Synthesis and Reactivity of 5,8-Dihydroxythioflavanone Derivatives

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The synthesis of substituted chalcones, thioflavanones, and thioflavones hydroxylated in both A and B rings is described. Acetoquinone (**1**) was transformed into 2,5-dihydroxy-6-(*p*-methoxybenzylmercapto)acetophenone (**2**) and subsequently into its 2,5-dimethoxy (**3**) and 2,5-dibenzyloxy (**4**) derivatives. Compounds **3** and **4** were condensed with suitable benzaldehydes to give chalcones **5**−**10**. The thiol group of the chalcones was deprotected by a cleavage of the *p*-methoxybenzyl protecting group using a new, mild method (silver nitrate in boiling ethanol, 2 h), and the products were cyclized to thioflavanones (**15**−**20**). Dehydrogenation of the thioflavanones gave related thioflavones (**25**−**27**). Deprotection of methoxy and benzyloxy groups is also described.

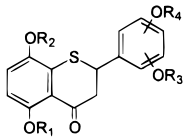
Constant interest in the synthesis of polyhydroxylated flavonoids stems from their diverse biological activity, including antimicrobial, mutagenic, cytotoxic, and antioxidant properties.[1−3] Thioflavonoids[4] constitute a still unexplored source of interesting analogues of biologically active flavonoids. It seems that the compounds do not attract much attention because of the inaccessibility of suitable starting materials, as substituted derivatives of thiophenol are scarce. Compounds which ultimately would result in the synthesis of flavonoids hydroxylated similarly as in natural flavonoids, in both A and B rings, are of special interest.

While looking for a method of synthesis of thioflavanones hydroxylated in both rings, attention was paid to the procedure published by Taylor and Dean,[5] who prepared thioflavanones by acid-catalyzed deprotection−cyclization of suitable 2′-methoxybenzylmercaptochalcones. On the basis of this concept, a synthesis starting from acetoquinone (**1**) was proposed, and even though the direct application of Taylor's method failed, its major modification resulted in a new procedure which led to the preparation of the desired compounds. Reaction of acetoquinone[6] (**1**) with 4-methoxy-α-toluenethiol led to the key intermediate **2** (Scheme 1). The liquid product was identified by NMR only and transformed directly into its methyl (**3**) or benzyl (**4**) derivatives. Protected derivatives **3** and **4** were condensed under phase transfer conditions with suitable benzaldehydes to give chalcones **5**−**10** (Scheme 2, Table 1). Attempted cyclization of the chalcones to corresponding thioflavanones using both formic and trifluoroacetic acid[5] failed. Complicated mixtures of products were obtained, and even though NMR

Table 1. Chalcones Formed in the Reaction of Acetophenone Derivatives 3 and 4 with Substituted Benzaldehydes

compd	OR_1	OR_2	OR_3	OR_4	yield, %
5	2′-OBn	5′-OBn	3-OBn	4-OBn	90
6	2′-OBn	5′-OBn	2-OBn	4-OBn	51
7	2′-OBn	5′-OBn	2-OBn	3-OBn	86
8	2′-OBn	5′-OBn	3-OMe	4-OMe	73
9	2′-OMe	5′-OMe	3-OBn	4-OBn	45
10	2′-OMe	5′-OMe	3-OMe	4-OMe	66

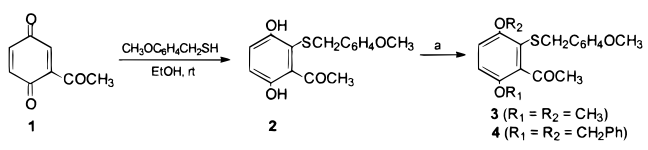
Table 2. Prepared Thioflavanone Derivatives



compd	OR_1	OR_2	OR_3	OR_4	yield, %
15	5-OMe	8-OMe	3′-OMe	4′-OMe	50
16	5-OBn	8-OBn	3′-OBn	4′-OBn	61
17	5-OBn	8-OBn	2′-OBn	4′-OBn	41
18	5-OBn	8-OBn	2′-OBn	3′-OBn	26
19	5-OBn	8-OBn	3′-OMe	4′-OMe	30
20	5-OMe	8-OMe	3′-OBn	4′-OBn	33
21	5-OH	8-OH	3′-OH	4′-OH	30[a], 0[b], 59[c]
22	5-OH	8-OH	2′-OH	4′-OH	28[d]
23	5-OH	8-OH	2′-OH	3′-OH	23[d]
24	5-OH	8-OMe	3′-OH	4′-OH	11[d]

Deprotection method: [a] $AlCl_3$−dimethylaniline from **16**; [b] $AlCl_3$−dimethylaniline from **20**; [c] boron trifluoride−dimethyl sulfide from **20**; [d] $AlCl_3$−dimethylaniline from **17**, **18**, and **20**, respectively.

Scheme 1



a: Me_2SO_4/K_2CO_3/acetone for **3**; $PhCH_2Br/K_2CO_3$/acetone for **4**

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‡ Taiho Pharmaceutical Co.

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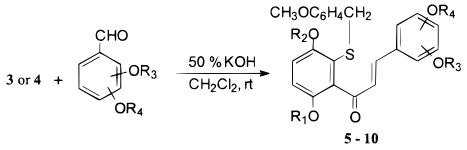
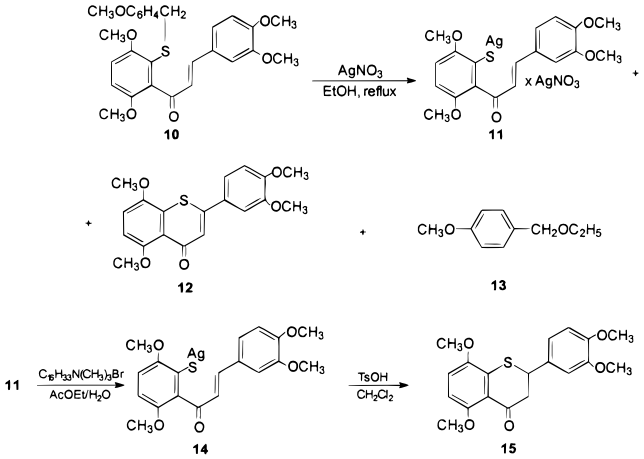
Scheme 2



Scheme 3



spectra proved that the mixtures contained the desired cyclic system, the compounds could not be isolated in pure form. It seems that observed side products were formed by deprotection of the hydroxy group in position 2′ of chalcones **5**−**10** and eventual cyclization through the hydroxyl to flavanones. Under these circumstances, the literature[5] procedure was abandoned, and a method depending on separation of the deprotection and cyclization steps was examined.

Typical procedures[7] for cleavage of *p*-methoxybenzyl thioethers use trifluoroacetic acid or a mixture of trifluoroacetic acid with mercury acetate and were not suitable for our purpose. It is known,[8] however, that some aryl alkyl thioethers can be cleaved by electrophilic metal ions such as Hg^{2+} or Ag^{+}. Mercury salts are likely to metalate phenols[9] even at room temperature, and for this reason, silver salts were chosen as the most promising to cleave *S*-*p*-methoxybenzyl thioethers **5**−**10**. Several attempts failed, but a three-step procedure presented in Scheme 3 gave satisfactory results. Reflux of chalcone **10** with an alcoholic solution of silver nitrate gave yellow precipitate **11**. NMR spectrum of the product demonstrated that the *p*-methoxybenzyl protecting group had been cleaved, and elemental analysis suggested strongly that the product contained two silver ions and a nitrate anion. Structure of the complex **11** was not studied further. Ethanolic filtrate and solutions from washing of **11** with ethanol were separated by chromatography to give thioflavone **12** and ethyl *p*-methoxybenzyl ether (**13**). Formation of the ether **13** proved that the *p*-methoxybenzyl cation formed by cleavage of thioether is quenched by solvent. It was supposed that silver cations could be removed from **11** by reaction with bromine anion.

A suspension of **11** in an ethyl acetate−water mixture was stirred with cetyltrimethylammonium bromide to give compound **14**. NMR spectrum of the compound was identical to that of **11**, but IR fingerprint regions of both compounds were different. Elemental analysis was done only for the analogous benzyl derivative from chalcone **5** and suggested that one silver cation is still present in the molecule. Cyclization of compound **14** to **15** was attempted using trifluoroacetic and formic acids, but the best results were achieved with *p*-toluenesulfonic acid in methylene chloride solution. The complex **11** treated with *p*-toluenesulfonic acid also gave thioflavanone **15**, but the reaction was not as clean as that starting from **14**. Chalcones **5**−**9** were transformed into related thioflavanones using the same procedure (Table 2, compounds **16**−**20**).

The obtained thioflavanones were deprotected using several methods. Catalytic hydrogenation of compound **16** over palladium on charcoal did not take place, most probably due to catalyst poisoning by the sulfur atom. Reaction of **16** with boron trifluoride−methyl sulfide complex gave a mixture of products which could not be separated. Synthesis of tetrahydroxyflavanone **21** was finally achieved using an aluminum chloride−dimethylaniline mixture. For dimethoxy dibenzyl derivative **20**, reaction with aluminum chloride complex gave a multicomponent mixture from which monomethoxy derivative **24** was isolated with a low yield, and deprotection with boron trifluoride−methyl sulfide complex cleanly gave tetrahydroxy derivative **21**. The obtained hydroxy derivatives of thioflavanones are listed in Table 2.

The above mentioned formation of side product **12** suggested that thioflavanones could be relatively easily dehydrogenated to thioflavones. The transformation was achieved, with preparatively satisfactory yields, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as dehydrogenating agent,[10] (Scheme 4). The obtained compounds (**25**−**27**) are listed, along with the products of their deprotection (**28**−**30**), in Table 3.

Thioflavonoids can be oxidized to related 1,1-dioxides,[4] and indeed both thioflavanone **16** and thioflavone **25** reacted smoothly with *m*-chloroperbenzoic acid to give dioxides **31** and **32**. Deprotection of the compounds by

Scheme 4

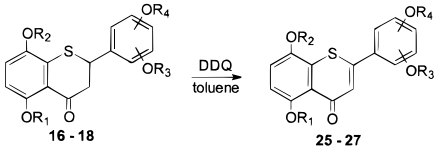
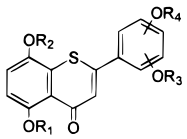


Table 3. Prepared Thioflavone Derivatives



compd	OR_1	OR_2	OR_3	OR_4	yield, %
25	5-OBn	8-OBn	3′-OBn	4′-OBn	55
26	5-OBn	8-OBn	2′-OBn	4′-OBn	62
27	5-OBn	8-OBn	2′-OBn	3′-OBn	64
12	5-OMe	8-OMe	3′-OMe	4′-OMe	18
28	5-OH	8-OH	3′-OH	4′-OH	30
29	5-OH	8-OH	2′-OH	4′-OH	16
30	5-OH	8-OH	2′-OH	3′-OH	19

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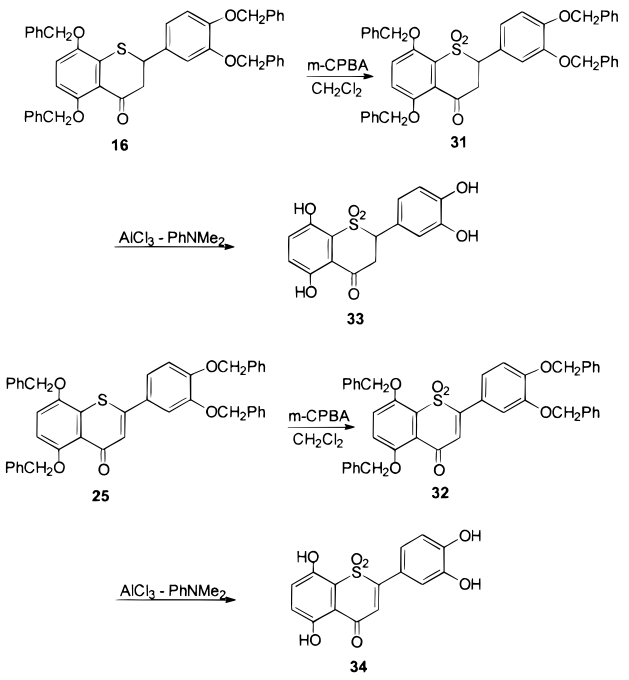
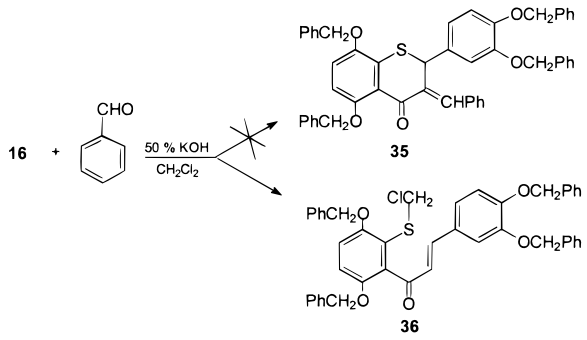
Scheme 5



Scheme 6



catalytic hydrogenation and by aluminum chloride−dimethylaniline gave hydroxy derivatives **33** and **34**, respectively. (Scheme 5). Another interesting transformation occurred during an attempted reaction of thioflavanone **16** with benzaldehyde under strongly alkaline conditions; instead of the expected ring-functionalized compound **35**, methylene chloride substituted chalcone **36** was formed (Scheme 6). Compound **36** seemed to be stable under the reaction conditions, and neither products of hydrolysis of the α-halogenoalkyl sulfide function nor products formed via a carbene intermediate were observed.[11]

The described transformations and the easily modified starting material (quinone) make the synthesis of many new analogues of thioflavonoids possible. The reported methods allow the synthesis of compounds hydroxylated in both A and B rings, which seems to be important for biological activity of flavonoids.

Experimental Section

General. All materials were used as obtained from commercial sources. TLC was performed using silica gel 60 F_{254} plates with visualization by UV. Melting points were determined in an open capillary apparatus and are uncorrected.

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2,5-Dihydroxy-6-(*p*-methoxybenzylmercapto)acetophenone (2). Acetoquinone[6] (**1**) (300 mg, 2 mmol) was added to a solution of *p*-methoxy-α-toluenethiol (0.7 mL, 4.2 mmol) in ethanol (4 mL). The solution was stirred at room temperature for 30 min and evaporated, and the residue was separated on a silica gel column in chloroform to give the product **2** as a yellow oil (550 mg, 90%): NMR (200 MHz, $CDCl_3$) δ 10.9 (bs), 7.12 (d, 1 H, J = 9.1 Hz), 6.97 (d, 1 H, J = 9.1 Hz), 6.87 (d, 2 H, J = 8.8 Hz), 6.75 (d, 2 H, J = 8.8 Hz), 3.78 (s, 3 H), 3.75 (s, 2 H), 2.71 (s, 3 H).

2,5-Dimethoxy-6-(*p*-methoxybenzylmercapto)acetophenone (3). A mixture of 2,5-dihydroxy-6-(*p*-methoxybenzylmercapto)acetophenone (**2**) (550 mg, 1.8 mmol), dimethyl sulfate (0.45 mL, 4.8 mmol), and anhydrous potassium carbonate (830 mg, 6 mmol) in acetone (10 mL) was refluxed with stirring for 30 min. The solvent was evaporated, and the residue was treated with water (20 mL) and extracted with chloroform (90 mL). The extract was washed with water (3 × 20 mL), 1 N HCl (1 × 20 mL), saturated sodium bicarbonate (1 × 20 mL), water (2 × 20 mL), and brine (1 × 20 mL) and dried ($MgSO_4$). The solution was evaporated and purified on a short silica gel column in chloroform to give **3** as an oil (540 mg, 90%): NMR (200 MHz, $CDCl_3$) δ 6.7−7.1 (m, 6 H), 3.96 (s, 3 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 2 H), 2.17 (s, 3 H).

2,5-Dibenzyloxy-6-(*p*-methoxybenzylmercapto)acetophenone (4). A mixture of 2,5-dihydroxy-6-(*p*-methoxybenzylmercapto)acetophenone (**2**) (550 mg, 1.8 mmol), benzyl bromide (0.52 mL, 4.3 mmol), and anhydrous potassium carbonate (650 mg, 4.7 mmol) in acetone (15 mL) was refluxed with stirring for 1.5 h. The solvent was evaporated, and the residue was treated with water (20 mL) and extracted with chloroform (90 mL). The extract was washed with water (3 × 20 mL), 1 N HCl (1 × 20 mL), saturated sodium bicarbonate (1 × 20 mL), water (2 × 20 mL), and brine (1 × 20 mL) and dried ($MgSO_4$). The solution was evaporated, and the residue was washed with methanol and recrystallized from the same solvent to give 576 mg (66%) of white crystals, mp 115−117 °C. Anal. Calcd for $C_{30}H_{28}O_4S$: C, 74.35; H, 5.82; S, 6.62. Found: C, 74.15; H, 5.73; S, 6.55. NMR (200 MHz, $CDCl_3$) δ 7.2−7.5 (m, 10 H), 6.94 (d, 2 H, J = 8.8 Hz), 6.78 (s, 2 H), 6.65 (d, 2 H, J = 8.8 Hz), 5.04 (s, 2 H), 4.98 (s, 2 H), 3.94 (s, 2 H), 3.68 (s, 3 H), 2.14 (s, 3 H).

General Procedure for Condensation of Benzaldehydes with 6-(*p*-Methoxybenzylmercapto)acetophenone Derivatives (3 or 4) under Phase Transfer Conditions. A mixture of suitable 6-(*p*-methoxybenzylmercapto)acetophenone (0.9 mmol), substituted benzaldehyde (1.35 mmol), and tetrabutylammonium chloride (64 mg, 0.2 mmol) in methylene chloride (4 mL) and 50% potassium hydroxide (4 mL) was stirred at room temperature for 50−70 h. The solution was diluted with methylene chloride (80 mL); washed with water (3 × 50 mL), 1 N HCl (1 × 20 mL), water (1 × 20 mL), saturated sodium bicarbonate (1 × 20 mL), water (2 × 20 mL), and brine (1 × 20 mL); dried ($MgSO_4$); and evaporated. The residue was purified either on a silica gel column or by crystallization.

2′,3,4,5′-Tetrabenzyloxy-6′-(*p*-methoxybenzylmercapto)chalcone (5). The residue after evaporation of solvent solidified upon the addition of methanol. It was filtered and recrystallized from chloroform−methanol, yield 90%, mp 159−161 °C. Anal. Calcd for $C_{51}H_{44}O_6S$: C, 78.03; H, 5.65; S, 4.08. Found: C, 77.89; H, 5.56; S, 3.87. NMR (200 MHz, $CDCl_3$) δ 6.78−7.54 (m, 28 H), 6.66 (d, 1 H, J = 15.5 Hz), 6.54 (d, 2 H, J = 8.6 Hz), 5.17 (s, 2 H), 5.13 (s, 2 H), 5.07 (s, 2 H), 4.97 (s, 2 H), 3.94 (s, 2 H), 3.57 (s, 3 H).

2,2′,4,5′-Tetrabenzyloxy-6′-(*p*-methoxybenzylmercapto)chalcone (6). The residue after evaporation of solvent was separated on a silica gel column in chloroform−ethyl acetate 50:1 solution and recrystallized from ethanol, yield 51%, mp 119−120 °C. Anal. Calcd for $C_{51}H_{44}O_6S$: C, 78.03; H, 5.65; S, 4.08. Found: C, 77.69; H, 5.67; S, 3.95. NMR (200 MHz, $CDCl_3$) δ 6.45−7.55 (m, 31 H), 5.08 (s, 2 H), 5.07 (s, 2 H), 4.97 (s, 2 H), 4.89 (s, 2 H), 3.93 (s, 2 H), 3.57 (s, 3H).

2,2′,3,5′-Tetrabenzyloxy-6′-(*p*-methoxybenzylmercapto)chalcone (7). The residue after evaporation of solvent was

separated on a silica gel column in chloroform to give an oil, yield 86%. Anal. Calcd for $C_{51}H_{44}O_6S$: C, 78.04; H, 5.65; S, 4.08. Found: C, 78.15; H, 5.71; S, 3.87. NMR (200 MHz, $CDCl_3$) δ 6.75−7.6 (m, 30 H), 6.57 (d, 1 H, J = 8.7 Hz), 5.12 (s, 2 H), 5.07 (s, 2 H), 4.87 (s, 2 H), 4.81 (s, 2 H), 3.94 (s, 2 H), 3.62 (s, 3 H).

2′,5′-Dibenzyloxy-3,4-dimethoxy-6′-(*p*-methoxybenzylmercapto)chalcone (8). The residue after evaporation of solvent solidified upon the addition of methanol. It was filtered and recrystallized from methanol, yield 73%, mp 117−118 °C. Anal. Calcd for $C_{39}H_{36}O_6S$: C, 74.03; H, 5.74; S, 5.07. Found: C, 74.28; H, 5.70; S, 5.00. NMR (200 MHz, $CDCl_3$) δ 6.55−7.55 (m, 21 H), 5.10 (s, 2 H), 5.01 (s, 2 H), 3.99 (s, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.64 (s, 3 H).

3,4-dibenzyloxy-2′,5′-dimethoxy-6′-(*p*-methoxybenzylmercapto)chalcone (9). The residue after evaporation of solvent was purified on a silica gel column in chloroform and recrystallized from ethanol, yield 45%, mp 92−94 °C. Anal. Calcd for $C_{39}H_{36}O_6S$: C, 74.03; H, 5.74; S, 5.07. Found: C, 73.95; H, 5.75; S, 4.95. NMR (200 MHz, $CDCl_3$) δ 6.55−7.55 (m, 21 H), 5.19 (s, 2 H), 5.16 (s, 2 H), 3.95 (s, 2 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.62 (s, 3 H).

2′,3,4,5′-Tetramethoxy-6′-(*p*-methoxybenzylmercapto)-chalcone (10). The residue after evaporation of solvent was purified on a silica gel column in chloroform. The obtained oil solidified under the influence of methanol. The product was recrystallized from chloroform−methanol, yield 66%, mp 158−160 °C. Anal. Calcd for $C_{27}H_{28}O_6S{\cdot}0.5\ H_2O$: C, 66.24; H, 5.97. Found: C, 66.18; H, 5.75. NMR (200 MHz, $CDCl_3$) δ 6.55−7.05 (m, 10 H), 6.67 (d, 1 H, J = 16.1 Hz), 3.91 (s, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 3.61 (s, 3 H).

Stepwise Synthesis of 3′,4′,5,8-Tetramethoxythioflavanone (15) by Deprotection using Silver Nitrate and Cyclization by *p*-Toluenesulfonic Acid. A suspension of 2′,3,4,5′-tetramethoxy-6′-(*p*-methoxybenzylmercapto)chalcone (**10**) (960 mg, 2 mmol) and silver nitrate (1360 mg, 4 mmol) in 90% ethanol (50 mL) was refluxed for 2 h. The solution was cooled and filtered, and the precipitate was washed with ethanol (4 × 10 mL) and water (4 × 10 mL) to give a yellow solid of silver complex **11** (660 mg, 52%), mp >205 °C. Anal. Calcd for $C_{19}H_{19}O_8SNAg_2$: C, 35.81; H, 3.00; S, 5.03; N, 2.20. Found: C, 36.22; H, 2.96; S, 4.94; N, 2.20. NMR (200 MHz, DMSO-d_6) δ 7.21 (bs, 1 H), 7.10 (d, 1 H, J = 16.0 Hz), 7.00 (bd, 1 H, J = 8.4 Hz), 6.88 (d, 1 H, J = 16.0 Hz), 6.80 (m, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.61 (s, 3 H), 3.52 (s, 3 H); IR (Nujol, cm^{-1}) 1700, 1620, 1595, 1515, 1320, 1290, 1180, 1160, 1130, 1065, 1040, 840, 820.

Collected filtrates were diluted with water and extracted with chloroform (200 mL). The organic layer was washed with water (3 × 100 mL) and brine (3 × 50 mL), dried ($MgSO_4$), and evaporated. The residue was separated on a silica gel column in chloroform to give **ethyl *p*-methoxybenzyl ether** (**13**) (250 mg, 75%): NMR (200 MHz, $CDCl_3$) δ 7.27 (d, 2 H, J = 8.7 Hz), 6.88 (d, 2 H, J = 8.7 Hz), 4.44 (s, 2 H), 3.80 (s, 3 H), 3.50 (q, 2 H, J = 7 Hz), 1.23 (t, 3 H, J = 7 Hz). A second fraction contained **3′,4′,5,8-tetramethoxythioflavone** (**12**) (130 mg, 18%). The compound was recrystallized from ethanol, mp 204−205 °C. Anal. Calcd for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06; S, 8.95. Found: C, 63.56; H, 5.12; S, 8.78. NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.40 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 7.29 (H-2′, under $CHCl_3$), 7.04 (d, 1 H, J = 8.8 Hz), 6.99 (d, 1 H, J = 8.3 Hz), 6.72 (d, 1 H, J = 8.8 Hz), 4.02 (s, 3 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.97 (s, 3 H).

A suspension of silver complex **11** (150 mg, 0.23 mmol) and cetyltrimethylammonium bromide (470 mg) in ethyl acetate (50 mL) and water (20 mL) was stirred at room temperature for 30 min. The organic layer was separated, diluted with ethyl acetate to 100 mL, washed with water (5 × 30 mL) and brine (4 × 30 mL), dried ($MgSO_4$), and evaporated. The obtained yellow solid was washed with methanol to give complex **14** (50 mg, 43%): NMR (200 MHz, DMSO) δ 7.20 (bs, 1 H), 7.09 (d, 1 H, J = 16.0 Hz), 6.96 (bd, 1 H, J = 8.4 Hz), 6.86 (d, 1 H, J = 16.0 Hz), 6.78 (m, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.61 (s, 3 H), 3.50 (s, 3 H); IR (Nujol, cm^{-1}) 1700, 1640, 1580, 1515, 1275, 1180, 1160, 1065, 1055, 830.

Complex **14** (110 mg, 0.22 mmol) was added to a solution of *p*-toluenesulfonic acid (80 mg, 0.46 mmol) in methylene chloride (5 mL); the mixture was stirred at room temperature for 30 min. The formed suspension was diluted with methylene chloride to 50 mL; washed with water (5 × 20 mL), $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL); dried ($MgSO_4$); and evaporated. The residue was separated on a silica gel column in chloroform to give **3′,4′,5,8-tetramethoxythioflavanone** (**15**) (40 mg, 50%). The compound was recrystallized from toluene−methanol, mp 134−135 °C. Anal. Calcd for $C_{19}H_{20}O_5S$: C, 63.31; H, 5.59. Found: C, 63.41; H, 5.50. NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 2.4 Hz), 6.97 (d, 1 H, J = 8.7 Hz), 6.97 (d, 1 H, J = 2.4 Hz), 6.87 (d, 1 H, J = 8.3 Hz), 6.73 (d, 1 H, J = 8.7 Hz), 4.60 (dd, 1 H, J_1 = 13.7 Hz, J_2 = 3.0 Hz), 3.92 (s, 3 H), 3.911 (s, 3 H), 3.908 (s, 3 H), 3.89 (s, 3 H), 3.35 (dd, 1 H, J_1 = 13.7 Hz, J_2 = 15.1 Hz), 3.14 (dd, 1 H, J_1 = 15.1 Hz, J_2 = 3.0 Hz).

General Procedure for Synthesis of Thioflavanone Derivatives (16−20). The method essentially follows the three-step procedure described above for methoxy derivative **15**: (step 1) 2 h of reflux with silver nitrate in ethanol; (step 2) 30 min of stirring at room temperature with cetyltrimethylammonium bromide in an ethyl acetate−water solution; and (step 3) 30 min of stirring at room temperature with *p*-toluenesulfonic acid in methylene chloride. The yields are given in Table 2 and were calculated for the whole process, starting from chalcones.

3′,4′,5,8-Tetrabenzyloxythioflavanone (16). Purification method, recrystallization from toluene, mp 168−169 °C. Anal. Calcd for $C_{43}H_{36}O_5S$: C, 77.68; H, 5.46; S, 4.82. Found: C, 78.16; H, 5.70; S, 4.31. NMR (500 MHz, $CDCl_3$) δ 7.15−7.6 (m, 20 H), 7.06 (d, 1 H, J = 2 Hz), 6.97 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 2 Hz), 6.96 (d, 1 H, J = 8.8 Hz), 6.94 (d, 1 H, J = 8.3 Hz), 6.72 (d, 1 H, J = 8.8 Hz), 5.19 (s, 4 H), 5.16 (d, 2 H, J = 11.7 Hz,), 5.11 (s, 2 H), 4.55 (dd, 1 H, J_1 = 13.7 Hz, J_2 = 2.7 Hz), 3.27 (dd, 1 H, J_1 = 15.1 Hz, J_2 = 13.7 Hz), 3.08 (dd, 1 H, J_1 = 15.1 Hz, J_2 = 2.7 Hz).

2′,4′,5,8-Tetrabenzyloxythioflavanone (17). Purification method, recrystallization toluene−methanol, mp 186−188 °C. Anal. Calcd for $C_{43}H_{36}O_5S$: C, 77.68; H, 5.46. Found: C, 77.10; H, 5.10. NMR (200 MHz, $CDCl_3$) δ 7.22−7.60 (m, 21 H), 6.92 (d, 1 H, J = 9.0 Hz), 6.67 (d, 1 H, J = 9.0 Hz), 6.57 (m, 2 H), 5.14 (dd, partly under next peak, 1 H, J_1 = 3.4 Hz), 5.13 (s, 2 H), 5.09 (s, 2 H), 5.07 (s, 2 H), 5.02 (s, 2 H), 3.32 (dd, 1 H, J_1 = 12.4 Hz, J_2 = 15.1 Hz), 3.07 (dd, 1 H, J_1 = 15.1 Hz, J_2 = 3.4 Hz).

2′,3′,5,8-Tetrabenzyloxythioflavanone (18). Purification method, silica gel column in chloroform, followed by recrystallization from benzene−methanol, mp 106−107 °C. Anal. Calcd for $C_{43}H_{36}O_5S$: C, 77.68; H, 5.46; S, 4.82. Found: C, 77.78; H, 5.43; S, 4.59. NMR (200 MHz, $CDCl_3$) δ 6.96−7.6 (m, 23 H), 6.92 (d, 1 H, J = 9 Hz), 6.69 (d, 1 H, J = 9 Hz), 5.15 (s, 2 H), 5.13 (s, 2 H), 5.10 (m, 3 H), 5.06 (s, 2 H), 3.25 (dd, 1 H, J_1 = 15.4 Hz, J_2 = 13.3 Hz), 2.87 (dd, 1 H, J_1 = 15.4 Hz, J_2 = 3.1 Hz).

5,8-Dibenzyloxy-3′,4′-dimethoxythioflavanone (19). Purification method, silica gel column in chloroform, followed by recrystallization toluene−methanol, mp 149−151 °C. Anal. Calcd for $C_{31}H_{28}O_5S$: C, 72.63; H, 5.51; S, 6.26. Found: C, 72.30; H, 5.47; S, 6.13. NMR (200 MHz, $CDCl_3$) δ 6.9−7.6 (m, 13 H), 6.83 (d, 1 H, J = 8.1 Hz), 6.67 (d, 1 H, J = 9 Hz), 5.05 (two d, 2 H), 5.03 (s, 2 H), 4.56 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 3.0 Hz), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.31 (dd, 1 H, J_1 = 15.0 Hz, J_2 = 13.4 Hz), 3.08 (dd, 1 H, J_1 = 15.0 Hz, J_2 = 3.0 Hz).

3′,4′-Dibenzyloxy-5,8-dimethoxythioflavanone (20). Purification method, silica gel column in chloroform, followed by recrystallization toluene−methanol, mp 118−120 °C. Anal. Calcd for $C_{31}H_{28}O_5S$: C, 72.63; H, 5.51; S, 6.26. Found: C, 72.86; H, 5.51; S, 6.18. NMR (200 MHz, $CDCl_3$) δ 6.8−7.5 (m, 14 H), 6.69 (d, 1 H, J = 9.1 Hz), 5.15 (s, 4 H), 4.51 (dd, 1 H, J_1 = 13.2 Hz, J_2 = 3.3 Hz), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.23 (dd, 1 H, J_1 = 15.0 Hz, J_2 = 13.2 Hz), 3.04 (dd, 1 H, J_1 = 15.0 Hz, J_2 = 3.3 Hz).

Deprotection of Thioflavanones with Aluminum Chloride−Dimethylaniline Complex. A suitable derivative of

thioflavanone (**16**−**18,20**) (1.5 mmol) and *N*,*N*-dimethylaniline (1.1 mL, 9 mmol) were dissolved in dry methylene chloride (40 mL) and cooled to 0 °C, and aluminum chloride (1.6 g, 12 mmol) was added. The mixture was stirred at room temperature for 1−4 h under argon. The mixture was concentrated by half, poured into ice-cooled 5% HCl (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water (2 × 30 mL), dried, and evaporated. The residue was purified on a silica gel column or recrystallized.

3′,4′,5,8-Tetrahydroxythioflavanone (21). Column eluted with chloroform−methanol solution 20:1, followed by recrystallization from acetone−chloroform, yield 30%, mp 214−222 °C. Anal. Calcd for $C_{15}H_{12}O_5S$: C, 59.20; H, 3.98; S, 10.54. Found: C, 58.75; H, 3.84; S, 10.19. NMR (200 MHz, acetone) δ 12.3 (s, 1 H), 8.1 (bs, 3 H), 7.08 (d, 1 H, J = 8.8 Hz), 7.01 (d, 1 H, J = 1.8 Hz), 6.86 (m, 2 H), 6.55 (d, 1 H, J = 8.8 Hz), 4.64 (dd, 1 H, J_1 = 13.2 Hz, J_2 = 2.8 Hz), 3.40 (dd, 1 H, J_1 = 13.2 Hz, J_2 = 16.5 Hz), 3.06 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 2.8 Hz).

2′,4′,5,8-Tetrahydroxythioflavanone (22). Column eluted with chloroform: methanol solution 100:1, followed by precipitation from acetone with chloroform, yield 28%, mp 267 °C, decomp. Anal. Calcd for $C_{15}H_{12}O_5S$: C, 59.20; H, 3.98. Found: C, 59.06; H, 4.27. NMR (200 MHz, acetone) δ 12.3 (s, 1 H), 8.73 (s, 1 H), 8.44 (s, 1 H), 8.39 (s, 1 H), 7.28 (d, 1 H, J = 8.3 Hz), 7.07 (d, 1 H, J = 8.8 Hz), 6.54 (d, 1 H, J = 8.8 Hz), 6.47 (d, 1 H, J = 2.4 Hz), 6.40 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 2.4 H), 5.00 (dd, 1 H, J_1 = 13.1 Hz, J_2 = 3.0 Hz), 3.48 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 13.1 Hz), 3.01 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 3.0 Hz).

2′,3′,5,8-Tetrahydroxythioflavanone (23). Column eluted with chloroform: methanol 20:1, followed by recrystallization from methanol − benzene − cyclohexane mixture, yield 23%, mp 232−233 °C. Anal. Calcd for $C_{15}H_{12}O_5S$: C, 59.20; H, 3.98; Found: C, 59.28; H, 3.92. NMR (200 MHz, acetone) δ 12.3 (s, 1 H), 8.69 (s, 1 H), 8.48 (s, 1 H), 7.77 (s, 1 H), 7.08 (d, 1 H, J = 8.8 Hz), 6.99 (dd, 1 H, J_1 = 9.4 Hz, J_2 = 1.6 Hz), 6.85 (dd, 1 H, J_1 = 7.9 Hz, J_2 = 1.6 Hz), 6.73 (t, 1 H, J = 7.7 Hz), 6.56 (d, 1 H, J = 8.8 Hz), 5.13 (dd, 1 H, J_1 = 12.5 Hz, J_2 = 3.0 Hz), 3.49 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 12.5 Hz), 3.09 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 3.0 Hz).

3′,4′,5-trihydroxy-8-methoxythioflavanone (24). Column eluted with chloroform: methanol 100:1, product washed with chloroform, yield 11%, mp 178−180 °C. Anal. Calcd for $C_{16}H_{14}O_5S$: C, 60.36; H, 4.43. Found: 60.17; H, 4.42. NMR (200 MHz, acetone) δ 12.3 (s, 1 H), 8.10 (s, 1 H), 8.07 (s, 1 H), 7.23 (d, 1 H, J = 9.0 Hz), 7.00 (s, 1 H), 6.85 (s, 2 H), 6.65 (d, 1 H, J = 9.0 Hz), 4.65 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 2.9 Hz), 3.83 (s, 3 H), 3.41 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 13.4 Hz), 3.05 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 2.9 Hz).

Deprotection of 3′,4′-Dibenzyloxy-5,8-dimethoxythioflavanone (20) with Boron Trifluoride−Methyl Sulfide Complex. A boron trifluoride−methyl sulfide complex solution in methylene chloride (8 mmol) was added to a stirred solution of **20** (0.25 mmol) in methylene chloride (2 mL), and the mixture was stirred at room temperature for 2 h. The solution was quenched with water (5 mL), diluted with ethyl acetate (50 mL), washed with water (4 × 20 mL) and brine (1 × 20 mL), and dried over $MgSO_4$. The crude product was purified on a silica gel column in chloroform − methanol 10:1 solution to give **3′,4′,5,8-tetrahydroxythioflavanone** (**21**), yield 59%. Analytical data of the product were identical with those for product obtained from tetrabenzyl derivative **16** by deprotection with aluminum chloride (see above).

Synthesis of Protected Derivatives of Thioflavones (25−27) by Dehydrogenation of Thioflavanones (16−18). A suitable thioflavanone (0.4 mmol) and DDQ (109 mg, 0.48 mmol) in dry toluene (5 mL) were refluxed with stirring for 2 h. The reaction mixture was diluted with chloroform (20 mL) and filtered. The filtrate was evaporated to dryness, and the residue was separated on a silica gel column.

3′,4′,5,8-Tetrabenzyloxythioflavone (25). Column eluted with chloroform, product recrystallized from toluene−methanol, yield 55%, mp 98−99 °C. Anal. Calcd for $C_{43}H_{34}O_5S$: C, 77.92; H, 5.17; S, 4.84. Found: C, 77.63; H, 5.11; S, 4.78. NMR (500 MHz, $CDCl_3$) δ 7.3−7.7 (m, 22 H), 7.14 (bs, 1 H), 7.09 (d, 1 H, J = 8.9 Hz), 7.03 (d, 1 H, J = 8.3 Hz), 6.96 (d, 1 H, J = 8.9 Hz), 5.26 (s, 2 H), 5.25 (s, 4 H), 5.23 (s, 2 H).

2′,4′,5,8-Tetrabenzyloxythioflavone (26). Purified by silica gel column in chloroform, yield 62%, mp 158−160 °C. Anal. Calcd for $C_{43}H_{34}O_5S$: C, 77.92; H, 5.17; Found: C, 77.28; H, 4.71. NMR (200 MHz, $CDCl_3$) δ 7.2−7.8 (m, 22 H), 7.15 (d, 1 H, J = 8.9 Hz), 6.93 (s, 1 H), 6.91 (d, 1 H, J = 2.4 Hz), 6.78 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 2.4 Hz), 5.31 (s, 2 H), 5.26 (s, 2 H), 5.20 (s, 4 H).

2′,3′,5,8-Tetrabenzyloxythioflavone (27). Purified by silica gel column in chloroform, followed by recrystallization from benzene−methanol, yield 64%, mp 130−131 °C. Anal. Calcd for $C_{43}H_{34}O_5S$: C, 77.92; H, 5.17; Found: C, 77.81; H, 4.98. NMR (200 MHz, $CDCl_3$) δ 6.96−7.7 (m, 25 H), 6.92 (d, 1 H, J = 8.9 Hz), 5.21 (s, 2 H), 5.17 (s, 2 H), 5.16 (s, 2 H), 5.03 (s, 2 H).

Deprotection of Thioflavones (25−27) with Aluminum Chloride−Dimethylaniline Complex. A suitable derivative of thioflavone (1 mmol) and *N*,*N*-dimethylaniline (1.5 mL, 12 mmol) were dissolved in dry methylene chloride (60 mL) and cooled to 0 °C, and aluminum chloride (2.4 g, 18 mol) was added. The mixture was stirred at room temperature for 1−4 h under argon. The mixture was concentrated by half, poured into ice- cooled 5% HCl (50 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with water (2 × 30 mL), dried, and evaporated. The residue was purified on a silica gel column or recrystallized.

3′,4′,5,8-Tetrahydroxythioflavone (28). The crude product was purified by multiple recrystallization from acetone−chloroform−hexane, yield 30%, mp 293 °C, decomp. Anal. Calcd for $C_{15}H_{10}O_5S$: C, 59.59; H, 3.33. Found: C, 59.47; H, 3.50. NMR (200 MHz, CD_3COCD_3) δ 13.53 (s, 1 H), 9.3 (bs, 1 H), 8.7 (bs, 1 H), 8.5 (bs, 1 H), 7.34 (d, 1 H, J = 2.3 Hz), 7.27 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 2.3 Hz), 7.22 (d, 1 H, J = 8.8 Hz), 7.02 (d, 1 H, J = 8.3 Hz), 7.02 (s, 1 H), 6.79 (d, 1 H, J = 8.8 Hz).

2′,4′,5,8-Tetrahydroxythioflavone (29). The crude product was purified by multiple recrystallization from methanol−chloroform, yield 16%, mp >300 °C decomp. Anal. Calcd for $C_{15}H_{10}O_5S$: C, 59.59; H, 3.33. Found: C, 59.32; H, 3.25. NMR (200 MHz, CD_3COCD_3) δ 13.6 (s, 1 H), 9.2 (bs, 2 H), 9.0 (bs, 1 H), 7.43 (d, 1 H, J = 8.4 Hz), 7.18 (d, 1 H, J = 8.8 Hz), 7.17 (s, 1 H), 6.77 (d, 1 H, J = 8.8 Hz), 6.60 (d, 1 H, J = 2.3 Hz), 6.55 (dd, 1 H, J_1 = 8.4 Hz, J_2 = 2.3 Hz).

2′,3′,5,8-Tetrahydroxythioflavone (30). The crude product was purified by silica gel column in chloroform: methanol 50:1, followed by recrystallization from methanol−benzene, yield 19%, mp >260 °C. Anal. Calcd for $C_{15}H_{10}O_5S$: C, 59.59; H, 3.33. Found: C, 59.51; H, 3.05. NMR (500 MHz, CD_3COCD_3) δ 13.52 (s, 1 H), 9.24 (bs, 1 H), 8.96 (bs, 1 H), 8.16 (bs, 1 H), 7.25 (d, 1 H, J = 8.8 Hz), 7.18 (s, 1 H), 7.07 (d, 2 H, J = 8.3 Hz), 6.90 (t, 1 H, J = 7.8 Hz), 6.83 (d, 1 H, J = 8.8 Hz).

Synthesis of 3′,4′,5,8-Tetrabenzyloxythioflavanone-1,1-dioxide (31). A solution of 3′,4′,5,8-tetrabenzyloxythioflavanone (**16**) (665 mg, 1 mmol) and *m*-chloroperbenzoic acid (520 mg, 2.4 mmol) in methylene chloride (15 mL) was stirred at room temperature for 1 h. The mixture was diluted with methylene chloride to 100 mL; washed with sodium bicarbonate (3 × 40 mL), water (3 × 40 mL), and brine (1 × 40 mL); dried ($MgSO_4$), and evaporated. The residue was purified on a silica gel column in chloroform and washed with ethanol to give **31**, yield 524 mg (75%), mp 78−80 °C. Anal. Calcd for $C_{43}H_{36}O_7S$: C, 74.12; H, 5.21; S, 4.60. Found: C, 73.93; H, 5.19; S, 4.53. NMR (200 MHz, $CDCl_3$) δ 6.9−7.6 (m, 25 H), 5.2 (m, 8 H), 4.73 (dd, 1 H, J_1 = 13.9 Hz, J_2 = 2.7 Hz), 3.79 (dd, 1 H, J_1 = 15.5 Hz, J_2 = 13.9 Hz), 3.08 (dd, 1 H, J_1 = 15.5 Hz, J_2 = 2.7 Hz).

Synthesis of 3′,4′,5,8-tetrabenzyloxythioflavone-1,1-dioxide (32). A solution of 3′,4′,5,8-tetrabenzyloxythioflavone (**25**) (320 mg, 0.5 mmol) and *m*-chloroperbenzoic acid (260 mg, 1.2 mmol) in methylene chloride (20 mL) was stirred at room temperature for 24 h. Additional *m*-chloroperbenzoic acid (100 mg) was added, and the stirring was continued for 10 h. The mixture was diluted with methylene chloride to 100 mL; washed with sodium bicarbonate (3 × 40 mL), water (3 × 40

mL), and brine (1 × 40 mL); dried ($MgSO_4$); and evaporated. The residue was recrystallized twice from benzene−methanol to give 320 mg (99%) of product, mp 99−100 °C. Anal. Calcd for $C_{43}H_{34}O_7S$: C, 74.33; H, 4.93; S, 4.61. Found: C, 74.56; H, 5.12; S, 4.42. NMR (200 MHz, $CDCl_3$) δ 7.14−7.58 (m, 24 H), 7.00 (d, 1 H, J = 8.5 Hz), 6.59 (s, 1 H), 5.31 (s, 2 H), 5.23 (s, 2 H), 5.21 (s, 2 H), 5.18 (s, 2 H).

Synthesis of 3′,4′,5,8-Tetrahydroxythioflavanone-1,1-dioxide (33). A solution of 3′,4′,5,8-tetrabenzyloxythioflavanone-1,1-dioxide (**31**) (116 mg, 0.17 mmol) in ethyl acetate (10 mL) was hydrogenated over 5% palladium on charcoal at room temperature for 1 h. The catalyst was filtered off, the solution was evaporated, and the residue was purified on a silica gel column in chloroform−methanol 5:1 solution. The product was washed with chloroform, yield 33 mg (59%), mp 225−227 °C. Anal. Calcd for $C_{15}H_{12}O_7S$: C, 53.57; H, 3.60; S, 9.53. Found: C, 53.41; H, 3.53; S, 9.60. NMR (200 MHz, CD_3COCD_3) δ 12.41 (s, 1 H), 8.8 (bs, 1 H), 8.3 (bs, 2 H), 7.38 (d, 1 H, J = 9.3 Hz), 7.26 (d, 1 H, J = 9.3 Hz), 7.05 (s, 1 H), 6.92 (s, 2 H), 5.30 (dd, 1 H, J_1 = 12.9 Hz, J_2 = 3.3 Hz), 3.97 (dd, 1 H, J_1 = 18.0 Hz, J_2 = 12.9 Hz), 3.34 (dd, 1 H, J_1 = 18.0 Hz, J_2 = 3.3 Hz).

Synthesis of 3′,4′,5,8-Tetrahydroxythioflavone-1,1-dioxide (34). To a solution of 3′,4′,5,8-tetrabenzyloxythioflavone-1,1-dioxide (**32**) (200 mg, 0.29 mmol) and *N*,*N*-dimethylaniline (0.4 mL, 3 mmol) in methylene chloride (10 mL) was added aluminum chloride (220 mg, 1.65 mmol) at 0 °C, under argon. The solution was stirred at room temperature for 1.5 h, cooled, and quenched with 2 N HCl. Ethyl acetate (60 mL) was added, and the solution was washed with water (3 × 30 mL) and brine (2 × 30 mL), and dried ($MgSO_4$). Evaporation gave a product which was purified on a silica gel column in chloroform: methanol 50:1 and recrystallized from benzene−methanol− cyclohexane, yield 55 mg (55%), mp 270 °C. Anal. Calcd for $C_{15}H_{10}O_7S$: C, 53.89; H, 3.01. Found: C, 53.37; H, 2.82. NMR (200 MHz, acetone) δ 12.6 (s, 1 H), 9.0 (bs, 3 H), 7.58 (d, 1 H, J = 2.3 Hz), 7.47 (d, 1 H, J = 9.2 Hz), 7.44 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 2.3 Hz), 7.22 (d, 1 H, J = 9.2 Hz), 7.00 (d, 1 H, J = 8.5 Hz), 6.80 (s, 1 H).

Attempted Reaction of 3′,4′,5,8-Tetrabenzyloxythioflavanone (16) with Benzaldehyde. A suspension of 3′,4′,5,8-tetrabenzyloxythioflavanone (**16**) (332 mg, 0.5 mmol), benzaldehyde (0.076 mL, 0.75 mmol), and tetrabutylammonium bromide (50 mg) in methylene chloride (4 mL) and 50% potassium hydroxide (4 mL) was stirred for 1.5 h. Methylene chloride (100 mL) was added, and the organic layer was separated; washed with water (2 × 20 mL), 1 N HCl (2 × 20 mL), water (4 × 20 mL), and brine (1 × 50 mL); and dried ($MgSO_4$). Evaporation of solvent gave a residue which was washed with methanol to give the crude product (310 mg, 77%). The crude product was purified on a silica gel column in methylene chloride−hexane 5:1 solution and recrystallized from acetone−methanol to give **2′,3,4,5′-tetrabenzyloxy-6′-chloromethylmercaptochalcone (36)**, yield 180 mg (45%), mp 144−146 °C. Anal. Calcd for $C_{44}H_{37}O_5SCl$: C, 74.09; H, 5.23; S, 4.50. Found: C, 73.96; H, 4.98, S, 4.36. NMR (500 MHz, $CDCl_3$) δ 7.24−7.5 (m, 20 H), 7.22 (d, 1 H, J = 16.1 Hz), 7.16 (d, 1 H, J = 1.7 Hz), 7.05 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 1.7 Hz), 6.96 (s, 2 H), 6.92 (d, 1 H, J = 8.3 Hz), 6.86 (d, 1 H, J = 16.1 Hz), 5.22 (s, 2 H), 5.17 (s, 2 H), 5.16 (s, 2 H), 5.05 (s, 2 H), 4.99 (s, 2 H).

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