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Structure–Activity Relationships and Structural Design Optimization of a Series of *p*-Hydroxycinnamic Acids-Based Bis- and Trisphenols as Novel Sustainable Antiradical/Antioxidant Additives

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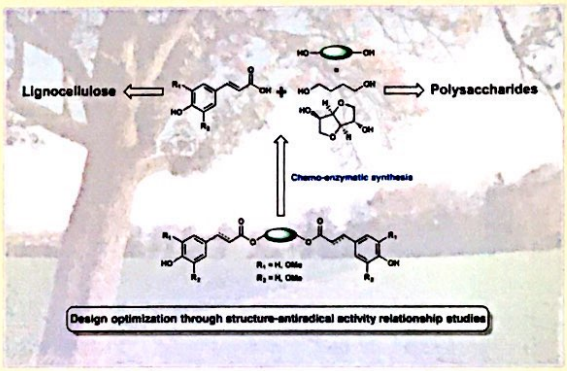
Supporting Information

ABSTRACT: Chemo-enzymatic synthesis and screening of a library of renewable saturated and unsaturated bis- and trisphenols deriving from *p*-hydroxycinnamic acids (i.e., *p*-coumaric acid, ferulic acid, and sinapic acid) and biobased diols/triol (i.e., isosorbide, 1,4-butanediol, glycerol) showed that these compounds were potent antioxidants/antiradicals. To optimize their antiradical activities, we assessed the structure–activity relationships (SAR) of these phenolics focusing on the internal diol/triol linker, the degree of methoxylation on the aromatic rings, and the C=C double bond of the α,β-unsaturated esters. We found that methoxylation degree and the unsaturation were critical for antiradical activity while the nature of the diol had a small impact. Indeed, SAR revealed that, for saturated compounds, the higher the methoxylation degree, the higher the antiradical activity; on the other hand, unexpectedly, the presence of the unsaturation had a negative impact on the activity. The antiradical activities of these bis- and trisphenols were then compared to that of Irganox 1010, a widely used antioxidant additive in polypropylene. The optimized compounds, i.e. those deriving from sinapic acid and with saturated esters, proved as effective while being 100% biobased and obtained through a more sustainable synthetic pathway. Thermal analyses (TGA) demonstrated that these bis- and trisphenols exhibit high thermal stability and that their T_d5% can be easily tailored by playing with the structure of the bisphenol core. *p*-Hydroxycinnamic acids-based bis- and trisphenols are thus promising easily accessible, eco-friendly, and biocompatible antiradical additives for a sustainable approach to the stabilization of polymers in packaging and other applications.



KEYWORDS: *Antiradical, Antioxidant, Ferulic acid, p-Coumaric acid, Sinapic acid, Lipase*

INTRODUCTION

In the past decade, there has been increasing demand on the part of both consumers and the industry for renewable nontoxic building blocks that could be used to replace fossil-based counterparts for the preparation of additives, polymers, and resins.[1−5] In this way, there have been various reports on the use of biobased phenolic functional polymers acting as flame retardants or antioxidants in polymer matrices.[6−9]

The market of plastics and rubber additives represents high volume of specialty chemicals, assuming important functions in the material, such as plasticizing or protection of the macromolecules against oxidative degradation. The addition of antioxidant phenolics is the most convenient and effective way to keep polymers, such as polyolefins and polyesters, from oxidative damages during melt processing, aging and weathering during usage. It is also well-known that hindered phenolics are widely used as antioxidant additives for polymers used in food packaging.[10−12] Indeed, oxidative deterioration of packaged food may be a major economic and health concern. To prevent oxidation, antioxidant additives, such as Irganox

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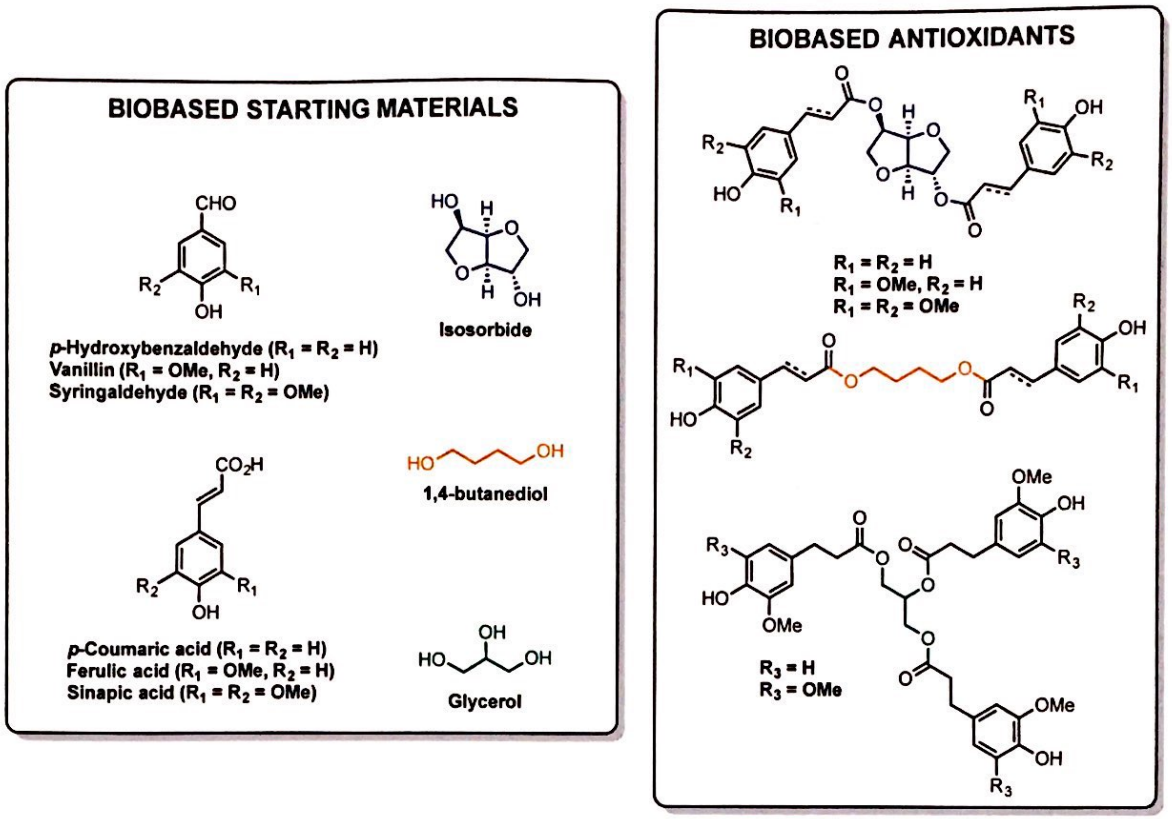

Figure 1. 100% biobased starting materials and antioxidants.

1010, butylated hydroxyanisole (BHA), 3,5-di-*t*-butyl-4-hydroxytoluene (BHT), *t*-butylhydroquinone (TBHQ), and propyl gallate, have been used in food product formulations.[13] However, issues regarding their potential toxic, mutagenic, and carcinogenic activities have been raised as such small phenolic antioxidants can get leached out from the polymer matrix during usage, giving rise to contamination of the environment.[14] In the aim of bettering the environmental impact of the plastics industry, it seemed interesting to develop novel biobased additives and to manage risks associated with leaching and introducing biobased molecules produced with environmentally improved processes.

Despite their very interesting antioxidant activity,[15,16] the use of *p*-hydroxycinnamic acids (*p*-coumaric acid, ferulic acid, and sinapic acid) and their ester derivatives as antioxidant additives in a polymer is relatively restricted due to their low thermal stability. Furthermore, in the aim of preventing leaching issues of small molecules from polymer matrices, substances with higher molecular mass (and therefore higher volume) are generally preferred. An interesting result on the diffusion properties of biphenylalkanes has been obtained recently by Fang et al.[17] They showed that the introduction of small aliphatic chains as a spacer between aromatic moieties decreased the diffusion coefficients by 1 order of magnitude per 1.3 carbon. At the same time, biobased bisphenols derived from ferulic acid and biobased diols (1,2-ethylene glycol, 1,3-propanediol, 1,4-butanediol, glycerol, and isosorbide) have been recently synthesized through a *Candida antarctica* lipase B-catalyzed transesterification using a solvent free reaction under mild conditions.[18] These aliphatic–aromatic structures have already been valorized as biobased monomers for the preparation of aliphatic–aromatic copolyesters,[19] poly(ester-urethane)s,[20] poly(ester-alkenamer)s,[21] and linear phenolic oligomers with guaiacol-type moieties.[22] All polymers and oligomers exhibited high thermal stability (over 250 °C) and a T_g that can be easily tailored by adjusting the chemical structure of bisphenols and comonomers.[5] Bearing two dihydroferulic acid moieties, these bisphenols can also be envisaged as potential antiradicals/antioxidants.

In the aim of developing biobased antioxidants challenging common polymer additives for polymers, we decided to start from these ferulic acid-based bisphenols and this lipase-catalyzed process to build a library of *p*-hydroxycinnamic acids-based bis- and trisphenols and evaluate their antioxidant activity to determine the structure/activity relationships needed to optimize their structural design (Figure 1). Commonly, the determination of antioxidant activity is performed in solid media (polymers matrices) at mild or high temperature, using standard aging tests or OIT (oxygen induction time) analysis, respectively.[23,24] Nevertheless these two techniques are time-consuming due to the preparation of the polymer samples prior analysis, and the time needed for the aging. In order to make an easy and quick first screening of a batch of potential antioxidant, several methods[14,25−27] have been developed over the years. These methods are based on the determination of the capacity of a potential antioxidant to scavenge free radicals in liquid media, which provide the antiradical activity. The correlation between antiradical and antioxidant activity being generally accepted, we assessed the impact of structural variations on antioxidant activity of the bis- and trisphenols by studying their radical scavenging activities toward DPPH free radical. The results of these analyses allowed us to (1) determine SARs, (2) optimize the structural design of the bisphenols accordingly, and (3) determine the bis- and trisphenols possessing the higher antiradical activity. Finally, the most promising compounds were benchmarked against

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.36M
500 mL

Irganox 1010 (tetrakis(methylene-(3,5-di-*t*-butyl-*p*-hydroxycinnamate))methane, CAS 6683-19-8), a petrochemical antioxidant additive widely used in polymers such as polypropylene. The aim of this paper is to report on these issues.

MATERIALS AND METHODS

Materials. All reagents and *Candida antarctica* lipase B immobilized on resin (ref L4777-10G, recombinant, expressed from *Aspergillus niger*, ≥5000 propyl laurate units g^{-1}) were purchased from Aldrich Chemical Co. and were used as received. Solvents were purchased from Thermo Fisher Scientific, deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO-d_6), and acetone (acetone-d_6) were purchased from Euriso-top.

Purification and Characterization. Column chromatography was carried out with an automated flash chromatography (PuriFlash 4100, Interchim) and prepacked INTERCHIM PF-30SI-HP (30 μm silica gel) columns. FT-IR and UV analyses were performed respectively on Cary 630 FTIR and Cary 60 UV−Vis from Agilent technologies. NMR analyses were recorded on a Bruker Fourier 300. ^{1}H NMR spectra of samples were recorded in $CDCl_3$ at 300 MHz, chemicals shifts were reported in parts per million relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm). ^{13}C NMR spectra of samples were recorded at 75 MHz ($CDCl_3$ DMSO-d_6 and acetone-d_6 residual signal at δ = 77.16, 39.52, and 29.84 ppm, respectively).

General Procedure of Esterification of *p*-Hydroxycinnamic Acids. To a stirred solution of *p*-hydroxycinnamic acid in ethanol (*C* = 0.36 M, 500 mL), a few drops of concentrated HCl were added. The reaction media was refluxed and left for 2 days. After cooling to room temperature, ethanol was evaporated under reduced pressure. The obtained oil was solubilized in ethyl acetate (250 mL) and successively washed with $NaHCO_3$ (2 × 100 mL) and brine (50 mL). The organic phase was dried over anhydrous $MgSO_4$, and the final product crystallized during the evaporation and did not need further purification.

General Procedure for Palladium-Catalyzed Hydrogenation of Ethyl *p*-Hydroxycinnamates. A solution of ethyl *p*-hydroxycinnamate in ethyl acetate (*C* = 0.3 M) was stirred under N_2 flow at room temperature. After 10 min, palladium on activated charcoal (Pd/C, 10% w/w) was added and the solution was stirred under N_2 for another 10 min before being submitted to H_2 flow until completion. The solution was centrifugated (5000 rpm, 10 °C, 45 min), filtered over a pad of Celite, and evaporated under reduced pressure. The final product crystallized during the evaporation and did not need further purification.

Sample Procedure for the Lipase-Catalyzed Synthesis of Saturated Bisphenols.[18] Isosorbide/1,4-butanediol (11.1 mmol, 1 equiv) and ethyl dihydro-*p*-hydroxycinnamate (33.3 mmol, 3 equiv) were melted and magnetically stirred at 75 °C before adding CAL-B (10% by weight relative to the total weight of polyol and ethyl dihydro-*p*-hydroxycinnamate). The reaction mixture was kept under reduced pressure until completion (for 4−72 h depending on diol/ethyl dihydro-*p*-hydroxycinnamate), then dissolved in acetone and filtered to remove CAL-B beads. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography on silica gel.

General Procedure for the Lipase-Catalyzed Synthesis of Saturated Trisphenol.[18] Glycerol (11.1 mmol, 1 equiv) and ethyl dihydro-*p*-hydroxycinnamate (100 mmol, 4.5 equiv) were melted and magnetically stirred at 75 °C before adding CAL-B (10% by weight relative to the total weight of polyol and ethyl dihydro-*p*-hydroxycinnamate). The reaction mixture was kept under reduced pressure until completion (for 4−72 h depending on polyol/ethyl dihydro-*p*-hydroxycinnamate), then dissolved in acetone and filtered to remove CAL-B beads. The solvent was then evaporated under vacuum and the crude product was purified by flash chromatography on silica gel.

Procedure for the Synthesis of Isosorbide-bischloroacetate and 1,4-Butanediol-bischloroacetate.[28,29] Chloroacetic anhydride (244 mmol, 2.2 equiv) was added in three portions to a stirred solution of diol (110 mmol, 1 equiv) in methylene chloride (220 mL, *C* = 0.5 M) and pyridine (2 M) at 0 °C (ice bath). The resulting solution was stirred at room temperature for 4 h. The reaction medium was diluted with 200 mL of methylene chloride at 0 °C and quenched with 150 mL of an aqueous solution of HCl (1 M). The organic layer was washed three times with brine (150 mL) until obtaining a clear organic phase. This layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to obtain the corresponding crude bischloroacetate as a solid that was used without further purification.

Sample Procedure for the Synthesis of Unsaturated Bisphenols via Wittig Reaction and Deacetylation. *"Double Wittig" Reaction.*[30] Isosorbide/1,4-butanediol bischloroacetate (3.7 mmol, 1 equiv), coumaraldehyde/vanillin/syringaldehyde acetate (7.4 mmol, 2 equiv), and PPh_3 (11.1 mmol, 3 equiv) were weighted in a round-bottom flask. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added at room temperature, and the mixture was stirred vigorously under N_2 at 80 °C during 60 min. After cooling, methylene chloride was added (50 mL). Layers were separated, and the organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated.

Sample Procedure for Deacetylation. Piperazine (100 mmol, 10 equiv) was added in one portion to a stirred solution of bisphenol acetate (10 mmol, 1 equiv) in THF (100 mL, *C* = 0.1 M) at room temperature, and the reaction was stirred at room temperature for 2 h. Ethyl acetate (200 mL) was then added, and the reaction mixture was washed 3 M HCl (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated.

Sample Procedure for the Synthesis of Saturated Bisphenols via Wittig Reaction, Hydrogenation, and Deacetylation. *Double Wittig Reaction.* Isosorbide/1,4-butanediol bischloroacetate (3.7 mmol, 1 equiv), coumaraldehyde/vanillin/syringaldehyde acetate (7.4 mmol, 2 equiv), and PPh_3 (11.1 mmol, 3 equiv) were weighted in a round-bottom flask. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added at room temperature, and the mixture was stirred vigorously under N_2 at 80 °C during 60 min. After cooling, methylene chloride was added (50 mL). Layers were separated and the organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated.

Palladium-Catalyzed Hydrogenation. A solution of the above compound in ethyl acetate (0.3 M) was stirred under N_2 flow at room temperature. After 10 min, palladium on activated charcoal (Pd/C, 10% w/w) was added and the solution was stirred under N_2 for another 10 min before being submitted to H_2 flow until completion. The solution was centrifugated (5000 rpm, 10 °C, 45 min), filtered over a pad of Celite, and evaporated under reduced pressure. The saturated bisphenol acetate crystallized during the evaporation and did not need further purification.

Sample Procedure for Deacetylation. Piperazine (100 mmol, 10 equiv) was added in one portion to a stirred solution of saturated bisphenol acetate (10 mmol, 1 equiv) in THF (100 mL, *C* = 0.1 M) at room temperature, and the reaction was stirred at room temperature for 2 h. Ethyl acetate (200 mL) was then added and the reaction mixture was washed with 3 M HCl (100 mL) and brine (100 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated.

DPPH Analysis. The free radical scavenging activity of synthesized bis- and trisphenols has been evaluated by DPPH assay using a modified version of the method reported by Brand-Williams and coworkers.[27]

The reaction is started by adding 190 μL of homogenate DPPH solution (200 μM) in ethanol to a well containing 10 μL of potential antiradical molecule solution in ethanol at different concentrations (from 200 to 0.5 μM). The reaction was carried out in a microplate Multiskan FC system, 1 scan was performed every 5 min for 7.5 h. According to these values of concentration and volumes, DPPH analysis reaction implies 40 nmol of DPPH and from 0.07 to 40 nmol of potential antioxidant. The use of different amounts of potential antioxidant give the EC_{50} value, which is the quantity needed to reduce half the initial population of DPPH radicals. The lower the EC_{50} value,

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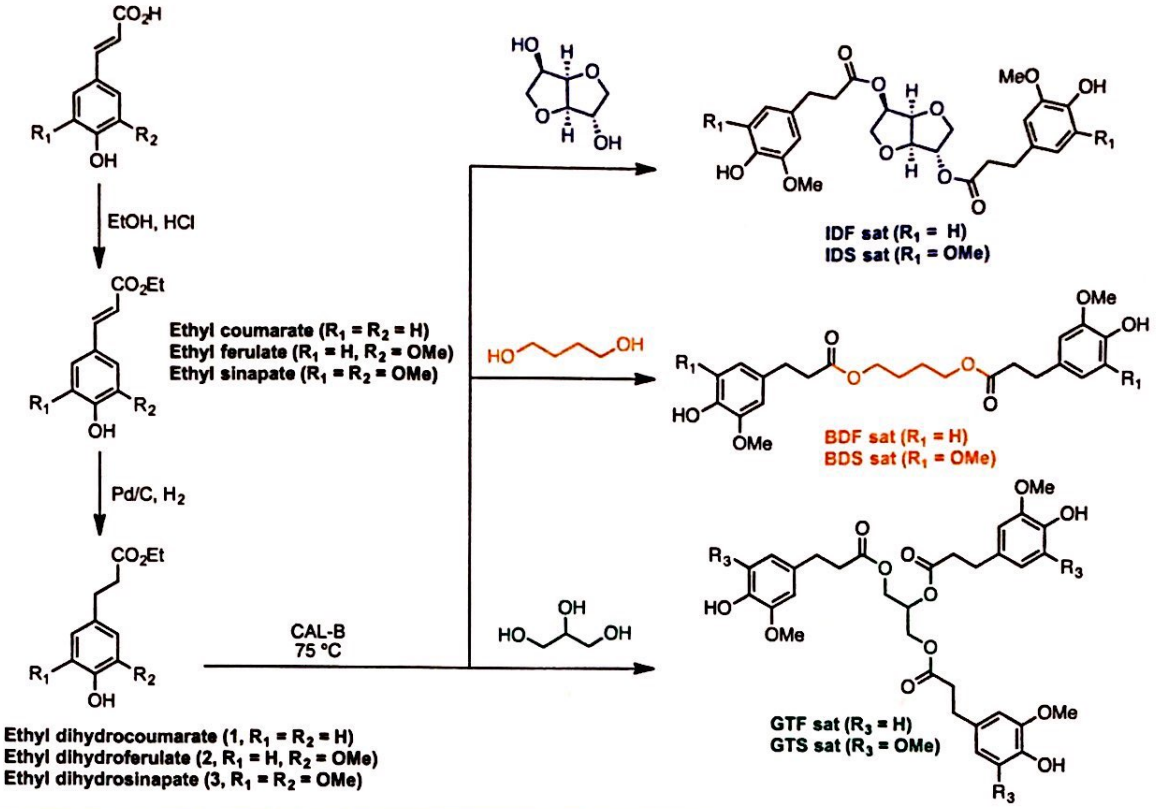
Scheme 1. Chemo-enzymatic Synthesis of Saturated Bis- and Trisphenols



the higher antiradical activity. In the literature, EC_{50} has been expressed as a concentration in moles per liter or as a ratio of concentration of DPPH/concentration of potential antioxidant.[27] In this study we decided to express this value as the amount of antioxidant (nmol) needed to reduce half of the initial population of DPPH. Each analysis was performed four times.

TGA. TGA were recorded under inert atmosphere at 10 °C·min^{-1} on a Q500 from TA Instrument.

RESULTS AND DISCUSSION

Synthesis of the Library of Bis- and Trisphenols. The library of bis- and trisphenols has been set up following three structural variations: presence or not of the conjugated unsaturation (α,β-unsaturated ester vs saturated ester), nature of the diol/triol linker between phenol moieties (rigid isosorbide vs flexible 1,4-butanediol), and the degree of methoxylation of the aromatic ring (i.e., coumaric = 0, ferulic = 1, sinapic = 2).

Isosorbide, readily obtained from corn,[31] was first chosen for its robust bicyclic structure,[32] potentially providing high thermal properties to the resulting bis- and trisphenols.[33,34] Moreover, its ester link is easily cleaved by esterases, enhancing the biodegradability of the materials. Furthermore, the influence of its bicyclic structure on the final properties of the resulting bisphenols was compared to that of aliphatic segments by using 1,4-butanediol, a readily available biobased diol that can be efficiently obtained via fermentation of sugars (from plant polysaccharides).[35−39] Finally, glycerol, which is produced in large scale from biobased triglycerides (plant oils),[40] was also used to provide a trisphenol.

For clarity, bis- and trisphenols will be named as follows: **XYZ sat/unsat**, where **X** = **I** (isosorbide), **B** (1,4-butanediol) or **G** (glycerol); **Y** = **D** (bisphenol) or **T** (trisphenol); and **Z** = **C** (coumaric), **F** (ferulic), or **S** (sinapic), with **sat** (saturated) or **unsat** (unsaturated). For example, **BDC sat** corresponds to the saturated bisphenol deriving from *p*-coumaric acid and 1,4-butanediol.

As we dedicate ourselves to the use of sustainable processes, for the setting up of the library we first envisaged the implementation on *p*-coumaric acid and sinapic acid of the ethyl dihydroferulate lipase-catalyzed transesterification method reported by Pion et al.[18] Indeed, the use of immobilized lipase offers many benefits and they are great tools for the development of sustainable processes: such an enzyme does not require the use of solvent, it is inactive toward phenolic hydroxyl groups and thus one avoids atom-, energy-, and time-consuming protection/deprotection sequence, and it can be reused for further reaction cycles. However, it was shown that *Candida antarctica* lipase B was much more active toward saturated ethyl ester than α,β-unsaturated ethyl ester and unsaturated acids moiety. In fact, the α,β-unsaturation confers more rigidity to the molecules and decreases the accessibility of the molecule to the active site of the lipase.[41] Several studies[42,43] also pointed out that α,β-unsaturation also favors the positive mesomeric effect of hydroxyl group in *ortho* and *para* position.

Accordingly, lipase-catalyzed transesterification was used exclusively for the preparation of the saturated bis- and trisphenols (Scheme 1). The derivatization of the three *p*-hydroxycinnamic acids into their corresponding ethyl dihydroxycinnamates was thus first performed using a two-step one pot reaction involving Fisher esterification (HCl, EtOH) and palladium-catalyzed hydrogenation, providing the corresponding ethyl dihydro-*p*-coumarate (**1**), ethyl dihydroferulate (**2**), and ethyl dihydrosinapate (**3**) in high yields (Table 1). With the three ethyl dihydro-*p*-hydroxycinnamates in hand, we then

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Table 1. Library of Compounds: Global Yield and Degradation Temperature (T_d5% and $T_d$max)

entry	compound	yield (%)	T_d5% (°C)[a]	$T_d$max (°C)[a]
1	ethyl *p*-coumarate	quant	164	216
2	ethyl dihydro-*p*-coumarate	quant	145	198
3	ethyl ferulate	quant	150	205
4	ethyl dihydroferulate	quant	136	188
5	ethyl sinapate	quant	174	229
6	ethyl dihydrosinapate	quant	162	217
7	**IDC sat**	31	277	308
8	**IDC unsat**	36	295	324
9	**BDC sat**	31	282	341
10	**BDC unsat**	31	280	344
11	**IDF sat**	92	270	350
12	**IDF unsat**	40	309	364
13	**BDF sat**	95	257	339
14	**BDF unsat**	31	290	352
15	**IDS sat**	29	290	345
16	**IDS unsat**	29	323	372
17	**BDS sat**	87	297	363
18	**BDS unsat**	38	316	369
19	**GTF sat**	92	286	344
20	**GTS sat**	38	304	378

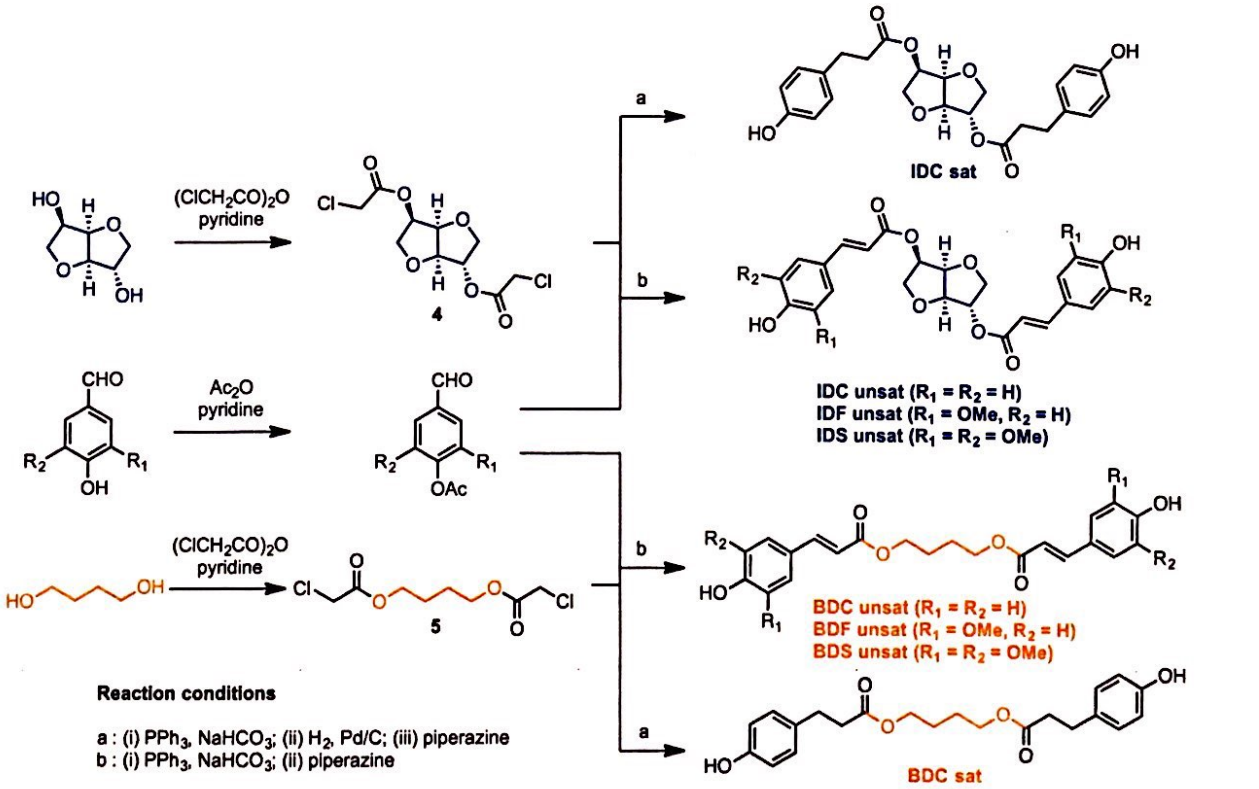
[a] T_d5% = thermal decomposition temperatures at 5% weight loss. $T_d$max = temperature where decomposition rate is maximal. TGA data recorded at 10 °C·min^{-1} under nitrogen (60 mL·min^{-1}).

proceeded to their transesterification with isosorbide and 1,4-butanediol in the presence of the lipase. While the ferulic acid- and sinapic-acid derived saturated bis- and trisphenols (**IDF sat, IDS sat, BDF sat, BDS sat, GTF sat**) were obtained in good to high yields, the saturated bisphenols deriving from *p*-coumaric acid (**IDC sat** and **BDC sat**) proved difficult to obtained in good yields. This behavior had been observed by Weitkamp and co-workers,[43] who reported that ferulic acid is a better substrate for *Candida antarctica* lipase B than *p*-coumaric acid since methoxy groups have an electronic impact on ester reactivity and also reduce the hydrophilicity of the molecule, thus allowing a better fitting into the hydrophobic crevice of *Candida antarctica* lipase B. Therefore, to efficiently access the saturated *p*-coumaric acid-based bisphenols (**BDC sat, IDC sat**) and also the unsaturated bisphenols, a new synthetic strategy had to be devised.

Since the transesterification of the ethyl *p*-hydroxycinnamates proved inefficient, we decided to overcome this difficulty by submitting the corresponding acetylated *p*-hydroxycinnamaldehydes to (1) a double Wittig-reaction[30] in the presence of a dichloromethylene ester derived from isosorbide or 1,4-butanediol whose syntheses were adapted from Enholm and co-workers,[28,29] followed by (2) a palladium-catalyzed hydrogenation of the resulting double α,β-unsaturated esters. It is noteworthy to mention that this double Wittig reaction strategy will be used also to synthesize the *p*-coumaric acid–based unsaturated bisphenols (**BDC unsat, IDC unsat**) as they cannot be efficiently obtained through lipase-catalyzed transesterification.

Isosorbide and 1,4-butanediol were first reacted with chloroacetic anhydride in pyridine to provide the corresponding dichloromethylene esters (**4**, 80%; **5**, 80%) which were then submitted to a one-pot two-step Wittig reaction[30] in the presence of the acetylated *p*-hydroxycinnamaldehydes (Scheme 2), leading to the desired acetylated α,β-unsaturated bisphenols with good yields (Table 1). At this stage, two ways were explored, the first one consisted in reducing and deacetylating

Scheme 2. "Double Wittig" Strategy



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the acetylated α,β-unsaturated bisphenols to access the saturated bisphenols **IDC sat** and **BDC sat**, while the second featured a simple deacetylation to access the corresponding unsaturated bisphenols **IDC unsat**, **BDC unsat**, **IDF unsat** and **BDF unsat**. Following these considerations, acetylated α,β-unsaturated bisphenols underwent a palladium-catalyzed hydrogenation followed by a piperazine treatment and provided the target saturated bisphenols in moderate overall yields (**IDC sat**, 31%; **BDC sat**, 31%). Similarly, treating acetylated α,β-unsaturated bisphenols by piperazine gave the target unsaturated bisphenols, also in moderate overall yields (**IDC unsat** 36%, **BDC unsat** 31%, **IDF unsat** 40%, **BDF unsat** 31%).

In summary, all the 20 desired targets were successfully synthesized using two strategies (Table 1). Ferulic acid and sinapic acid-derived saturated phenols were efficiently obtained through a three-step chemo-enzymatic process involving Fisher esterification/palladium-catalyzed hydrogenation/lipase-catalyzed transesterification, whereas *p*-coumaric acid saturated and all unsaturated bisphenols were obtained through a synthetic pathway involving double Wittig reaction/palladium-catalyzed hydrogenation/deacetylation and double Wittig reaction/deacetylation, respectively.

Thermal stability of all target compounds from the library was evaluated by thermogravimetry (TGA) and reported in Table 1. Data revealed a thermostability in the range of 308–378 °C, depending on the methoxylation degree. Indeed the higher the degree of methoxylation, the more thermostable the antioxidant.

Analysis of the Structure/Antiradical Activity Relationships. All the compounds of the library were screened for their antiradical activity (EC_{50}) by using the DPPH analysis that determines the H-donor capacity of the antioxidant as quencher of the stable DPPH free radical (Table 2).[27] When it gets protonated (reduced), the purple DPPH turns yellow, therefore the monitoring of the protonation of DPHH can be easily performed by UV spectroscopy at 515 nm (purple). The results of these DPPH tests were further used to establish the SARs and consecutively optimize the structural design of the bis- and trisphenols.

Table 2. Antiradical Activity of All the Compounds of the Library and of Irganox 1010 (Benchmark)

entry	compound	EC_{50} (nmol)
1	*p*-coumaric acid	>150.00
2	ethyl *p*-coumarate	>150.00
3	ethyl dihydro-*p*-coumarate	>150.00
4	ferulic acid	10.08 ± 0.55
5	ethyl ferulate	11.70 ± 0.36
6	ethyl dihydroferulate	6.85 ± 0.52
7	sinapic acid	9.19 ± 0.46
8	ethyl sinapate	13.67 ± 0.66
9	ethyl dihydrosinapate	5.53 ± 0.27
10	**IDC sat**	>150.00 (357 ± 47.6)
11	**IDC unsat**	>150.00 (858 ± 18.1)
12	**BDC sat**	>150.00 (351 ± 29.7)
13	**BDC unsat**	>150.00 (900 ± 17.5)
14	**IDF sat**	4.97 ± 0.70
15	**IDF unsat**	8.34 ± 0.69
16	**BDF sat**	3.94 ± 0.31
17	**BDF unsat**	6.22 ± 0.76
18	**IDS sat**	2.98 ± 0.08
19	**IDS unsat**	11.70 ± 0.22
20	**BDS sat**	2.75 ± 0.25
21	**BDS unsat**	9.97 ± 0.13
22	**GTF sat**	3.61 ± 0.17
23	**GTS sat**	2.41 ± 0.31
24	Irganox 1010	2.75 ± 0.28

***p*-Hydroxycinnamic Acids and Esters (Table 2, Entries 1–9).** Data in Table 2 demonstrate that, whatever the *p*-hydroxycinnamate ester, the absence of α,β-unsaturation significantly improved the antiradical activity. These results are in total contradiction with the generally accepted scientific principle that conjugation allows a better delocalization and stability of the radical and therefore a better scavenging activity.[43] However, data reported by Takahashi[44] and Silva,[45] also showed that the reduction of the double bond of *p*-hydroxycinnamic acids improves antiradical activity. Interestingly, such a negative impact of the saturation has been observed in the case of caffeic acid and dihydrocaffeic acid.[46−48] Two hypotheses have been put forward by Takahashi to explain this behavior.[44] The first one is that dihydro-*p*-hydroxycinnamic derivatives possess side bonds that allow the phenyl group to have a certain flexibility to rotate and therefore to stabilize the radical. The second hypothesis is based on the report from Guyton[49] showing that BHT can be transformed to the quinone methide by two-electron oxidation via the abstraction of a proton at the 4-methyl group (dismutation); dihydro-*p*-hydroxycinnamic acid derivatives would undergo the same antiradical mechanism and thus show more potent radical scavenging activity than *p*-hydroxycinnamic acid derivatives by regenerating a new phenol (Scheme 3).

As previously described by Nenadis[50] and Kikuzaki,[51] regardless the degree of substitution of the aromatic ring, the esterification of the carboxylic acid group with ethanol in *p*-hydroxycinnamic acids decreases the antiradical activity (Table 2, entries 5 vs 4, entries 8 vs 7). It is also worth mentioning that, for ethyl *p*-hydroxycinnamate esters, the higher the degree of methoxylation the better the antiradical activity (Table 2, entries 2, 5, and 8). Such an increase of the radical scavenging capacity is probably due to the fact that methoxy groups are electron-donating groups that can stabilize the phenoxy radical.[52,53] This trend is also observed for *p*-hydroxycinnamic acids (Table 2, entries 1, 4, and 7) and is in agreement with previous studies dedicated to the determination of the antiradical activity of *p*-hydroxycinnamic acids where the activity of sinapic acid was observed to be higher than that of ferulic acid.[53−56]

In the case of unsaturated ethyl *p*-hydroxycinnamates (i.e., ethyl ferulate and ethyl sinapate), however, the degree of methoxylation has apparently a negative impact on the antiradical activity (Table 2, entries 5 vs 8). Taking into account the dismutation process described above (Scheme 3), the extra methoxy group present at the 5-position (R_1 = OMe) in sinapic acid-based derivatives would stabilize further the transient radical at the 1-position favoring the 1-*O*-4 coupling and thus preventing the regeneration of a new phenol.

As expected, the presence of a third phenolic moiety—in the case of **GTF sat** and **GTS sat**—increases antiradical activity (Table 2, entries 22 vs 14/16 and entries 23 vs 18/20).

Bisphenols: Influence of the Nature of the Diol/Triol on the Antiradical Activity. The influence of the nature of the diol/triol was the first factor to be studied. The two diols used in this study differ mainly by their rigidity as isosorbide is a rigid bicyclic molecule whereas 1,4-butanediol is a flexible

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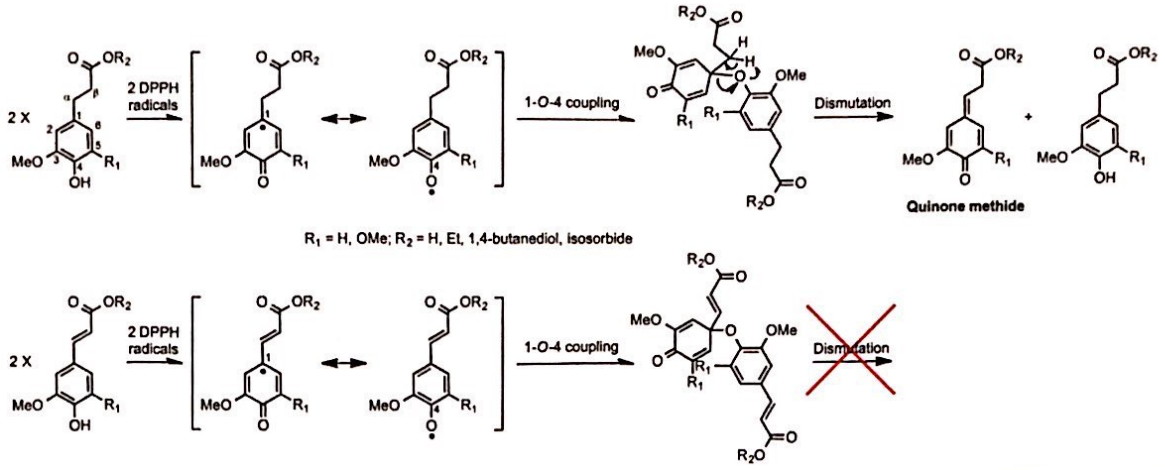
Scheme 3. Hypothetical Formation of Inter- or Intramolecular Quinone Methide through Dismutation of Saturated *p*-Hydroxycinnamic Derivatives



aliphatic diol. Results show that, whatever the presence of the unsaturation or not, the flexibility of the diol globally slightly influences the antiradical activity, the 1,4-butanediol-derived bisphenols being the more active (Table 2, entries 14 vs 16, entries 15 vs 17). These findings are in good agreement with the results previously reported by Torres de Pinedo[52] and Teixeira[53] showing that an increase of the length of the alkyl chain of *p*-hydroxycinnamate esters increases the radical scavenging activity. Indeed, because of the bicyclic structure of isosorbide, the distance between the two phenol moieties in isosorbide-based bisphenols is shorter than that of 1,4-butanediol-based bisphenols. These minimal but subtle differences in antiradical activity spurred us on to commit ourselves further to studying the influence of the degree of methoxylation and unsaturation.

Bisphenols: Influence of the Unsaturation on the Antiradical Activity. We then focused on the influence of the α,β-unsaturation on the antiradical activity. As observed with dihydro-*p*-hydroxycinnamate esters, data in Table 4 show that

Table 3. Antiradical Activity of Isosorbide-Based Bisphenols vs 1,4-Butanediol-Based Bisphenols

entry	compound	EC_{50} (nmol)
1	BDF unsat	6.22
	IDF unsat	8.34
2	BDF sat	3.94
	IDF sat	4.97
3	BDS unsat	9.97
	IDS unsat	11.70
4	BDS sat	2.75
	IDS sat	2.98

regardless the dihydro-*p*-hydroxycinnamate, the absence of α,β-unsaturation significantly improved the antiradical activity of the bisphenols. It is also noteworthy to mention that the antiradical activity of sinapic acid–based bisphenols is the more impacted by the unsaturation (gain factor of ca. 3.77 vs 1.63, respectively). The great difference observed between unsaturated ferulic acid–based bisphenols and unsaturated sinapic acid–based bisphenols could be due to the extra methoxy group at the 5-position that stabilizes further the quinone methide. Finally, the lower antiradical activities observed with

Table 4. Antiradical Activity of Saturated vs Unsaturated Bisphenols

entry	compound	EC_{50} (nmol)	gain factor
1	BDF unsat	6.22	1.58
	BDF sat	3.94	
2	IDF unsat	8.34	1.68
	IDF sat	4.97	
3	BDS unsat	9.97	3.62
	BDS sat	2.75	
4	IDS unsat	11.70	3.92
	IDS sat	2.98	

isosorbide-based bisphenols can be explained by the fact that isosorbide disfavors the 1-*O*-4 intramolecular coupling due to its higher rigidity (Table 3, entries 2 and 4).

In terms of sustainability, the fact that unsaturated bisphenols are the less active is particularly fortunate as their preparations require a relatively large number of steps and generate byproducts (e.g., triphenylphosphine oxide) in relatively large amounts.

Bisphenols: Influence of the Methoxylation Degree of the Aromatic Rings on the Antiradical Activity. The last structural variation explored was the degree of methoxylation. As expected, with saturated bisphenols, the higher the degree of methoxylation, the lower the EC_{50} value is (Table 5, entries 2 vs 4, entries 6 vs 8). It is noteworthy to mention that the activity of *p*-couramic acid-derived bisphenols is at least 100 times less than that of ferulic acid-based counterparts. These results

Table 5. Effect of Degree of Methoxylation on Antiradical Activity of Bisphenols

entry	diol	constant factor	structural variation	compound	EC_{50} (nmol)
1	1,4-butanediol	ferulic	unsaturated	BDF unsat	6.22
2	1,4-butanediol	ferulic	saturated	BDF sat	3.94
3	1,4-butanediol	sinapic	unsaturated	BDS unsat	9.97
4	1,4-butanediol	sinapic	saturated	BDS sat	2.75
5	isosorbide	ferulic	unsaturated	IDF unsat	8.34
6	isosorbide	ferulic	saturated	IDF sat	4.97
7	isosorbide	sinapic	unsaturated	IDS unsat	11.70
8	isosorbide	sinapic	saturated	IDS sat	2.98

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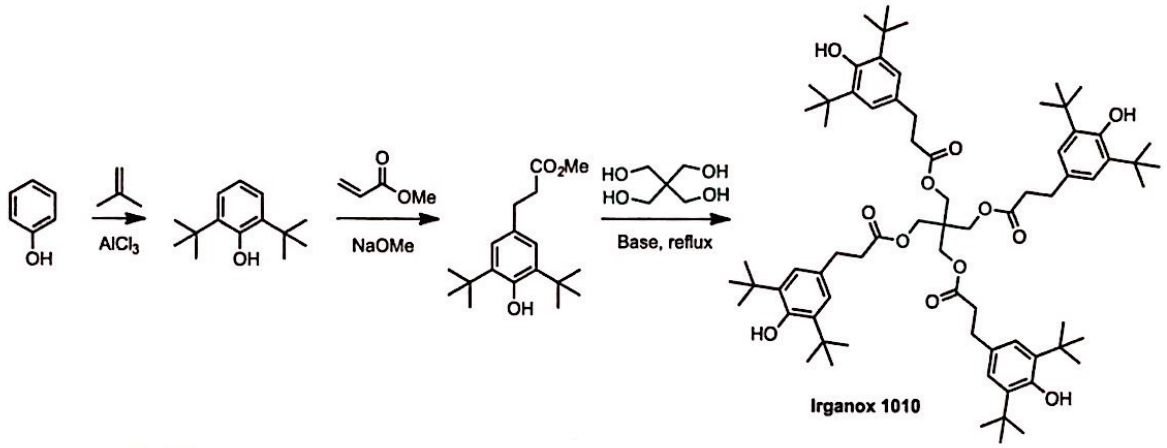
Table 6. Effect of Degree of Methoxylation vs Saturation on Antiradical Activity of Bisphenols

entry	diol	constant factor	structural variation	compound	EC_{50} (nmol)	gain factor
1	1,4-butanediol	ferulic	saturation	BDF unsat	6.22	1.58
				BDF sat	3.94	
2	1,4-butanediol	unsaturation	degree of methoxylation	BDF unsat	6.22	−0.62
				BDS unsat	9.97	
3	1,4-butanediol	sinapic	saturation	BDS unsat	9.97	3.63
				BDS sat	2.75	
4	1,4-butanediol	saturation	degree of methoxylation	BDF sat	3.94	1.43
				BDS sat	2.75	
5	isosorbide	ferulic	saturation	IDF unsat	8.34	1.68
				IDF sat	4.97	
6	isosorbide	unsaturation	degree of methoxylation	IDF unsat	8.34	−0.71
				IDS unsat	11.70	
7	isosorbide	sinapic	saturation	IDS unsat	11.70	3.93
				IDS sat	2.98	
8	isosorbide	saturation	degree of methoxylation	IDF sat	4.97	1.68
				IDS sat	2.98	

Scheme 4. Industrial Synthesis of Irganox 1010



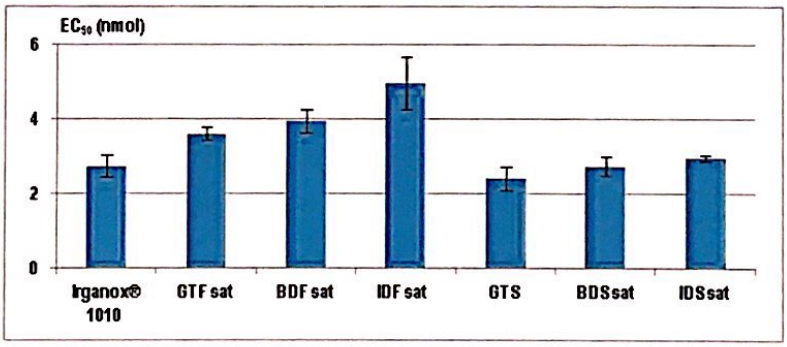


Figure 2. Benchmarking against Irganox 1010.

confirm the significant positive impact of methoxy group on both radical stability (+M, mesomeric effect) and antiradical activity already reported in the literature.[54−56] As already observed with *p*-hydroxycinnamate esters, the degree of methoxylation of unsaturated bisphenols has a negative impact on their antiradical activity (Table 5, entries 1 vs 3 and 5 vs 7).

Results reported in Table 6 also show that the saturation has a stronger impact on antiradical activity than the degree of methoxylation (entries 1 vs 2, 3 vs 4, 5 vs 6, and 7 vs 8).

In summary, a minimum degree of methoxylation of 1 (i.e., ferulic acid) is needed to observe a significant antiradical activity, and higher activities are obtained by using saturated sinapic acid-based bis- and trisphenols (Table 2, entries 18, 20 and 23). From all the above data, we are now able to determine the SAR for the optimization of the structural design with regards to the antiradical activity. The bisphenols exhibiting the higher antiradical activities are those possessing saturated esters and sinapic moieties. Saturated ferulic acid–based bisphenols come in second, whereas *p*-coumaric ones (saturated and unsaturated) are definitely ruled out.

Benchmarking against Irganox 1010. To evaluate the potential of these ferulic acid- and sinapic acid-based

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bisphenols, we have conducted a benchmarking test using Irganox 1010 which is a commercially available antioxidant/antiradical commonly used in polyolefins as well as in olefin copolymers such as ethylene vinyl acetate copolymers. Having a good compatibility, high resistance to extraction, low volatility, and odorless it is also recommended for the processing of polyacetals, polyamides, polyurethanes and polyesters. Irganox 1010 potent antioxidant/antiradical activity originates from the four di-2,6-*t*-butyl substituted phenolics that highly stabilize the phenoxy radical formed after H-transfer (Scheme 4).

Contrary to the bis- and trisphenols above that are 100% biobased and obtained through a sustainable chemo-enzymatic pathway, Irganox 1010 is usually obtained from phenol, isobutene, methyl metacrylate, and pentaerythritol using a three-step synthetic pathway involving Friedel–Crafts alkylation, aromatic alkylation, and base-catalyzed transesterification (Scheme 4). Apart from phenol and pentaerythritol which are fossil-based, methyl metacrylate[57] and isobutene[58,59] can be potentially obtained from biobased starting materials through white biotechnologies. However, these technologies are not industrially mature yet and these chemicals are still produced from fossil resources.

Results in Table 2 and Figure 2 demonstrate that Irganox 1010 possesses an EC_{50} of 2.75 nmol which is comparable to that of **BDS sat** and **IDS sat** (entries 18 and 20). The use of this tetraphenolic antiradical with di-2,6-*t*-butyl substituted aromatic moieties can thus be advantageously replaced by a biobased sinapic acid-based bisphenol, providing a more sustainable alternative (atom-economy, 100% biobased chemicals, chemo-enzymatic synthetic pathway). Interestingly, **BDS sat**—which is the most antiradical among the two latter bisphenols—is also the one obtained in higher yield (Table 1, entries 15 and 17). It is also noteworthy to mention that, if one wants to work with ferulic acid, the closest compound in terms of antiradical activity is the **GTF sat** trisphenol with an EC_{50} of 3.94 nmol.

CONCLUSION

In summary, a library of potential antioxidants was constituted in order to determine the SAR and to further optimize their antiradical activities. DPPH analysis of the compounds from the library showed that the degree of methoxylation of the phenolic group and the absence of the α,β-unsaturation were the critical factors; whereas the nature of the diol impacted slightly the antioxidant activity. Thanks to the established SAR, we identified saturated bisphenolic compounds deriving from ferulic acid and sinapic acid as the most potent antiradicals. Indeed, when compared to Irganox 1010, a recognized, industrialized and commercially available antioxidant, these bisphenols exhibit comparable antiradical activity. Furthermore, the main advantage of these saturated bisphenols over Irganox 1010 is that they are 100% biobased and prepared by an ecofriendly, chemo-enzymatic pathway. Thermal analyses (TGA) demonstrated that these bis- and trisphenols exhibit high thermal stability and that their T_d5% values can be easily tailored by playing with the structure of the bisphenol core. On the basis of these results, these renewable bis- and trisphenols are promising new efficient biocompatible antioxidant additives for a sustainable approach to polymer stabilization with considerable potential advantages over commonly used low molecular weight phenolic antioxidant such as reduced tendency of leaching, high stability to thermal and oxidative injury, lower toxicity, and biodegradation ability due to the esters linkages.

Finally, although the DPPH radical scavenging analysis used to evaluate antiradical activities is useful to do a screening of several molecules in liquid solutions, it does not necessarily reflect the antioxidant activity as well as their behavior/mobility in solid media. Further work such as OIT analysis or thermal aging of additive polymers matrices will be required to establish the actual antioxidant activity of these compounds in polymer matrices.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b01281.

Analytic details (FT-IR, UV, NMR, HRMS) as well as ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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