

## An Easy Synthesis of 3,5-Disubstituted 1,2,4-oxadiazoles from Carboxylic Acids and Arylamidoximes Mediated by Ethyl Chloroformate

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### Experimental

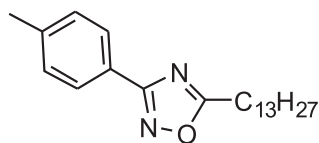
#### General experimental procedures

All reagents were obtained from commercial sources and used without further purification. Infrared spectra were recorded on a Perkin-Elmer model 283 spectrometer in KBr discs. <sup>1</sup>H and <sup>13</sup>C NMR spectra of CDCl<sub>3</sub> solutions were obtained in a Varian 300-MHz instrument using tetramethylsilane (TMS) as the internal standard. Elemental analysis was performed with a Carlo Erba instrument model E-1110. Carboxylic acids **1a-f** were obtained from commercial sources while **1g** and arylamidoximes **4h-j** were prepared following the procedure reported earlier.<sup>1,2</sup>

#### Typical experimental procedure

A suitable carboxylic acid **1a-f** (1.6 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) and placed in a round bottom flask followed by the addition of K<sub>2</sub>CO<sub>3</sub> (0.332g, 2.4 mmol) under stirring and kept as such for 30 min at room temperature. Later ethyl chloroformate **2** (0.2 mL, 2.4 mmol) was added to the same flask and stirred for an additional 30 min. Finally, the addition of an appropriate amidoxime **4h-j** (1.6 mmol) with continuous agitation for 2h completed the reaction. Filtration and solvent evaporation under reduced pressure furnished the crude product which upon heating in an oil bath at 120 °C for 4h gave the desired compounds which were crystallized from EtOH.

#### 3-(4-Tolyl)-5-tridecanyl-1,2,4-oxadiazole (**6k**)

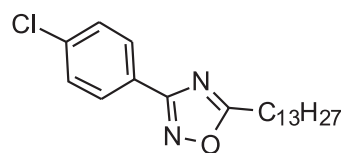


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<sup>#</sup>Taken in part from the M. Sc. Dissertation (2007) of Natércia M. M. Bezerra, Universidade Federal de Pernambuco, Recife, PE, Brazil

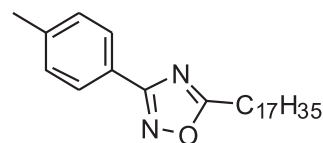
Yield: 86%; colorless crystals; mp 45 °C; R<sub>f</sub> 0.61 (CHCl<sub>3</sub>:C<sub>6</sub>H<sub>12</sub>, 1:1). IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup>: 3049, 2922, 2926, 2846, 1576. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); δ 0.87 (t, J 7.5 Hz, 3H), 1.25-1.48 (bs, 22H), 1.86 (quintet, J 7.5 Hz, 2H), 2.93 (t, J 7.5 Hz, 2H), 2.41 (s, 3H), 7.23 (d, J 8.4 Hz, 2H), 7.96 (d, J 8.4 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>); δ 14.13, 21.56, 22.68, 26.67, 29.03, 29.34, 29.54, 29.62, 31.90, 124.07, 127.27, 129.51, 141.34, 168.51, 179.91. Anal. Calc. for C<sub>22</sub>H<sub>36</sub>N<sub>2</sub>O, C, 76.69; H, 10.53; N, 8.13. Found: C, 76.43; H, 10.98; N, 8.21.

#### 3-(4-Chlorophenyl)-5-tridecanyl-1,2,4-oxadiazole (**6l**)



Yield: 80%; colorless crystals; mp 51 °C; R<sub>f</sub> 0.62 (CHCl<sub>3</sub>:C<sub>6</sub>H<sub>12</sub>, 1:1). IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup>: 3049; 2920; 2925; 2843; 1572; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>); δ 0.88 (t, J 7.2 Hz, 3H), 1.25-1.49 (bs, 22H), 1.86 (quintet, J 7.8 Hz, 2H), 2.93 (t, J 7.5 Hz, 2H), 7.45 (d, J 8.4 Hz, 2H), 8.01 (d, J 8.7 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>); δ 14.1, 22.7, 26.6, 29.0, 29.1, 29.3, 29.5, 29.6, 29.65, 29.68, 31.9, 125.4, 128.7, 129.1, 137.2, 167.4, 180.3. Anal. Calc. for C<sub>21</sub>H<sub>33</sub>ClN<sub>2</sub>O, C, 69.11; H, 9.11; N, 7.68. Found: C, 69.21; H, 9.54; N, 7.58.

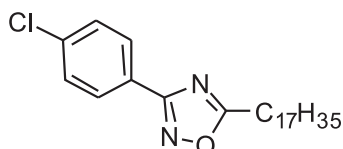
#### 5-Heptadecanyl-3-p-tolyl-1,2,4-oxadiazole (**6m**)



Yield: 83%; colorless crystals; mp 56 °C; R<sub>f</sub> 0.60 (CHCl<sub>3</sub>:C<sub>6</sub>H<sub>12</sub>, 1:1). IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup>: 3049, 2921, 2846, 1576. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.87 (t, J 5.4 Hz, 3H), 1.25-1.50 (bs, 28H), 1.86 (quintet, J 6.9 Hz, 2H), 2.41 (s,

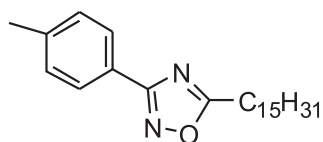
3H), 2.93 (t,  $J$  6.9 Hz, 2H), 7.23 (d,  $J$  8.1 Hz, 2H), 7.96 (d,  $J$  8.1 Hz, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ );  $\delta$  14.1, 22.7, 26.7, 29.0, 29.3, 29.5, 29.6, 31.9, 125.4, 128.7, 129.1, 137.2, 167.4, 180.3. Anal. Calc. for  $\text{C}_{26}\text{H}_{42}\text{N}_2\text{O}$  C, 78.34; H, 10.62; N, 7.03; Found: C, 78.68; H, 10.58, N, 7.21%.

**3-(4-Chlorophenyl)-5-heptadecanyl-1,2,4-oxadiazole (6n)**



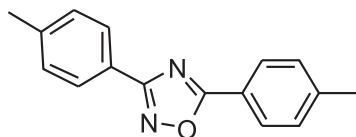
Yield: 79%; colorless crystals; mp 53 °C;  $R_f$  0.53. ( $\text{CHCl}_3$ : $\text{C}_6\text{H}_{12}$ , 1:1). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3048, 2925, 2925, 2847, 1574.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01 (d,  $J$  8.7 Hz, 2H), 7.45 (d,  $J$  8.7 Hz, 2H), 2.94 (t,  $J$  8.1 Hz, 2H), 1.86 (quintet,  $J$  8.1 Hz, 2H), 1.25 (m, 28H), 0.88 (t,  $J$  6.6 Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ );  $\delta$  14.1, 22.7, 26.6, 29.0, 29.1, 29.3, 29.5, 29.6, 29.64, 29.67, 31.9, 125.4, 128.7, 129.1, 137.2, 167.4, 180.3. Anal. Calc. for  $\text{C}_{25}\text{H}_{39}\text{ClN}_2\text{O}$  C, 71.66; H, 9.38; N, 6.69. Found: C, 72.01; H, 9.47; N, 6.98%.

**5-Pentadecanyl-3-p-tolyl-1,2,4-oxadiazole (6o)**



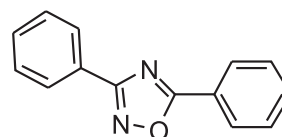
Yield: 90%; colorless crystals; mp 57 °C (lit.<sup>2</sup> mp 57.1 °C);  $R_f$  0.51 ( $\text{CHCl}_3$ : $\text{C}_6\text{H}_{12}$ , 1:1). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3063, 2954, 2917, 2848, 1588.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  0.88 (t,  $J$  6.9 Hz, 3H), 1.25-1.44 (bs, 24H), 1.86 (quintet,  $J$  7.8 Hz, 2H), 2.41 (s, 3H), 2.93 (t,  $J$  7.8 Hz, 2H), 7.23 (d,  $J$  8.1 Hz, 2H), 7.95 (d,  $J$  8.1 Hz, 2H).

**3,5-Di-p-tolyl-1,2,4-oxadiazole (6p)**



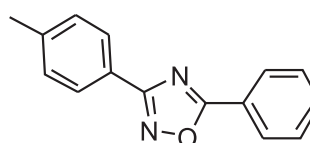
Yield: 75%; colorless crystals; mp 133 °C (lit.<sup>2</sup> mp 134 °C);  $R_f$  0.72 ( $\text{CHCl}_3$ ). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3023, 2920, 2850, 1594.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  2.39 and 2.40 (2s, 6H), 7.27 (d,  $J$  7.6 Hz, 2H), 7.28 (d,  $J$  7.8 Hz, 2H), 8.05 (d,  $J$  7.8 Hz, 2H), 8.06 (d,  $J$  7.6 Hz, 2H).

**3,5-Diphenyl-1,2,4-oxadiazole (6q)**



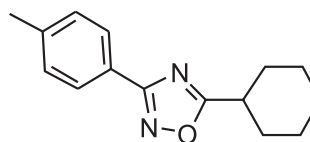
Yield: 86%; colorless crystals; mp 108-109 °C (lit.<sup>2</sup> mp 110 °C);  $R_f$  0.70 ( $\text{CHCl}_3$ ). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3022, 2920, 2839, 1594.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  7.51-7.62 (m, 6H), 8.14-8.25 (m, 4H).

**3-Phenyl-3-p-tolyl-1,2,4-oxadiazole (6r)**



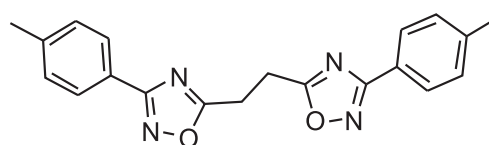
Yield: 93%; colorless crystals; mp 105-106 °C (lit.<sup>2</sup> mp 105-106 °C);  $R_f$  0.52 ( $\text{CHCl}_3$ : $\text{C}_6\text{H}_{12}$ , 1:1). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3049, 2955, 2915, 1560.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  2.44 (s, 3H), 7.32 (d,  $J$  9.6 Hz, 2H), 7.55-7.60 (m, 3H), 8.07 (d,  $J$  8.7 Hz, 2H), 8.22 (d,  $J$  9.6 Hz, 2H).

**5-Cyclohexyl-4-p-tolyl-1,2,4-oxadiazole (6s)**



Yield: 91%; colorless crystals; mp 55 °C;  $R_f$  0.80 ( $\text{CHCl}_3$ ). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3035, 2918, 2852, 1589.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$  1.25-2.15 (m, 10H), 2.41 (s, 3H), 3.00 (tt,  $J_{\text{ax-ax}}$  11.1 Hz,  $J_{\text{ax-eq}}$  3.6 Hz, 1H), 7.27 (d,  $J$  8.4 Hz, 2H), 7.96 (d,  $J$  8.4 Hz, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ );  $\delta$  21.5, 25.3, 25.5, 30.2, 36.3, 124.2, 127.3, 129.4, 141.2, 168.0, 182.7. Anal. Calc. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$  C, 74.35; H, 7.49; N, 11.56; Found: C, 74.48; H, 7.33; N, 11.62.

**1,2-bis(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethane (6t)**



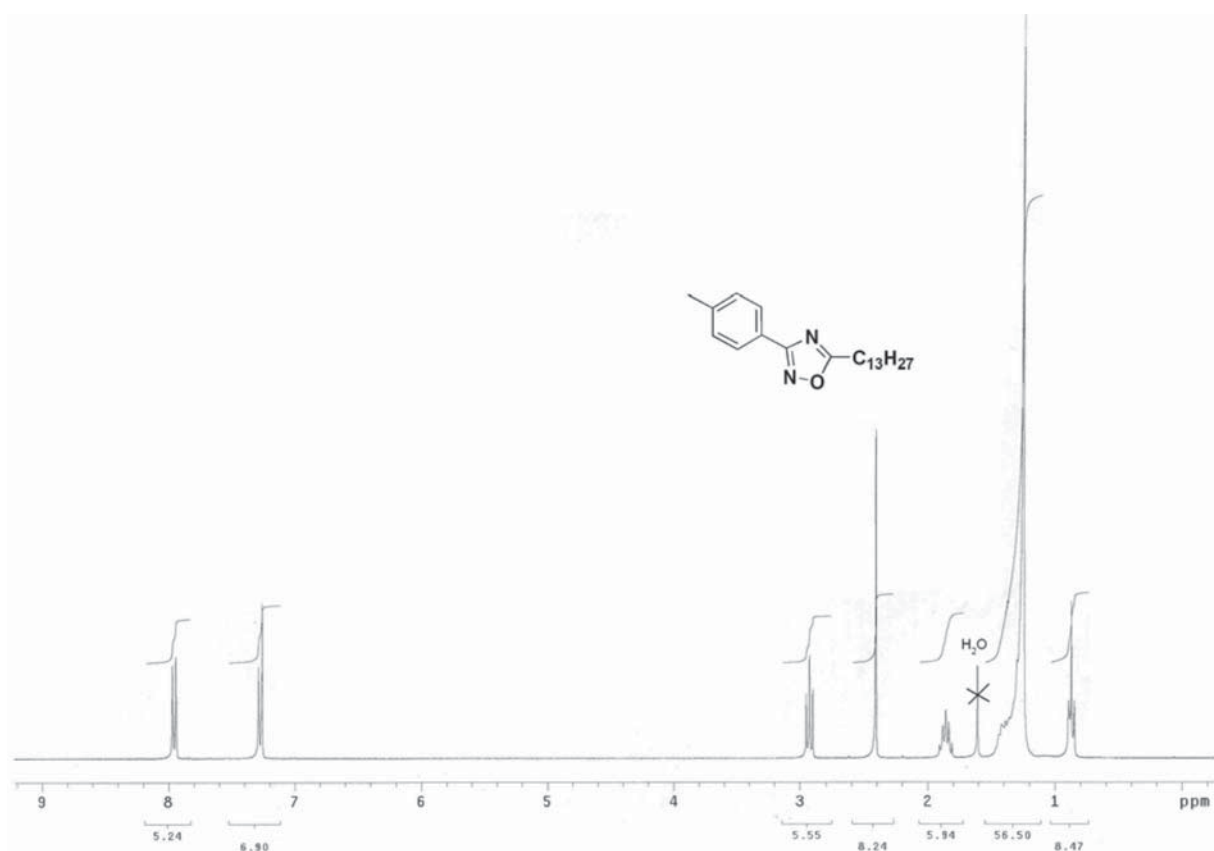
Yield: 84%; colorless crystals; mp 169-170 °C (lit.<sup>2</sup> mp 171-172 °C);  $R_f$  0.73 ( $\text{CHCl}_3$ ). IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3032, 2926, 2854, 1590.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ );  $\delta$

2.41 (s, 6H), 3.57 (s, 4H), 7.28 (d, *J* 8.4 Hz, 4H), 7.95 (d, *J* 8.4 Hz, 4H).

## References

1. Srivastava, R. M.; Brinn, I. M.; Machuca-Herrera, J. O.; Faria, H. B.; Carpenter, D. G. B.; Venkatesh, C. G.; de Morais, L. P. F.; *J. Mol. Struct.* **1997**, *406*, 159.

2. For compounds **6o-r** see: Bezerra, N. M. M.; Oliveira, S. P.; Srivastava, R. M.; da Silva, J. R.; *Il Farmaco* **2005**, *60*, 955. Leite, L. F. C.; Srivastava, R. M.; Cavalcanti, A. P.; *Bull. Soc. Chim. Belges* **1989**, *98*, 203. Goetz, N.; *Synthesis* **1976**, *4*, 268. Chiou, S.; *J. Heterocycl. Chem.* **1989**, *26*, 125. For compound **6t** see: Srivastava, R. M.; da Silva, A. J. C. N.; de Oliveira, M. L.; *J. Braz. Chem. Soc.* **1993**, *4*, 84.



**Figure S1.** <sup>1</sup>H NMR (300 MHz) spectrum of compound **6k** in CDCl<sub>3</sub>.

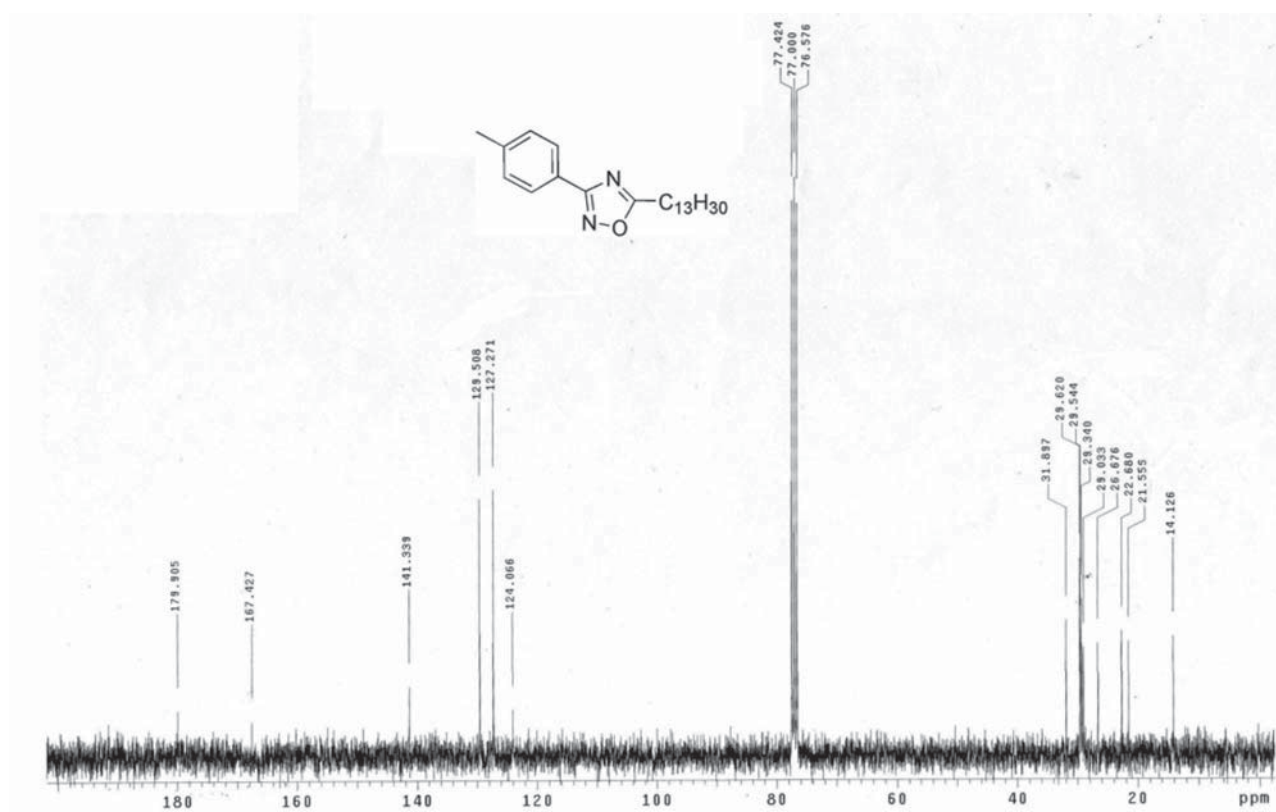


Figure S2.  $^{13}\text{C}$  NMR (75 MHz) spectrum of compound **6k** in  $\text{CDCl}_3$ .

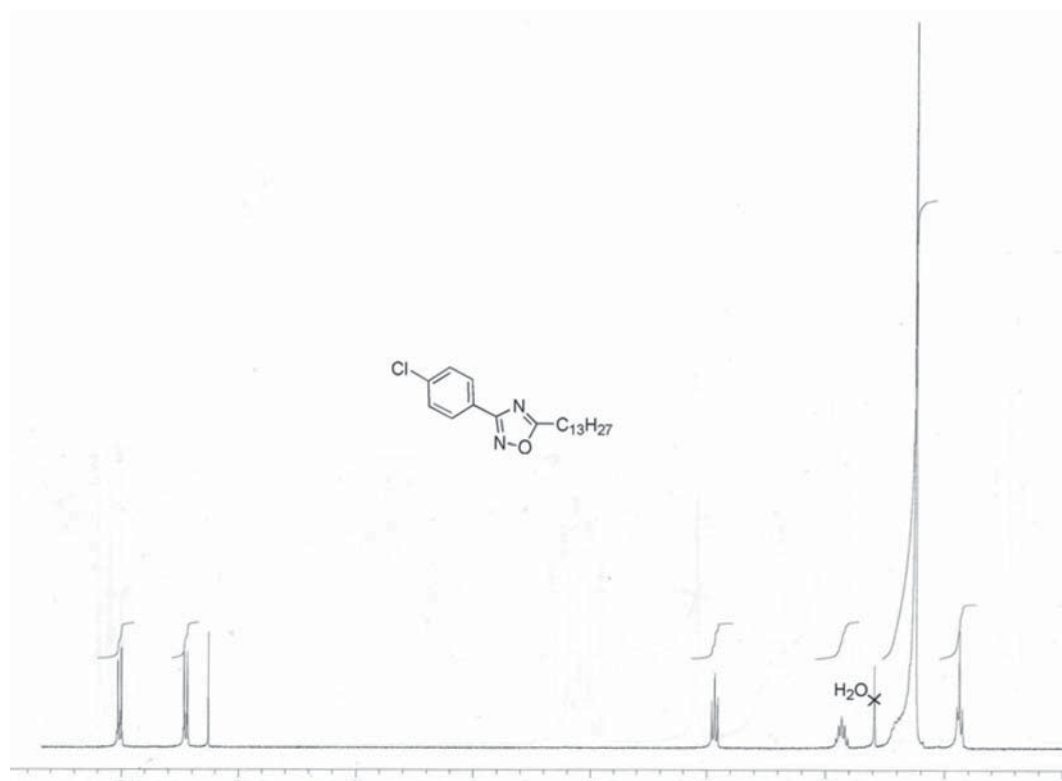


Figure S3.  $^1\text{H}$  NMR (300 MHz) spectrum of compound **6l** in  $\text{CDCl}_3$ .

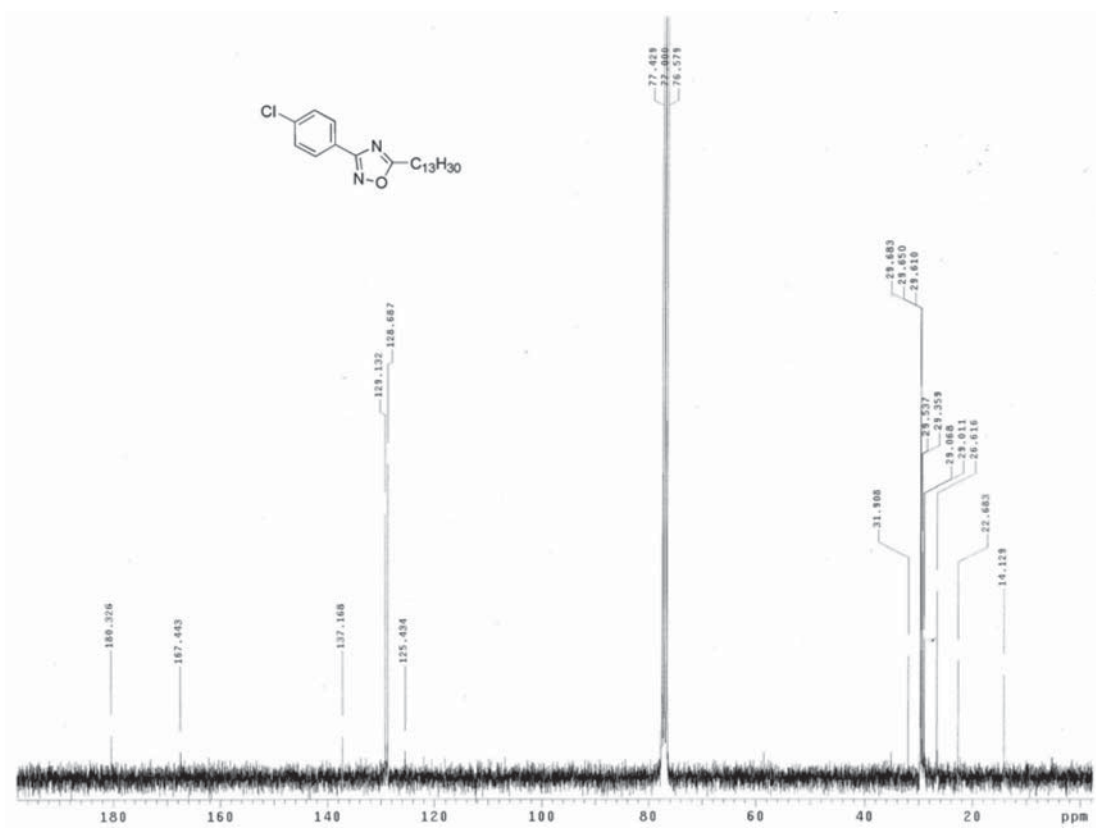


Figure S4. <sup>13</sup>C NMR (75 MHz) spectrum of compound **6l** in CDCl<sub>3</sub>.

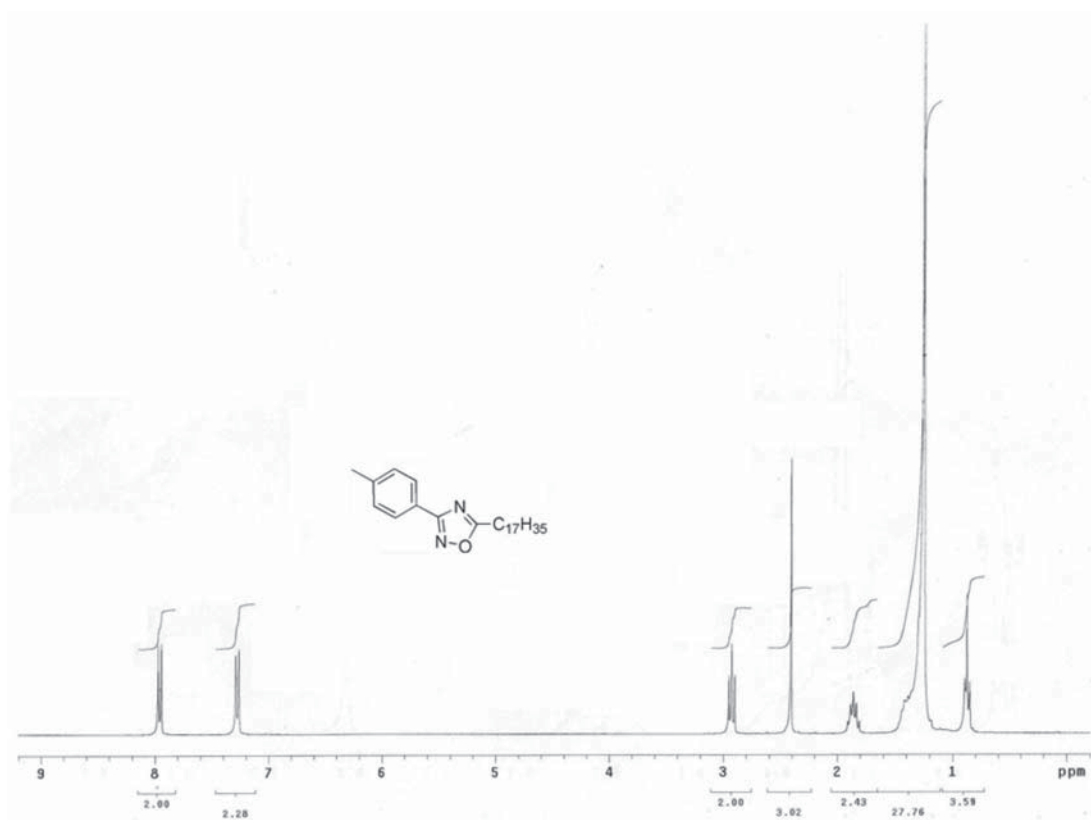


Figure S5. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6m** in CDCl<sub>3</sub>.

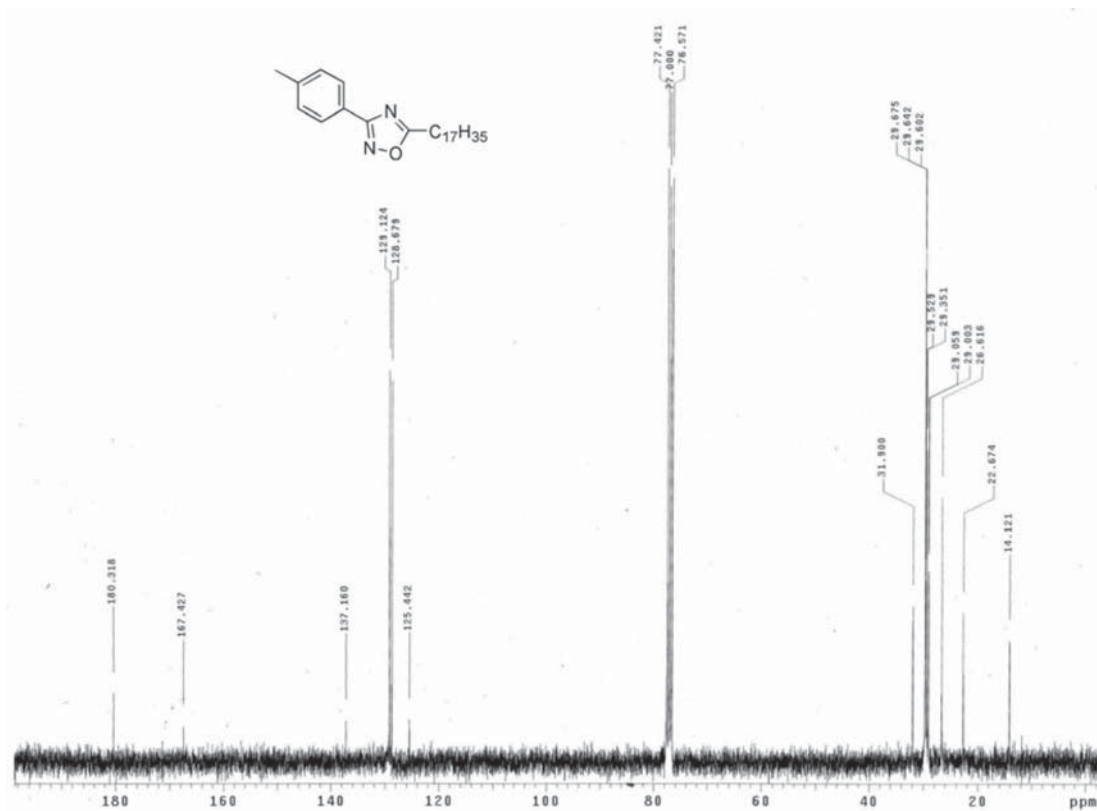


Figure S6.  $^{13}\text{C}$  NMR (75 MHz) spectrum of compound **6m** in  $\text{CDCl}_3$ .

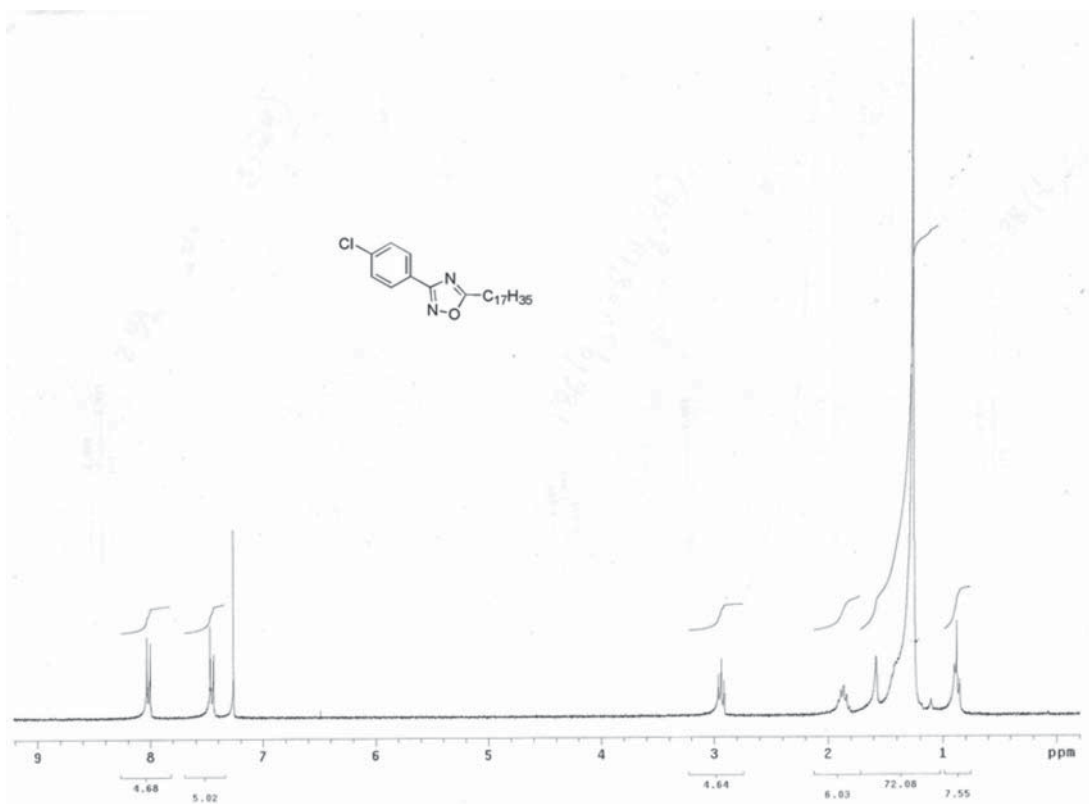


Figure S7.  $^1\text{H}$  NMR (100 MHz) spectrum of compound **6n** in  $\text{CDCl}_3$ .

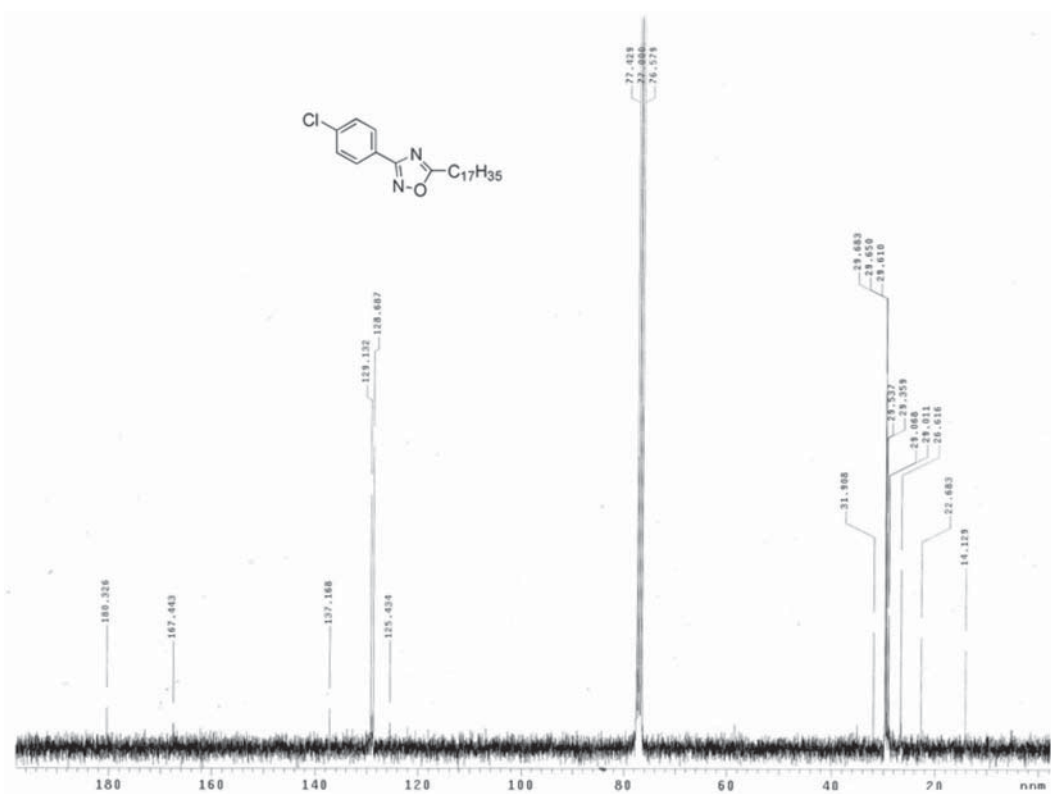


Figure S8.  $^{13}\text{C}$  NMR (75 MHz) spectrum of compound **6n** in  $\text{CDCl}_3$ .

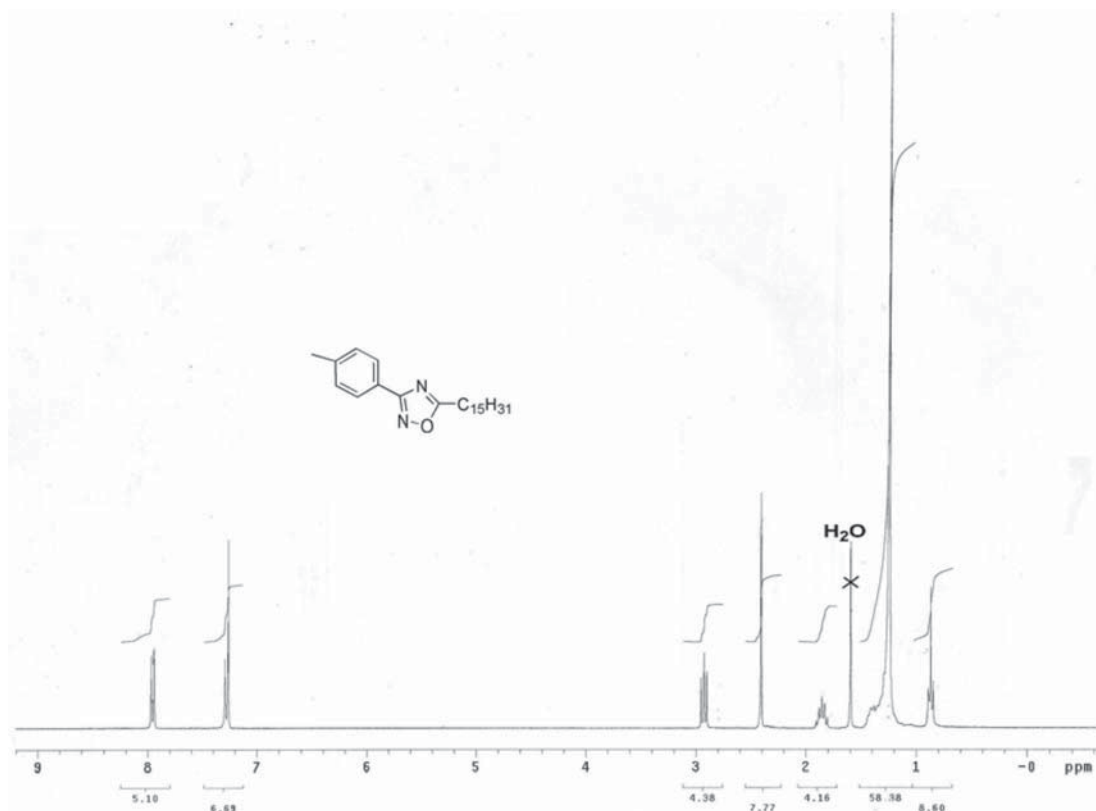


Figure S9.  $^1\text{H}$  NMR (300 MHz) spectrum of compound **6o** in  $\text{CDCl}_3$ .

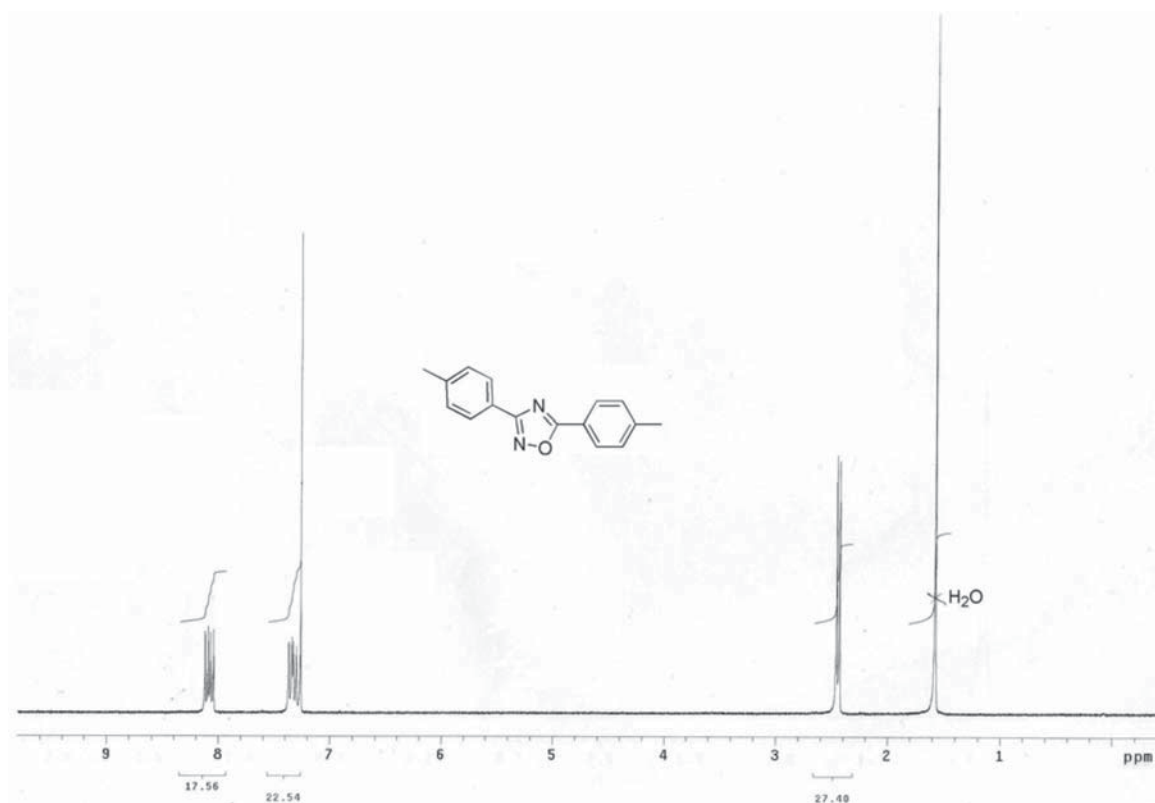


Figure S10. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6p** in CDCl<sub>3</sub>.

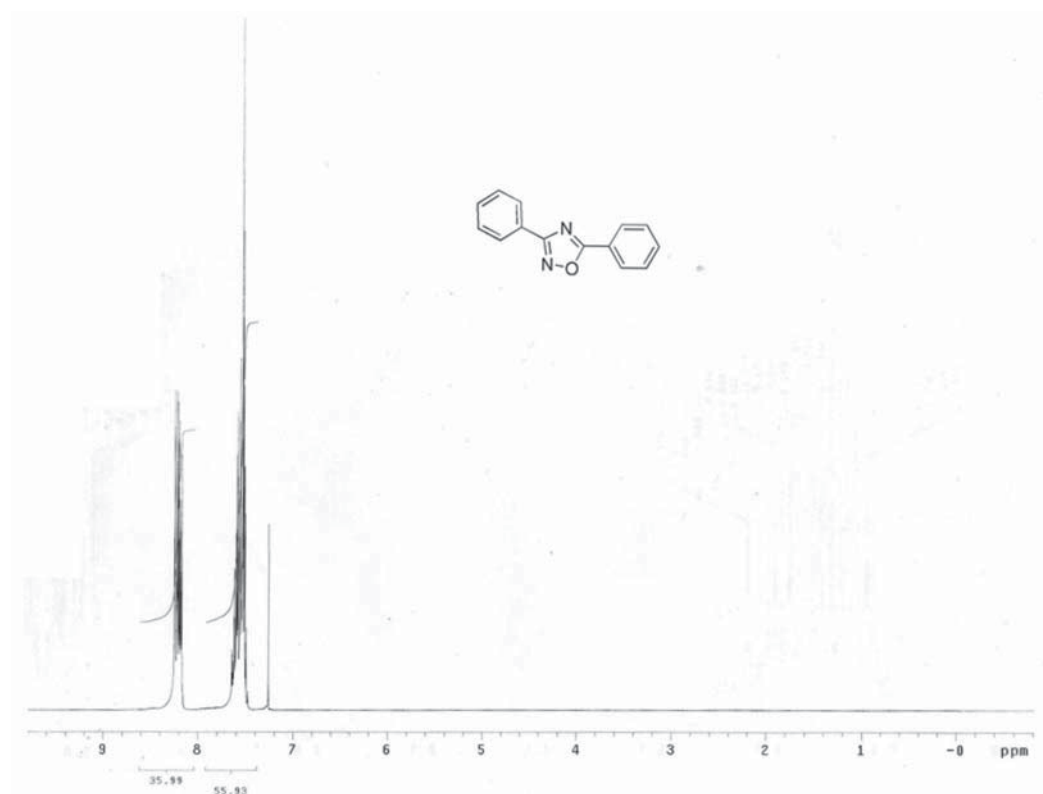


Figure S11. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6q** in CDCl<sub>3</sub>.



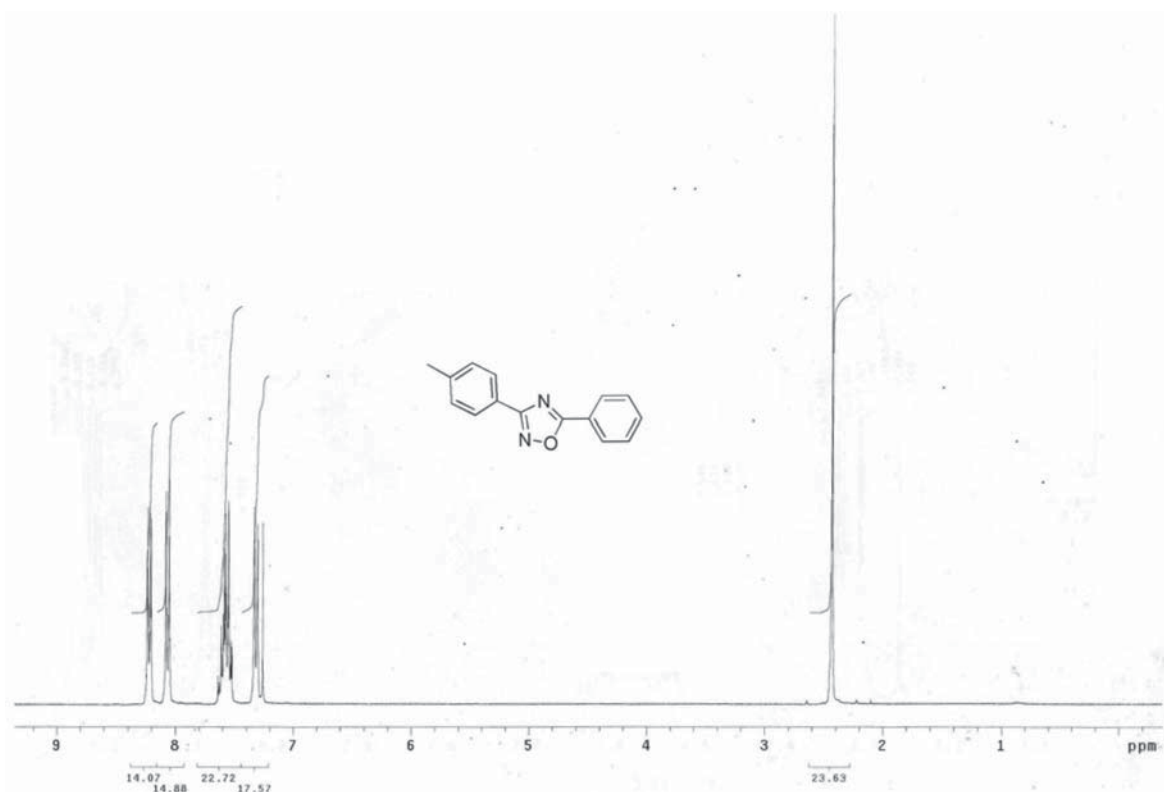


Figure S12. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6r** in CDCl<sub>3</sub>.

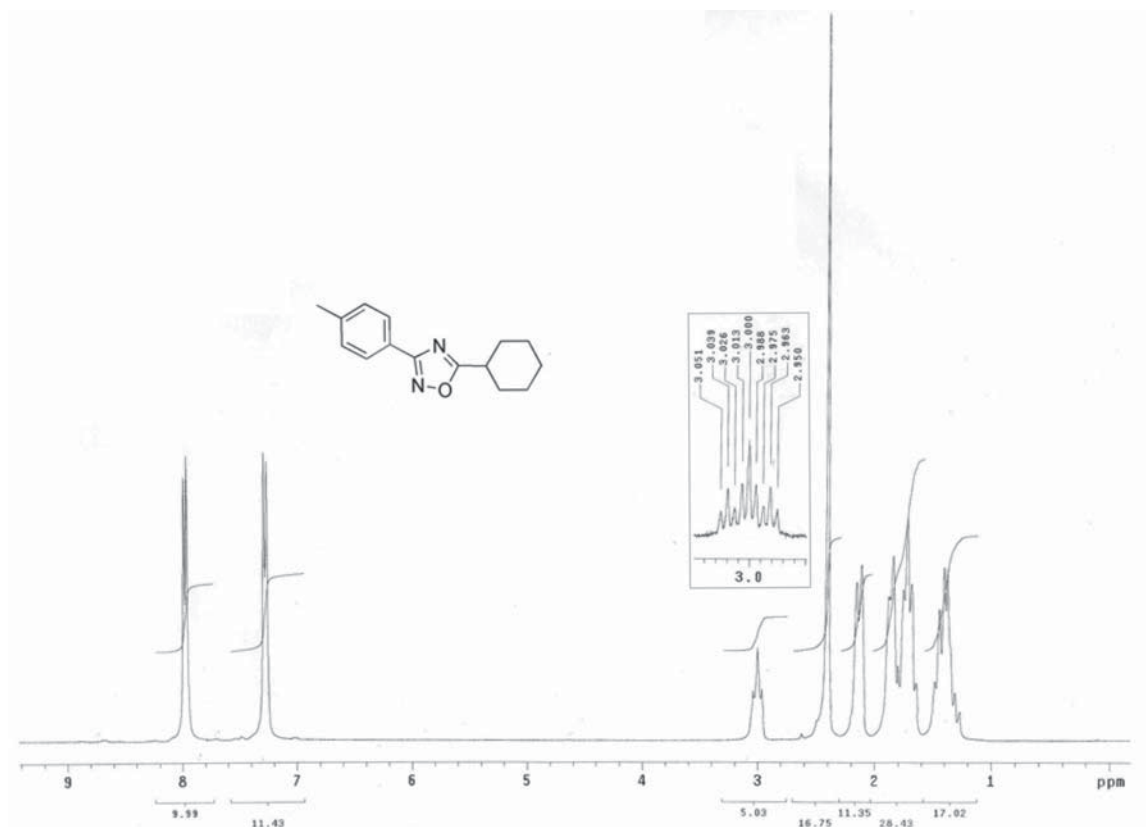


Figure S13. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6s** in CDCl<sub>3</sub>.

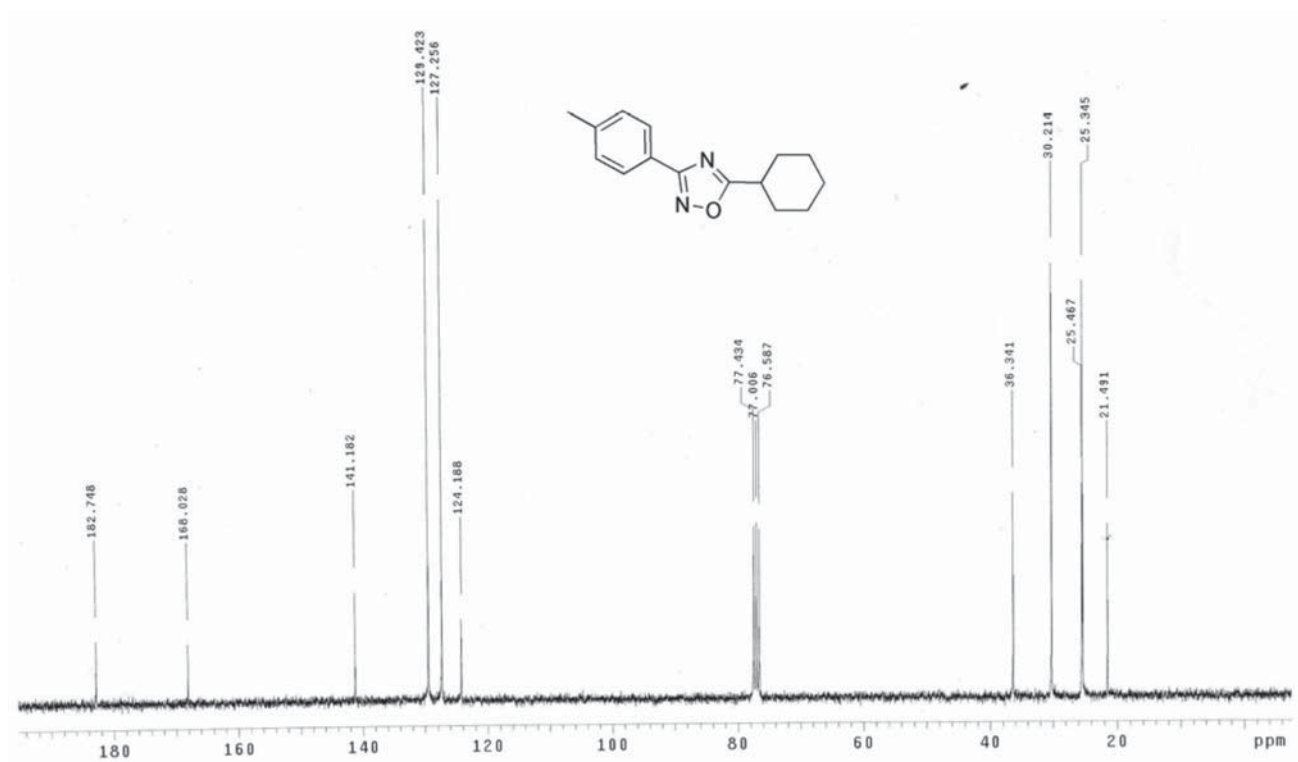


Figure S14. <sup>13</sup>C NMR (75 MHz) spectrum of compound **6s** in CDCl<sub>3</sub>.

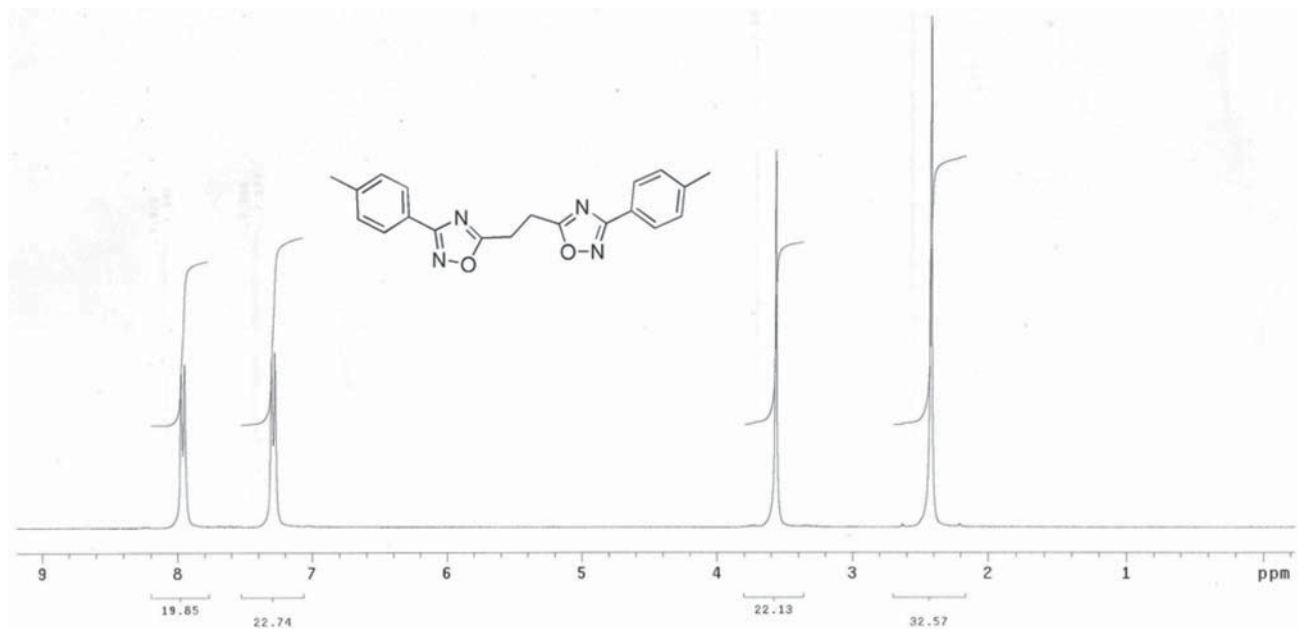


Figure S15. <sup>1</sup>H NMR (300 MHz) spectrum of compound **6t** in CDCl<sub>3</sub>.