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Bactericidal and Toxicidal Activity of Metal Peroxo Complexes of Thorium (IV) Synthesizing with Organic Acids and Amine Bases

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Abstract

Peroxo metal complexes have an important place within the medicinal inorganic chemistry since they exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals led to the recent development to of drugs which are based on metals and are considered to be potential candidates for pharmacological and the rapeutic applications. Both the ligand and the metal complexes of Th(IV) were screened for their antibacterial activity against *Pseudomonas aeruginosa, Sarcina lutea, Streptococcus bodyii, Streptococcus-β-haemolyticus. Escherichia coli, Bacillus megaterium, B. subtilis, Shigella sonnei, S.flexneri, S.dysenteriae*, *S.bodyii* and *S.shiga*. The toxicidal activity of the ligand and its complexes against the brine shrimp was also investigated. The screening results revealed that the compound K[ThO(O_2)(ala)(4-pic)] has a strong inhibition and active antimicrobial activities against the bacteria compared to other compound tested. Results also showed that the lethal toxicity of peroxo complexes of metal Th(IV) varied significantly against the mortality of brine shrimp at different exposure periods. The complex K[ThO(O_2)(gly)(2-pic)] was found to be more toxic against the mortality brine shrimp indicating the lower values of 8.49 and 203.8µg/mL lethal concentration for 50 (LC_{99}) and 99% (LC_{99}) respectively at both exposures of 36-h.

Keywords

Peroxo Complexes, Bactericidal Activity, Cytotoxicity, Lethal Toxicity, Microbial Activity

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1. Introduction

Exposure of metals is being frequently induced carcinogenic effects into human and animals [1]. It has been reported that several essential transition metals, including zinc, iron, copper, cobalt and manganese involve in the control of various metabolic and signalling pathways [2-3]. Previous studies reveal that the rich coordination chemistry and redox properties are readily capable of escaping out of the control mechanisms such as homeostasis, transport, and binding to the tissue and cell constituents [4-5]. The toxic and carcinogenic metals are also capable of interacting with nuclear proteins and DNA causing oxidative deterioration of biological macromolecules. Several researchers reported that the wide spectrum of nuclei base products can cause metal-induced genotoxic damage which is typical for the oxygen attack on DNA in cultured cells and animals [6-8]. Moreover, the metals like iron, copper, cadmium, chromium, mercury, nickel, vanadium hold the ability to make reactive radicals, resulting in DNA damage as well as altering the profiles of lipid and protein. It has been reported that the metals carcinogenic effect may be induced by targeting a number of cellular regulatory proteins or signalling proteins participating in cell growth, apoptosis, and DNA repair [9-10]. The carcinogenic effects of certain metals have been related to the activation of cell transcription and these factors usually influence the protective

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genes expression which is ultimately repairing DNA damage, boosting the immune system, halting the proliferation of damaged cells, and inducing apoptosis [11]. Previous findings showed that the decompartmentalize iron may enhance the genotoxicity of many chemical compounds [12]. In addition to synergising the oxidation of polyunsaturated fatty acids, "loose" intracellular iron may also promote DNA damage. Many earlier studies suggest that the hydroxyl radical is responsible for most aggressive species for oxidising or modifying DNA, while super oxide radicals had no or very little effect on the oxidation of DNA in the absence of adventitious metals which clearly indicates that the role of super oxide in DNA oxidation is simply as a constituent of the Haber-Weiss reactions to produce the hydroxyl radical [13-15].

It has been found that the gram-negative bacteria own mechanisms specialized in the extrusion of strange substances out of the cell (efflux bomb), limiting the access of antimicrobial agents to its active site. Consequently, it inhibits the accumulation of antibiotics in side of cell, and also the action of antimicrobial agents [16]. The Gram-positive bacteria protect their cytoplasmic membrane with a thick cell wall in an analog way. Ozcankaya and Delibas [17] reported that the iron(II) binds to high–and lower–affinity metal–bindings sites on the protein, most probably involving in the amino acids.

It has been reported that the interaction of metal ions with organic ligands exhibits excellent antimicrobial activity compared to free ligands (not coordinated) since it justifies the investigation of new drugs with unknown mechanism of action against pathogenic bacteria [18]. Furthermore, the use of these new compounds have great potential against pathogenic bacteria, none the less, the need for new methodologies of evaluation of antimicrobial activity can not be demoted to the background [19]. As recent literature reveals that there was no enough information regarding the use of specific bioassays involving metal complexes particularly with Th(IV). Although, the susceptibility of bacteria to antimicrobial agents *in vitro* could be measured since there are several promising laboratory methods. Therefore, the purpose of this research was to evaluate the antimicrobial activity of some metal peroxo complexes of Th(V) against the Gram-positive and Gram-negative bacteria. In addition, this work also reports the cytotoxicity of peroxo complexes of Th(V) against the brine shrimp *nauplii* eggs (*Ariemia salina* L.) *in vivo*.

2. Method and Materials

2.1. Preparation of Compounds

General method for the preparation of the complexes of the type $[Th(O_2)\ (amH).L]NO_3$ [where amH=deprotonated glycine, alanine; L=quinoline, isoquinoline, pyridine] [20].

The aqueous solution of Thorium nitrate (2.85g, 0.005mol) and amino acids like glycine (0.3754g, 0.005mol) or alanine (0.4455g, 0.005mol) containing minimum amount of KOH (to make soluble) were mixed in a molar ratio of 1:1 and then allowed to stand for about ten minutes. A solution of 'L' (0.01mol) in ethanol was then added with continuous stirring to the above mixture followed by the addition of 30% H_2O_2 (2ml). The precipitate appeared which was filtered and washed several times successively with ethanol. It was then dried and stored in *Vacuo* over P_4O_{10}.

2.2. Reaction of the Complexes of 1 and 2 with Allyl Alcohol

The complexes 1 and 2 (1.05g, 0.003 mol) were suspended in THF (30ml) and astoichio metric amount of allyl alcohol was added. The mixture was stirred under reflux at 60°C for 48 hours, but it failed to produce any reaction product and complexes 1 and 2 were recovered unchanged.

2.3. Reaction of the Compounds 3 and 4 with Triphenyl arsine

A solution of triphenyl arsine (0.981g, 0.003mol) in THF (30ml) was added to a suspension of compounds 3 and 4 (1.52g, 0.003 mol) or 7 (1.72g, 0.003mol) in the THF(40ml). The mixture was refluxed for 48 hours at 60°C. TLC indicated that triphenyl arsine was completely converted into triphenyl arsine oxide. The reaction mixture was filtered and the residue was collected. Evaporation of the filtrate yielded the product, m.p. 188-189°C. (m.p.190-192°C).

2.4. Antimicrobial Sensibility Testing by Disk Diffusion

The microbial toxicity of the complexes was performed using the disk diffusion methods (Kirby-Bauer method). For obtaining the minimum inhibition of concentrations (MIC), the sterile filter paper discs saturated with solutions were adjusted for each compound. The bacterial inocula were produced with an incubation time for 24h, and adjusted to the standard solution of the 0.5 McFarland scale. The antimicrobial plates impregnated with the compounds were placed in each Petri plate. A disk was set in the center of the plate and the others around it, making sure that the distance from the center to another disc was no less than 20mm, and that the disc was not close to the border.

After that, the plates were then kept in an incubator at a temperature of 35°C for 20h. The inhibition halos produced around the disc (including the diameter of the disc) were measured, using a digital calliper rule. The inhibition zones having higher than 7 mm in diameter were to be considered as positive results. The Petri dish containing only the Miller-Hinton culture medium was included in each incubation phases which considered as negative control. There were three Petri dishes

which contained standard anti microbial discs were incubated for control of the bacterial inoculums. The bioassays were three replications for each of the microbial test for minimizing error. The measurements of the inhibition halos were evaluated statistically. The peroxo complexes of Th(IV) were tested against the pathogenic fungi *viz. Pseudomonas aeruginosa, Sarcina lutea, Streptococcus bodyii, Streptococcus-β-haemolyticus, Escherichia coli, Bacillus megaterium, B. subtilis, Shigella sonnei, S. flexneri, S. dysenteriae*, *S. bodyii* and *S. shiga* as a concentration of 200 µg/disc for each. The antimicrobial activity was determined after 72 h of incubation at room temperature (30ºC). The media used in these respects were nutrient agar (DIFCO) for anti bacterial assay.

2.5. Cytotoxicity Bioassay

The toxicity of peroxo complexes of Th(IV) against brine shrimp was determined for lethality bioassay [21]. In the present investigation, *in vivo* lethality test was performed against the brine shrimp nauplii eggs (*Ariemia salina* L.). The eggs were placed on one side of a small tank divided by a net containing 3.8% NaCl solution for hatching. After two days of hatching, the *nauplii* were ready for the experiment as described previously. 3mg of the of each complex was taken and dissolved in 0.6 ml of DMSO to get a concentration of 5mg/ml. From stock solutions, 10, 20, 40, 80 and 160 µl were taken in 5 different vials making the volume upto 5ml. Ten brine shrimp *nauplii* were then placed in each vial. The vial containing the same volume of DMSO plus water upto 5ml was used as a control batch. After 16h and 36h of incubation, the number of survivors of brine shrimp *nauplii* in each vial was recorded. The percentage of mortality of the *nauplii* was calculated for each concentration and lethal mortality for 50 (LC_{50}) and 99 (LC_{99}) percent were determined using probit analysis.

3. Results and Discussion

3.1. Screening of Antibacterial Activity

The screening results of the present investigation revealed that the peroxo complexes of Th(IV) exhibit higher antibacterial activity against the bacteria tested. The complexes K[ThO(O_2)(gly)(2-pic)] and K[ThO(O_2)(ala)(2-pic)] showed less microbial activity against all the bacteria compared to other peroxo complexes since they did not inhibit the bacterial halo zones (Table 1). On the other hand, the complex K[ThO(O_2)(gly)(py)] did not inhibit the halo zones against all the bacteria except the *S. -β-haemolyticus* in which halo zone (8mm) was noticed (Table 1). Moreover, the halo zones 8mm and 16 mm were noticed in the complex K[ThO(O_2) (ala)(2-pic)] while used against *Escherichia coli* and *Shigella sonnei* respectively (Tables 2 and 3). As shown in Table 3, the complex K[ThO(O_2)(ala)(2-pic)] exhibits higher microbial activity indicating 16mm compared to other complexes. The present results also revealed that the complex K[ThO(O_2)(ala)(4-pic)] showed higher microbial activity against all the bacteria forming the halo zones except *S. -β-haemolyticus* and *Shigella sonnei.* This K[ThO(O_2) (ala) (2-pic)] also shows the similar trends of microbial activity having the similar size of halo zones which ranged between 9-11mm.

Table 1. Antibacterial activity of the complexes of Th(IV) against, *Pseudomonas aeruginosa, Sarcinalutea, Streptococcus bodyii* and *Streptococcus-β-haemolyticus.*

No.	Complexes	Diameter of zone inhibition (mm)200 µg/disc			
		P. auriginosa	*S. lutea*	*S. bodyii*	*S.-β-haemolyticus*
1	K[ThO(O_2)(gly)(py)]	-	-	-	8
2	K[ThO(O_2)(gly)(2-pic)]	-	-	-	-
3	K[ThO(O_2)(ala)(2-pic)]	-	-	-	-
4	K[ThO(O_2)(ala)(4-pic)]	10	9	11	-

Table 2. Antibacterial activity of the complexes of Th(IV) against *Escherichia coli, Bacillus megaterium* and *B.subtilis.*

No.	Complexes	Diameter of zone inhibition (mm)200µg/disc		
		E. coli	*B. megatrium*	*B. subtilis*
1	K[ThO(O_2)(gly)(py)]	-	-	-
2	K[ThO(O_2)(gly)(2-pic)]	-	-	-
3	K[ThO(O_2)(ala)(2-pic)]	8	-	-
4	K[ThO(O_2)(ala)(4-pic)]	10	11	9

Table 3. Antibacterial activity of the complexes of Th(IV) against *Shigella sonnei, S. flexneri, S. dysenteriae*, *S. bodyii* and *S. shiga.*

No.	Complexes	Diameter of zone inhibition (mm)200µg/disc			
		S. sonnei	*S. flexneri*	*S. dysenteriae*	*S. shiga*
1	K[ThO(O_2)(gly)(py)]	-	-	-	-
2	K[ThO(O_2)(gly)(2-pic)]	-	-	-	-
3	K[ThO(O_2)(ala)(2-pic)]	16	-	-	-
4	K[ThO(O_2)(ala)(4-pic)]	-	10	10	10

3.2. Toxicidal Effect Against Brine Shrimp

Results showed that the lethal toxicity of peroxo complexes of metal Th(IV) varied significantly against the mortality of brine shrimp at different exposure periods (Table 4, Figures 1&4). The complex K[ThO(O_2) (gly) (2-pic)] was found to be more toxic against the mortality brine shrimp indicating the lower values of 8.49 and 203.8 µg/mL lethal concentration for 50 (LC_{50}) and 99% (LC_{99}) respectively at both exposures of 36-h (Table 4). Moreover, the complex K[ThO(O_2) (gly) (py)] shows less toxic against the mortality of brine shrimp indicating higher values of lethal concentration at both 16h and 36 h exposure. Results also revealed that 100% mortality of brine shrimp was achieved at the concentrations of 80 and 160 µg/mL for the complex of K[ThO(O_2) (ala) (4-pic)] at 36 h exposure (Figure 2) while less than 20% mortality was noticed at these concentrations for the K[ThO(O_2)(gly) (py)] at 36h exposure. As shown in Figures 3 and 4, the complex K[ThO(O_2) (gly)(2-pic)] was found to be more active against the mortality of brine shrimp requiring the minimum concentrations for both the 50 and 99% mortality level at 16 and 36 h exposure periods. In addition, the similar patterns of mortality (>80%) were recorded for the complexes K[ThO(O_2) (ala) (2-pic)] and K[ThO(O_2) (ala) (4-pic)] at 36 h exposure level (Figure 2). Moreover, the mortality rates in brine shrimp larvae increase steadily as the concentrations increased for both the exposures (Figures 1 and 2).

Table 4. Lethal toxicity of peroxo complexes of metal Th(IV) against brine shrimp at different exposure periods.

SampleNo.	Complexes	Exposure 16 h		Exposure 36 h	
		LC_{50}µg/mL	LC_{99}µg/mL	LC_{50}µg/mL	LC_{99}µg/mL
1	K[ThO(O_2)(gly)(py)]	666.50	39796.0	4522.5	42576.8
2	K[ThO(O_2)(gly)(2-pic)]	284.86	6401.0	8.49	203.8
3	K[ThO(O_2)(ala)(2-pic)]	909.28	30983.7	23.94	1360.0
4	K[ThO(O_2)(ala)(4-pic)]	80.51	9171.8	145.94	27407.8

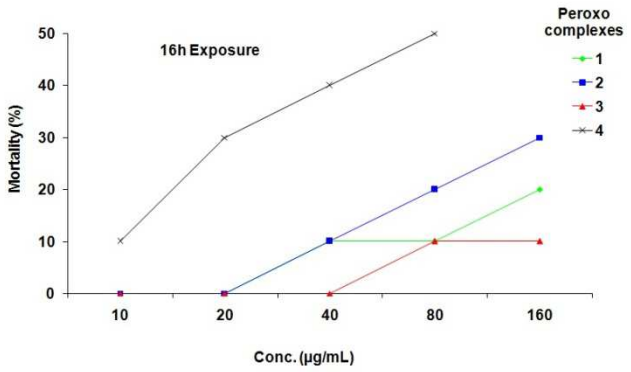

Figure 1. Efficacy of toxicity of peroxo complexes of metal Th(IV) against the percent mortality of brine shrimp at 16h exposure period.

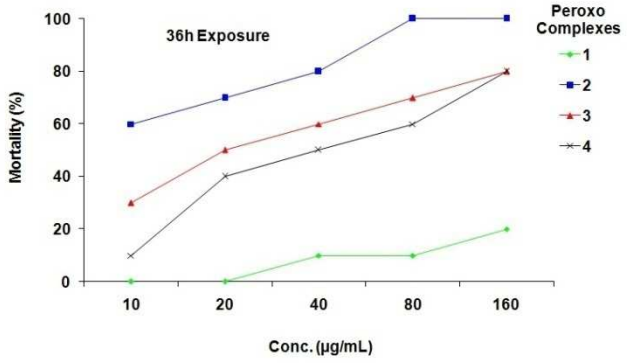

Figure 2. Efficacy of toxicity of peroxo complexes of metal Th(IV) against the percent mortality of brine shrimp at 36h exposure period.

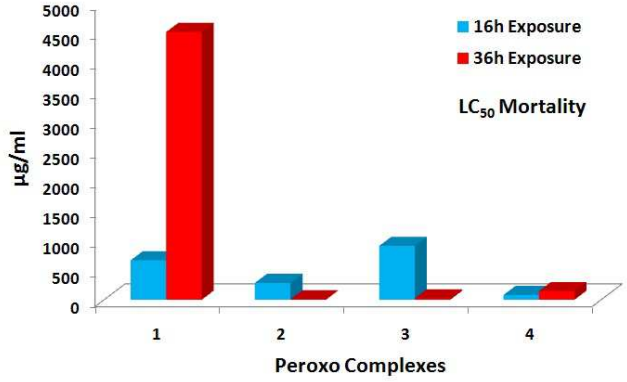

Figure 3. Lethal concentration for LC_{50} percent mortality in brine shrimp as treated with different peroxo complexes of metal Th(IV) at 16-and36-h exposure.

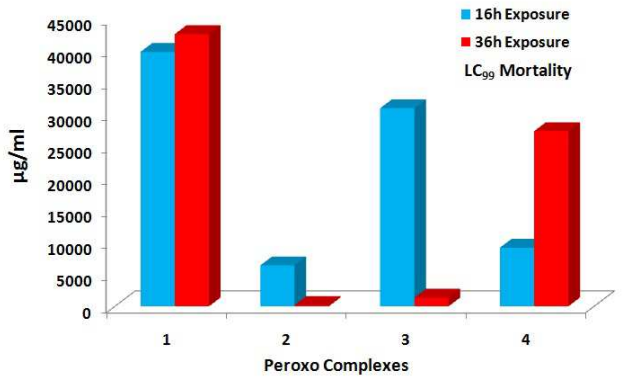

Figure 4. Lethal concentration for LC_{99} percent mortality in brine shrimp as treated with different peroxo complexes of metal Th(IV) at 16-and 36-h exposure.

Metal peroxo complexes play important roles in biological processes and the field of knowledge relating to the application of inorganic chemistry [22]. Among the natural sciences, medicinal inorganic chemistry has been practiced in pharmaceutical industry since ancient civilizations of Mesopotamia, Egypt, South East Asia. The bioinorganic chemistry is being considered as the introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases [23]. Recently, the researchers focus on the heterocyclic ligands and their metal complexes as their pharmacological studies [24]. A wide range of biological activities such as antibacterial, antifungal, antitumor and antiviral activities are exhibited by the peroxo metal complexes. The transitional metal complexes contribute two distinct advantages as DNA-binding agents. First and foremost, transition metal centers are particularly attractive moieties for reversible recognition of nucleic acids research because they exhibit well-defined coordination geometries. Moreover, they often exhibit the distinct electrochemical or photophysical properties, thereby increasing the functionality of the binding agent.

Thorium considers as an important trace element involved in the structure of certain enzymes catalyzing redox reactions [25]. It can form complexes with numerous physiologically important compounds, it was supposed that this trace element is absorbed, transported and excreted. The same concentration-dependent effects have been observed in some other biological processes influenced by Thorium. It has been also found that Thorium significantly affects protein synthesis, as well as metabolism of phosphorus, sulfur, potassium, copper, zinc, and iodine. Peroxo complexes with transition metals play a prime role in the development of coordination chemistry [26]. Synthesis of metal peroxo complexes has attracted wide spread attention due to their diverse biological activities. Many of these compounds possess antibacterial [27], antifungal [28] and insecticidal [29] activities.

Coordination compounds of Thorium can catalyze a variety of industrially important chemical reactions. The useful role of Thorium is not restricted to artificial catalysis alone, since it is a inessential element in diverse biological systems. Transition metal peroxo complexes have played an important role in the epoxidation of alkene substrates to the irrespective epoxide products and quite a number of studies have been conducted.

There are several metal ions which are being regarded as coordination centers of potential anticancer agents and these metal ions are the essential elements present in the biological intra cellular environment of living organisms [30]. They are most abundantly found trace elements present in biological systems to gather with iron and most of the metallo proteins have these elements [31]. These metal ions are now a days present in several inorganic pharmaceuticals used as drugs against a variety of diseases, ranging from antibacterial and antifungal to anticancer applications. Another fact for targeting these particular metal ions is their less toxic nature which can be further decreased when coordinated with the ligands. Though there are in numerable ligands available, the chosen amino acids, N-heterocycles (1,10 Phenanthroline, Bipyridine) and pyrazolones each have an added benefit to their properties which is a major advantage in designing an ideal drug.

4. Conclusions

The screening results indicated that the all compounds (compounds**1**-4) did not exhibit antibacterial activities. The compound 4, K[ThO(O_2) (ala) (4-pic)] showed the greatest inhibitory against the tested microbes. Moreover, further studies relating to mechanism of action, structure activity relationship, and toxicological evaluation are to be solicited including the identification the active constituents in the peroxo complexes in future.

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