Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis of 4-Subsituted Pyrazole-3,5-diamines via Suzuki-Miyaura Coupling and Iron-Catalyzed Reduction

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Materials and methods.

Boronic acids, MIDA esters and precatalysts were bought from commercial suppliers. All reactants and catalysts were weighted under air and then transferred into a sealed tube. All cross-coupling reactions were performed in a sealed tube which was thoroughly flushed with a stream of argon before closing with a screw cap. The reaction tube was then inserted into a preheated oil bath. Progress of the reaction was monitored by LCMS and TLC (Kiesegel 60, visualization by UV). Crude products were purified by a column chromatography over silica gel silica gel (35 - 70 μm particle size). Reaction workup and column chromatography were performed with commercial grade solvents without further purification. Purified products were characterized by NMR and HRMS. NMR spectra were recorded on a Jeol 400 MHz spectrometer in DMSO. Chemical shifts are reported in ppm and referenced to the residual solvent peak. HRMS data were recorded using electrospray ionisation and time of flight detector.

Microwave reactions for dehalogenation experiments were carried out in a CEM-Discover microwave reactor operating at 2.45 GHz with continuous irradiation of 300W maximum power. The microwave irradiation of required watts was used and the temperature was continuously raised for 2 minutes. Once the desired temperature was reached, the mixture was held at this temperature for given time (typically 20 minutes).

Optimization of reaction conditions (Table 1).

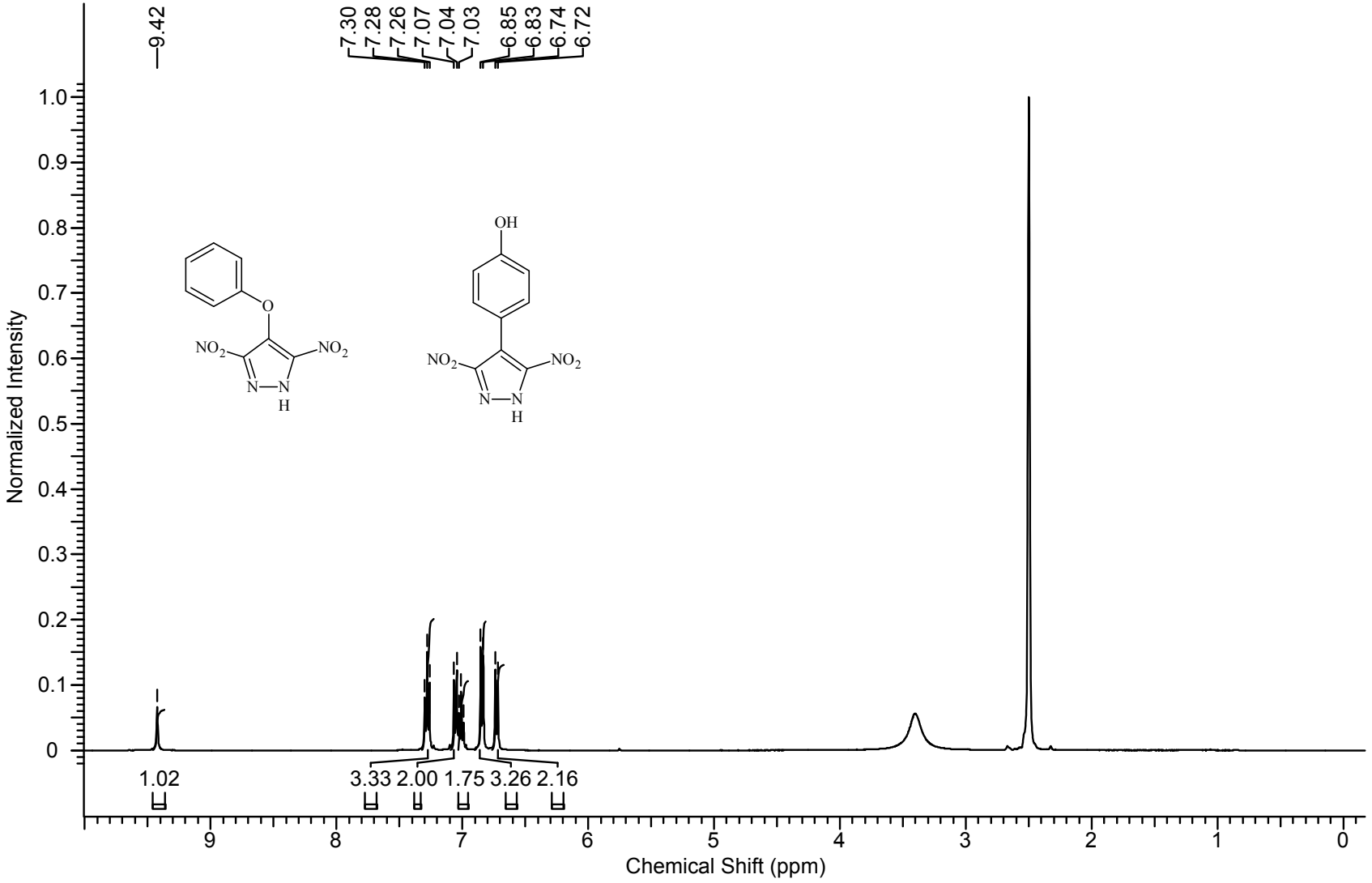
Into a vial was weighted pyrazole **2** (59 mg, 0.25 mmol), base (4 equiv.) and *p*-tolylboronic acid **3a** (36 mg, 0.262 mmol). Dioxane (1 mL) and H_2O (0.25 mL) were added and the content of the tube was thoroughly degassed by a stream of argon for 15 min. Pd-source (0.025 mol%) and ligand (0.05 mol%) were added and the mixture was again thoroughly degasses by a stream of argon. The vial was capped with crew cap and inserted into a preheated oil bath (20 h reaction time). After the given time, the crude reaction mixture was analyzed by the LCMS using Fmoc-Ala-OH as an internal standard.

4-(3,5-dinitro-1*H*-pyrazol-4-yl)phenol (4f).

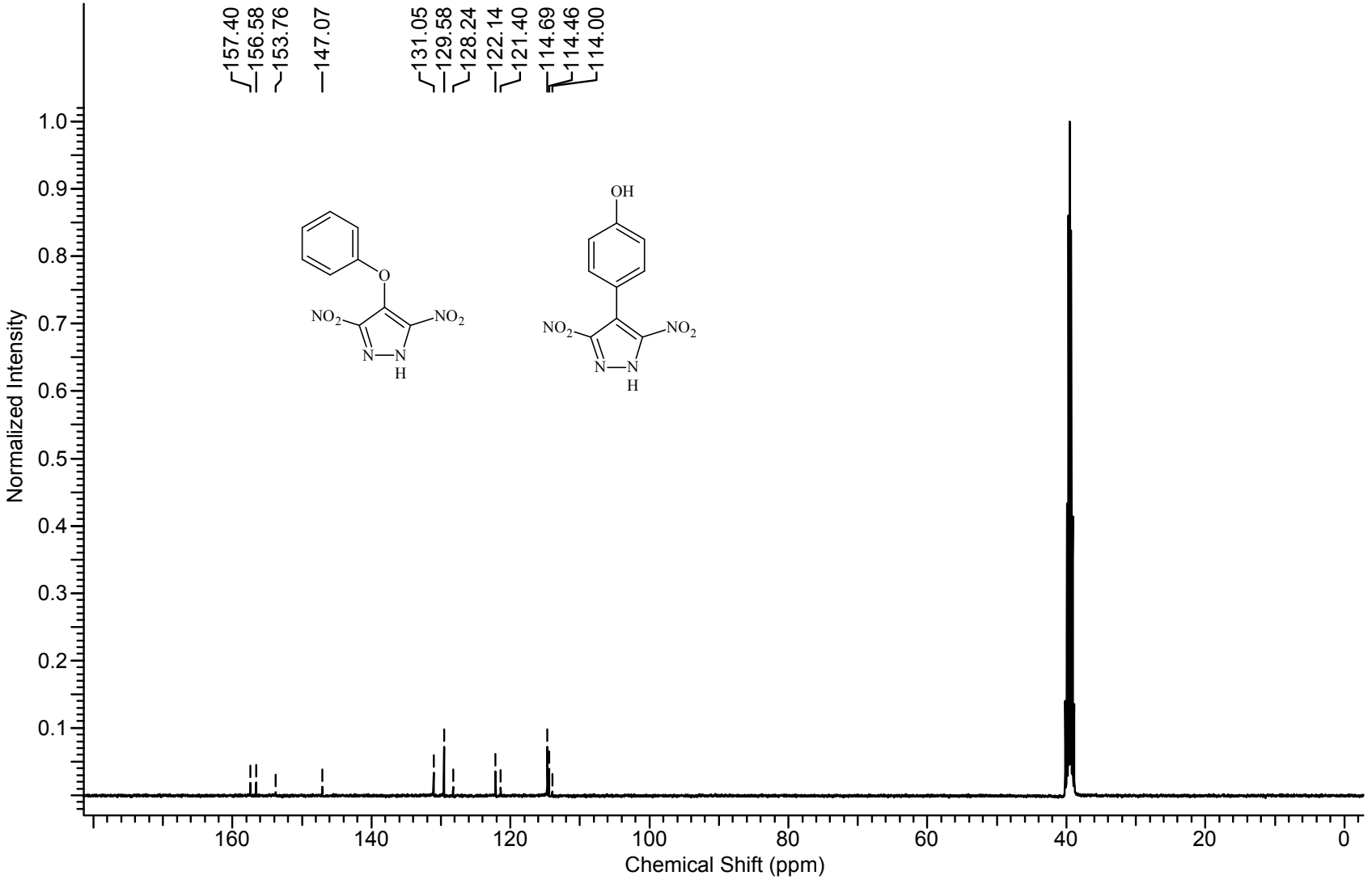
Pyrazole **2** (236 mg, 1.0 mmol), boronic acid **3f** (207 mg, 1.5 mmol), and K_3PO_4 (848 mg, 4.0 mmol) were weighed into a vial and suspended in dioxane (4 mL) and water (1 mL). The mixture was degassed with argon for 15 min. Then, precatalyst XPhos Pd G2 (16 mg, 0.02 mmol) was added and the vial was quickly closed and inserted into an oil bath preheated to 100 °C. The mixture was vigorously stirred at 100 °C for 20 h. Then, analysed by TLC ($CHCl_3$:MeOH 5:1), pyrazole **2** observed. Thus, additional amount of **3f** (207 mg, 1.5 mmol) was added into reaction mixture, degassed by argon for 15 minutes and then precatalyst XPhos Pd G2 (16 mg, 0.02 mmol) was added and the vial was placed back to the oil bath preheated to 100°C. Then, after 20 h again TLC showed unconsumed **2**. Again **3f** (207 mg, 1.5 mmol) was added, degassed by argon, followed by addition of XPhos Pd G2 (16 mg, 0.02 mmol). Reaction mixture was stirred for next 20 h at 100°C. Then, the vial was pulled out from the oil bath and acidified by hydrochloric acid to reach pH 1. Then the solvent was evaporated under reduced pressure to dryness. Product was isolated according procedure *Method B* and purified by column chromatography with the mobile phase: petroleum ether:EtOAc:MeOH (5:5:0 - 5:5:2).

A mixture of two products according HPLC and NMR was observed: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.42 (s, 1 H), 7.28 (t, J=7.8 Hz, 3 H), 7.05 (d, J=8.7 Hz, 2 H), 7.01 (t, J=7.6 Hz, 2 H), 6.84 (d, J=7.8 Hz, 2 H), 6.73 (d, J=8.7 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.4, 156.6, 153.8, 147.1, 131.0, 129.6, 128.2, 122.1, 121.4, 114.7, 114.5, 114.0. HRMS (ESI-TOF): calcd for $C_9H_6N_4O_5$ $[M-H]^-$ 249.0260, found 249.0261. Yellow solid 105 mg was gained after column chromatography.

A mixture of 4-(3,5-dinitro-1*H*-pyrazol-4-yl)phenol (4f) and 3,5-dinitro-4-phenoxy-1*H*-pyrazole.



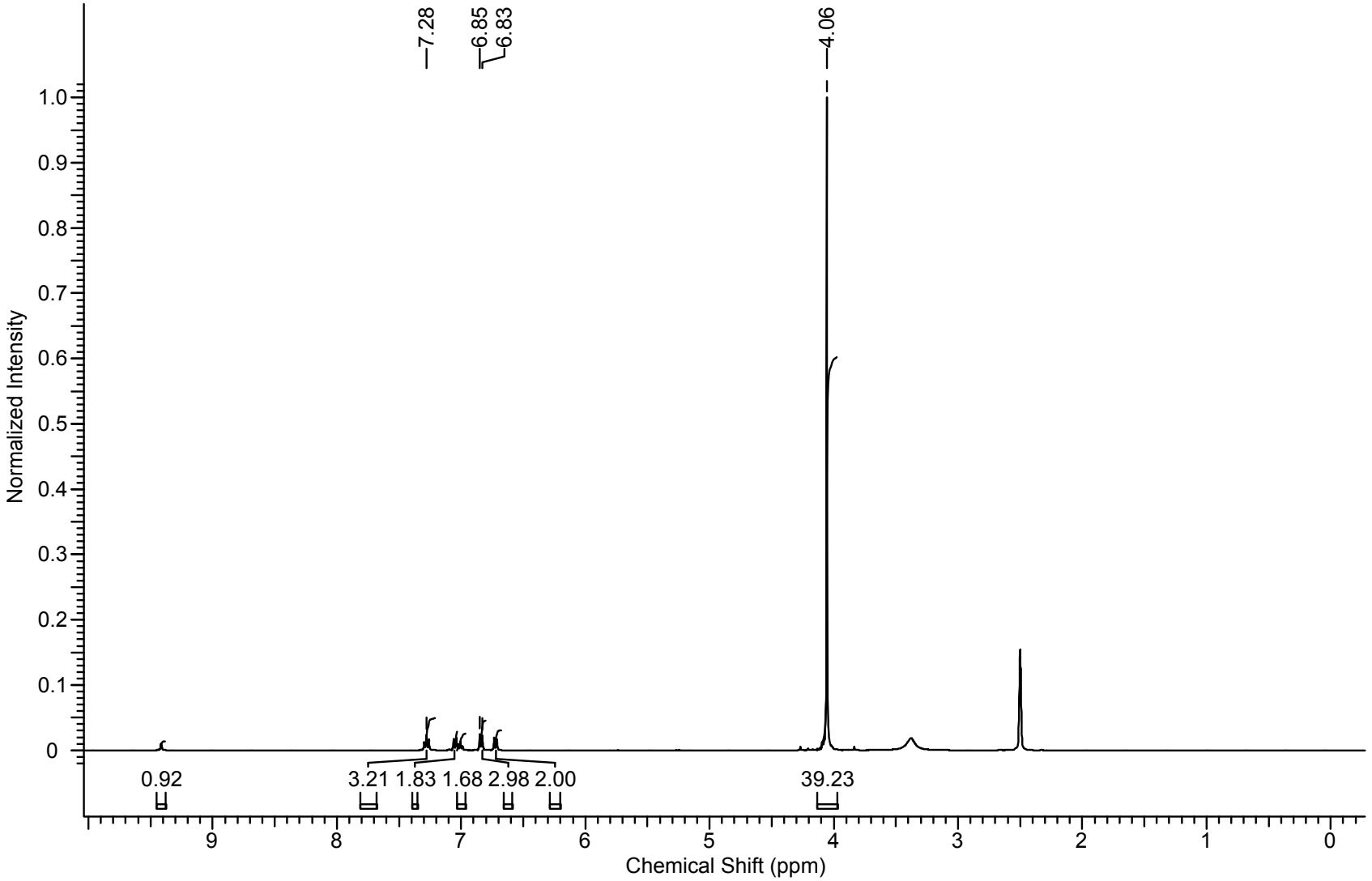
A mixture of 4-(3,5-dinitro-1*H*-pyrazol-4-yl)phenol (4f) and 3,5-dinitro-4-phenoxy-1*H*-pyrazole.



^{1}H NMR for quantitative analysis of the mixture of 4-(3,5-dinitro-1*H*-pyrazol-4-yl)phenol (4f) and 3,5-dinitro-4-phenoxy-1*H*-pyrazole.

The mixture (10.6 mg) was analyzed by ^{1}H NMR to quantify both isomers. CH_2I_2 was added as intern standard (20 µl, 0.321 mmol). Calculated yield of **4f** in the mixture was 4 mg and 3,5-dinitro-4-phenoxy-1*H*-pyrazole 6.6 mg. Recalculation to 105 mg yield after column chromatography gave 16% yield of **4f**.

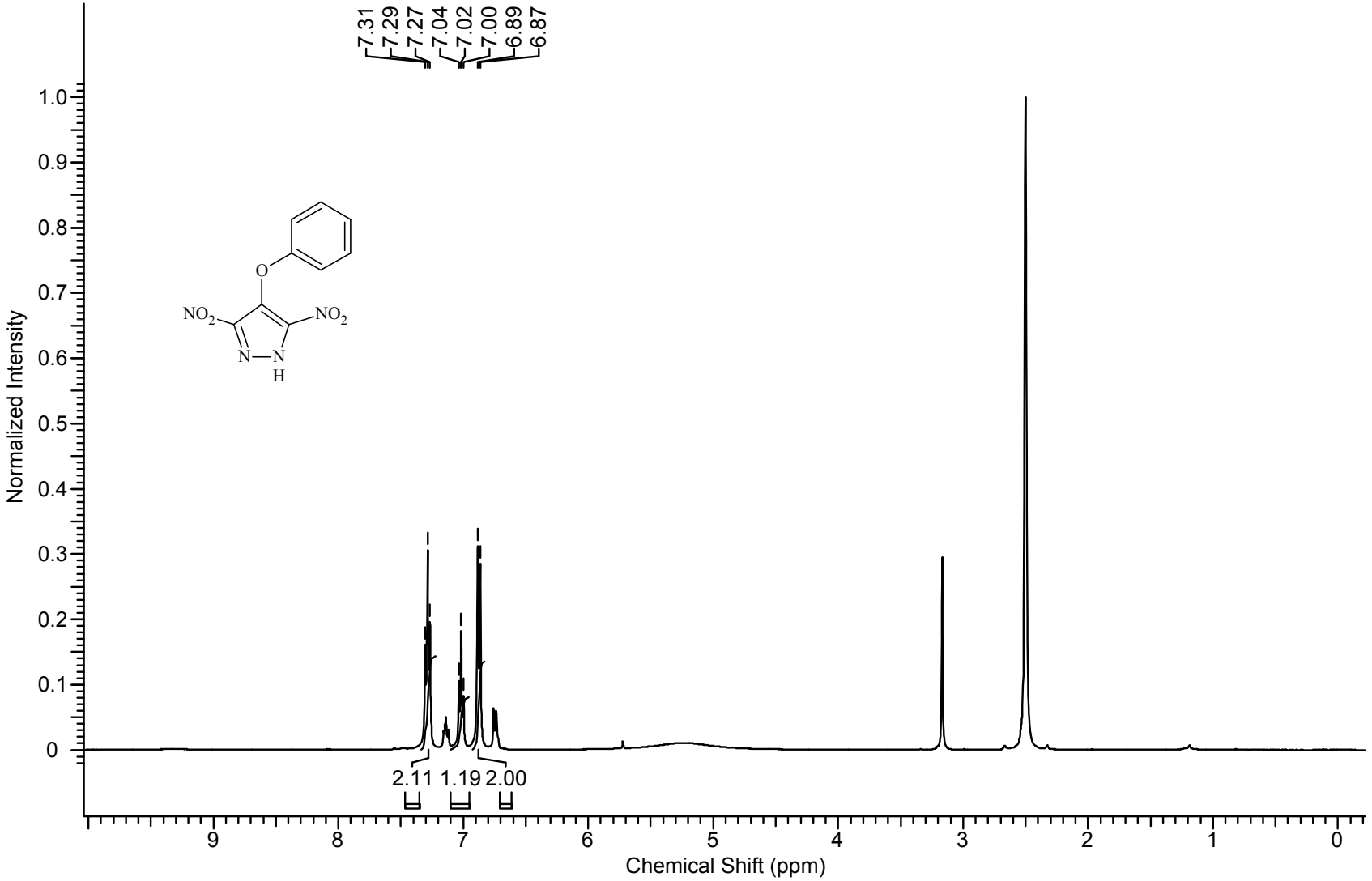
^{1}H NMR for quantitative analysis of the mixture of 4-(3,5-dinitro-1*H*-pyrazol-4-yl)phenol (4f) and 3,5-dinitro-4-phenoxy-1*H*-pyrazole.



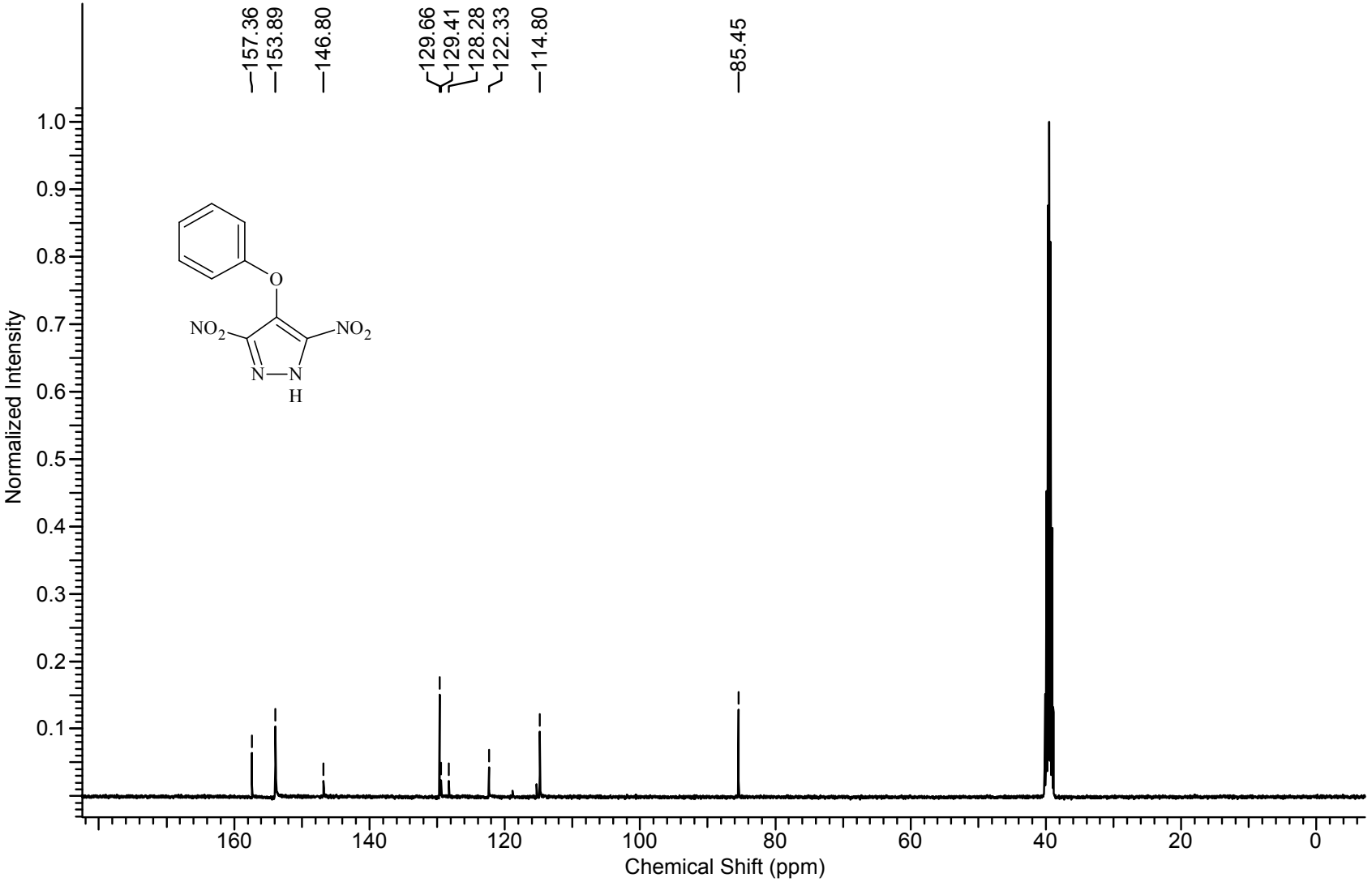
Coupling with phenol.

A mixture of pyrazole **2** (236 mg, 1.0 mmol), phenol (188 mg, 2.0 mmol), and K_3PO_4 (848 mg, 4.0 mmol) was placed into a vial and suspended in dioxane (4 mL) and water (1 mL). The reaction mixture was degassed with argon for 15 min. Then, precatalyst XPhos Pd G2 (16 mg, 0.02 mmol) was added and the vial was quickly closed and inserted into an oil bath preheated to 100 °C. The mixture was vigorously stirred at 100 °C for 20 h. Then, the vial was pulled out from the oil bath and acidified by hydrochloric acid to reach pH 1. Then the solvent was evaporated under reduced pressure to dryness. Product was isolated according procedure *Method B* and the mixture of 3,5-dinitro-4-phenoxy-1*H*-pyrazole and pyrazole **2** was analysed by NMR. ^{1}H NMR (400 MHz, DMSO- d_6) δ: 7.29 (t, J=7.8 Hz, 2 H), 7.02 (t, J=7.6 Hz, 1 H), 6.88 (d, J=7.8 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.4, 153.9 (impurity: pyrazole **2**), 146.8 129.7, 128.3, 122.3, 114.8, 85.5 (impurity: pyrazole **2**).

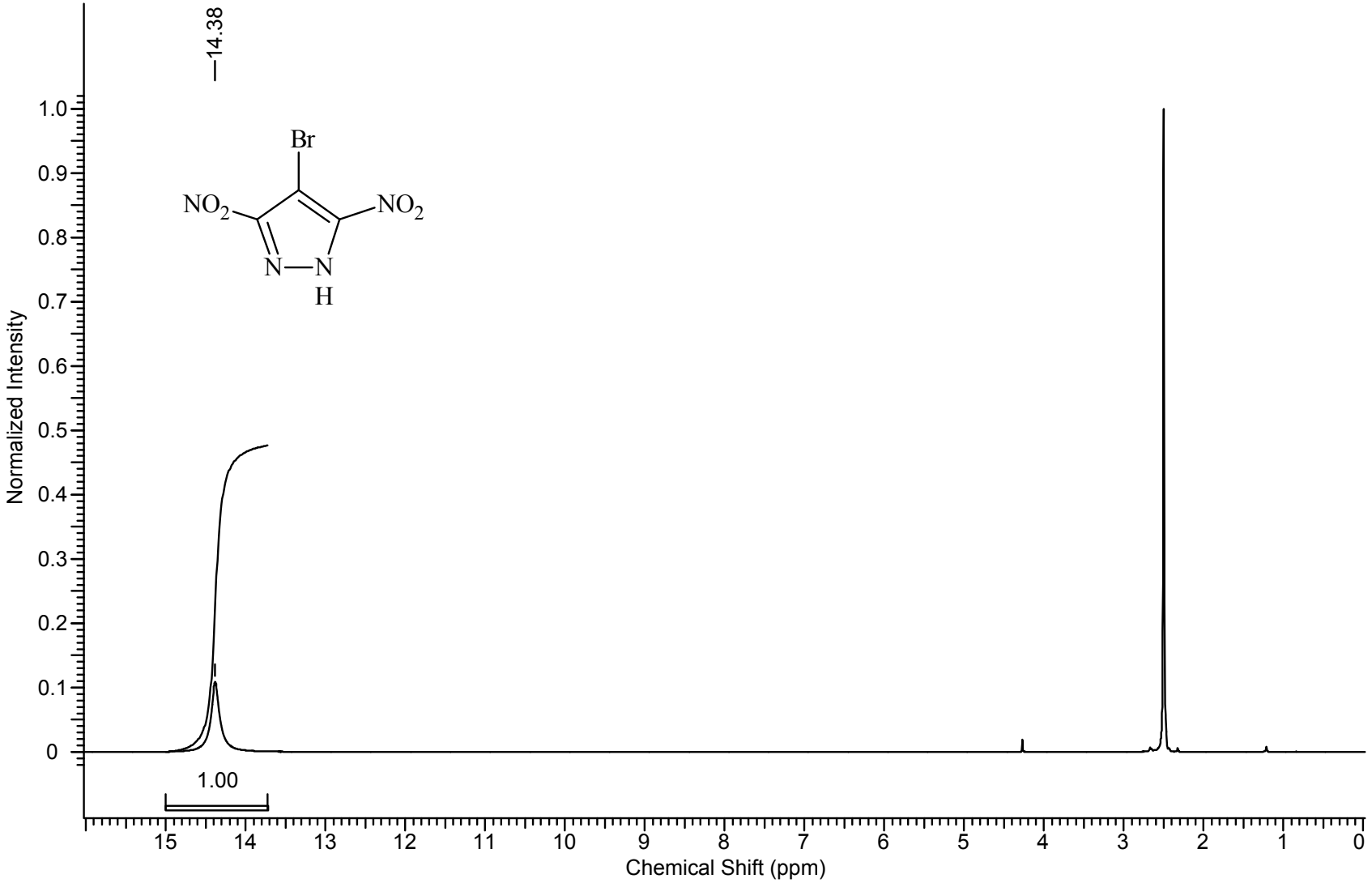
3,5-dinitro-4-phenoxy-1*H*-pyrazole.



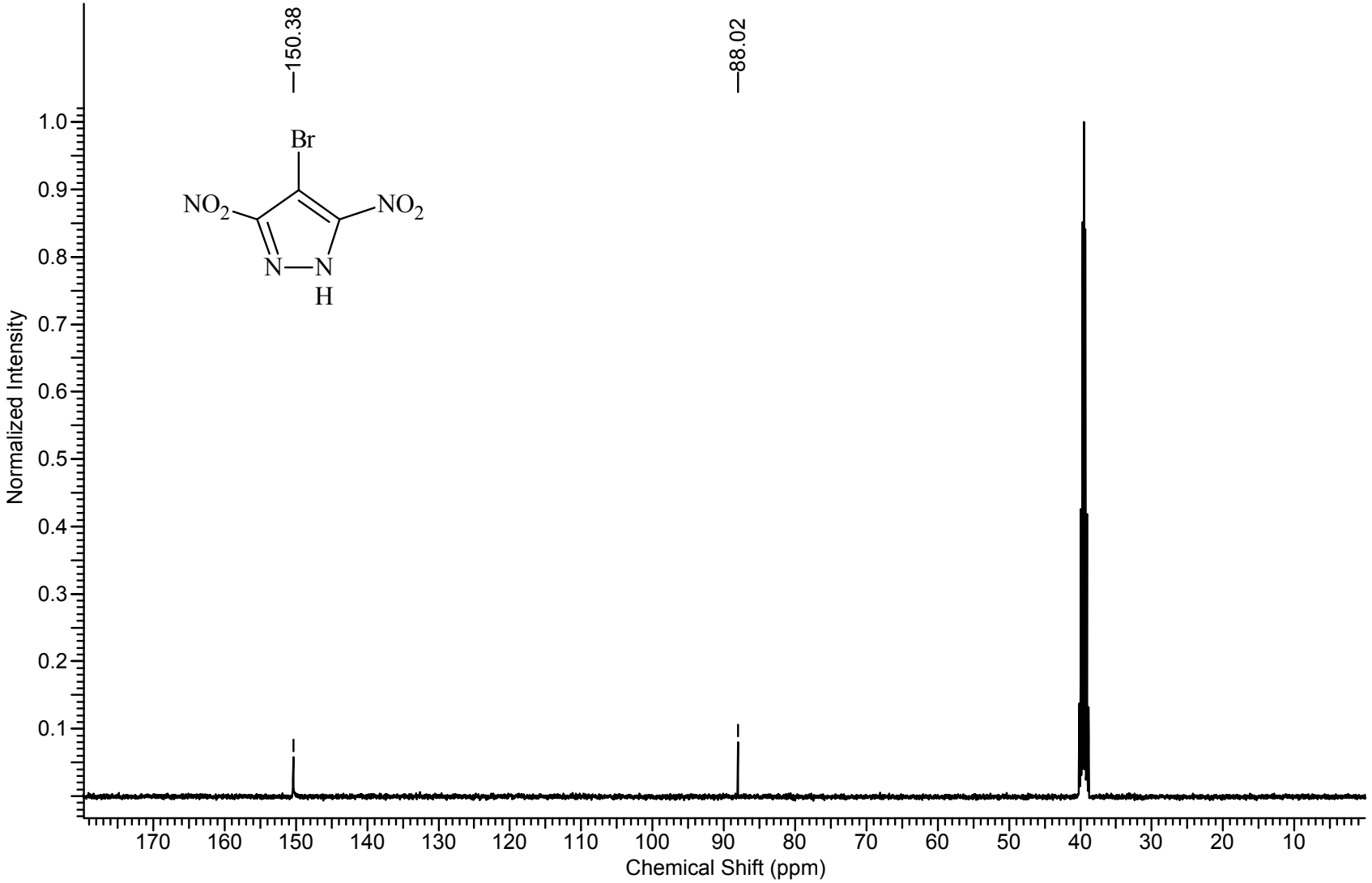
3,5-dinitro-4-phenoxy-1*H*-pyrazole.



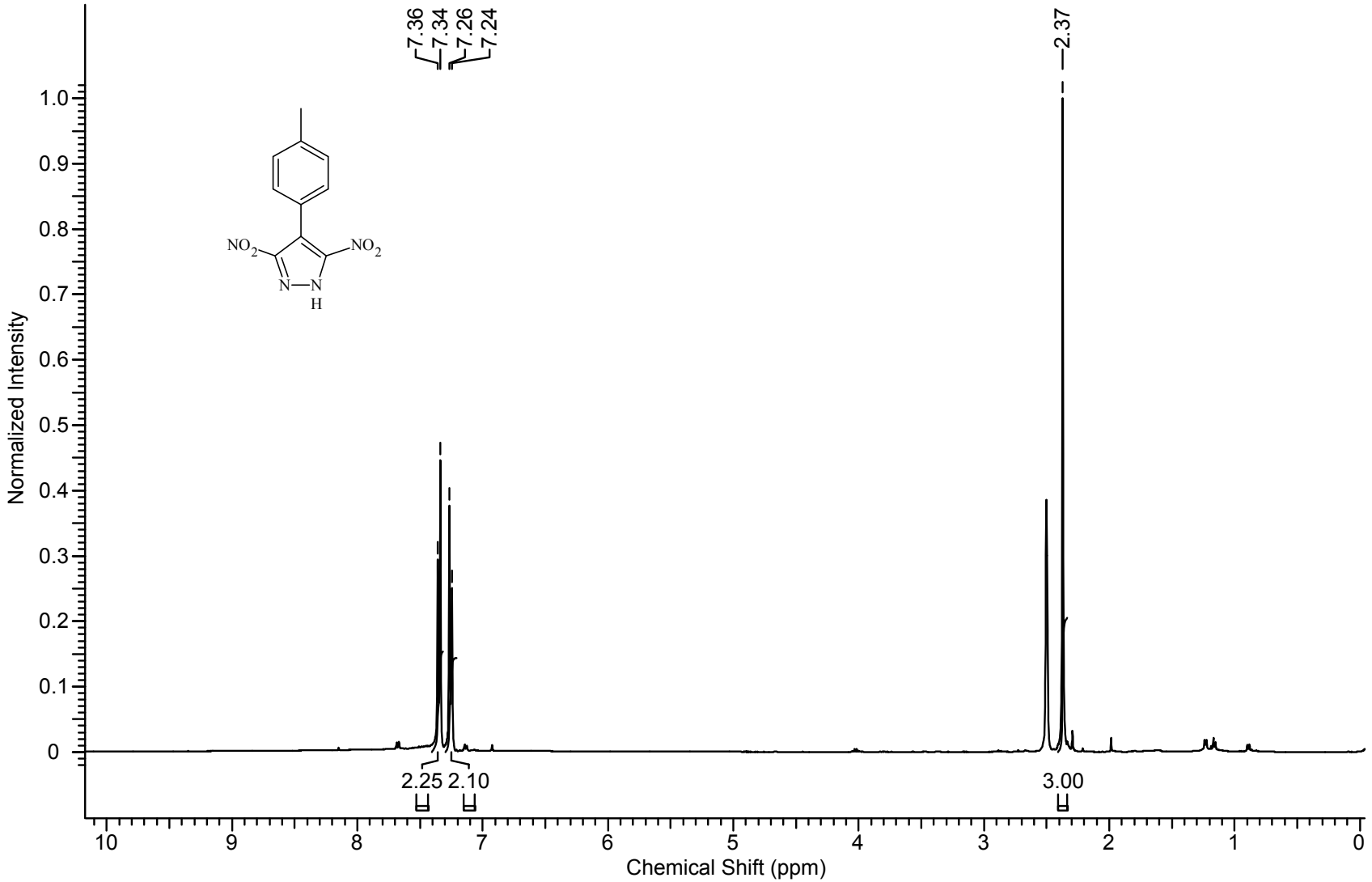
4-bromo-3,5-dinitro-1*H*-pyrazole (2).



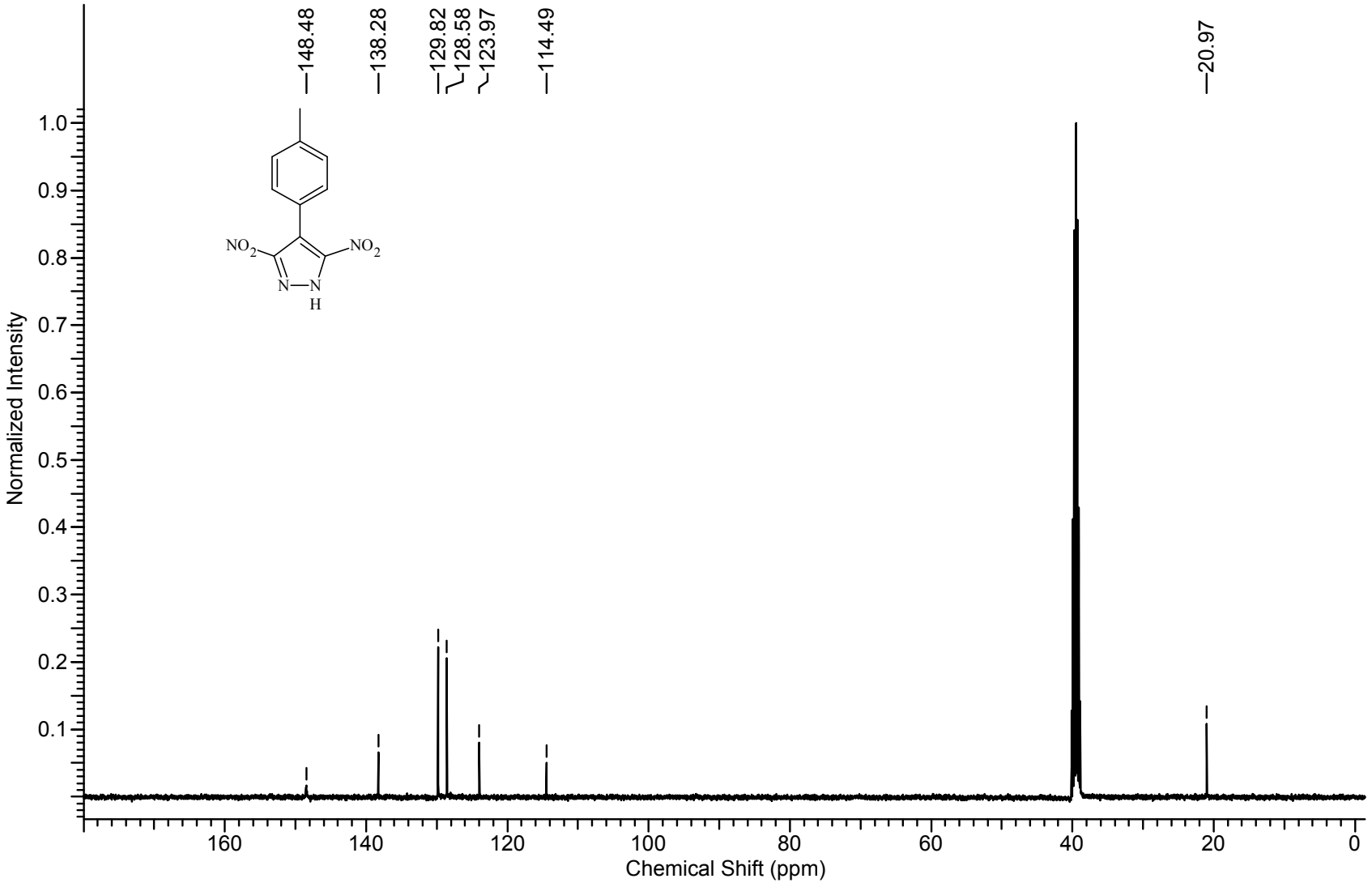
4-bromo-3,5-dinitro-1*H*-pyrazole (2).



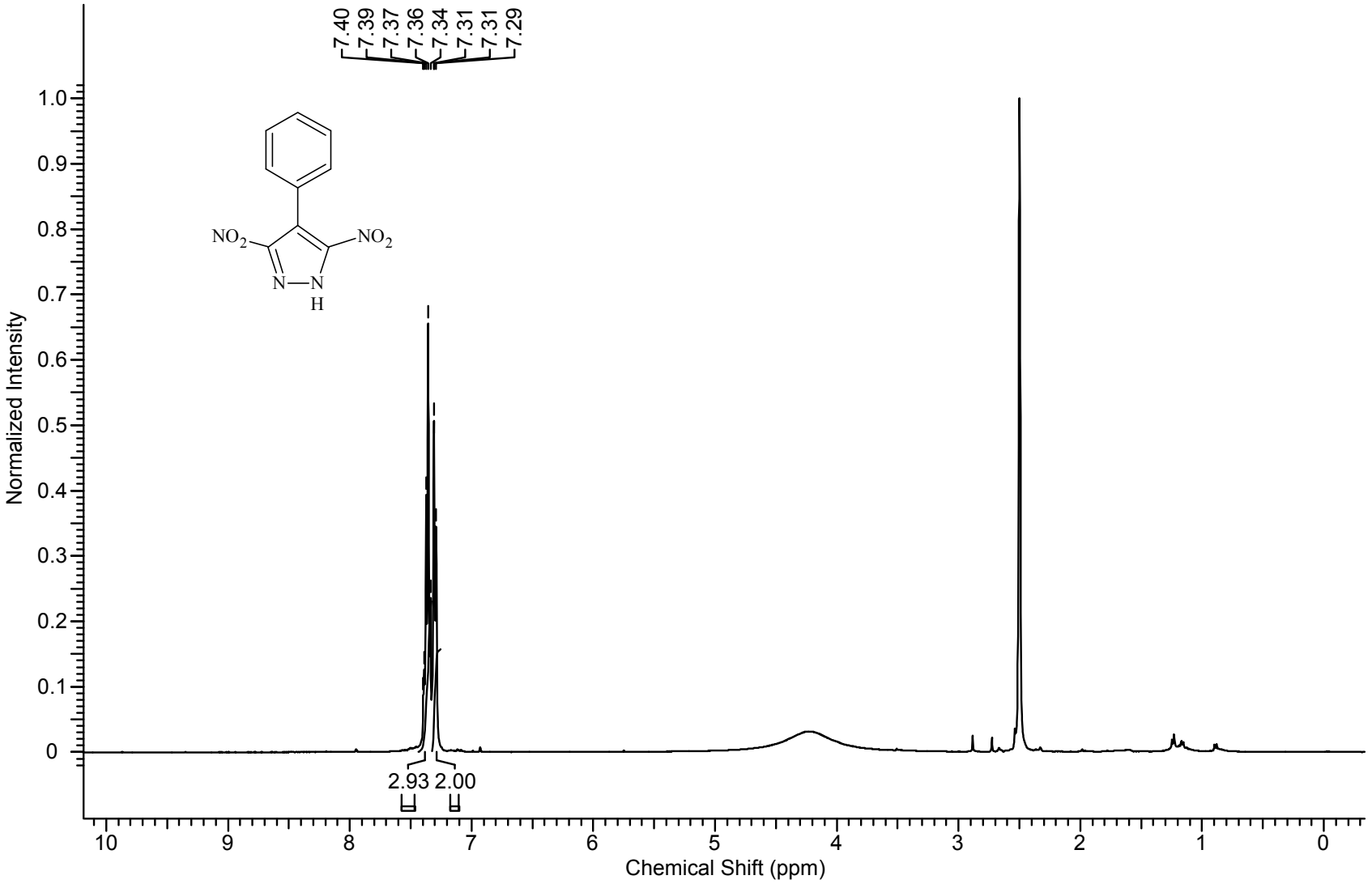
3,5-dinitro-4-(*p*-tolyl)-1*H*-pyrazole (4a).



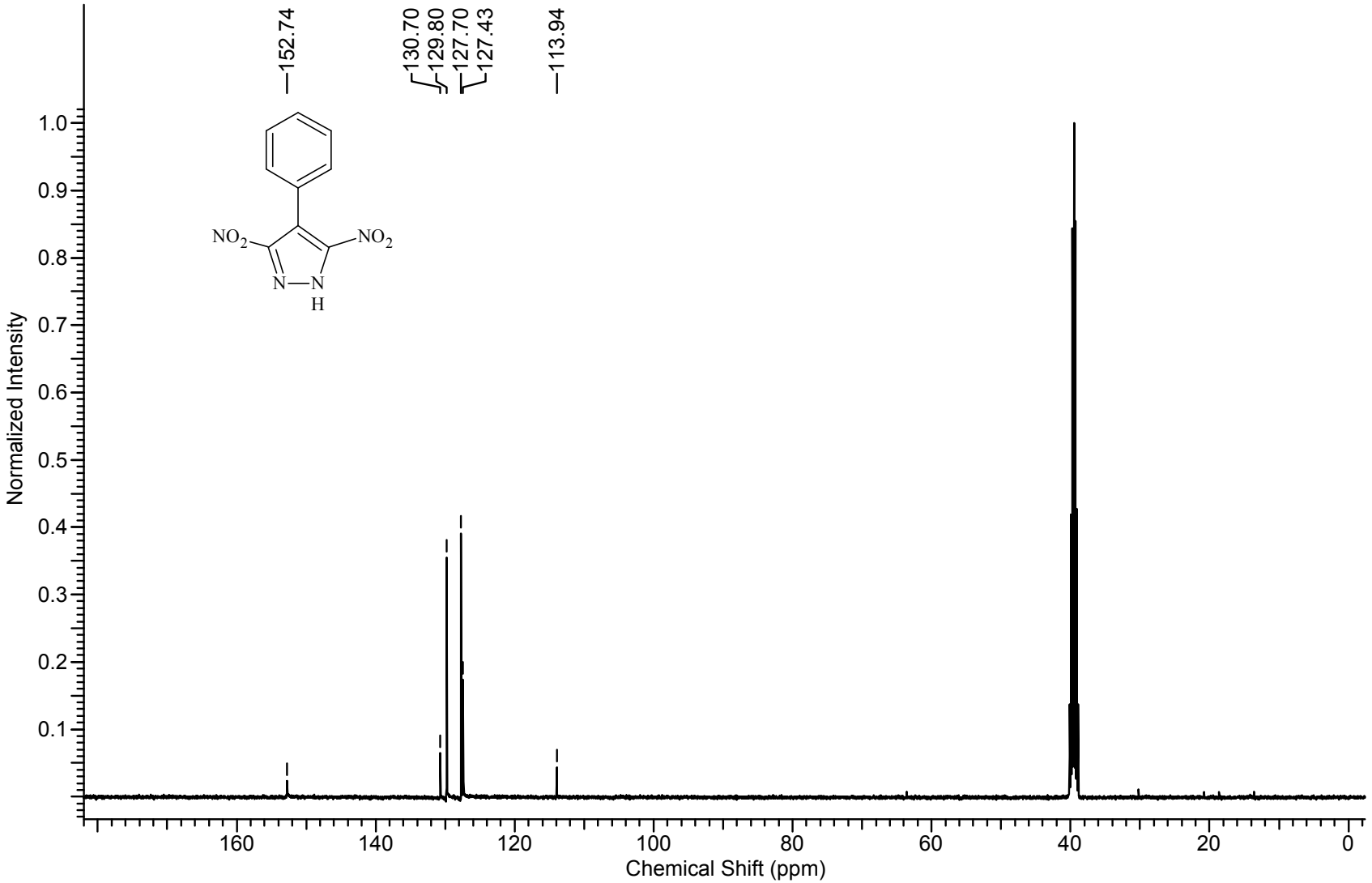
3,5-dinitro-4-(*p*-tolyl)-1*H*-pyrazole (4a).



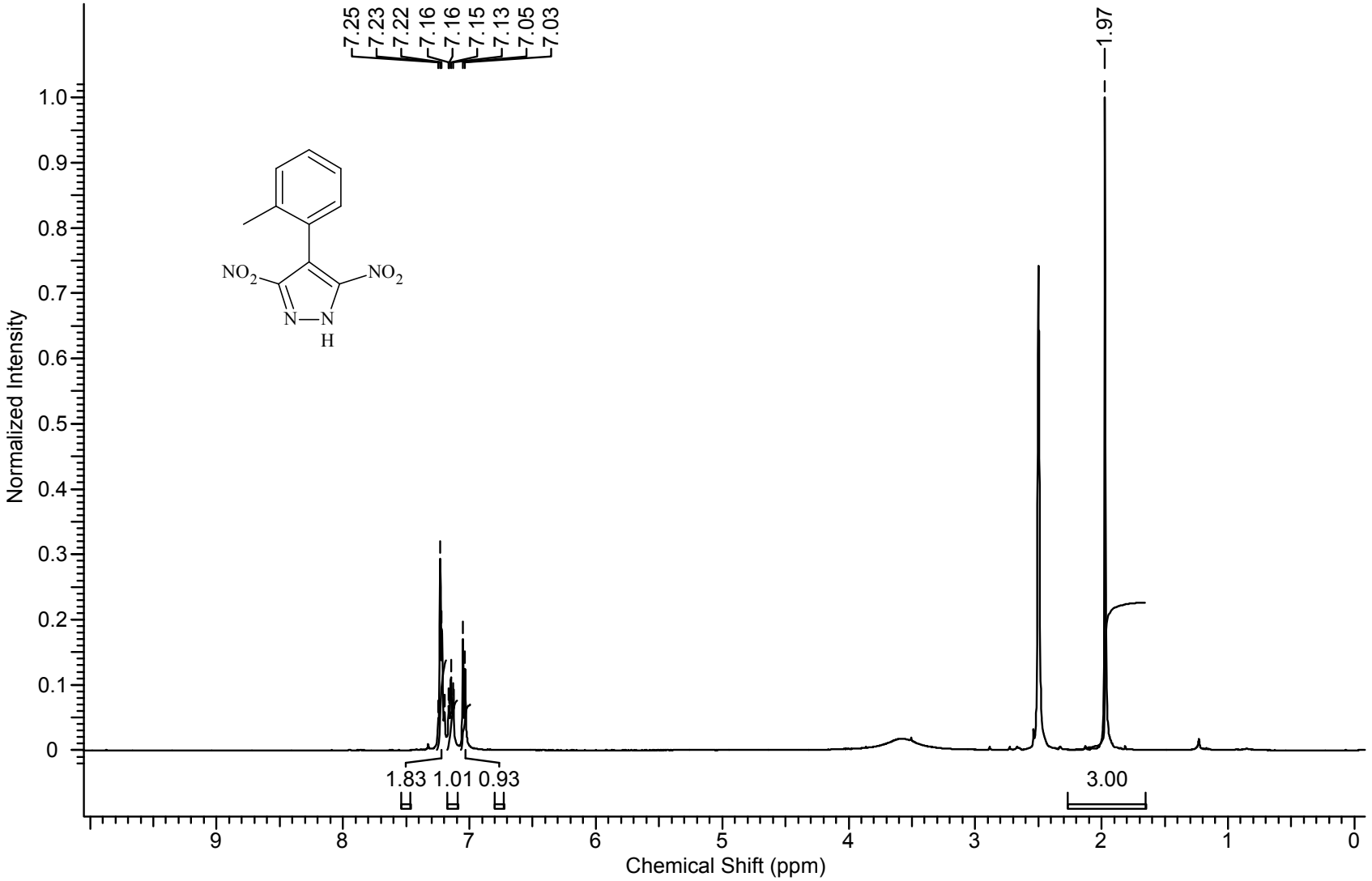
3,5-dinitro-4-phenyl-1*H*-pyrazole (4b).



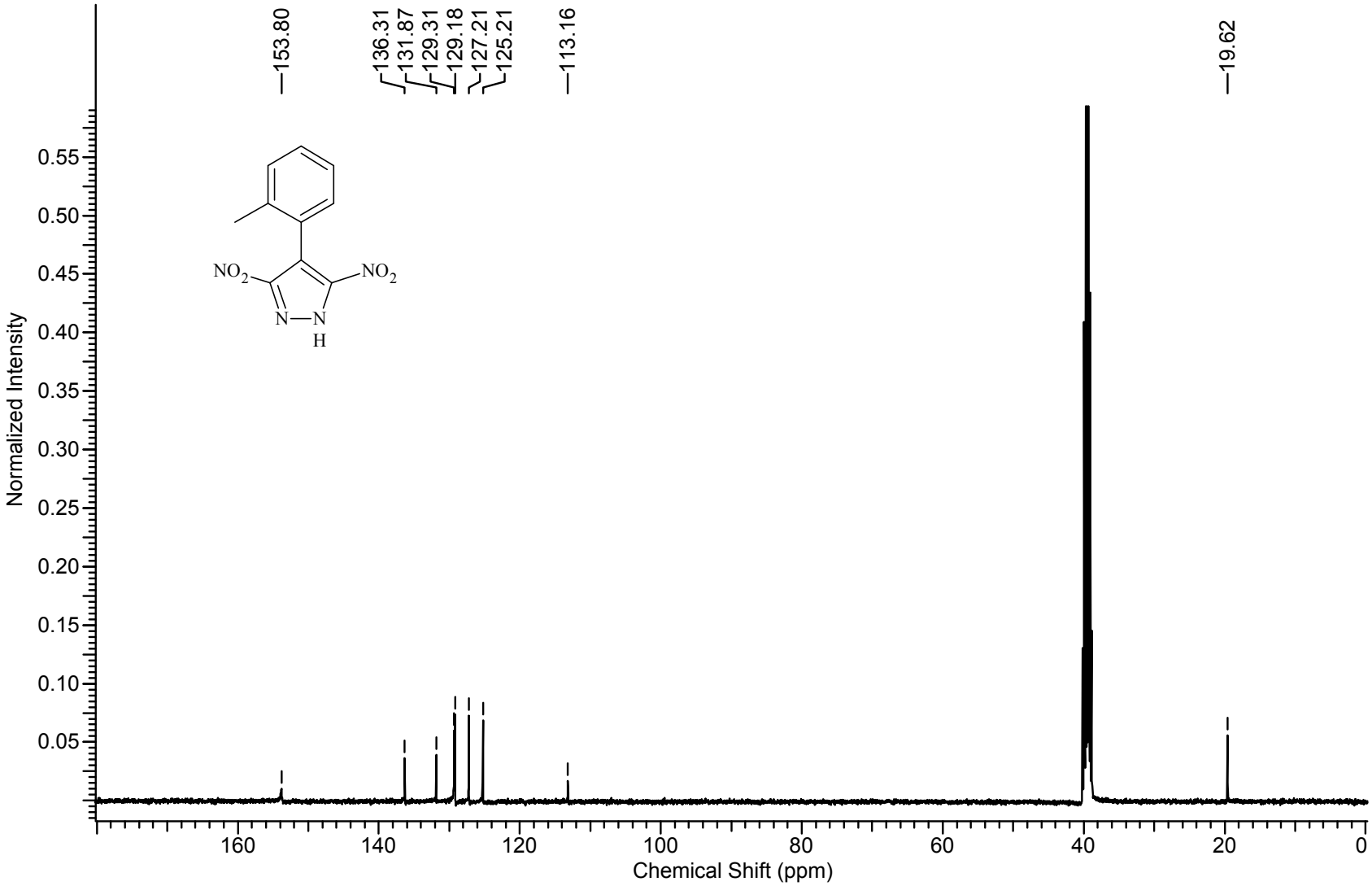
3,5-dinitro-4-phenyl-1*H*-pyrazole (4b).



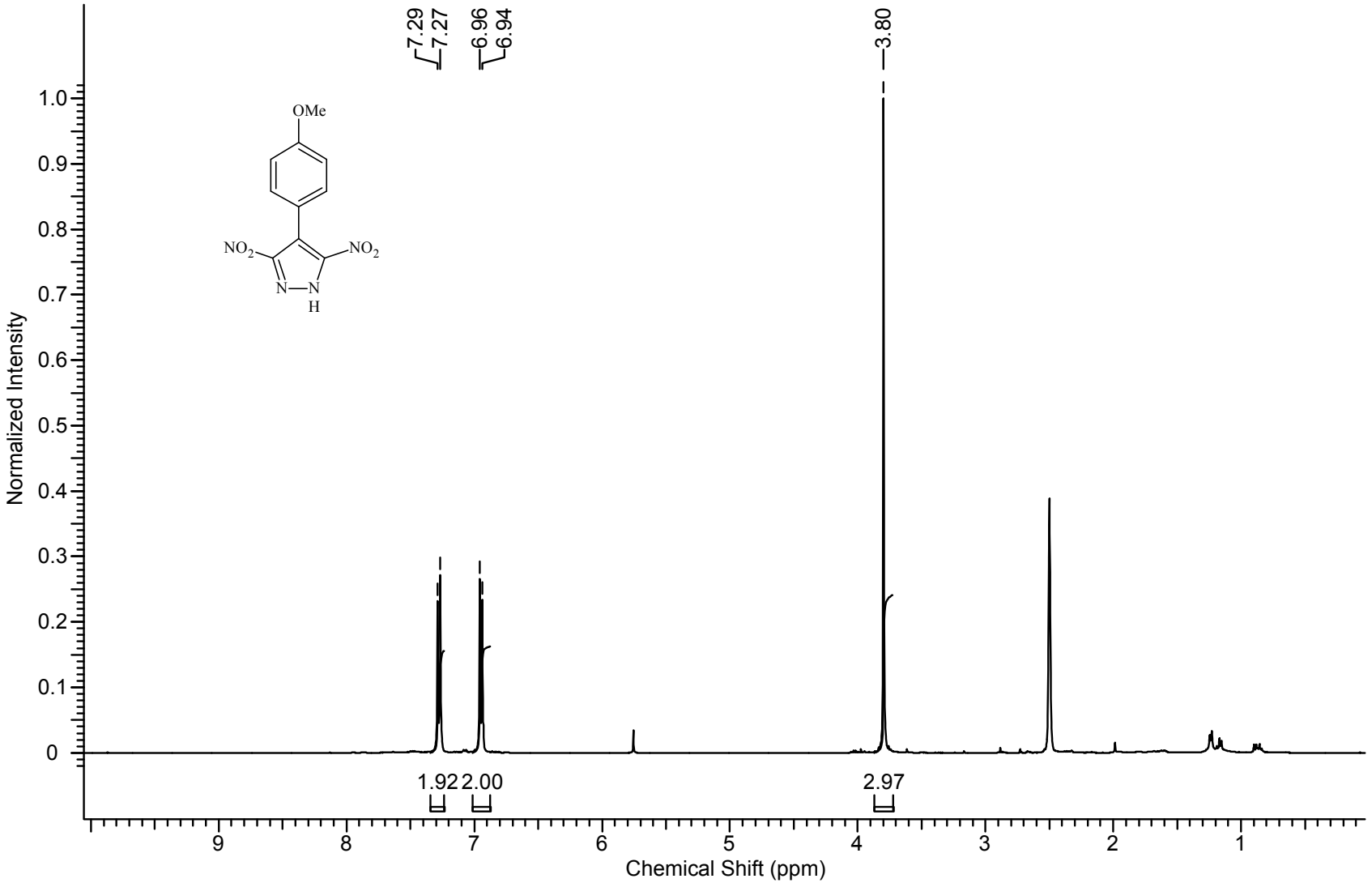
3,5-dinitro-4-(*o*-tolyl)-1*H*-pyrazole (4c).



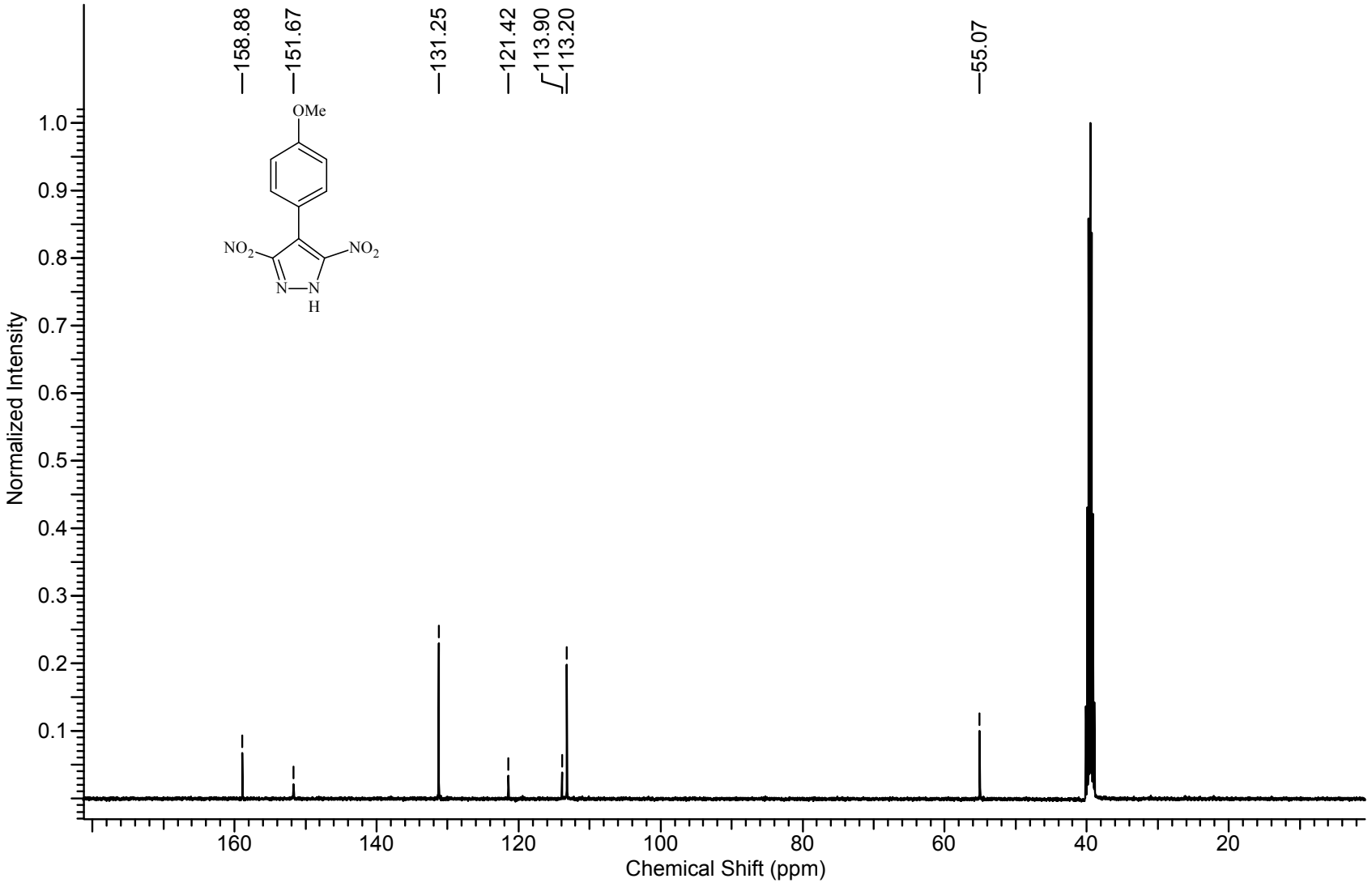
3,5-dinitro-4-(*o*-tolyl)-1*H*-pyrazole (4c).



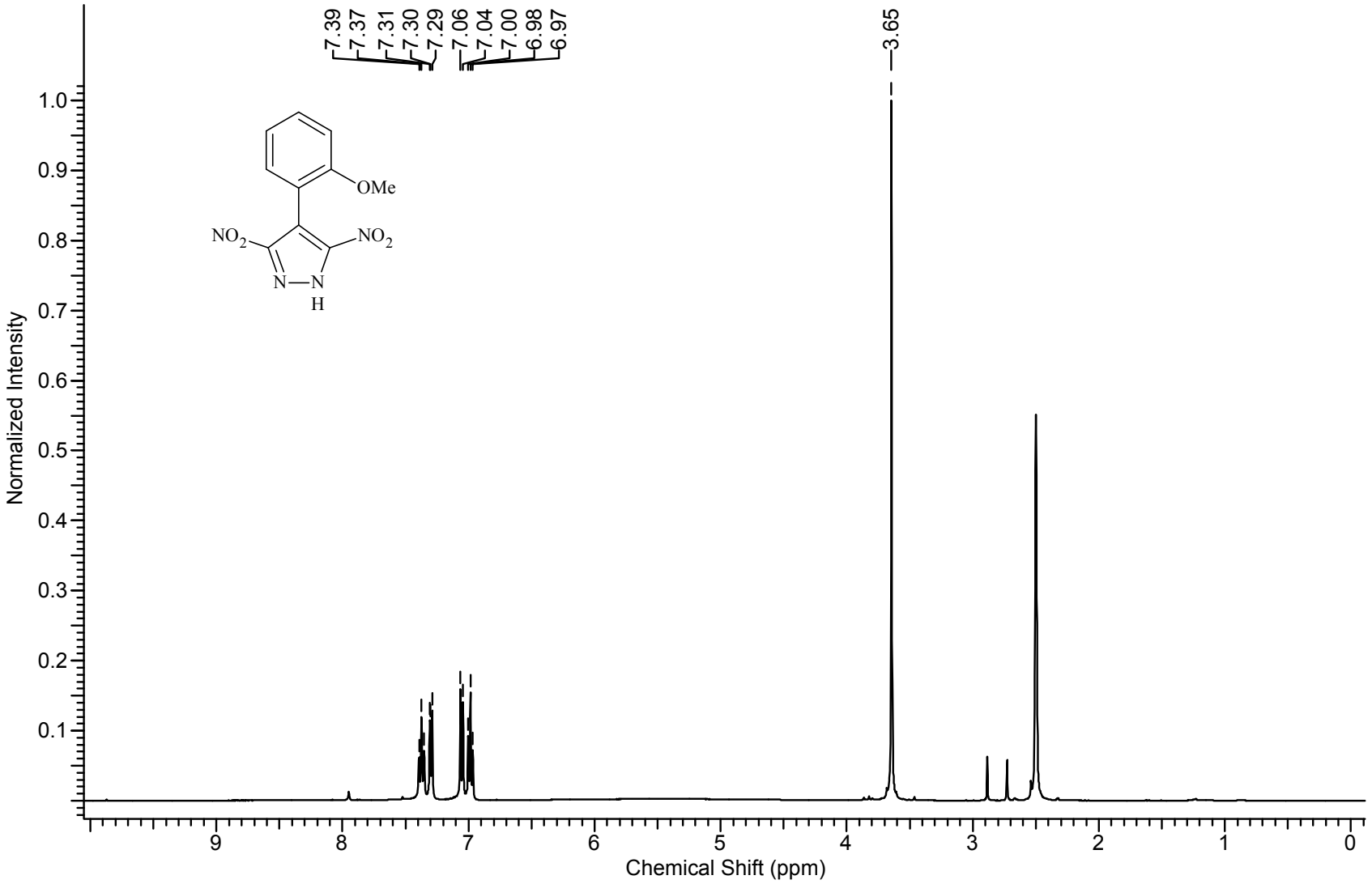
4-(4-methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4e).



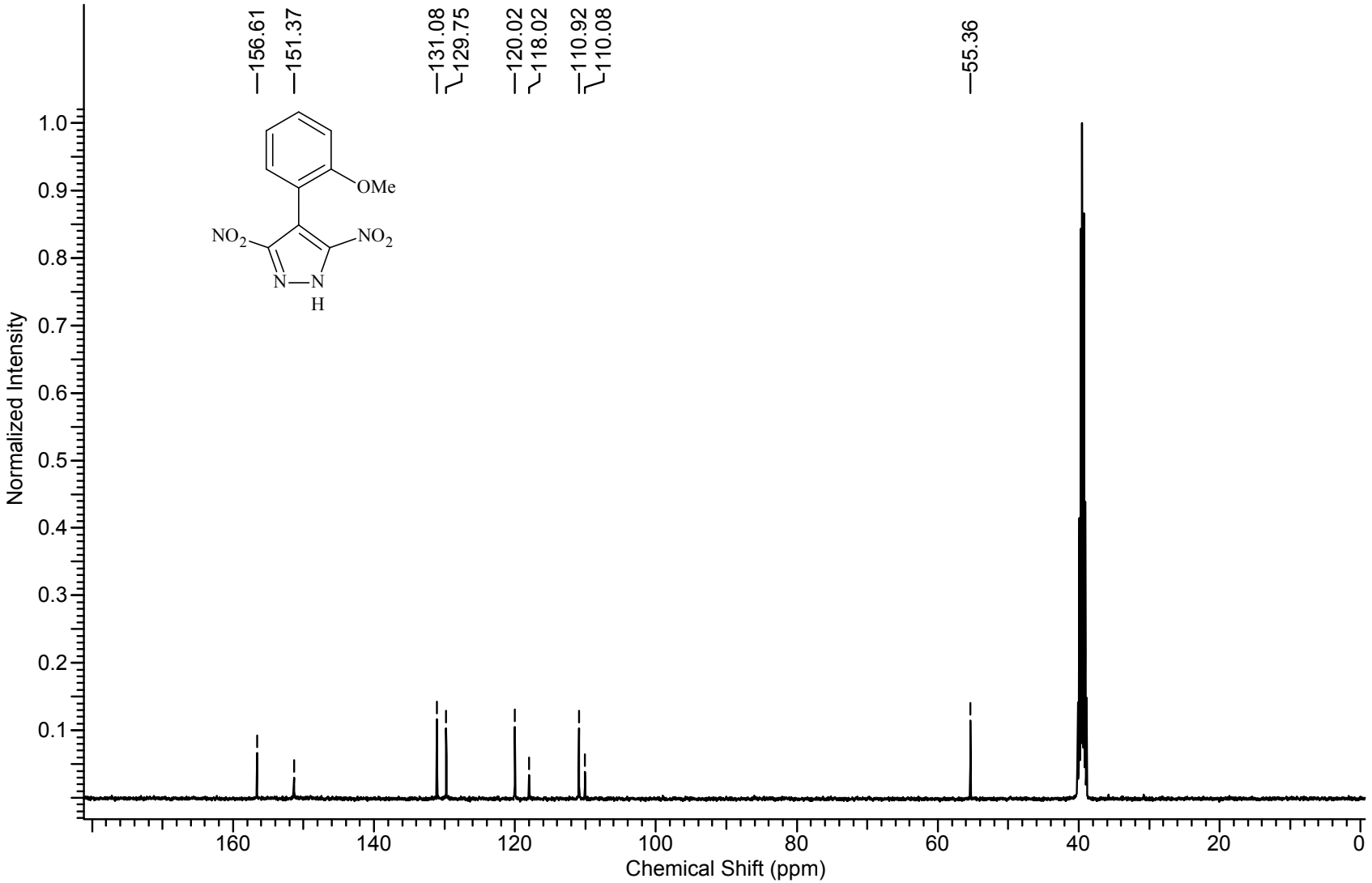
4-(4-methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4e).



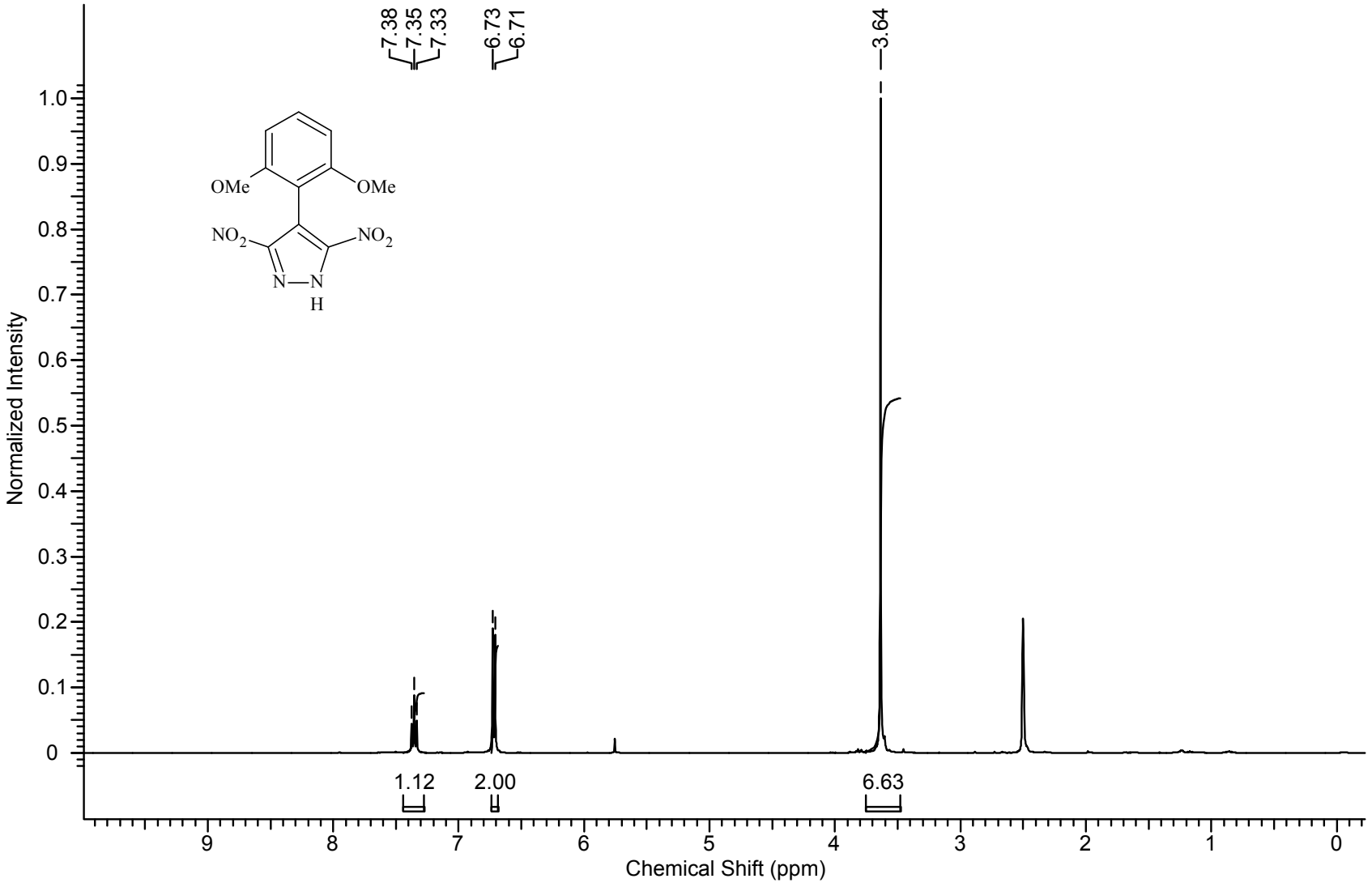
4-(2-methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4g).



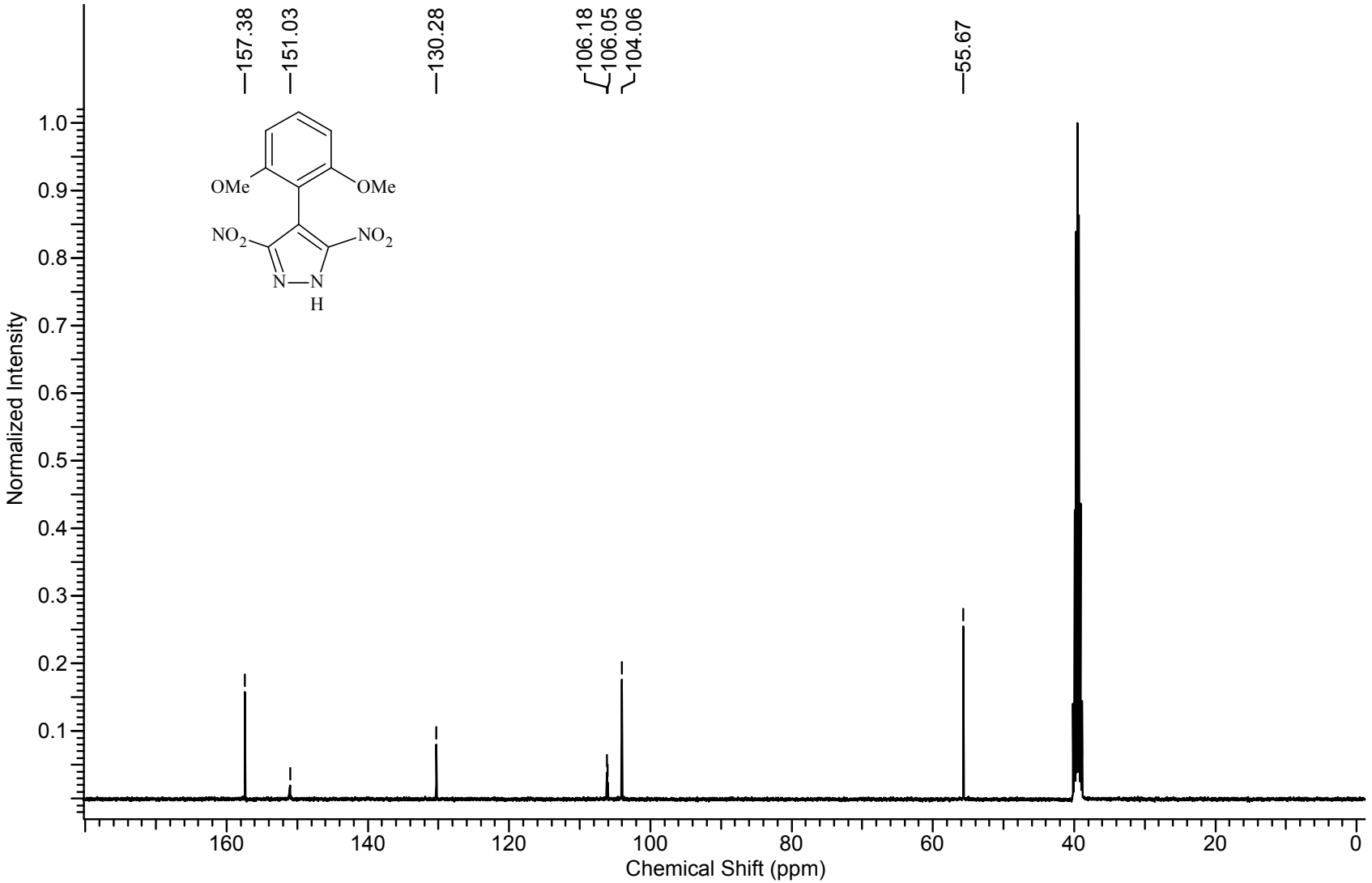
4-(2-methoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4g).



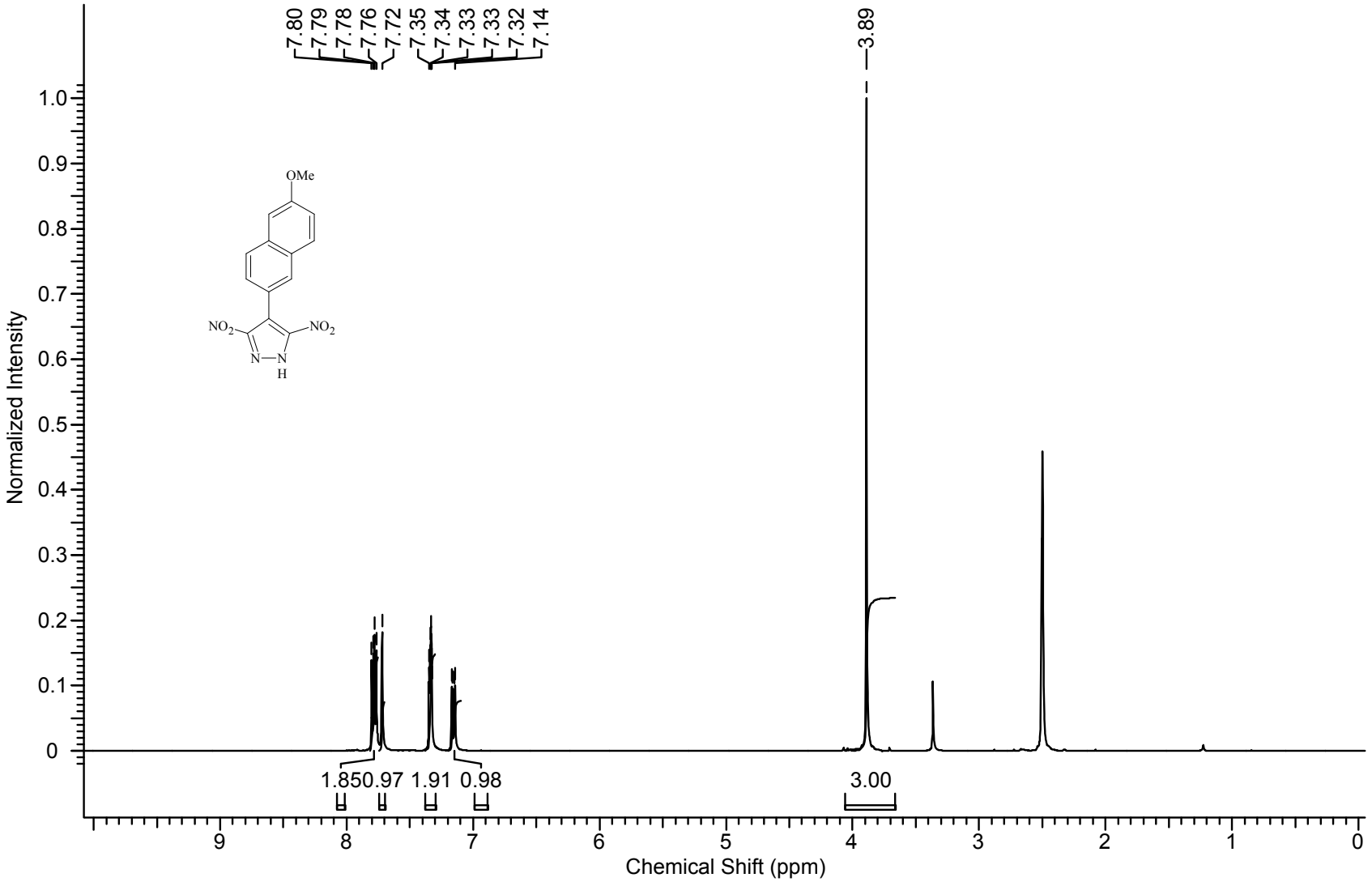
4-(2,6-dimethoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4h).



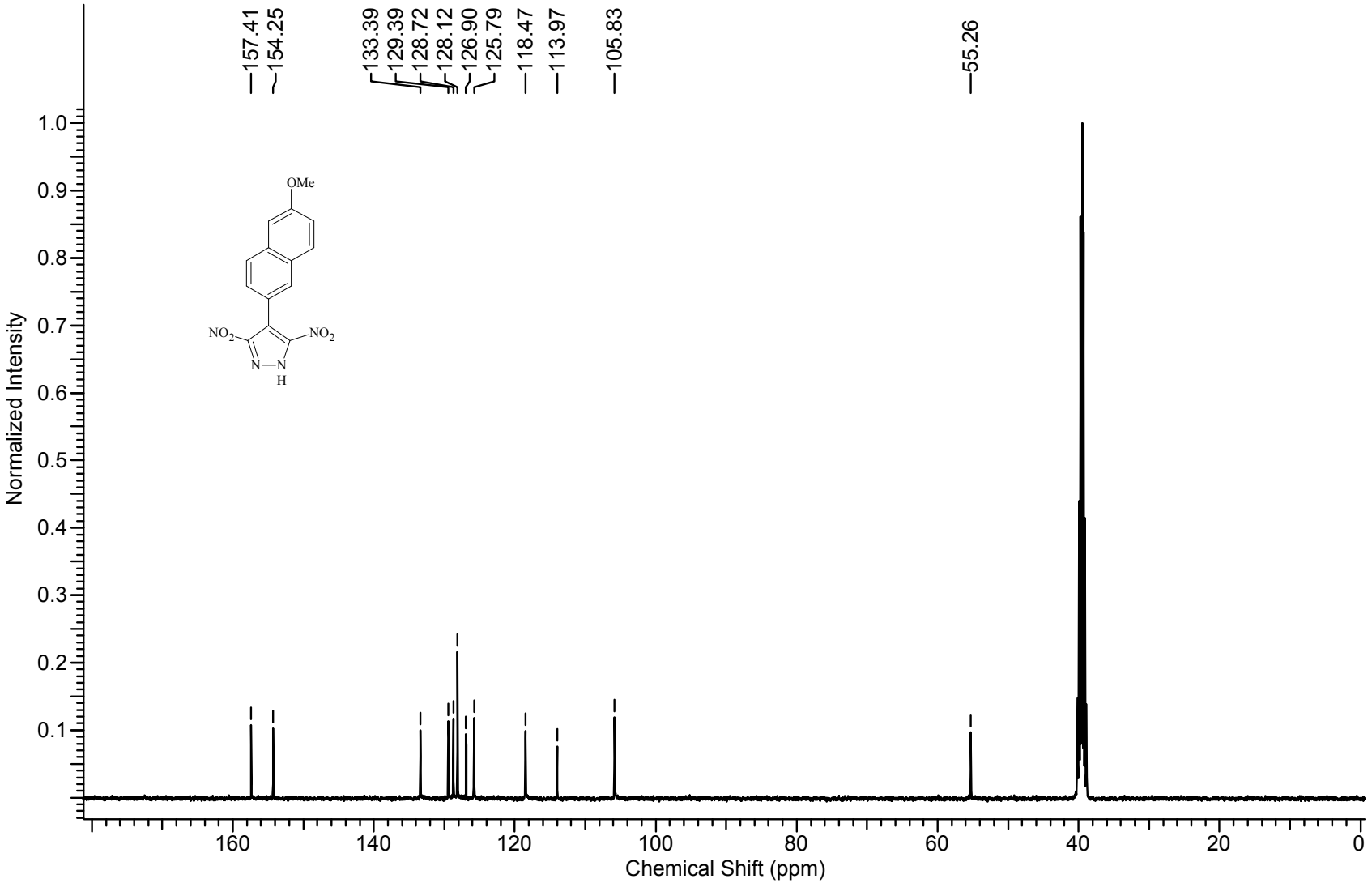
4-(2,6-dimethoxyphenyl)-3,5-dinitro-1*H*-pyrazole (4h).



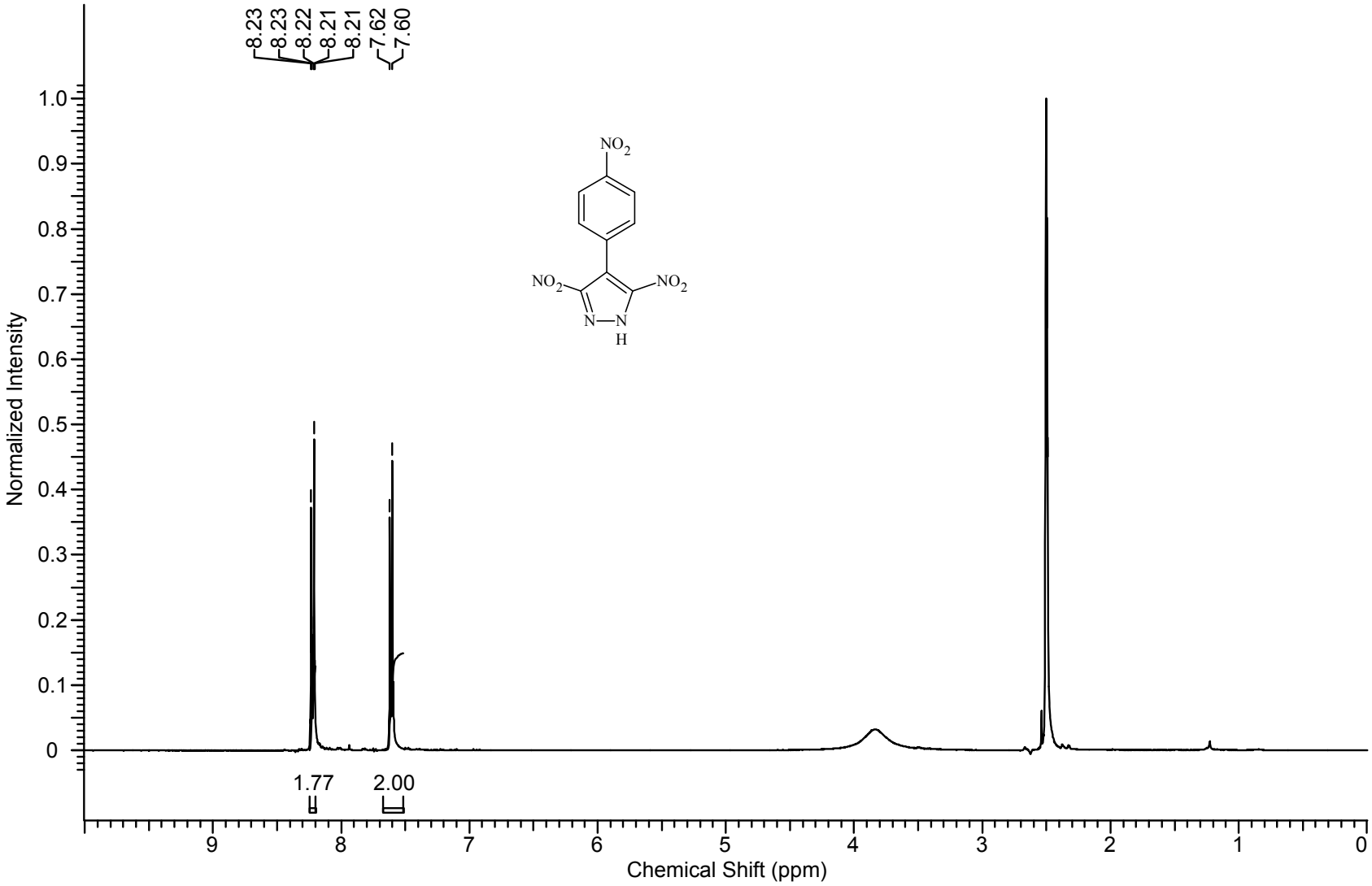
4-(6-methoxynaphtalen-2-yl)-3,5-dinitro-1*H*-pyrazole (4i).



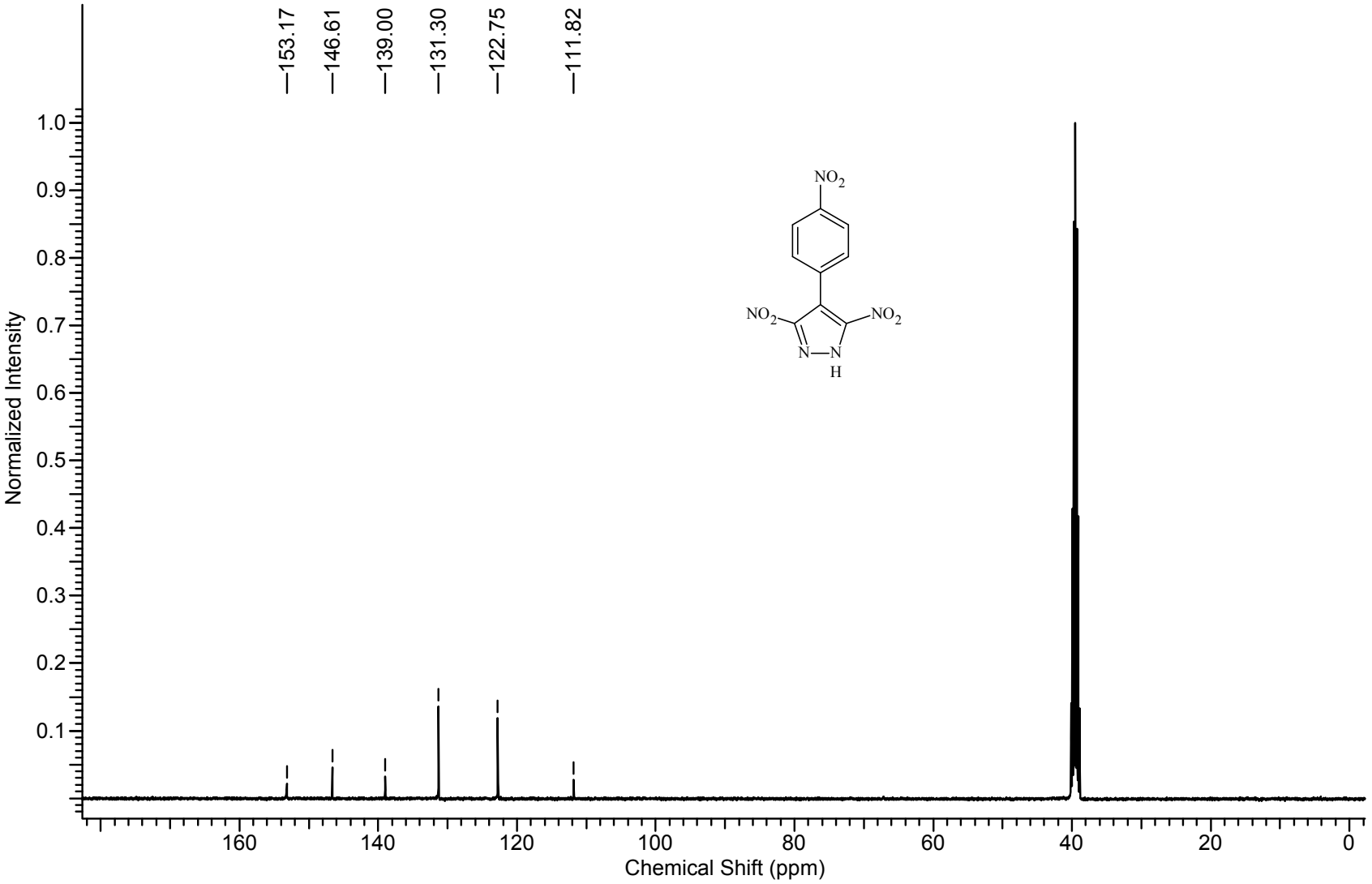
4-(6-methoxynaphtalen-2-yl)-3,5-dinitro-1*H*-pyrazole (4i).



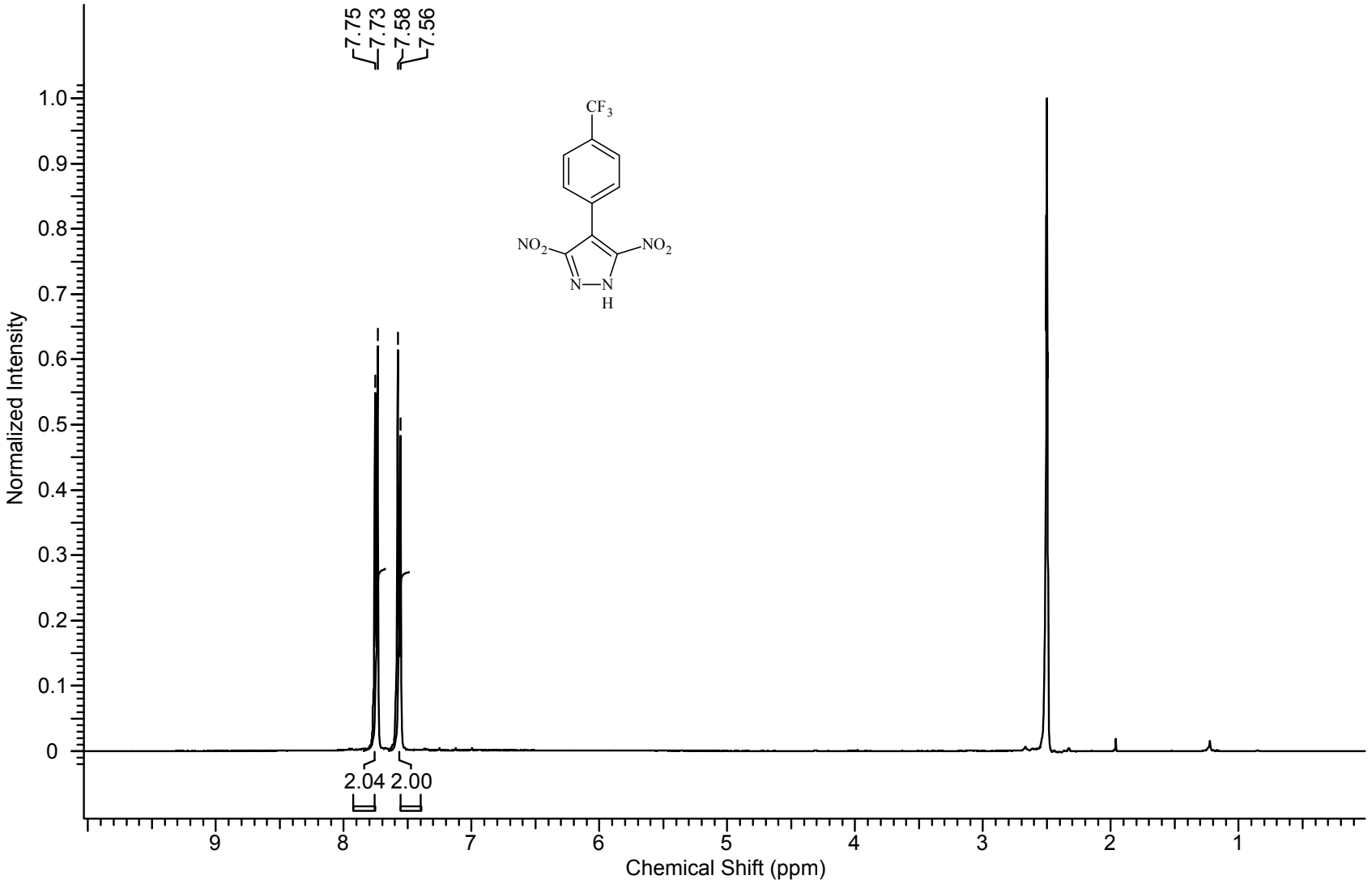
3,5-dinitro-4-(4-nitropenyl)-1*H*-pyrazole (4j).



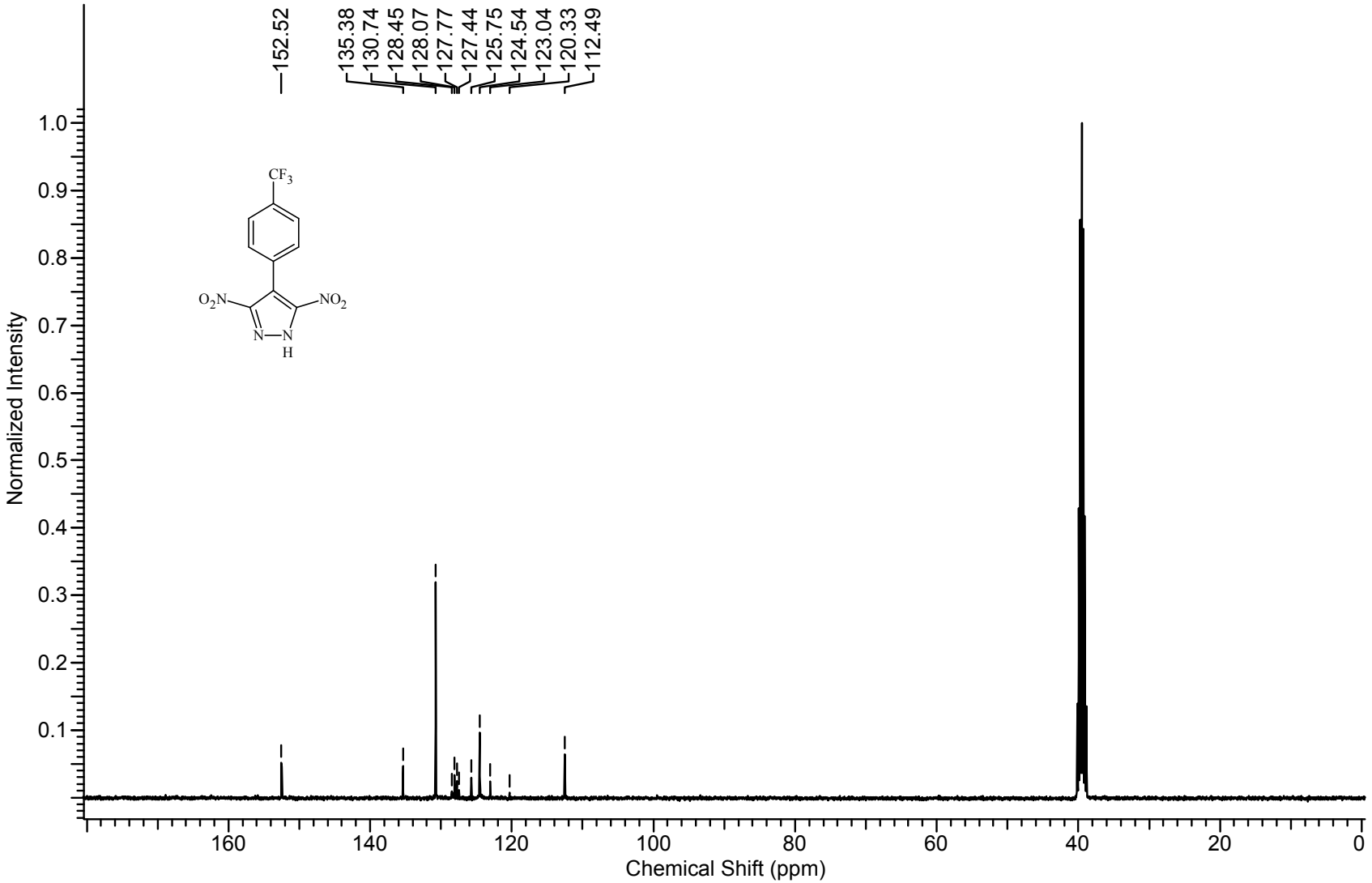
3,5-dinitro-4-(4-nitropenyl)-1*H*-pyrazole (4j).



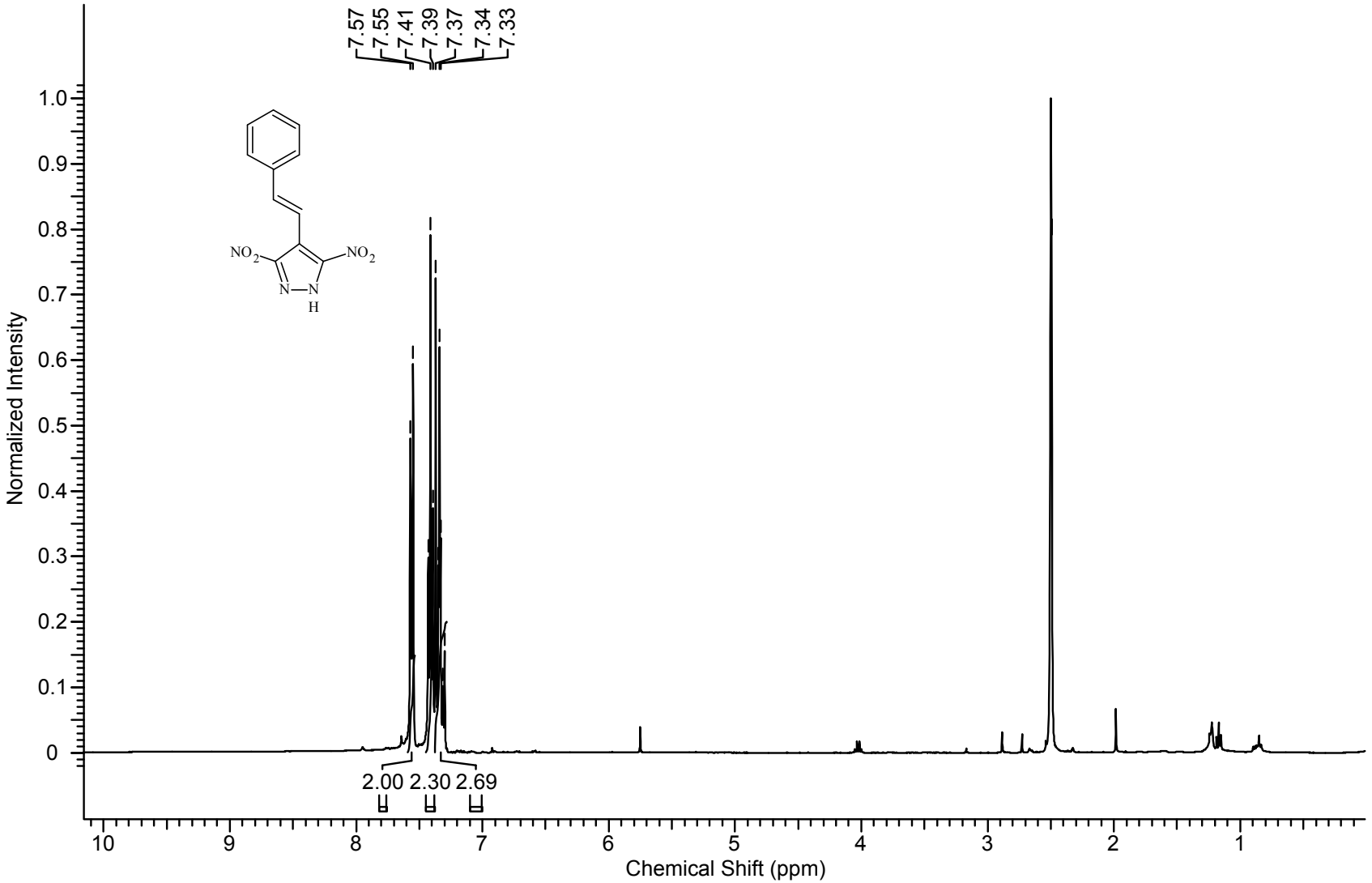
3,5-dinitro-4-(4-trifluoromethyl)phenyl)-1*H*-pyrazole (4k).



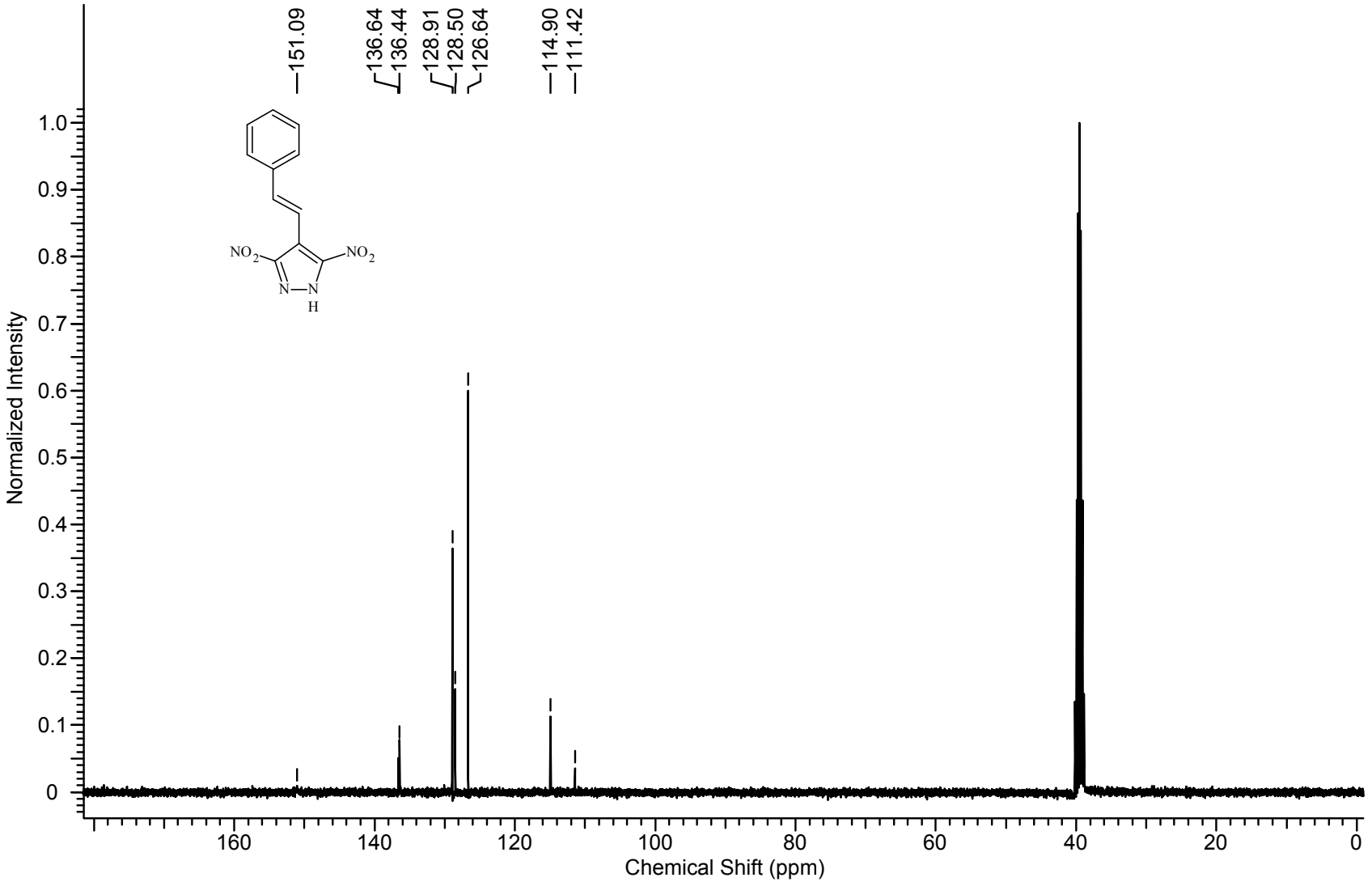
3,5-dinitro-4-(4-trifluoromethyl)phenyl-1*H*-pyrazole (4k).



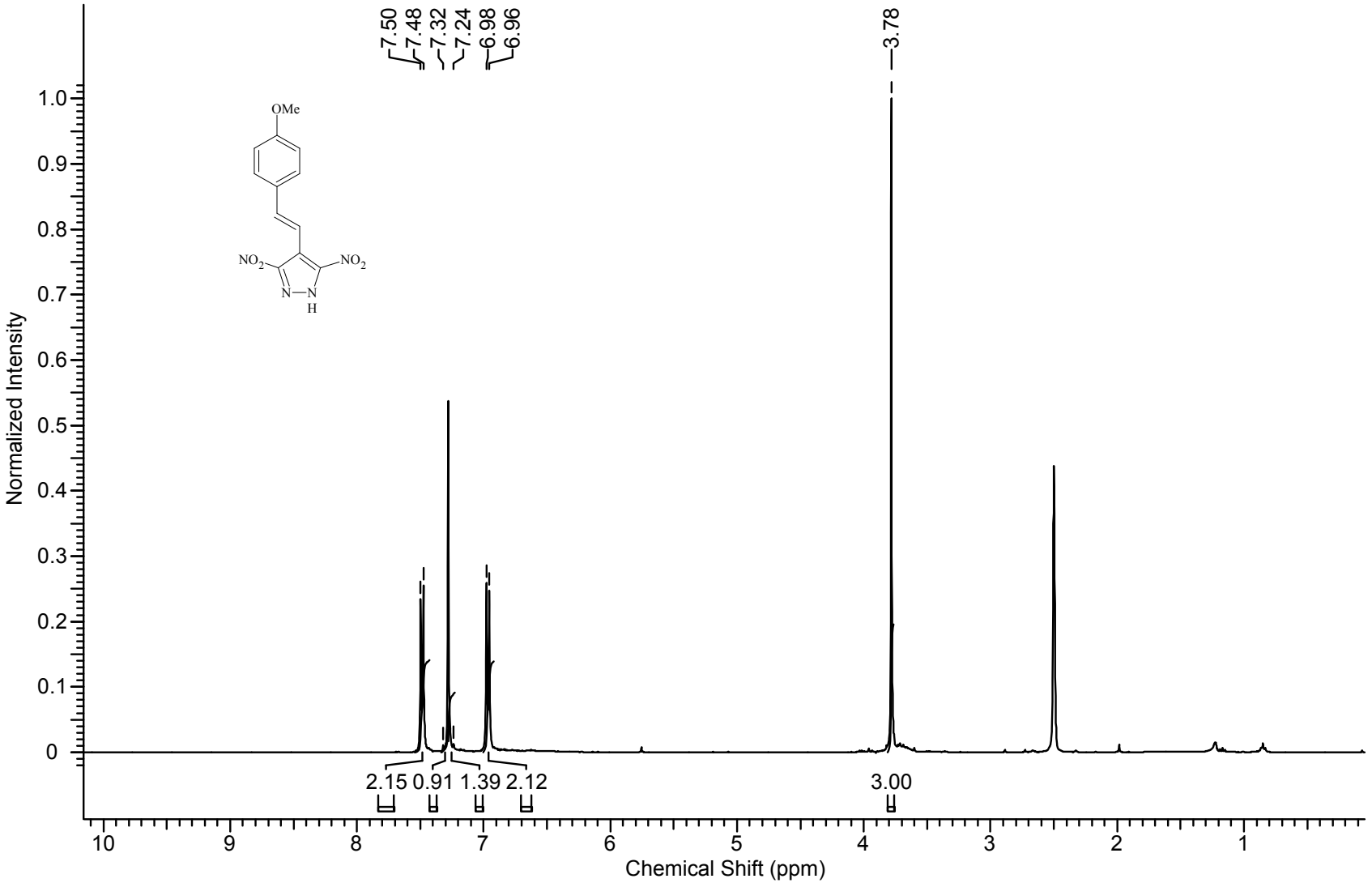
(*E*)-3,5-dinitro-4-styryl-1*H*-pyrazole (4l).



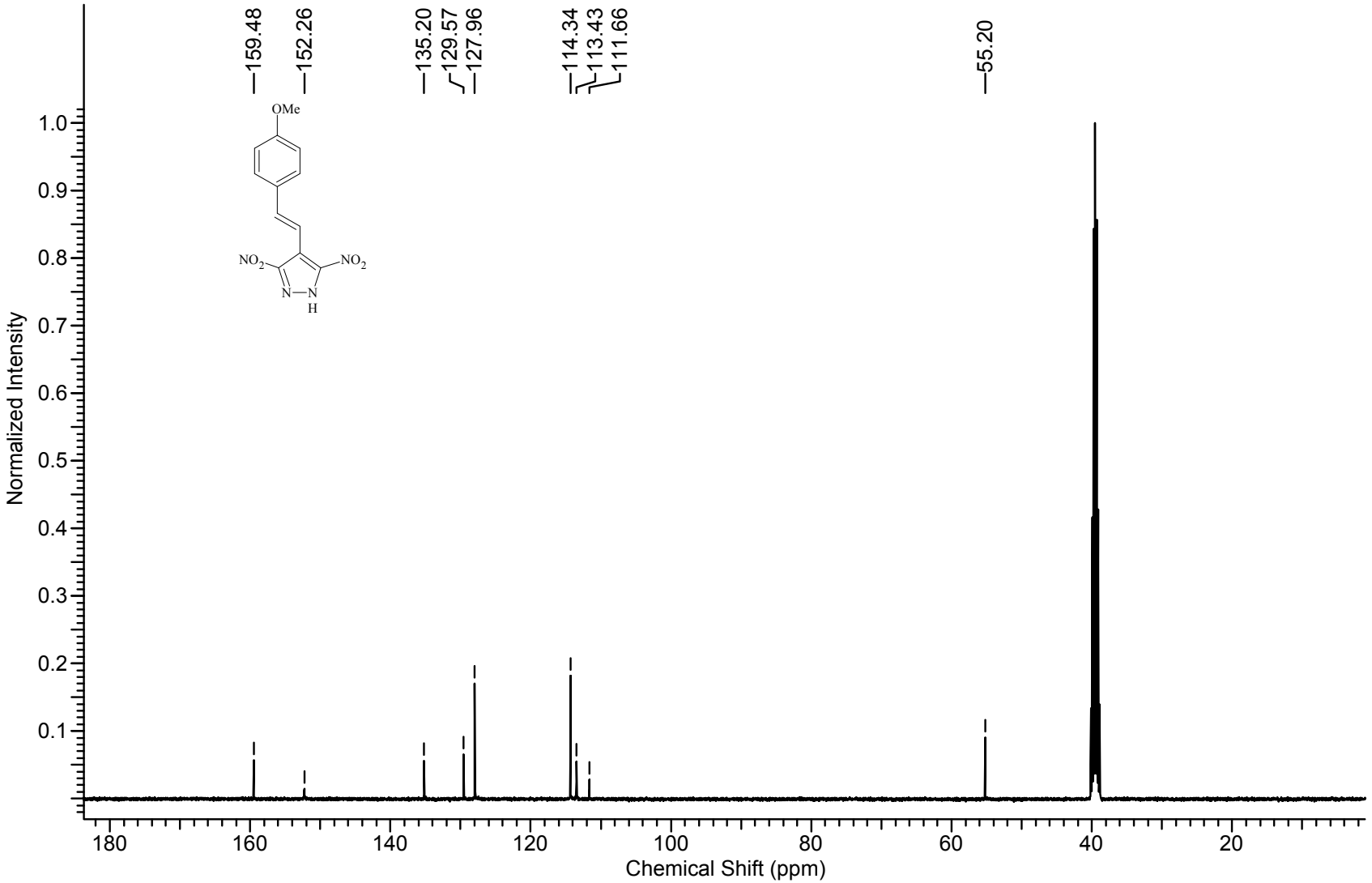
(*E*)-3,5-dinitro-4-styryl-1*H*-pyrazole (4l).



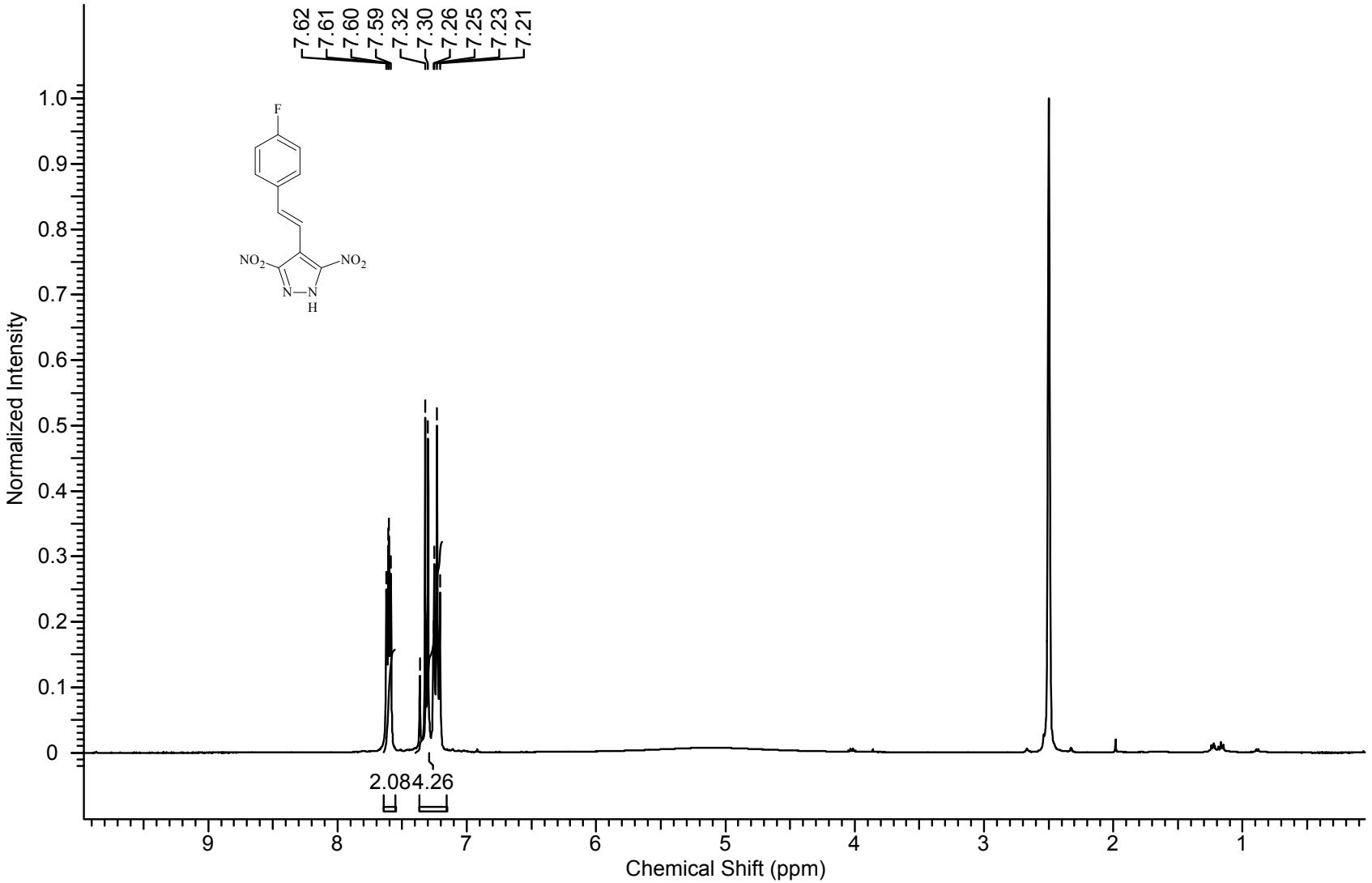
(*E*)-4-(4-methoxystyryl)-3,5-dinitro-1*H*-pyrazole (4m).



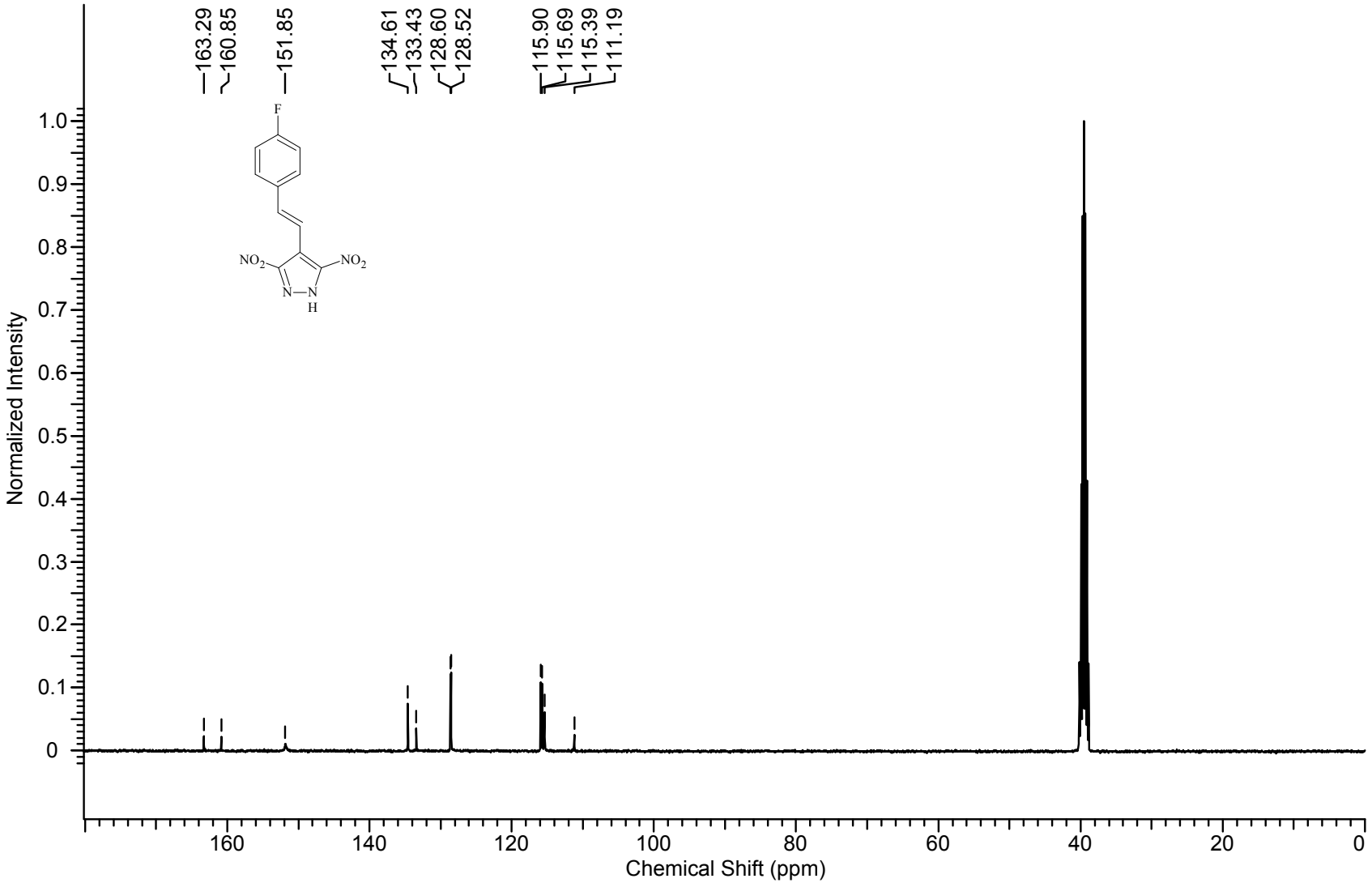
(*E*)-4-(4-methoxystyryl)-3,5-dinitro-1*H*-pyrazole (4m).



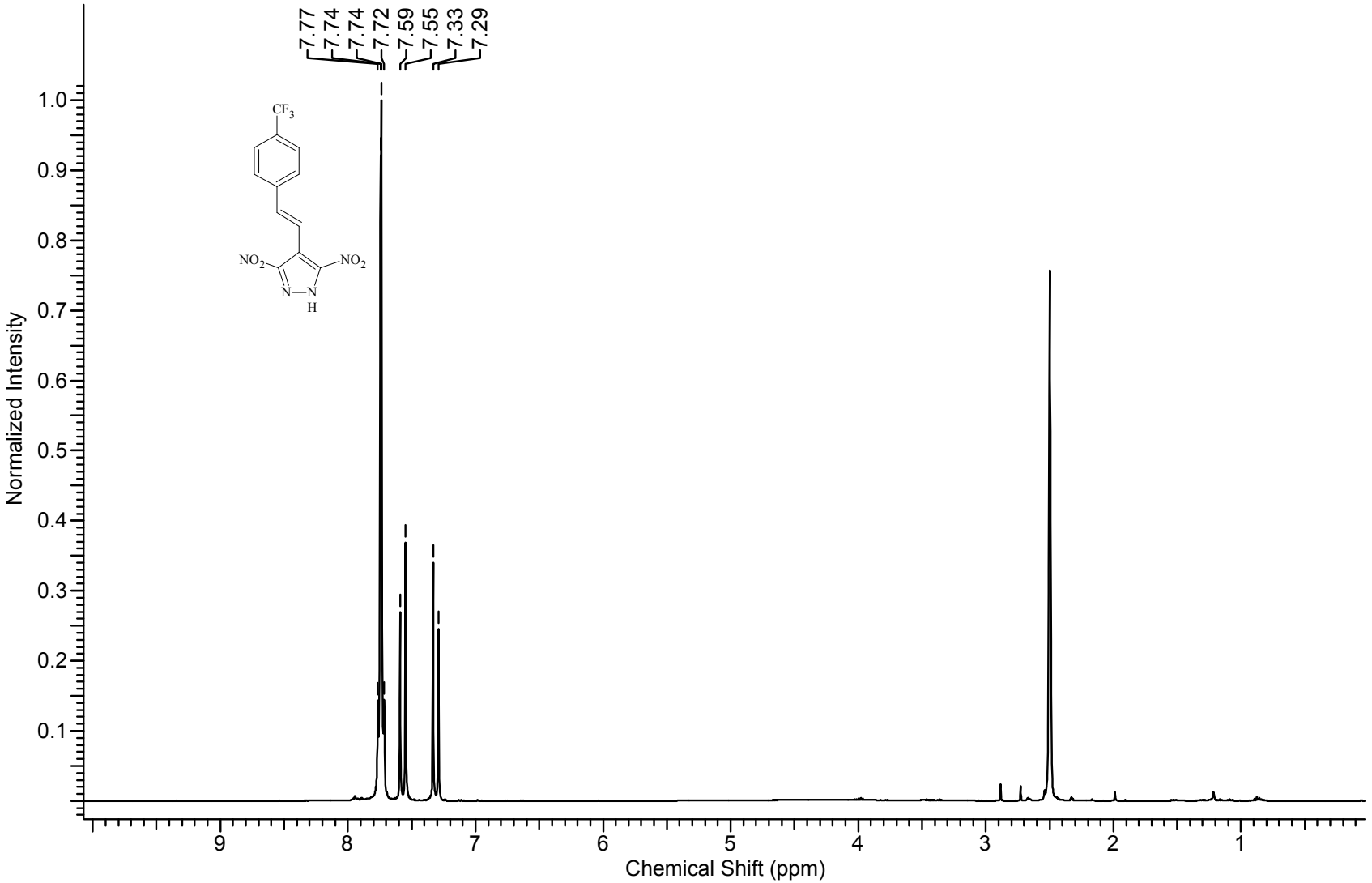
***(E)*-4-(4-flourostyryl)-3,5-dinitro-*1H*-pyrazole (4n).**



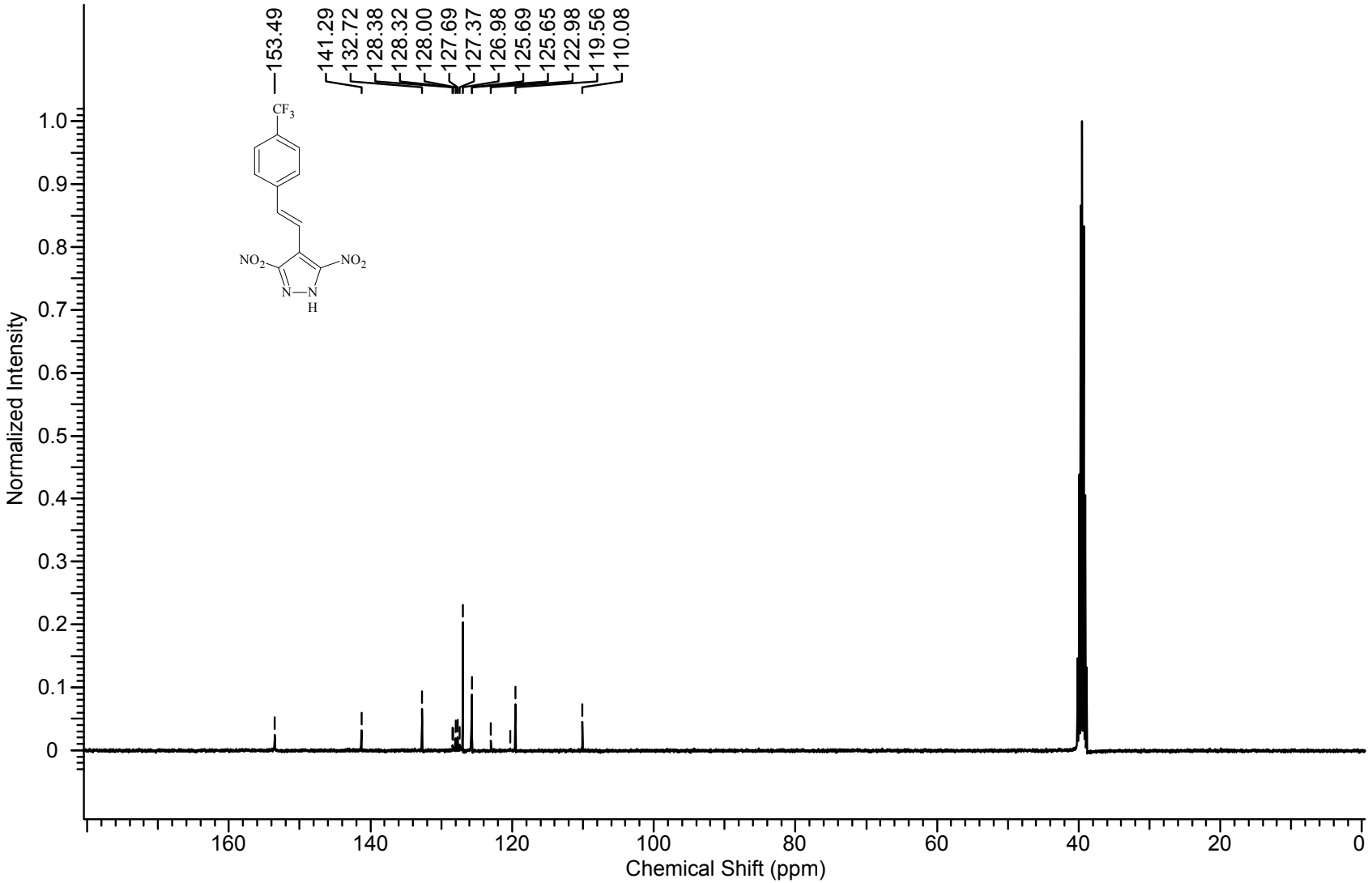
***(E)*-4-(4-flourostyryl)-3,5-dinitro-*1H*-pyrazole (4n).**



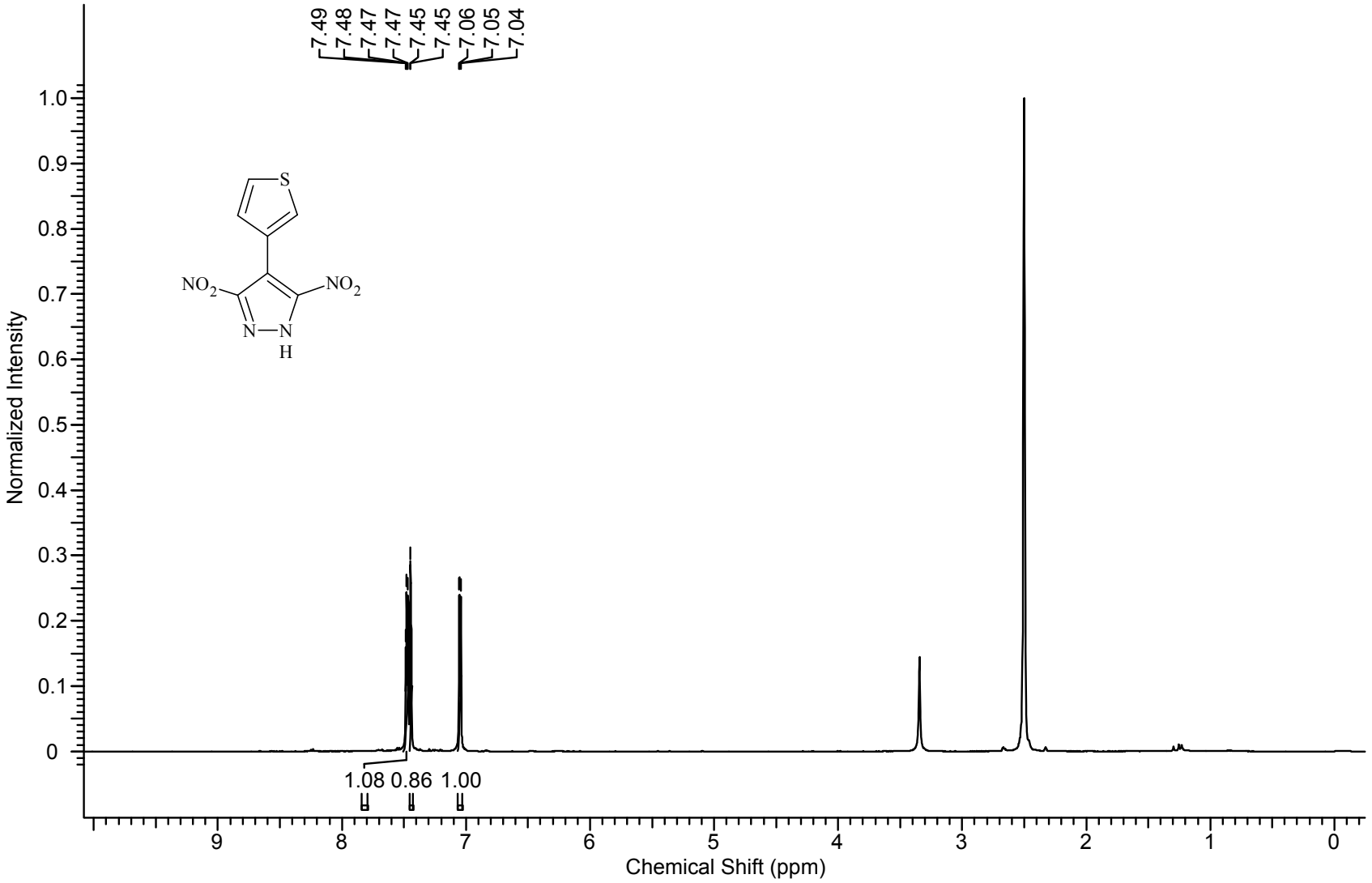
***(E)*-3,5-dinitro-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazole (4o).**



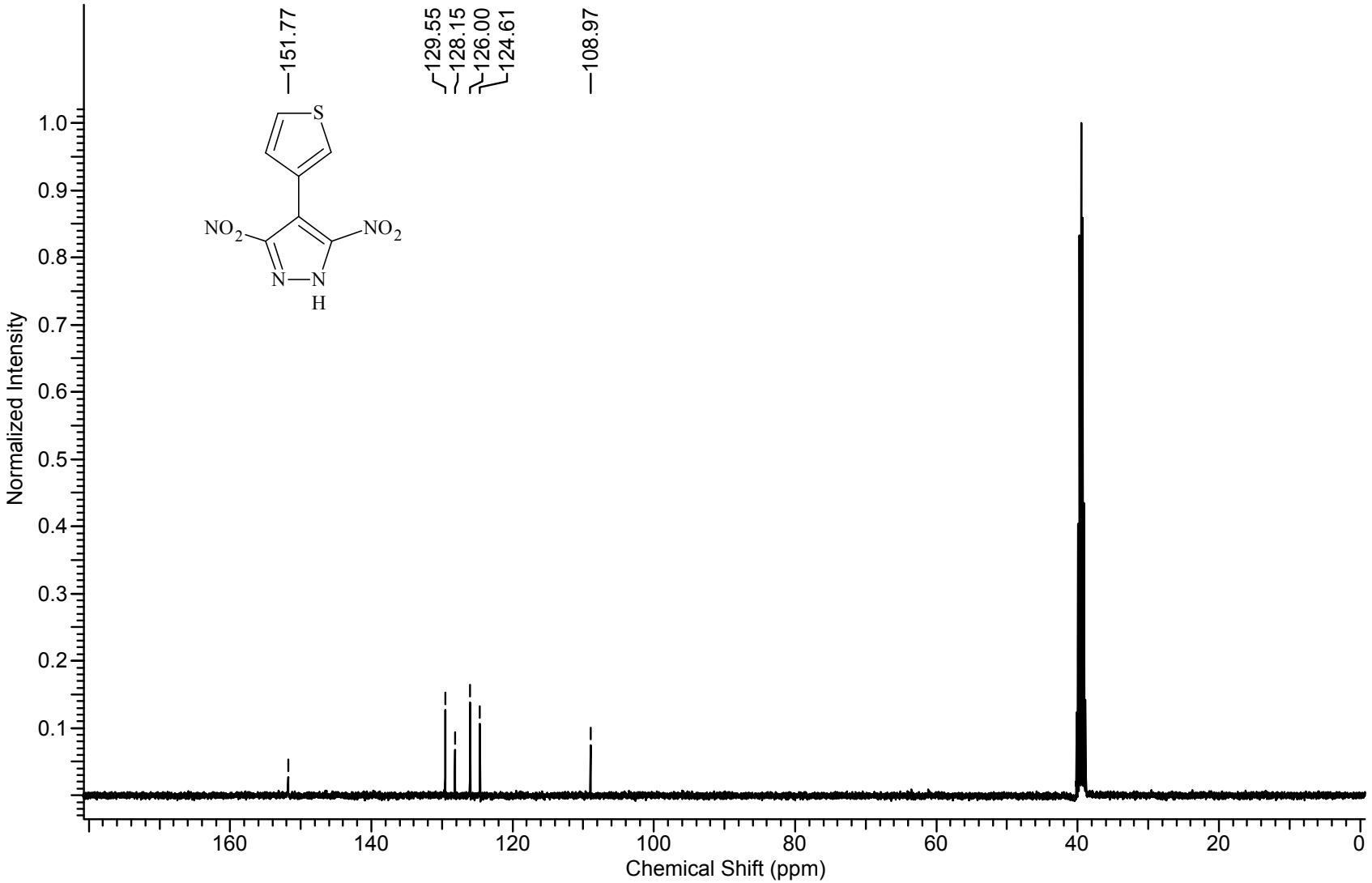
***(E)*-3,5-dinitro-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazole (4o).**



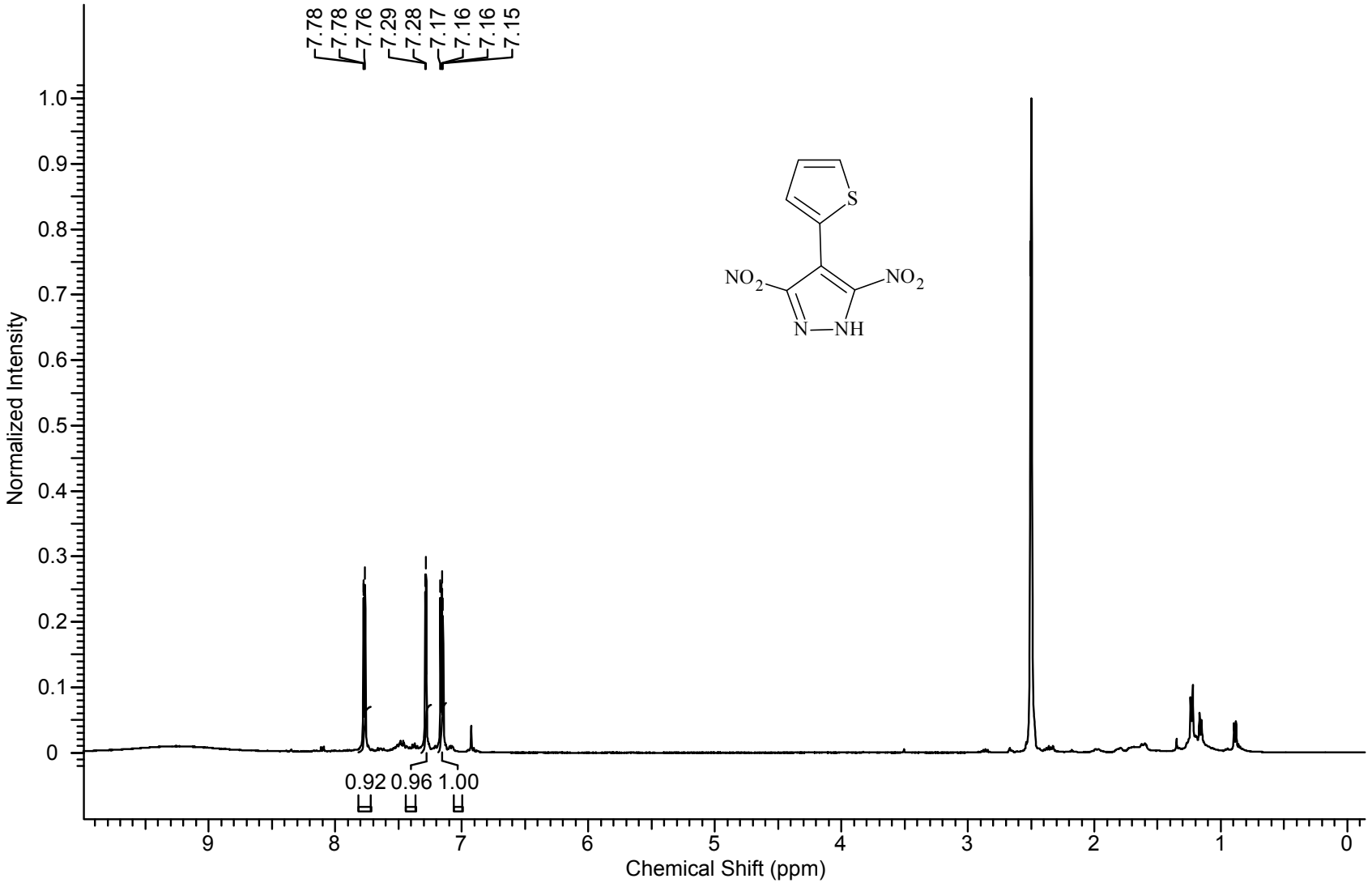
3,5-dinitro-4-(thiophen-3-yl)-1*H*-pyrazole (4p).



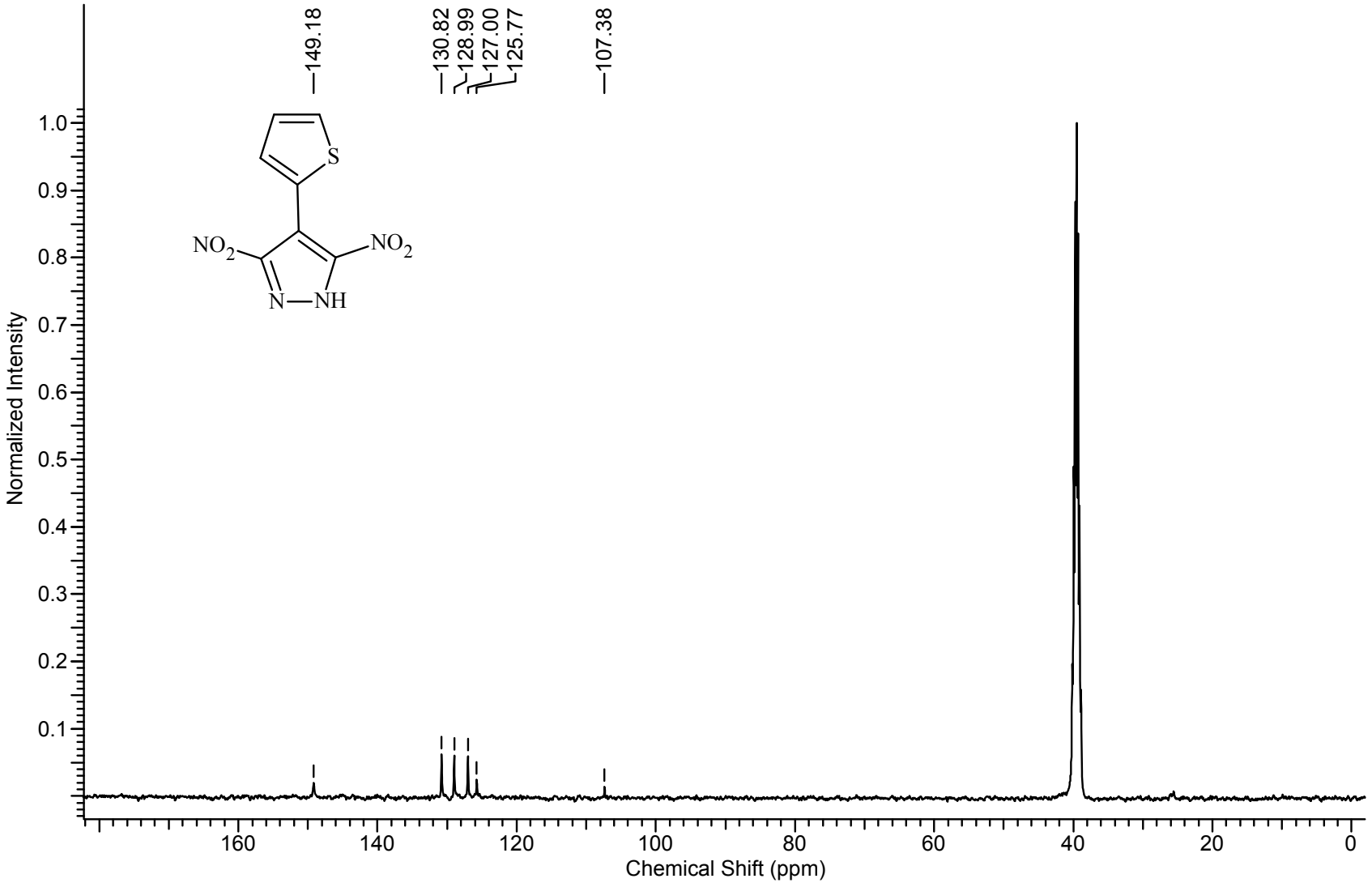
3,5-dinitro-4-(thiophen-3-yl)-1*H*-pyrazole (4p).



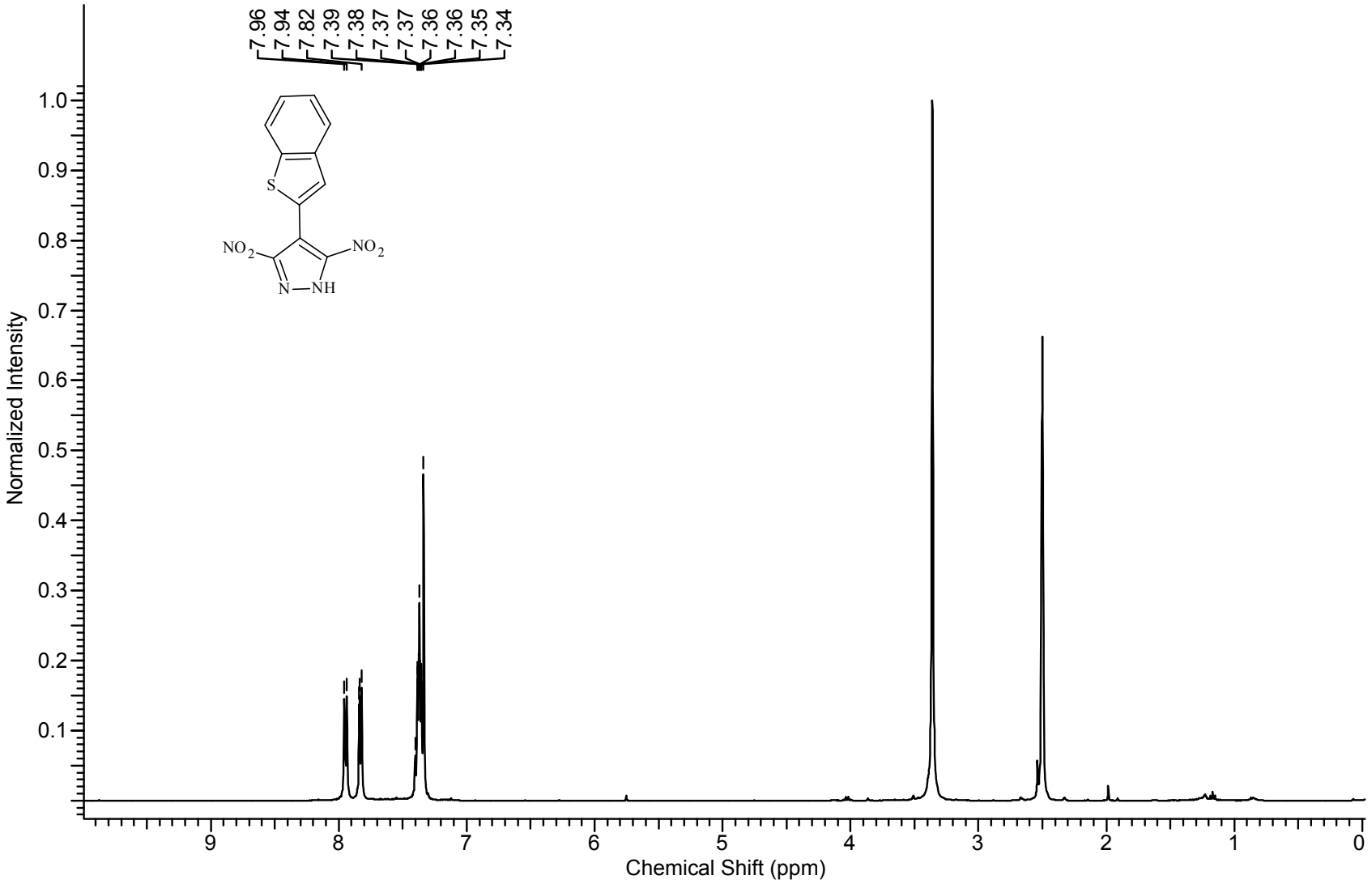
3,5-dinitro-4-(thiophen-2-yl)-1*H*-pyrazole (4q).



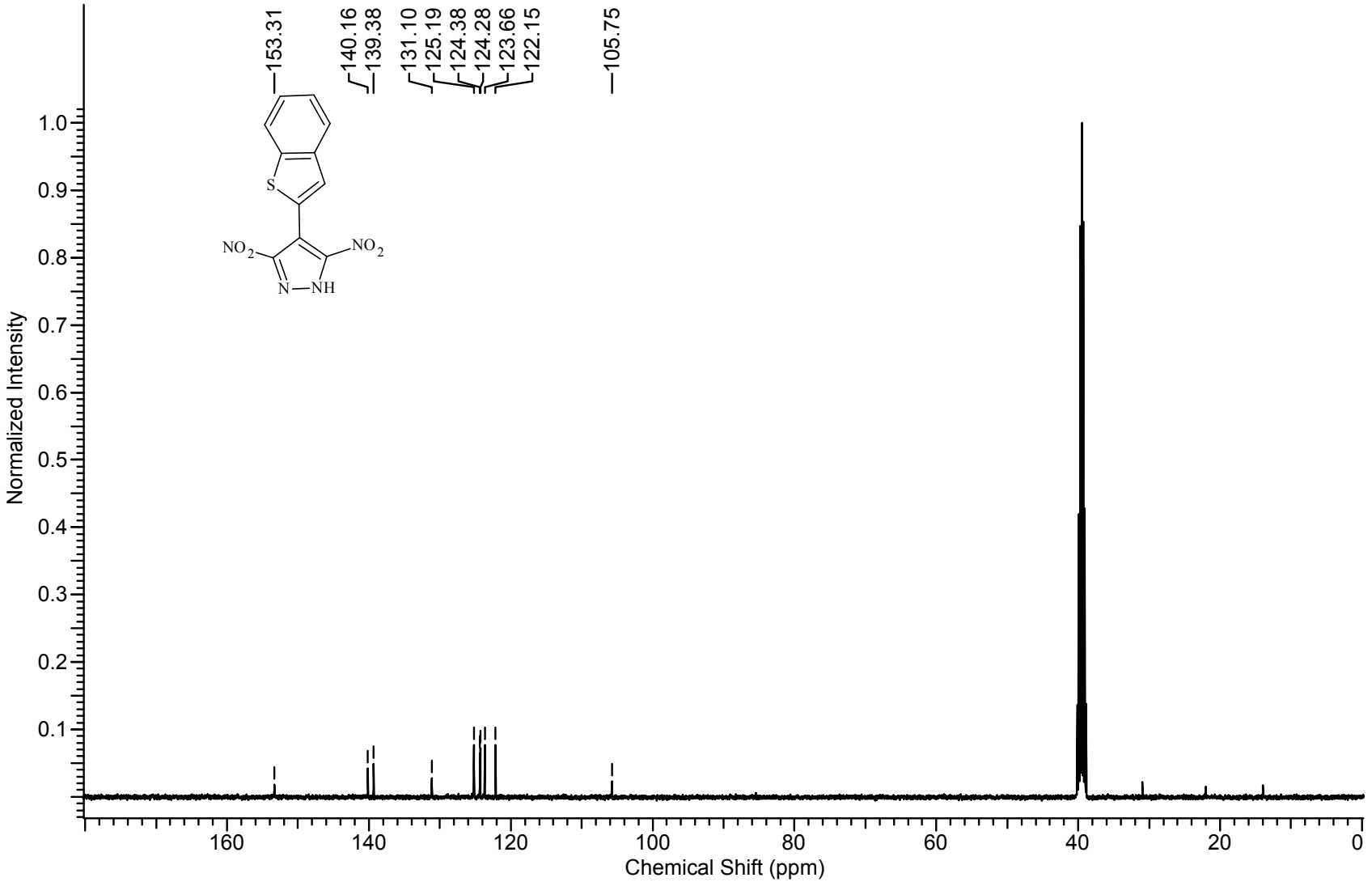
3,5-dinitro-4-(thiophen-2-yl)-1*H*-pyrazole (4q).



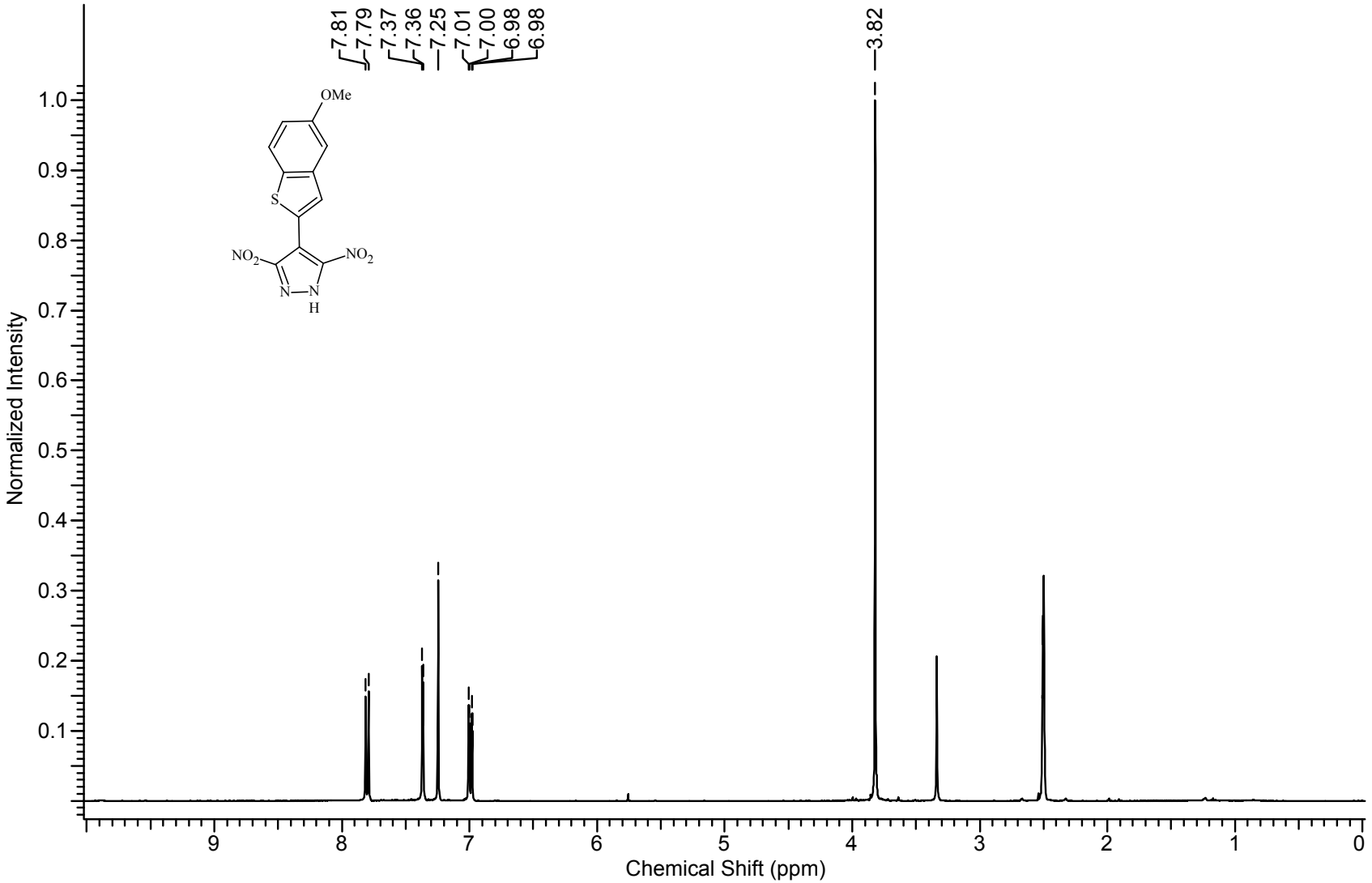
4-(benzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4r).



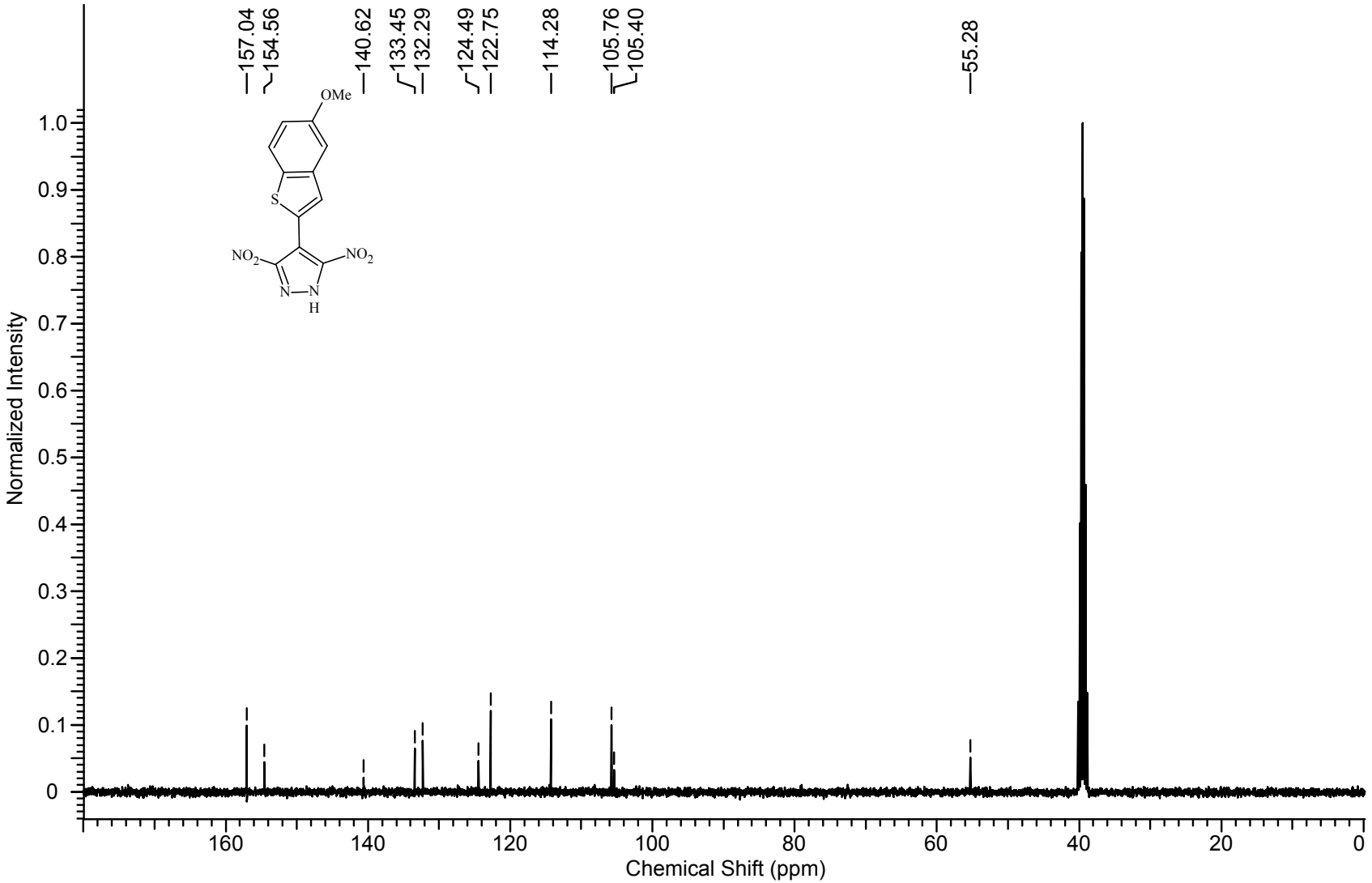
4-(benzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4r).



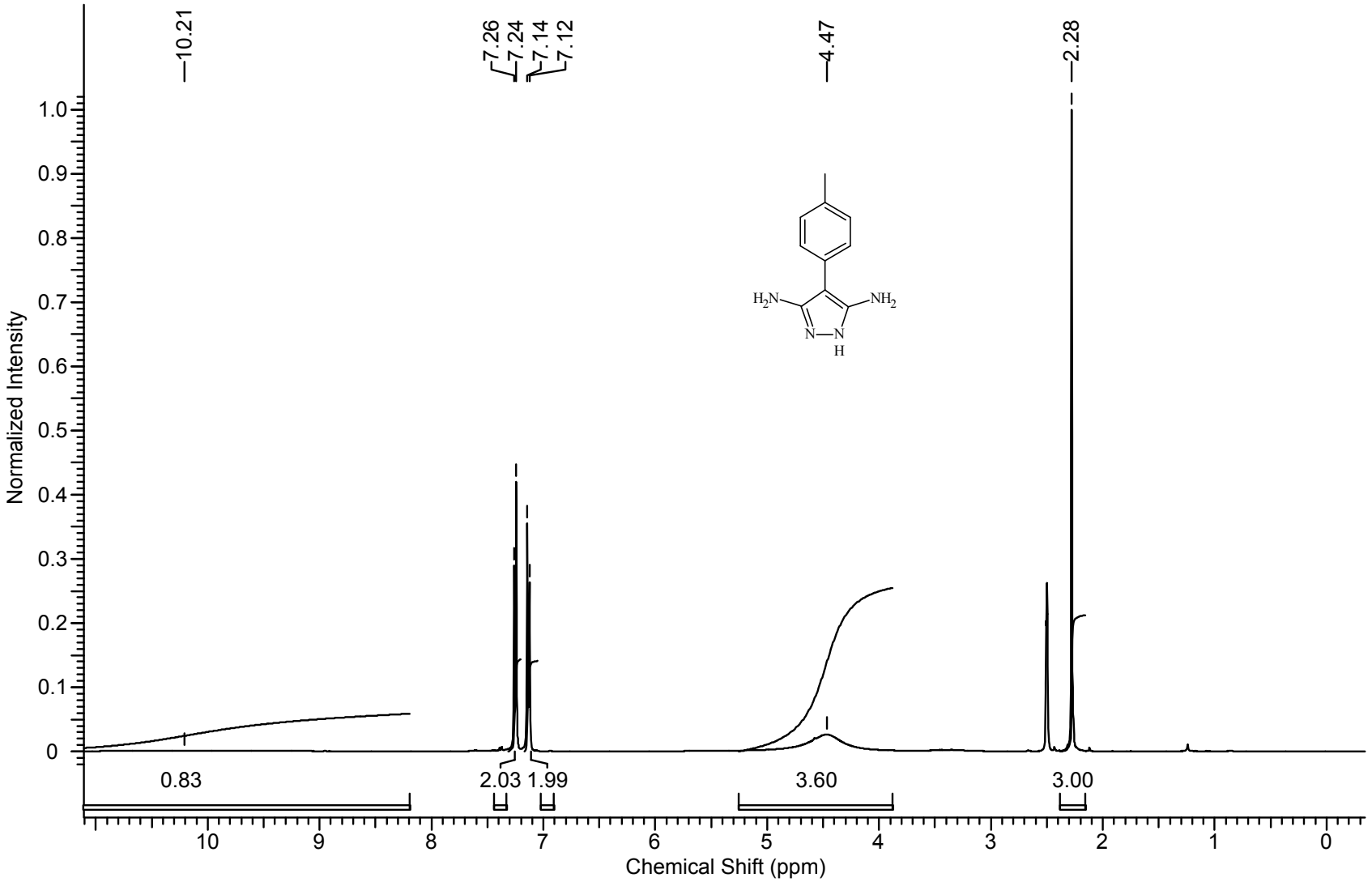
4-(5-methoxybenzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4s).



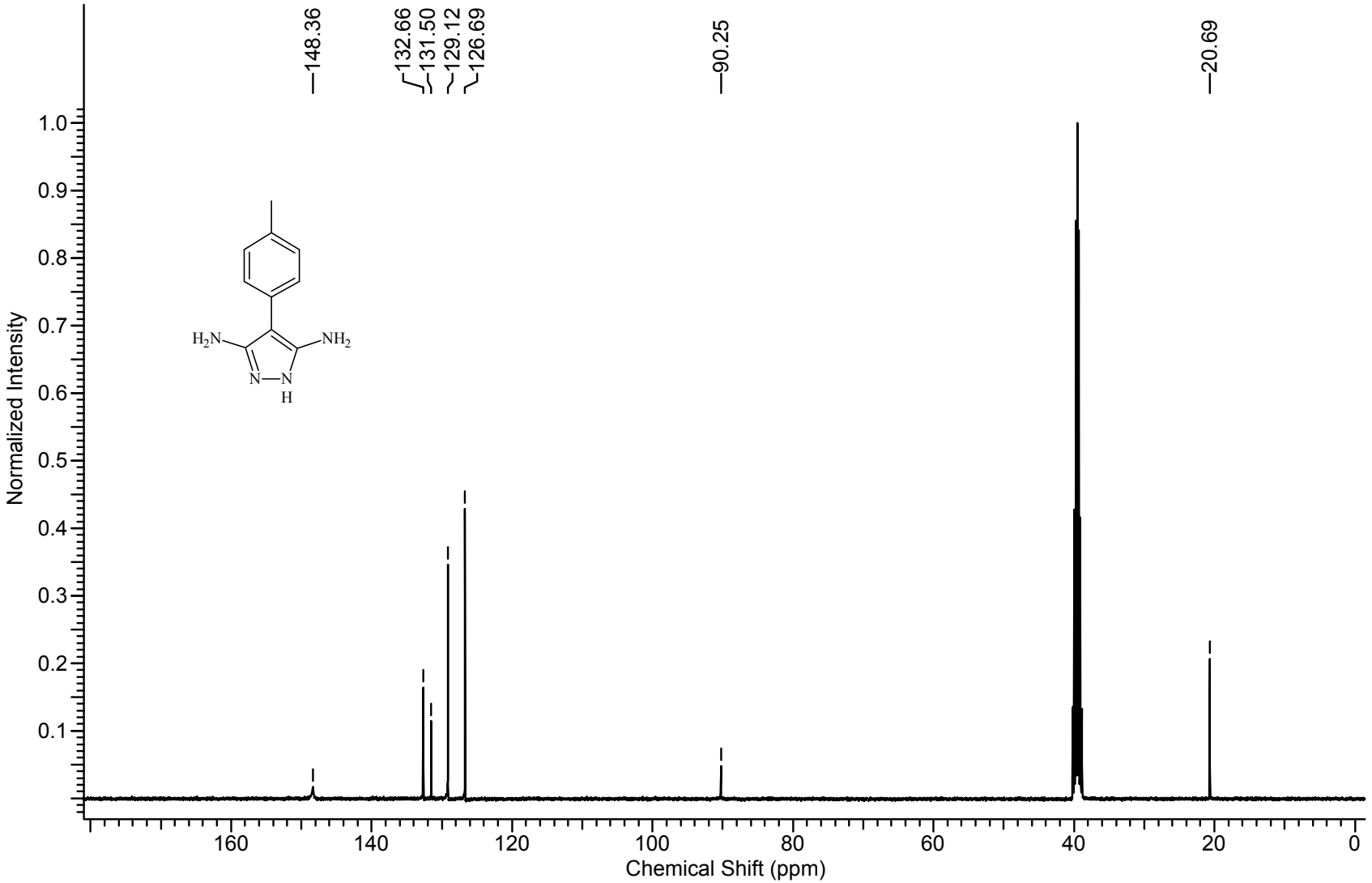
4-(5-methoxybenzo[*b*]thiophen-2-yl)-3,5-dinitro-1*H*-pyrazole (4s).



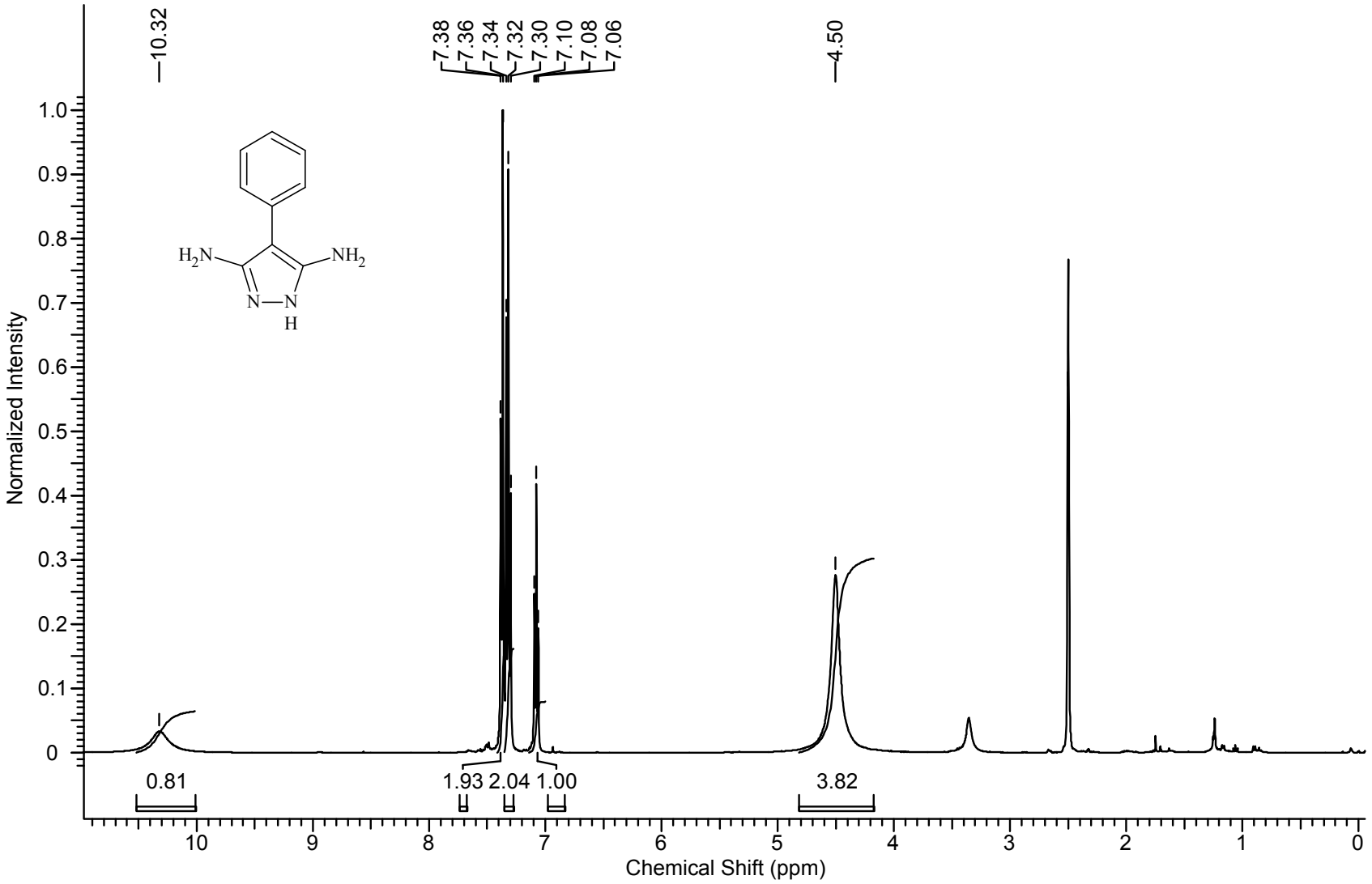
4-(*p*-tolyl)-1*H*-pyrazole-3,5-diamine (5a).



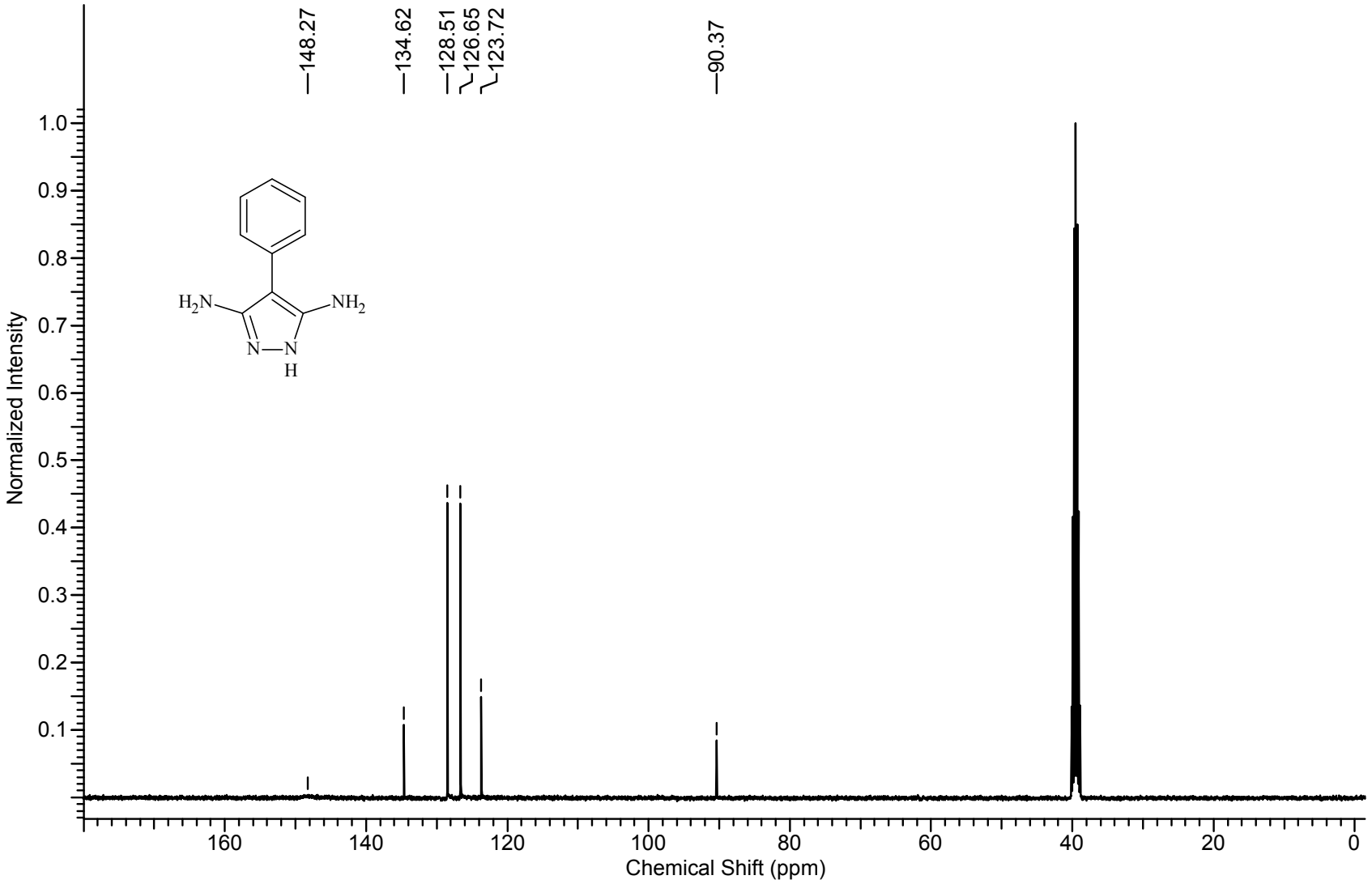
4-(*p*-tolyl)-1*H*-pyrazole-3,5-diamine (5a).



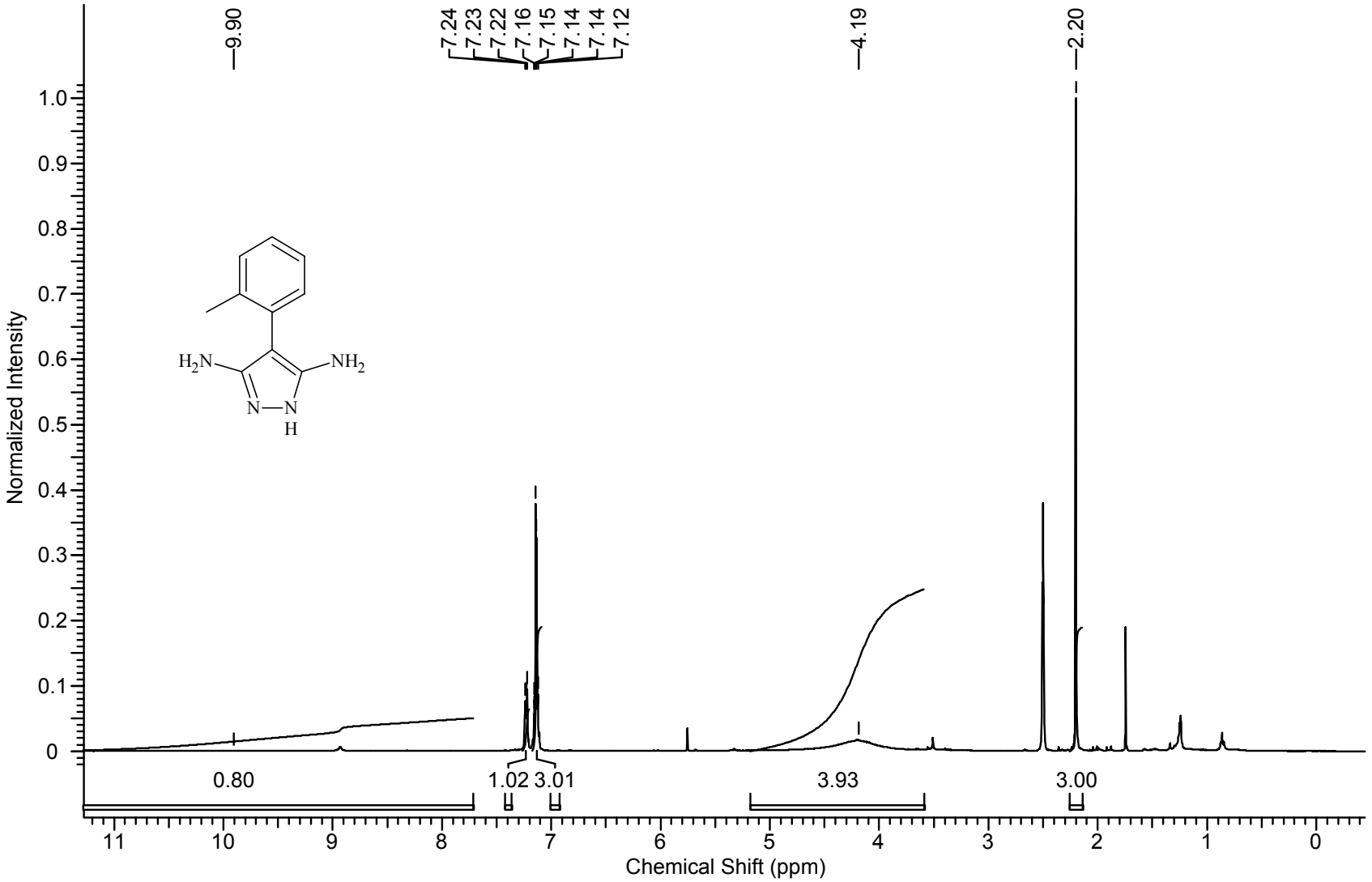
4-phenyl-1*H*-pyrazole-3,5-diamine (5b).



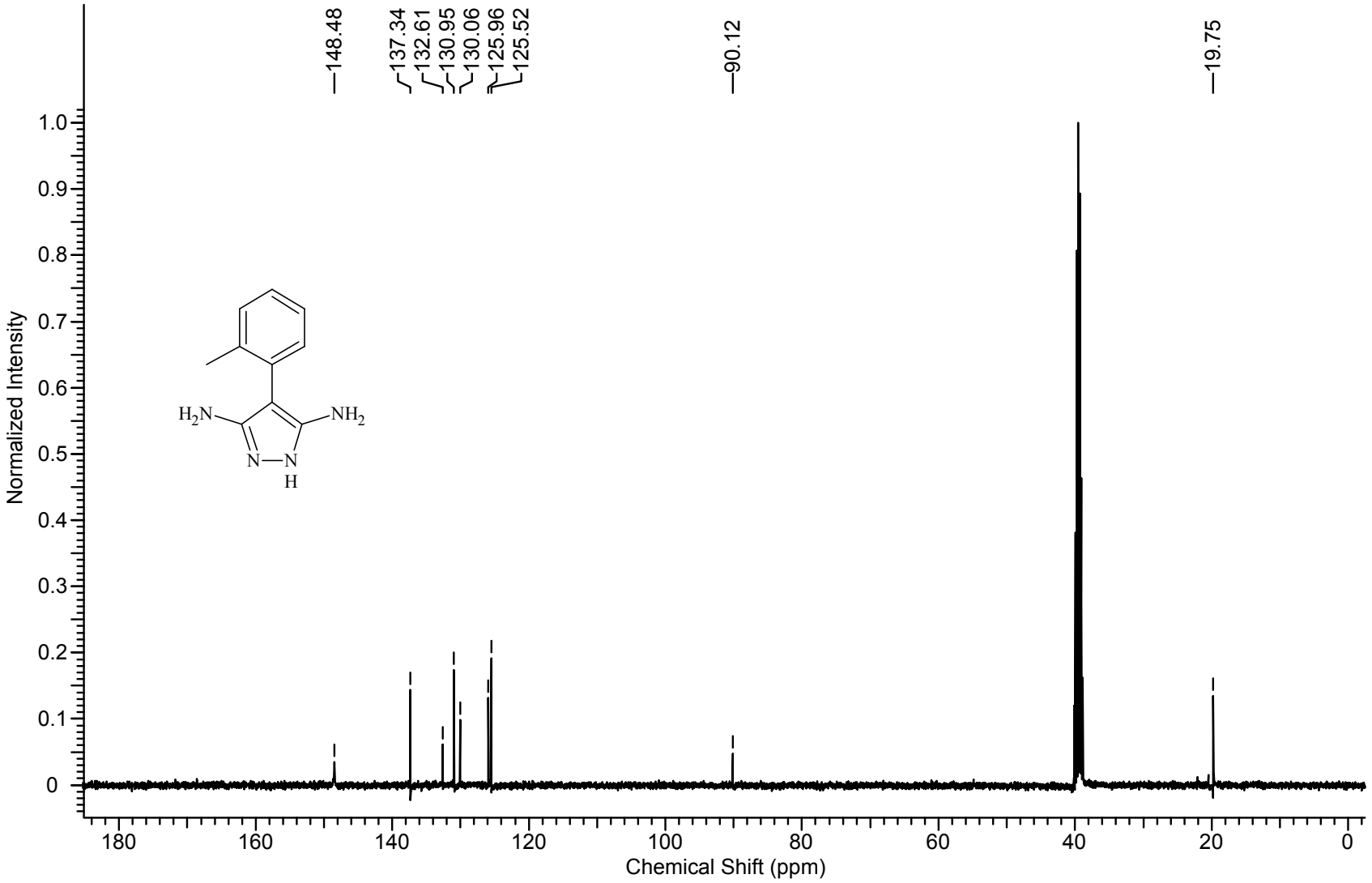
4-phenyl-1*H*-pyrazole-3,5-diamine (5b).



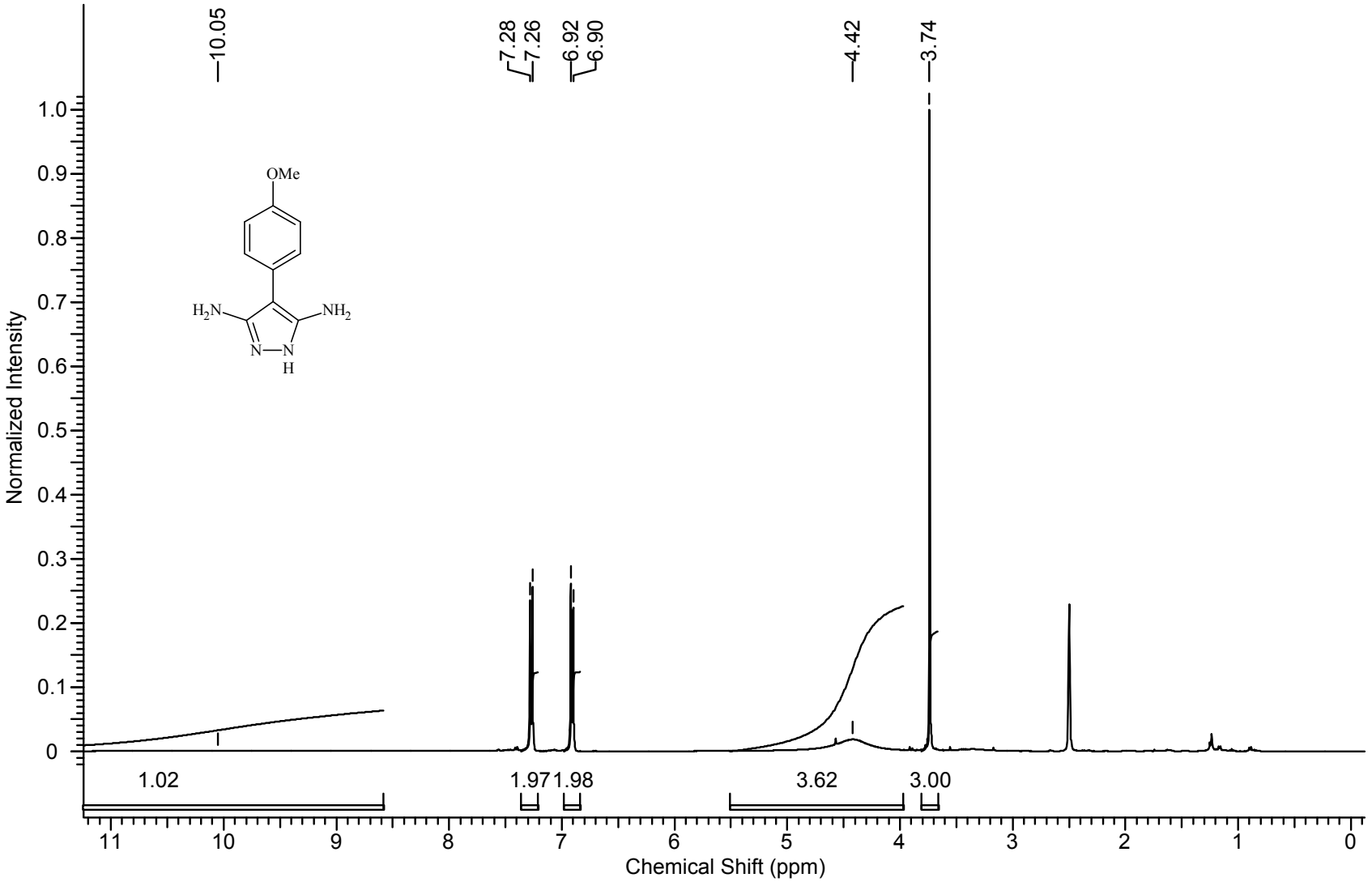
4-(*o*-(tolyl)-1*H*-pyrazole-3,5-diamine (5c).



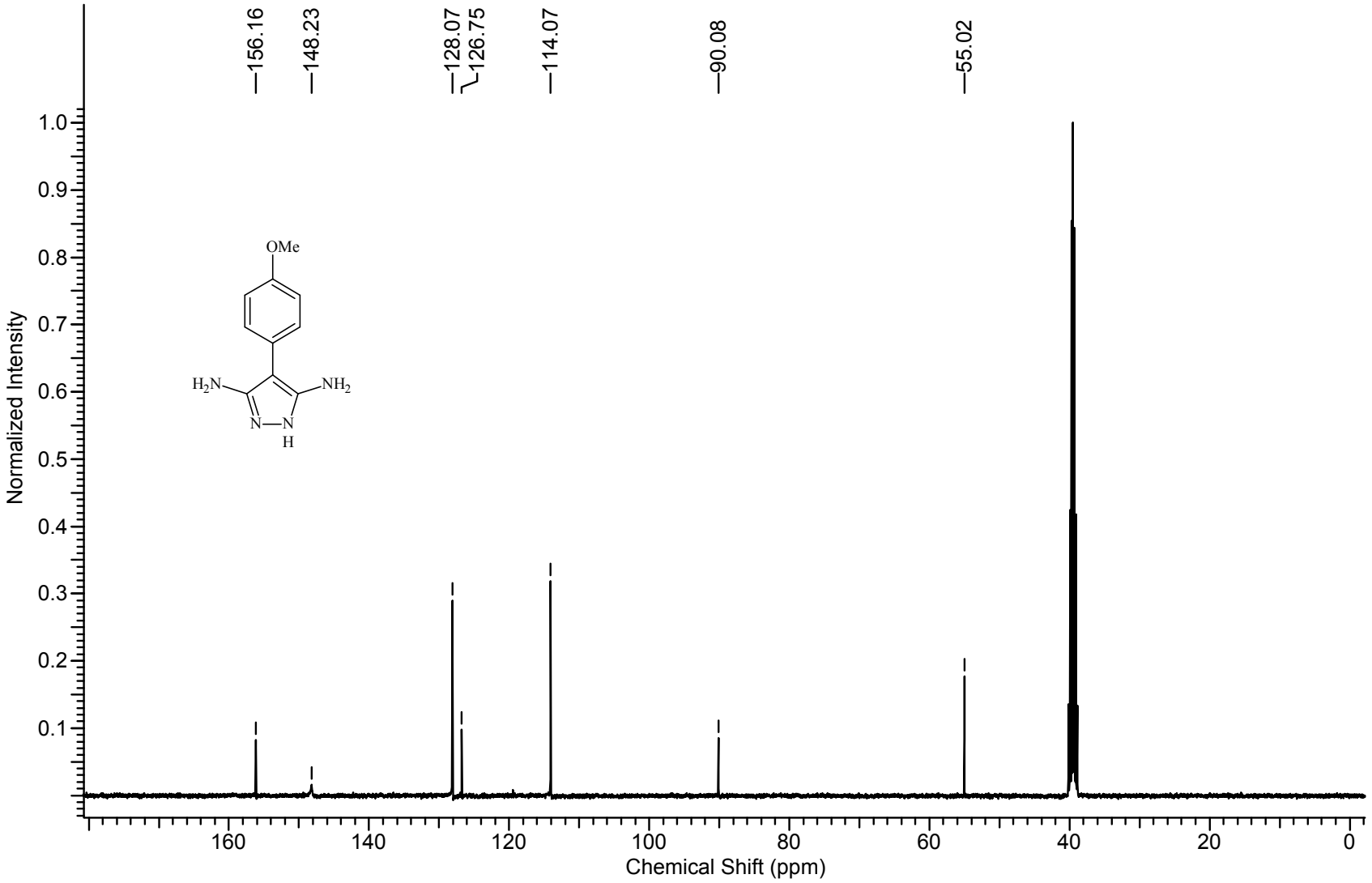
4-(*o*-(tolyl)-1*H*-pyrazole-3,5-diamine (5c).



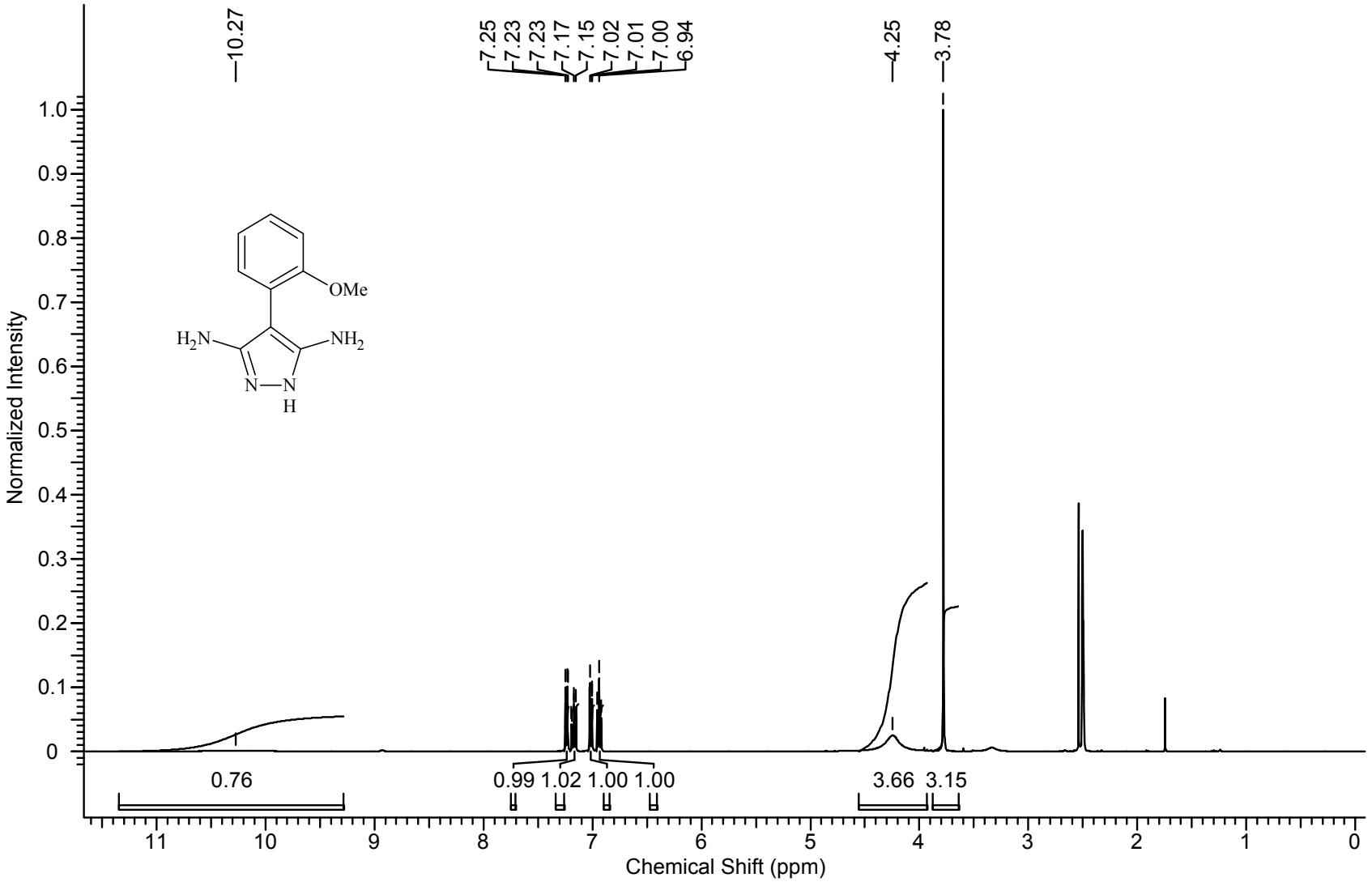
4-(4-methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5e).



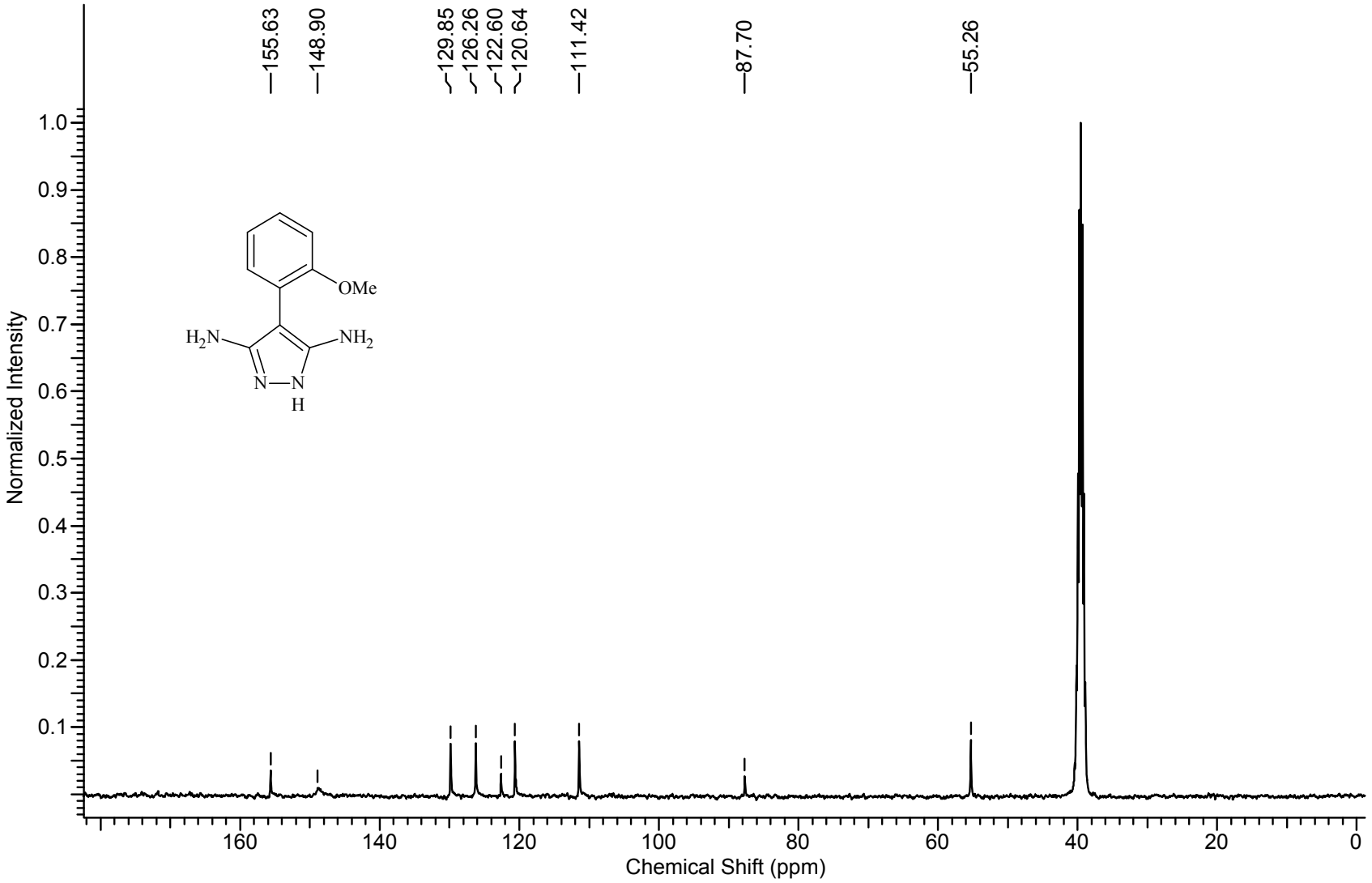
4-(4-methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5e).



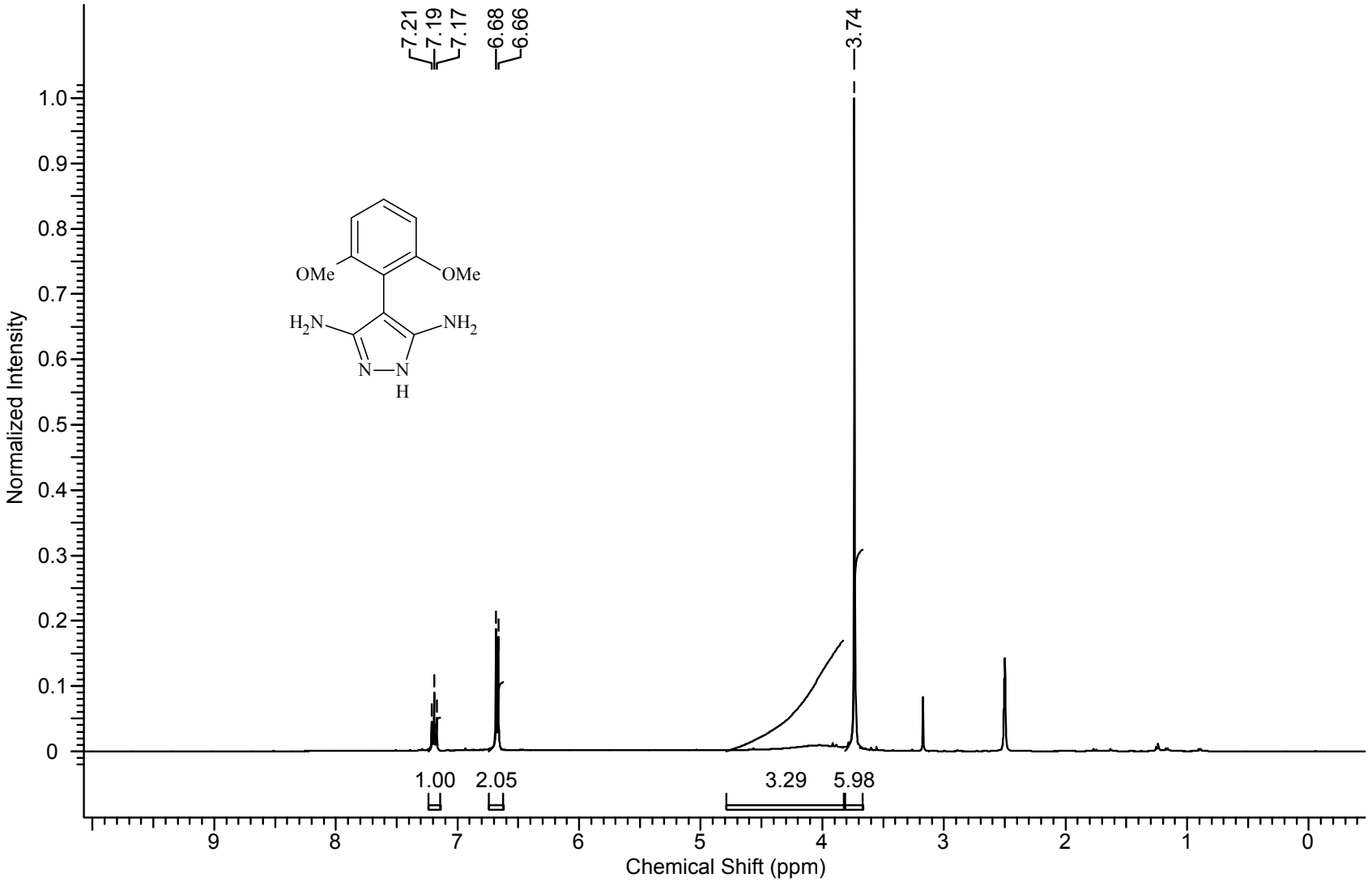
4-(2-methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5g).



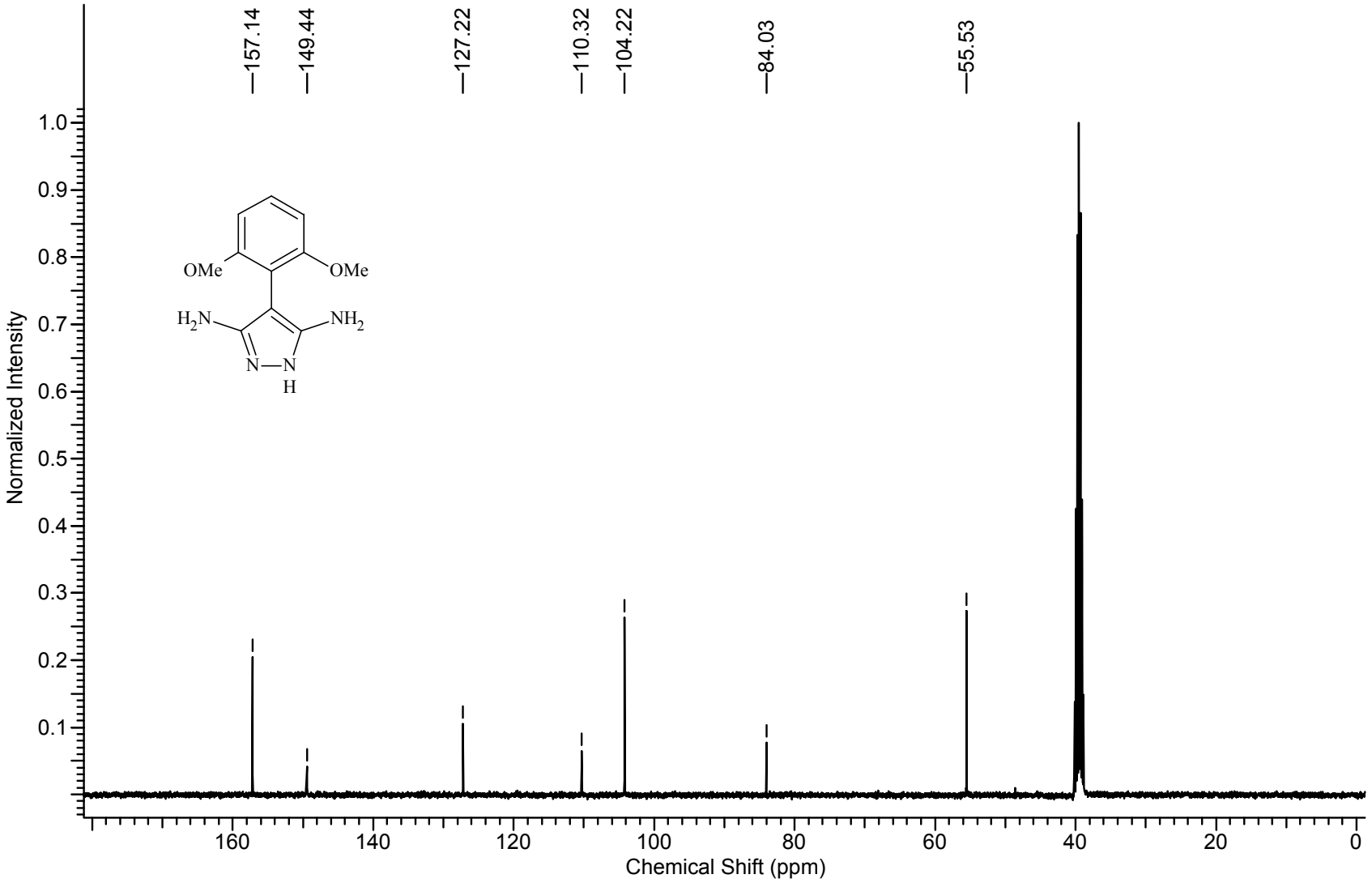
4-(2-methoxyphenyl)-1*H*-pyrazole-3,5-diamine (5g).



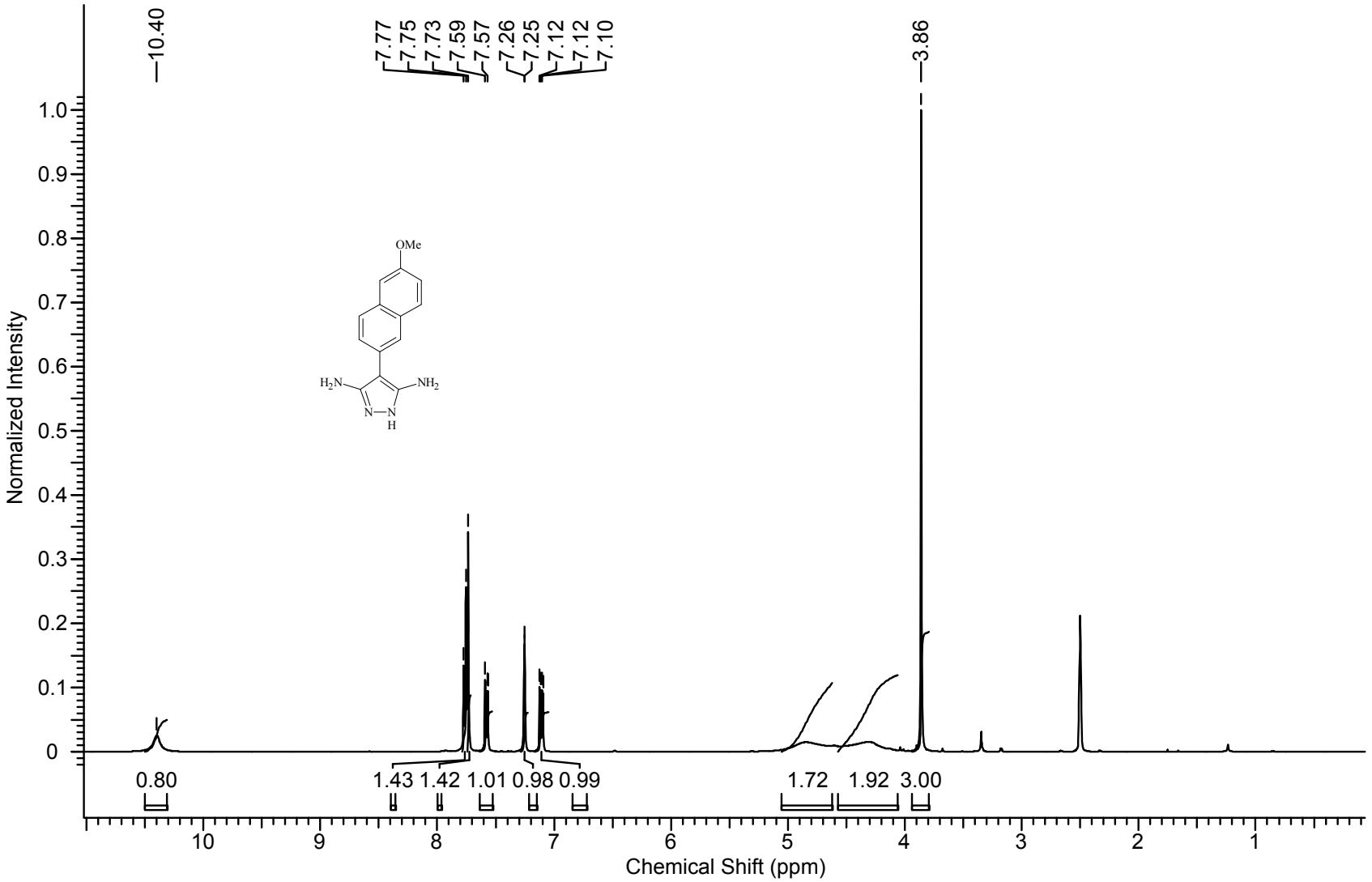
4-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3,5-diamine (5h).



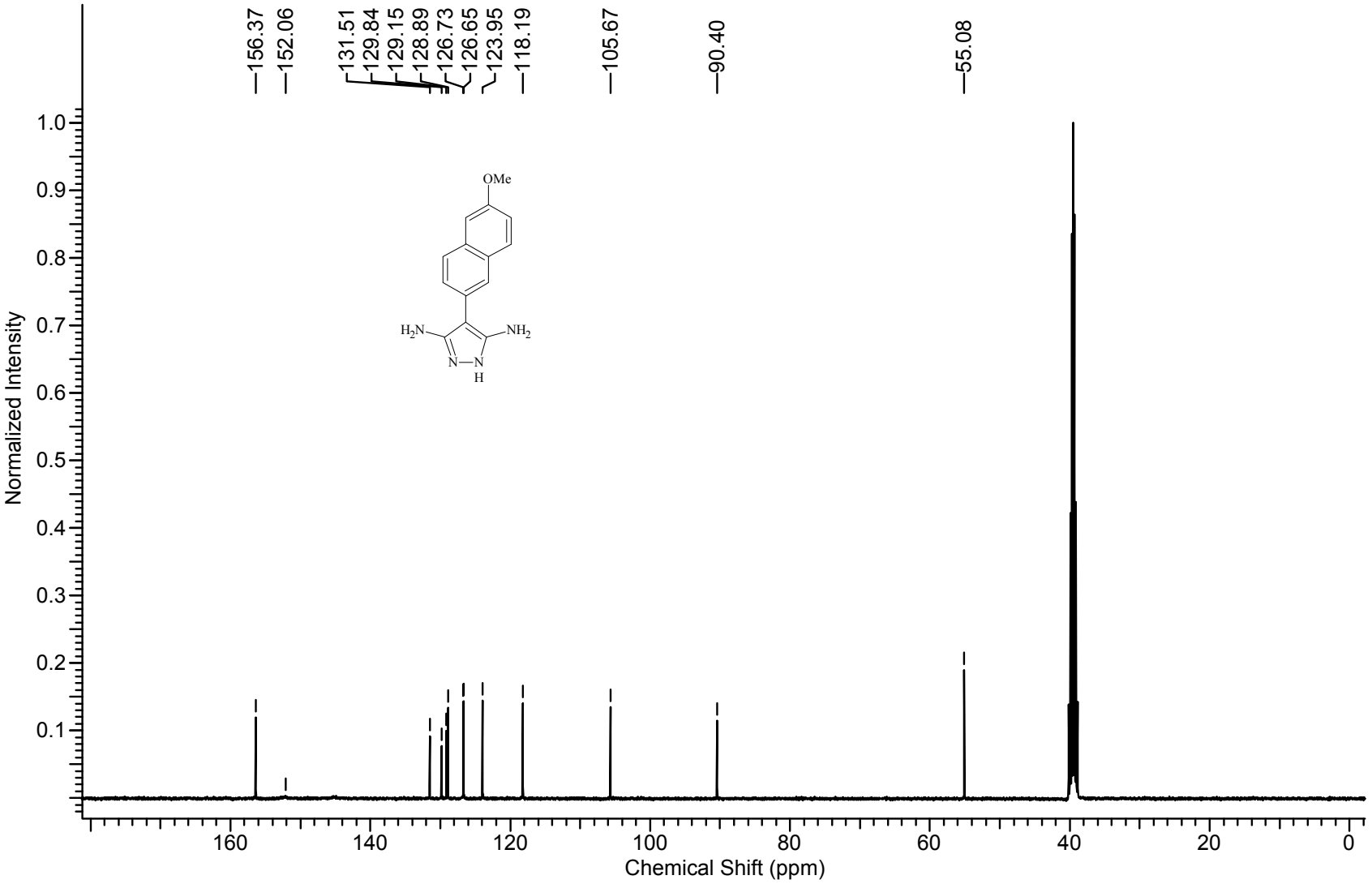
4-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3,5-diamine (5h).



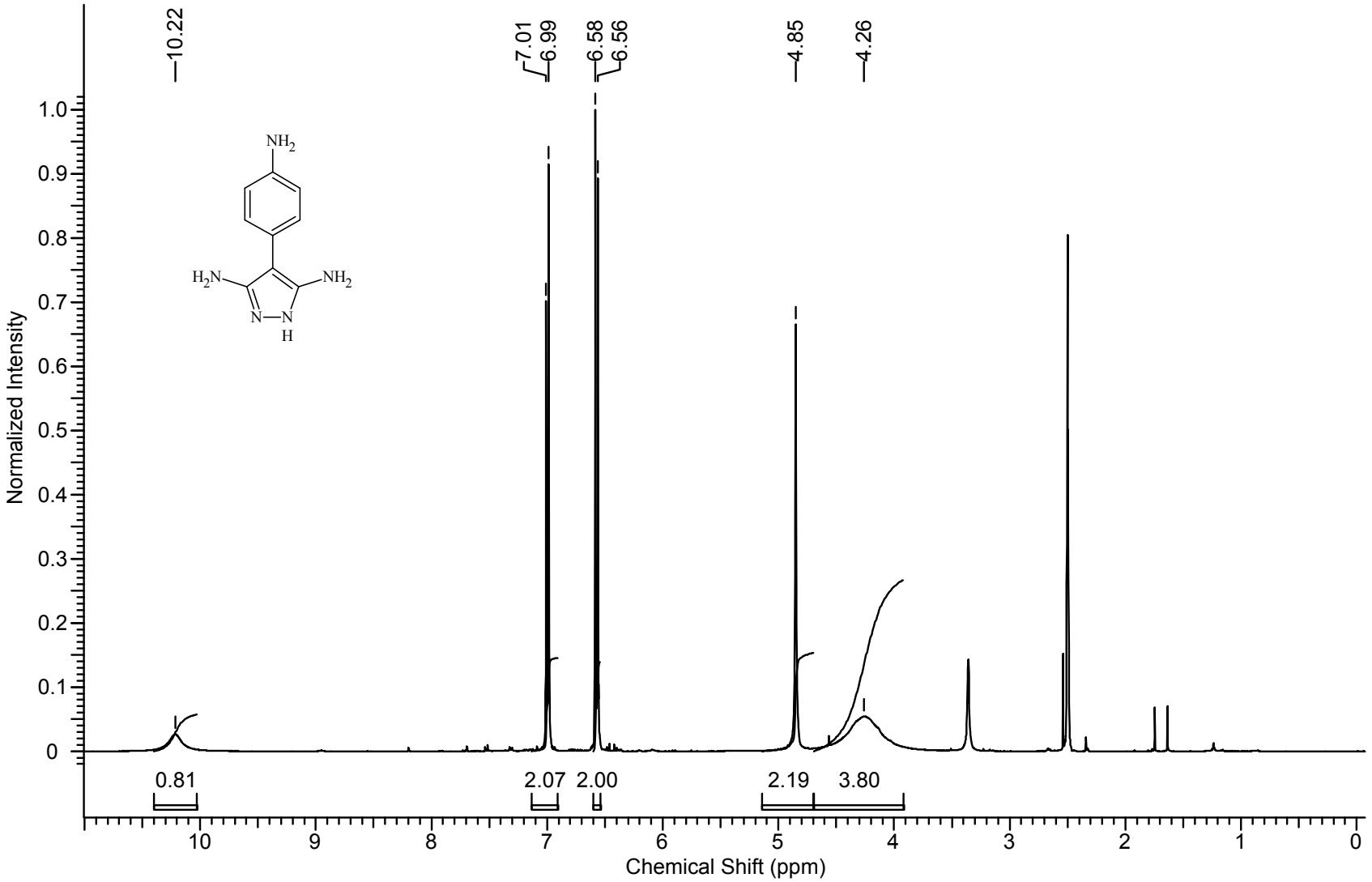
4-(6-methoxynaphtalen-2-yl)-1*H*-pyrazole-3,5-diamine (5i).



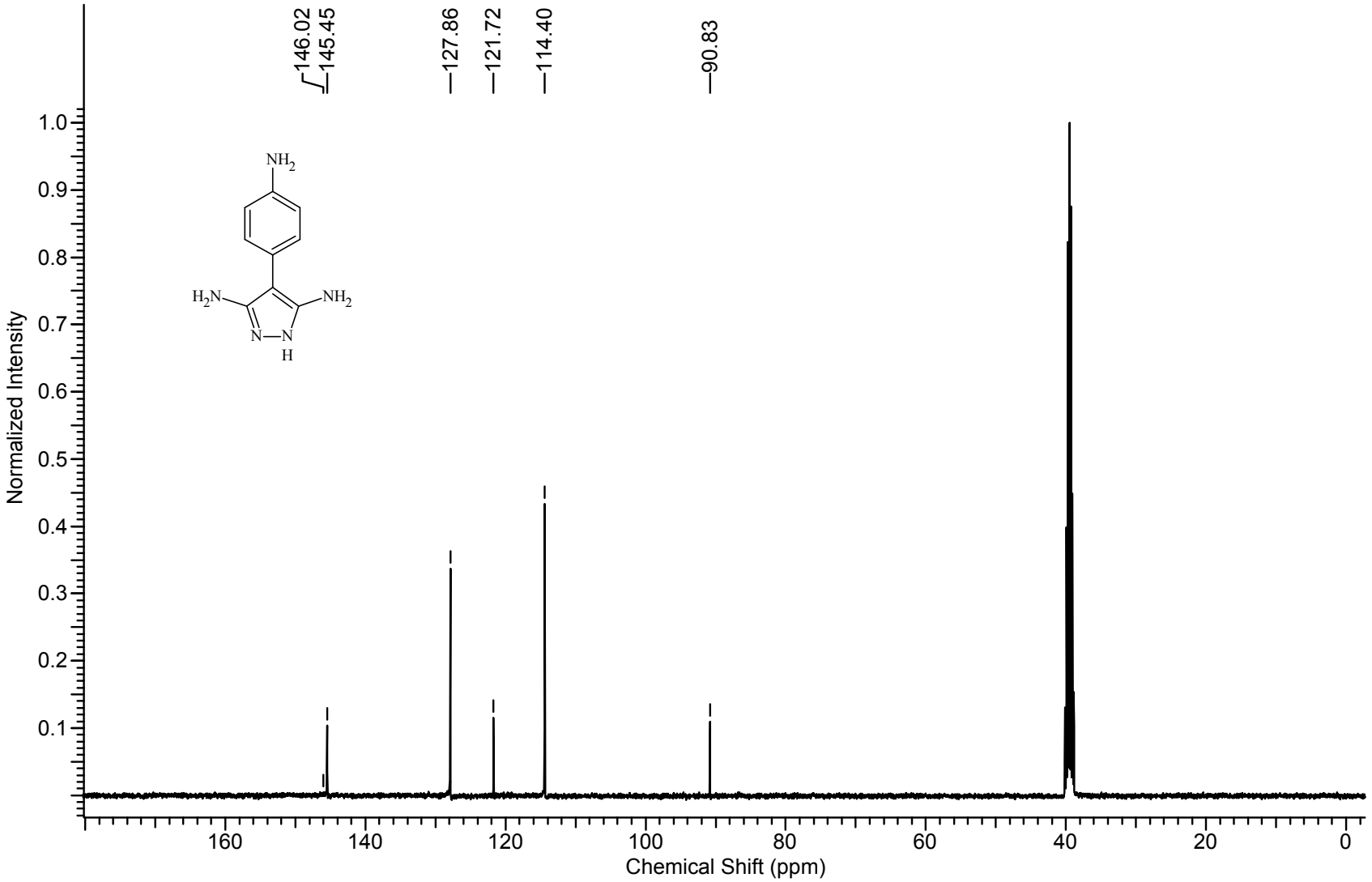
4-(6-methoxynaphtalen-2-yl)-1*H*-pyrazole-3,5-diamine (5i).



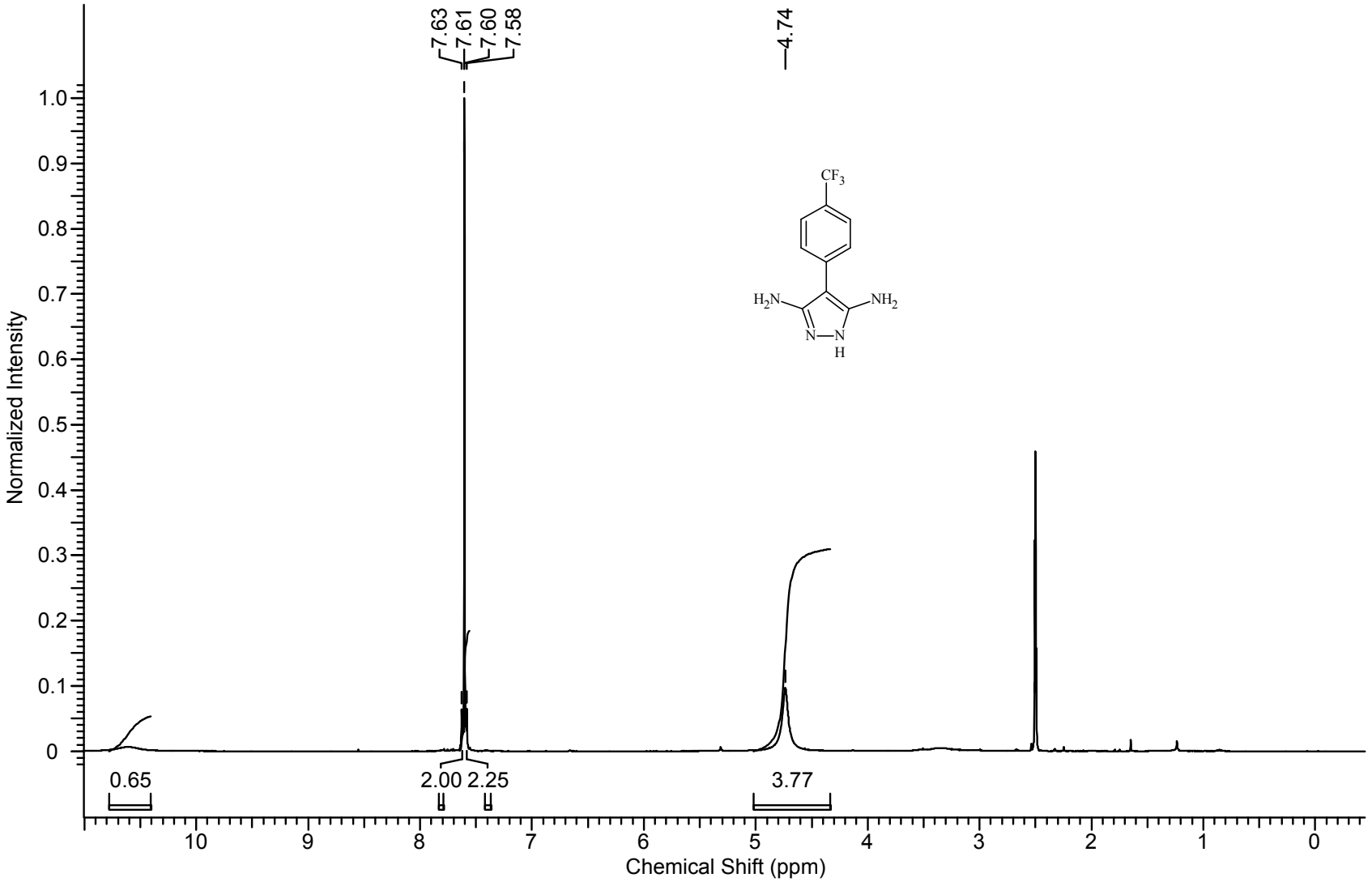
4-(4-aminophenyl)-1*H*-pyrazole-3,5-diamine (5j).



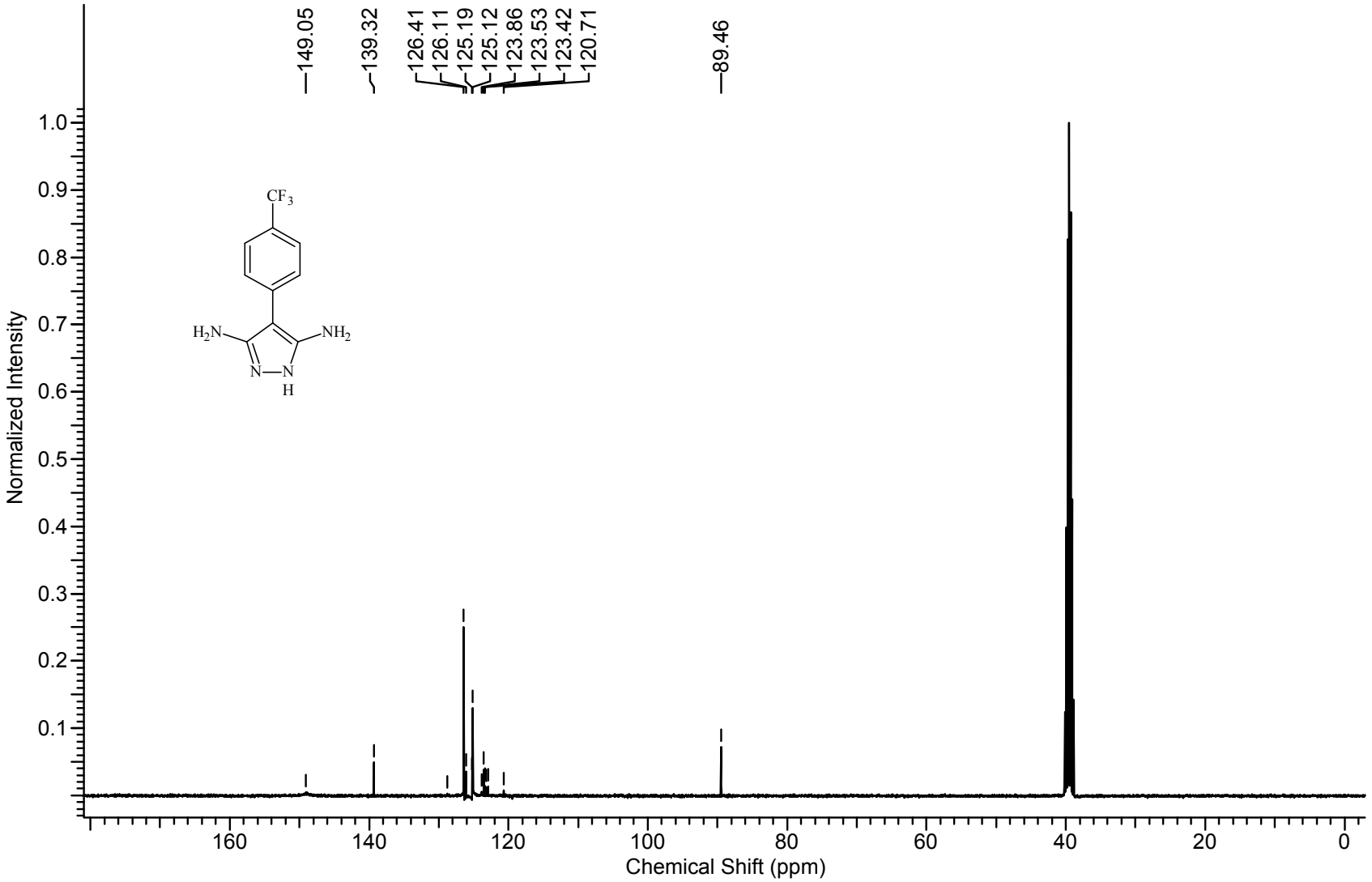
4-(4-aminophenyl)-1*H*-pyrazole-3,5-diamine (5j).



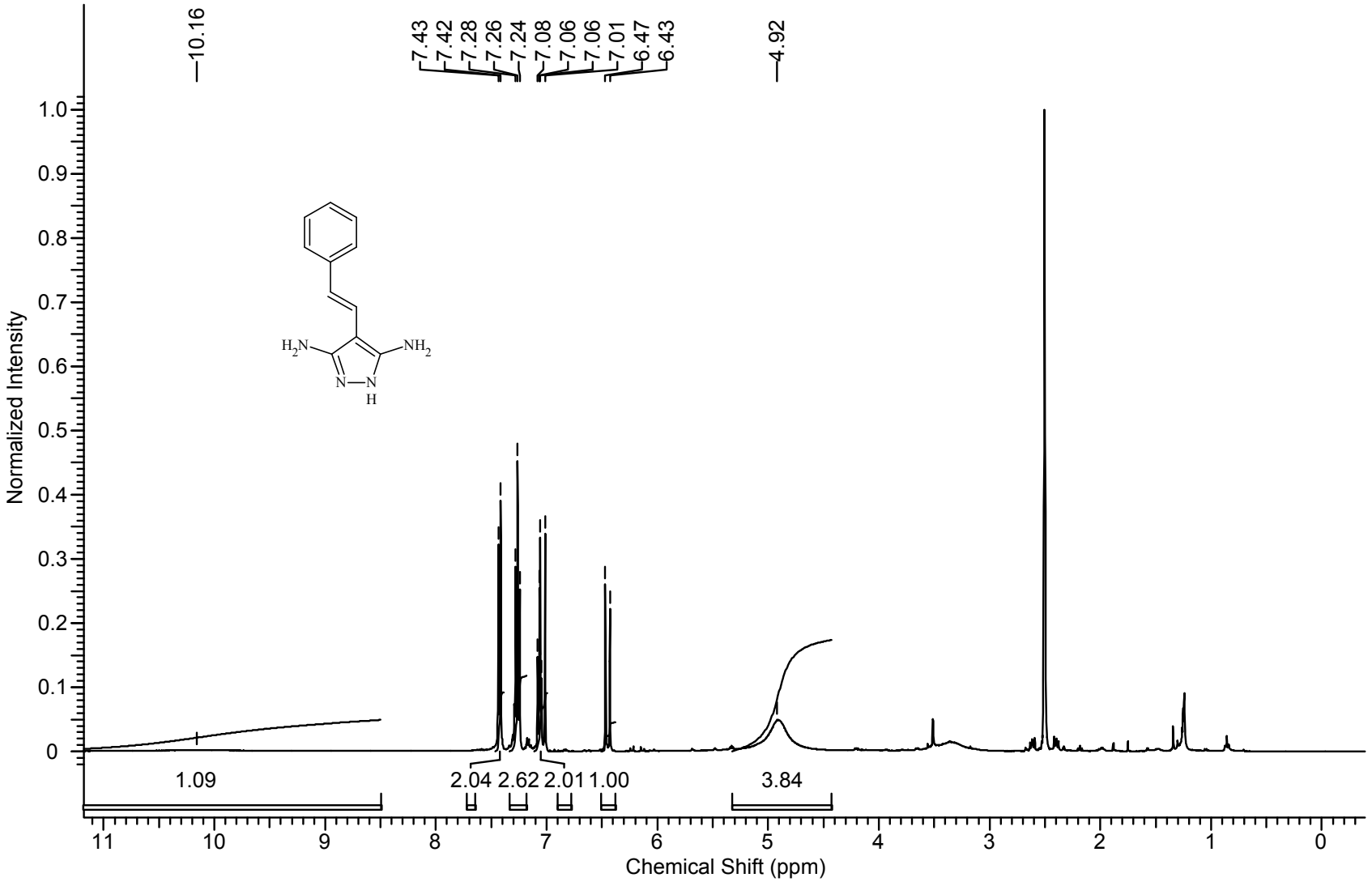
4-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3,5-diamine (5k).



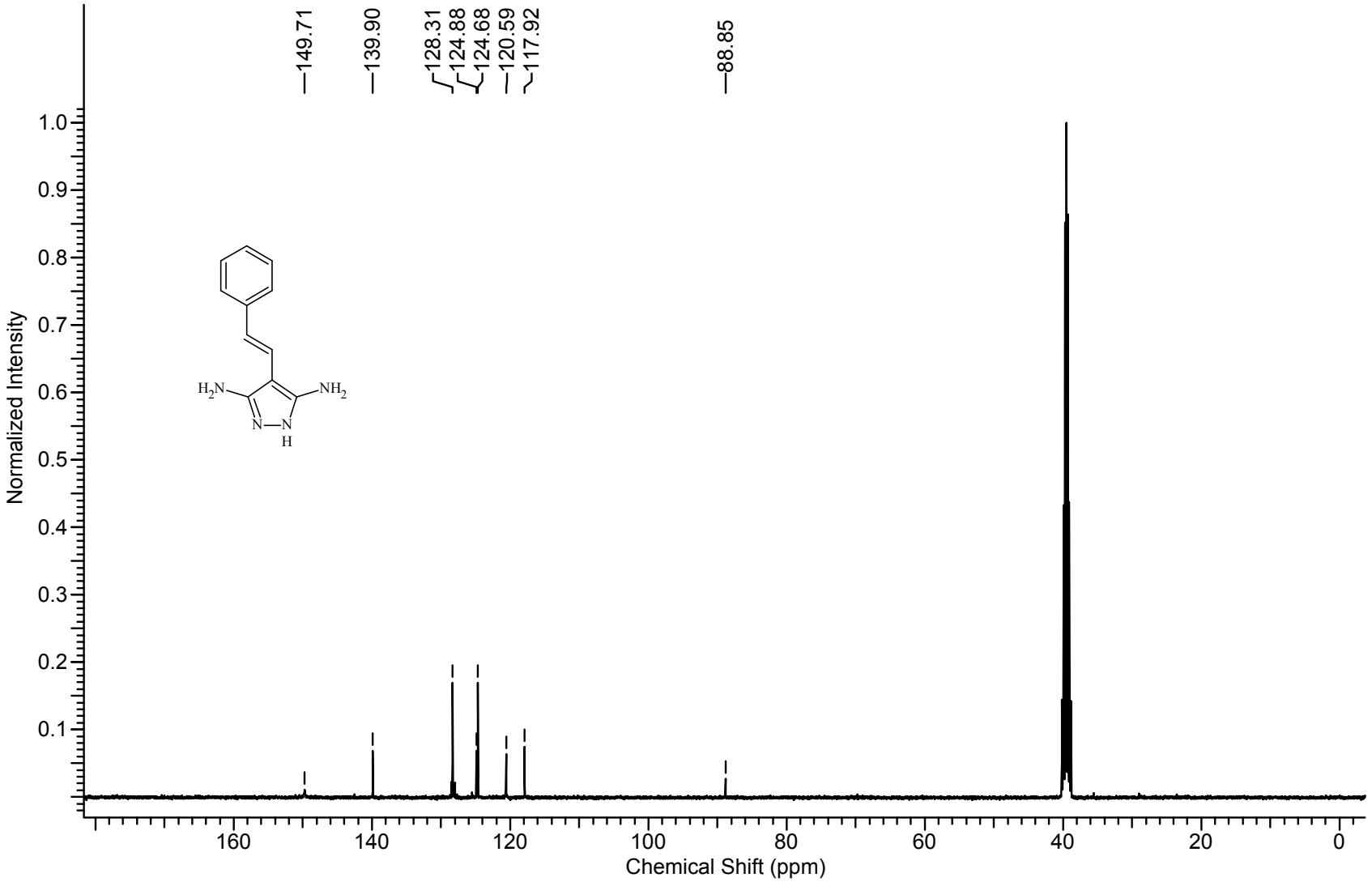
4-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3,5-diamine (5k).



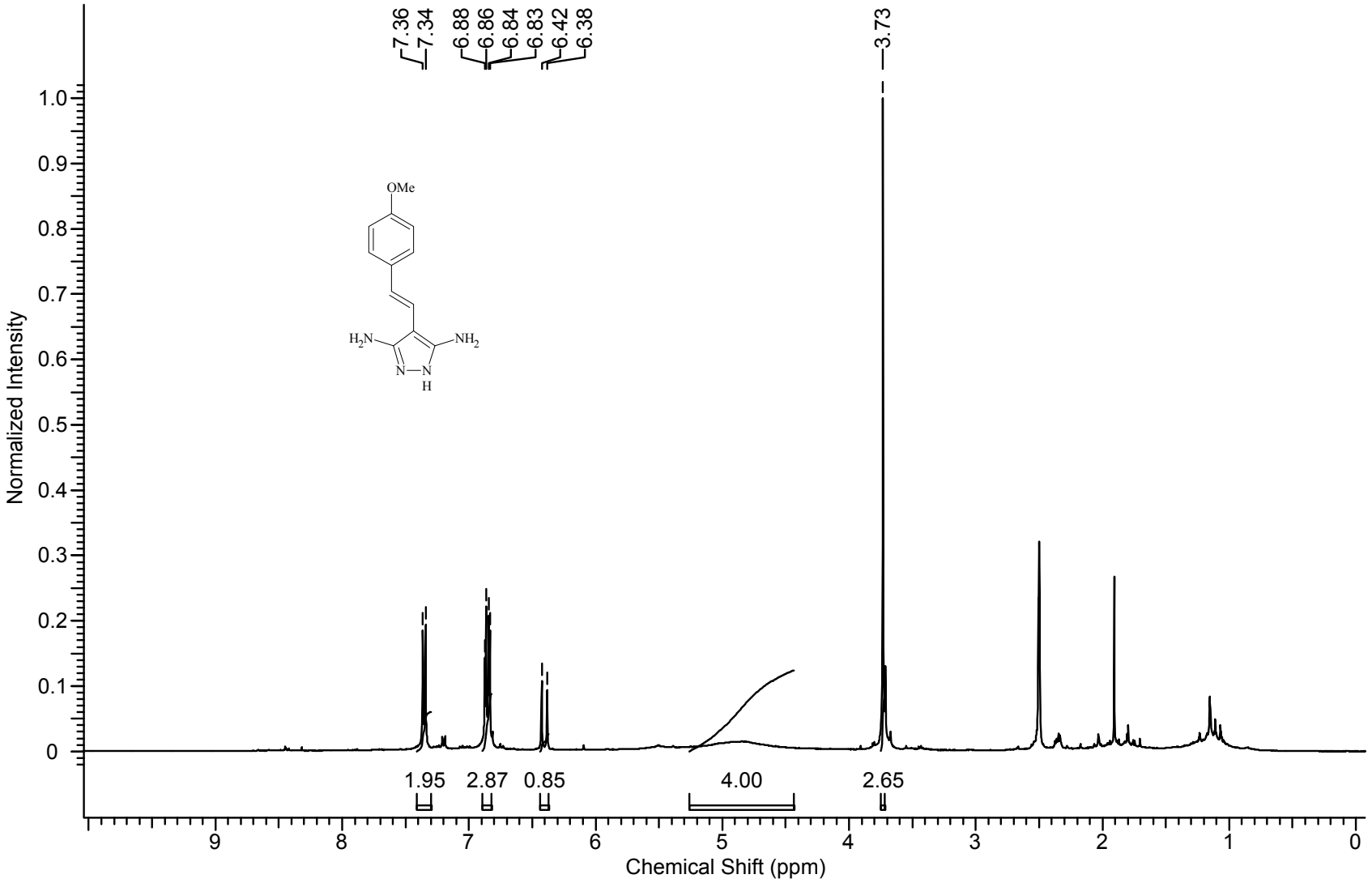
(*E*)-4-styryl-1*H*-pyrazole-3,5-diamine (5l).



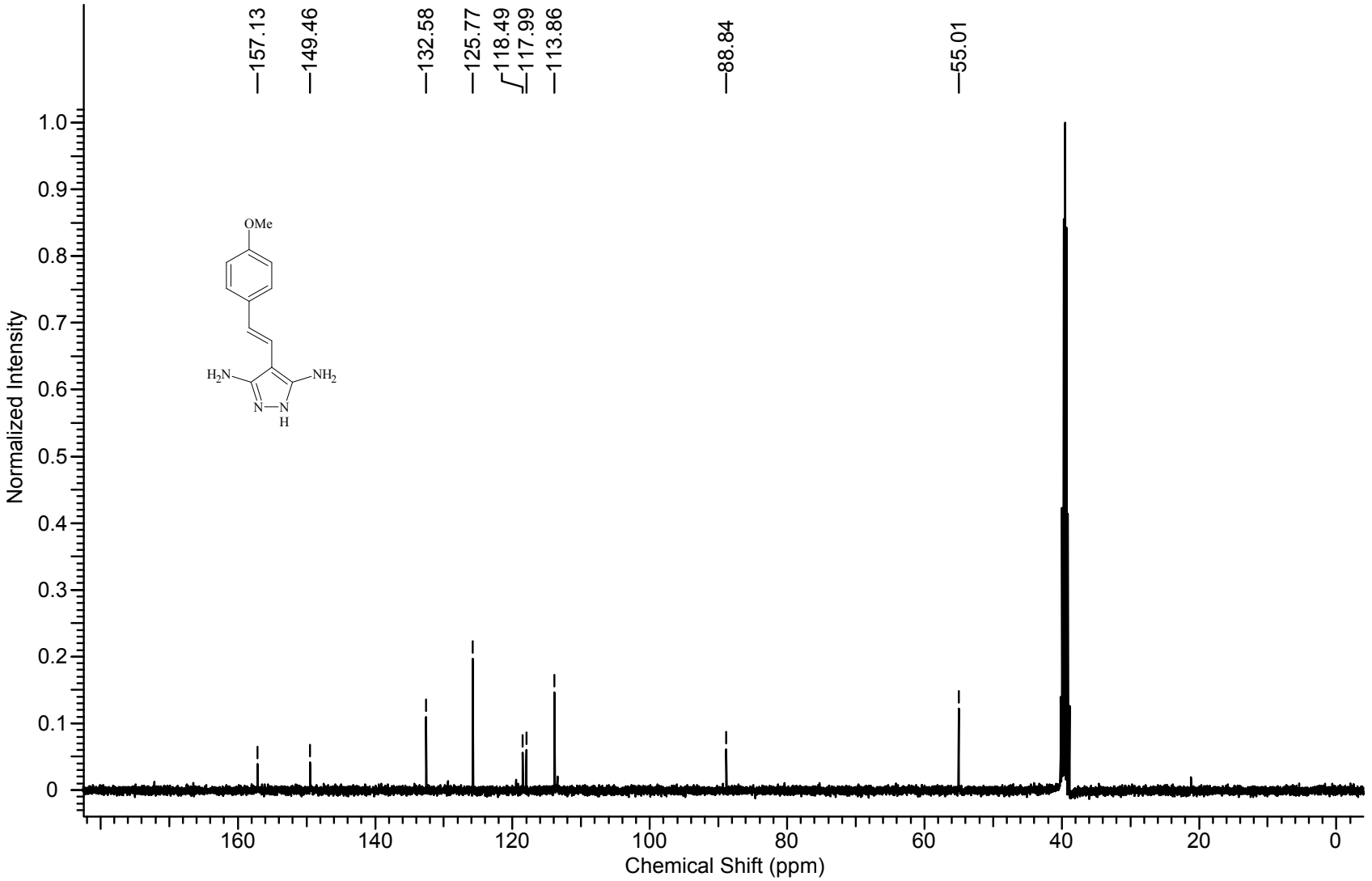
(*E*)-4-styryl-1*H*-pyrazole-3,5-diamine (5l).



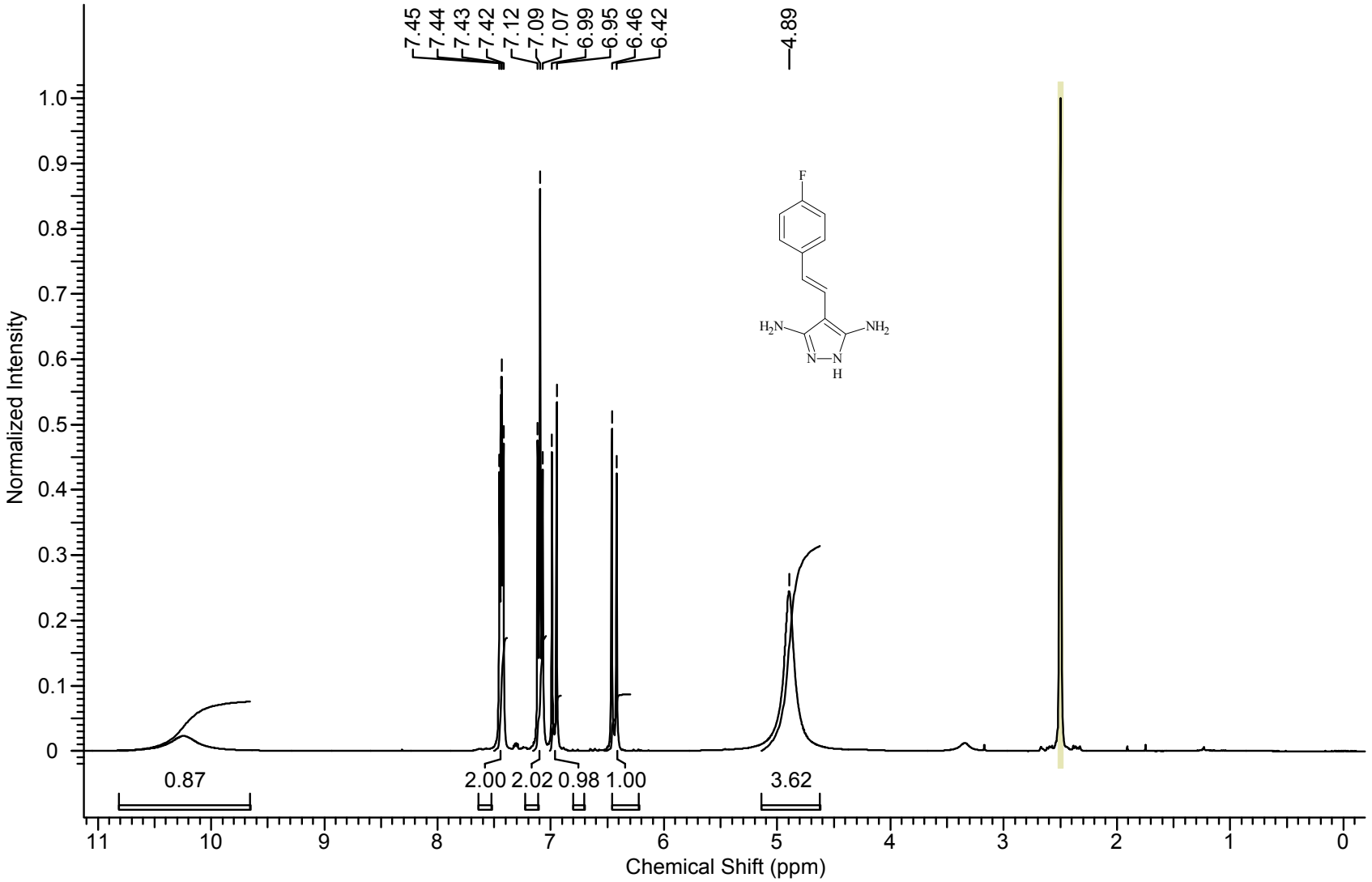
(*E*)-4-(4-methoxystyryl)-1*H*-pyrazole-3,5-diamine (5m).



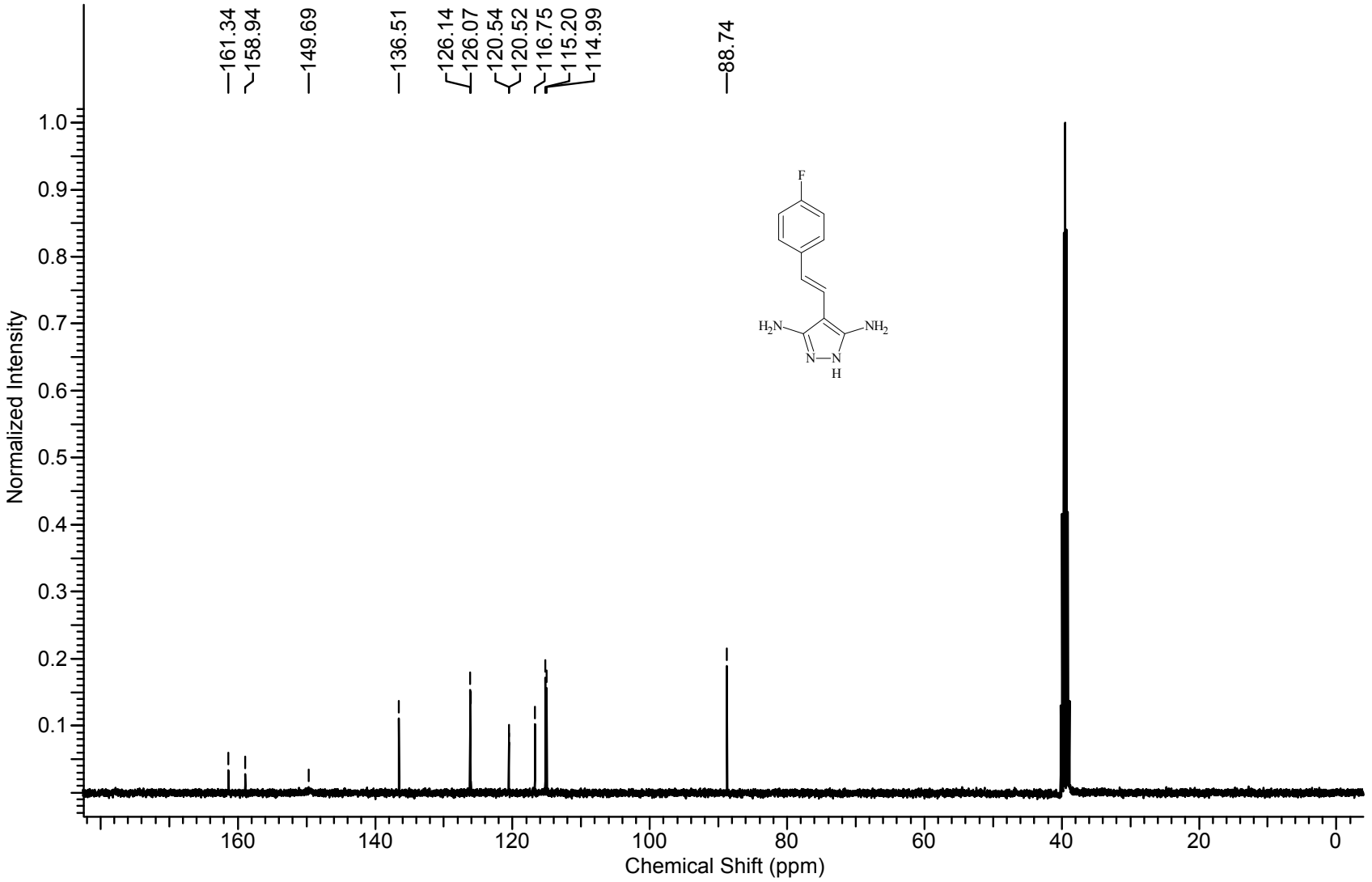
(*E*)-4-(4-methoxystyryl)-1*H*-pyrazole-3,5-diamine (5m).



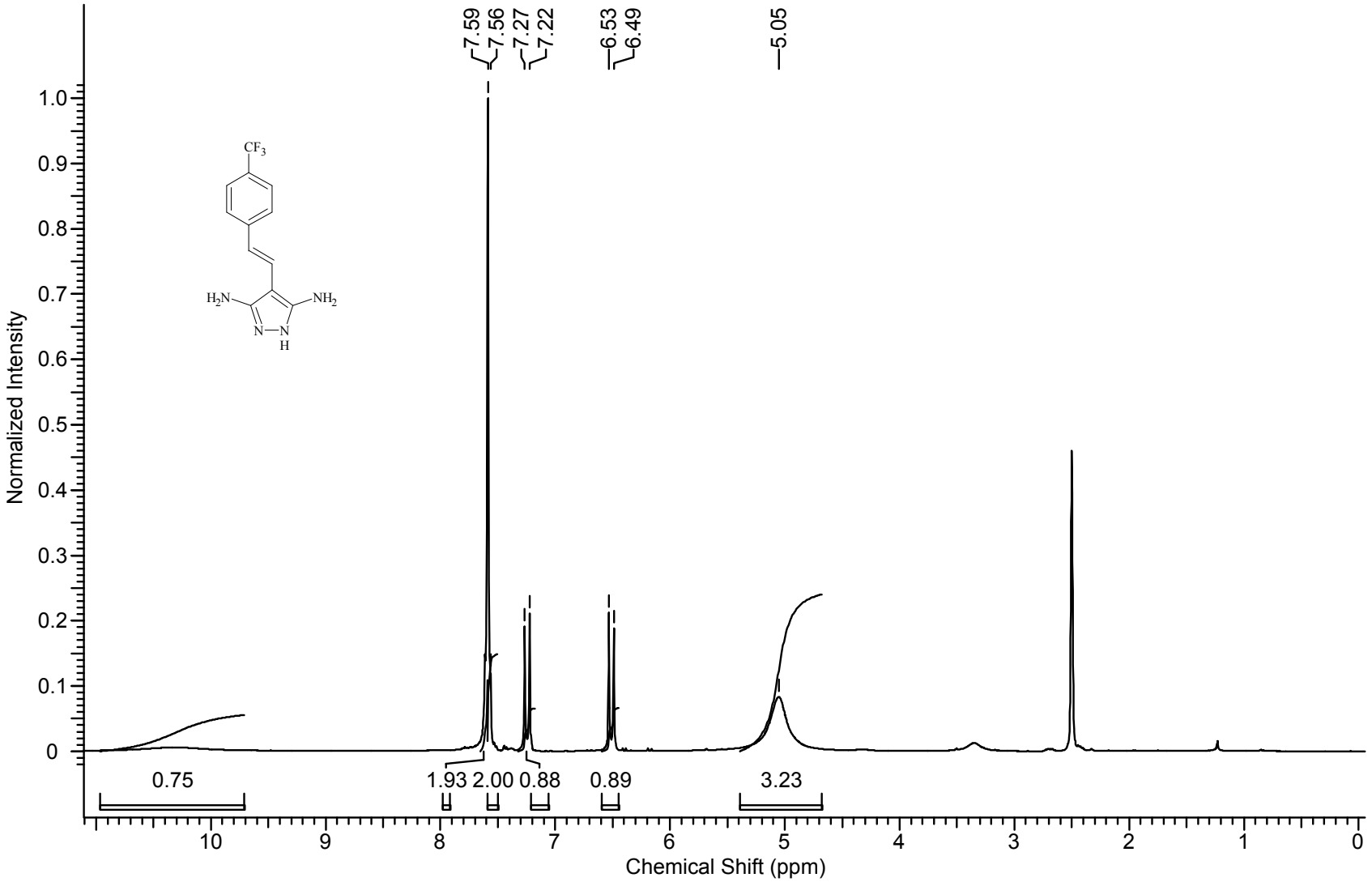
(*E*)-4-(4-fluorostyryl)-1*H*-pyrazole-3,5-diamine (5n).



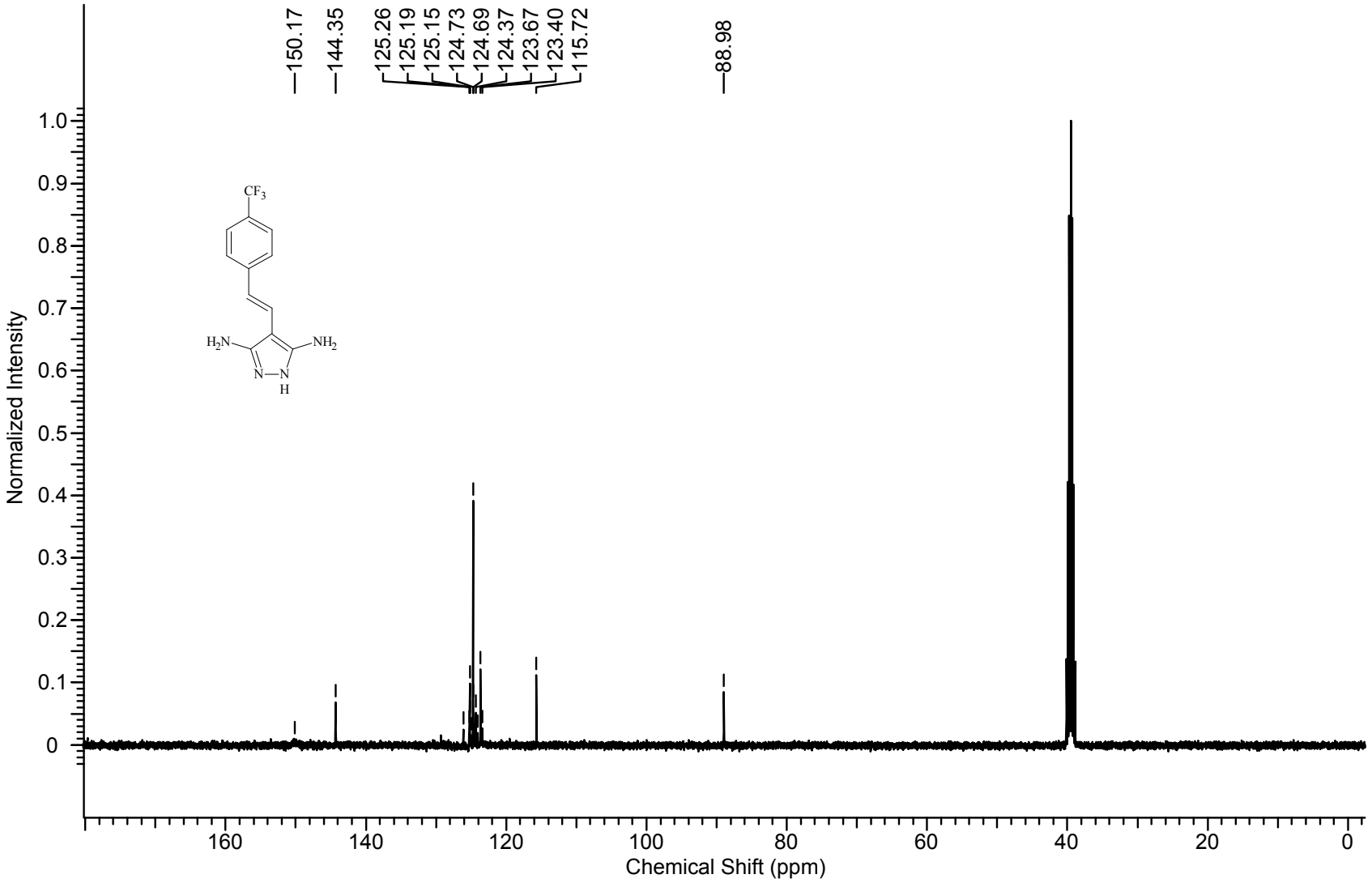
(*E*)-4-(4-fluorostyryl)-1*H*-pyrazole-3,5-diamine (5n).



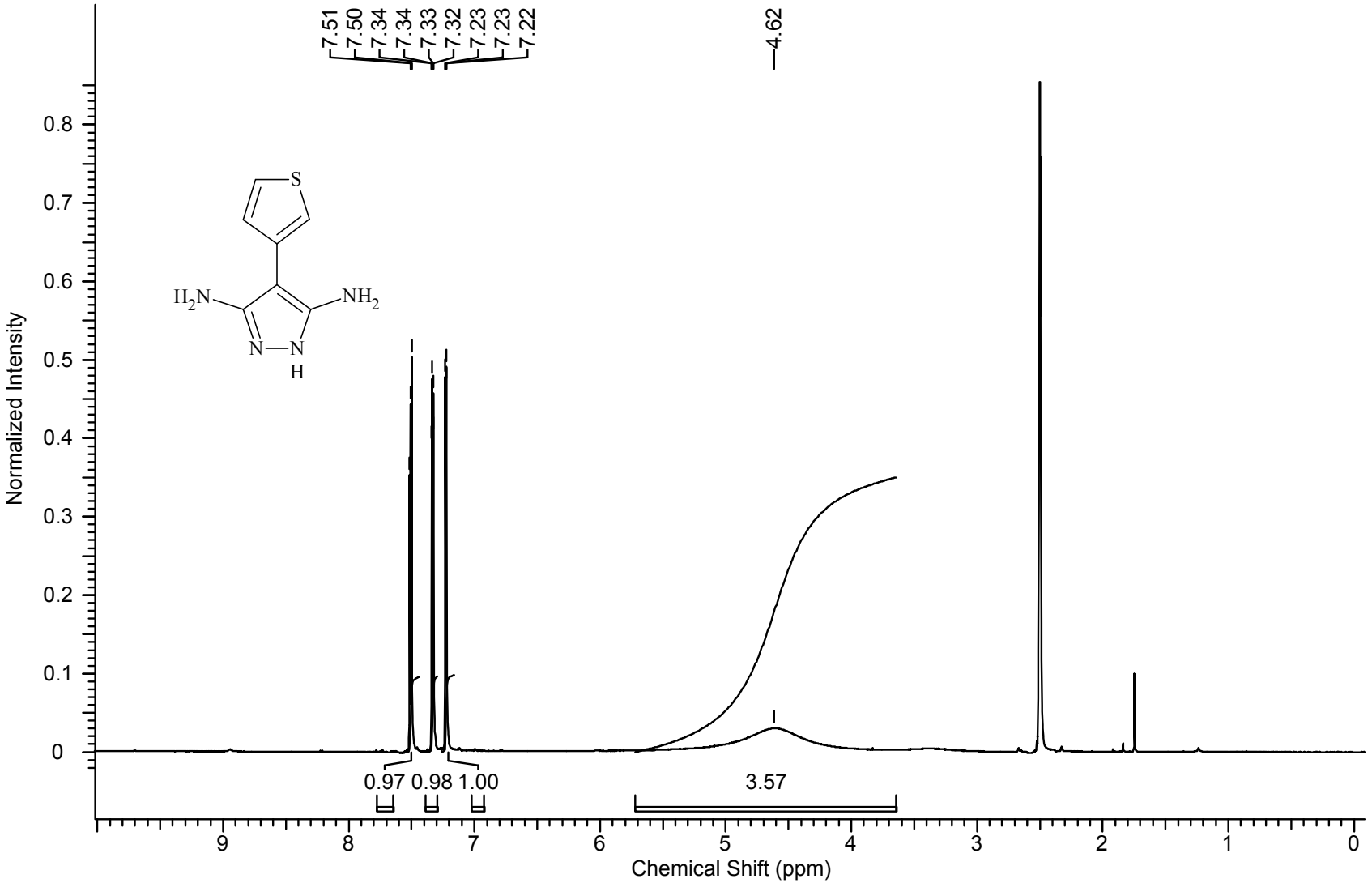
(*E*)-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazole-3,5-diamine (5o).



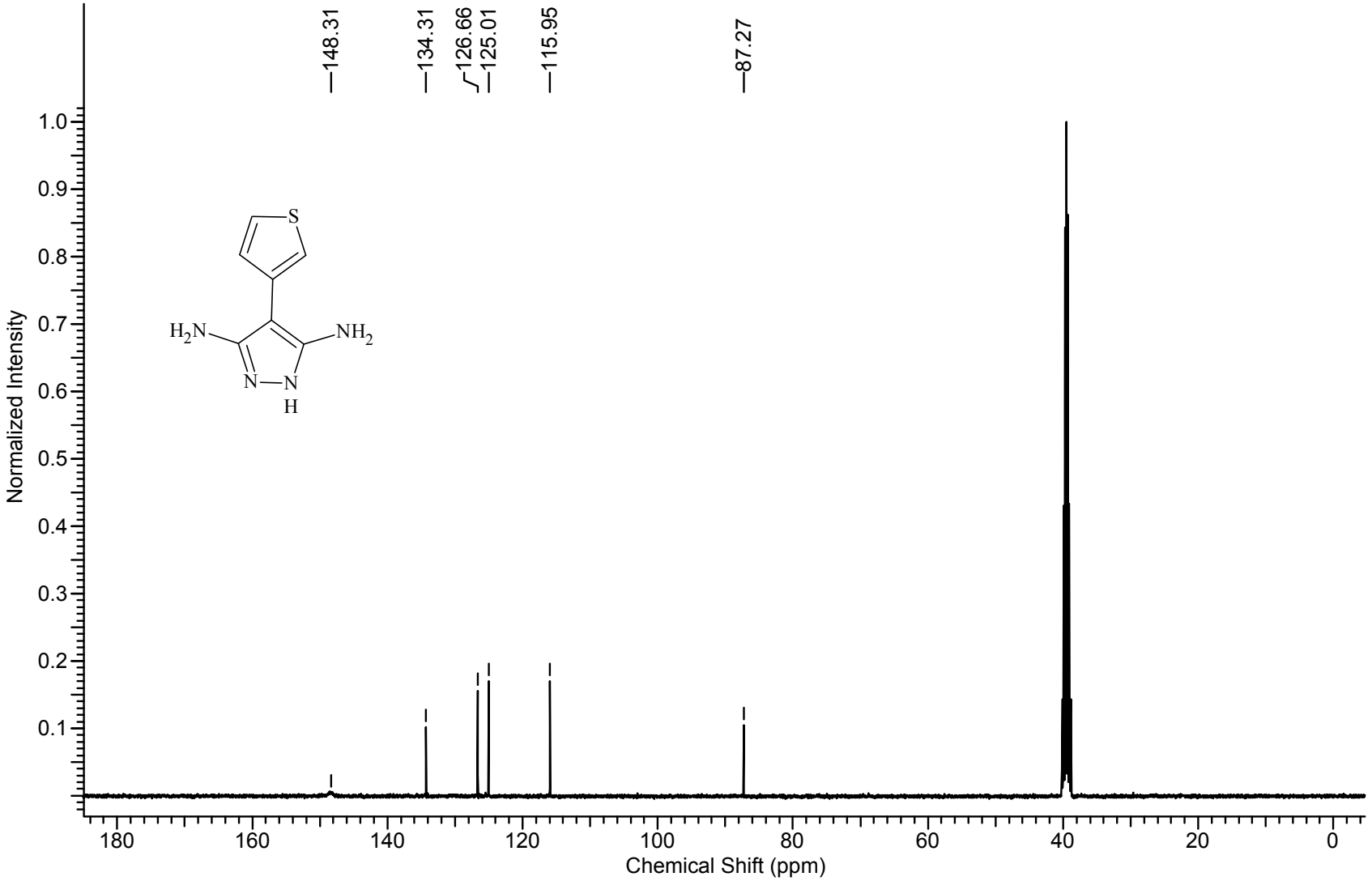
(*E*)-4-(4-(trifluoromethyl)styryl)-1*H*-pyrazole-3,5-diamine (5o).



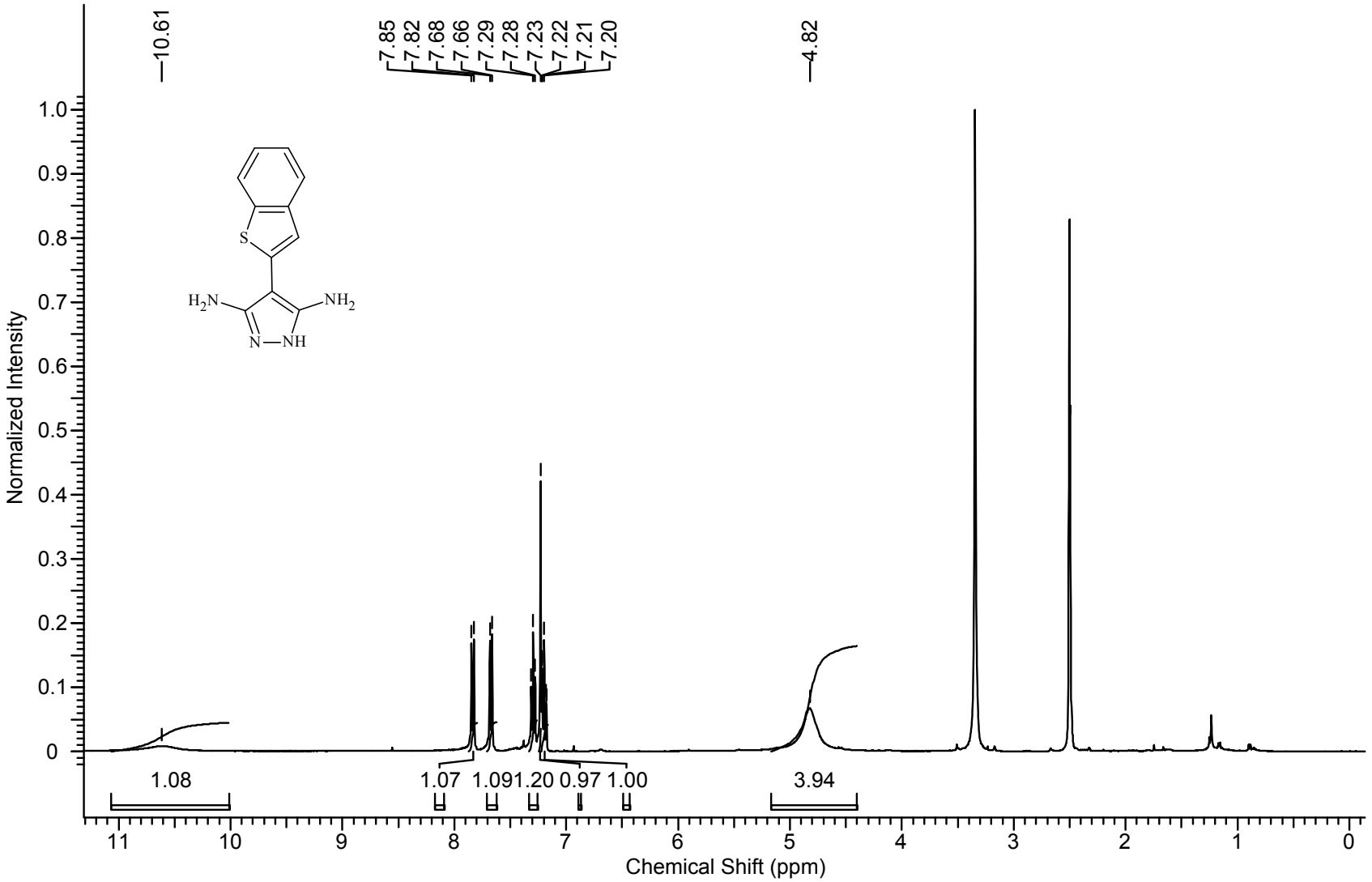
4-(thiophen-3-yl)-1*H*-pyrazole-3,5-diamine (5p).



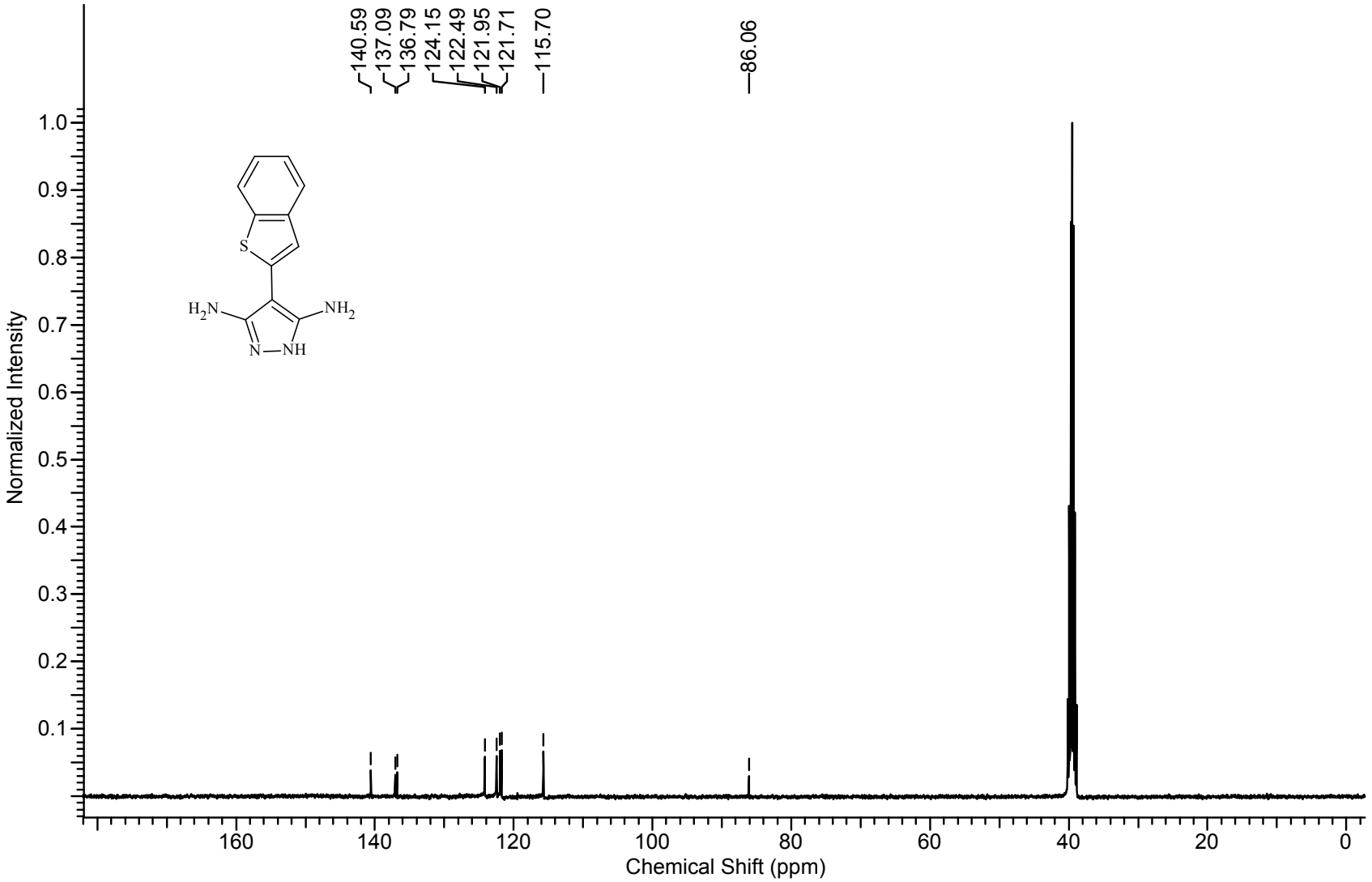
4-(thiophen-3-yl)-1*H*-pyrazole-3,5-diamine (5p).



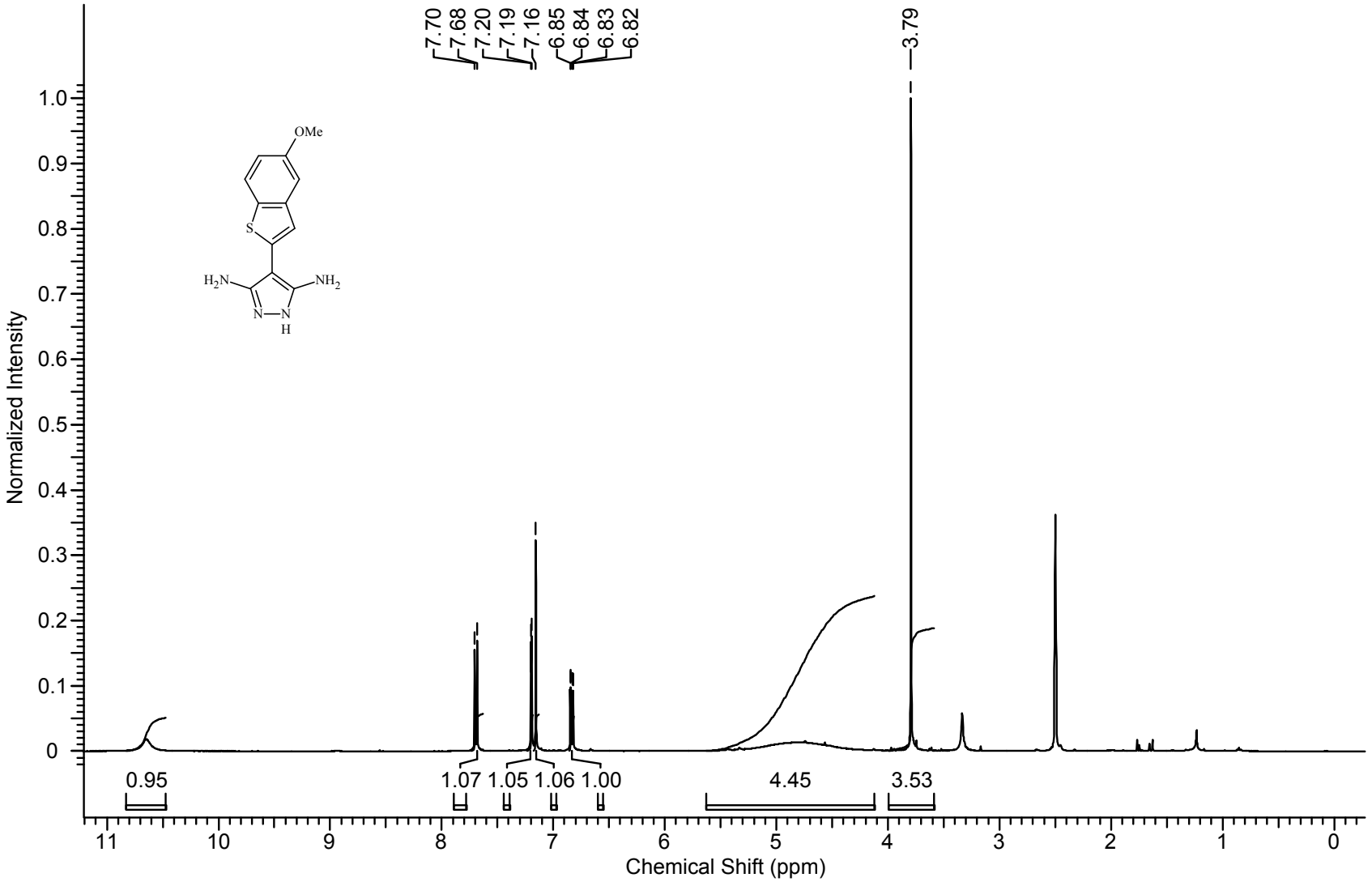
4-(benzo[*b*]thiophen-2-yl)-1*H*-pyrazole-3,5-diamine (5r).



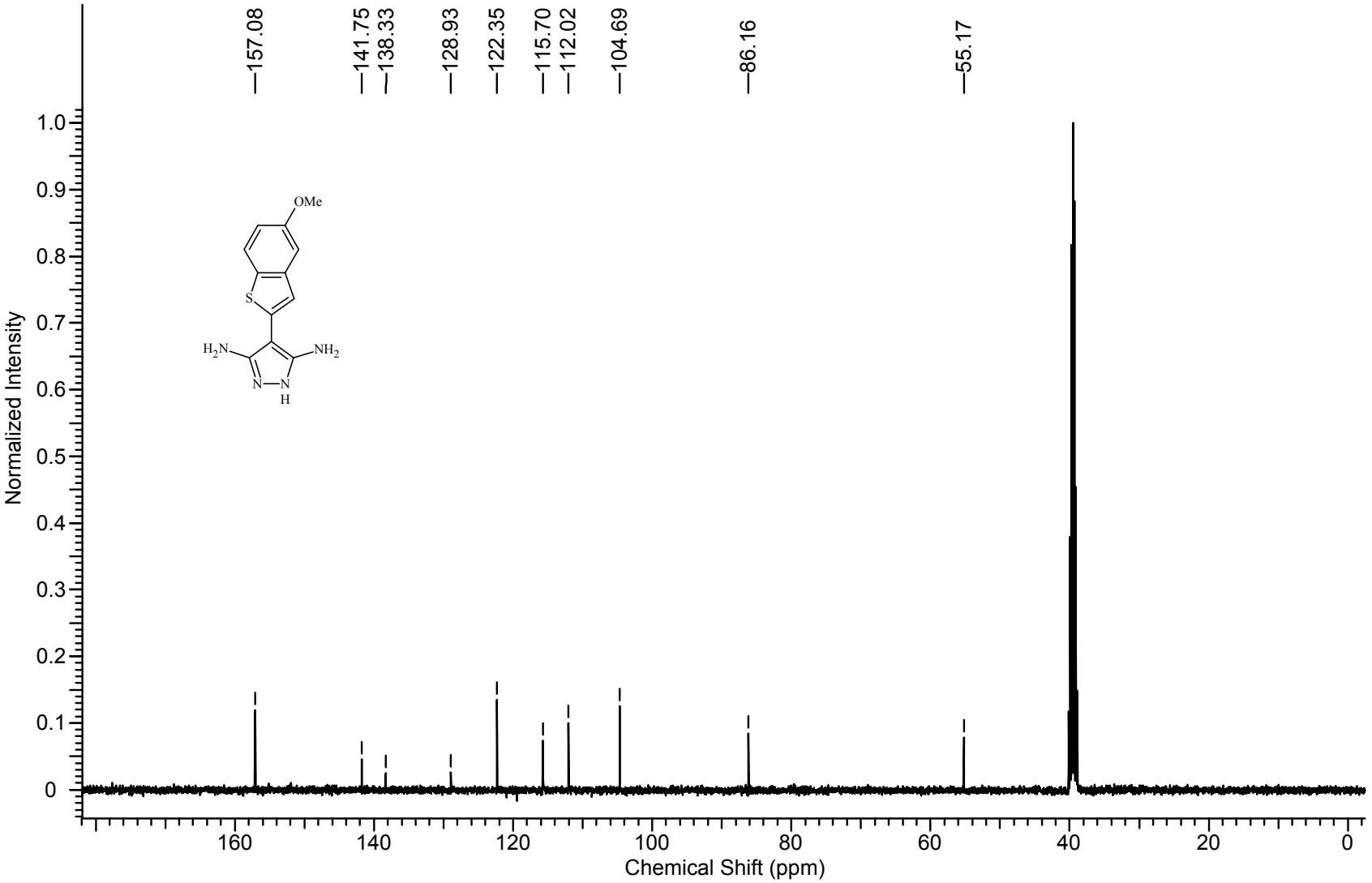
4-(benzo[*b*]thiophen-2-yl)-1*H*-pyrazole-3,5-diamine (5r).



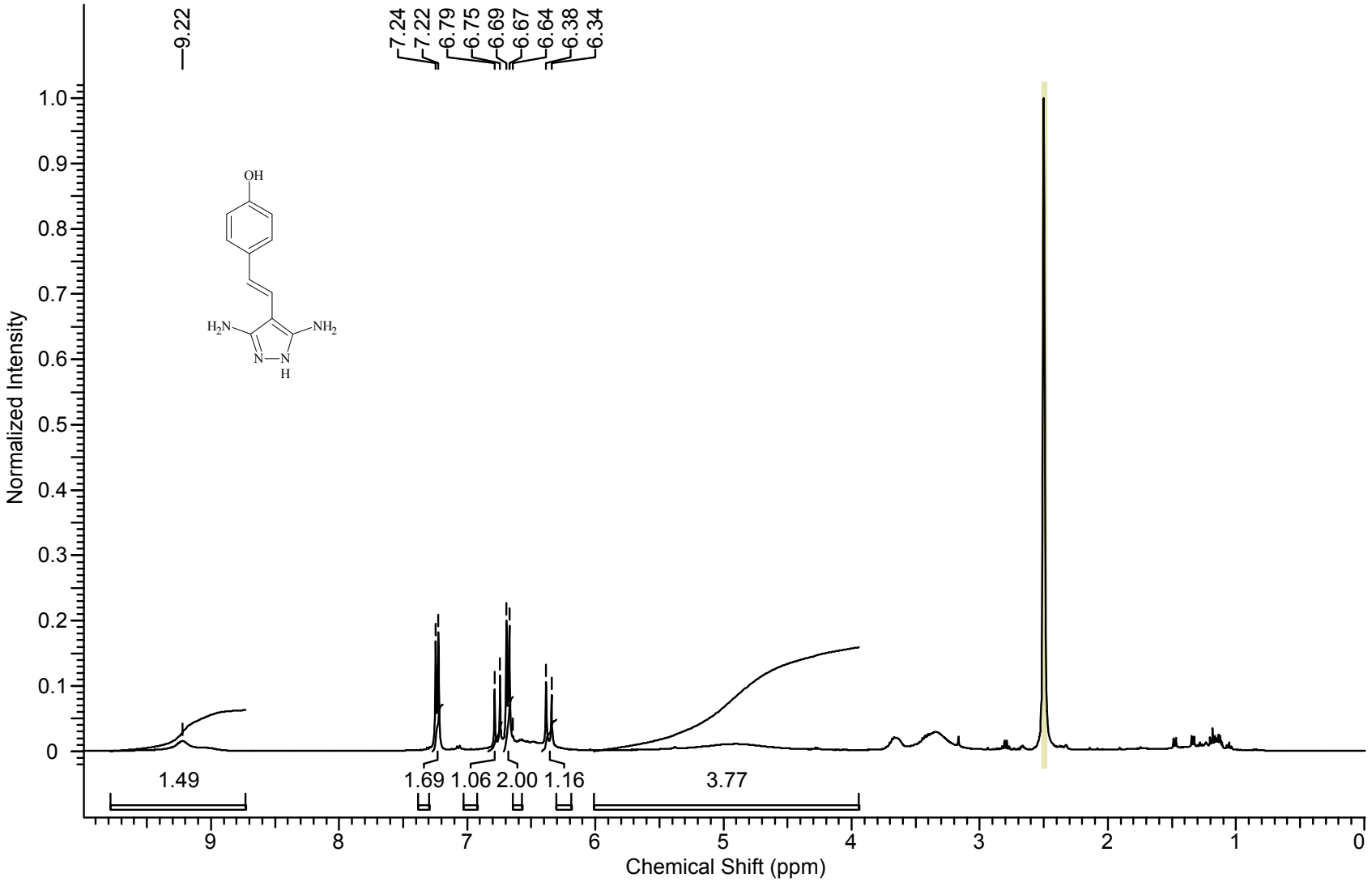
4-(5-methoxybenzo[*b*]thiophene-2-yl)-1*H*-pyrazole-3,5-diamine (5s).



4-(5-methoxybenzo[*b*]thiophene-2-yl)-1*H*-pyrazole-3,5-diamine (5s).



4-(2-(3,5-diamino-1*H*-pyrazol-4-yl)vinyl)phenol (1).



4-(2-(3,5-diamino-1*H*-pyrazol-4-yl)vinyl)phenol (1).