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**RESEARCH ARTICLE**

# Sulfur-mediated synthesis and antimicrobial activity of 4-thioisosteres of flavanoids

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Each step of the synthetic sequence inverse electron-demand hetero-Diels–Alder reaction of *o*-thioquinones with styrenes, oxidation at sulfur, and Pummerer rearrangement allowed the preparation of 4-thioisosteres of flavanoids, namely thiaflavans, thiaflavanones and thiaflavanols. A preliminary screening indicates a clear, though moderate, antimicrobial activity of such compounds that depends upon the substitution pattern and the oxidation state at sulfur.

*Keywords*: Sulfur heterocycles; *o*-Thioquinones; Flavanoid thioisosteres; Sulfoxides; Pummerer rearrangement



## 1. Introduction

Flavonoids (figure 1) are flavan skeleton-containing, naturally occurring polyphenolic compounds that are almost ubiquitous in vascular plants where they exert protection against UV irradiation, insect attack and oxidation [1]. Moreover their action as hormone regulators and colour providers is also well known [1]. A diet rich in flavonoids, due to their ability as free radical scavengers, has been indicated to prevent several diseases such as cardiovascular diseases, stroke and numerous types of cancer [2]. Moreover the antimicrobial activity of flavonoids as pure compounds or in plant extracts has been reported [3], and, recently, the ability of some flavanoids to act as inhibitors of *S. aureus* Multidrug Resistance Pump (MDRP) has been reported [4].

We recently described a new approach to benzoxathiin derivatives having the 4-thiaflavan skeleton (figure 1), and demonstrated their ability as radical scavenger, highlighting the role of the sulfur atom in such behaviour [5].

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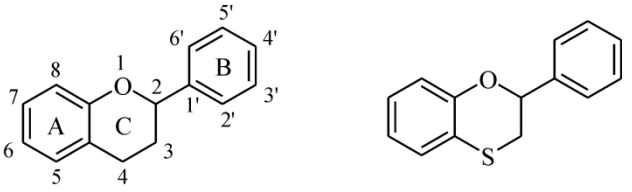



Figure 1. Flavan and 4-thiaflavan skeletons.

Our preparation of 4-thiaflavanes is based on the hetero-Diels–Alder reaction of *o*-thioquinones, used as electron-poor dienes, with styrenes, acting as electron-rich dienophiles, a successful strategy [6] for the synthesis of these valuable heterocycles [7]. The presence of the sulfur atom in position 4 of the C ring suggested the possibility of further exploiting its chemistry to synthesize other flavanoids thioisosteres. Thus, the sequence of cycloaddition, oxidation, and Pummerer reaction can be anticipated as suitable for preparing the 4-thia derivatives of flavans, flavanones and flavanols, respectively (figure 2).

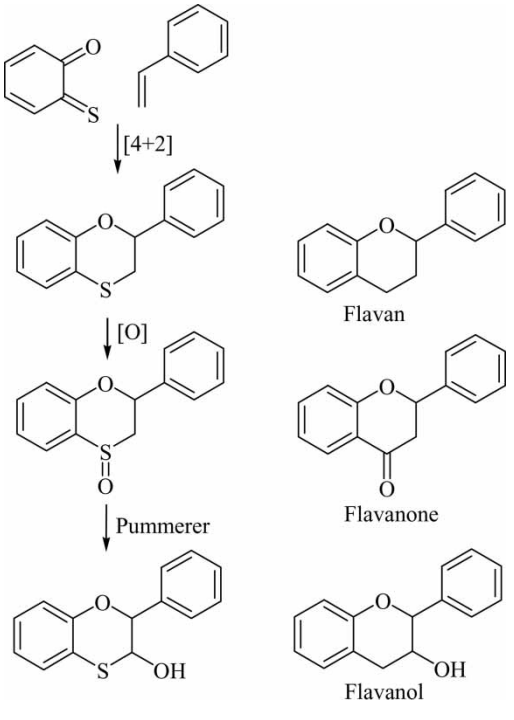


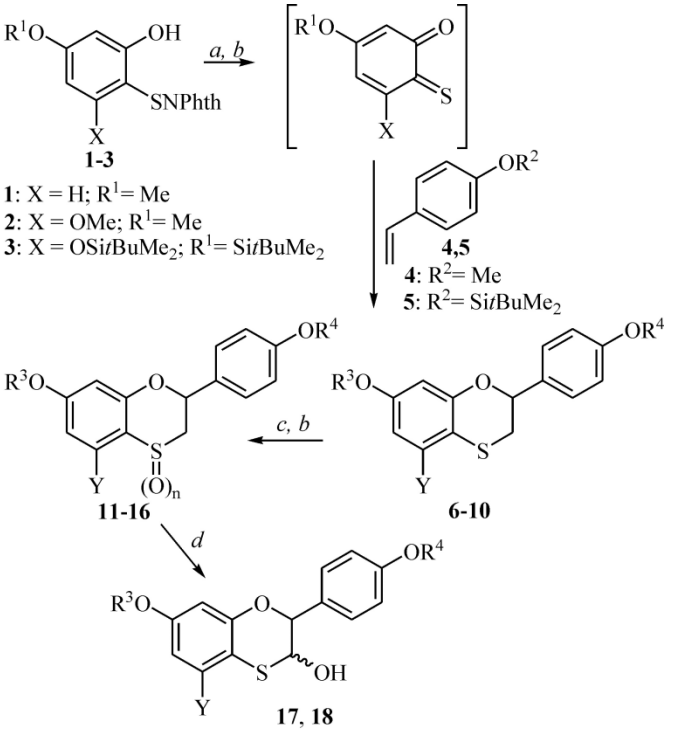

Figure 2. Sulfur-mediated synthesis of 4-thioisoteres of flavonoids.

In this paper we report the preparation of hydroxy- and methoxy-substituted 4-thiaflavanoids, exploiting the above-mentioned procedures, and an initial screening on their antimicrobial activity against *S. aureus*, *C. albicans*, *P. aeruginosa* and *E. coli*.

## 2. Results and discussion

Derivatives containing the 4-thiaflavan skeleton were obtained by reacting *o*-hydroxythiophthalimides **1–3** with 1 equiv of $Et_3N$ in $CHCl_3$ at 60 °C to generate *in situ* the corresponding

transient dienic *o*-thioquinones, which are trapped with styrenes **4** and **5**, used as electron rich-dienophiles, to give the expected benzoxathiin cycloadducts through a regiospecific inverse electron demand Diels–Alder reaction [5, 6]. To prepare hydroxyl derivatives **8–10**, initial protection as *t*-butyldimethylsilyl ethers was chosen for the diene and/or the dienophile counterpart. This permitted the formation of reasonably soluble reagents in the solvent of choice for the cycloaddition ($CHCl_3$), and easily isolable intermediates at the end of the process. Desilylation with TBAF · $3H_2O$ in THF led to the isolation of the required 4-thiaflavanes **8–10** (scheme 1).



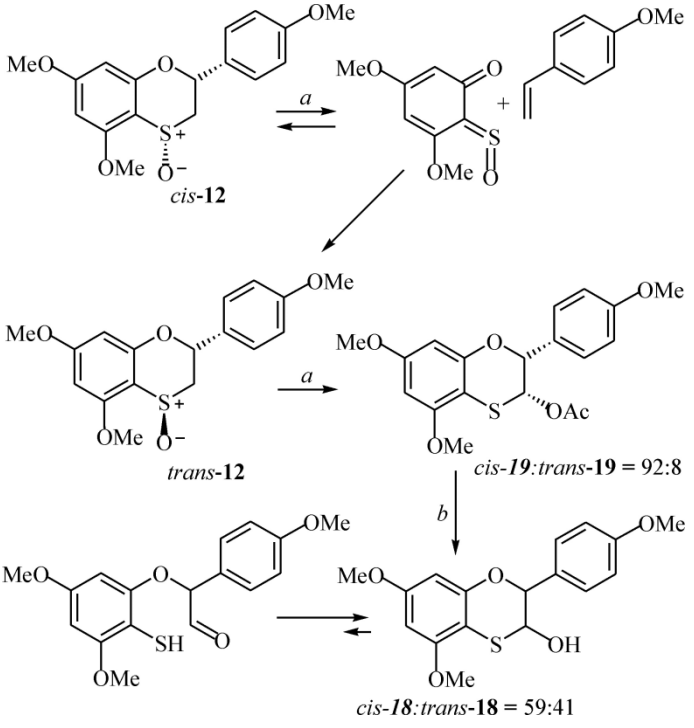

| Product | Y | $R^3$ | $R^4$ | n |
|---|---|---|---|---|
| **6** | H | Me | Me | - |
| **7** | OMe | Me | Me | - |
| **8** | OMe | Me | H | - |
| **9** | OH | H | Me | - |
| **10** | OH | H | H | - |
| **11** | H | Me | Me | 1 |
| **12** | OMe | Me | Me | 1 |
| **13** | OH | H | Me | 1 |
| **14** | OH | H | H | 1 |
| **15** | OMe | Me | Me | 2 |
| **16** | OH | H | Me | 2 |
| **17** | H | Me | Me | - |
| **18** | OMe | Me | Me | - |

SCHEME 1 Reagents and conditions. *a*. $Et_3N$ (1 equiv), $CHCl_3$, 60 °C, 20–120 h; *b*. TBAF·$3H_2O$, THF, 0 °C, 30 min–1 h; *c*. For **11–14**: MCPBA (1 equiv) $CH_2Cl_2$, −15 to 0 °C, 0.5–2 h; for **15** and **16**: MCPBA (2.5 equiv) $CH_2Cl_2$, room temperature, 4–8 h; *d*. See scheme 2.

Oxidation at sulfur with 1 equiv of MCPBA of 4-thiaflavans allowed the isolation of the sulfoxides, which are 4-thioisosteres of flavanones [8]. As expected [5, 9], oxidation afforded

a mixture of *cis*- and *trans*-sulfoxides with the *trans*-isomer dominant with the aryl group in position 2 being pseudo-equatorial in both isomers (from 77:23 to 93:7, see Experimental). Routine flash chromatography on silica gel allowed the isolation of the major isomers, which were tested as single compounds, and of sulfoxides **11** and **12** of the minor isomers as well. Desilylation was also performed as a final step of the synthetic procedure in this case to obtain *trans*-sulfoxides **13** and **14** (scheme 1). To gain more information on the effect of the sulfur atom at different oxidation states on the biological properties of 4-thiaflavanoids, sulfones **15** and **16** were also prepared using an excess of MCPBA (scheme 1).

Eventually, 4-thia-3-hydroxy derivatives analogues of flavanols **17** and **18** were prepared by Pummerer rearrangement *via* reaction of the corresponding sulfoxides **11** and **12** with an excess of $Ac_2O$–AcOH in refluxing benzene followed by hydrolysis of the intermediate acetate. Some comments are necessary on the stereochemical outcome of this reaction. Under Pummerer reaction conditions, both *cis*- and *trans*-sulfoxide **12** afforded the same mixture of *cis*- and *trans*-acetyl derivatives **19**; the former is the major product (*cis*-**19**:*trans*-**19** = 92:8), with the 2-aryl group being pseudo-equatorial and the 3-acetyl moiety pseudo-axial (scheme 2).




SCHEME 2 Reagents and conditions. *a*. $Ac_2O$–AcOH 2:1 (15 equiv), $C_6H_6$, reflux, 50 h; *b*. MeONa–MeOH, room temperature, 1 h, then HCl (1%)–MeOH.

Pummerer reactions of both isomers of sulfoxide **12** yielded tiny amounts of sulfoxide starting materials. Thus, we could verify that, under rearrangement conditions, *cis*-**12** was transformed into *trans*-**12**. This can be explained considering that, while *trans*-**12** rearranges to give **19**, the *cis*-isomer undergoes preferentially a retro-Diels–Alder process with formation of an *o*-thioquinone-*S*-oxide [9] and styrene **4**, which can react together to reform *trans*-**12** and, eventually, acetyl derivatives **19** (scheme 2).

Alkaline hydrolysis of acetyl derivatives **19**, followed by acidification, allowed the isolation of thiaflavanol **18** as a 59:41 mixture of *cis*- and *trans*-isomers. Any attempt to separate the

diastereoisomers was unsuccessful and we observed the same amount of each isomer in all chromatographic fractions. This can be justified by considering that hemithioacetals **18** equilibrate through an intermediate ring-opened aldehyde (scheme 2).

Exactly the same considerations apply to the Pummerer reaction of sulfoxide **11**; thus **17** and **18** were obtained and tested as mixtures of *cis*- and *trans*-thiaflavanol. Unfortunately, the Pummerer reaction failed for derivatives **13** and **14** since, probably, these sulfoxides, regardless of the relative stereochemistry, preferentially underwent a retro-Diels–Alder process [9] and a consequent decomposition rather than rearrangement.

We tested the antibacterial and antifungal activities of **7–18** on the following standard strains of pathogenic bacteria: *Escherichia coli* (strain ATCC 1128), *Staphylococcus aureus* (strain ATCC 25923), *Pseudomonas aeruginosa* (strain ATCC 15442) and *Candida albicans* (strain ATCC 10231) [10]. We determined the presence or absence of inhibition halos in Müller-Hinton II agar around paper disks imbued with 20 μL of a 20 mg per mL solution of each thiaflavane in dimethyl sulfoxide (DMSO) after the incubation time, at 37 °C, of 24–48 h for *E. coli* and *S. aureus* and 72 h for *P. aeruginosa* and *C. albicans*. Data reported as mm of inhibition halos [11] are shown in table 1.

Table 1. Inhibition halos (mm) of *S. aureus*, *P. aeruginosa*, *C. albicans* and *E. coli* in the presence of 4-thiaflavonoids **7–18**.

| Compound | *S. aureus* | *P. aeruginosa* | *C. albicans* | *E. coli* |
|---|---|---|---|---|
| **7** | 0 | 0 | 0 | 0 |
| **8** | 15 | 15 | 10 | 0 |
| **9** | 22 | 22 | 10 | 0 |
| **10** | 12 | 11 | 0 | 0 |
| **11**[a] | 0 | 0 | 0 | 0 |
| **12**[a] | 0 | 0 | 0 | 0 |
| **13**[a] | 0 | 0 | 0 | 0 |
| **14**[a] | 10 | 0 | 0 | 0 |
| **15** | 0 | 0 | 0 | 0 |
| **16** | 14 | 0 | 0 | 0 |
| **17**[b] | 15 | 20 | 13 | 0 |
| **18**[b] | 0 | 0 | 11 | 0 |

[a]Tested as pure *trans*-isomer. [b]Tested as a mixture of *cis*- and *trans*-isomers.

We verified that none of the compounds showed activity against *E. coli*, while some derivatives demonstrated a certain effect against either Gram positive (*P. aeruginosa*) or Gram negative (*S. aureus*) bacteria as well as against fungi (*C. albicans*). Thiaflavans **8** and **9** and thiaflavanol **17** were the most active compounds. As expected, in comparison with data available for polyphenolic natural compounds [3], none of the derivatives tested showed activity in the absence of hydroxyl groups. Conversely, compound **10** with an OH moiety either on A and B ring was less active than **8** or **9**, which have only one hydroxyl-substituted ring. Due to the limited information on the mechanism of antimicrobial activity of natural flavonoids it is very difficult to rationalize our data; however, the oxidation at sulfur clearly strongly influences the interaction between the thiaflavonoids and the micro-organisms since the activity vanishes upon transforming the sulfide into sulfoxide or sulfone (*i.e.* from **9** to **13** or **16**) and is, at least in part, re-established on shifting from sulfoxide to $\alpha$-hydroxy-sulfide (*i.e.* from thiaflavanone **11** to thiaflavanol **17**).

## 3. Conclusions

Exploiting the reactivity of *o*-thioquinones as electron-poor dienes and the transformations on the sulfur atom, it is possible to prepare several 4-thioisosteres of flavanoids which, depending on the aromatic substitution and the sulfur oxidation, show an evident antimicrobial activity. Further applications of these valuable sulfur heterocycles are under investigation in this laboratory.

## 4. Experimental

General: $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini and on a Varian Mercury at 200 or 300 and 50 or 75 MHz respectively, in $CDCl_3$ (unless otherwise specified) using residual $CHCl_3$ at $\delta_H = 7.26$ (for $^1$H) and a central peak of $CDCl_3$ at $\delta_D = 77.0$ (for $^{13}$C) as reference lines. Melting points are uncorrected. Mass spectra were registered with a Carlo Erba QMD 1000 instruments. Analyses were obtained with a Perkin-Elmer CHNS/O 2400II Elementary Analyser. $CHCl_3$, $CH_2Cl_2$, THF, DMF and $Et_3N$ were dried following standard procedures, and all commercial reagents were used, without further purification, as obtained from freshly opened containers. Derivative **3** was prepared by silylation of the corresponding phenol with TBDMSCl and imidazole in dry DMF. Similarly, styrene **5** was obtained from 4-hydroxybenzaldehyde by silylation followed by Wittig reaction. Phthalimidesulfenyl chloride and the sulfenylation of phenols, to obtain sulfenamides **1–3**, were realized as reported elsewhere [6].



### 4.1 *Cycloaddition reactions. General procedures*

To a solution of *N*-thiophthalimide in dry $CHCl_3$ (roughly 0.1 M), the styrene (1 equiv) and freshly distilled $Et_3N$ (1 equiv) were added in sequence, the reaction mixtures were then heated at 60 °C and monitored, either by $^1$H NMR or TLC, till the disappearance of thiophthalimide (20–120 h). Evaporation of the solvent and flash chromatography on silica gel allowed the isolation of the cycloadducts. Spectroscopic data are as follows, silylated cycloadduct are indicated as **8′**, **9′** and **10′** respectively.

*4-Thiaflavan* **6**: Obtained as a yellow solid by flash chromatography on silica gel with light petroleum–dichloromethane (1:1) as eluent; mp 75 °C, 68% yield. $^1$H NMR (200 MHz) $\delta$ (ppm): 3.02 (dd, $J = 14.0$, 2.2 Hz, 1H), 3.24 (dd, $J = 14.0$, 9.6 Hz, 1H), 3.75 (s, 3H), 3.83 (s, 3H), 5.16 (dd, $J = 9.6$, 2.2 Hz, 1H), 6.51–6.55 (m, 2H), 6.92–6.95 (m, 2H), 7.20 (s, 1H), 7.32–7.35 (m, 2H); $^{13}$C NMR ($CD_3COCD_3$, 50 MHz) $\delta$ (ppm): 31.5 (t, 1C), 55.2 (q, 1C), 55.3 (q, 1C), 76.7 (d, 1C), 103.7 (d, 1C), 107.7 (s, 1C), 109.0 (d, 1C), 114.1 (d, 2C), 127.3 (d, 2C), 132.4 (s, 1C), 153.2 (s, 1C), 158.0 (s, 1C), 159.7 (s, 1C). Anal. (%) for $C_{16}H_{16}O_3S$, calcd.: C, 66.64; H, 5.59; found: C, 66.83; H, 5.67. MS $m/z$ (int. rel.): 288 ($M^{+\cdot}$, 27%), 134 (100).

*4-Thiaflavan* **7**: Obtained as a yellow oil by flash chromatography on silica gel with light petroleum–ethyl acetate (100:1) as eluent; 45% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.03 (dd, $J = 12.0$, 2.2 Hz, 1H), 3.17 (dd, $J = 12.0$, 9.2 Hz, 1H), 3.73 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 5.10 (dd, $J = 9.2$, 2.2 Hz, 1H), 6.14 (d, $J = 2.2$ Hz, 1H), 6.19 (d, $J = 2.2$ Hz, 1H), 6.91–6.95 (m, 2H), 7.31–7.35 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 30.6 (t, 1C), 55.2 (q, 1C), 55.3 (q, 1C), 55.9 (q, 1C), 76.6 (d, 1C), 92.6 (d, 1C), 95.6 (d, 1C), 97.5 (s, 1C), 113.9 (d, 2C), 127.2 (d, 2C), 132.4 (s, 1C), 153.4 (s, 1C), 156.2 (s, 1C), 158.0 (s, 1C), 159.5 (s, 1C). MS, $m/z$ (int. rel. %): 318 ($M^{+\cdot}$, 66); 134 (100). Anal. (%) for $C_{17}H_{18}O_4S$, calcd.: C, 64.13; H, 5.70; found: C, 64.21; H, 5.49.

*4-Thiaflavan* **8′**: Compound **8′** was obtained as a yellow solid by flash chromatography on silica gel with light petroleum–ethyl acetate (from 100:1 to 6:1) as eluent; mp 84 °C, 32% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 0.21 (s, 6H), 0.99 (s, 9H), 3.03 (dd, $J = 13.0$, 2.2 Hz, 1H), 3.16 (dd, $J = 13.0$, 9.0 Hz, 1H), 3.74 (s, 3H), 3.85 (s, 3H), 5.08 (dd, $J = 9.0$, 2.2 Hz, 1H), 6.14 (d, $J = 2.6$ Hz, 1H), 6.20 (d, $J = 2.6$ Hz, 1H), 6.85–6.89 (m, 2H), 7.25–7.29

(m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): −4.9 (q, 2C), 18.1 (s, 1C), 25.6 (q, 3C), 30.8 (t, 1C), 55.4 (q, 1C), 56.0 (q, 1C), 76.8 (d, 1C), 92.7 (d, 1C), 95.6 (d, 1C), 97.6 (s, 1C), 120.2 (d, 2C), 127.3 (d, 2C), 133.1 (s, 1C), 153.6 (s, 1C), 155.8 (s, 1C), 156.4 (s, 1C), 158.1 (s, 1C). MS $m/z$ (int. rel. %): 418 ($M^{+\cdot}$, 15); 177 (100). Anal. (%) for $C_{22}H_{30}O_4SSi$, calcd.: C, 63.12; H, 7.22; found: C, 63.55; H, 7.44.

*4-Thiaflavan* **9′**: Obtained as a white solid by flash chromatography on silica gel with light petroleum–ethyl acetate (100:1 → 6:1) as eluent; mp 96–99 °C, 64% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 0.17 (s, 6H), 0.26 (s, 6H), 0.96 (s, 9H), 1.04 (s, 9H), 3.00 (dd, $J$ = 13.0, 1.8 Hz, 1H), 3.16 (dd, $J$ = 13.0, 9.4 Hz, 1H), 3.82 (s, 3H), 5.05 (dd, $J$ = 9.4, 1.8 Hz, 1H), 6.02 (d, $J$ = 2.4 Hz, 1H), 6.15 (d, $J$ = 2.4 Hz, 1H), 6.91–6.96 (m, 2H), 7.31–7.35 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): −4.9 (q, 2C), −4.3 (q, 2C), 18.2 (s, 1C), 18.3 (s, 1C), 25.6 (q, 3C), 25.7 (q, 3C), 31.1 (t, 1C), 55.3 (q, 1C), 76.5 (d, 1C), 102.2 (d, 1C), 103.8 (d, 1C), 104.6 (s, 1C), 114.1 (d, 2C), 127.4 (d, 2C), 132.8 (s, 1C), 152.1 (s, 1C), 153.3 (s, 1C), 153.7 (s, 1C), 159.7 (s, 1C). MS $m/z$ (int. rel.,%): 518 ($M^{+\cdot}$, 19); 461 (50); 73 (100). Anal. (%) for $C_{27}H_{42}O_4SSi_2$, calcd.: C, 62.52; H, 8.17; found: C, 62.67; H, 8.22.

*4-Thiaflavan* **10′**: Obtained as a yellow oil by flash chromatography on silica gel with light petroleum–ethyl acetate (100:1 → 6:1) as eluent; 55% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 0.17 (s, 6H), 0.20 (s, 6H), 0.26 (s, 6H), 0.95 (s, 9H), 0.99 (s, 9H), 1.03 (s, 9H), 2.99 (dd, $J$ = 13.0, 2.2 Hz, 1H), 3.14 (dd, $J$ = 13.0, 9.7 Hz, 1H), 5.02 (dd, $J$ = 9.7, 2.2 Hz, 1H), 6.01 (d, $J$ = 2.4 Hz, 1H), 6.15 (d, $J$ = 2.4 Hz, 1H), 6.83–6.88 (m, 2H), 7.23–7.27 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): −4.6 (q, 2C), −4.4 (q, 2C), −4.3 (q, 2C), 18.2 (s, 2C), 18.3 (s, 1C), 25.6 (q, 6C), 25.8 (q, 3C), 31.2 (t, 1C), 76.6 (d, 1C), 103.9 (d, 1C), 104.6 (d, 1C), 105.8 (s, 1C), 120.2 (d, 2C), 127.3 (d, 2C), 133.3 (s, 1C), 153.1 (s, 1C), 153.3 (s, 1C), 153.7 (s, 1C), 155.8 (s, 1C). MS $m/z$ (int. rel.,%): 619 ($M^{+\cdot}$, 12); 385 (9); 233 (11); 73 (100).



### 4.2 *Oxidation reactions*

(a) Sulfoxides **11**, **12** and silylated sulfoxides indicated as **13′** and **14′**: To a solution of the cycloadduct in $CH_2Cl_2$ (0.04 M) kept at −15 to 0 °C, a solution of MCPBA (1 equiv) in $CH_2Cl_2$ was added and the reaction monitored by TLC until the disappearance of the sulfide (30 min–1 h). The mixture was then diluted with $CH_2Cl_2$, washed with $Na_2S_2O_3$ 10%, saturated $NaHCO_3$ and water. The organic phase was then 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 of the residue by flash chromatography on silica gel allowed the isolation of *cis*- and *trans*-**11** and -**12** and *trans*-**13′** and -**14′**.

(b) Sulfone **15** and silylated sulfone **16′**: To a solution of sulfide in $CH_2Cl_2$ (0.04 M) at room temperature, a solution of MCPBA (2.5 equiv) in $CH_2Cl_2$ was added and the reaction monitored by TLC until the disappearance of starting material (4–8 h). The mixtures were subsequently diluted with $CH_2Cl_2$, washed with $Na_2S_2O_3$ 10%, saturated $NaHCO_3$ and water. The organic phase was then dried over anhydrous $Na_2SO_4$ and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the desired sulfones.

*4-Thiaflavone* **11**: Derivative **11** was obtained as an 84:16 mixture of *trans*- and *cis*-isomers in 87% overall yield. Flash chromatography on silica gel with light petroleum–ethyl acetate (1:1) as eluent allowed the isolation of both isomers: *trans*-**11**: white solid, mp 73–76 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.04 (dd, $J$ = 14.3, 11.7 Hz, 1H), 3.23 (dd, $J$ = 14.3, 1.8 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 5.69 (dd, $J$ = 11.3, 1.8 Hz, 1H), 6.55 (d, $J$ = 2.6 Hz, 1H), 6.67 (dd, $J$ = 8.8, 2.6 Hz, 1H), 6.94–6.99 (m, 2H), 7.40–7.45 (m, 2H), 7.57 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 49.1 (t, 1C), 55.1 (q, 1C), 55.3 (q, 1C), 67.1 (d, 1C), 102.4 (d, 1C), 109.5 (d, 1C), 114.1 (d, 2C), 114.7 (s, 1C), 127.8 (d, 1C), 130.2 (s, 1C), 133.5 (d, 1C), 154.9 (s, 1C), 159.8 (s, 1C), 164.1 (s, 1C). MS $m/z$ (int. rel.,%): 304 ($M^{+\cdot}$, 1); 288 (45); 134 (56); 57 (100).

*cis*-**11**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.36 (dd, $J$ = 12.0, 11.0 Hz, 1H), 3.67 (d, $J$ = 12.0 Hz, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 5.23 (d, $J$ = 11.0 Hz, 1H), 6.46 (d, $J$ = 2.2 Hz, 1H), 6.74 (dd, $J$ = 8.8, 2.2 Hz, 1H), 6.94–6.99 (m, 2H), 7.36–7.39 (m, 2H), 7.63 (d, $J$ = 8.8 Hz, 1H).

*4-Thiaflavone* **12**: Derivative **12** was obtained as a 77:23 mixture of *trans*- and *cis*-isomers in 79% overall yield. Flash chromatography on silica gel with light petroleum–ethyl acetate (1:2) as eluent allowed the isolation of both isomers: *trans*-**12**: pale yellow solid, mp 145–147 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 2.87 (dd, $J$ = 14.0, 11.4 Hz, 1H), 3.17 (d, $J$ = 14.0 Hz, 1H), 3.75 (s, 3H) 3.80 (s, 3H), 3.90 (s, 3H), 5.55 (d, $J$ = 11.4 Hz, 1H); 6.11 (d, $J$ = 2.2 Hz, 1H), 6.13 (d, $J$ = 2.2 Hz, 1H), 6.91–6.95 (m, 2H), 7.37–7.41 (m, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 41.2 (t, 1C), 55.2 (q, 1C), 55.4 (q, 1C), 56.3 (q, 1C), 67.5 (d, 1C), 92.5 (d, 1C), 94.3 (d, 1C), 105.8 (s, 1C), 114.1 (d, 2C), 127.9 (d, 2C), 130.6 (s, 1C), 156.2 (s, 1C), 159.9 (s, 1C), 161.1 (s, 1C), 164.8 (s, 1C). Anal. (%) for $C_{17}H_{18}O_5S$, calcd.: C, 61.06; H, 5.43; found: C, 60.82; H, 5.42.

*cis*-**12**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.45 (d, $J$ = 11.8 Hz, 1H), 3.76 (m, 5H), 3.82 (s, 3H), 3.92 (s, 3H), 5.09 (d, $J$ = 11.8 Hz, 1H), 6.10 (d, $J$ = 2.4 Hz, 1H), 6.16 (d, $J$ = 2.4 Hz, 1H), 6.91–6.96 (m, 2H), 7.33–7.38 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 53.0 (t, 1C), 55.3 (q, 1C), 55.5 (q, 1C), 56.5 (q, 1C), 75.6 (d, 1C), 93.7 (d, 1C), 94.7 (d, 1C), 107.6 (s, 1C), 114.3 (d, 2C), 127.7 (d, 2C), 129.8 (s, 1C), 157.3 (s, 1C), 160.1 (s, 1C), 161.6 (s, 1C), 164.2 (s, 1C).

*4-Thiaflavone* **13′**: Obtained as a 93:7 mixture of *trans*- and *cis*-isomers in 64% overall yield. Flash chromatography on silica gel with light petroleum–ethyl acetate (4:1) as eluent allowed the isolation of the major isomer as a glassy solid: *trans*-**13′**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 0.20 (s, 6H), 0.31 (s, 3H), 0.34 (s, 3H), 0.96 (s, 9H), 1.08 (s, 9H), 2.91 (dd, $J$ = 13.7, 11.6 Hz, 1H), 3.18 (d, $J$ = 13.7 Hz, 1H), 3.83 (s, 3H), 5.59 (d, $J$ = 11.6 Hz, 1H), 6.02 (d, $J$ = 2.2 Hz, 1H), 6.15 (d, $J$ = 2.2 Hz, 1H), 6.40–7.00 (m, 2H), 7.40–7.44 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): −4.4 (q, 2C), −4.4 (q, C), −4.3 (q, C), 18.4 (s, 2C), 25.6 (q, 3C), 25.6 (q, 3C), 49.6 (t, 1C), 55.9 (q, 1C), 67.5 (d, 1C), 102.8 (d, 1C), 103.9 (d, 1C), 105.4 (s, 1C), 114.3 (d, 2C), 128.0 (d, 2C), 131.0 (d, 1C), 156.0 (s, 1C), 158.0 (s, 1C), 160.0 (s, 1C), 161.0 (s, 1C). MS $m/z$ (int. rel.%): 534 ($M^{+\cdot}$, 0.4); 134 (72); 73 (100). Anal. (%) for $C_{27}H_{42}O_5SSi_2$, calcd.: C, 60.63; H, 7.91; found: C, 60.68; H, 7.89.

*4-Thiaflavone* **14′**: Obtained as an 86:14 mixture of *trans* and *cis*-isomers in 63% overall yield. Flash chromatography on silica gel with light petroleum–ethyl acetate (6:1) as eluent allowed the major isomer to be isolated as a glassy solid: *trans*-**14′**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 0.20 (s, 6H), 0.21 (s, 6H), 0.31 (s, 3H), 0.34 (s, 3H), 0.96 (s, 9H), 0.99 (s, 9H), 1.08 (s, 9H), 2.88 (dd, $J$ = 14.2, 11.6 Hz, 1H), 3.14 (d, $J$ = 14.2 Hz, 1H), 5.56 (d, $J$ = 11.6 Hz, 1H), 6.02 (d, $J$ = 2.2 Hz, 1H), 6.15 (d, $J$ = 2.2 Hz, 1H), 6.87–6.91 (m, 2H), 7.33–7.37 (m, 2H).

*Sulfone* **15**: This was obtained as a yellow solid by flash chromatography on silica gel with light petroleum–ethyl acetate (6:1) as eluent; 85% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.42 (dd, $J$ = 14.0, 1.2 Hz, 1H), 3.66–3.71 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 5.62 (d, $J$ = 11.0 Hz, 1H), 6.10 (d, $J$ = 2.2 Hz, 1H), 6.16 (d, $J$ = 2.2 Hz, 1H), 6.93–6.99 (m, 2H), 7.34–7.38 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 55.4 (t, 1C), 55.6 (q, 1C), 56.6 (q, 1C), 57.9 (q, 1C), 77.2 (d, 1C), 92.0 (d, 1C), 94.3 (d, 1C), 108.3 (s, 1C), 114.4 (d, 2C), 127.7 (d, 2C), 128.9 (s, 1C), 156.3 (s, 1C), 159.6 (s, 1C), 160.4 (s, 1C), 164.5 (s, 1C). MS $m/z$ (int. rel.%): 350 ($M^{+\cdot}$, 12); 134 (100). Anal. (%) for $C_{17}H_{18}O_6S$, calcd.: C, 58.27; H, 5.18; found: C, 58.54; H, 5.34.

*Sulfone* **16′**: Obtained as a yellow solid directly from the work-up of the reaction in 93% yield: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 0.20 (s, 6H), 0.34 (s, 6H), 0.95 (s, 9H), 1.07 (s, 9H), 3.36 (dd, $J$ = 13.9, 1.3 Hz, 1H), 3.71 (dd, $J$ = 13.9, 12.1 Hz, 1H), 3.83 (s, 3H), 5.59 (br d, 1H, $J$ = 11.1 Hz), 6.04 (d, $J$ = 2.2 Hz, 1H), 6.08 (d, $J$ = 2.2 Hz, 1H), 6.94–6.97 (m, 2H), 7.34–7.37 (m, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm): −4.4 (q, 2C), −4.2 (q, 1C), −4.1

(q, 1C), 18.2 (s, 1C), 18.3 (s, 1C), 25.5 (q, 3C), 25.6 (q, 3C), 55.4 (q, 1C), 55.8 (t, 1C), 77.1 (d, 1C), 102.3 (d, 1C), 103.4 (d, 1C), 114.5 (d, 2C), 127.7 (d, 2C), 127.9 (s, 1C), 129.3 (s, 1C), 154.9 (s, 1C), 156.0 (s, 1C), 160.5 (s, 1C), 160.6 (s, 1C).

### 4.3 *Desilylation reaction. General procedure*

To a solution of silylated cycloadduct in THF (0.04 M) at 0 °C, a solution of TBAF · $3H_2O$ in $CH_2Cl_2$ (1 equiv for each TBDMSO group) was added and the reaction monitored by TLC until the disappearance of the starting material (1–2 h). The crude mixture was then diluted with ethyl acetate, and washed with saturated $NH_4Cl$ and water. The organic phase was then dried over anhydrous $Na_2SO_4$ and evaporated to dryness. Subsequent purification of the residue by flash chromatography on silica gel afforded the desired product.

*4-Thiaflavan* **8**: Obtained as a yellow solid by flash chromatography on silica gel with dichloromethane–methanol (20:1) as eluent; 32% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.03 (dd, $J$ = 14.0, 2.2 Hz, 1H), 3.16 (dd, $J$ = 14.0, 9.0 Hz, 1H), 3.74 (s, 3H), 3.85 (s, 3H), 5.09 (dd, $J$ = 9.0, 2.2 Hz, 1H), 5.16 (s, 1H), 6.14 (d, $J$ = 2.2 Hz, 1H), 6.19 (d, $J$ = 2.2 Hz, 1H), 6.84–6.89 (m, 2H), 7.26–7.30 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 30.8 (t, 1C), 55.5 (q, 1C), 56.0 (q, 1C), 76.7 (d, 1C), 92.8 (d, 1C), 95.7 (d, 1C), 111.6 (s, 1C), 115.5 (d, 2C), 127.5 (d, 2C), 128.0 (s, 1C), 153.5 (s, 1C), 155.8 (s, 2C), 158.0 (s, 1C). MS $m/z$ (int. rel.%): 304 ($M^{+\cdot}$, 54); 184 (14) 120 (36); 84 (100). Anal. (%) for $C_{16}H_{16}O_4S$, calcd.: C, 63.14; H, 5.30; found: C, 63.47; H, 5.65.

*4-Thiaflavan* **9**: Obtained as a white solid by flash chromatography on silica gel with dichloromethane–ethyl acetate (3:1) or dichloromethane–methanol (7:1) as eluent; mp 167–170 °C, 84% yield. $^1$H NMR ($CD_3COCD_3$, 300 MHz) $\delta$ (ppm): 3.08–3.11 (m, 2H), 3.83 (s, 3H), 5.05–5.09 (m, 1H), 6.10 (d, $J$ = 2.4 Hz, 1H), 6.11 (d, $J$ = 2.4 Hz, 1H), 6.94–6.98 (m, 2H), 7.37–7.41 (m, 2H), 8.09 (s, 1H), 8.66 (s, 1H); $^{13}$C NMR ($CD_3COCD_3$, 75 MHz) $\delta$ (ppm): 31.1 (t, 1C), 55.5 (q, 1C), 77.4 (d, 1C), 96.3 (s, 1C), 97.1 (d, 1C), 98.1 (d, 1C), 114.7 (d, 2C), 128.3 (d, 2C), 133.9 (s, 1C), 154.8 (s, 1C), 155.0 (s, 1C), 156.3 (s, 1C), 160.6 (s, 1C). MS $m/z$ (int. rel.%): 290 ($M^{+\cdot}$, 21); 119 (24); 134 (100). Anal. (%) for $C_{15}H_{14}O_4S$, calcd.: C, 62.05; H, 4.86. found C, 61.88; H, 4.73.

*4-Thiaflavan* **10**: Obtained as a reddish solid by flash chromatography on silica gel with dichloromethane–methanol (6:1) as eluent; mp 60 °C dec., 28% yield. $^1$H NMR ($CDCl_3$ + $CD_3OD$ 200 MHz) $\delta$ (ppm): 4.63 (m, 1H), 5.59 (d, $J$ = 2.6 Hz, 1H), 5.72 (d, $J$ = 2.6 Hz, 1H), 6.43–6.47 (m, 2H), 6.80–6.84 (m, 2H), 8.30 (s, 1H), 8.69 (s, 1H), 8.97 (s, 1H). $^{13}$C NMR ($CDCl_3$ + $CD_3OD$ 50 MHz) $\delta$ (ppm): 58.4 (t, 1C), 76.8 (d, 1C), 95.1 (s, 1C), 96.1 (d, 1C), 97.2 (d, 1C), 115.3 (d, 2C), 127.2 (d, 2C), 131.4 (s, 1C), 153.6 (s, 1C), 153.6 (s, 1C), 154.6 (s, 1C), 156.8 (s, 1C). MS $m/z$ (int. rel.%): 276 ($M^{+\cdot}$, 45); 120 (100). Anal. (%) for $C_{14}H_{12}O_4S$, calcd.: C, 60.86; H, 4.38; found C, 60.51; H, 4.11.

*4-Thiaflavanone* **13**: Obtained as a white solid by flash chromatography on silica gel with dichloromethane–methanol (6:1) as eluent; mp 195 °C dec., 77% yield. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 2.75–3.46 (m, 2H), 3.75 (s, 3H), 5.45–5.50 (m, 1H), 5.96 (s, 1H), 6.11 (s, 1H), 6.85–6.89 (m, 2H), 7.31–7.36 (m, 2H), 9.24 (s, 1H), 9.94 (s, 1H). MS $m/z$ (int. rel.%): 306 ($M^{+\cdot}$, 0.1); 134 (100). Anal. (%) for $C_{15}H_{14}O_5S$, calcd.: C, 58.81; H, 4.61; found C, 58.65; H, 4.66.

*4-Thiaflavanone* **14**: Obtained as a white solid by flash chromatography on silica gel with dichloromethane–methanol (6:1) as eluent; 76% yield. $^1$H NMR ($CD_3SOCD_3$, 200 MHz) $\delta$ (ppm): 5.29 (m, 1H), 5.82 (d, $J$ = 2.0 Hz, 1H), 6.04 (d, $J$ = 2.0 Hz, 1H), 6.79–6.83 (m, 2H), 7.30–7.34 (m, 2H), 8.94 (s, 1H), 9.61 (s, 1H), 10.01 (s, 1H); $^{13}$C NMR ($CD_3SOCD_3$, 50 MHz) $\delta$ (ppm): 48.0 (t, 1C), 67.1 (d, 1C), 95.1 (d, 1C), 95.5 (d, 1C), 104.0 (s, 1C), 115.2 (d, 2C), 128.4 (d, 2C), 129.3 (s, 1C), 155.4 (s, 1C), 157.7 (s, 1C), 159.5 (s, 1C), 162.4 (s, 1C). Anal. (%) for $C_{14}H_{12}O_5S$, calcd.: C, 57.53; H, 4.14; found C, 57.48; H, 4.35.

*Sulfone* **16**. This was obtained as a white solid by flash chromatography on silica gel with dichloromethane–ethyl acetate (2:1) or dichloromethane–methanol (6:1) as eluent; mp 216–219 °C, 92% yield. $^1$H NMR ($CD_3COCD_3$, 300 MHz) $\delta$ (ppm): 3.49 (dd, $J = 13.8, 1.5$ Hz, 1H), 3.84 (s, 3H), 3.90 (dd, $J = 13.8, 12.1$ Hz, 1H), 5.62 (dd, $J = 12.1, 1.5$ Hz, 1H), 6.00 (d, $J = 2.1$ Hz, 1H), 6.19 (d, $J = 2.1$ Hz, 1H), 7.00–7.05 (m, 2H), 7.52–7.58 (m, 2H), 9.36 (br s, 1H); $^{13}$C NMR ($CD_3COCD_3$, 75 MHz) $\delta$ (ppm): 55.6 (q, 1C), 57.8 (t, 1C), 78.1 (d, 1C), 96.7 (d, 1C), 98.3 (d, 1C), 107.9 (s, 1C), 114.9 (d, 2C), 129.2 (d, 2C), 130.6 (s, 1C), 157.1 (s, 1C), 158.6 (s, 1C), 161.3 (s, 1C), 163.1 (s, 1C). MS $m/z$ (int. rel.%): 322 ($M^{+\cdot}$, 19); 156 (46); 134 (100). Anal. (%) for $C_{15}H_{14}O_6S$, calcd.: C, 55.89; H, 4.38; found: C, 55.67; H, 4.17.

*Pummerer reaction of sulfoxides* **11** *and* **12**. To a solution of the sulfoxide in dry $C_6H_6$ a mixture of $Ac_2O$–AcOH (2:1) (15 equiv) was added and the solution heated at reflux for 50 h. The crude mixture was then washed with saturated $NaHCO_3$ and with brine, dried over $Na_2SO_4$ and evaporated to yield the crude 2-acetyl-4-thiaflavanols **17′** and **19**.

*Acetyl derivative* **17′**: Obtained as a 87:13 inseparable mixture of *cis*- and *trans*-isomers in 70% yield. Data of major *cis*-isomer: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 2.10 (s, 3H), 3.78 (s, 6H), 5.40 (d, $J = 4.0$ Hz, 1H), 6.23 (d, $J = 4.0$ Hz), 6.52–6.65 (m, 2H), 6.83–6.95 (m, 3H), 7.25–7.30 (s, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 21.1 (q, 1C), 55.2 (q, 1C), 55.4 (q, 1C), 72.6 (d, 1C), 76.9 (d, 1C), 103.8 (d, 1C), 106.2 (s, 1C), 109.3 (d, 1C), 113.9 (d, 2C), 127.2 (d, 2C), 127.9 (d, 1C), 129.6 (s, 1C), 150.9 (s, 1C), 158.7 (s, 1C), 159.5 (s, 1C), 169.8 (s, 1C). MS $m/z$ (int. rel.%): 346 ($M^{+\cdot}$, 33); 287 (6); 150 (100).

*Acetyl derivative* **19**: Obtained as a 92:8 mixture of *cis*- and *trans*-isomers in 77% yield. Flash chromatography on silica gel with light petroleum–ethyl acetate (1:2) allowed the isolation of *cis*-**19** as a pure, yellow solid, mp 120–122 °C. $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 2.10 (s, 3H), 3.77 (s, 3H), 3.78 (s, 6H), 5.42 (d, $J = 3.7$ Hz, 1H), 6.14 (d, $J = 2.2$ Hz, 1H), 6.28 (d, $J = 3.7$ Hz), 6.31 (d, $J = 2.2$ Hz, 1H), 6.82–6.86 (m, 2H), 7.24–7.28 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 21.1 (t, 1C), 55.2 (q, 1C), 55.4 (q, 1C), 55.9 (q, 1C), 71.0 (d, 1C), 92.9 (d, 1C), 95.5 (d, 1C), 95.7 (s, 1C), 113.9 (d, 2C), 127.1 (d, 2C), 129.5 (s, 1C), 150.9 (s, 1C), 156.2 (s, 1C), 158.8 (s, 1C), 159.5 (s, 1C), 169.9 (s, 1C). MS $m/z$ (int. rel.%): 376 ($M^{+\cdot}$, 13); 150 (100). Anal. (%) for $C_{19}H_{20}O_6S$, calcd.: C, 60.63; H, 5.36; found: C, 60.60; H, 5.43.

*4-Thiaflavanol* **17**: Obtained by hydrolysis of **17′** with an excess of MeONa in MeOH–$CH_2Cl_2$ (2:1) followed by acidification with HCl 1% in MeOH. Evaporation of the solvent and flash chromatography on silica gel with light petroleum–ethyl acetate (3:1) as eluent gave alcohol **17** as an inseparable 1:1 mixture of *cis* and *trans* isomers (oil 77% yield). $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.76 + 3.77 + 3.78 + 3.83 (s, $OCH_3$), 5.23–5.32 (m, OCH + SCH), 6.57–7.47 (m, arom + OH). MS $m/z$ (int. rel.%): 304 ($M^{+\cdot}$, 9); 273 (100); 150 (99). Anal. (%) for $C_{16}H_{16}O_4S$, calcd.: C, 63.14; H, 5.30; found: C, 60.10; H, 5.38. (Correct for $C_{16}H_{16}O_4S \cdot H_2O$).

*4-Thiaflavanol* **18**. This was obtained by hydrolysis of **19** with an excess of MeONa in MeOH–$CH_2Cl_2$ (2:1) followed by acidification with HCl 1% in MeOH. Evaporation of the solvent and flash chromatography on silica gel with light petroleum–ethyl acetate (4:1) as eluent, gave alcohol **18** as an inseparable 59:41 mixture of *cis* and *trans* isomers (oil 94% yield). Spectroscopic data of major and minor isomer were tentatively obtained from the spectra of the mixture. *Major* **18**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.75 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 5.18 (s, 1H), 5.27 (s, 1H), 6.18 (d, $J = 2.6$ Hz, 1H), 6.27 (d, $J = 2.6$ Hz, 1H), 6.92–6.97 (m, 2H), 7.42–7.47 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 55.2 (q, 1C), 55.4 (q, 1C), 56.0 (q, 1C), 71.1 (d, 1C), 79.3 (d, 1C), 93.6 (d, 1C, CH), 95.7 (d, 1C, CH), 96.4 (s, 1C), 113.9 (d, 2C, CH), 127.9 (d, 2C, CH), 129.9 (s, 1C), 156.4 (s, 1C), 158.6 (s, 2C), 159.6 (s, 1C). MS $m/z$ (int. rel.%): 334 ($M^{+\cdot}$, 13); 150 (28); 121 (100). Analysis of the mixture (%) for $C_{17}H_{18}O_5S$, calcd.: C, 61.06; H, 5.43; found: C, 60.88; H, 5.51.

*Minor* **18**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 3.76 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.30 (s, 2H), 6.13 (d, $J = 2.7$ Hz, 1H), 6.28 (d, $J = 2.7$ Hz, 1H), 6.83–6.87 (m, 2H), 7.21–7.26 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 55.2 (q, 1C), 55.4 (q, 1C), 55.8 (q, 1C), 71.4 (d, 1C), 79.0 (d, 1C), 93.0 (d, 1C), 95.5 (d, 1C), 97.1 (s, 1C), 113.9 (d, 2C), 127.3 (d, 2C), 130.0 (s, 1C), 156.4 (s, 1C), 158.6 (s, 1C), 158.6 (s, 1C), 159.6 (s, 1C).

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[8] These compounds similarily suffer from the lack of planarity and less efficient H-bond donor aptitude of the sulfoxide with respect to the carbonyl group.

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[10] Standard strains of pathogenic bacteria as indicated by ATCC: American Type Collection Control.

[11] Inhibition halos range of sensitivity (mm) as indicated by NCCLS: National Committee for Clinical Laboratory Standards. *Escherichia coli* 17–22 mm, *Staphylococcus aureus* 14–36 mm, *Pseudomonas aeruginosa* 12–33 mm, *Candida albicans* 14–32 mm.