

Supplementary Material

Metal-free synthesis of 4-(methylthio)isoxazoles with acetylenic oximes and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSM)

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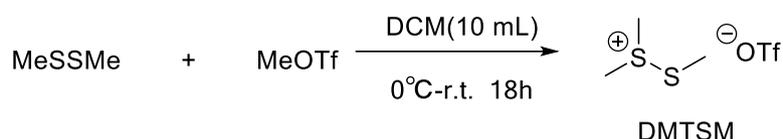
I. General Information

All reagents were purchased from Aladdin, Macklin, or Merck and directly used without further purification. Column chromatography separations were carried out on silica gel (200–300 mesh).

NMR spectra were performed on a Bruker 400MHz (^1H : 400 MHz; ^{13}C : 100 MHz ; ^{19}F : 376 MHz) spectrometer, using CDCl_3 as a solvent and TMS as the internal standard. Melting points are uncorrected. The NMR results were processed using MestReNova software. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF).

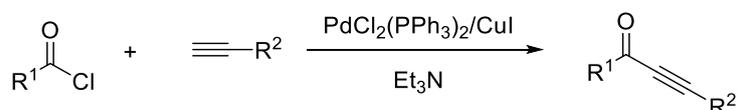
II. Experimental Procedures

General procedure for the synthesis of DMTSM¹:

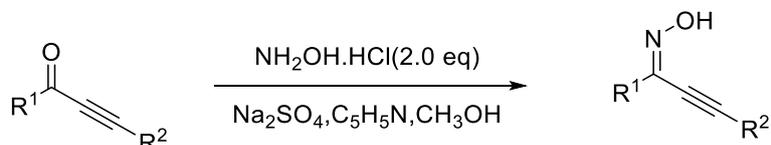


At 0 °C (ice bath), to a solution of methyl trifluoromethanesulfonate (12 mmol, 1.36 mL, 1.2 equiv) in CH_2Cl_2 (10 mL), Me_2S_2 (10 mmol, 0.89 mL, 1.0 equiv) was added dropwise in 30 min. The mixture was stirred for 1h at that temperature, following by 18 h at room temperature. Upon completion, the result white solid was collected by filtration and washed with fresh distilled Et_2O under nitrogen atmosphere, affording dimethyl(methylthio)sulfonium trifluoromethanesulfonate (2.27 g, 88% yield) as a white solid.

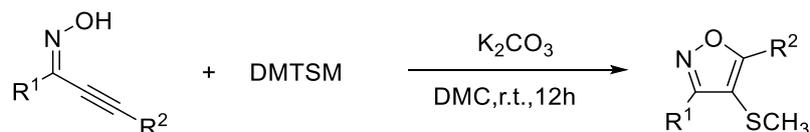
General procedure for the synthesis of alkynones²:



To a flask were added CuI (0.05 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.01 mmol) and triethylamine (5 mL). The flask was flushed with argon and the terminal acetylene (2.5 mmol) was added to the stirred suspension, followed by immediate dropwise addition of benzoyl chloride (3.25 mmol, 1.3 equiv). The resulting mixture was allowed to stir at room temperature overnight, water (5 mL) was added, and the aqueous layer was extracted with hexanes. The organic layers were combined, dried and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel to afford the desired alkynone.

General procedure for the synthesis of acetylenic oximes^{2,3}

The alkyne(7.0 mmol), hydroxylamine hydrochloride (14.0 mmol, 0.97 g), Na₂SO₄ (14.0 mmol, 1.99 g) and pyridine (2 mL) in methanol (20 mL) were stirred at room temperature. Benzene was added as a co-solvent in cases where the alkyne showed poor solubility in methanol. In some cases, the reaction required refluxing conditions to reach completion. The reaction was monitored by TLC until the reaction was complete. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine, dried and evaporated. The residue was then purified by column chromatography on silica gel to afford the desired acetylenic oximes.

General procedure for the synthesis of 4-(methylthio)isoxazole:

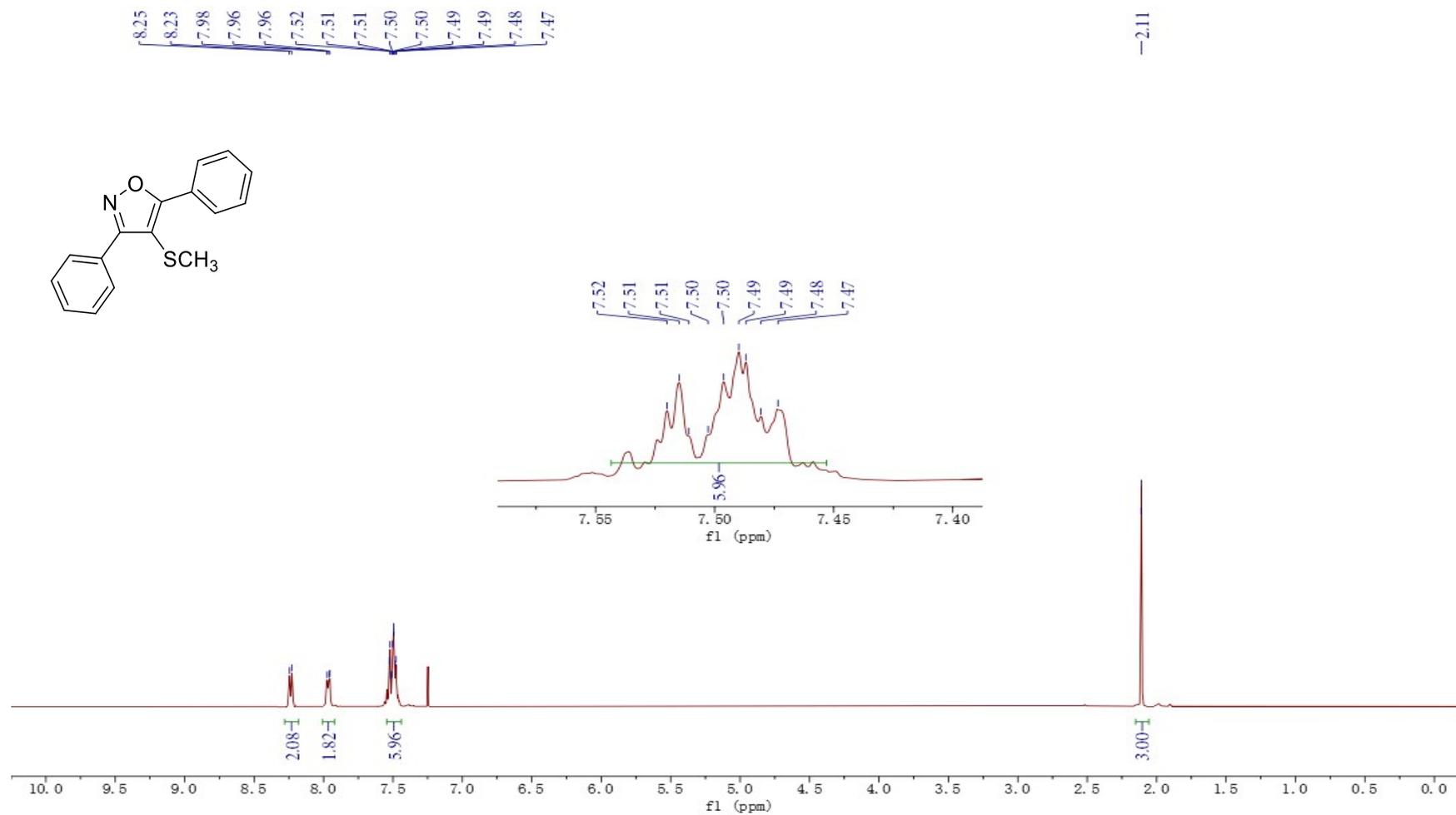
At room temperature, to a solution of alkyne oxime (0.5mmol, 1 equiv) in CH₂Cl₂ (2 mL), DMTSM (0.6mmol, 1.2 equiv) and K₂CO₃ (0.75mmol, 1.5 equiv) were added into the solvent. The mixture was stirred for 12h (TLC monitored). The reaction mixture was extracted with CH₂Cl₂ after adding the saturated brine. Then the organic phase was combined and dried with anhydrous Na₂SO₄. The solvent was evaporated in vacuo, the crude product was purified by column chromatography, eluting with petroleum ether/ethyl acetate to afford the desired products.

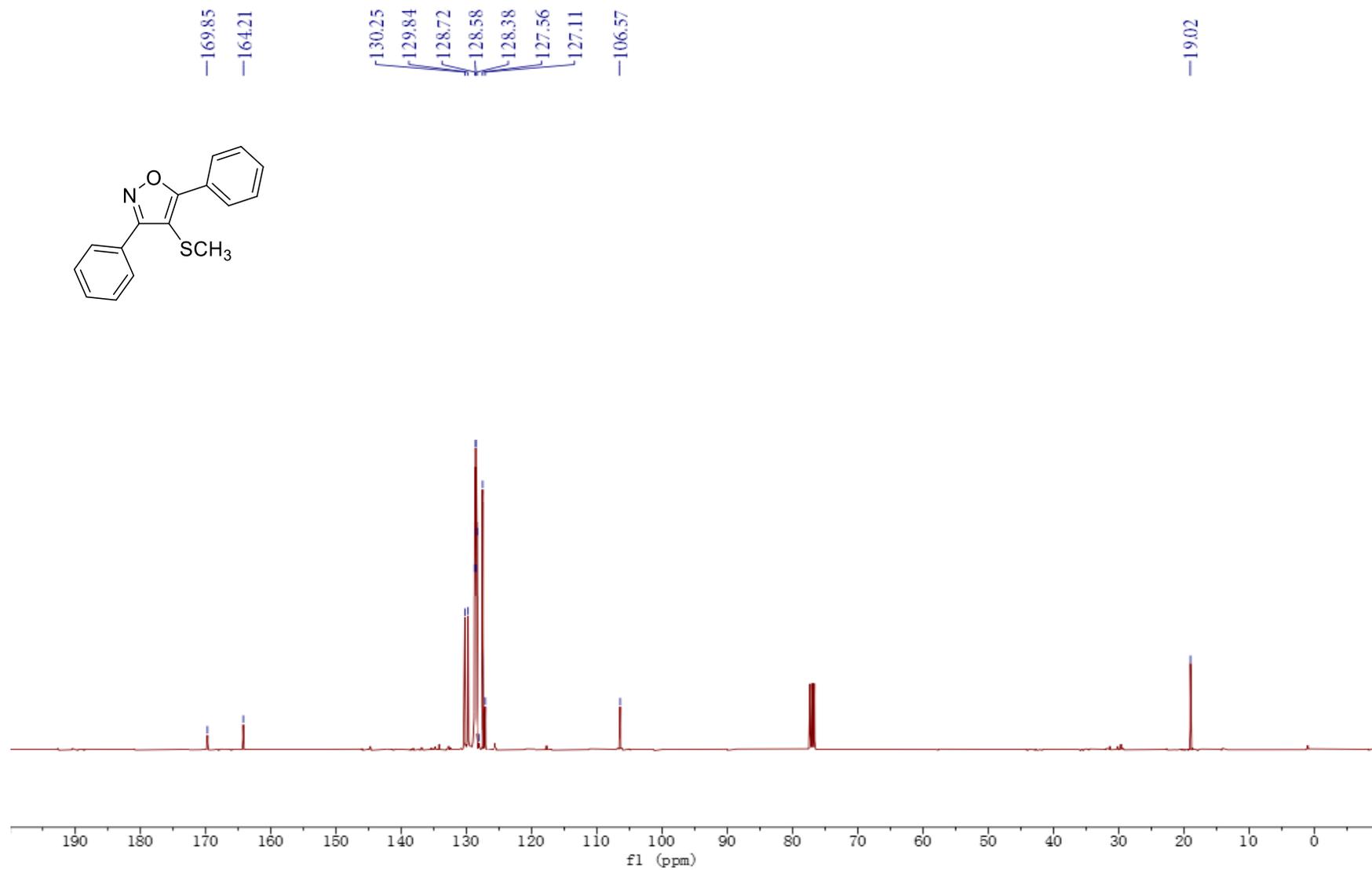
III. Reference

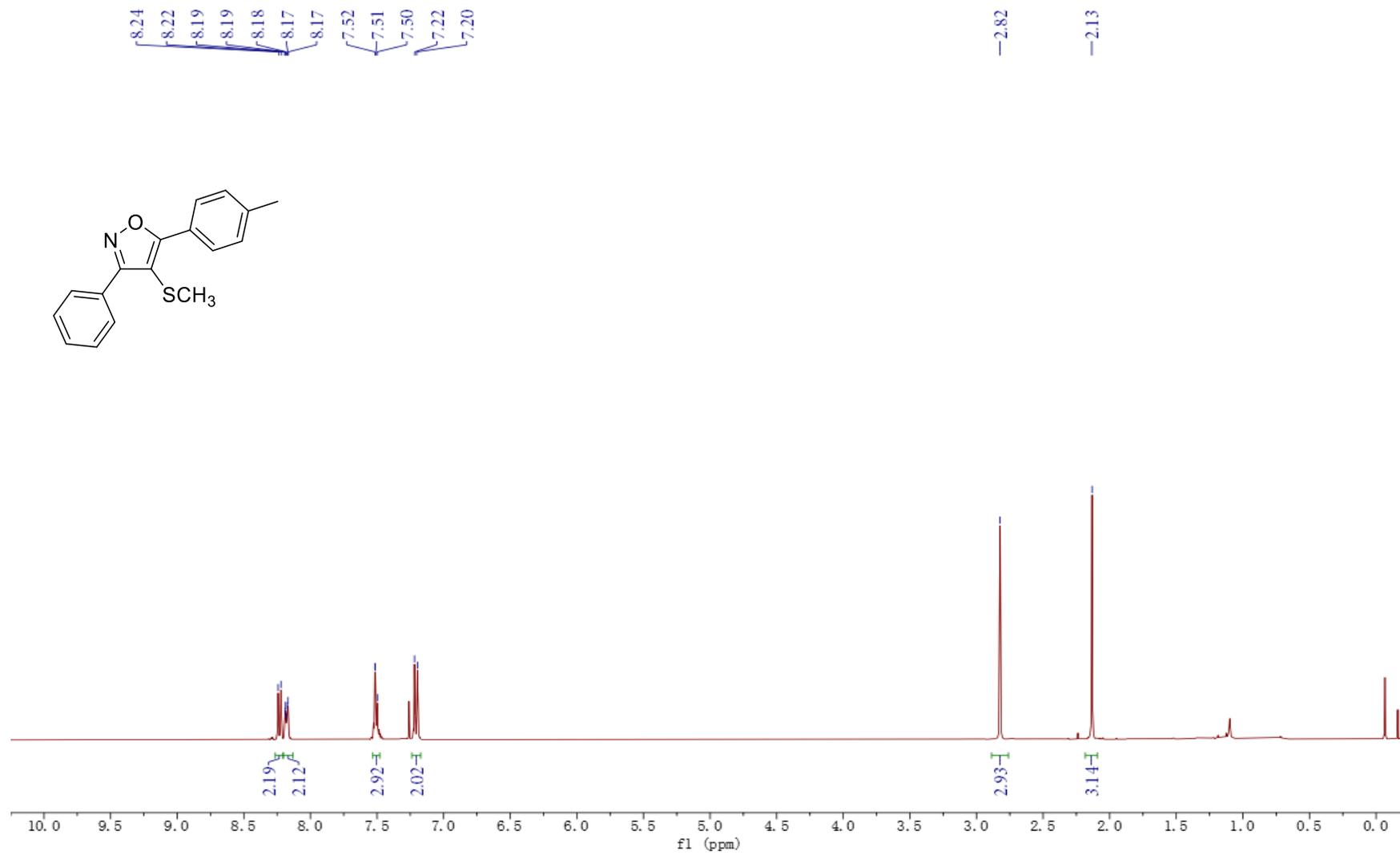
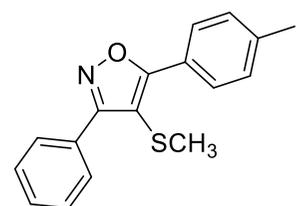
1. Tang, M.; Wei, Y.; Huang, S.; Xie, L.-G. *Org. Lett.* **2022**, *24*, 7026.
2. Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203.
3. Jeyaveeran, J. C.; Praveen, C.; Arun, Y.; M Prince, A. A.; Perumal, P. T *J. Chem. Sci.* **2016**, *128*, 73.

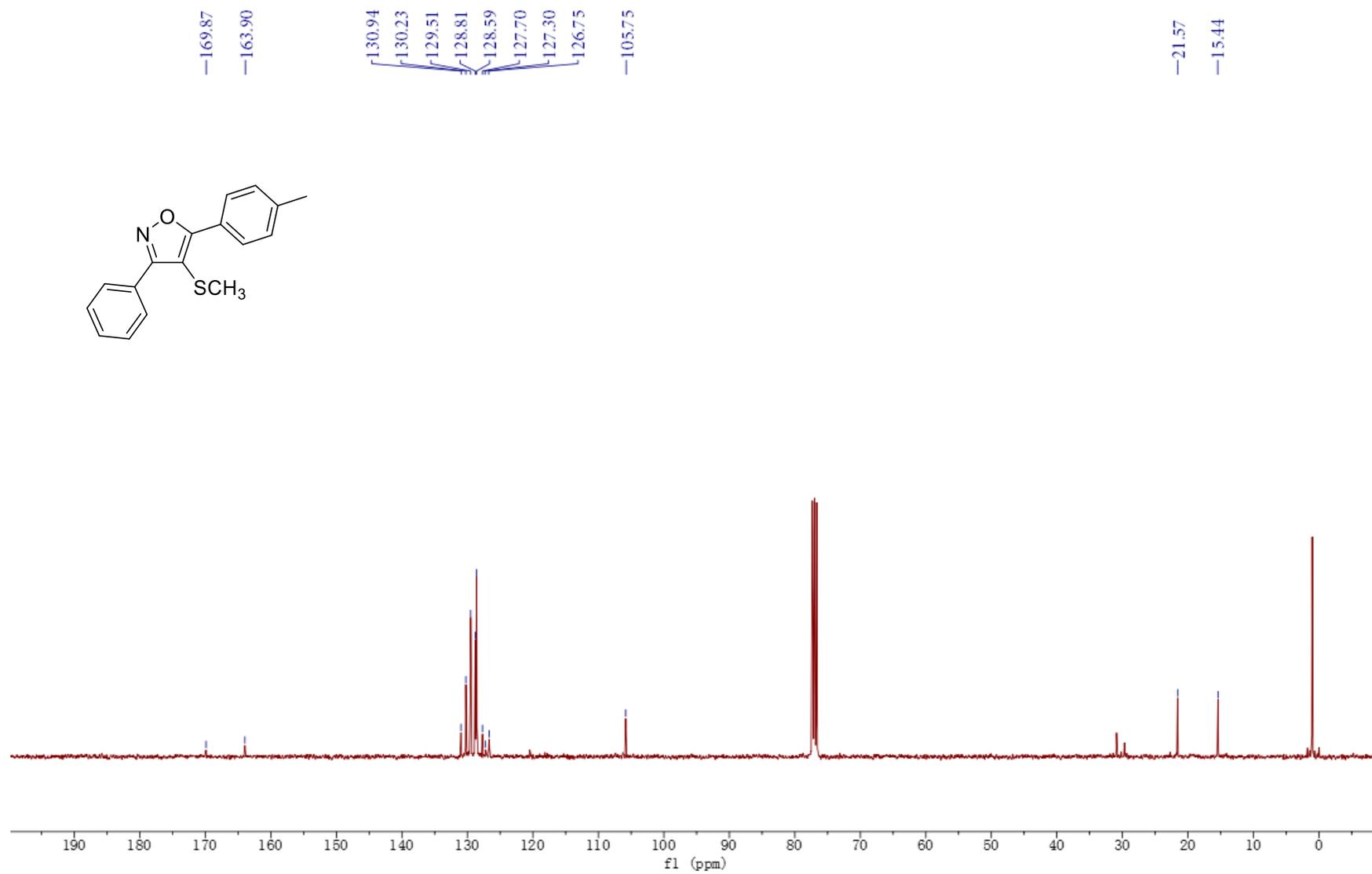
IV. NMR spectra

(1). 4-(methylthio)-3,5-diphenylisoxazole

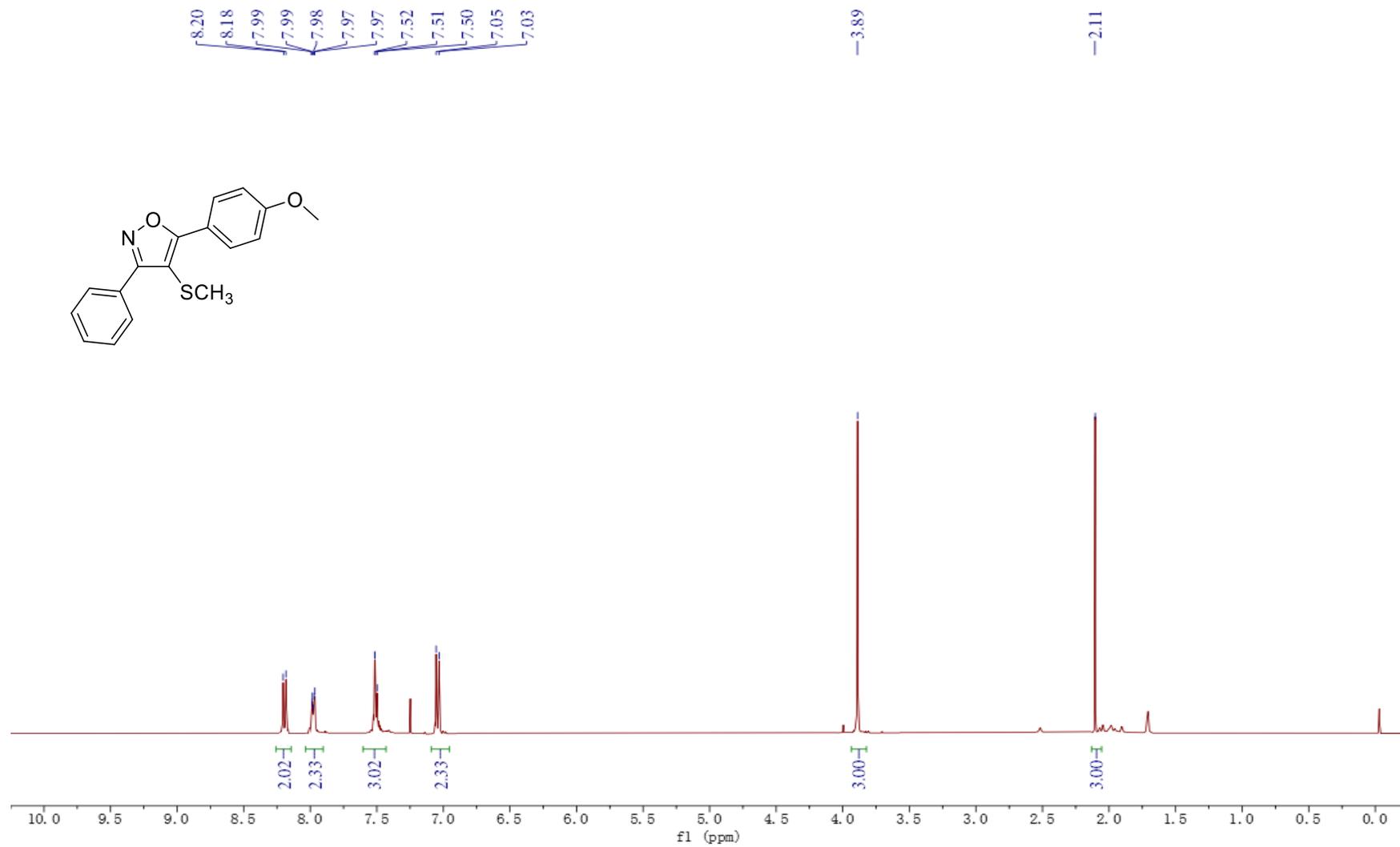


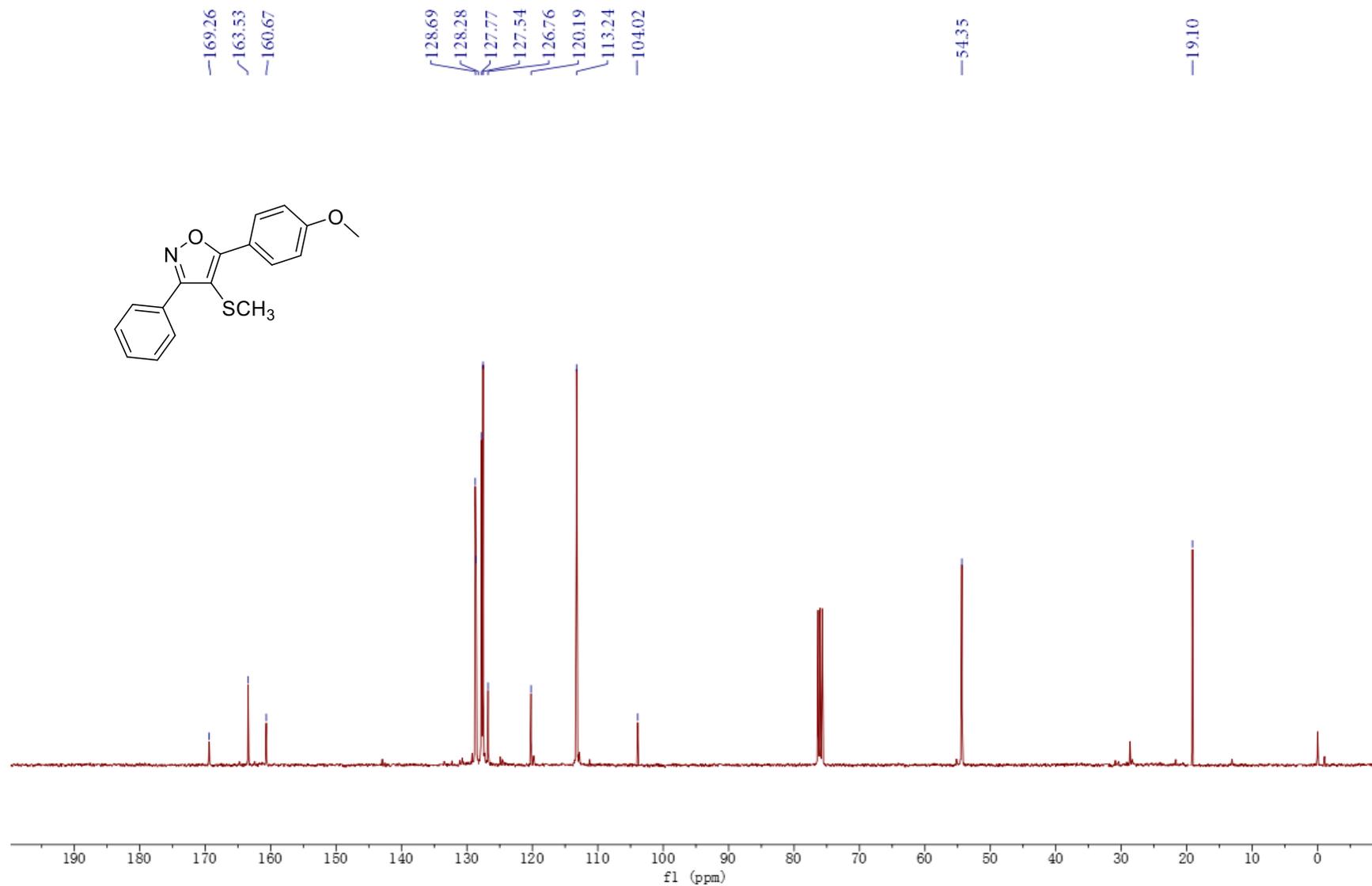


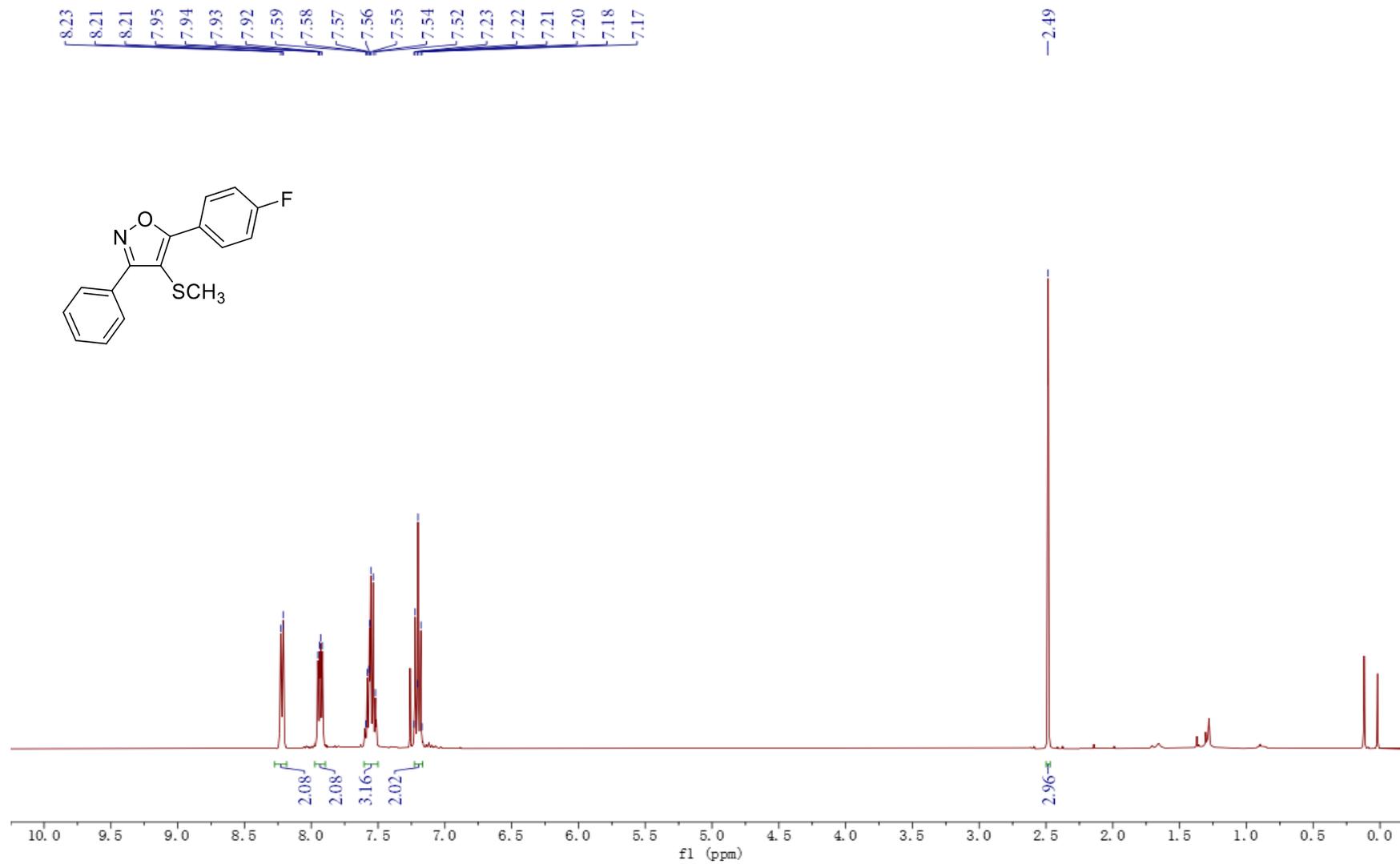
(2). 4-(methylthio)-3-phenyl-5-(p-tolyl)isoxazole

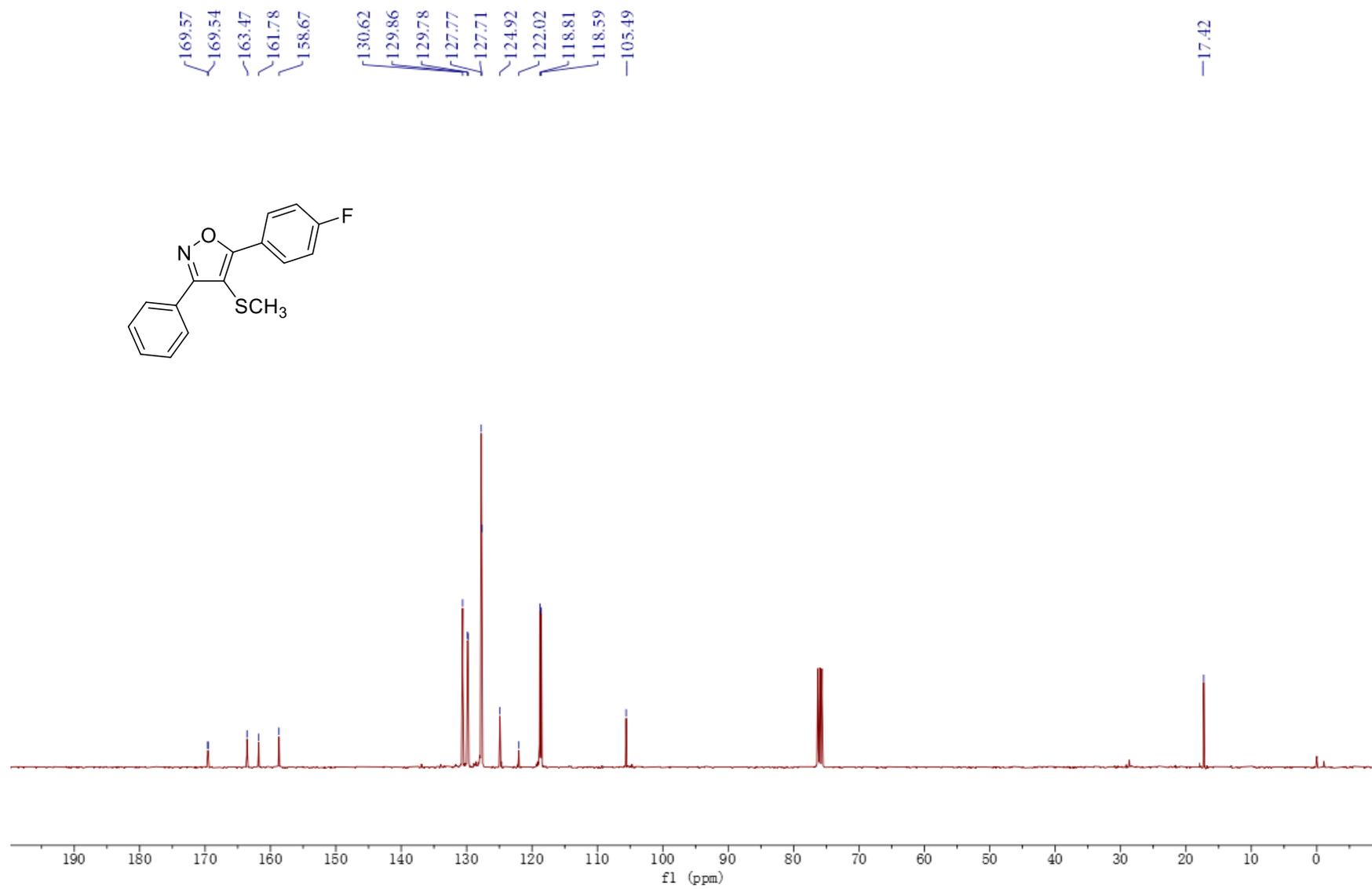


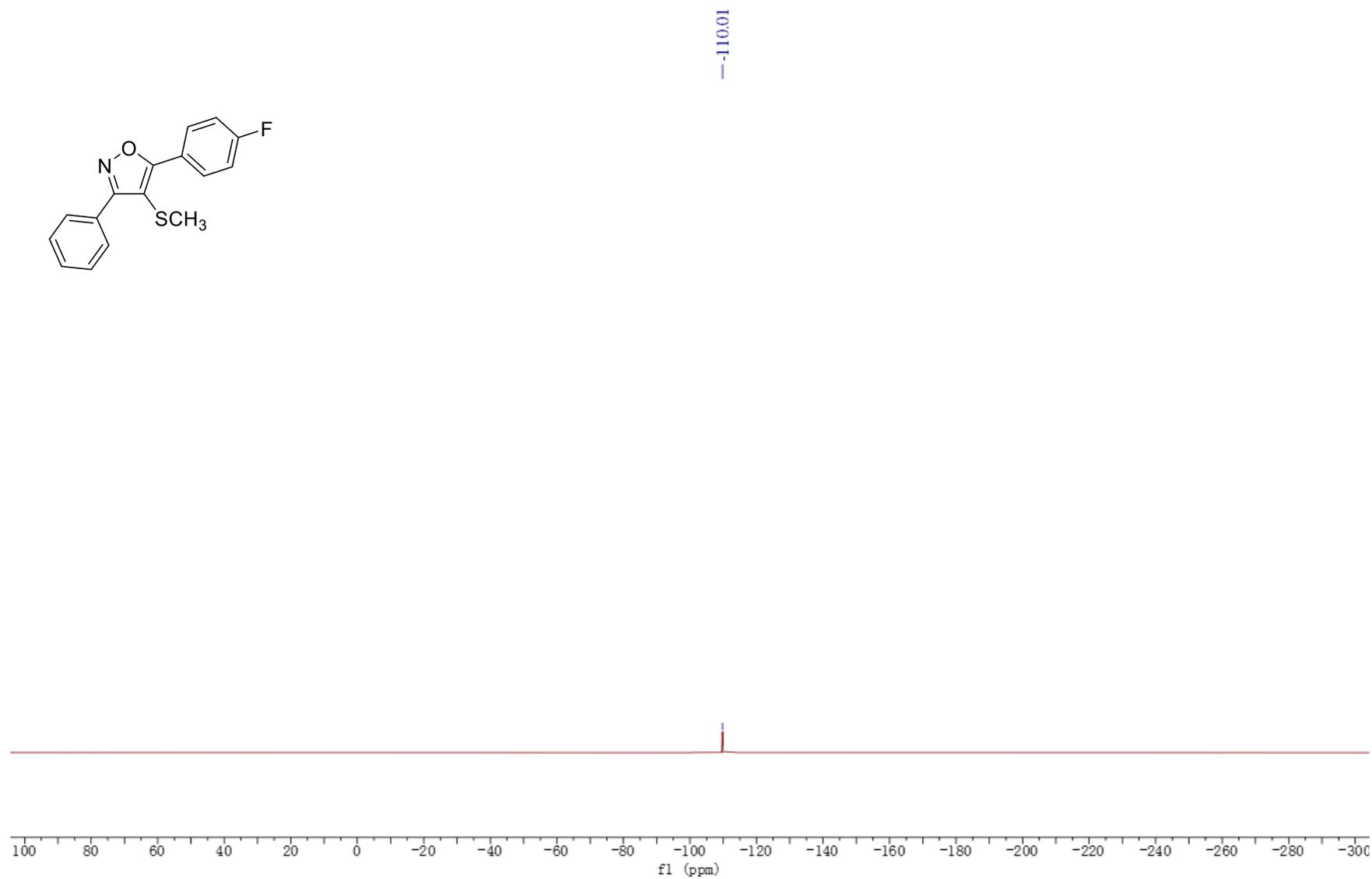
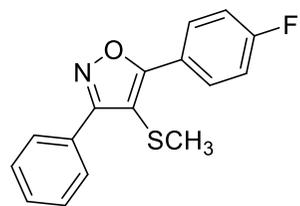
(3). 5-(4-methoxyphenyl)-4-(methylthio)-3-phenylisoxazole



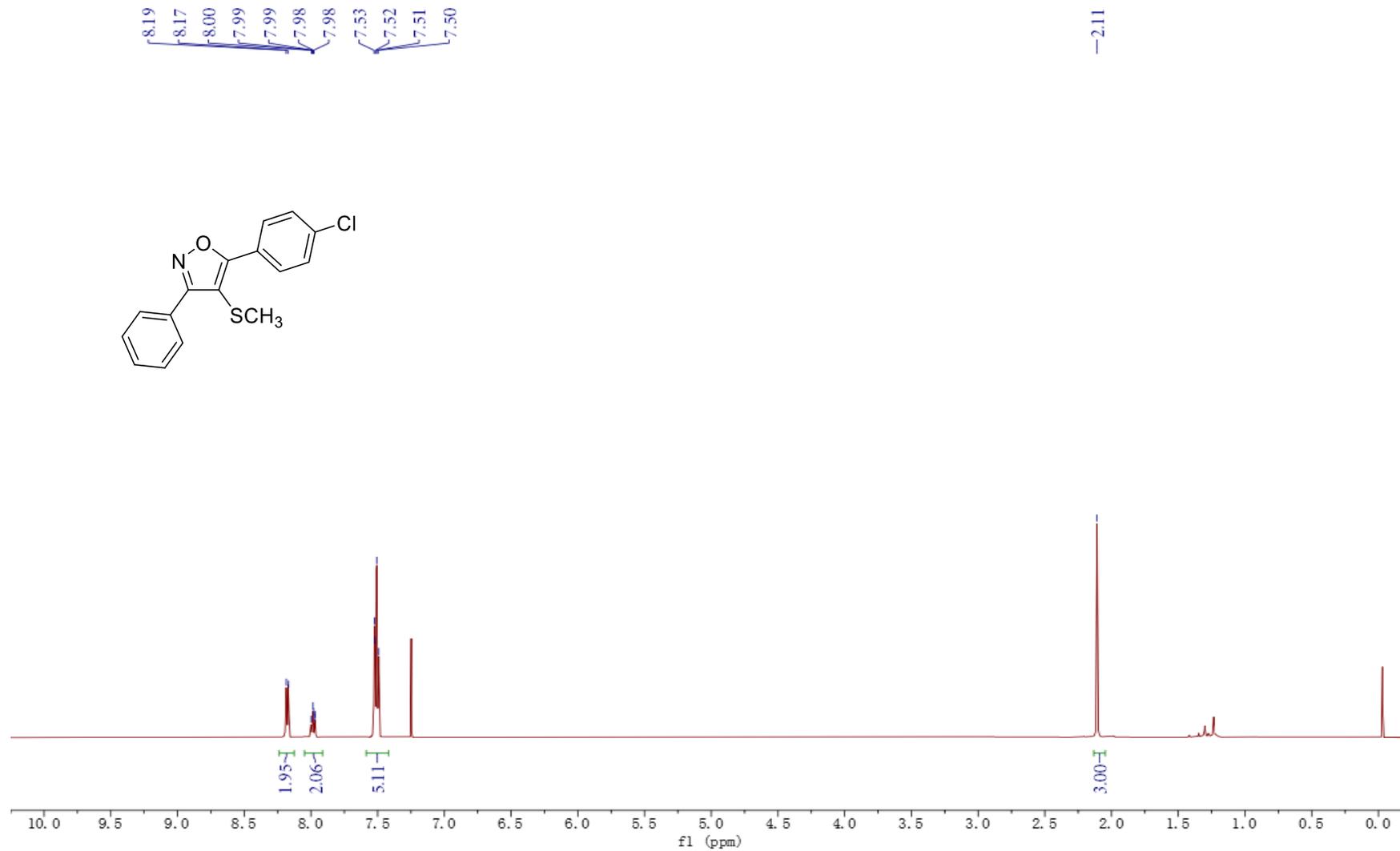
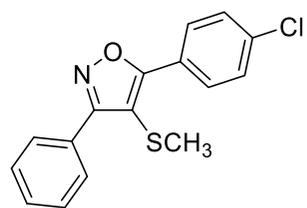


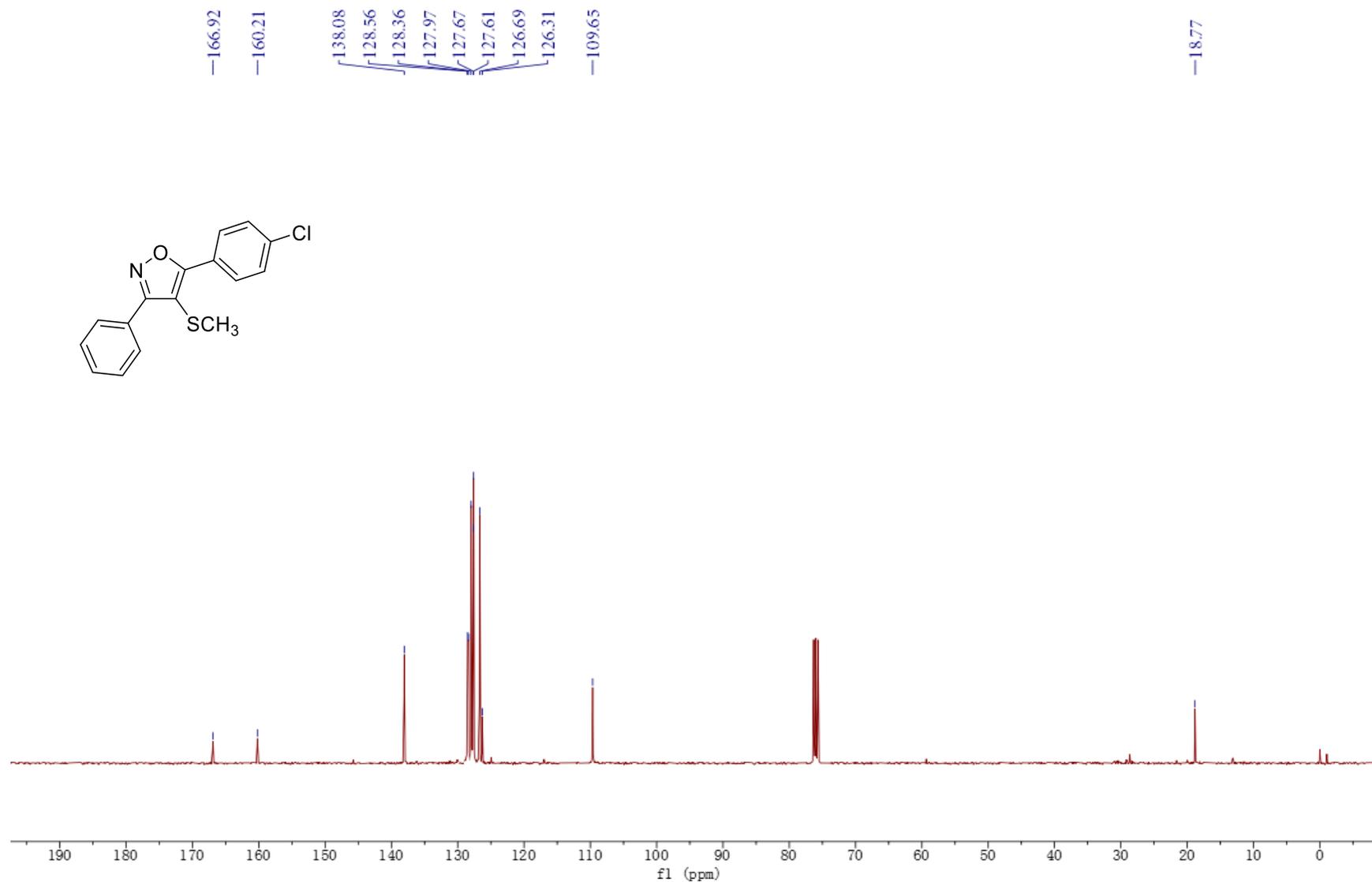
(4). 5-(4-fluorophenyl)-4-(methylthio)-3-phenylisoxazole



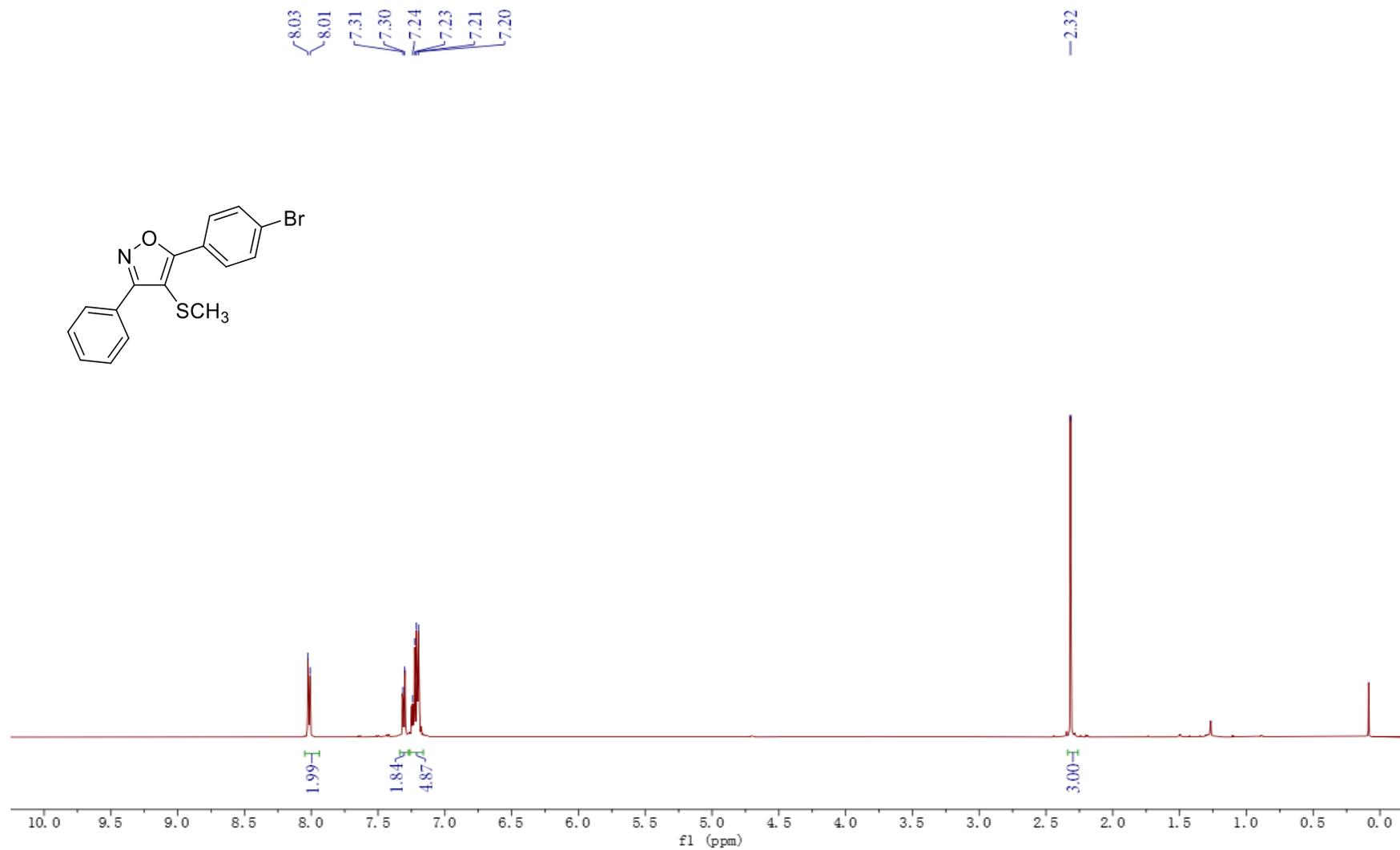


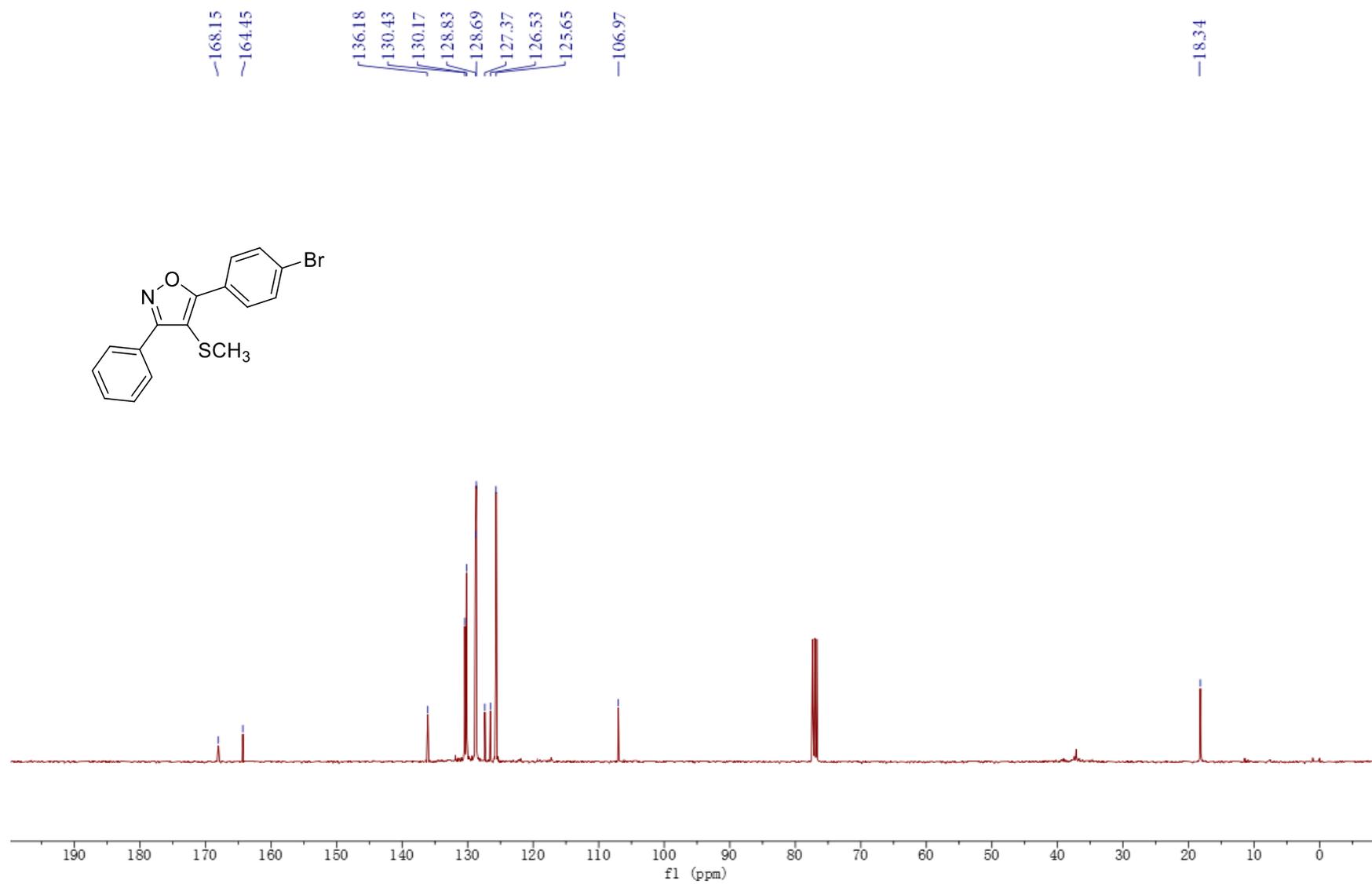
(5). 5-(4-chlorophenyl)-4-(methylthio)-3-phenylisoxazole



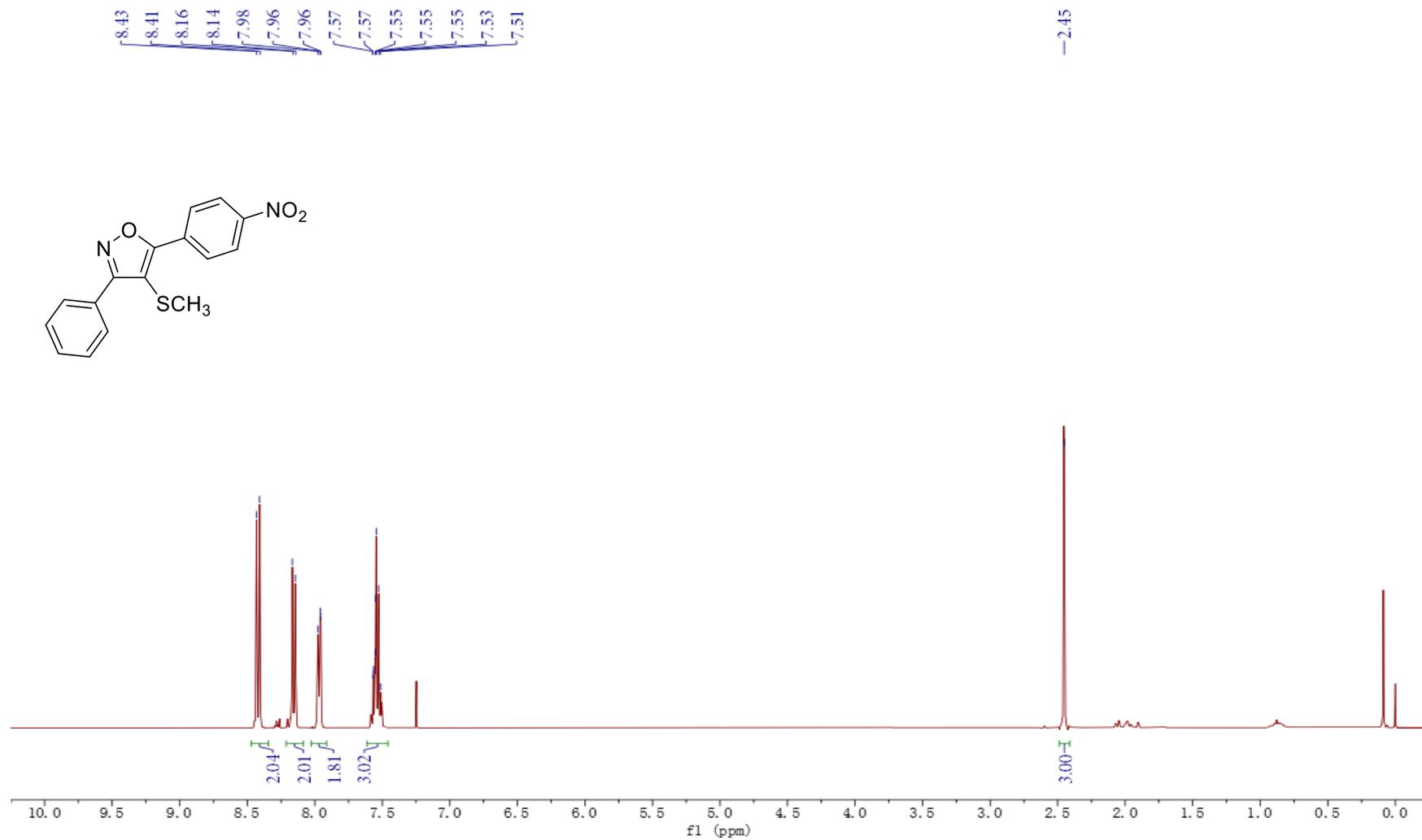


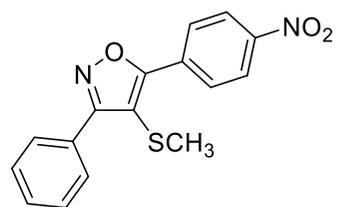
(6). 5-(4-bromophenyl)-4-(methylthio)-3-phenylisoxazole





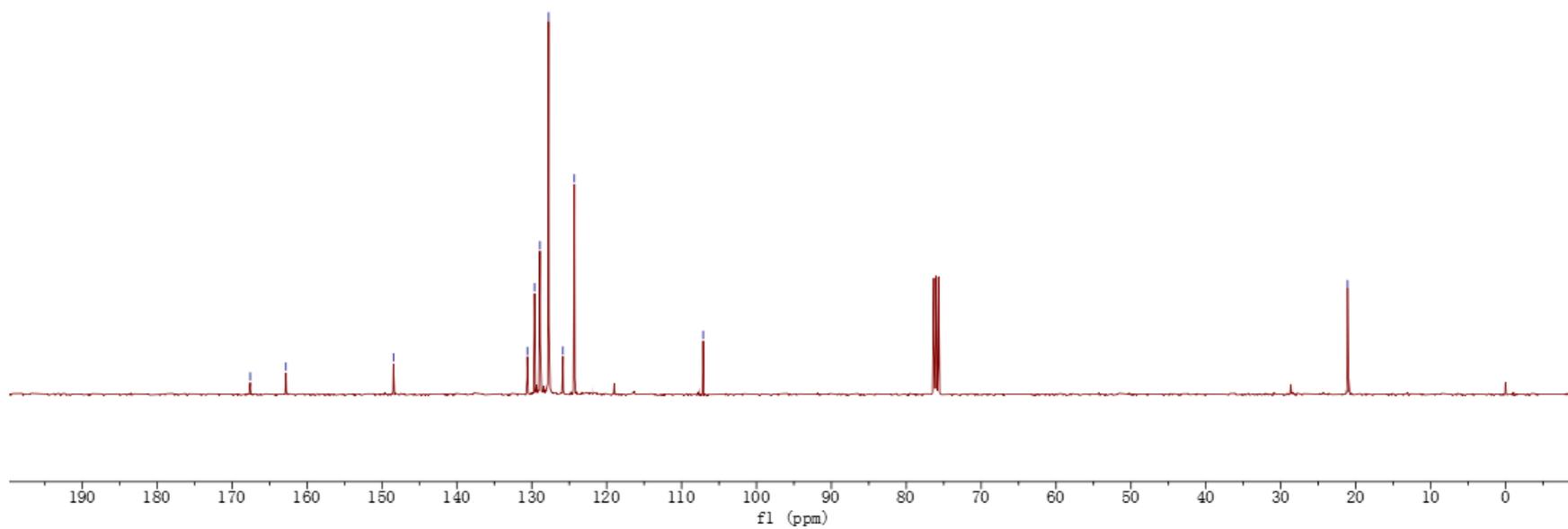
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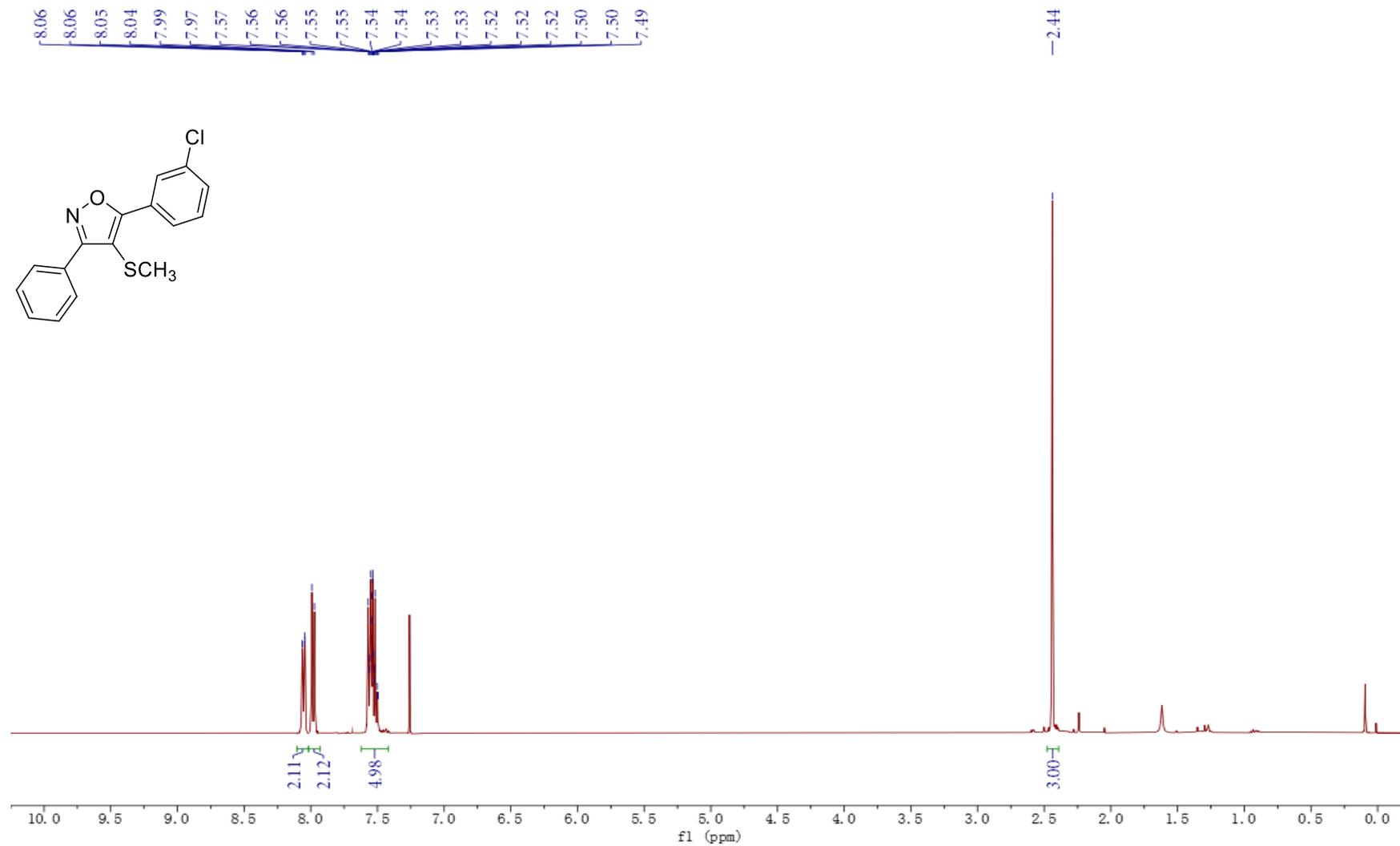


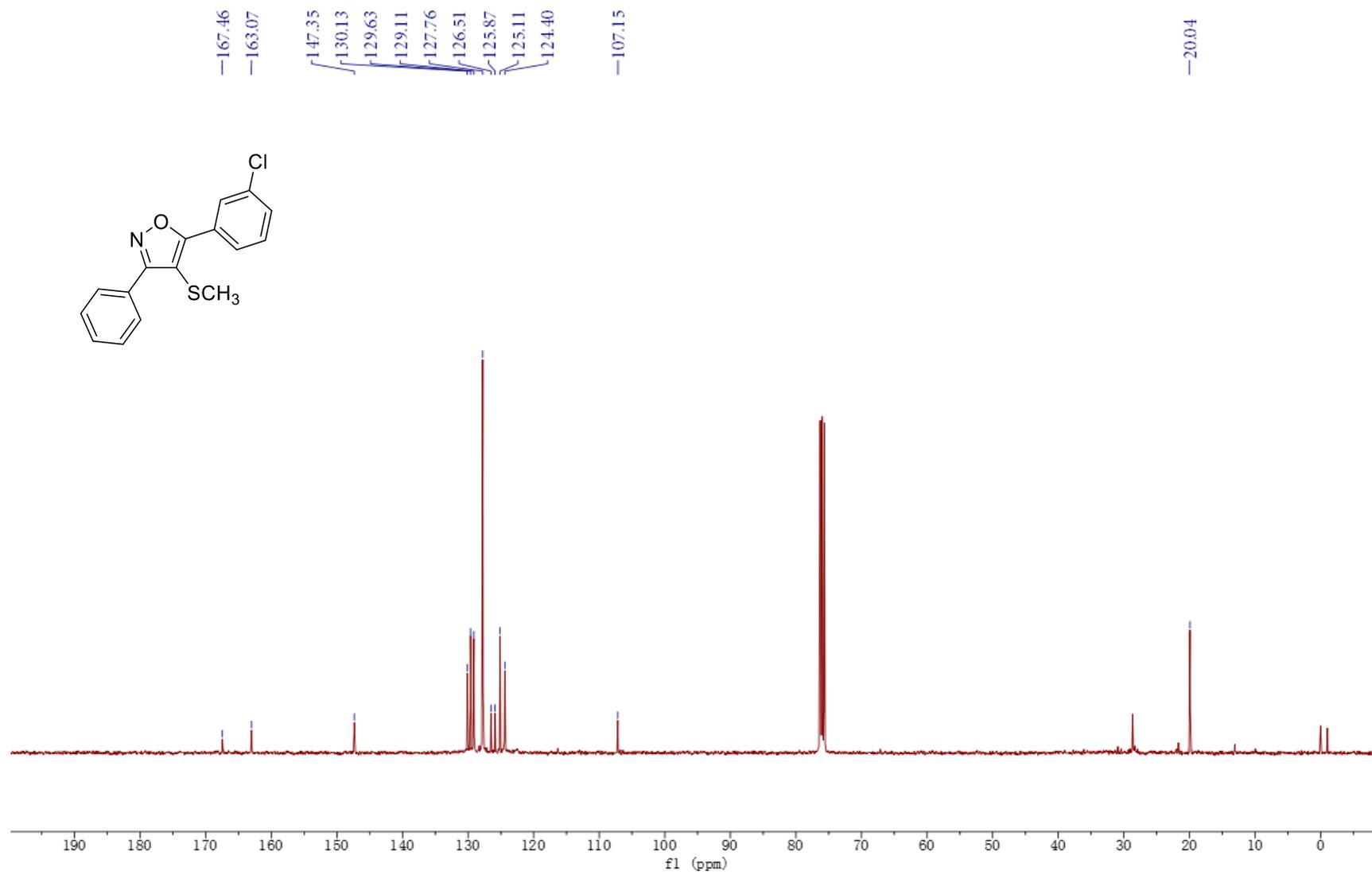


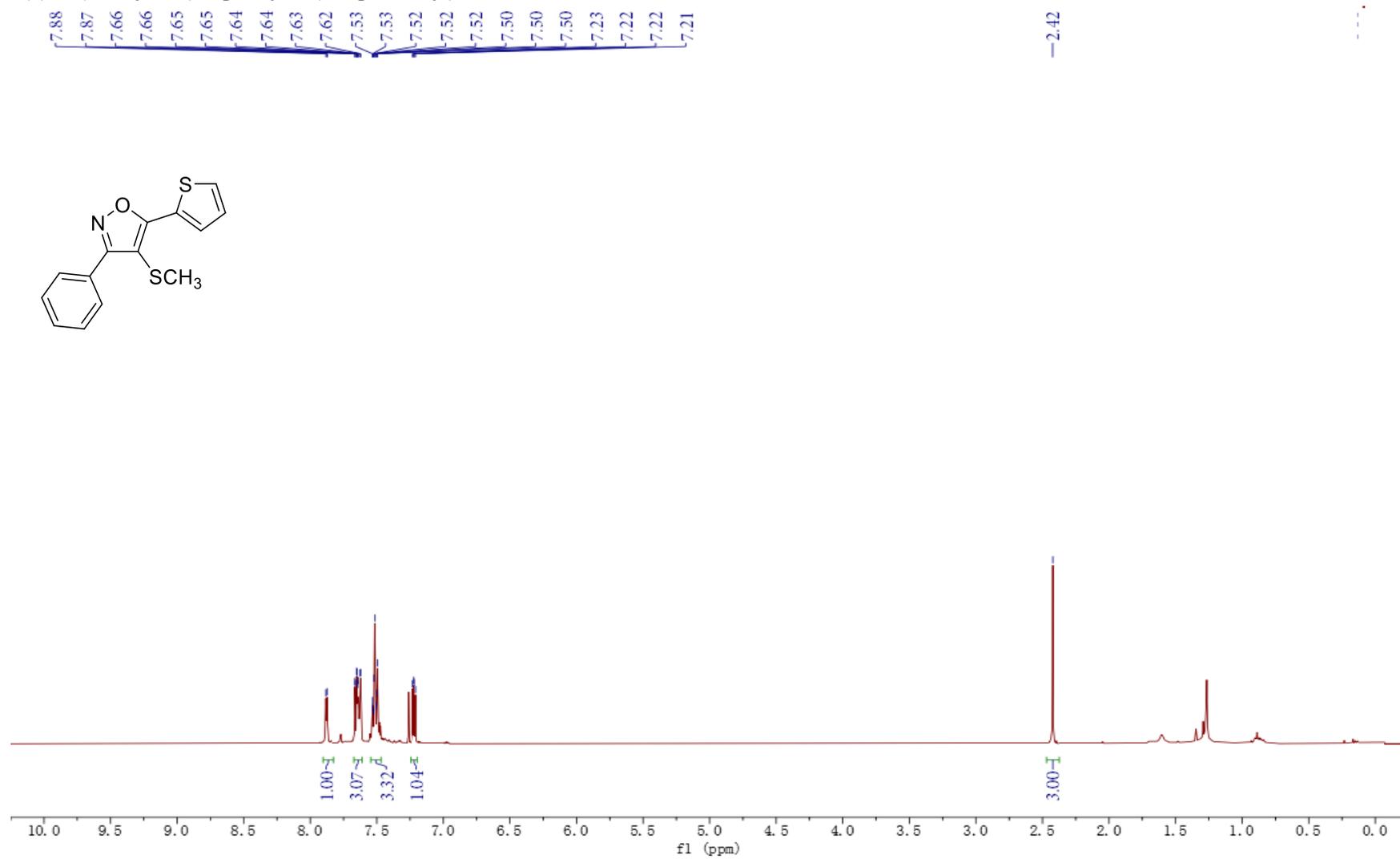
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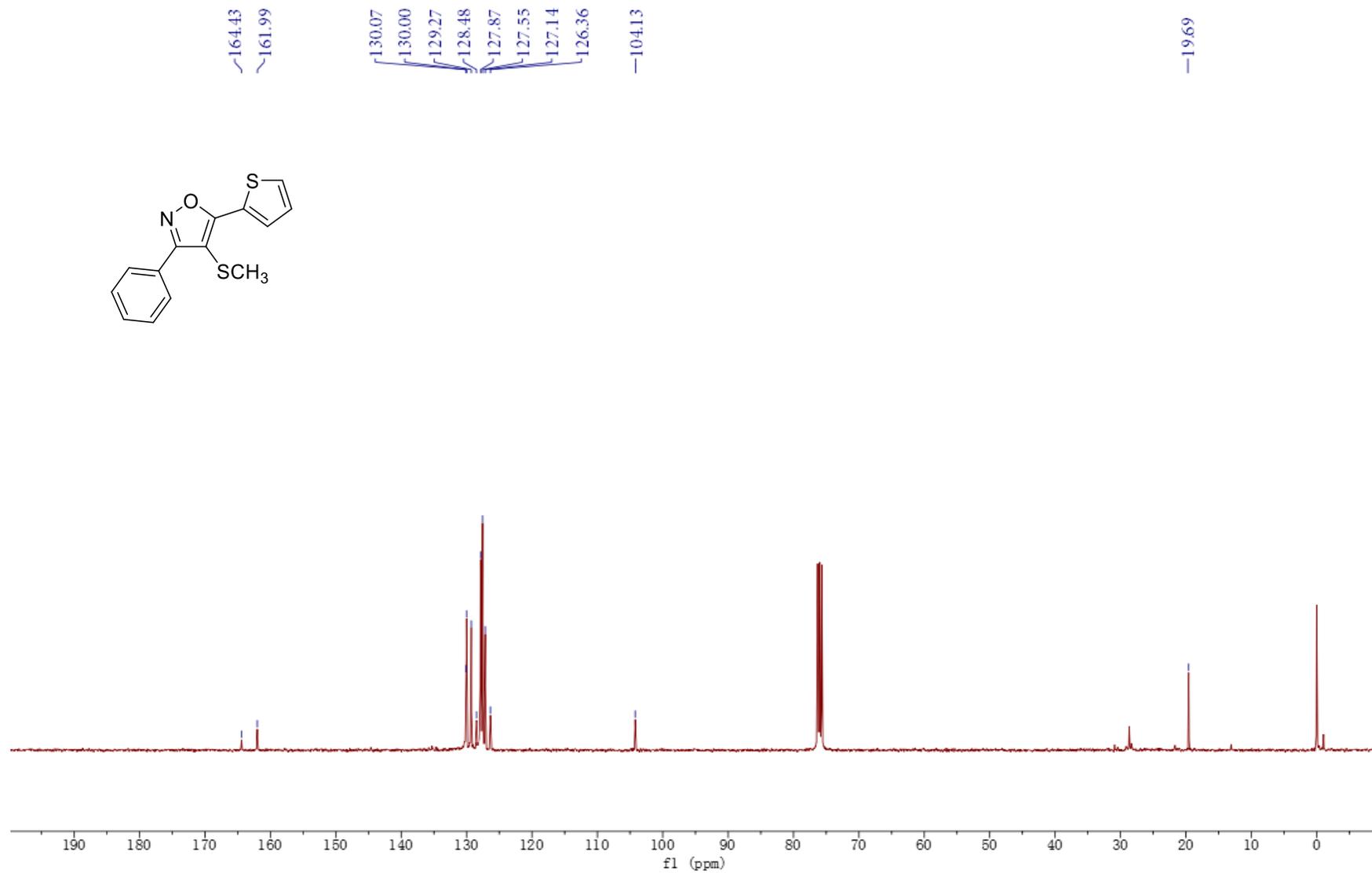
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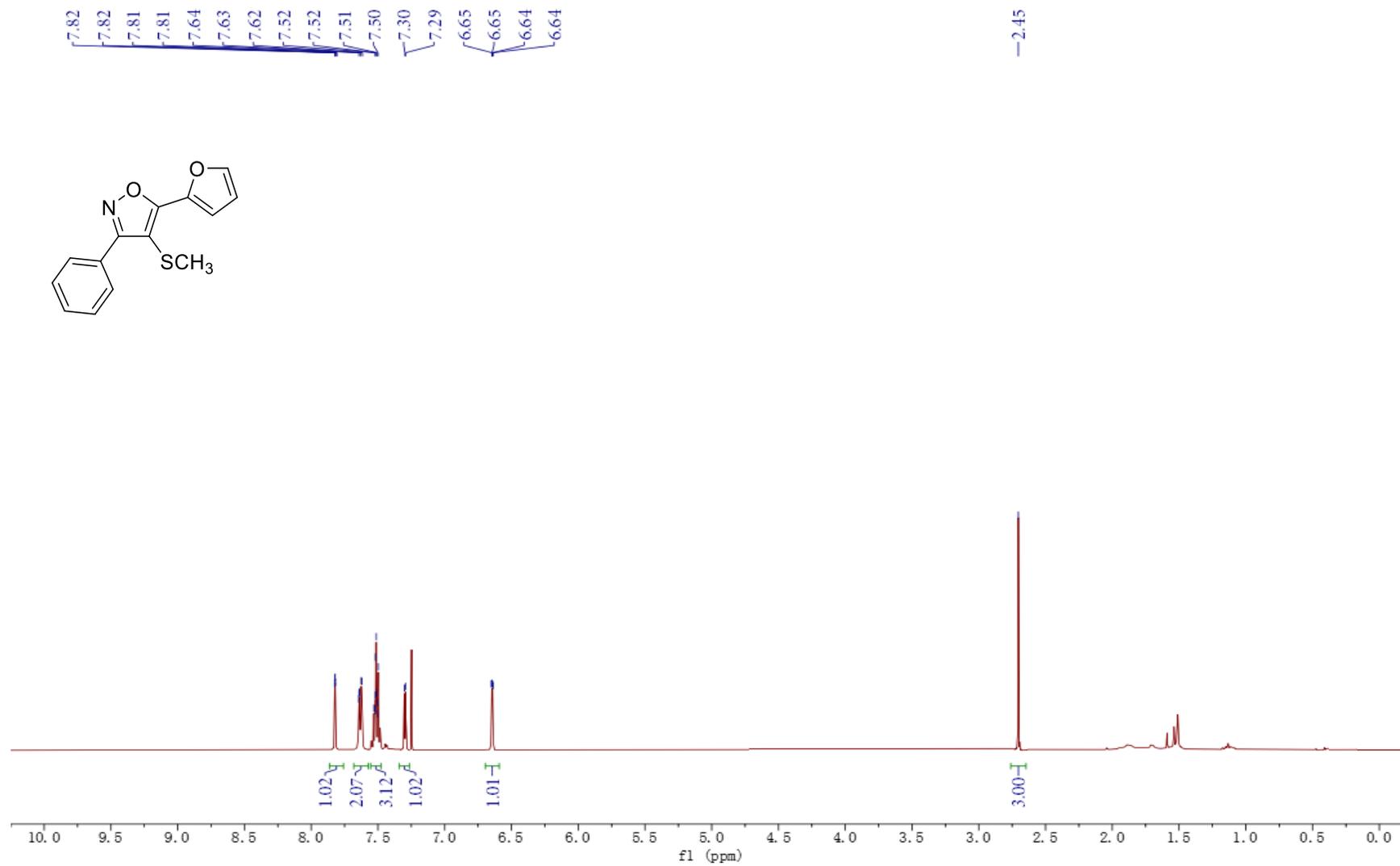


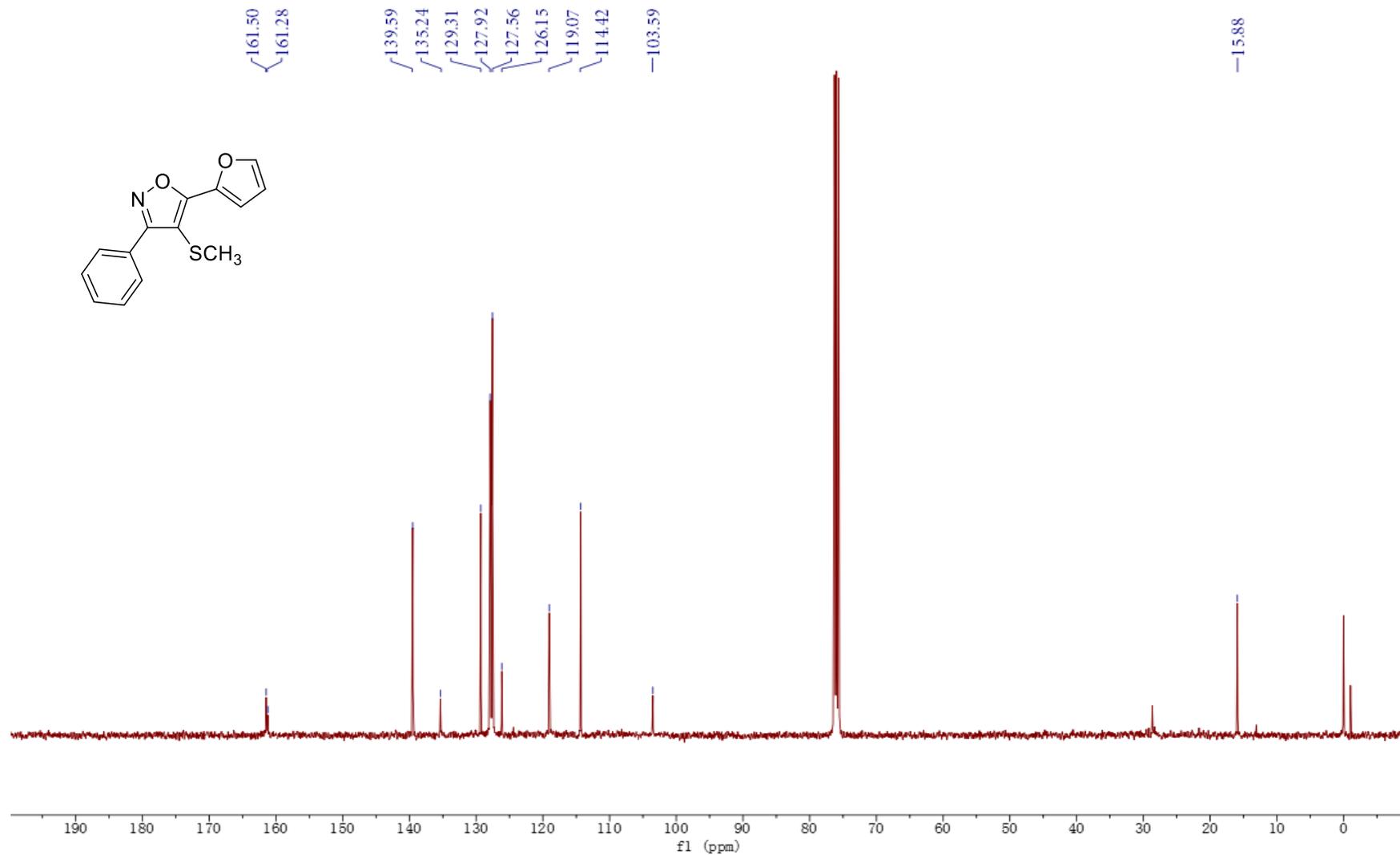
(8). 5-(3-chlorophenyl)-4-(methylthio)-3-phenylisoxazole



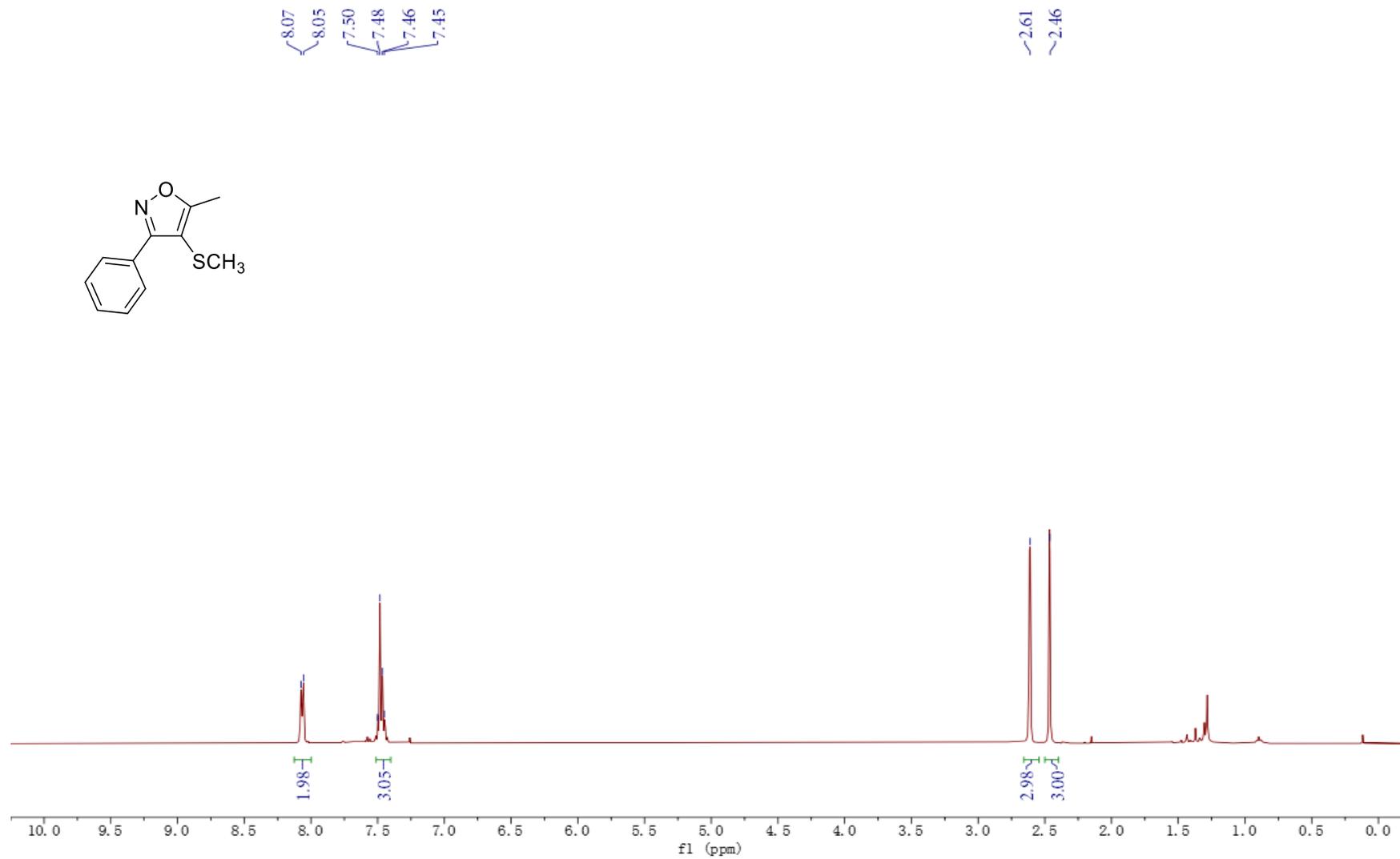
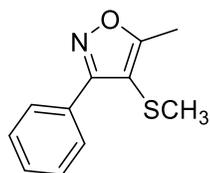
(9). 4-(methylthio)-3-phenyl-5-(thiophen-2-yl)isoxazole

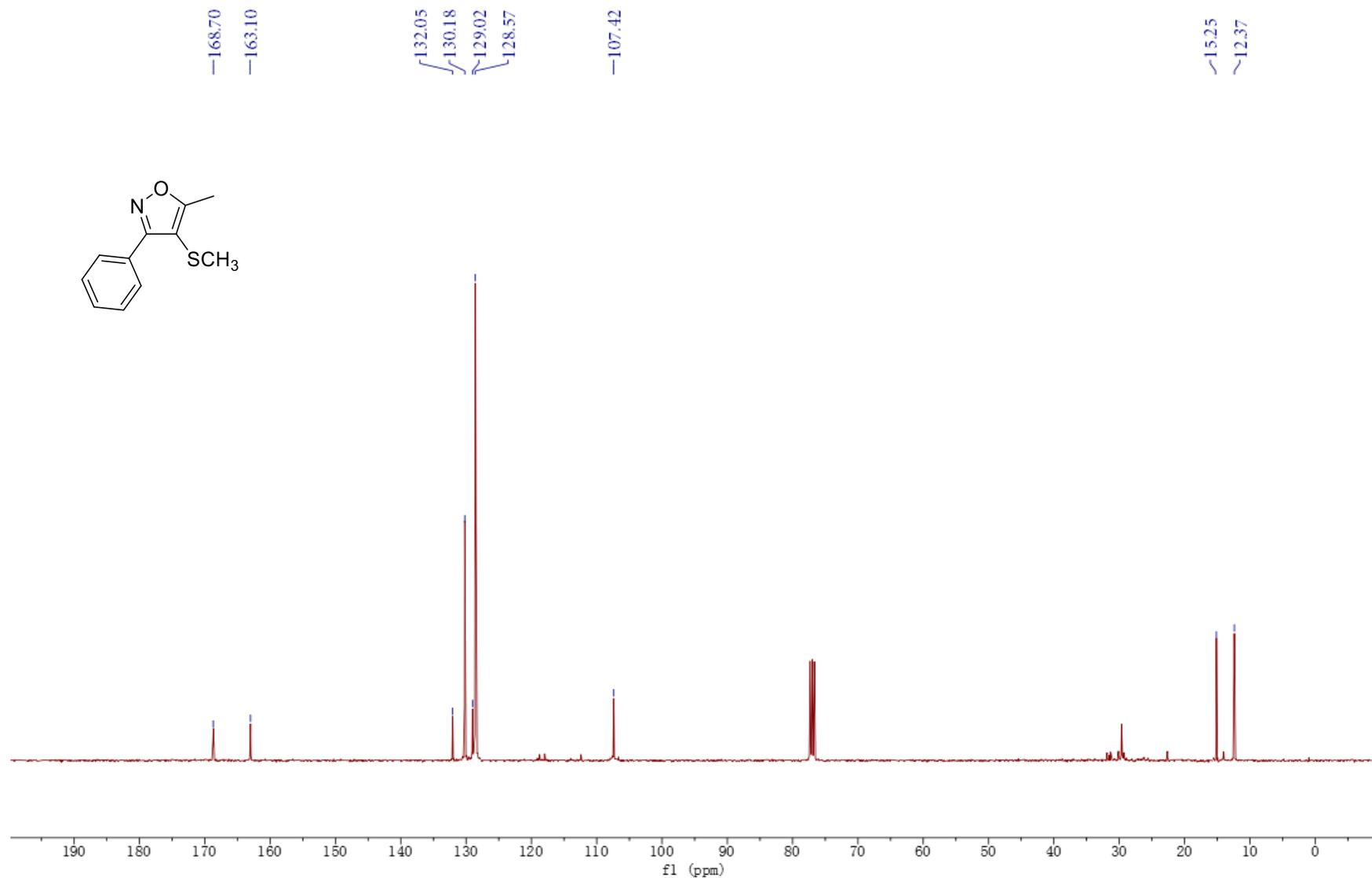


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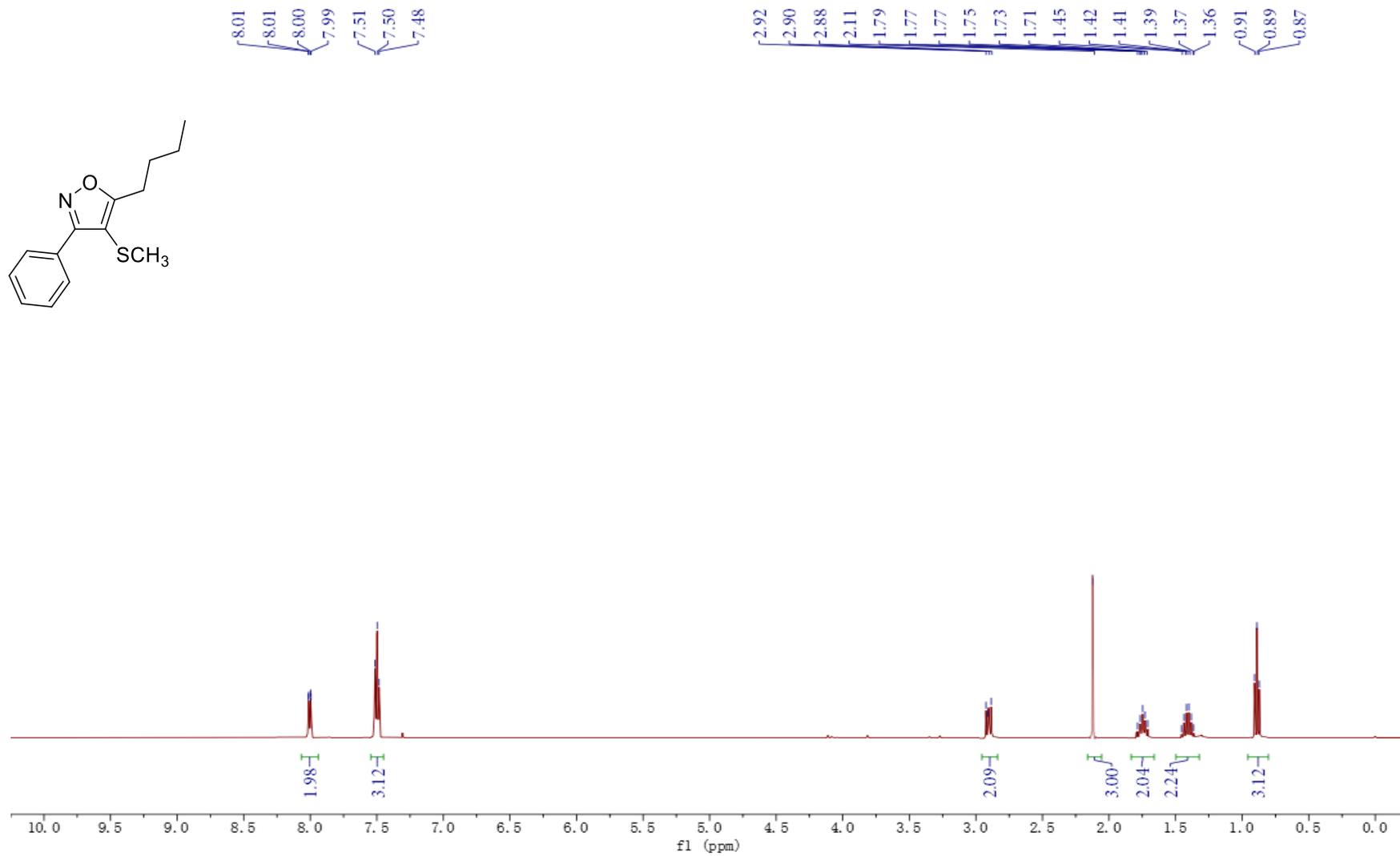
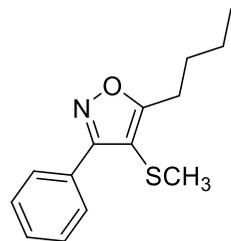


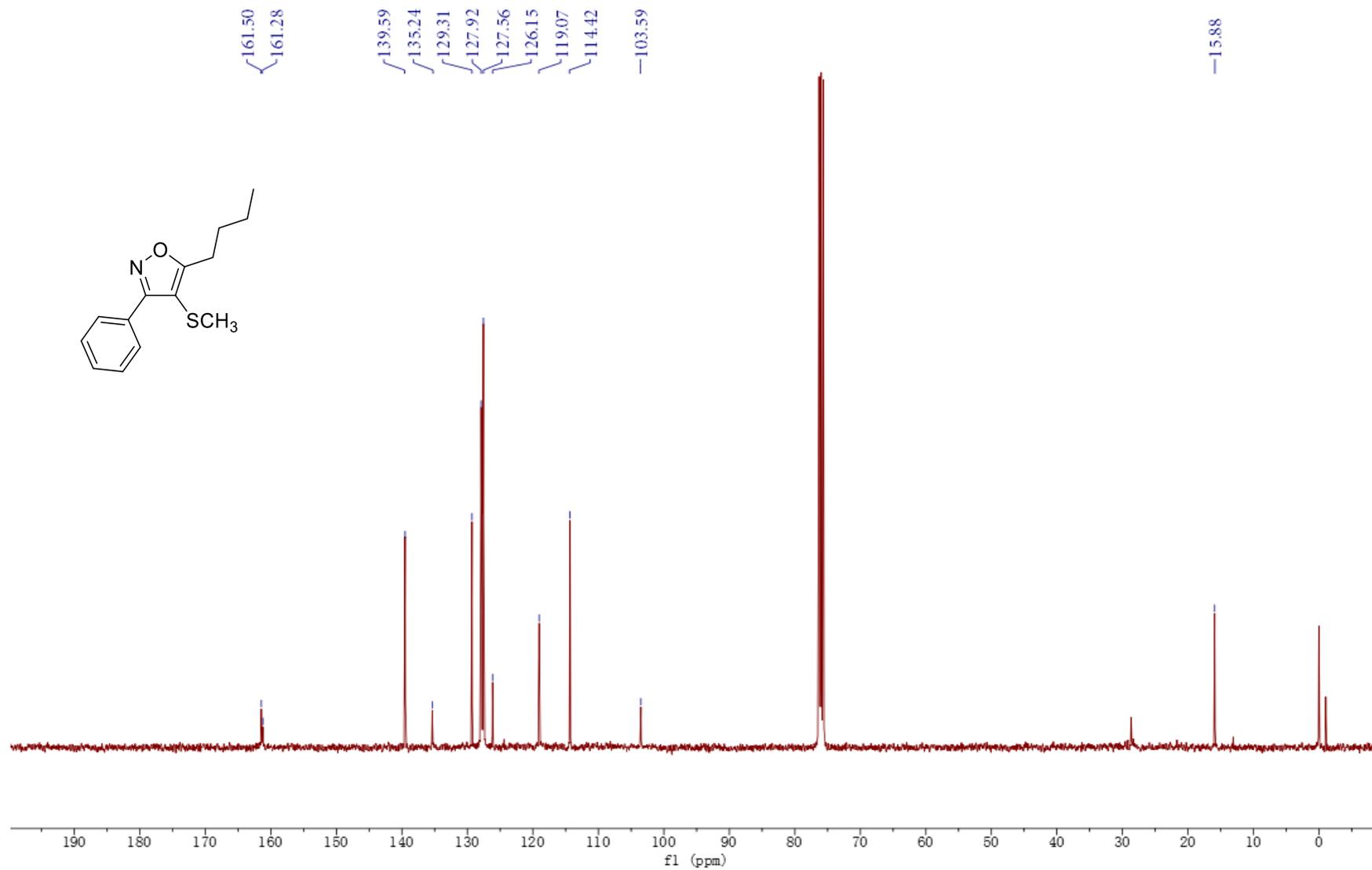
(11). 5-methyl-4-(methylthio)-3-phenylisoxazole



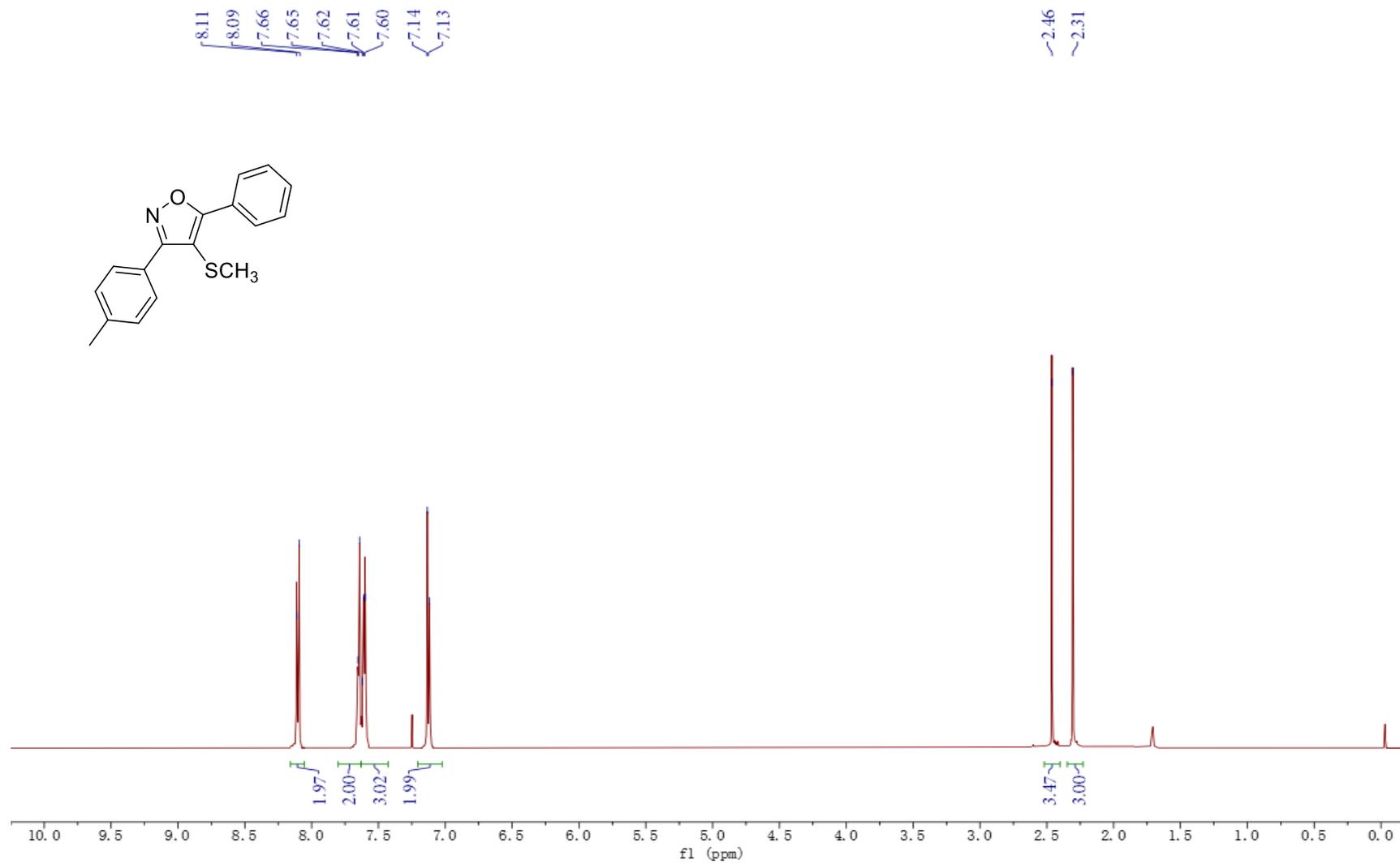


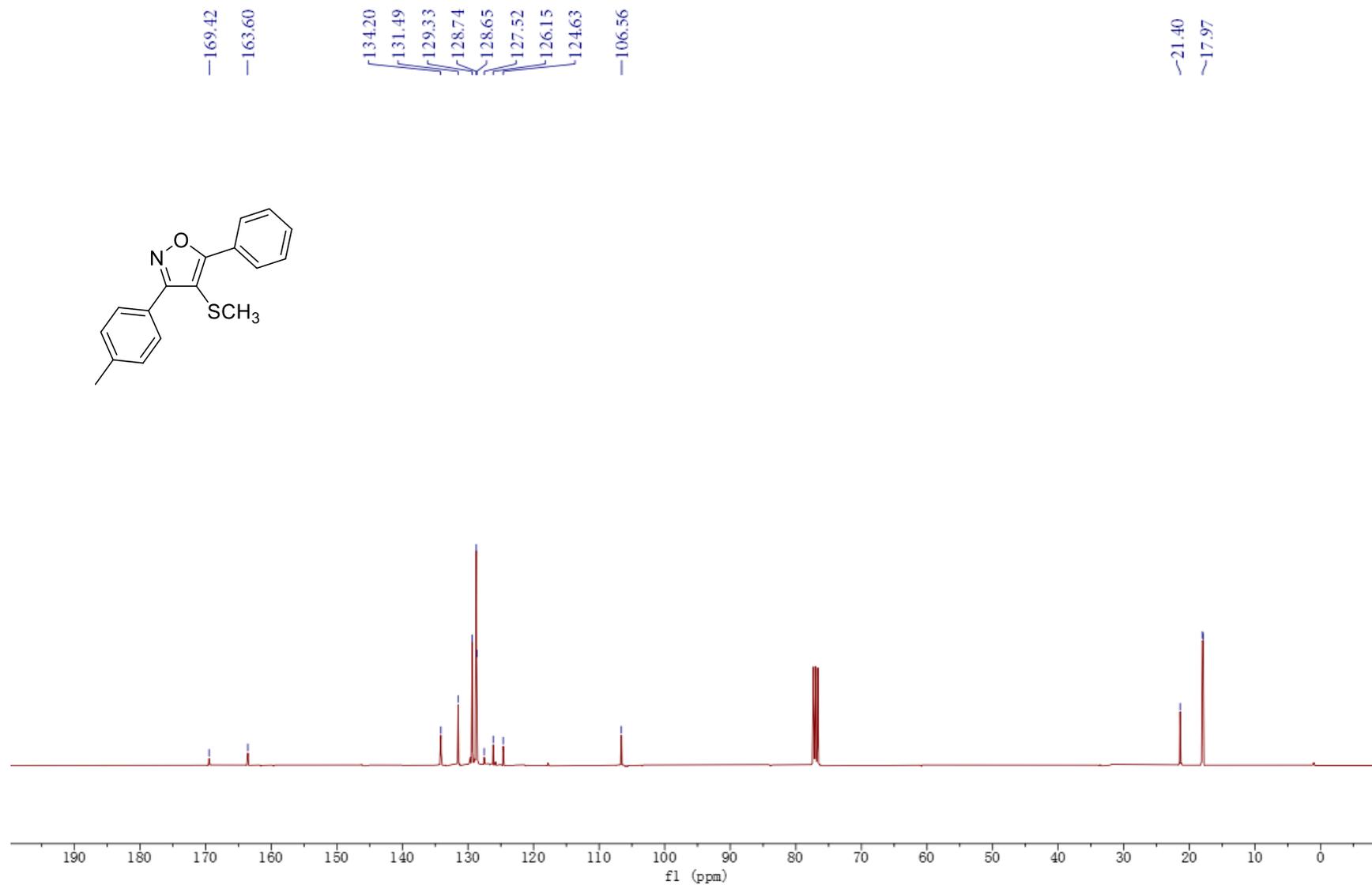
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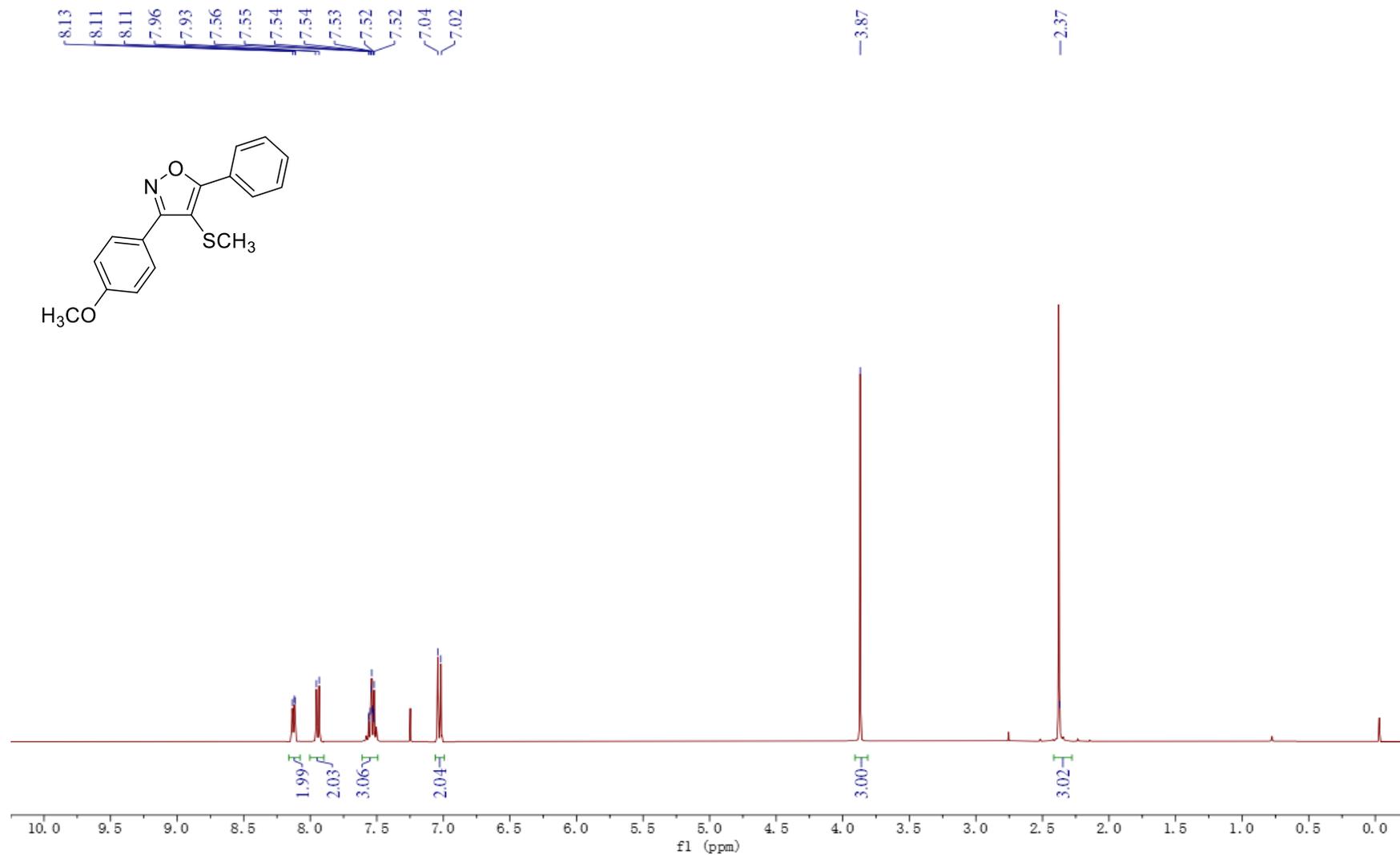


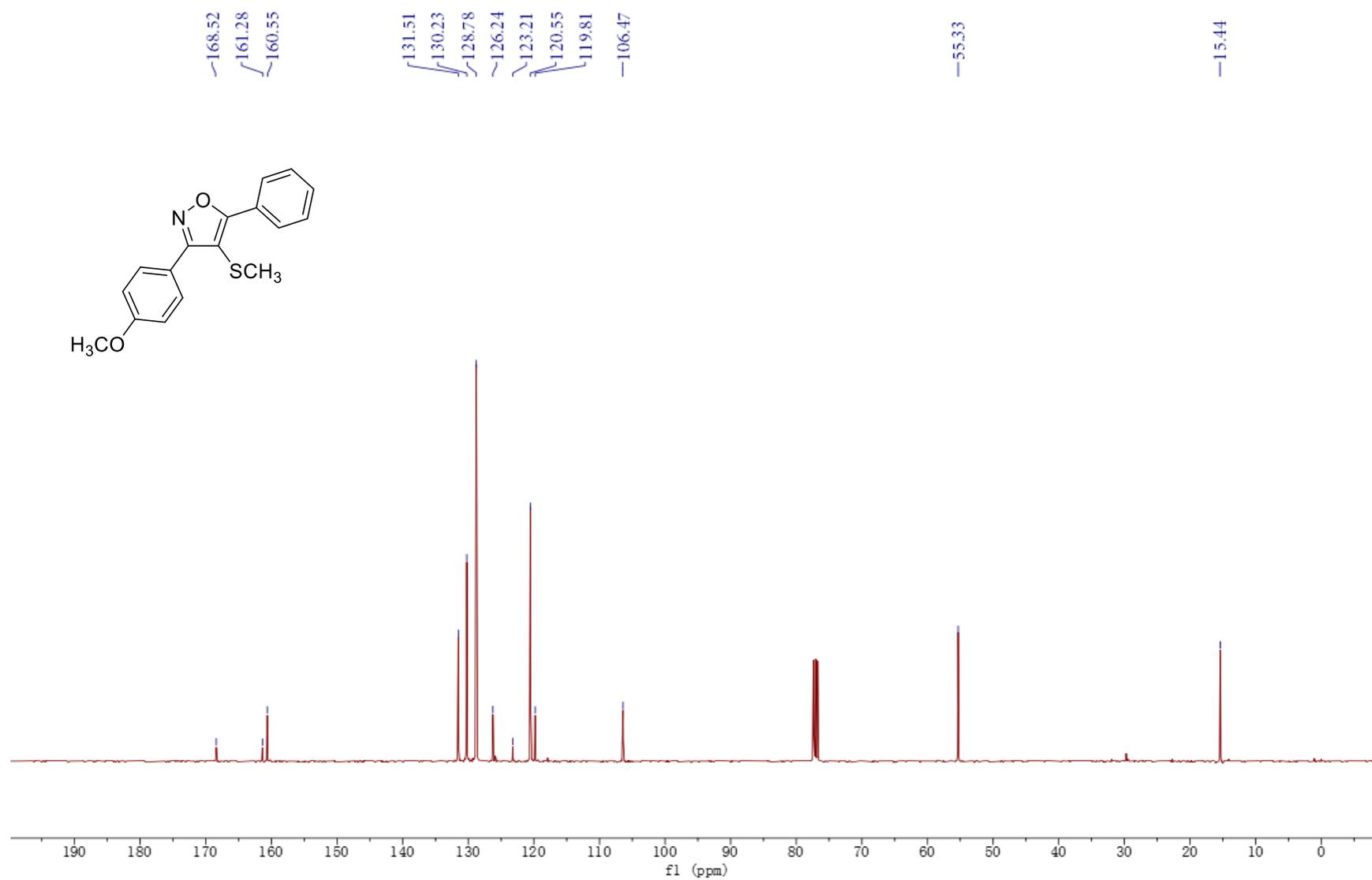


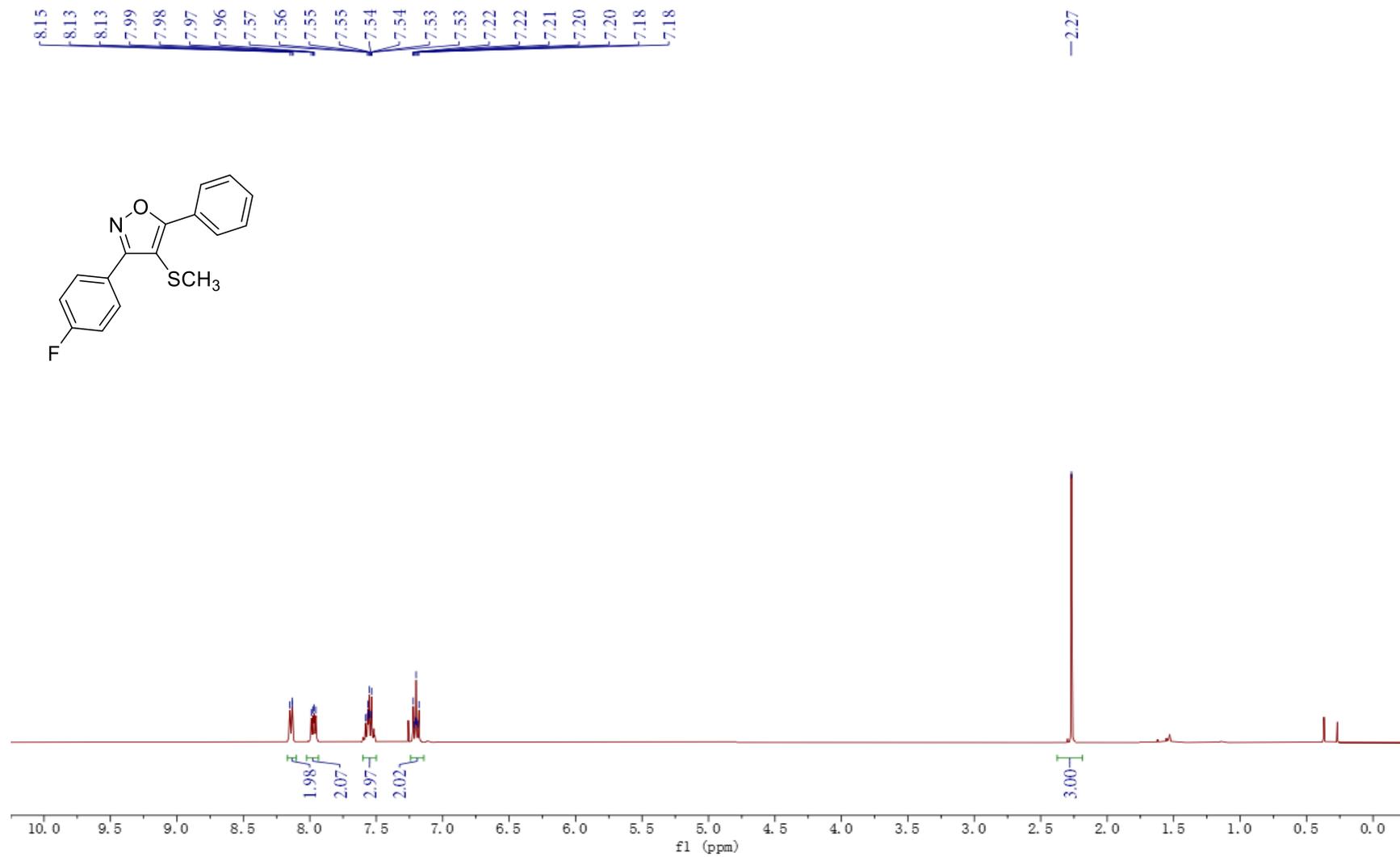
(13). 4-(methylthio)-5-phenyl-3-(p-tolyl)isoxazole

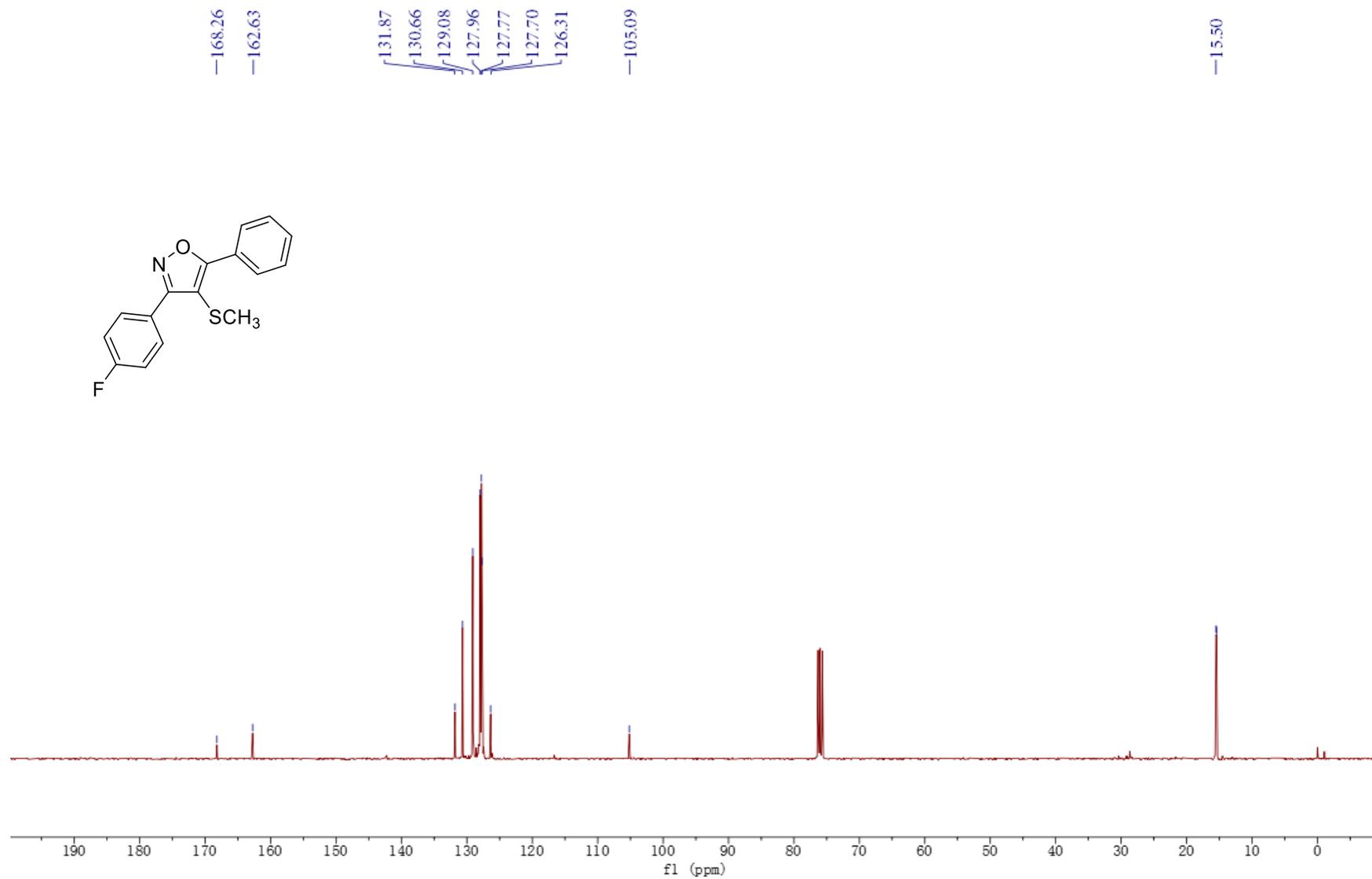
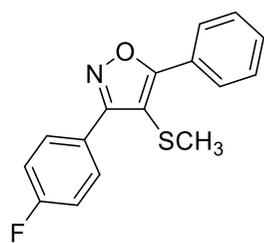


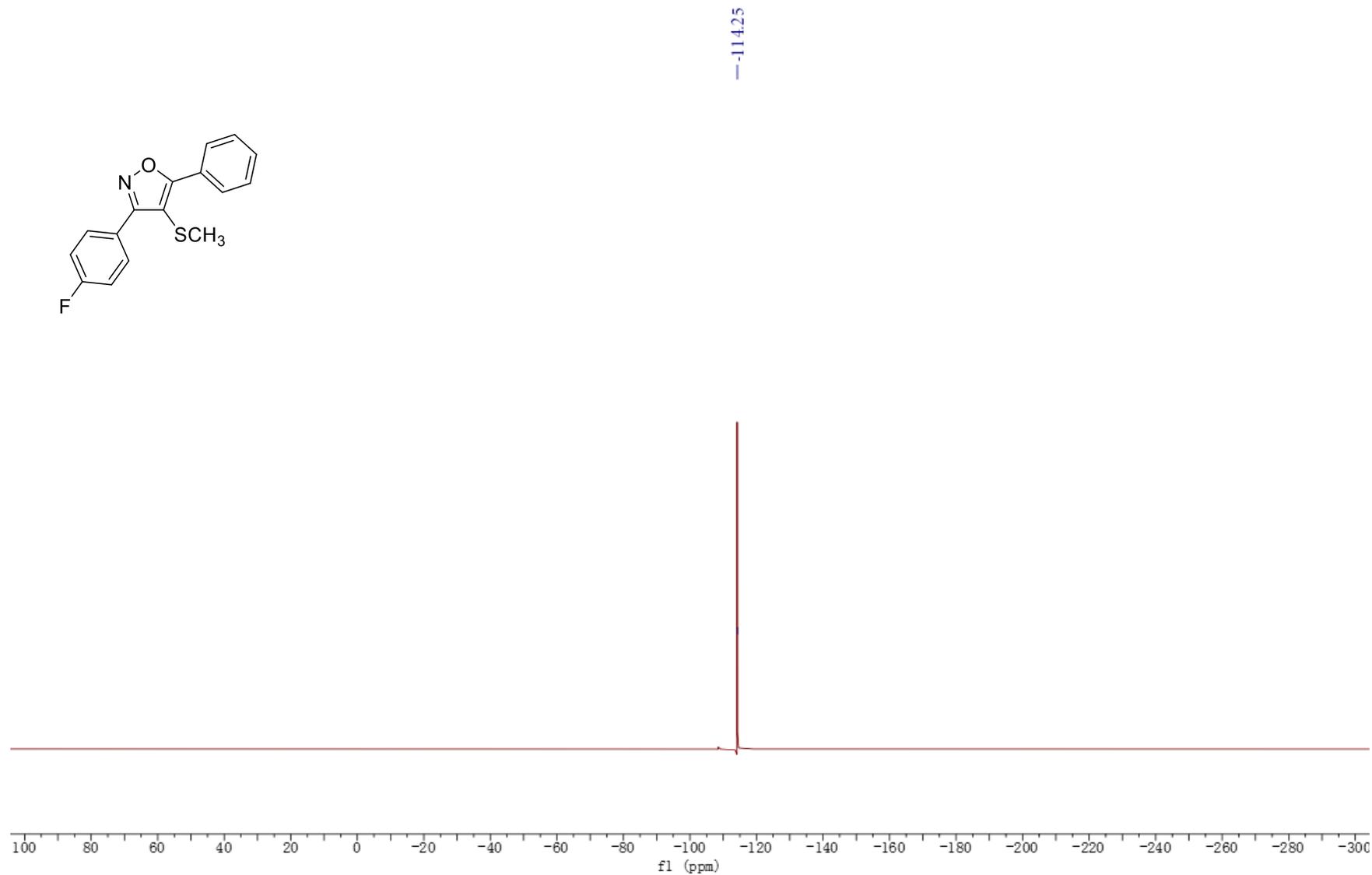
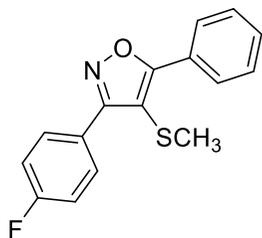


(14). 3-(4-methoxyphenyl)-4-(methylthio)-5-phenylisoxazole

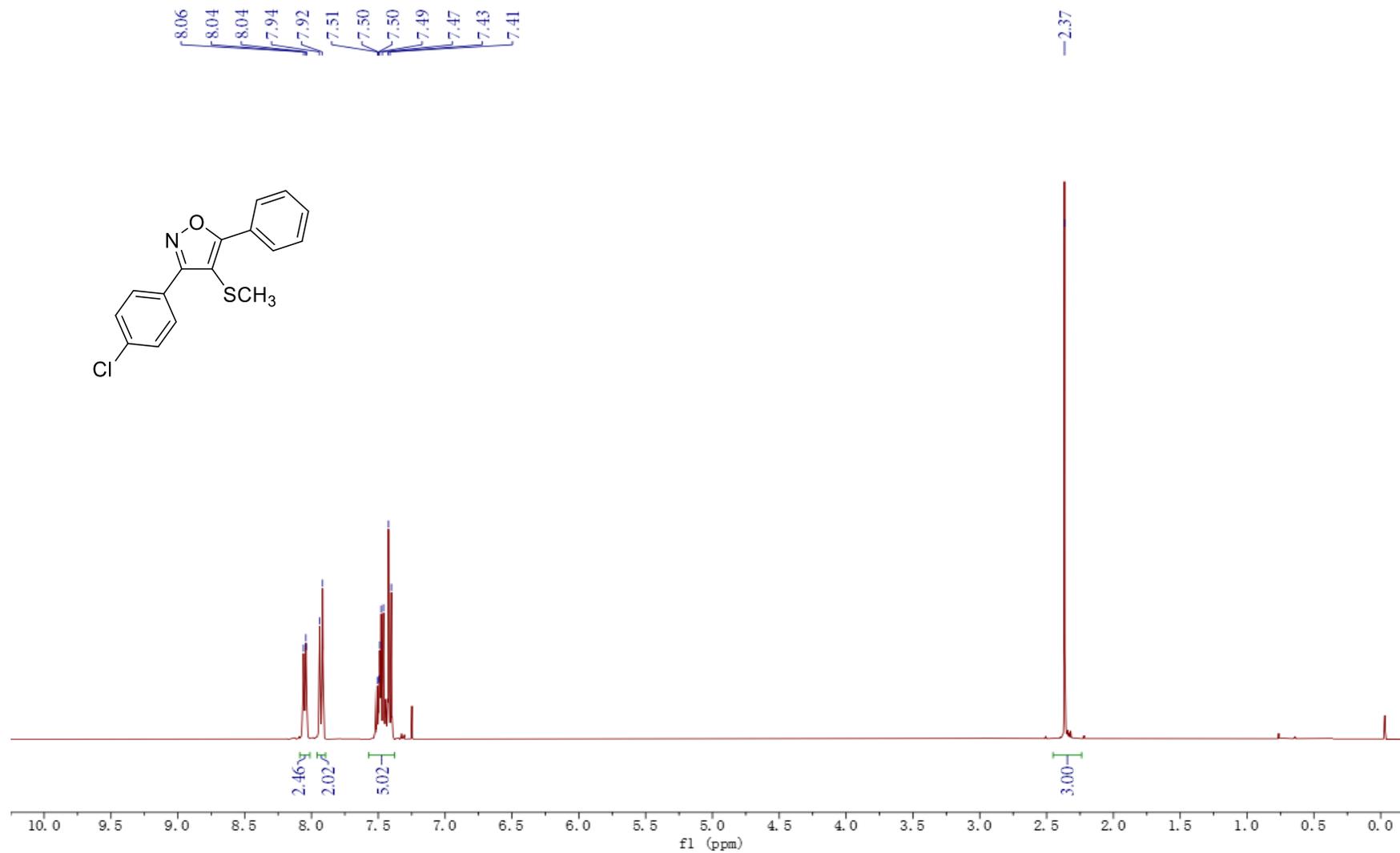


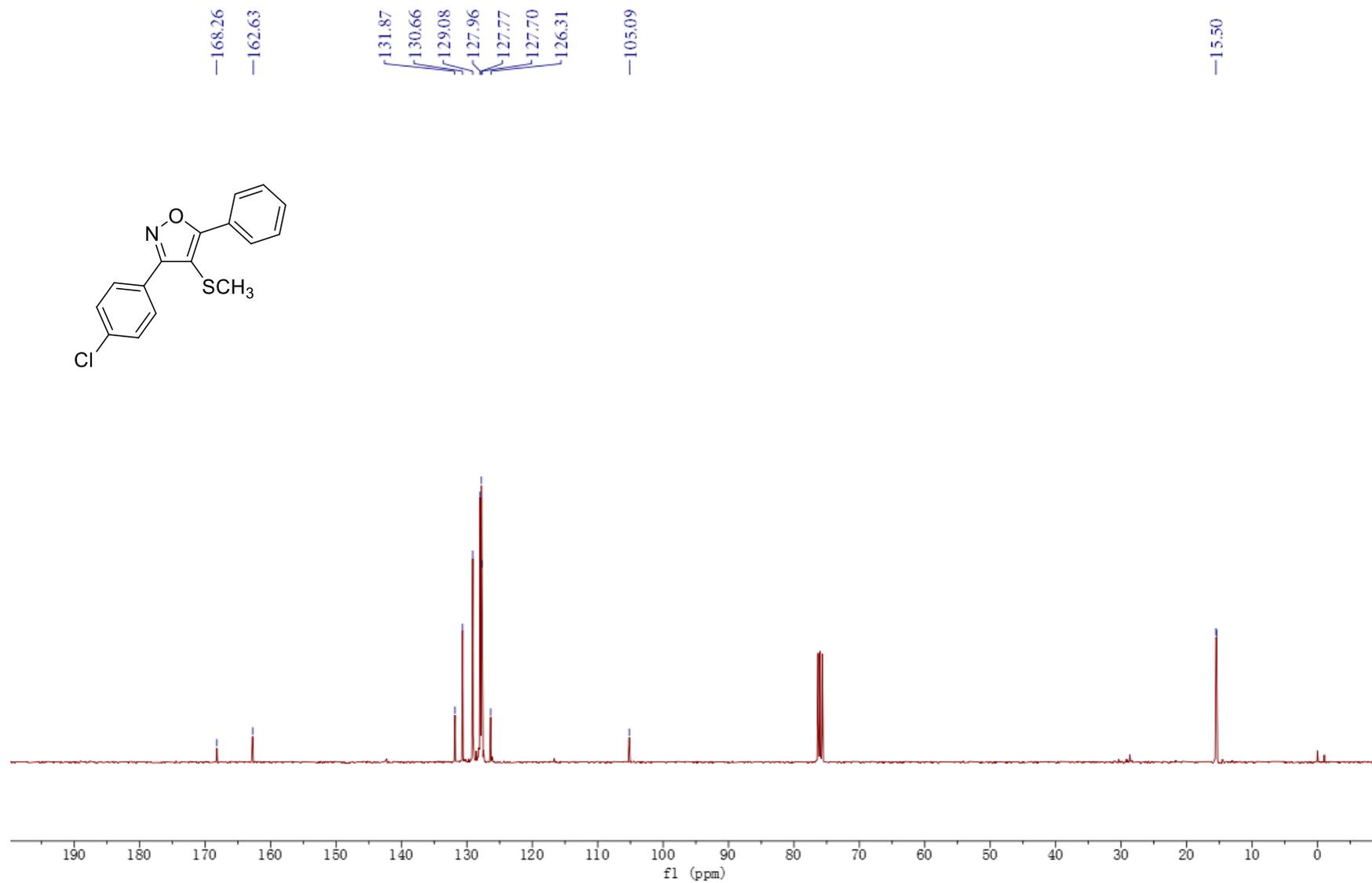
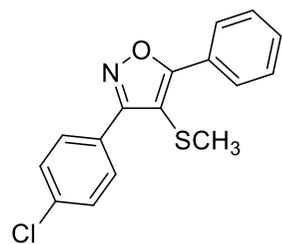
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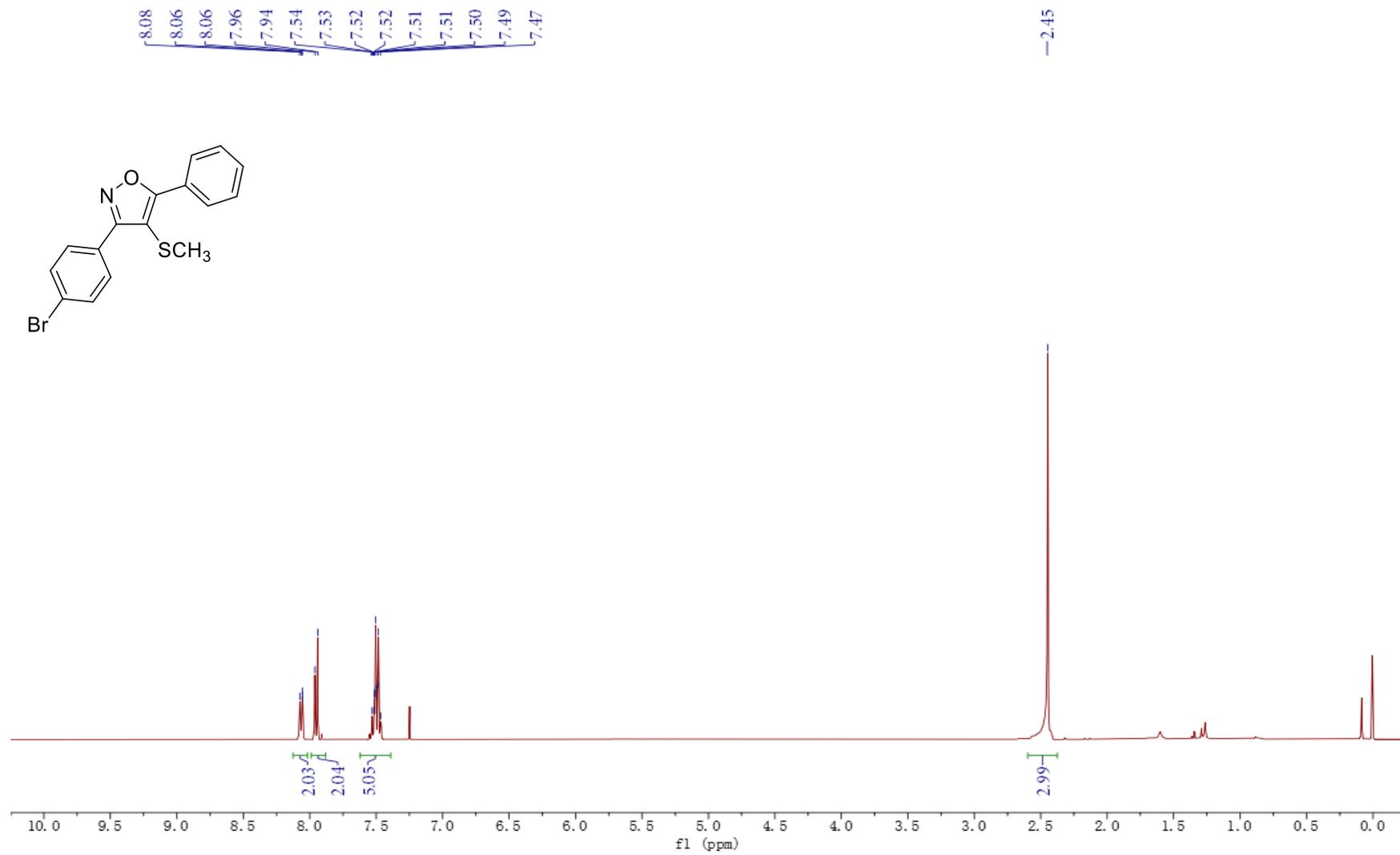


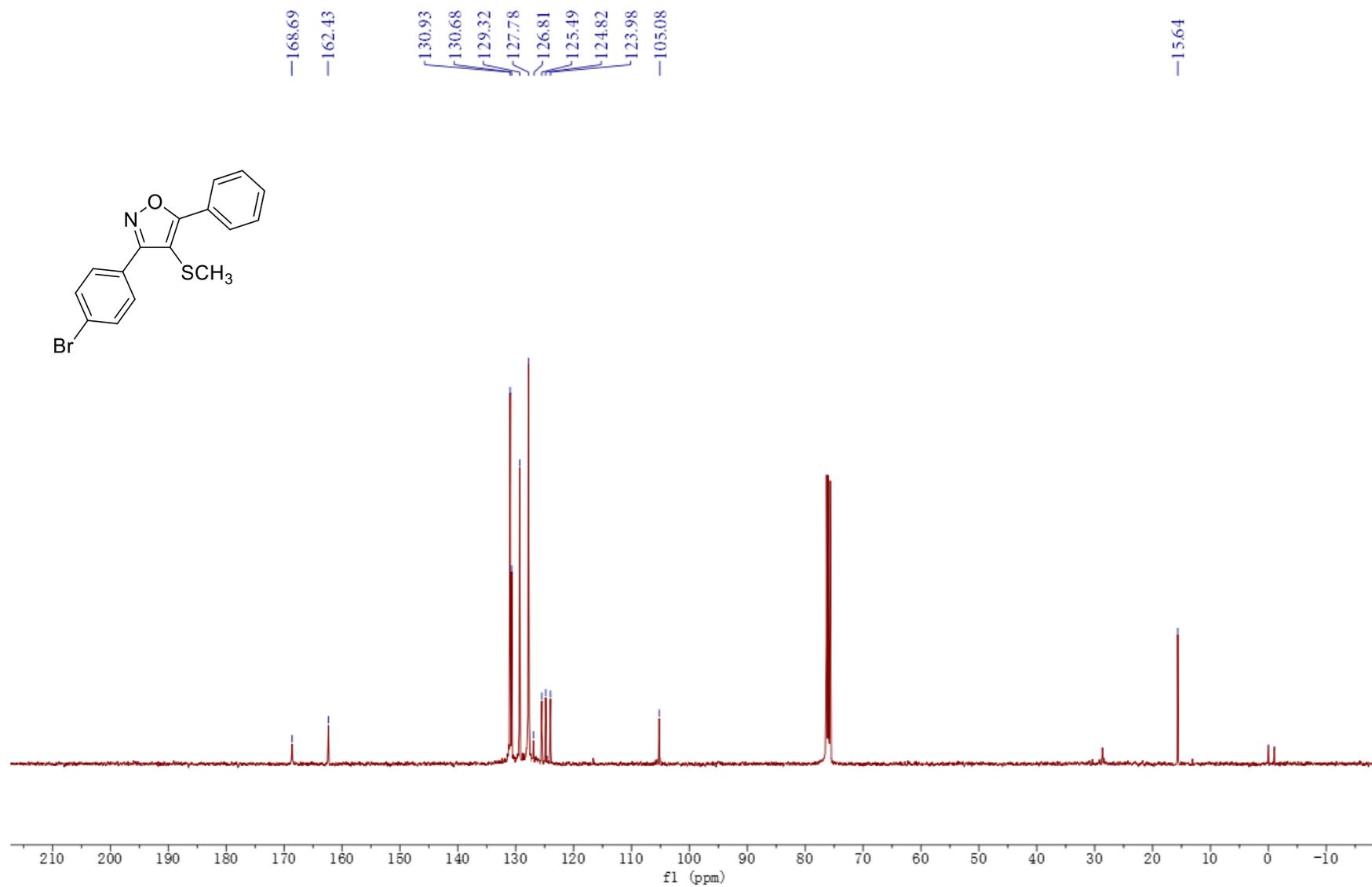


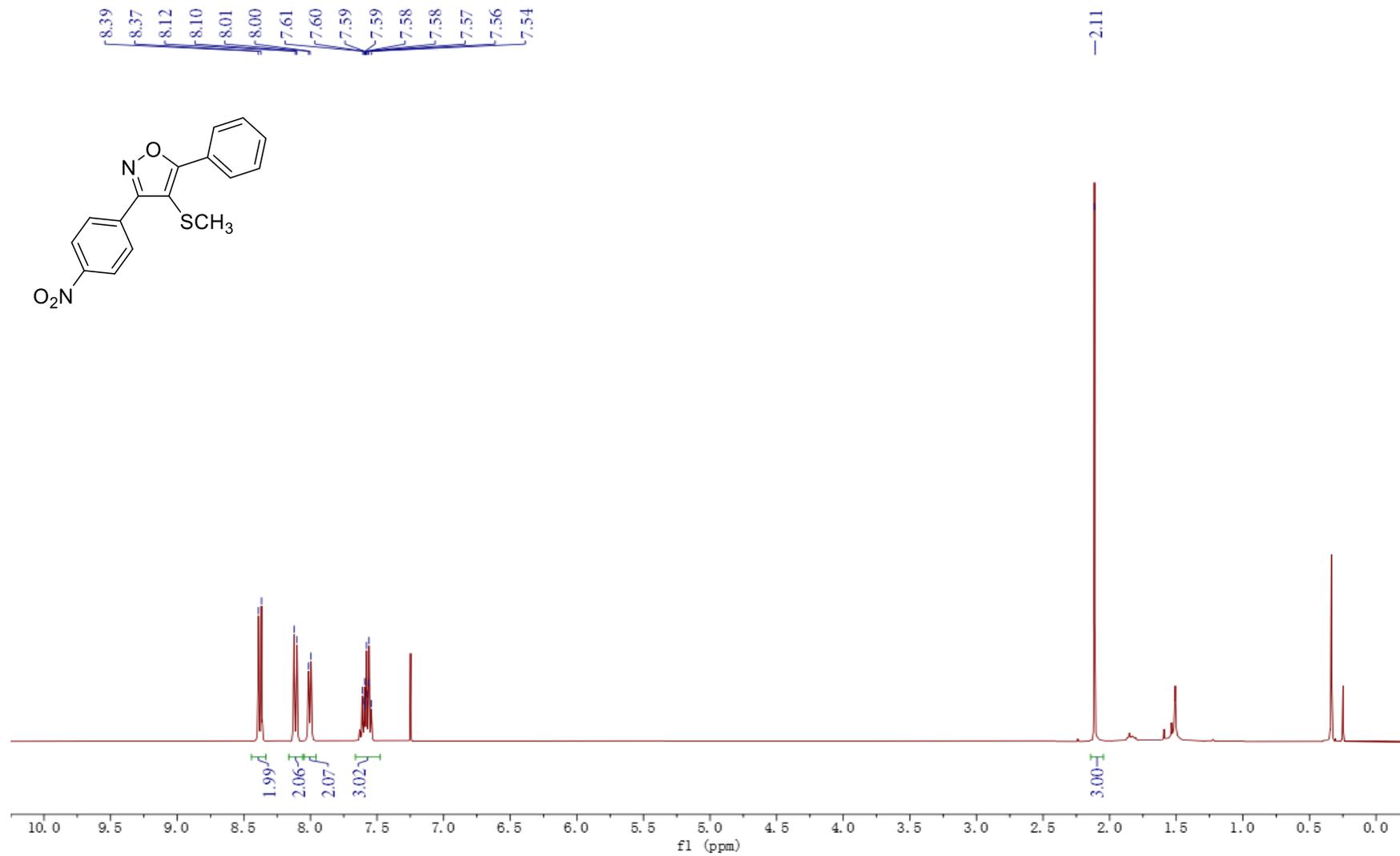
(16). 3-(4-chlorophenyl)-4-(methylthio)-5-phenylisoxazole

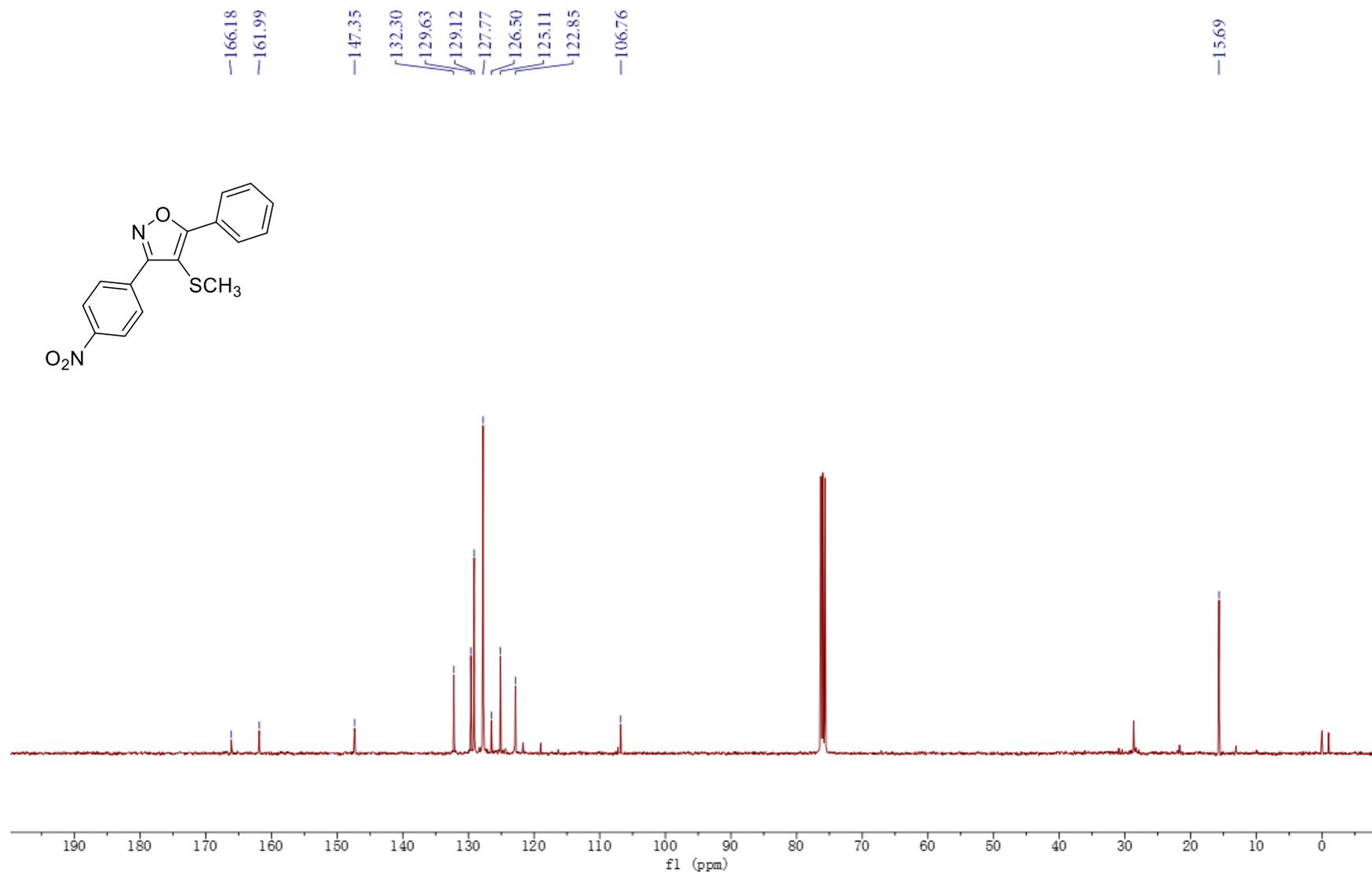


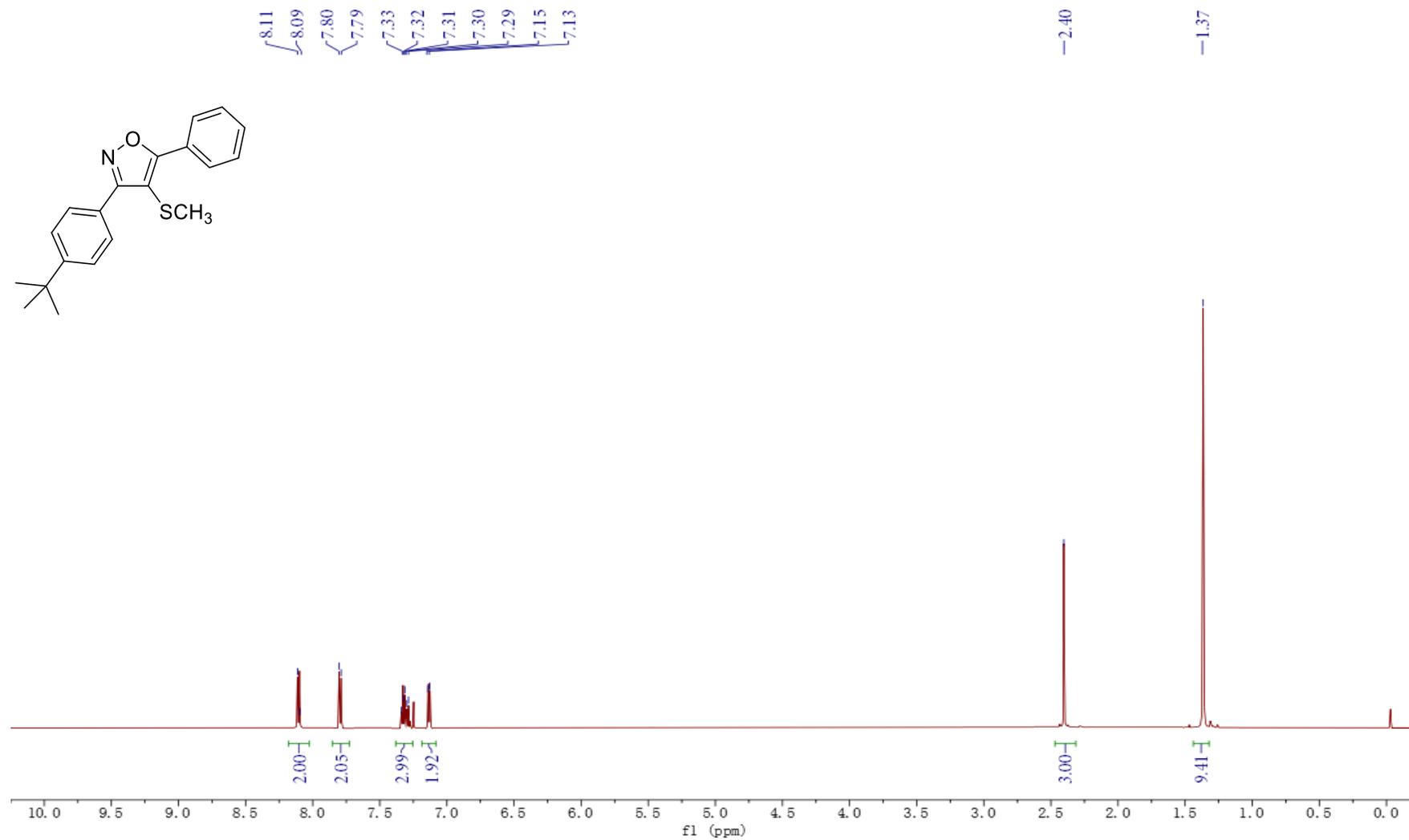


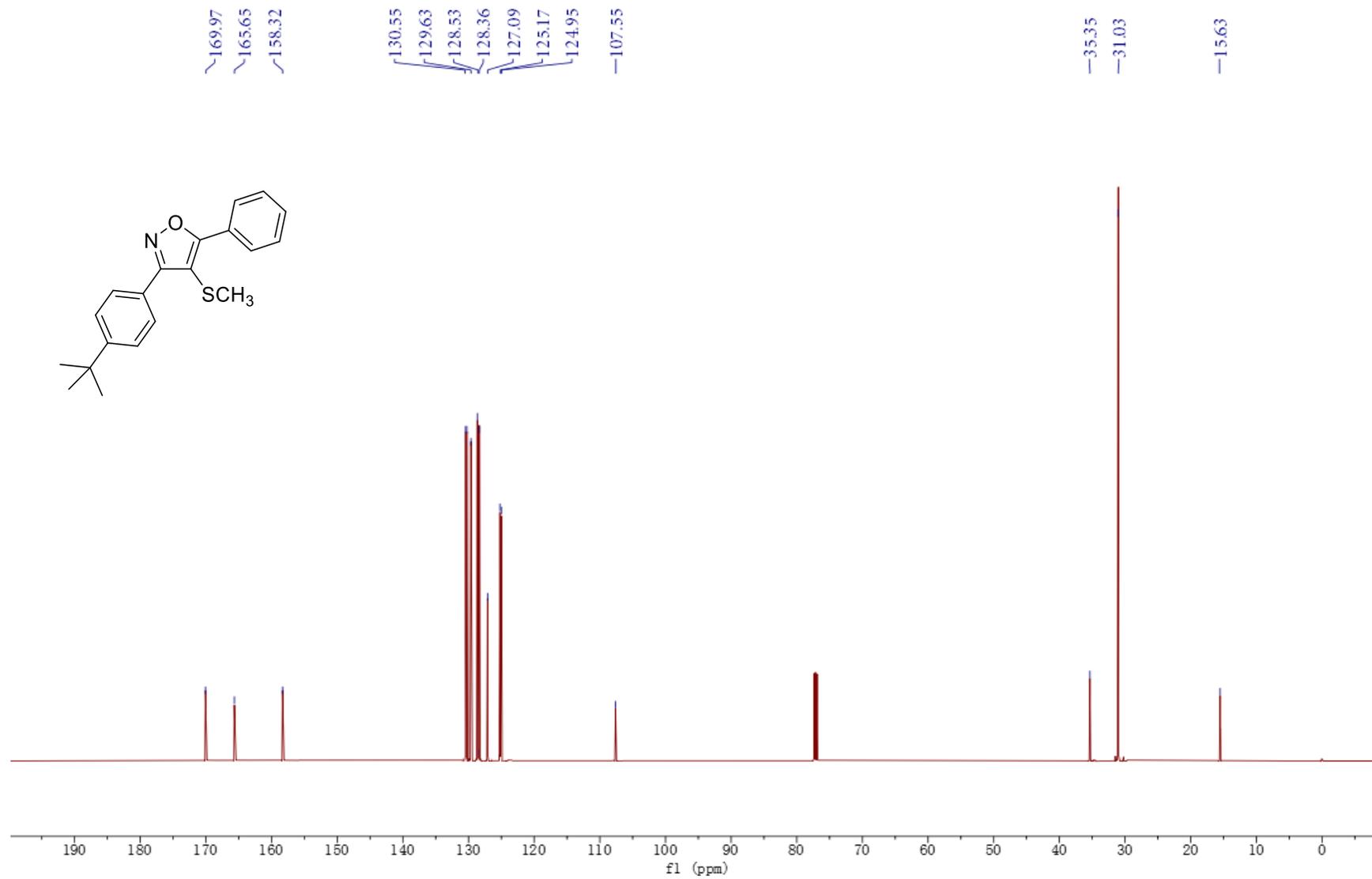
(17). 3-(4-bromophenyl)-4-(methylthio)-5-phenylisoxazole

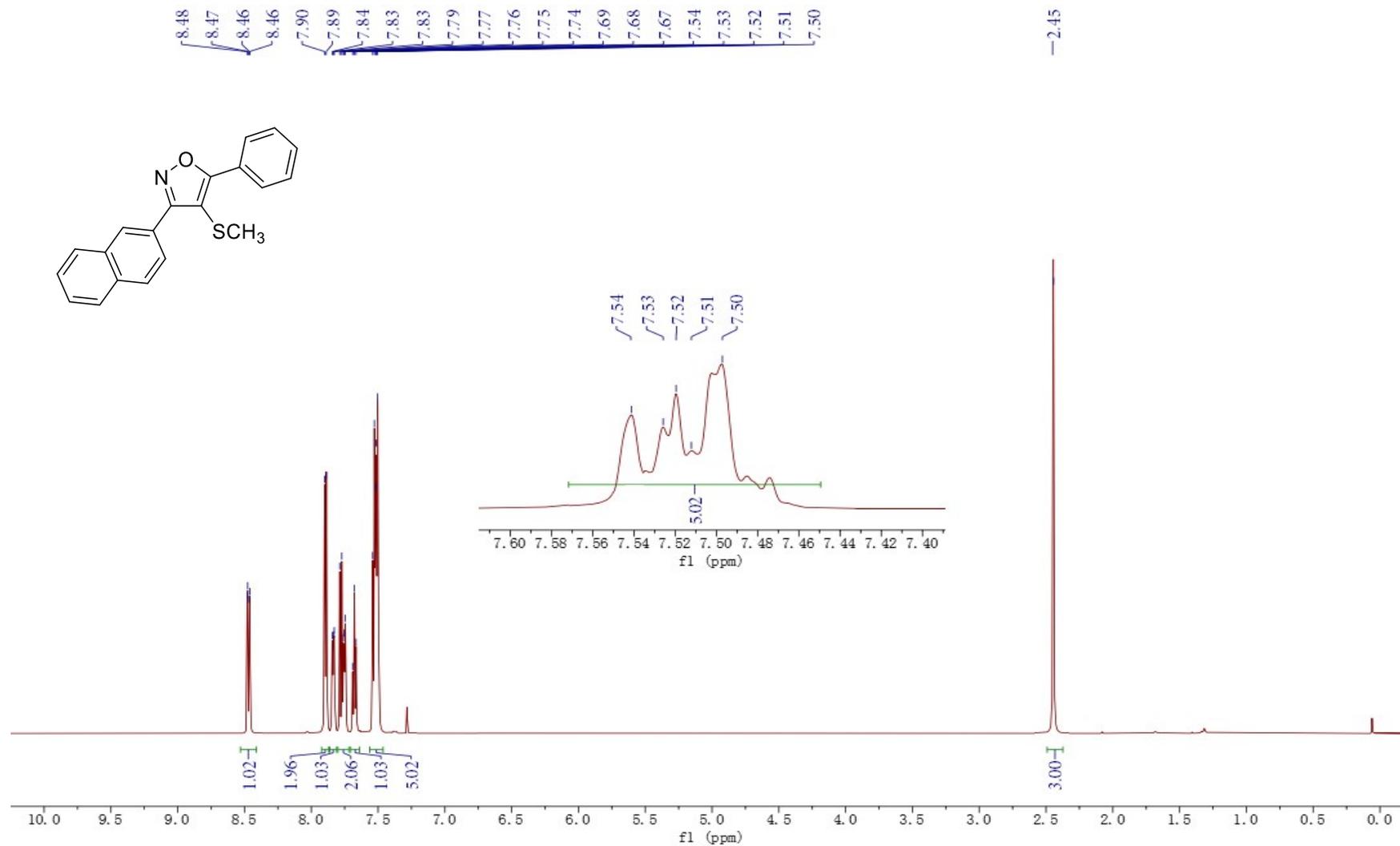


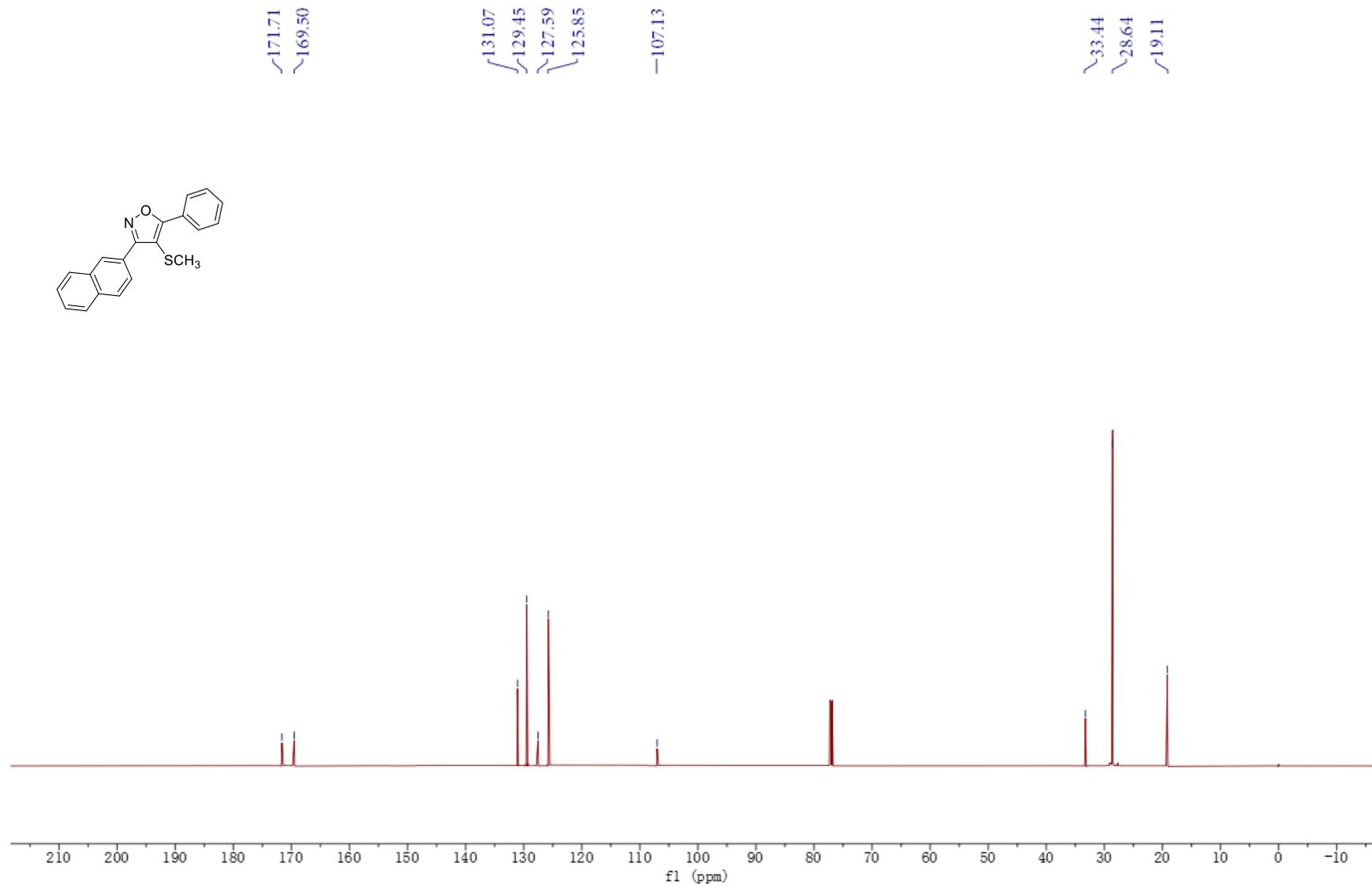
(18). 4-(methylthio)-3-(4-nitrophenyl)-5-phenylisoxazole



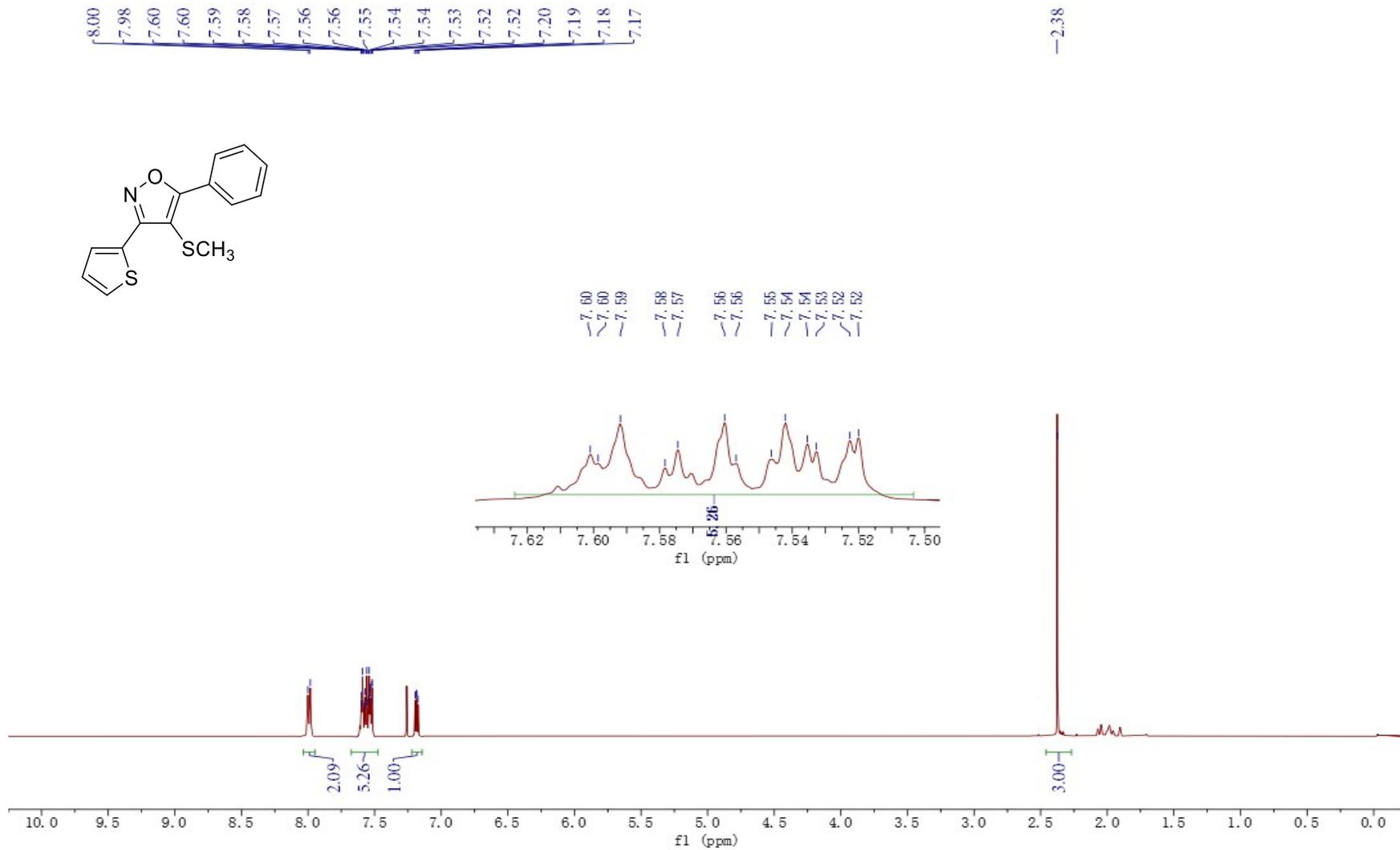
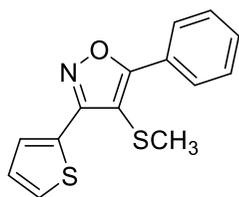
(19). 3-(4-(tert-butyl)phenyl)-4-(methylthio)-5-phenylisoxazole

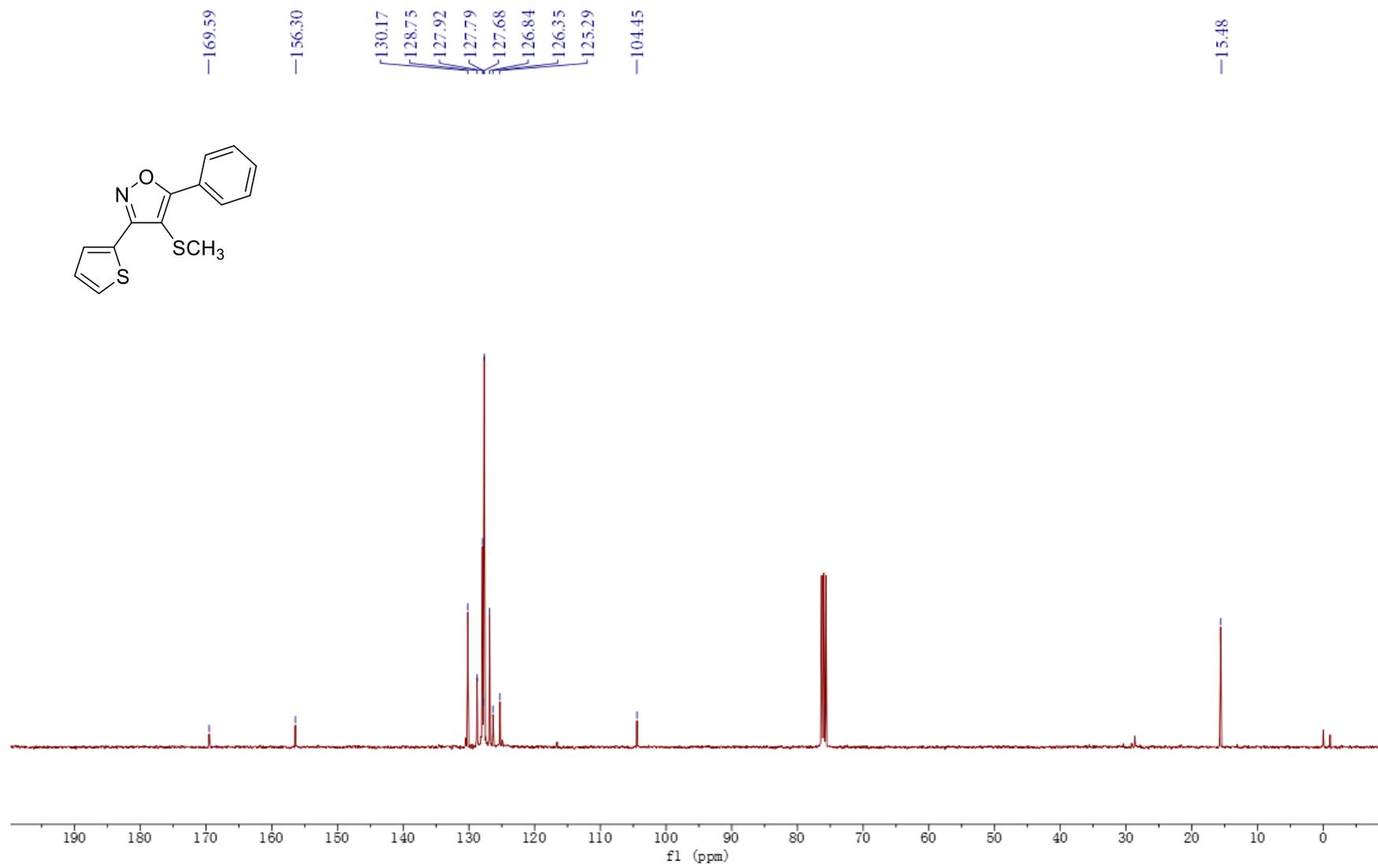
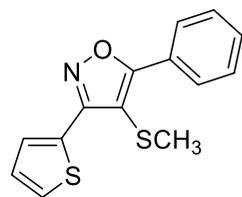


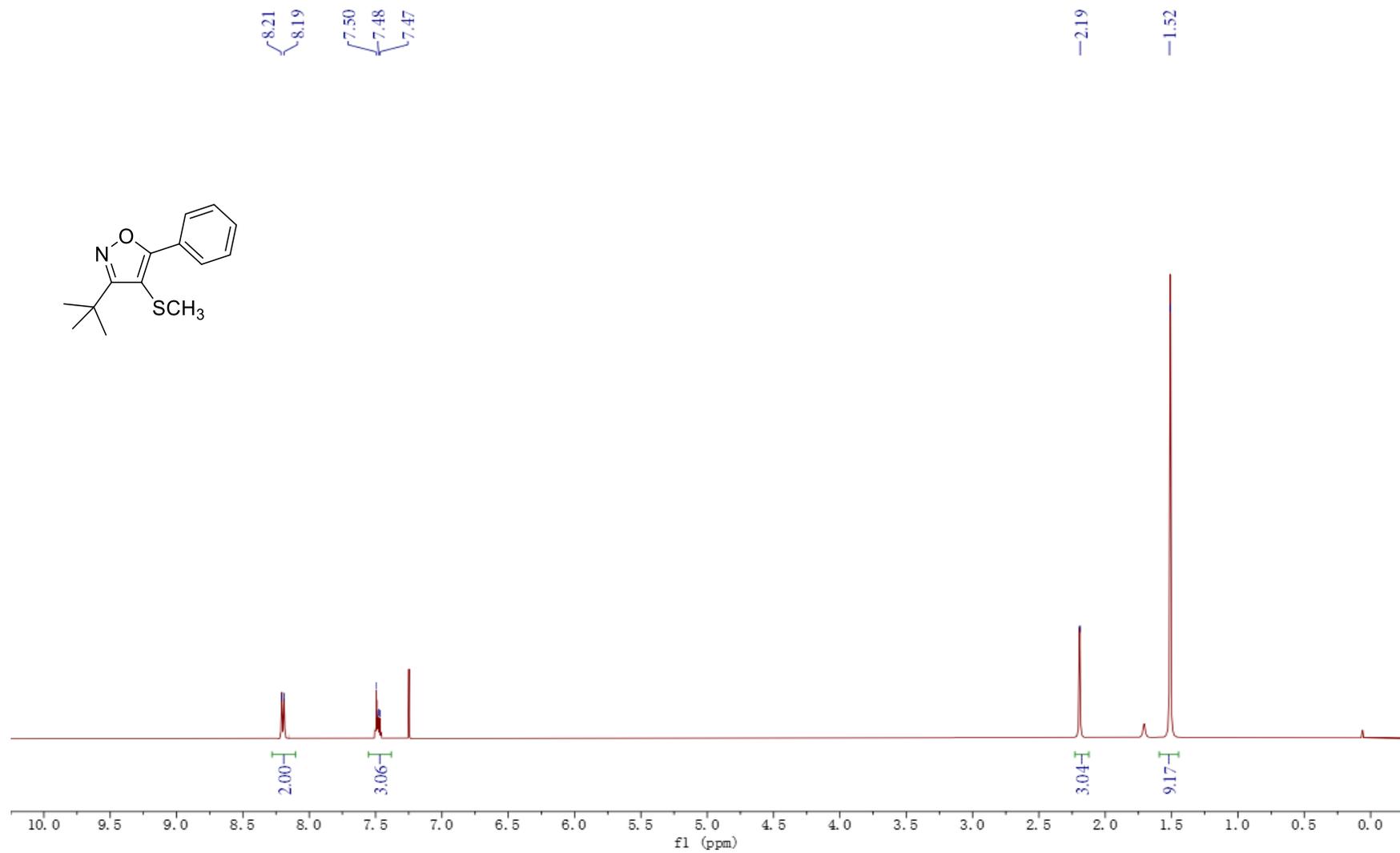
(20). 4-(methylthio)-3-(naphthalen-2-yl)-5-phenylisoxazole

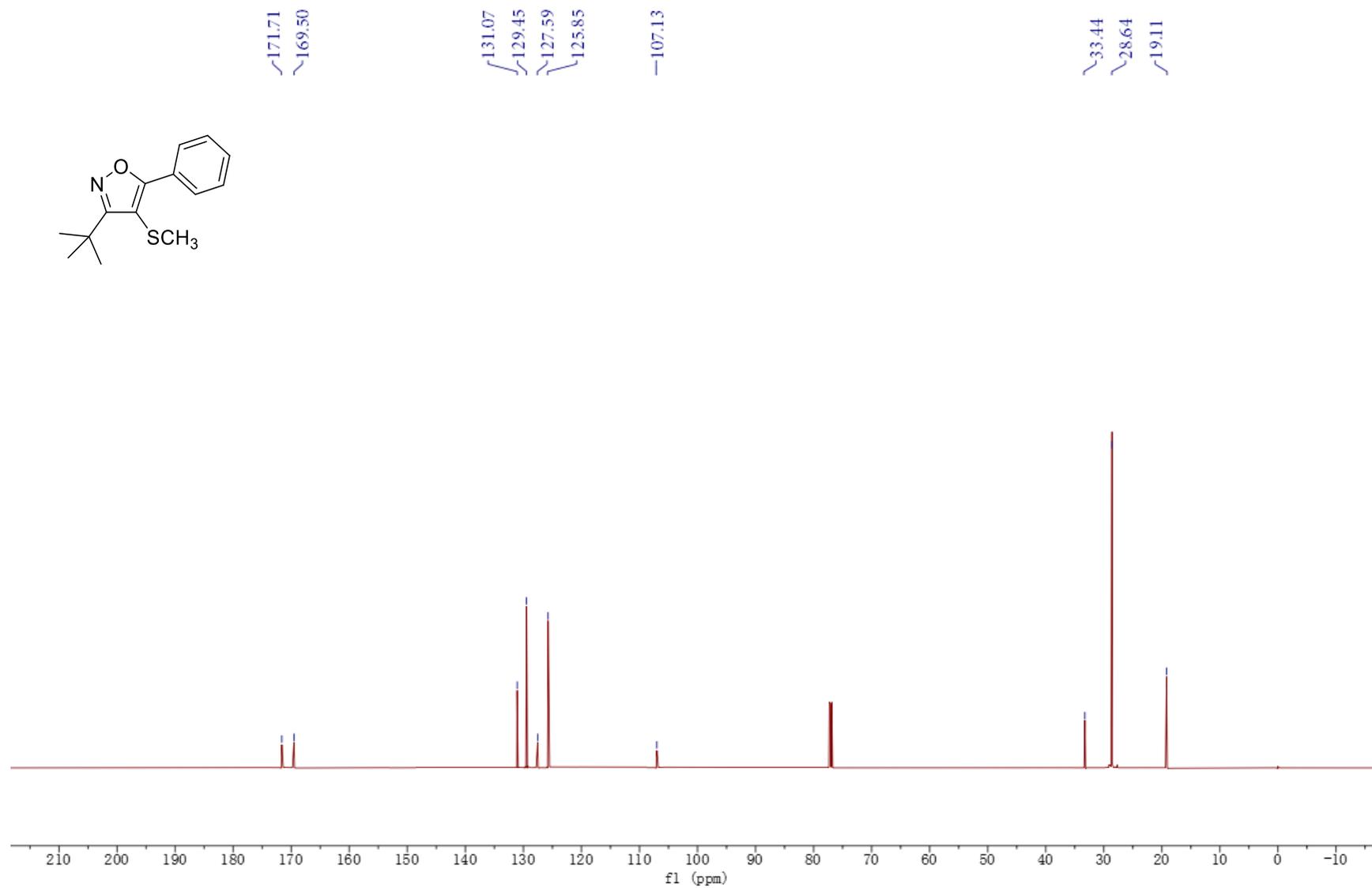


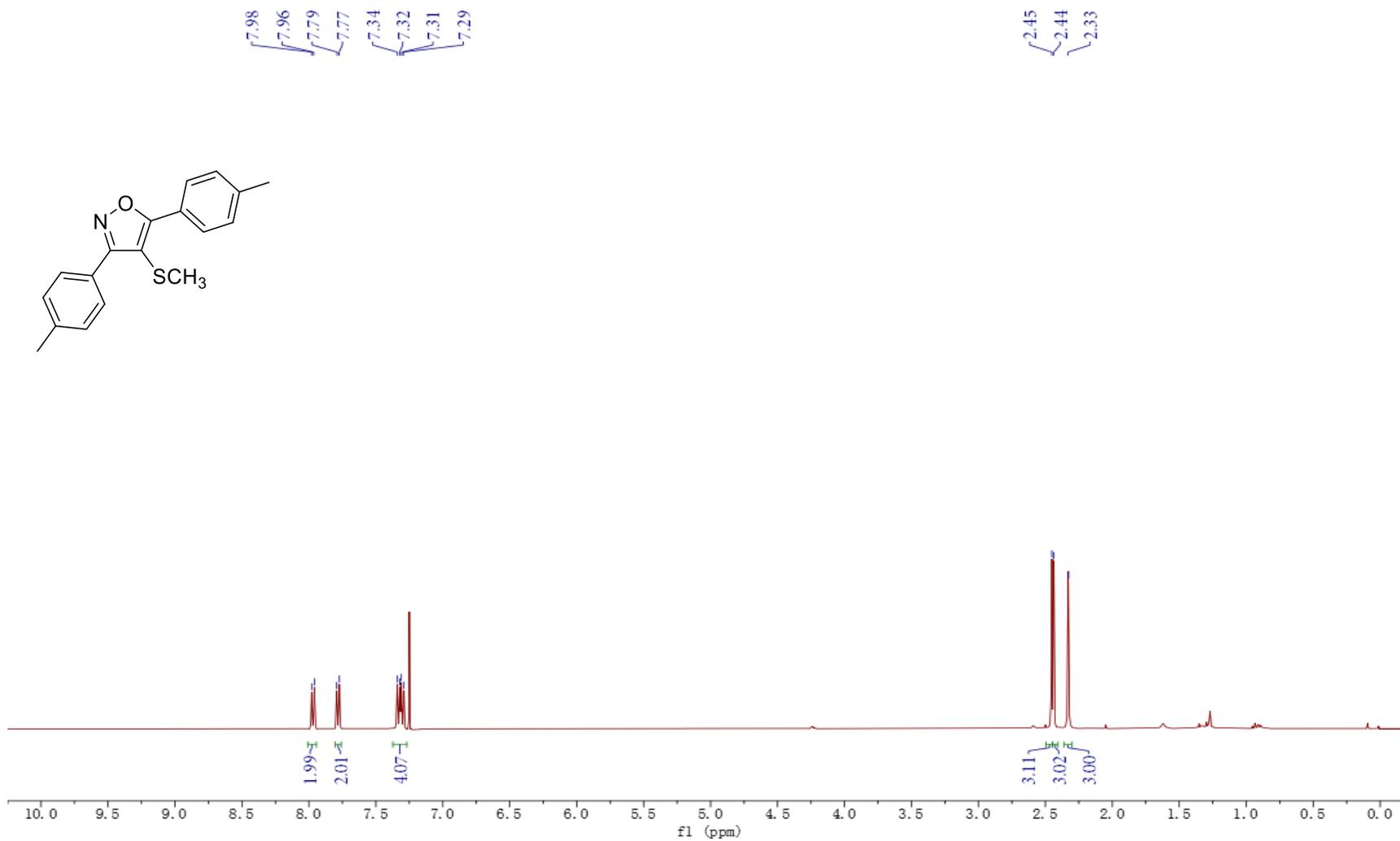
(21). 4-(methylthio)-5-phenyl-3-(thiophen-2-yl)isoxazole

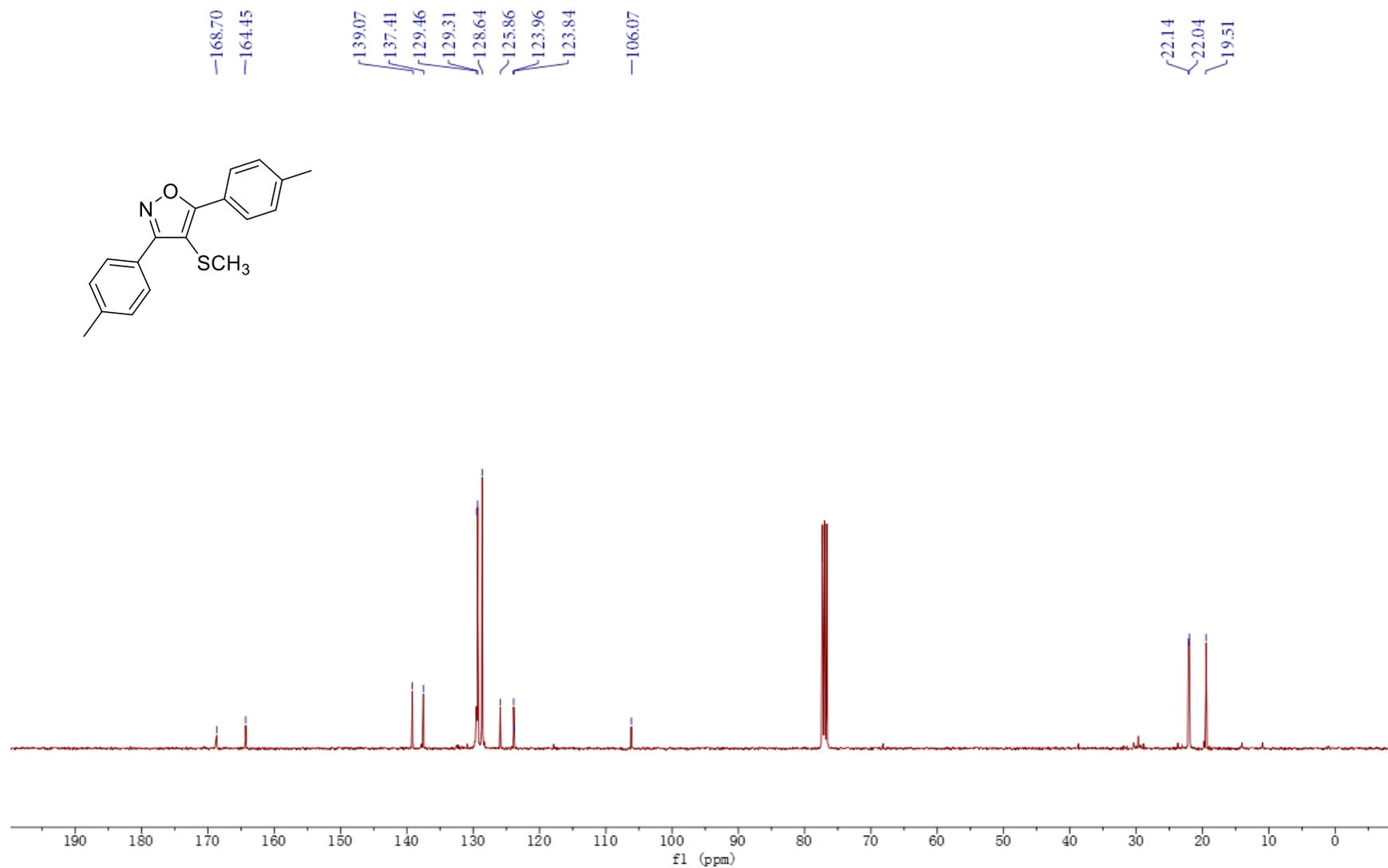




(22). 3-(*tert*-butyl)-4-(methylthio)-5-phenylisoxazole



(23). 4-(methylthio)-3,5-di-p-tolylisoxazole



(24). 3,5-bis(4-methoxyphenyl)-4-(methylthio)isoxazole