

Full Length Research Paper

Sustainable health in view: Synthesis, characterization and antibacterial activity of cobalt complex of thiosemicarbazide and 4-aminoquinoline mixed ligand

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In the present study, complex of cobalt(II) with mixed ligand of thiosemicarbazide and 4-aminoquinoline was reported. The complex was characterized by physical and spectral analysis. Antibacterial activity was carried out on the complex against *Salmonella typhi*, *Shigella* species, *Escherichia coli*, *Klebsiella* species, *Staphylococcus auerus*, *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. The complex of the type ML_1L_2 [$M=Co(II)$, L_1 = thiosemicarbazide and L_2 = chloroquine] was formed. The complex was non-electrolyte in methanol. The resulting complex was characterized by conductivity measurements and spectral studies. The mixed ligand used act as a neutral tridentate compound with tentative octahedral geometry with metal ions. The findings, using the chemical, spectroscopic analysis and physical properties showed that the ligand employed in this work coordinated to metals in 1:1:1 metal-ligand 1-ligand 2. The antibacterial activity was also carried out. The results showed that the complex possesses greater biological activity against the bacterial used and the metal complex possesses greater biological activities than the parent compounds. Thus, they could be promising candidates for novel drugs in pharmaceutical research.

Key word: Mixed ligand, antibacterial activity, metal complex, characterization, pharmaceutical research.

INTRODUCTION

Life threatening infections and diseases that are spreading all over the world daily, demand development of new antimicrobial agents that are highly efficient with lesser side effects and equally cost effective (Joseph et al., 2012). Metal complexes are preferred to simple ligands due to an increased activity and several sulphur containing metal chelates have been reported with significant antibacterial and antifungal activities (Bharty

et al., 2015; Yousef et al., 2015). Most thiosemicarbazones have been extensively studied because of their antibacterial, antifungal, antitumor, antiviral and anticancer activities (Beraldo and Gambino, 2004). Transition metal complexes of thiosemicarbazone have attracted the attention of chemists due to the presence of hard nitrogen and soft sulphur donor atoms which permits coordination with a

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metal ion in different binding mode yielding stable and intensely coloured complexes (Lobana et al., 2006). This versatile nature of the ligand has encouraged the authors to explore the coordination chemistry further and to make mixed ligand complexes together with a second ligand in such a way that it enhances biological activity (Brindha and Vijayanthimala, 2016).

For several decades, the 4-aminoquinolines(4A), chloroquine (CQ) and amodiaquine (AQ) were considered the most important drugs for the control and eradication of malaria. The success of this class has been based on excellent clinical efficacy, limited host toxicity, ease of use and simple, cost-effective synthesis. Importantly, chloroquine therapy is affordable enough for use in the developing world (O'Neill et al., 2011). Thiosemicarbazones are an important class among the sulfur-containing compounds, in view of their versatility in the coordination behavior and pharmacological applications. Thiosemicarbazones and their metal complexes are well known for their anticarcinogenic, antibacterial and antifungal properties (Quiroga and Raming, 2004).

It has been shown in the literature that the metal derivatives are more effective than the free ligands in anticancer activity. One of the many reasons is that the binding affinity of metals to proteins or enzymes will change the interaction process with DNA, thereby affecting DNA replication and cell proliferation (Saha et al., 2002). In this context, hybrid chelate ligands containing mixed functionalities are widely used as ligands for the isolation of interesting and important metal complexes (Cowley et al., 2006). Thiosemicarbazide is a white crystalline powder and is odorless. This material is used as a reagent for ketones and certain metals, for photography and as a rodenticide. It is also effective for the control of bacterial leaf blight of rice. It is not a registered pesticide in the U.S. It is a chemical intermediate for herbicides and a reagent for detection of metals (EPA, 1998)

Statement of problem

The serious medical problem of bacterial and fungal resistance and the rate at which it develops has led to increasing levels of resistance to classical antibiotics (AL-Daher et al., 2011). The discovery and development of effective antibacterial and antifungal drugs with novel mechanism of action have become an urgent task for infectious diseases research programs (Jin et al., 2005). Many investigations have proved that binding of drug to metallic element enhances its activity and in some cases, the complexes possess even more heating properties than the parent drug (Gupta et al., 2007). Al-Amiery et al. (2011) reported the synthesis characterization and biological properties of Co(II), Ni(II) and Cu(II) complexes with N-amino quinolone derived

from 2-hydroxybenzaldehyde (for L1) and (1-(1H indol -3-yl) ethanone for L2, and Hassan (2017) reported the preparation, characterization and antimicrobial of some new complexes formed by the reaction of manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II) salt with Schiff bases derived from reaction of N-amino quinolone with benzoin and 4-acetylpyriden.

Also, Adekanmbi (2015) reported on synthesis, characterization and antibacterial activity of cobalt(ii) complex of 8-hydroxyquinoline mixed with hydrazine and Kulkarni et al. (2010) reported on spectroscopy, electrochemistry and structure of 3d-transition metal complexes of thiosemicarbazones with quinoline core: Evaluation of antimicrobial property.

The present research reports the preparation, characterization and antimicrobial of new complex formed by the reaction of cobalt(II) salt with Schiff base derived from reaction of 4-aminoquinolone with thiosemicarbazide.

Objective

1. To synthesize mixed ligand of 4-aminoquinoline and thiosemicarbazide
2. To complex the mixed ligand with cobalt(II) salt.
3. To characterize both the ligand and the cobalt(II) complex.
4. To analyze the antibacterial activity of both the ligand and the complex.

METHODOLOGY

Synthesis of 4-aminoquinoline-thiosemicarbazide mixed ligand

4-Aminoquinoline (0.01 mol) in ethanol (100 mL) was treated with thiosemicarbazide (0.01 mol) in methanol (100 mL). The reaction mixture was refluxed for 3 to 4 h and the yellow solid separated was filtered, washed two to three times with ethanol, and dried (Scheme 1) (Kulkarni et al., 2010).

Synthesis of cobalt(II) complex of the mixed ligand

Ligand (0.001 mol) was taken in 35 to 40 mL of hot ethanol. To this, a hot ethanolic solution of metal chloride (0.001 mol) was added drop-wise with stirring at 60 to 65°C. After complete addition of metal salt solution, the reaction mixture was stirred for another 30-40 min at the same temperature and refluxed for 3-4 h in a water bath. The isolated complexes were filtered in hot condition, washed with hot ethanol and dried (Kulkarni et al., 2010).

Antimicrobial activity

The individual organism were individually grown overnight on nutrient agar slant at 35°C. The suspension was then prepared by washing the growth off with the normal saline solution and further serially diluted with sterile 20 ml phosphate buffer to give counts of factor of 1×10^6 cfu/ml. The ligand and its Co(II) complex was studied for their antibacterial activities by agar

Table 1. Physical properties of ligand and complex.

Sample number	Ligand	Colour of product	Nature of product	Percentage yield (%)	Melting point (°C)
A	(TSC-4A)	White	Amorphous powder	73	195
B	Co(TSC-4A)	Pink	Crystalline salt	67	235

Table 2. Solubility data of the ligand and metal complex

Sample number	Ligand/complex	Distilled water	Methanol	Ethanol	Acetone	DMF	DMSO	DiI Hcl
A	TSC-4A	SC SH	NSC SSH	SC-SH	SSC SSH	SC SH	SC SH	SC SH
B	Co(TSC- 4A)	NSC SSH	NSC SSH	SC SH	SSC SSH	SC SH	SC SH	SSCSH

SC- soluble in cold, SH- soluble in hot, NSC- soluble in cold, NSH- not soluble in hot, SSC- sparingly soluble in cold and SSH- sparingly soluble in hot.

Table 3. Result of metal content analysis

Sample number	Complex	Concentration (Mg/L)
B1	Co(TSC-4A)	240.73

Table 4. Result of conductivity measurement of ligand and metal complex.

Sample number	Compound molecular formular	Molar mass	Conductivity($\Omega\text{cm}^2\text{Mol}^{-1}$)
A	TSC-4A	410.50	-
B	Co(TSC-4A)	504.93	1.6×10^{-4}

diffusion method, respectively, in DMF solvent against *Salmonella typhi*, *Shigella* species, *Escherichia coli*, *Klebsiella* species, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae* bacterial species using agar nutrient as the medium and gentamycin as the standard drug. The stock solution (10 mg/10 mL) was prepared by dissolving the compounds in DMF.

A circular well was made at the center of each Petri dish with a sterilized steel borer. Then, 0.1 mL of each test solution was added to the well using a micropipette and the plate was incubated for 24 h for bacteria growth and the diameter of inhibition zone was noted (Halli et al., 2012).

RESULTS

The physical properties of the products are presented in the Table 1 and the result of the solubility tests carried out on the products is presented in Table 2. Also, the result of the metal content analysis is presented in Table 3 and conductivity measurement is presented in Table 4, while UV-visible and infrared spectral analysis result are presented in the Tables 5 and 6, respectively. The reaction mechanism is as follows: $\text{MX}_2 \cdot n\text{H}_2\text{O} + \text{L}_1\text{L}_2$ (where $\text{M}=\text{Co}$, $n=2, 4$, L_1 = thiosemicarbazide, L_2 = 4-aminoquinoline).

DISCUSSION

The complex obtained in the present study was non-hygroscopic and in the form of amorphous powder. The metal complex is easily soluble in DMSO and DMF and sparingly soluble in ethanol and methanol. Mixed metal complexes were obtained in good yield by the condensation reaction of aqueous/alcoholic solutions of chloroquine and the corresponding thiosemicarbazide. The mixed ligand (TSC-4A) is mainly white in colour, soluble in water and organic solvents. On heating, especially in the presence of metal ions, due to complexation, their solubility shows a dramatic increase. The molar conductivity of aqueous solution of these ligands corresponds to 1:1:1 of type non-electrolyte. The complex was obtained by the simple template method, that is, by the reaction of ready-made mixed ligand and metal salt, mainly in warm alcoholic (less often aqueous) solution under an air atmosphere. Considering the metal complex been prepared and investigated, the composition can be represented by the following general formulas

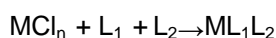


Table 5. Ultraviolet-visible spectra.

No.	Compound	Wavelength (nm)			
		Band 1	Band 2	Band 3	Band 4
A	TSC-4A	190	215	280	345
B	Co(TSC-4A)	190	215	255	-

Table 6. Infrared spectra.

A – TSC-4A	3362.63	3164.83	-	1616.35	1273.00	-
B – Co(TSC-4A)	3752.74	3129.00	2351.64	1618.67	-	578.34
Tentative assignment	υ N-H str. of NH ₂	υ N-H str.	υ S-H str.	SO ₂ -N	C-N str.	M-L

Where, $M=Co^{2+}$, $L_1 = 4$ -aminoquinoline and $L_2 =$ thiosemicarbazide.

Ligand and complex formed exhibited various colour characteristics. They vary from white powdery to pink powdery salt. The complex is well soluble in DMF and DMSO, less soluble in MeOH, EtOH and H₂O. The TLC of the metal complex showed a single spot, implying the complex is pure. The spot of the complex and the ligand appear at very closer range, since they have similar functional group. The molar conductance of the solid complex ($\lambda m \Omega^{-1} cm^{-2} mol^{-1}$) was calculated. The DMF solubility of the complex made calculations of the molar conductivity (λm) of $10^{-3} mol dm^{-3}$ solution at 25°C possible. The data in Table 4 showed that the molar conductance is of relatively low value for the Co(II), indicating the non-electrolytic nature of this complex.

Spectra analysis of the complex

UV-visible absorption of TSC-4A and its Co(II) complex

The absorption bands for chloroquine-thiosemicarbazide and its cobalt complex showed that Co complex gave strong absorption bands and within the range of 190 and 345 nm. These bands are tentatively assigned to charge transfer and intra-ligand transitions, based on other relative intensities and positions. UV-Visible spectra of this ligands and its complex have been interpreted in terms of charge transfer transitions from the metals to the antibonding orbital of the ligand and of the $\pi \rightarrow \pi^*$ transitions of the ligand. The ultraviolet spectrum of the free TSC- 4A showed five absorption bands at 190, 215, 250, 310 and 345 nm. These transits involve energies of 52631, 46511, 40000, 32258 and 28985 cm^{-1} . These bands are assigned to $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ transition, respectively. These bands undergo hypsochromic and bathochromic shifts in the metal complexes due to complexation.

Co-TSC4A complex has an electronic configuration of d^7 and a spectroscopic ground state term symbol of $4F$. The $4F$ orbital is split in an octahedral field into sub-energy levels. Three absorption bands were observed in the spectrum of this complex at wavelength 190, 215 and 255 nm. Transition involved is $52631 nm^{-1}$, and 46511 and $39215 cm^{-1}$; they are assigned to charge transfer transitions. However, other expected higher transitions for the complex appear to have been submerged by the more intense transition because of their low intensity.

IR-spectra of the mixed thiosemicarbazide-4-aminoquinoline and its metal complex

The important IR spectra bands of both the ligand and the metal complex with their assignment are given in the Table 6. The IR spectrum of the ligand exhibited a very strong broad bands with a peak maximum at 3364 and 3368 cm^{-1} , which are ascribed to the $\nu(N-H)$ vibration of amine group and H₂O along with $\nu(N-H)$ vibrations. Similar bands were observed for the complex but with reduction in intensity and also red shift when compared with the ligand. The increase and shifts in the absorption frequency of the $\nu(N-H)$ band for the complex relative to free ligand is a strong evidence of coordination with one of the N-H bands of thiosemicarbazide. The very strong $\nu(C-N)$ band in 4-aminoquinoline was at 1643 cm^{-1} . This is close to the value characteristic for the majority of the ligand, in the complexes shifted to higher energies by 10-20 cm^{-1} . A number of bands in the range of 1433-1150 cm^{-1} in the spectra of both ligands and complexes are ascribed to $\nu(S=O)$, $C=S$, $\delta(NH_2)$ and $C=C$ of the aromatics.

Discussion of the antimicrobial assay minimum inhibitory concentration in mm

Generally, the ligands and metal complexes showed antimicrobial effect against the tested organism species.

Neissera gonorrhoea and *Pseudomonas aeruginosa* was the most sensitive organism to the mixed ligand and its metal complex. Metal complex showed comparable activity or greater activity against some of the micro-organisms in comparison with the parent compounds.

For a particular antibacterial, the organism involved is an important factor, *S. typhi*, *S. species* and *P. aureginosa* sensitive to the metal complex than the organism *Klebsiella species*, *E. coli* and *S. aureus*.

Conclusion

Synthesis and analysis

Thiosemicarbazide represents a relative group of tridentate ligands of the Schiff-base type, exhibiting good complexing properties. Depending primarily on the synthesis conditions, pH and nature of the metal ion, they coordinated with transition metals as single and mixed ligands. Chloroquine is an antimalarial compound belonging to a group of aminoquinoline compounds. They also possess good complexing properties with potential binding sites like N and S. Under the different conditions isolated, they were found to be mainly powder and crystalline salts. The compounds have varying colours depending on the metal salts used. The stoichiometries and the structure of the different types of complex reported here are based mainly on the micro analytical and spectroscopic data. The ratio of metal to ligand of the complex is 1:1:1 for double ligand complex. The complex shows 6-coordinated geometry. It was observed from study that thiosemicarbazide coordinate to metal through the sulphur and nitrogen of the hydrazine and amine, while 4-aminoquinoline is through one of the nitrogen of hydrazine and that of the quinolone ring. These were also confirmed from the infrared spectra. The UV-Visible spectra displayed no d-d transition in the complexes due to very low intensity of the peaks.

The complex showed good solubility in DMF and DMSO solvents but fairly in ethanol, methanol and others. Attempt to grow single crystal from the powdered sample failed.

Biological studies

The metal complex studied for its antibacterial activities showed comparable and even higher activity than the parent compounds. In general, the metal complex was most active against *N. gonorrhoea*.

Contributions to knowledge

More effective antimicrobial complexes could be

synthesized using transition metals together active ligands.

RECOMMENDATIONS

It is suggested that the complex be tested on virus as well. The ligands should be used to synthesize other metal complex using copper, nickel and other transition metals and tested accordingly. The antimicrobial activities should be compared amongst various metal complexes of CQ-TSC. The electrochemistry of the complex should be studied to characterize the redox process which may occur in the ligand and complex.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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