Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Hydrogen bonding and π–π stacking in 7-{2-[4-(4-methoxyphenyl)piperazin-1-yl]ethoxy}-4-methyl-2*H*-chromen-2-one monohydrate

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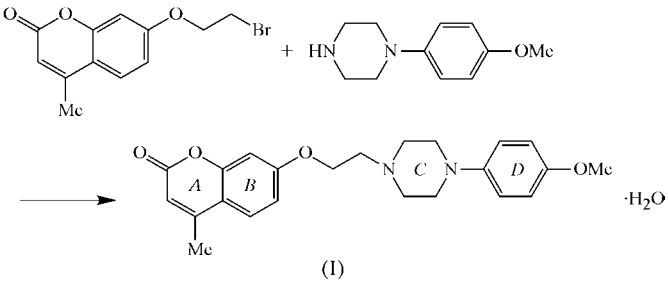
Received 14 November 2005
Accepted 6 December 2005
Online 14 January 2006

In the title compound, $C_{23}H_{26}N_2O_4\cdot H_2O$, the benzopyran ring system is planar. The piperazine ring adopts an almost perfect chair conformation, and the methoxy group is coplanar with its parent benzene ring. Hydrogen bonds link two water molecules and two piperazine molecules into tetrameric units. The adjacent benzopyran moieties within these units also interact *via* π–π stacking interactions, and a sheet is formed by the propagation of these interactions. The bioassay results have shown α_1-adrenoceptor antagonistic activity through *in vitro* animal experiments.

Comment

Coumarin is the parent organic compound of a class of naturally occurring phytochemicals with fragrance found in many plant species, and these compounds have received significant attention for many years. Natural or synthetic compounds comprising a coumarin backbone have a wide range of biological activities, such as anti-inflammatory (Kontogiorgis & Hadjipavlou-Litina, 2005), antitumour (Dexeus *et al.*, 1990), anti-allergic (Buckle *et al.*, 1979) and anti-HIV-1 (Lunney *et al.*, 1994) activities. Compounds possessing a piperazine ring are being studied extensively as potential psychotropic agents (Lopez-Rodriguez *et al.*, 1999). The neuroleptic and anxiolytic (tranquilizer) properties of these compounds are due to their interaction with dopamine and serotonin receptors. According to the hypothetical views on the topography of the α_1-adrenoceptor antagonists (Kenny *et al.*, 1997; Bremner *et al.*, 2000; Dardonville *et al.*, 2000), the basic pharmaphore of an α_1-adrenoceptor antagonist should include a basic nitrogen center (BNC), hydrophobic groups (HP), an aromatic ring (AR) linked to the BNC directly, and a hydrogen-bond donor or receptor (HB). We have designed and synthesized a series of coumarin derivatives containing a piperazine ring on the basis of the abovementioned structure–activity relationships. The structure elucidation of these compounds is important for understanding the molecular mechanisms of their biological activities. However, reports about the crystal structures of this kind of compound are scarce (Estrada *et al.*, 2000). In this context, the crystal structure of the monohydrate of one of the prepared novel coumarin derivatives, *viz.* the title compound, (I), is reported here.



(I)

A view of the molecular structure of (I) is shown in Fig. 1. The bond lengths and angles in (I) are comparable to the average values reported in the literature for atoms in similar environments (Allen *et al.*, 1987). The benzopyran ring (O1/C1–C9) is planar, with a mean deviation of the constituent atoms from their least-squares plane of 0.006 Å. The molecule of (I) has a fully extended conformation, similar to its analog *trans*-1-(2-methoxyphenyl)-4-[4-(2-phthalimido)cyclohexyl]-piperazine (Dalpiaz *et al.*, 1996). In (I), the dihedral angle between the plane of the non-fused benzene ring and the least-squares plane of the piperazine ring is 17.42 (10)°, while Kuipers *et al.* (1997) reported that the angle between the plane of the benzene and piperazine rings in bis(*N*-{2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-*cis*-2,6-dimethyl-1-piperazinyl]-ethyl}-4-fluorobenzenecarboxamido)fumarate is approximately 30°. In (I), the distances from the central N atom, N1, to the centroid of the non-fused benzene ring, to the hydrogen-bond donor C23 and to the centroid of the coumarin moiety, the hydrophobic centre, are 5.689 (4), 9.265 (7) and 7.175 (4) Å, respectively. The corresponding distances reported by Li & Xia (2005) for α_1-adrenoceptor antagonists are 5.82, 9.08 and 7.53 Å, respectively. The angle between the coumarin moiety and benzene ring *D* is 65.44 (8)° in (I) and 67.8° in the report by Paluchowska *et al.* (1999). The similarity between the key geometric parameters of (I) and those given by Paluchowska *et al.* (1999) and Li & Xia (2005) suggests that the title compound may have potential biological activity. Actually, the bioassay results for tests of the α_1-adrenoceptor antagonistic activity of (I) through *in vitro* animal experiments in the New Drugs Screening Center of Jiangsu province of China have shown a slightly lower activity than prozosin, the

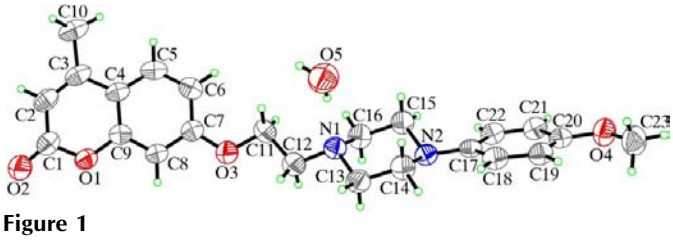


Figure 1
A view of the asymmetric unit of (I), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

  DOI: 10.1107/S0108270105040928

most accepted positive control substance for α_1-adrenoceptor antagonistic activity (Ford *et al.*, 1994).

The piperazine ring adopts an almost perfect chair conformation, as in the case of *N*,*N*′-dimethylpiperazine (Parkin & Parsons, 2002). This is confirmed by the puckering parameters [Q = 0.566 (2) Å, q_2 = 0.008 (2) Å, q_3 = −0.566 (2) Å, θ = 180.0 (2)° and φ_2 = 108 (14)°] for the atom sequence N1—C13—C14—N2—C15—C16 (Cremer & Pople, 1975) and the intra-ring torsion angles shown in Table 1. The N atoms are substituted in equatorial positions, which meets the requirements for the bioactive conformation of an α_1-adrenoceptor antagonist (Kuipers *et al.*, 1997). The length of the C17—N2 bond is somewhat shorter (Table 1) than that of the C12—N1 bond as a result of conjugation between atom N2 and the 4-methoxyphenyl ring to which it is bonded. The methoxy group is coplanar with ring *D* (Table 1).

The title compound crystallized as a monohydrate. Each water molecule donates two hydrogen bonds to two adjacent piperazine molecules (Table 2). These interactions link two water molecules and two piperazine molecules alternately across a centre of inversion into a tetrameric unit. The interactions that lead to this unit can be described by an overall graph-set motif of $R_4^4(26)$ (Bernstein *et al.*, 1995; Desiraju, 1995). In addition, each water molecule accepts two soft C—H···O interactions (Desiraju, 1996) from two piperazine molecules not involved in the original tetramer, so that each water molecule is surrounded by four piperazine molecules (Fig. 2).

Additional π–π stacking interactions are present between the pyran ring (*A*; π-electron deficient) and the benzene ring (*B*; π-electron rich) of the adjacent centrosymmetrically related (symmetry code: $2-x, 1-y, -z$) benzopyran group within the hydrogen-bonded tetrameric unit (Fig. 3). The plane of ring *A* makes an angle of 0.38° with that of ring *B* of the opposing molecule and the two rings overlap with an intercentroid distance of 3.643 (3) Å. The perpendicular

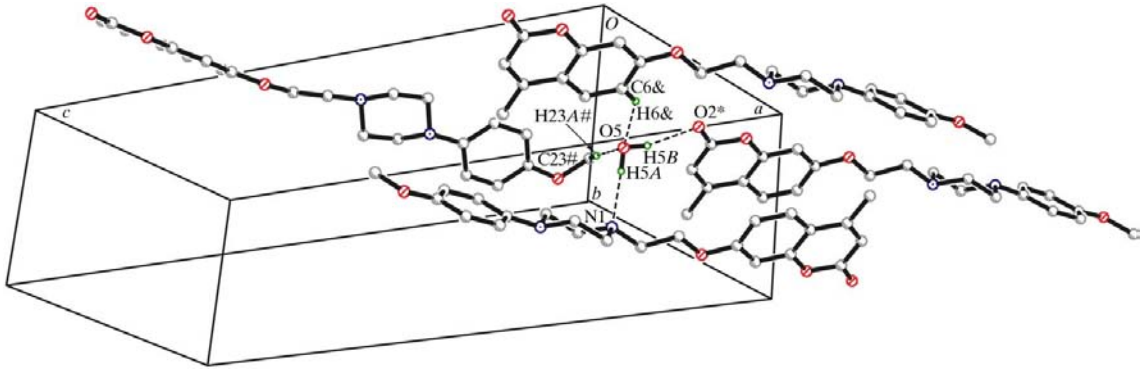


Figure 2
Part of the crystal packing of (I), showing the interactions involving the water molecule. Atoms marked with an asterisk (*), hash (#) or ampersand (&) are at the symmetry positions $(2-x, 1-y, -z)$, $(\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z)$ and $(1-x, 1-y, -z)$, respectively. Some H atoms have been omitted for clarity.

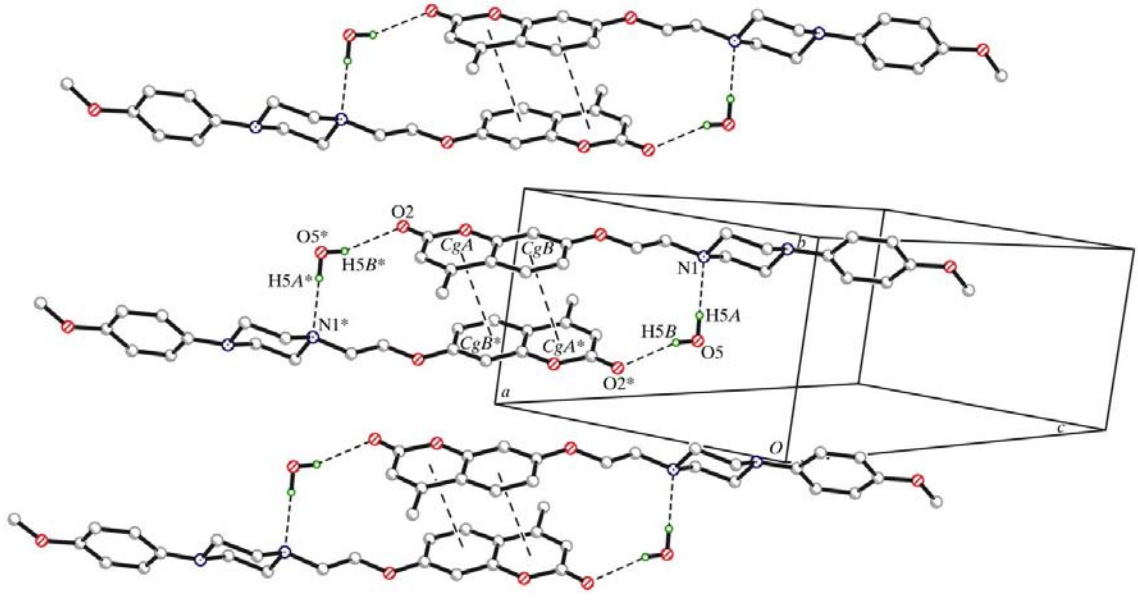


Figure 3
Part of the crystal structure of (I), showing the formation of the stacked dimers *via* hydrogen bonds and π–π stacking interactions. Atoms marked with an asterisk (*) are at the symmetry positions $(2-x, 1-y, -z)$. Some H atoms have been omitted for clarity.

distance from the centre of gravity of each ring to the plane of the opposing ring is 3.50 Å, with a slippage from the centroid of the opposing ring of 0.85 Å.

Experimental

The synthesis of (I) was performed according to the method of Jain *et al.* (1967). A mixture of 7-bromoethoxy-4-methylcoumarin (566 mg, 2 mmol), 1-(4-methoxyphenyl)piperazine (457 mg, 2 mmol) and anhydrous K_2CO_3 (276 mg, 2 mmol) was stirred at reflux in acetone (5 ml) and anhydrous ethanol (5 ml) for 48 h. The precipitate was filtered off and washed with fresh chloroform. The solvent was evaporated under reduced pressure from the combined filtrate and washings. The residue was chromatographed on a silica-gel column by eluting with a cyclohexane/acetone mixture (8:1 *v*/*v*) to give a colorless solid (170 mg, 21%, m.p. 511 K). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (*d*, 1H, H-5, J = 8.91 Hz), 6.95 (*m*, 4H, Ph), 6.86 (*dd*, 1H, H-6, J = 8.80 and 2.60 Hz), 6.82 (*d*, 1H, H-8, J = 2.60 Hz), 6.15 (*s*, 1H, H-3), 4.10 (*t*, 2H, CH_2O, J = 6.30 Hz), 3.77 (*s*, 3H, OCH_3), 3.10 [*m*, 4H, N4 $(CH_2)_2$], 2.85 [*m*, 4H, $(CH_2)_2$N1], 2.60 (*m*, 2H, N1CH_2), 2.38 (*s*, 3H, CH_3). A crystal suitable for diffraction analysis was obtained by slow evaporation of a solution of (I) in a mixture of ethanol and ethyl acetate (1:1 *v*/*v*) at room temperature.

Crystal data

$C_{23}H_{26}N_2O_4\cdot H_2O$	D_x = 1.305 Mg m^{-3}
M_r = 412.47	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 2841 reflections
a = 10.776 (7) Å	θ = 2.2–24.1°
b = 7.483 (5) Å	μ = 0.09 mm^{-1}
c = 26.381 (18) Å	T = 298 (2) K
β = 99.406 (10)°	Prism, colorless
V = 2099 (2) Å^3	0.53 × 0.48 × 0.27 mm
Z = 4	

Data collection

Bruker SMART CCD area-detector diffractometer	3684 independent reflections
	2296 reflections with $I > 2\sigma(I)$
φ and ω scans	R_{int} = 0.038
Absorption correction: multi-scan (*SADABS*; Bruker, 2000)	θ_{max} = 25.0°
	$h = -12 \rightarrow 10$
T_{min} = 0.962, T_{max} = 0.985	$k = -8 \rightarrow 8$
10516 measured reflections	$l = -31 \rightarrow 31$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.055P)^2 + 0.28P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.046	
$wR(F^2)$ = 0.124	$(\Delta/\sigma)_{max} < 0.001$
S = 1.03	$\Delta\rho_{max}$ = 0.17 e Å^{-3}
3684 reflections	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
273 parameters	
H-atom parameters constrained	

The positions of the H atoms of the water molecule were found initially in a difference Fourier map and then constrained to ride on the parent O atom, with U_{iso}(H) values of 1.5U_{eq}(O). The methyl H atoms were constrained to an ideal geometry, with C—H distances of 0.96 Å and U_{iso}(H) values of 1.5U_{eq}(C), but were allowed to rotate freely about the C—C bonds. All remaining H atoms were placed in geometrically idealized positions (C—H = 0.93–0.97 Å) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C)].

Data collection: *SMART* (Bruker, 2000); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 2000); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL* and *WinGX* (Version 1.7; Farrugia, 1999).

Table 1
Selected geometric parameters (Å, °).

N1—C16	1.465 (3)	N2—C14	1.452 (2)
N1—C12	1.461 (3)	N2—C15	1.466 (3)
N1—C13	1.467 (3)	C13—C14	1.496 (3)
N2—C17	1.414 (3)	C15—C16	1.505 (3)
C16—N1—C12	111.81 (17)	C14—N2—C15	109.19 (16)
C16—N1—C13	108.22 (17)	N1—C13—C14	112.53 (17)
C12—N1—C13	109.31 (16)	N2—C14—C13	111.34 (17)
C17—N2—C14	116.81 (15)	N2—C15—C16	111.45 (17)
C17—N2—C15	116.63 (16)	N1—C16—C15	111.33 (17)
N1—C13—C14—N2	−57.7 (2)	C23—O4—C20—C19	−2.7 (3)
N2—C15—C16—N1	58.4 (2)	C23—O4—C20—C21	177.91 (19)

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5A···N1	0.88	2.08	2.955 (3)	172
O5—H5B···O2^{i}	0.87	2.19	2.989 (3)	152
C6—H6···O5^{ii}	0.93	2.61	3.369 (3)	139
C23—H23B···O5^{iii}	0.96	2.63	3.579 (4)	170

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

The use of the Bruker X-ray Crystallographic Service at Liaocheng University and the valuable assistance of Professor Daqi Wang there are gratefully acknowledged.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1189). Services for accessing these data are described at the back of the journal.

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