

Review

Ultraviolet Filters for Cosmetic Applications

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Abstract: Sunscreens reduce the occurrence risk of skin disorders such as sunburn, skin aging, and cancer through their ability to absorb, reflect, and scatter ultraviolet (UV) radiation. This review provides an overview of UV filters as active ingredients of sunscreen products, emphasizing their classification and structural characteristics. Their photostability, mechanism of action of ultraviolet radiation absorption, optical properties, and regulatory status are discussed based on their chemical structure. The main classes of organic UV filters presented include aminobenzoic acid derivatives, salicylic acid derivatives, cinnamic acid derivatives, benzophenones, dibenzoylmethane derivatives, benzylidene camphor derivatives, triazines, benzimidazole derivatives, and benzotriazole derivatives. The pursuit of new UV filters through research is crucial in advancing sunscreen technology and ensuring the availability of effective and safe options for sun protection.

Keywords: UV absorption chromophore; octisalate; octinoxate; ecamsule; benzophenone; avobenzone; bisoctrizole; bemotrizinol

1. Introduction

A high quantity of scientific evidence has established that photoprotectors, particularly sunscreens, play a vital role in reducing the occurrence of skin disorders (caused by UV radiation) [1]. Sunscreens were commercially introduced on the market almost a century ago and have constantly gained global recognition as an essential component of sun protection strategies [2]. Their efficacy in preventing and mitigating the detrimental effects of UV light stems from their capacity to absorb, reflect, and scatter solar rays. Throughout the years, sunscreens have undergone progressive improvements, both in terms of their active ingredients and also in terms of their cosmetic formulation [3,4].

Researchers and manufacturers are actively working on developing new UV filters with improved photostability and reduced environmental impact. Alternative ingredients and formulations are being explored to provide effective sun protection while minimizing potential risks [3]. Regulatory bodies are also implementing stricter regulations and restrictions on the use of UV filters to protect both human health and the environment [5,6].

In this review, we have carried out an extensive literature survey with respect to the emerging concerns over the efficiency and safety of existing chemical UV filters used in current topical sunscreen products. This article comprehensively reviews the properties, safety, health, and environmental concerns of various UV filters in direct relationship with their chemical structures.

2. Physical and Biological Properties of UV Radiation

Solar light represents the electromagnetic radiation emitted by the sun. The portion of the electromagnetic spectrum perceived with the human eye is known as the visible spectrum and consists of wavelengths ranging from approximately 380 nm, which appears as violet, to 700 nm, which appears as red. Ultraviolet (UV) radiation ranges from 100 to 380 nm and, based on its wavelength, can be categorized as UVA (320–380 nm), UVB



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(280–320 nm), and UVC (100–280 nm) [7]. It should be noted that these values for the delimitation of specific UV bands are mainly used in a biology setting, and differ slightly from the standard ones imposed by the Commission Internationale de l’Eclairage (CIE, International Commission on Illumination, Vienna, Austria) [8].

UVA rays have wavelengths ranging from 320 to 400 nm and lower energy compared with UVB radiation, but higher dermic penetration. Their spectrum is typically divided into short-wave UVA (UVA2, 320–340 nm) and long-wave UVA (UVA1, 340–400 nm) [9].

In radiometry, UV radiation is described by its power, typically expressed in watts per square meter (W/m^2), and by transmitted energy received over a given time period. It is usually expressed in joules per square meter (J/m^2) [10]. In the context of the biological effects of skin exposure to light, these measurements are rarely used. The preferred measurement is the minimal erythematous dose (MED). It refers to the smallest amount of UV radiation exposure required to produce a sharp-edge erythema after a specific unit of time [11].

UV radiation has predominantly been associated with detrimental impacts on the skin, leading to sunburn, inflammation, skin cancer, and premature aging. Continuous exposure to UVA radiation prompts the thickening of the outermost layer of the skin (epidermal hyperplasia) and modifies the thickness of the protective layer, called the stratum corneum. On the other hand, chronic UVB exposure triggers harmful consequences, such as DNA damage and the generation of reactive oxygen species (ROS) [12,13]. UV radiation also has beneficial effects; it interacts with 7-dehydrocholesterol (provitamin D) and converts it into vitamin D. Vitamin D plays a crucial role in facilitating the absorption of calcium, necessary for the formation and maintenance of healthy bones. Since only approximately half of the required vitamin D amount is obtained through dietary sources, it is essential to have adequate exposure to UVR in order to maintain optimal health [14].

3. Chemical Characteristics of UV Filters

A sunscreen is defined as a commercial topical preparation capable of providing skin protection against the harmful effects of UV radiation through various mechanisms [1]. A UV filter is a compound that impedes the passage of UV radiation by absorbing or blocking it [15]. A sunscreen is a multicomponent product that contains at least one UV filter, but frequently a mixture of them, and additional substances like surfactants, preservatives, and stabilizers [16,17]. The term “sunscreening agent” is an ambiguous term and should not be used.

The most-used classification of UV filters categorizes them as inorganic and organic compounds [1,2]. The organic filters are often called “chemical” filters, in opposition to the inorganic filters that are considered to have a “physical” mechanism. The term is regarded by some authors as misleading because it induces the idea of the existence of “nonchemical” filters [18].

UV filters are characterized primarily by the value of their absorption peak, also known as lambda max (λ_{max}), referring to the wavelength of light at which the substance absorbs the most, and the value of the molar absorptivity coefficient (ϵ) at the peak’s wavelength [19,20]. These parameters are directly influenced by the chemical structure and determine the range of UV protection. The λ_{max} conditions refer to which portion of the UV spectrum the filter effectively absorbs and is used for. Thus, UV filters can be classified as UVA, UVB, or broad-spectrum UV filters (UVA and UVB) [5].

Even if the whole chemical structure can influence the optical properties of the compound, the most important element is the structure of the chromophore. With a few exceptions, all the approved UV filters contain an aromatic ring and a carbonyl group bound directly to the aromatic core or linked by a carbon-carbon double bond, forming multiple conjugated π -electron systems [15]. The aromatic ring is usually substituted with an electron-donating group in the *para* or in the *ortho* positions. The influence of the substitution position can be observed by analyzing the values of the absorption peaks and the molar absorptivity coefficients of the aminobenzoic acid esters. The compounds

substituted in *para* have a lower λ_{max} compared with those substituted in *ortho*, but a significantly higher absorption capacity. The same bathochromic and hypochromic effect can be observed when comparing the absorption peaks of the salicylic acid esters with their analogs, the parabens [20]. Some compounds were developed based on the combination of chromophores.

The UV filters also contain various structural elements essential for their specific physico-chemical profile. Many compounds contain a branched alkyl or cycloalkyl fragment that renders the molecule highly lipophilic, while other compounds contain ionizable groups as a strategy for salt formation. The sulfonic acid moiety emerges as the most used.

The water solubility is used as a predictor of the aquatic toxicity. Therefore, it is expected that the compounds containing sulphonic acid moieties present higher toxicities. On the other hand, the lipophilic compounds have a high tendency for bioaccumulation and accumulation in sediments or soils [21].

The organic UV filters are classified based on common chemical scaffolds, and the most important classes are: aminobenzoic acid derivatives, salicylic acid derivatives, cinnamic acid derivatives, benzophenones, dibenzoylmethane derivatives, benzylidenecamphor derivatives, triazines, benzimidazole derivatives, and benzotriazole derivatives.

4. *para*-Aminobenzoic Acid Esters

para-aminobenzoic acid (PABA) was a key ingredient in many sunscreen products used during the mid-20th century due to its ability to absorb UVB rays and provide protection against sunburns. Its use diminished greatly over the years because of its low photostability and the risks of producing skin irritation, allergies, and contact dermatitis in some individuals [22]. Several esters of PABA, like glyceryl PABA (synonym: lisadimate), amyl 4-(dimethylamino)benzoate (synonym: padimate A), and isoamyl 4-(dimethylamino)benzoate (synonym: padimate), were frequently used in the past, but were abandoned because of the associated risk of phototoxic reactions [23,24]. In the case of the glyceryl PABA, the photocontact allergy seems to be produced by chemical impurities, and not by the substance itself [25].

The PABA derivatives absorb wavelengths in the 290–320 nm range, being effective against UVB radiation and with little effect against UVA radiation [26].

The structures of representative PABA esters are presented in Figure 1.

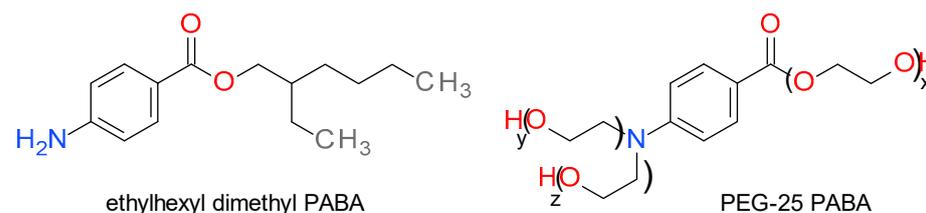


Figure 1. The structures of ethylhexyl dimethyl PABA (padimate O) and ethoxylated ethyl-4-aminobenzoate (PEG-25 PABA).

4.1. Ethylhexyl Dimethyl PABA

2-Ethylhexyl 4-(dimethylamino)benzoate (INCI), also identified in the literature as padimate O (USAN) and octyl dimethyl PABA, is a sunscreen agent approved by both the US Food and Drug Administration (FDA) and the European Union (EU) in all types of cosmetic products at concentrations up to 8% [27,28]. It is a yellow oily liquid insoluble in water, but soluble in ethanol, and chemically very similar to amyl 4-(dimethylamino)benzoate [29]. It has a λ_{max} of 311 nm and the value of ϵ is referenced as $27,300 \text{ mol}^{-1} \text{ cm}^{-1}$ [20]. A stability test indicated a rapid decomposition after irradiation with UVA light through a N-dealkylation reaction, and by a N-oxidation reaction, without considerably altering the absorption spectrum [30].

The risk assessment study concluded that ethylhexyl dimethyl PABA produces no significant reproductive and developmental toxicity or genotoxicity, carcinogenicity, skin sensitization or irritation, or phototoxicity [31].

4.2. Ethoxylated Ethyl-4-aminobenzoate

Ethoxylated ethyl-4-aminobenzoate (INCI), also referred to in the literature as polyethylene glycol (25) PABA or PEG-25 PABA, is approved by the EU, but not by the FDA. It can be used in all types of cosmetic products at concentrations up to 10%. Chemically, it is a PABA moiety ethoxylated with an average of 25 oxy-1,2-ethanediyl units [7,28].

5. Salicylic Acid Derivatives

The benzyl salicylate is credited as the first UV filter used in a cosmetic product [32]. Due to its *ortho* substitution, it is able to form intramolecular hydrogen bonds and exhibit peak absorption at higher values (~ 300 nm) compared with its non-*ortho* substituted analogs [33]. Salicylates are weak UVB absorbers and are generally used in combination with other UV sunscreens [34,35]. Due to their photostability, they are frequently combined with photolabile UVA filters, such as avobenzone [2]. Regardless of their low extinction coefficients, salicylates have the advantage of a minimal solvatochromic shift and, therefore, a wider range of possible formulations with little effect on the wavelengths' protection range [36].

The structures of representative salicylic acid derivatives used as UV filters are presented in Figure 2.

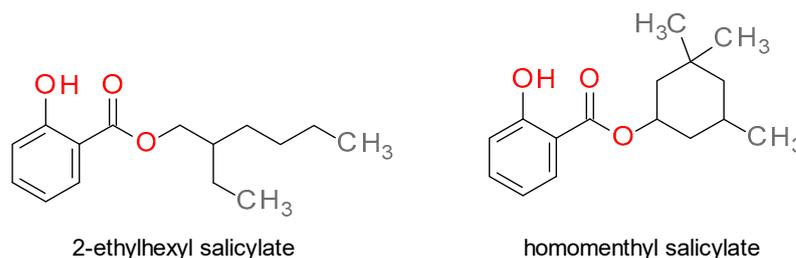


Figure 2. The structures of 2-ethylhexyl salicylate (octisalate) and homosalate (homomenthyl salicylate).

5.1. 2-Ethylhexyl Salicylate

This is also referred to as octisalate (INN) [37] and is structurally similar to padimate O, differing only in the substitution of the *para*-dimethylamino moiety with the *ortho*-hydroxyl group. It is approved by the FDA and the EU in all types of cosmetic products at concentrations up to 5% [38].

A randomized clinical trial (NCT03582215) concluded that the maximum plasma concentration of octisalate was greater than the FDA's systemic exposure threshold (0.5 ng/mL) for waiving additional safety studies [39]. Nevertheless, these findings offer no evidence of systemic toxicity, only highlighting that there are insufficient data to determine whether octisalate can be classified as safe [40].

5.2. Homosalate

Homosalate (INN), also known as homomenthyl salicylate, is chemically referred to as 3,3,5-trimethylcyclohexyl 2-hydroxybenzoate. Its maximum absorption wavelength is 306 nm, almost equal to that (307 nm) of its structural analog, octisalate. The value of ϵ is $4300 \text{ mol}^{-1} \text{ cm}^{-1}$ [35]. It is approved by the FDA for a maximum concentration of 15% and is one of the most frequently used UVB filters in sunscreen products in the US [35,41]. In the EU, it is approved at a concentration up to 7.34% for face products, with the exception of propellant spray products [38]. The Scientific Committee on Consumer Safety (SCCS) has conducted a safety assessment of homosalate and has raised concerns about its endocrine-disrupting properties, recommending a maximum concentration of 1.4% in the final product [42].

The clinical assessment of the systemic absorption found maximum plasma concentrations over the 0.5 ng/mL threshold [39]. The observed concentrations were bigger than those observed for octisalate, probably because of its higher lipophilicity.

6. Cinnamic Acid Derivatives

Several esters of cinnamic acid derivatives are used as UVB absorbers and, due to their properties, are considered a better alternative to PABA derivatives [43]. The unsaturated bond between the aromatic ring and the carboxyl group improves the capacity for absorption in UV conditions [44]. The structures of representative cinnamic acid derivatives used as UV filters are presented in Figure 3.

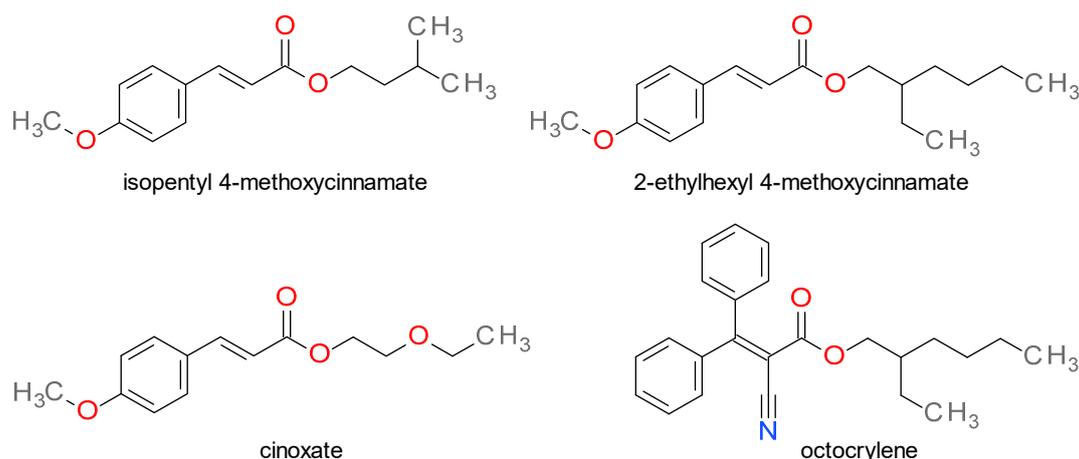


Figure 3. The structures of isopentyl 4-methoxycinnamate (amiloxate), 2-ethylhexyl 4-methoxycinnamate (octinoxate), 2-ethoxyethyl 4-methoxycinnamate (cinoxate), and octocrylene.

6.1. Isopentyl 4-Methoxycinnamate

The isoamyl *p*-methoxycinnamate (INCI), also known as amiloxate (INN), is the ester of 4-methoxycinnamic acid with isopentanol [45]. The maximum absorption wavelength is 308 nm and the molar absorption coefficient is 24,355. Its use is approved in the EU, Australia, China, and India in all types of cosmetic products at concentrations up to 10%. It is not authorized in the US [43].

6.2. 2-Ethylhexyl 4-Methoxycinnamate

The 2-ethylhexyl ester of 4-methoxycinnamic acid, also referred to as octinoxate (INN), is structurally similar to octisalate and padimate O, all sharing the 2-ethylhexyl ester group [46]. It has a λ_{max} of 311 nm and the value of ϵ is referenced as 23,300 mol⁻¹ cm⁻¹ [20]. In the EU, China, and Australia, the maximum allowed concentration is regulated as 10%, while in the US and Canada the concentration is 7.5%. In Japan, it is accepted as high as 20% [47]. The use of octinoxate-based products is banned in the state of Hawaii because of its toxic risks for the marine ecosystem [48].

6.3. Cinoxate

2-Ethoxyethyl 4-methoxycinnamate is the ester of 4-methoxycinnamic acid and 2-ethoxyethanol. The values of the absorption peak (308 nm) and the molar absorptivity coefficient (20,650 mol⁻¹ cm⁻¹) are very similar to those for amiloxate and octinoxate [49]. The presence of the ethoxyethanol fragment provides a considerably higher water solubility and lower lipophilicity compared with octinoxate. It is approved as a UV filter in the US, Canada, and Australia, but not in the EU [43].

6.4. Octocrylene

Chemically, it is the 2-ethylhexyl ester of 2-cyano-3,3-diphenylacrylic acid. It is approved in the EU and considered safe in various products such as creams, lotions, pump sprays, face or hand creams, and lipsticks, as long as the concentration does not exceed 10%. The concentration in propellant spray products is limited to 9% [50]. The chemical difference with the other cinnamate UV filters can be observed in the almost half ϵ value (12,290) for the 303 nm peak [20].

A study on 28 healthy volunteers indicated a significant plasma concentration after dermal exposure to a commercial sunscreen containing octocrylene [39].

In chlorination experiments, it was found to be stable even at high chlorine concentrations, while octinoxate was not [51,52]. The difference between the two cinnamic acid derivatives is probably due to the electron-withdrawing effect of the nitrile group on the double bond [51]. It is resistant to abiotic hydrolysis and photolysis and it is considered poorly biodegradable [51]. It has a good chemical stability and, correlated with its high lipophilicity, it has a persistence in sediments and a high bioaccumulation rate in organisms [52].

After a 6-week accelerated-stability aging test, several sunscreen products were examined. It was found that the products containing octocrylene exhibited concentrations of benzophenone ranging from 6 mg/kg to 186 mg/kg. The observed phenomenon is attributed to the slow retro-aldol condensation reaction of octocrylene, leading to the formation of benzophenone [53]. The health impact of these results is contested by several specialists [54,55].

7. Benzylidenecamphor Derivatives

The compounds in this class are α,β -unsaturated carbonyl compounds, relatively similar structurally to the cinnamic acid derivatives. The conjugated double bond system functions as a chromophore, but is also susceptible to Michael addition reactions that can lead skin toxicity.

After sunlight exposure, the photostability of these types of compounds was demonstrated, showing that their UV spectral profiles remained almost unchanged after irradiation. The UV absorption process for the camphor derivatives occurs through photo-induced reversible *trans*–*cis* isomerization [33]. The structures of representative camphor derivatives are presented in Figure 4.

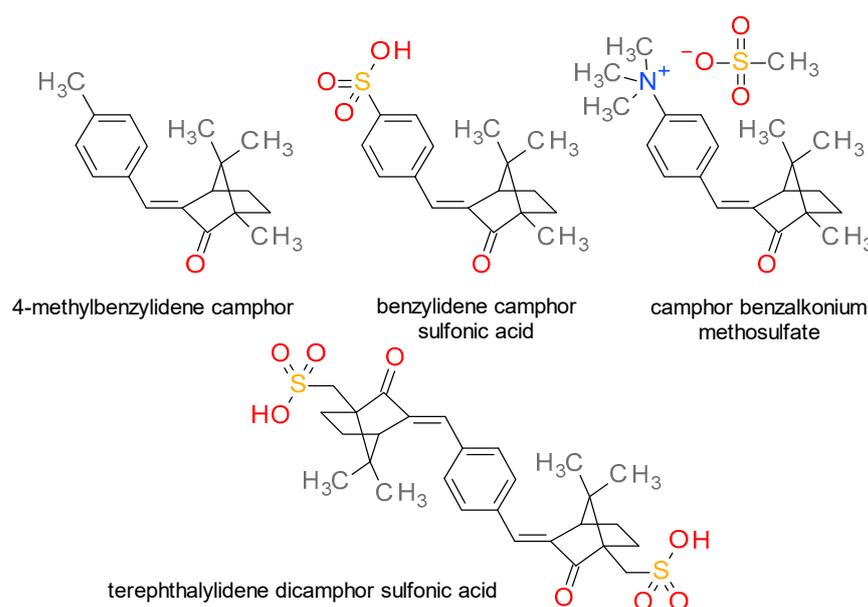


Figure 4. The structures of 4-methylbenzylidene camphor (enzacamene), benzylidene camphor sulfonic acid, camphor benzalkonium methosulfate, and terephthalylidene dicamphor sulfonic acid.

7.1. 4-Methylbenzylidene Camphor

Enzacamene (USAN), also known as (4-MBC) or under its trade names Parsol 5000 or Eusolex 6300, chemical name 3-(4'-methylbenzylidene)-dl-camphor, is a UVB filter with a λ_{\max} of 300 nm [49] approved to be used up to 4% in Canada and the EU. It has a large molar absorption coefficient of $24,500 \text{ M}^{-1} \text{ cm}^{-1}$ at 300 nm [33]. Due to its perfect photostability, it was widely used in sunscreen between 1994 and 2006 [56].

Several studies revised by Ruszkiewicz and colleagues showed that this highly lipophilic compound is resorbed through the skin after dermal administration and it accumulates in plasma and urinary excretion [57].

Its endocrine-disrupting properties were thoroughly studied [58,59] and discussed by many researchers [6,60] so that the latest SCCS opinion decided that there is sufficient evidence that 4-MBC may act as an endocrine disruptor and has effects on both the thyroid and estrogen systems, but the effects on the androgen system are not so evident, as only in vitro evidence is available. However, the maximum concentration of 4% is not yet reduced, but the SCCS conclusion is that the use of 4-MBC at the maximum concentration of 4% in cosmetic ingredients would not be safe [61]. For the same reasons, its unmethylated derivate (3-benzylidene camphor) was banned for use in cosmetics products in 2018 [62].

7.2. Benzylidene Camphor Sulfonic Acid

Chemically, it can be viewed as a derivative of enzacamene where the methyl group was changed with a sulfonic acid, a moiety capable of forming salts. This UVB filter ($\lambda_{\max} = 294 \text{ nm}$) [49] is chemically known as α -(2-oxoborn-3-ylidene)toluene-4-sulphonic acid. It can be used in the EU, Australia, and Japan up to 6% (as an acid). In addition to its acid form, its salts can also be used in sunscreen products [38,63]. Because it is considered a low-risk substance [64], it was not a priority for research.

7.3. Camphor Benzalkonium Methosulfate

This photostable [65] UVB filter ($\lambda_{\max} = 284 \text{ nm}$, $\epsilon = 24,500$) [49], chemically named N,N,N-trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulphate, and also known by the trade name Mexoryl SO, is approved for use in Australia and the EU up to 6% in sunscreen products [38,63]. In 2006, the Scientific Committee on Consumer Product (SCCP) requested a new dermal absorption study, but the applicant did not perform it, so in 2008 the SCCP recommended a reduction in the maximum concentration from 6% to 3% [66]. Regarding its safety for humans and the environment, according to Lodén and colleagues, it has no risk to the environment, and there were no data available for potential health risks or contact allergies [67].

7.4. Terephthalylidene Dicamphor Sulfonic Acid

This water-soluble UVA I filter ($\lambda_{\max} = 345 \text{ nm}$, $\epsilon = 47,100$), chemically named 3,3'-(1,4-phenylenedimethylene) bis (7,7-dimethyl-2-oxobicyclo-[2.2.1] hept-1-ylmethanesulfonic acid), also known as ecamsule, was developed and patented by L'Oreal in 1982 and has the trade name Mexoryl SX [68]. The higher peak value can be explained by the extended conjugated system as compared with the other camphor derivatives. Its use is approved worldwide, with the exception being the US (10% maximum concentration as an acid) [49]. Although the FDA needs more data to approve ecamsule [69] as a sunscreen ingredient, it can be found in some of the best-selling facial sunscreens online [70] and in the sunscreen "Anthelios SX", which was approved by the FDA in 2006 [56].

Due to its absorption spectrum, this filter completed the exiting formulation enlarging the photoprotection domain, but cannot be used as a single ingredient. Regarding its photostability, some authors declare that ecamsule is photostable [71,72], but in a more recent study it was found to be very photo-unstable and photodegraded with the irradiation of UV light [73,74]. However, several studies showed that the addition of ecamsule increased the sunscreen's efficacy and photostability [75,76]. Also, Fourtanier and colleagues made a review of clinical studies that were conducted until 2008 and concluded that the addition

of ecamsule in sunscreens increased the efficacy of these products against a large number of biological damages induced by UVA, SSR, and sun exposure [77].

7.5. Polyacrylamidomethyl Benzylidene Camphor

This UVB filter ($\lambda_{\text{max}} = 297 \text{ nm}$, $\epsilon = 19,700$) [49], chemically named as a polymer of N-[(2 and 4)-(2-oxoborn-3-ylidene)methyl]benzyl]acrylamide, is approved in the EU to be used in sunscreens up to 6% [38]. It is commercialized under the trade name Mexoryl SW [78] and it is considered a non-phototoxic chemical [79]. Other properties of this compound have not been found and, because its polymeric nature, the predictions are not reliable [64].

8. Benzophenone Derivatives and Structural Analogs

The common scaffold is represented by two benzene rings connected by a carbonyl group. Additionally, they have an *ortho* substitution with a hydrogen-donor group and a *para* substitution with an electron-donating group [80]. The structures of the most important derivatives are presented in Figure 5.

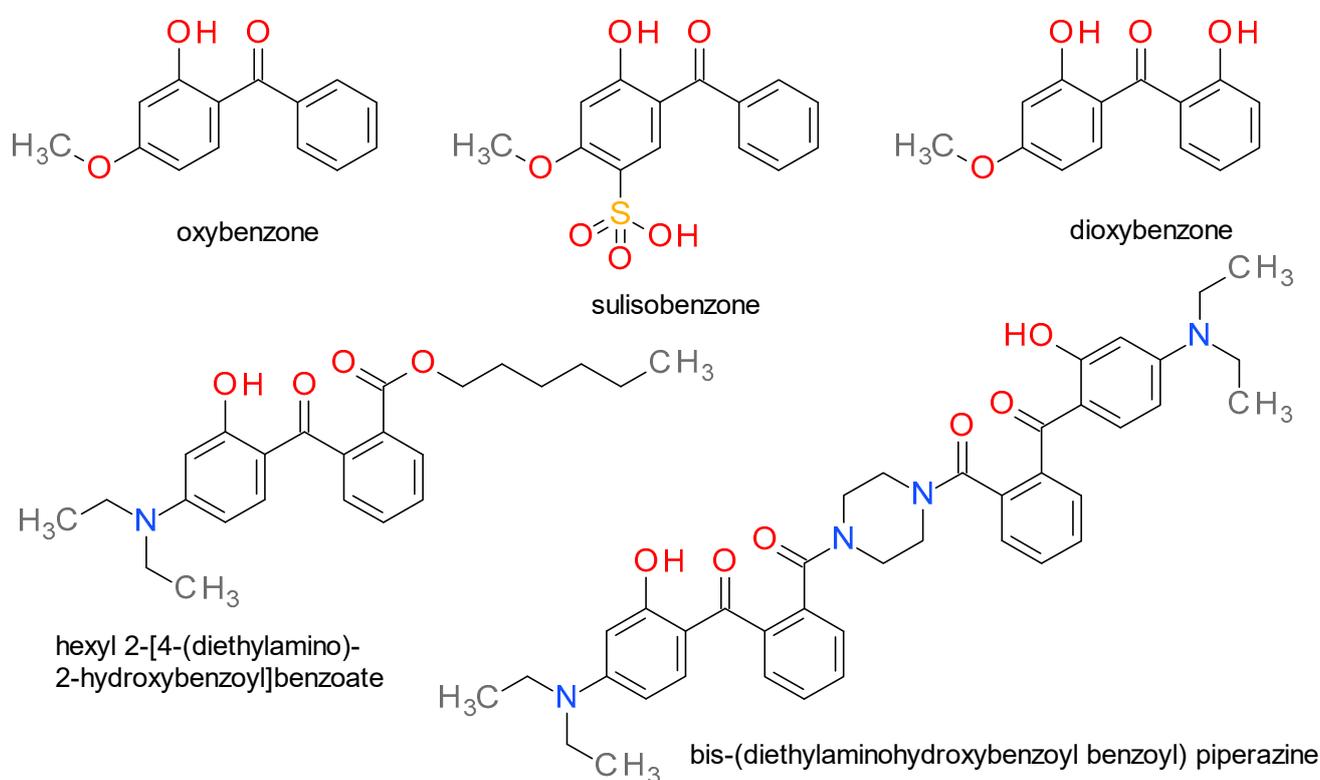


Figure 5. The structures of oxybenzone (benzophenone-3, BP-3), sulisobenzene (benzophenone-4, BP-4), dioxybenzone (benzophenone-8, BP-8), hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate, and bis-(diethylaminohydroxybenzoyl benzoyl) piperazine.

8.1. Oxybenzone

Benzophenone-3 (BP-3), chemically known as 2-hydroxy-4-methoxybenzophenone, is commonly referred to as oxybenzone. It appears as a white to pale-yellow solid with a melting point around 66 °C. It absorbs in the UVB (280–315 nm) and short-wavelength UVA (315–355 nm) ranges and has been approved by the FDA since the 1980s. It is approved in the EU [81].

BP-3 is demonstrated to have some degree of skin absorption, although the extent of absorption can vary depending on various factors such as the concentration of BP-3 in the product [82]. The potential endocrine-disrupting effect of oxybenzone prompted the SCCS to perform a safety assessment and recommend a maximum concentration of 2.2%

in body creams, in propellants, and in pump sprays, and as 6% in face or hand cream and lipsticks [80].

Because of its highly lipophilic character, BP-3 exhibits slow biodegradation, a propensity to adsorb into suspended solids and sediments, and a low potential for volatilization from water surfaces [83].

8.2. Sulisobenzone

It is also named benzophenone-4 and it is the sulfonic acid derivative of oxybenzone; the chemical name is 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid. It has two peaks, at 286 nm and 440 nm, with molar absorptivity coefficients of $13,400 \text{ mol}^{-1} \text{ cm}^{-1}$ and $8400 \text{ mol}^{-1} \text{ cm}^{-1}$ [20]. It is approved in the EU as a UV filter in sunscreen products at a concentration up to 5%. Benzophenone-5 is the sodium salt of benzophenone-4 [6].

8.3. Dioxybenzone

It is also called benzophenone-8 (BP-8) or 2,2'-dihydroxy-4-methoxy benzophenone and it is chemically similar to BP-3. It is very similar structurally to BP-3, having one additional hydroxyl group. It is approved at concentrations up to 3% [82].

8.4. Hexyl 2-[4-(Diethylamino)-2-hydroxybenzoyl]benzoate

Diethylamino hydroxybenzoyl hexyl benzoate (DHHB) received approval in the EU in 2005 and demonstrated remarkable absorption capabilities within the UVA spectrum, with a peak absorption at 354 nm. It exhibits excellent photostability properties, ensuring its effectiveness over extended periods of sun exposure [82]. It is rapidly degraded in water, with the reaction rate being higher in the presence of active chlorine or at an acidic pH [84].

8.5. Bis-(diethylaminohydroxybenzoyl benzoyl) Piperazine (BDBP)

This compound, together with its nano form, referred to as HAA299, was added to Annex VI of Regulation No 1223/2009 in 2022. It can be used in nano form as well, with the maximum concentration allowed being 10% (either alone or combined with the nano form) [85]. BDBP absorbs between 350 and 425 nm; hence, it is a UVA1 filter, but this compound also has protective effects for visible light. Recently, it has been proven that visible light (385–405 nm) contributes to skin pigmentation. The addition of BDBP in a sunscreen product afforded significantly more protection against pigmentation in a study conducted on nine volunteers [86]. The UV absorption of HAA299 particles increases with decreasing particle size, leading to a significant advantage for HAA299 (nano) versus HAA299 (non-nano). Even in nano form, it is a practically insoluble material considered safe to be applied on the skin due to the very low dermal absorption. However, after acute inhalation exposure, it has caused inflammatory effects on the lungs. Therefore, the SCCS does not recommend the use of HAA299 (nano) in applications that could lead to the exposure of the consumer's lungs via inhalation [85].

9. Dibenzoylmethane Derivatives

Avobenzone

Avobenzone, also known as butyl methoxydibenzoylmethane or chemically as 1-(4-tert-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione (Figure 6), is a highly effective UVA filter. It is recognized as one of the most prominent UVA filters due to its ability to absorb a wide range of UVA rays, especially the UVA I spectrum; the maximum absorption peak is at 357 nm ($\epsilon = 34,140 \text{ mol}^{-1} \text{ cm}^{-1}$). Adding avobenzone to a sunscreen formulation allows one to obtain broad-spectrum protection against UV radiation, hence its wide use in sunscreens.

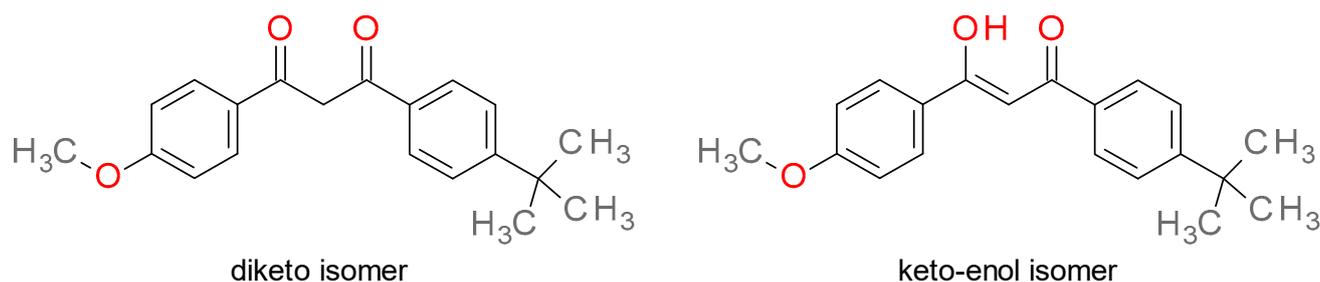


Figure 6. The structure of avobenzone.

It is approved to be used worldwide in maximum concentrations that vary from 3% in the US and Canada [87,88] to 5% in Australia and the EU [38,63].

Being oil-soluble and with a molecular weight less than 500 g/mol (310.4 g/mol), avobenzone has a good permeability through the skin varying from 1.8 ng/mL to 4.3 ng/mL [89]. However, the FDA considers that absorption does not equal risk, but further studies are needed in order to update the regulatory framework for sunscreens [90]. Its major drawback is its photodegradation. The keto-enol tautomerism is responsible for its instability. The enol form is planar, photostable, and absorbs in the UVA range (315–400 nm), while the keto form absorbs in the UVC range (200–280 nm) and is prone to degradation [91].

The research to combat the photodegradation of avobenzone is numerous. Gholap and colleagues [74] reviewed the strategies used for avobenzone stabilization and grouped them in three categories: the addition of antioxidants (e.g., diethyl hexyl syringylidenemalonate), the addition of stabilizers (e.g., bemotrizinol, diethylamino hydroxy benzoyl hexyl benzoate, octocrylene), or novel formulations such as inclusion complexes or carriers. In addition to those mentioned, Lionetti and colleagues [92] highlight the importance of avoidance formaldehyde donors or the association with metal ions as well as the importance of the solvent used (paraffin is bad, ethanol is good). On the other hand, the association with OMC contributes to the loss of UV protection because of the production of non-UV light-absorbing photoproducts [93]. Furthermore, avobenzone is incompatible with caprylic capric triglyceride, propylparaben, and butylhydroxytoluene [94].

10. Benzimidazole and Benzotriazole Derivatives

10.1. Phenylbenzimidazole Sulfonic Acid

It is frequently referred to as ensulizole (USAN), while its chemical name is 2-phenylbenzimidazole-5-sulphonic acid (PBSA). The chemical structure is presented in Figure 7, along similar derivatives. It is used worldwide as a UVB filter (absorption peak 310 nm). The acid form has poor water solubility, but it can be increased by transforming into the corresponding salts with sodium hydroxide, potassium hydroxide, or with triethylamine (TEA) [95]. In the EU, it can be used at concentrations up to 8% (expressed as an acid), but in the US, Canada, and Australia the maximum concentration is 4% [38,63,87,88,96]. The study of PBSA's effect on DNA showed that ensulizole protected against the formation of cyclobutane pyrimidine dimers after UVB exposure, but photosensitized the formation of oxidized guanine after UVA or UVB irradiation even at 4 mM, which is a very low concentration as compared with the 147 mM authorized by the FDA [97].

The season, the latitude, and also the weather can influence photodegradation rates [98]. Due to its photo-oxidizing properties, PBSA's usefulness in sunscreen products can be questionable. The formation of free radicals can be inhibited by complexation with cyclodextrin [99], and its protective effect can be increased via incorporation in chitosan microparticles [100] or carboxymethyl chitosan and carboxymethyl-cellulose carriers [101].

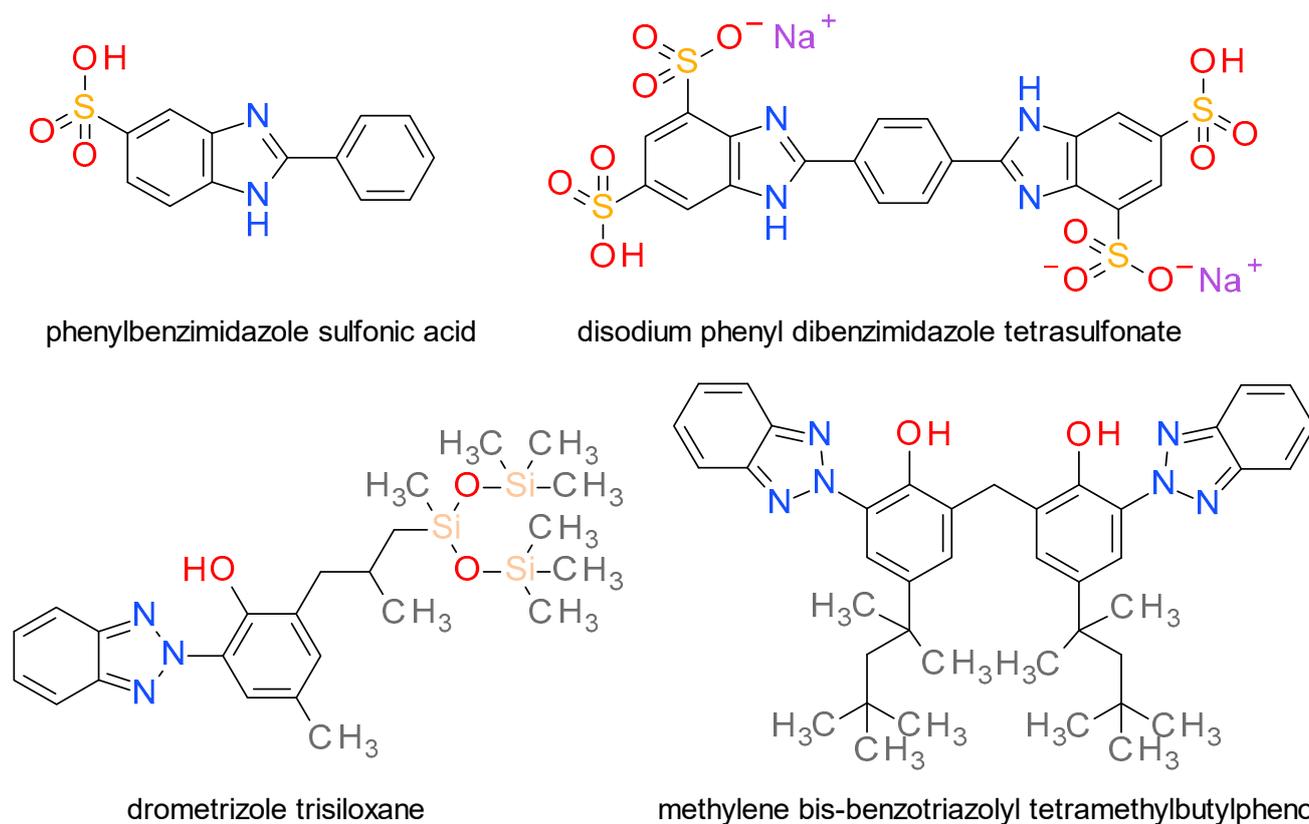


Figure 7. The structures of phenylbenzimidazole sulfonic acid (ensulizole), disodium phenyl dibenzimidazole tetrasulfonate (bisdisulizole disodium), drometrizole trisiloxane, and methylene bis-benzotriazolyl tetramethylbutylphenol (bisotrizole).

10.2. Disodium Phenyl Dibenzimidazole Tetrasulfonate

It is also known as bisdisulizole disodium (USAN). Chemically, it can be viewed as a dimer analog of ensulizole. This UVA II filter, with a peak absorbance at 335 nm, was developed by Symrise (Holzminden, Germany), trade name Neo Heliopan[®] AP, [102] and it has been approved in the EU [38] since 2000 and in Australia [63] since 2005, with a maximum concentration of 10%. In the US [103] and Canada [87], it is not approved yet. Because it is a hydrophilic compound with a big molecular weight (674.57 g/mol), it has a very low skin penetration (around 1% of the dose applied) [104]; therefore, it has a good safety profile.

10.3. Drometrizole Trisiloxane

It has a 2-(2-hydroxyphenyl)-2H-benzotriazole scaffold common with a large class of ultraviolet stabilizers used especially for plastic materials [105]. The phenolic hydroxyl is essential for the optic properties of the compound by forming an intramolecular hydrogen bond with the nitrogen atom in the benzotriazole ring [106]. It presents two peaks, at 303 nm and 341 nm, with molar absorptivity coefficients of $16,200 \text{ mol}^{-1} \text{ cm}^{-1}$ and $15,500 \text{ mol}^{-1} \text{ cm}^{-1}$ [20]. The siloxane moiety makes it compatible with silicon oils that can be used as solvents for cosmetics [107].

It is a lipophilic derivative and is marketed as Meroxyl XL by L'Oreal (Clichy, France), currently being used almost worldwide, with the exception of the US [108], where the FDA considers that it needs additional data to recognize it as safe and effective [109]. In the EU and Canada, drometrizole trisiloxane (DTS) can be used in concentrations up to 15% [38,87], but in Australia the maximum concentration allowed is 10% [63]. The photostability and broad protection spectrum, UVB and UVA, are its biggest advantages. After being exposed to acidic, basic, photolytic, oxidative, and thermal conditions in order to determine its

stability, it has been shown that extensive degradation is obtained after acid and base hydrolysis, but not from photolytic stress [110].

A study conducted on 1082 patients between 2004 and 2006 on a commercial sunscreen containing DTS produced only five relevant reactions, concluding that DTS is not a common allergenic. The presence of an allergic reaction to the commercial product without an allergic reaction to octocrylene was considered positive for DTS. Two out of these five patients were tested with 5% DTS in petrolatum, and both presented a reaction at the photo-irradiated sites [111].

10.4. Methylene Bis-benzotriazolyl Tetramethylbutylphenol

Its structure comprises a 2-(2-hydroxyphenyl)-2H-benzotriazole scaffold bond together with a methylene group.

It is a broad-spectrum UV filter, also known as bisoctrizole (INN) or MBBT, and is used in the EU and Australia at concentrations up to 10% [38,63], while in Canada only in combinations with a maximum concentration of 5% [87]. The combination of MBBT, water, decyl glucoside, propylene glycol, and xanthan gum has the trade name Tinosorb[®] M and is produced by BASF (Ludwigshafen, Germany). Its uniqueness is the micro-fine organic particle technology, the mixture being dispersible in water, soluble in polar cosmetic oils at 25 °C [112], functioning as a chemical filter, but also has a fraction of the solid particles, with insolubility increasing the photoprotection by scattering [113].

Data regarding its safety are still needed. The currently available scientific evidence shows an overall very low dermal absorption of MBBT in nano- or larger particle forms; therefore, the SCCS's opinion is that MBBT at concentrations up to 10% is considered to not pose a risk of adverse effects in humans after application on healthy, intact skin [112]. The literature reported some allergic contact dermatitis cases after topical application of sunscreen products containing Tinosorb[®] M, but the allergen was proved to be decyl glucoside, not MBBT [114–116]. An in vitro study showed that this compound does not possess intrinsic estrogenic/antiestrogenic or androgenic/antiandrogenic activity [117].

11. Triazine Derivatives

The analysis of the pharmaceutical development process for agents applied topically argued that the molecular weight of a compound should be under 500 g/mol in order to be absorbed through the skin [118]. The compounds in this class share a triazine ring and a high molecular weight (Figure 8). All compounds detailed here are approved in the EU, three are approved in Australia (ethylhexyl triazone, bemotrizinol, and tris-biphenyl triazine), and only bemotrizinol is approved in Canada, but none are approved in the US [38,63,87,88]. They do not have skin penetration and, subsequently, the adverse reactions. Until now, they have been considered safe, but more studies are needed [37].

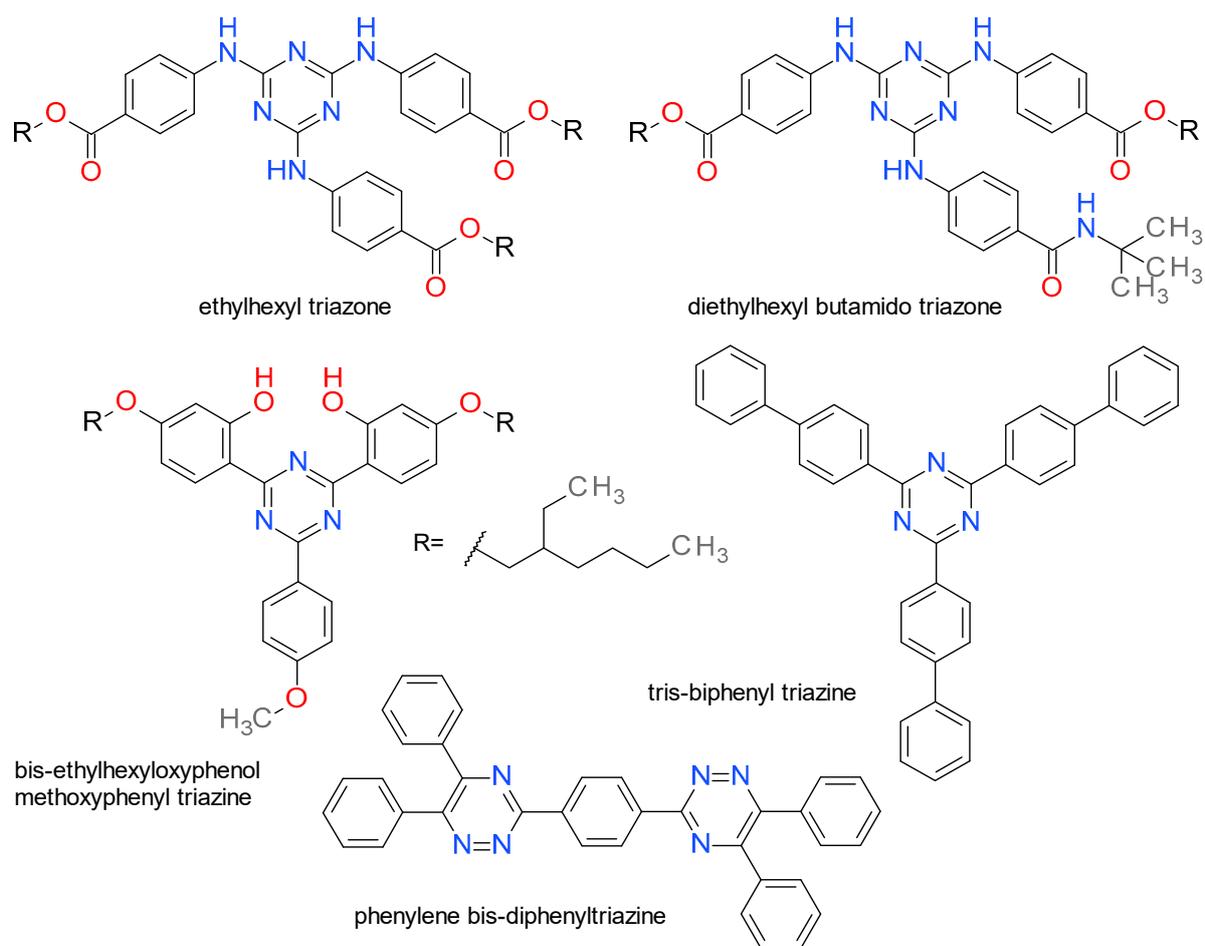


Figure 8. The structures of triazine derivatives: ethylhexyl triazone, diethylhexyl butamido triazone (iscotrizinol), bis-ethylhexyloxyphenol methoxyphenyl triazine (bemotrizinol), tris-biphenyl triazine, and phenylene bis-diphenyltriazine.

11.1. Ethylhexyl Triazone

The compound's chemical name is 2,4,6-trianilino-(*p*-carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine. It has a central triazine ring that acts like a linker for three 2-ethylhexyl 4-aminobenzoate fragments. Because of this, it is very similar structurally to padimate O. It has a very similar peak wavelength (314 nm), but a higher absorbance capacity due to the presence of three chromophore groups [20]. The name ethylhexyl triazone (EHT) can be confusing, because chemically it is a triazine derivative, and not a triazone.

This UVB filter can be used in sunscreen formulations at a maximum concentration of 5% [38,63]. In addition to its effective protective action against UV radiation, it also has good photostability [27] and low skin penetration [119], but it is practically insoluble in water. Therefore, obtaining oil-free formulations is almost impossible [120]. Even though it is oil-soluble, it is frequently used in sunscreen products, with 38% frequency in sunscreens for adults and almost 45% in sunscreens for children [27]. Due to all the advantages, new delivery systems have been developed, such as encapsulation in lipid microparticles [120] or nanostructured lipid carriers [121,122].

11.2. Diethylhexyl Butamido Triazone

The chemical name is benzoic acid, 4,4-[[6-[[[(1,1-dimethylethyl)amino]carbonyl]phenyl]amino]-1,3,5-triazine-2,4-diyl]diimino]bis-, bis(2-ethylhexyl)ester, but it is frequently referred to as iscotrizinol or DEBT. It has a similar chemical structure to ethylhexyl triazone, differing in the substitution of an ethylhexyl ester moiety with a *t*-butyl amide fragment.

This UVB filter, approved to be used up to 10% in the EU and up to 5% in Japan, is considered one of the most photostable filters available on the market [123]. It has great oil solubility [124]; thus, it can be added in the oil phase of an oil–water (O/W) emulsion. It has anti-inflammatory properties similar to those of ketoprofen [125]. According to the SCCS opinion from 1998, it has an excellent safety profile, with low percutaneous absorption and no capacity to produce skin irritation, photo-irritation or photosensitization, photo-mutagenicity, or photo-clastogenicity. Even more, it has been found to be a non-irritant and hypoallergenic [126].

11.3. *Bis-ethylhexyloxyphenol Methoxyphenyl Triazine*

The chemical name is 2,4-bis-([4-(2-ethyl-hexyloxy)-2-hydroxy]-phenyl)-6-(4-methoxy-phenyl)-(1,3,5)-triazine, but it is usually cited as bemotrizinol (USAN), anisotriazine, or, shortly, BEMT.

It is an oil-soluble broad-spectrum UV filter [127] approved to be used up to 10% in the EU and Australia and only up to 6% in Canada [38,63,87]. It has also low skin penetration [119], even lower when it is incorporated in nanostructured lipid carriers, without losing its photostability [128]. Due to high photoprotective effectiveness and photostability, the usage frequency of BEMT almost doubled between 2015 and 2021 [27]. Similar to EHT, a water-dispersible inclusion complex has been developed, in this case being observed as a shift of the maximum absorption from 380 nm to 345 nm for the inclusion complex [127], meaning a loss in UVA protection. The latest SCCS opinion is from 1999, where there was no evidence of any kind of toxicity or allergenicity [129].

11.4. *Tris-biphenyl Triazine*

Chemically, it is 2,4,6-tri([1,1'-biphenyl]-4-yl)-1,3,5-triazine (TBPT). It differs from ethyl-hexyl triazone due to the substitution of the PABA ester moieties with biphenyl fragments.

This very efficient filter in both UVB and UVA regions was added to Annex VI of the Cosmetics Regulation (EC) No. 1223/2009 of the European Parliament and of the Council in 2016 and the maximum concentration allowed is 10%. In addition to its effectiveness, it is also very photostable [130]. Thus, it is used as well as a photo-stabilizer [131] for avobenzene. The nano form allowed to be used in sunscreen formulations must have: a median primary particle size >80 nm; a purity \geq 98%; and must be uncoated. Also, this form must not be used in sprays [38]. Due to its molecular weight and polarity, this compound exceeds the limits where skin absorption is expected. Also, as a nanomaterial, it can be considered an insoluble substance, which means the balance between (bio)availability and safety goes to safety [132].

11.5. *Phenylene Bis-diphenyltriazine*

It is also cited by its chemical name, 3,3'-(1,4-phenylene)bis(5,6-diphenyl-1,2,4-triazine). This broad-spectrum filter is considered safe for use at a concentration up to 5% by the SCCS, but it should not be used in products that may lead to lung exposure [133]. As well as the other triazine derivatives, this one can offer protection against UVB and all UVA rays, but its particularity is that it can protect also against blue light [134]. This heterocyclic compound, bearing a triazine scaffold in which three carbon-hydrogen units of the benzene ring are replaced by nitrogen atoms, is a chromophore for sunlight. Being insoluble and with a particle size outside the nano domain, its penetration rate through the skin is predicted to be low, hence its very low toxicity. Among the other qualities, it is photostable and has cellular protective properties [135]. Therefore, we expect this compound to be used more and more in sunscreen formulations and, of course, in research.

12. Other Compounds

12.1. *Methoxypropylamino Cyclohexenylidene Ethoxyethylcyanoacetate*

For simplicity, this is commonly referred to as MCE or by the commercial name, Mexoryl 400. Chemically, the compound belongs to the class of cyclic merocyanines, a class

characterized by high absorption coefficients (Figure 9). The UV-filtering mechanism is explained by the transfer of charge from the amino group to the ketone group through the polyene chain [136]. This new UVA1 filter exhibiting a peak of absorption at 385 nm was approved by the SCCS for use in sunscreen products up to 3% in 2020, but not in applications that may lead to exposure of the end-user's lungs via inhalation [38].

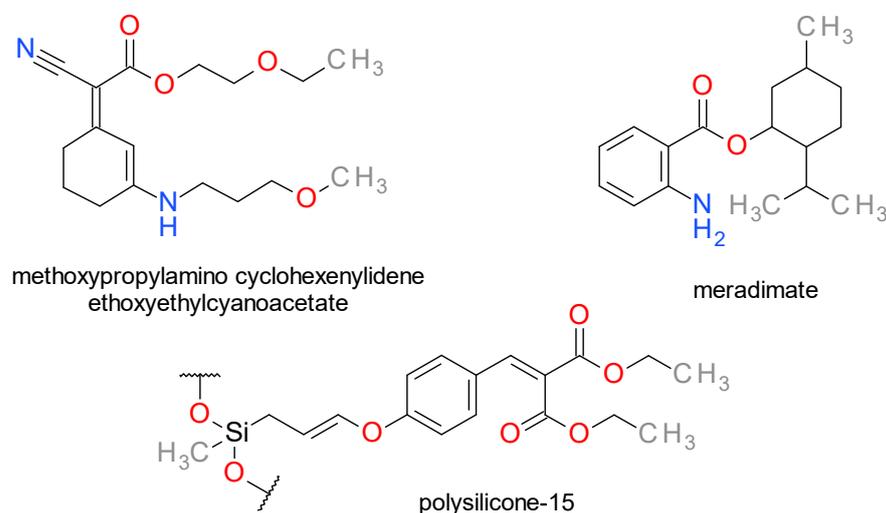


Figure 9. The structures of methoxypropylamino cyclohexenylidene ethoxyethylcyanoacetate, meradimate, and polysilicone-15.

Several recent clinical trials conducted by L'Oréal employees evaluated the photoprotection afforded by the sunscreen formulas containing MCE. In an initial study, a trial was performed on 19 volunteers using a monocentric, double-blinded, randomized comparative approach. The results demonstrated that the addition of MCE (the name of the substance) prolonged the range of absorption up to 400 nm. Additionally, it was found to diminish the adverse effects caused by UVA1 radiation on the skin, including alterations at the cellular, biochemical, and molecular levels. Moreover, the inclusion of MCE was observed to reduce UVA1-induced pigmentation [137]. Three other studies revealed that incorporating MCE into sunscreen products, specifically targeting longer UVA1 wavelengths, resulted in a more effective prevention of hyperpigmentation compared with standard products. Notably, no associated side effects were observed [138]. Lastly, another study proved that there is no significant difference between the photoprotective efficacy of 1%, 1.5%, and 2% MCE, concluding that 1% MCE suffices to reach the highest level of efficacy [139].

12.2. Polysilicone-15

It is also known as dimethicodiethylbenzalmalonate. It can be considered a derivative of cinnamic acid. It is made of diethyl benzylidenemalonate, which functions as chromophores attached to a polysiloxane chain. It has an average molecular weight over 6000 g/mol; therefore, it has low skin permeability [18].

It is a UVB filter approved in the EU and Australia for use in sunscreen formulations at a concentration up to 10% [38,63]. Its SPF, measured *in vitro*, had a low value (3.64), with a peak absorbance at 312 nm [140]. Thus, it needs to be combined with a UVA filter. The combination with avobenzone not only increases the spectrum, but polysilicone-15 is also a good stabilizer for avobenzone [92].

12.3. Meradimate

This compound, also known as menthyl anthranilate, is a UVA II filter approved to be used at concentrations up to 5% in the US, Australia, and Canada [63,87,88], but not in the EU [38]. Some authors mistakenly consider meradimate as "methyl anthranilate", probably because of the one-letter difference. Chemically, it is similar to the PABA derivatives,

but their optical properties are significantly different because of the electronic effects and hydrogen intramolecular bond of the *ortho* amino substitution [20].

Meradimate is utilized in various products, like lip balms, lipsticks, and moisturizers, due to its ability to filter both UVA and UVB radiation. Even if it is considered an agent with a broad spectrum of protection, its coverage of UVA rays is limited, extending only up to 336 nm. Despite having a theoretical protective range between 200 and 380 nm, empirical evidence confirms this limitation [141,142].

13. Organic versus Inorganic UV Protection

The discussion of mineral filters is beyond the scope of this review, but it is important to highlight the main difference between these two main categories in order to better understand the advantages and the drawbacks of organic filters. Both zinc oxide and titanium dioxide are approved and widely used as active ingredients in sunscreen products [37,41]. Titanium dioxide is the most frequently used inorganic UV filter due to its photo- and chemical stability. Although it has been included in Annex VI of Regulation No 1223/2009 since 2019, the nano form is much more often found in adult sunscreen products than the micro form, probably because of its more discreet appearance on the skin. The nano-sized titanium dioxide induces lower skin irritability than most organic sunscreens and is less photoreactive [17,143]. However, when titanium dioxide nanoparticles are exposed to UV radiation, there is a possibility of generating reactive oxygen species (ROS) as a result of a photochemical reaction, leading to potential adverse effects [144]. Zinc oxide is the other inorganic UV filter included by the European Commission in Annex VI, with its both nano and non-nano forms [145].

The human health risks with inorganic filters are considered to be low given a lack of percutaneous absorption; however, there is potential risk when exposed via inhalation, prompting recommendations against spray sunscreen products. The known risk to the environment is low, though the risk stratification may evolve with increasing usage of these filters and higher environmental concentrations [146].

14. Conclusions

The UV filters play a crucial role in reducing the risk of various skin disorders, including sunburn, skin aging, and cancer. This review has provided an overview of organic UV filters as active ingredients in sunscreen products, highlighting their classification and structural characteristics. Despite their important advantages, the mineral filters leave a white or chalky residue on the skin, which may be cosmetically undesirable for some individuals and, in general, result in lower SPF values compared with most organic filters, requiring frequent reapplication, highlighting the significance of organic UV filters.

In summary, this review has provided valuable insights into the main classes of organic UV filters by examining factors like photostability, mechanisms of action, optical properties, and regulatory status in relation to their chemical structure. This knowledge contributes to a better understanding of sunscreen technology and emphasizes the importance of ongoing research in the development of new UV filters. The pursuit of new UV filters through research is crucial for advancing sunscreen technology and ensuring the availability of effective and safe options for sun protection.

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