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Template Synthesis and Biological Study of Ni (II) Complexes derived from ethylenediamine and 2,4-pentanedione

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ABSTRACT

In this study, nickel (II) complexes having formulae $[Ni(en)_2(acac)]$ and $[Ni(acac)_2.2H_2O]$, have been synthesised from bis-ethylenediamine nickel (II) chloride, nickel bromide hexahydrate and 2,4-pentanedione as starting material. The complexes were characterised using various physicochemical analysis such as Infrared, electronic spectra, elemental analysis, molar conductivity, thermo gravimetric analysis (TGA) and high resolution mass spectroscopy (HRMS). The IR spectral data of the complexes indicates the possible bonding/coordination of the ligands with the metal ion through oxygen and nitrogen atoms of the carbonyl and amine respectively, given rise to octahedral geometry. The elemental analysis and HRMS data obtained also agreed with the proposed molecular formula of the complexes. The result of molar conductivity studies in methanol solution (10^{-3}M) showed that the complexes are electrolytes, and they are also soluble in polar solvents which include: methanol, ethanol, DMF, DMSO and slightly soluble in distilled water. The complexes has been tested for biological activities (anti-microbial and anti-fungal) using disc diffusion method and poisoned food techniques for anti-microbial and anti-fungal, respectively against Gram-positive bacteria: *Staphylococcus aureus*-ATCC 25923, *Streptococcus Pyogene*-ATCC 19615, *Bacillus Subtilis*-ATCC 23857, Gram-negative bacteria: *Escherichia Coli*- ATCC 25922, *Salmonella typhi*-ATCC 6539, *Klebsiella Pneumonioe*-ATCC 13883, *Pseudomonas aeruginosa*- ATCC 27853 and fungus: *Candida albicam*-ATCC 10231, using different concentrations (30, 20 and 10 μgmL^{-1}) of the complexes. The comparative study of anti-microbial and anti-fungal activities of complexes with standard drugs, streptomycin and Fluconazole indicated that the complexes exhibit less activity as compared to the standard drugs at all the concentrations tested.

Keywords: Antibiotics, Complexes, Microbial, Transition metals

INTRODUCTION

Microbial resistance to antibiotics is an issue of global concern, which requires concerted efforts to address it (Frei *et al.*, 2020 and Worthington and Melandar, 2013). The mortality rate due to the infections caused by the bacterial resistance to available antibiotics use for the treatment is also increasing at alarming rate annually (WHO, 2019). The infections caused by these antibiotic-resistant bacteria affect lives everyday causing a threat to health similar to influenza, tuberculosis and HIV combined (Cassini *et al.*, 2018; Francesca *et al.*, 2015 and Jennifer 2016). Bacteria usually developed different resistance mode to overcome the extended spectrum of antibiotics (Worthington and Melandar, 2013), and the mechanism through which this resistance evolved as acknowledge by the microbiologist, include enzymatic degradation by the lactamases, destruction of lactam ring and its re-configuration (Wanda, 2018). This has resulted to series of research which aimed at increasing the efficacy of the anti-microbial agent against the resistance micro-organisms. As a result, there is a growing interest toward developing lead compounds that can address the problem of bacteria resistance to antibiotics (Natalie, 2016).

In search for new antimicrobial agents that can help in tackling the issue of infections caused by multi-drug resistant bacteria, metallo-pharmaceutical research takes the centre stage (Morones *et al.*, 2005). In this strategy, compounds containing metals are being used owing to their therapeutic role, and one of such metals is transition metal (Mjos and Orvig, 2014). Transition metals have gained recognitions in the field of metallo-pharmaceutical and have long history of use as antimicrobial agents since ancient period (Muthusamy and Natarajan, 2016 and John and Ben, 2018). Literature survey reveals the existence of some research works conducted on synthesis and characterization of transition metal complexes using ethylenediamine and 2,4-pentanedione as ligands, but to the best of our knowledge none of these researches shows the use of the two ligands together in one complex with antimicrobial studies.

Herein, our focus is on template synthesis, characterization and biological (anti-microbial and anti-fungal) studies of Ni(II) complexes derived from ethylenediamine and 2,4-pentanedione as mixed ligands.

MATERIALS AND METHODS

Chemicals and reagents

The chemicals and reagents used are of analytical grade (AR) and were used without further purification. They were commercially obtained from Sigma Aldrich.

Instrumentations

The Melting points of the complexes and the ligands were obtained using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. FT–IR spectra were recorded using Tensor 27 Bruker and Perking Elmer FT–IR Spectrum BX in the range of 4000–400 cm^{-1}. Elemental analyses were performed on a vario Elementar III microbe CHNS analyser. The metal content was determined using Atomic Adsorption Spectroscopy (AAS), Perkin-Elmer Spectrometer, model 3110. The Electronic absorption Spectra of the complexes and ligands were determined on UV–2550 Shimadzu Spectrometer in range of 200–800 nm. High resolution mass spectra (HRMS) were performed on a Waters acquity UPLC Synapt G2 HD Mass Spectrometer instrument at University of Pretoria, South Africa.

Anti-microbial Studies

The *in-vitro* antimicrobial activities of the complexes and the standard drug (Streptomycin) were assayed using disc diffusion method as reported by Anacona and Da-Silva, (2005) and Waziri, *et al.*, (2017), against the following micro-organism; s*taphylococcus aureus*–ATCC25923, *Streptococcus Pyogene*–ATCC19615, *Bacillus Subtilis*–ATCC23857 (Gram-positive bacteria) and *Escherichia Coli*–ATCC25922, *Salmonella typhi*–ATCC6539, *Klebsiella Pneumonioe*–ATCC 13883, *Pseudomonas aeruginosa*–ATCC 27853 (Gram-negative bacteria). The cultures of the test organism were kept on nutrient agar culture media and subculture before testing as reported by Ngankeu, *et al.*, (2016). This was done at concentrations of 30, 20 and 10 μgmL^{-1}, respectively of the compounds and the experiment was repeated three times.

Anti-fungal activity

Poisoned food technique was used to check *in-vitro* anti-fungal activity of synthesized complexes and the standard drug (Fluconazole) against fungus: *Candida albicam*–ATCC 10231, as reported by Al- Burtamani et al., (2005). Fungal strain was grown on Sabouraud dextrose agar (SDA) at 28 °C for 7 days. For performing anti-fungal activity of test compounds, one week old fungal culture was used as inoculums. Fluconazole was used as reference anti-fungal drug and the medium with methanol as solvent was used as a negative control. Solution of the test compounds (complexes) and reference drug were dissolved in methanol at concentrations of 30, 20 and 10 μgmL^{-1}, respectively. Molten SDA was poisoned by the addition of 100 µl of prepared inoculants and poured into sterile Petri-plates. The prepared plates containing the test compound were inoculated with fungal plugs (6 mm diameter) obtained from the activity growing margins of fungal plates. Plates were inoculated at 28 °C for one week. Each assay was performed in duplicate and repeated three times. Anti-fungal activity data of compounds were expressed as percent inhibition calculated from the diameter of inhibition zone. The percent inhibition was determined using equation 1:

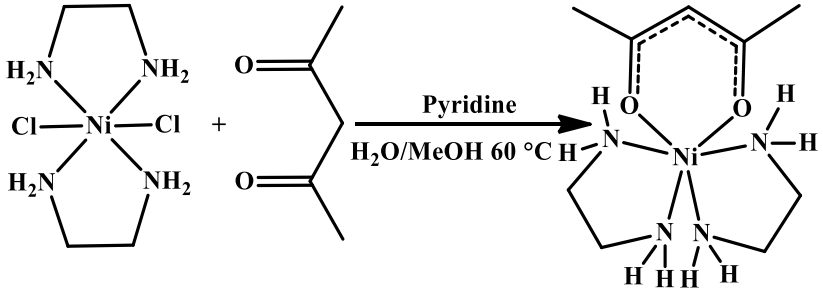
$$\% \text{ Inhibition} = (C - T) .100 / C \quad (1)$$

Where C is the diameter of the fungal colony in the control plate and T is the diameter of the microbial colony in the tested plate after same incubation period.

SYNTHESIS OF THE COMPLEXES

Synthesis of $[Ni(en)_2(acac)]$

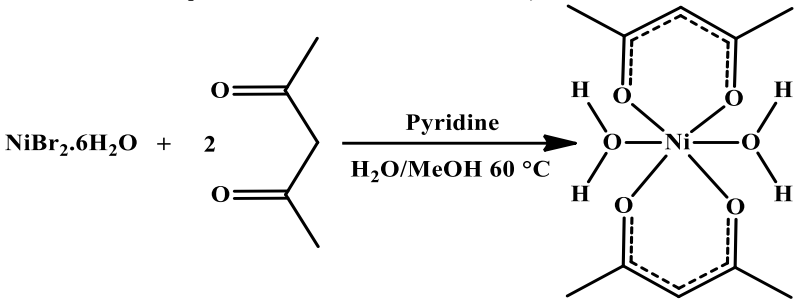
In a 100 mL round bottom flask, 2,4-pentanedione (0.5006 g, 5.00 mmol, 1 eq) was dissolved in 10 mL methanol, and bis-ethylenediamine nickel (II) chloride (1.250 g, 5.00 mmol, 1 eq) was dissolved in 10 mL of distilled water, followed by addition of two drops of pyridine. The two solutions were mixed together, this result to blue-green mixture. The mixture was refluxed for 2 h to afford brown colour solution. The solution was allowed to cool overnight and brown product was formed. The product was filtered and washed with 1:1 (v/v) water/methanol. Yield: (0.949 g, 3.38 mmol, 67.51%). Scheme: 1.



Scheme 1: Synthesis of $[Ni(en)_2(acac)]$

Synthesis of [Ni(acac)$_2$2H$_2$O]

In a 100 mL round bottom flask, nickel bromide hexahydrate (2.250 g, 6.89 mmol, 1 eq) was dissolved in 10 mL of water, followed by addition of two drops of pyridine. 2,4-pentanedione (1.380 g, 13.78 mmol, 2 eq) was dissolved in 10 mL methanol and mixed with the aqueous solution of nickel bromide hexahydrate. The mixture was refluxed for 2 h to afford blue-green colour solution. The solution was allowed to cool overnight and blue-green product was formed. The product was filtered and washed with 1:1 (v/v) water/methanol. Yield: (1.560 g, 5.34 mmol, 77.50%). Scheme: 2.



Scheme 2: Synthesis of [Ni(acac)$_2$2H$_2$O]

RESULTS AND DISCUSSIONS

Physical properties

Nickel (II) complexes of the formulae [Ni(en)$_2$(acac)] and [Ni(acac)$_2$.2H$_2$O], where en = ethylenediamine and acac = 2,4-pentanedione were synthesised in moderate yield, and they are air and moisture stable. The melting points of the complexes were comparatively lower than those of the starting material. This suggests change in the composition of the starting material due to complexation. Similar observation was noted by Waziri, *et al.,* (2018). The result of molar conductivity of the complexes at ambient temperature (10^{-3} M) in methanol was found to be 110 and 128 $\Omega^{-1}mol^{-1}cm^2$, respectively (Table 1) indicating electrolytic nature (Imran, *et al*., 2013). The complexes are colored (brownish and blue-green), Table 1. Furthermore, the color transformation from blue in the starting material (due to weak field ligand and lower energy absorption) to brown as obtained in one of the complex might be due to the mixed ligands that coordinated to the nickel ion. This result to change in the relative energies of the orbital that electrons are transitioning between and subsequently lead to drastic shift in the color of light absorbed. Hence, this might result to difference in color of the complex from what is originally expected. The complexes were also found to be soluble in polar solvents, Table 2.

Infrared spectra

The infrared (IR) spectral data of the complexes are presented in (Table 3). The bands at 3376, 1700–1725, 1680 and 1098 cm^{-1} were assigned to NH$_2$, C=O, C=C and C–N, respectively (Table 3), similar band assignments was reported by Andrea, *et al.,* (2019). Similarly, the IR spectra showed strong band stretching at 420 cm^{-1}, which clearly indicate the presence of new bond between nickel and nitrogen (Ni–N) in [Ni(en)$_2$(acac)] through the lone pair of electron on nitrogen and maintaining the two amine proton in covalent fashion, forming a coordinate-covalent bond between nitrogen and metal (nickel), this signifies the formation of complex between nitrogen and nickel (Table 3). In the same vein, the broad band stretches in the region of 3200–3360 cm^{-1} also confirmed the existence of coordinated water in [Ni(acac)$_2$.2H$_2$O] complex. Presence of coordinated water is further proved by the existence of non–ligand in 830–840 cm^{-1} assignable to the shaking form of water, (Table 3) (Anacona, *et al.,* 2018). Furthermore, metal oxygen bond (Ni–O) was confirmed through appearance of band at 523 and 550 cm^{-1} suggesting coordination through carbonyl oxygen (C=O) in both the complexes (Table 3), (Phanjoubam and Rajkumari, 2017).

Table 1: Physicochemical Properties of the Complexes

Compound	Molecular formula	Molecular weight	Color	Melting point ˚C	Molar conductance $\Omega^{-1}mol^{-1}cm^2$	Experimental (Theoretical)			
						C	H	N	Ni
$[Ni(en)_2(acac)]$	$C_9H_{23}N_4NiO_2$	279.1129	Brown	236	110	38.53 (38.88)	8.15 (8.34)	20.11 (20.15)	21.10 (21.11)
$[Ni(acac)_22H_2O]$	$C_{10}H_{18}NiO_6$	294.0411	Blue-green	223	128	40.87 (41.00)	6.14 (6.19)	—	19.93 (20.04)

Table 2: Solubility of the complexes in different polar and non-polar solvents

Compound	Water	Methanol	Ethanol	Acetone	DMSO	DMF	Ether	Hexane	Benzene
$[Ni(en)_2(acac)]$	s	s	s	ss	s	s	In	In	In
$[Ni(acac)_22H_2O]$	s	s	s	ss	s	s	In	In	In

Key: s = soluble, ss = slightly soluble and In = insoluble

Table 3: The IR spectral data of the complexes (cm^{-1})

Compound	Coordinated water υ(OH)	υ(C=C)	υ(C–N)	υ(C=O)	υ(NH_2)	υ(Ni–N)	υ(Ni–O)
$[Ni(en)_2(acac)]$	–	–	1098	1723	3376	420	550
$[Ni(acac)_22H_2O]$	3332	1680	–	1700	–	–	523

Electronic spectra

Electronic absorption spectroscopy (UV–Vis) is generally used to investigate the nature of coordination mode of the metal to the ligand through the vacant orbital of the metal (Chantal, 2003). Herein, the electronic absorption spectral data of the complexes in methanol solution (10^{-3} M) are presented in (Table 4). The complexes displayed three absorption maxima in the region of 9800 cm^{-1}, 15500 cm^{-1} and 25000 cm^{-1} assignable to $^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$(v1), $^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)$(v2) and $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$(v3) transition, respectively and (v3/v2) was found to be 1.58–1.62, which is in accordance with octahedral geometry around Ni(II) ion (Mandeep, 2017; Rahab, 2016), Table 4. The Recah inter-electronic repulsion parameters B and β calculated for the complexes were found to be around 916–922 cm^{-1} and 0.848–0.854 respectively. The B value is less than that of free nickel ion value of (1080 cm^{-1}) due to the decrease in inter-electronic repulsion from electronic delocalization during complexation process Mandeep, (2017), Table 4.

Table 4: UV-visible Spectral Data of the Complexes

Compound	$\lambda_{max}(cm^{-1})$	Band assignment	B cm^{-1}	β	v3/v2	Δ_o cm^{-1}	Geometry
$[Ni(en)_2(acac)]$	24820	$^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$	922	0.854	1.62	9220	
	15324	$^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)$	–	–	–		Octahedral
	9734	$^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$	–	–	–		
$[Ni(acac)_2 2H_2O]$	24310	$^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$	916	0.848	1.58	9160	Octahedral
	15430	$^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)$	–	–	–		
	9858	$^3A_{2g}(F)\rightarrow{}^3T_{2g}(F)$	–	–	–		

Elemental analysis

The elemental analysis data of the complexes corresponds with those of the theoretical data (Table 1). Also, the empirical formula calculated on the basis of this data corresponds to the theoretical values. Furthermore, the result of HRMS of the complexes agrees with this data.

Thermal studies

Because the IR spectra of $[Ni(acac)_2 2H_2O]$ complex indicate presence of water molecules, thermal analyses (TGA and DTG) was undertaken to ascertain their nature. This was performed at a temperature range from 0–800 ˚C, Figure 6. The mass losses were estimated and compared with those of elemental analysis, decomposition temperature and mass spectroscopy. From the result obtained three steps decomposition of The $[Ni(acac)_2 2H_2O]$ was observed, Figure 6. The temperature of the first step from 25 ˚C to 120 ˚C corresponds to the loss of two molecule of water ($2H_2O$), which represents 12.24%. The temperature of the second step from 125 ˚C to 350 ˚C is assigned to the loss of the organic fragment ($C_{10}H_{18}O_3$) represent 63.25%. Finally, the residual appraises in the temperature range of 350˚C to 800˚C corresponds to (NiO) which represent 25.40%, Figure 6.

Mass spectra

The mass spectrum of the complexes is shown in Figures 4 and 5. The molecular ion peak [m/z] at 280.0602 which corresponds to the theoretical value of 280.1129 was assigned to $[Ni(en)_2(acac)]$ and molecular ion peak [m/z] at 294.0300 corresponds to the theoretical value of 294.0411 is for $[Ni(acac)_2 2H_2O]$ complex, (Figures 4 and 5). This matches with the proposed structures of the complexes. The fragmentation pattern of $[Ni(en)_2(acac)]$ complex shows that the dissociation pattern start with losing (acac) [m/z] = 100.25 to give $[Ni(en)_2]$ [m/z] = 118. 79 and the fragmentation pattern of $[Ni(acac)_2 2H_2O]$ shows lost of two water molecules ($2H_2O$) [m/z] = 35.65 to give $[Ni(acac)_2]$ [m/z] = 258.0211, followed by ($C_{10}H_{18}O$) [m/z] = 187.50 to give $[NiO]^-$ [m/z] = 74.69, respectively. To further affirms that the proposed structures of the complexes are correct; the results of elemental and thermal analyses are taking as additional evidence for the proposed structures.

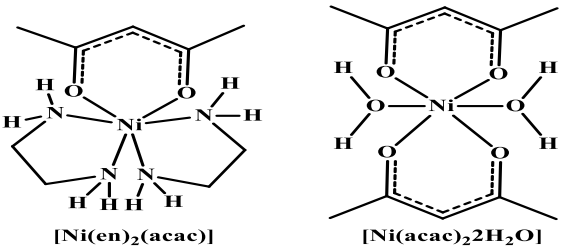
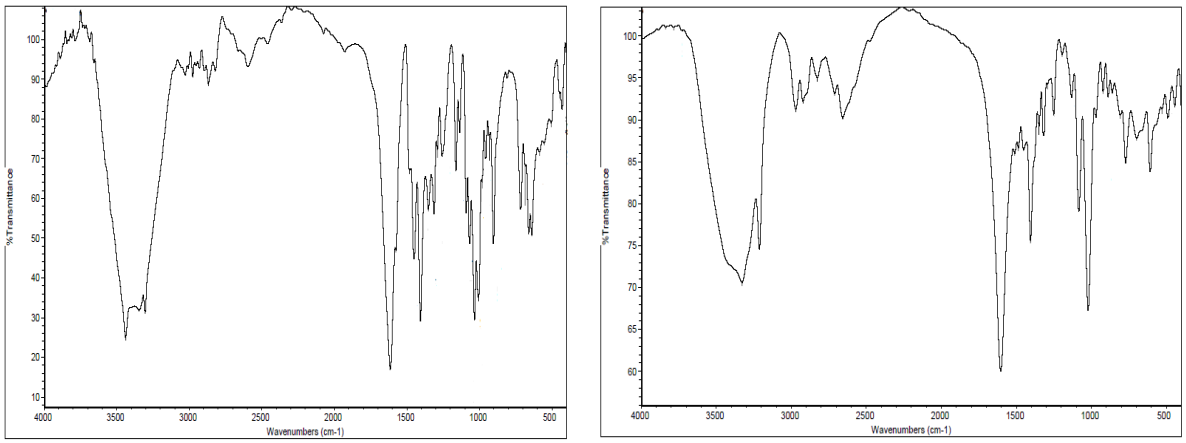
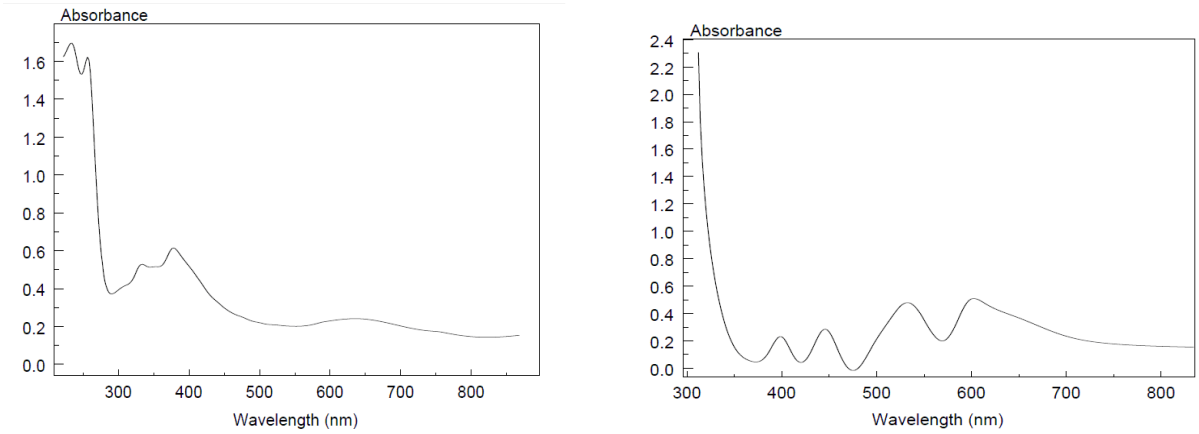


Fig. 1: Proposed structure of the complexes



[Ni(en)$_2$(acac)] **[Ni(acac)$_2$2H$_2$O]**

Fig. 2: FT–IR Spectrum of the Complexes



[Ni(en)$_2$(acac)] **[Ni(acac)$_2$2H$_2$O]**

Fig. 3: UV–Vis Spectrum of the Complexes

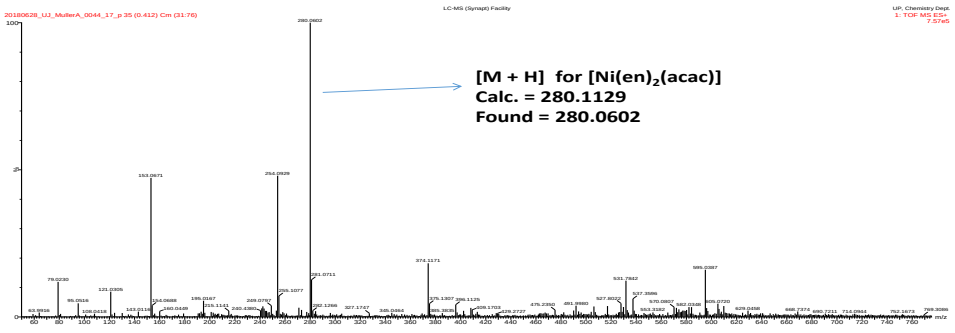


Fig. 4: HRMS spectra of **[Ni(en)$_2$(acac)]**

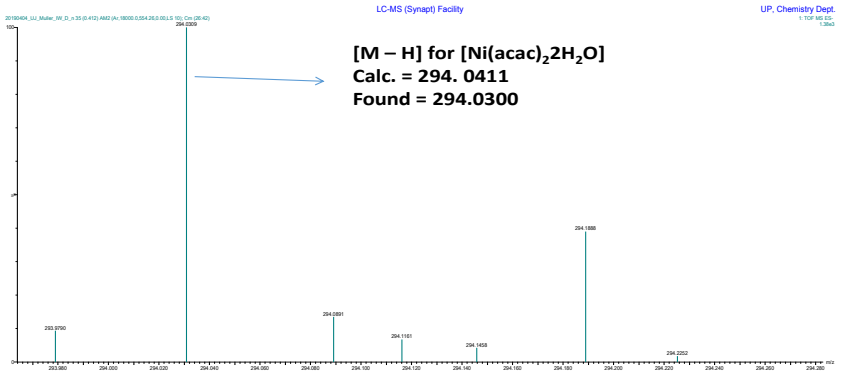


Fig. 5: HRMS spectra of **[Ni(acac)$_2$.2H$_2$O]**

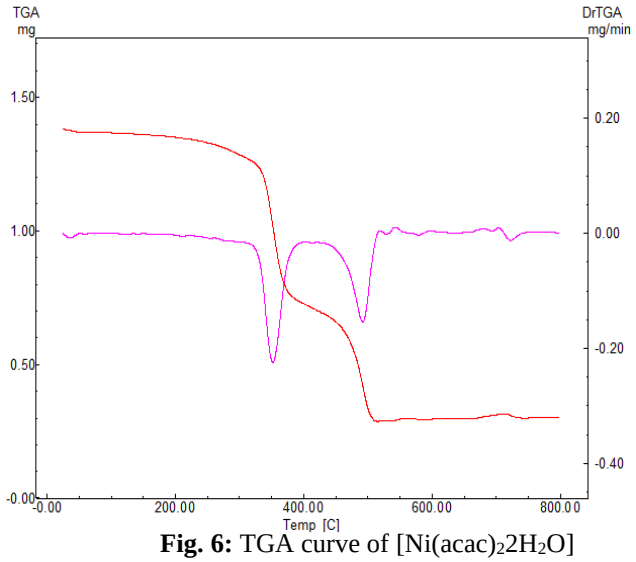


Fig. 6: TGA curve of [Ni(acac)$_2$2H$_2$O]

BIOLOGICAL STUDIES

Anti-bacterial studies

The *in-vitro* antibacterial activity of the synthesized complexes and the standard drug (streptomycin) were evaluated *in-vitro* against Gram-positive bacteria: s*taphylococcus aureus*–ATCC25923, *Streptococcus Pyogene*–ATCC19615, *Bacillus Subtilis*–ATCC23857 and Gram-negative bacteria: *Escherichia Coli*–ATCC25922, *Salmonella typhi*–ATCC6539, *Klebsiella Pneumonioe*–ATCC 13883, *Pseudomonas aeruginosa*–ATCC 27853 using disc diffusion method (Anacona, *et al.*, 2018), and the results obtained are presented in Figure: 7, 8 and 9 respectively. From the data obtained, it shows that the complexes are less toxic on the tested microorganism as compared to the standard drug at all concentrations, (Figure 7, 8 and 9). However, [Ni(acac)$_2$.2H$_2$O] complex displayed moderate activity at concentration of 30 µgmL^{-1} as compared to [Ni(en)$_2$(acac)] complex (Figure 7). Similarly, the activity of complexes decreases drastically at concentrations of 20 and 10 µgmL^{-1} respectively compared to the activity of the standard drug, as shown in Figure 8 and 9. Therefore, it can be concluded that the complexes are less active against the tested organism.

Anti-fungal studies

The *in-vitro* anti-fungal activity of the synthesised complexes and the standard drug (Fluconazole) was carried out using poisoned food technique on *Candida albicam*–ATCC 10231 at concentrations of 30, 20 and 10 µgmL^{-1} of the complexes and Fluconazole. The data obtained are presented together with the results of anti-bacterial studies in Figure 7, 8 and 9 respectively. From the data obtained, the complexes displayed activity similar to that of anti-bacterial studies. The result shows that all the complexes showed less activity

compared to the standard drug at all concentrations (Figure 7, 8 and 9). The zone of inhibition exhibited by complexes were found to be 5 and 15 mm at 30 μgmL^{-1}, 3 and 10 mm at 20 μgmL^{-1} and 0 and 2 mm at 10 μgmL^{-1} for $[Ni(en)_2(acac)]$ and $[Ni(acac)_2.2H_2O]$ complexes, respectively (Figures 7, 8 and 9). The standard drug (Fluconazole) zone of inhibition was found to be 43 mm, 28 mm and 11 mm at concentrations of 30, 20 and 10 μgmL^{-1} respectively, Figure 7, 8 and 9. The low activity of the complexes as compared to the standard drugs might be due to their lower lipophilicity, this causes decrease in their penetration ability through the lipid membrane and which could neither block nor inhibit the growth of the microorganism. Similar observations were reported by Dharmaray, *et al.*, (2002).

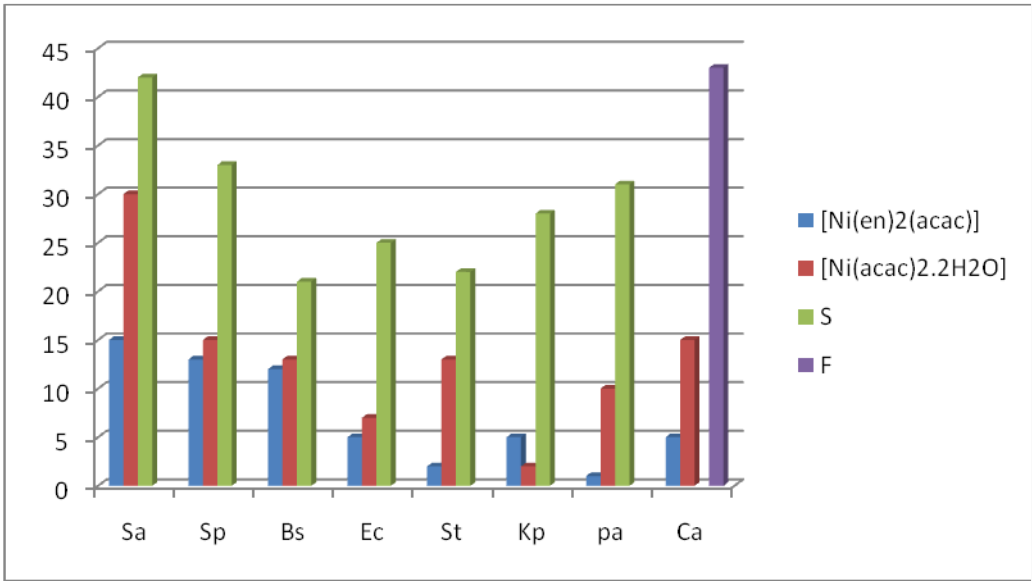


Fig 7: The results of *in-vitro* anti-bacterial and anti-fungal studies of the complexes at 30 μgmL^{-1}

Sa = *Staphylococcus aureus*, **Sp** = *Staphylococcus pyogene*, **Bs** = *Bacillus subtilis*, **Ec** = *Escherichia coli*, **St** = *Salmonella typhi*, **Kp** = *Klebsiella pneumonioe*, **Pa** = *Pseudomonas aeruginosa*, **Ca** = *Candida albicam*, **S** = Streptomycin and **F =** Fluconazole

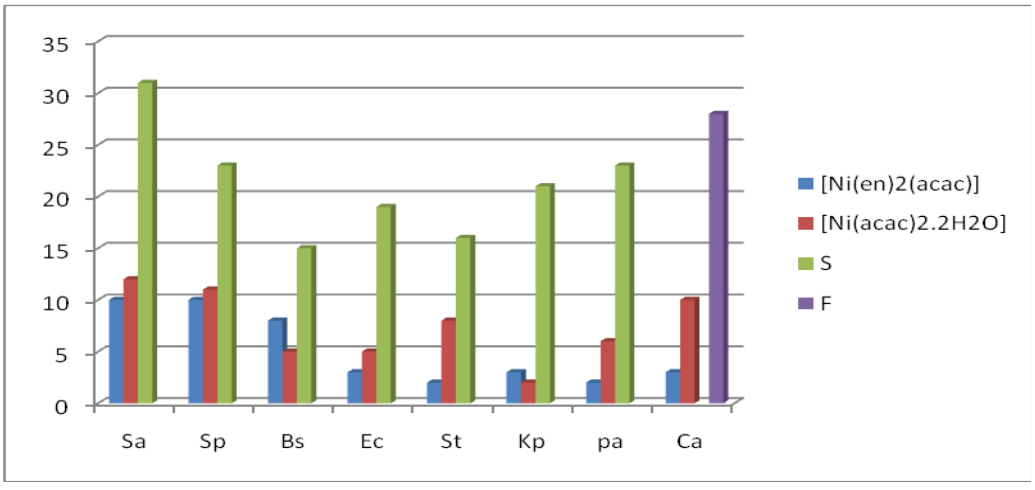


Fig. 8: The results of *in-vitro* anti-bacterial and anti-fungal studies of the complexes at 20 μgmL^{-1}

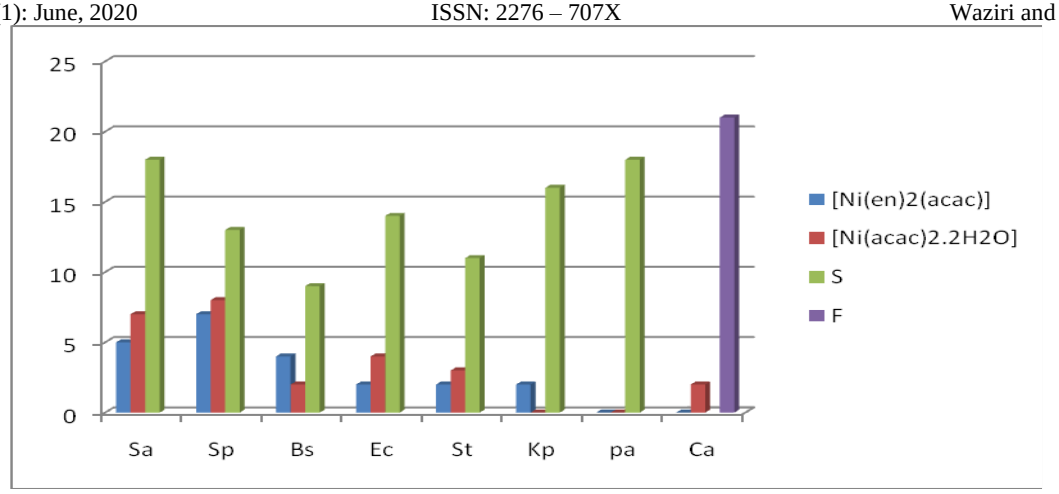


Fig. 9: The result of *in-vitro* anti-bacterial and anti-fungal studies of the complexes at 10 µgmL^{-1}

Fig. 10: Representative culture plates showing the zone of inhibition of the complexes against the bacteria

CONCLUSION

Two Ni(II) complexes derived from ethylenediamine and 2,4-pentanedione were synthesized using template synthesis concept. The physicochemical and spectral studies conducted on the complexes provide data that are in agreement with the proposed structures of the complexes. Infra-red (IR) spectral data revealed the possible point of coordination of the ligands to the metal ion through nitrogen and oxygen atoms of amine and carbonyl groups respectively. Electronic absorption spectra suggested octahedral geometry around nickel ion. *In-vitro* anti-bacterial and anti-fungal study shows that the synthesized complexes are biologically less active against the tested organism compared to the standard drugs used.

Contribution of Authors

All authors participated in the conceptualisation of the study, in the drafting of the manuscript, the interpretation of the data and the experimental work.

Conflict of Interest

The authors declare no conflict of interest.

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