Crystal Structure of Epalrestat Non-Solvate

Ryota IGARASHI,* Hiromasa NAGASE,*† Takayuki FURUSHI,* Tomohiro ENDO,* Kazuo TOMONO,** and Haruhisa UEDA*

*Department of Physical Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan

**Laboratory of Pharmaceutics, School of Pharmacy, Nihon University,
7-7-1 Narashinodai, Funabashi-shi, Chiba 274-8555, Japan

The crystal structure of epalrestat non-solvate ($C_{15}H_{13}NO_3S_2$) was determined by X-ray crystallography. The compound crystallized in a triclinic system and was characterized as follows: $P\bar{1}$, $a = 8.20888(15)\text{\AA}$, $b = 11.6639(2)\text{\AA}$, $c = 16.3107(3)\text{\AA}$, $\alpha = 96.5985(8)^\circ$, $\beta = 93.8393(8)^\circ$, $\gamma = 104.6780(8)^\circ$, $Z = 4$, $V = 1493.22(5)\text{\AA}^3$. Neighboring epalrestat molecules formed intermolecular hydrogen bonds between the carboxyl group and the carbonyl group of the rhodanine ring and the cyclic structure from four molecules.

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Epalrestat (5-[(1Z,2E)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid, Fig. 1), a potent aldose reductase inhibitor, is used to treat diabetic peripheral neuropathy.¹ In general, it is preferable that the active pharmaceutical ingredient (API) does not include organic solvents. Although the crystal structure of the ethanol solvate has been reported,² there are no reports on the crystal structure of the non-solvate form.

Single crystals of the non-solvate were obtained from ethanol (JIS special grade, $\geq 99.5\%$) by slow evaporation at room temperature ($\sim 20^\circ\text{C}$). Slow evaporation of the ethanol solution at 35°C in a chamber also resulted in the formation of single crystals suitable for X-ray analysis. An orange plate crystal measuring $0.58 \times 0.19 \times 0.13\text{ mm}$ was used for X-ray analysis. Crystal and experimental data are given in Table 1. The structure was solved by a direct method (SIR2002),³ and refined by a full-matrix least-squares procedure. All hydrogen atoms were refined using a riding model. Most of the calculations were performed using the CrystalStructure crystallographic software package.⁴ Mercury software 3.1 was used to calculate the best planes, measure the distance between two planes related by centrosymmetry and draw them.

Although the crystallization solvent was identical to that reported previously,² non-solvate crystals could be obtained by

crystallization from ethanol. The asymmetric unit is composed of two crystallographically independent epalrestat molecules (designated here as A and B). An ORTEP drawing of the title compound is shown in Fig. 2. The methylpropenylidene (defined by C3, C6–C9 and C15) had a planar arrangement, and the torsion angles C2–C3–C6–C7, C3–C6–C7–C8, C6–C7–C8–C9, and C7–C8–C9–C10 were all close to $\pm 180^\circ$. The dihedral angles between the methylpropenylidene and the phenyl moiety (defined by C9–C14), or the rhodanine moiety (defined by C1–C4, N1, O1, S1 and S2) were $1.92(13)^\circ$ and $0.97(5)^\circ$, respectively. These dihedral angles of molecule B are $1.7(2)^\circ$ and $3.3(5)^\circ$. The corresponding dihedral angles in ethanol

Fig. 1 Chemical structure of epalrestat.

Table 1 Crystal and experimental data

Chemical formula: $C_{15}H_{13}NO_3S_2$	
Formula weight = 319.39	
$T = 289\text{ K}$	
Crystal system: triclinic	Space group: $P\bar{1}$
$a = 8.20888(15)\text{\AA}$	$\alpha = 96.5985(8)^\circ$
$b = 11.6639(2)\text{\AA}$	$\beta = 93.8393(8)^\circ$
$c = 16.3107(3)\text{\AA}$	$\gamma = 104.6780(8)^\circ$
$V = 1493.22(5)\text{\AA}^3$	$Z = 4$
$D_x = 1.421\text{ g/cm}^3$	
Radiation: Cu K_α ($\lambda = 1.54187\text{ \AA}$)	
Crystal size = $0.58 \times 0.19 \times 0.13\text{ mm}^3$	
No. of reflections collected = 16752	
No. of independent reflections = 5319	
No. of observations ($I > 2\sigma(I)$): 5319	
$2\theta_{\text{max}} = 136.4^\circ$ with Cu K_α	
Data/Restraints/Parameters = 5319/0/384	
Goodness-of-fit on $F^2 = 1.081$	
R indices [$I > 2\sigma(I)$]: $R1 = 0.0460$, $wR2 = 0.1315$	
$(\Delta\sigma)_{\text{max}} = 0.001$	
$(\Delta\rho)_{\text{max}} = 0.30\text{ e\AA}^{-3}$	$(\Delta\rho)_{\text{min}} = -0.34\text{ e\AA}^{-3}$
Measurement: Rigaku RAXIS-RAPID II	
Programs system: CrystalStructure 4.0	
Structure determination: SHELXL-97	
CCDC deposition number: 924186	

† To whom correspondence should be addressed.
E-mail: nagase@hoshi.ac.jp

Fig. 2 ORTEP drawing of epalrestat molecules (A and B), drawn with 50% probability ellipsoids, and with hydrogen atoms shown as circles of arbitrary radius.

Fig. 3 Intermolecular hydrogen bonding between four epalrestat molecules with a numbering scheme for the hydrogen-bonded atoms. The hydrogen bonds are shown as dashed black lines.

solvate² are $12.5(2)^\circ$ and $6.7(2)^\circ$, which were calculated using CIF data provided from CCDC. Consequently, the epalrestat molecules of non-solvate have higher planarity than that of ethanol solvate, with the exception of the carboxy group.

Observations of the intermolecular interactions (Fig. 3) revealed that four epalrestat molecules formed intermolecular hydrogen bonds between the proton of the carboxyl group and the carbonyl group of the rhodanine ring [O3...O1'(i) 2.699(3)Å, O3-H3...O1'(i) 165.38° , O3...O1(ii) 2.783(3)Å, O3'-H3'...O1(ii) 172.53° , symmetry codes: (i) $-x, -y+2, -z+2$, (ii) $x, y-1, z$].

Fig. 4 Stacking diagram of two molecules A related by centrosymmetry. The best planes of the methylpropenylidene, rhodanine and phenyl moieties are coloured red, green and cyan, respectively.

The crystal packing was similar to that of ethanol solvate (Ref. 2). For ethanol solvate, two epalrestat molecules formed an extensive stacking pair, and were related by a center of symmetry. A stacking diagram of two molecules A is shown in Fig. 4. In this figure, the best planes of the methylpropenylidene, rhodanine and phenyl moieties are drawn and the spacing between two parallel planes related by a symmetric element is described. The stacking distance between two molecules was estimated by the average of the three spacings. These values were $3.59(3)\text{Å}$ for molecules A and $3.71(19)\text{Å}$ for molecules B. The corresponding average spacing for ethanol solvate² was $3.47(2)\text{Å}$, suggesting that epalrestat molecules of non-solvate stacked more loosely than that of ethanol solvate.

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