Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

6β-Methyl-*B*-norandrostenedione

L. C. R. Andrade,[a]* M. J. M. de Almeida,[a] M. A. C. Neves,[b] T. C. P. Dinis[b] and M. L. Sá e Melo[b]

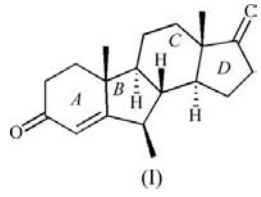
[a]CEMDRX, Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade de Coimbra, P-3004-516 Coimbra, Portugal, and [b]Centro de Estudos Farmacêuticos, Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, P-3000-548 Coimbra, Portugal
Correspondence e-mail: lourdes@pollux.fis.uc.pt

Received 9 December 2009
Accepted 12 February 2010
Online 6 March 2010

The title compound, $C_{19}H_{26}O_2$, a *B*-norandrogen with a 6β-methyl group, is a recently identified and experimentally tested potent new aromatase inhibitor. It shares structural and physicochemical similarities both with the natural substrate of the enzyme, androstenedione, and with exemestane, another potent aromatase inhibitor having a 6-methylidene group. X-ray diffraction results indicate that the *B*-nor molecule and exemestane have nearly the same oxygen–oxygen and methyl–methyl separations, though they have distinct configurations of the hydrophobic groups at the 6-position. These structural comparisons allow correlations to be inferred between the active site geometry of the molecules and the aromatase inhibition power of the studied compound.

Comment

6β-Methyl-*B*-norandrostenedione, (I) (Fig. 1), is a potent aromatase inhibitor recently identified on the NCI open chemical repository collection following a new steroid–pharmacophore virtual screening strategy developed by our group



(I)

(Neves *et al.*, 2009). This molecule was tested experimentally on a biochemical assay with aromatase extracted from human term placenta, and was found to be able to block the enzyme with strong potency and a competitive mechanism of inhibition (IC_{50} = 0.274 μ*M*; IC_{50} is the half-maximal inhibitory concentration). Aminoglutethimide, a first-generation aromatase inhibitor, was tested in the same assay conditions (IC_{50} = 10 μ*M*). To the best of our knowledge, this is the first report of a *B*-norandrogen as an aromatase inhibitor. Therefore, these compounds represent an important new structural class of anti-aromatase agents and should be further optimized.

Compound (I) shares structural and physicochemical similarities with the natural substrate of the enzyme, androstenedione (Busetta *et al.*, 1972), and with exemestane (Gorlitzer *et al.*, 2006), an important aromatase inhibitor, suggesting a common aromatase recognition mechanism. In particular, the three compounds have very hydrophobic scaffolds and two hydrogen-bond acceptors at equivalent positions, *viz.* O3 and O17. These are important active sites for either androstenedione or exemestane to bind with aromatase (Ghosh *et al.*, 2009). According to these authors, the 17-keto O atom makes a hydrogen bond with the backbone amide of Met 374 and a weak contact with N—H1 of Arg 195. In addition, the 3-keto O atom interacts with the carboxylate group of Asp 309, assumed to be protonated. The *B*-ring of the nor steroid, a cyclopentane, is less bulky than the cyclohexane in androstenedione; however, this is well balanced with a 6β-methyl group. Moreover, the C6 functionality is similar to that in exemestane, which can interact with a hydrophobic pocket within the active site of the enzyme delimited by Phe 221, Trp 224, Val 369, Val 370 and Leu 477 (Ghosh *et al.*, 2009), increasing the anti-aromatase potency. Futhermore, according to the same authors, the C19 methyl group is another important interaction position between the inhibitor and the aromatase heme Fe. On this basis, the detailed knowledge of the crystal structure of 6β-methyl-*B*-norandrostenedione is important for the design of new potent aromatase inhibitors.

The crystal structure analysis of (I) shows that the distance between terminal atoms O3 and O17 is 10.408 (3) Å, which can be compared with distances of 10.401 (2) and 10.681 Å for exemestane and androstenedione, respectively. The agreement between the *B*-nor and exemestane values is notable and certainly consistent with their similar biological activity. Considering possible variations in C═O···H hydrogen-bond lengths (Jeffrey, 1997), a difference of about 0.28 Å in length for the androstenedione molecule is not sufficient to prevent the establishment of such bonds both with the head and the tail of the steroid.

For the *B*-nor structure, ring *A*, with a C═C double bond, adopts a 1α-sofa conformation [asymmetry parameters (Duax & Norton, 1975): $\Delta C_s(1)$ = 3.7 (2)°, $\Delta C_2(3,4)$ = 22.2 (3)° and $\Delta C_2(2,3)$ = 51.9 (3)°]. Ring *C* has a slightly flattened chair

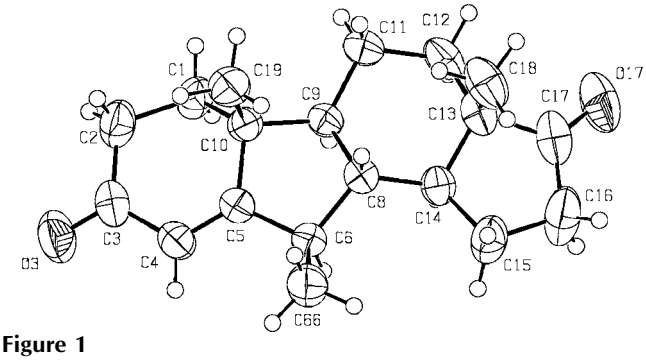


Figure 1
The molecular structure of the title compound. Displacement ellipsoids are drawn at the 50% probability level.

 doi:10.1107/S0108270110005871

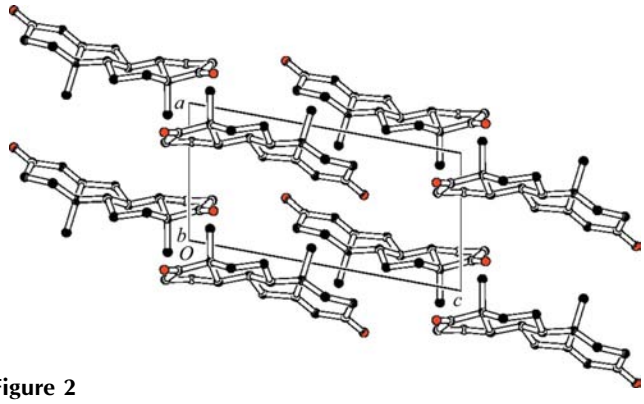


Figure 2
View of the unit cell parallel to the *ac* plane.

conformation evidenced by an average torsion angle value of 56.7 (3)°. The five-membered *D* ring assumes a 14α-envelope conformation [puckering parameters (Cremer & Pople, 1975): q_2 = 0.427 (3) Å and φ_2 = 211.0 (4)°; pseudorotation (Altona *et al.*, 1968) and asymmetry parameters: Δ = 25.6 (2)°, φ_m = 43.6 (2)°, $\Delta C_s(14)$ = 4.7 (3)° and $\Delta C_2(13,14)$ = 15.3 (3)°]. The conformational parameters of these three rings are very similar to the corresponding androstenedione values, and to those of exemestane if one considers only rings *C* and *D*.

The cyclopentane *B*-nor ring assumes a 9α-envelope conformation [puckering parameters: q_2 = 0.435 (2) Å and φ_2 = 288.2 (3)°; pseudorotation and asymmetry parameters: Δ = 181.3 (2), φ_m = 44.2 (1), $\Delta C_s(9)$ = 1.0 (2), $\Delta C_2(8,9)$ = 22.4 (2)°]. The pseudo-torsion angle C19—C10···C13—C18 of 6.9 (2)° indicates that the *B*-nor steroid molecule is twisted compared with androstenedione or exemestane, for which values of −1.57 and 0.1 (2)°, respectively, were determined by Busetta *et al.* (1972) and Gorlitzer *et al.* (2006). This twist can be understood as a normal consequence of the replacement of the six-membered *B* ring by a five-membered ring.

For the *B*-nor structure, the 6-methyl group is in a β-bisectional position, with an angle of 51.6 (1)°, which can be compared with the quasi-equatorial position of the 6β-CH_2 group in exemestane, with an angle 68.19 (9)°. The C19···C66 distances for the *B*-nor steroid and the exemestane molecules are, respectively, 3.994 (3) and 3.995 (2) Å. Moreover, when one tries to superimpose the three molecules it is possible to have atoms O3, O17 and C19 almost coincident. However, the positions of the C6 hydrophobic groups for the *B*-nor steroid and exemestane are clearly distinct, as indicated by the C19—C10···C6—C66 pseudo-torsion angles for the two molecules [24.6 (3) and 48.4 (2)°, respectively]. This apparently indicates that the hydrophobic crevice in the aromatase active site is large enough to accommodate groups in different orientations.

Since there are no strong intermolecular bonds, the crystal packing (Fig. 2) can only be the result of weak van der Waals interactions, which do not appear to be responsible for the conformational aspects of the molecule.

Experimental

Compound (I) was obtained from the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis of the National Cancer Institute. The crystal used for analysis was chosen directly from the purchased sample.

Crystal data

$C_{19}H_{26}O_2$
M_r = 286.40
Monoclinic, $P2_1$
a = 6.2000 (12) Å
b = 10.890 (2) Å
c = 12.530 (3) Å
β = 100.49 (3)°
V = 831.9 (3) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 293 K
0.28 × 0.24 × 0.21 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.980, T_{max} = 0.985
18767 measured reflections
2063 independent reflections
1681 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.100
S = 1.06
2063 reflections
193 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.11 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

All H atoms were refined as riding on their parent atoms, with C—H = 0.93–0.98 Å and U_{iso}(H) values set at 1.5U_{eq}(C) for methyl groups and at 1.2U_{eq}(C) otherwise. The absolute structure cannot be determined reliably from the X-ray data, so the Friedel pairs were merged before refinement. The absolute configuration used in the model was chosen arbitrarily.

Data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

This work was supported by Fundação para a Ciência e Tecnologia.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ3232). Services for accessing these data are described at the back of the journal.

References

Altona, C., Geise, H. J. & Romers, C. (1968). *Tetrahedron*, **24**, 13–32.
Bruker (2003). *SMART* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.
Busetta, B., Comberton, G., Courseille, C. & Hospital, M. (1972). *Cryst. Struct. Commun*. **1**, 129–133.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc*. **97**, 1354–1358.
Duax, W. L. & Norton, D. A. (1975). In *Atlas of Steroid Structure*, Vol. 1. New York: Plenum.
Ghosh, D., Griswold, J., Erman, M. & Pangborn, W. (2009). *Nature* (*London*), **457**, 219-223.
Gorlitzer, K., Bonnekessel, Ch., Jones, P. G., Palusczak, A. & Hartmann, R. W. (2006). *Pharmazie*, **61**, 575–581.
Jeffrey, G. A. (1997). In *An Introduction to Hydrogen Bonding*. New York: Oxford University Press.
Johnson, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Neves, M. A. C., Dinis, T. C. P., Colombo, G. & Sáe Melo, M. L. (2009). *Eur. J. Med. Chem.* **44**, 4121–4127.
Sheldrick, G. M. (2000). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.