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Antibacterial 4-amino-*N*-(5-methylisoxazol-3-yl)-*N*-[(4-oxo-2-phenyl-4*H*-1-benzopyran-6-yl)methyl]benzenesulfonamide

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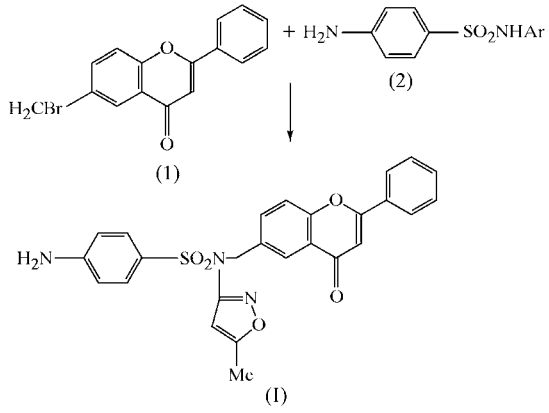
In the molecule of the title compound, $C_{26}H_{21}N_3O_5S$, a new type of sulfonamide derivative with potential antibacterial activity, the flavone moiety is almost planar. The isoxazole and aminophenyl rings are also planar and make dihedral angles of 77.0 (2) and 81.4 (1)°, respectively, with the best plane of the flavone ring system. The crystal structure is stabilized by intra- and intermolecular hydrogen bonds.

Comment

Flavonoids form a class of benzo-γ-pyrone derivatives and include flavones, flavanes, flavonols, anthocyanidines and catechins. They possess a wide spectrum of biological activities, such as anticancer (Zharko *et al.*, 1986), antibacterial (Mori *et al.*, 1987), antifungal (Perry & Foster, 1994), antiviral (Wleklik *et al.*, 1988), spasmolytic (Ertan *et al.*, 1989), hypoglycaemic (Bozdağ-Dündar *et al.*, 2001), antihistaminic (Amella *et al.*, 1985) and antioxidant properties (Czompa *et al.*, 2000). Furthermore, it is well documented that sulfonamide derivatives have been used in particular against urinary tract infections caused by *Escherichia coli* (Mutschler *et al.*, 2001). In view of reports indicating that derivatives of flavone exhibit antimicrobial activity (Ayhan-Kilcigil *et al.*, 1999; Ayhan-Kilcigil & Altanlar, 2000; Tunçbilek *et al.*, 1999), we have described the synthesis and antimicrobial evaluation of new sulfonamide derivatives having a flavone ring system (Ayhan-Kilcigil *et al.*, 2003).

In order to gain more information about the relationship between structural features and biological properties, in the last decade we have also carried out crystallographic studies on several molecules of this family (Kendi *et al.*, 1994, 1995*a*,*b*, 1996, 2000; Özbey *et al.*, 1997, 1999; Ayhan-Kilcigil *et al.*, 1998; Tunçbilek *et al.*, 1999). As part of this research, we present here the crystal structure of the title novel sulfonamide derivative, (I). The compound was also tested for antimicrobial activity by the agar diffusion method against *E. coli* and the result was compared with that of the corresponding sulfonamide derivative, (2). According to the results of this test, compound (I) shows better activity than the corresponding sulfonamide against *E. coli* (Ayhan-Kilcigil *et al.*, 2003).



The molecule of the title compound consists of sulfamethoxazole and flavone moieties. The flavone moiety of the molecule is almost planar; the dihedral angle between the best planes of the benzopyran and phenyl rings, which are both planar as expected, is 2.8 (2)°. This value is comparable with those of 5,7-dihydroxy-8-methoxyflavone (2.8°; Jiang *et al.*, 2002), 5,7-dihydroxy-4′-methoxyflavone (3.1°; Cantrell, 1986) and ethyl allyl 1,4-dihydro-2,6-dimethyl-4-[4-(4*H*-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridinedicarboxylate (3.3°; Kendi *et al.*, 1994). However, it is significantly smaller than those in flavone-3′-sulfonamide (8.3°; Kendi *et al.*, 2000), 2-(2-ethoxycarbonyl-1,4-benzodioxan-7-yl)-4*H*-1-benzopyran-4-one (13.9°; Özbey *et al.*, 1997), diethyl 2,6-dimethyl-4-(2-phenyl-4-oxo-4*H*-1-benzopyran-6-yl)-1,4-dihydropyridine-3,5-dicarboxylate (10.7°; Özbey *et al.*, 1999) and 2′-methyl-3′-nitroflavone (139.8°; Kendi *et al.*, 1996) due to the steric hindrance caused by the groups attached to the phenyl ring.

The coplanarity of the phenyl ring and the benzopyran plane has been attributed to a short intramolecular hydrogen

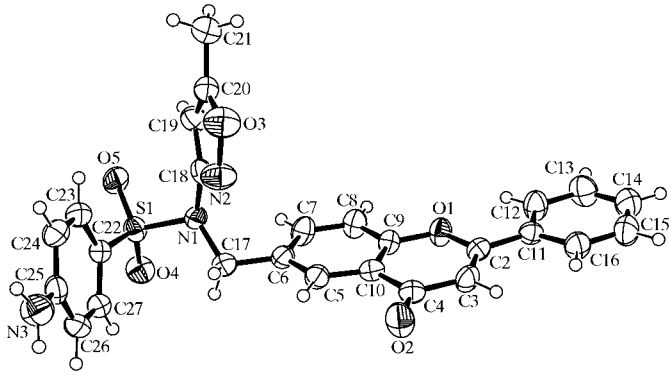


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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contact between a H atom of the phenyl and pyrone atom O1 (Table 2). Similar intramolecular hydrogen-bond interactions are reported for 2′-methoxyflavone (Wallet *et al.*, 1990), 6-(3-hydroxy-3-methylbut-1-yl)flavone and 6-(3-methylbut-3-en-1-ynyl)flavone (Artali *et al.*, 2003), and 2-(2-ethoxycarbonyl-1,4-benzodioxan-7-yl)-4*H*-1-benzopyran-4-one (Özbey *et al.*, 1997).

The atoms around the sulfonamide S atom in (I) are arranged in a slightly distorted tetrahedral configuration. The largest deviation is in the angle O4—S1—O5 [119.9 (2)°], but it conforms to the non-tetrahedral nature commonly observed in sulfonamides (Chatterjee *et al.*, 1982; Haridas *et al.*, 1984; Ghosh *et al.*, 1991; Kendi *et al.*, 2000; Takasuka & Nakai, 2001). In this configuration, sulfonyl atom O4 takes part in short intramolecular hydrogen contacts with atoms C17 and C27, forming a five-membered ring structure.

The isoxazole and aminophenyl rings at N1 and S1, respectively, are essentially planar and form an angle of 40.7 (2)°. In related molecules, the torsion angles ε_1 (C—C—S—N) and ε_2 (C—S—N—C) defining the conformation of the sulfonamide group are reported to lie in the ranges 70–120 and 60–90°, respectively (Kálmán *et al.*, 1981). In the present structure, the C23—C22—S1—N1 and C22—S1—N1—C17 torsion angles of 81.4 (3) and 64.2 (3)°, respectively, lie within these ranges. The flavone moiety is rotated around the N1—C17 and C17—C6 bonds, giving torsion angles S1—N1—C17—C6 = 158.0 (2)° and N1—C17—C6—C5 = 140.6 (4)°. The interatomic distances and bond angles of both the sulfamethoxazole and the flavone moieties of (I) agree well with their equivalents in similar structures.

The packing of the molecules and the hydrogen bonding in the structure are shown in Fig. 2. All O and N atoms, except N1 and O3, participate in hydrogen bonds and short intramolecular contacts (Table 2). Atom N3 of the arylamino moiety is involved in two intermolecular hydrogen bonds with sulfonyl atom O5 and flavone atom O2. Isoxazole atom N2 takes part in a relatively weak hydrogen bond with atom C16 of the flavone. The packing is also characterized by an overlap of the benzopyran moieties, related by a centre at ($\frac{1}{2}$, 0, 0), the interplanar distance being less than 3.7 Å.

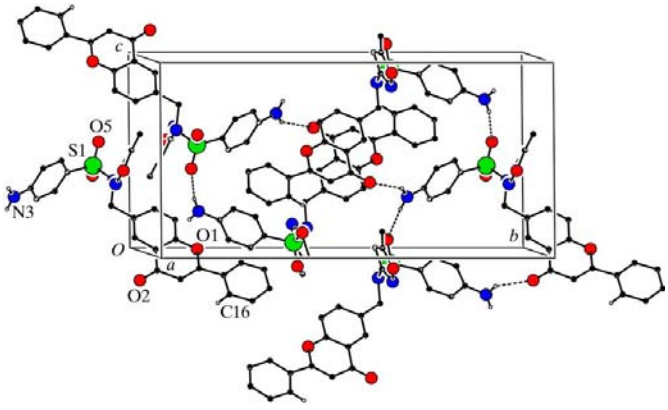

Figure 2
The crystal packing arrangement for (I). Hydrogen bonds are depicted as dashed lines.

Experimental

The synthesis of compound (I) was performed according to the method of Ayhan-Kilcigil *et al.* (2003). A mixture of 6-bromomethylflavone, (1) (157 mg, 0.5 mmol), 4-amino-*N*-(5-methyl-3-isoxazoyl)benzenesulfonamide, (2) (0.5 mmol), and anhydrous potassium carbonate (69 mg, 0.5 mmol) was stirred at 333 K in dimethylformamide (10 ml) until the starting materials were used up. Water was added (25 ml) and the mixture was extracted with $CHCl_3$. The extract was washed with water and purified by column chromatography and then recrystallized from ethanol. The structure was assigned according to the results of NMR and mass spectroscopic and elemental analyses.

Crystal data

$C_{26}H_{21}N_3O_5S$
M_r = 487.53
Monoclinic, $P2_1/c$
a = 8.824 (2) Å
b = 23.183 (4) Å
c = 11.305 (3) Å
β = 96.185 (2)°
V = 2299.2 (9) Å^3
Z = 4
D_x = 1.408 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 9.2–18.1°
μ = 0.19 mm^{-1}
T = 295 (2) K
Prism, colourless
0.48 × 0.36 × 0.21 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non-profiled ω scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.923, T_{max} = 0.962
4875 measured reflections
4641 independent reflections
2022 reflections with $I > 2\sigma(I)$
R_{int} = 0.080
θ_{max} = 26.3°
$h = -10 \rightarrow 10$
$k = 0 \rightarrow 28$
$l = 0 \rightarrow 14$
3 standard reflections
frequency: 120 min
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.055
$wR(F^2)$ = 0.146
S = 0.97
4641 reflections
322 parameters
H-atom treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0555P)^2 + 0.04\sin\theta/\lambda]$ where $P = 0.33333F_o^2 + 0.66667F_c^2$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C2—C3	1.339 (5)	C18—N2	1.289 (4)
C2—O1	1.349 (4)	C18—N1	1.420 (4)
C2—C11	1.474 (5)	C19—C20	1.332 (5)
C4—O2	1.239 (4)	C25—N3	1.367 (5)
C6—C17	1.509 (5)	N1—S1	1.676 (3)
C9—O1	1.370 (4)	O4—S1	1.427 (3)
C17—N1	1.476 (4)	O5—S1	1.433 (2)
C2—C3—C4	122.5 (4)	O4—S1—O5	119.89 (16)
N1—C17—C6	111.7 (3)	O5—S1—N1	105.49 (15)
C18—N1—C17	115.4 (3)	O4—S1—C22	109.70 (17)
C18—N1—S1	114.8 (2)		
O1—C2—C11—C16	177.8 (3)	C6—C17—N1—S1	158.0 (2)
C5—C6—C17—N1	140.6 (4)	C18—N1—S1—C22	−72.4 (3)
N2—C18—N1—S1	117.6 (3)	C27—C22—S1—N1	−89.5 (3)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C12—H12···O1	0.93	2.34	2.680 (5)	101
C17—H17A···O4	0.97	2.45	2.916 (4)	109
C27—H27···O4	0.93	2.57	2.940 (5)	104
N3—H32···O5^{i}	0.86 (5)	2.29 (4)	3.120 (5)	164 (4)
N3—H31···O2^{ii}	0.83 (4)	2.25 (4)	2.951 (5)	142 (4)
C16—H16···N2^{iii}	0.93	2.49	3.309 (5)	148

Symmetry codes: (i) $x, -y-\frac{1}{2}, z-\frac{1}{2}$; (ii) $x, -y-\frac{1}{2}, z+\frac{1}{2}$; (iii) $-x+2, -y, -z$.

The H atoms on N3 were located in a difference Fourier map and refined with fixed individual displacement parameters [U_{iso}(H) = 1.2U_{eq}(N3)]. The methyl H atoms were also located by difference Fourier synthesis and refined as a rigid group, with U_{iso}(H) = 1.5U_{eq}(C21). All other H atoms were placed in idealized positions and refined using a riding model, with C—H distances of 0.93 (aromatic) and 0.97 Å (methylene).

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1251). Services for accessing these data are described at the back of the journal.

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