Electronic Supplementary Information

Direct Synthesis of Pyrazoles from Esters using *tert*-Butoxide-Assisted C-(C=O) Coupling

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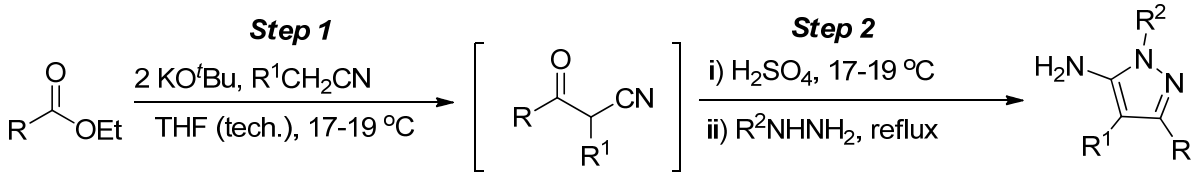
Contents of Supplementary Information

1. General Methods and Instrument Details

All of the reagents used in this work were purchased from commercial suppliers (Aldrich, TCI, Alfa Aesar or Acros Organics companies) and used without further purification. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-NMR Advance-300 spectrometer at 300 MHz and 75 MHz, respectively, with chemical shift (δ) values reported in ppm relative to an internal standard (TMS). Fourier transform infrared (FT-IR) spectra were obtained on a Varian 640-IR spectrophotometer. High-resolution mass spectra were obtained on a GC Mate 2, JEOL. Reactions were monitored by thin layer chromatography (TLC) with Merck's DC-Fertigiplatterm Kiegel 60 GE_{254} plates. Visualization was accomplished with either UV light, or by immersion in solution of phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 sec. Purification of reaction products was carried out by flash column chromatography using silica gel produced by Merck (Silica gel 60; 63 – 200 mesh, ASTM).

2. Synthetic Methods

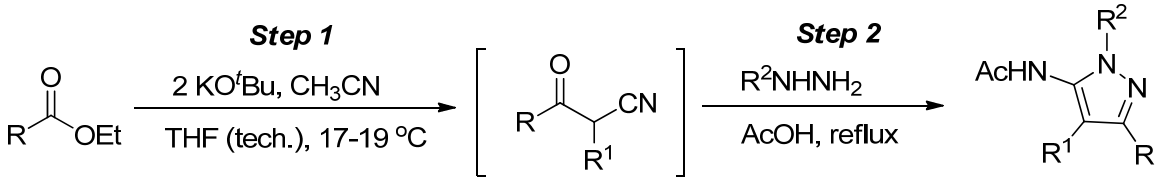
2.1. Synthesis of 5-Aminopyrazoles



Ethyl ester (3.3 mmol) was dissolved in THF (30 mL, technical grade containing 0.2% water) with stirring (about 230 rpm) at ambient temperature for 5 min. Potassium *tert*-butoxide (6.6 mmol, 95%) was added immediately to the THF solution. The corresponding

cyanomethylene (3.3 mmol; R^1CH_2CN) was then added to the reaction mixture. The resulting mixture was stirred at ambient temperature until ester disappeared on TLC monitoring. Sulfuric acid (3.3 mmol, conc.) was added dropwise to the reaction mixture. The mixture was stirred at ambient temperature for 5 min. Hydrazine hydrate (4.9 mmol, 50% for entries 1-9 in Table 1), free hydrazine (4.9 mmol for entries 7-9 in Table 1), or hydrazine hydrochloride (4.9 mmol for entry 10 in Table 1) was slowly added, and the resulting mixture was refluxed until *β*-ketonitrile was consumed. The reaction was monitored by TLC. The reaction mixture was cooled to ambient temperature, and then evaporated under reduced pressure. The resulting residue was dissolved in THF (20-50 mL) and filtered. The precipitate was washed with THF (about 10 mL). The resulting filtrates were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (for 5-amino-3-phenyl, 5-amino-3-(4-chlorophenyl), 5-amino-3-(4-chlorophenyl)-4-ethyl, 5-amino-4-ethyl-3-phenyl-, and 5-amino-3-(isopropyl)-1*H*-pyrazole: 3 × 11-15 cm, CH_2Cl_2:THF:MeOH (10:1:1, v/v/v); for 5-amino-4-ethyl-3-phenyl-1*H*-pyrazole: 3.5 × 15 cm, THF:*n*-hexane (2:1, v/v); for 5-amino-1,3-diphenyl and 5-amino-1-(4-nitrophenyl)-3-phenyl-1*H*-pyrazole: 3 × 13-15 cm, *n*-hexane:ethyl acetate (3:1, v/v); 5-amino-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazoles: 3 × 13 cm, *n*-hexane:ethyl acetate (2:1, v/v); for 5-amino-1-methyl-3-phenyl-1*H*-pyrazole: 3 × 15 cm, CH_2Cl_2:THF:ethyl acetate (2:1:1, v/v/v)). Fractions containing the product were combined and evaporated under reduced pressure to obtain the corresponding 5-aminopyrazoles.

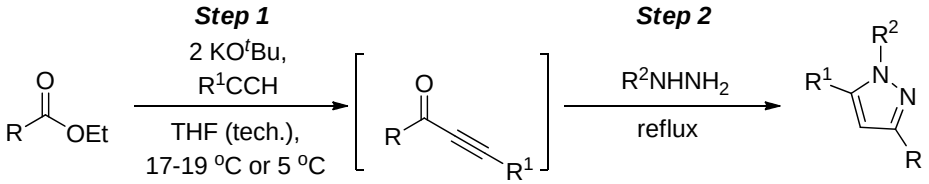
2.2. Synthesis of 5-Acetamidopyrazoles



Ethyl ester (3.3 mmol) was dissolved in THF (30 mL, technical grade involving 0.2% water) with stirring (about 230 rpm) at ambient temperature for 5 minutes. Potassium *tert*-butoxide (6.6 mmol, 95%) was added immediately to the THF solution. Acetonitrile (3.3 mmol) was then added to the reaction mixture, which was stirred at ambient temperature until ester disappeared on TLC monitoring. Acetic acid (30 mL) was slowly added in the reaction mixture. After adding slowly hydrazine hydrate (4.9 mmol, 50% for entries 1-3 in Table 2) or free hydrazine (4.9 mmol for entry 4 in Table 2), the mixture was refluxed until *β*-ketonitrile was consumed. The reaction was monitored by TLC. After cooling the reaction mixture to room temperature, water (20 mL) and ethyl acetate (20 mL) were added. The reaction mixture was neutralized with $NaHCO_3$ (aq., sat.). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The resulting filtrates were concentrated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (for 5-acetamido-3-phenyl, 5-acetamido-3-isopropyl and 5-acetamido-3-(4-chlorophenyl)-1*H*-pyrazoles: 4 × 11-15 cm, ethyl acetate; for 5-acetamido-1,3-diphenyl-1*H*-pyrazole: 3 × 15 cm, *n*-hexane:ethyl acetate (5:1, v/v)). Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding 5-acetamidopyrazoles.

2.3. Synthesis of 3,5-Disubstituted or 1,3,5-Trisubstituted-pyrazoles

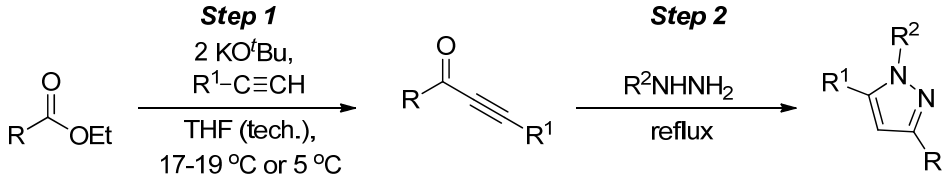
2.3.1. Method A (using partially purified *α*,*β*-alkynone)



Potassium *tert*-butoxide (6.4 mmol, 95%) was dissolved in THF (30 mL, technical grade involving 0.2% water) and the THF solution of ethyl ester and acetylene, which was dissolved ester (3.2 mmol) and acetylene (3.2 mmol; R^1CCH) in THF (10 mL), was dropped immediately for 1 min in the above solution at 5 °C ice bath. After the consumption of acetylene or ester was confirmed on TLC monitoring, the reaction mixture was poured into the mixture of ethyl acetate (10 mL) and ice powder (10-15 g). (When we used other solvents such as CH_2Cl_2, $CHCl_3$ and acetonitrile, unknown byproducts were formed.) The organic layer was separated. Water layer was washed with ethyl acetate (10mL) once more. The organic layers were combined in the flask where hydrazine hydrate (4.9 mmol, 50% for entries 1-7 in Table 4) or free hydrazine (4.9 mmol for entry 8 in Table 4) was slowly added. The reaction mixture was then refluxed until *α,β*-alkynone was consumed. The reaction was monitored by TLC. After cooling the mixture, the solvent was evaporated under reduced pressure. THF (10 mL) was added to the mixture with stirring. The reaction mixture was filtered, and the resulting filtrate was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (for 3-methyl-5-phenyl-**,** 3-methyl-5-(cyclohex-1-en-1-yl)-, 3-isopropyl-5-phenyl-, 3-isopropyl-5-(4-(*n*-hexylphenyl))-, 3-phenethyl-5-phenyl-, 3-cyclohexyl-5-phenyl-, 3-heptyl-5-phenyl-1*H*-pyrazoles: 3 × 8-15 cm, *n*-hexane:ethyl acetate (3:1, v/v); for 3-(2-(5-phenyl-1*H*-pyrazol-3-yl)ethyl)pyridine: 3.5 × 15 cm, ethyl acetate; for 3-methyl-1,5-diphenyl-1*H*-

pyrazole: 3 × 15 cm, *n*-hexane:ethyl acetate (10:1, v/v)). Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding 3,5-disubstituted-pyrazoles.

2.3.2. Method B (using pure α,β-alkynone)

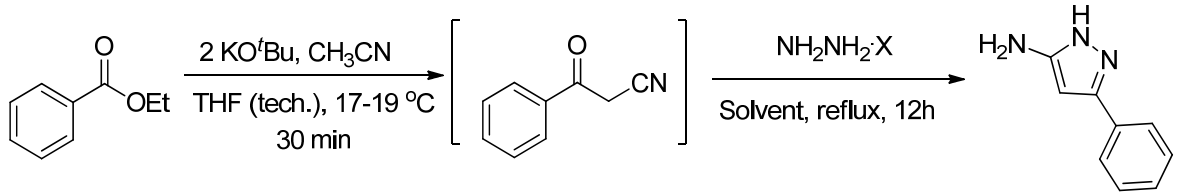


Potassium *tert*-butoxide (6.4 mmol, 95%) was dissolved in THF (30 mL, technical grade involving 0.2% water) and the THF solution of ethyl ester and acetylene, which was dissolved ester (3.2 mmol) and acetylene (3.2 mmol; R^1CCH) in THF (10 mL), was dropped immediately for 1 min in the above solution at ambient temperature or 5 ^oC ice bath. After stirring at ambient temperature for 3-10 min, the reaction mixture was quenched by addition of water (20 mL). The mixture was poured into the mixture of ethyl acetate (60 mL) and ice powder (25-30 g). The organic layer was separated and dried over anhydrous $MgSO_4$. After filtering the mixture, the resulting filtrate was concentrated under reduced pressure at 80 ^oC (for α,β-alkynones corresponding to 3-methyl-5-phenyl-1*H*-pyrazole and 3-heptyl-5-phenyl-1*H*-pyrazole) or 40 ^oC below (for α,β-alkynones corresponding to 3-methyl-5-(cyclohex-1-en-1-yl)-, 3-isopropyl-5-phenyl-, 3-isopropyl-5-(4-(*n*-hexylphenyl))-, 3-phenethyl-5-phenyl-, 3-cyclohexyl-5-phenyl-1*H*-pyrazoles). The resulting residue was applied to the top of an open-bed silica gel column (for 3-methyl-5-phenyl-**,** 3-methyl-5-(cyclohex-1-en-1-yl)-, 3-

isopropyl-5-phenyl-, 3-isopropyl-5-(4-(*n*-hexylphenyl))-, 3-cyclohexyl-5-phenyl-, 3-heptyl-5-phenyl-1*H*-pyrazoles: 3 × 8-15 cm, *n*-hexane/ethyl acetate (3:1, v/v); 3-phenethyl-5-phenyl-1*H*-pyrazole: 3 × 5 cm, *n*-hexane / ethyl acetate (10 : 1, v/v); 3-(2-(5-phenyl-1*H*-pyrazol-3-yl)ethyl)pyridine: 3 × 15 cm, ethyl acetate). Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding *α,β*-alkynones. Pure *α,β*-alkynones were dissolved in EtOH (10 mL) and hydrazine hydrate (1.5 mmol, 50% for entries 1-7 in Table 4) or free hydrazine (1.5 mmol for entry 8 in Table 4) was slowly added. The mixture was then refluxed until *α,β*-alkynone was consumed. The reaction was monitored by TLC. After cooling of the mixture, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (for 3-methyl-5-phenyl-**,** 5-(cyclohex-1-en-1-yl)-3-methyl-, 3-isopropyl-5-phenyl-, 5-(4-(*n*-hexylphenyl))-3-isopropyl-, 3-phenethyl-5-phenyl-, 3-cyclohexyl-5-phenyl-, 3-heptyl-5-phenyl-1*H*-pyrazoles : 3 × 8-15 cm, *n*-hexane: ethyl acetate (3 : 1, v/v); for 3-(2-(5-Phenyl-1*H*-pyrazol-3-yl)ethyl)pyridine: 3.5 × 15 cm, ethyl acetate; for 1,3-diphenyl-5-methyl-1*H*-pyrazole: 3 × 11 cm, *n*-hexane:ethyl acetate (4:1, v/v)). Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding 3,5-disubstitutedpyrazoles.

3. Supplementary Tables and Figure

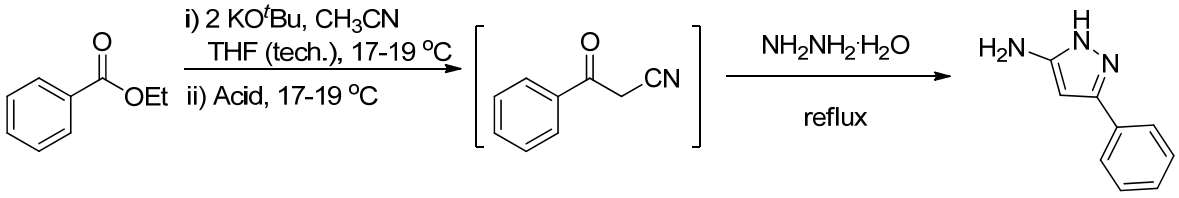
Table S1. Screening of Hydrazines



entry	NH_2NH_2·X (equiv.)	solvent	time (h)	5-amino-3-phenyl-1*H*-pyrazole yield (%)[a]
1	$NH_2NH_2·H_2O$ (3)	THF	12	—
2	$NH_2NH_2·H_2O$ (3)	EtOH	12	—
3	$NH_2NH_2·H_2O$ (3)	Toluene	12	—
4	$NH_2NH_2·H_2SO_4$ (1.5)	THF	12	65
5	$NH_2NH_2·H_2SO_4$ (2)	THF	12	61
6	$NH_2NH_2·H_2SO_4$ (3)	THF	12	67
7	$NH_2NH_2·H_2SO_4$ (3)	THF/H_2O =1:6 (v/v)	12	34

[a]Isolated yield; and overall yield for two sequential reactions in one-pot synthesis.

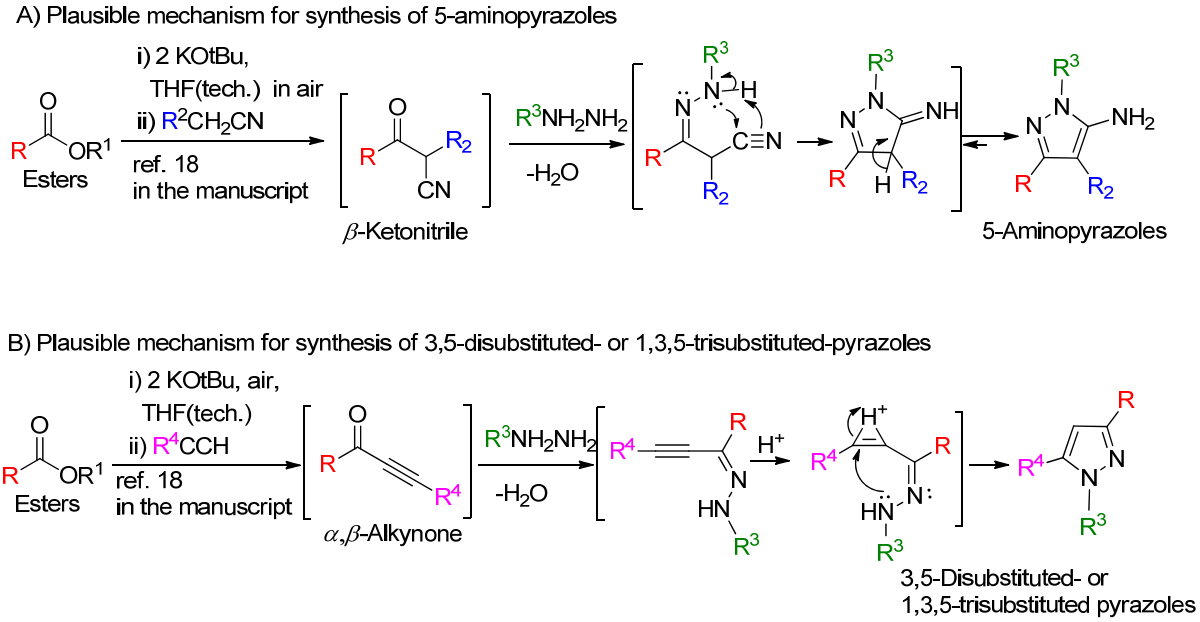
Table S2. Screening of Protic Acid



entry	Protic acid (equiv)	time (h)	5-amino-3-phenyl-1*H*-pyrazole yield (%)[a]
1	H_2SO_4 (1)	0.6	78
2	H_2SO_4 (1.5)	0.6	76
3	H_2SO_4 (2)	1	78
4	H_2SO_4 (2.5)	6	17
5	HCl (1)	3	13
6	HCl (2)	1	78
7	HNO_3 (1)	3	13
8	HNO_3 (2)	1	78
9	H_3PO_4 (1)	4	60
10	H_3PO_4 (2)	4	63

[a] Isolated yield; and overall yield for two sequence reactions in one-pot synthesis.

Figure S1. Plausible mechanisms for the reactions to afford pyrazole derivatives from esters via potassium *tert*-butoxide-assisted C-(C=O) coupling.



4. Analytical Data

The compounds shown in Table 1 in the manuscript.

5-Amino-3-(4-chlorophenyl)-1*H*-pyrazole (entry 1): Yield: 400 mg (77%); Ivory solid. mp 174-175 °C (lit.[1] 173-175 °C); IR (KBr) 3434, 3362, 3315, 3205, 3111, 3067, 3049, 2993, 2937, 2871, 1625, 1607, 1512, 1499, 1480, 1090, 997, 831 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.04 (br s, NH_2, D_2O exchangeable), 5.79 (s, 1H), 7.42 (d, 2H, J = 8.5 Hz), 7.70 (d, 2H, J = 8.5 Hz), 11.79 (br s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 87.3, 126.8, 128.7, 129.0, 132.0, 145.6, 152.9. HRMS (EI) m/z: $[M]^+$ calcd. for $C_9H_8ClN_3$ 193.0407; Found: 193.0409.

5-Amino-3-(4-chlorophenyl)-4-ethyl-1*H*-pyrazole (entry 2): Yield: 314 mg (53%); Light

yellow liquid; IR (KBr) 3395, 3361, 3332, 3306, 3210, 2964, 2929, 1682, 1649, 1618, 1560, 1539, 1500, 1460, 1471, 1265, 1090, 832 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.03 (t, 3H, J = 7.3 Hz), 2.42 (q, 2H, J = 7.4 Hz), 5.39 (br s, 3H, D_2O exchangeable), 7.45-7.53 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.66, 15.85, 105.7, 128.5, 128.9, 129.7, 133.8, 141.0, 152.4. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{11}H_{12}ClN_3$ 221.0720; Found: 221.0720.

5-Amino-4-benzyl-3-phenyl-1*H*-pyrazole (entry 3): Yield: 508 mg (61%); Yellow liquid; IR (KBr) 3141, 3309, 3204, 3059, 3028, 2992, 2957, 2908, 1691, 1606, 1500, 1447, 1315, 1272, 1235, 1072, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H), 6.73 (br s, 3H, D_2O exchageable), 7.15-7.34 (m, 8H), 7.39-7.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 101.7, 126.3, 127.6, 128.1, 128.2, 128.4, 128.7, 128.9, 129.9, 130.6, 140.0, 143.0, 153.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{16}H_{15}N_3$ 249.1266; Found: 249.1267.

5-Amino-4-ethyl-3-phenyl-1*H*-pyrazole (entry 4): Yield: 340 mg (55%); Yellow liquid; IR (KBr) 3415, 3359, 3333, 3212, 2963, 2974, 2866, 1696, 1680, 1617, 1561, 1533, 1500, 1452, 1267, 1070, 960 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.06 (t, 3H, J = 7.5 Hz), 2.45 (q, 2H, J = 7.6 Hz), 5.40 (br s, 3H, D_2O exchangeable), 7.31 (t, 1H, J = 7.2 Hz), 7.40-7.51 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.74 15.88, 105.7, 127.4, 128.0, 128.7, 131.2, 141.5, 152.9. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{11}H_{13}N_3$ 187.1109; Found: 187.1110.

5-Amino-3-isopropyl-1*H*-pyrazole (entry 5): Yield: 428 mg (80%); Yellow liquid; IR (KBr) 3324, 3213, 2964, 2928, 2871, 1617, 1576, 1366, 1275, 1262, 1092, 1065, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, 2H, J = 6.9 Hz), 2.78-2.94 (m, 1H), 4.63 (bs, 3H, D_2O

exchangeable), 5.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.23, 26.19, 89.69, 152.1, 154.2. HRMS (EI) m/z: $[M]^+$ calcd. for $C_6H_{11}N_3$ 125.0953; Found: 125.0951.

5-Amino-3-phenyl-1*H*-pyrazole (entry 6): Yield: 410 mg (78%); Ivory solid. mp 120-122 °C (lit.[2] 124-126 °C); IR (KBr) 3396, 3292, 3196, 3171, 3108, 3059, 2963, 1620, 1583, 1567, 1507, 1476, 1004, 785 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (br s, 3H, D_2O exchangeable), 5.77 (s, 1H), 7.18-7.26 (m, 1H), 7.44-7.46 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.17, 125.4,128.2, 128.8, 130.4, 145.8, 154.0. HRMS (EI) m/z: $[M]^+$ calcd. for $C_9H_9N_3$ 159.0796; Found: 159.0797.

5-Amino-1,3-diphenyl-1*H*-pyrazole (entry 7): Yield: 450 mg (58%); Light brown solid. mp 125-127 °C (lit.[2] 124-126 °C); IR (KBr) 3426, 3305, 3025, 3185, 3139, 3058, 1627, 1594, 1560, 1502, 1477, 1452, 1375, 1131, 1066, 954, 775 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.53 (br s, NH_2, D_2O exchangeable), 5.99 (s, 1H), 7.31-7.44 (m, 4H), 7.52 (t, 2H, *J* = 7.8 Hz), 7.72 (d, 2H, *J* = 7.8 Hz), 7.81 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 87.6, 123.3, 125.5, 126.7, 128.0, 129.0, 129.6, 134.1, 139.7, 148.7, 150.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{15}H_{13}N_3$ 235.1109; Found: 235.1109.

5-Amino-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazole (entry 8): Yield: 480 mg (56%); Light brown solid. mp 159-161 °C (lit.[3] 160-163 °C); IR (KBr) 3423, 3305, 3207, 3183, 2952, 2929, 2832, 1627, 1560, 1513, 1481, 1450, 1417, 1378, 1295, 1249, 1176, 1141, 1103, 1041, 1022, 952, 838, 748 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 5.35 (br s, NH_2, D_2O exchangeable), 5.90 (s, 1H), 7.06 (d, 2H, *J* = 8.7 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 7.38 (t,

2H, J = 7.5 Hz), 7.54 (d, 2H, J = 9.0 Hz), 7.75 (d, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.8, 87.0, 114.7, 125.3, 125.4, 127.8, 128.9, 132.7, 134.2, 148.5, 149.9, 158.2. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{16}H_{15}N_3O$ 265.1215; Found: 265.1214.

5-Amino-1-(4-nitrophenyl)-3-phenyl-1*H*-pyrazole (entry 9): Yield: 340 mg (37%); Yellow solid. mp 196-198 °C (lit.[3] 192-194 °C); IR (KBr) 3367, 3311, 3226, 1637, 1590, 1564, 1500, 1475, 1448, 1419, 1375, 1332, 1214, 1108, 1072, 1025, 946, 865, 852, 752 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.86 (br s, NH_2, D_2O exchangeable), 6.06 (s, 1H), 7.33-7.44 (m, 3H), 7.83 (d, 2H, J = 7.2 Hz), 8.06 (d, 2H, J = 9.0 Hz), 8.36 (d, 2H, J = 9.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 89.2, 122.3, 125.3, 125.8, 128.6, 129.0, 133.3, 144.6, 145.1, 149.9, 152.2. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{15}H_{12}N_4O_2$ 280.0960; Found: 280.0961.

5-Amino-1-methyl-3-phenyl-1*H*-pyrazole (entry 10): Yield: 240 mg (42%); Ivory liquid; IR (KBr) 3297, 3181, 3124, 3052, 2956, 2919, 2850, 1617, 1558, 1506, 1452, 1373, 1257, 1087, 1016 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.57 (s, 3H), 5.29 (br s, NH_2, D_2O exchangeable), 5.69 (s, 1H), 7.32 (t, 2H, J = 7.5 Hz), 7.50 (t, 1H, J = 6.6 Hz), 7.65 (d, 2H, J = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.7, 85.5, 125.0, 127.2, 128.8, 129.0, 148.1, 148.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{10}H_{11}N_3$ 173.0953; Found: 173.0954.

The compounds shown in Table 2 in the manuscript.

5-Acetamido-3-phenyl-1*H*-pyrazole (entry 1): Yield: 355 mg (53%); Light brwon solid. mp 228-230 °C; IR (KBr) 3322, 3215, 2964, 2931, 2871, 1660, 1617, 1593, 1582, 1548, 1497, 1490, 1396, 1365, 1172, 1090, 958 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.08 (s, 3H),

6.91(s, 1H), 7.32-7.48 (m, 3H), 7.75 (d, 2H, J = 7.5Hz), 10.51 (br s, 1H, D_2O exchangeable), 12.83 (bs, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.01, 93.41, 124.8, 127.8, 128.6(1), 128.8(4), 141.8, 148.2, 167.4. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{11}H_{11}N_3O$ 201.0902; Found: 201.0902.

5-Acetamido-3-isopropyl-1*H*-pyrazole (entry 2): Yield: 338 mg (47%); Ivory solid. mp 169-171 ^oC; IR (KBr) 3324, 3213, 2964, 2928, 2871, 1617, 1576, 1366, 1275, 1262, 1092, 1065, 997 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.19 (d, 6H, J = 6.9 Hz), 1.98 (s, 3H), 2.82-2.96 (m, 1H), 6.26 (s, 1H), 10.25 (bs, 1H, D_2O exchangeable), 11.98 (br s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.20, 23.01, 25.37, 92.65, 147.1, 149.1, 167.1. HRMS (EI) m/z: $[M]^+$ calcd. for $C_8H_{13}N_3O$ 167.1059; Found: 167.1057.

5-Acetamido-3-(4-chlorophenyl)-1*H*-pyrazole (entry 3): Yield: 548 mg (86%); Ivory solid. mp 257-260 ^oC; IR (KBr) 3228, 3185, 3166, 3100, 3066, 3035, 3014, 2971, 2940, 2860, 1663, 1613, 1591, 1569, 1559, 1498, 1491, 1396, 1367, 1173, 1090, 958 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H), 6.85 (s, 1H), 7.48 (d, 2H, J = 8.5Hz), 7.74 (d, 2H, J = 8.5 Hz), 10.47 (br s, 1H, D_2O exchangeable), 12.82 (br s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.54, 94.48, 127.1, 129.4, 132.8, 140.8, 148.7, 168.0. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{11}H_{10}ClN_3O$ 235.0512; Found: 235.0510.

5-Acetamido-1,3-diphenyl-1*H*-pyrazole (entry 4): Yield: 750 mg (82%); Light brown solid. mp 145-148 ^oC (lit.[4] 148-150 ^oC); IR (KBr) 3257, 3208, 3041, 1668, 1592, 1558, 1537, 1496, 1456, 1436, 1417, 1365, 1268, 1157, 1022, 950, 912, 802 cm^{-1}; ^1H NMR (300 MHz, DMSO-

d_6) δ 2.08 (s, 3H), 7.00 (s, 1H), 7.37 (t, 1H, J = 7.4 Hz), 7.43-7.50 (m, 3H), 7.56 (t, 2H, J = 7.8 Hz), 7.67 (d, 2H, J = 7.8 Hz), 7.95 (d, 2H, J = 7.5 Hz), 10.15 (br s, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.3, 100.2, 124.2, 125.6, 128.0, 128.5, 129.2, 129.7, 133.4, 137.9, 139.1, 150.6, 169.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{17}H_{15}N_3O$ 277.1215; Found: 277.1213.

The compound shown in Table 3 in the manuscript.

3-Methyl-5-phenyl-1*H*-pyrazole: Yield: 520 mg (58%); Ivory solid. mp 124-125 ^oC (lit.[5] 124-125 ^oC); IR (KBr) 3193, 3134, 3101, 3018, 2954, 1589, 1572, 1459, 1410, 1293, 1274, 1202, 1155, 1074, 1026, 1000, 963, 804, 764 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 6.43 (s, 1H), 7.36-7.93 (m, 3H), 7.73-7.76 (m, 2H), 12.54 (br s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.9, 101.3, 125.3, 127.5, 128.9, 139.9, 150.8, 157.4. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{10}H_{10}N_2$ 158.0844; Found: 158.0852.

The compounds shown in Table 4 (entry 1) in the manuscript.

5-(Cyclohex-1-en-1-yl)-3-methyl-1*H*-pyrazole (entry 1): Yield: 281 mg (31%, Method A), 653 mg (72%, Method B); Yellow liquid; IR (KBr) 3185, 3130, 3096, 3024, 2978, 2927, 2858, 1575, 1475, 1433, 1280, 1013, 915, 843 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59-1.74 (m, 4H), 2.12-2.35 (m, 7H), 5.99 (s, 1H), 6.18(s, 1H), 10.28 (br s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.20, 22.19, 22.56, 25.39, 26.09, 100.53, 124.4, 128.6, 144.3, 149.6. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{10}H_{14}N_2$ 162.1157; Found: 162.1161.

3-Isopropyl-5-phenyl-1*H*-pyrazole (entry 2): Yield: 411 mg (51%, Method A), 476 mg

(59%, Method B); Colorless solid. mp 107-109 °C (lit.[6] 109.5 °C); IR (KBr) 3169, 3122, 3068, 2995, 2964, 2870, 1604, 1569, 1463, 1341, 1206, 1075, 1007, 964, 911, 880, 841, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 6H, *J* = 6.9 Hz), 2.79-2.93 (m, 1H), 6.28 (s, 1H), 7.16-7.28 (m, 3H), 7.68 (d, 2H, *J* = 6.9 Hz), 12.44 (bs, 1H, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.65, 26.49, 99.03, 125.8, 127.6, 128.6, 132.8, 149.4, 154.1. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{12}H_{14}N_2$ 186.1157; Found: 186.1157.

5-(4-Hexylphenyl)-3-isopropyl-1*H*-pyrazole (entry 3): Yield: 310 mg (27%, Method A), 505 mg (44%, Method B); mp 58-60 °C; IR (KBr) 3187, 3134, 3089, 3011, 2957, 2923, 2857, 1572, 1509, 1455, 1331, 1267, 1002, 961, 830, 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 6.6 Hz), 1.50-1.58 (m, 12H), 1.82-1.89 (m, 2H), 2.86 (t, 2H, *J* = 7.6 Hz), 3.14-3.28 (m, 1H), 6.57 (s, 1H), 7.40 (d, 2H, *J* = 7.8 Hz), 7.88 (d, 2H, *J* = 7.8Hz), 10.21 (br s, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.22, 22.67, 22.75, 26.55, 29.10, 31.51, 31.87, 35.83, 98.75, 125.7,128.6, 130.1,142.3, 149.2, 154.3. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{18}H_{26}N_2$ 270.2096; Found: 270.2093.

3-Phenethyl-5-phenyl-1*H*-pyrazole (entry 4): Yield: 263 mg (38%, Method A), 388 mg (56%, Method B); Light yellow solid. mp 74-76 °C (lit.[7] 75-76 °C); IR (KBr) 3188, 3131, 3084, 3063, 3026, 2953, 2926, 2860, 1650, 1603, 1572, 1559, 1540, 1519, 1494, 1455, 1275, 1261, 1154, 1073, 1027, 963, 804 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.87-2.99 (m, 4H), 6.49 (s, 1H), 7.17-7.31 (m, 6H), 7.38 (t, 2H, *J* = 7.6 Hz), 7.74 (d, 2H, *J* = 7.7 Hz), 12.68 (bs, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.36, 35.49, 101.3, 125.7, 126.1, 127.9, 128.4(0), 128.4(7), 128.7, 132.4, 141.0, 147.5, 149.4. HRMS (EI) m/z: $[M]^+$ calcd. for

$C_{17}H_{16}N_2$ 248.1313; Found: 248.1313.

3-Cyclohexyl-5-phenyl-1*H*-pyrazole (entry 5): Yield: 200 mg (28%, Method A), 357 mg (50%, Method B); White solid. mp 138-140 ^oC (lit.[8] 141-143 ^oC); IR (KBr) 3127, 3082, 3057, 3028, 2935, 2918, 2849, 1532, 1487, 1327, 1082, 889, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11-1.42 (m, 5H), 1.65 (m, 3H), 1.88-1.92 (m, 2H), 2.47-2.55 (m, 1H), 7.22-7.31 (m, 3H), 7.72 (d, 2H, *J* = 6.9 Hz), 11.91 (bs, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.97, 26.12, 32.96, 35.76, 99.05, 125.7, 127.5, 128.6, 133.1, 149.8, 152.8. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{15}H_{18}N_2$ 226.1470; Found: 226.1472.

3-Heptyl-5-phenyl-1*H*-pyrazole (entry 6): Yield: 197 mg (28%, Method A), 331 mg (47%, Method B); Ivory solid. mp 90-92 ^oC; IR (KBr) 3168, 3136, 3111, 2955, 2926, 2853, 1567, 1462, 1434, 1421, 1373, 1306, 1288, 1267, 1255, 1237, 1214, 1072, 1017, 959, 797 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-0.89 (m, 3H), 1.25-1.30 (m, 8H), 1.58-1.72 (m, 2H), 2.58 (t, 2H, *J* = 7.8 Hz), 6.34 (s, 1H), 7.23-7.38 (m, 3H), 7.69-7.72 (m, 2H), 11.54 (bs, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.12, 22.67, 26.33, 29.06, 29.23, 31.73, 31.78, 101.0, 125.7, 127.8, 128.7, 132.4, 147.7, 149.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{16}H_{22}N_2$ 242.1783; Found: 242.1784.

3-(2-(5-Phenyl-1*H*-pyrazol-3-yl)ethyl)pyridine (entry 7): Yield: 80 mg (11%, Method A), 58 mg (8%, Method B); Clear liquid; IR (KBr) 3188, 3131, 3092, 3084, 3026, 2786, 2655, 1484, 1431, 1416, 1331, 1268, 1222, 1197, 1095, 1050, 1001, 995, 963, 928, 822, 767, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 2H), 2.98 (s, 2H), 6.36 (s, 1H), 7.78 (q, 1H, *J* =

4.2 Hz), 7.28-7.46 (m, 4H), 7.68-7.71 (m, 2H), 8.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.34, 32.75, 101.32, 123.4, 123.7, 125.4, 125.6, 128.0, 128.8, 136.0, 147.3, 149.7. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{16}H_{15}N_3$ 249.1266; Found: 249.1267.

3-Methyl-1,5-diphenyl-1*H*-pyrazole (entry 8): Yield: 410 mg (20%, Method A), 610 mg (46%, Method B); Yellow liquid; IR (KBr) 3054, 2977, 2952, 2915, 1590, 1546, 1494, 1450, 1407, 1359, 1255, 1132, 1068, 1010, 948, 906, 790 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 6.47 (s, 1H), 7.27-7.48 (m, 8H), 7.85 (d, 2H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.66, 104.5, 125.0, 125.7, 127.6, 127.8, 128.6, 129.1, 133.4, 139.9, 140.2, 151.5. HRMS (EI) m/z: $[M]^+$ calcd. for $C_{16}H_{14}N_2$ 234.1157; Found: 234.1153

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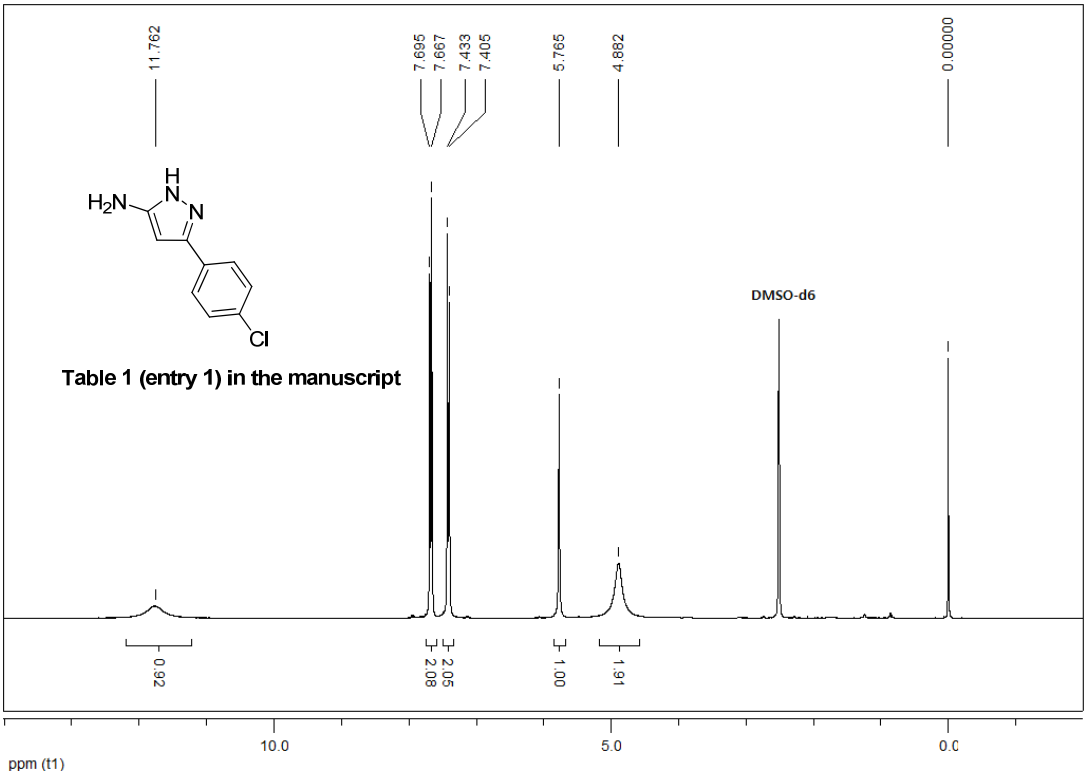
6. ^{1}H and ^{13}C NMR Spectra of Pyrazoles

Figure S2. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 1 (entry 1) in text



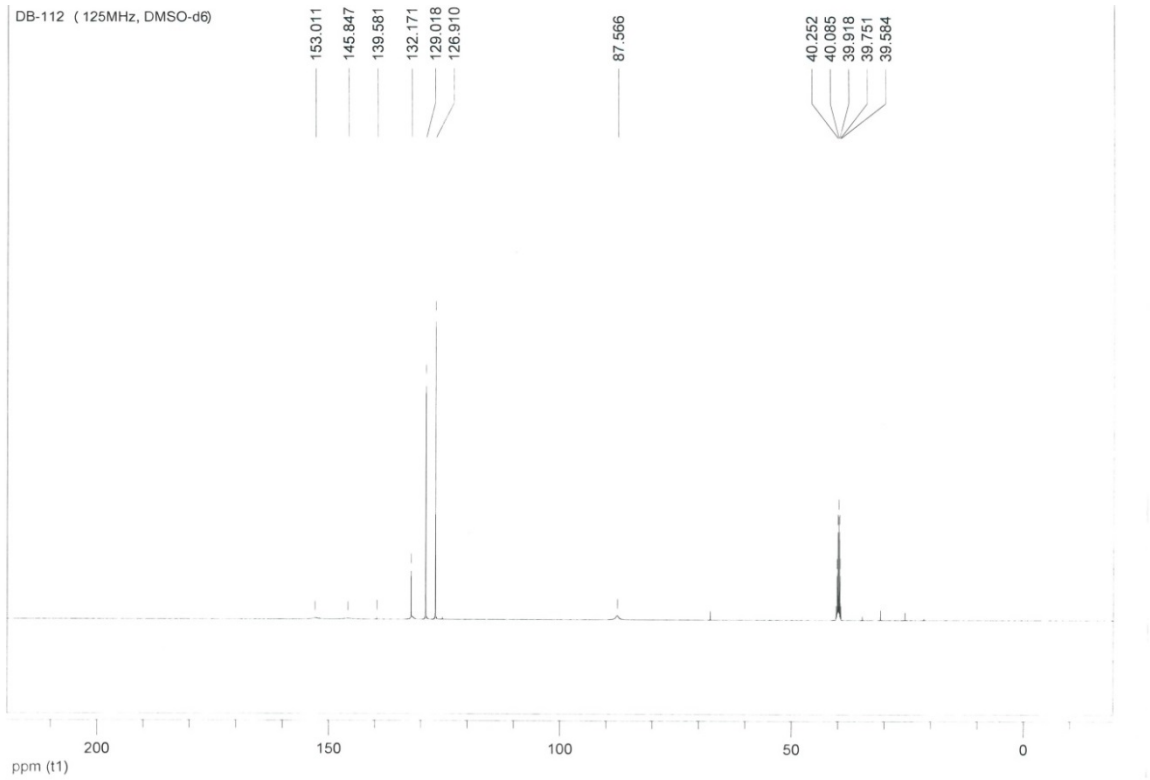


Figure S3. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 1 (entry 2) in text

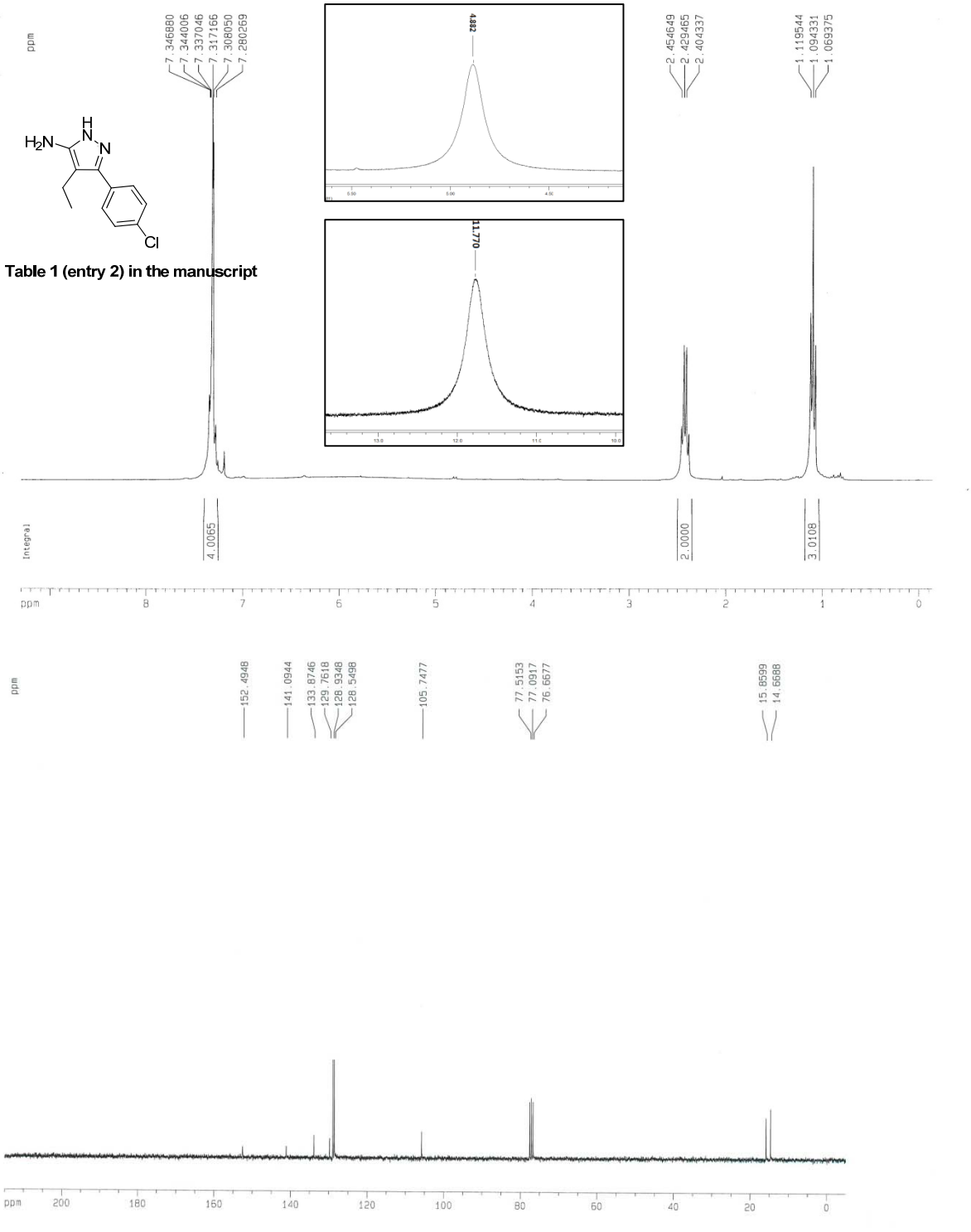
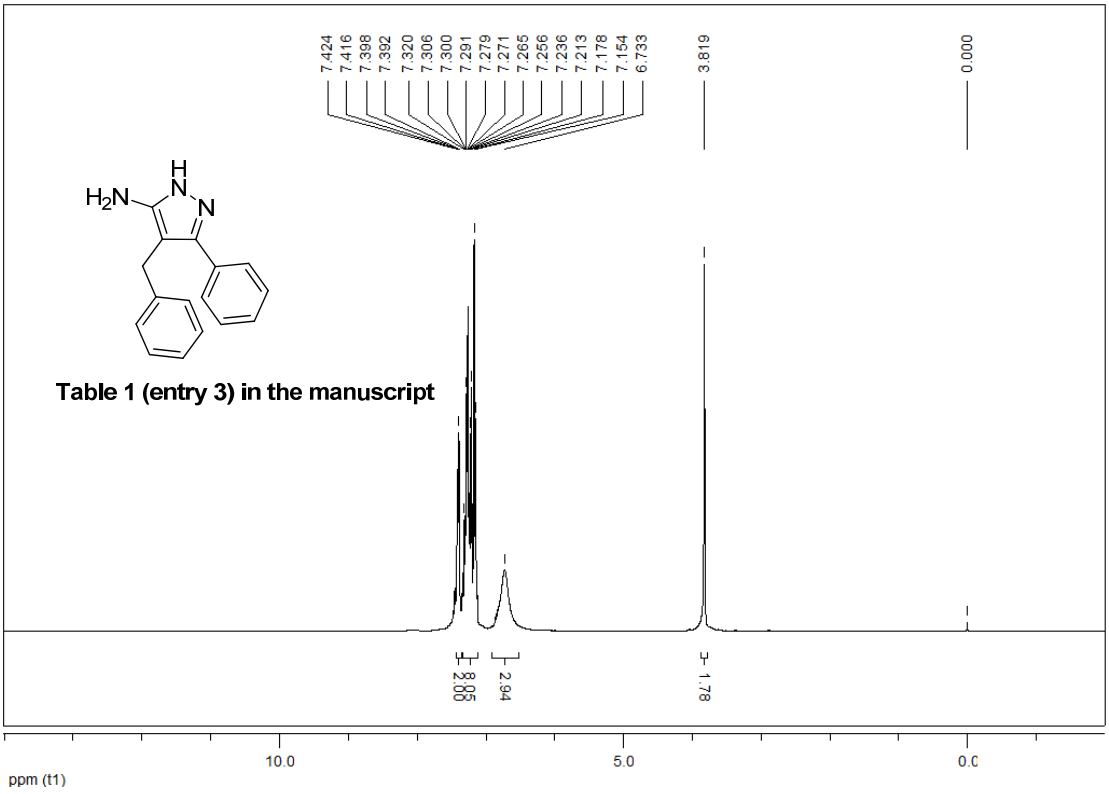


Figure S4. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 1 (entry 3) in text



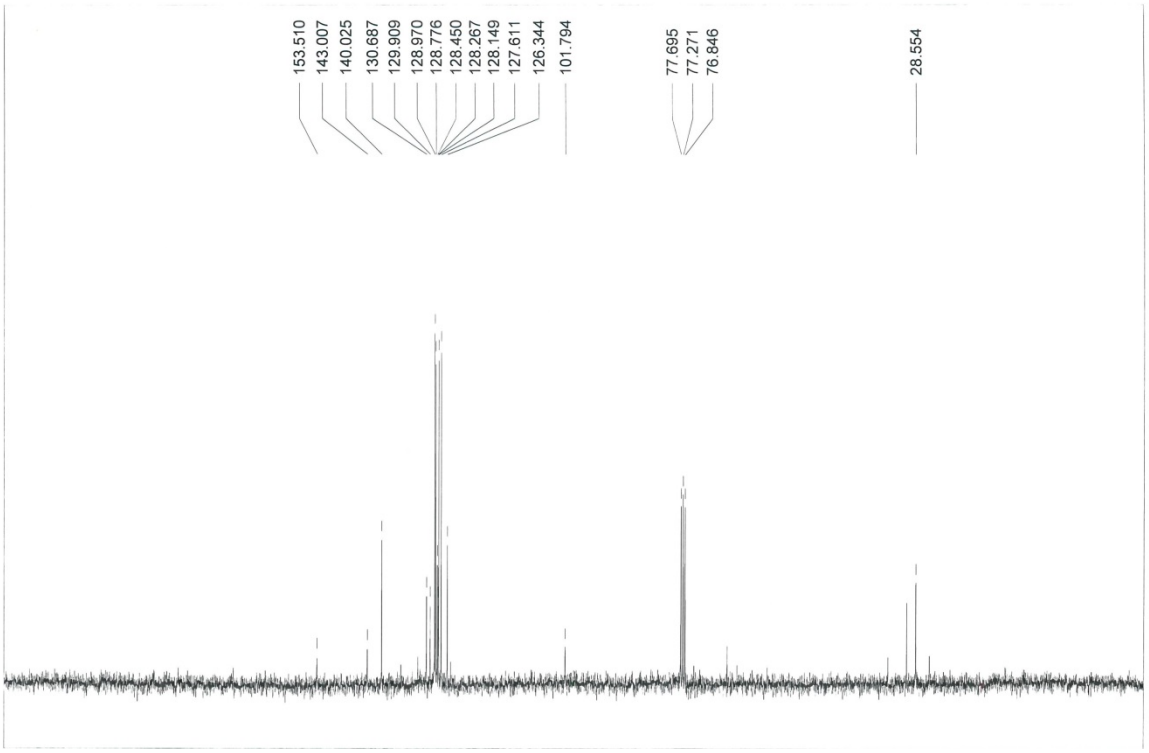


Figure S5. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 1 (entry 4) in text

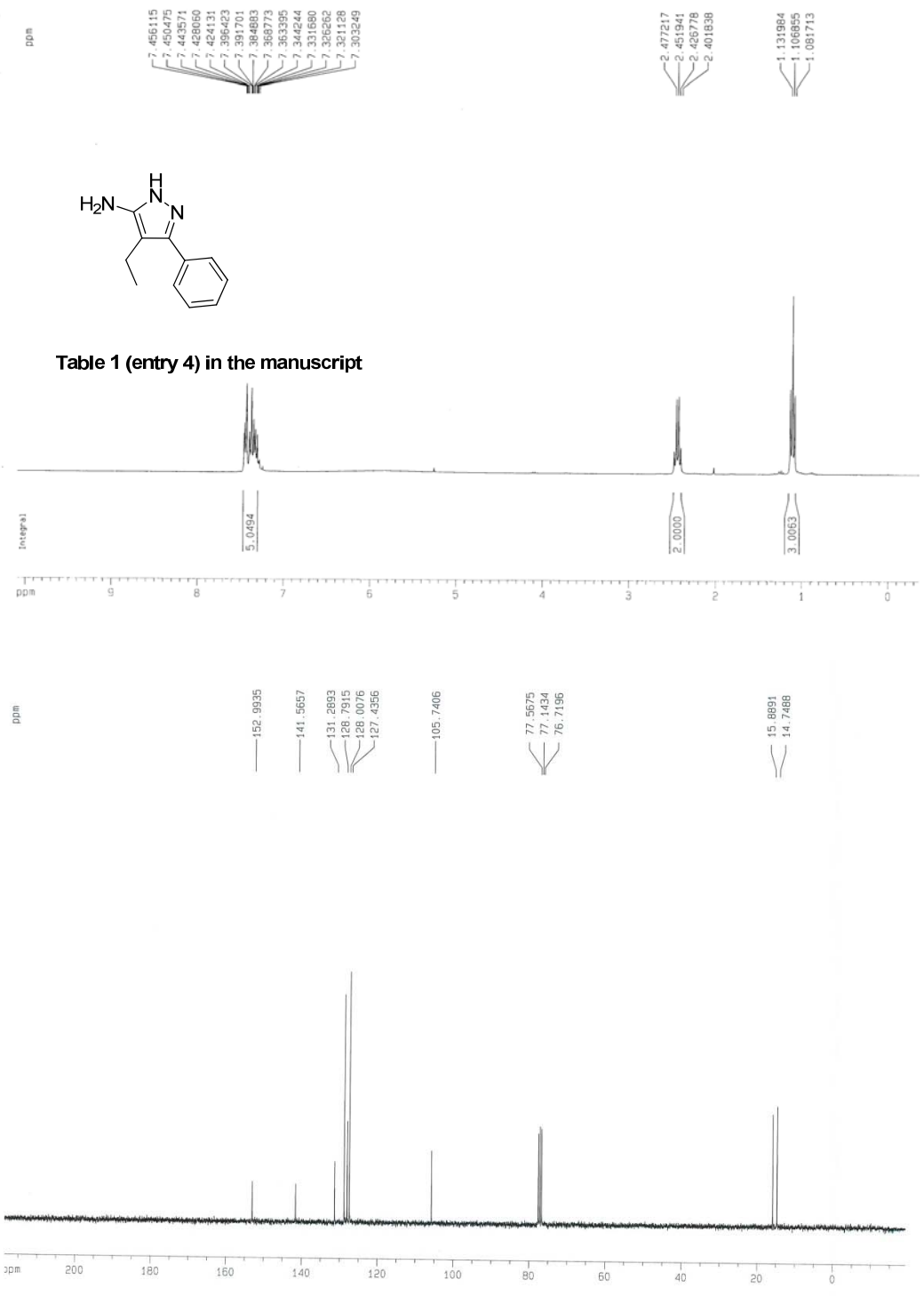
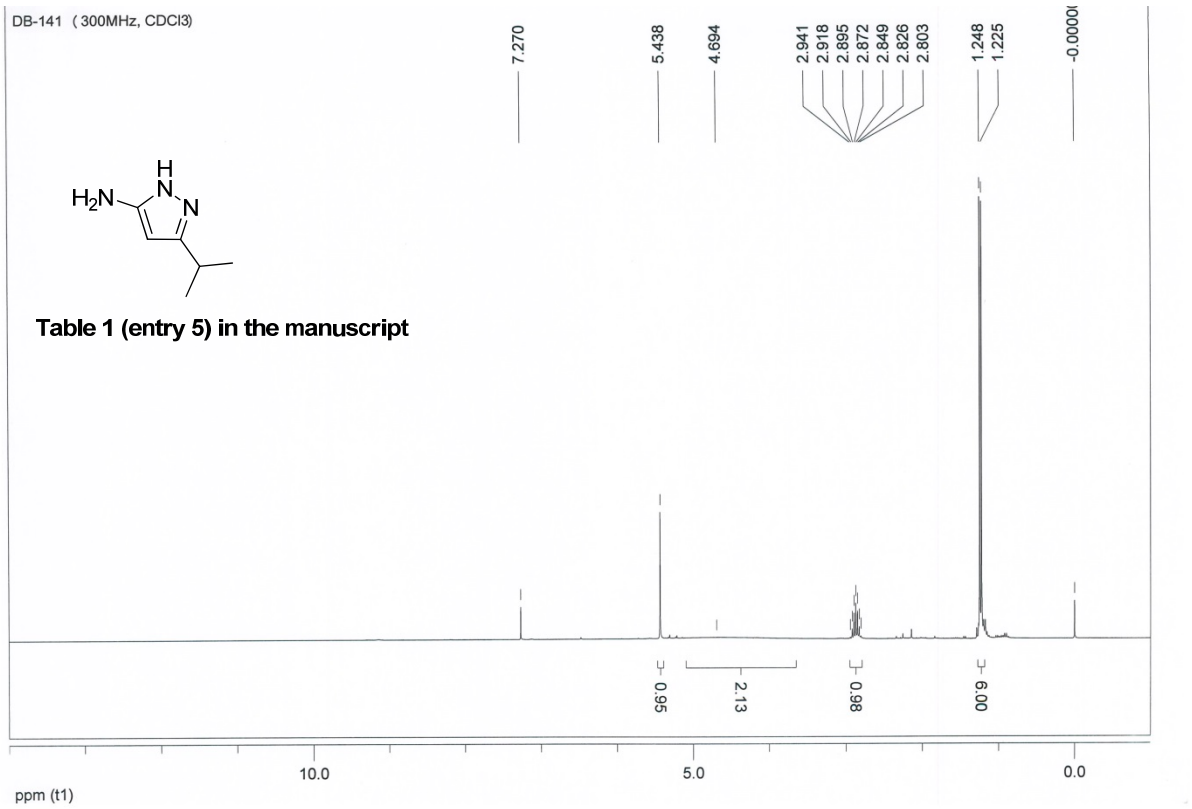


Figure S6. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 1 (entry 5) in text



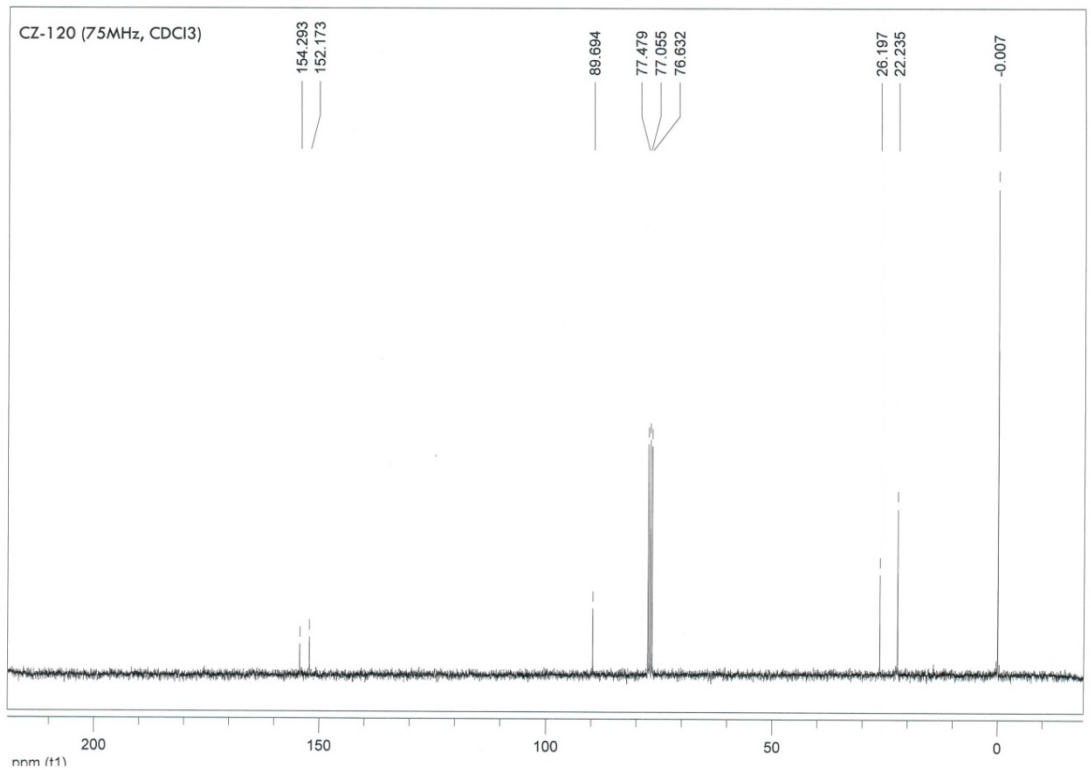


Figure S7. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 1 (entry 6) in text

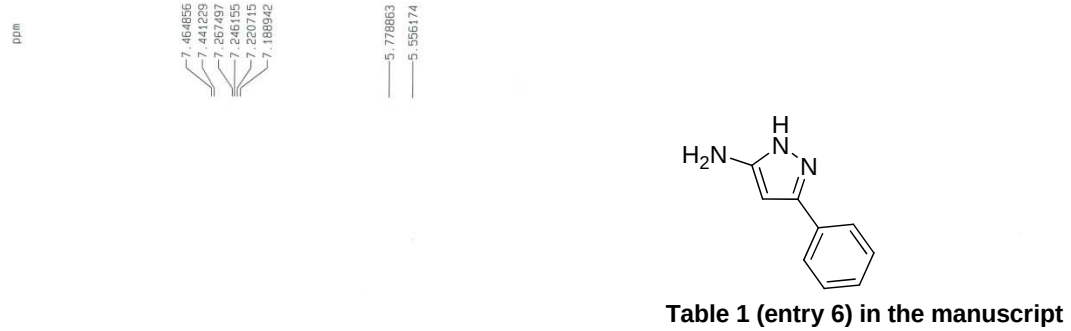
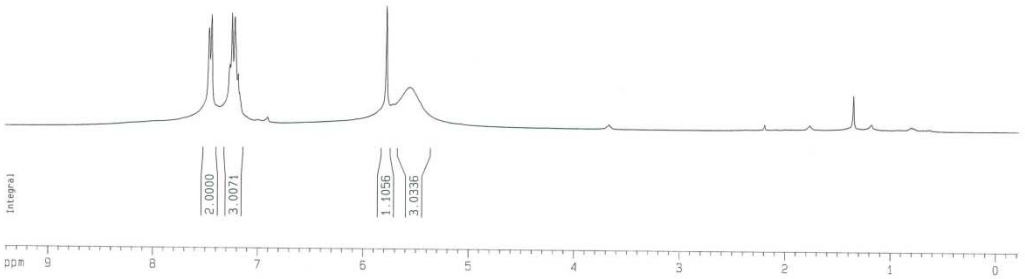


Table 1 (entry 6) in the manuscript



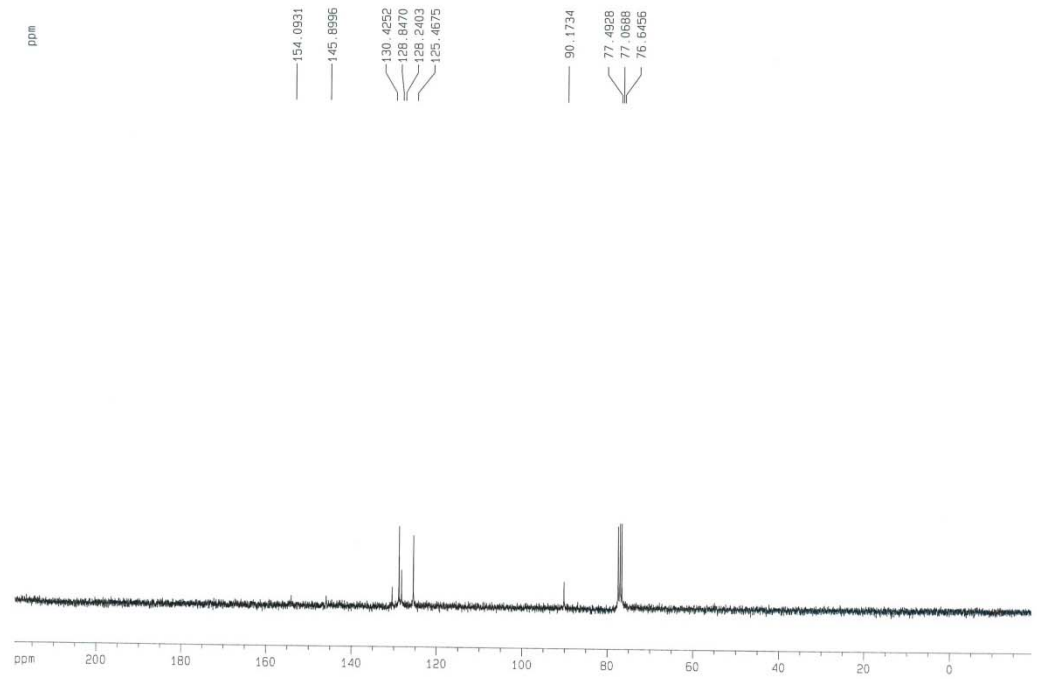


Figure S8. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 1 (entry 7) in text

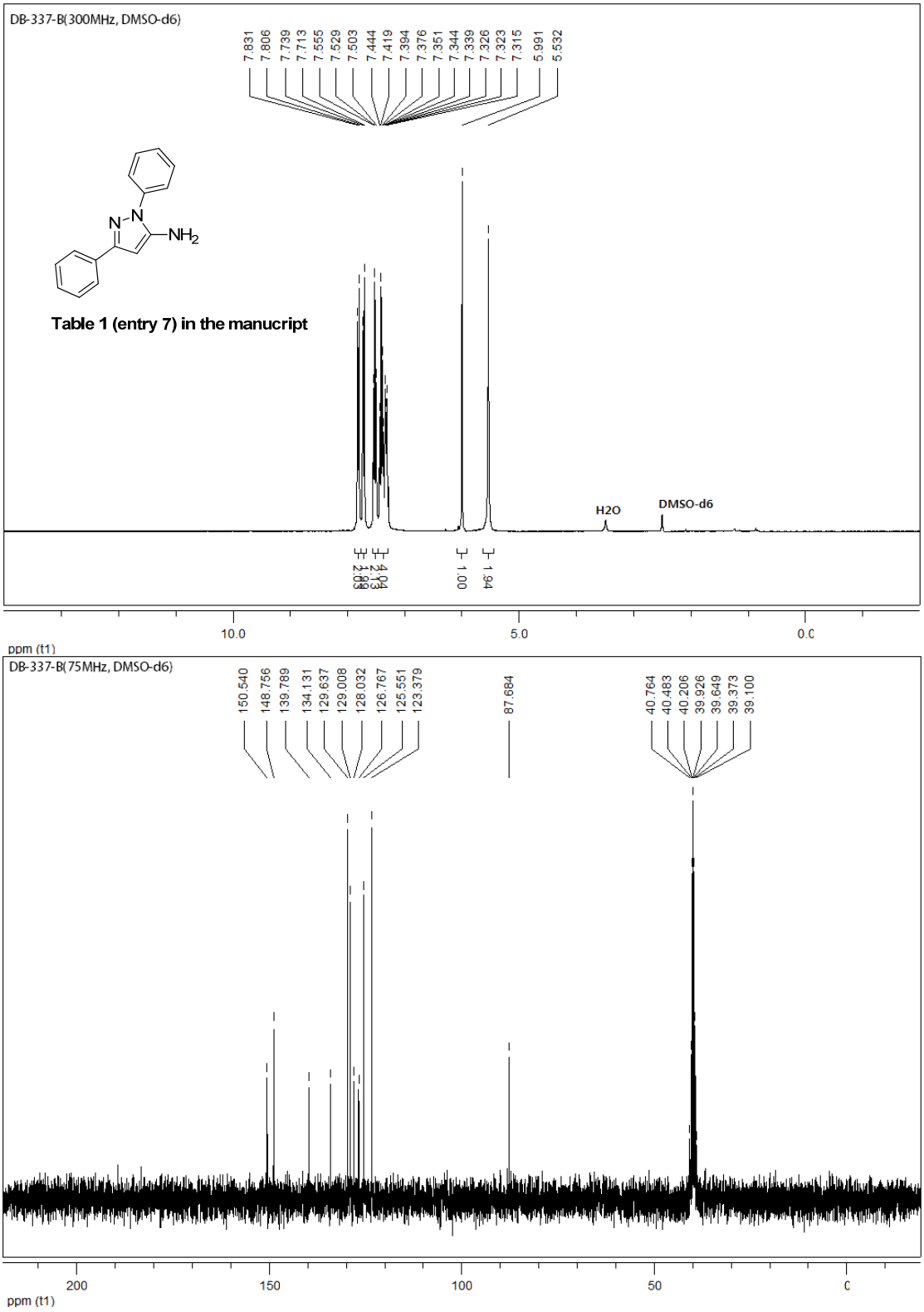
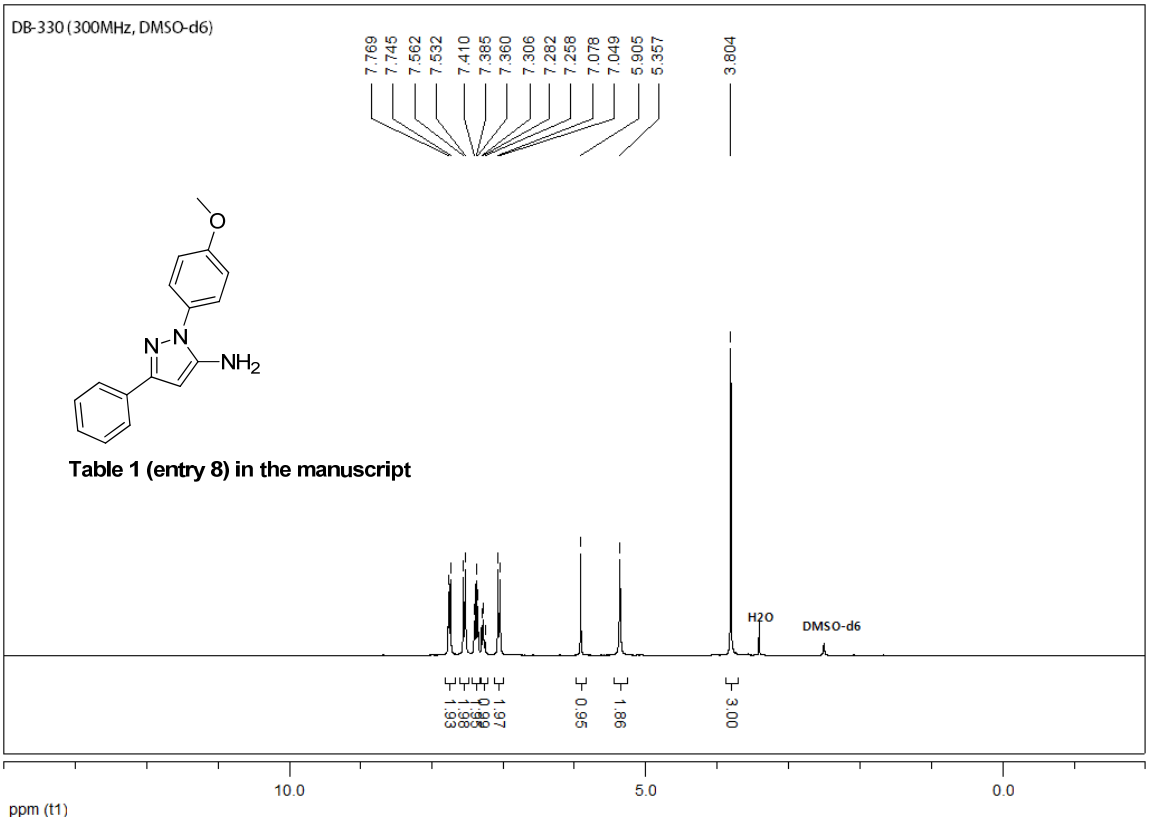


Figure S9. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 1 (entry 8) in text



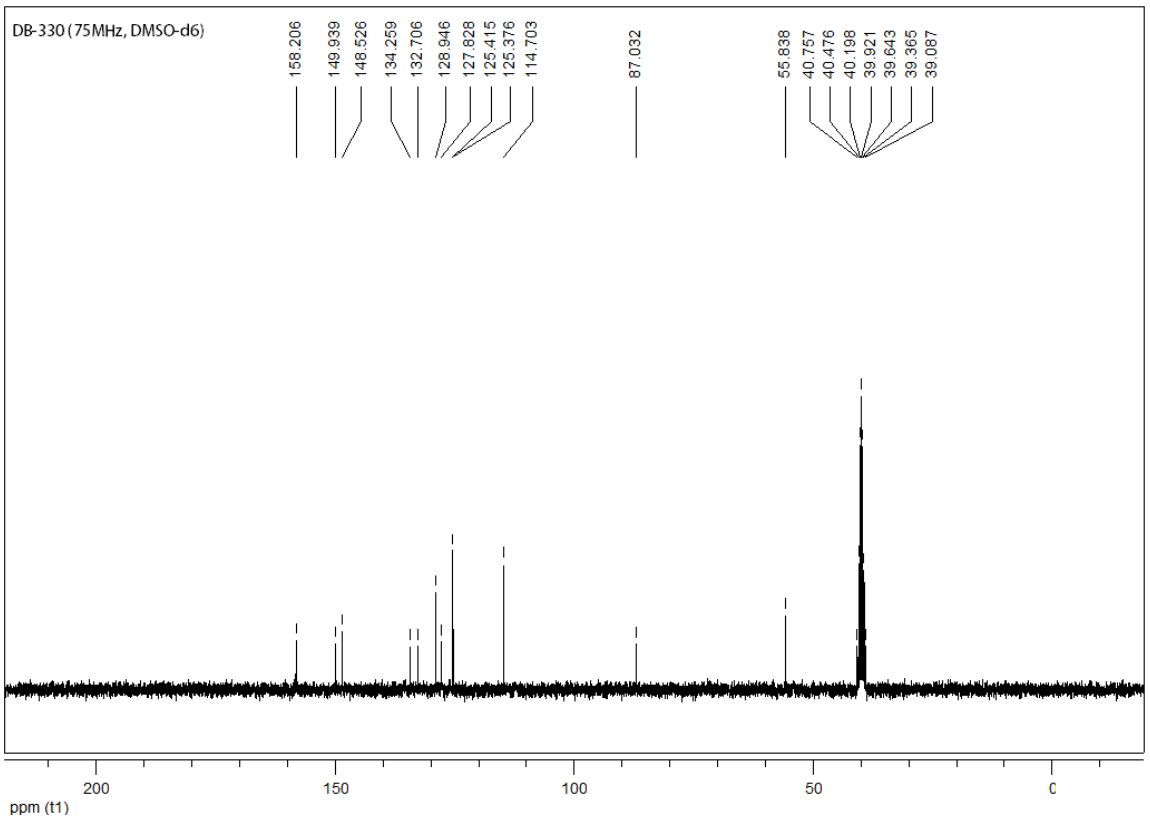
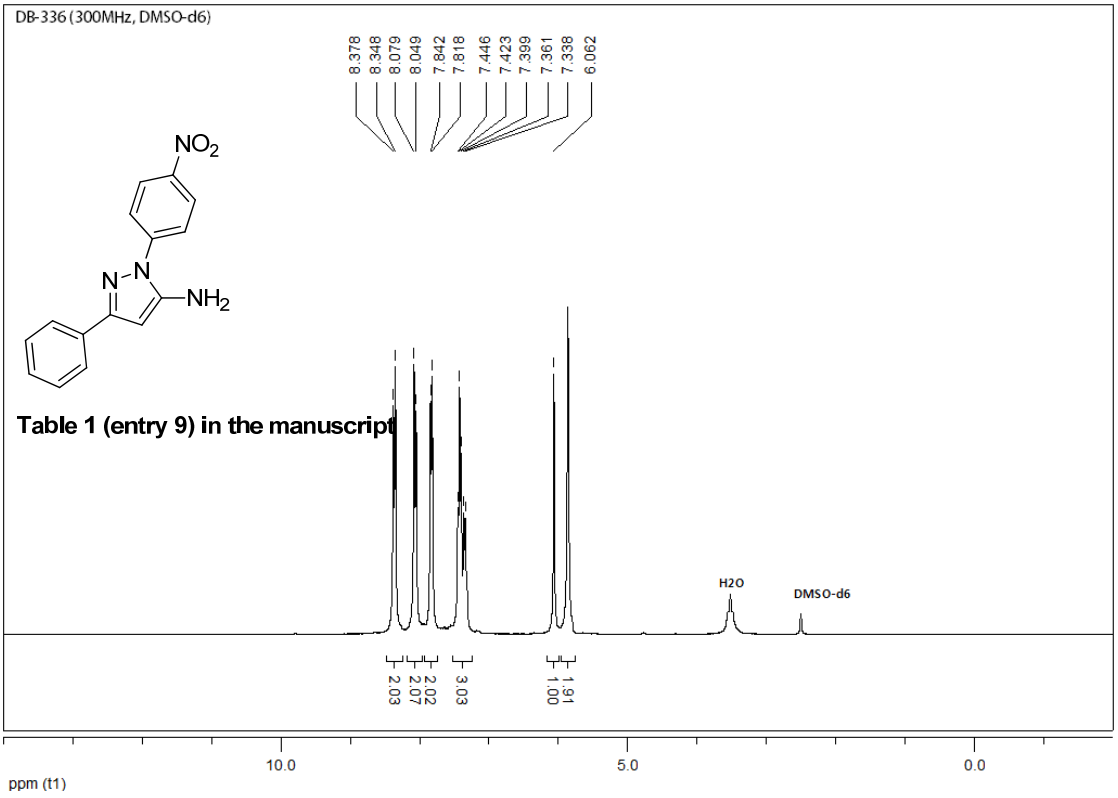


Figure S10. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 1 (entry 9) in text



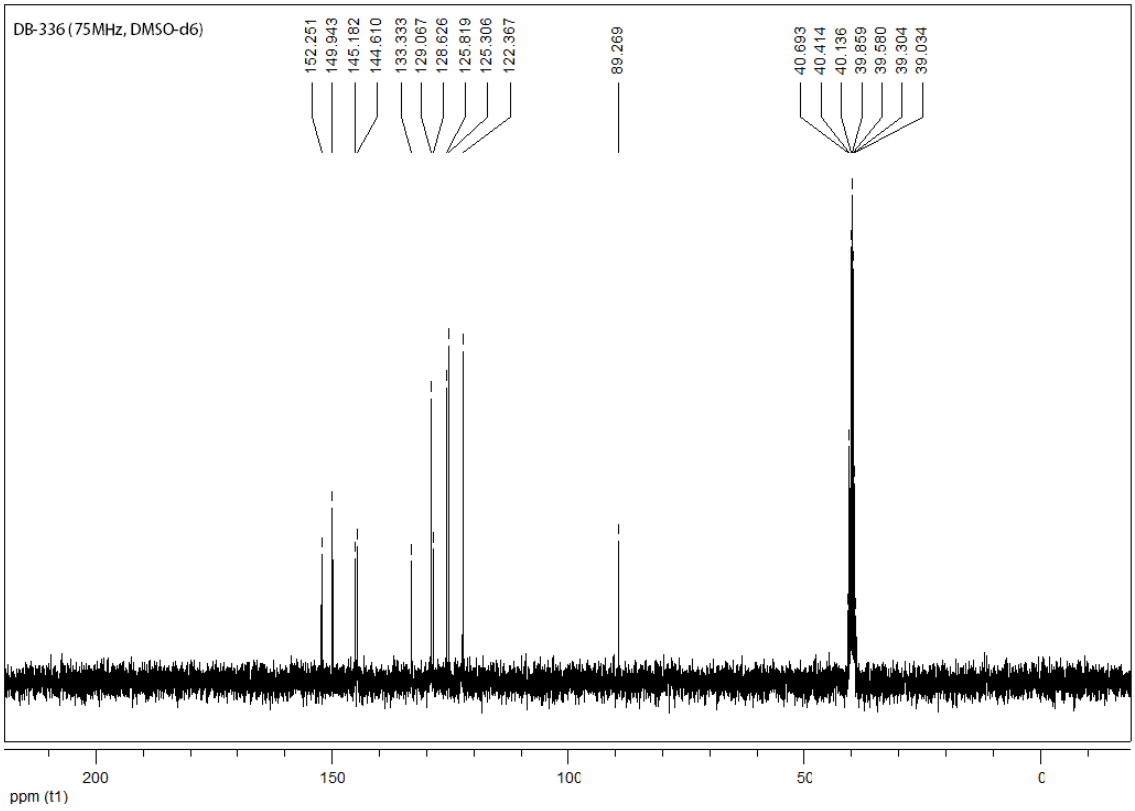
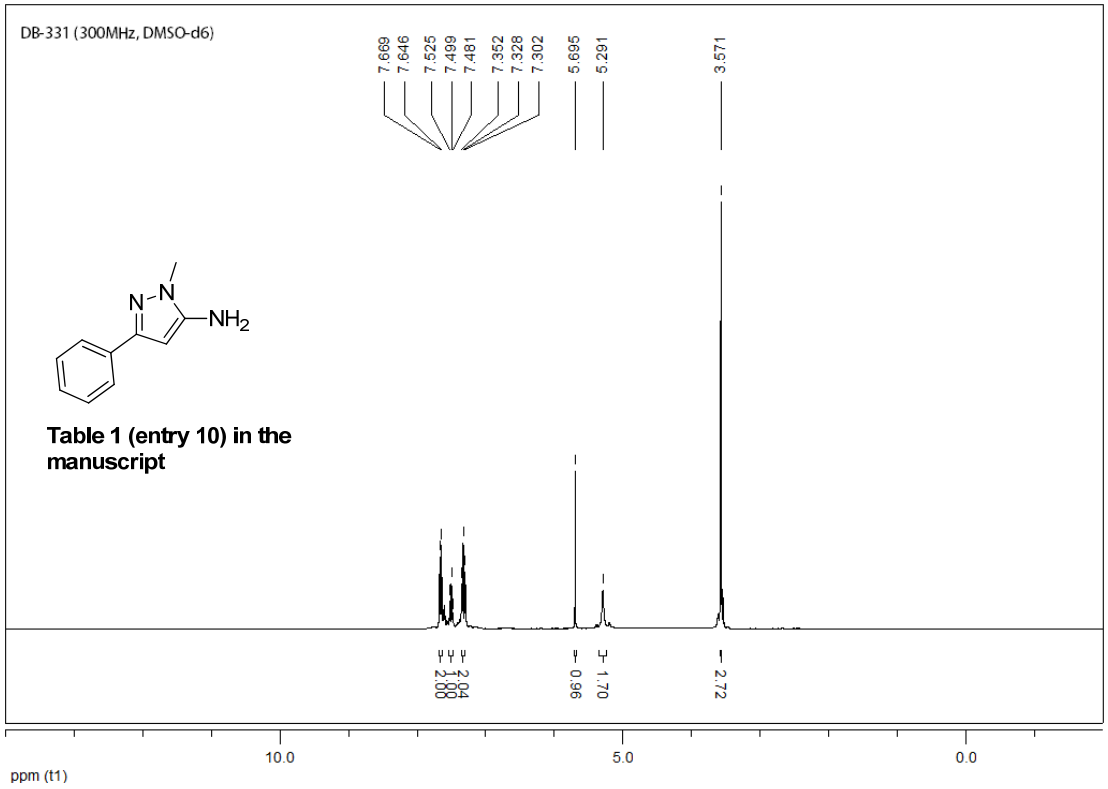


Figure S11. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 1 (entry 10) in text



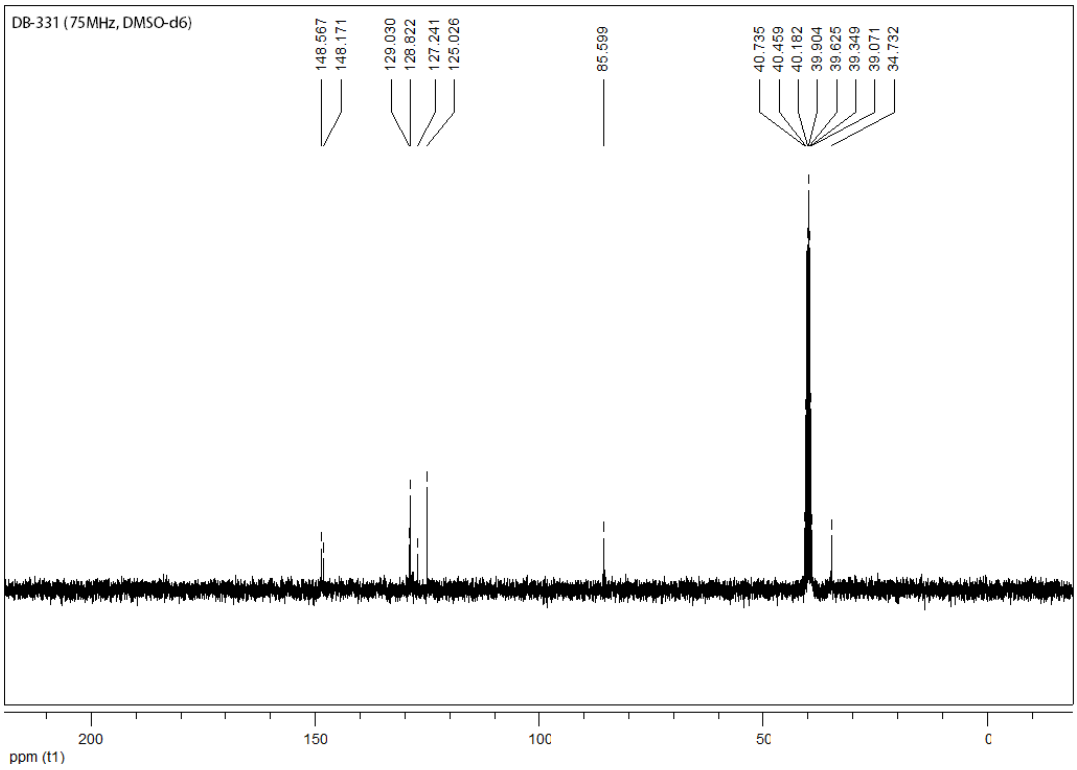
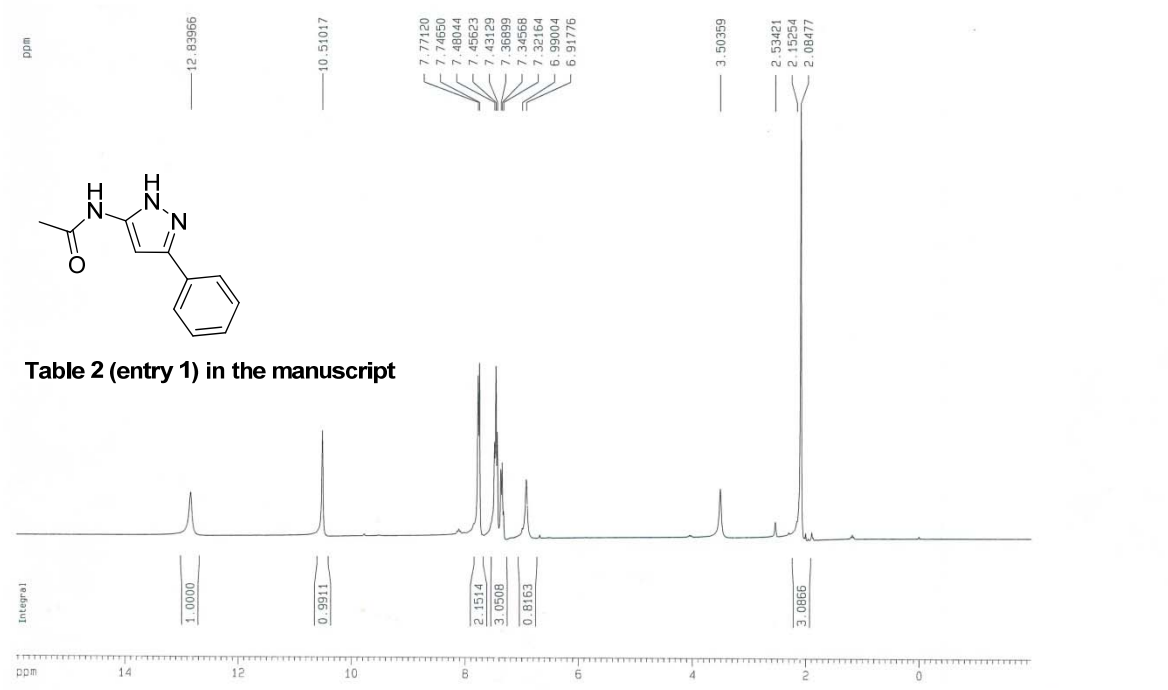


Figure S12. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 2 (entry 1) in text



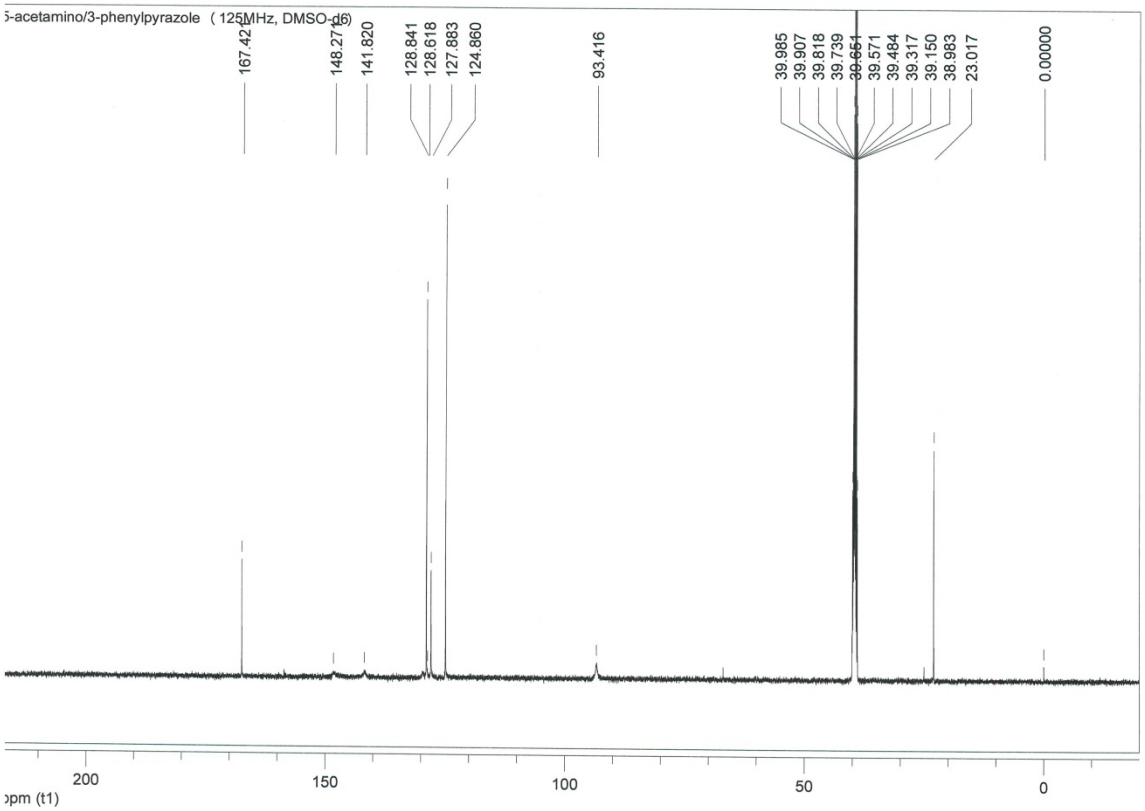
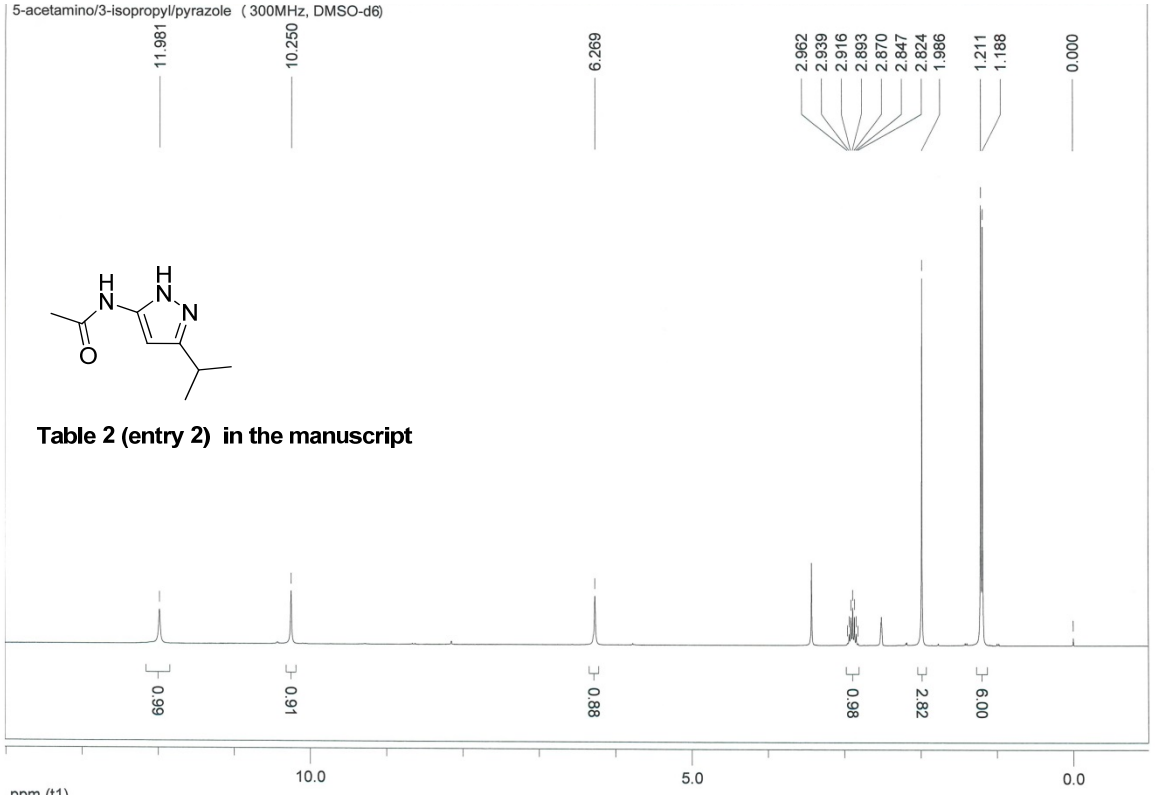


Figure S13. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 2 (entry 2) in text



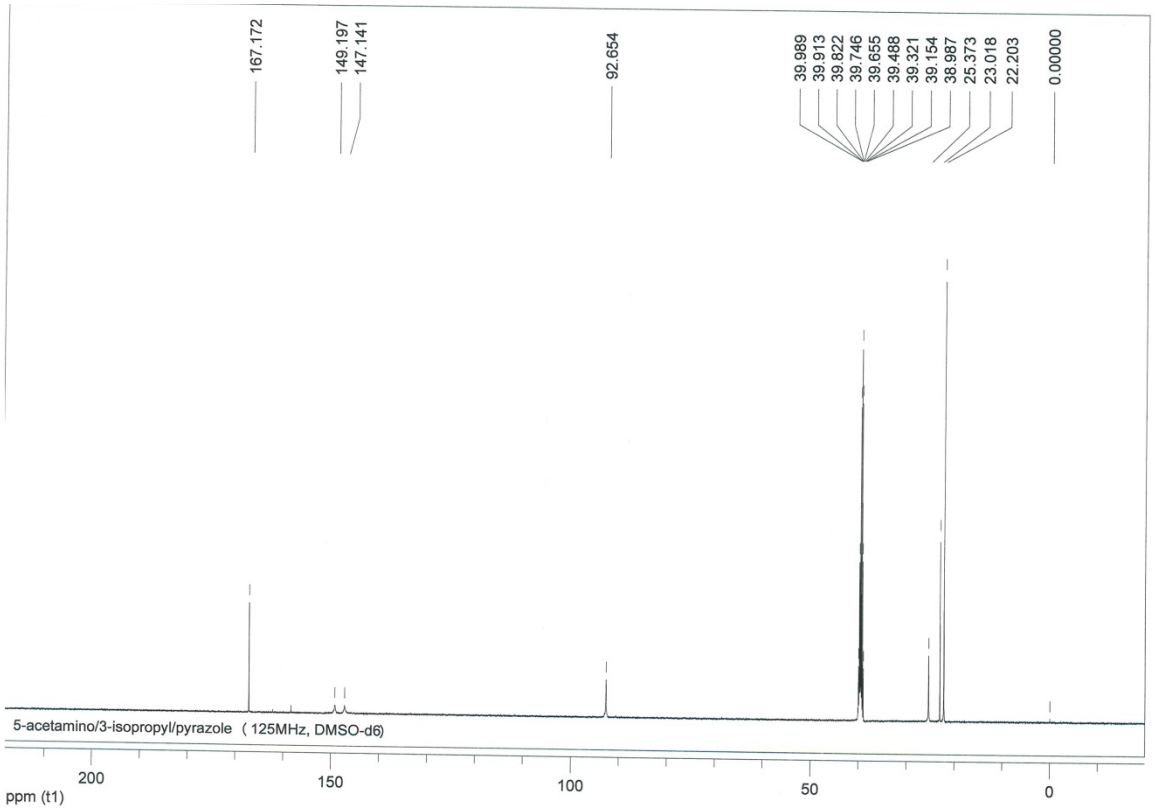


Figure S14. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 2 (entry 3) in text

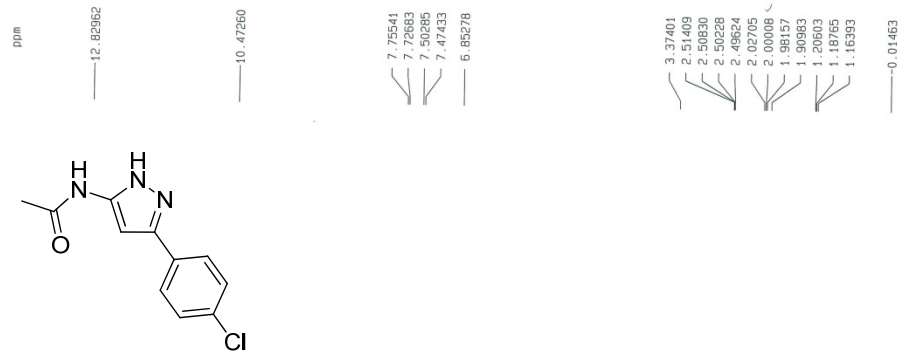
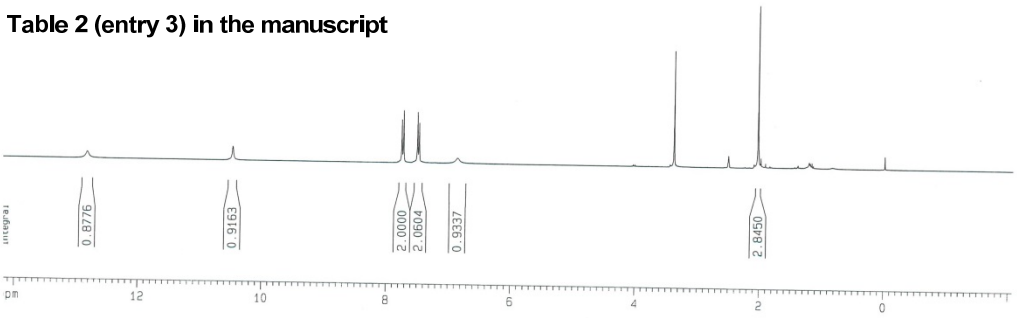


Table 2 (entry 3) in the manuscript



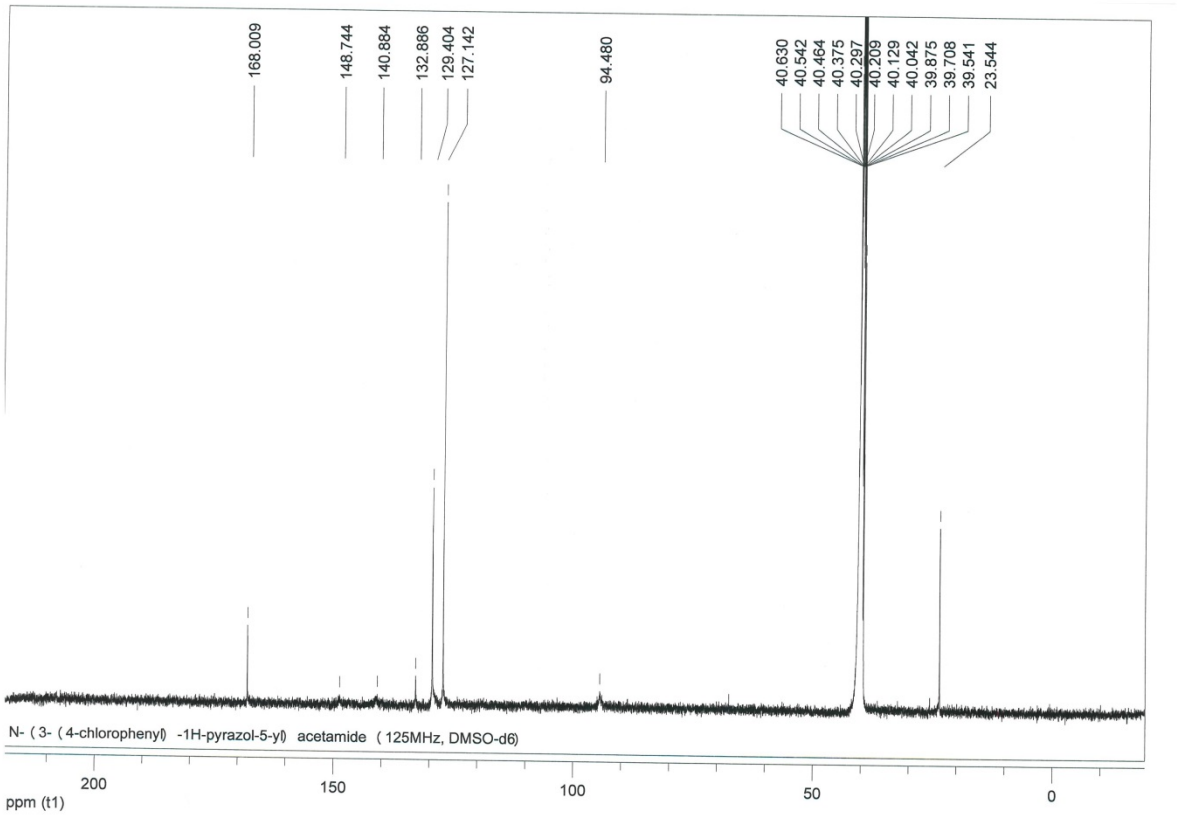
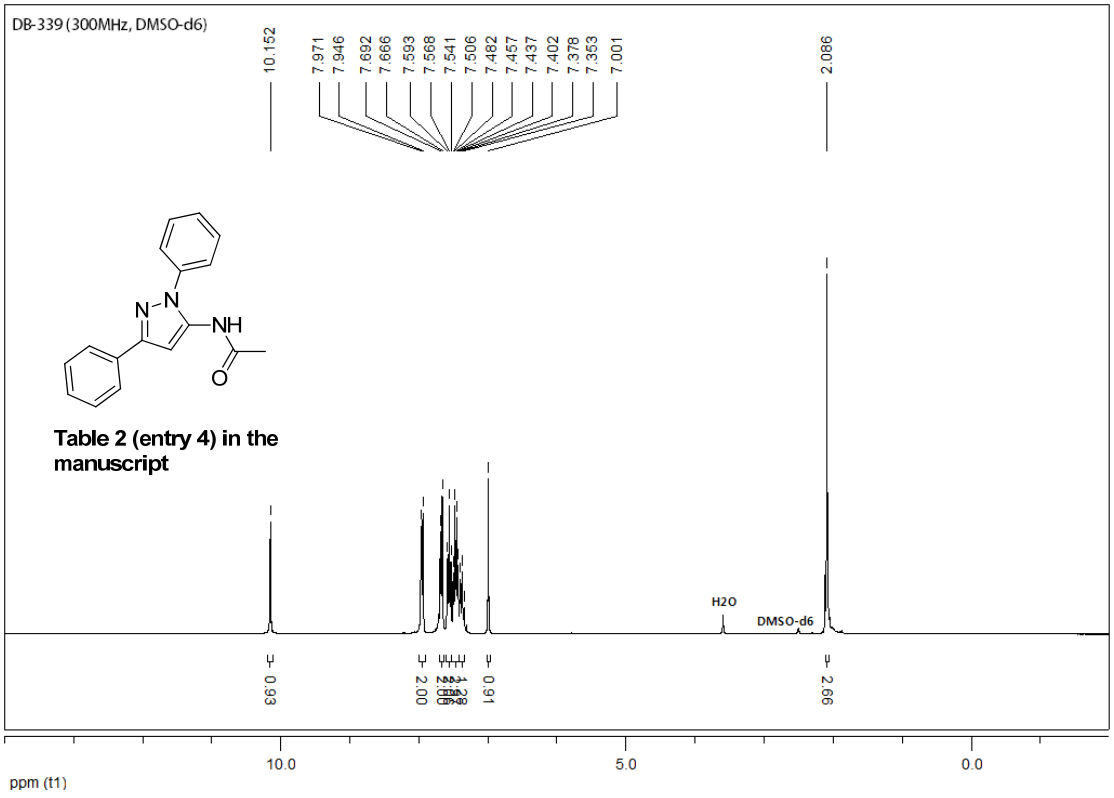


Figure S15. ^{1}H (top) and ^{13}C NMR (bottom) spectra in DMSO-d_6 of Table 2 (entry 4) in text



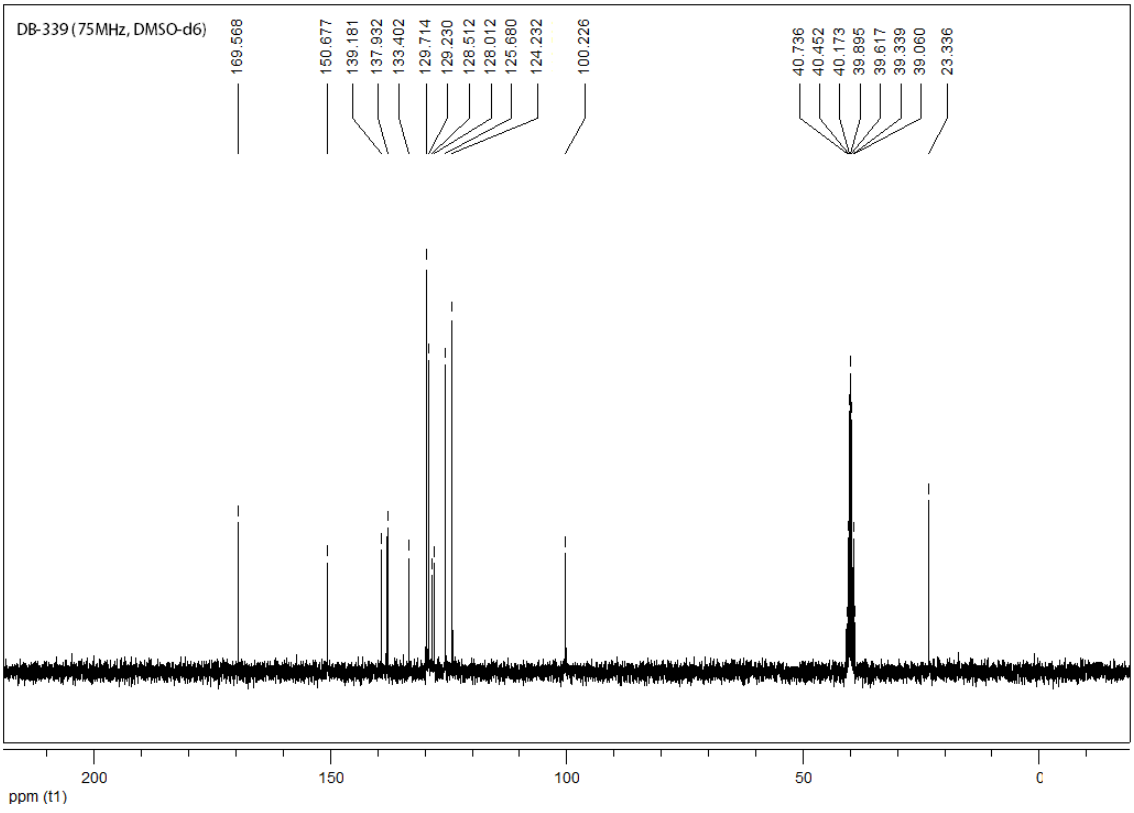
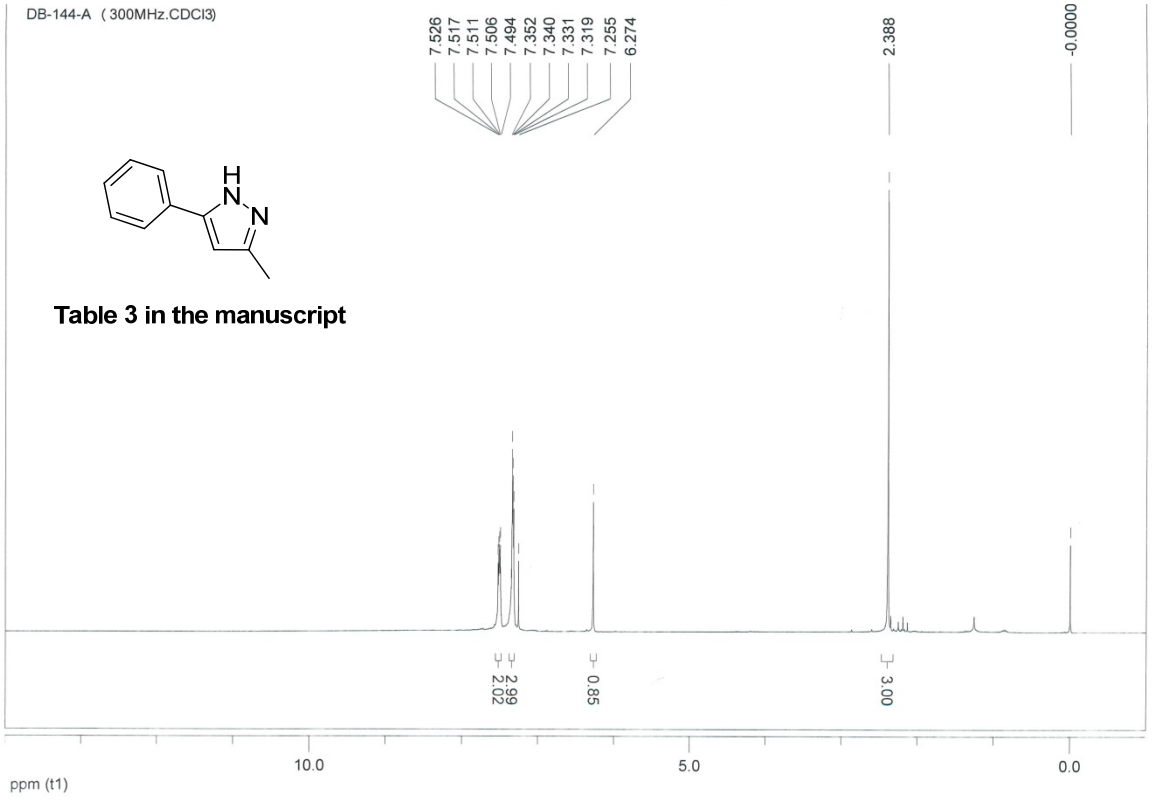


Figure S16. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 3 in text



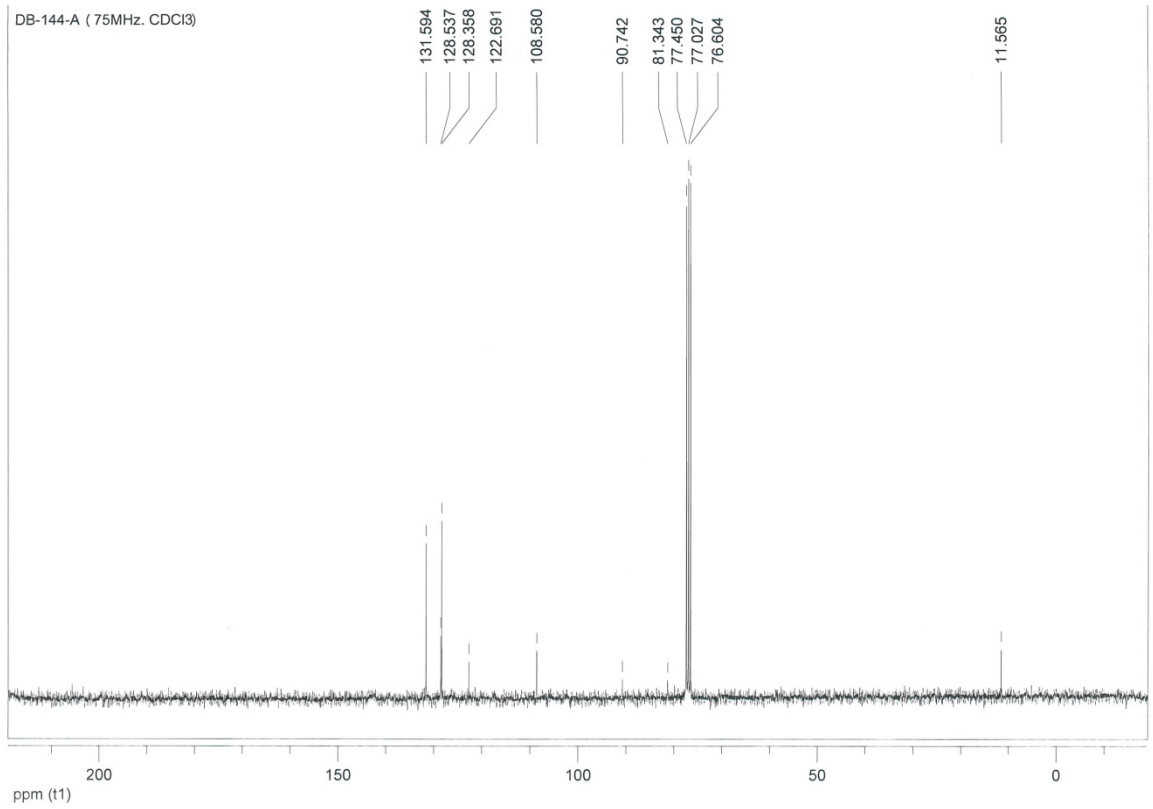


Figure S17. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 1) in text

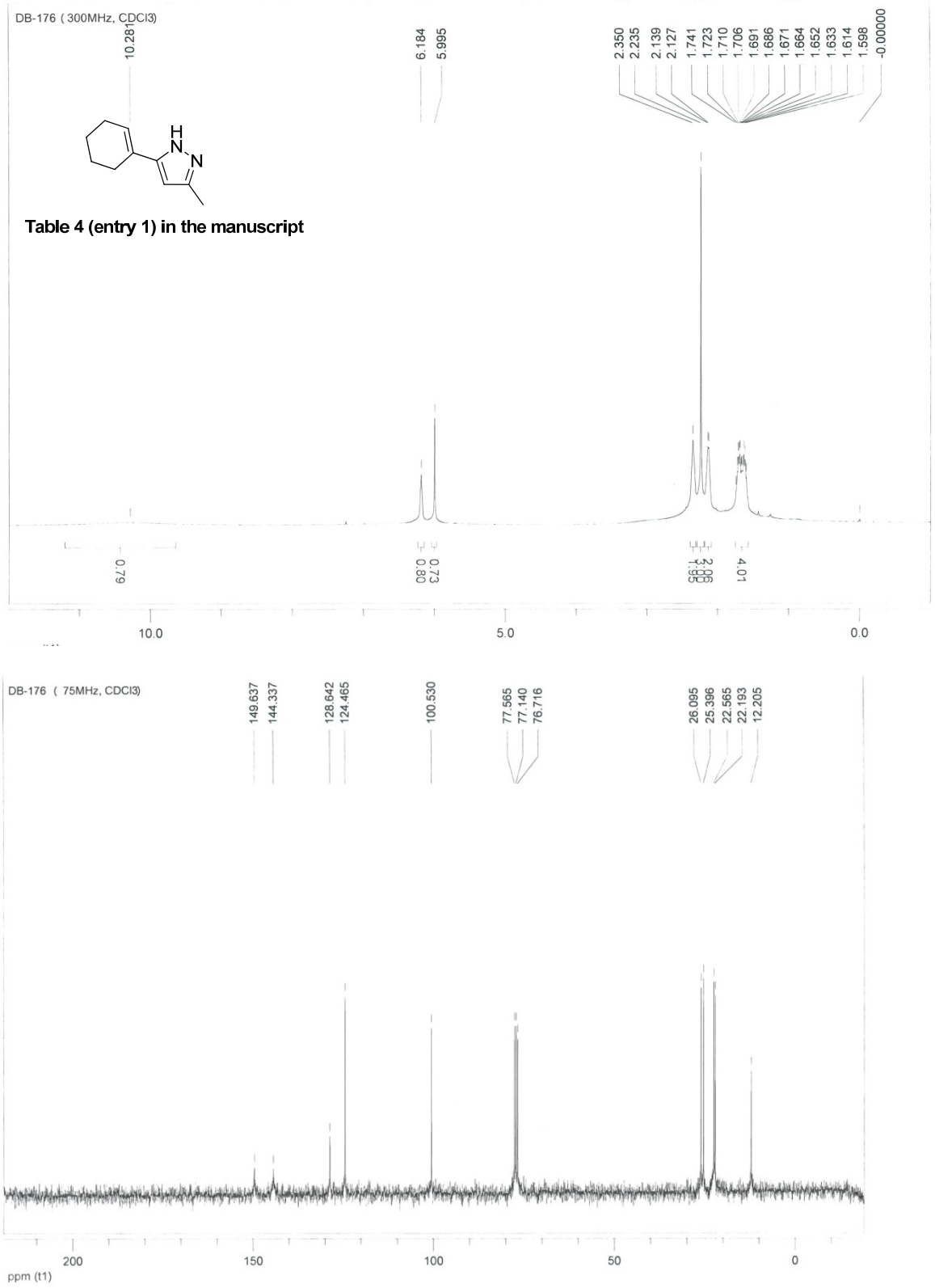
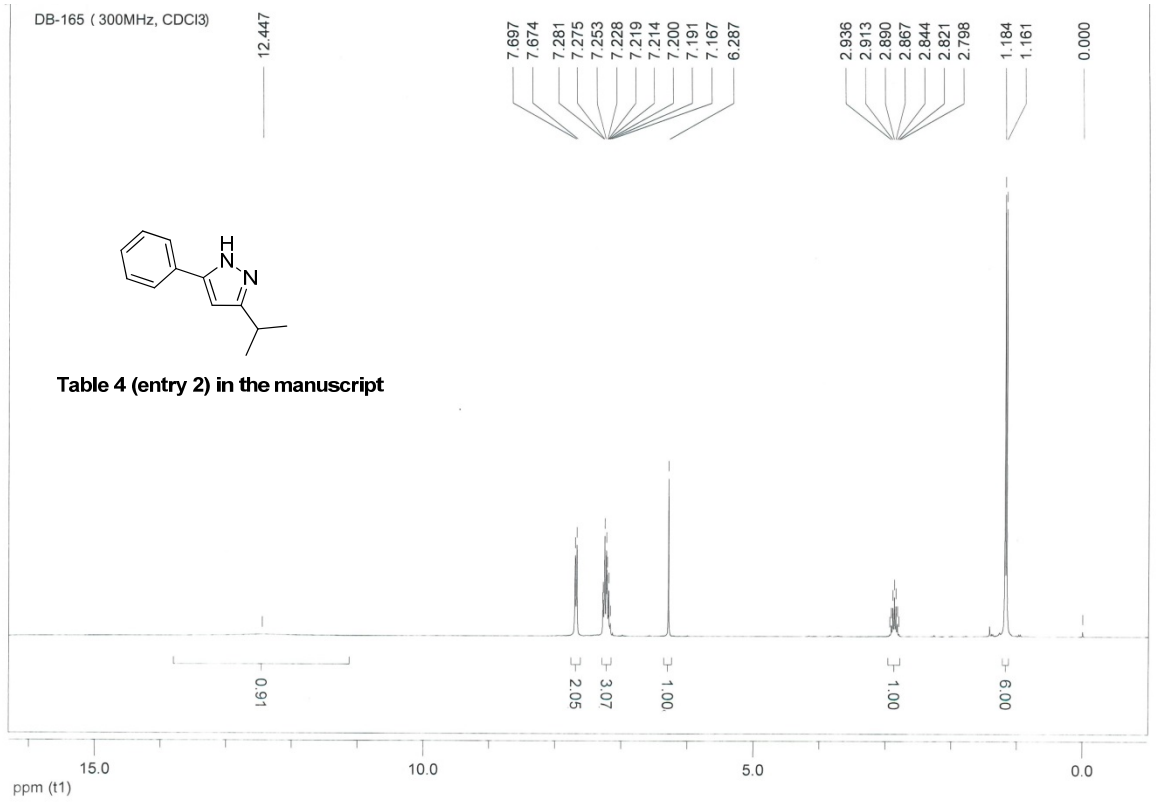


Figure S18. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 2) in text



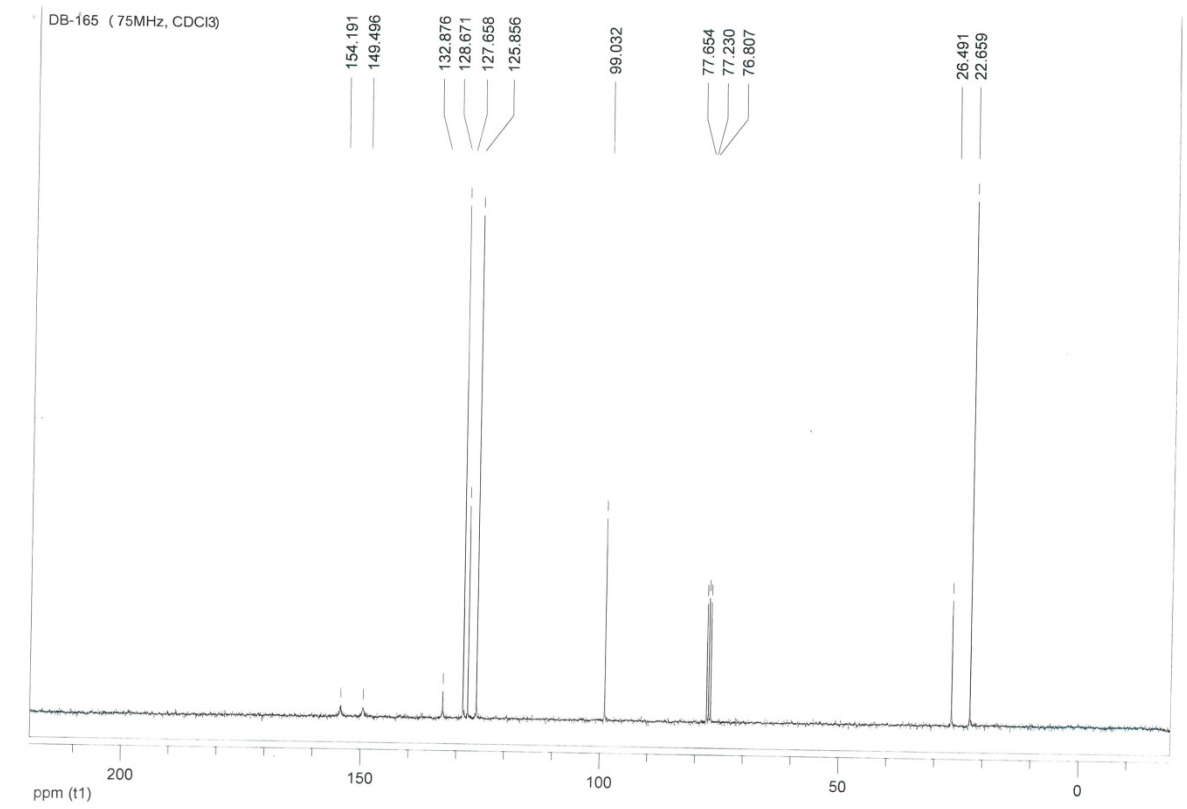
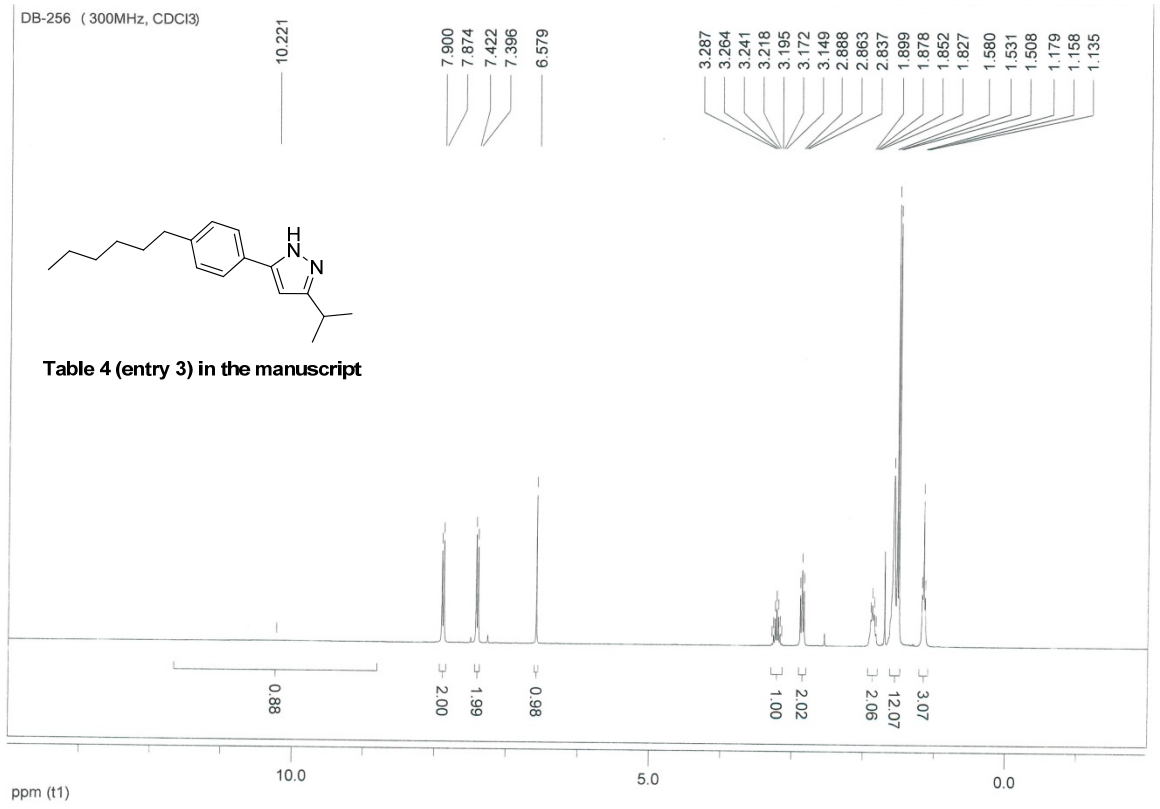


Figure S19. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 3) in text



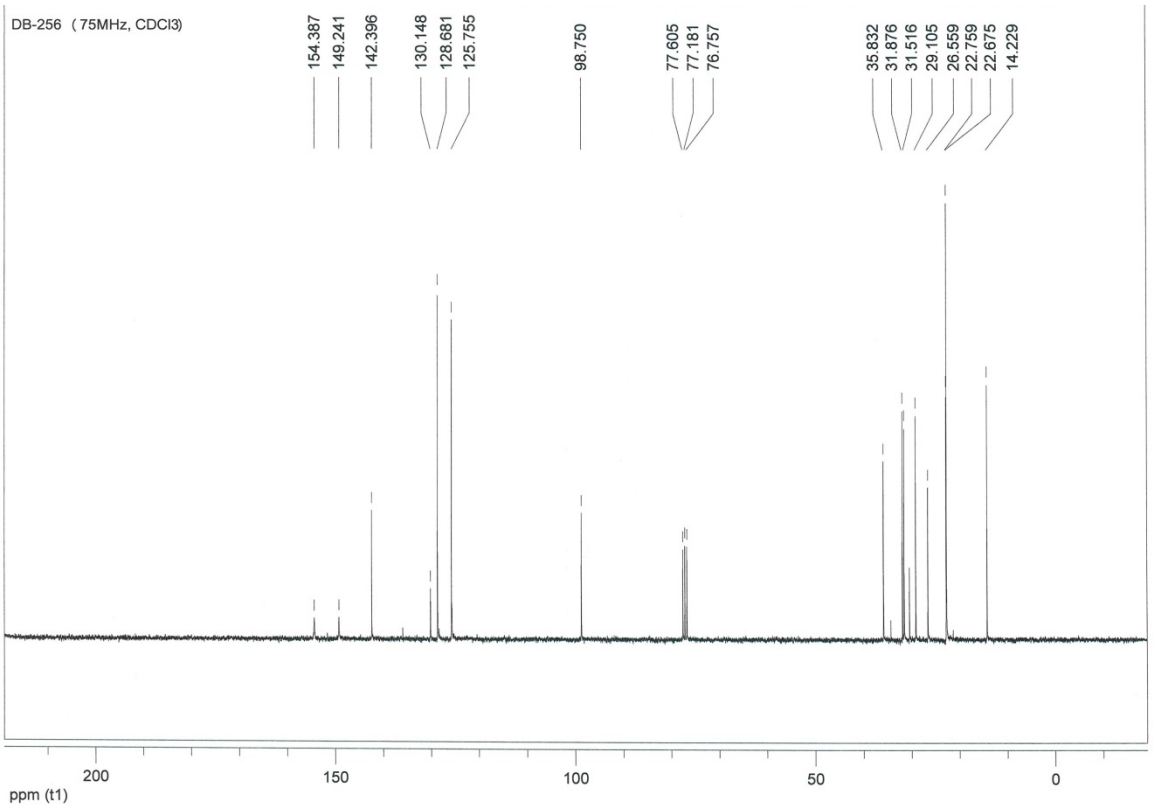
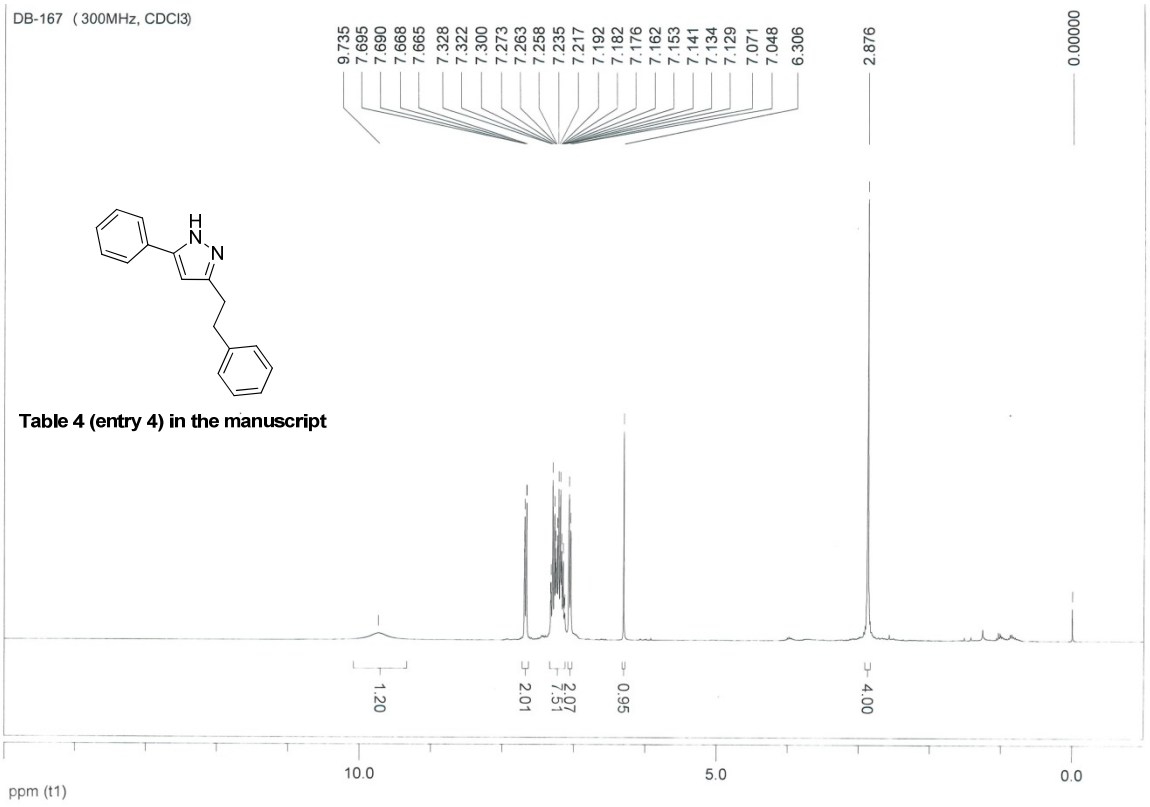


Figure S20. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 4) in text



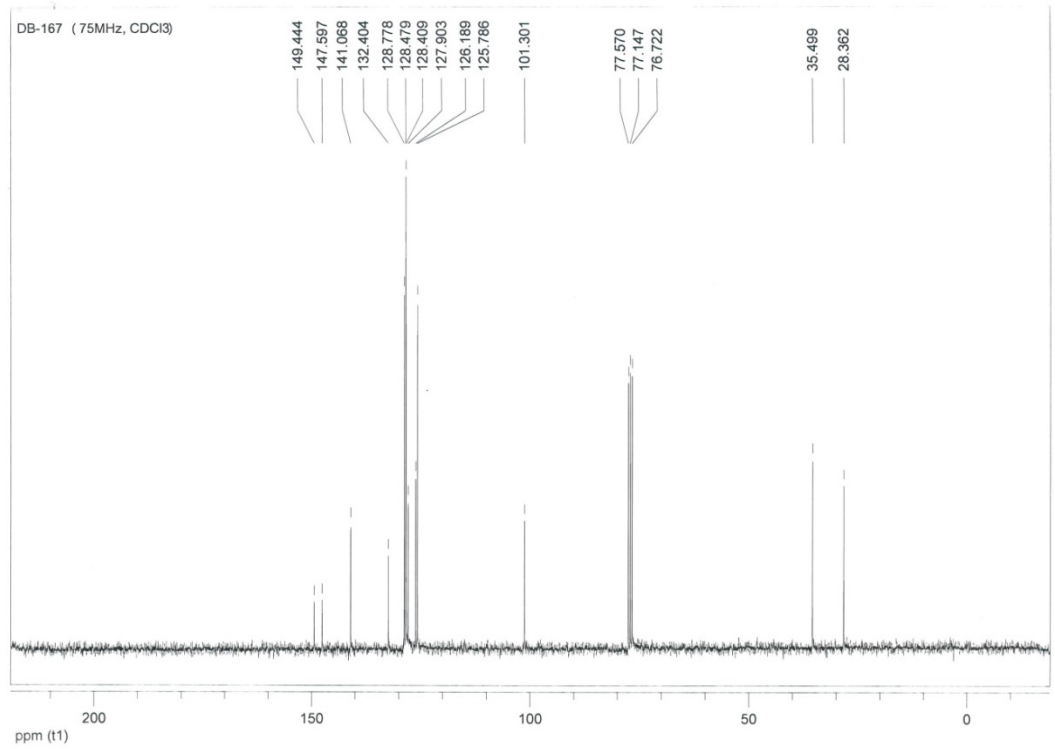
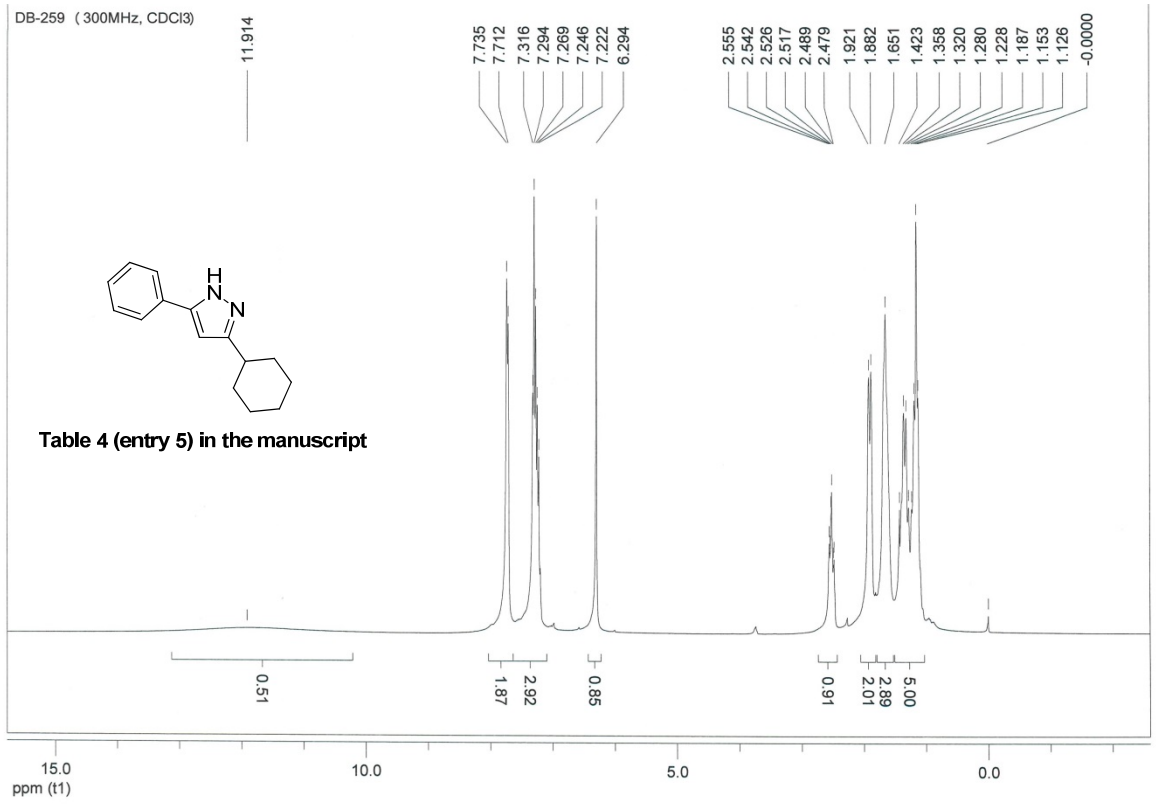


Figure S21. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 5) in text



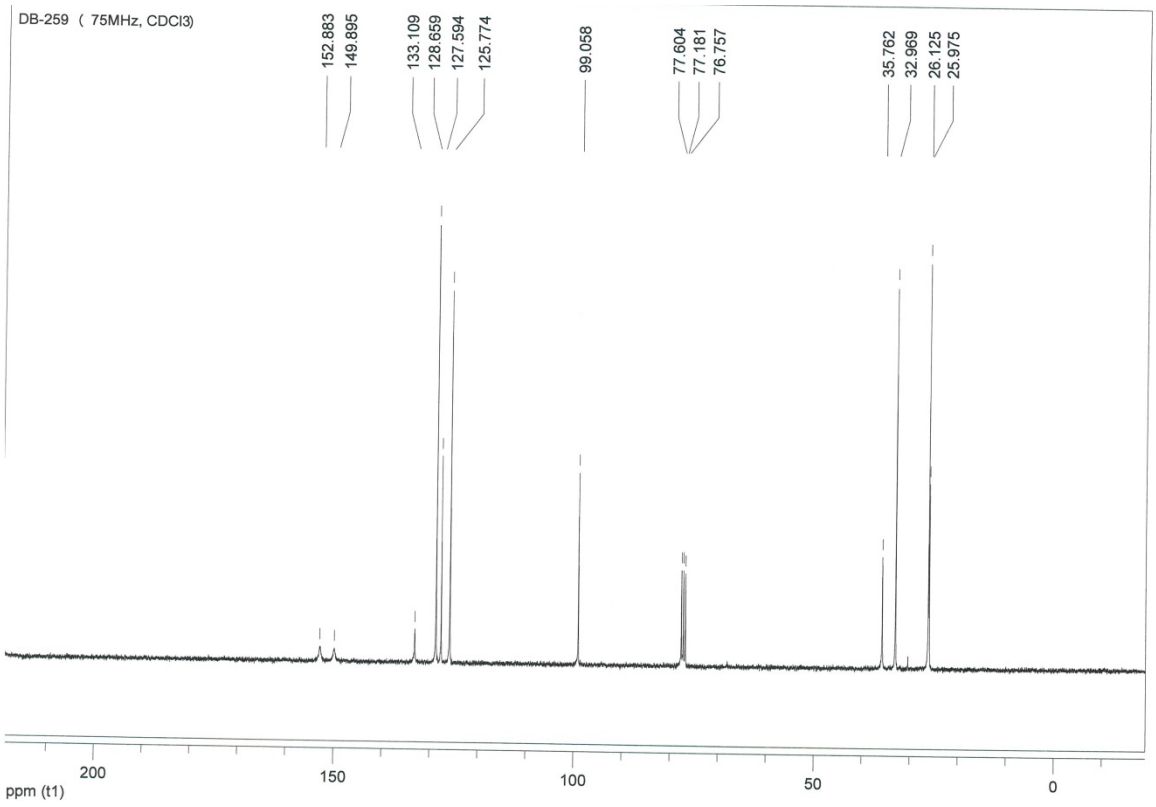
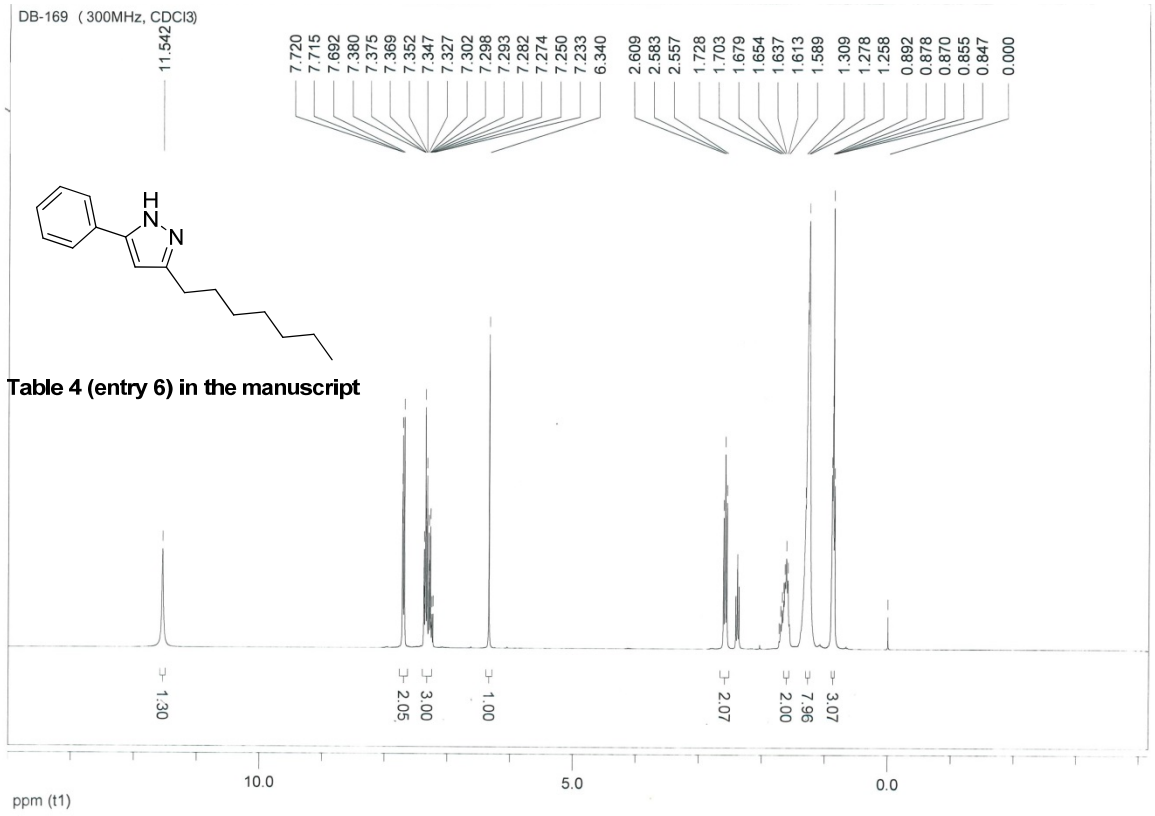


Figure S22. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 6) in text



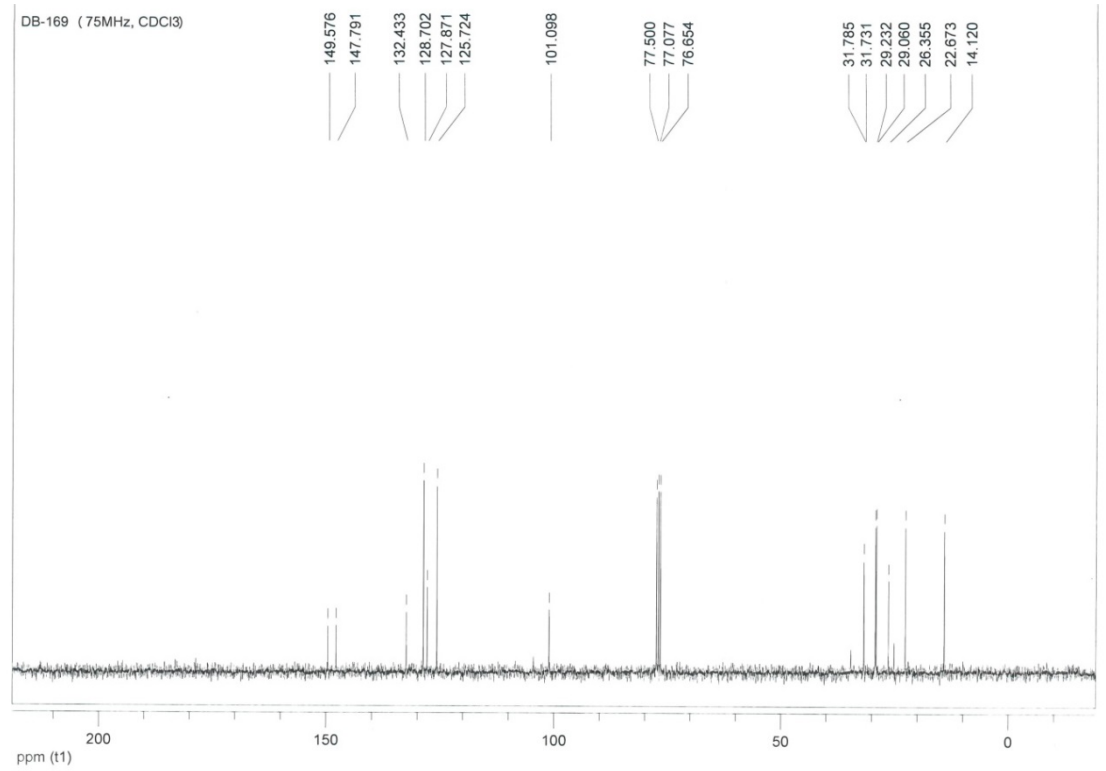
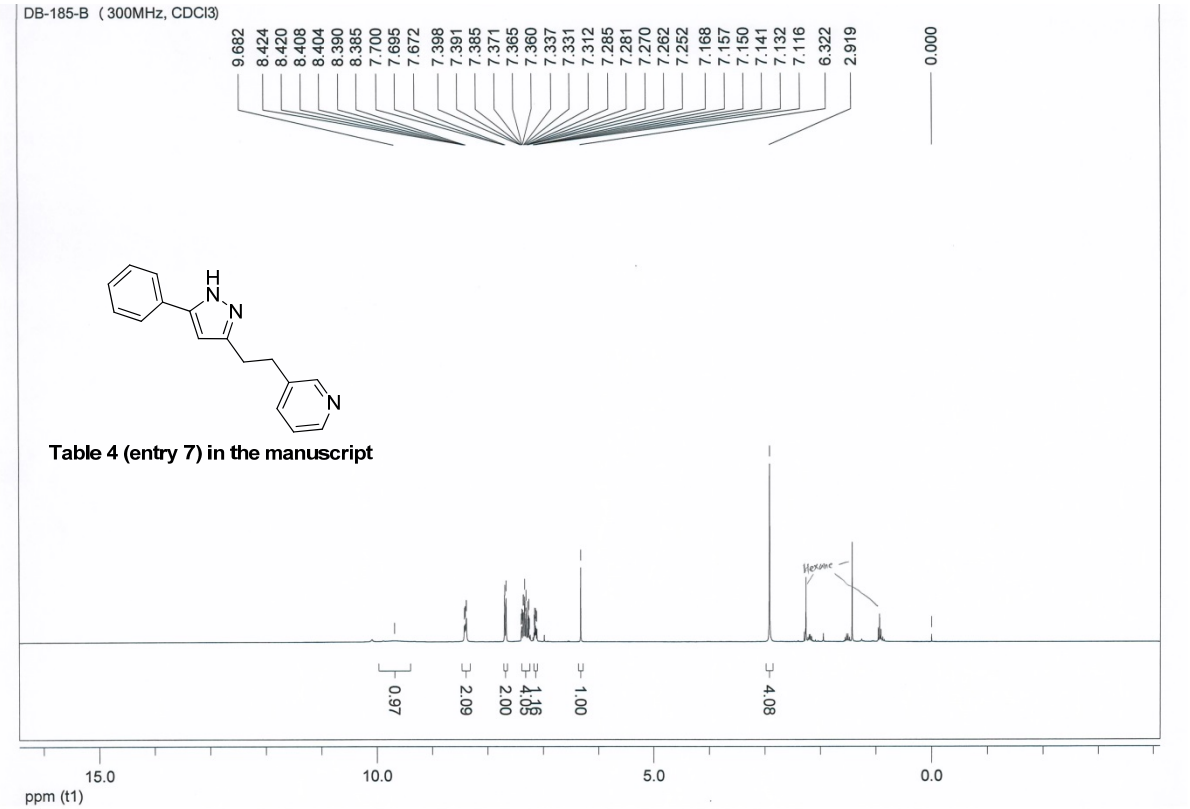


Figure S23. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 7) in text



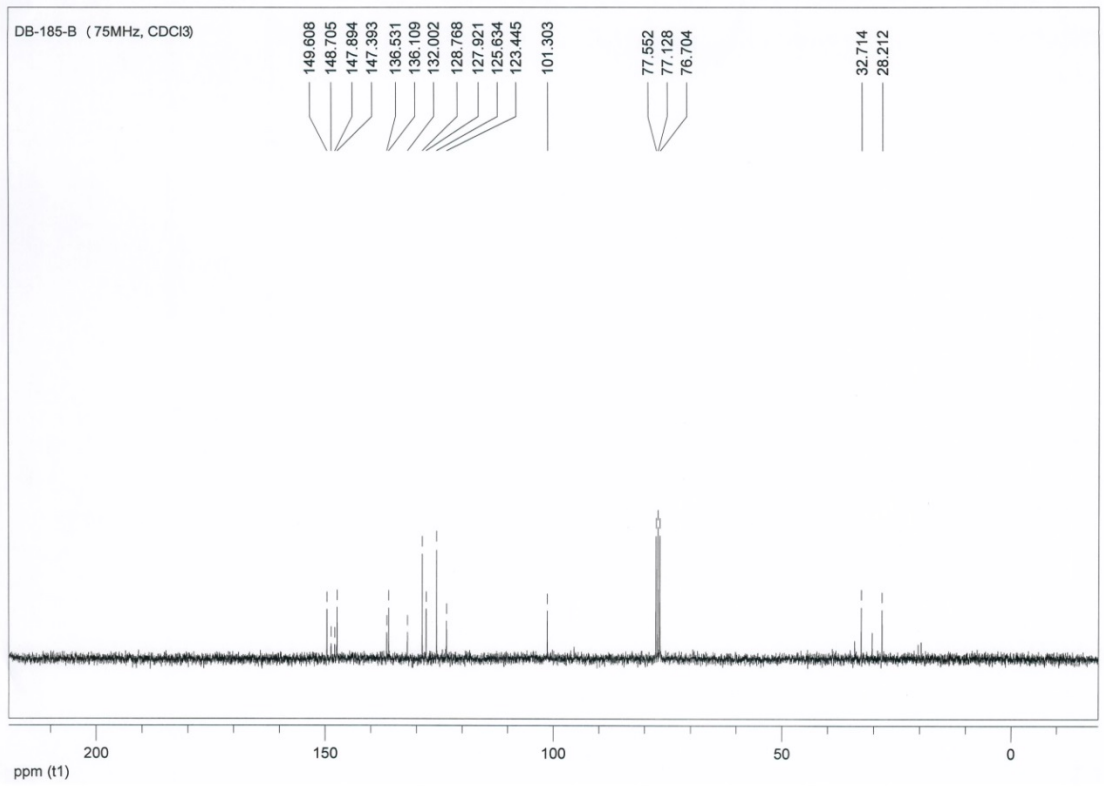


Figure S24. ^{1}H (top) and ^{13}C NMR (bottom) spectra in $CDCl_3$ of Table 4 (entry 8) in text