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ORIGINAL PAPER

Crystal Structure of 3-Oxo-4-Aza-5-Alpha-Androstone-17 *β-Tert*-Butyl Carboxamide with an O···H–(C, N) Acceptor Four-Center Hydrogen Bond

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Abstract The title compound, $C_{23}H_{38}N_2O_2$, is the saturated form of a modified steroid derivative Finasteride, containing a δ-lactamide ring, fused to successive cyclohexane and cyclopentane rings which contain a *tert*-butylamide residue. It crystallizes in the monoclinic space group *C2* with unit cell parameters $a = 9.99450(10)$, $b = 7.67870(10)$, $c = 28.4954(3)$, Å, $\beta = 93.8706(10)°$, $Z = 4$. Crystal packing effects are influenced by intermolecular hydrogen bond interactions dominated by an acceptor O···H–(C, N) four-center hydrogen bond interaction around the keto oxygen atom from the δ-lactamide ring in the asymmetric unit. Intramolecular three-center C–H···O hydrogen bonds around the *tert*-butylamide oxygen atom appear to have little effect on crystal packing. A comparison of the geometric parameters of the asymmetric unit (a 5α isomer) is made and with a solvated analog compound (a 5β isomer) and some solvated Finasteride compounds which differ only in the unsaturation of the C1=C2 bond in the δ-lactamide ring. The dihedral angle between the mean planes of the fused δ-lactamide and cyclohexane rings is 2.5(8)° which differs significantly from the 74.8(8) and 76.1(9)° values observed in the solvated analog compound and with its geometry optimized (MOPAC) computed structure, respectively.

Keywords Androstone · Carboxamide · Finasteride · δ-Lactamide ring · Acceptor atom · Four-center hydrogen bond

Introduction

The title compound, $C_{23}H_{38}O_2N_2$ (I), (Fig. 1) is the saturated form [C(1)–C(2) versus C(1)=C(2)] of the drug Finasteride (17b-(*N-tert*-butyl-carbamoyl)-4-aza-5a-androst-1-en-3-one), (II), (Fig. 2) a modified steroid derivative with two peptide groups (the ring A contains a lactam group and the *tert*-butylamide residue is the substituent at C17). These two groups have generally affected the strength and pattern of intermolecular contacts between neighboring molecules in the solid state. Finasteride is a synthetic 4-azasteroid compound, which is a 5-α-reductase inhibitor that interferes with the effects of certain male hormones (androgens) on the prostate [1]. It was originally used to treat enlarged prostate glands (benign prostatic hyperplasia) by the US PDF [2]. Finasteride was approved initially in 1992 as Proscar, a treatment for prostate enlargement, whereby the sponsor had studied a 1 mg sample of Finasteride and demonstrated hair growth in male pattern hair loss [3]. It is used in the prevention of prostate cancer [4]. The synthesis of the 17-aza isomer of Finasteride is described with the side chain amide group

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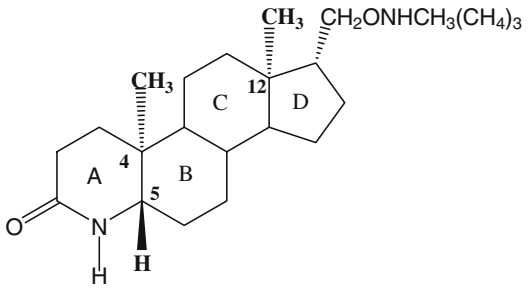
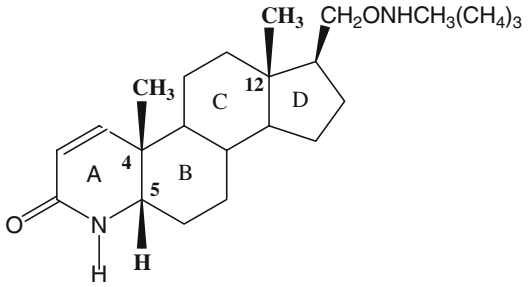


(I)

Fig. 1 Chemical structure of the title compound, $C_{23}H_{38}N_2O_2$, (I). The methyl groups at C(4) and C(12) are *anti* to the hydrogen atom at C(5)



(II)

Fig. 2 Chemical structure of Finastride, $C_{23}H_{36}N_2O_2$ (II). The methyl groups at C(4) and C(12) are *syn* to the hydrogen atom at C(5)

of the compound existing in the Z configuration as the structure is similar to one of the two favored conformations of Finasteride. Also, a series of 4,17-diazasteroids has been assayed against the isoenzymes of human 5α-reductase [5]. The existence of two Finasteride polymorphs was first reported dependent upon the solvent used for crystallization and the mode of crystal treatment, but structural details were not discussed [6]. Recent studies of related structures have included a vinyl fluoride mimic of the 'intermediate' enol form of Finasteride in the 5α-reductase transformation and was reported as the synthesis and in vitro activity of (*N*-1′,1′-dimethylethyl)-3-haloandrost-3,5-diene-17β-carboxamides [7]. The structures of related compounds of Finasteride [8], include *N*-*tert*-butyl-3-oxo-4-aza-5β,17β-androstane-17-carboxamide methanol solvate [a Finasteride impurity and nearly identical to the title compound, (I)] [9], 17-oxo-5α-androstane-3α,4β-diyl diacetate [10] and 17-oxo-5β-androstane-3α,4β-diyl diacetate [10]. Most recently a structural study of Finasteride solvate solid forms has revealed three new crystal structures [11] that are isomorphous with the ethyl acetate solvate reported earlier [12]. In view of the importance of title compound, the crystal structure of an unsolvated $C_{23}H_{38}N_2O_2$, (I), is reported here.

Experimental

3-Oxo-4-aza-5-alpha-androstone-17-β *tert*-butyl carboxamide (I) (a 5a-isomer) was obtained as gift samples from INTERMED LABS PVT LTD., Bangalore, India. X-ray quality crystals were grown from methanol by slow evaporation of the solvent. The melting range was found to be 522–525 K.

Structure Determination and Refinement

X-ray data for (I) was collected with an Oxford Diffraction Gemini R CCD area detector using *CrysAlisPro* software and graphite-monochromated Cu-Kα ($\lambda = 1.54184$ Å) at 200(2) K. The structure was solved by direct methods using SHELXS97 [13] and all of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using SHELXL97 [13]. The hydrogen atoms were placed in their calculated positions and included in the refinement using the riding model. An absorption correction was performed using *CrysAlis RED* and all calculations were performed using SHELXTL [14]. Additional bond and geometry calculations were performed using the software PLATON [15]. Crystal and experimental data for (I) are listed in Table 1. A scheme for the molecular structure of (I) is shown in Fig. 1. Bond lengths and bond angles are within expected ranges, Table 2 [16].

Results and Discussion

The title compound, $C_{23}H_{38}N_2O_2$, (I), is the saturated form [at C(1)–C(2)] of a modified steroid derivative called Finasteride containing a δ-lactamide ring (A), fused to successive cyclohexane (B & C) and cyclopentane (D) rings containing a *tert*-butylamide residue at C(16) [17] (Fig. 3). All of the C–C bonds in the molecule are single bonds with angles close to normal tetrahedral angles (Table 2). Because the methyl groups at carbon 4 and 12 are *anti* to the hydrogen atom at carbon 5 in (I) and *syn* in (II), only a limited comparison of bond lengths and angles involving these groups can be effectively made in these regions. However, when the bonds and angles of a solvated, 5β-isomer, analog, (II), [9] is compared to the title compound, (I), a 5α-isomer, some similarities are observed (Fig. 2). In (I), the somewhat long C(4)–C(9) [=1.5573(19) Å] and C(8)–C(9) [=1.546(2) Å] bonds are affected by crowding between the methyl groups at C(4) and C(8) where the separation between H(8A) and H(17C) is only 2.07(7) Å. The C(1)–O(1) bond (=1.235(2) Å) is slightly longer than the C(19)–O(2) bond (=1.222(2) Å) which is most likely due to effects from the acceptor O···H–(C, N) inter and intra-molecular four-center hydrogen bond

Table 1 Crystal and experimental data for (I)

(I)	
CCDC deposit No.	701192
Formula	$C_{23}H_{38}N_2O_2$
Formula weight	374.55
Crystal color, habit	Colorless, plate
Crystal size (mm)	0.55 × 0.47 × 0.18
Crystal system	Monoclinic
Space group, Z	*C*2, 4
Temperature (K)	200(2)
a (Å)	9.99450(10)
b (Å)	7.67870(10)
c (Å)	28.4954(3)
β (°)	93.8706(10)
Volume, Å^3	2181.88(4)
$F_{(000)}$	824
Absorption coef (mm^{-1})	0.559
D_{calc} (Mg m^{-3})	1.140
No. of reflections	$[I > 2\sigma(I)]$ 3332
$2\theta_{max}$ (°) with Cu K_a	147.34
R, R_w $[I > 2\sigma(I)]$	0.0418, 0.1140
$(\Delta\rho)_{max}$ (e Å^{-3})	0.276
$(\Delta\rho)_{min}$ (e Å^{-3})	−0.220
GOF on F^2	1.069
Absolute structure parameter	0.6(3)
Measurement	*GEMINI* (Oxford Diffraction, 2007)
Program system	*CrysAlisPro*
Structure determination	*SHELXS97*
Refinement	Full-matrix least-squares on F^2 (*SHELXL97*)

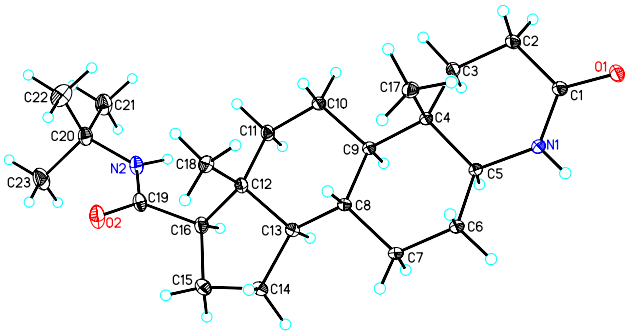


Fig. 3 ORTEP drawings of (I) showing the atom numbering scheme of the asymmetric unit and 50% probability displacement ellipsoids of non-H atoms

Table 3 Hydrogen bonds for (I) (Å and °)

D–H···A	*d*(D–H)	*d*(H···A)	*d*(D···A)	<(DHA)
N(1)–H(1A)···O(1)#1	0.88	2.12	2.909(2)	148.5
C(2)–H(2A)···O(1)#2	0.99	2.62	3.379(2)	133.1
C(17)–H(17B)···O(1)#3	0.98	2.64	3.442(2)	138.7
N(1)–H(1A)···O(1)	0.88	2.12	2.908(6)	127.1
C(15)–H(15B)···O(2)	0.98	2.43	2.869(8)	106
C(22)–H(22B)···O(2)	0.98	2.53	3.117(6)	118
C(23)–H(23A)···O(2)	0.98	2.47	3.071(5)	119

Symmetry transformations used to generate equivalent atoms: #1, $-x + 3/2$, $y - 1/2$, $-z + 2$; #2, $-x + 3/2$, $y + 1/2$, $-z+2$; #3, $-x + 1$, y, $-z + 2$

interactions that exist for O(1) (O(1)···H(2A)–C(2), O(1)···H(17B)–C(17), O(1)···H(1A)–N(1) and O(1)···H(1A)–N(1), respectively). Details of these hydrogen bonds are given in Table 3. Bond lengths and bond angles of (I) show a high degree of similarity with those for the 5*β*-isomer, methanol solvate form, of the molecule isolated during impurity profiling of Finasteride [9] as shown in Table 2 with a comparison of selected geometric parameters. In this molecule, the C(1)–O(1) bond (=1.219(8) Å) is slightly shorter than the C(19)–O(2) bond (=1.225(7) Å). The only major difference in angles between these two molecules (I and II) is observed in the N(1)–C(5)–C(6)–C(7) torsion angle which at 72.4(6)° (II) is significantly changed from that observed for (I) (=−173.46(14)°) which can be related to the difference in *anti* versus *syn* location of the methyl group at C(4) versus the hydrogen atom at C(5). This also appears to be influenced by one of the four-center hydrogen bonds [O(1)···H(1A)–N(1)] around oxygen atom (O1) in the asymmetric unit in (I). In (II) this interaction includes a

Table 2 Selected geometric parameters for (I) (Å, °)

O(1)–C(1)	1.235(2)	[1.219(8)]*	O(2)–C(19)	1.222(2)	[1.225(7)]*
C(1)–N(1)	1.337(2)	[1.328(7)]*	C(19)–N(2)	1.350(3)	[1.337(7)]*
O(1)–C(1)–N(1)	121.49(17)	[120.6(6)]*	O(2)–C(19)–N(2)	123.58(17)	[122.5(6)]*
N(1)–C(5)–C(6)	110.47(14)	[108.9(5)]*	C(3)–C(4)–C(9)	111.47(12)	[111.3(4)]*
C(11)–C(12)–C(16)	115.84(14)	[115.9(4)]*	C(8)–C(13)–C(14)	119.22(14)	[119.6(4)]*
O(1)–C(1)–N(1)–C(5)	−172.34(16)	[−175.3(5)]*	N(1)–C(5)–C(6)–C(7)	−173.46(14)	[72.4(6)]*
O(2)–C(19)–N(2)–C(20)	0.5(3)	[2(1)]*	O(2)–C(19)–C(16)–C(15)	27.2(3)	[−25.4(9)]*
C(7)–C(8)–C(13)–C(14)	54.7(2)	[−59.5(6)]*	C(11)–C(12)–C(16)–C(19)	−80.43(19)	[81.6(6)]*

* Comparison to [9], (Å, °)

Table 4 Comparison of fused ring shapes [18] for (I), [9] and related Finasteride analogs

		A	B	C	D
$C_{23}H_{38}N_2O_2$ (I)	Q	0.512(0)	0.588(1)	0.578(4)	
	θ	136.4(5)	7.3(4)	176.1(1)	
	ϕ	43.586(1)	17.571(3)	93.042(7)	12.610(6)
		Sofa	Chair	Chair	Envelope
Details for solvated analog					
$C_{23}H_{38}N_2O_2.C_1H_4O_1$ [9] (CSD: BEQKEN)	Q	0.485(4)	0.558(8)	0.570(7)	
	θ	123.7(9)	176.6(0)	6.4(2)	
	ϕ	42.302(9)	77.716(5)	250.903(3)	191.985(5)
		Sofa	Chair	Chair	Envelope
Details for related Finasteride analogs					
$C_{23}H_{36}N_2O_2$ [19] (CSD: WOLXOK02)	Q	0.507(3)	0.590(3)	0.578(3)	
	θ	63.2(4)	0.0(3)	7.3(3)	
	ϕ	277.3(4)	284(9)	269(3)	191.9(5)
		Envelope	Chair	Chair	Envelope
$C_{23}H_{36}N_2O_2$ [19] (CSD: WOLXOK03)					
Molecule A	Q	0.496(6)	0.624(6)	0.574(8)	
	θ	64.2(7)	4.6(6)	4.6(8)	
	ϕ	279.3(8)	314(9)	289(8)	185.3(8)
		Envelope	Chair	Chair	Envelope
Molecule B	Q	0.506(6)	0.626(7)	0.588(6)	
	θ	61.5(7)	5.5(6)	5.6(6)	
	ϕ	277.9(8)	342(7)	289(6)	187.3(8)
		Envelope	Chair	Chair	Envelope
Details for Bis (Finasteride) monosolvate monohydrates [11]					
$2(C_{23}H_{36}N_2O_2)$, (H_2O_1) $(C_4H_8O_2)$ (Dioxane solvate hydrate, 11; CCDC: #638162)					
Molecule A	Q	0.484(4)	0.6000(5)	0.579(4)	
	θ	117.6(3)	174.0(4)	177.8(4)	
	ϕ	100.2(3)	125(3)	68(6)	11.3(5)
		Envelope	Chair	Chair	Envelope
Molecule B	Q	0.480(4)	0.590(4)	0.580(4)	
	θ	118.5(5)	173.4(4)	176.9(4)	
	ϕ	98.2(3)	127(3)	95(6)	8.7(6)
		Envelope	Chair	Chair	Envelope
$2(C_{23}H_{36}N_2O_2)$, (H_2O_1) $(C_3H_8O_1)$ (IPA solvate hydrate, 11; CCDC: #638163)					
Molecule A	Q	0.486(4)	0.597(4)	0.582(4)	
	θ	117.9(5)	173.4(4)	175.3(4)	
	ϕ	99.9(5)	123(3)	62(5)	10.3(5)
		Envelope	Chair	Chair	Envelope
Molecule B	Q	0.494(4)	0.594(4)	0.577(4)	
	θ	117.3(5)	173.3(4)	175.5(4)	
	ϕ	97.3(6)	124(3)	81(5)	9.8(6)
		Envelope	Chair	Chair	Envelope
$2(C_{23}H_{36}N_2O_2)$, (H_2O_1) $(C_4H_8O_2)$ (THF solvate hydrate, 11; CCDC: #638164)					
Molecule A	Q	0.483(5)	0.596(5)	0.596(5)	
	θ	116.2(6)	174.1(5)	174.1(3)	
	ϕ	98.0(7)	122(5)	122(5)	10.5(7)
		Envelope	Chair	Chair	Envelope
Molecule B	Q	0.482(5)	0.589(5)	0.56(85)	
	θ	116.8(7)	174.5(5)	176.1(5)	
	ϕ	98.2(7)	126(5)	100(8)	9.2(8)
		Envelope	Chair	Chair	Envelope

N(1)–H(1)···O(3) hydrogen bond interaction between N(1) from the the δ-lactamide ring and solvent oxygen atom O(3) and the N(2)–H(29)···O(1) hydrogen bond interaction between the keto oxygen atom [O(1)] in the δ-lactamide ring with the *tert*-butylamide nitrogen atom [N(2)] from a nearby $C_{23}H_{38}N_2O_2$ molecule [$x - 1/2$, $-y + 3/2$, $-z + 2$]. While small differences are observed for C(1)–N(1) (=1.328(7) Å) [9] versus (=1.337(2) Å) (I) and C(19)–N(2) (=1.337(7) Å) [9] versus (=1.350(3) Å) (I) bond lengths., no conclusions can be made here since data collection in each venue was not made at comparable temperatures and appropriate corrections were not considered. It is interesting to note that in (I), no intermolecular interactions are observed with the *tert*-butylamide nitrogen atom, N(2). Even though the N(2)–C(19)–O(2) group forms a dialkyl *trans* secondary amide with considerable steric projection, it displays only a series of weak C–H···O intramolecular hydrogen bonds that appears to have little effect on crystal packing (Table 2). In contrast, the *cis* lactamide group [N(1)–C(1)–O(1)] has both donors and acceptors and intermolecular contacts which form a hydrogen-bonded chain between the molecules around the twofold screw axis along the crystallographic (unique) *b* axis of type C11(4) and therefore does influence crystal packing.

The two *trans* fused cyclohexane rings (B & C) in (I) form a slightly distorted chair–chair (or double-chair) conformation and is confirmed by the ring torsion angles and the puckering parameters θ [18] which are 7.3(4)° [C(4)–C(9)] and 176.1(1)° [C(8)–C(13)] for rings B and C, respectively (for an ideal chair $\theta = 0°$ or 180°−0°). These values are in general agreement with reported values for the identical, saturated, solvated molecule in [9] (CSD refcode BEQKEN [9]) and closely related unsaturated Finasteride structures (CSD refcodes WOLXOK02 [19] and WOLXOK03 [19]; Table 4). The methyl groups in (I) at C(4) and C(12), the heaviest substituents in the cyclohexane rings occupy axial positions. In WOLXOK02, WOLXOK03, and in each of the three related Bis(Finasteride) monosolvate monohydrate compounds (#638162, #638163 and #638614) these methyl groups are *anti* to the hydrogen atom at C(5) making comparisons to them more relevant (Tables 4, 5, 6).

The dihedral angle between the mean planes of the mean planes of the fused rings (A & B; B & C; C & D) in (I) is 2.5(8)°, 4.4(5)° and 7.1(0)° while the dihedral angle between the mean plane of ring D and the best plane of the keto group [N(2)–C(19)–O(2)–C(16)] is 54.8(7)°, respectively, Table 5. These values are somewhat similar to those

Table 5 Comparison of dihedral angles between fused rings and ring D versus C–C(=O)–N (keto group) for (I) (°), [9], [19] and [21]

	A & B	B & C	C & D	D & keto
($C_{23}H_{38}N_2O_2$) (I)	2.5(8)	4.4(5)	7.1(1)	54.8(7)
Details for solvated analog				
($C_{23}H_{38}N_2O_2$), ($C_1H_4O_1$) [9] (CSD: BEQKEN)	74.8(8)	4.0(1)	5.9(1)	52.9(4)
$C_{23}H_{38}N_2O_2$, ($C_1H_4O_1$) [9] (MOPAC-AM1)	76.1(9)	5.4(1)	9.5(7)	45.8(3)
Details for related Finasteride analogs				
($C_{23}H_{36}N_2O_2$) [19] (CSD: WOLXOK02)	9.9(1)	2.5(8)	4.6(9)	56.0(8)
($C_{23}H_{36}N_2O_2$) [19] (CSD: WOLXOK03)				
Molecule A	9.5(4)	3.7(2)	6.4(1)	56.3(0)
Molecule B	8.7(3)	1.5(3)	5.7(8)	55.4(5)
($C_{23}H_{36}N_2O_2$), $C_2H_4O_2$ [21] (CSD: WOLXEA)	6.1(6)	5.5(2)	8.7(3)	55.4(6)
2($C_{23}H_{36}N_2O_2$), ($C_4H_8O_2$), (H_2O_1) [20] (CSD: WOLXIE)				
Molecule A	5.8(1)	3.9(1)	9.9(6)	48.6(5)
Molecule B	5.5(3)	5.4(6)	8.7(5)	53.9(0)
Details for Bis (Finasteride) monosolvate monohydrates [11]				
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_4H_8O_2$) (Dioxane solvate hydrate, 11; CCDC: #638162)				
Molecule A	9.0(4)	5.4(9)	6.0(9)	54.8(1)
Molecule B	8.4(1)	5.0(9)	6.1(2)	46.8(9)
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_3H_8O_1$) (IPA solvate hydrate, 11; CCDC: #638163)				
Molecule A	9.1(2)	4.6(7)	5.7(3)	55.3(8)
Molecule B	7.8(1)	4.3(6)	5.5(4)	49.4(1)
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_4H_8O_2$) (THF solvate hydrate, 11; CCDC: #638164)				
Molecule A	8.6(7)	5.5(4)	5.0(6)	54.5(4)
Molecule B	7.4(5)	4.8(7)	5.3(4)	46.3(2)

Table 6 Comparison of selected geometric parameters for (I) (Å, °), [9], [19] and [21]

($C_{23}H_{38}N_2O_2$) [I]	C1–C2	1.530(9)	C1–O1	1.234(8)
			C19–O2	1.222(4)
Details for solvated analog				
($C_{23}H_{38}N_2O_2$), ($C_1H_4O_1$) [9] (CSD: BEQKEN)	C1–C2	1.495(2)	C1–O1	1.218(2)
			C19–O2	1.225(4)
($C_{23}H_{38}N_2O_2$), ($C_1H_4O_1$) [9] (MOPAC-AM1)	C1–C2	1.49(5)	C1–O1	1.24(4)
			C19–O2	1.24(8)
Details for related Finasteride analogs				
($C_{23}H_{36}N_2O_2$) [19] (CSD: WOLXOK02)	C1–C2	1.330(4)	C3–O1	1.230(3)
			C19–O2	1.219(4)
($C_{23}H_{36}N_2O_2$) [19] (CSD: WOLXOK03)				
Molecule A	C1–C2	1.350(8)	C3–O1	1.210(7)
			C19–O2	1.214(7)
Molecule B	C24–C25	1.365(8)	C3–O1	1.242(7)
			C42–O4	1.232(7)
($C_{23}H_{38}N_2O_2$), $C_2H_4O_2$ [21] (CSD: WOLXEA)	C1–C2	1.334(6)	C3–O1	1.250(5)
			C19–O2	1.217(5)
2($C_{23}H_{38}N_2O_2$), ($C_4H_8O_2$), (H_2O_1) [20] (CSD: WOLXIE)				
Molecule A	C1–C2	1.354(16)	C3–O1	1.280(16)
			C19–O2	1.181(19)
Molecule B	C24–C25	1.326(16)	C3–O1	1.204(16)
			C42–O4	1.260(17)
Details for Bis(Finasteride) monosolvate monohydrates [11]				
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_4H_8O_2$) (Dioxane solvate hydrate, 11; CCDC: #638162)				
Molecule A	C1–C2	1.337(5)	C3–O3	1.248(4)
			C20–O20	1.227(5)
Molecule B	C26–C27	1.320(5)	C28–O28	1.246(4)
			C45–O45	1.206(8)
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_3H_8O_1$) (IPA solvate hydrate, 11; CCDC: #638163)				
Molecule A	C1–C2	1.345(5)	C3–O3	1.262(4)
			C20–O20	1.234(5)
Molecule B	C26–C27	1.331(5)	C28–O28	1.245(7)
			C45–O45	1.234(7)
2($C_{23}H_{36}N_2O_2$), (H_2O_1) ($C_4H_8O_2$) (THF solvate hydrate, 11; CCDC: #638164)				
Molecule A	C1–C2	1.341(7)	C3–O3	1.258(6)
			C20–O20	1.237(7)
Molecule B	C26–C27	1.334(7)	C28–O28	1.240(6)
			C45–O45	1.211(9)

in [9] with the exception of (A & B) which has a value of 74.8(8)° by comparison. This dramatic difference in the dihedral angle between (A & B) is also most likely due to the close intermolecular interaction of the solvent molecule in [9] with the δ-lactamide ring as well as the difference between the *anti* and *syn* relationships of the two methyl groups at C4 and C12 with the hydrogen aton at C(5). In addition, in (II), there is a significant influence of the N(1)–H(1)···O(3) hydrogen bond interaction between N(1) from the the δ-lactamide ring and solvent oxygen atom O(3) and the N(2)–H(29)···O(1) hydrogen bond interaction between the keto oxygen atom [O(1)] in the δ-lactamide ring with the *tert*-butylamide nitrogen atom, N(2), from a nearby $C_{23}H_{38}N_2O_2$ molecule [$x-1/2, -y+3/2, -z+2$]. *MOPAC* calculations (AM1 approximation together with the Hartree-Fock closed-shell restricted wave function was used and minimizations were teminnated at an r.m.s. gradient of less than 0.01 kJ mol^{-1} $Å^{-1}$) [20] on the solvated molecule [9] support this observation with a calculated (A & B) separation of 76.1(9)°.

A comparison of the dihedral angles between the mean planes of the fused rings (A & B; B & C; C & D) as well as

between the mean plane of ring D and the N–(C=O)–C keto group with a few solvated Finasteride analog molecules [19, 21, 11] indicate that the solvents present in the crystal packing for these molecules do not alter the angles between these rings significantly from that seen in (I) (Table 5). This is most likely because of greater intermolecular distances between these species (>4 Å) as observed in the unit cell for a typical hydrogen bond interaction.

The C(1)–C(2) bond length in (I) (=1.530(9) Å) being slightly shorter that a normal C–C single bond reflects the effects of one of the four-center intermolecular hydrogen bond interactions [C(2)–H(2A)···O(1)] from the cyclopentane D ring (C(2)–H(2A)···) and a keto group [···O(1)–C(1)] of a nearby molecule ($-x + 3/2$, $y + 1/2$, $-z + 2$). In comparison to that observed in [9] involving solvent interaction in this region of the molecule, whereby the C(1)–C(2) bond length becomes 1.495(2) Å, it is clear that factors such as nearby solvent attraction [N(1)–H(1)···O(3)] from the δ-lactamide ring as well as intermolecular hydrogen bond interactions [N(2)–H(29)···O(1)] from the *tert*-butylamide residue (N(2)–H(29)···) and nearby symmetry related keto oxygen atom [O(1)] ($x-1/2$, $-y + 3/2$, $-z + 2$) affects the hybridization of the C(1) and C(2) atoms giving them some partial double bond character (Table 6). A MOPAC calculation which included the solvent molecule gives the C(1)–C(2) bond length of 1.49(5) Å. The varied differences in bond lengths for the unsaturated [C(1)=C(2)] bond character observed for related Finasteride analogs provides support for our observations of the saturated single bond character of these molecules indicating that the influence of intermolecular hydrogen bond interactions and various packing effects do in fact play a role in the shapes of these types of structurally related molecules.

Differences in bond lengths and geometric parameters of the keto groups from the δ-lactamide ring, C(1)=O(1) (=1.235(2) Å), as well as from the *tert*-butylamide residue, C(19)=O(2) (=1.222(2) Å) in (I) are observed and again can be related to intermolecular hydrogen bond interactions and packing effects somewhat similar to those described above (Table 6). The four-center intermolecular hydrogen bond around O(1) and a three-center intramolecular hydrogen bond around O(2) (C(15)–H(15B)···O(2), C(22)–H(22B)···O(2), C(23)–H(23A)···O(2) (see Table 3 for details) provide support to the influence of nearby atoms on these two separate keto bond lengths. In [9], this bond length is 1.218(2) Å with the N(2)–H(29)···O(1) intermolecular interaction providing the major influence on its length.

The molecules in (I) align themselves in a three-dimensional network in chains diagonal to the *bc* plane and along the (011) axis of the unit cell. A view of the N(1)–H(1A)···O(1) component of the four-center hydrogen bond can be seen along the *c* axis of the unit cell (Fig. 4). A view of two components of the four-centered hydrogen bond

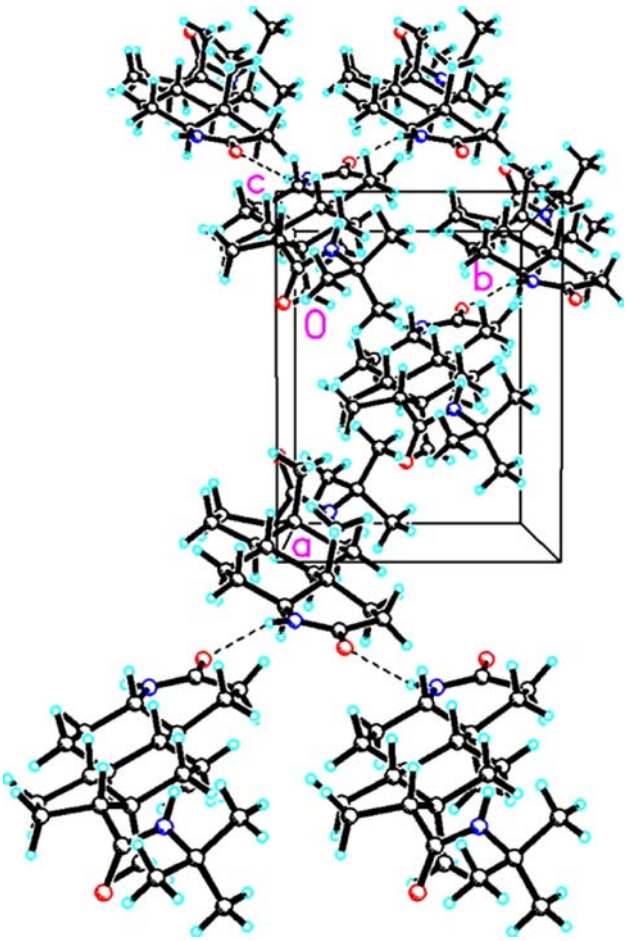


Fig. 4 The molecular packing for (I) viewed down the *c* axis. *Dashed lines* indicate intermolecular N(1)–H(1A)···O(1) hydrogen bonds

(O(1)···H(1A)–N(1) and O(1)···H(2A)···C(2) hydrogen) can be seen when viewed down the *a* axis (Fig. 5). The C(17)–H(17B)···O(1) intermolecular hydrogen bond can be seen when viewed down the *b* axis (Fig. 6).

In conclusion, the geometrical parameters of title compound, $C_{23}H_{38}N_2O_2$, (I), containing a δ-lactamide ring (A), fused to successive cyclohexane (B & C) and cyclopentane (D) rings containing a *tert*-butylamide residue at C(17) [17] shows much similarity to an analog compound [9] as well

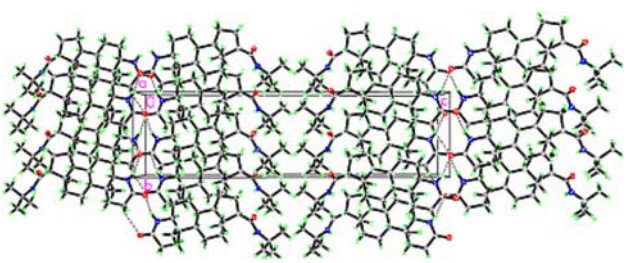


Fig. 5 The molecular packing for (I) viewed down the *a* axis. *Dashed lines* indicate intermolecular bifurcated acceptor O(1)···H(1A)–N(1) and O(1)···H(2A)–C(2) hydrogen bonds

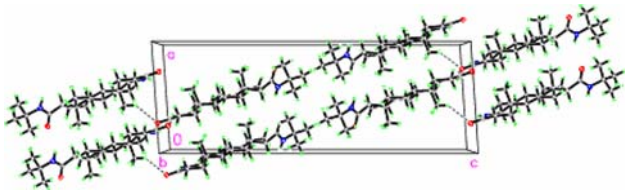


Fig. 6 The molecular packing for (I) viewed down the *b* axis. *Dashed lines* indicate intermolecular C(17)–H(17B)···O(1) hydrogen bonds

as to a number of related unsaturated, solvated derivatives of the compound, Finasteride. Crystal packing effects are influenced by intermolecular hydrogen bond interactions which include acceptor O···H–(C, N) intermolecular four-center hydrogen bond interactions around the keto oxygen atom from the δ-lactamide ring as well as an intramolecular three-center C–H···O hydrogen bond around the *tert*-butylamide oxygen atom in the asymmetric unit. It is apparent that the introduction of solvation in addition to observed intermolecular hydrogen bonding interactions play a significant role in the geometric structure and packing effects in title compound as well as in its closely related analogs.

Supporting Information Available

X-ray crystallographic files, in Cif format, for the structure determinations of (I) (701192) has been deposited with the Cambridge Crystallographic Date Center, CCDC: 26091. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ (Fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk).

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