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Supporting Information

A protocol for directly accessing geminal C-4 diarylated pyrazol-5(4H)-ones via tandem C-H aryne insertion and their inceptive neurobiological evaluation

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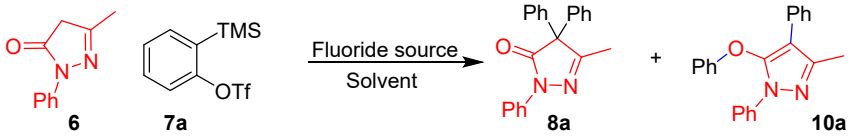
Table of Contents

Optimization table

Table S1: Optimization of diarylation on pyrazolone[a]



6 7a 8a 10a

Entry	Base	1a:2a:fluoride source	Solvent	Temp^r (^{0}C)	Time (h)	Yield (%) 8a	Yield (%) 10a
1	CsF	1:2.5:5	MeCN	RT	24	-	-
2	CsF	1:2.5:5	MeCN	50	24	10	-
3	CsF	1:2.5:5	MeCN	100	16	50	-
4	CsF	1:1.1:2.5	MeCN	100	16	25	-
5[c]	CsF	1:2.5:5	THF	100	16	39	-
6[c]	CsF	1:2.5:5	MeCN	100	16	70	-
7[c]	CsF	1:3.5:7	MeCN	100	16	72	-
8[c]	CsF	1:2.5:5	MeCN	100	8	43	-
9[c]	CsF	1:2.5:5	MeCN	100	24	73	-
10[c]	CsF	1:2.5:5	MeCN	110	16	66	-
11[c]	NH_4F	1:2.5:5	MeCN	100	16	-	-
12[c]	KF	1:2.5:5	MeCN	100	16	45	-
13[c]	TBAF	1:2.5:5	THF	100	16	38	47

[a] Reaction Condition: *O*-silyl aryl triflate (0.25 mmol), edaravone (0.1 mmol), fluoride source, solvent (1 mL); [b] isolated yield; [c] 4A^o Molecular seives added.

General Remarks

All reagents, starting materials were of technical grade and purchased from available commercial sources. Solvents used for reaction were dried before use. All the reactions were performed under moisture free N_2 atmosphere. Progress of reactions were monitored by TLC with UV light, iodine and p-anisaldehyde solution spray visualization technique. Products were purified by Column chromatography (100-200 mesh silica gel as stationary phase) with hexane and ethyl acetate as eluent. Melting point were recorded on Polmon MP96 instrument. ^{1}H NMR 400 or 500 MHz and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker NMR spectrometer. The Chemical shift values are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$, and peak splitting patterns are denoted as s = singlet, d = doublet, dd = doublet of doublet and t = triplet. Coupling constants (*J*) were reported in hertz. Liquid Chromatography-Mass Spectrometry (LC-MS) were recorded on Shimadzu technology LCMS-8040 instrument. Shimadzu technology LAB solution instrument was used for HPLC separation of the compounds. IR spectra were recorded on an ECO-ATR, ALPHA BRUKER spectrometer. Waters-TOF spectrometer was used to record high-resolution mass spectra (HRMS).

Preparation of pyrazolones and aryne precursors

All the pyrazolone moieties were prepared by following known literature procedures.[1] *o*-silyl aryl triflates were used as aryne precursors and synthesized by known procedures.[2]

X-ray Crystallography Information

X-ray data for the compounds **8a, 9a** and **10a** were collected at room temperature on a Bruker D8 QUEST instrument with an IμS Mo microsource (λ = 0.7107 A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs.[3] The structure was solved using intrinsic phasing method[4] and further refined with the SHELXL[4] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(C)$ for other H atoms]. Crystal suitable for single crystal X-ray was grown in diethyl ether/hexane (4:6) at 4 ^{o}C in a refrigerator.

General procedure for the synthesis of geminal diarylated product:

An oven dried ace pressure tube was charged with pyrazolone (0.1 mmol), CsF (0.5 mmol), aryne precursor (0.25 mmol) and 4 Å molecular sieves (100 mg) in acetonitrile medium (1 mL) under nitrogen atmosphere. The tube was then tightly capped and heated at 100 °C for 16 hours. After completion of the reaction, water was added and the reaction mixture was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduce pressure. The crude mixture was purified by column chromatography using hexane:ethyl acetate (98:2) mixture as an eluent.

General procedure for the synthesis of geminal C-diarylated product along with C, O-diarylated product:

An oven dried ace pressure tube was charged with pyrazolone (0.1 mmol), 1M solution of TBAF (0.5 mmol) in THF, aryne precursor (0.25 mmol) and 4 Å molecular sieves (100 mg) in THF medium (1 mL) under nitrogen atmosphere. The tube was then tightly capped and heated at 100 °C for 16 h. After completion of the reaction, water was added and the reaction mixture was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduce pressure. The crude residue was purified by column chromatography using hexane:ethyl acetate (98:2) mixture as an eluent to obtain mixture of geminal C-diarylated and C, O- diarylated products. The mixture of geminal C-diarylated and C, O- diarylated was separated further by using HPLC. For this protocol yields are calculated on the basis of LC-MS data. HPLC separations are performed in Shimadzu UFLC instrument with LUNA C8 column by using acetonitrile and 0.1% formic acid in water as eluent.

Biological experiments:

1. **Sulforhodamine B (SRB) assay**

The cytotoxicity against Neuro 2a (N2A) cell line were assessed with three different concentrations (1μM,0.1 μM,0.01 μM) through SRB assay after 24 h of incubation. N2A cells were passaged and seeded in 96 well plates at a density of 9600 cm2 per well. After 24 hours, the cells were treated with ice cold 50% TCA and incubated at 4°C for 1 hour. The plates were rinsed and dried in slow flowing water before being incubated in room temperature with 0.04% SRB dye for 1 hour. The plates were then rinsed with 1% acetic acid and dried at room temperature. After adding 10mM Tris base to each well, the absorbance was measured at 510 nm using a microplate reader.

2. **IC_{50} determination**

The most popular and useful method of determining a drug effectiveness is by calculating its half-maximal inhibitory concentration (IC_{50}). It provides a gauge of a drug's efficacy in pharmacological research by showing the amount of drug required to block a biological process by 50%. Plotting x-y and fitting the data with a straight line is the simplest way to estimate the IC_{50} (linear regression). Next, using the fitted line, the IC_{50} value is calculated, as follows:

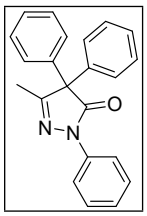
Y = a * X+ b, IC50 = (0.5 - b)/a.

3. **AChE inhibitory activity**

The AChE inhibitory activity of 16 compounds were screened in vitro in n2a cell line using *Ellman*'s spectrophotometric method. The chemical principle of *Ellman*'s method involves hydrolysis of acetylcholine by acetyl cholinesterase to produce acetic acid and choline, which reacts with *Ellman*'s reagent (5,5′-bisdithionitrobenzoic acid [DTNB]) to form a compound exhibiting light absorbance at 412 nm. Galantamine was used as positive control and test was conducted in triplicate.

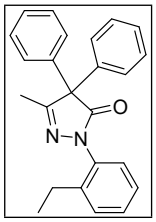
Spectroscopic data

3-Methyl-1, 4, 4-triphenyl-1*H*-pyrazol-5(4H)-one (8a):



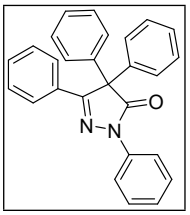
(23 mg, 70% and 12 mg, 38%); Yellow solid; mp 68-70 °C; IR (KBr, cm^{-1}): υ 2922, 1714, 1593, 1495, 1356, 1269, 1159, 748, 692; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.0 Hz, 2H); 7.42-7.35 (m, 8H); 7.25-7.17 (m, 5H); 2.17 (s, 3H) ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 161.8, 138.1, 137.3, 130.3, 129.1, 128.9, 128.5, 128.2, 125.2, 122.8, 120.5, 118.9, 69.0, 15.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1486 found 327.1490.

1-(2-Ethylphenyl)-3methyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (8b):



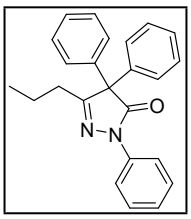
(24 mg, 68%); Yellow oil; IR (KBr, cm^{-1}): υ 2966, 2922, 1717, 1597, 1495, 1447, 1361, 1268, 1163, 752, 698; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45-7.35 (m, 6H); 7.33-7.25 (m, 8H); 2.59 (q, *J* = 7.5 Hz, 2H); 2.14 (s, 3H); 1.14 (t, *J* = 7.5Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 161.5, 141.5, 137.3, 135.1, 129.4, 129.1, 129.0, 128.5, 128.2, 127.5, 126.7, 115.5, 67.6, 24.7, 15.6, 14.6. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O$ 355.1799 found 355.1809.

1, 3, 4, 4-Tetraphenyl-1*H*-pyrazol-5(4H)-one (8c):



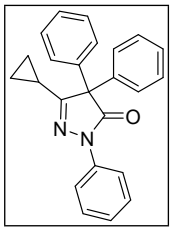
(23 mg, 59% and 18 mg, 46%); Yellow solid; mp 144-146 °C; IR (KBr, cm^{-1}): υ 2923, 2852, 1714, 1594, 1491, 1374, 1293, 1162, 756, 690; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 2H); 7.75 (d, *J* = 8.4 Hz, 2H); 7.47-7.41 (m, 6H); 7.37-731 (m, 7H); 7.30-7.27 (m, 2H); 7.25-7.21 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 160.2, 138.1, 136.6, 130.9, 130.2, 129.0, 128.9, 128.4, 128.2, 127.6, 125.4, 119.1, 67.7; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O$ 389.1643 found 389.1646.

1, 4, 4-Triphenyl-3-propyl-1*H*-pyrazol-5(4H)-one (8d):



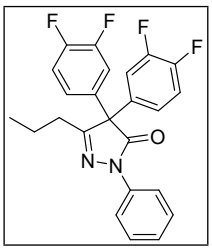
(23 mg, 65%); Yellow solid; ; mp 81-83 °C; IR (KBr, cm^{-1}): υ 2925, 2851, 1711, 1642, 1595, 1493, 1449, 1357, 1272, 1159, 1032, 755, 696; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.6 Hz, 2H); 7.42-7.33 (m, 8H); 7.24-7.17 (m, 5H), 2.41 (t, *J* = 7.2 Hz, 2H); 1.68-1.60 (m, 2H); 0.93 (t, *J* = 7.6 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 164.8, 138.3, 137.5, 133.5, 130.3, 129.0, 128.5, 128.2, 125.0, 122.3, 120.5, 119.0, 115.5, 69.2, 31.3, 19.0, 13.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O$ 355.1805 found 355.1804.

3-Cyclopropyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (8e):



(25 mg, 70%); White solid; mp 136-138 °C; IR (KBr, cm^{-1}): υ 2923, 2853, 1711, 1592, 1551, 1490, 1344, 1261, 1187, 1110, 807, 769, 698; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.5 Hz, 2H); 7.40-7.33 (m, 12H); 7.17 (t, *J* = 7.5 Hz, 1H); 1.70-1.64 (m, 1H); 1.08-1.05 (m, 2H); 0.93-0.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 167.1, 138.3, 137.7, 128.9, 128.8, 128.7, 128.1, 125.0, 118.8, 69.4, 10.6, 9.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{21}N_2O$ 353.1658 found 353.1652.

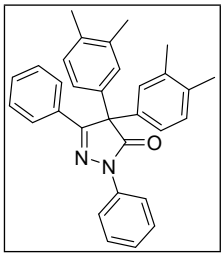
4,4-Bis(3,4-difluorophenyl)-1-phenyl-3-propyl-1*H*-pyrazol-5(4H)-one (8f):



(26 mg, 62%); Yellow oil; IR (KBr, cm^{-1}): υ 2963, 2930, 1716, 1604, 1674, 1500, 1423, 1284, 1213, 1120, 776; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.5 Hz, 2H); 7.42 (t, *J* = 8.25 Hz, 2H); 7.24-7.17 (m, 3H); 7.07-7.03 (m, 2H); 6.96-6.93 (m, 2H); 2.38 (t, *J* = 7.5 Hz, 2H); 1.70 (q, *J* = 7.5 Hz, 2H); 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 163.2, 151.9, 151.8, 151.6; 149.4, 149.3, 149.1, 137.8, 133.6, 129.0, 125.6, 124.6, 124.5, 124.5, 118.9, 118.2, 118.0, 118.0, 117.8, 67.3, 31.2, 19.0, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$) : δ -

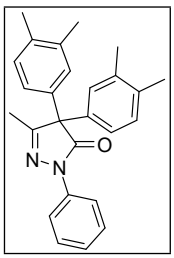
134.71, -134.76, -136.70, -136.76; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}F_4N_2O_3$ 427.1428 found 427.1426.

4,4-bis(3,4-Dimethylphenyl)-1, 3-diphenyl-1*H*-pyrazol-5(4H)-one (8g):



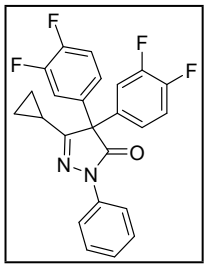
(28 mg, 64%); Yellow solid; m.p. 88-90 °C; IR (KBr, cm^{-1}): υ 2921, 2854, 1721, 1596, 1497, 1371, 1293, 1154, 1071, 871, 796, 693; ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.0 Hz, 1H); 7.77-7.75 (m, 2H); 7.63-7.61 (m, 1H); 7.43 (t, *J* = 7.5 Hz, 1H); 7.37 (t, *J* = 7.5 Hz, 1H); 7.34-7.30 (m, 2H); 7.28 (d, *J* = 7.5 Hz, 1H); 7.25- 7.20 (m, 2H); 7.17 (s, 1H); 7.13 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H); 7.07 (d, *J* = 8.0 Hz, 1H); 7.00-6.95 (m, 1H); 6.65-6.54 (m, 1H); 2.22 (s, 4H); 2.19 (s, 5H); 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 160.6, 155.0, 149.3, 138.3, 137.1, 136.7, 135.0, 134.1, 131.2, 130.0, 129.5, 129.0, 128.9, 128.3, 128.1, 127.8, 126.9, 126.5, 125.2, 122.4, 119.1, 116.9, 112.5, 67.2, 20.0, 19.5; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{29}N_2O$ 445.2274 found 445.2264

4,4-bis(3,4-Dimethylphenyl)- 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one (8h):



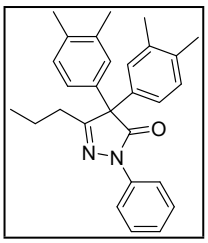
(28 mg, 73%); White solid; mp 143-144 °C; IR (KBr, cm^{-1}): υ 2920, 2861, 1715, 1596, 1497, 1355, 1269, 1115,1021, 756; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.6 Hz, 2H); 7.41 (t, *J* = 7.6 Hz, 2H); 7.19 (t, *J* = 7.6 Hz, 1H); 7.13 (d, *J* = 8.0 Hz, 2H); 6.99 (s, 2H); 6.96 (d, *J* = 7.6 Hz, 2H); 2.26 (s, 6H); 2.24 (s, 6H); 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 162.4, 138.3, 137.4, 136.7, 134.7, 130.2, 129.2, 128.8, 125.9, 125.0, 118.9, 68.6, 20.0, 19.5, 15.6; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O$ 383.2118 found 383.2117

3-Cyclopropyl-4,4-bis(3,4-difluorophenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (8i):



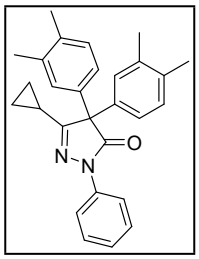
(25 mg, 60%); Yellow solid; mp 102-104 °C; IR (KBr, cm^{-1}): υ 3065, 3008, 1705, 1610, 1596, 1517, 1499, 1414, 1354, 1283, 1224, 1122, 762; ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 2H); 7.40 (t, *J* = 8.0 Hz, 2H); 7.23-7.15 (m, 5H); 7.09-7.06 (m, 2H); 1.62-1.57 (m, 1H); 1.14-1.11 (m, 2H); 1.01-0.98 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 165.7, 151.8, 151.8, 151.7, 151.6, 149.3, 149.3, 149.2, 149.1, 137.8, 133.8, 128.9, 125.5, 124.7, 118.8, 118.1, 117.9, 67.3, 10.6, 10.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -134.98, -135.03, -136.89, -136.95; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{17}F_4N_2O$ 425.1272 found 425.1269

4,4-bis(3,4-Dimethylphenyl)- 3-propyl-1-phenyl-1*H*-pyrazol-5(4H)-one (8j):



(28 mg, 68%); Yellow oil; IR (KBr, cm^{-1}): υ 2699, 2922, 1716, 1638, 1498, 1452, 1351, 109, 1115, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H); 7.42-7.37 (m, 2H); 7.17 (t, *J* = 7.6 Hz, 1H); 7.11 (d, *J* = 7.6 Hz, 2H); 6.97 (s, 2H); 6.94 (d, *J* = 7.6 Hz, 2H); 2.38 (t, *J* = 7.6 Hz, 2H); 2.25 (s, 6H); 2.22 (s, 6H); 1.67 (q, *J* = 7.6 Hz, 2H); 0.95 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 165.3, 138.5, 137.2, 136.6, 134.9, 130.1, 129.5, 128.8, 125.9, 124.8, 118.9, 68.7, 31.2, 20.0, 19.5, 18.9, 14.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}N_2O$ 411.2431 found 411.2445.

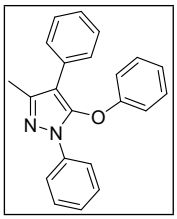
3-Cyclopropyl-4,4-bis(3,4-difluorophenyl)-1-phenyl-1H-pyrazol-5(4H)-one (8k):



(30 mg, 73%); White Solid; m.p. 108-110 °C; IR (KBr, cm^{-1}): υ 2920, 1711, 1657, 1592, 1450, 1345, 1220, 1156, 1082, 1027, 906, 885, 802; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.5 Hz, 2H); 7.37 (t, *J* = 7.5 Hz, 2H); 7.15-7.04 (m, 7H); 2.26 (s, 6H); 2.23 (s, 6H); 1.69-1.64 (m, 1H); 1.09-1.06 (m, 2H); 0.92-.089 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 167.4, 158.9, 138.4,

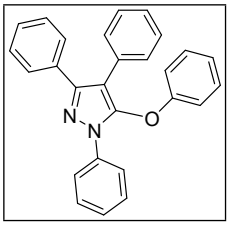
137.1, 136.4, 135.0, 129.9, 129.6, 128.7, 126.1, 124.7, 118.7, 68.9, 20.0, 19.4, 10.4, 10.2; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_2O$ 409.2274 found 409.2267.

3-Methyl-5-phenoxy-1, 4-diphenyl-1H-pyrazole (10a):



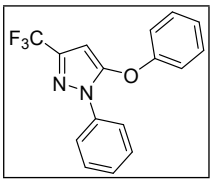
(15 mg, 47%); White solid; mp 68-72 °C; IR (KBr, cm^{-1}): υ 2923, 2853, 1714, 1495, 1385, 1356, 1269, 1159, 1110, 1034, 975, 748, 692; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.6 Hz, 2H); 7.39-7.29 (m, 6H); 7.25-7.09 (m, 4H); 6.91 (t, *J* = 7.5 Hz, 1H); 6.83 (d, *J* = 8.4 Hz, 2H); 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3; 148.9; 138.4; 132.2; 132.1, 132.0; 129.9; 129.0; 128.6; 128.5; 126.5; 124.5; 122.2; 118.1; 91.8; 14.6; HPLC: tR = 4.36 min (for **8a**) tR = 7.61 min (for **10a**) (LUNA C8, 65% ACN-0.1% FA in water, 1 mL/min); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_2O$ 327.1486 found 327.1488.

5-Phenoxy-1, 3, 4-triphenyl-1H-pyrazole (10b):



(12 mg, 32%); White solid; mp 127-130 °C; IR (KBr, cm^{-1}): υ 2924, 2854, 1714, 1593, 1491, 1453, 1425, 1372, 1294, 1210, 1163, 1120, 1072, 1027, 963, 757, 694; ^1H NMR (500 MHz, $CDCl_3$): 8.10 (d, *J* = 8.0 Hz, 1H); 7.76-7.73 (m, 2H); 7.60-7.58 (m, 1H); 7.46-7.42 (m, 3H); 7.39-7.30 (m, 7H); 7.30-7.28 (m,1H); 7.24-7.13 (m, 4H); 6.91-6.84 (m, 1H) ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6, 150.9, 146.0, 138.2, 136.6, 133.3, 130.2, 129.6, , 129.1, 128.9, 128.3, 128.0, 127.7, , 126.9, 125.4, 123.2, 122.5, 119.2, 115.6; HPLC: tR = 9.196 min (for **8c**) tR = 10.341 min (for **10b**) (LUNA C8, 70% ACN-0.1% FA in water, 1 mL/min); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O$ 389.1643 found 389.1646

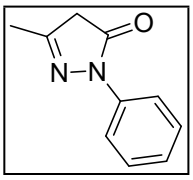
5-Phenoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (9a):



(24 mg, 80%); Yellow solid; IR (KBr, cm^{-1}): υ 2929, 1730, 1595, 1556, 1490, 1454, 1399, 1245, 1139, 1091, 968, 756, 690; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.2 Hz, 2H); 7.47 (t, *J* = 7.6 Hz,

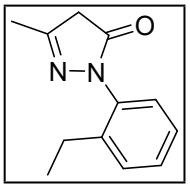
2H); 7.43-7.35 (m, 3H); 7.25-7.21 (m, 1H); 7.18-7.15 (m, 2H); 5.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.6; 152.3; 142.2, 141.8, 137.5, 130.2, 129.2, 128.0, 125.5, 123.1, 122.2, 119.5, 118.5, 89.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.23; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}F_3N_2O$ 305.0896 found 305.0902.

3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one (Edavarone, 6):[5a]



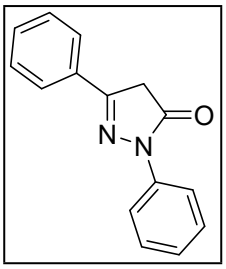
(1.48 g, 85%); White solid; m.p 125-127 °C; IR (KBr, cm^{-1}): 3064, 1712, 1595, 1563, 1498, 1404, 1363, 1155, 1028, 757, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H); 7.39 (t, *J* = 7.6 Hz, 2 H); 7.18 (t, *J* = 7.2 Hz, 2H); 3.44 (s, 2H); 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 156.4, 138.1, 128.9, 125.1, 118.9, 43.1, 17.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_{11}N_2O$ 175.0871 found 175.0866.

3-Methyl-1(2-ethylphenyl)-1H-pyrazol-5(4H)-one (6a):[5b]



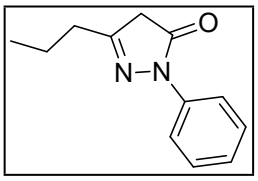
(1.67 g, 83%); White soild; m.p 115-117 °C; IR (KBr, cm^{-1}): 2968,1710,1607,1558,1492,1455,1397,1158,1030,757,673; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.32 (m, 2H); 7.27-7.26 (m, 2H); 3.41 (s, 2H); 2.63 (q, *J* = 7.5 Hz, 2H); 2.18 (s, 3H); 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 156.1, 141.2, 135.1, 129.3, 129.0, 127.2, 126.7, 41.7, 24.6, 17.1, 14.3 HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{15}N_2O$ 203.1184 found 203.1179

1,3-Diphenyl-1H-pyrazol-5(4H)-one (6b):[5c]



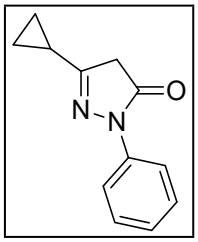
(1.84 g, 78%); Yellow solid; m.p 139-141 °C; IR (KBr, cm^{-1}): 3064,1718,1597,1562,1497,1396,1333,1183,1119,757,692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.4 Hz, 2 H); 7.77-7.74 (m, 2H); 7.45-7.40 (m, 5H); 7.21 (t, *J* = 7.6 Hz, 1H); 3.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 154.7, 138.1, 130.9, 130.8, 129.0, 128.9, 126.0, 125.4, 119.1, 39.7. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_2O$ 237.1028 found 237.1024

1-Phenyl-3-propyl-1H-pyrazol-5(4H)-one (6c):[5d]



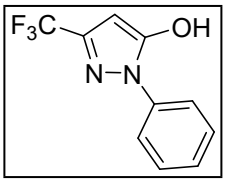
(1.65 g, 82%); White soild; m.p 110-112 °C; IR (KBr, cm^{-1}): 2962,1714,1596,1562,1498,1408,1312,1155,1005,756,692; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88-7.86 (m, 2H); 7.39 (t, *J* = 7.6 Hz, 2H); 7.18 (t, *J* = 7.2 Hz, 2H); 3.42 (s, 2H), 2.48 (t, *J* = 7.6 Hz, 2H); 1.74-1.65 (m, 2H); 1.03 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.9, 155.2, 133.4, 124.1, 120.3, 114.2, 37.0, 28.4, 15.3, 9.1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{15}N_2O$ 203.1184 found 203.1179

3-Cyclopropyl-1-phenyl-1H-pyrazol-5(4H)-one (6d):[5e]



(1.32 g, 66%); Light yellow solid; m.p 99-101 °C; IR (KBr, cm^{-1}): 3011, 1710, 1597, 1565, 1499, 1420, 1346, 1058, 1025, 756, 693; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.4 Hz, 2H); 7.38 (t, *J* = 7.6 Hz, 2H); 7.17 (t, *J* = 7.2 Hz, 1H); 3.30 (s, 2H); 1.91-1.84 (m, 1H); 1.05-1.00 (m, 2H); 0.91-0.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 161.6, 138.1,128.8, 125.0, 118.9, 40.1, 12.2, 7.9; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$ 201.1028 found 201.1020.

1-Phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (6e):[5g]



(1.50 g, 66%); Light yellow solid; m.p 195-197 °C; IR (KBr, cm^{-1}): 2920, 1598, 1569, 1507, 1410, 1339, 1263, 1157, 1123, 985, 761, 691; ^1H NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 1H); 7.75 (d, *J* = 8.0 Hz, 2H); 7.45 (t, *J* = 8.0 Hz, 2 H); 7.32 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6): δ 153.7, 141.5, 141.1, 138.3, 129.0, 127.0, 122.8, 122.4, 120.1, 86.1; ^{19}F NMR (376 MHz, DMSO-d_6) δ -57.07; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{10}H_8F_3N_2O$ 229.0589 found 229.0583

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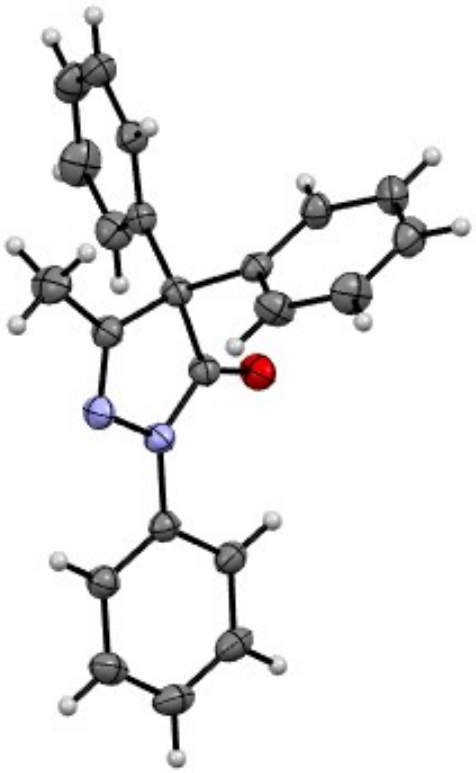
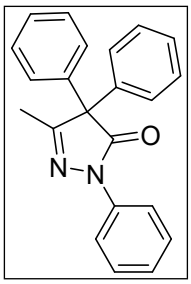
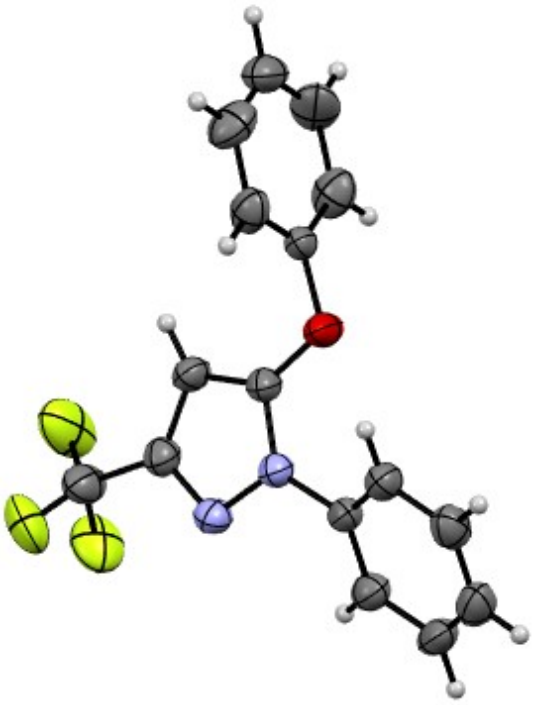
5. (a) L. Li, P. Luo, Y. Deng, Z. Shao, *Angew. Chem. Int. Ed.* 2019, **58**, 4710. (b) M. A. MacLean, E. Diez-Cecilia, C. B. Lavery, M. A. Reed, Y. Wang, D. F. Weaver, M. Stradiotto *Bioorg.. Med. Chem. Lett.* 2016, **26**, 100. (c) C. Yan, D. Theodorescu, B. Miller, A. Kumar, V. Kumar, D. Ross, M. F. Wempe, *Bioorg. Med. Chem. Lett.* 2016, **26**, 5815. (d) F. Lehmann, M. Holm, S. Laufer, *J. Comb. Chem.* 2008, **10**, 364. (e) M. Desroses, M.-C. Jacques-Cordonnier, S. Llona-Minguez, S. Jacques, T. Koolmeister, T. Helleday, M. Scobie, *Eur. J. Org. Chem*. **2013**, 5879. (f) S. Bhavanarushi, Z.-B. Luo, G. Bharath, J. Rani, I. Khan, Y. Xu, B. Liu, J. Xie *J. Heterocyclic Chem.* 2020, **57**, 751. (g) J. Zhang, S. Yang, K. Zhang, J. Chen, H. Deng, M. Shao, H. Zhang, W. Cao, *Tetrahedron*, 2012, **9**, 2121.

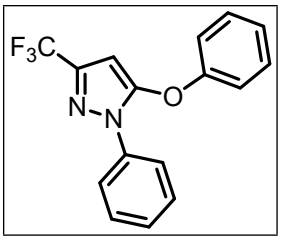




Ortep diagram of 3-methyl-1, 4, 4-triphenyl-1H-pyrazol-5(4H)-one (**8a**) with 30% probability ellipsoid

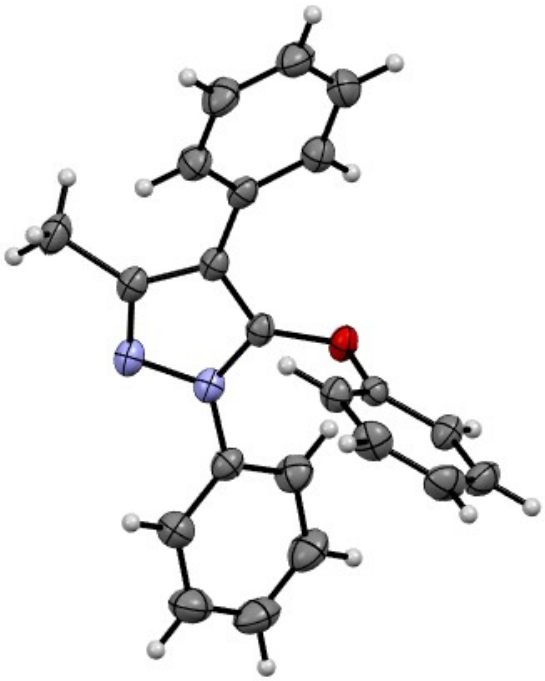
Empirical Formula	$C_{22}H_{18}N_2O$
Formula weight	326.38
Crystal system	Monoclinic
Space group	P 2_1/c
a (Å)	9.12630(10)
b (Å)	10.1687(2)
c (Å)	19.2429(3)
α	90
β	98.9070(5)
γ	90
V (Å^3)	1764.26 (5)
Z	4
ρ_{calcd}(g/cm^3)	1.229
Reflections measured	4453
Unique reflections	3018
R1	0.0491
wR2	0.1301
CCDC No	2175625

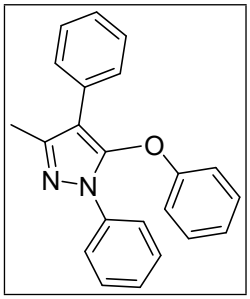




Ortep diagram of 5-phenoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**9a**) with 30% probability ellipsoid

Empirical Formula	$C_{16}H_{11}F_3N_2O$
Formula weight	304.27
Crystal system	Monoclinic
Sapce group	P 2_1
a (Å)	6.2516(2)
b (Å)	12.1242(4)
c (Å)	19.5002(7)
α	90
β	91.0124(9)
γ	90
V ($Å^3$)	1477.80(9)
Z	4
$\rho_{calcd}(g/cm^3)$	1.368
Reflections measured	7270
Unique reflections	3290
R1	0.0743
wR2	0.1574
CCDC No	2175627



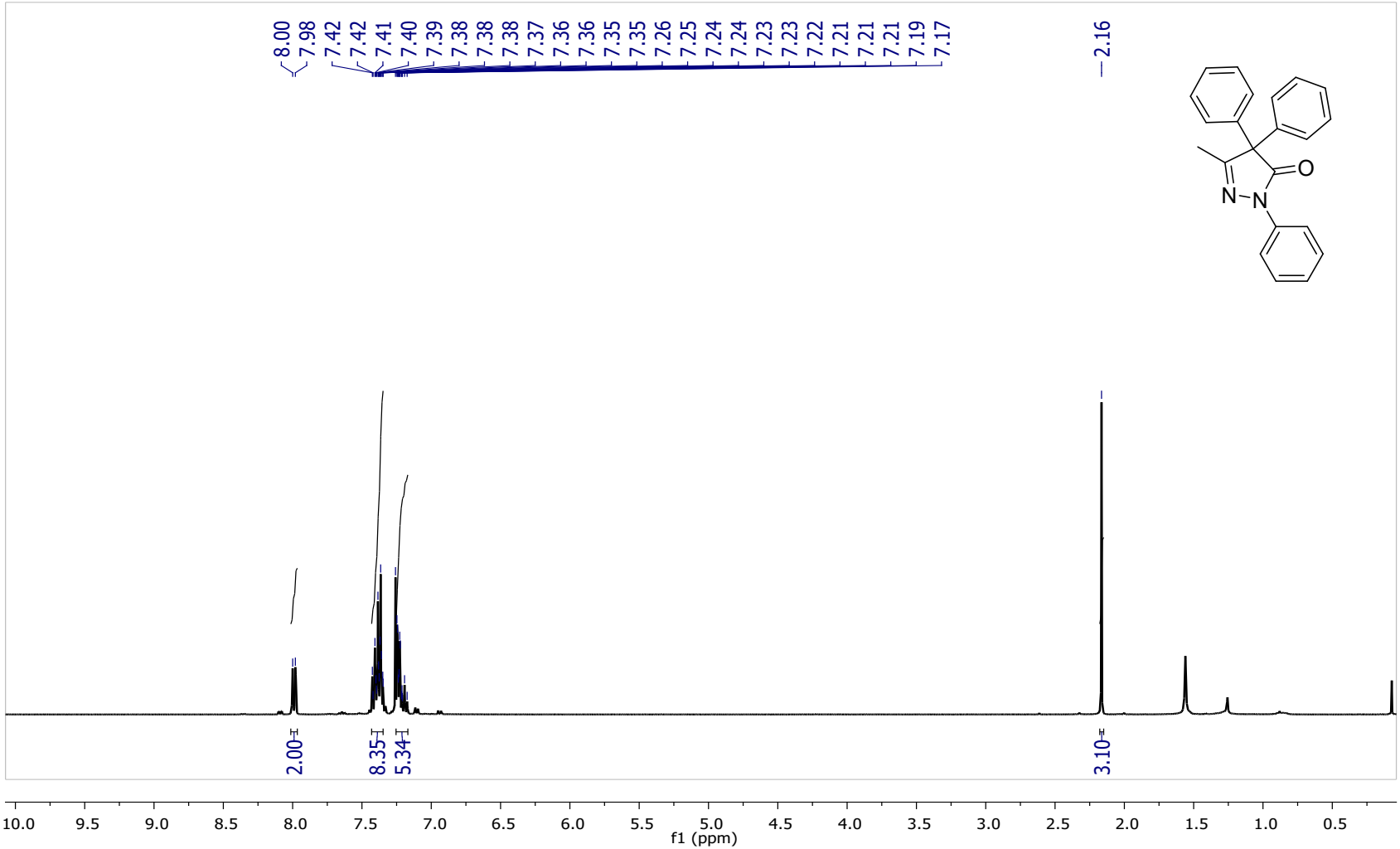


Ortep diagram of 3-methyl-5-phenoxy-1, 4-diphenyl-1H-pyrazole (**10a**) with 30% probability ellipsoid

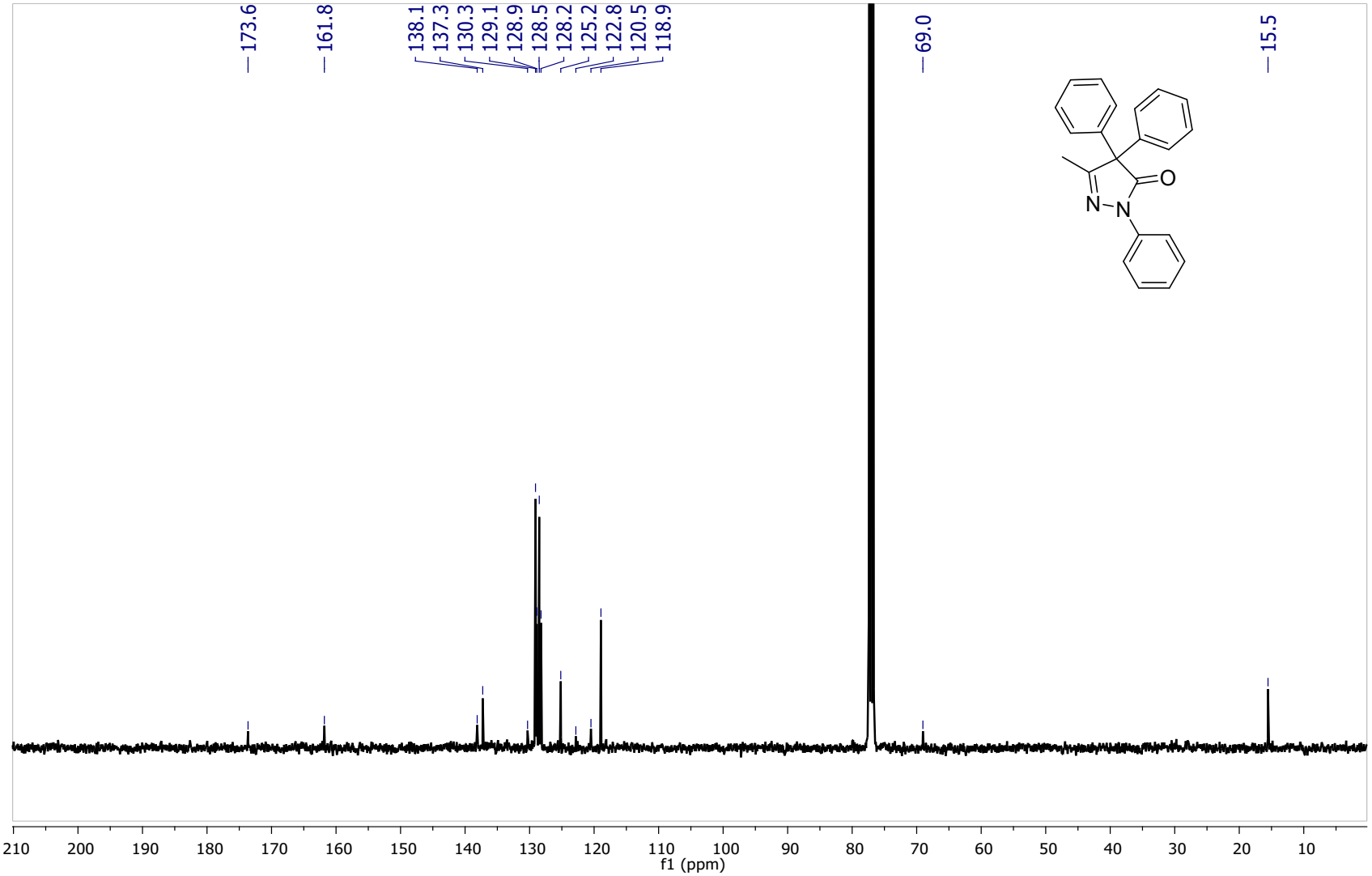
Empirical Formula	$C_{22}H_{18}N_2O$
Formula weight	326.38
Crystal system	Monoclinic
Space group	P 2_1/c
a (Å)	13.9291(3)
b (Å)	8.5789(2)
c (Å)	15.4251(3)
α	90
β	108.4620(8)
γ	90
V (Å^3)	1748.38 (7)
Z	4
ρ_{calcd}(g/cm^3)	1.240
Reflections measured	5395
Unique reflections	2877
R1	0.0598
wR2	0.1561
CCDC No	2175626

NMR Spectra

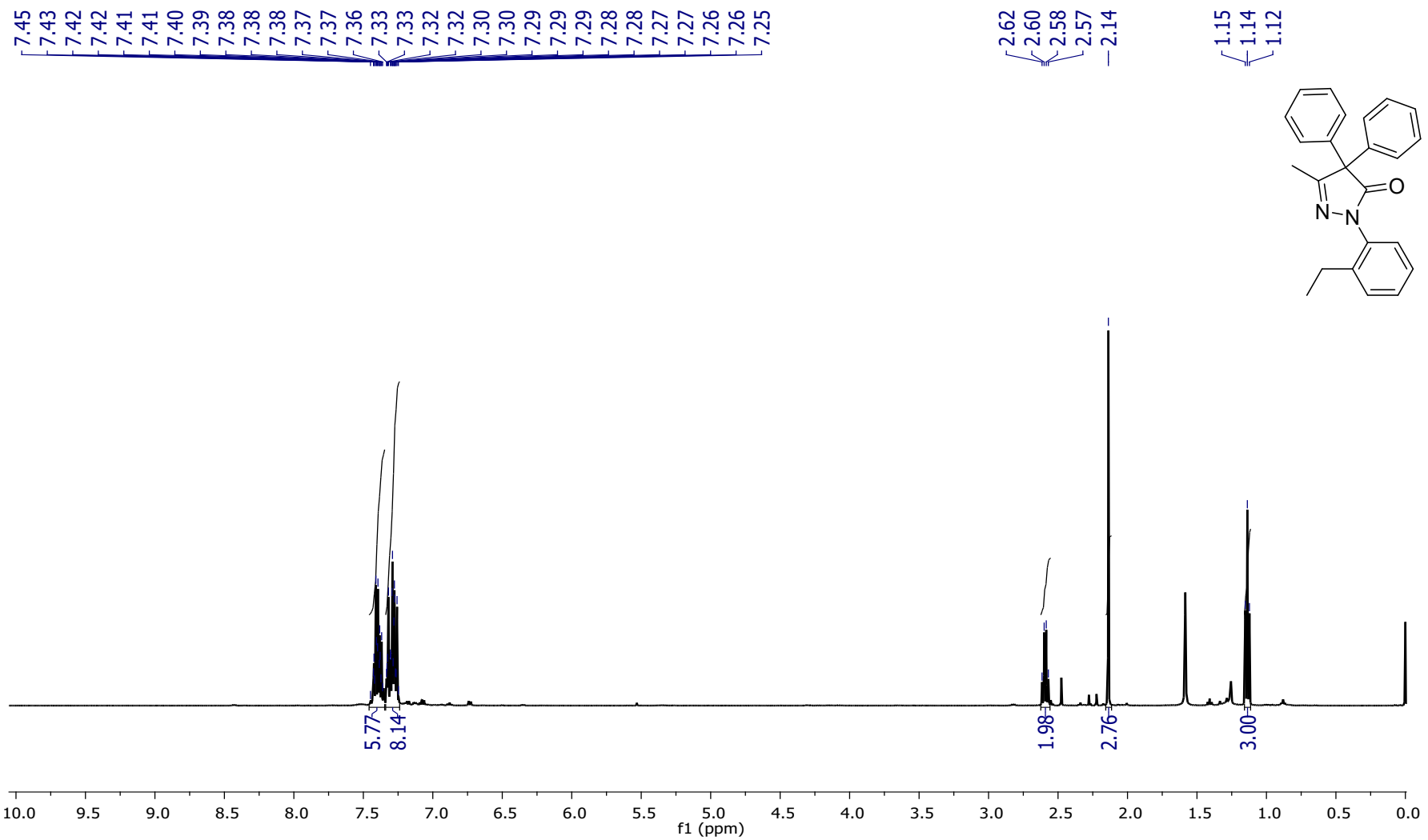
^{1}H NMR (400 MHz, $CDCl_3$) of 3-methyl-1, 4, 4-triphenyl-1*H*-pyrazol-5(4H)-one (**8a**):



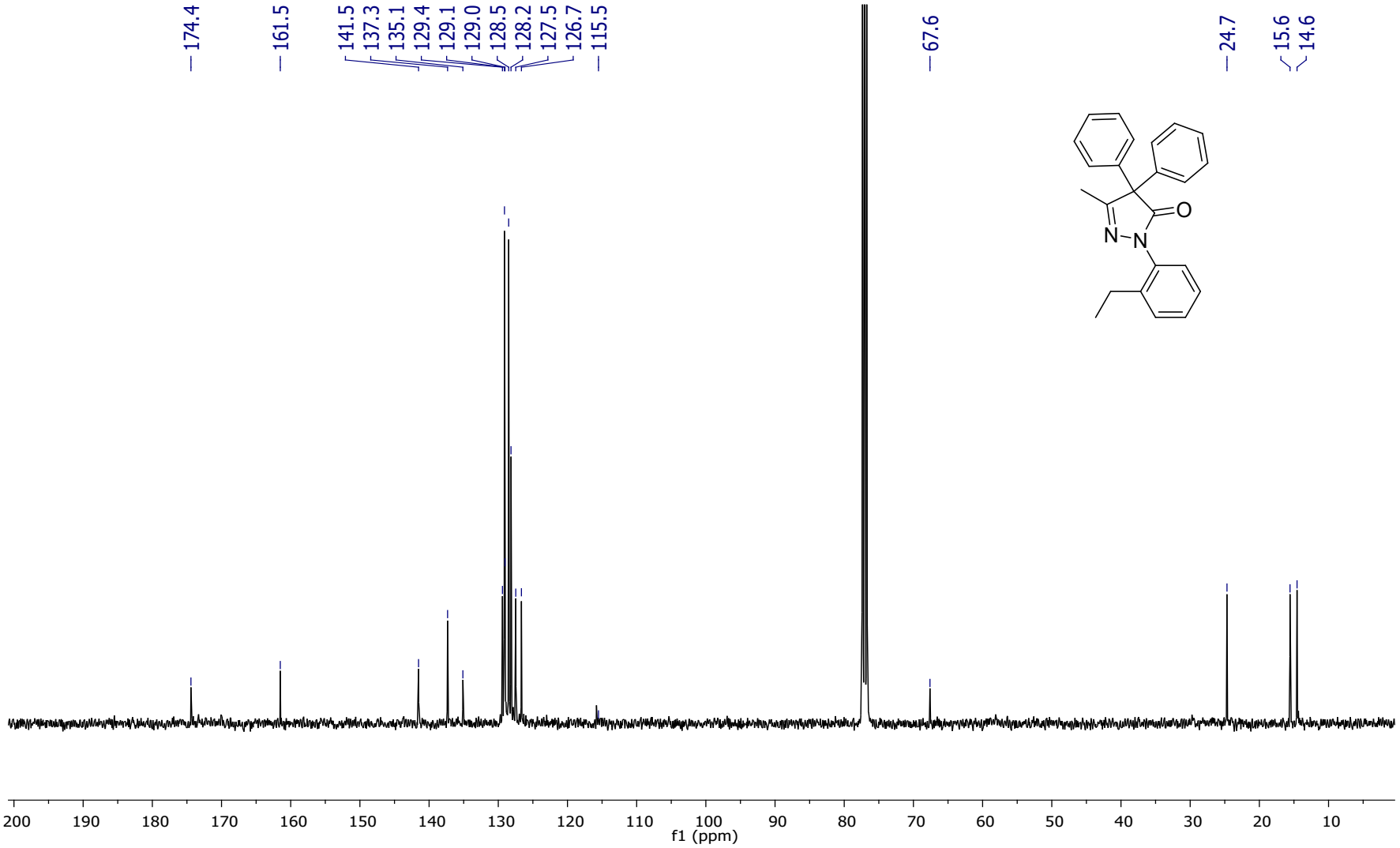
^{13}C NMR (101 MHz, $CDCl_3$) of 3-methyl-1, 4, 4-triphenyl-1*H*-pyrazol-5(4H)-one (**8a**):



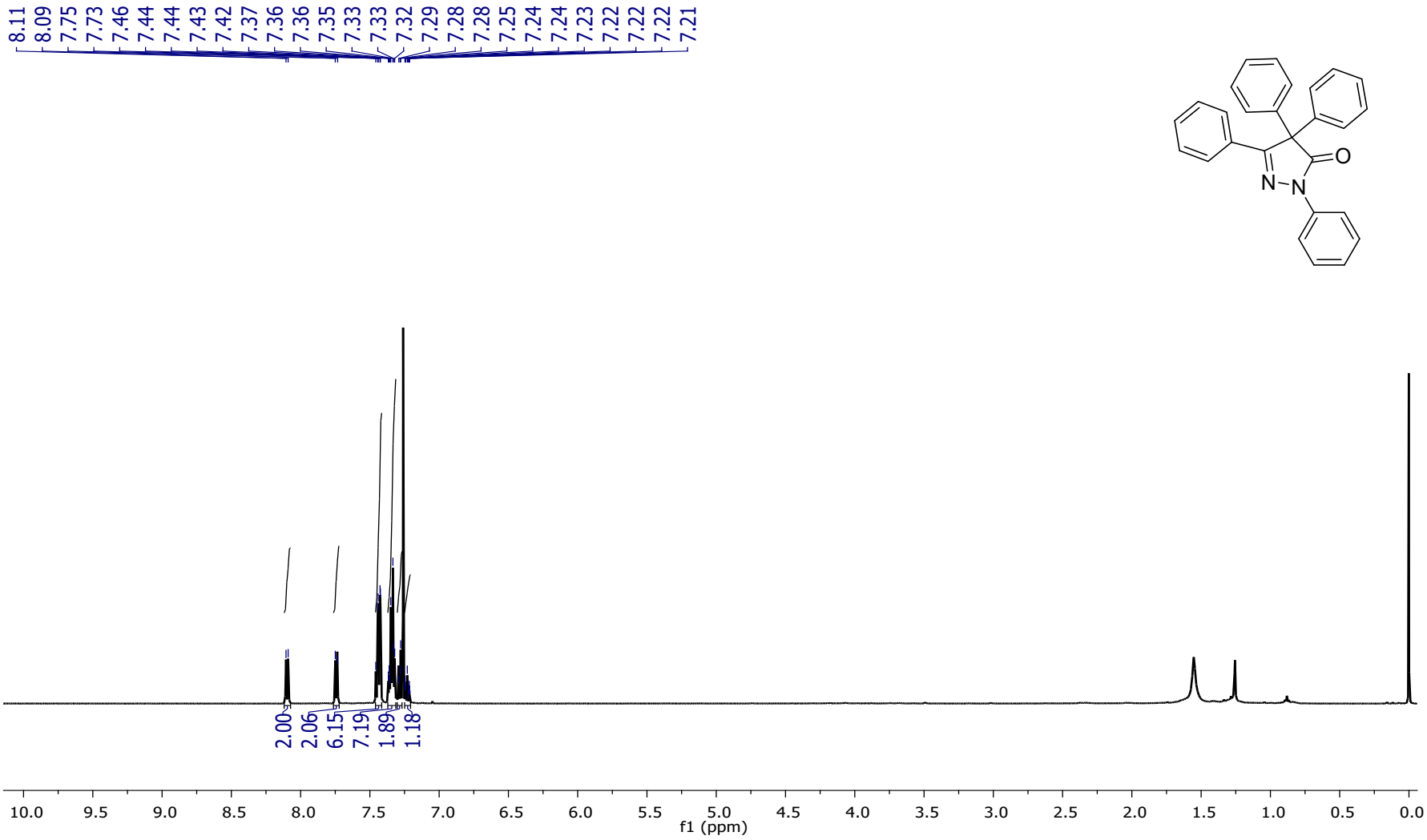
^{1}H NMR (500 MHz, $CDCl_3$) of 1-(2-ethylphenyl)-3methyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (**8b**):



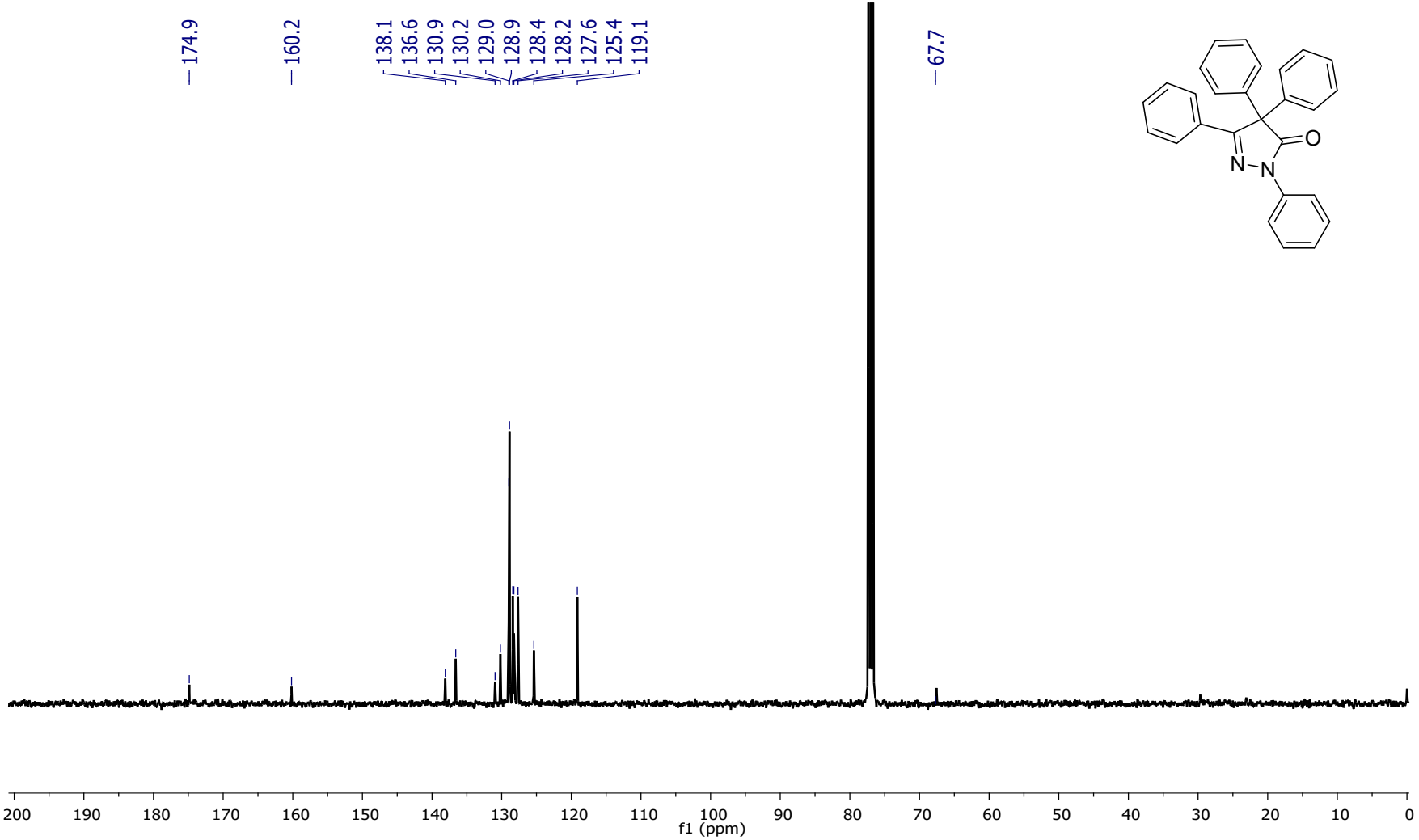
^{13}C NMR (101 MHz, $CDCl_3$) of 1-(2-ethylphenyl)-3methyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (**8b**)



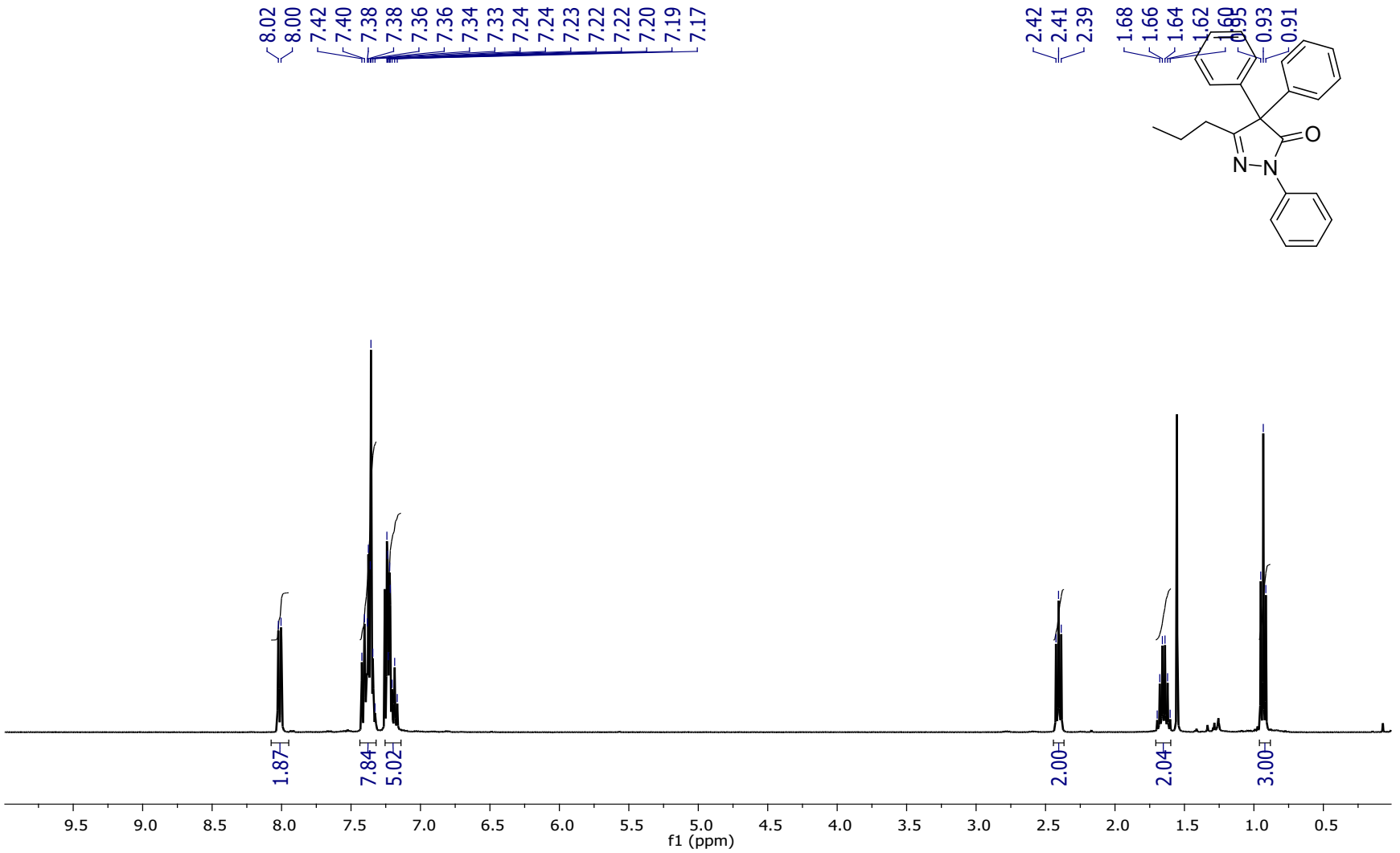
^{1}H NMR (400 MHz, $CDCl_3$) of 1, 3, 4, 4-tetraphenyl-1*H*-pyrazol-5(4H)-one (**8c**):



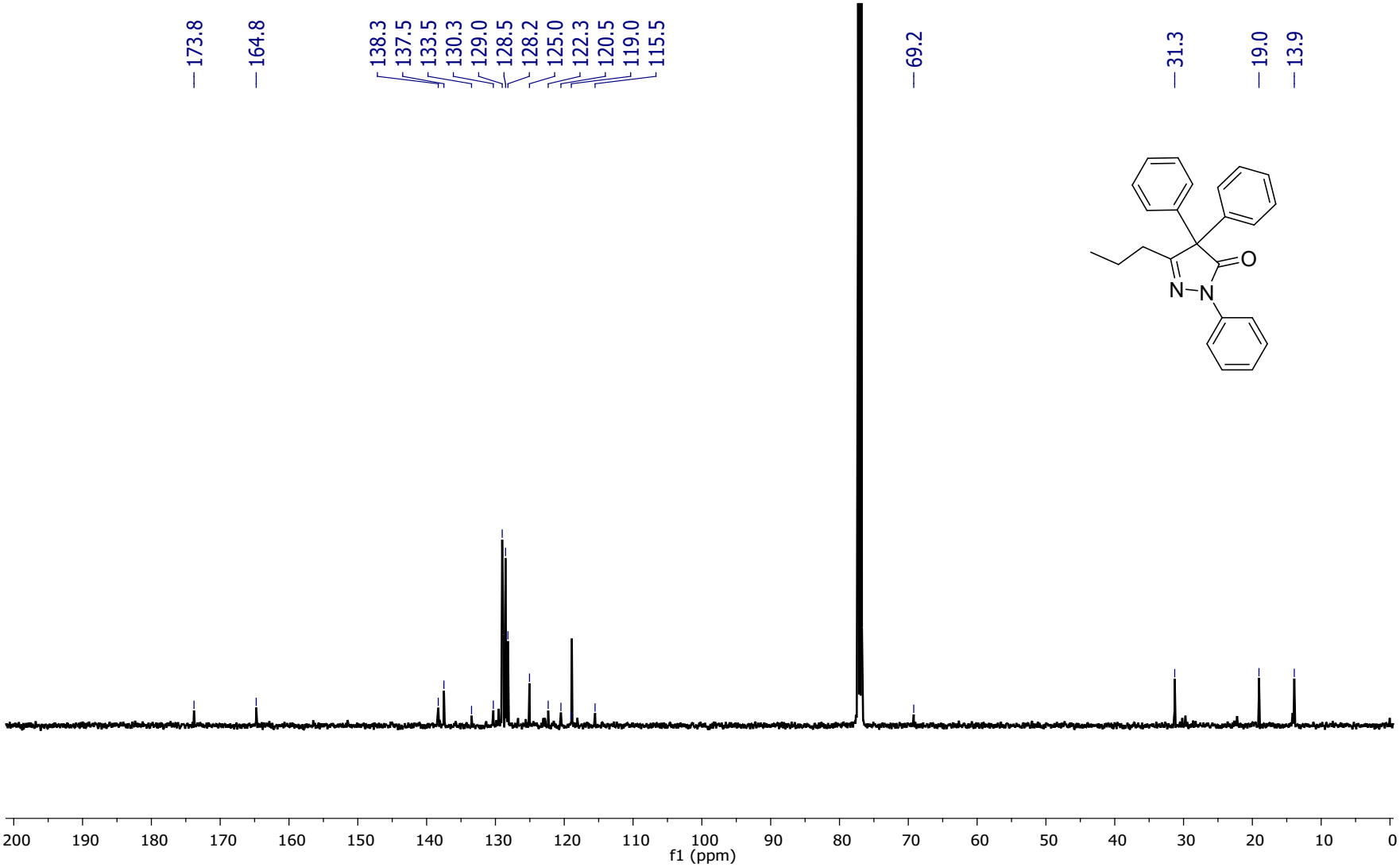
^{13}C NMR (101 MHz, $CDCl_3$) of 1, 3, 4, 4-tetraphenyl-1*H*-pyrazol-5(4H)-one (**8c**):



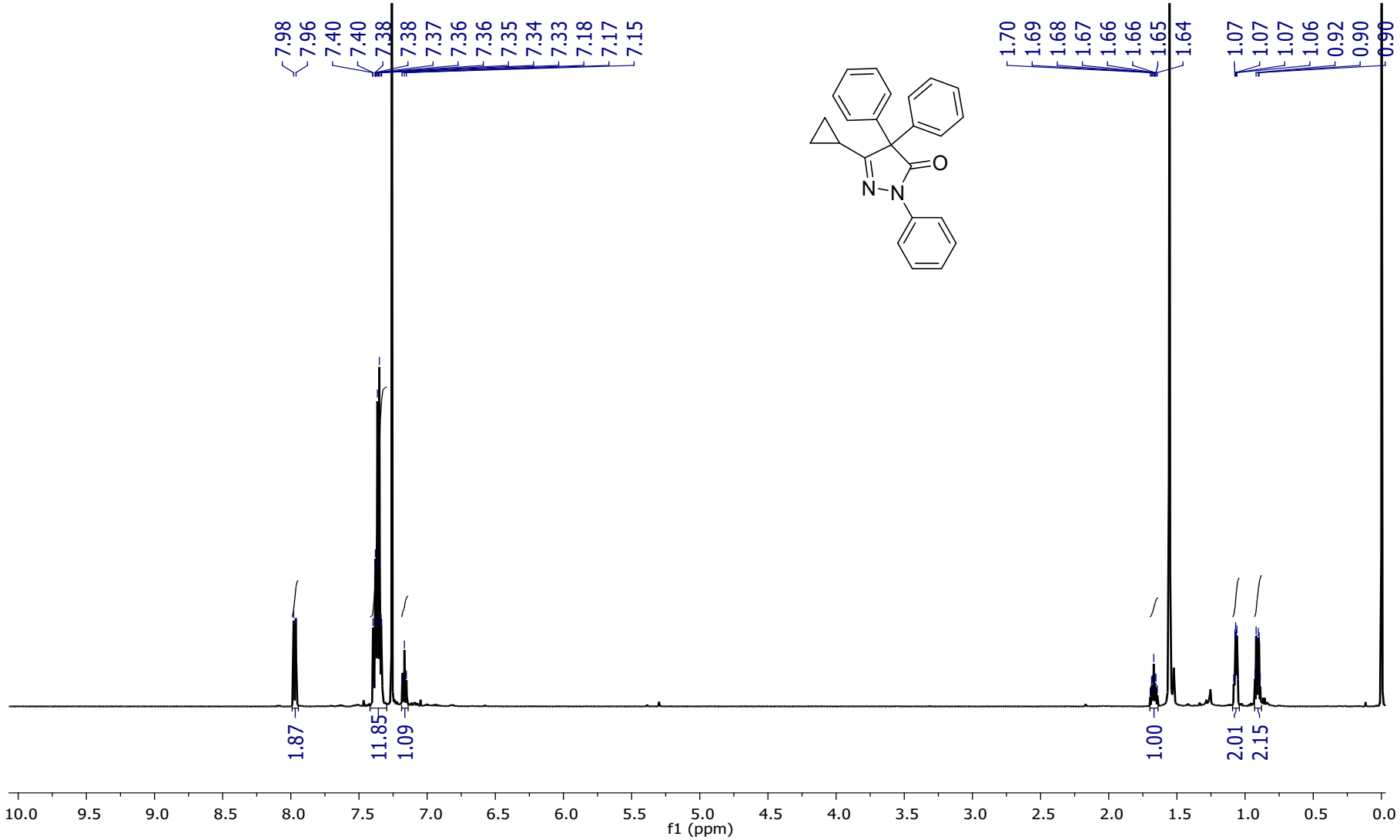
^{1}H NMR (400 MHz, $CDCl_3$) of 1, 4, 4-triphenyl-3-propyl-1*H*-pyrazol-5(4H)-one (**8d**):



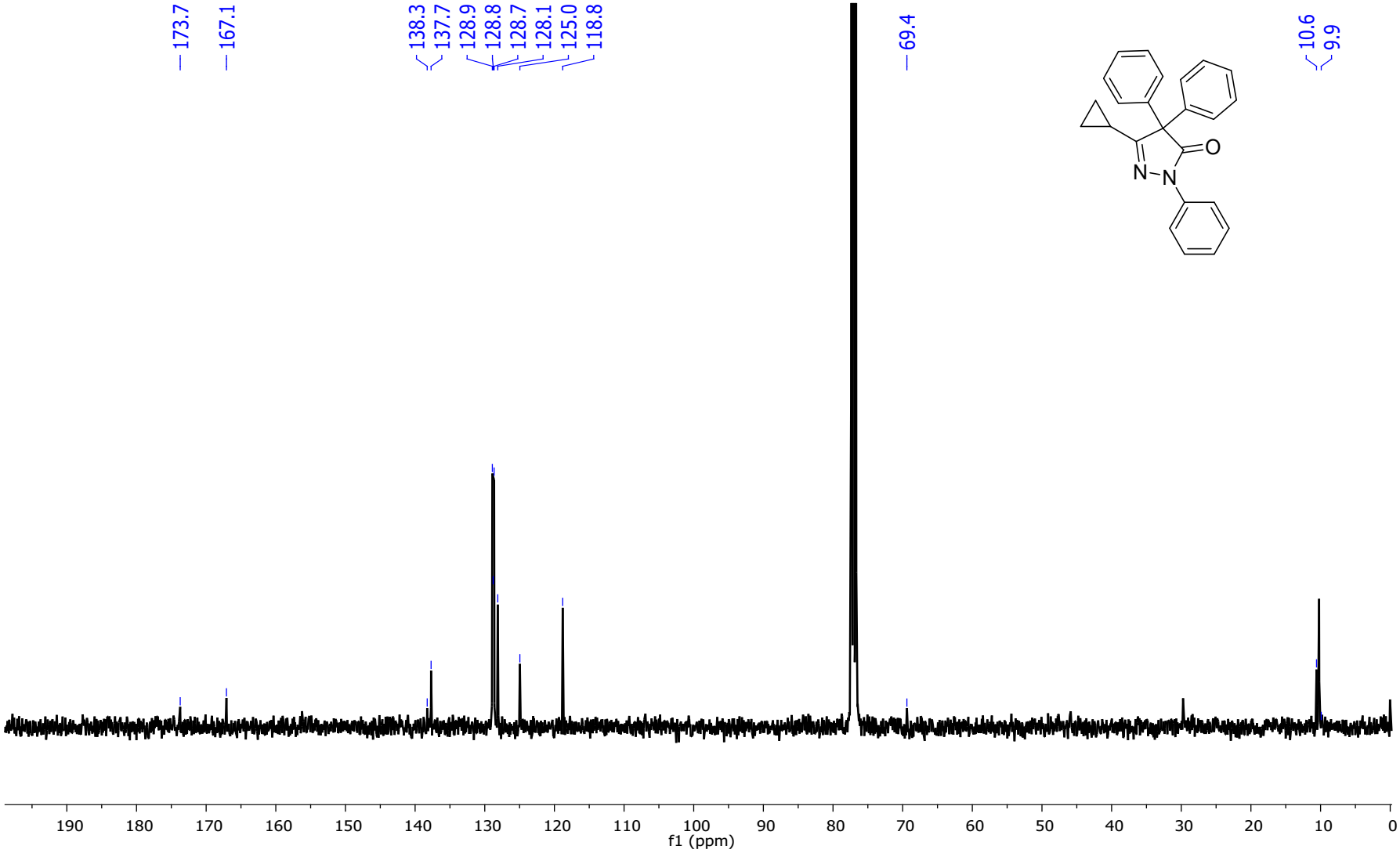
^{13}C NMR (101 MHz, $CDCl_3$) of 1, 4, 4-triphenyl-3-propyl-1*H*-pyrazol-5(4H)-one (**8d**):



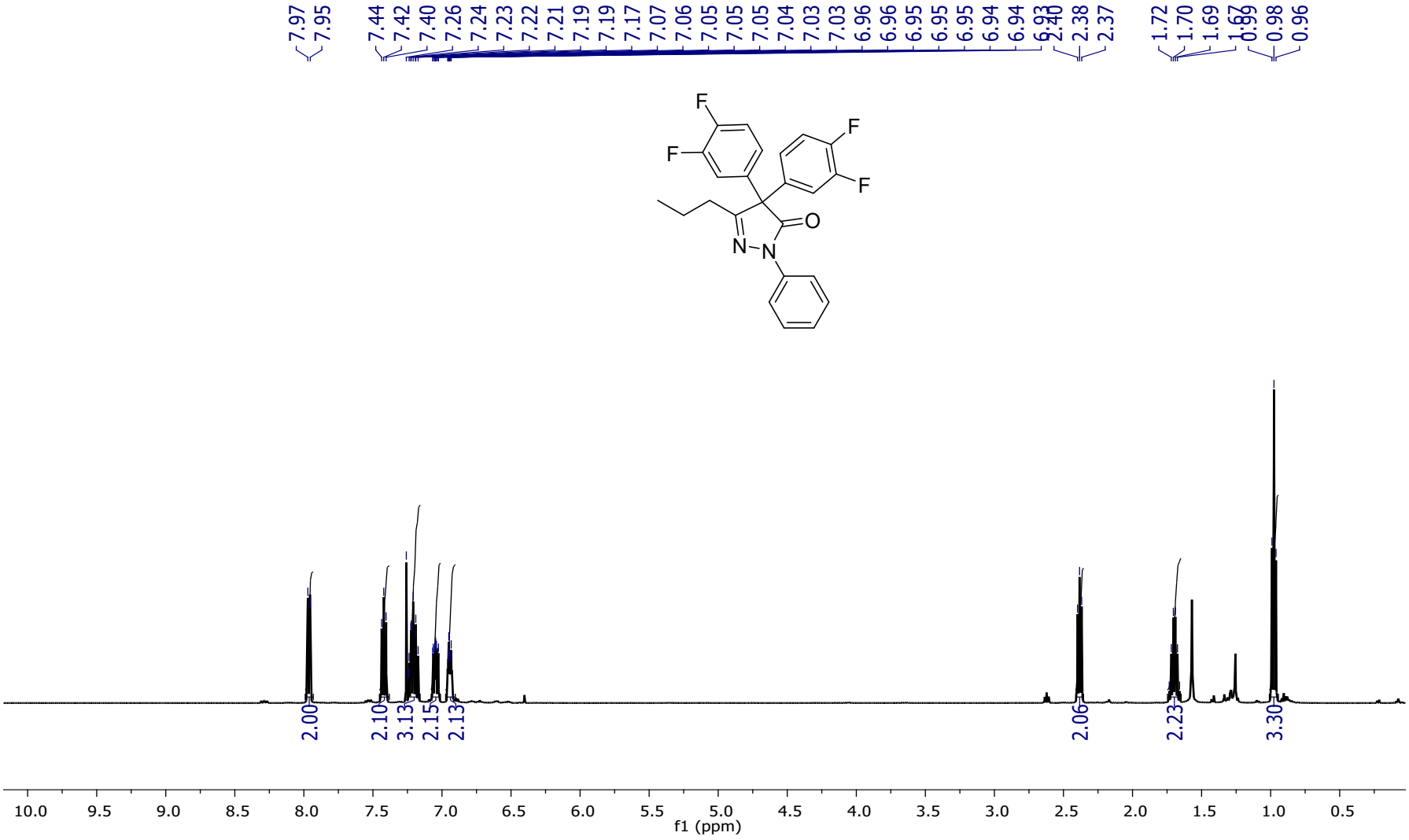
^{1}H NMR(500 MHz, $CDCl_3$) of 3-cyclopropyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (**8e**)



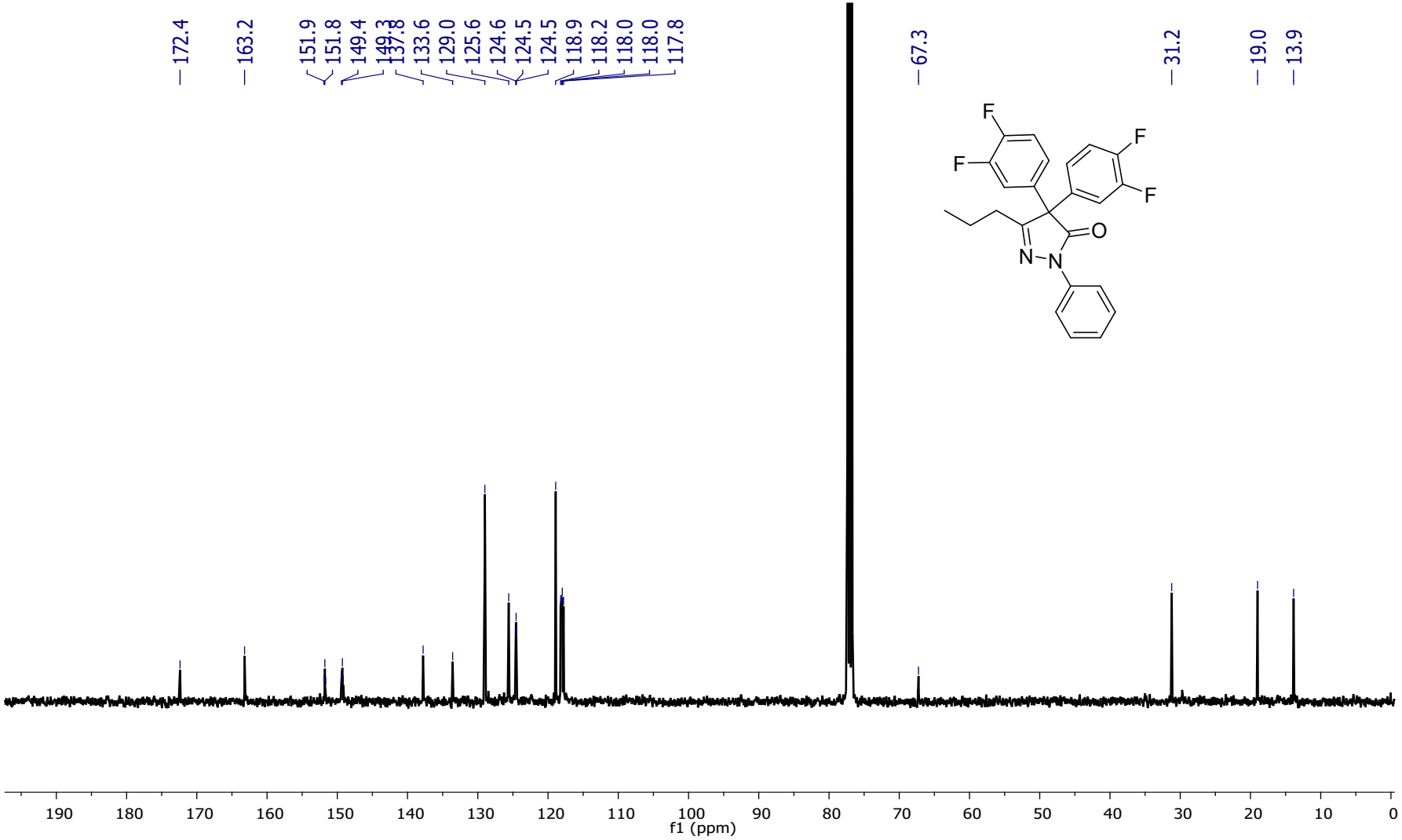
^{13}C NMR(101 MHz, $CDCl_3$) of 3-cyclopropyl-4, 4-diphenyl-1*H*-pyrazol-5(4H)-one (**8e**)



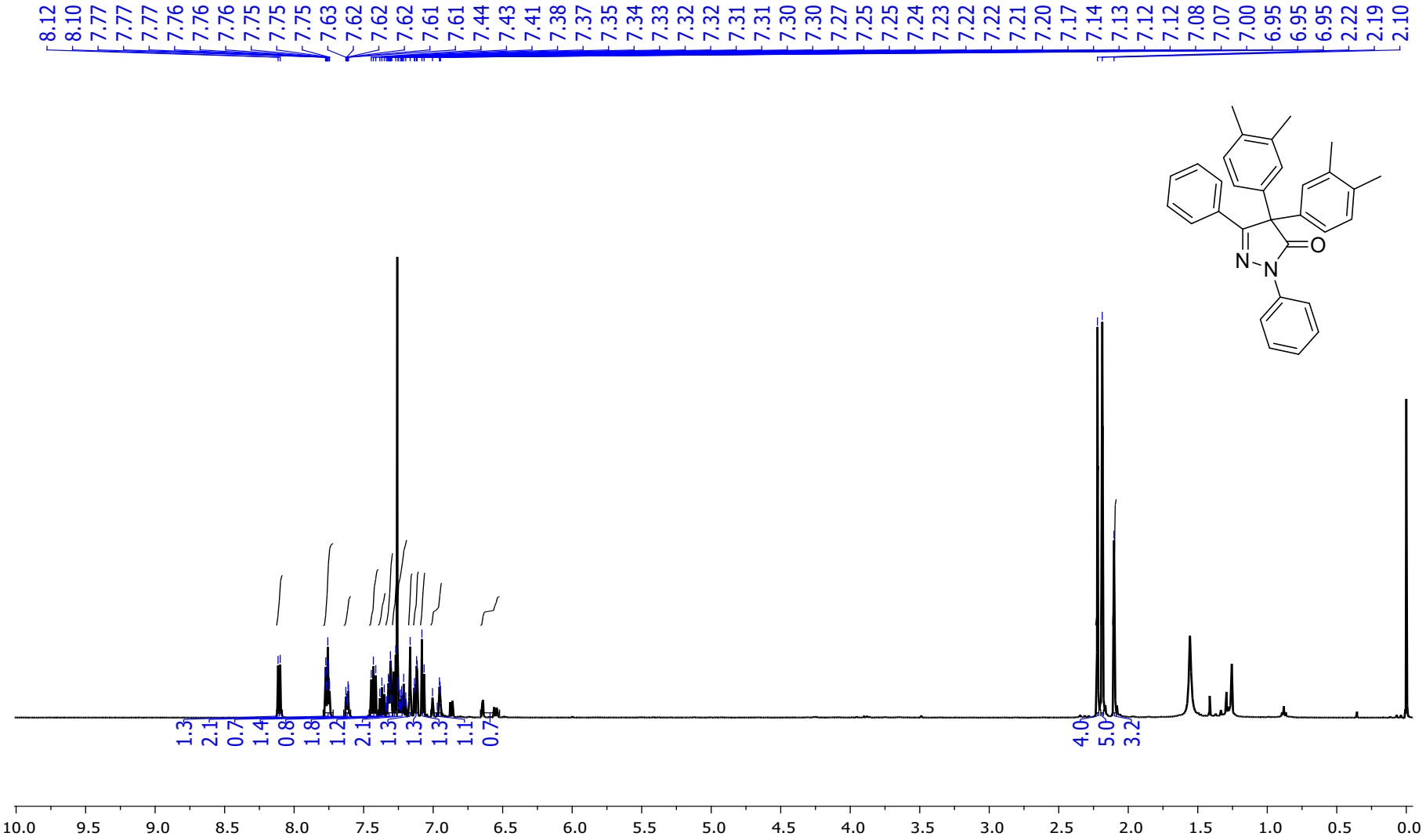
^{1}H NMR (500 MHz, $CDCl_3$) of 4,4-bis(3,4-difluorophenyl)-1-phenyl-3-propyl-1*H*-pyrazol-5(4H)-one (**8f**):



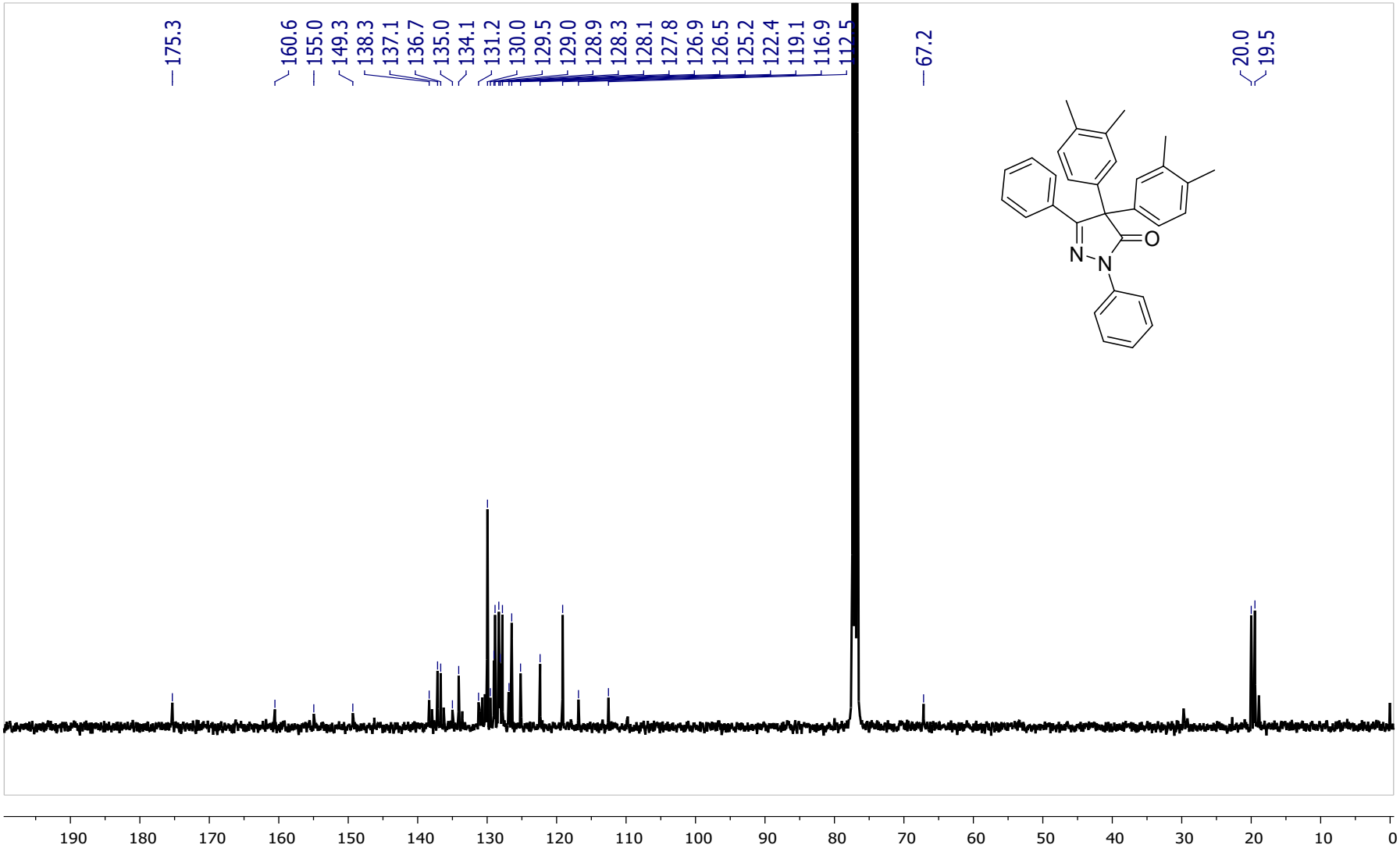
^{13}C NMR (101 MHz, $CDCl_3$) *of* 4,4-bis(3,4-difluorophenyl)-1-phenyl-3-propyl-1*H*-pyrazol-5(4H)-one (**8f**):



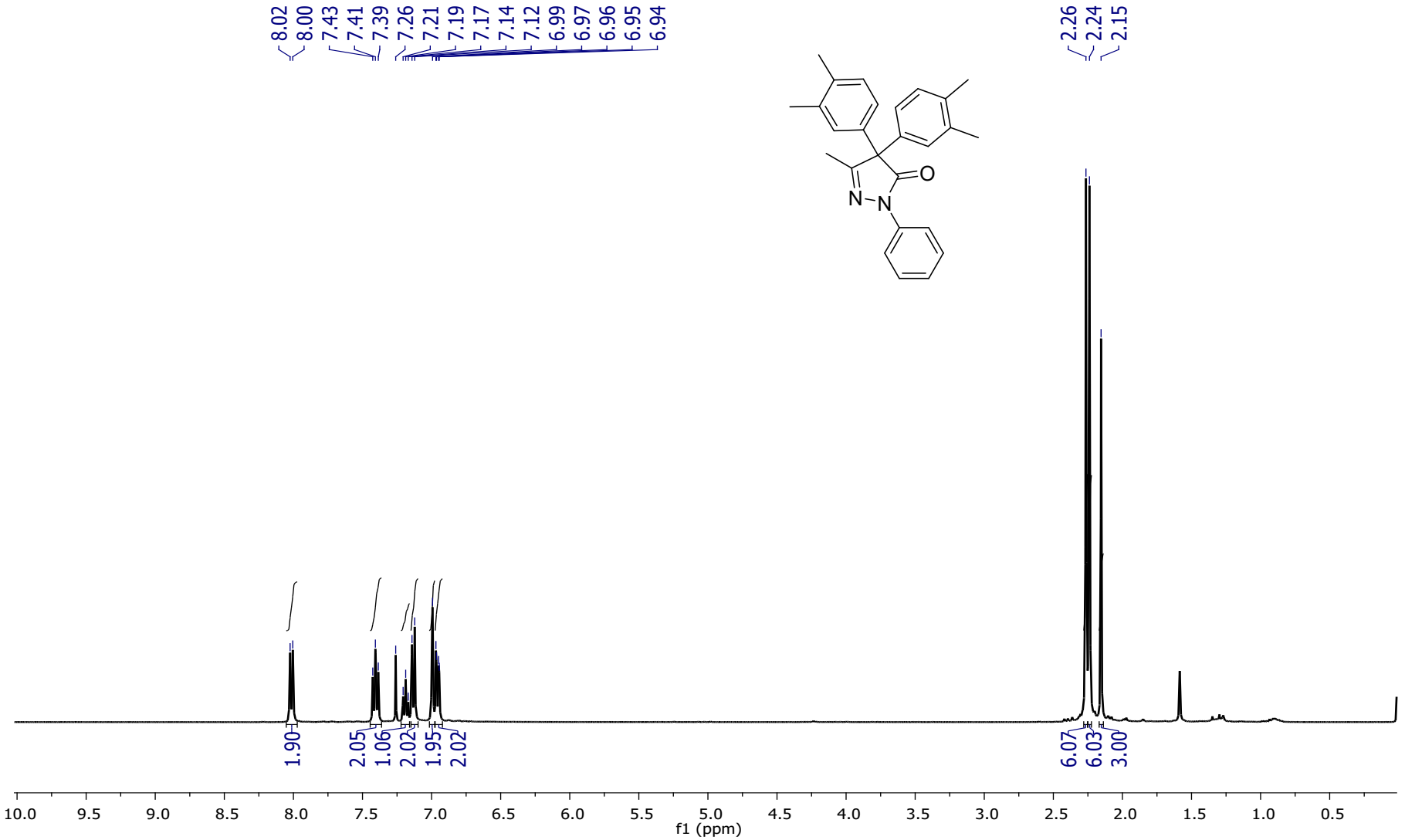
^{1}H NMR (500 MHz, $CDCl_3$) *of* 4,4-bis(3,4-dimethylphenyl)-1, 3-diphenyl-1*H*-pyrazol-5(4H)-one (**8g**):



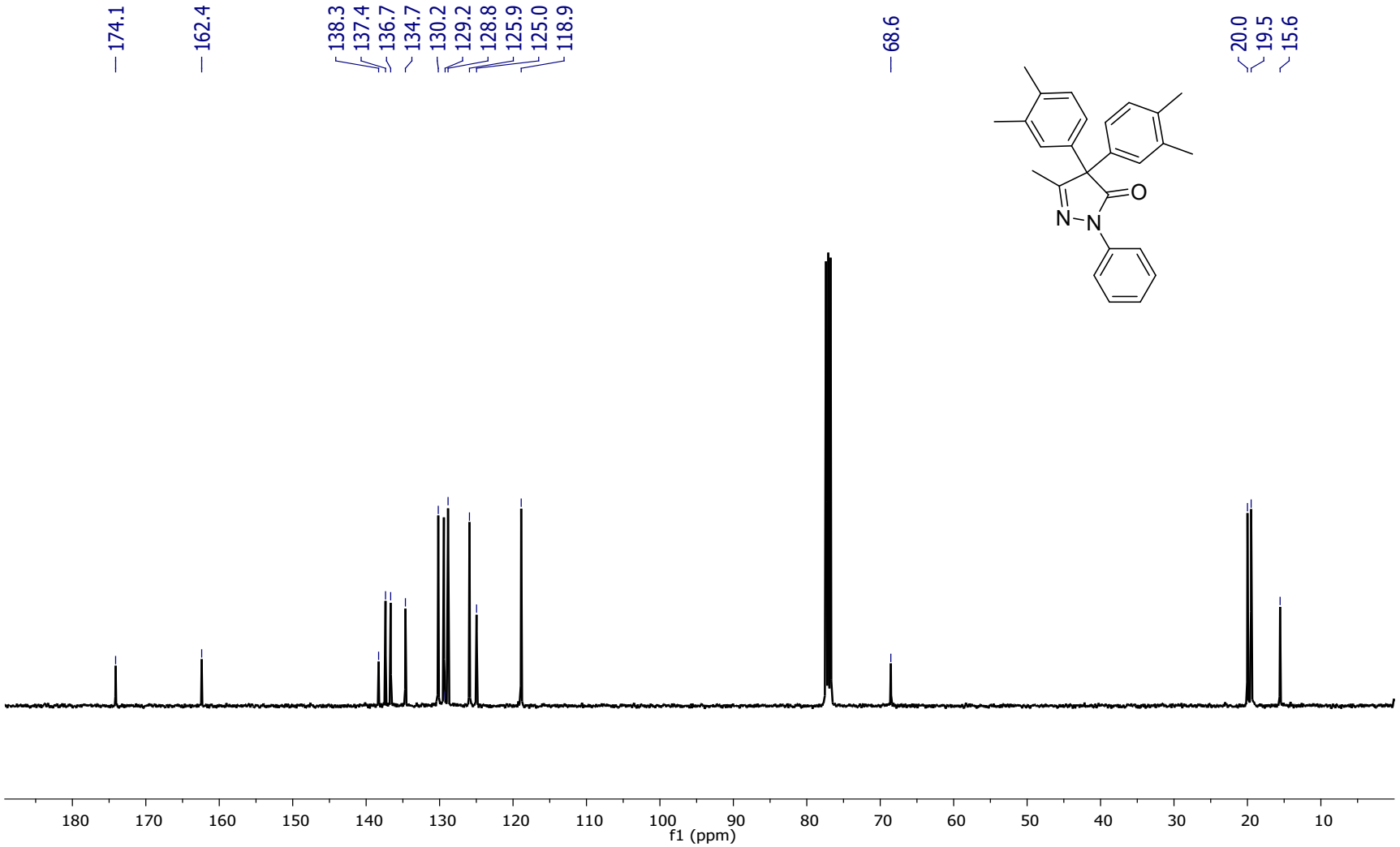
^{13}C NMR (101 MHz, $CDCl_3$) *of* 4,4-bis(3,4-dimethylphenyl)-1, 3-diphenyl-1*H*-pyrazol-5(4H)-one (**8g**):



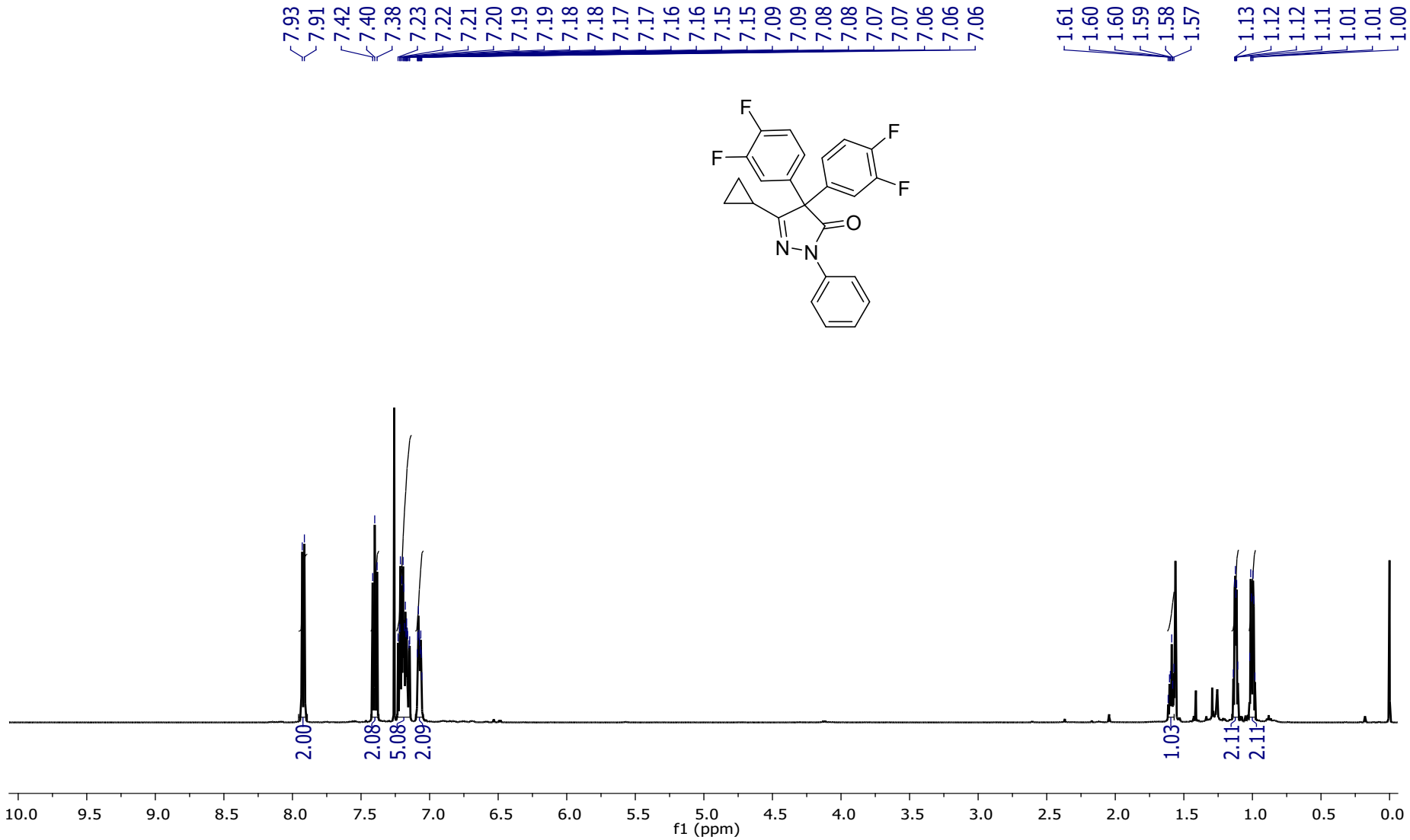
^{1}H NMR(400 MHz, $CDCl_3$) of 4,4-bis(3,4-dimethylphenyl)- 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one (**8h**):



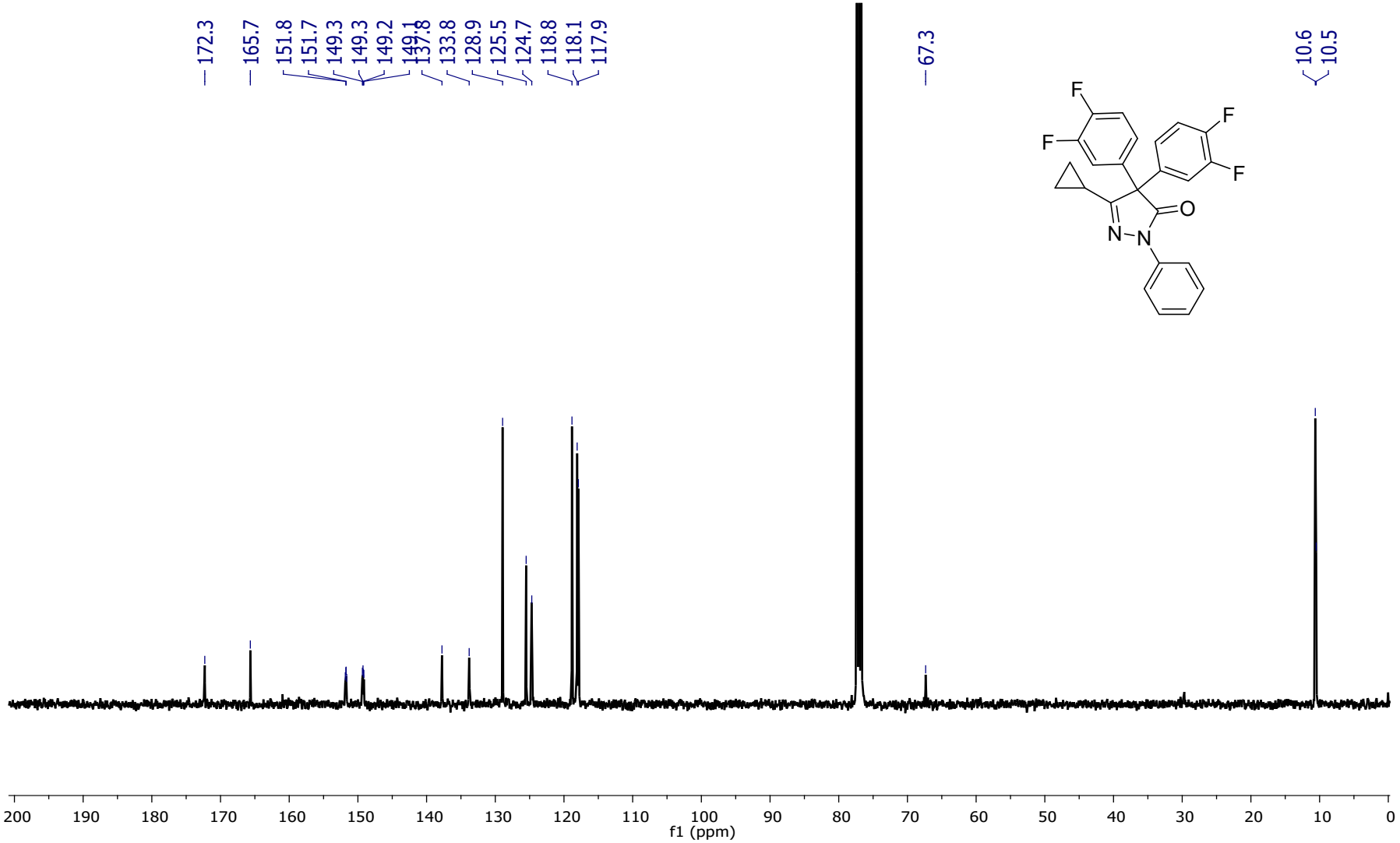
^{13}C NMR(101 MHz, $CDCl_3$) of 4,4-bis(3,4-dimethylphenyl)- 3-methyl-1-phenyl-1*H*-pyrazol-5(4H)-one (**8h**) :



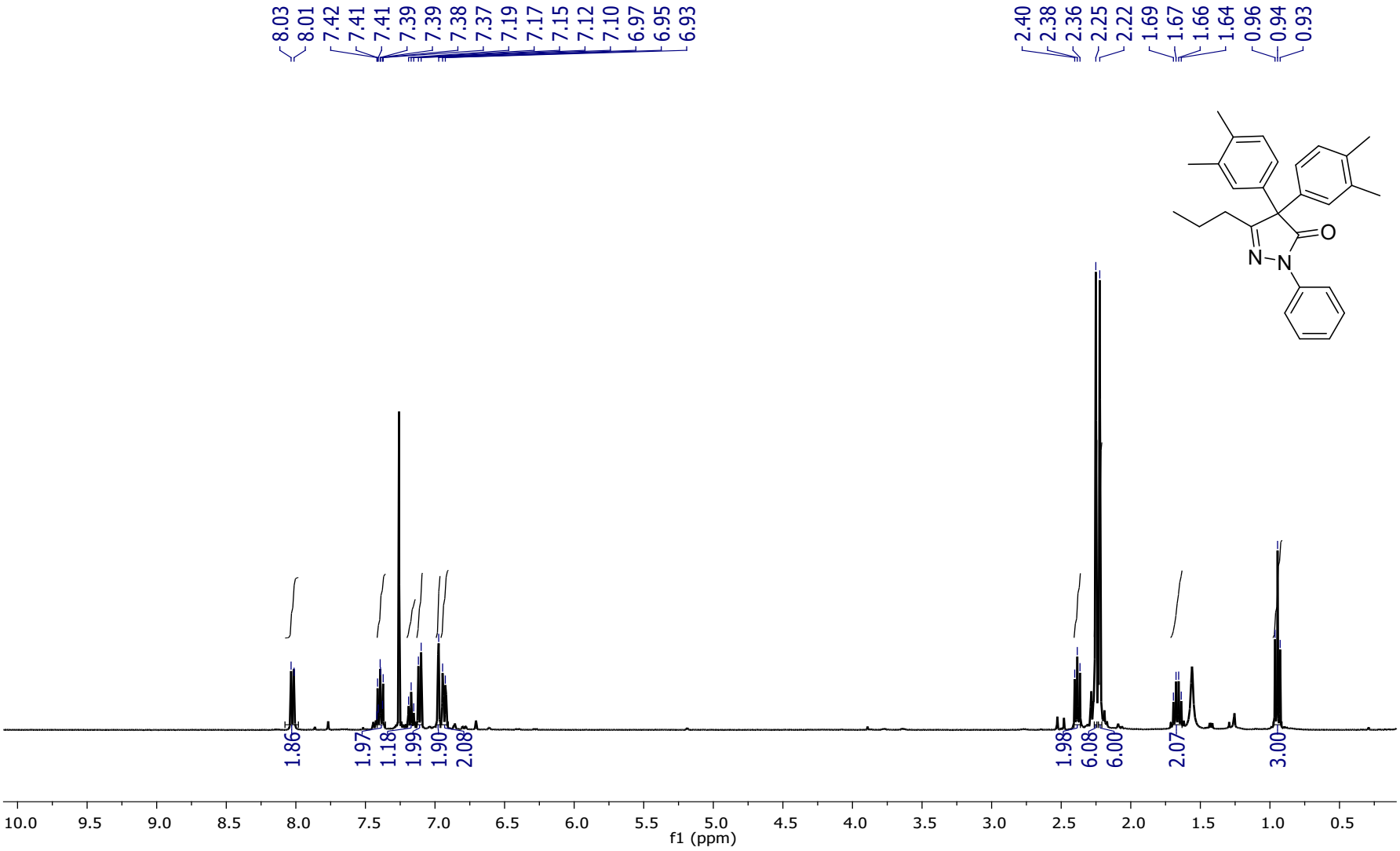
^{1}H NMR(500 MHz, $CDCl_3$) of 3-cyclopropyl-4,4-bis(3,4-difluorophenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (**8i**)



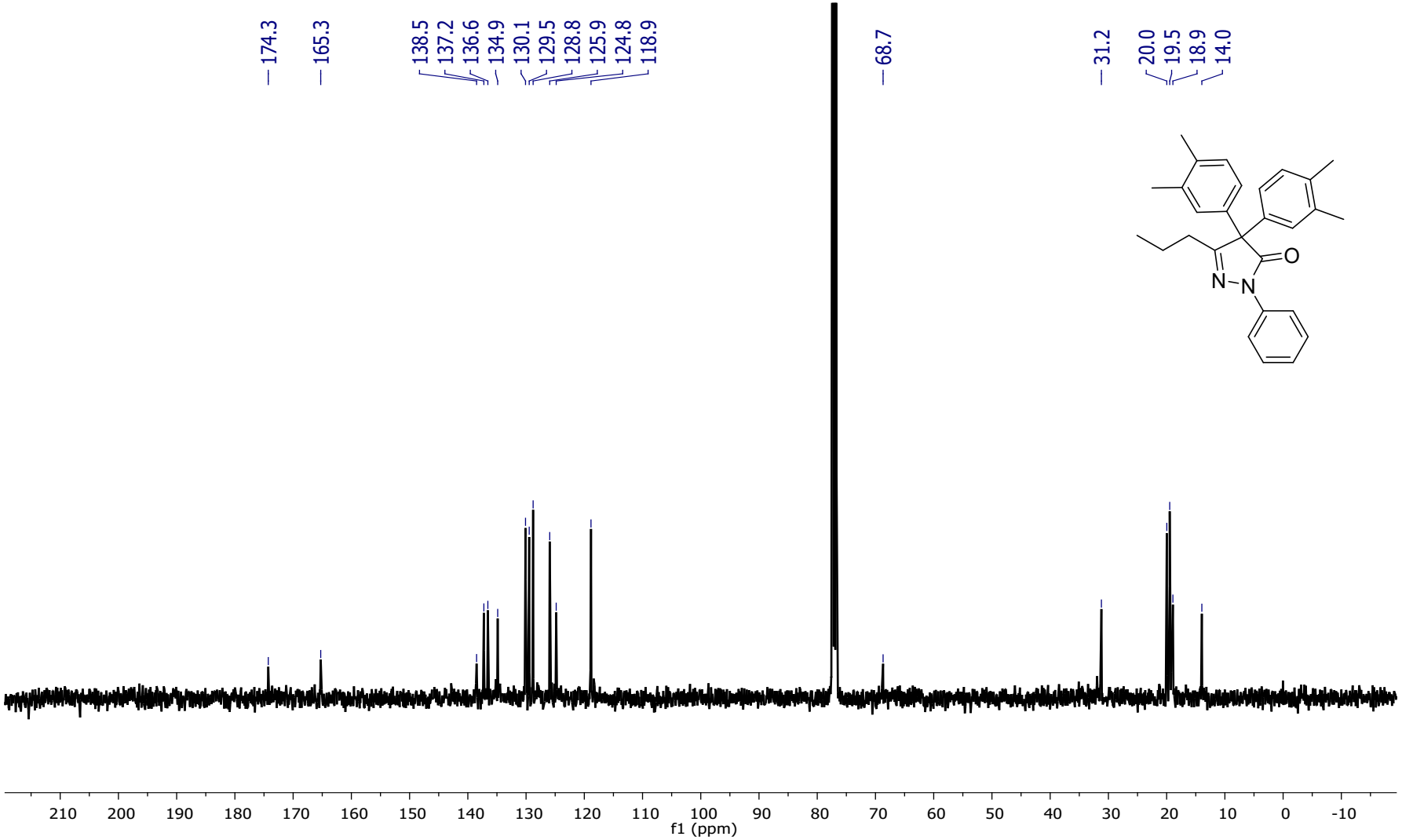
^{13}C NMR(101 MHz, $CDCl_3$) of 3-cyclopropyl-4,4-bis(3,4-difluorophenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (**8i**)



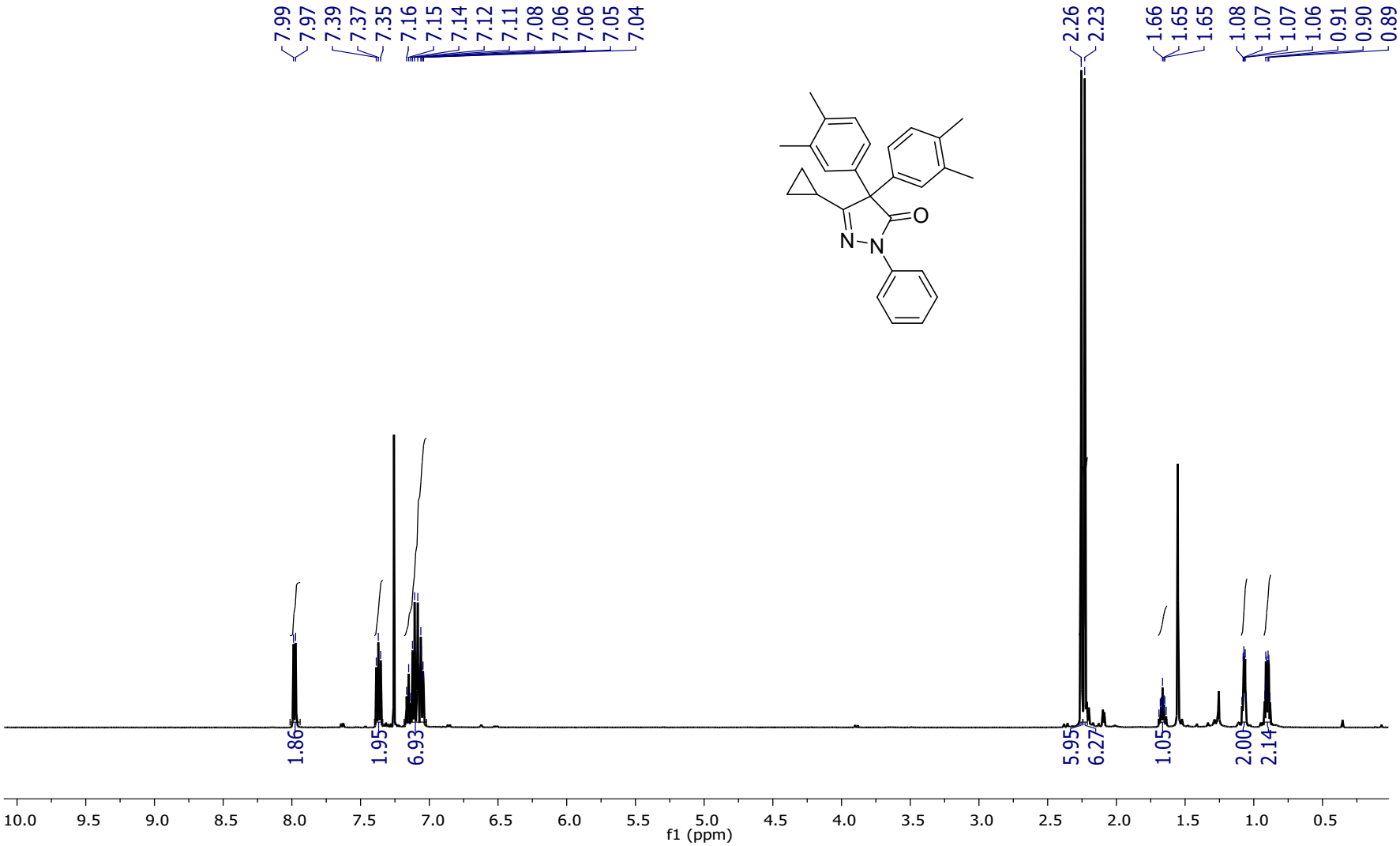
^{1}H NMR (400 MHz, $CDCl_3$) of 4,4-bis(3,4-dimethylphenyl)- 3-propyl-1-phenyl-1*H*-pyrazol-5(4H)-one (**8j**):



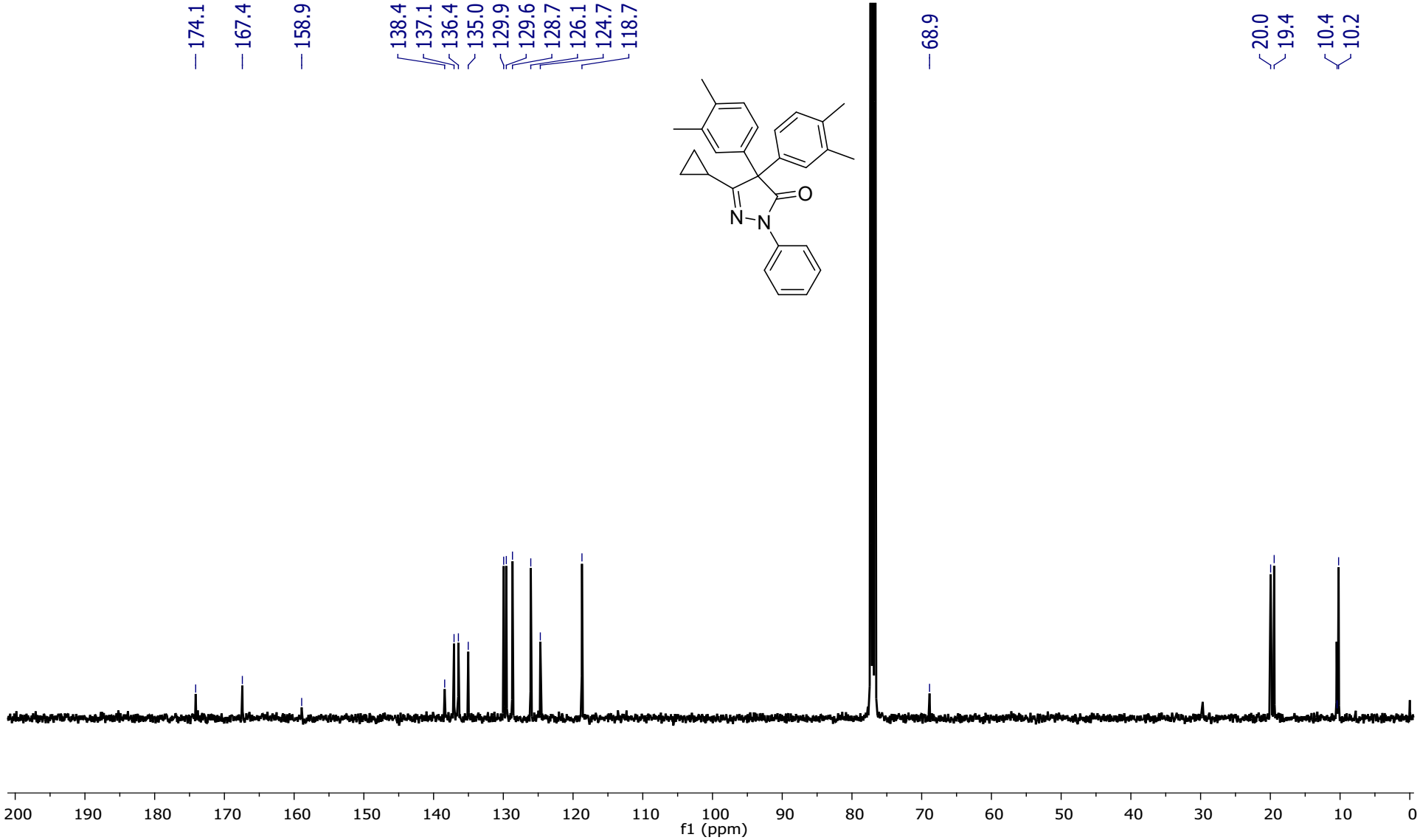
^{13}C NMR (101 MHz, $CDCl_3$) of 4,4-bis(3,4-dimethylphenyl)- 3-propyl-1-phenyl-1*H*-pyrazol-5(4H)-one (**8j**):



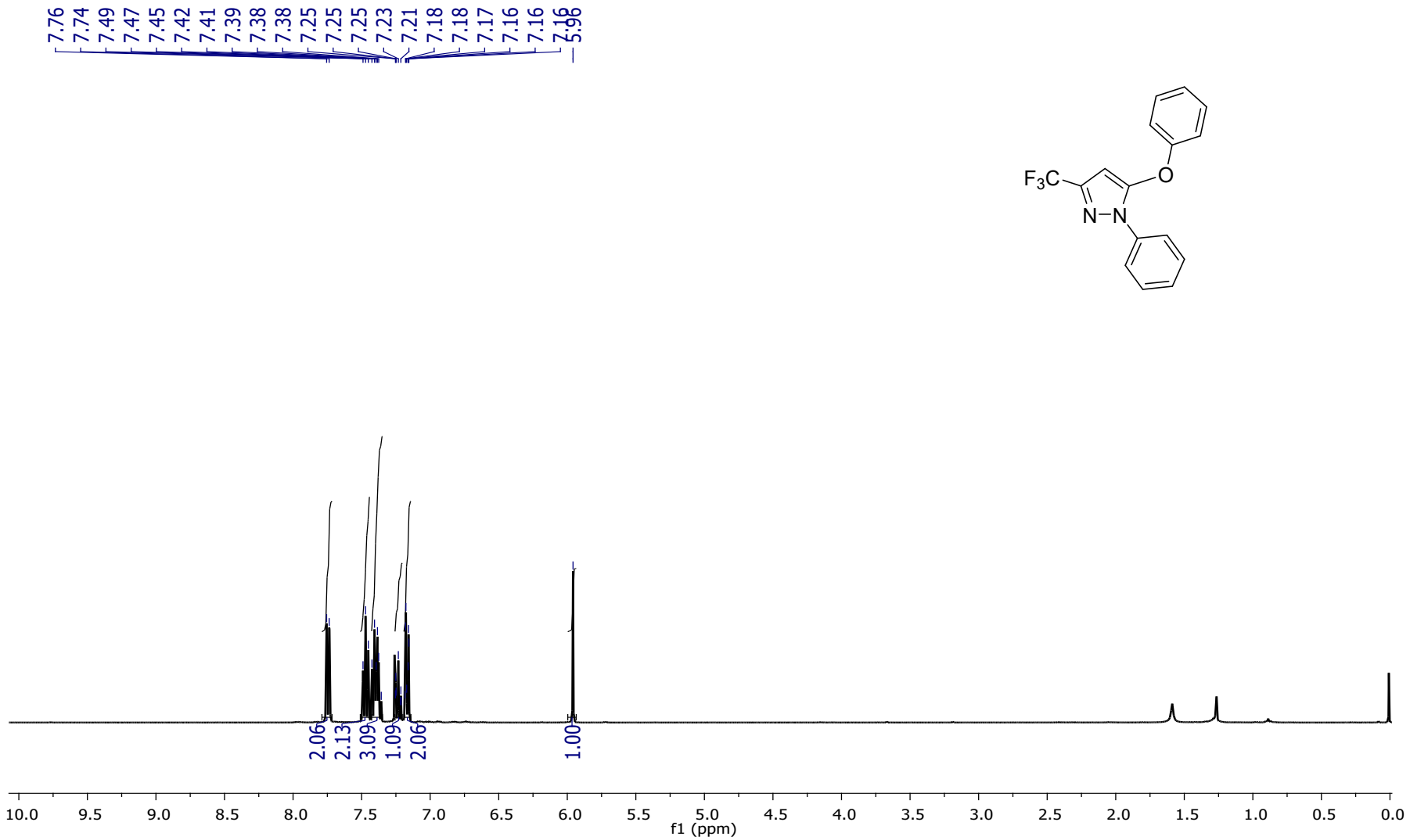
^{1}H NMR (500 MHz, $CDCl_3$) of 3-cyclopropyl-4,4-bis(3,4-dimethylphenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (**8k**)



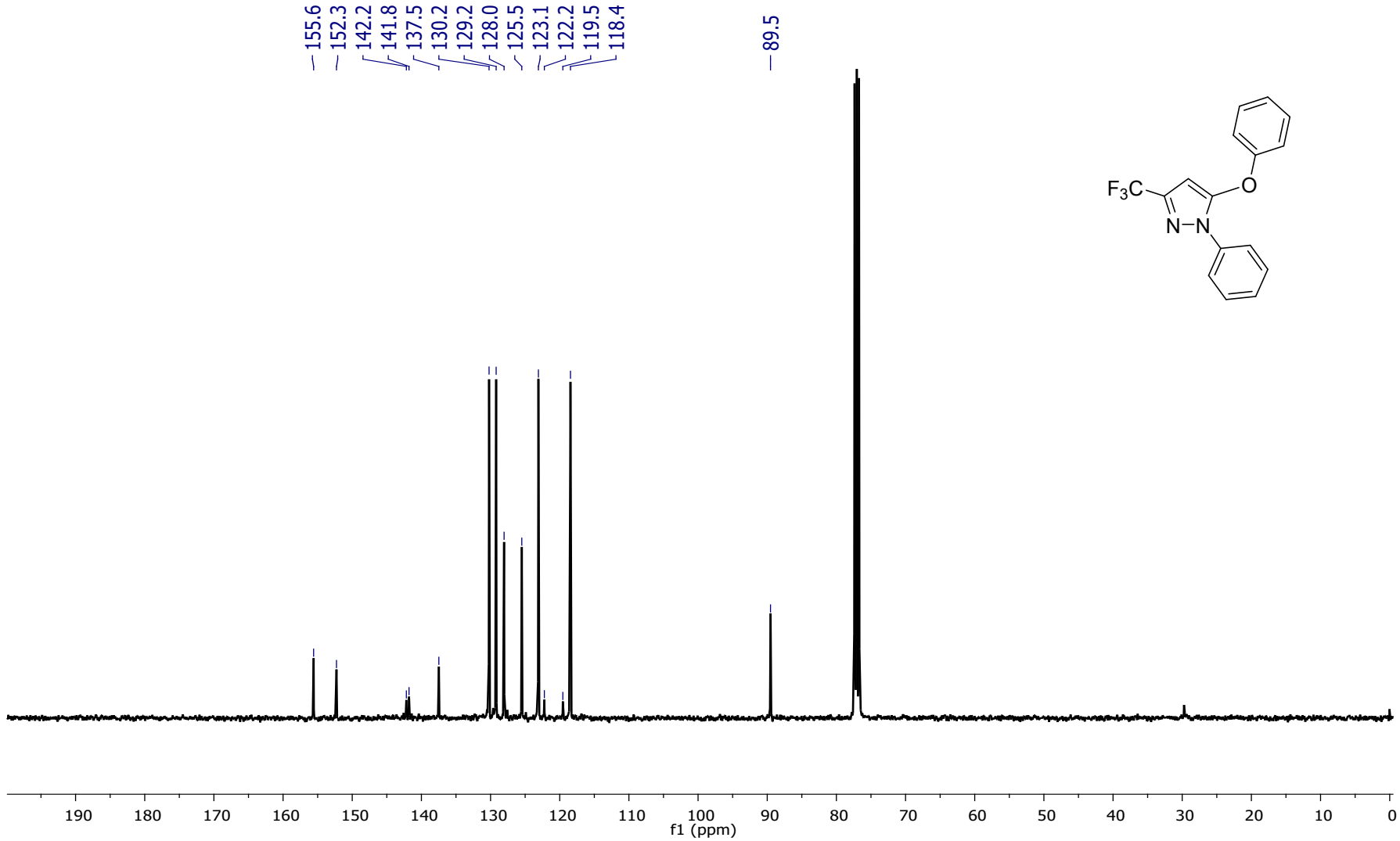
^{13}C NMR (101 MHz, $CDCl_3$) of 3-cyclopropyl-4,4-bis(3,4-dimethylphenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (**8K**):



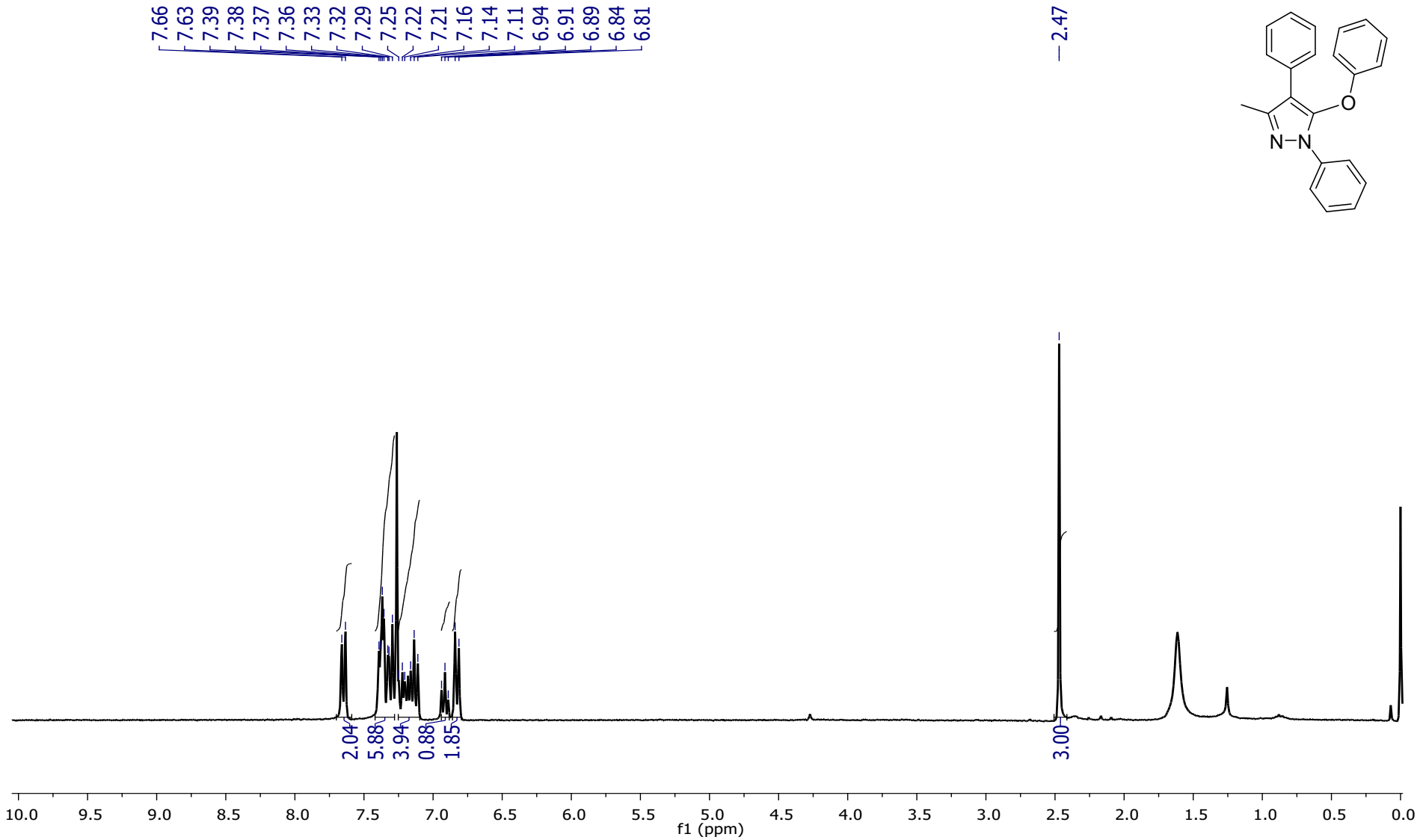
^{1}H NMR (400 MHz, $CDCl_3$) of 5-phenoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**9a**)**:**



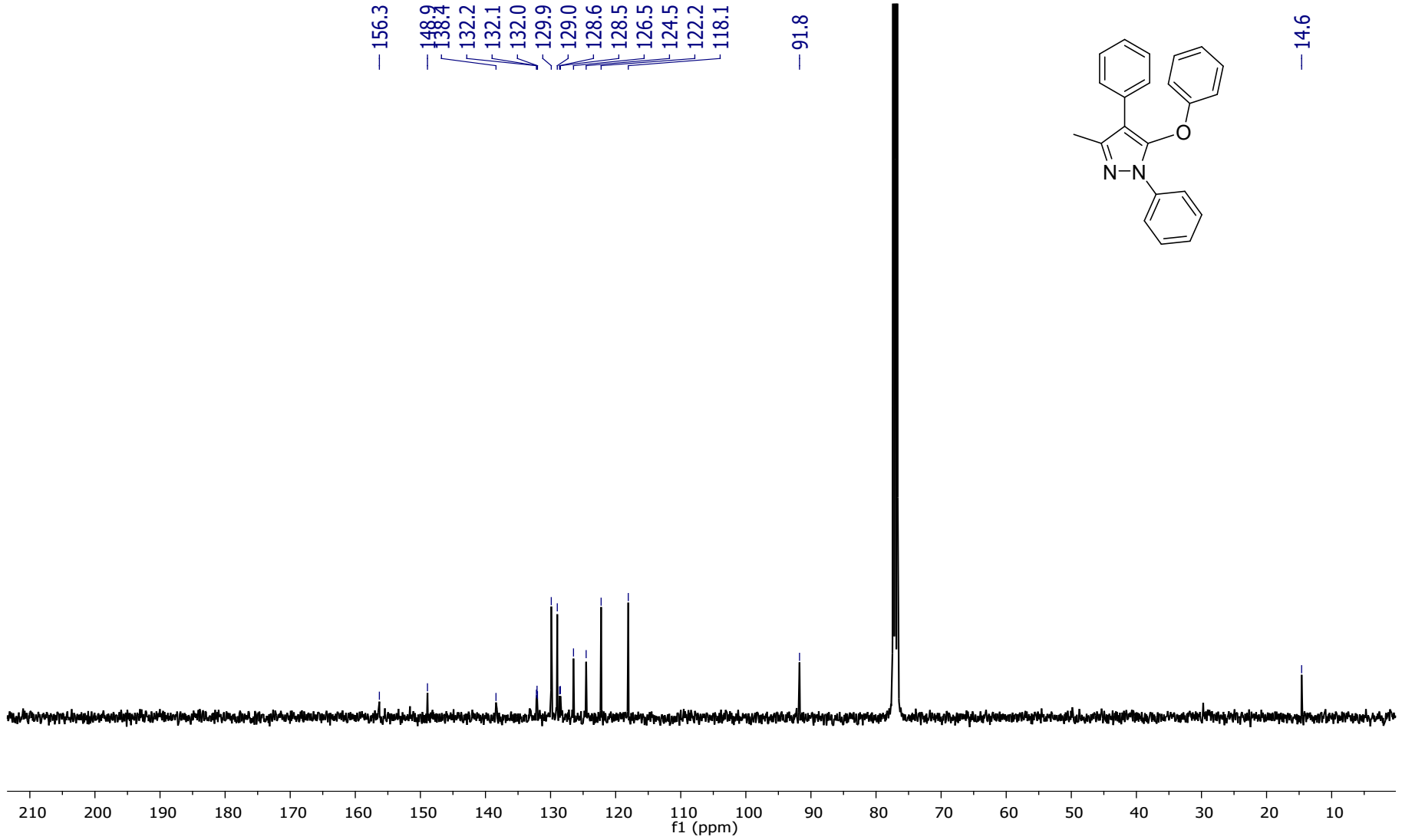
^{13}C NMR (101 MHz, $CDCl_3$) of 5-phenoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**9a**):



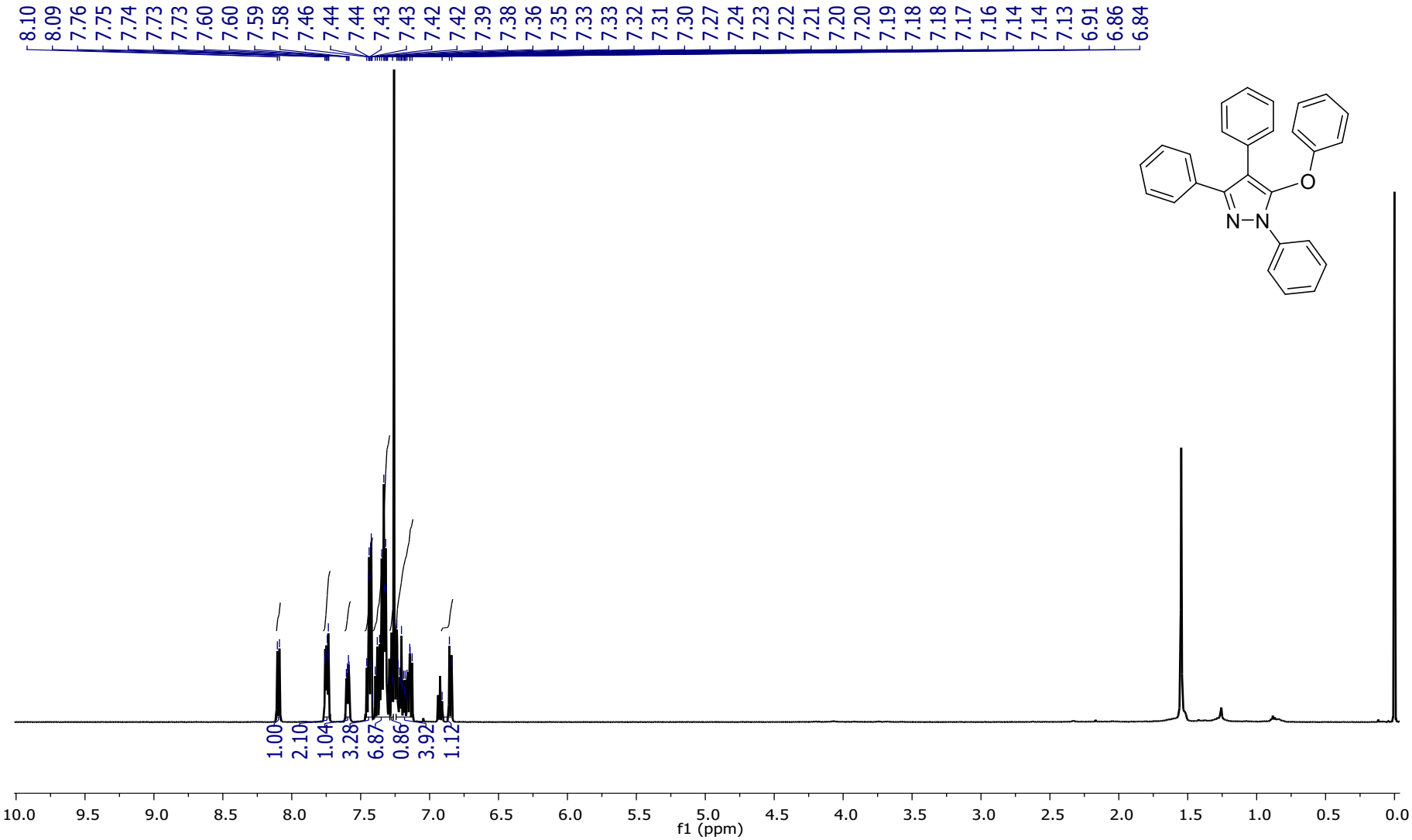
^{1}H NMR (300 MHz, $CDCl_3$) of 3-methyl-5-phenoxy-1, 4-diphenyl-1H-pyrazole (**10a**):



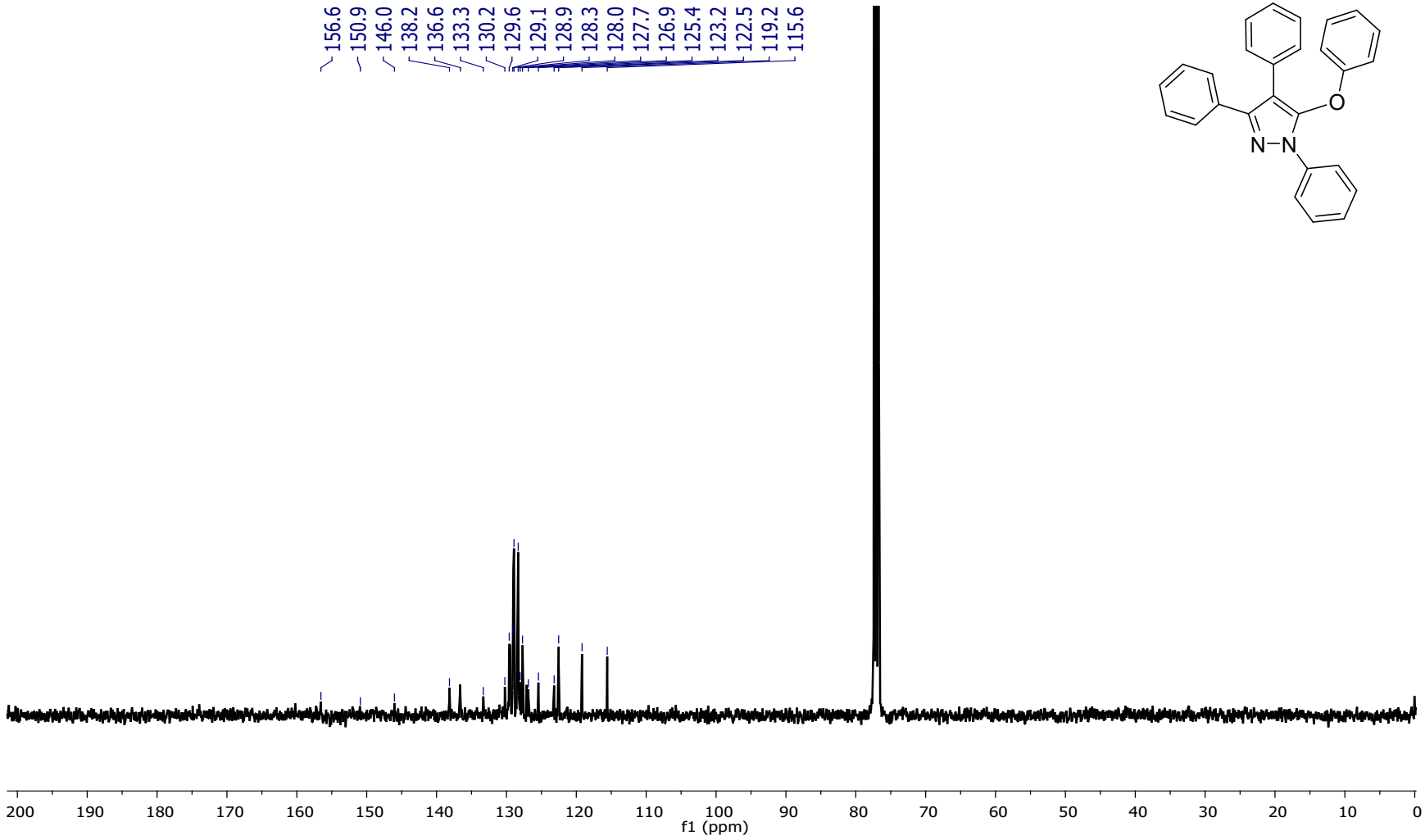
^{13}C NMR (101 MHz, $CDCl_3$) of 3-methyl-5-phenoxy-1, 4-diphenyl-1H-pyrazole (**10a**):



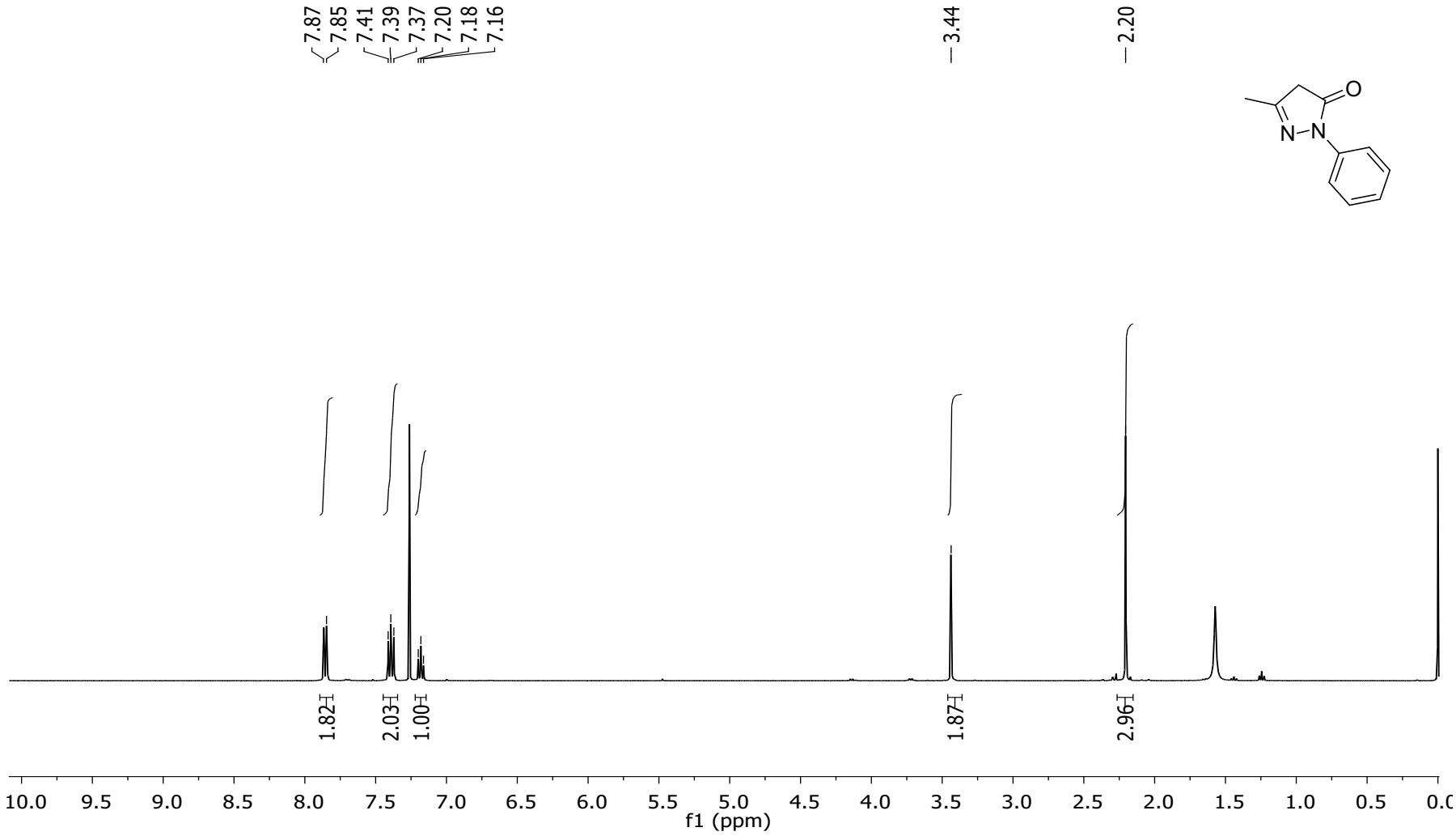
^{1}H NMR (400 MHz, $CDCl_3$) of 5-phenoxy-1, 3, 4-triphenyl-1H-pyrazole (**10b**):



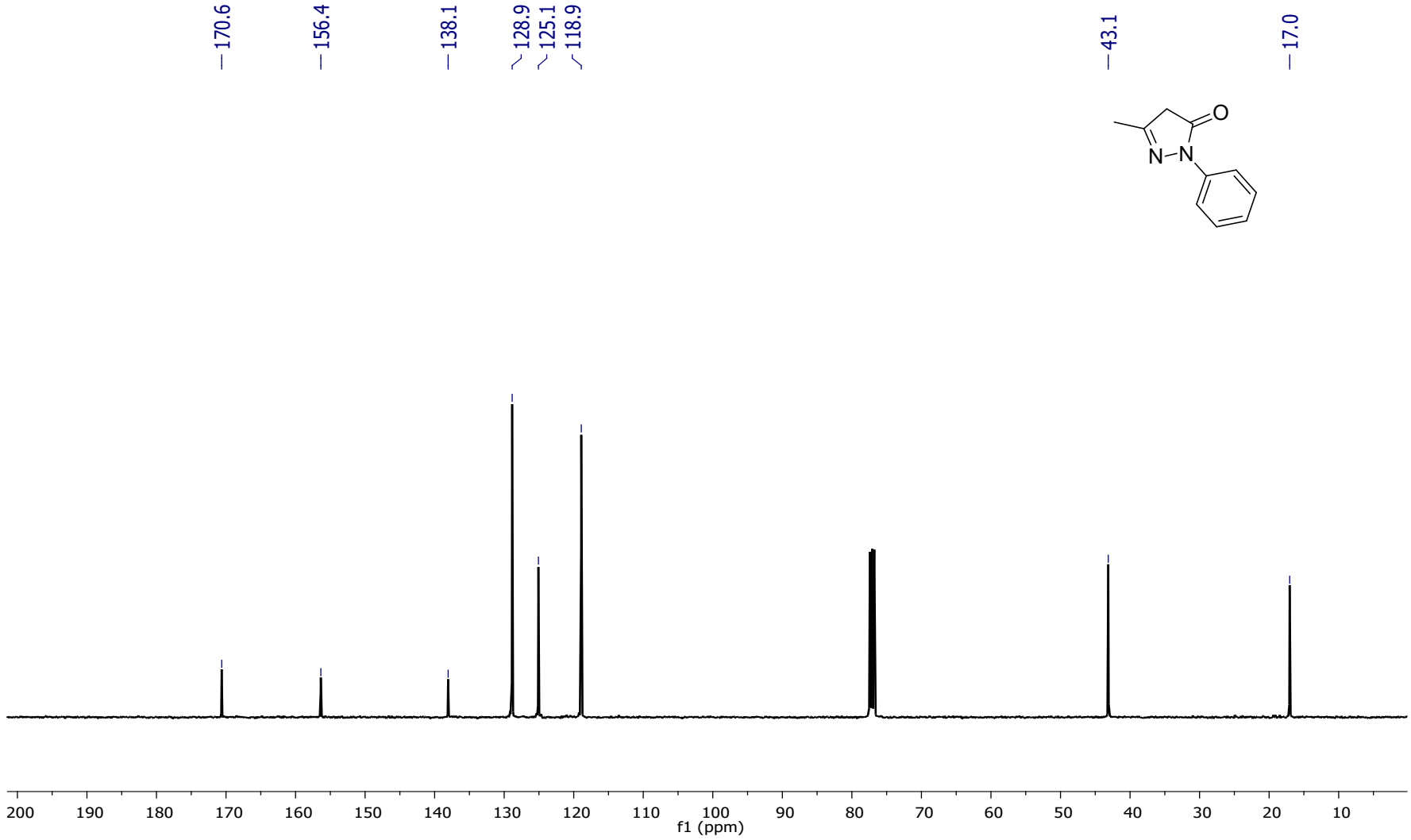
^{13}C NMR (400 MHz, $CDCl_3$) of 5-phenoxy-1, 3, 4-triphenyl-1H-pyrazole (**10b**):



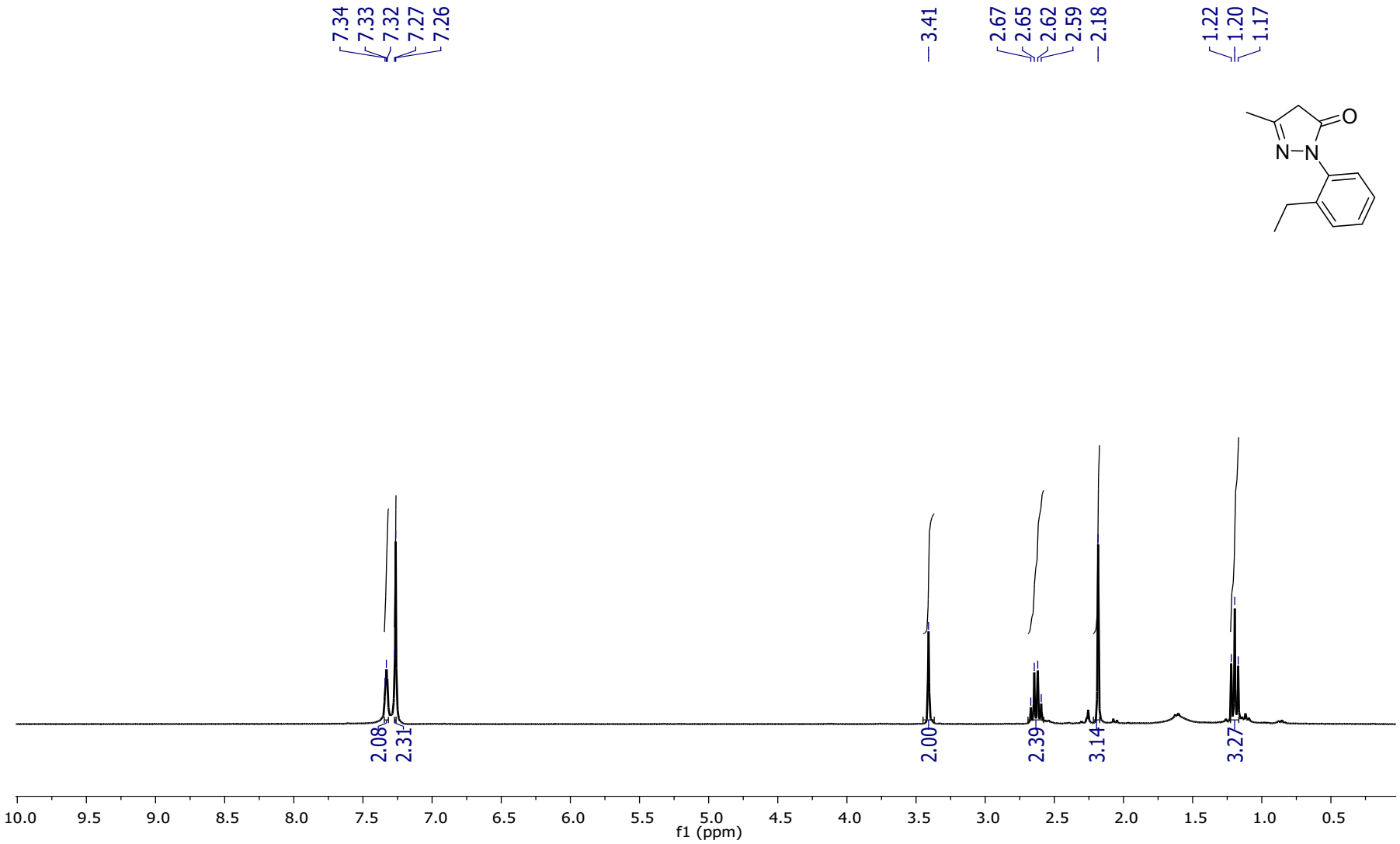
^{1}H NMR (400 MHz, $CDCl_3$) of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**6**)



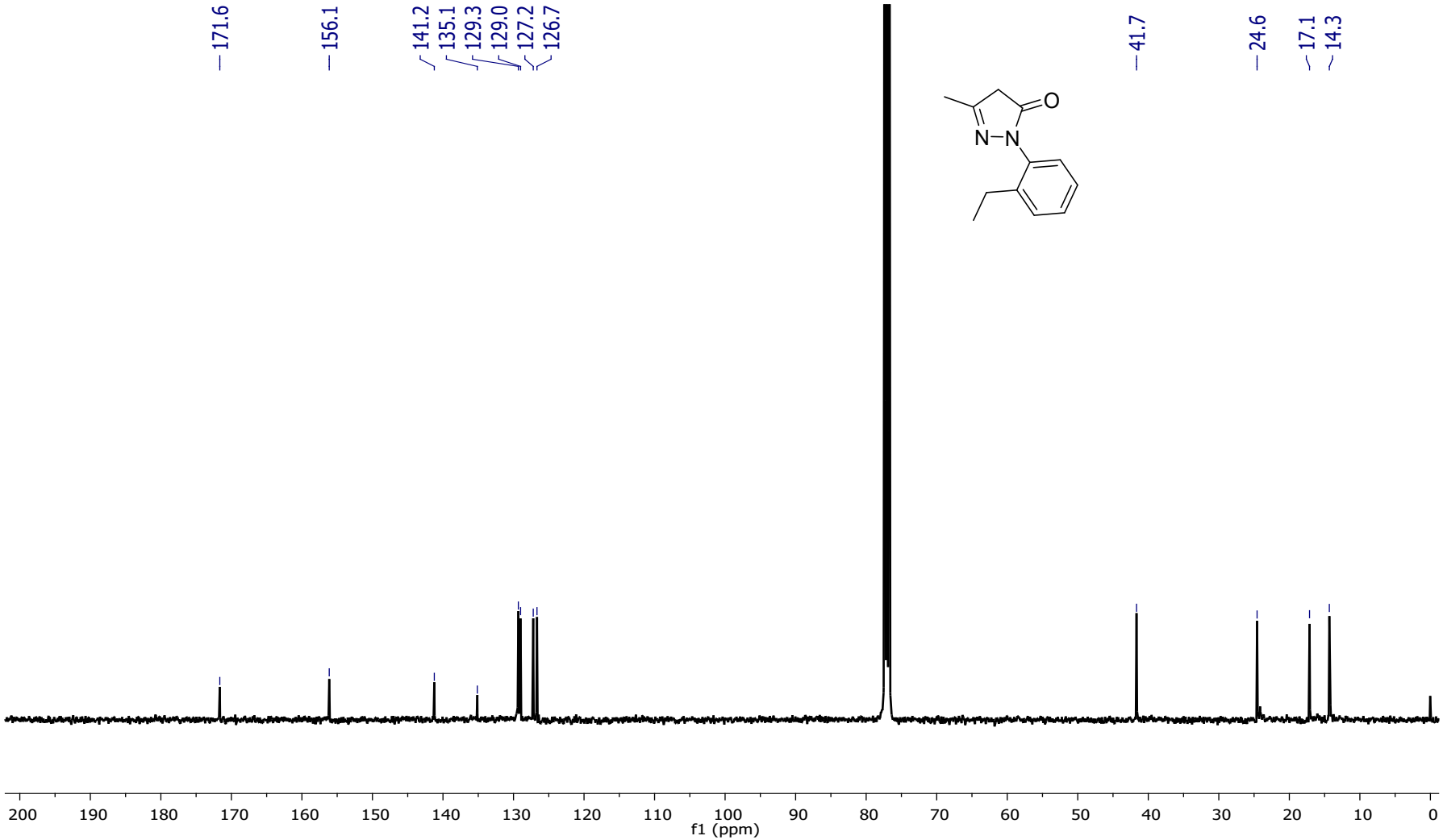
^{13}C NMR (101 MHz, $CDCl_3$) of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**6**)



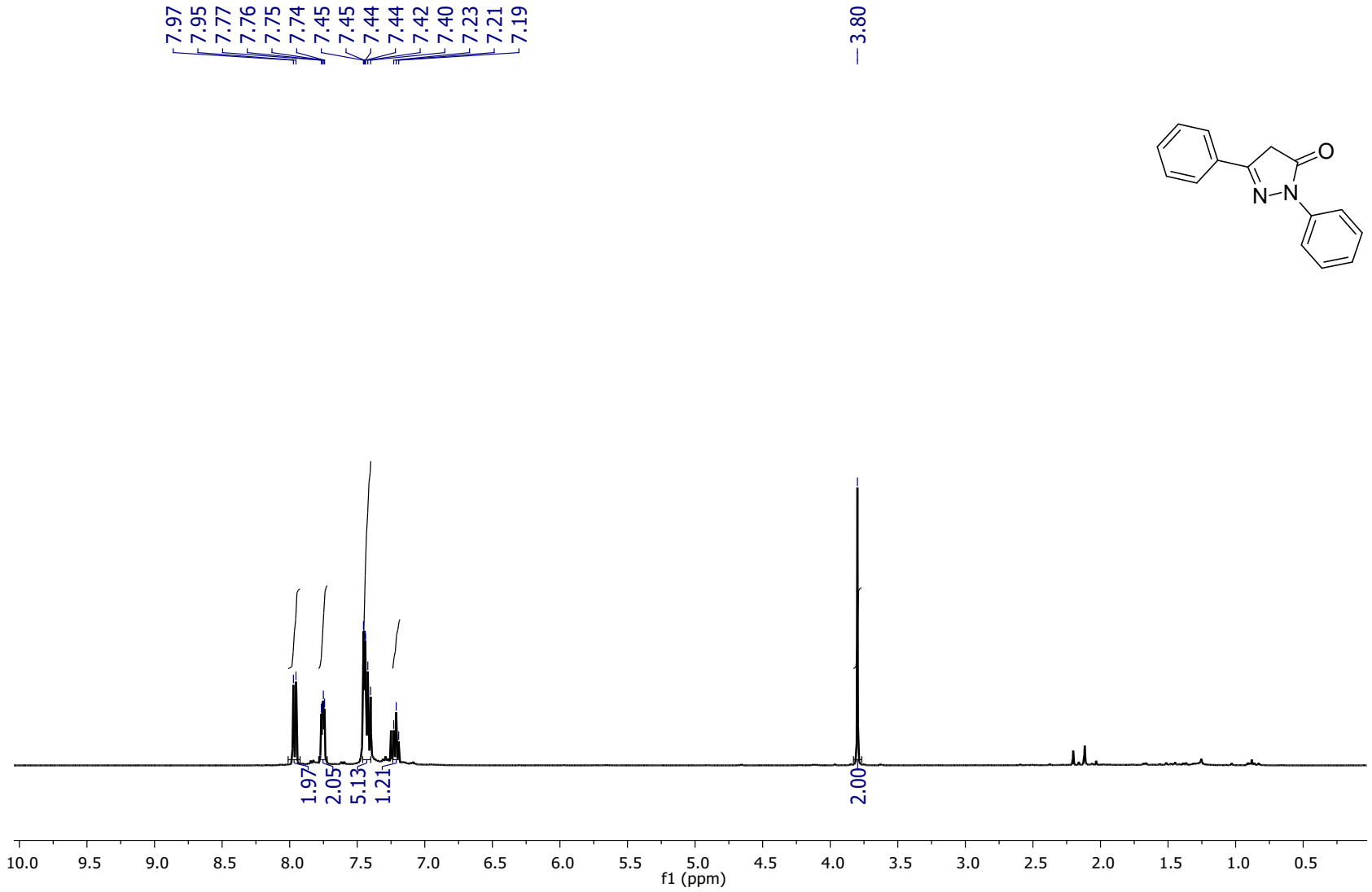
^{1}H NMR (300 MHz, $CDCl_3$) of 3-methyl-1(2-ethylphenyl)-1H-pyrazol-5(4H)-one (**6a**)



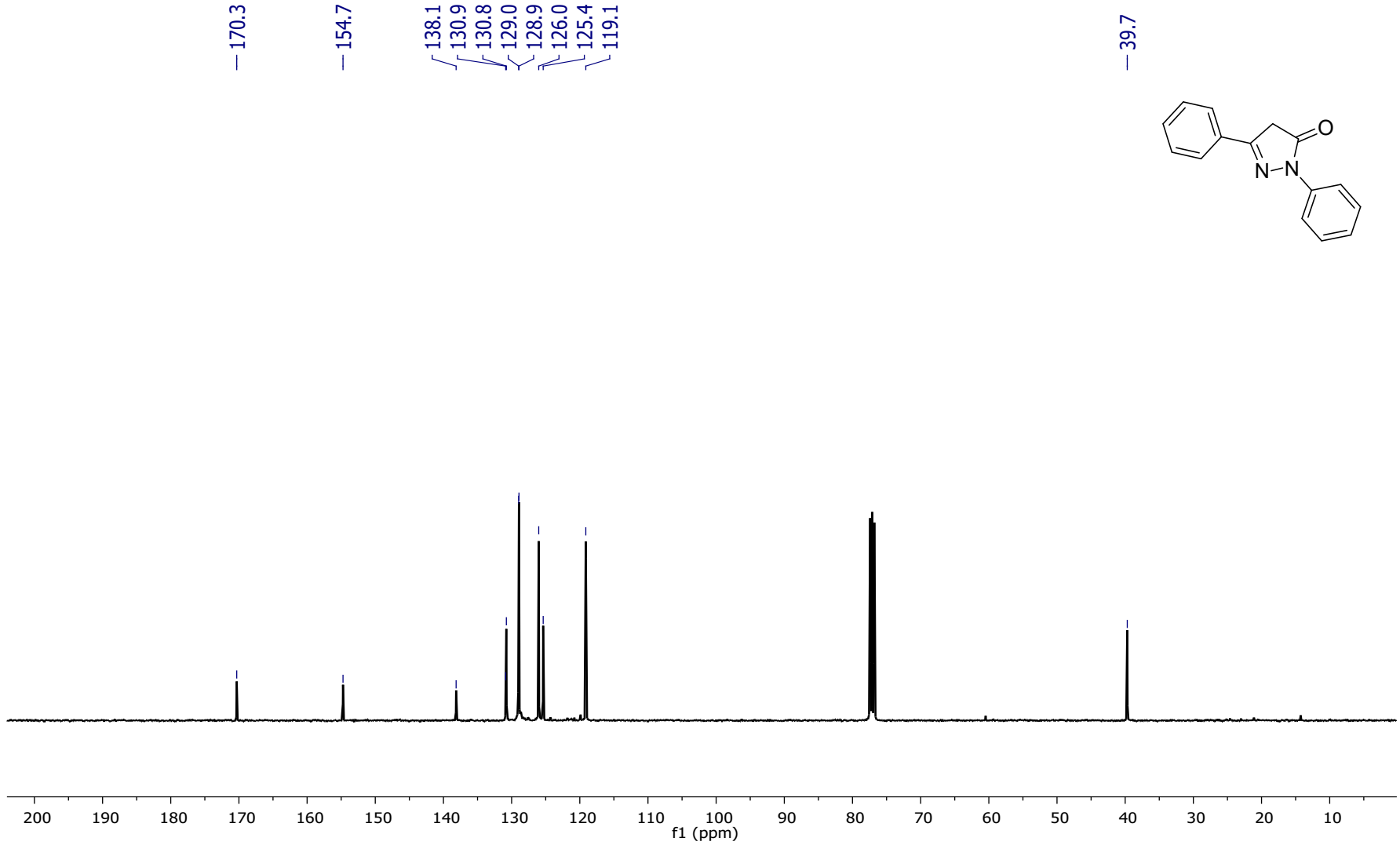
^{13}C NMR (101 MHz, $CDCl_3$) of 3-methyl-1(2-ethylphenyl)-1H-pyrazol-5(4H)-one (**6a**)



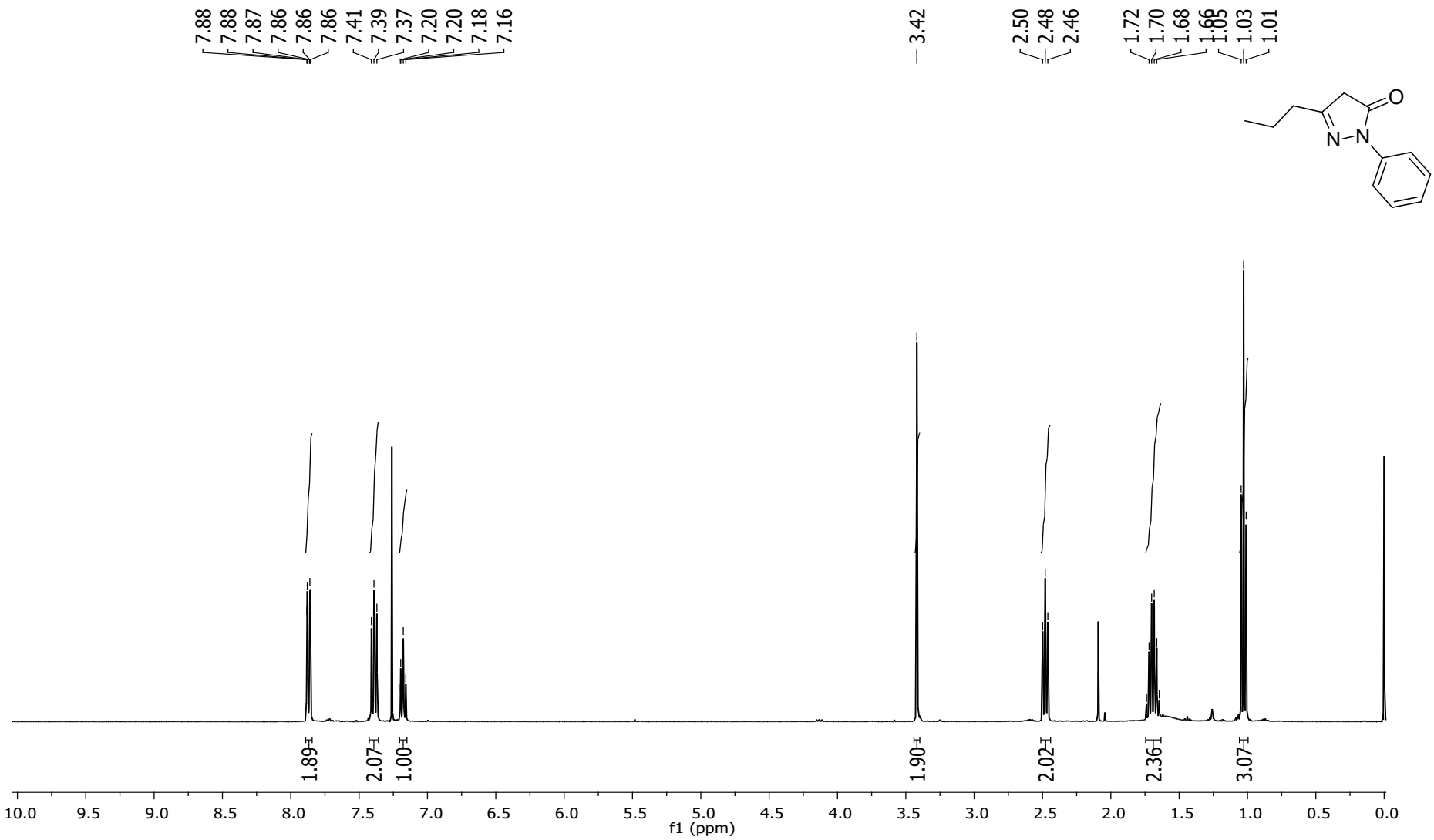
^{1}H NMR (500 MHz, $CDCl_3$) of 1,3-diphenyl-1H-pyrazol-5(4H)-one (**6b**)



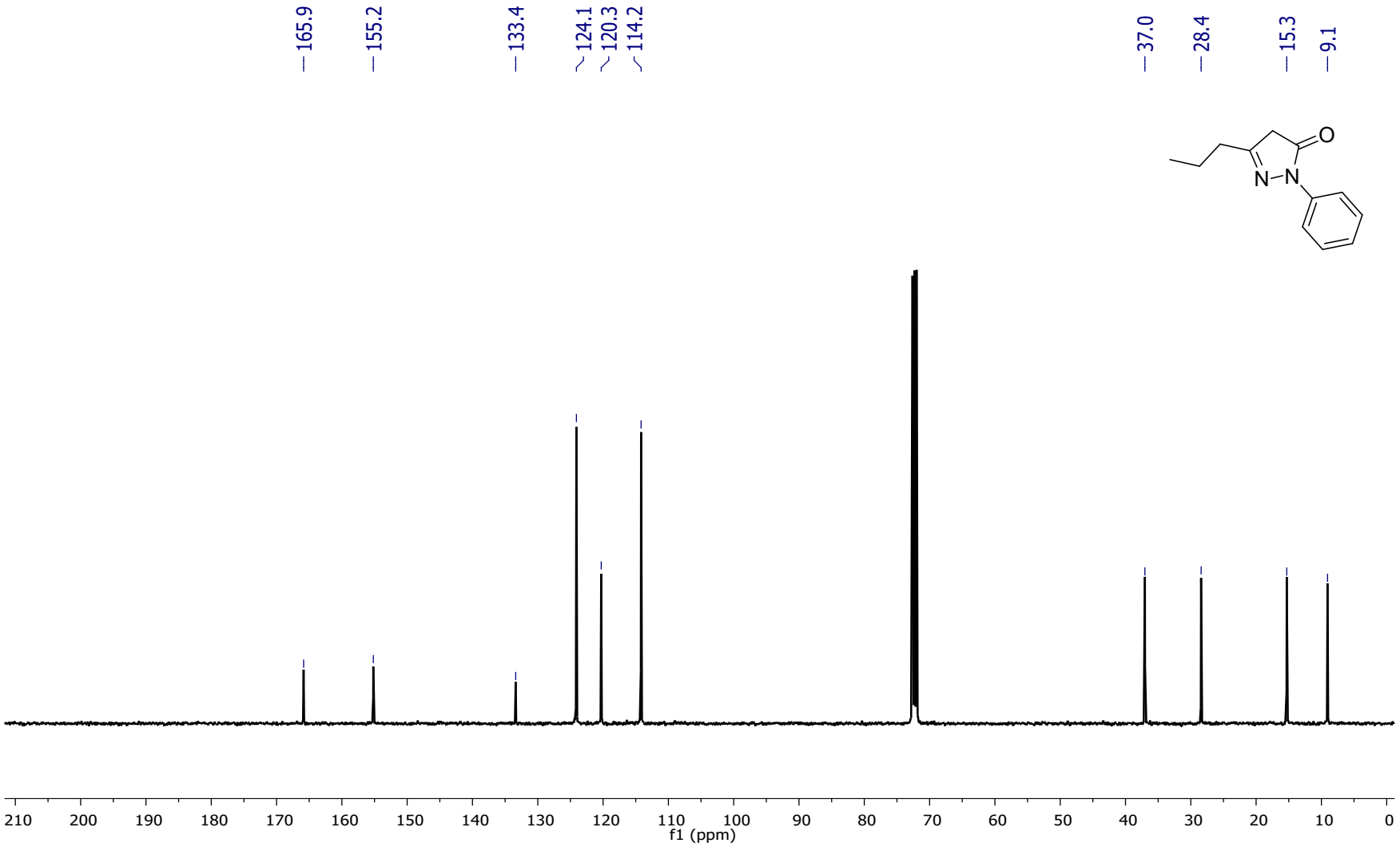
^{13}C NMR (101 MHz, $CDCl_3$) of 1,3-diphenyl-1H-pyrazol-5(4H)-one (**6b**)



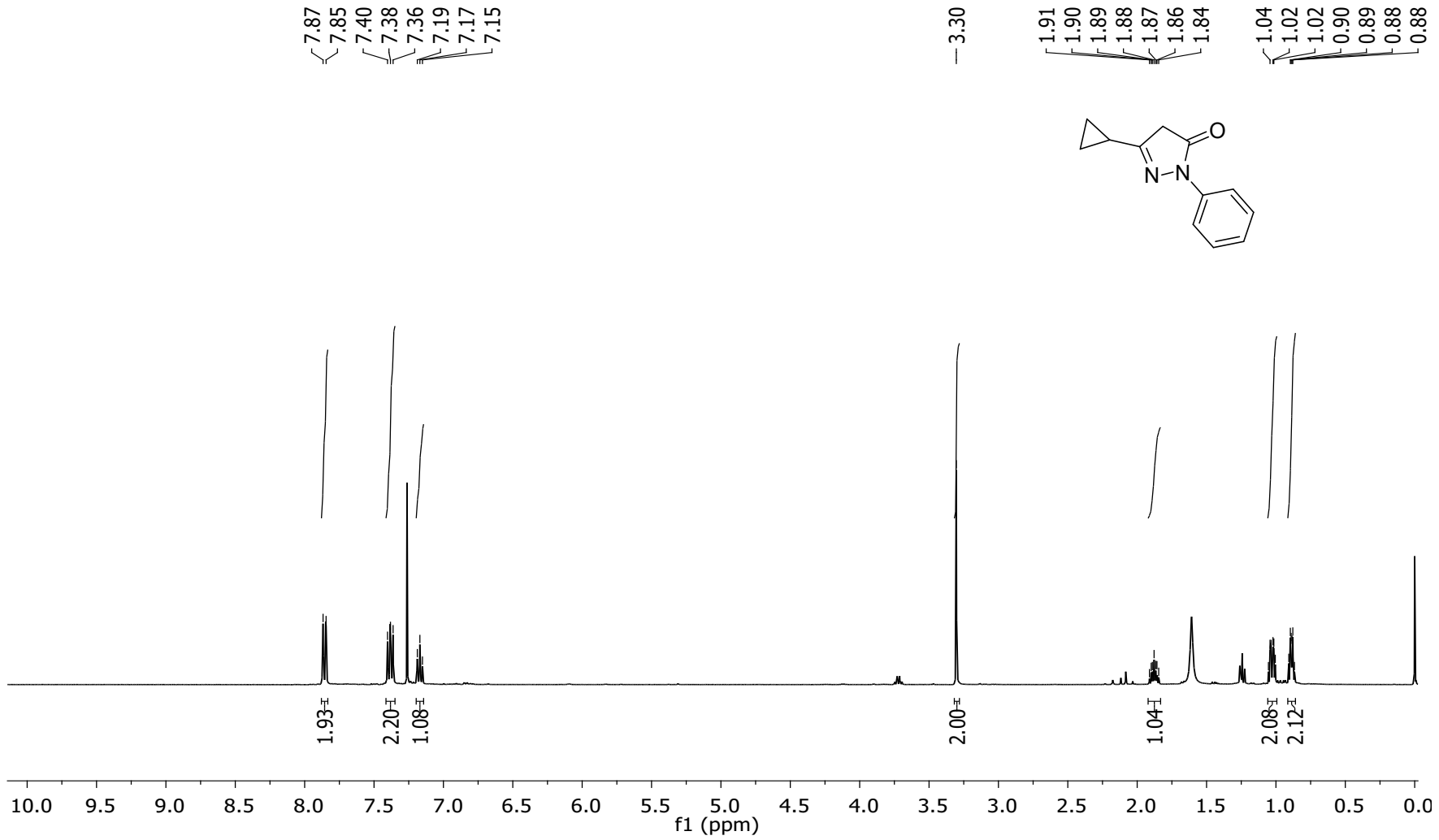
^{1}H NMR (400 MHz, $CDCl_3$) of 1-phenyl-3-propyl-1H-pyrazol-5(4H)-one (**6c**)



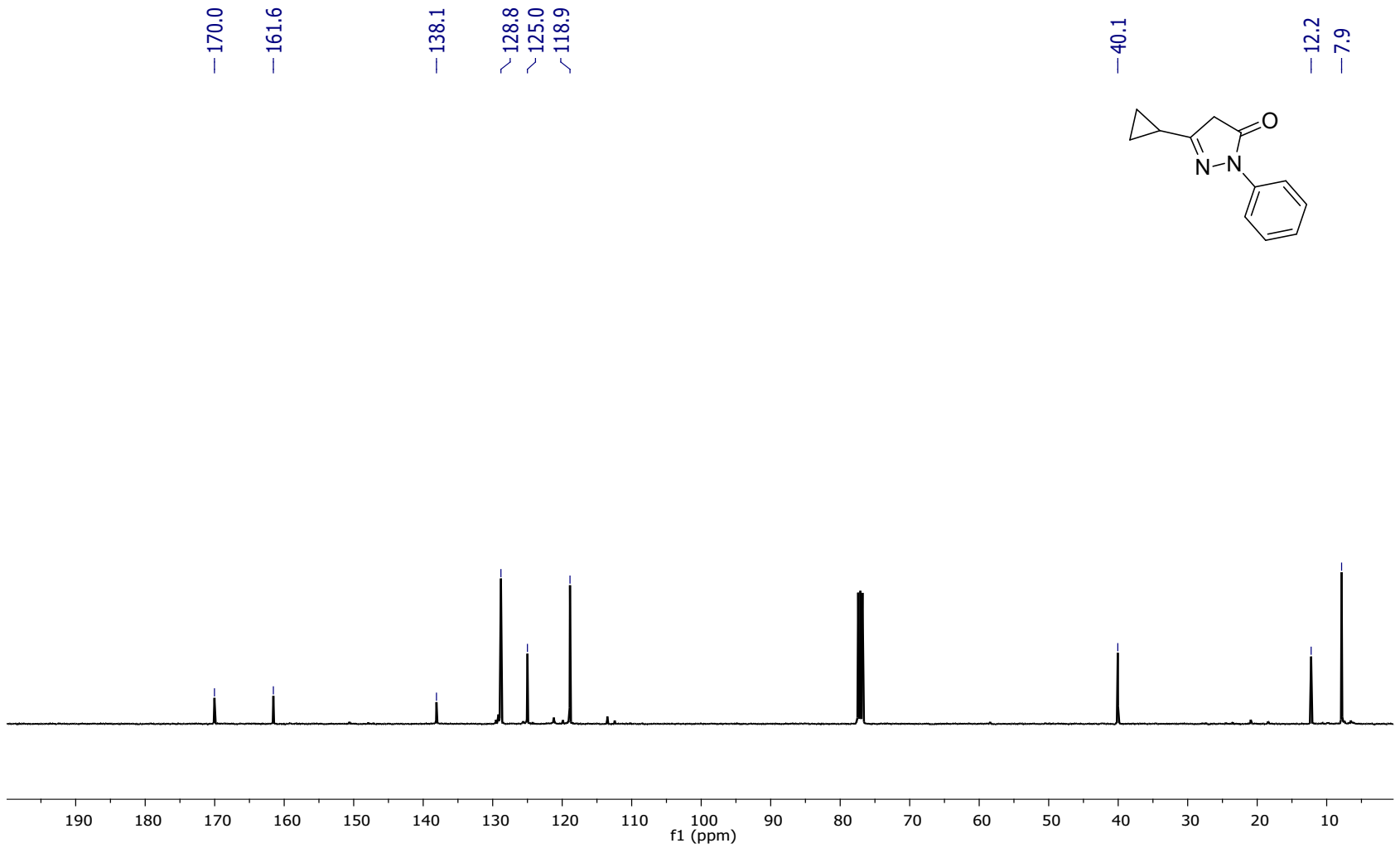
^{13}C NMR (101 MHz, $CDCl_3$) of 1-phenyl-3-propyl--1H-pyrazol-5(4H)-one (**6c**)



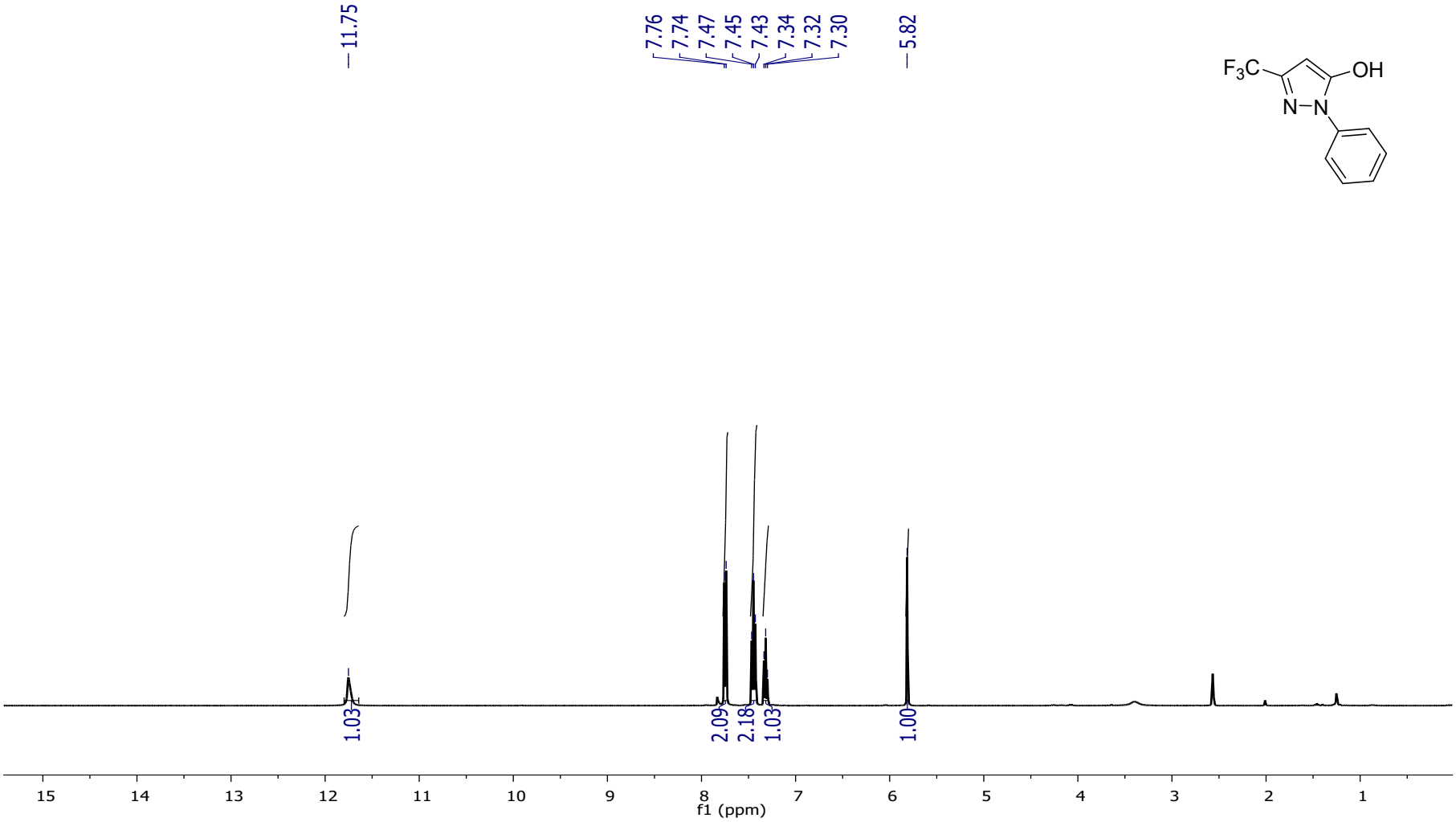
^{1}H NMR (400 MHz, $CDCl_3$) of 3-cyclopropyl-1-phenyl-1H-pyrazol-5(4H)-one (**6d**)



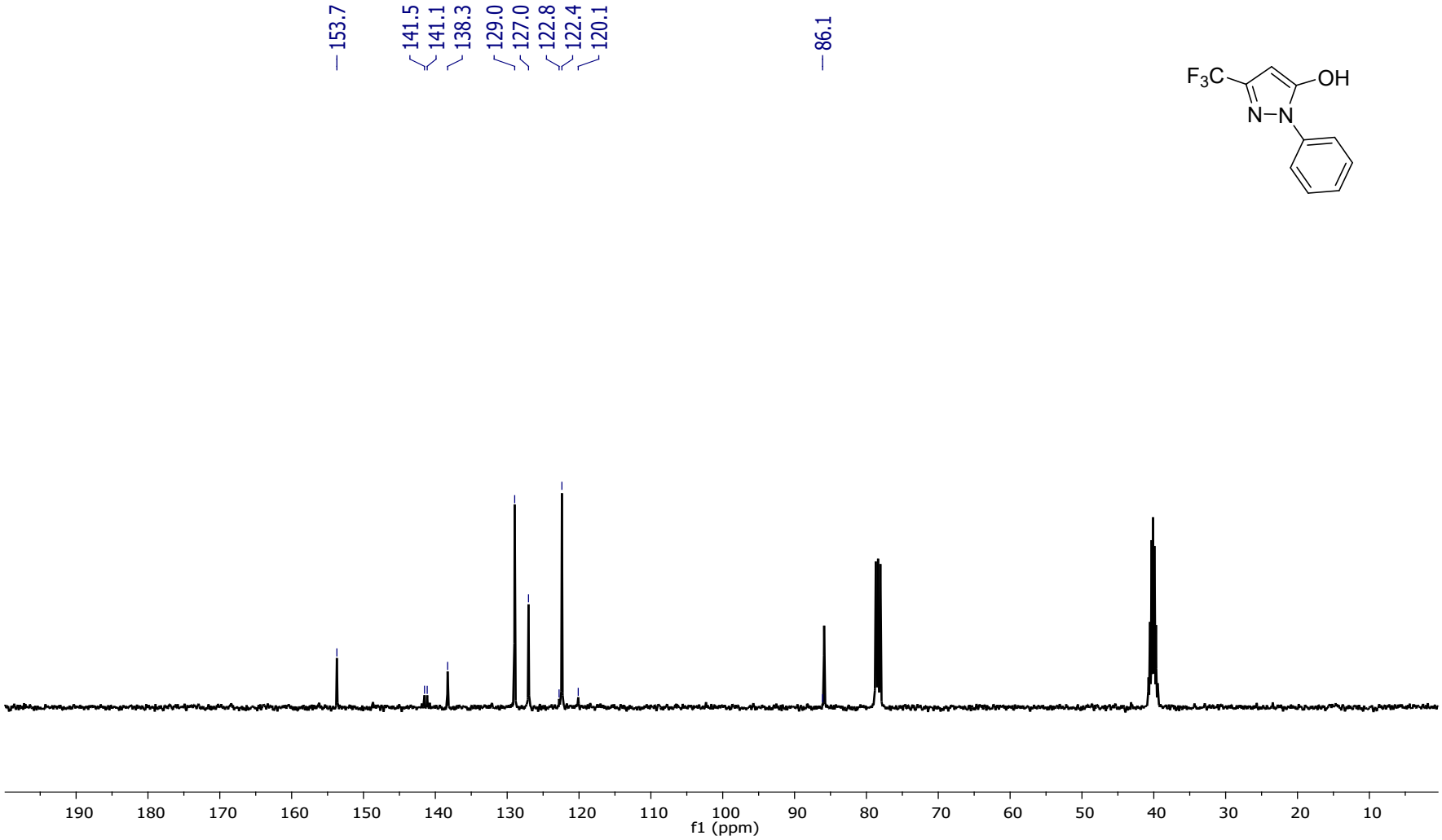
^{13}C NMR (101 MHz, $CDCl_3$) of 3-cyclopropyl-1-phenyl-1H-pyrazol-5(4H)-one (**6d**)



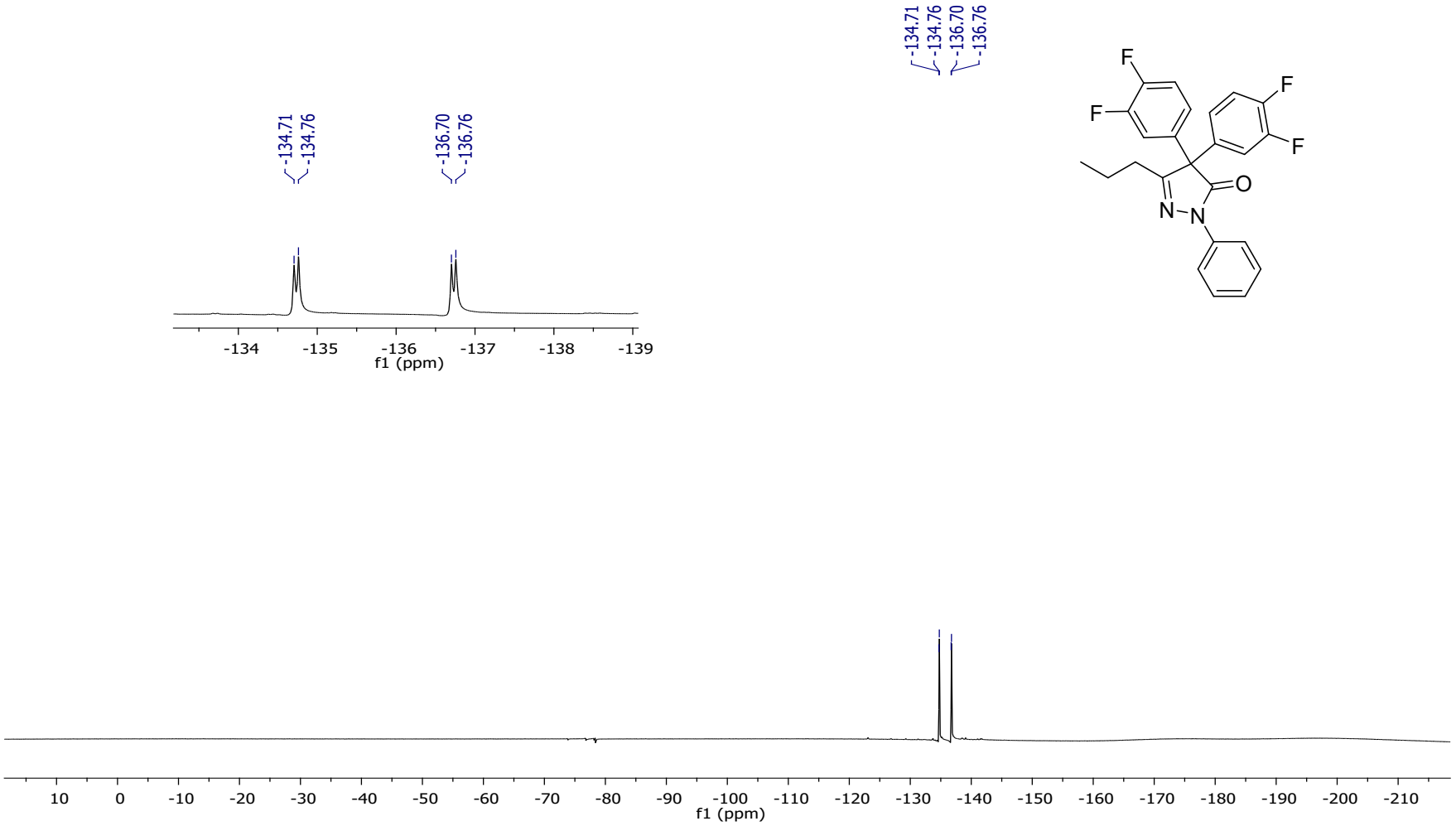
^{1}H NMR (400 MHz, $CDCl_3$) of 1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (**6e**):



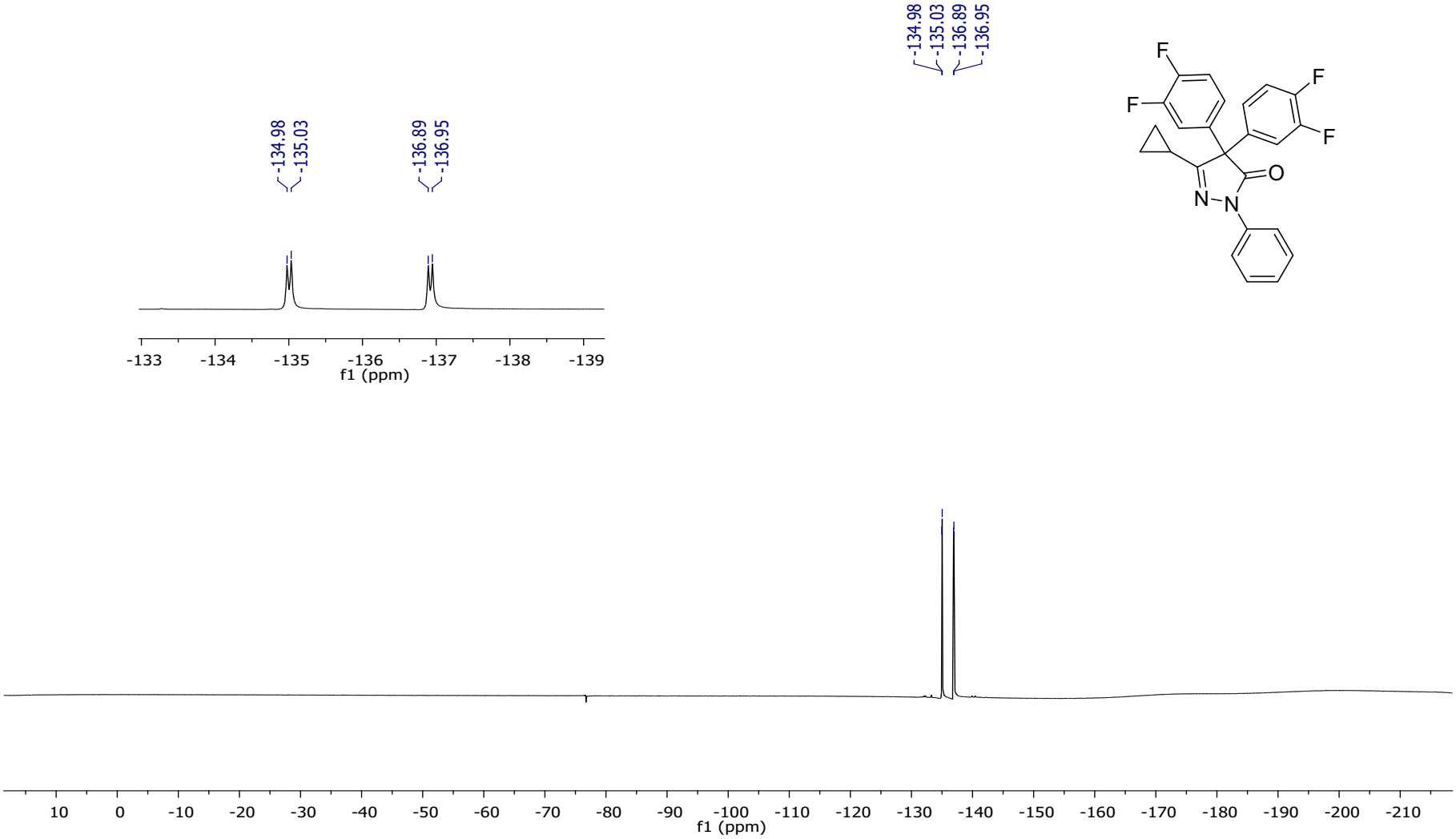
^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6) of 1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (**6e**):



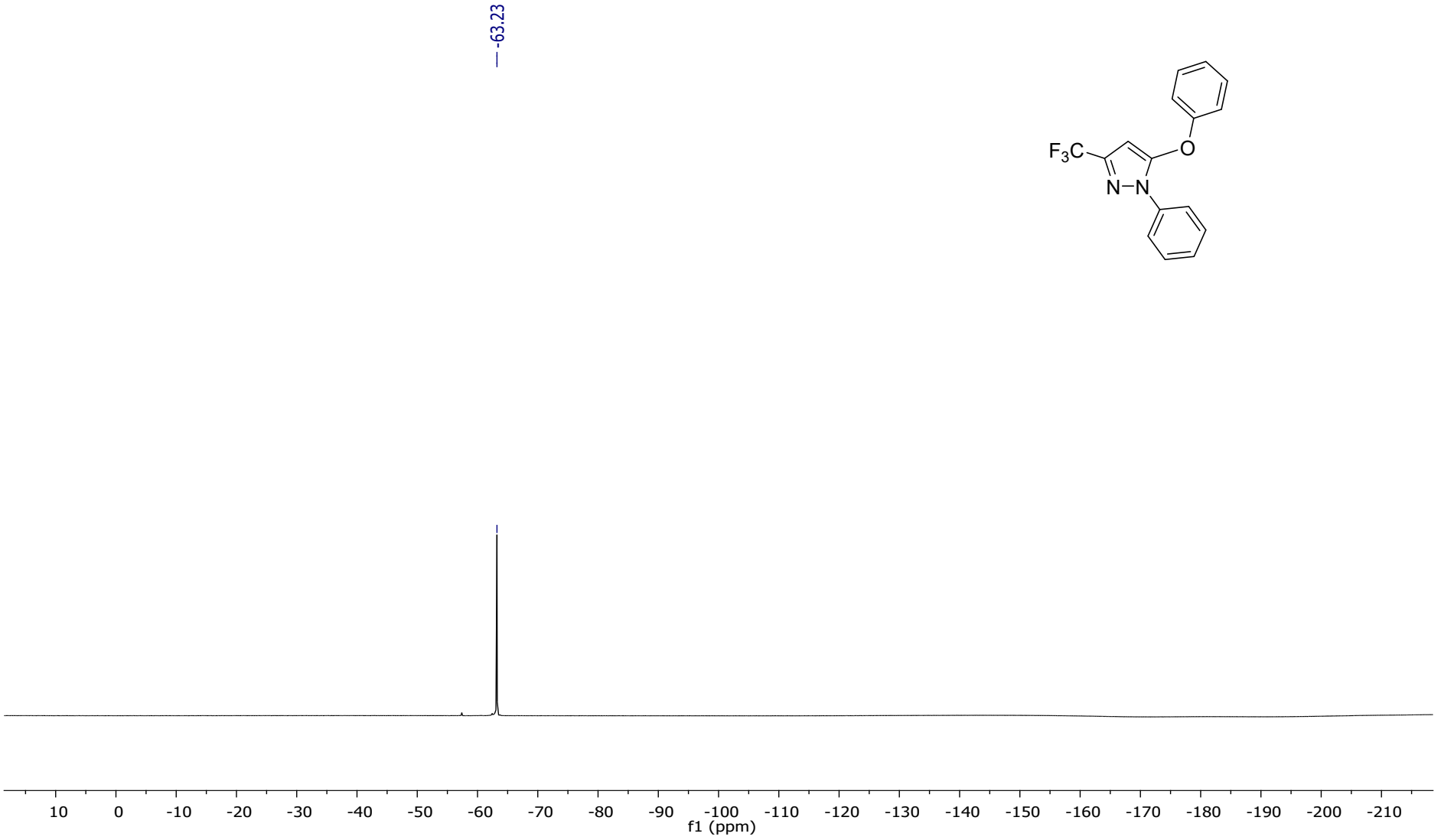
^{19}F NMR (376 MHz, $CDCl_3$) of 4,4-bis(3,4-difluorophenyl)-1-phenyl-3-propyl-1*H*-pyrazol-5(4H)-one (**8f**):



^{19}F NMR (376 MHz, $CDCl_3$) of 3-cyclopropyl-4,4-bis(3,4-difluorophenyl)-1-phenyl-1*H*-pyrazol-5(4H)-one (**8i**):



^{19}F NMR (376 MHz, $CDCl_3$) of 5-phenoxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazole (**9a**)**:**



^{19}F NMR (376 MHz, DMSO-d_6) of 1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-ol (**6e**):