

# Synthesis of Novel Pyrazole Derivatives and Their Tumor Cell Growth Inhibitory Activity

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## Synthesis of intermediates

### *2-Chloro-1-(2,4-dihydroxyphenyl)ethan-1-one*

To a mixture of resorcinol (500 mg, 4.5 mmol) and chloroacetonitrile (0.35 mL, 5.5 mmol) in ether (10 mL) was added anhydrous  $\text{ZnCl}_2$  (300 mg, 2.3 mmol). The solution was cooled to 0 °C and HCl gas was bubbled through the reaction mixture for 2 h. The solution was left in 4 °C overnight and HCl gas was bubbled into the reaction mixture again for 2 h. Then the solution was left in the 4 °C for 2 days. The precipitated imine was filtered off and washed three times with ether. The imine was dissolved in 15 mL of water and reflux for 1 h. The solution was extracted with EtOAc (3 × 45 mL), washed with brine (30 mL), and dried over  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:4) to afford pure 2-chloro-1-(2,4-dihydroxyphenyl)ethan-1-one as a white solid. Yield 790 mg (94%), m.p.: 106-107 °C.  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$  11.67 (s, 1H), 10.69 (s, 1H), 7.74 (d,  $J$  = 7.1 Hz, 1H), 6.41 (dd,  $J$  = 1.8, 7.0 Hz, 1H), 6.34 (d,  $J$  = 1.8 Hz, 1H), 5.01 (s, 2H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ )  $\delta$  193.7, 165.9, 164.0, 133.3, 112.1, 109.1, 103.2, 48.3. MS (ESI)  $[\text{M} + \text{H}]^+$ : 164.99.

### *6-Hydroxybenzofuran-3(2H)-one*

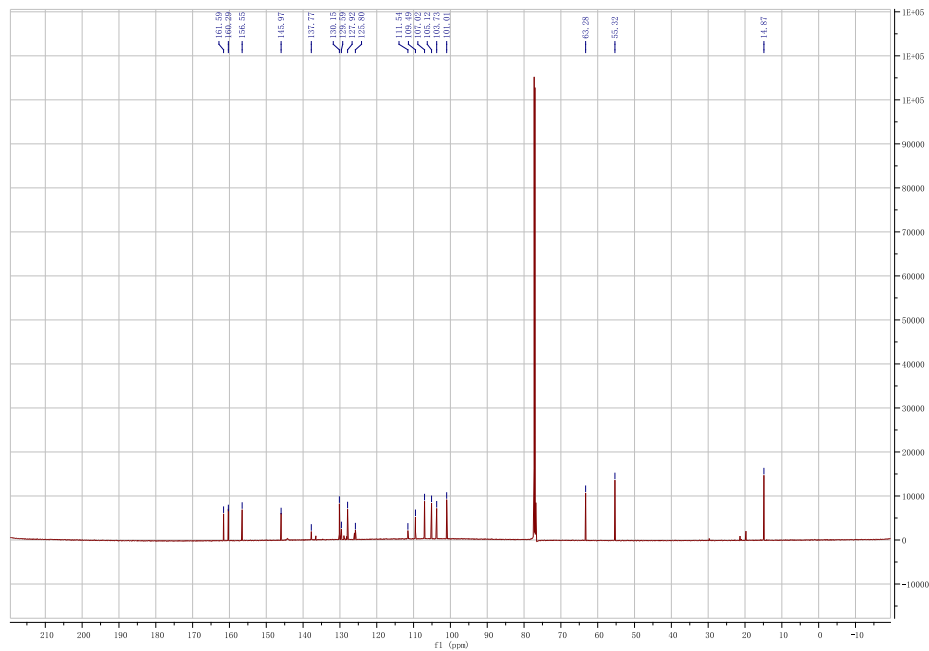
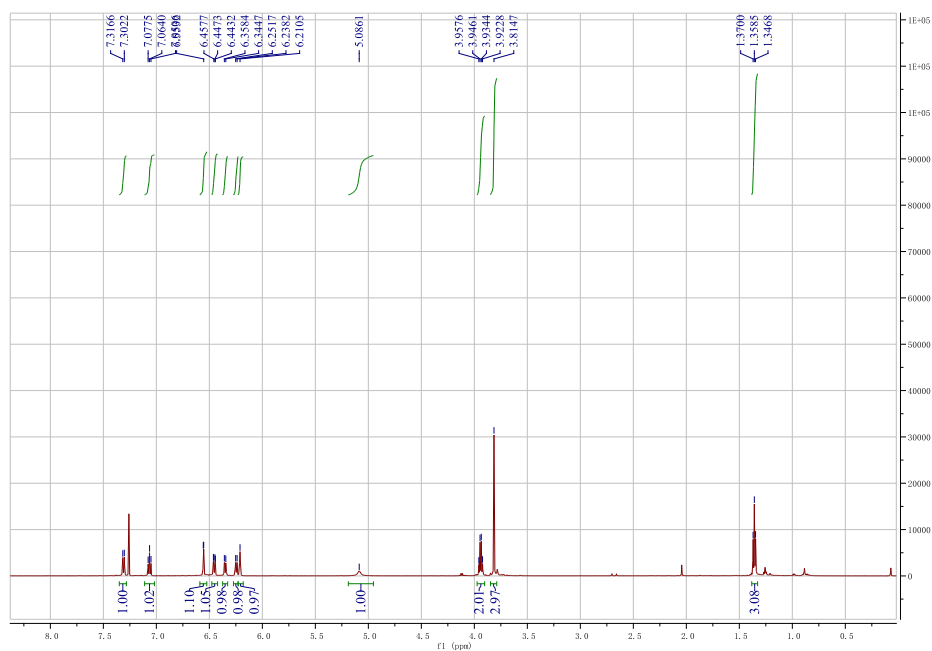
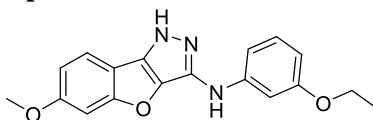
To a solution of 2-chloro-1-(2,4-dihydroxyphenyl)ethan-1-one (160 mg, 0.86 mmol) in EtOH (5 mL), sodium acetate (85 mg, 1.03 mmol) was added. The mixture was heated to 60 °C and stirred vigorously for 5 h. The solution was evaporated and water (25 mL) was added. The resulting precipitate was filtered and dried to give 70 mg (54%) of 6-hydroxybenzofuran-3(2H)-one as a white solid, m.p.: >220 °C.  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$  10.93 (s, 1H), 7.47 (d,  $J$  = 6.8 Hz, 1H), 6.59 (d,  $J$  = 1.6, 6.8 Hz, 1H), 6.51 (d,  $J$  = 1.5 Hz, 1H), 6.34 (d,  $J$  = 1.8 Hz, 1H), 4.71 (s, 2H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ )  $\delta$  197.3, 176.1, 167.2, 125.5, 113.4, 112.2, 98.8, 75.7. MS (ESI)  $[\text{M} - \text{H}]^-$ : 185.05.

### *6-Methoxybenzofuran-3(2H)-one*

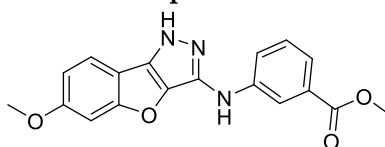
To a mixture of 6-hydroxybenzofuran-3(2H)-one (60 mg, 0.4 mmol) and  $\text{K}_2\text{CO}_3$  (56 mg, 0.4 mmol) in DMF (3 mL), dimethyl sulfate (43  $\mu\text{L}$ , 0.4 mmol) was added. The mixture was stirred vigorously for 50 min at room temperature. The water (30 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (40 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:6) to give 56 mg (86%) of 6-methoxybenzofuran-3(2H)-one as a light yellow solid, m.p.: 112-114 °C.  $^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$  7.54 (d,  $J$  = 6.9 Hz, 1H), 6.82 (d,  $J$  = 1.6 Hz, 1H), 6.72 (dd,  $J$  = 1.6, 6.9 Hz, 1H), 4.77 (s, 2H), 3.87 (s, 3H).  $^{13}\text{C}$ -NMR (DMSO- $d_6$ )  $\delta$  197.6, 176.3, 168.2, 125.1, 114.5, 112.0, 97.2, 76.0, 56.6. MS (ESI)  $[\text{M} - \text{H}]^-$ : 149.06.

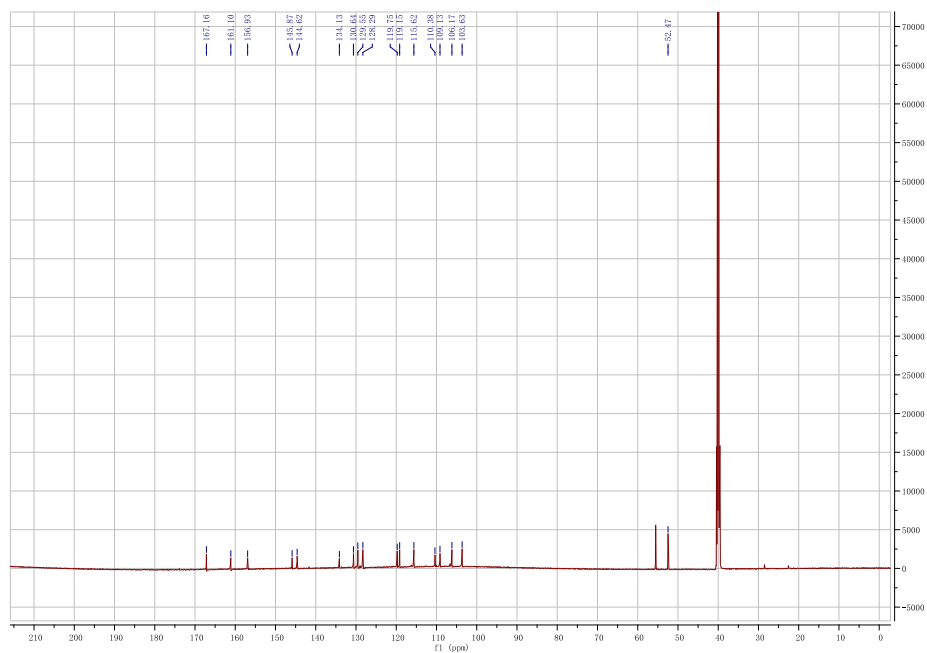
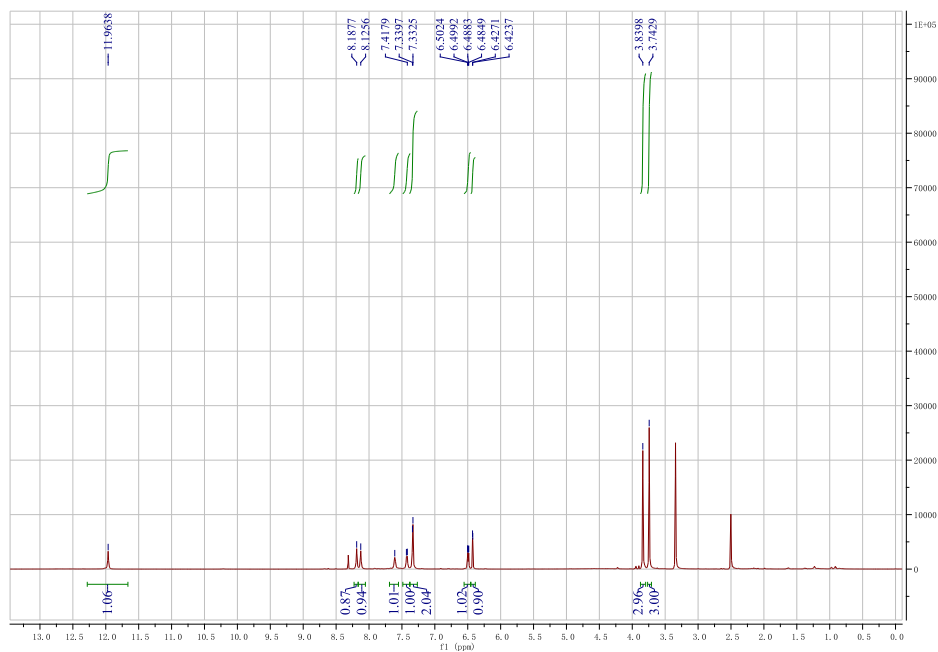
# <sup>1</sup>H and <sup>13</sup>C NMR spectra for the synthesized compounds

Compound 4a

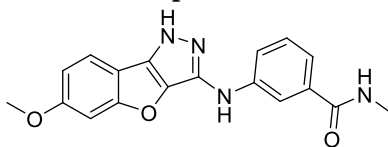


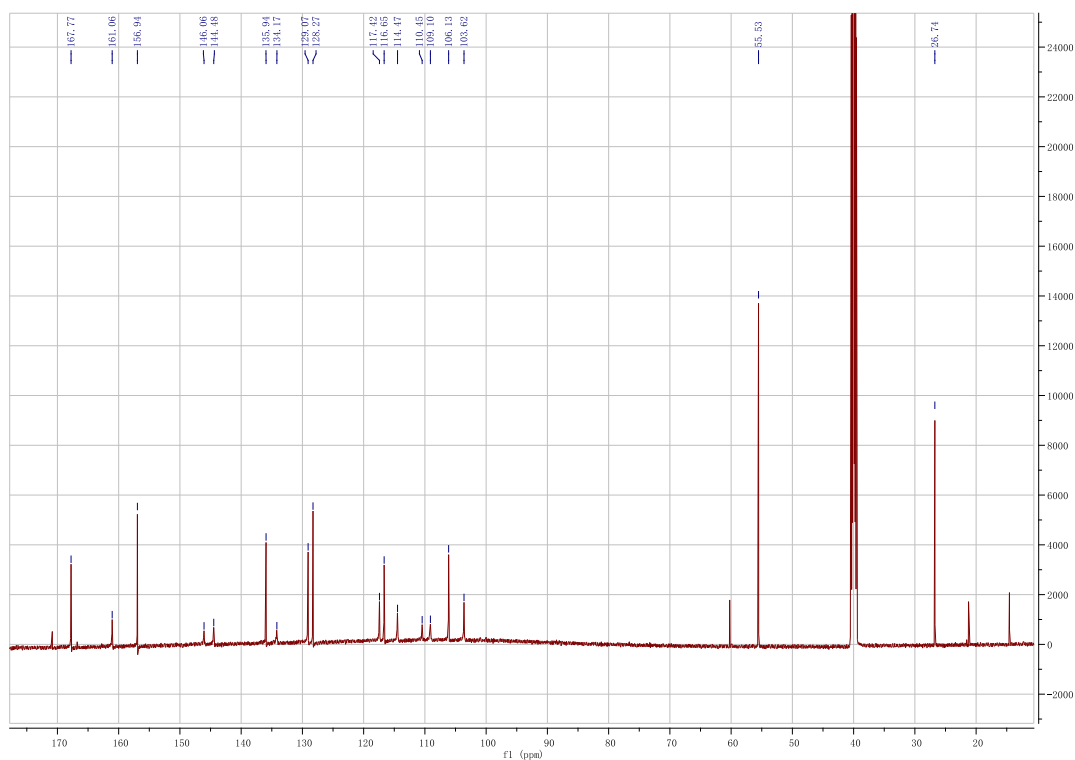
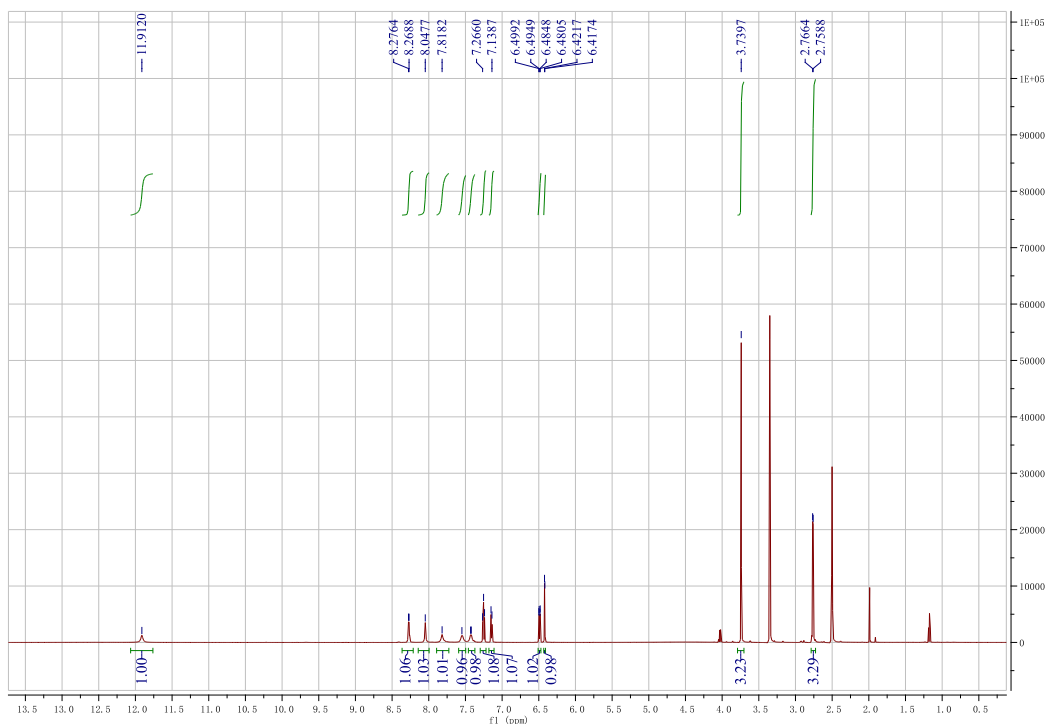
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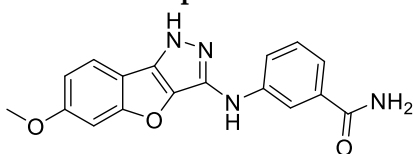


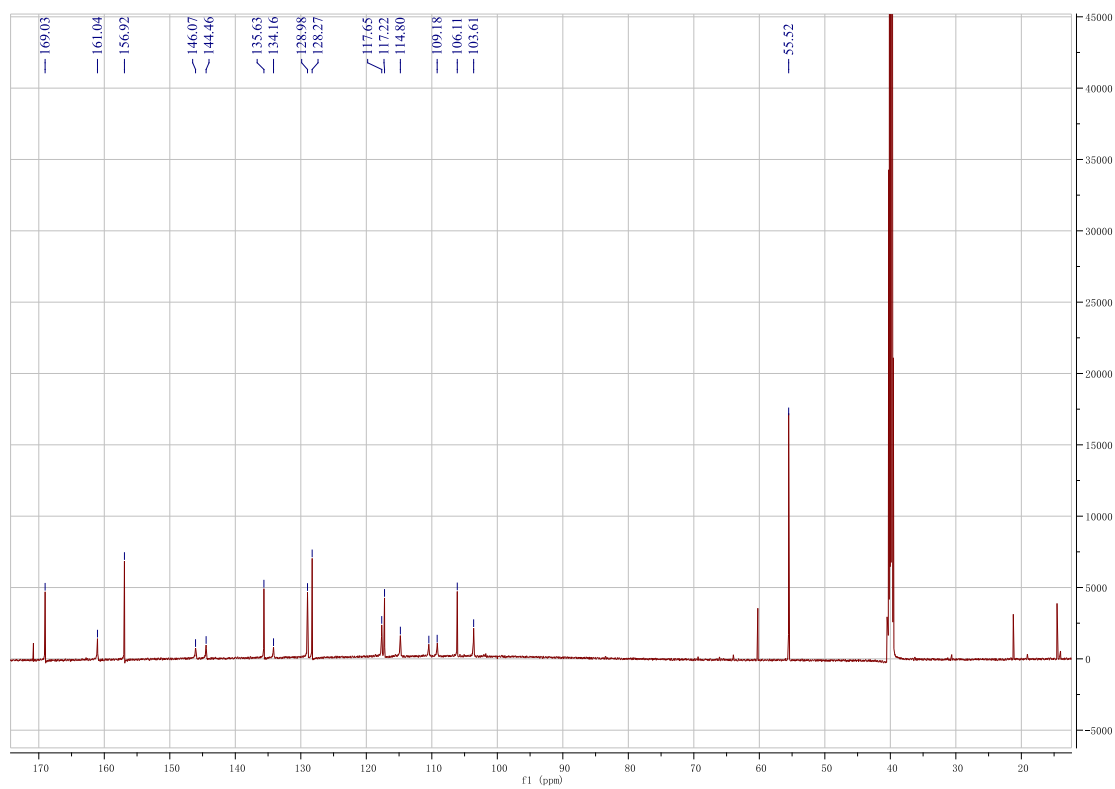
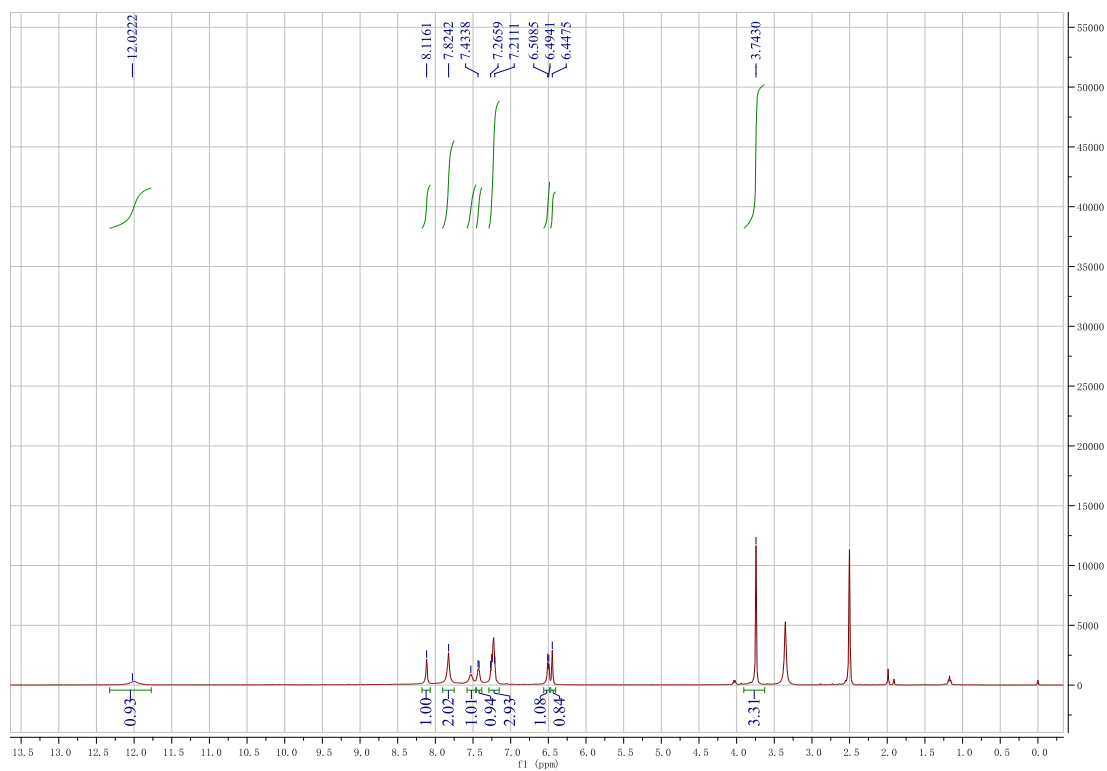
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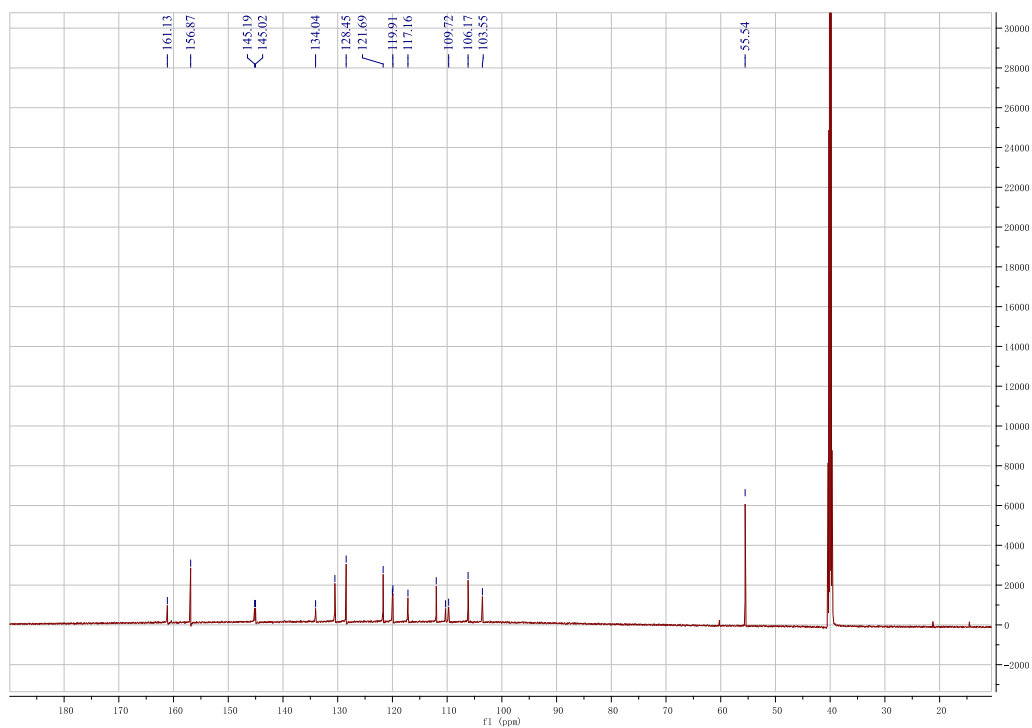
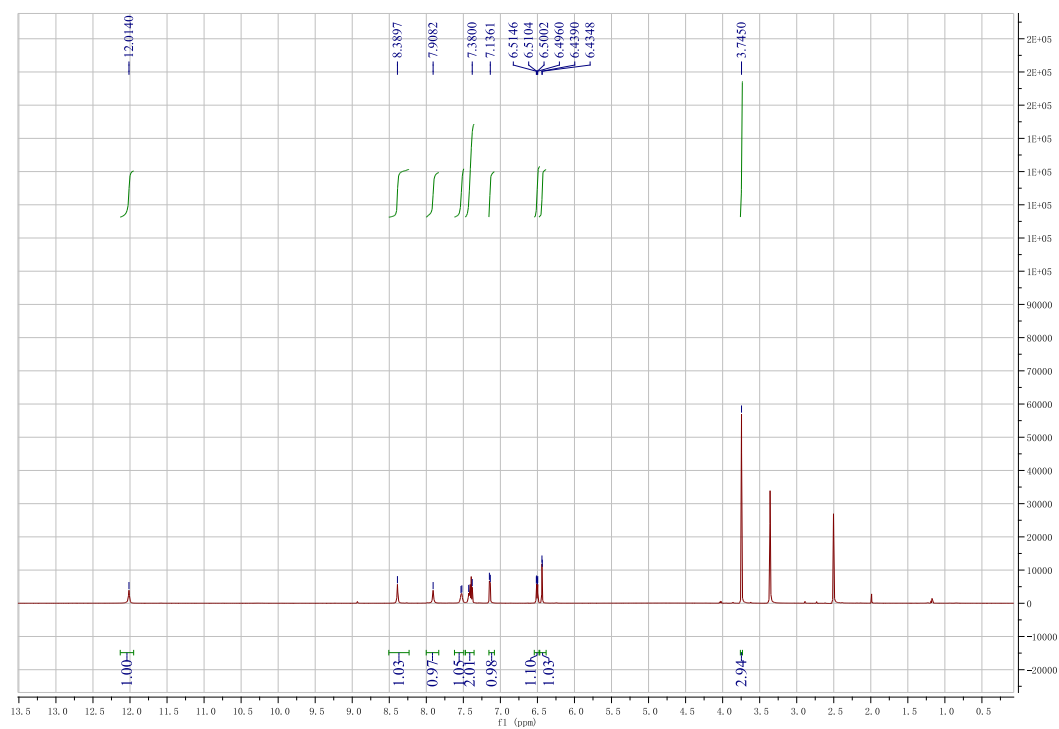
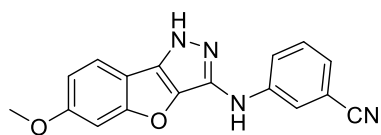


**Compound 4d**

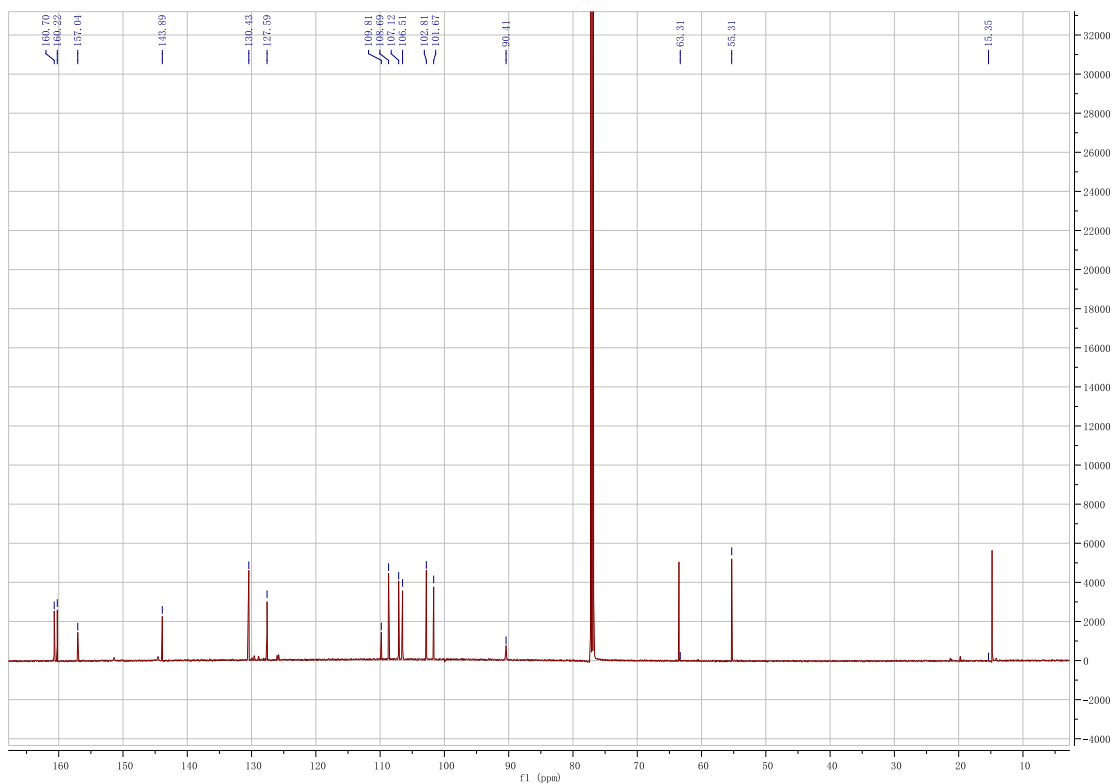
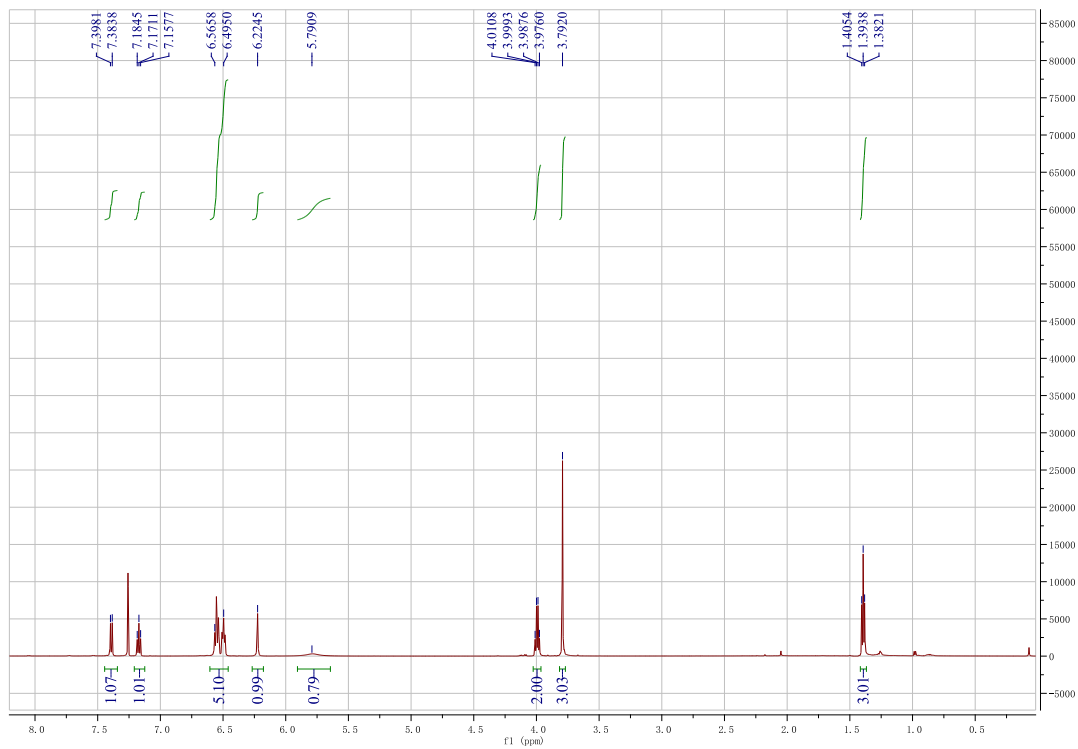
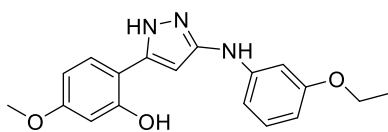




**Compound 4e**

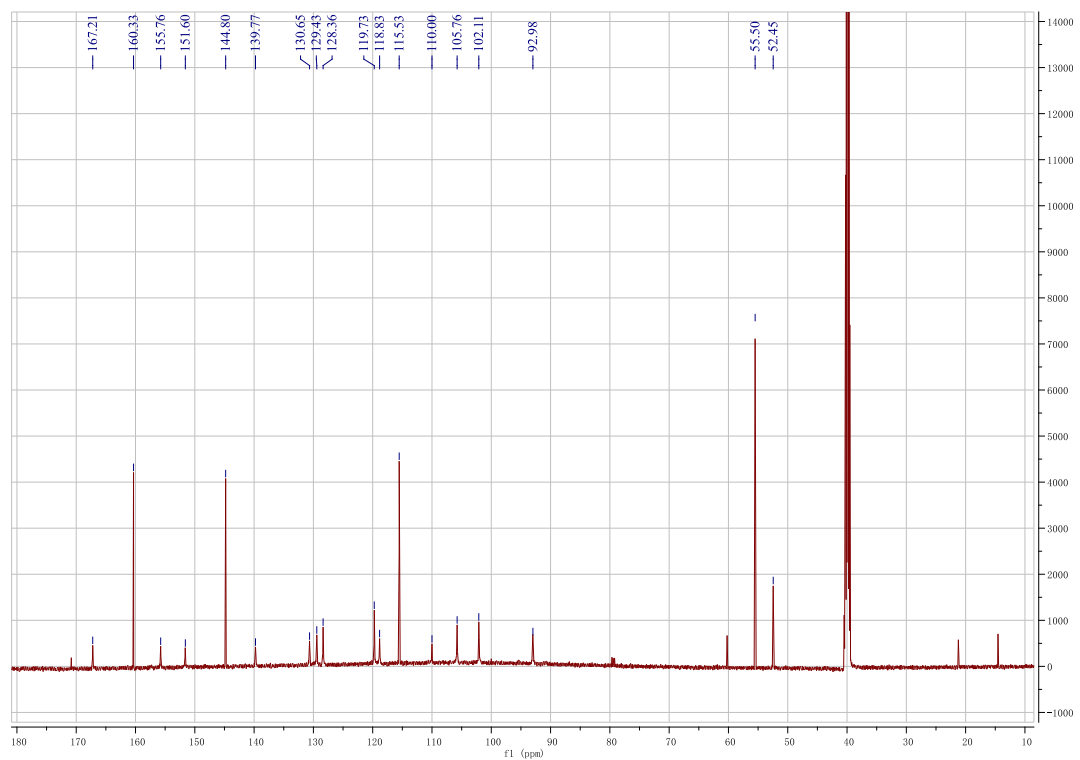
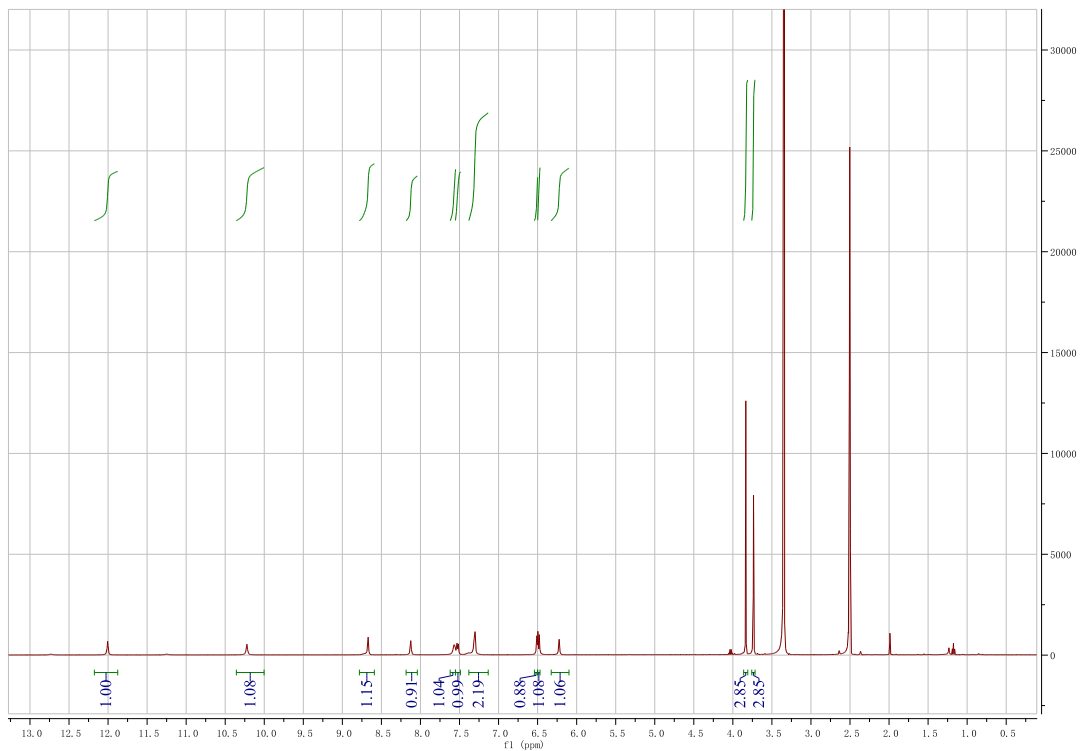
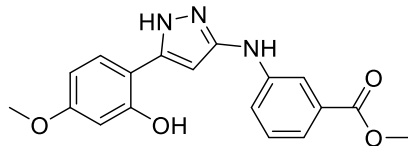


# Compound 5a

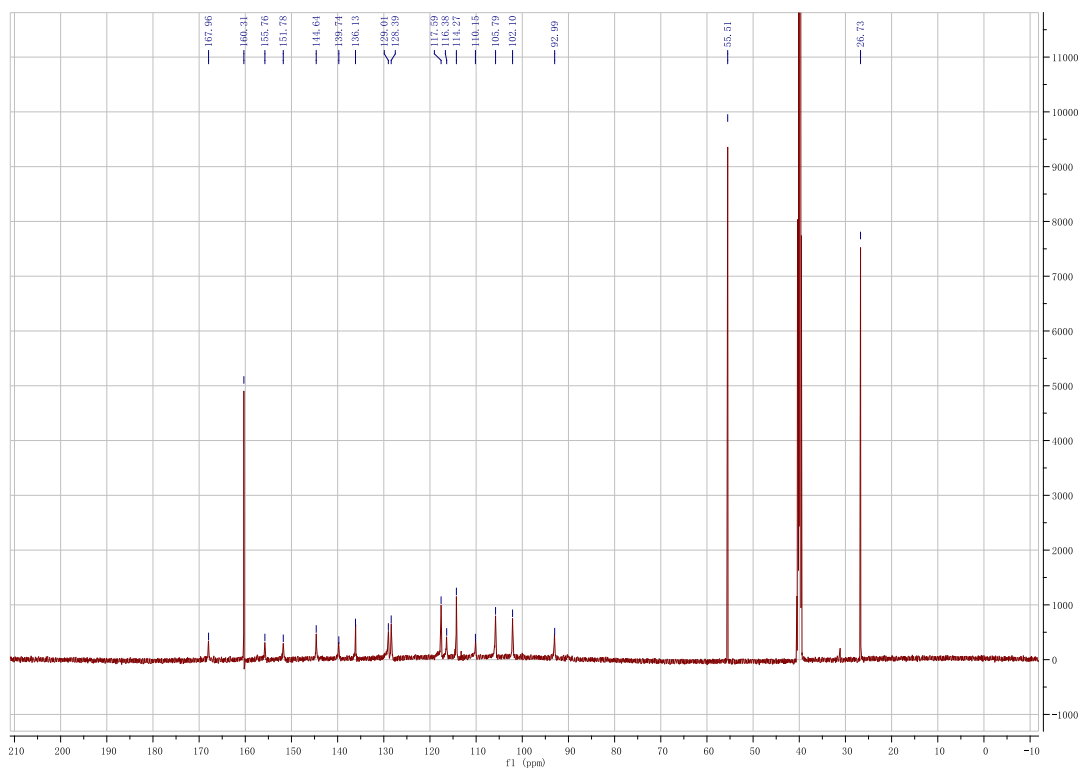
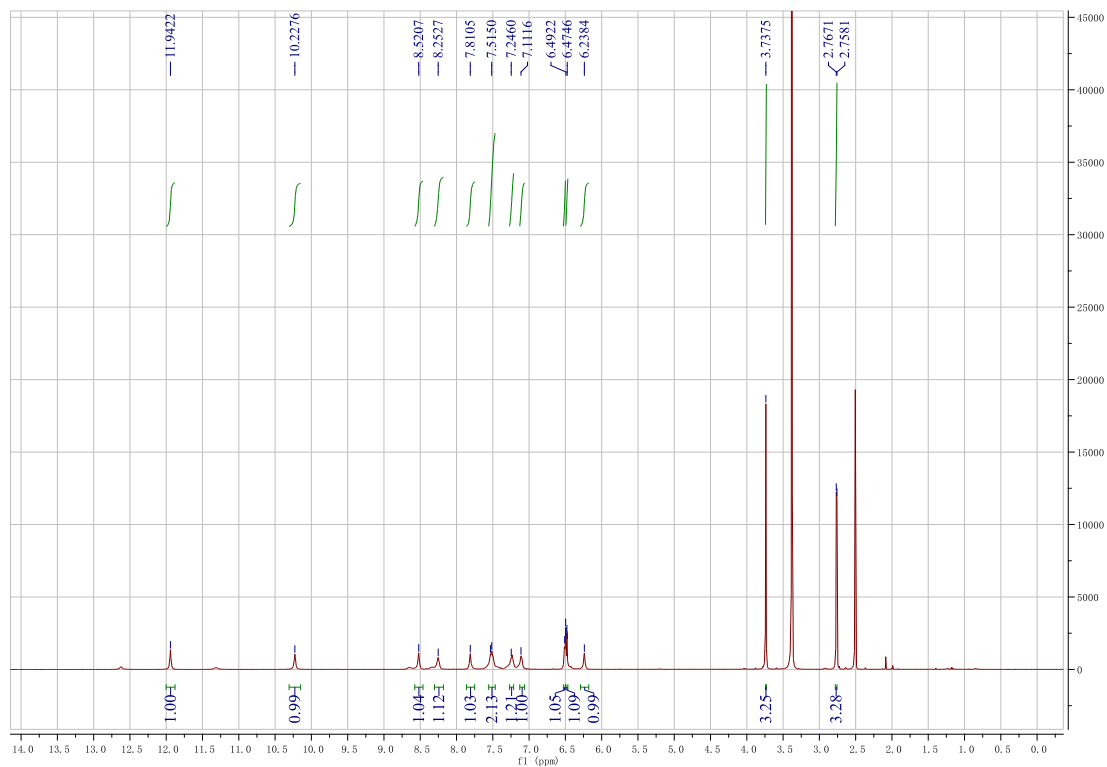
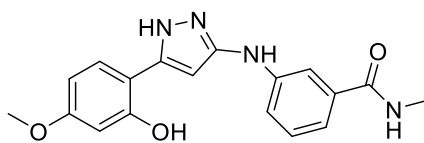




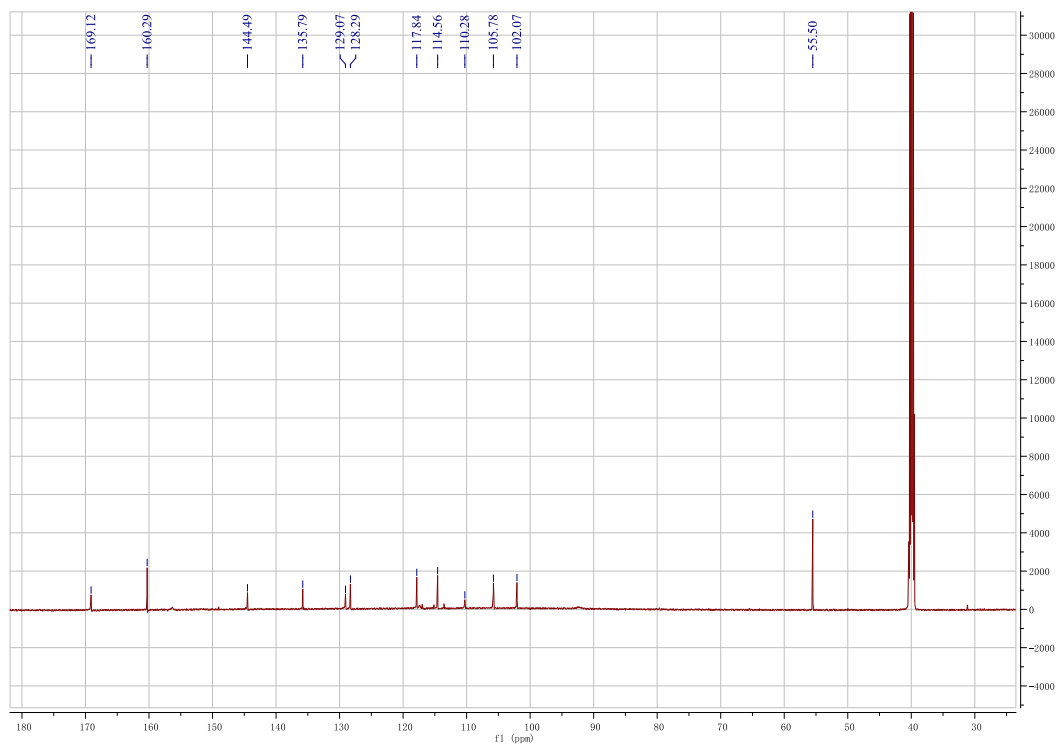
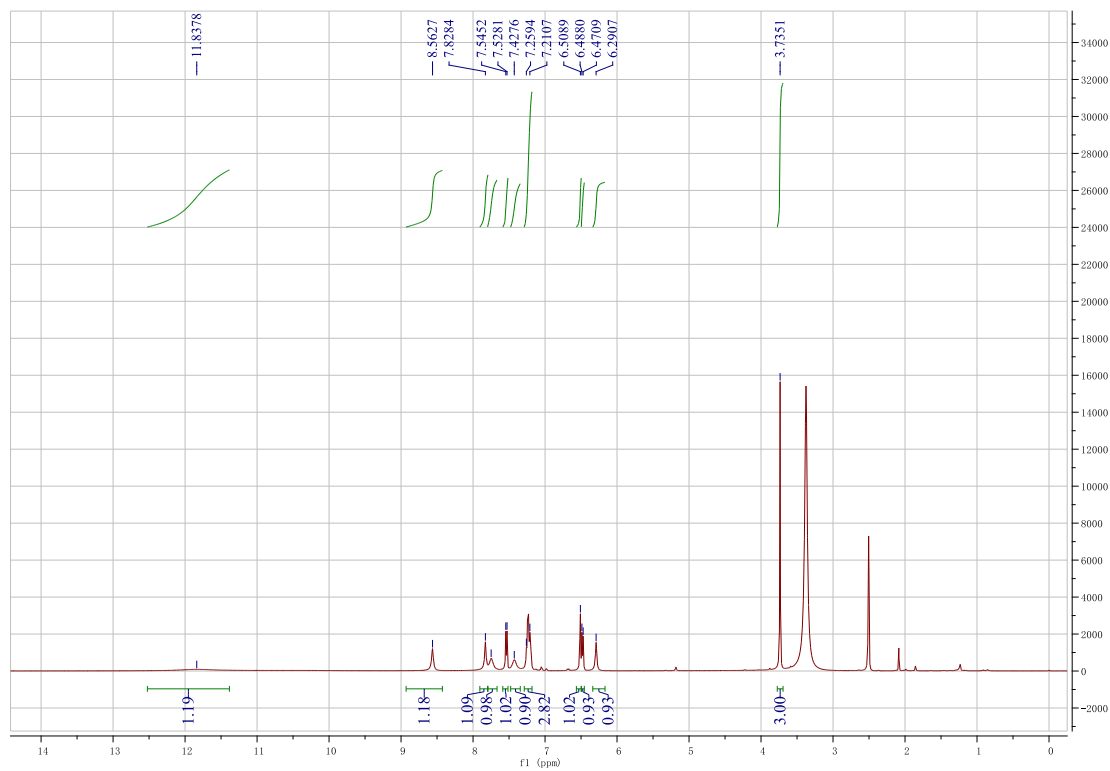
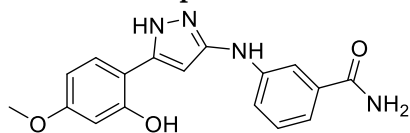
**Compound 5b**



# Compound 5c



# Compound 5d



Compound 5e

