Discovery of Novel UV-Filters with Favorable Safety Profiles in the 5-Arylideneimidazolidine-2,4-dione Derivatives Group

Justyna Popiół, Agnieszka Gunia-Krzyżak, Kamil Piska, Dorota Żelaszczyk, Paulina Koczurkiewicz, Karolina Słoczyńska, Katarzyna Wójcik-Pszczoła, Anna Krupa, Agata Kryczyk-Poprawa, Ewa Żesławska, Wojciech Nitek, Paweł Żmudzki, Henryk Marona, Elżbieta Pękala

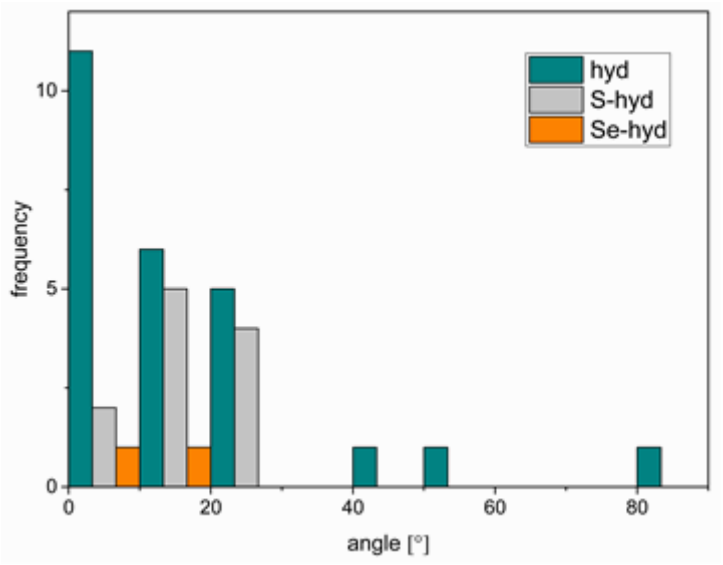

Figure S1. The distribution of the angle values between the planes of hydantoin and aromatic rings in crystal structures containing a 5-benzylidenehydantoin (hyd), 5-benzylidene-2-thiohydantoin (S-hyd) or 5-benzylidene-2-selenohydantoin (Se-hyd) fragment retrieved from the CSD.

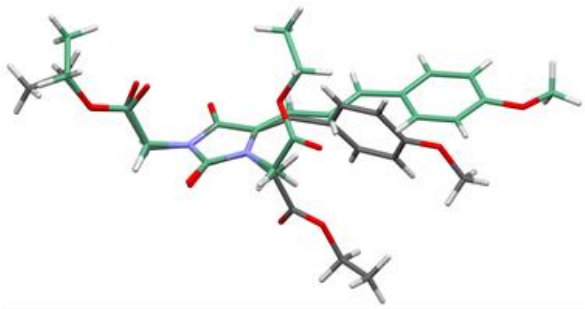

Figure S2. The overlap of hydantoin rings of **3b** (carbon atoms in grey) and **4g** (carbon atoms in green). The disordered fragment of **3b** is depicted only for major occupancy (**A**).

Table S1. Parameters of intermolecular interactions in the crystal structures of **3b** and **4g**

	D-H···A	H···A (Å)	D···A (Å)	D-H-A (°)	Symmetry codes
3b	C8-H8A···O4	2.56	3.519(2)	163	−x + 1, −y + 2, −z + 2
	C8-H8B···O4	2.64	3.400(2)	134	x, −y + 2, z + ½
	C9-H9A···O6A	2.52	3.415(5)	152	x, y + 1, z
	C10-H10A···O2	2.29	3.130(2)	142	−x + 1/2, −y + 3/2, −z + 2
	C14-H14···O1	2.76	3.354(1)	121	−x + 1, −y + 2, −z + 2
	C16-H16···O1	2.63	3.383(2)	137	−x + 1, −y + 2, −z + 2
	C21-H21B···O4	2.54	3.495(2)	165	x, y + 1, z
4g	C6-H6A···O7	2.64	3.328(2)	127	−x + 1/2, y−1, −z
	C6-H6B···O1	2.59	3.399(2)	139	−x + 1/2, y, −z
	C13-H13C···O6	2.54	3.470(2)	160	−x, y + 1/2, −z + ½
	C14-H14···O4	2.22	2.965(2)	134	−x + 1/2, −y + 3/2, z
	C16-H16···O4	1.68	2.586(2)	158	−x + 1/2, −y + 3/2, z
	C19-H19···O2	2.49	3.425(2)	168	−x + 1/2, y + 1/2, −z
	C23-H23C···O5	2.65	3.310(2)	125	x + 1/2, −y + 2, z

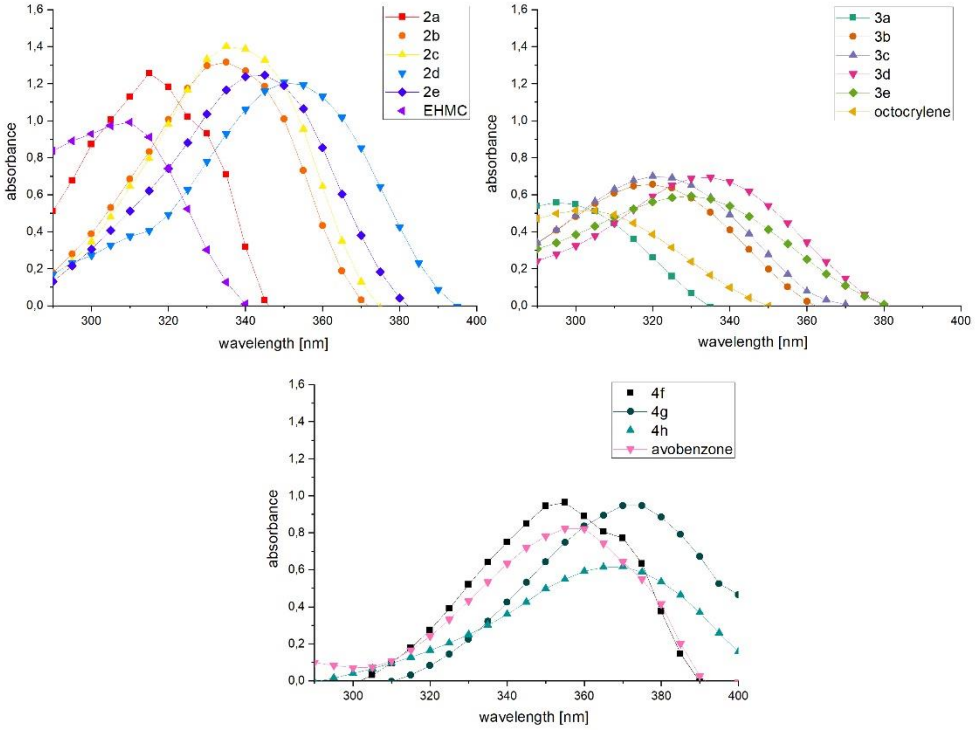

Figure S3. UV-absorption spectra of tested compounds and reference UV filters obtained in methanolic solutions (for **2a**–**2e**, **3a**–**3e**, octocrylene and EHMC at 50 μM, for **4f**–**4h** and avobenzone at 25 μM).

Table S2. UV absorption changes after 1h irradiation at 500 W/m² of methanol solution of tested compounds and reference UV-filters.

Compd	λ_{max} pre-irradiation	λ_{max} post-irradiation	% of initial AUC post-irradiation
1e	341	346	95.38
2a	316	317	70.45
2b	334	341	95.67
2c	336	344	96.89
2d	349	354	100.96
2e	344	351	97.8
3a	295	301	122.34
3b	318	326	114.39
3c	321	329	119.42
3d	333	342	111.55
3e	329	340	129.32
4f	354	354	59.12
4g	379	378	80.15
4h	370	370	98.55
4-MBC	299	303	87.76
EHMC	309	307	63.26

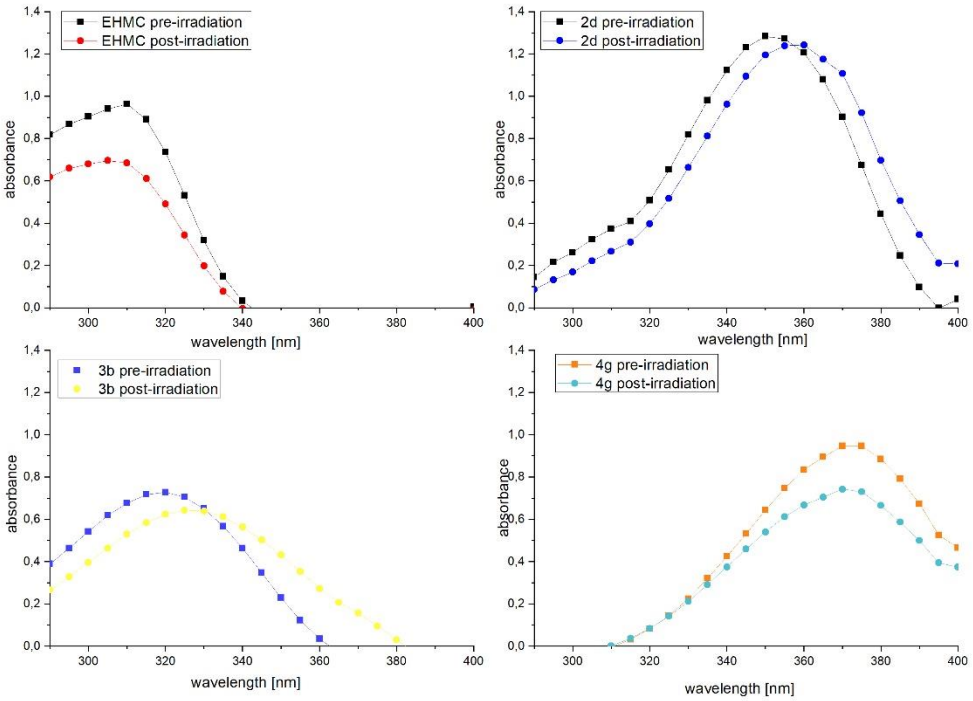

Figure S4. UV absorption spectra of tested compounds and EHMC obtained pre-irradiation and 1 hour after irradiation with solar light simulator conducted at 500 W/m² in 25 μM (**4g**) or 50 μM (**2d**, **3b**, EHMC) methanol solutions.

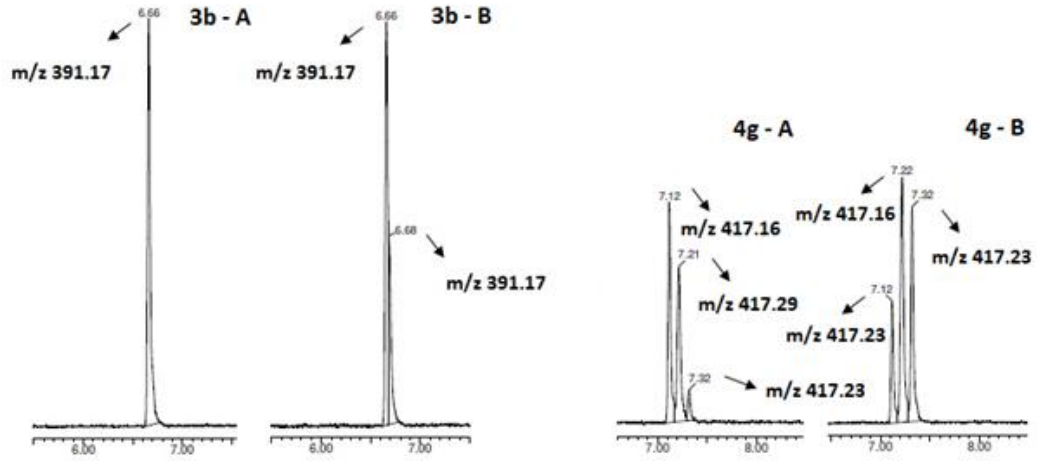

Figure S5. The chromatograms and mass spectra of methanol solutions of compounds **3b** and **4g** pre-irradiation (**A**) and 1 hour after irradiation (**B**) with solar light simulator conducted at 500 W/m^2.

Table S3. Mutagenic activity of compounds **4g** and **3b** tested with the Ames assay.

		Positive wells per microplate									
		S. typhimurium								***E. coli***	
		TA98		**TA100**		**TA1535**		**TA1537**		**WP2**	
		–S9	**+S9**	**–S9**	**+S9**	**–S9**	**+S9**	**–S9**	**+S9**	**–S9**	**+S9**
Compound	**Conc. (mM)**	**FIB***									
4g	0.1	0.5	0.3	1.1	0.7	0.3	0.3	0.3	1.4	0.3	0.6
	0.2	0.9	0.4	0.3	0.5	1.4	0.7	1.7	1.1	1.3	1.0
	0.5	0.2	0.6	0.6	0.5	0.6	0.3	0.5	0.8	1.3	0.7
	PC**	25.3	12.6	4.3	3.1	40.0	16.5	48.0	38.3	25.7	4.0
3b	0.1	0.9	0.2	1.1	0.7	0.8	0.5	0.3	1.1	0.3	0.7
	0.2	0.2	0.4	0.8	0.6	0.6	0.1	0.3	1.1	0.7	0.6
	0.5	0.9	0.3	0.7	0.6	1.7	0.1	0.3	0.3	0.3	0.4
	PC**	25.3	12.6	4.3	3.1	40.0	16.5	48.0	38.3	25.7	4.0

*FIB–fold induction over baseline (baseline = mean zero-dose control + 1 SD); SD–standard deviation
**Positive controls: 2-Nitrofluorene (2-NF) at 2 μg/mL (TA98, –S9); 4-Nitroquinoline-*N*-oxide (4-NQO) at 0.1 μg/mL (TA100, –S9); N4-Aminocytidine (N4-ACT) at 100 μg/mL (TA1535, –S9); 9-Aminoacridine (9-AAc) at 15 μg/mL (TA1537, –S9); 4-NQO at 2 μg/mL (*E.coli uvrA*[pKM101], –S9); 2-Aminoanthracene (2-AA) at 0.5 μg/mL (TA98, +S9); 2-AA at 1.25 μg/mL (TA100, +S9); 9-AA at 2.5 μg/mL (TA1535 and TA1537, +S9); 2-Aminofluorene (2-AF) at 400 μg/mL (*E.coli uvrA*[pKM101], +S9).