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Review

Synthesis of 2-Substituted Benzimidazole Derivatives as a Platform for the Development of UV Filters and Radical Scavengers in Sunscreens

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Abstract: The modern trend in sunscreen products is towards the development of UV filters with multi-functional properties, to provide a broad shielding against ultraviolet radiation, antioxidant activity, and the prevention of skin cancer. Additionally, they should also be safe for humans as well as the environment. The benzimidazole heterocycle is a suitable platform for the development of such multifunctional molecules with potential application in cosmetic formulations, due to their ability to act as both UV protectors and reactive pharmacophores. This review presents for the first time the progress in the synthesis and optimization of benzimidazole compounds as UV sunscreen filters. The modifications to the substitution pattern of the lead compound and structure–activity relationships are discussed, as well as the synthetic approaches for the preparation of 2-substituted benzimidazoles. These aggregated data will be useful in future in the development of modern benzimidazole-based sunscreen.

Keywords: 2-arylbenzimidazoles; 2-substituted benzimidazole derivatives; UV filters; antioxidant activity; antiproliferative activity; multifunctional molecules

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1. Introduction

Sun care products are the first line of defense against the harmful effects of sun ultraviolet A (UVA) (320–400 nm) and ultraviolet B (UVB) rays (280–320 nm). UV rays are considered the main cause for a number of adverse clinical effects on human skin, such as sunburn (erythema), pigmentation (tanning), photoaging, photosensitization, and skin cancer. These effects are based on DNA damage, the generation of reactive oxygen species (ROS), melanogenesis, apoptosis, and the expression of genes and related proteins [1]. Longwave UVA radiation is known to penetrate deeper into the skin and may reach the level of the dermis, damaging the collagen structure and contributing to premature skin aging [2]. UVB radiation has lower penetration capabilities, and can only penetrate down to the epidermal layer [3]. On the other hand, it has been found that the sun's ultraviolet radiation (UVR) induces the expression of the endogenous opioid beta-endorphin, which is responsible for good moods and the feeling of well-being, as well as the addictive behavior of tan seekers [4]. Awareness of the harm of ultraviolet radiation on the skin has made many people realize the need to use sunscreen as a daily beauty ritual, not just when at the beach or around the pool. In connection with this, in 2021, the global sunscreen market generated a revenue of USD 8.28 billion [5] and is expected to reach USD 16.11 billion by 2030 [6].

UV filters, the shield ingredients of sunscreens against the negative effects of solar radiation, interact with UVR via three fundamental mechanisms: reflection, scattering, and absorption. According to their method of action, they are classified into physical blockers (inorganic) and chemical absorbers (organic compounds) [3]. Inorganic filters reflect or scatter incident UVR through an optical mechanism. They give broader spectrum

protection (covering UVA and UVB) than their organic partners, are photostable, maintain photoprotection for long periods of UVR exposure, and have low allergenic potential, and are therefore suitable for use on children's skin. However, they are more difficult to incorporate into cosmetic systems and demand more technical care to maintain the stability of the formulation [7]. Organic photoprotective agents usually have one or more aromatic rings, sometimes conjugated with carbon–carbon double bonds and/or carbonyl groups, that are responsible for absorbing UV light. Energy from UV radiation excites electrons in these compounds. This energy is dissipated by the emission of higher wavelengths or relaxation by the isomerization of the molecule and is released as a negligible amount of heat rather than affecting the skin. An electron in a photostable molecule will return to its ground state, and the process will repeat. However, organic UV filters have the potential to degrade in the presence of light (photo-instability), and this process can produce toxic photodegradation and photoisomerization products as well as reactive oxygen species (ROS). These products can negatively affect human health and may also affect the stability of the other ingredients present in the sunscreen formulation. The photostability of UV filters can be improved by the inclusion of antioxidants in the sunscreen's formulation [8–10] and encapsulation [11–13], the use of a combination of UV filters [14,15], the addition of quenching molecules [16], or agents provided with both UV filtering and antioxidant capacities [17]. UV filters can also be classified into UV-A or UV-B, or into broad-spectrum UV filters (UVA and UVB), depending on which UV radiation they absorb [18]. Usually, broad-spectrum protection is achieved by combining several filters, but this leads to a reduction in their photostability [19].

Since the discovery of the first UV filter—the acidified quinine sulfate [20]—in 1820, about 30 substances have been applied in the cosmetic industry to date. Annex VI of the REGULATION (EC) № 1223/2009 [21] contains a list of approved UV filters for cosmetic use in the European Union (EU). In this list, only two UV filters are of inorganic origin (TiO_2 and ZnO), the rest belong to different classes of organic compounds depending on their structure derivatives of benzophenone, camphor, benzotriazole, benzimidazole, and cinnamic acid.

The choice of filters for inclusion in cosmetic products is relatively limited because they must meet a number of requirements, such as a wide range of therapeutic safety measures under normal or even excessive conditions of use, nontoxicity to humans and marine organisms, photostability, broad-spectrum UV protection, water resistance, chemical inertness, and compatibility with the other components of the cosmetic form [22]. The protective ability of sunscreen also depends on the actual amount of sunscreen applied, as well as the user's respective skin type, frequency of reapplication, subsequent activities such as swimming, drying of the skin, contact with sand, and the general composition of the product [23].

The ideal photoprotective agent does not exist and studies in recent decades have highlighted the negative impact of toxic products generated by photoisomerization and the photodegradation of UV filters on humans and marine organisms [18,24,25]. Therefore, there is a need to develop new broad-spectrum UV filters which are able to protect the human skin against the acute and chronic consequences of UVR while also being more photostable and safe for both humans and the environment.

Benzimidazoles have long been a research focus as UV-protective agents owing to their significant merits, such as UV filtering ability, a simple molecular structure, easy production on an industrial scale, high water solubility, and a good safety profile. The popular benzimidazole-based commercial UV filters, widely used in sunscreen and cosmetics formulations, are Ensulizole® (INCI: 2-phenyl-1*H*-benzimidazole-5-sulphonic acid, PBSA), UVB filter, and Bisdisulizole, Neo Heliopan® AV (INN: Sodium salt of 2,2′-bis(1,4-phenylene)-1*H*-benzimidazole-4,6-disulfonic acid, DPDT). Ensulizole® is a UVB filter, while Bisdisulizole absorbs mainly in the UVA range (Figure 1).

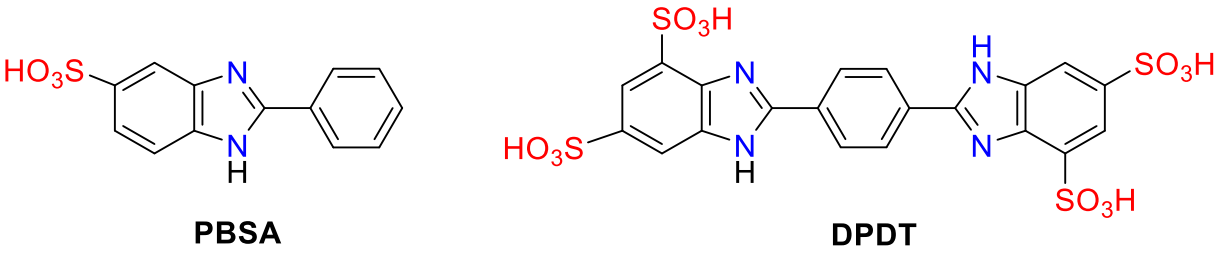


Figure 1. Structures of benzimidazole-based commercial UV filters.

In addition to their application as UV filters in sunscreens, the benzimidazole derivatives have a wide range of biological activities, such as antibacterial, antimicrobial, antiparasitic, antiallergic, antiulcer, antitumor, antioxidant, anti-inflammatory, etc. [26–34].

UV rays are responsible for external damage to the skin and for the production of ROS, which consequently induce aging and the development of skin cancer. In this connection, the development of multifunctional benzimidazole-based compounds which combine photoprotective, antioxidant, and anti-melanoma activity would be a good solution in the fight against the complex pathologies of solar radiation-induced skin damage.

The design strategies of benzimidazole compounds as UV filters with improved filtering capacity and minimized side effects and the processes for their preparation have not been reviewed formerly, as far as we know. Therefore, they are the focus of this review. We also discuss strategies for the development of multifunctional molecules that are simultaneously UV filters, ROS-inhibitors, and anti-melanoma agents. The structure–activity relationship of these multifunctional compounds is clearly illustrated.

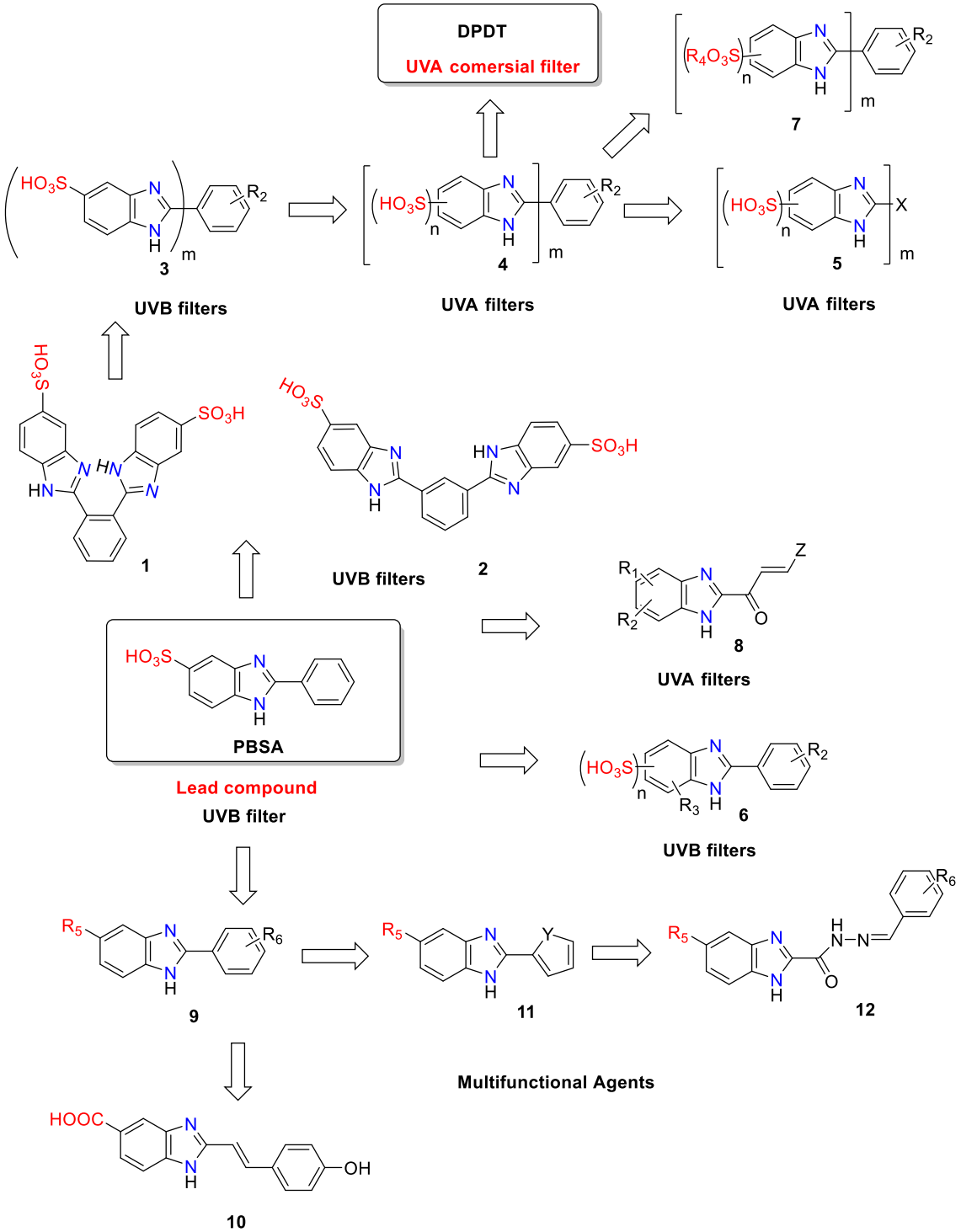
2. 2-Substituted Benzimidazoles as Photo-Protective Agents: Discovery and Development

Since the discovery of 2-phenyl-1*H*-benzimidazole-5-sulfonic acid (Scheme 1) in 1933 [35] as a UV filter, multiple benzimidazole compounds have been designed and synthesized to form a new class of sunscreen molecules.

PBSA is a water-soluble white powder with a high melting point that absorbs strongly at UV-B wavelengths. It has a moderate to high extinction coefficient of 26,000 and λ_{max} about 310 nm. However, PBSA has also been reported to generate a variety of free radicals and exhibit photosensitizing activity, raising the risk of phototoxic damage to DNA and other cellular components [36–38].

This necessitates the additional inclusion of antioxidants in the sunscreen product or the development of dualistic molecules able to act as photoprotective agents and inhibitors of the formation of radical species [39].

DE1282855 describes the use of 1,2-bis-(5-sulfobenzimidazol-2-yl)-benzene **1** and 1,3-bis-(5-sulfobenzimidazol-2-yl)-benzene **2** (Scheme 1) as water-soluble UVB filters [40]. Patent application WO93/15061 [41] was related to an improved process for preparing arylbenzimidazoles with general formula **3** (Scheme 1). The compounds containing at least two benzimidazole rings in combination with a sulfo group in each of the heterocycles are useful as UVB absorbers in sunscreen products. Surprisingly, it was found that after introducing two or more sulfo groups into the bis-benzimidazole-benzenes, the compounds **4** (Scheme 1) had an absorption maximum in the range UV-A-II and protected against the dangerous short-wave UVA rays through strong absorption [42]. In addition, these UVA filters have excellent light fastness, good thermal stability, toxicological and dermatological harmlessness, and good solubility in cosmetic solvents. The commercial UVA filter DPDT belongs to this family of polysulfonated bis-benzimidazole analogs.



Scheme 1. Evolution of the 2-substituted benzimidazole derivatives as UV filtering agents. Where R_1 = COOH; $COOC_1$-C_6-Alkyl; COCl; COBr or CN; R_2 = one or more C_1-C_6-Alkyl; C_1-C_6-Alkoxy; OH; F; Br; R_3 = C_1-C_8-Alkyl; C_1-C_8-Alkoxy; R_4 = linear, branched or cyclic C_{16}-C_{50}-Alkyl; R_5 = H; SO_3H; CN; COOH; R_6 = one or more OH; OCH_3; Cl; Br; $N(Et)_2$; X = (un)substituted naphthalene; (un)substituted 1,1′-biphenyl; (un)substituted thiophene; (un)substituted furan; (un)substituted pyrrole; Y = O; S; NH; Z = X or R_6-substituted phenyl; m = 1–3; n = 2–3.

More benzimidazole derivative **5** (Scheme 1), characterized by different substitution patterns at the five-membered heterocyclic (thiophene, furan, or pyrrole) ring at position 2 of benzimidazole moiety, were also prepared. Some compounds **5** absorbing in the UVA

range were obtained with a naphthalene or biphenyl linker between the benzimidazole cores [42].

Although they possess desirable photoprotective properties, water-soluble benzimidazole filters can be formulated in an alkaline environment since sulfonic acid precipitates at pH values below 7. It has been found that some polysulfonated benzimidazoles **6** (Scheme 1) or their salts can be easily incorporated into cosmetic formulations while avoiding the precipitation problem [43]. 2-Phenyl-1*H*-benzimidazole-4,6-disulfonic acid in the form of betaine salt is particularly preferred in this case.

The water-soluble salts of aryl benzimidazole sulfonic acids are insoluble in organic solvent systems. As a result, they must be incorporated into the aqueous phase of a sunscreen formulation, where they have the potential to be washed off the skin by perspiration or exposure to water. Furthermore, the use of salts constrains the cosmetic formulators to produce waterproof sunscreens with acceptable aesthetics. For example, the effectiveness of carbomers, as well as some waterproofing polymers such as Diglycol/CHDM/Isophthalates/SIP Copolymer, is diminished in the presence of various levels of salt [44]. A solution to overcome the water resistance challenge of benzimidazole filters in sunscreen formulation is the use of aryl benzimidazole sulfonic acid esters **7** (Scheme 1) with alcohols and/or silicones with a branched, linear, or cyclic C_{16}-C_{50} chain. These compounds show increased substantiality, water resistance, sweat resistance, friction resistance, and improved solubility in the oil phase of cosmetic compositions. Due to the high extinction coefficient of the C_{16}-C_{50} alkyl esters of the aryl benzimidazole sulfonic acids, high levels of photoprotection can be achieved with small amounts of sunscreen.

A new series of benzimidazoles **8** (Scheme 1) was synthesized and assayed with the goal of obtaining new compounds that protect the skin and hair against UVA rays. The new derivatives differ from the previous benzimidazole sunscreen molecules in the side chain linked at the C-2 position. 2-(3'-Arylacryloyl)benzimidazole derivatives have good photostability and molar extinction coefficients between 25,000 and 40,000 [45].

The introduction of hydroxyl groups to the C-2 phenyl part of PBSA and substituent R_5 in position 5 of the benzimidazole ring led to the discovery of a series of hydroxy-phenyl-1*H*-benzimidazoles **9** (Scheme 1). These molecules were found to act as radical scavengers as well as UV-protective agents [39].

In general, all compounds **9** have demonstrated an antioxidant efficacy greater than PBSA. Derivatives **9a**, **9b**, and **9c** (Figure 2), with hydroxyl at positions 3 and 4 of the phenyl core, showed good filtering and high antioxidant power (also in the cosmetic formulation). Among them, **9a** had the highest level of sun protection factor (SPF) 9.83, which is twice the SPF of PBSA. The SPF is a quantitative measure of the efficacy of sun protection products, defined for the first time by the chemist Franz Greiter in 1962 [22], as the quotient between the minimal erythema dose (MED) with applied sunscreen and the MED without sunscreen. However, since SPF does not consider the protection against UVA radiation, prolonged exposure to the sun even when using high SPF products can leave the skin defenseless against UVA radiation. To ensure that sunscreens will protect consumers against both UVB and UVA radiation, the European Commission (EC) issued a recommendation in 2006 [21] for including UVA protection in their composition. It is recommended that the minimum degree of protection provided by sunscreen products be as follows: SPF 6 against UVB; UVA protective factor/SPF ratio of at least 1:3, i.e., the protection against UVA radiation is at least one-third of the protection against UVB radiation (SPF); and a critical wavelength (λ_c) of 370 nm. The critical wavelength is defined as the wavelength at which the integral of the spectral absorbance curve reaches 90% of the area under the curve from 290 to 400 nm [46].

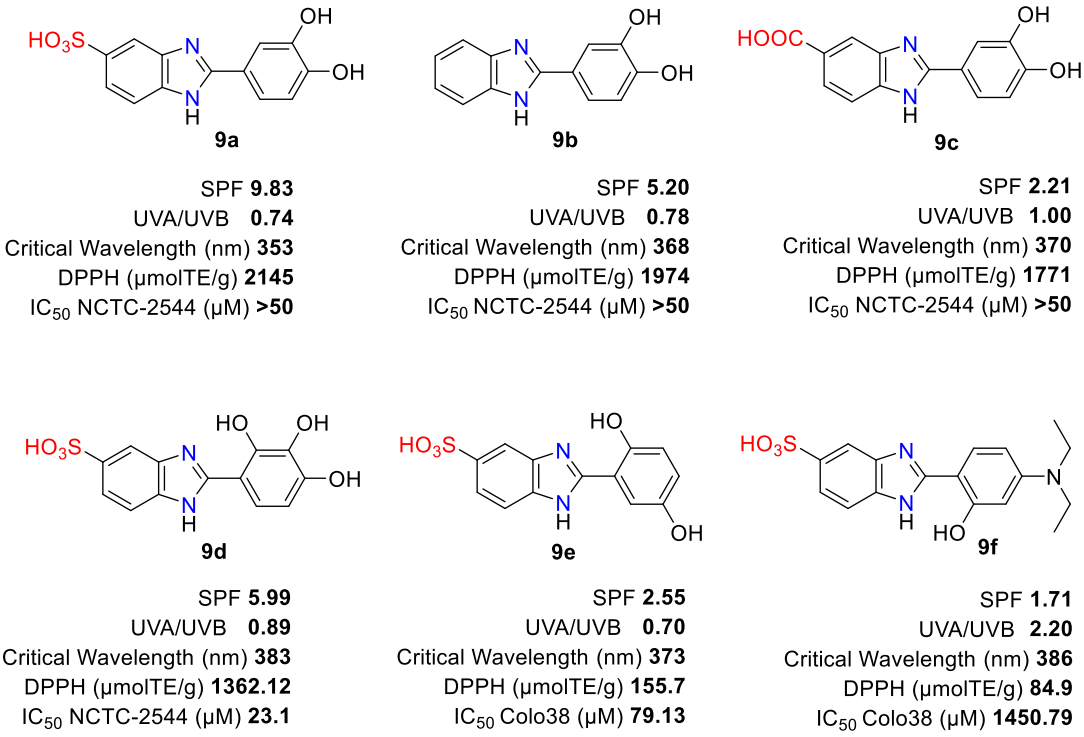


Figure 2. Chemical structure of the compounds of 2-arylbenzimidazole family with the best multifunctional profile.

In comparison with **9a**, molecules **9b** and **9c** presented a higher UVA/UVB ratio and critical wavelength. 2-(2,3,4-Trihydroxy-phenyl)-1*H*-benzimidazole-5-sulfonic acid **9d** had good UVA filtering parameters, its critical wavelength was the highest (λ_c = 383 nm), and its SPF was higher than PBSA. The cytotoxicity and phototoxicity assays using a specific cell line of human keratinocytes (NCTC-2544) showed that derivative **9d** was the most cytotoxic among all the tested compounds. Molecule **9c** achieved the best results regarding UV-filtering and antioxidant capacity, cytotoxicity, phototoxicity, stability, and photostability. It cannot be defined as a sunscreen filter but is an example of a booster molecule that provided very potent antioxidant activity and is capable of improving the activity of a known sunscreen.

In an attempt to obtain more potent multifunctional compounds, a three series of 2-arylbenzimidazoles **9** were synthesized by different substitution patterns C-5 (R_5 = CN, COOH and SO_3H) in the benzimidazole ring and were assayed for UV-filtering and antioxidant and antiproliferative activity [47]. In general, 2-arylbenzimidazole-5-sulphonic acids showed the best broad-spectrum solar protection against UVA and UVB rays. In particular, the presence of a tertiary amino group on the aromatic ring (compound **9f**) promotes the shift of the maximum absorption peak to the right in the spectrum (bathochromic shift). The most interesting data showed **9f** and its ciano analog (R_5 = CN), with the best UVA protection factor value of 15.77 and 14.30, respectively. Compound **9e** maintained its filtering profile even when incorporated into formulations for topical use and was chosen as a lead compound for further development. The UV absorption spectra of all tested 2-arylbenzimidazoles showed λ_{max} shifted toward longer wavelengths as compared to the reference PBSA. The derivatives bearing 5-cyano or 5-carboxyl groups have shown medium to high antioxidant activity, while the presence of a sulfo group at the 5-position of the benzimidazole nucleus is the least favorable in terms of antioxidant activity.

The 2-styryl-benzimidazole **10** (Scheme 1) was the best in terms of broad-spectrum filtering activity [47]. Furthermore, the same compound was the best in antiproliferative activity on human melanoma Colo38 cells with an IC_{50} value 6.20 μM.

In the search for scaffolds for multifunctional compounds, Djuidje and co-workers [48] synthesized benzimidazole derivatives **11** bearing a five-membered ring and tested their photoprotective profile against UV rays, their in vitro antioxidant capacity against different radicals (DPPH and FRAP test), the antifungal inhibitory activity, and the antiviral and antiproliferative activity. According to the results from the in vitro photoprotective activity, none of the compounds **11** had a broad-spectrum profile (λ_c < 370 nm). The highest SPF value was shown by the derivative characterized by the presence of furan in position 2 of the benzimidazole ring and without a functional group in position 5. The SPF value was decreased by replacing the furan with the pyrrole. Thus, by keeping the group present in position-5 of benzimidazole and by varying the five-membered ring at position-2, the order of protection against UVB is as follows—furan > pyrrole > thiophene. Furthermore, the photoprotective activity against the UVB radiation of the benzimidazoles **11** does not depend only on the substitution in the 2-position of the benzimidazole ring, but also on the groups present in position 5. In this regard, according to the R_5 group, the structure–activity relationship of this group of compounds is -H > -COOH > -SO_3H.

Based on the results of the biological tests, the best multifunctional molecule of this series is the 2-(1*H*-pyrrol-2-yl)-1*H*-benzimidazole, which was slightly more UVB protective than other tested compounds, but with good antioxidant (IC_{50} = 64.098 µg/mL in 1,1-diphenyl-2-picryl-hydroxyl radical (DPPH) assay), antifungal (IC_{50} values in the range of 0.97–3.80 µg/mL), and antiproliferative (IC_{50} = 9.7 µM against human melanoma SK-Mel 5 cells) activity.

In the search for new multifunctional molecules with improved UV protection parameter values and antioxidant and anti-proliferative activity (in particular against melanoma cells), Baidisserotto A. et al. [49] investigated a series of benzimidazole-containing hydrazone derivatives **12** (Scheme 1), in which the benzimidazole scaffold was connected by a hydrazone linker and an aromatic nucleus with different substituents, in particular, hydroxy, methoxy, and diethylamino groups.

Regarding the photoprotective activity, in general, the hydrazone derivatives showed better UV-filtering than the reference PBSA sunscreen filter. Researchers note that the SPF parameter does not always have a direct influence in proportion to the number of hydroxy groups in the substituent. The presence of a methoxy group or the 2-hydroxy-4-(diethylamino) moiety positively influences the filtering parameters. The 4-hydroxylphenyl derivative had the highest SPF, of 12.32. In general, an inverse relationship is observed between the SPF value and λ_c, i.e., the hydrazones with the highest SPF possessed λ_c < 370 nm. However, among broad-spectrum derivatives, the SPF value was noticeable only for compounds **12a** and **12b** (Figure 3). On the other hand, of all compounds tested, only **12a** and its 3-OH-phenyl analog showed a UVA/UVB ratio of less than 1/3, which is lower than the aforementioned EU recommendation. The antioxidant data deriving from the study of benzimidazolehydrazone derivatives **12** confirm what was reported by the previous series 2-arylbenzimidazoles **9**. The best antioxidant activity was shown by the hydrazones with at least two hydroxy groups (**12a**, **12b**) or a 2-hydroxy and a 4-methoxy group. Among the best antioxidant hydrazones tested against human melanoma Colo38 cells, compound **12c** showed the best anti-proliferative effect with IC_{50} = 0.50 µM.

The introduction of a hydrazone linker in 2-arylbenzimidazoles **9** resulted in more potent multifunctional molecules **12** (**12a** vs. **9e**; **12c** vs. **9f**, Figures 2 and 3).

Isosteric modifications of PBSA represent a strategy that has been employed by the research group of Prof. Manfredini. They designed and synthesized derivatives of PBSA in order to realize multifunctional compounds with good antioxidant activity, broad UV A-B filter capabilities, and good antineoplastic activity. For this purpose, PBSA was modified by replacing the benzimidazole core with other fused bicyclic heterocycles such as benzofuran, indole, benzoxazole, or 6-hydroxyproline (Figure 4) [48–51].

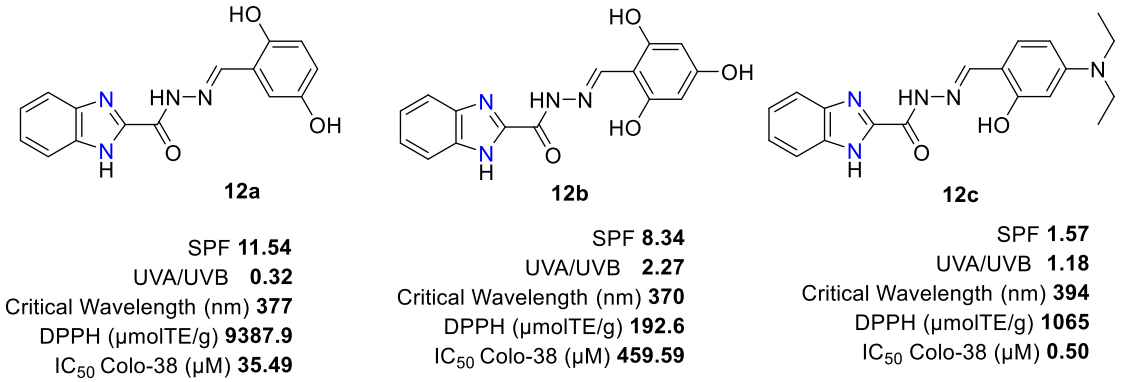


Figure 3. Chemical structure of the benzimidazolehydrazone derivatives with the best multifunctional profile.

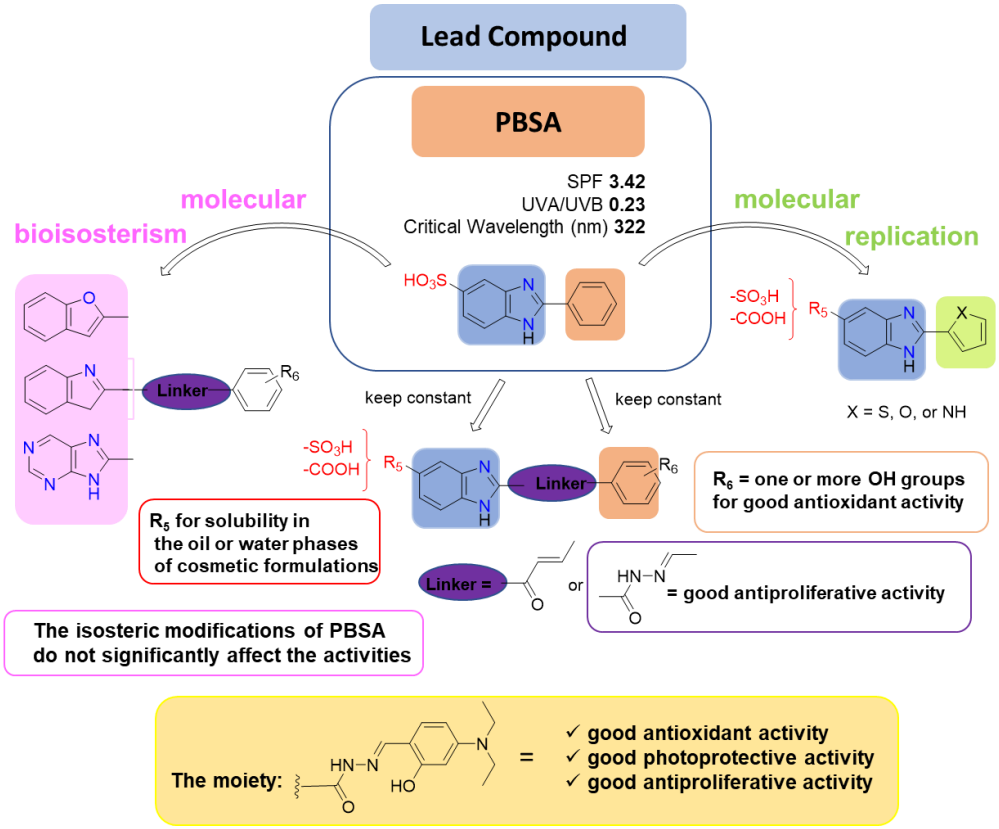
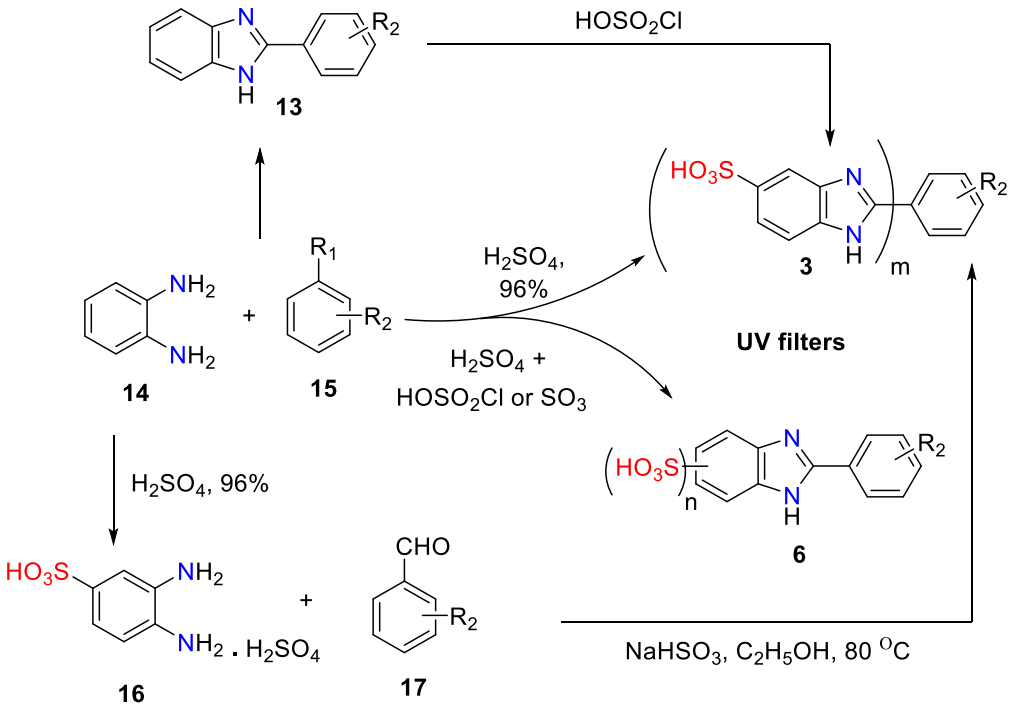


Figure 4. Modifications to the substitution pattern of PBSA that affected the multifunctional activity.

The data of structure–activity relationships (SAR) revealed a correlation between the number and position of hydroxyl groups on the arylidene portion and the antioxidant activity. With regard to the photoprotective capacity, all the hydrazone derivatives series showed better in vitro SPF profiles as compared to the commercial reference PBSA filter. The hydrazone linker was responsible for the antiproliferative activity of the compounds. In general, the isosteric modifications of PBSA did not significantly affect the activities. The investigations have shown that the presence of the 2-hydroxy-4-diethylamino moiety is related to the antioxidant, photoprotective, and antiproliferative activity in all series of hydrazones, and can therefore be considered the focus of the multifunctional profile of these derivatives (Figure 4).

3. Synthetic Approaches to 2-Substituted Benzimidazoles-Based UV Filters

The solubility of the filter substances in the oil or water phases is of decisive importance for cosmetic formulation. If the 2-aryl(het)benzimidazole compounds contain carboxy or sulfo groups, their water solubility after neutralization with common bases (e.g., sodium hydroxide, potassium hydroxide, triethanolamine, monoethanolamine, tetra hydroxypropyl ethylenediamine, tris (hydroxymethyl) aminomethane, etc.) increases considerably, which leads to easy incorporation into the cosmetic composition. The sulfonic acid products can be obtained using the methods presented in Scheme 2. One possible route involves a synthesis of 2-aryl-1*H*-benzimidazole **13** and the subsequent treatment of **13** with oleum, sulfuric acid, or chlorosulfonic acid for the preparation of mono- or polysulfonated products [52].



where: R_1 = COOH; $COOC_1$-C_6-Alkyl; COCl; COBr or CN; R_2 = one and more C_1-C_6-Alkyl; C_1-C_6-Alkoxy; OH; F, Cl, Br; m = 1-3; n = 2-3

Scheme 2. Synthesis of mono- and polysulfonated 2-phenyl benzimidazoles.

The compounds **13** traditionally are obtained from o-phenylenediamines **14** via condensation with carboxylic acids or their derivatives **15** (esters, anhydrides, acid halides, amides, nitriles, etc.) under dehydrating conditions (a Phillips–Ladenburg reaction) or by oxidative coupling with aldehydes. We noted that there have been excellent reviews on the synthesis of 2-(het)aryl-benzimidazole published in past years, which discuss the different synthetic routes to the construction of 2-hetaryl- and 2-arylbenzimidazole molecular scaffolds. These emphasize the recent trends and modifications to the Phillips–Ladenburg and Weidenhagen reactions, as well as entirely new methods of synthesis, involving oxidative cyclization, ring distortion strategy, and rearrangements, carried out under eco-friendly conditions [53–57].

Patent application WO9315061A1 [41] describes an industrial process for preparing 2-phenylbenzimidazoles starting from 1,2-phenylenediamine **14** and the bisulfite adduct of (un)substituted benzaldehyde or from **14** and the relevant aryl carboxylic acid in the presence of polyphosphoric acid. These processes nevertheless have some disadvantages. For example, the sodium hydrogen sulfite must be used in large excess, so that large amounts of sulfur dioxide are given off during working up. Additionally, 1-benzyl-2-

phenylbenzimidazole can be formed as a byproduct, which can be hard to separate. In the second process for preparing 2-aryl-benzimidazole **13** from aryl carboxylic acid, phosphoric acid passes into the wastewater and causes pollution. Furthermore, the product may be contaminated by 2-phenylbenzimidazoledisulfonic acid.

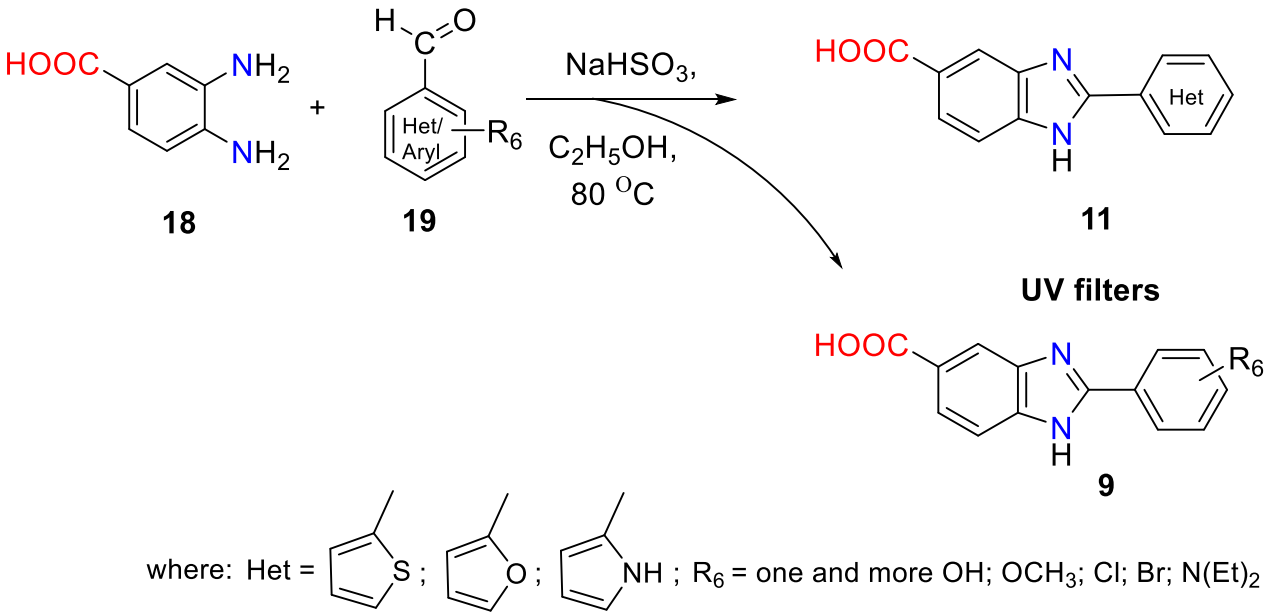
The reaction of compound **13** with chlorosulfonic acid yields sulfonic acid 3 (Scheme 2). According to Sayapin V.G. et al. [58], the sulfonic acid product exists in the strongly acidic reaction medium as the salt of chlorosulfonic acid or hydrochloric acid. The structure of this salt, depending on the nature of the substituent in position 2 of the benzimidazole core, determines whether the chlorosulfonation reaction will occur further, i.e., the nucleophilic replacement of the OH on the sulfonic acid group by a chlorine atom. The higher the electrophilic nature of R_2, the more readily the sulfonyl chloride is formed. Using chlorosulfonic acid in industrial settings causes problems since benzimidazole disulfonic acids can be formed, which are difficult to separate.

The aforementioned drawbacks of the two-step processes for the preparation of compound **3** can be avoided if the condensation reaction of **14** with an aryl carboxylic acid or its derivative **15** and the sulfonation is carried out in excess of 96% sulfuric acid (preferably, from 3 to 8 moles of sulfuric acid are used per 1 mol of o-phenylenediamine) (Scheme 2). According to the single-stage method, the benzoic acid derivative **15** is introduced into the sulfuric acid at room temperature, which generally causes the mixture to warm to temperatures between 80 °C and 140 °C. The o-phenylenediamine is slowly added at this temperature and the reaction mixture is heated at reflux (165–250 °C) for 1 to 5 h [59]. The yields of the target sulfonic acids are comparable to or greater than those in the two-step process. Bis- and tris-5-sulfobenzimidazoles **3** (m = 2–3) are prepared analogously: from terephthalic acid—1,4-bis-(5-sulfobenzimidazol-2′-yl)benzene; from isophthalic acid—1,3-bis-(5-sulfobenzimidazol-2′-yl)benzene; and from 1,3,5-benzenetricarboxylic acid—1,3,5-tris-(5-sulfobenzimidazol-2′-yl)benzene, respectively.

An activated sulfuric acid is used for the preparation of polysulfonated benzimidazoles **6** in one step procedure (Scheme 2) [43]. Sulfuric acid alone is not strong enough to act as a reagent for this process because it is believed that water, which forms during the reaction, dilutes the sulfuric acid and decreases its reactivity. It is preferred in industrial conditions to activate sulfuric acid with oleum instead of chlorosulfonic acid, since hydrogen chloride gas is not evolved during the reaction, meaning that pressure regulation and, accordingly, the collection and disposal of this aggressive gas, is not necessary. After the hydrolysis of the oleum, sulfuric acid is present which can be recycled, with relative ease, while the recycling of the chloride-containing sulfuric acid resulting from the use of chlorosulfonic acid is more difficult. Furthermore, chloride-containing sulfuric acid requires the presence of extremely corrosion-resistant apparatus. Compounds **6** were prepared using an arylcarboxylic acid in a 1:1 ratio to o-phenylenediamine, heating the reaction mixture at temperatures between 150 °C and 250 °C for 2 to 8 h. At a reaction time of fewer than 2 h, monosulfonation products could be observed.

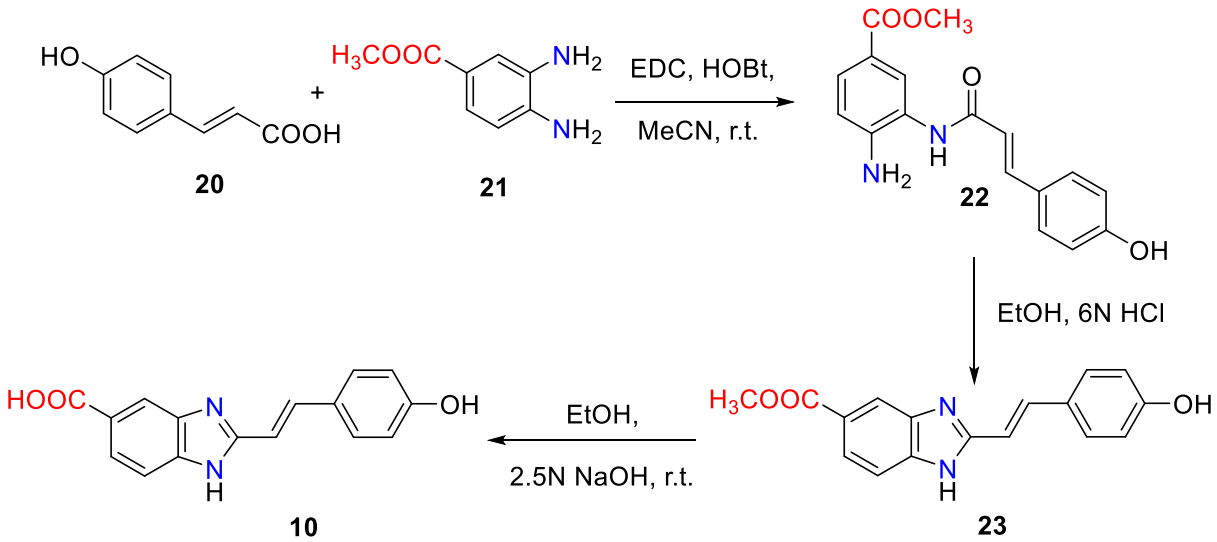
Buno A. et al. [39] reported that the reaction of a 3,4-diamino-benzene sulfonic acid **16** with hydroxy-substituted benzaldehyde **17** catalyzed by a solution of sodium bisulfite 1N in water, by heating under reflux for 24 h, gave a corresponding benzimidazole-5-sulfonic acid **3** with 60–80% yield (Scheme 1). As can be seen from the generalized schemes of the reactions (Scheme 2), using 96% sulfuric acid and o-phenylenediamine, it is possible to synthesize **16** [59]. In general, the reaction of 1,2-diaminobenzene bearing electron-withdrawing groups (-SO_3H, COOH), with aldehyde, afforded the desired 2-substituted benzimidazole product in a lower yield than using unsubstituted o-phenylene diamine. According to [60], with an increase in the number of electron-donating groups in the molecule of the aldehyde partner, the yield of the reaction decreases as well.

Djuidje, E.N. and co-workers reported a synthesis of 2-heteryl-1*H*-benzimidazoles **11** (Scheme 3) via the inter-reaction of commercially available 3,4-diaminobenzoic acid **18** and heterocyclic aldehyde **19** in the presence of $NaHSO_3$ as an oxidant agent [48]. The preparation of 2-aryl-benzimidazole-5(6)-carboxylic acids was also described in [61].



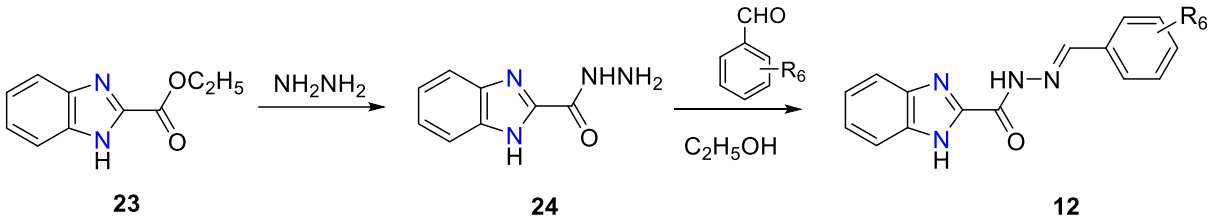
Scheme 3. Synthesis of 2-phenyl/2-heteryl-1*H*-benzimidazole-5-carboxylic acid.

Benzimidazole derivative **10** was obtained following the reaction sequence shown in Scheme 4. 4-Hydroxycinnamic acid **20** was coupled with methyl 3,4-diaminobenzoate **21** to give the intermediate **22**. The benzimidazole ring closure was performed in 6N hydrochloric acid to give the compound **23**. The ester derivative **23** was hydrolyzed to afford the 2-styryl-benzimidazole **10** [48].



Scheme 4. Synthesis of 2-(4-hydroxystyryl)-1*H*-benzimidazole-5-carboxylic acid **10**, where EDC is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and HOBt is hydroxybenzotriazole.

The starting material for the synthesis of the multifunctional hydrazones with wide UV filter capabilities was a benzimidazole heterocycle functionalized with an ethyl ester group in the C-2 position (Scheme 5). The hydrazinolysis of the esters was achieved upon refluxing for 3 h in an ethanolic solution of the corresponding ethyl ester **23** and hydrazine hydrate. The target hydrazones **12** were obtained in good to excellent yield by coupling the hydrazide **24** with appropriate hydroxyarylaldehydes in ethanol [49,51].



Scheme 5. Synthetic route to N′-(4-arylidene)-1*H*-benzimidazole-2-carbohydrazides **12**.

The presented synthetic routes to obtain the 2-substituted benzimidazoles are characterized by the use of accessible starting materials, a simplicity of implementation, and good yields of the target compounds. Thus, they are promising procedures for implementation on an industrial scale.

4. Conclusions

The popularity of sunscreen products has increased dramatically in recent years due to the increased incidence of melanomas and other skin diseases caused by UV rays. Currently, about thirty commercial UV filters meeting the strict regulatory requirements for efficacy and safety are used in sunscreen products. However, the low photostability and susceptible toxicity to humans and aquatic organisms reported for some of them have caused concern in the scientific community. Therefore, there is a need for the development of new effective and safe photoprotective compounds.

The benzimidazole heterocycle is a suitable scaffold for the preparation of innovative UV sunscreen filters effective in fighting free radicals and preventing melanoma due to its appropriate photoprotective profile and desirable pharmacological properties like antioxidant and antiproliferative activity.

In light of the above facts, this review is an attempt to summarize the contributions of the researchers in the field of the development of benzimidazole-based UV filters for the first time. Here, we traced the advance in the area chronologically from the first commercial benzimidazole UVB filter, PBSA, to recently discovered UV photoprotective agents possessing attractive multi-functional characteristics. We discussed the modification in the structure of PBSA to obtain more broad-spectrum UV filters with improved water or oil solubility, appropriate for cosmetic application. In addition, we summarized the studies of the SAR of the photoprotective benzimidazole derivatives as antioxidant and anti-melanoma agents.

The second part of the review focused on the synthetic approaches toward the 2-substituted benzimidazole derivatives. A greater part of this information is available only in the patent literature and reflected the advantages and disadvantages of the processes for preparing 2-arylbenzimidazole sulfonic acids on an industrial scale.

In conclusion, although the development of better and more effective UV filters for cosmetic applications needs the collaboration of multidisciplinary researchers such as synthetic chemists, photochemical specialists, chemical engineers, biologists, and others, we believe that this review will be useful to researchers in the design and synthesis of benzimidazole compounds as modern multifunctional sunscreen filters.

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