Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

7-Cyclopentyl-5-(4-phenoxyphenyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine-4-ylamine, an lck tyrosine kinase inhibitor

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Received 10 May 2001
Accepted 11 May 2001
Online 17 May 2001

The molecular and crystal structures of the potent and selective lck tyrosine kinase inhibitor, $C_{23}H_{22}N_4O$, have been determined by single-crystal X-ray diffraction. The pyrrolopyrimidine and phenyl rings are planar while the cyclopentyl ring adopts a conformation between envelope and half-chair. The overall conformation is defined by the spatial arrangement of the ring moieties.

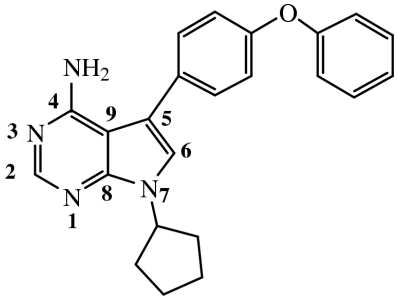
Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.009 Å
R factor = 0.061
wR factor = 0.136
Data-to-parameter ratio = 15.5

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

Comment

Lck (lymphoid cell protein-tyrosine kinase), a Src family protein-tyrosine kinase (Hanks *et al.*, 1988; Thomas & Brugge, 1997) has an important role in the immune response and is mainly expressed in T lymphocytes. As lck is only one of the members of the Src family of tyrosine-specific protein-kinases, and all members share considerable amino acid sequence homology, a challenge in the discovery of a lck inhibitor lies in achieving selectivity within this family. A selective inhibitor of lck should specifically inhibit T-cell activation and have use in the treatment of autoimmune and inflammatory diseases, and also in organ transplantation.



(I)

It has recently been found that a series of pyrrolo[2,3-*d*]-pyrimidines exhibit good selectivity for lck over other Src kinases (Arnold *et al.*, 2000; Burchat *et al.*, 2000). Furthermore, the title compound, (I), was shown to be a potent inhibitor of IL-2 production in Jurkat cells and in mice.

A search of the Cambridge Structural Database (Version 5.20, October 2000; Allen & Kennard, 1993) revealed that no crystal structures of the derivatives similar to the studied compound have been solved. The molecular structure of the title compound is shown in Fig. 1. Its overall conformation is defined by the conformation and spatial arrangement of the

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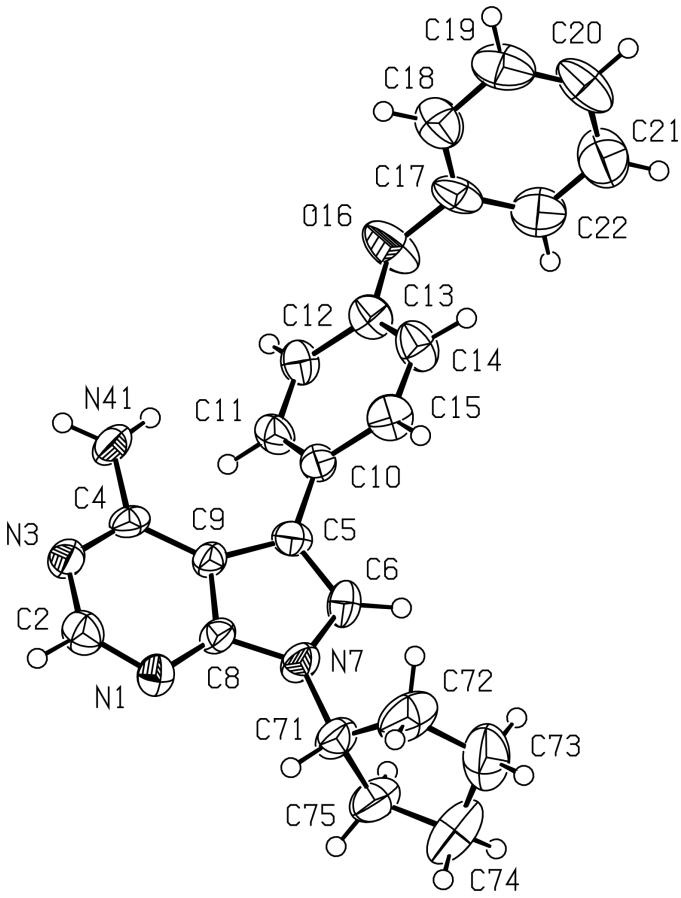

Figure 1
The molecular structure of the title compound with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level.

ring moieties (Table 1). The pyrrolopyrimidine system is planar with the maximum displacement from the best least-squares plane of 0.049 (5) Å for atom C9. The amino group at N41, as well as atoms C10 and C71, lie slightly out of the plane of the pyrrolopyrimidine system. The phenyl-ring plane (atoms C10–C15) makes an angle of 50.7 (2)° with the pyrrolopyrimidine-ring plane. The second phenyl ring (atoms C17–C22) is almost perpendicular to the first (atoms C10–C15); the angle between phenyl-ring planes equals 80.2 (3)°. Very similar asymmetry parameters (Duax *et al.*, 1974; Griffin *et al.*, 1984) for the local pseudo-mirror plane ΔC_s(C74) = 8.7 (7)° and local pseudo-twofold axis ΔC_2(C71) = 8.1 (7)° for the cyclopentyl ring support the fact that the cyclopentyl ring adopts a conformation between envelope ${}^{C74}E$ and half-chair ${}^{C74}H_{C73}$; the degree of cyclopentyl ring puckering is best described by Cremer & Pople (1975) total puckering amplitude Q = 0.363 (7) Å. The plane through the cyclopentyl ring is almost perpendicular to the pyrrolopyrimidine ring plane; the angle between the two planes is 84.0 (2)°.

In the title compound, there is only one atom which can act as hydrogen-bond donor, *i.e.* the amino N41 atom. It donates one of its H atoms to the nitrogen N1 of the pyrimidine ring which acts as acceptor in the intermolecular hydrogen bond (N41—H41A···N1, Table 2). In that way, in the crystal structure of the title compound, chains along the crystallographic axis b are formed (Fig. 2). The other hydrogen H41B of the amino group at N41 does not participate in the hydrogen-bonding scheme; it is involved in the short contact with H11 at N11. Intra- and intermolecular C—H···O/N hydrogen bonds, C71—H71···N1 and C6—H6···O16, should also be noted (Table 2).

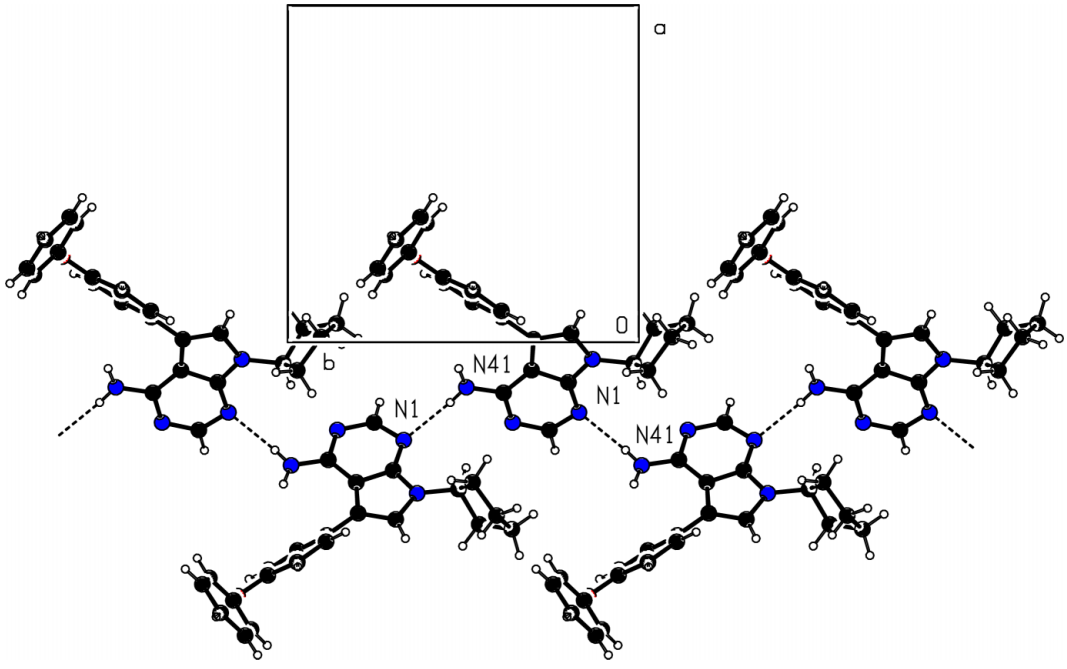

Figure 2
Hydrogen bonds in the crystal packing of the title compound forming chains parallel to the crystallographic b axis.

Experimental

The title compound was prepared according to Arnold *et al.* (2000). Crystals suitable for X-ray diffraction were obtained from an ethyl acetate–*n*-hexane mixture by overnight cooling in a refrigerator.

Crystal data

$C_{23}H_{22}N_4O$
M_r = 370.45
Orthorhombic, *Pbca*
a = 11.914 (2) Å
b = 12.399 (5) Å
c = 26.133 (5) Å
V = 3860.4 (18) Å^3
Z = 8
D_x = 1.275 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 3.1–10.6°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colourless
0.20 × 0.16 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
3910 measured reflections
3910 independent reflections
819 reflections with $I > 2\sigma(I)$
θ_{max} = 26.3°
$h = 0 \rightarrow 14$
$k = -15 \rightarrow 0$
$l = 0 \rightarrow 32$
3 standard reflections
frequency: 120 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.136
S = 0.84
3910 reflections
253 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0182P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected torsion angles (°).

N1—C8—C9—C5	−175.5 (5)	C14—C13—O16—C17	8.3 (9)
N7—C8—C9—C4	176.0 (5)	C13—O16—C17—C18	98.4 (7)
C6—C5—C10—C11	−130.1 (6)	C13—O16—C17—C22	−87.4 (8)
C6—C5—C10—C15	49.4 (8)	C6—N7—C71—C72	−57.3 (7)
C9—C5—C10—C11	49.3 (9)	C6—N7—C71—C75	62.2 (7)
C9—C5—C10—C15	−131.2 (6)	C8—N7—C71—C72	118.3 (6)
C12—C13—O16—C17	−175.2 (5)	C8—N7—C71—C75	−122.1 (6)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N41—H41A···N1^{i}	0.86	2.13	2.960 (6)	162
C6—H6···O16^{ii}	0.93	2.47	3.380 (7)	165
C71—H71···N1	0.98	2.60	3.014 (7)	106

Symmetry codes: (i) $-\frac{1}{2}-x, y-\frac{1}{2}, z$; (ii) $\frac{1}{2}-x, \frac{1}{2}+y, z$.

All H atoms were generated according to stereochemistry and were refined using the riding model in *SHELXL*97 (Sheldrick, 1997).

Data collection: *EXPRESS* in *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *SET*4 and *CELDIM* in *CAD*-4 *Software*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1998); software used to prepare material for publication: *PLATON*.

The authors are thankful to the Laboratory for Chemical and Biological Crystallography of the Rudjer Bošković Institute, Zagreb, Croatia (Dr Biserka Kojić–Prodić, Head), for data collection and use of data processing software.

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