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# Synthesis, characterization and DFT studies of 6-bis(2-(thiazol-4-yl)benzimidazol-1-yl)hexane hemihydrate crystal : Experimental and theoretical investigation

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# Abstract

6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane has been efficiently synthesized by direct alkylation of 2-(4-thiazolyl)benzimidazole with 1,6-dibromohexane via phase-transfer catalysis. The desired compound was obtained in high yield and its structural characterization was performed by FTIR and NMR spectroscopies. A suitable single crystal of the compound for X-ray structure analysis was obtained and analyzed. The organic salt 1,6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl) hexane (Bis-TBZ 0.5H<sub>2</sub>O) crystallizes in the monoclinic space group *I*2/*a* (#15). The optimized geometries, IR frequencies, <sup>1</sup>H and <sup>13</sup>C-NMR chemical shifts and frontier molecular orbital energies (HOMO, LUMO) of the compound have been calculated by Density Functional Theory at the B3LYP/6-311G++(d,p) level of theory. All the available theoretical results were compared with the experimental data. The X-ray parameters of the title compound agree with the theoretically obtained values. The computed vibrational wavenumbers, <sup>1</sup>H and <sup>13</sup>C-NMR chemical shifts of the compound show good correlation with the corresponding experimental ones. Finally, the calculated HOMO and LUMO energies revealed that charge transfer occurs in the molecule.

**Keywords:** Thiabendazole, 1,6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane, X-ray structure, Spectroscopic analysis, DFT calculation, HOMO-LUMO.

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# 1. Introduction

The chemical and biological properties of 2-(4-thiazolyl)benzimidazole have been attracting considerable scientific attention in recent years rendering them suitable for a wide range of applications in different fields. Thiabendazole belongs to the benzimidazole group and its derivatives are an important class of sulfur/nitrogen-containing aromatic heterocyclic compounds, and have aroused a great deal of interest owing to their broad-spectrum biological activities, namely antiproliferative activity against a panel of human cancer cell lines [1,2], antimicrobial and photodynamic effects [3], as a fungicide effect against potato tuber diseases [4], biomimetic activity [5], anti-angiogenesis as well as vascular disrupting agents [6]. These compounds have also found several application in the food industry [7,8].

Another important characteristic attributed to thiabendazole derivatives concerns their ability to coordinate with transition metal ions [9,10]. In this sense, several thiabendazole compounds have been successfully designed and used as ligands in coordination chemistry. K. Mothilal et al. [11] investigated the site symmetry and metal/ligand interaction in the octahedral cobalt complex of thiabendazole  $[Co(tbz)_2(NO_3)(H_2O)]$  by using Cu(II) as an EPR probe. In another work, three cobalt(II) coordination polymers were prepared from flexible bis(thiabendazole) and dicarboxylate ligands under hydrothermal conditions. The photocatalytic performances of the complexes were also investigated [12]. In the same context, Zhang et al. [13] reported the synthesis and structural properties of four flexible bis-thiabendazole-based Cd(II) coordination polymers with various aromatic carboxylates as co-ligands. Their catalytic behaviors in degrading methyl orange were discussed. Furthermore, thiabendazole derivatives have also found applications in the preparation of clay-based organic-inorganic hybrid materials [14,15]. Recent investigations in our laboratory showed that the Ni- or Cothiabendazole complexes confined in interlayer space of montmorillonite present a new class of reactive materials valuable to design single-site catalysts for heterogeneous reactions [16]. In our previous work, several thiabendazole derivatives including a geminal benzimidazolium surfactant and N-alkyl substituted quaternary thiabendazolium salts have been synthesized and used as organic modifiers for the preparation of polymer organo-clay nanocomposites materials [17,18]. Therefore, the great importance of these derivatives in several fields including biology, chemistry and agriculture has attracted the attention of many researchers to develop various synthetic pathways for their preparations and to find new applications soon. Alternatively, a great deal of attention has been paid to density functional theory (DFT) as the

most specific and efficient computational method for the quantum chemical modeling and electronic structure of organic compounds [19–22]. More recently, Mekhzoum *et al.* [23] used

DFT at the B3LYP/6-311G++(d,p) level of theory to study the optimized geometrical parameters and vibrational frequencies of *N*-benzothiazolium salt. Results showed that the experimental data complements with the theoretical finding. To the best of our knowledge, reports are not available regarding DFT and experimental studies of 1,6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane. The present work deals with synthesis and characterization of this bis-thiabendazole compound using different spectroscopic techniques such as IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR spectroscopy and single crystal X-ray diffraction. Moreover, comparison of experimental with corresponding computational values (DFT) was carried out. In addition, the HOMO and LUMO analysis was used to elucidate the information regarding charge transfer within the molecule.

#### 2. Experimental

## 2.1. Materials and measurements

All reagents and solvents used in this study were purchased from commercial sources and used without further purification. The purity of synthesized compound was checked by TLC on ready-made silica gel plates (silica gel matrix with fluorescent indicator 254nm) and visualized under an Ultraviolet lamp. IR spectra were recorded on ABB Bomem FTLA 2000–102 FTIR instrument using KBr pellets in the 400-4000 cm<sup>-1</sup> range. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer. The chemical shifts ( $\delta$ ) are expressed in parts per million (ppm) downfield from TMS as an internal reference. The melting point (mp) of the bis-TBZ was measured in open capillary tubes on Melting Point Apparatus SMP30.

### 2.2. Experimental procedure for the Synthesis of title compound

To a mixture of 2-(4-thiazolyl)benzimidazole (9.94 mmol) in *N*,*N*-dimethylformamide (DMF), potassium carbonate (12.42 mmol) was added. The resulting mixture was stirred for 30 min, after that the corresponding 1,6-dibromohexane (5.95 mmol) and tetra-*n*-butylammonium bromide (TBAB) (1 mmol) were added. The reaction was stirred for 48 hours at room temperature until complete as monitored by TLC. After removal of salt by filtration, DMF was evaporated under reduced pressure, the residue obtained is dissolved in dichloromethane, and remaining salt is extracted with distilled water. The product was recrystallized from ethanol to furnish the title compound as white crystals. Yield: 82%; mp 176 °C; FTIR (KBR) : 3112 (CH<sub>Ar</sub>), 2952 (CH<sub>2</sub>), 1664 (C=N), 1608 (C=C), 759 (C-S); <sup>1</sup>H

NMR (600 MHz, DMSO)  $\delta$  (ppm): 1.22 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.67 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 4.68 (t, 2H, NCH<sub>2</sub>), 7.25-7.67 (m, 4H, CH<sub>Ar</sub>), 8.48 (d, J= 2.1 Hz, 1H, SCH<sub>thiazole</sub>), 9.28 (d, J= 2.1 Hz, 1H, NCH<sub>thiazole</sub>); <sup>13</sup>C NMR (151 MHz, DMSO)  $\delta$ (ppm): 25.98 CH<sub>2</sub> (17), 29.99 CH<sub>2</sub> (16), 44.52 NCH<sub>2</sub> (15), 111.17 CH<sub>Ar</sub> (8), 119.50 CH<sub>Ar</sub> (7), 122.66 CH<sub>Ar</sub> (6), 122.88 CH<sub>Ar</sub> (5), 123.15 Cq (10), 136.02 Cq (9), 142.87 Cq (4), 146.82 Cq (2), 147.46 S<u>C</u>C (14), 155.66 NCS (12).

# 2.3. X-ray data collection, structure solution and refinement

Single crystals of Bis-TBz 0.5 H<sub>2</sub>O (C<sub>26</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub>S<sub>2</sub>) were grown from cooling of an EtOH solution. A suitable crystal was selected and mounted with Paratone<sup>TM</sup> oil using a MiTeGen 100µm loop on a SuperNova, Dual, Cu at home, Pilatus 200K diffractometer. The crystal was kept at 100.01(10) K during data collection. Using Olex2 [24], the structure was solved with the ShelXT [25] structure solution program using Intrinsic Phasing and refined with the ShelXL [26] refinement package using Least Squares minimisation. Half the molecule comprises the asymmetric unit, centrosymmetrically related to the other half, and associates with one molecule of H<sub>2</sub>O. The 4-thiazolyl ring is rotationally disordered with respect to the plane of the 2-benzimidazole ring and a two-part disorder model was developed in Olex2 using suitable restraints. The refined occupancy of the two components is 0.500(11). Postrefinement data analysis and preparation of graphic material employed Mercury CSD, release 4.1.3 [27]. Crystal Data for  $C_{26}H_{28}N_6O_2S_2$  (M = 520.66 g/mol): monoclinic, space group I2/a (no. 15), a = 17.38696(15) Å, b = 4.87663(4) Å, c = 30.6179(2) Å,  $\beta = 105.0597(8)^{\circ}$ ,  $V = 100.0597(8)^{\circ}$ 2506.92(4) Å<sup>3</sup>, Z = 4, T = 100.01(10) K,  $\mu$ (CuK $\alpha$ ) = 2.225 mm<sup>-1</sup>,  $D_{calc} = 1.380$  g/cm<sup>3</sup>, 92423 reflections measured (10.538°  $\leq 2\theta \leq 161.04^{\circ}$ ), 2741 unique ( $R_{int} = 0.0786$ ,  $R_{sigma} = 0.0139$ ) which were used in all calculations. The final  $R_1$  was 0.1022 (I > 2 $\sigma$ (I)) and  $wR_2$  was 0.3172 (all data). The rather large  $R_1$  value is likely due to a somewhat weakly diffracting crystal  $(R_{int})$  and the encountered positional disorder. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre under CCDC 1945115.

# 2.4. Computational study

DFT calculations with Becke's three-parameter hybrid exchange functional and the correlation functional of Lee, Yang and Parr (B3LYP) were performed on a personal computer using Gaussian 09 software. The entire calculations in the present study including optimized geometrical parameters, calculated vibrational wavenumbers, theoretical NMR spectrum and electronic properties such as HOMO and LUMO energies of 1,6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane (Bis-TBz), were performed at the B3LYP/6-311G++(d.p) level of theory. The normal modes assignment of the theoretical IR frequencies was visualized and

substantiated with the help of Gaussview 5.0.9 visualization program. There is no negative frequency in the calculated IR spectrum which confirms that the optimized geometry of the compound is located at a minimum on the potential energy surface. The <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are calculated with a gauge-including atomic orbital (GIAO) approach using the optimized parameters obtained from B3LYP/6-311++(d,p) method in DMSO solution and gas phase. TMS (Tetramethylsilane) is used as reference in both experimental and theoretical studies. Root mean square (RMS) were calculated for X-ray, IR and NMR analysis.

$$RMS = \sqrt{\frac{1}{n} \sum_{i}^{n} (x_{i}^{calc} - x_{i}^{exp})^{2}}$$

where  $x_i^{calc}$  and  $x_i^{exp}$  are the theoretical and experimental values, respectively.

# 3. Results and Discussion

The bis-thiabendazole, 1,6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane (Bis-TBZ), was subsequently prepared through one step. The synthetic route for title compound investigated in this research is outlined in Scheme 1. The bis-thiabendazole compound was synthesized from thiabendazole as a starting material, 1,6-dibromohexane as alkylating agent and TBAB as catalyst under phase transfer catalysis conditions. The work-up of the reaction, followed by purification of the crude by SiO<sub>2</sub> column chromatography using cyclohexane/ethyl acetate (70:30 v/v) as eluent. The product with a good yield of 82% was obtained by recrystallization from ethanol. The detailed synthetic procedure for the formation of Bis-TBZ is given under the experimental section. The spectral IR and NMR data confirmed the structure of the synthesized product.



Scheme 1. Synthetic pathway used for the Bis-TBZ compound with the atomic numbering

# 3.1. Description of crystal structure

**Bis-TBz-0.5 H<sub>2</sub>O** crystallizes as a semi-hydrate on a centre of inversion in space group I2/a (Wyckoff position 4*a*) midway along the C17–C17' bond (Figure 1) and is associated with one bridging water molecule that hydrogen-bonds to N3. The 4-thiazolyl ring is rotationally disordered with respect to the plane of the 2-benzimidazole ring and a two-part disorder model was developed in Olex2 using suitable restraints (see Figure SI5). The refined occupancy of the two components is 0.500(11). The two thiazolyl rings rotate by +15.7 (5)° and -18.3 (5)° from the 2-benzimidazole. The hexyl bridge also describes a least-squares plane that is rotated 86.3 (3)° from that of the benzimidazole. Despite the complexity of the bridged geometry it thus crystallizes very symmetrically.

The geometry can be compared with three previously reported structures wherein Bis-TBz functions as a ligand towards Co(II) or Cd(II). In the published structure with CSD Refcode [45] ITIXOA,  $bis(\mu-(2-(1,3-\text{thiazol-4-yl})-1-(6-(2-(1,3-\text{thiazol-4-yl})-1\text{H-benzimidazol-1-yl})hexyl)-1\text{H-benzimidazole}))-bis(3-nitrophthalato)-di-cobalt(II) [46], two full Bis-TBz chelate to two different Co(II) ions to form a small coordination pocket. In$ *catena-[bis*(m-1,1'-(hexane-1,6-diyl)bis(2-(1,3-thiazol-4-yl)-1Hbenzimidazole))-bis(2,5-

dicarboxyterephthalato)-di-cadmium], CSD Refcode NATZUG, two independent molecules of Bis-TBz bridge Cd(II) ions, leading with other co-ligands to a coordination polymer [47]. In one of the two ligands, the hexyl linker is structurally disordered in the lattice. Finally, in *catena-[bis*( $\mu$ -biphenyl-4,4'-dicarboxylato)-( $\mu$ -2-(1,3-thiazol-4-yl)-1-(6-(2-(1,3-thiazol-4-yl)-

1*H*-benzimidazol-1-yl)hexyl)-1*H*-benzimidazole)-dicadmium(II)], CSD Refcode REYCEG, a single Bis-TBz bridges Cd(II) ions to also form a polymer [13]. As in the structure reported here, the ligand crystallizes centrosymmetrically with half the ligand as the asymmetric unit. The bond distances in the free ligand are mostly indistinguishable at the 99% confidence level from those of the five symmetry unique sets of bond distances in the complexes. The N1–C2 distance is marginally longer than the average of 1.3618(15)Å in the complexes, while the N1–C15 distance is marginally shorter than the average of 1.471(4)Å, possibly reflecting a consequence of coordination on the imidazole geometry. A significant difference can be seen in angles associated with coordination. Thus, the N1–C2–C10 and N11–C10–C2 angles of 124.2(4)° and 122.7(7)° are much larger in the free ligand than the average of the metal chelated geometries, clearly reflecting compression to maximize the coordination.

In addition, the geometry of the synthesis compound were examined by the use of DFT calculation method using B3LYP at 6-311++G(d,p) basis and compared with the experimental

data obtained from X-ray crystal structure. The theoretical geometry parameters and the experimental values are listed in Table 1. As seen from this table, there are a slight difference between calculated and experimental results. This negligible deviation may come from the environment of the compound (the structure crystalizes with water molecules). For example, For the (C7–C8) group bond length in the aromatic ring was observed at 1.382 Å whereas the calculated bond length was about 1.390 Å. Similarly, the bond length of N3–C2 is about 1.326 Å and 1.318 Å as observed and calculated values respectively. As well, the bond angle of C9–N1–C2 was observed at 106.3°, which is in consistent with calculated value of 105.86°. In the phenyl ring, the angle for C5–C6–C7 was calculated about 121.2° whereas the observed value is 121.3°. In order to investigate the performance and molecular geometry for the title compound root mean square value (RMS) was calculated. RMS errors were found in the region 0.0150 and 0.5850, respectively for bond distances and angles. According to this data, most of obtained results by X-ray diffraction were found to be agreeable with the computed molecular geometry of the synthesized compound.



**Figure 1.** Displacement ellipsoids plot (40% probability) of the structure of *bis*-TBz $\cdot$ 0.5 H<sub>2</sub>O as found in the crystal lattice. The main molecule crystalizes on a centre of symmetry, located between C17 and C17<sup>1</sup>, the unique atoms have been labeled and the major component of the disordered 4-thiazolyl ring is shown. The hydrogen bonding to water is shown by the dashed purple line; hydrogen atoms are draw with arbitrarily small radii.

Table 1. Experimen	tal and calculated	d interatomic	distances	and ang	les in the	e crystal	structure
of <i>bis</i> -TBz							

Demonstern	Lengt	h (Å)	Damanatan	Length	Length (Å)	
Parameter	XRD	DFT	- Parameter	XRD	DFT	
N1-C2	1.386(6)	1,3867	C10–C14	1.342(12)	1,3728	

		Joi	urnal Pre-proof		
N1-C9	1.382(6)	1,3855	C15–C16	1.515(7)	1,5321
N1-C15	1.456(6)	1,4653	C16–C17	1.530(7)	1,532
N3-C2	1.326(6)	1,3186	C17–C171	1.517(10)	1,5331
N3-C4	1.391(7)	1,376	S13-C12	1.699(12)	1,7428
C2C10	1.446(7)	1,4641	S13-C14	1.722(11)	1,7216
C4–C5	1.392(7)	1,4005	N11-C12	1.300(13)	1,2971
C4–C9	1.401(7)	1,4135	C10-N11A	1.363(11)	1,3815
C5–C6	1.392(8)	1,3878	C10-C14A	1.417(13)	1,3728
C6–C7	1.402(8)	1,409	S13A-C12A	1.704(12)	1,7428
C7–C8	1.382(7)	1,3904	S13A-C14A	1.715(12)	1,7216
C8–C9	1.396(7)	1,3966	N11A-C12A	1.305(12)	1,2971
C10-N11	1.381(11)	1,3815			
Daramatar	Angle/°		Daramatar	Angl	e/°
r arameter	XRD	DFT	— Parameter	XRD	DFT
C2-N1-C15	130.5(4)	129,99	N11-C10-C2	122.7(7)	122,72
C9-N1-C2	106.3(4)	105,86	C14–C10–C2	123.7(6)	122,44
C9-N1-C15	123.1(4)	124,13	C14-C10-N11	113.4(8)	114,83
C2-N3-C4	105.2(4)	105,59	N1-C15-C16	113.4(4)	113,1
N1-C2-C10	124.2(4)	125,58	C15-C16-C17	110.9(4)	112,06
N3-C2-N1	112.6(4)	113	C171–C17–C16	113.4(5)	113,15
N3-C2-C10	123.1(5)	121,42	C12-S13-C14	87.7(6)	88,91
N3-C4-C5	129.6(5)	130,06	C12-N11-C10	110.5(11)	111,15
N3-C4-C9	109.8(4)	109,89	N11-C12-S13	116.3(11)	114,89
C5-C4-C9	120.5(5)	120,05	C10-C14-S13	111.9(7)	110,22
C4-C5-C6	117.6(5)	118,02	N11A-C10A-C2A	123.8(7)	122,72
C5-C6-C7	121.2(5)	121,33	C14A-C10A-C2A	116.1(8)	122,44
C8–C7–C6	121.8(5)	121,53	C14A-C10A-N11A	119.7(6)	114,83
C7–C8–C9	116.7(5)	116,94	C12A–S13A–C14A	90.7(7)	88,91
N1-C9-C4	106.1(4)	105,66	C12A-N11A-C10	110.0(11)	111,15
N1-C9-C8	131.7(5)	132,2	N11A-C12A-S13A	116.0(11)	114,89
C8–C9–C4	122.1(5)	122,13	C10-C14A-S13A	107.3(8)	110,22

<sup>1</sup> 1-x, 1-y, 1-z

The lattice is stabilized by a hydrogen-bonding network in *bis*-TBz·0.5 H<sub>2</sub>O (Fig. 2 and SI6; Table 2). The hydrogen bond distances are long and other short contacts in the lattice that may contribute significantly to the lattice stabilization (S13…N11' at 3.16(1) Å; S13…S13' at 3.395(5) Å; and  $\pi$ -stacking at 3.598(8) Å between the imidazole C2 and benzene C8). There is a level 1  $D_1^1(2)$  link between N3 and O-H1A, which by symmetry generates the level 1  $D_2^2(14)$  link at the two ends of the chain-linked 2-benzimidazoles. There is a level 1  $C_1^1(2)$ 

link between O1-H1B and O1' and by extension a level 2  $C_3^3(17)$  link between water molecule at opposite ends of the molecule. Thus, via the bridging water molecules, an extended lattice containing level 2  $R_8^8(28)$  rings form that pack the heterocycles into stacks parallel to the crystallographic *b* axis.



**Figure 2.** Hydrogen bonds *a* between N3 and O1 and *b* between O1 and O1', resulting in level 2  $R_8^8(28)$  rings and extended chains linked to the next stack of *bis*-TBz. The chains of water molecules form helixes around lattice  $2_1$  axes.

Donor-H	d(D-H), Å	d(H…A), Å	<dha, th="" °<=""><th>d(D…A), Å</th><th>Acceptor (sym. gen.)</th></dha,>	d(D…A), Å	Acceptor (sym. gen.)
O1-H1A	0.73(8)	2.24(8)	167(9)	2.957(5)	N3 ( <i>x</i> , <i>y</i> , <i>z</i> )
O1-H1B	0.87(9)	2.859(6)	165(8)	2.859(6)	O1 (- <i>x</i> +2, <i>y</i> +1/2, - <i>z</i> +3/2)

Table 2. Hydrogen bonding parameters in the crystal structure of bis-TBz

# 3.2. NMR spectra analysis

NMR spectroscopy is a powerful technique for structural studies of chemical compounds [28]. The experimental <sup>1</sup>H and <sup>13</sup>C-NMR spectra in DMSO solution of the title compound are shown in Supporting Information (S1, S2, S3). The theoretical NMR spectra of the title molecule are recreated by using B3LYP method and 6-311G++(d,p) as basis set. The <sup>1</sup>H and <sup>13</sup>C experimental and calculated chemical shifts of Bis-TBZ are tabulated in SI4. These chemical shifts obtained experimentally were compared subsequently with those calculated theoretically using optimized molecular structure at DFT/B3LYP/6-311G++(d,p) level of theory using the GIAO method which is one of the most common approaches for calculating nuclear magnetic shielding tensors [29,30]. The linear regressions between the experimental and calculated <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are illustrated in Figure 3(a, b), respectively. It was found that the correlation coefficient (R<sup>2</sup>) value for the proton chemical shifts is

0.9963, while that of carbon chemical shifts is 0.9957. The root mean square (RMS) values of experimental with theoretical (B3LYP/6-311++G(d,p) basis set) <sup>1</sup>H and <sup>13</sup>C chemical shifts were found to be similar,. Atomic numbering for carbon NMR interpretation is given in Scheme 1.

The symmetrical title compound has eight hydrogen atoms attached to benzimidazole rings, four hydrogen atoms attached to thiazole rings and twelve hydrogens linked to the carbon atoms of the alkyl chain. From the <sup>1</sup>H NMR spectrum, a multiplet was observed at 1.22 ppm for two protons corresponding to CH<sub>2</sub> group (C17) of the N-alkyl chain, while the calculated one appeared at 1.58 ppm. Besides, another multiplet appears at 1.67 ppm experimentally for the two protons assigned to CH<sub>2</sub>CH<sub>2</sub> (C16) of the alkyl chain and 1.93 ppm theoretically. A triplet with two protons integral at 4.68 ppm is conveniently assigned to the NCH<sub>2</sub> (C15) linked directly to the nitrogen atom. In general, the chemical shifts of aromatic protons of organic compounds are usually recorded in the range of 7.00–8.00 ppm [31]. A multiplet was raised for the four aromatic protons in the region of 7.25-7.67 ppm which is always assigned to the aromatic ring of benzimidazole [32]. The experimental values were found to be similar with the calculated ones. Further, a doublet at 8.48 ppm was appeared for the SCH<sub>thiazole</sub> proton having a coupling constant of J = 2.1 Hz (Calcd= 8.74 ppm), whereas the doublet signal resonating at 9.28 ppm corresponds to the NCH<sub>thiazole</sub> proton with the same coupling constant (Calcd = 8.97 ppm). Taking the literature into account, these data are in good correlation for structurally similar molecules [33,34].

In the <sup>13</sup>C NMR spectrum, the appearance of thirteen distinct carbon signals confirms the molecular structure of the synthesized compound. The experimental chemical shift value of the carbon atom (C17) attributed to CH<sub>2</sub> group was observed at 25.98 ppm, the signal at 29.99 ppm was assigned to CCH<sub>2</sub> group of *N*-aliphatic chain, while the group NCH<sub>2</sub> (C15) appears at 44.52 ppm. These experimentally observed ppm values are correlated well with the predicted ones. Typically, aromatic carbons give resonances in overlapped areas of the spectrum with chemical shift values > 100 ppm [35]. The chemical shifts of aromatic carbon atoms of benzimidazole ring from C5 to C8 of the Bis-TBz molecule are calculated at 123.4, 126.5, 127.4, 113.5, but observed at 122.88, 122.66, 119.50, and 111.17, respectively. The remaining signals appearing at 123.15, 136.02, 142.87 and 146.82 ppm are assigned for carbon atoms C10, C9, C4 and C2 respectively, the experimentally chemical shifts for the quaternary carbon atoms (nitrogen and sulfur) in the thiazole ring, the carbon atoms

of the thiazole moiety (C12 and C14) have larger <sup>13</sup>C NMR chemical shifts than the other carbon atoms. As a result, the N<u>C</u>S<sub>thiazole</sub> (C12) as well as S<u>C</u>C<sub>thiazole</sub> (C14) show downfield effect and the corresponding experimental chemical shifts were observed at 155.66 and 147.47 ppm, and calculated at 163.3 and 132.4 ppm, respectively. From these data, we can conclude that most of the computed NMR chemical shifts show good agreement with the measured values (Figure 3).



**Figure 3.** The linear regression between the experimental and theoretical  ${}^{1}$ H NMR (a) and  ${}^{13}$ C NMR (b) of synthesized compound.

## 3.3. FT-IR spectra analysis

Infrared spectroscopy has been extensively used for structural determination and provides useful information about the functional groups in the molecular structure under experimental and theoretical studies [21,36]. The Bis-TBZ has N = 58 atoms including nitrogen and sulphur and possesses C<sub>1</sub> point group symmetry, therefore the compound has 168 (3N-6) vibrational normal modes which include 57 stretching, 56 bending, 45 torsion and 10 out-of-plane vibrations. All the 168 fundamental vibrations are IR active modes. The theoretical investigation of the vibrational frequencies for normal modes has been carried out using the DFT method at B3LYP level with 6-311G++(d,p) basis set. The experimental and calculated (unscaled) of some important vibrational frequencies (labeled with the numbers 1–138), and assignments of the normal modes in terms of percent PED of internal coordinates are collected in Table 3. The experimental FT-IR spectra with the corresponding theoretically simulated one displayed various band in the 4000-400  $\text{cm}^{-1}$  frequency region and are shown in Figure 4. It is important to note that all calculated wavenumber values are positive which confirms the stability of the optimized structure of the title molecule. Additionally, the computed wavenumbers belong to gaseous phase of isolated molecular state whereas the experimental ones correspond to solid state spectra. Some bands in theoretical IR spectra were

not observed in the experimental one. Usually, the calculated vibrational wave numbers are higher than their experimental ones for most of the normal modes. As can be seen from Table 2, the computational frequencies are in good agreement with the observed results. The fundamental vibrational assignments for the Bis-TBZ molecule could be discussed in more detail under the following sections:

# **C-H** vibrations

Aromatic rings show multiple weak bands of the C-H stretching vibrations in the region 3112-3035 cm<sup>-1</sup>, which is the characteristic region for ready identification of C-H stretching vibrations[37,38]. These stretching bands were calculated to be found in the range 3154-3025 cm<sup>-1</sup> which are completely consistent with the experimental results. According to the literature, the appearance of aromatic C-H in-plane bending vibrations lies in the range of 1300-1000 cm<sup>-1</sup> [39]. In our present investigation, the C-H in-plane bending vibrations are observed at 1454 and 1359 cm<sup>-1</sup> which are in accordance to the theoretical values ranging between 1441-1084 cm<sup>-1</sup>.

# CH<sub>2</sub> group vibrations

The methylene stretching vibrations are expected in the regions 3000-2900 cm<sup>-1</sup>. Thus, the bands in the region 2927-2858 cm<sup>-1</sup> are attributed to stretching modes of the methylene group (experimentally), while the corresponding theoretical bands are predicted in the region 2962-2891 cm<sup>-1</sup>, which indicates a good agreement with the DFT data. The deformation modes of the methylene group are observed at 1459, 1438, 1435 and 1365 cm<sup>-1</sup> theoretically and at 1471 cm<sup>-1</sup> in the FTIR spectra.

# C-C, C=C vibrations

Generally, the ring C-C and C=C stretching vibrations are highly characteristic of the aromatic ring and usually expected in the range between 1650 to 1200 cm<sup>-1</sup>. For instance, Puviarasan *et al.* [38] assigned carbon-carbon stretching absorption in the region of 1435-1323 cm<sup>-1</sup>. In the present study, the carbon-carbon stretching bands of aromatic rings are observed at 1608, 1583, 1672, 1664, 1581 and 1330 cm<sup>-1</sup>. These stretching bands are calculated to be found in the region 1591-1313 cm<sup>-1</sup>. The CCC in-plane bending vibrations give rise to bands at 1583 and 1058 cm<sup>-1</sup>. In the computed FT–IR spectrum, the CCC in-plane bending vibrations were observed at 1562, 1086, 1065 and 880 cm<sup>-1</sup> with PED contributions of 12-57%.

# C-N, C=N vibrations

The C=N stretching vibrations are usually blended with other bands and can be found in the region of 1616-1618 cm<sup>-1</sup> [40]. In the same context, Ramesh Babu *et al.* [41] assigned the

C=N stretching vibration at 1611 cm<sup>-1</sup>. In this work, the C=N stretching vibrations are observed in variable intensities in the region of 1664-1037 cm<sup>-1</sup>. Their corresponding theoretical wavenumber is calculated between 1469-733 cm<sup>-1</sup> with PED contributions of 10-71%.

# C-S vibrations

Literature survey revealed that the band with a moderate intensity occurring in the region 700-600 cm<sup>-1</sup> correspond to the C-S stretching modes [42]. The C-S stretching vibration is found at 759 cm<sup>-1</sup> in the IR spectrum. This value is in good agreement with calculated value in region 857-755 cm<sup>-1</sup> with a PED between 11-32%. These vibrations are very close to the values reported in literature [43,44].



Figure 4. FTIR spectra of compound bis-TBZ: a) Experimental, b) DFT calculation

**Table 3**. Major observed and calculated vibration frequencies  $(cm^{-1})$  of Bis-TBZ at B3LYP/6-311++G(d, p) level and their assignments.

Mode No	Experimental frequency (cm <sup>-1</sup> )	Calculated frequency (cm <sup>-1</sup> )	Assignments [PED (> %10)]
1	3112 (m)	3154	100 γ(CH)
2	-	3105	99 γ (CH)
3	3082 (w)	3082	93 γ (CH)
4	-	3075	82 γ (CH)
5	-	3064	98 γ(CH)

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6	3056 (w)	3054	94 γ(CH)
7	3035 (w)	3025	92 γ(CH)
8	3001(w)	2966	85 γ(CH)
9	2927 (m)	2962	80 γ(CH)
10	-	2944	96 γ(CH)
11	2858 (m)	2942	91 γ(CH)
12	2709(w)	2931	92 γ(CH)
13	2925 (m)	2919	91 γ(CH)
14	2860 (m)	2911	85 γ(CH)
15	2567 (m)	2897	92 γ(CH)
16	2707 (w)	2891	97 γ(CH)
17	1608(m)	1591	68 γ(CC)
18	1583(w)	1562	11 γ(CC) + 13 β(CCC) + 11 β(CNC)
19	1672(w)	1508	39 γ(CC) + 12 β(NCN)
20	1664(m)	1469	31 γ(NC) + 11 γ(CC)
21	1608(m)	1460	36 γ(CC) + 11 β(HCC)
22	1581 (m)	1459	18 γ(CC) + 11 β(HCC) + 35 β(HCH)
23	1542 (m)	1450	76 β(HCH)
24	1471 (m)	1441	63 β(HCH) + 17 τ(HCNC)
25	1454 (m)	1438	70 β(НСН)
26	-	1435	68 β(HCH)
27	-	1434	76 β(HCH)
28	-	1424	24 β(HCC) + 17 β(HCC)
29	1404 (s)	1408	71 γ(NC)
30	1402 (s)	1407	69 γ(NC)
31	1359 (s)	1365	15 β(HCH) + 54 τ(HCNC)
32	1328 (s)	1362	31 τ(HCNC) + 14 τ(HCCC)
33	1357(m)	1358	21 γ(NC) + 26 β(HCN)
34	-	1334	30 γ(NC)
35	1330(m)	1332	12 γ(CC) + 32 γ(NC)
36	-	1320	60 τ(HCNC)
37	-	1313	25 γ(CC)
38	1301(s)	1311	36 γ(NC)
39	1276(m)	1294	32 γ(NC) + 15 β(HCN)
40	1274(m)	1293	34 γ(NC) + 16 β(HCN)
41	-	1291	48 β(HCC) + 20 τ(HCCN)
42	-	1288	69 β(HCC)
43	-	1280	37 β(HCC) + 12 τ(HCNC)
44	-	1269	14 γ(NC) + 19 β(HCC) + 13 β(HCC)
45	-	1266	22 γ(NC) + 13 τ(HCCN)
46	-	1263	67 τ(HCCN)

		Journal Pre-proo	f
47	1249(m)	1256	18 γ(NC)
48	1246(m)	1233	17 γ(NC) + 12 β(HCN)
49	-	1231	11 γ(NC) + 25 β(HCN)
	-	1223	12 γ(CC) + 19 β(HCN) + 16 β(HCN)
50		1223	+ 12 τ(HCNC)
51	1213(w)	1205	89 τ(HCCN)
52	-	1195	27 β(HCN)
53	1172(m)	1182	27 β(HCN) + 20 τ(HCNC)
54	1147(m)	1154	11 β(HCN) + 25 β(HCS) + 15 β(HCN)
55	-	1142	$p(\pi c N)$ 22 $\beta(\mu c S) \pm 16 \tau(\mu c N c)$
55	_	1142	$22 \beta(HCC) + 10 \beta(HCC)$
50	_	1137	$36 \beta(HCC) + 24 \beta(HCC)$
57	_	1133	20 p(HCC) + 24 p(HCC)
58	_	1113	$11 \gamma(NC) + 19 p(NCC)$
59	_	1086	$16\beta(HCC) + 12\beta(CCC)$
60	_	1080	10 p(nec) + 12 p(eec)
61	1058(m)	1065	$12 \gamma(RC) + 13 \beta(RCC)$
62	-	1041	$42 \gamma(CC) + 44 \beta(CCC)$
63	1037(s)	1041	14 $\gamma(NC)$ + 40 $\beta(HCS)$
64	-	1038	$15 \gamma(NC) + 40 p(HCS)$
65	1004(m)	1023	84 y(CC)
66	-	1011	$81 \gamma(CC)$
67		992	$21 \gamma(CC) + 11 p(HCC) + 11 p(CCN)$
68	_	979	$67 \gamma(CC) + 21 p(CCN)$
69		971	$30 p(HCC) + 20 n(HCCC) + 11  \tau(HCNC)$
70		968	85 2((())
70	<u>J</u>	939	$54 \tau$ (HCCC) + 14 $\tau$ (CCCN)
71 72	918(m)	912	26 B(CNC)
72	-	905	$74 \tau$ (HCCC)
73	-	901	$12 \gamma(NC) + 33 \beta(CNC)$
74 75	889(m)	882	$53 \beta(CNC)$
75	-	880	$57 \beta(CCC)$
70 רר	-	857	$28 \sqrt{SC} + 11 \beta(CCN) + 11 \beta(CCN)$
//	_	037	$32 \sqrt{SC} + 16 \beta(CNC) + 13 \beta(CCN) + 16 \beta(CNC) + 16 \beta(CNC) + 16 \beta(CNC) + 16 \beta(CCN) + 16 \beta($
78		854	13 β(CCN)
79	-	848	32 β(CNC) + 27 τ(HCNC)
80	829(s)	821	76 τ(HCCC) + 13 ω(CCNC)
81	-	802	11 γ(SC) + 11 β(CNC)
82	784(m)	794	87 τ(HCNC)
83	-	762	14 γ(SC) + 16 β(HCC) + 22 τ(HCNC)

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84	759(w)	755	19 γ(SC) + 16 β(CNC)
85	-	745	61 ω(CCNC)
86	-	742	20 γ(NC)
87	-	736	11 γ(NC) + 20 τ(HCNC)
88	-	734	51 τ(HCSC) + 11 ω(CCNC)
89	-	733	10 γ(NC) + 21 τ(HCNC)
90	729(vs)	722	68 τ(HCCC)
91	-	716	12 β(HCC) + 70 τ(HCCN)
92	-	707	21 β(HCC) + 67 τ(HCCC)
93	-	701	39 τ(HCNC) + 11 ω(CCNC)
	-	701	30 $\tau$ (HCSC) + 11 $\tau$ (CCCS) + 13
94		701	ω(CCNC)
95	651(w)	639	68 ω(CCNC)
96	632(w)	638	51 ω(CCNC)
97	615(w)	617	57 β(CCS)
98	-	601	11 γ(CC) + 11 β(CNC) + 11 β(CCN)
99	-	596	16 γ(CC) + 11 β(CNC)
100	-	572	11 $\beta$ (CCN) + 12 $\beta$ (CCN)
101	-	572	51 β(CCN)
102	-	569	33 τ(CCCN)
103	-	568	38 τ(CCCN)
104	-	559	12 $\beta$ (CCC) + 17 $\beta$ (CCC)
105	-	556	14 β(CCC)
	-	483	16 β(CCC) + 47 τ(CCNC) + 11
106		105	ω(CNNC)
107		478	61 τ(CCNC)
108	<u> </u>	463	46 β(CCC)
109	-	426	11 τ(HCCC) + 54 ω(CCNC)
110	-	423	12 τ(HCCC) + 61 ω(CCNC)
111	-	393	23 β(CCN)
112	-	391	69 β(CCC)
113	-	341	31 ω(CNNC)
114	-	326	31 ω(CNNC)
115	-	317	23 β(CNC) + 38 τ(CCCS)
116	-	306	21 $\beta$ (CNC) + 12 $\tau$ (CCCS)
117	-	294	42 β(CNC)
118	-	289	31 β(CCN)
119	-	279	18 τ(NCCN) + 26 ω(CCCN)
120	-	276	32 γ(CC)
121	-	221	23 ω(CCNC) + 11 τ(CCCC) + 14 τ(CCCN)

		Journal Pre-proo	f
122	-	191	57 β(CCC)
123	-	186	71 τ(CCCS)
124	-	146	16 γ(CC) + 11 β(CCN) + 16 β(CCC)
125	-	145	37 τ(HCCN) + 51 τ(CCCC)
126	-	130	65 τ(CCCC)
127	-	113	60 β(CCN)
128	-	96	25 β(CCN) + 11 τ(NCCN)
129	-	94	23 β(CCC) + 15 τ(CNCN) + 12 ω(CCCN)
130	-	86	15 τ(HCNC) + 57 τ(CNCC)
131	-	65	65 τ(CNCC)
132	-	58	60 ω(CNNC)
133	-	57	62 τ(CCCN)
134	-	45	12 β(CCC) + 27 τ(NCCN) + 14 τ(NCCN)
135	-	36	32 β(CCC) + 47 τ(NCCN)
136	-	24	36 τ(NCCN)
137	-	18	36 β(CCC) + 33 τ(NCCN)
138	-	17	53 τ(CNCC)

 $\gamma$ -stretching,  $\beta$ -bending,  $\tau$ -torsion,  $\omega$ -out of plane, vs-very strong, s-strong, m-medium, w-weak, potential energy distribution (PED  $\geq 10\%$ ) is given in brackets in the assignment column.

# 3.4. HOMO-LUMO analysis

Generally speaking, the frontier molecular orbitals called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), are the main orbitals that take part in chemical stability [48]. These orbitals are the key parameter in determining the molecular properties as well as predicting the most reactive position in  $\pi$ -electron system [49]. The HOMO energy represents the ability to donate an electron whereas the LUMO designates the electron accepting ability. The LUMO-HOMO energy gap is the most important parameter for the chemical reactivity which explains the charge transfer interaction within the molecule and its chemical hardness [50]. A molecule with a small LUMO-HOMO energy gap is generally associated with a high chemical reactivity, therefore an easier electron transfers from HOMO to LUMO orbital. Higher LUMO-HOMO gap means high stability for the molecule, thus less reactivity [51,52]. To evaluate the energies behavior of the title compound, The HOMO, LUMO and the energy gap have been calculated by B3LYP level

with 6-311G++(d,p) method. The atomic orbital of LUMO-HOMO diagram are shown in Figure 2. In this title compound. HOMO and LUMO are calculated about -6.02 eV and -1.67 eV, respectively. HOMO orbital is accumulated on the benzimidazole ring and a bit in thiazole ring. In case of LUMO the charge density is confined mainly over the thiazole ring and slightly on the benzimidazole ring. However, neither LUMO nor HOMO are located at alkyl chain, indicating low reactivity of this part of the molecule. In this regard, the large energy gap of 4.35 eV for the Bis-TBZ shows that it would be less chemically reactive and thermodynamically stable.



Figure 5. The atomic orbital compositions of the frontier molecular orbital for Bis-TBZ compound

# 4. Conclusion

In the present contribution, we report the design and synthesis of a novel bis-ligand based on thiabendazole under phase-transfer conditions with high yield. The synthesized compound was characterized by FT-IR, <sup>1</sup>H & <sup>13</sup>C NMR and single crystal X-ray diffraction. The structure of the product was studied using the computational method of DFT/B3LYP with the 6-311++G (d, p) basis set, with full optimization of the molecular structure. The optimized

geometric parameters (bond lengths and bond angles) are theoretically determined and compared with the experimental ones. The theoretical vibrational frequencies of the fundamental modes of Biz-TBZ was assigned, analyzed and then compared with the experimental vibrations. In addition, the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts have been calculated by GIAO method in DMSO and compared with the experimental ones. All the DFT results indicates overall good agreement with the experimental measurements. HOMO and LUMO analysis was also used to determine the charge transfer within the molecules. This study provides a detail investigation of the structural and physicochemical properties of the thiabendazole compound by combining experimental and theoretical approaches. According to their excellent biological properties reported in the literature, furthermore from the results obtained in this study, the title compound derivatives can be used in biological field as well as in manufacturing of new materials.

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# Highlights

- 6-bis(2-(thiazol-4-yl)-benzimidazol-1-yl)hexane was synthesized by alkylation.
- The structure was characterized by FT-IR, <sup>1</sup>H & <sup>13</sup>C NMR and single crystal XRD.
- DFT/B3LYP with 6-311++G (d,p) basis allowed attribution of the vibration spectrum.
- HOMO-LUMO analysis was used to determine the charge transfer within the molecules.

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#### **Declaration of interests**

 $\boxtimes$  The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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