Easy synthesis of polyphenolic 4-thiaflavans with a 'double-faced' antioxidant activity

Giuseppe Capozzi,*[a] Pierandrea Lo Nostro,[b] Stefano Menichetti,*[c] Cristina Nativi[a] and Paolo Sarri[a]

[a] *Centro C.N.R. 'Chimica dei Composti Eterociclici', Dipartimento di Chimica Organica, Università di Firenze, Via G. Capponi 9, I-50121, Firenze, Italy*
[b] *Dipartimento di Chimica e CSGI, Università di Firenze, Via G. Capponi 9, I-50121, Firenze, Italy*
[c] *Dipartimento di Chimica Organica e Biologica, Università di Messina, Salita Sperone 31, I-98166, Messina, Italy. E-mail: menichet@isengard.unime.it*

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Inverse electron demanding Diels–Alder reactions of *o*-thioquinones with styrenes, followed by simple manipulations of the obtained cycloadducts, allowed the synthesis of polyphenolic 4-thiaflavans which showed antioxidant activity miming either flavonoid or tocopherol behaviour.

Flavonoids, natural products containing the 2-phenylchromane skeleton, are almost ubiquitous in higher plants and have been related to a huge number of biological effects[1] including anti-inflammatory, anti-viral and anti-cancer activity. Flavonoids bearing OH groups on A, B and C rings (Fig. 1) represent one of the most important families of natural antioxidants, able to prevent oxidation by oxyl radicals.[2] A high polyphenolic flavonoid content in the diet has been indicated as the reason why certain populations show statistically low levels of cardiovascular disease (the so-called *French paradox*) and most types of cancer.[3]

We have reported that *o*-hydroxy-*N*-thiophthalimides, prepared by *N*-phthalimidesulfenylation of activated phenols, are suitable precursors of *ortho*-thioquinones, a synthetically useful class of electron-poor heterodienes, which react with styrenes giving rise to the formation of aryl-substituted benzoxathiin cycloadducts with complete regioselectivity.[4]

This hetero Diels–Alder approach, can be involved in the preparation of 4-thiaflavan derivatives as shown in Fig. 1. Thus we decided to exploit this procedure for access to polyphenolic 4-thiaflavans with the aim of verifying their potential performance as antioxidants.

We focused our attention on the 5,7,3′,4′ and 5,7,4′ substitution patterns, two of the more common structural characteristics in natural flavonoids.[1]

The sulfenylation of 3,5-dimethoxyphenol and 3,5-(dimethyl-*tert*-butylsilyloxy)phenol with phthalimidesulfenyl chloride gave, as expected, the sulfenamide derivatives **1** and **2** as suitable precursors of the corresponding *o*-thioquinones.†

The reaction of compounds **1** or **2** with styrenes **3**–**5** in $CHCl_3$ at 60 °C, in the presence of TEA,[4] allowed the isolation of the required cycloadducts which were transformed into the hydroxy derivatives **6**–**12** by direct fluoro desilylation using wet TBAF in THF at 0 °C.‡ For sulfoxides **7**, **11** and **12** the oxidation with *m*CPBA of the corresponding sulfides was performed before the deprotection of the silyl ethers (Scheme 1).§

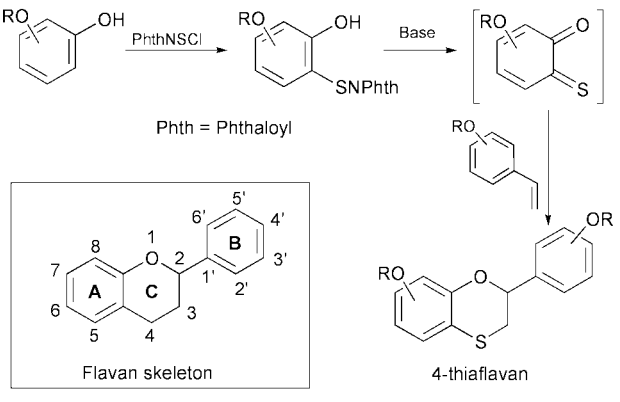
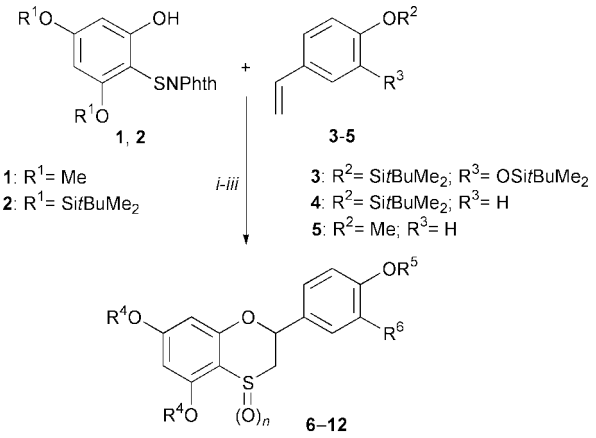
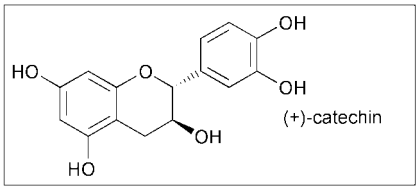


Fig. 1 Flavan skeleton and access to 4-thiaflavan structure.

The antioxidant activity of compounds **6**–**12** was evaluated,[5] as fading of the purple colour of commercially available DPPH radical measured at 517 nm. Thus the value of the absorbance of a 10^{-4} M solution of DDPH in absolute ethanol (A_0) and the absorbance after 20 min from its mixing with an equimolar solution of the thiaflavans (A_1), were used for calculating the reducing activity ***RA*** as: $\boldsymbol{RA} = [(A_0 - A_1)/A_0] \times 100$. The obtained ***RA*** for derivatives **6**–**12** and the one measured for commercially available (+)-catechin hydrate are reported in Scheme 1.



Product	R^4	R^5	R^6	*n*	Yield (%)	***RA***
6	H	H	OH	0	36	***83***
7	H	H	OH	1	26	***83***
8	H	H	H	0	34	***85***
9	Me	H	H	0	38	—
10	H	Me	H	0	42	***83***
11	H	H	H	1	28	***23***
12	H	Me	H	1	30	***6***
(+)-catechin						***83***



Scheme 1 *Reagent and conditions. i*: TEA (1 equiv.), $CHCl_3$, 60 °C, 20–120 h; *ii* (only for **7**, **11** and **12**): *m*CPBA (1 equiv.) CH_2Cl_2, 0 °C, 0.5–2h; *iii*: TBAF (1–4 equiv.), THF, 0 °C, 1–2 h.

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Satisfactorily, derivatives **6** and **7** showed the same activity as catechin. The high efficiency as antioxidants of natural flavonoids showing a catechol-like ring B, has been explained on the basis of the formation of a stable *o*-quinone species arising from two consecutive hydrogen abstractions by the radical reagent.[2] Clearly thiaflavans **6** and **7** could show a similar behaviour demonstrating that the above mentioned catechol-like mechanism is maintained with the introduction of a sulfide or a sulfoxide sulfur into the C ring.

Surprisingly compound **8**, bearing only one hydroxy group on C4′ of ring B, was even more efficient than previously considered 4-thiaflavans and catechin. This is in sharp contrast with the literature data on antioxidant activity of flavonoids[2] and prompted us to envisage a different oxidation mechanism probably involving the A and C rings. This hypothesis was corroborated by the substitution of hydroxy by methoxy groups on the A ring which caused a complete loss of consumption of DPPH colour for derivative **9**, while compound **10**, bearing a methoxy group on the B ring but hydroxy groups on the A ring, exhibited the same activity as **8**. Moreover the transformation of sulfides **8** and **10** into the corresponding sulfoxides **11** and **12** gave rise to an almost complete loss of activity. Thus the observed antioxidant activity of compounds **8** and **10** requires both hydroxy groups on the A ring and a sulfide sulfur in the C ring (Scheme 1).

A simple rationalization of these results can be obtained by considering that a 5,7-dihydroxy-4-thiaflavan moiety, like in **8** or **10**, could behave as an antioxidant with the same mechanism operative in tocopherols and related compounds, which, with flavonoids, represent the most important families of natural antioxidants (Fig. 2).

Literature data regarding the activity of modified tocopherols[6] are in perfect agreement with the observed high efficiency of 4-thiaflavans **8** and **10**. Actually it is known that the introduction of electron donating groups in the aromatic ring (*i.e*. OH on C5) facilitates hydrogen abstraction by the oxyl radical, while the substitution of the oxygen by the sulfur atom, on the saturated condensed ring, increases the stability of the intermediate radical[7] (Fig. 2).

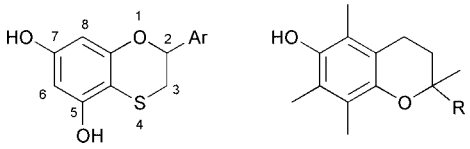

Fig. 2 4-Thiaflavan and tocopherol skeletons.

The oxidation of the sulfide sulfur causes the decrease of activity exhibited by sulfoxides **11** and **12** since it introduces an electron withdrawing group which, at the same time, is known to possess less ability in stabilizing radicals.[8]

These results seem to indicate that both the flavonoid-like and the tocopherol-like mechanisms are operative in compound **6**. Recent observations indicate that '*in vivo*' these two classes of natural polyphenols have to operate synergistically for a fast and safe protection against LDL (low density lipoprotein) damaging radicals.[9] Thus the possibility of joining in a single compound the very fast reaction of flavonoids with oxyl radicals and the high chain breaking ability of tocopherols, makes these thiaflavans very stimulating and promising new 'double-faced' antioxidant derivatives.

Moreover, since several 4-thiaflavans, including derivatives **8**–**10**, appeared active against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans* growth,[10] more detailed studies on the activity of 4-thiaflavans as antioxidants and antimicrobials are in progress in these laboratories.

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Notes and references

† 3,5-(Dimethyl-*tert*-butylsilyloxy)phenol was prepared by direct silylation of 1,3,5-trihydroxybenzene hydrate (fluorglucinol hydrate) with *t*-Bu-Me_2SiCl and imidazole in DMF.

‡ Representative experimental procedure: to a solution of **2** (150 mg, 0.28 mmol) and *p*-methoxystyrene (**5**) (38 mg, 0.28 mmol) in dry $CHCl_3$ (3 mL), TEA (28 mg, 0.28 mmol) was added and the mixture heated at 60 °C for 22 h. Evaporation of the solvent and flash chromatography afforded the required cycloadduct (145 mg, 60%), which was directly desilylated by reaction with TBAF hydrate (146 mg, 0.56 mmol) in THF (5 mL) for 35 min at 0 °C. Evaporation of the solvent and flash chromatography gave derivative **10** (57 mg, 70%) as a white solid; mp 169 °C.

§ Sulfoxides **7**, **11** and **12** were obtained, and tested, as 82 : 18, 86 : 14 and 93 : 7 mixtures of *trans* and *cis* isomers, respectively. For the synthesis and geometry of related sulfoxides see: G. Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron*, 1996, **52**, 12 233. Using 1 equiv. of *m*CPBA the formation of sulfones is not observed, the latter can be easily prepared carrying out the oxidation with 2 equiv. of *m*CPBA at rt for 2–12 h.

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