A concise synthesis of cyclobrassinin and its analogues via thiyl radical aromatic substitution

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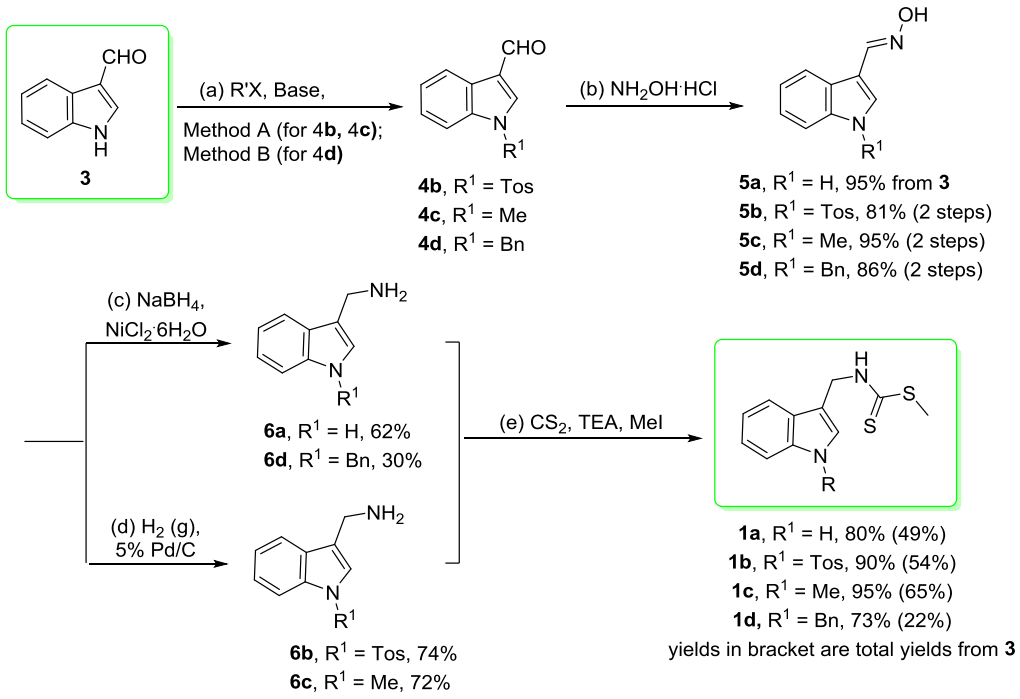
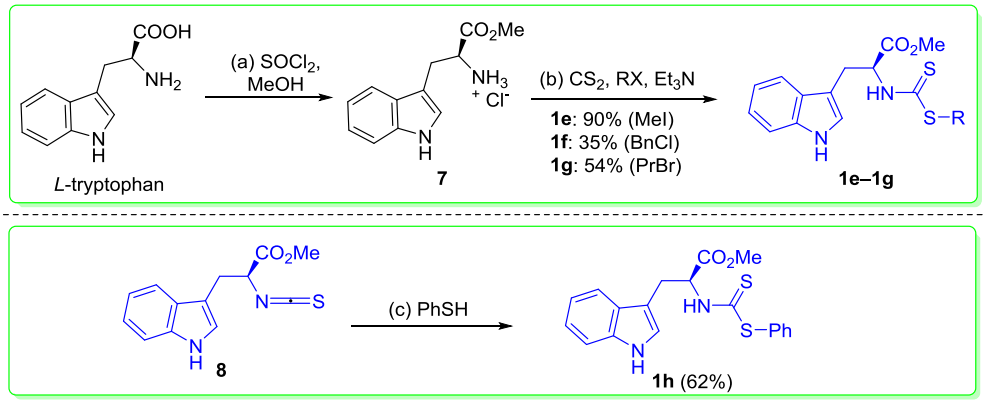
Electronic Supporting Information

Contents

1. Detailed information of Schemes 2 and 3



Scheme 2. Synthesis of brassinin (**1a**) and its analogues (**1b**–**1d**). Reagents and condition: (a) Method A: TsCl (for **4b**) or MeI (for **4c**), TBAB (0.1 equiv), NaOH (50% aq)/PhH = 1:1, 4 h; Method B: BnBr (1.1 equiv), Cs_2CO_3 (1.1 equiv), dry CH_3CN reflux 2 h. (b) $NH_2OH{\cdot}HCl$ (1.5 equiv), Na_2CO_3 (0.75 equiv), EtOH/H_2O = 10:1, r.t. 30 min. (c) $NaBH_4$ (7.0 equiv), $NiCl_2{\cdot}6H_2O$ (1.1 equiv), 0 °C, 5–10 min. (d) Pd/C (5%), H_2 (g), MeOH/HCl (36%) = 15:1, overnight. (e) CS_2 (3.0 equiv.), Et_3N (3.0 equiv), MeI (1.1 equiv), 0 °C to r.t. 1–3 h.

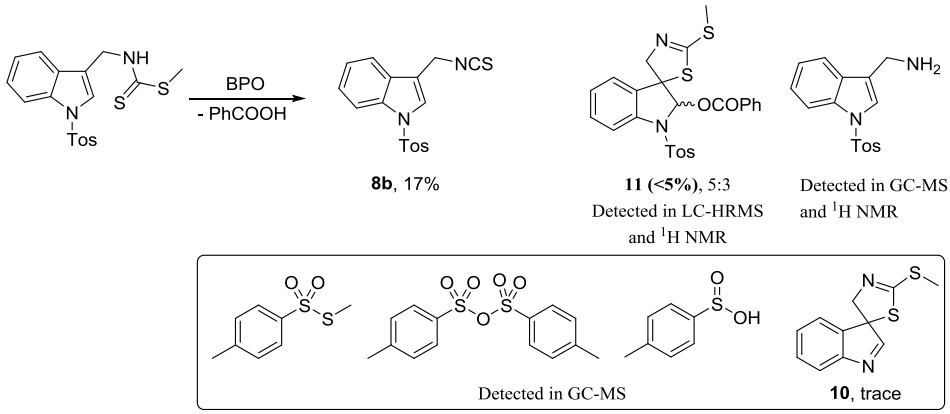


Scheme 3. Synthesis of dithiocarbamates **1e**–**1h** from *L*- indole-3-carbaldehyde. Reagents and condition: (a) $SOCl_2$ (2.2 equiv), MeOH, 0 °C then reflux overnight. (b) Na_2CO_3 (0.6 equiv), MeOH/H_2O = 10:1, 0 °C, then Et_3N (2.0 equiv), MeI (2.0 equiv) or BnCl (1.05 equiv) or *n*-PrBr (2.0 equiv), 0 °C to r.t. (traced by TLC). (c) PhSH (1.5 equiv), Et_3N (1.0 equiv), dry PhMe, reflux 8 h.

2. Detailed information of the reaction of 1b with BPO

The reaction procedure: Under the nitrogen protection, dithiocarbamate **1b** (117.2 mg, 0.3 mmol) and benzoyl peroxide [109 mg, 0.45 mmol was dissolved in 1,2-dichloroethane (1.5 mL). The reaction mixture vessel was put into a pre-heated oil bath to reflux for 2 h. After cooling to room temperature, the reaction system was washed with satuarated $NaHCO_3$ aqueous solution (2 mL) to remove benzoic acid. The aqueous phase was extracted with 1,2-dichloroethane (2 × 9 mL) and then dried over anhydrous Na_2SO_4. We then analysed the reaction system through GC-MS, LC-MS and ^{1}H NMR analyses.

The major products are listed below (Scheme 1S):



Scheme S1. The reaction of **1b** with BPO

Although we didn't obtain the desired cyclobrassinin devirative **2b** (0%), instead, an interest spirobrassinin derivative **11** was detected in both HRMS and ^{1}H NMR albeit with very low yield. We tried our best to isolated and purified, but finally failed not only for the low yield, but the other impurities with silimar polarity. The 'purest' ^{1}H NMR is shown below (Figure S1): There are 2 pairs of doublets from 3.7 to 4.6 ppm with coupling constant of 15.3 Hz, identifying that a spirobrassinin was generated.

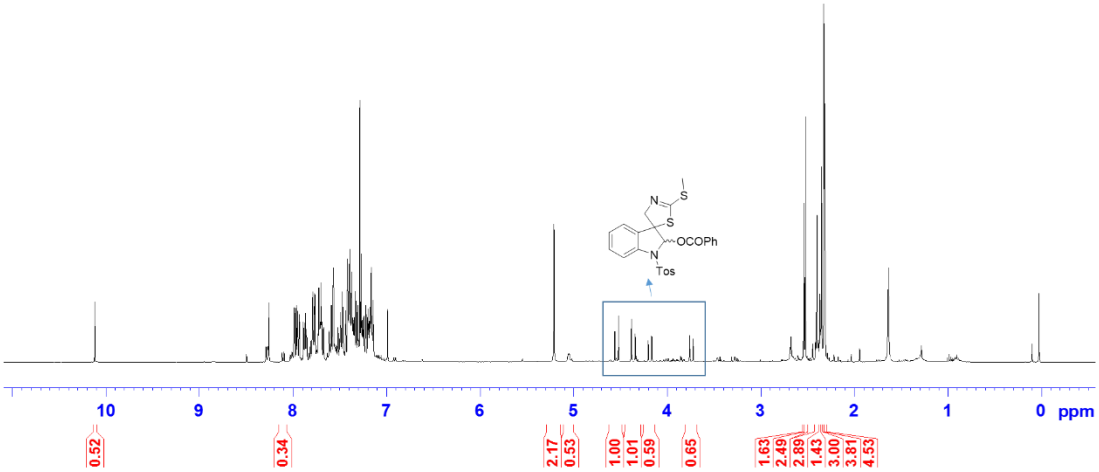


Figure S1 ^{1}H NMR of **11** (not pure)

LC-HRMS was then measured to further identify the structure (Figure S2). The calculated ion for $[M+H]^+$ of **11** is 511.0814, and the found are 511.0816 and 511.0823, respectively, at 10.16 and 10.26 min (two pairs of diastereomers), perfectly matched the structure.

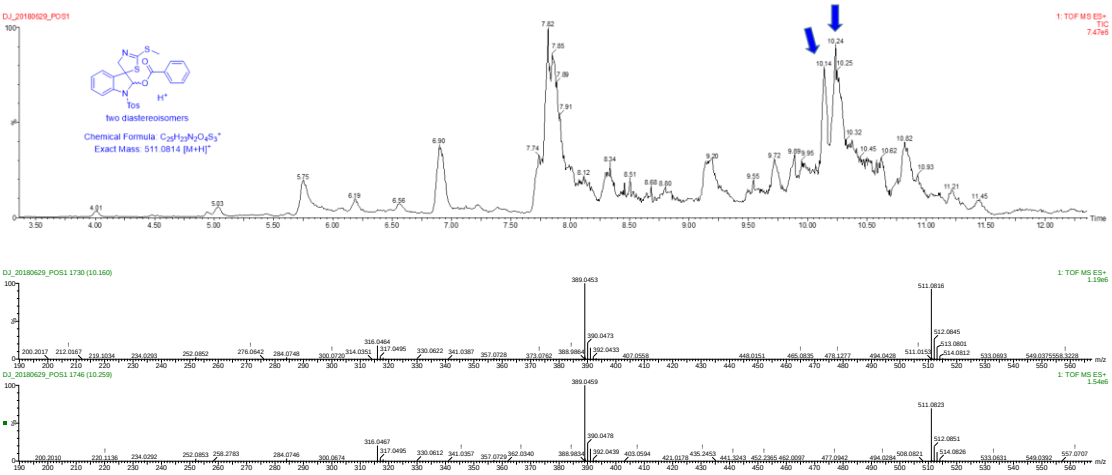
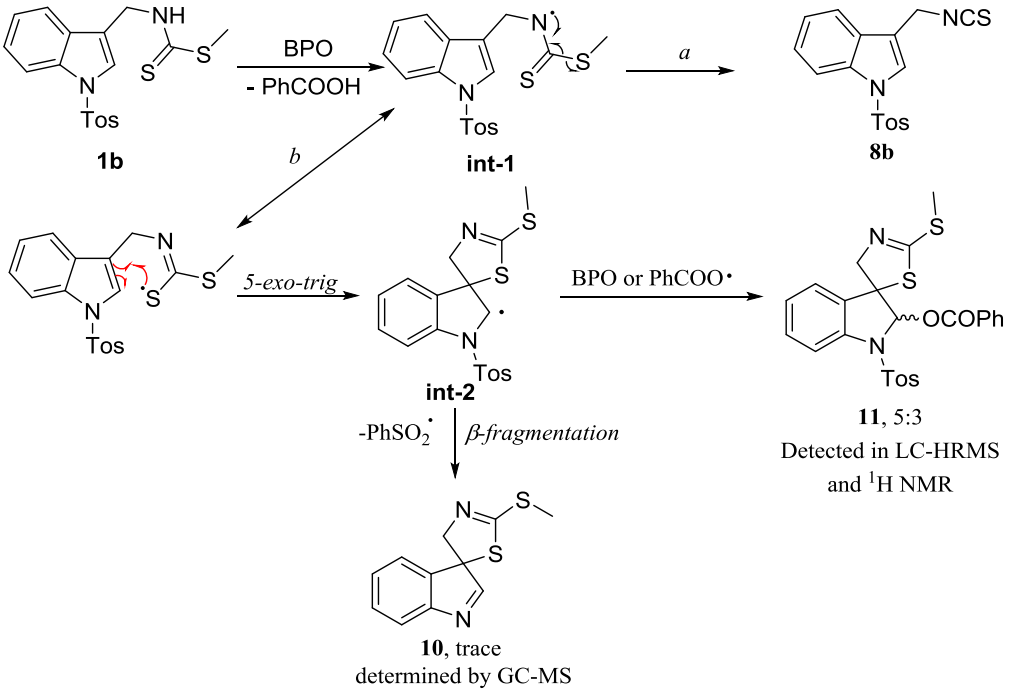


Figure S2 LC-^{1}H NMR of **11** (not pure; ESI, postive mode)

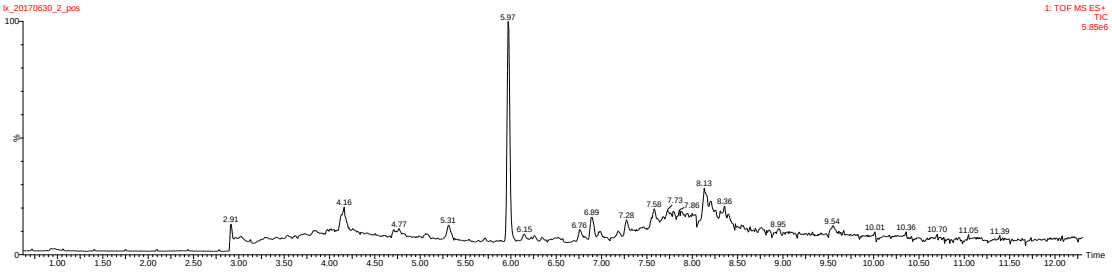
The reaction process is briefly listed in Scheme S2. After abstracting a hydrogen by BPO, **1b** generates a radical intermediate **int-1**. There are two possible way for **int-1**. The one is the β-cleavage of C-S bond to afford **8b** (*route a*), and the other is the thiyl-radical-mediated 5-*exo*-trig cyclization to afford **int-2** (*route b*), which then abstracts a benzoyloxy radical to obtain the desired spirobrassinin derivative **11**. Besides that, **int-2** can also undergo a β-cleavage of C-S bond to lose a tosyl radical to afford the cyclic imine **10**.



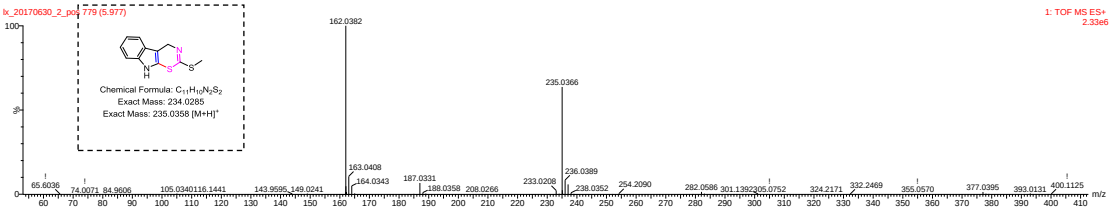
Scheme S2 The reaction process for the formation of **8** and **11**

3. Copies of LC-HRMS and ^{1}H-NMR spectra for the reaction system in the synthesis of cyclobrassinin

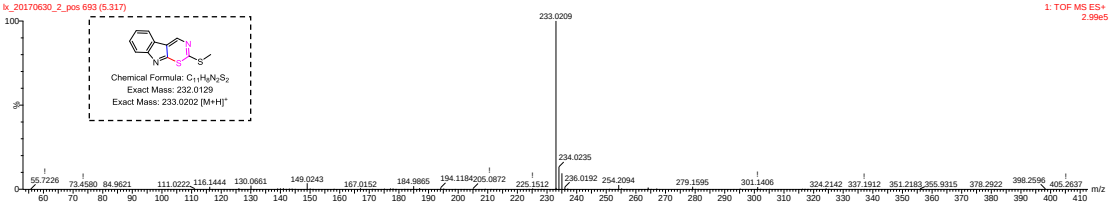
LC-HRMS system (ESI positive)



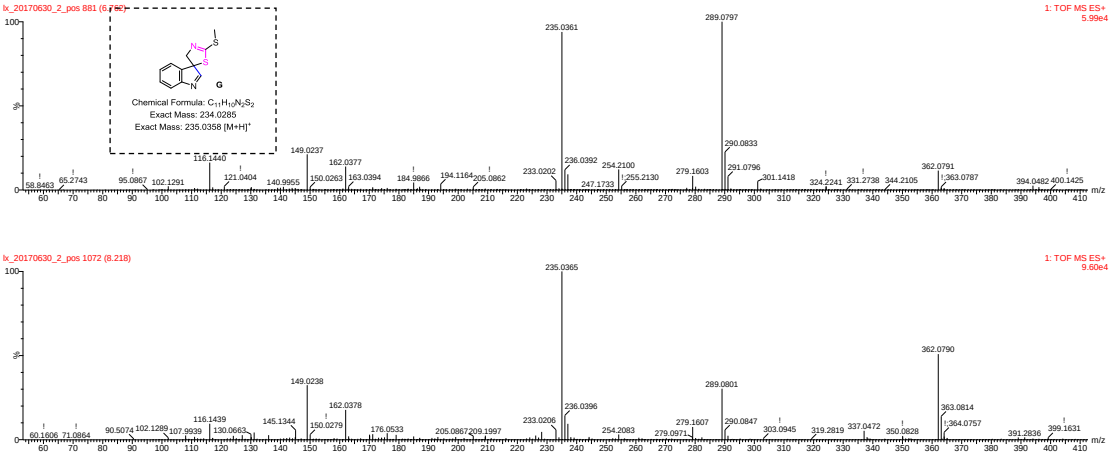
5.97 min:



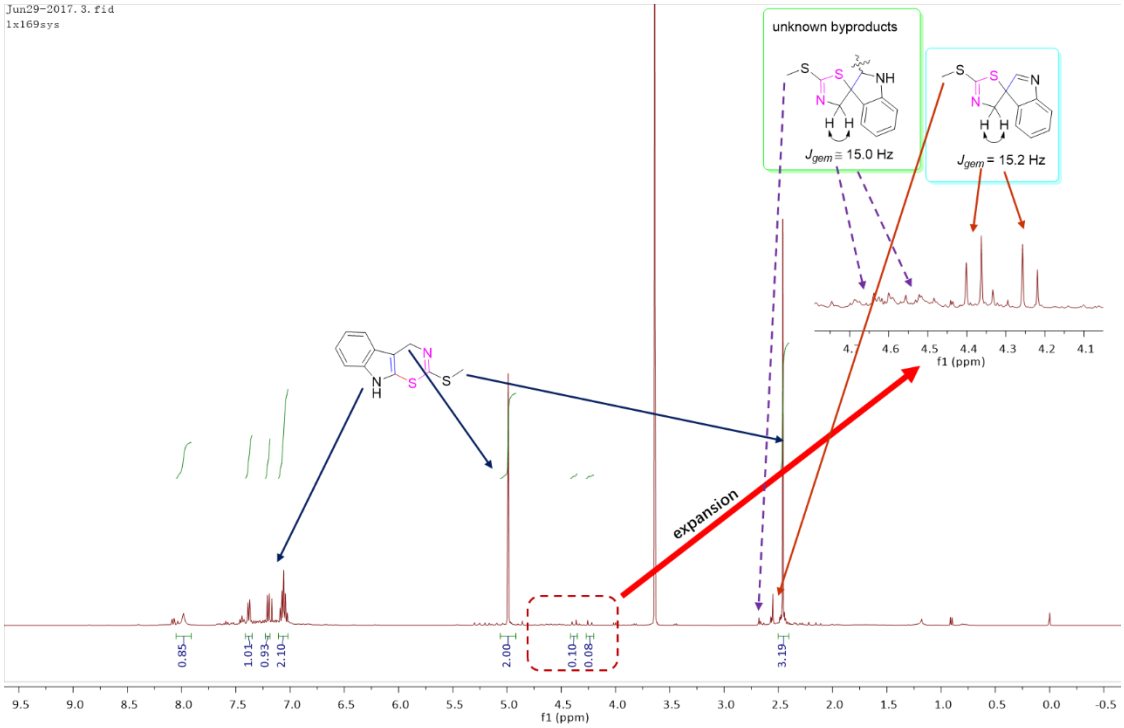
5.31 min:



6.76 min to 8.21 min: there are several peaks containing *m/z* 235 as the base peaks in LC, which might be the intermediate **G** (Scheme 4).

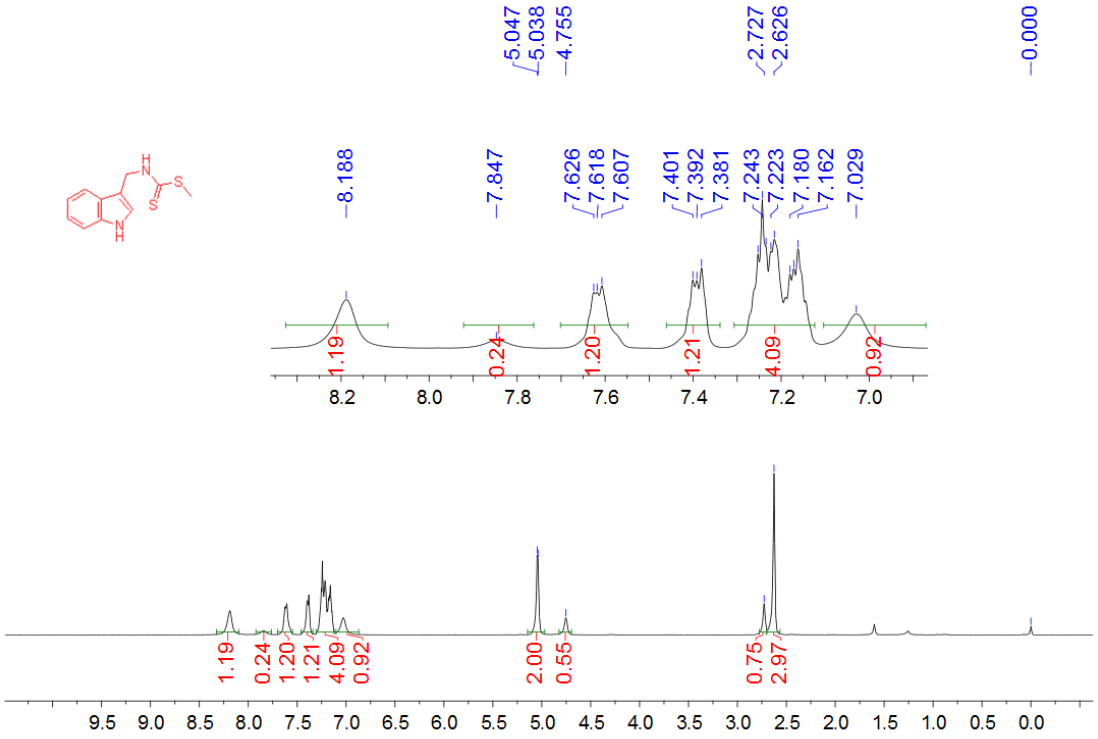


4. Copy of ^{1}H-NMR spectrum for the reaction of 1a and BPO (after washing with saturated aqueous Na_2CO_3 to remove benzoic acid)

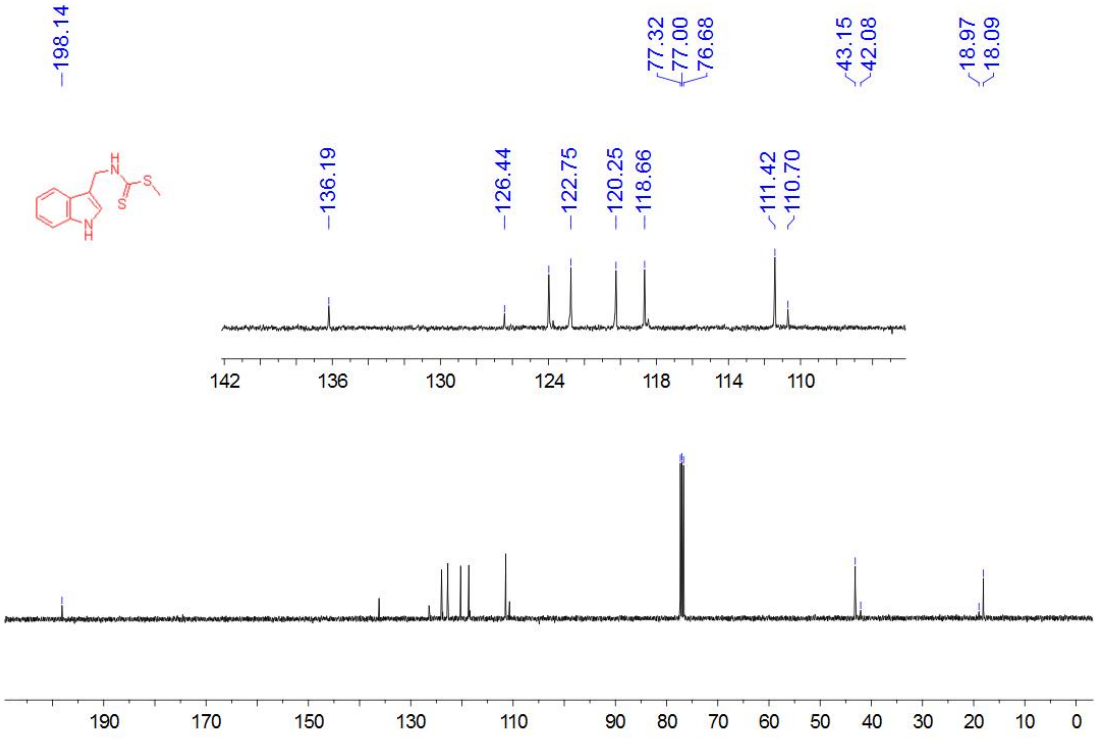


5. Copies of ^{1}H and ^{13}C-NMR spectra of dithiocarbamates 1

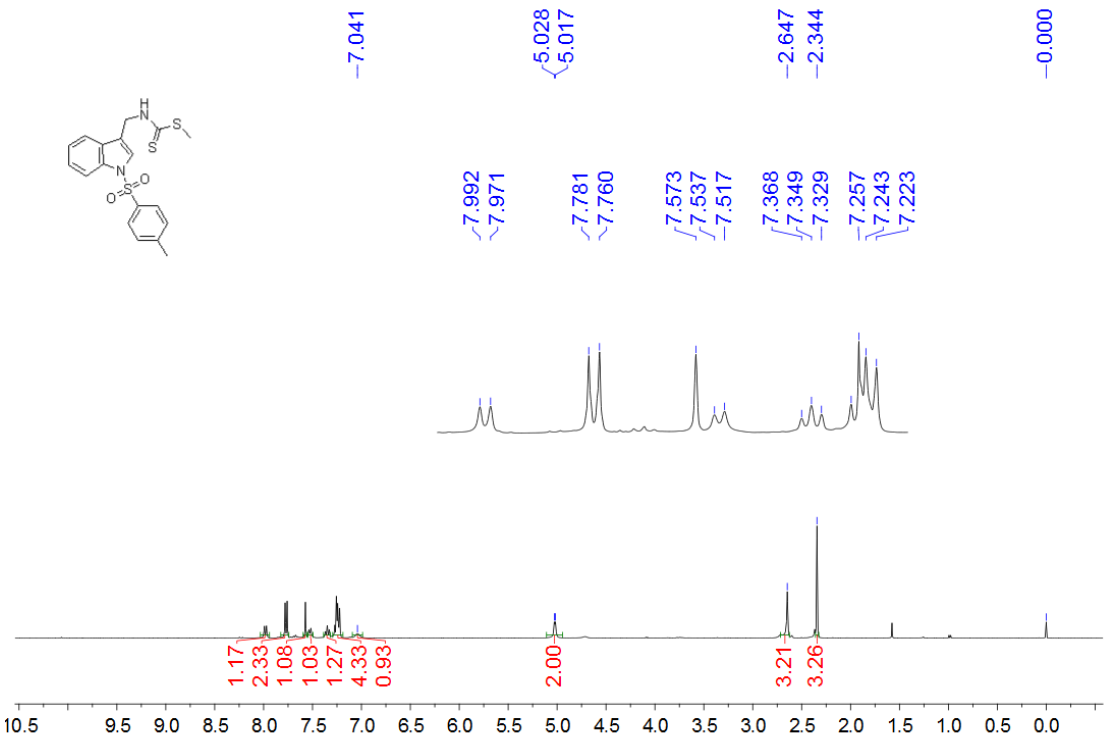
^{1}H NMR (400 MHz, $CDCl_3$) of **1a**



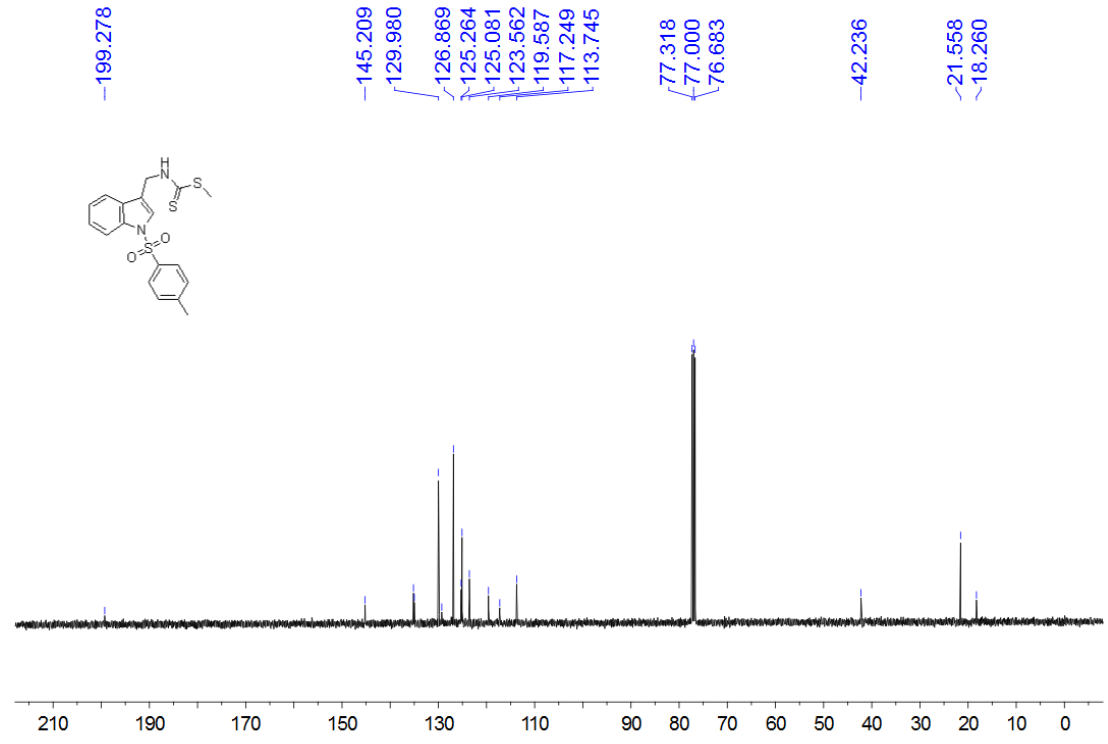
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1a**



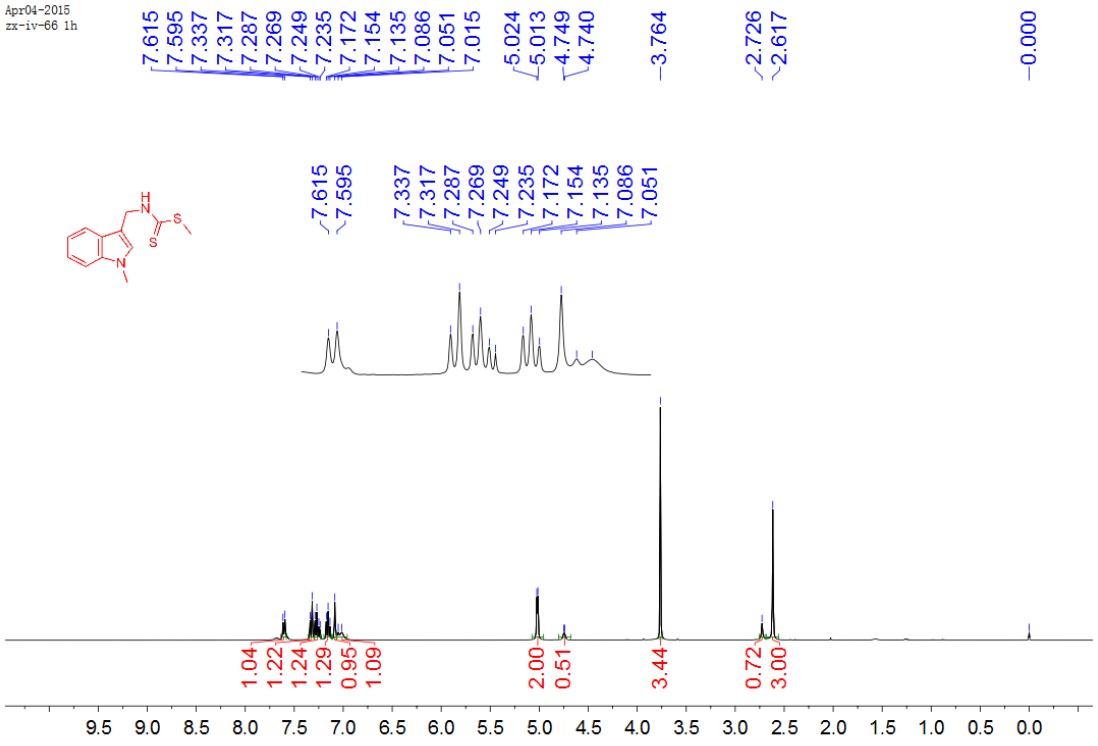
^{1}H NMR (400 MHz, $CDCl_3$) of **1b**



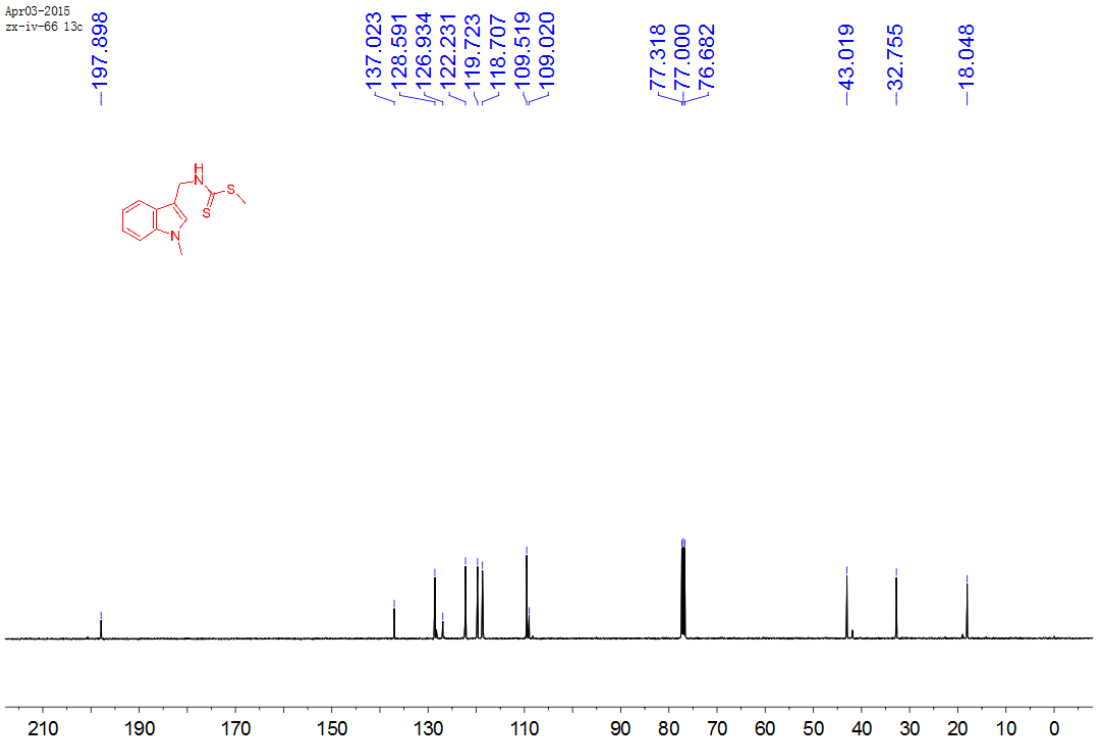
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1b**



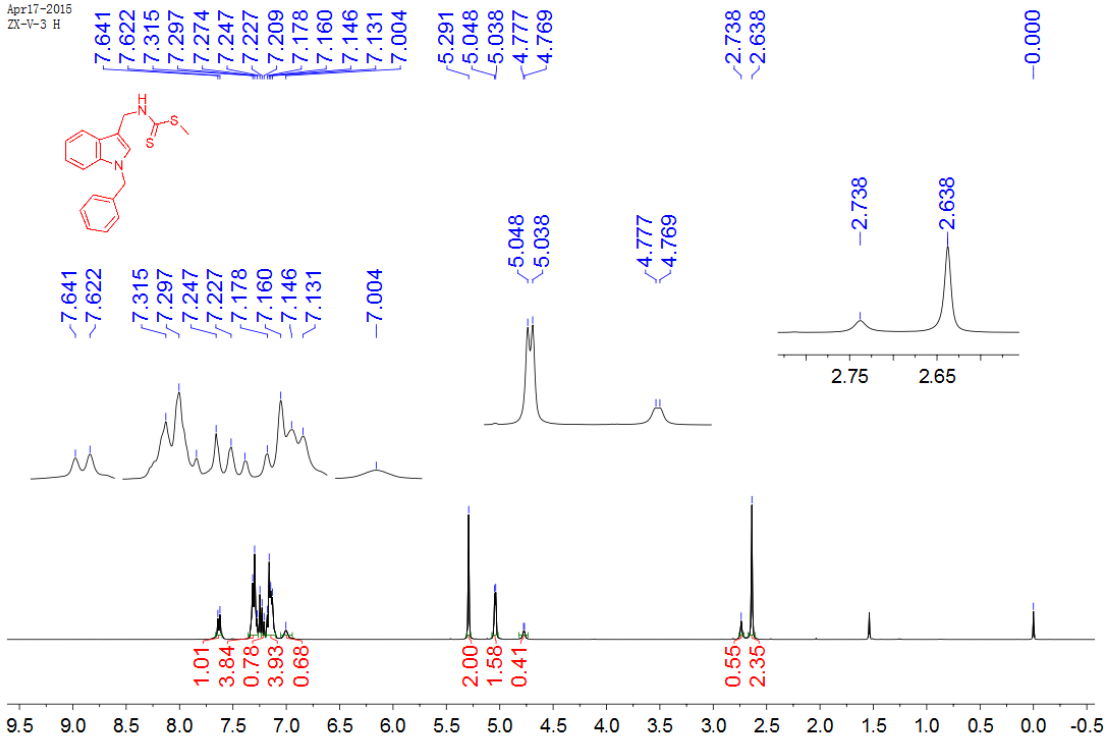
^{1}H NMR (400 MHz, $CDCl_3$) of **1c**



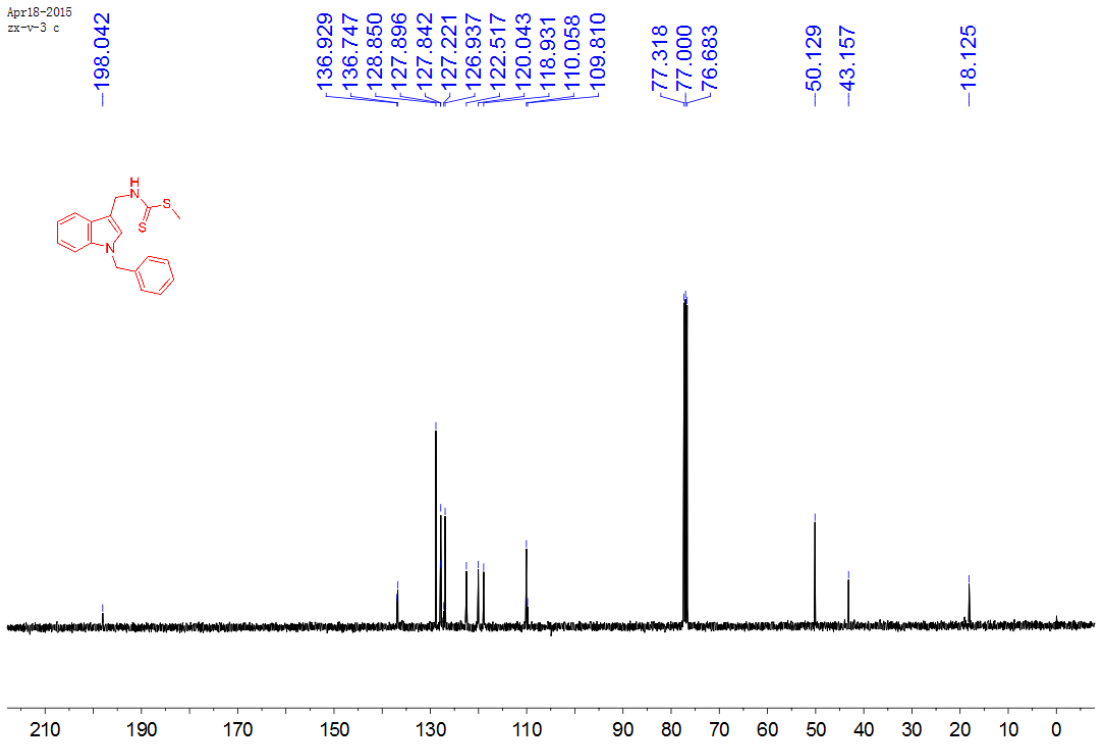
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1c**



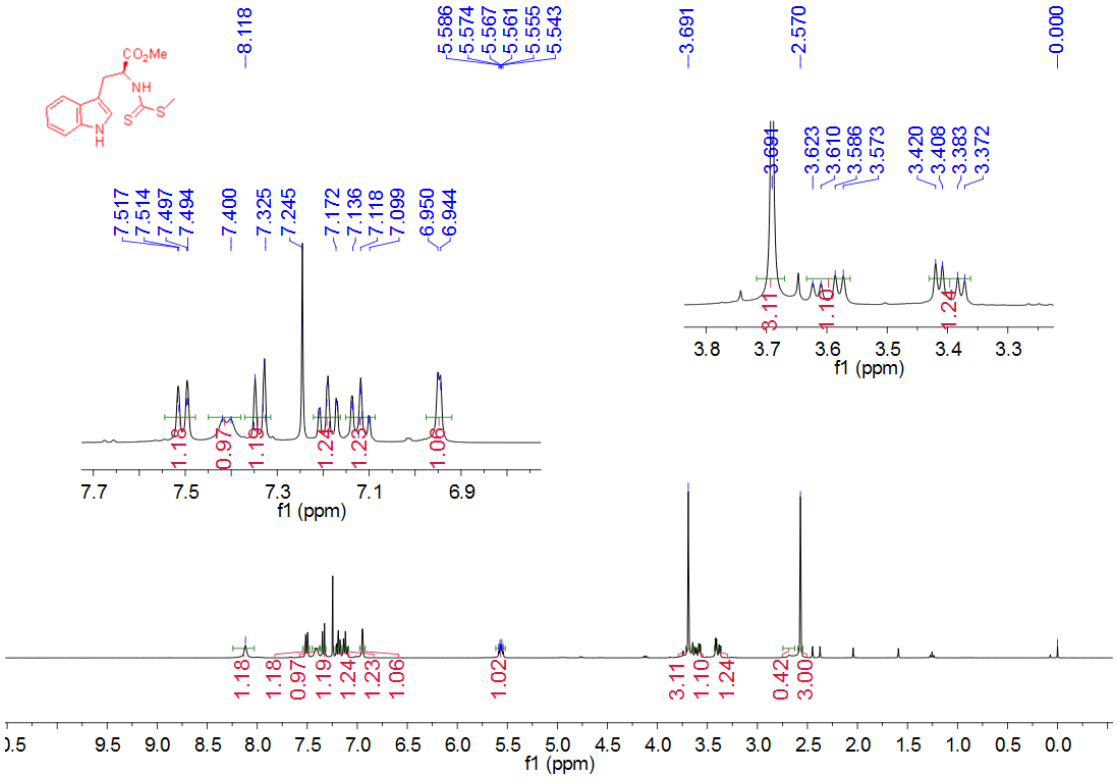
^{1}H NMR (400 MHz, $CDCl_3$) of of **1d**



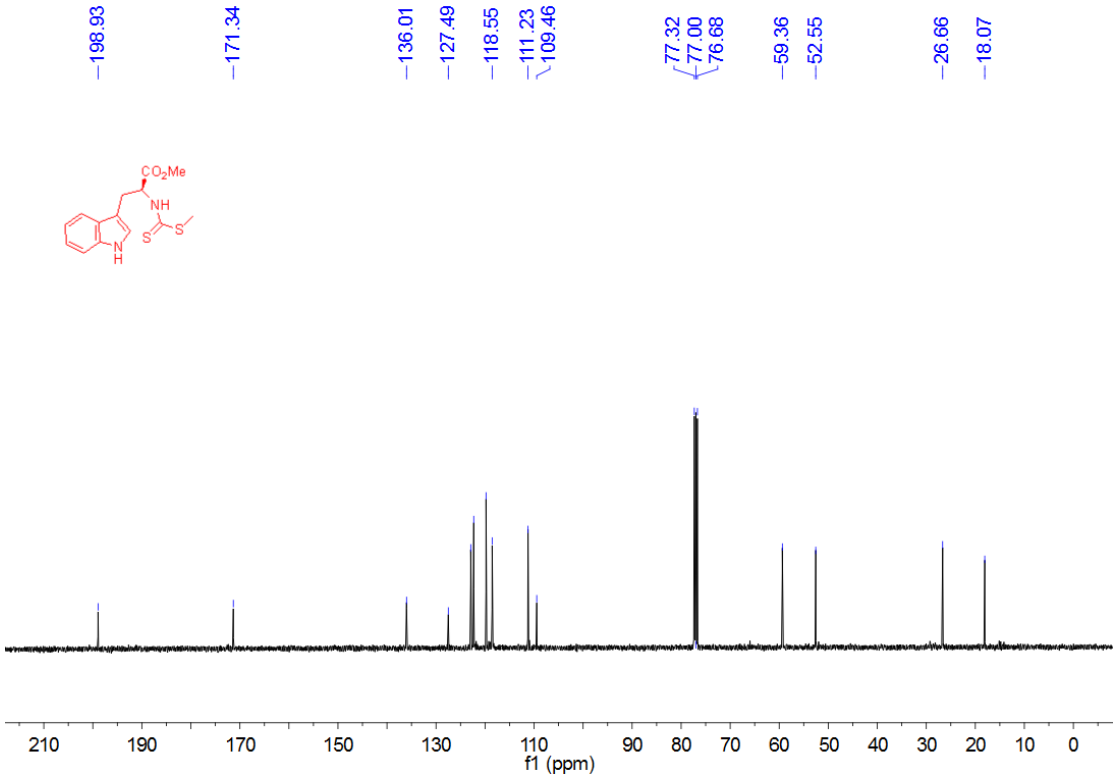
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1d**



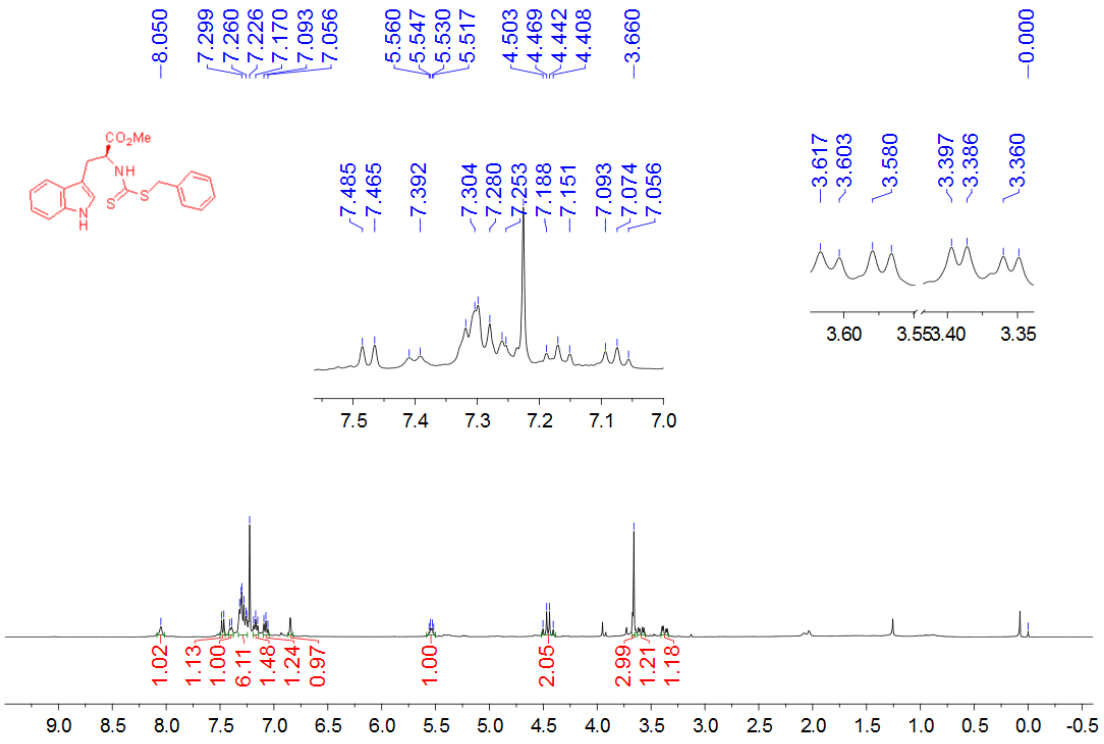
^{1}H NMR (400 MHz, $CDCl_3$) of **1e**



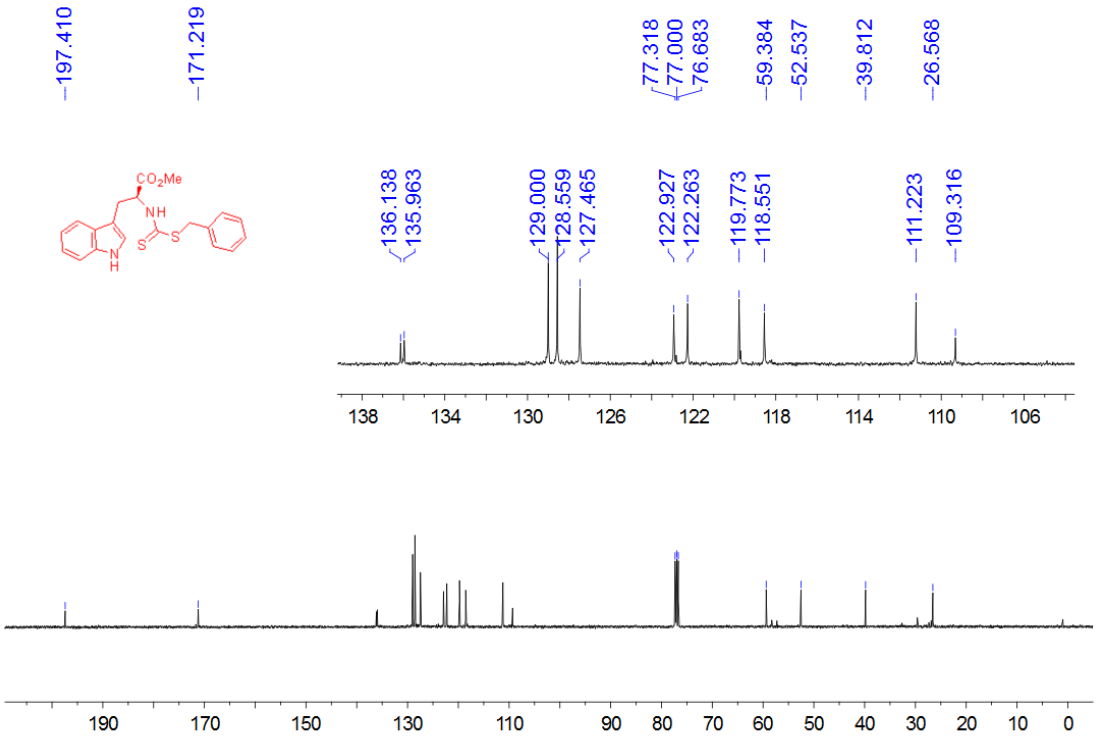
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1e**



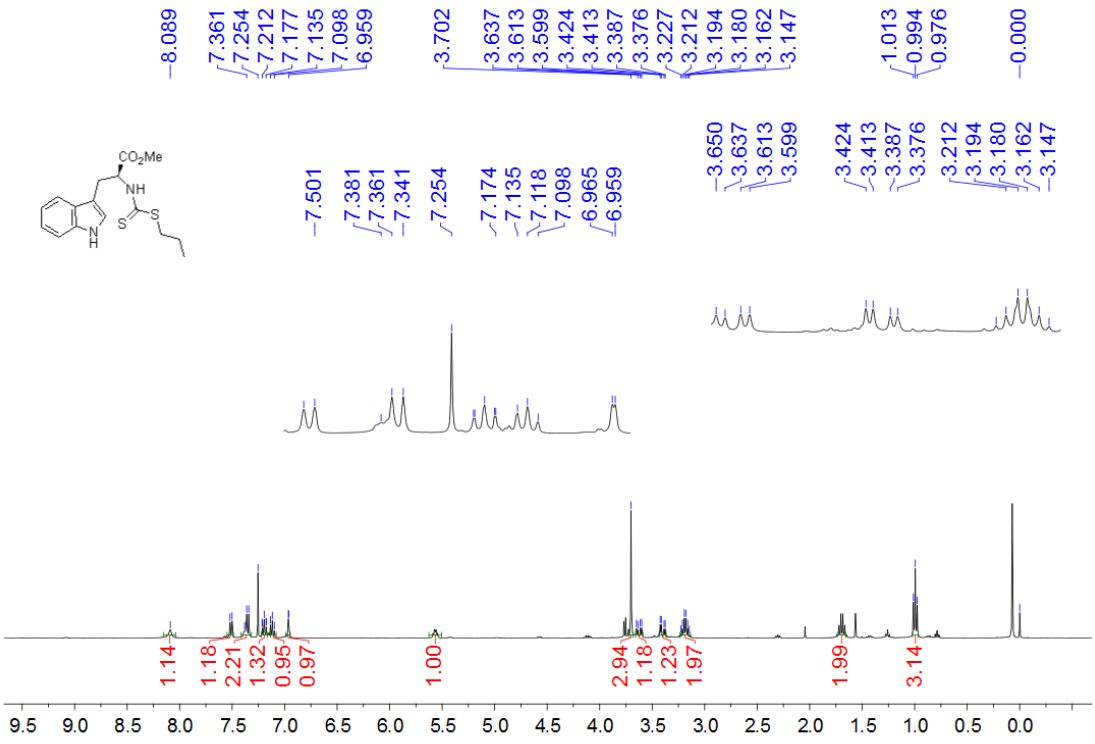
^{1}H NMR (400 MHz, $CDCl_3$) of **1f**



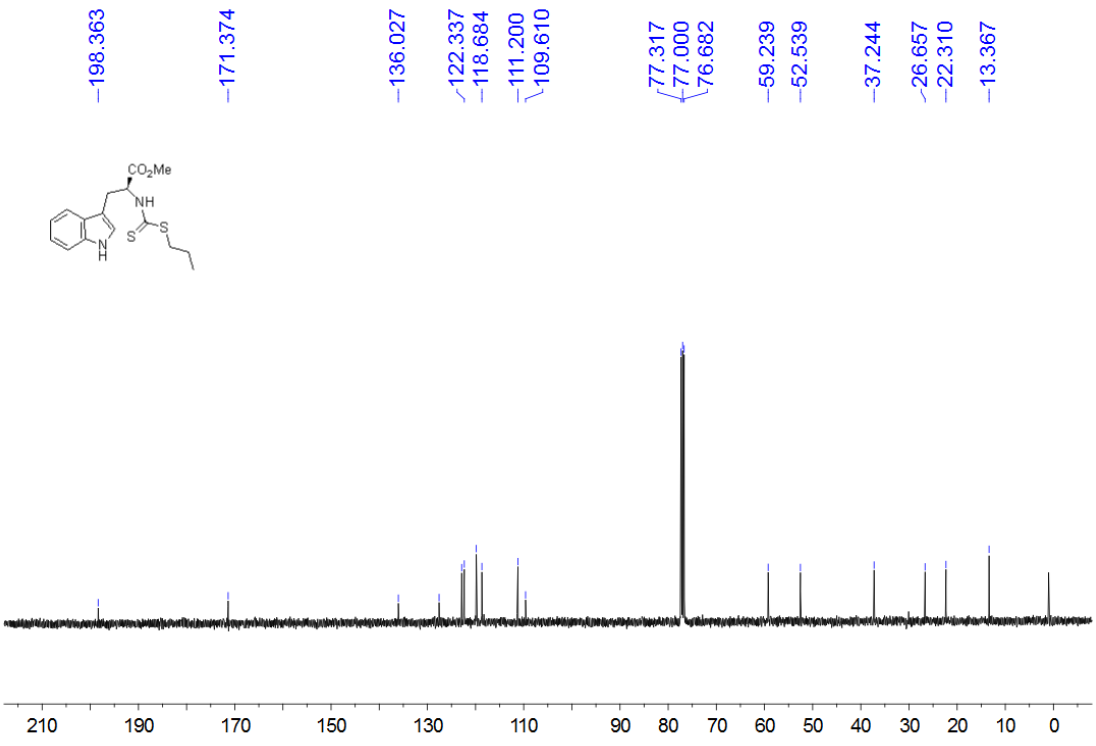
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1f**



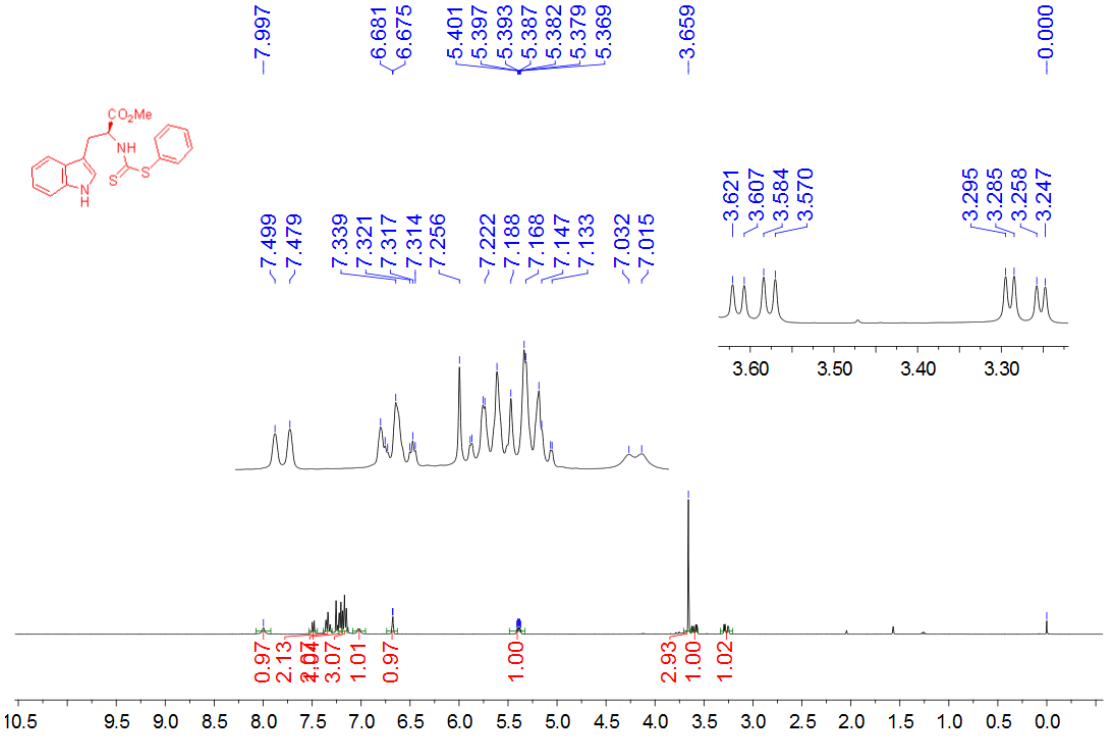
^{1}H NMR (400 MHz, $CDCl_3$) of **1g**



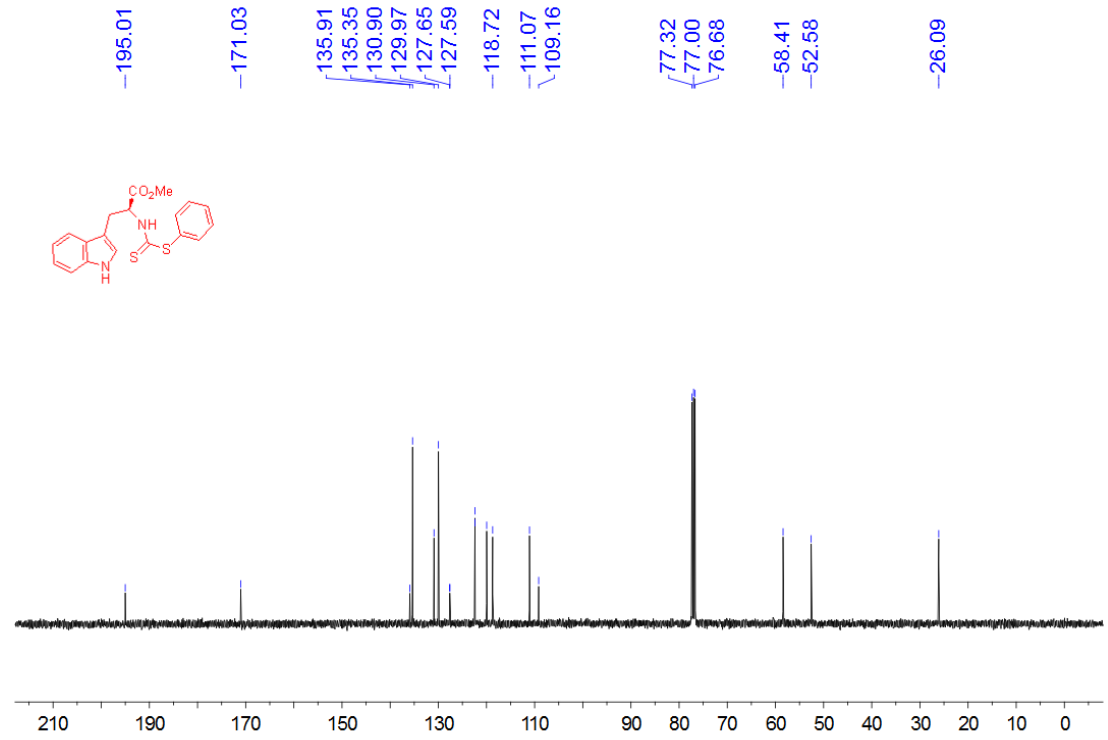
^{13}C NMR (100.6 MHz, $CDCl_3$) of **1g**



^{1}H NMR (400 MHz, $CDCl_3$) of **1h**

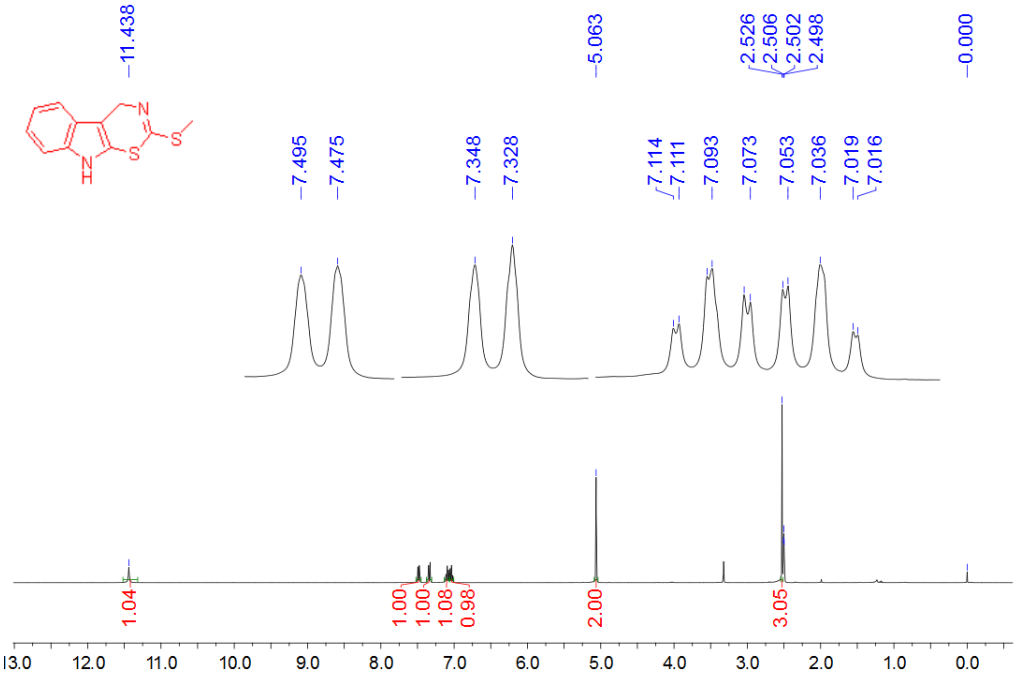


^{13}C NMR (100.6 MHz, $CDCl_3$) of **1h**

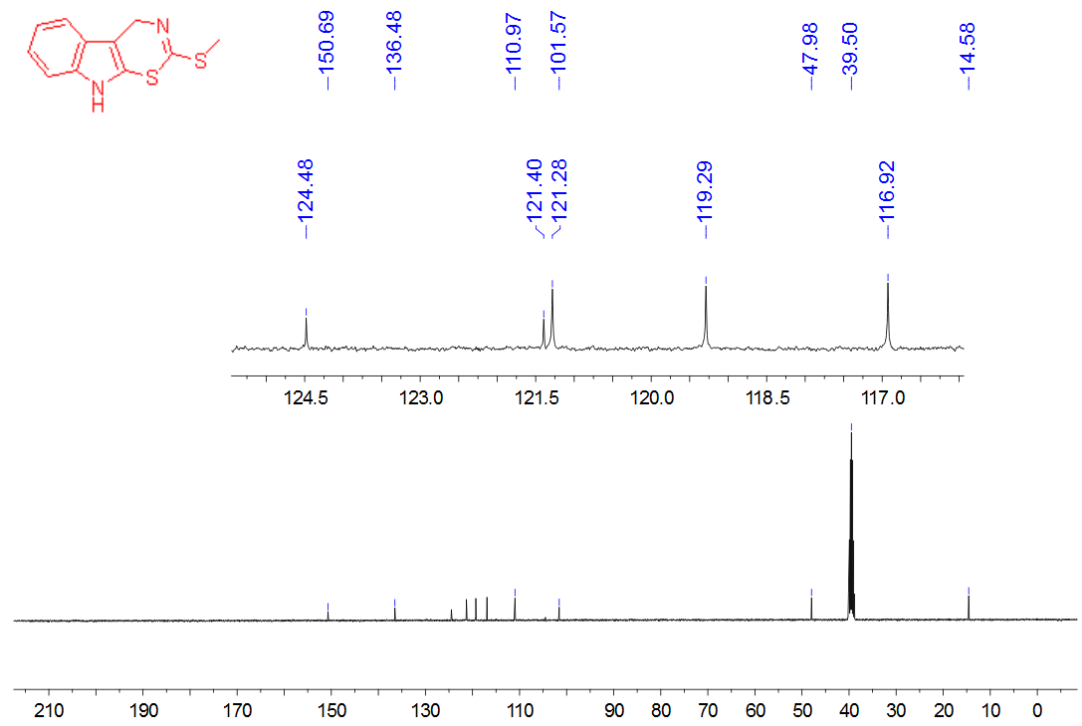


6. Copies of ^{1}H and ^{13}C-NMR spectra of cyclobrassinin and its analogs 2

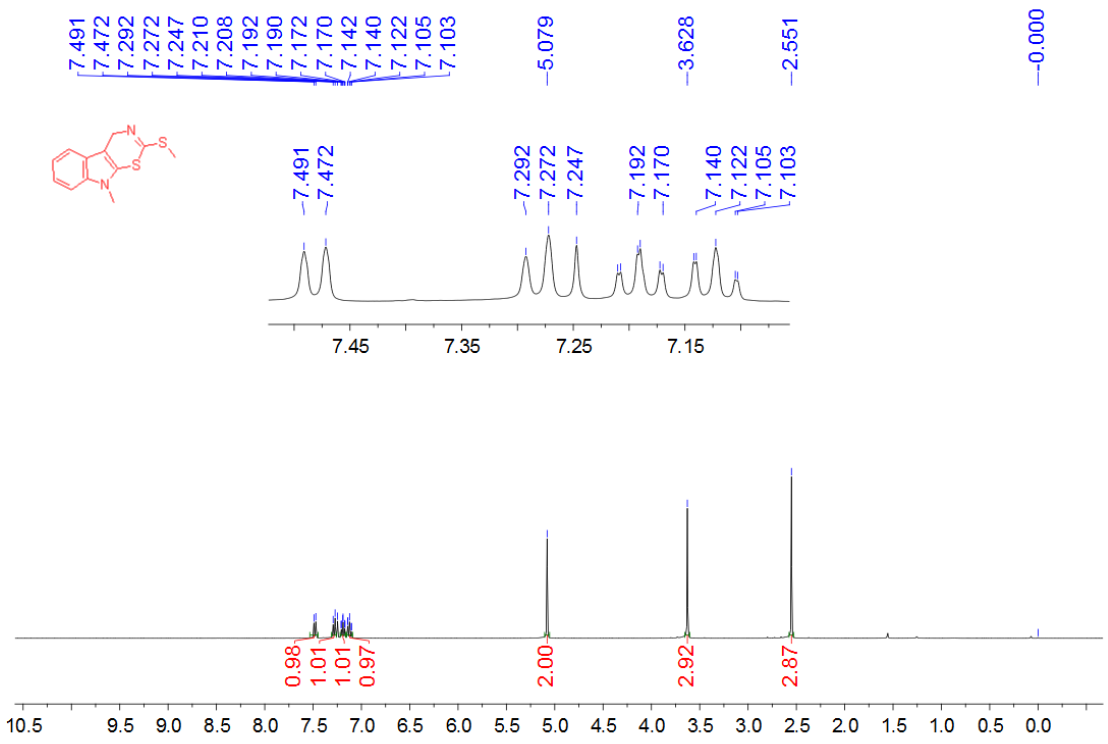
^{1}H NMR (400 MHz, DMSO-d_6) of **2a**



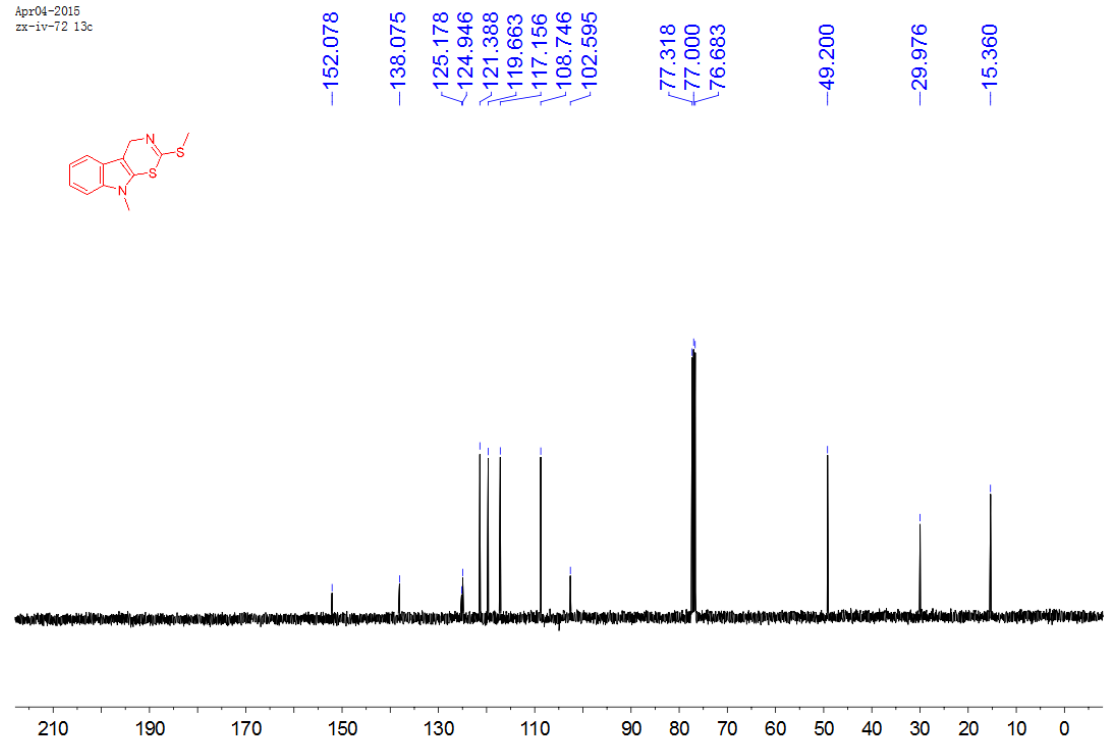
^{13}C NMR (100.6 MHz, DMSO-d_6) of **2a**



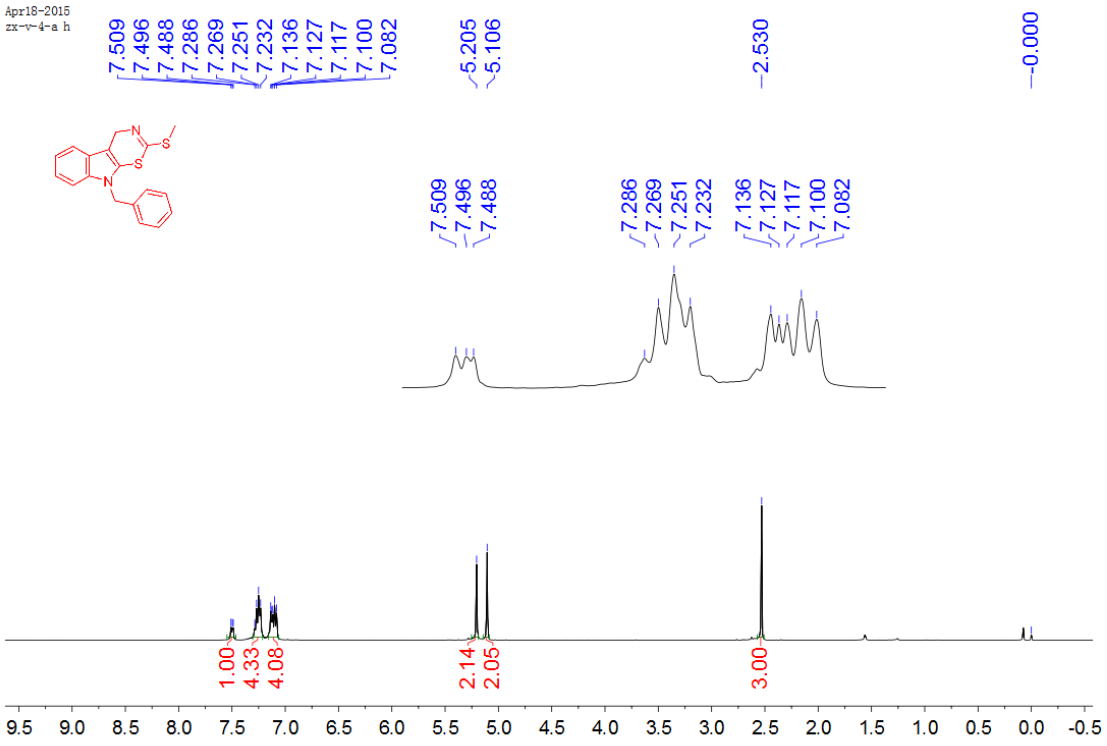
^{1}H NMR (400 MHz, $CDCl_3$) of **2c**



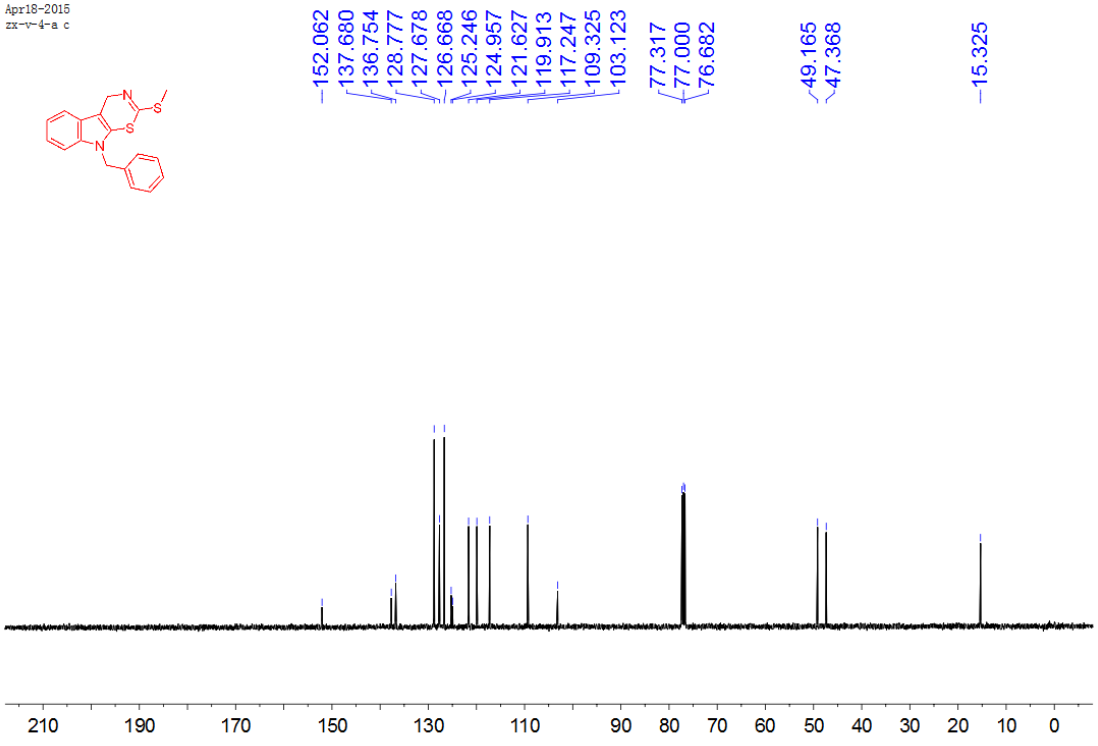
^{13}C NMR (100.6 MHz, $CDCl_3$) of **2c**



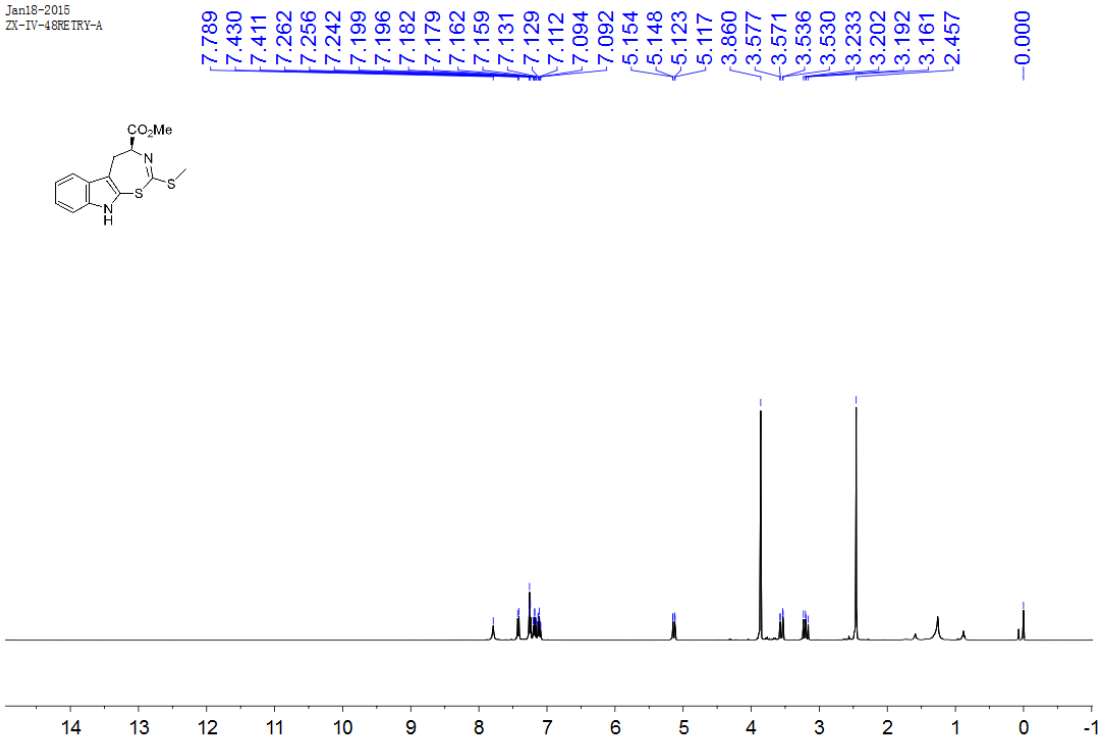
^{1}H NMR (400 MHz, $CDCl_3$) of **2d**



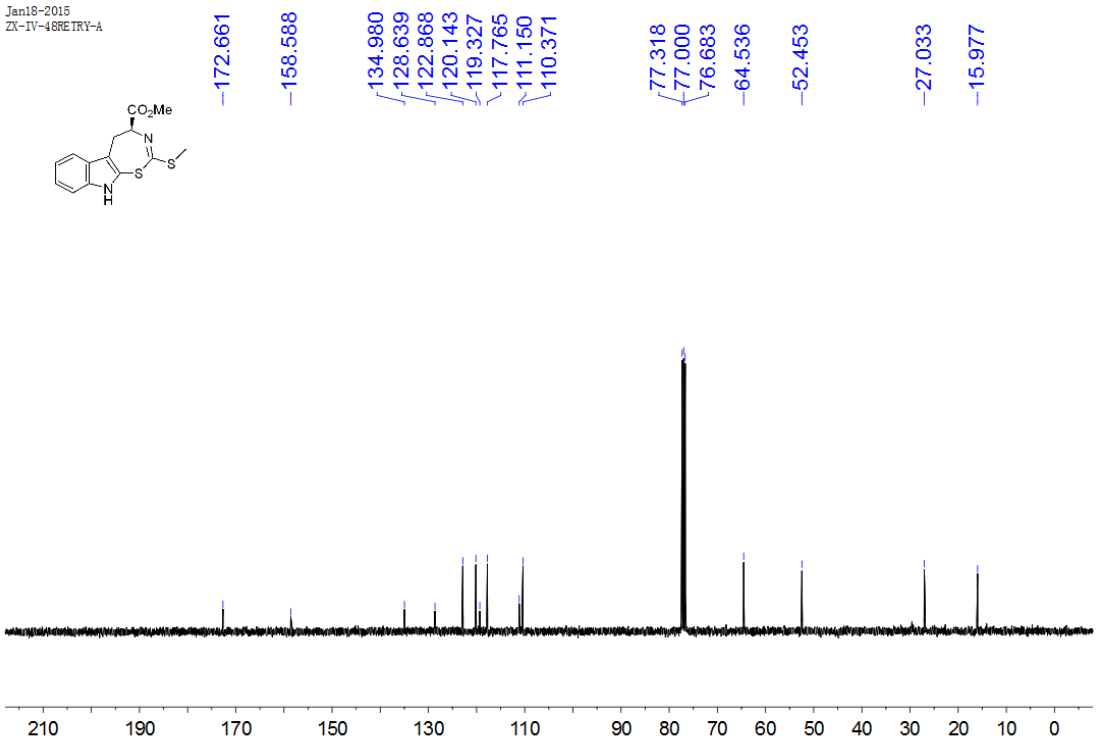
^{13}C NMR (100.6 MHz, $CDCl_3$) of **2d**



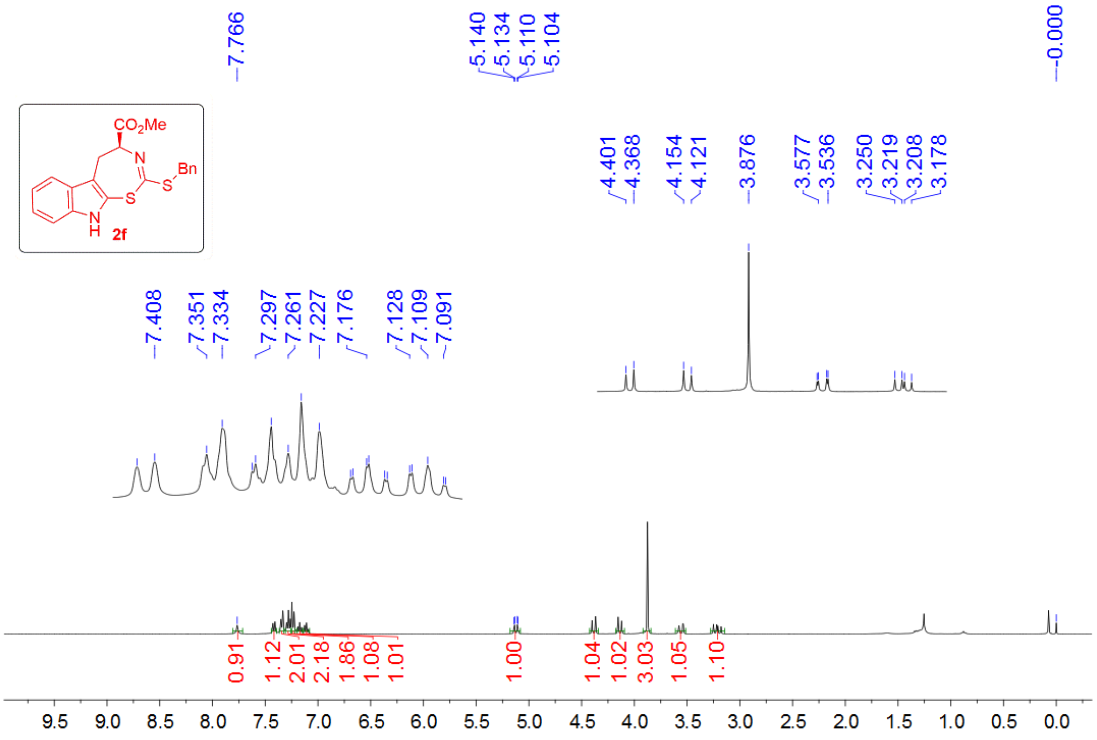
^{1}H NMR (400 MHz, $CDCl_3$) of **2e**



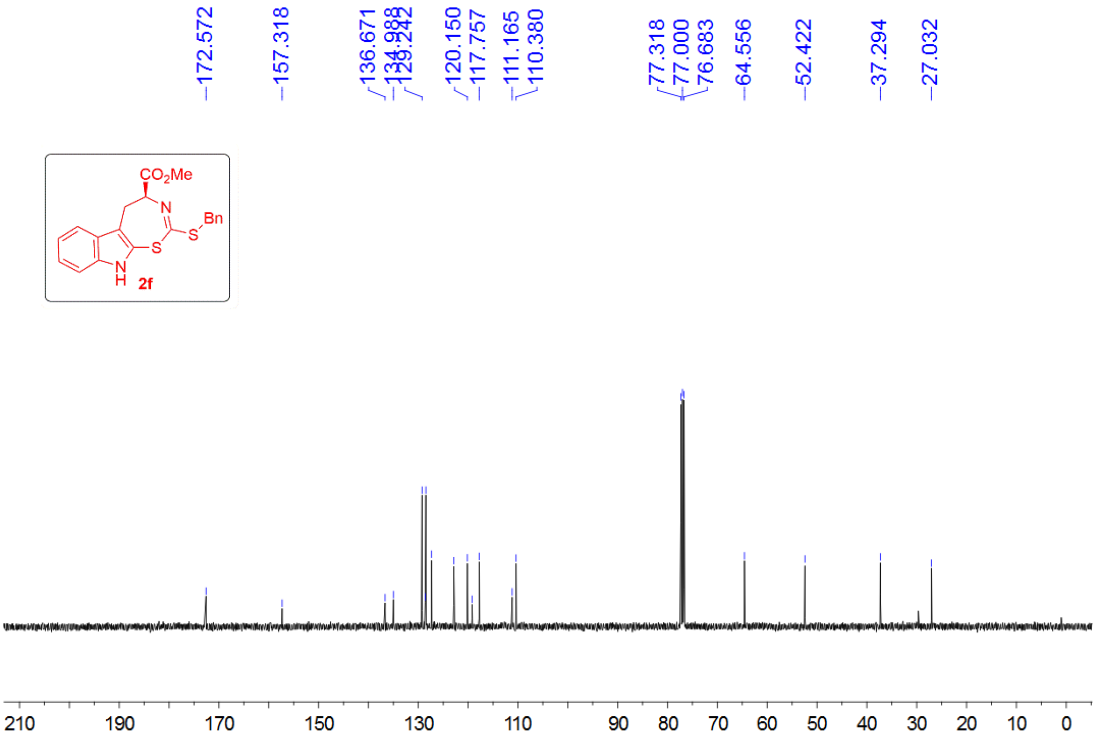
^{13}C NMR (100.6 MHz, $CDCl_3$) of **2e**



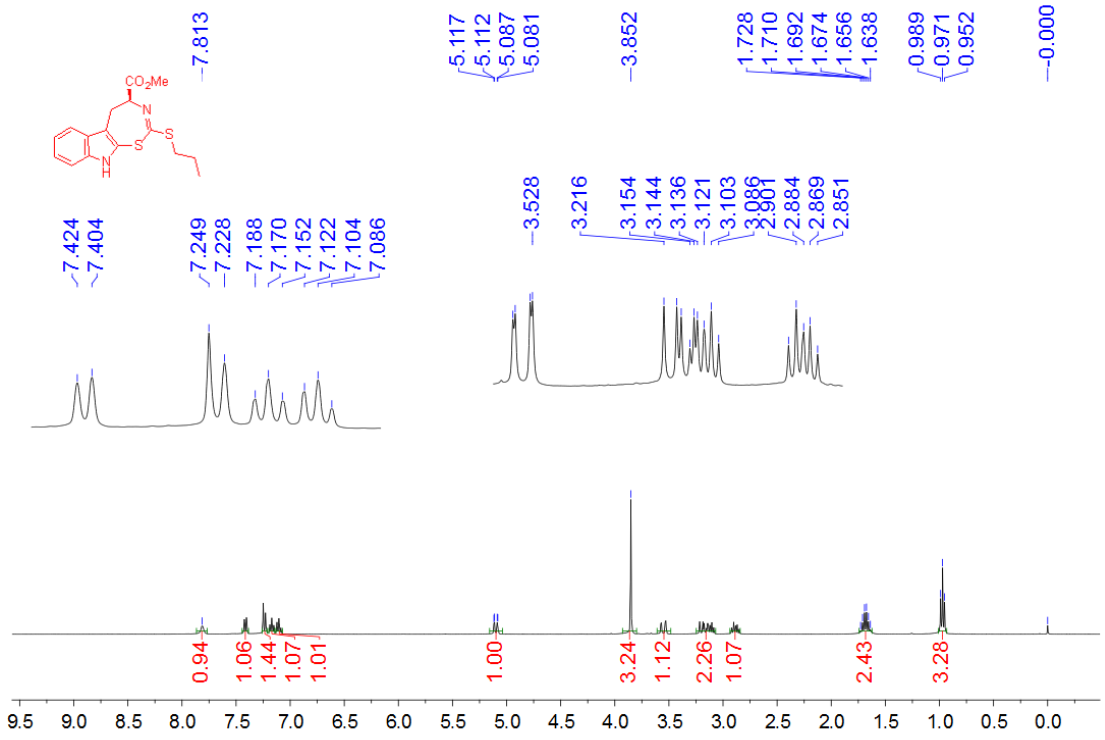
^{1}H NMR (400 MHz, $CDCl_3$) of **2f**



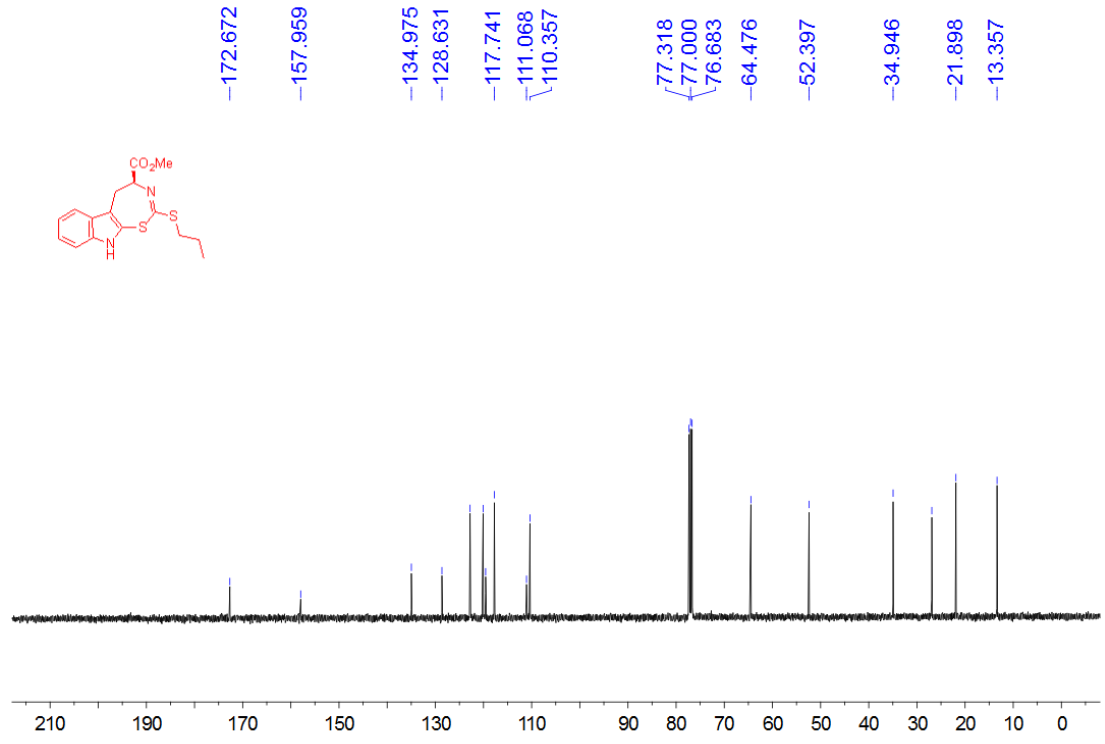
^{13}C NMR (100.6 MHz, $CDCl_3$) of **2f**



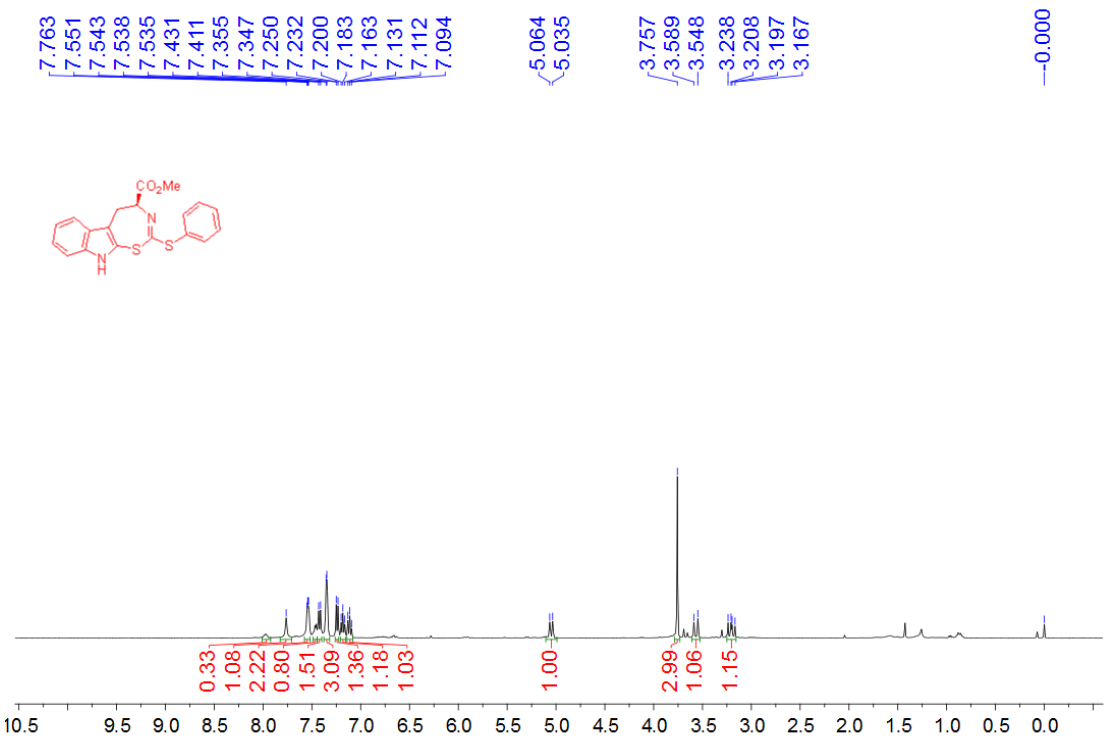
^{1}H NMR (400 MHz, $CDCl_3$) of **2g**



^{13}C NMR (100.6 MHz, $CDCl_3$) of **2g**



^{1}H NMR (400 MHz, $CDCl_3$) of **2h**



^{13}C NMR (100.6 MHz, $CDCl_3$) of **2h**