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Losartan, an antihypertensive drug

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Key indicators

Single-crystal X-ray study
T = 110 K
Mean σ(C–C) = 0.002 Å
R factor = 0.041
wR factor = 0.109
Data-to-parameter ratio = 18.3

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, 2-butyl-4-chloro-1-[2′-(2*H*-tetrazol-5-yl)-1,1′-biphenyl-4-ylmethyl]-1*H*-imidazole-5-methanol, $C_{22}H_{23}ClN_6O$, was precisely characterized at *ca.* 110 K, revealing a perfectly ordered structure (as opposed to earlier determinations) stabilized by intermolecular O—H···N and N—H···N hydrogen bonding.

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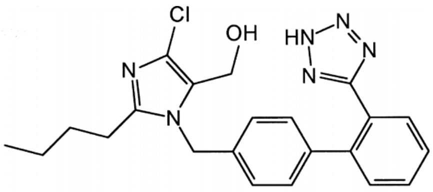
Comment

Losartan, (I), is an antihypertensive drug, characterized as an angiotensin II receptor antagonist (Fernández *et al.*, 2002, and references therein). Earlier structure determinations of this compound relate only to its ethanol solvate and its potassium salt, suffering, however, from poor crystal quality (Okazaki *et al.*, 1998; *R* = 0.084) or severe conformational disorder (Fernández *et al.*, 2002). The present report provides, for the first time, a precise structure determination of this pharmaceutically important compound in its parent form, (I) (Fig. 1). The imidazole, tetrazole and benzene rings are each essentially planar. The dihedral angle between the two benzene rings is 51.95 (4)°. That between the tetrazole and the attached benzene plane is 50.98 (6)°. The second benzene ring is nearly orthogonal to the imidazole plane, the two rings forming a dihedral angle of 88.3 (4)°. The observed overall conformation of the molecular framework is similar to that found in the crystal structure of the potassium salt (Fernández *et al.*, 2002). Noteworthy in the present structure is the perfectly ordered conformation of the aliphatic butyl residue, due to an efficient intermolecular packing.



(I)

In the crystal structure, every molecule is effectively hydrogen bonded to two neighboring species *via* four intermolecular hydrogen bonds, taking advantage of its complementary proton donating and proton accepting capacity. This involves the O1—H(hydroxyl) and N3—H(tetrazole) as proton donors, and N1(tetrazole) and N6(imidazole) as proton acceptors (Table 1 and Fig. 2). The bent conformation of the individual units gives rise to the formation of helical hydrogen-bonded chains, which, in the crystal structure, effectively lock into one another through apparent aryl–aryl interactions between the aromatic rings of adjacent chains. Within each hydrogen-bonded array, the aliphatic butyl resi-

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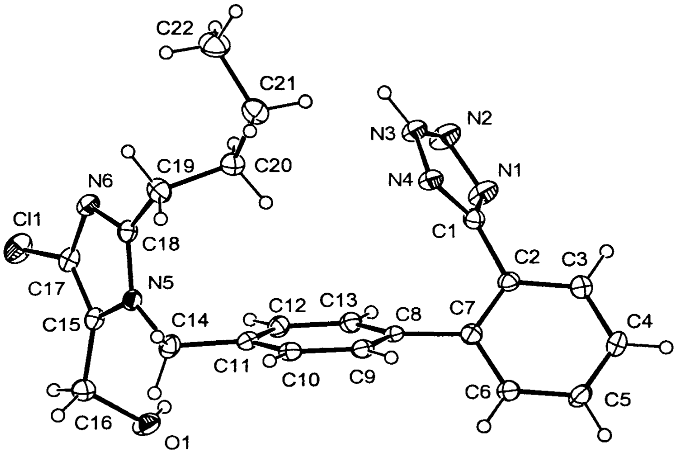

Figure 1
The molecular structure of the parent form of Losartan, showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

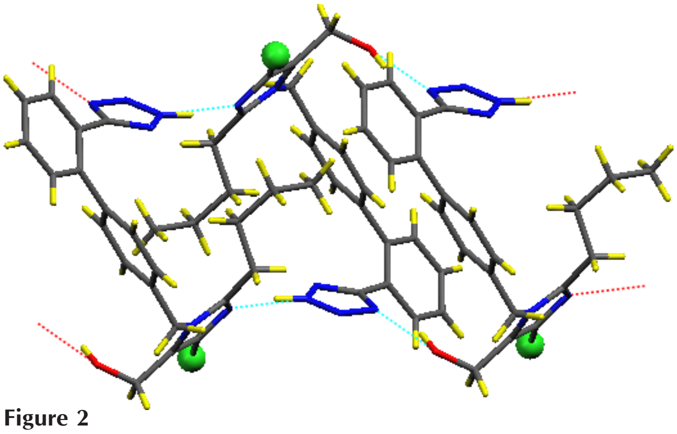

Figure 2
The intermolecular hydrogen-bonding scheme in (I), showing a central molecule linked by pairs of hydrogen bonds to two adjacent species, at O1$\cdots$N1^{i} = 2.8384 (16) Å and N3$\cdots$N6^{ii} = 2.7242 (16) Å [symmetry codes: (i) $-x$, $-y$, $1-z$; (ii) $1-x$, $-y$, $1-z$]. Color code: C gray, H yellow, Cl green spheres, N blue and O red. Hydrogen bonds are indicated by dotted lines.

dues of neighboring molecules are aligned parallel to each other at normal van der Waals contact distances, the terminal methyl group of one species being directed perpendicular to the benzene ring face of an adjacent molecule (Fig. 2). Packing of the hydrogen-bonded chains, which propagate along the *a* axis of the crystal structure, is depicted in Fig. 3.

Experimental

The title compound was crystallized in its parent form by slow evaporation of a dioxan solution.

Crystal data

$C_{22}H_{23}ClN_6O$
M_r = 422.91
Monoclinic, $P2_1/n$
a = 10.3002 (1) Å
b = 11.7916 (2) Å
c = 17.5843 (2) Å
β = 101.2700 (9)°
V = 2094.53 (5) Å^3
Z = 4

D_x = 1.341 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4597 reflections
θ = 1.4–28.2°
μ = 0.21 mm^{-1}
T = 110 (2) K
Prism, colorless
0.35 × 0.30 × 0.20 mm

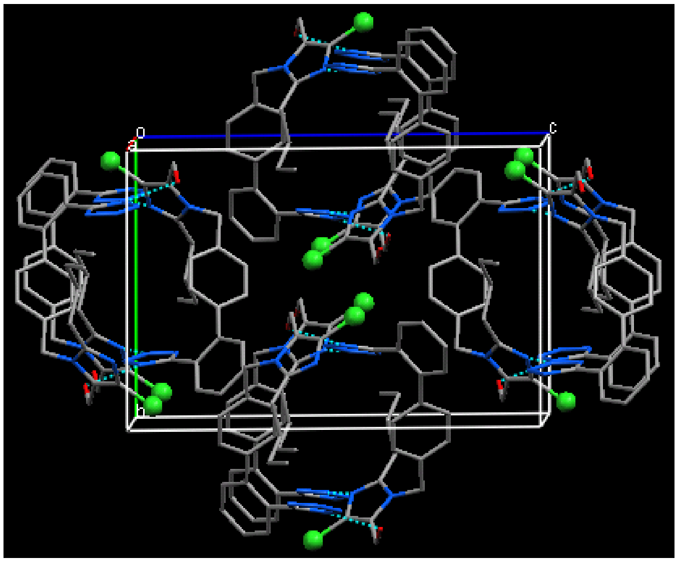

Figure 3
Perspective view of the crystal structure down the *a* axis (*c* is horizontal), showing tight van der Waals side-packing of four neighboring hydrogen-bonded chains that propagate perpendicular to the shown projection. H atoms have been omitted for clarity. The shortest halogen–halogen intermolecular distance is marked, *viz*. Cl1$\cdots$Cl1($1-x$, $-1-x$, $1-z$) = 3.671 (2) Å.

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
16 317 measured reflections
5018 independent reflections
4125 reflections with $I > 2\sigma(I)$

$R_{\rm int}$ = 0.030
$\theta_{\rm max}$ = 28.2°
$h = -13 \rightarrow 13$
$k = -14 \rightarrow 15$
$l = -23 \rightarrow 22$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.109$
S = 1.02
5018 reflections
274 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0546P)^2 + 0.9659P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max}$ = 0.27 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.36 e Å^{-3}

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O1—HO1$\cdots$N1^{i}	0.94	1.94	2.8384 (16)	159
N3—HN3$\cdots$N6^{ii}	0.97	1.78	2.7242 (16)	164

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

H atoms bound to carbon were included in idealized positions (C—H = 0.95–0.99 Å). Those attached to N and O atoms were located in difference Fourier maps. They were refined using a riding-model approximation with fixed displacement parameters [$U_{\rm iso}$ = 1.2$U_{\rm eq}$ (1.5$U_{\rm eq}$ for methyl) of the atom to which they are bonded].

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SIR*-92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL*97.

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