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1-{[4-(4-Chlorophenyl)-1*H*-pyrrol-3-yl](2,4-dichlorophenyl)methyl}-1*H*-imidazole (RDS 416)

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.004 Å
R factor = 0.041
wR factor = 0.056
Data-to-parameter ratio = 10.5

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

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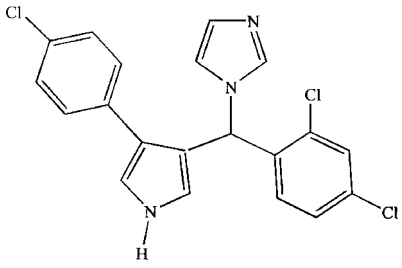
The crystal structure of the title compound, $C_{20}H_{14}Cl_3N_3$, a potent antifungal agent discovered recently, is here reported. The elucidation of the structure may be useful to provide a better understanding of the interaction of imidazole agents with P-450-dependent enzymes involved either in ergosterol biosynthesis (in fungi) or in hormones biosynthesis (in humans).

Comment

Cytochromes P-450 are a superfamily of enzymes which catalyzes the oxidation of a large number of biological substrates (Ortiz de Montellano, 1986). In particular, cytochrome P-450-dependent lanosterol 14α-demethylase (P-450$_{DM}$) catalyzes in fungi the first step of the lanosterol conversion to ergosterol, by removal the 14α-methyl group from lanosterol (Vanden Bossche, 1988). Azole antifungals are known to inhibit fungal P-450$_{DM}$ leading to accumulation of 14α-methylated sterols which cause inhibition of fungi growth by changing the membrane permeability (Adams & Metcalf, 1990; Yeagle *et al.*, 1977, and references cited therein). In fact, the antimycotic derivatives bind to P-450$_{DM}$ by coordination of the ring N atom to the sixth coordination position of the Fe atom of the enzymatic protoporphyrin system (Hitchcock *et al.*, 1990).

Starting from 1960, a number of potent antifungal azole derivatives, such as bifonazole, miconazole, econazole, ketoconazole and fluconazole (Fromtling, 1986; D'Arcy & Scott, 1987; Kerridge, 1988; Koltin, 1990) were synthesized and are now used in clinical practice against topical or systemic fungal infections. More recent biological studies showed some P-450-dependent enzymes to be inhibited by azole derivatives, thus opening new frontiers in the research on azole drugs. Aromatase (Banting *et al.*, 1989) and C17,20-lyase (Njar & Brodie, 1999) are crucial targets for inhibition of mammalian or prostatic cancer, respectively. Unfortunately, aromatase, C17,20-lyase and 14α-demethylase stuctures have not been completely elucidated to date and theoretical approaches have been made in recent years to better understand the interaction of azole derivatives with P-450-dependent enzymes (Tafi *et al.*, 1996; Ji *et al.*, 2000). Our ten-year interest in antifungal drugs led us to discover several classes of azole derivatives endowed with interesting antimicotic activities (Artico *et al.*, 1993, 1995; Di Santo *et al.*, 1993, 1994, 1997; Massa, Di Santo, Retico *et al.*, 1992; Massa, Di Santo, Artico, Costi, Di Filippo *et al.*, 1992; Massa, Di Santo, Costi, Simonetti *et al.*, 1993; Massa, Di Santo, Costi, Mai *et al.*, 1993; Tafi *et al.*, 1996). In particular, we reported about the high anti-Candida potency of a new class of imidazole derivatives, namely 3-aryl-4-[α-(1*H*-imidazol-1-yl)-arylmethyl]pyrroles, which were highly effective, either *in*

vitro or *in vivo*, against *Candida albicans* at doses lower than that of bifonazole used as reference drug (Artico *et al.*, 1995). One of the most potent compounds was 1-{[4-(4-chlorophenyl)-1*H*-pyrrol-3-yl](2,4-dichlorophenyl)methyl}-1*H*-imidazole (RDS 416), (I), which showed comparable topical efficacy to that of bifonazole in *in vivo* inhibition of cutaneous candidiasis (*C. albicans* A170) in white male rabbits. The aim of this work is to elucidate the spatial disposition of RDS 416, for a better understanding of its interaction with 14α-lanosterol demethylase.



(I)

The crystal structure of (I) consists of one molecule in the asymmetric unit. The geometry of the four rings is in good agreement with the accepted values. The three angles around C5 involving non-H substitutents are wider than the theoretical tetrahedral value of 109.5°, but the three angles involving the H atom are smaller; this tetrahedral deformation is explained in terms of the bulkiness of the non-H substituents together with the small volume of the H atom. The dihedral angle between the pyrrol ring plane and its attached Cl–phenyl group [52.9 (1)°] shows absence of mesomeric effect. The only short intermolecular distance observed is N1$\cdots$C7^{i} of 2.940 (3) Å [symmetry code: (i) $1-x, \frac{1}{2}+y, \frac{3}{2}-z$].

Experimental

The title compound was synthesized previously by Artico *et al.* (1995).

Crystal data

$C_{20}H_{14}Cl_3N_3$
M_r = 402.71
Monoclinic, $P2_1/c$
a = 6.887 (1) Å
b = 18.847 (3) Å
c = 14.947 (3) Å
β = 105.08 (1)°
V = 1873.2 (5) Å^3
Z = 4
D_x = 1.428 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 38 reflections
θ = 4.3–18.3°
μ = 0.50 mm^{-1}
T = 293 K
Prism, brown
0.40 × 0.20 × 0.15 mm

Data collection

Siemens $P3$ four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: empirical *via* ψ scan (North *et al.*, 1968)
T_{min} = 0.82, T_{max} = 0.93
17 474 measured reflections
15 414 independent reflections
2474 reflections with $F > 6\sigma(F)$
R_{int} = 0.028
θ_{max} = 45.1°
$h = 0 \rightarrow 13$
$k = 0 \rightarrow 37$
$l = -29 \rightarrow 28$
3 standard reflections
every 97 reflections
intensity decay: none

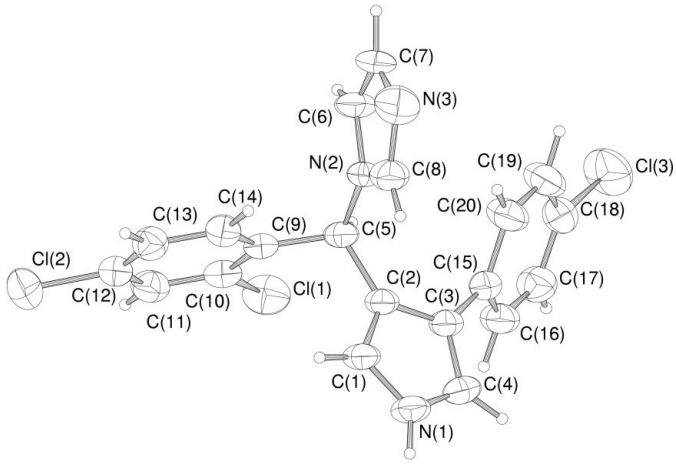


Figure 1
The molecular structure with 50% probability ellipsoids.

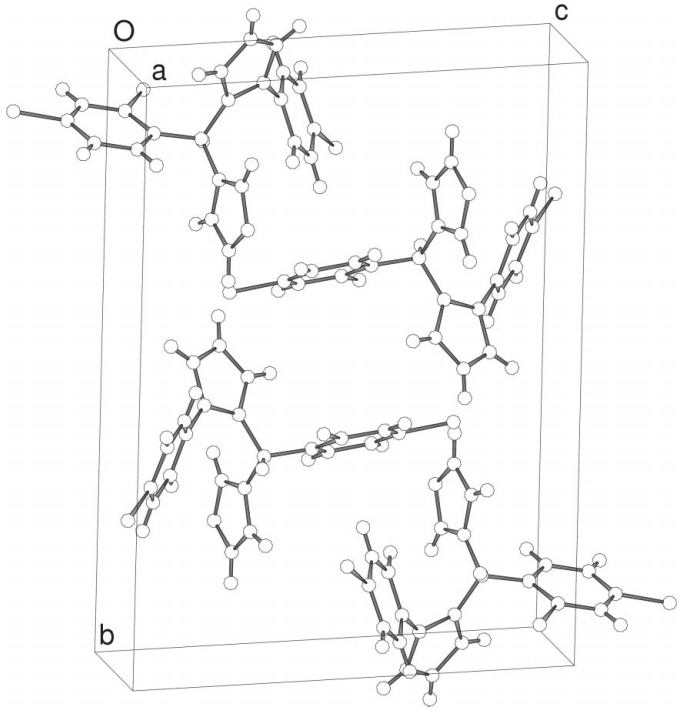


Figure 2
The unit-cell contents viewed approximately along the *a* axis.

Refinement

Refinement on F
R = 0.041
wR = 0.056
S = 0.90
2474 reflections
235 parameters
H-atom parameters constrained
$w = 1/(0.0009 + 0.0108F + 0.0032F^2)$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.42 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}

The H atoms were placed in calculated positions (N—H and C—H = 0.96 Å).

Data collection: *R*3*m*/*V* (Siemens, 1989); cell refinement: *R*3*m*/*V*; data reduction: *XDISK* (Siemens, 1989); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1999); program(s) used to refine

structure: *CAOS* (Camalli & Spagna, 1994); molecular graphics: *CAOS*; software used to prepare material for publication: *CAOS*.

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