Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (3): 1213-1222

(International Peer Reviewed Journal)

Structural Characterization Antimicrobial and Antioxidant Properties of Novel 4-(2,3-dimethoxyphenyl)-2,6-bis(1,3-thiazol-2-yl)pyridine and its Cu(II) and Ni(II) Complexes

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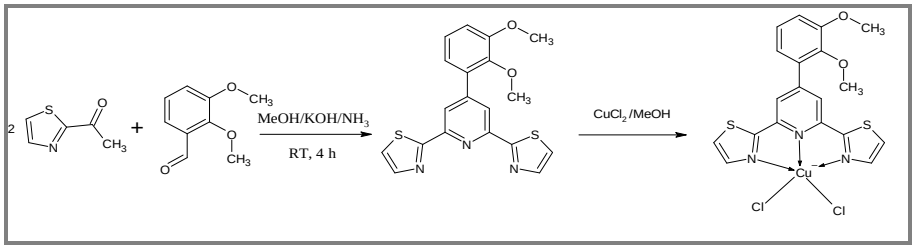
Accepted on 8th April, 2019

ABSTRACT

*4-(aryl)-modified-2,6-di(1,3-thiazol-2-yl) pyridine are an interesting ligands and have attracted significant attention due to their complexes forming ability with various transition metals. So here we synthesized a novel ligand 4-(2,3-dimethoxyphenyl)-2,6-bis(1,3-thiazol-2-yl)pyridine and its Cu(II) and Ni(II) complexes. All the prepared compounds have been characterized by ^{1}H NMR, ^{13}C NMR, ESI mass, FT-IR,UV. Newly synthesized ligand and its Cu(II) and Ni(II) metal complexes were screened for their antibacterial and antifungal activity by minimum inhibitory concentration (MIC) method. Also, all the synthesized compounds were studied for their antioxidant activity and hemolytic activity. The antioxidant activity of the ligand (**L**) and its metal complexes were evaluated by reduction of 1,1-diphenyl-2-picryl hydrazyl (DPPH). Interestingly, ligands and its complexes exhibit non-toxic property as it did not cause any effect human erythrocyte suggesting its nontoxic property.*

Graphical Abstract



Synthesis of Ligand(L).

Keywords: Ligands, Complexes, Antibacterial, Antifungal, Antioxidant activity.

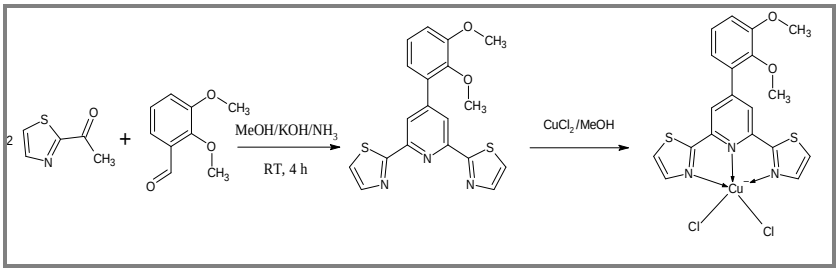
INTRODUCTION

Thiazoles are a very important class of heterocyclic compounds possessing various biological and pharmaceutical activities, such as antibacterial, antifungal, antioxidant, antitumor, anti-inflammatory, antiviral, antidiabetic and antitubercular etc [**1-10**]. The discovery of compound 2,2':6',2''-terpyridines (tpy), have attracted widespread attention because of their excellent complexing capacity as N-donor ligands towards various transition-metal and lanthanide cations [**11-16**] Compounds containing acetylthiazole or acetylpyridine are the starting material for the formation a ligand by Kroenke pyridine ligand synthesis. The copper complex of bis-phenanthroline Cu (phen)2 $^{2+}$ was first reported as an effective DNA cleaving agent. Many copper based chemical nucleases have attracted significant attention. So many novel ligands and metal complexes were reported on 2,2':6',2''-terpyridines derivatives but very few ligands and Metal complexes of 4-(aryl)-modified-2,6-di(1,3-thiazol-2-yl) pyridine were known. Also, metal complexes of 4-(aryl)-modified-2,6-di(1,3-thiazol-2-yl) pyridine have attracted widespread scientific attention because of their capability to form complexes with various transition metals and in view of their interesting photophysical, electronic, photonic, magnetic, reactive and structural properties, as well as promising applications in supramolecular chemistry, catalysis, molecular magnetism, molecular electronics, and anti-tumor therapy. These ligands and their various transition metal complexes also extensively studied for their photophysical and various biological and pharmacological activities like DNA binding, DNA cleaving agents, cytotoxicity, DNA interaction, anticancer activity, DFT calculations, photoluminescence and catalytic activity, antitumor, antimicrobial, or anti-HIV agents [**17-26**].

MATERIALS AND METHODS

General and Instrumental: Reagents required for the synthesis of ligand and its metal complexes were purchased commercially from Merck and Sigma Aldrichand used without any further purification. Solvents purchased from Spectrochem and were of analytical grades..Melting points of the compounds were recorded on a hot stage Gallen Kamp melting point apparatus. By using FTIR.8300 Shimadzu spectrophotometer,IR spectra of samples were recordedin the frequency range of 4000-200 cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker 400 MHz spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. Elemental analysis carried out by a standard method and UV spectra recorded using UV spectrophotometer [**2, 14**]. Mass spectrum recorded on Mass Spectrophotometer.Elemental analysis was done by standard methods.

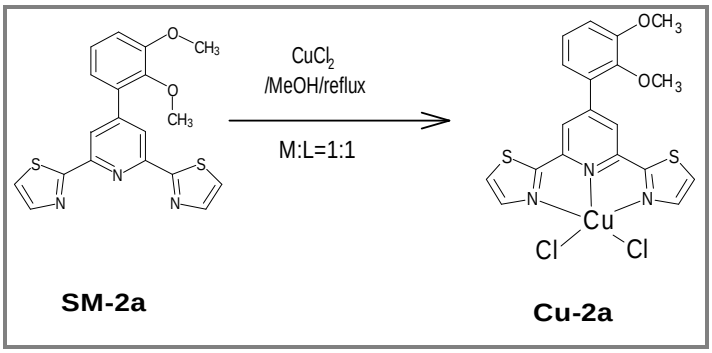
Preparation of2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole (L^{1}): 2-acetylthiazole (2 mmol) taken in a 100 mL round-bottom flask, was added MeOH (30 mL), KOH pellets (0.560 g, 4 mmol) and 2 mL of water, the mixture was stirred 10 min and then added the corresponding 2,3-dimethoxybenzaldehyde (1 mmol) at room temperature continued stirring at 4 h.The solid was filtered and washed with methanol and then diethyl ether. The yellow colored solid with 85% yield obtained. The ligand obtained used for complexation without further purification [**16-18**].



Scheme 1. Synthesis of Ligand(L).

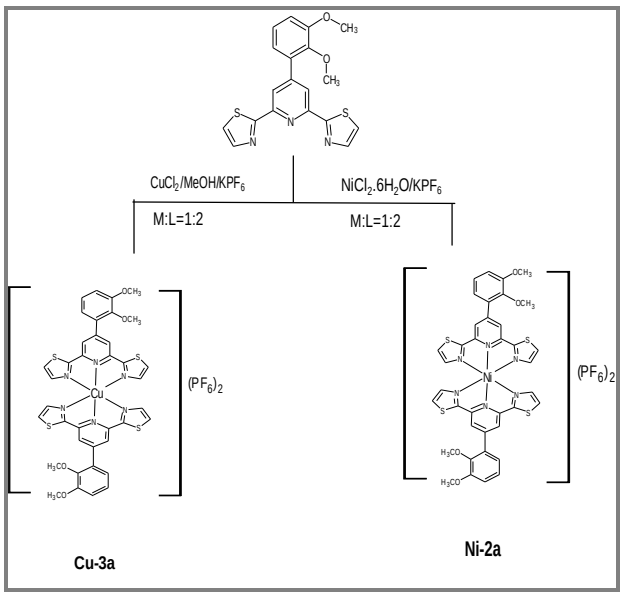
^{1}H NMR (400 MHz, d6-DMSO): δ 8.400 (s, 2H, $H^{B3,5}$), 7.927-7.935 (d, 2H, J = 3.2 Hz, H^{A2}), 7.462-7.469 (d, 2H, J =2.8 Hz, H^{A3}), 7.126-7.166 (t, 1H, J = 7 Hz, ArH), 7.073-7.097 (d, 1H, ArH), 6.994-7.018 (d, 1H, ArH), 3.919 (s, 3H, OCH_3), 3.730 (s, 3H, OCH_3), ;^{13}C{^{1}H} NMR (100 MHz, δ ppm): 168.853, 153.179, 150.961, 148.762, 146.923, 144.141, 132.466, 124.332, 122.017, 121.637, 120.626, 113.543, 61.083, 56.053; FT-IR (ν, cm^{-1}): 3066, 1585, 1536, 1466, 1427, 1323, 1272, 1215, 1112, 1044, 993, 862, 794.

Preparation of Copper metal complexes (M:L=1:1): A solution of $CuCl_2{\cdot}2H_2O$ (1 mmol) dissolved in 5 mL methanol was added to a methanolic solution (10 mL) of the 2,2'-(4-(2,3-dimethoxyphenyl) pyridine-2,6-diyl)dithiazole (L^1). The mixture was stirred at room temperature overnight. The green precipitate was collected and dried with diethyl ether, recrystallized in methanol. The obtained product was identified by IR spectra. Cu(**L^1**)Cl_2: 3020, 1613, 1564, 1471, 1414, 1262, 1221, 1112, 1016, 978, 788.



Scheme 2. Synthesis of Cu(II) Complex.

Preparation of Copper/Nickel metal complexes (M:L=1:2): Cu-3a and **Ni-2a** complex was prepared by same procedure as Cu-2a by taking Metal to ligand ratio 1:2.Then2 equivalents of KPF_6added as counter ion. A green precipitate filtered and dried with diethyl ether. Copper complex, **[Cu-2a] :**Dark Green solid: **FT-IR** (ν, cm^{-1}): 3012, 2677, 1641 (C=N), 1602(C=C), 1311(C-N); **UV-Vis.:** λ_{max}: 462nm, **Nickel complex, [Ni-2a]:** light green solid: **FTIR** (ν,cm^{1}):2815, 1738(C=N), 1575(C=C), 1318(C-N); **UV-Vis.:** λ_{max}: 495 nm.



Scheme 3. Synthesis of Cu, Ni Complexes.

Table 1. Analytical Data of Metal Complexes

Compound	L	Cu-2a	Cu-3a	Ni-2a
Empirical Formula	$C_{19}H_{15}N_3O_2S_2$	$C_{19}H_{15}Cl_2CuN_3O_2S_2$	$C_{38}H_{30}CuF_{12}N_6O_4P_2S_4$	$C_{38}H_{30}NiF_{12}N_6O_4P_2S_4$
Mol.Wt	381.47	515.91	1116.41	1111.56
C	59.72	44.32	40.85	41.16
H	3.46	2.74	2.70	2.62
N	11.00	8.11	7.50	7.66
O	8.40	6.12	5.13	5.54
S	16.21	12.24	11.54	11.25
Cl	-	13.74	-	-
P	-	-	5.51	5.74
F	-	-	5.60	5.62
M (Cu, Ni)	-	12.20	5.60	5.20

Antibacterial and antifungal assay: Thiazoles are found to exhibit various biological and pharmaceutical activities, such as antifungal, antibacterial, and hence all the synthesized compounds were screened for their antimicrobial evaluation.

The antibacterial activities of compounds were determined against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) bacteria by tube dilution method [27]. For bacteria double strength nutrient broth-(I.P.) media and for fungi sabourand's glucose broth media (I.P.) were used. For bacteria, the samples were incubated at 36°C for 24 h. For fungi, the samples were incubated at 25°C for 7 days for A. Niger and for C. albicans, the samples incubated at 37°C for 2 days. The results obtained were recorded in terms of minimum inhibitory concentration (MIC). Ciprofloxacin and fluconazole were taken as standard drugs for antibacterial and antifungal activity, respectively [28]. To determine the MIC of compounds, dilution of standard drugs and test compound were prepared in test medium to give a concentration of 50, 25, 12.5, 6.25, 3.125 and 1.56 µg mL^{-1} from a stock solution (100 µg mL^{-1}). All the samples were inoculated with a 0.1ml suspension of bacteria in saline and incubated at the required temperature. MIC was determined by the lowest concentration of sample that prevents the development of turbidity. Compounds showed significant antimicrobial activity against different strains.

Table 2. Antibacterial activity

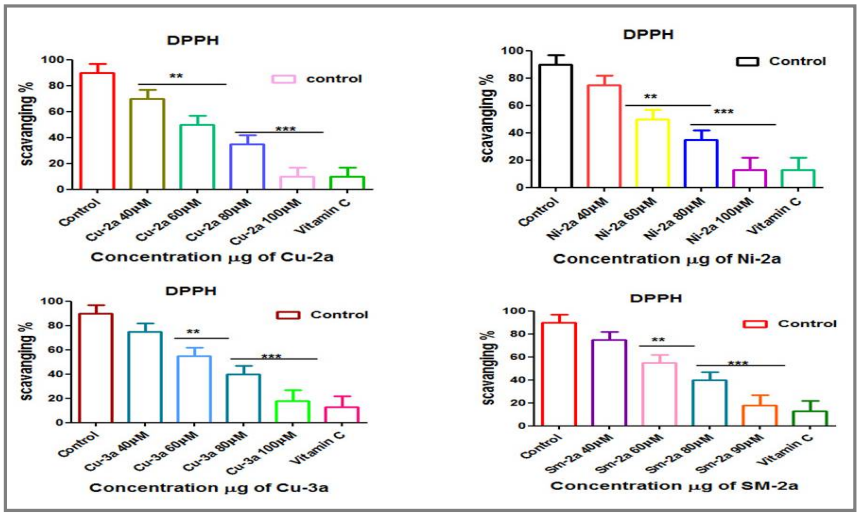
Compounds	Bacterial strains		Fungal strains	
	S. aureus	*E. coli*	*C. albicans*	*A. niger*
L	1.271	1.271	1.213	1.213
Cu-2a	1.012	1.012	1.012	1.013
Cu-3a	1.160	1.160	1.160	1.160
Ni-2a	1.869	1.869	1.869	1.869
standard	0.471	0.471	0.510	0.510

Standard: Ciprofloxacin (antibacterial) and Fluconazole (antifungal)

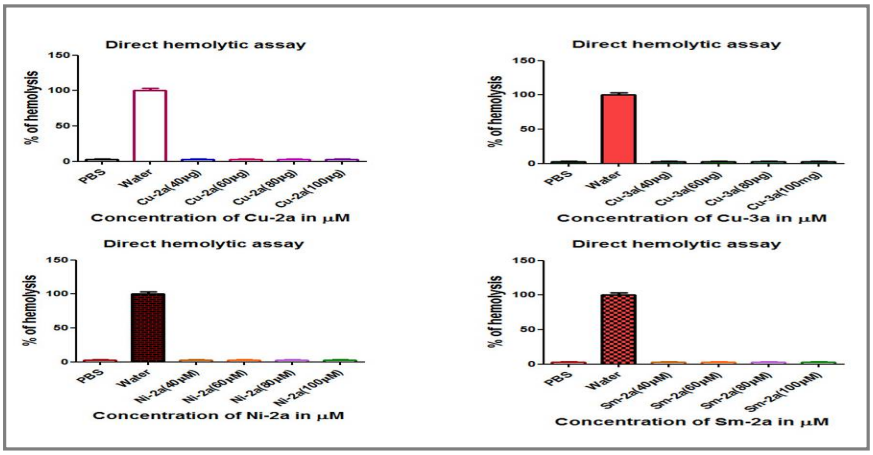
DPPH free radical scavenging assay: 1, 1-diphenyl-2-picryl-hydrazine (DPPH), free radical scavenging activity of present **Cu-2a, Ni-2a, Cu-3a and Sm-2a**was studied by reported method [29]. Different concentration of present **Cu-2a, Ni-2a, Cu-3a and Sm-2a** (20, 40, 60, 80 and 100 µM mL^{-1}) was added at 1 mL to 3 mL methanol solution of DPPH (10 mg 250 mL^{-1}) (Assay 1). The mixture was shaken and then incubated in a dark place at room temperature for 30 min. Finally, the absorbance of each mixture was recorded at 517 nm. The absorbance of DPPH (containing no sample) was recorded as a control. The experiment was done in triplicates. Vitamin C was performed as the standard antioxidant. The percentage of free radical scavenging was calculated using this formula.

Direct hemolytic activity by the colorimetric method: Direct hemolytic activity was determined using washed human RBC. Briefly, packed human erythrocytes and PBS (1:9 v/v) were mixed; 1 mL

of this suspension was incubated independently with the various concentrations of **Cu-2a, Ni-2a, Cu-3a and Sm-2a** (20, 40, 60, 80 and 100 µM mL^{-1}) for 1 h at 37°C. The reaction was stopped by adding 9 ml of ice-cold PBS and centrifuged at 1000 g for 10 min at 37°C (Assay 2). The amount of hemoglobin released in the supernatant was measured at 540 nm. Activity was expressed as the percentage of hemolysis against 100% lysis of cells due to the addition of water that served as positive control and PBS served as negative control.



Assay 1. 1, 1-diphenyl-2-picryl-hydrazine (DPPH), free radical scavenging activity.



Assay 2. Direct hemolytic activity

RESULTS AND DISCUSSION

All the synthesized ligand and metal complexes are colored solids, amorphous. Elemental analysis carried out by standard methods and there good correlation between theoretical and experimental values, analytical data given in table 1**.**

^{1}H NMR and ^{13}C NMR Spectrum: ^{1}H NMR (400 MHz, d6-DMSO): δ 8.400 (s, 2H, $H^{B3,5}$), 7.927-7.935 (d, 2H, J = 3.2 Hz, H^{A2}), 7.462-7.469 (d, 2H, J =2.8 Hz, H^{A3}), 7.126-7.166 (t, 1H, J = 7 Hz, ArH), 7.073-7.097 (d, 1H, ArH), 6.994-7.018 (d, 1H, ArH), 3.919 (s, 3H, OCH_3), 3.730 (s, 3H, OCH_3);^{13}C{^{1}H} NMR (100 MHz, δ ppm): 168.853, 153.179, 150.961, 148.762, 146.923, 144.141, 132.466, 124.332, 122.017, 121.637, 120.626, 113.543, 61.083, 56.053; FT-IR (ν, cm^{-1}): 3066, 1585, 1536, 1466, 1427, 1323, 1272, 1215, 1112, 1044, 993, 862, 794.

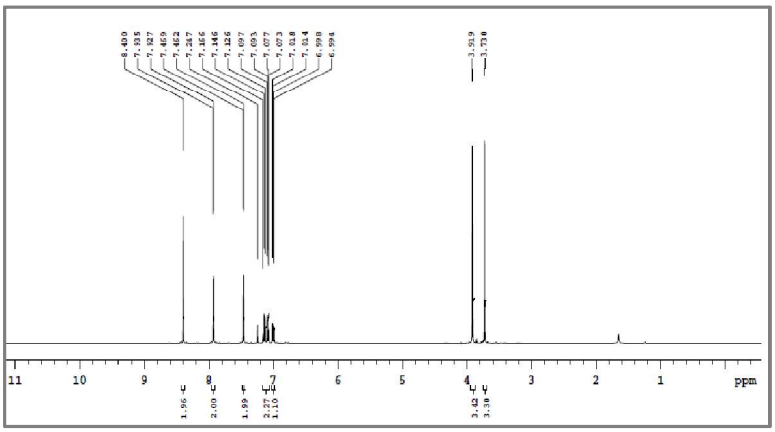


Figure 1. ^{1}H NMR (400 MHz)spectrum of 2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole (SM-2a) in $CDCl_3$.

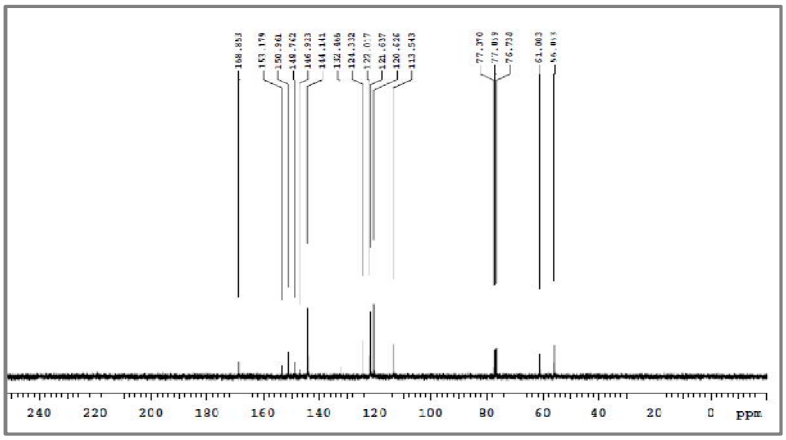


Figure 2. ^{13}C -NMR (100.6 MHz) spectrum of 2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole (SM-2a) in $CDCl_3$.

Mass Spectrum: In the mass spectrum of ligand2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl) dithiazole the molecular ion was displayed at$M^{+\cdot}$382 which is equal to its molecular weight, this on the loss of hydrogen radical gave fragment ions peak recorded as m/z 381 (100%)which also a base peakas shown in figure 3.

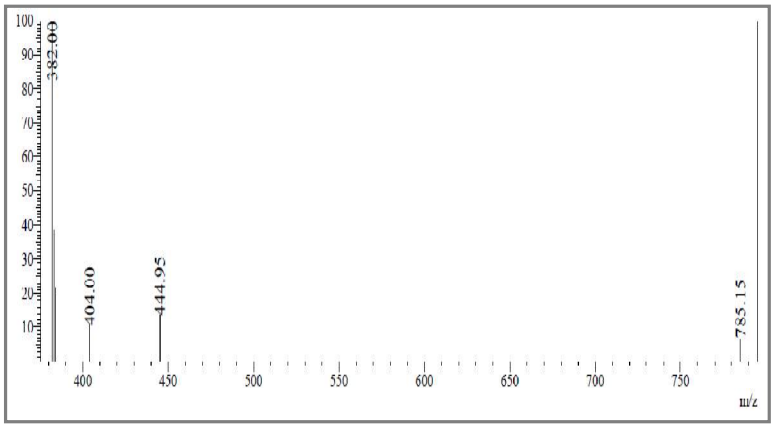


Figure 3. Mass Spectrum of 2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole.

FTIR Spectrum: The IR spectrum exhibits the absorption band at 1742(w) cm^{-1} due to terpyridine stretching, the absorption band at 1195(M) cm^{-1} due to -C-N stretching and 3167 cm^{-1}, 3073 cm^{-1} due to –C-H stretching and 1406 cm^{-1}(s) due to (C-O) (Figure 4)

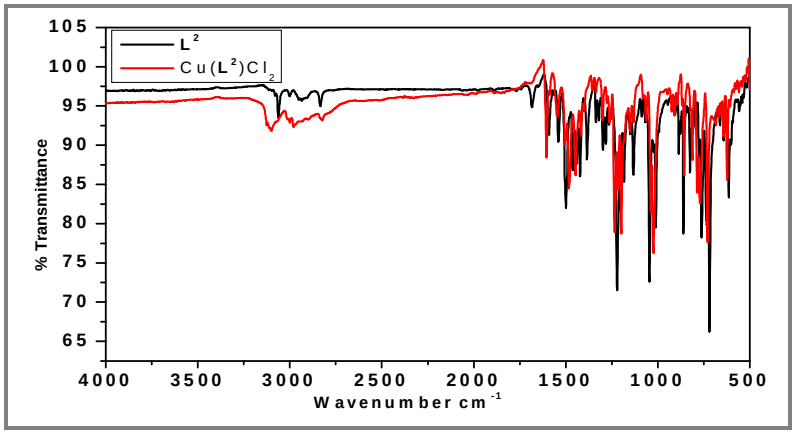


Figure 4. FTIR Spectrum of Ligand and Complex.

UV-Visible Spectrum: The UV-visible absorbance spectra of the synthesized2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole were studied in $CHCl_3$. The absorption spectra of ligand exhibit broad absorption bands between 300 and 331 nm. These absorption bands were attributed due tostrong π-π* transitions of delocalized π electrons in the **SM-2a.**

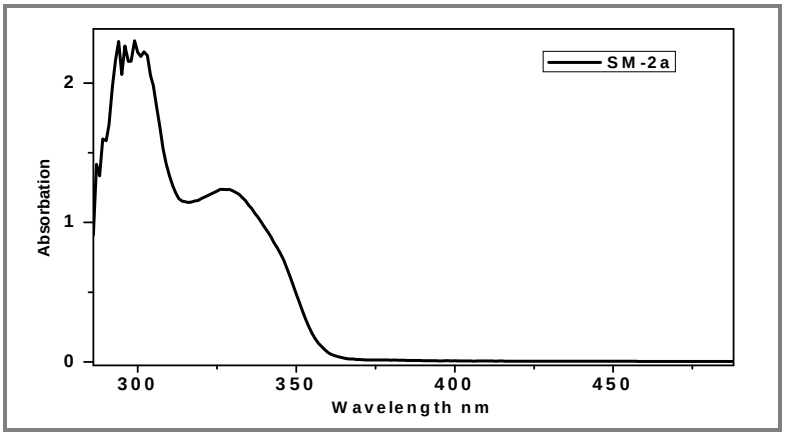


Figure 5. UV Spectrum of Ligand and Complex.

Antibacterial and antifungal assay: All the synthesized compounds showed significant antimicrobial activity against bacterial strains and fungal strains. Interestingly, Copper complexes showed more antimicrobial activity as compared with the ligand.

DPPH free radical scavenging assay: The efficiency of **Cu-2a, Ni-2a, Cu-3a and Sm-2a**is highly potential due to its scavenging therefore, it is ideal for the **Cu-2a, Ni-2a, Cu-3a and Sm-2a**to possess radical scavenging property to fill in the place of **Cu-2a, Ni-2a, Cu-3a and Sm-2a**. Consequently, **Cu-2a, Ni-2a, Cu-3a and Sm-2a**derivatives were analyzed for their free-radical scavenging. Direct hemolytic activity was determined using washed human RBC and results shown that all the synthesizedcompounds are non-toxic.

APPLICATION

The synthesized ligand and metal complexes are biologically important molecules because they possess significant antibacterial, antifungal, antioxidant activities and nontoxicity.

CONCLUSION

The novel ligand 2,2'-(4-(2,3-dimethoxyphenyl)pyridine-2,6-diyl)dithiazole and its Copper and Nickel complexes were synthesized in good yield. All the synthesized compounds were characterized by spectroscopic and analytical methods. The synthesized ligand and metal complexes found to be biologically potent molecules as they possess significant antibacterial, antifungal, antioxidant activities and nontoxicity.

ACKNOWLEDGEMENT

The authors are thankful to Dr. Raghavendra Kumar for providing lab facility. Also the authors are grateful Dr.Devaraja, Department of Biochemistry for providing lab facility and support to study bacterial, fungal and antioxidant activities. Special thanks to National Chemical Company limited, for providing acetyl thiazole.

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