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Losartan potassium, a non-peptide agent for the treatment of arterial hypertension

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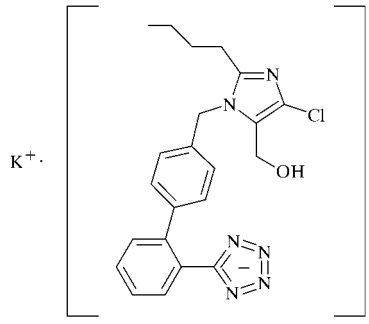
In the title compound, potassium 2-butyl-4-chloro-1-{[2′-(5-tetrazolido)biphenyl-4-yl]methyl}-1*H*-imidazol-5-ylmethanol, $K^+\cdot C_{22}H_{22}ClN_6O^-$, the imidazole and tetrazole rings are at angles of 85.0 (2) and 51.8 (1)°, respectively, to the phenyl rings to which they are attached, while the dihedral angle between the latter two rings is 46.7 (1)°. The coordination sphere of the metal cation consists of six tetrazoyl N atoms, the methanol O atom and the π cloud of one of the phenyl rings. These interactions determine the formation of columns of molecular anions that lie parallel to the *b* axis, while hydrogen bonding contributes to intercolumnar cohesion. Far from the centre of the columns, the hydrocarbon chain is immersed in a hydrophobic environment.

Comment

Losartan potassium, (I), is a potent and orally effective pharmaceutical product used for the treatment of arterial hypertension (Birkenhager & de Leeuw, 1999; Goa & Wagstaff, 1996; Gavras & Salerno, 1996). Designed as a peptidomimetic of the hormone angiotensin II, devoid of partial agonist activity and with a good oral bioavailability (Johnson *et al.*, 1990), it acts by selectively binding to and blocking the angiotensin II type 1 receptor, thus interfering with the renin–angiotensin system, an important regulator of normal blood pressure (Wexler *et al.*, 1996).

Structurally, losartan is a biphenyltetrazole ring system attached to a substituted imidazole ring through a methylene spacer. Recently, a single-crystal X-ray determination of the structure of the free acid of losartan (ethanol solvate) was reported by Okazaki *et al.* (1998). However, in the final publication, the crystal structure was not actually described and only an ellipsoid plot was included. Also, only the unit-cell parameters of this structure are available from the Cambridge Structural Database (CSD; Allen *et al.*, 1983) (CSD refcode PUSMIZ; Okazaki *et al.*, 1998). By spectroscopic (Raghavan *et al.*, 1993) and thermal (Wu *et al.*, 1993) powder diffraction studies, two polymorphic modifications of the drug have been identified. Unfortunately, we could obtain single crystals of only one of the two polymorphs. The structure of (I) has been investigated by our group as part of an ongoing study of biologically active pharmaceuticals (Vega *et al.*, 2001), in this case, a specific ligand of the angiotensin II receptor.



(I)

Losartan potassium, (I), crystallizes in space group $P2_1/c$ with one molecular anion and one K^+ cation in the asymmetric unit (Fig. 1). In the molecular anion, the C1—N1—N2—N3—N4 tetrazole ring is affected by electron delocalization of the single negative charge among its atoms, and the bond lengths

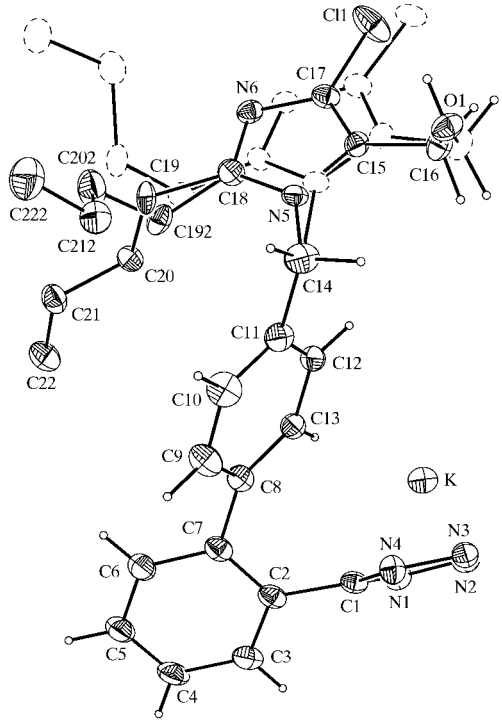


Figure 1
A view of the structure of (I), showing the atom-numbering scheme, with displacement ellipsoids drawn at the 30% probability level. The atoms of the minor-occupancy disorder component, N51, N61, Cl2 and C151–C221, are sketched with dashed ellipsoid boundaries. For clarity, all H atoms of the disordered butyl groups have been omitted.

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range from 1.318 (3) Å for N2—N3 to 1.360 (3) Å for N1—N2. The ring is planar, with a mean deviation of 0.0023 Å. The phenyl rings of the biphenyltetrazole, C2–C7 and C8–C13, sustain a mutual dihedral angle of 46.7 (1)°, while the dihedral angle between the tetrazole ring and the former ring is 51.8 (1)°. Such an arrangement is observed in nearly all structures of the biphenyltetrazole class of drugs, with the dihedral angle between the planes of the phenyl rings in the range 41.7–51.3°, and the phenyl and tetrazole rings sustaining a dihedral angle in the range 52.4–58.8° (data from 13 structures deposited in the CSD; Version 5.22 of October 2001). The C8–C13 phenyl ring is nearly perpendicular to the plane of the N5—C15—N6—C17—C18 imidazole ring [dihedral angle 85.0 (2)°], while the hydroxymethyl group is oriented in the opposite direction in relation to the former [C17—C15—C16—O1 112.8 (9)° and C15—N5—C14—C11 −125.2 (6)°].

On inspecting Fig. 1, it seems that the methylene spacer atom (C14) functions like a 'hinge' connecting the least perturbed part of the structure, the biphenyltetrazole moiety, with the most agitated part, the imidazole ring. Thermal motion appears to be conspicuous for the members and substituents of this ring, and it runs approximately in the direction of the largest atomic displacement parameter of atom Cl1.

The final structure was modelled with a major component (N5/N6/Cl1/C15–C18) accounting for 70% of the occupancy, and a minor component (30%) consisting of the imidazole ring (N51/N61/Cl2/C151–C181) and the C191–C221 butyl chain. In the major component, the butyl chain attached to C18 was further split over two positions of equal occupancy (35%), C19–C22 and C192–C222. Neither imidazole ring deviates significantly from planarity and they are separated by less than 7°. The three disordered chains have extended conformations, as indicated by the torsion angles C19—C20—C21—C22 [−178.4 (8)°], C191—C201—C211—C221 [168.9 (8)°] and C192—C202—C212—C222 [175.9 (11)°]. The first chain is oriented below the plane of the imidazole ring, and in the opposite direction with respect to the others, as indicated by the torsion angles N5—C18—C19—C20 [−101.6 (9)°], N5—C18—C192—C202 [98.1 (10)°] and N51—C181—C191—C201 [83.4 (14)°].

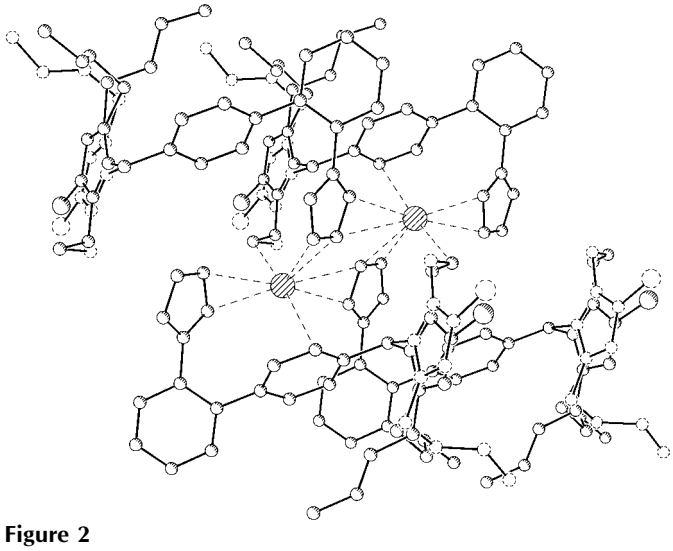

Figure 2
A partial structure diagram for (I), showing the K coordination sphere.

This behaviour may be explained by considering the way in which the packing of the crystal is achieved. From Fig. 2, it is clear that the K^+ cation is 'nested' within the biphenyltetrazole moiety, where it is coordinated by several of its atoms. In contrast, the imidazole ring only coordinates to the K^+ cation through atom O1. Thus, the members and substituents of the imidazole ring, excepting atom O1, have a less interconnected environment, so that they pivot without difficulty around atom C14 by bending the C16 bond angle (Table 1). In addition, the more hydrophobic atoms are stretched far away from the metal centre, thus creating an apolar environment, within which the butyl chain is able to rotate freely around the $C_{imidazole}—C_{butyl}$ bond. As a possible consequence of this motion, the atoms of the chain and those of the ring are highly agitated and disordered.

The coordination sphere of the K^+ cation consists of the π cloud of the C8–C13 ring, the methanol O atom and three pairs of tetrazoyl N atoms from three symmetry-related molecular anions (Fig. 2). The K···C(π) contact distances are within a narrow range, from K···C12 3.434 (2) Å to K···C8 3.739 (2) Å, while atom N4 forms the shortest of the six K···N contacts. Of the remaining N atoms participating in the coordination sphere of the K^+ cation, only N1 acts, like N4, as a monodentate ligand; in contrast, atoms N2 and N3, located in the outermost edge of the tetrazole ring, function as bridging ligands and enable a $K···K^{i}$ contact distance of 4.88 Å between metal centres [symmetry code: (i) $-x, 1-y, -z$]. To complete the coordination sphere, a fourth molecular anion donates the $O1^{i}$ atom, so that the metal cation is surrounded by an eightfold polyhedron, in which the contact distances are K···N (average) 3.00 Å, K···O 2.75 Å and K···*Cg* 3.31 Å (*Cg* is the centroid of the C8–C13 ring).

These interactions contribute greatly to the packing of the crystal, which consists of chains of molecular anions formed by [010]-translated losartan molecules coordinated to the metal cation by atoms N3 and N4, the π cloud of the C8–C13 phenyl ring and atoms N1 and $N2^{iii}$ [symmetry code: (iii) $x, 1+y, z$]. Meanwhile, the K^+ cation is coordinated by centrosymmetrically related molecular anions *via* atoms N2, $N3^{ii}$ and $O1^{i}$ [symmetry code: (ii) $-x, -y, -z$], and hence a pair of parallel chains packs into a column. Inside this column, the polar parts of the losartan molecule are oriented towards the metal cation, while the hydrophobic parts project outside as far as possible. Parallel columns are hydrogen bonded through the O1—H1···N6 interaction (Table 2). In this way, they interdigitate, by juxtaposition at the imidazole of screw-related chains, and the offset between a pair of interdigitated chains is equal to $0.5 \times d_{010}$.

Experimental

The title compound was obtained from Laboratorios Gador SA, Buenos Aires, Argentina. Crystals of (I) suitable for X-ray diffraction were obtained on slow evaporation of a water solution.

Crystal data

$K^+ \cdot C_{22}H_{22}ClN_6O^-$	$D_x = 1.381$ Mg m^{-3}
$M_r = 461.01$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 34 378 reflections
$a = 15.5724$ (3) Å	$\theta = 1.0$–$27.5°$
$b = 7.4976$ (2) Å	$\mu = 0.39$ mm^{-1}
$c = 24.2640$ (5) Å	$T = 120$ (2) K
$\beta = 128.4980$ (10)°	Thin plate, colourless
$V = 2217.16$ (9) Å^3	0.22 × 0.12 × 0.04 mm
$Z = 4$	

Data collection

Nonius KappaCCD area-detector diffractometer	3888 independent reflections
φ scans with κ at 0°, and ω scans	3184 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)	$R_{int} = 0.026$
$T_{min} = 0.920$, $T_{max} = 0.985$	$\theta_{max} = 25°$
7037 measured reflections	$h = -18 \rightarrow 18$
	$k = -8 \rightarrow 8$
	$l = -28 \rightarrow 28$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0557P)^2 + 1.2280P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F) = 0.043$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.116$	$\Delta\rho_{max} = 0.45$ e Å^{-3}
$S = 1.03$	$\Delta\rho_{min} = -0.36$ e Å^{-3}
3888 reflections	
392 parameters	
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

K—O1^{i}	2.7535 (14)	K—N3^{ii}	3.2384 (19)
K—N4	2.7824 (18)	K—N2^{iii}	3.265 (2)
K—N2^{ii}	2.840 (2)	K—C12	3.434 (2)
K—N1^{iii}	2.8479 (19)	Cl1—C17	1.705 (4)
K—N3	3.0726 (19)	Cl2—C171	1.704 (9)
C14—N5—C18	129.4 (3)	C151—N51—C181	110.1 (14)
C14—N5—C15	123.1 (5)	N5—C14—C11	112.5 (3)
C15—N5—C18	107.5 (5)	N51—C14—C11	115.1 (6)
C14—N51—C181	123.5 (11)	O1—C16—C15	117.3 (5)
C14—N51—C151	126.4 (16)	O1—C161—C151	104.3 (19)
N4—C1—C2—C7	49.6 (3)	C12—C11—C14—N51	38.2 (6)
C2—C7—C8—C13	47.7 (3)	C17—C15—C16—O1	112.8 (9)
C12—C11—C14—N5	51.9 (3)	C171—C151—C161—O1	122.7 (19)

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

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1···N6^{iv}	0.84	2.05	2.874 (4)	167

Symmetry codes: (iv) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

The positional parameters of the H atoms were constrained to have C—H distances of 0.98 Å for primary, 0.99 Å for secondary and 0.95 Å for aromatic H atoms, while the O—H distance was constrained to 0.84 Å. The H atoms were treated as riding and their isotropic displacement parameters were constrained to be 1.2 times those of their hosts (1.5 for methyl and OH groups). The atomic displacement parameters of various atoms of the disordered part of losartan, namely N51, C151, C161 and C171, were constrained using the *EADP* command in *SHELXL*97 (Sheldrick, 1997).

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC* (Sheldrick, 1991); software used to prepare material for publication: *PARST* (Nardelli, 1995) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1578). Services for accessing these data are described at the back of the journal.

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