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# Evaluation of MAA Analogues as Potential Candidates to Increase Photostability in Sunscreen Formulations

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**Abstract:** Avobenzone is one of the most widely used sunscreens in skin care formulations, but suffers from some drawbacks, including photo instability. To mitigate this critical issue, the use of octocrylene as a stabilizer is a common approach in these products. However, octocrylene has been recently demonstrated to show potential phototoxicity. The aim of this work is to analyze the performance of a series of mycosporine-like amino acid (MAA)-inspired compounds to act as avobenzone stabilizers as an alternative to octocrylene. Different avobenzone/MAA analogue combinations included in galenic formulations were followed under increasing doses of solar-simulated UV radiation. Some of the synthetic MAA analogues analyzed were able to increase by up to two times the UV dose required for 50% of avobenzone photobleaching. We propose some of these MAA analogues as new candidates to act as avobenzone-stabilizing compounds in addition to their UV absorbance and antioxidant properties, together with a facile synthesis.

**Keywords:** sunscreens; photoprotection; UV radiation; MAAs; photochemistry



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## 1. Introduction

Sunlight exposition has been increasing for the last decades. This is induced by our outdoors habits and, in combination with the decrease of the ozone layer, it causes increased UV exposure in humans. Due to this, the impact of melanoma and other types of skin cancer has been increasing through the last decades [1]. To avoid UV radiation damaging effects, scientists have develop a series of sunscreen formulations to protect humans from potential UV damage [2], in addition to natural protection [3]. Nowadays, none of the commercially available sunscreen molecules present ideal behavior as a photoprotector, as these molecules should fulfill a long list of requirements [4,5]. These compounds should present, among other features, very large photostability together with broad and intense absorption in the UV region. These properties should also be combined with negligible toxicity or phototoxicity. Potential side effects, like photosensitization or photoreactivity, that could induce toxic effects in living organisms, should be considered as a major drawback and should be avoided. Complementarily, the environmental impact and bioaccumulation effect on the ocean's ecosystem should be taken into consideration. Due to these side problems, the development of safer and environmentally friendly systems has gained a lot of interest, mainly from the industrial sector. The previously mentioned problems are only related to human care, but equally important is the environmental impact that can induce the massive use of sunscreen lotions.

Even if there are many ingredients that can be used in sunscreen formulations [2], the actual legislation in Europe allows 48 compounds to be used as photoprotectors (Annex

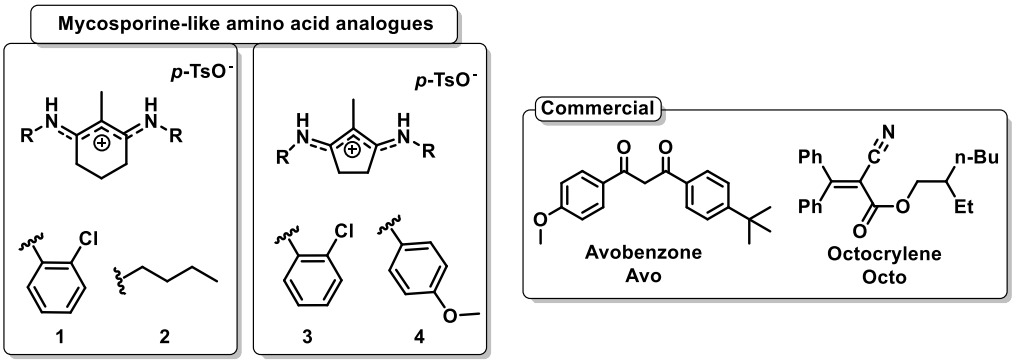
VI, Regulation 1223/2009/EC on Cosmetic Products, as amended by Regulation (EU) 2022/2195, OJ L 292, 11 November 2022). Despite this large number of UV blockers, the most used ones are still the avobenzone/octocrylene pair. These compounds are quite far from behaving as ideal sunscreens, but their combinations provide adequate practical results. In particular, avobenzone is known to undergo fast photobleaching due to the population of the keto-keto form, which leads to undesired photo instability [6,7]. Due to this, the combined use of avobenzone with octocrylene is almost mandatory due to the strong stabilization that can be achieved in combination. However, octocrylene presents its own drawbacks, as it is known that it can cause phototoxicity [8,9] and act as an endocrine disruptor [10]. Therefore, it is urgently necessary to find new alternatives for the design of sunscreen formulations which could provide a photostable mixture using safer substances.

Using photoprotective natural compounds as inspiration, we developed a versatile and efficient route to prepare synthetic analogues of the well-known natural compounds called mycosporine-like amino acids (MAA). These low molecular weight compounds are widely available on the planet and present really efficient sunscreen capabilities [11]. These compounds are thermally and photochemically stable, and present a considerable absorption coefficient and lack of fluorescence, photoreactivity, and toxicity [12]. These properties make these compounds quite close to the ideal features of sunscreens [12–14]. In this context, we aimed to study these compounds as avobenzone stabilizers. In the literature, there have been a considerable number of attempts to stabilize avobenzone [15]. The most common approach is the use of octocrylene, with the previously mentioned drawbacks. Other employed strategies are the combination with (2-hydroxy)propyl-β-cyclodextrin, which also provides a significant stabilization due to encapsulation [16], as well as micellar encapsulation [17]. In addition, the use of antioxidant molecules [18,19], other sunscreens, like bisethylhexyloxyphenol methoxyphenyltriazine (BEMT) [20], or complex structures like zeolites have been explored in this topic. Additionally, an innovative approach was the use of light to induce and control avobenzone production through a photochemical transformation [21]; this is a potent strategy but could have serious flaws due to the photo reactivity in a complex and more rigid environment, i.e., a cosmetic formulation.

In this paper, we aim to explore the capabilities of MAA analogues to stabilize cosmetic formulations containing avobenzone by chemical combination. For this, we have prepared a series of cosmetic formulations and studied their behavior against different doses of light. For our experiments, we have prepared a series of compounds with large photostability (negligible degradation with an equivalent dose of irradiation higher than 6 h, according to previously carried out experiments in solution detecting through $^{1}$H NMR spectrometry) aiming to stabilize avobenzone in cosmetic formulations under realistic conditions in galenic formulations and to study the possible effects of concentration for the photostability of avobenzone.

## 2. Results and Discussion

A series of four compounds (Scheme 1) was prepared, aiming to provide high absorbance in the UV region. For this, we used an amine condensation with the 1,3-diketo compounds under Dean–Stark conditions as described in more detail in Section 4 [12]. In a preliminary step, the UV-Vis spectra of all the compounds were measured in solution. All the compounds featured an absorbance maximum at the UVB region (Figure 1). Noteworthily, all of them also featured impressively high photostability in solution, as previously measured by $^{1}$H-NMR [12]. This extremely stable behavior suggests great potential to be used as a sunscreen ingredient. Also, the facile synthesis, with only one step, easy purification, the use of precipitation, and high yields offers a great alternative to approach the excellent properties of natural MAAs in a more sustainable way with respect to extraction from algae. This work presents a preliminary screening of those candidates in formulation, aiming at the stabilization of other ingredients present in the formula.




**Scheme 1.** Structures of the commercial and the prepared MAA analogues. Note the difference between the core between **1**–**2** and **3**–**4**.

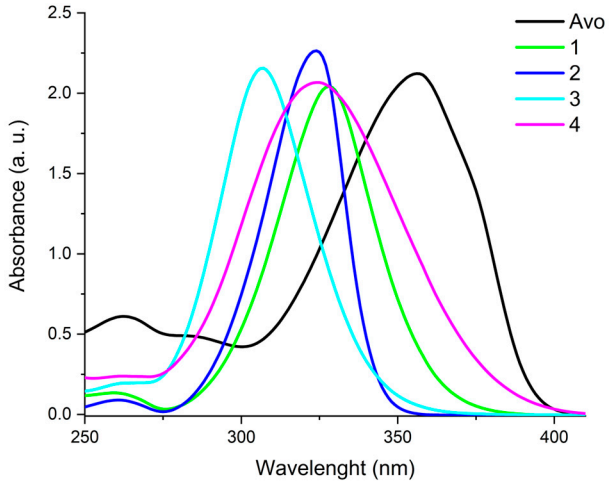



**Figure 1.** UV-Vis spectra of the studied compounds in $1 \times 10^{-4}$ M solution in methanol.

Aiming to prove the ability of our compounds to be formulated in stable cosmetic formulations, we have produced a series of galenic formulations using different mixtures of avobenzone (Avo), octocrylene (Octo), and **1** to **4**. We intended to test these combinations in the same interval of concentrations as the standard filters approved by international legislation regarding cosmetic products (for instance, the 76/768/CEE directive of the European Union), using between 5 and 10% *w*/*w*, similar to the current practical use for avobenzone and octocrylene. Due to this, the compounds were studied at 5% in a prototype 10 g of NeoPCL formulation prepared as described in Section 4. All the compounds presented an appropriate absorption for use as UV blockers, as shown in Figure 1. But in contrast to the high absorbance found in solution, the absorbance or transmittance measured in formulation decreased considerably; see Figure 2. It is also worth mentioning that there is a minimal absorbance overlap with avobenzone in formulation, allowing a proper monitorization of the photobleaching of Avo against UV doses, while the range of photon absorption is increased in the mixtures compared with the isolated compounds. With these initial promising features, we aimed for the incorporation of these combinations into more complex galenic formulations. To further evaluate their photochemical properties, we irradiated the samples using the standardized methacrylate (PMMA) plates using a solar-like irradiation source with a combination of UVB–UVA lamps (see more details in Section 4). The temporal evolution of the samples was monitored by absolute irradiance measurements at increasing UV doses of radiation. To provide a standardized analysis, the irradiance data were converted to transmittance, dividing the irradiance of the lamp through the sample by the irradiance of the plate impregnated with an equivalent amount of Vaseline. At that point, the different compounds could be compared independently and

could be converted to absorbance directly. Looking at the results shown in Figure 2, we found a clear behavior, as expected for commercial sunscreen Avo, which presented low photostability. In the case of avobenzone, it almost fully decomposes under the experiment dose, depicting a non-efficient deactivation mechanism (i.e., photoreactivity). In contrast, the four prepared compounds **1**–**4** exhibited higher photostability, remaining unaltered after comparable doses. The temporal or dose evolution can be seen in Figure 2. The irradiation of those samples yielded to a critical bleaching of avobenzone, decreasing to 50% after only 200 kJ/m$^2$ and being fully decomposed after 450 kJ/m$^2$ of total UV dose. Compounds **1** to **4** did not present any noticeable decomposition measured at their corresponding absorption maxima after the maximum dose. The initial increase in Avo is attributable to insufficient dryness before the first measurement, possibly due to the more viscous character of the formulation respect to the others. This can yield a higher evaporation during the irradiation, which is only notable at short times (5 min) and no longer noted afterwards.

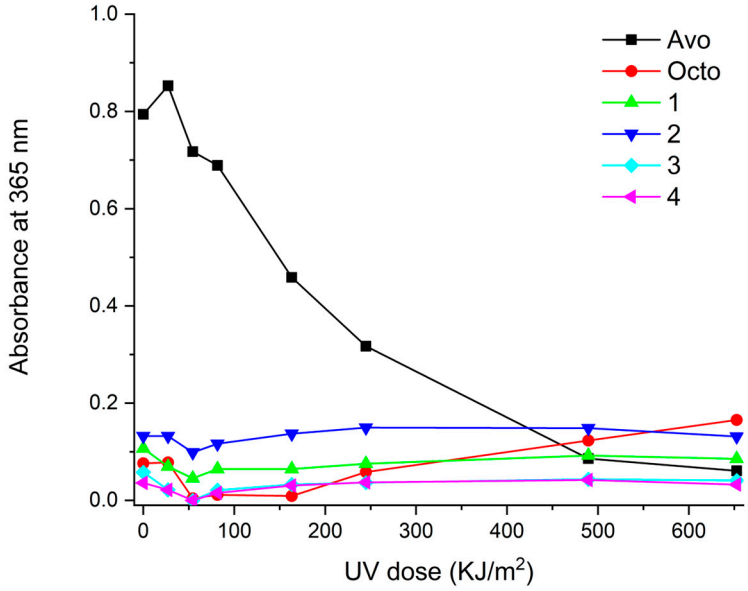



**Figure 2.** Photostability of the studied samples at 5%. Monitored by absorbance measurements at Avo maximum.

Even with this poor photostability, avobenzone is one of the most widely used sunscreens in cosmetics. In commercial formulations, this is possibly due to the inclusion of other ingredients as stabilizers. The combination of at least two UV absorbents is the most used strategy to provide photostability to cosmetic formulations. In this scenario, it is possible to decrease the absolute quantity of each compound in the formulation. As already mentioned, octocrylene is broadly used as an avobenzone stabilizer, so we moved to assay our compounds with this role, aiming to propose some alternatives to the use of the problematic octocrylene. In the literature, it is widely reported that octocrylene reacts with amines [22] which, in humans, are mainly found in the form of lysine residues. Then, it can undergo an initial Michael-type addition followed by a reaction sequence corresponding to a retro-aldol reaction and the formation of immunogenic hapten–protein complexes. This follows a mechanism closely related to the Schiff base mechanism and is often considered when aldehydes form those immunogenic complexes [23].

Notwithstanding, the presented compounds have not been tested in biotoxicity assays, but we hypothesized that they cannot undergo this reaction because they do not have an $\alpha$,$\beta$-unsaturated carbonyl structure nor a strong nucleophilic or electrophilic center. Even if octocrylene has strong absorption in the UVB, its main application is as a stabilizer of other photoprotectors such as avobenzone, with the previously mentioned disadvantages [8].

Therefore, we irradiated a series of formulations containing the different ingredients in combination with Avo at 5% and 10% to study their photochemical behavior in cosmetic formulations. In Figure 3, we can see that Octo is in fact the best performer for avobenzone stabilization at high UV doses. However, it is clear that compound **4** performs quite well in comparison with free Avo. In fact, the absorption provided by mixtures of **4** + Avo is even better at low UV doses, especially for low concentrations (5%), where it increases the absorption of Avo with respect to the result achieved in the sample with Octo at equivalent concentration.

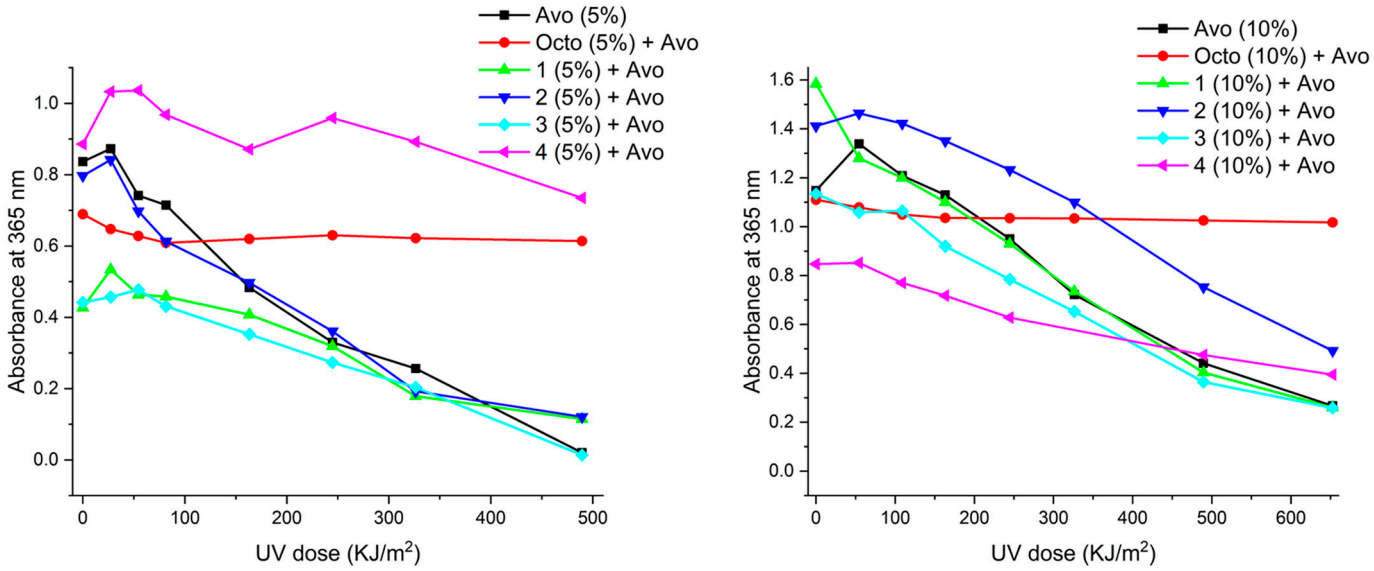



**Figure 3.** Time evolution of mixtures of Avo with **1**–**4** and Octo, at 5% on the left and 10% (*w*/*w*) on the right for all the ingredients. All the values were obtained from the transmittance spectra and converted to absorbance for easier interpretation. In case of sample **4** (10%) + Avo (right graph in purple), we discarded the spectrum at 60 min (326 kJ/m$^2$) due to an unknown drastic change in the transmission spectrum.

As can be seen in Figure 3, left, at 5% we can observe that compound **4** offers an extra boost to the absorption (ca. 16%), which will yield an increase in the eventual solar protective factor of the formula. This appears to be in combination with a noticeable stabilization in Avo photobleaching, increasing its stability by at least a factor of two. In this line, a small effect can also be noted for compounds **1** and **3**, which looking the slope of degradation offers slightly slower bleaching. This is in contrast with the behavior found at 10%, which resulted in lower stabilization from almost all the studied MAA analogues. This was quite surprising, but we were not able to provide a rationalization according to the principles ruling the conventional absorption processes occurring in diluted solutions. The only compound that exhibited an observable change in the slope of the decomposition trend was compound **4** but the observed boost in the absorbance at 5% was completely quenched here, even yielding into a decrease in the Avo intensity. In contrast to this, a small potentiation was induced by compound **2**, but at the end it did not result in effective stabilization. The broad conclusion that we can extract from these experiments is that we are quite far off a model to predict how the cosmetic ingredients could behave in cosmetic formulations. This can be justified from different points; firstly, the matrix effect, with all the additives and excipients, could play a substantial role and will vary completely between different lotions. On the other hand, the photophysical properties and photochemical mechanisms could be drastically affected by having the sunscreen molecules in a less flexible environment. This could drastically hinder the molecular movement, resulting in a potential diminution of the sunscreen efficiency, which would be a great inconvenience in

the molecules, which would dissipate the exceeding energy by vibrational relaxation, as happens in MAA analogues.

As a final summary, we have calculated the required doses to reach 50% decomposition of Avo; this offers a proper overview of the activity of each ingredient and will highlight the most interesting results. Those values are shown in Table 1.

**Table 1.** Estimated 50% decomposition times of Avo and the required UV doses to induce it. * The value is approximated from the measured values represented in Figures 2 and 3.

| Formulation | 50% Decomposition Time * | UV Dose (kJ/m$^2$) * |
|---|---|---|
| Avobenzone (5%) | 35 min | 200 |
| Avobenzone (10%) | 75 min | 400 |
| Octocrylene (5%) | >120 min | >652 |
| **1** (5%) | >120 min | >652 |
| **2** (5%) | >120 min | >652 |
| **3** (5%) | >120 min | >652 |
| **4** (5%) | >120 min | >652 |
| Avo (5%) + Octo (5%) | >120 min | >652 |
| Avo (5%) + **1** (5%) | 65 min | 350 |
| Avo (5%) + **2** (5%) | 35 min | 200 |
| Avo (5%) + **3** (5%) | 65 min | 350 |
| Avo (5%) + **4** (5%) | >120 min | >652 |
| Avo (10%) + Octo (10%) | >120 min | >652 |
| Avo (10%) + **1** (10%) | 75 min | 400 |
| Avo (10%) + **2** (10%) | 100 min | 550 |
| Avo (10%) + **3** (10%) | 75 min | 400 |
| Avo (10%) + **4** (10%) | >120 min | 650 |

The presented results suggest that the proposed compounds could be used to prepare formulations providing different degrees of stabilization of avobenzone under high UV doses. In the case of compound **2**, it shows poor stabilizing ability, not affecting the photodecomposition of Avo. This suggests that this specific compound does not interact with Avo, at least in an efficient manner. In contrast, a larger effect is observed for **4**. In fact, this compound performs quite similarly to Octo for high UV doses or could be even better at lower concentrations due to the obtained boost to the absorption. This turns this compound into a promising candidate to replace octocrylene as an avobenzone photostabilizer for potentially safer commercial formulations.

We have shown that the prepared compounds are compatible with avobenzone in real formulations. In addition, avobenzone is stabilized by our new sunscreens and some of them could be used to replace octocrylene. Further studies to understand the complex interactions between Avo and the MAAs analogues are underway. This should allow us to design new and improved versions of our compounds with increased performance.

## 3. Conclusions

In this contribution, we have studied the use of mycosporine-like amino acid analogues as potential replacements for octocrylene in cosmetic formulations as avobenzone stabilizers. Our results have shown that the overall stabilization provided by the new compounds is lower than the one found for octocrylene. However, the new compounds also have a significant effect on the avobenzone photodecomposition, enhancing the stability by a factor of two in some cases and approaching octocrylene in terms of supported UV

dose. The best candidate is capable of maintaining the same stabilization of avobenzone in typical erythematic doses required during the real application of cosmetic formulations. Therefore, we have proved a series of MAA analogues to act as stabilizers for avobenzone comparable to octocrylene while offering an expected lower induced toxicity.

## 4. Materials and Methods

The studied compounds were synthetized according to the previously reported protocol by refluxing a mixture of the corresponding amine with *p*-toluene sulfonic acid and 1,3-cyclopentadione or 1,3-cyclohexadione in dry toluene using Dean–Stark apparatus to remove the water from the condensation for 24–48 h. Afterwards, the toluene was removed under rotatory evaporation and the crude residue was crystallized from $CH_2Cl_2$ by n-hexane addition and collected by filtration as a solid. In case of need, some excess $CH_2Cl_2$ can be used for washing to fully remove the exceeding amine, obtaining the desired compounds as powder solids with high yields between 75 and 95% [12]. The present counterion (*p*-toluene sulfonate) was observed using NMR. All reagents and solvents were used as received from commercial sources without further purification steps. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker ARX-300 spectrometer (Billerica, MA, USA). Methanol-*d4* has been used as the usual deuterated solvent, using its signal as standard. Chemical shifts are given in ppm and coupling constants in Hertz. High Resolution Mass Spectrometry was performed using a Microtof-Q electrospray source in positive-ion mode. Absorption molecular spectra were recorded on an Ocean Optics USB4000 UV-Vis diode array spectrophotometer (200–850 nm). All the experiments were carried out in quartz cuvettes (1 cm path length) using methanol $1 \times 10^{-4}$ M solutions. Those compounds are very soluble in alcohols, moderately in halogenated ones and mainly insoluble in water and non-polar non-protic solvents.

All the assays in galenic formulation were made using a solid phase cream-like substance based on a self-emulsifiable O/W "NeoPCL" base at 20% (*w*/*w*) + propylene glycol (PEG) (0.05 mL) (Acofarma, Barcelona, Spain) and distilled water to reach the total weight of cream (*ca*. 1 g). A detailed list of components is shown in ESI. We have chosen the simplest and easiest preparation base for the formulation, aiming to minimize the possible matrix effect and maximize the observation of our compounds of interest. It is also a nonionic formula broadly approved by cosmetic regulations worldwide.

We have prepared the formulas using a two-component mixture. The water phase (water + PEG+ **1**–**4**) and the hydrophobic phase (NeoPCL) were both heated to 60 °C.

Once they were liquified and under intense mechanical agitation, the hydrophilic phase was slowly added to the hydrophobic one until we obtained a homogenous formula through continuous agitation. The color of the galenic formulas depends on the color of the MAA analogue used. Also, the texture of the formula slightly changed between the different samples. Galenic formulations were always freshly prepared prior to analysis and base formulation (vehicle) was used as control. But even with these cautions, the preparation of these simple formulations is always challenging for achieving robust replicas due to the huge impact of the emulsion on the physical properties, which can motivate some uncontrollable effects, like different scattering patterns.

All the measurements were made according to the international standard ISO-24443:2021 [24], using standardized $5 \times 5$ cm PMMA plates with 1.3 mg/cm$^2$ of cream. The spectral distribution of the light source as well as its transmitted spectral distribution by control and samples probes in PMMA plates was measured by means of a double monochromator attached to a Ulbrich sphere (MACAM SR9910-v7, Irradian, Scotland, UK). The use of an irradiation sphere offers a partial solution to minimize the effects of inhomogeneity from the samples, minimizing the influence of scattering in the obtained data.

The irradiation was implemented by a solar simulating combination of fluorescent lamps in a Daavlin irradiator model consisting of 2 Qpanel-340 36 W lamps and a Philips TL 10/36 W black light lamp [25,26]. The spectral irradiance distribution of the lamp system compared to that of the Sun at the Earth's surface in southern Europe at midday

in a typical summer day is shown in ESI, Figure S3. The total UV irradiance (290–400 nm) emitted by the lamp was 90.64 $W/m^2$ and the transmitted spectral distribution of the samples and control was measured at intervals of approximately 15 min in a total exposure time of 2 h, corresponding to a total UV dose of 652 $kJ/m^2$. In terms of erythemal dose, total UV exposure corresponded to 8 minimal erythemal doses for phototype II (MED was defined as 250 $J/m^2$). The irradiation time was not extended due to the appearance of some small cracks on the top of the PMMA plates, which promoted the appearance of higher absorbance spots, making the analysis of the formulation extremely dependent on the chosen spot. Due to this, the longer acquired times at 3 h were discarded and not included in the results.

The transmittance was calculated using as reference a PMMA plate impregnated with 1.3 $mg/cm^2$ of glycerol (Vaseline). The total transmittance was obtained using the relation between the sample and blank irradiances, according to the following equation:

$$\text{Total transmittance}_{(\lambda)} = \text{measured Irradiance}_{(\lambda)}/\text{glycerol Irradiance}_{(\lambda)}$$

Also, the conversion to absorbance was undertaken by $A = -\log(T)$ to present the data in a more intuitive way.

*Analytical Data*

The prepared compounds present the following characterization data.

Compound **1**:

$^1$H-NMR (300 MHz, MeOD) δ ppm 7.70 (d, *J* = 8.2 Hz, 2H), 7.65 (m, *J* = 5.4, 3.4, 1.2 Hz, 2H), 7.55–7.41 (m, 6H), 7.27–7.19 (m, 2H), 2.42 (t, *J* = 6.3 Hz, 4H), 2.37 (s, 3H), 2.15 (s, 3H), 1.82 (q, *J* = 6.3 Hz, 2H).
$^{13}$C-NMR (75 MHz, MeOD) δ = 173.5, 143.7, 141.5, 135.9, 133.0, 131.5, 131.4, 130.8, 129.7, 129.5, 126.9, 101.6, 28.3, 21.3, 21.1, 9.7.
UV-Vis ($CH_3CN$): λ (nm) = 330 (ε = 26,400 $M^{-1}cm^{-1}$).
ES-MS (+) ($C_{19}H_{18}Cl_2N_2$ + H): calc. 345.0920, found 345.0927

Compound **2**:

$^1$H-NMR (300 MHz, MeOD) δ ppm 7.70 (bs, 2H), 7.24 (bs, 2H), 2.89 (bs, 4H), 2.60 (bs, 4H), 2.37 (bs, 6H), 1.94–1.62 (m, 2H), 1.61 (bs, 4H), 1.39 (bs, 4H), 0.96 (bs, 6H).
$^{13}$C-NMR (75 MHz, MeOD) δ ppm 170.1, 143.5, 141.7, 129.8, 126.9, 79.4, 40.5, 33.1, 30.6, 26.2, 21.3, 20.6, 13.8, 8.9.
UV-Vis ($CH_3CN$): λ (nm) = 324 (ε = 4200 $M^{-1}cm^{-1}$).
ES-MS (+) ($C_{15}H_{28}N_2$ + H): calc. 237.2325, found 237.2327

Compound **3**:

$^1$H-NMR (300 MHz, MeOD) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.64–7.57 (m, 2H), 7.55–7.39 (m, 6H), 7.24–7.17 (m, 2H), 2.80–2.51 (m, 4H), 2.35 (s, 3H), 2.09 (s, 3H).
$^{13}$C-NMR (75 MHz, MeOD) δ = 142.3, 140.2, 134.8, 131.1, 130.2, 130.1, 128.8, 128.4, 128.2, 125.6, 27.7, 20.0, 5.8.
UV-Vis ($CH_3CN$): λ (nm) = 306 (ε = 32,400 $M^{-1}cm^{-1}$).
ES-EM (+) ($C_{18}H_{16}Cl_2N_2$ + H): calc. 331.0763, found 331.0776.

Compound **4**:

$^1$H-NMR (400 MHz, MeOD) δ ppm 7.70 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 4H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 4H), 3.82 (s, 6H), 2.79 (s, 4H), 2.36 (s, 3H), 1.97 (s, 3H).
$^{13}$C-NMR (100 MHz, MeOD) δ ppm 180.5, 160.5, 143.7, 141.6, 131.9, 129.8, 127.5, 126.9, 115.7, 106.9, 56.0, 29.1, 21.3, 7.3.
UV-Vis ($CH_3CN$): λ (nm) = 328 (ε = 34,560 $M^{-1}cm^{-1}$).
ES-EM (+) ($C_{20}H_{22}N_2O_2$ + H): calc. 323.1754, found 323.1760.

## 5. Patents

The synthesis of these compounds was included in a Spanish patent application: ES2550374A1.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/photochem4010007/s1, Figure S1: NMR spectra of **1**. Figure S2: NMR spectra of **3**. Figure S3: Spectral irradiance used for the irradiation experiments. Figure S4: PMMA plates with the prepared formulations of **1**–**4** at 5%.

**Author Contributions:** Conceptualization, R.L., J.A., M.V.d.G. and D.S.; methodology, J.S., J.A. and R.L.; synthesis, L.L.-C. and B.P.; writing—original draft preparation, J.S. and R.L.; writing—review and editing, all authors; supervision, J.A., M.V.d.G., D.S. and R.L.; project administration, D.S.; funding acquisition, D.S. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The data presented in this study are available upon request from the corresponding author.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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