

Article

Absorption and Photo-Stability of Substituted Dibenzoylmethanes and Chalcones as UVA Filters

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Abstract: There is still an international need to develop broad-spectrum sunscreen products with an adequate UVB/UVA balance, while the approved filters available in the UVA are scarce. Currently, one of the few UVA filters approved in the United States and Europe is *tert*-butylmethoxydibenzoylmethane (BMDM, avobenzone). However, this compound is unstable from a photochemical point of view and cannot be used in combination with certain sunscreens. In this paper, we investigate the photochemical behavior of a set of dibenzoylmethanes and chalcones. In particular, we carry out their absorption and emission spectra, evaluate their photochemical degradation, and study their generation of free radicals and singlet oxygen photoproduction. Two compounds resulted in having the basic properties of UVA filters (2'-hydroxy-4-methoxychalcone and 2'-hydroxy-4-methoxydibenzoylmethane). Further studies are proposed, such as formulating the compounds into emulsions or other common cosmetic presentations, as well as combining them with broadly-used UVB filters. We have also considered the need to establish its toxicological profile.

Keywords: UVA filters; dibenzoylmethanes; chalcones; photo-stability

1. Introduction

Moderate exposure to sunlight has several beneficial effects on human health [1–3]. However, excessive exposure to UV radiation causes various damages to the body, including burns, photoaging and skin cancer [4–6]. The first commercially-available sunscreen appeared in 1928, it contained benzyl salicylate and benzyl cinnamate [7]. Currently, these substances are, not only incorporated in sunscreens, but also in a large number of cosmetics for skin and haircare [7].

Different substances are approved as solar filters for humans, according to regional requirements. According to Shaath [8], in 2010, there were 55 UV filters approved in different parts of the world; of these, only 10 were globally approved.

Currently-authorized UV filters are classified into two types: Inorganic and organic. The inorganic filters used are ZnO and TiO₂. Both are considered broad spectrum because they absorb or reflect UVB and UVA rays. Organic filters are classified according to their structure (Figure 1). There are several important aspects to be taken into account, such as the photostability of the sunscreen, its toxicity in humans, and its final disposal into the environment.

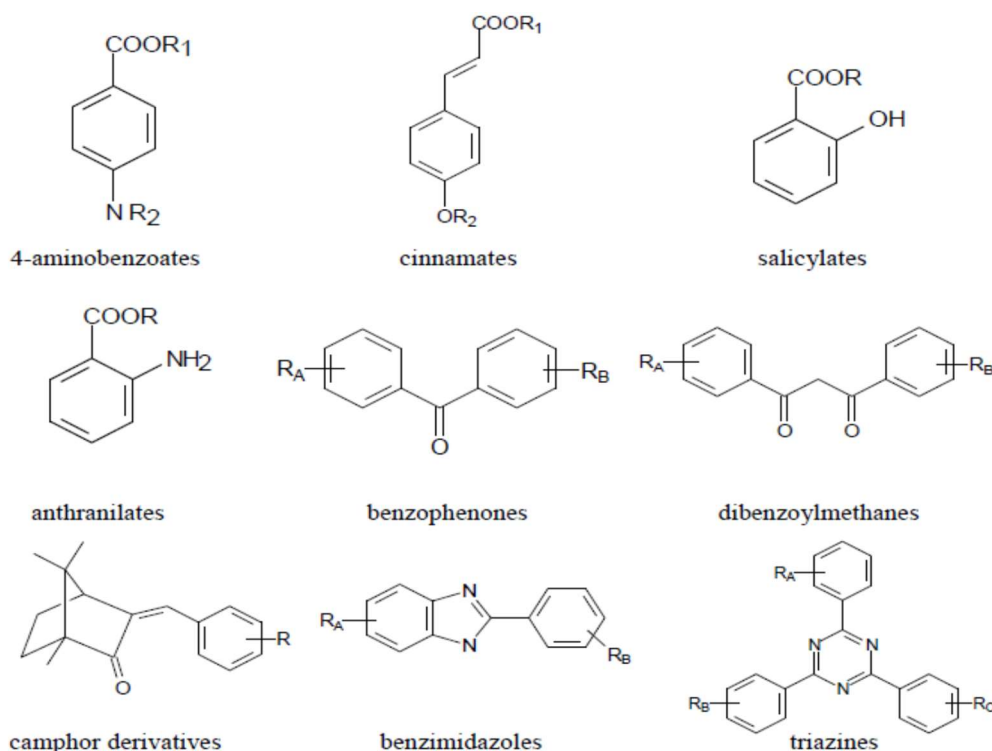


Figure 1. General structures of the most important currently-approved organic filters.

Photodegradation causes a loss of UV protection because of resulting photoproducts that show UV-absorption at lower wavelengths than their parent compounds [9–11]. For example, nano-TiO₂ (particle size < 25 nm) causes photodegradation of avobenzone (BMDM) and octocrylene (OC) [12]. An important issue to be considered at the level of skin or percutaneous absorption is the toxicity of sunscreens, either per se or caused by their decomposition products.

In the 1980s, 4-isopropylidibenzoylmethane was used as a sunscreen, but in 1993 it was eliminated from the market for causing allergies. It was only in this century that we became fully aware of the need to obtain an adequate balance of UVB/UVA protection; legislation and control methods are still not in full agreement [13]. Currently, one of the few UVA filters approved in the United States and Europe is tert-butylmethoxydibenzoylmethane (avobenzone), which shows light absorption $\lambda_{\max} = 357$ nm. However, this compound is unstable from the photochemical point of view and can't be used in combination with certain sunscreens.

Recent studies show that the irradiation of avobenzone causes a breakdown of the molecule in radicals, this generates compounds, such as arylglyoxals and benzyls (Figure 2) [14], or react with other sunscreens [15]. In Figure 2, H[•] refers to the capture of a hydrogen atom from another molecule (generally the solvent). Studies of the biological properties of photodecomposition products indicate that arylglyoxals are strong photosensitizers. They are also very electrophilic and react quickly with arginine of proteins. On the other hand, benzyls are cytotoxic [6].

Different ways to photostabilize avobenzone have been reported. Among them are UV pearls (encapsulated sunscreens), microspheres (hollow spheres of styrene-acrylate copolymers), ROS (reactive oxygen species) trappers, and inhibitors of the triplet-triplet and singlet-singlet mechanism [8]. Moreover, several patents have been published claiming different strategies to solve the intrinsic instability of dibenzoylmethane compounds subjected to UV radiation, such as synthesizing diorgano-polysiloxane derivatives or derivatives of other polymers [16], including the formulation of esters or diesters of α -naphthalenesulphonic acid [17]. Two ideas were also proposed, firstly to include in the formulas a thickening polymer, having a small polar tail from an α,β -unsaturated monocarboxylic acid, linked to a heavier non-polar moiety of alkyl-methacrylate or alkylstyrene

polymer [18]; secondly, to synthesize a quaternary compound of dibenzoylmethane [19]. Finally, it was also proposed to protect avobenzone with anti-oxidants such as vitamins C and E [20].

Some authors have tried to switch the keto-enol tautomerism of avobenzone (whose enol structure is more stable to radiation) by introducing different substituents to the aromatic rings and consequently modifying the absorption maxima wavelength and intensity [21–24]. These different substituents include chlorides, fluorides, acetamides, hydroxy, methoxy and nitro groups, and long aliphatic chains. None of these proposals seem to have been successful. The solution should not be to use photochemically unstable molecules that require additional molecules to make them stable in a cosmetic formulation. According to Gonzenbach [25], using a UV filter to avoid photodecomposition of another UV filter is similar to protecting an umbrella from getting wet by placing a second umbrella over it. If the umbrella does not repel the rain, it must be improved in some way.

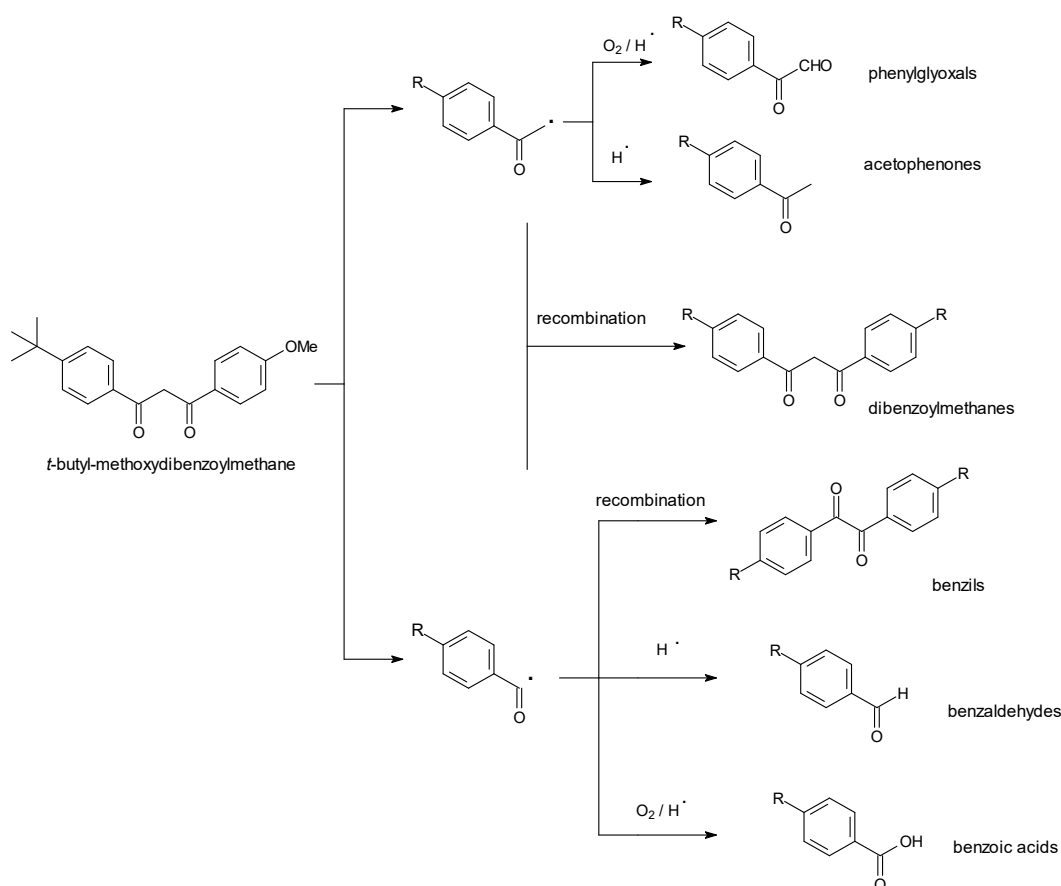


Figure 2. Photodegradation of dibenzoylmethanes (adapted from Schwack et al. [11]).

On the other hand, several studies have been made both in solution [11], formulated into emulsions, or by irradiating a thin film to simulate application to the skin [26].

It must be noted that none of the compounds previously studied belong to the set tested in our work. In almost every case, when subjected to the radiation of solar simulators, they showed decomposition in the range of 3.6 to 40%. When dissolved in non-polar solvents they decomposed easily; however, the stability improved when short chain alcohols, such as methanol and isopropanol were used as solvents. Deflandre and Lang [26] also found more stability when an –OH was present at the *ortho* position to a carbonyl group. Other recent studies [27] show that the keto-enol tautomerism not only shifts the absorption maxima, but it is also responsible for the photo-degradation of the molecules.

Another important problem is environmental pollution. Because coastal tourism is rapidly growing, sunscreen is now considered an emerging pollutant [28]. Sunscreens are formulated to resist

being washed out while bathing, however, it is estimated that after 20 min of immersion, 25% of the ingredients are released into the water. Several ecological problems have been reported in recent years [29–34].

Chalcones are a type of flavonoid with the structure $C_6-C_3-C_6$ and are widely distributed in the vegetable kingdom. Many natural and synthetic chalcones have some kind of biological activity in animals and humans, or are used in industries. Chalcones have $\lambda_{\max} \sim 350$ nm, so are useful as UV absorbers and can be incorporated in paints, plastics, synthetic fibers and cosmetics [35–38]. Lahorkar reported that some chalcones (butein, monospermoside) enhance the stability of avobenzone [39].

Considering this background, and due to the growing demand for sunscreen, the discovery of new, safer and more effective compounds is of great importance. In this paper we describe the photochemical behavior of a small set of dibenzoylmethanes and chalcones. More specifically, we have carried out their absorption and emission spectra, evaluated their photochemical degradation and studied their generation of free radicals and singlet oxygen photoproduction.

2. Materials and Methods

The following compounds were tested (Figure 3):

Dibenzoylmethanes:

- (a) 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione (DBM1)
- (b) 1-(2-hydroxyphenyl)-3-(4-methylphenyl)-1,3-propanedione (DBM2)
- (c) 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-1,3-propanedione (DBM11)
- (d) (4E)-1-(2-hydroxyphenyl)-5-phenyl-4-penten-1,3-dione (DBM4)

Chalcones:

- (e) (2E)-1,3-diphenyl-2-propen-1-one (CH00)
- (f) (2E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (CH11)
- (g) 1-(2-hydroxyphenyl)-5-phenyl-(2E,4E)-2,4-pentadien-1-one (CHCIN)

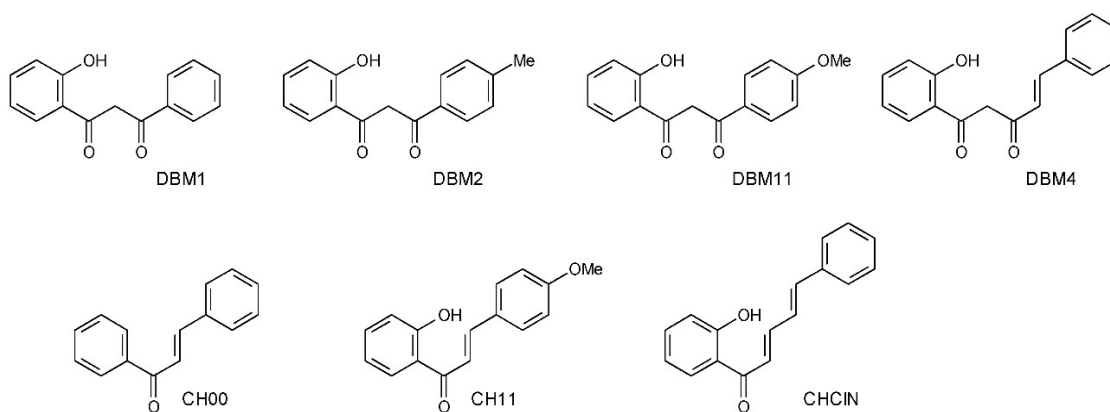


Figure 3. Dibenzoylmethanes and chalcones tested in this study.

All compounds were synthesized, purified and characterized at the Department of Organic Chemistry, Universidad de la República (UDELAR), Montevideo, Uruguay. The chalcones were prepared by aldol condensation of the corresponding 2'-hydroxyacetophenones and benzaldehydes [40]. The dibenzoylmethanes were prepared using Baker-Venkataraman rearrangement, which rearranged the corresponding 2-acetyl phenyl benzoates [41]. All compounds were purified by column chromatography and characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, mass spectrometry, and elemental analysis.

The spectroscopic and photochemical studies were performed at the INQUIMAE (Instituto de Química Física de los Materiales, Medio Ambiente y Energía), CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and FCEN (Facultad de Ciencias Exactas y Naturales), Universidad de Buenos Aires (UBA). The samples a–g were dissolved in absolute Ethanol P.A. and scanned between 200 and 500 nm with a UV-VIS Shimadzu UV-3600 spectrophotometer (Shimadzu Corp., Kyoto, Japan) to obtain their absorption spectra. The emission spectra and the calculations used to obtain the quantum fluorescence yields, were performed between 400 and 650 nm with Photon Technology International QM-1 spectrofluorometer (Photon Technology Inc., Birmingham, NJ, USA). The excitation wavelengths used coincided with the absorption maxima of each substance.

To measure photo-stability, the samples were subjected for two hours to the radiation of a solar simulator (290–340 nm). The experiments were done using a quartz Philips 7748SEHJ lamp (24 V–250 W, Philips Lighting, Amsterdam, The Netherlands), which has a UV-transparent quartz bulb with XHP technology and is an alternative to classical Xe sources. The lamp was then collimated with an adequate lens and further filtered through a 10 cm water filter to eliminate the IR radiation. A cut off filter Schott UG11 was also interposed in the optical path of the sample to eliminate the UVC radiation.

The UV radiation incident placed perpendicular to a 10×10 mm stirred quartz cell containing the sample solutions through a limiting window. The spectral distribution obtained was similar to the one of commercial sources manufactured by Berger [42]. The calculated irradiance, estimated with Field Master equipment during the first set of tests, was of $105.5 \mu\text{W}/\text{cm}^2$; later on it was increased by shortening the optical pass to $8.56 \text{ mW}/\text{cm}^2$ for the more promising samples.

In all cases, Lambert-Beer's law was verified. The singlet oxygen studies were performed employing difenilisobenzofurane (DBPF) as the control molecule [43]. The fluorophore incorporated to verify free radical generation was 2',7'-dichlorodihydrofluoresceindiacetate, which is a probe that becomes fluorescent under oxidation and emits a green color. The quantum yields were obtained taking rhodamine 101 dissolved in ethanol ($\Phi_F = 0.96$) as a references [43,44].

3. Results

3.1. Absorption Spectra

Figure 4A–D shows the absorption spectra obtained for the dibenzoylmethanes and the different concentrations tested for each one of the four samples in this study.

Concentrations are expressed as weight/volume % (P/V %).

Figure 5A–C shows the absorption spectra obtained for the three chalcones tested under this study. Concentrations are expressed as weight/volume % (P/V %).

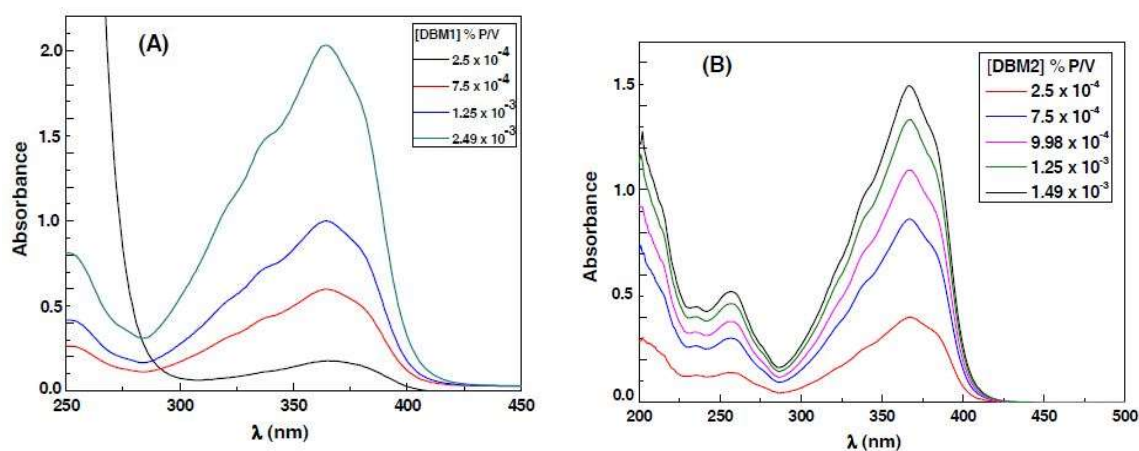


Figure 4. Cont.

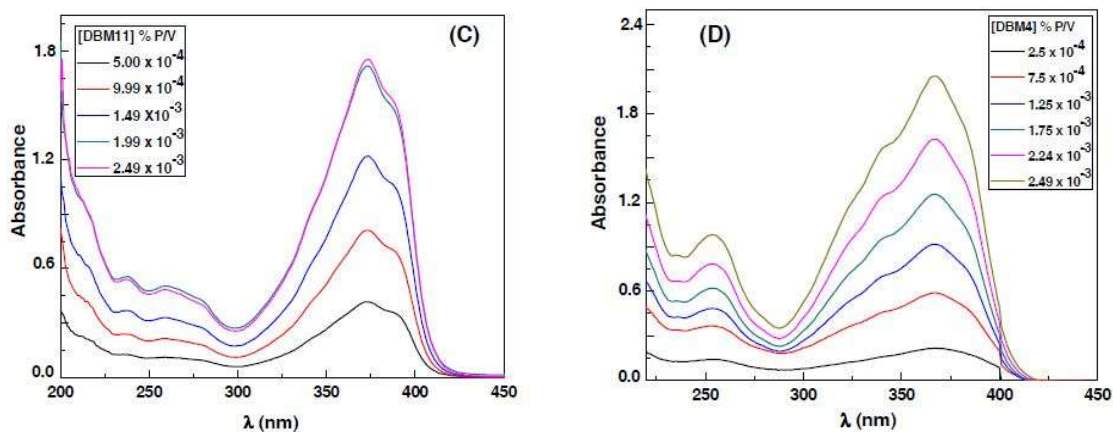


Figure 4. Absorption spectra of dibenzoylmethanes: (A) DBM1; (B) DBM2; (C) DBM11; (D) DBM4.

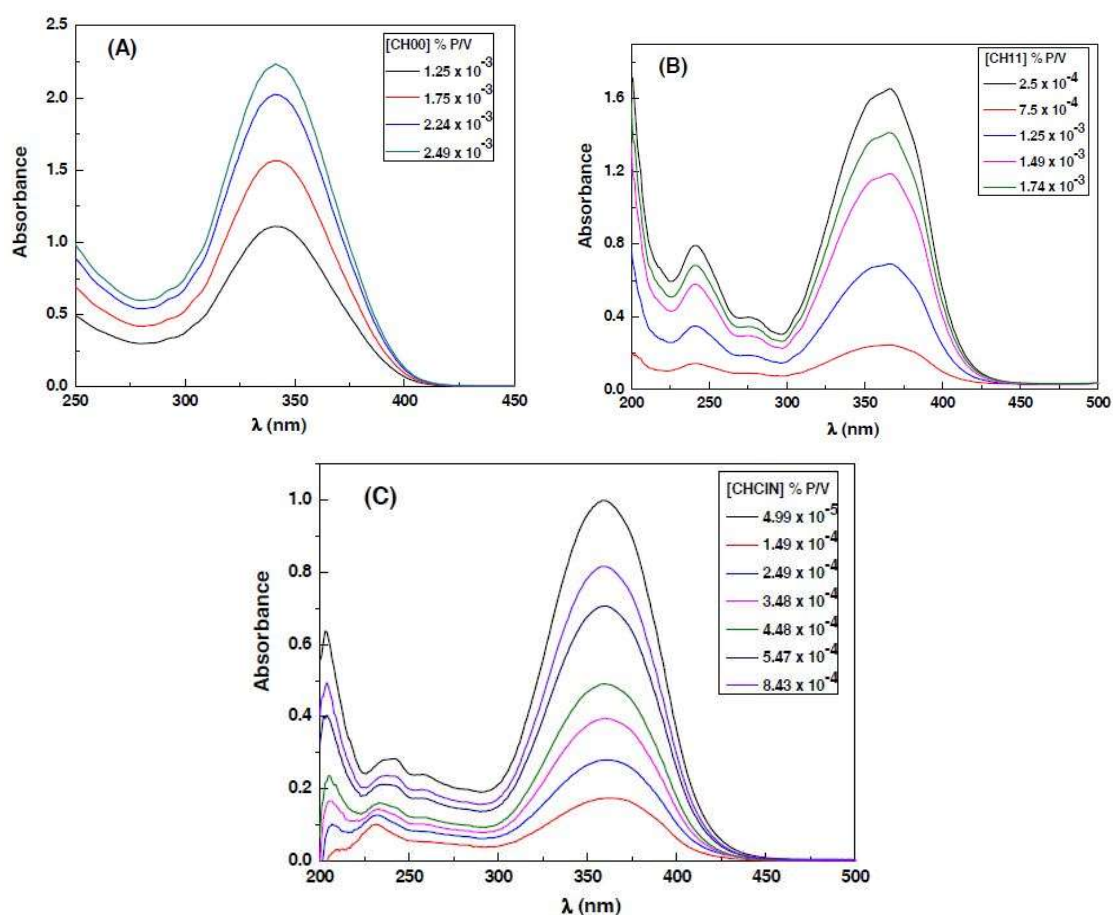


Figure 5. Absorption spectra of chalcones: (A) CH00; (B) CH11; (C) CHCIN.

In the latter case, we found that the absorption maxima of chalcones were close to the formerly studied dibenzoylmethane compounds. Thus, they could also be used in combination with UVB filters to formulate broad-spectrum sunscreens.

3.2. Emission Spectra

Figure 6 shows the emission spectra obtained from the different filters tested.

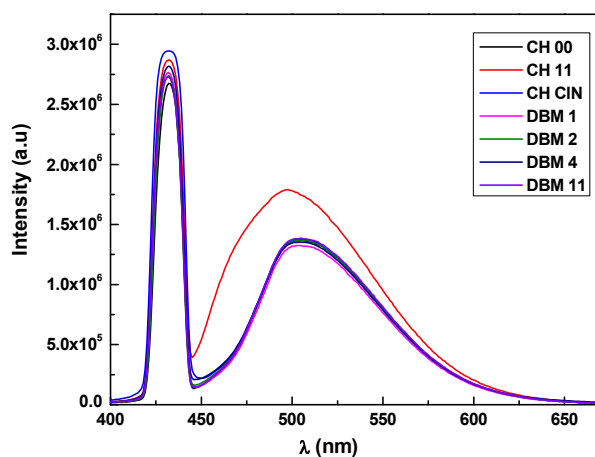


Figure 6. Fluorescence spectra of the different compounds tested.

The quantum yields obtained for all the tested compounds, relative to Rhodamine as a fluorescent probe (Table 1), were very feeble.

The experimental results show a low quantum fluorescence yield and no generation of free radicals or singlet molecular oxygen; therefore, the only way of decaying to ground state is through energy transfer as heat to the environment.

Table 1. Quantum yields relative to rhodamine 101 in ethanol ($\Phi_F = 0.96$).

Sample	Absorption at $\lambda = 350$ nm	Emission Area	Absorption Intensity	Quantum Yield (Fluorescence)
Rod 101	0.0134	528628676.92	0.03038	0.96
DBM 1	0.1387	162205046.87	0.27339	0.033
DBM 2	0.3064	99573752.80	0.50614	0.011
DBM4	0.1788	169868850.73	0.33747	0.028
DBM11	0.3223	168263751.04	0.52389	0.018
CH00	0.1736	162546475.64	0.32949	0.027
CH11	0.2316	225362192.66	0.41332	0.030
CHCIN	0.3777	179803227.87	0.58092	0.017

3.3. Decomposition Kinetics

Figure 7A–D (for the dibenzoylmethanes) and Figure 8A–C (for the substituted chalcones) show what happened when the samples were irradiated with $105.5 \mu\text{W}/\text{cm}^2$ UV light for two hours. Concentrations are expressed as weight/volume % (P/V %).

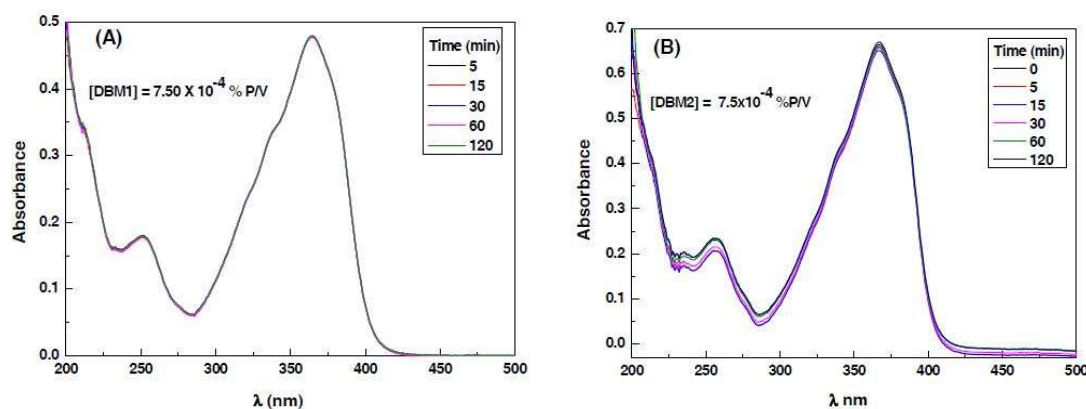


Figure 7. Cont.

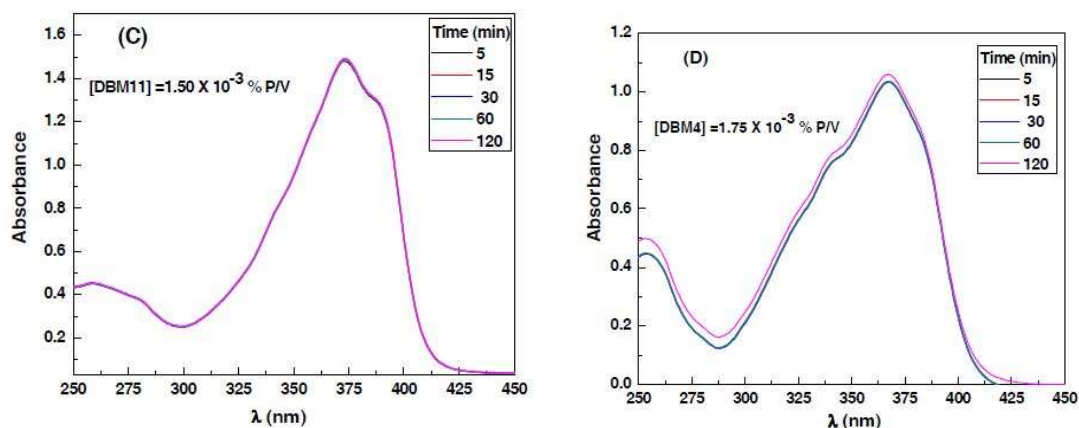


Figure 7. Photodecomposition of dibenzoylmethanes: (A) DBM1; (B) DBM2; (C) DBM11; (D) DBM4.

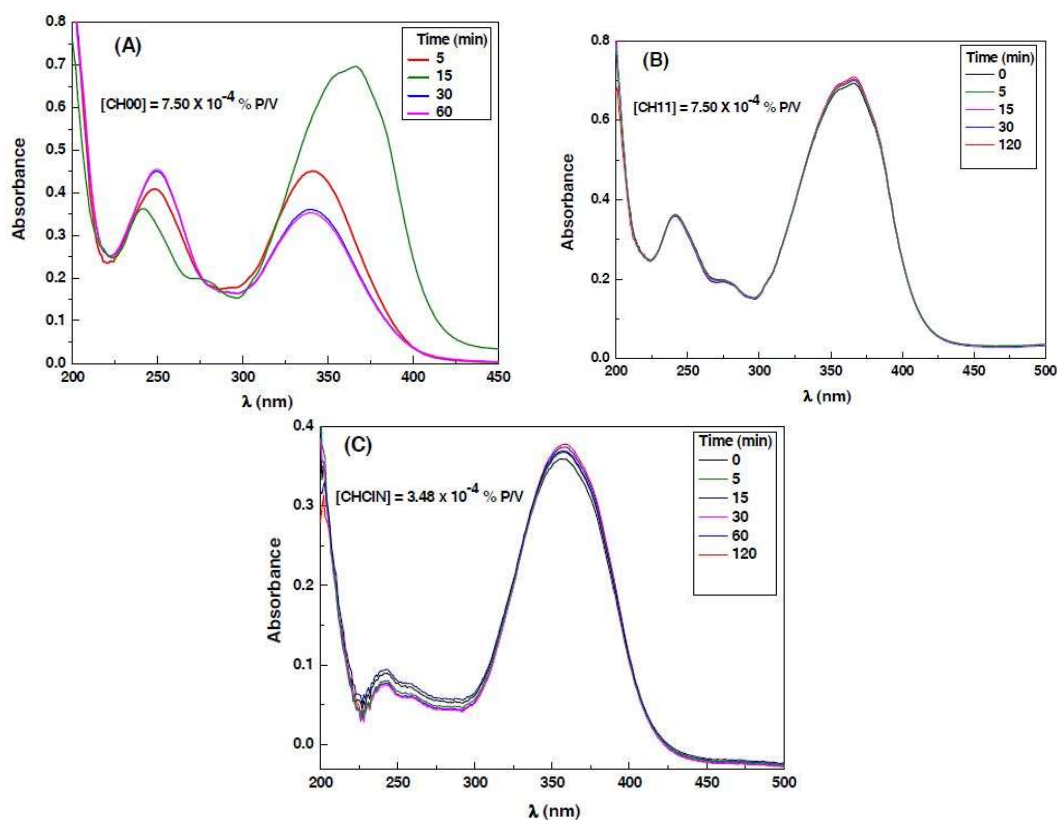


Figure 8. Photodecomposition of chalcones: (A) CH00; (B) CH11; (C) CHCIN.

The two more stable dibenzoylmethanes, when submitted to UV irradiation from our solar simulator, were DBM1 and DBM11. We decided to continue further with DBM11 because it had a better fluorescence profile (the lowest within the stable molecules). The unsubstituted chalcone was extremely unstable, showing almost 50% decomposition after one hour. Instead, CH11 proved to be quite stable during our experiment.

3.4. Singlet Oxygen and Free Radicals Studies

Figure 9A,B corresponds to the singlet oxygen studies in the presence of difenilisobenzofurane (DBPF). The black line corresponds to DBPF alone, the red one to CH11 or DBM11 alone, while the other colors correspond to the mixtures of DBPF with the two filters at different times of irradiation.

No significant variations were detected in their absorption; the two stable compounds did not generate singlet oxygen when they were irradiated in the presence of DPBF.

Neither did we detect the generation of free radicals by fluorescence when the mixtures of DBM11 and CH11 with dichlorofluorescein were irradiated with UV light.

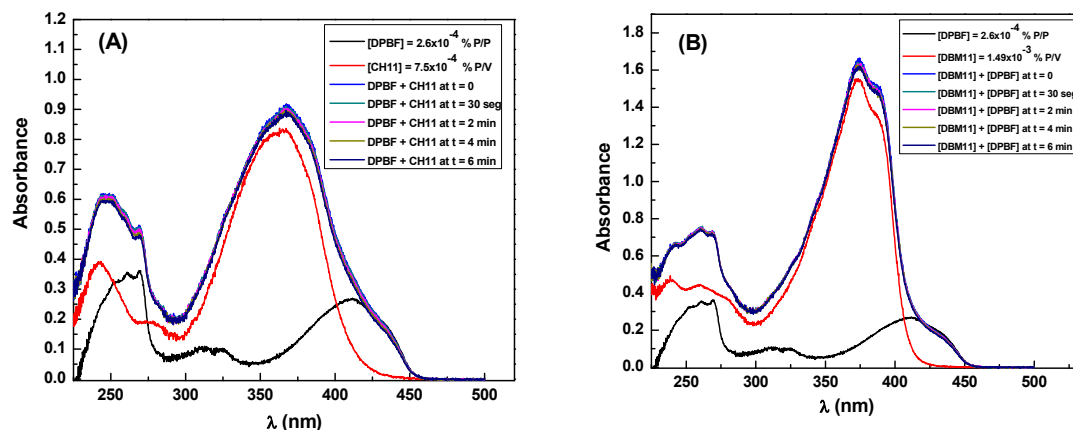


Figure 9. Spectra of CH11 (A) and DBM11 (B) mixed with difenilisobenzofurane (DPBF).

3.5. Decomposition Kinetics under More Stringent Conditions

Figure 10A,B shows the samples behavior when irradiated for two hours with 8.56 mW/cm² light. Concentrations are expressed as weight/volume % (P/V %).

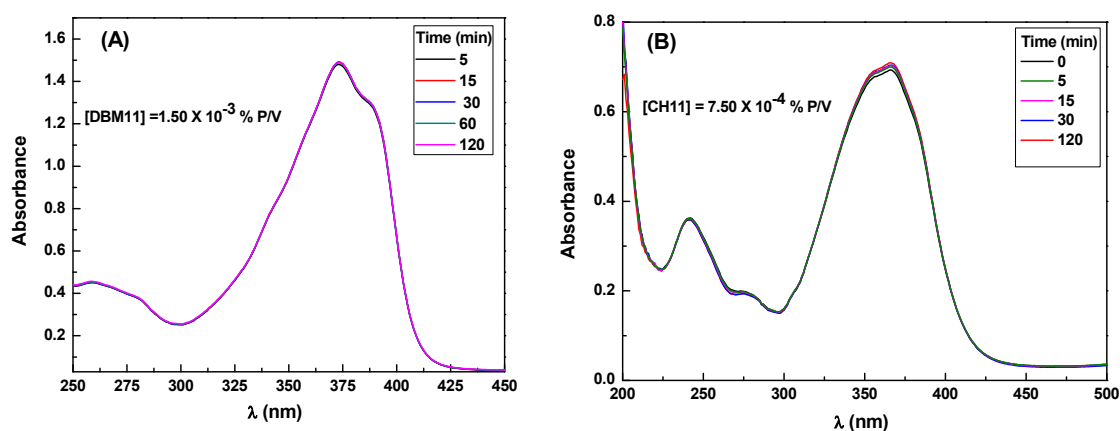


Figure 10. Photodecomposition of DBM11: (A) and CH11 (B) with 8.56 mW/cm².

Results show that DBM11 was not degraded by irradiation, while CH11 suffered a very small degree of degradation, estimated at 1.3% from the areas under the curves.

4. Discussion

Two out of the seven compounds studied are promissory to be considered as potential UVA filters: 2'-hydroxy-4-methoxy chalcone (CH11) and 2'-hydroxy-4-methoxydibenzoylmethane (DBM11). Both were able to resist a UV irradiation of 8.56 mW/cm² for two hours, receiving an accumulated energy of 61.6 J/cm².

The DBM 11 sample showed practically zero decomposition, while the CH11 sample lost 1.3% of the original concentration, as calculated from the area under the curve. We estimated that the total power delivered in this battery of tests corresponds to double what a sample would receive as a mean in America during summer between the +25N and −25S parallels [45].

On the other hand, the energy absorbed by these two compounds in the UV is dissipated mostly as heat and very little as fluorescence. Moreover, during the decay, they do not generate reactive species (singlet oxygen or free radicals) that could damage the skin during the process, as shown in Section 3.4.

They present the basic characteristics of actual chemical UV filters: they have aromatic structures conjugated with carbonyl groups that absorb energy from the photons UV radiation and by means of resonance delocalization, jump to an excited state. Then they decay to their fundamental state emitting energy of longer wavelengths into the infrared (as heat) or visible fluorescence, satisfying the laws of energy conservation [46,47].

The other possible route of decay is by photochemical reactions that generate non-desired by-products that could be irritating, toxic [11], or even react with other filters in the formulations, impairing their protective action to the skin.

The results obtained up to this stage, lead us to think that we have found two possible candidates that deserve further study. Both present absorption maxima in the range of 350–370 nm and show good photostability when dissolved in low molecular weight alcohol (ethanol). These two molecules would meet the need that consumers, formulators, and the whole industry are looking for: better sunscreens with adequate UVB/UVA balance, without having to resort to gadgets to protect other essentially unstable molecules.

We will continue our studies to verify if once formulated into an emulsion and combined with other filters, namely UVB filters as 2-ethylhexylmethoxy cinnamate or octyltriazone, they keep their stability when a thin film of the product [26,46,48,49] is irradiated with a solar simulator and if this process does not generate undesirable decay by-products. We also envisage toxicological in vitro assays on the pure materials and in the formulations to establish a toxicological profile and the future possibility of predicting their spectral properties by in silico studies, based on density functional theory [50].

In fact, the latter is already underway by the research team of Dr. Darío Estrin at DQIAQF—INQUIMAE, FCEN—UBA.

5. Conclusions

We identified two molecules that have the basic properties of the UVA filters. They present an absorption maximum in the range of 350–370 nm. When irradiated they jump from the ground state to an excited one, decaying basically by emission in the IR. Almost no visible emission is detected (fluorescence). We did not detect any decomposition in the case of 2'-hydroxy-4-methoxydibenzoylmethane (DBM11) and only a very slight one for 2'-hydroxy-4-methoxy chalcone (CH11). Generation of singlet molecular oxygen and free radicals was not detected either. We can confirm that if an –OH group is positioned at the *ortho* position of carbonyl, then both molecules are more stable. Furthermore, both have a methoxy group in position 4, which caused us to think that in terms of delocalization of electrons, there exists similitudes that could explain their favorable behavior under UV irradiation.

Author Contributions: G.S. synthesized and identified all the tested compounds. S.Q.L. studied their photochemical behavior at DQIAQF-FCEN-UBA while working at fabriQUIMICA under the responsibility of F.S. and with the direction of L.D. F.S. co-ordinated the joint research and wrote the initial version of the paper and subsequent corrections.

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

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