Crystal Structure of an Epalrestat Dimethanol Solvate

Hiromasa Nagase,*† Masaru Kobayashi,** Haruhisa Ueda,** Takayuki Furushii,*** Mihoko Gunji,†† Tomohiro Endo,** and Etsuo Yonemochi***

*Central Research Laboratories, Hoshi University, 2-4-41 Ebara, Shinagawa, Tokyo 142-8501, Japan
**Faculty of Pharmaceutical Sciences, Nihon Pharmaceutical University, 10281 Komuro, Ina-machi, Kitaadachi, Saitama 362-0806, Japan
***Department of Physical Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa, Tokyo 142-8501, Japan

The crystal structure of epalrestat dimethanol-solvate (C15H13NO3S2·2CH3OH) was determined by X-ray crystallography. The crystal is a pseudopolymorphic form of the previously reported monomethanol solvate. The compound crystallized in a monoclinic system, and was characterized as follows: PT, a = 7.8868(2) Å, b = 8.1577(3) Å, c = 16.1069(5) Å,  α = 85.5626(19)°, β = 77.790(2)°, γ = 67.5381(18)°, Z = 2, V = 936.00(5) Å³. The pattern of the hydrogen bonds is designated by the graph-set R2(16), composed of two epalrestat and four methanol molecules. The planarity of the epalrestat molecules is lower than that of all other reported polymorphic forms of epalrestat.

(Received October 24, 2015; Accepted December 24, 2015; Published on web March 10, 2016)

Epalrestat (5-[(1Z,2E)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid, Fig. 1), is an inhibitor of aldose reductase, which transforms glucose into sorbitol. Because the accumulation of sorbitol prevents the peripheral nerves from functioning properly, epalrestat is used to treat diabetic peripheral neuropathy.† The crystal pseudopolymorphic form of the monomethanol solvate.‡ The crystals were obtained from a methanol solution of saccharine and ethanol solvates, and non-solvates. The crystallographic independent methanol molecules. An orange plate-like crystal measuring 0.49 × 0.46 × 0.11 mm³ was used for X-ray analysis. Crystal and experimental data are given in Table 1. The structure was solved by a direct method (SIR2008), and refined by a full-matrix least-squares procedure using SHELXL 2013. The positions of all H-atoms, except for those of hydroxyl groups, were calculated geometrically. The atoms attached to the O atoms were found in a difference Fourier map, and we refined them to an ideal geometry [O–H = 0.840 Å]. All hydrogen atoms were treated with a riding model. Most of the calculations were performed with the CrystalStructure software package. The asymmetric unit is composed of one epalrestat and two crystallographically independent methanol molecules. An ORTEP drawing of the title compound is shown in Fig. 2. The pattern of the hydrogen bonds is designated by the graph-set R2(16) has the position around center of symmetry and is composed of the molecules in an asymmetric unit and the molecules related to those in the asymmetric unit by centrosymmetry (Fig. 3). The hydrogen bond lengths are given in Table 2. The dihedral angles between the methylpropenylidene (defined

![Chemical structure of epalrestat](image)

Fig. 1 Chemical structure of epalrestat.

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

Table 1 Crystal and experimental data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula: C15H13NO3S2·2CH3OH</td>
<td>Formula weight = 383.49</td>
</tr>
<tr>
<td>structure = 0.49 × 0.46 × 0.11 mm³</td>
<td>T = 113 K</td>
</tr>
<tr>
<td>T</td>
<td>Crystal system: triclinic</td>
</tr>
<tr>
<td>α = 7.8868(2) Å</td>
<td>Space group: P1</td>
</tr>
<tr>
<td>b = 8.1577(3) Å</td>
<td>α = 85.5626(19)°</td>
</tr>
<tr>
<td>c = 16.1069(5) Å</td>
<td>β = 77.790(2)°</td>
</tr>
<tr>
<td>V = 936.00(5) Å³</td>
<td>γ = 67.5381(18)°</td>
</tr>
<tr>
<td>D₀ = 1.361 g/cm³</td>
<td>Z = 2</td>
</tr>
</tbody>
</table>

Radiation: Cu Kα (λ = 1.54187 Å)

Crystal size = 0.49 × 0.46 × 0.11 mm³

No. of reflections collected = 15744

No. of independent reflections = 3383

θ range for data collection: 11.24 to 136.66°

Data/Restraints/Parameters = 3383/0/232

Goodness-of-fit on F² = 1.178

R indices (I > 2σ(I)): R1 = 0.0558, wR2 = 0.1730

R indices (all data): R1 = 0.0658, wR2 = 0.1730

(Δρ)max = 0.000

(Δρ)max = 0.40 e Å⁻³

Measurement: Rigaku RAXIS-RAPIDII

Program system: SHELXL-2013, CrystalStructure 4.1

Structure determination: SIR2008

CCDC deposition number: 1432237
The dihedral angle between the planes is given in Table 3. The planarity of the epalrestat molecules in this study was lower than those in the previously reported polymorphic forms.\textsuperscript{2–4}

### Acknowledgements

It is pleasure to thank Miss H. Tamaru, Mr. Y. Shuda and Mr. K. Takeuchi for their help in crystallization and measurements.

### References

1. Interview Form “KINEDAK®Tablets 50 mg”. Ono Pharmaceutical Co., Ltd., November 2009.