Metal-Free Sulfonylation of Quinoxalinones with Sodium Sulfinates via Oxidative O-S Cross-Coupling

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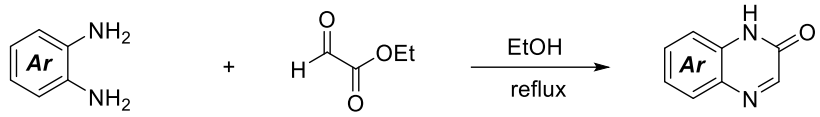
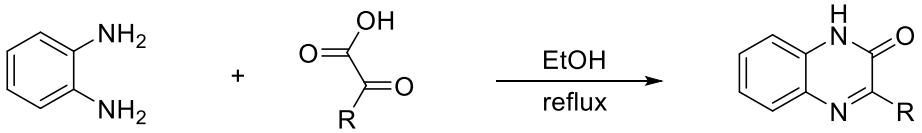
1. General information

Chemicals and solvents were either purchased from commercial suppliers (Titan) or purified by standard techniques. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with GF254 indicator (Yantai Jiangyou Silica gel Development Co., Ltd.) and compounds were visualized by irradiation with UV light at 254 nm. Flash chromatography was carried out utilizing silica gel 200-300 mesh (Qingdao Haiyang Chemical Co., Ltd.). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Plus-400 spectrometer (400 MHz and 100 MHz, respectively). Chemical shifts were reported in ppm downfield and referenced as follows: ^{1}H: TMS (0.00 ppm) or residual internal $CHCl_3$ (δ 7.26 ppm); ^{13}C: internal $CDCl_3$ (δ 77.16 ppm). Coupling constants were quoted in Hz (J). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High resolution mass spectral analysis (HRMS) data were measured on a GCT Premier CAB 048.

2. General procedure for the synthesis of quinoxalinones[1]

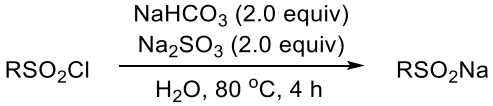


To a solution of 1,2-phenylenediamines (5 mmol, 1.0 equiv.) in ethanol (30 mL) was added ethyl glyoxalate (6 mmol, 1.2 equiv.). The reaction system was stirred and heated to reflux at 85 °C for 1 h, then stirred at room temperature for 16 h. After the reaction was completed (as monitored by TLC), the precipitate was filtered and washed with ethanol (3 × 5 ml), and finally dried to give quinoxalinones.



1,2-Phenylenediamine (5 mmol, 1.0 equiv) and corresponding pyruvic acid (6 mmol, 1.2 equiv) were dissolved in EtOH (30 mL) and heated to reflux. After ~1.5 h, heat was removed and product spontaneously precipitated. Crude product was collected and recrystallized from EtOH to the desired product.

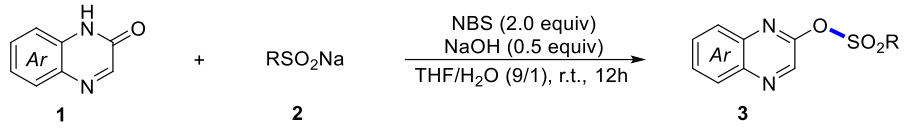
3. General procedure for the synthesis of sodium sulfinates[2]



Sulfonyl chlorides (5.00 mmol) were added to a solution of sodium sulfites (10.0 mmol) and sodium bicarbonate (840 mg, 10.0 mmol) in water (5 mL, 1 M) and heated at 80 °C for 4 h, after cooling to room temperature the volatiles were removed in vacuo. The resultant solids

were repeatedly washed with ethanol. The combined ethanol washes were evaporated under reduced pressure to yield the titled sulfinates as an amorphous solid.

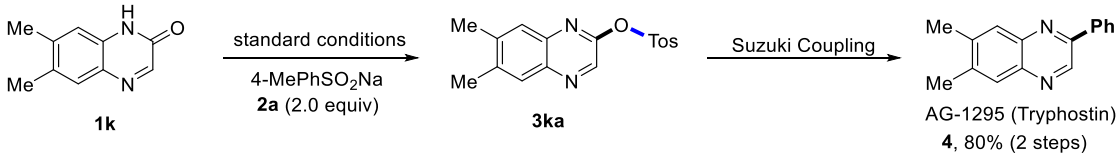
4. General procedure for metal-free oxidation induced selective O-S cross-coupling



To a round-bottom tube was added the corresponding sodium sulfinates **1** (1.0 mmol) and NBS (1.0 mmol), the mixture was stirred at room temperature for 2 min, then THF (1.7 mL) and H_2O (0.3 mL) were added and was stirred for 3 min, finally THF (1 mL), quinoxalinones **2** (0.5 mmol) and NaOH (0.25 mmol) were added. The resulting solution was continued to stir at room temperature for 12 h. Upon completion of the reaction, the mixture was evaporated via rotary evaporator and the residue was purified with flash chromatography to afford the desired product.

5. Synthetic Application to Preparation of Bioactive Molecules[3]

The preparation of 4: An oven dried screw cap glass test tube (25 mL), which was equipped with magnetic stir bar, was charged with **3k** (1.0 mmol), $Pd(OAc)_2$ (4 mol %), XPhos (8 mol%), corresponding boronic acid (2.0 mmol) and K_3PO_4 (3.0 mmol) followed by evacuation of the reaction vessel and backfilling with nitrogen. Anhydrous toluene (8 mL) was then added and the mixture was stirred at 100 °C for 4 h. After completion of the reaction, the cooled suspension was diluted with ethyl acetate (5 mL) and washed with saturated NaCl solution (5 mL) and water (5-10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then purified using column chromatography (PE/EtOAc, 30/1).



6. Mechanistic Experiments

Procedure for the Mechanistic Experiment (Scheme 5, a). To a round-bottom tube was added quinoxalinone (0.5 mmol, 1.0 equiv), sodium sulfinates (1.0 mmol, 2.0 equiv), NBS (1.0 mmol, 2.0 equiv), 3 mL of THF/H_2O (9/1) and TEMPO (2.0 equiv). The resulting solution was continued to stir at room temperature for 12 h. Upon completion of the reaction, the mixture was evaporated via rotary evaporator and the residue was purified with flash chromatography to afford the desired product with 86%.

Procedure for the Mechanistic Experiment (Scheme 5, b). To a round-bottom tube was added sodium sulfinates (1.0 mmol, 2.0 equiv) and NBS (1.0 mmol, 2.0 equiv), 3 mL of THF/H_2O (9/1). And then the mixture was stirred at r.t. for 12 h. Finally, 4-$MePhSO_2Br$ was produced in 48% isolated yield after flash chromatography.

Procedure for the Mechanistic Experiment (Scheme 5, c). To a round-bottom tube was added quinoxalinone (0.5 mmol, 1.0 equiv), 4-methyl-benzenesulfonyl bromide (1.0 mmol, 2.0 equiv), 3 mL of THF/H_2O (9/1), and NaOH (0.0 equiv), NaOH (0.5 equiv), NaOH (1.0 equiv), respectively. And then the mixture was stirred at r.t. for 12 h. Finally, **3a** was afforded via flash chromatography with trace, 43% and 89%, respectively.

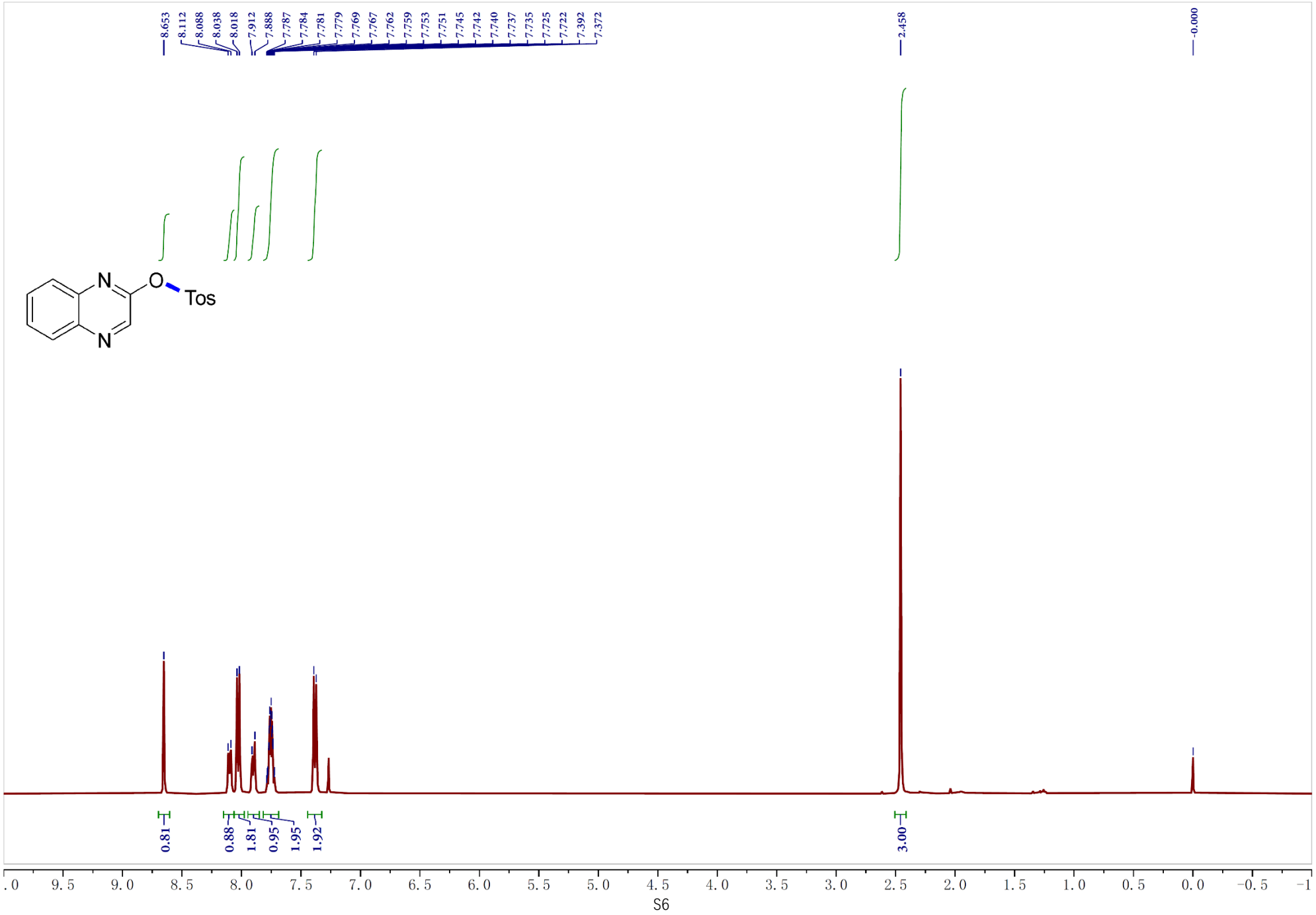
7. References

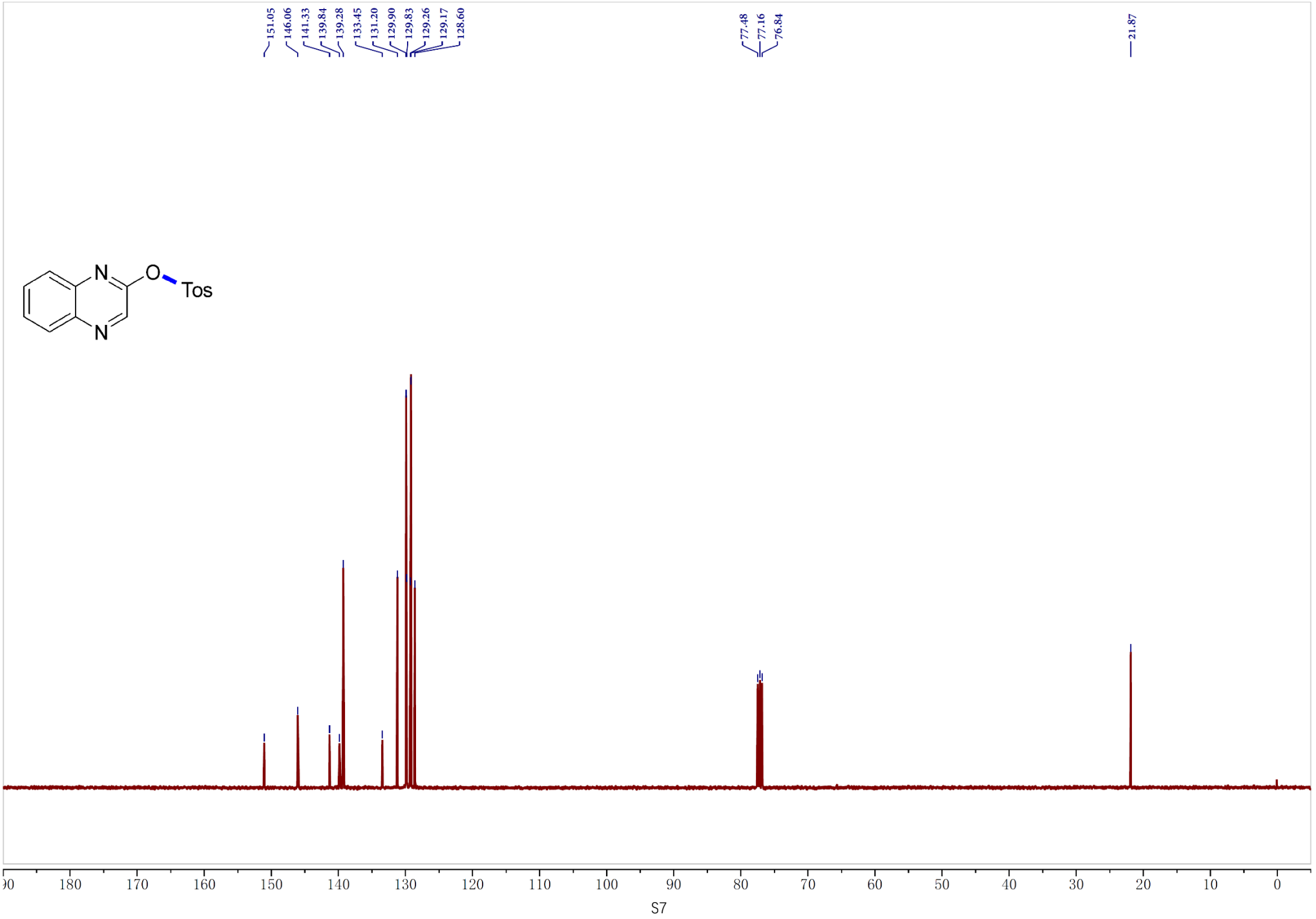
1. (a) Lawrence, D. S.; Copper, J. E.; Smith, C. D. J. Med. Chem. **2001**, *44*, 594; (b) Dou, G.-Y.; Jiang, Y.-Y.; Xu, K.; Zeng, C.-C. *Org. Chem. Front.* **2019**, *6*, 2392.

2. Jiang, M.; Yuan, Y.; Wang, T.; Xiong, Y.; Li, J.; Guo, H.; Lei, A. *Chem. Commun.* **2019**, *55*, 13852.

3. Maichrowski, J.; Hübner, E. G.; Kaufmann, D. E. *Eur. J. Org. Chem.* **2013**, 8185

8. Copies of Product NMR Spectra

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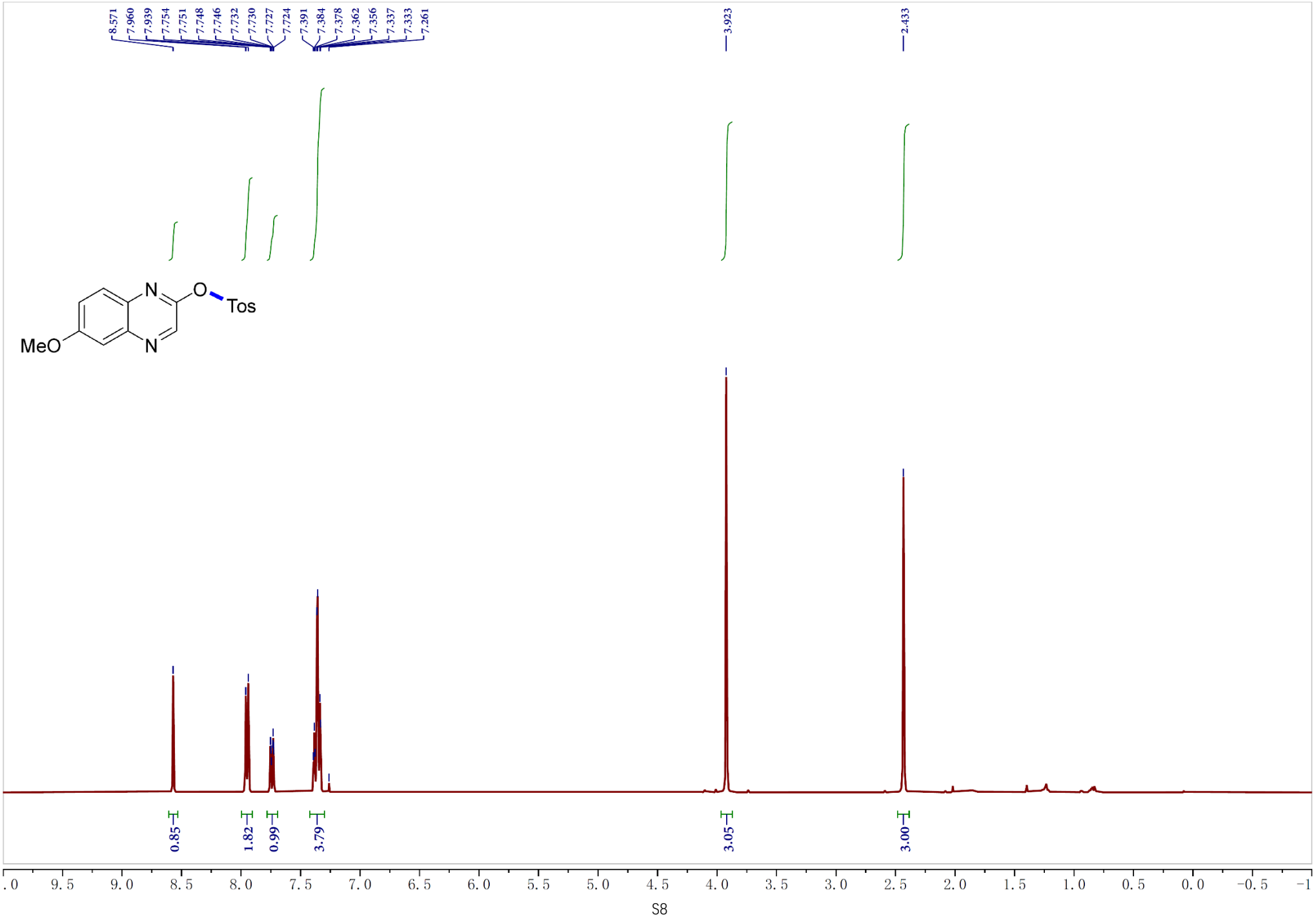
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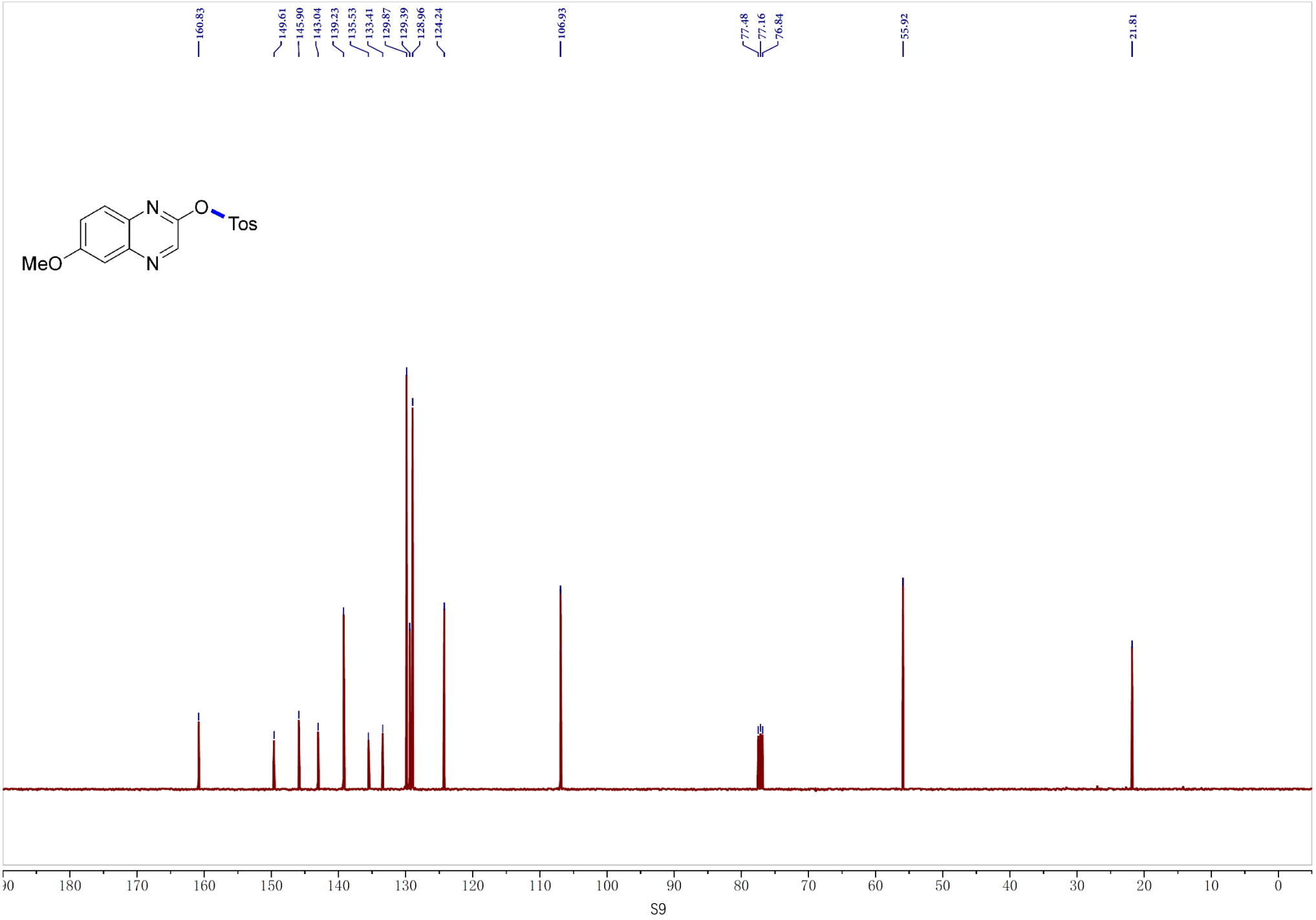
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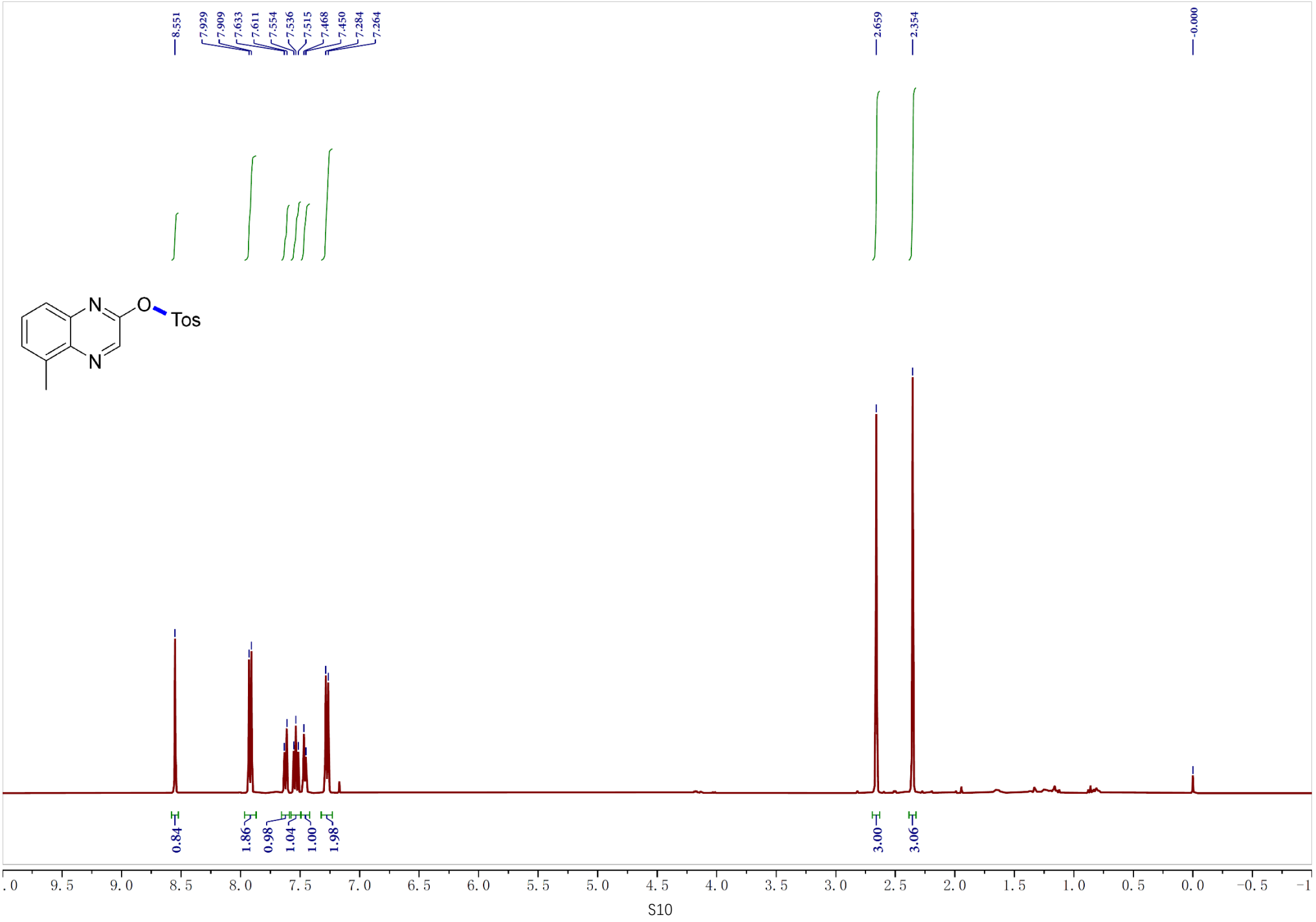
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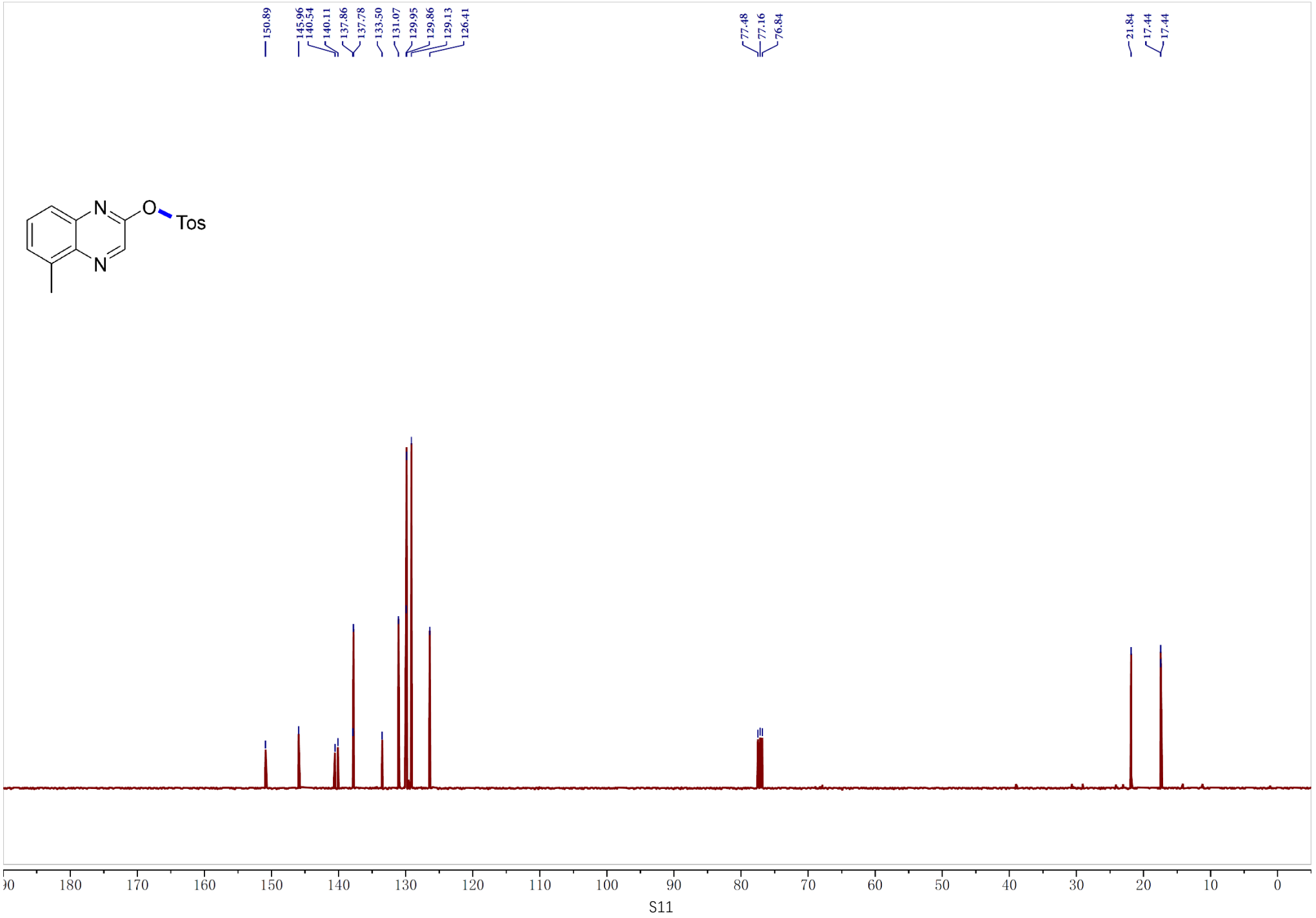
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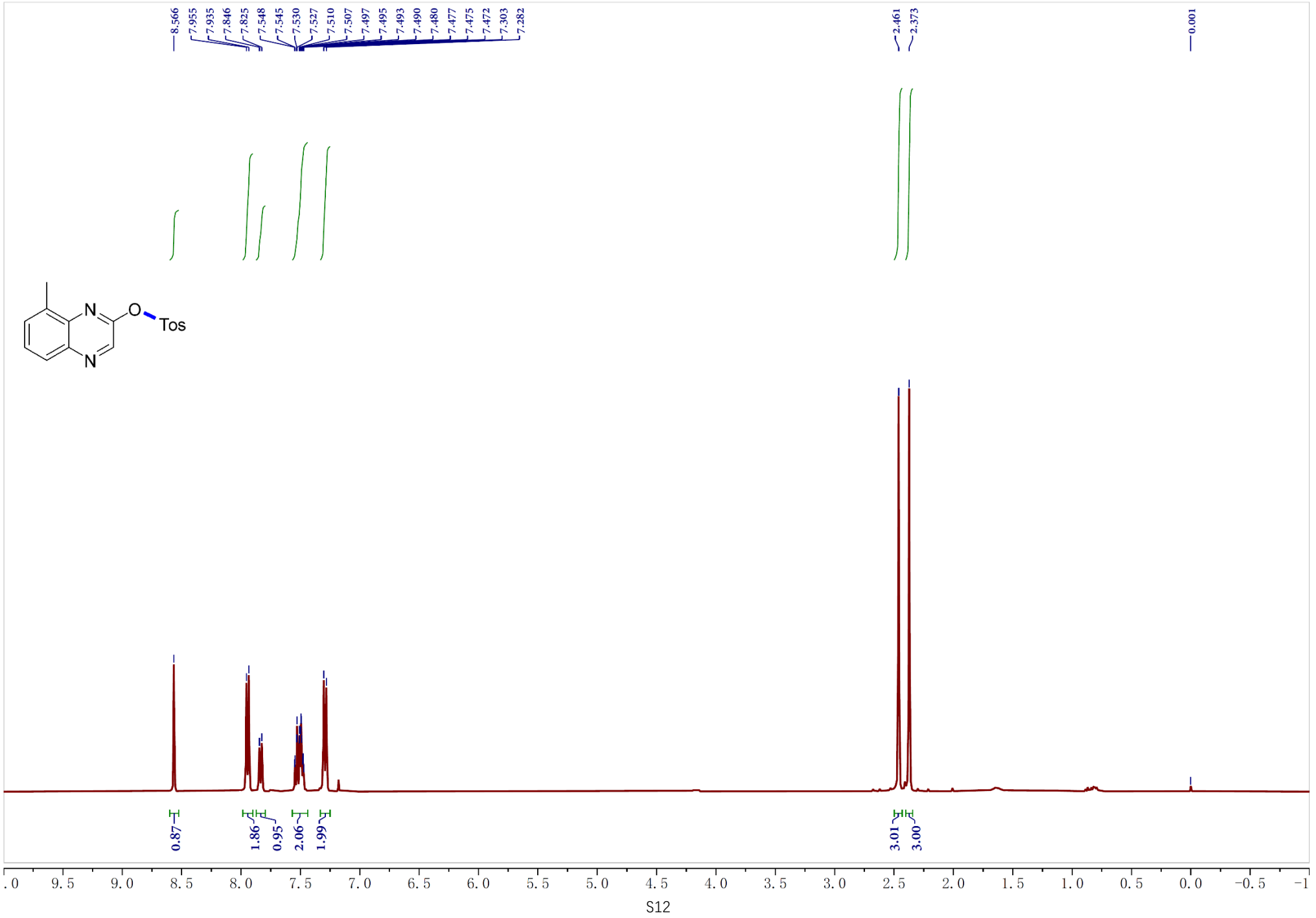
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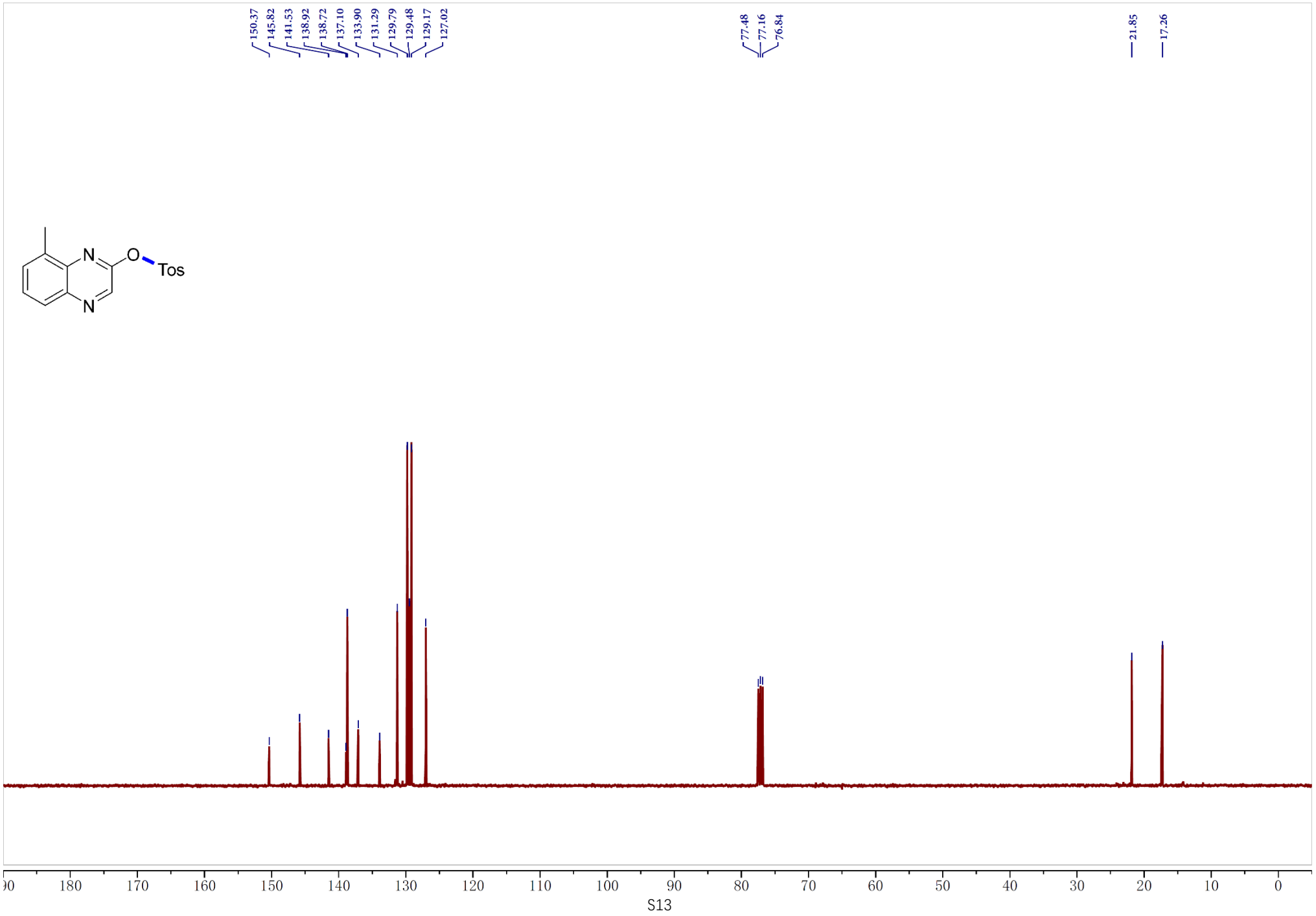
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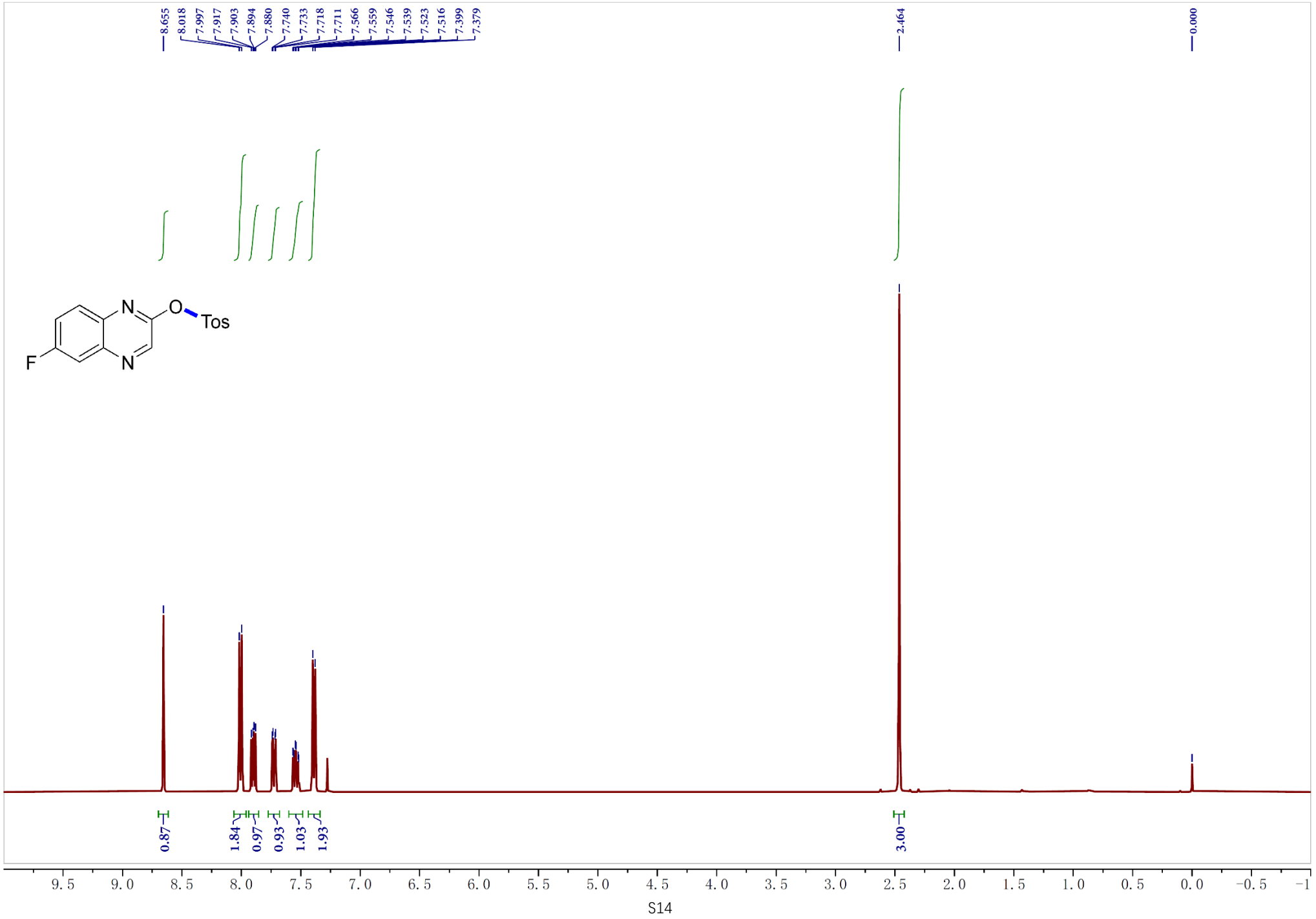
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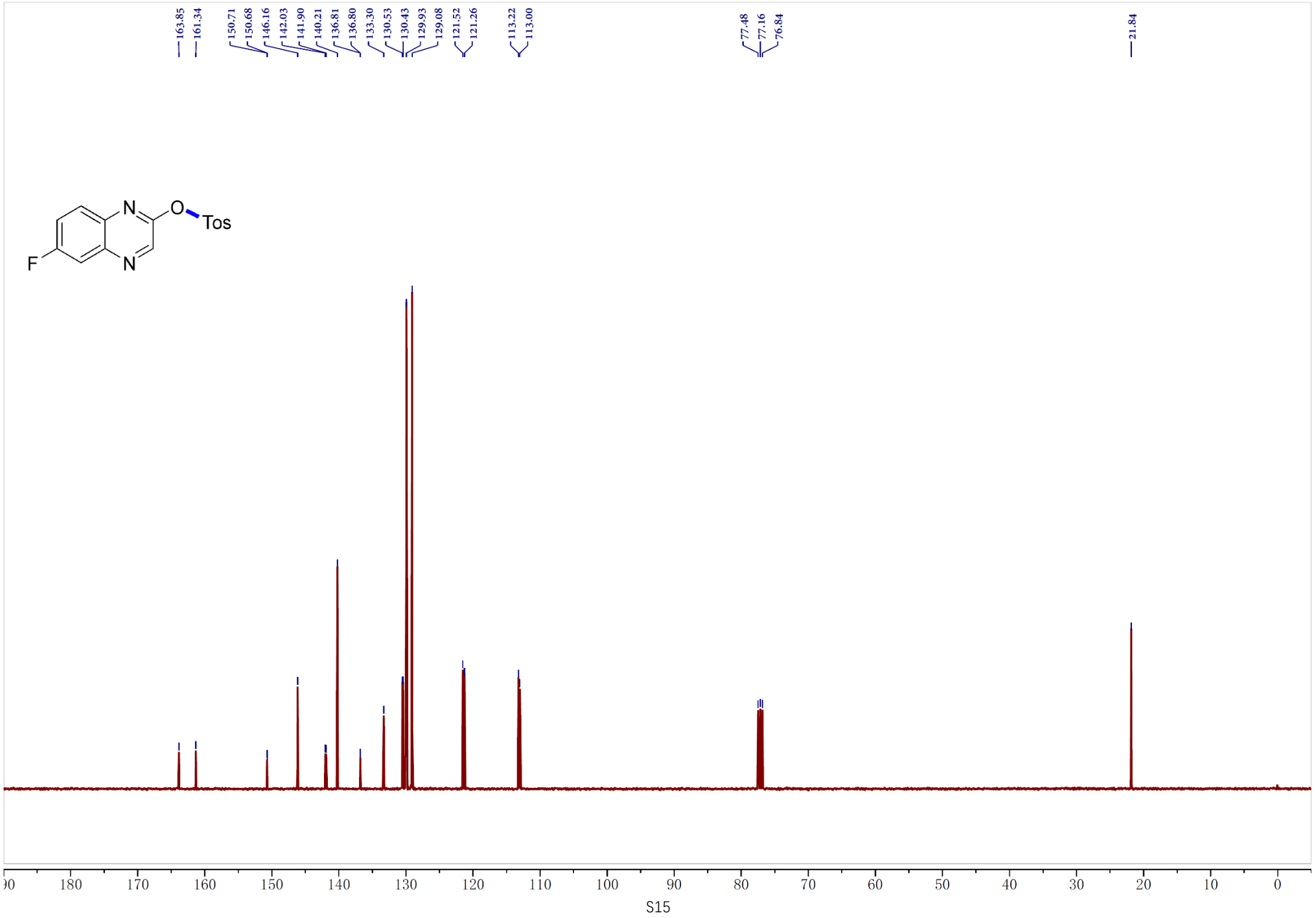
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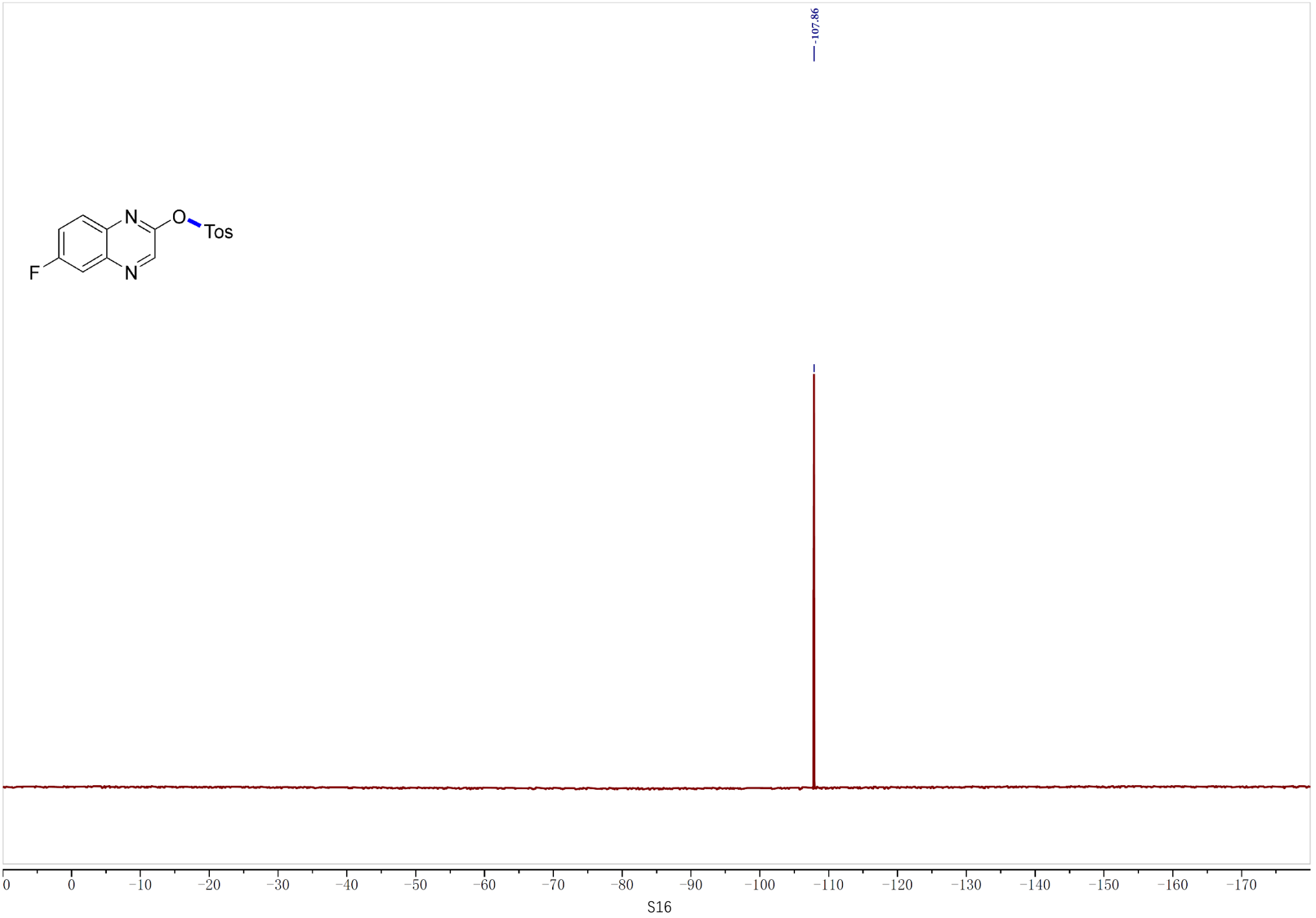
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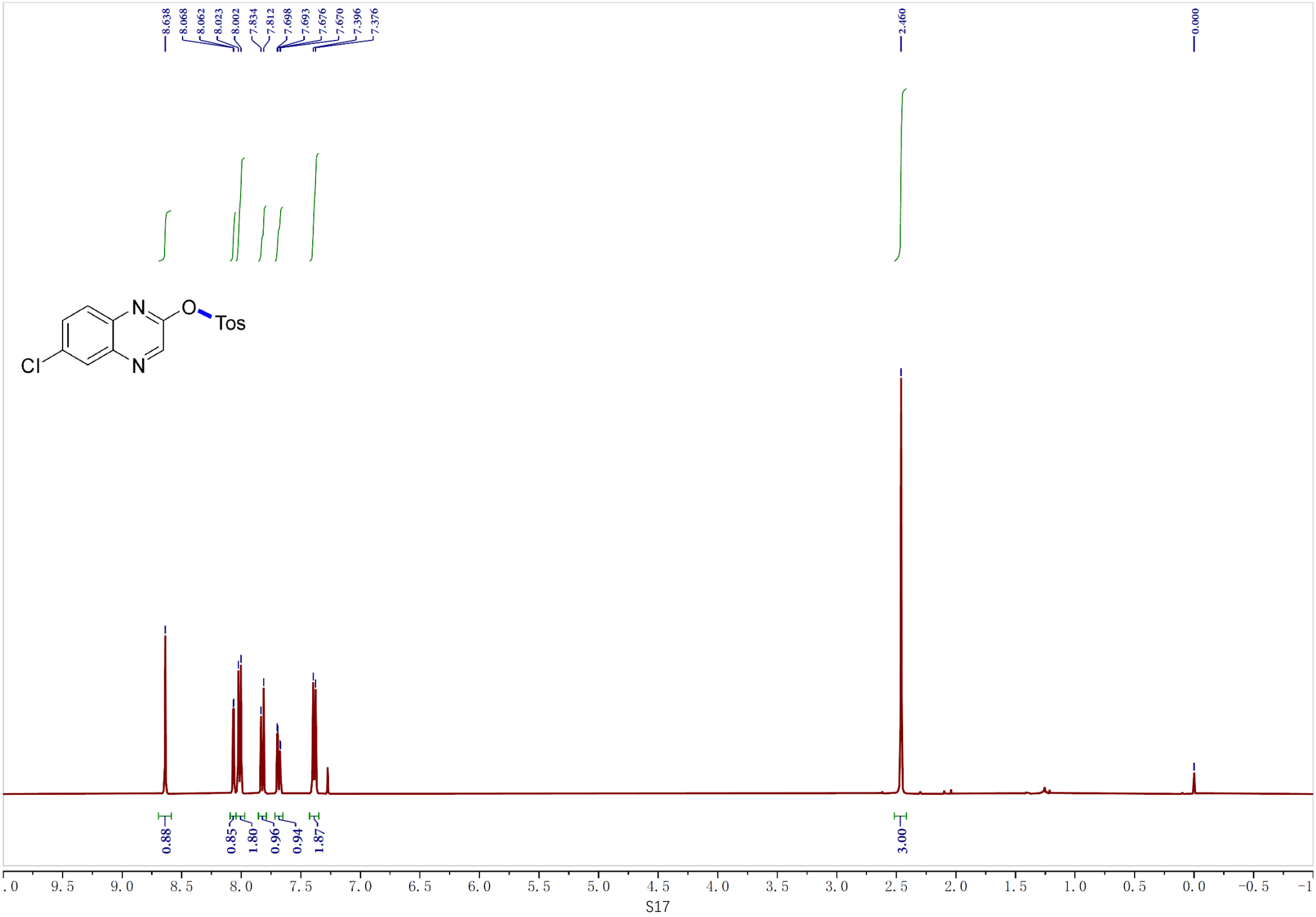
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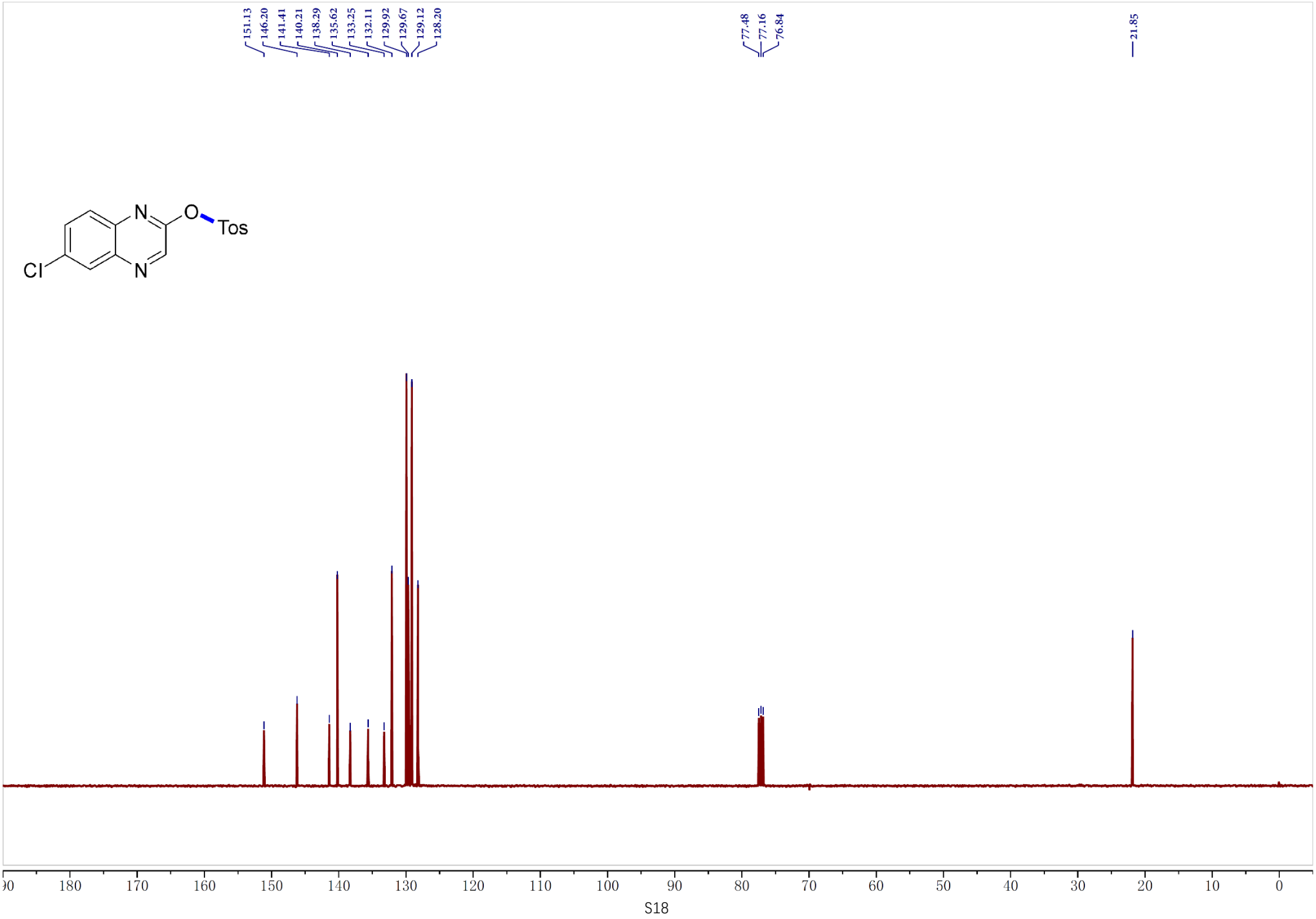
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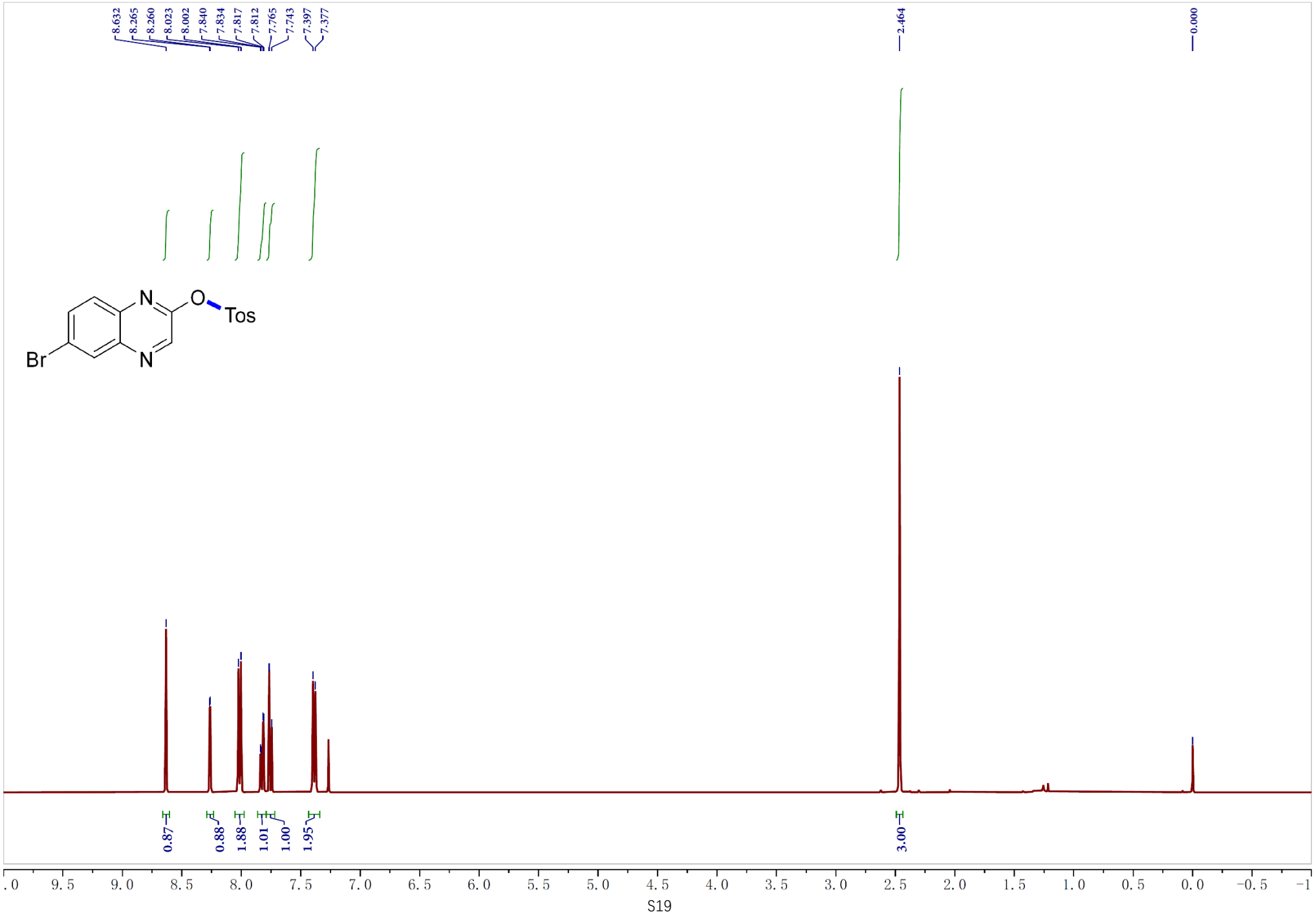
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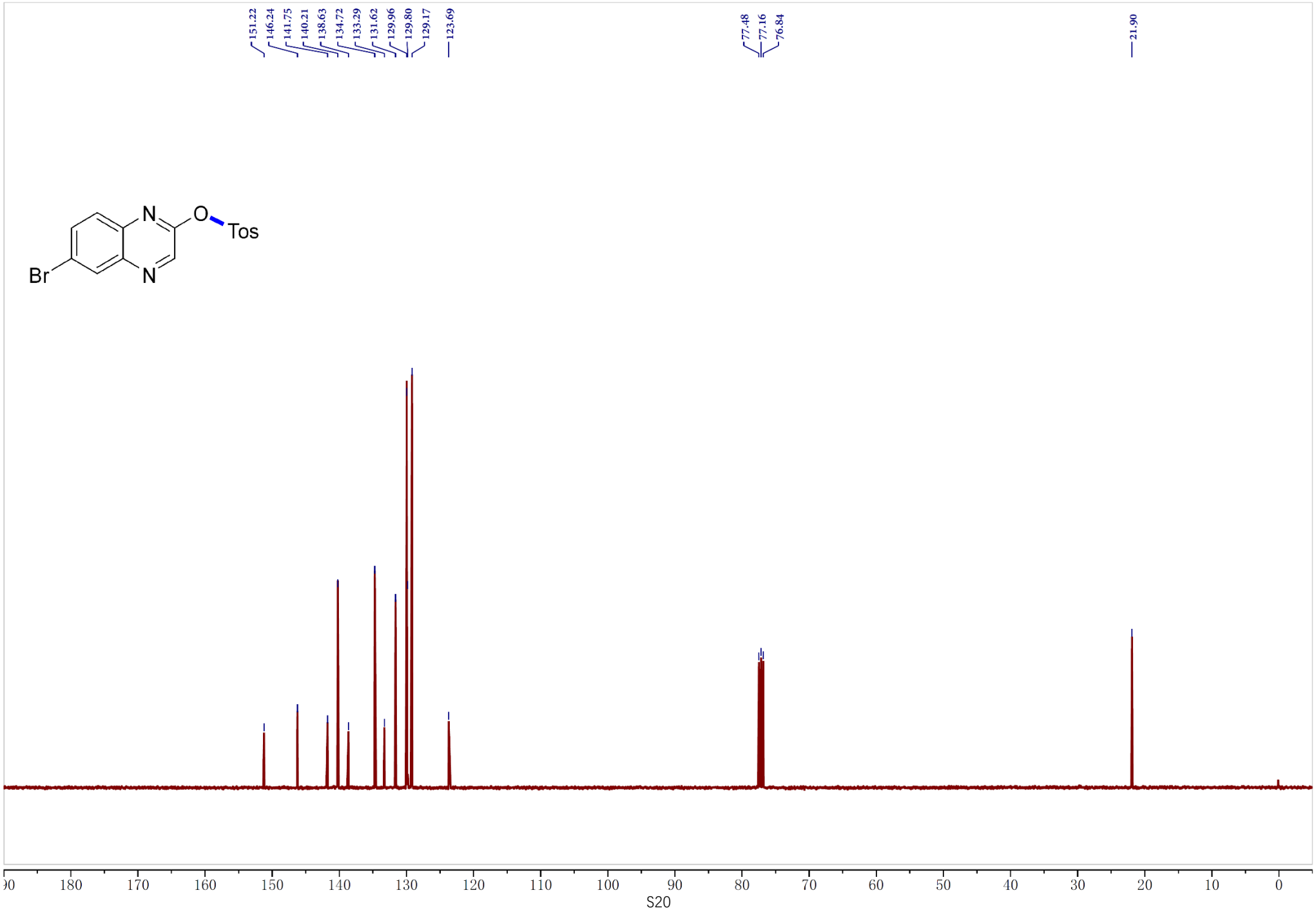
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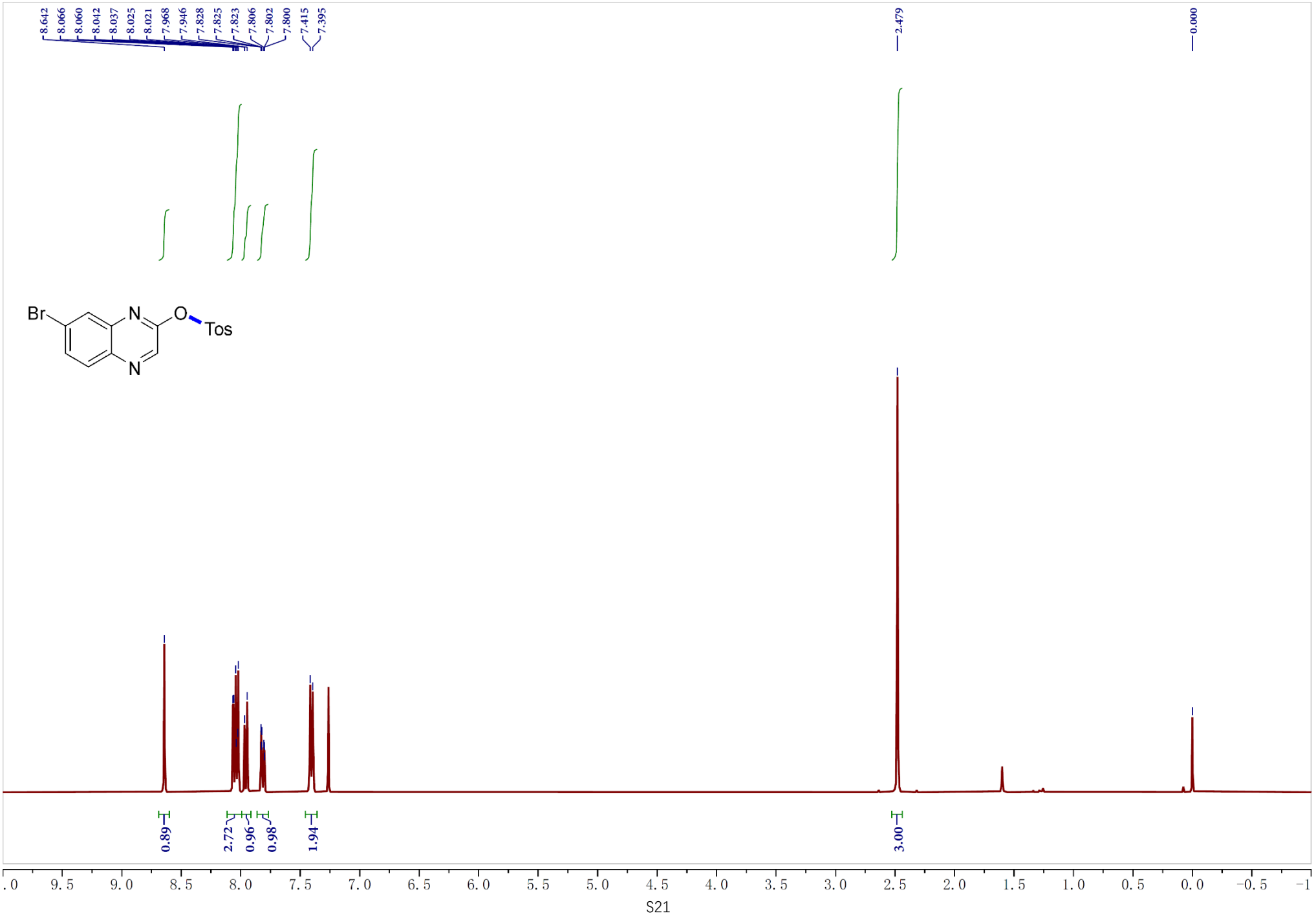
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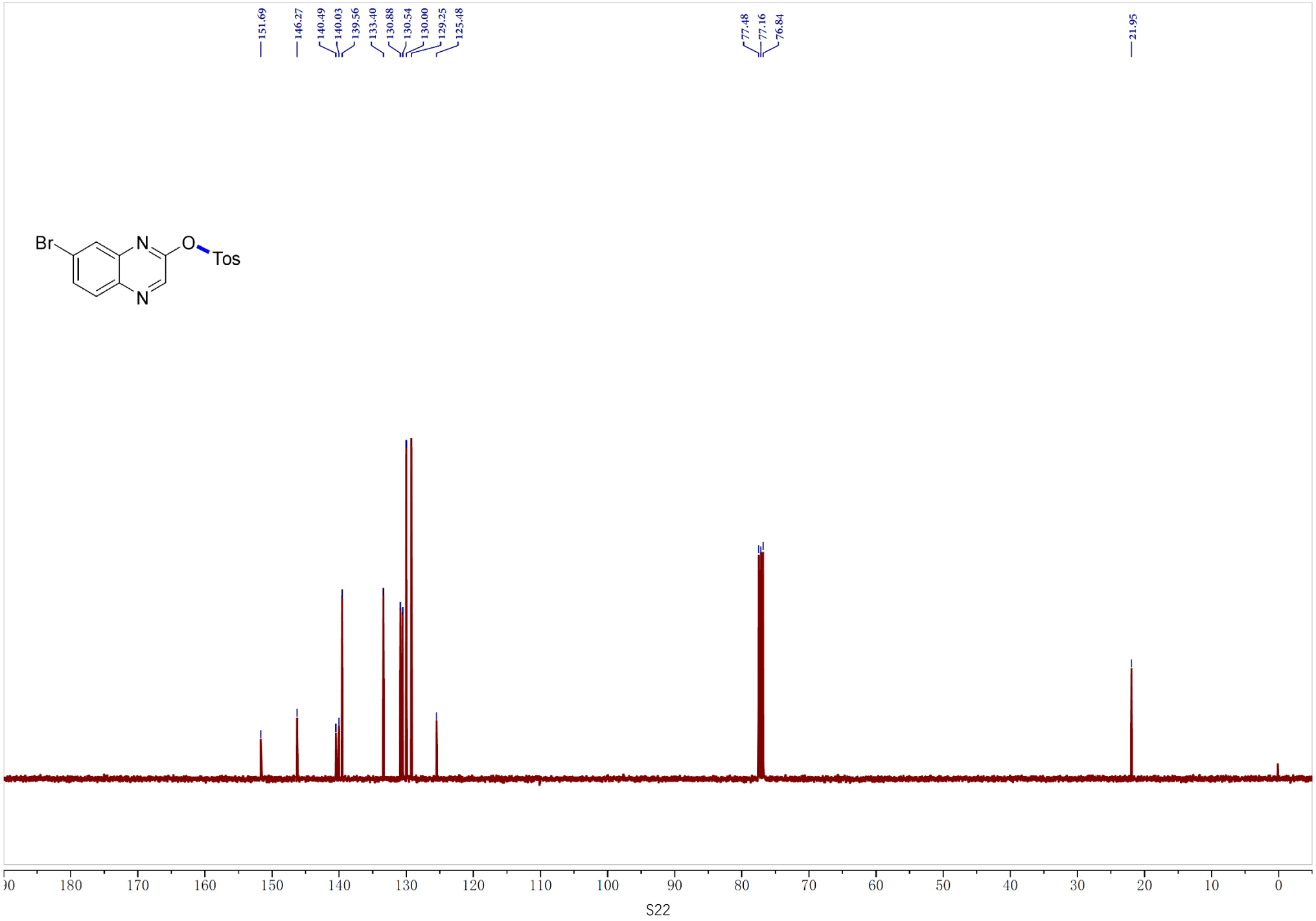
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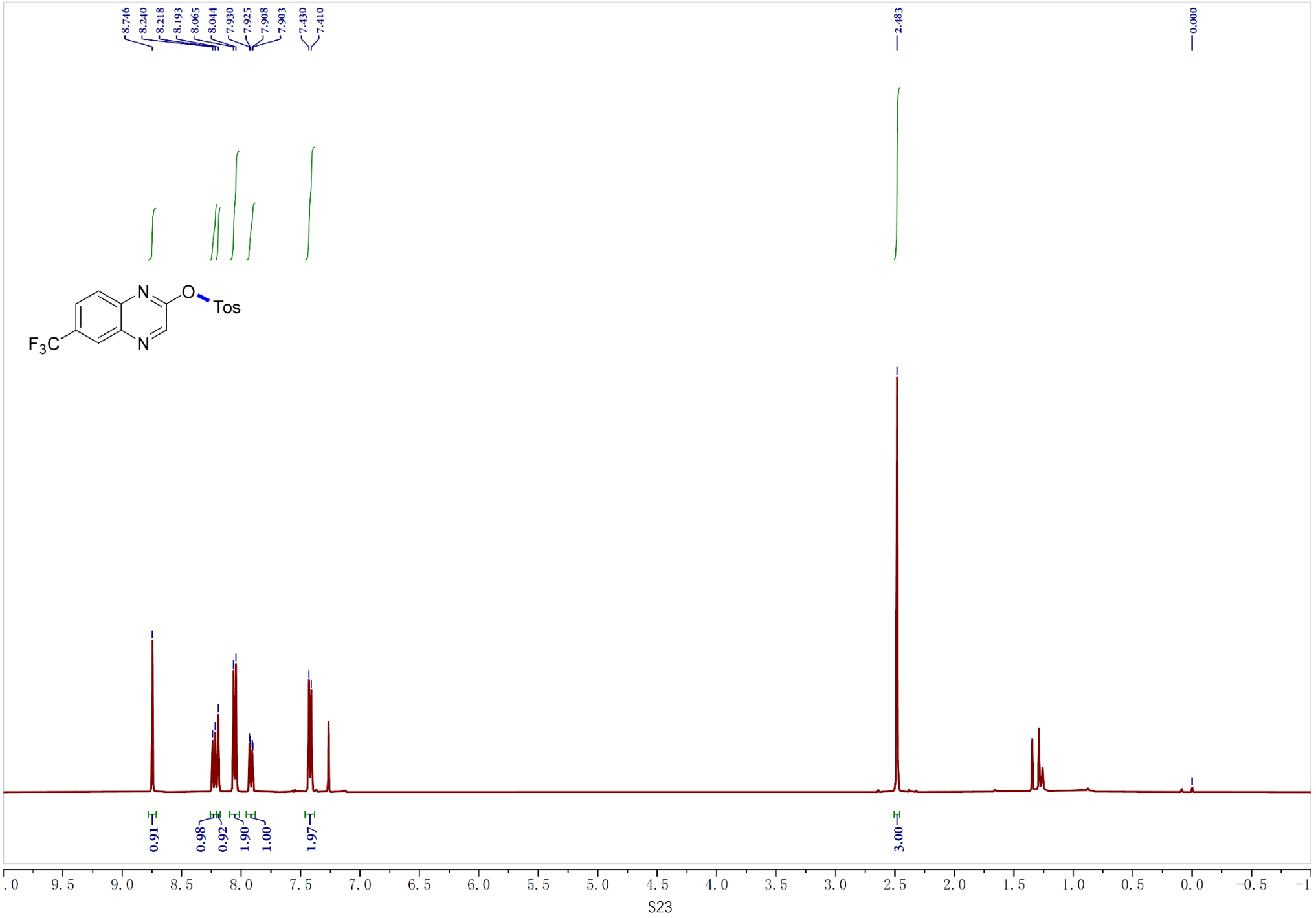
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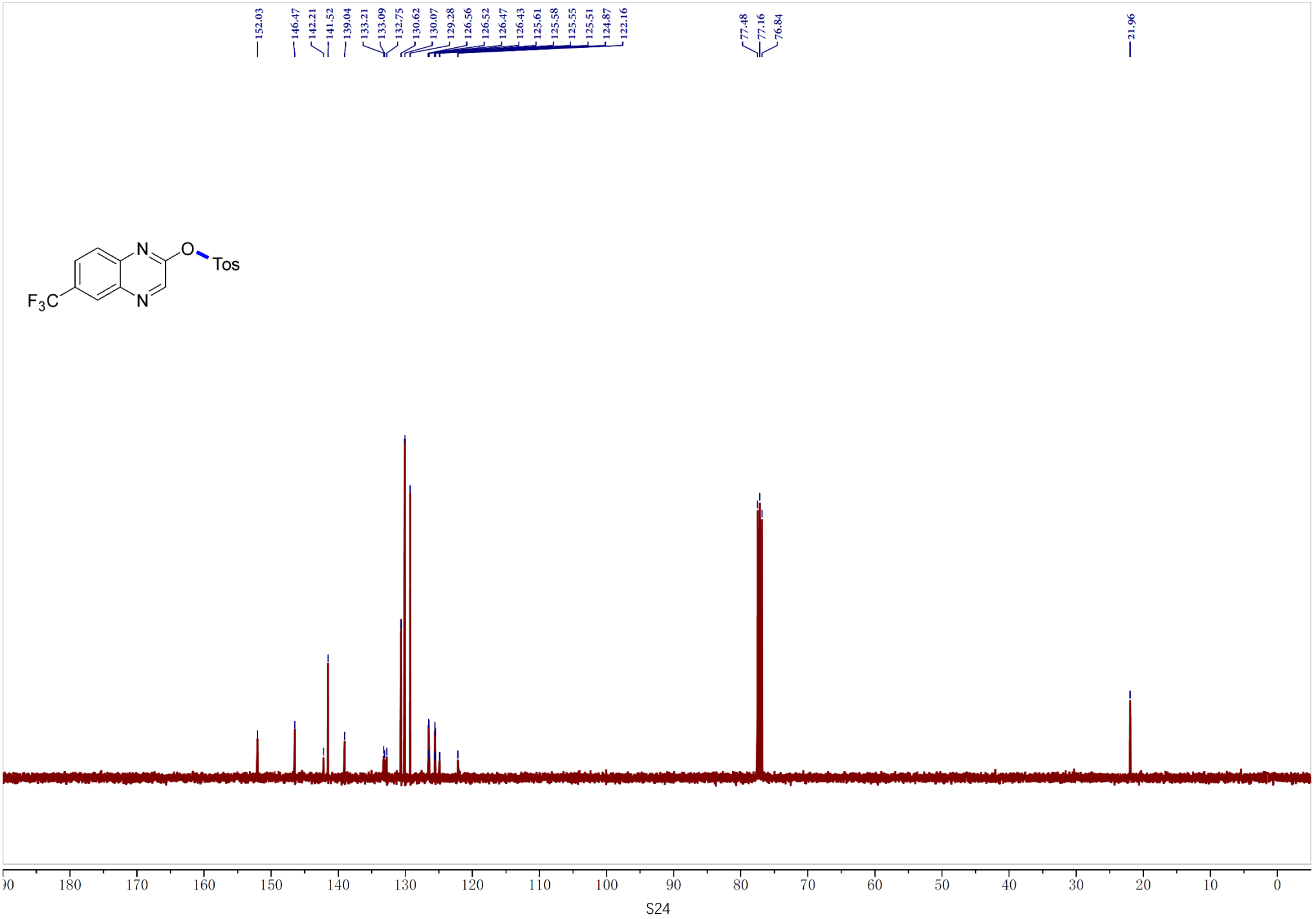
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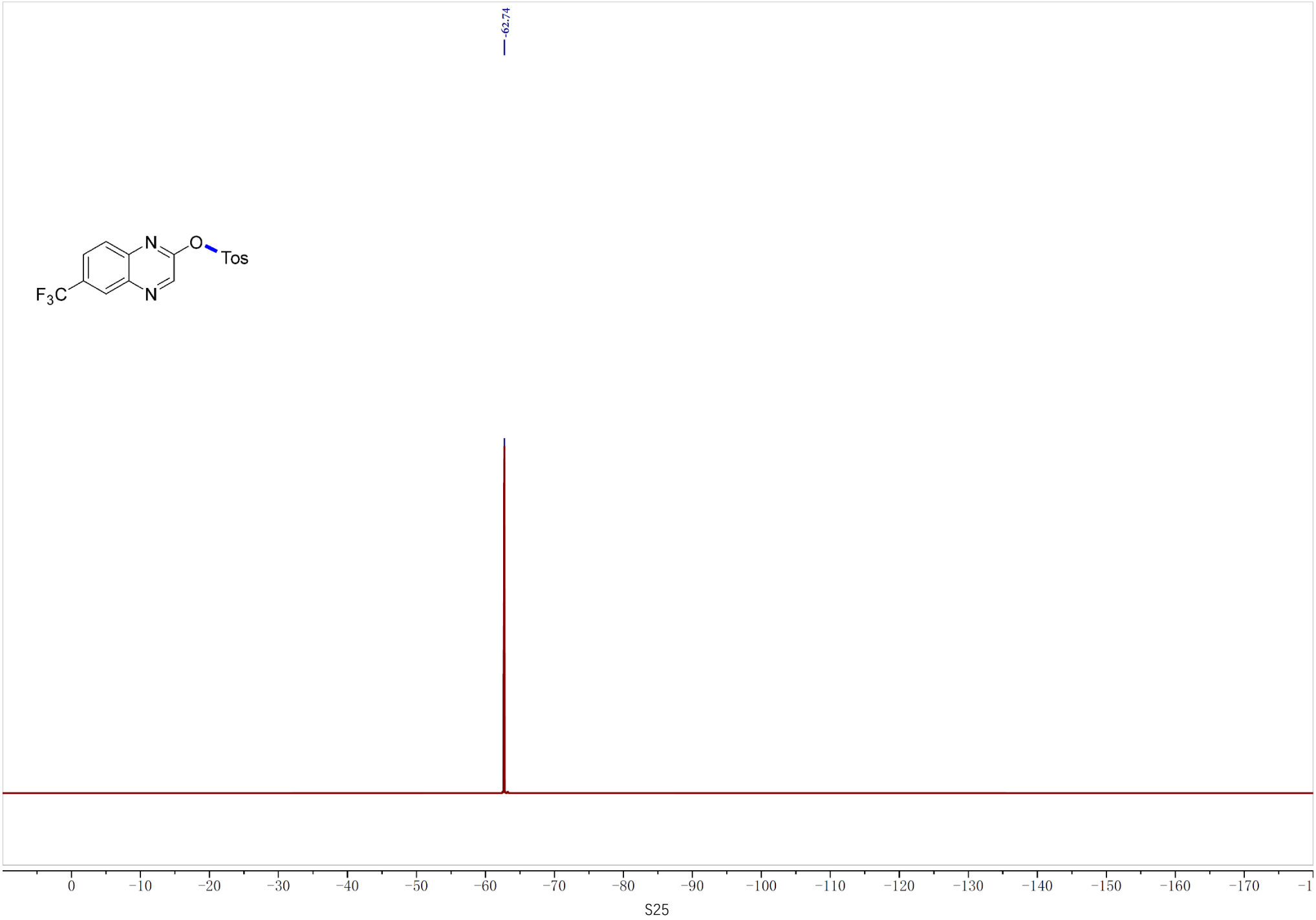
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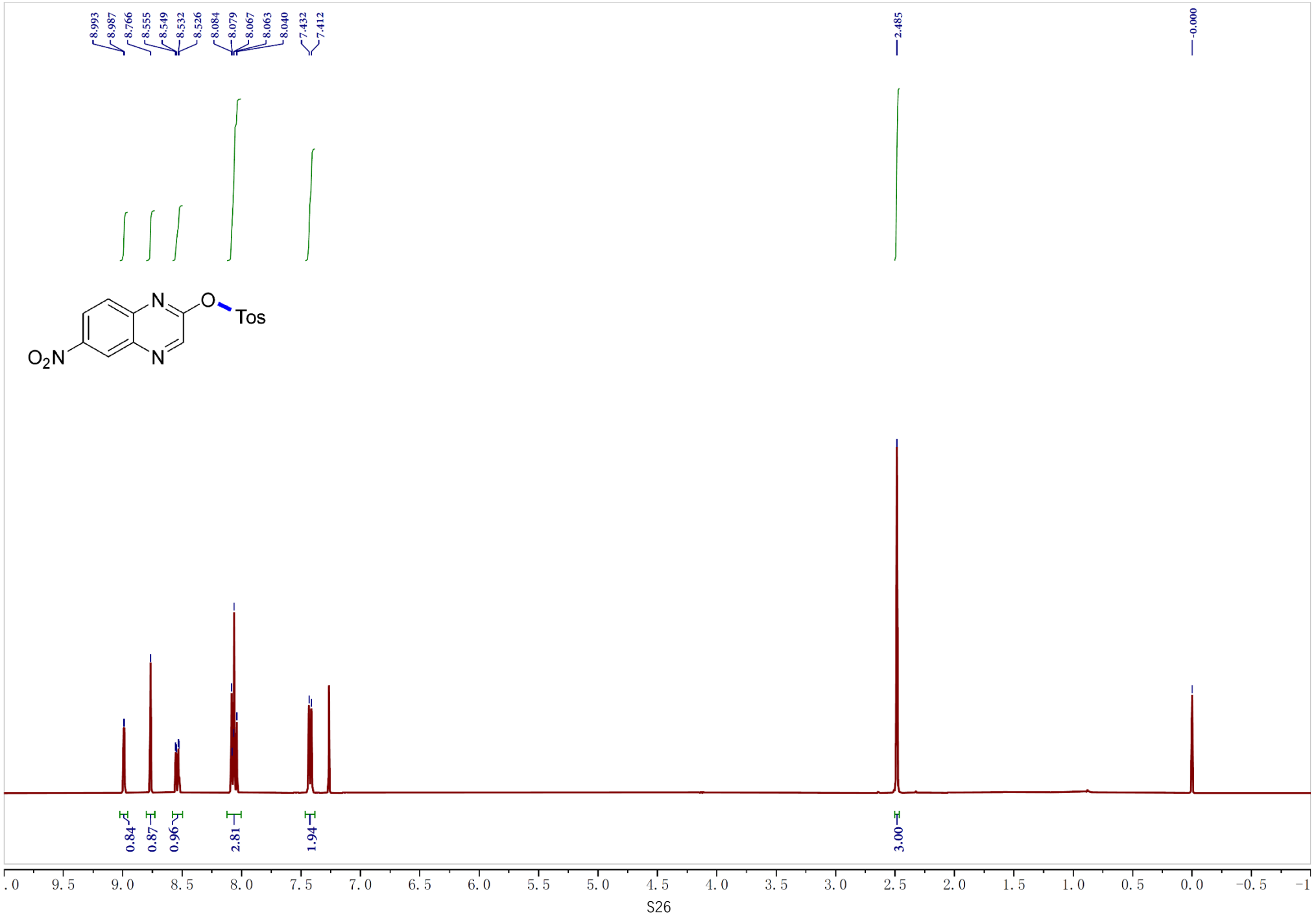
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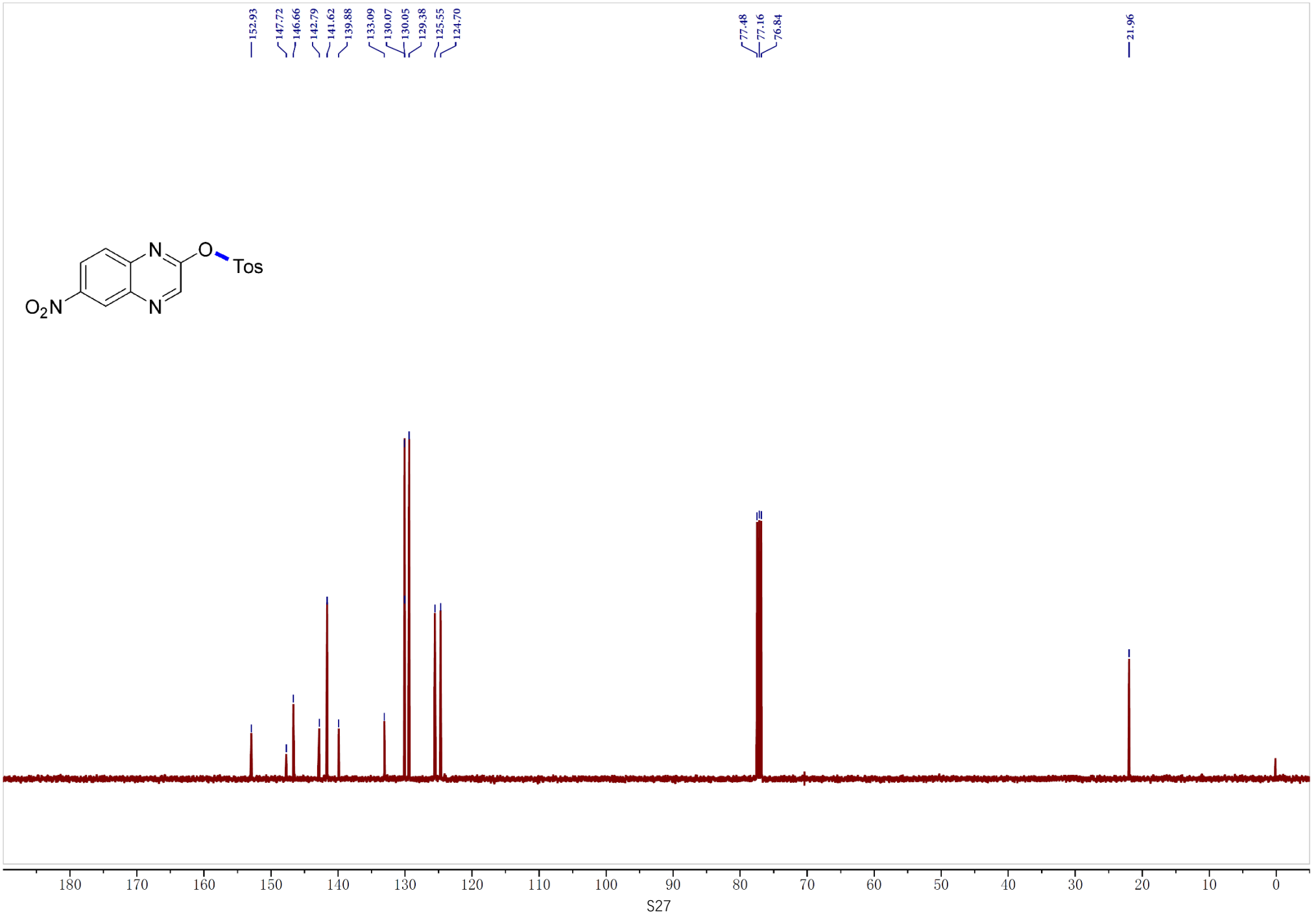
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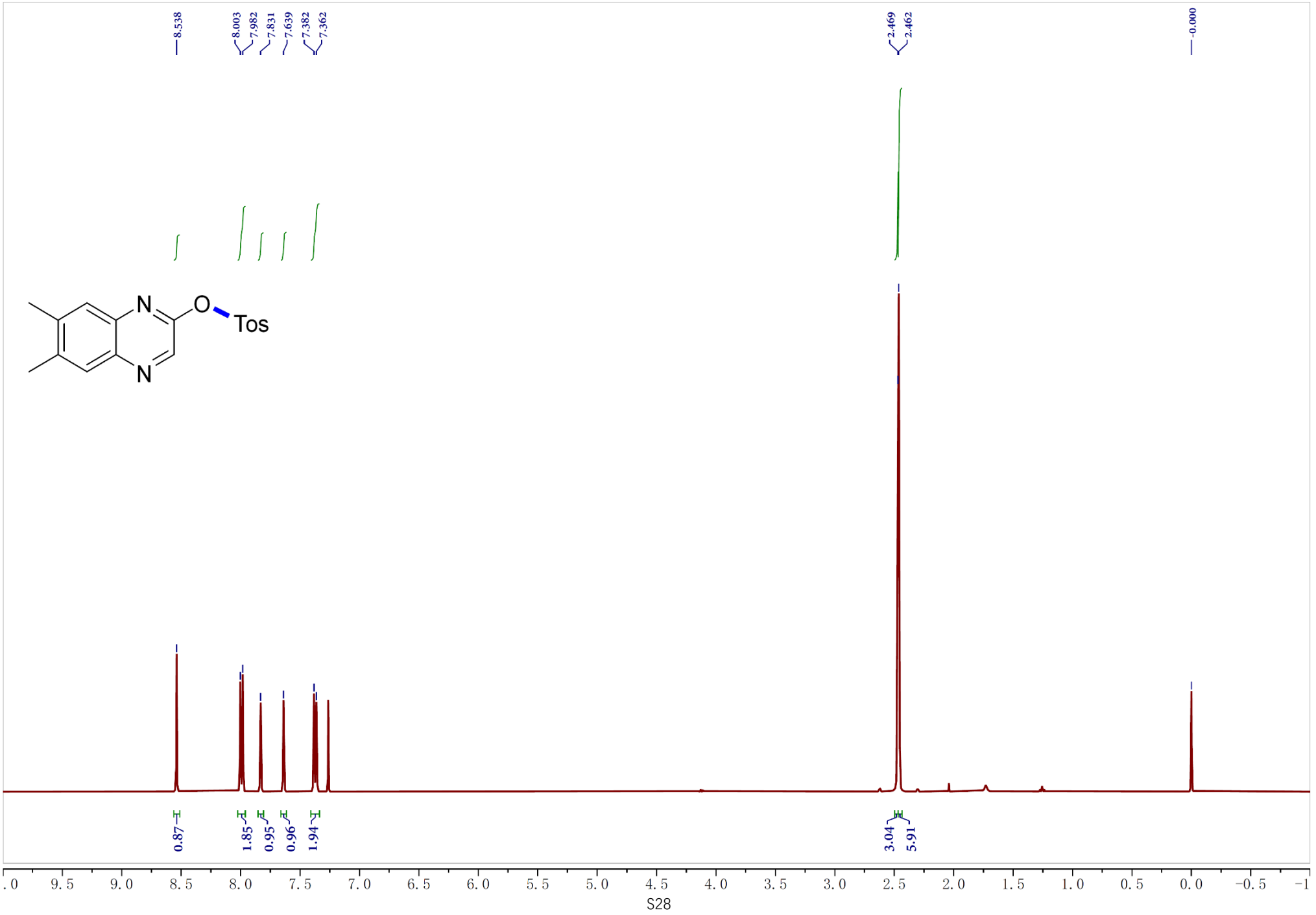
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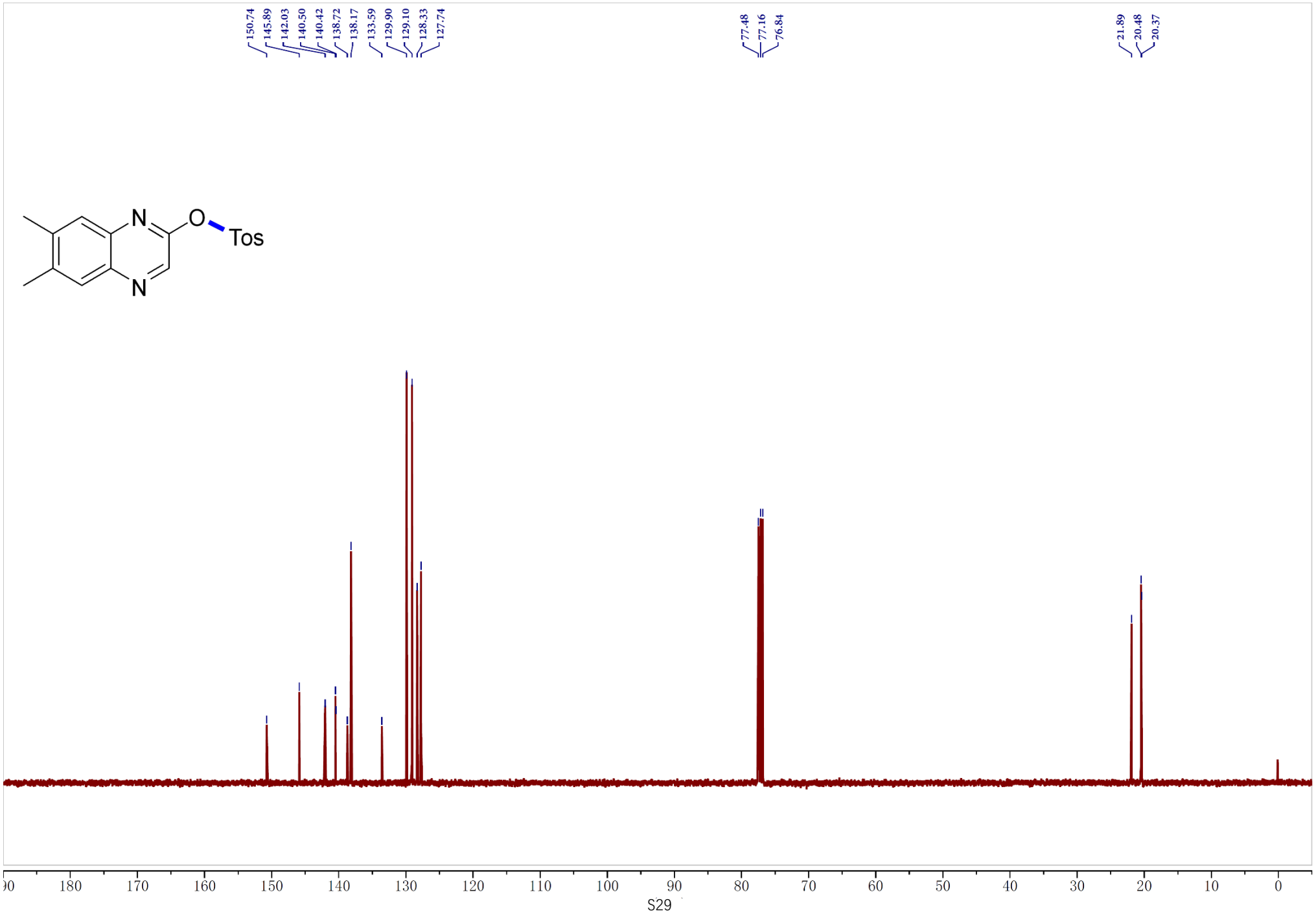
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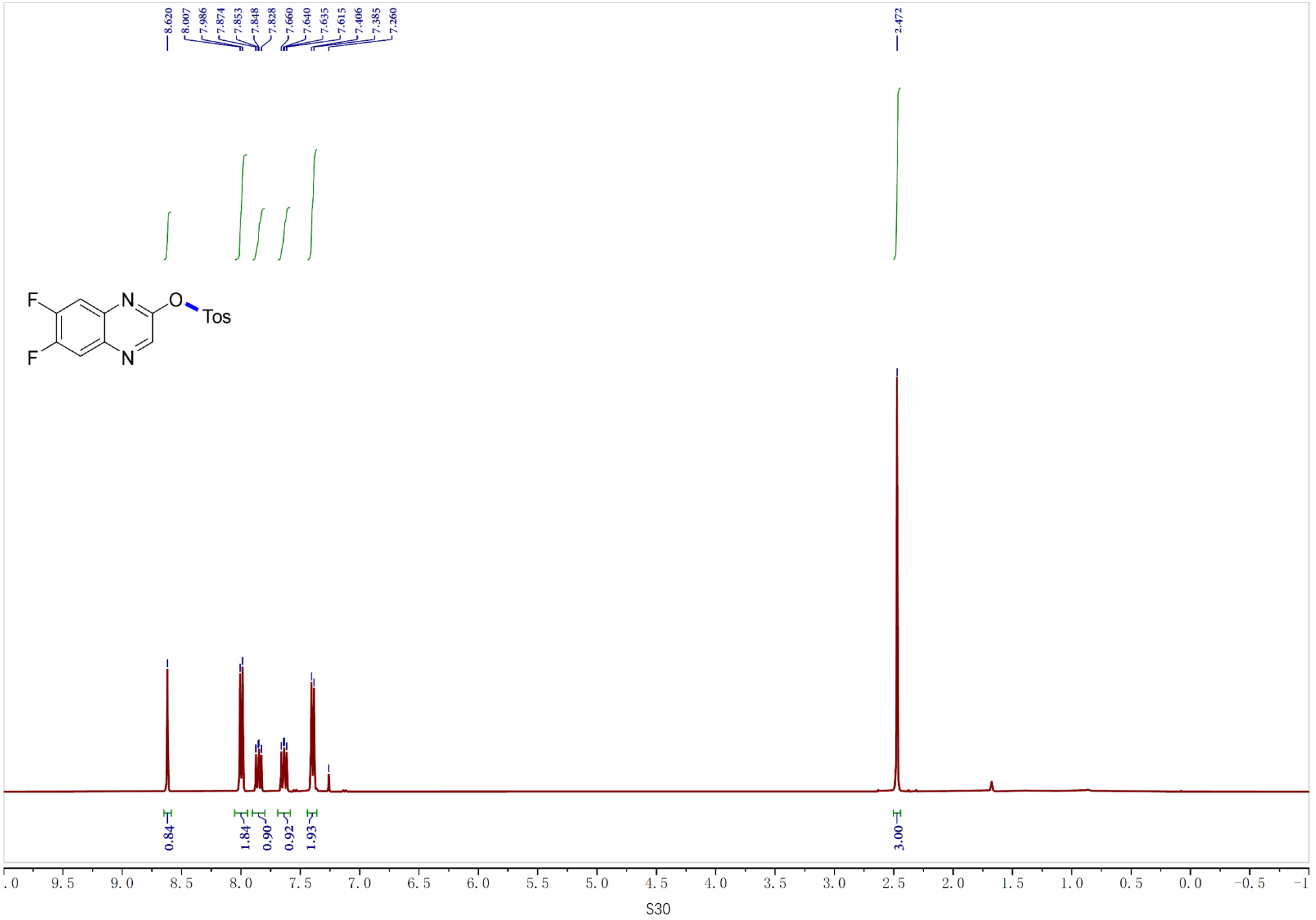
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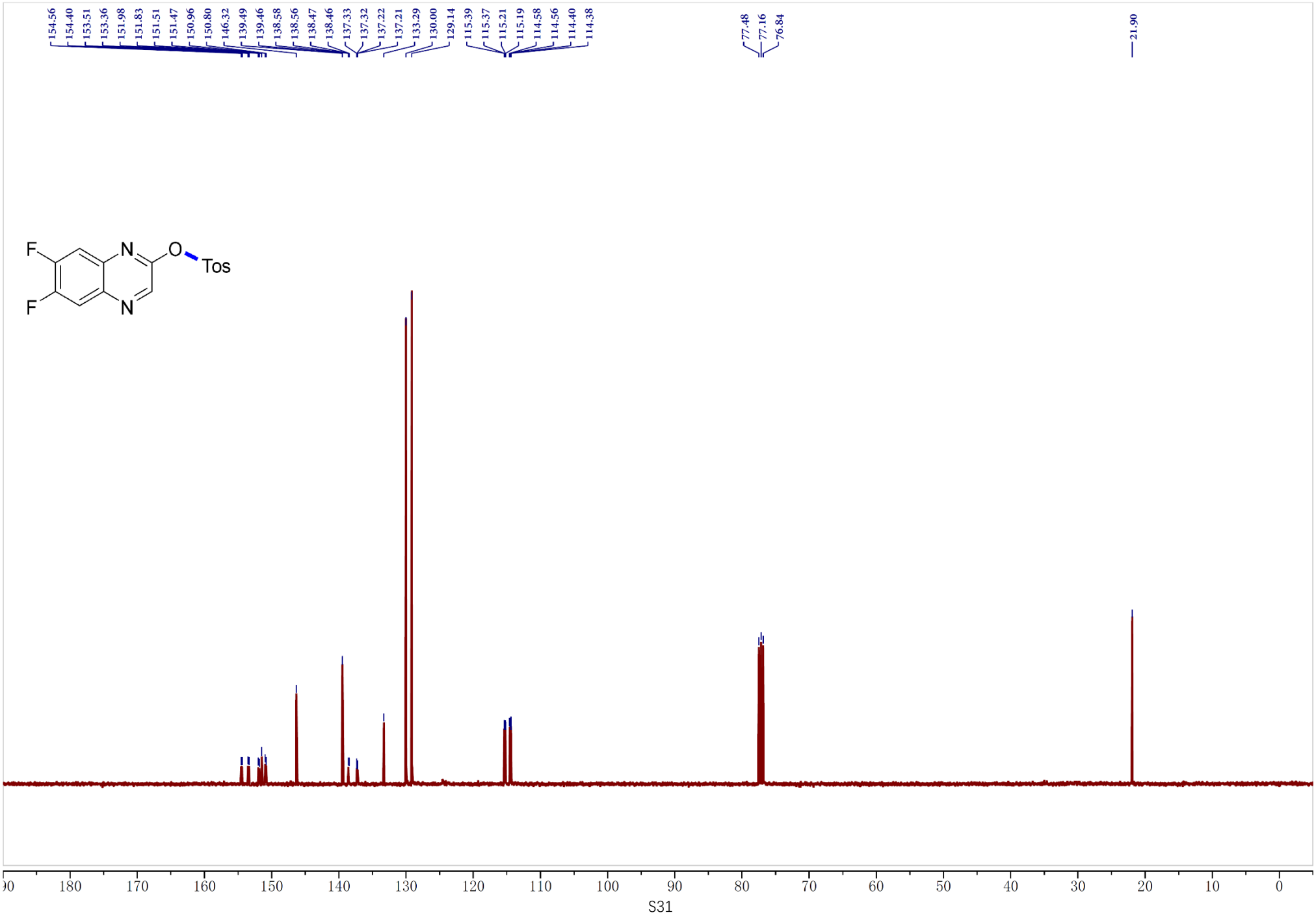
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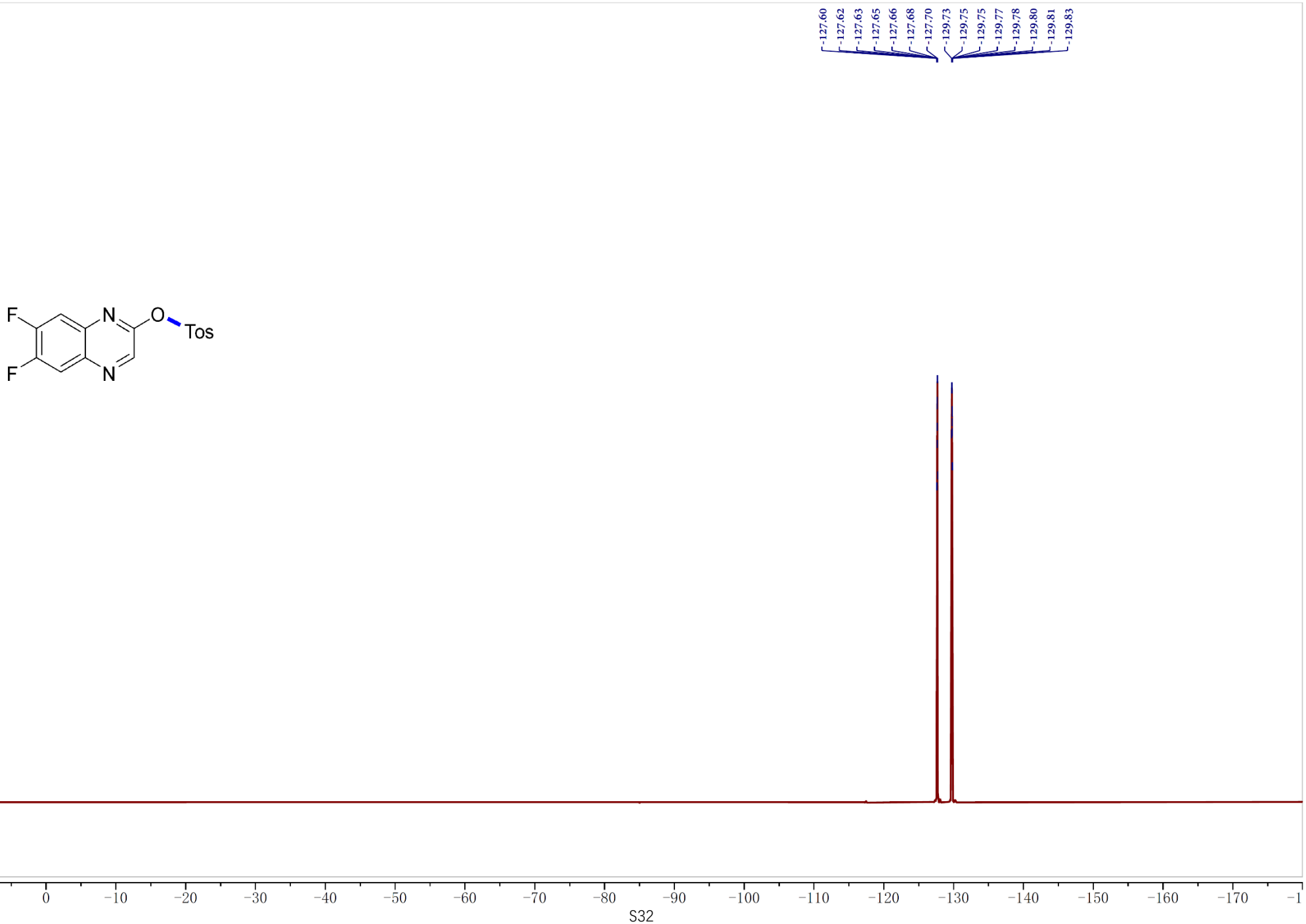
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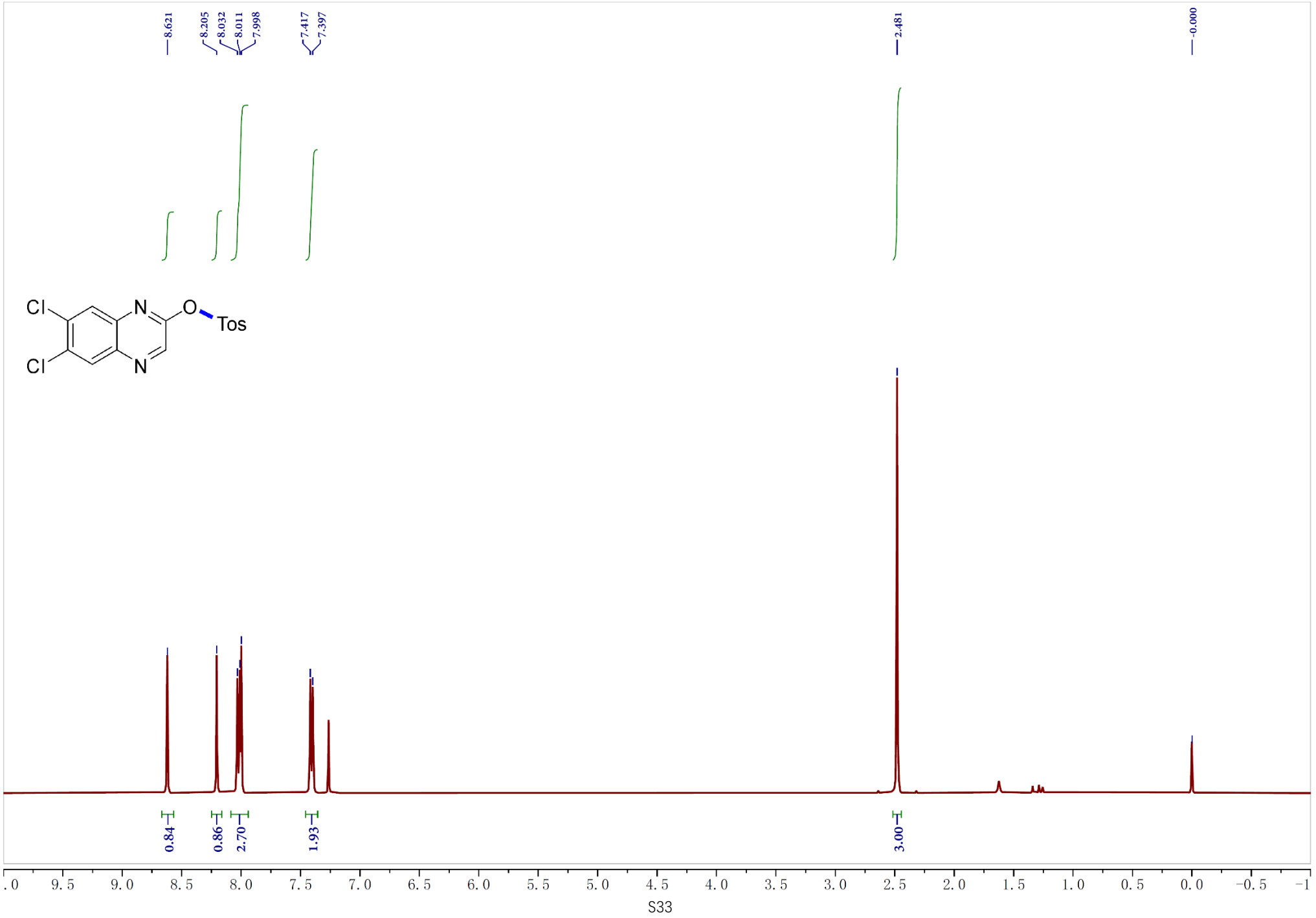
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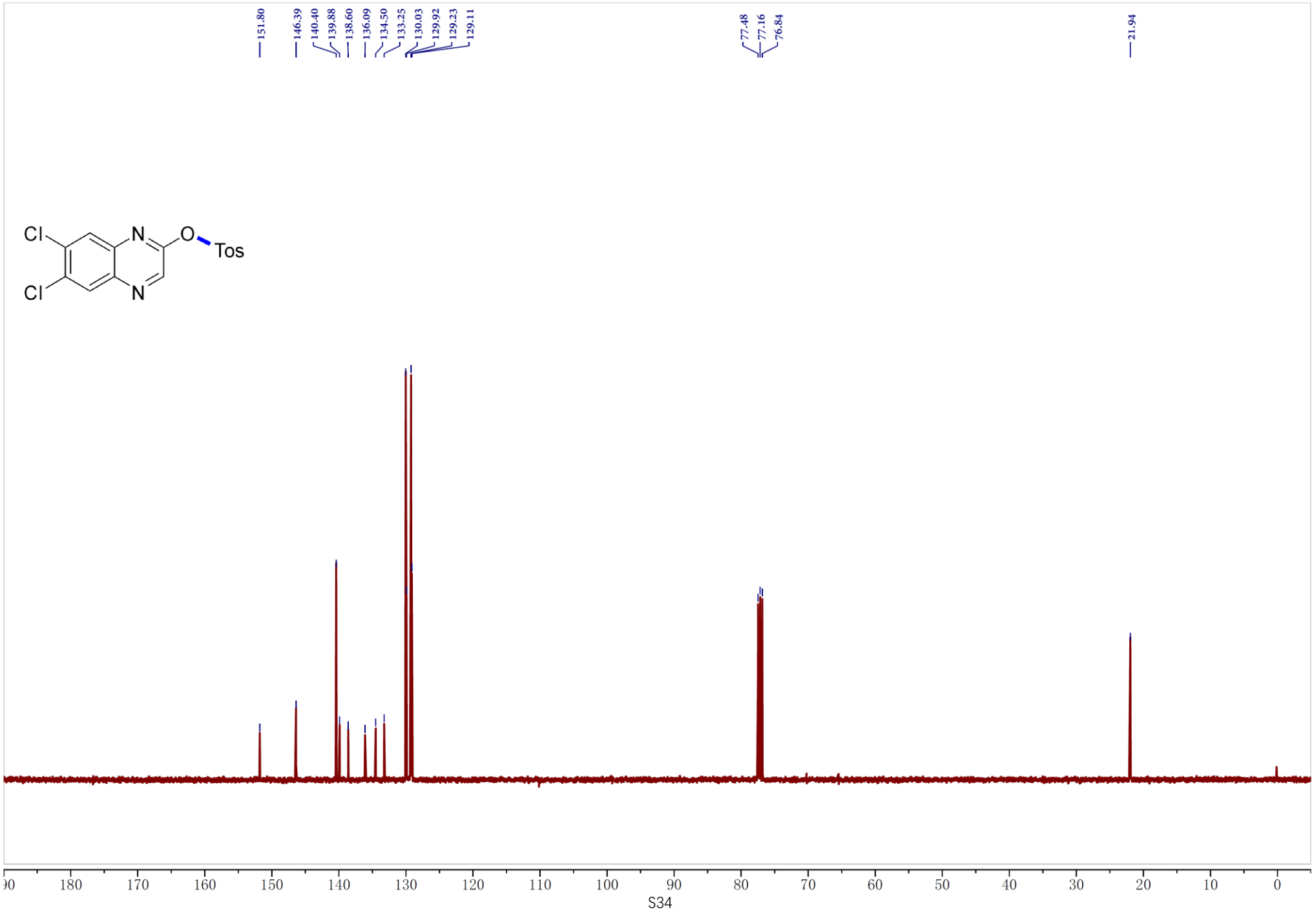
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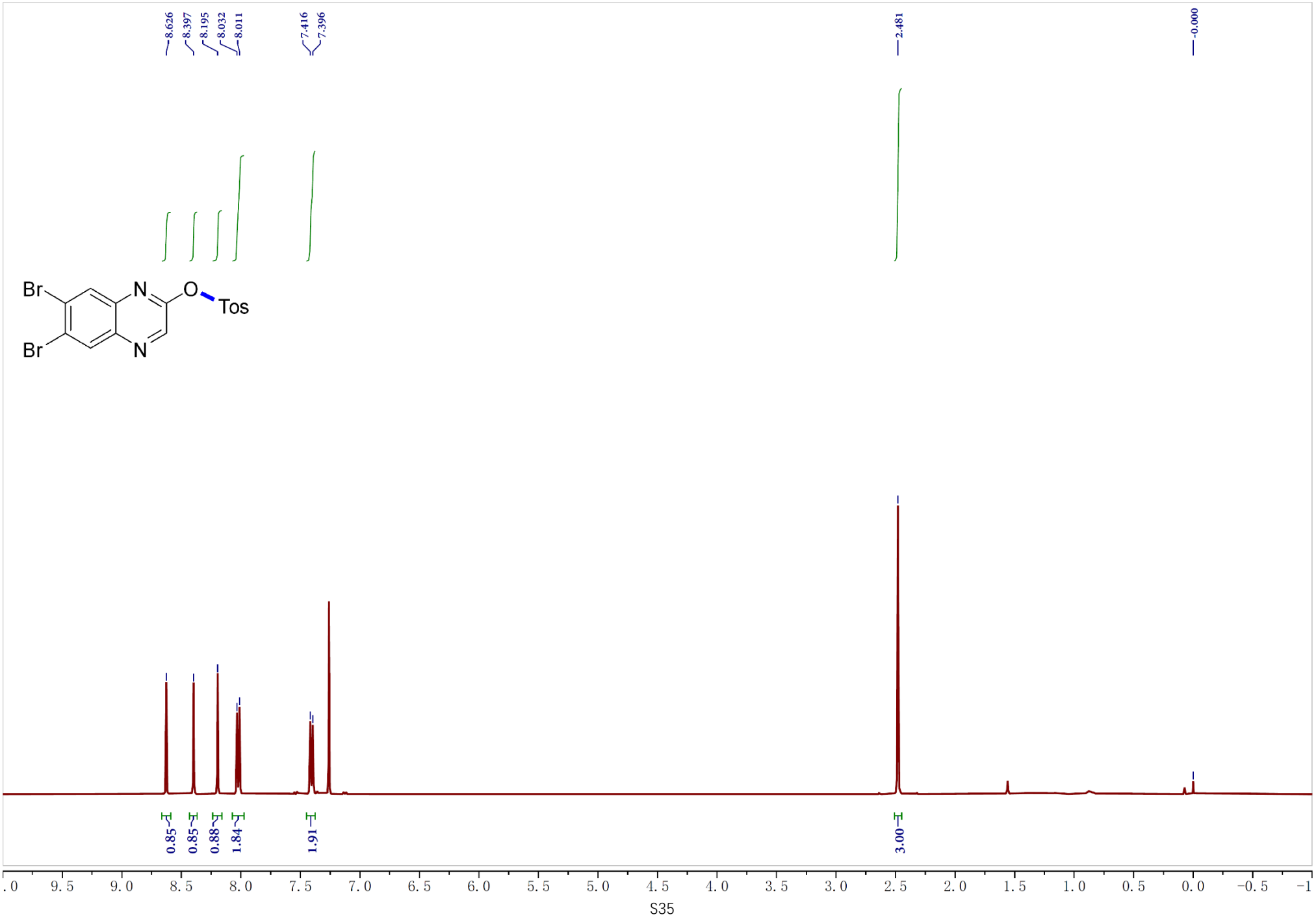
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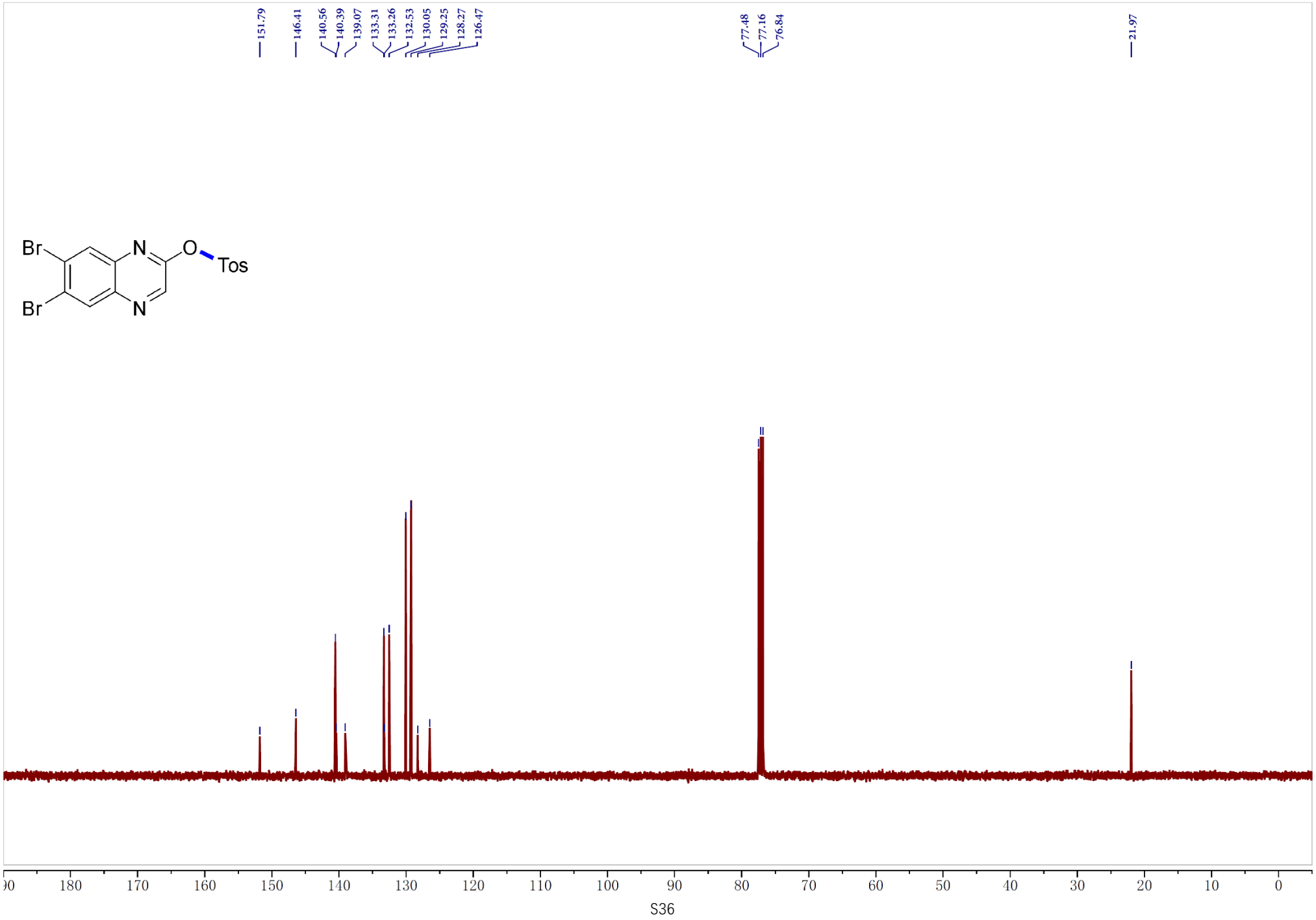
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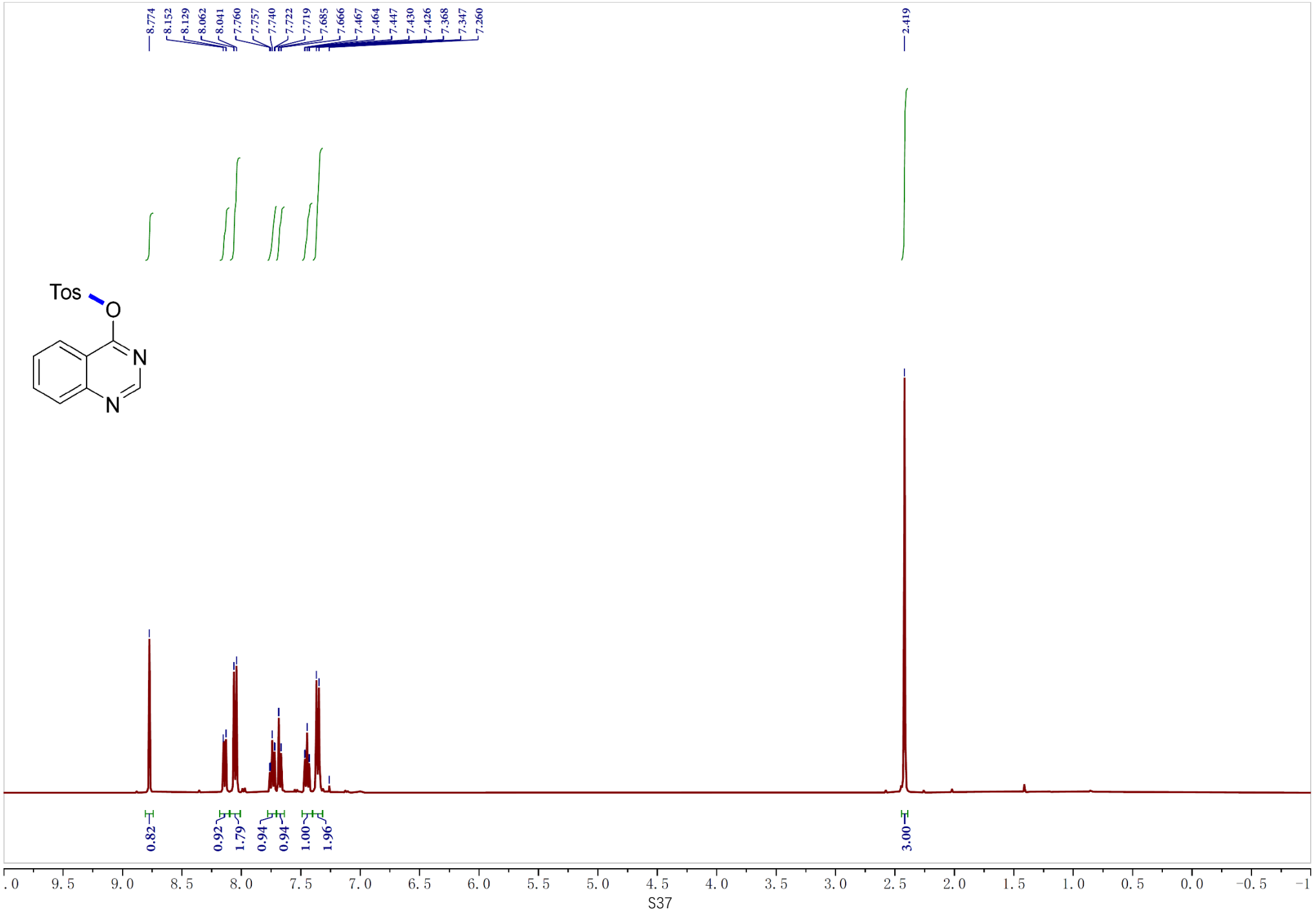
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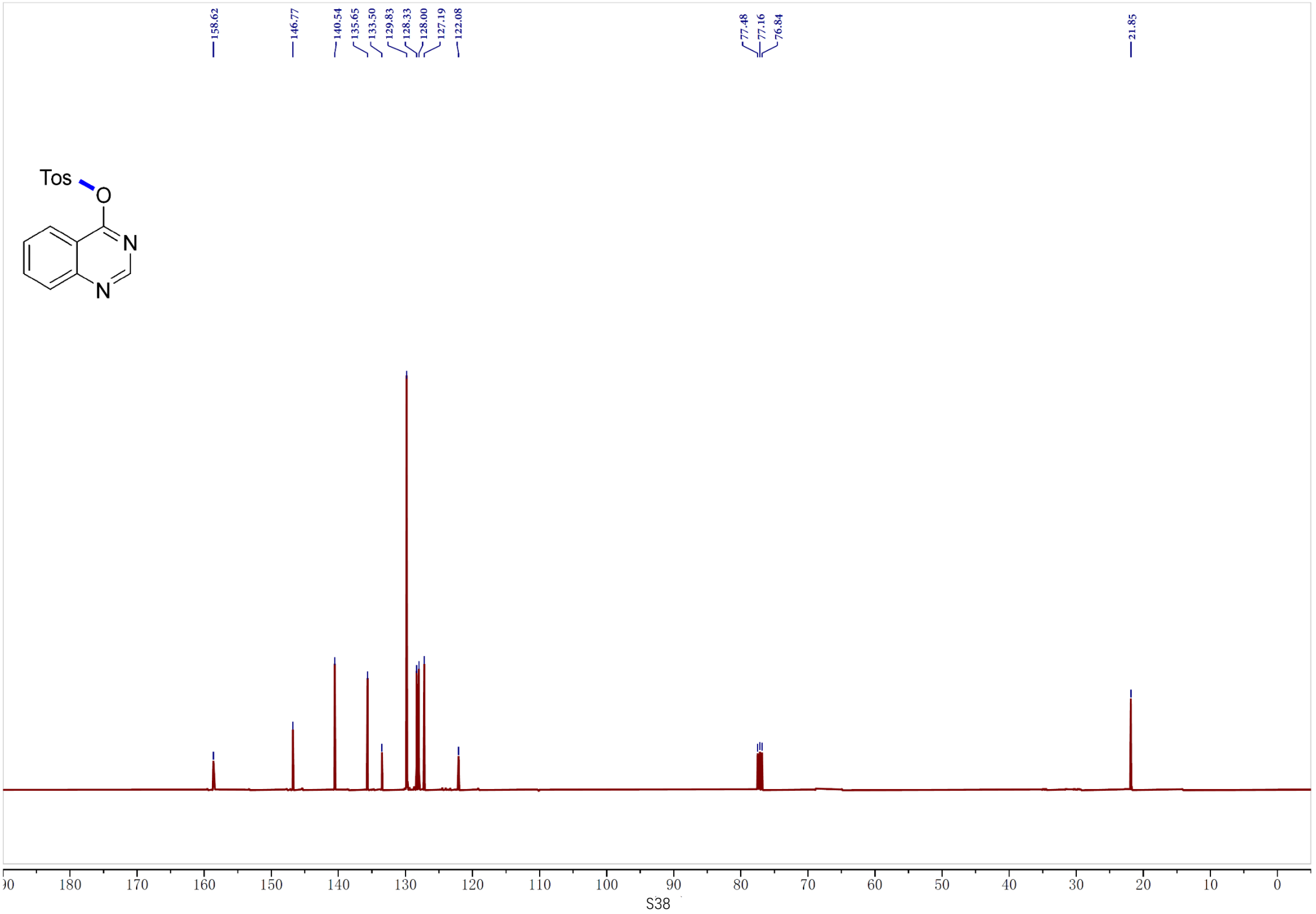
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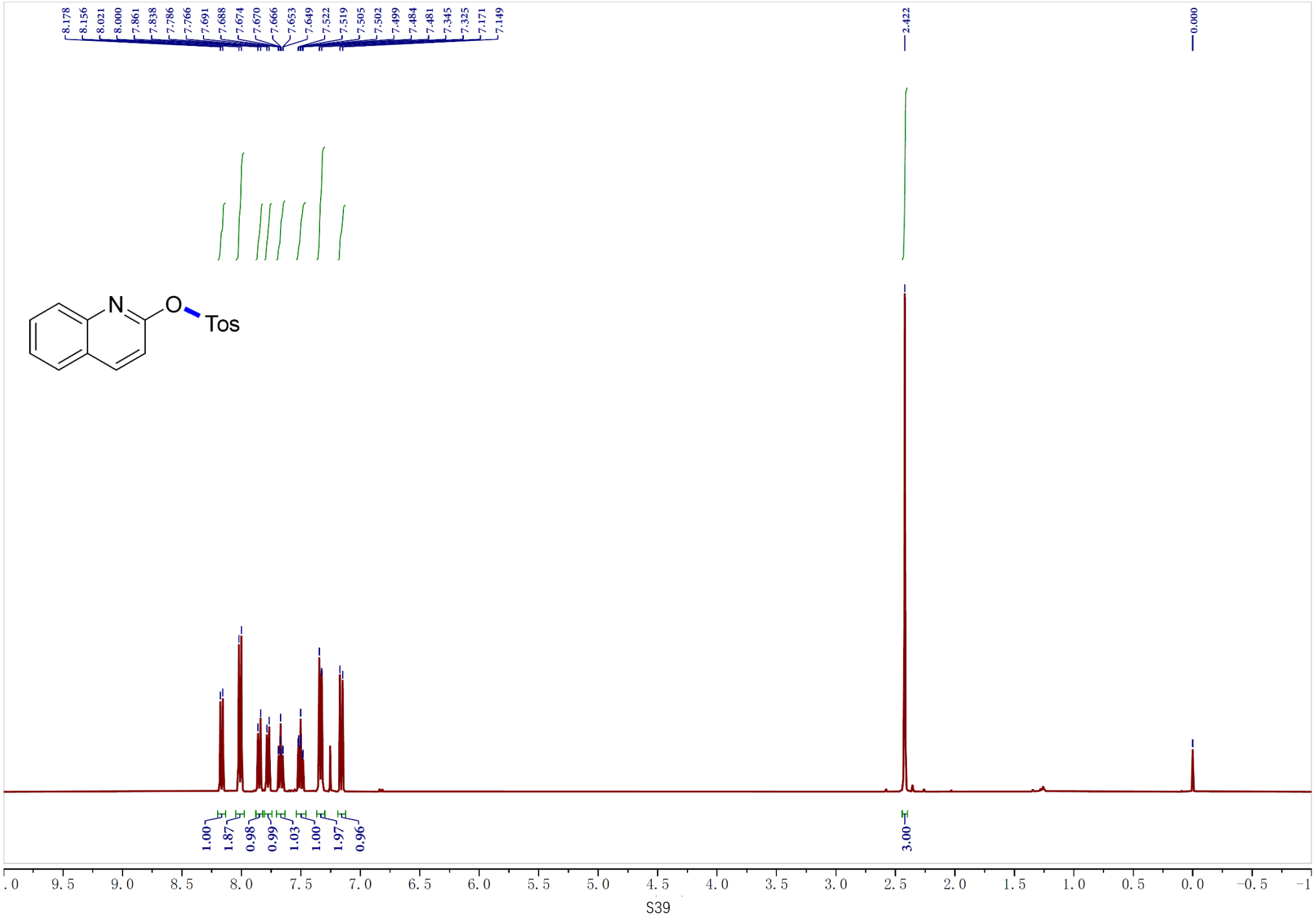
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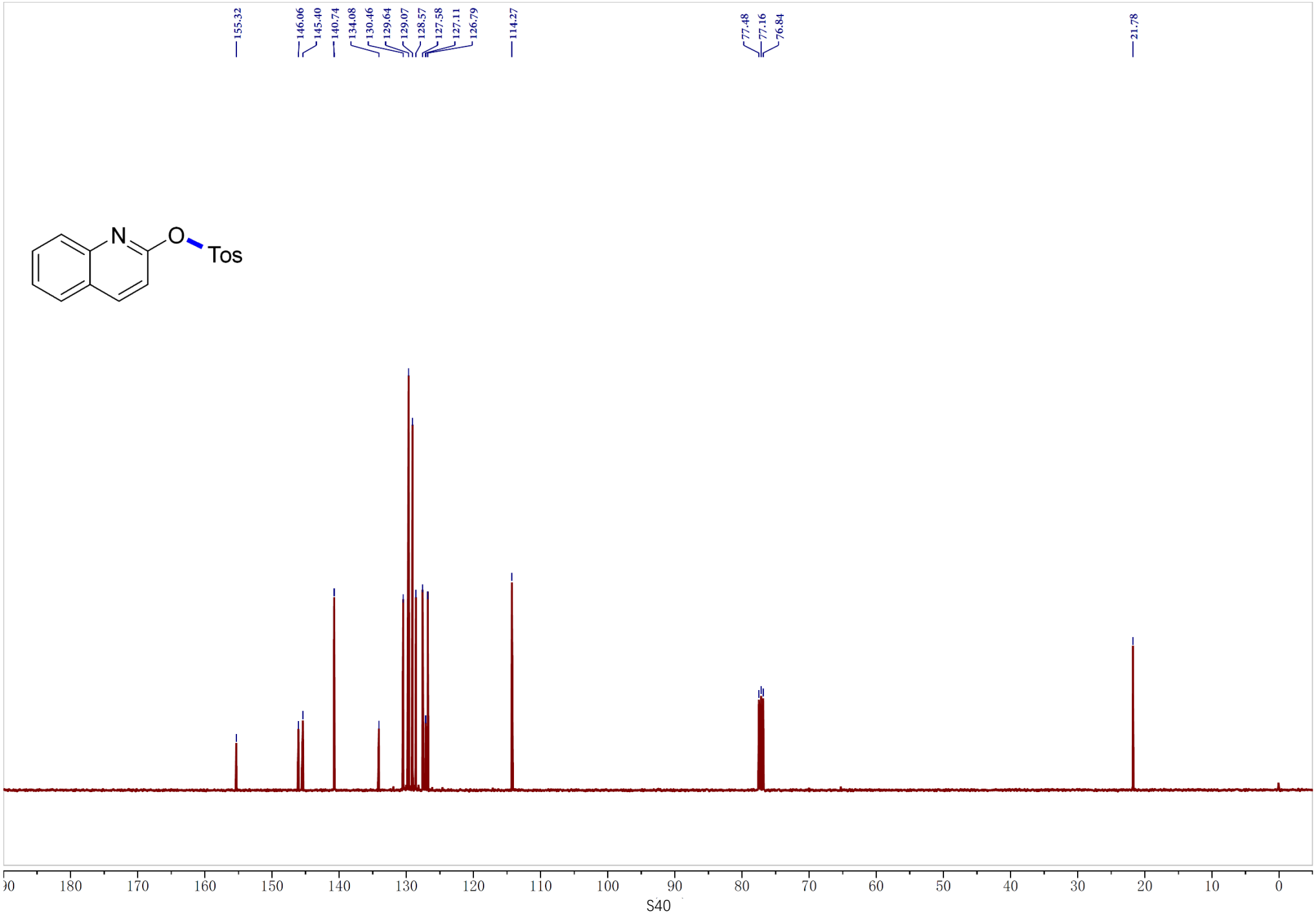
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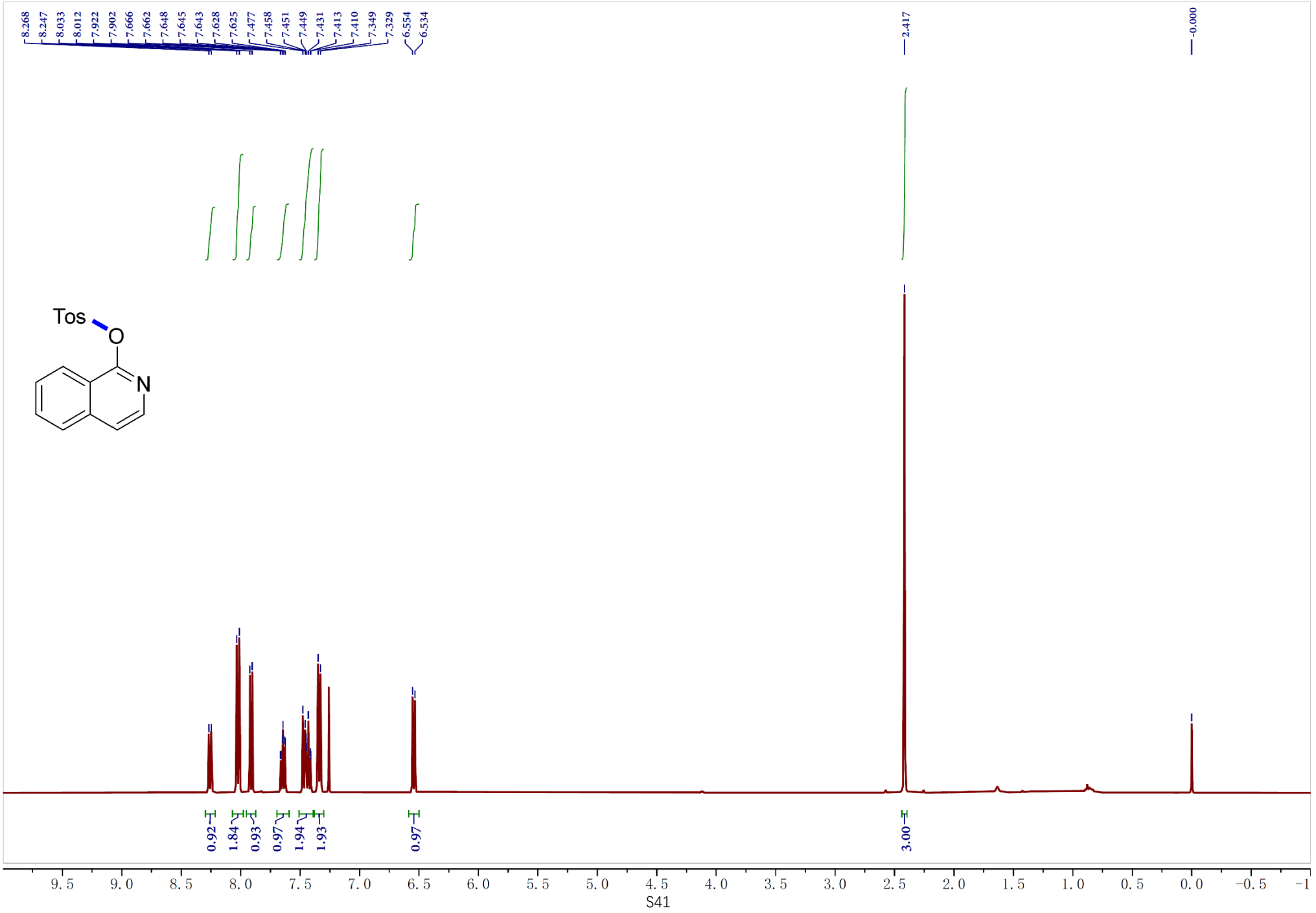
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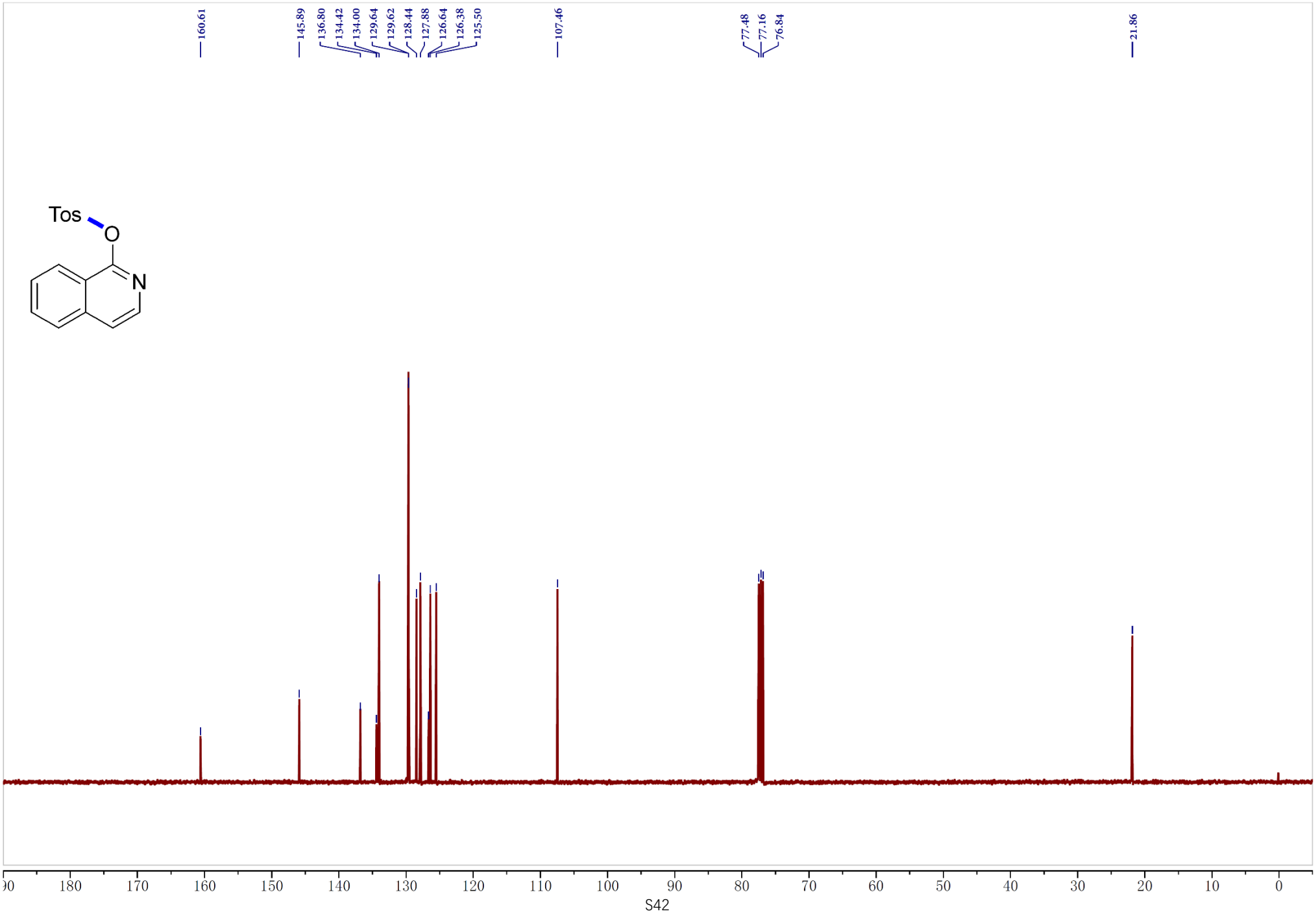
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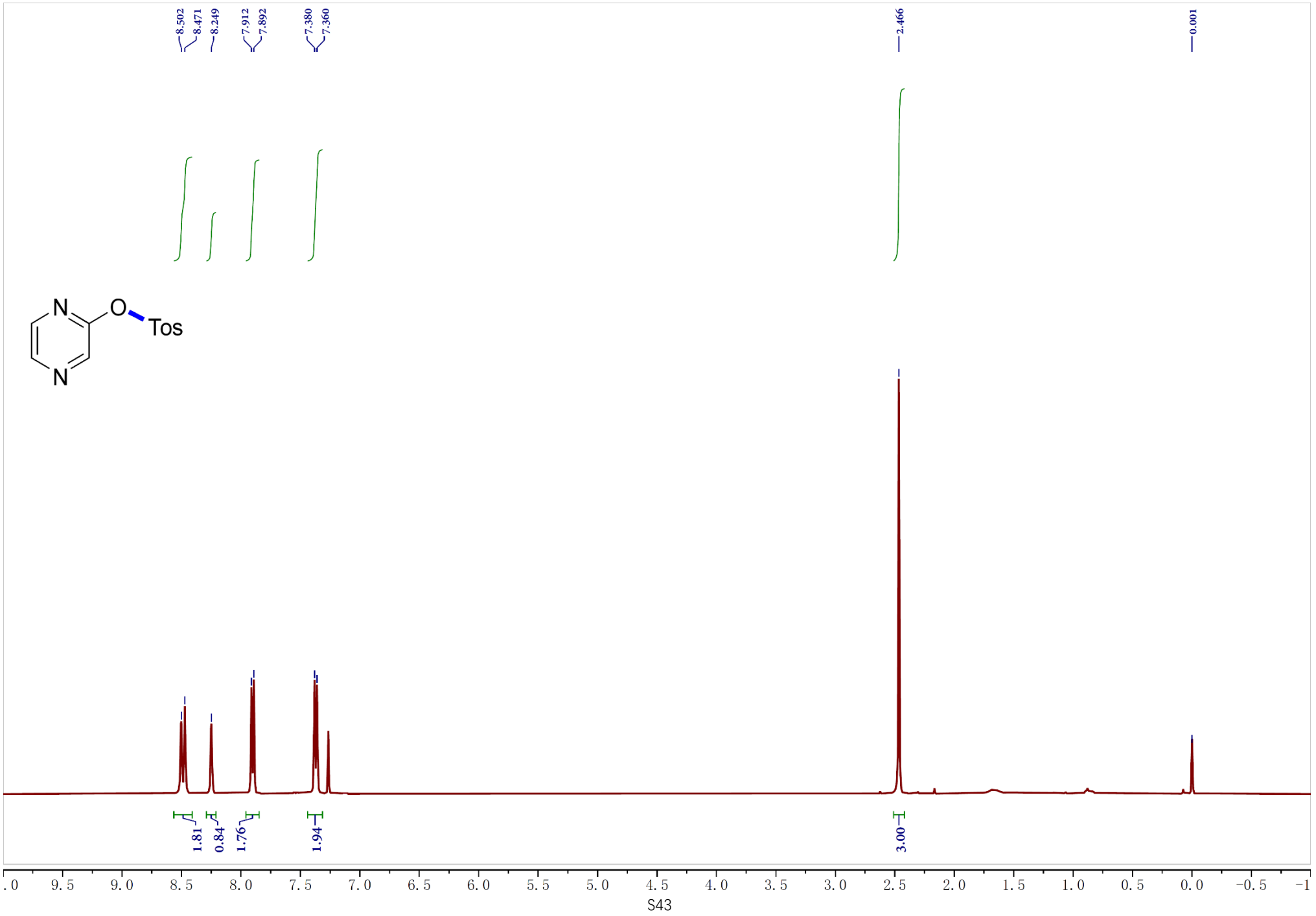
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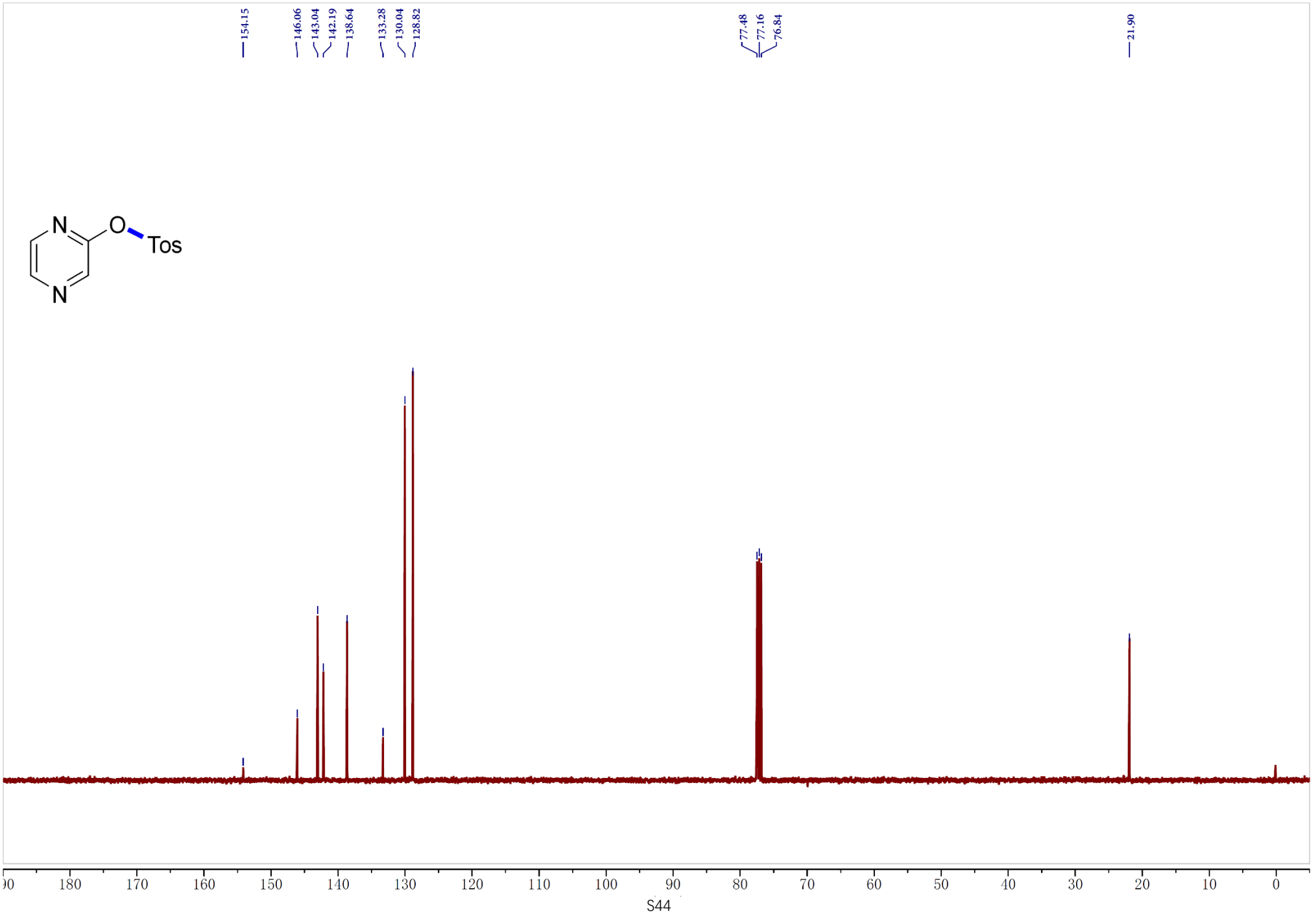
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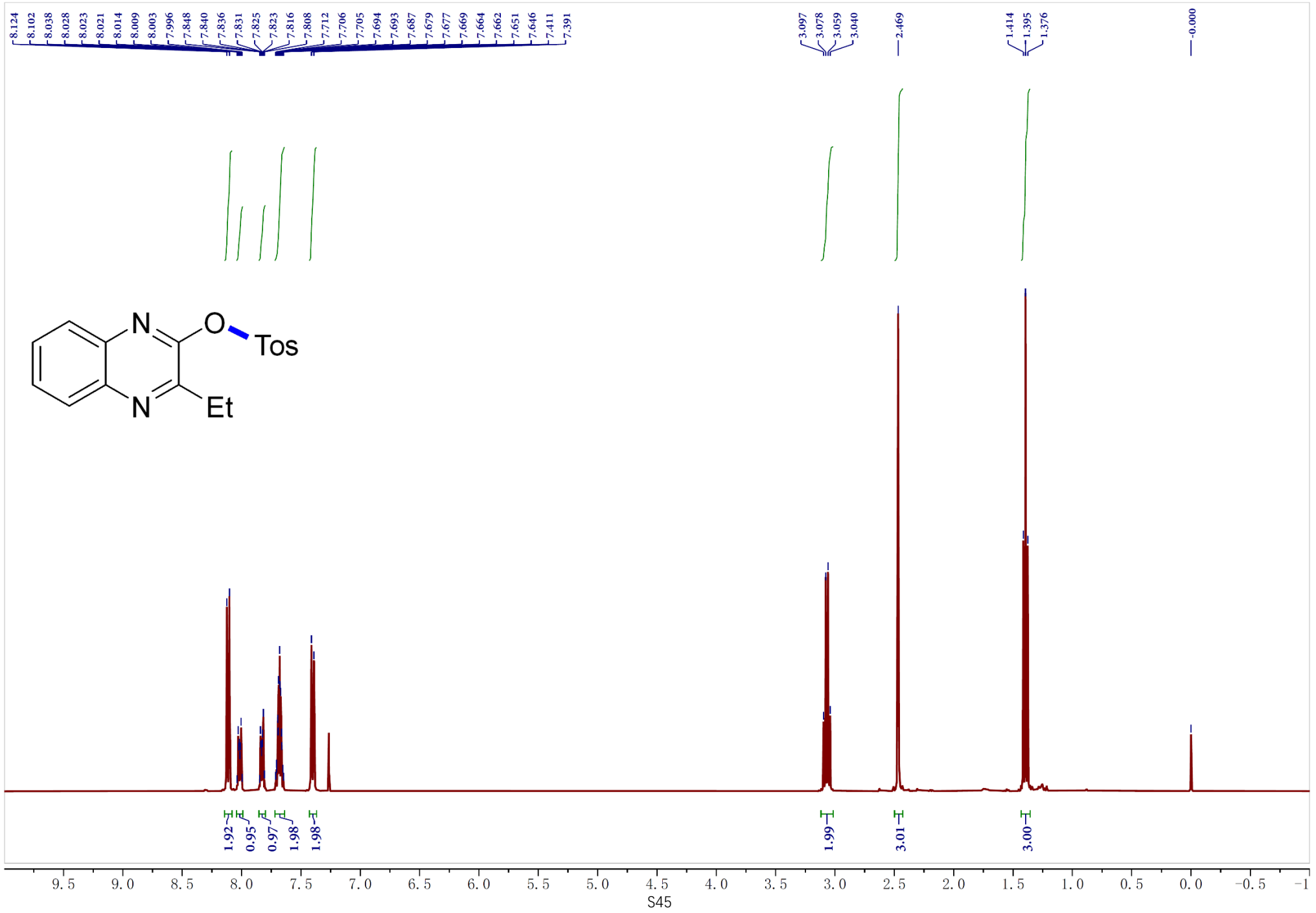
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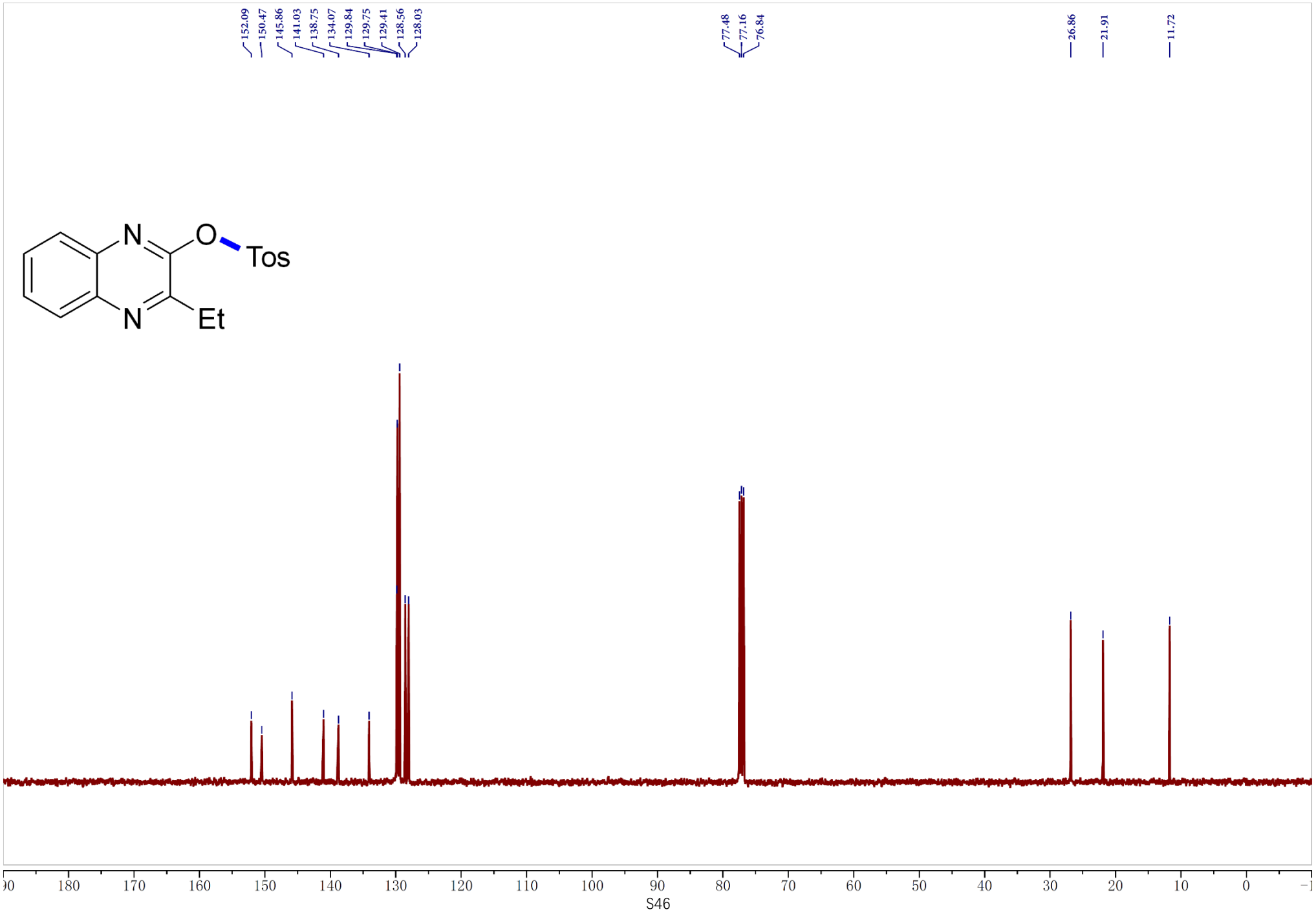
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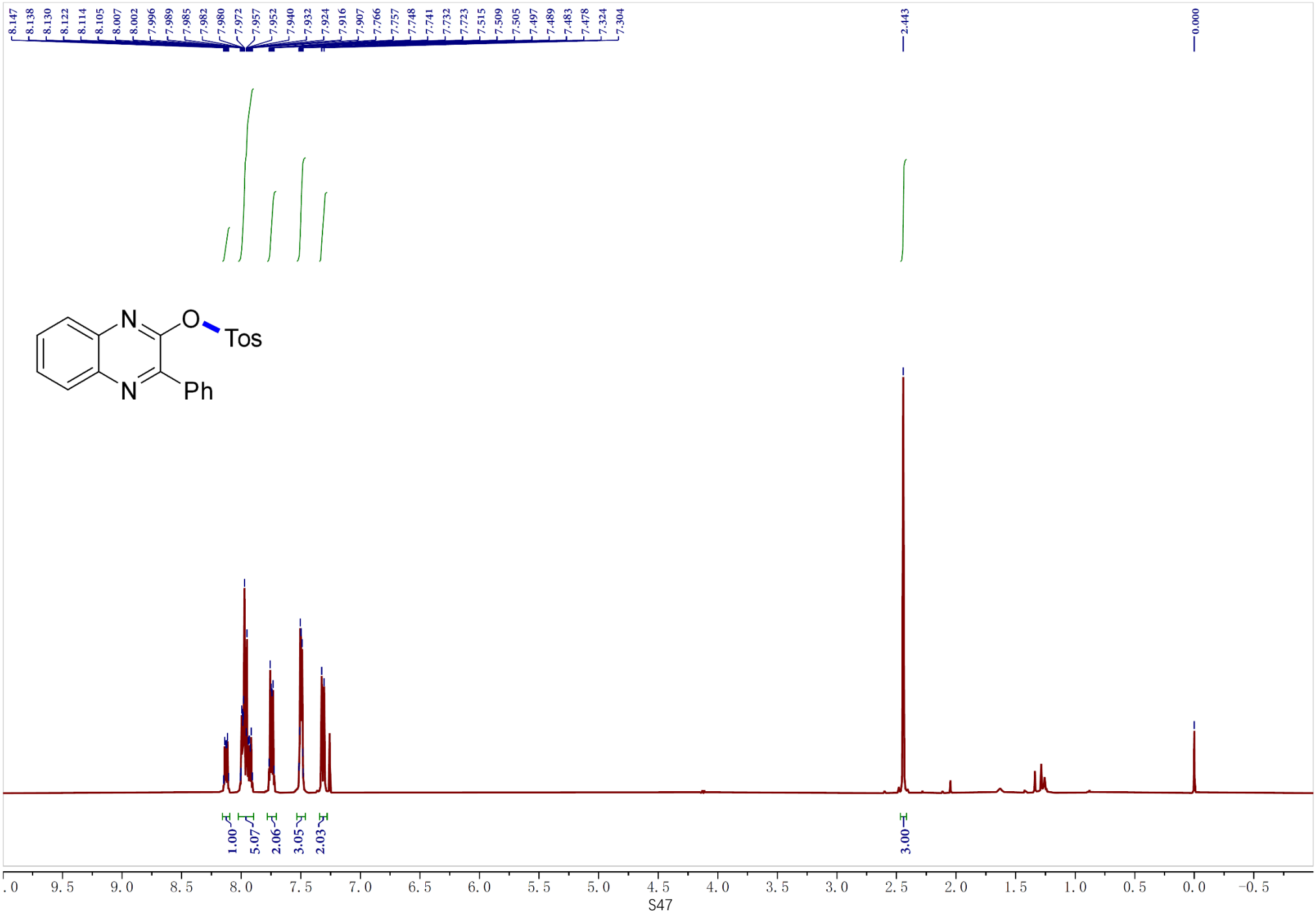
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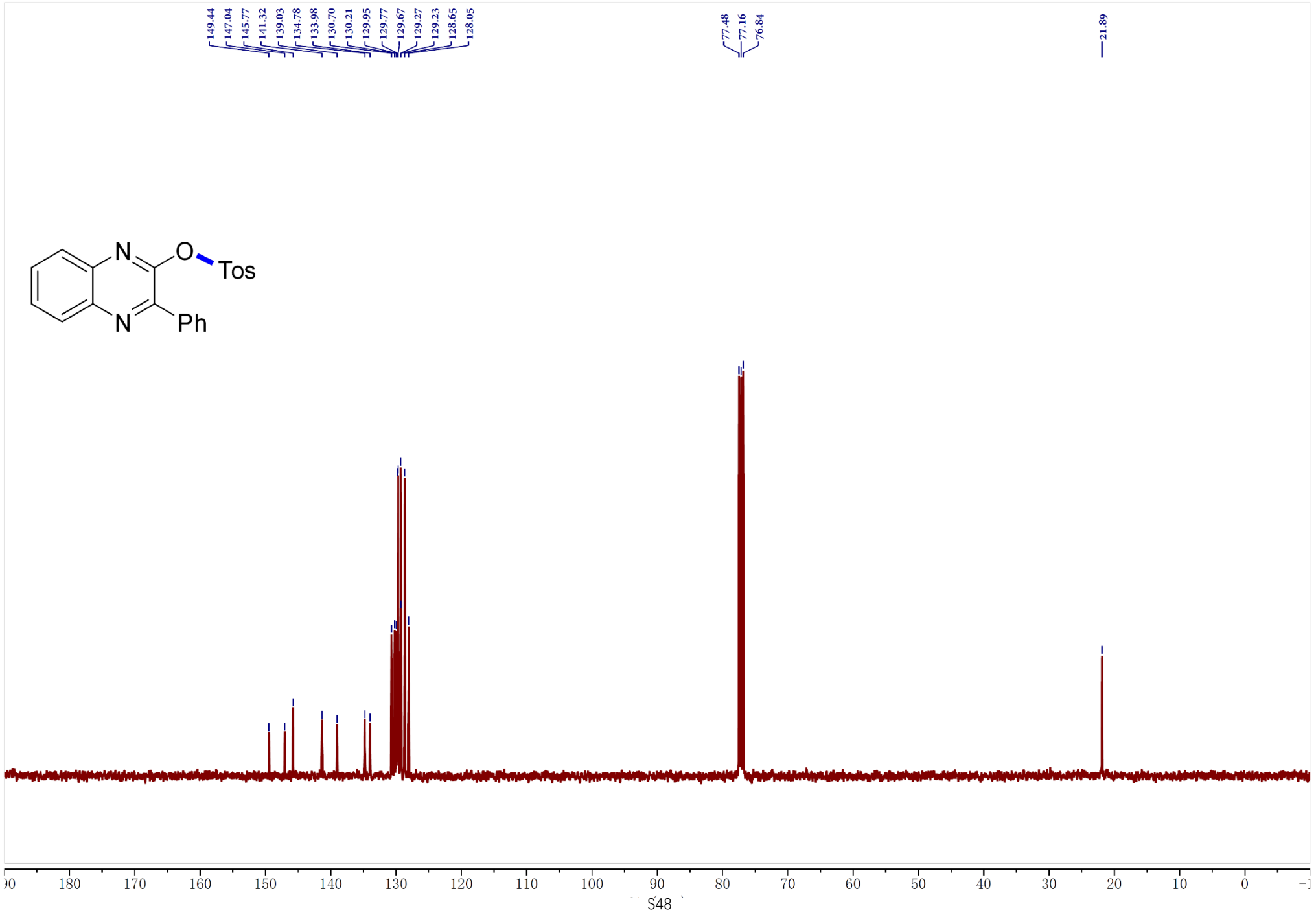
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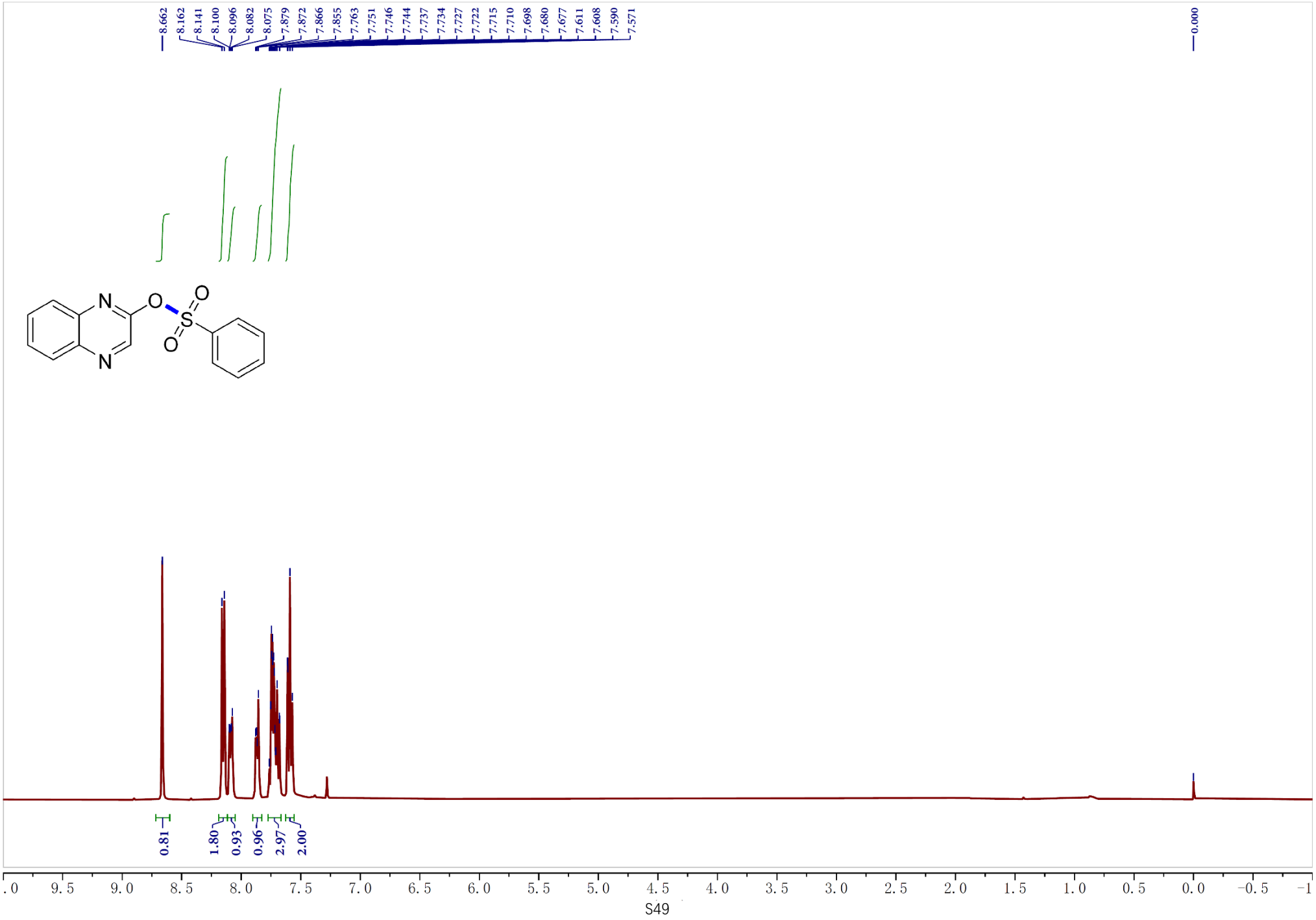
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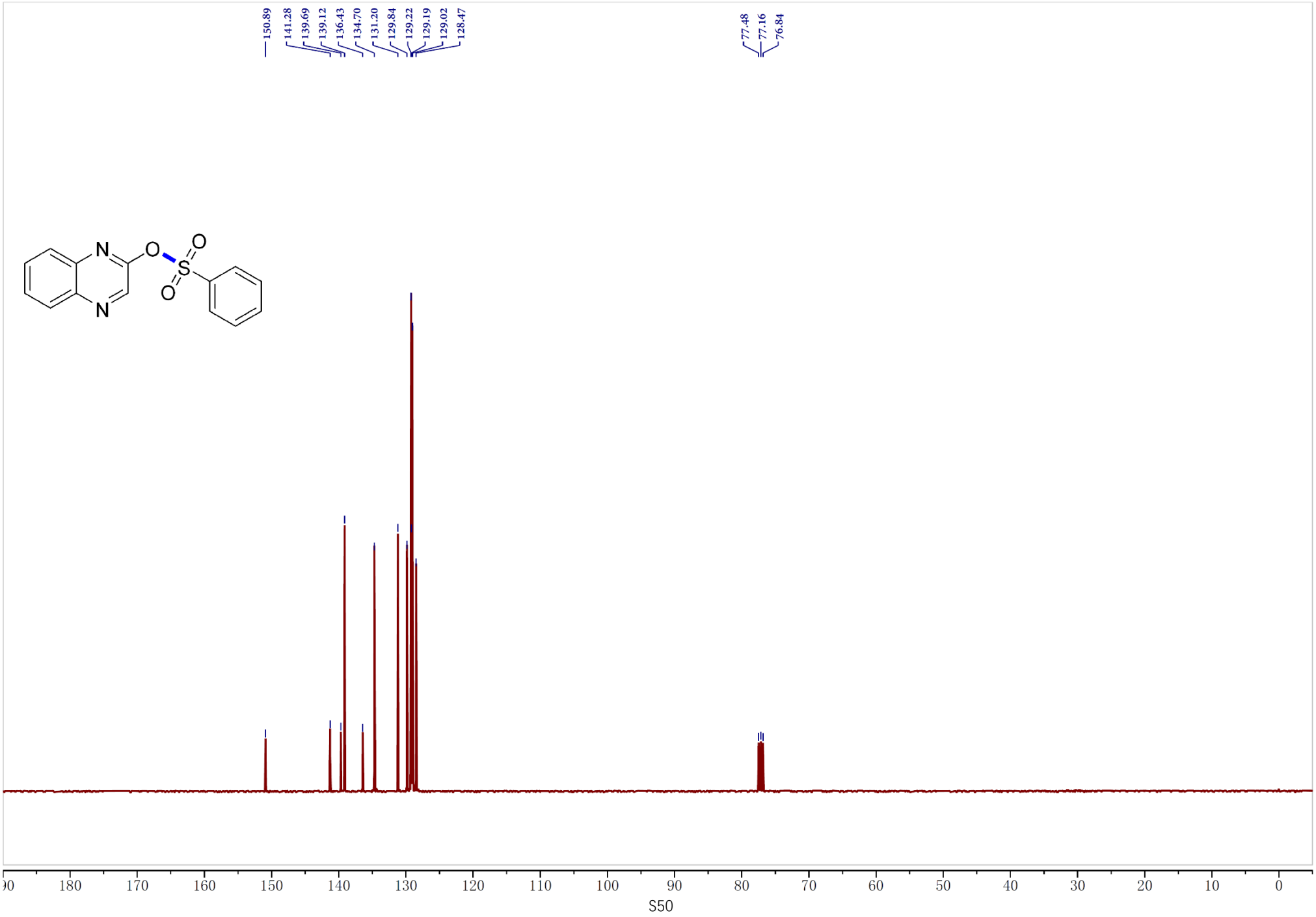
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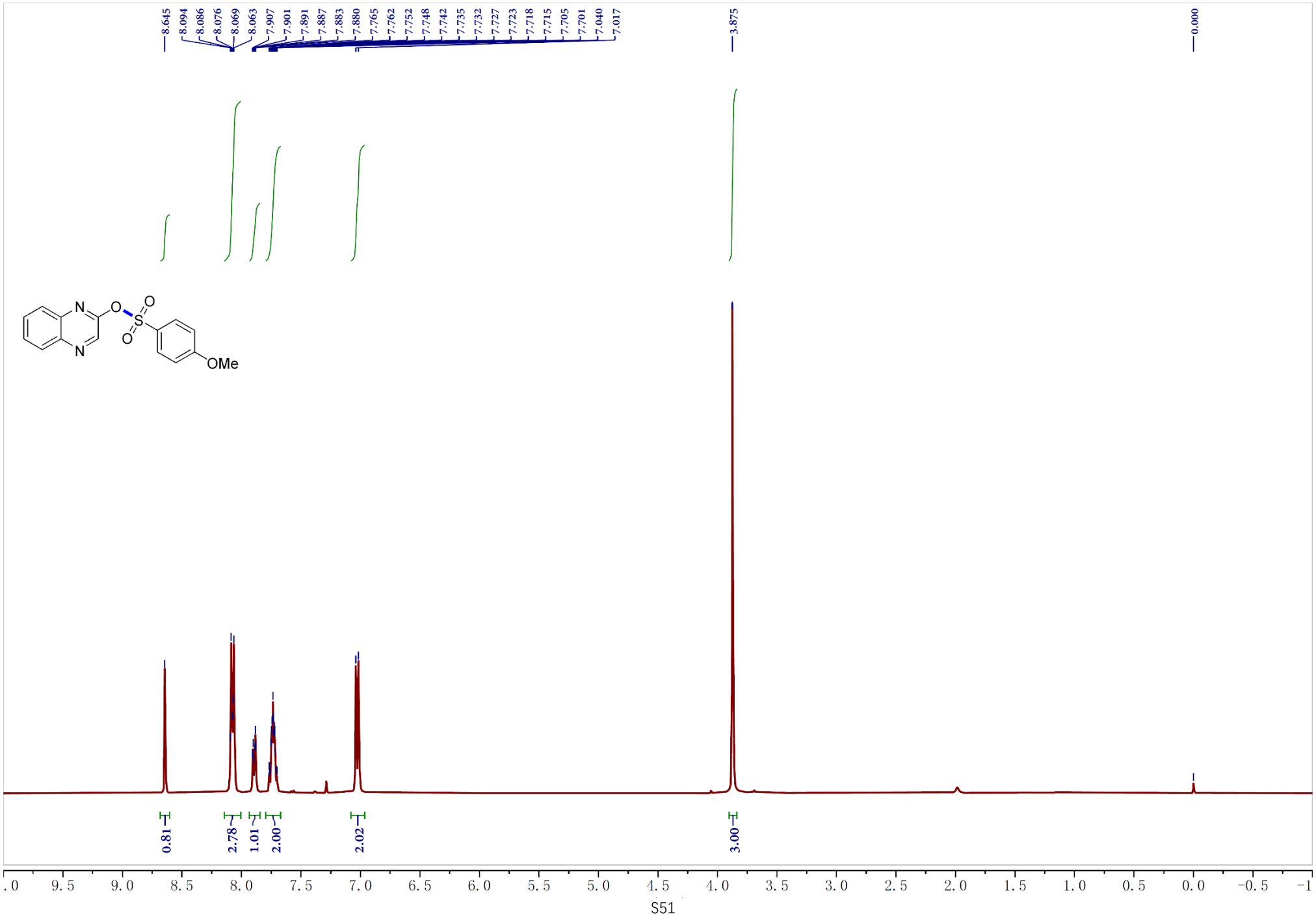
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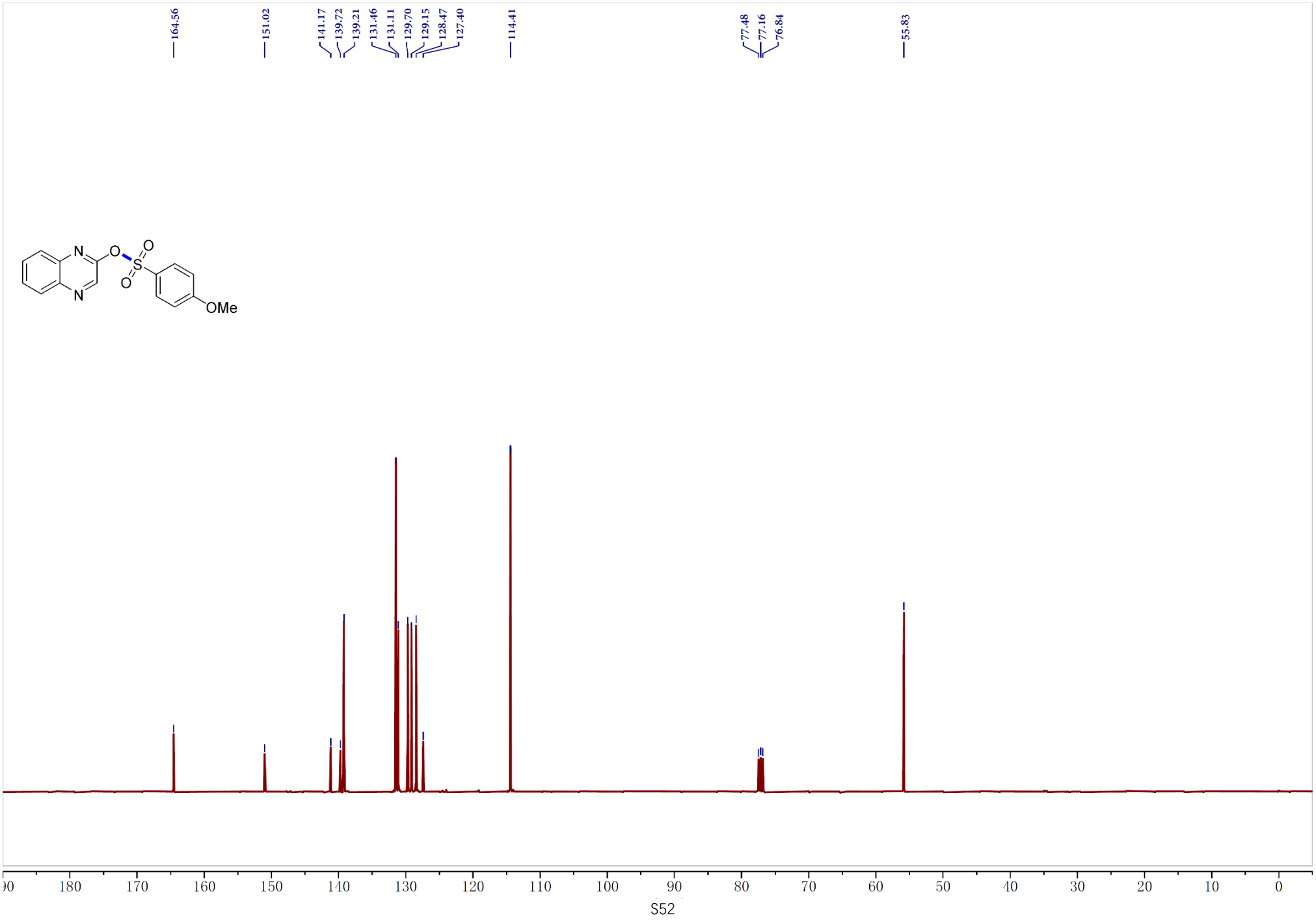
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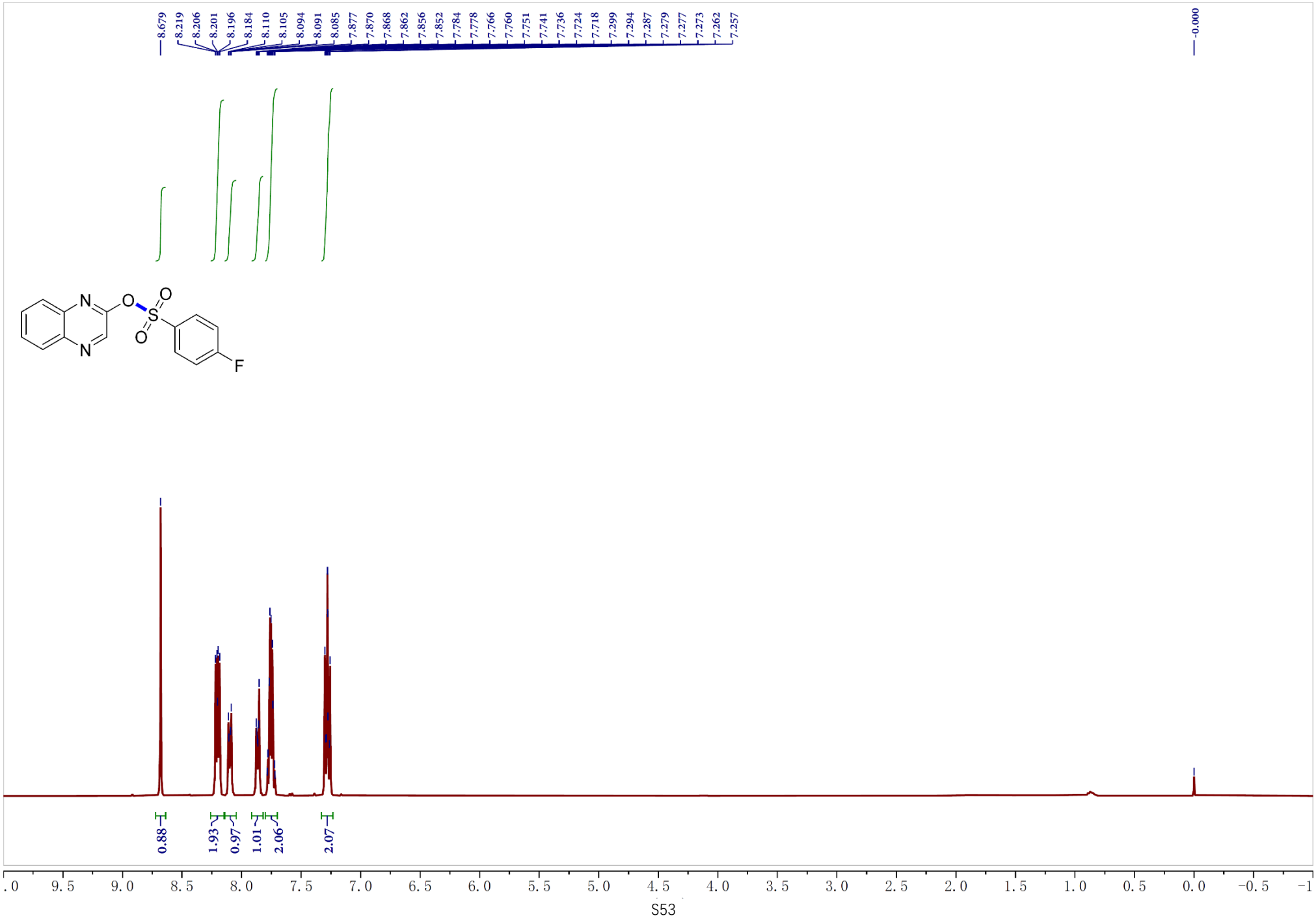
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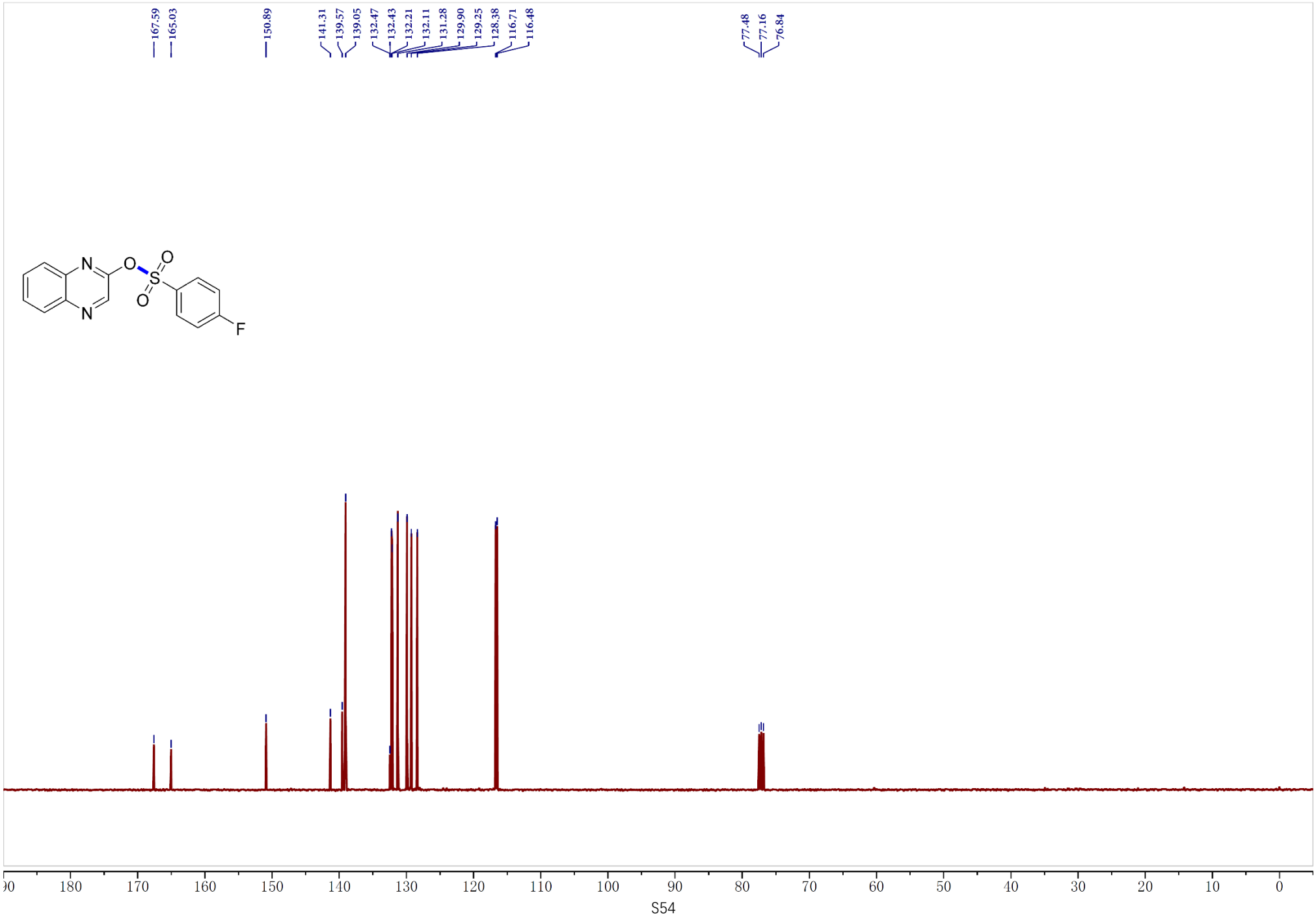
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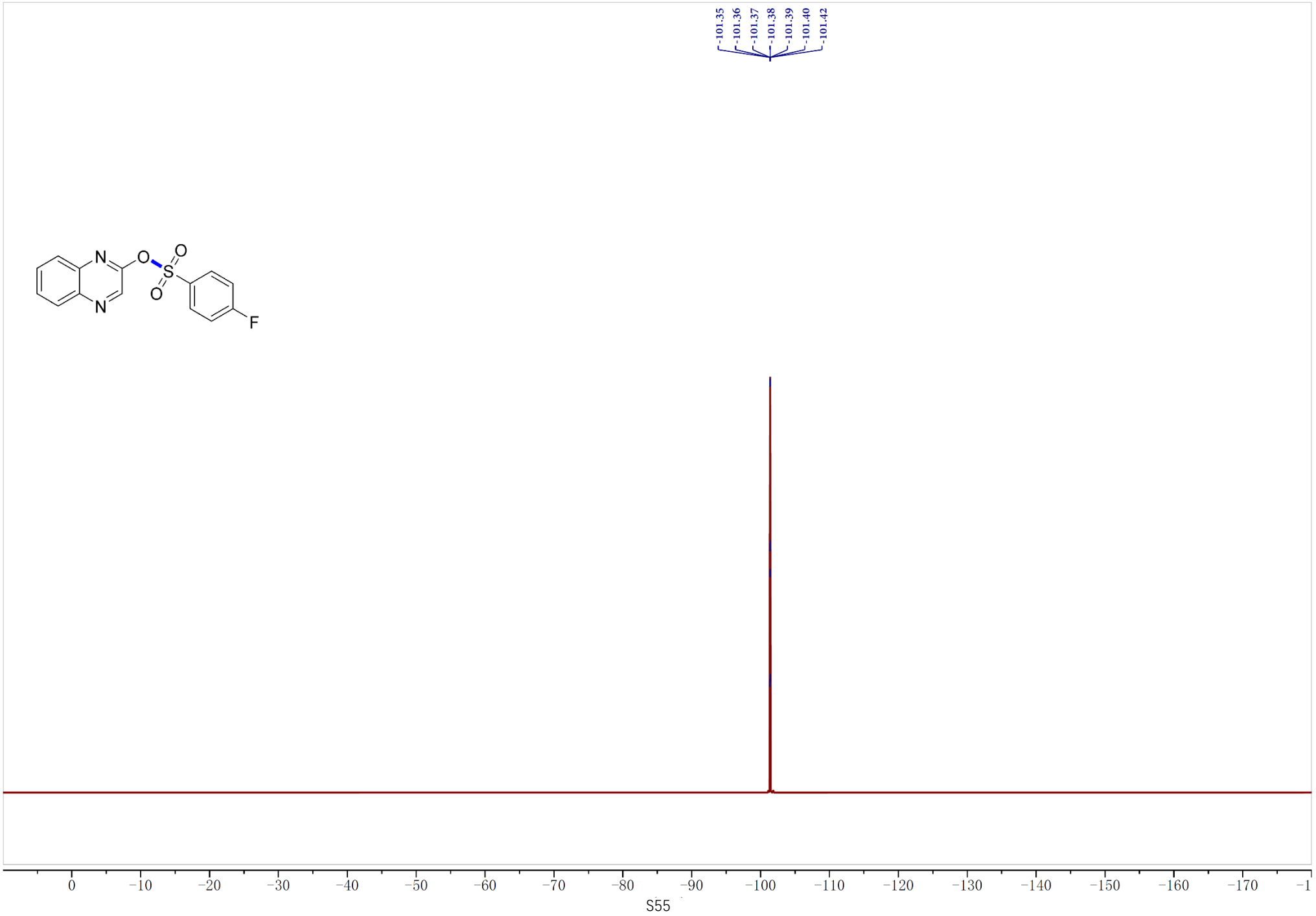
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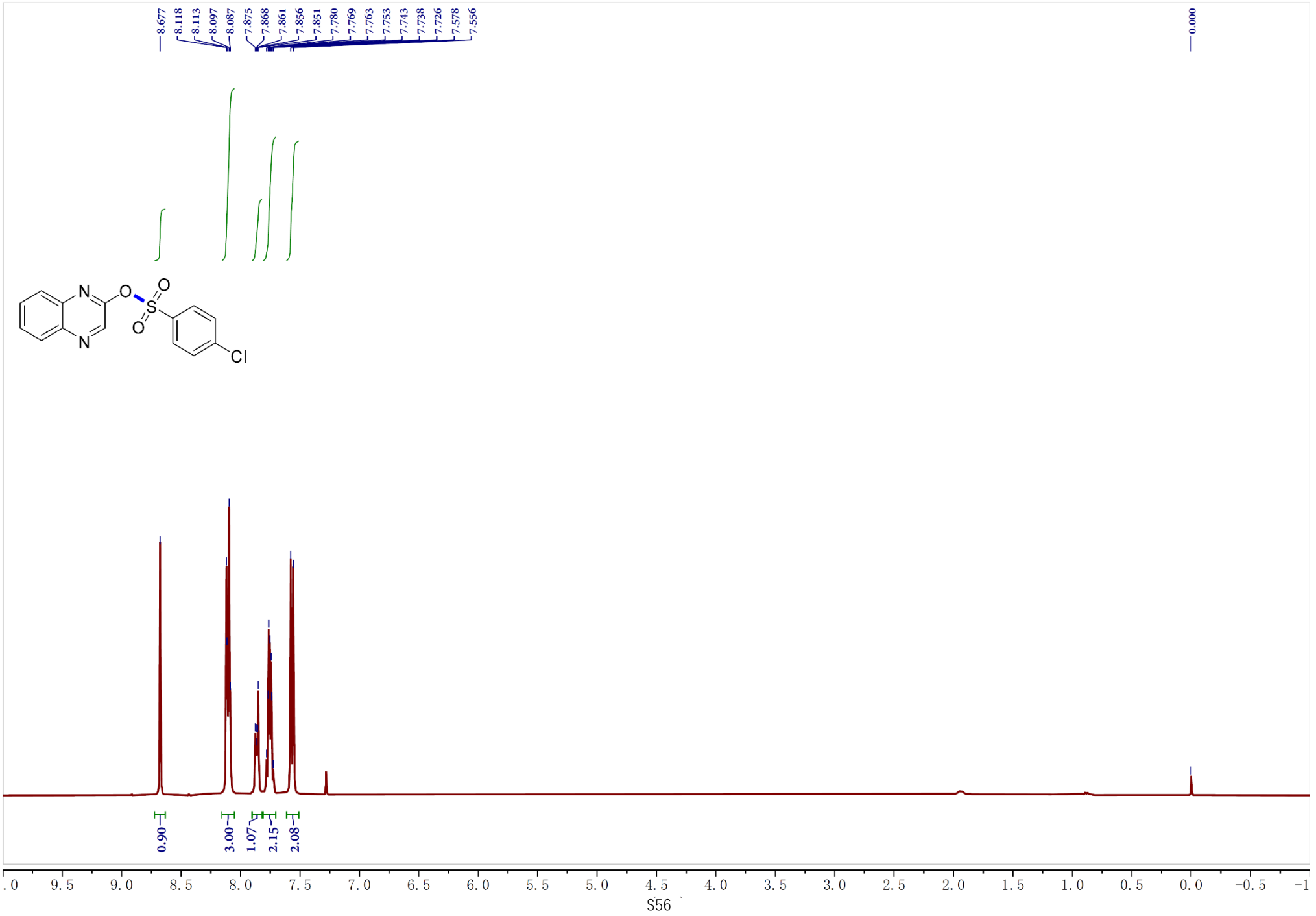
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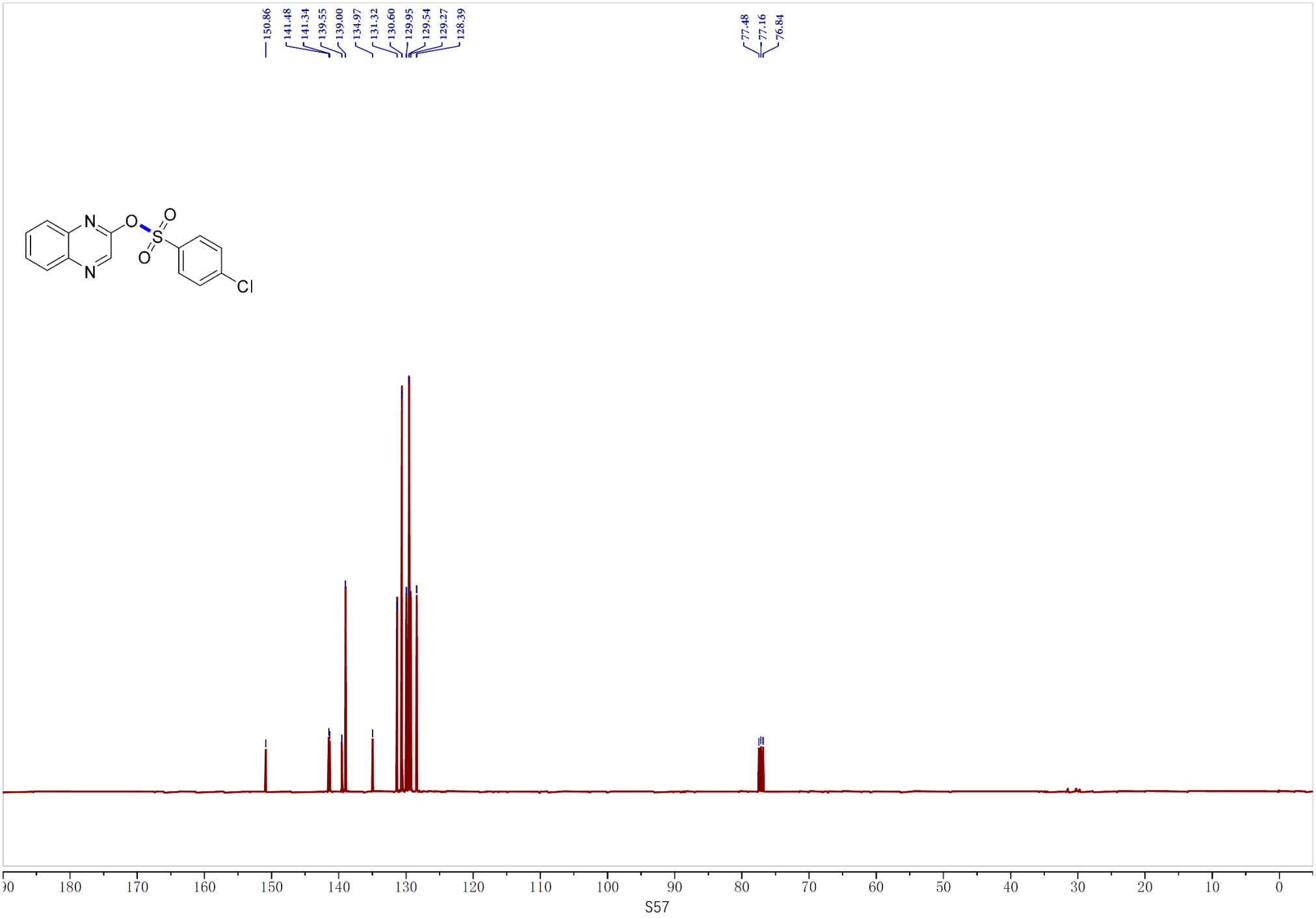
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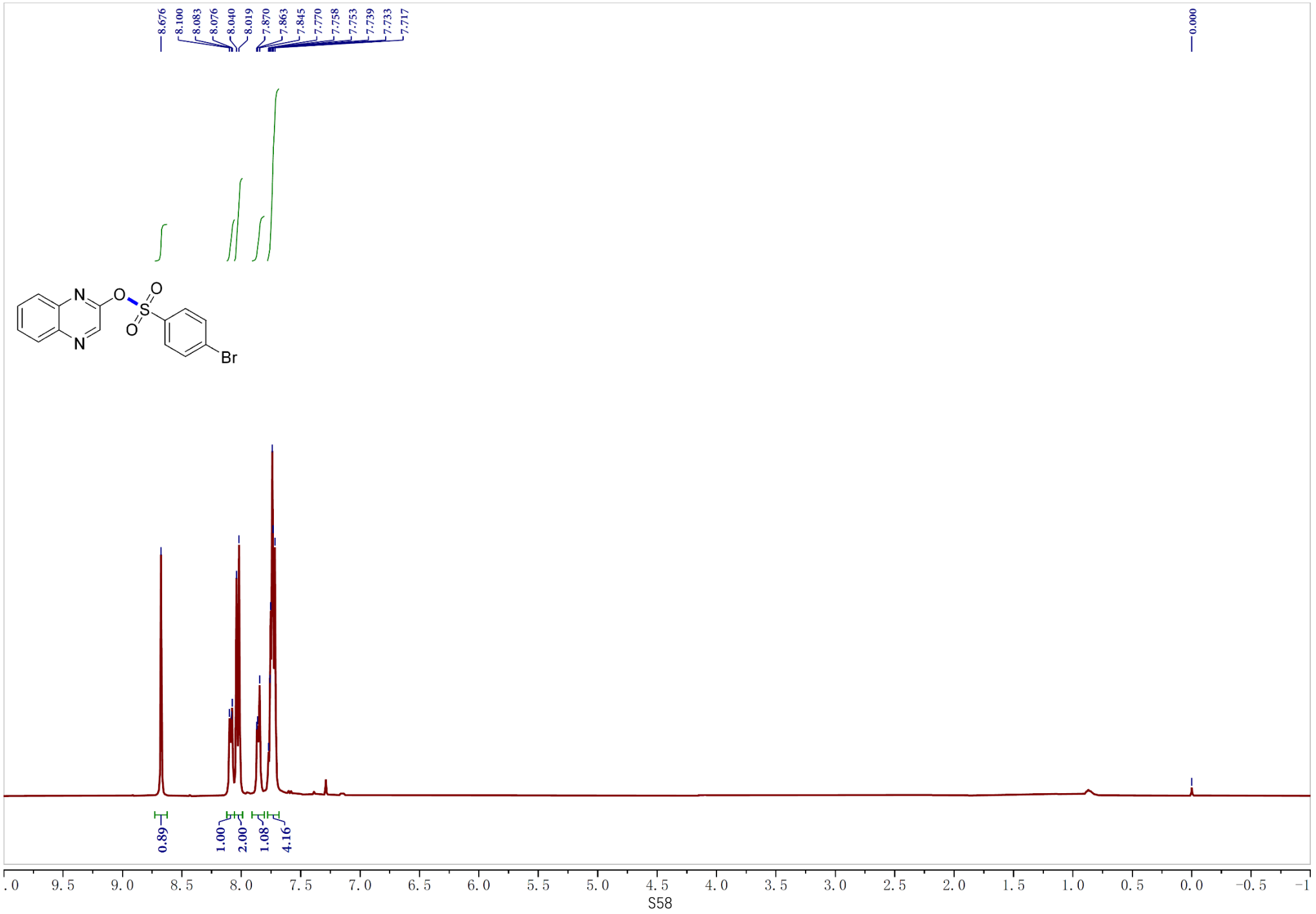
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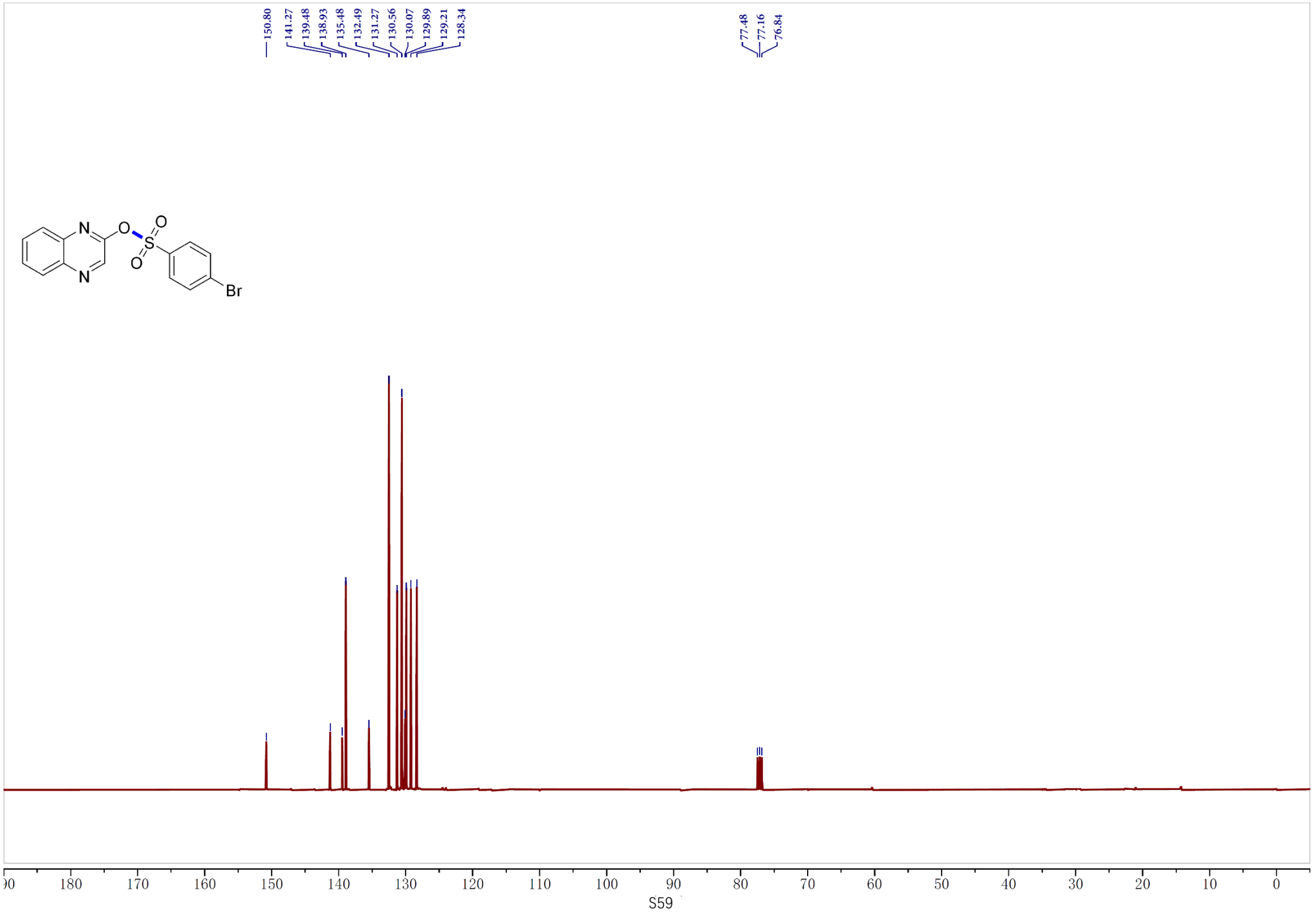
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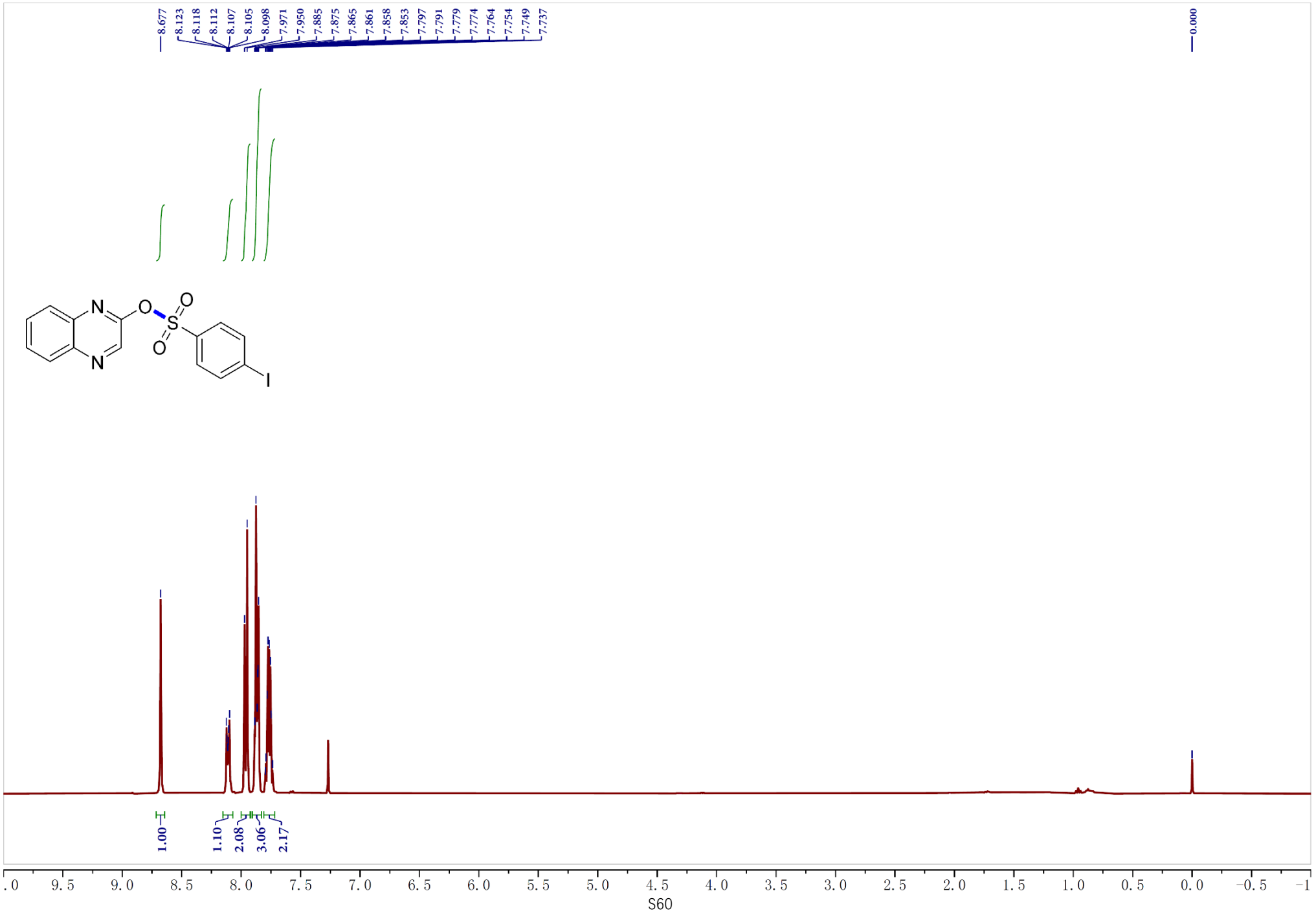
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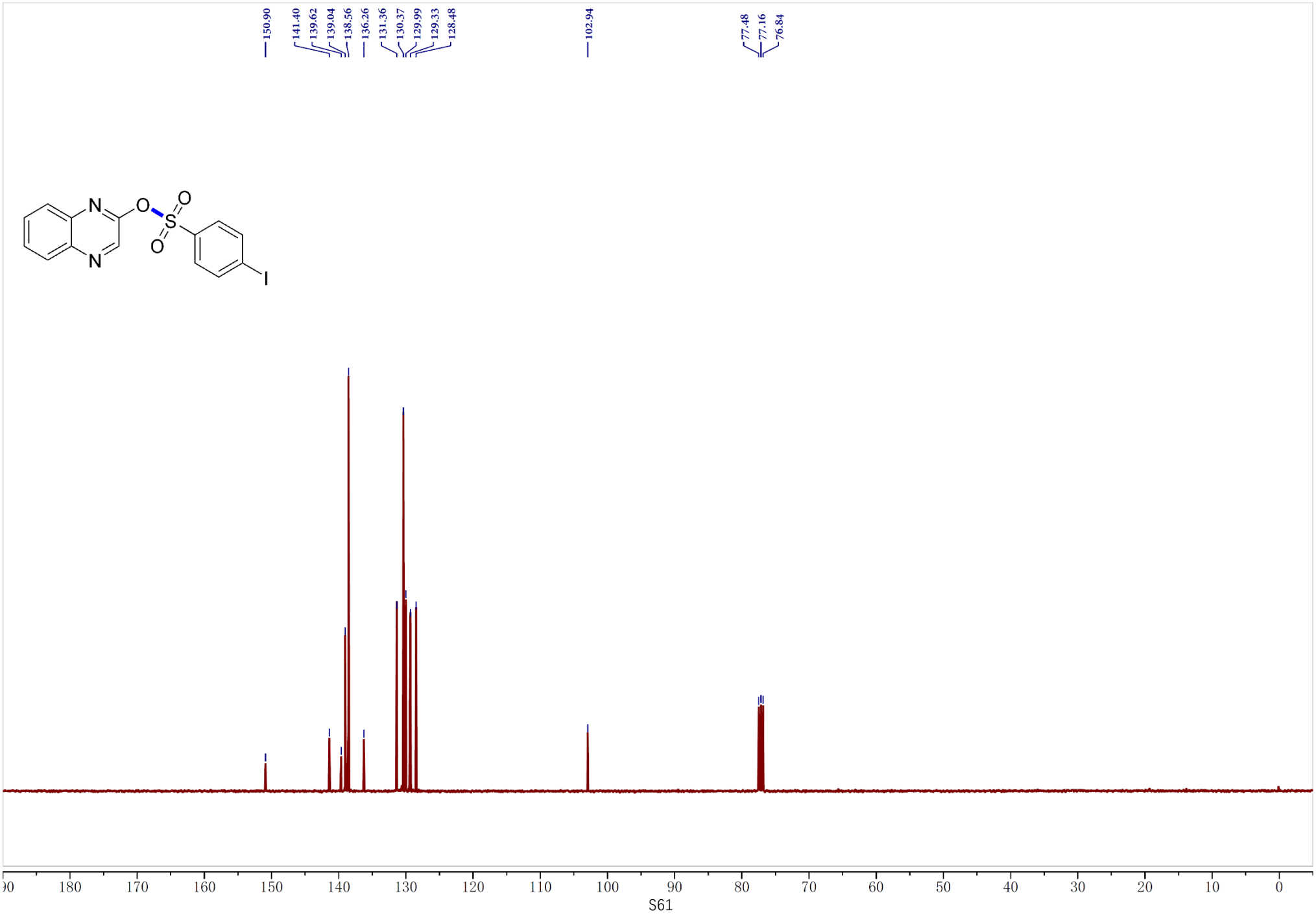
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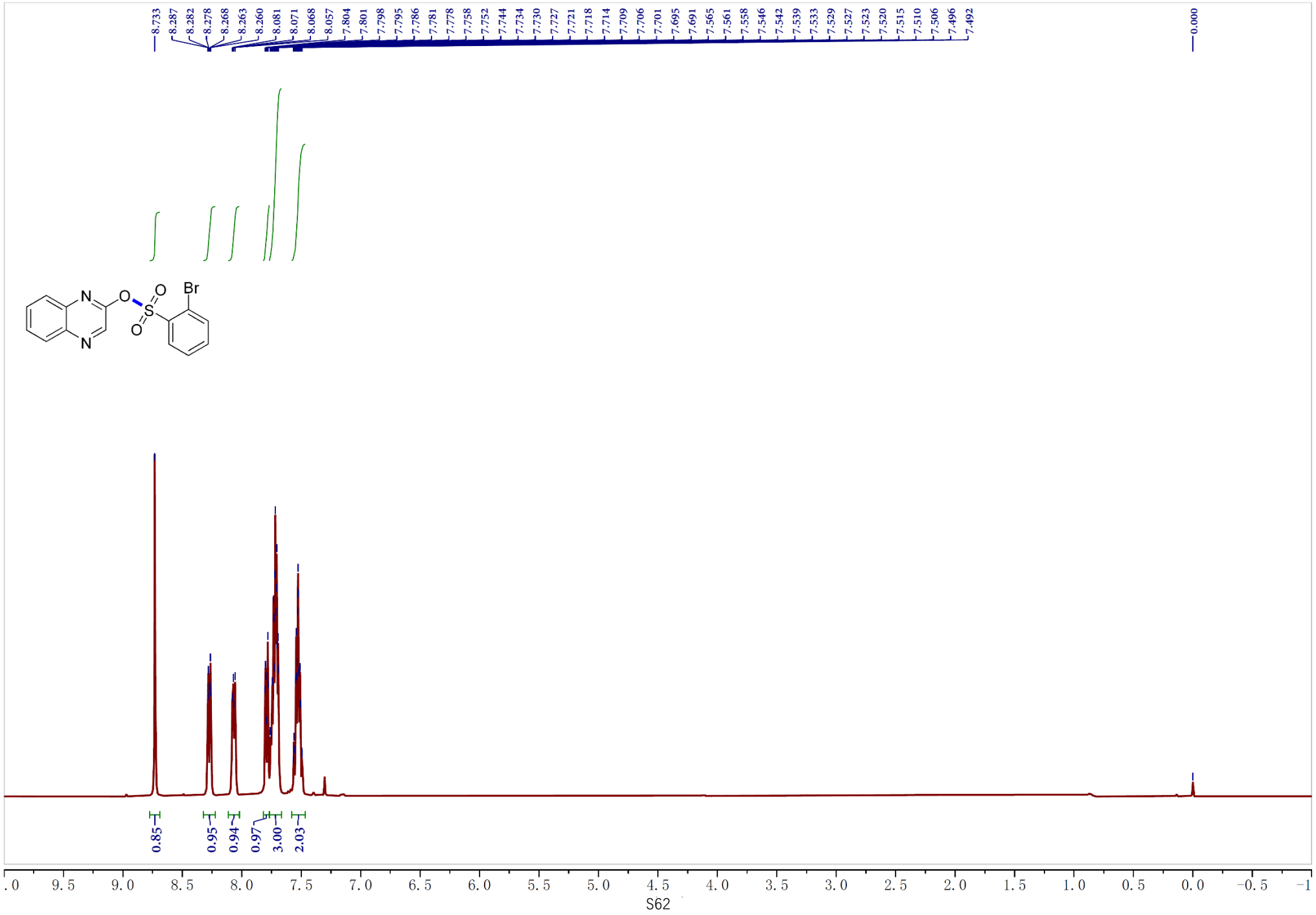
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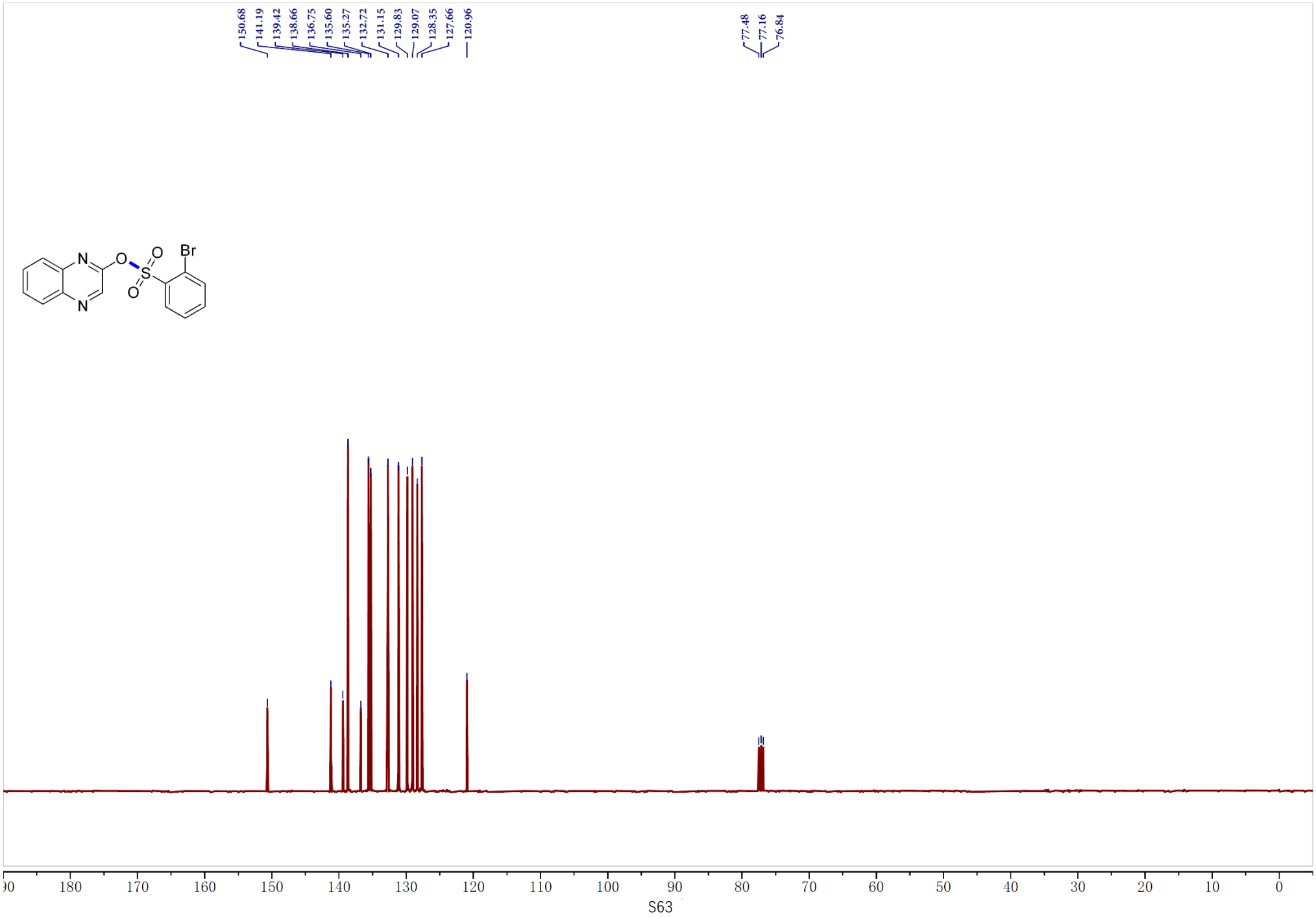
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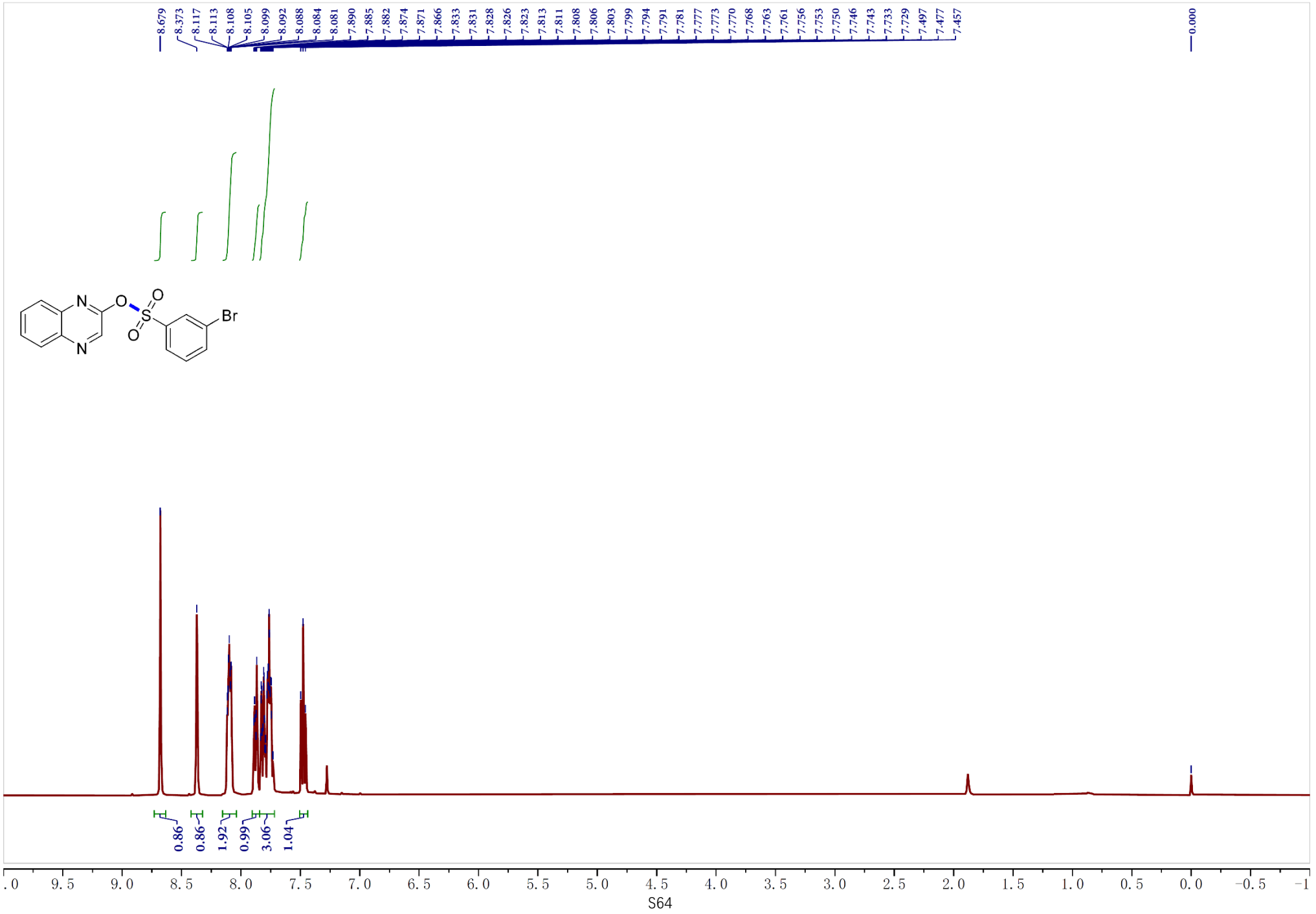
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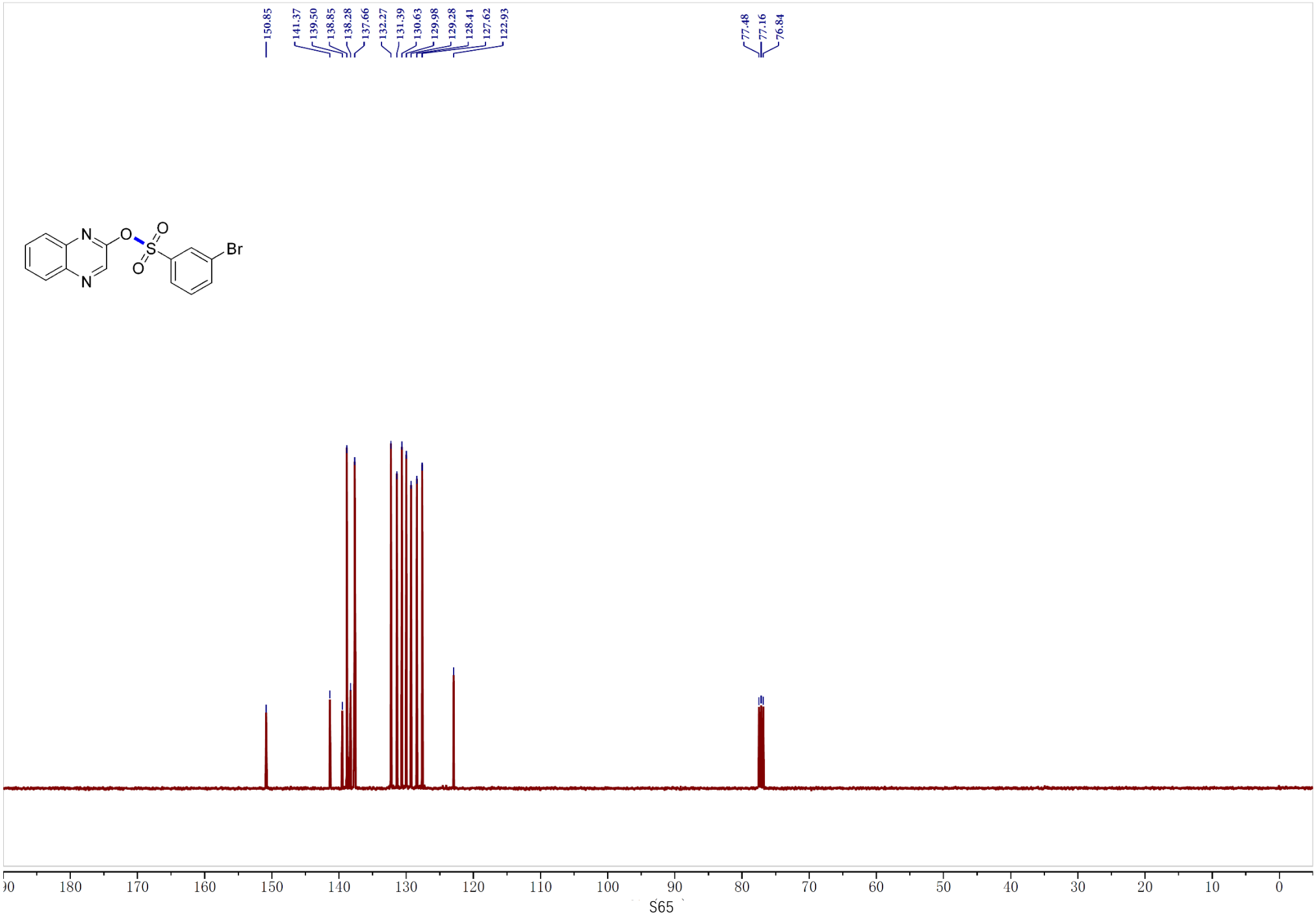
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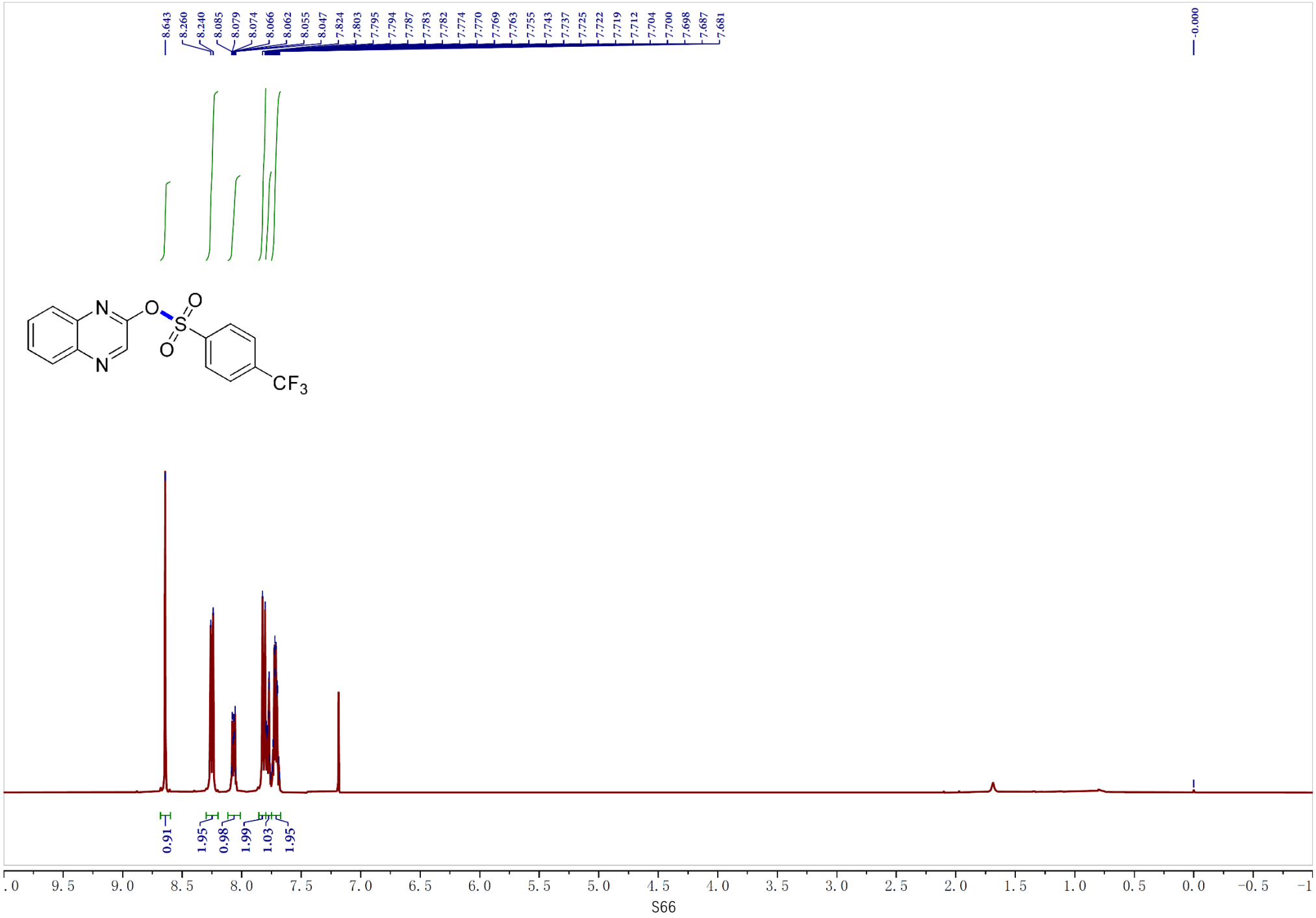
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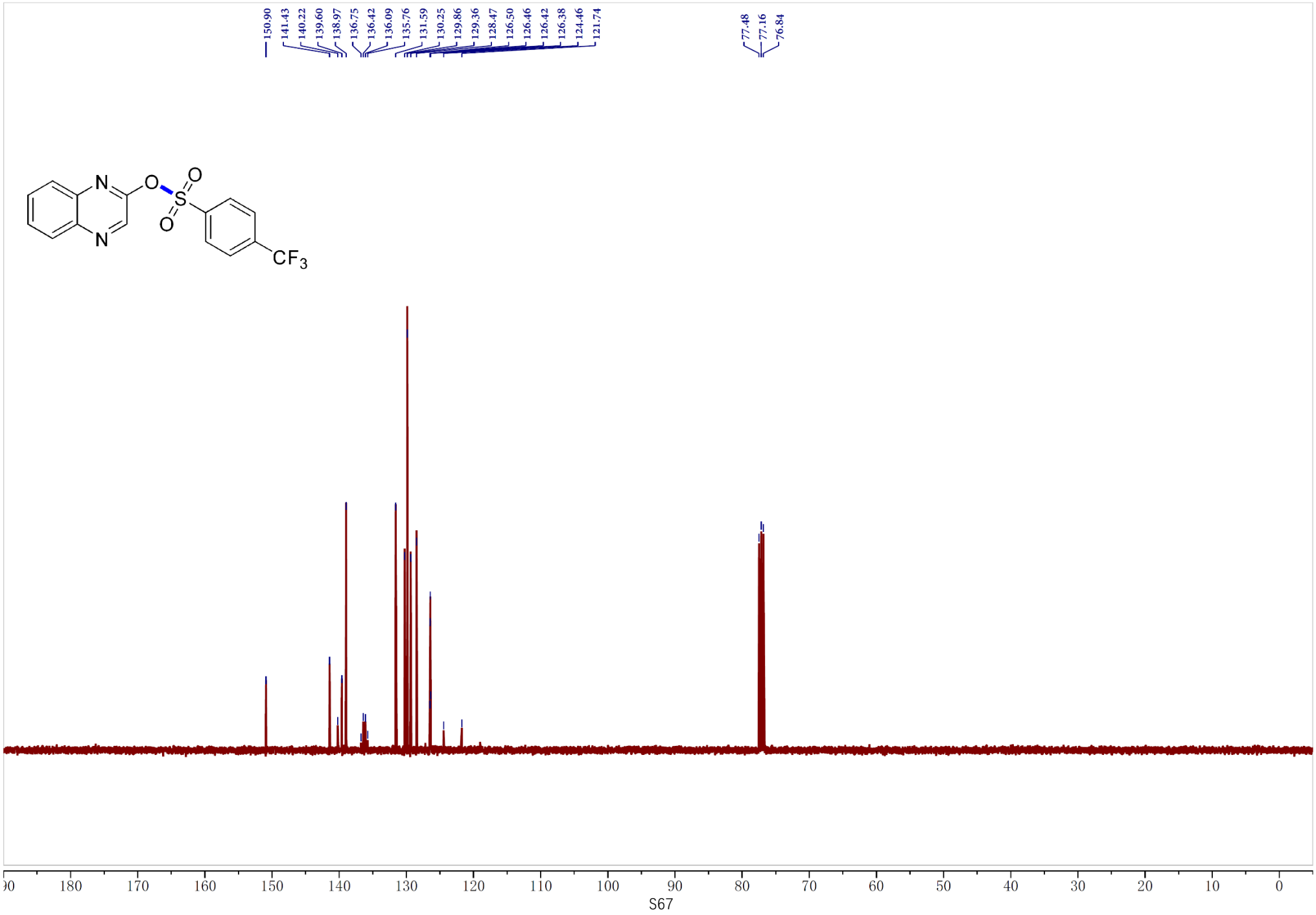
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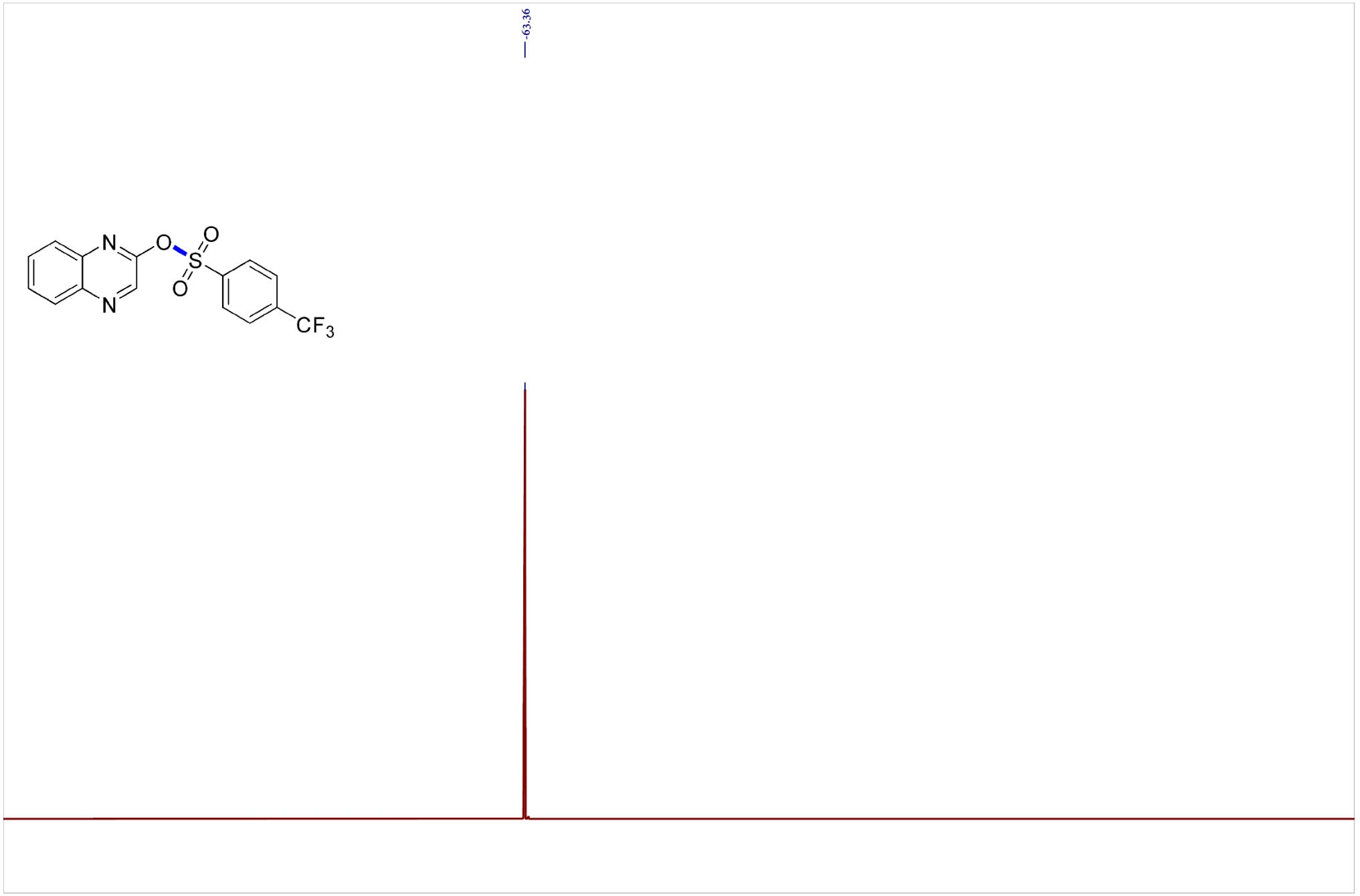
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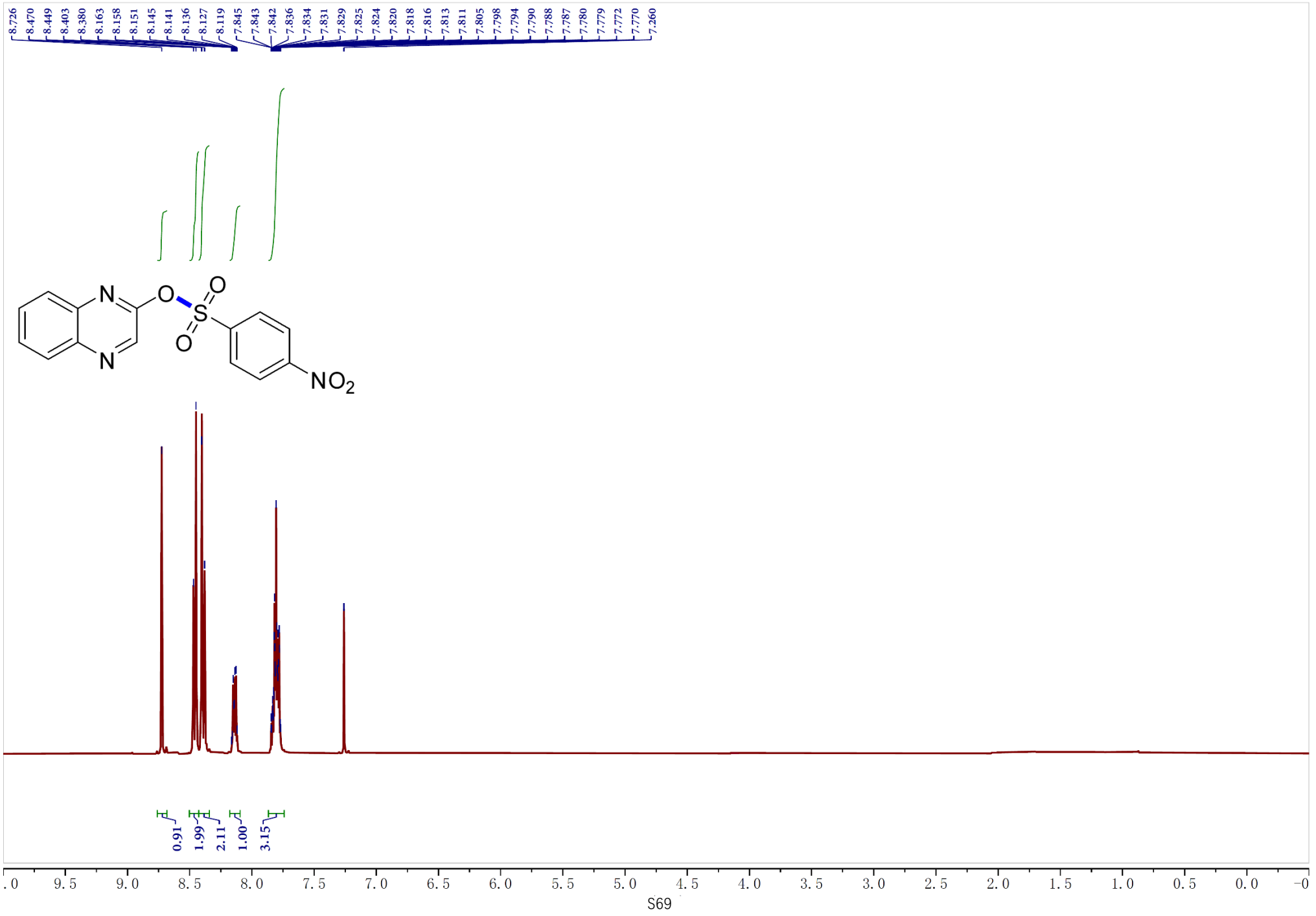
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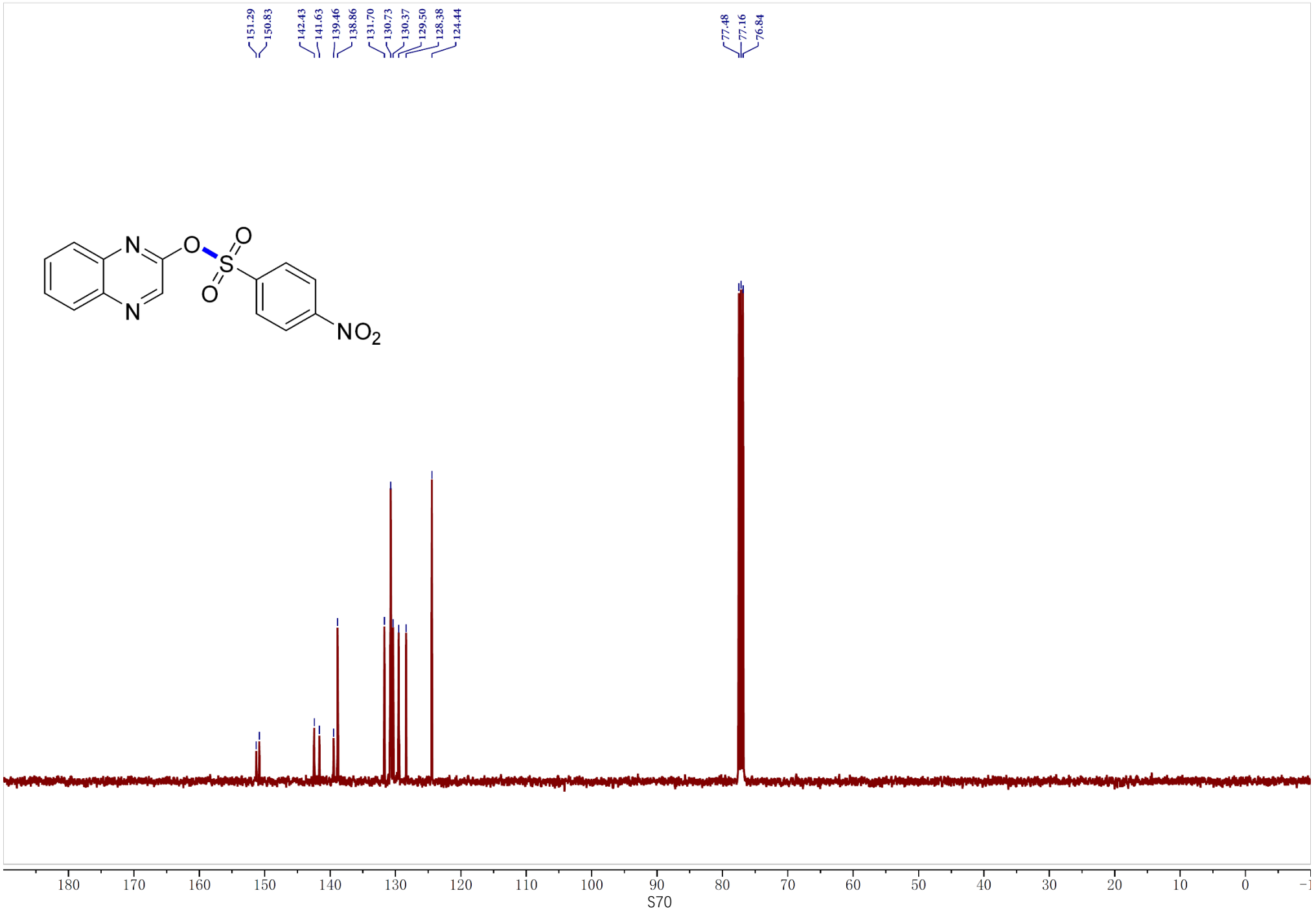
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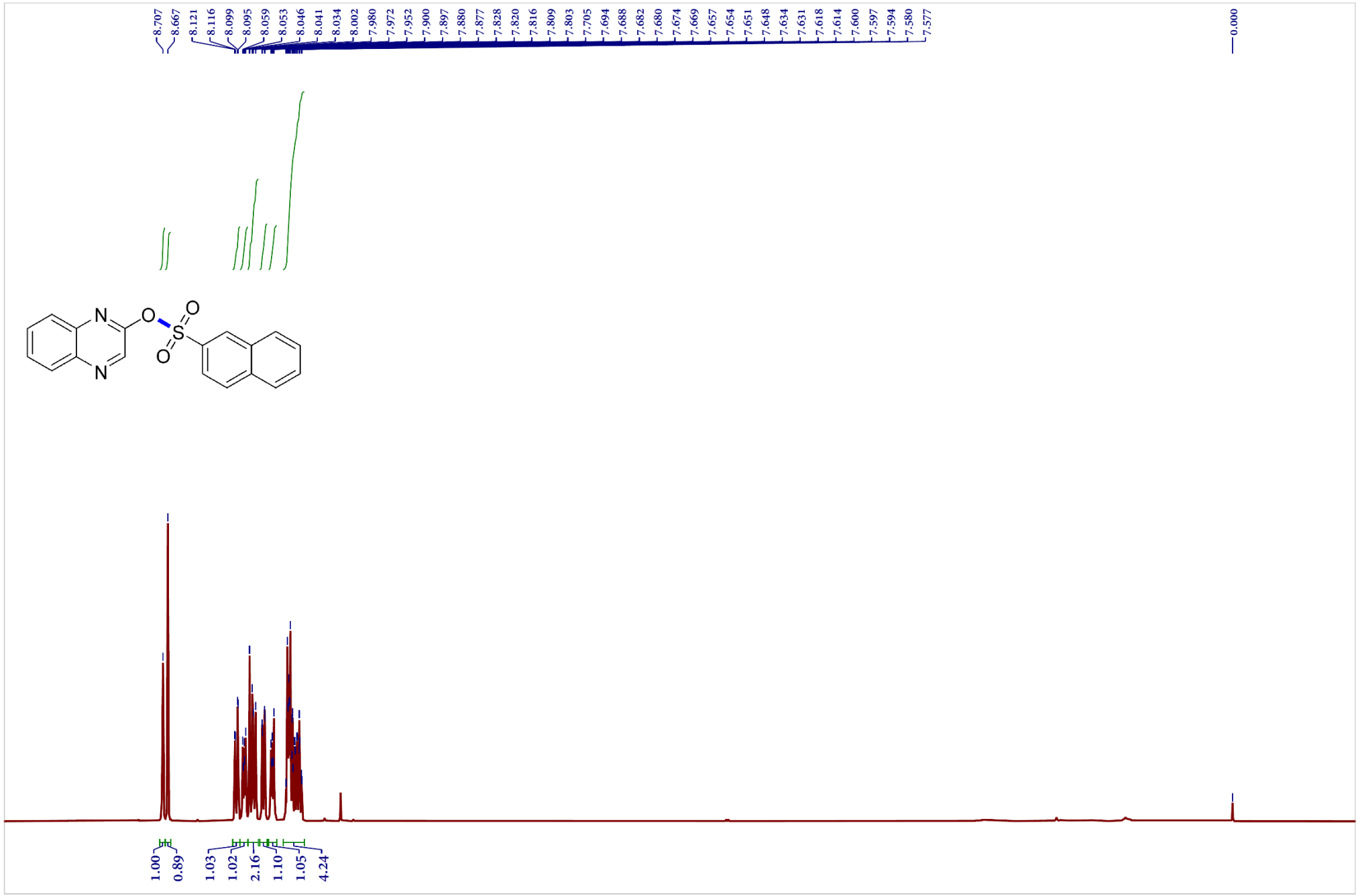
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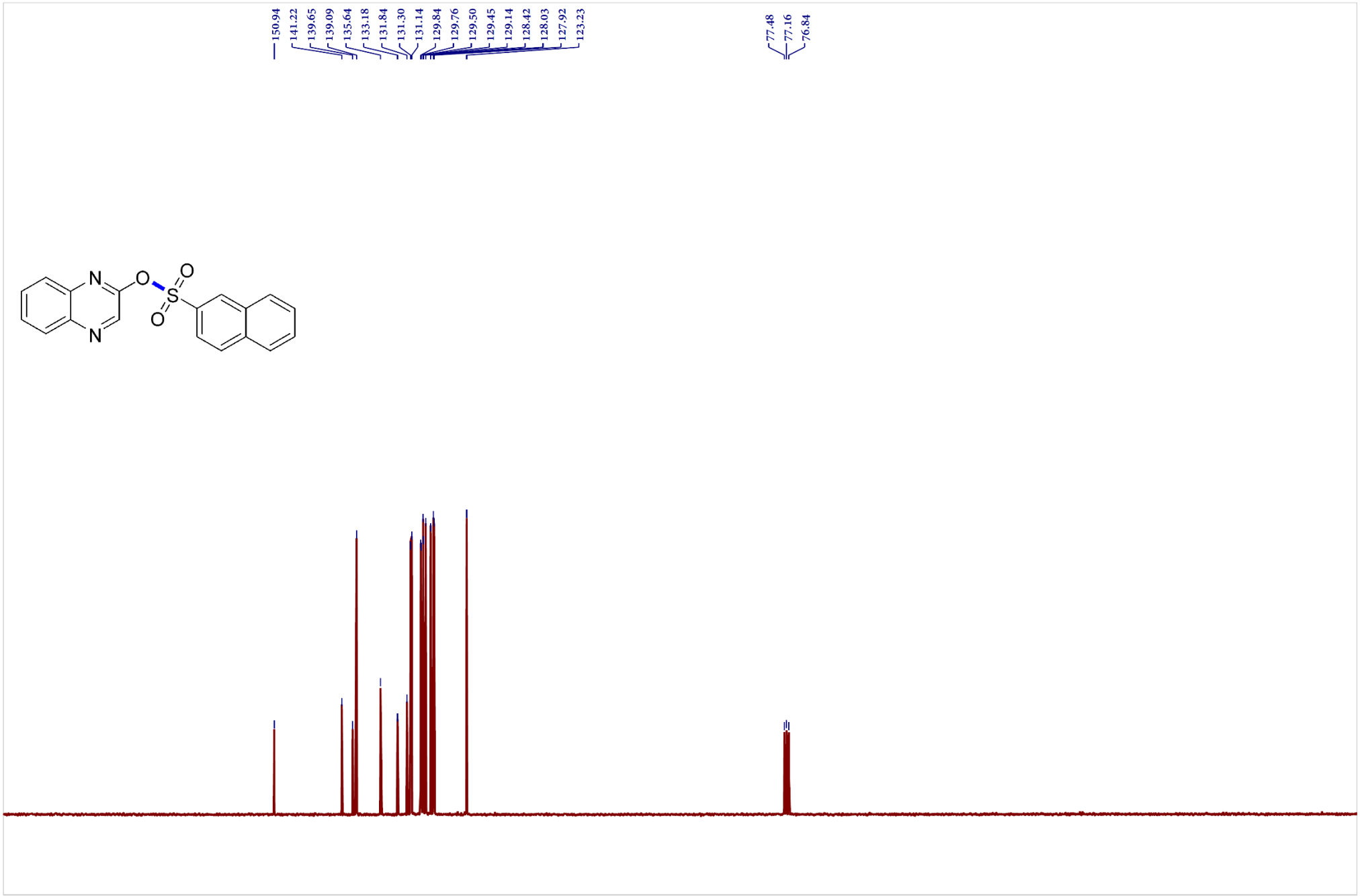
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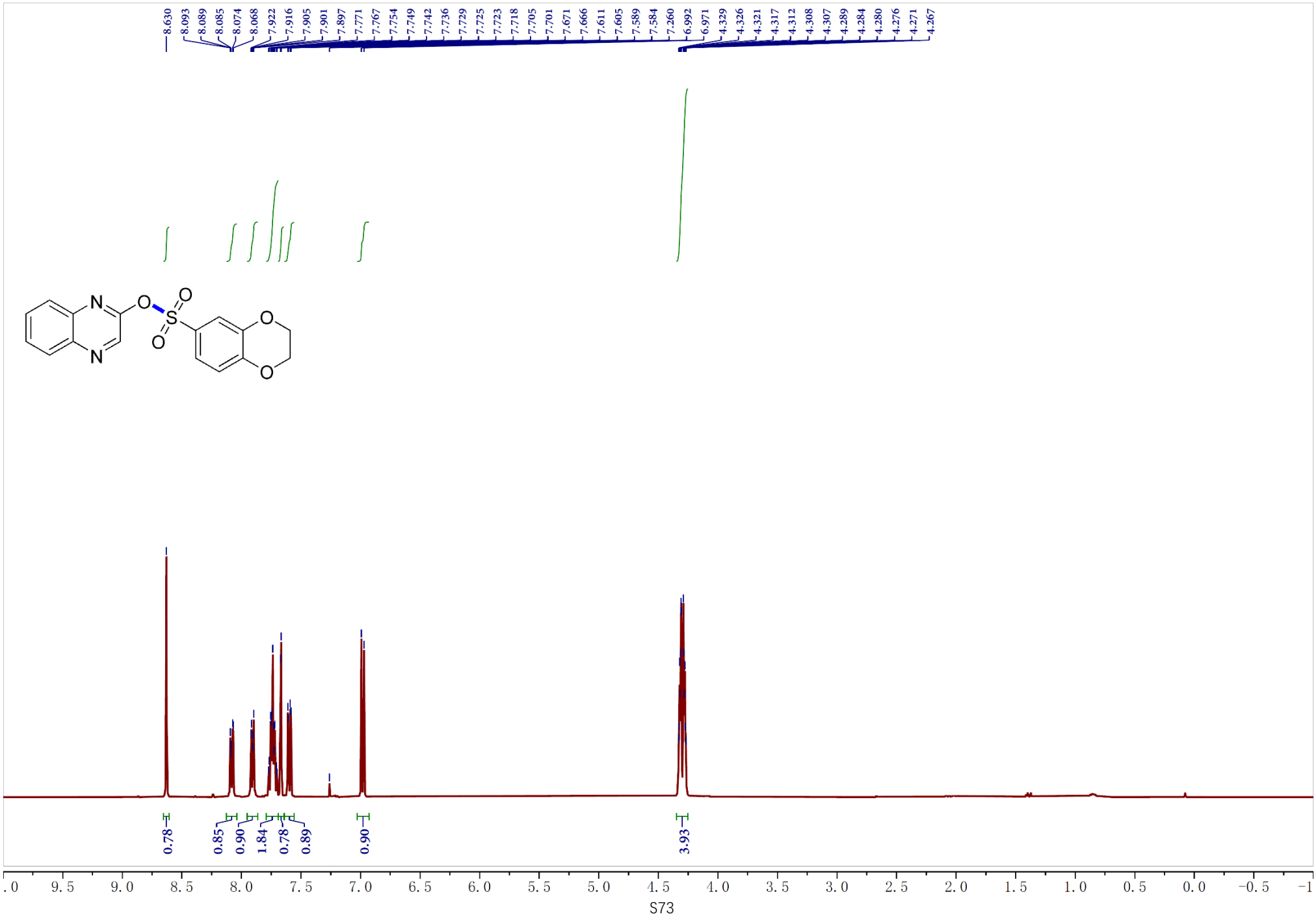
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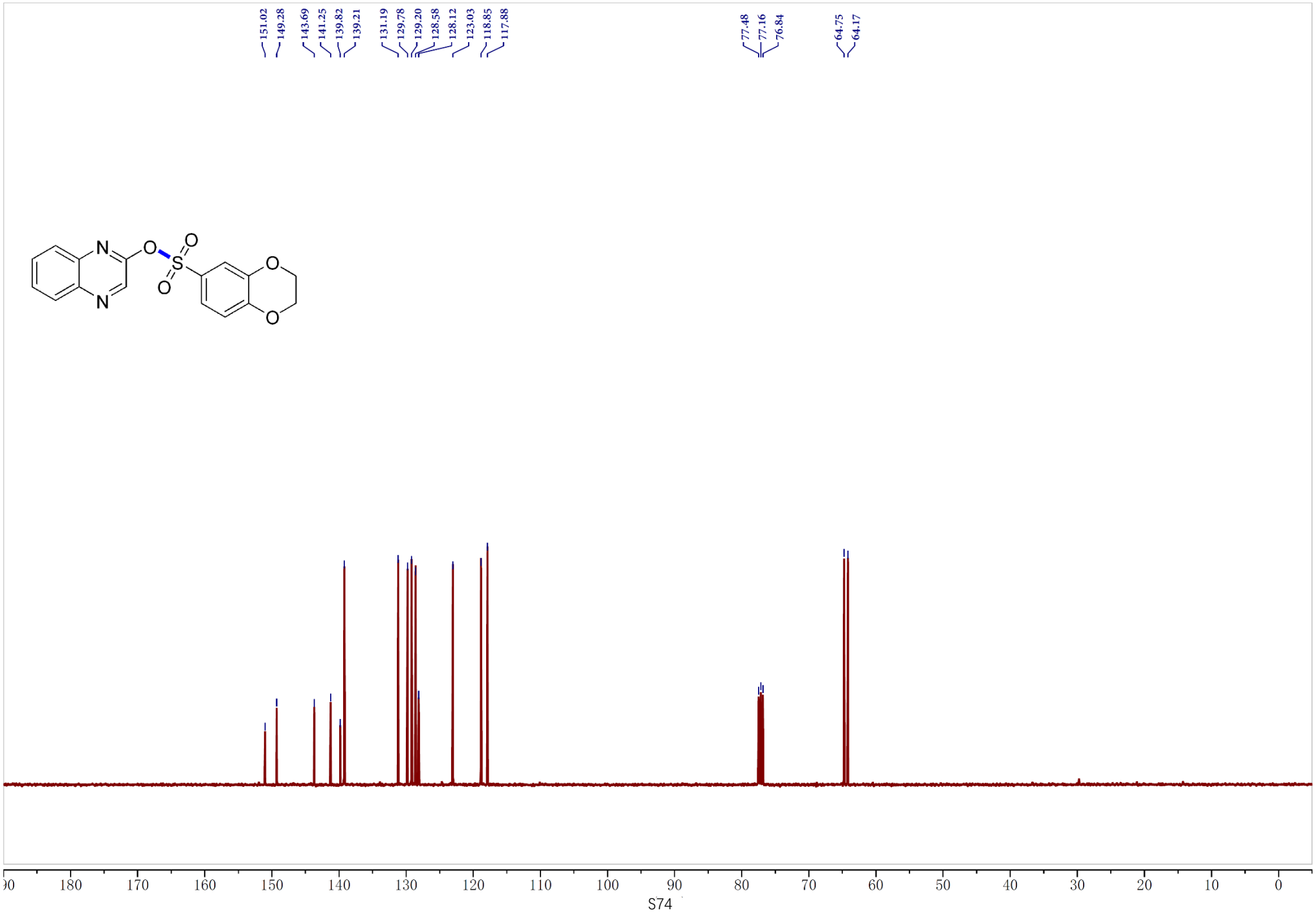
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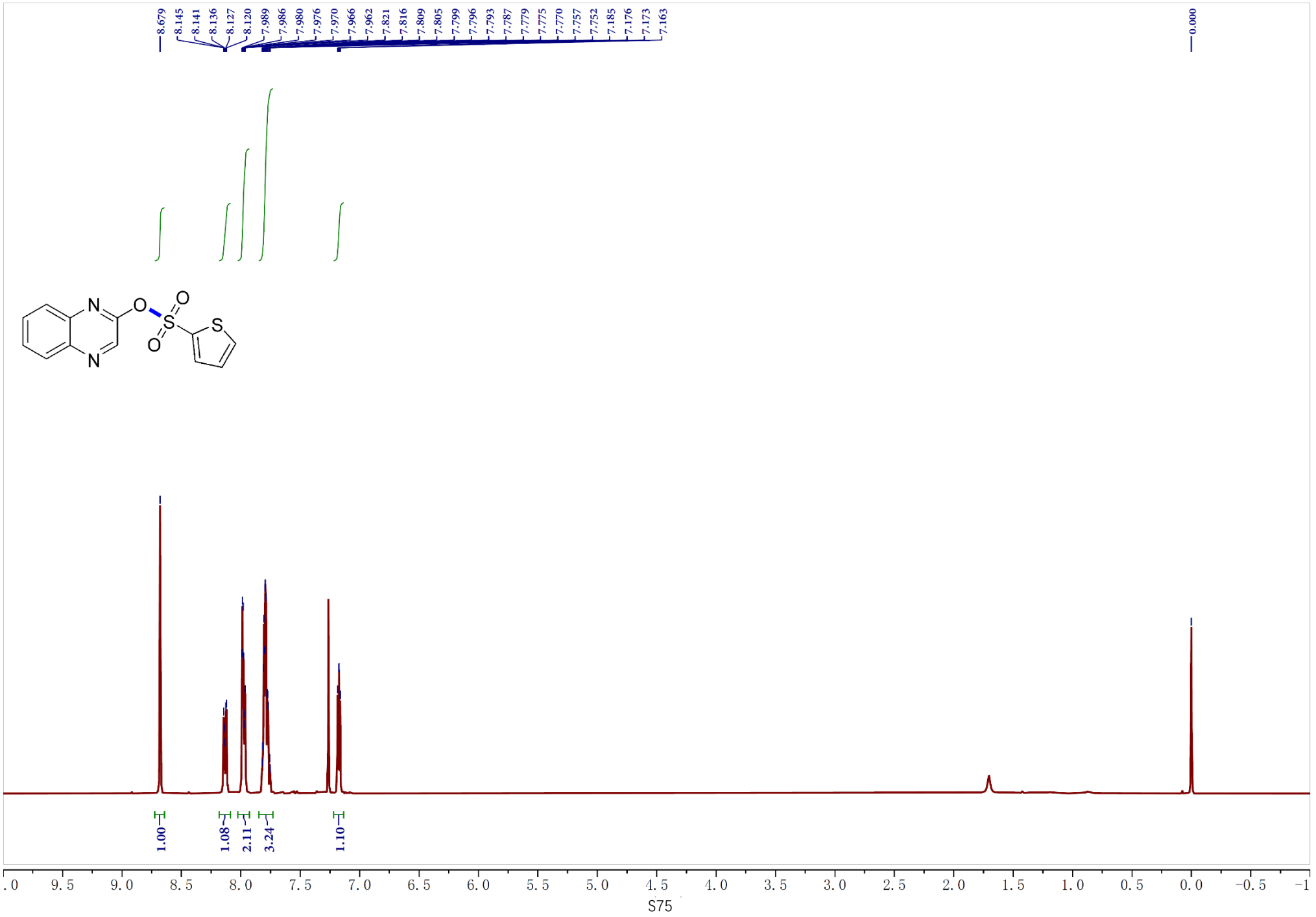
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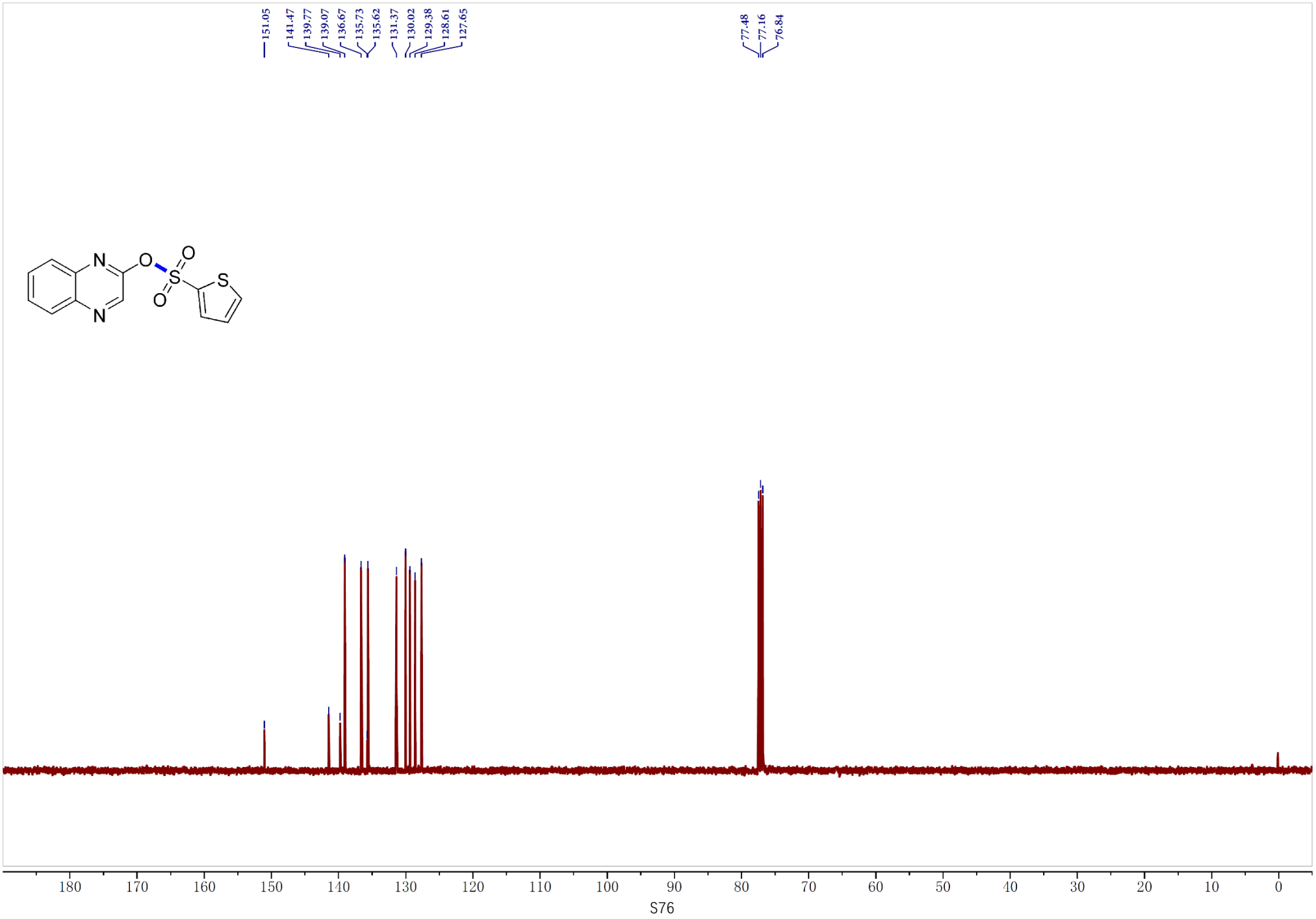
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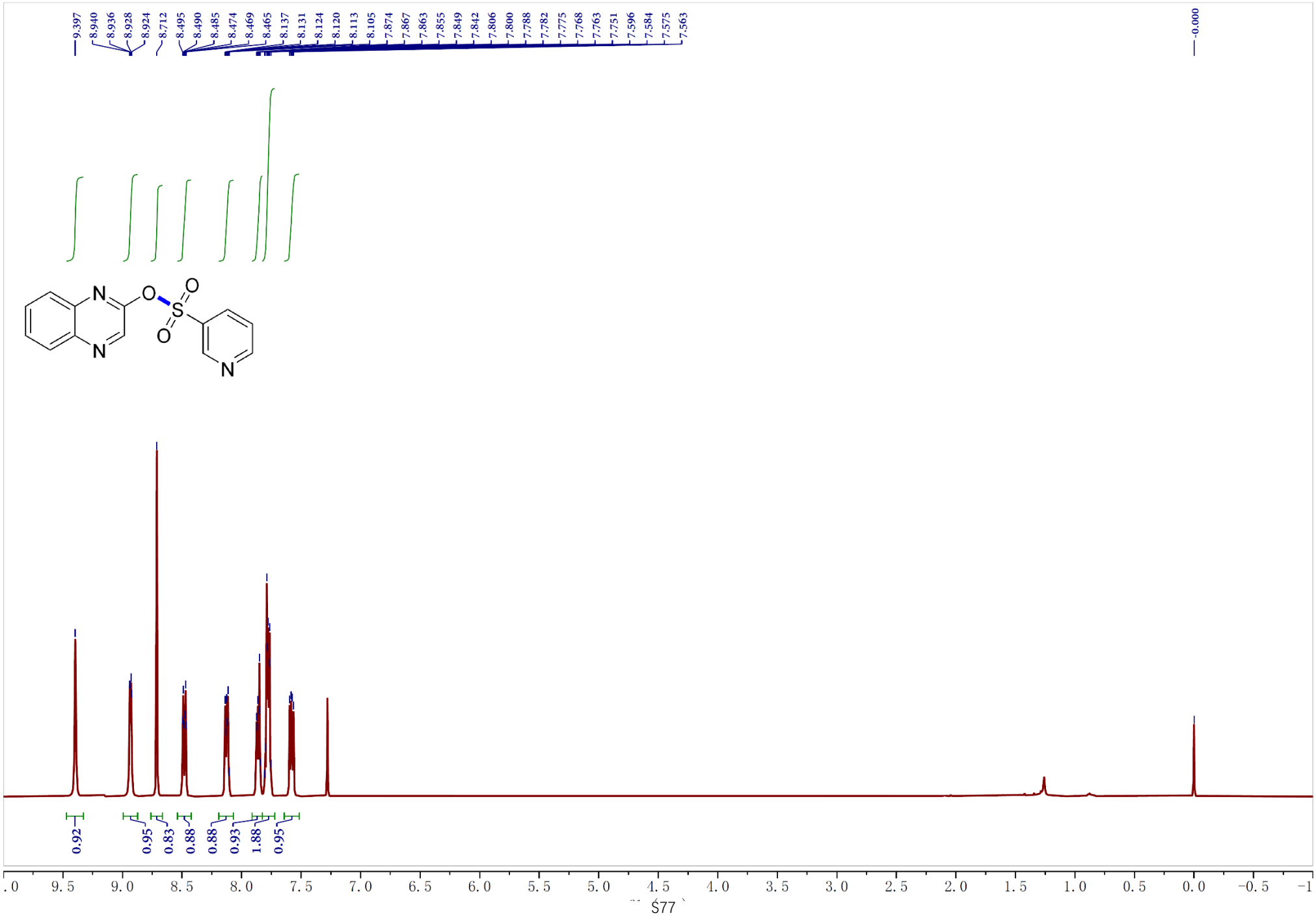
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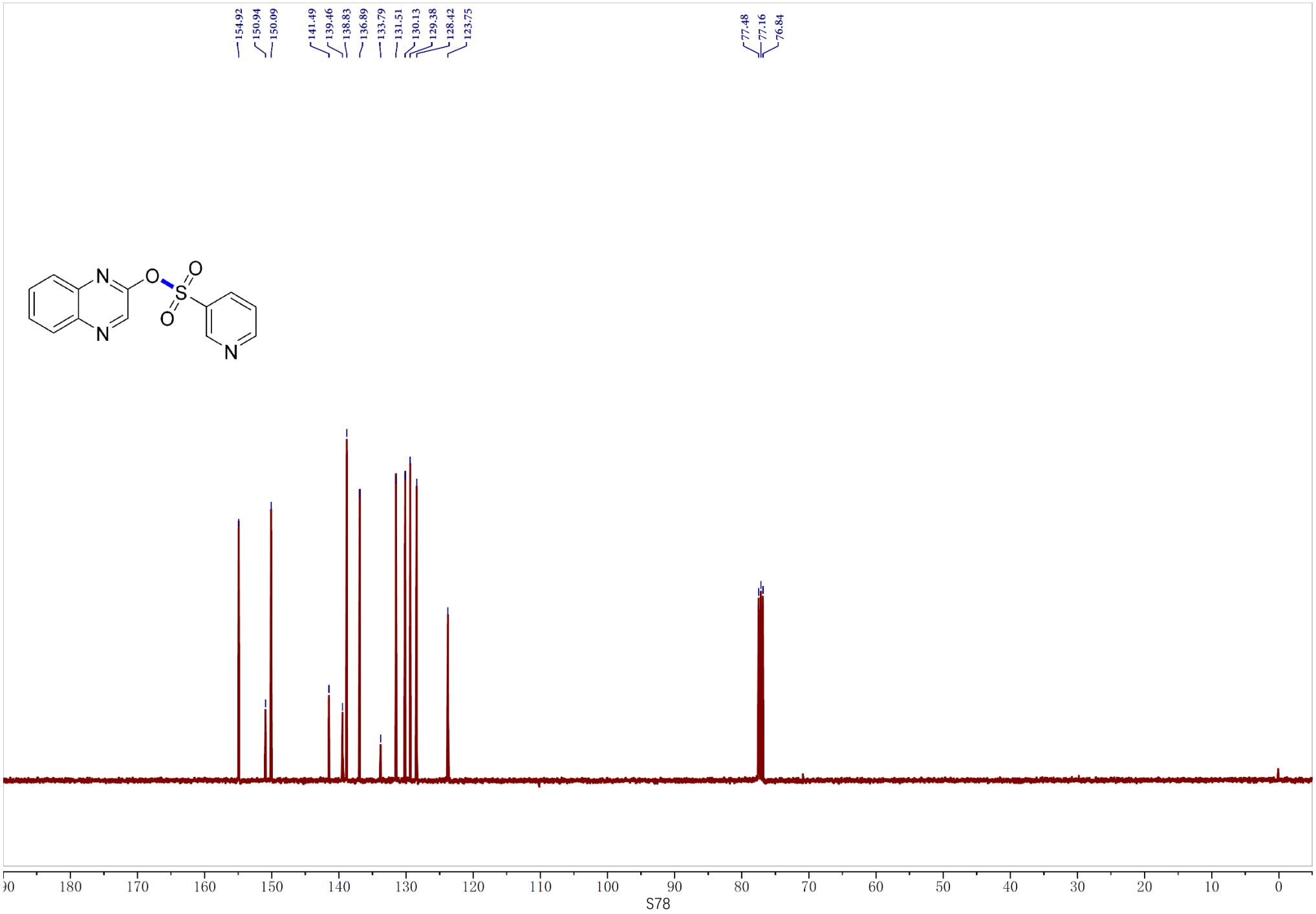
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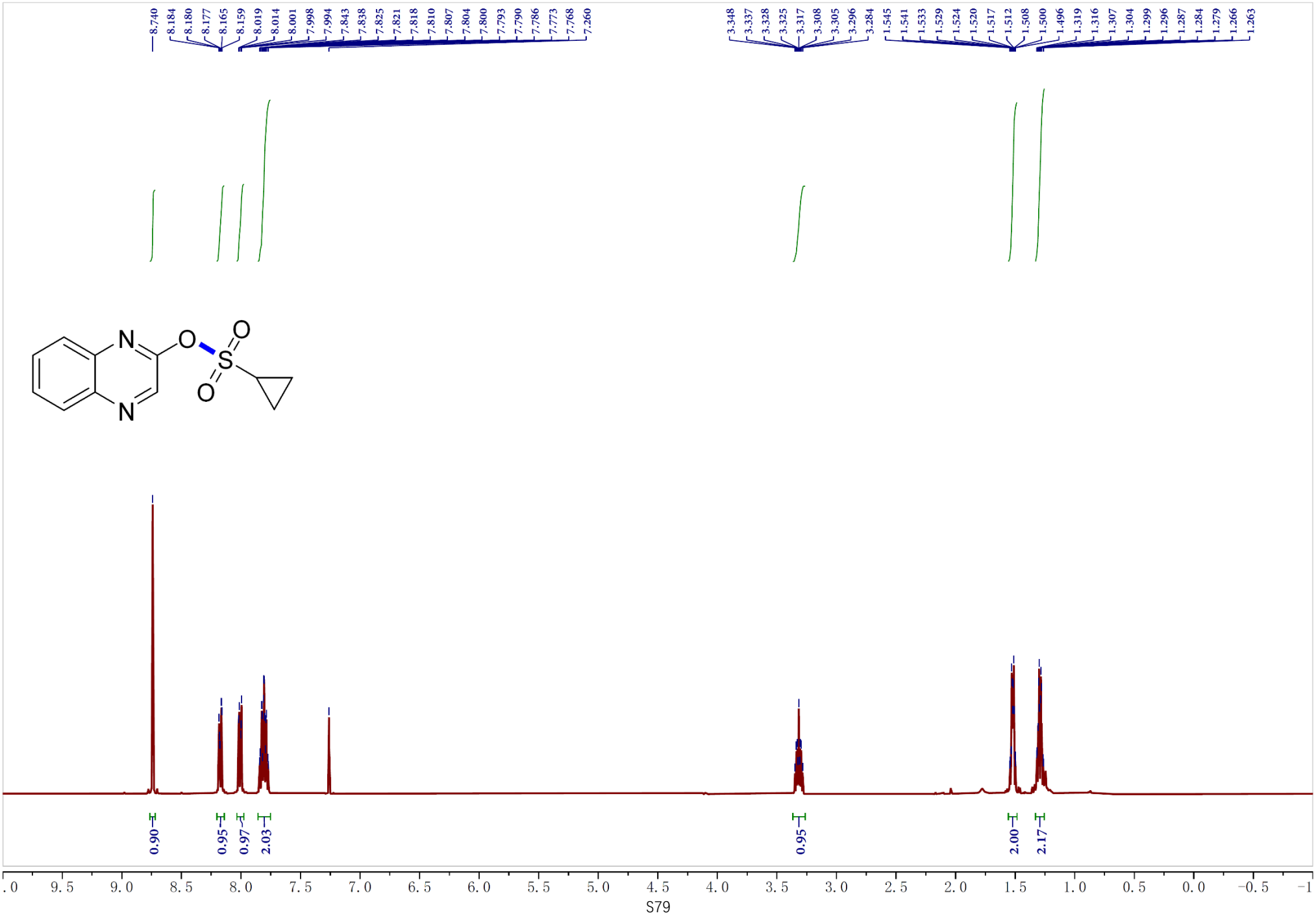
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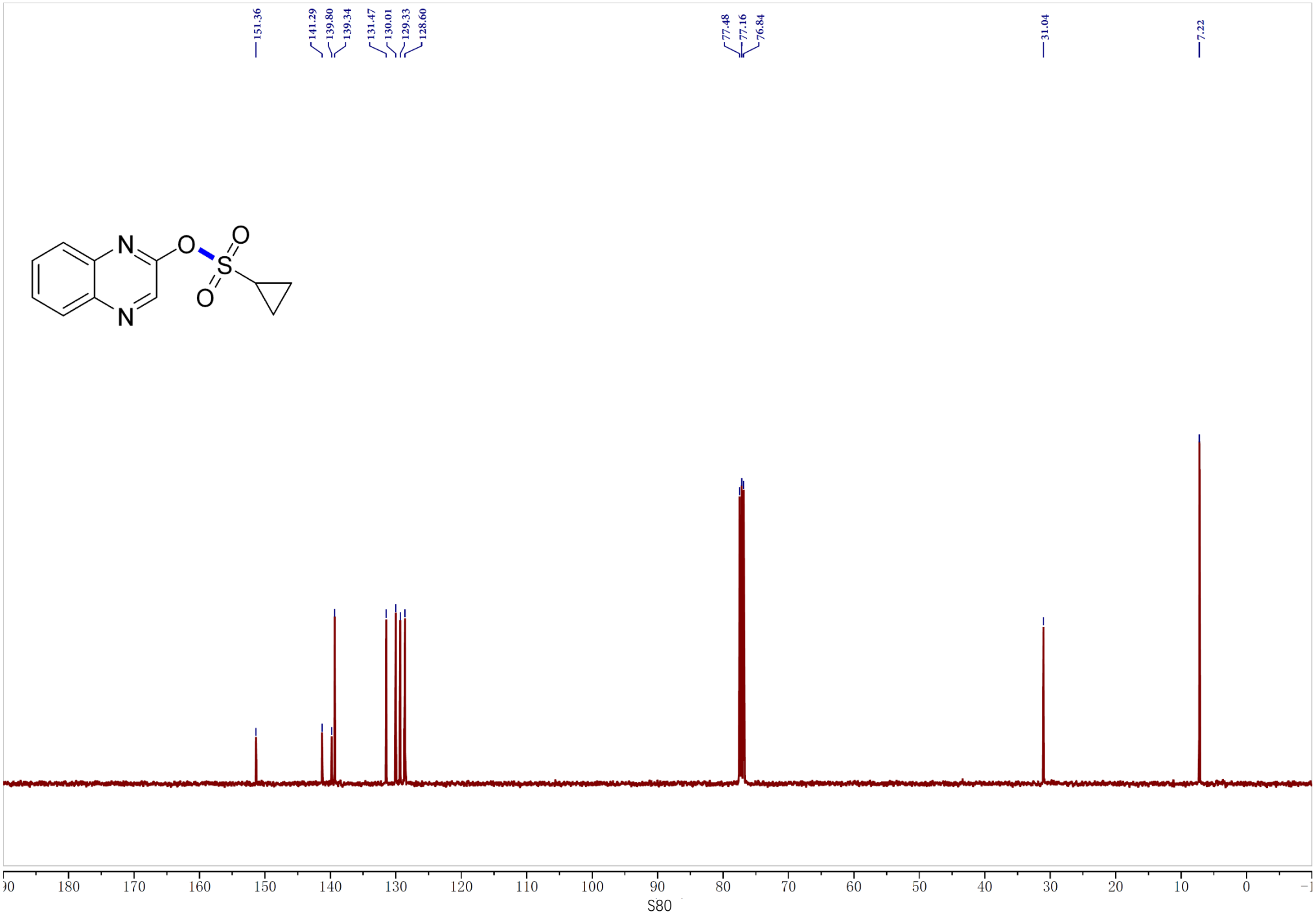
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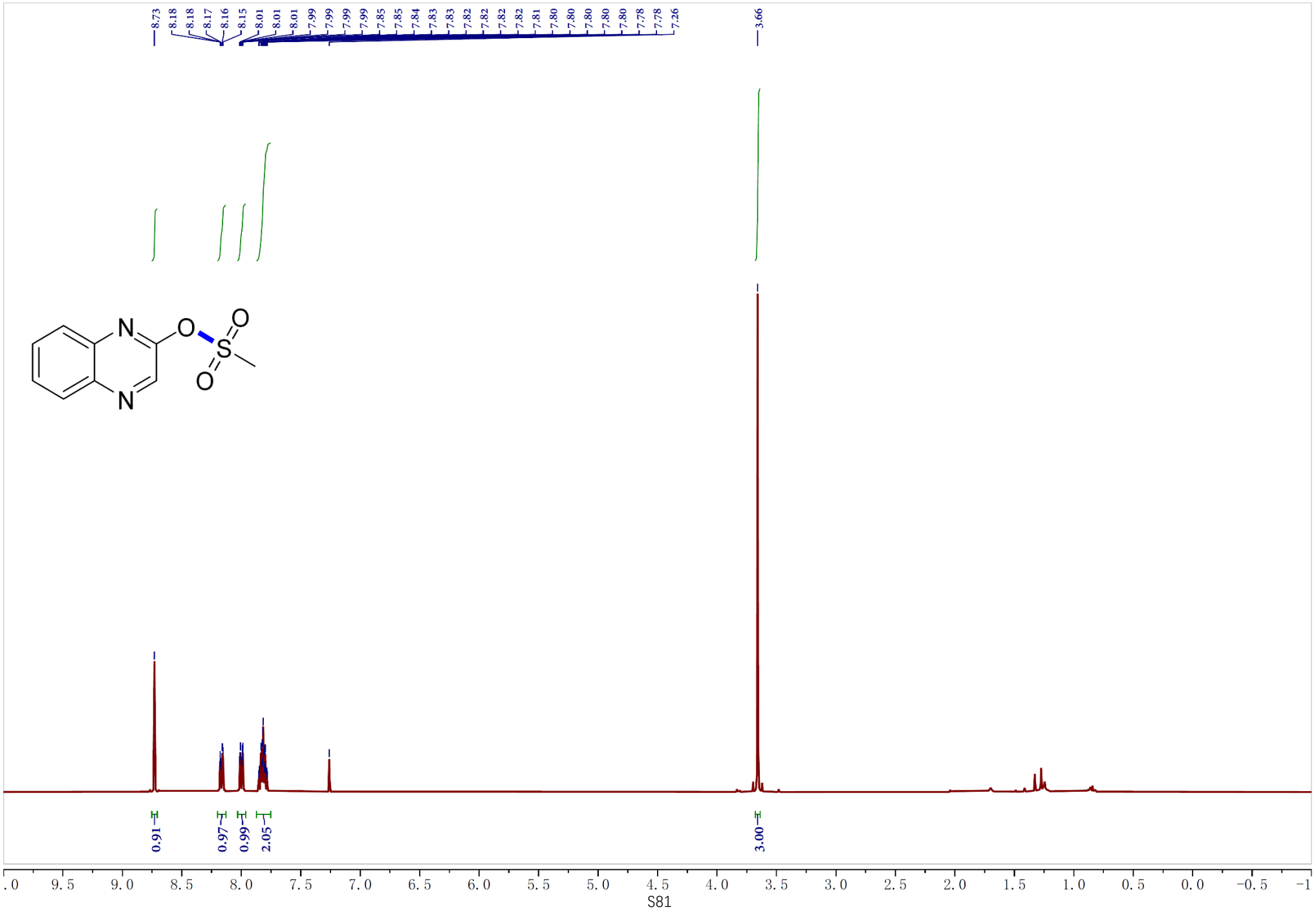
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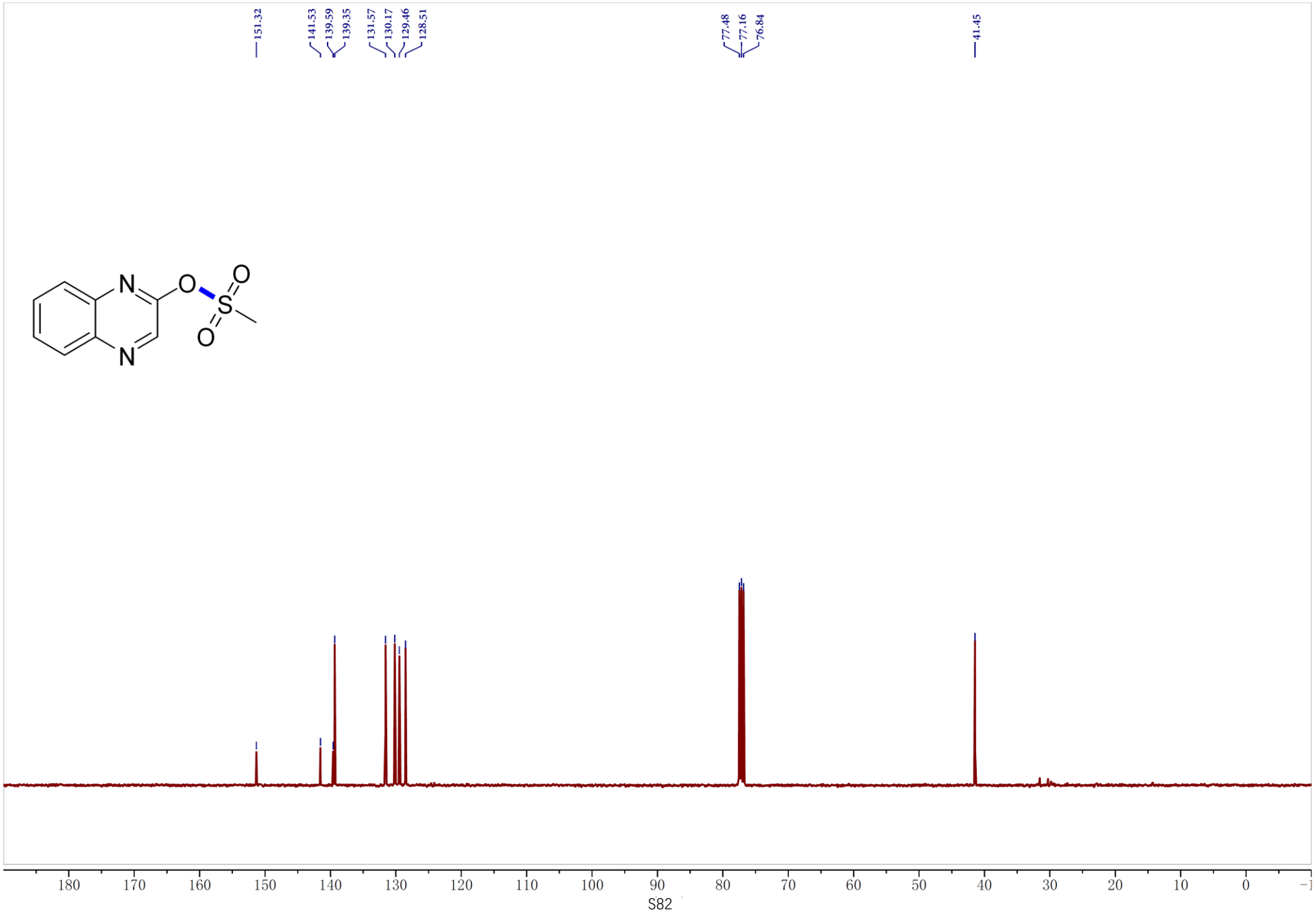
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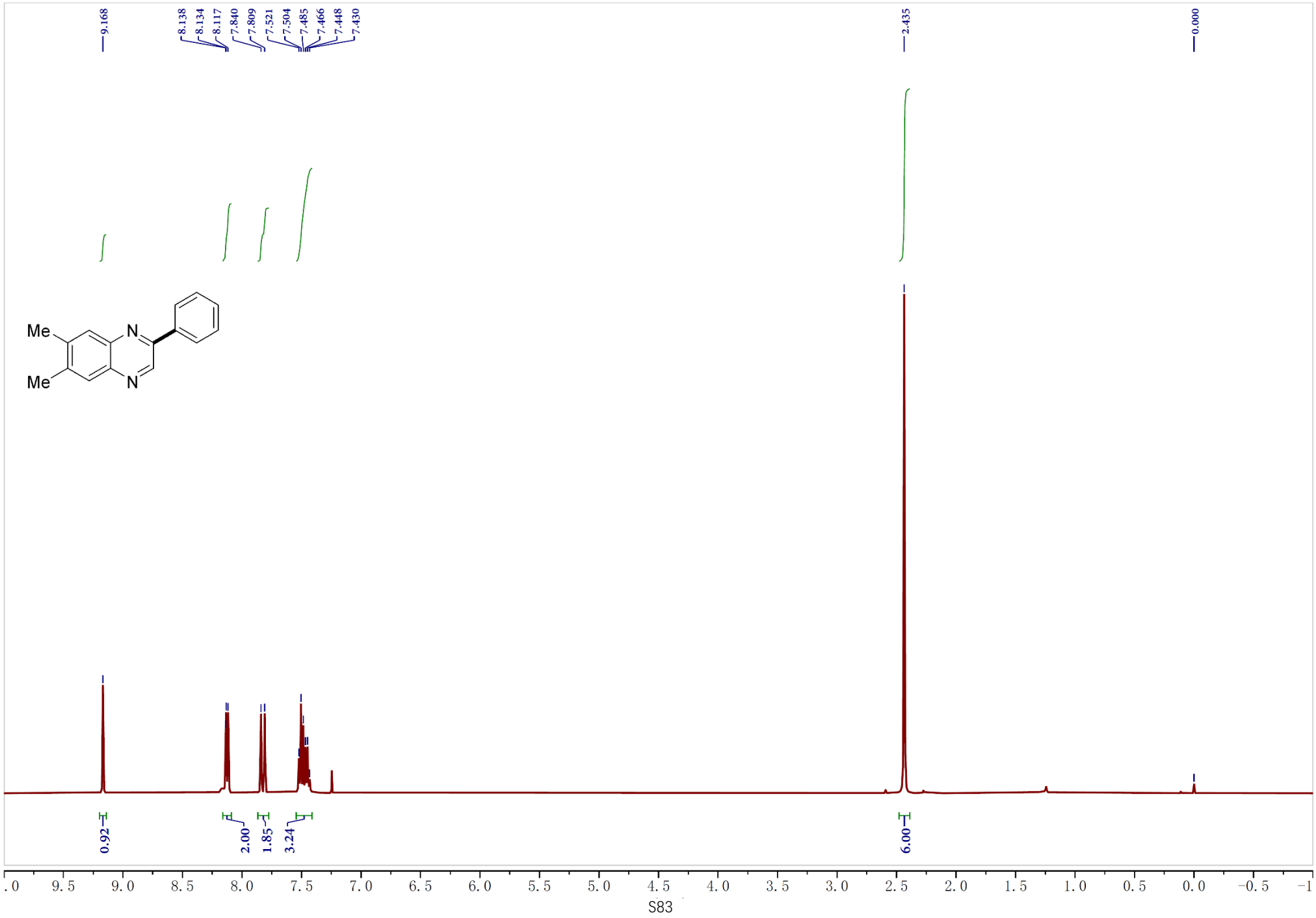
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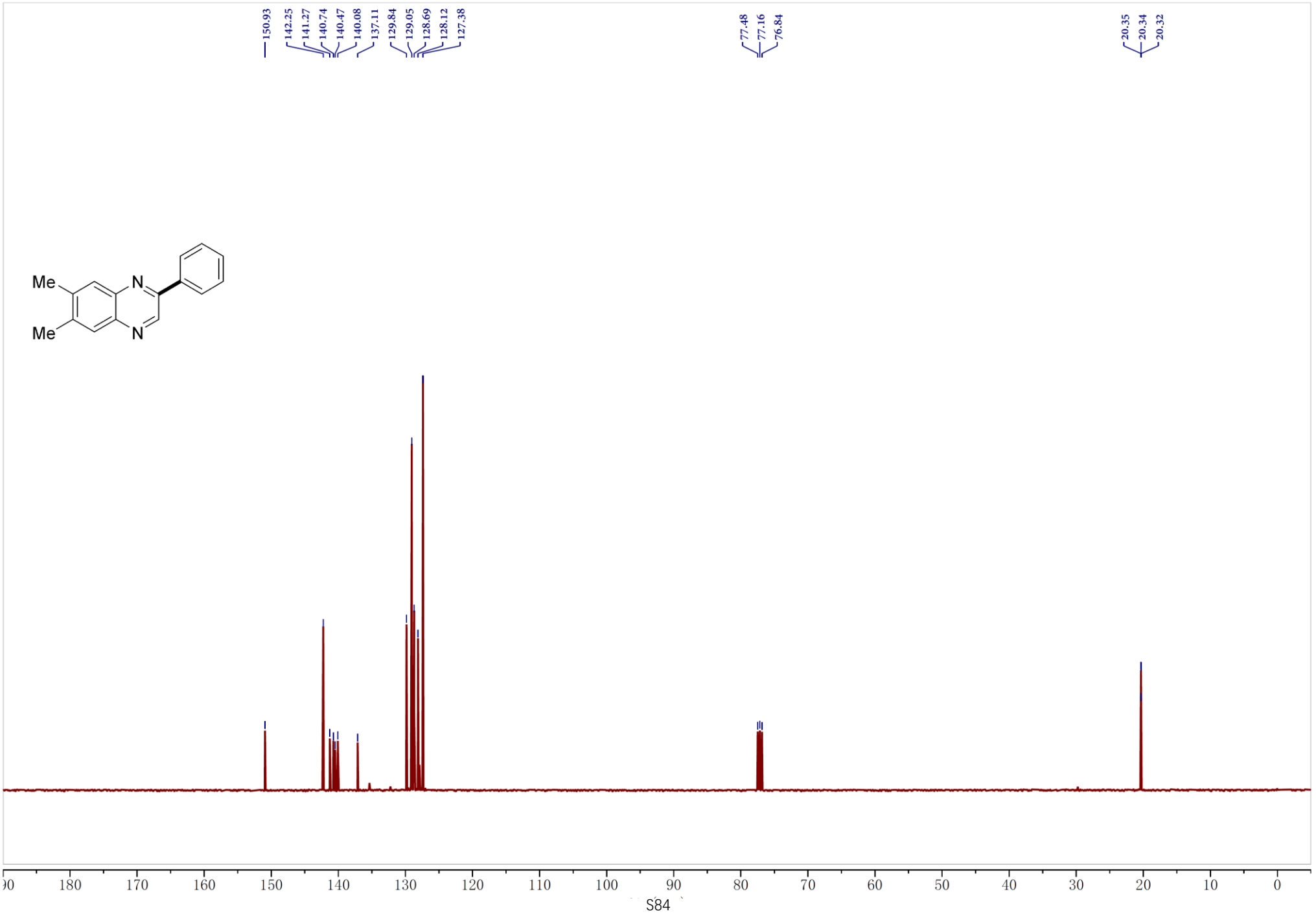
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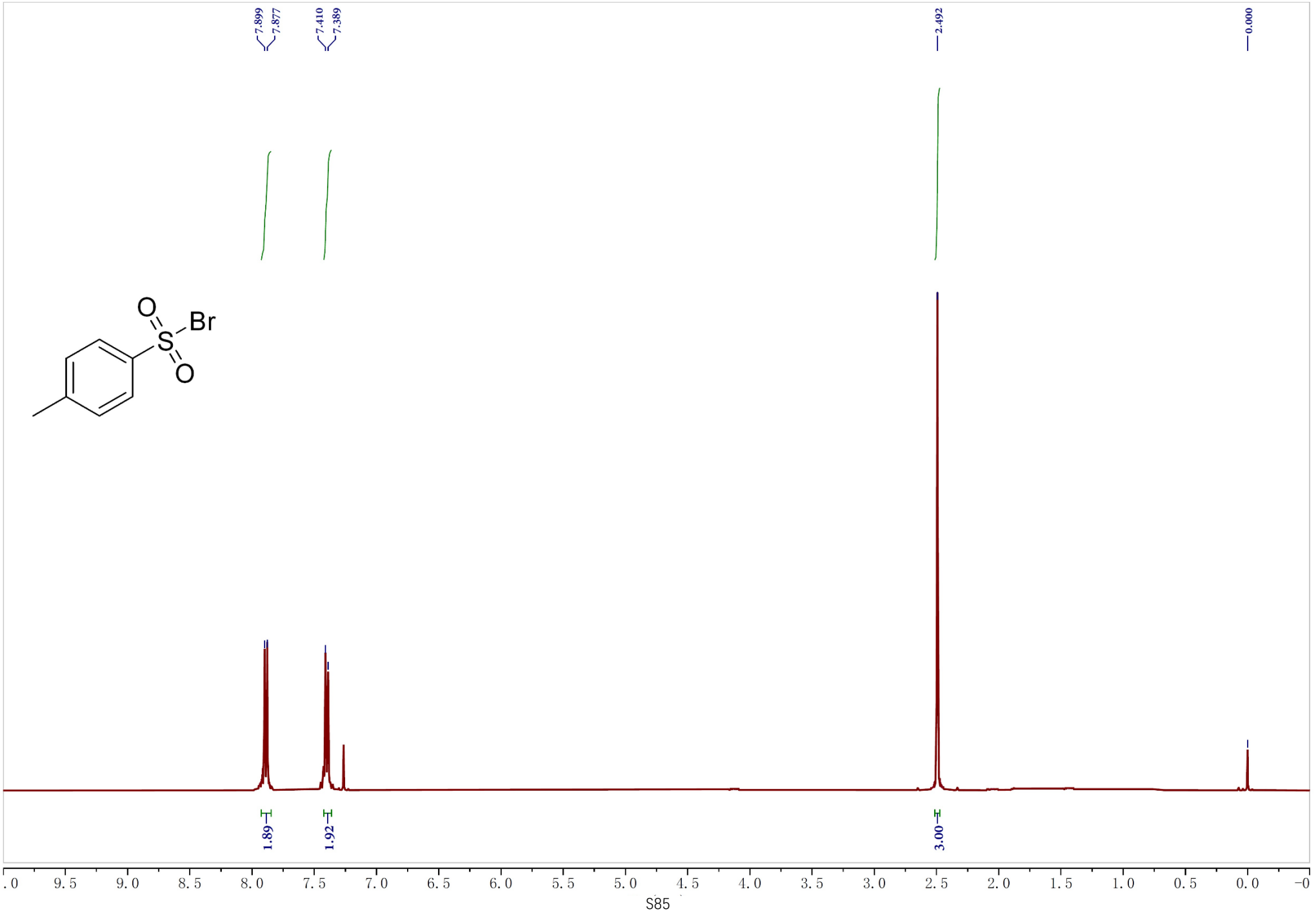
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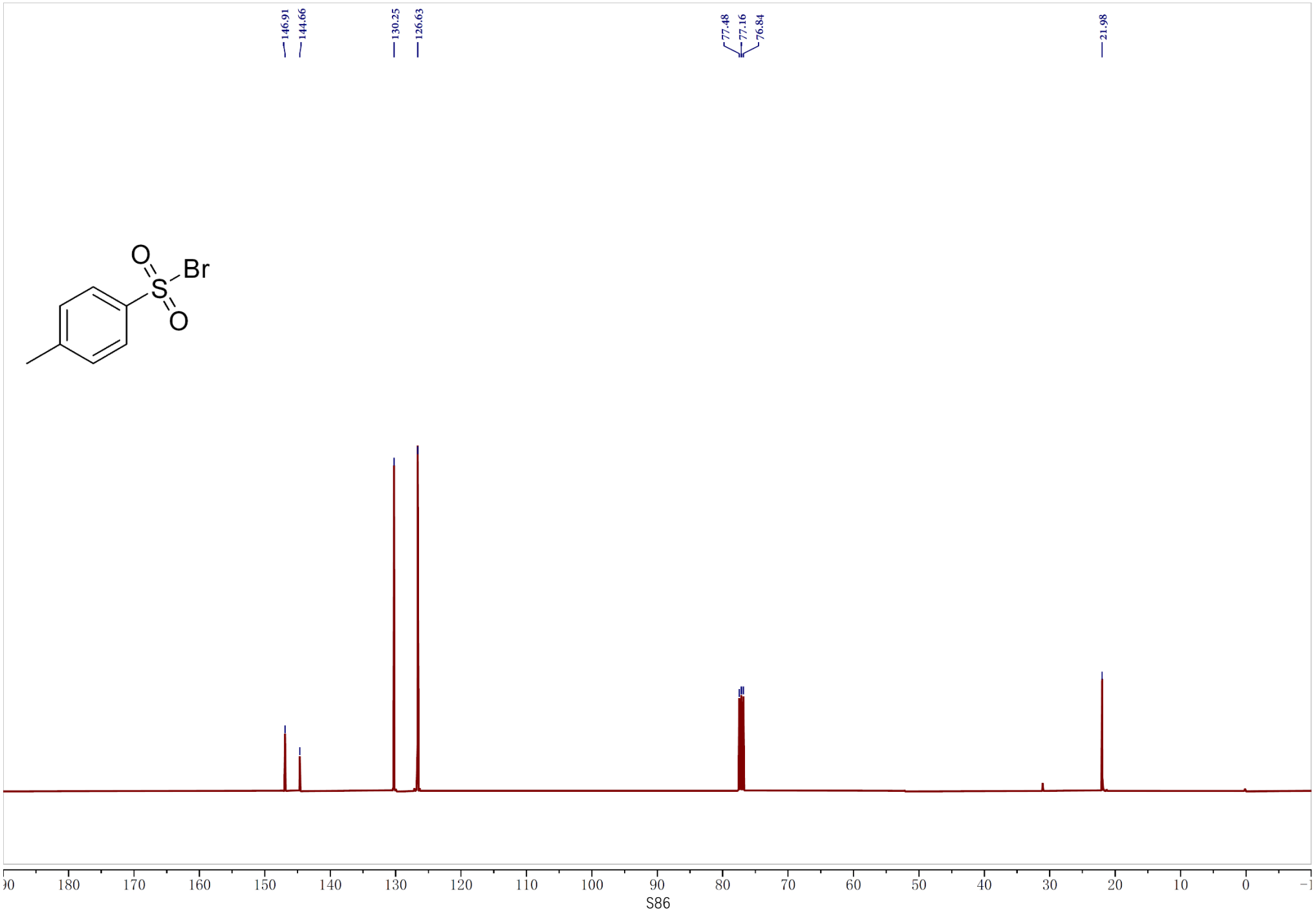
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