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New cinnamic acid sugar esters as potential UVB filters: Synthesis, cytotoxicity, and physicochemical properties

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A B S T R A C T

Cinnamic Acid Sugar Ester Derivatives (CASEDs) are a class of natural compounds that exhibit several interesting biological activities. However, to date, no examples of their use in sunscreen formulations have been reported. Here, we describe the synthesis of a series of novel cinnamic acid esters of glucose (**4a-g**), ribose (**4h**) and lactose (**4i**) starting from the respective acetals **3**. The latter were obtained through oxidative alkoxycarbonylation of olefins. For all compounds **3** and **4**, UV–Vis spectra were recorded and lipophilicity (i.e., clogP) and cytotoxicity were evaluated. All but one of the synthesized compounds were found to be non-cytotoxic at the concentrations tested and, as expected, absorption spectra depended only on the substituents on the aromatic ring. Finally, the *ad hoc* synthesized compound **3k**, featuring a 4-methoxy substituent on the phenyl ring and a 1,2-*O*-isopropylidene ribose moiety, provided the most promising results for a possible use as a sunscreen. Indeed, its Sun Protection Factor (SPF), calculated *in vitro*, was higher with respect to that of ethylhexyl methoxycinnamate (EHMC), which is already utilized in sun care products. Moreover, **3k** showed greater antioxidant properties than EHMC, effectively protecting keratinocytes against H_2O_2-induced oxidative damage. At the same time, it showed no cytotoxic effects and preserved cellular metabolic activity and protein content. Based on these results, we believe that CASEDs could find valid applications in the skincare and cosmetics sectors.

1. Introduction

Cinnamic Acid Sugar Ester Derivatives (CASEDs) are a class of naturally occurring compounds consisting of a cinnamate moiety linked, *via* ester bond, to the non-anomeric carbon of a glycosyl skeleton. CASEDs have been found in several Chinese medicinal plants [1], as they possess a variety of biological activities. In particular, these compounds have been found to possess anti-depression [2–5], neuroprotective [6,7], anticancer [8–11], antioxidant [12–17], anti-inflammatory [18–20] and antiviral [21–23] properties, which can vary based on (i) the substituents on the aromatic ring (usually OH or OMe), (ii) the number and the position of the phenylacrylic moieties linked to the sugar, and (iii) the glycosyl group, which can be a monosaccharide, a disaccharide or an oligosaccharide. However, to the best of our knowledge, applications of CASEDs in cosmetic fields are still missing. It is known that cinnamates possess the ability to block UV radiations [24] and, besides all, octyl methoxycinnamate (Scheme 1a), also known as ethylhexyl methoxycinnamate (EHMC) or octinoxate, is already widely utilized in sun care products, fragrances, hand and body lotions, facial treatment products, and lipsticks as an UV filter, due to its capability of absorbing UVB radiations (280–320 nm). Unfortunately, this compound and its photolysis derivatives are harmful for the marine ecosystem [25] and its *cis*-isomer, which is formed during the exposition to sunlight, is dangerous for the human DNA [26], as well as being less stable than the *trans*-one [25]. In this sense, the use of CASEDs as UV blockers, would represent an improvement, since some advantages can be clearly envisioned. To start with, carbohydrates can be usefully obtained from lignocellulosic biomass [27–29], thus improving the sustainability of the whole synthetic process. Moreover, hydrolysis or photolysis would produce at least a biocompatible molecule (i.e. the sugar) and, depending on the application, the water solubility of the final molecule can be appropriately modulated by selectively protecting the glycosyl hydroxyl groups.

Unfortunately, due to selectivity issues, arising from the high number of hydroxyl groups in sugars, chemical syntheses that provide high yields of these products are not present. Moreover, enzymatic syntheses, which are usually utilized in carbohydrate-related syntheses, have generally led to low productivities with long reaction times [30–34]. Recently, we have developed an efficient Pd-catalyzed carbonylative

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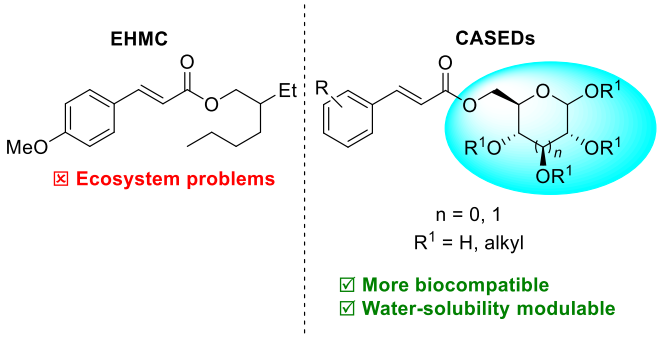


Scheme 1. Comparison between EHMC and CASEDs as potential UVB filters.

coupling that allows the one-step synthesis of various protected 6-*O* cinnamic acid sugar monoester derivatives starting from a styrene derivative and 1,2-*O*-isopropyliden-α-D-glucofuranose [35]. This reaction, which proceeds under particularly mild conditions and with equimolar amounts of the olefin and the sugar, has allowed the unprecedented synthesis of glucose, ribose and lactose acetal cinnamic acid esters with high yields [35].

Intrigued by all these considerations, in this paper we have synthesized a series of new CASEDs, having both protected and unprotected sugars (Scheme 1b) and various substituents on the cinnamic moiety. Foreseeing a possible application as UV filters, our entire library constituted by the molecules obtained both in the previous [35] and in this work, was tested to obtain biological and physicochemical information. For the most promising molecules, the Sun Protection Factor (SPF) values were determined at different concentrations and compared with EHMC.

2. Materials and methods

2.1. General experimental methods

All the carbonylation reactions were performed under nitrogen atmosphere with dry solvents under anhydrous conditions, by using Schlenk technique. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz), using CD_3OD, or $CDCl_3$ as solvent. Chemical shifts are reported in the δ scale relative to residual $CHCl_3$ (s, 7.26 ppm) or MeOH (p, 3.31 ppm) and to the central line of $CDCl_3$ (77.16 ppm) or CD_3OD (49.00 ppm) for ^{13}C NMR. ^{13}C NMR were recorded with ^{1}H broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, br = broad, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). ESI-MS spectra were recorded on Waters Micromass ZQ 4000, using electrospray ionization techniques, with samples dissolved in MeOH or CH_3CN. Carbon monoxide (Cp grade 99.99 %) was supplied by Air Liquide (carbon monoxide is a toxic gas with potentially lethal action, therefore adequate precautions must be observed). The *p*-benzoquinone was purchased by Alfa Aesar (Italy) and was filtered off a plug of silica gel washing with CH_2Cl_2, obtaining a yellow solid after drying the solution under vacuum. Anhydrous THF was distilled from sodium-benzophenone. Pure compounds were isolated through flash column chromatography on silica gel 60 (40–60 μm, 230–400 mesh). TLC analyses were performed using Merck (Silica gel 60-F254) TLC plates and visualized by exposure to ultraviolet light and/or by exposure to an aqueous solution of ceric ammonium molybdate and plate heating.

4-Vinylanisole was purchased from BLD Pharma (Germany), filtered through a plug of neutral Al_2O_3 and used without further purification. $Pd(TFA)_2$ was purchased by Flurochem (United Kingdom). The ligand **L1** was synthesized according to a literature procedure [36]. Compounds **3a-3d**, **3f-3j**, **4e** were synthesized in our precedent work [35] and directly utilized here. All other chemicals were purchased from Merck Sigma-Aldrich (Italy) and used without further purification. All solid reagents were weighed in an analytical balance without excluding moisture and air. All the tested compounds were >95 % pure by ^{1}H NMR analysis.

2.2. Procedure for the synthesis of compound *3e*

To a solution of compound **3d** (200 mg, 0.49 mmol) in CH_3CN (4.9 mL, 0,1 M), hydrazine monohydrate (221 mg, 4.41 mmol) was added and the reaction was stirred at room temperature for 1 h. A saturated solution of NH_4Cl (5 mL) was added and the mixture was stirred for a further 10 min. Then it was diluted with H_2O and extracted with EtOAc (3x10 mL). The organic phases were dried over anhydrous Na_2SO_4 filtered and concentrated. The product **3e** was obtained as a white solid after column chromatography on silica gel (CH_2Cl_2: MeOH = 95:5) with 87 % yield. Characterization data can be found in the Supporting Information.

2.3. Procedure for the synthesis of compounds *3k*

In a nitrogen-flushed dried Schlenk tube, equipped with a magnetic stirring bar, $Pd(TFA)_2$ (8.3 mg, 0.025 mmol) and THF (1.0 mL) were added in sequence. After the mixture turned in a red/brown color (10 min), ligand **L1** (13.8 mg, 0.0275 mmol) was added. The mixture was left under stirring for 10 min, turning in a dark orange color. Then, *p*-benzoquinone (108 mg, 1.0 mmol), *p*-TSA·H_2O (1.9 mg, 0.01 mmol), 1,2-*O*-Isopropylidene-α-D-ribofuranose (95.1 mg, 0.5 mmol), and 4-vinylanisole (67 μL, 0.5 mmol) were added in sequence. The reaction was vigorously stirred at 50 °C under balloon pressure of CO, for 17 h and then CO was removed. The crude was dried under reduced pressure and product **3k** was eventually obtained after column chromatography on silica gel with 71 % yield. Characterization data can be found in the Supporting Information.

2.4. General procedure for the synthesis of compounds *4a-4h*

To a solution of compounds **3a-3h** (0.15 mmol) in CH_2Cl_2 and H_2O, trifluoroacetic acid was added (CH_2Cl_2:H_2O:HTFA = 40:1:24, 0.038 M) at 0 °C and the reaction was left under stirring until complete consumption of the starting material monitored by TLC (CH_2Cl_2/MeOH = 90:10). The crude was dried under reduced pressure and the products **4a-4h** were eventually obtained after column chromatography on silica gel. Characterization data can be found in the Supporting Information.

2.5. Procedure for the synthesis of compound *4i*

To a solution of **3i** (58 mg, 0.089 mmol) in CH_3CN (712 μL, 0.125 M), H_2O (7.12 μL) and HBF_4·OEt_2 (1.42 μL) were added and the reaction was stirred for 1 h. A white precipitate was formed that was filtered and washed with CH_3CN and dried in an oven, obtaining **4i** with 53 % yield. Characterization data can be found in the Supporting Information.

2.6. UV–vis measurements

UV–Vis absorption spectra were recorded on a UV–Visible spectrophotometer (T92+ model, PG Instruments) from 200 to 800 nm.

2.6.1. UV–vis spectra records

Compounds **3a-3k** were dissolved in CH_3CN to prepare a stock solution 10^{-3} M. Then 100 μL of this solution were diluted to 10 mL with distilled water to obtain a solution 10^{-5} M. The absorption spectra of the samples were recorded in the range 200–800 nm using 1 cm quartz cell and 0.1 % v/v CH_3CN in distilled H_2O as a blank.

Compounds **4a-4i** were dissolved in distilled water to prepare a stock solution 10^{-3} M. Then 100 μL of this solution were diluted to 10 mL with

distilled water to obtain a solution 10^{-5} M. The absorption spectra of the samples were recorded in the range 200–800 nm using 1 cm quartz cell and distilled H_2O as a blank.

2.6.2. Sample preparation for SPF measurements

All samples for the UV–Vis measurements were prepared starting from different stock solutions (10^{-2} M) in CH_3CN for EHMC, **3e** and **3k**, while in distilled H_2O for **4e**. Next, these solutions were diluted with CH_3CN obtaining samples at different concentrations (75 μM, 25 μM and 5 μM). The absorption spectra of the samples were recorded in the range 200–800 nm using 1 cm quartz cell, and CH_3CN as a blank in the case of EHMC, **3e** and **3k**, while CH_3CN and different percentages of H_2O in the case of **4e** (% H_2O: 0.75 % for the 75 μM, 0.25 % for the 25 μM and 0.5 % for the 5 μM solution of **4e**).

2.7. Biological studies

2.7.1. DPPH assay

The antioxidant capacity of compounds **3** and **4** was evaluated as a preliminary screening in a cell-free system by the 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH) radical scavenging assay, as previously described [37]. Test compounds were first solubilized in DMSO as a 100 mM stock solution and then diluted in ethanol at the desired concentrations (100 μM). DPPH (Merck, Italy) was also prepared in ethanol (final concentration 100 μM). The scavenger effect was expressed as % = [(OD 517 nm control) - (OD 517 nm sample/OD 517 nm control)] x 100 and the EC_{50} value was then calculated. Quercetin was used as a reference antioxidant molecule to check the accuracy of the procedure.

2.7.2. Cytotoxicity assays

Cytotoxicity tests were performed on HaCaT cells (immortalized human keratinocytes) from CLS-Cell Lines Service GmbH (Germany). Cells were seeded in 96-well plates (5×10^3/well) and incubated for 24 h with the test compounds (100 μM) or vehicle (DMSO 0.1 %). After treatment, molecules were removed and fresh medium containing WST-8 (Merck, Italy) was added to each well to evaluate cell metabolic activity. Color development was monitored up to 4 h at 450 nm in a multiwell plate reader (Multiskan FC, Thermo Scientific). As previously published [38], the sulforhodamine B (SRB) test was then performed in the same 96-well plate to quantify cell protein content. Briefly, cells were fixed with 50 % trichloroacetic acid and stained with 0.4 % SRB (Merck, Italy). Protein bound SRB was subsequently solubilized with 10 mM Tris and the absorbance was read at 570 nm. Cell viability was expressed as a percentage (%) versus non-treated cells (controls) and IC_{50} values were calculated.

2.7.3. DCFH-DA assay

The antioxidant properties of some selected compounds (**3k** and EHMC) were further investigated by the use of the probe 2′,7′-dichlorofluorescein diacetate (DCFH-DA, Merck, Italy) in HaCaT cells seeded in black 96-well plates (1×10^4/well), as previously described [39]. In the preincubation experiments, test compounds were administered to the cells for 2 h and then removed before DCFH-DA (5 μM) addition and cell oxidation by hydrogen peroxide (H_2O_2, 100 μM). In the coincubation experiments, cells incorporating DCFH-DA were directly oxidized by H_2O_2 in the presence of the test molecules. Increments of fluorescence emission upon probe oxidation were monitored for 1 h at ex/em 485/520 nm in the multiwell plate reader FluoStar Optima (BMG Labtech, Germany). Data were expressed as relative oxidation versus non-oxidized cells.

2.7.4. Statistical analysis

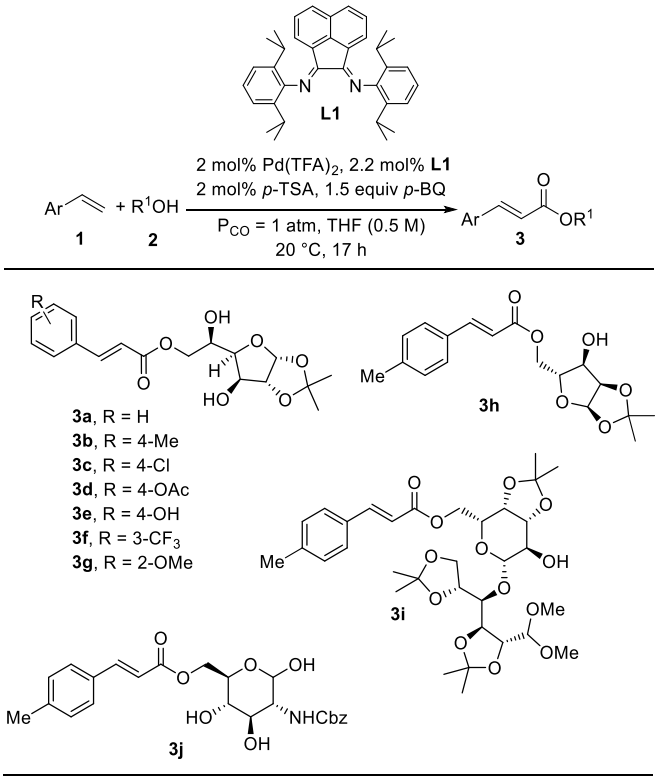
Results from DPPH, cytotoxicity and DCFH-DA assays were presented as mean ± SD of three independent experiments. Differences between two groups were analyzed by the two-tailed Student's test and those between three or more groups were analyzed by using the one-way analysis of variance test (ANOVA) followed by Tukey's test. A P value < 0.05 was considered statistically significant. Statistics were performed using GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, USA).

3. Results and discussion

Recently, compounds **3a-d** and **3f-j** of Scheme 2 were synthesized through palladium catalyzed oxidative alkoxycarbonylation of the respective styrene derivatives **1**, using as nucleophile a protected monosaccharide (i.e., 1,2-*O*-Isopropylidene-α-D-glucofuranose, 1,2-*O*-Isopropylidene-α-D-ribofuranose or *N*-Cbz-D-glucosamine) or a disaccharide (i.e., lactose tetraacetal, LTA) **2**, under atmospheric carbon monoxide pressure (Scheme 2) [35]. The reaction proved to be stereoselective (only the (*E*) isomer is formed) and regioselective (it involves exclusively the primary hydroxyl group of the sugar) and allowed to obtain the desired products **3** in good to excellent yields (39–94 %). Compound **3e** (Scheme 2), bearing a hydroxyl group in the *para* position of the phenyl ring and a glucofuranose derivative, was obtained in 87 % yield by basic hydrolysis of **3d**, using hydrazine monohydrate in CH_3CN at room temperature.

As known, acetals protecting groups can be easily removed under acidic conditions. In fact, by letting compounds **3a-h** react in a mixture of CH_2Cl_2:TFA:H_2O = 40:24:1 v/v until the complete consumption of the starting material, the respective unprotected glucose and ribose cinnamic acid esters **4a-h** were obtained with yields ranging from 54 % to 96 % (Fig. 1).

Notably, compound **4e** is a natural product [40–43], which possesses a series of biological activities [44–46]. The deprotection of compound **3i** was also carried out under acidic conditions, but using a slightly different modality. In particular, **3i** was allowed to react in a mixture of $HBF_4{\cdot}Et_2O$:H_2O:CH_3CN = 1:5:500 v/v, leading to the deprotected



Scheme 2. – Room temperature oxidative alkoxycarbonylation of styrenes. for the synthesis of CASEDs **3** using 1,2-*O*-Isopropylidene-α-D-glucofuranose (**3a-g**), 1,2-*O*-Isopropylidene-α-D-ribofuranose (**3h**), *N*-Cbz-D-glucosamine (**3j**) or lactose tetraacetal LTA (**3i**) as sugars [35]. Compound **3e** is obtained by deacetylation of compound **3d**.

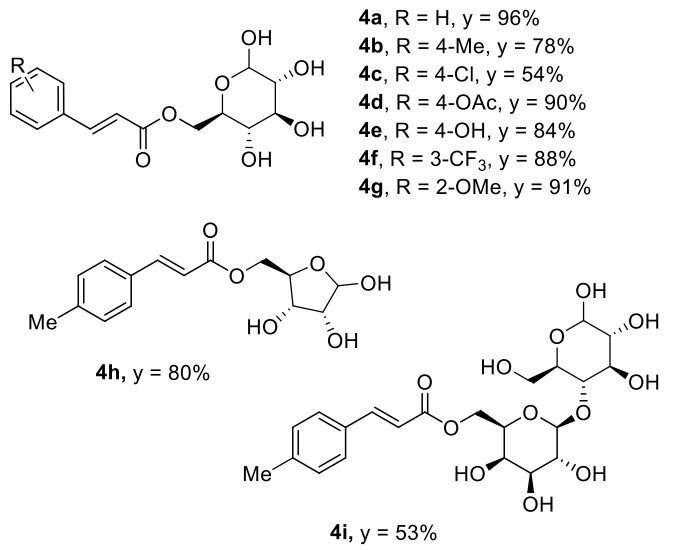


Fig. 1. Synthesized CASEDs **4**.

lactose ester **4i** as a white precipitate with 53 % yield [34].

With this small library in hand, foreseeing a possible use of our synthesized compounds as UVB filters, we proceeded to evaluate some of their biological and chemical-physical properties.

To start with, all compounds **3** and **4** were screened for their biocompatibility using a widely employed *in vitro* model of human keratinocytes (HaCaT cell line). Two different cytotoxicity tests were performed: the WST-8 assay, evaluating cell metabolic activity, and the SRB test, quantifying cell protein content. Comparable results were obtained with both tests after compound administration to HaCaT cells for 24 h. At the maximum concentration tested (100 μM), compounds **3** and **4** displayed no cytotoxic effects toward keratinocytes (cell viability not significantly different from non-treated control cells), with the exception of **3j**, showing an IC_{50} value of approximately 12 μM (see Supporting Information). It should be noted that **3j** is the only amino sugar derivative and therefore a different biological behavior can be expected.

The same molecules were also screened for their antioxidant potential using the DPPH test as a cell-free radical scavenger assay. At the concentration tested (100 μM), compounds **3** and **4** did not present a marked ability to scavenge the DPPH radicals. In fact, compound **3g**, displaying a weak but detectable scavenger capacity, had an EC_{50} value in the low millimolar range (1.45 mM) (see Supporting Information).

The UV–Vis spectra from 200 to 800 nm were then recorded in distilled water or CH_3CN/H_2O mixtures (see Supporting Information). In Table 1 the value of the wavelength of maximum absorbance (λ_{max}) and the molar absorption coefficient (ε_{max}) are reported.

For all the spectra, the strongest π → π* transition deriving from the cinnamate moiety is observed between 272 nm and 311 nm, depending on the aryl substituent. In the case of compounds **3c**, **3d**, **3e**, **4c**, **4d** and **4e**, this band overlaps another band that probably results from a n → π* transition and in the spectra of **3g** and **4g**, having an *ortho*-methoxy substituent on the aromatic ring, the two different bands can be clearly distinguished, having their maximum at 279 nm and 325 nm (see Supporting Information). Additional strong bands appear in the spectrum below 250 nm that we have not considered for our purpose, since UVC radiation (100–280 nm) does not reach earth's surface as it is blocked by the ozonosphere. As expected, the absorption spectrum in the UVB region only depends on the cinnamic acid moiety of the molecule. Indeed, almost identical bands were observed for compounds that differ only for the sugar fragment. This is particularly evident when comparing compounds **3b**, **3h**, **3i**, **3j**, **4b**, **4h** and **4i**, all containing the 3-(*p*-tolyl) acrylate fragment. Although no linear correlation is detectable, a general trend can deduced plotting the λ_{max} of the various compounds and the Hammett substituent constants σ [48], as reported in Fig. 2. In particular, it appears that the higher is the value of σ, the lower is the λ_{max}. Analogous correlations were also found for cinnamic acids [49].

Table 1
Values of λ_{max} (nm) and ε (mol^{-1}•L•cm^{-1}) in the UVB region and clogP for compounds **3** and **4**.

Entry	Compound	λ_{max} (nm)	ε•10^{-2} (mol^{-1} L•cm^{-1})	clogP[a]
1	**3a**	281	223	0.74
2	**3b**	290	235	1.09
3	**3c**	286	255	1.35
4	**3d**	282	247	0.73
5	**3e**	311	261	0.40
6	**3f**	272	215	1.59
7	**3g**	279	157	0.67
8	**3h**	292	264	1.66
9	**3i**	292	200	1.53
10	**3j**	291	230	1.61
11	**4a**	281	226	−0.36
12	**4b**	292	215	−0.02
13	**4c**	287	239	0.24
14	**4d**	283	216	−0.38
15	**4e**	311	282	−0.71
16	**4f**	273	163	0.49
17	**4g**	279	156	−0.43
18	**4h**	291	223	0.49
19	**4i**	292	252	−1.86

[a] Calculated octanol–water portion coefficient clogP (by OSIRIS Property Explorer) [47].

In Table 1, clogP [47,50] is also reported. This value can essentially be considered as a descriptor of lipophilicity that can help to predict and understand the transport and impact of compounds in physiological systems, crucial for sun care and skin care products [51–53]. As expected, compounds **4**, showing more unprotected glycosyl hydroxyl groups, are generally more hydrophilic than compounds **3**, with the lactose derivative **4i** (disaccharide derivative) being the most hydrophilic and **3h** (1,2-*O*-isopropylidene ribose derivative) the most lipophilic. As the emulsion is the most utilized type of product format for sunscreen products [54], for the new compounds **4**, the HLB (hydrophilic–lipophilic balance) [55] was also calculated (see Supporting Information).

Based on all the acquired results, we decided to synthesize compound **3k**, where the presence of the 4-methoxy substituent on the phenyl ring (as in EHMC) should produce the desired UVB absorption and the 1,2-*O*-isopropylidene ribose moiety should ensure a higher clogP. In fact, for sunscreen formulations active ingredients showing a lipophilic character are usually utilized [51–53] and comparing the clogP, for compounds having the same cinnamic fragment, 1,2-*O*-isopropylidene-D-ribose gave the best result in this sense (compare entries

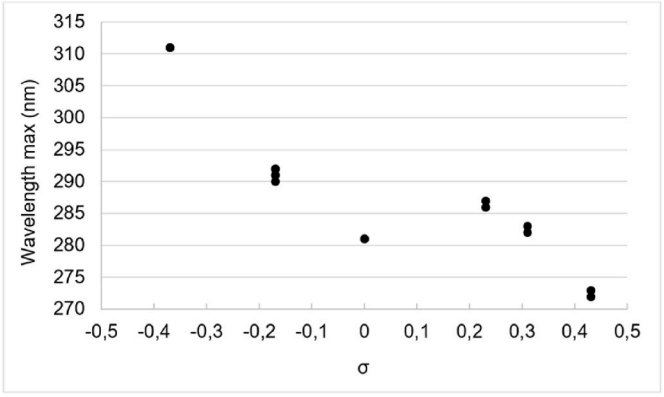


Fig. 2. Relationship between λ_{max} values for the strongest π → π* transition and σ values.

2, 8, 9, 10, 12, 18, 19 of Table 1). Since in our precedent study we observed that incomplete 1,2-*O*-isopropylidene-α-D-ribofuranose conversion occurred for a similar reaction [35], the oxidative alkoxycarbonylation reaction of this ribofuranose and the 4-vinylanisole was performed at 50 °C, which eventually afforded product **3k** in 71 % isolated yield (Scheme 3).

For CASED **3k**, the UV spectrum was registered and the clogP was evaluated (Scheme 3 and Supporting Information). Moreover, the molecule resulted to be no cytotoxic on HaCaT cells at the tested concentrations (100 μM) by both WST-8 and SRB cell viability assays (see Supporting Information). As expected, a higher lipophilicity (clogP = 1.24) with respect to most of the compounds reported in Table 1 was obtained and the UV spectra showed a band of maximum absorption at 311 nm.

We then compared our best compounds with EHMC. It is known that the UV–Vis spectrum of EHMC has a band with λ_{max} around 310 nm [56], therefore, considering both their neglectable cytotoxicity and superimposable absorption spectra, compounds **3k**, **3e** and **4e** represent our best candidates for replacing EHMC and its analogues in sun care products. Due to the high lipophilicity of EHMC its UV spectrum was recorded in CH_3CN and compared with the spectra of **3k**, **3e** and **4e**, acquired at the same concentration and in the same solvent (Fig. 3). Gratifyingly, our synthesized cinnamates show UV–Vis spectra similar to EHMC. It is worth mentioning that since these molecules possess tunable hydrophilicity, different final applications can be envisioned.

For these four compounds (i.e., EHMC, **3k**, **3e** and **4e**), we then evaluated the Sun Protection Factor (SPF) [57] as reported in Fig. 4. The values have been calculated *in vitro* utilizing UV spectrophotometry [58] (see Supporting Information).

Higher SPF values are obtained for higher amounts of active sunscreen ingredient [57]. Although this value is usually calculated for formulations or creams, pure isolated compounds can be utilized, as in this case, as they are directly compared with the EHMC [59]. According to our results, the lowest SPF values are achieved for **4e**, while compound **3e** gave higher sun protection factor values, but still lower if compared with the standard EHMC. Gratifyingly, the *ad hoc* synthesized compound **3k** exhibits slightly higher SPF values for all the concentrations tested, thus being the most promising candidate for future applications.

As detailed in Supporting Information, **3k** was also checked for its antioxidant potential both in a cell-free system using DPPH as a radical molecule, and in an *in vitro* cell model using H_2O_2 as an oxidant agent. At the concentration tested (100 μM), **3k** showed a weak capacity to scavenge the DPPH radicals, displaying an EC_{50} value in the low millimolar range (1.20 mM). Intriguingly, at the dose 100 μM, **3k** significantly reduced the intracellular oxidation levels of HaCaT cells treated with H_2O_2, revealing its ability to protect keratinocytes against the oxidative insult when coincubated with the oxidant. If pre-incubated with the cells and then removed before H_2O_2 addition, **3k** was not

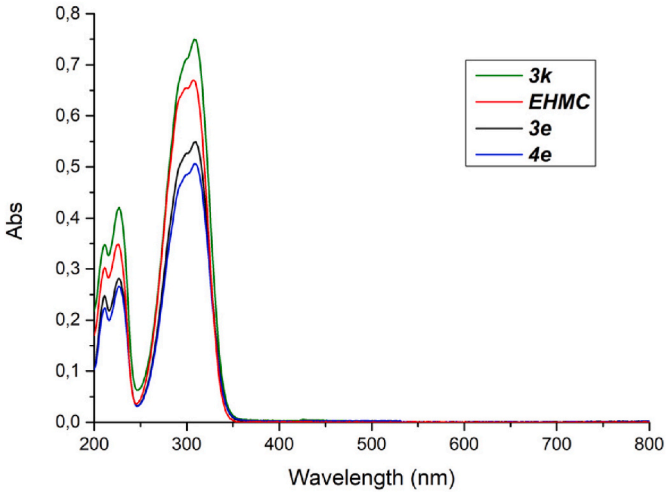


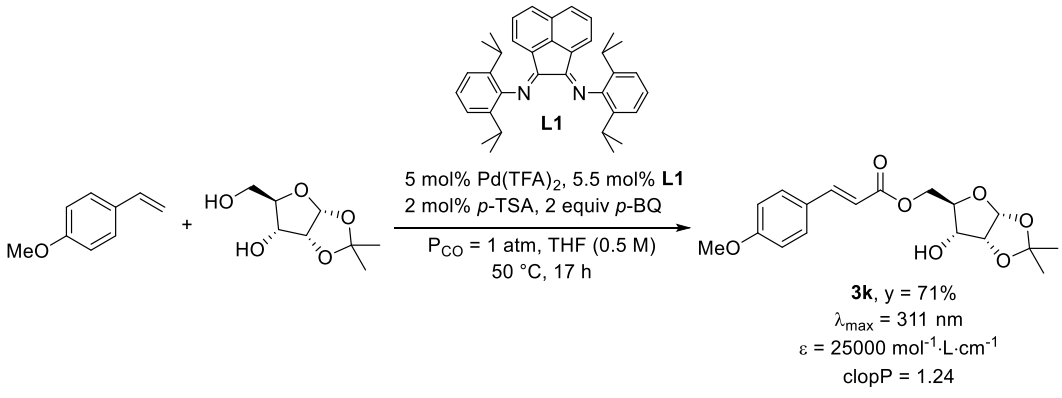
Fig. 3. UV–Vis spectra (from 200 to 800 nm) of compounds EHMC, **3e**, **3k**, **4e** (25 μM) acquired in CH_3CN.

effective in protecting HaCaT from intracellular oxidation, probably due to its low cell membrane permeability. The same antioxidant tests conducted on EHMC (100 μM) demonstrated that the standard did not present DPPH radical scavenger ability nor antioxidant properties towards H_2O_2 (see Supporting Information). Overall, these promising results on keratinocytes suggest that **3k** could provide active cell protection against UVB-induced skin oxidative damage, strongly encouraging further studies in this field. In this sense, the optimization of a model for studying the effects of UV exposure on HaCaT cells is currently under investigation in our laboratory.

4. Conclusion

A series of new glucose, ribose and lactose cinnamic acid esters **4** have been synthesized from the respective sugar acetals **3**. For all compounds **3** and **4**, the cytotoxicity, UV–Vis absorption and lipophilicity have been evaluated. Interestingly, our study shows a correlation between the Hammett constant (σ) of the substituent on the aromatic ring and the maximum absorption wavelength (λ_{max}) of the synthesized molecules. In particular, for lower values of σ, generally higher λ_{max} are observed. The lipophilicity/hydrophilicity of the synthesized CASEDs could possibly be finely tuned by the type of carbohydrate and the grade of protection of the sugar hydroxyl groups. As expected, compounds possessing the same aromatic moiety but a different saccharide exhibit almost identical UV absorption spectra but completely diverse lipophilicity (i.e., clogP).

Based on the knowledge acquired, compound **3k**, bearing a 4-



Scheme 3. Synthesis of compound **3k**, *via* oxidative alkoxycarbonylation of the 4-vinylanisole.

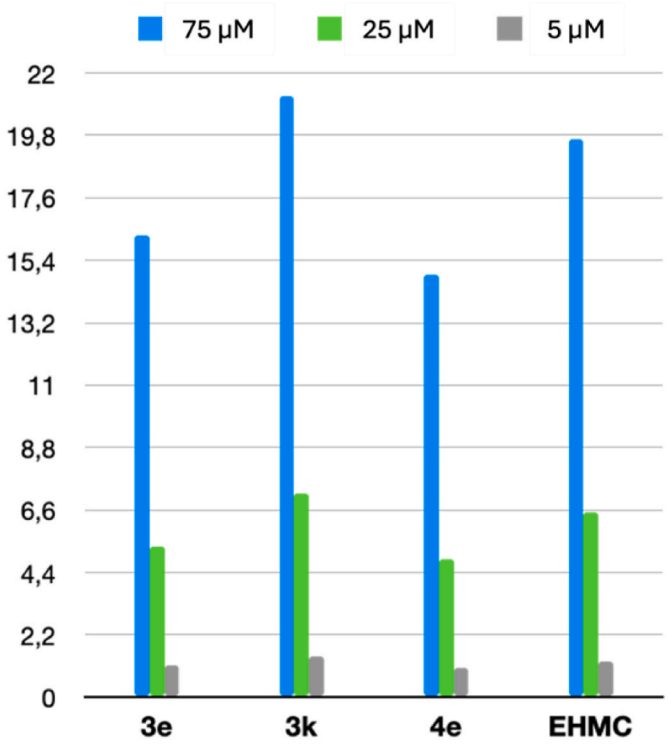


Fig. 4. SPF values for **3e**, **3k**, **4e** and EHMC at different concentrations (75 μM, 25 μM and 5 μM).

methoxy group on the cinnamic moiety and a 1,2-*O*-isopropylidene ribose fragment, was *ad hoc* synthesized and analyzed. In addition to **3k**, also compounds **3e** and the natural compound **4e**, bearing a 4-hydroxyl group on the cinnamic moiety and a pyranose fragment, have shown promising results for the replacement of the EHMC in sunscreen products. In particular, **3k** showed a higher Sun Protection Factor (SPF) value at all the tested concentrations (75 μM, 25 μM and 5 μM) with respect to EHMC, proving to be the most promising candidate for future uses. This was also confirmed by the evidence that **3k** displayed greater antioxidant properties than EHMC, by effectively protecting keratinocytes against H_2O_2-induced oxidative damage**.** At the same time, **3k** had no cytotoxic effects and well-preserved cell metabolic activity and protein content**.** Since the incorporation of sugars, possibly obtainable by waste material, clearly improves the biocompatibility of the final molecule, also allowing the easy modulation of some properties (e.g., hydrophilicity), we believe that CASEDs can actually find interesting applications in skincare and cosmetic fields. Studies are currently underway in our laboratory to evaluate the possibility of using these molecules in actual sunscreen formulations.

CRediT authorship contribution statement

Diego Olivieri: Writing – original draft, Investigation, Data curation, Conceptualization. **Michele Verboni:** Writing – original draft, Methodology, Investigation. **Serena Benedetti:** Writing – original draft, Methodology, Investigation. **Daniele Paderni:** Writing – original draft, Methodology, Investigation. **Carla Carfagna:** Writing – review & editing, Resources. **Andrea Duranti:** Writing – review & editing, Resources. **Simone Lucarini:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2025.109405.

Data availability

Data available within the article or its supplementary materials

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