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Ecocatalysed Hurtley reaction: synthesis of urolithin derivatives as new potential RAGE antagonists with anti-ageing properties

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Abstract

Two ecocatalysts Eco-MG1 and Eco-MG2 were obtained from the biomass of *Miscanthus x giganteus* cultivated *in situ* on metal-contaminated soils from the North-of-France region. Ecocatalysts have been characterized by SEM-EDS analyses and flame atomic absorption spectrometry and used to synthesize new urolithins A and B derivatives, metabolites of ellagic acid, through Hurtley reaction between polyphenols and bromobenzoic acids in water and/or in ethanol. Eco-MG2 was the most

effective catalyst in the synthesis of urolithin derivatives and exceeded the catalytic power of copper sulphate (CuSO₄) conventionally used in this benzo[*c*]chromene ring-closure Hurltley reaction. Newly synthesized urolithins **1-24** have been evaluated for their ability to inhibit the AGE2-BSA/sRAGE interaction and compared to known RAGE antagonists (Azeliragon, FPS-ZM1, etc). Urolithins showed excellent inhibitory activities equivalent to reference Azeliragon and constitute promising RAGE antagonists with anti-ageing properties. The first SAR were identified and open the way to the development of new series of experimental drugs targeting RAGE.

Introduction

Fruits and nuts, such as pomegranate, strawberry, raspberry, blackberry, grapes, walnuts, and chestnuts are widely consumed and recognized for their health benefits. These last have been associated with a high level of antioxidant polyphenols, particularly ellagitannins, which have presented various biological properties including antioxidant¹, antiviral², antimutagenic³, antimicrobial^{4, 5} and antitumor activities^{6, 7}. Ellagic acid is one of the most common hydrolysates of ellagitannins⁸, which is itself then metabolized by the action of unidentified colonic bacteria in urolithin compounds⁹, the most common found in humans and animals being urolithins A and B⁹ (Figure 1). These last consist of a benzo[*c*]chromene ring with different phenolic hydroxylation patterns. In addition to presenting many biological activities⁹⁻¹⁵, recent studies have demonstrated their anti-aging activities^{16, 17} and especially their capacity to inhibit the formation of Advanced Glycation End-products¹⁸ (AGEs).

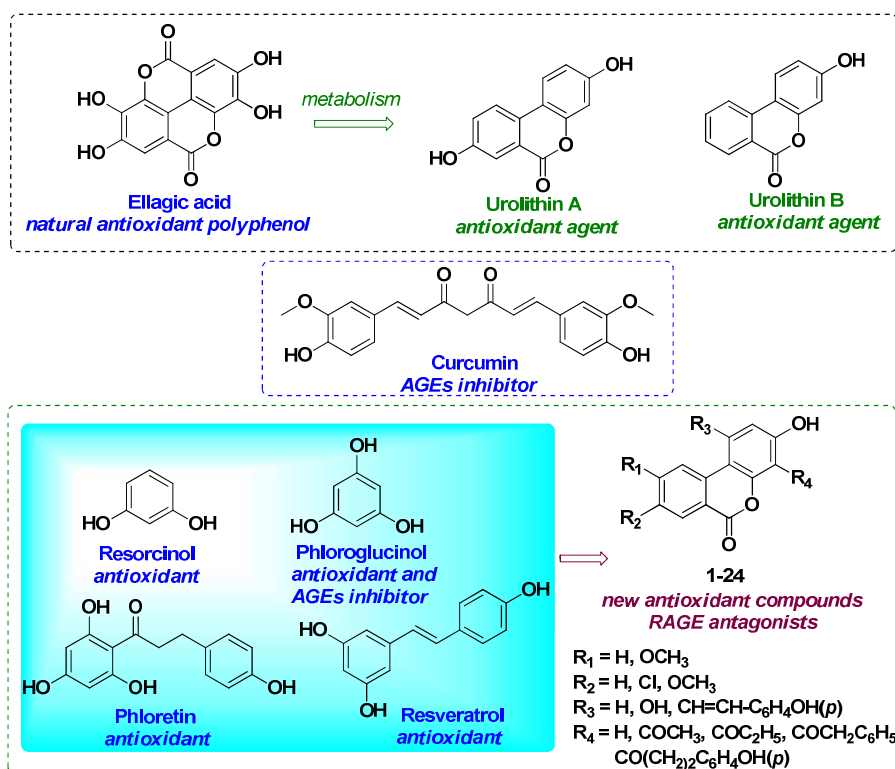


Figure 1. Structures of naturally occurring ellagic acid and urolithins A and B, of curcumin and starting reagents (resorcinol, phloroglucinol, phloretin and resveratrol) used to access new target urolithins **1-24**

Our group is interested in organic and sustainable chemistry applied to the biology of aging by studying AGEs and the consequences of their interaction with the Receptor of Advanced Glycation End-products (RAGE), as well as the development of experimental drugs targeting RAGE. We hypothesize that RAGE is at the center of multiple inflammatory mechanisms and is involved in organ senescence. RAGE acts as a key receptor involved in "inflammation" for which we are seeking to develop an innovative therapy. Blocking RAGE via antagonist molecules will prevent and control not only acute inflammation, but also chronic inflammation and aging. Consequently, this study describes the green synthetic access to new urolithin analogues **1-24** (Figure 1) and their biological evaluation as RAGE antagonists using an ELISA assay.

Important biological activities were attributed to phloroglucinol which is the main ingredient of antispasmodic marketed Spasfon® and to phloretin which is used as flavour enhancer and is present in many cosmetic formulas. The antioxidant power of these molecules is well-documented and, interestingly, phloroglucinol was also reported as moderate inhibitor of AGEs production.¹⁹ In the same manuscript, curcumin (Figure 1) was reported as slightly more efficient AGEs inhibitor than phloroglucinol (curcumin: IC₅₀ = 80.87 µg/mL and phloroglucinol: IC₅₀ = 128.9 µg/mL).¹⁹ This suggested that bulkier polyphenolic compounds may represent an interest as AGEs inhibitors. In addition to these target anti-ageing properties, the synthesis of new polyphenolic analogues is still relevant today given the plethora of their fields of use.

Since the chemical construction of the target benzo[*c*]chromene ring involved the use of metal catalysts, the most common being the copper salts, our group studied the possibility to apply ecological metal-based catalyst to access this important class of urolithins. Important areas of soils of the North of France region are highly MTE-contaminated, especially with Zn, Cd, Fe but also Cu. Consequently, the synthetic strategy was further based on the potential use of ecocatalysts to promote the benzo[*c*]chromene formation as an alternative to commercial copper salts.

Results and discussion

Ecocatalyst preparation and characterisation

In a context of green chemistry, the development of new ecomaterials which can be used as biosourced Lewis acids has become a research area of interest. This concept has been introduced by Pr. Grison a decade ago and is better known as « ecocatalysis »²⁰. This consists of using hyperaccumulative plants on metal contaminated soils which become, after metal-uptake, biomasses enriched with metals. These last are then extracted from the biomasses in the form of Lewis acids, thus constituting plant-based catalyst, also called ecocatalyst. This technology has been applied and has been effective in a wide range of chemical transformations²¹ including cross-coupling transformation such as Suzuki and Heck²² but also Ullmann reactions²³.

If the concept of ecocatalysis was originally developed from hyperaccumulating plants, recent studies have shown that it was possible to extend the technology to so-called "tolerant" plants. Indeed,

ecocatalysts have been developed by Professor Grison's team from different tree species and have been shown to be effective for Knoevenagel condensation²⁴, esterification and epoxidation reaction²⁵. Moreover, our group previously identified tolerant biomasses such as *Lolium perenne* L.^{26, 27, 28} and *Miscanthus x giganteus*^{29, 30} that have also enabled to design new ecocatalysts that have catalyzed amidification reactions^{28,30}. In this article, the new ecocatalysts obtained from *Miscanthus x giganteus* (Eco-MG) which has been produced *in situ* on heavy-metal contaminated soil were prepared and characterized.

Based on our previous studies^{29, 30}, it was shown that stems of miscanthus are the most appropriate organs to produce ecocatalyst since the concentration of metals was higher than in leaves. Consequently, stems and leaves on miscanthus were sampled separately. After extracting metals from stems using HCl 2M according to the procedure described in literature³⁰, the resulting yellow solution was concentrated under vacuum to provide a yellow-pale residue (Eco-MG1). The total concentration of metals (Cd, Pb, Zn, Fe, Mn, Cu, Ca, Mg, Na and K) measured in the mixture of salts was 295.37 g kg⁻¹. The distribution of metal was reported in Table 1 and shows that K is the predominant species (69.21%). Some other interesting catalyst precursors were measured (*e.g.* Fe, Zn, Mn, Mg, Ca), while the proportion of Cd and Pb were insignificant. These preliminary data were completed using SEM-EDS experiments. These analyses allowed to understand the distribution of predominant metal species present in the Eco-MG1 and envisage the necessity of acetone wash of the raw material to concentrate interesting catalyst precursors species such as Cu or Zn and obtain Eco-MG2. Results highlighted different domains containing high amounts of K and Cl, Na and Cl, and Ca, S and O that can be related to the presence of sylvite (KCl), halite (NaCl), anhydrite (CaSO₄). Surprisingly, other domains were rich in Mg, K and Cl (Figure 2). This domain could be composed of KMgCl₃, a very strong Lewis acid that has been already identified in other studies^{24,25}. Due to the high proportion of K in Eco-MG1, a part of it was washed with acetone in order to separate a large amount of K from the other cations. After washing, the resulting solution has been concentrated under vacuum to obtain a white powder (Eco-MG2). The total concentration of metals was 465.56 g kg⁻¹ and the distribution of them (Table 1), confirmed an enrichment in metals of interest (Zn, Fe, Mg). The Figure 3 clearly shows the

presence of metals like Zn, Fe, Mn, Mg, Ca, K and Na. Other elements appeared (*e.g.* P, O) and domains with P, O and Mg were highlighted suggesting the presence of magnesium phosphate ($\text{MgP}_4\text{O}_{11}$). Further analyses are necessary to identify the crystalline phases (*e.g.* KMgCl_3 , K_2ZnCl_4) in this second ecocatalyst Eco-MG2.

Table 1. Distribution of metals in Eco-MG1 and Eco-MG2

Material	Distribution of metals (%)									
	Cd	Pb	Zn	Fe	Mn	Cu	Ca	Mg	Na	K
Eco-MG1 ^a	0.05	1.16	2.62	1.66	0.27	0.61	16.26	3.93	4.21	69.21
Eco-MG2 ^b	0.52	13.06	28.33	16.66	2.60	7.00	6.30	22.76	1.00	1.78

^aEco-MG1=crude Lewis acids obtained after treating ashes with 2M HCl aqueous solution

^bEco-MG2=crude Lewis acids obtained after washing with acetone Eco-MG1

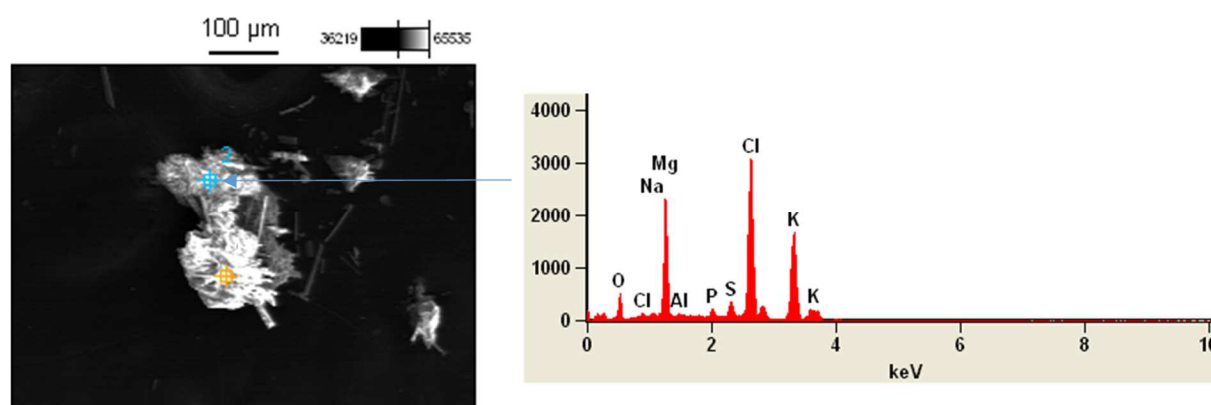


Figure 2. SEM image and EDS spectrum of Eco-MG1

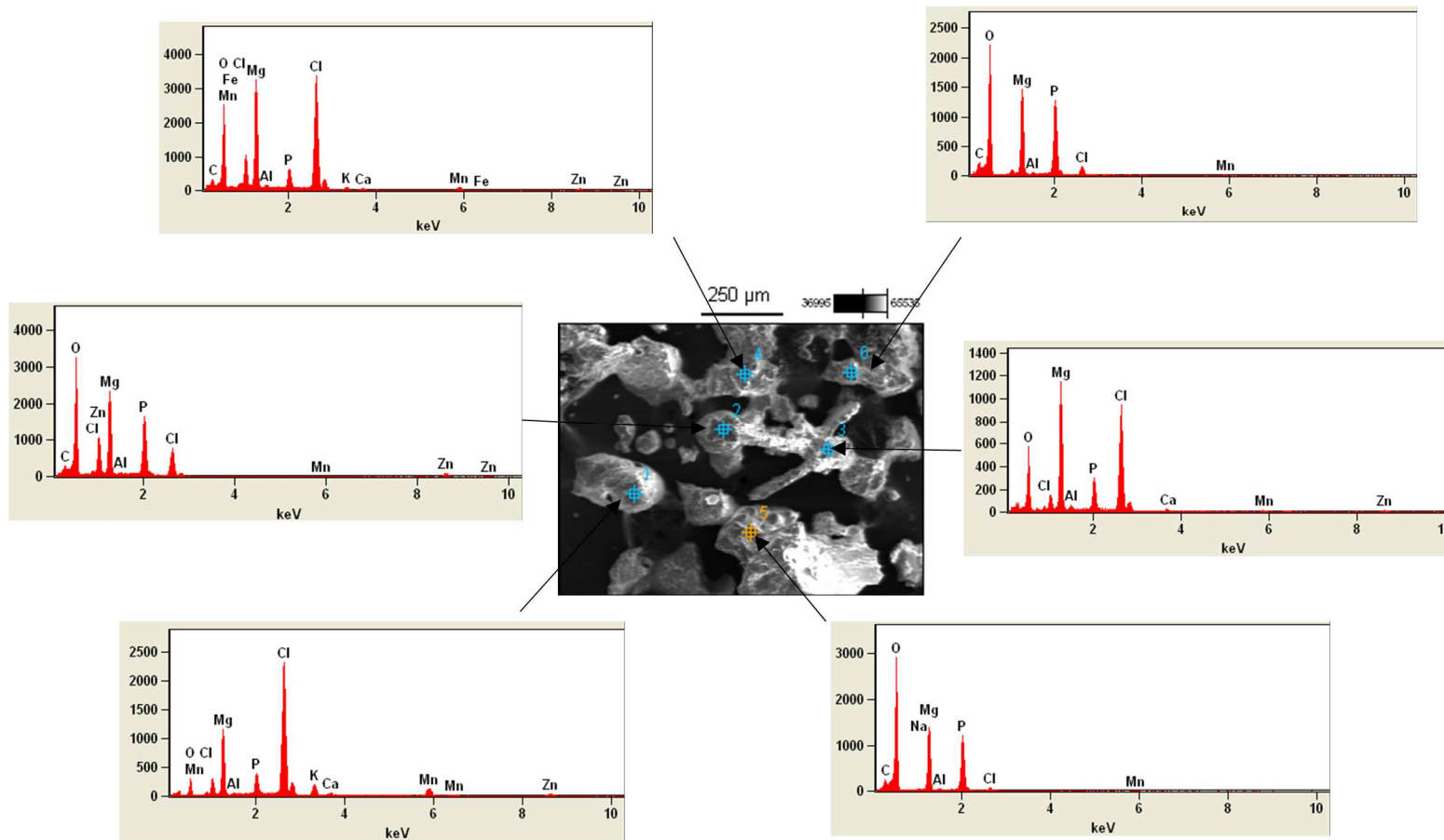


Figure 3. SEM image and EDS spectrum of Eco-MG2

Ecocatalyzed synthesis of urolithin B derivatives

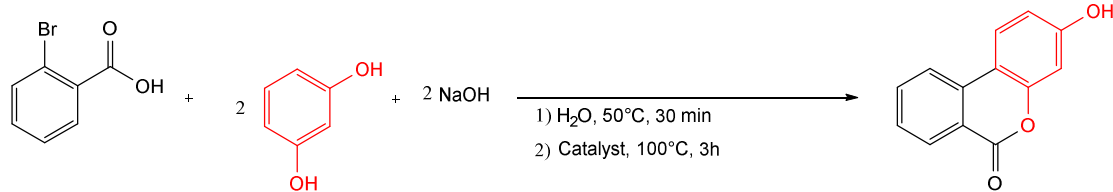
Several synthetic pathways exist to produce urolithin compounds such as Suzuki-Coupling,³¹ Kolbe oxidative cyclization,³² intramolecular biaryl coupling of 2-halobenzoates³³ including the basic strategy of Bringmann's 'lactone concept'³⁴ or Pechmann reaction³⁵, but the most common method is the Hurtley reaction (often seen as a sub-category of Ullmann's reaction³⁶ which has been discovered almost a century ago³⁷ by reacting 2-bromobenzoic acid with resorcinol using Cu-based Lewis acid as catalyst. In this section, the comparison of the catalytic activities of the miscanthus-based ecocatalysts with conventional commercial Cu-based catalytic species to synthesize urolithin derivatives through Hurtley reaction was realized systematically. Starting materials of natural origin (resorcinol, phloroglucinol, phloretin and resveratrol, Figure 1) were used in a major part of syntheses. The reactions were carried out in water and/or in ethanol. The reaction media resulted systematically in complete dissolution of reagents and catalyst.

The model reaction was the synthesis of urolithin B **1**. First, the reaction of 2-bromobenzoic acid with resorcinol in aqueous sodium hydroxide and in the absence of catalyst only provided urolithin B **1** in very low 5% yield (entry 1, Table 2). This underlined the importance of the catalyst for this transformation. Using the initial protocol with 1.6 wt% (2 mol%) CuSO₄ as catalyst¹² resulted in 61% yield of urolithin B **1** (entry 2, Table 2). The first designed eco-catalyst Eco-MG1 was tested at different ratios (10 wt% to 50 wt%) in the same Hurtley reaction and the final yield did not exceed 32% (entries 3-8, Table 2), Eco-MG1 displaying reduced catalytic efficiency compared to commercial CuSO₄. Conversely, Eco-MG2 showed improved potential allowing a maximum of 70% yield of urolithin B **1**, reached when using 6 wt% of ecocatalyst (entry 12, Table 2). The reduction of the catalytic charge (3 wt%, 1.5 wt% then 1 wt%) gradually reduced the yield of the reaction to 41%, 34% and 30%, respectively (entries 9-12, Table 2), while the increase in the catalytic load to 10 wt% did not permit to exceed the efficiency of 70% yield obtained using 6 wt% also (entry 13, Table 2). Next, the influence of different copper salts was studied (entries 14-16, Table 2). Interestingly, copper (II) chloride showed equipotent catalytic activity as Eco-MG2 (entry 14, Table 2). The oxidation state of copper does not seem to have a major impact on the reaction progress since the use of copper (I)

chloride resulted in 62% slightly decreased yield while the copper (I) iodide was beneficial and exceeded the catalytic effectiveness of the other considered catalysts (77% yield) (entries 15 and 16, Table 2). Similar yield was obtained by using classical Ullmann conditions previously described by our group (0.5 eq. CuI, 1 eq. *N,N'*-DMEDA, 2 eq. Cs₂CO₃, dioxane, under inert atmosphere).³⁸ Although we have not carried out any mechanistic study, it is reasonable to postulate a mechanism similar to Ullmann-type reactions for the formation of urolithin B.

Since the ecocatalysts contain multiple metallic species (*e.g.* Cu, Zn, Cd, Pb, Mn and Fe), the commercial corresponding Lewis acids were next tested (2 mol% of metal) in order to learn more about active species responsible of the catalytic efficiency. The use of ZnCl₂, CdCl₂ and PbCl₂ was detrimental for the reaction progress, inducing only 11-14% yields of urolithin B (entries 17-19, Table 2). The manganese salts (MnSO₄ and MnCl₂) were completely ineffective and did not show any catalytic power. The final yields were similar to the reaction realized in the absence of catalyst (compare entries 20, 21 and 1, Table 2). On the contrary, pure iron chlorides (FeCl₂ and FeCl₃) were more effective and allowed to obtain urolithin B in 28% and 10% yield, respectively (entries 22 and 23, Table 2). This study suggested that the interesting catalytic activity of bio-sourced Eco-MG2 was due to a synergistic effect of its metallic species and no pure Lewis acid tested was responsible of the catalytic activity alone.

Additional experiments were carried out by varying the amount of NaOH and resorcinol but these were not conclusive, they permitted to verify that, according to what was described in the presence of CuSO₄,¹² 2 eq. of NaOH and 2 eq. of resorcinol were necessary to obtain a good yield >60%.

Table 2. Catalytic study of the Urolithin B synthesis

Entry	Catalyst	Eq (w/w) ^a	Yield (%)
1	-	-	5
2	CuSO ₄	0.016 ^b	61
3	Eco-MG1	0.010	11
4	Eco-MG1	0.050	16
5	Eco-MG1	0.100	20
6	Eco-MG1	0.150	26
7	Eco-MG1	0.200	30
8	Eco-MG1	0.500	32
9	Eco-MG2	0.010	30
10	Eco-MG2	0.015	34
11	Eco-MG2	0.030	41
12	Eco-MG2	0.060	70
13	Eco-MG2	0.100	70
14	CuCl ₂	0.013 ^b	70
15	CuCl	0.010 ^b	62
16	CuI	0.019 ^b	77
17	ZnCl ₂	0.014 ^b	11
18	CdCl ₂	0.018 ^b	13
19	PbCl ₂	0.028 ^b	14
20	MnSO ₄	0.015 ^b	5
21	MnCl ₂	0.012 ^b	6
22	FeCl ₂	0.012 ^b	28
23	FeCl ₃	0.016 ^b	10

(a) Regarding bromobenzoic acid reactant

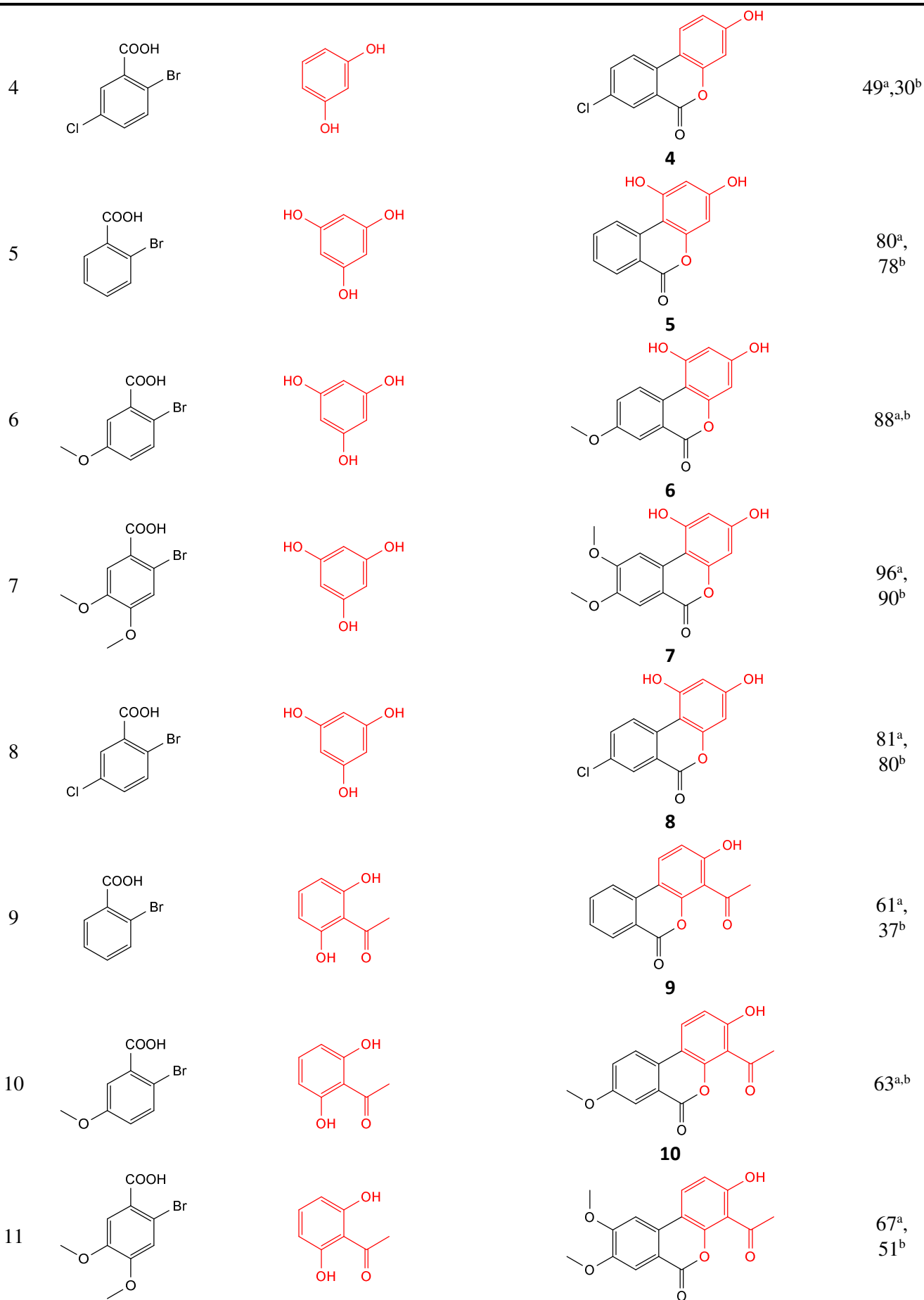
(b) 2% mol of metals

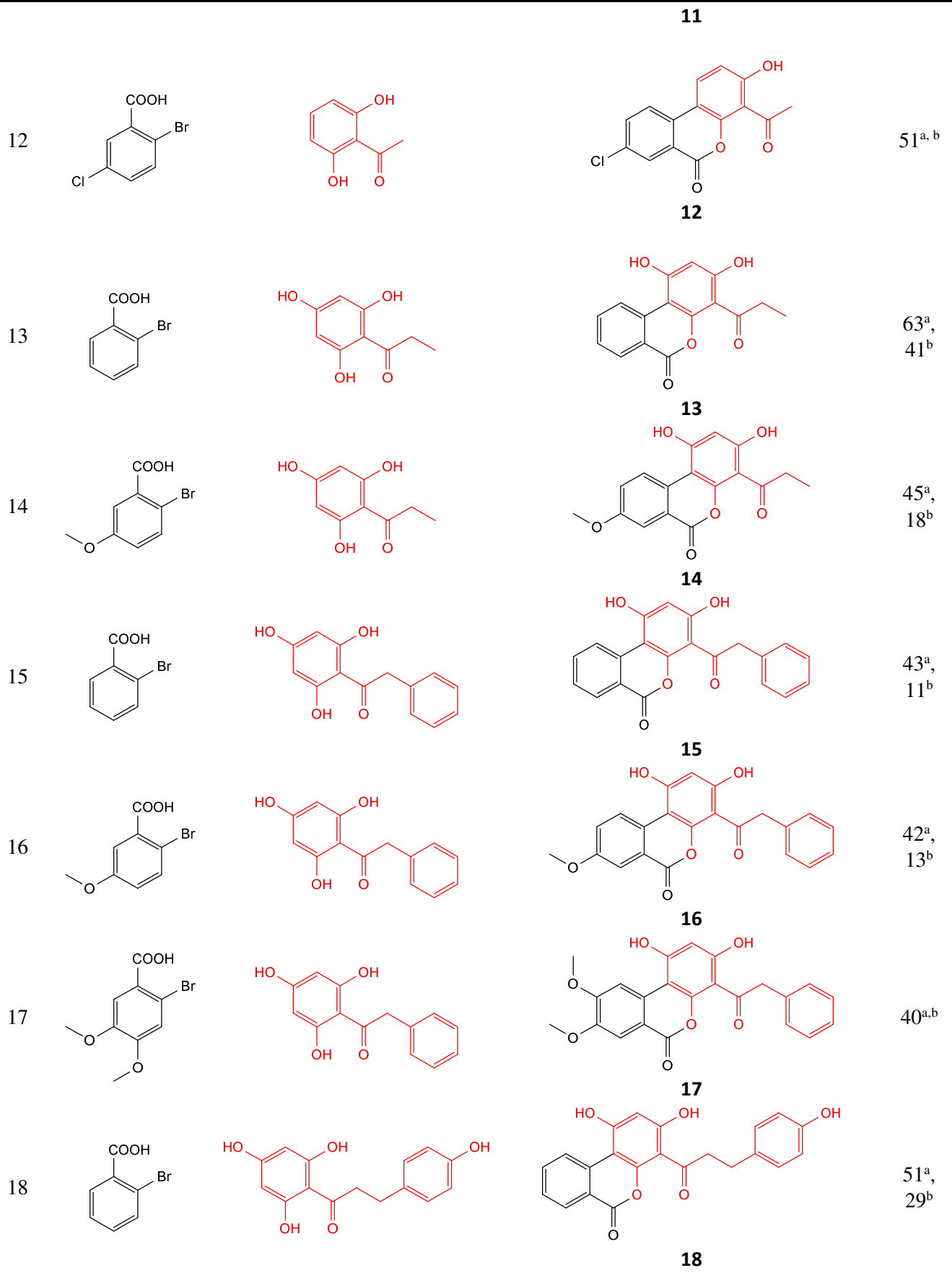
The reagents and the biosourced catalyst being selected (entry 12, Table 2), efforts were deployed to obtain a series of natural and synthetic urolithin analogues **1-24**. Reactions were conducted in water and/or ethanol. The different bromobenzoic acids and polyphenols used as starting materials are reported in Table 3. All reactions were carried out in duplicate and by systematically comparing the efficacy of Eco-MG2 to that of classical CuSO₄. Compounds **1-24** have been synthesized in variable yields (Table 3). Eco-MG2 showed superior catalytic activity in most of the transformations carried out (entries 1-5, 7, 9, 11, 13-16, 18, 19, 21 and 22, Table 3) or equivalent to CuSO₄ in some cases

(entries 6, 8, 10, 12, 17, 20 and 24, Table 3). The bromobenzoic acids substituted by a chloro unit were the least reactive and resulted in yields inferior to their methoxy-substituted congeners (compare entries 2 and 4, 10 and 12, 22 and 24, Table 3). The best yields were registered in the reaction of phloroglucinol with 2-bromobenzoic acids (entries 5-8, Table 3, ranging from 80 to 96%) and the most modest were observed with resveratrol as starting material (entries 21-24, Table 3, ranging from 6 to 54%). Compounds **8-24** have been synthesized for the first time and were fully characterized (see Supplementary information section). To be noted, the same reaction carried out with 3-aminophenol or 3-mercaptophenol and 2-bromobenzoic acid did not allow to obtain the corresponding products, highlighting the specificity of this reaction for polyphenols.

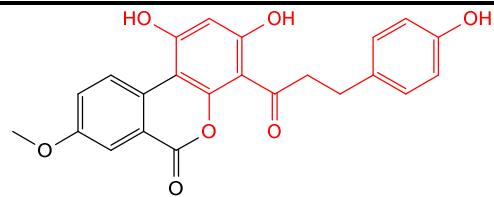
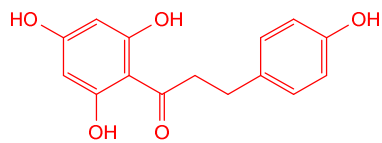
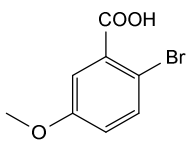
Table 3. Synthesis of urolithin derivatives

Entry	Bromobenzoic acid	Polyphenol	Product	Yield (%)
1				70 ^a , 61 ^b
2				78 ^a , 62 ^b
3				80 ^a , 75 ^b



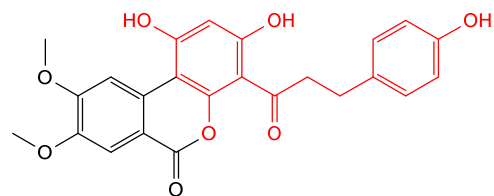
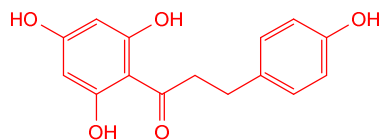
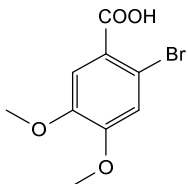


19

52^a,
35^b

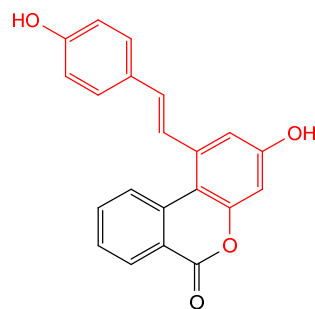
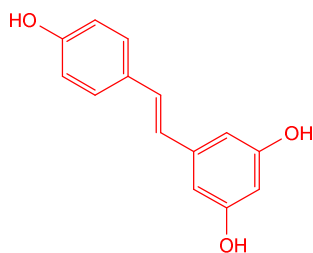
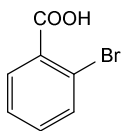
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20

54^{a,b}

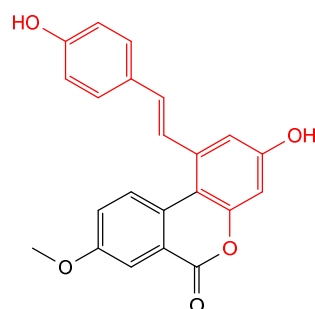
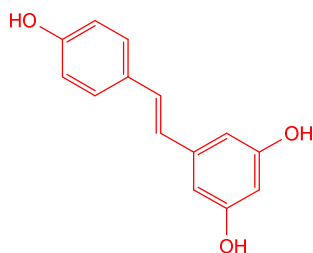
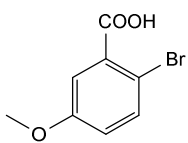
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21

50^a,12^b

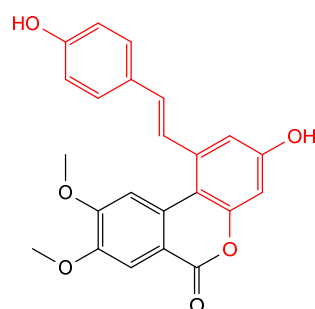
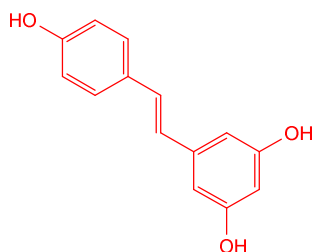
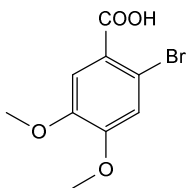
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22

54^a,
13^b

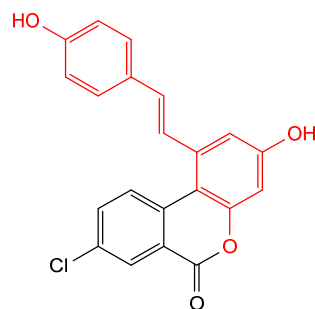
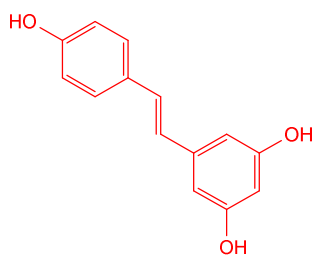
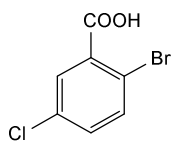
22

23

47^{a,b}

23

24

6^a,5^b

-
- (a) Yield obtained with Ecocat-MG2
(b) Yield obtained with CuSO₄

Biological evaluation

The inhibitory activity of the experimental drug candidates **1-24** was evaluated against AGE2-BSA/sRAGE binding using the Creative BioMart® ELISA kit according to the manufacturer's instructions. Plates were pre-coated with AGE2-BSA, which can bind to recombinant His-tagged sRAGE. Horse radish peroxidase (HRP)-conjugated anti-His-tag monoclonal antibody specifically reacted with recombinant His-tagged sRAGE that was trapped with AGE2-BSA immobilized on the microplate well surface. Finally, an incubation with a substrate chromogenic reagent (TetraMethylBenzidine) was realized. The effective inhibition was measured spectrophotometrically and resulted in a decrease in the staining of the medium of the well compared to the well containing no experimental drug. The wells were washed and the relative amounts of the His-tagged sRAGE in the wells were evaluated spectrophotometrically using Horse radish peroxidase (HRP)-conjugated anti-His-tag monoclonal antibody. Known RAGE antagonists have been used as positive references: Azeliragon, FPS-ZM1, curcumin, urolithins A and B and papaverine, while DMSO was used as a negative control. Azeliragon is currently one of the most promising RAGE antagonists, reaching phase III clinical trials to prevent the advancement of the disease in patients with mild Alzheimer's disease and the only experimental RAGE antagonist to have been studied in clinical trials so far.³⁹ FPS-ZM1 was also described as a potent RAGE antagonist.⁴⁰ Curcumin and urolithins are inhibitors of the production of AGEs,^{18,19} while papaverine was identified as inhibitor of HMGB1/RAGE interaction, HMGB1 being an excellent RAGE ligand and critical for acute and chronic inflammatory disorders.⁴¹ All the starting materials resorcinol, phloroglucinol, 2,6-dihydroxyacetophenone, 2',4',6'-trihydroxypropiofenone, 2',4',6'-trihydroxy-2-phenylacetophenone, phloretin and resveratrol were also evaluated to estimate the contribution of the chemical modulations carried out on these raw materials on the biological activity of final products and conclude on the interest of these modulations. Compounds were first tested at initial concentration of 100 µM or at 10 µM for references Azeliragon and papaverine and molecules displaying more than 70% inhibition rate of AGE2-BSA/sRAGE were selected for further IC₅₀ value determination. Results are illustrated in Table 4. To be noted, the starting materials showed no inhibition potential of AGE2-BSA/RAGE interaction at 100 µM concentration (entries 1-7, Table 4), while the newly synthesized

urolithin derivatives showed excellent inhibitory activities (entries 8-31, Table 4). For the reference FPS-ZM1, we did not obtain any inhibition in this assay (entry 33, Table 4). This result corroborated well with that recently published by Mizukami et al.⁴² Indeed, FPS-ZM1 was not efficient to inhibit the AGE-RAGE interaction using the ELISA Circulex AGE-RAGE *in vitro* Binding Assay kit (MBL, Nagoya, Japan).⁴² On the contrary, Azeliragon was identified as effective inhibitor of the AGE2-BSA/sRAGE interaction with an IC₅₀ value of approximately 10 μM (entry 32, Table 4). This value was in perfect agreement with that found by Mizukami et al. and defined as 13.4 ± 2.8 μM.⁴² Urolithin A was less active than urolithin B **1** (compare entries 34 and 8, Table 4) showing 20% inhibition *versus* 76%. Urolithin B **1** was indeed identified as a promising inhibitor of AGE2-BSA/sRAGE interaction with a value of IC₅₀ of 25.3 μM. Curcumin and papaverine showed moderate inhibitory effects with 43% inhibition at 100 μM concentration and 26% inhibition at 10 μM concentration, respectively (entries 35 and 36, Table 4).

Now, based on the results obtained with urolithin B **1** derivatives **2-24**, some important structure-activity relationships could be established: *i*) the benzo[*c*]chromene derivatives are favorable to inhibit the interaction of s-RAGE with its ligand AGE2-BSA, blocking their binding and consequently, benzo[*c*]chromene derivatives may present an interest in blocking the inflammatory biological phenomena triggered following this binding and activation of RAGE; *ii*) four points of chemical modulation have been studied (positions 1, 4, 8 and 9 of the benzo[*c*]chromene ring); the presence of the hydroxy substituent in position 1 was tolerated and generally improved the inhibition potential (compare compounds **3** and **7**); *iii*) the bulky substituents in position 1 or in position 4 of the benzo[*c*]chromene ring diminished the biological activity (compare compounds **9-11** to **15-17** and **21-24**, Table 4); *iv*) the OMe substituent in position 8 seemed favorable for the inhibition of AGE2-BSA/sRAGE interaction, especially when the positions 3 and 4 were substituted with a hydroxy and a small propanoyl group, respectively (*e.g.* compare compounds **2** (IC₅₀=31.6 μM), **6** (IC₅₀=14.2 μM) and **14** (IC₅₀=17.6 μM), Table 4) while the Cl substitution was less tolerated (compound **4** (51% inhibition at 100 μM) and compound **8** (44% inhibition at 100 μM), Table 4); *v*) in the same line, the presence of two methoxy substituents in positions 8 and 9 was tolerated only when the position 4 was unsubstituted (*e.g.* compound **5** (IC₅₀=67.3 μM) and compound **7** (IC₅₀=12.8 μM), Table 4). Moreover, urolithin B **1** has been selected by the National Cancer Institute (NCI) (Germantown, USA) for biological evaluation of the cytotoxic potential on a panel of 60 cancer cell lines. No cytotoxicity was observed for urolithin B **1** at a 10 μM concentration. This result consolidates the

positioning of urolithin derivatives as safe RAGE antagonists with interesting potential for further development of urolithin-inspired drug candidates (see supplementary information section for full graph of one-dose NCI assay of urolithin B **1** tested at 10 μ M concentration).

Table 4. AGE2-BSA/sRAGE inhibitory activity of urolithin derivatives **1-24** and of known positive references

Entry	Compound	% Inh AGE2-BSA/sRAGE ^[a,b]	IC ₅₀ (AGE2-BSA/sRAGE) μ M
1	Resorcinol	0	N.D.
2	Phloroglucinol	0	N.D.
3	2,6-Dihydroxyacetophenone	0	N.D.
4	2',4',6'-Trihydroxypropiophenone	0	N.D.
5	2',4',6'-Trihydroxy-2-phenylacetophenone	0	N.D.
6	Phloretin	0	N.D.
7	Resveratrol	0	N.D.
8	1	76	25.3
9	2	100	31.6
10	3	100	29.7
11	4	51	N.D.
12	5	88	67.3
13	6	91	14.2
14	7	92	12.8
15	8	44	N.D.
16	9	100	34.8
17	10	100	34.5
18	11	89	65.0
19	12	66	N.D.
20	13	5	N.D.
21	14	72	17.6
22	15	53	N.D.
23	16	69	N.D.
24	17	58	N.D.
25	18	62	N.D.
26	19	58	N.D.
27	20	62	N.D.
28	21	38	N.D.
29	22	63	N.D.
30	23	66	N.D.
31	24	26	N.D.
32	Azeliragon	49 ^[c]	N.D.
33	FPS-ZM1	14	N.D.
34	Urolithin A	20	N.D.
35	Curcumin	43	N.D.
36	Papaverine	26 ^[c]	N.D.

[a] Inhibition of AGE2-BSA/sRAGE interaction at a 100 μ M concentration. [b] Values represent mean of three experiments. [c] Tested at 10 μ M concentration. N.D. Not determined.

Conclusion

In summary, two miscanthus-based ecocatalysts Eco-MG1 and Eco-MG2 have been produced and successfully investigated as green alternative catalysts for the Hurtley reaction of polyphenols with 2-bromobenzoic acids to produce urolithin derivatives **1-24**. Eco-MG2 displayed excellent catalytic activity compared to classical CuSO₄ catalyst used for this

transformation. In a context of environmental respect, the purity of final compounds has been analysed by SFC, a green analytical technique. Natural and synthetic urolithins **1-24** have been evaluated for their inhibitory activity of the AGE2-BSA/s-RAGE interaction and displayed excellent potential, equipotent to Azeliragon, the most advanced molecule to date in drug development as a RAGE antagonist. Important SAR features have been identified. Further biological studies will be realized *in vitro* and *in vivo* to explore the potential positioning of urolithins as nutraceutical and/or pharmacological anti-ageing agents.

Experimental section

Reagents and products characterization

Plant samples were collected from 5 to 6 years old *Miscanthus x giganteus* plantations established at a density of 20,000 plants ha⁻¹ in contaminated agricultural plots located not far away from the former Metaleurop Nord plant (Hauts-de-France region, France). Reagents and solvents were purchased from commercial sources (TCI Europe N.V., Sigma Aldrich, Acros Organics) and were used without further purification.

Conception of biosourced catalysts

668 g of miscanthus stems powder were transformed into ashes in a muffle furnace (Nabertherm P330, Lilienthal, Germany) and treated with HCl following the procedure detailed in Guérin et al.³⁰ The resulting solid was dried at 80 °C for 12 h, to provide 26.7 g of a white powder. From this, 6.7 g were used as such and constituted the crude ecocatalyst (Eco-MG1) and the remaining 20 g were washed with acetone with a weight/ratio powder/acetone: 1/20 at 20 °C during 2 h in order to solubilize some metallic salts. The suspension was then filtered on sintered glass and the filtrate was evaporated to dryness to provide 0.751 g of purified ecocatalyst (Eco-MG2).

Analysis of ashes and biosourced catalysts

The concentration of heavy (Cd, Pb, Zn, Cu, Mn and Fe), alkali (Na and K) and alkaline earth (Ca and Mg) metals in the mixture of extracted Lewis acids from plants were determined by flame atomic absorption spectrometry (AA-6800, Shimadzu, Tokyo, Japan) following the recommendations described in the literature²⁶. Moreover, microstructures of the two biosourced catalysts were examined using scanning electron microscope (SEM; Hitachi S-4300SE/N) fitted with a Thermo Scientific Ultra Dry energy dispersive X-ray spectrometer (EDS) in order to assess structural chemical analyses⁴³.

Synthetic chemistry

Nuclear Magnetic Resonance (NMR) spectra were acquired at 400 MHz for ¹H NMR and at 100 MHz for ¹³C NMR, on a Varian 400-MR spectrometer at 25 °C with tetramethylsilane (TMS) as internal standard, DMSO- δ_6 . Chemical shifts (δ) are expressed in ppm relative to TMS. Splitting patterns are designed: s, singlet; d, doublet; t, triplet; q, quadruplet. Coupling constants (J) are reported in Hertz (Hz).

Melting points were measured on a MPA 100 OptiMelt® apparatus and are uncorrected. IR spectra were recorded on an Agilent Technologies FT-IR Cary 630. Flash chromatography was performed with a CombiFlash Rf Companion (Teledyne-Isco System) using RediSep packed columns.

The purity of final compounds has been verified by supercritical fluid chromatography (SFC), a green analytical technique using a binary mobile phase consisting of CO₂ in supercritical state and a small volume of organic co-solvent (ethanol was used as co-solvent in this study) compared to classical liquid chromatography (see Supplementary Information section for SFC chromatograms of synthesized compounds). The chiral analytical column used for this study, was a C18 column, purchased from Chiral Technologies Europe (Illkirch, France). This column had dimensions 250 mm x 4.6 mm i.d. with 5 μ m particle size and was coated on a silica-gel support. The chromatographic system used was an SFC-PICLAB hybrid 10-20 apparatus (PIC Solution, Avignon, France) equipped with an autosampler comprised a 48-vial plate and a 24-vial plate (model Alias, Emmen, Netherlands), three model 40P pumps: two for CO₂ and a third for the modifier (Knauer, Berlin, Germany), a column oven with a Valco ten-position column selection valve, and a Valco six-position solvent

switching valve. The pressure was 150 bars, the mobile phase was EtOH/CO₂ 30/70 and the flow 4 mL/min.

LC-MS was accomplished using an HPLC combined with a Surveyor MSQ (Thermo Electron) equipped with APCI source.

General procedure for the synthesis of urolithin-type compounds 1-24

In a 50 mL round-bottom flash equipped with a magnetic stirrer were added the bromobenzoic acid (0.5 g, 1 equiv.), sodium hydroxide pellets (2 equiv.), the 1,3-diphenol derivative (2 equiv.) and 3 mL of water (or a 1/1 mixture of water-absolute ethanol). The reaction medium was stirred at 50 °C until homogenization, and the cocatalyst Eco-MG2 was then added (6% wt, regarding the bromobenzoic acid). The resulting mixture was stirred at 100 °C for 3 h. After cooling to room temperature, the crude solid product was isolated and purified by a simple filtration of the reaction medium followed by washing with absolute ethanol or purified by flash chromatography using *n*-heptane/EtOAc 100/0 to 0/100 as eluent on silica pre-packed column only when recrystallization has failed. After crystallization from EtOH or flash chromatography purification, urolithin B and derivatives have been analyzed by Electrothermal Atomic Absorption Spectroscopy (ETAAS) to highlight possible traces of metals due to the cocatalyst. The concentrations of metals were below the limit of detection of the equipment (*e.g.* LD_{Cd}=0.02 µg/L; LD_{Pb}=0.06µg/L).

3-Hydroxy-6H-benzo[c]chromen-6-one (Urolithin B) (1). The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and resorcinol (0.548 g, 4.98 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **1** as a beige solid in 70% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.76 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 6.85 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-*H*), 7.57 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-*H*), 7.89 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-*H*), 8.18 (td, *J* = 7.7, 1.1 Hz, 1H, Ar-*H*), 8.27 (d, *J* = 8.6 Hz, 1H, Ar-*H*).

3-Hydroxy-8-methoxy-6H-benzo[c]chromen-6-one (2). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and resorcinol (0.476 g, 4.32 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **2** as a beige solid in 78% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.89 (s, 3H, OCH₃), 6.74 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar-*H*), 7.49 (dd, *J* = 8.8, 3.0 Hz, 1H, Ar-*H*), 7.60 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 8.08 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 8.20 (d, *J* = 8.7 Hz, 1H, Ar-*H*).

3-Hydroxy-8,9-dimethoxy-6H-benzo[c]chromen-6-one (3). The general procedure was used with 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and resorcinol (0.422 g, 3.84 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **3** as a beige solid in 80% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.87 (s, 3H, OCH₃), 4.01 (s, 3H, OCH₃), 6.72 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 6.82 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar-*H*), 7.52 (s, 1H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 8.16 (d, *J* = 8.4 Hz, 1H, Ar-*H*).

8-Chloro-3-hydroxy-6H-benzo[c]chromen-6-one (4). The general procedure was used with 2-bromo-5-chlorobenzoic acid (0.5 g, 2.12 mmol) and resorcinol (0.467 g, 4.24 mmol) in 3 mL of water. The

product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **4** as a brown solid in 49% yield; mp (EtOH): 170-172 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.73 (s, 1H, Ar-*H*), 6.84 (d, *J* = 9.3 Hz, 1H, Ar-*H*), 7.90 (d, *J* = 9.3 Hz, 1H, Ar-*H*), 8.08 (s, 1H, Ar-*H*), 8.13 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 8.26 (d, *J* = 9.2 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 102.9 (CH), 108.3 (CH), 113.4 (CH), 120.3 (C), 123.9 (C), 124.9 (CH), 128.4 (CH), 131.6 (C), 134.0 (CH), 135.0 (C), 152.1 (C), 159.5 (C), 160.7 (C). IR ν (cm⁻¹): 3295 (C-OH), 1696 (C=O), 1629 (C=C), 1599 (C=C). LC/MS (APCI⁺) *m/z* 247.35 (MH⁺) (calcd for C₁₃H₇ClO₃: 246.65 g/mol), tr 3.26 min.

*1,3-Dihydroxy-6H-benzo[*c*]chromen-6-one (5)*. The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and phloroglucinol (0.628 g, 4.98 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **5** as a beige solid in 80% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.27 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 6.41 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 7.46 (t, *J* = 7.5, 1H, Ar-*H*), 7.80 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 8.16 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 8.94 (d, *J* = 7.5 Hz, 1H Ar-*H*).

*1,3-Dihydroxy-8-methoxy-6H-benzo[*c*]chromen-6-one (6)*. The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and phloroglucinol (0.542 g, 4.32 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **6** as a beige solid in 88% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.88 (s, 3H, OCH₃), 6.26 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 6.40 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 7.46 (dd, *J* = 8.8, 2.8 Hz, 1H, Ar-*H*), 7.63 (d, *J* = 2.8 Hz, 1H, Ar-*H*), 8.92 (d, *J* = 8.8 Hz, 1H, Ar-*H*).

*1,3-Dihydroxy-8,9-dimethoxy-6H-benzo[*c*]chromen-6-one (7)*. The general procedure was used with 0.5g of 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and phloroglucinol (0.484 g, 3.84 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **7** as a beige solid in 96% yield with the same physico-chemical characteristics as previously reported;¹² ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.87 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 6.25 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 6.39 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.57 (s, 1H, Ar-*H*), 8.58 (s, 1H, Ar-*H*).

*8-Chloro-1,3-dihydroxy-6H-benzo[*c*]chromen-6-one (8)*. The general procedure was used with 2-bromo-5-chlorobenzoic acid (0.5 g, 2.12 mmol) and phloroglucinol (0.535 g, 4.24 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **8** as a beige solid in 81% yield; mp (EtOH): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.28 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.42 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.88 (dd, *J* = 8.5, 2.7 Hz, 1H, Ar-*H*), 8.11 (d, *J* = 2.7 Hz, 1H, Ar-*H*), 8.96 (d, *J* = 8.5 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 95.1 (CH), 98.0 (CH), 99.8 (C), 120.0 (CH), 127.9 (C), 128.1 (CH), 130.4 (C), 134.1 (C), 134.7 (CH), 153.1 (C), 157.6 (C), 159.5 (C), 159.6 (C). IR ν (cm⁻¹): 3183 (C-OH), 1703 (C=O), 1602 (C=C), 1562 (C=C). LC/MS (APCI⁺) *m/z* 263.36 (MH⁺) (calcd for C₁₃H₇ClO₄: 262.65 g/mol), tr 3.52 min.

*4-Acetyl-3-hydroxy-6H-benzo[*c*]chromen-6-one (9)*. The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and 2,6-dihydroxyacetophenone (0.758 g, 4.98 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **9** as a brown solid in 61% yield; mp (EtOH): 192-193 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.63 (s, 3H, CH₃), 6.97 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 7.61 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.92 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 8.20 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 8.29 (dd, *J* = 7.8 Hz, 2.4 Hz, 2H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 32.4 (CH₃), 109.3 (CH), 113.4 (CH), 116.2 (CH), 118.6 (C), 121.8 (CH), 126.3 (C), 128.0 (CH), 129.6 (CH), 134.6 (C), 135.4 (CH), 148.7 (C), 157.8 (C), 159.7 (C), 200.6 (C). IR ν (cm⁻¹): 1748 (C=O), 1632 (C=O), 1595 (C=C). LC/MS (APCI⁺) *m/z* 254.93 (MH⁺) (calcd for C₁₅H₁₀O₄: 254.24 g/mol), tr 3.00 min.

4-Acetyl-3-hydroxy-8-methoxy-6H-benzo[*c*]chromen-6-one (10). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and 2,6-dihydroxyacetophenone (0.657 g, 4.32 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **10** as a brown solid in 63% yield; mp (EtOH): 191-192 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.63 (s, 3H, CH₃), 3.90 (s, 3H, OCH₃), 6.94 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.51 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.58 (s, 1H, Ar-*H*), 8.21 (t, *J* = 7.2 Hz, 2H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 33.0 (CH₃), 56.1 (CH₃), 110.1 (CH), 111.2 (CH), 113.9 (C), 116.3 (C), 120.3 (CH), 124.4 (C), 124.6 (CH), 126.5 (C), 128.5 (CH), 148.3 (C), 157.6 (C), 159.3 (C), 160.1 (C), 201.3 (C). IR ν (cm⁻¹): 1729 (C=O), 1629 (C=O), 1588 (C=C). LC/MS (APCI⁺) *m/z* 284.97 (MH⁺) (calcd for C₁₆H₁₂O₅: 284.27 g/mol), tr 2.78 min.

4-Acetyl-3-hydroxy-8,9-dimethoxy-6H-benzo[*c*]chromen-6-one (11). The general procedure was used with 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and 2,6-dihydroxyacetophenone (0.584 g, 3.84 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **11** as a brown solid in 67% yield; mp (EtOH): 152-153 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.63 (s, 3H, CH₃), 3.89 (s, 3H, OCH₃), 4.02 (s, 3H, OCH₃), 6.95 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.55 (s, 1H, Ar-*H*), 7.71 (s, 1H, Ar-*H*), 8.34 (s, 1H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 32.5 (CH₃), 55.7 (CH₃), 56.2 (CH₃), 103.6 (CH), 109.5 (CH), 109.6 (CH), 111.3 (C), 113.0 (C), 115.6 (C), 126.5 (C), 130.0 (CH), 148.4 (C), 149.1 (C), 155.3 (C), 157.3 (C), 159.4 (C), 200.9 (C). IR ν (cm⁻¹): 1707 (C=O), 1606 (C=O), 1520 (C=C). LC/MS (APCI⁺) *m/z* 314.99 (MH⁺) (calcd for C₁₇H₁₄O₆: 314.29 g/mol), tr 3.12 min.

4-Acetyl-8-chloro-3-hydroxy-6H-benzo[*c*]chromen-6-one (12). The general procedure was used with 2-bromo-5-chlorobenzoic acid (0.5 g, 2.12 mmol) and 2,6-dihydroxyacetophenone (0.645 g, 4.24 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **12** as a brown solid in 51% yield; mp (EtOH): 196-197 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.62 (s, 3H, CH₃), 6.95 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 7.89 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar-*H*), 8.06 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 8.24 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 8.4 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 32.5 (CH₃), 108.5 (CH), 113.6 (C), 116.1 (C), 120.2 (C), 124.2 (CH), 126.4 (C), 128.4 (CH), 132.2 (C), 133.5 (CH), 135.15 (CH), 148.4 (C), 158.2 (C), 158.7 (C), 200.4 (C). IR ν (cm⁻¹): 3075 (C-OH), 1737 (C=O), 1633 (C=O), 1592 (C=C). LC/MS (APCI⁺) *m/z* 289.38 (MH⁺) (calcd for C₁₅H₉ClO₄: 288.68 g/mol), tr 3.26 min.

1,3-Dihydroxy-4-propanoyl-6H-benzo[*c*]chromen-6-one (13). The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and 1-(2,4,6-trihydroxyphenyl)propan-1-one (0.907 g, 4.98 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **13** as a beige solid in 63% yield; mp (EtOH): 166-167 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.11 (t, *J* = 6.9 Hz, 3H, CH₃), 3.15 (q, *J* = 6.9 Hz, 2H, CH₂), 6.35 (s, 1H, Ar-*H*), 7.53 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.84 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.18 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 8.93 (d, *J* = 7.6 Hz, 1H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 8.78 (CH₃), 37.7 (CH₂), 95.5 (CH), 99.2 (C), 106.8 (C), 119.1 (CH), 126.2 (CH), 127.5 (C), 130.0 (CH), 134.7 (CH), 135.7 (C), 156.9 (C), 160.4 (C), 162.5 (C), 165.4 (C), 208.7 (C). IR ν (cm⁻¹): 3257 (C-OH), 1700 (C=O), 1610 (C=O), 1539 (C=C). LC/MS (APCI⁺) *m/z* 284.98 (MH⁺) (calcd for C₁₆H₁₂O₅: 284.27 g/mol), tr 3.19 min.

1,3-Dihydroxy-8-methoxy-4-propionyl-6H-benzo[*c*]chromen-6-one (14). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and 1-(2,4,6-trihydroxyphenyl)propan-1-one (0.787 g, 4.32 mmol) in 3 mL of water. The product was purified by simple filtration and absolute ethanol washing of the precipitate to obtain pure compound **14** as a yellow solid in 45% yield; mp (EtOH): 183-184 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 1.11 (t, *J* = 7.6 Hz, 3H, CH₃), 3.17 (q, *J* = 7.6 Hz, 2H, CH₂), 3.88 (s, 3H, OCH₃), 6.36 (s, 1H, Ar-*H*), 7.47 (dd, *J* = 9.1, 3.0 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 8.89 (d, *J* = 9.1 Hz, 1H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-

d_6) (ppm): 8.28 (CH₃), 37.2 (CH₂), 55.4 (CH₃), 94.8 (CH), 98.9 (C), 106.4 (C), 111.2 (C), 119.9 (CH), 123.2 (CH), 127.5 (CH), 127.6 (C), 155.5 (C), 157.7 (C), 159.8 (C), 161.1 (2C), 208.2 (C). IR ν (cm⁻¹): 3216 (C-OH), 1696 (C=O), 1614 (C=O), 1565 (C=C). LC/MS (APCI⁺) m/z 314.99 (MH⁺) (calcd for C₁₇H₁₄O₆: 314.29 g/mol), tr 3.23 min.

1,3-Dihydroxy-4-(2-phenylacetyl)-6H-benzo[c]chromen-6-one (15). The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and 2-phenyl-1-(2,4,6-trihydroxyphenyl)ethan-1-one (1.22 g, 4.98 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **15** as a white solid in 43% yield; mp (EtOAc/*n*-heptane): 175-176 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 4.53 (s, 2H, CH₂), 6.41 (s, 1H, Ar-*H*), 7.22–7.36 (m, 5H, Ar-*H*), 7.55 (t, $J = 7.4$ Hz, 1H, Ar-*H*), 7.87 (t, $J = 7.4$ Hz, 1H, Ar-*H*), 8.22 (d, $J = 7.4$ Hz, 1H, Ar-*H*), 8.97 (d, $J = 7.4$ Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 49.7 (CH₂), 95.1 (CH), 98.9 (C), 106.5 (C), 118.6 (CH), 125.7 (C), 126.4 (C), 127.1 (CH), 128.1 (CH), 129.5 (2CH), 129.8 (2CH), 134.1 (CH), 135.0 (CH), 135.5 (C), 156.8 (C), 160.0 (C), 162 (C), 165.0 (C), 205.2 (C). IR ν (cm⁻¹): 3268 (C-OH), 1700 (C=O), 1603 (C=O), 1521 (C=C). LC/MS (APCI⁺) m/z 347.04 (MH⁺) (calcd for C₂₁H₁₄O₅: 346.34 g/mol), tr 3.31 min.

1,3-Dihydroxy-8-methoxy-4-(2-phenylacetyl)-6H-benzo[c]chromen-6-one (16). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) 2-phenyl-1-(2,4,6-trihydroxyphenyl)ethan-1-one (1.06 g, 4.32 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **16** as a yellow solid in 42% yield; mp (EtOAc/*n*-heptane): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.88 (s, 3H, OCH₃), 4.52 (s, 2H, CH₂), 6.42 (s, 1H, Ar-*H*), 7.22–7.36 (m, 5H, Ar-*H*), 7.48 (dd, $J = 9.2, 2.8$ Hz, 1H, Ar-*H*), 7.64 (d, $J = 2.8$ Hz, 1H, Ar-*H*), 8.90 (d, $J = 9.2$ Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 49.7 (CH₂), 55.4 (CH₃), 95.0 (CH), 99.0 (C), 106.5 (C), 111.3 (2CH), 119.9 (CH), 123.3 (C), 126.4 (C), 127.6 (CH), 128.1 (2CH), 129.8 (2CH), 135.0 (C), 155.8 (C), 157.8 (2C), 159.7 (2C), 205.1 (C). IR ν (cm⁻¹): 3351 (C-OH), 1692 (C=O), 1606 (C=O), 1562 (C=C). LC/MS (APCI⁺) m/z 376.98 (MH⁺) (calcd for C₂₂H₁₆O₆: 376.36 g/mol), tr 3.36 min.

1,3-Dihydroxy-8,9-dimethoxy-4-(2-phenylacetyl)-6H-benzo[c]chromen-6-one (17). The general procedure was used with 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and 2-phenyl-1-(2,4,6-trihydroxyphenyl)ethan-1-one (0.938 g, 3.84 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **17** as a yellow solid in 40% yield; mp (EtOAc/*n*-heptane): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.85 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 4.49 (s, 2H, CH₂), 6.31 (s, 1H, Ar-*H*), 7.22–7.36 (m, 5H, Ar-*H*), 7.48 (s, 1H, Ar-*H*), 8.38 (s, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 50.1 (CH₂), 55.9 (CH₃), 56.0 (CH₃), 95.5 (CH), 99.5 (C), 106.9 (C), 108.0 (C), 110.3 (CH), 111.8 (CH), 127.0 (C), 128.6 (CH), 129.9 (2CH), 130.3 (2CH), 135.6 (C), 148.3 (C), 154.8 (C), 157.0 (C), 159.9 (C), 161.6 (C), 164.7 (C), 205.6 (C). IR ν (cm⁻¹): 3213 (C-OH), 1696 (C=O), 1603 (C=O), 1513 (C=C). LC/MS (APCI⁺) m/z 406.93 (MH⁺) (calcd for C₂₃H₁₈O₇: 406.39 g/mol), tr 3.14 min.

1,3-Dihydroxy-4-(3-(4-hydroxyphenyl)propanoyl)-6H-benzo[c]chromen-6-one (18). The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and phloretin (1.29 g, 4.98 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **18** as a red solid in 51% yield; mp (EtOAc/*n*-heptane): 167-168 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.86 (t, $J = 7.3$ Hz, 2H, CH₂), 3.32 (t, $J = 7.3$ Hz, 2H, CH₂), 6.44 (s, 1H, Ar-*H*), 6.67 (d, $J = 8.3$ Hz, 2H, Ar-*H*), 7.09 (d, $J = 8.3$ Hz, 2H, Ar-*H*), 7.56 (t, $J = 7.6$ Hz, 1H, Ar-*H*), 7.86 (t, $J = 7.6$ Hz, 1H, Ar-*H*), 8.21 (d, $J = 7.6$ Hz, 1H, Ar-*H*), 9.02 (d, $J = 7.6$ Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 29.0 (CH₂), 46.0 (CH₂), 99.2 (CH), 99.5 (CH), 106.1 (C), 114.9 (2CH), 118.1 (CH), 126.1 (CH), 127.1 (C), 129.1 (2CH), 131.0 (CH), 134.7 (2C), 135.1 (C), 152.4 (C), 155.3 (C), 159.5 (C), 161.1 (C), 161.3 (C), 203.0 (C). IR ν (cm⁻¹):

3187 (C-OH), 1718 (C=O), 1610 (C=O), 1513 (C=C). LC/MS (APCI⁺) *m/z* 376.98 (MH⁺) (calcd for C₂₂H₁₆O₆: 376.36 g/mol), tr 3.10 min.

1,3-Dihydroxy-4-(3-(4-hydroxyphenyl)propanoyl)-6H-benzo[c]chromen-6-one (**19**). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and phloretin (1.16 g, 4.32 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **19** as a yellow solid in 52% yield; mp (EtOAc/*n*-heptane): 179-180 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.86 (t, *J* = 6.9 Hz, 2H, CH₂), 3.32 (t, *J* = 6.9 Hz, 2H, CH₂), 3.89 (s, 3H, OCH₃), 6.43 (s, 1H, Ar-*H*), 6.66 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.09 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.49 (dd, *J* = 9.1, 3.2 Hz, 1H, Ar-*H*), 7.64 (d, *J* = 3.2 Hz, 1H, Ar-*H*), 8.97 (d, *J* = 9.1 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 29.1 (CH₂), 46.1 (CH₂), 55.4 (CH₃), 94.9 (CH), 99.0 (C), 106.5 (C), 111.3 (CH), 115.0 (2CH), 119.9 (CH), 123.3 (C), 127.4 (CH), 127.6 (C), 129.1 (2CH), 131.1 (C), 155.4 (C), 155.7 (C), 157.7 (C), 159.7 (C), 161.0 (C), 164.0 (C), 206.9 (C). IR ν (cm⁻¹): 3261 (C-OH), 1703 (C=O), 1610 (C=O), 1513 (C=C). LC/MS (APCI⁺) *m/z* 407.09 (MH⁺) (calcd for C₂₃H₁₈O₇: 406.39 g/mol), tr 3.08 min.

1,3-Dihydroxy-4-(3-(4-hydroxyphenyl)propanoyl)-8,9-dimethoxy-6H-benzo[c]chromen-6-one (**20**). The general procedure was used with 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and phloretin (0.992 g, 3.84 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **20** as a beige solid in 54% yield; mp (EtOAc/*n*-heptane): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 2.81 (t, *J* = 7.2 Hz, 2H, CH₂), 3.30 (t, *J* = 7.2 Hz, 2H, CH₂), 3.83 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 6.19 (s, 1H, Ar-*H*), 6.69 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.06 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 8.34 (s, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 29.5 (CH₂), 46.5 (CH₂), 55.8 (CH₃), 55.9 (CH₃), 99.4 (CH), 106.7 (C), 107.8 (CH), 110.1 (C), 111.6 (CH), 115.6 (2CH), 129.6 (2C), 131.7 (2CH), 148.1 (2C), 154.7 (C), 155.9 (2C), 156.7 (C), 159.8 (C), 161.7 (C), 207.0 (C). IR ν (cm⁻¹): 3314 (C-OH), 1700 (C=O), 1606 (C=O), 1513 (C=C). LC/MS (APCI⁺) *m/z* 437.03 (MH⁺) (calcd for C₂₄H₂₀O₈: 436.42 g/mol), tr 2.92 min.

(E)-3-Hydroxy-1-(4-hydroxystyryl)-6H-benzo[c]chromen-6-one (**21**). The general procedure was used with 2-bromobenzoic acid (0.5 g, 2.49 mmol) and (*E*)-5-(4-hydroxystyryl)benzene-1,3-diol (resveratrol) (1.14 g, 4.98 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **21** as a yellow solid in 50% yield; mp (*n*-heptane/EtOAc): 166-168 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.73 (d, *J* = 2.6 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.87 (d, *J* = 2.6 Hz, 1H, Ar-*H*), 6.98 (d, *J* = 15.8 Hz, 1H, CH), 7.41 (d, *J* = 15.8 Hz, 1H, CH), 7.52 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.57 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 7.3 Hz, 1H, Ar-*H*), 8.15 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 8.25 (d, *J* = 7.3 Hz, 1H, Ar-*H*); ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 102.2 (CH), 107.8 (CH), 113.4 (2CH), 115.6 (CH), 119.8 (CH), 125.5 (CH), 126.0 (CH), 127.1 (C), 127.6 (C), 128.2 (C), 129.9 (2CH), 131.3 (CH), 134.7 (CH), 135.4 (C), 139.0 (C), 152.7 (C), 157.7 (C), 158.6 (C), 160.4 (C). IR ν (cm⁻¹): 3165 (C-OH), 1700 (C=O), 1614 (C=C), 1588 (C=C). LC/MS (APCI⁺) *m/z* 331.01 (MH⁺) (calcd for C₂₁H₁₄O₄: 330.34 g/mol), tr 2.68 min.

(E)-3-hydroxy-1-(4-hydroxystyryl)-8-methoxy-6H-benzo[c]chromen-6-one (**22**). The general procedure was used with 2-bromo-5-methoxybenzoic acid (0.5 g, 2.16 mmol) and resveratrol (0.986 g, 4.32 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **22** as a yellow solid in 54% yield; mp (*n*-heptane/EtOAc): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.88 (s, 3H, OCH₃), 6.71 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 6.80-6.86 (m, 3H, Ar-*H*), 6.95 (d, *J* = 16.3, 1H, CH), 7.37 (d, *J* = 16.3 Hz, 1H, CH), 7.48-7.53 (d, *J* = 16.3 Hz, 3H, Ar-*H*), 7.67 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 8.09 (d, *J* = 9.5 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 55.6 (CH₃), 102.2 (CH), 107.9 (CH), 111.7 (CH), 113.4 (2CH), 115.6 (C), 121.1 (CH), 122.7 (CH), 126.0 (C), 127.3 (CH), 127.7 (C), 128.2 (2CH),

128.7 (CH), 131.2 (C), 138.1 (C), 151.7 (C), 157.6 (C), 157.7 (C), 157.9 (C), 160.3 (C). IR ν (cm⁻¹): 3280 (C-OH), 1692 (C=O), 1595 (C=C), 1502 (C=C). LC/MS (APCI⁺) m/z 361.06 (MH⁺) (calcd for C₂₂H₁₆O₆: 360.36 g/mol), tr 2.72 min.

(*E*)-3-Hydroxy-1-(4-hydroxystyryl)-8,9-dimethoxy-6H-benzo[*c*]chromen-6-one (**23**). The general procedure was used with 2-bromo-4,5-dimethoxybenzoic acid (0.5 g, 1.92 mmol) and resveratrol (0.876 g, 3.84 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **23** as a yellow solid in 47% yield; mp (*n*-heptane/EtOAc): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 3.70 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 6.68 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 6.79 (s, 1H, Ar-*H*), 6.81 (s, 1H, Ar-*H*), 6.87 (d, *J* = 16.2 Hz, 1H, CH), 7.50–7.59 (m, 4H, Ar-*H* + CH), 7.70 (s, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 55.0 (CH₃), 55.5 (CH₃), 102.1 (CH), 107.5 (CH), 107.8 (CH), 110.0 (CH), 112.5 (CH), 113.4 (2CH), 115.5 (C), 126.0 (CH), 127.4 (C), 128.0 (C), 130.5 (2CH), 131.4 (C), 138.3 (C), 147.9 (C), 152.4 (C), 153.7 (C), 157.6 (C), 157.8 (C), 160.0 (C). IR ν (cm⁻¹): 3276 (C-OH), 1700 (C=O), 1606 (C=C), 1588 (C=C). LC/MS (APCI⁺) m/z 391.09 (MH⁺) (calcd for C₂₃H₁₈O₆: 390.39 g/mol), tr 2.8 min.

(*E*)-8-Chloro-3-hydroxy-1-(4-hydroxystyryl)-6H-benzo[*c*]chromen-6-one (**24**). The general procedure was used with 2-bromo-5-chlorobenzoic acid (0.5 g, 2.12 mmol) and resveratrol (0.968 g, 4.24 mmol) in 3 mL of water/ethanol 1/1. After filtration of the reaction mixture, the crude product has been purified by flash chromatography to obtain pure compound **24** as a yellow solid in 6% yield; mp (*n*-heptane/EtOAc): > 200 °C; ¹H NMR (400 MHz, DMSO-*d*₆) (ppm): 6.74 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.88 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.99 (d, *J* = 16.7 Hz, 1H, CH), 7.38 (d, *J* = 16.7 Hz, 1H, CH), 7.52 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.96 (dd, *J* = 8.8, 2.3 Hz, 1H, Ar-*H*), 8.15 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 8.18 (d, *J* = 2.3 Hz, 1H, Ar-*H*). ¹³C NMR (100 MHz, DMSO-*d*₆) (ppm): 102.2 (CH), 107.1 (CH), 113.6 (2CH), 115.6 (C), 121.5 (CH), 125.5 (CH), 127.5 (C), 127.6 (C), 128.4 (CH), 128.7 (CH), 131.4 (2CH), 131.8 (C), 134.2 (CH), 134.6 (C), 139.6 (C), 152.7 (C), 157.8 (C), 158.9 (C), 159.4 (C). IR ν (cm⁻¹): 3168 (C-OH), 1700 (C=O), 1610 (C=C), 1588 (C=C). LC/MS (APCI⁺) m/z 365.48 (MH⁺) (calcd for C₂₁H₁₃ClO₄: 364.78 g/mol), tr 2.86 min.

Biological evaluation

ELISA assay

The *in vitro* inhibitors screening of AGE2 (glyceraldehyde-modified AGE)-sRAGE interaction (soluble RAGE) was performed using a 96-well AGE-BSA-coated plate (Creative BioMart® ELISA kit), according to the manufacturer's instructions. Briefly, 100 UA/mL soluble RAGE (sRAGE) was incubated with 10 or 100 μ M of the tested compounds or 0.05% DMSO as a negative control on an AGE2-BSA-coated plate at room temperature for 60 minutes, shaking at 300 rpm on an orbital microplate shaker. After incubation, the wells were washed 4 times with wash buffer and horseradish peroxidase (HRP)-labeled anti-RAGE antibody was added and the plate was further incubated at room temperature for 60 minutes, shaking at 300 rpm on an orbital microplate shaker. After incubation, the wells were washed 4 times with wash buffer and the Substrate Reagent was added to each well. After an incubation at room temperature for 7 minutes, the HRP-labeled antibody-sRAGE-AGE complex

was then detected by measuring the absorbance at 450 nm using the microplate reader Varioskan (Thermo Fischer Scientific). These experiments were repeated three times.

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CRedit authorship contribution statement

Théo Guérin: Methodology, Investigation, Cowriting-original draft. **Christophe Waterlot:** Conceptualization of ecocatalysts, Methodology, Flame atomic absorption spectrometry analyses, Writing-review. **Emmanuelle Lipka:** SFC and LC/MS analyses. **Philippe Gervois:** ELISA assay. **David Bulteel:** SEM-EDS analyses, interpretation of results. **Damien Betrancourt:** SEM-EDS analyses, interpretation of results. **Carla Moignard:** Synthesis methodology. **Adrian Sorin Nica:** Conceptualization. **Christophe Furman:** ELISA assay, Supervision. **Alina Ghinet:** Conceptualization, Supervision, Resources, Methodology, Cowriting-original draft, review & editing final draft.

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Natural source of ecocatalysts



steps



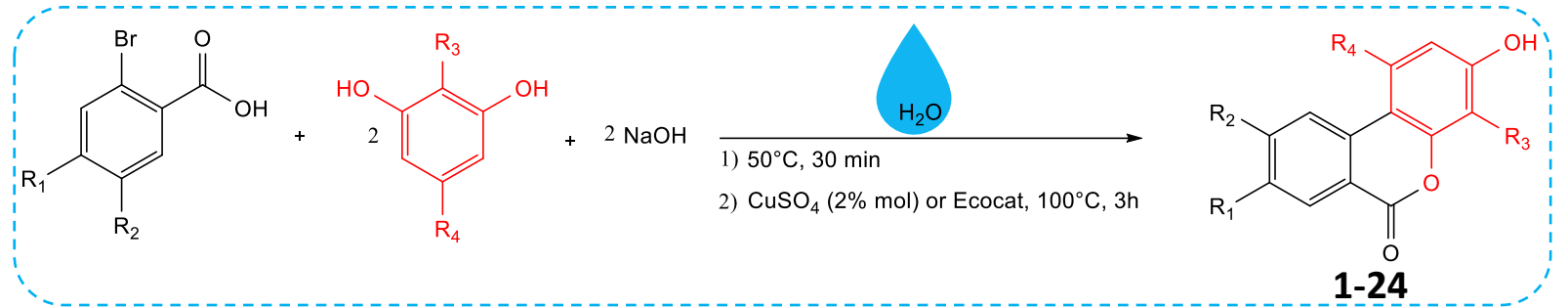
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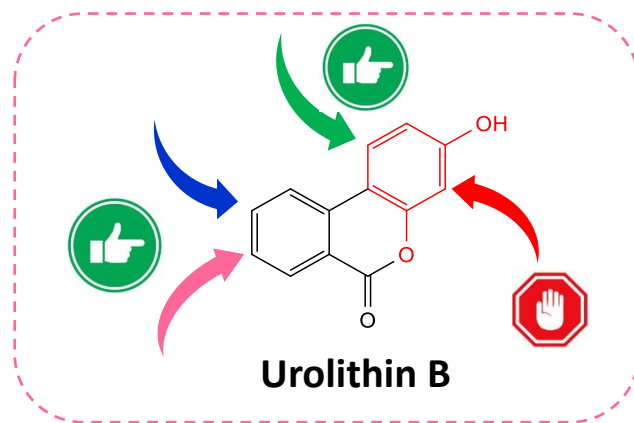
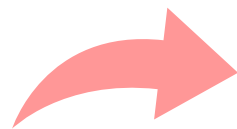
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UROLITHINS
ANTIAGEING
ANALYSIS
ECOCATALYSTS



Pomegranate:
Natural source of urolithins



Favorable modulation for blocking RAGE activity



Disadvantageous for blocking RAGE activity

- ✓ *Miscanthus-based ecocatalysts*
- ✓ *Green ecocatalysed synthesis*
- ✓ *24 synthesized urolithins*
- ✓ *Biological evaluation on AGE2-BSA/sRAGE interaction*
- ✓ *4 points of pharmacomodulation*
- ✓ *First SAR as RAGE antagonists*