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Synthesis and "double-faced" antioxidant activity of polyhydroxylated 4-thiaflavans†

Stefano Menichetti,*[a] Maria Chiara Aversa,[b] Francesco Cimino,[c] Alessandro Contini,[d] Caterina Viglianisi[b] and Antonio Tomaino[c]

[a] *Dipartimento di Chimica Organica, Polo Scientifico-Università di Firenze, via della Lastruccia 13, 50019, Sesto Fiorentino, Firenze, Italy. E-mail: stefano.menichetti@unifi.it; Fax: 39-055-4573531; Tel: 39-055-4573535*

[b] *Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, 98166, Messina, Italy*

[c] *Dipartimento Farmaco-Biologico, Università di Messina, Viale SS Annunziata, Messina, Italy*

[d] *Istituto di Chimica Organica "A. Marchesini" Università di Milano, Via Venezian 21, 20133, Milano, Italy*

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A simple synthetic methodology, based on the inverse electron demand hetero Diels–Alder reaction of electron-poor dienic *o*-thioquinones with electron-rich styrenes used as dienophiles, allowed the preparation of several polyhydroxylated 4-thiaflavans. Such compounds, as a function of the nature and position of the substituents on the aromatic rings, as well as of the oxidation state of the sulfur atom, are able to behave *in vitro* as efficient antioxidants mimicking the action of catechol containing flavonoids or/and tocopherols. The possibility of joining together the potentialities of two relevant families of natural polyphenolic antioxidants appears particularly appealing since an efficient protection against free radicals and other reactive oxygen species (ROS) depends *in vivo* upon the synergic action of different antioxidant derivatives.

Introduction

Formation of free radicals and other reactive oxygen species (ROS) in the human body is an unavoidable consequence of metabolism.[1] Despite it now being widely recognized that oxygen centred free radicals are crucially involved in several biochemical transformations,[2] it is even more clear that an anomalously high concentration of ROS is strictly related to the "oxidative stress" of tissues and to the origin and consequence of the main part of the more dangerous diseases and ageing itself.[3] Evolution provided endogenous and exogenous defences for keeping ROS concentrations under control. For example, the expression of specific enzymes able to avoid the formation of free radicals (*i.e.* super-oxide dismutase, catalase and several oxygenases) is one of the endogenous answers to this problem.[1] On the other hand, the comsumption of a diet high in small molecules able to break the chain radical reactions leading to the oxidative damage is the more simple and efficient exogenous solution.[1] A diet rich in antioxidants can have a crucial role on health, most of all in those countries where the factors in charge of dangerously increasing ROS concentrations (stress, smoking, over-alimentation, alcohol and/or drug abuse and pollution) are frequent components of the style of living.

The more important antioxidant small molecules to be associated with diet are vitamins: ascorbic acid (vitamin C), β-carotenes and vitamin A, tocopherols (vitamin E), as well as polyphenolic flavonoids (called vitamin P). These latter compounds, possessing the 2-phenylchromane skeleton (see Fig. 1), are almost ubiquitous in vascular plants where, for example, they provide the colour of flowers and leaves, or supply protection against insects and micro-organism attack, as well as UV irradiation.[4]

Owing to their diffusion in edible plants, flavonoids are commonly present in our diet, with a daily intake ranging from only a few to hundreds of mg. The consumption of these polyphenolic species [like (±)-catechin (**1**), Fig. 1] is generally considered a healthy habit[5] and regarded as a reason for the unexpectedly low incidence of cardiovascular diseases, stroke and several types of cancer in those populations that associate a risky high consumption of animal fats with a high intake of flavonoids, usually from red wine; the so called "French paradox".[6] Despite the lack of definitive evidence for their action *in vivo*, the powerful *in vitro* antioxidant ability of flavonoids[7] is indicated as the key reason for the beneficial response of a robust intake of these polyphenols.[8]

On the other hand, α-tocopherol (**2**) (Fig. 1), the main component of vitamin E, is known as the best chain breaking lipophilic antioxidant and the foremost responsible for protection against low density lipoprotein (LDL) oxidation in the human body.[9]

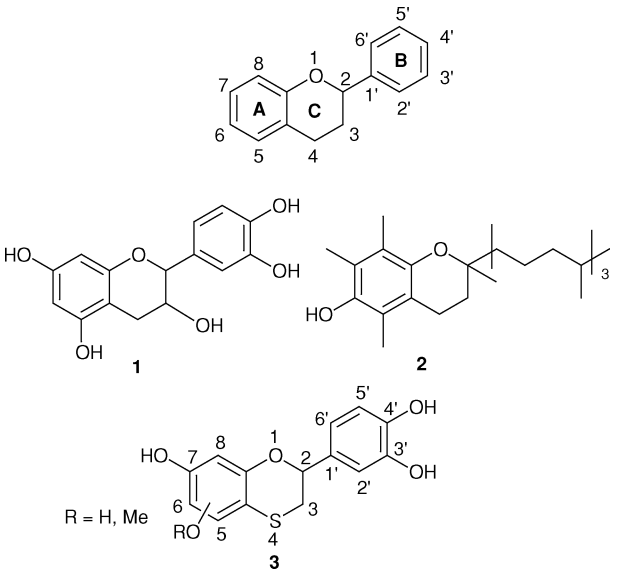

Fig. 1 Natural phenolic antioxidants catechin (**1**) and α-tocopherol (**2**), containing the chromane skeleton, and 4-thiaflavans **3**.

† Electronic supplementary information (ESI) available: full experimental and spectroscopic data and BDE values for compounds **9**, **10**, **11** and **12**. See http://dx.doi.org/10.1039/b507496g

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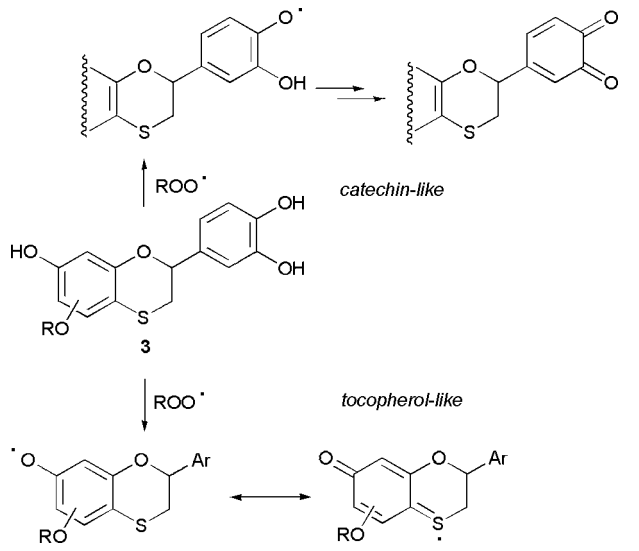
We recently reported[10] that 3′,4′-dihydroxy- or/and 7-hydroxy-4-thiaflavans of type **3** (Fig. 1) show what we called a "double-faced" antioxidant activity. A thiaflavan 3′,4′-dihydroxy substituted B ring can behave in a similar manner to catechin (**1**) and flavonoids containing a catechol moiety, quenching two eq. of an oxygen centred radical to give a stable and "safe" *o*-quinone compound (Scheme 1). We proved that the sulfur atom in the C ring is poorly involved in such "catechin-like" performance and it can be oxidized without affecting the radical scavenger ability.[10] On the other hand, a 7-hydroxy-4-thiaflavan can mimic the behaviour of tocopherol **2** since the sulfur atom ensures the formation of a stabilized radical intermediate (Scheme 1). Indeed the "tocopherol-like" behaviour requires sulfide sulfur in position 4 and oxidation at sulfur strongly depletes the antioxidant ability.[10]



Scheme 1 "Double-faced" antioxidant activity of 4-thiaflavans.

These preliminary results prompted us to keep investigating this subject for a number of reasons. First of all we were interested in investigating the substitution effects on the A and B rings, as well as the role that sulfur in its different oxidation states, plays on the antioxidant activity of thiaflavans. Moreover, the possibility that both "catechin-like" and "tocopherol-like" mechanisms could operate together was an open question. Connecting together the features of different natural antioxidants is a modern trend in drug discovery.[11] In fact, protection against ROS by small molecules has to face the problem that any new radical formed, even when stabilized, retains a pro-oxidant effect,[12] *i.e.* the possibility of damaging the tissue where it was generated. It is well demonstrated that an effective protection against ROS requires the synergic action of different antioxidants, ensuring a cascade of redox reactions from a highly reactive free radical to a safe molecule.[13]

Therefore, we decided to prepare several hydroxy substituted thiaflavans **3** and measure their antioxidant activity *in vitro* focusing our attention on the effect of substitution on the A and B rings, the role of the sulfur atom and the actual "double-faced" character of these molecules.

Results and discussion

Synthesis

Polyhydroxy 4-thiaflavans required for this study were prepared from easily available phenols **4a–f**[14] which were sulfenylated with phthalimidesulfenyl chloride PhtNSCl (Pht = phthaloyl) to the corresponding *o*-hydroxythiophthalimides **5a–f** obtained with complete regioselectivity (Fig. 2).[15]

Compounds **5** were treated with Et_3N in chloroform at 60 °C to give transient *o*-thioquinones **6a–f** (Scheme 2).

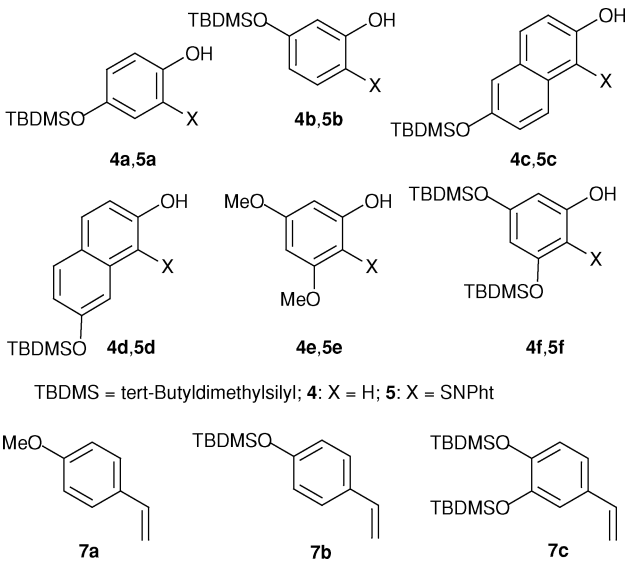
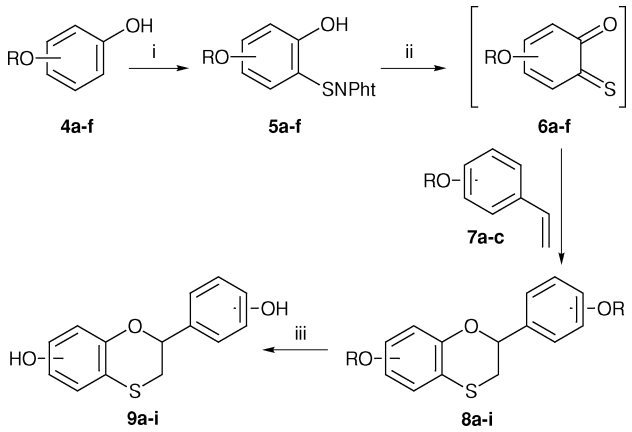


Fig. 2 Starting materials for the preparation of polyphenolic 4-thiaflavans.



Scheme 2 *Reagents and conditions*: i) PhtNSCl, $CHCl_3$, rt; ii) Et_3N, $CHCl_3$, 60 °C; iii) TBAF·$3H_2O$, THF, 0 °C.

These efficient electron-poor dienes reacted with electron rich styrenes **7a–c**[16] (Fig. 2) to give benzoxathiin cycloadducts **8a–i** (Scheme 2) through an inverse electron demand hetero Diels–Alder reaction.[10,17]

This simple procedure allowed the regiocontrolled construction of a 4-thiaflavan ring and was accomplished by desilylation of the phenoxy groups using tetrabutylammonium fluoride hydrate (TBAF·$3H_2O$) in THF[18] to obtain the phenolic derivatives **9a–i** (Scheme 2 and Fig. 3).

Derivatives **8a–8b** were also oxidized at sulfur with 1 eq. of *m*-chloroperoxybenzoic acid (MCPBA) in DCM to obtain the expected silylated sulfoxides (see Experimental). Desilylation with TBAF afforded hydroxylated sulfoxides **10a–10b** obtained as mixtures of the two possible stereoisomers. Analysis of ^{1}H NMR spectra of the crude reaction mixtures, in comparison with data of similar compounds,[19] allowed the attribution of the relative geometry of diastereoisomeric sulfoxides. Oxathiin ring hydrogen ^3J values indicate a pseudo-equatorial position for the 2-aryl group in both isomers (Fig. 4). Coupling constants and chemical shifts mutually indicate that oxidation affords as a major isomer (85 : 15 for **10a**, 90 : 10 for **10b**) the sulfoxide with the oxygen laying in a pseudo-axial position[19,20] (*i.e.* the *trans*-isomers, Fig. 4).

Flash chromatography allowed the isolation of *trans*-**10a** and both diastereoisomers of **10b**. We observed that *cis*-**10b** was unstable in solution. A pure sample of *cis*-**10b**, kept in $CDCl_3$ for several hours, showed by ^{1}H NMR the formation of *trans*-isomer together with styrene **7a**. As expected[19] oxidation at

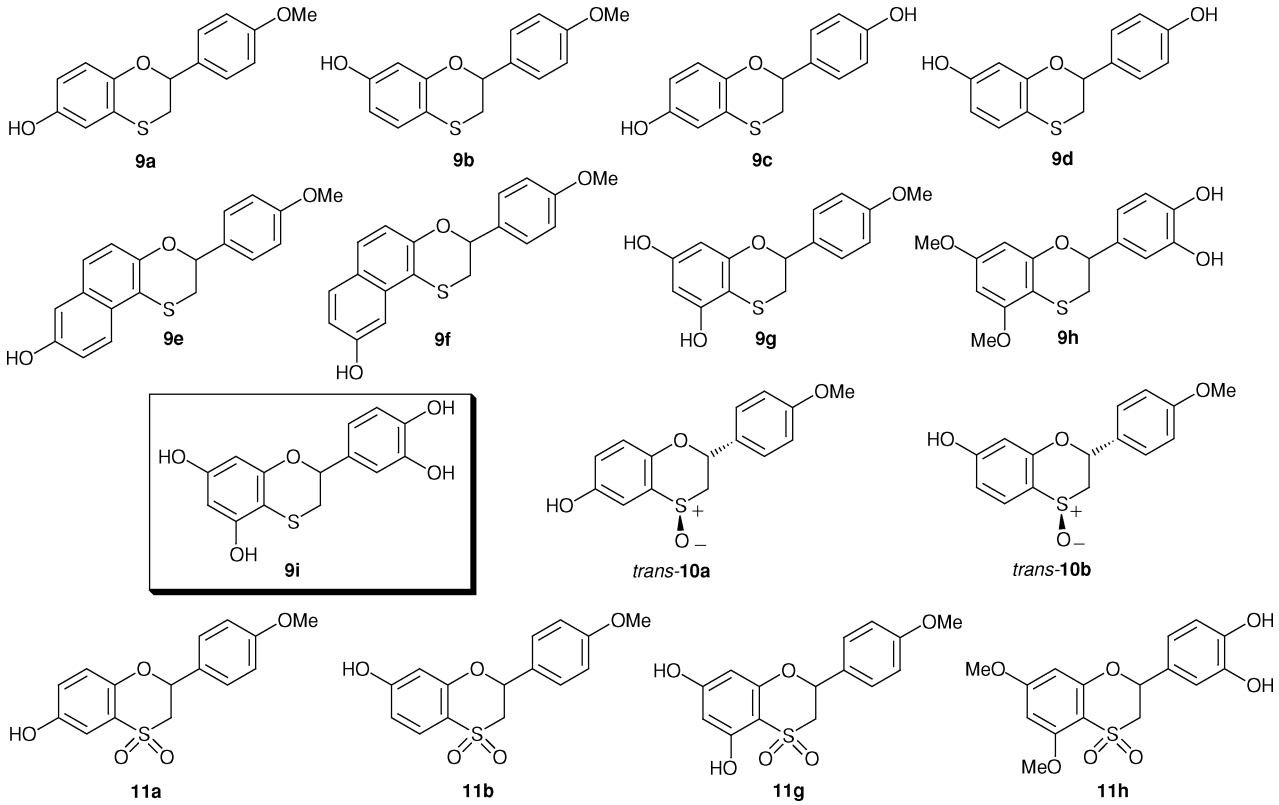


Fig. 3 Thiaflavans **9**, **10** and **11** prepared and tested in this study.

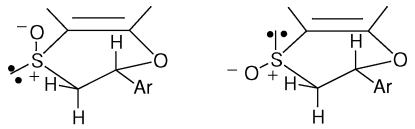
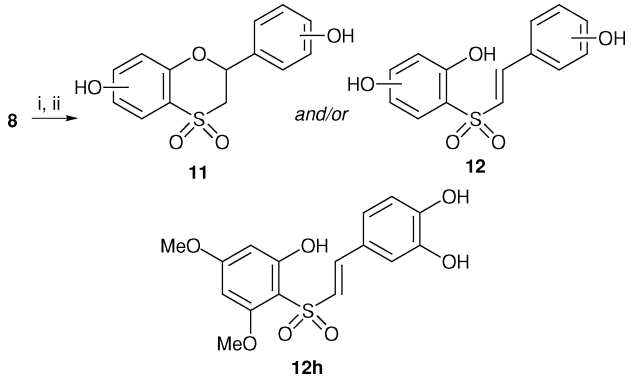


Fig. 4 Relative geometry of *cis*- and *trans*-sulfoxides **10a** and **10b**.

sulfur, and probably also desilylation,[21] facilitate a retro Diels–Alder process with formation of **7a** and an *o*-thioquinone *S*-oxide, even at room temperature, which react together to give the thermodynamically favoured sulfoxide *trans*-**10b**.[19]

The same process probably prevented the isolation of *cis*-**10a**, thus vanishing the possibility of measuring the antioxidant activity of *cis*-sulfoxides (*vide infra*).

Thiaflavans **8a–8b** and **8g–8h** were oxidized using 2.2 eq. of MCPBA in DCM to give the corresponding silylated sulfones, which in turn were reacted with TBAF to obtain hydroxy sulfones **11a–11b** and **11g–11h** (Scheme 3, see Experimental).



Scheme 3 *Reagents and conditions*: i) MCPBA 2.2 eq., DCM, rt; ii) TBAF·3H_2O, THF, 0 °C.

Deprotection of silylated sulfones must be carefully controlled to avoid a base mediated ring opening of the oxathiin ring. This process causes to the formation of vinyl sulfones **12**, which become the major, or exclusive, products working with an excess of TBAF at room temperature (Scheme 3).[22] Under these conditions derivative **12h** was isolated and used for antioxidant testing, despite the lack of thiaflavan skeleton.

The whole synthetic procedure has been optimized with overall yields of sulfenylation, cycloaddition, possible oxidation and desilylation ranging from 25 to 48%. All thiaflavans **9**, *trans*-sulfoxides **10** and sulfones **11** were stable compounds, storable for months without appreciable decomposition either as pure sample or in solution (acetone or ethanol).

The antioxidant activity of these derivatives has been measured *in vitro*, as reported in the next section.

Antioxidant activity

In our previous report on the antioxidant activity of some 4-thiaflavans[10] we measured their reducing activity (RA) as fading of the purple colour ($\lambda = 515$ nm) of a methanolic solution of the commercially available 2,2-diphenyl-1-picrylhydrazyl radical (DPPH, Fig. 5) after mixing with an equimolar amount of the substrate. Despite being simple, well-liked and very practical from a qualitative point of view,[23] this assay did not allow to quantify the "catechin-like" *vs.* "tocopherol-like" mechanisms and, above all, to verify the possibility that both these features work together.

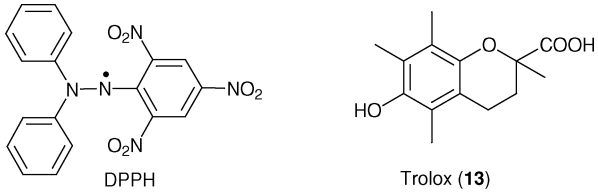


Fig. 5 DPPH and trolox (**13**) structures.

Table 1 SC_{50} values of 4-thiaflavans **9a–i**, **10a–b**, **11a–b**, **11g–h** and sulfone **12h** tested in this study

Entry	Compound	SC_{50}/μM, ± 8%	*A*	*SF*
1	Catechin (**1**)	15	1	3.4
2	Trolox (**13**)	16	0.9	3.1
3	**9a**	23	0.6	2.2
4	**9b**	18	0.8	2.8
5	**9c**	23	0.6	2.2
6	**9d**	19	0.8	2.7
7	**9e**	26	0.6	1.9
8	**9f**	40	0.4	1.3
9	**9g**	12	1.2	4.1
10	**9h**	16	0.9	3.1
11	**9i**	8	1.9	6.4
12	**10a**	Nd[a]	—	—
13	**10b**	Nd[a]	—	—
14	**11a**	210	0.1	0.2
15	**11b**	Nd[a]	—	—
16	**11g**	301	0.05	0.2
17	**11h**	15	1.0	3.3
18	**12h**	13	1.1	3.8

[a] Quenching of 50% DPPH was higher than 300 μM.

In this paper we measured the SC_{50} of derivatives **9**, **10**, **11** and **12h** as the μM concentration of substrate required to quench 50% of a 100 μM solution of DPPH in methanol.[24] In order to compare results of our substrates with those of two well known and highly efficient radical scavenger derivatives, which undoubtedly operate by one of the mechanisms proposed for thiaflavans, the SC_{50} values were also determined for (±)-catechin (**1**) and trolox (**13**) (Fig. 5), commonly used as a tocopherol substitute for antioxidant measurements in polar media.

Collected data are reported in Table 1. Column A shows the thiaflavan SC_{50} values, normalized by considering unitary the value measured for the catechin (**1**). Column *SF* (stoichiometric factor) indicates the number of reduced DPPH radicals per antioxidant molecule: $SF = C/2SC_{50}$, where C is the initial DPPH concentration (100 μM).

Chain breaking antioxidant polyphenols effect their activity in reactions with ROS, typically peroxyl radicals (ROO$^{\bullet}$), by hydrogen transfer and formation of stabilized phenoxyl radicals (ArO$^{\bullet}$).[1,7,9] The measures performed with DPPH stand exactly on the same mechanism. Thus, we can consider that hydroxy 4-thiaflavans (ThFlav–OH) react with purple DPPH radicals by hydrogen transfer, with the formation of a phenoxyl radical (ThFlav–O$^{\bullet}$) and the colourless species DPPH–H.

The ability of a generic phenol to react with DPPH strongly depends upon the reaction conditions used to carry out the experiment. For example, the solvent, or pH, chosen has an effect on the antioxidant activity measured for hydroxyphenols.[25–27]

However, the ability as a radical scavenger of a phenolic species can be easily related to the whole skeleton of the compound.[28] Since our goal was to study the characteristics of the thiaflavan structure with a maximized "catechin-like" or/and "tocopherol-like" radical scavenger ability, we decided to test our derivatives in comparison with catechin (**1**) and trolox (**13**) and to address the data merged from the measurements in terms of effect of the substituents on antioxidant ability.

Derivative **9h** (Table 1, entry 10), where only the B ring can act as radical scavenger, showed a SC_{50} value similar to that of catechin (**1**). Several papers address the relationship between the structure of flavonoids and their antioxidant activity.[7,29] However, strictly considering their ability as radical scavengers, the presence of a 1,2-dihydroxy moiety on the B ring and the planarity of the three rings of the flavan skeleton[30] represent the crucial requirements.

Our data are in agreement with such observations. In fact, derivative **9h**, with any other hydroxy group neither on the A ring nor on position 3 of the C ring, gave the same result as that obtained with the racemic catechin.

On the other hand, either derivative **11h**, with the sulfur atom oxidized to sulfone, or compound **12h**, which despite the opening of the C ring maintains the cathecol moiety, showed an activity similar to **9h** (and **1**), supporting the primary role of the *o*-dihydroxy substituted B ring in the "catechin-like" behaviour of these derivatives. The little improvement moving from **11h** to **12h** can be rationalized by considering for the former the additional effect of the conjugated double bond.[30]

More of our efforts were devoted to better understanding the role of the substitution and the sulfur atom on the "tocopherol-like" antioxidant mechanism played by the A and C rings.

As expected, compound **9a** (entry 3), with a 6-OH substitution, was less active than trolox. To our surprise, compound **9b**, showing the sulfur atom conjugated with the 7-OH group, was more active than **9a** and only little less active than trolox (**13**) (entry 4). A rational explanation could be related to the ability of the sulfur atom to stabilize the phenoxyl radical formed by the reaction with DPPH, an aptitude claimed to be better than that of the oxygen.[31] However, it must be considered that literature data are quite puzzling with regard to the role of sulfur. For example, synthetic thiatocopherol was reported to show a slight reduction of the antioxidant activity compared with vitamin E,[32] while the passing from oxygen to sulfur produced a weak increase of 2,3-dihydrobenzo[*b*]thiophene-5-ol activity.[33]

We reported that sulfur oxidation on the C ring does not play any role in the "catechin-like" mechanism expressed by the 3′,4′-dihydroxy substituted B ring, while it strongly influences the "tocopherol-like" activity.[10] The SC_{50} values obtained for sulfoxides **10a–b** and sulfones **11a–b** are shown in Table 1, entries 12–15. In any case, the sulfur oxidation produces a dramatic decrease of radical scavenger capability. This can be explained if it is taken into account that the transformation of a sulfide sulfur into a sulfoxide, or sulfone, introducing an electron withdrawing group on the A ring, increases the bond dissociation enthalpy (BDE) values of the OH group (*vide infra*).[30] Moreover, in compounds **10b** and **11b** the oxidation modifies the electronic characteristics of the sulfur atom directly conjugated to the potential radical centre[31] and resulted in **11b** being significantly less active than **11a**.

As already mentioned, sulfoxides **10a–b** were tested as pure *trans*-isomers. In our opinion, the sulfoxide geometry is also related with their very low antioxidant ability. It has been reported that the stability of *p*-alkoxy substituted phenoxyl radicals depends upon the possibility that one of the oxygen lone pairs of the alkoxy group is parallel to the aromatic p-orbitals.[9,33,34] On this basis, the higher activity of 2,3-dihydrobenzo[*b*]furan-5-ol, with respect to the corresponding 6-hydroxychromanes, was explained by taking into account that in the more rigid five-member ring one of the lone pairs of the furan oxygen is forced in an orthogonal localization to the aromatic ring.[9,33,34] As reported in Fig. 4, *trans*-sulfoxides **10a–b** bear the oxygen–sulfur bond in a pseudo-axial position, *i.e.* the free sulfur lone pair is almost perpendicular to the aromatic p-orbitals and hence is unable to stabilize the phenoxyl radical by conjugation. Unfortunately the instability of *cis*-sulfoxides did not allow us to verify this hypothesis by measuring SC_{50} for the minor isomers. On the other hand, at the moment we have no rational explanation for the small increase of activity observed moving from sulfoxide **10a** to sulfone **11a**.

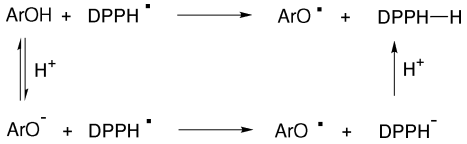
Compounds **9c** and **9d** (Table 1, entries 5 and 6) gave results similar to those of **9a** and **9b** and, in fact, a single OH group on the B ring plays a marginal role on the whole antioxidant activity.

Moreover, we tried to evaluate the effect of an extended conjugation by testing derivatives **9e** and **9f**. The obtained data (Table 1, entries 7 and 8) seem to indicate that, surprisingly, the effect of an additional condensed aromatic ring is quite poor. On the contrary, the effect of extra electron donating group (EDG) substituents on the A ring is significant. Entry 9 reports the SC_{50} value of compound **9g** with a 5,7-dihydroxy substituted A ring,

whose ability as radical scavenger was higher than for trolox and catechin, indicating the substantial effect of the additional 5-OH group. Also for **9g**, oxidation at sulfur causes a dramatic decrease of the radical scavenger aptitude, as indicated by SC_{50} value of sulfone **11g** (Table 1, entry 16).

To our pleasure, derivative **9i** showed a SC_{50} similar to the sum of that of trolox and catechin (Table 1, entry 11). This result indicates that the 5,7,3′,4′-tetrahydroxy substitution provides to this thiaflavan the ability of working as a "double-faced" antioxidant polyphenol, where both the "catechin-like" and "tocopherol-like" mechanisms are operative.

Recently, Litwinienko and Ingold[25] and Foti *et al*.[26] reported for phenols an abnormal solvent effect on hydrogen atom abstraction by DPPH working in alcohol solvents. This is due to the role played by a single electron transfer (SET) mechanism from the phenoxy anion ArO^- to the DPPH radical that is very fast in alcohols and leads to overestimate the reaction kinetics in such solvents (Scheme 4).



Scheme 4 The two mechanisms operative in the reaction of phenols with DPPH radicals.

This seems to be confirmed by the kinetic measurements carried out on thiaflavans **9g–i**, which are reported in Table 2. Parameter *n*, indicating the number of DDPH moles reduced by one mole of thiaflavan, is in accord with the *SF* values reported in Table 1 and suggests a rather complex mechanism operatiing in solution between the several radical species formed.[35] Both *n* and kinetic constant *k* values are in agreement with those measured under the same conditions for cathecol containing natural antioxidants[26] and used to verify the SET mechanism.

However, as Litwinienko and Ingold underline,[25] the use of DPPH for "titration" of total antioxidant ability of phenolic compounds in methanol or ethanol remains a perfectly valid procedure, since the direct hydrogen transfer or the sequence, deprotonation–SET–protonation, have the same stoichiometry (Scheme 4). Indeed, kinetic parameters perfectly match the trend of SC_{50} values for the same compounds **9g–i**.

The aptitude to give a hydrogen transfer reaction depends upon the ionization potential (IP) of the whole molecule and the BDE of the specific OH group involved in the transfer reaction. Table 3 shows BDE values achieved by semi-empirical calculations[36] for **9i**, catechin and trolox, compared those obtained by considering the additive contribution of the substituents on the phenolic ring as reported by Wright and coworkers.[28,37] In Table 3 we also report the BDE values recently calculated by Zhang *et al*. for catechin[38] and **9i**.[39] Despite semi-empirical calculation seeming to underestimate all the O–H bond energies,[40] the calculated and estimated BDE values are in agreement with the SC_{50} measurements for these species.[36] The possibility that **9i** can behave as a "double-faced" antioxidant is corroborated by the efficiency of the catechol moiety on the B ring[38] and the ability of the 5,7-dihydroxy substituted A ring coupled with sulfide sulfur on the C ring. In fact, BDE values for 7-OH and 5-OH 4-thiaflavans (with the latter OH group claimed to play an unexpected role in such activity[38]) are similar to those calculated for trolox[36] or experimentally measured for 2,2,5,7,8-pentamethylchromane (BDE = 78.25 Kcal mol^{-1}).[41]

Table 2 Kinetic parameters *k* and *n* for selected thiaflavans **9g–i**

Compound	k/$mol^{-1}s^{-1}$	n
9g	2129 ± 116	3.03 ± 0.28
9h	1954 ± 99	2.97 ± 0.30
9i	5383 ± 250	6.37 ± 0.54

Table 3 Calculated and estimated O–H BDE (Kcal mol^{-1}) values for thiaflavan **9i**, catechin (**1**) and trolox (**13**)

Compound	Radical	O–H BDE calculated[35]	O–H BDE estimated[28,36]	O–H BDE lit. data
9i	4′-O•	72.26	75.35	78.18[38]
	3′-O•	72.49	77.45	
	7-O•	77.07	79.95	83.35[38]
	5-O•	76.36	79.65	79.35[38]
1	4′-O•	72.11	75.35	71.93[37]
	3′-O•	72.35	77.45	
	7-O•	77.94	83.55	
	5-O•	76.89	84.05	
13	6-O•	73.50	76.15	

The calculated BDE values for all prepared thiaflavans[36] parallel the general trend merged from SC_{50} measurements.† Thus, oxidation at sulfur leads to higher BDE values above all for directly conjugated 7-OH groups. However, our data are not completely homogeneous and, for example, calculations invert the lowest activity between sulfoxides and sulfones. This can be ascribed to the calculation level and/or to the lack of suitable parameters for the sulfur substituents at the different oxidation states; a problem which would probably deserve a dedicated further investigation.

Conclusions

We have shown that a new class of polyphenolic antioxidants, possessing the 4-thiaflavan skeleton, can be prepared through a simple hetero Diels–Alder reaction of *o*-thioquinones used as electron-poor dienes. As a consequence of substitution on the A and B aromatic rings and the oxidation state of the sulfur atom on the C ring, such thiaflavans are able to imitate the mechanisms operative in the two more valuable families of natural polyphenolic antioxidants: flavonoids and tocopherols. The synthesis of a derivative with both the structural requirements allowed the availability of a compound showing the sum of the activities of catechin and trolox *in vitro*.

The feasibility of the synthetic procedure allows foreseeing stimulating modifications to our 4-thiaflavans, currently under development in our laboratories, together with *in vivo* testing of these new antioxidants.

Experimental

General: ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 and 75 MHz respectively, in $CDCl_3$ for silylated compounds and acetone-d_6 for hydroxy thiaflavans, unless otherwise specified, using signals of residual non-deuterated solvents as reference lines. Melting points are uncorrected. $CHCl_3$, DCM, THF, DMF and Et_3N were dried following standard procedures. All the other commercial reagents were used as obtained from freshly opened containers. Silylated phenols **4a–d** and **4f** were prepared by reaction of the commercially available hydroxy arenes with TBDMSCl and imidazole in dry DMF. Styrenes **7a–b** were obtained from 3-hydroxy- and 3,4-dihydroxy-benzaldehyde by silylation and subsequent Wittig reaction.[17] PhtNSCl and *N*-thiophthalimides **5** were prepared as reported elsewhere.[15,17] SC_{50} values[24] and kinetic parameters[26,40] *n* and *k* have been obtained following literature methods. General procedures for the cycloaddition, oxidation and desilylation and spectroscopic data of derivatives **8a**, **10a** and **11a** are given as an example. Full experimental and spectroscopic data, including calculated BDE, for compounds **8**, **9**, **10**, **11** and **12** are available as supplementary information.†

Cycloaddition reactions. General procedure

To a solution of thiophthalimides **5** in dry $CHCl_3$ (roughly 0.1 M), styrenes **7** (1 eq.) and freshly distilled Et_3N (1 eq.) were

added in sequence, the reaction mixtures heated at 60 °C and monitored either by ^{1}H NMR or TLC until the disappearance of **5**. Evaporation of the solvent and flash chromatography on silica gel allowed the isolation of cycloadducts **8**. Spectroscopic data of silylated derivative **8a** are as follows.

6-(*tert*-Butyl-dimethyl-silanyloxy)-2,3-dihydro-2-(4-methoxy-phenyl)-1,4-benzoxathiin (8a)

Compound **8a** was obtained as a white solid by flash chromatography on silica gel with petroleum ether–DCM, 4 : 1, as eluent; mp 89–90 °C, (67%). ^{1}H NMR δ: 0.17 (s, 6H), 0.97 (s, 9H), 3.01 (dd, J = 13.0, 1.8 Hz, 1H), 3.28 (dd, J = 13.0, 9.6 Hz, 1H), 3.82 (s, 3H), 5.05 (dd, J = 9.6, 1.8 Hz, 1H), 6.51 (dd, J = 8.7, 2.7 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 6.93–6.95 (m, 2H), 7.32–7.35 (m, 2H); ^{13}C NMR δ: −4.5 (q, 2C), 18.1 (s, 1C), 25.6 (q, 3C), 31.8 (t, 1C), 55.2 (q, 1C), 76.1 (d, 1C), 114.0 (d, 2C), 117.3(d, 1C), 117.6 (1s, 1d, 2C), 119.1 (d, 1C), 127.3 (d, 2C), 132.6 (s, 1C), 147.0 (s, 1C), 149.7 (s, 1C), 159.6 (s, 1C).

Oxidation reactions to silylated sulfoxides (indicated as 10a′ and 10b′). General procedure

To a solution of cycloadduct **8a** or **8b**, in DCM (0.04 M) kept at 0 °C, a solution of MCPBA (1 eq.) in DCM was added and the reactions monitored by TLC until the disappearance of sulfide **8** (30–40 min). The mixtures was diluted with DCM, washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ and water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. ^{1}H NMR of the crude mixture allowed the attribution of the *cis–trans* ratio, purification by flash chromatography on silica gel allowed the isolation of *trans*-**10a**′ and *cis*- and *trans*-**10b**′.

trans-6-(*tert*-Butyl-dimethyl-silanyloxy)-2,3-dihydro-2-(4-methoxy-phenyl)-1,4-benzoxathiin 4-oxide (*trans*-10a′)

Compound *trans*-**10a**′ was obtained as a white solid by flash chromatography on silica gel with petroleum ether–ethyl acetate, 2 : 1, as eluent; mp 139 °C dec., (65%). ^{1}H NMR δ: 0.20 (s, 6H), 0.99 (s, 9H), 3.07 (dd, J = 14.4, 12.0 Hz, 1H), 3.24 (dd, J = 14.4, 1.5 Hz, 1H), 3.84 (s, 3H), 5.61 (br d, 1H), 6.94–6.98 (m, 4H), 7.13–7.14 (m, 1H), 7.40–7.45 (m, 2H); ^{13}C NMR δ: −4.5 (q, 2C), 18.1 (s, 1C), 25.6 (q, 3C), 49.8 (t, 1C), 55.3 (q, 1C), 67.4 (d, 1C), 114.2 (d, 2C), 120.2 (d, 1C), 122.1 (d, 1C), 122.4 (s, 1C), 126.9 (d, 1C), 127.9 (d, 2C), 130.6 (s, 1C), 147.7 (s, 1C), 149.7 (s, 1C), 160.1 (s, 1C).

Oxidation reactions to silylated sulfones (indicated as 11a′, 11b′, 11g′, 11h′). General procedure

To a solution of cycloadducts **8**, in DCM (0.04 M) at rt, a solution of MCPBA (2.2 eq.) in DCM was added and the reactions monitored by TLC until the disappearance of sulfides **8** (4–8 h). The mixtures were diluted with DCM, washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ and water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness to give sulfones **11**′, which did not require purification before desilylation.

6-(*tert*-Butyl-dimethyl-silanyloxy)-2,3-dihydro-2-(4-methoxy-phenyl)-1,4-benzoxathiin 4,4-dioxide (11a′)

Compound **11a**′ was obtained as a white solid; mp 93–96 °C, (99%). ^{1}H NMR δ: 0.21 (s, 6H), 0.98 (s, 9H), 3.46 (dd, J = 14.1, 1.5 Hz, 1H), 3.71 (dd, J = 14.1, 12.0 Hz, 1H), 3.84 (s, 3H), 5.70 (dd, J = 12.0, 1.5 Hz, 1H), 6.91–6.99 (m, 4H), 7.24–7.26 (m, 1H), 7.36–7.40 (m, 2H); ^{13}C NMR δ: −4.5 (q, 2C), 18.1 (s, 1C), 25.6 (q, 3C), 55.4 (t, 1C), 55.9 (q, 1C), 77.3 (d, 1C), 113.4 (d, 1C), 114.5 (d, 2C), 120.0 (d, 1C), 125.5 (s, 1C), 127.1 (d, 1C), 127.7 (d, 2C), 129.3 (s, 1C), 147.6 (s, 1C), 150.5 (s, 1C), 160.5 (s, 1C).

Desilylation reactions. General procedure

To a solution of compounds **8**, **10**′ and **11**′, in dry THF (0.04 M) at 0 °C, a solution of TBAF·3H_2O in DCM (1 eq. for each TBDMSO group) was added and the reaction monitored by TLC until the disappearance of the silylated starting products. The crude mixture was diluted with ethyl acetate, washed with saturated NH_4Cl and water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the required products **9**, **10** and **11**. Spectroscopic data are as follows.

2,3-Dihydro-2-(4-methoxy-phenyl)-1,4-benzoxathiin-6-ol (9a)

Compound **9a** was obtained as a white solid by flash chromatography on silica gel with DCM–ethyl acetate, 20 : 1, as eluent; mp 110–111 °C, (95%). ^{1}H NMR δ: 3.12 (dd, J = 13.2, 2.1 Hz, 1H), 3.25 (dd, J = 13.2, 9.3 Hz, 1H), 3.80 (s, 3H), 5.02 (dd, J = 9.3, 2.1 Hz, 1H), 6.51 (dd, J = 8.7, 3.0 Hz, 1H), 6.57 (d, J = 3.0 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.93–6.98 (m, 2H), 7.37–7.42 (m, 2H), 8.01 (br s, 1H); ^{13}C NMR δ: 32.1 (t, 1C), 55.5 (q, 1C), 76.8 (d, 1C), 113.3 (d, 1C), 113.6 (d, 1C), 114.7 (d, 2C), 118.9 (s, 1C), 120.0 (d, 1C), 128.3 (d, 2C), 133.8 (s, 1C), 146.7 (s, 1C), 152.5 (s, 1C), 160.6 (s, 1C). Found: C, 65.71; H, 5.17%. Calc. for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14%.

trans-2,3-Dihydro-2-(4-methoxy-phenyl)-4-oxo-1,4-benzoxathiin-6-ol (*trans*-10a)

Compound *trans*-**10a** was obtained as a white solid by flash chromatography on silica gel with ethyl acetate–DCM, 2 : 1, as eluent; mp 178 °C dec., (65%). ^{1}H NMR (DMSO-d_6) δ: 3.26 (dd, J = 14.5, 1.2 Hz, 1H), 3.47 (dd, J = 14.5, 12.0 Hz, 1H), 3.77 (s, 3H), 5.38 (br d, J = 11.1 Hz, 1H), 6.94–7.02 (m, 5H), 7.44–7.48 (m, 2H), 9.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 48.4 (t, 1C), 55.2 (q, 1C), 67.1 (d, 1C), 114.0 (d, 2C), 116.5 (d, 1C), 119.8 (d, 1C), 122.0 (d, 1C), 123.1 (s 1C), 128.5 (d, 2C), 130.9 (s, 1C), 145.5 (s, 1C), 151.3 (s, 1C), 159.5 (s, 1C). Found: C, 62.25; H, 4.69%. Calc. for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86%.

2,3-Dihydro-2-(4-methoxy-phenyl)-4,4-dioxo-1,4-benzoxathiin-6-ol (11a)

Compound **11a** was obtained as a white solid by flash chromatography on silica gel with DCM–ethyl acetate, 1 : 1, (or DCM–methanol, 6 : 1) as eluent; mp 201–206 °C, (79%). ^{1}H NMR δ: 3.63 (dd, J = 14.1, 1.5 Hz, 1H), 3.83 (s, 3H), 3.94 (dd, J = 14.1, 12.1 Hz, 1H), 5.65 (dd, J = 12.1, 1.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 6.00–7.08 (m, 3H), 7.17 (d, J = 2.7 Hz, 1H), 7.54–7.56 (m, 2H), 8.71 (br s, 1H); ^{13}C NMR δ: 55.6 (q, 1C), 55.8 (t, 1C), 78.3 (d, 1C), 108.6 (d, 1C), 114.9 (d, 2C), 121.0 (d, 1C), 123.3 (d, 1C), 127.0 (s, 1C), 129.1 (d, 2C), 130.8 (s, 1C), 147.4 (s, 1C), 152.8 (s, 1C), 161.3 (s, 1C). Found: C, 58.97; H, 4.69%. Calc. for $C_{15}H_{14}O_5S$: C, 58.81; H, 4.61%.

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