

# Supporting Information

## Drug-Clinical Agent Molecular Hybrid: Synthesis of Diaryl(trifluoromethyl)pyrazoles as Tubulin Targeting Anticancer Agents

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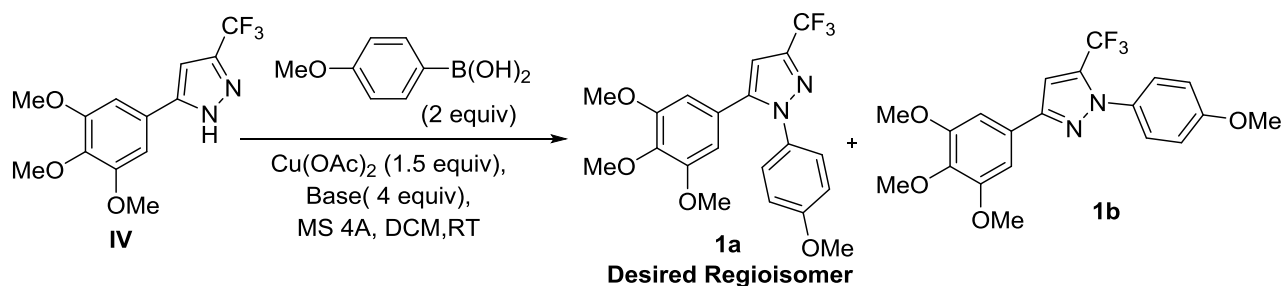
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# 1. Optimization studies towards the synthesis of the desired regioisomer, 1-(4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole

## 1.1 Supplementary Table S1. Evaluation of reaction conditions for *N*-arylation via Chan Lam coupling<sup>a</sup>

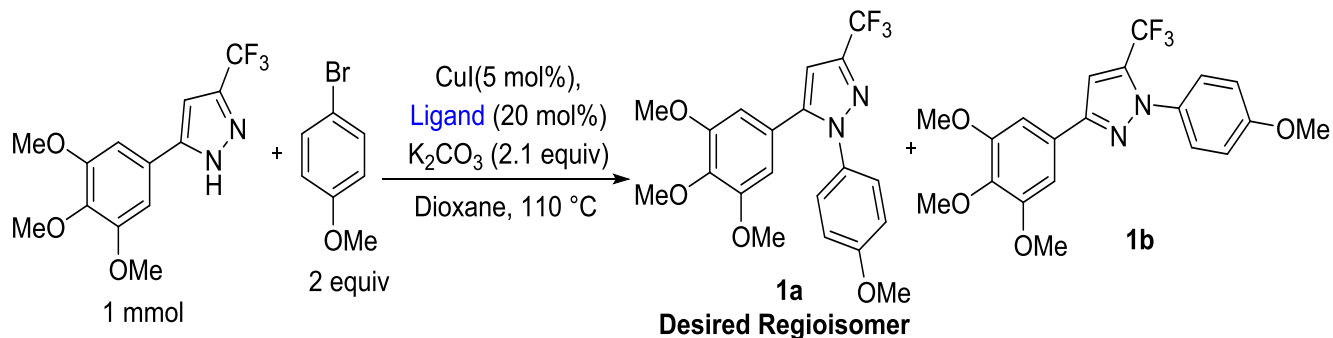


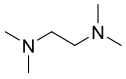

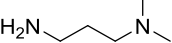
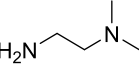
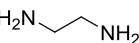
Entry	Base	Yield of <b>1a</b> (%)	Yield of <b>1b</b> (%)
1 <sup>b</sup>	Pyridine	36	13
2 <sup>b</sup>	$\text{Et}_3\text{N}$	42	13
3 <sup>b,c</sup>	$\text{Et}_3\text{N}$	43	12

<sup>a</sup>Reaction done at 0.5 mmol scale; <sup>b</sup>incomplete conversion after 48 h; <sup>c</sup> Under oxygen

## 1.2 Evaluation of reaction conditions for *N*-arylation via Ullmann-Goldberg coupling<sup>a</sup>

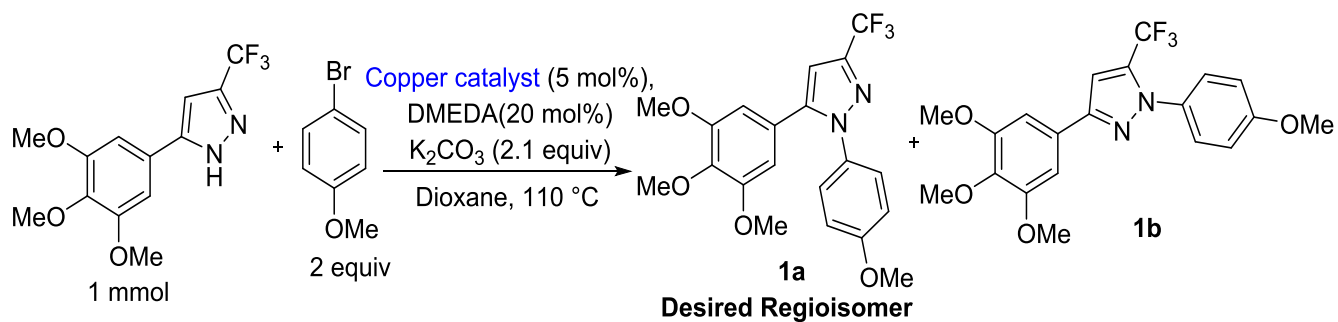
### 1.2.1 Supplementary Table S2. Evaluation of ligands<sup>a,d</sup>



#	Ligand (20 mol%)	Yield (%) of desired regioisomer (1a, 1b)
1 <sup>b</sup>	Cyclohexane-1,2- diamine (cis +trans)	15, 4
2	Bipyridyl	NR
3	1,10-phenanthroline	NR
4 <sup>b</sup>	2-picolinic acid	5, 2
5 <sup>b</sup>	 TMEDA	0, several non-isolable side products.
6	 DMEDA	<b>93, 4</b>
7		34, 11
8		28, 9
9		trace
10	Et <sub>3</sub> N	NR
11	Hunig's base	NR
12	Pyridine	trace
13	<i>N,N</i> -Dimethylcyclohexaneamine	NR
14	Et <sub>2</sub> NH	NR

<sup>a</sup>Reaction done at 0.25 mmol scale; <sup>b</sup>incomplete conversion; <sup>c</sup>40 mol % of monodentate ligand; <sup>d</sup>Reaction monitored upto 48 h

### 1.2.2 Supplementary Table S3: Evaluation of copper catalysts:<sup>a,b</sup>



#	Copper catalysts (5 mol%)	Yield(%) of desired regioisomer(1a, 1b)
1	CuI	93, 4
2	CuBr	87, 7
3	CuCl	89, 6
4	CuOTf	88, 8
5	Cu <sub>2</sub> O	90, 4
6	CuSO <sub>4</sub> ·5H <sub>2</sub> O	81, 10
7	Cu(OAc) <sub>2</sub>	82, 9
8	CuBr <sub>2</sub>	86, 8
9	Cu(OTf) <sub>2</sub>	85, 9
10	CuCl <sub>2</sub>	81, 10
11	CuO	81, 9

<sup>a</sup>Reaction done at 0.25 mmol scale; <sup>b</sup>Reaction monitored upto 12 h

## 2. General Procedures

**2.1 Experimental procedure for synthesis of 3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (IV):** A solution of hydrazine hydrate (5 mmol, 0.24 mL, 5 equiv) and 4,4,4-trifluoro-3-hydroxy-1-(3,4,5-trimethoxyphenyl)but-2-en-1-one (1 mmol, 306 mg) in ethanol (2 mL) was heated at reflux with stirring. After completion of reaction (12 h), the mixture was cooled to 25 °C. The reaction mixture was concentrated by rotary evaporator under reduced pressure to give a crude solid which was purified by silica gel column chromatography using hexane-ethyl acetate (2:1, v/v) as eluent. It provided 3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (IV) (181 mg, 60%).

**2.2 Representative experimental procedure for synthesis of 1-(4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (1):** 3-(Trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (compound IV, 1mmol, 302 mg), CuI(0.05 mmol, 9.5 mg, 5 mol%, ), potassium carbonate (2.10 mmol, 290 mg, 2.1 equiv) were taken under argon in an oven-dried sealed tube equipped with a rubber septum and magnetic bar. 4-Bromoanisole (2 mmol, 0.25 mL, 2 equiv), *N,N'*-Dimethylethylenediamine (DMEDA) (0.2 mmol, 0.02 mL, 0.2 equiv), and dioxane (anhyd., 2 mL) were then added successively under argon. The tube was then sealed. The mixture was stirred at 110 °C and the reaction was monitored by TLC. After completion of reaction (12 h), the mixture was allowed to cool to room temperature and diluted with EtOAc (50 mL). The resultant mixture was filtered through celite and the filtrate was washed with 10% aqueous ammonia solution (3×20 mL). The combined organic solution was washed with water (2×5 mL) and then with brine (1×5 mL), dried with anhyd. Na<sub>2</sub>SO<sub>4</sub>, and concentrated by rotary evaporator under reduced pressure. The column chromatographic purification of crude mass was performed on silica gel (100-200 mesh) using Hexane-Dichloromethane (20:80) as eluting solvent. It provided 1-(4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (1) (379 mg, 93%).

Products (2-23, Table 1 of manuscript) were also prepared following this representative procedure.

### 3. Spectral data

#### Characterization data of the synthesized compounds (IV, 1-23)

**3-(Trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (IV):** White solid; 181 mg, 60%; mp 190 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 12.65 (s, 1H), 6.79 (s, 2H), 6.69 (s, 1H), 3.88 (s, 3H), 3.84 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.8, 145.2, 143.4 (q, *J*<sub>C-C-F</sub> = 32 Hz), 139.1, 123.4, 121.1 (q, *J*<sub>C-F</sub> = 267 Hz), 102.9, 100.7, 60.9, 56.0 ppm; IR (KBr): ν<sub>max</sub> 3137, 2947, 1593, 1473, 1253, 1118, 1042, 998 cm<sup>-1</sup> HRMS (ESI) m/z : calcd for C<sub>13</sub>H<sub>14</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 303.0956, found: 303.0941.

**1-(4-Methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (1):** White solid; 379 mg, 93%; mp 170 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.26 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.73 (s, 1H), 6.41 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.68 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 159.6, 153.2, 144.5, 142.7 (q, *J*<sub>C-C-F</sub> = 38 Hz), 138.5, 132.4, 127.0, 124.4, 121.3 (q, *J*<sub>C-F</sub> = 267 Hz), 114.2, 106.1, 104.7 (d(AB-q), *J*<sub>C-C-C-F</sub> = 2 Hz), 60.9, 56.0, 55.6 ppm; IR (KBr): ν<sub>max</sub> 2926, 1609, 1585, 1239, 1112, 1003 cm<sup>-1</sup>; HRMS (ESI) m/z : calcd for C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M + Na]<sup>+</sup> 431.1195, found: 431.1181.

**1-(Quinolin-3-yl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (2):** White solid; 300 mg, 70%; mp 170 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.81 (d, *J* = 2.5 Hz, 1H), 8.28 (d, *J* = 2.3 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 (dd, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.62 (dd, *J* = 7.1 Hz, *J* = 1.0 Hz, 1H), 6.83 (s, 1H), 6.44 (s, 2H), 3.85 (s, 3H), 3.60 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.6, 147.0, 146.8, 145.3, 144.2 (q, *J*<sub>C-C-F</sub> = 38 Hz), 139.1, 132.8, 131.1, 130.6, 129.4, 128.1, 127.9, 127.1, 123.8, 121.1 (q, *J*<sub>C-F</sub> = 267 Hz), 106.4, 105.9 (d (AB-q), *J*<sub>C-C-C-F</sub> = 1 Hz), 60.9, 56.1 ppm; IR (KBr): ν<sub>max</sub> 2939, 1585, 1480, 1248, 1229, 1154, 1124, 1003 cm<sup>-1</sup>; HRMS (ESI) m/z : calcd for C<sub>22</sub>H<sub>19</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 430.1378, found: 430.1373.

**1-(3-Hydroxy-4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (3):** White solid; 403 mg, 95%; mp 142 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.97 – 6.96 (m, 1H), 6.83 – 6.78 (m, 2H), 6.71 (s, 2H), 6.43 (s, 2H), 5.73 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.69 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.2, 146.8, 145.9, 144.6, 142.7 (q, *J*<sub>C-C-F</sub> = 38 Hz), 138.6, 132.9, 124.4, 121.3 (q, *J*<sub>C-F</sub> = 267 Hz), 117.7, 112.6, 110.3, 106.1, 104.7 (d

(AB-q),  $J_{C-C-F} = 2$  Hz), 60.9, 56.2, 56.1 ppm; IR (KBr):  $\nu_{\max}$  3399, 2940, 1587, 1481, 1238, 1153, 1124, 1099, 1004  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$  425.1324, found: 425.1317.

**1-(3-Hydroxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (4):** White solid; 355 mg, 90%; mp 148 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.19 (dd,  $J = 8.12$  Hz,  $J = 8.08$  Hz, 1H), 6.91 (dd,  $J = 2.2$  Hz,  $J = 2.2$  Hz, 1H), 6.84 – 6.78 (m, 2H), 6.74 (s, 1H), 6.43 (s, 2H), 6.09 (s, 1H), 3.85 (s, 3H), 3.67 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  156.9, 153.2, 144.9, 142.9 (q,  $J_{C-C-F} = 39$  Hz), 139.8, 138.6, 130.0, 124.0, 121.1 (q,  $J_{C-F} = 267$  Hz), 117.8, 116.3, 113.3, 106.1, 104.9, 60.9, 56.0 ppm; IR (KBr):  $\nu_{\max}$  3568, 3139, 2942, 1587, 1480, 1260, 1244, 1154, 1124, 999  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$  395.1218, found: 395.1214

**1-(2-Methyl-6-quinolinyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (5):** White solid; 332 mg, 75%; mp 146 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03–7.99 (m, 2H), 7.86 (d,  $J = 2.3$  Hz, 1H), 7.59 (dd,  $J = 9$  Hz,  $J = 2.4$  Hz, 1H), 7.34 (d,  $J = 8.5$  Hz, 1H), 6.79 (s, 1H), 6.44 (s, 2H), 3.84 (s, 3H), 3.59 (s, 6H), 2.76 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.5, 153.4, 146.9, 144.9, 143.5 (q,  $J_{C-C-F} = 38$  Hz), 138.8, 136.4, 136.3, 129.7, 126.7, 126.1, 124.2, 123.6, 123.2, 121.2 (q,  $J_{C-F} = 268$  Hz), 106.3, 105.5 (d (AB-q),  $J_{C-C-C-F} = 1$  Hz), 60.9, 56.0, 25.4 ppm; IR (KBr):  $\nu_{\max}$  2938, 1585, 1478, 1232, 1121, 1097, 1002  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_3$   $[\text{M} + \text{H}]^+$  444.1535, found: 444.1540.

**1-(3,4-Dimethoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (6):** White solid; 412 mg, 94%; mp 154 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.93 (d,  $J = 1.3$  Hz, 1H), 6.85–6.80 (m, 2H), 6.74 (s, 1H), 6.43 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.69 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.2, 149.14, 149.11, 144.6, 142.8 (q,  $J_{C-C-F} = 38$  Hz), 138.5, 132.4, 124.5, 121.3 (q,  $J_{C-F} = 267$  Hz), 118.1, 110.7, 109.2, 106.1, 104.8 (d (AB-q),  $J_{C-C-C-F} = 1$  Hz), 60.9, 56.2, 56.11, 56.06 ppm; IR (KBr):  $\nu_{\max}$  2941, 1600, 1582, 1483, 1219, 1117, 1102, 1005  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_5$   $[\text{M} + \text{H}]^+$  439.1481, found: 439.1471.

**1-Phenyl-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (7):** White solid; 340 mg, 90%; mp 167 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43–7.38 (m, 3H), 7.36–7.33 (m, 2H),



6.76 (s, 1H), 6.39 (s, 2H), 3.86 (s, 3H), 3.65 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.2, 144.6, 143.1 (q,  $J_{\text{C-C-F}} = 38$  Hz), 139.3, 138.6, 129.2, 128.6, 125.7, 124.3, 121.3 (q,  $J_{\text{C-F}} = 267$  Hz), 106.1, 105.0 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 60.9, 55.9 ppm; IR (KBr):  $\nu_{\text{max}}$  2946, 1587, 1479, 1241, 1127, 1108, 1004  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{19}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$  379.1269, found: 379.1263.

**1-(3,5-Dimethoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (8) :** White solid; 372 mg, 85%; mp 132/ °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.74 (s, 1H), 6.49 (d,  $J = 2.2$  Hz, 2H), 6.46–6.45 (m, 3H), 3.86 (s, 3H), 3.71 (s, 6H), 3.70 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.9, 153.2, 144.6, 142.9 (q,  $J_{\text{C-C-F}} = 38$  Hz), 140.7, 138.7, 124.4, 121.3 (q,  $J_{\text{C-F}} = 268$  Hz), 106.1, 105.1 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 104.1, 100.9, 60.9, 56.1, 55.6 ppm; IR (KBr):  $\nu_{\text{max}}$  2941, 1614, 1594, 1477, 1218, 1152, 1118, 998  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_5$  [ $\text{M} + \text{H}$ ] $^+$  439.1481, found: 439.1478.

**1-(Benzo[d][1,3]dioxol-5-yl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (9) :** White solid; 384 mg, 91%; mp 151 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.84–6.83 (m, 1H), 6.81–6.78 (m, 2H), 6.71 (s, 1H), 6.44 (s, 2H), 6.02 (s, 2H), 3.87 (s, 3H), 3.72 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.3, 147.9, 147.8, 144.7, 142.8 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.7, 133.4, 124.3, 121.2 (q,  $J_{\text{C-F}} = 268$  Hz), 108.1, 107.2, 106.1, 104.8 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 101.9, 60.9, 56.1 ppm; IR (KBr):  $\nu_{\text{max}}$  2911, 1586, 1478, 1217, 1149, 1123, 1113, 1001  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_5$  [ $\text{M} + \text{Na}$ ] $^+$  445.0988, found: 445.0976.

**1-(3-Methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (10) :** White solid; 355 mg, 87%; mp 114 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.29–7.25 (m, 1H), 6.93–6.87 (m, 3H), 6.75 (s, 1H), 6.43 (s, 2H), 3.86 (s, 3H), 3.76 (s, 3H), 3.68 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.1, 153.3, 144.7, 143.1 (q,  $J_{\text{C-C-F}} = 37$  Hz), 140.3, 138.7, 129.8, 124.3, 121.3 (q,  $J_{\text{C-F}} = 267$  Hz), 117.9, 114.7, 111.2, 106.1, 105.1 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 60.9, 56.1, 55.6 ppm; IR (KBr):  $\nu_{\text{max}}$  2925, 1605, 1588, 1480, 1220, 1118, 1000  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$  [ $\text{M} + \text{Na}$ ] $^+$  431.1195, found: 431.1191.

**1-(4-(Trifluoromethoxy)phenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (11) :** White solid; 393 mg, 85%; mp 131 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (d,  $J = 9$  Hz, 2H), 7.27–7.25 (m, 2H), 6.76 (s, 1H), 6.38 (s, 2H), 3.87 (s, 3H), 3.68 (s, 6H) ppm

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.4, 148.8 (d,  $J_{\text{C-O-C-F}} = 2$  Hz), 144.8, 143.6 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.9, 137.8, 127.1, 123.9, 121.7, 121.1 (q,  $J_{\text{C-F}} = 260$  Hz), 120.4 (q,  $J_{\text{C-F}} = 257$  Hz), 106.2, 105.5 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 61.0, 56.0 ppm; IR (KBr):  $\nu_{\text{max}}$  2942, 1586, 1480, 1260, 1126, 1010, 974  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{20}\text{H}_{17}\text{F}_6\text{N}_2\text{O}_4$   $[\text{M} + \text{H}]^+$  463.1092, found: 463.1093.

**3-(Trifluoromethyl)-1,5-bis(3,4,5-trimethoxyphenyl)-1H-pyrazole (12)** : White solid; 412 mg, 88%; mp 148 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.75 (s, 1H), 6.57 (s, 2H), 6.46 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.73 (s, 6H), 3.71 (s, 6H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.34, 153.28, 144.6, 142.9 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.7, 138.2, 134.8, 124.4, 121.2 (q,  $J_{\text{C-F}} = 267$  Hz), 106.2, 104.9, 103.4, 61.02, 60.99, 56.3, 56.2 ppm; IR (KBr):  $\nu_{\text{max}}$  2937, 1585, 1482, 1230, 1117, 1104, 1000  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_6$   $[\text{M} + \text{H}]^+$  469.1586, found: 469.1580.

**1-(p-Tolyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (13)** : White solid; 353 mg, 90%; mp 160 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.20 (AB-q,  $J = 8.8$  Hz, 4H), 6.73 (s, 1H), 6.39 (s, 2H), 3.86 (s, 3H), 3.66 (s, 6H), 2.37 (s, 3H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.2, 144.6, 142.9 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.7, 138.5, 136.9, 129.7, 125.6, 124.4, 121.3 (q,  $J_{\text{C-F}} = 267$  Hz), 106.1, 104.9 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 60.9, 55.9, 21.1 ppm; IR (KBr):  $\nu_{\text{max}}$  3005, 1587, 1480, 1260, 1125, 1113, 1007  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{20}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3$   $[\text{M} + \text{H}]^+$  393.1426, found: 393.1428.

**3-(Trifluoromethyl)-1-(3,4,5-trifluorophenyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (14)** : White solid; 353 mg, 90%; mp 143 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.06 (dd,  $J = 7.8$  Hz,  $J = 6.1$  Hz, 2H), 6.73 (s, 1H), 6.43 (s, 2H), 3.89 (s, 3H), 3.76 (s, 6H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.7, 150.8 (d of multiplet,  $J = 251$  Hz), 145.0, 143.9 (q,  $J_{\text{C-C-F}} = 39$  Hz), 139.6 (d of dd,  $J = 254$  Hz,  $J = 16$  Hz,  $J = 15$  Hz), 139.4, 134.4 (m), 123.5, 120.9 (q,  $J_{\text{C-F}} = 267$  Hz), 110.08 (d,  $J = 25$  Hz), 110.08 (d,  $J = 11$  Hz), 106.32 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 106.25, 61.0, 56.3 ppm; IR (KBr):  $\nu_{\text{max}}$  2934, 1586, 1482, 1253, 1238, 1126, 1051, 1005, 973  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{19}\text{H}_{14}\text{F}_6\text{N}_2\text{O}_3$   $[\text{M} + \text{Na}]^+$  455.0807, found: 455.0797.

**1-(4-fluorophenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (15)** : White solid; 317 mg, 80%; mp 154 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36–7.32 (m, 2H), 7.12–7.07

(m, 2H), 6.74 (s, 1H), 6.39 (s, 2H), 3.86 (s, 3H), 3.69 (s, 6H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  162.2 (d,  $J_{\text{C-F}} = 248$  Hz), 153.3, 144.7, 143.2 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.8, 135.4 (d,  $J_{\text{C-C-C-F}} = 3$  Hz), 127.5 (d,  $J_{\text{C-C-C-F}} = 9$  Hz), 124.1, 121.2 (q,  $J_{\text{C-F}} = 267$  Hz), 117.2, 116.1 (d,  $J_{\text{C-C-F}} = 23$  Hz), 106.1, 105.2 (d (AB-q),  $J_{\text{C-C-C-F}} = 1$  Hz), 60.9, 56.0 ppm; IR (KBr):  $\nu_{\text{max}}$  3008, 1586, 1479, 1259, 1225, 1111, 1002, 973  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{19}\text{H}_{17}\text{F}_4\text{N}_2\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$  397.1175, found: 397.1171.

**1-(4-Chlorophenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (16) :** White solid; 338 mg, 82%; mp 183  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36 (d,  $J = 6.8$  Hz, 2H), 7.29 (d,  $J = 6.8$  Hz, 2H), 6.74 (s, 1H), 6.39 (s, 2H), 3.87 (s, 3H), 3.69 (s, 6H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.4, 144.7, 143.4 (q,  $J_{\text{C-C-F}} = 39$  Hz), 138.9, 137.8, 134.4, 129.3, 126.7, 124.1, 121.2 (q,  $J_{\text{C-F}} = 268$  Hz), 106.2, 105.5 (d (AB-q),  $J_{\text{C-C-C-F}} = 2$  Hz), 61.0, 56.1 ppm; IR (KBr):  $\nu_{\text{max}}$  2938, 1585, 1479, 1237, 1129, 1114, 1006  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{19}\text{H}_{16}\text{ClF}_3\text{N}_2\text{O}_3$  [ $\text{M} + \text{Na}$ ] $^+$  435.0700, found: 435.0690.

**1-(4-Acetyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (17) :** White solid; 386 mg, 92%; mp 165  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (d,  $J = 6.8$  Hz, 2H), 7.47 (d,  $J = 6.8$  Hz, 2H), 6.76 (s, 1H), 6.41 (s, 2H), 3.87 (s, 3H), 3.68 (s, 6H), 2.62 (s, 3H) ppm  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.4, 144.9, 143.8 (q,  $J_{\text{C-C-F}} = 39$  Hz), 138.9, 136.3, 129.2, 125.1, 124.1, 121.2 (q,  $J_{\text{C-F}} = 267$  Hz), 106.2, 106.1 (d (AB-q),  $J_{\text{C-C-C-F}} = 1$  Hz), 61.0, 56.1, 26.7 ppm; IR (KBr):  $\nu_{\text{max}}$  2925, 1682, 1585, 1479, 1234, 1124, 1007  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$  [ $\text{M} + \text{Na}$ ] $^+$  443.1195, found: 443.1183.

**1-(Indol-5-yl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (18):** White solid; 313 mg, 75%; mp 203  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.58 (s, 1H), 7.64 (d,  $J = 1.8$  Hz, 1H), 7.26–7.25 (m, 2H), 7.05 (dd,  $J = 8.6$  Hz,  $J = 1.96$  Hz, 1H), 6.77 (s, 1H), 6.51 (dd,  $J = 2.1$  Hz,  $J = 2.0$  Hz, 1H), 6.41 (s, 2H), 3.83 (s, 3H), 3.55 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.0, 144.8, 142.4 (q,  $J_{\text{C-C-F}} = 38$  Hz), 138.2, 135.4, 131.9, 127.8, 126.3, 124.7, 121.5 (q,  $J_{\text{C-F}} = 267$  Hz), 119.9, 118.4, 111.3, 106.1, 104.3 (d,  $J_{\text{C-C-C-F}} = 2$  Hz), 103.1, 60.9, 55.9 ppm; IR (KBr):  $\nu_{\text{max}}$  3223, 3005, 1588, 1482, 1275, 1261, 1128, 998  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  : calcd for  $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_3\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$  418.1378, found: 418.1374.

**1-(Pyridin-3-yl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (19):** White solid; 296 mg, 78%; mp 130 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.63–8.61 (m, 2H), 7.75–7.72 (m, 1H), 7.39–7.36 (m, 1H), 6.78 (s, 1H), 6.39 (s, 2H), 3.86 (s, 3H), 3.69 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.5, 149.3, 146.3, 145.2, 144.1 (q, *J*<sub>C-C-F</sub> = 39 Hz), 139.1, 135.9, 132.5, 123.7, 123.5, 121.0 (q, *J*<sub>C-F</sub> = 268 Hz), 106.3, 105.9 (d (AB-q), *J*<sub>C-C-C-F</sub> = 2 Hz), 60.9, 56.1 ppm; IR (KBr): *v*<sub>max</sub> 2941, 1584, 1477, 1236, 1123, 1005 cm<sup>-1</sup>; HRMS (ESI) *m/z* : calcd for C<sub>18</sub>H<sub>17</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 380.1222, found: 380.1215.

**1-(Thiophen-2-yl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (20):** White solid; 211 mg, 55%; mp 130 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.24 (dd, *J* = 5.3 Hz, *J* = 1.5 Hz, 1H), 6.93–6.89 (m, 2H), 6.72 (s, 1H), 6.50 (s, 2H), 3.87 (s, 3H), 3.73 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.3, 146.2, 143.6 (q, *J*<sub>C-C-F</sub> = 39 Hz), 140.4, 138.9, 125.7, 124.6, 124.0, 123.6, 120.9 (q, *J*<sub>C-F</sub> = 268 Hz), 106.0, 105.0 (d (AB-q), *J*<sub>C-C-C-F</sub> = 2 Hz), 60.9, 56.1 ppm; IR (KBr): *v*<sub>max</sub> 2925, 1584, 1481, 1275, 1261, 1155, 1000 cm<sup>-1</sup>; HRMS (ESI) *m/z* : calcd for C<sub>17</sub>H<sub>16</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S [M + H]<sup>+</sup> 385.0833, found: 385.0826.

**1-(3-(Benzyloxy)-4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (21):** Yellow semi-solid; 437 mg, 85%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.36–7.26 (m, 5H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.86–6.85 (m, 2H), 6.70 (s, 1H), 6.37 (s, 2H), 5.03 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.65 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 153.2, 149.8, 148.3, 144.5, 142.7 (q, *J*<sub>C-C-F</sub> = 38 Hz), 138.5, 136.2, 132.3, 128.6, 128.1, 127.2, 124.4, 121.3 (q, *J*<sub>C-F</sub> = 268 Hz), 118.7, 111.8, 111.3, 105.9, 104.7 (d (AB-q), *J*<sub>C-C-C-F</sub> = 2 Hz), 71.2, 60.9, 56.2, 56.0 ppm; IR (KBr): *v*<sub>max</sub> 2938, 1586, 1480, 1234, 1124, 1099, 1003 cm<sup>-1</sup>; HRMS (ESI) *m/z* : calcd for C<sub>27</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 515.1794, found: 515.1786.

**1-(3-(Benzyloxy)phenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (22):** Yellow semi-solid; 437 mg, 85%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.37–7.29 (m, 5H), 7.27–7.25 (m, 1H), 7.02–6.97 (m, 2H), 6.90–6.88 (m, 1H), 6.74 (s, 1H), 6.40 (s, 2H), 5.02 (s, 2H), 3.86 (s, 3H), 3.66 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 159.2, 153.2, 144.6, 143.1 (q, *J*<sub>C-C-F</sub> = 38 Hz), 140.3, 138.7, 136.3, 129.9, 128.6, 128.2, 127.4, 124.3, 121.3 (q, *J*<sub>C-F</sub> = 268 Hz), 118.3, 115.5, 112.4, 106.1, 105.0 (d (AB-q), *J*<sub>C-C-C-F</sub> = 2 Hz), 70.3, 60.9, 56.0 ppm; IR (KBr): *v*<sub>max</sub> 2939, 1586, 1479, 1241, 1123, 1101, 1005 cm<sup>-1</sup>; HRMS (ESI) *m/z* : calcd for C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 485.1688, found: 485.1685.

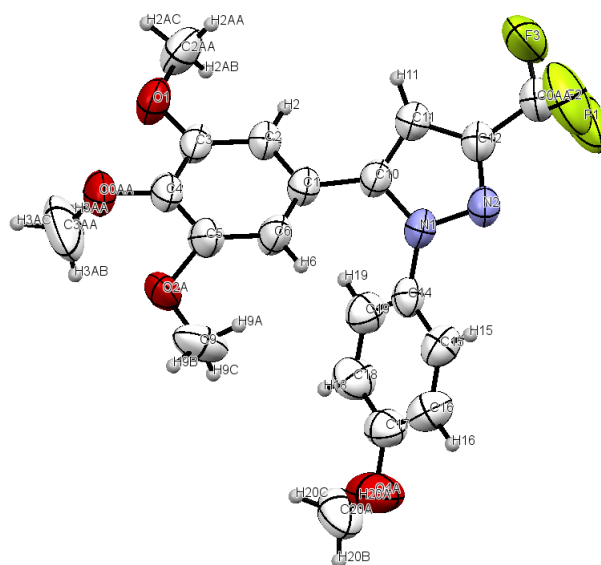
**1-((4-methoxycarbonyl)phenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-**

**pyrazole (23)** :White solid; 388 mg, 89%; mp 159 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.06 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.76 (s, 1H), 6.40 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.68 (s, 6H) ppm <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>): δ 166.0, 153.4, 144.9, 143.8 (q, *J*<sub>C-C-F</sub> = 39 Hz), 142.7, 138.9, 130.5, 129.8, 125.10, 124.0, 121.1 (q, *J*<sub>C-F</sub> = 267 Hz), 106.2, 105.9 (d (AB-q), *J*<sub>C-C-F</sub> = 1 Hz), 61.0, 56.1, 52.4 ppm; IR (KBr): *v*<sub>max</sub> 2990, 1724, 1585, 1479, 1235, 1126, 1009 cm<sup>-1</sup>; HRMS (ESI) *m/z* : calcd for C<sub>21</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 437.1324, found: 437.1324.

**4. X-ray crystallographic data and ORTEP diagrams for compound 1:****Crystal data and structure refinement for 1-(4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (1 (Entry 1, Table 1)) (CCDC 1545464):**

Identification code	<b>1</b>
Empirical formula	C <sub>20</sub> H <sub>19</sub> F <sub>3</sub> N <sub>2</sub> O <sub>4</sub>
Formula weight	408.37
Temperature	293 K
Wavelength	0.71073 Å
Space group	P-1
Crystal system	triclinic
Unit cell dimensions	<i>a</i> = 9.3321(5) Å, <i>α</i> = 71.842(12)°, <i>b</i> = 9.3369(4) Å, <i>β</i> = 79.501(13), <i>c</i> = 12.2142(3) Å, <i>γ</i> = 79.226(12)°
Volume	984.63(11) Å <sup>3</sup>
Z, Calculated density	2, 1.377 g/cm <sup>3</sup>
Absorption coefficient	0.115 mm <sup>-1</sup>
<i>F</i> <sub>000</sub>	424.0
Theta (max)	27.896
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.936

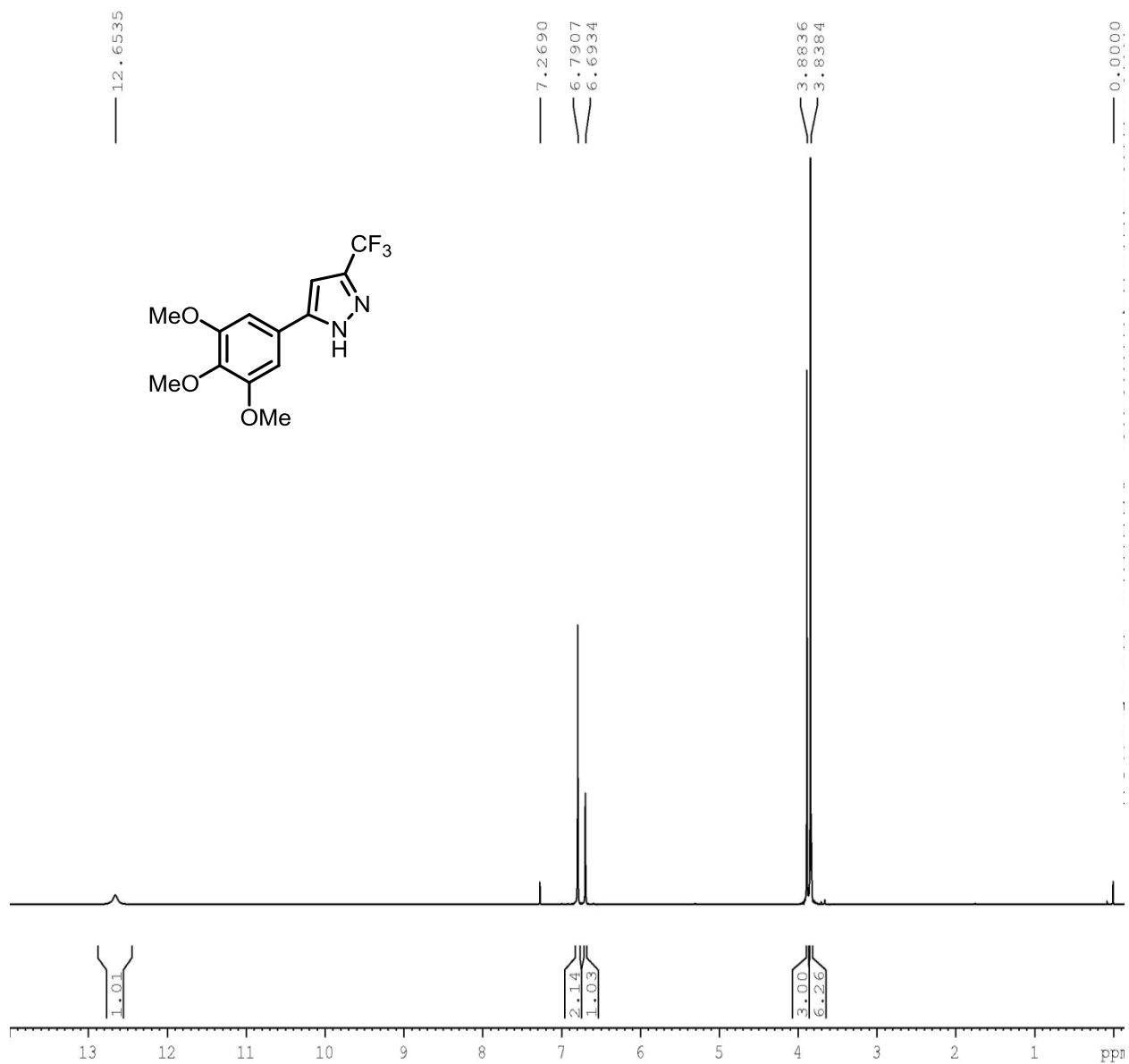
**ORTEP Diagram for compound 1 (entry 1, Table 1)**



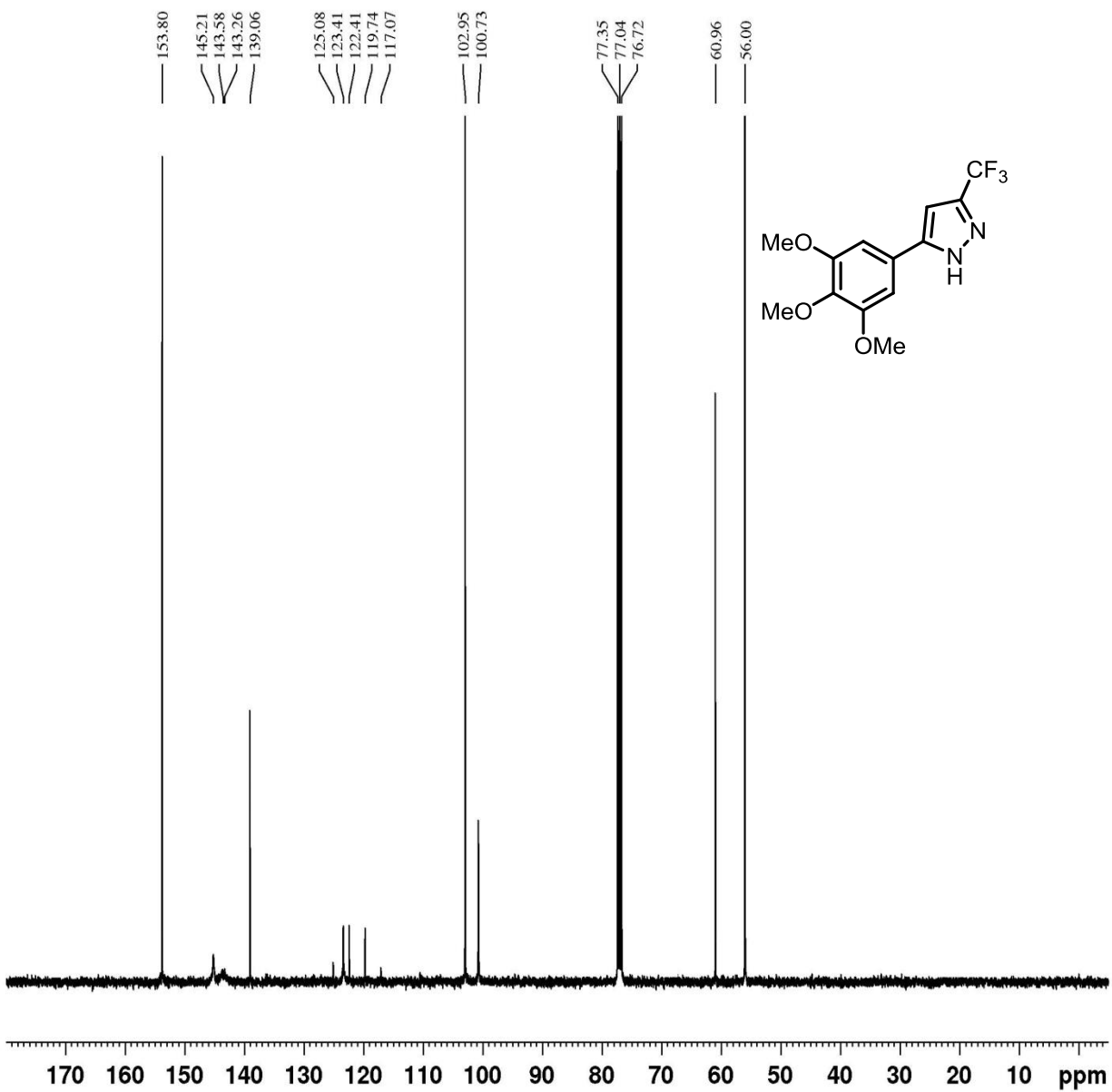
**Supplementary Figure S1.** The molecular structure of 1-(4-methoxyphenyl)-3-(trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrazole (1), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

## 5. NMR spectra of compounds (IV, 1-23)

Supplementary Figure S2 (Scheme 1, Compound IV:  $^1\text{H}$  NMR)

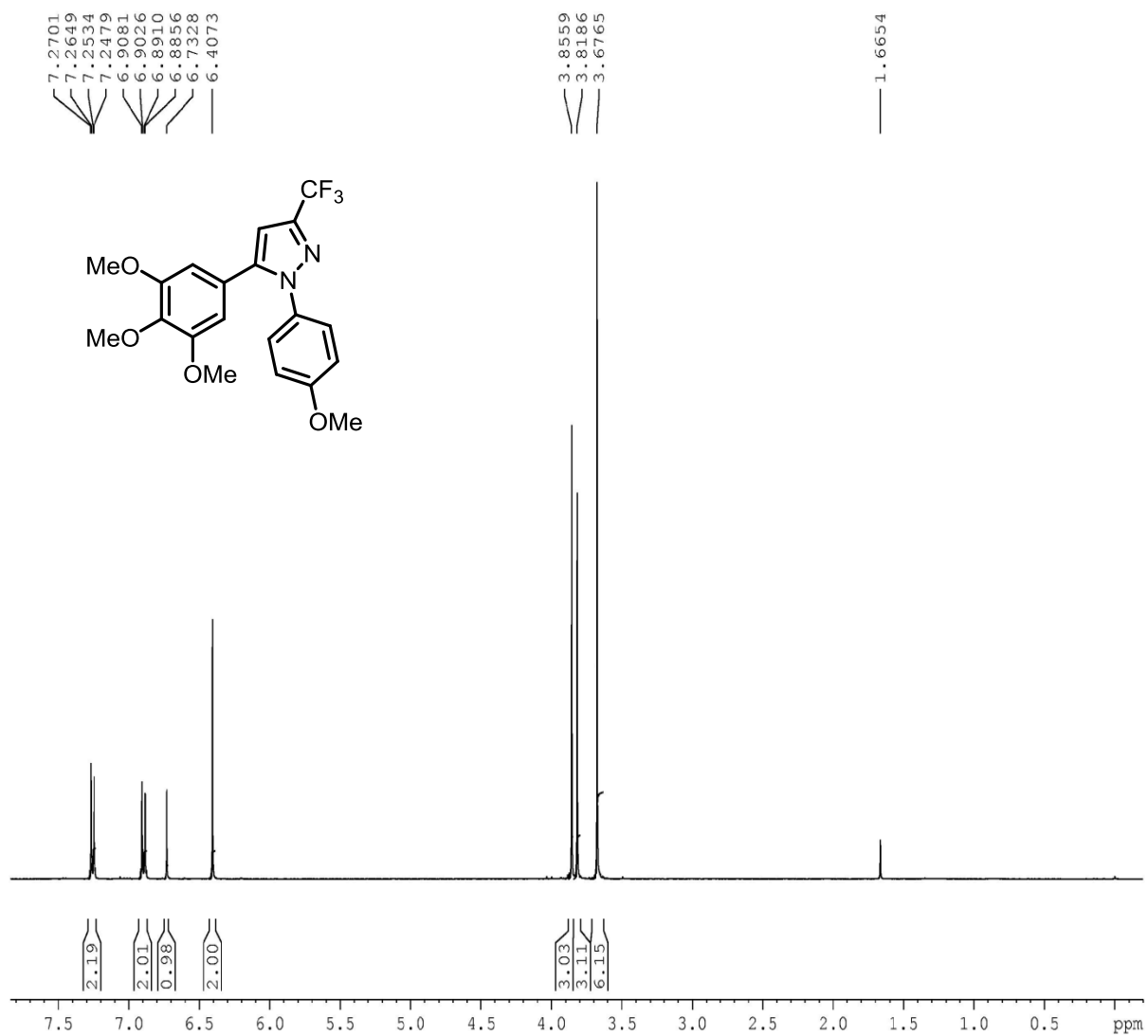


Supplementary Figure S3 (Scheme 1, Compound IV:  $^{13}\text{C}$  NMR)

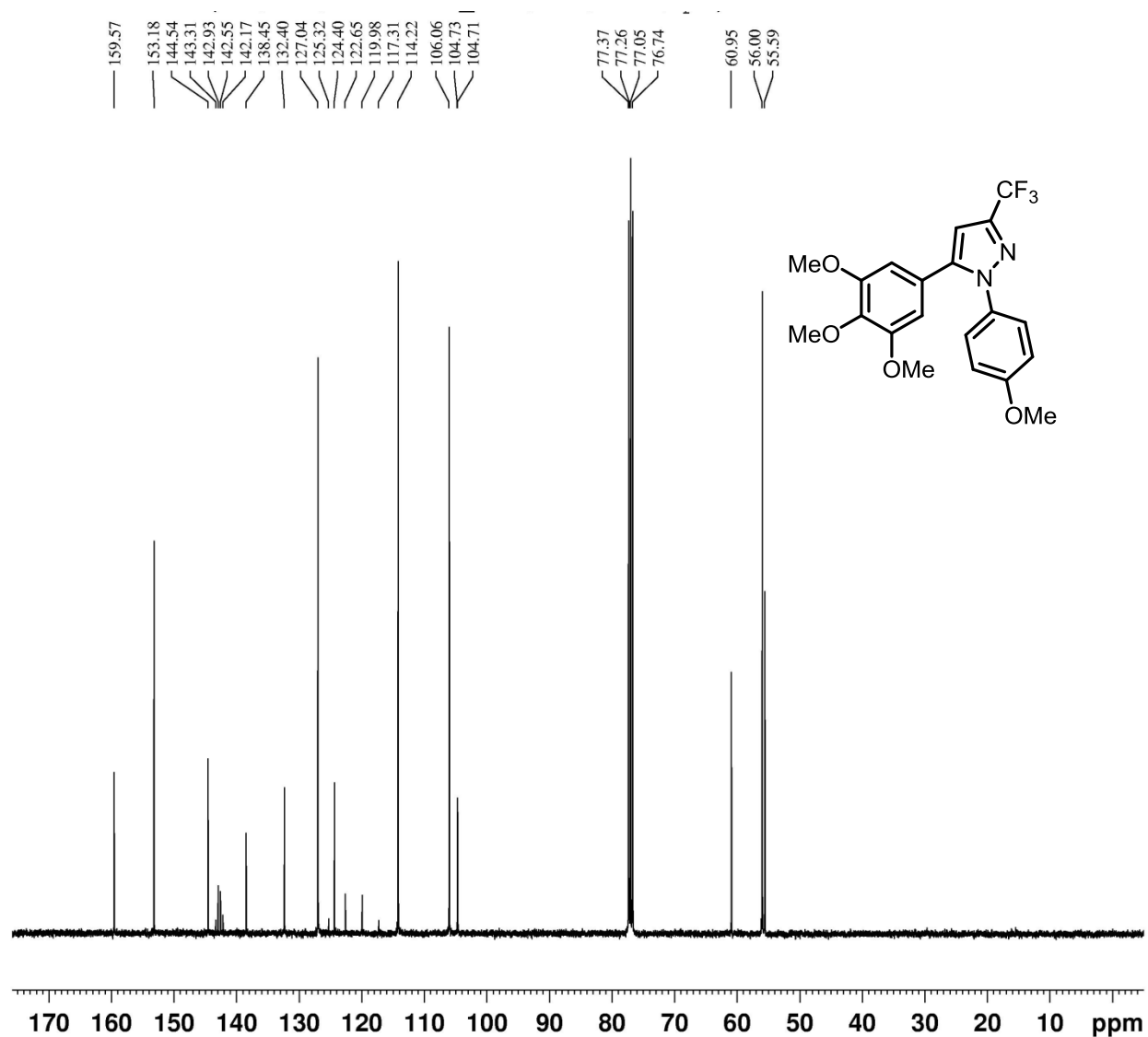




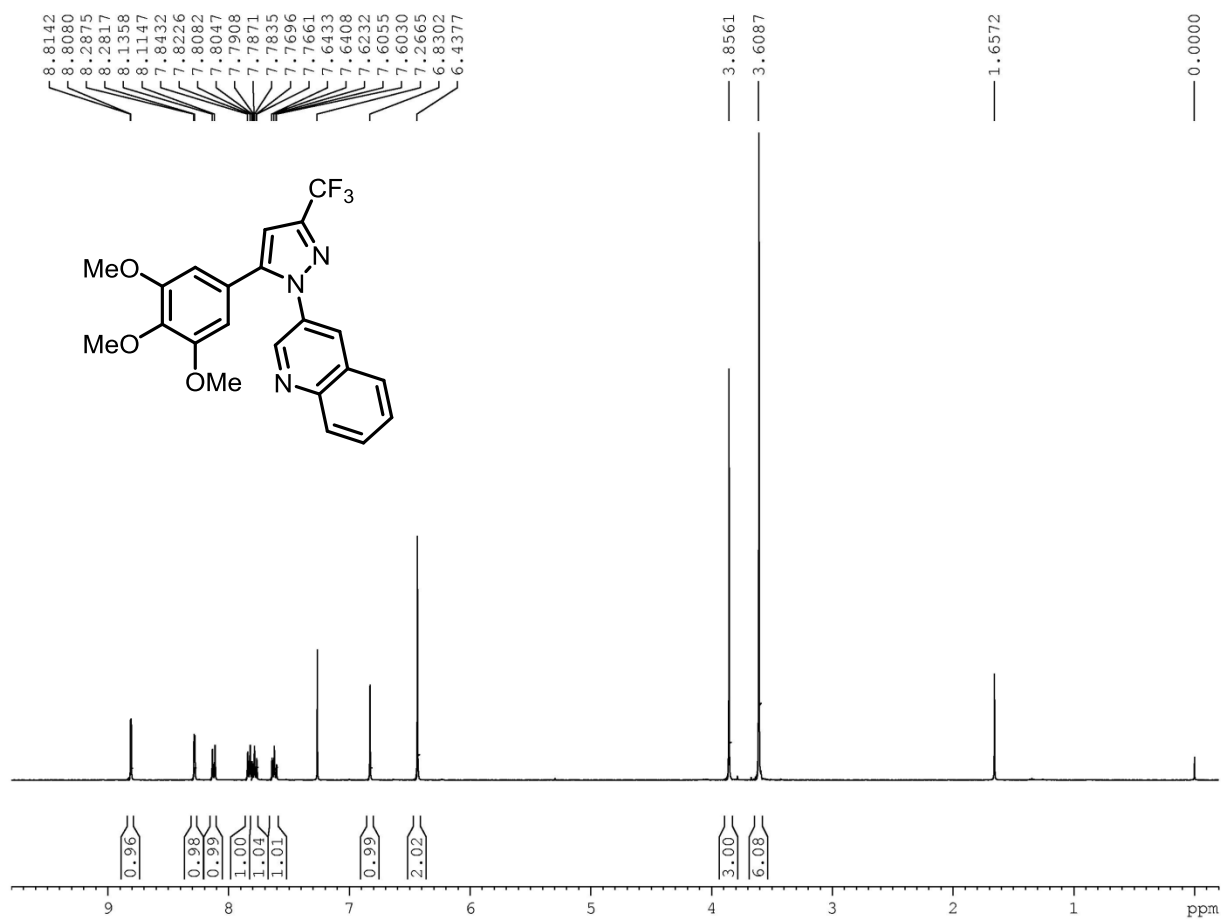
Supplementary Figure S4 (Table 1, Entry 1 (1):  $^1\text{H}$  NMR)



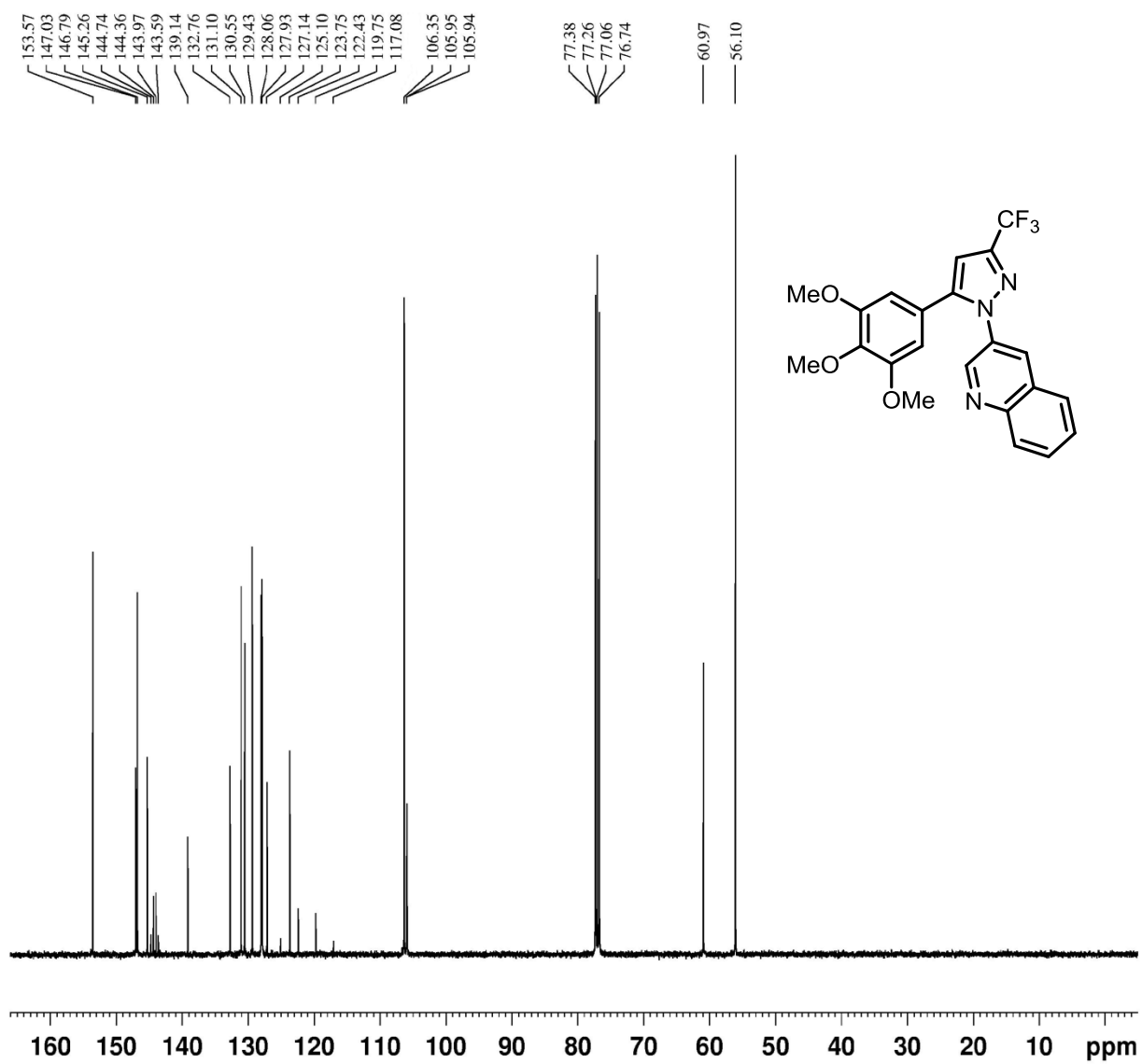
Supplementary Figure S5 (Table 1, Entry 1 (1):  $^{13}\text{C}$  NMR)



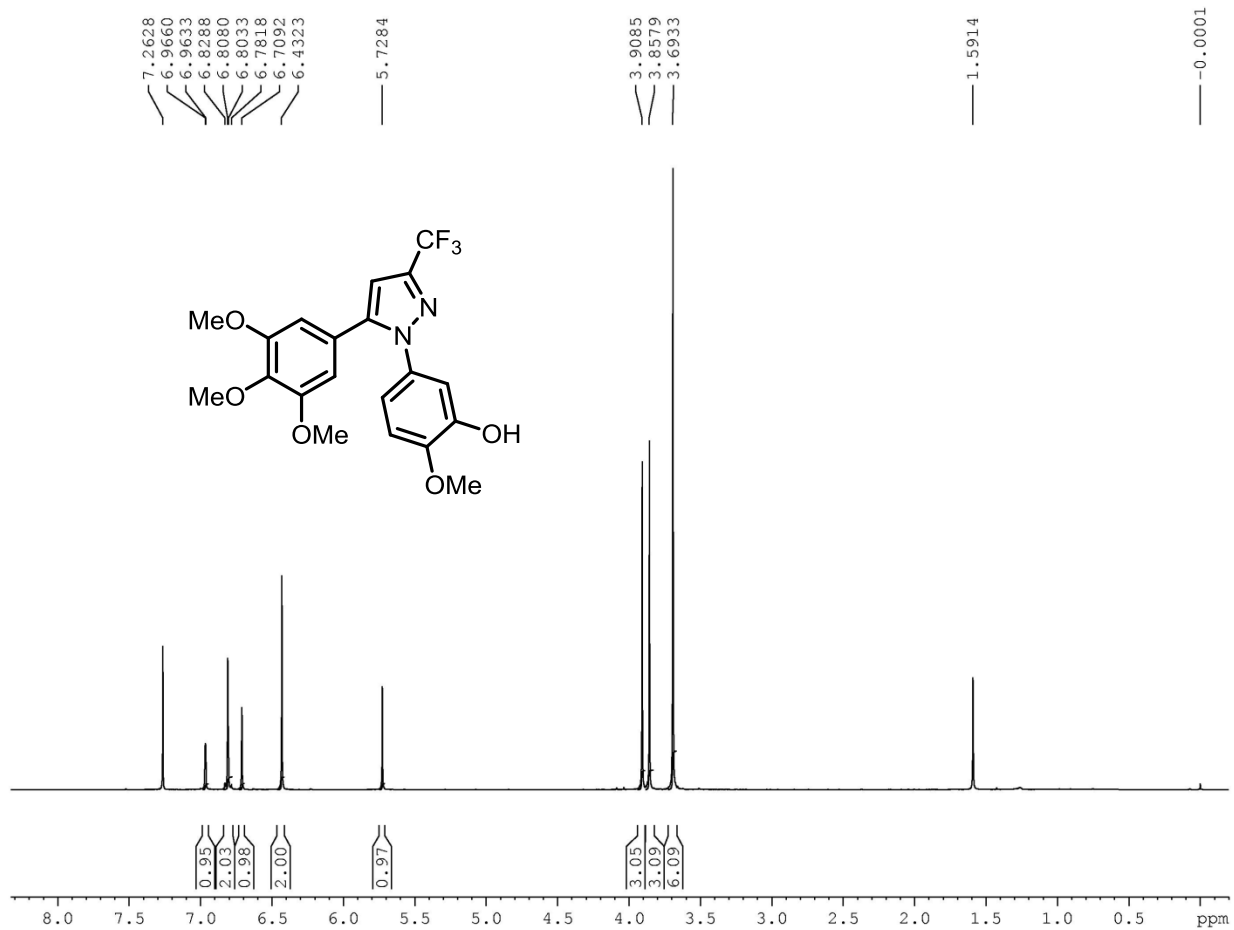
Supplementary Figure S6 (Table 1, Entry 2 (2):  $^1\text{H}$  NMR)



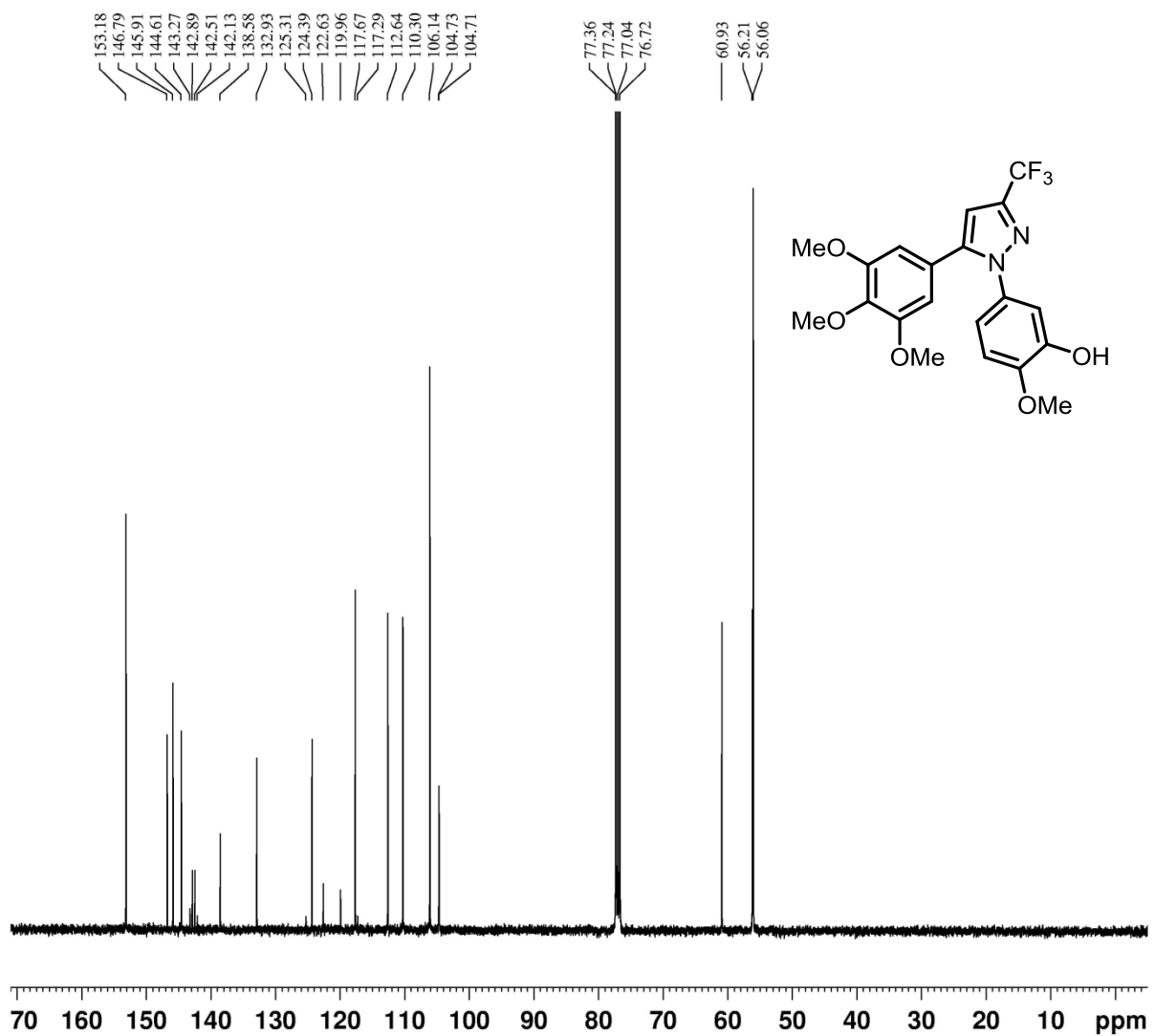
Supplementary Figure S7 (Table 1, Entry 2 (2):  $^{13}\text{C}$  NMR)



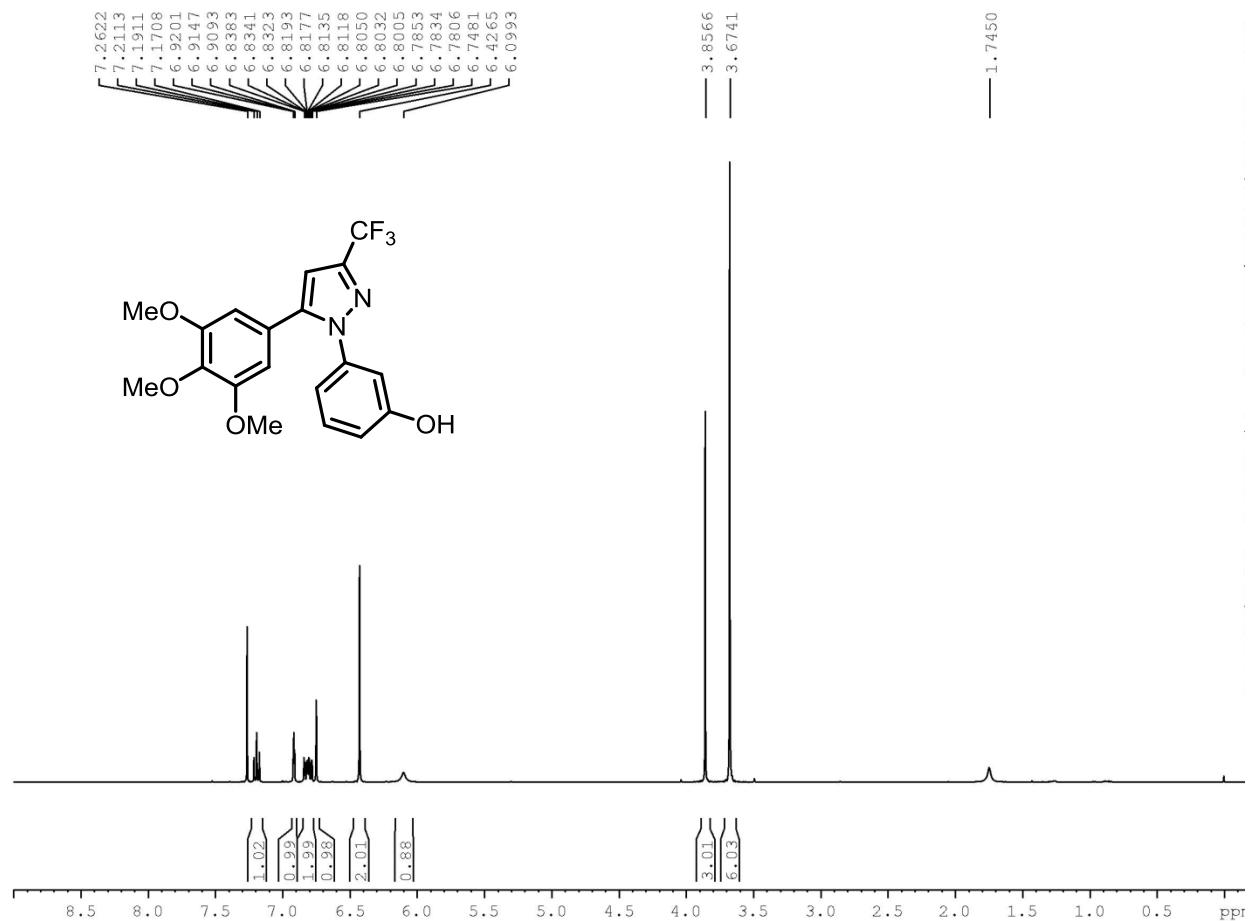
Supplementary Figure S8 (Table 1, Entry 3 (3):  $^1\text{H}$  NMR)



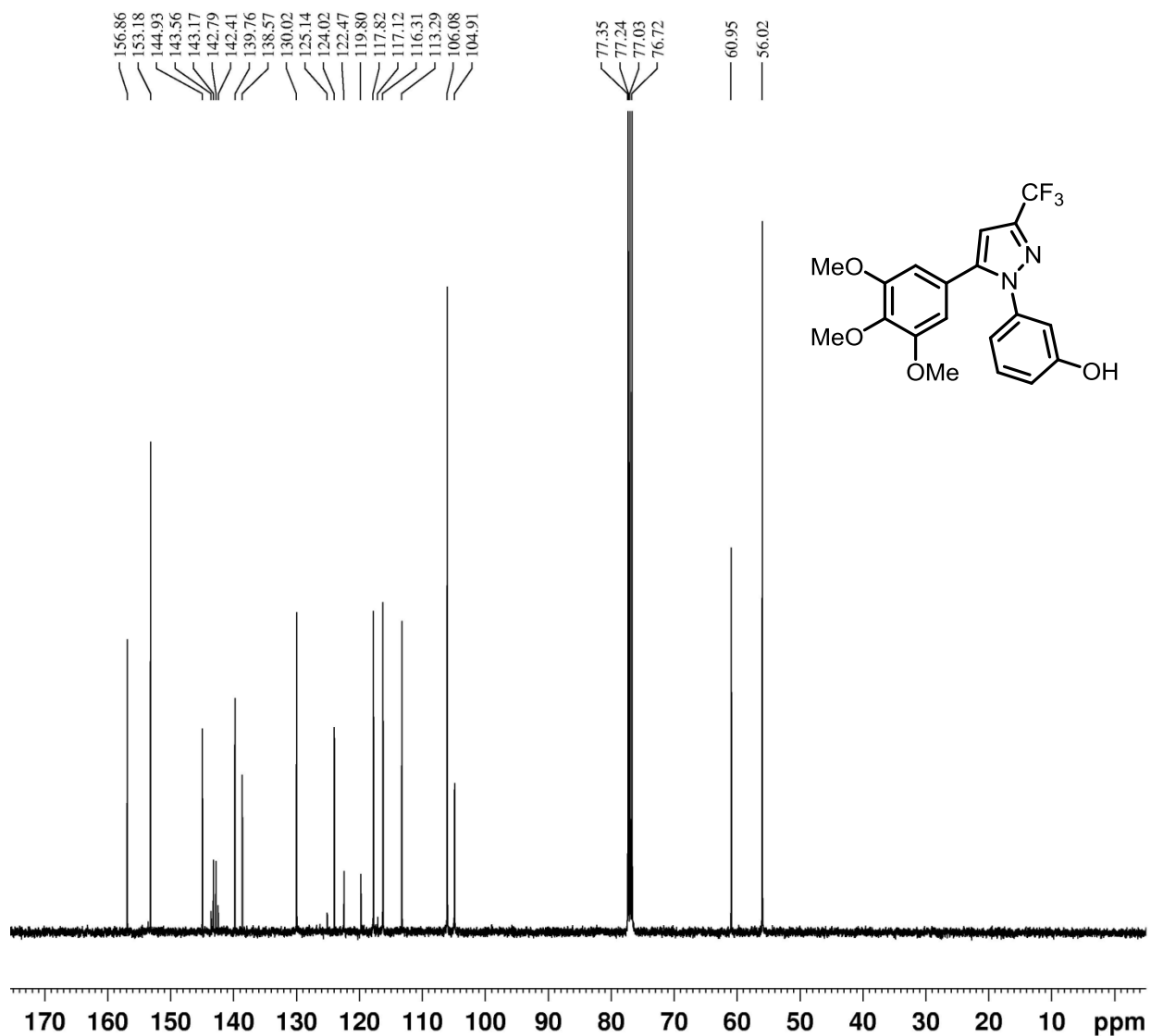
Supplementary Figure S9 (Table 1, Entry 3) ( $^{13}\text{C}$  NMR)



Supplementary Figure S10 (Table 1, Entry 4 (4):  $^1\text{H}$  NMR)

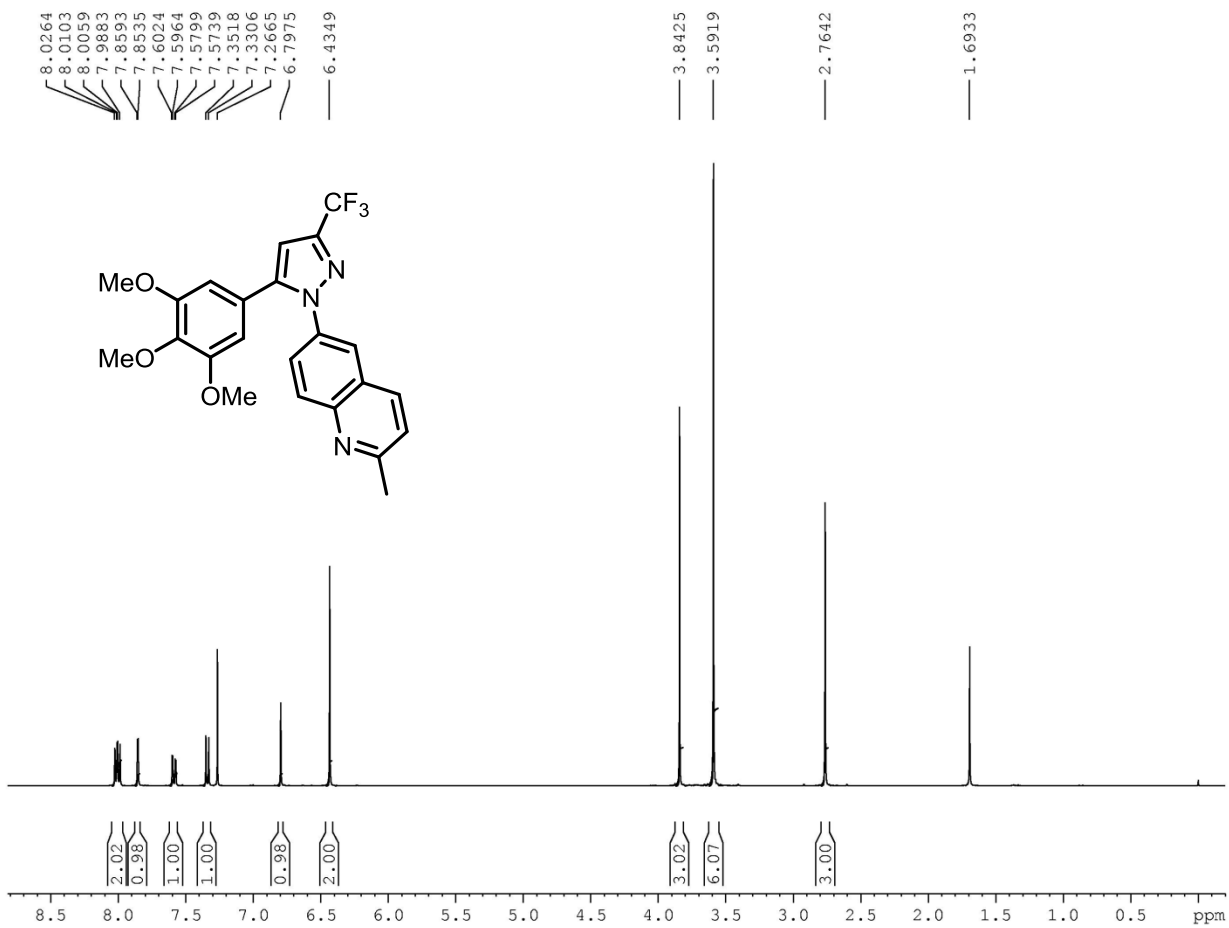


Supplementary Figure S11 (Table 1, Entry 4 (4):  $^{13}\text{C}$  NMR)

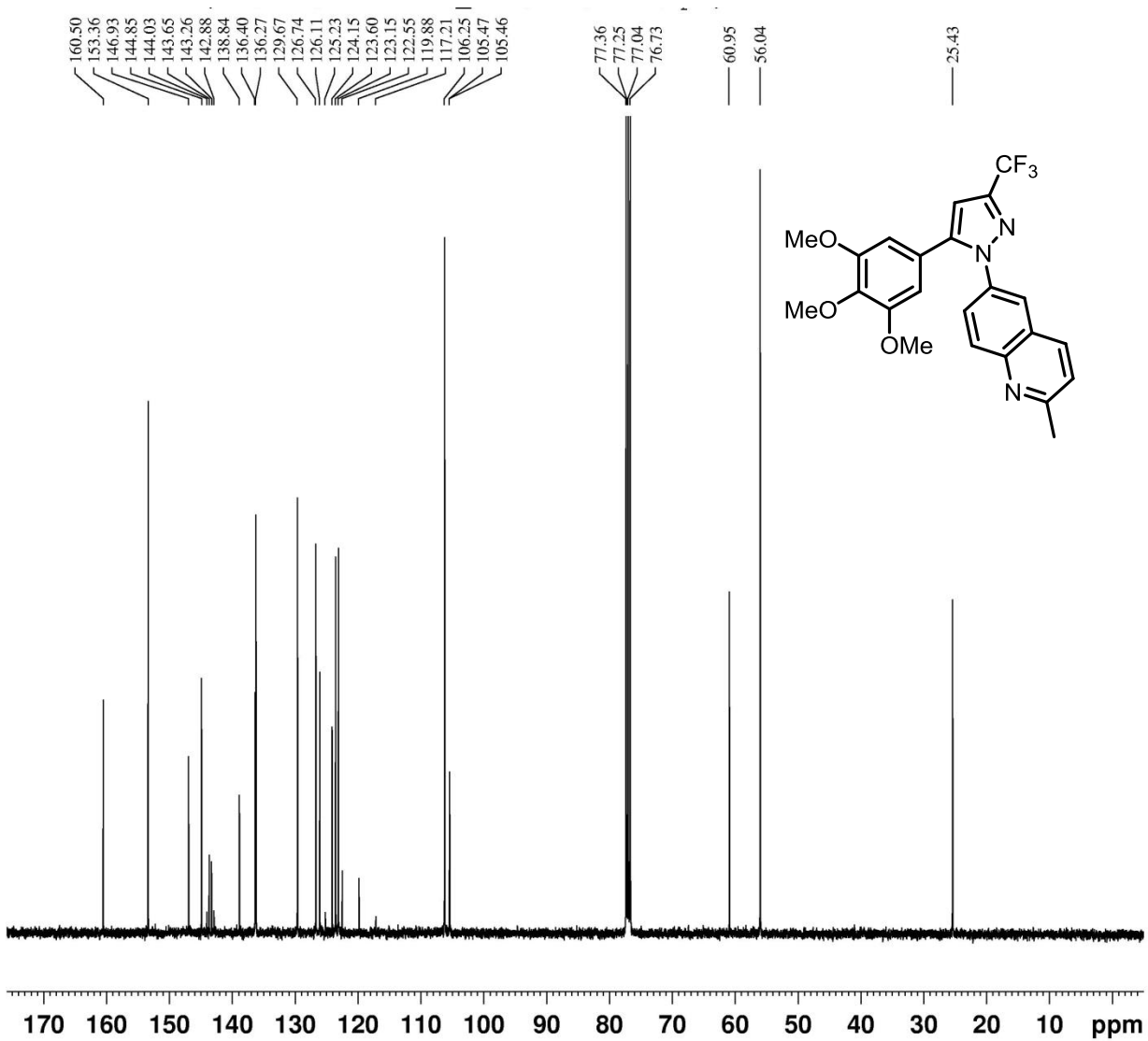




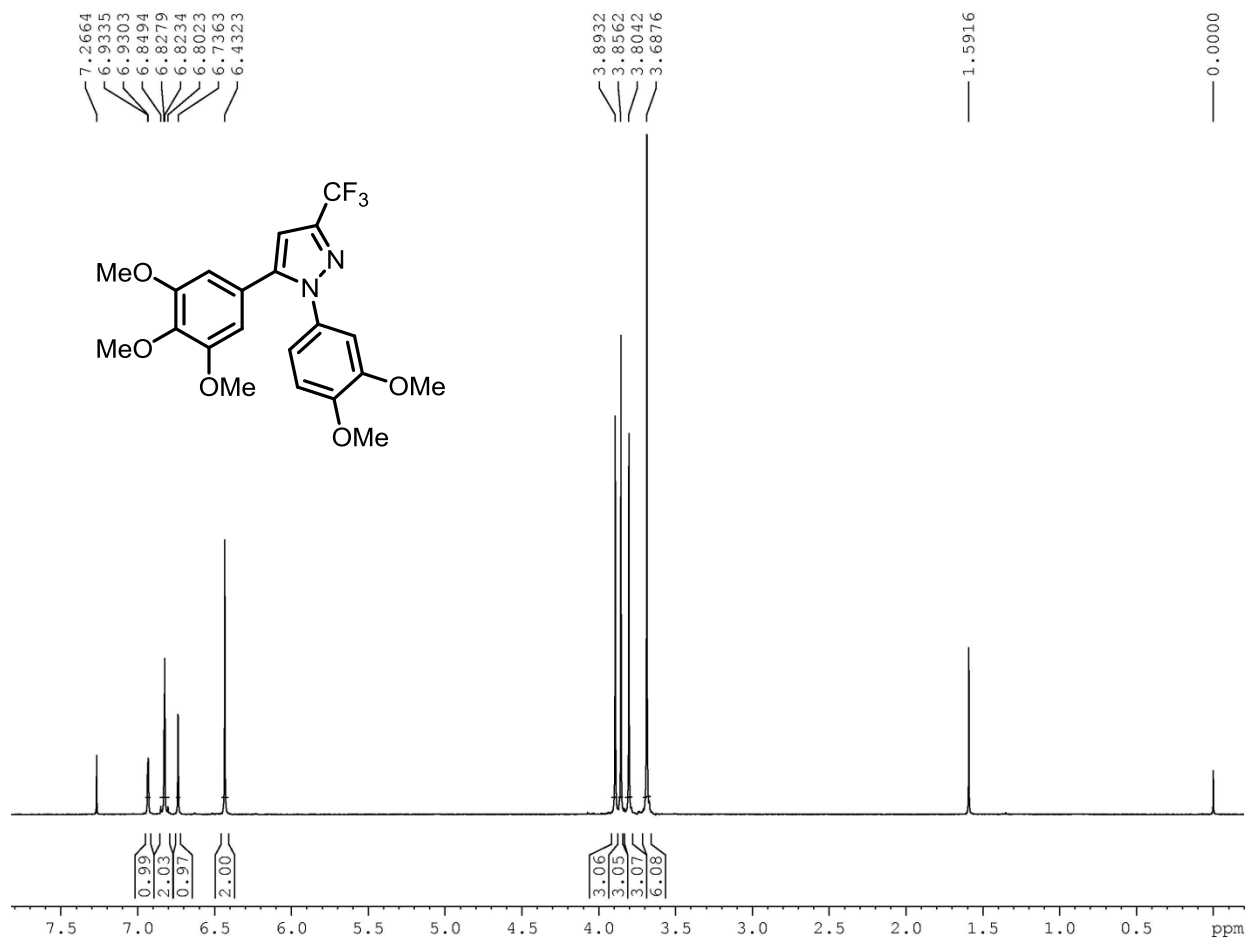
Supplementary Figure S12 (Table 1, Entry 5 (5):  $^1\text{H}$  NMR)



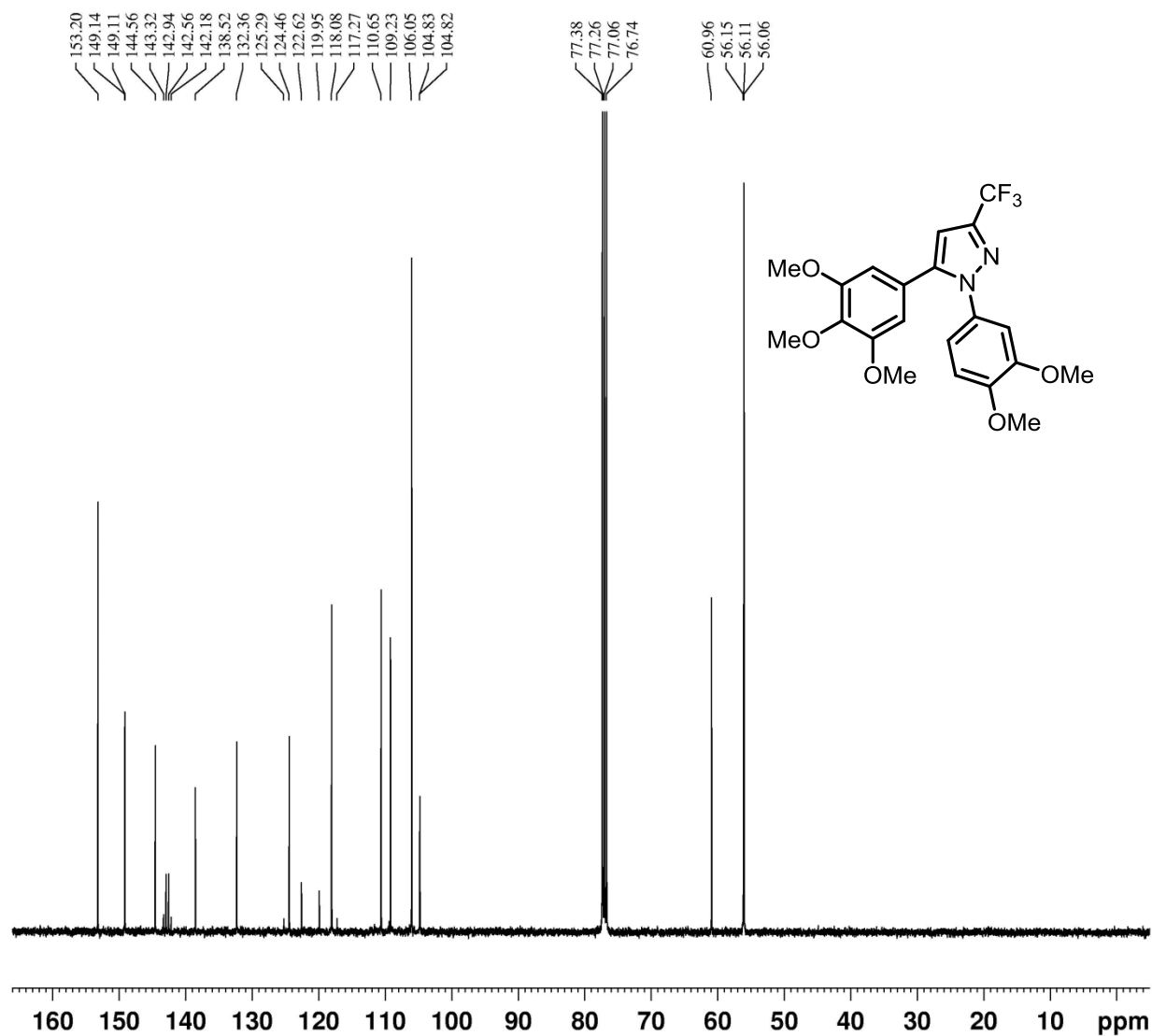
Supplementary Figure S13 (Table 1, Entry 5 (5):  $^{13}\text{C}$  NMR)



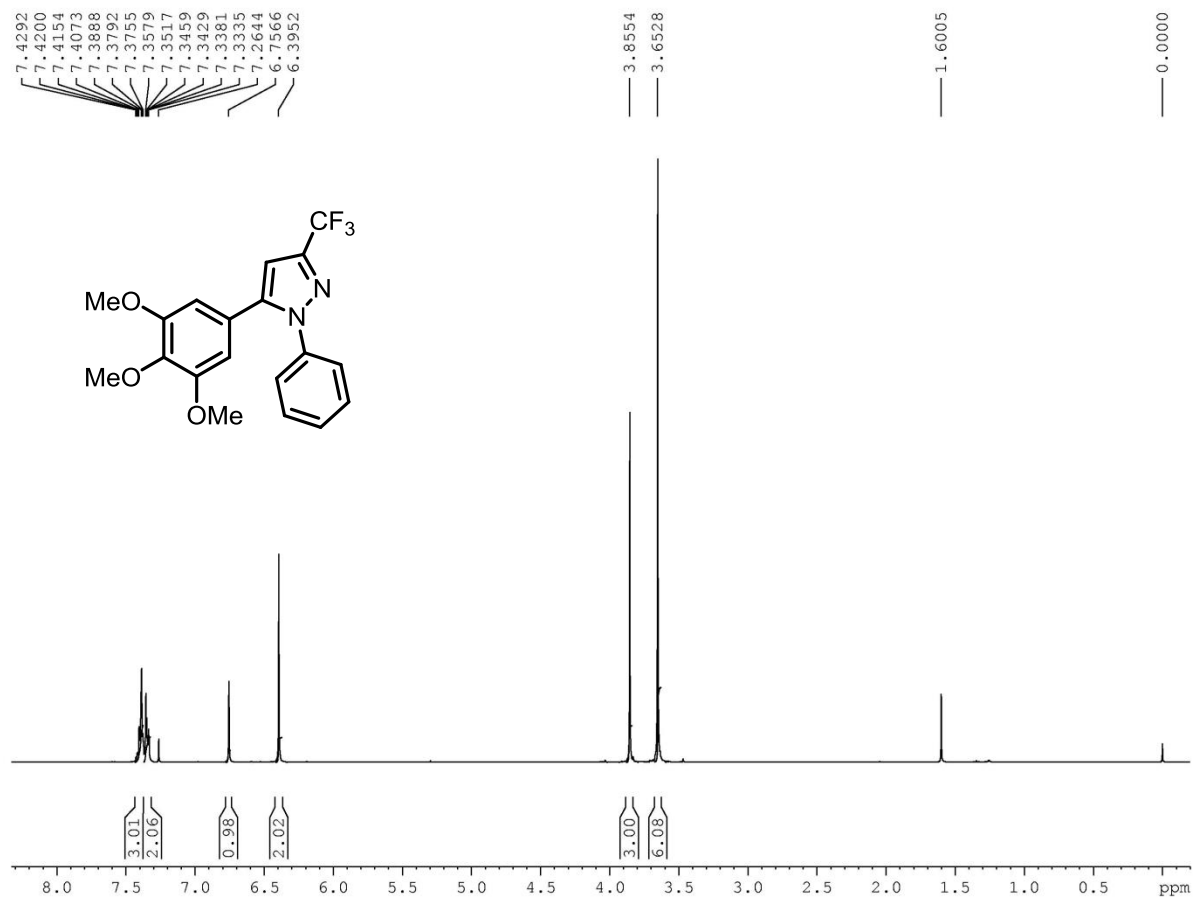
Supplementary Figure S14 (Table 1, Entry 6 (6):  $^1\text{H}$  NMR)



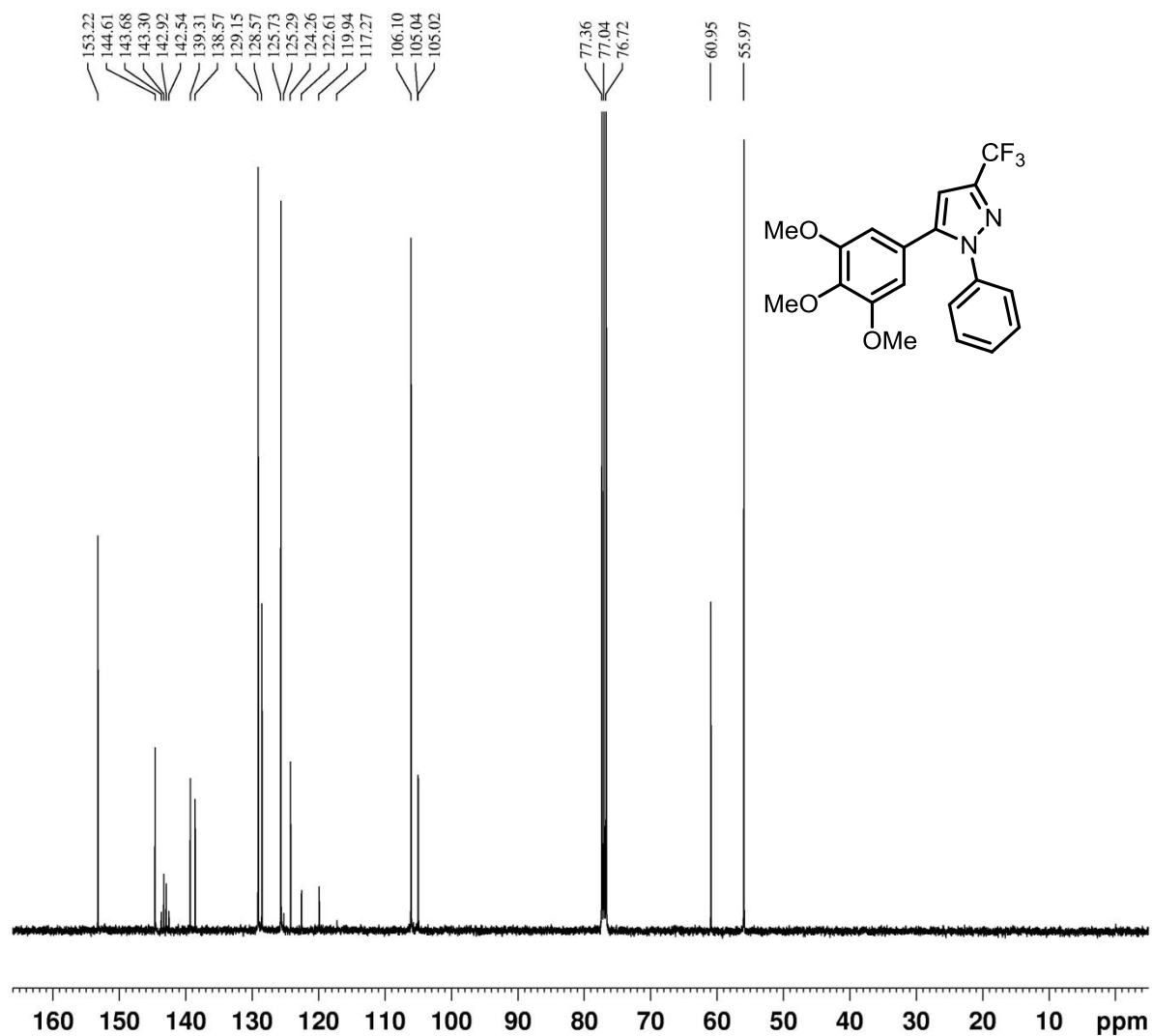
Supplementary Figure S15 (Table 1, Entry 6 (6):  $^{13}\text{C}$  NMR)



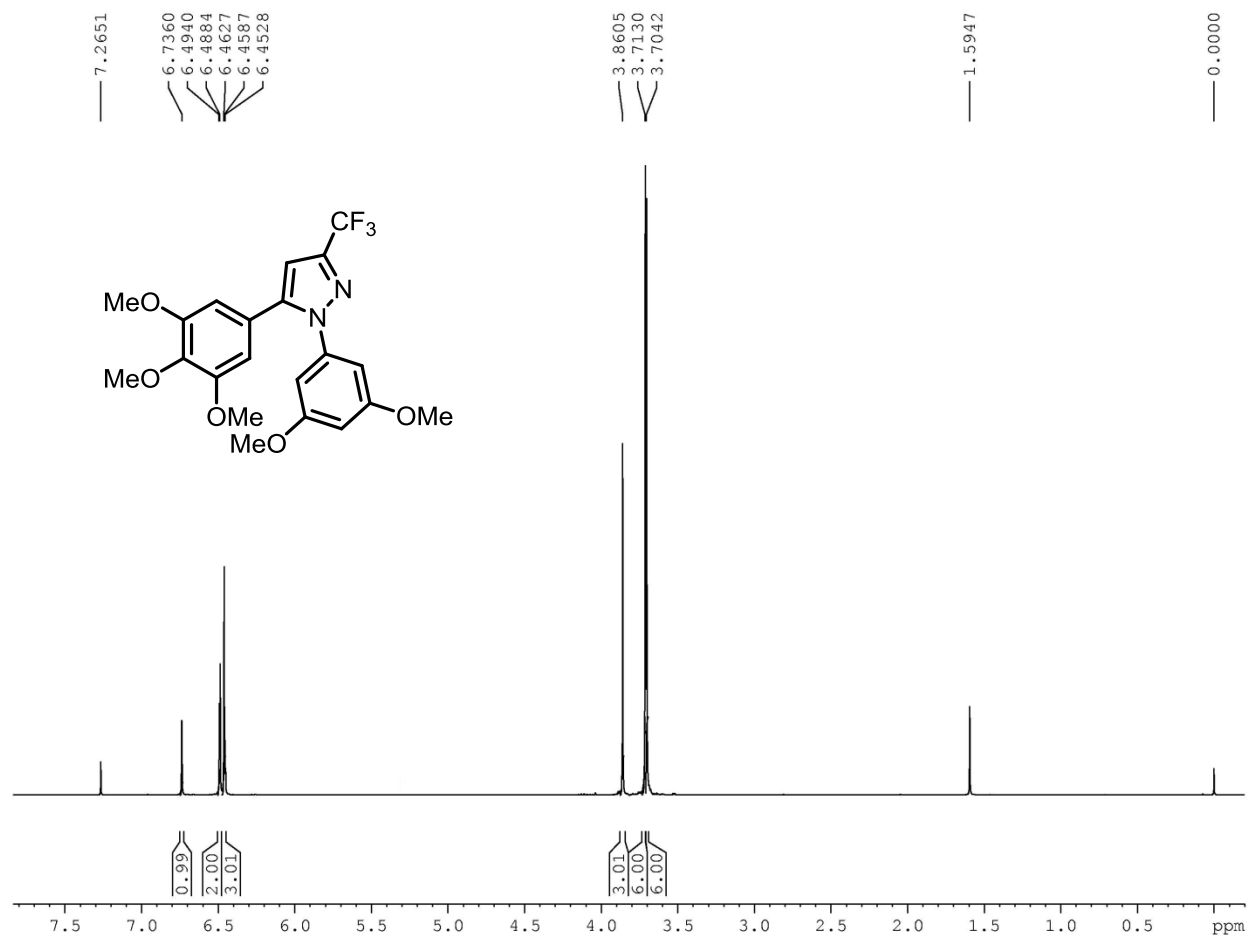
Supplementary Figure S16 (Table 1, Entry 7 (7):  $^1\text{H}$  NMR)



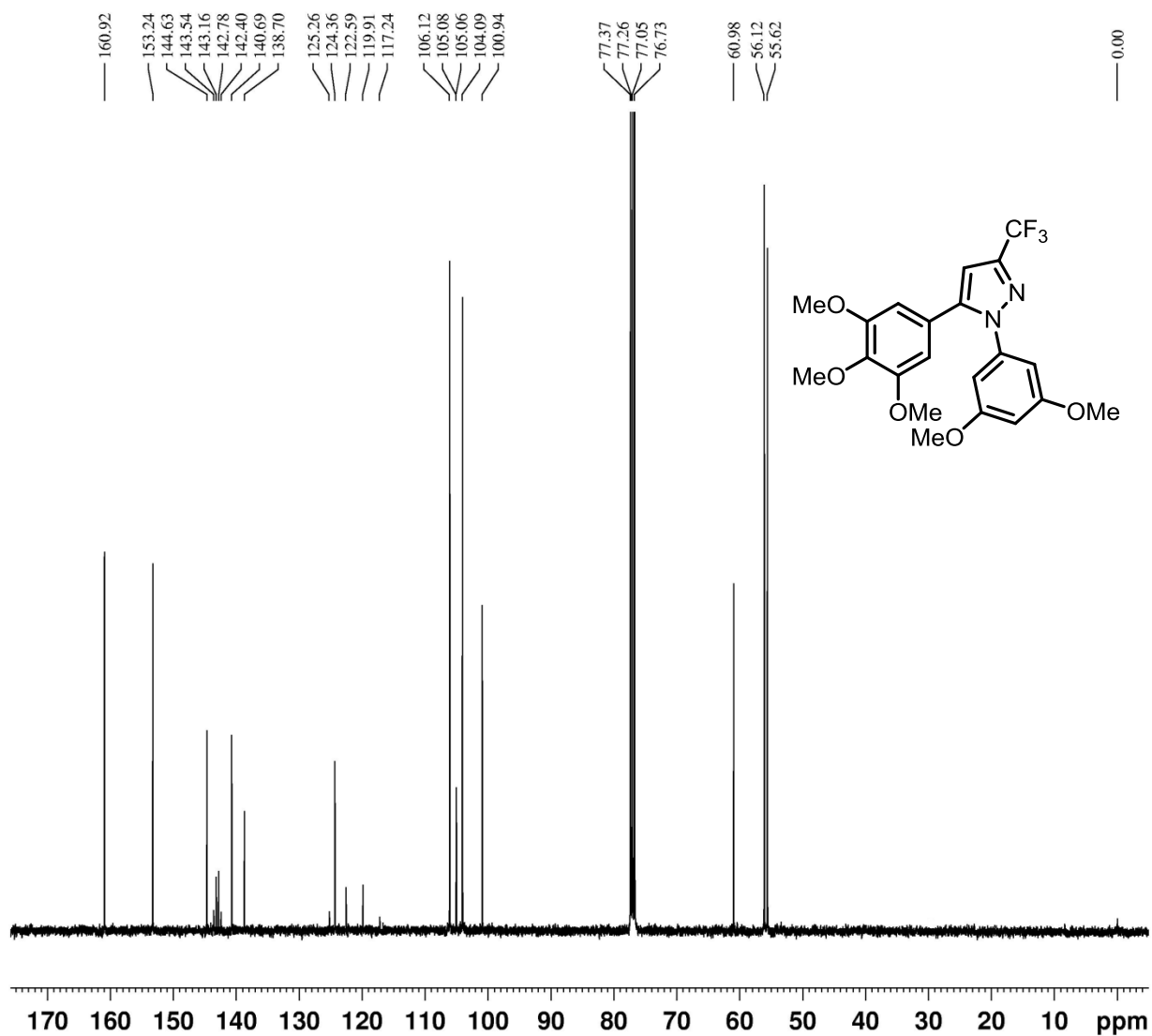
Supplementary Figure S17 (Table 1, Entry 7 (7):  $^{13}\text{C}$  NMR)



Supplementary Figure S18 (Table 1, Entry 8 (8):  $^1\text{H}$  NMR)

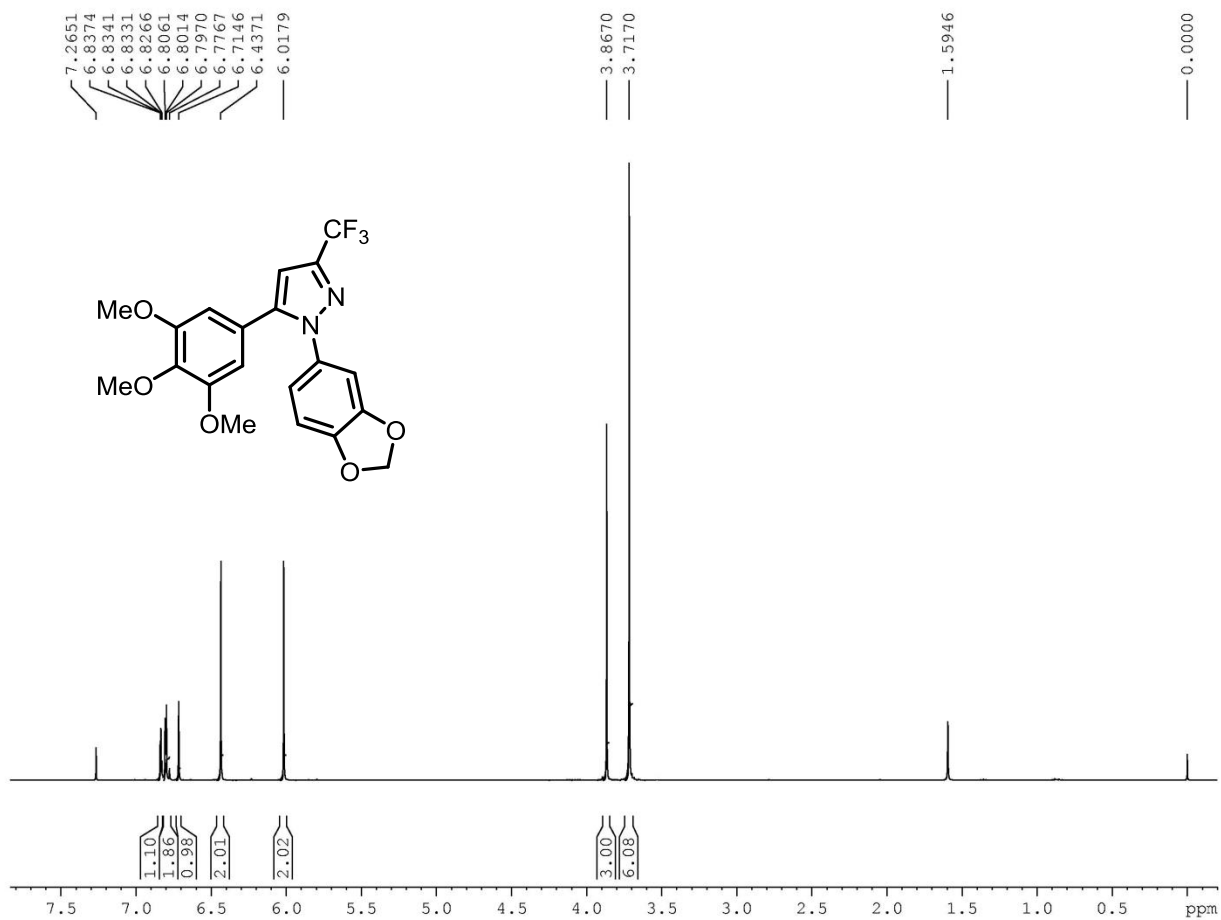


Supplementary Figure S19 (Table 1, Entry 8 (8):  $^{13}\text{C}$  NMR)

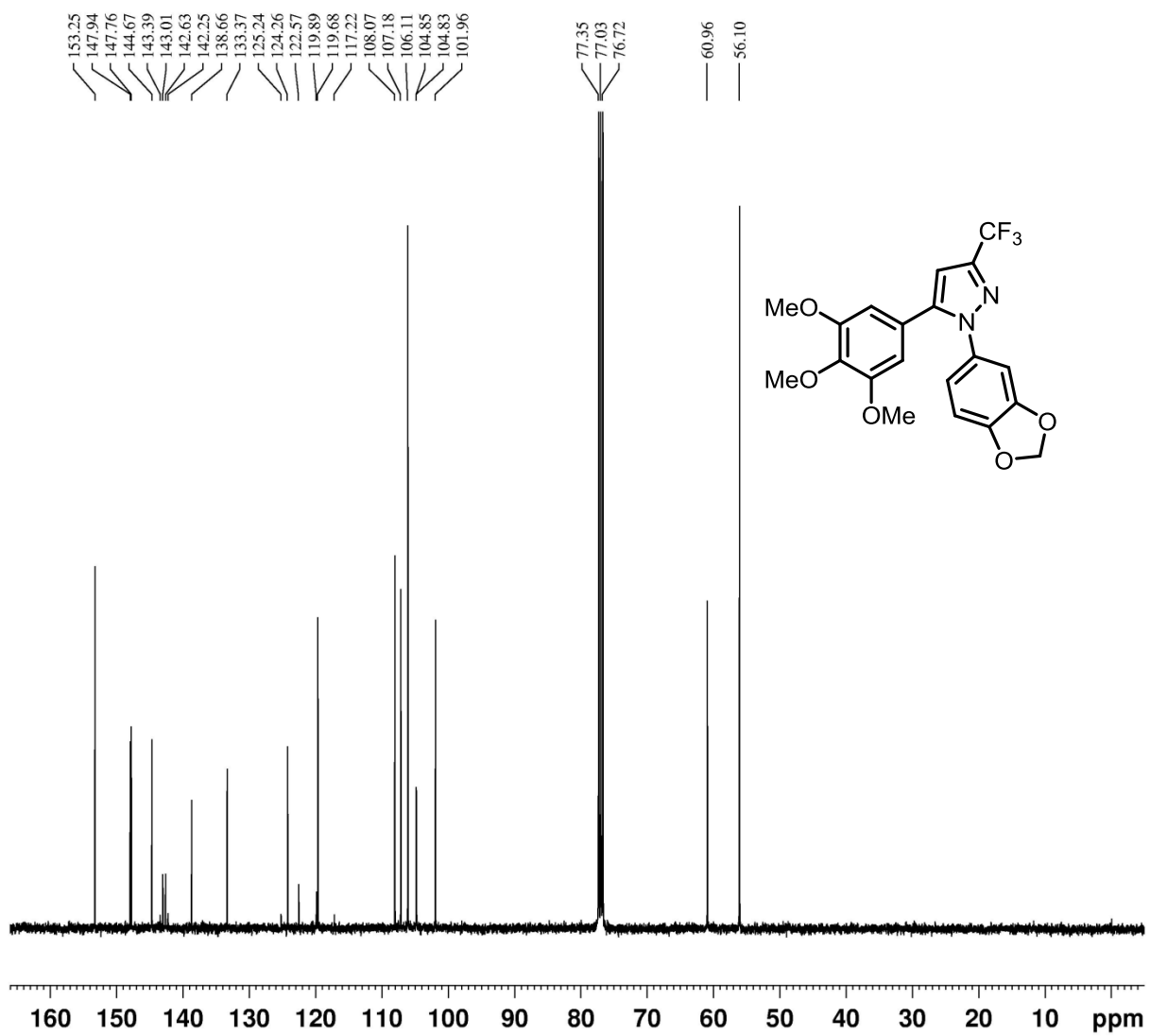




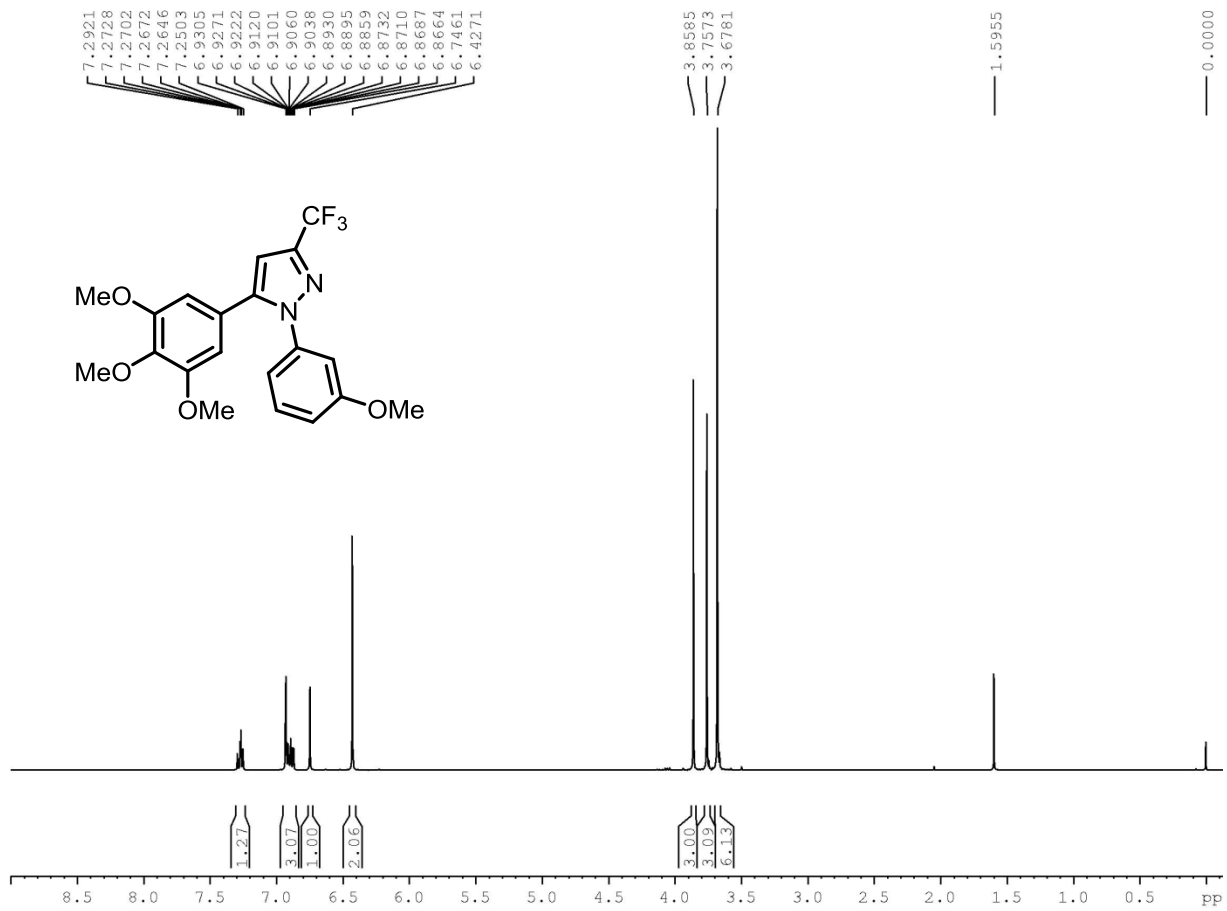
Supplementary Figure S20 (Table 1, Entry 9 (9): <sup>1</sup>H NMR)



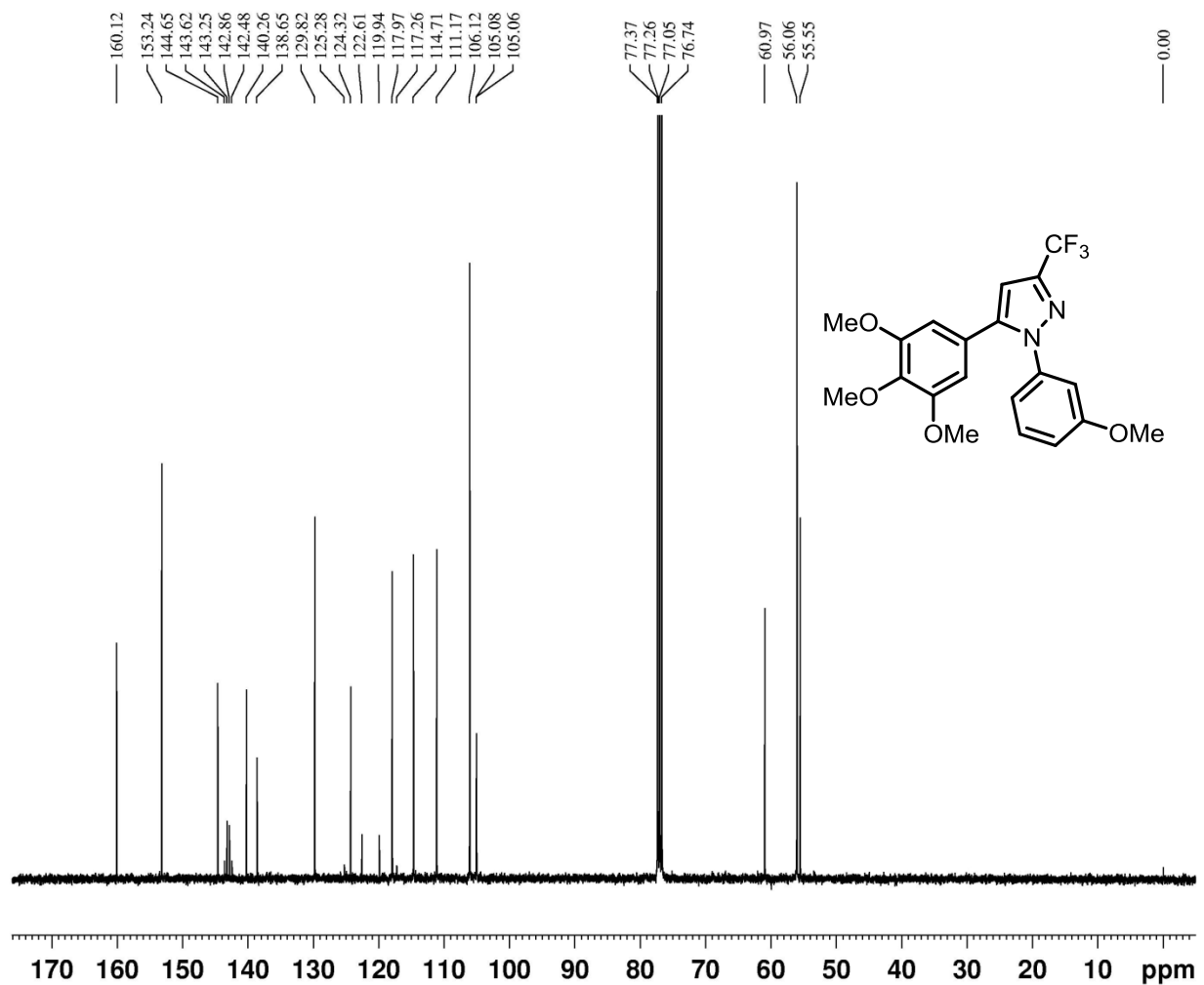
Supplementary Figure S21 (Table 1, Entry 9 (9):  $^{13}\text{C}$  NMR)



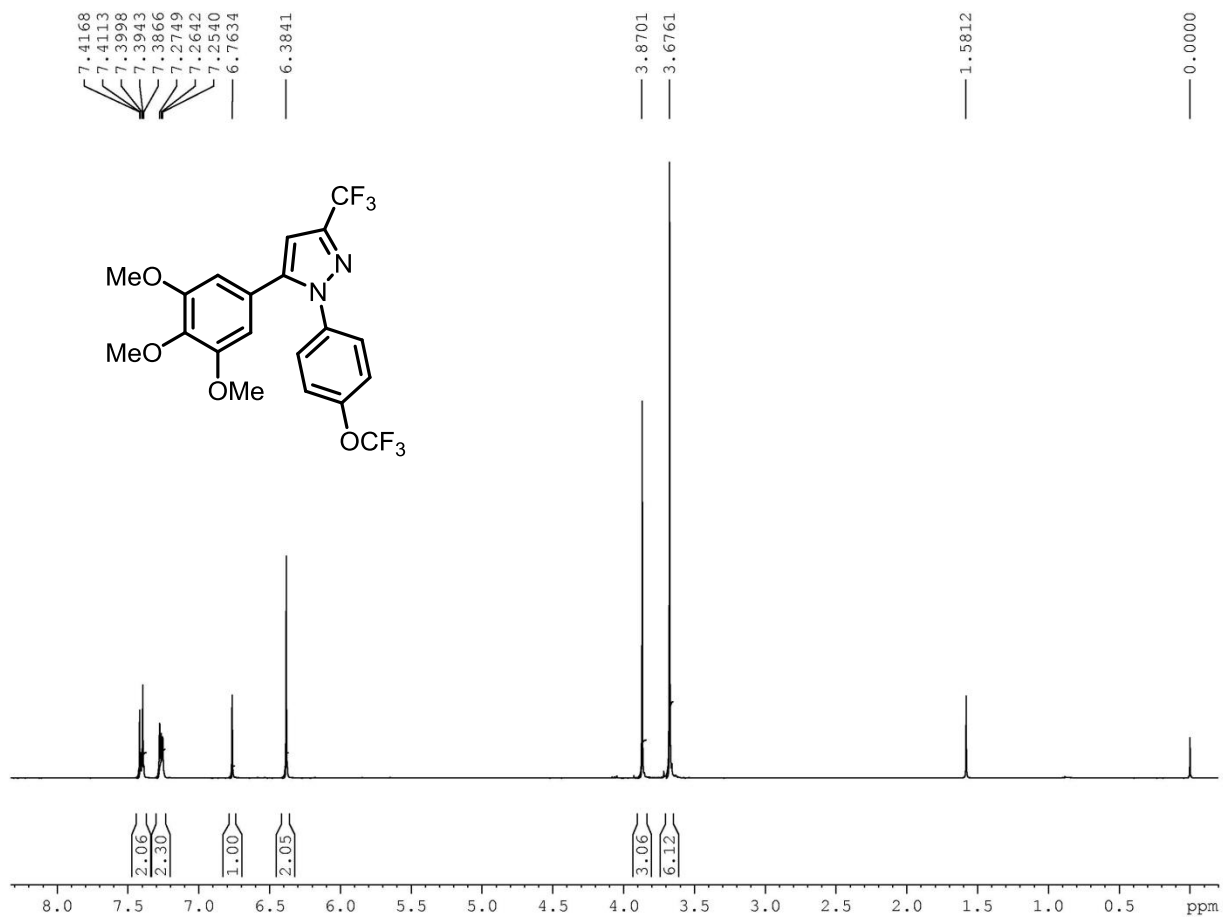
Supplementary Figure S22 (Table 1, Entry 10 (10): <sup>1</sup>H NMR)



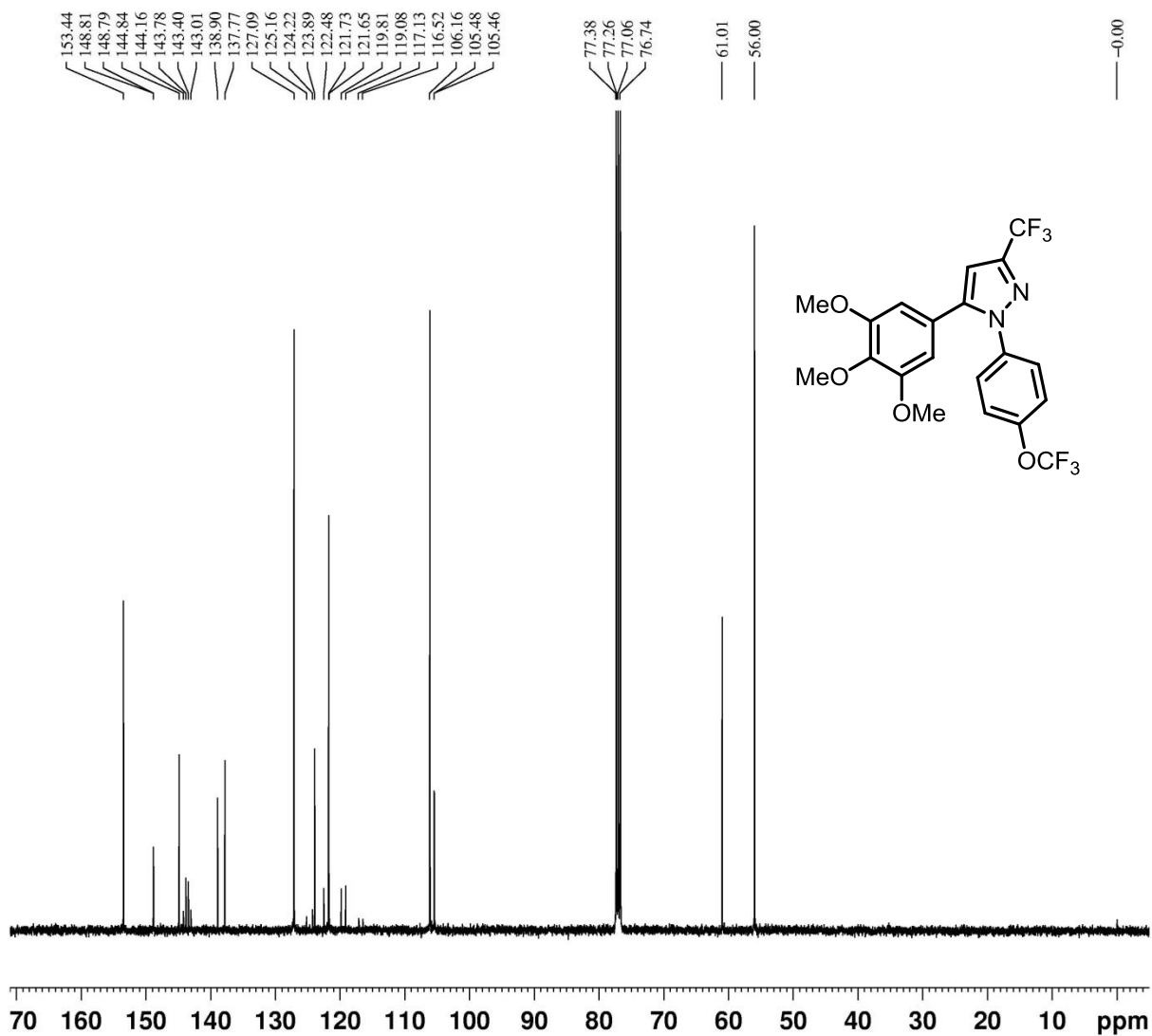
Supplementary Figure S23 (Table 1, Entry 10 (10):  $^{13}\text{C}$  NMR)



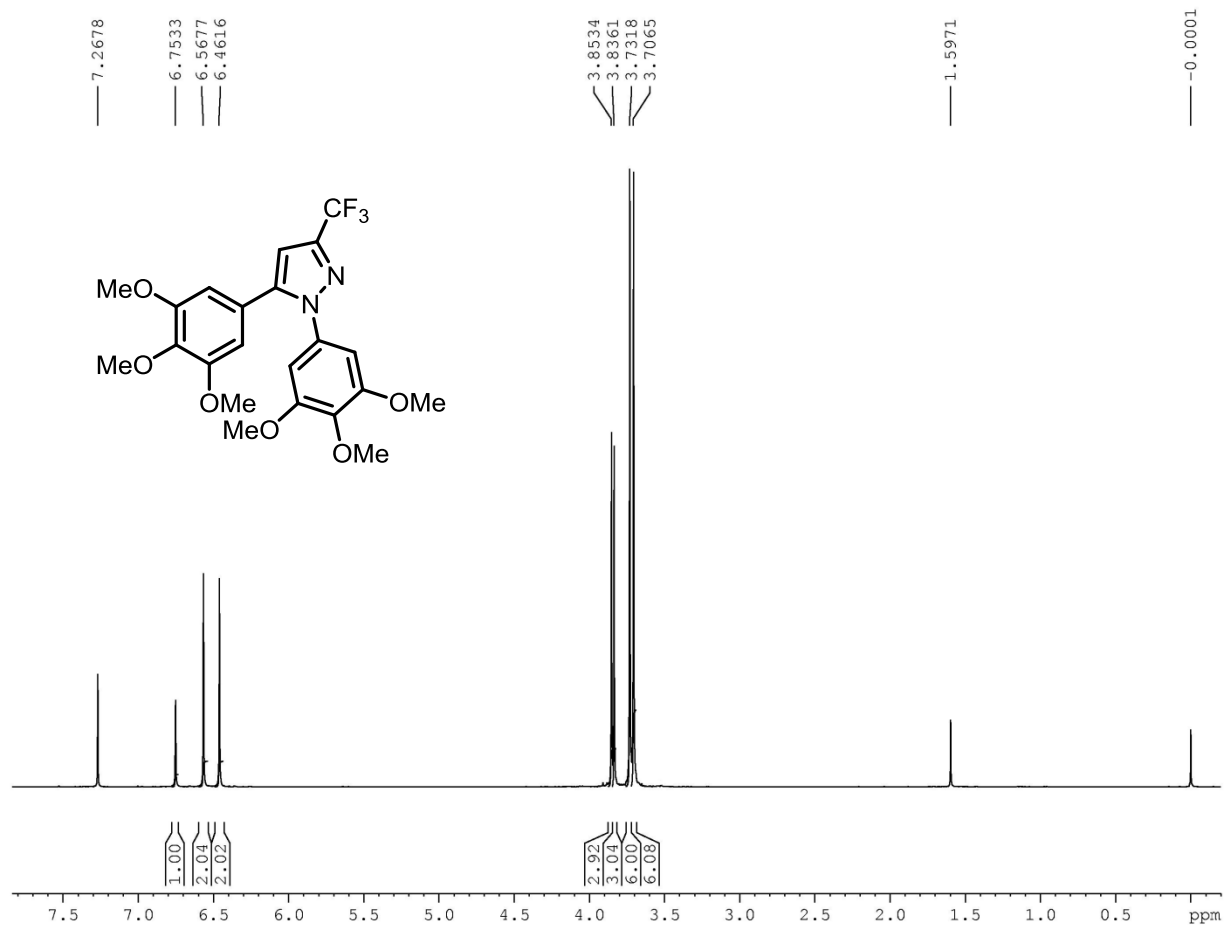
Supplementary Figure S24 (Table 1, Entry 11 (11): <sup>1</sup>H NMR)



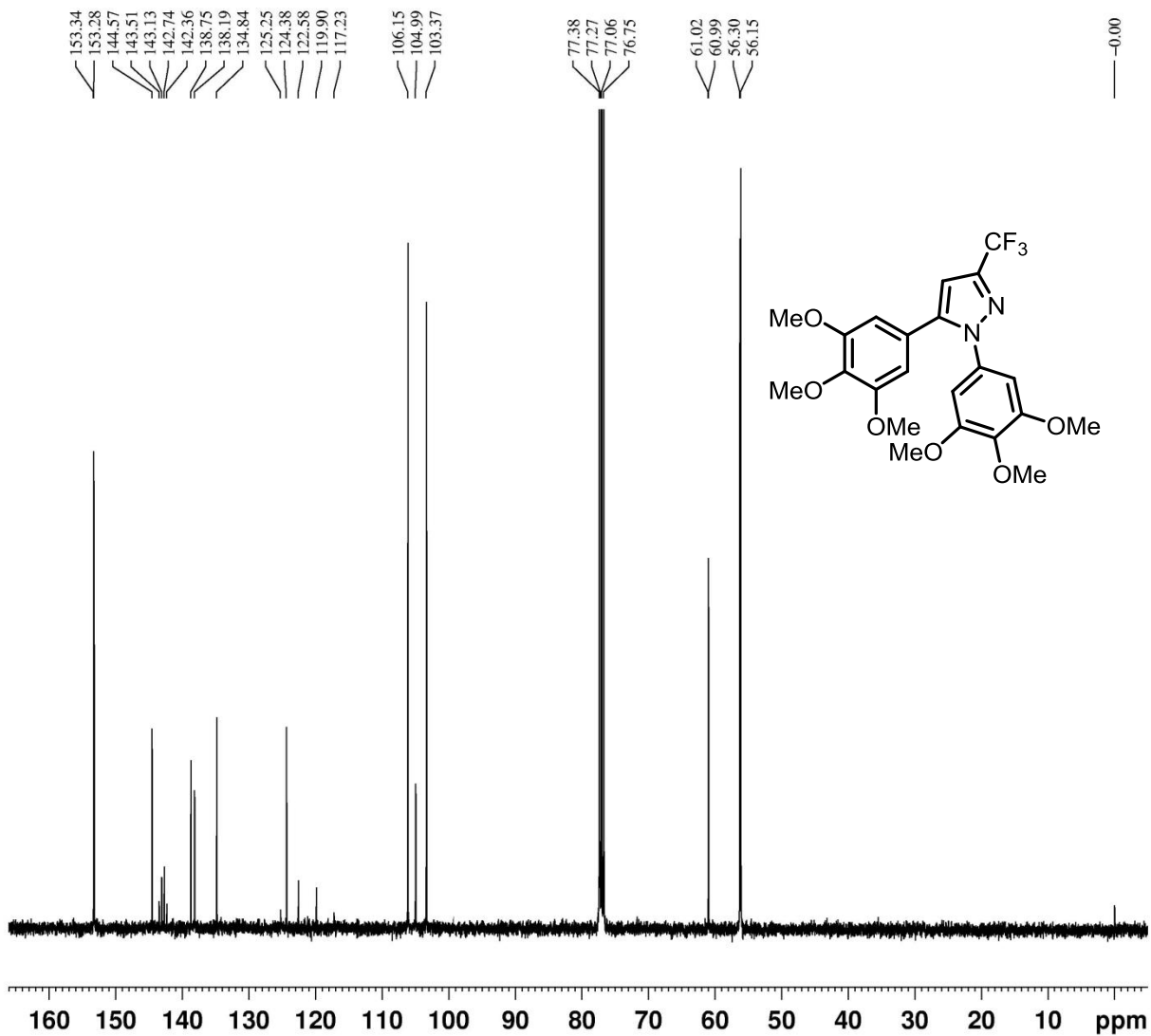
Supplementary Figure S25 (Table 1, Entry 11 (11): <sup>13</sup>C NMR)



Supplementary Figure S26 (Table 1, Entry 12 (12): <sup>1</sup>H NMR)

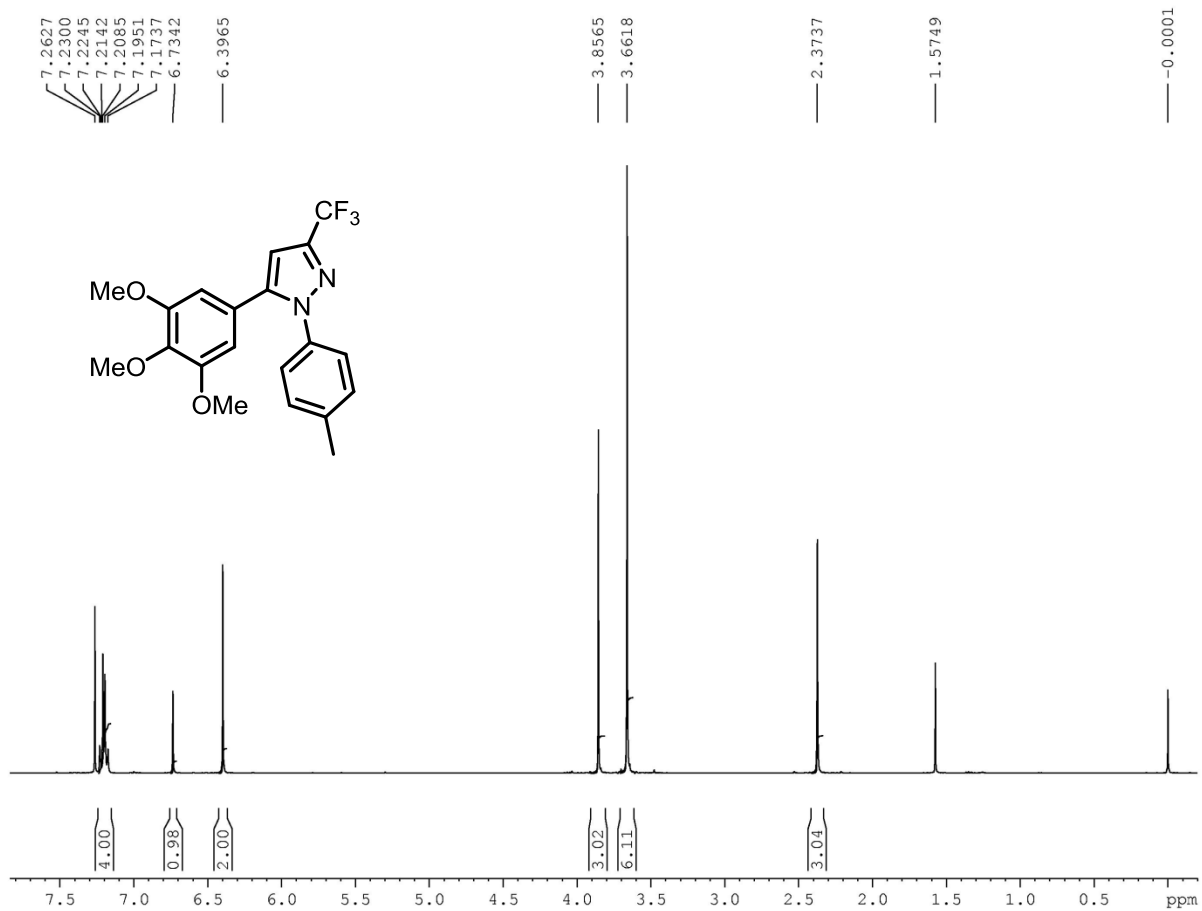


Supplementary Figure S27 (Table 1, Entry 12 (12): <sup>13</sup>C NMR)

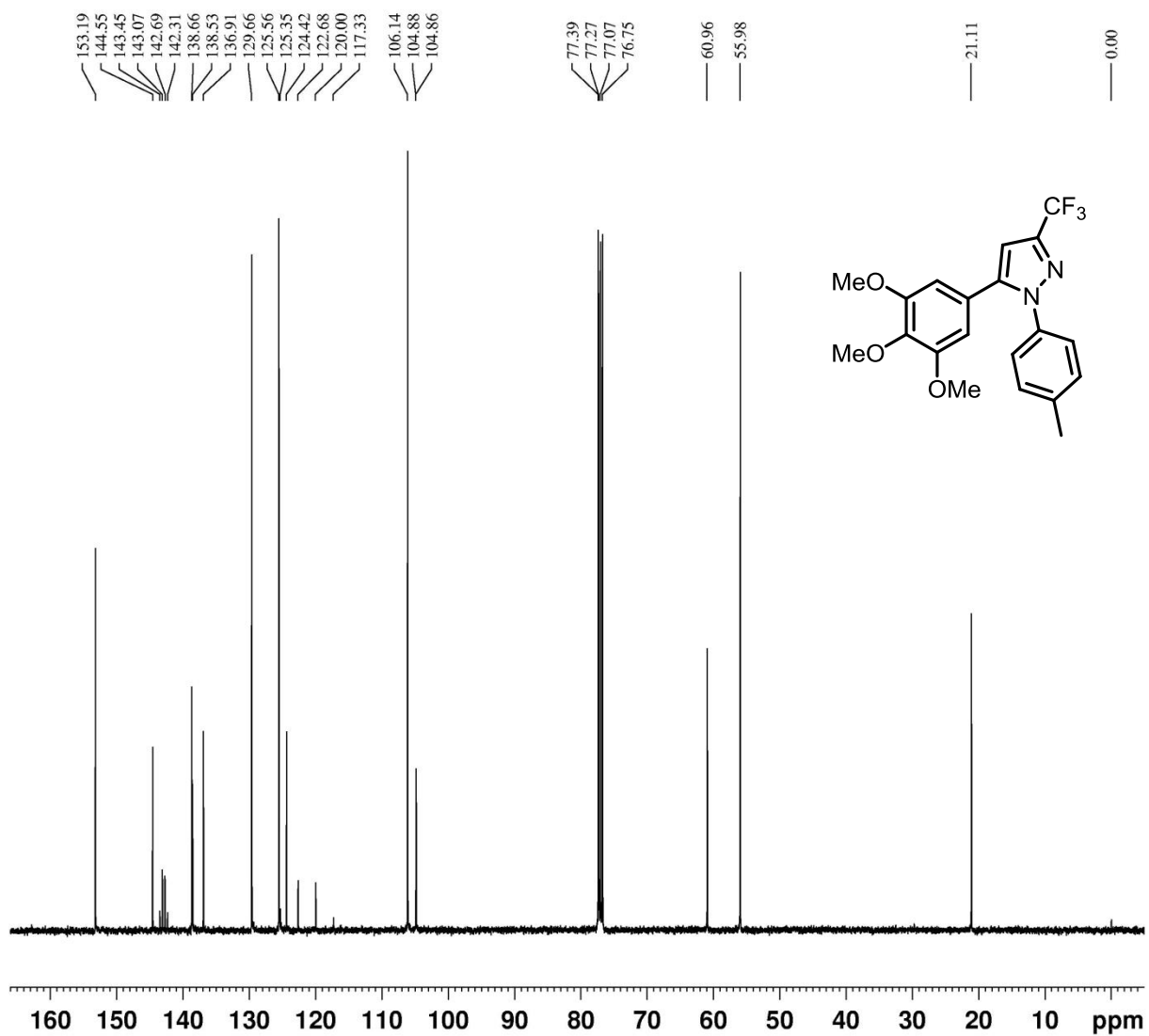




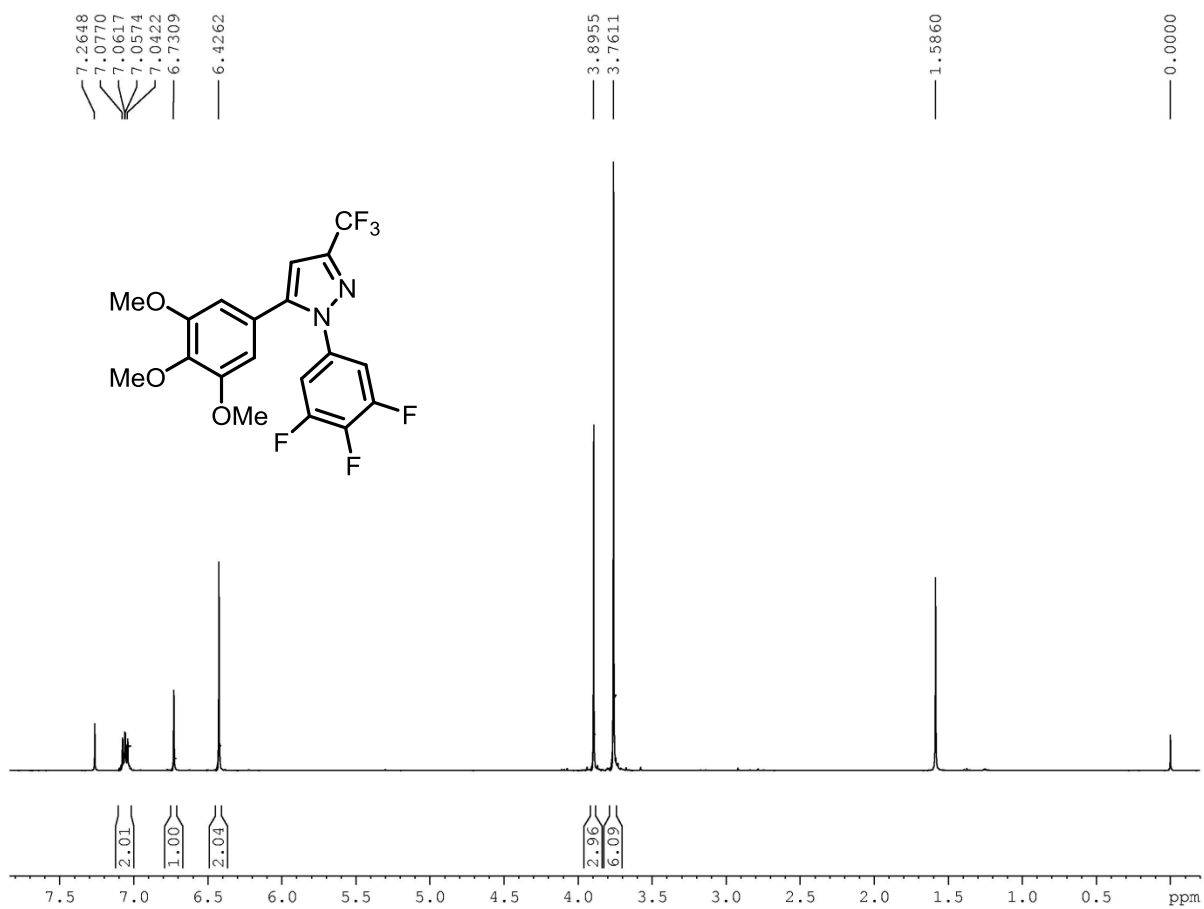
Supplementary Figure S28 (Table 1, Entry 13 (13): <sup>1</sup>H NMR)



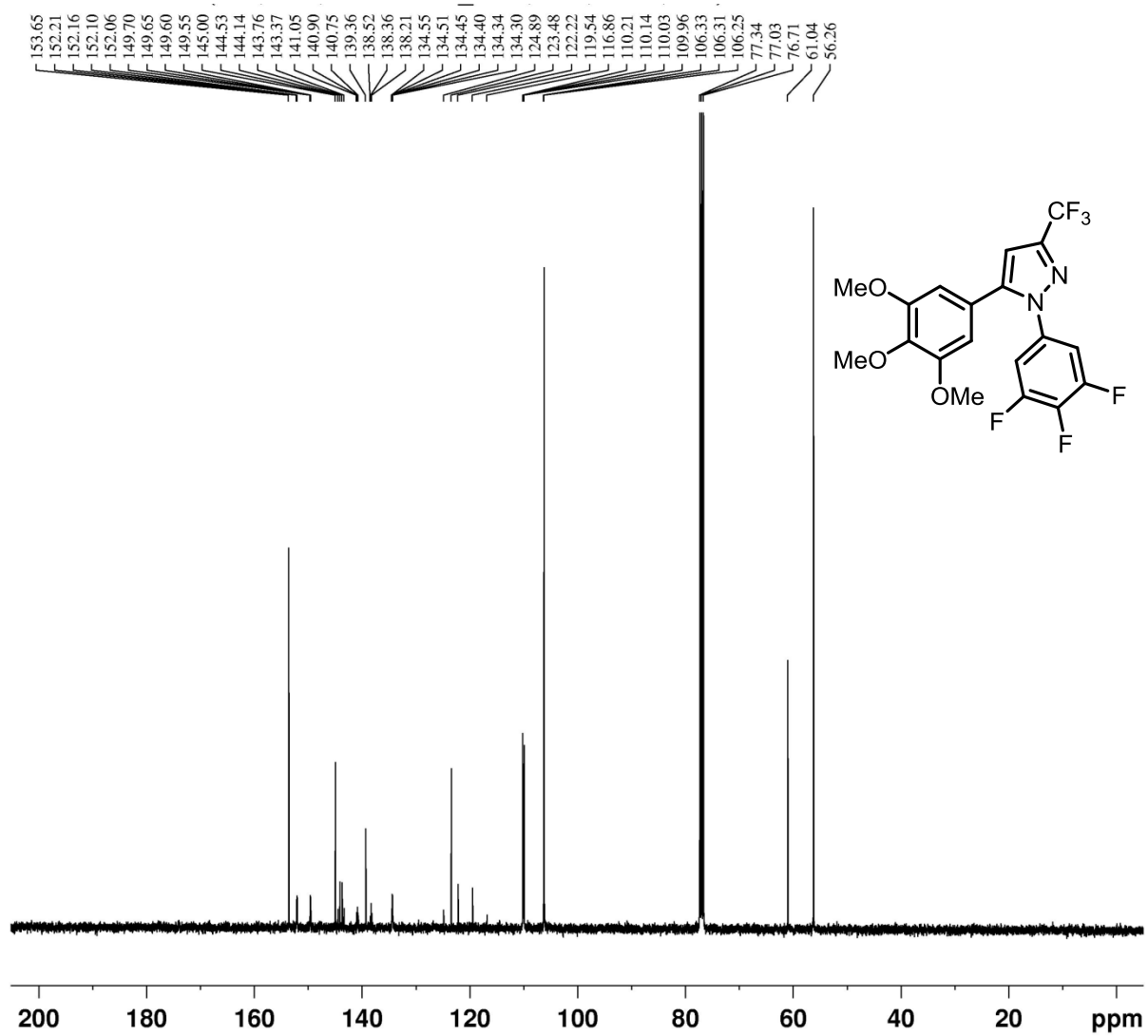
Supplementary Figure S29 (Table 1, Entry 13 (13):  $^{13}\text{C}$  NMR)



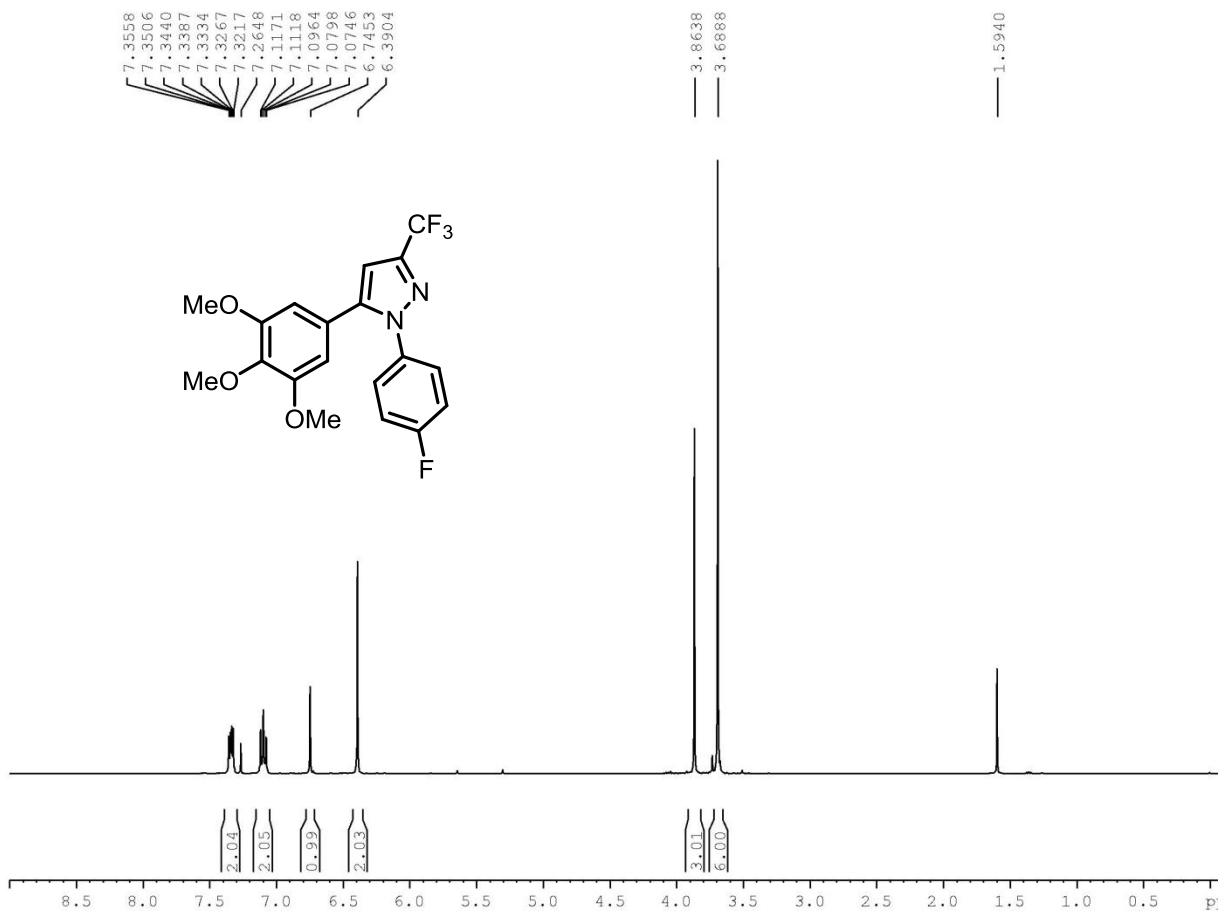
Supplementary Figure S30 (Table 1, Entry 14 (14):  $^1\text{H}$  NMR)



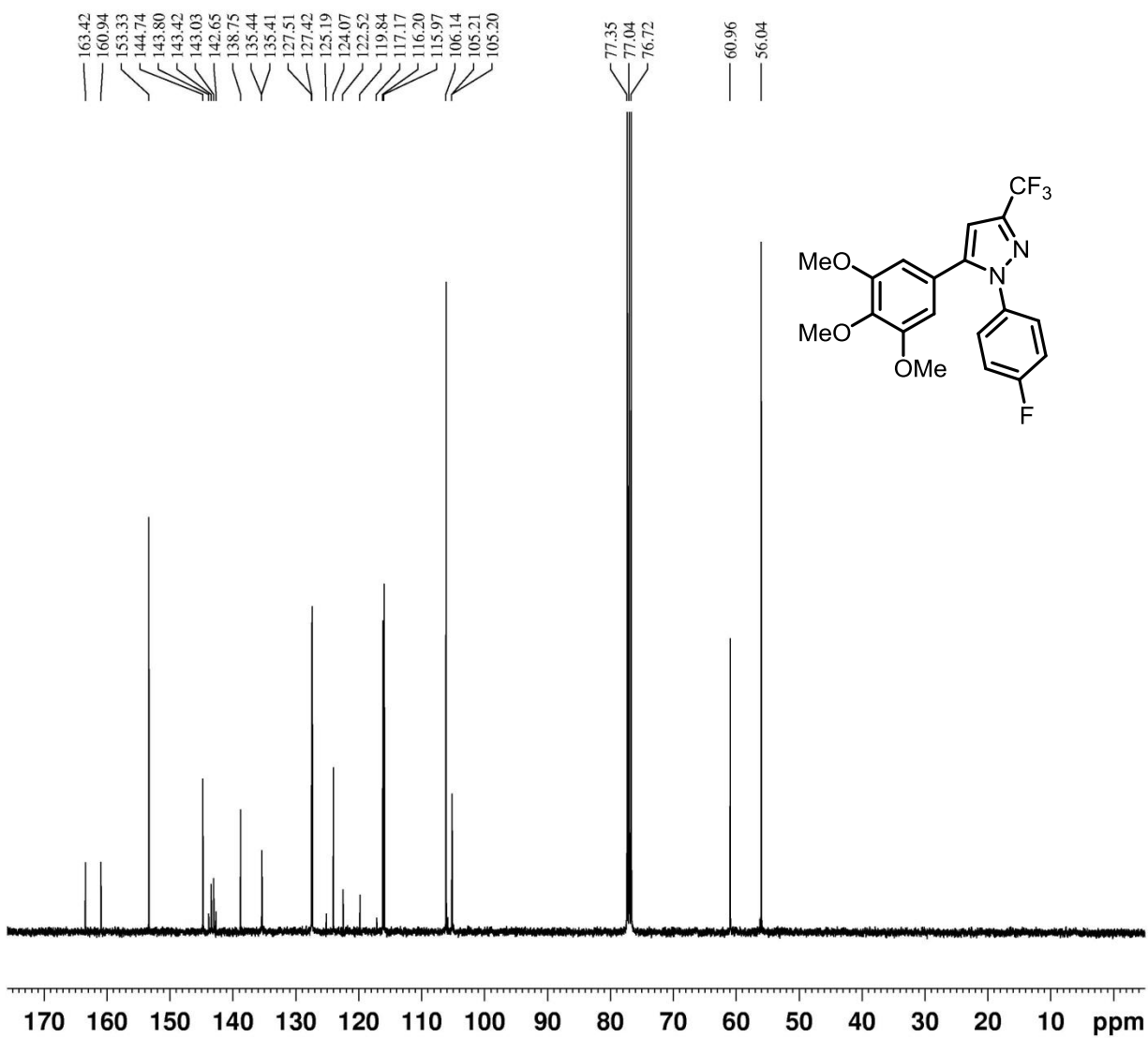
Supplementary Figure S31 (Table 1, Entry 14 (14):  $^{13}\text{C}$  NMR)



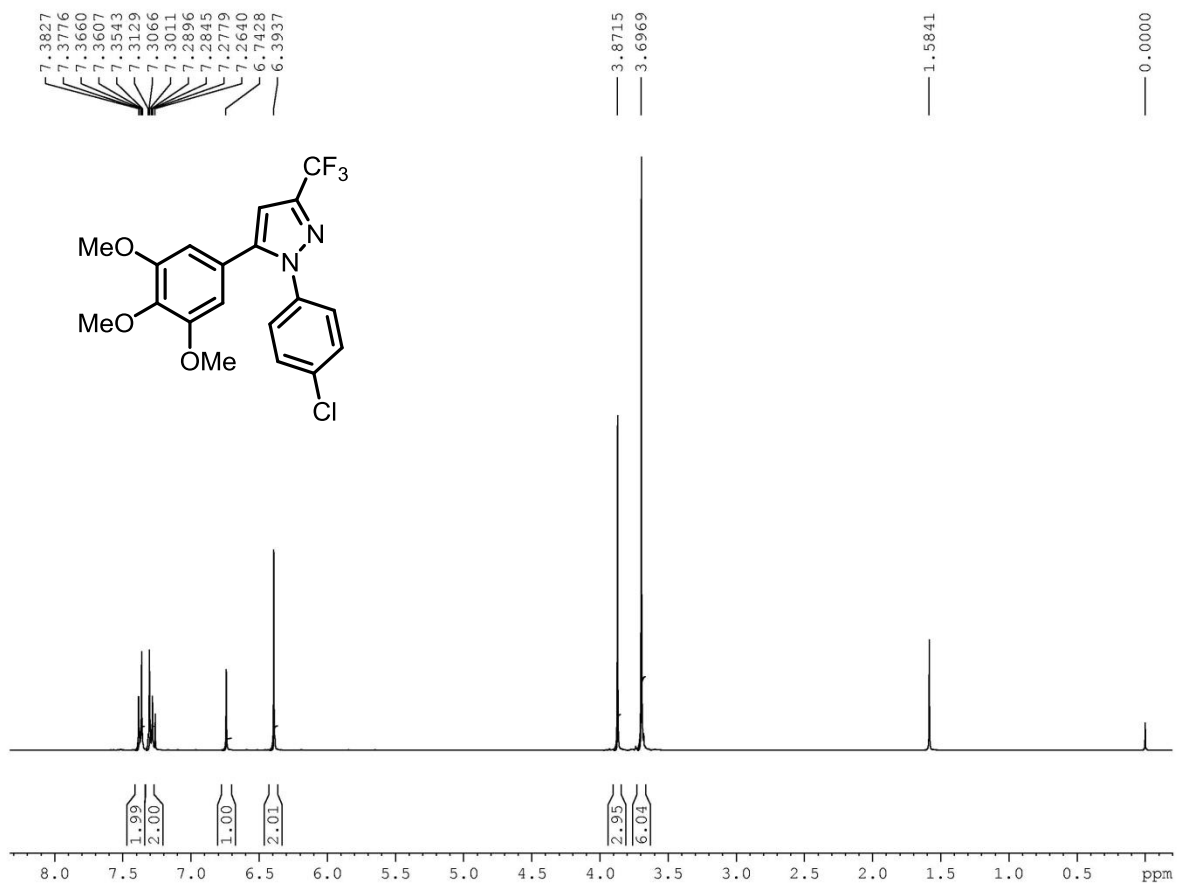
Supplementary Figure S32 (Table 1, Entry 15 (15): <sup>1</sup>H NMR)



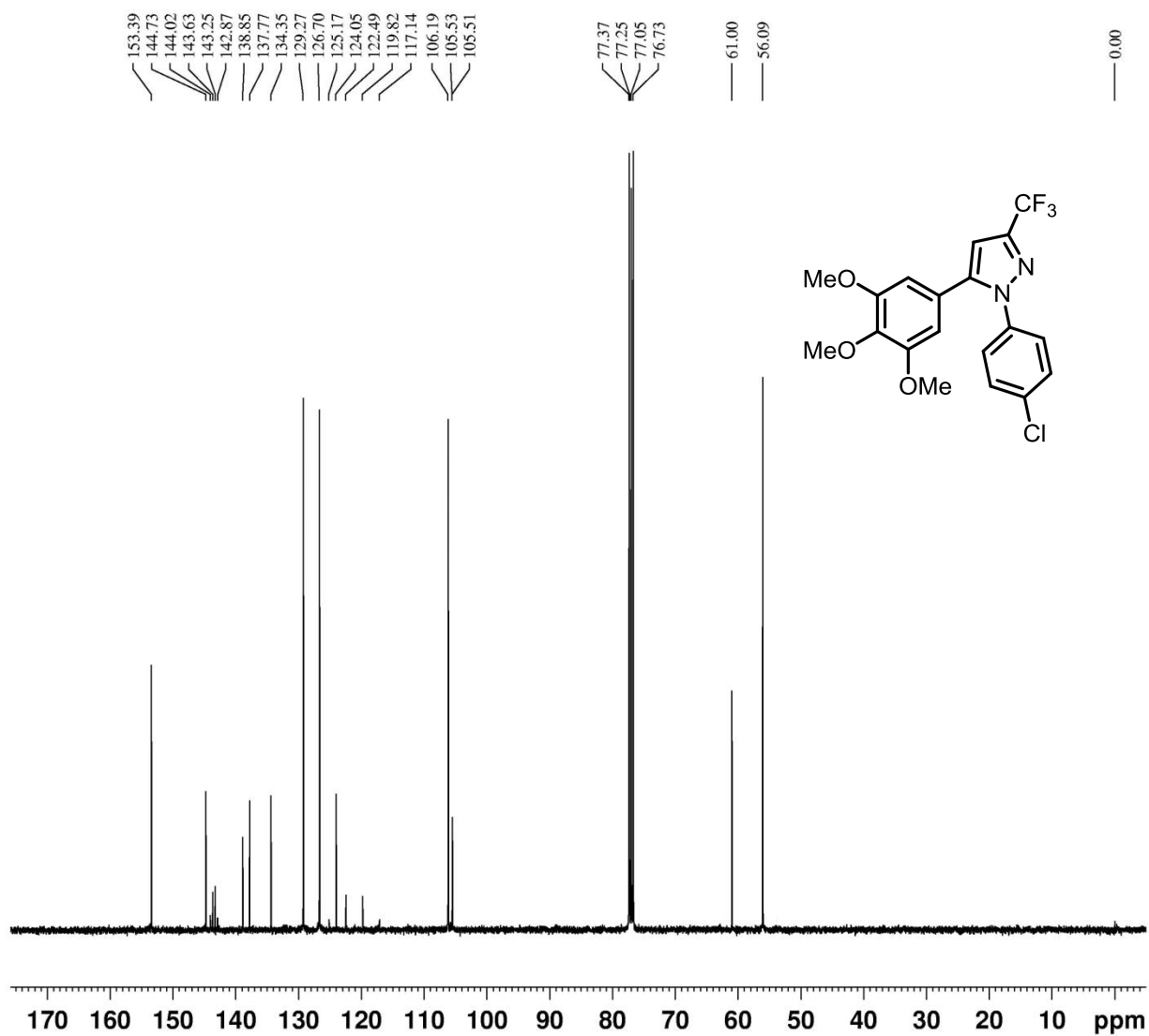
Supplementary Figure S33 (Table 1, Entry 15 (15):  $^{13}\text{C}$  NMR)



Supplementary Figure 34 (Table 1, Entry 16 (16):  $^1\text{H}$  NMR)

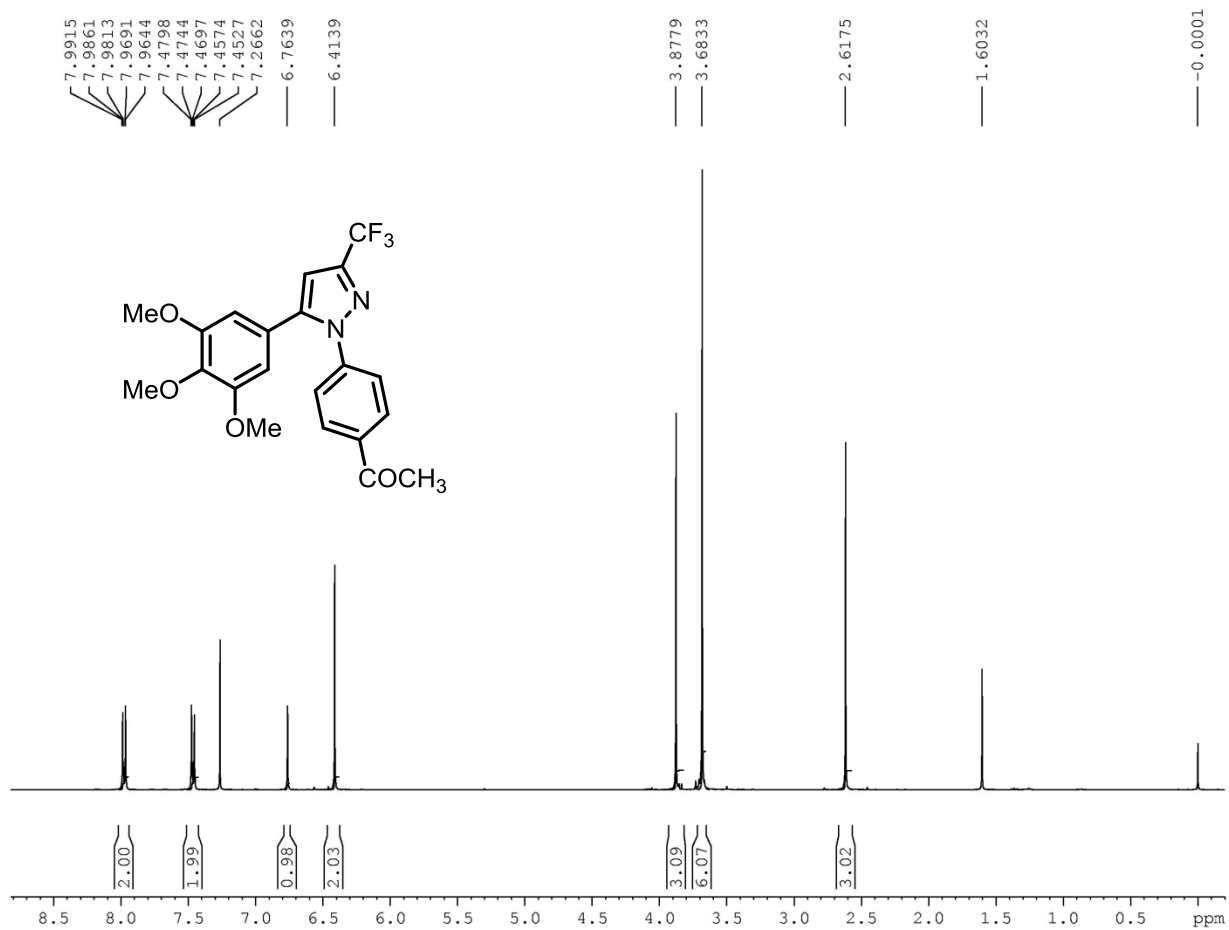


Supplementary Figure S35 (Table 1, Entry 16 (16):  $^{13}\text{C}$  NMR)

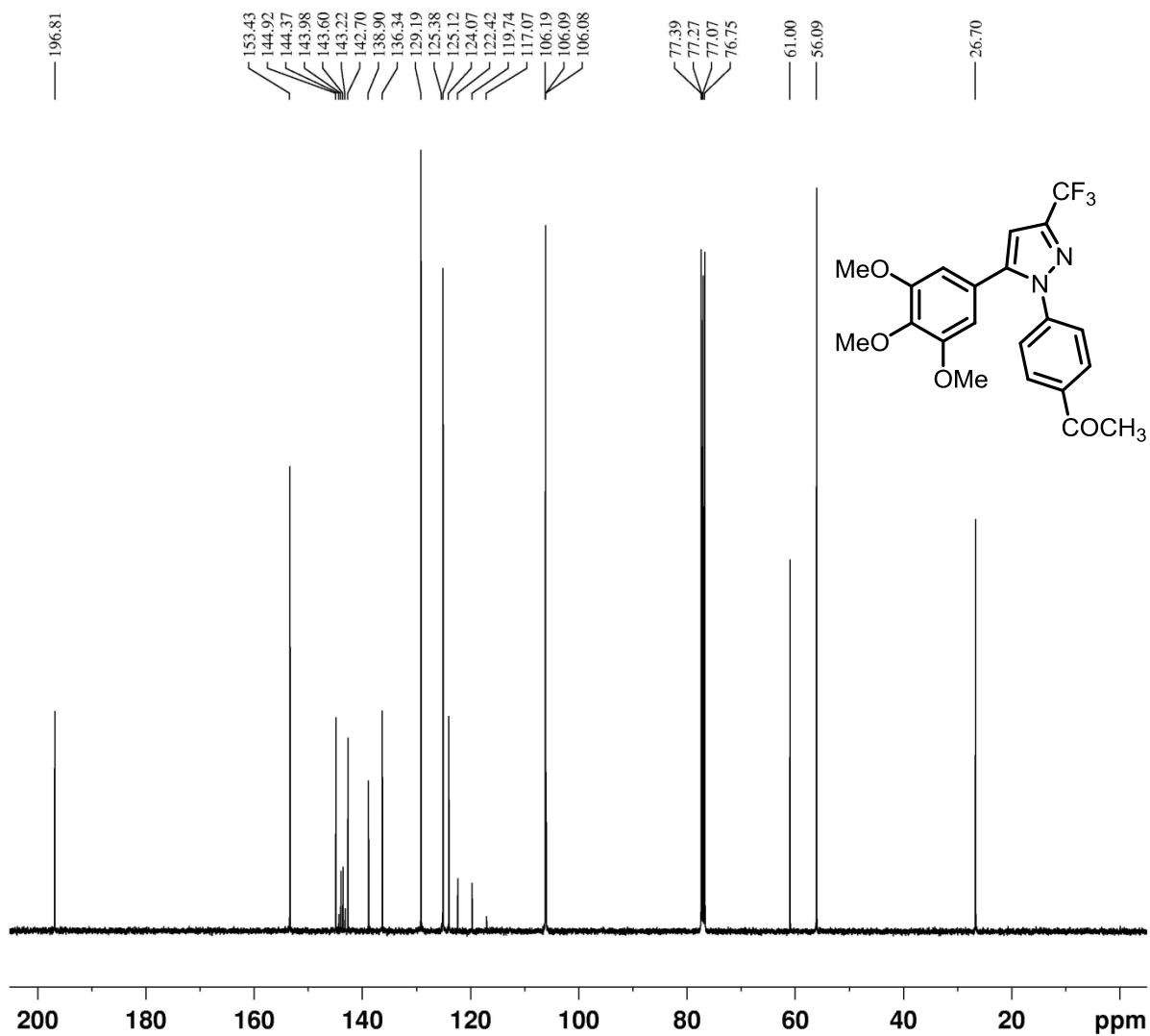




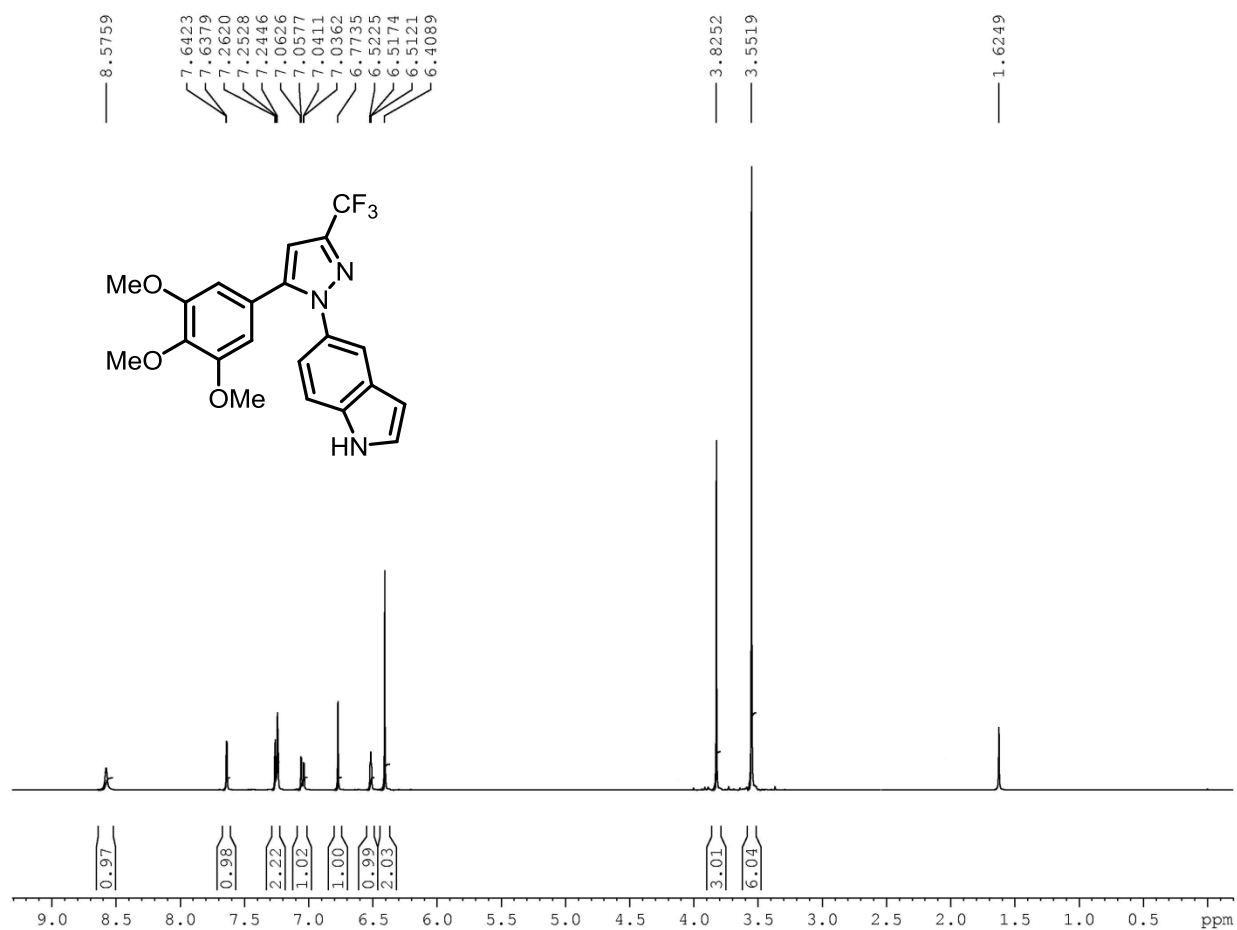
Supplementary Figure S36 (Table 1, Entry 17 (17):  $^1\text{H}$  NMR)



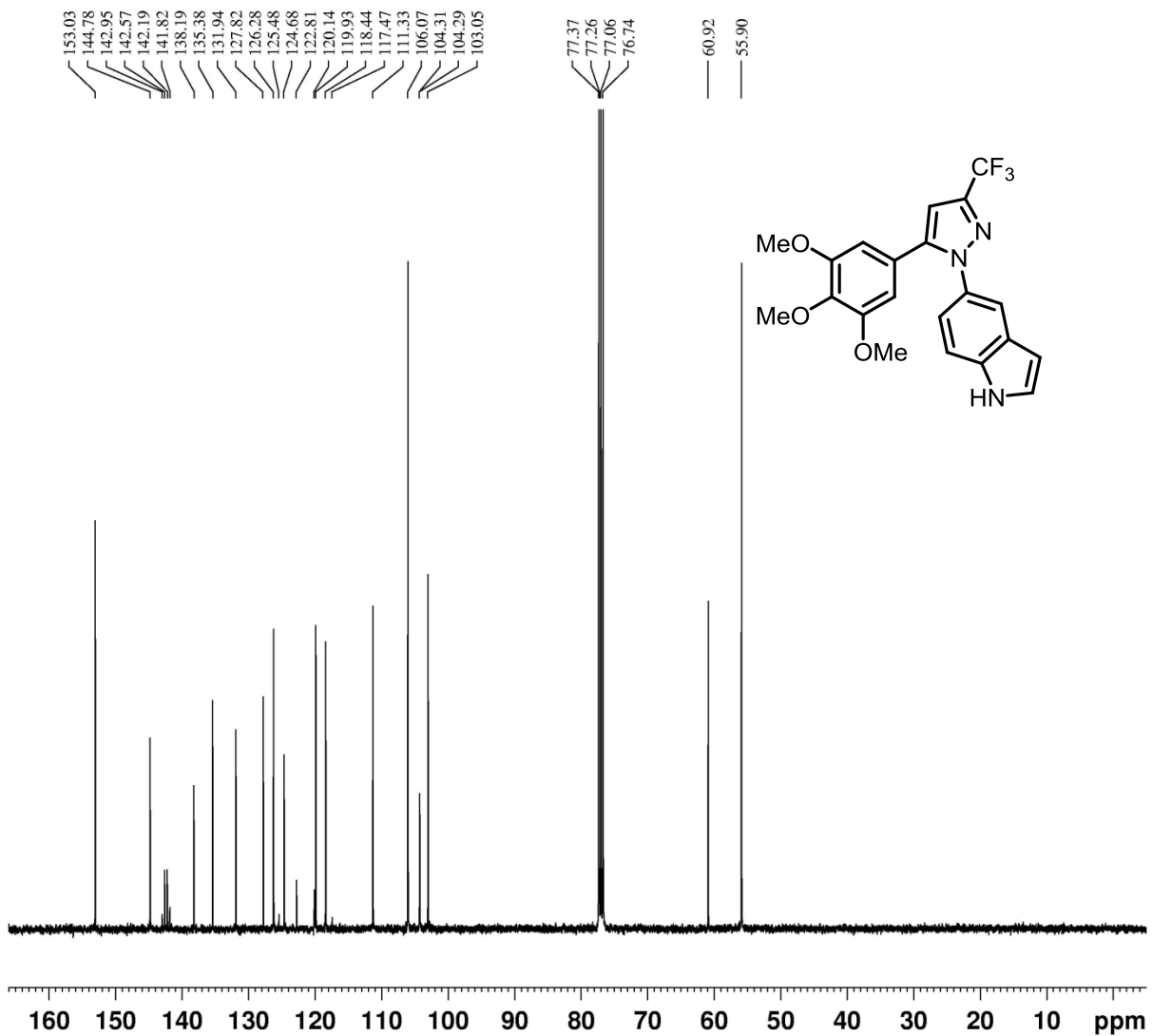
Supplementary Figure S37 (Table 1, Entry 17 (17): <sup>13</sup>C NMR)



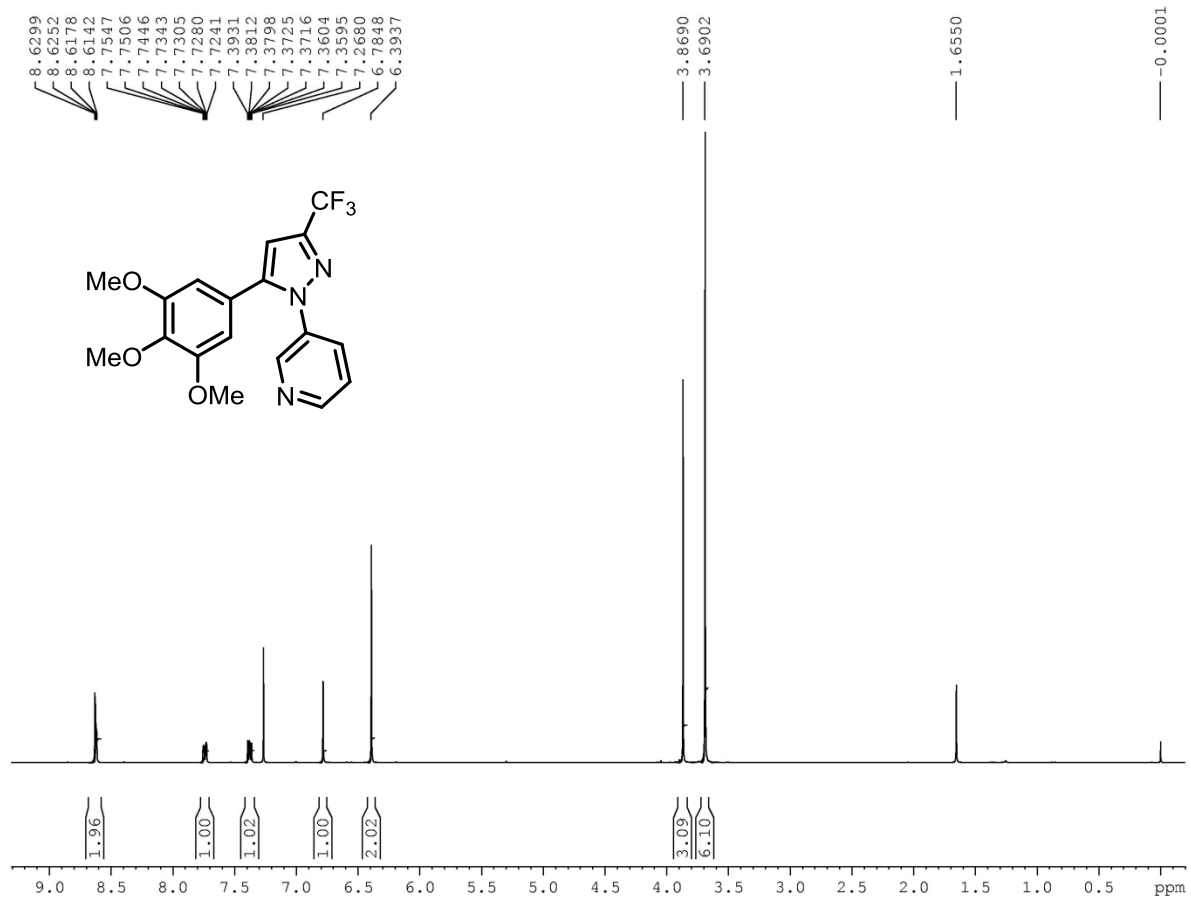
Supplementary Figure S38 (Table 1, Entry 18 (18):  $^1\text{H}$  NMR)



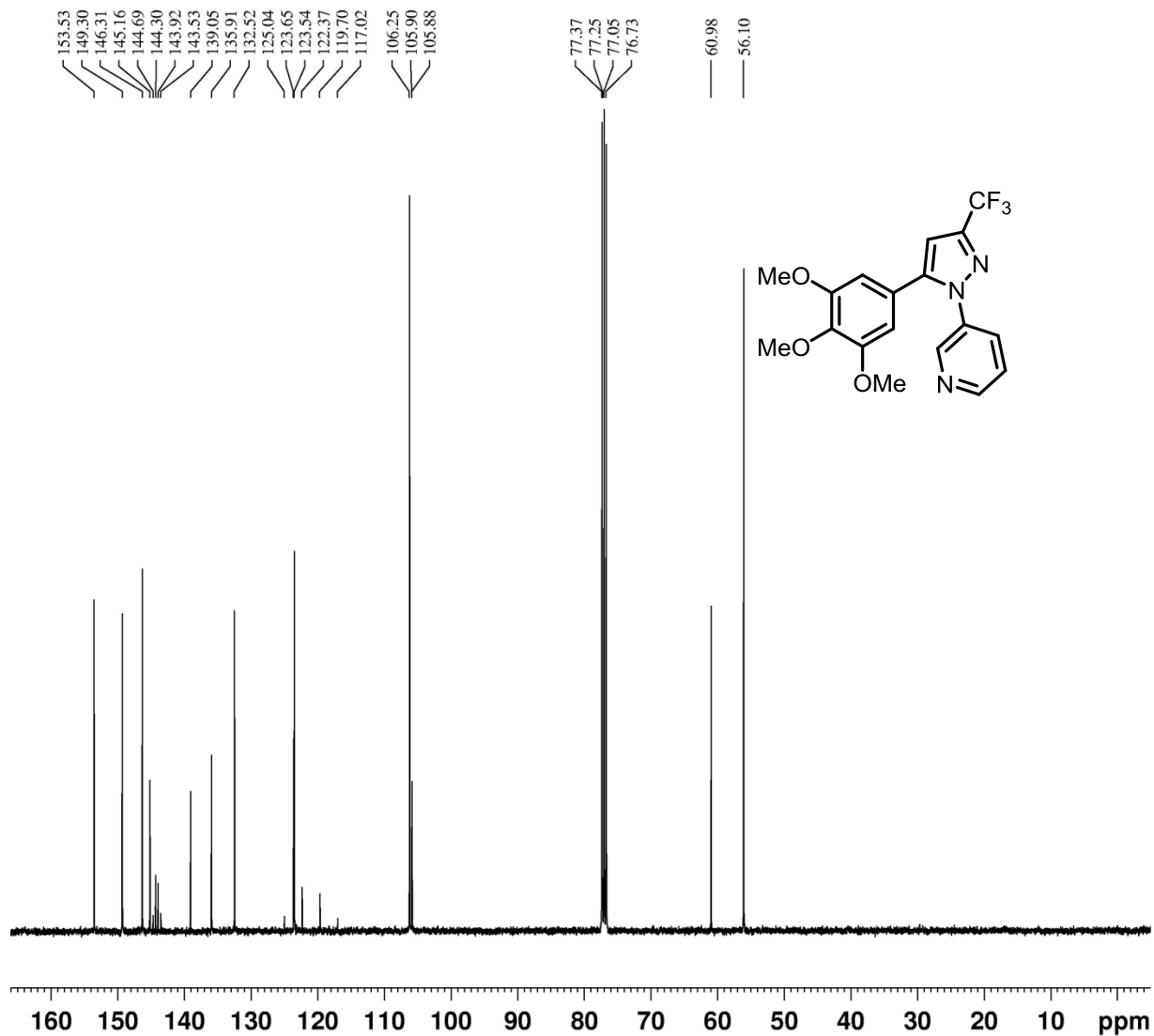
Supplementary Figure S39 (Table 1, Entry 18 (18): <sup>13</sup>C NMR)



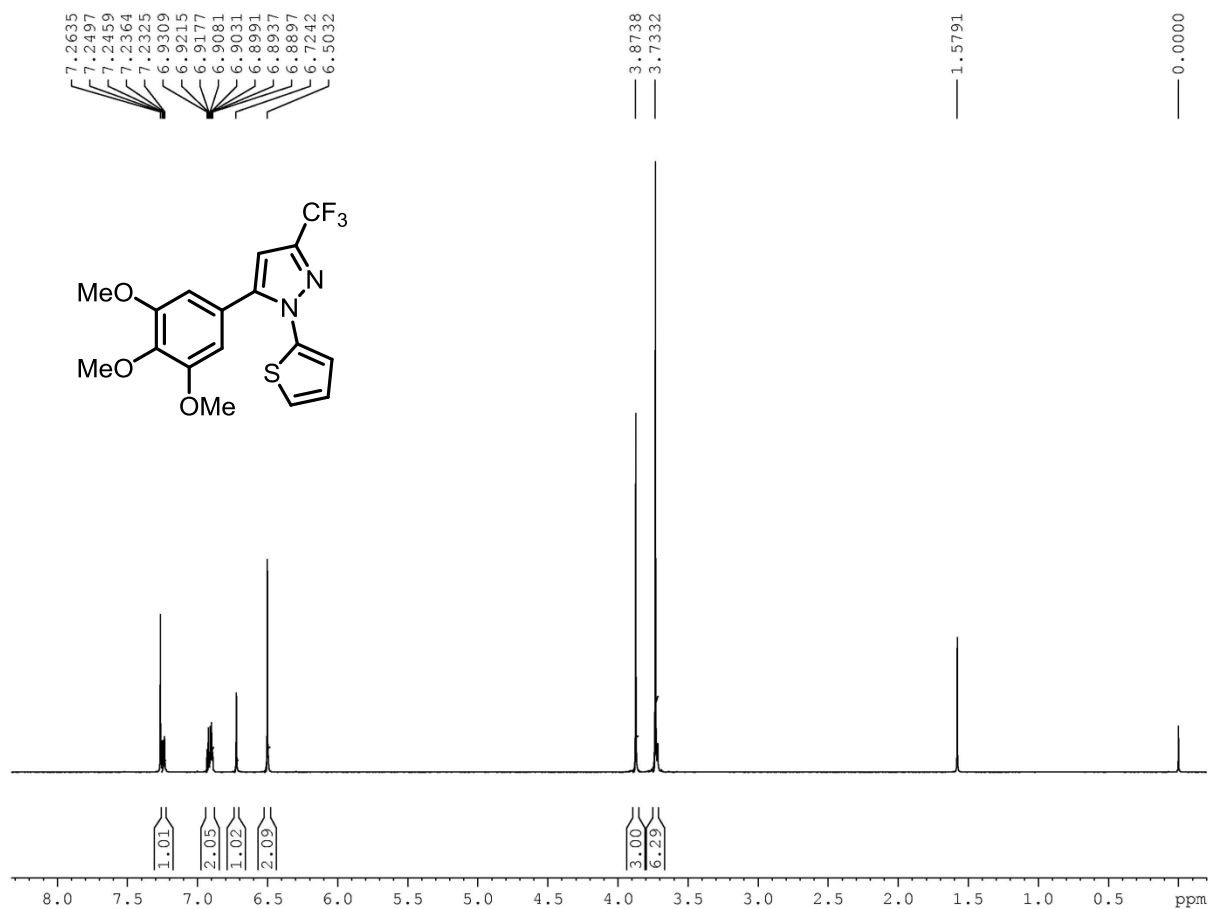
Supplementary Figure S40 (Table 1, Entry 19 (19): <sup>1</sup>H NMR)



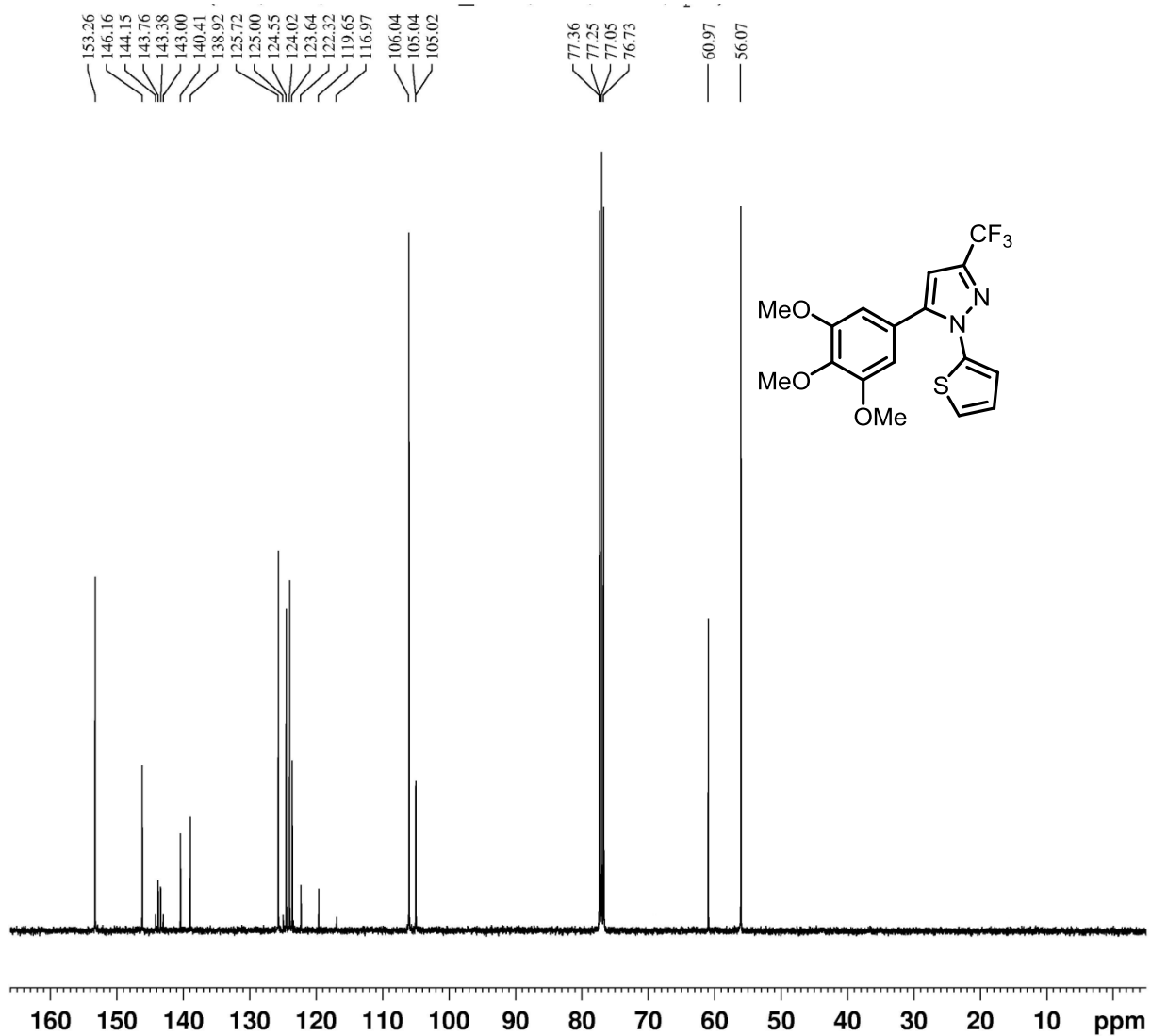
Supplementary Figure S41 (Table 1, Entry 19 (19): <sup>13</sup>C NMR)



Supplementary Figure S42 (Table 1, Entry 20 (20): <sup>1</sup>H NMR)

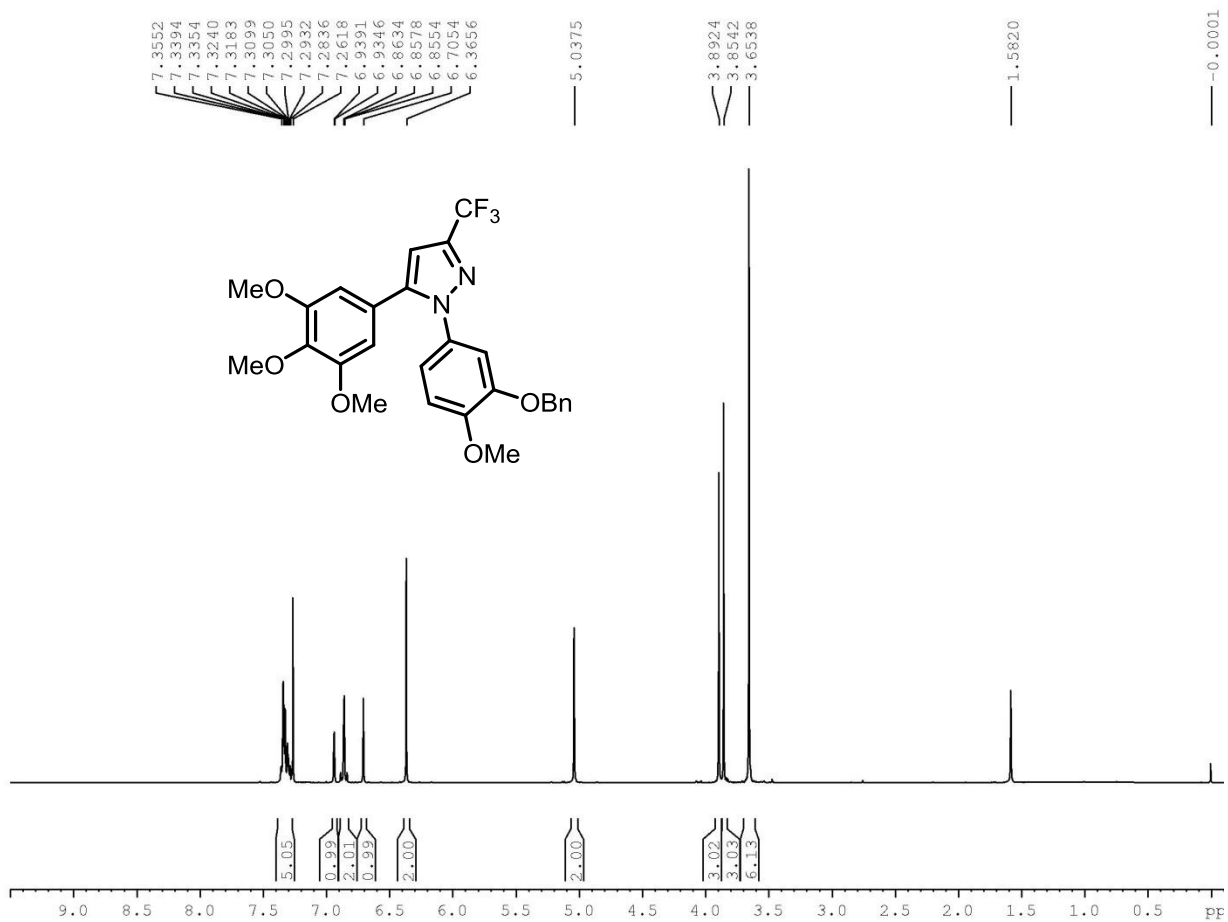


Supplementary Figure S43 (Table 1, Entry 20 (20):  $^{13}\text{C}$  NMR)

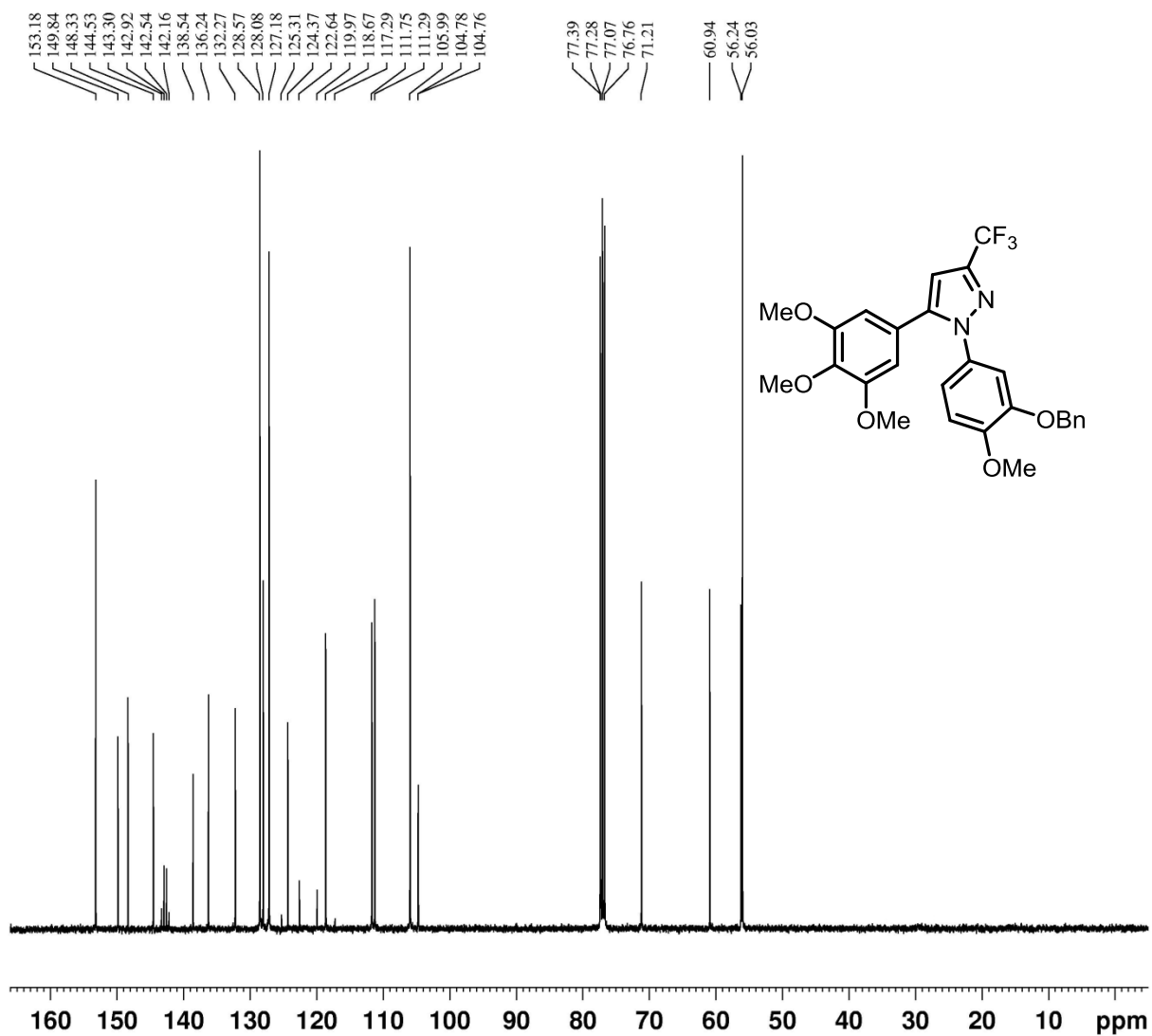




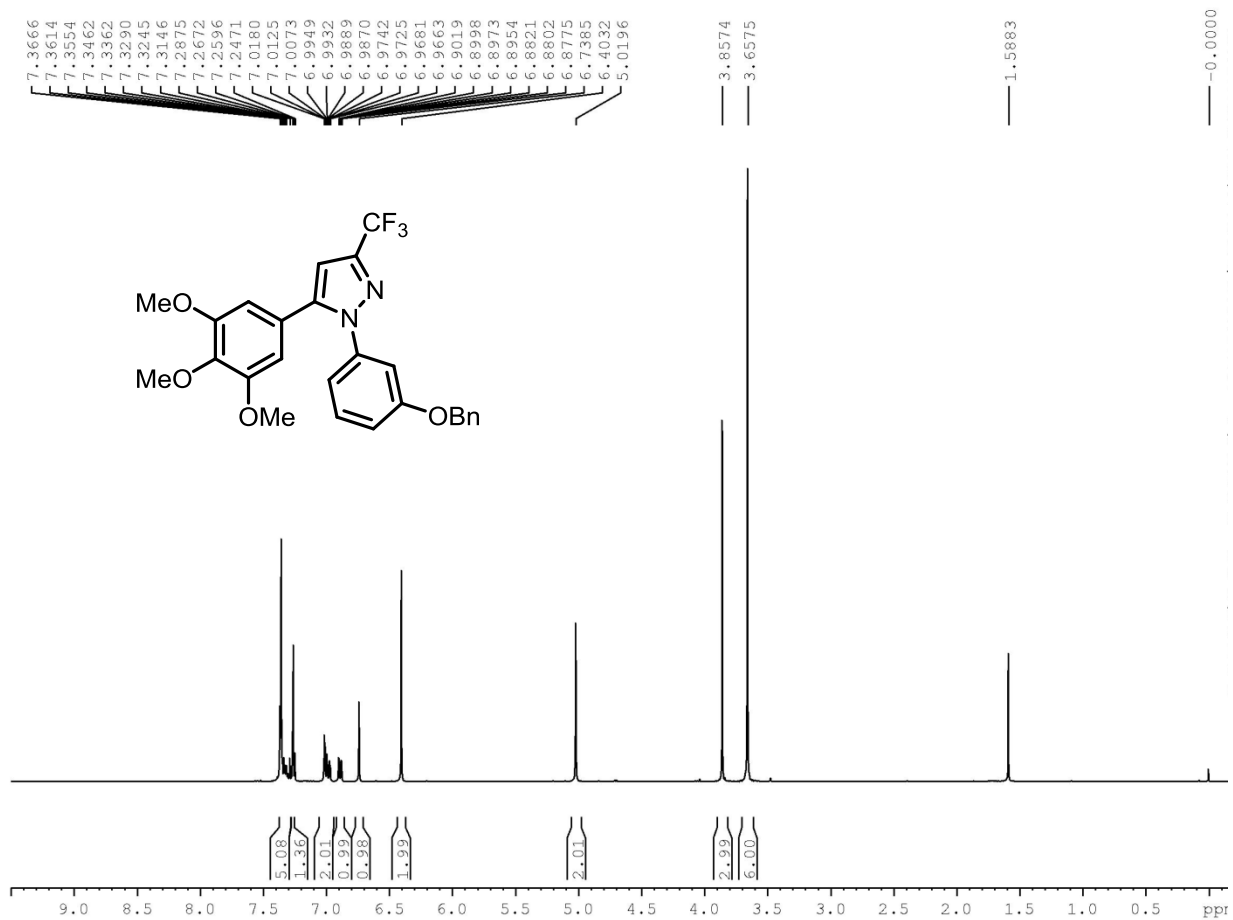
Supplementary Figure S44 (Table 1, Entry 21 (21):  $^1\text{H}$  NMR)



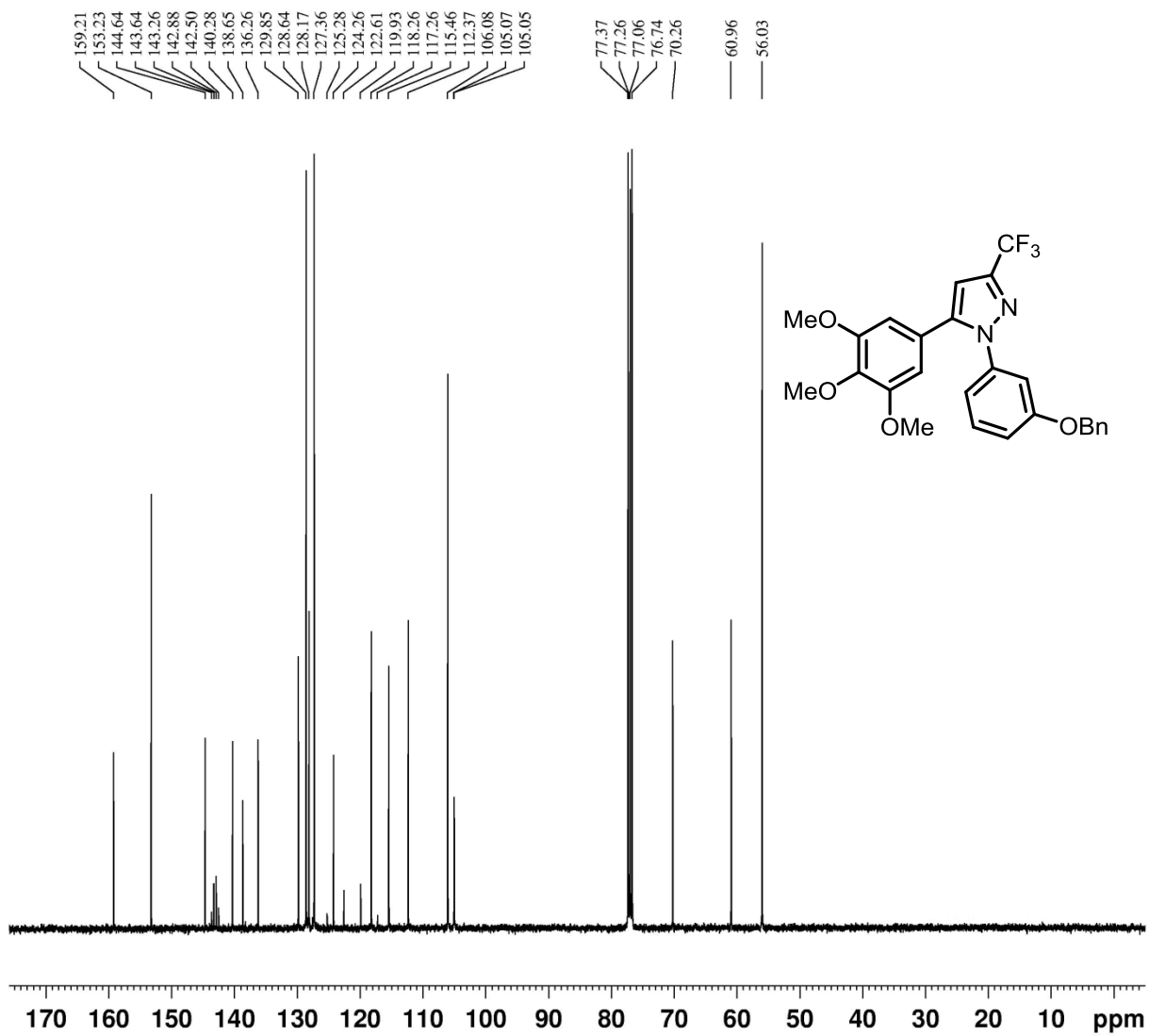
Supplementary Figure S45 (Table 1, Entry 21 (21):  $^{13}\text{C}$  NMR)



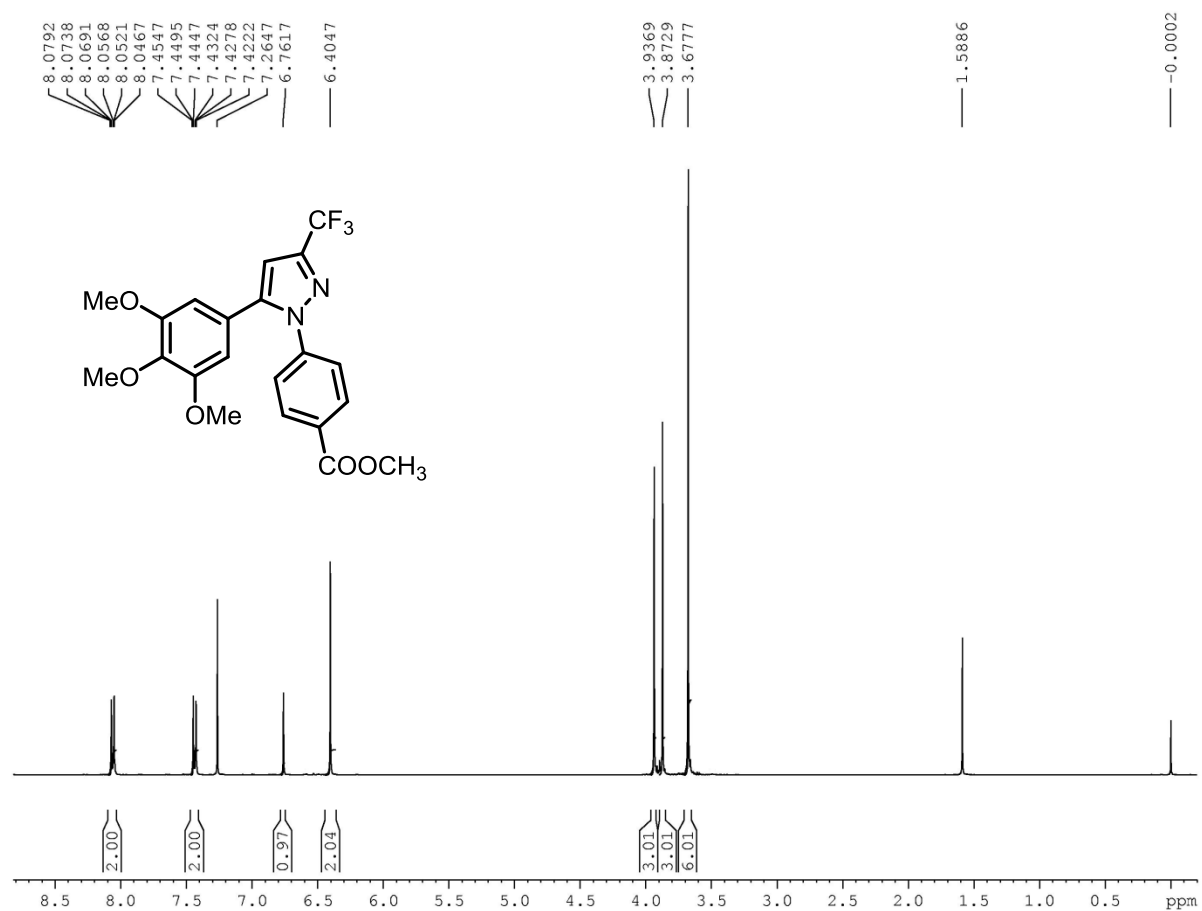
Supplementary Figure S46 (Table 1, Entry 22 (22):  $^1\text{H}$  NMR)



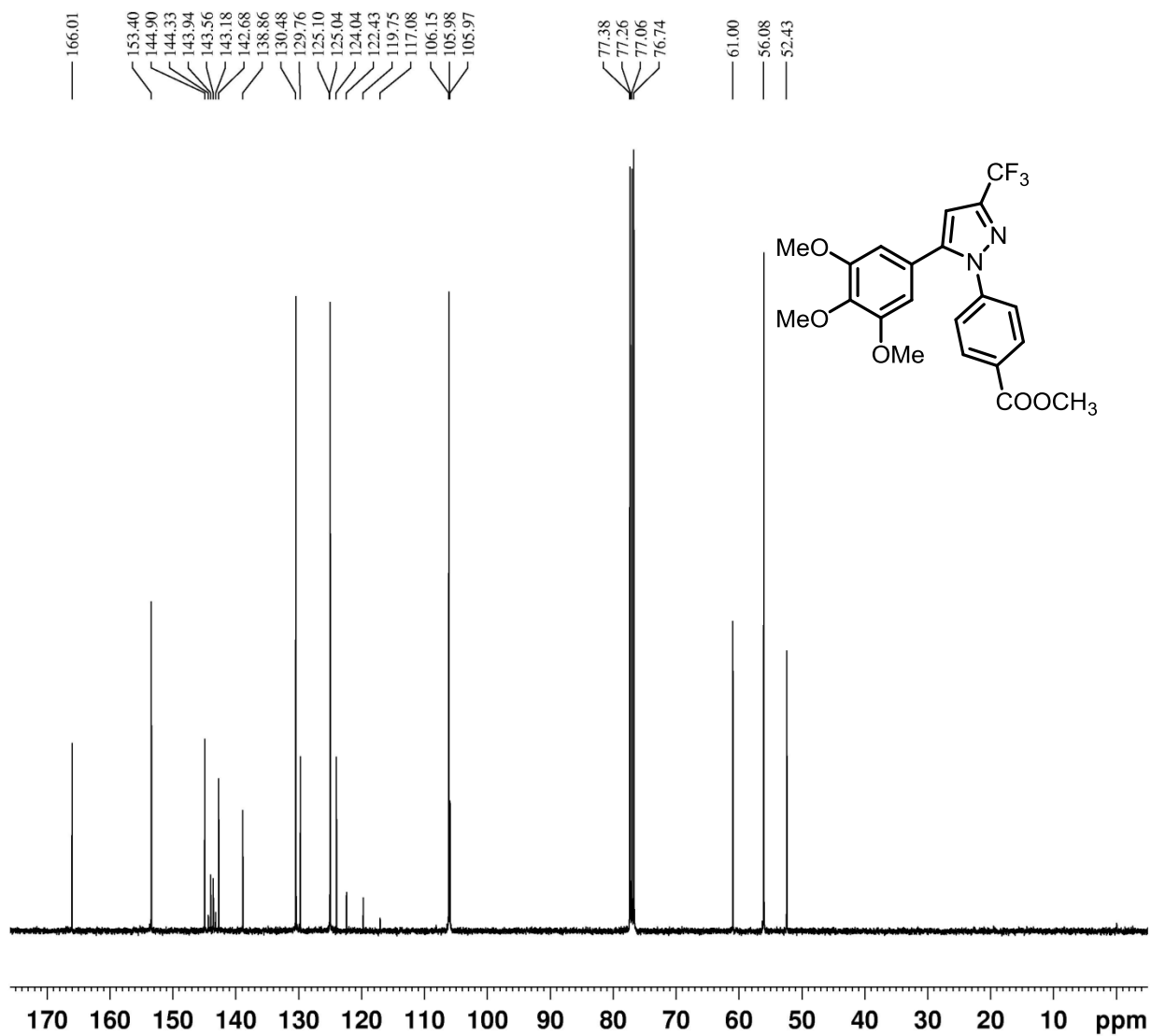
Supplementary Figure S47 (Table 1, Entry 22 (22):  $^{13}\text{C}$  NMR)



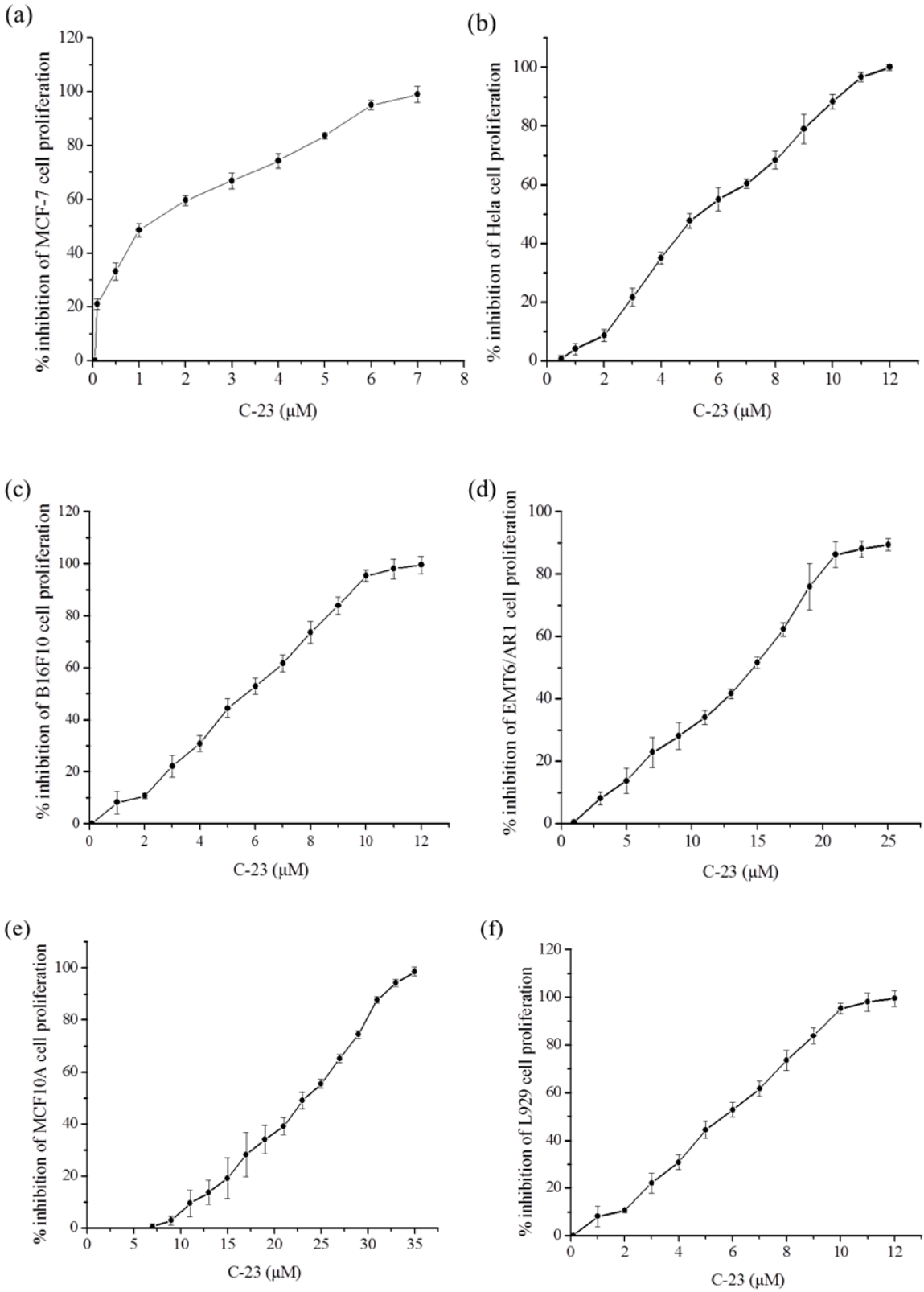
Supplementary Figure S48 (Table 1, Entry 23 (23):  $^1\text{H}$  NMR)



Supplementary Figure S49 (Table 1, Entry 23 (23):  $^{13}\text{C}$  NMR)



## 6. Biological results



**Supplementary Figure S50. Antiproliferative activity of C-23 against various cells.** Effect of **C-23** on the proliferation of cancer cell lines (a) MCF-7 (b) HeLa (c) B16F10 and (d) EMT6/AR1 and noncancerous cells (e) MCF10A and (f) L929 measured using sulforhodamine B assay. The experiment was done three times and average data was plotted. Error bar represents standard deviation.