

Research Article

Exploring the Biological Activity of Organically Ligated Metal–Peroxo Complexes

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Abstract

Metal-based complexes have attracted considerable attention due to their diverse biological activities and potential applications as antimicrobial agents. In this study, a series of previously synthesized metal complexes of Molybdenum(VI), Uranium(VI), Zirconium(IV), and Thorium(IV) were systematically evaluated to investigate their antifungal, antibacterial, and cytotoxic properties. The primary objective of this work was to assess the bioactive potential of these complexes and to identify promising candidates for antimicrobial applications. The antifungal activity of the complexes was examined against *Aspergillus niger*, *A. fumigatus*, and *A. flavus* using the agar diffusion method. Antibacterial efficacy was determined by minimum inhibitory concentration (MIC) assays against both Gram-negative (*Pseudomonas aeruginosa* and *Escherichia coli*) and Gram-positive (*Streptococcus* β -haemolyticus and *Bacillus subtilis*) bacterial strains. Cytotoxicity was evaluated using the brine shrimp lethality assay as a preliminary indicator of biological safety. The results demonstrated that all tested complexes exhibited varying degrees of antifungal and antibacterial activity. Notably, the Mo(VI) complex 2 showed the highest antifungal activity against *A. flavus*, producing a zone of inhibition of 14 mm. In antibacterial studies, Mo(VI) complex 4 displayed the lowest MIC values, indicating superior antibacterial potency, followed by the U(VI) complex 8, while Th(IV) complexes showed comparatively weaker activity. Cytotoxicity assessment revealed that Mo(VI) complex 5 exhibited the highest toxicity, whereas complexes 1 and 2 were comparatively less toxic. Overall, the findings suggest that Mo(VI) complexes possess significant antimicrobial potential and represent promising candidates for further development as bioactive agents.

Keywords

Metal–peroxo Complexes, Organic Ligands, Molybdenum (VI), Uranium (VI), Zirconium (IV), Thorium (IV), Antimicrobial Activity

1. Introduction

Organometallic and coordination compounds have long served as the foundation for the development of novel therapeutic agents due to their diverse structural possibilities and unique reactivity profiles. Among these, metal–peroxo complexes—species in which a peroxo (O_2^{2-}) ligand is coordinated to a metal center—have garnered significant attention

for their potential biological activity, including antimicrobial, antioxidant, and general cytotoxic effects [1–4]. These complexes often mimic the behavior of natural metalloenzymes such as peroxidases, monooxygenases, and catalases, making them promising candidates for biomedical applications and catalysis in oxidative processes [5, 6].

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The peroxo moiety, known for its oxidative potential, imparts redox versatility and enables such complexes to participate in biologically relevant electron-transfer reactions [7]. Transition metals such as vanadium, molybdenum, titanium, cobalt, iron, and copper form structurally diverse peroxo species, and the nature of the coordinated ligands significantly influences their chemical stability, reactivity, and biological behavior [8, 9]. However, many of these complexes are inherently unstable unless stabilized by suitable electron-donating ligands.

Organic acids and amine bases, particularly those capable of chelating through multiple coordination sites, serve as ideal ligands to stabilize metal–peroxo cores. Their incorporation introduces functional groups that can modulate lipophilicity, solubility, target specificity, and cell membrane permeability, thus enhancing biocompatibility and pharmacological potential [10–12]. For example, carboxylic acids can provide hydrogen-bonding capacity and ionic interactions, while amines often coordinate strongly to metal centers and can engage in secondary interactions with biomolecular targets [13].

Despite the recognized relevance of peroxo complexes, systematic investigations on their biological properties—particularly those ligated with organic acids and amine bases—remain limited. Previous studies have focused primarily on catalytic applications [14] or structural characterization [15], leaving a gap in understanding the structure–activity relationship (SAR) between ligand architecture and biological effects. In particular, toxicity assessments such as brine shrimp lethality assays provide only preliminary indications of general cytotoxicity rather than direct evidence of anticancer activity, underscoring the need for cautious interpretation of biological data.

In this work, we present the synthesis, spectral characterization, and biological evaluation of a series of metal–peroxo complexes viz. Molybdenum (VI), Uranium (VI), Zirconium (IV), and Thorium (IV) ligated with selected organic acids and amine bases. The biological activity of the synthesized complexes was assessed using in vitro antimicrobial and antioxidant assays, along with general toxicity screening. This study contributes to the growing field of bioinorganic medicinal chemistry and offers a framework for developing functionally tailored metal–peroxo complexes.

2. Materials and Methods

2.1. Preparation of Compound

The metal complexes were synthesized following the methodology described by Nasrin [16].

2.2. Antifungal Activity Assay

2.2.1. Test Organisms

The antifungal activity of the synthesized metal–peroxo

complexes was evaluated against *Aspergillus niger*, *A. fumigatus*, and *A. flavus* using the disc diffusion method [17]. All fungal strains were obtained from a microbial culture collection and maintained on Potato Dextrose Agar (PDA) slants under refrigeration.

2.2.2. Culture Media

(i). Potato Dextrose Agar (PDA) Medium Prepared as Follows for 1000 mL

- 1) Potato (sliced) – 200 g
- 2) D-glucose – 20 g
- 3) Agar – 20 g
- 4) Distilled water – 1000 mL
- 5) pH adjusted to 5.6 using lactic acid

The potatoes were boiled for 1 hour in distilled water, filtered, and the final volume adjusted to 1000 mL. Glucose and agar were added, and the pH was adjusted. The medium was sterilized at 121 °C for 15 minutes under 15 psi pressure.

(ii). Sabouraud Dextrose Agar Medium Composition per 1000 mL

- Peptone – 10 g
- D-glucose – 20 g
- Agar – 20 g
- Distilled water – 1000 mL
- pH adjusted to 6.5

Ingredients were dissolved in water, and the final volume was adjusted. The medium was sterilized under the same autoclaving conditions.

2.2.3. Procedure

Sterile Petri dishes were poured with PDA/Sabouraud media and allowed to solidify. Fungal spores were swabbed uniformly over the surface. Sterile paper discs (6 mm diameter) impregnated with the test compounds (dissolved in DMSO) were placed on the agar surface. DMSO was used as the negative control. Plates were incubated at 28 °C for 48–72 hours, and zones of inhibition were measured in millimeters (mm).

2.3. Determination of Minimum Inhibitory Concentration (MIC)

2.3.1. Test Organisms

The MIC values of the compounds were determined against four pathogenic bacteria:

- 1) *Pseudomonas aeruginosa*
- 2) *Streptococcus β-haemolyticus*
- 3) *Escherichia coli*
- 4) *Bacillus subtilis*

2.3.2. Principle

The MIC is defined as the lowest concentration of an antimicrobial agent that inhibits visible microbial growth. Here, the serial dilution method in nutrient broth medium was employed.

2.3.3. Inoculum Preparation

Test organisms were cultured overnight at 37.5 °C on nutrient agar. Bacterial suspensions were prepared in Sterile Saline TS and standardized to match McFarland 0.5 turbidity standard. The suspensions were further diluted to 1:200 in Mueller-Hinton broth to achieve approximately 10^6 CFU/mL.

- 1) McFarland 0.5 Standard: 0.5 mL of 1.7% $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ + 99.5 mL of 1% H_2SO_4 .
- 2) Saline TS: 0.5 g NaCl in 1000 mL distilled water.

2.3.4. Sample Preparation

Stock solution was prepared by dissolving 1.024 mg of the test compound in 2 mL methanol, giving a concentration of 512 $\mu\text{g/mL}$.

2.3.5. Serial Tube Dilution Method

Twelve sterile test tubes were arranged:

- 1) Nine for serial dilutions
- 2) Three controls: CM (medium only), CA (medium + compound), CI (medium + inoculum)

Each tube received 1 mL nutrient broth. Serial dilutions were prepared by transferring 1 mL from tube to tube, halving the concentration at each step. Each tube was inoculated with 10 μL of bacterial suspension, except CM and CA. Tubes were incubated at 37.5 °C for 18 hours.

The MIC was recorded as the lowest concentration at which no visible growth (turbidity) was observed.

2.4. Brine Shrimp Lethality Bioassay

2.4.1. Principle

The cytotoxicity as well as efficacy of bioactive complexes against brine shrimp was determined for lethality bioassay [18]. This assay evaluates general cytotoxicity and preliminary anticancer potential using *Artemia salina* (brine shrimp) larvae. It is rapid, cost-effective, and correlates reasonably with antitumor activity.

2.4.2. Materials

- 1) *Artemia salina* (brine shrimp eggs)
- 2) Artificial sea salt (38 g/L)
- 3) Small hatching tank with a partition and light source
- 4) Dimethyl sulfoxide (DMSO)
- 5) Micropipettes and vials

2.4.3. Procedure

(i). Preparation of Artificial Sea Water

38 g of sea salt was dissolved in 1 L of distilled water and filtered.

(ii). Hatching of Brine Shrimp

Shrimp eggs were added to one side of a partitioned tank filled with sea water. The side was darkened while the other side was illuminated to attract hatched nauplii after 48 hours. Hatched nauplii were collected using a pipette.

(iii). Preparation of Test Solutions

Test compounds (10 mg) were dissolved in 1 mL DMSO to obtain a stock solution of 10 $\mu\text{g}/\mu\text{L}$. Aliquots of 10, 20, 40, 80, and 160 μL were each added to vials containing 5 mL sea water and 10 nauplii, resulting in final concentrations of 10, 20, 40, 80, and 160 $\mu\text{g/mL}$, respectively. Three replicates per concentration were tested. A control vial containing DMSO only was included.

(iv). Observation and Data Analysis

After 16 and 36 hours, the number of surviving nauplii was counted under a magnifying glass. Percentage mortality was calculated for each concentration. Probit analysis was performed to determine LC_{50} and LC_{99} values.

3. Results

Based on the combined interpretations of IR and NMR spectroscopic data, the possible molecular structure of the peroxo complexes can be proposed and is illustrated in Figure 1. The IR spectra display characteristic bands attributed to the O–O stretching vibration, typically appearing in the range expected for coordinated peroxo ligands, along with additional signals corresponding to metal–oxygen interactions. These vibrational features strongly support the presence of an η^2 -peroxo binding mode around the metal center. Furthermore, the NMR spectroscopic results complement the IR findings. The observed chemical shifts, signal broadening, and coordination-dependent deshielding patterns indicate changes in the electronic environment surrounding the metal ion upon peroxo coordination. Such NMR signatures are consistent with the formation of a side-on peroxo unit and help in distinguishing between possible structural isomers. Together, the IR and NMR analyses provide coherent evidence for the proposed structural arrangement. Thus, the spectroscopic characteristics validate the molecular structure of the peroxo complexes as depicted in Figures 1-4, offering insight into the bonding nature, geometry, and stability of the complexes [16-18].

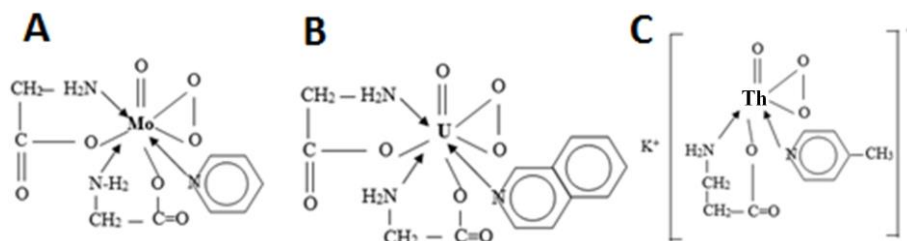


Figure 1. Proposed structure of complexes: A. $[\text{MoO}(\text{O}_2)(\text{gly})_2(\text{py})]$; B. $\text{IUO}(\text{O}_2)(\text{gly})_2(\text{Q})$ and C. $\text{K}[\text{ThO}(\text{O}_2)(\text{ala})(4\text{-pic})]$ [Adopted from Nasrin ¹⁶⁻¹⁸].

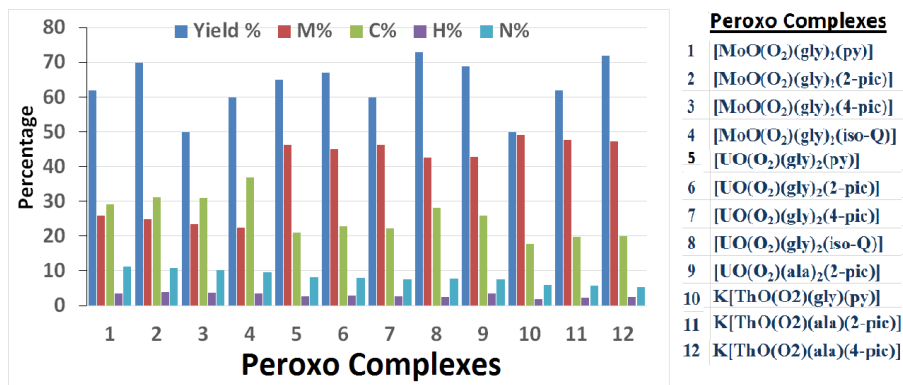


Figure 2. Calculated Values for Physico-Analytical Data of Different Peroxo Complexes (Adopted from Nasrin ^[16-18]).

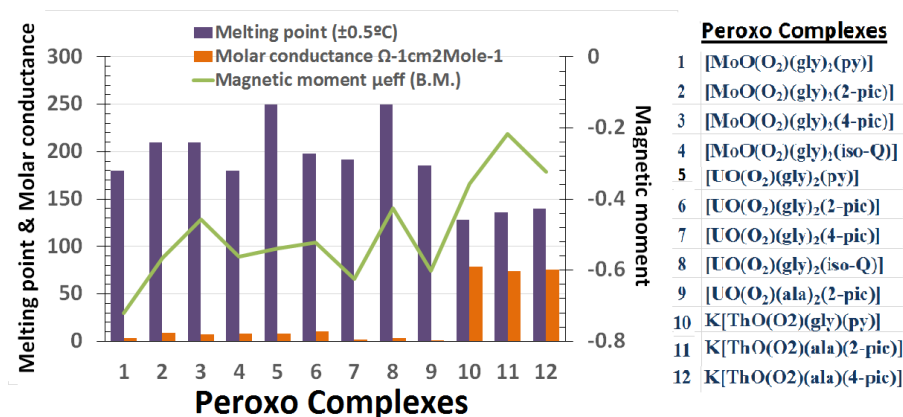


Figure 3. Electronic Transition Assignment and Magnetic Moment Data for the Studied Compounds. (Adopted from Nasrin ^[16-18]).

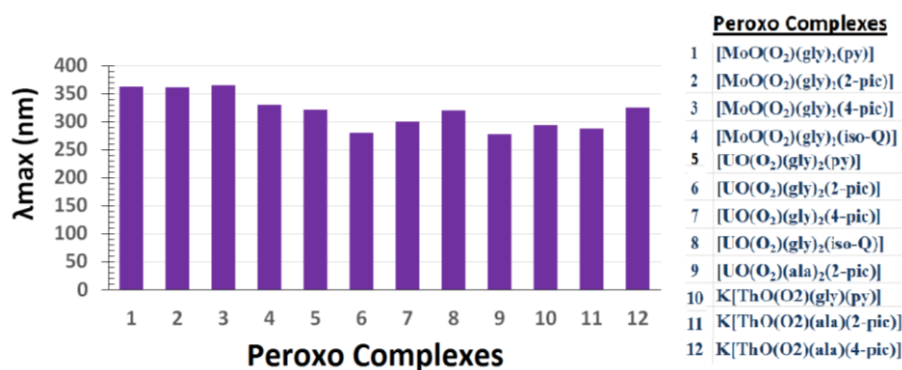


Figure 4. Electronic spectral profiles of the synthesized peroxo complexes illustrating key absorption bands associated with peroxo coordination (Adopted from Nasrin ^[16-18]).

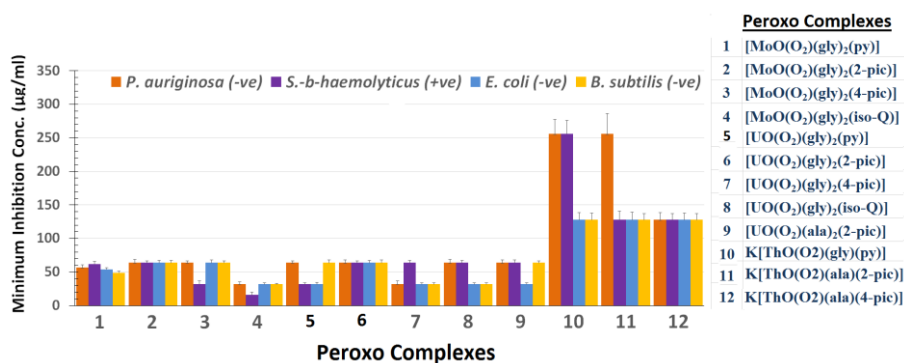


Figure 5. Minimum Inhibitory Concentration (MIC) Values of the Mo(VI), U(VI), and Th(IV) Complexes Against *Pseudomonas Aeruginosa*, *Staphylococcus β-haemolyticus*, *Escherichia Coli*, and *Bacillus Subtilis*.

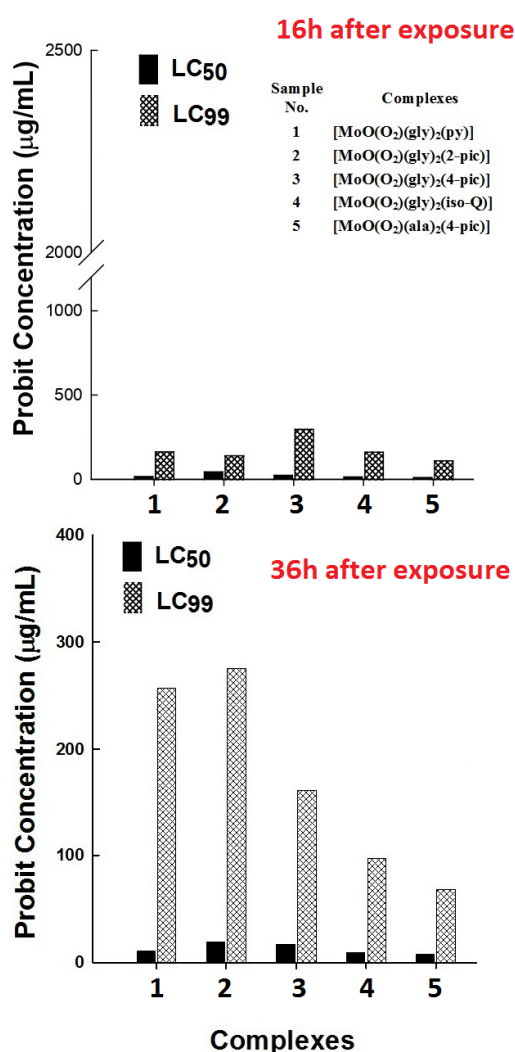


Figure 6. Probit Values for Brine Shrimp Lethality Bioassay for Mo(VI) and U(VI) After 16h and 36h of Exposure.

3.1. Antifungal Activity

The activity of peroxo complexes on fungal activity significantly varied (Table 1). The antifungal activity of the

synthesized metal complexes was significantly inhibited against three pathogenic fungal strains: *Aspergillus niger*, *A. fumigatus*, and *A. flavus* (Table 4). The results, summarized in Table 4, indicate that all metal complexes— Zr (IV) and Th(IV))—completely exhibited measurable inhibitory effects against the tested fungi.

Table 1. ANOVA for the physical properties of peroxo complexes.

Source of Variation	SS	df	MS	F	P-value	F crit
Peroxo complexes	235.1843	11	21.38039	0.439855	0.928954	2.014046
Physical Properties	28675.88	4	7168.969	147.4859	6.96E-25	2.583667
Error	2138.744	44	48.60782			
Total	31049.81	59				

Meanwhile, the Zr(IV) and Th(IV) complexes also displayed consistent antifungal activity across all three fungal strains, underscoring their potential as broad-spectrum antifungal agents. These findings highlight the promising antifungal properties of the metal complexes, particularly those of Mo(VI), which showed superior activity against *A. flavus*.

3.2. Minimum Inhibitory Concentration (MIC) Assay

The antibacterial activity of the synthesized metal complexes was evaluated by determining their Minimum Inhibitory Concentrations (MICs) using the standard serial dilution method. Both the complexes and bacterial activity varies significantly (Complexes: $F_{10,12}=13.13$, $P<001$; Fungal: $F_{3,12}=2.42$, $P<001$) (Table 2). The assay was performed against a panel of both Gram-positive and Gram-negative

pathogenic bacteria, including *Pseudomonas aeruginosa*, *Streptococcus β-haemolyticus*, *Escherichia coli*, and *Bacillus subtilis*. Additionally, the antibacterial efficacy of the purified

antibiotic was assessed at a concentration of 100 µg/disc for comparative purposes (Figure 5).

Table 2. ANOVA for the MIC Values of the Complexes of Mo(VI), U(VI) and Th(IV) Against Bacteria *P. Auriginosa*, *S.-β-Haemolyticus*, *E. coli*, *B. Subtilis*.

Source of Variation	SS	df	MS	F	P-value	F crit
Peroxo complexes	117050.2	10	11705.02	13.13757	1.97E-08	2.16458
Bacteria	6487.273	3	2162.424	2.427079	0.084899	2.922277
Error	26728.73	30	890.9576			
Total	150266.2	43				

The MIC values obtained are summarized in Figure 5 and Table 2. Among the tested compounds, complex 4 of Mo(VI) exhibited the strongest antibacterial activity, as indicated by the lowest MIC value against *S. β-haemolyticus*. This was followed by complex 8 of U(VI), which also demonstrated notable potency across the tested bacterial strains. In contrast,

complex 11 of Th(IV) showed the least antibacterial activity, requiring significantly higher concentrations to inhibit bacterial growth. A similar trend of lower efficacy was observed for complexes 10 and 11 of Th(IV), which also exhibited higher MIC values across all tested organisms.

Table 3. IR Spectral Profiles of the synthesized peroxo complexes showing characteristic O–O stretching and metal–oxygen vibrational bands (Adopted from Nasrin [16-18]).

No	ν (N-H) cm ⁻¹	ν (C=O) cm ⁻¹	ν (C-O) cm ⁻¹	ν (M=O) cm ⁻¹	ν (M-N) cm ⁻¹	γ_1 (O-O) cm ⁻¹	ν_3  cm ⁻¹	ν_2  cm ⁻¹
1	3386 br	1609 vs	1559 w	965 s	455 w	896 vs	608 s	552 m
2	3385 br	1684 w	1516 s	944 m	414 w	905 s	621 m	552 w
3	3384 br	1683 w	1399 s	901 s	449 w	842 vs	614 m	520 m
4	-	1600 vs	1559 s	958 s	402 w	909 s	627 m	497 w
5	3197 br	1652 w	1576 m	903 vs	430 w	850 w	665 w	530 w
6	3202 br	1653 m	1584 s	809 s	433 m	797 m	668 s	523 w
7	3208 br	1683 w	1575 m	903 s	426 w	804 s	665 m	529 s
8	3229 br	1575 w	1521 vs	936 vs	-	845 m	665 w	531 s
9	3304 br	1627 s	1505 m	994 s	-	844 m	636 w	599 w
10	3315 br	1607 s	1391 s	910 m	289 m	816 s	668 m	600 w
11	3274 br	1610 s	1388 s	942 m	310 w	800 s	672 m	615 w
12	3386 br	1625 s	1375 s	940 m	305 w	815 s	666 w	616 w

These findings suggest that among the tested metal series, Mo(VI) and U(VI) complexes generally possess superior antibacterial properties compared to the Th(IV) analogues.

The pronounced activity of Mo(VI) complexes, particularly complex 4, highlights their potential as promising antibacterial agents for further study.

Table 4. Antifungal Activity of the Complexes of Zr (IV) and Th(IV) Against *Aspergillus niger*, *A. fumigatus*, *A. Flavus*.

No.	Complexes	Diameter of zone inhibition (mm) 200 µg/disc		
		<i>A. niger</i>	<i>A. fumigatus</i>	<i>A. flavus</i>
1	K[ZrO(O ₂)(pha)(py)]	-	-	-
2	K[ZrO(O ₂)(leu)(py)]	-	-	-
3	K[ThO(O ₂)(gly)(py)]	-	-	-
4	K[ThO(O ₂)(gly)(2-pic)]	-	-	-

3.3. Brine Shrimp Lethality Assay

The cytotoxicity of the synthesized metal complexes was evaluated using the brine shrimp (*Artemia salina*) lethality assay. The mortality rate of brine shrimp nauplii increased proportionally with the concentration of all tested complexes, as summarized in Table 5 and illustrated in Figure 6. Among the complexes, complex 5 of Mo(VI) exhibited the highest toxicity, reflected by its lower lethal concentration values

compared to other complexes. Conversely, complexes 1 and 2 of Mo(VI) demonstrated markedly lower toxicity, requiring higher concentrations to induce comparable mortality rates.

These results clearly indicate that the Mo(VI) complexes possess significantly greater cytotoxicity against brine shrimp nauplii than their U(VI) counterparts. The differential toxicity profiles suggest distinct biological interactions and potential variations in safety or therapeutic index among the complexes, warranting further investigation.

Table 5. Probit Values for Brine Shrimp Lethality Bioassay for Mo(VI) Complexes.

Sample No.	Complexes	Exposure 16 h		Exposure 36 h	
		LC50 µg/mL	LC99 µg/mL	LC50 µg/mL	LC99 µg/mL
1	[MoO(O ₂)(gly) ₂ (py)]	22.17	168.46	12.54	257.74
2	[MoO(O ₂)(gly) ₂ (2-pic)]	49.67	145.18	20.84	276.48
3	[MoO(O ₂)(gly) ₂ (4-pic)]	29.14	301.52	18.70	161.88
4	[MoO(O ₂)(gly) ₂ (iso-Q)]	20.26	166.30	10.87	98.21
5	[MoO(O ₂)(ala) ₂ (4-pic)]	16.28	115.29	9.22	69.62

4. Discussion

The present study demonstrates the notable biological potential of Mo(VI), U(VI), Zr(IV), and Th(IV) metal complexes through their antifungal, antibacterial, and general cytotoxic effects. The antifungal assays revealed that all synthesized complexes inhibited the growth of *Aspergillus niger*, *A. fumigatus* and *A. flavus*. Among these, the Mo(VI) complex 2 exhibited the highest inhibitory activity against *A. flavus*, which may reflect enhanced ligand–metal stabilization, improved cellular uptake, or stronger interaction with fungal

biomolecules. These observations are consistent with earlier studies reporting the antifungal efficacy of molybdenum-based complexes, which are proposed to disrupt fungal cell wall components or interfere with key metabolic enzymes [19, 20].

No significant variation was observed between Mo(VI) and U(VI) complexes in antifungal performance, suggesting comparable bioavailability or mechanistic pathways. This agrees with previous findings that certain actinide complexes can exhibit biological behavior similar to transition metal analogues [21, 22]. Zr(IV) and Th(IV) complexes also showed broad-spectrum antifungal activity, though with

somewhat reduced potency, possibly due to differences in coordination geometry, ligand lability, and transport across fungal cell membranes [23].

The MIC results further support the antibacterial potential of the synthesized complexes. In particular, Mo(VI) complex 4 displayed the lowest MIC value against *Streptococcus β-haemolyticus*, indicating strong bacteriostatic or bactericidal properties. The generally higher antibacterial effectiveness of Mo(VI) and U(VI) complexes compared to Th(IV) counterparts may stem from more favorable redox activity and ligand exchange characteristics, which facilitate interaction with bacterial DNA, proteins, or membrane structures [24, 25]. The relatively elevated MIC values of Th(IV) complexes may reflect reduced uptake or weaker binding to bacterial targets, consistent with earlier reports on thorium coordination compounds [26].

Toxicity screening using the brine shrimp lethality assay showed a dose-dependent increase in mortality for all complexes, with Mo(VI) derivatives displaying comparatively higher general cytotoxicity. This elevated toxicity may be linked to their redox-active nature or enhanced capacity for generating reactive oxygen species (ROS), resulting in oxidative stress in biological systems [26, 27]. Conversely, complexes 1 and 2 exhibited lower toxicity, suggesting a comparatively safer profile from a preliminary toxicity perspective.

It is important to emphasize that brine shrimp lethality assays provide only an initial indication of general cytotoxicity. The model does not reliably predict anticancer activity, and therefore cannot be used to support claims of anticancer potential. Any therapeutic relevance requires substantially more rigorous evaluation, including studies with mammalian cell lines and in vivo toxicity models [28-30].

The bioactivity of the synthesized metal-peroxo complexes is strongly influenced by the nature of the coordinated ligands, which regulate both the chemical stability of the metal center and its biological interactions. Organic acids and amine bases used in this study provide distinct coordination environments that modulate lipophilicity, ligand field strength, and electron-donating capacity. For instance, carboxylic acid-based ligands enhance hydrogen-bonding ability and may facilitate interaction with fungal and bacterial cell walls, thereby improving antimicrobial efficacy. In contrast, amine ligands, with their stronger σ -donor character, stabilize the peroxo moiety and may promote redox activity, contributing to the higher cytotoxicity observed in some Mo(VI) complexes. Additionally, more hydrophobic ligands are likely to increase membrane permeability, enabling greater cellular uptake and correspondingly stronger biological responses. These ligand-dependent variations in electronic properties, sterics, and solubility collectively illustrate how subtle changes in ligand architecture can significantly alter the antimicrobial and cytotoxic profiles of the metal-peroxo complexes [31, 32].

Overall, the results underscore the promising anti-

microbial properties of the Mo(VI) complexes, particularly complex 5, while also highlighting the need for careful dose consideration due to observed cytotoxicity. To advance the biomedical relevance of these complexes, further mechanistic investigations—such as molecular docking, enzymatic interaction studies, ROS quantification, and in vivo toxicity assessments—are essential for defining their modes of action and evaluating their safety margins [33-36].

Abbreviations

Mo(VI)	Molybdenum (VI)
U(VI)	Uranium (VI)
Zr(IV)	Zirconium (IV)
Th(IV)	Thorium (IV)
MIC	Minimum Inhibitory Concentration
SAR	Structure Activity Relationship
PDA	Potato Dextrose Agar
DMSO	Dimethyl Sulfoxide
IR	Infrared Radiation
NMR	Nuclear Magnetic Resonance
ROS	Reactive Oxygen Species

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Author Contributions

Jahanara Nasrin is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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