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Protonation site and hydrogen bonding in anhydrous and hydrated crystalline forms of doxazosin mesylate from powder data

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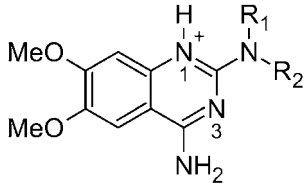
The three-dimensional solid-state structures of two modifications of doxazosin mesylate $C_{23}H_{26}N_5O_5^+\cdot CH_3SO_3^-$, 4-amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline methanesulfonate, a commonly used antihypertensive agent, have been determined by synchrotron X-ray powder diffraction. An anhydrous form (*A*) and a dihydrate form (*dG*) crystallize in monoclinic space groups. In both forms the doxazosin molecule is protonated at the N1 atom of the quinazoline bicycle. The N1 atom, and the amino H atoms and O atoms of the mesylate moieties are involved in three-dimensional hydrogen-bonding networks, while solvent water molecules and carboxamide O atoms are also incorporated in a hydrogen-bonding network in *dG*.

1. Introduction

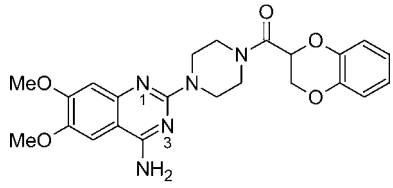
The selective α_1-adrenoceptor antagonist doxazosin is an effective antihypertensive agent used either by itself or in combination with agents from other antihypertensive classes in patients with poorly controlled hypertension and benign prostatic hyperplasia (Guthrie *et al.*, 1999). It has beneficial effects on insulin sensitivity, on plasma lipid contents (Ulahannan *et al.*, 2002) and on arterial elasticity (Bratteli & Glasser, 2002). Doxazosin remains a commonly used antihypertensive agent, although its use has been tainted by recent findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (Furberg *et al.*, 2000). Drug-delivery forms of doxazosin are usually prepared as solid-state forms of doxazosin mesylate (Klein *et al.*, 1999; Grafe & Moersdorf, 2000*a*,*b*,*c*; Thyes *et al.*, 2000; Giridar *et al.*, 2002; Arnalot *et al.*, 2000). Seven polymorphic modifications of doxazosin mesylate, $C_{23}H_{26}N_5O_5^+\cdot CH_3SO_3^-$, designed as forms *A*, *D*, *E*, *F*, *G*, *H* and *I*, have been discovered (Grčman *et al.*, 2002) since the first production of doxazosin in 1987 (Campbell *et al.*, 1987). It is known (Grčman *et al.*, 2002) that form *G* is hygroscopic and at ambient conditions it tends to form a hydrate. A molecule of doxazosin has several alternative protonation sites. It was suggested previously (Campbell, 1984; Campbell *et al.*, 1987) that the key pharmacophore for initial α_1-receptor recognition by 2,4-diamino-6,7-dimethoxyquinazoline derivatives was the N1 protonated species (1).



(1)

Semi-empirical quantum chemical calculations at the INDO level (Campbell *et al.*, 1987) indicated that N1 protonation is preferred over the N3 alternative, whereas protonation of the exocyclic N atoms is even less favored. In spite of the last statement the recent single-crystal structure determination of diprazosin tetrachlorocopper(II) (Bontchev *et al.*, 2001) revealed exocyclic nitrogen protonation. Therefore, in our case of anhydrous and hydrated solid forms of doxazosin mesylate it is important to clearly identify the protonation site responsible for the biopharmaceutical properties of doxazosin. However, no crystal structure of any form of doxazosin or doxazosin mesylate has been reported so far, because of problems with producing crystals of sufficient size and quality suitable for single-crystal X-ray diffraction. In cases when solid organic materials can be prepared only in a polycrystalline form, new modern methods, which are mainly based on the direct space approach and global optimization (David *et al.*, 2002; Le Bail, 1994–2003; Harris *et al.*, 2001; Chernyshev, 2001), for structure determination from powder data can be used.

The objectives of this study were the crystal structure determination of two forms of doxazosin mesylate – the anhydrous form *A* and the hydrated form *dG*. This study establishes the protonation site and conformation of doxazosin (2) and investigates hydrogen bonding in both forms.



(2)

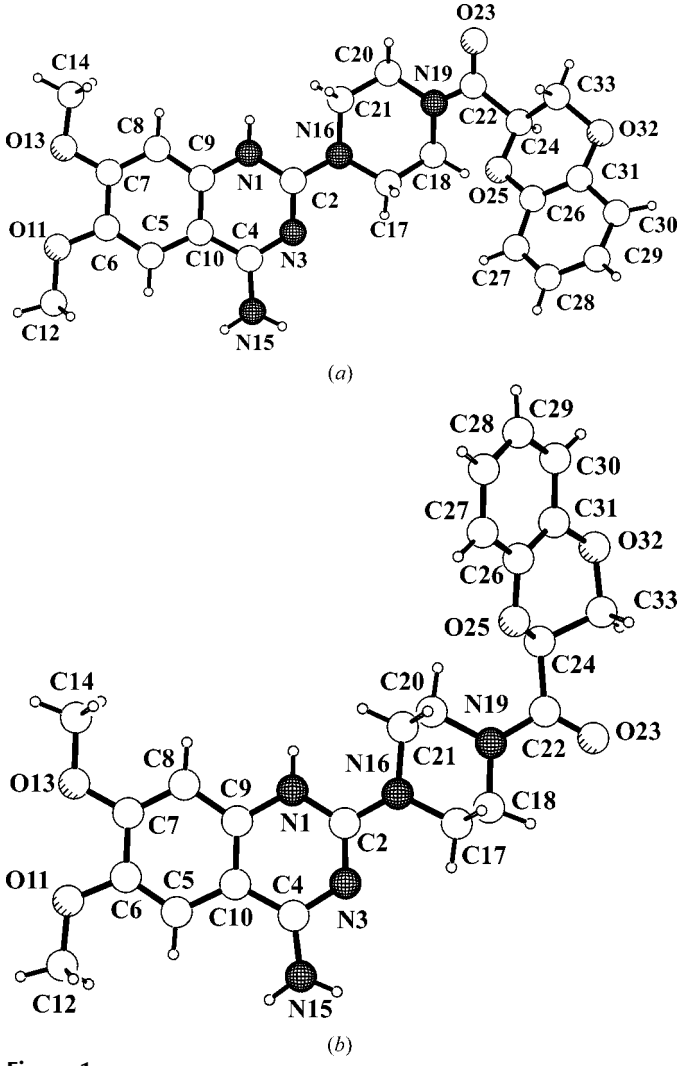


Figure 1
Atom numbering and conformations of the protonated form of doxazosin in (*a*) *A* and (*b*) *dG*.

2. Experimental

2.1. Synthesis

All the compounds used were synthesized as polycrystalline powders in the Department of Medicinal Chemistry, State Scientific Centre of Antibiotics, Moscow, Russia. 4-Amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline was prepared as described in the literature (Campbell *et al.*, 1987).

The anhydrous form *A* was prepared following the method described by Klein *et al.* (1999): methanesulfonic acid (1.75 ml, 26.8 mmol) was added to 4-amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline (11.00 g, 24.4 mmol) in a mixture of methanol (100 ml) and *N*-methyl-2-pyrrolidone (25 ml). The precipitate obtained was dissolved, and the solution was filtered and stirred at room temperature for 6 h. The precipitate was filtered off, washed with 2 × 10 ml of methanol and refluxed in 200 ml of ethanol for 4 h. The product was filtered off and dried *in vacuo* at 353 K. Yield: 9.72 g (73%) of 4-amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline methanesulfonate in crystalline form *A*.

The hydrated form *dG* was obtained while preparing the anhydrous form *G* following the method described by Grafe & Moersdorf (2000*a*): to a suspension of 4-amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline (11.25 g, 25 mmol) in *n*-butanol (50 ml) and water (14 ml) was added formic acid (3.2 ml, 85 mmol). The solution obtained was filtered and methanesulfonic acid (1.95 ml, 30 mmol) was added. The mixture was stirred at 313 K for 6 h and kept overnight at room temperature. The

Table 1
Experimental details.

	A	*dG*
Crystal data		
Chemical formula	$C_{23}H_{26}N_5O_5^+ \cdot CH_3SO_3^-$	$C_{23}H_{26}N_5O_5^+ \cdot CH_3SO_3^- \cdot 2H_2O$
M_r	547.58	583.61
Cell setting, space group	Monoclinic, *C*2/*c*	Monoclinic, $P2_1/c$
a, *b*, *c* (Å)	35.259 (2), 7.7634 (5), 20.9373 (12)	8.2956 (6), 32.1542 (15), 10.6473 (8)
β (°)	118.715 (7)	107.372 (7)
V (Å^3)	5026.4 (5)	2710.5 (3)
Z	8	4
D_x (Mg m^{-3})	1.447	1.430
Radiation type	Synchrotron	Synchrotron
μ (mm^{-1})	0.19	0.19
Temperature (K)	295 (2)	295 (2)
Specimen form, color	Cylinder (particle morphology: no specific habit), white	Cylinder (particle morphology: no specific habit), white
Specimen size (mm)	15 × 1 × 1	15 × 1 × 1
Data collection		
Diffractometer	BM1B, ESRF powder diffractometer	ID31, ESRF powder diffractometer
Data collection method	Specimen mounting: specimen was sealed in a 1 mm diameter borosilicate glass capillary; mode: transmission; scan method: continuous	Specimen mounting: specimen was sealed in a 1 mm diameter borosilicate glass capillary; mode: transmission; scan method: continuous
Absorption correction	None	None
2θ (°)	$2\theta_{min}$ = 2.030, $2\theta_{max}$ = 35.525, increment = 0.005	$2\theta_{min}$ = 2.049, $2\theta_{max}$ = 30.999, increment = 0.003
Refinement		
Refinement on	I_{net}	I_{net}
R factors† and goodness-of-fit	R_p = 0.040, R_{wp} = 0.056, R_{exp} = 0.025, *S* = 2.27	R_p = 0.049, R_{wp} = 0.072, R_{exp} = 0.026, *S* = 2.63
Wavelength of incident radiation (Å)	0.79985 (1)	0.69999 (1)
Profile function	Split-type pseudo-Voigt (Toraya, 1986)	Split-type pseudo-Voigt (Toraya, 1986)
No. of parameters	177	185
H-atom treatment	Not refined	Not refined
Weighting scheme	Based on measured s.u.'s	Based on measured s.u.'s
$(\Delta/\sigma)_{max}$	0.03	0.03
Preferred orientation correction	Symmetrized harmonics expansion up to the fourth order (Ahtee *et al.*, 1989; Järvinen, 1993)	Symmetrized harmonics expansion up to the fourth order (Ahtee *et al.*, 1989; Järvinen, 1993)

† R_p, R_{wp} and R_{exp} are defined according to Young & Wiles (1982). Computer programs used: *LSPAID* (Visser, 1986), *MRIA* (Zlokazov & Chernyshev, 1992), *PLATON*92 (Spek, 2003).

product was filtered off, washed in methanol and dried *in vacuo* over P_2O_5. Yield: 10.55 g (72%) of 4-amino-2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxyquinazoline methanesulfonate dihydrate in crystalline form. The measured powder pattern of the obtained sample did not correspond to those described in the original patent (Grafe & Moersdorf, 2000*a*) for preparing the anhydrous form *G*.

2.2. Data collection and indexing

High-resolution synchrotron powder diffraction data were collected at room temperature in the capillary mode at the powder diffraction beamlines BM1B (Swiss-Norwegian Beam Line BM1B; http://www.snbl.org) and ID31 (Fitch, 1996) at the ESRF, Grenoble, France. To evaluate the degree of the possible preferred orientation in both samples additional measurements in the Bragg–Brentano mode were undertaken on the high-resolution powder diffractometer on beamline No. 2 of the VEPP-3 storage ring (Shmakov *et al.*, 1994) at the Siberian Synchrotron Radiation Center, Novosibirsk, Russia. A comparison for both samples of two powder patterns measured in two different geometries revealed only weak texture effects. The monoclinic unit-cell dimensions of *A* and *dG* were determined with *TREOR*90 (Werner *et al.*, 1985) and *AUTOX* (Zlokazov, 1992, 1995). A few weak lines from an unidentified impurity were observed for *dG* (*d* spacings: 9.563, 8.496, 6.618, 6.260 Å). The space groups for both compounds were determined on the basis of systematic extinctions. The unit-cell parameters and space groups were tested further using Pawley's fit (Pawley, 1981), which gave R_{wp} = 0.047 for *A* and R_{wp} = 0.059 for *dG*, and confirmed by crystal structure solution. Crystallographic data for *A* and *dG* are summarized in Table 1.[1]

2.3. Structure solution from powder data

The structures were solved with the systematic grid search procedure (Chernyshev & Schenk, 1998), varying by only nine degrees of freedom – three translational parameters for the mesylate moiety, three translational, two rotational and one torsional parameter for the doxazosin moiety, and using 120 X_{obs} (Chernyshev & Schenk, 1998) low-angle values. The total number of checked variants was 7×10^8 and required 20 h for computations on a Pentium 933 MHz PC for each structure. The initial geometrical model of doxazosin was taken from the literature (Campbell *et al.*, 1987) and another model was obtained by rotating the carboxamide 180° around the N19—C22 bond (Fig. 1). The only torsional degree of freedom during the grid search with the two initial models was a rotation of 2,3-dihydro-1,4-benzodioxine around the C22—C24 bond in the

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX5006). Services for accessing these data are described at the back of the journal.

Table 2
N—H···O and O—H···O hydrogen-bonding geometry (Å, °) for *A* and *dG*.

The O atoms O35, O37 and O38 are from mesylate, and O23 is from carboxamide. O39 and O40 are from water molecules in *dG*.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Form *A*				
N1—H1···O38^{i}	0.86	1.96	2.76 (1)	155
N15—H15*A*···O35^{ii}	0.86	1.96	2.79 (1)	163
N15—H15*B*···O37^{iii}	0.86	2.30	3.15 (1)	171
Form *dG*				
N1—H1···O39	0.86	2.05	2.89 (1)	164
O39—H39*B*···O40	0.90	1.95	2.84 (1)	180
O40—H40*A*···O37	0.90	1.84	2.72 (1)	168
N15—H15*A*···O38^{iv}	0.86	2.17	3.01 (1)	166
N15—H15*B*···O38^{v}	0.86	2.05	2.88 (1)	162
O39—H39*A*···O35^{vi}	0.90	1.79	2.69 (1)	180
O40—H40*B*···O23^{vii}	0.90	2.12	3.02 (1)	180

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

carboxamide moiety. The variation of the torsion angle about the C2—N16 bond was not allowed, as it was not observed in the related structures (Campbell *et al.*, 1987; Alabaster *et al.*, 1987; Bontchev *et al.*, 2001). Based on the crystal packing of 2-[4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazin-1-yl]-6,7-dimethoxy-4-(dimethylamino)quinazoline (Campbell *et al.*, 1987), an assumption was made that in *A* and *dG* the doxazosin moieties are packed in a manner such that the planar quinazoline fragments form stacks along the shortest unit-cell dimension with interplanar distances of approximately 3.5 Å. This assumption allowed us to keep the normal to the quinazoline plane at a constant angle to the *b* axis for *A* (26°) and to the *a* axis for *dG* (33°), which requires only one rotational degree of freedom, and to rotate the doxazosin moiety around the normal using the second rotational degree of freedom. The correct locations of the doxazosin and mesylate moieties were confirmed by a preliminary Rietveld refinement and reasonable intermolecular distances. The relatively high value of R_{wp} = 0.1375 (compared with R_{wp} = 0.0591 from the Pawley fit) obtained at this stage for *dG* was an indicator that the structure of *dG* was not complete. The asymmetric unit of *dG* was scanned again with an O atom with the grid search procedure and two water oxygen positions were found and refined freely. The correct orientations of the mesylate moieties were further obtained with the orientational grid search (three degrees of freedom) and tested by the final Rietveld refinement. The correctness of the solutions of *A* and *dG* was also checked by the Rietveld refinement without H atoms and without restrictions on the geometric parameters of the structures, which remained stable although the substantial distortions of the bond lengths and bond angles were observed.

2.4. Rietveld refinement

In the final bond-restrained Rietveld refinement all patterns were fitted with the program *MRIA* (Zlokazov & Chernyshev, 1992) using a split-type pseudo-Voigt peak profile function (Toraya, 1986), taking into account anisotropic line-broadening (Popa, 1998) and the symmetrized harmonics expansion texture formalism (Ahtee *et al.*, 1989; Järvinen, 1993). The minimal and maximal texture corrections for the intensities of reflections were 0.90 and 1.07 for *A*, and 0.86 and 1.11 for *dG*, respectively. The following constraints and restraints were applied (the atomic numbering scheme is given in Fig. 1):

(i) three common isotropic displacement parameters were refined for *A* – one for N1—C24, one for O25—C33 and one for the mesylate moiety. Two more isotropic displacement parameters were refined for *dG* – for O atoms O39 and O40 from the water molecules;

(ii) restraints were applied to the intramolecular bond lengths and contacts in the doxazosin and mesylate moieties. The strength of the restraints was a function of interatomic separation and, for intramolecular bond lengths, corresponded to an r.m.s. deviation of 0.03 Å;

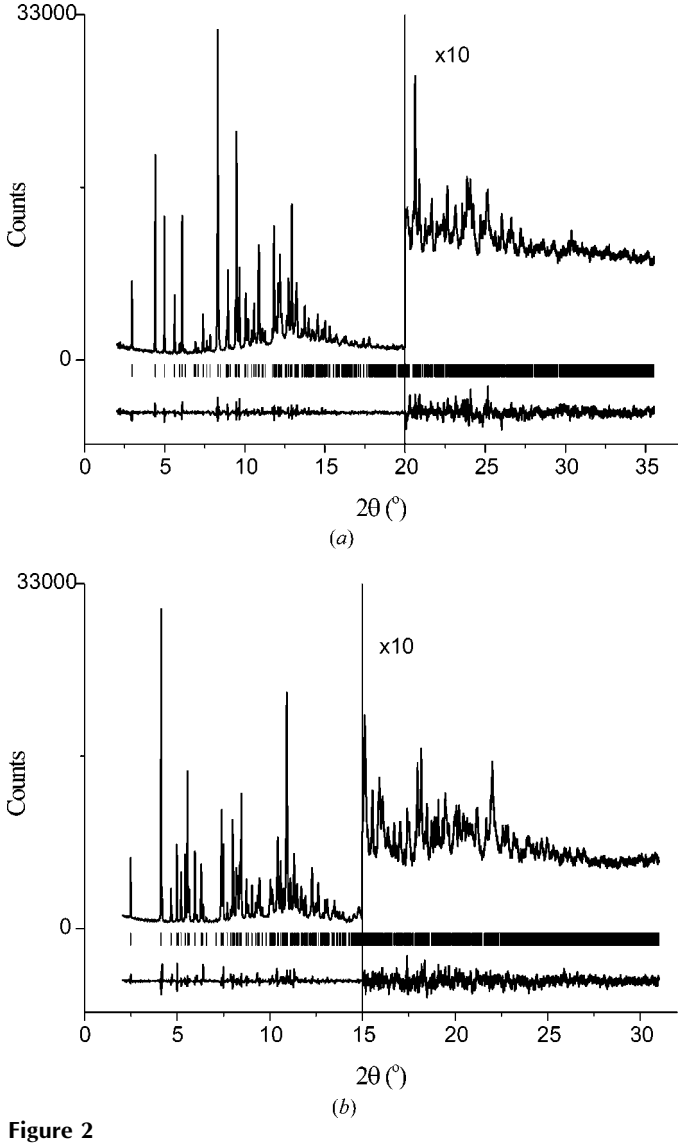


Figure 2
Rietveld plots of (*a*) *A* and (*b*) *dG*.

(iii) additional restraints were applied to the planarity of the following fragments – (1) N1–C17, C21 (18 atoms), (2) C18—C20, C22–C24 (six atoms) and (3) O25–O32 (eight atoms).

H atoms were positioned geometrically with C—H 0.93–0.98 Å and N—H 0.86 Å. The H atoms from two water molecules in *dG* were placed at 0.9 Å from the O atoms in the directions of the short intermolecular O···O contacts with the H—O—H angle of 110°. The conformations of the protonated doxazosin moieties in *A* and *dG* are shown in Fig. 1. The diffraction profiles and the differences between the measured and calculated profiles after the final bond-restrained Rietveld refinement are shown in Fig. 2.

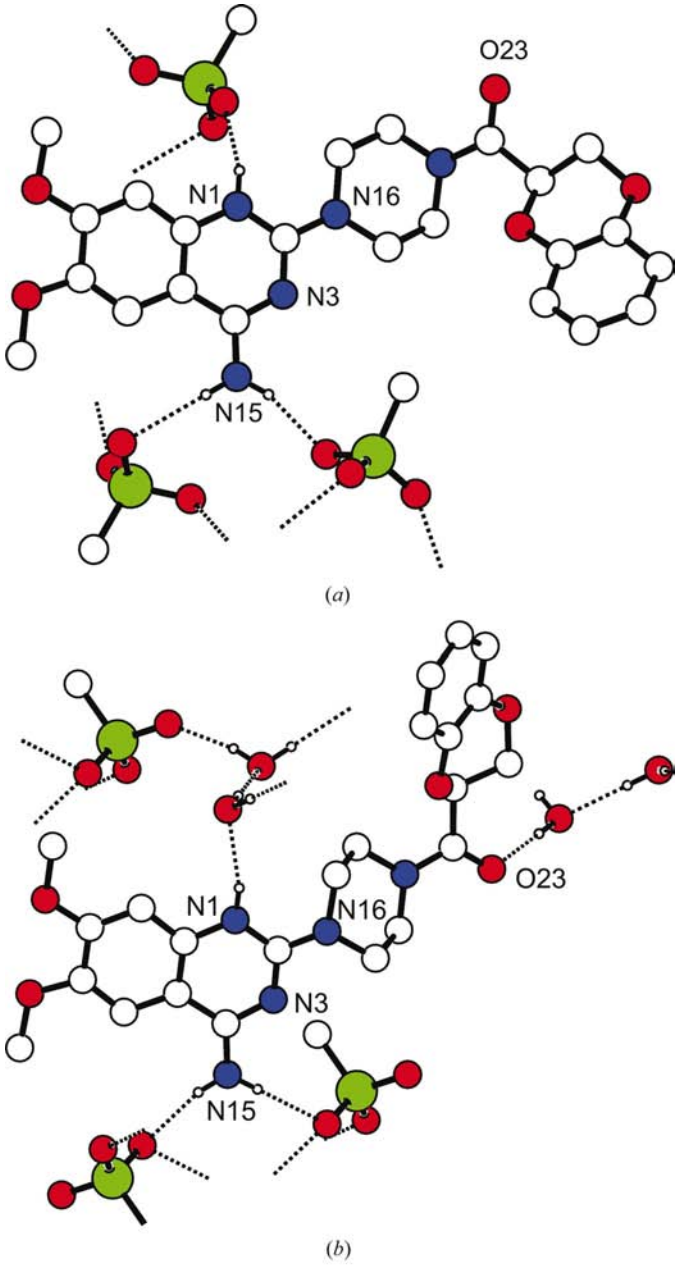


Figure 3
Hydrogen bonding in (*a*) *A* and (*b*) *dG*.

3. Results and discussion

The three-dimensional structures of *A* and *dG* demonstrate close N1···O contacts (Table 2) – 2.76 Å in *A* and 2.89 Å in *dG* – which allow the unambiguous identification of N1 protonation in both structures (Fig. 3). The position of the H1 atom, attached to N1, can also be found in a difference-Fourier map among the ten highest positive peaks. However, we cannot consider this finding as evidence of N1 protonation, because the five highest positive peaks concentrate around the mesylate ion. Obviously, the accuracy of the current powder study is not sufficient for the reliable location from a difference-Fourier map of only one H atom, which introduces 0.3% to the total scattering power. Once the hydrogen contribution to the total scattering power is more than 1%, high-resolution synchrotron powder data can provide its reliable location on a difference-Fourier map (Dinnebier *et al.*, 1999; Chernyshev *et al.*, 1999).

In addition to the opposite orientations of 2,3-dihydro-1,4-benzodioxine moieties (Fig. 1), the main conformational differences are associated with the piperazine rings. In *dG* piperazine has a classical chair conformation, while in *A* its conformation can be classified as a distorted chair (Fig. 4*a*). It should be emphasized that the conformation of piperazine obtained in *A* was not caused by restraints imposed in the Rietveld refinement – attempts to keep the geometry of piperazine in a classical chair conformation gave a poorer R_{wp} value (0.086 *versus* 0.056). Another unusual conformation of a piperazine ring – a twisted form (Fig. 4*c*) – was reported recently (Bontchev *et al.*, 2001). Rich three-dimensional hydrogen-bonding networks are observed in *A* and *dG* (Table 2). These networks are formed by N1 and the amino H atoms and O atoms of the mesylate moieties, while solvent water molecules and carboxamide oxygen are also incorporated in the hydrogen-bonding network in *dG* (Fig. 3). In both structures quinazoline groups form stacks stretched along [010] and [100] in *A* and *dG*, respectively. The interstack area is filled by interlaced piperazine and benzodioxine moieties. In *dG* mesylate anions and water molecules fill interstack channels. The crystal packings of *A* and *dG* are shown in Fig. 5, prepared using *PLATON* (Spek, 2003).

The present study allowed the definitive detection of the N1 protonation site in anhydrous and hydrated solid forms of doxazosin mesylate as a result of crystal structure determination from powder data. This work is in line with the crystal structure determinations of the metastable phase of piracetam (Louër *et al.*, 1995), capsaicin, thiothixene and promazine

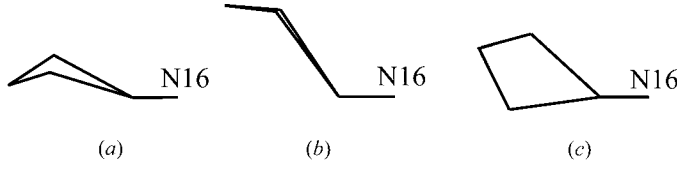


Figure 4
Conformations of the piperazine ring in (*a*) *A*, (*b*) *dG* and (*c*) prazosin (Bontchev *et al.*, 2001).

(David *et al.*, 1998), fluticasone propionate (Kariuki *et al.*, 1999), hydrated and two anhydrous forms of zopiclone (Shankland *et al.*, 2001), two crystalline modifications of telmisartan (Dinnebier *et al.*, 2000), the metastable polymorphic form of acetohexamide (Stephenson, 2000), tetracaine hydrochloride (Nowell *et al.*, 2002), and ranitidine hydrochloride (Huq & Stephens, 2003), which demonstrate the growing opportunities of high-resolution powder diffraction in pharmaceutical analysis.

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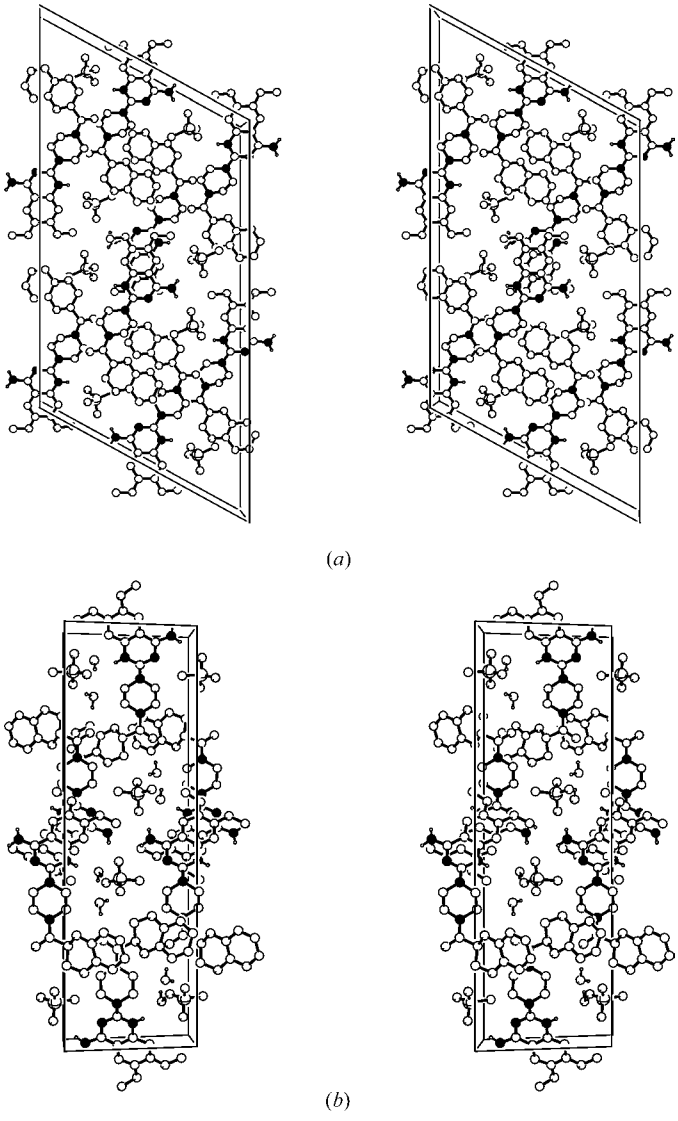

Figure 5
Stereoview of crystal packing in (*a*) *A*, viewed along the *b* axis, and (*b*) in *dG*, viewed along the *a* axis.

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