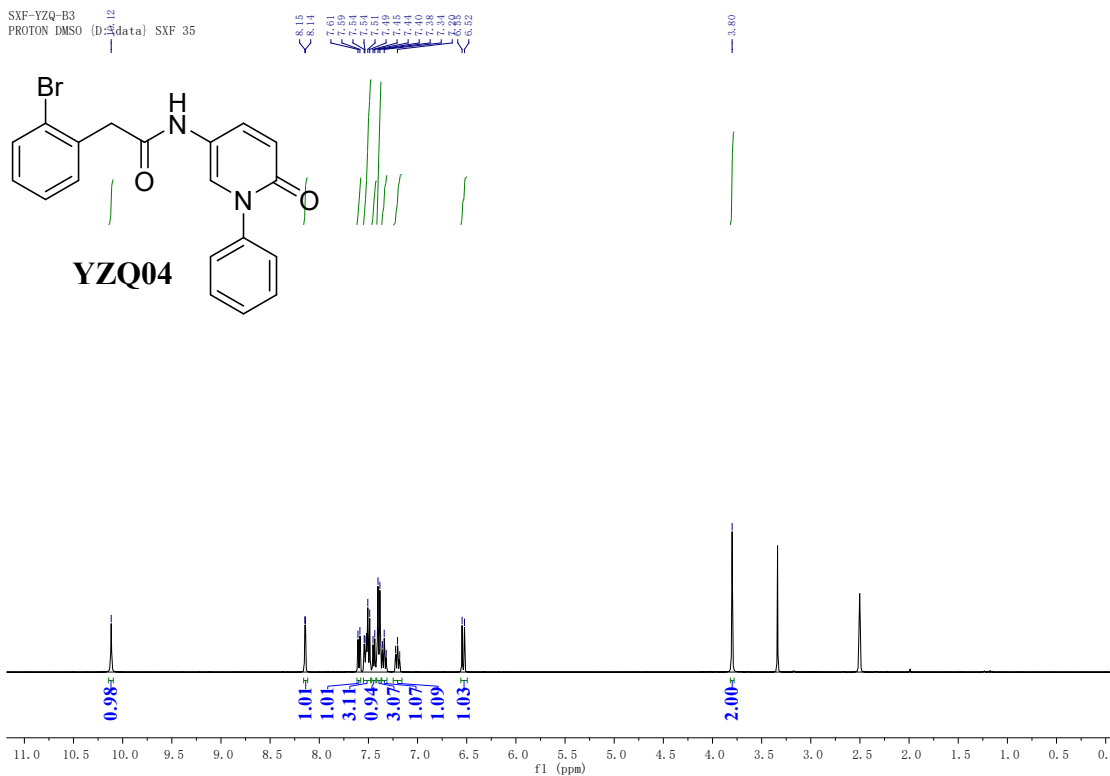
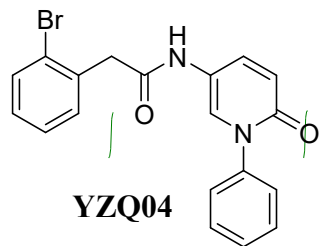




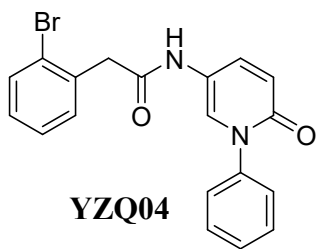
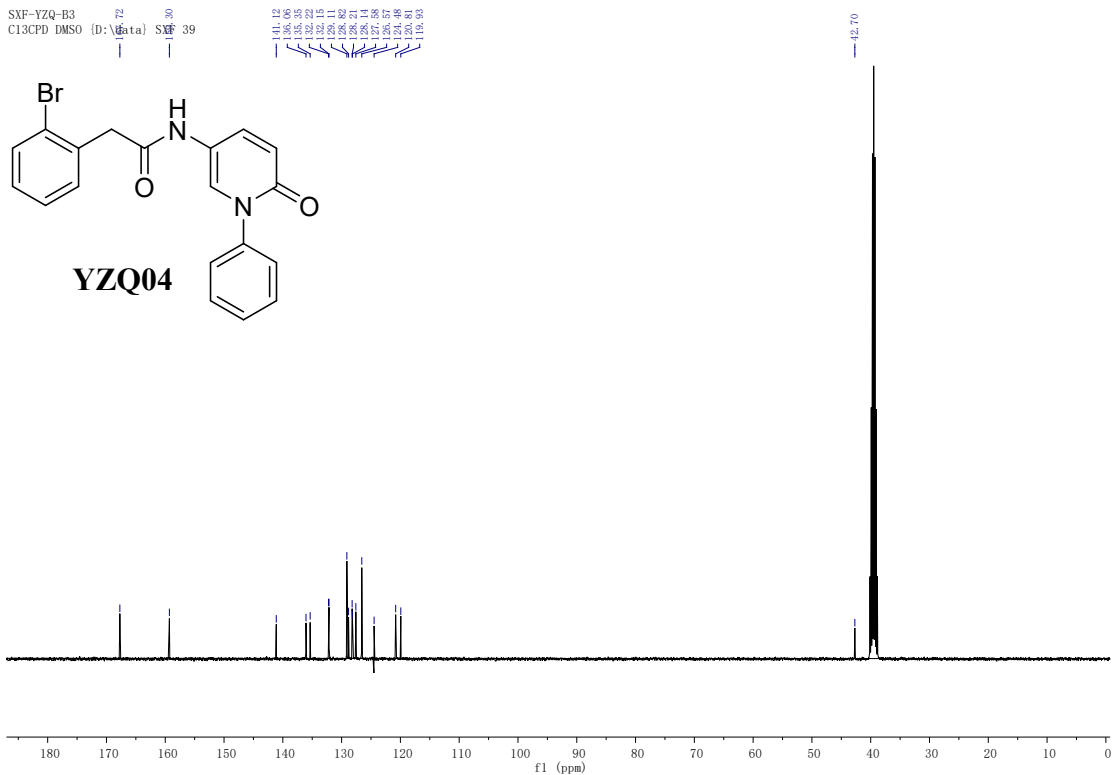
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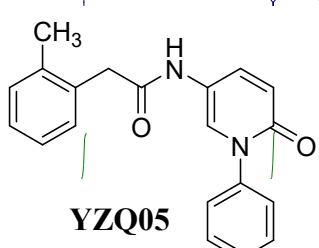
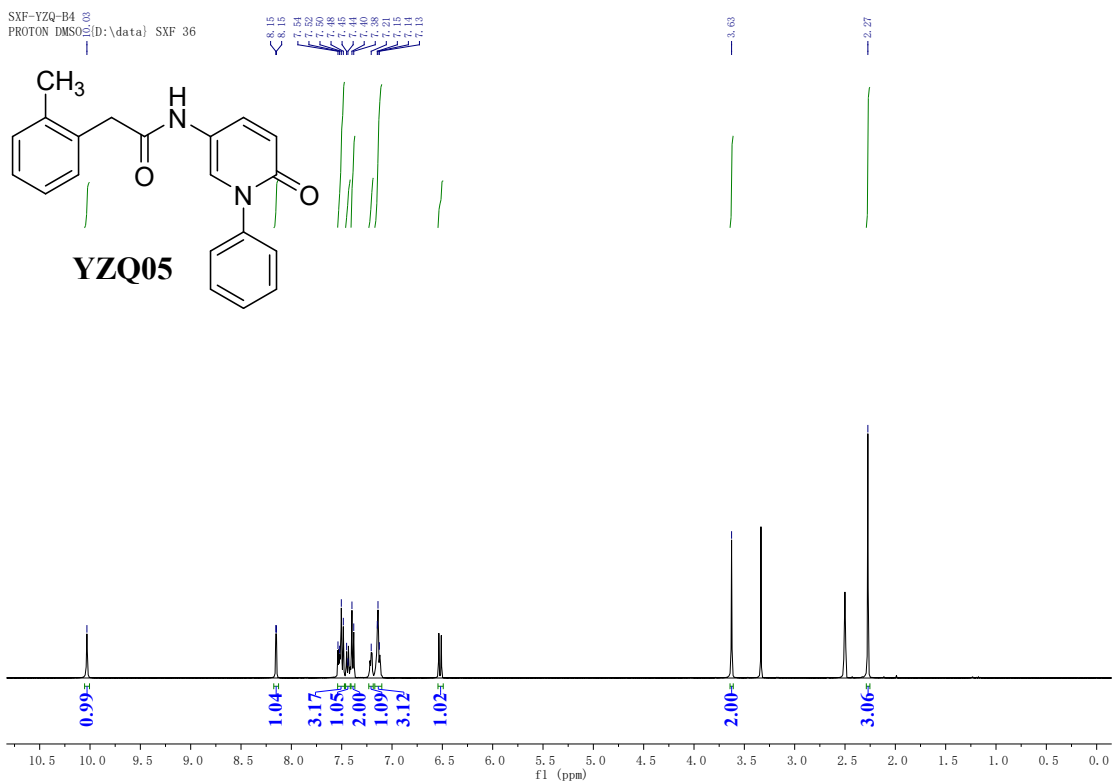
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PROTON DMSO



SXF-YZQ-B3  
C13CPD DMSO (D:\data) SXF 39

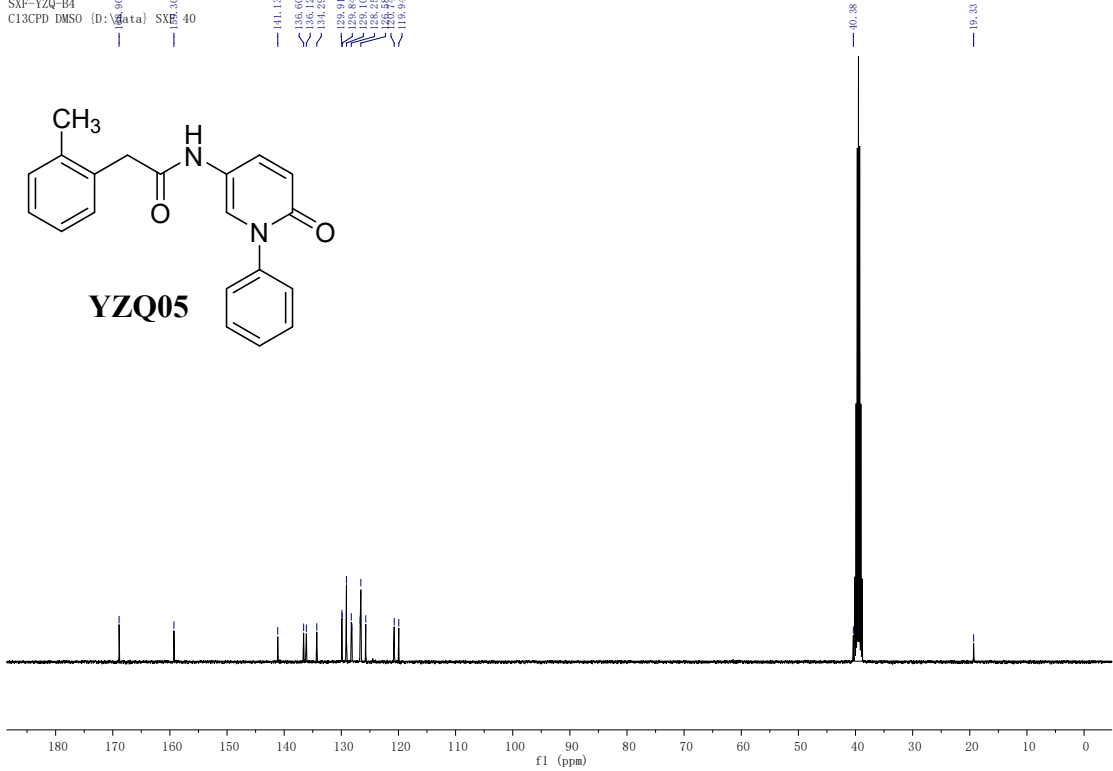
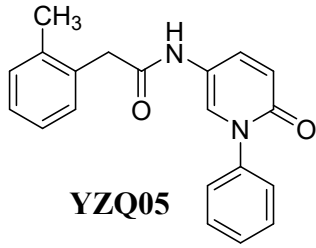


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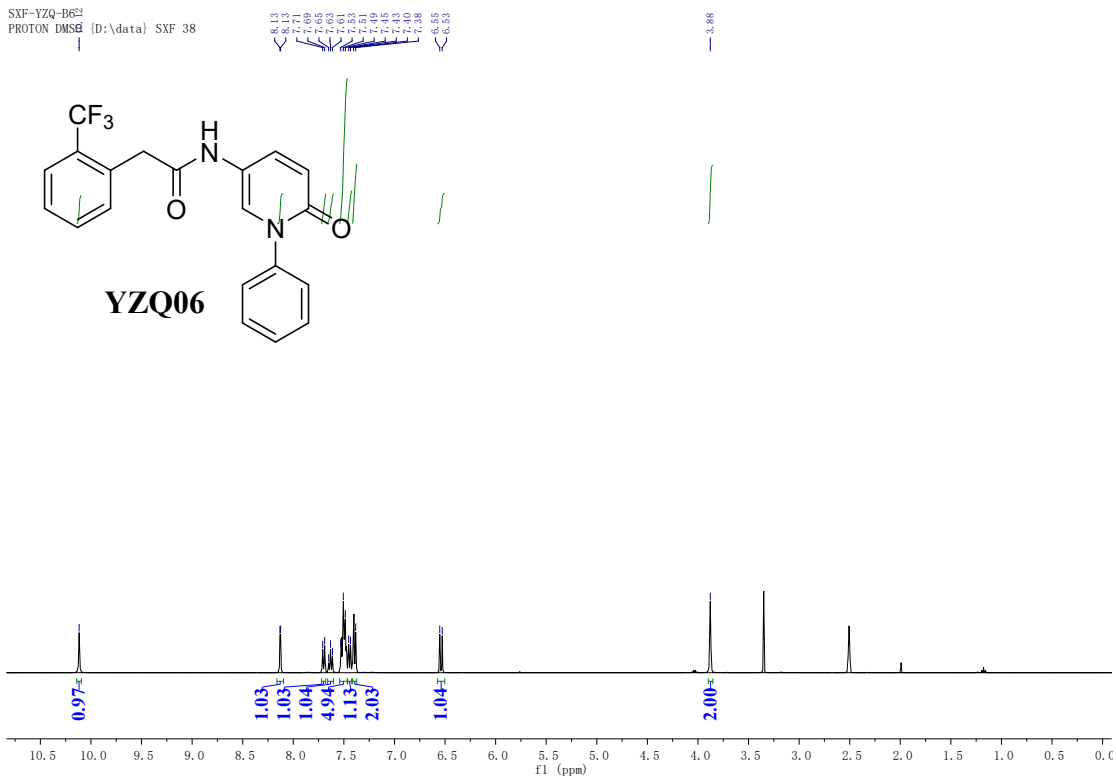
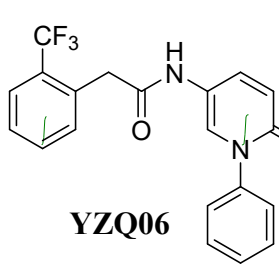
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SXF-YZQ-B623  
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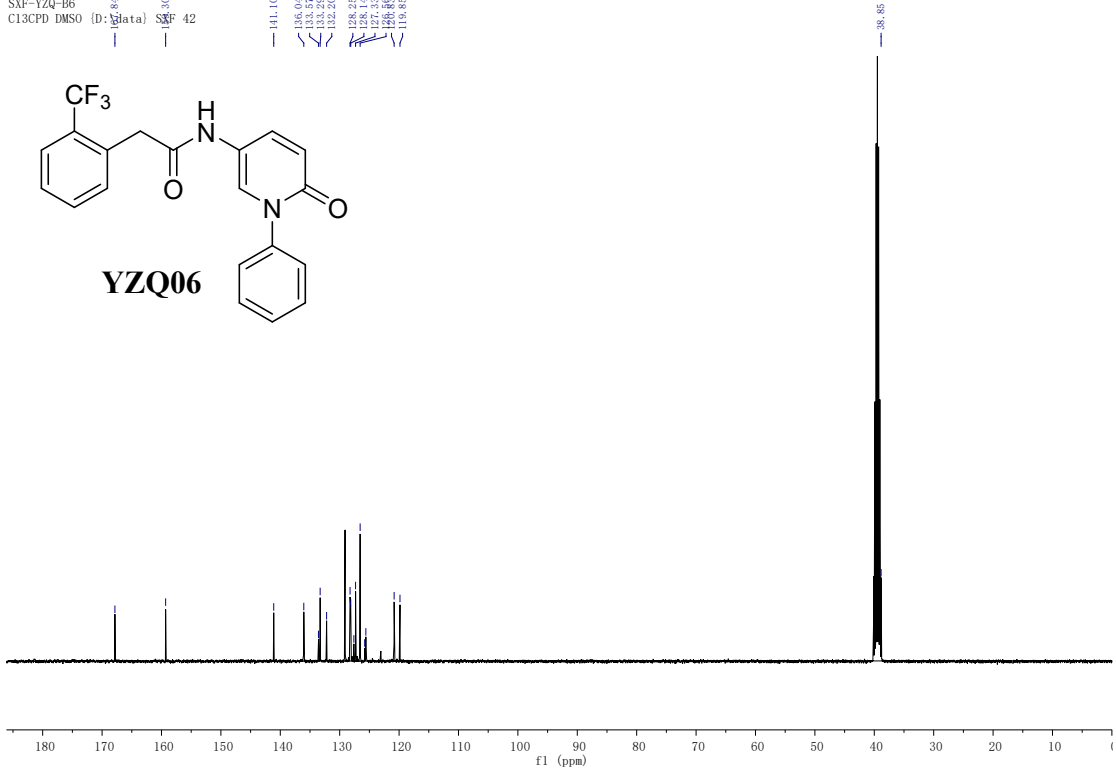
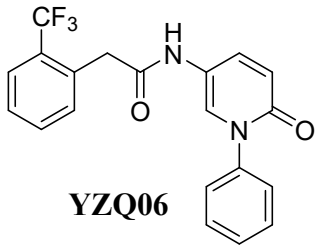
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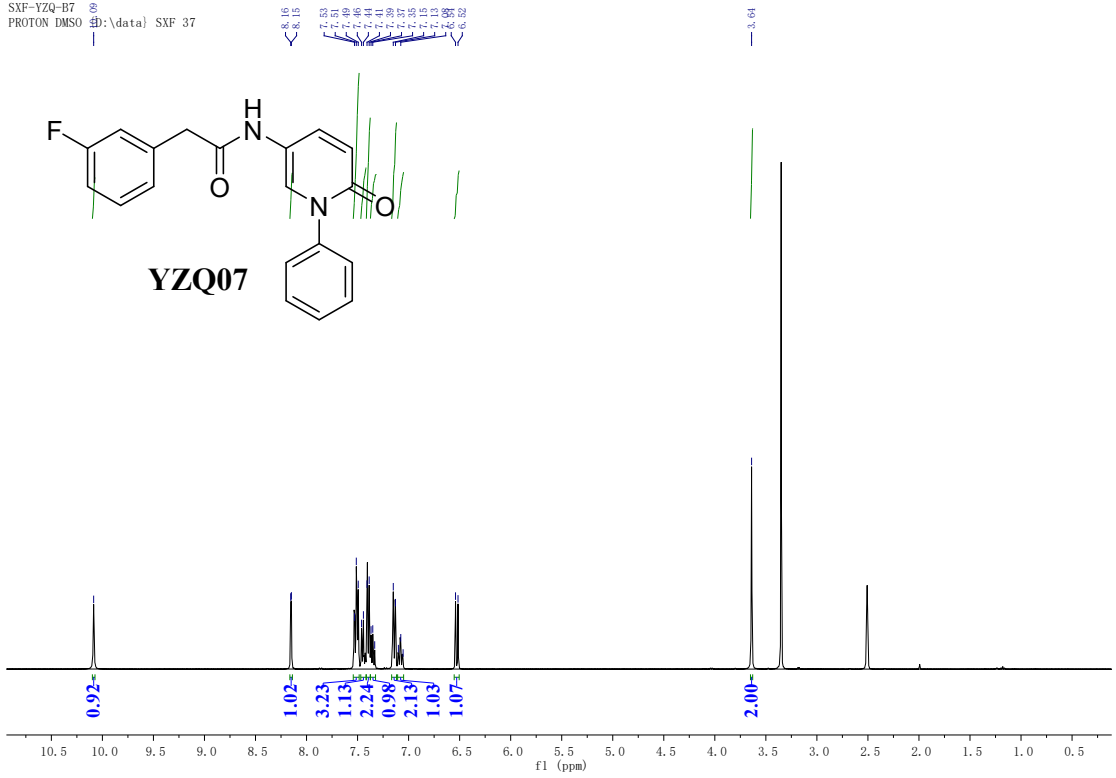
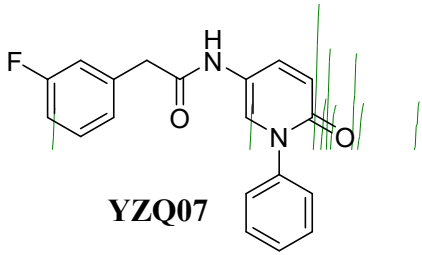
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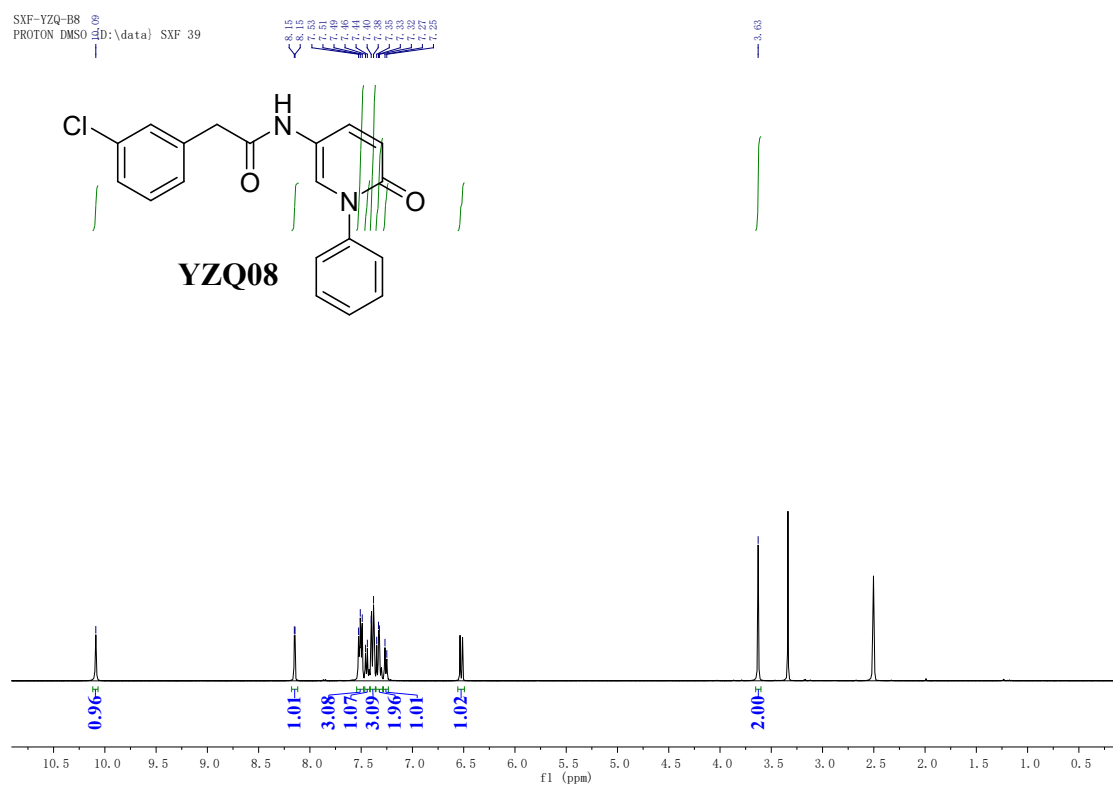
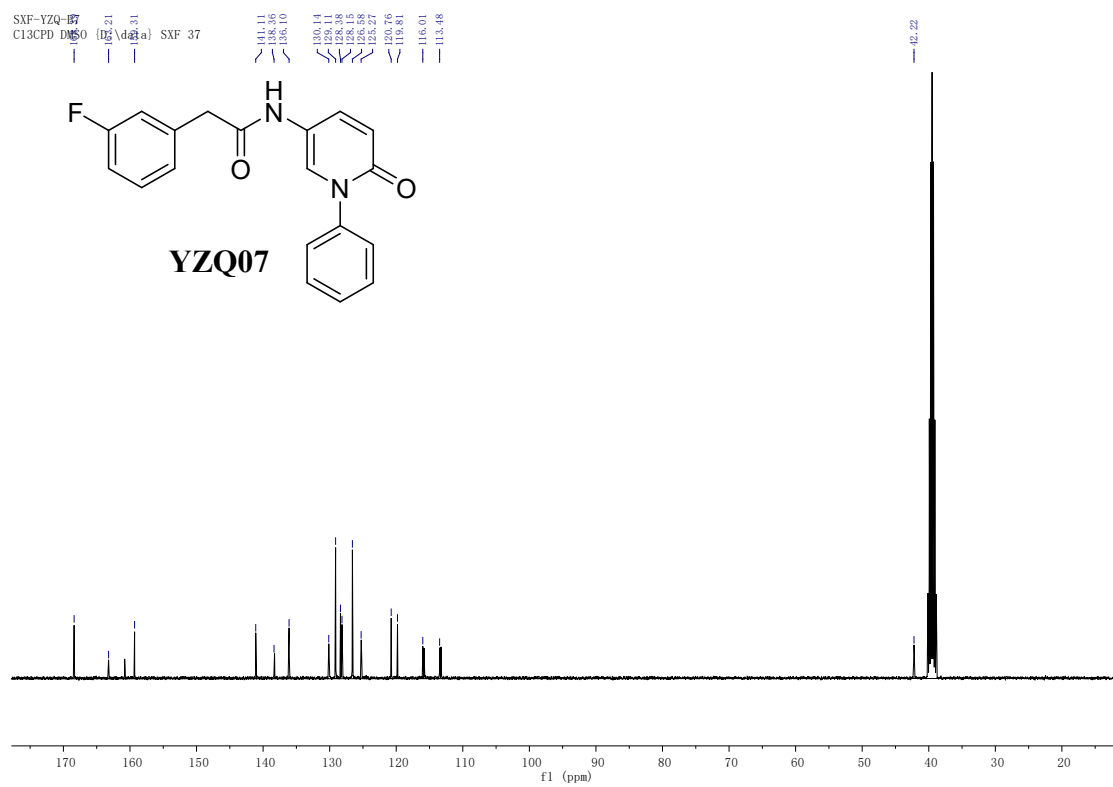
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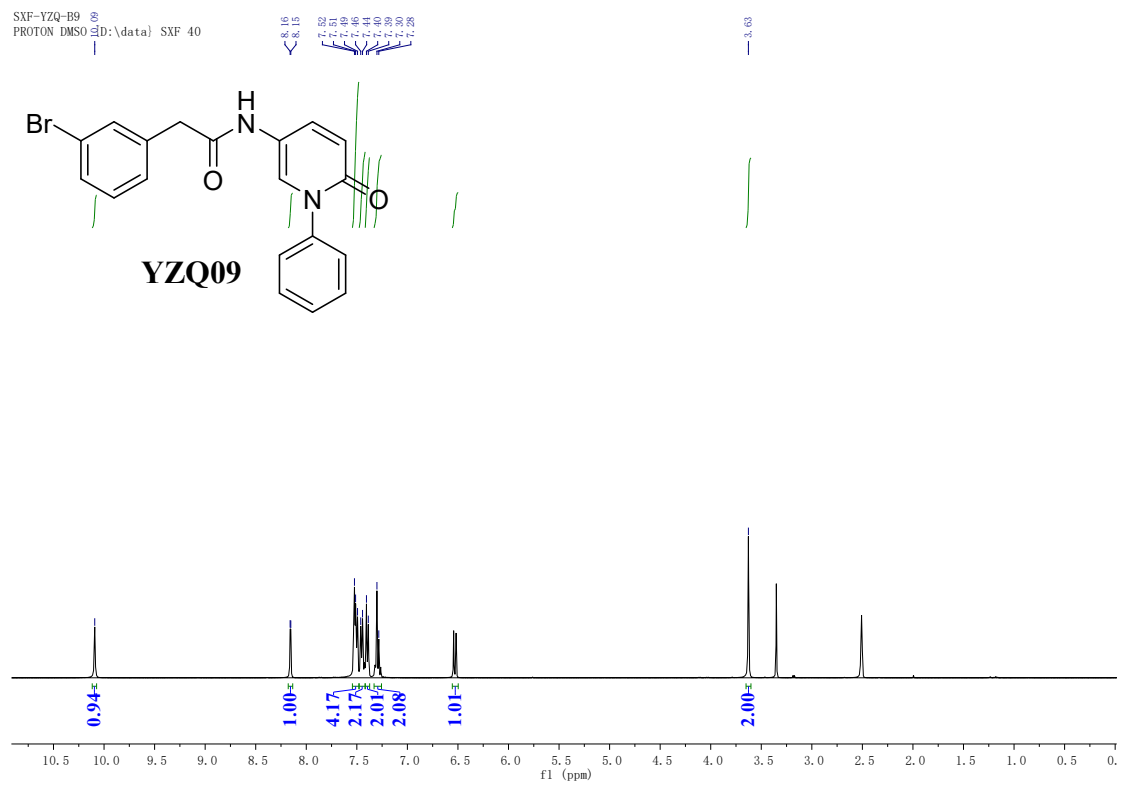
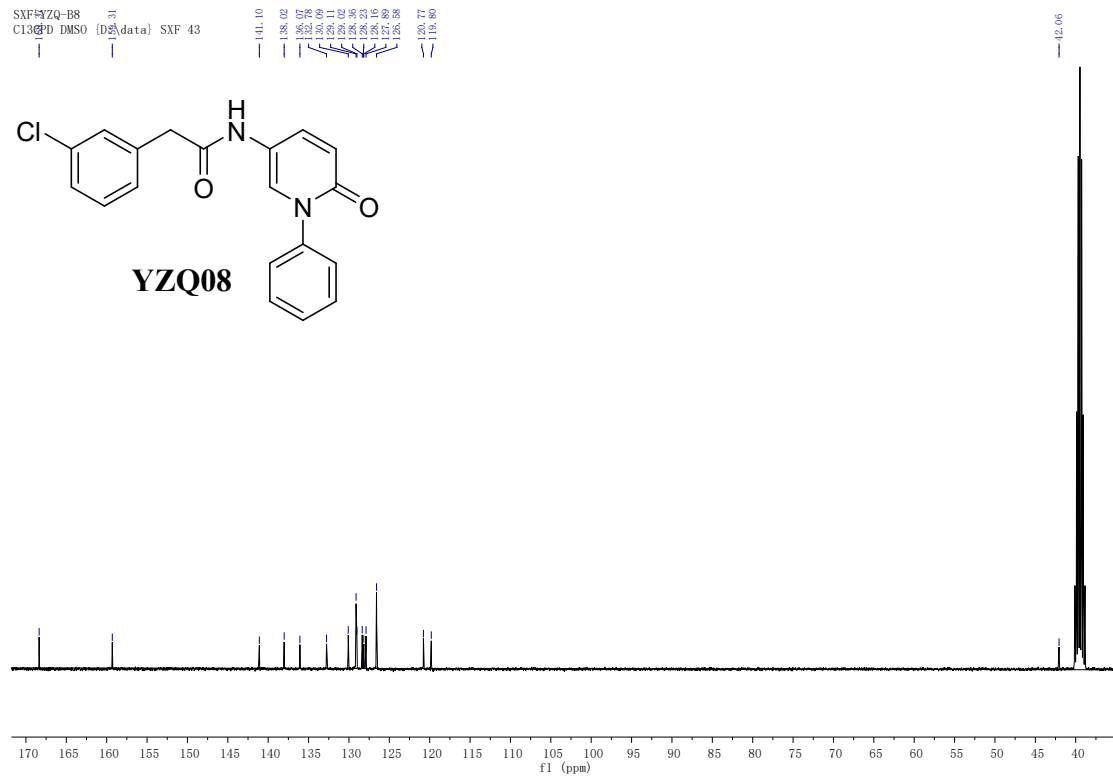


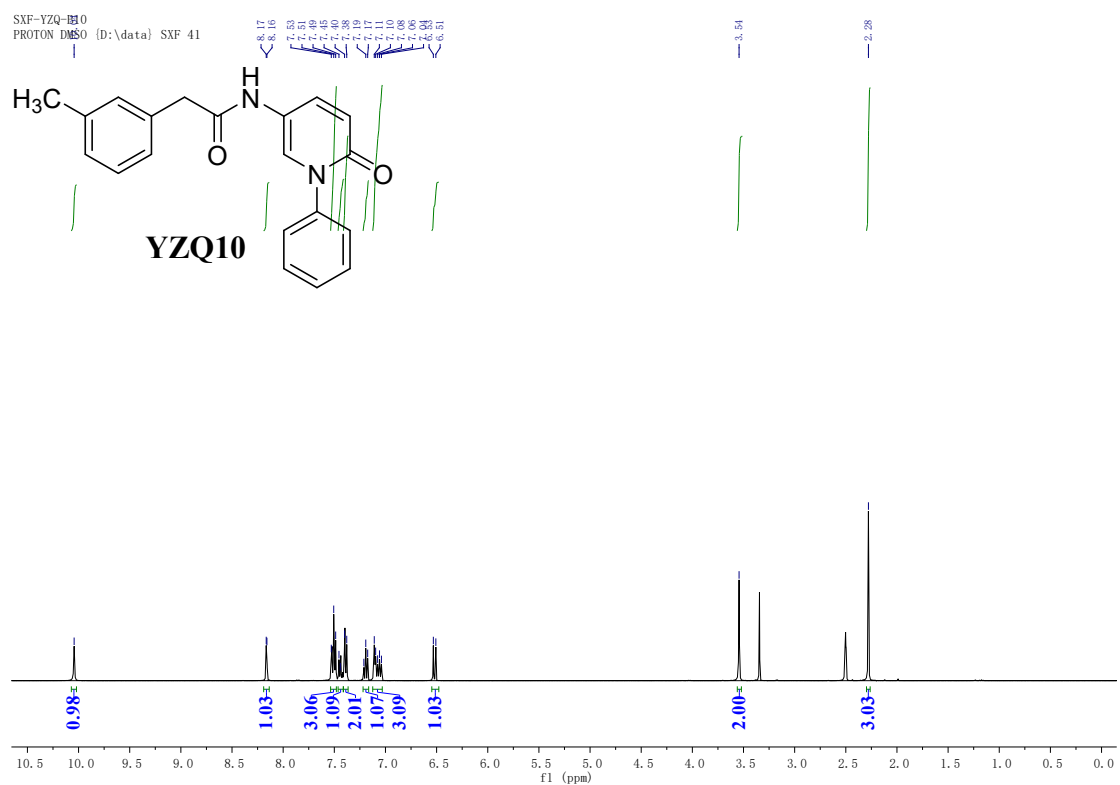
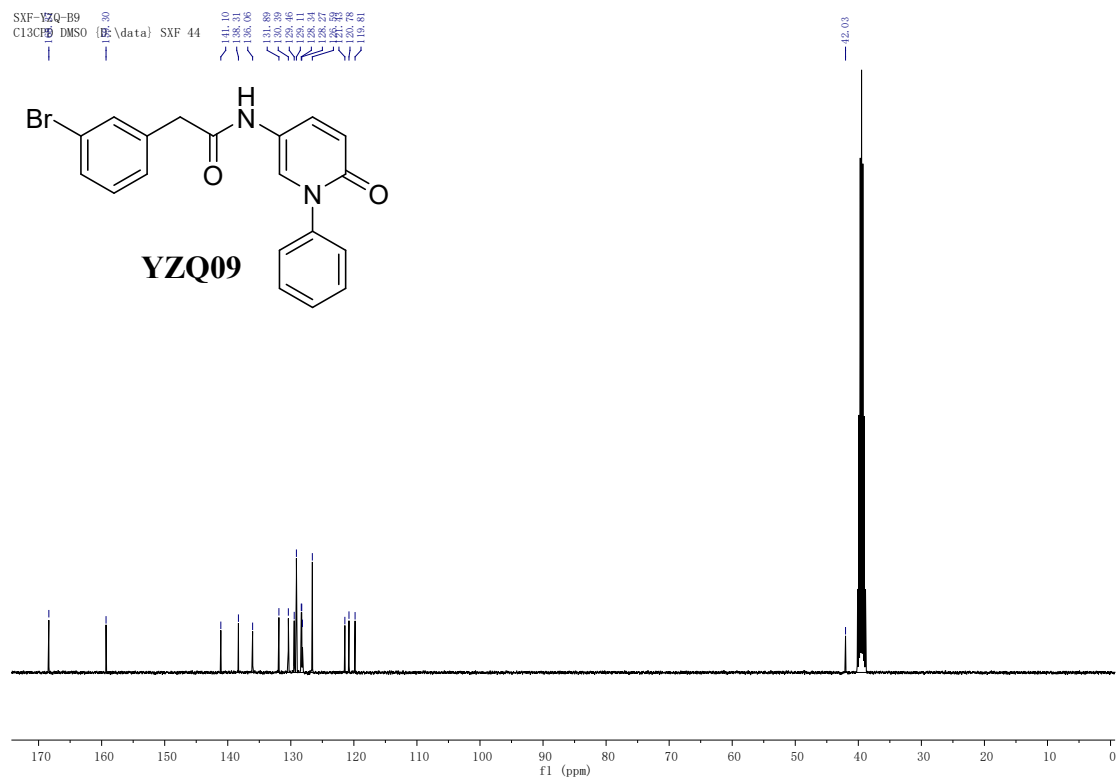
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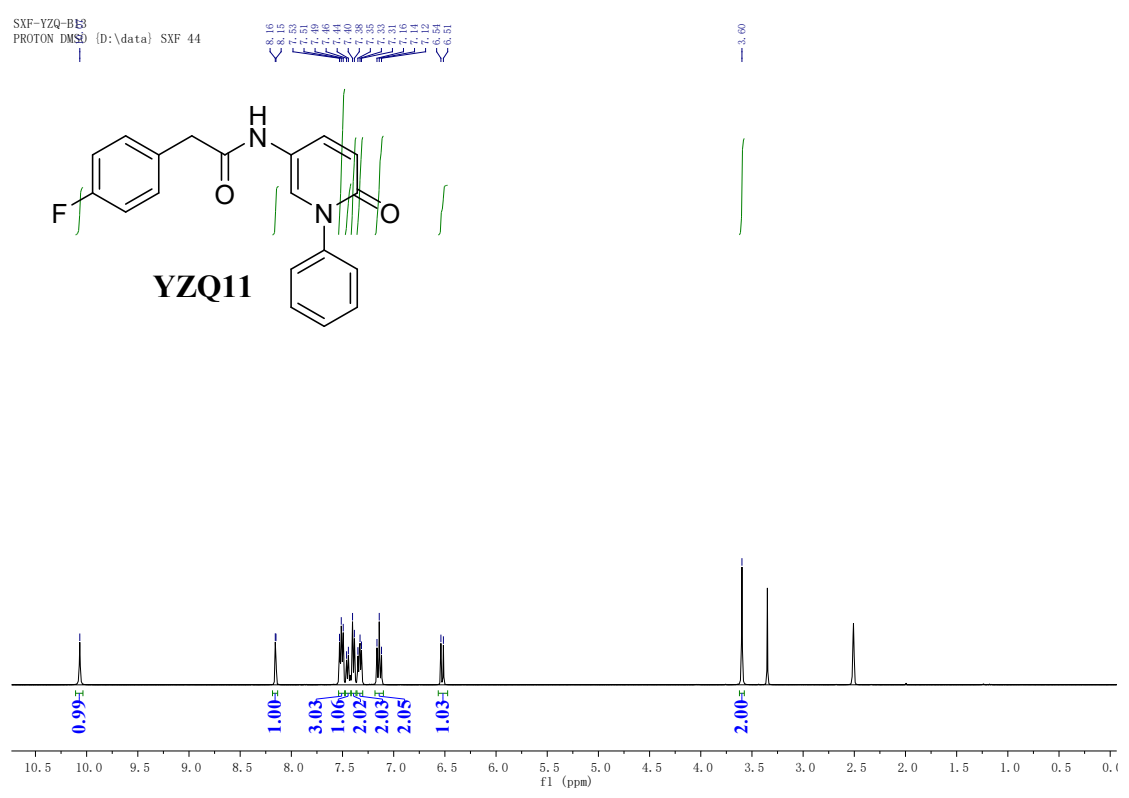
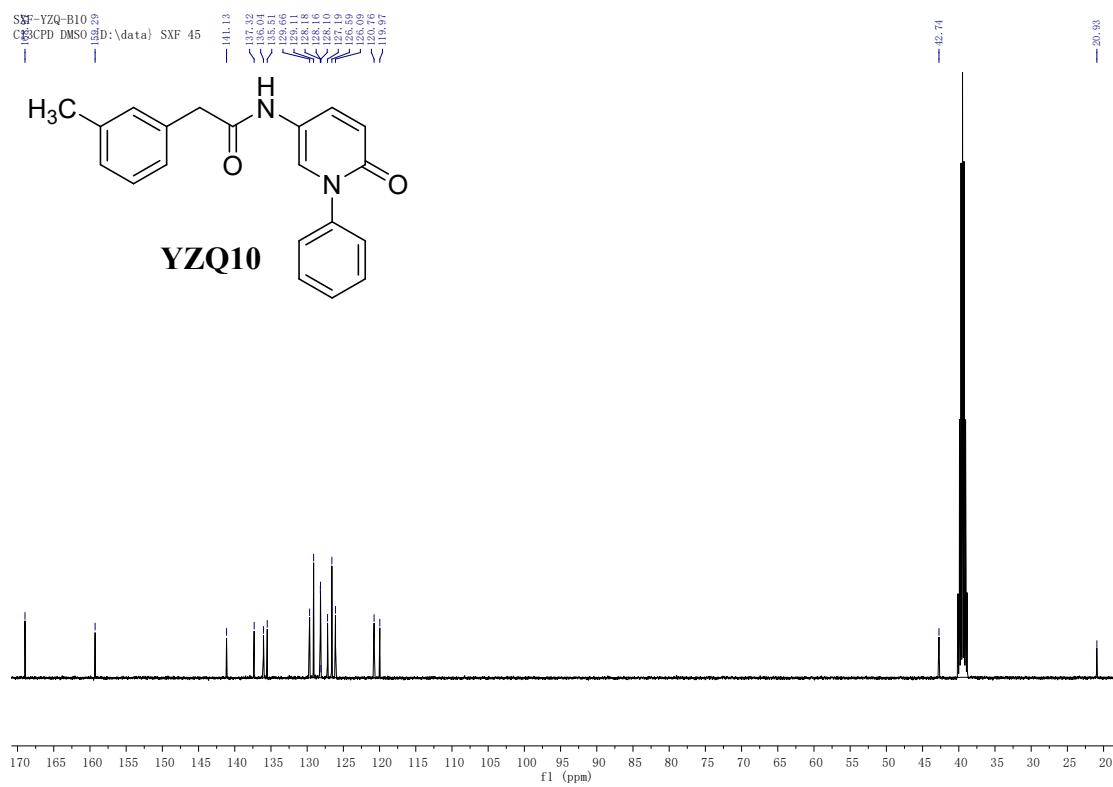
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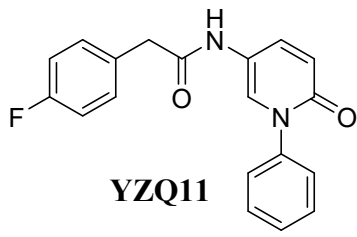
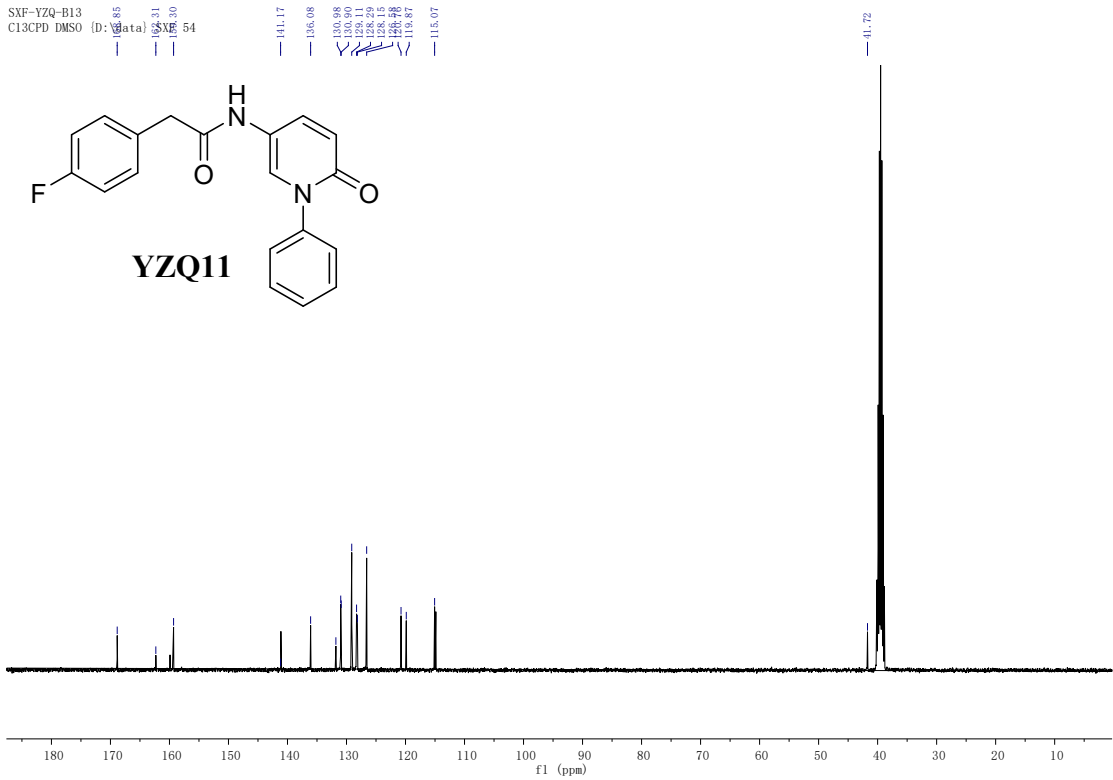




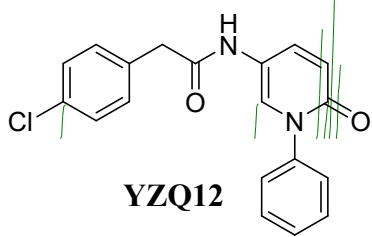
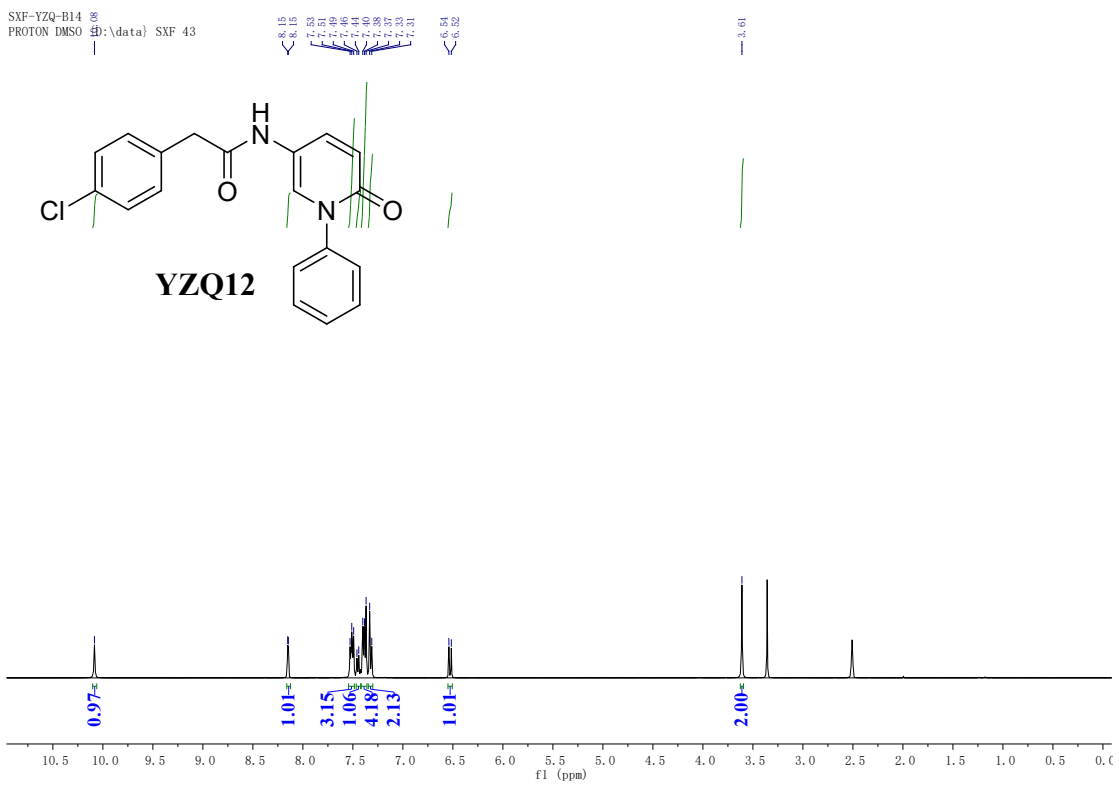


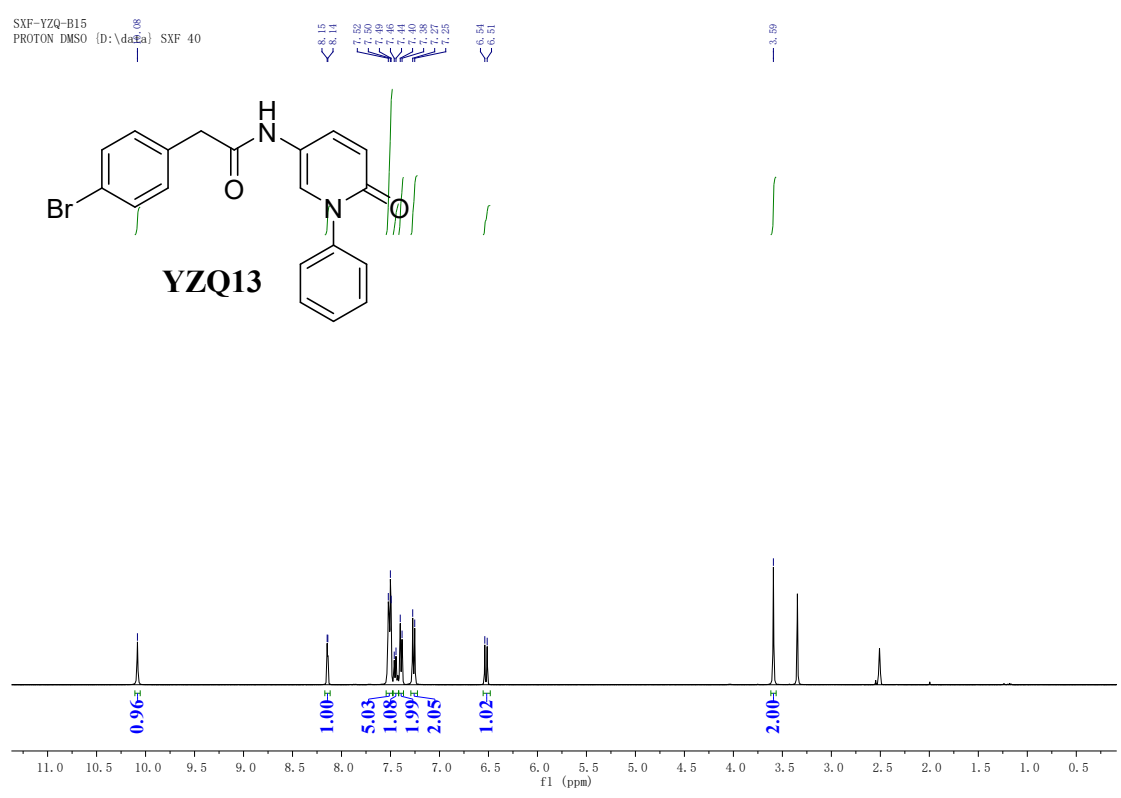
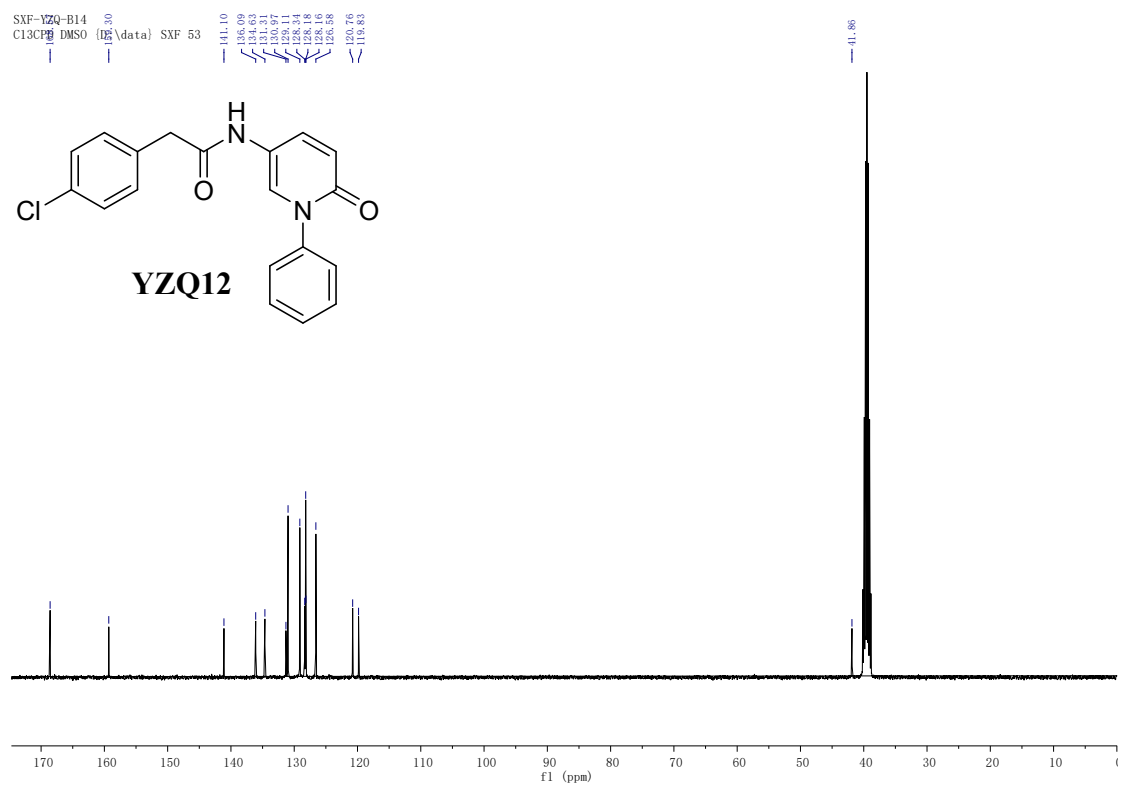


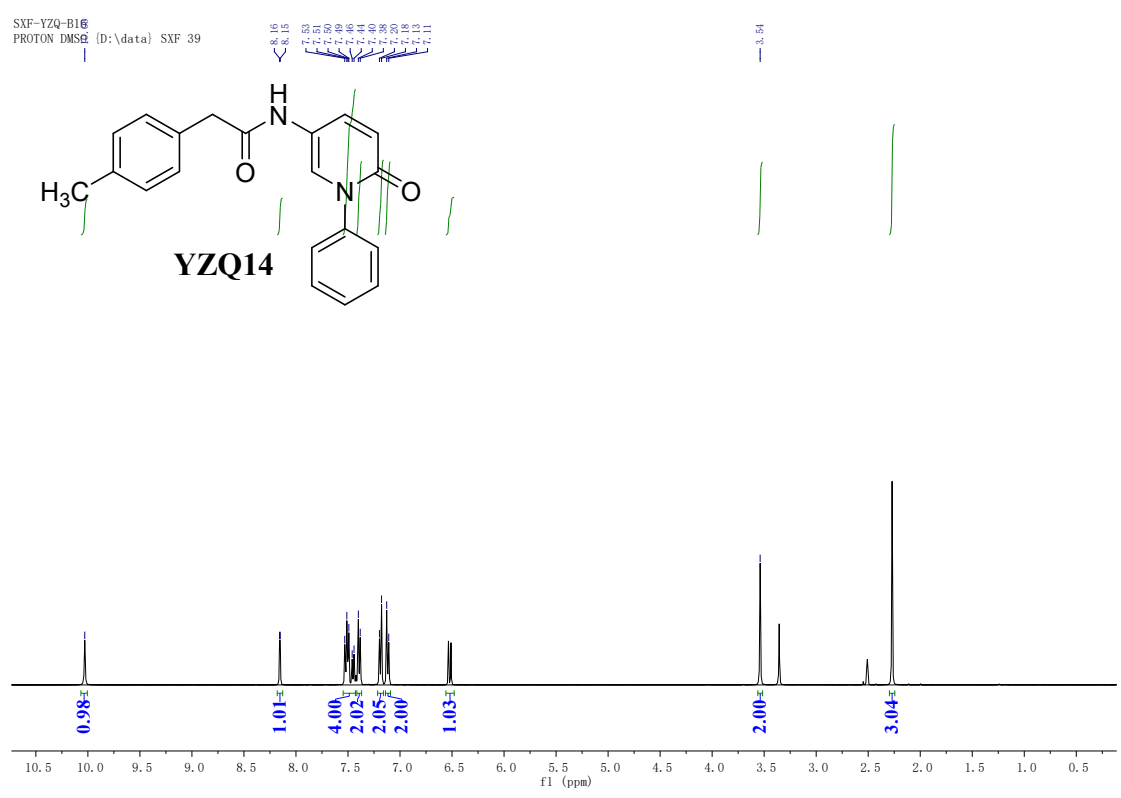
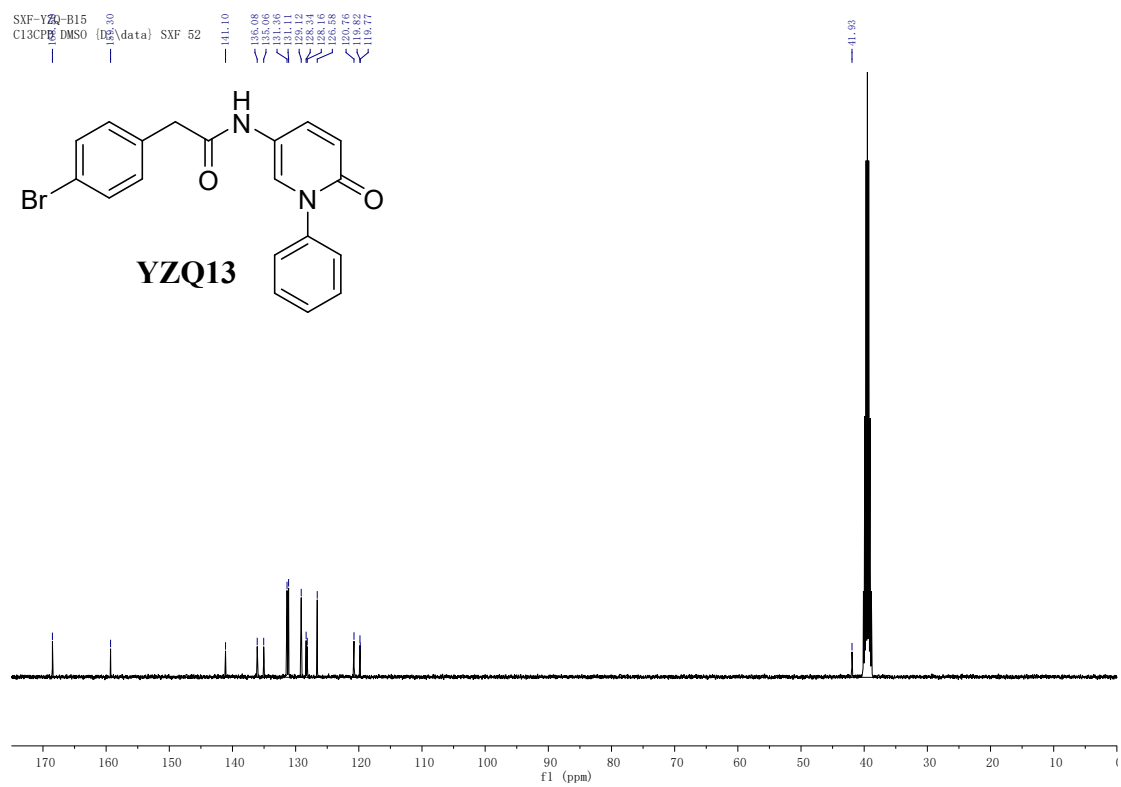
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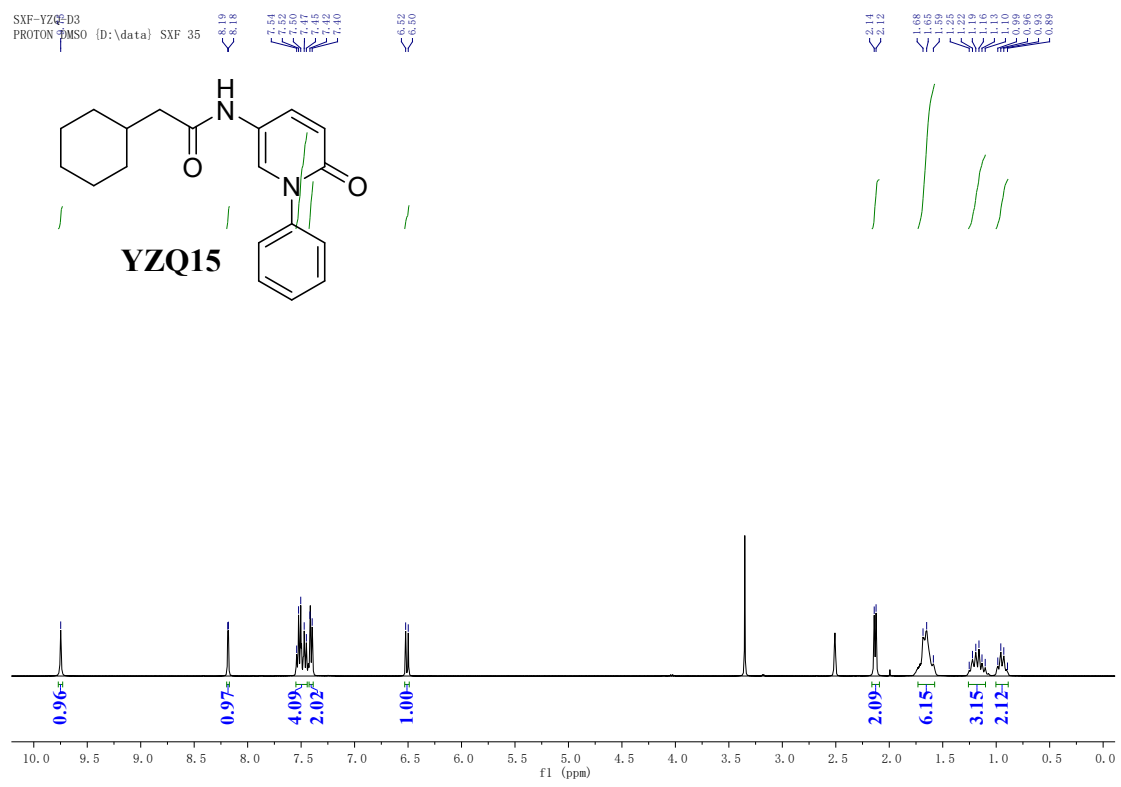
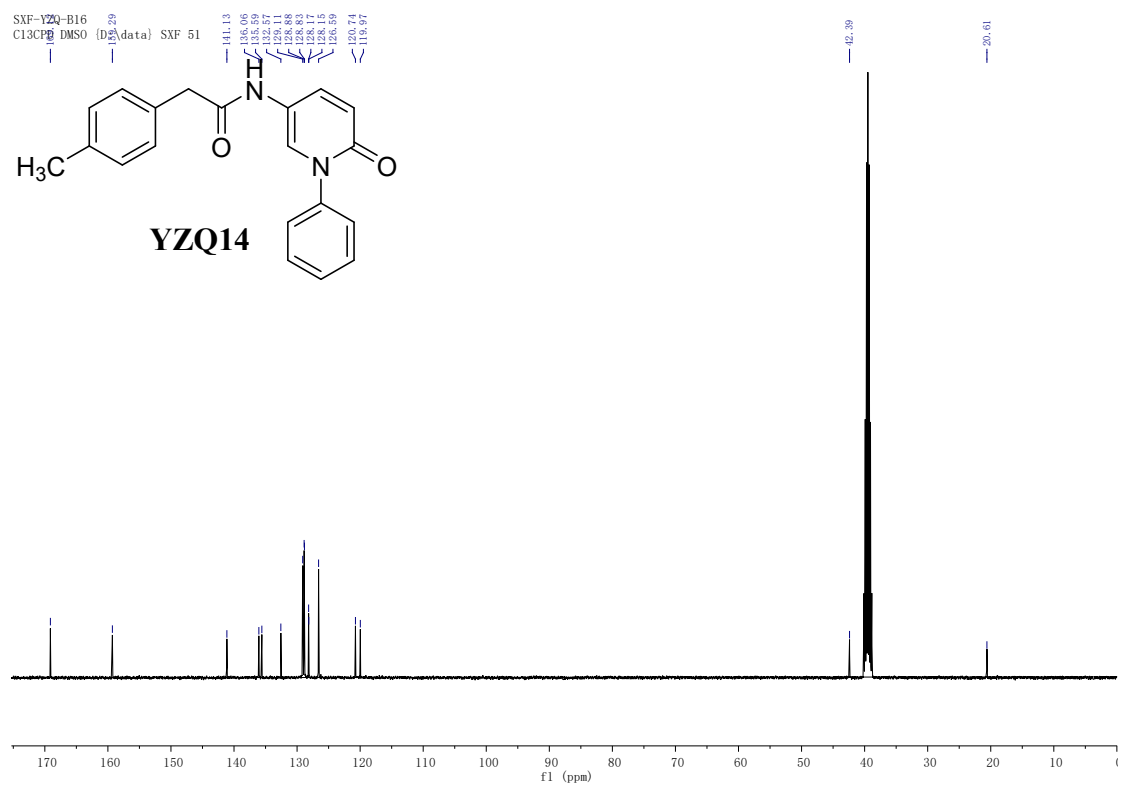
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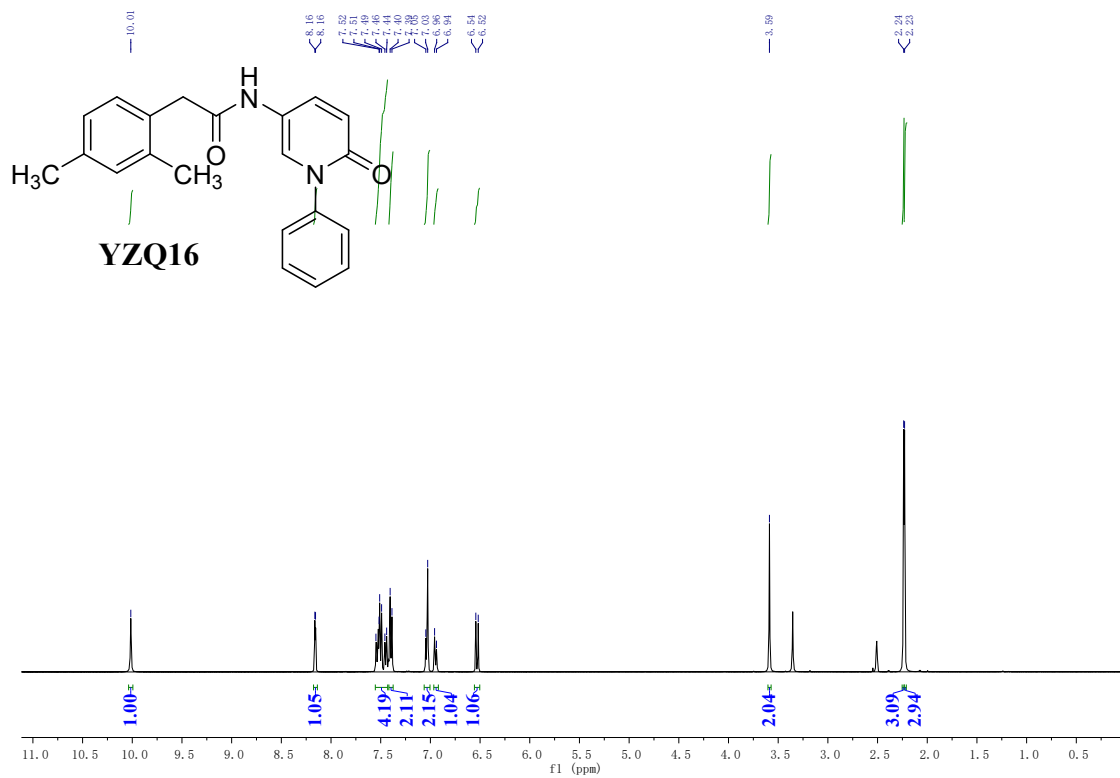
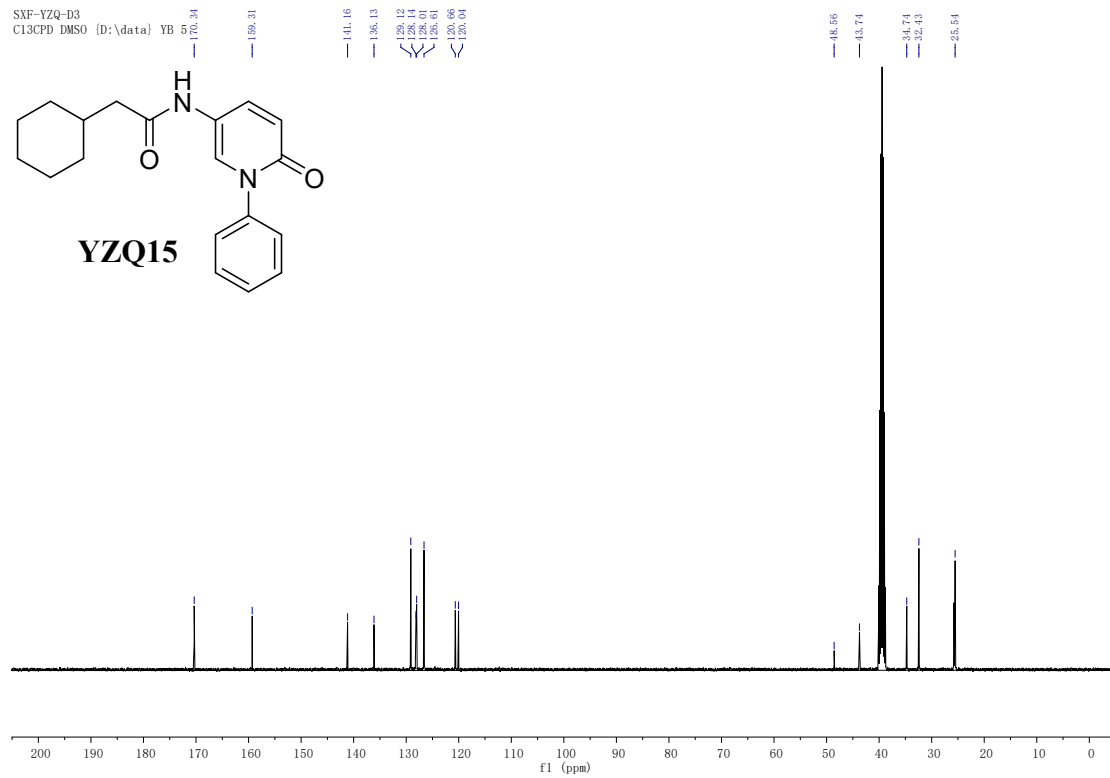






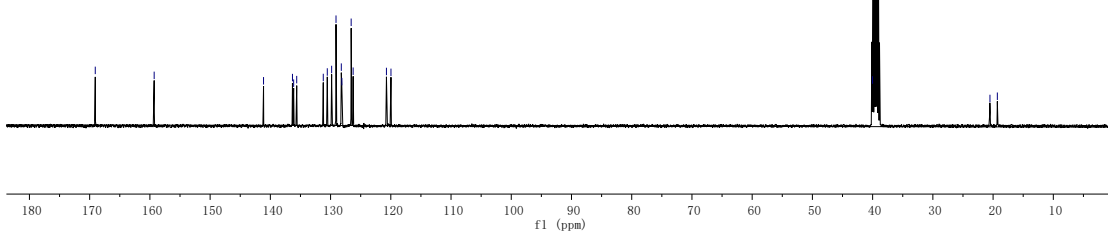
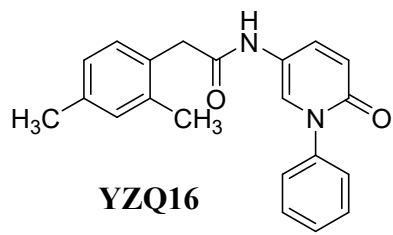






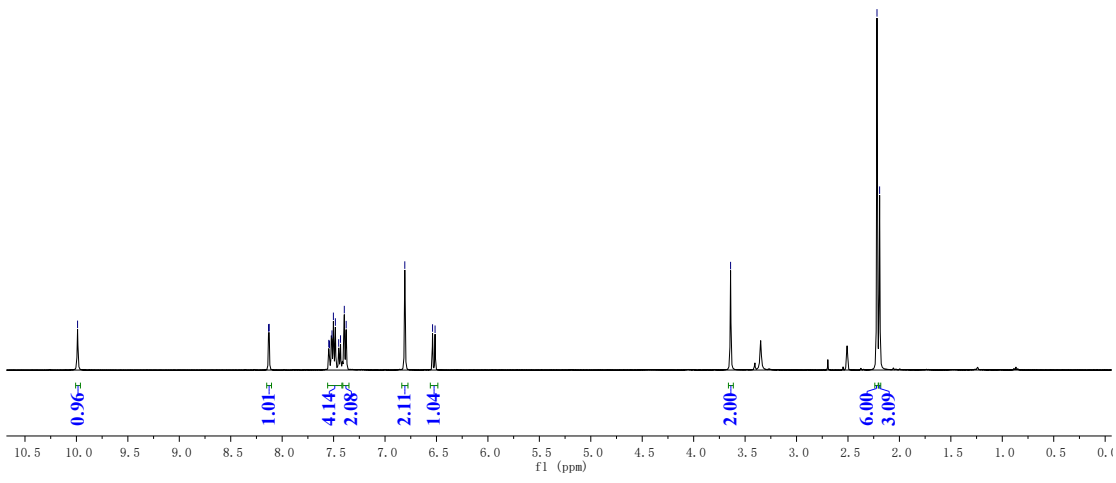
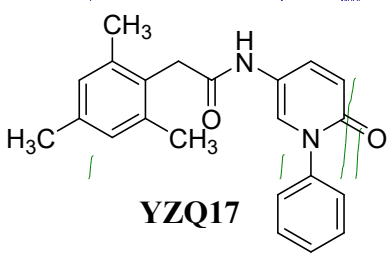
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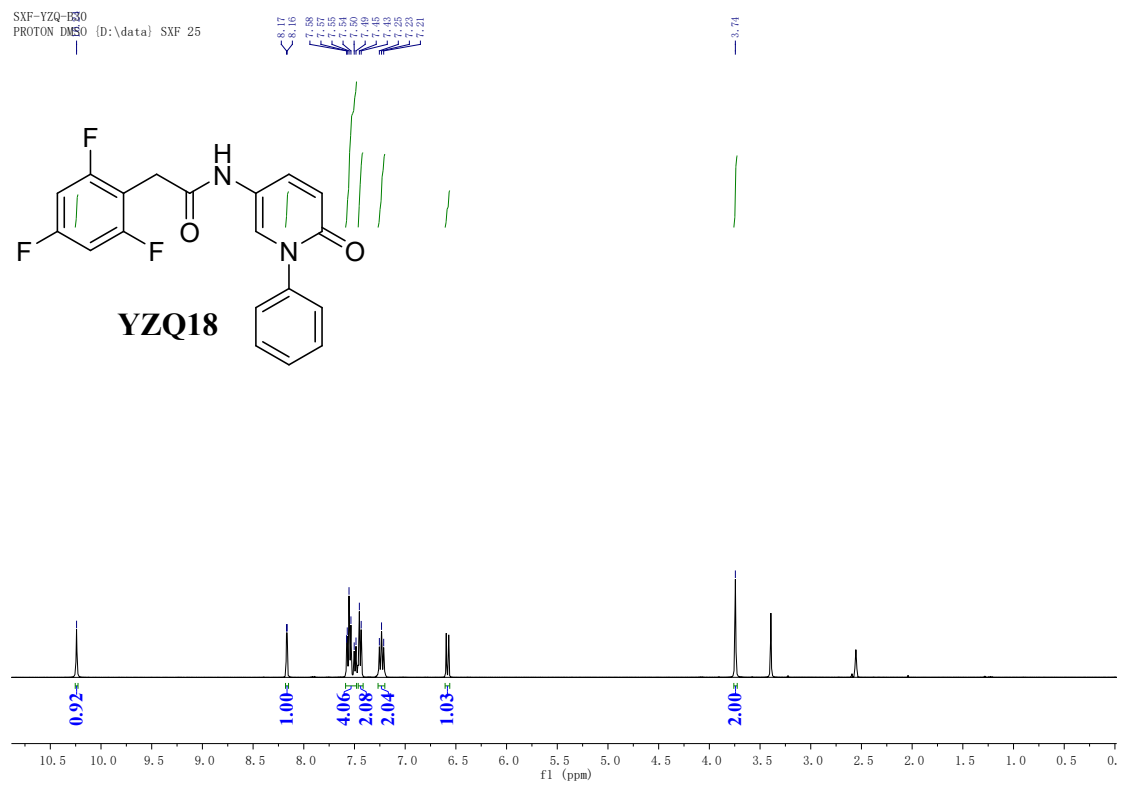
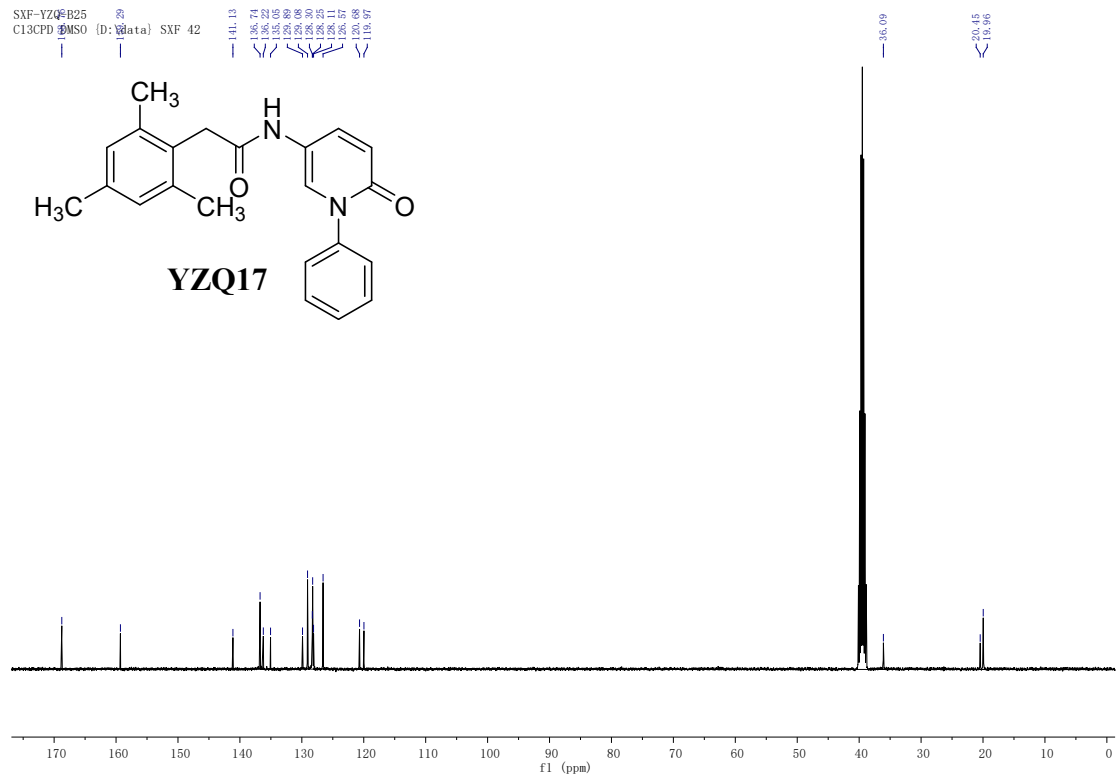
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SXF-YZQ-B25  
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