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Pifithrin-β

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Key indicators

Single-crystal X-ray study
T = 160 K
Mean σ(C–C) = 0.002 Å
Disorder in main residue
R factor = 0.038
wR factor = 0.103
Data-to-parameter ratio = 16.8

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

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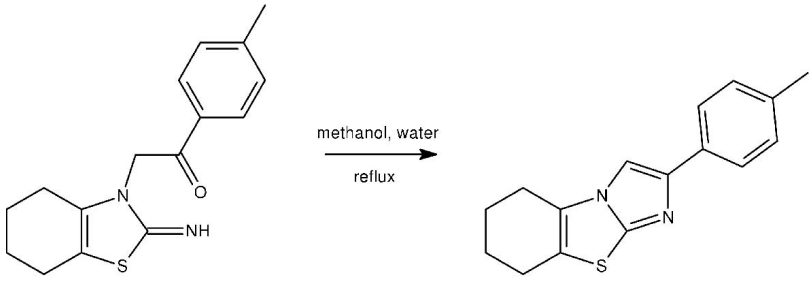
The title compound, 2-*p*-tolyl-5,6,7,8-tetrahydrobenzo[*d*]-imidazo[2,1-*b*]thiazole, $C_{16}H_{16}N_2S$, is a condensation product of pifithrin-α, which has been previously reported as an inhibitor of the tumour suppressor protein p53. The molecule contains a planar fused pair of heterocyclic five-membered rings and the attached *p*-tolyl substituent is also essentially coplanar.

Comment

The compound pifithrin-α [2-(2-imino-4,5,6,7-tetrahydrobenzothiazol-3-yl)-1-(4-methylphenyl)ethanone, (1)] was previously reported to inhibit, *in vitro*, a number of processes involving the tumour suppressor protein p53; it was thus of interest in the development of cancer therapies (Komarov *et al.*, 1999). During a further evaluation of the effectiveness of pifithrin-α, a crystalline sample was obtained and its structure investigated by X-ray diffraction. However, the material was found to be a condensation product of pifithrin-α, from which water had been eliminated in a ring closure. The product, referred to as pifithrin-β, (2), is more stable than pifithrin-α in tissue culture medium. The revelation of this transformation through crystallographic identification of the condensation product has led to an expansion of the original evaluation of pifithrin-α to include also pifithrin-β, and the recognition that some of the inhibitory effects previously ascribed to pifithrin-α are probably due instead to pifithrin-β or a combination of the two compounds (Walton *et al.*, 2005).



(1) (2)

The molecule of pifithrin-β (Fig. 1) contains three fused rings with a *p*-tolyl substituent. The cyclohexene ring (or tetrahydrobenzo group) is disordered over two conformations, in which the two saturated C atoms furthest from the double bond lie one on each side of the mean plane of the other atoms of the ring [by 0.377 (4) and 0.375 (4) Å for the major component]; the two disorder components have opposite senses of twist for this CH_2CH_2 segment (see the torsion angles in Table 1). The fused thiazole and imidazole rings are individually planar (r.m.s. deviations < 0.003 Å) and form a

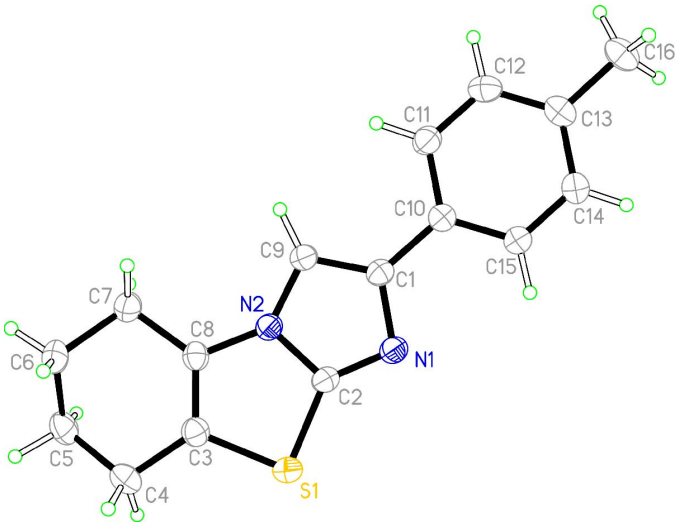


Figure 1
The molecular structure of (2) with atom labels and 50% probability ellipsoids for non-H atoms. The minor disorder component has been omitted.

single planar unit [r.m.s. deviation 0.009 Å; dihedral angle between the two five-membered rings = 1.32 (5)°]. Such imidazo[2,1-*b*]thiazole fused ring systems have been found in ten other crystal structures in the Cambridge Structural Database (Version 5.26 plus one update, February 2005; Allen, 2002), and they are all planar.

The benzene ring of the *p*-tolyl substituent makes a dihedral angle of 2.32 (5)° with the imidazole ring to which it is attached. The whole molecule, excluding H atoms and the disordered CH_2CH_2 linkage, is thus essentially planar, with an r.m.s. deviation of 0.039 Å. There are no notable intermolecular interactions in the crystal structure. The molecules lie in almost planar sheets parallel to (001) (Fig. 2).

Experimental

The compound was prepared by a condensation reaction of pifithrin-α, initially unintentionally during a study of anti-tumour agents, and subsequently by refluxing in aqueous methanol (Walton *et al.*, 2005). It was recrystallized from methanol.

Crystal data

$C_{16}H_{16}N_2S$
M_r = 268.37
Monoclinic, $P2_1/c$
a = 7.1729 (4) Å
b = 13.5386 (8) Å
c = 14.3530 (8) Å
β = 103.917 (2)°
V = 1352.92 (13) Å^3
Z = 4
D_x = 1.318 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 9390 reflections
θ = 2.1–28.5°
μ = 0.23 mm^{-1}
T = 160 (2) K
Block, colourless
0.44 × 0.30 × 0.26 mm

Data collection

Bruker SMART 1K CCD diffractometer
Thin-slice ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.91, T_{max} = 0.94
11454 measured reflections
3222 independent reflections
2871 reflections with $I > 2\sigma(I)$
R_{int} = 0.022
θ_{max} = 28.5°
$h = -9 \rightarrow 9$
$k = -17 \rightarrow 17$
$l = -18 \rightarrow 18$

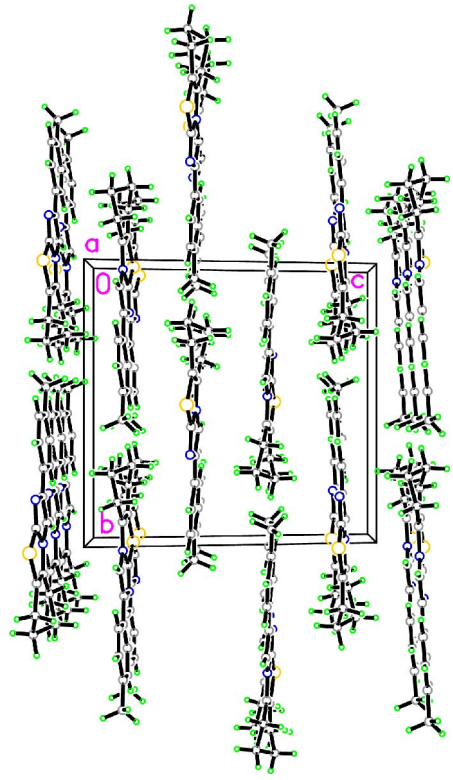


Figure 2
The crystal packing, viewed along the *a* axis, showing almost planar sheets of molecules parallel to (001).

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.103
S = 1.05
3222 reflections
192 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0542P)^2 + 0.5147P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C1	1.3949 (17)	S1—C2	1.7391 (13)
N1—C2	1.3147 (17)	S1—C3	1.7650 (14)
N2—C2	1.3666 (16)	C1—C9	1.3760 (18)
N2—C8	1.3991 (16)	C3—C8	1.3447 (19)
N2—C9	1.3770 (17)		
C1—N1—C2	103.49 (11)	N1—C2—S1	136.19 (10)
C2—N2—C8	115.28 (11)	N2—C2—S1	110.23 (10)
C2—N2—C9	106.49 (11)	S1—C3—C4	123.59 (10)
C8—N2—C9	138.21 (11)	S1—C3—C8	112.18 (10)
C2—S1—C3	90.36 (6)	C4—C3—C8	124.22 (13)
N1—C1—C9	111.16 (11)	N2—C8—C3	111.96 (11)
N1—C1—C10	121.52 (11)	N2—C8—C7	122.51 (11)
C9—C1—C10	127.32 (12)	C3—C8—C7	125.52 (12)
N1—C2—N2	113.56 (11)	N2—C9—C1	105.31 (11)
C3—C4—C5—C6	−45.8 (3)	C5*X*—C6*X*—C7—C8	41.1 (9)
C4—C5—C6—C7	64.3 (3)	C5—C6—C7—C8	−45.5 (3)
C3—C4—C5*X*—C6*X*	47.9 (8)	N1—C1—C10—C15	−1.16 (19)
C4—C5*X*—C6*X*—C7	−61.1 (10)	C9—C1—C10—C11	−1.5 (2)

H atoms were positioned geometrically (C—H = 0.95–0.99 Å) and refined with a riding model (including free rotation about the C—C bond for the methyl group), and with U_{iso} values constrained to be 1.2

(1.5 for methyl groups) times U_{eq} of the carrier atom. Twofold disorder was resolved and refined for the central CH_2CH_2 linkage of the cyclohexene ring, with occupancy factors 0.766 (6):0.234 (6).

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2001); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* and local programs.

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