# organic compounds

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

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In the title compound,  $C_{23}H_{26}N_2O_4$ ·H<sub>2</sub>O, 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*  $\pi$ - $\pi$  stacking interactions, and a sheet is formed by the propagation of these interactions. The bioassay results have shown  $\alpha_1$ -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  $\alpha_1$ -adrenoceptor antagonists (Kenny et al., 1997; Bremner et al., 2000; Dardonville et al., 2000), the basic pharmaphore of an  $\alpha_1$ -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.



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-(2,3dihydro-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  $\alpha_1$ -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  $\alpha_1$ -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.

most accepted positive control substance for  $\alpha_1$ -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  $[Q = 0.566 (2) \text{ Å}, q_2 = 0.008 (2) \text{ Å}, q_3 = -0.566 (2) \text{ Å}, \theta =$  $180.0 (2)^{\circ}$  and  $\varphi_2 = 108 (14)^{\circ}$ ] 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  $\alpha_1$ -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  $\pi$ - $\pi$  stacking interactions are present between the pyran ring (A;  $\pi$ -electron deficient) and the benzene ring (B;  $\pi$ -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  $\pi$ - $\pi$  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<sub>2</sub>CO<sub>3</sub> (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). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  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<sub>2</sub>O, J = 6.30 Hz), 3.77 (s, 3H, OCH<sub>3</sub>), 3.10 [m, 4H, N4 (CH<sub>2</sub>)<sub>2</sub>], 2.85 [m, 4H, (CH<sub>2</sub>)<sub>2</sub>N1], 2.60 (m, 2H, N1CH<sub>2</sub>), 2.38 (s, 3H, CH<sub>3</sub>). 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 <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub> ·H <sub>2</sub> O $M_r = 412.47$ Monoclinic, $P2_1/n$ a = 10.776 (7) Å b = 7.483 (5) Å c = 26.381 (18) Å $\beta = 99.406$ (10)° V = 2099 (2) Å <sup>3</sup> Z = 4	$D_x = 1.305 \text{ Mg m}^{-3}$ Mo <i>Ka</i> radiation Cell parameters from 2841 reflections $\theta = 2.2-24.1^{\circ}$ $\mu = 0.09 \text{ mm}^{-1}$ T = 298 (2)  K Prism, colorless $0.53 \times 0.48 \times 0.27 \text{ mm}$
Data collection	
Bruker SMART CCD area-detector diffractometer $\varphi$ and $\omega$ scans Absorption correction: multi-scan ( <i>SADABS</i> ; Bruker, 2000) $T_{min} = 0.962, T_{max} = 0.985$ 10516 measured reflections	3684 independent reflections 2296 reflections with $I > 2\sigma(I)$ $R_{int} = 0.038$ $\theta_{max} = 25.0^{\circ}$ $h = -12 \rightarrow 10$ $k = -8 \rightarrow 8$ $l = -31 \rightarrow 31$
Refinement	
Refinement on $F^2$ $R[F^2 > 2\sigma(F^2)] = 0.046$ $wR(F^2) = 0.124$ S = 1.03 3684 reflections 273 parameters	$w = 1/[\sigma^{2}(F_{o}^{2}) + (0.055P)^{2} + 0.28P]$ where $P = (F_{o}^{2} + 2F_{c}^{2})/3$ $(\Delta/\sigma)_{max} < 0.001$ $\Delta\rho_{max} = 0.17 \text{ e} \text{ Å}^{-3}$ $\Delta\rho_{min} = -0.22 \text{ e} \text{ Å}^{-3}$

H-atom parameters constrained

## 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)
$C_{16}N_{1}C_{12}$	111.81 (17)	$C_{14}N_{2}C_{15}$	109 19 (16)
C16 - N1 - C12	108.22(17)	N1 - C13 - C14	112.53 (17)
C12-N1-C13	109.31 (16)	$N_2 - C_{14} - C_{13}$	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,	°).

$D - H \cdot \cdot \cdot A$	$D-\mathrm{H}$	$H \cdot \cdot \cdot A$	$D \cdots A$	$D - \mathbf{H} \cdots A$
$O5-H5A\cdots N1$	0.88	2.08	2.955 (3)	172
$O5-H5B\cdots O2^{i}$	0.87	2.19	2.989 (3)	152
C6−H6···O5 <sup>ii</sup>	0.93	2.61	3.369 (3)	139
$C23-H23B\cdots O5^{iii}$	0.96	2.63	3.579 (4)	170

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

SHELXTL (Bruker, 2000); software used to prepare material for publication: SHELXTL and WinGX (Version 1.7; Farrugia, 1999).

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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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strained to ride on their parent atoms $[U_{iso}(H) = 1.2U_{eq}(C)]$ .	
Data collection: SMART (Bruker, 2000); cell refinement: SMAR	T;
data reduction: SAINT (Bruker, 2000); program(s) used to sol	ve
structure: SHELXS97 (Sheldrick, 1997); program(s) used to refi	ne
structure: SHELXL97 (Sheldrick, 1997); molecular graphi	cs:

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 con-

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