Synthesis of Flavone-3-sulfonylureas

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Received December 29, 1995

Dedicated to the memory of Professor Nicholas Alexandrou

The synthesis of new flavone-3-sulfonylurea derivatives is hereby described. The influence of a phenyl group in the 2-position and an acetate group in the 8-position at the chromone nucleus on the activity was studied. Only weak cytostatic activity of the new compounds was found.

J. Heterocyclic Chem., **33**, 943 (1996).

1. Introduction

The diarylsulfonylurea, Solufenur (**1a**, LY 186641) represents a new class of anticancer agents which appear to be unique in structure and mode of action. They demonstrate activity against solid tumors in animals. Solufenur has an exceedingly broad *in vivo* spectrum of activity against solid tumors in conjunction with low toxicity. In an *in vitro* human tumor colony-forming assay, it had median IC_{50} of 100 to 2225 mcg/ml against primary cultures from five types of clinical tumor specimens, with breast, lung and colon tumors being the most sensitive. Clinical efficacy studies in a number of solid tumors are in progress. Several sulfonylureas with arylsulfonylalkylurea type structures are clinically effective as hypoglycemics, but Solufenur was devoid of this property.

Solufenur's mechanism of action remains unclear, but it appears to be distinct from other antitumor compounds [1,2]. Unlike conventional antineoplastic chemotherapeutic agents, Solufenur does not induce alopecia and it is neither myelosuppressive, cardiotoxic nor nephrotoxic.

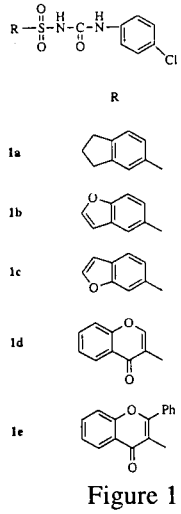


Figure 1

Boder *et al.* optimized the pharmacological profile of the diarylsulfonylureas. They also discovered 1-(5-benzofuransulfonyl)-3-(4-chlorophenyl)urea (**1b**, LY280256) and 1-(6-benzofuransulfonyl)-3-(4-chlorophenyl)urea (**1c**, LY287609), which were approximately two-times more potent than Solufenur in an *in vivo* rodent model [3]. In previous work [4], we reported the synthesis of a chromone-3-sulfonylurea (**1d**), which showed no activity in the antitumor screening program of the National Cancer Institute. In this paper, we describe the synthesis of the more lipophilic flavone-3-sulfonylurea derivative **1e** and assess the influence of the additional phenyl substitution in the 2-position of the chromone nucleus (Figure 1).

Flavone-8-acetic acid **2** is also a target structure for the development of new cytotoxic drugs [5]. Flavone-8-acetic acid shows high activity against advanced solid tumors in mice but, unfortunately, no activity in human cancer. The mode of action is proposed as a biological response modifier [6].

Different attempts have been made to improve the the biological profile of **2**, *e.g.*, by introducing different substituents in the flavone or phenyl rings [7,8,9] or including other related analogues of flavone-8-acetic acid, such as xanthone-4-acetic acid [10]. Although the mode of action of the diarylsulfonylureas and the flavone-8-acetic acid derivatives is not completely understood, we com-

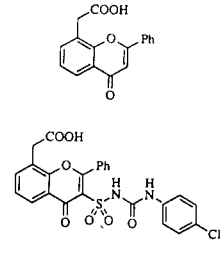


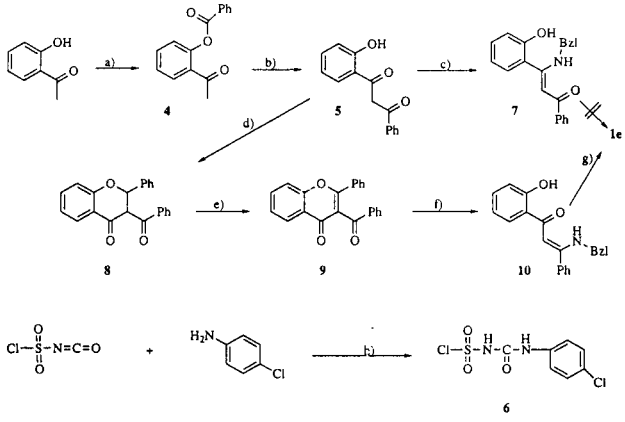
Figure 2

bined their structural patterns in the same molecule to obtain the target structure **3**, in expectation of interesting pharmacological results.

2. Chemistry

The flavone-3-sulfonylurea **1e** was synthesized as depicted in Scheme 1. Treatment of *o*-hydroxyacetophenone with benzoyl chloride in pyridine afforded the benzoyl ester **4**. Baker-Venkataraman rearrangement of **4** with potassium hydroxide in pyridine led to the 1,3-diketone **5** [11]. For electrophilic substitution with the 3-(4-chlorophenyl)-1-chlorosulfonylurea **6**, which can be prepared from 4-chloro aniline with equimolar amounts of

Scheme 1

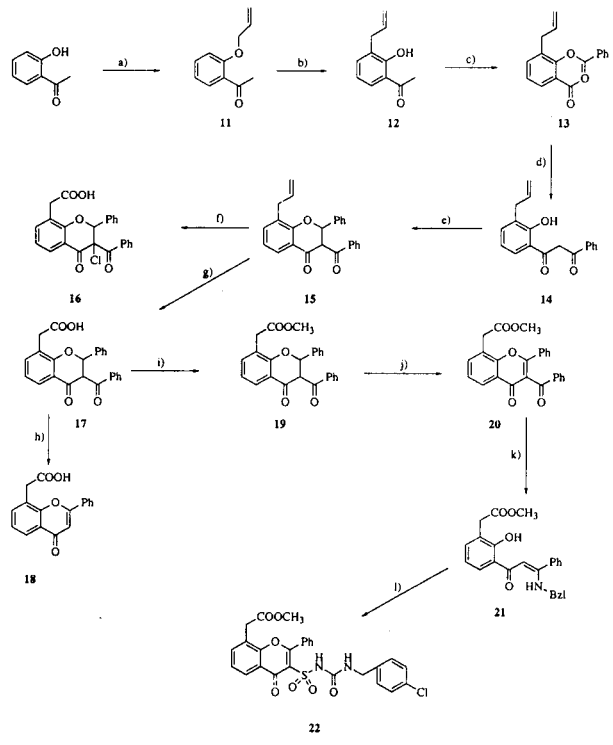


a) BzCl, py ΔT; b) KOH, py ΔT; c) $BzlNH_2$, EtOH ΔT; d) benzaldehyde, piperidine, EtOH ΔT; e) SeO_2, *n*-pentanol ΔT; f) $BzlNH_2$, toluene ΔT; g) **6**, 60°; h) dioxane/ether 0° to RT.

chlorosulfonyl isocyanate *in situ* [12], we tried to transform the 1,3-diketone **5** directly to the required enaminone **10**. When **5** was boiled with benzylamine in ethanol, the nucleophile attacked the hydrogen bonding carbonyl group, resulting in the formation of the undesired isomer **7** in 70% yield. The structure of the latter was established from the chemical shift of the NH proton, which is shifted further downfield (δ = 11.76 ppm, J = 6.0 Hz) than the OH proton (δ = 10.12 ppm). All attempts to substitute **7** with the electrophilic compound failed. However we were able to prepare **10** *via* a route reported by Baker [13]. Knoevenagel reaction of **5** with benzaldehyde and a catalytic amount of piperidine pro-vided the 3-benzoylflavanone **8**.

Oxidation of **8** with selenium dioxide in *n*-pentanol led to the 3-benzoylflavone **9**. Subsequent treatment of **9** with an excess of benzylamine afforded the desired enaminone **10** in 54% yield. The mechanism of this reaction involves initial addition of the primary amine to the activated C-2 of the flavone nucleus, which is followed by spontaneous cleavage of the formated hemiaminal. An excess of benzylamine is added to the carbonyl of the 3-acyl group, followed by removal of the benzoyl group as benzoylbenzylamide. The ^{1}H-nmr spectra of **10** showed that the OH signal (δ = 13.39 ppm) had then shifted further downfield than the NH proton (δ = 11.20, J = 6.2 Hz). The reaction of **10** with the chlorosulfonyl urea **6** yielded the required flavone-3-sulfonyl urea **1e** directly with elimination of benzylamine hydrochloride.

Scheme 2



a) Allyl bromine, K_2CO_3, KI, acetone ΔT; b) ΔT; c) BzCl, py ΔT; d) *t*-BuOK, DMF 0°; e) benzaldehyde, piperidine, EtOH ΔT; f) $RuCl_3$, $NaIO_4$, $MeCN/CCl_4/H_2O$ RT; g) $RuCl_3$, $NaIO_4$, $MeCN/ether/H_2O$ RT h) DDQ, SeO_2 or I_2; i) MeOH, H_2SO_4 ΔT; j) SeO_2, DMSO ΔT; k) $BzlNH_2$, toluene ΔT; l) **6**, 60°.

The synthetic route of the flavone derivative, including an additional acetate group in position 8 of the flavone nucleus, is depicted in Scheme 2. Standard procedures were used to convert *o*-hydroxyacetophenone to its allyl ether derivative **11**. Claisen rearrangement of **11** gave the best results by heating the ether derivative under a nitrogen atmosphere of 260-270°, which led to the 3-allyl-2-hydroxyacetophenone **12** [14]. Benzoylation with benzoyl chloride in pyridine provided the ester **13**. Subsequent treatment of **13** with of potassium *t-b*utoxide in DMF under a nitrogen atmosphere at 0°C [11] yielded the diketone **14**. Cyclization of **14** with benzaldehyde as in preparation of the flavanone **8**, gave the 8-allyl-3-benzoylflavanone **15**. However, all attempts to prepare the carboxylic acid by oxidation of the allyl group with potassium permanganate in pyridine or under phase transfer conditions with dicyclohexano-18-crown-6 [15] failed. *Via* ruthenium tetroxide oxidation of **15** under phase transfer

conditions (carbon tetrachloride/acetonitrile solution and stirring a catalytic amount ruthenium trichloride with a slight excess of aqueous sodium periodate [16]), the flavanone was converted to the corresponding acid **16**, but with an additional chlorine atom in position 3. Using ether instead of carbon tetrachloride led to the required 3-benzoyl-flavanone-8-acetic acid **17** in 63% yield. Although the influence of the additional acetate group in **17** should be marginal with respect to structure **8**, all attempts to prepare the corresponding flavone derivative failed. Treatment with selenium dioxide in *n*-pentanol [17], DDQ in dioxan [18], and iodine in acetic acid/sodium acetate [19] afforded the debenzoylated flavone-8-acetic acid **18**. An interesting finding is that, after esterification of **17** with methanol to form the methyl acetate derivate **19**, subsequent oxidation could be achieved with selenium dioxide in DMSO, which afforded the flavone **20** in 75% yield. The appropriate enaminone **21** was obtained by heating **20** with an excess of benzylamine in toluene. Cyclization of **21** with the chlorosulfonylurea **6** by electrophilic substitution to the desired substituted flavone-3-sulfonylurea **22** was accomplished by a previously reported method [4]. Cleavage of the ester **22** under different reaction conditions failed. Nevertheless, compound **22** comprises a prodrug of the free acid, and we selected it for the pharmacological tests.

3. *In vitro* Cytotoxic Effects.

Compounds **1e** and **22** were submitted to the National Cancer Institute (NCI) for testing in its new *in vitro* disease oriented antitumor screening program [20,21]. This assay involves determination of a test agent's effect on growth parameters against a panel of approximately 60 cell lines derived from human cancers, which consisted largely of solid tumors and a few leukemia lines. The cytotoxic activities (IC_{50} values) were determined using a colorimetric assay, which is based on an indirect messurement of the protein mass with sulforhodamine B. The cells were exposed to the test compounds for 48 hours; controls were incubated in medium alone.

In contrast to compound **1d**, which showed no activity in NCI antitumor screening, **1e** demonstrated its best but weak activity against the melanoma cell line UACC-62 with an IC_{50} of $2 \cdot 10^{-6}$ *M*. Unexpectedly, compound **22** showed the best activity against the leukemia cell line K-562 with an IC_{50} of $4 \cdot 10^{-6}$ *M*. (IC_{50} are concentrations which reduce cell growth to 50% of the level at the start of experiments).

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were determined with a Bruker AC 300 (300 MHz) spectrometer containing tetramethylsilane as internal standard. Infrared spectra were determined with a Perkin-Elmer 297 spectrophotometer. Mass spectra were obtained on a CH-7A-Varian MAT (70 eV) instrument, FAB mass spectra on a CH-5-DF-MAT-Varian (80 eV) spectrometer. Microanalyses were performed with a Perkin-Elmer 240 B and C analyzer. Thin layer chromatography was performed on Merck precoated tlc plates with silica gel 60-F254. Column (flash) chromatography was performed with Merck silica gel 60 (230-400 mesh).

3-Benzylamino-3-(2-hydroxyphenyl)-1-phenyl-2-propenone (**7**).

A solution of 5.0 g (20.8 mmoles) **5** in 30 ml of ethanol was treated with 2.23 g (20.8 mmoles) of benzylamine and was warmed to reflux for 3 hours. After cooling, the precipitate was collected, washed with ethanol and recrystallized from ethanol to afford 4.8 g (70%) of **7**, mp 171°C (ethanol); ir (potassium bromide): ν 3052 (OH, NH), 1590 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 4.36 (br, 2H, CH_2-benzyl), 5.72 (s, 1H, 2-H), 6.90 (t, J = 7.4 Hz, 1H, aromatic H), 6.98 (d, J = 8.1 Hz, 1H, aromatic H), 7.23-7.52 (m, 10H, aromatic H), 7.85 (d, J = 6.8 Hz, 2H, aromatic H), 10.12 (s, 1H, OH), 11.76 (t, J = 6.0 Hz, 1H, NH); ms: (70 eV) m/z = 329 ($M^{+\bullet}$, 24%).

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.16; H, 5.91; N, 4.30.

(+/-)-*E*-3-Benzoyl-2-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (**8**).

Piperidine (0.5 ml) was added to a solution of 22.0 g (92 mmoles) of **5** and 9.72 g (92 mmoles) of benzaldehyde in 300 ml of ethanol and heated to reflux for 30 minutes The solution was stored for 2 hours in a refrigerator whereupon a precipitate appeared. The solid was filtered, washed with ethanol and recrystallized from the same solvent to provide the product as a white solid (20.1 g, 67%); mp 146°C (ethanol); ir (potassium bromide): ν 1696, 1675 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 5.93 (d, J = 12.3 Hz, 1H, 2-H), 6.04 (d, J = 12.3 Hz, 1H, 3-H), 7.13-7.18 (m, 2H, aromatic H), 7.30-7.37 (m, 3H, aromatic H), 7.47 (t, J = 7.8 Hz, 2H, aromatic H), 7.57-7.70 (m, 4H, aromatic H), 7.81 (dd, J = 1.6/6.4 Hz, 1H, aromatic H), 7.95 (d, J = 7.3 Hz, 2H, aromatic H); ms: (70 eV) m/z = 328 ($M^{+\bullet}$, 14%).

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.41; H, 4.93.

3-Benzoyl-2-phenyl-4*H*-1-benzopyran-4-one (**9**).

Compound **8** (19.0 g, 58 mmoles) and 19.0 g (171 mmoles) freshly sublimed selenium dioxide were heated in 100 ml *n*-pentanol to reflux for 12 hours. The warm solution was filtered, then stored for 12 hours at 4°C. The precipitate was collected, washed with ethanol and recrystallized from the same solvent to provide the product as a white solid (14.9 g, 79%), mp 133°C (ethanol) (ref [13] 130-131°C); ir (potassium bromide): ν 1670, 1627 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.42-7.65 (m, 9H, aromatic H), 7.82 (d, J = 8.1 Hz, 1H, 8-H), 7.90-7.96 (m, 3H, aromatic H), 8.08 (dd, J = 1.5/6.4 Hz, 1H, 5-H); ms: (70 eV): m/z = 326 ($M^{+\bullet}$, 38%).

Anal. Calcd. for $C_{22}H_{14}O_3$: C, 80.97; H, 4.32. Found: C, 80.99; H, 4.46.

3-Benzylamino-1-(2-hydroxyphenyl)-3-phenyl-2-propenone (**10**).

A solution of 5.0 g (15.3 mmoles) of **9** in 50 ml of toluene

was treated with 3.28 g (30.6 mmoles) benzylamine and was warmed to an internal temperature of 100°C for 14 hours. After cooling, the solvent was removed and the residue was triturated with petroleum ether (40-60°C). After crystallization was complete, the residue was recrystallized two times from ethanol to provide the product as a yellow solid (2.71 g, 54%). More product could be isolated from the mother liquids, mp 98°C (ethanol); ir (potassium bromide): ν 3407 (NH, OH), 1603 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 4.48 (d, J = 6.3 Hz, 2H, CH_2-benzyl), 5.91 (s, 1H, 2-H), 6.78-6.86 (m, 2H, aromatic H), 7.21 (d, J = 6.9 Hz, 2H, aromatic H), 7.26-7.53 (m, 9H, aromatic H), 7.81 (d, J = 6.9 Hz, 1H, 6'-H), 11.20 (t, J = 6.2 Hz, 1H, NH), 13.39 (s, 1H, OH); ms: (70 eV) m/z = 329 ($M^{+\bullet}$, 46%).

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H,5.81; N,4.25. Found C, 80.15; H, 5.91; N, 4.34.

3-(4-Chlorophenyl)-1-(2-phenyl-4-oxo-4H-1-benzopyran-3-sulfonyl)urea (**1e**).

The solution of 893 mg (7 mmoles) of 4-chloroaniline in 10 ml of anhydrous 1,4-dioxane was added to a stirred solution of 991 mg (7 mmoles) chlorosulfonyl isocyanate in a mixture of 50 ml of anhydrous 1,4-dioxane and 10 ml of anhydrous ether over a 20-minute period and was then cooled in an ice bath. The solution was stirred for a further 60 minutes at 20°C and was then treated with 2.31 g (7 mmoles) of **10** as a solid. The mixture was stirred for 60 minutes at 60°C, cooled to room temperature and then placed on 300 g of crushed ice. The precipitate was collected, washed with brine (200 ml) and dried. The solution of this solid in chloroform/methanol (9+1) was purified by flash chromatography with the same solvent as eluent to provide the product as a white solid (1.06 g, 33%), mp 188°C; ir (potassium bromide): ν 3350, 3054 (NH), 1703, 1650, 1541 (C=O),1356, 1160 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.31 (d, J = 9.0 Hz, 2H, 2"-H, 6"-H), 7.38 (d, J = 9.0 Hz, 2H, 3"-H, 5"-H), 7.54-7.63 (m, 4H, 3'-H, 4'-H, 5'-H, 6'-H), 7.73 (d, J = 8.3 Hz, 1H, 8-H), 7.83 (d, J = 6.8 Hz, 2H, 2'-H, 6'-H), 7.92 (t, J = 7.1 Hz, 1H, 7-H), 8.14 (d, J = 7.9 Hz, 1H, 5-H), 9.07 (s, 1H, NH-3), 10.68 (s br, 1H, NH-1); ms: (FAB positive (dimethyl sulfoxide/glycerol) m/z = 455 ($[M+H]^+$, 12%, ^{35}Cl); (FAB negative (dimethyl sulfoxide/glycerol): m/z = 453 ($[M-H]^-$, 100%, ^{35}Cl).

Anal. Calcd. for $C_{22}H_{15}ClN_2O_5S$: C, 58.09; H, 3.32; N, 6.16. Found: C, 57.69; H, 3.42; N, 6.06.

(2-(2-Propenyloxy)phenyl)ethanone (**11**).

2-Hydroxyacetophenone (68.1 g, 0.5 mole), 65.0 g (0.54 mole) of allyl bromide and 70.0 g of potassium carbonate were refluxed in 70.0 ml of 2-butanone for 8 hours. After cooling 200 ml of water was added to the resulting suspension. The organic layer was separated, washed with 100 ml of 10% sodium hydroxide, dried over potassium carbonate and finally destilled under reduced pressure. The isolated compound is a pale yellow liquid with bp 141-142°C (1.4 kP_a), yield 82.6 g (76%); ir (sodium chloride-film): ν 1673 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.55 (s, 3H, 2-H), 4.71 (d, J = 5.2 Hz, 2H, 1"-H), 5.31 (dd, J = 1.3/9.3 Hz, 1H, 3"-H), 5.45 (dd, J = 1.5/15.8 Hz, 1H, 3"-H), 6.04-6.17 (m, 1H, 2"-H), 7.02 (t, J = 7.6 Hz, 1H, 5'-H), 7.16 (d, 8.4 Hz, 1-H, 3'-H), 7.49-7.59 (m, 2H, 4'-H, 6'-H); ms: (70 eV) m/z = 175 ($M^{+\bullet}$, 16%).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 74.50; H, 6.96.

[2-Hydroxy-3-(2-propenyl)phenyl]ethanone (**12**).

Fifty g (0.28 mole) freshly distilled **11** was heated under a nitrogen atmosphere up to 260-270°C for 30 minutes. After cooling, 200 ml of ether was added and the product was extracted with 10% sodium hydroxide (3 x 100 ml). After acidification of the combined aqueous layers with 6*N* aqueous hydrochloric acid, the product was extracted with ether (3 x 100 ml) and the combined ether phase was dried with sodium sulfate. The solvent was removed and the residue was purified by distillation *in vacuo* to provide **12** as a colourless liquid (23.0 g, 46%), bp 135-136°C (1.8 kP_a) (ref [14] bp 136-138°C (2.7 kP_a); ir (sodium chloride film): ν 3068 (OH), 1636 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.66 (s, 3H, CH_3), 3.36 (d, J = 6.4 Hz, 2H, 1"-H), 5.07 (m, 2H, 3"-H), 5.90-6.03 (m, 1H, 2"-H), 6.93 (t, J = 7.7 Hz, 1H, 5'-H), 7.43 (d, J = 7.3 Hz, 1H, 4'-H), 7.84 (d, J = 8.0 Hz, 1H, 6'-H), 12.62 (s, 1H, OH); ms: (70 eV) m/z = 176 ($M^{+\bullet}$, 90%).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 75.31; H, 6.67.

1-[2-Hydroxy-3-(2-propenyl)phenyl]-3-phenylpropane-1,3-dione (**14**).

A solution containing 55.7 g (316 mmoles) of **12** in 80 ml of pyridine was treated slowly with 46.0 g (327 mmoles) benzoyl chloride over a 30 minute period. The mixture was stirred for 30 minutes and then added to 800 ml of 2*N* hydrochloric acid cooled in an ice bath. The organic layer was seperated and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic layers were washed with 5% aqueous sodium hydroxide (3 x 75 ml) and dried (magnesium sulfate). The solvent was removed *in vacuo*. The crude oily [2-acetyl-6-(2-propenyl)phenyl]benzoate **13** was used for the Baker-Venkataraman rearrangement without further purification.

The solution containing 83.4 g (298 mmoles) of crude **13** in 240 ml of DMF was treated under a nitrogen atmosphere with the solution of 66.8 g (595 mmoles) of potassium *t*-butoxide in 150 ml of DMF over a 60 minute period at 0°C. After stirring for additional 60 minutes at 20°C, the mixture was added to 1.2 l of 3% aqueous hydrochloric acid cooled in an ice bath. The precipitate was collected, washed with water (200 ml) and recrystallized from ethanol to provide the title compound as a yellow solid (49.1 g, 55%), mp 91°C (ethanol); ir (potassium bromide): ν 3401 (OH), 1721 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.48 (d, J = 6.0 Hz, 2H, 1'-H allyl), 5.04-5.17 (m, 2H, 3'-H allyl), 5.92-6.14 (m, 1H, 2'-H allyl), 6.91-8.19 (m, 9H, aromatic H and 2-H), 12.23 (s, 1H, OH), 15.60 (s br, 1H, OH enol); ms: (70 eV) m/z = 280 ($M^{+\bullet}$, 21%).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.29, H, 5.75.

(+/-)-3-Benzoyl-2-phenyl-8-(2-propenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (**15**).

Piperidine (0.5 ml) was added to a solution of 45.0 g (160.5 mmoles) **14** and 17.5 g (165 mmoles) of benzaldehyde in 300 ml of ethanol and the mixture was heated to reflux for 4 hours. After cooling, the precipitate was collected, washed with a small amount of ethanol and recrystallized from ethanol to provide the product as a light yellow solid (50.2 g, 85%), mp 119°C (ethanol); ir (potassium bromide): ν 1685, 1667 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.33 (d, J = 6.4 Hz, 2H, 1'-H allyl), 5.01-5.07 (m, 2H, 3'-H allyl), 5.89-6.01 (m, 3H, 2-H, 3-

H, 2'-H allyl), 7.07-7.65 (m, 10H, aromatic H), 7.70 (dd, J = 1.5/6.3 Hz, 1H, 5-H), 7.96 (d, J = 7.4 Hz, 2H, 2-H, 6-H benzoyl); ms: (70 eV) m/z = 368 ($M^{+\bullet}$, 26%).

Anal. Calcd. for $C_{25}H_{20}O_3$: C, 81.50; H, 5.47. Found: C, 81.44; H, 5.40.

(+/-)-(3-Benzoyl-3-chloro-2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-8-yl)acetic Acid (**16**).

Twenty g (54.3 mmoles) of **15** was dissolved in a mixture of 250 ml of carbon tetrachloride and 250 ml of acetonitrile. The solution of 58.0 g (271 mmoles) of sodium periodate and 100 mg of ruthenium trichloride in 500 ml of water was then added. This biphasic mixture was stirred 24 hours at room temperature. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were extracted with 10% aqueous sodium hydroxide. The combined aqueous layers were acidified with concentrated aqueous hydrochloric acid and reextracted with ethyl acetate (3 x 100 ml). The combined ethyl acetate phase was washed with 20% sodium thiosulfate solution (2 x 50 ml) and dried (magnesium sulfate), and the solvent was removed. The residue was treated with petroleum ether (40-60°C). After crystallization was complete, the crude product was recrystallized from methanol to provide **16** as a light yellow solid (19.4 g, 92%), mp 173°C (methanol); ir (potassium bromide): ν 1705 (COOH), 1663 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.53 (d, J = 16.6 Hz, 1H, 2-H), 3.61 (d, J = 16.6 Hz, 1H, 2-H), 6.04 (s, 1H, 2'-H), 6.97-7.78 (m, 13H, aromatic H), 12.32 (s br, 1H, COOH); ms: (70 eV) m/z = 420 ($M^{+\bullet}$, 2%, ^{35}Cl).

Anal. Calcd. for $C_{24}H_{17}ClO_5$: C, 68.50; H, 4.07. Found: C, 68.19; H, 4.07.

(+/-)-(3-Benzoyl-2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-8-yl)acetic Acid (**17**).

This product was synthesized as depicted in the above procedure, but 250 ml of ether was used instead of carbon tetrachloride. The isolation provided **17** as a light yellow solid (13.2 g, 63%), mp 172°C (methanol); ir (potassium bromide): ν 1708 (COOH), 1670 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.56-3.71 (m, 2H, CH_2), 5.86 (d, J = 12.2 Hz, 1H, 2-H), 5.95 (d, J = 12.3 Hz, 1H, 3-H), 7.02-7.77 (m, 11H, aromatic H), 7.97 (d, J = 7.3 Hz, 2H, 2-H benzoyl, 6-H benzoyl), 12.36 (br, 1H, COOH); ms: (70 eV) m/z = 386 ($M^{+\bullet}$, 28%).

Anal. Calcd. for $C_{24}H_{18}O_5$: C, 74.60; H, 4.70. Found: C, 74.37; H, 4.74.

(2-Phenyl-4-oxo-4*H*-1-benzopyran-8-yl)acetic Acid (**18**).

A solution containing 460 mg (1.19 mmoles) of **17** and 500 mg (4.5 mmoles) of freshly sublimed selenium dioxide in 10 ml of DMSO was heated to 120°C in an oil bath for 60 minutes. After cooling to room temperature, the mixture was filtered and added to 80 g of crushed ice. The precipitate was collected and recrystallized from ethanol to provide the title compound as a white solid (350 mg, 76%), mp 234°C (ethanol) (ref [5] mp 234°C); ir (potassium bromide): ν 2560, 1740 (COOH), 1625 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 4.03 (s, 2H, CH_2), 7.08 (s, 1H, 3-H), 7.46 (t, J = 7.6 Hz, 1H, 4-H phenyl), 7.57-8.15 (m, 7H, aromatic H), 12.69 (s br, 1H, COOH); ms: (70 eV) m/z = 280 ($M^{+\bullet}$, 100%).

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.61; H, 4.40.

(+/-)-Methyl (3-Benzoyl-2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-8-yl)acetate (**19**).

A solution of 6.1 g (15.8 mmoles) of **17** in 40 ml of anhydrous methanol was treated with 1 ml of concentrated sulfuric acid and heated to reflux for 8 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was added to 100 g of crushed ice. The suspension was extracted with ethyl acetate (3 x 50 ml), the combined organic phase was washed with water (3 x 25 ml), with saturated aqueous sodium bicarbonate solution and dried (magnesium sulfate), and the solvent was removed *in vacuo*. The residue was recrystallized from methanol to provide **19** as a tan solid (5.3 g, 84%), mp 142°C (methanol); ir (potassium bromide): ν 1735 (COOR), 1692, 1670 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.51 (s, 3H, CH_3), 3.67-3.71 (m, 2H, CH_2), 5.85 (d, J = 12.2 Hz, 1H, 2-H), 5.96 (d, J = 12.1 Hz, 1H, 3-H), 7.10-7.97 (m, 13H, aromatic H); ms: (70 eV) m/z = 400 ($M^{+\bullet}$, 1%).

Anal. Calcd. for $C_{25}H_{20}O_5$: C, 74.99; H, 5.03. Found: C, 74.63; H, 5.01.

Methyl (3-Benzoyl-2-phenyl-4-oxo-4*H*-1-benzopyran-8-yl)-acetate (**20**).

The solution of 2.00 g (5.0 mmoles) of **19** and 2.00 g (18.0 mmoles) of sublimed selenium dioxide in 30 ml DMSO was heated to 120°C in an oil bath for 70 minutes. After cooling to room temperature, the mixture was filtered and added to 200 g of crushed ice. The precipitate was collected, dissolved in chloroform and purified by flash chromatography with chloroform/ethyl acetate (9+1) to provide the title compound as a white solid (1.48 g, 75%), mp 157°C; ir (potassium bromide): ν 1734 (COOR), 1671, 1628 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.64 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 7.44-7.67 (m, 9H, aromatic H), 7.88 (d, J = 7.2 Hz, 1H, aromatic H), 7.93 (d, J = 7.3 Hz, 2H, aromatic H), 8.01 (d, J = 6.7 Hz, 1H, aromatic H); ms: (70 eV) m/z = 398 ($M^{+\bullet}$, 50%).

Anal. Calcd. for $C_{25}H_{18}O_5$: C, 75.37; H, 4.55. Found: C, 75.48; H, 4.67.

Methyl [3-(3-Benzylamino-3-phenyl-2-propenon-1-yl)-2-hydroxyphenyl]acetate (**21**).

A solution of 1.0 g (2.51 mmoles) **20** in 20 ml of toluene was treated with 538 mg (5.02 mmoles) freshly distilled benzylamine and warmed to reflux for 14 hours. After cooling, the solvent was removed and the oily residue was purified by flash chromatography with chloroform/ethyl acetate (9+1). The product was recrystallized from *n*-hexane/dichloromethane to provide the title compound as a yellow solid (490 mg, 49%); mp 99°C (*n*-hexane/dichloromethane); ir (potassium bromide): ν 3426 (NH),1731 (COOR), 1599 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): d 3.60 (s, 3H, CH_3), 3.62 (s, 2H, 2-H), 4.49 (d, J = 6.2 Hz, 2H, CH_2 benzyl), 5.91 (s, 1H, CH), 6.74-7.77 (m, 13H, aromatic H), 11.17 (t, J = 5.9 Hz, 1H, NH), 13.93 (s, 1H, OH); ms: (70 eV) m/z = 401 ($M^{+\bullet}$, 36%).

Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.78; N, 3.49. Found: C, 74.80; H, 5.76; N, 3.56.

Methyl {3-[3-(4-Chlorophenyl)ureidosulfonyl]-2-phenyl-4-oxo-4*H*-1-benzopyran-8-yl}acetate (**22**).

The solution of 305 mg (2.39 mmoles) 4-chloroaniline in 5 ml of anhydrous 1,4-dioxane was added to a stirred solution of 338

mg (2.39 mmoles) of chlorosulfonyl isocyanate in a mixture of 10 ml of anhydrous 1,4-dioxane and 10 ml of anhydrous ether over a 20-minute period and was subsequently cooled in an ice bath. The solution was then stirred for 60 minutes at 20°C, then treated with 960 mg (2.39 mmoles) of **21** as a solid. The mixture was stirred for 90 minutes at 60°C and cooled to room temperature. The solvent was removed *in vacuo*. The residue was purified by flash chromatography with ethyl acetate/formic acid (99+1) as eluent to provide the product as a white solid (630 mg, 50%), mp 107°C; ir (potassium bromide): ν 3401 (NH), 1736 (COOR), 1624 (C=O), 1595, 1536, 1364, 1141 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.55 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 7.32 (d, J = 9.0 Hz, 2H, 2-H, 6-H 4-chlorophenyl), 7.39 (d, J = 9.0 Hz, 2H, 3-H, 5-H, 4-chlorophenyl), 7.54-7.88 (m, 7H, aromatic H), 8.06 (d, J = 6.6 Hz, 1H, 5'-H), 9.01 (s, 1H, NH-3), 10.64 (s br, 1H, NH-1); ms: (FAB negative dimethyl sulfoxide/glycerol) m/z = 525 ([M-H]$^-$, 47%, ^{35}Cl).

Anal. Calcd. for $C_{25}H_{19}CN_2O_7S \cdot 1/2\ H_2O$: C, 56.03; H, 3.76; N, 5.23. Found: C, 55.94; H, 3.80; N, 5.21.

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