

**A crystallographic study of Bis[S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonothioate] disulfide solvated with dimethylsulfoxide.**

**Mohd Abdul Fatah Abdul Manan<sup>1</sup>, M. Ibrahim M. Tahir<sup>2</sup>, Karen A. Crouse<sup>2</sup>,  
Fiona N.-F. How<sup>2</sup> and David J. Watkin<sup>3</sup>**

<sup>1</sup>*Faculty of Applied Sciences,*

*Universiti Teknologi MARA, 40450 Shah Alam, Selangor*

<sup>2</sup>*Department of Chemistry, Faculty of Science,*

*Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.*

<sup>3</sup>*Chemical Chemistry Research Laboratory,*

*University of Oxford, South Parks Road OX1 3QA, Oxford, UK*

<sup>1</sup>*Email: abdfatah@salam.uitm.edu.my*

**ABSTRACT**

The crystal structure of the title compound has been determined. The compound crystallized in the triclinic space group  $P\bar{1}$ ,  $Z = 2$ ,  $V = 1839.42(18) \text{ \AA}^3$  and unit cell parameters  $a = 11.0460(6) \text{ \AA}$ ,  $b = 13.3180(7) \text{ \AA}$ ,  $c = 13.7321(8) \text{ \AA}$ ,  $\alpha = 80.659(3)^\circ$ ,  $\beta = 69.800(3)^\circ$  and  $\gamma = 77.007(2)^\circ$  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)  $\text{ \AA}$  and 1.788(8)  $\text{ \AA}$  indicate that both of the molecules are connected by the disulfide bond [S20-S21 2.055(2)  $\text{ \AA}$ ] 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-oxindole 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-oxindole 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*-benzylthiocarbamate 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<sub>50</sub> 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<sub>50</sub> 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-benzylthiocarbamate with isatin derivatives, we are reporting here the crystallographic study of bis[S-benzyl-5-bromo-2-oxoindolin-3-ylidenemethanehydrazonothioate] disulfide solvated with dimethylsulfoxide.

## Experimental

### Synthesis

S-benzyl 2-(5-bromo-2-oxoindolin-3-ylidene)hydrazinecarbodithioate was prepared as reported previously [28]. S-benzylthiocarbamate, 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-ylidenemethanehydrazonothioate] 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 K $\alpha$  radiation,  $\lambda = 0.71073 \text{ \AA}$ ). 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)
$\alpha$ (°)	80.659(3)
$\beta$ (°)	69.800(3)
$\gamma$ (°)	77.007(2)
$V$ (Å <sup>3</sup> )	1839.42(18)
$Z$	2
Mo $K\alpha$ (Å)	0.7107
T (K)	150
Density (calculated) Mg m <sup>-3</sup>	1.60
Absorption coefficient (mm <sup>-1</sup> )	2.531
$F(000)$	552
Crystal size (mm)	0.10 x 0.20 x 0.30
$\theta$ range for data collection (°)	5 to 27
Index ranges	$(-12 \leq h \leq 14)$ $(-17 \leq k \leq 17)$ $(-17 \leq l \leq 17)$
Reflections collected	14020
Independent reflections	8270 [ $R(\text{int}) = 0.0702$ ]
Refinement method	Full-matrix least-squares on $F$
Data/restraints/parameters	4010 / 6 / 469
Goodness-of-fit on $F^2$	1.1548
Final $R$ indices [ $I > 2\sigma > (I)$ ]	$R_1=0.0724$ $wR_2=0.0713$
$R$ indices (all data)	$R_1=0.1595$ $wR_2=0.1284$

Largest diff. peak and hole ( $e \text{ \AA}^{-3}$ )

-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.

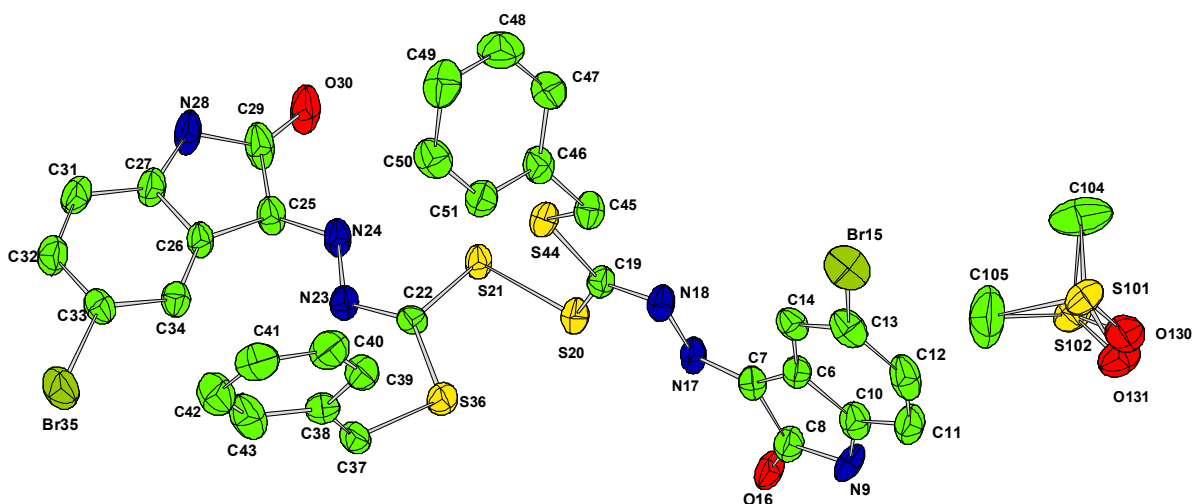


Figure 1: The ORTEP diagram of Bis[S-benzyl-5-bromo-2-oxindolin-3-ylidene]methanehydrazonothioate] disulfide with dimethylsulfoxide solvate, hydrogen atoms are omitted for clarity.

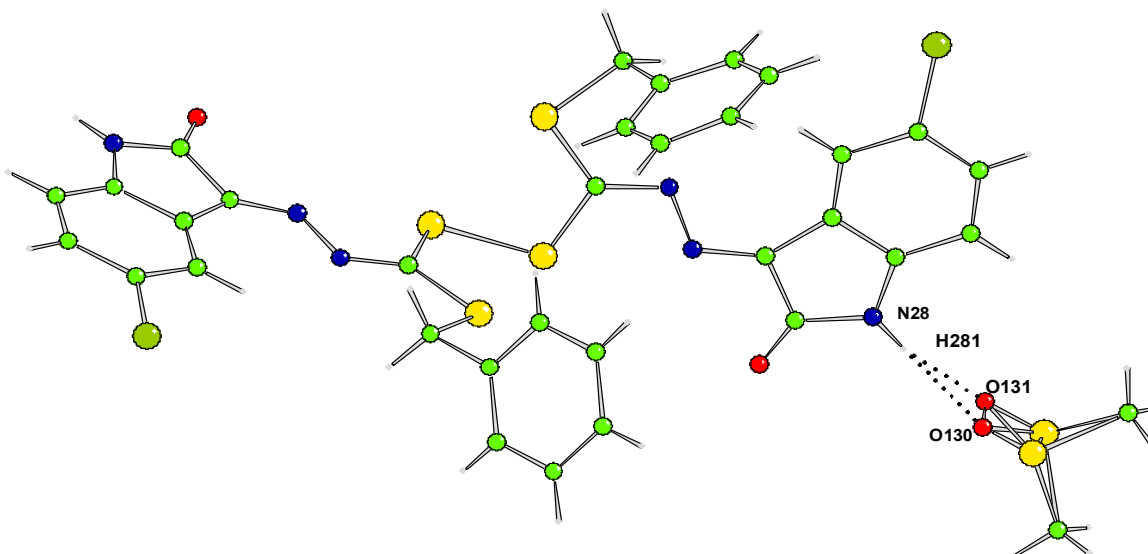


Figure 2: N28-H281...O131 and N28-H281...O130 intermolecular hydrogen bonds between the solvent molecule.

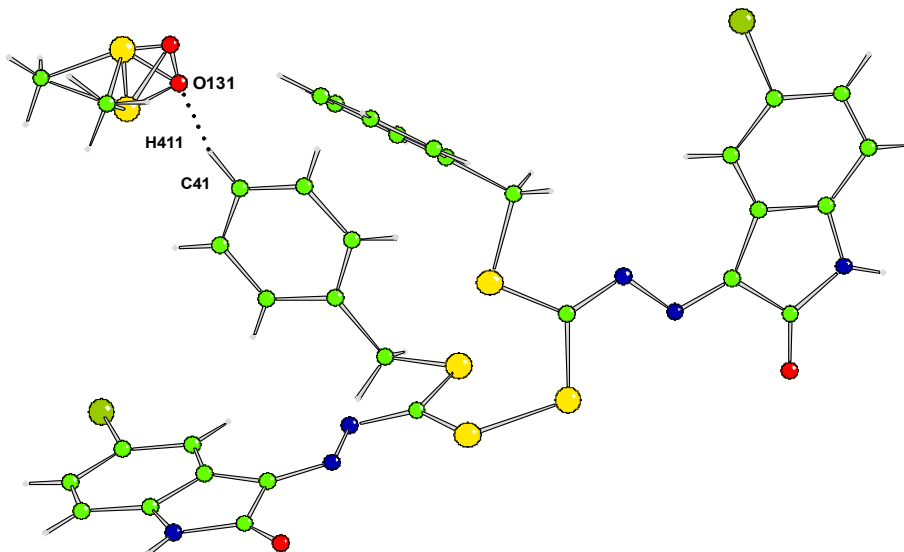


Figure 3: C41-H411...O131 intermolecular hydrogen bonding

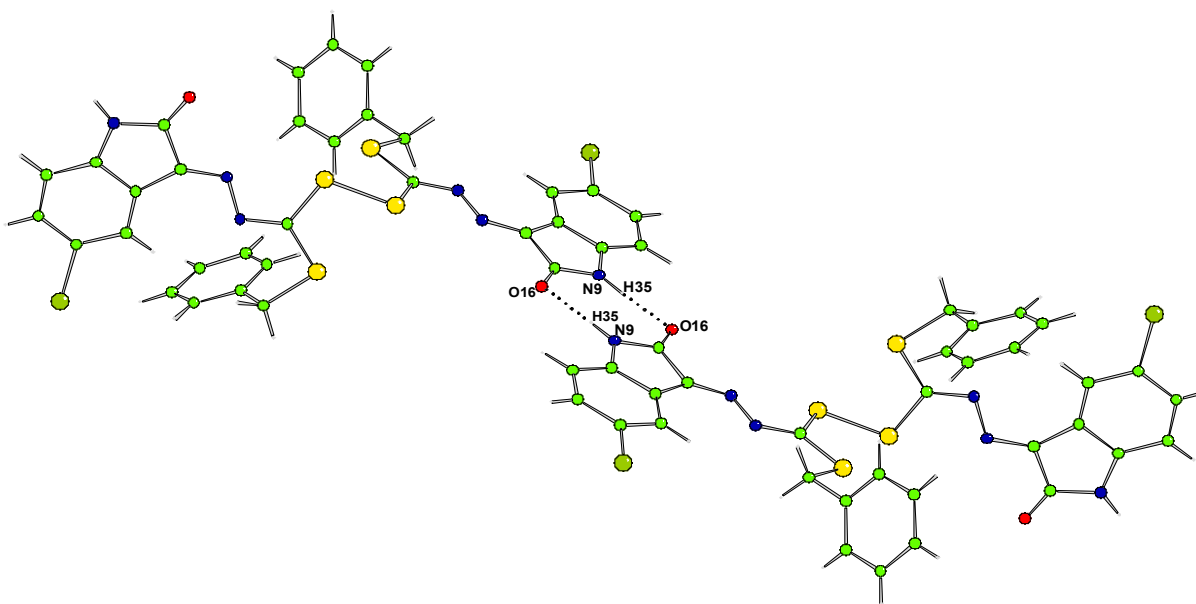


Figure 4: N9-H35...O16 intermolecular hydrogen bonding

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  $2.61^\circ$  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  $1.02^\circ$  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  $82.26^\circ$  and  $86.71^\circ$  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  $-87.78^\circ$ . Whereas the S-20-S21-C22-S36 and S21-S20-C19-S44 chains are almost coplanar with the torsion angles of  $0.65^\circ$  and  $1.22^\circ$  respectively. The S20-C19-S44-C45 and S21-C22-S36-C37 chains adopt *trans* conformation with the torsion angles of  $174.75^\circ$  and  $177.77^\circ$

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-H...A	D-H	H...A	D...A	D-H...A
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 characterized 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 dithiocarbamate are in the *cis* configuration with respect to [S21-S20 and C19-S44] and [S20-S21 and C22-S36] bonds.

## Acknowledgements

We thank the Faculty of Applied Sciences Universiti Teknologi MARA for the provision of laboratory facilities. This work was funded by a grant from the Research Management Institute (RMI), UiTM (Grant no. 600/RMI/ST/DANA 5/3/Dst (31/2009)).

**References**

- [1] A. H. Abadi, S. M. Abou-Seri, D. E. Abdel-Rahman, C. Klein, O. Lozach and L. Meijer, 2006. Synthesis of 3-substituted-2-oxoindole analogues and their evaluation as kinase inhibitors, anticancer and antiangiogenic agents, *European Journal of Medicinal Chemistry*, vol. 41, pp. 296–305.
- [2] V. M. Sharma, P. Prasanna, V. A. Seshu, B. Renuka, V. L. Rao, G. S. Kumar, C. P. Narasimhulu, P. A. Babu, R. C. Puranik, D. Subramanyam, A. Venkateswarlu, S. Rajagopal, K. B. S. Kumar, C. S. Rao, N. V. S. R. Mamidi, D. S. Deevi, R. Ajaykumar and R. Rajagopalan, 2002. Novel Indolo [2,1-b] quinazoline analogues as cytostatic agents : synthesis, biological evaluation and structure–activity relationship, *Bioorganic and Medicinal Chemistry Letters*, vol. 12, pp. 2303–2307.
- [3] S. N. Pandeya, S. Smitha, M. Jyoti and S. K. Sridhar, 2005. Biological activities of isatin and its derivatives, *Acta Pharmaceutica*, vol. 55, pp. 27-46.
- [4] M. J. Moon, S. K. Lee, J. W. Lee, W. K. Song, S. W. Kim, J. I. Kim, C. Cho, S. J. Choi and Y. C. Kim, 2006. Synthesis and structure–activity relationships of novel indirubin derivatives as potent anti-proliferative agents with CDK2 inhibitory activities, *Bioorganic and Medicinal Chemistry*, vol. 14, pp. 237–246.
- [5] S. N. Pandeya and D. Sriram, 1998. Synthesis and screening for antibacterial activity of Schiff's and Mannich bases of isatin and its derivatives, *Acta Pharmaceutica Turcica*, vol. 40, pp. 33-38.
- [6] M. Sarangapani and V. M. Reddy, 1994. Pharmacological evaluation of 1-(N,N-disubstituted aminomethyl)-3-imino-(2-phenyl-3,4-dihydro-4-oxo-quinazolin-3-yl) indolin-2-ones, *Indian Journal of Pharmaceutical Sciences* vol. 56, pp. 174-177.

- [7] R. Pignatello, A. Panico, P. Mazzane, M. R. Pinizzotto, A. Garozzo, P. M. Fumeri, 1994. Schiff bases of *N*-hydroxy-*N'*-aminoguanidines as antiviral, antibacterial and anticancer agents, *European Journal of Medicinal Chemistry*, vol. 29, pp. 781-785.
- [8] S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq, 1999. Synthesis, Antibacterial, Antifungal and Anti-HIV activity of Schiff and Mannich bases of Isatin with *N*-[6-Chlorobenzothiazol-2-yl]Thiosemicarbazide, *Indian Journal of Pharmaceutical Sciences*, vol. 61, pp. 358-361
- [9] S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq, 1999. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Norfloxacin Mannich bases, *Scientia Pharmaceutica*, vol. 67, pp. 103-111.
- [10] S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq, 1999. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4(3H)-one, *Pharmaceutica Acta Helveticae*, vol. 74, pp. 11-17.
- [11] R. S. Varma and W. L. Nobles, 1967. Synthesis Antiviral and Antibacterial activity of certain *N*-Dialkylaminomethylisatin- $\beta$ -Thiosemicarbazones, *Journal of Medicinal Chemistry*, vol. 10, pp. 972-974.
- [12] S. P. Singh, S. K. Shukla and L. P. Awasthi, 1983. Synthesis, Antiviral and Antibacterial Activity of Certain *N*-Dialkylaminomethylisatin  $\beta$ -Thiosemicarbazones, *Current Science*, vol. 52, pp. 766-769.
- [13] J. C. Logan, M. P. Fox, J. M. Morgan, A. M. Makohon and C. J. Pfau, 1975. Arenavirus Inactivation on Contact with *N*-substituted Isatin beta thiosemicarbazones and Certain Cations, *Journal of General Virology*, vol. 28, pp. 271-283.

- [14] S. N. Pandeya, P. Yogeswari, D. Sriram, E. De Clercq, C. Pannecouque and M. Witvrouw, 1999. Synthesis and screening for anti-HIV activity of some N-Mannich bases of isatin derivatives, *Chemotherapy*, vol. 45, pp. 192-195.
- [15] S. N. Pandeya, D. Sriram, G. Nath and E. Clercq, 2000. Synthesis, antibacterial, antifungal and anti-HIV activities of norfloxacin Mannich bases, *European Journal of Medicinal Chemistry*, vol. 35, pp. 249-255.
- [16] S. N. Pandeya, D. Sriram, G. Nath and E. Clercq De, 2000. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin and its derivatives with triazole, *Arzneimittelforschung*, vol. 50, pp. 55-59.
- [17] S. A. Imam and R. S. Varma, 1975. Isatin-3-anils as excystment and cysticidal agents against *Schizopyrenus russelli*, *Experientia*, vol. 31, pp. 1287-1288.
- [18] R. S. Varma and I. A. Khan, 1977. Synthesis of 3-arylimino-2-indolinones, and their 1-methyl- and 1-morpholino/piperidinomethyl derivatives as excystment and cysticidal agents against *Schizopyrenus russelli*, *Polish Journal of Pharmacology and Pharmacy*, vol. 29, pp. 549-594.
- [19] S. E. Sarciron, P. Audin, I. Delebre, C. Gabrion, A. F. Petavy and J. Paris, 1993. Synthesis of propargylic alcohols and biological effects on *Echinococcus multilocularis metaces-todes*, *Journal of Pharmaceutical Sciences*, vol. 82, pp. 605-609.
- [20] E. A. El-Sawi, T. B. Mostaza and B. B. Mostaza, 1998. Studies on the molluscicidal action of some isatin derivatives against *Biomphalaria alexandrina* in Egypt, *Journal of Egyptian Society of Parasitology*, vol. 28, pp. 481-486.
- [21] K. W. Chi, G. G. Furin, I. Y. Bagryanskay and Y. V. Gatilov, 2000. Reaction of perfluoro-2-methylpent-2-ene and perfluoro-5-azanon-4-ene with aniline and its derivatives, *Journal of Fluorine Chemistry*, vol. 104, pp. 263-271.

- [22] F. Sandrine, D. George, S. William and R. Eric. 2007. Molecular basis for Sunitinib efficacy and future clinical development. *Nature Reviews Drug Discovery*, vol. 6, pp. 734-745.
- [23] A. L. Cheryl, B. M. Phyllis, L. W. F. Stacey, F. B. Joseph, W. R. Anthony, M. P. Rosenberg, C. J. Henry, K. L. Mitchener, M. K. Klein, J. G. Hintermeister, P. J. Bergman, G. C. Couto, G. N. Mauldin and G. M. Michels. 2009. Multi-center, Placebo-controlled, Double-blind, Randomized Study of Oral Toceranib Phosphate (SU11654), a Receptor Tyrosine Kinase Inhibitor, for the Treatment of Dogs with Recurrent (Either Local or Distant) Mast Cell Tumor Following Surgical Excision, *Clinical Cancer Research*, vol. 15, pp. 3856-3865.
- [24] R. Sabet, M. Mohammadpour, A. Sagedhi and A. Fassihi, 2010. QSAR study of isatin analogues as in vitro anti-cancer agents, *European Journal of Medicinal Chemistry*, vol. 45, pp. 1113-1118.
- [25] K. L. Vine, J. M. Locke, M. Ranson, S. G. Pyne and J. B. Bremner, 2007. In vitro cytotoxicity evaluation of some substituted isatin derivatives. *Bioorganic and Medicinal Chemistry*, vol. 15, pp. 931-938.
- [26] L. Qiu, A. Burgess, D. P. Fairlie, H. Leonard, P. G. Parsons and B.G. Gabrielli. 2000. Histone deacetylase inhibitors trigger a G2 checkpoint in normal cells that is defective in tumor cells. *Molecular Biology of the Cell*, vol. 11, pp. 2069-2083.
- [27] S. N. Ononye, M. V. Heyst, E. M. Falcone, A. C. Anderson and D. L. Wright. 2012. Toward isozyme-selective inhibitors of histone deacetylase as therapeutic agents for the treatment of cancer. *Pharmaceutical Patent Analyst*, vol. 1, pp. 207-221.

- [28] M. A. F. A. Manan, K. A. Crouse, M. I. M. Tahir, R. Rosli, F. N. F. How, D. J. Watkin and A. M. Z. Slawin. 2011. Synthesis, characterization and cytotoxic activities of S-benzylthiocarbamate Schiff bases derived from 5-fluoroisatin, 5-chloroisatin, 5-bromoisatin and their crystal structures. *Journal of Chemical Crystallography*, vol. 41, pp. 1630-1641.
- [29] Z. Otwinowski and W. Minor, 1997. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods of Enzymology* (eds. R. M. Sweet and C. W. Carter), vol. 276, pp. 307-326, Academic Press, New York.
- [30] A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, 1994. SIRPOW.92 - a program for automatic solution of crystal structures by direct methods optimized for powder data, *Journal of Applied Crystallography*, vol. 27, pp. 435-436.
- [31] D. J. Watkin, C. K. Prout, J. R. Carruthers and P. W. Betteridge, 1996. CRYSTALS, Issue 10 ed, Chemical Crystallography Laboratory, University of Oxford.
- [32] L. X. Cheng, C. B. Ma, M. Q. Hu and C. N. Chen, 2005. ( $\mu_4$ -Disulfido-1:2 $\kappa^2$ S,S;3:4 $\kappa^2$ S',S')bis( $\mu_2$ -ethylthiolato- $\kappa^2$ S:S)tetrakis[tricarboxyliron(II)(Fe-Fe), *Acta Crystallographica Section E*, vol. 61, pp. m892-m894.
- [33] M. T. H. Tarafder, T. J. Khoo, K. A. Crouse, M. A. Ali, B. M. Yamin and H. K. Fun, 2002. Coordination chemistry and bioactivity of some metal complexes containing two isomeric bidentate NS Schiff bases derived from S-benzylthiocarbamate and the X-ray crystal structures of S-benzyl- $\beta$ -N-(5-methyl-2-furylmethylene)dithiocarbamate and bis[S-benzyl- $\beta$ -N-(2-furylmethylketone)dithiocarbamate]cadmium(II), *Polyhedron*, vol. 21, pp. 2691-2698.
- [34] Y. X. Sun, Z. L. You and H. L. Zhu, 2004. N,N'-Bis(4-nitrobenzylidene)ethane-1,2-diamine, *Acta Crystallographica Section E*, vol. 60, pp. o1707-o1708.

- [35] Z. L. You, L. L. Tang and H. L. Zhu, 2004. A dinuclear oxygen-bridged Schiff base iron(III) complex derived from *N,N'*-bis(2-hydroxybenzylidene)-1,2-diaminopropane, *Acta Crystallographica Section E*, vol. 61, pp. m36-m38.
- [36] S. S. S. Raj, B. M. Yamin, Y.A. Yussof, M. T. H. Tarafder, H.K. Fun and K. A. Crouse, 2000. *trans-cis* S-Benzyl dithiocarbazate, *Acta Crystallographica Section E*, vol. 56, pp. 1236-1237.