Supplementary material to

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

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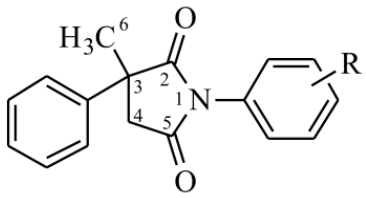
CHARACTERIZATION OF INVESTIGATED COMPOUNDS



No.	R
1	4-OH
2	4-OMe
3	4-Me
4	H
5	4-F
6	4-Cl
7	3-Cl
8	4-Br
9	3-Br
10	4-COOH
11	4-CN
12	4-NO_2

1-(4-Hydroxyphenyl)-3-methyl-3-phenylpyrrolidine-2,5-dione (**1**, $C_{17}H_{15}NO_3$). White solid; Yield: 52%; mp: 173.2–174.9 °C; FT-IR (KBr): |ν| cm^{-1} = 1774 (C=O), 1687 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 9.78 (s, 1H, –OH), 7.50–7.27 (m, 5H, $–C_6H_5$), 7.12 (d, *J* = 8.0 Hz, 2H, $–C_6H_4–$), 6.87 (d, *J* = 8.0 Hz, 2H, $–C_6H_4$), 3.13 (s, 2H, $–CH_2–$), 1.73 (s, 3H, $–CH_3$); ^{13}C 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 $C_{17}H_{15}NO_3$: 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**, $C_{18}H_{17}NO_3$). Black solid; Yield: 62%; mp: 104.0–126.0 °C; FT-IR (KBr): |ν| cm^{-1} = 1772 (C=O), 1710 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.52–7.31 (m, 5H, $–C_6H_5$), 7.25 (d, *J* = 8.0 Hz, 2H, $–C_6H_4–$), 7.05 (d, *J* = 8.0 Hz, 2H, $–C_6H_4–$), 3.79 (s, 3H, $–OCH_3$), 3.14 (ABq, 2H, $\Delta\nu_{AB}$ = 8.72 Hz, *J* = 18Hz, $–CH_2–$), 1.74 (s, 3H, $–CH_3$); ^{13}C 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 ($–O\underline{C}H_3$), 47.58 (C4), 44.61 (C3), 24.45 (C6). Anal. calcd. for $C_{18}H_{17}NO_3$: 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, $C_{18}H_{17}NO_2$). White solid; Yield: 55%; mp: 105.5–106.6 °C; FT-IR (KBr): |ν| cm^{-1} = 1772 (C=O), 1707 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.53–7.20 (m, 9H, $–C_6H_5$ and $N–C_6H_4–$), 3.17 (ABq, 2H, *J* = 18Hz, $–CH_2–$), 2.35 (s, 3H, $Ph–CH_3$), 1.75 (s, 3H, $succ–CH_3$); ^{13}C 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 ($–\underline{C}H_3$). Anal. calcd. for $C_{18}H_{17}NO_2$: 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**, $C_{17}H_{15}NO_2$). White solid; Yield: 45%; mp: 105.5–106.6 °C; FT-IR (KBr): |ν| cm^{-1} = 1784 (C=O), 1721 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.56–7.28 (m, 10H, $–C_6H_5$ and $N–C_6H_5$), 3.18 (ABq, 2H, *J* = 18Hz, $–CH_2–$), 1.75 (s, 3H, $–CH_3$); ^{13}C 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 $C_{17}H_{15}NO_2$: 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**, $C_{17}H_{14}NO_2F$). White solid; Yield: 57 %; mp: 119.8–121.1 °C; FT-IR (KBr): |ν| cm^{-1} = 1782 (C=O), 1712 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.54–7.28 (m, 9H, –C_6H_5 and N–C_6H_4–), 3.18 (s, 2H, –CH_2–), 1.76 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{14}NO_2F$: 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**, $C_{17}H_{14}NO_2Cl$). White solid; Yield: 65%; mp: 120.2–122.2 °C; FT-IR (KBr): |ν| cm^{-1} = 1778 (C=O), 1710 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.63–7.27 (m, 9H, –C_6H_5 and N–C_6H_4–), 3.18 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.75 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{14}NO_2Cl$: 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**, $C_{17}H_{14}NO_2Cl$). White solid; Yield: 66%; mp: 128.6–130.3 °C; FT-IR (KBr): |ν| cm^{-1} = 1774 (C=O), 1709 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.56–7.28 (m, 9H, –C_6H_5 and N–C_6H_4–), 3.17 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.76 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{14}NO_2Cl$: 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**, $C_{17}H_{13}NO_2Br$). White solid; Yield: 66%; mp: 112.3–114.4 °C; FT-IR (KBr): |ν| cm^{-1} = 1776 (C=O), 1709 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.73 (d, *J* = 8 Hz, 2H, –C_6H_4–), 7.53–7.27 (m, 7H, –C_6H_5 and N–C_6H_4–), 3.18 (ABq, 2H, $\Delta\nu_{AB}$ = 8.72 Hz, *J* = 18Hz, –CH_2–), 1.75 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{14}NO_2Br$: 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**, $C_{17}H_{13}NO_2Br$). White solid; Yield: 66%; mp: 118.8–121.1 °C; FT-IR (KBr): |ν| cm^{-1} = 1772 (C=O), 1709 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.69–7.28 (m, 9H, –C_6H_5 and N–C_6H_4–), 3.17 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.76 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{14}NO_2Br$: 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**, $C_{18}H_{15}NO_4$). White solid; Yield: 61%; mp: 173.5–174.7 °C; FT-IR (KBr): |ν| cm^{-1} = 1783 (C=O), 1710 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 13.15 (bs, 1H,–COOH), 8.09 (d, *J* = 10 Hz, 2H, –C_6H_4–), 7.54–7.28 (m, 7H, –C_6H_5 and N–C_6H_4–), 3.21 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.76 (s, 3H, –CH_3); ^{13}C NMR (50 MHz, DMSO): |δ| ppm = 179.85 (C2), 174.44 (C5), 166.76 (–<u>C</u>OOH), 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 $C_{18}H_{15}NO_4$: 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**, $C_{18}H_{14}N_2O_2$). White solid; Yield: 58%; mp: 93.9–95.3 °C; FT-IR (KBr): |ν| cm^{-1} = 1784 (C=O), 1713 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 8.01 (d, *J* = 8 Hz, 2H, –C_6H_4–), 7.63 (d, *J* = 10 Hz, 2H, –C_6H_4–), 7.55–7.28 (m, 5H, –C_6H_5), 3.21 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.77 (s, 3H, –CH_3); ^{13}C 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 (–<u>C</u>N), 111.09 (Ph), 47.81 (C4), 44.62 (C3), 24.61 (C6). Anal. calcd. for $C_{18}H_{14}N_2O_2$: 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**, $C_{17}H_{13}N_2O_4$). White solid; Yield: 60%; mp: 106.9–108.1 °C; FT-IR (KBr): |ν| cm^{-1} = 1773 (C=O), 1705 (C=O); ^{1}H NMR (200 MHz, DMSO): |δ| ppm = 7.95 (d, *J* = 8 Hz, 2H, –C_6H_4–), 7.71 (d, *J* = 10 Hz, 2H, –C_6H_4–), 7.55–7.27 (m, 5H, –C_6H_5), 3.23 (ABq, 2H, $\Delta\nu_{AB}$ = 12.65 Hz, *J* = 18Hz, –CH_2–), 1.85 (s, 3H, –CH_3); ^{13}C 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 $C_{17}H_{13}N_2O_4$: C, 66.00; H, 4.24; N, 9.06; Found: C, 59.94; H, 4.26; N, 9.09.

*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**
$\nu_{max} \times 10^{-3}$ / cm^{-1}	43.48	43.48	45.87	48.31	46.30	44.44	47.62	43.48	47.62	41.67	41.32	36.63
$\sigma_{p/m}$	-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. ^{13}C NMR chemical shifts (δ/ppm) of the investigated succinimides.

No.	Substituents	δ / ppm	
		C2	C5
1	4-OH	0.30	0.31
2	4-OCH_3	0.21	0.22
3	4-CH_3	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-NO_2	-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 and the statistical Boltzmann distribution weighted values (ω) of all isomers for compound **4** obtained with B3LYP and M06-2X methods and 6-311G(d,p) basis set.*

Conf.	**B3LYP**											
	Vacuum				**Ethanol**				**DMSO**			
	Energy, kcal/mol			ω	Energy, kcal/mol			ω	Energy, kcal/mol			ω
	E_{HF}	E_{ZPE}	E_R		E_{HF}	E_{ZPE}	E_R		E_{HF}	E_{ZPE}	E_R	
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 most stable conformer

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

	B3LYP								
	Vakuum			Etanol			DMSO		
	E_{HOMO} / eV	E_{LUMO} / eV	ΔE / eV	E_{HOMO} / eV	E_{LUMO} / eV	ΔE / eV	E_{HOMO} / eV	E_{LUMO} / eV	ΔE / 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

	B3LYP								
	Vakuum			Etanol			DMSO		
	E_{HOMO} / eV	E_{LUMO} / eV	Δ*E* / eV	E_{HOMO} / eV	E_{LUMO} / eV	Δ*E* / eV	E_{HOMO} / eV	E_{LUMO} / eV	Δ*E* / eV
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 *P*[c]	Hydrogen bonds		Rotatable bonds	Polar surface area, Å^{2c}
			Donors[a]	Acceptors[b]		
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 from program Molinspiration.

*Table S6. PASS prediction of the investigated succinimides (**1**–**12**).* P*a and* P*i represent probabilities that investigated molecule can 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	*P*i	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**)

*P*a	*P*i	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**)

*P*a	*P*i	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**)

*P*a	*P*i	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**)

*P*a	*P*i	Receptors
0.748	0.008	Anticonvulsant

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

*P*a	*P*i	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**)

*P*a	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**)

*P*a	*P*i	Receptors
0.778	0.006	Anticonvulsant

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

*P*a	*P*i	Receptors
0.807	0.005	Anticonvulsant

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

*P*a	*P*i	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

*P*a	*P*i	Receptors
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**)

*P*a	*P*i	*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**)

*P*a	*P*i	*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

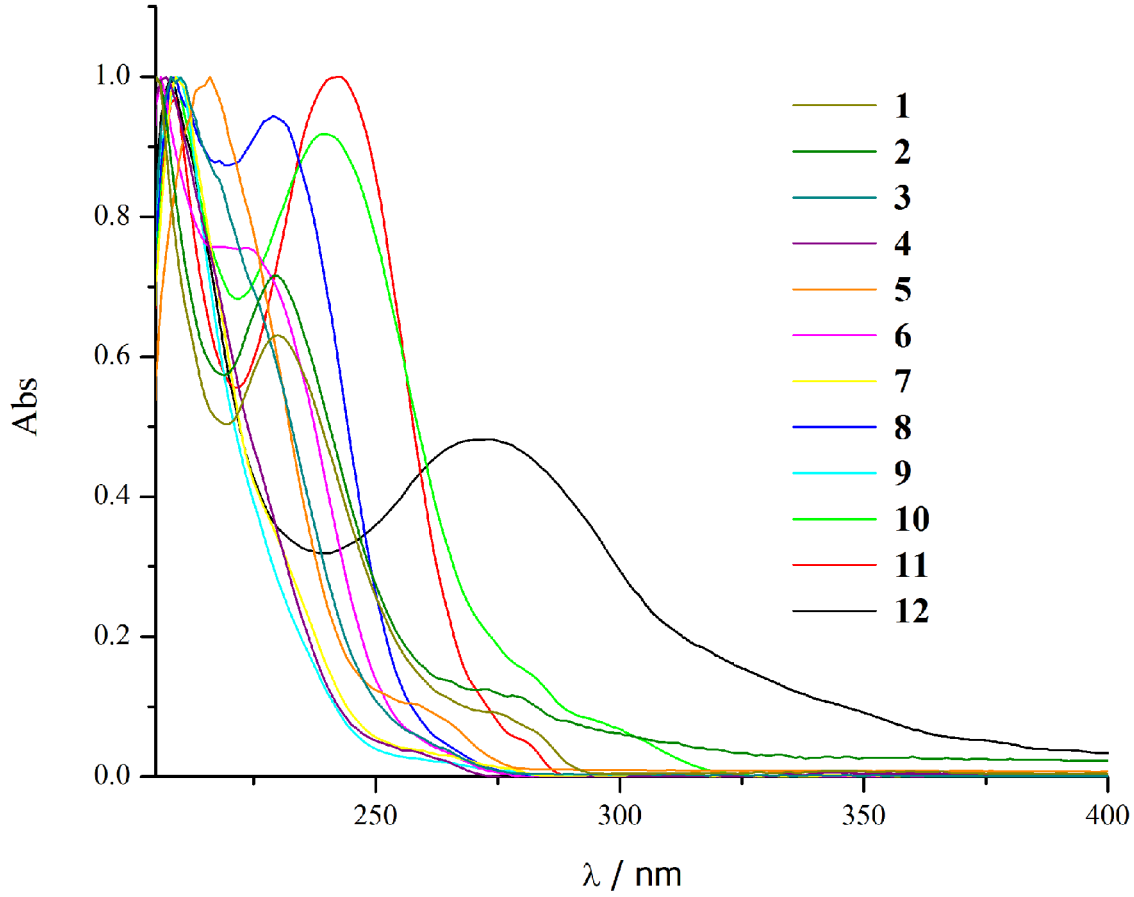


Figure S1. Normalized UV absorption spectra of investigated compounds in ethanol.

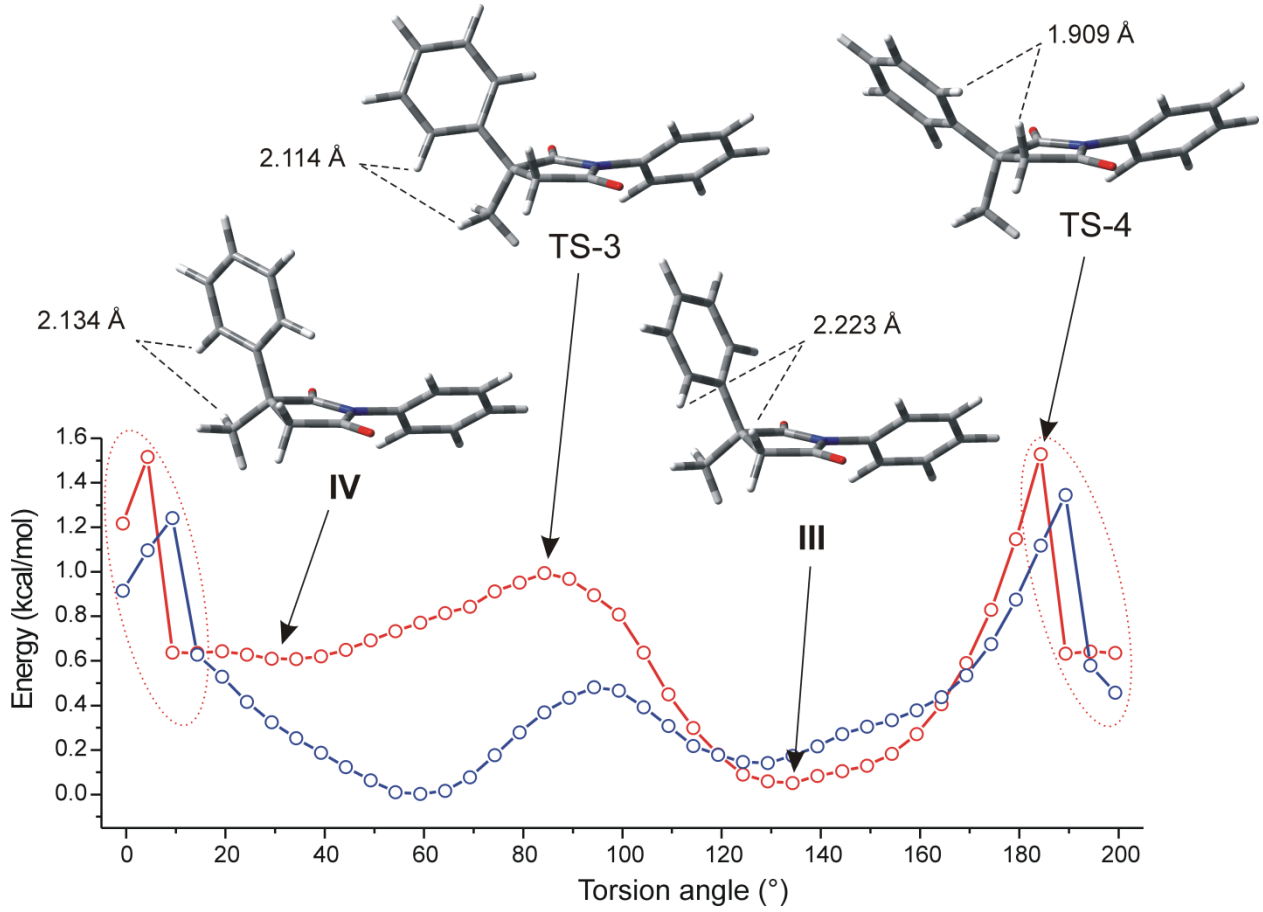


Figure S2. The potential energy scans for rotation of 3-phenyl group, in the vacuum (red) and ethanol (blue) done by B3LYP/6-311G(d,p) method (N-phenyl group torsion angle of ~ 136°).

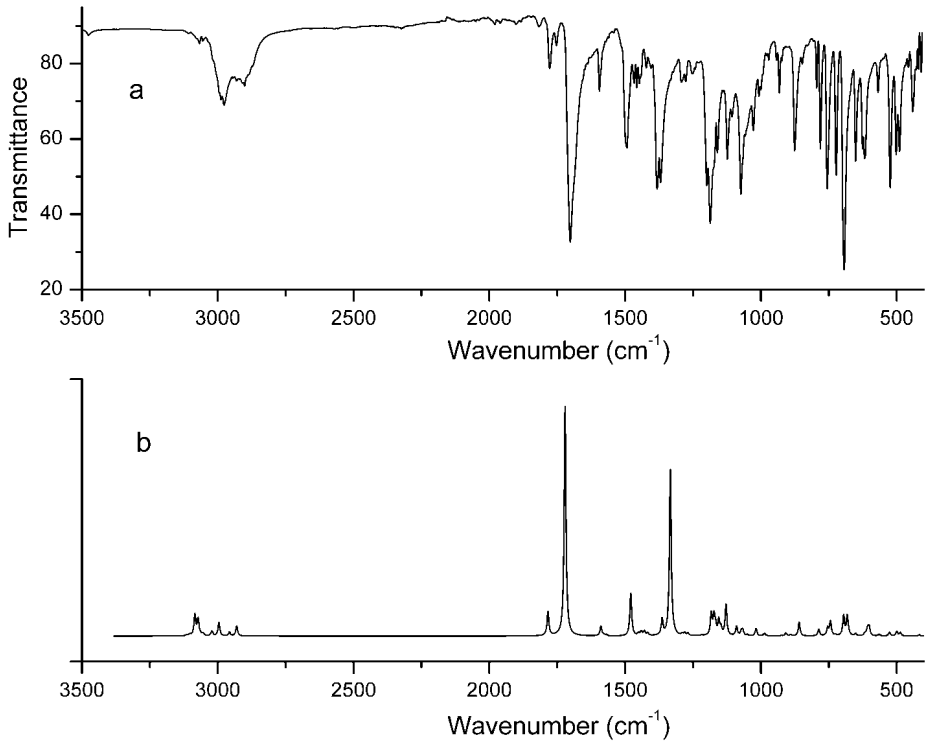


*Figure S3. The experimental a) and calculated b) infrared spectrum of **4***

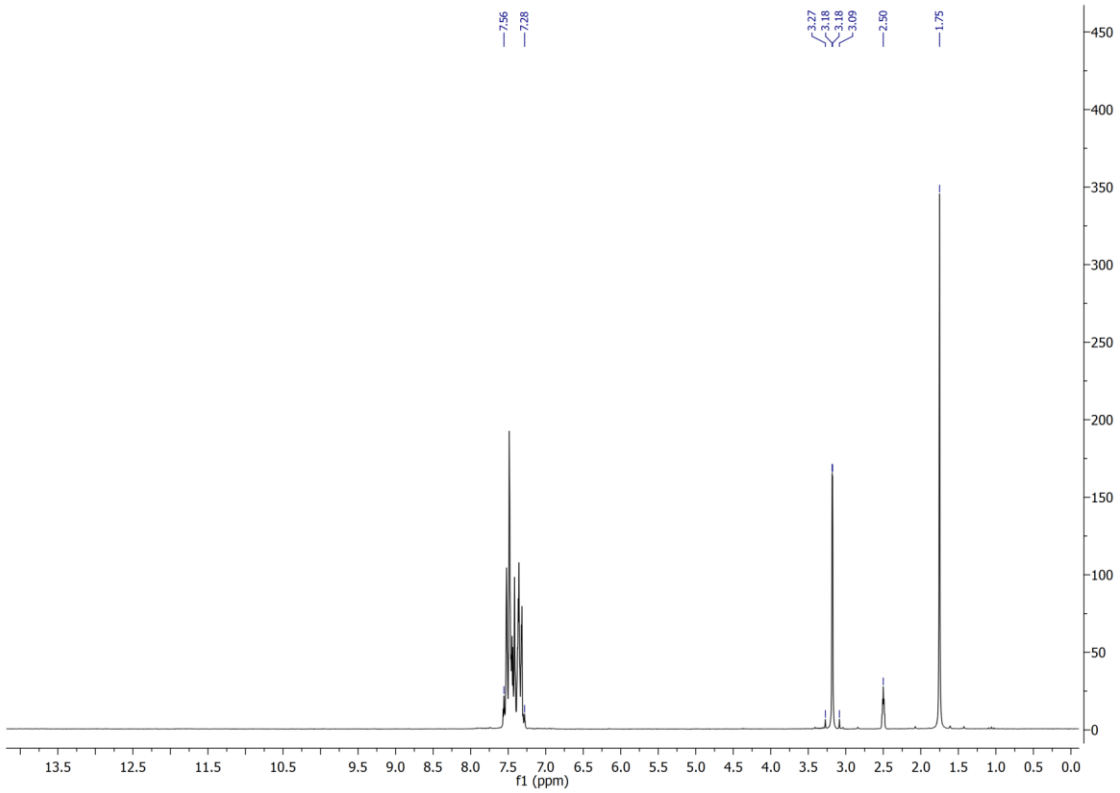


*Figure S4. The ^{1}H NMR spectrum of **4** recorded in DMSO-d_6.*

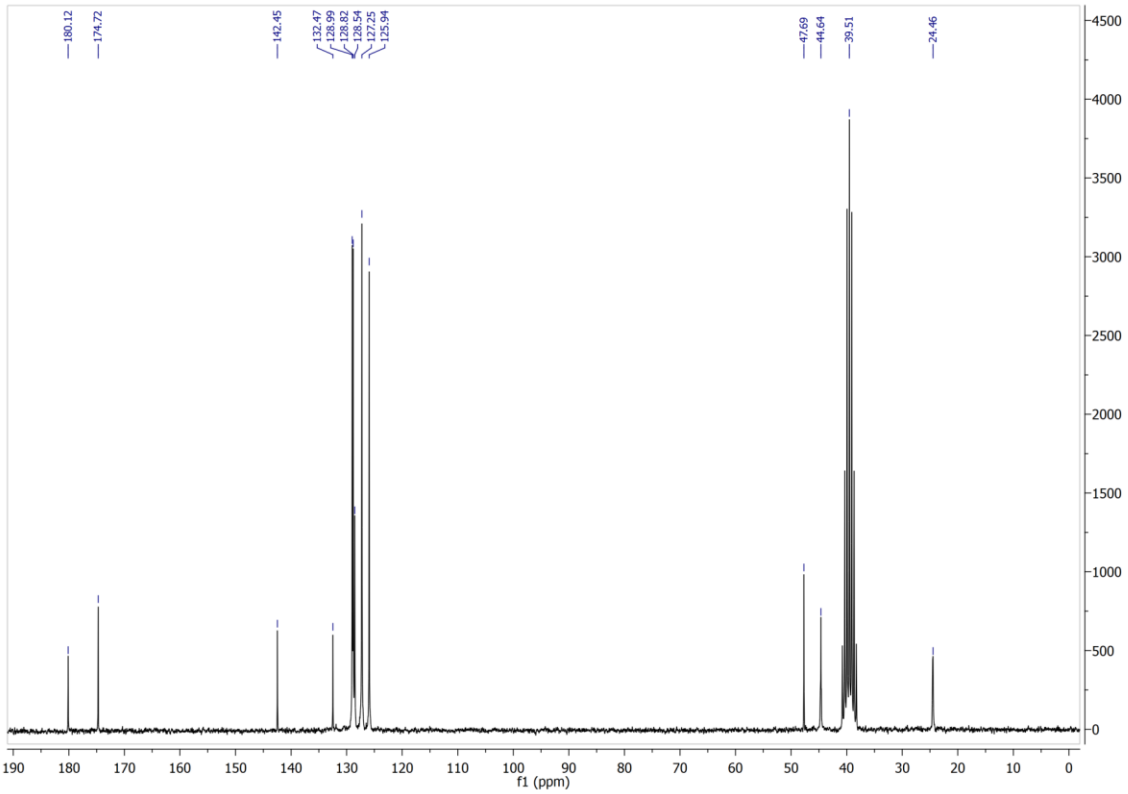


*Figure S5. The ^{13}C NMR spectrum of **4** recorded in DMSO-d_6.*