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Recent Advancements in Bismuth Complexes: Computational Strategies for Biological Activities †

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Abstract: Bismuth (Bi) and its compounds are generally recognized for their biological safety and non-toxicity, making them highly valuable for the large-scale synthesis of various Bi-based complexes for their use in diverse biological applications. Bi drugs are among the few antimicrobial agents that have not developed drug resistance and have a synergistic effect with antibiotics. Studies have established that the biological activities of Bi complexes are influenced by the properties and positions of the substituted groups on ligand. Even slight modifications have profound effects on their efficacy. Computational methods, such as Density Functional Theory (DFT) and Molecular Docking (MD) offer a greener approach and provide detailed information into the structure, stability, and reactivity of compounds. This review presents insights into the factors influencing the biological activity of Bi complexes through computational techniques.

Keywords: bismuth complexes; computational studies; biological application; DFT

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1. Introduction

Bi is a heavy metal with unique properties, such as low toxicity, high biological safety, and minimal side effects, making it highly suitable for pharmaceutical applications [1]. Bismuth-subsalicylate is a Bi-based compound that is widely used for gastrointestinal disorders [2]. Research has highlighted the potential of Bi compounds in combating drug-resistant bacteria, cancer, and other diseases, further expanding its biomedical significance [3,4]. An increasing number of Bi complexes were investigated for the treatment of several diseases, such as cancer, fungal and bacterial infections, and in each case, the therapy showed good and desirable efficacy as well as unexpectedly low toxicity [5].

Bi predominantly exists in the +3 and +5 oxidation states and forms stable complexes with a broad range of ligands, including nitrogen, oxygen, and sulfur donors [6]. Common ligands in Bi complexes include Schiff bases, thiols, carboxylates, and nitrogen-containing heterocycles. Bismuth–thiol complexes have demonstrated strong activity against *Helicobacter pylori* (*H. pylori*) [7]. Complexes with thiosemicarbazones (TSCs) showed increased antibacterial activity against various Gram-positive and Gram-negative bacteria [8,9]. Bi hydrazone complexes are also extensively studied for their antimicrobial properties and have shown significant antitumor activity against human lung cancer cell lines [10]. The Bi(III)

complexes containing asymmetric [NN'O] ligands exhibited significant cytotoxicity against chronic myelogenous leukemia cells and demonstrated strong activity against several bacterial strains [11]. Study report that Bi complexes with carboxylates exhibit significant antileishmanial activity [12]. The ligand environment plays a critical role in determining the geometry of Bi complexes, which can adopt distorted tetrahedral, trigonal bipyramidal, or octahedral configurations. Modifications in ligand structure, through the addition or replacement of substituents, can alter the biological activities of Bi complexes. This study introduces an innovative strategy to enhance the antimicrobial activity of Bismuth–thiolato complexes by substituting hydrocarbon ligands with mercaptocarborane ligands. It demonstrates that such ligand modifications can significantly improve antimicrobial efficacy against *S. aureus*, offering valuable insights for the design of more effective Bi-based therapeutic agents [13]. Similarly, Jia et al. designed four Bi(III) 2-thiazolecarboxaldehyde thiosemicarbazone complexes (C1–C4) with distinct N-4 substitutions. A structure–activity relationship analysis indicated that the C4 complex exhibited the strongest antitumor activity, suppressing tumor growth by inhibiting apoptosis and angiogenesis while causing minimal side effects [14]. These findings demonstrated the critical role of ligand design in optimizing the biological efficacy of Bi complexes.

Computational methods, particularly DFT, have played a pivotal role in understanding the properties of Bi complexes. DFT studies provide insights into their stable geometries, electronic structures, and vibrational properties, which are often in agreement with experimental findings [15,16]. Computational approaches are not only cost-effective and time-saving, but also enable a deeper understanding of the structure–property relationships in Bi complexes, facilitating the rational design of more potent therapeutic agents [17]. This review discusses a computational approach to the structural, electronic, and biological aspects of Bi complexes, emphasizing the role of ligands in drug discovery.

2. Biological Activities of Bismuth Complexes

In recent years, research on Bi complexes has expanded beyond gastrointestinal treatments to explore their broader therapeutic potential. Studies have demonstrated that Bi complexes exhibit antibacterial, antifungal, antiviral, antileishmanial, and anticancer properties. Some recently synthesized Bi complexes and their biological activities are described in Table 1.

Table 1. Some recently synthesized Bi complexes and their biological activities.

S.No.	Bi Complex	Ligand	Biological Activity	Ref.
1.	Bi(III) flavonolate, $[BiPh(L_1)_2]$	Flavonolate (L_1)	Antibacterial	[18]
2.	Di-Aryl Bi phosphinates, $[BiAr_2(O(O)PRR')]$	Ar, R or R′ = phenyl, ortho-methoxyphenyl, meta-methoxyphenyl, meta-tolyl and para-tolyl	Antibacterial and Anticancer	[19]
3.	Heteroleptic triorganobismuth(V) biscarboxylates of type $[BiR_3(O_2CR')_2]$	R = C_6H_5 and p-$CH_3C_6H_4$R′= bicarboxylates	Antileishmanial	[12]
4.	Bi(III) dithiocarbamate derivative	Diethyldithiocarbamate	Anticancer	[20]
5.	Bi(III)imidazolidine-2-thione	Imidazolidine-2-thione	Anticancer	[21]
6.	Dithia-heterocycles of Bi(III) with dithiocarbamates.	Pyrrolidineditiocarbamate of dithia-bismolane, bismane, oxodithia- and trithia-bismocane	Antibacterial and Antiproliferative	[22]

Table 1. *Cont.*

S.No.	Bi Complex	Ligand	Biological Activity	Ref.
7.	Homoleptic Bi(III)dithiocarbamates	Dithiocarbamate derivatives	Antileishmanial	[23]
8.	Heteroleptic six-coordinate Bi(III) complexes.	2-acetylthiophene TSCs	Antiproliferative and Antibacterial	[8]
9.	Bi(III) complex [$BiLCl_2$]	L = Quinoline-2-carboxaldehyde-N4-phenyl-3-thiosemicarbazone	Antibacterial	[9]

2.1. Antibacterial

Various studies on Bi complexes have been carried out and their results have established Bi complexes as potential drugs for Gram-positive and Gram-negative bacteria [24]. Liam et al. have established Bi as an alternative drug to combat antibacterial drug resistance [25]. The group synthesized and characterized a number of Bi–thiolate and Bi–mixed ligand thiolate complexes. TSC was reported to have antibacterial activity. Its activity against *S. aureus*, *S. epidermidis*, and *E. faecalis* was found to increase manyfold on complexation with Bi(III). These biological studies observed that the BiL_3 type of complexes are inactive, whereas the mixed-ligand complexes showed cytotoxic activity through their binding to the cell membrane of the microbes [25]. Almeida et al. demonstrated the antimicrobial activity of Bi–pyrazine formamide-TSC complexes [26]. Ozturk et al. synthesized supramolecular Bi(III) halide complexes with organic moieties 5-ethoxy-2-mercaptobenzimidazole, 5-methoxy-2-mercaptobenzimidazole and *N*-methyl benzothiazole, and their research group was the first to establish a cis sulfur arrangement in di-nuclear bridged Bi complexes. These microbial complexes were reported to be active for *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923, and *E. faecalis* ATCC 29212 bacteria [27].

2.2. Antiviral

Yang and his co-workers demonstrated the effective inhibition of the nucleoside triphosphate hydrolase by ranitidine bismuth citrate (RBC). This Bi-compound is reported to lower the replication of SARS coronavirus (SCV) helicase by uncoiling the DNA strands of affected cells, thus causing cell decay [28]. Marrone et al. employed a multilevel computational approach to investigate the antiviral mechanism of bismuth drugs. Their findings indicate that the substitution of Zn^{2+} with Bi^{3+} in non-structural protein 13 (nsp13) induces structural changes that alter its geometrical and ionization properties. These modifications weaken the interaction between nsp13 and nsp12, thereby disrupting viral replication and the infection mechanism of SARS-CoV-2 [29]. Dawara et al. reported on the complex ($[Cl_2Bi(L_2)]$) with the ligand 3-acetylcoumarinTSC (L_2) (Figure 1). This complex was found to exhibit pesticidal activity against *Corcyra cephalonica* [30].

Lessa et al. synthesized TSCs and bis(TSCs) complexes of Bi and demonstrated the enhanced antibacterial activity of these complexes against *S. aureus*, *S. epidermidis*, *E. faecalis*, and *P. aeruginosa* [31].

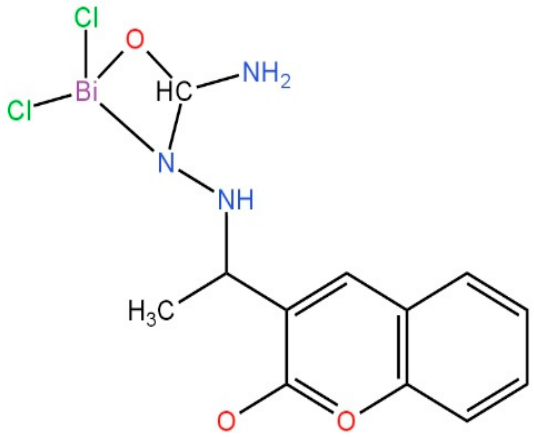


Figure 1. Structure of $[Cl_2Bi(L_2)]$ complex.

2.3. Antileishmanial

Lizarazo et al. synthesized Bi complexes with ligand dipyrido[3,2-a:2′,3′-c]phenazine (dppz). These complexes were found to inhibit the activity of Leishmania strains by binding to the DNA of affected cells [32]. Ong and his research group synthesized a series of carboxylate complexes of Bi(V) with the general formula $[BiPh_3(O_2CR)_2]$. The activity studies of these complexes established their strong cytotoxicity for Leishmania major promastigotes and human fibroblasts [33]. Triphenyl Bi, on complexation with acetylsalicylic acid and 3-acetoxybenzoic acid, was reported to exhibit good antileishmanial and antibacterial activities with decreased toxicity toward murine macrophages [34]. Homoleptic Bi(III) dithiocarbamates were investigated for their antileishmanial activity. The presence of electron-donating or -withdrawing substituents on the dithiocarbamate ligands modulates the electronic properties of the Bi(III) center, affecting its interaction with biological targets. Structure–activity relationship studies indicate that aryl-substituted dithiocarbamates exhibit enhanced stability and prolonged activity, whereas alkyl-substituted derivatives demonstrate improved membrane permeability [23].

2.4. Anticancer

The cytotoxic activity of the Bi(III)-sulphapyridine complex, with the general formula $[BiCl_3(C_{11}H_{11}N_3O_2S)_3]$ (Figure 2), was reported to be notably higher against cell lines *S. typhimurium*, *S. aureus*, *S. dysenteriae*, *S. sonnei*, *P. aeruginosa*, and *E. coli*, and to reduce the growth of leukemia cells [35].

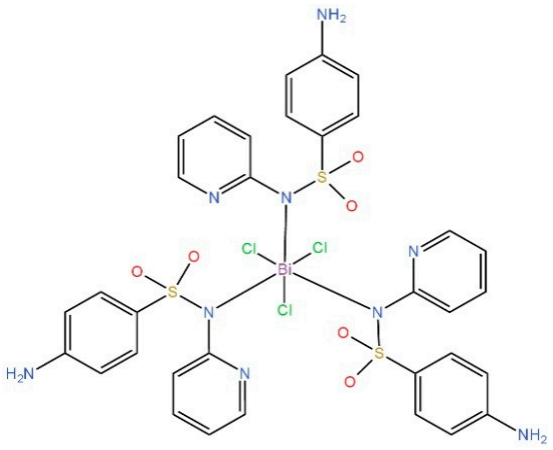


Figure 2. Structure of Bi(III)-sulphapyridine complex $[BiCl_3(C_{11}H_{11}N_3O_2S)_3]$.

Islam et al. synthesized novel Bi complexes with 2-acetylbenzoic acid, 4-acetylbenzoic acid, and 5-acetylsalicylic acid. These complexes were reported to be cytotoxic for cancerous malignant leukemia K562 and B16F10 and murine fibroblasts, L929 and murine melanocytes (Melan-A) [36]. Yang et al. revealed that blending the antitumor drug 6-Mercaptopurine (6-MP) with trivalent Bi enhances the anticancer activity 6-MP [37]. Ouyang et al. explored various novel complexes of Bi with organic and inorganic ligands. The group synthesized Bi–mixed-ligand complexes using the one-pot method and, later, in 2017, synthesized Bi(III) -2,6-pyridinedicarboxaldehyde bis(4*N*-methylTSC). Both in vitro and in vivo studies of biological assays proved these complexes to exhibit anticancer activity against human lung cancer cell lines A549 and H460 and, due to their nontoxic nature, they are considered safe drugs [38,39]. The evaluation of the IC_{50} values of some novel Bi(III) aromatic TSC complexes suggested them to be better inhibitors of lipoxygenase with low toxicity compared to cisplatin [40]. Adeyemi and his co-workers established the high potential anticancer activity of Bi–dithiocarbamate complexes [41].

3. Computational Approaches in Bismuth Complexes Research

Computational chemistry has become a vital tool in the study and design of metal complexes, complementing experimental methods by providing deeper insights into their electronic structure, stability, and reactivity. These methods help in understanding how variations in ligand structure and complex geometry influence biological activity [15,42]. The most commonly used computational techniques in metal complexes research include DFT, MD, and Molecular Dynamics Simulations (MDS).

Computational approaches, particularly MD and DFT calculations, are integral to understanding the structure–property relationships of Bi complexes. In a study involving Bi(III) complexes with substituted hydrazones, both experimental synthesis and computational evaluations were performed to explore their potential biological applications. The geometry of the synthesized Bi(III) complexes reveals key parameters such as bond lengths and bond angles [43]. Shorter bond lengths typically indicate stronger coordination, which enhances the rigidity and structural integrity of the complex, improving its binding affinity with biological targets [44]. The Bi–O bond lengths in the complexes ranged from 2.1 to 2.4 Å, indicating strong coordination between Bi and the oxygen donor atoms of the ligand. A shorter Bi–O bond may increase the ability of the complex to coordinate with oxygen-containing functional groups in enzymes, enhancing their inhibitory activity [43]. Bond angles around the Bi center define the overall geometry of the complex (e.g., tetrahedral, trigonal bipyramidal, or octahedral). The geometry directly influences the steric compatibility of the complex with the binding pocket of a biological target. Proper bond angles allow the ligand to orient functional groups into optimal positions for interaction with amino acid residues in the target's active site [45]. The Bi–N–C bond angles observed in the range from 115° to 125° might fit perfectly into an enzyme's active site, leading to an enhanced inhibitory action. DFT calculations provided insight into the electronic properties of the complexes. The HOMO-LUMO gap, which indicates the stability and reactivity of the molecules, ranged from 3.5 to 4.0 eV. A smaller gap correlates with higher reactivity, suggesting that these complexes could have an enhanced interaction potential with biomolecules such as enzymes and DNA [46]. MD simulations were performed to evaluate the binding energy of the Bi complexes with a target protein. The docking results revealed binding energies in the range of −6.5 to −8.2 kcal/mol, indicating strong binding interactions. The complexes primarily interacted with the active sites of the protein through hydrogen bonding and metal–ligand coordination, which are key to their biological activity. The docking results highlighted that critical hydrogen bonds formed between the Bi

complexes and amino acid residues like Aspartic Acid (Asp) and Histidine (His), which contribute to enzyme inhibition [43].

In another study, researchers employed both experimental and computational methods to investigate the interaction between a binuclear Bi(III) complex and bovine liver catalase (BLC). MD simulations revealed that the Bi complex binds to BLC with significant affinity, exhibiting binding energies ranging from approximately −40.6 to −34.7 kJ/mol across nine poses. The most favorable binding conformation demonstrated an affinity of −40.6 kJ/mol. These interactions were primarily stabilized through hydrogen bonds with residues such as ALA122, THR124, and ARG126, as well as van der Waals interactions with residues including VAL125, ILE204, ALA249, and ALA253 (Figure 3).

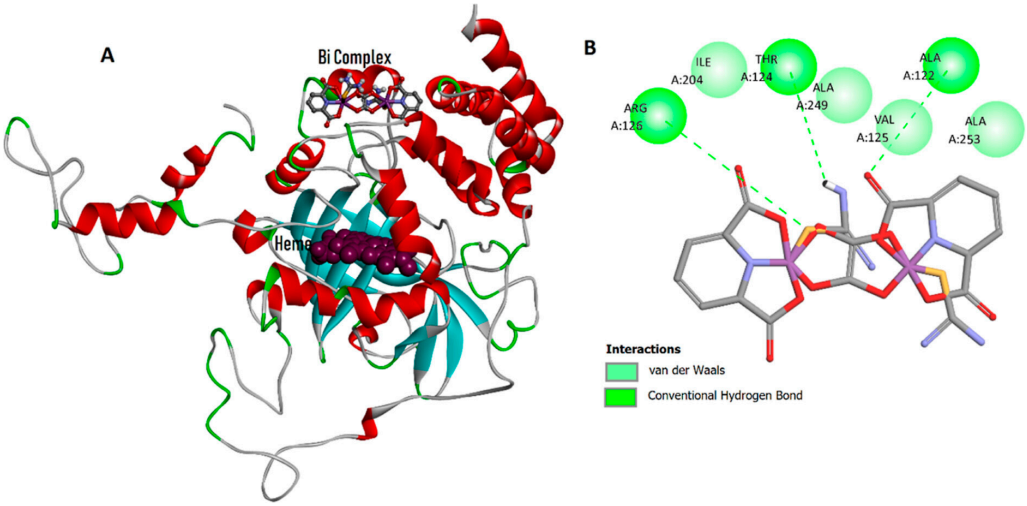


Figure 3. (**A**) Representation of the binding sites of the Bi complex on BLC; (**B**) 2D visualization of the docking interactions between the Bi complex and BLC.

Fluorescence quenching studies indicated that the Bi complex interacts with BLC via a static quenching mechanism, suggesting the formation of a stable Bi complex–BLC adduct. The complex demonstrated significant antioxidant activity (Figure 4) by enhancing the catalytic efficiency of BLC in decomposing hydrogen peroxide, increasing its activity by up to 39.2% at a concentration of 4.55 × 10^{-7} M (Figure 5) [47].

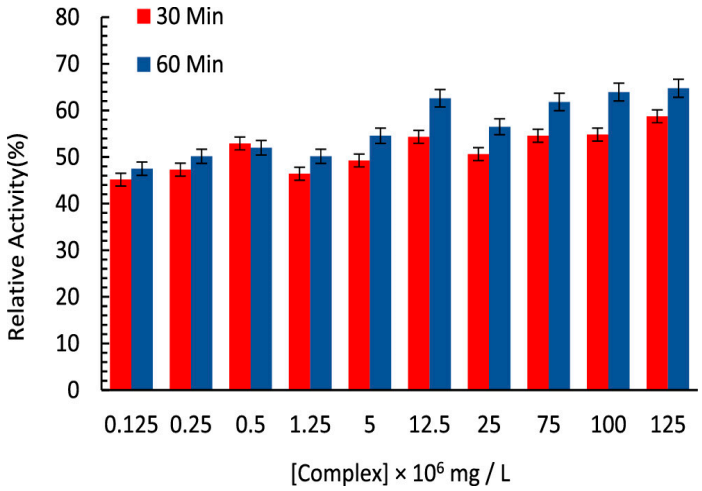


Figure 4. Antioxidant activity of the Bi complex at different concentrations.

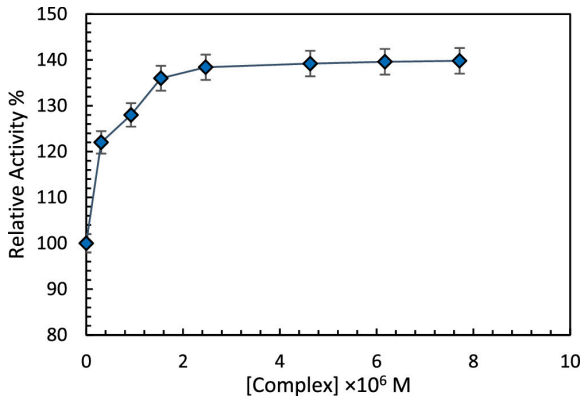


Figure 5. Variations in BLC activity influenced by the Bi complex. [BLC]: 1.0×10^{-8} M; [Bi complex]: 0–8.0×10^{-6} M.

The study on Bioactive heteroleptic Bi(V) complexes highlights the role of experimental and computational methods in understanding the structure–activity relationships of the complexes. DFT calculations and XRD analysis revealed key structural parameters, with Bi–O bond lengths of 2.05–2.12 Å and Bi–N bond lengths of 2.28–2.35 Å, indicating strong coordination and stability. The HOMO-LUMO gap, calculated at 3.1–3.8 eV, demonstrated moderate reactivity suitable for biological applications. MD showed binding energies of -6.7 to -8.1 kcal/mol, indicating strong interactions like hydrogen bonding and π-π stacking. This study exemplifies how computational approaches complement experimental methods in optimizing Bi complexes for enhanced biological activity [48].

These studies have demonstrated that ligand substitution significantly influence both the geometry and biological properties of Bi complexes. By introducing different functional groups to the ligands, the electronic environment around the Bi center can be modulated, resulting in changes in reactivity and binding efficiency. Complexes with electron-donating groups exhibited higher binding affinities (lower ΔG values), indicating that ligand modification can enhance biological efficacy [49,50].

4. Conclusions

Bi complexes have shown significant promise in medicinal chemistry due to their low toxicity, high biological safety, and broad spectrum of biological activities. Both experimental and computational studies emphasize the critical role of ligand design, geometry, and electronic properties in enhancing biological efficacy. Computational approaches such as DFT, MD, and MDS have proven invaluable in understanding and predicting the behavior of these complexes. These methods provide insights into the mechanistic pathways for biological activity, such as enzyme inhibition or DNA binding, which are often challenging to capture experimentally. The combination of experimental and computational methods has the potential to speed up the exploration of Bi complexes in the search for novel drugs.

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