

Synthesis, spectral and evaluation of biological activity of Ni(II) mixed ligand complex containing 2-aminothiazole and triphenylphosphine

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ABSTRACT

A mixed ligand Ni(II) complex has been synthesized using 2-aminothiazole and triphenylphosphine in good yield. The structure was characterized by physico-chemical. The antimicrobial activity of the synthesized compound was evaluated against bacterias (*Staphylococcus aureus*, *Staphylococcus epidemidis*, *Bacillus cereus*, *P.aeruginosa*, *Vibrio cholerae* and *E. coli*) and two phytopathogens fungi (*Aspergillus aureus* and *Aspergillus fumigates*) using standard method at MIC level. Further the compounds are subject to insilco molecular docking studies on antibacterial receptor 1STE, the lowest docking results concludes that the compounds showing good intarctions with amino acids active sits of the receptor this evidence that the compounds binds to active sits of the receptor and suggesting that it can be a good antimicrobial agent. The complex showed significant antioxidant activity.

Keywords: Antimicrobial and antioxidant activities, Molecular docking studies.

INTRODUCTION

The drug resistance property of bacteria and fungi becoming a major worldwide problem. It is therefore need to design a suitable potent drug that overcome this resistance has become one of the most important area of research today [1]. During recent years coordination compounds of biologically active ligands [2] have received much attention. The presence of nitrogen, oxygen and sulphur in these complexes can enhance antitumor, antibacterial and antifungal activities of transition metal complexes [3]. Phosphine based ligands have widespread pharmacological applications including antiviral, antioxidant, antifungal, anticancerogenic, antibacterial and antitumor [4]. Particularly phosphine based nickel(II) complex has been reported to possess significant bioactivities [5]. These metals play vital role in controlling gene expression, inhibiting cell division and hence are used as valuable anticancer drugs. However, problem associated with such complexes is their ready dissociation in solution leading to very reactive species that are unable to reach their pharmacological targets such as DNA. This rapid aquation and formation of very reactive species could be overcome if nickel(II) complex are stabilized by bulky ligands such as triphenylphosphine. In this context, an attempt has been made to synthesize a pharmacological active new mixed ligand Ni(II) metal complex. The antimicrobial activity, molecular docking and the In-vitro antioxidant scavenging activity of the metal complex have been evaluated.

MATERIALS AND METHODS

General Experiments

2-Aminothiazole, Triphenylphosphine, Nickel chloride, LR grade methanol, LR grade were procured from Sigma-Aldrich (INDIA), Himedia (INDIA), Labo Chemicals (INDIA) were used as received without further purification. Freshly distilled ethanol and methanol solvents were employed for all synthetic purposes. Spectroscopic grade solvents were employed for spectral works.

The products of this reaction was authenticated by matching spectroscopic data of the products obtained with those of the reported in the literature. ¹H NMR spectrum recorded on Bruker 400 MHz spectrometer at IISc, Bengaluru, Karnataka, India. An elemental analysis was carried out with a Perkin-Elmer 2400 Series II C, H, N analyzer. Molecular weights of unknown compounds were characterized by LC-MS spectroscopy, Centralized instrumentation facility, Mysore University, Karnataka, India. Uv-vis spectra recorded on varian, Cary 5000. The Fourier transform infrared (FT-IR) spectrum of the compound was taken as KBr pellet (100 mg) the usage of a Shimadzu Fourier Transform Infrared (FT-IR) spectrometer. Melting point was determined in an electrically heated apparatus by taking the sample in a glass capillary sealed at one end.

Synthesis of [Ni(PPh₃)(ATH)Cl₂] (Ni(II) complex)

An ethanolic solution of NiCl₂ (0.5g, 3.6 mmol) was mixed with a hot stirring ethanolic solution of the 2-aminothiazole (0.36g, 3.6 mmol) and triphenylphosphine (0.94g, 3.6 mmol). The mixture was stirred with heating for 6 h, when the solid precipitated. The excess solvent was removed by filtration. The solid product was recrystallized from the methanol and the obtained complex was kept in a vacuum desiccator. The

melting point of the greenish coloured solid product was 190 - 196 °C. Yield: 65 %. Elemental analysis (%) found (Calculated) for $C_{21}H_{19}Cl_2N_2NiPS$: C - 51.81 (51.22), H - 4.13 (3.89), N - 5.69 (5.01), Ni -11.92 (11.99). $C_{21}H_{19}Cl_2N_2NiPS = 491.987$ g/mol (Fig.1).

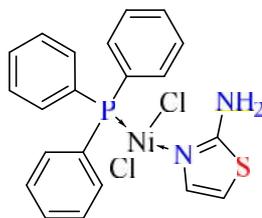


Fig. 1 Proposed structure of metal complex

Antibacterial screening

The antibacterial activity of the metal complex was tested against five different bacteria namely *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Vibrio cholerae* and *Escherichia coli* by agar well diffusion method as our previous paper [6].

Antifungal screening

Antifungal activity of the metal complex was evaluated against *Aspergillus aureus* and *Aspergillus fumigates* fungus, using the sabouraud dextrose agar diffusion method [6].

Molecular docking studies

The molecular docking study was done by following the procedure reported [6]. The insilico molecular docking has been carried out on the antibacterial receptor on PDB code: 1STE, the crystal structure of the receptor has been obtained from the protine data bank.

Antioxidant activity

This activity for the synthesized Ni(II) complex was performed using DPPH method as per literature [7].

RESULTS AND DISCUSSION

Chemistry

Synthesis of mononuclear mixed ligand Ni(II) complex was achieved by mixing stoichiometric amounts of 2-aminothiazole and triphenylphosphine (Fig.1). The metal complex is amorphous in nature and soluble in DMSO and DMF. The analytical data of the compound are consistent with their proposed molecular formula. The molar conductivities of 10^{-3} M of the complex (dissolved in DMF) at room temperature was measured and it was found that the value $4.29 \Omega^{-1}mol^{-1}cm^2$. Melting point found was 190 - 196 °C. Yield: 65 %. The elemental analyses of the Ni(II) complex was consistent with the calculated results from the empirical formula. Elemental analysis (%) found (Calculated) $C_{21}H_{19}Cl_2N_2NiPS$: C - 51.81 (51.22), H - 4.13 (3.89), N - 5.69 (5.01), Ni -11.92 (11.99). $C_{21}H_{19}Cl_2N_2NiPS = 491.987$ g/mol.

IR spectral studies

The infrared spectral data of the $[NiCl_2(pph_3)(Ath)]$ represented in Fig 2. The metal complex displayed a characteristic (ν_{N-H}) band at 3378 cm^{-1} , a medium intensity band at 1674 assigned to ($\nu_{C=N}$) the thiazole moiety. A broad band at 1645 cm^{-1} is the aromatic $\nu_{C=C}$ stretching. The band due to the ν_{S-CH_2} appeared at 720 cm^{-1} . the bands 620 and 480 cm^{-1} less intense absorption bands indicating ν_{M-O} and ν_{M-P} respectively.

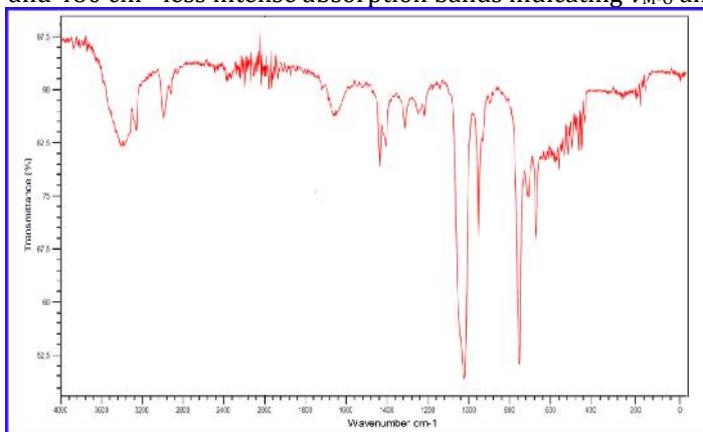


Fig 2. IR spectrum of $[NiCl_2(pph_3)(Ath)]$

Electronic absorption studies

The electronic spectrum (Fig 3) of the square planar nickel complex shows the two bands at 16,657, 18518 and 22,222 cm^{-1} which are attributed to ${}^3A_{1g} \rightarrow {}^3T_{2g}(v_1)$, ${}^3A_{1g} \rightarrow {}^3T_{1g}(v_2)$ and ${}^3A_{1g} \rightarrow {}^3T_{1g}(P)$ (v_3) transitions. These transitions, as well as the measured value of the magnetic moment ($\text{eff} = 0$) suggest a square-planar stereochemistry of the compound

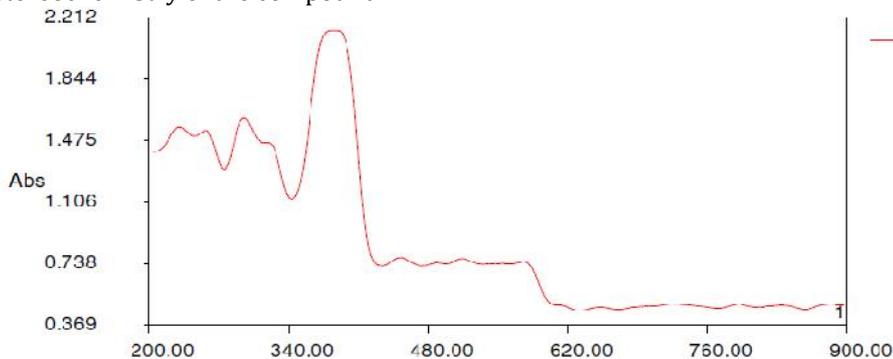


Fig 3. Uv-visible spectrum of $[\text{NiCl}_2(\text{pph}_3)(\text{Ath})]$

NMR spectral studies

The ${}^1\text{H}$ NMR spectrum of the $[\text{NiCl}_2(\text{pph}_3)(\text{Ath})]$ (Fig. 4) was obtained in DMSO-d_6 at room temperature. The spectrum of the Ni(II) complex showed a singlet due to the proton of thiazole -NH at 9.79 ppm. The multiplets appeared in the range 7.68 - 7.53 ppm for the aromatic ring protons of the triphenylphosphine and another two multiplets in the range 7.19 - 7.16 ppm represents the ring protons of the thiazole.

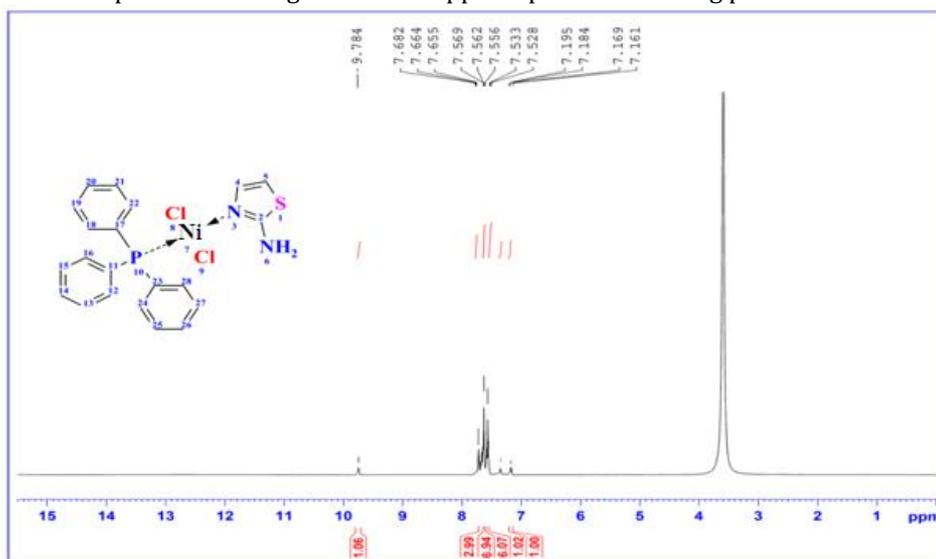


Fig 4. ${}^1\text{H}$ NMR spectrum of $[\text{NiCl}_2(\text{pph}_3)(\text{Ath})]$

In vitro antibacterial and antifungal activity

The results of antimicrobial activity in different concentrations metal complex is collected in Table 1. The inhibitory activity of complex is related to the cell wall structure of the microbes, which is essential to the survival of bacteria. We confirm that the toxicity of the complex can be related to the strengths of the M-L bond, size of the cation and receptor sites. In the present study, the Ni(II) metal complex are active against the bacteria and fungi, which may indicate broad-spectrum properties. The mode of action may involve the formation of a hydrogen bond through the tertiary nitrogen of the thiazole and phosphate of triphenylphosphine of rings with the active centers of the cell constituents, resulting in interference with the normal cell process.

As a result of this, the primary screening against the bacterial strains in different concentrations showed good zone of inhibition as shown in Fig 5 and Fig 6. The Ni(II) complex showed good antibacterial activity towards *B cereus*, *S aureus* and *E coli* respectively and the Ni(II) complex performs highest antifungal activity against *A aureus* and *A fumigates*, the primary screening against the fungal strains in different

concentrations showed good zone of inhibition as shown in Fig 4 and Fig 5. The MIC study of metal complex against bacterial and fungal strains at different concentrations i.e., 1, 10, 25, 50, and 100 µg/mL was evaluated. The MIC data of antimicrobial activity of the metal complex are reported in Table 2. The Fig 7 and 8 represents the MIC activity against bacterial and fungal strains. The Ni(II) complex showed potential MIC values against bacterial and fungal strains.

Table 1 Antimicrobial activity of Ni(II) complex

Entry	Conc µg/ml	Growth inhibition against <i>bacteria</i> in mm					Growth inhibition against <i>fungicides</i> in mm	
		P.aeruginosa	S.aureus	V.cholerae	S.epidermidis	B.subtilis	A.aureus	A.fumigatus
[Ni(PPH ₃)(Ath)Cl ₂]	25	18.06±0.05	12.03±0.2	18.10±0.26	19.03±0.25	14.01±0.2	12.17±0.2	18.20±0.20
	50	21.19±0.05	15.00±0.2	21.03±0.31	22.10±0.26	16.05±0.0	15.13±0.3	21.30±0.20
	100	22.06±0.04	17.06±0.0	22.13±0.31	25.00±0.20	19.00±0.1	17.00±0.2	22.27±0.23
Stnd ^a	100	30.00±0.01	18.12±0.0	19.25±0.14	29.03±0.31	28.05±0.45	-	-

*Each value is expressed as mean ± SD of three replicates for the zone of inhibition

*Stnd^a : Ciprofloxacin and Stnd^b : Fluconazole

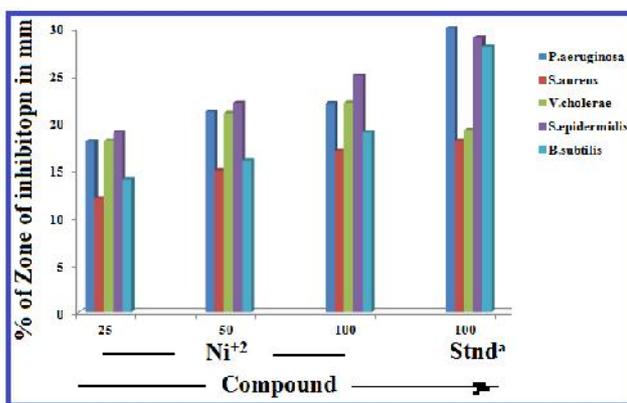


Fig 5. Antibacterial activity

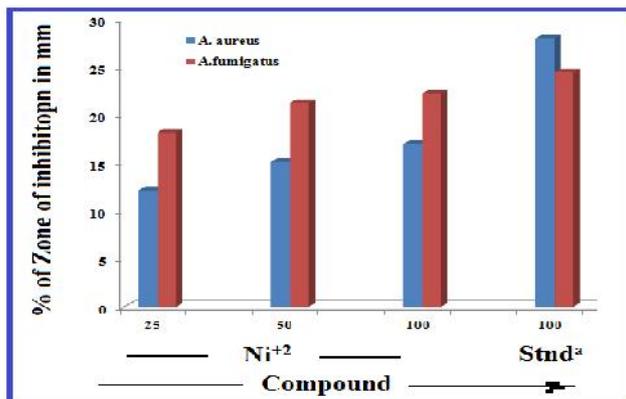


Fig 6. Antifungal activity

Table 2. MIC data of antimicrobial activity of the Ni(II) complex

Compound	Growth inhibition against bacteria in mm						
	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>V. cholerae</i>	<i>S. epidermidis</i>	<i>B. subtilis</i>	<i>A. aureus</i>	<i>A. fumigatus</i>
[Ni(PPh ₃)(ATh)Cl ₂]	500	250	500	500	250	250	500
Stnd ^a	250	250	250	NT	NT	-	-
Stnd ^b	-	-	-	-	-	250	NT

*Stnd^a: Ciprofloxacin and Stnd^b: Fluconazole

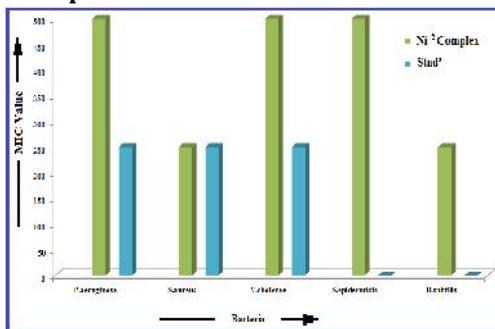


Fig 7. Antibacterial activity

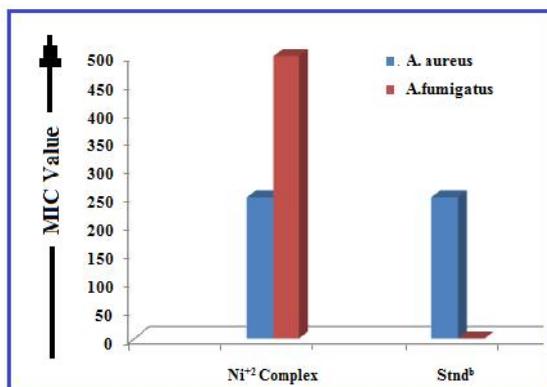


Fig 8. Antifungal activity

Molecular docking studies.

The results of the molecular docking revealed that the complex showd good binding intarctions with the antimicrobial receptor 1STE, which evident that they showd excelleant docking score -333.25 kcalmol⁻¹. The lowest binding scores indicates the best docking intractions with the selected antimicrobial receptor and it supports for the wet analysis which is to be carried out on the different bacterial strains. The complex showed their best docking intarctions with different amino acid residues as shown in Table 3 and indexed in the Fig 9.

Table 3. Intarction of complex with amino acids residues of receptor and binding score values

Docking receptor	Binding energy (kcal/mol)	Amino acid residues	Receptor PDB
Ni(II)	-333.25	Asn88, His31, Tyr32, Lys56, Leu56, Leu58, His78, Gln81, Pro749	PDB code: 1STE in Staphylococcus aureus

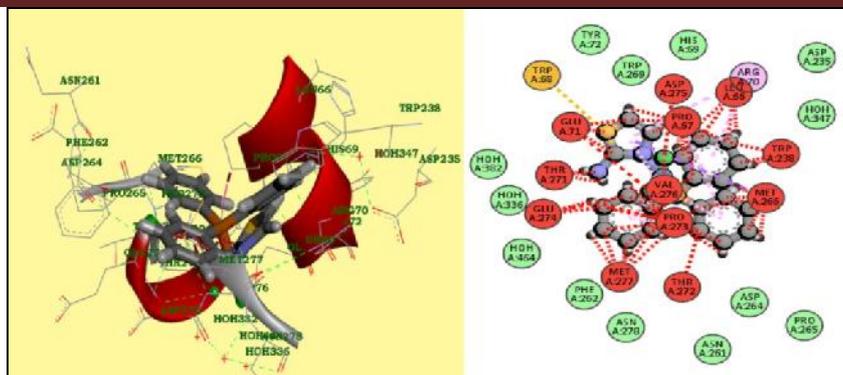


Fig 9. 2D and 3D interactions of Ni complex with (PDB code: 1STE) in *Staphylococcus aureus*

Antioxidant activity

The DPPH radical scavenging activity data represented in Table 4 and Fig 10. If DPPH abstracts a hydrogen radical from an external source, the absorption decreases stoichiometrically depending on the number of electrons or hydrogen atoms [8]. The metal complex showed significantly lower activity when compared to ascorbic acid (vitamin C) as standard. The Ni²⁺ complex exhibited better inhibitions activity against free radical.

Table 4: Radical scavenging activity of complex

Concentration (μL)	[Ni(pph ₃)(Ath)Cl ₂]
0	-
5	114.24 ± 0.01
10	84.75 ± 0.39
15	40.95 ± 0.14
20	29.60 ± 0.02
25	29.25 ± 0.18

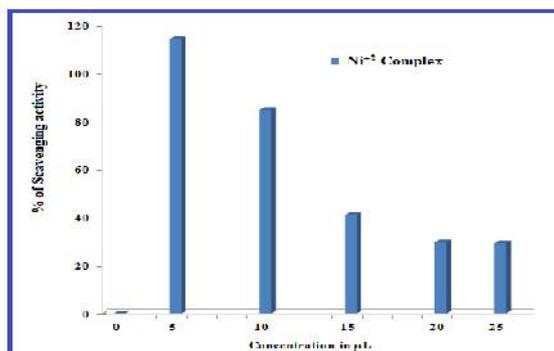


Fig 10. Antioxidant activity of complex

CONCLUSION

In the present work, we successfully designed and developed a mixed ligand Ni(II) mixed ligand complex. The Ni(II) complex have been characterized by various analytical techniques. The metal complex was further studied on its pharmacology by exposing to antimicrobial and antioxidant activity in different concentration. The Ni(II) mixed ligand complex performs good activity against both bacterial and fungal strains. The MIC studies of metal complex against bacterial and fungal strains at serial dilution were evaluated. Molecular docking studies reveals that Ni(II) complex have comparatively good binding interactions at amino acid residues presents at the active core of the receptor which evident that they are more biological potent this computational study is further supported from the *invitro* biological studies on bacterial and fungal strains.

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The richest man is not he who has the most, but he who needs the least.

~ Unknown Author