New Crystalline Forms of Piroxicam

Anatoly Mishnev and Glebs Kiselovs

Latvian Institute of Organic Synthesis, 21 Aizkraukles street, Riga, LV-1006, Latvia

Reprint requests to Anatoly Mishnev. E-mail: mishnevs@osi.lv

Z. Naturforsch. **2013**, *68b*, 168 – 174 / DOI: 10.5560/ZNB.2013-2268
Received October 12, 2012

Four new crystalline forms of piroxicam have been obtained and studied by single-crystal X-ray structure analysis. These comprise an addition salt with hydrochloric acid, acetic and isobutyric acids solvates, as well as piroxicam and furosemide cocrystal acetone solvate. All these new structures contribute to the variety of already known piroxicam crystalline forms. The analysis of conformations and tautomeric forms of piroxicam molecules in different crystal forms is presented.

Key words: Piroxicam, X-Ray Crystal Structure, Crystal Forms, Cocrystals

Introduction

An important step in the drug development process is the selection of an appropriate solid form of an active pharmaceutical ingredient (API). Bases, salts, cocrystals, hydrates, solvates or polymorphs of APIs may be selected for development. The API's solid form defines its physicochemical properties such as solubility, dissolution rate, hygroscopicity, physical and chemical stability, and mechanical properties. In general the most important properties that determine the API "to be, or not to be" a drug are solubility and stability of the best-available crystal form. From this point of view search for new crystalline forms of APIs is an important step of pharmaceutical research. The limitation on the number of possible crystal forms imposed by the finite number of "pharmaceutically acceptable" acids and bases [1] can be overcome by means of co-crystallization of APIs with other APIs chosen in a rational way.

Piroxicam (Fig. 1) is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis and acute gout disease [2]. Piroxicam has three crystalline polymorphic forms, β-monoclinic I [3], α-orthorhombic [4] and β-monoclinic II [5] given in the chronological order of their disclosure. Vrecer *et al.* [6] characterized piroxicam crystal modifications using different physicochemical methods. In particular it was shown that dissolution rates of different polymorphic forms in gastric fluid vary strongly [6]. Ref. [7] reviews papers on piroxicam polymorphism attempting to clarify the nomenclature and hydrogen bonding patterns that were in confusion. Another study [8] examined the effect of the ethanolamine salts of piroxicam on the pharmacokinetics of piroxicam after oral administration. In ref. [9] it was stressed that for analgetics like piroxicam activation time intervals shorter than two hours are necessary. Thus one has a good reason for further optimization of piroxicam crystal forms.

Up to now piroxicam was already subjected to intensive studies aimed to obtain crystal forms with improved properties. More than 50 piroxicam co-crystals with 23 carboxylic acids have been detected and characterized [9]. Single-crystal X-ray structures were re-

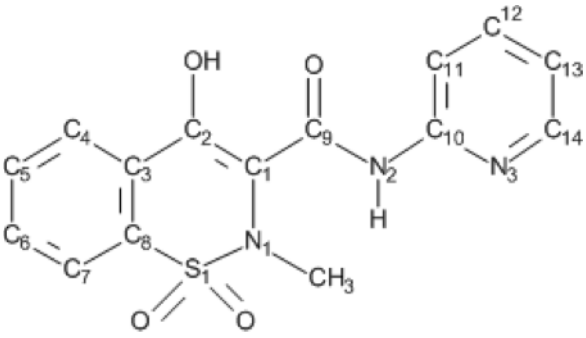

Fig. 1. Molecular diagram of piroxicam and atom numbering scheme.

© 2013 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com

Table 1. Crystalline forms of piroxicam deposited at CCDC [11].

Crystal form	Ligand/guest molecule	Ratio	CCDC Ref. code/deposition no.
Polymorphs			
β-monoclinic I	–		BIYSEH, BIYSEH01/03/04
β-monoclinic II	–		BIYSEH05/06
α-orthorhombic	–		BIYSEH02
Solvates	H_2O	1 : 1	CIDYAP/01
	p-dioxane	4 : 1	DIKDUX
	acetic acid	1 : 1	CCDC 840408
	isobutyric acid	1 : 1	CCDC 890344
Salts	ethanolamine	1 : 1	SECDAF
	hydrochloric acid	1 : 1	CCDC 840409
Cocrystals	succinic acid	2 : 1	DIKCIK
	1-hydroxy-2-naphthoic acid	1 : 1	DIKCOQ
	caprylic acid	1 : 1	DIKCUW
	malonic acid	–	DIKDAD
	4-hydroxybenzoic acid, form I	1 : 1	DIKDEH
	4-hydroxybenzoic acid, form II	1 : 1	NIFKIX
	fumaric acid	4 : 1	DIKDIL
	benzoic acid	1 : 1	DIKDOR
	saccharin	1 : 1	YANNEH
Cocrystal solvate	furosemide, acetone	1 : 1 : 1	CCDC 890345

ported only for 8 out of the 50 piroxicam cocrystals and for one solvate of piroxicam with dioxane. Salts of piroxicam with other active pharmaceutical ingredients, such as doxepin, pirbuterol, isoproterenol, pyridoxine, and trimazosin were reported but their X-ray crystal structures were not provided [10]. A search of the Cambridge Structural Database (CSD) at the Cambridge Crystallographic Data Centre (CCDC) [11] revealed 15 crystal structures with piroxicam (excluding structures of its organometallics) which are listed in Table 1 together with four new crystal forms of piroxicam developed in this work. Thereby on the whole there are 19 crystal structures containing 24 independent piroxicam molecules.

It is surprising that in spite of the large number of the piroxicam crystal structures studied the analysis of intramolecular hydrogen bonds (H bonds) given in [6, 7, 10] was not complete. For unknown reasons researchers missed the third intramolecular hydrogen bond of the C–H···O type present in the piroxicam molecule. In this paper we consider this interaction. Formation of H bonds of the type C–H···O is a well established fact [12, 13], and have been termed weak hydrogen bonds of electrostatic or mostly electrostatic nature [14].

To describe the conformation of the piroxicam molecule we define the three torsion angles ω_1 = C2–C1–C9–N2, ω_2 = C1–C9–N2–C10 and ω_3 = C9–N2–C10–N3 according to notations shown in Fig. 1. We use these torsion angles to classify all possible conformations into groups as follows. When all ω values are close to 180° we assign the molecule *trans-trans-trans* conformation. In case ω_2 is close to 180° but ω_1 and ω_3 are both close to zero, the molecule assumes *cis-trans-cis* conformation. Piroxicam molecule conformations in relation to tautomeric forms are summarized in Table 2 for all 19 crystal structures.

Results and Discussion

*Crystal structure of piroxicam hydrochloride (**1**)*

The crystal structure shown in Fig. 2 as an ORTEP-III [15, 16] drawing contains a piroxicam molecule protonated at pyridine nitrogen atom as a cation and a chloride anion. The conformation of the cation is *trans-trans-trans* with the torsion angles values ω_1, ω_2 and ω_3 given in Table 2. As mentioned in the introduction, unlike cited in earlier publications we observe three intramolecular hydrogen bonds O2–H···O1, N2–H···N1 and C11–H···O1 in the crystal which stabilize the *trans-trans-trans* conformation and make the piroxicam molecule nearly rigid. The geometry of the intra- and interionic hydrogen bonds found in piroxicam hydrochloride (**1**) is given in Table 3. The chloride anion as H bond participates as acceptor in two

Table 2. Tautomeric forms and conformations of piroxicam in different crystal forms.

Crystal form/Ref.code	Tautomer	ω_1	ω_2	ω_3	Conformation
Polymorphs					
BIYSEH	non-ionized	174.29	177.90	174.74	*trans-trans-trans*
BIYSEH05	non-ionized	175.18	176.40	175.09	*trans-trans-trans*
BIYSEH02	non-ionized	172.37	174.79	171.27	*trans-trans-trans*
Solvates					
CIDYAP ($Z' = 2$)	zwitterion	−11.99/	176.99/	12.18/	*cis-trans-cis*
	zwitterion	−0.86	−170.01	−5.91	*cis-trans-cis*
CIDYAP01 ($Z' = 2$)	zwitterion	0.8/	176.53/	−13.45/	*cis-trans-cis*
	zwitterion	2.74	−169.72	6.95	*cis-trans-cis*
DIKDUX ($Z' = 2$)	zwitterion	−1.7/	176.7/	11.3/	*cis-trans-cis*
	zwitterion	−0.3	169.8	5.6	*cis-trans-cis*
Acetic acid	non-ionized	173.1	175.8	−170.3	*trans-trans-trans*
Isobutyric acid	non-ionized	171.9	−179.4	178.5	*trans-trans-trans*
Salts					
SECDAF	ionized	4.8	177.6	−158.3	*cis-trans-trans*
Hydrochloric acid	ionized	179.1	−175.8	176.3	*trans-trans-trans*
Cocrystals					
DIKCIK	non-ionized	169.4	171.9	168.5	*trans-trans-trans*
DIKCOQ	non-ionized	177.8	179.8	180.0	*trans-trans-trans*
DIKCUW	non-ionized	169.3	168.8	168.5	*trans-trans-trans*
DIKDAD	non-ionized	172.4	179.1	176.8	*trans-trans-trans*
DIKDEH	non-ionized	173.4	174.9	169.7	*trans-trans-trans*
NIFKIX	zwitterion	0.7	172.0	6.8	*cis-trans-cis*
DIKDIL ($Z' = 2$)	non-ionized/	168.0/	−178.2/	163.1/	*trans-trans-trans*
	zwitterion	4.2	178.6	10.4	*cis-trans-cis*
DIKDOR	zwitterion	2.9	177.7	6.0	*cis-trans-cis*
YANNEH	zwitterion	1.0	171.8	3.0	*cis-trans-cis*
Cocrystal solvate					
Furosemide, acetone	non-ionized	178.1	177.4	177.4	*trans-trans-trans*

hydrogen bonds N3–H···Cl and N2–H···Cl. The hydrogen at the N2 nitrogen atom forms bifurcated H bonds. According to the nomenclature introduced by Etter [17], the intramolecular C11–H···O1 H bond motif can be written as $S(6)$ while the intermolecular H bond network in the structure **1** is $R_1^2(6)$. The two other intramolecular hydrogen bonds O2–H···O1 and N2–H···N1 in piroxicam [7] were ascribed by $S(6)$ and $S(5)$ graph sets.

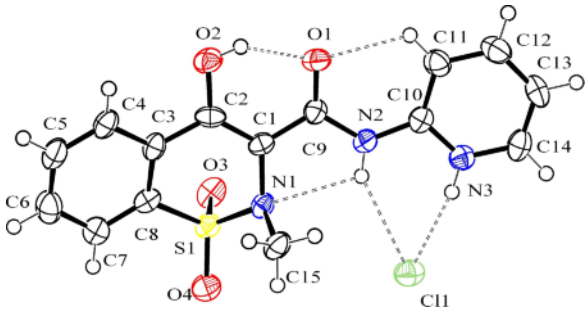

Fig. 2. ORTEP-III view of the crystal structure of piroxicam hydrochloride (**1**) with H bonds.

On the whole bond lengths and angles in the four piroxicam crystal forms are close to their standard values [18]. However a comparison of the molecular geometry indicates that the bonds N2–C9 and N2–C10 in piroxicam hydrochloride **1** are almost equal and are close to the average value of 1.382 Å. In the structures **2**–**4** these bonds are more differentiated in length and assume average values of 1.355 and 1.411 Å for N2–C9 and N2–C10 bonds, respectively.

*Crystal structure of piroxicam acetic acid solvate (**2**)*

The crystal structure of piroxicam acetic acid solvate **2** (Fig. 3) comprises the nonionized tautomeric form of piroxicam and an acetic acid molecule. The conformation of the former is *trans-trans-trans* (see also Table 2). There are three intramolecular H bonds in the piroxicam molecule in the structure of **2**. The geometry of the intra- and intermolecular hydrogen

Table 3. Hydrogen bonding geometry (Å, deg) for **1**.

D–H···A	H···A	D···A	∠ D–H···A
O2–H···O1[a]	1.79	2.520	147
N2–H···N1[a]	2.39	2.799	109
C11–H···O1[a]	2.23	2.808	119
N3–H···Cl1	2.15	2.998	168
N2–H···Cl1	2.57	3.331	148
C11–H···O4[b]	2.35	3.184	149
C14–H···O3[c]	2.32	3.181	154

[a] Intramolecular H bond; [b] sym. code: $1+x, y, z$; [c] sym. code: $1-x, 1/2+y, 1-z$.

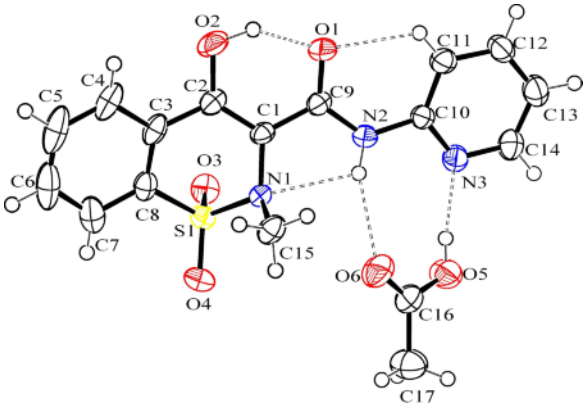

Fig. 3. ORTEP-III view of the crystal structure of piroxicam acetic acid solvate (**2**) with H bonds.

bonds found in the piroxicam acetic acid solvate **2** is given in Table 4. The intermolecular H-bonding motif in **2** is $R_2^2(8)$.

*Crystal structure of piroxicam isobutyric acid solvate (**3**)*

The crystal structure of the piroxicam isobutyric acid solvate **3** (Fig. 4) contains a nonionized tautomeric form of piroxicam and one isobutyric acid molecule.

Table 4. Hydrogen bonding geometry (Å, deg) for **2**.

D–H···A	H···A	D···A	∠ D–H···A
O2–H···O1[a]	1.68	2.529	143
N2–H···N1[a]	2.34	2.769	111
C11–H···O1[a]	2.25	2.837	120
N2–H···O6[b]	2.29	3.097	156
O5–H···N3[b]	1.88	2.698	171
C5–H···O4[c]	2.29	3.184	167

[a] Intramolecular H bond; [b] sym. code: $1-x, -y, 1-z$; [c] sym. code: $-x, 1/2+y, 3/2-z$.

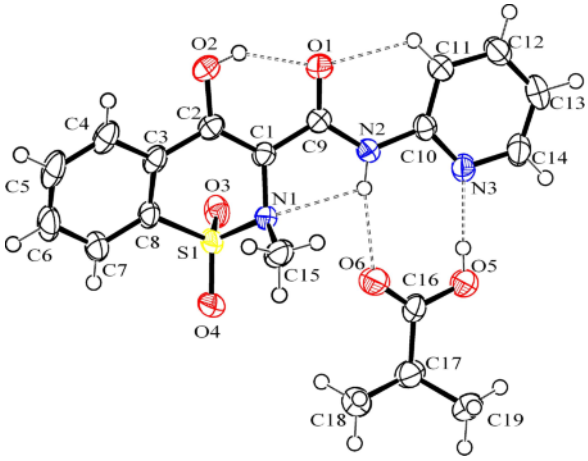

Fig. 4. ORTEP-III view of the crystal structure of piroxicam isobutyric acid solvate (**3**) with H bonds.

Table 5. Hydrogen bonding geometry (Å, deg) for **3**.

D–H···A	H···A	D···A	∠ D–H···A
O2–H···O1[a]	1.86	2.572	148
N2–H···N1[a]	2.35	2.771	111
C11–H···O1[a]	2.24	2.837	121
N2–H···O6[b]	2.12	2.968	168
O5–H···N3[c]	1.83	2.642	169

[a] Intramolecular H bond; [b] sym. code: $1+x, y, z$; [c] sym. code: $-1+x, y, z$.

The isobutyric acid is disordered and assumes two different positions with refined occupation factors of approximately 80 % and 20 %. Only the dominating solvate molecule is depicted in Fig. 4. The piroxicam molecule adopts *trans-trans-trans* conformation (torsion angles are given in Table 2). Again there are three intramolecular H bonds in the piroxicam molecule. The geometry of the H-bonding network in the structure of **3** is given in Table 5. The H-bonding motif connecting piroxicam and isobutyric acid molecules according to Etter [17] is $R_2^2(8)$.

*Crystal structure of piroxicam and furosemide cocrystal acetone solvate (**4**)*

The crystal structure of **4** (Fig. 5) is built up from nonionized molecules of piroxicam, furosemide and acetone forming a piroxicam and furosemide cocrystal acetone solvate. Thus the structure of **4** represents a two-component pharmaceutical solid comprising the NSAID drug piroxicam and the diuretic

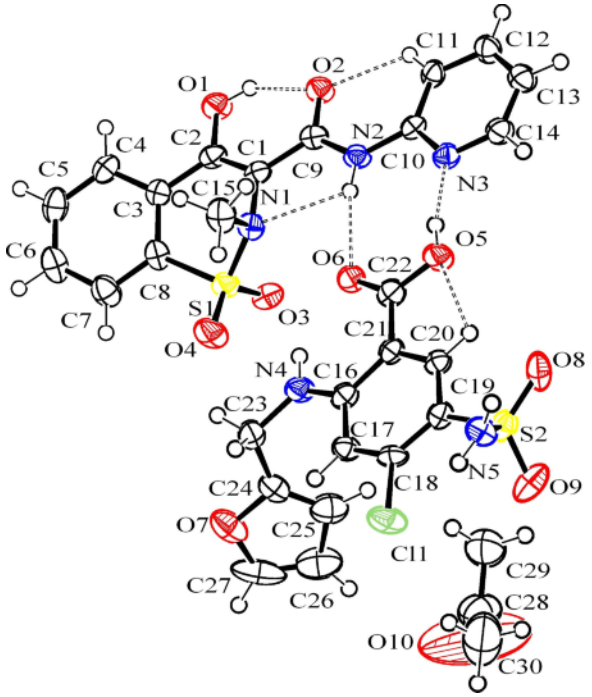

Fig. 5. ORTEP-III view of the crystal structure of piroxicam furosemide cocrystal acetone solvate (**4**) with H bonds.

Table 6. Hydrogen bonding geometry (Å, deg) for **4**.

D–H···A	H···A	D···A	∠ D–H···A
O1–H···O2[a]	1.79	2.525	146
N2–H1···N1[a]	2.37	2.784	109
C11–H···O1[a]	2.17	2.788	121
N4–H···O6[a]	2.04	2.716	133
C20–H···O5[a]	2.33	2.696	102
N2–H···O6[b]	2.26	3.131	168
O5–H···N3[b]	1.82	2.649	168
N5–H···O1[c]	2.31	2.922	127

[a] Intramolecular H bond; [b] sym. code: $1-x, 1-y, 1-z$; [c] sym. code: $1+x, 1+y, z$.

furosemide (4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid) [2]. In this rational combination furosemide removes the side effect of liquid accumulation in the body inherent to NSAIDs [19]. The piroxicam molecule assumes *trans-trans-trans* conformation (see Table 2) and has three intramolecular H bonds. The furosemide molecule in turn has two intramolecular H bonds of N–H···O and C–H···O types (see Table 6) forming a $S(6)$ and $S(5)$ graph set. Piroxicam and furosemide molecules are connected by three intermolecular H bonds listed in Table 6.

It is worth noting that both substances forming the crystal of **4** are polymorphic; piroxicam is known to exist in three polymorphic forms [3 – 5], and furosemide also has three known polymorphs [20, 21]. As we could see the piroxicam molecule in *trans-trans-trans* conformation retains its shape like a rigid body. The polymorphism of piroxicam therefore is positional. In contrast, the furosemide molecule is very flexible, and its polymorphism is conformational. To demonstrate its flexibility, some torsion angles for the furosemide molecule in the crystal of **4** and in three known polymorphic forms are listed in Table 7.

The data listed in Table 7 demonstrate that the torsion angles which define the shape of the furosemide molecule can assume arbitrary values; this means that the furosemide molecule has no stable dominant conformation. Apparently, due to its flexibility, furosemide can be considered as a useful cocrystal former, capable of adopting the conformation required for a particular crystalline environment and content.

Tautomeric forms of piroxicam and conformations

Conformations of the piroxicam molecule and its tautomeric forms are summarized in Table 2 for 19 known crystal structures containing 24 independent piroxicam molecules. All twelve nonionized piroxicam molecules adopt *trans-trans-trans* conformation, and the ten zwitterionic tautomeric forms have *cis-trans-cis* conformation. In case of piroxicam salts the conformation depends on the counterion character. In case of the ethanolamine salt, the piroxicam anion adopts the *cis-trans-trans* conformation, but in the hydrochloride structure it has *trans-trans-trans* conformation.

Maximal deviations of torsion angles ω from the ideal *trans-trans-trans* conformation are 12.0°, 11.2°

Furosemide crystal form	C24–C23–N4–C16	O7–C24–C23–N4	C18–C19–S2–N5
Furosemide in **4**	−76.3(5)	−168.7(5)	−60.7(4)
Polymorphic form I	83.6(6)/−63.0(5)	−67.2(5)/−53.9(6)	−166.3(6)/164.9(5)
Polymorphic form II	−166.4(3)	−78.2(4)	−79.9(3)
Polymorphic form III	91.3(4)	60.0(4)	55.7(3)

Table 7. Selected torsion angles characterizing the flexibility of the furosemide molecule.

and 21.7°, respectively, and 4.2°, 10.3° and 13.4° for the *cis-trans-cis* conformation.

Conclusion

Four new crystal forms of piroxicam comprising a salt with hydrochloric acid, and solvates with acetic and isobutyric acid, as well as a piroxicam and furosemide cocrystal acetone solvate have been obtained, and their molecular and crystal structures have been determined. Together with the structures studied in this work, the number of piroxicam crystal structures amounts to 19 that contain 24 independent molecules. Attention has been drawn to the existence of the third hydrogen bond of C–H···O type in the piroxicam molecule. In case of the non-ionized tautomer, three intramolecular H bonds stabilize the *trans-trans-trans* conformation of piroxicam that keeps the molecule nearly rigid. For twelve crystal structures the maximal deviations from the ideal *trans-trans-trans* conformation are 12.0°, 12.2° and 21.7° . In case of a zwitterionic tautomer having two intramolecular H bonds the *cis-trans-cis* conformation of the piroxicam molecule is more planar. Ten zwitterionic tautomeric forms demonstrate maximal deviations of 4.2°, 10.3° and 13.4° from the ideal conformation. For the first time piroxicam has been cocrystallized with another drug, furosemide, giving a pharmaceutical solid designed in accordance with drug combination rational principles.

Experimental Section

Sample preparation and crystallization

Chemically pure reagents and solvents for single-crystal growth were used. The β-monoclinic form I of piroxicam and the triclinic form I polymorph of furosemide were used as reagents for the preparation of new forms. Piroxicam hydrogen chloride was obtained by evaporation at room temperature of a solution in formic acid and hydrochloric acid in 1 : 1 volume ratio. Single crystals of piroxicam acetic acid solvate were grown from concentrated acetic acid by the method of slow evaporation. Single crystals of piroxicam isobutyric acid solvate were grown by slow evaporation from a hot isobutyric acid solution of piroxicam. Piroxicam and furosemide cocrystal acetone solvate was obtained from acetone solution of a 1 : 1 stoichiometric mixture of piroxicam and furosemide by slow evaporation.

Table 8. Crystallographic data and numbers pertinent to data collection and structure refinement for **1**, **2**, **3**, and **4**.

	1	**2**	**3**	**4**
Formula	$C_{15}H_{14}N3O_4SCl$	$C_{17}H_{17}N_3O_6S$	$C_{19}H_{19}N_3O_5S$	$C_{30}H_{30}N_5O_{10}S_2Cl$
M_r	367.80	391.40	419.45	720.16
Crystal size, mm^3	$0.32 \times 0.16 \times 0.12$	$0.42 \times 0.13 \times 0.08$	$0.23 \times 0.15 \times 0.10$	$0.28 \times 0.18 \times 0.10$
Crystal system	monoclinic	monoclinic	triclinic	triclinic
Space group	$P2_1$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
a, Å	9.2760(8)	16.6340(6)	8.4482(3)	9.2984(5)
b, Å	6.8080(7)	15.4410(5)	10.3605(4)	11.3622(7)
c, Å	12.6070(14)	6.9830(2)	11.7943(4)	16.5509(9)
α, deg	90	90	83.3780(10)	102.649(3)
β, deg	91.360(4)	100.480(1)	74.6530(10)	97.867(3)
γ, deg	90	90	78.673(2)	107.374(3)
V, A^3	795.92(14)	1763.63(10)	973.93(6)	1589.45(16)
Z	2	4	2	2
D_{calcd}, g cm^{-3}	1.54	1.47	1.48	1.51
μ(Mo$K\alpha$), cm^{-1}	4.0	2.3	2.1	3.2
F(000), e	380	816	440	748
hkl range	−10→12	±21	±10	−10→12
	−8→7	−8→20	±13	−14→12
	−16→15	±19	±15	±12
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.6527	0.6499	0.6497	0.6519
Refl. measd / unique / R_{int}	7549 / 2786 / 0.0539	9482 / 4013 / 0.0394	6188 / 4426 / 0.0203	22014 / 7178 / 0.0581
Param. refined	217	244	287	433
$R(F)$ / $wR(F^2)$ (all refl.)	0.1090 / 0.3586	0.0914 / 0.1369	0.0637 / 0.1145	0.1907 / 0.3023
GoF (F^2)	1.044	1.036	1.020	1.034
Flack x parameter	0.3(14)	–	–	–
$\Delta\rho_{fin}$ (max / min), e A^{-3}	0.29 / −0.28	0.44 / −0.63	0.24 / −0.54	0.94 / −0.67

X-Ray structure determination

The unit cell parameters and experimental reflection intensities were measured at 190 K on a Bruker Nonius KappaCCD diffractometer with graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). The data collections were performed using KappaCCD Server Software [22], cell refinement was done with SCALEPACK [23], and data were reduced with DENZO and SCALEPACK [23]. The structures were solved by Direct Methods (SHELXS-97 [24, 25]) and refined anisotropically on F^2 values using the program SHELXL-97 [26, 27]. All hydrogen atoms were positioned geometrically and refined with the riding model on the adjacent non-hydrogen atoms. Crystallographic data and details of the refinement of the structures are listed in Table 8.

CCDC 840408, 840409, 890344, and 890345 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[1] P. H. Stahl, C. G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts*, IUPAC, Wiley-VCH, Zürich, **2001**, pp. 374.
[2] J. E. F. Reynolds, A. B. Prasad (Eds.), *Martindale: The Extra Pharmacopoeia*, 28th edition, The Pharmaceutical Press, London, **1982**, pp. 276.
[3] B. Kojic-Prodic, Z. Ruzic-Toros, *Acta Crystallogr.* **1982**, *B38*, 2948 – 2951.
[4] G. Reck, G. Dietz, G. Laban, W. Gunther, G. Bannier, E. Hohne, *Pharmazie* **1988**, *43*, 477.
[5] A. R. Sheth, S. Bates, F. X. Muller, D. J. W. Grant, *Cryst. Growth Des.* **2005**, *5*, 571 – 578.
[6] F. Vrecer, M. Vrbinc, A. Meden, *Int. J. Pharm.* **2003**, *256*, 3 – 15.
[7] A. R. Sheth, S. Bates, F. X. Muller, D. J. W. Grant, *Cryst. Growth Des.* **2004**, *4*, 1091 – 1098.
[8] H.-S. Gwak, J.-S. Choi, H.-K. Choi, *Int. J. Pharm.* **2005**, *297*, 156 – 161.
[9] S. L. Childs, K. I. Hardcastle, *Cryst. Growth Des.* **2007**, *7*, 1291 – 1304.
[10] J. G. Lombardino, US 4,567,179, **1986**.
[11] F. H. Allen, *Acta Crystallogr.* **2002**, *B58*, 380 – 388.
[12] R. Taylor, O. Kennard, *J. Am. Chem. Soc.* **1982**, *104*, 5063 – 5070.
[13] T. Steiner, *Crystallogr. Rev.* **1996**, *6*, 1 – 57.
[14] G. Gilli in *Fundamentals of Crystallography*, (Ed.: C. Giacovazzo), Oxford University Press, Oxford, **2002**, pp. 585 – 666.
[15] C. K. Johnson, M. N. Burnett, ORTEP-III (version 1.0.2), Rep. ORNL-6895, Oak Ridge National Laboratory, Oak Ridge, TN (USA) **1996**. Windows version: L. J. Farrugia, University of Glasgow, Glasgow, Scotland (UK) **1999**.
[16] L. J. Farrugia, *J. Appl.Crystallogr.* **1997**, *30*, 565.
[17] M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120 – 126.
[18] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.
[19] M. L. Toews, D. B. Bylund, *Proc. Am. Thorac. Soc.* **2005**, *2*, 282 – 289; doi:10.1513/pats.200504-037SR.
[20] J. Lamotte, H. Campsteyn, L. Dupont, M. Vermeire, *Acta Crystallogr.* **1978**, *B34*, 1657 – 1661.
[21] N. J. Babu, S. Cherukuvada, R. Thakuria, A. Nangia, *Cryst. Growth Des.* **2010**, *10*, 1979 – 1989.
[22] KappaCCD Server Software, Nonius BV, Delft (The Netherlands) **1997**.
[23] Z. Otwinowski, W. Minor in *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, Eds.: C. W. Carter Jr, R. M. Sweet, Academic Press, New York, **1997**, pp. 307 – 326.
[24] G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**.
[25] G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467 – 473.
[26] G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen (Germany) **1997**.
[27] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.