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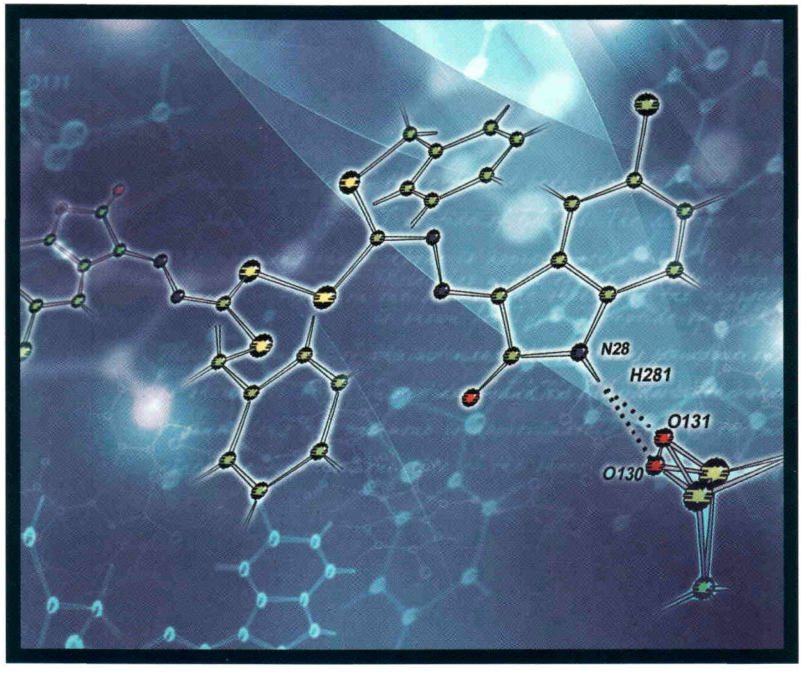

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A Crystallographic Study of Bis [S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonthioate] Disulfide Solvated with Dimethylsulfoxide

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ABSTRACT

The crystal structure of the title compound has been determined. The compound crystallized in the triclinic space group P -1, Z = 2, V = 1839.42(18) Å^3 and unit cell parameters a = 11.0460(6) Å, b = 13.3180(7) Å, c = 13.7321(8) Å, a = 80.659(3)°, b = 69.800(3)° and g = 77.007(2)° with one disordered dimethylsulfoxide solvent molecule with the sulfur and oxygen atoms are distributed over two sites; S101/S102 [site occupancy factors: 0.6035/0.3965] and O130/O131 [site occupancy factor 0.3965/0.6035]. The C22-S21 and C19-S20 bond distances of 1.779(7) Å and 1.788(8) Å indicate that both of the molecules are connected by the disulfide bond [S20-S21 2.055(2) Å] in its thiol form. The crystal structure reveals that both of the 5-bromoisatin moieties are *trans* with respect to the [S21-S20 and C19-N18] and [S20-S21 and C22-N23] bonds whereas the benzyl group from the dithiocarbazate are in the *cis* configuration with respect to [S21-S20 and C19-S44] and [S20-S21 and C22-S36] bonds. The crystal structure is further stabilized by intermolecular hydrogen bonds of N9-H35···O16 formed between the two molecules and N28-H281···O130, N28-H281···O131 and C41-H411···O131 with the solvent molecule.

Keywords: *Dithiocarbazate, 5-bromoisatin, Dimethylsulfoxide, Disordered, Disulfide*

INTRODUCTION

Isatin is the active chemical with a broad spectrum of biological properties [1-4]. Extensive research has been carried out on Schiff bases and Mannich bases of isatin as they were reported to possess antibacterial [5-7], antifungal [8-10], antiviral [11-13], anti-HIV [14-16], antiprotozoal [17, 18], and antihelminthic [19, 20] activities. Several of halogenated containing compounds have drawn much attention due to their biological activities. Many of fluorine containing aromatic compounds have been used as new medicines or as precursors for the synthesis of biologically active compounds [21]. Sunitinib, a 5-fluoro-3-substituted-2-oxoindole is a small-molecule inhibitor of multiple receptor tyrosine kinase (RTK) involved in cancer. This compound was approved by the United States Food and Drug Administration (US FDA) for the treatment of Gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma in January 2006 and European Union approval in January 2007 [22]. Another compound which has a similar chemical structure to Sunitinib known as Toceranib Phosphate was approved by USFDA for the treatment of tumors with or without regional node involvement [23]. Tyrindoleninone (6-bromo-2-methylthio-3*H*-indol-3-one) a brominated marine compound was found to have a stronger anti-cancer activity against a human lymphoma cell line in comparison with 6-bromoisatin [24, 25]. Histone deacetylase (HDAC) enzymes affect many basic cellular processes related to differentiation and proliferation. Targeting this enzymes with different inhibitors has been recognized as a new and successful strategy for the development of anticancer agents. It has been reported that normal cells are relatively resistant to the treatment with HDAC inhibitors [26], whereas tumor cells are more sensitive and undergo growth arrest which will lead to cell death. A compound containing a 5-fluoro-3-substituted-2-oxoindole framework was found to inhibit Class 1 enzymes (97 %) and HDAC4/5 (85 %) with significantly less inhibition of HDAC7 (35%) [27].

Recently, we reported on the synthesis, characterization and cytotoxic activity of S-benzyldithiocarbazate Schiff bases derived from 5-fluoroisatin, 5-chloroisatin, 5-bromoisatin and their crystal structures [28]. The Schiff bases were found to be selective active against MCF-7 cell lines whereupon Schiff bases of SB5BrISA and SB5FISA were found to be the most active compounds with the IC_{50} values of 2.6 μg/ml and 3.2 μg/ml respectively

while Schiff base of SB5ClISA was found to be weakly active with the IC_{50} value of 14.0 μg/ml. It is anticipated that compound with halogen substituent groups in the isatin ring would exhibit strong activity and would be promising candidates for the development of anticancer agents and HDAC inhibitors. Therefore, as part of our ongoing study on ligands derived from S-benzyldithiocarbazate with isatin derivatives, we are reporting here the crystallographic study of bis[S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonthioate] disulfide solvated with dimethylsulfolxide.

EXPERIMENTAL

Synthesis

S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate was prepared as reported previously [28]. S-benzyldithiocarbazate, SBDTC (1.98 g, 0.01 mole) was dissolved in hot ethanol (50 ml) and to this solution was added an equimolar amount of 5-bromoisatin (2.26 g, 0.01 mole). The mixture was heated while being stirred for 15 minutes and later allowed to stand for 20 minutes which dark orange product formed, which was filtered off, wash with ethanol and recrystallized from ethanol. Light orange crystals of bis[S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonthioate] disulfide were obtained after crystallization in dimethylsulfoxide. It was expected that two molecules of S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate was connected together through the disulfide bond in its thiol forms forming the title compound.

X-Ray Crystallography

The crystal structure data collection were measured using an Enraf-Nonius Kappa CCD diffractometer (graphite-monochromatic Mo Kα radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package [29]. These crystal structures were solved using the direct-methods program SIR92 [30] which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement on F (amplitudes) was carried out using CRYSTALS Program Suite [31]. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. Hydrogen atoms were positioned geometrically after each cycle of refinement. Refinement converged satisfactorily to give good R (residual factor) and R_w (weighted

residual factor) value with the best residual electron density minimum and maxima. Table 1 summarizes crystal data and structure refinement results of the title compound.

Table 1: Crystal Data and Experimental Parameters

Chemical formula	**$C_{34}H_{25}Br_2N_6O_3S_5$**
Formula weight	885.75
Crystal class	Triclinic
Space group	*P* -1
a (Å)	11.0460(6)
b (Å)	13.3180(7)
c (Å)	13.7321(8)
α (°)	80.659(3)
β (°)	69.800(3)
γ (°)	77.007(2)
V (Å^3)	1839.42(18)
Z	2
Mo Kα (Å)	0.7107
T (K)	150
Density (calculated) Mg m^{-3})	1.60
Absorption coefficient (mm^{-1})	2.531
F (000)	552
Crystal size (mm)	0.10 x 0.20 x 0.30
q range for data collection (°)	5 to 27
Index ranges	(-12 ≤ h ≤ 14)
	(-17 ≤ k ≤ 17)
	(-17 ≤ l ≤ 17)
Reflections collected	14020
Independent reflections	8270 [*R*(int) = 0.0702]
Refinement method	Full-matrix least-squares on F
Data/restrains/parameters	4010 / 6 / 469
Goodness-of-fit on F^2	1.1548
Final *R* indices [*I* > 2s > (*I*)]	R_1=0.0724 wR_2=0.0713
R indices (all data)	R_1=0.1595 wR_2=0.1284
Largest diff. peak and hole (e Å^{-3})	-1.04 and 0.97

RESULTS AND DISCUSSION

The molecular structure of the title compound with atom numbering scheme and its intermolecular hydrogen bonds are shown in Figure 1, Figure 2, Figure 3 and Figure 4 respectively.

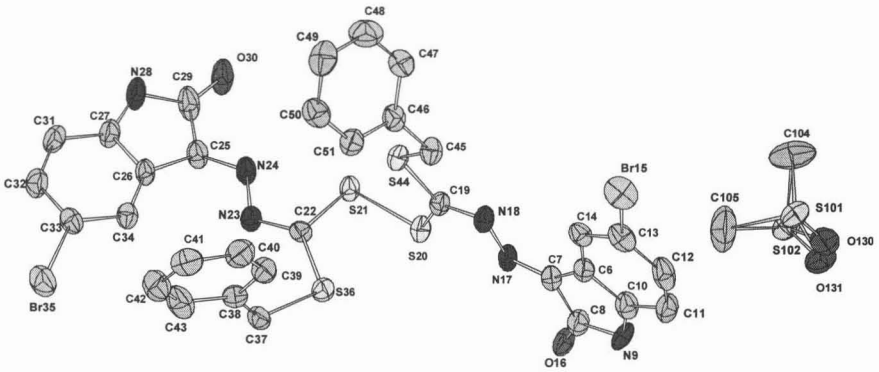

Figure 1: The ORTEP Diagram of Bis[S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonthioate] Disulfide with Dimethylsulfoxide Solvate, Hydrogen Atoms are Omitted for Clarity

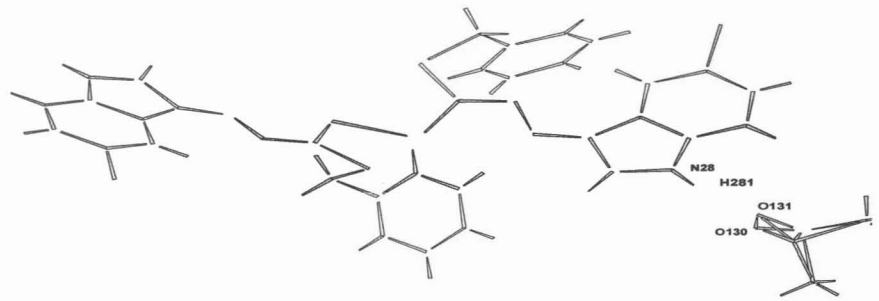

Figure 2: N28-H281···O131 and N28-H281···O130 Intermolecular Hydrogen Bonds Between the Solvent Molecule

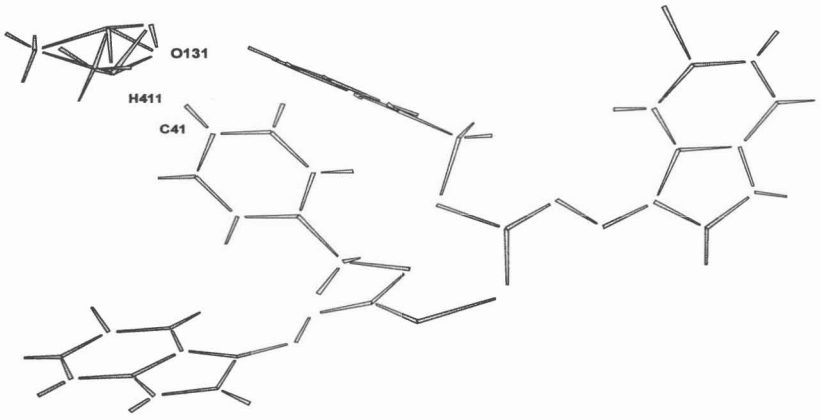

Figure 3: C41-H411···O131 Intermolecular Hydrogen Bonding

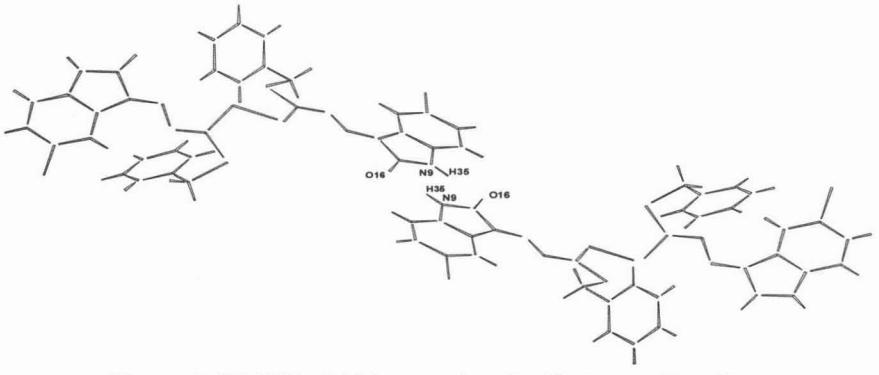

Figure 4: N9-H35···O16 Intermolecular Hydrogen Bonding

The compound crystallized in a triclinic crystal system and *P* -1 space group with one disordered dimethylsulfoxide solvent molecule with the sulfur and oxygen atoms are distributed over two sites; S101/S102 [site occupancy factors: 0.6035/0.3965] and O130/O131 [site occupancy factor 0.3965/0.6095]. According to the crystal structure, both of the 5-bromoisatin moieties are *trans* with respect to the [S21-S20 and C19-N18] and [S20-S21 and C22-N23] bonds whereas the benzyl group from the dithiocarbazate are in the *cis* configuration with respect to [S21-S20 and C19-S44] and [S20-S21 and C22-S36] bonds. The six- and five-membered rings of the 5-bromoisatin moiety which consists of (C25-C26-C27-C29-N8 and C26-C27-C31-C32-C33-C34) are not exactly planar with dihedral angles of 2.61° whereas the

six- and five-membered rings of the 5-bromoisatin moiety which consists of (C6-C7-C8-C10-N9 and C6-C10-C11-C12-C13-C14) are almost coplanar to each other with the dihedral angle of 1.02° between the two mean planes. The benzyl ring and dithiocarbazate planes of (C45-C46-C47-C48-C49-C50-C51 and C45-S44-C19-S20-N17-N18) and (C37-C38-C39-C40-C41-C42-C43 and C37-S36-C22-S21-S20-N23-N24) are nearly perpendicular to each other with the dihedral angles of 82.26° and 86.71° respectively.

The geometric parameters of this title compound are almost similar with the S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate which was reported previously [28] with the exception that in this reported structure, both of the Schiff base molecules are connected by disulfide bond [S20-S21 2.055(2) Å]. This disulfide S-S bond is comparable with the single S-S bond in elemental sulfur (2.106(3) Å) [32]. The C22-S21 and C19-S20 bond distances of 1.779(7) Å and 1.788(8) Å indicate single bond character which support the suggestion that both of the molecules are connected by disulfide bond in its thiol form [33]. The C19-N18 and C22-N23 bond distances of 1.291(9) Å and 1.282(9) Å conform to the value for a C=N double bond [34, 35]. The N23-N24 bond distance of (1.404(8) Å) is in agreement with corresponding bond length in unsubstituted SBDTC (1.406(3) Å) [36]. This is in contrast with the N17-N18 bond distance (1.386(9) Å) which is found to be slightly shorter compared to the value found in the unsubstituted SBDTC [34-36]. However, this value is found to be in agreement with those observed in the S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate and S-benzyl 2-(5-chloro-2-oxoindolin-3-ylidene)hydrazinecarbodithioate reported previously [28].

The C19-S20-S21-C22 chain is almost perpendicular with the torsion angle of -87.78°. Whereas the S-20-S21-C22-S36 and S21-S20-C19-S44 chains are almost coplanar with the torsion angles of 0.65° and 1.22° respectively. The S20-C19-S44-C45 and S21-C22-S36-C37 chains adopt *trans* conformation with the torsion angles of 174.75° and 177.77° respectively. In the crystal lattice, the intermolecular hydrogen bonding are observed between N9-H35···O16 [N9···O16 = 2.776(13) Å, N9-H35 = 0.85 Å], which is formed between the two molecules, and N28-H281···O130 [N28···O130 = 2.850(13), N28-H281 = 0.86 Å], N28-H281···O131 [N28···O131 = 2.807(13), N28-H281 = 0.86 Å] and C41-H411···O131 [C41···O131 = 3.172(13), C41-H411 = 0.93 Å] which occur between the

molecule and the dimethylsulfoxide. Selected bond lengths and bond angles, torsional angles and intermolecular hydrogen bonding are listed in Table 2, Table 3 and Table 4 respectively.

Table 2: Selected Bond Lengths (Å) and Bond Angles (°)

C29-O30	1.203(10)	C8-O16	1.203(10)
C25-N24	1.280(10)	C7-N17	1.280(9)
N23-N24	1.404(8)	N17-N18	1.386(9)
C22-N23	1.282(9)	C19-N18	1.291(9)
C22-S36	1.742(7)	C19-S20	1.788(8)
C22-S21	1.779(7)	C45-S44	1.811(7)
C33-Br35	1.888(7)	C13-Br15	1.866(9)
S20-S21	2.055(2)		
C25-N24-N23	114.7(6)	C7-N17-N18	115.0(6)
N24-N23-C22	108.6(5)	N17-N18-C19	109.0(6)
N23-C22-S36	122.2(5)	N18-C19-S44	121.2(6)
N23-C22-S21	119.6(5)	N18-C19-S20	120.0(6)
C22-S21-S20	102.8(2)	C19-S21-S20	102.8(3)
S20-C19-S44	118.8(4)	S21-C22-S36	118.2(4)

Table 3: Selected Torsional Angles (°)

C19-S20-S21-C22	-87.78
S-20-S21-C22-S36	0.65
S21-S20-C19-S44	1.22
S20-C19-S44-C45	174.75
S21-C22-S36-C37	177.77

Table 4: Intermolecular Hydrogen Bonds (Å, °)

D-H¼A	D-H	H¼A	D¼A	D-H¼A
N9-H35···O16	0.85	1.94	2.776(13)	168
N28-H281···O130	0.86	2.02	2.850(13)	164
N28-H281···O131	0.86	1.97	2.807(13)	167
C41-H411···O131	0.93	2.50	3.172(13)	129

D-donor; A-Acceptor; H-Hydrogen

CONCLUSION

Novel disulfide bridging compound has been obtained from the crystallization of S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate in DMSO. This compound has been characterised using single crystal x-ray diffraction. The compound crystallized in the triclinic space group *P* -1, with one disordered dimethylsulfoxide solvent molecule. Both of the 5-bromoisatin moieties are *trans* with respect to the [S21-S20 and C19-N18] and [S20-S21 and C22-N23] bonds whereas the benzyl group from the dithiocarbazate are in the *cis* configuration with respect to [S21-S20 and C19-S44] and [S20-S21 and C22-S36] bonds.

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