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Optimization of the Antioxidant Activity of Hydroxy-Substituted 4-Thiaflavanes: A Proof-of-Concept Study

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Abstract: The design and the synthesis of a new family of hydroxy-4-thiaflavanes, in which the reactive phenolic OH is *ortho* to the sulfur atom of the benzofused oxathiin ring, allowed to prepare antioxidants that show rate constants for the reaction with peroxyl radicals (k_{inh}), and bond dissociation energies (BDE), of the ArO–H group identical to those of α-tocopherol, the main component of vitamin E and the most effective lipophilic antioxidant known in nature. The peculiar conformation of the six-membered heterocyclic ring prevents the formation of an intramolecular hydrogen bond between the OH group and the S atom, while ensuring a good stabilization by electron donation of the phenoxyl radical formed after the reaction with peroxyl radicals. The preparation of these compounds was achieved through an inverse electron demand hetero Diels–Alder reaction of styrenes with *o*-thioquinones, in turn prepared from accurately designed 1,3-dihydroxy arenes. Properly arranging the substitution pattern on the aromatic ring, as in derivatives **9** and **11**, allowed to reach values of k_{inh} up to $4.0\times10^{6}\,M^{-1}s^{-1}$ and $BDE_{(OH)}$ of $77.2\,kcal\,mol^{-1}$. This approach represents an innovative way to obtain highly active antioxidants without using strongly electron donating alkylamino groups which are associated with adverse toxicological profiles.

Keywords: 4-thiaflavane · antioxidants · cycloaddition · sulfur heterocycles · tocopherols

Introduction

The autoxidation of unsaturated hydrocarbons and lipids is one of the most studied reactions, both for technological reasons and for its relevance in biological environments, because this process accounts for the damage caused by free radicals to organic and bioorganic systems. This reaction can be inhibited, or at least retarded, by chain-breaking antioxidants capable of trapping free radicals without transforming themselves in reactive intermediates. Phenols, which represent the main family of antioxidants, can donate the phenolic hydrogen atom to the chain-carrying peroxyl radicals to form a phenoxyl radical stabilized by resonance, hence they are relatively unreactive toward oxygen and organic materials.[1] The extent to which the autoxidation is retarded by phenols depends upon the rate constant of the inhibition reaction between antioxidant and peroxyl radicals k_{inh} [Eq. (1)].

$$ROO^{\bullet} + ArOH \xrightarrow{k_{inh}} ROOH + ArO^{\bullet} \quad (1)$$

Over recent decades, much work has been done to clarify the basic principles that determine the rates of Reaction (1) and to synthesize compounds that show k_{inh} values similar (or higher) to those of α-tocopherol (α-TOH),[2] which is the most effective lipid-soluble antioxidant present in nature.[2,3] Actually, some of the synthetic phenols developed show excellent features, such as very high reactivity towards peroxyl radicals and improved air stability.[4]

Another active area of research is the study of preventive antioxidants,[5] compounds often containing divalent S, Se, or Te atoms in the molecular skeleton,[6] which inhibit the formation of initiating free radicals by decomposing hydroperoxides by a nonradical process. Chalcogen-substituted phenols have been found to possess both chain-breaking and preventive antioxidant activities.[7] Recently, an original hetero Diels–Alder approach, consisting of the reaction of electron-poor *o*-thioquinones with suitable alkenes (Scheme 1),[8] has been used to prepare hydroxylated sulfur heterocycles with a structure resembling natural polyphenols present in plants (compounds **1**–**4**).[9–11]

The main appeal of this new family of phenolic compounds is that both the diene and the dienophile can be easily modified to obtain a final benzoxathiine cycloadduct with the required structural characteristics. In previous studies, several sulfur-containing analogues of flavonoids, like

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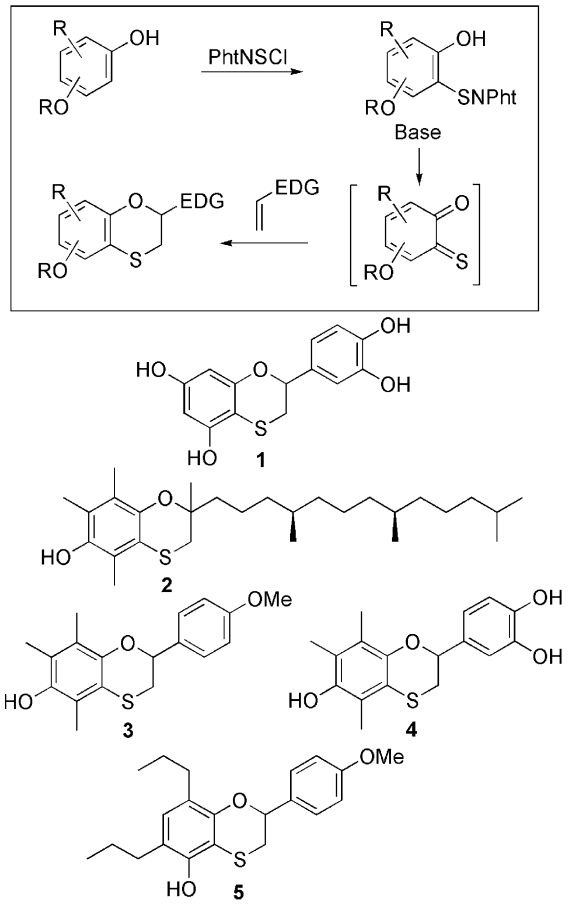
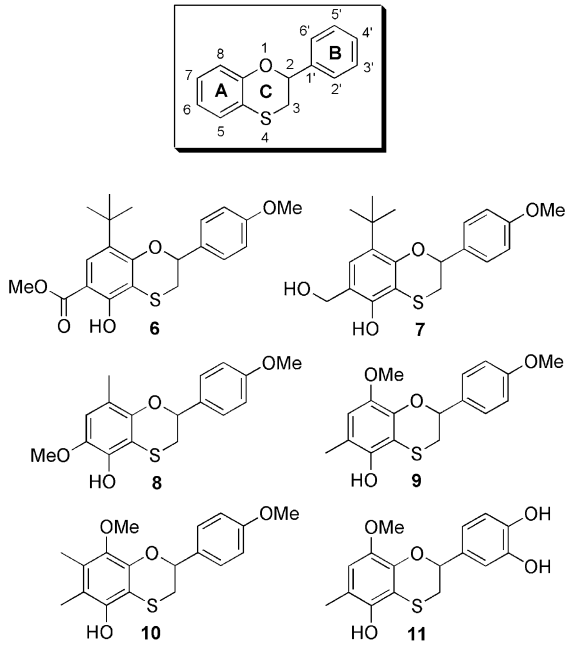


Scheme 1. Hetero Diels–Alder approach used and selected lead 4-thiaflavane antioxidants **1**–**5** prepared prior to this study. EDG = electron-donating group, Pht = phthaloyl.

1,[9] or tocopherols, like **2**,[10] or compounds possessing a structure related to both these families of powerful antioxidant polyphenols, like **3** and **4**,[11] were synthesized and tested for their antiradical activity in model and/or in biological systems. Moreover, 4-thiaflavanes bearing an OH group *ortho* to the heterocyclic sulfur, like **5**, have been used as suitable models to rationalize the mechanism of action of galactose oxidase (GOase), a copper metalloenzyme that catalyses the two-electrons oxidation of primary alcohols to aldehydes.[12] Herein, we report how the data collected studying the relationship between stereoelectronic features and chain-breaking activity of these 4-thiaflavanes have been exploited to design and prepare a new class of efficient and air stable phenolic antioxidants.

Results

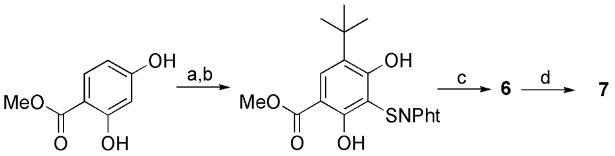
Syntheses: The antioxidant activity of the several 4-thiaflavanes previously investigated by our research group suggested to focus our attention toward derivatives **6**–**11** that bear as common feature an OH group on C5. Additional substitutions on the **A** ring were chosen to further modulate their antioxidant ability, while the catechol moiety on the **B** ring



Scheme 2. 4-Thiaflavane antioxidants **6**–**11** prepared in this study.

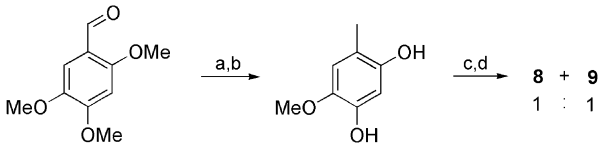
was introduced to ensure the multidefence aptitude of these compounds (Scheme 2).

To prepare derivatives **6**–**11** we adapted our general procedure based on an inverse electron demand hetero Diels–Alder reaction of *o*-thioquinones with styrenes using as starting phenols proper substituted resorcines. Compound **6** was obtained starting from 2,4-dihydroxymethyl benzoate which was *t*-butylated and sulfenylated with phthalimidesulfenyl chloride **12** (PhtNSCl) without any protection at the hydroxy groups but using a stoichiometry amount of 2,6-di-*t*-butylpyridine to intercept the HCl formed during the reaction which, otherwise, causes a dramatic decrease of the final yield (Scheme 3). Generation of the thioquinone in the



Scheme 3. Reagents and conditions: a) *t*BuOH, H_2SO_4, 60 °C, 94 h, 91 %. b) PhtNSCl (**12**), 2,6-di-*t*-butylpyridine, $CHCl_3$, 0 °C–RT, 45 h, 80 %. c) *p*-Methoxystyrene (**13**), Et_3N, $CHCl_3$, 60 °C, 4 h, 68 %. d) $LiAlH_4$, THF, −10 °C, 30 min, 72 %.

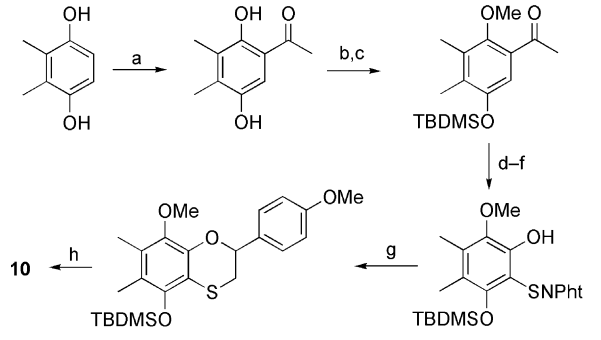
presence of *p*-methoxystyrene (**13**) gave benzoxatiine **6** isolated as single regioisomer. Hence, only one of the free OH groups participate to the formation of the dienic thioquinone, and we deduced that the intramolecular hydrogen bond (IHB) between the ester group and the adjacent OH group prevents its involvement into the cycloadditon. Reduction of the ester moiety with $LiAlH_4$ in dry THF, allowed the isolation of hydroxymethyl derivative **7** as reported in Scheme 3.



Scheme 4. Reagents and conditions: a) $AlCl_3$, CH_2Cl_2, RT, 24 h, 71%. b) $NaCNBH_3$, THF, RT, 4 h, 76%. c) **12**, $CHCl_3$, 0°C–RT, 17 h. d) **13**, $CHCl_3$, 60°, 18 h, 38% overall over two steps.

The possibility to run sulfenylation of 1,3-dihydroxy aryl derivatives with **12** avoiding OH protection, suggested a short path to thiaflavanes **8** and **9** as described in Scheme 4. Selective 2,4-demethylation of 2,4,5-trimethoxybenzaldeyde with $AlCl_3$,[13] followed by $NaCNBH_3$[14] reduction of the aldehyde to methyl group, allowed the isolation of 4-methoxy-6-methyl resorcine which was sulfenylated with **12**. All attempts to isolate the corresponding *N*-thiophthalimide were unsuccessful since it demonstrated a poor stability on standing and completely decomposed on silica gel, thus it was reacted, as crude material, with **13** in the presence of Et_3N. In this case both OH groups participate to the *o*-thioquinone formation giving rise to a pair of dienes, and eventually to a mixture of two regioisomeric cycloadducts **8** and **9** which were obtained in moderate yields in roughly 1:1 ratio, and separated by an accurate flash chromatography (Scheme 4).

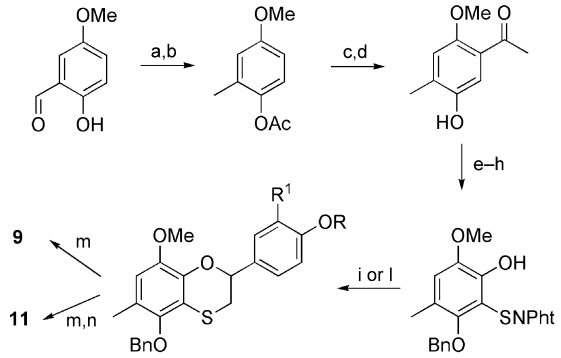
The preparation of 6,7-dimethyl derivative **10** was achieved starting from 2,3-dimethyl hydroquinone which was acetylated and then orthogonally protected at the OH groups by a selective silylation of the phenolic OH not engaged in an IHB with the acetyl group, followed by an exhaustive methylation. A Baeyer–Villiger oxidation allowed the introduction of the third aryl–oxygen bond followed by, in sequence, saponification, sulfenylation, and cycloaddition (see the Supporting Information for details). Desilylation of *t*-butyldimethylsilyl ether at position 5 allowed the isolation of 4-thiaflavane **10** as described in Scheme 5. The overall yield was modest, however, the results obtained by measuring the antioxidant activity of derivatives **6–11**, vide infra,



Scheme 5. Reagents and conditions: a) AcOH, $BF_3 2H_2O$, 120°C, 20 h, 65%. b) $tBuMe_2SiCl$, IMI, DMF, RT, 18 h, >98%. c) CH_3I, K_2CO_3, DMF, 100°C, 15 h, 75%. d) *m*-CPBA, *p*-TsOH, CH_2Cl_2, RT, 24 h, 68%. e) KOH, DMF/CH_3OH, RT, 18 h. f) **12**, $CHCl_3$, 0°C–RT, 5 h, 45% over two steps. g) **13**, Et_3N, $CHCl_3$, 60°C, 18 h. h) TBAF$3H_2O$, THF, 0°C–RT, 3 h, 67% over two steps.

suggested it was worthless to consume time in optimization of the synthetic procedure required for the synthesis of **10**.

On the contrary, the good antioxidant performances showed by compound **9** prompted us to design a new synthetic path which allowed its preparation, as well as that of related 4-thiaflavanes possessing the same substitution pattern on the **A** ring, as a single regioisomer in acceptable overall yield. Thus, 2-methyl-4-methoxy phenol, obtained by Wolf–Kishner reduction of the corresponding commercial available benzaldehyde, was acetylated at the OH group with Ac_2O in TEA followed by ring acylation with AcCl/$AlCl_3$. A quantitative acetyl/benzyl protecting group switching, followed by Baeyer–Villiger oxidation and saponification, allowed the preparation of the required phenol which was sulfenylated with **12**, and a stoichiometry amount of 2,6-di-*t*-butylpyridine to obtain the precursor of the corresponding *o*-thioquinone. Cycloaddition with **13** or with *t*-butyldimethylsilylether of 3,4-dihydroxystyrene (**14**) led to the formation of the required cycloadducts which were debenzylated[15] (and desilylated) to isolate 4-thiaflavanes **9** and **11** as reported in Scheme 6.



Scheme 6. Reagents and conditions: a) N_2H_4, KOH, glycol, RT, 150°C, 19 h, >98%. b) Ac_2O, TEA, CH_2Cl_2, RT, 16 h, >98%. c) AcCl, $AlCl_3$, CH_2Cl_2, 0°C–RT, 3 h, 64%. d) NaOH, H_2O/THF, RT, 16 h, >98%. e) BnBr, NaH, THF, 0°C–RT, 24 h, >98%. f) *m*-CPBA, *p*-TsOH, CH_2Cl_2, RT, 24 h. g) NaOH, H_2O/CH_3OH, RT, 24 h, 80% over two steps. h) **12**, 2,6-di-*t*-butylpyridine, $CHCl_3$, 0°C–RT, 24 h, 75%. i) **13**, $CHCl_3$, 60°C, 72 h, 74%. l) **14**, $CHCl_3$, 60°C, 72 h, 83%. m) Pd, NH_4COOH, EtOH/AcOEt/H_2O (7:2:1), 90°C, 4 h, >98%. n) TBAF$3H_2O$, AcOH, THF, 0°C–RT, 1 h, 80%.

Antioxidant activity: The antioxidant activity of 4-thiaflavanes was evaluated by measuring the rate constant (k_{inh}) for their reaction with peroxyl radicals (ROO•), that are responsible for the propagation step of peroxidation processes in many natural and man-made materials. The values of k_{inh} were determined by studying the inhibition of the thermally initiated autoxidation of either styrene or cumene [Eqs. (2)–(7)] under controlled conditions, using chlorobenzene as a solvent.[2,3,16] Being less oxidizable than styrene, cumene was used to study weak antioxidants (see Table 1). In the case of styrene, the propagation step [Eq. (4)] consists of the addition of peroxyl radicals to the olefinic double bond of styrene.[2]

Table 1. Kinetic rate constants for the reaction of the investigated compounds with peroxyl radicals (k_{inh}), and number of radicals trapped by each antioxidant molecule (n).

Phenol	Substrate[a]	k_{inh} [M^{-1} s^{-1}][b]	n[b]
6	C	$<10^2$	–[c]
7	C	3.5×10^4	2.0
8	C,S	1.0×10^5	1.2
9	S	3.4×10^6	1.8
10	S	1.2×10^6	1.8
11	S	4.0×10^6	3.6
PMHC[d]	–	3.2×10^6	2.0

[a] C = cumene; S = styrene. [b] Error within 15%. [c] Not measurable. [d] From Ref. [2].

$$\text{Initiator} \xrightarrow{R_i} R^{\bullet} \quad (2)$$

$$R^{\bullet}+O_2 \rightarrow ROO^{\bullet} \quad (3)$$

$$ROO^{\bullet}+RH \xrightarrow{k_p} ROOH+R^{\bullet} \quad (4)$$

$$ROO^{\bullet}+ROO^{\bullet} \xrightarrow{2k_t} \text{Nonradical products} \quad (5)$$

$$ROO^{\bullet}+ArOH \xrightarrow{k_{inh}} ROOH+ArO^{\bullet} \quad (6)$$

$$ROO^{\bullet}+ArO^{\bullet} \rightarrow \text{Nonradical products} \quad (7)$$

These reactions were performed at 30°C by using azobis(isobutyronitrile) as initiator, and were followed by monitoring the oxygen consumption in an oxygen-uptake apparatus based on a differential-pressure transducer.[17] In the presence of good antioxidants, oxidation of the substrate and oxygen consumption are much slower than in their absence, and a clear inhibition period is observed (compare traces c–e with trace a in Figure 1). On the other hand, weak antioxidants only afford a retardation of the oxygen consumption (trace b). As the rate of O_2 consumption during the inhibition period is inversely dependent on k_{inh} and the concentration of the antioxidant (see Experimental Section for kinetic details),[2,3] the rate constant for the reaction between ROO• radicals and phenols **6–11** could be easily obtained. The number of radicals trapped by each antioxidant molecule (n) was obtained from the length of the inhibition period, by comparison with the reference antioxidant 2,2,5,7,8-pentamethyl-6-chromanol (PMHC), a model for the physiological antioxidant α-tocopherol, for which $n=2$.[2] For inhibitors which act by reactions 6 and 7, a n value of 2 is expected.[2] The values of k_{inh} and n, calculated from the slope and the length of the inhibited period are reported in Table 1.

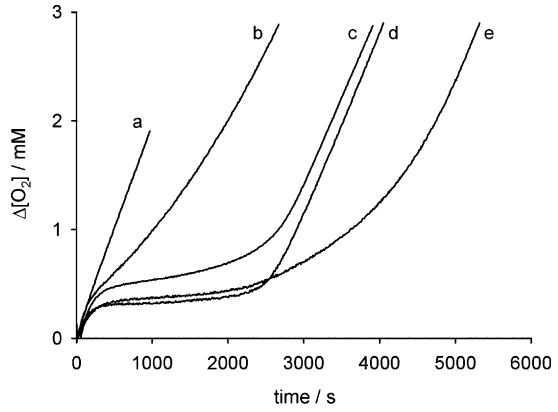


Figure 1. Oxygen consumption traces observed during the autoxidation of styrene (4.3 M) initiated by AIBN (0.05 M) at 30°C in a) chlorobenzene in the absence of antioxidants or b) in the presence of **8** (1×10^{-5} M); c) **10** (8.5×10^{-6} M), d) **9** (8.5×10^{-6} M), and e) **11** (8.5×10^{-6} M).

From Table 1, it can be seen that the 4-thiaflavanes having in *ortho* position strong H-bond accepting groups (i.e., **6**, **7**, and **8)** are weak inhibitors of the autoxidation reaction.[18] Values of k_{inh} comparable to that of PMHC were obtained in the case of **9** and **11**, while the presence of an additional methyl group in **10** caused a small reactivity decrease. The stoichiometric coefficients smaller than 2 in the case of **9**, **10**, and especially **8**, indicate that the phenoxyl radicals from the antioxidants (ArO•) have some attitude to propagate the oxidative chain, presumably by fragmentation of the methoxyl group to form a quinone and a methyl radical, which in turn generates another peroxyl radical.[19] As expected, the presence of two antioxidant moieties in compound **11** (hydroxy 4-thiaflavane and catechol) afforded a n value slightly smaller than 4 (see also Figure 1).[11]

EPR spectra and determination of the $BDE_{(O-H)}$ values: When photolyzing, inside the EPR cavity, oxygen-free solutions of **7–10** in benzene containing di-*t*-butylperoxide (5% v/v), EPR spectra characterized by *g*-factors and splitting constants typical of aryloxyl radicals were observed (see Table 2). In the case of **7**, the coupling with one hydrogen of the *o*-CH_2OH group and three smaller couplings were detected. The non-equivalence of the CH_2 protons suggests that there is slow rotation around the Ar–CH_2 bond, likely because of the existence of an IHB between the alcoholic OH group and the phenoxyl oxygen. The *g* values were similar to that measured previously for the phenoxyl radical from **5** ($g=2.0049$).[12]

Table 2. EPR spectral parameters of the aryloxyl radicals from **7–10**.

Phenol	Hyperfine splittings (gauss)	*g* value
7	3.00 (1H); 1.12 (1H); 1.07 (1H); 0.99 (1H)	2.0048
8	10.06 (3H); 1.50 (3H); 0.53 (1H); 1.70 (1H); 1.82 (1H)	2.0048
9	6.84 (3H); 1.45 (3H); 1.59 (1H); 0.93 (1H); 0.35 (1H)	2.0048
10	5.52 (3H); 1.08 (3H); 0.74 (3H); 2.02 (1H)	2.0049

$$ArOH + Ar'O^{\bullet} \overset{K_8}{\rightleftharpoons} ArO^{\bullet}+Ar'OH \quad (8)$$

$$BDE_{(ArOH)} = BDE_{(Ar'OH)} - RT\ln K_8 \quad (9)$$

The BDE of the O–H bond in compounds **7–10** was determined by using the electron paramagnetic resonance radical equilibration technique (Req-EPR).[16,20] The equilibrium constant K_8 of two equilibrating phenols and the corresponding phenoxyl radicals [Eq. (8)] was measured in ben-

zene by determining the relative concentrations of the phenoxyl radicals generated by photolyzing a deoxygenated mixture of the investigated compound (ArOH) and a reference phenol (Ar′OH) (Figure 2). The reference was 2,6-di-*t*-butyl-4-methoxyphenol (dBHA, BDE = 77.2 kcal mol^{-1})[20,21] and 2,6-di-*t*-butyl-4-methylphenol (BHT, BDE = 79.9 kcal mol^{-1}).[20,21] As the entropic term in H-atom transfer equilibria is negligible,[22] the $BDE_{(OH)}$ was determined by Equation (9) from the measured K_8 values, as reported in Table 3.

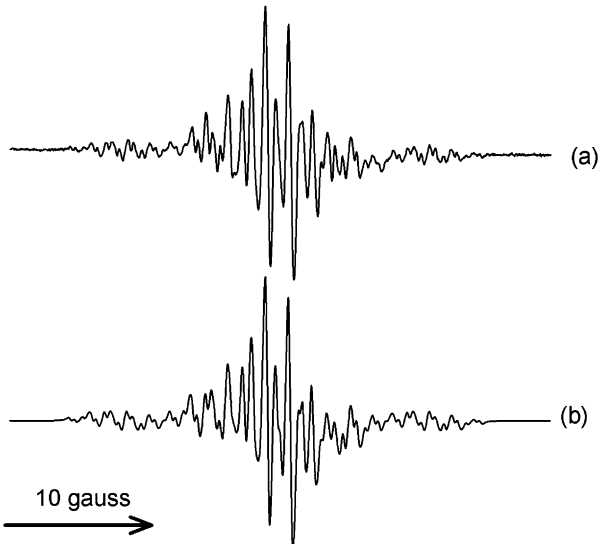


Figure 2. a) Experimental and b) computer simulated EPR spectrum observed when photolyzing a mixture of **9** and dBHA in a concentration ratio 1:1.

Table 3. Req-EPR equilibrium constants and corresponding $BDE_{(OH)}$ for 4-thiaflavanes **7**–**10** at 298 K.

Phenol	Reference	K_8	BDE [kcal mol^{-1}]
7	BHT	0.4 ± 0.1	80.4 ± 0.02
8	BHT	0.99 ± 0.08	79.9 ± 0.02
9	dBHA	0.9 ± 0.1	77.2 ± 0.02
10	dBHA	0.06 ± 0.01	78.8 ± 0.02
α-TOH	–	–	77.2[a]

[a] From Refs. [20] and [21].

The low solubility in benzene of compound **11** prevented the determination of its BDE. However, kinetic studies suggest that the hydroxy-4-thiaflavane moiety should have a $BDE_{(OH)}$ almost coincident to that of **9**, and the catecholic portion should have a BDE similar to that of 4-methylcatechol (ca. 79.2 kcal mol^{-1}).[20–22]

IR spectroscopy: To assess the role of the IHB on the kinetics of the hydrogen atom transfer to peroxyl radicals, the FT-IR spectra of phenols **7**–**10** were recorded in diluted CCl_4 solutions, taking care to avoid phenol autoassociation (Figure 3). In the case of **9** and **10**, two different absorptions were observed in the OH stretching region: a broad band at about 3540 cm^{-1} attributed to a weakly intramolecularly H-bonded species (*syn* conformation with respect to the sulfur atom) and a sharp peak typical of the "free" OH (*anti* conformation), at about 3612 cm^{-1}.

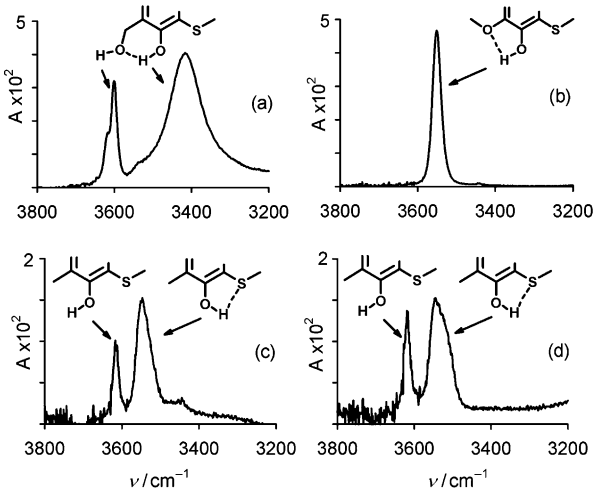


Figure 3. Infrared spectra in the OH stretching region of diluted CCl_4 solutions of: a) **7**, b) **8**; c) **9**; d) **10**. Assignments of IR bands are indicated.

As we pointed out in the case of **5**, the inclusion of the *ortho* S-alkyl substituent in a six-membered ring dramatically reduces the ability of the S atom to act as H-bond acceptor because of the directionality of the sulfur lone pairs.[12] Actually, a phenol having in *ortho* position a -SCH_3 group showed only one absorption band at 3375 cm^{-1}, indicating a strong IHB with the sulfur atom.[23] The IR spectrum of compound **8** showed a single peak at 3549 cm^{-1}, at a frequency slightly lower than that of 2-methoxyphenol (3558 cm^{-1}).[18b] Since in this molecule the S atom is a rather weak H-bond acceptor, it can be supposed that in **8** the OH group forms a strong IHB with the oxygen atom of the *ortho* OMe group. The spectrum of **7** showed a band at 3418 cm^{-1} due to the phenolic OH donating a IHB to the alcoholic oxygen atom, and two overlapping bands at 3600–3615 cm^{-1} owing to different conformations of the free alcoholic OH.[24]

Discussion

Our 'first generation' 4-thiaflavanes were built by considering Flavonoids as natural antioxidant models.[9] The structure of derivative **1** was inspired to that of catechin, a well-known natural polyphenolic antioxidant bearing a 3′,4′-dihydroxy (i.e., catechol) fragment as **B** ring. Similarly to catechin, **1** showed good chain-breaking antioxidant activity ($k_{inh} = 6 \times 10^5$ M^{-1} s^{-1})[9d] that was almost completely due to the catechol moiety. It was also demonstrated that 4-thiaflavanes behaved as preventive antioxidants, thanks to their activity as metal chelators, and as hydroperoxide quenchers, due to the oxidation of the S-alkyl group to a sulfoxide. These findings allowed us to consider them distinctive multipotent antioxidants.[9–11]

However, since the overall antioxidant activity of **1**, in terms of k_{inh}, was roughly 5 times lower than that of vitamin E, we designed a 'second generation' of 4-thiaflavane antioxidants possessing the **A** and **C** rings identical to the trimethylchromanol ring of α-TOH. By exploiting the flexibility of our hetero Diels–Alder based synthetic procedure, we could prepare α-4-thiatocopherol **2**,[10] with exactly the same structure of natural vitamin E but with the sulfur atom on position 4, as well as compounds like **3** and **4** with a molecular skeleton resembling both flavonoid and tocopherol structures.[11] When a *o*-dihydroxy substituted **B** ring was present, like in **4**, the inhibition time and the number of intercepted peroxyl radicals (n) were doubled.[11] By increasing the similarities of our compounds with α-tocopherol, we actually increased the antioxidant ability of 4-thiaflavanes since the k_{inh} values of **2**–**4** were a third of that of α-TOH, and the $BDE_{(OH)}$ values were roughly 2 kcal mol^{-1} higher.[11]

Despite their structural similarity to α-TOH, derivatives **2**–**4** were less reactive toward ROO$^{\bullet}$ than α-TOH, because of the substitution of a methylene bridge with a sulfide bridge. A rational explanation for this result arose from the X-ray analysis of 4-thiaflavanes, such as **3**, when considering the change in the dihedral C10-C9-O1-C2 angle (θ) induced by replacing the carbon atom with the sulfur atom in **C** ring (Figure 4).[11] It is well known that the presence of the condensed, saturated ring in chromanols is important for their good antioxidant activity, as it forces the $2p_z$ orbital of the heterocyclic oxygen atom, which is sp^2 hybridized and conjugates better with the aromatic ring.[3] The presence of the sulfur atom in the saturated condensed ring affected the geometries of both phenol and phenoxyl radical, and the experimental (X-ray) and the computed [(B3LYP/6-31+G-(2d,p)//B3LYP/6–31G(d)] θ values of **3** were larger by 12° and 5° than those of PMHC[3] (Figure 4). This difference implies that thiaflavanes, such as **3**, have, in the preferred geometry, the C2 atom remarkably out of the aromatic plane, hence the conjugation between the aromatic ring and the lone pair of the oxygen atom is noticeably decreased with respect to α-TOH in both phenol and phenoxyl radical.[11]

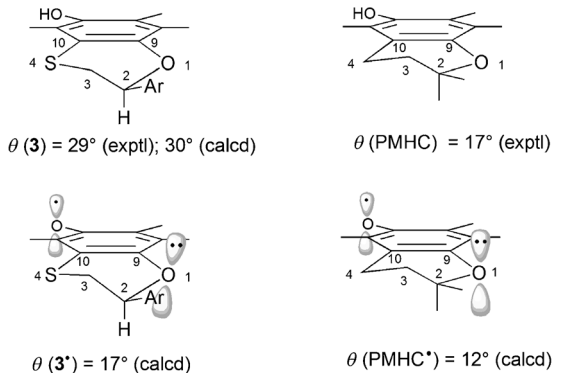


Figure 4. Experimental and calculated dihedral angles θ (C10-C9-O1-C2) for 4-thiaflavane **3**,[11] PMHC[3] and the corresponding phenoxyl radicals.

Actually, the decrease in conjugative stabilization of the phenoxyl radical as a result of the decreased overlap between the p orbitals of the aromatic ring and the $2p_z$ orbital of the heterocyclic oxygen atom is responsible for the larger $BDE_{(OH)}$ value observed in **3** than in PMHC.[11]

The analysis of conformational preferences of 4-thiaflavanes suggested further important considerations. In fact, while C2 is significantly out of the aromatic ring plane, C3 is almost coplanar and, consequently, the C9-C10-S4-C3 dihedral angle is very small (2° for **3**, 8° for **5**).[11,12] This is particularly important in the case of 5OH substituted 4-thiaflavanes, such as derivative **5**. FT-IR studies demonstrated that the strength of the intramolecular OH···S bond in **5** was nearly zero, differently from *o*-alkylthio phenols in which strong IHBs are formed if the substituent is free to rotate about the aryl–sulfur bond (see Figure 5).

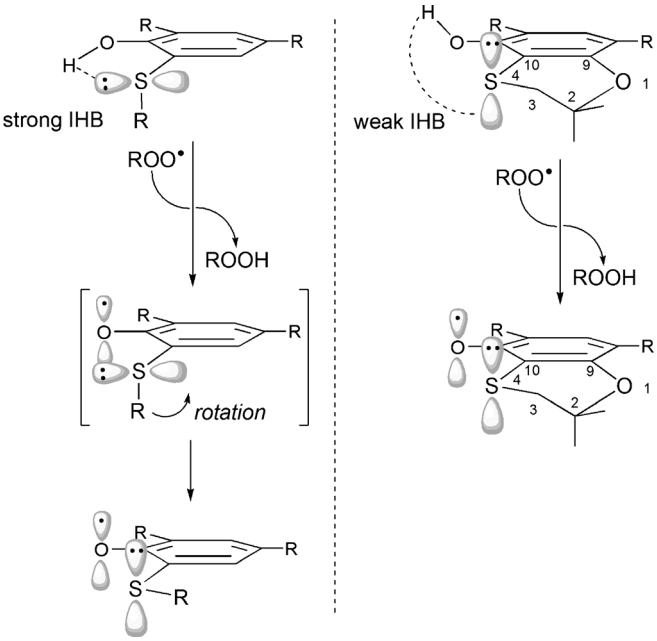


Figure 5. IHB and conjugative phenoxyl radical stabilization in free to rotate vs. conformationally constrained *o*-sulfanyl phenols.

This behavior has been described previously by Schaefer et al.[25] and has been explained by considering the poor tendency of alkylthio substituents to conjugate with the phenolic aromatic ring and their preference to form a stereospecific IHB using a 3p lone pair on sulfur that uses almost pure 3p orbitals to form its bonds.[26] As a matter of facts, compound **5** showed a smaller $BDE_{(OH)}$ and a larger k_{inh} with respect to the corresponding *o*-alkylthio derivatives, because of the absence of an IHB in the parent phenol and the large conjugative stabilization of the phenoxyl radical by the S atom (see Figure 5).[12] Such behavior is absolutely peculiar of the sulfur atom since *o*-alkoxy substituents, despite their superior electron-donating ability, give an overall smaller $BDE_{(OH)}$ decreasing contribution, since the phenol

stabilization effect caused by the IHB is strong and unaffected by rotation around the Ar–OR bond.[18]

Initially, we utilized such observation to give a contribution on understanding the mechanism of action of the enzyme galactose oxidase (GOase),[12] then we realized it could be exploited to design a 'third generation' of 4-thiaflavane antioxidants. In fact, an OH group in position 5, an alkyl group in position 6 and other appropriate electron-donating groups on the **A** ring, could be considered as the substitution pattern of choice for an optimized 4-thiaflavane antioxidant. Thus, we decided to focus our synthetic efforts on 4-thiaflavane derivatives similar to **5** using suitable 1,3-dihydroxyarenes (resorcines) as suitable starting phenols.

Since 4,6-disubstituted-1,3-dihydroxy benzenes can be sulfenylated with **12** avoiding protection of the phenolic OH, we initially prepared derivatives **6** as reported in Scheme 3. It is worth of mention that only the OH group not involved in an IHB with the ester group participates to the formation of the intermediate *o*-thioquinone, thus the cycloaddition gave a single regioisomeric 4-thiaflavane (**6**). The antioxidant ability of derivative **6** was, as expected, very low due to the presence of the electron-withdrawing ester group in position 6 that, additionally, engages in a strong IHB the phenolic OH responsible for the reaction with ROO$^\bullet$ radicals. In fact, as reported in Table 1, the corresponding k_{inh} was under the limit of our measure ($<10^2\,M^{-1}s^{-1}$). Reduction of the ester group, to give hydroxymethyl derivative **7**, removes almost entirely the electron-withdrawing character of the substituent in position 6 and ensures a weaker IHB. In fact, alcohol **7** was a much better inhibitor than **6** ($BDE_{(OH)}=80.4\,kcal\,mol^{-1}$; k_{inh} $3.5\times10^4\,M^{-1}s^{-1}$) even if it is far to be considered a good antioxidant. The step forward was achieved by preparing 4-methoxy-6-methyl-1,3-dihydroxy benzene which was sulfenylated with **12** and directly used to generate the corresponding *o*-thioquinone(s) (Scheme 4). In this case, both OH groups participate to the 1,4-elimination at the sulfur atom, giving rise to two dienic *o*-thioquinones and, consequently, to a mixture of regioisomeric 4-thiaflavanes **8** and **9** formed in roughly 1:1 ratio. Having these two derivatives in hand we could demonstrate our aforementioned deductions about the stereoelectronic influence of the heterocyclic sulfur atom on the reaction of an *o*-OH group with peroxyl radicals. In fact, the k_{inh} and BDE of derivative **8** are typical of a weak antioxidant (very similar to **7**), since the 6-methoxy group causes the formation of an IHB with the 5OH, while the methyl group in position 8 gives only a small contribution to phenoxyl radical stabilization.[20] On the contrary in derivative **9** both the methyl group on the 6 position and, above all, the 8-methoxy EDGs strongly contribute to increase the stability of intermediate phenoxyl radical, while the phenolic OH is not stabilized by IHB with the heterocyclic sulfur atom in position 4 that is structurally prevented to act as HB acceptor, as confirmed by FT-IR experiments. In fact, with our great satisfaction, compound **9** showed k_{inh} and $BDE_{(OH)}$ better than any other 4-thiaflavane prepared so far and identical to those of α-TOH.[2,3]

Once determined the optimized **A** ring substitution pattern we decided to prepare 6,7-dimethyl-8-methoxy derivative **10** to verify whether the introduction of an extra methyl group in position 7 could further increase the antioxidant activity. As described in Scheme 5, the preparation of **10** was designed considering the selective protection of one of the OH group, hence avoiding the formation of a mixture of regioisomeric thiaflavanes. As reported in Table 1, despite the extra ED methyl group, k_{inh} and $BDE_{(OH)}$ of compound **10** are little worse than those of compound **9**. This has been rationalized considering that the methyl group in position 7 is likely to prevent the methoxy group in position 8 from adopting the conformation required for an optimal stabilization of the incipient phenoxyl radical (Figure 6), similarly to what previously reported for methyl substituted *p*-methoxyphenols.[2,3]

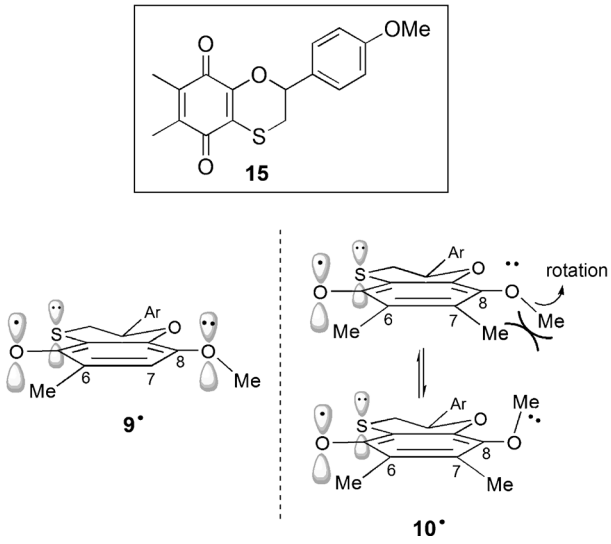


Figure 6. Structure of quinone **15**; and effect of the C7 methyl group on the conjugative stabilization of phenoxyl radicals **9**$^\bullet$ and **10**$^\bullet$ produced by the C8 methoxy group.

Attempts to obtain crystals of **10** to verify the position of methoxy group in the solid state were unsuccessful, as dark red crystals of quinone **15** (Figure 6), were collected when a diluted solution of **10** in CCl_4 was slowly evaporated at room temperature for 3 weeks. This reaction, which probably involves molecular oxygen as oxidizing agent, was not observed for any of the other 5-hydroxy-4-thiaflavanes reported in this paper.

On the light of these latter results, we redesigned a synthetic procedure (see Scheme 6) that allowed the preparation of derivative **9** as single regioisomer, and of compound **11**, which contains also a dihydroxy-functionalized **B** ring. From the oxygen uptake plots reported in Figure 1, it can be seen that in **11** both antioxidant moieties contributed to the inhibition of styrene autoxidation, as the strongly inhibited period due to the 5-hydroxy-4-thiaflavane is followed by a weaker inhibition due to the catecholic group. Therefore,

the number of intercepted peroxyl radicals for each molecule of **11** was doubled with respect to **9** (Table 1).

Conclusion

The unique stereoelectronic features of 5-hydroxy-4-thiaflavanes allowed the synthesis of a new class of phenolic antioxidants having rate constants for the reaction with peroxyl radicals, k_{inh}, and bond dissociation energy of the ArO–H group, similar or slightly better than those of α-tocopherol, the main component of vitamin E and the more efficient lipophilic antioxidant known in nature. In these compounds, the cyclic *o*-alkylthio substituent stabilizes the phenoxyl radical formed on H-atom transfer to ROO$^{\bullet}$, while having no aptitude to accept intramolecular hydrogen bonding from the reactive OH, which would decrease the reactivity. This approach may represent an advantageous way to obtain highly active antioxidants, not containing the chromane moiety, without using strongly electron-donating alkylamino groups that could cause toxicity problems.[27]

Experimental Section

See below for spectroscopic data of thiaflavanes **6**–**11**, autoxidation studies, EPR spectroscopy, and IR measurements. All the other experimental details are available in the Supporting Information.

Methyl 8-*t*-butyl-2,3-dihydro-5-hydroxy-2-(4-methoxyphenyl)benzo[*b*]-[1,4]oxathiine-6-carboxylate (6): After the cycloaddition the crude reaction mixture was purified by flash chromatography on silica gel, using petroleum ether/EtOAc from 20:1 to 5:2 as eluent, to give derivative **6** as a yellow oil (68% yield); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.29$ (s, 9H), 3.08 (dd, $J=13.0$ and 1.6 Hz, 1H), 3.27 (dd, $J=13.0$ and 9.8 Hz, 1H), 3.84 (s, 3H), 3.93 (s, 3H), 5.07 (dd, $J=9.6$ and 1.6 Hz), 6.95 (m, 2H), 7.26 (s, 1H), 7.35 (m, 2H), 7.52 (s, 1H), 11.30 ppm (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=29.9$ (3C), 30.7, 34.6, 52.1, 55.3, 76.5, 104.3, 106.6, 114.2 (2C), 122.8, 127.4 (2C), 131.3, 132.0, 157.0, 157.3, 159.8, 170.7 ppm; elemental analysis calcd (%) for $C_{21}H_{24}O_5S$: C 64.93, H 6.23; found: C 65.25, H 6.51.

8-*t*-Butyl-2,3-dihydro-6-(hydroxymethyl)-2-(4-methoxyphenyl)benzo[*b*]-[1,4]oxathiin-5-ol (7): To a suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in dry THF (1 mL) under a nitrogen atmosphere was added at −10 °C a solution of **6** (64 mg, 0.15 mmol) in dry THF (2 mL) and stirred at this temperature for 30 min. After this time the mixture was diluted with H_2O (30 mL) and acidified with a 10% solution of HCl in MeOH. The solution was extracted with Et_2O (3×50 mL) and washed with H_2O (3× 100 mL) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure give derivative **7** as a colorless oil (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.28$ (s, 9H), 3.07 (dd, $J=12.8$ and 1.8 Hz, 1H), 3.27 (dd, $J=12.8$ and 10.0 Hz, 1H), 3.84 (s, 3H), 4.82 (s, 2H), 4.98 (dd, $J=10.0$ and 1.8 Hz), 6.70 (s, 1H), 6.94–6.97 (m, 2H), 7.35–7.37 (m, 2H), 7.57 ppm (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=30.1$ (3C), 31.4, 34.5, 55.3, 64.9, 75.9, 107.2, 114.0 (2C), 115.7, 121.0, 127.2 (2C), 130.9, 132.5, 150.2, 152.2, 159.3 ppm; elemental analysis calcd (%) for $C_{20}H_{24}O_4S$: C 66.64, H 6.71; found C 66.85, H 6.59.

2,3-Dihydro-6-methoxy-2-(4-methoxyphenyl)-8-methylbenzo[*b*]-[1,4]oxathiin-5-ol (8): After the cycloaddition and column flash chromatography on silica gel using CH_2Cl_2/petroleum ether = 8:1 as eluent, compound **8** was isolated as a pale yellow solid; m.p. 138–143 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.16$ (s, 3H), 3.04–3.23 (m, AB part of an ABX system, $J_{AB}=13.2$ Hz, 2H), 3.83 (s, 6H), 5.06 (dd, X part of an ABX system $J=8.5$ and 2.9 Hz, 1H), 5.71 (s, 1H, OH), 6.50 (s, 1H), 6.92–6.97 (m, 2H), 7.34–7.39 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=16.0$, 31.1, 55.3, 56.7, 75.7, 104.9, 109.7, 113.9 (2C) 117.6, 126.9 (2C) 132.8, 139.2, 139.5, 144.8, 159.3 ppm; IR (CCl_4 0.01 M): $\tilde{\nu}$(OH) = 3550; (CCl_4 0.001 M): 3550 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{18}O_4S$: C 64.13, H 5.70; found: C 63.96, H 5.89.

2,3-Dihydro-8-methoxy-2-(4-methoxyphenyl)-6-methylbenzo[*b*]-[1,4]oxathiin-5-ol (9): Directly after the cycloaddition (see Scheme 4), or after cycloaddition and deprotection (see Scheme 6), a column flash chromatography on silica gel, using CH_2Cl_2/petroleum ether = 8:1 as eluent, allowed the isolation of compound **9** as a pale pink solid; m.p. 140–145 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.20$ (s, 3H), 3.10–3.24 (m, AB part of an ABX system, $J_{AB}=12.8$ Hz, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 4.47 (s, 1H, OH), 5.20 (dd, X part of an ABX system $J=6.6$ and 4.4 Hz, 1H), 6.49 (s, 1H), 6.89–6.94 (m, 2H), 7.32–7.37 ppm (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=15.7$, 31.0, 55.3, 57.0, 75.9, 106.7, 111.3, 113.9 (2C), 114.6, 127.2 (2C), 132.1, 140.9, 143.0, 143.1, 159.4 ppm; IR (CCl_4 0.01 M): $\tilde{\nu}$(OH) = 3612, 3545; (CCl_4 0.001 M): 3436 cm^{-1} (br); elemental analysis calcd (%) for $C_{17}H_{18}O_4S$: C 64.13, H 5.70; found: C 64.49, H 5.29.

2,3-Dihydro-8-methoxy-2-(4-methoxyphenyl)-6,7-dimethylbenzo[*b*]-[1,4]oxathiin-5-ol (10): After cycloaddition and desilylation the crude was purified by column flash chromatography on silica gel, using CH_2Cl_2 as eluent, to give derivative **10** as a glassy yellowish solid (67% yield over two step); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.12$ (s, 3H), 2.18 (s, 3H), 3.10–3.15 (m, AB part of an ABX system, $J_{AB}=13.0$ Hz, 2H), 3.72 (s, 3H), 3.83 (s, 3H), 4.57 (br s, 1H, OH), 5.18 (t, X part of an ABX system, $J=5.8$ Hz, 1H), 6.92–6.95 (m, 2H), 7.34–7.38 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=11.7$, 12.2, 31.2, 55.3, 60.7, 76.2, 103.0, 114.0, 114.9, 127.1, 127.3, 132.5, 141.6, 144. 0, 145.0, 159.6 ppm; IR (CCl_4 0.01 M): $\tilde{\nu}$(OH) = 3614, 3549 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{20}O_4S$: C 65.04, H 6.06; found: C 64.92, H 6.13.

4-(2,3-Dihydro-5-hydroxy-8-methoxy-6-methylbenzo[*b*][1,4]oxathiin-2-yl)benzene-1,2-diol (11): After cycloaddition and deprotection the crude reaction mixture was purified by flash chromatography over silica gel, using CH_2Cl_2/EtOAc = 2:1 as eluent, to give derivative **11** (80% yield) as dark pink glassy solid; ^{1}H NMR (400 MHz, [D6]aceton): $\delta=2.21$ (s, 3H), 3.12–3.20 (m, AB part of an ABX system, $J_{AB}=12.9$ Hz, 2H), 3.73 (s, 3H), 4.96 (dd, X part of an ABX system, $J=7.4$ and 3.8 Hz, 1H), 6.55 (s, 1H), 6.88 (s, 2H), 7.02 (s, 1H), 7.21 (s, 1H, OH), 7.976 (s, 1H, OH), 7.984 ppm (s, 1H, OH); ^{13}C NMR (100 MHz, [D6]aceton): $\delta=15.2$, 30.4, 56.3, 75.6, 111.4, 113.4, 115.1, 115.3, 117.8 (2C), 132.6, 141.6, 143.4, 144.2, 145.1 ppm (2C); elemental analysis calcd (%) for $C_{16}H_{16}O_5S$: C 59.99, H 5.03; found: C 59.96, H 5.17.

Autoxidation studies: The chain-breaking antioxidant activity of the title compounds was evaluated by studying the inhibition of the thermally initiated autoxidation of either styrene or cumene (RH) in chlorobenzene. Autoxidation experiments were performed in a two-channel oxygen-uptake apparatus, based on a Validyne DP 15 differential pressure transducer.[16] In a typical experiment, an air-saturated chlorobenzene solution of styrene or cumene containing AIBN (0.05 M) was equilibrated with an identical reference solution containing also an excess of PMHC (1×10^{-3} M) in the same solvent at 30 °C. When a constant oxygen consumption was observed, the antioxidant was injected into the sample flask, and the oxygen consumption was measured, after calibration of the apparatus, from the differential pressure recorded with time between the two channels. This experimental setting allowed us to subtract, from the autoxidation oxygen consumption, the N_2 produced during AIBN decomposition and the O_2 consumed by the initiating radicals.[16] The value of k_{inh} was determined from the oxygen consumption during the inhibition period by using Equation (10), which is the integrated form of Equation (11).[2] In Equations (10) and (11), k_p is the propagation rate constant of the oxidizable substrate (41 M^{-1}s^{-1} for styrene[28] and 0.32 M^{-1}s^{-1} for cumene[23]) and τ is the length of the induction period (an example of the use of Equation (10) is reported in the Supporting Information). In the case of compounds **7** and **8**, which did not afford a clear induction period, the k_{inh} was determined using a different equation (see the Supporting Information).[17] The coefficient n was determined experimentally from τ using Equation (12).[2]

$$-\Delta[O_2]_t = \frac{k_p[RH]}{k_{inh}} \ln \frac{(1-t)}{\tau} \quad (10)$$

$$-\frac{d[O_2]}{d_t} = \frac{k_p[RH]R_i}{n\,k_{inh}[AH]} \quad (11)$$

$$n = \frac{R_i \tau}{[AH]} \quad (12)$$

EPR spectroscopy: Spectra were recorded in quartz tubes at 298 K on a Bruker Elexsys 500 X-band spectrometer equipped with a Bruker VT-1000 variable temperature unit. Spectral analysis was optimized by means of computer simulations and subjected to a least-squares fitting procedure based on the systematic application of the Monte Carlo method, available in WinESR Commander V.1.0 software, developed by Prof. Marco Lucarini (University of Bologna). Spectra were recorded in deoxygenated benzene solutions containing 10% (v/v) *t*BuOO*t*Bu, by irradiating the samples with a 500W high-pressure Hg lamp and using calibrated metal sectors to modulate the intensity of irradiation. Measured *g*-factors were corrected using those of reference compounds in benzene: BHT, $g = 2.0046$ and dBHA $g = 2.0047$.[20]

IR measurements: FT-IR spectra of compounds **7**–**10**, were measured in diluted tetrachloromethane solutions (0.01–0.003 M) in a sealed KBr cell with a 0.5 mm optical path.

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[26] As a referee suggested, the orbital situation around the O and S atoms in 4-thiaflavanes and in the corresponding phenoxyl radicals is more complex than those reported in Figure 4 and Figure 5. However, as it has already been done,[3,11,25] with the aim to better understand and visualize the stereoelectronic contributions to phenoxyl radicals stabilization we decided to indicate exclusively the p orbitals in charge for delocalization.
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