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8-Chloro-5-(4-chlorophenyl)-5*H*-indeno-[1,2-*d*]pyrimidine

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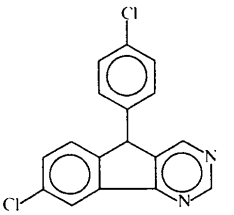
Abstract

The title compound, $C_{17}H_{10}Cl_2N_2$, crystallizes with two independent molecules in the asymmetric unit, with little conformational difference between them. The molecules have two planar components and the angle between the two planes is 95.5° in molecule I and 97.3° in molecule II. The crystal structure exhibits only van der Waals interactions. The three-dimensional structure and folding of the two independent molecules in the asymmetric unit are reminiscent of other P450 aromatase inhibitors.

Comment

The conversion of steroidal androgens (C_{19} compounds containing a methyl group at the C-19 position) to steroidal estrogens (C_{18} compounds with an aromatic *A* ring) in humans is catalyzed in three steps by aromatase (P450 arom, CYP19). Steroidal and non-steroidal inhibitors of these reactions are used clinically to treat estrogen-dependent disorders. Among the most potent non-steroidal inhibitors are aminogluthemide (Mason *et al.*, 1987), fadrozole (Furet *et al.*, 1993), vorozole (De Coster *et al.*, 1990; Peeters *et al.*, 1993), letrozole (Bhatnagar *et al.*, 1990) and anastrozole (Dukes *et al.*, 1996). The title compound, LY113174, is part of a family of substituted pyrimidines (Taylor *et al.*, 1987; Jones *et al.*, 1990) that show varying degrees of inhibitory activity towards aromatase (Hirsch *et al.*, 1987). The structure determination of LY113174 was carried out in order to characterize this aromatase inhibitor of known activity.



LY113174

Perspective views showing the atomic numbering schemes for the two independent molecules, both with the *S* configuration at the chiral center, are given in Fig. 1. The bond lengths and angles of the two molecules are similar and a search of the April 1997 version of the Cambridge Structural Database (Allen *et al.*, 1979) for the three-ring moiety produced no hits. A least-squares superposition of the two molecules shows only a slight variation in the two conformations. The angle between the two planar components of the twisted molecules is 95.5° for molecule I and 97.3° for molecule II (this is illustrated in a figure deposited with the supplementary material). Relevant torsion angles which help to illuminate the three-dimensional twist in the title compound are given in Table 1, the first four values referring to the first molecule and second four giving the corresponding parameters for the second independent molecule.

The two principal molecular planes, *i.e.* the tricyclic plane and the phenyl plane, contain essentially all the atoms. In molecule I, the atom that is furthest from the tricyclic plane (containing atoms C7–C17, N1 and N2) is C17 at a distance of −0.021 (3) Å. The Cl2 atom is in the tricyclic plane and the Cl1 atom is in the plane defined by atoms C1–C6. For molecule II, the two atoms showing the greatest deviation from the tricyclic plane are C107 and N102 at distances of 0.033 (3) and −0.023 (3) Å, respectively. The Cl atoms, Cl101 and Cl102, do not deviate from their respective planes. The *p*-Cl atoms cause the expected increase in the ring angle in which the central atom is that bonded to the chlorine and a decrease in the two adjacent ring angles (Brisse & Sygusch, 1974; Domenicano & Murray-Rust, 1979) from 120°.

There is only one intermolecular contact per molecule that is less than the sum of the van der Waals radii of the atoms. In molecule I, atoms Cl1 and Cl2(x, y, $z+1$) are 3.660 (1) Å apart, while in molecule II, atoms Cl101 and Cl102(x, y, $z+1$) are 3.840 (1) Å apart.

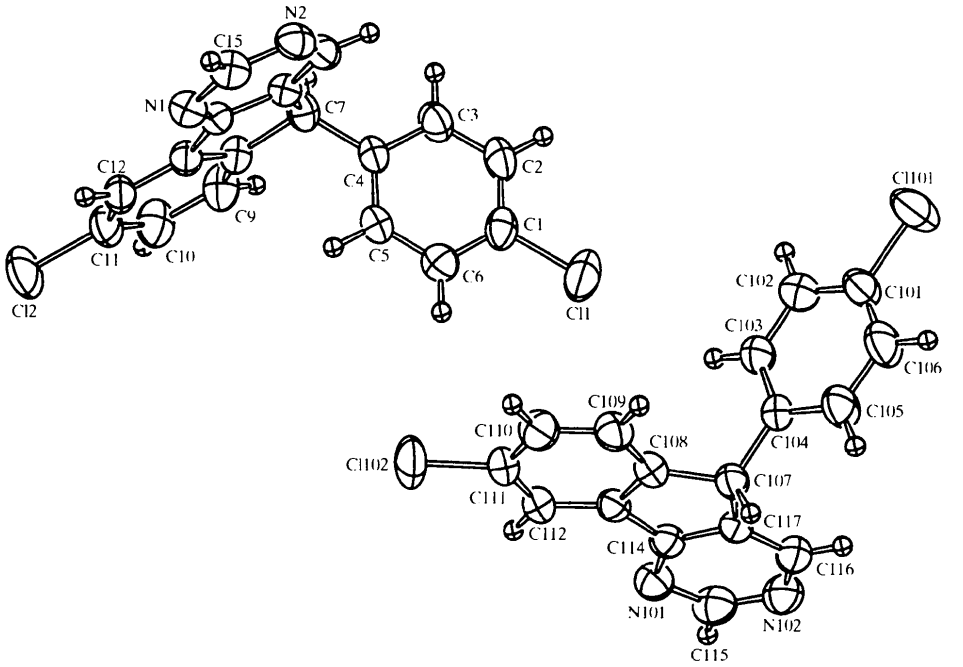
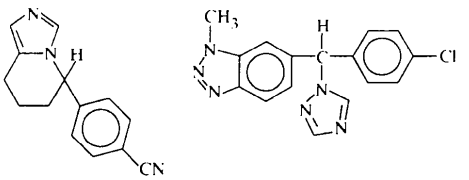


Fig. 1. Perspective views of the two independent molecules of LY113174. Displacement ellipsoids are plotted at the 50% probability level.

The aromatase inhibitors described earlier all have a basic heterocyclic N atom which can bond to the heme iron at the active site of aromatase (Type II binding). X-ray structure reports on fadrozole [(II); Furet *et al.*, 1993] and vorozole [(III); Peeters *et al.*, 1993] reveal



(II) (III)

some structural features which are common to these inhibitors. The active *S* enantiomer of fadrozole has a twisted shape similar to the title compound, with an angle of 107° between the two planes. A tertiary C atom connects a *p*-cyanophenyl ring with a fused two-ring nitrogen heterocycle. Vorozole shows a structure in which the central tertiary C atom joins a *p*-chlorophenyl ring to two different nitrogen heterocyclic units. The angles between the three rings in vorozole (free base) are 85° between the benzotriazole and triazole rings, 105° between the triazole and chlorophenyl rings, and 81° between the benzotriazole and chlorophenyl rings. For vorozole hydrobromide, the equivalent angles are 79, 110 and 109°. Defining a pharmacophore for aromatase has proven difficult. Nonetheless, common features are: (i) a tertiary C atom with bulky substituents that confer a preferred minimum-energy conformation based mainly on steric effects; (ii) a nitrogen-containing heterocycle with a basic N atom that is three or four atoms away from the tetrahedral juncture and that can bind with the heme iron; (iii) at least one of the groups on the tertiary C atom being a phenyl group with substituents such as CN, OCH_3 and Cl, that change its electron-density distribution. The altered electron density will modulate the hydrophobicity and polarity of the phenyl group so that the molecule can participate in van der Waals interactions with the protein.

Experimental

Crystals of the title compound suitable for X-ray diffraction analysis were obtained by crystallization from methanol. The material was a gift from Dr M. Niedenthal of Eli Lilly and Co.

Crystal data

$C_{17}H_{10}Cl_2N_2$
M_r = 313.19
Monoclinic
$P2_1/a$
a = 11.922 (1) Å
b = 18.963 (2) Å
c = 12.826 (1) Å
β = 90.83 (1)°
V = 2899.4 (5) Å^3
Z = 8
D_x = 1.435 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 35–55°
μ = 3.962 mm^{-1}
T = 293 K
Prism
0.35 × 0.35 × 0.25 mm
Colorless

Data collection

Syntex diffractometer
θ–2θ scans

R_{int} = 0.024
θ_{max} = 70°

Absorption correction:
ψ scan (*XEMP*; Siemens, 1994)
T_{min} = 0.264, T_{max} = 0.371
5981 measured reflections
5650 independent reflections
3876 reflections with
$F > 4\sigma(F)$
$h = 0 \rightarrow 14$
$k = 0 \rightarrow 22$
$l = -15 \rightarrow 15$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F
R = 0.044
wR = 0.056
S = 0.986
3876 reflections
379 parameters
H atoms: see below
$w = 1/(0.52883 + 0.00952F_o + 0.00037F_o^2)$
$(\Delta/\sigma)_{max}$ = 0.03
$\Delta\rho_{max}$ = 0.254 e Å^{-3}
$\Delta\rho_{min}$ = −0.271 e Å^{-3}
Extinction correction: none
Scattering factors from
International Tables for Crystallography (Vol. C)

Table 1. *Selected torsion angles (°)*

C3—C4—C7—C8	141.8 (3)
C3—C4—C7—C17	−103.7 (3)
C5—C4—C7—C8	−42.3 (4)
C5—C4—C7—C17	72.1 (3)
C105—C104—C107—C108	135.5 (3)
C105—C104—C107—C117	−108.1 (3)
C103—C104—C107—C108	−45.9 (4)
C103—C104—C107—C117	70.5 (3)

Each H atom was assigned the equivalent isotropic displacement parameter of the parent C atom and allowed to ride (0.96 Å). The H atom of C107 was localized in a difference Fourier map and refined keeping U_{iso} fixed.

Data collection: Syntex diffractometer software. Cell refinement: Syntex diffractometer software. Data reduction: Syntex diffractometer software. Program(s) used to solve structure: *SHELXTL* (Siemens, 1994). Program(s) used to refine structure: *CAOS* (Camalli & Spagna, 1994). Molecular graphics: *VIEW* (Carrell, 1994). Software used to prepare material for publication: *CAOS*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1053). Services for accessing these data are described at the back of the journal. A figure showing the superposition of the two molecules in the asymmetric unit has also been deposited.

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[1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-pyrazol-5-yl]acetonitrile

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Abstract

The title compound, $C_{18}H_{14}ClN_3O$, was obtained as one of the products from the condensation of 4-chlorophenylhydrazine hydrochloride with 6-(4-methoxyphenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile. The best planes through the phenyl rings in the methoxyphenyl and chlorophenyl groups are aligned at angles of 7.02 (8) and 56.19 (4)°, respectively, relative to the pyrazole ring.

Comment

Pyrazole derivatives are principally used in medicine; many alkyl pyrazoles have shown quite significant bacteriostatic, bacteriocidal and fungicidal actions (Herrman & Grabliks, 1961; Rich & Horsfall, 1952; McNew & Sundholm, 1949). Nitrogen heterocycles,