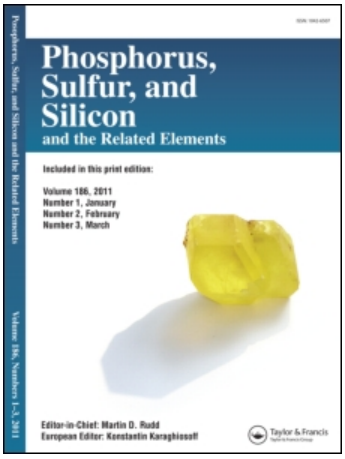

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CHLOROSULFONATION OF FLAVONES

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CHLOROSULFONATION OF FLAVONES

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The chlorosulfonation of flavone and 4′-methoxyflavone with chlorosulfonic acid occurs regioselectively in ring B. The chlorosulfonyl flavones were converted into their corresponding sulfonamides and sulfonates by reaction with alkylamines, anilines, isopropyl alcohol and *p*-chlorophenol. Two-dimensional (COSY and HETCOR) and one-dimensional selective INEPT experiments were carried out in order to unequivocally assign all the signals in the NMR spectra of compounds.

Keywords: chlorosulfonation; flavones; chlorosulfonic acid; sulfonamides; sulfonates

INTRODUCTION

Flavones are a family of compounds abundantly distributed throughout the plant kingdom[1] and are known to exhibit a wide variety of biological activities.[2–4] During the last years, we have been undertaking studies aiming the establishment of new and simple synthetic methods leading to new derivatives of flavones,[5] and other chromones,[5,6] with potential biological activities. As part of that work, we decided to prepare some novel sulfonated derivatives of flavone **1** and 4′-methoxyflavone **2**, for further evaluation of their biological activities. Our interest for this type of derivatives is related to the well-established antibacterial,[7] antifungal,[8] and herbicidal[9] activities of the sulfonyl compounds (namely sulfonamides, sulfonylureas and sulfonylhydrazides).

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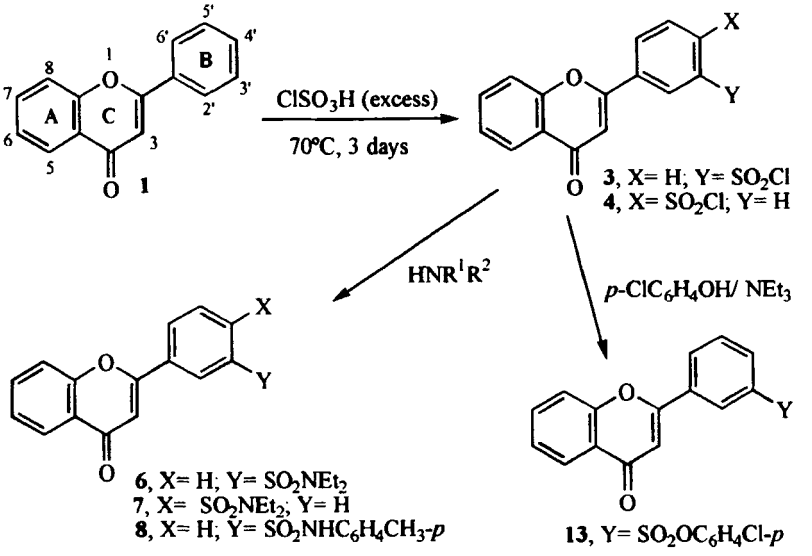
RESULTS AND DISCUSSION

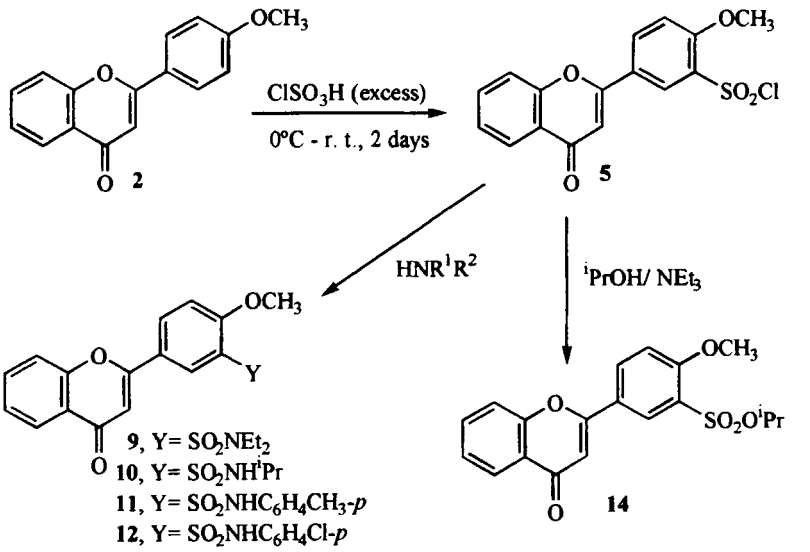
Flavones **1** and **2** were synthesised according to well known procedures.[10] Their chlorosulfonyl derivatives **3–5** were obtained by reaction with chlorosulfonic acid, following a general procedure for the chlorosulfonation of aromatic compounds.[11]

We have found that with flavones **1** and **2** chlorosulfonation occurs exclusively in ring B (Schemes 1and 2). This is, probably, due to the protonation of the carbonyl group and the consequent deactivation of ring A.[12]



SCHEME 1

The presence of the activating 4′-methoxy group in flavone **2** allows this compound to react with chlorosulfonic acid even at 0°C; this exothermic reaction is accompanied with the evolution of hydrogen chloride. As expected, and confirmed by NMR, the chlorosulfonyl group goes only to the 3′-position (78%). Flavone **1** is much less reactive than flavone **2**; its reaction with $ClSO_3H$ at 55 °C during 28 h resulted in the recovery of more than 50% of the starting material. The reaction is complete only after three days at 70 °C. The chlorosulfonation of **1** gives a mixture of the two



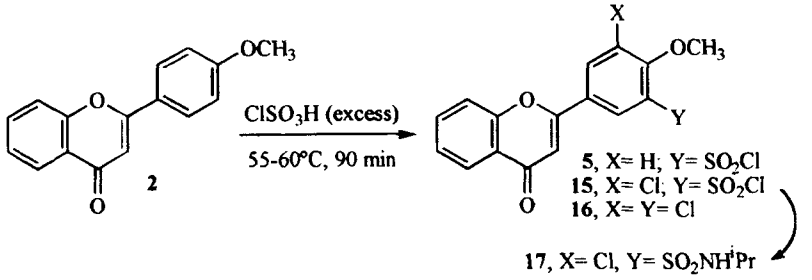
SCHEME 2

regioisomers **3** and **4** (Scheme 1) in approximately 3:1 proportion.[13] These compounds can not be separated by TLC but when left in dichloromethane/hexane, the main isomer **3** crystallises and gives pure, well defined light-brown crystals. The two isomers are easily distinguished by NMR (*vide infra*). The predominant formation of **3** is attributed to the deactivating effect of the α,β-unsaturated carbonyl system.

The sulfonyl chlorides **3–5** were transformed into the corresponding *N*-alkyl and *N*-arylsulfonamides **6–12** and also into alkyl and arylsulfonates **13** and **14.** These transformations occurred under very mild conditions (room temperature to 60 °C) and gave good yields of the desired products. Purification of the products just by crystallisation gave, in most cases, sufficiently pure compounds for characterisation by NMR and MS.

Aiming to increase the yield of the reaction of chlorosulfonation of flavone **2,** we tried to warm it up at 55–60 °C for 90 minutes. Unfortunately, the yield did not improve and, together with the expected sulfonyl chloride **5** (main product), two other minor compounds were formed (Scheme 3). These were separated by preparative TLC and identified as the chlorinated flavones **15** and **16** on the basis of their mass and ^{1}H and ^{13}C NMR spectra. The formation of these halogenated compounds is not a surprising

result since similar chlorination of aromatic compounds with chlorosulfonic acid has already been reported.[14] Treatment of the sulfonyl chloride **15** with excess isopropylamine gave the corresponding sulfonamide **17** in good yield.



SCHEME 3

All new compounds were characterised by ^{1}H and ^{13}C NMR and mass spectrometry. For a complete and unequivocal assignment of all signals in the NMR spectra of the compounds, two-dimensional (COSY and HETCOR) and one-dimensional selective INEPT experiments[15] were carried out. The latter were especially important for the assignment of the resonances of the quaternary carbons.

The signals corresponding to the resonances of H-3 and C-3 atoms are the most characteristic in the ^{1}H and ^{13}C NMR spectra of the flavone derivatives. For the compounds presented in this paper they appear, respectively, at δ 6.74–7.03 and 106.5 – 109.8 ppm.

The distinction between the regioisomers **3** and **4** was easily done by ^{1}H NMR spectroscopy. In the case of 3'-chlorosulfonylflavone **3,** we can observe the proton resonances of a 1,3-disubstituted B ring; the H-2′ appears at δ 8.61 ppm as a triplet (*J* 1.8 Hz) due to the couplings with H-4′ and H-6′ protons. In the ^{1}H NMR spectrum of compound **4** an AB spin system was observed for ring B proton resonances; this is only compatible with a 1,4-disubstitution pattern. In the ^{13}C NMR spectra of the regioisomers **3** and **4,** the carbon bonded to the chlorosulfonyl group appears, respectively, at δ 145.3 and 146.0 ppm. This does not allow a distinction between them.

Detailed analysis of the ^{1}H NMR spectrum of compound **5** confirmed the 1,3,4-substitution pattern in ring B. The H-2′ resonance appears at δ

8.56 ppm as a doublet with a small coupling constant (*J* 2.4 Hz), due to the coupling with H-6′. Its high resonance value is due to the presence of the chlorosulfonyl group in position 3′.

The proton and carbon resonances of the flavone nucleus, for compounds **6–14**, are very similar to those of the above discussed starting materials **3–5**. In the sulfonamide series, the NH proton resonance appears at δ ~5 ppm in the *N*-alkyl-sulfonamide **10** and at δ ~10 ppm for the *N*-aryl derivatives **8**, **11** and **12**.

The structure of the 3′,5′-dichloro-4′-methoxyflavone **16** was deduced on the basis of results obtained by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. Its ^{1}H NMR spectrum shows that ring B has substituents in positions 3′, 4′ and 5′; protons H-2′ and H-6′ appear as a singlet. The mass spectrum of this compound shows parent ions with m/z = 324, 322 and 320 which are compatible with the presence of two chlorine atoms. The structure of compound **15** was deduced from the spectra of sulfonamide **17** (obtained after addition of isopropilamine to the sulfonyl chloride **15**). The mass spectrum shows that only one chlorine atom is present (m/z= 409 and 407); also informative is the fact that in the ^{1}H NMR of this sulfonamide, the H-2′ and H-6′ resonances appear as doublets (*J* 2.3 Hz).

EXPERIMENTAL

NMR spectra were recorded on a Brucker AMX 300 spectrometer. Tetramethylsilane was used as internal standard and $CDCl_3$ as solvent, unless otherwise stated. Coupling constants (*J*) are in Hz. Mass spectra were recorded under electron impact (EI) at 70 eV on a VG AutoSpec-Q instrument. Melting points were determined with a Reichert Thermovar electric apparatus and are uncorrected.

Chlorosulfonation of flavone 1

3′- and 4′-Chlorosulfonylflavone (3 and 4)

Flavone **1** (6.21 g; 28 mmol) was slowly added to ice-cooled chlorosulfonic acid (11.2 ml; 0.17 mol) with constant stirring. The reaction mixture was allowed to warm up to room temperature and then left for three days at 70 °C, with constant stirring and protected from moisture. The mixture

was then slowly and carefully poured onto crushed ice, with stirring. The precipitate was filtered off and washed with cold water. The solid was dissolved in chloroform, the organic solution was washed with water and dried (Na_2SO_4). After concentration, the sulfonyl chlorides were precipitated with petroleum ether (5.5 g; 62.4%). The two isomers were then separated by slow crystallisation in dichloromethane/ petroleum ether.

3′-Chlorosulfonylflavone, **3: m.p.** 142–145°C; **^{1}H NMR** δ 6.92 (H-3, s), 7.48 (H-6, ddd, *J* = 7.7, 7.5 and 1.0), 7.65 (H-8, dd, *J*= 8.0 and 1.0), 7.76 (H-7, ddd, *J*= 8.0, 7.7 and 1.8), 7.84 (H-5′, t, *J*= 8.0), 8.19–8.29 (H-4′,5,6′, m), 8.61 (H-2′, t, *J*=1.8); **^{13}C NMR** δ 109.0 (C-3), 118.2 (C-8), 123.8 (C-10), 124.6 (C-2′), 125.8 (C-5,6), 129.2 (C-6′), 130.6 (C-5′), 132.4 (C-4′), 133.9 (C-1′), 134.4 (C-7), 145.3 (C-3′), 156.1 (C-9), 160.1 (C-2), 177.9 (C-4); **MS (EI)** m/z (rel. int.) 322 ($M^{+\cdot}$, ^{37}Cl; 62), 320 ($M^{+\cdot}$, ^{35}Cl; 100), 294 (27), 292 (53), 285 (20), 222 (71), 221 (45), 194 (18), 193 (22), 165 (49), 120 (74), 92 (70).

4′-Chlorosulfonylflavone, **4** (calculated from the spectra of a 1 : 1 mixture with isomer **3**) **^{1}H NMR** δ 6.94 (H-3, s), 7.48 (H-6, dd, *J* = 7.8 and 7.6), 7.62 (H-8, d, *J* = 8.2), 7.78 (H-7, ddd, *J*= 8.2, 7.8 and 1.6), 8.18 (H-3′, 5′, d, *J*= 8.3), 8.22 (H-2′, 6′, d, *J*= 8.3), 8.24 (H-5, d, *J*= 7.6); **^{13}C NMR** δ 109.8 (C-3), 118.1 (C-8), 123.8 (C-10), 125.8 (C-5,6), 127.4 (C-3′,5′), 127.7 (C-2′,6′), 134.5 (C-7), 138.2 (C-1′), 146.0 (C-4′), 156.1 (C-9), 160.2 (C-2), 177.9 (C-4).

Chlorosulfonation of flavone 2

3′-Chlorosulfonyl-4′-methoxyflavone, 5

Flavone **2** (4.59 g; 18 mmol) was slowly added to ice-cooled chlorosulfonic acid (7.3 ml; 0.11 mol) with constant stirring. As HCl evolved from the reaction mixture this was allowed to warm up to room temperature and left for two days (protected from moisture). The mixture was then slowly and carefully poured onto crushed ice, with constant stirring. The precipitate was filtered off and washed with cold water. The solid was dissolved in chloroform, the organic solution was washed with water and dried (Na_2SO_4). After concentration, the sulfonyl chloride was precipitated with petroleum ether. The product (4.93 g; 78%) was used in the subsequent reactions without further purification. Cream powder, **m.p.** 197–200 °C; **^{1}H NMR** δ 4.18 (OCH_3, s), 6.79 (H-3, s), 7.30 (H-5′, d, *J*= 8.9), 7.45

(H-6, ddd, *J*= 7.7, 7.6 and 1.0), 7.61 (H-8, d, *J* = 7.8), 7.74 (H-7, ddd, *J* = 7.8, 7.6 and 1.7), 8.20 (H-6′, dd, *J*= 8.9 and 2.4), 8.22 (H-5, dd, *J*= 7.7 and 1.7), 8.56 (H-2′, d, *J*= 2.4 Hz); **^{13}C NMR** δ 57.2 (OCH_3), 107.5 (C-3), 113.9 (C-5′), 118.1 (C-8), 123.8 (C-10), 124.2 (C-1′), 125.6 (C-6), 125.7 (C-5), 127.9 (C-2′), 132.4 (C-3′), 134.1 (C-6′), 134.6 (C-7), 156.0 (C-9), 159.2 (C-4′), 160.5 (C-2), 177.9 (C-4); **MS (EI)** m/z (rel. int) 352 ($M^{+\cdot}$, ^{37}Cl; 61), 350 ($M^{+\cdot}$, ^{35}Cl; 100), 322 (12), 315 (10), 252 (34), 251 (22), 236 (15), 221 (33), 165 (19), 132 (18), 120 (68), 116 (20), 104 (18), 101 (12), 92 (50).

Reaction of the Sulfonyl Chlorides with Amines Typical Procedure

3′-N-Isopropylsulfamoyl-4′-methoxyflavone, 10

Isopropylamine (0.5 ml; 5.8 mmol) was slowly added to a solution of the sulfonyl chloride **5** (0.35 g; 1 mmol) in acetonitrile (15 ml) at 0 °C. The mixture was stirred at this temperature for one hour and then for two hours at room temperature. The mixture was then poured onto crushed ice, with constant stirring. The precipitate was filtered off and washed with cold water. The solid was dissolved in chloroform and the organic solution was washed with water. The solvent was evaporated and the sulfonamide was recrystallized from methanol. Yellowish crystals (0.35 g; 94%), **m.p.** 180–183 °C; **^{1}H NMR** δ 1.11 (CH_3, d, *J* = 7.1), 3.49 [$CH(CH_3)_2$, oct, *J*= 7.1], 4.10 (s, OCH_3), 4.97 (NH, d, *J*= 7.1), 6.82 (H-3, s), 7.20 (H-5′, d, *J*= 8.8), 7.44 (H-6, ddd, *J*= 7.7, 7.6 and 0.9), 7.61 (H-8, d, *J*= 7.8), 7.73 (H-7, ddd, *J*= 7.8, 7.6 and 1.6), 8.09 (H-6′, dd, *J* = 8.8 and 2.4), 8.22 (H-5, dd, *J* = 7.7 and 1.6), 8.55 (H-2′, d, *J*= 2.4); **^{13}C NMR** δ 23.6 (CH_3), 46.5 (CH), 56.7 (OCH_3), 107.2 (C-3), 112.7 (C-5′), 118.1 (C-8), 123.8 (C-10), 124.4 (C-1′), 125.4 (C-6), 125.6 (C-5), 128.2 (C-2′), 129.6 (C-3′), 132.1 (C-6′), 133.9 (C-7), 156.1 (C-9), 158.3 (C-4′), 161.6 (C-2), 178.2 (C-4); **MS (EI)** m/z (rel. int.) 373 ($M^{+\cdot}$, 92), 358 (100), 315 (37), 252 (13), 251 (48), 236 (25), 223 (13), 221 (43), 179 (10), 165 (14), 121 (13), 120 (11), 116 (22), 104 (10), 92 (20).

3′-N,N-Diethylsulfamoylflavone, 6

Yield= 75%; **m.p.** 153–155 °C; **^{1}H NMR** δ 1.18 (CH_3, t, *J*= 7.1), 3.32 (CH_2, q, *J*= 7.1), 6.88 (H-3, s), 7.46 (H-6, ddd, *J*= 7.9, 7.6 and 0.9), 7.62 (H-8, d, *J*= 8.0), 7.75 (H-7, ddd, *J* = 8.0, 7.6 and 1.6), 7.69 (H-5′, dd, *J*=

7.9 and 7.6), 7.98 (H-6′, ddd, *J*= 7.9, 1.6 and 1.0), 8.09 (H-4′, ddd, *J*= 7.6, 1.6 and 1.0), 8.24 (H-5, dd, *J*= 7.7 and 1.6), 8.38 (H-2′, t, *J*= 1.6); **^{13}C NMR** δ 14.1 (CH_3), 42.1 (CH_2), 108.5 (C-3), 118.1 (C-8), 123.8 (C-10), 124.6 (C-2′), 125.5 (C-6), 125.7 (C-5), 129.5 (C-6′), 129.6 (C-4′), 129.9 (C-5′), 133.0 (C-1′), 134.1 (C-7), 141.8 (C-3′), 156.1 (C-9), 161.4 (C-2), 178.1 (C-4); **MS (EI)** m/z (rel. int.) 357 ($M^{+\cdot}$, 40), 344 (19), 343 (39), 342 (100), 285 (28), 221 (82), 220 (37), 193 (14), 171 (11), 165 (37), 120 (10), 101 (9), 92 (23); **Anal.** calcd. for $C_{19}H_{19}O_4NS$: C, 63.85; H, 5.36; N, 3.92; S, 8.97; found: C, 63.68; H, 5.38; N, 3.97; S, 8.70.

4′-N,N-Diethylsulfamoylflavone, 7

Yield= 82%; **m.p.** 173–175 °C; **^{1}H NMR** δ 1.17 (CH_3, t, *J* = 7.2), 3.30 (CH_2, q, *J* = 7.2), 6.89 (H-3, s), 7.47 (H-6, dd, *J*=7.9 and 7.5), 7.60 (H-8, d, *J*= 8.0), 7.75 (H-7, ddd, *J* = 8.0, 7.5 and 1.6), 7.97 (H-2′,6′, d, *J*= 8.6), 8.06 (H-3′,5′, d, *J*= 8.6), 8.25 (H-5, dd, *J* = 7.9 and 1.6); **^{13}C NMR** δ 14.2 (CH_3), 42.1 (CH_2), 108.9 (C-3), 118.1 (C-8), 123.9 (C-10), 125.6 (C-6), 125.8 (C-5), 126.9 (C-3′,5′), 127.6 (C-2′,6′), 134.2 (C-7), 135.3 (C-1′), 143.1 (C-4′), 156.2 (C-9), 161.4 (C-2), 178.2 (C-4); **MS (EI)** m/z (rel. int.) 357 ($M^{+\cdot}$, 47), 344 (20), 343 (42), 342 (100), 285 (37), 221 (97), 220 (43), 193 (17), 171 (11), 165 (48), 120 (13), 101 (10), 92 (25); **Anal.** calcd. for $C_{19}H_{19}O_4NS$; C, 63.85; H, 5.36; N, 3.92; S, 8.97; found: C, 63.69; H, 5.25; N, 4.03; S, 8.64.

3′-N-(p-Methylphenyl)sulfamoylflavone, 8

Yield= 60%; **m.p.** 254–257 °C; **^{1}H NMR** (DMSO-d_6) δ 2.15 (4′′-CH_3, s), 7.03 (H-3, s), 7.04 (H-2′′,3′′,5′′,6′′, s), 7.50 (H-6, dd, *J* = 7.6 and 7.4), 7.71 (H-8, d, *J* = 7.9), 7.72 (H-5′, dd, *J*= 8.1 and 7.4), 7.85 (H-7, ddd, *J* = 7.9, 7.4 and 1.6), 7.90 (H-6′, d, *J*= 7.4), 8.04 (H-5, dd, *J*= 7.6 and 1.6), 8.29 (H-4′, δ, *J*= 8.1), 8.34 (H-2′, s broad); **^{13}C NMR** (DMSO-d_6) δ 20.3 (4′′-CH_3), 108.0 (C-3), 118.4 (C-8), 121.2 (C-2′′,6′′), 123.3 (C-10), 124.0 (C-2′), 124.9 (C-5), 125.7 (C-6), 129.4 (C-6′), 129.7 (C-3′′,5′′), 130.2 (C-5′), 130.6 (C-4′), 132.2 (C-4′′), 134.0 (C-1′), 134.6 (C-7), 134.7 (C-1′′), 140.5 (C-3′), 155.6 (C-9), 160.8 (C-2), 177.0 (C-4); **MS (EI)** m/z (rel. int.) 391 ($M^{+\cdot}$, 15), 222 (51), 165 (13), 106 (100), 92 (16).

3′-N,N-Diethylsulfamoyl-4′-methoxyflavone, 9

Yield= 60%; **m.p.** 170–172°C; **^{1}H NMR** δ 1.15 (CH_3, t, *J*= 7.1), 3.40 (CH_2, q, *J*= 7.1), 4.04 (OCH_3, s), 6.79 (H-3, s), 7.16 (H-5′, d, *J*= 8.8), 7.43

(H-6, ddd, J = 7.7, 7.6 and 1.0), 7.61 (H-8, d, J= 7.9), 7.72 (H-7, ddd, J= 7.9, 7.6 and 1.6), 8.05 (H-6′, dd, J= 8.8 and 2.4), 8.21 (H-5, dd, J = 7.7 and 1.6), 8.55 (H-2′, d, J = 2.4); **^{13}C NMR** δ 14.2 (CH_3), 44.8 (CH_2), 56.3 (OCH_3), 106.9 (C-3), 112.5 (C-5′), 118.1 (C-8), 123.7 (C-10), 123.8 (C-1′), 125.3 (C-6), 125.5 (C-5), 129.3 (C-2′), 130.0 (C-3′), 131.8 (C-6′), 133.8 (C-7), 156.0 (C-9), 158.8 (C-4′), 161.7 (C-2), 178.1 (C-4); **MS (EI)** m/z (rel. int.) 387 ($M^{+\cdot}$, 61), 373 (23), 372 (100), 315 (30), 252 (13), 251 (46), 236 (25), 223 (13), 221 (41), 208 (9), 165 (15), 121 (10), 120 (10), 116 (20), 92 (50); **Anal.** calcd. for $C_{20}H_{21}O_5NS$: C, 62.00; H, 5.46; N, 3.62; found: C, 61.61; H, 5.29; N 3.31

3′-N-(p-Methylphenyl)sulfamoyl-4′-methoxyflavone, 11

Yield= 53%; **m.p.** 253–257 °C; **^{1}H NMR** (DMSO-d_6) δ 2.12 (CH_3, s), 4.00 (OCH_3, s), 6.96 (H-3, s), 6.89 and 7.04 (AB, H-3″,5″ and H-2″,6″, J= 8.7), 7.35 (H-5′, d, J= 8.8), 7.48 (H-6, ddd, J= 7.6, 7.5 and 0.9), 7.74 (H-8, d, J= 7.7), 7.81 (H-7, ddd, J= 7.7, 7.5 and 1.3), 8.02 (H-5, dd, J= 7.7 and 1.3), 8.28 (H-6′, dd, J= 8.8 and 2.3), 8.33 (H-2′, d, J= 2.3), 10.05 (s broad, NH); **^{13}C NMR** (DMSO-d_6) δ 20.3 (4″-CH_3), 56.8 (OCH_3), 106.5 (C-3), 113.7 (C-5′), 118.5 (C-8), 120.4 (C-2″,6″), 122.9 (C-10), 123.2 (C-1′), 124.8 (C-5), 125.6 (C-6), 127.2 (C-3′), 127.8 (C-2′), 129.5 (C-3″,5″), 133.2 (C-6′), 133.3 (C-4″), 134.3 (C-7), 134.8 (C-1″), 155.5 (C-9), 158.7 (C-4′), 161.1 (C-2), 176.9 (C-4); **MS (EI)** m/z (rel. int.) 421 ($M^{+\cdot}$, 35), 252 (31), 251 (46), 223 (35), 222 (14), 221 (10), 165 (10), 120 (10), 107 (16), 106 (100), 92 (13); **Anal.** calcd. for $C_{23}H_{19}O_5NS.1/4\ H_2O$: C, 64.85; H, 4.61; N, 3.29; S, 7.53; found: C, 64.82; H, 4.31; N 3.40; S, 7.47.

3′-N-(p-Chlorophenyl)sulfamoyl-4′-methoxyflavone, 12

Yield= 68%; **m.p.** 157–159 °C; **^{1}H NMR** (DMSO-d_6) δ 3.98 (OCH_3, s), 7.00 (H-3, s), 7.15 (H-2″, 6″, d, J = 8.9), 7.27 (H-3″, 5″, d, J= 8.9), 7.36 (H-5′, d, J = 8.9), 7.49 (H-6, ddd, J= 7.6, 7.5 and 1.2), 7.76 (H-8, d, J= 7.5), 7.82 (H-7, dt, J= 7.5 and 1.4), 8.03 (H-5, dd, J=7.6 and 1.4), 8.31 (H-6′, dd, J = 8.9 and 2.3), 8.38 (H-2′, d, J = 2.3), 10.41 (NH, s broad,); **^{13}C NMR** (DMSO-d_6) δ 56.8 (OCH_3), 106.6 (C-3), 113.9 (C-5′), 118.5 (C-8), 121.2 (C-2″,6″), 123.1 (C-1′), 123.3 (C-10), 124.8 (C-5), 125.9 (C-6), 126.9 (C-3′), 127.9 (C-4′), 128.0 (C-2′), 129.1 (C-3″,5″), 133.5 (C-6′), 134.3 (C-7), 136.6 (C-1″), 155.6 (C-9), 158.7 (C-4′), 161.0 (C-2), 176.9 (C-4); **MS (EI)** m/z (rel. int.) 443 ($M^{+\cdot}$, ^{37}Cl; 67), 441 ($M^{+\cdot}$, ^{35}Cl;

100), 377 (12), 376 (10), 346 (18), 327 (10), 315 (16), 252 (33), 251 (64), 239 (21), 236 (32), 223 (25), 222 (15), 221 (65), 208 (16), 193 (10), 165 (32), 140 (14), 132 (14), 128 (38), 127 (36), 126 (82), 121 (30), 120 (17), 116 (34), 101 (27), 99 (41), 92 (38).

3'-Chloro-5'-N-isopropylsulfamoyl-4'-methoxyflavone, 17

m.p. 187–189 °C; **^{1}H NMR** δ 1.11 (CH_3, d, *J*= 7.0), 3.52 [CH(CH_3)$_2$, oct, *J*= 7.0], 4.15 (s, OCH_3), 4.87 (NH, d, *J*= 7.0), 6.83 (H-3, s), 7.46 (H-6, ddd, *J*= 7.7, 7.6 and 1.1), 7.63 (H-8, dd, *J*= 7.9 and 1.1), 7.75 (H-7, ddd, *J*= 7.9, 7.6 and 1.7), 8.13 (H-6', d, *J*= 2.3), 8.24 (H-5, dd, *J*= 7.7 and 1.7), 8.39 (H-2', d, *J*= 2.3); **^{13}C NMR** δ 23.6 and 23.7 (*C*H$_3$), 46.9 (*C*H), 62.8 (O*C*H$_3$), 108.5 (C-3), 118.5 (C-8), 123.8 (C-10), 125.7 (C-5,6), 125.8 (C-2'), 128.8 (C-1'), 130.2 (C-3'), 132.4 (C-6'), 134.2 (C-7), 137.6 (C-5'), 155.4 (C-4'), 156.1 (C-9), 160.1 (C-2), 177.9 (C-4); **MS (EI)** m/z (rel. int.) 409 ($M^{+\cdot}$, ^{37}Cl; 68), 407 ($M^{+\cdot}$, ^{35}Cl; 68), 394 (67), 393 (48), 392 (100), 349 (15), 287 (34), 286 (23), 285 (77), 270 (10), 257 (22), 255 (24) 221 (16), 220 (19), 199 (10), 196 (15), 192 (25), 163 (10), 150 (25), 135 (10), 122 (12), 121 (48), 120 (22), 99 (10), 92 (39).

3',5'-Dichloro-4'-methoxyflavone, 16

m.p. 199–202 °C; **^{1}H NMR** δ 3.99 (s, OCH_3), 6.74 (H-3, s), 7.44 (H-6, ddd, *J*= 7.6, 7.3 and 0.9), 7.58 (H-8, dd, *J*= 8.1 and 0.9), 7.73 (H-7, ddd, *J*= 8.1, 7.6 and 1.6), 7.86 (H-2',6', s), 8.22 (H-5, dd, *J*= 7.3 and 1.6); **^{13}C NMR** δ 61.0 (O*C*H$_3$), 108.1 (C-3), 118.1 (C-8), 123.8 (C-10), 125.6 (C-6), 125.8 (C-5), 126.7 (C-2',6'), 129.0 (C-1'), 130.4 (C-3',5'), 134.1 (C-7), 154.8 (C-4'), 156.1 (C-9), 160.3 (C-2), 178.0 (C-4); **MS (EI)** m/z (rel. int.) 324 ($M^{+\cdot}$, 2 x ^{37}Cl; 24), 322 ($M^{+\cdot}$, ^{37}Cl^{35}Cl; 76), 320 ($M^{+\cdot}$, 2 × ^{35}Cl; 100), 305 (10), 279 (26), 277 (38), 249 (10), 202 (14), 200 (23), 187 (10), 185 (15), 157 (10), 120 (47), 92 (36).

Reaction of the Sulfonyl Chlorides with Phenols

3'-(p-Chlorophenoxy)sulfonylflavone, 13

A mixture of the sulfonyl chloride **3** (0.48 g; 1.5 mmol), 4-chlorophenol (0.24 g; 1.87 mmol) and triethylamine (2 ml; 14.4 mmol) in acetonitrile (10 ml) was stirred for one hour at room temperature and then at 55–60 °C for an extra hour. After cooling to room temperature, the reaction mixture

was then poured onto crushed ice, with constant stirring. The precipitate was filtered off and washed with cold water The solid was dissolved in chloroform and the organic solution was washed with water. The solvent was evaporated and the sulfonate was recrystallized from methanol. Cream crystals (0.4 g; 64.5%), **m.p.** 158–163 °C; **^{1}H NMR** δ 6.86 (H-3, s), 6.99 (H-2″,6″, d, *J* = 8.9), 7.30 (H-3″,5″, d, *J* = 8.9), 7.47 (H-6, ddd, *J* = 7.8, 7.5 and 0.9), 7.60 (H-8, d, *J* = 7.9), 7.74 (H-5′, dd, *J* = 8.6 and 7.8), 7.76 (H-7, ddd, *J* = 7.9, 7.5 and 1.6), 7.98 (H-6′, dd, *J*= 7.8 and 1.6), 8.21 (H-4′, dd, *J*= 8.6 and 1.5), 8.24 (H-5, dd, *J*= 7.8 and 1.6), 8.41 (H-2′, dd, *J*= 1.6 and 1.5); **^{13}C NMR** δ 108.8 (C-3), 118.2 (C-8), 123.7 (C-2″,6″), 123.9 (C-10), 126.0 (C-2′), 125.7 (C-6), 125.8 (C-5), 130.0 (C-3″,5″), 130.2 (C-5′), 130.9 (C-6′), 131.7 (C-4′), 133.2 (C-1′), 133.4 (C-1″), 134.3 (C-7), 136.4 (C-4′), 147.7 (C-3′), 156.1 (C-9), 160.5 (C-2), 178.0 (C-4).

3′-Isopropoxysulfonyl–4′-methoxyflavone, 14

Sodium metal (46 mg; 2 mmol atoms) was added to isopropyl alcohol (10 ml). After all sodium had reacted, sulfonyl chloride **5** (0.35 g; 1 mmol) was added to this solution. The resulting suspension was stirred at room temperature for five hours. The reaction mixture was then poured onto crushed ice, with constant stirring. After a few minutes a precipitate was formed; it was filtered off and washed with cold water. The solid was dissolved in chloroform, the organic solution was washed with water and then it was dried (Na_2SO_4). Part of the solvent was evaporated and the sulphonate was recrystallized from dichloromethane/petroleum ether. Cream crystals (0.1 g; 27%), **m.p.** 161–163 °C; **^{1}H NMR** δ 1.37 (CH_3, d, *J*= 6.2), 4.08 (OCH_3, s), 4.92 [$CH(CH_3)_2$, hep, *J*= 6.2 Hz], 6.80 (H-3, s), 7.21 (H-5′, d, *J* = 8.8), 7.44 (H-6, dd, *J*= 7.8 and 7.5), 7.61 (H-8, d, *J*= 8.0), 7.73 (H-7, ddd, *J*= 8.0, 7.5 and 1.5), 8.12 (H-6′, dd, *J* = 8.8 and 2.3), 8.23 (H-5, d, *J* = 7.8), 8.56 (H-2′, d, *J* = 2.3); **^{13}C NMR** δ 22.9 (CH_3), 56.7 (OCH_3), 78.4 (CH), 107.2 (C-3), 113.0 (C-5′), 118.1 (C-8), 123.8 (C-10), 124.1 (C-1′), 125.5 (C-6), 125.7 (C-5), 126.3 (C-3′), 129.3 (C-2′), 133.1 (C-6′), 134.0 (C-7), 156.1 (C-9), 159.5 (C-4′), 161.3 (C-2), 178.1 (C-4); **MS (EI)** m/z (rel. int.) 374 ($M^{+\cdot}$, 42), 334 (19), 333 (40), 332 (100), 331 (10), 315 (10), 304 (22), 251 (10), 221 (15), 212 (13), 165 (13), 121 (14), 120 (39), 116 (15), 104 (12), 92 (35).

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