Spirocyclic β-Oxo Sulphoxides and Sulphones as Potential Aldose Reductase Inhibitors

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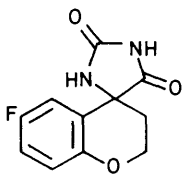
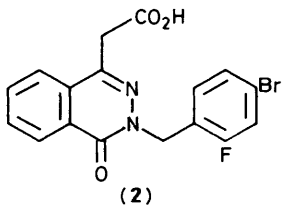
Two isomeric five-membered spirocyclic β-oxo sulphones (**4c**) and (**5**), based on the 6-fluorochroman nucleus, have been prepared. The diastereoisomeric sulphoxides (**4d**) and (**4e**) corresponding to (**4c**) were also prepared. In addition, a related six-membered β-oxo sulphoxide (**6b**) of a spirocyclic 1,3-dithiane has been synthesized. In this case the corresponding sulphone was unstable under the reaction conditions. These compounds were prepared as potential aldose reductase inhibitors but were found to be devoid of this activity.

It has been hypothesised that the chronic complications of diabetes mellitus may be treated or prevented by inhibiting the enzyme aldose reductase.[1] The majority of aldose reductase inhibitors fall into the general classes of spirohydantoins *e.g.*, sorbinil (**1**)[2] and acetic acids *e.g.* 'Statil'† (**2**).[3] We have been seeking alternative pharmacophores to the spirohydantoin moiety and report here a series of β-oxo sulphoxides and sulphones based on the 6-fluorochroman nucleus.



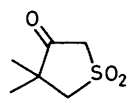
(**1**)



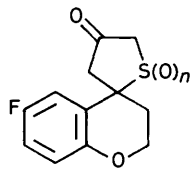
(**2**)

Sorbinil has a pK_a of 7.85[4] (measured as 8.2 in water in this investigation) and the acetic acids generally have pK_a's in the range 2.5—3.5 depending on substituents. We were seeking a functionality that would be sterically akin to the spirohydantoins, yet be closer to the acetic acids in acidity. In general, β-oxo sulphones are comparable in acidity to the hydantoins but apparently, if this group is contained within a five-membered ring, its acidity is much increased. For example, the β-oxo sulphone (**3**) has a pK_a of 5.8.[5] Thus we chose to synthesize the spirocyclic β-oxo sulphones (**4c**) and (**5**) as well as the related six-membered analogue (**6**; $n = 2$). In the event the successful synthesis of (**4c**) and its sulphoxides (Scheme 1), and (**5**) (Scheme 2) was achieved but only (**6b**) could be prepared (Scheme 3) due to the instability of the bis sulphoxide and sulphones.

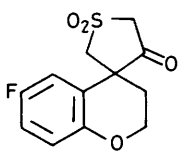
For the synthesis of (**4c**), the acrylic ester (**8**) was prepared from 6-fluorochroman-4-one (**7**)[2a] by a Peterson-type reaction using ethyl lithiotrimethylsilylacetate,[6] as this gave higher yields than the Wadsworth-Emmons-Horner method. Ester (**8**) was obtained as a 4:1 mixture of *Z*:*E* isomers. It would seem that the piperidine-catalysed addition of methyl thioacetate to give the diester (**9**) not only occurred selectively with the *Z* isomer but also caused some isomerisation of *Z* to *E* isomer, as more *E* isomer was recovered from the reaction than went into it. When the diester (**9**) was subjected to Dieckmann cyclisation,



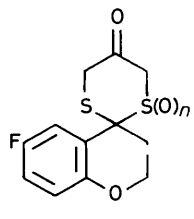
(**3**)



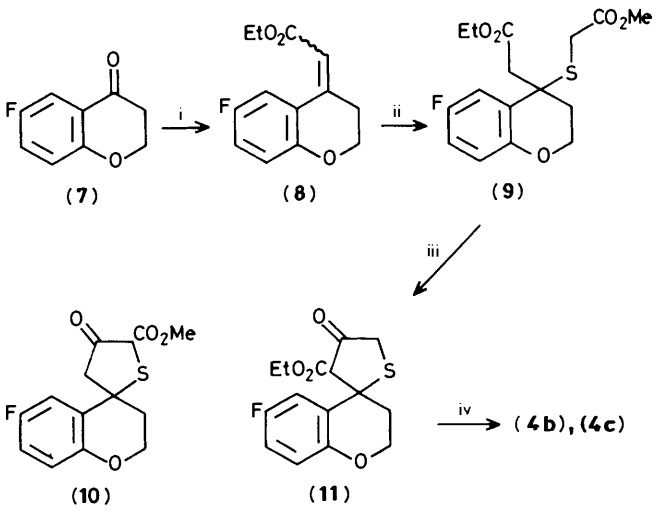
(**4**) **a**; $n = 0$
b; $n = 1$
c; $n = 2$



(**5**)



(**6**) **a**; $n = 0$
b; $n = 1$

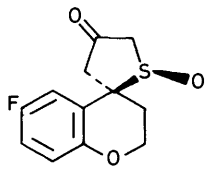


(**7**) (**8**) (**9**) (**10**) (**11**)

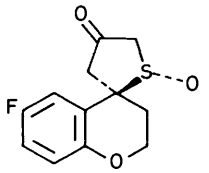
Scheme 1. *Reagents and conditions:* i, $TMSCH_2CO_2Et$, LDA–THF; ii, $HSCH_2CO_2Me$, piperidine; iii, LiHMDS–THF or $KOBu^t$–THF; iv, H^+–EtOH then Oxone–THF

† Ponalrestat: 'Statil' is a trademark, the property of Imperial Chemical Industries PLC.

a mixture of oxo esters (**10**) and (**11**), readily distinguishable by the different ester groups, was obtained using lithium bis(trimethylsilyl)amide in tetrahydrofuran (THF). Use of potassium t-butoxide (KOBu^t) in THF gave (**10**) exclusively but the yield was low. Hydrolysis and decarboxylation of diastereoisomers (**10**) and/or (**11**) gave the oxo sulphide (**4a**), which was oxidised using potassium peroxymonosulphate (Oxone).*[7] Aqueous 1,2-dimethoxyethane (DME) was found to be a particularly good solvent for this reaction and either the two separable diastereoisomeric β-oxo sulphoxides (**4d**) and (**4e**) or the β-oxo sulphone (**4c**) were obtained, depending on the quantity of Oxone used. The stereochemistry of the sulphoxides was readily deduced from the n.m.r. spectra, where the proton attached to C-5 is shielded by the sulphoxide group in (**4d**) and appears at higher field than in (**4e**) (6.49 *vs.* 7.30).

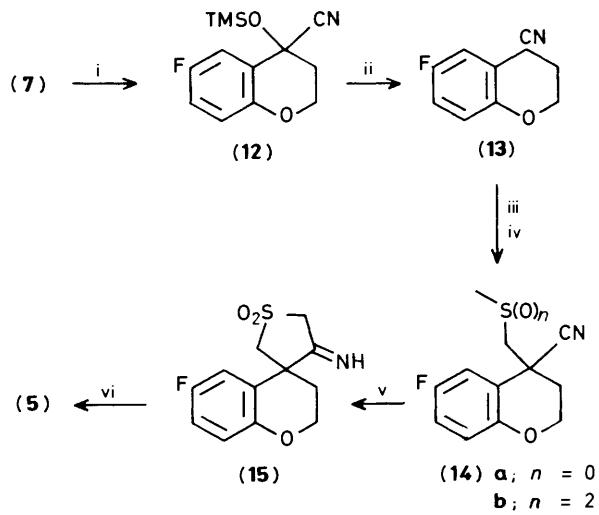


(**4d**)



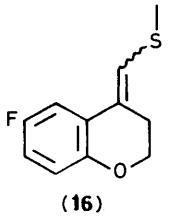
(**4e**)

Our synthesis of the isomeric ring system (**5**) proceeded *via* the novel nitrile (**13**). After investigating a number of different reaction conditions, it was eventually found that the readily available silylated cyanohydrin (**12**)[8] could be converted into (**13**) *via* the unsaturated nitrile, using toluene-*p*-sulphonic acid monohydrate (PTSA) in hot toluene followed by reduction using a sodium borohydride–reduced palladium chloride

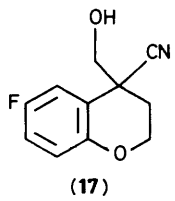


Scheme 2. *Reagents and conditions:* i, TMSCN–ZnI_2; ii, PTSA–toluene, 100 °C then $PdCl_2$–$NaBH_4$, H_2–MeOH; iii, $ClCH_2SMe$, KOBu^t–THF, −20 °C; iv, Oxone–THF; v, NaOEt–EtOH; vi, H_2SO_4–MeOH

catalyst.[9] The alkylation of (**13**) with chloromethyl methyl sulphide was not straightforward. Butyl-lithium at −70 °C gave the vinyl sulphide (**16**) whilst phase-transfer conditions afforded the hydroxymethyl nitrile (**17**). A moderate yield of (**14a**) was obtained using KOBu^t in THF at −20 °C. This sulphide was smoothly oxidised to the sulphone (**14b**), which underwent



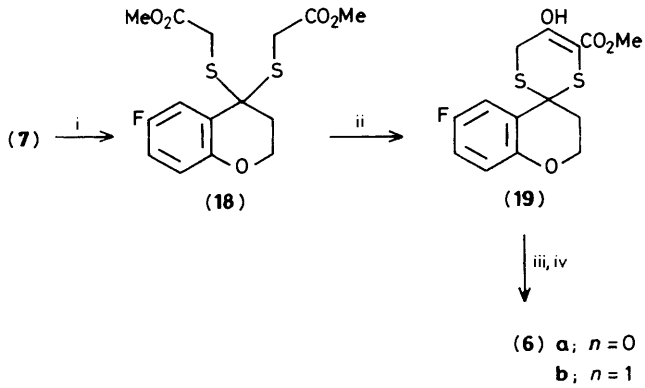
(**16**)



(**17**)

cyclisation with sodium ethoxide in ethanol (cf. ref. 5) to the spirocyclic β-imino sulphone (**15**). This compound and/or its hydrolysis product (**5**) is readily decomposed by strong acid (t.l.c. evidence) but controlled acidic hydrolysis did furnish the required β-oxo sulphone (**5**). The pK_a of this compound was 4.1 and that of its isomer (**4c**) was 4.4, (both measured in water) again demonstrating the effect of constraining this functionality in a five-membered ring, the value being lowered further in this case by the presence of the spiro ring junction. The sulphoxides (**4d**) and (**4e**) had values of 6.6 and 7.25 respectively.

The synthesis of the six-membered analogue (**6**) again started with 6-fluorochroman-4-one (**7**). Attempts to synthesize (**6a**) directly from (**7**) using 1,3-dimercaptoacetone[10] under a variety of conditions were not successful, although the reaction is successful with aldehydes (ref. 11 and unpublished observations). The bis sulphide (**18**) was obtained in poor yield using



Scheme 3. *Reagents and conditions:* i, $TMSSCH_2CO_2Me$, ZnI_2–CH_2Cl_2; ii, NaH–THF; iii, H_2SO_4–1,4-dioxane, reflux, 3 h; iv, Oxone–DME

PTSA in toluene under Dean and Stark conditions but the method of Evans[12] using the *S*-trimethylsilyl derivative of methyl thioacetate[13] gave (**18**) in excellent yield. Dieckmann cyclisation by the method of Lüttringhaus and Prinzbach[14] then set up the required ring system. Hydrolysis and decarboxylation gave (**6a**) which was smoothly oxidised to sulphoxide (**6b**) using Oxone. All attempts to prepare bis sulphoxide or sulphone analogues using Oxone, peracids, or methods used for the synthesis of the parent *meta*-dithianone[15] were unsuccessful, as the products readily decomposed to the starting chromanone (**7**) under the reaction conditions. We have been able to prepare bis sulphoxides and sulphones from *meta*-dithianones derived from aromatic aldehydes rather than ketones (unpublished observations).

Although the majority of the syntheses proved successful, none of the target compounds exhibited aldose reductase inhibitory properties in an *in vitro* assay using the isolated enzyme.[3a]

Experimental

THF was routinely dried by passage through neutral alumina. Oxone refers to potassium peroxomonosulphate complex as

* 'Oxone' is a trademark, the property of E I Dupont Co.

supplied by the Aldrich Chemical Co. Ltd. Organic solutions were routinely dried over Na_2SO_4 and evaporation refers to solvent removal on a rotary evaporator under reduced pressure. Flash chromatography refers to the method of Still *et al.*[16] M.p.s were determined on a Büchi-Tottoli apparatus and are uncorrected. N.m.r. spectra were recorded on Varian EM390, JEOL FX90Q, Bruker AM200, or Bruker AC250 instruments. TMS was used as internal standard. Electron impact (e.i.) mass spectra were obtained on Vacuum Generators VG 1212 or VG 70/250SE instruments.

(Z)- *and* (E)-*Ethyl* 6-*Fluoro*-3,4-*dihydro*-2H-1-*benzopyran*-4-*ylideneacetate* (**8**).—Lithium di-isopropylamide was prepared from di-isopropylamine (8.5 ml, 60 mmol) and butyl-lithium (1.6M in hexane, 38 ml, 60 mmol) in THF (30 ml) under an atmosphere of argon and the mixture stirred at −70 °C for 15 min. A solution of ethyl trimethylsilylacetate (11.0 ml, 60 mmol) in THF (10 ml) was added to the above solution dropwise during 15 min whilst maintaining the temperature at −70 °C; this was followed by a similar addition of a solution of 6-fluorochroman-4-one (**7**) (10.0 g, 60 mmol) in THF (100 ml). The solution was allowed to come to room temperature slowly and maintained thus overnight. Finely ground sodium hydrogensulphate monohydrate (12.4 g, 90 mmol) was added and, after stirring for 30 min, the solution was filtered and diluted with water (100 ml). The organic phase was separated and the aqueous phase extracted with ether (100 ml). The combined organic phases were washed successively with water, 1M HCl, and brine, dried, and evaporated to an oil. Flash chromatography [ethyl acetate–hexane (1:9, v/v)] followed by Kugelrohr distillation (95 °C, 0.01 mbar) to remove unchanged ethyl trimethylsilylacetate, gave acrylic esters (**8**) as a mixture of *E* and *Z* isomers (1:4), (7.0 g, 49%) which was used without further purification; δ_H (250 MHz; $CDCl_3$) 1.25—1.36 (3 H, m, CH_2CH_3), 2.6—2.67 (1.6 H, m, *Z* CH_2CH_2O), 3.32—3.41 (0.4 H, m, *E* CH_2CH_2O), 4.15—4.38 (2 H, m, CH_2CH_2O), 5.73 (0.8 H, s, *Z* =CH), 6.28 (0.2 H, s, *E* =CH), 6.72—7.03 (2 H, m, 7-H and 8-H), 7.28 (0.2 H, dd, *E* 5-H), and 7.65 (0.8 H, dd, *Z* 5-H).

Ethyl 6-*Fluoro*-3,4-*dihydro*-4-*methoxycarbonylmethylthio*-2H-1-*benzopyran*-4-*ylacetate* (**9**).—A mixture of the *E* and *Z* acrylic esters (**8**) (6.0 g, 25 mmol), methyl mercaptoacetate (2.3 ml, 25 mmol) and piperidine (0.1 ml, 1 mmol) was allowed to stand at room temperature overnight under an atmosphere of argon. The reaction mixture was subjected to flash chromatography. Toluene eluted the *E* acrylic ester (**8**) (2 g), whilst the required adduct (**9**) was eluted with dichloromethane. Kugelrohr distillation (180 °C, 0.05 mbar) gave the product as a viscous oil (5.1 g, 59%) which was used without further purification; δ_H (200 MHz, $CDCl_3$) 1.13 (3 H, t, CH_2CH_3), 2.2 (1 H, m, 3-H), 2.7 (1 H, m, 3-H), 3.1 (2 H, dd, CCH_2CO), 3.2 (2 H, s, SCH_2CO), 3.68 (3 H, s, OCH_3), 4.03 (2 H, q, CH_2CH_3), 4.16—4.51 (2 H, m, CH_2CH_2O), 6.72—6.92 (2 H, m, 7-H and 8-H), and 7.05—7.14 (1 H, dd, 5-H); *m/z* 342 (M^+, 18%) and 237 (100).

6-*Fluorospiro*[2H-1-*benzopyran*-4(3H),2(3′H)-*thiophen*]-4′(5′H)-*one* (**4a**).—Butyl-lithium (1.5M in hexane, 10 ml, 15 mmol) was added dropwise to a stirred solution of hexamethyldisilazane (3.0 ml, 14 mmol) in THF (20 ml) at −60 °C and the resultant solution stirred at this temperature for 15 min. A solution of diester (**9**) (5.0 g, 15 mmol) in THF (15 ml) was added dropwise during 5 min, the reaction mixture was stirred at −60 °C for 1 h and then allowed to warm slowly to room temperature. The reaction mixture was added to ice (25 g) and 1M HCl (25 ml) and the organic layer extracted with ether. The ether extracts were washed with brine, dried, and evaporated and the residue purified by flash chromatography [ethyl acetate–hexane (1:4, v/v)] giving compounds (**10**) and (**11**) as a mixture of diastereoisomers (3.5 g). This mixture was dissolved in ethanol (30 ml) and 10% v/v sulphuric acid (30 ml) and refluxed for 3 h. The reaction mixture was cooled, diluted with water (50 ml), and extracted with dichloromethane; the organic extract was washed with brine, dried, and evaporated to a gum. Flash chromatography [dichloromethane–hexane (3:1, v/v)] gave compound (**4a**) as an off-white solid (1.7 g, 49%), m.p. 122—124 °C (from ethanol–water) (Found: C, 60.4; H, 4.7. $C_{12}H_{11}FO_2S$ requires C, 60.5; H, 4.7%); δ_H (200 MHz; $CDCl_3$) 2.12—2.3 (2 H, m, CH_2CH_2O), 2.75 (1 H, d, *J* 17 Hz, 1 H of CH_2CO), 3.16 (1 H, d, *J* 17 Hz, 1 H of CH_2CO), 3.5 (1 H, d, *J* 18 Hz, 1 H of SCH_2), 3.67 (1 H, d, *J* 18 Hz, 1 H of SCH_2), 4.19—4.45 (2 H, m, OCH_2), 6.72—6.94 (2 H, m, 7-H and 8-H), and 7.17 (1 H, dd, 5-H); *m/z* 238 (M^+, 100%), 205 (39), and 191 (67).

6-*Fluorospiro*[2H-1-*benzopyran*-4(3H),2′(3′H)-*thiophen*]-4′(5′H)-*one* 1′-*Oxide* (**4b**).—The oxo sulphide (**4a**) (500 mg, 2.1 mmol) was stirred in DME (10 ml) and a solution of Oxone (760 mg, 1.25 mmol) in water (5 ml) was added. The reaction was exothermic to 30 °C. After 1 h the mixture was diluted with water (20 ml) and extracted with dichloromethane. The organic extract was washed with brine, dried, and evaporated giving the diastereoisomeric sulphoxides (**4b**). Flash chromatography (ether) gave compound (**4d**) (246 mg, 46%) as a white solid followed by compound (**4e**) (100 mg, 19%) as a white solid. A sample of the less polar sulphoxide (**4d**) was recrystallised, m.p. 107—109 °C (from ethanol–water) (Found: C, 56.5; H, 4.3. $C_{12}H_{11}FO_3S$ requires C, 56.7; H, 4.4%); δ_H (200 MHz; $CDCl_3$) 2.2—2.4 (1 H, m, 1 × 3-H), 2.7—2.85 (1 H, m, 1 × 3-H), 2.97 (1 H, d, *J* 18 Hz, 1 × 3′-H), 3.17 (1 H, d, *J* 18 Hz, 1 × 3′-H, 3.5 (1 H, d, *J* 18 Hz, 1 × 5′-H), 3.89 (1 H, d, *J* 18 Hz, 1 × 5′-H), 4.36—4.61 (2 H, m, 2 × 2-H), 6.49 (1 H, dd, 5-H), and 6.82—7.03 (2 H, m, 7-H and 8-H). A sample of the more polar sulphoxide (**4e**) was recrystallised, m.p. 138—139 °C (from ethanol–water) (Found: C, 56.6; H, 4.3. $C_{12}H_{11}FO_3S$ requires C, 56.7; H, 4.4%); δ_H (200 MHz; $CDCl_3$) 1.83—2.18 (2 H, m, 2 × 3-H), 2.78 (1 H, d, *J* 18 Hz, 1 × 3′-H), 3.51 (1 H, d, *J* 18 Hz, 1 × 3′-H), 3.60 (1 H, d, *J* 18 Hz, 1 × 5′-H), 3.79 (1 H, d, *J* 18 Hz, 1 × 5′-H), 4.14—4.35 (2 H, m, 2 × 2-H), 6.82—7.08 (2 H, m, 7-H and 8-H), and 7.30 (1 H, dd, 5-H).

6-*Fluorospiro*[2H-1-*benzopyran*-4(3H),2′(3′H)-*thiophen*]-4′(5′H)-*one* 1′,1′-*Dioxide* (**4c**).—The oxo sulphide (**4a**) (500 mg, 2.1 mmol) was stirred in DME (10 ml) and a solution of Oxone (1.9 g, 3.1 mmol) in water (5 ml) was added. The reaction was exothermic to 30 °C. After being stirred overnight at room temperature, the mixture was diluted with water (20 ml) and extracted with dichloromethane. The organic extract was washed with brine, dried, and evaporated. Flash chromatography (ether) gave the oxo sulphone (**4c**) as a white solid (43 mg, 7.6%), m.p. 150 °C (decomp.) (from toluene–hexane) (Found: C, 53.4; H, 4.1. $C_{12}H_{11}FO_4S$ requires, 53.3; H, 4.1%); δ_H (200 MHz, $CDCl_3$) 2.09—2.27 (1 H, m, 1 × 3-H), 2.61—2.74 (1 H, m, 1 × 3-H), 3.02 (1 H, d, *J* 18 Hz, 1 × 3′-H), 3.42 (1 H, d, *J* 18 Hz, 1 × 3′-H), 3.88 (1 H, d, *J* 18 Hz, 1 × 5′-H), 4.01 (1 H, d, *J* 18 Hz, 1 × 5′-H), 4.3—4.6 (2 H, m, 2 × 2-H), and 6.86—7.1 (3 H, m, ArH).

6-*Fluoro*-3,4-*dihydro*-2H-1-*benzopyran*-4-*carbonitrile* (**13**).—Toluene-*p*-sulphonic acid monohydrate (17.6 g, 92 mmol) was added to a stirred solution of the silylated cyanohydrin (**12**) (23.1 g, 87 mmol) in toluene (100 ml) pre-heated to 65 °C and the mixture was stirred at 100 °C for 90 min. After being cooled, the reaction mixture was diluted with toluene (100 ml) and washed with water (3 × 50 ml) and saturated aqueous sodium hydrogen carbonate solution (2 × 50 ml). The solution was dried and evaporated to a semi-solid which was partially purified by flash chromatography [hexane–dichloromethane

(3:2, v/v)] giving 6-fluoro-2*H*-1-benzopyran-4-carbonitrile (6.77 g) as an off-white solid, δ_H (90 MHz, $CDCl_3$) 4.87 (2 H, d, *J* 4 Hz, 2 × 2-H), 6.59 (1 H, t, *J* 4 Hz, 3-H), and 6.65—7.15 (3 H, m, ArH). The crude unsaturated nitrile was hydrogenated in methanol (125 ml) at room temperature in the presence of a catalyst prepared[9] from palladium chloride (222 mg, 1.25 mmol) and sodium borohydride (95 mg, 2.25 mmol) for 3 h. The catalyst was removed by filtration through Celite and evaporation of the solvent gave the nitrile (**13**) as a buff solid (6.96 g, 45%). Recrystallisation from cyclohexane gave a white solid, m.p. 65—66 °C (Found: C, 67.3; H, 4.5; N, 7.7. $C_{10}H_8FNO$ requires C, 67.8; H, 4.5; N, 7.9%); δ_H (90 MHz, $CDCl_3$) 2.20—2.41 (2 H, m, CH_2CH_2O), 4.0 (1 H, t, *J* 6.4 Hz, 4-H), 4.08—4.46 (2 H, m, CH_2O), and 6.67—7.08 (3 H, m, ArH).

6-*Fluoro*-3,4-*dihydro*-4-*methylthiomethyl*-2H-1-*benzopyran*-4-*carbonitrile* (**14a**).—A solution of the nitrile (**13**) (5.0 g, 28 mmol) and chloromethyl sulphide (2.35 ml, 28 mmol) in THF (50 ml) was stirred at −20 °C under an atmosphere of argon. Potassium t-butoxide (4.75 g, 42 mmol) was added during 15 min and the reaction mixture stirred at −20 °C for 5 h, allowed to warm to room temperature, and added to 1M hydrochloric acid (100 ml). The solution was extracted with ethyl acetate (2 × 50 ml) and the combined extracts were dried and evaporated to give an off-white solid. Recrystallisation from propan-2-ol gave the thioether (**14a**) as a white solid (3.02 g, 45%), m.p. 72—73 °C (Found: C, 60.8; H, 5.2; N, 5.8. $C_{12}H_{12}FNOS$ requires C, 60.7; H, 5.1; N, 5.9%); δ_H (200 MHz, $CDCl_3$) 2.32 (3 H, s, SCH_3), 3.0 (1 H, d, *J* 13 Hz, 1 H of CH_2S), 3.18 (1 H, d, *J* 13 Hz, 1 H of CH_2S), 4.1—4.35 (2 H, m, CH_2O), 6.79—7.01 (2 H, m, 7-H and 8-H), and 7.12—7.18 (1 H, dd, 5-H), *m/z* 237 (M^+, 8%) and 61 (100).

6-*Fluoro*-3,4-*dihydro*-4-*methylsulphonylmethyl*-2H-1-*benzopyran*-4-*carbonitrile* (**14b**).—A solution of the sulphide (**14a**) (2.82 g, 11.9 mmol) in THF (30 ml) was treated with a solution of Oxone (21.8 g, 35 mmol) in water (30 ml) and stirred at room temperature overnight. The reaction mixture was added to water (100 ml) and the aqueous mixture was extracted with ethyl acetate (3 × 20 ml). The combined extracts were dried and evaporated to a straw-coloured oil which crystallised on trituration with hexane giving the sulphone (**14b**) as a white crystalline solid (2.80 g, 87%), m.p. 135—137 °C (propan-2-ol) (Found: C, 53.7; H, 4.5; N, 5.2. $C_{12}H_{12}FNO_3S$ requires C, 53.5; H, 4.5; N, 5.2%); δ_H (90 MHz, $CDCl_3$) 2.7—2.9 (2 H, m, CH_2CH_2O), 3.13 (3 H, s, SO_2CH_3), 3.48 (1 H, d, *J* 15 Hz, 1 H of CH_2SO_2), 4.04 (1 H, d, *J* 15 Hz, 1 H of CH_2SO_2), 4.35 (2 H, t, OCH_2), and 6.78—7.3 (3 H, m, ArH); *m/z* 269 (M^+, 76%), 190 (96), and 176 (100).

6-*Fluoro*[2H-1-*benzopyran*-4(3H),3′(2′H)*thiophen*]-4(5′H)-*one* 1′,1′-*Dioxide* (**5**).—The sulphone (**14b**) (269 mg, 1 mmol) was added to a stirred ethanolic solution of sodium ethoxide [prepared from sodium metal (23 mg, 1 mmol) and ethanol (3 ml)] under an atmosphere of argon. The reaction mixture was stirred at reflux for 2 h, then the deep yellow solution was cooled and added to ice–water (25 ml). The mixture was stirred for 1 h and the solid was filtered and dried to give the imine (**15**) (110 mg, 41%), m.p. 201—202 °C (propan-2-ol); $\nu_{max.}$(Nujol) 3 220—3 480 (5 bands) (NH), 1 650 (C=N) cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.3—2.6 (2 H, m, CH_2CH_2O), 3.52 (2 H, s, $SO_2CH_2C{=}N$), 3.82—4.58 (4 H, m, OCH_2 and CH_2SO_2), 5.65 (1 H, s, NH), and 6.73—7.10 (3 H, m, ArH); *m/z* 269 (M^+, 62%), 164 (100), and 149 (58). The foregoing imine (87 mg, 0.32 mmol) was stirred in a mixture of acetone (3 ml) and 10% v/v sulphuric acid (1 ml) at room temperature overnight. The reaction mixture was diluted with water (25 ml) and extracted with ether (4 × 20 ml). The combined extracts were washed with water (25 ml), dried and, evaporated to a clear oil which slowly crystallised. The β-oxo sulphone (**5**) was obtained as an off-white solid (34 mg, 39%), m.p. 182—184 °C (propan-2-ol) (Found: C, 53.2; H, 4.3. $C_{12}H_{11}FO_4S$ requires C, 53.3; H, 4.1%); $\nu_{max.}$(Nujol) 1 750 (CO) cm^{-1}; δ_H (90 MHz, $CDCl_3$) 2.42 (2 H, t, CH_2CH_2O), 3.68 (1 H, d, *J* 14 Hz, 1 H of CH_2SO_2), 3.95 (1 H, d, *J* 14 Hz, 1 H of CH_2SO_2), 4.06 (2 H, s, SO_2CH_2CO, exchanges with CD_3CO_2D), 3.8—4.4 (2 H, m, OCH_2), and 6.65—7.02 (3 H, m, ArH), *m/z* 270 (M^+, 22%), 164 (100), and 149 (72).

6-*Fluoro*-3,4-*dihydro*-4,4-*bis*(*methoxycarbonylmethylthio*)-2H-1-*benzopyran* (**18**).—A solution of 6-fluorochroman-4-one (**7**) (7.7 g, 46 mmol) and methyl trimethylsilylthioacetate (16.5 g, 93 mmol) in dichloromethane (25 ml) was stirred under an argon atmosphere at room temperature. Zinc iodide (1.48 g, 4.6 mmol) was added and the suspension stirred at room temperature. The reaction was mildly exothermic and solution was attained within 30 min. After 3 h the solution was evaporated and the residue submitted to flash chromatography (dichloromethane) giving the bis sulphide (**18**) (12.8 g, 77%) as a pale brown oil which solidified on standing overnight; $\nu_{max.}$(Nujol) 1 730 (ester) cm^{-1}; δ_H (90 MHz; $CDCl_3$) 2.5 (2 H, t, 2 × 3-H), 3.63 (6 H, s, 2 × OMe), 2.77 (4 H, s, 2 × SCH_2), 4.42 (2 H, t, 2 × 2 H), 6.7—7.1 (2 H, m, 7-H and 8-H), and 7.4 (1 H, dd, 5-H). This material was used without further purification.

Methyl 6-*Fluoro*-5′-*hydroxyspiro*{2H-1-*benzopyran*-4(3H),2′(4′H)-[1,3]*dithiine*}-6′-*carboxylate* (**19**).—Sodium hydride (55% dispersion in mineral oil; 3.3 g, 76 mmol) was suspended in THF (100 ml) under an atmosphere of argon. The suspension was heated to 75 °C (oil bath) and a solution of bis sulphide (**18**) in THF (40 ml) added during 1.25 h. The resultant brown solution was stirred at 75 °C for 3 h and cooled overnight. Ethanol (5 ml) was added cautiously to destroy the excess of sodium hydride, the reaction mixture was then added to ice (100 g) and 2M HCl (100 ml), and extracted with ethyl acetate (2 × 75 ml). The combined extracts were washed with brine and evaporated to a semi-solid. Flash chromatography [toluene–hexane (3:2, v/v)] gave the oxo ester (**19**) as a white solid (7.47 g, 64%), m.p. 105—107 °C (from cyclohexane) (Found: C, 51.1; H, 4.0. $C_{14}H_{13}FO_4S_2$ requires C, 51.2; H, 4.0%); $\nu_{max.}$(Nujol) 1 635 (enolic ester), 1 590 (C=C) cm^{-1}; δ_H (90 MHz; $CDCl_3$) 2.2—2.65 (2 H, m, CH_2CH_2O), 3.47 (1 H, d, *J* 15 Hz, SCH_2), 3.84 (3 H, s, OMe), 3.92 (1 H, d, *J* 15 Hz, SCH_2), 4.1—4.7 (2 H, m. OCH_2), 6.7—7.1 (2 H, m, 7-H and 8-H), 7.45 (1 H, dd, 5-H), and 12.62 (1 H, s, enolic OH); *m/z* 328 (M^+, 27%), 296 (35), and 182 (100).

6-*Fluorospiro*{2H-1-*benzopyran*-4(3H),2′-[1,3]*dithian*}-5′-*one* (**6a**).—The β-oxo ester (**19**) (7.37 g, 22.5 mmol) was stirred in 1,4-dioxane (40 ml) and 2M sulphuric acid (75 ml) at reflux for 3 h. The cooled reaction mixture was diluted with water (100 ml) and extracted with dichloromethane. The organic extract was washed with brine, dried, and evaporated to a mobile oil which crystallised on trituration in hexane. The ketone (**6a**) was obtained as a white solid (3.94 g, 65%), m.p. 93—95 °C (from cyclohexane) (Found: C, 53.3; H, 4.0. $C_{12}H_{11}FO_2S_2$ requires C, 53.3; H, 4.1%); δ_H (90 MHz; $CDCl_3$) 2.6 (2 H, t, CH_2CH_2O), 3.62 (4 H, s, 2 × SCH_2), 4.37 (2 H, t, CH_2O), 6.65—7.05 (2 H, m, 7-H and 8-H), and 7.45 (1 H, dd, 5-H).

6-*Fluoro*-2,3-*dihydrospiro*{2H-1-*benzopyran*-4(3H),2′-[1,3]-*dithian*}-5′-*one* 1′-*Oxide* (**6b**).—The dithiinone (**6a**) (500 mg, 1.85 mmol) was stirred in DME (10 ml) and a solution of Oxone (683 mg, 1.11 mmol) in water (5 ml) added. The reaction was exothermic and a white precipitate formed. After 30 min the reaction mixture was diluted with water (35 ml), cooled, and filtered. The pasty solid was dried and recrystallised from propan-2-ol (25 ml) giving the sulphoxide (**6b**) (210 mg, 40%),

m.p. 163—168 °C (decomp.) (Found: C, 50.2; H, 3.9. $C_{12}H_{11}FO_3S_2$ requires C, 50.4; H, 3.9%); δ_H (90 MHz; [$^2H_6$]DMSO 2.68—3.0 (2 H, m, CH_2CH_2O), 3.15 (1 H, d, *J* 13.5 Hz, $SOCH_2$), 4.02 (1 H, d, *J* 13.5 Hz, $SOCH_2$), 4.12 (2 H, s, SCH_2), 4.18—4.67 (2 H, m, OCH_2), and 6.9—7.3 (3 H, m, ArH); *m/z* 286 (M^+, 66%) and 181 (100).

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