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Rational Design and Synthesis of Efficient Sunscreens To Boost theSolar Protection Factor

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Abstract: Skin cancer incidence has been increasing in the lastdecades, but most of the commercial formulations used as sunscreens are designed to protect only against solar erythema.Many of the active components present in sunscreens showcritical weaknesses, such as low stability and toxicity. Thus, thedevelopment of more efficient components is an urgent healthnecessity and an attractive industrial target. We have rationallydesigned core moieties with increased photoprotective capacities and a new energy dissipation mechanism. Using thesescaffolds, we have synthesized a series of compounds withtunable properties suitable for their use in sunscreens, andenhanced properties in terms of stability, light energy dissipation, and toxicity. Moreover, some representative compounds were included in final sunscreen formulations and a relevant solar protection factor boost wasmeasured.

Skin cancer has been steadily increasing during the last years,[1] being the most common type of cancer.[2,3] Melanomas, a type of skin cancer, are responsible for the majority of deaths (22 000 in Europe in 2012,[4] 76 000 cases expected in USA in 2016).[5] This has been related to both the depletion ofthe ozone layer and an increase in sunlight exposure time, which exceeds the requirement for light-mediated synthesis of vitamin D and promotes skin cellular problems.[6] Using sunscreens, compounds designed to minimize the solar light transmission in the ultraviolet A (315–400 nm) and B (280–315 nm) regions, has become the most effective way to avoid this deleterious effect of sunlight.[7] However, commercial compounds have several problems, such as low photostability,safety concerns (endocrine disruption properties,[8] skin penetration[9]), biodegradability, and lack of effectiveness in skin protection. Moreover, only a limited number of compounds with comparable structures and analogous features are allowed to be incorporated into formulations. Additionally, the mechanism of energy dissipation at the molecular level is only poorly understood.[10] An ideal sunscreen should feature strong UV absorption, energy dissipation as heat,a short-lived excited state to avoid photochemical reactions, and high stability (Figure 1 a). Surprisingly, no commercial filters cover these features completely, and some have had to be retired from the market, such as *p*-aminobenzoic acid,[11] octocrylene,[12,13] or oxybenzone.[14] In contrast, Nature has developed very efficient sunscreens[15] that allow living beings to cope with radiation, such as the mycosporine-like amino- acids (MAAs, see the Supporting Information).[16–19] MAAs consist of a family of compounds with a cyclohexenone or cyclohexenimine basic structure (Figure 1 b). MAAs are low- weight, water-soluble, thermally and photochemically stable, and non-fluorescent compounds with a strong absorption between 310 and 360 nm.[20] UV-induced synthesis and accumulation of MAAs under UV-stress have been reported,[16] although the use of natural sources is hampered by the small quantities available and inefficient synthetic preparation (15 steps, 1 % of overall yield). However, their use have been proposed directly from extracts[20] or through total synthesis,[21,22] and their photoprotective properties havebeen previously evaluated.[23] This fact, in conjunction with

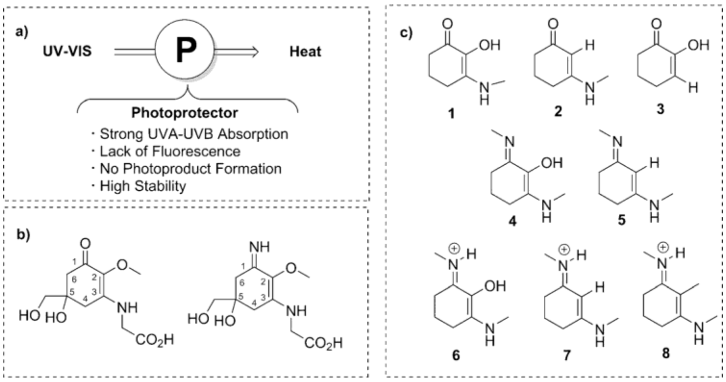

Figure 1. a) General features of efficient sunscreens. b) Structures of mycospor-ine-glycine (left) and palythine (right). c) Core structures of considered com- pounds.

the potential impact in public health and industrial applications of sunscreens,[24] prompted us to rationally design a new family of photoprotective compounds inspired by MAAs.

Based on the active core of MAAs, we performed an in silico evaluation of several basic scaffolds, 1–8 (Figure 1 c), avoiding the "decorating substituents" that come from the biosynthetic route,[25] to identify the simplest compound that fulfills the requisites for efficient sunscreens. We used the CASPT2//CASSCF methodology to compute the absorption spectrum, the critical points along the potential energy surface (PES) and the minimum energy paths (MEPs) connecting them, together with non-adiabatic molecular dynamics (NAMD) performed at the CASSCF level of theory to calculate the exited state lifetimes. With this methodology, we could rapidly evaluate the photostability, the radiative processes, and the exited state lifetime of 1–8. In addition, this screening allowed us to assess the differences between the cyclohexenone and the cyclohexenimine moieties (1–3 and 4–5), the influence of substituents in positions 2 and 3 (1/2, 4/5, 6/7, 6/8, and 1/3), and the effect of the positive charge in the iminic nitrogen atom (4/6, 5/7), which is a common feature in isolated MAAs[20] and known to enhance photoprotection.[23]

In the case of 1, excitation leads to S_2 and energy redistribution causes a geometric distortion to a non-planar S_2/S_1 conical intersection (CI) and a subsequent planar minimum is found in the S_1 PES (Figure 2 a), suggesting a radiative decay to the ground state (Supporting Information).[26] Thus, 1 will not behave as an ideal sunscreen. In contrast, 6 features excellent properties, such as strong absorption ($f = 1.10$) and no minimum in the excited state (Figure 2 b). Thus, no fluorescence is expected and the decay to the ground state will be ultrafast, as reported for related compounds.[18] The MEPs of other scaffolds were also analyzed (Supporting Information). Regarding to the CIs, an out-of-plane movement (an aborted geometrical deformation) of the substituents in positions 1, 2, and 3 was observed for all of the species.[18,23] This mechanism differs from most of the reported sunscreens, which implies a double bond isomerization (cinnamates, although the low lying n-p states are also relevant[10]) or an excited state proton transfer (avobenzone). Interestingly, this mechanism is unprecedented in commercial compounds.

Higher energy CIs (1–3) imply the presence of a minimum in the excited state, while low energy CIs (4–8) are reached through a barrier-less path. The substituent effect in position 2 (OH, Me) seems to be not relevant. On the contrary, the positive charge causes stronger, red-shifted absorption bands. As a conclusion, 6, 7, and 8 are the most promising cores. However, 7 is known[31,32] to be chemically unstable due to the H in position 2. In addition, a fast decay to the ground state was demonstrated for 6 and 8 by NAMD (Supporting Information), with an averaged S_1 life-time of 239 65 fs (8), on the same order as the natural sunscreen eumelanin,[27] but much faster than commercial sunscreens components (6 ps for avobenzone in S_1[28] and 665 ns in T_1,[29] 600 fs and 2–3 ps for oxybenzone[30]).

Based on the in silico rational design, three different routes were used to prepare 6 and 8 derivatives. In all of these cases, a maximum of five steps was required, starting from common and cheap materials and using simple methods. Up to 20 different compounds modifying all of the critical structural features (cycle size, substituents, counterions) were prepared, and representative examples (9–17) were studied (Figure 3) to evaluate their properties. All of the prepared compounds are crystalline solids and stable for months at room temperature in the presence of air and light. The UV/Vis absorption spectra (Figure 4, left) of the synthesized compounds showed a tunable wavelength (λ_{max} 306–360 nm) with very high absorption coefficients (even higher than commercial photoprotectors; Supporting Information). The solvent effect was also analyzed but minimal influence was found. Interestingly, no degradation was observed by NMR after 16 h of irradiation, in contrast with commercial sunscreens (Figure 4, right and Supporting Information). We also tested a solution of 9 for a whole summer and no sign of decomposition was found.[33] As predicted by the calculations, no significant emission (fluorescence quantum yield $F_f < 1\%$) was found.

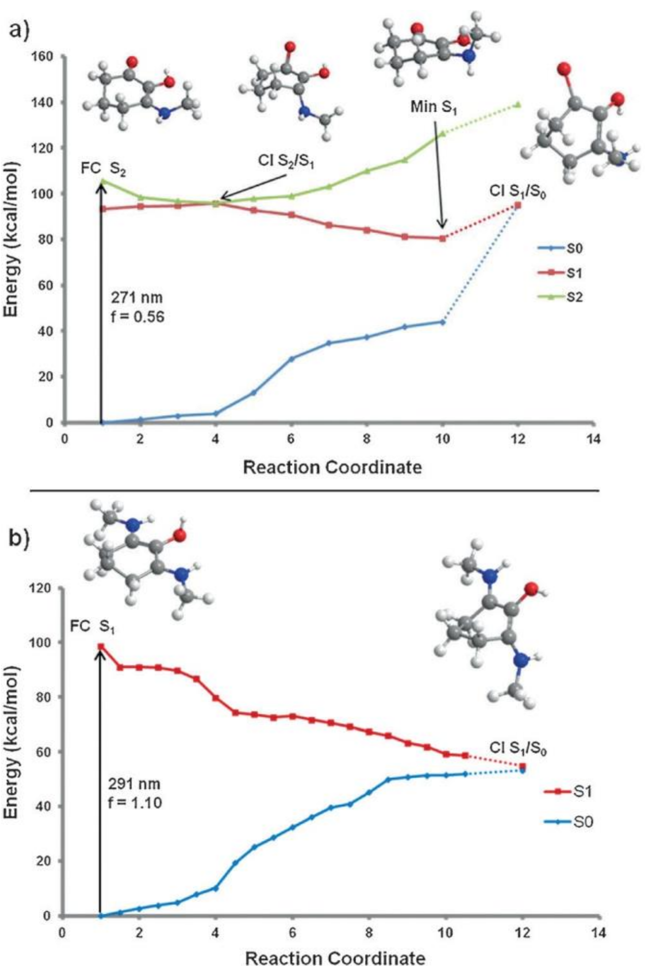

Figure 2. Computed MEPs. a) Cyclohexenone 1. b) Cyclohexenimine 6, f is the transition oscillator strength.

A strong absorption together with high photostability and lack of fluorescence implies a very efficient light energy dissipation into heat. However, excessive heating could be a drawback in sunscreens applied onto the skin. This was

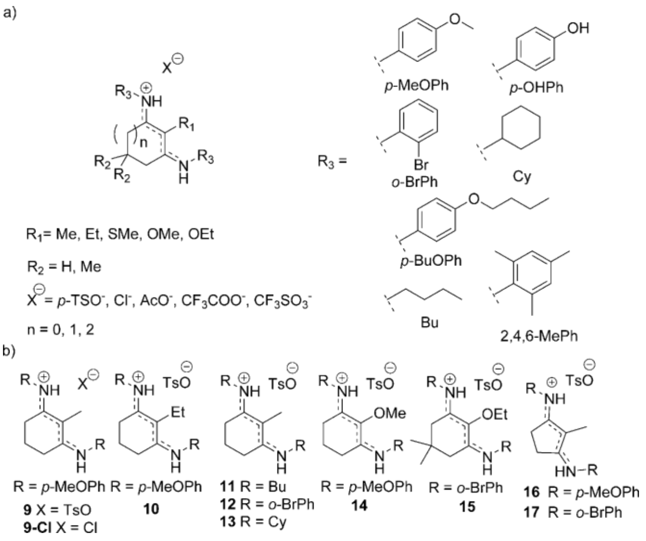

Figure 3. a) General structure of potential sunscreens. b) Selected examples used to test the properties.

tested by calorimetric studies after one-hour irradiation. Non-significant temperature increments were observed for solutions of 1–2 % of 9 in methanol. The thermal stability and solubility, as critical factors for practical applications, were also checked (Supporting Information). These compounds were found to be stable up to 270 8C, and their solubility in water or organic solvents may be tuned.

Finally, we measured the solar protection factor (SPF) and UVA protection factor in real sunscreen formulations (Table 1 and Supporting Information). Three different formulations were prepared and measured following the industrial standard.[34] M1 included 10 % of 16 and 10 % of 17 as active species. M2 included 10 % of octinoxate and 5% of avobenzone. M3 included a mixture of the four components in the same amount as above (10 % of 16, 17, and octinoxate, and 5% of avobenzone). In these tests, we employed the maximum amount allowed to be used in commercial formulations.

Table 1: SPF (media ±standard deviation) and UVA-PF for the prepared formulations.

	SPF	UVA-PF
M1	5.9 : 0.7	4.5 : 0.4
M2	28.6 : 4.5	11.7 : 1.1
M3	72.8 : 10.8	23.0 : 1.3

A clear SPF and UVA-PF boost was measured when the prepared compounds were added to real formulations including commercial sunscreens (M3), drastically increasing the protection in the UVB (SPF) and UVA (UVA-PF) regions. The value for M3 is an excellent and promising result, even higher than the one obtained by similar formulations with commercial components (Supporting Information).

Inspired by MAAs as very effective photoprotectors already in use,[35] we have prepared a new family of potential UV filters. The easy and versatile synthetic routes provide a suitable source for commercial applications. Several properties could be tuned to match the practical requirements for the preparation of polymers, resins, paints, or coatings. These compounds clearly outperform most of the commercially available UV filters, and their use in real formulations was shown to boost the SPF. These new compounds expand the few available components for sunscreens in two different directions, as they show a different mechanism of action and excellent properties. These features turn them into promising candidates for a new generation of more efficient sunscreens.[36]

Experimental Section

Synthetic general procedure: To a suspension of the enaminone (1 mmol) in dry toluene (50 mL), *p*-toluenesulfonic acid monohydrate (190.2 mg, 1 mmol) was added. The mixture was stirred for five minutes, the amine (6 mmol) was added, and the mixture was refluxed from 24 to 84 h. After cooling, the reaction mixture was concentrated under vacuum and purified by crystallization from CH_2Cl_2 by *n*-hexane addition to obtain 9–17 (50–95%).

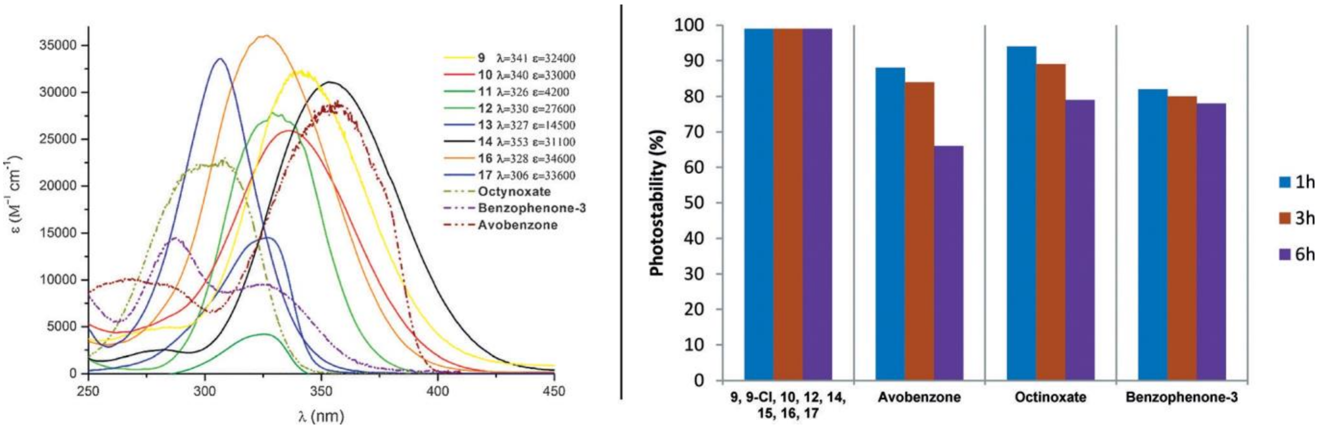

Figure 4. Left: UV/Vis spectra of selected compounds. Right: Photostability of selected compounds.

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