Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Polymorphic forms of cilostazol

Linda B. Whittall, Robert R. Whittle* and Grayson W. Stowell

aaiPharma, 2320 Scientific Park Drive, Wilmington, North Carolina 28405, USA
Correspondence e-mail: bob.whittle@aai-research.com

Received 20 June 2002
Accepted 15 July 2002
Online 31 July 2002

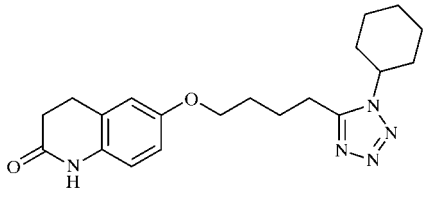
Two unique conformational polymorphic forms of the compound 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydroquinolin-2(1*H*)-one (cilostazol), $C_{20}H_{27}N_5O_2$, have been discovered and characterized using single-crystal X-ray structural analysis. A third polymorph also exists, but acceptable crystals could not be obtained. Features of both reported polymorphic structures include a chair conformation of the cyclohexyl ring and puckering in the quinolinone ring. The major feature distinguishing the two polymorphic forms is a rotational twisting of the butoxy chain between the tetrazole and quinolinone rings. This difference in conformation influences the intermolecular forces, and hence the packing of the two molecules during crystallization.

Comment

The title compound, 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-3,4-dihydroquinolin-2(1*H*)-one (cilostazol), (I), belongs to a class of compounds with proven activity as antithrombotic agents. Recently, two additional thermally produced crystalline polymorphic forms of this material were discovered, *i.e.* (I*B*) and (I*C*) (Stowell & Whittle, 2002; Stowell *et al.*, 2002). Due to the poor solubility of the currently marketed active pharmaceutical ingredient, (I*A*), new polymorphs are of significant interest to the pharmaceutical industry, as they may have enhanced solubility, bioavailabilty, stability and other desirable characteristics. This paper presents the single-crystal analysis of (I*A*) and (I*C*). Suitable crystals of (I*B*) could not be isolated. To our knowledge, these are the first reported crystal structure determinations of (I*A*) and/or (I*C*).

The present X-ray data allowed the determination of the molecular conformation and packing for cilostazol, (I*A*) (Fig. 1). The structural data for (I*C*) (Fig. 2) showed distinct differences in the molecular conformation and packing diagrams compared with (I*A*). The bond lengths and angles for (I*A*) and (I*C*) are in accordance with anticipated values.

In (I*A*), the puckering parameters (Cremer & Pople, 1975), generated by *PLATON* (Spek, 1990), for the six-membered cyclohexyl ring (C21–C26) are q_2 = 0.010 (2) Å, φ_2 = 93 (10)° and θ = 1.0 (2)°. The latter value is close to zero, indicating a chair conformation of the ring. Puckering parameters for the quinolinone ring (N1/C2/C3/C4/C5/C10) are q_2 = 0.395 (2) Å, φ_2 = 146.2 (2)° and θ = 59.1 (2)°. The values for φ_2 and θ indicate a skew-boat conformation for this ring.



(I)

In (I*C*), the puckering parameters for the six-membered cyclohexyl ring (C21–C26) are q_3 = 0.556 (2) Å, φ_2 = 10.9 (46)° and θ = 1.4 (2)°. These match the parameters for (I*A*), indicating that the rings in (I*A*) and (I*C*) share the same molecular conformation. The puckering parameters for the quinolinone ring (N1/C2–C5/C10) are q_2 = 0.407 (2) Å, φ_2 = 322.1 (2)° and θ = 64.2 (3)°. The values for φ_2 and θ indicate a skew-boat conformation for this ring, matching the conformation for (I*A*).

A comparison of the additional structural features of these two polymorphs reveals significant differences between them. A comparison of the torsion angles shows a twisting of the molecules, from atom O11 extending through to the cyclohexyl ring (Tables 1 and 2); additional geometric details are available in the archived CIF. The O11—C12—C13—C14, C12—C13—C14—C15 and C14—C15—C16—N20 torsion angles demonstrate the most significant differences between

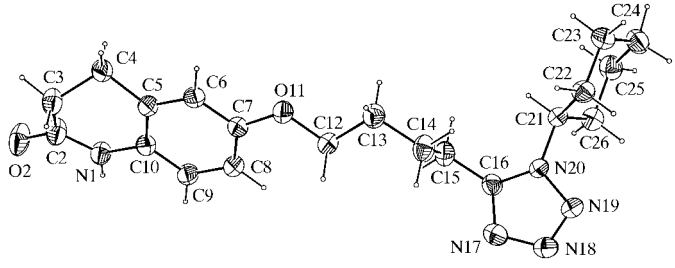


Figure 1
A molecular view of (I*A*), showing 30% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii. For clarity, atoms C3*A* and C4*A* of the minor conformation of the 3,4-dihydroquinolin-2(1*H*)-one ring are not shown.

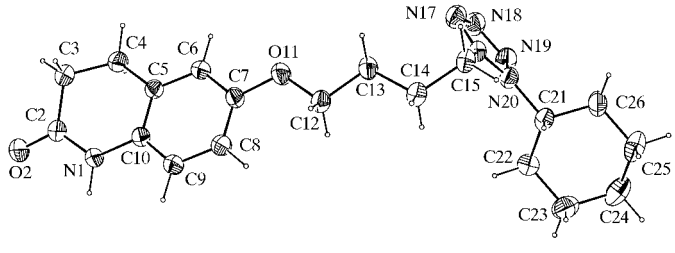


Figure 2
A molecular view of (I*C*), showing 30% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii.

 DOI: 10.1107/S0108270102012544

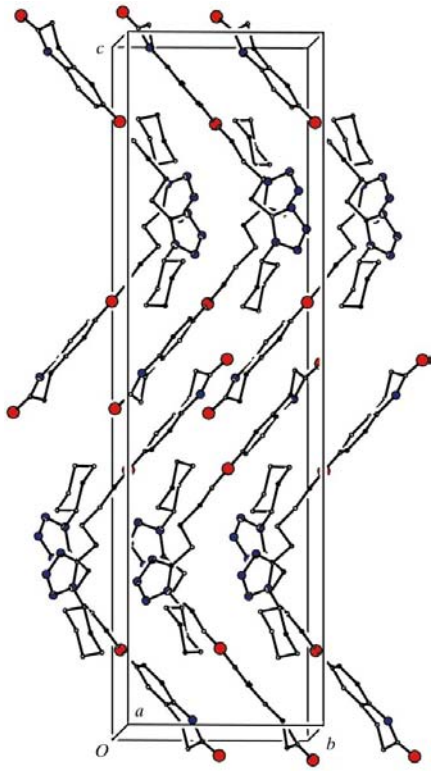


Figure 3
A drawing of the unit cell of (I*A*), viewed along **a**.

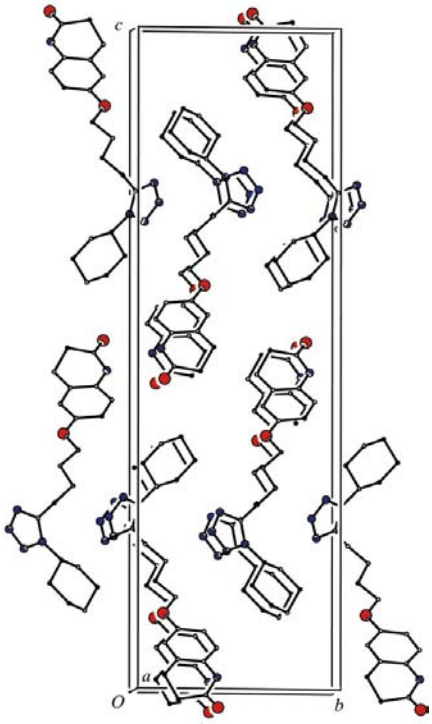


Figure 4
A drawing of the unit cell of (I*C*), viewed along **a**.

the two polymorphs. Figs. 3 and 4 illustrate the unit-cell packings and show the differences between the packings of the two polymorphs.

Experimental

Cilostazol, form (I*A*), was isolated without recrystallization from the bulk active pharmaceutical ingredient received from Laboratorios Phoenix, Buenos Aires, Argentina (Lot 1 002 974 001). A colorless needle-like crystal of (I) was isolated from this lot and was found to have crystallized in the orthorhombic space group *Pbca*. Cilostazol, form (I*C*), was isolated from material recovered after performing heat-cycling experiments using differential scanning calorimetry (Stowell & Whittle, 2002; Stowell *et al.*, 2002). The material used for heat cycling was obtained from Laboratorios Phoenix, Buenos Aires, Argentina (Lot 1 002 974 001). A single colourless plate-like crystal isolated from the resulting heat-cycled material was found to have crystallized in the monoclinic space group $P2_1/n$.

Compound (I*A*)

Crystal data

$C_{20}H_{27}N_5O_2$
M_r = 369.47
Orthorhombic, *Pbca*
a = 11.324 (1) Å
b = 9.855 (1) Å
c = 35.012 (1) Å
V = 1945.4 (4) Å^3
Z = 8
D_x = 1.26 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3849 reflections
θ = 1.1–25.4°
μ = 0.08 mm^{-1}
T = 294 (1) K
Needle, colorless
0.58 × 0.08 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Area-detector scans
4045 measured reflections
3548 independent reflections
2341 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 25.4°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 11$
$l = -42 \rightarrow 0$

Refinement

Refinement on F
R = 0.042
wR = 0.042
S = 2.00
2540 reflections
255 parameters
H-atom parameters constrained
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0001F_o^4]$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: isotropic (Zachariasen, 1963)
Extinction coefficient: 1.2770 × 10^{-6}

Table 1
Selected torsion angles (°) for (I*A*).

C12—O11—C7—C8	−8.0 (2)	C12—C13—C14—C15	71.0 (2)
C16—N20—C21—C22	97.2 (1)	C13—C14—C15—C16	179.7 (1)
C16—N20—C21—C26	−138.0 (1)	C14—C15—C16—N17	64.9 (2)
O11—C12—C13—C14	174.7 (1)	C14—C15—C16—N20	−111.7 (2)

Compound (I*C*)

Crystal data

$C_{20}H_{27}N_5O_2$
M_r = 369.47
Monoclinic, $P2_1/n$
a = 5.148 (1) Å
b = 10.739 (1) Å
c = 35.279 (1) Å
β = 94.070 (1)°
V = 1945.3 (6) Å^3
Z = 4
D_x = 1.26 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3878 reflections
θ = 1.4–27.5°
μ = 0.08 mm^{-1}
T = 294 K
Plate, colorless
0.22 × 0.12 × 0.06 mm

Data collection

Nonius KappaCCD area-detector diffractometer	$R_{int} = 0.026$
	$\theta_{max} = 27.5^\circ$
Area-detector scans	$h = 0 \rightarrow 6$
4572 measured reflections	$k = 0 \rightarrow 13$
4343 independent reflections	$l = -45 \rightarrow 45$
2223 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F	$(\Delta/\sigma)_{max} = 0.001$
$R = 0.043$	$\Delta\rho_{max} = 0.13$ e Å^{-3}
$wR = 0.041$	$\Delta\rho_{min} = -0.12$ e Å^{-3}
$S = 1.62$	Extinction correction: isotropic (Zachariasen, 1963)
2223 reflections	
245 parameters	Extinction coefficient: 3.7536×10^{-6}
H-atom parameters constrained	
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0004F_o^4]$	

Table 2
Selected torsion angles (°) for (I*C*).

C12—O11—C7—C6	−176.9 (1)	C12—C13—C14—C15	178.5 (1)
C16—N20—C21—C22	116.9 (2)	C13—C14—C15—C16	−64.5 (2)
C16—N20—C21—C26	−118.5 (2)	C14—C15—C16—N17	80.6 (2)
O11—C12—C13—C14	−174.7 (1)	C14—C15—C16—N20	−94.9 (2)

For (I*A*), atoms C3 and C4 were disordered with a site-occupancy factor of 0.80, while atoms C3*A* and C4*A* had a site-occupancy factor of 0.20. Atoms C3*A* and C4*A* were located in difference Fourier maps; however, all parameters were fixed in the final cycles of refinement. The H atoms on C3*A* and C4*A* were calculated and fixed, with C—H = 1.00 Å and U_{iso}(H) = 1.3U_{eq}(C). All other H atoms in both polymorphs were initially located in a difference Fourier map, but were calculated and fixed in the final cycles of refinement to an ideal geometry, with C—H = 1.00 Å and U_{iso}(H) = 1.3U_{eq}(C), and N—H = 0.95 Å and U_{iso}(H) = 1.3U_{eq}(N).

For both polymorphs, data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *KappaCCD Server Software*; data reduction: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR* (Burla *et al.*, 1989); program(s) used to refine structure: *LSFM* in *OpenMolEN* (Nonius, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *CIFGEN* in *OpenMolEN*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1656). Services for accessing these data are described at the back of the journal.

References

Burla, M. C., Camalli, M., Cascarano, G., Giacovazzo, C., Polidori, G., Spagna, R. & Viterbo, D. (1989). *J. Appl. Cryst.* **22**, 389–393.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Nonius (1997). *KappaCCD Server Software* (Windows 3.11 Version) and *OpenMolEN* (Version of March 1997). Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Spek, A. L. (1990). *Acta Cryst.* A**46**, C-34.
Stowell, G. W., Behme, R. J., Denton, S. M., Pfeiffer, I., Sancilio, F. D., Whittall, L. B. & Whittle, R. R. (2002). *J. Pharm. Sci.* In the press.
Stowell, G. W. & Whittle, R. R. (2002). US Patent 6 388 080.
Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.