**Supplementary material**

**Spectroscopic and quantum chemical elucidation of newly synthesized 1-aryl-3-methyl-3-phenylpyrrolidine-2,5-diones as potential anticonvulsant agents**

Jelena Petković Cvetković1, Bojan Božić2,\*, Nebojša Banjac3, Jelena Lađarević1, Vesna Vitnik4, Željko Vitnik4, Nataša Valentić1, Gordana Ušćumlić1

1 Faculty of Technology and Metallurgy, University of Belgrade, Karnegijeva 4, P. O. Box 3503, 11120, Belgrade, Serbia

2 Faculty of Biology, Institute of Physiology and Biochemistry, University of Belgrade, Studentski trg 16, 11000 Belgrade, Serbia

3 Faculty of Agriculture, Food Technology and Biochemistry, University of Belgrade, Nemanjina 6, 11080, Belgrade, Zemun, Serbia

4 Department of Chemistry, ICTM, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia

\*Correspondence: Bojan Božić

Faculty of Biology, Institute of Physiology and Biochemistry, University of Belgrade, Studentski trg 16, 11000 Belgrade, Serbia

E-mail address: bbozic@bio.bg.ac.rs (B. Božić)

Contents

[Characterization of investigated compounds 2](#_Toc1037594)

[Tables 6](#_Toc1037595)

[Figures 17](#_Toc1037596)

# Characterization of investigated compounds

**Untitled-1.tif**

*1-(4-Hydroxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (1, C17H15NO3). White solid; Yield: 52%; mp: 173.2–174.9 ºC; FT-IR (KBr): |ν| cm–1 = 1774 (C=O), 1687 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 9.78 (s, 1H, –OH), 7.50–7.27 (m, 5H, –C6H5), 7.12 (d, *J* = 8.0 Hz, 2H, –C6H4–), 6.87 (d, *J* = 8.0 Hz, 2H, –C6H4), 3.13 (s, 2H, –CH2–), 1.73 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 180.42 (C2), 175.03 (C5), 157.49 (Ph), 142.59 (Ph), 128.81 (Ph), 128.44 (Ph), 127.24 (Ph), 125.90 (Ph), 123.52(Ph), 115.49 (Ph), 47.53 (C4), 44.60 (C3), 24.51 (C6). Anal. calcd. for C17H15NO3: C, 72.58; H, 5.37; N, 4.98; Found: C, 72.44; H, 5.31; N, 4.89.

*1-(4-Methoxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (2, C18H17NO3). Black solid; Yield: 62%; mp: 104.0–126.0 ºC; FT-IR (KBr): |ν| cm–1 = 1772 (C=O), 1710 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.52–7.31 (m, 5H, –C6H5), 7.25 (d, *J* = 8.0 Hz, 2H, –C6H4–), 7.05 (d, *J* = 8.0 Hz, 2H, –C6H4–), 3.79 (s, 3H, –OCH3), 3.14 (ABq, 2H, ΔνAB = 8.72 Hz, *J* = 18Hz, –CH2–), 1.74 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 180.33 (C2), 174.94 (C5), 159.10 (Ph), 142.54 (Ph), 128.80 (Ph), 128.47 (Ph), 127.25 (Ph), 125.93 (Ph), 125.02 (Ph), 114.21 (Ph), 55.40 (–OCH3), 47.58 (C4), 44.61 (C3), 24.45 (C6). Anal. calcd. for C18H17NO3: C, 73.20; H, 5.80; N, 4.74; Found: C, 73.14; H, 5.71; N, 4.63.

*1-(4-Methylphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (3, C18H17NO2). White solid; Yield: 55%; mp: 105.5–106.6 ºC; FT-IR (KBr): |ν| cm–1 = 1772 (C=O), 1707 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.53–7.20 (m, 9H, –C6H5 and N–C6H4–), 3.17 (ABq, 2H, *J* = 18Hz, –CH2–), 2.35 (s, 3H, Ph–CH3), 1.75 (s, 3H, succ–CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 180.17 (C2), 174.77 (C5), 142.79 (Ph), 138.05 (Ph), 129.88 (Ph), 129.44 (Ph), 128.80 (Ph), 127.24 (Ph), 126.99 (Ph), 125.90 (Ph), 47.63 (C4), 44.62 (C3), 24.45 (C6), 20.71 (–CH3). Anal. calcd. for C18H17NO2: C, 77.40; H, 6.13; N, 5.01; Found: C, 77.34; H, 6.01; N, 4.93.

*1-phenyl-3-methyl-3-phenylpyrrolidine-2,5-dione* (4, C17H15NO2). White solid; Yield: 45%; mp: 105.5–106.6 ºC; FT-IR (KBr): |ν| cm–1 = 1784 (C=O), 1721 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.56–7.28 (m, 10H, –C6H5 and N–C6H5), 3.18 (ABq, 2H, *J* = 18Hz, –CH2–), 1.75 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 180.12 (C2), 174.72 (C5), 142.45 (Ph), 132.47 (Ph), 128.99 (Ph), 128.82 (Ph), 128.54 (Ph), 127.25 (Ph), 125.94 (Ph), 47.69 (C4), 44.64 (C3), 24.46 (C6). Anal. calcd. for C17H15NO2: C, 76.96; H, 5.70; N, 5.28; Found: C, 76.87; H, 5.61; N, 5.30.

*1-(4-Fluorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (5, C17H14NO2F). White solid; Yield: 57%; mp: 119.8–121.1 ºC; FT-IR (KBr): |ν| cm–1 = 1782 (C=O), 1712 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.54–7.28 (m, 9H, –C6H5 and N–C6H4–), 3.18 (s, 2H, –CH2–), 1.76 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 180.10 (C2), 174.68 (C5), 161.62 (d, *J* = 244.0 Hz, Ph), 142.41 (Ph), 129.49 (d, *J* = 9.0 Hz, Ph), 128.80 (Ph), 128.69 (d, *J* = 3 Hz, Ph), 127.28 (Ph), 125.98 (Ph), 115.91 (d, *J* = 22.5 Hz, Ph), 47.67 (C4), 44.64 (C3), 24.54 (C6). Anal. calcd. for C17H14NO2F: C, 72.07; H, 4.98; N, 4.94; Found: C, 72.00; H, 4.86; N, 4.30.

*1-(4-Chlorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (6, C17H14NO2Cl). White solid; Yield: 65%; mp: 120.2–122.2 ºC; FT-IR (KBr): |ν| cm–1 = 1778 (C=O), 1710 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.63–7.27 (m, 9H, –C6H5 and N–C6H4–), 3.18 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.75 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.90 (C2), 174.47 (C5), 142.32 (Ph), 133.02 (Ph), 131.29 (Ph), 129.03 (Ph), 128.78 (Ph), 127.28 (Ph), 125.96 (Ph), 47.70 (C4), 44.61 (C3), 24.58 (C6). Anal. calcd. for C17H14NO2Cl: C, 68.12; H, 4.71; N, 4.67; Found: C, 68.04; H, 4.59; N, 4.59.

*1-(3-Chlorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (7, C17H14NO2Cl). White solid; Yield: 66%; mp: 128.6–130.3 ºC; FT-IR (KBr): |ν| cm–1 = 1774 (C=O), 1709 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.56–7.28 (m, 9H, –C6H5 and N–C6H4–), 3.17 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.76 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.82 (C2), 174.37 (C5), 142.28 (Ph), 133.79 (Ph), 133.04 (Ph), 130.60 (Ph), 128.77 (Ph), 128.55 (Ph), 127.27 (Ph), 126.11 (Ph), 126.01 (Ph), 47.71 (C4), 44.68 (C3), 24.56 (C6). Anal. calcd. for C17H14NO2Cl: C, 68.12; H, 4.71; N, 4.67; Found: C, 68.07; H, 4.60; N, 4.59.

*1-(4-Bromophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (8, C17H13NO2Br). White solid; Yield: 66%; mp: 112.3–114.4 ºC; FT-IR (KBr): |ν| cm–1 = 1776 (C=O), 1709 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.73 (d, *J* = 8 Hz, 2H, –C6H4– ), 7.53–7.27 (m, 7H, –C6H5 and N–C6H4–), 3.18 (ABq, 2H, ΔνAB = 8.72 Hz, *J* = 18Hz, –CH2–), 1.75 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.86 (C2), 174.44 (C5), 142.32 (Ph), 131.99 (Ph), 131.73 (Ph), 129.35 (Ph), 128.80 (Ph), 127.29 (Ph), 125.97 (Ph), 121.53 (Ph), 47.72 (C4), 44.62 (C3), 24.57 (C6). Anal. calcd. for C17H14NO2Br: C, 59.32; H, 4.10; N, 4.07; Found: C, 59.25; H, 4.01; N, 3.99.

*1-(3-Bromophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (9, C17H13NO2Br). White solid; Yield: 66%; mp: 118.8–121.1 ºC; FT-IR (KBr): |ν| cm–1 = 1772 (C=O), 1709 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.69–7.28 (m, 9H, –C6H5 and N–C6H4–), 3.17 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.76 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.82 (C2), 174.38 (C5), 142.27 (Ph), 133.91 (Ph), 131.42 (Ph), 130.86 (Ph), 130.06 (Ph), 128.76 (Ph), 127.26 (Ph), 126.50 (Ph), 126.01 (Ph), 121.22 (Ph), 47.70 (C4), 44.68 (C3), 24.56 (C6). Anal. calcd. for C17H14NO2Br: C, 59.32; H, 4.10; N, 4.07; Found: C, 59.22; H, 4.03; N, 3.97.

*1-(4-Carboxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (10, C18H15NO4). White solid; Yield: 61%; mp: 173.5–174.7 ºC; FT-IR (KBr): |ν| cm–1 = 1783 (C=O), 1710 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 13.15 (bs, 1H,–COOH), 8.09 (d, *J* = 10 Hz, 2H, –C6H4– ), 7.54–7.28 (m, 7H, –C6H5 and N–C6H4–), 3.21 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.76 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.85 (C2), 174.44 (C5), 166.76 (–COOH), 142.31 (Ph), 136.27 (Ph), 130.68 (Ph), 130.02 (Ph), 128.85 (Ph), 127.36 (Ph), 127.25 (Ph), 125.99 (Ph), 47.81 (C4), 44.65 (C3), 24.58 (C6). Anal. calcd. for C18H15NO4: C, 69.89; H, 4.89; N, 4.53; Found: C, 69.72; H, 4.73; N, 4.46.

*1-(4-Cyanophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (11, C18H14N2O2). White solid; Yield: 58%; mp: 93.9–95.3 ºC; FT-IR (KBr): |ν| cm–1 = 1784 (C=O), 1713 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 8.01 (d, *J* = 8 Hz, 2H, –C6H4– ), 7.63 (d, *J* = 10 Hz, 2H, –C6H4– ), 7.55–7.28 (m, 5H, –C6H5), 3.21 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.77 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.61 (C2), 174.17 (C5), 142.18 (Ph), 136.51 (Ph), 133.08 (Ph), 128.80 (Ph), 127.34 (Ph), 128.05 (Ph), 126.01 (Ph), 118.35 (–CN), 111.09 (Ph), 47.81 (C4), 44.62 (C3), 24.61 (C6). Anal. calcd. for C18H14N2O2: C, 74.47; H, 4.86; N, 9.65; Found: C, 74.39; H, 4.79; N, 9.67.

*1-(4-Nitrophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione* (12, C17H13N2O4). White solid; Yield: 60%; mp: 106.9–108.1 ºC; FT-IR (KBr): |ν| cm–1 = 1773 (C=O), 1705 (C=O); 1H NMR (200 MHz, DMSO): |δ| ppm = 7.95 (d, *J* = 8 Hz, 2H, –C6H4– ), 7.71 (d, *J* = 10 Hz, 2H, –C6H4– ), 7.55–7.27 (m, 5H, –C6H5), 3.23 (ABq, 2H, ΔνAB = 12.65 Hz, *J* = 18Hz, –CH2–), 1.85 (s, 3H, –CH3); 13C NMR (50 MHz, DMSO): |δ| ppm = 179.61 (C2), 174.17 (C5), 142.15 (Ph), 138.05 (Ph), 128.82 (Ph), 128.21 (Ph), 127.37 (Ph), 128.05 (Ph), 126.03 (Ph), 112.42 (Ph), 47.86 (C4), 44.61 (C3), 24.60 (C6). Anal. calcd. for C17H13N2O4: C, 66.00; H, 4.24; N, 9.06; Found: C, 59.94; H, 4.26; N, 9.09.

# Tables

Table S1. Long-frequencies UV absorption maxima of 1-aryl-3-methyl-3-pheylpyrrolidine-2,5-diones **1**–**12** in ethanol and Hammett constants for corresponding substituents.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Comp. No. | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| νmax × 10-3 | 43.48 | 43.48 | 45.87 | 48.31 | 46.30 | 44.44 | 47.62 | 43.48 | 47.62 | 41.67 | 41.32 | 36.63 |
| σp/m | -0.37 | -0.27 | -0.17 | 0.00 | 0.06 | 0.23 | 0.37 | 0.23 | 0.39 | 0.45 | 0.66 | 0.78 |

Table S2. 13C NMR chemical shifts (δ/ppm) of the investigated succinimides.

|  |  |  |  |
| --- | --- | --- | --- |
| No. | Substituents | SCS in δ/ppm | |
| C2 | C5 |
| **1** | 4-OH | 0.30 | 0.31 |
| **2** | 4-OCH3 | 0.21 | 0.22 |
| **3** | 4-CH3 | 0.05 | 0.05 |
| **4** | H | 180.12 | 174.72 |
| **5** | 4-F | -0.02 | -0.04 |
| **6** | 4-Cl | -0.22 | -0.25 |
| **7** | 3-Cl | -0.30 | -0.35 |
| **8** | 4-Br | -0.11 | -0.15 |
| **9** | 3-Br | -0.30 | -0.34 |
| **10** | 4-COOH | -0.27 | -0.28 |
| **11** | 4-CN | -0.51 | -0.55 |
| **12** | 4-NO2 | -0.51 | -0.55 |

Table S3. Electronic energies (*E*HF) and ZPE corrected energies (*E*ZPE) in a.u., relative energies (*E*R) in kcal mol-1 and the statistical Boltzmann distribution weighted values (*ω*) of all isomers for the compound **4** obtained by B3LYP and M06-2X methods and a 6-311G(d,p) basis set.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Conf.** | **B3LYP** | | | | | | | | | | | |
|  | **Vacuum** | | | | **Ethanol** | | | | **DMSO** | | | |
|  | *E*HF | *E*ZPE | *E*R | *ω* | *E*HF | *E*ZPE | *E*R | *ω* | *E*HF | *E*ZPE | *E*R | *ω* |
| **I** | -862.292747 | -862.012164 | 0.02 | 35.3 | -862.305019 | -862.024885 | 0.15 | 22.2 | -862.305319 | -862.025215 | 0.15 | 22.2 |
| **II** | -862.292075 | -862.011389 | 0.51 | 15.6 | -862.305248 | -862.025033 | 0.05 | 25.9 | -862.305575 | -862.025370 | 0.05 | 26.2 |
| **III** | -862.292670 | -862.012202 | 0 | 36.7 | -862.305021 | -862.024943 | 0.11 | 23.6 | -862.305319 | -862.025249 | 0.13 | 23.1 |
| **IV** | -862.291781 | -862.011169 | 0.65 | 12.4 | -862.305242 | -862.025118 | 0 | 28.3 | -862.305575 | -862.025450 | 0 | 28.5 |
|  | **M06-2X** | | | | | | | | | | | |
| **I** | -861.944531 | -861.660608 | 0.16 | 23.9 | -861.957569 | -861.674089 | 0.49 | 16.2 | -861.957887 | -861.674422 | 0.48 | 16.2 |
| **II** | -861.944911 | -861.660861 | 0 | 31.1 | -861.958511 | -861.674864 | 0 | 36.5 | -861.958832 | -861.675192 | 0 | 36.4 |
| **III** | -861.944588 | -861.660724 | 0.09 | 27.0 | -861.957522 | -861.674065 | 0.50 | 15.7 | -861.957828 | -861.674373 | 0.51 | 15.3 |
| **IV** | -861.944568 | -861.660342 | 0.33 | 18.0 | -861.958265 | -861.674728 | 0.09 | 31.6 | -861.958595 | -861.675074 | 0.07 | 32.1 |

*E*R = *E*ZPE (i) - *E*ZPE (0); *E*ZPE (0) - ZPE corrected energy of the most stable conformer

Table S4. Energy of HOMO and LUMO, and HOMO-LUMO energy gaps (eV) obtained by B3LYP and M06-2X calculations for the investigated succinimides in vacuum, ethanol and DMSO

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | B3LYP | | | | | | | | |
|  | Vacuum | | | Ethanol | | | DMSO | | |
|  | *E*HOMO | *E*LUMO | Δ*E* | *E*HOMO | *E*LUMO | Δ*E* | *E*HOMO | *E*LUMO | Δ*E* |
|  | eV | eV | eV | eV | eV | eV | eV | eV | eV |
| **1** | -6.24 | -0.83 | -5.40 | -6.52 | -0.89 | -5.63 | -6.54 | -0.90 | -5.65 |
| **2** | -6.14 | -0.79 | -5.34 | -6.43 | -0.88 | -5.55 | -6.44 | -0.89 | -5.55 |
| **3** | -6.57 | -0.84 | -5.74 | -6.90 | -0.91 | -5.99 | -6.88 | -0.89 | -5.98 |
| **4** | -6.82 | -0.89 | -5.93 | -7.01 | -0.91 | -6.09 | -7.01 | -0.92 | -6.09 |
| **5** | -6.79 | -0.98 | -5.81 | -7.00 | -0.94 | -6.06 | -7.00 | -0.94 | -6.06 |
| **6** | -6.80 | -1.11 | -5.69 | -7.00 | -1.13 | -5.86 | -7.00 | -1.13 | -5.87 |
| **7** | -6.94 | -1.13 | -5.81 | -7.02 | -1.16 | -5.87 | -7.03 | -1.15 | -5.88 |
| **8** | -6.74 | -1.11 | -5.63 | -6.95 | -1.14 | -5.81 | -6.94 | -1.15 | -5.78 |
| **9** | -6.84 | -1.12 | -5.72 | -7.01 | -1.15 | -5.86 | -7.01 | -1.15 | -5.86 |
| **10** | -7.10 | -1.76 | -5.34 | -7.04 | -1.90 | -5.14 | -7.04 | -1.91 | -5.13 |
| **11** | -7.22 | -1.87 | -5.35 | -7.05 | -1.94 | -5.12 | -7.05 | -1.94 | -5.11 |
| **12** | -7.27 | -2.67 | -4.60 | -7.06 | -2.89 | -4.17 | -7.06 | -2.90 | -4.16 |
|  | M06-2X | | | | | | | | |
| **1** | -7.49 | 0.12 | -7.61 | -7.78 | 0.14 | -7.92 | -7.79 | 0.14 | -7.93 |
| **2** | -7.39 | 0.16 | -7.56 | -7.71 | 0.10 | -7.81 | -7.71 | 0.08 | -7.79 |
| **3** | -7.80 | 0.08 | -7.88 | -8.10 | 0.01 | -8.11 | -8.11 | 0.01 | -8.13 |
| **4** | -8.05 | 0.02 | -8.07 | -8.35 | -0.04 | -8.30 | -8.35 | -0.04 | -8.31 |
| **5** | -8.04 | -0.03 | -8.01 | -8.30 | 0.01 | -8.31 | -8.31 | 0.01 | -8.32 |
| **6** | -8.04 | -0.20 | -7.84 | -8.27 | -0.25 | -8.02 | -8.31 | -0.16 | -8.15 |
| **7** | -8.19 | -0.21 | -7.98 | -8.42 | -0.26 | -8.16 | -8.43 | -0.26 | -8.16 |
| **8** | -7.98 | -0.11 | -7.87 | -8.20 | -0.27 | -7.93 | -8.21 | -0.27 | -7.93 |
| **9** | -8.11 | -0.23 | -7.88 | -8.35 | -0.27 | -8.08 | -8.36 | -0.28 | -8.08 |
| **10** | -8.32 | -0.76 | -7.56 | -8.44 | -0.93 | -7.51 | -8.44 | -0.94 | -7.50 |
| **11** | -8.46 | -0.92 | -7.54 | -8.46 | -0.99 | -7.47 | -8.47 | -0.96 | -7.51 |
| **12** | -8.63 | -1.51 | -7.12 | -8.48 | -1.73 | -6.75 | -8.47 | -1.73 | -6.74 |

Table S5. Evaluation of drug candidates.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| No. | Molecular weight | log *Pc* | Hydrogen bonds | | Rotatable bonds | Polar surface area/Å2c |
| Donorsa | Acceptorsb |
| **1** | 281.31 | 2.09 | 1 | 4 | 2 | 57.61 |
| **2** | 295.34 | 2.63 | 0 | 4 | 3 | 46.61 |
| **3** | 279.34 | 3.02 | 0 | 3 | 2 | 37.38 |
| **4** | 265.31 | 2.57 | 0 | 3 | 2 | 37.38 |
| **5** | 283.30 | 2.73 | 0 | 3 | 2 | 37.38 |
| **6** | 299.76 | 3.25 | 0 | 3 | 2 | 37.38 |
| **7** | 299.76 | 3.23 | 0 | 3 | 2 | 37.38 |
| **8** | 344.21 | 3.38 | 0 | 3 | 2 | 37.38 |
| **9** | 344.21 | 3.36 | 0 | 3 | 2 | 37.38 |
| **10** | 309.32 | 2.48 | 1 | 5 | 3 | 74.68 |
| **11** | 290.32 | 2.33 | 0 | 4 | 2 | 61.17 |
| **12** | 310.31 | 2.53 | 0 | 6 | 3 | 83.20 |
| Methsuximide | 203.24 | 1.34 | 0 | 3 | 1 | 37.38 |
| Ideal compound | <500 | <5 | <5 | <10 | <8 | <140 |

a A donor indicates any O–H or N–H group.

b An acceptor indicates any O or N including those in donor groups.

c Parameters calculated by the program Molinspiration.

Table S6. PASS predictions for the investigated succinimides (**1**–**12**). *Pa* and *Pi* represent probabilities that the investigated molecule will be active and inactive, respectively.

*Note*: Only the results with *Pa* > 0.7 are presented

*1-(4-Hydroxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**1**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.853 | 0.023 | CYP2C12 substrate |
| 0.796 | 0.020 | Antiseborrheic |
| 0.788 | 0.028 | Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 0.733 | 0.004 | Tetrahydroxynaphthalene reductase inhibitor |
| 0.730 | 0.010 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.718 | 0.016 | Glutathione thiolesterase inhibitor |
| 0.731 | 0.054 | Aspulvinone dimethylallyltransferase inhibitor |
| 0.721 | 0.061 | Ubiquinol-cytochrome-c reductase inhibitor |

*1-(4-Methoxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**2**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.764 | 0.044 | Aspulvinone dimethylallyltransferase inhibitor |
| 0.735 | 0.038 | Gluconate 2-dehydrogenase (acceptor) inhibitor |
| 0.721 | 0.053 | CYP2C12 substrate |

*1-(4-Methylphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**3**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.783 | 0.030 | Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 0.735 | 0.010 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.712 | 0.046 | CYP2J substrate |
| 0.717 | 0.054 | CYP2C12 substrate |

*1-phenyl-3-methyl-3-phenylpyrrolidine-2,5-dione*(**4**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.823 | 0.020 | Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 0.806 | 0.005 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.746 | 0.008 | Anticonvulsant |
| 0.731 | 0.005 | CYP2A8 substrate |
| 0.740 | 0.050 | CYP2C12 substrate |
| 0.703 | 0.015 | Phosphatidylcholine-retinol O-acyltransferase inhibitor |
| 0.727 | 0.042 | CYP2J substrate |
| 0.705 | 0.022 | Lysase inhibitor |

*1-(4-Fluorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**5**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.748 | 0.008 | Anticonvulsant |

*1-(4-Chlorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**6**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.830 | 0.003 | CYP2A8 substrate |
| 0.809 | 0.005 | Anticonvulsant |
| 0.803 | 0.005 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.764 | 0.048 | Phobic disorders treatment |
| 0.734 | 0.039 | CYP2J substrate |
| 0.709 | 0.021 | 5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor |
| 0.704 | 0.034 | Glycosylphosphatidylinositol phospholipase D inhibitor |

*1-(3- Chlorophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**7**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.835 | 0.005 | Anticonvulsant |
| 0.809 | 0.004 | CYP2A8 substrate |
| 0.774 | 0.007 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.734 | 0.027 | Glycosylphosphatidylinositol phospholipase D inhibitor |
| 0.731 | 0.062 | Phobic disorders treatment |
| 0.706 | 0.048 | CYP2J substrate |

*1-(4-Bromophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**8**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.778 | 0.006 | Anticonvulsant |

*1-(3- Bromophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**9**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.807 | 0.005 | Anticonvulsant |

*1-(4-Carboxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**10**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.909 | 0.005 | Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 0.848 | 0.004 | Phosphatidylcholine-retinol O-acyltransferase inhibitor |
| 0.825 | 0.006 | Pullulanase inhibitor |
| 0.823 | 0.005 | Glutathione thiolesterase inhibitor |
| 0.823 | 0.005 | Ribulose-phosphate 3-epimerase inhibitor |
| 0.803 | 0.004 | Electron-transferring-flavoprotein dehydrogenase inhibitor |
| 0.798 | 0.004 | Cholestanetriol 26-monooxygenase inhibitor |
| 0.799 | 0.006 | Creatininase inhibitor |
| 0.806 | 0.017 | Alkenylglycerophosphocholine hydrolase inhibitor |
| 0.798 | 0.019 | Antieczematic |
| 0.787 | 0.009 | Fusarinine-C ornithinesterase inhibitor |
| 0.781 | 0.004 | Arylalkyl acylamidase inhibitor |
| 0.772 | 0.004 | Phenol O-methyltransferase inhibitor |
| 0.767 | 0.005 | 1,4-Lactonase inhibitor |
| 0.772 | 0.011 | 5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor |
| 0.763 | 0.004 | Ferredoxin-NAD+ reductase inhibitor |
| 0.763 | 0.004 | Naphthalene 1,2-dioxygenase inhibitor |
| 0.775 | 0.017 | Taurine dehydrogenase inhibitor |
| 0.768 | 0.011 | Glucan endo-1,6-beta-glucosidase inhibitor |
| 0.761 | 0.007 | 3-Hydroxybenzoate 6-monooxygenase inhibitor |
| 0.760 | 0.009 | UDP-N-acetylglucosamine 4-epimerase inhibitor |
| 0.756 | 0.006 | L-glutamate oxidase inhibitor |
| 0.773 | 0.025 | Chlordecone reductase inhibitor |
| 0.757 | 0.010 | NADPH-cytochrome-c2 reductase inhibitor |
| 0.751 | 0.007 | Gluconate 5-dehydrogenase inhibitor |
| 0.756 | 0.016 | Glutamyl endopeptidase II inhibitor |
| 0.750 | 0.010 | Bisphosphoglycerate phosphatase inhibitor |
| 0.748 | 0.008 | Polyamine-transporting ATPase inhibitor |
| 0.744 | 0.005 | Chenodeoxycholoyltaurine hydrolase inhibitor |
| 0.740 | 0.005 | Tryptophanamidase inhibitor |
| 0.741 | 0.008 | Methylamine-glutamate N-methyltransferase inhibitor |
| 0.743 | 0.010 | Dimethylargininase inhibitor |
| 0.740 | 0.008 | Pterin deaminase inhibitor |
| 0.735 | 0.004 | Cyclohexyl-isocyanide hydratase inhibitor |
| 0.736 | 0.012 | Alkane 1-monooxygenase inhibitor |
| 0.727 | 0.004 | Mannan endo-1,4-beta-mannosidase inhibitor |
| 0.735 | 0.018 | Dehydro-L-gulonate decarboxylase inhibitor |
| 0.724 | 0.007 | Spermidine dehydrogenase inhibitor |
| 0.719 | 0.008 | Poly(alpha-L-guluronate) lyase inhibitor |
| 0.715 | 0.005 | (R)-Pantolactone dehydrogenase (flavin) inhibitor |
| 0.717 | 0.012 | 2-Hydroxymuconate-semialdehyde hydrolase inhibitor |
| 0.709 | 0.004 | N-acetylneuraminate synthase inhibitor |
| 0.708 | 0.005 | Opheline kinase inhibitor |
| 0.708 | 0.005 | Taurocyamine kinase inhibitor |
| 0.708 | 0.006 | Aminobutyraldehyde dehydrogenase inhibitor |
| 0.707 | 0.005 | Long-chain-aldehyde dehydrogenase inhibitor |
| 0.713 | 0.013 | 2-Hydroxyquinoline 8-monooxygenase inhibitor |
| 0.728 | 0.028 | Sugar-phosphatase inhibitor |
| 0.712 | 0.012 | N-acetylneuraminate 7-O(or 9-O)-acetyltransferase inhibitor |
| 0.705 | 0.007 | NADH kinase inhibitor |
| 0.704 | 0.008 | Gamma-guanidinobutyraldehyde dehydrogenase inhibitor |
| 0.706 | 0.009 | Mitochondrial processing peptidase inhibitor |
| 0.702 | 0.007 | Peptide alpha-N-acetyltransferase inhibitor |
| 0.713 | 0.022 | Sphinganine kinase inhibitor |
| 0.713 | 0.026 | Glutamate-5-semialdehyde dehydrogenase inhibitor |
| 0.715 | 0.063 | Ubiquinol-cytochrome-c reductase inhibitor |

*1-(4-Cyanophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**11**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.864 | 0.020 | CYP2C12 substrate |
| 0.770 | 0.005 | Neurotransmitter uptake inhibitor |

*1-(4-Nitrophenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione*(**12**)

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.770 | 0.013 | Lysase inhibitor |
| 0.792 | 0.036 | Ubiquinol-cytochrome-c reductase inhibitor |
| 0.766 | 0.011 | Fusarinine-C ornithinesterase inhibitor |
| 0.759 | 0.012 | Glucan endo-1,6-beta-glucosidase inhibitor |
| 0.721 | 0.009 | Anticonvulsant |
| 0.701 | 0.044 | Acrocylindropepsin inhibitor |
| 0.701 | 0.044 | Chymosin inhibitor |
| 0.701 | 0.044 | Saccharopepsin inhibitor |

**Parent compound**: Methsuximide

|  |  |  |
| --- | --- | --- |
| *Pa* | *Pi* | *Receptors* |
| 0.909 | 0.004 | Anticonvulsant |
| 0.847 | 0.003 | CYP2A8 substrate |
| 0.823 | 0.020 | Testosterone 17beta-dehydrogenase (NADP+) inhibitor |
| 0.772 | 0.014 | Nicotinic alpha2beta2 receptor antagonist |
| 0.745 | 0.005 | 4-Nitrophenol 2-monooxygenase inhibitor |
| 0.738 | 0.005 | CYP2A2 substrate |
| 0.767 | 0.044 | CYP2C12 substrate |
| 0.740 | 0.023 | Nicotinic alpha6beta3beta4alpha5 receptor antagonist |
| 0.727 | 0.010 | 27-Hydroxycholesterol 7alpha-monooxygenase inhibitor |
| 0.703 | 0.015 | Phosphatidylcholine-retinol O-acyltransferase inhibitor |
| 0.709 | 0.047 | CYP2J substrate |

# Figures

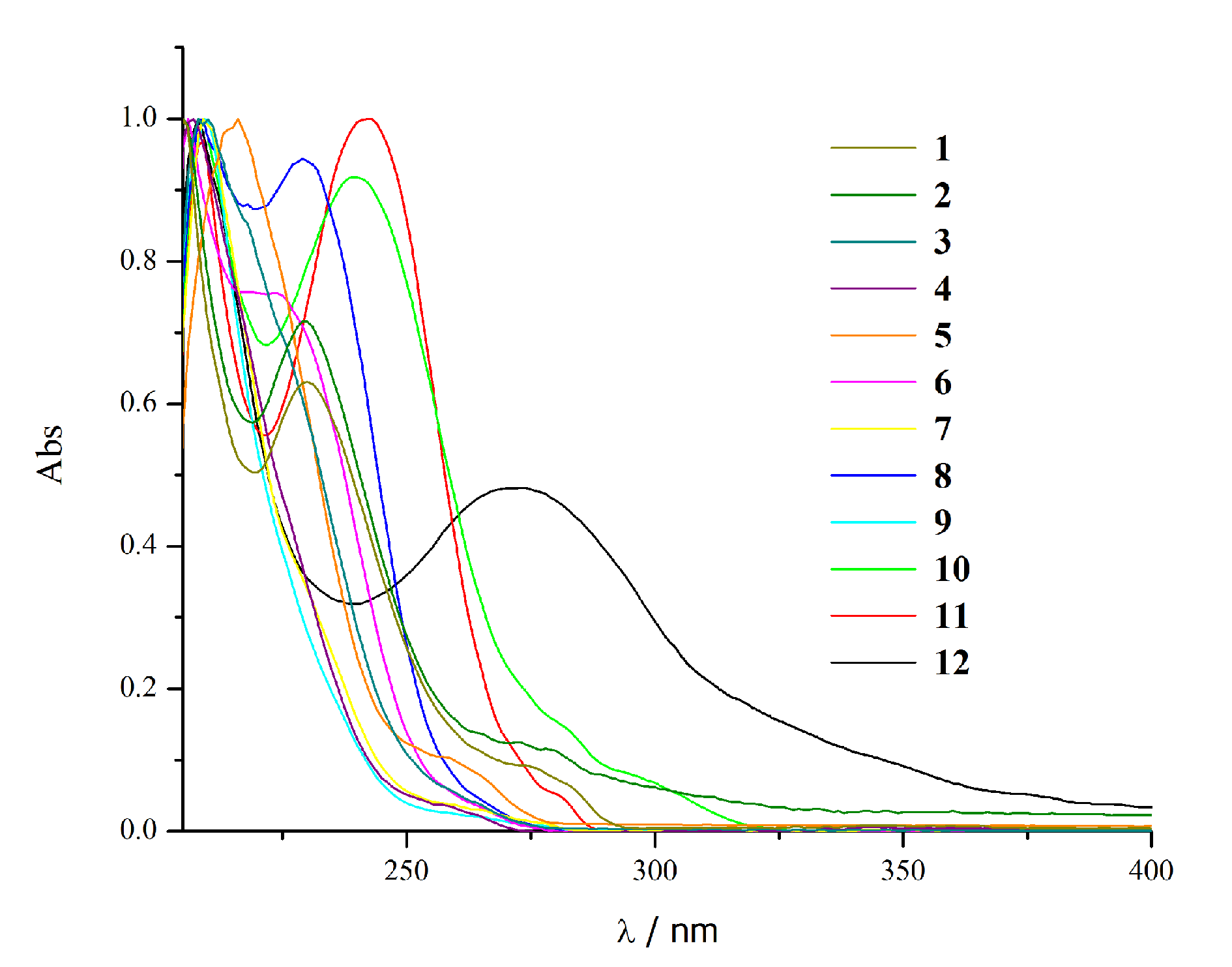


Figure S1. Normalized UV absorption spectra of the investigated compounds in ethanol.

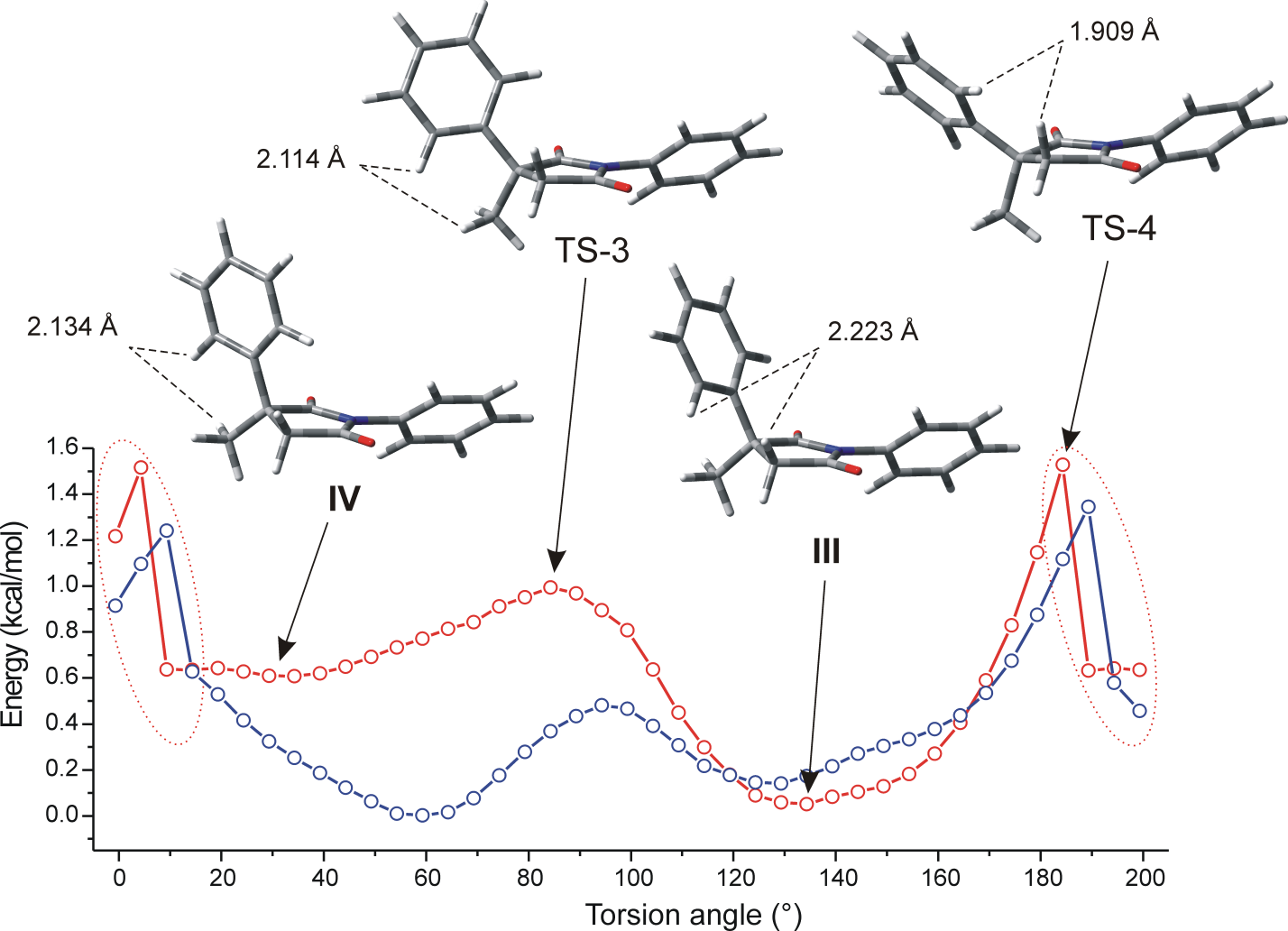


Figure S2. Potential energy scans for rotation of the 3-phenyl group, in vacuum (red) and ethanol (blue) carried out by the B3LYP/6-311G(d,p) method (*N*-phenyl group torsion angle of ~136°).

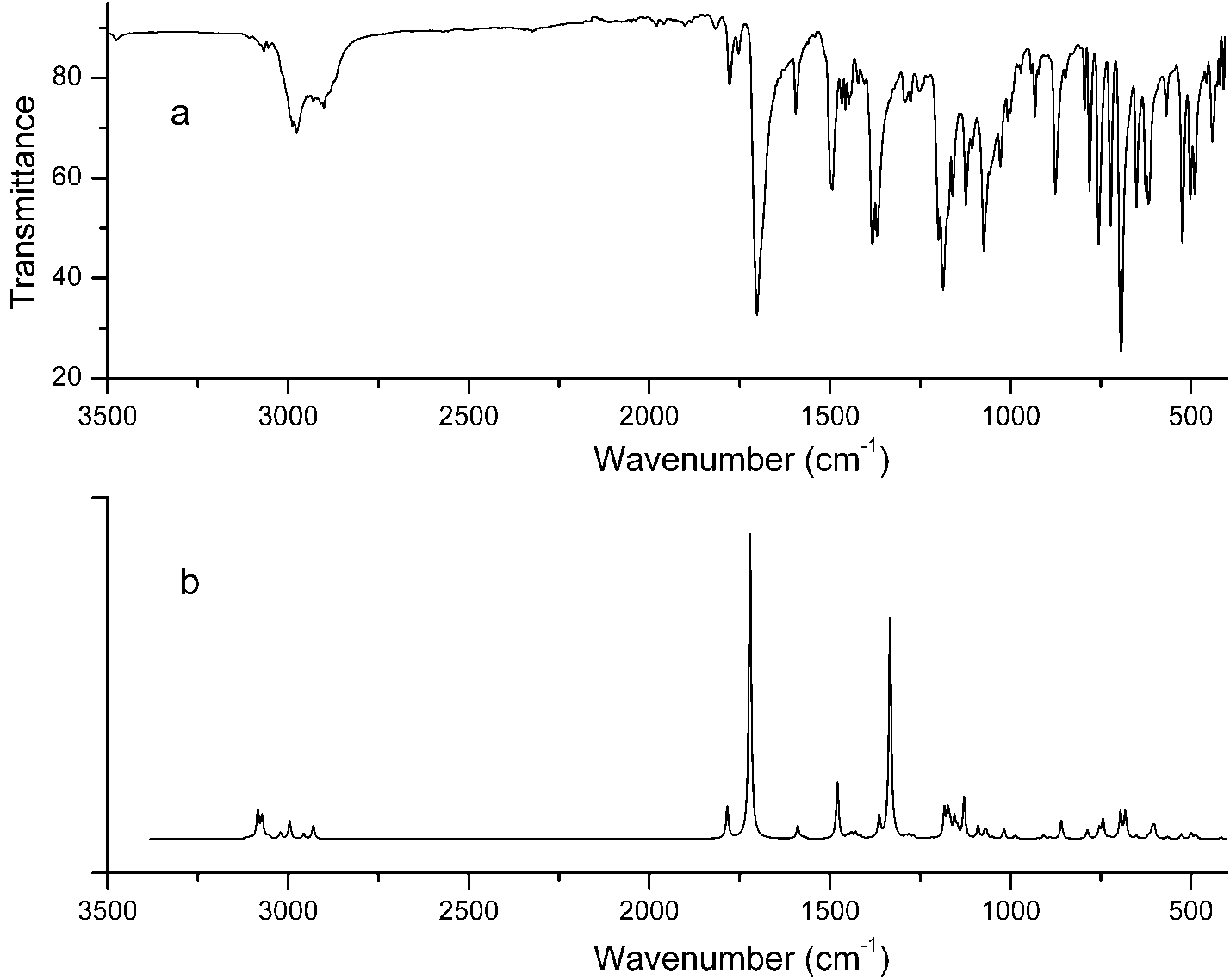


Figure S3. The experimental a) and calculated b) infrared spectrum of the compound **4**.

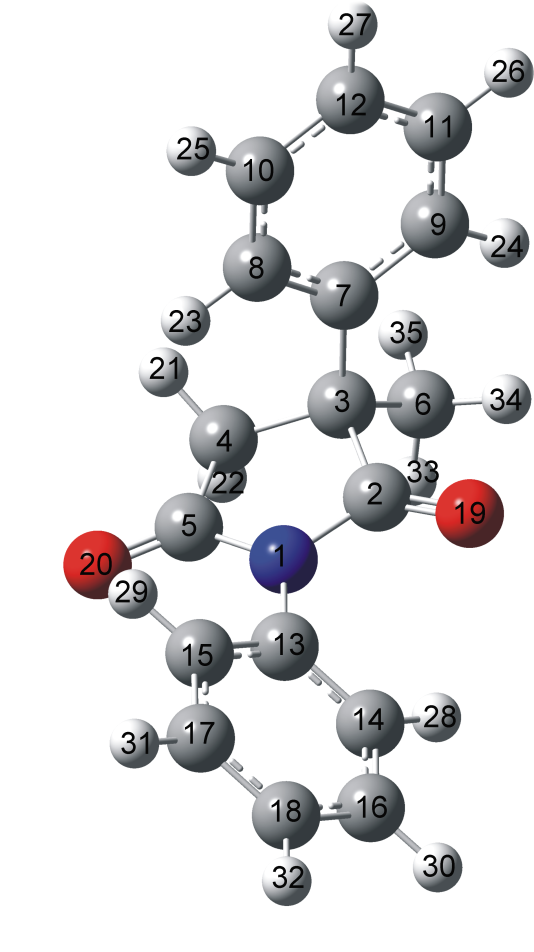


Figure S4. Atom numbering in the investigated succinimide **4**.

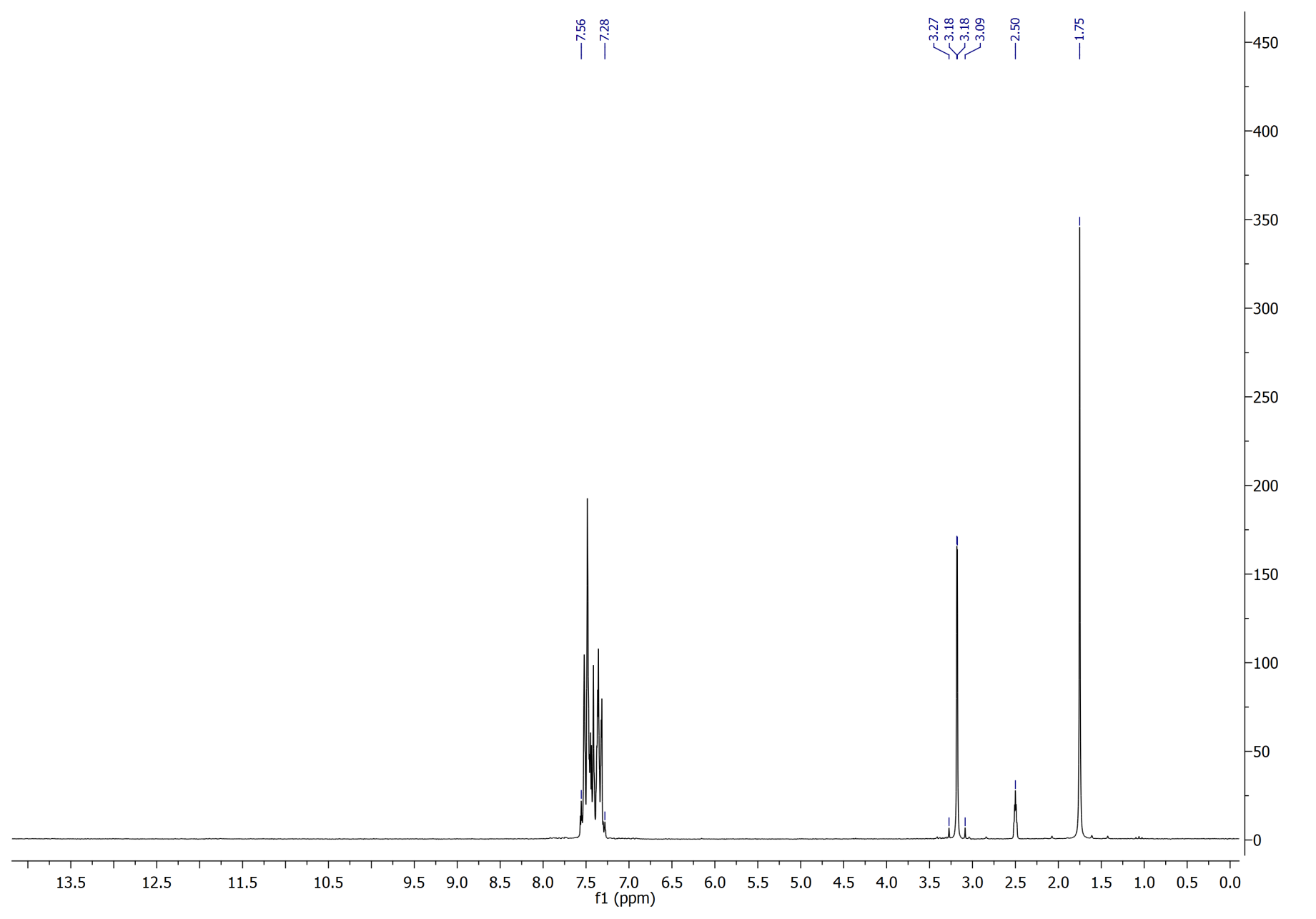


Figure S5. The 1H NMR spectrum of the compound **4** recorded in DMSO-*d6*.

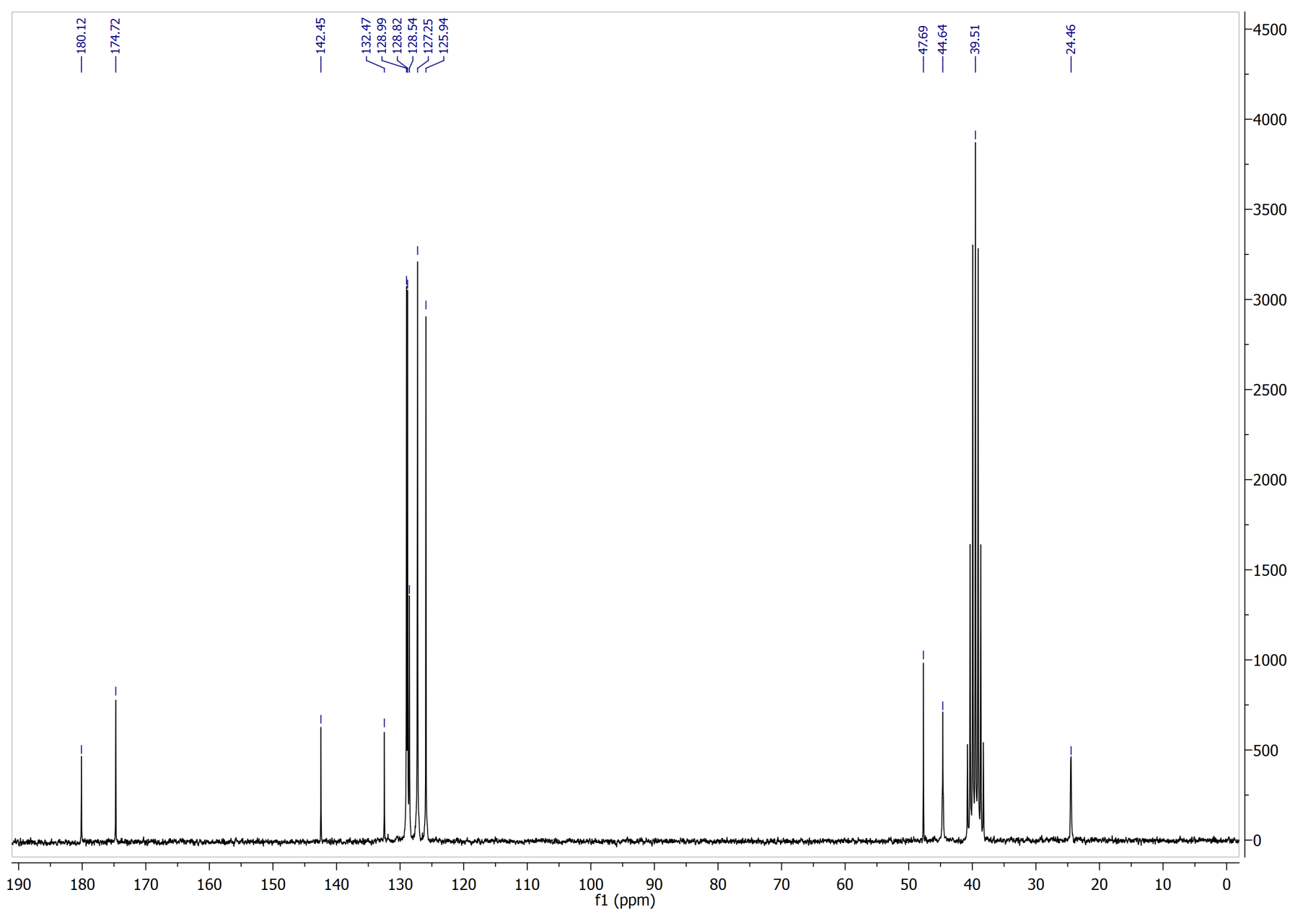


Figure S6. The 13C NMR spectrum of the compound **4** recorded in DMSO-*d6*.