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Original Research

Computer-Aided Study on Metal Complexes with Benzohydrazide Schiff Base as Potential Bacterial and Fungi Inhibitors

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Abstract

The biochemical properties of metal complexes containing benzo hydrazide Schiff base have been reported by numerous researchers worldwide in various ways. In this work, the evaluation of biochemical roles of the metal complexes with benzo hydrazide Schiff base activity as anti-gram positive and gram-negative bacteria, as well as antifungal agents, were observed. The use of various techniques, including the induced fit docking methodology, the density functional theory method, and pharmacokinetics investigations with the ADMETsar software, this work has shown the antibacterial and antifungal properties of the examined

compounds have been observed to enhance the novelty of work. Thus, the non-bonding interaction between the studied ligands and *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m), Gram Negative Bacteria (GNCA) Class A beta-lactamase (PDB ID: 5fqm), and fungal 1,3-beta-glucan synthase (PDB ID: 8jzn) was investigated using molecular operating environment (MOE) software. The optimization of the studied compounds was carried out using the density functional theory method via Spartan 14 software. Furthermore, the ADMETSar software was used to carry out the pharmacokinetics. Compound M4 outperformed the other compounds in this experiment in terms of HOMO energy interaction. Also, regarding energy gap and electron acceptance from neighboring molecules, compound M2 had a higher propensity than the other compounds under investigation. Moreover, compound M6 showed the most significant potential to inhibit all the investigated targets compared to the reference molecule and the other studied compounds using the molecular modeling method. In addition, the ability of compound M6 to function as a drug-like agent was demonstrated by the ADMET research when compared with the reference compound.

Keywords
Metal; complex; benzohydrazide; docking; drug-like

1. Introduction

Bacteria are living creatures that exist freely, and they are also considered by many researchers to be universal [1, 2]. Bacteria have a single biological cell and have been reported to establish a vast area of prokaryotic microbes [3, 4]. They could be found in various areas such as radioactive leftover materials, soil, water etc. [5]. More so, the roles of multiple forms of antibiotics to combat microbial activities in human beings have been reported by several scientists [6, 7]; yet, the unpleasant role that is being played by bacterial in everyday activities of human beings calls for urgent attention to curb this menace [8]. According to Li *et al*., 2024, antibiotic-resistant pathogens (ABRP) have been observed to pose dangerous coercions to human life [9] due to the continuous hindrance of efficient antibiotic agents.

More so, 1,3-Beta-glucan synthase is crucial in producing beta-glucan in fungi by catalyzing glucosyltransferase reactions [10]. Several scientists have used this enzyme as a drug target which has resulted to the development of various drug-like agents [11, 12]. According to CAZy (carbohydrate-active enzyme database) classification, the glycosyltransferase 48 family encompasses fungi and many other plants such as 1,3-beta-glucan synthase constituents, and this comprises Gls1, Gls2, and Gls3, which originated from yeast [13]. According to Meetei *et al*., 2016, this enzyme can catalyze the creation of a beta-1,3-glucan polymer, which remains a crucial constituent of the fungal cell wall [14].

According to numerous experts, inorganic compounds have been reported to be responsible for critical biological processes like immune response, energy production, metabolism, and cell signaling in the human system [15, 16]. Benzoylhydrazide derivatives have drawn the attention of many researchers in various fields due to their high level of biological activities and capacity to

react with neighboring compounds [17, 18]. As reported by Konovalova *et al*., 2020, numerous benzohydrazide derivatives showed the ability to inhibit many diseases, such as cancer, bacteria, fungi, etc. [19]. Furthermore, they exhibited photoprotective, antioxidant, and anti-tubercular activities, etc. [20]. More so, the human body has benefited from the activities of various metal ions, and researchers have focused on using these metal ions due to their crucial properties [21-23]. A lack of specific metal ions can cause diseases such as pernicious anemia due to iron deficiency, growth retardation from inadequate zinc intake, and heart problems in infants linked to a deficiency in copper. Also, the rise of antibiotic resistance is escalating rapidly, leading to a significant decline in the effectiveness of antibiotics against both Gram-negative and Gram-positive bacteria. Therefore, there is an urgent need to develop new compounds that not only exhibit a broad range of efficacy but also utilize novel mechanisms of action [24, 25]. Thus, the metal complexes with benzohydrazide Schiff base are expected to play crucial roles as antibacterial and antifungal agents. Therefore, this work aims to evaluate the biochemical roles of the metal complexes with benzo hydrazide Schiff base activity as anti-gram-positive and gram-negative bacteria and antifungal agents.

2. Methodology

2.1 Electronic-Based Descriptors Calculation via DFT Method

The structure of the studied compounds, which were synthesized by Pallai *et al*., 2024 [26], was modeled in a two-dimensional format using ChemDraw 22.2.0 via 32-bit software. The correctness of the structures was ascertained before they were transformed into a three-dimensional format. The studied compounds were optimized in the gap phase via Spartan 14 software [27] (Figure 1), and the completed optimization of the investigated compounds generated various electronic descriptors, which revealed the features of individual ligands.

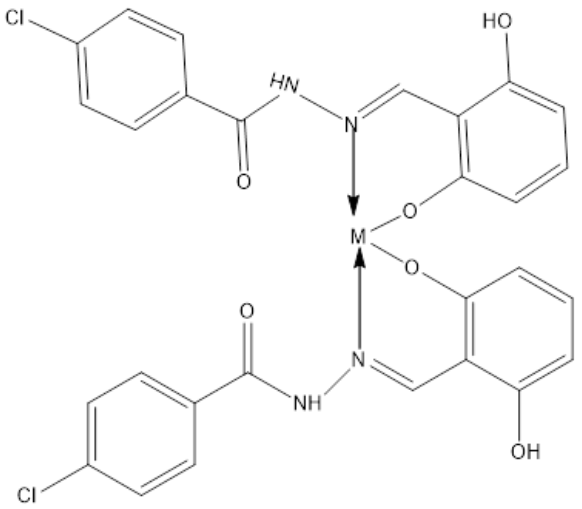


Figure 1 Two-dimensional structures of the studied compounds. M = Fe(M1); Co(M2); Ni(M3); Pd(M4); Cu(M5); Zn(M6); Cd(M7); Hg(M8); Mn(M9).

2.2 Induced Fit Docking Analysis

The inhibiting capability of individual studied compound against *Staphylococcus aureus* glutamine amidotransferase GatD (for gram-positive bacteria) (PDB ID: 5n9m) [28], Gram Negative Bacteria (GNCA) Class A beta-lactamase (for gram-negative bacteria) (PDB ID: 5fqm) [29] and fungal 1,3-beta-glucan synthase (for fungi) (PDB ID: 8jzn) [30] were examined using molecular operating environment (MOE) software [31]. The receptors were retrieved from the protein data bank and subjected to MOE software to remove impurities from the targets. The downloaded receptors were optimized to repair every possible breakage, and the binding sites for individual receptors were located and set for docking calculation using the quick prep tool before saving it in. more format. More so, the studied metal complexes with benzohydrazide Schiff base were optimized and saved in moe format before docking calculation. In this work, the induced fit docking method was selected for the calculation, and the output was saved in .mdb format before interpretation.

2.3 Pharmacokinetic Study of Studied Metal Complexes with Benzohydrazide Schiff Base

The Lipinski rule of five features and other pharmacokinetic properties for compound M6 and the referenced compounds were observed and documented. To perform this analysis, ADMETSar 1 was utilized, and the results were accurately presented.

3. Results and Discussion

3.1 Calculated Descriptors for Optimized Metal Complexes with Benzohydrazide Schiff Base

Nine studied compounds were optimized, and the various descriptors were retrieved from the optimized compounds. According to reports in Table 1, the highest occupied molecular orbital energy (HOMO energy) describes the strength of any reacting molecules to donate electrons to any compounds with the ability to receive to establish a reaction. More so, compound M4 with -5.26 eV exhibited a more extraordinary potential ability to donate electrons than other studied compounds. As shown in Table 1, this ability to donate electrons compared to other studied compounds could be attributed to the presence of palladium (Pd) in the studied parent compound.

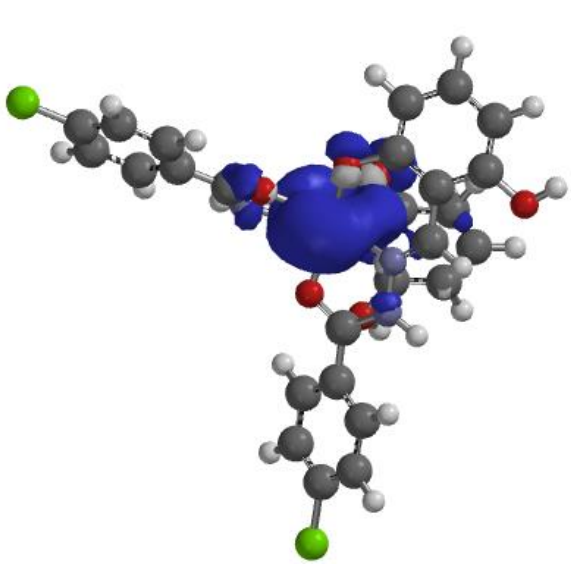
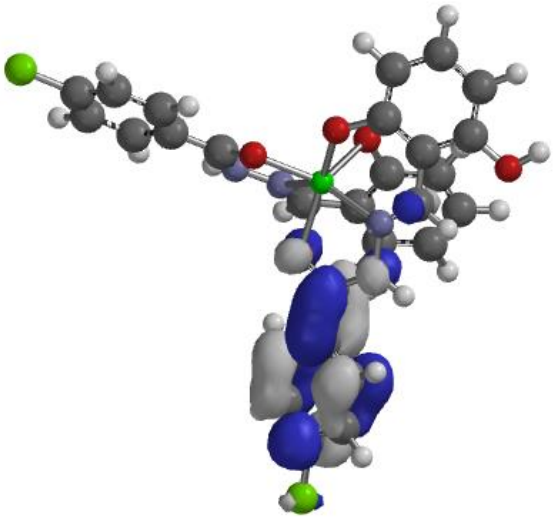
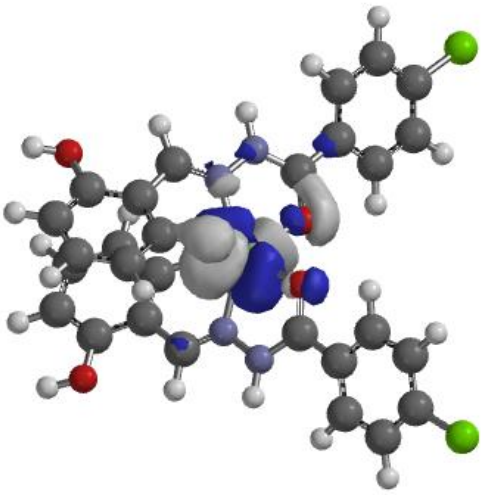
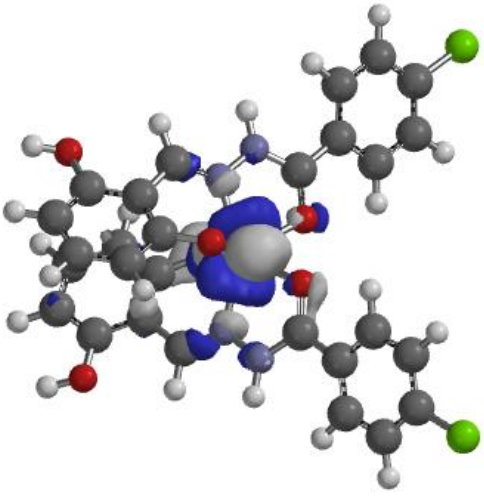
Table 1 Calculated descriptors for studied heterocyclic compounds.

	HOMO (eV)	LUMO (eV)	EG (eV)	MW (amu)	PSA	OVA	HBD	HBA
M1	-6.12	-1.43	4.69	635.243	109.878	1.75	4	10
M2	-6.59	-3.07	3.52	638.329	112.265	1.76	4	10
M3	-7.25	-1.22	6.03	638.086	115.366	1.76	4	10
M4	-5.26	-1.32	3.94	685.816	97.983	1.67	4	10
M5	-7.96	-1.23	6.73	642.942	109.013	1.74	4	10
M6	-7.96	-1.80	6.16	644.786	117.017	1.78	4	10
M7	-6.92	-1.17	5.75	691.807	100.741	1.70	4	10
M8	-8.42	-1.69	6.73	779.986	117.689	1.79	4	10
M9	-5.56	-1.64	3.92	634.334	114.929	1.78	4	10

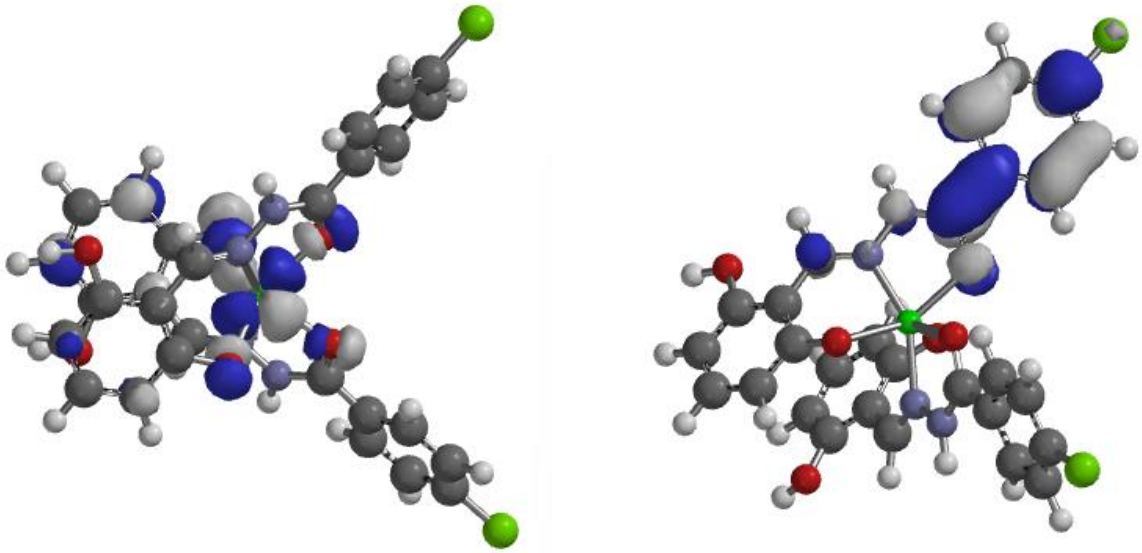
Note: MW-molecular weight; LogP-Lipophilicity; pol-polarizability; HBA-hydrogen bond acceptor; HBD-hydrogen bond donor.

Also, the receptivity of any compound to accept electron from enabled electron donating compound play a crucial role in chemical reactivity. The lowest the value acquired for LUMO energy for any investigated molecule, the better the reactivity of such compound; thus, compound M2 portrayed a potential capacity to react better than other studied compounds in terms of LUMO energy (Table 2). More so, the role played by the energy gap in the reactivity of any molecule has been considered crucial by several scientists [32]. According to Semire *et al*., 2012 [33], a lower energy gap facilitates stronger interaction between organic compounds, and it also denotes the stability of any compound; therefore, compound M2 exhibited the most significant tendency to interact strongly with other examined compounds. In this work, other calculated descriptors are presented in Table 1.

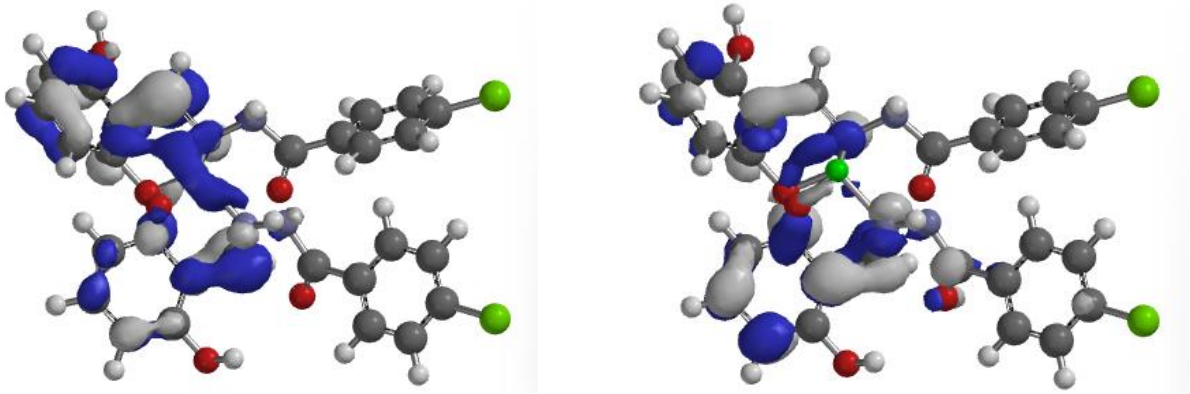
Table 2 Predicted HOMO-LUMO overlay for metal complexes with benzo hydrazide Schiff base.

	HOMO	LUMO
M1		
M2		

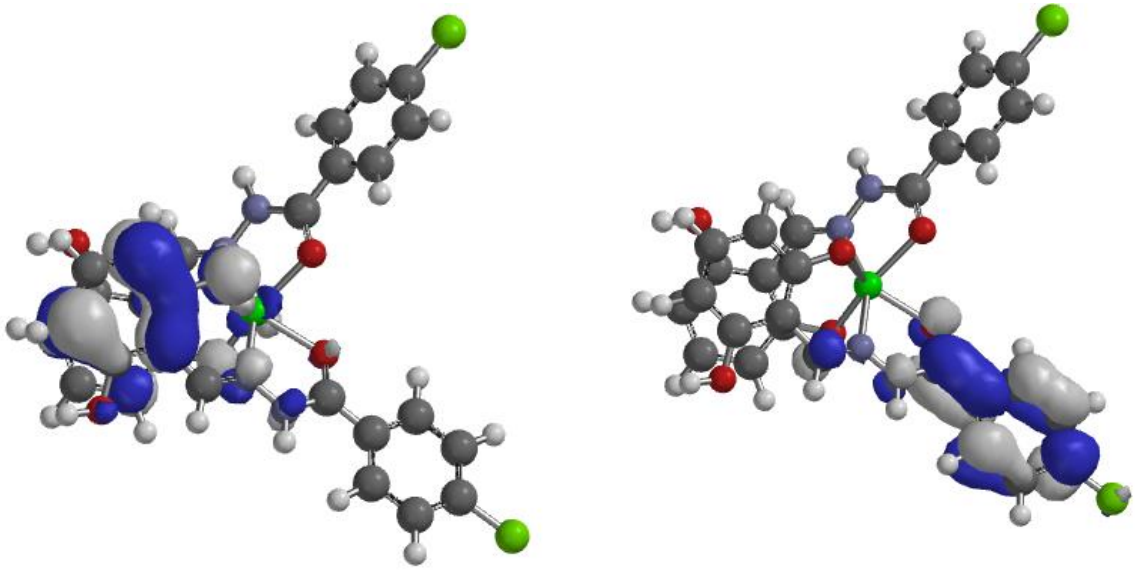
M3



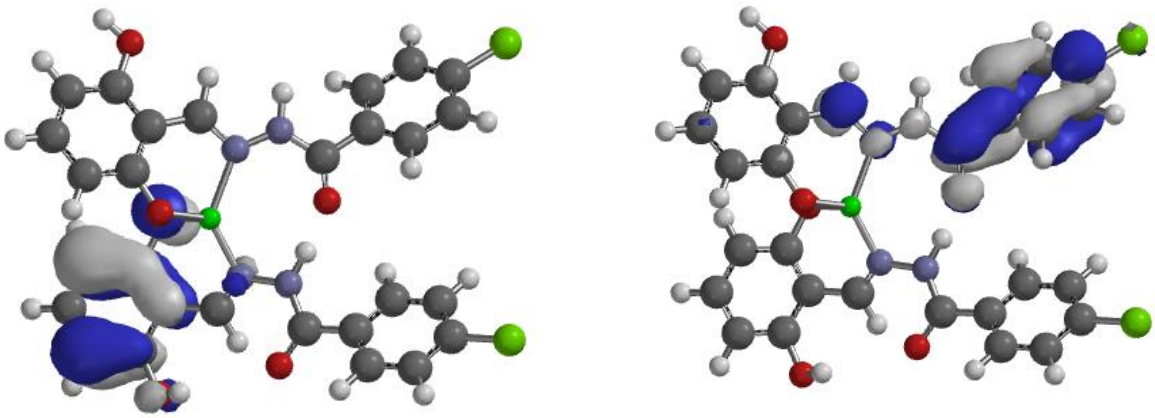
M4



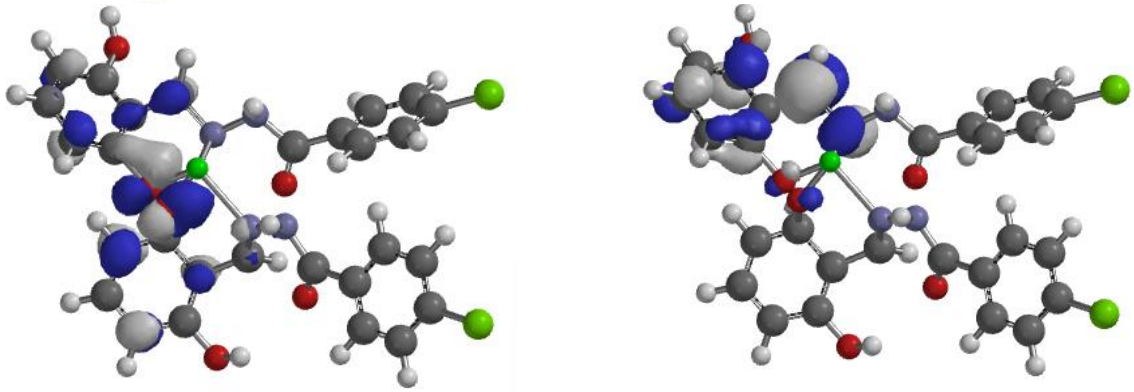
M5



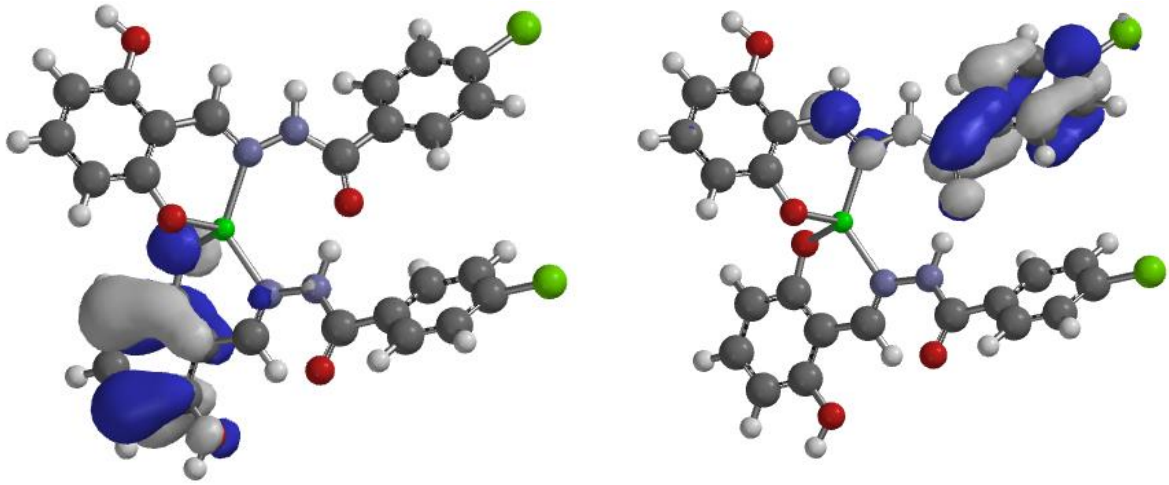
M6



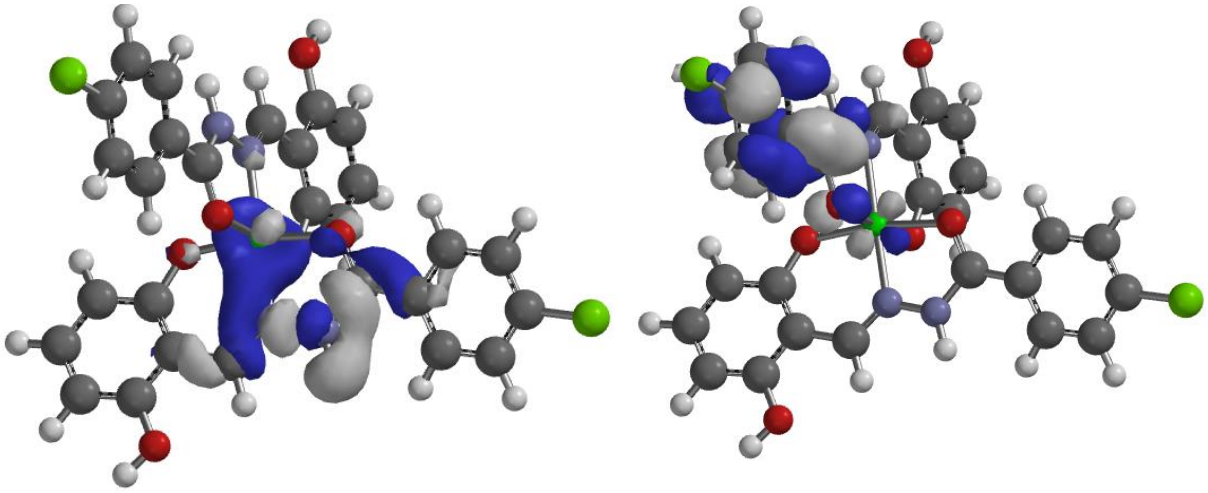
M7



M8



M9



The potential efficiency of compounds M2 and M4 was observed to be greater than some organic-based antibacterial and antifungal agents, as described in our previous work [34]. The calculated HOMO, LUMO, and energy gap values range from -6.40 eV to -5.94 eV, -1.03 eV to -0.7 eV, and 5.16 eV to 5.61 eV, respectively. Meanwhile, the involvement of metal ions in the studied organic compound re-routes the interaction path and enhances the potential interaction efficiency of compound M1 to M9. The calculated HOMO, LUMO and energy gap values for the studied compounds ranges from -8.42 eV to -5.56 eV; -3.07 eV to -1.17 eV; and 3.52 eV to 6.73 eV respectively.

3.2 Scoring Values for Metal Complexes with Benzohydrazide Schiff Base with Studied Targets

The inhibiting ability of the studied compounds with different metal atoms was investigated via the induced fit docking method using molecular operation environment software. Various binding affinities were observed for ligands against *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m), Gram Negative Bacteria (GNCA) Class A beta- lactamase (PDB ID: 5fqm) and fungal 1,3-beta-glucan synthase (PDB ID: 8jzn) respectively. The calculated binding affinity for M1-M9 against *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m) were -7.38778782 kcal/mol, -6.71977568 kcal/mol, -6.43348598 kcal/mol, -7.22689915 kcal/mol, -6.31406641 kcal/mol, -9.35251904 kcal/mol, -8.43199348 kcal/mol, -8.03963661 kcal/mol, and -6.13375711 kcal/mol. Also, the scoring for metal complexes with Benzohydrazide Schiff base - gram negative bacteria (GNCA) Class A beta- lactamase (PDB ID: 5fqm) complexes were -6.73157215 kcal/mol, -6.30270576 kcal/mol, -5.89666605 kcal/mol, -8.20620728 kcal/mol, -6.22765636 kcal/mol, -9.63592815 kcal/mol, -7.57985878 kcal/mol, -7.85171318 kcal/mol, and -6.36694098 kcal/mol; while the binding affinity obtained after docking calculations between the studied compounds and fungal 1,3-beta-glucan synthase (PDB ID: 8jzn) were -6.60745668 kcal/mol, -6.74145126 kcal/mol, -7.59932566 kcal/mol, -8.08610249 kcal/mol, -7.13527727 kcal/mol, -10.3727274 kcal/mol, -6.91363144 kcal/mol, -6.89560175 kcal/mol, and -6.63469505 kcal/mol for M1-M9 (Figure 2, Figure 3, Figure 4).

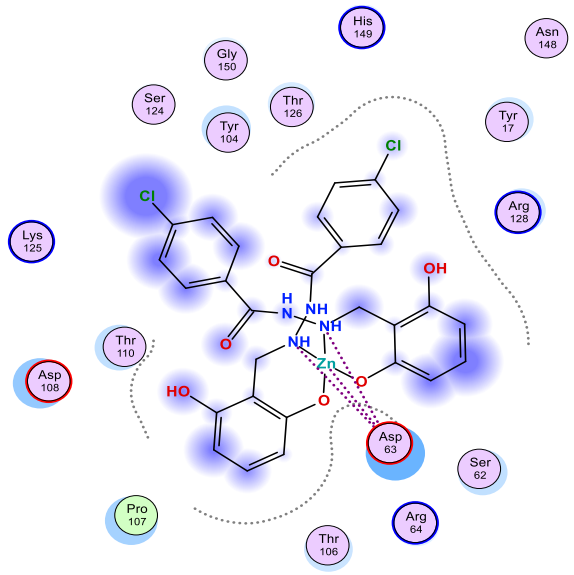


Figure 2 Pictorial presentation of docked compound M6 against Staphylococcus aureus glutamine amidotransferase GatD (PDB ID: 5n9m).

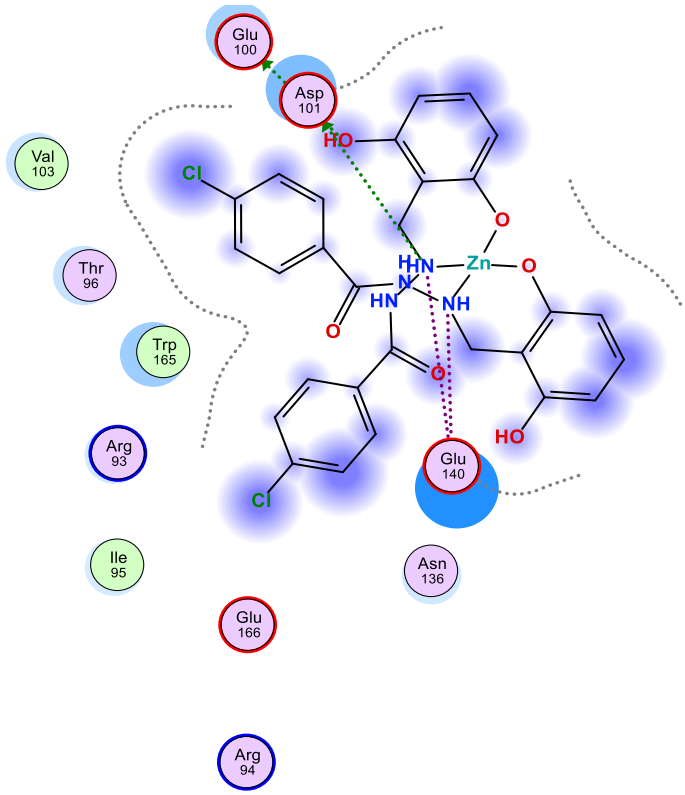


Figure 3 Pictorial presentation of docked compound M6 against Gram Negative Bacteria (GNCA) Class A beta-lactamase (PDB ID: 5fqm).

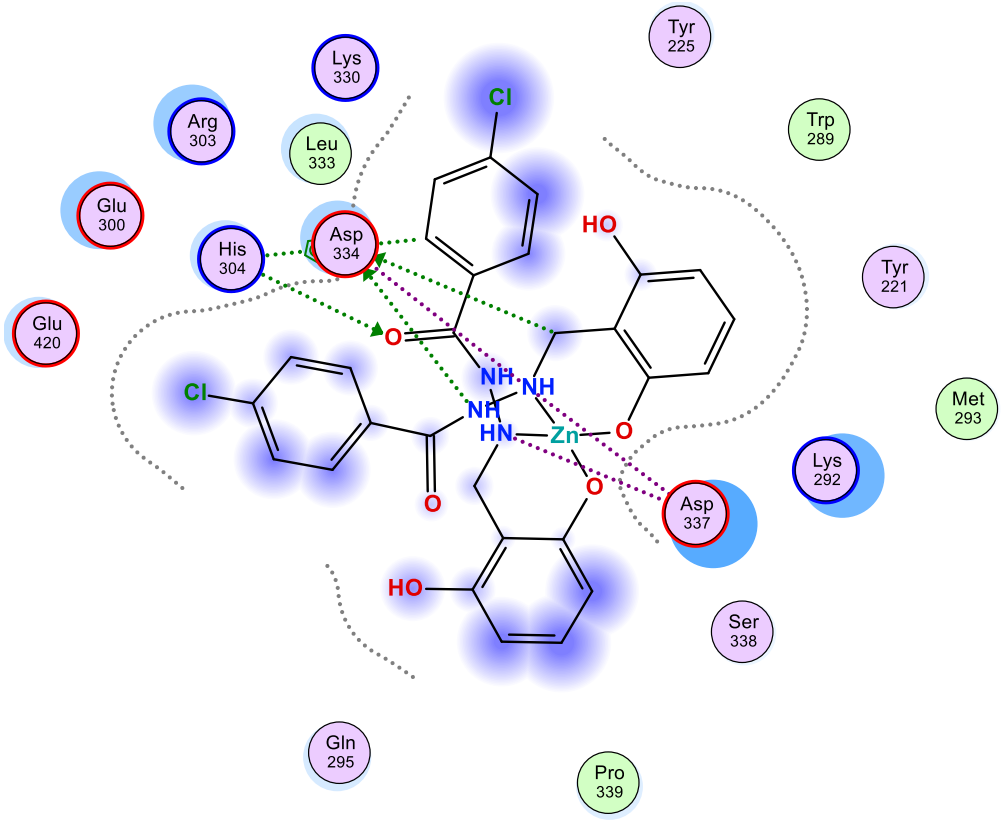


Figure 4 Pictorial presentation of docked compound M6 against fungal 1,3-beta-glucan synthase (PDB ID: 8jzn).

Furthermore, M6 (-9.35251904 kcal/mol for *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m); -9.63592815 kcal/mol for Gram Negative Bacteria (GNCA) Class A beta- lactamase (PDB ID: 5fqm); and -10.3727274 kcal/mol for fungal 1,3-beta-glucan synthase (PDB ID: 8jzn)) was observed to possess highest binding affinity than other studied compounds and Streptomycin as well as Fluconazole. The efficiency of compound M6 proved to be greater when compared to the work carried out by Gosu *et al.* 2024 [35], and this could be attributed to the presence of metal ions present in the studied compound. Also, Zinc as the metal ion present in the parent compound was observed to play crucial role in inhibiting the studied targets in this research.

More so, as shown in Table 3, it was observed that 33.3% of the entire compounds proved to be more active to inhibit *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m) and Gram Negative Bacteria (GNCA) Class A beta- lactamase (PDB ID: 5fqm) than the referenced compound. Also, all the compounds under study inhibited fungal 1,3-beta-glucan synthase (PDB ID: 8jzn) than fluconazole. This revealed that the studied compounds were more active against fungi than bacteria.

Table 3 Calculated Binding Affinity for the studied complexes.

	Staphylococcus aureus glutamine amidotransferase GatD (PDB ID: 5n9m)	Gram Negative Bacteria (GNCA) Class A beta-lactamase (PDB ID: 5fqm)	fungal 1,3-beta-glucan synthase (PDB ID: 8jzn)
M1	-7.38778782	-6.73157215	-6.60745668
M2	-6.71977568	-6.30270576	-6.74145126
M3	-6.43348598	-5.89666605	-7.59932566
M4	-7.22689915	-8.20620728	-8.08610249
M5	-6.31406641	-6.22765636	-7.13527727
M6	-9.35251904	-9.63592815	-10.3727274
M7	-8.43199348	-7.57985878	-6.91363144
M8	-8.03963661	-7.85171318	-6.89560175
M9	-6.13375711	-6.36694098	-6.63469505
Streptomycin	-7.66394281	-7.54684019	-
Fluconazole	-	-	-5.61544132

3.3 Pharmacokinetics Study of M6 and Reference Compounds

The pharmacokinetic analysis of the chosen drug (M6) and the reference compound was conducted using ADMETSAR software. Physical and chemical characteristics, medicinal chemistry, absorption, distribution, metabolism, excretion, toxicity, environmental toxicity, tox21 route, and toxicophore rules were the factors that were observed. The parameters considered were compared to the ADMET features examined for the reference chemical compounds, as indicated in Table 4, Table 5, and Table 6, and it was found that the features taken into consideration were reasonably connected. This demonstrated the potential pharmacological effects of the lead chemical (M6). The features obtained for M6 were compared to the properties obtained for streptomycin and fluconazole which were used as the reference compounds in this study. It was observed that the features obtained for compound M6 were more outstanding than 0.5, and the

values obtained were closer to the values obtained for the referenced compounds. More so, this clearly showed that M6 is relatively safe in term toxicity, as reported by Pindjakova et al., 2022 [36].

Table 4 Predicted ADMET features for M6.

ADMET Predicted Profile --- Classification		
Model	**Result**	**Probability**
Absorption		
Blood-Brain Barrier	BBB-	0.5542
Human Intestinal Absorption	HIA-	0.5203
Caco-2 Permeability	Caco2-	0.6011
P-glycoprotein Substrate	Non-substrate	0.5472
P-glycoprotein Inhibitor	Non-inhibitor	0.8792
	Non-inhibitor	0.9036
Renal Organic Cation Transporter	Non-inhibitor	0.9141
Distribution		
Subcellular localization	Mitochondria	0.5891
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7016
CYP450 2D6 Substrate	Non-substrate	0.8368
CYP450 3A4 Substrate	Non-substrate	0.5174
CYP450 1A2 Inhibitor	Non-inhibitor	0.5334
CYP450 2C9 Inhibitor	Non-inhibitor	0.5720
CYP450 2D6 Inhibitor	Non-inhibitor	0.8605
CYP450 2C19 Inhibitor	Non-inhibitor	0.5799
CYP450 3A4 Inhibitor	Non-inhibitor	0.5520
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.6323
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9207
	Non-inhibitor	0.8118
AMES Toxicity	AMES toxic	0.5549
Carcinogens	Non-carcinogens	0.7099
Fish Toxicity	High FHMT	0.9433
Tetrahymena Pyriformis Toxicity	High TPT	0.9921
Honey Bee Toxicity	Low HBT	0.8274
Biodegradation	Not ready biodegradable	0.9679
Acute Oral Toxicity	III	0.6250
Carcinogenicity (Three-class)	Non-required	0.5913
ADMET Predicted Profile --- Regression		
Model	**Value**	**Unit**
Absorption		
Aqueous solubility	-3.8276	LogS
Caco-2 Permeability	0.4085	LogPapp, cm/s

Toxicity		
Rat Acute Toxicity	2.4562	LD50, mol/kg
Fish Toxicity	1.3139	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.8417	pIGC50, ug/L

Table 5 Predicted ADMET features for Streptomycin.

ADMET Predicted Profile --- Classification		
Model	**Result**	**Probability**
Absorption		
Blood-Brain Barrier	BBB-	0.9712
Human Intestinal Absorption	HIA-	0.8824
Caco-2 Permeability	Caco2-	0.6968
P-glycoprotein Substrate	Substrate	0.5531
P-glycoprotein Inhibitor	Non-inhibitor	0.7577
	Non-inhibitor	0.8382
Renal Organic Cation Transporter	Non-inhibitor	0.7782
Distribution		
Subcellular localization	Lysosome	0.4518
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7053
CYP450 2D6 Substrate	Non-substrate	0.8177
CYP450 3A4 Substrate	Non-substrate	0.5275
CYP450 1A2 Inhibitor	Non-inhibitor	0.9045
CYP450 2C9 Inhibitor	Non-inhibitor	0.9072
CYP450 2D6 Inhibitor	Non-inhibitor	0.9230
CYP450 2C19 Inhibitor	Non-inhibitor	0.9026
CYP450 3A4 Inhibitor	Non-inhibitor	0.8867
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.8818
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9924
	Non-inhibitor	0.9009
AMES Toxicity	AMES toxic	0.9107
Carcinogens	Non-carcinogens	0.9528
Fish Toxicity	Low FHMT	0.7366
Tetrahymena Pyriformis Toxicity	High TPT	0.9400
Honey Bee Toxicity	Low HBT	0.5908
Biodegradation	Not ready biodegradable	0.9821
Acute Oral Toxicity	IV	0.6171
Carcinogenicity (Three-class)	Non-required	0.5741
ADMET Predicted Profile --- Regression		
Model	**Value**	**Unit**
Absorption		
Aqueous solubility	-2.0122	LogS

Caco-2 Permeability	-0.5128	LogPapp, cm/s
Toxicity		
Rat Acute Toxicity	1.8409	LD50, mol/kg
Fish Toxicity	1.5640	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.2635	pIGC50, ug/L

Table 6 Predicted ADMET features for Fluconazole.

ADMET Predicted Profile --- Classification		
Model	**Result**	**Probability**
Absorption		
Blood-Brain Barrier	BBB+	0.9382
Human Intestinal Absorption	HIA+	0.9894
Caco-2 Permeability	Caco2+	0.8867
P-glycoprotein Substrate	Non-substrate	0.6008
P-glycoprotein Inhibitor	Non-inhibitor	0.8782
	Non-inhibitor	0.9004
Renal Organic Cation Transporter	Non-inhibitor	0.6461
Distribution		
Subcellular localization	Mitochondria	0.8498
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.7898
CYP450 2D6 Substrate	Non-substrate	0.9116
CYP450 3A4 Substrate	Non-substrate	0.5650
CYP450 1A2 Inhibitor	Non-inhibitor	0.6312
CYP450 2C9 Inhibitor	Non-inhibitor	0.5497
CYP450 2D6 Inhibitor	Non-inhibitor	0.8090
CYP450 2C19 Inhibitor	Inhibitor	0.5320
CYP450 3A4 Inhibitor	Non-inhibitor	0.8196
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.5240
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.8229
	Non-inhibitor	0.6614
AMES Toxicity	Non-AMES toxic	0.5480
Carcinogens	Non-carcinogens	0.7298
Fish Toxicity	High FHMT	0.7896
Tetrahymena Pyriformis Toxicity	High TPT	0.8590
Honey Bee Toxicity	Low HBT	0.8709
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.7944
Carcinogenicity (Three-class)	Warning	0.5196
ADMET Predicted Profile --- Regression		
Model	**Value**	**Unit**
Absorption		

Aqueous solubility	-1.8626	LogS
Caco-2 Permeability	1.3598	LogPapp, cm/s
Toxicity		
Rat Acute Toxicity	2.4136	LD50, mol/kg
Fish Toxicity	1.4529	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.5995	pIGC50, ug/L

4. Conclusion

The biochemical activities of metal complexes with benzo hydrazide Schiff base were studied using computational methods. The optimization of the studied chemical compounds led to several descriptors that describe the activities of the studied ligands. Compound M4 proved to possess the potential ability to interact well with other studied compounds in terms of HOMO energy. Compound M2 showed a greater tendency to accept electrons from nearby compounds than other studied compounds and also in terms of the energy gap. Also, compound M6 proved to be more potent to inhibit *Staphylococcus aureus* glutamine amidotransferase GatD (PDB ID: 5n9m), Gram Negative Bacteria (GNCA) Class A beta- lactamase (PDB ID: 5fqm) and fungal 1,3-beta-glucan synthase (PDB ID: 8jzn) than other studied compounds as well as the referenced compounds using molecular modeling methods. Also, the ADMET study for compound M6 exposed its ability to act as a drug-like agent when compared to the reference compounds. Our findings may open the door for the design and development of a library of efficient metal complexes with benzo hydrazide Schiff base as potential bacterial and fungi inhibitors.

Author Contributions

Abel Kolawole Oyebamiji: Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Ifeoluwa Samson Ajayi: Visualization, Writing – original draft, Writing – review & editing. Faith Eniola Olujinmi: Writing – original draft, Writing – review & editing. Godwin O. Olutona: Methodology, Validation, Visualization. Sunday A. Akintelu: Validation, Visualization, Writing – original draft, Writing – review & editing. Emmanuel T. Akintayo: Validation, Visualization, Writing – original draft, Writing – review & editing. Cecilia O. Akintayo: Validation, Visualization, Writing – original draft, Writing – review & editing. Oluwakemi Ebenezer: Visualization, Writing – original draft, Writing – review & editing.

Competing Interests

The authors have declared that no competing interests exist.

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