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Archives of Clinical and Experimental Pathology

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Research Article

Synthesis of dibenzoylmethane-flavonoid hybrids as potential uv filters. Hybrids of chalcones.

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Received date: September 12, 2022; **Accepted date:** September 19, 2022; **Published date:** September 26, 2022

Citation: Gabriel Sagrega, Federico Svarc, Yanina Minaberry. (2022) Synthesis of Dibenzoylmethane-Flavonoid Hybrids as Potential UV Filters. Hybrids of Chalcones. Archives of Clinical and Experimental Pathology.1(1); Doi:10.31579/2834-8508/002

Abstract

Background: It has been reported that chalcones (a family of flavonoids) have activity as UV rays absorbers. Previously we have reported that the compounds 2´-hydroxy-4- methoxychalcone and 2´-hydroxy-4-methoxy dibenzoyl methane have the basic properties of UVA filters (both show their maximum absorption in the range 350-370 nm with good photostability)

Objective: in this work, we describe a new series of chalcone-dibenzoylmethane hybrid candidates as syntheticUV filters and flavonoids

Method: The compounds resulted from multi-step synthesis starting from 4 – formylbenzoic acid and 2´- hydroxy acetophenone. Purification was done by recrystallization or column chromatography.

Results: The compounds were obtained with good yields and characterized by spectroscopy.

Conclusion: They are good candidates for UVA filters in cosmetics. Drs. Svarc and Minaberry will perform the corresponding photostability studies.

Keywords: uv filters; dibenzoylmethanes; chalcones; flavonoid hybrids; photostability

Introduction

Originally, the term "flavonoid" comes from the fact it is structurally related to flavane (2 – phenyl cromane) (Figure 1) [1-4].

More correctly, they should be considered as derivatives of 1,3-diphenyl propane (C_6- C_3-C_6 skeleton). Other compounds that are structurally related to flavonoids are the derivatives of 1,2-diphenyl propane (isoflavonoids) and 1,1-diphenyl propane (neoflavonoids).

In all of the three cases, fragment C3 can take part in a closed ring or stay as an open chain.

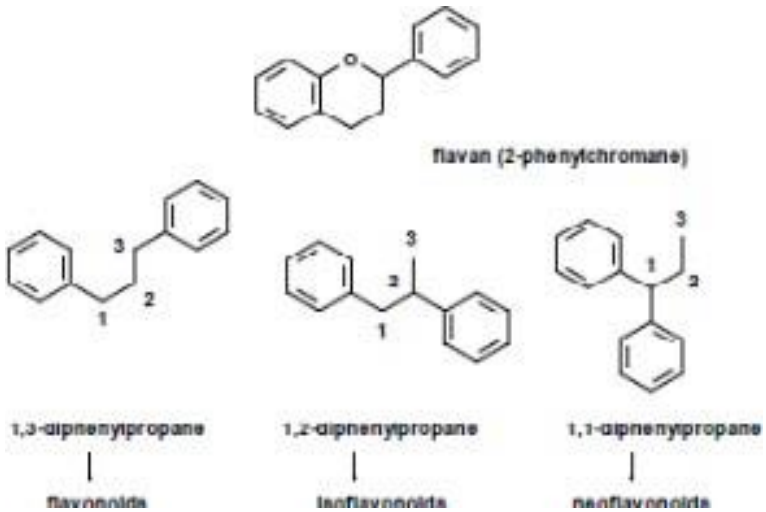


Figure 1: *Flavonoids, isoflavonoids, and neoflavonoids basic skeleton*

Flavonoids possess the same basic skeleton. The different types and families differ structurally because of their substituent pattern and oxidation level of C in the C3 fragments (or as a part of a heterocycle), while different compounds within a family differ in the substitution pattern of the rings A and B. Figure 2.

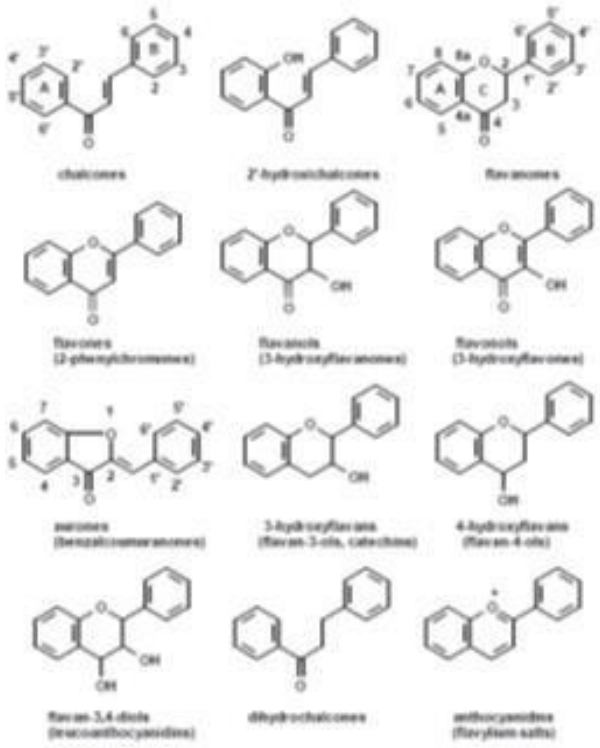
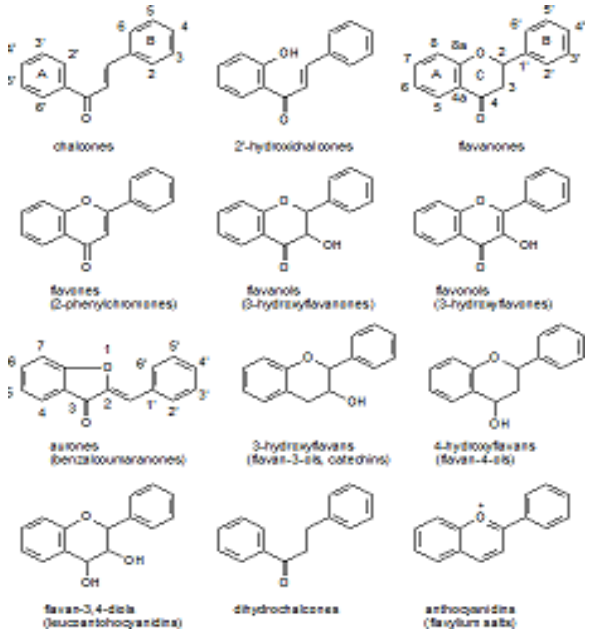


Figure 2. *Structure, nomenclature, and numbering of some flavonoids.*



Flavonoids are widely distributed in nature, mostly in the vegetal kingdom, and their range of biological activities is large. They are one of the most important secondary metabolites of plants with structural and functional capabilities. Many natural and synthetic flavonoids have some type of biological activity in animals and men, being used in the industry too.

Flavonoids are found everywhere in the vegetal kingdom, almost in every terrestrial plant (superior and inferior), and also in some algae [3]. Around 2000 more than 8000 individual compounds [5] were known. They play different roles in the plant´s ecology, acting as antioxidants, antimicrobials, photoreceptors, UV protectants, visual attractors,chemical attractors, or repellents and inductors of nodulation in bacteria fixing Nitrogen. They also act as protectants from oxidative stress, trapping reactive oxygen species (ROS) produced during photosynthesis. Due to their capacity to absorb UV radiation from the sun, they protect the plants from damage caused and trap the ROS generated [6].

Flavonoids have a wide range of biological activities [7], within them as antioxidants, antimicrobials (including bacteria, fungi, viruses, plasmoids), anti-tumoral, chimo, and cytotoxic-preventive. Also possess anti-allergic, anti-inflammatory, hypotensive, vasodilator, gastroprotection, anti-diabetes properties and help to fight against capillary fragility and platelet aggregation.

As for other natural compounds, the bioactivity of flavonoids depends on the nature, number, and position of the substituents on their skeleton [8,9]. Frequently the biological activity is related to free hydroxyl moieties. As an example, the antioxidant capacity increases with the number of hydroxiles. It is widely accepted that fruits and vegetals have many healthy properties. People whoconsume a good quantity of those have a healthy style of life, which is important in faceof chronic diseases. We think that a supplement of antioxidants (particularly flavonoids)by daily ingesta of food gives additional protection against *in vivo* oxidation of biomolecules in the cells. Studies *in vitro* and on animals have been made to prove this hypothesis. There exists enough epidemiological evidence showing a correlation between individuals that keep a diet rich in fresh fruits and vegetals with benefit on health. They contribute to avoiding degenerative processes, diminishing particularly incidence and mortality from cancer, heart disease, and brain vascularization [10-14].

It has been reported that some of the chalcones are capable of the negative effects of UV radiation. Their protective activity against the sun is generated by a high UV absorbance in the region UVB-UVA [15], corresponding to the electronic transition n and * of HOMO and LUMO energy levels in the conjugated electronic system of these molecules. By the introduction of electron donor substituents (bathochromic change) or acceptor substituents (hypsochromic change) in both rings othe UV absorbing range of chalcones can be displaced, being the major change on ring A [16] (Figure 2).

One of the drawbacks to using chalcones as solar filters is their relatively low photostability and their photodecomposition products [17-19].

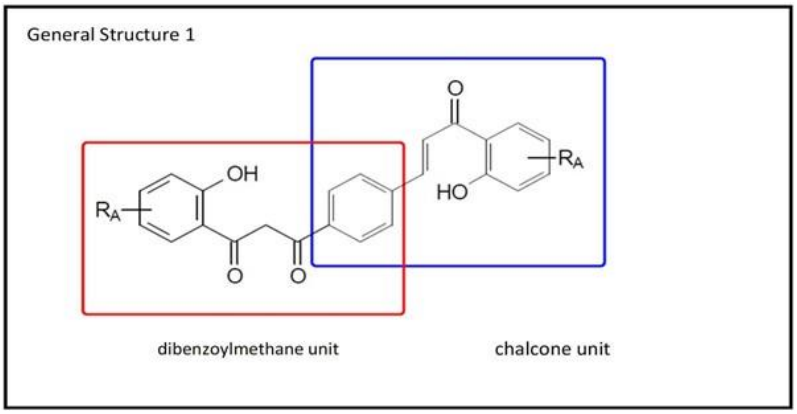
Many chalcones show protective action on deleterious effects produced by UV rays, as trans-chalcone, buteine, monospermoside, lico-chalcone A, florentin, and hesperidin derivatives. Non-

substituted trans-chalcones did not show in rats any potential activity towards inflammation and oxidative stress. A formulation with 1% of non-substituted trans-chalcones can protect the skin from UVB radiation by reducing the level of the alfatumoral necrosis factor (TNF- and by improving the detoxification and antioxidant systems increasing haemo-oxygenase 1 (HO-1)[18,19].

Systemic administration of trans-chalcone seems to inhibit UV-induced skin inflammation and prevent oxidative stress targeting the nicotinamide adenine dinucleotide phosphate H (NADPH) oxidase and cytokine generation [18].

In vitro and in vivo studies showed that the licochalcone A has a huge protectant effectagainst oxidative stress and UVB-induced inflammation. It inhibits prostaglandin E2, cyclooxygenase (COX-2), lipoxygenase, and the nuclear factor kappa enhancer belonging to the light chain of B activated cells (NF- B) and Nrf2 [20-22].

An in vivo study has shown that a topical formulation of licochalcone A reduced in a significant way erythema, irritation, and oxidative processes induced by UV rayson the skin [21-23].



Hesperidin methyl chalcone and related compounds also exhibit a high degree of protection in the UV [24].

Figure 3. *General Structure of the compounds to be Synthesized*

The topical and systemic administration of hesperidin-methyl chalcone on mice inhibits the oxidative stress induced by UVB rays by reduction of ROS and other free radicals, improves endogen antioxidants, and inhibits inflammation by cytokine suppression[25].

Chalcones have maximum absorption of around 350 nm, thus they are useful as UV absorbents and can be incorporated into paints, plastic materials, synthetic fibers, and cosmetics [27-30].

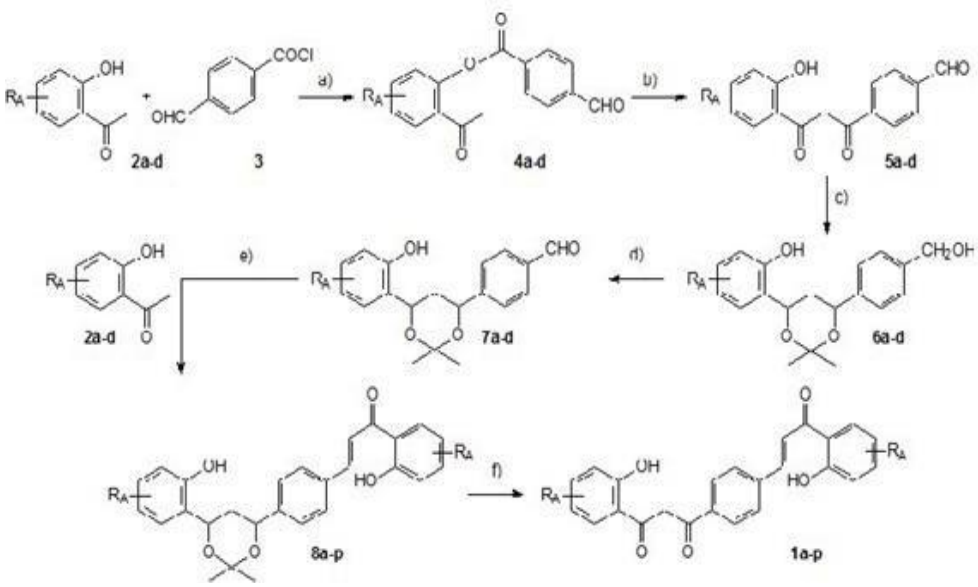
Lahorkar has reported that some chalcones (butein, monospermoside) increase Avobenzone stability.

Our research group has reported that a 2-OH group in the A ring (Figure 2) of a chalcone or dibenzoyl methane increases the photostability of the molecules. In this sense, 2-hydroxy-4-methoxy-chalcone and 2´-hydroxy-4-methoxy-dibenzoylmethane present a good photostability and are candidates to be used as UVA filters in cosmetic formulations [32].

As a consequence of a research line related to the synthesis of dibenzoylmethanes and flavonoids, this work describes the preparation of a small library of chalcone-dibenzoylmethane hybrids, for their subsequentevaluation as sunscreens. Their general structure1 is shown in Figure 3.

Materials And Methods

All compounds were prepared by typical organic chemistry reactions (aldol condensation, oxidative cyclization, acid chloride formation, esterification, and Baker-Venkataraman rearrangement) using previously optimized conditions reported by us [33,34]. Some reactions were carried out in a nitrogen atmosphere. All reactions were monitored by thin-layer chromatography (TLC). The compounds were isolated by common procedures (extraction with organic solvents, washing with brine, drying of the organic layers, and concentration in vacuo), and purified by recrystallization or column chromatography (CC). The compounds were characterized by proton and carbon nuclear magnetic resonance spectroscopy (1H-NMR and 13C-NMR) and mass spectrometry (MS).



All reagents were purchased from commercial sources and used without purification unless otherwise indicated. All solvents were dried and distilled before use. AcOEt and hexanes were dried over $MgSO_4$ and distilled. THF was treated with CaH_2 to remove peroxides, and dried by refluxing with benzophenone over Na wire until a blue color persisted, then distilled and collected. CH_2Cl_2 was dried by refluxing over P_2O_5 for 3 h, then distilled and collected. Pyridine was dried by heating under reflux over anhydrous KOH and then distilled. All reactions were monitored by TLC on polyester plates coated with Alugram Sil G/UV254 using various solvent systems. Column chromatography was carried out on silica gel (Merck, 60–230 mesh) using hexanes as the initial eluent, followed by a suitable solvent gradient. ^1H

and ^{13}C NMR spectra were recorded at 30 °C on a Bruker DPX-400 spectrometer at 400 MHz and 100 MHz, respectively.

First, acetophenones not available in our laboratory were synthesized. 2'-hydroxy-4'- butyloxyacetophenone was prepared from 2', 4'-dihydroxyacetophenone and 2'-hydroxy-4',6'- dimethoxy acetophenone from phloroglucinol. The hybrid compounds were prepared in several steps, using previously optimized conditions [33,34] (Figure 4):

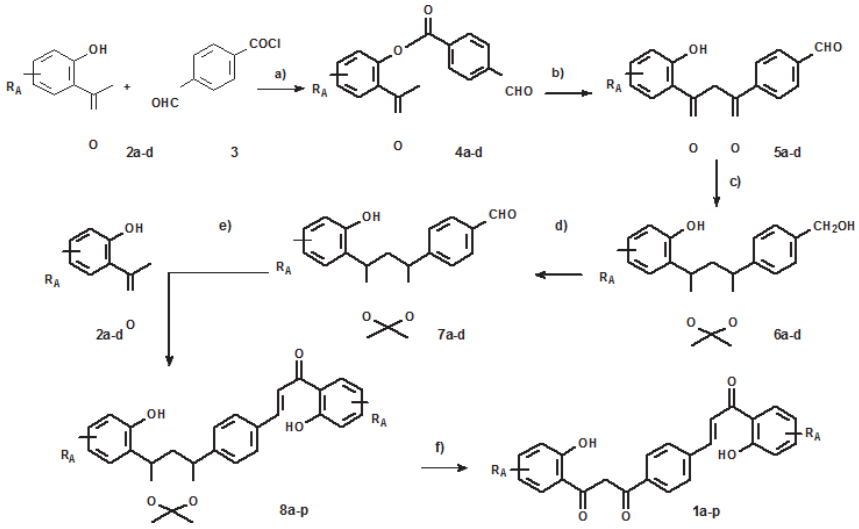


Figure 4: *Sintesis of hybrid molecul*

Experimental

a) synthesis of esters from 4-formylbenzoic acid and acetophenones **2a-d**. First, the chloride of 4-formylbenzoic acid is prepared by treating the acid with $SOCl_2$ in CH_2Cl_2. The acid chloride is not purified and was reacted with acetophenones

2a-d to form esters **4a-d**

b) Baker-Venkataraman rearrangement to form dibenzoylmethanes **5a-d**

Subsequently, carbonyl groups of the dibenzoylmethanes were protected to prepare the chalcones by aldol condensation.

This is done in 3 steps:

c1) reduction of carbonyl groups

c2) formation of an acetonide with the hydroxyl groups in position 1,3

d) mild oxidation of the CH_2OH group to regenerate the aldehyde group

e) aldol condensation with acetophenone **2a-d** to form hybrid compound **a-p**

f) f1) removal of the acetonide group

f2) mild oxidation of 1,3 hydroxyl groups to regenerate dibenzoylmethaneR_A = H, 4'-OMe, 4'-OBu, 4',6'-diOMe

Synthesis of 4-formylbenzoic acid chloride

$SOCl_2$ (20 mmol) and 3 drops of DMF (catalyst) were added to a suspension of 4-formylbenzoic acid (10 mmol) in CH_2Cl_2 (10 mL). The reaction mixture is refluxed for 3 h. The reaction mixture is allowed to cool to r.t. and the solvent was evaporated under reduced pressure. The product was not purified and is used directly in the next step.

General method 1: Synthesis of 2'-hydroxy acetophenone esters

A solution of the corresponding 2'-hydroxy acetophenone (10 mmol) and the acid chloride (10 mmol) in anhydrous pyridine (15 mL) was stirred at r.t. for 2 h. After this time, the mixture was neutralized with 10% HCl and extracted with AcOEt (3 X 50 mL). The combined organic layers were washed with water until neutrality (3 x 50 mL), with saturated NaCl solution (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by CC.

General method 2: Synthesis of dibenzoylmethanes (Baker-Venkataraman rearrangement)

To a solution of the corresponding 2'-hydroxy acetophenone ester (1 mmol) in anhydrous pyridine (5 mL), KOH (850 mg, 15 mmol) was added. The reaction mixture was heated to 60 °C for 30 minutes. After this time the mixture was neutralized with 10% HCl and extracted with AcOEt (3 X 50 mL). The combined organic layers were washed with water until neutrality (3 x 50mL), with saturated NaCl solution (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by CC.

General method 3. Reduction of carbonyl groups

To a solution of the corresponding dibenzoylmethane (2 mmol) in absolute EtOH (40 mL) at 0

°C, $NaBH_4$ (80 mg, 2.1 mmol) was added. The suspension was stirred at 0 °C for 8 h. The reactionmixture was poured into H_2O (100 mL) and stirred until the evolution of H_2 ceases, it was carefully neutralized with a 10% HCl solution and extracted with AcOEt (3 x 50 mL). The combined organic layers were washed with water until neutrality, with saturated NaCl solution(50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressureand the product was purified by CC.

General method 4. Formation of acetonides

To a solution of 1,3-diol (1 mmol) in anhydrous acetone (10 mL), and under N_2 atmosphere with vigorous stirring anhydrous, *p*-TsOH (0.1 mmol) was added. The reaction mixture was refluxed for 5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with water until neutrality (3 x 20 mL), with saturated NaCl solution (20 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporatedunder reduced pressure and the product was purified by CC.

General method 5. Oxidation of the -CH_2OH group

To a solution of acetonide (1 mmol) in CH_2Cl_2 (10 mL), under N_2 atmosphere and with vigorous stirring, PCC/alumina (25% by weight) was added. The reaction mixture was stirred at r.t. for 2h. The solvent was evaporated under reduced pressure and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with water until neutrality (3 x 20 mL), with saturated NaCl solution (20 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by CC

General method 6. Synthesis of 2'-hydroxy chalcones

To a solution of the corresponding 2'-hydroxy acetophenone (10 mmol) in anhydrous THF (25 mL), NaH (1.2 g dispersion in mineral oil at 50%, 25 mmol), was added in portions, under N_2 atmosphere, and with vigorous stirring. When the evolution of H_2 ceased, a solution of the corresponding benzaldehyde (10 mmol) in anhydrous THF (25 mL) was added dropwise over 15min and the mixture was stirred at r.t. for 16 h. The mixture was poured cautiously over ice water (50 mL) to destroy excess NaH and stirred until the evolution of H_2 ceased. The mixture was acidified with 25% HCl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (50 mL) and dried (anhydrous $MgSO_4$). The soln was concentrated under vacuum at 40 °C until it reached one-third of its original volume. The solution was cooled to 0 °C for 12 h to give a crystalline product which was separated by filtration. The 2'-hydroxy chalcones obtained in this way are sufficiently pure for most purposes.

General method 7. Deprotection of alcoholic groups

To a solution of the corresponding acetonide (1 mmol) in MeOH-water (1:1 v/v; 20 mL), anhydrous *p*-TsOH (10 mg, 0.058 mmol) was added. The reaction mixture was stirred for 2 h at r.t. and then the solvent was evaporated under reduced pressure. After this, water (50 mL) wasadded and the mixture was extracted with AcOEt (3 x 50 mL). The combined organic layers werewashed with water until neutrality (3 x 50 mL),

with saturated NaCl solution (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by CC.

General method 8. Oxidation of alcoholic groups (1,3-diols)

To a solution of the corresponding diol (1 mmol) in CH_2Cl_2 (10 mL), under N_2 atmosphere and with vigorous stirring, PCC/alumina (25% by weight) was added. The reaction mixture was stirred at r.t. for 2 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with water until neutrality (3 x 20 mL),with saturated NaCl solution (20 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the product was purified by CC.

Results

Sixteen compounds were prepared from readily available reagents with 18-27% overall yields and a fair degree of purity. All compounds were characterized spectroscopically by NMR and MS.

Discussion

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 [32].

Recent studies show that the irradiation of avobenzone causes a breakdown of the molecule in radicals, which generates compounds, such as arylglyoxals and benzyls [35], or react with other sunscreens [36].

Studies of the biological properties of photodecomposition products indicatethat arylglyoxals are strong photosensitizers. They are also very electrophilic and react quickly withthearginine of proteins. On the other hand, benzyls are cytotoxic [37].

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 [38].

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. [32].

Considering this background, and due to the growing demand for sunscreen, the discoveryof new, safer, and more effective compounds is of great importance. In this paper, we described the synthesis of a set of dibenzoylmethanes and chalcones hybrids as potentially promising UV filters.

Continuing previous work [32] Drs. Svarc and Minaberry will test these compounds for their photostability at Buenos Aires University.

Conclusion

Sixteen compounds were prepared from readily available reagents in good yields. All compounds were characterized spectroscopically by NMR and MS. Since these techniques are simple, they are suitable for the preparation of a large number of compounds in a convenient quantity and degree of purity. In a later stage, the determination of UV parameters and photodegradation studies will be carried out.

List Of Abbreviations

UV: ultraviolet

NMR: nuclear magnetic resonance

^{1}H-NMR and: proton nuclear magnetic resonance^{13}C-NMR: 13-carbon nuclear magnetic resonance

MS: mass spectrometry

Py: pyridine

p-TsOH: *para*-toluene sulfonic acidTLC: thin layer chromatography CC: column chromatography AcOEt: ethyl acetate

PCC: pyridinium chlorochromateTHF: tetrahydrofuran

DMF: dimethylformamide

Conflict Of Interest: The authors declare no conflicts of interest.

Acknowledgments: We thank the UDELAR (Uruguay) that allowed and financed the work of Gabriel Sagrera and INQUIMAE (CONICET—UBA) where all the photochemical measurements are done.

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