Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

Candesartan cilexetil, an antihypertensive agent containing an extended double ester chain

Daniel Fernández,[a]* Daniel Vega[b] and Javier A. Ellena[c]

[a]Escuela de Ciencia y Tecnología, Universidad Nacional de General San Martín, Calle 91 3391, 1653 Villa Ballester, Buenos Aires, Argentina, [b]Unidad de Actividad Física, Comisión Nacional de Energía Atómica, Av. Gral. Paz 1499, 1650 San Martín, Buenos Aires, Argentina, and [c]Departamento de Física e Informática, Instituto de Física de São Carlos, Universidade de São Paulo, Caixa Postal 369 – CEP 13560-970, São Carlos, SP, Brazil

Correspondence e-mail: fernande@tandar.cnea.gov.ar

Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.007 Å
Disorder in main residue
R factor = 0.088
wR factor = 0.292
Data-to-parameter ratio = 13.1

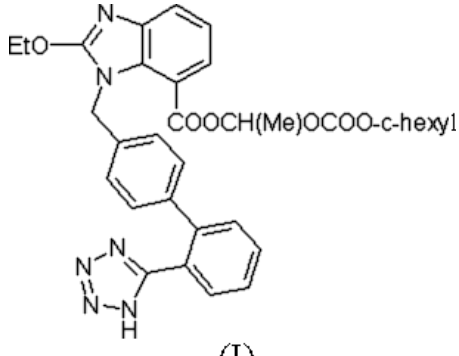
For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Received 16 December 2004
Accepted 4 January 2005
Online 15 January 2005

In the title compound (systematic name: (±)-1-[(cyclohexyloxy)carbonyloxy]ethyl 2-ethoxy-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate), $C_{33}H_{34}N_6O_6$, the biphenyltetrazole moiety projects almost perpendicularly from the benzimidazole group. The planes of the three rings in the biphenyltetrazole moiety are staggered with respect to one another. In the benzimidazole system, the 2-ethoxy group is extended in the opposite direction with respect to the CH(Me)OCOO-c-hexyl double ester chain. An N—H···N hydrogen bond joins [010]-translated molecules to form a chain running along the *b* axis.

Comment

Candesartan cilexetil is an antihypertensive drug belonging to the class of biphenyltetrazole-containing compounds. Developed as nonpeptide mimics of the hormone angiotensin II, these compounds are orally effective and potent pharmaceuticals, which act by the selective blocking of the binding of angiotensin II to its protein receptors (Johnson *et al.*, 1990; Wexler *et al.*, 1996). This inhibits the last step in the renin–angiotensin system, which mediates key biochemical processes involved in blood pressure regulation and electrolyte/fluid homeostasis, resulting in an antihypertensive effect (Garrison & Peach, 1993). Members of this family, including candesartan cilexetil, are indicated as therapy for hypertension and heart failure (Johnson & Nale, 2001). Candesartan cilexetil has good oral bioavailability (Gleiter & Mörike, 2002) and, once the active metabolite candesartan (*i.e.* the 2-ethoxybenzimidazole carboxylic acid) is released, it binds tightly to angiotensin II type 1 receptors, thus allowing prolonged activity (See & Stirling, 2000).



(I)

In the development of the title compound, it has been observed that minor chemical modifications in the CH(Me)OCOO-c-hexyl double ester chain have a large effect

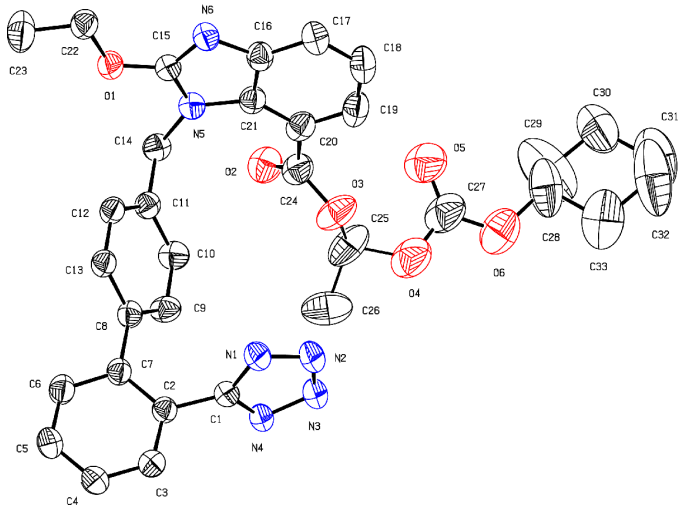


Figure 1
View of (I) (*PLATON*; Spek 2003), illustrating the numbering scheme used and displacement ellipsoids drawn at the 30% probability level. H atoms have been omitted for clarity. Only the atoms of the major disorder component (C25 and C26) are shown.

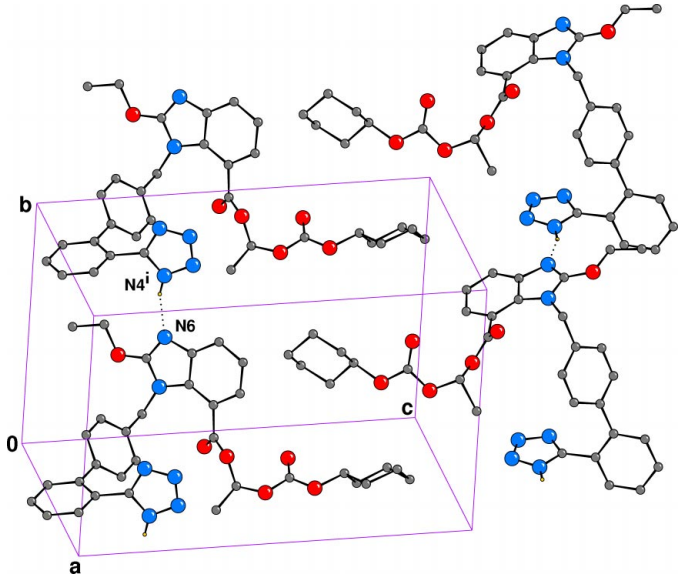


Figure 2
Simplified packing diagram (*CAMERON*; Watkin *et al.* 1996) showing the hydrogen-bonding scheme (hydrogen bonds represented as dashed lines) [symmetry code: (i) $x, y+1, z$]. H atoms have been omitted.

on the ability of the esterases to degrade it and transform the prodrug into the active form (Kubo, Kohara *et al.*, 1993). A structural analysis of the prodrug could give a better understanding of the relationship between the chemical structure and enzymatic degradation of this class of pharmaceuticals in biological systems. In addition, the investigation of the conformational space available to members of the biphenyltetrazole class of compounds has attracted much attention, since the three-dimensional structure of angiotensin II protein receptor has yet to be determined. In this context, and as a part of an ongoing study of molecules possessing biological activity (Fernández *et al.*, 2002), the crystal structure determination of the antihypertensive (I) is reported here.

The title compound, (I), consists of the biphenyltetrazole moiety, the 2-ethoxybenzimidazole group and the CH(Me)OCOO-c-hexyl double ester chain (Fig. 1). In the biphenyltetrazole moiety, the angles between the planes of the tetrazole and benzene rings are 72.8 (2)° (for C2–C7) and 62.4 (2)° (C8–C13), while an angle of 50.20 (17)° is observed between both benzene rings. This geometry is in good agreement with that observed previously in related structures. By comparison, 51.9, 58.0 and 48.3° are the corresponding angles in the most closely related compound, 2-butyl-1-[[2′(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid methanol solvate [Cambridge Structural Database (CSD; Allen, 2002) refcode PELXAG (Kubo, Inada *et al.*, 1993)]. The tetrazole ring is protonated at N4 and donates a hydrogen bond to atom N6 of a 2-ethoxybenzimidazole group in an [010]-translated molecule (Table 2). The intermolecular N—H···N interaction arranges the molecules of (I) in a chain that propagates along the *b* axis (Fig. 2).

As indicated by the C11—C14—N5—C21 torsion angle [83.8 (3)°], the biphenyltetrazole moiety projects out almost perpendicularly from the 2-ethoxybenzimidazole group. The latter is planar [its constituent atoms deviate from the mean plane by 0.014 (4) Å], and forms angles of 15.34 (19), 68.88 (16) and 72.04 (15)° with the planes of the tetrazole, C2–C7 and C8–C13 rings, respectively. The ethoxy group at C15 is *trans* [C23—C22—O1—C15 = −176.6 (3)°], while the C24 carbonyl group is twisted with respect to the mean plane by 43.6 (2)°. An intramolecular interaction between atoms O2 and C14 forms a seven-membered ring (Table 2). A similar configuration is also seen for PELXAG, where the geometry of the interaction is $D\cdots A$ = 2.881 Å, H···A = 2.158 Å and D—H···A = 121°, and the planes are at 20.2°.

The crystallization of (I) provided racemic crystals. A search of the CSD revealed that, for structures of known compounds possessing the CH(Me)OCOO double ester chain, this process involved separation of one of the enantiomers. Such a phenomenon is reported to take place with prodrugs of β-lactam antibiotics [CSD refcodes BENPEN10 (Csöregh & Palm, 1977) and BACMEC10 (Palm & Csöregh, 1978)] and a contrast agent for medical diagnosis (ZORYAG; Tønnessen *et al.*, 1995). In these cases, the separate crystallization of the enantiomers seems to be more favourable than the formation of racemic crystals; however, this does not occur in the prodrug (I). The CH(Me)OCOO-c-hexyl double ester chain attached to O3 extends in the opposite direction with respect to the 2-ethoxy group. The two carbonyl planes, containing atoms C24 and C27, respectively, make a dihedral angle of 72.1 (4)°. The torsion angle involving the chiral atom C25 [*i.e.* C24—O3—C25—O4 = 141.9 (4)°] indicates a distorted *anti* conformation, possibly owing to steric strain. The c-hexyl ring adopts the conformation of an almost perfect chair, where atoms C28, C29, C31 and C32 are in the mean plane [the r.m.s. deviation of the fitted atoms from the plane is 0.007 (4) Å], while atoms C30 and C33 depart from it by −0.748 (14) and

0.730 (16) Å, respectively. As can be seen from Fig. 1, the atoms of the c-hexyl ring are distinguished by large displacement parameters. This fact could be in part ascribed to the flexibility of the double ester chain (possibly by rotating the O6—C28 bond) and/or the presence of an alternative conformation of the ring. The hydrophobic environment of the ring (Fig. 2) may also contribute to this behaviour. No solvent of crystallization seems to be incorporated in the crystal structure (see *Experimental*), so stabilization of the double ester chain by such an interaction is not possible.

Experimental

A powdered sample of the title compound was obtained from Laboratorios Gador SA, Buenos Aires, Argentina. Crystals suitable for X-ray diffraction were obtained by evaporating a solution of (I) in acetone at room temperature.

Crystal data

$C_{33}H_{34}N_6O_6$
M_r = 610.66
Monoclinic, $P2_1/c$
a = 16.3545 (4) Å
b = 10.8868 (3) Å
c = 18.4635 (5) Å
β = 104.102 (2)°
V = 3188.32 (15) Å^3
Z = 4
D_x = 1.272 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 10 007 reflections
θ = 1.0–25°
μ = 0.09 mm^{-1}
T = 120 (2) K
Needle, colourless
0.34 × 0.08 × 0.06 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ scans with κ at 0°, and ω scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.971, T_{max} = 0.997
10 191 measured reflections
5575 independent reflections
3772 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 25.0°
$h = 0 \rightarrow 19$
$k = 0 \rightarrow 12$
$l = -21 \rightarrow 21$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.088
$wR(F^2)$ = 0.292
S = 1.05
5575 reflections
426 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.01767P)^2 + 1.1617P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.008
$\Delta\rho_{max}$ = 0.79 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.030 (5)

Table 1
Selected geometric parameters (Å, °).

N5—C14	1.468 (3)	C7—C8	1.487 (4)
C1—C2	1.482 (4)	C11—C14	1.503 (5)
N1—C1—C2	126.4 (3)	N5—C14—C11	113.7 (2)
C2—C7—C8	122.3 (3)		
N1—C1—C2—C7	73.7 (4)	C23—C22—O1—C15	−176.6 (3)
C2—C7—C8—C9	49.6 (4)	C24—O3—C25—O4	141.9 (4)
C11—C14—N5—C21	83.8 (3)	O4—C27—O6—C28	−176.2 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···N6^{i}	0.86	2.01	2.835 (4)	160
C14—H13···O2	0.97	2.24	3.061 (4)	142

Symmetry code: (i) $x, y-1, z$.

Atoms C25 and C26 are disordered and were refined in two positions with a ratio of 0.75:0.25. The C25—C26 (major occupancy atoms) and C251—C261 (minor occupancy atoms) bond distances, as well as those between atom C251 and atoms O3 and O4, were restrained. In the cyclohexyl ring, the 1,2 and 1,3 bond distances were also restrained. The atomic displacement parameters of atoms C28–C33 suggested that they could be distributed over more than one location; however, a split model of these atoms yielded no better results. Atoms C25 and C26 are disordered and were refined in two positions (C251 and C261 are their partners, respectively). Until the final cycles of refinement, their site-occupation factors were refined as variables in the forms x (for C25/C26) and $1 - x$ (C251/C261), while their atomic displacement parameters were thoroughly scrutinized. Depending on the dimensions of the latter, the site-occupation factors chosen in the final model were in a ratio of 0.75:0.25, *i.e.* C25/C26 are the major occupancy disorder components and C251/C261 the minor ones. Bond distances C25—C26 and C251—C261 were restrained to target values 1.54 (2) and 1.540 (10) Å, respectively. For C251, the C251—O3 and C251—O4 distances were restrained to target values 1.45 (3) and 1.45 (2) Å, respectively. Assays to adjudicate one electron-density peak as a disordered O atom (a possible 'O41') bonded to atom C251 atom gave no better results. Therefore, the BIND command of *SHELXL97* was used for C251—O4. In the cyclohexyl ring, the 1,2- and 1,3-bond distances were restrained at the target values C28—C29 = 1.540 (5) Å, C30—C31 = 1.540 (10) Å and C31—32 = 1.540 (5) Å while the six bond angles, *i.e.* C28—C30, C29—31, and so on, were restrained at the target value 2.40 (2) Å. Finally, a similar restraint was applied for the bonds O6—C29 and O6—C33 [2.40 (2) Å]. Also, a complete examination of the atomic displacement parameters for atoms C28–C33 was carried out. Their dimensions, remarkably for atoms C29 and C32, suggested that they could be distributed over more than one location; however, a split model of these atoms yielded no better results. H atoms were refined using a riding model (C—H = 0.93–0.98 Å and N—H = 0.86 Å) while keeping their isotropic displacement parameters constrained to 1.2 (for H atoms attached to aromatic, methine and methylene C atoms) and 1.5 (H atoms attached to methyl C and N atoms) times U_{eq} of their carrier atoms. A potential solvent-accesible void accounting for 2.9% of the unit-cell volume (or 91.3 Å^3) was identified by *PLATON* (Spek, 2003). However, attempts to refine a model including a solvent molecule in any of the possible locations failed. The maximum residual density peak is 2.02 Å from disordered methyl atom C261.

Data collection: *COLLECT* (Nonius, 2000); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *CAMERON* (Watkin *et al.*, 1996) and *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON* and *WinGX* (Farrugia, 1999).

The authors thank Dr Dora Tombari for suggesting the problem and for helpful discussions. This work has been funded through a project of the Universidad Nacional de General San Martín.

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Blessing, R. H. (1995). *Acta Cryst.* A**51**, 33–38.
Csöregh, I. & Palm, T.-B. (1977). *Acta Cryst.* B**33**, 2169–2174.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Fernández, D., Vega, D., Ellena, J. A. & Echeverría, G. (2002). *Acta Cryst.* C**58**, m418–m420.
Garrison, J. C. & Peach, M. J. (1993) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Section VII, ch. 31, pp. 731–746. México: Editorial Médica Panamericana.
Gleiter, C. H. & Mörike, K. E. (2002). *Clin. Pharmacokinet.* **41**, 7–17.
Johnson, A. L., Carini, D. J., Chiu, A. T., Duncia, J. V., Price, W. A. Jr, Wells, G. J., Wexler, R. R., Wong, P. C. & Timmermans, P. B. M. W. M. (1990). *Drug News Perspect.* **3**, 337–351.
Johnson, P. H. & Nale, P. (2001). Editors. *Pharmacist's Drug Handbook*, pp. 18–20, 222–223. Bethesda, MD, USA: American Society of Health–System Pharmacists and Springhouse Corporation.
Kubo, K., Inada, Y., Kohara, Y., Sugiura, Y., Ojima, M., Itoh, K., Furukawa, Y., Nishikawa, K. & Naka, T. (1993). *J. Med. Chem.* **36**, 1772–1784.
Kubo, K., Kohara, Y., Yoshimura, Y., Inada, Y., Shibouta, Y., Furukawa, Y., Kato, T., Nishikawa, K. & Naka, T. (1993). *J. Med. Chem.* **36**, 2343–2349.
Nonius (2000) *COLLECT*. 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.
Palm, T.-B. & Csöregh, I. (1978). *Acta Cryst.* B**34**, 138–143.
See, S. & Stirling, A. L. (2000). *Am. J. Health Syst. Pharm.* **57**, 739–746.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Spek A. L. (2003). *PLATON*. Utrecht University, The Netherlands.
Tønnessen, L. E., Fossheim, R., Klaveness, J., Pedersen, B. F. & Thomassen, T. (1995). *Acta Chem. Scand.* **49**, 625–631.
Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, University of Oxford, England.
Wexler, R. R., Greenlee, W. J., Irvin, J. D., Goldberg, M. R., Prendergast, K., Smith, R. D. & Timmermans, P. B. M. W. M. (1996). *J. Med. Chem.* **39**, 631–656.