

Supporting information

Cannabidiol-Based Thiosemicarbazones: A Preliminary Study Evaluating Their Anti-tyrosinase properties

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General Considerations. All chemicals and reagents were purchased from Sigma-Aldrich. Anhydrous tetrahydrofuran was dried over sodium and used freshly. HPLC-grade acetonitrile and formic acid were used. Flash column chromatography was performed with Merck ultra-pure silica gel (230-400 mesh). Yields refer to isolated compounds greater than 95% purity as determined by proton Nuclear Magnetic Resonance spectroscopy (¹H-NMR), High-performance liquid chromatography (HPLC), and Gas chromatography (GC) analysis.

HPLC Analysis

HPLC analysis was performed with UHPLC connected to a photodiode array detector (Agilent 1290), with a reverse-phase column (Phenomenex RP-18, 150 X 4.6 mm, 3 μm). The mobile phase was a mixture of (A) double-distilled water (DDW) with 0.1% formic acid and (B) acetonitrile with 0.1% formic acid with a flow of 0.5ml/min and gradient starting with 5% B and increasing in a concentration to 95% B for 30 min and then kept at 95% B for an additional 5 min.

LC-MS Analysis

The LC-MS analysis was performed with a heated electrospray ionization (ESI) source connected to a waters ZQ mass detector. The ESI capillary voltage was set to 3900 V, capillary temperature to 250°C, and gas temperature to 350°C. Nitrogen gas (N₂) was used. The MS conditions were set as follows: the flow rate of sheath gas, aux gas, and sweep gas was kept at 35 L/min, 10 L/min, and 1 L/min, respectively.

GC-MS analysis

The analysis of the compounds was performed using gas chromatogram instrument (Agilent 7890A), equipped with Phenomenex Zebron ZB-5 column (30m, 0.32mm, 0.25μm) coupled with mass spectrometer (Agilent 5975C). The injection was made in split mode (10:1) with an injection volume of 1μl. The injector temperature was set to 240 °C. Helium was used as a carrier gas at a constant flow rate of 1 ml/min. The initial oven

temperature was held at 50 °C for 5 min, then increased to 300 °C at a rate of 10 °C/min, and finally held at this temperature for 5 min (total time 35 min)

NMR analysis:

The synthesized compounds were dissolved in deuterated chloroform or dimethyl sulfoxide (CDCl_3 or $(\text{CD}_3)_2\text{SO}$). ^1H - NMR spectra were recorded at room temperature with a Bruker 400 MHz instrument, with chemical shifts reported in ppm relative to the residual deuterated solvent.

FTIR and UV spectroscopic analysis:

FTIR spectra were recorded in the Nicolet™ iS™ 10 FTIR Spectrometer (Thermo Scientific™). UV spectra were recorded by Tecan Infinite 200 PRO spectrophotometer.

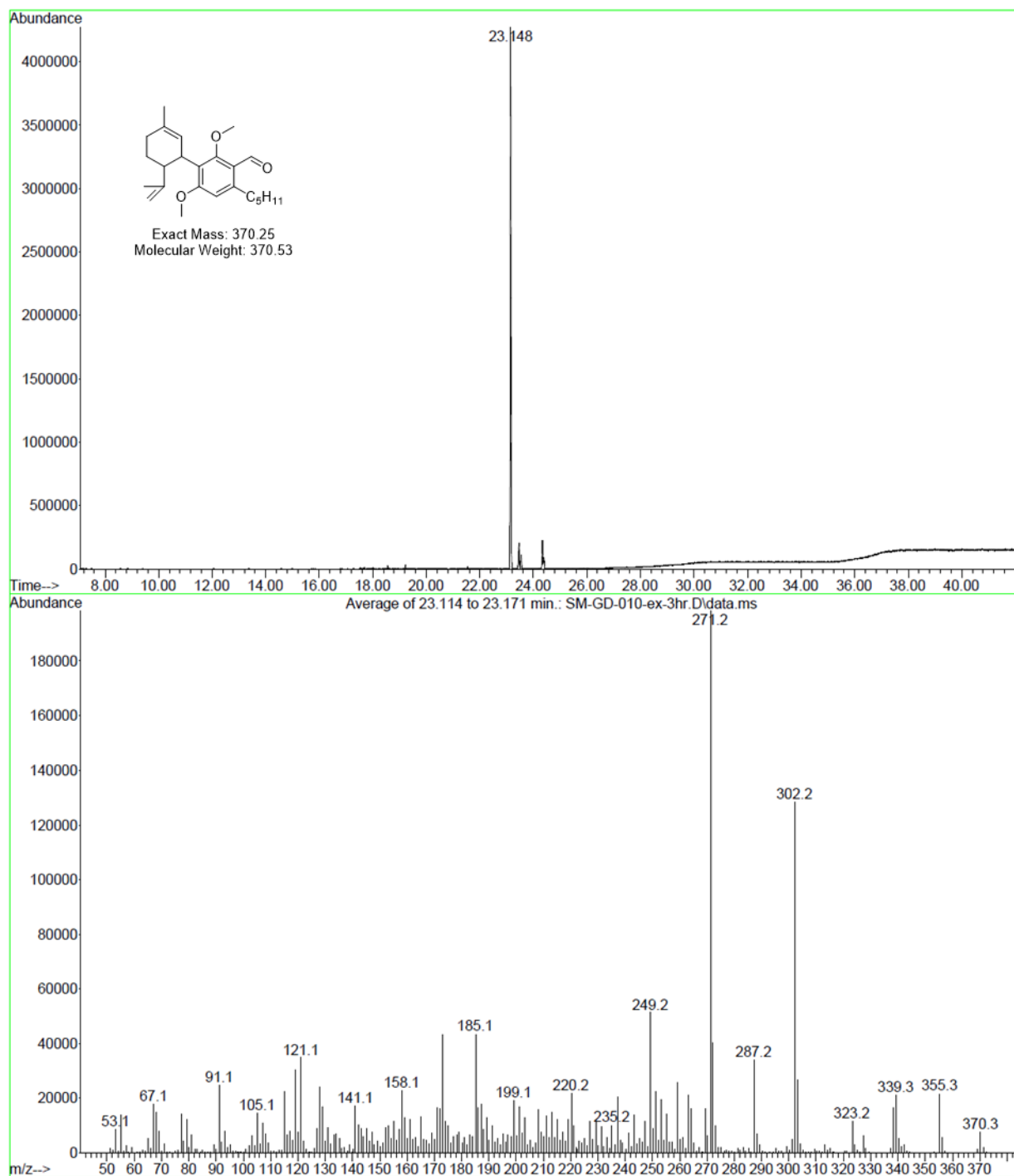
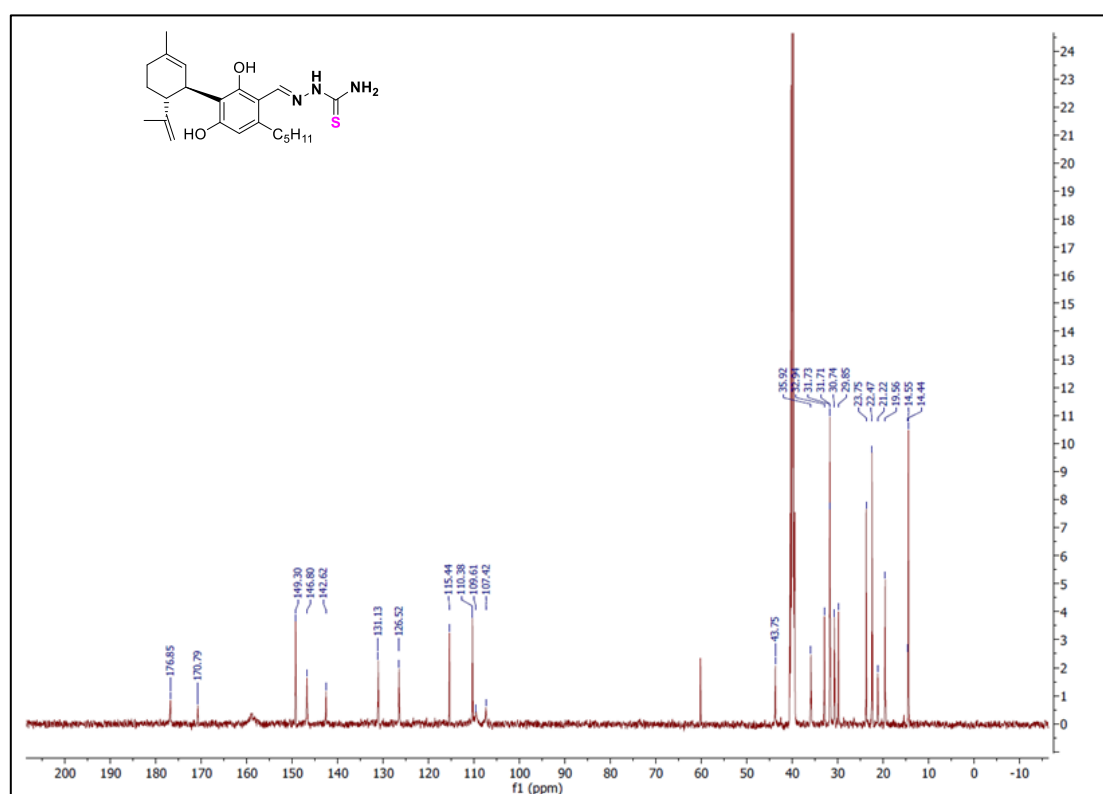
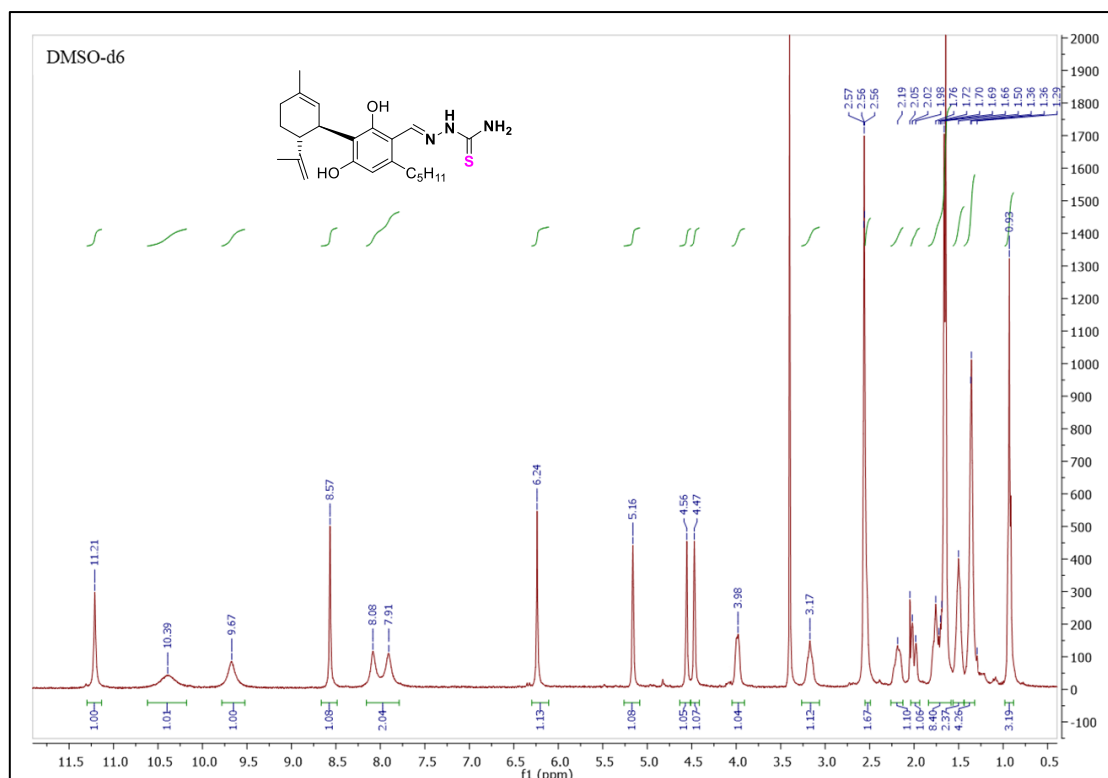
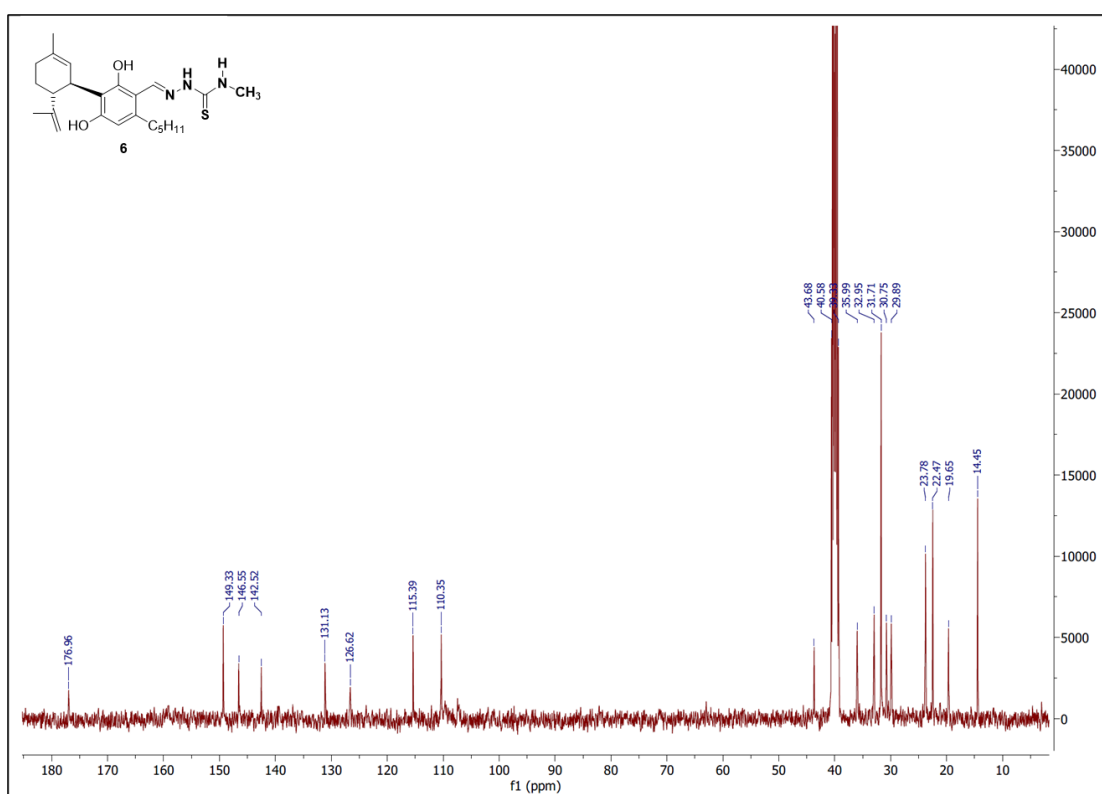
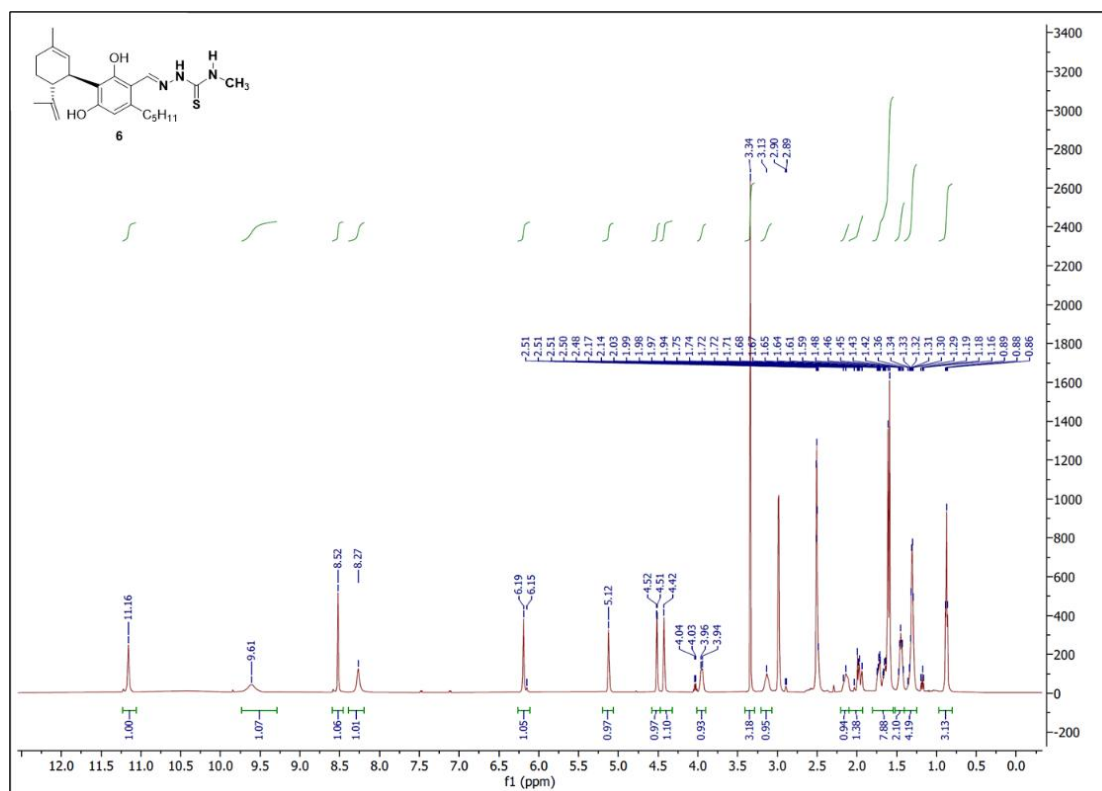
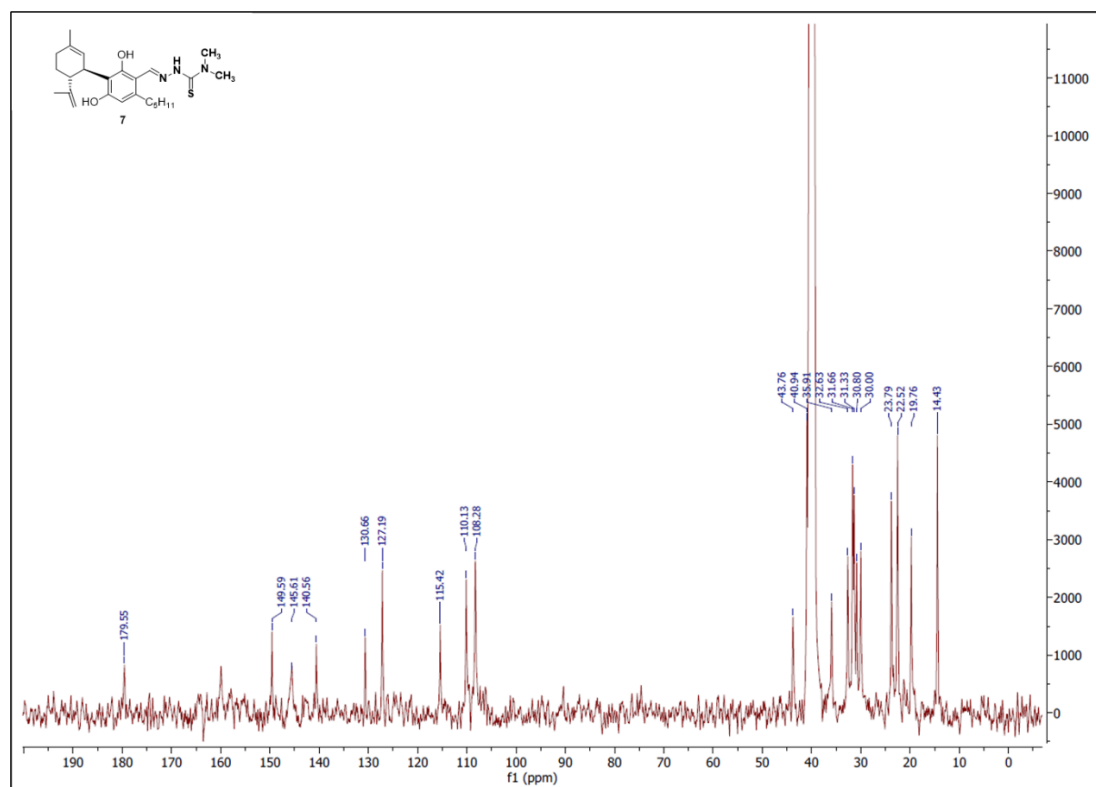
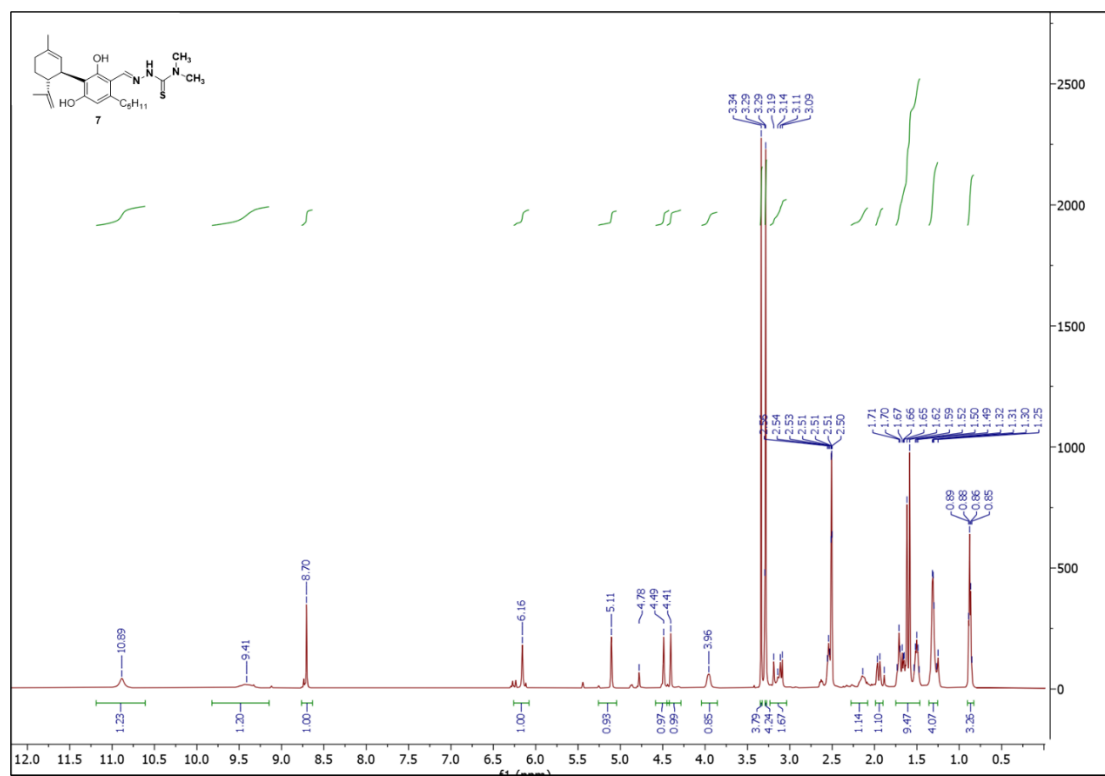


Figure S1. GCMS of compound 3-formyl cannabidiol dimethyl ether







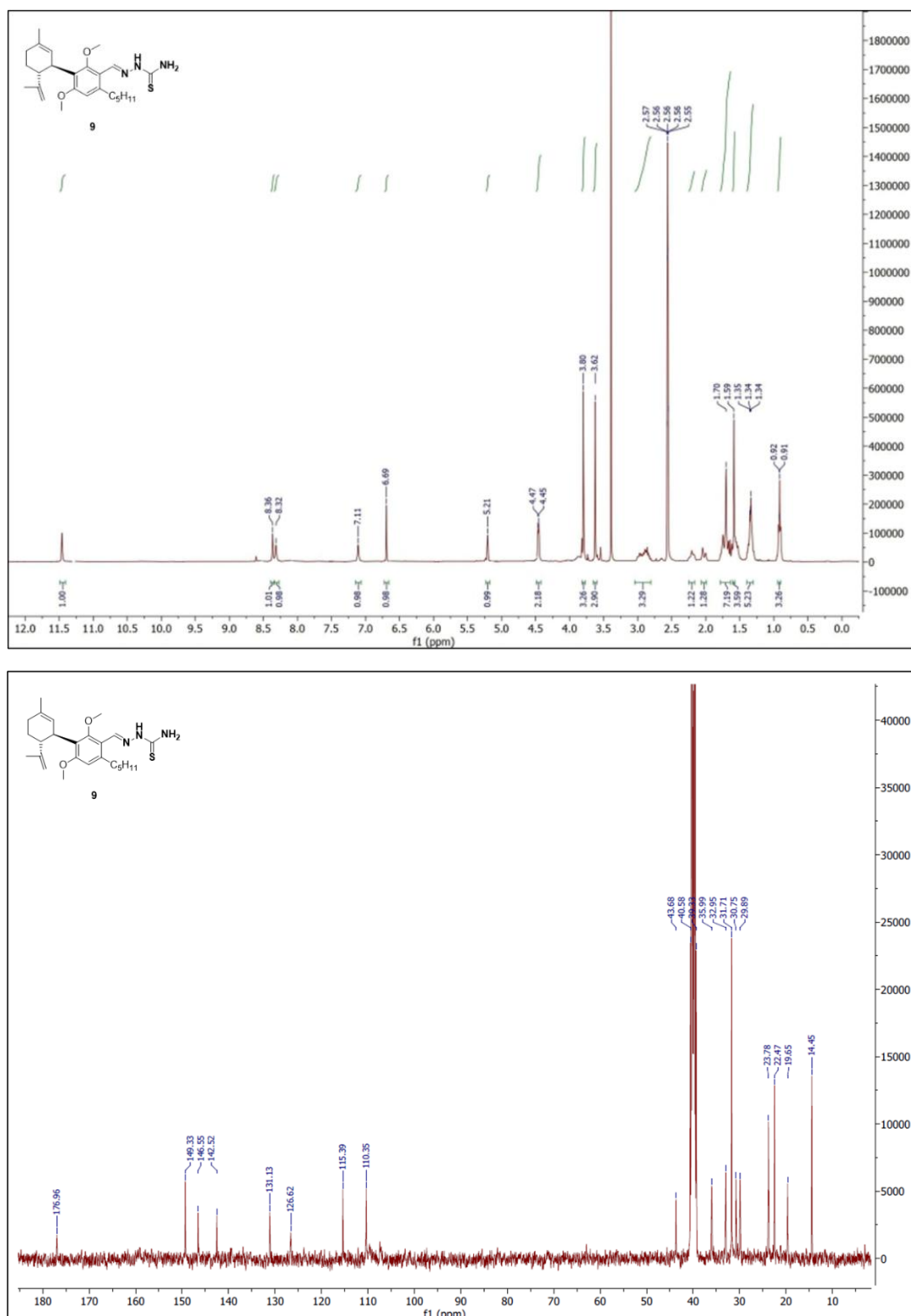
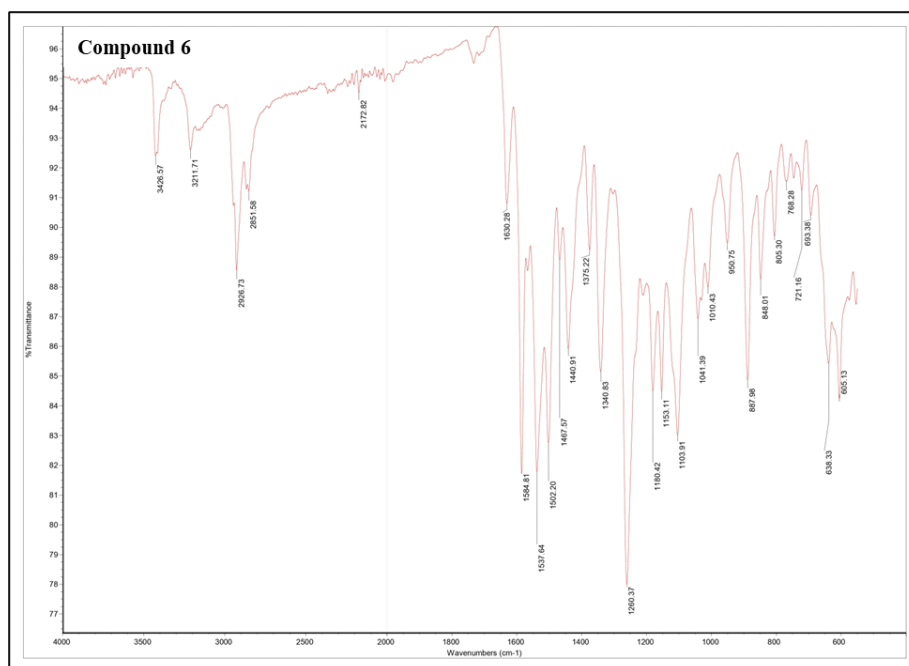
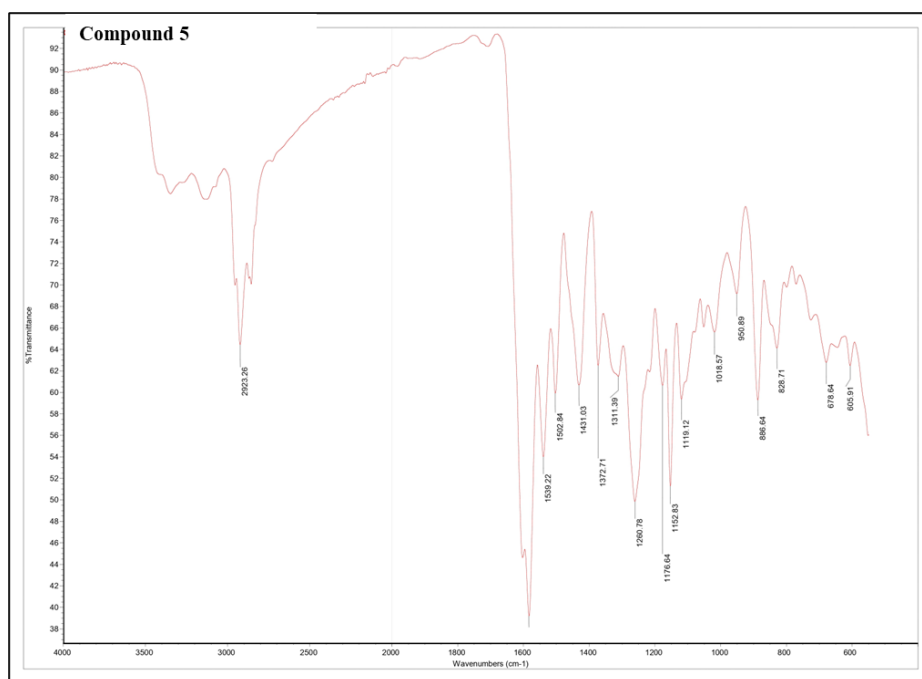
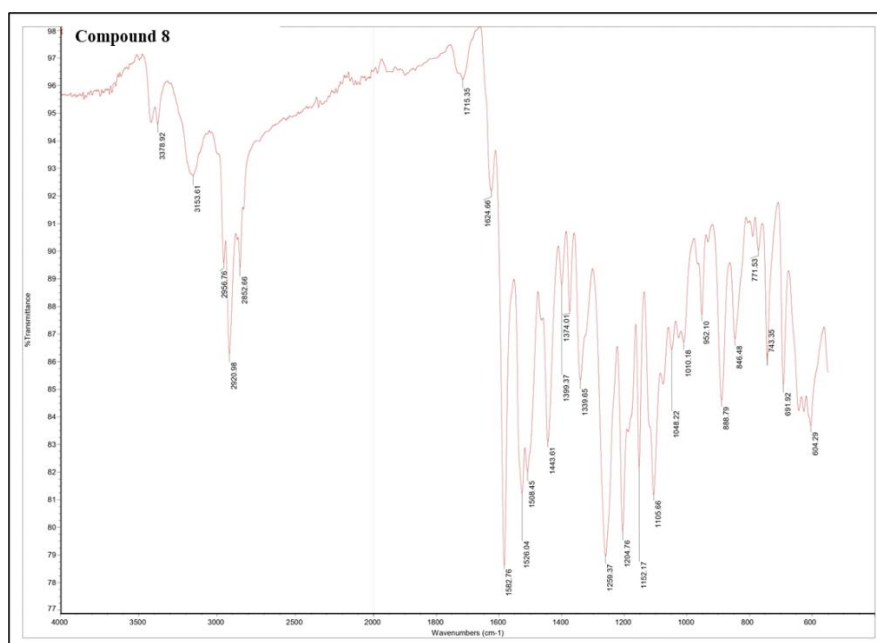
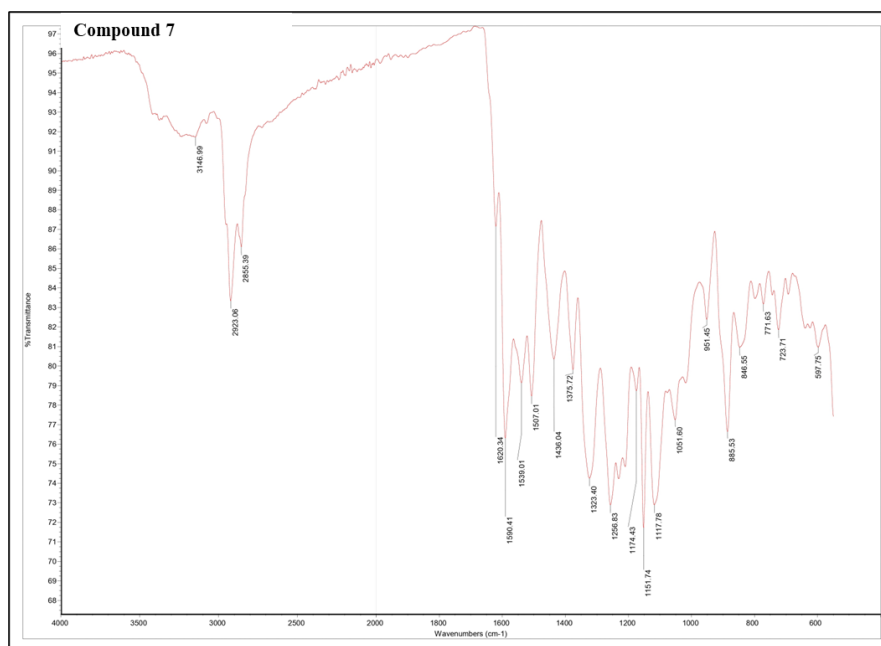


Figure S2. ¹H- and ¹³C-NMR spectra of compound 5-9, 400 MHz. DMSO-d₆ was used as the deuterated solvent.





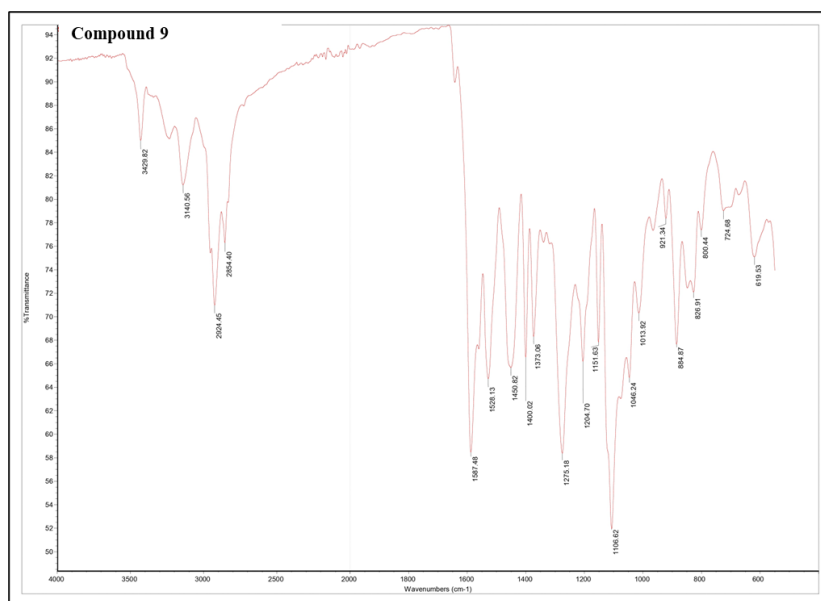
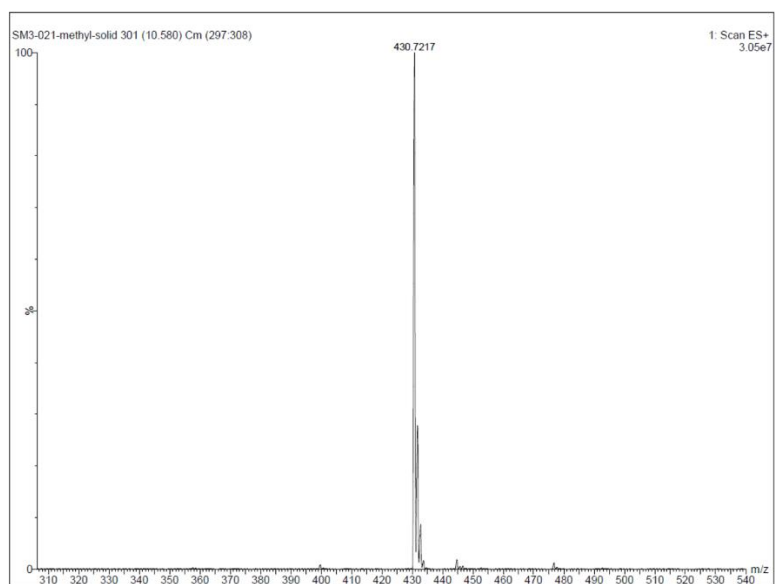
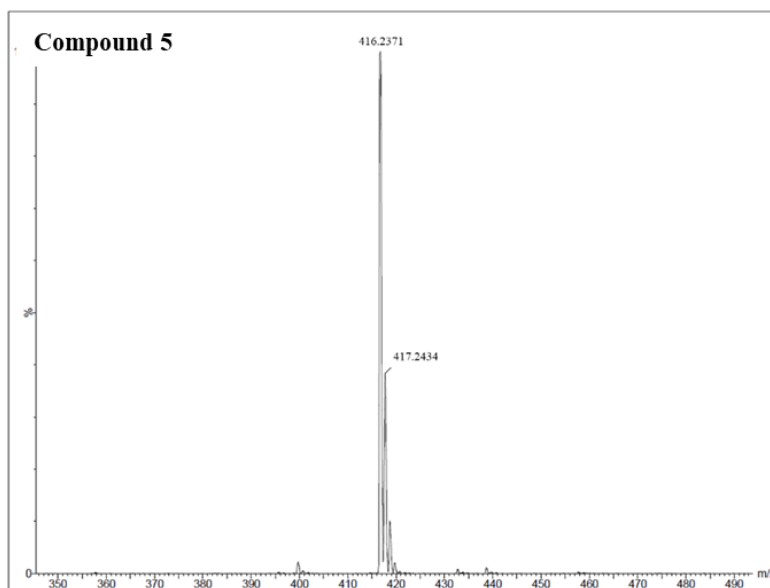


Figure S3. FTIR spectra of compounds 5-9.



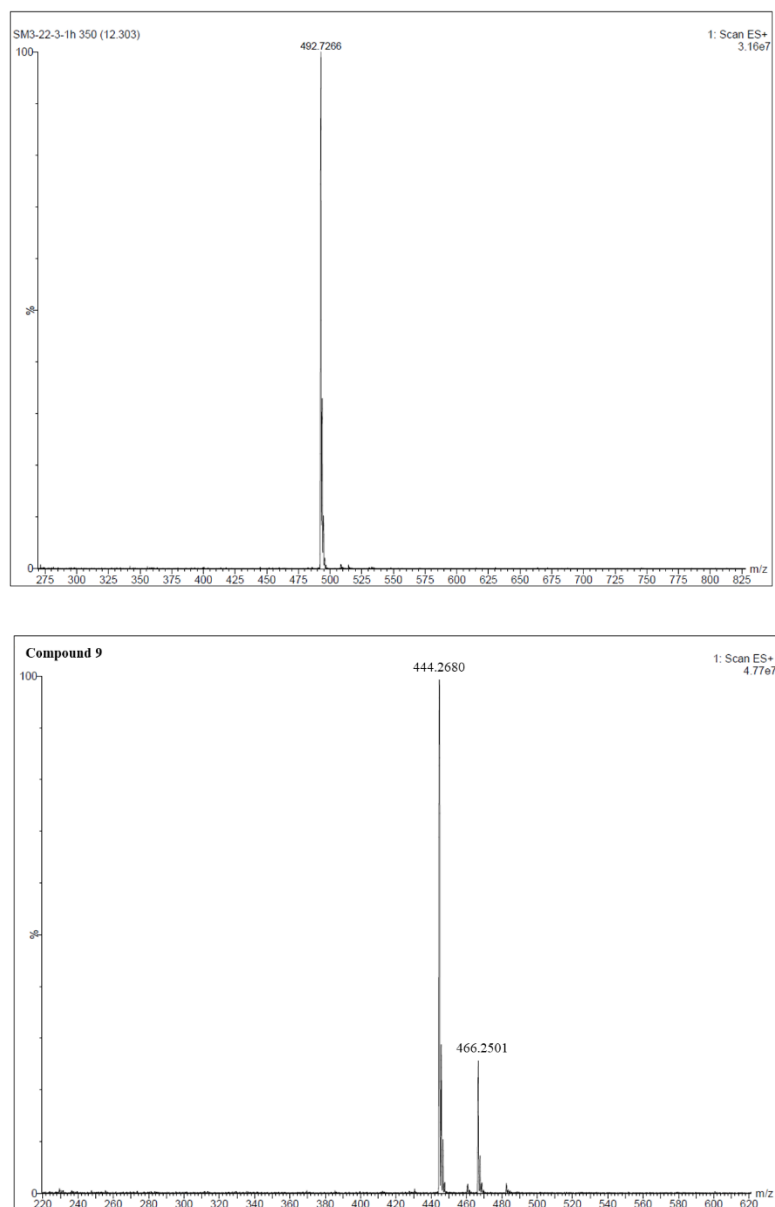


Figure S4. ESI-MS spectra of compounds 5-9.

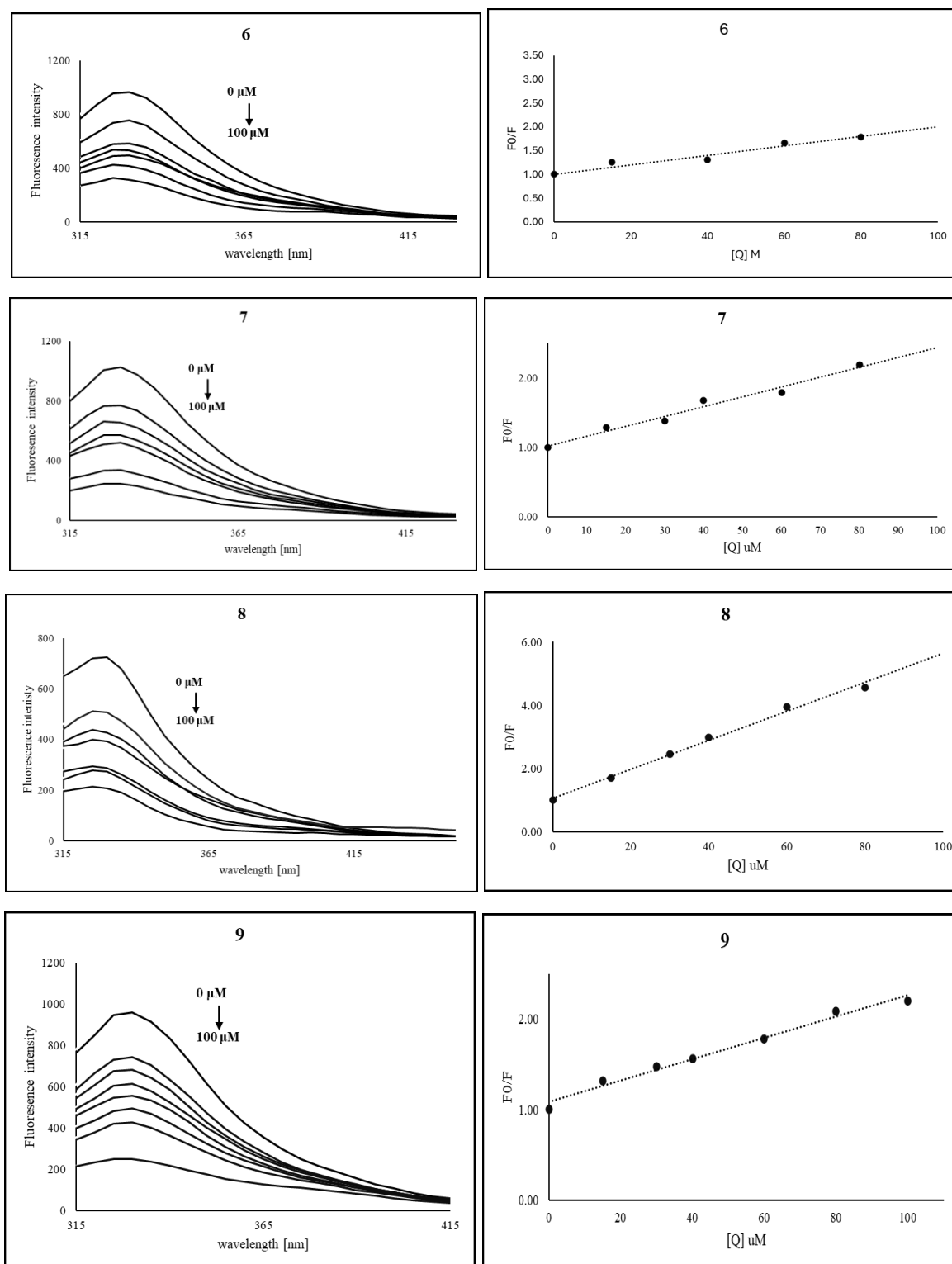
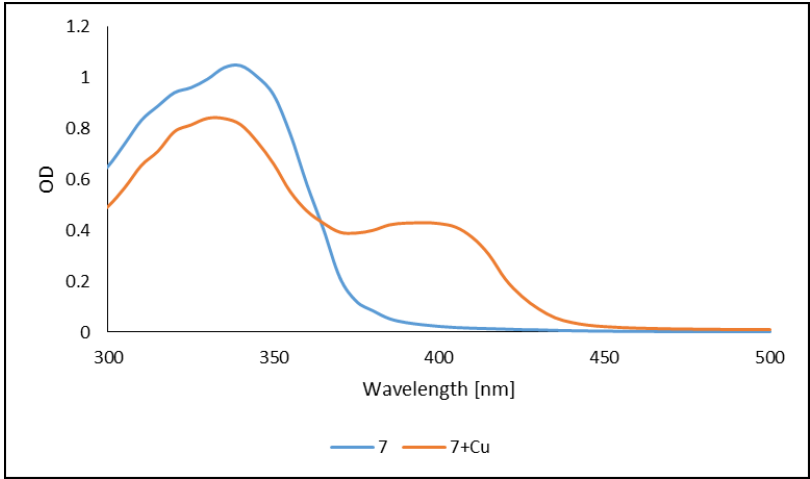
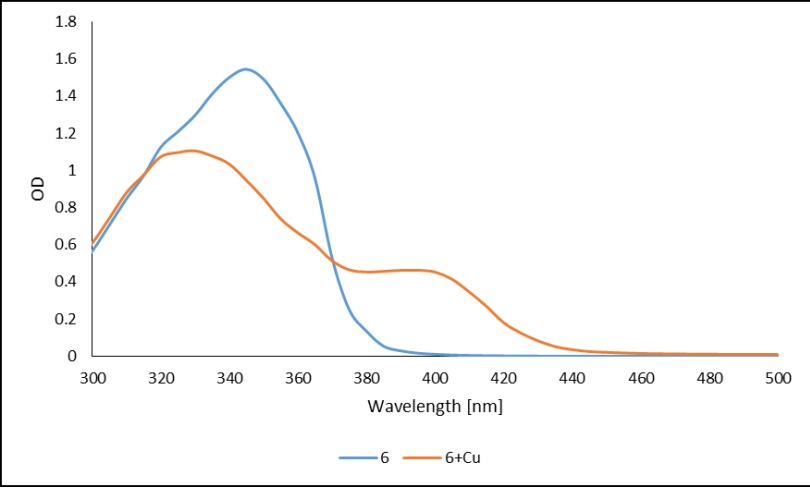
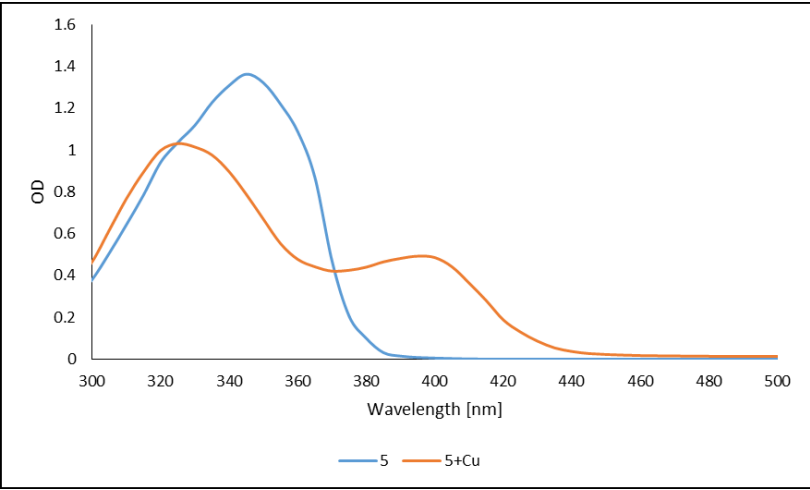


Figure S5. (left) Fluorescence quenching of TYR at $\lambda_{ex}=280$ nm in increasing concentrations of **6-9** at 310 K. (right) Stern-Volmer plots of each tested compound.



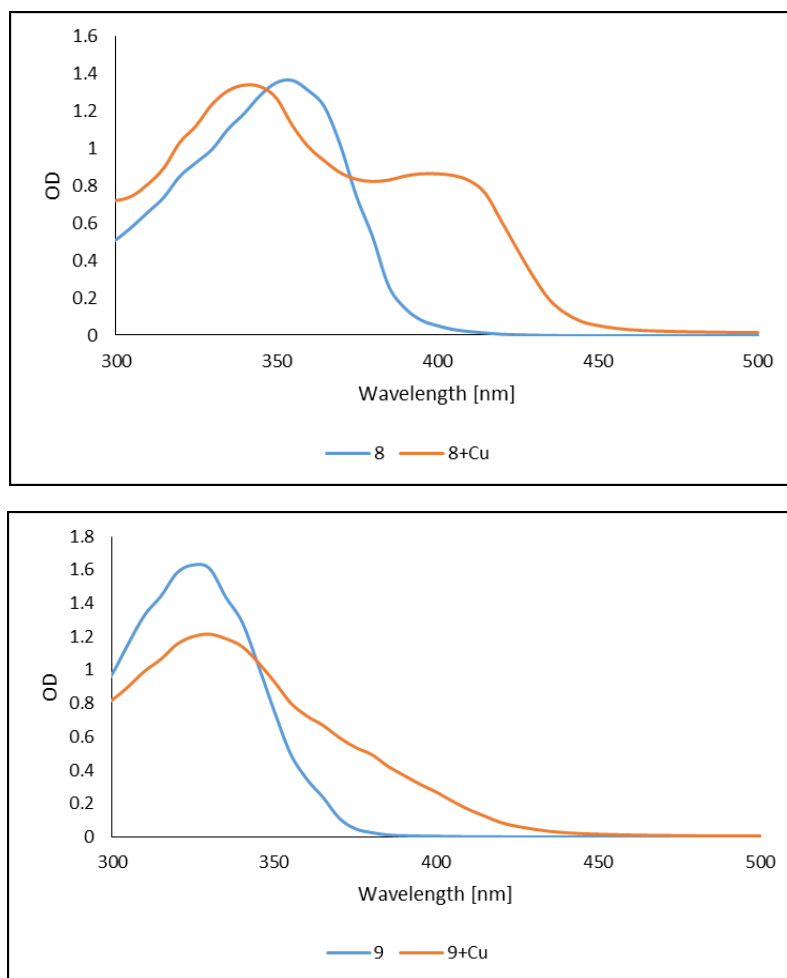
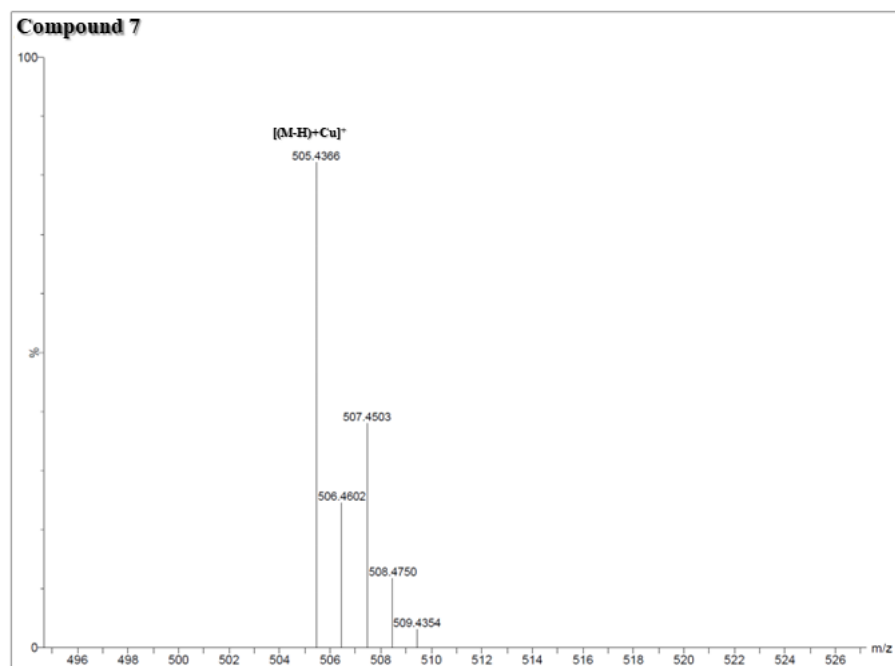
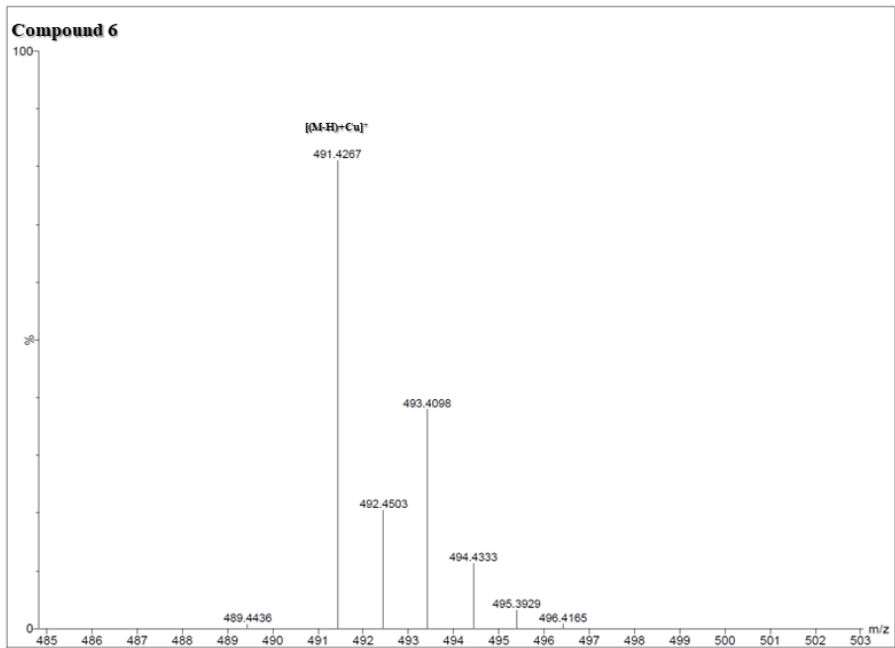


Figure S6. UV-Vis spectra of compounds **5-9** (blue line) and their copper complexes (orange line).



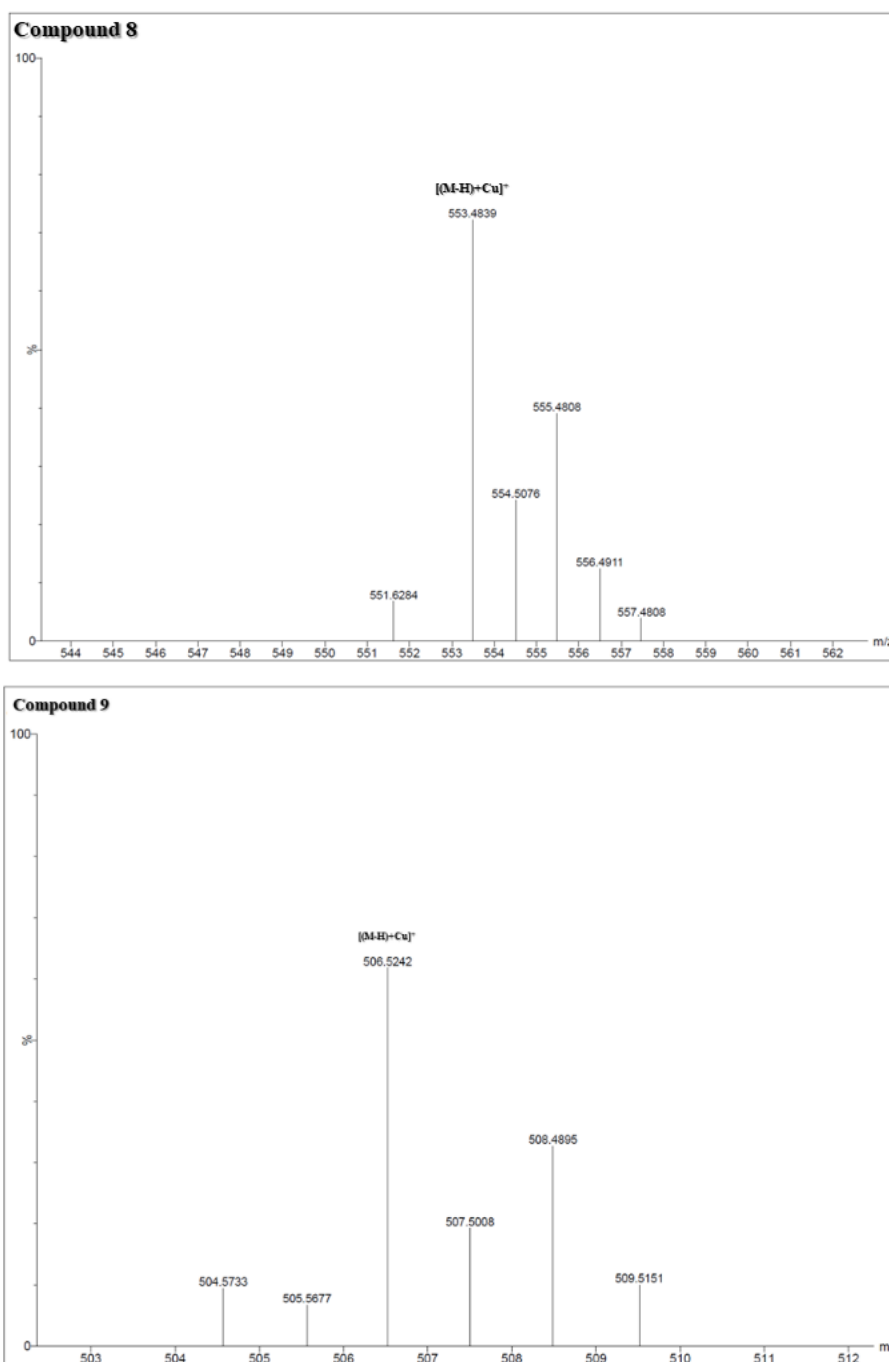


Figure S7. ESI-MS spectra of copper complexes of compounds **6-9**.