

Research Article

Biological Potent Heteroaryl Ketone Schiff Base and Thorium(IV) Complexes of 2-Benzoaminothiazole

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Abstract

Metal-based antioxidants has received effort in order to identify the compounds having high free radical scavenging capacity related to various disorders and diseases associated with oxidative damage due to reactive oxygen species (ROS). Two mononuclear Th(IV) complexes were derived from 2,3-dihydro-1*H*-indolo[2,3-*b*]phenazine-4(5*H*)-ylidene)benzothiazole-2-amine (L¹), and 3-(ethoxymethylene)-(2,3-dihydro-1*H*-indolo[2,3-*b*]phenazine-4(5*H*)-ylidene)benzothiazole-2-amine (L²) with properties of pharmacologically interest. The compounds were characterized by elemental analyses, molar conductance, magnetic susceptibility measurements, FTIR, UV-Vis, ¹H NMR, TGA, XRD, SEM studies. In both complexes 2:1 ligand-to-metal ratio has been observed.

Keywords: Antioxidant, Metal Complex, Metal Organic Frame Work etc.

Introduction

Oxidative stress, cause high levels of protein carbonyl content (CO) groups have been observed in diseases such as Alzheimer's disease (AD), rheumatoid arthritis, diabetes, sepsis, chronic renal failure, and respiratory distress syndrome [1]. Schiff base are typically synthesized from an aldehyde or ketone with a primary amine and a wide variety of steric and electronic features into their structure [2-6]. Green chemistry, also known as sustainable chemistry, is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances [7-9]. Metals are indispensable for life, as they are involved in many fundamental biological processes, including osmotic regulation, catalysis, metabolism, bio mineralization, and signal transduction. Metal-based compounds have an increasing importance in most prominent biomedical applications, as they offer the possibility of exploring a higher variety of structural motifs and reactivity patterns when compared with purely organic molecules [10]. Thorium(IV) metal ions have atomic radii 1.17 Å and have high positive charge, so that these metals can easily achieve high coordination number. Thorium show complexation tendency in its +4 oxidation easily [7]. Complexes of Th(IV) formed with humates, indicating that Th(IV) preferentially binds to carboxylate groups, which in turn allow for predicting the per mass thorium binding capacity of natural organic matter. The oxidative damage caused by ROS on lipids, proteins, and nucleic acids plays a significant role in the development of life limiting chronic diseases such as cancer, hypertension, cardiac infarction, arteriosclerosis, rheumatism, and cataracts [11,12]. The activity is usually increased by complexation, therefore to understand the properties of both ligands and metal can lead to the synthesis of highly active compounds. C. Prabhakaran and co-workers introduced [13] Ni(II) complex of Schiff base showed has an excellent DPPH radical-scavenging effect higher than that of well-known ascorbic acid. Li et al. [14] explained *in vitro* antioxidant activities of ligands and Sm, La, Nd, and Yb complexes. The results of *in vitro* SOD and H₂O₂ scavenging activities of chromone-3-carbaldehyde-(isonicotinoyl) hydrazone ligands and their respective metal complexes showed that ligands and their complexes more effective than ascorbic acid. Neelima et al. [15]

investigated complex of Th(IV) complexes and their ligands derived from 2,3-dihydro-1*H*-indolo[2,3-*b*]phenazine-4(5*H*)-ylidene)thiazole-2-amine (L¹), and 3-(ethoxymethylene)-(2,3-dihydro-1*H*-indolo[2,3-*b*]phenazine-4(5*H*)-ylidene)thiazole-2-amine (L²) have shown antioxidant activities by DPPH and H₂O₂ scavenging activities methods. Their perceptible binding ability for Th(IV) endows them with potential to reduce the generation of ROS. In this perspective, this finding is an important influence towards mechanistic aspects associated with the promising pharmacological applications and these studies may help to predict the new and novel therapeutic strategies for the treatment of human oxidative-stress based disorders such as muscular dystrophy (MD), Parkinson's diseases, cancer, and arthritis Alzheimer's. Additionally, we also explore excellent antimicrobial activities of ligands and metal complexes by micro broth dilution method.

Materials and Methods

Materials

All reagents were obtained chemically pure and were of analytical reagent grade. The solvents were dried and distilled before used. Thorium metal salt and 2-benzoaminothiazole were purchased from Sigma Aldrich and used without further purification. Antimicrobial strains were tested against two-gram positive *Staplococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC 6633, gram negative bacteria *Escherichia coli* ATCC 25922 and yeast like fungi *Candida tropicalis* ATCC 13803, and *Aspergillus niger* MTCC 282.

Characterization

Melting points were recorded in capillary tubes on a digital Buchi apparatus and are uncorrected. Elemental analyses were performed

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using a Perkin Elmer 2400 series II instrument and metal content was determined by gravimetrically as metal oxide. Fourier transform infrared (FTIR) spectra were recorded on a Bruker Vertex 70 FTIR spectrometer by using KBr pallets in the transmission mode, in the range 400–4000 cm^{-1} at room temperature with a resolution of 2 cm^{-1} . The ^1H NMR spectra were recorded on a Bruker Advance II spectrometer and measured at 400 MHz. The magnetic susceptibilities measurements on powder form of the complexes with magnetic susceptibility balance (Mk_1) of Sherwood Scientific Corporation, UK using MgSO_4 as a celebrant at room temperature. Molar ionic conductance of the complexes was determined in DMSO using a solution of about 10^{-3} M concentration on ESICO model-1601 microprocessor based conductivity meter with a dip type cell with platinized electrode. G3 Heidolph rotary evaporator was used for the evaporation of solvents. Microwave assisted procedure was carried out in microwave synthesizer CEM-Discover- 925105 of Lab India. TGA studies were carried out by using Perkin Elmer TGA-4000. Data of the scavenging activity were expressed as the mean \pm SEM from three independent experiments. One-way ANOVA and Dunnett's multiple comparisons test was performed using graph pad prism (Version 5.01) software for significance test, using a p value ≤ 0.05 .

Procedure

Syntheses of Schiff base ligands

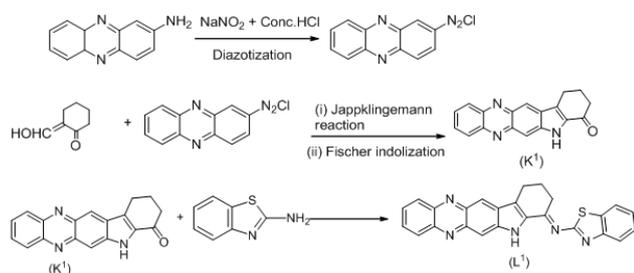
Synthesis of ligand L¹ Ligand (L^1) was prepared in ethyl alcohol (2 ml) by the condensation with 2-aminobnzothiazole and ketone (K^1) [16] in 1:1 equimolar ratio along with catalytic amount of hydrochloric acid, and the resulting mixture was irradiated under microwave for 4-5 min. Allowed to cool to ambient temperature, acidified with acetic acid (pH 5.7) and then refluxed for 1 min. The extra solvent was removed by rotary evaporator. Brown precipitate was collected by filtration and drying (Scheme 1). The product was recrystallized from the same solvent and dried.

Synthesis of ligand L² Ligand L^2 was synthesized by same procedure methods in scheme 2.

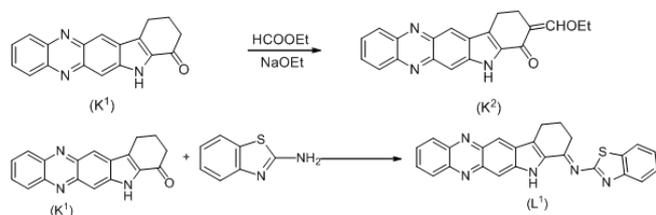
Syntheses of complexes

Syntheses of $[\text{Th}(L^1)_2(\text{NO}_3)_2\text{NO}_3] \cdot 6\text{H}_2\text{O}$ and $[\text{Th}(L^2)_2(\text{NO}_3)_2\text{NO}_3] \cdot 6\text{H}_2\text{O}$

Synthesis of $[\text{Th}(L^1)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$: A methanolic solution of $\text{Th}(\text{NO}_3)_4 \cdot 6\text{H}_2\text{O}$ salt 0.058 g (0.0001 mol) were poured to the methanolic solution of ligand (L^1) 0.071 g (0.0002 mol) in 1:2 metal



Scheme 1: Synthesis of ligand L^1



Scheme 2: Synthesis of ligand L^1

ligand stoichiometry ratio. The reaction mixtures were subjected to energy source of microwave for 5–6 min. The product was recrystallized with mixture of ethanol and ether, and finally dried by rotavapour. The progress of the reaction and purity of the product was monitored by TLC using silica gel [Figure 1].

Synthesis of $[\text{Th}(L^2)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$: The calculated amount of $\text{Th}(\text{NO}_3)_4 \cdot 6\text{H}_2\text{O}$ 0.058 g (0.0001 mol) and 0.091 g (0.0002 mol) ligand (L^2) in 1:2 molar ratio dissolved in methanol stirred for 6 min under microwave irradiation at pH 7–8. The precipitate was filtered and washed with methanol. The product was recrystallized with mixture of ethanol and ether, and finally dried by rotavapour. The progress of the reaction and purity of the product was monitored by TLC using silica gel [Figure 2].

Antimicrobial activity

Antimicrobial activities of the ligands and its complexes were screened by the determination of minimum inhibitory concentration (MIC, $\mu\text{g}/\text{ml}$) using a micro-broth dilution method [17]. A stock solution of each antimicrobial compound in dimethylsulfoxide (DMSO) was prepared according to national committee for clinical laboratory standards guidelines [18,19]. The MIC was determined in standard sterile 96 well flat bottom microtitre plates, and the layout was designed so that each row covered the final antimicrobial dilution of 0.5–500 $\mu\text{g}/\text{ml}$ with one control well. Using sterilized micropipette 40 μl of the selected antimicrobial with the correct concentration was added to each well, and another well was loaded with the same volume of control (DMSO solvent). Then 150 μl of Mueller Hinton media was added to all wells, followed by 10 μl of the respective bacterial suspension to give final concentration of 5×10^7 cfu/ml in each well. The plates were sealed and incubated at 37°C under atmospheric conditions. After 24 h incubation the microtitre plates were analysed using the ELIZA reader, and the lowest concentration with optical density less than control was defined as the MIC.

Results and Discussion

Elemental analyses, Magnetic properties Molar conductance:

Elemental analyses of $\text{Th}(\text{IV})$ complexes of ligands are showed 1:1 electrolytic in natures of the complexes [20]. Magnetic moment

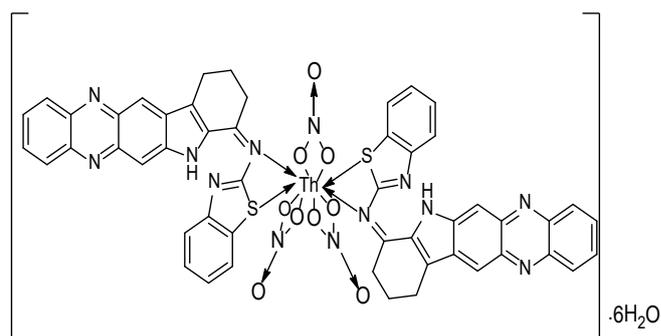


Figure 1: Structure $[\text{Th}(L^1)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$ complex.

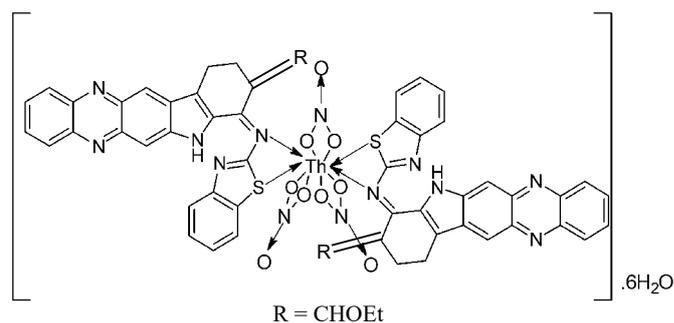


Figure 2: Structure $[\text{Th}(L^2)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$ complex.

recorded for Th(IV) complex is due to the presence of one unpaired electron [21]. The calculated and experimental values of CHNSO for ligands and their complexes are agreed with the proposed formulae. Table 1.

Spectral Characterization: FTIR analysis: The FTIR spectra of the free ligands were compared with the spectra of their metal complexes. The significant broad band was obtained at 1623–1618 cm^{-1} [22] corresponding to imine group stretching, which shifted toward lower frequency in metal complexes than the free ligands. The broad absorption band in the region 3395–3288 cm^{-1} indicates the presence of water molecule in the complexes and results were further confirmed by TGA studies [23]. These bands are conformed the participation of the N and S in the thorium metal complexation. These peaks are expected to be changed upon chelation [24,25]. 427 cm^{-1} corresponding to S group taking the participation to the thorium metal complex [Figure 3,4].

Electronic spectra: In the electronic spectra the most characteristic band for the Schiff bases is assigned to $\pi-\pi^*$ transitions of the C=N group, which was recorded in the region 252–254 nm. The spectra of complexes indicate slightly shifted 253–256 nm that thorium has no significant absorption in the visible region due to absence of f-f transition [26]. Figure 5.

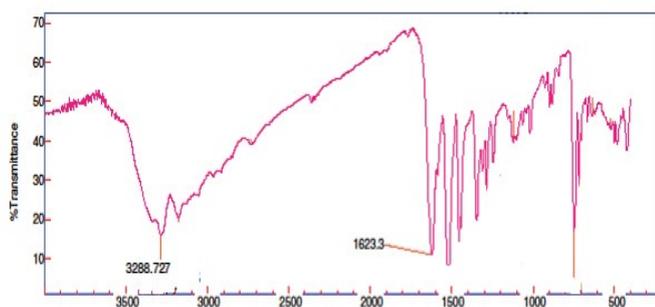


Figure 3: FTIR spectra of ligand (L¹).

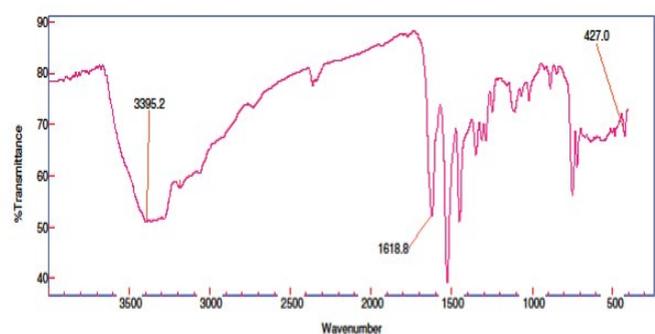


Figure 4: FTIR spectra of [Th(L¹)₂(NO₃)₃]NO₃·6H₂O complex.

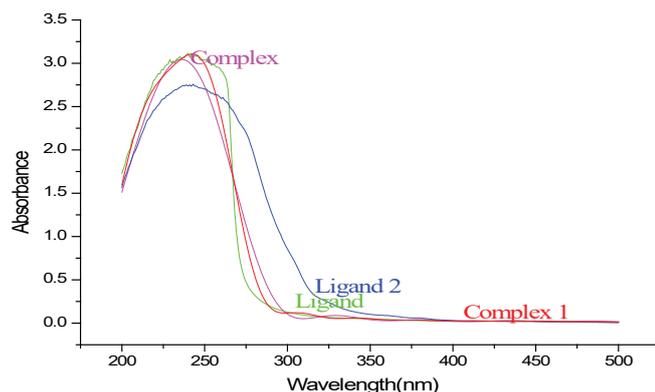


Figure 5: Electronic spectra of ligands (L¹ & L²) and complexes.

NMR analysis: An analysis of novel exposed that the NMR spectroscopy has been proved valuable in establishing the character and structure of several ligands as well as its complexes in solutions.

¹H NMR spectrum of ligand (L¹) (400 MHz, DMSO-*d*₆): δ = 8.85 ppm (s, 1H, -NH, indole), δ = 7.69–7.46 ppm (m, 6H, Ar-H), δ = 7.44–7.03 ppm (m, 2H, thiazole), δ = 3.32 ppm (s, 2H, methylene), δ = 2.49 ppm (s, 2H, methylene), δ = 5.03–5.00 ppm (s, 1H, ethylene), δ = 1.01 ppm (t, 3H, methyl). ¹H NMR spectrum of metal complex (400 MHz, DMSO-*d*₆): δ = 8.85 ppm (s, 2H, -NH indole), δ = 7.67–7.61 ppm (m, 12H, Ar-H), δ = 7.43–7.31 ppm (s, 4H, thiazole), δ = 3.34–3.33 ppm (s, 4H, methyl), δ = 5.02–4.99 ppm (s, 2H, ethylene), δ = 2.49–2.06 ppm (s, 4H, methylene), δ = 1.11 ppm (t, 6H, methyl). Figure 6,7.

TGA: The first step in the temperature range of 110–180°C with mass loss of 8.51% (calcd: 8.54%) is in accordance with the loss of lattice water molecules. The second step of decomposition occurred within the range of 180–255°C with a percentage weight loss of 11.93 (calcd: 11.77%) is due to the loss of three coordinate nitrates atoms. The third step of decomposition occurred within the range of 255–310°C which is considered the loss of 4.31 (calcd: 4.13%) lattice nitrate atom. The fourth observed in the range of 310–400°C showed a weight loss of 29.55 (calcd: 29.10%) framework of the ligands. The fifth and last step observed range of 400–550°C 22.39 (calcd: 22.77%) of stable oxide ThO₂. Figure 8.

XRD analysis: The diffractogram of complex has five reflections with 2 θ values from 30.01° to 74.52° corresponding to d value 1.2722 Å to 3.981 Å, respectively. The unit cell of complex yielded values of lattice constants, a = 5.0890 Å, b = 5.0890 Å, c = 5.0890 Å. In concurrence with these cell parameters, and unit cell volume V = 131.79 (Å)³, calculated density 11.69 g/cm³ with these cell parameters, the conditions such as a = b = c and $\alpha = \beta = \gamma = 90^\circ$. The conditions such as $\alpha = \beta = \gamma = 90^\circ$, required to be cubic crystal system were tested and found to be

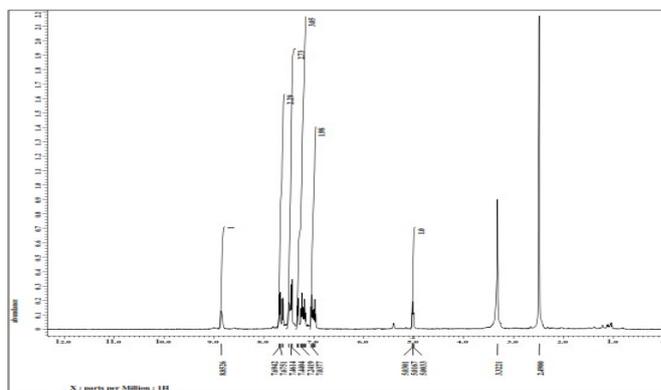


Figure 6: ¹H NMR spectrum of ligand (L¹)

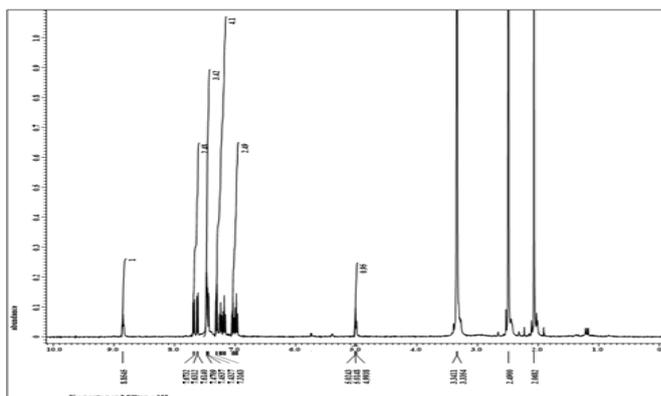


Figure 7: ¹H NMR spectrum of [Th(L¹)₂(NO₃)₃]NO₃·6H₂O complex.

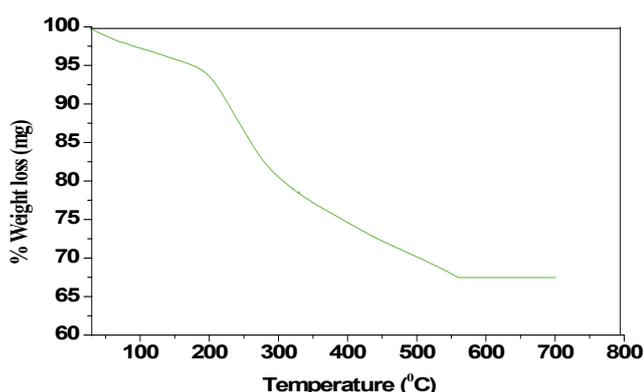


Figure 8: Thermal degradation of $[\text{Th}(\text{L}^1)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$ complex.

satisfactory. Figure 9.

Biological activities

Antimicrobial activity: The antibiotics activities of the compounds were assayed using the micro-broth dilution method against gram positive bacteria *Staplococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC 6633, gram negative bacteria *Escheriechiacoli* ATCC 25922 and yeast like fungi *Candida tropicalis* ATCC 13803, and *Aspergillus niger* MTCC 282. A comparative study of MIC values of Schiff bases and its complexes are presented in Figure 10 and 11, which are indicated that metal complexes exhibit higher antimicrobial activity than the free Schiff base ligands.

Complexes showed higher activity against both types of bacteria than the free ligand L^1 and L^2 . This enhancement in the activity can be explained on the basis of chelation theory [27]. Chelation reduces the polarity of the Th(IV) ions due to the partial sharing of positive charge with the imine and oxygen donor atoms and possibly the electron delocalization over the whole chelates ring system [28]. Therefore, chelating activities increases the lipophilic nature of the central metal atom, which enhances the penetration of the complexes into the lipid membrane of the microorganism cell wall and thus raising the activity of the complex and restricts the further growth of the organism [29,30].

Conclusion

On the basis of physicochemical and analytical studies discussed, bicapped square antiprismatic geometry for Th(IV) complexes is proposed. Antibacterial and antifungal studies confirmed that the ligands are biologically active and their Th(IV) complexes show enhanced activity against different strains, and same trend was followed for MIC. The interesting properties like porosity behavior may also be investigated in future studies.

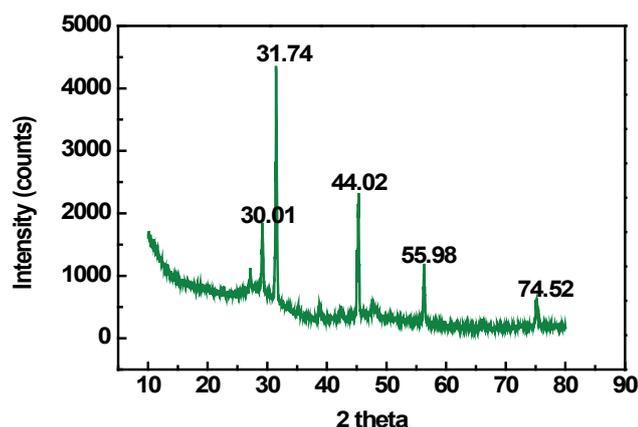


Figure 9: XRD spectra of $[\text{Th}(\text{L}^2)_2(\text{NO}_3)_3]\text{NO}_3 \cdot 6\text{H}_2\text{O}$ complex.

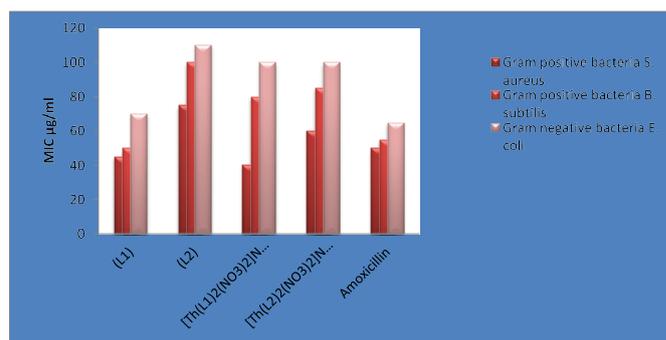


Figure 10: Antibacterial activities against ligands and their metal complexes.

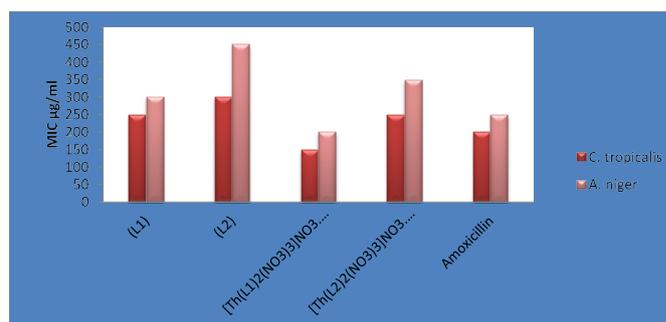


Figure 11: Antifungal activities against ligands and their metal complexes.

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