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ORIGINAL PAPER

Crystal Structure of Ethyl (2Z, 5R)-2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5H-[1,3] Thiazolo [3,2-a] Pyrimidine-6-carboxylate

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Abstract The title compound, $C_{23}H_{20}N_2O_3S$, (I), crystallizes in the orthorhombic space group, *Pna* 2_1, with cell parameters $a = 18.7975(6)$, $b = 12.5173(4)$, $c = 8.4804(3)$ Å, $Z = 4$. The molecular structure consists of a central pyrimidine ring which is significantly puckered to assume a screw-boat conformation fused to a thiazole ring with benzyl, carboxylate, methyl, phenyl and oxy groups bonded around this fused-ring moiety. The dihedral angle between the mean planes of the thiazole, benzyl and phenyl groups and the mean plane of the pyrimidine ring is 6.1(4)°, 83.8(7)° and 6.8(4)°, respectively. The dihedral angle between the mean planes of the benzyl and phenyl rings is 88.3(5)° while between the mean planes of the phenyl and thiazole groups measures 12.6(6)°. In the absence of expected hydrogen bonding interactions, the crystal packing is influenced by a collective action of strong intramolecular C–H···S hydrogen bond interactions, close C–H···O intramolecular contacts and O–Cg π-ring interactions. A DFT molecular orbital calculation gives support to these observations.

Keywords Thiazole · Pyrimidine · Ring puckering · Benzene · DFT calculations

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Introduction

The remarkable biological activities of fused pyrimidines which give rise to antiviral, anticancer, anti-inflammatory and antihypertensive actions [1, 2], continue to bring this class of heterocyclic compounds to the forefront of interest and study. The title thiazolo[3,2-a]pyrimidine compound, (I), exhibits both anticancer and anti-inflammatory activity. In support of these observations, an anticancer drug screen has been carried out using a diverse panel of cultured human tumor cell lines [3]. Anti-inflammatory activity has been determined by examination of inhibition by the Carageena-induced rat paw edema method [4]. In view of these observations and in the continuation of our recent studies on thiazolo[3,2-a]pyrimidine compounds [5–8], we have been investigating the influence of different substituent's on the structural parameters of these compounds as well as crystal packing when relating these properties to the biological effects of these compounds. We report herethe crystal structure of the title compound, $C_{23}H_{20}N_2O_3S$, (I).

Synthesis of Ethyl (2Z, 5R)-2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5H-[1,3] thiazolo [3,2-a] pyrimidine-6-carboxylate

A mixture of ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01 mol), chloroacetic acid (0.01 mol), fused sodium acetate (6 g) in glacial acetic acid (25 mL), acetic anhydride (10 mL) and benzaldehyde (0.01 mol) was refluxed for 3 h. The reaction mixture was cooled and poured into cold water. The resulting solid was collected and crystallized from methanol to obtain the final product (86% yield, mp 443 K). The compound was recrystallized by slow evaporation of a

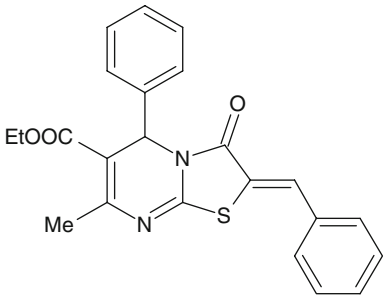

Fig. 1 Chemical scheme for of Ethyl (2Z, 5R)-2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5H-[1,3] thiazolo [3,2-a] pyrimidine-6-carboxylate, (I)

benzene-ethanol solution (8:2) yielding yellow plate-like single crystals suitable for X-ray diffraction. A scheme for the molecular structure of (I) is shown in Fig. 1.

Structure Determination and Refinement

X-ray data were collected with a Bruker AXS Kappa APEXII CCD diffractometer using APEXII software and graphite-monochromated Mo-Kα ($\lambda = 0.71073$ Å) radiation at 293(2) K. The structure was solved by direct methods using SIR92 [9]. All of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using SHELXL97 [10]. All H atoms were allowed to ride on the parent atom in the model during refinement. An absorption correction was performed using SADABS [11] and all calculations were performed using PLATON [12]. Crystal and experimental data for (I) are listed in Table 1.

Results and Discussion

The molecular structure of $C_{23}H_{20}N_2O_3S$, (I), consists of a central pyrimidine ring which is significantly puckered to assume a screw-boat conformation fused to a thiazole ring with benzyl, carboxylate, methyl, phenyl and oxy groups bonded at the C2, C3, C4, C6 and C5 positions, respectively, around this fused-ring moiety. The dihedral angle between the mean planes of the thiazole, phenyl and benzyl groups and the mean plane of the pyrimidine ring is 6.1(4)°, 6.8(4)°, and 83.8(7)°, respectively. The dihedral angle between the mean planes of the benzyl and phenyl rings is 88.3(5)° while between the mean planes of the phenyl and thiazole groups measures 12.6(6)°. The ring puckering parameters [13] for the pyrimidine ring are $\theta = 68.1(1)°$ and $\phi = 163.3(6)°$; the idealized values are $\theta = 67.5°$ and $\phi = (60k + 30)^o$, where k is an integer. All the bond lengths and angles in the pyrimidine ring have normal values except C(1)–N(1) [1.276(3) Å] and N(1)–C(4) [1.398(4) Å] which are similar to earlier reported structures. The corresponding average values in the Cambridge Structural Data Base (Version 5.30 and November 2008 updates) [14] for these bonds differ slightly, viz 1.31 and 1.39 Å, respectively, from that seen here. The fused thiazole ring has similar geometry as observed in other fused thiazolopyrimidine compounds [1–4, 15, 16]. The short C(9)–C(10) distance [1.404(5) Å] may be due to a collective interaction of C10 with the nearby ethoxy group, an intramolecular close contact interaction with the nearby carbonyl oxygen atom (C9–H9B···O3; see Table 2), and/or an O3–Cg1 π-ring interaction (C8–O3···Cg1; $x, y, -1 + z$; C8···Cg1 = 3.912(7) Å; O3–C8···Cg1 = 111°; O3···Cg1 = 4.48(1) Å) that may influence the bond strength of the C9–C10. The ethoxy group lies in a *trans* configuration about the O(2)–C(9) bond (torsion angles C(3)–C(8)–O(2)–C(9) = 0.8(4)° and C(8)–O(2)–C(9)–C(10) = 115.1(4)°, respectively).

Table 1 Crystal and experimental data for (I)

Formula	$C_{23}H_{20}N_2O_3S$
Formula weight	404.47
Crystal color, habit	Yellow, plate
Crystal size (mm)	0.45 × 0.3 × 0.2
Crystal system	Orthorhombic
Space group, Z	*Pna* 2_1, 4
Temperature (K)	293(2)
a (Å)	18.7975(6)
b (Å)	12.5173(4)
c (Å)	8.4804(3)
V (Å^3)	1,995.39(11)
D_{calc} (g cm^{-3})	1.346
No. of reflections [I > 2σ(I)]	2,923
$2\theta_{\mu\alpha\xi}$ (°) with Mo K_a	49.98
R, R_w [I > 2σ(I)]	0.0347/0.0864
$(\Delta\sigma)_{max}$	0.002
$(\Delta\rho)_{max}$ (e Å^{-3})	0.160
$(\Delta\rho)_{min}$ (e Å^{-3})	−0.165
Measurement	*APEX2*, [11]
Program system	*APEX2/SAINT*
Structure determination	*SIR92*
Refinement	Full-matrix least-squares on F^2 (*SHELXL97*)

Table 2 Intramolecular hydrogen bond interactions for I (Å and °)

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
C(9)–H(9B)···O(3)	0.97	2.25	2.680(3)	106
C(17)–H(17)···O(1)	0.93	2.57	2.907(6)	106
C(19)–H(19)···S(1)	0.93	2.47	3.163(3)	132

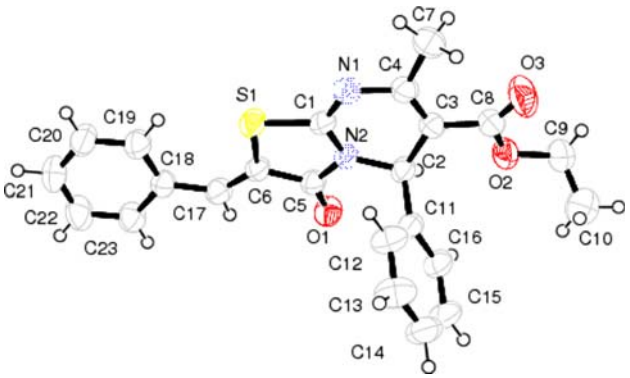

Fig. 2 *ORTEP* drawing of $C_{23}H_{20}N_2O_3S$, (I), showing the atom numbering scheme and 50% probability displacement ellipsoids

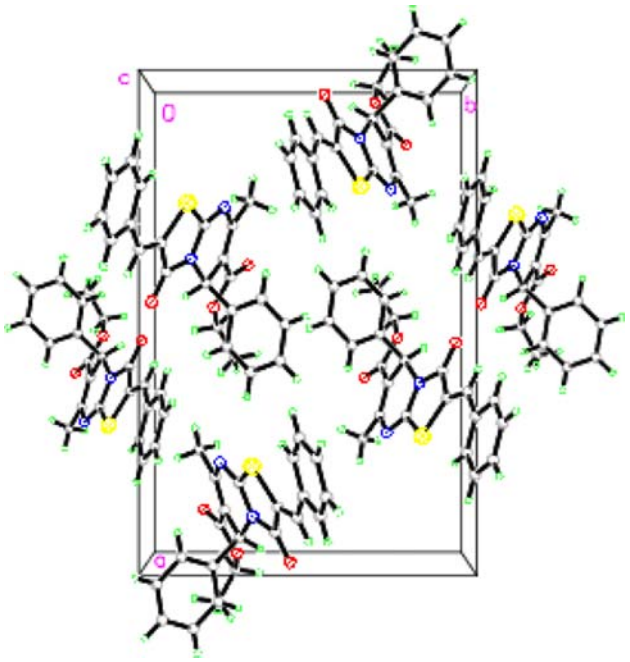

Fig. 3 The molecular packing for (I) viewed down the *c* axis

The molecules pack in a stacking like mode, arranged in an alternating pattern diagonally across the *bc* plane of the unit cell (Figs. 2, 3, 4). Strong intramolecular C–H···S hydrogen bond interactions (Table 2) exist with C19–H19···S1 forming a pseudo-six-membered ring of S(6) graph-set motif [17]. Weak C–H···O intramolecular contacts with C9–H19B···O3 and C17–H17···O1 forming a second pseudo-5-membered ring of O(5) graph-set motif [17] also influence crystal packing. [12]. There are no hydrogen bond, C–H···π or π–π stacking interactions present in the structure of (I), which is in contrast to the presence of such interactions in similar structures reported earlier [1–4]. It is noted that these structures all crystallize in the monoclinic or triclinic space group while the title

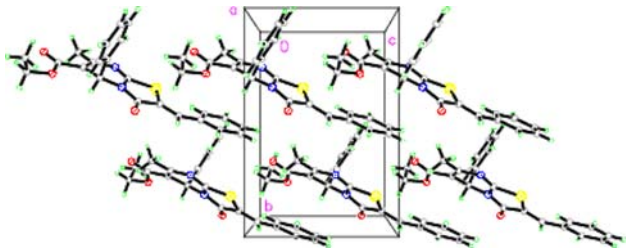

Fig. 4 The molecular packing for (I) viewed down the *a* axis

compound here crystallizes in the orthorhombic space group.

A Density Functional Theory (DFT) geometry optimization molecular orbital calculation (*WebMO Pro* [18]) with the GAUSSIAN-03 program package [19] employing the B3LYP (Becke three parameter Lee-Yang-Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke [20, 21] with the gradient-correlation functional of Lee, Yang and Parr [22] and the 3-21G basis set [23] was performed on the title molecule, (I). Starting geometries were taken from X-ray refinement data. The N–C, C–C and C–O bond distances involving atoms involved in the intramolecular hydrogen bond interactions and close intermolecular contacts in the DFT calculated model are all slightly longer that those determined experimentally (Table 3). The largest discrepancies of 0.025(6), 0.125(5), 0.054(7), 0.033(6), and 0.051(7) Å are for N(1)–C(4), C(9)–C(10), C(8)–O(2), C(9)–O(2), and C(8)–O(3), respectively, with the C(9)–C(10) bond difference being the largest. The differences

Table 3 Selected geometric parameters for (I) and DFT calculation (Å, °)

	X-ray	DFT
N(1)–C(1)	1.276(3)	1.280
N(1)–C(4)	1.398(4)	1.424
N(2)–C(1)	1.364(3)	1.374
C(9)–C(10)	1.404(5)	1.530
C(8)–O(2)	1.332(3)	1.387
C(9)–O(2)	1.451(4)	1.485
C(8)–O(3)	1.184(3)	1.236
C(1)–N(2)–C(5)	116.65(19)	118.42
C(5)–N(2)–C(2)	123.33(17)	121.72
N(2)–C(2)–C(3)	108.29(17)	108.48
N(1)–C(2)–N(2)	126.9(2)	126.55
C(9)–O(2)–C(8)–C(3)	179.7(3)	178.46
C(8)–O(2)–C(9)–C(1)0	115.0(4)	78.57
C(4)–N(1)–C(1)–S(1)	−173.50(17)	−171.23
S(1)–C(6)–C(17)–C(18)	2.3(4)	−0.13
C(11)–C(2)–C(3)–C4	−104.4(3)	−100.19
C(4)–C(3)–C(8)–O(3)	11.4(4)	3.01

between the calculated and observed geometry could be related to the crystal packing in the molecules. However, the observation of a collection of strong C–H···S intramolecular hydrogen bond interactions, close C–H···O intramolecular contacts and weak O–Cg π-ring interactions provide evidence of a collective effect of all of these interactions on crystal packing in the unit cell.

After the calculation, the dihedral angle between the mean planes of the thiazole, phenyl and benzyl groups and the mean plane of the pyrimidine ring became 1.34°, 11.34°, 84.79°, respectively. This represents a change of 4.8(0)°, 4.5(0)° and 0.9(2)°, large for the thiazole and phenyl groups and small for the benzyl group, each with respect to the pyrimidine group. The angle between the mean planes of the thiazole ring and phenyl ring changed from 12.6(6)° in the crystal to 1.3(4)° after the calculation, a difference of 11.3(2)°. The small change in the C3–C2–C11–C16 torsion angle between the pyrimidine and benzyl rings, from −115.1(2)° in the crystal to −154.3(1)° with the DFT calculation, supports the absence of any significant crystalline intermolecular interactions with the benzyl ring. The changes in the angle between the crystalline and DFT calculational mean planes of the thiazole and phenyl rings with that of the pyrimidine ring, as seen above, supports the observation that strong C–H···S intramolecular hydrogen bond interactions, close C–H···O intramolecular contacts and weak O–Cg π-ring interactions do, therefore, collectively have a significant influence on the crystalline environment of the title compound, $C_{23}H_{20}N_2O_3S$, (I) and more specifically in this region of the molecule.

Supporting Information Available

X-ray crystallographic files, in Cif format, for the structure determinations of (I) (CCDC 714517) has been deposited with the Cambridge Crystallographic Date Center, CCDC: 26091. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax: +44-1223-336033; email: deposit@ccdc.cam.uk or at http://www.ccdc.cam.ac.uk.

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