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Rosiglitazone maleate 0.25-hydrate: a pseudopolymorphic form

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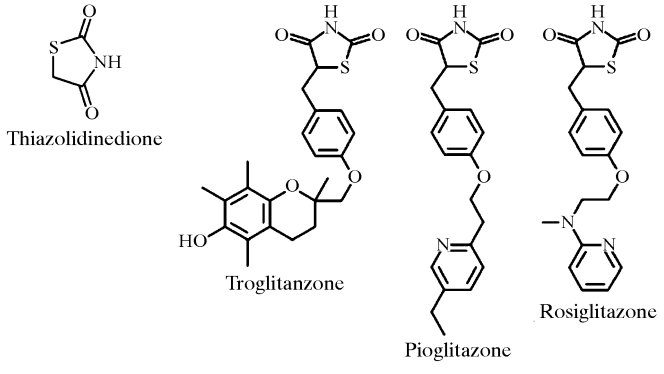
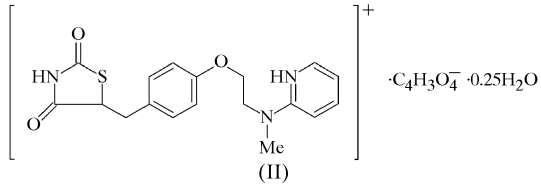
The present 0.25-hydrated form of rosiglitazone maleate [systematic name: (±)-2-({2-[2,4-dioxo-1,3-thiazolidin-5-ylmethyl)phenoxy]ethyl}methylamino)pyridinium maleate 0.25-hydrate], $C_{18}H_{20}N_3O_3S^+\cdot C_4H_3O_4^-\cdot 0.25H_2O$, is a racemate with two independent moieties in the unit cell. Although the cation geometry does not differ substantially from that in the previously reported hydrochloride, the packing is quite different, the main feature being the formation of hydrogen-bonded tetramers, linked head-to-tail into weakly interacting chains.

Comment

Several drugs in the thiazolidinedione group (see scheme) have been reported to present antidiabetic effects, such as troglitazone, pioglitazone and rosiglitazone. Probably as a consequence of having appeared on the market previously, troglitazone and pioglitazone have already been the subject of a thorough structural characterization of the many polymorphic or pseudopolymorphic forms known, and a number



of entries can be found in the Cambridge Structural Database (CSD, version of November 2006 with 2007 updates; Allen, 2002). Rosiglitazone (either as such or in its protonated version, hereinafter H-rosiglitazone) presents instead an interesting challenge from a structural point of view: two main forms with similar therapeutic properties are on the pharmaceutical market to date, namely the hydrochloride monohydrate, (I), and the maleate, nebulously described in different



patents (for example, Blackler *et al.*, 1999*a*,*b*; Blackler, Browne *et al.*, 2000; Blackler, Giles *et al.*, 2000; Blackler, Giles & Sasse, 2000; Giles *et al.*, 1999; Lynch *et al.*, 1999) in a variety of hydration states ($\cdot nH_2O$, where n ranges from zero to 0.6) and with significant differences in their X-ray powder diffraction diagrams. So far, only the hydrochloride monohydrate, (I), has been structurally characterized (Cantello *et al.*, 1994) in an enantiomerically pure sample of biochemical origin.

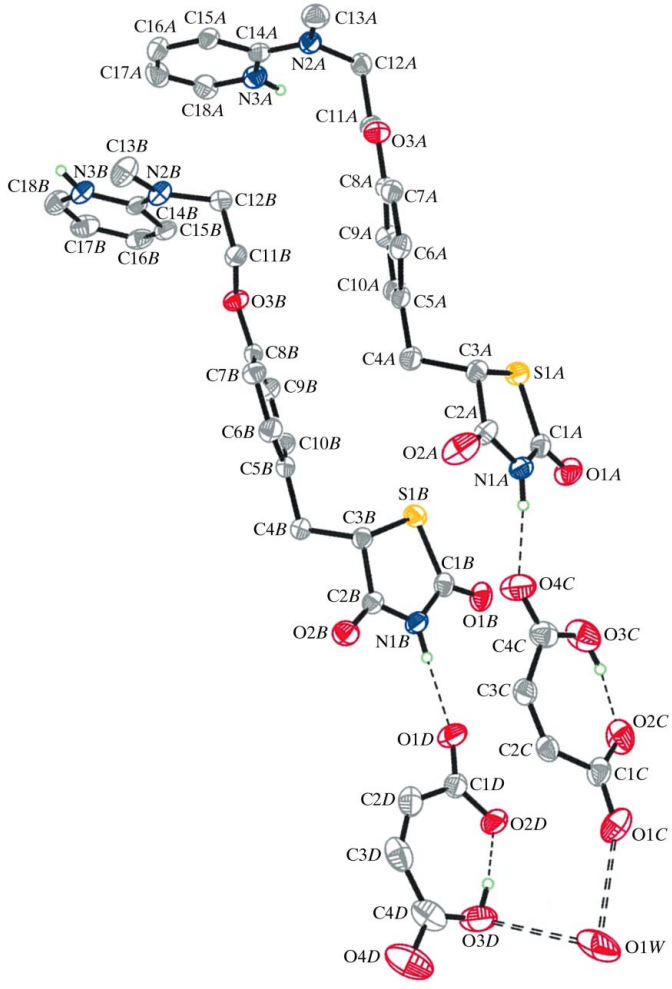


Figure 1
The asymmetric unit of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms have been omitted for clarity.

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In the present work, we try to fill this gap in the literature, reporting the crystal and molecular structure of the title maleate 0.25-hydrate, (II), hitherto structurally uncharacterized. Our results show that compound (II), as formed by crystallization from ethyl acetate of a commercial sample of synthetic origin, is a racemate, in the space group $P2_1/n$, composed of two independent units (hereinafter *Za* and *Zb*) of the protonated H-rosiglitazone cation (±)-2-({2-[2,4-dioxo-1,3-thiazolidin-5-ylmethyl)phenoxy]ethyl}methylamino)pyridinium, with the charge balance provided by two independent hydrogen maleate anions (hereinafter Hma^-), and one-half of a solvent water molecule, thus giving a minimum formula of $C_{18}H_{20}N_3O_3S^+\cdot C_4H_3O_4^-\cdot 0.25H_2O$. As in (I), both *Z* units in (II) are cationic, bearing one H atom at N3. In the former structure, charge balance is achieved through the presence of a Cl^- counter-ion, whereas in (II), the counter-ions are two Hma^- ions.

A general view of the full asymmetric unit of (II) (Fig. 1) shows most of the key points. Firstly, it is apparent that both independent cations (*Za* and *Zb*) in (II) are geometrically very similar, both to one another and to the cation in (I), despite the presence in (I) of just a single enantiomer. The main overall differences reside in the C8—O3—C11—C12 torsion angle at the ethoxy site (179.2° for *Za*, 20.5° for *Zb* and 177.9° for *Zc*) [*Zc* is the cation in (I)] and the C13—N2—C14—N3 torsion angle at the methylpyridylamino site (−178° for *Za*, 7.7° for *Zb* and 1.5° for *Zc*), which result in the terminal groups being oriented in different directions. Fig. 2 clarifies these differences through the least-squares fitting of individual moieties onto each other. It is apparent that the conformation of the cation *Zc* in (I) is somewhere between those of *Za* and *Zb* in (II).

The unique acidic H atoms in both anions make two rather strong almost linear intramolecular O···H—O hydrogen bonds (Table 1) defining a closed ring each and giving the molecule the appearance of a 'crab'. This is rather common in isolated Hma^- units: a search of the CSD gave a total of 115 reported cases of uncoordinated singly protonated Hma^- anions, of which 113 showed this arrangement, while the H-atom locations in the remaining two structures were uncertain. Although unusually short for conventional O···H—O interactions, the H···O distances in (II) (1.576 and 1.617 Å) lie in the longest quartile of the reported H···O range for uncoordinated Hma^- units (1.809–1.1223 Å). Thus, the intramolecular maleate hydrogen bonds found in (II) can be

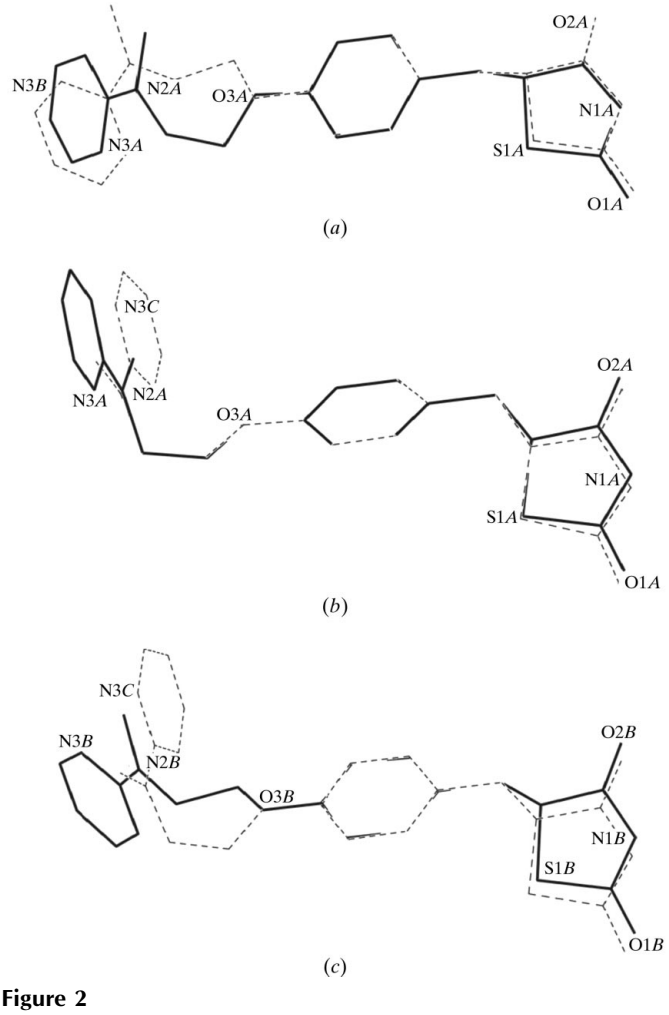

Figure 2
Schematic least-squares fitting of the different moieties of H-rosiglitazone, showing (*a*) *Za* in (II) *versus Zb* in (II), (*b*) *Za* in (II) *versus Zc* in (I) and (*c*) *Zb* in (II) *versus Zc* in (I). (See *Comment* for details.)

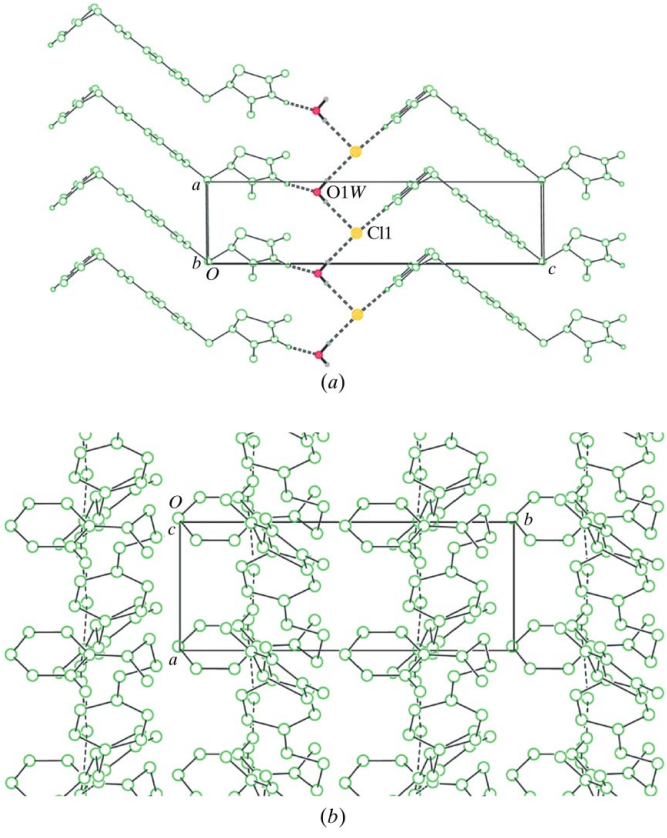

Figure 3
(*a*) The hydrogen-bonding scheme in the hydrochloride, (I). (*b*) A packing view normal to that shown in (*a*).

typified as comparatively weak when contrasted with their counterparts in the literature, in spite of their strength when evaluated in absolute terms.

It is interesting to compare the packing schemes of (I) and (II). The former presents, as characteristic features, a unique enantiomer and a counter-ion which can only behave as a hydrogen-bond acceptor, whereas the latter is a racemate counterbalanced by a flexible hydrogen-bonding donor/acceptor. Fig. 3 shows schematically the way in which the hydrochloride (I) packs, with the independent components defining a two-dimensional structure, tightly bound in a plane and loosely connected in the perpendicular direction by much weaker interactions. Structure (II) instead presents a much more complex disposition: the two independent *Za* and *Zb* molecules are tightly related to their counterparts at $(1-x, -y, 1-z)$ through hydrogen-bonding interactions mediated by N—H groups in the molecules and O—H groups in the Hma^- anions (Fig. 4 and Table 1). Thus, a kind of tetramer builds up with two representatives of each hand, which only leaves available for inter-tetrameric interaction two out of the four N3—H3N groups, *viz*. N3*B*—H3N*B* and its symmetric image through the tetramer centring. The remaining two, in turn, are devoted to construction of the tetramer *via* intra-tetrameric hydrogen bonds (Table 1). Thus, the external linkage is achieved at both sides of the rod-like group, defining a zigzag chain running along [011]. Interchain interactions, as in the case of (I), involve the much weaker C—H···O bonds (Table 1).

The (depleted) solvent water molecule attaches *via* hydrogen bonding (only inferred by the O···O distances and their relative disposition) at the extreme end of the tetramers, occupying a sort of capping position (Fig. 1). Its occupation factor of 0.5 is a result of the position of the solvate in the 'exclusion zone' of a centre of symmetry in the structure: the solvate lies *ca* 2.6 Å away from its own symmetry-related image and accordingly they are mutually exclusive, leading to a maximum possible presence for each one of 0.5, precisely as deduced from the refinement.

Comparison of the (calculated) X-ray powder diffraction of (II) with the experimental diagrams presented in the different patents in the literature suggests a best match with that in WO 9931093 (Lynch *et al.*, 1999). The water fraction, however, is slightly lower (0.25 mol in the present form *versus* 0.40 mol in the patent), a fact which should not surprise since the result from the Karl Fischer titration employed in the patent characterization may include some surface-adsorbed water, in contrast with the purely crystallographic water reported here.

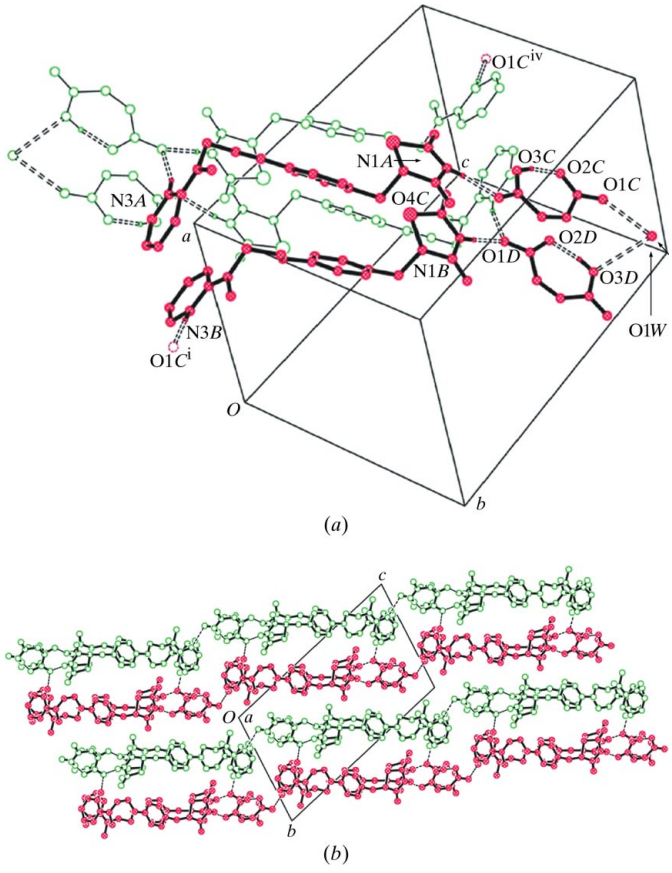

Figure 4
(*a*) The hydrogen-bonding scheme in the maleate, (II), leading to tetramer formation. [Symmetry codes: (i) $x, y-1, z-1$; (iv) $-x+1, -y+1, -z+2$.] (*b*) A packing view of (II), showing the chain formation in the cell.

Experimental

The raw material (a commercial sample of anhydrous rosiglitazone maleate, obtained from Dr Reddy's Laboratories) was recrystallized from ethyl acetate, and the title hydrate was reproducibly obtained, though in a low yield, as colourless needles suitable for single-crystal X-ray diffraction. The X-ray powder diffraction diagram of this product, (II), showed significant differences from the starting material, but since the solvent was used as bought, without further purification, the origin of the (depleted) solvent water molecule cannot be determined with certainty.

Crystal data

$C_{18}H_{20}N_3O_3S^+\cdot C_4H_3O_4^-\cdot 0.25H_2O$
M_r = 478.01
Triclinic, $P\overline{1}$
a = 9.3145 (8) Å
b = 12.3555 (10) Å
c = 20.8280 (17) Å
α = 105.475 (2)°
β = 96.330 (3)°
γ = 93.276 (2)°
V = 2286.6 (3) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.19 mm^{-1}
T = 298 (2) K
0.52 × 0.12 × 0.11 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2001)
T_{min} = 0.90, T_{max} = 0.98
19294 measured reflections
9856 independent reflections
5102 reflections with $I > 2\sigma(I)$
R_{int} = 0.058

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.154
S = 0.95
9856 reflections
624 parameters
6 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.43 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

H atoms attached to C atoms were placed in geometrically idealized positions and allowed to ride, with C—H = 0.93–0.98 Å. H atoms bonded to N and O atoms in the organic components were clearly

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3*C*—H3*OC*···O2*C*	0.87 (3)	1.58 (3)	2.420 (4)	164 (5)
N1*A*—H1N*A*···O4*C*	0.84 (3)	1.94 (3)	2.767 (4)	167 (3)
N1*B*—H1N*B*···O1*D*	0.85 (3)	1.95 (3)	2.795 (3)	176 (3)
O3*D*—H3O*D*···O2*D*	0.85 (3)	1.62 (3)	2.452 (3)	167 (5)
N3*B*—H3N*B*···O1*C*^{i}	0.86 (3)	1.88 (3)	2.724 (3)	168 (3)
N3*A*—H3N*A*···O1*D*^{ii}	0.87 (3)	2.02 (3)	2.858 (4)	161 (3)
C3*B*—H3*B*···O2*A*^{iii}	0.98	2.45	3.289 (4)	144
C6*B*—H6*B*···O2*A*^{iii}	0.93	2.33	3.187 (4)	153
C15*A*—H15*A*···O1*W*^{iii}	0.93	2.30	3.189 (8)	159

Symmetry codes: (i) $x, y-1, z-1$; (ii) $-x+1, -y, -z+1$; (iii) $-x+1, -y+1, -z+1$.

located in a difference Fourier map and were refined with restrained distances of N—H = O—H = 0.85 (3) Å. In all cases, U_{iso}(H) = 1.2U_{eq}(parent).

The occupancy of the water molecule was clearly less than unity, and its site-occupancy factor refined to ∼0.5; the occupancy was then fixed at 0.5. The H atoms of the water component could not be found and were omitted from the model.

Data collection: *SMART-NT* (Bruker, 2001); cell refinement: *SAINT-NT* (Bruker, 2001); data reduction: *SAINT-NT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL-NT* (Bruker, 2001); software used to prepare material for publication: *SHELXTL-NT* and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD3164). Services for accessing these data are described at the back of the journal.

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