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Irbesartan Crystal Form B

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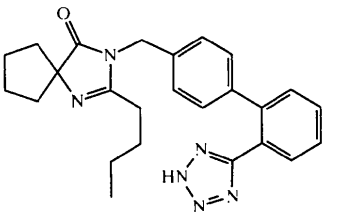
Abstract

Irbesartan (2-butyl-3-{[2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-diazaspiro[4.4]non-1-en-4-one, $C_{25}H_{28}N_6O$), a highly selective angiotensin II receptor (AT_1) antagonist was found to exist in two distinct crystal forms (A and B). This paper describes the crystal structure of irbesartan form B.

Comment

Irbesartan, (I), belongs to a new class of antihypertensive agents which interfere with the renin angiotensin system. It is a highly selective non-peptide antagonist of angiotensin II AT_1 receptors, which has shown clinical benefits in the treatment of hypertension.



(I)

Irbesartan exists in the solid state as two distinct forms. It provides a rare example of desmotropy (Lempert *et al.*, 1973) in which tautomeric equilibrium exists in the liquid state, and individual tautomers can be isolated in the solid state, each with unique and stable crystal forms. Each crystal form exhibits unique properties when examined by optical microscopy, differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR) spectroscopy and powder X-ray diffraction (XRDP). A thorough examination of the crystallographic data is an essential component in our understanding of not only pharmaceutical activity, but also the physicochemical and solid-state NMR data.

It is known from the literature (Elguero *et al.*, 1976) that a monosubstituted tetrazole ring can undergo a tautomeric process according to the scheme below. If both tautomers can be crystallized then we face a case of desmotropy (Foces-Foces *et al.*, 1994), which seems to be a very rare phenomenon.

The crystal structure determination proved unambiguously that form B is a 2*H*-tautomer, *i.e.* the tetrazole ring carries the H atom at the N25 atom (Fig. 1). Difference–Fourier calculations indicated the presence

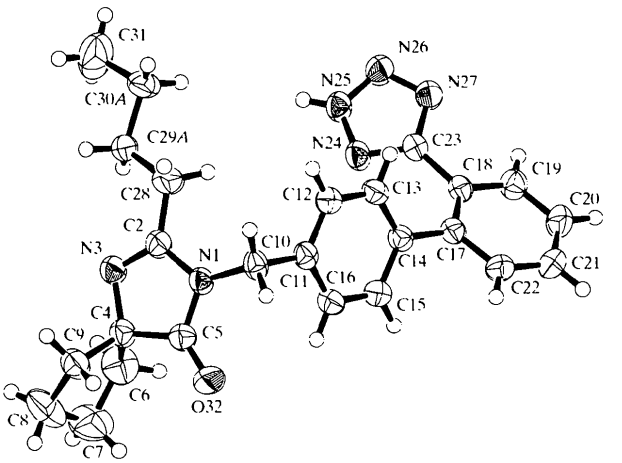


Fig. 1. The molecular structure and atomic numbering for irbesartan.

† Deceased.

of this H atom also. Furthermore, among the endocyclic bond angles of the tetrazole ring, that involving N25 as the central atom is the largest (Table 1). This is in accord with the valence-shell electron-pair repulsion (VSEPR) theory, which claims that repulsion of the lone pair electron is stronger than that belonging to the N—H bond. Furthermore, atom N25 is intermolecularly hydrogen bonded to the acceptor N3 atom.

From bond-length data (Table 1), it seems that the C2—N3 bond has a strong double-bond character, although it is delocalized with the amide moiety involving the N1 atom. Atoms C25 and C30 are disordered and, for clarity, are not shown in Fig. 1.

The cyclopentane ring has a ^{C4}E conformation and its general plane is perpendicular to the imidazoline ring. Torsion angles characteristic of the spatial relations of the different rings of the molecule are also given in Table 1.

The 2*H*-tetrazole desmotropic form contains an N25—H25···N3 hydrogen bond which leads to the formation of a dimer around an inversion center (Fig. 2). The hydrogen bond can be characterized by the following data: N25···N3^{i} 2.784 (3), H25···N3^{i} 1.938 (3) Å and N25—H25···N3^{i} 167.36 (8)° [symmetry code: (i) $-x, 1-y, -1-z$].

Attempts to prepare form A crystals of appropriate quality for single-crystal diffraction analysis have been unsuccessful, although efforts are on-going. The unique nature of the crystal forms isolated for irbesartan is, however, revealed in the powder-diffraction patterns obtained for forms A and B. The powder-diffraction patterns are shown in Fig. 3, together with the calculated pattern of form B, which fits extremely well that obtained experimentally. Solid NMR studies (C^{13}–N^{15}) are underway to further define the crystal forms isolated for irbesartan.

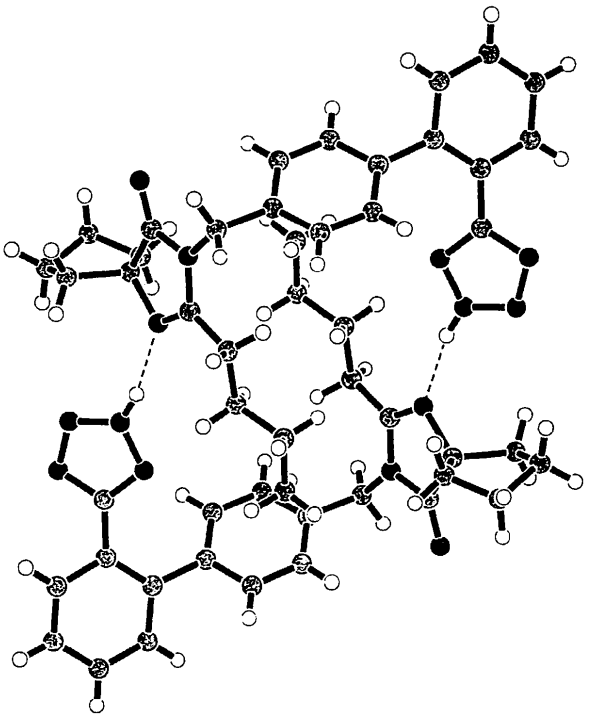


Fig. 2. A cyclic dimer formed through hydrogen bonds in crystal form B of irbesartan.

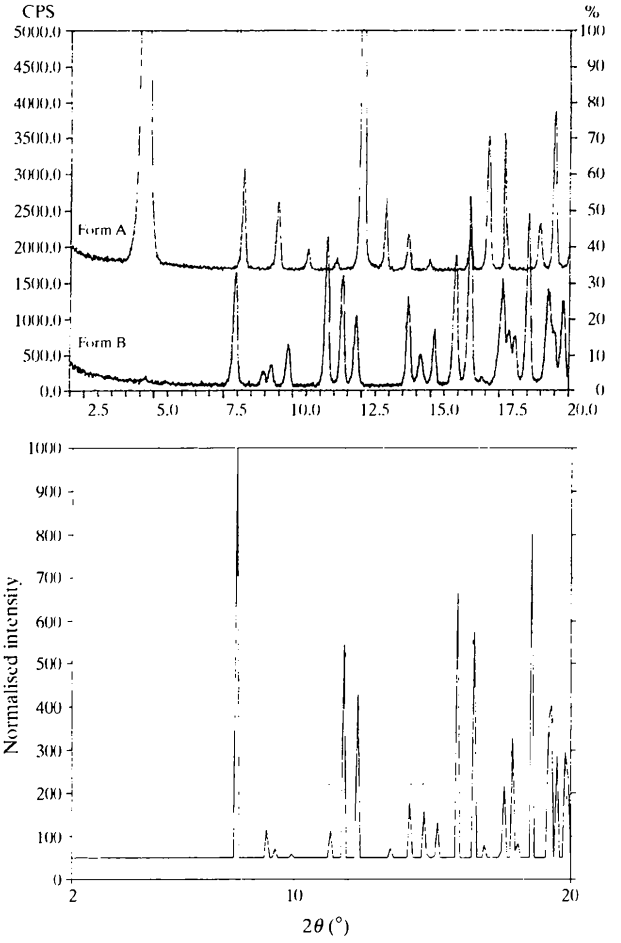


Fig. 3. Powder diagrams of both crystal forms of irbesartan (upper part) and the calculated diagram of form B (lower part).

Experimental

Irbesartan was prepared according to Caron *et al.* (1995). Crystal form B was prepared from irbesartan by adding it to a pH 2.0 solution of aqueous HCl. The suspension was stirred for 36 h at room temperature and then filtered using a 0.2 μm nylon filter. Crystal form B was obtained from the filtrate after drying at ambient temperature.

Crystal data

$C_{25}H_{28}N_6O$ — Cu $K\alpha$ radiation
M_r = 428.53 — λ = 1.5418 Å

Triclinic
$P\bar{1}$
a = 11.170 (5) Å
b = 12.181 (4) Å
c = 9.366 (4) Å
α = 90.75 (4)°
β = 105.24 (4)°
γ = 112.92 (3)°
V = 1122.9 (8) Å^3
Z = 2
D_x = 1.267 Mg m^{-3}
D_m not measured

Cell parameters from 9 reflections
θ = 40.2–51.6°
μ = 0.643 mm^{-1}
T = 293 (2) K
Plate
1.0 × 0.8 × 0.4 mm
Transparent

Data collection

Rigaku AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.667, T_{max} = 0.773
4509 measured reflections
4312 independent reflections

3624 reflections with $I > 2\sigma(I)$
R_{int} = 0.090
θ_{max} = 75.16°
h = −8 → 12
k = −15 → 14
l = −11 → 11
3 standard reflections
every 150 reflections
intensity decay: 1.09%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.204
S = 1.029
4305 reflections
312 parameters
Only H-atom U's refined
$w = 1/[\sigma^2(F_o^2) + (0.0867P)^2 + 0.8048P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.297 e Å^{-3}
$\Delta\rho_{min}$ = −0.387 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.0105 (12)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1985, 1992). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Software used to prepare material for publication: *TEXSAN*.

This paper is presented in dedication to the memory of Dr Renée Rao.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1039). Services for accessing these data are described at the back of the journal.

Table 1. *Selected geometric parameters (Å, °)*

N1—C5	1.367 (3)	C6—C7	1.499 (5)
N1—C2	1.382 (3)	C7—C8	1.485 (6)
N1—C10	1.469 (3)	C8—C9	1.507 (4)
C2—N3	1.282 (3)	C10—C11	1.508 (3)
C2—C28	1.482 (4)	C18—C23	1.477 (3)
N3—C4	1.470 (3)	C23—N24	1.330 (3)
C4—C5	1.514 (3)	C23—N27	1.352 (3)
C4—C6	1.546 (4)	N24—N25	1.324 (3)
C4—C9	1.548 (3)	N25—N26	1.302 (3)
C5—O32	1.203 (3)	N26—N27	1.315 (3)
N26—N25—N24	114.2 (2)		
C5—N1—C2—N3	0.1 (3)	C9—C4—C6—C7	−20.1 (3)
N1—C2—N3—C4	−0.2 (3)	C4—C6—C7—C8	36.5 (4)
C2—N3—C4—C5	0.2 (3)	C6—C7—C8—C9	−39.0 (4)
C2—N3—C4—C6	−120.7 (2)	C7—C8—C9—C4	26.0 (4)
C2—N3—C4—C9	121.4 (2)	N3—C4—C9—C8	119.2 (3)
C2—N1—C5—C4	0.0 (2)	C5—C4—C9—C8	−124.3 (3)
C6—C4—C5—O32	−58.9 (4)	C6—C4—C9—C8	−3.4 (3)
C9—C4—C5—O32	57.6 (4)	C5—N1—C10—C11	95.7 (3)
N3—C4—C5—N1	−0.1 (2)	N1—C10—C11—C12	110.3 (2)
C6—C4—C5—N1	121.3 (2)	C13—C14—C17—C22	128.2 (2)
C9—C4—C5—N1	−122.1 (2)	C13—C14—C17—C18	−49.6 (3)
N3—C4—C6—C7	−143.0 (3)	C17—C18—C23—N24	−28.3 (3)
C5—C4—C6—C7	100.9 (3)		

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