Preparation and crystal structure of genistein benzenesulfonate prodrugs

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In order to improve bioavailability and anticancer activity of genistein, a series of novel sulfonic acid ester prodrugs of the isoflavone genistein were synthesised in high yield with excellent regioselectivity. Their structures were characterised by IR, MS, elemental analysis and ^{1}H NMR spectra. The crystal structure was examined by X-ray diffraction. X-ray structure determination revealed that all the aromatic rings in the compound are not coplanar. In the crystal structure, molecules are linked through intermolecular C–H···O hydrogen bonds, forming layers parallel to the *ab* plane.

Keywords: synthesis, pro-drug, sulfonic acid ester, crystal structure, hydrogen bonding

Genistein, a natural kudzuvine root isoflavone, possesses many biological activities such as phytoestrogen,[1] antidysrhythmic[2] and antioxidant.[3,4] Especially, it is arousing infinite interests in the world because it can restrain manifold cancer cells.[5] Unfortunately, its poor lipophilicity and first pass effect will result to weak bioavailability due to three polar hydroxyls.[6] Accordingly, we have developed a program to prepare isoflavone analogues.[7] The title compounds, **3**–**9** are prodrugs of genistein with potential anticancer activities. In order to further improve the bioavailability and biological activity of the genistein and study metabolic mechanism of its derivatives, we now present the first chemical synthesis of its sulfonic acid esters and crystal structure of its analogue **9**. X-ray structure determination revealed that all the aromatic rings in the compound are not coplanar with each other. In the crystal structure **9** (a = 14.802(3) Å, b = 6.088(2) Å, c = 28.648(6) Å, $\alpha = \beta = \gamma = 90^o$, V = 2581.6(9) Å^3, Z = 4, space group $Pca2_1$), molecules are linked through intermolecular C–H···O hydrogen bonds, forming layers parallel to the *ab* plane.

Yellow block crystals suitable for single crystal X-ray diffraction were obtained by slow evaporation of the solvent from CH_2Cl_2 solution. A single crystal selected for investigation had dimensions of 0.28 mm × 0.27 mm × 0.27 mm. Figure 1 gives a perspective view of the molecular structure of compound **9** with the atomic labelling system. Selected bond lengths and angles are summarised in Table 1. The compound is composed of three aromatic rings and a chromen ring, C1–C6 (A), C7–C15/O6 (B), C17–C22 (C), C23–C28 (D), a methoxy moiety, and two bridging SO_3 moieties. All the bond lengths and angles in the compound are within normal ranges.[8] To avoid steric conflicts, the rings B and C are not coplanar, with the dihedral angle of 51.6(2)^o. The C16 atom deviates from the parent ring B by 0.486(2) Å. As expected, each S atom is located at the centre of the tetrahedral geometry. The bond angles subtended at the S1 and S2 atoms are ranged from 102.1(2)–121.0(2)^o and 100.0(2)–118.0(2)^o, respectively, indicating that the tetrahedral geometries are deviated from the ideal tetrahedral configurations. The dihedral angle between the rings A and B is 43.6(3)^o, and that between rings C and D is 11.6(3)^o. The torsion angles C1–S1–O3–C7 and C20–O7–S2–C23 are 65.9(2)^o and 11.2(2)^o, respectively. In the crystal structure, molecules are linked through intermolecular C–H···O hydrogen bonds, forming layers parallel to the *ab* plane (Fig.2). Hydrogen bonds are listed in Table 2.

In addition, relatively shorter centroid distances (Table 3) among the rings are observed, implying the existence of π–π stacking interactions in the compound.

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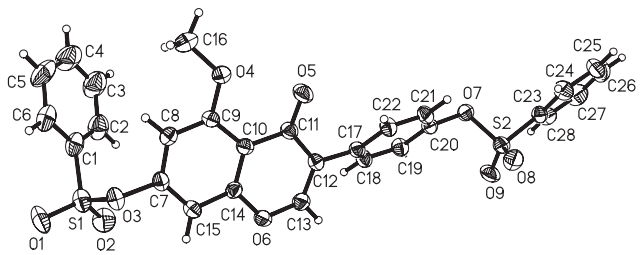


Fig. 1 Molecular structure of **9**. Displacement ellipsoids are plotted at the 30% probability level.

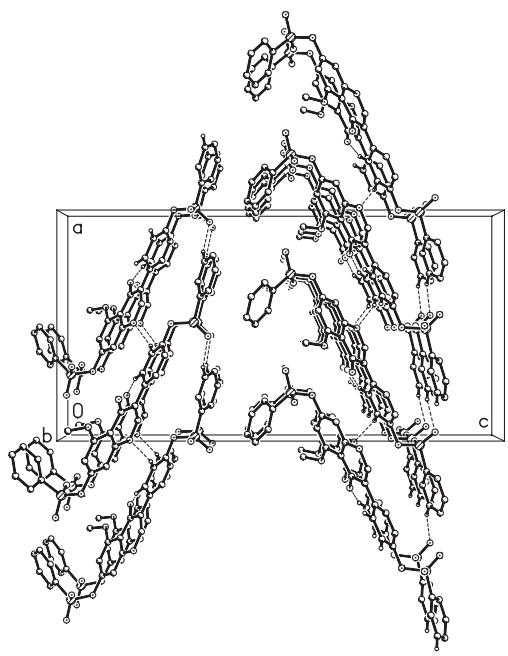


Fig. 2 Molecular packing of **9**, viewed along the *b* axis. Hydrogen bonds are shown as dashed lines.

The possible main reason of the poor bioavailability of genistein is its first pass effect *in vivo*. Consequently, in this experiment in order to enhance bioavailability of genistein, its 7-hydroxyl was esterified for stopping the first pass effect according to the prodrug barnbuterol of terbutaline design idea.[10]

Despite the acidity of 7-OH in the genistein exhibits a hundred-fold compared to the 4'-hydroxy group and 5-OH is stabilised by hydrogen-bond,[10] we tried to use different equivalent of acyl chloride by using pyridine as base and CH_2Cl_2 as solvent at low temperature, the major product

Table 1 Selected bond distances (Å) and angles (°) for **3**

Bond distances			
S1–O2	1.421(3)	S1–O1	1.422(3)
S1–O3	1.594(3)	S1–C1	1.762(5)
S2–O8	1.421(3)	S2–O9	1.423(3)
S2–O7	1.589(2)	S2–C23	1.736(4)
O3–C7	1.432(4)	O4–C9	1.362(4)
O4–C16	1.418(4)	O5–C11	1.228(4)
O6–C13	1.356(4)	O6–C14	1.373(4)
O7–C20	1.439(4)	C12–C17	1.477(5)
Bond angles			
O2–S1–O1	121.0(2)	O2–S1–O3	109.9(2)
O1–S1–O3	102.9(2)	O2–S1–C1	108.7(2)
O1–S1–C1	110.5(2)	O3–S1–C1	102.1(2)
O8–S2–O9	118.0(2)	O8–S2–O7	109.2(2)
O9–S2–O7	108.8(2)	O8–S2–C23	110.2(2)
O9–S2–C23	109.2(2)	O7–S2–C23	100.0(2)
C7–O3–S1	117.5(2)	C9–O4–C16	119.4(3)
C13–O6–C14	117.4(3)	C20–O7–S2	115.0(2)
C2–C1–S1	119.6(4)	C6–C1–S1	118.2(4)
C15–C7–O3	118.7(3)	C8–C7–O3	116.8(3)
O4–C9–C8	122.9(4)	O4–C9–C10	116.3(3)
O5–C11–C10	124.2(4)	O5–C11–C12	120.8(3)
C13–C12–C17	120.4(3)	C11–C12–C17	121.3(3)
C22–C17–C12	121.0(3)	C18–C17–C12	120.1(3)
C19–C20–O7	119.5(3)	C21–C20–O7	118.0(3)
C28–C23–S2	119.8(3)	C24–C23–S2	119.0(3)

Table 2 Geometrical parameters for hydrogen bonds for **3**

Hydrogen bonds	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
C2–H2···O2	0.93	2.55	2.917(3)	104
C18–H18···O5$^{\#1}$	0.93	2.31	3.212(3)	163
C19–H19···O6$^{\#2}$	0.93	2.53	3.404(3)	156
C22–H22···O5	0.93	2.58	2.942(3)	104
C27–H27···O8$^{\#2}$	0.93	2.54	3.435(3)	163
C28–H28···O9	0.93	2.54	2.900(3)	104

$^{\#1}$ x, 1 + y, z, $^{\#2}$ –1/2 + x, 2 – y, z

isoflavone 4',5,7-triesters **3** formed. When we controlled the reaction condition using different equivalent of acyl chloride of benzenesulfonyl chloride in THF solvent system, the compounds **4** and **5** formed in high yields respectively. Possibly, the solvent effect resulted to the good regioselectivity.

The title compound **6** was synthesised by ethylation from the compound **4**. We use excess diethyl sulfate (10 fold equiv.), the title compound **6** is the only product and 4',5-diethyl-7-phenylsulfonylgenistein cannot be obtained. The hydrogen-bond stabilised 5-hydroxy group in genistein might not react at 0 °C. When we improved the reaction temperature, the compound **4** undergo desulfonate and ethylation of all hydroxyl. The results showed that the effect of hydrogen-bond stabilisation exceeds activity of alkylation rection of 5-hydroxy group in genistein. Also we cannot obtain the ethylation product of **5**. If we improve the reaction temperature for the reaction of **5** and diethylsulfate, byproduct 4',5,7-triethylgenistein formed alike.

The title compounds were synthesised with high yield and high regioselectivity as shown in Scheme 1. The studies on the solubility and lipid/water partition coefficient log *P* of the title compounds are in progress.

Experimental

^{1}H NMR spectra was recorded in $CDCl_3$ on Varian INOVA 400 MHz spectrometer, using TMS as internal standard. FT-IR spectra were recorded on a Nicocet 5700 FT-IR spectrophotometer. MS spectra were recorded on a Waters ZQ4000/2695 micromass. Melting points were determined with a WARR Melting Point Apparatus and are uncorrected. The crystal structure was determined using a Bruker SMART CCD area-detector diffractometer. Elemental analysis was performed by Central Service of Nanchang University, People's Republic of China, and the result was found to be within ±0.3% of predicted values for compounds **3**–**9**.

Synthetic procedure

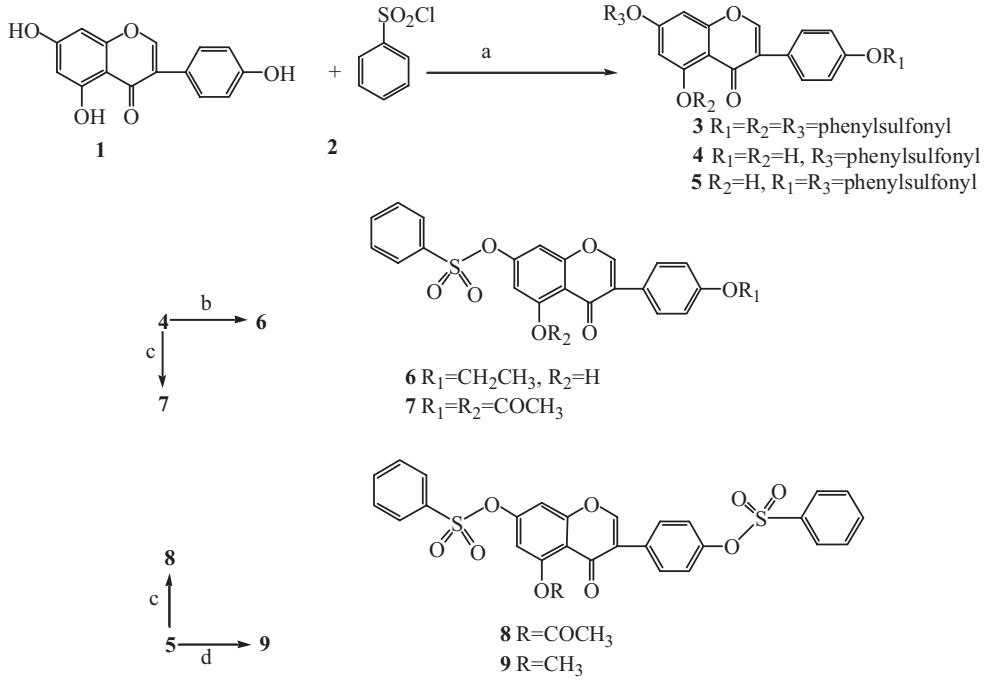
Preparation of 3-(4-benzenesulfonylphenyl)-5,7-bis(benzenelsulfonyl)-4H-chromen-4-one (**3**): A solution of genistein 0.270 g (1 mmol) and benzenesulfonic acid chloride 0.58 ml(4.5 mmol) in 5 ml pyridine was stirred at –20 °C for 3 h under Ar. Pouring it into ice water followed by extraction with ether/ethyl acetate (1/2), washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. Purification by flash chromatography (silica, CH_2Cl_2) yields white solid **3**(0.683 g, 99% yield); m.p. 150–152 °C; IR (KBr): 3092, 1659; ^{1}H NMR($CDCl_3$) δ: 7.98–7.90(m, 6H, 2", 2"', 2"", 6", 6"',6"" –benH), 7.82(s, 1H, 2-H), 7.77–7.72(m, 3H, 4", 4"', 4""-H), 7.58(m, 6H, 3", 3"', 3"",5",5"',5""-benH), 7.39 (d, 2H, 2',6'-ArH, J = 8.5 Hz), 7.22(d, 1H, 8-ArH, J = 1.88 Hz), 7.05(d, 2H, 3',5'-ArH, J = 8.5 Hz), 6.81(d, 1H, 6-ArH, J = 1.5 Hz); *m/z* (EI) 691.18 (M^+ + 1, 100%). Anal. Calcd for $C_{33}H_{22}O_{11}S_3$: C 57.38, H 3.21, S 13.93; found C 57.30, H 3.22, S 13.91.

Preparation of 3-(4-hydroxylphenyl)-5-hydroxy-7-benzenelsulfonyl-4H-chromen-4-one (**4**): A solution of genistein 0.270 g (1 mmol) and 1 ml pyridine in dry THF (4 ml) was stirred at –20 °C for 0.5 h under Ar, the benzenesulfonic acid chloride 0.2 ml (1.5 mmol) in THF (3 ml) was added to this solution over 15 minutes and the reaction continued for 5 min. Pouring it into ice water followed by extraction with ether/ethyl acetate (1/2), washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. Purification by flash chromatography (silica, $CHCl_3$/$(CH3)_2CO$, 10/1) yields white solid **4**(0.369 g, 90% yield). m.p. 154–156 °C; IR (KBr): 3081, 1616; ^{1}H NMR($CDCl_3$) δ:12.7(s, 1H, 5-OH), 7.94(s, 1H, 2-H), 7.90(d, 2H, 2",6"-benH, J = 7.7 Hz), 7.72(t, 1H, 4"-H, J = 7.5 Hz), 7.59(t, 2H, 3",5"-benH, J = 7.7 Hz), 7.39 (d, 2H, 2',6'-ArH, J = 8.5 Hz), 6.90(d, 2H, 3',5'-ArH, J = 8.5 Hz), 6.77(d, 1H, 8-ArH J = 2.0 Hz), 6.39(d, 1H, 6-ArH, J = 2.0 Hz), 5.39(s, 1H, 4'-OH); *m/z* (EI) 411.08 (M^+ + 1, 100%). Anal. Calcd for $C_{21}H_{14}O_7S$: C 61.46, H 3.44, S 7.81; found C 61.37, H 3.44, S 7.79.

Table 3 Parameters between the planes for **9**

Cg	Distance between ring centroids/Å	Dihedral angle/°	Perpendicular distance of Cg(I) on Cg(J)/Å	Perpendicular distance of Cg(J) on Cg(I)/Å
Cg(1) → Cg(3)[1545]	5.501	3.46	3.063	2.942
Cg(1) → Cg(3)[4565]	5.954	58.70	3.250	3.307
Cg(1) → Cg(4)[4465]	4.203	6.31	3.466	3.364
Cg(1) → Cg(5)[4465]	5.799	11.07	4.826	4.272
Cg(2) → Cg(3)[1555]	4.577	44.16	2.767	3.560
Cg(1) → Cg(5)[3554]	4.728	50.53	2.428	4.675
Cg(3) → Cg(4)[4465]	3.749	8.60	3.592	3.395
Cg(4) → Cg(5)[4455]	5.205	45.30	2.073	4.840
Cg(4) → Cg(5)[4465]	4.523	45.30	4.308	2.550
Cg(5) → Cg(2)[3545]	5.049	50.53	1.817	4.663

Cg(1): C(1) → C(2) → C(3) → C(4) → C(5) → C(6) →
Cg(2): C(7) → C(8) → C(9) → C(10) → C(14) → C(15) →
Cg(3): C(17) → C(18) → C(19) → C(20) → C(21) → C(22) →
Cg(4): C(23) → C(24) → C(25) → C(26) → C(27) → C(28) →
Cg(5): O(6) → C(13) → C(12) → C(11) → C(10) → C(9) → C(8) → C(7) → C(15) → C(14) →



a: pyridine, dry THF, Ar, –20 °C b: KOH, diethylsulfate, acetone, 0 °C
c: acetic anhydride, dry pyridine, 0 °C d: K_2CO_3, dry acetone, dimethylsulfate, 0 °C

Scheme 1 Structures of isoflavone genistein sulfonic acid esters

Preparation of 3-(4-benzenesulfonylphenyl)-7-benzenelsulfonyl-5-hydroxy-4H-chromen-4-one (**5**): A solution of genistein 0.270 g (1 mmol) and 0.1 g potassium *tert*-butoxide in dry THF (2 ml) was stirred at –20 °C for 0.5 h under Ar, the benzenesulfonic acid chloride 0.4 ml (2.6 mmol) in THF (3 ml) was instilled to this solution in 15 minutes and the reaction continued for 3 h. Pouring it into ice water followed by extraction with ether/ethyl acetate (1/2), washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. Purification by flash chromatography (silica, CH_2Cl_2/PE, 4/1) yields white solid **5** (0.446 g, 81% yield). m.p. 158–159 °C. IR (KBr): 3081, 1642; ^{1}H NMR($CDCl_3$) δ: 12.7(s, 1H, 2-OH), 7.95(s, 1H, 2-H), 7.90(d, 4H, 2",6"-benH, 2"',6"'-benH, J = 8.7,9.3 Hz), 7.72(m, 2H, 4", 4"'-H), 7.58(m, 4H, 3", 3"', 5",5"' -benH),7.46 (d, 2H, 2',6'-ArH, J = 8.5 Hz), 7.09(d, 2H, 3',5'-ArH, J = 8.5 Hz), 6.77(d, 1H, 8-ArH, J = 1.5 Hz), 6.39(d, 1H, 6-ArH, J = 1.5 Hz); *m/z* (EI) 550.96 (M^+ + 1, 90%). Anal. Calcd for $C_{27}H_{18}O_9S_2$: C 58.90, H 3.30, S 11.65; found C 58.80, H 3.31, S 11.63.

Preparation of 3-(4-ethoxyphenyl)-5-hydroxy-7-benzenelsulfonyl-4H-chromen-4-one (**6**): A solution of **2**(0.123 g,0.3 mmol) and 0.0957 g KOH in 20 ml acetone was stirred at 0 °C for 30 min, the diethylsulfate 0.4 ml(3.0 mmol) in acetone (5 ml) was instilled to this solution in 15 min and the reaction continued for 24 h. Pouring it into ice water followed by extraction with ethyl acetate, washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. The crude product was recrystallised in MeOH to produce a white crystal **6**(0.118 g, 90%yield). m.p. 110–111 °C; IR (KBr): 3069,1650; ^{1}H NMR($CDCl_3$) δ: 12.9(s, 1H, 5-OH), 7.94(s, 1H, 2-H), 7.92(d, 2H, 2",6"-benH, J = 7.8 Hz), 7.72(t, 1H, 4"-H, J = 7.4 Hz), 7.59(t, 2H, 3",5"-benH, J = 7.7 Hz),7.39 (d, 2H, 2',6'-ArH, J = 8.4 Hz), 6.90(d, 2H, 3',5'-ArH, J = 8.4 Hz), 6.77(s, 1H, 8-ArH), 6.39(s, 1H, 6-ArH), 4.08(dd, 2H, 4'-OCH_2-, J = 6.9 Hz), 1.45(t, 1H, 4'-CH_3, J = 6.9 Hz); *m/z* (EI) 439.26 (M^+ + 1, 100%). Anal. Calcd for $C_{23}H_{18}O_7S$: C 63.01, H 4.14, S 7.31; found C 62.85, H 4.15, S 7.29.

Preparation of 3-(4-acetoxyphenyl)-5-acetyl-7-benzenelsulfonyl-4H-chromen-4-one (**7**): A solution of **2**(0.205 g,0.5 mmol) and 0.23 ml acetic anhydride in 20 ml dry pyridine was stirred at 0 °C for 24 h. Pouring it into ice water followed by extraction with ethyl acetate, washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. The crude product was recrystallised in EtOH to produce a white crystal **7**(0.242 g, 98%yield). m.p. 169–170 °C; IR (KBr):3087, 1747, 1649; ^{1}H NMR ($CDCl_3$) δ:7.90(d, 2H, 2",6"-benH, J = 8.0 Hz), 7.88(s, 1H, 2-H), 7.73(t, 1H, 4"-H, J = 7.5 Hz), 7.59(t, 2H, 3",5"-benH, J = 7.7 Hz), 7.47 (d, 2H, 2',6'-ArH, J = 8.5 Hz), 7.15(d, 2H, 3',5'-ArH, J = 8.5 Hz), 7.11(d, 1H, 8-ArH, J = 2.0 Hz), 6.68(d, 1H, 6-ArH, J = 2.0 Hz), 2.38(s, 3H, 5-$OCCH_3$), 2.31(s, 3H, 4'-$OCCH_3$); *m/z* (EI) 495.38 (M^+ + 1, 100%). Anal. Calcd for $C_{25}H_{18}O_9S$: C 60.73, H 3.67, S 6.45; found C 60.61, H 3.68, S 6.44.

Preparation of 3-(4-benzenelsulfonylphenyl)-7-benzenelsulfonyl-5-acetyl-4H-chromen-4-one (**8**): A solution of **3**(0.205 g,0.5 mmol) and 0.11 ml acetic anhydride in 20 ml dry pyridine was stirred at 0 °C for 24 h. Pouring it into ice water followed by extraction with ethyl acetate, washing with aqueous $NaHCO_3$, drying and removal of solvent under reduced pressure gives the crude product. The crude product was recrystallised in EtOH to produce a white solid **8** (0.290 g, 98%yield). m.p. 187–188 °C; IR (KBr): 3100, 1767, 1646 cm^{-1};

Table 4 Crystal data and refinement parameters for **9**

CCDC deposit no.	676225
Molecular formula	$C_{28}H_{20}O_9S_2$
Molecular weight	564.56
Temperature (K)	298(2)
Radiation λ	Mo K α(0.71073 Å)
Crystal system	Orthorhombic
Space group	*Pca*2$_1$
a/Å	14.802(3)
b/Å	6.088(2)
c/Å	28.648(6)
V/Å^3	2581.6(9)
Z	4
D_{calc} (g cm^{-3})	1.453
Crystal size (mm)	0.28 × 0.27 × 0.27
Crystal colour	Colourless
Absorption coefficient (cm^{-1})	0.262
Absorption correction T_{min} and T_{max}	0.930 and 0.933
F(000)	1168
Reflections collected/unique	16270/5301 [R_{int} = 0.0682]
Range/indices (*h*, *k*, *l*)	–18, 18; –7, 7; –35, 35
θ limit (°)	2.75–26.50
No. of observed data, $I > 2\sigma(I)$	2485
No. of variables	354
No. of restraints	1
Goodness of fit on F^2	0.839
R_1, wR_2 [$I \geq 2\sigma(I)$]^a	0.0403, 0.0808
R_1, wR_2 (all data)^a	0.1113, 0.0940

$^aR_1 = \Sigma||Fo|-|Fc||/\Sigma|Fo|$, $wR_2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma w(Fo^2)^2]^{1/2}$, $w = [\sigma^2(Fo)^2 + (0.0417(Fo^2 + 2Fc^2)/3)^2]^{-1}$.

^{1}H NMR($CDCl_3$) δ: 7.90(dd, 4H, 2",2"',6",6"'-benH, *J* = 2.5, 8.0 Hz), 7.86(s, 1H, 2-H), 7.73(m, 2H, 4"',4"-H), 7.59(m, 4H, 3",3"',5",5"'-benH),7.40 (d, 2H, 2',6'-ArH, *J* = 8.4 Hz), 7.17(d, 1H, 8-ArH, *J* = 2.0 Hz),7.05(d, 2H, *J* = 8.4 Hz, 3',5'-ArH, *J* = 8.4 Hz), 6.68(d, 1H, 6-ArH, *J* = 2.0 Hz), 2.37(s, 3H, 5-$OCCH_3$); *m/z* (EI) 593.23 (M^+ + 1, 100%). Anal. Calcd for $C_{29}H_{20}O_{10}S_2$: C 58.78, H 3.40, S 10.82; found C 58.65, H 3.40, S 10.79.

Preparation of 3-(4-benzenesulfonylphenyl)-7-benzenesulfonyl-5-methoxy-4H-chromen-4-one (**9**): A solution of **5**(0.165 g, 0.3 mmol) and 0.601 g K_2CO_3 in 30 ml dry acetone was stirred at 0°C for 30 min, the dimethylsulfate 0.36 ml(3.8 mmol) in dry acetone (5 ml) was instilled to this solution in 15 min and the reaction continued for 24 h. Filtering and removal of acetone under reduced pressure gives the crude product. The crude product was recrystallised in EtOH to produce a white crystal **9** (0.157 g, 95%yield). m.p. 80–81°C; IR (KBr):1767, 1645; ^{1}H NMR($CDCl_3$) δ: 7.90(dd, 4H, 2",2"',6",6"'-benH, *J* = 2.5,8.0 Hz), 7.80(s,1H, 2-H.), 7.75 (m, 2H, 4"',4"-H), 7.58(m, 4H, 3",3"',5",5"'-benH), 7.45 (d, 2H, 2',6'-ArH, *J* = 8.4 Hz), 7.02(d, 2H, 3',5'-ArH, *J* = 8.4 Hz), 6.76(s, 1H, 8-ArH, *J* = 2.0 Hz),6.42(s, 1H, 6-ArH, *J* = 2.0 Hz), 3.82(s, 3H, CH_3); MS, *m/z*: 565.26 (M^+ + 1). Anal. Calcd for $C_{28}H_{20}O_9S_2$: C 59.57, H 3.57, S 11.36. Found: C 59.43, H 3.57, S 11.33.

X-ray diffraction analysis

The data were collected on a Bruker SMART CCD area-detector diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) by ω scan mode within the angular range 2.75° < θ < 26.50°. The collected data were reduced using the SAINT program,[11] and empirical absorption corrections were performed using the SADABS program.[12] The structure was solved by direct methods and refined against F^2 by full-matrix least-squares methods using the SHELXTL program.[13] All of the non-hydrogen atoms were refined anisotropically. All hydrogen atoms were set in idealised positions and refined using the riding model. The details of the crystallographic data are summarised in Table 4. Crystallographic data for **9** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 676225). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: (44)01223 336033); e-mail: deposit@ccdc.ac.uk).

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