SYNTHESIS, CHARACTERIZATION, THERMAL AND BIOLOGICAL EVALUATION OF 4-ACYL PYRAZOLONE BASED Ni(II) COMPLEXES AS POTENTIAL ANTIBACTERIAL AND ANTI-MALARIAL AGENTS.

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Abstract

The current research conducted a comprehensive analysis of the thermal and biological properties of novel Ni(II) complexes of pyrazolone. To synthesize these compounds, various 4-acyl pyrazolones were utilized, and the resulting ligands were characterized using 1H NMR, IR, 13C NMR, elemental analysis, and UV spectroscopy. Additionally, the complexes were characterized using elemental analysis, UV spectroscopy, IR spectroscopy, and thermal analysis techniques such as TGA/DTG and DSC. To assess their potential, all the compounds underwent antibacterial and antimalarial testing. The findings revealed significant promise, warranting further investigation in this field.

Keywords: Schiff base, acyl pyrazolone, thermal Study, biological Activity, metal complexes.

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INTRODUCTION

Pyrazolone derivatives, a class of heterocyclic compounds, have garnered attention in heterocyclic chemistry due to their wide range of applications in different fields.[1-7] They are widely used in industries such as medicine, agriculture, and manufacturing, where they serve as color couplers, sensitizers, super sensitizers, developers, color fitters, and antihalation agents. Pyrazolones have also shown promising potential as antifungal, antibacterial,[8] anticancer,[9] and antihyperglycemic[10] agents in medical therapies. Metal complexes of pyrazolones have gained considerable interest in drug discovery and development due to the demonstrated ability of metals to enhance the activity of ligands.

Phenyl hydrazine, an organic compound consisting of a phenyl group attached to a hydrazine moiety (-NH-$_{NH2)}$, serves as a key precursor for the synthesis of a wide range of ligands. The distinctive electronic and steric properties of the phenylhydrazine scaffold make it an ideal platform for the design and modification

of ligands with tailored properties. The presence of the hydrazine moiety provides opportunities for various functional group transformations, enabling the introduction of diverse substituents and coordination sites[11-12]. One notable feature of phenyl hydrazine-based ligands is their ability to act as bidentate or tridentate ligands, forming stable complexes with transition metals.[13-14] The coordination of phenyl hydrazine ligands can occur through different coordination modes, such as N, N-chelating or N,O-chelating, depending on the nature of the ligand and the metal center. This flexibility in coordination allows for the formation of complexes with diverse geometries and electronic structures, which ultimately influence their properties and reactivity.

The coordination chemistry of semicarbazone ligands has attracted significant attention in recent years. Semicarbazones exhibit a wide range of coordination modes, including mono- or bidentate coordination through the hydrazone nitrogen and/or oxygen atoms. These ligands have demonstrated the ability to form stable complexes with various transition metal ions, providing opportunities for the development of metal-based catalysts and materials. The coordination of semicarbazone ligands to metal centers can impart enhanced stability, alter the electronic properties of the metal complexes, and introduce selectivity in catalytic or biological processes.[15]

In perspective on the significance of transition metal-based complexes and our curiosity in the science of coordination compounds of pyrazolone based phenyl hydrazine and semicarbazone ligands in present work, we illustrate synthesis, spectroscopic, thermal[16] and antimicrobial screening of some Ni(II)complexes and the common structure is shown in Figure 1.

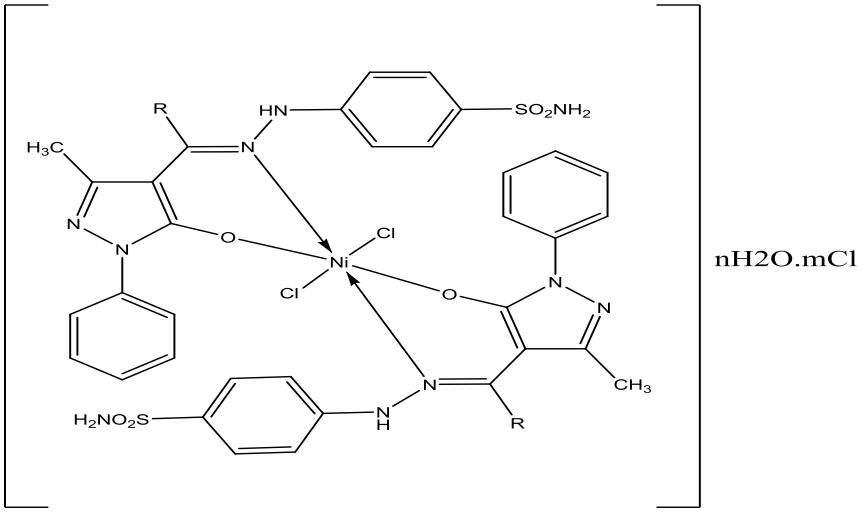


Figure-1: Proposed structure of Ni(II) complex

Sr.No.	Ligand	R
1	L1	$-CH_3$
2	L2	$-CH_2CH_3$
3	L3	$-CH_2CH_2CH_3$
4	L4	$-C_6H_5$
5	L5	$-C_6H_5NO_2$
6	L6	$-C_4H_3O$

EXPERIMENTAL

The compounds l-phenyl-3-methyl-5-pyrazolone was purchased from Sigma Ltd (India). Semicarbazide hydrochloride was purchased from Sigma-Aldrich. Acyl chlorides were purchased from Spectrochem, Mumbai used without further purification.

Detection Methods: Using KBr pellets and a Nicolet-400D spectrophotometer, FT-IR spectra were collected. In DMSO-d6 solvent, 1H NMR spectra were captured using Bruker Advance 400 FT-NMR equipment. A model 5000/2960 SDT apparatus was used to carry out simultaneous TGA/DTG and DSC studies. The trials were conducted at a temperature of 100°C per minute in a nitrogen (N2) environment.

General procedure: In 50 mL of methanol Sulphonamide phenyl hydrazine and 1-phenyl 3-methyl 5-pyrazolone were mixed in a 1:1 molar ratio to create the ligands. A catalytic quantity of acetic acid is added to the mixture and given heat for 3- 4 hours while TLC analysis tracked the

reaction's progress. After being crystallized in methanol(50 mL) and then wash it with diethyl ether, the resultant substance took on the appearance of primrose cream. Utilizing 1H NMR, mass spectrometry, and IR spectroscopy methods, the final ligands were confirmed.

All data of synthesized ligands like Elemental analysis, FT-IR reports Molecular formula, practical yield melting point, and 1H NMR data are shown in below tables 1 &2.

Table 1: Physico-analytical data of ligands

Sr No.	Ligand	Molecular formula	Melting point	Color % Yield	Elemental Analysis of ligand					
					Found (%)			Calculated (%)		
					C	H	N	C	H	N
1	4-Acylated hydrazine-pyrazolone	$C_{18}H_{19}N_5O_3S$	211°C	Light pink [81%]	56.12	4.99	18.09	56.09	4.97	18.17
2	4-Propiyonal hydrazine-pyrazolone	$C_{19}H_{21}N_5O_3S$	218°C	Cream powder [71%]	57.15	5.32	17.55	57.13	5.30	17.53
3	4-Butyryl hydrazine-pyrazolone	$C_{20}H_{23}N_5O_3S$	220°C	White powder [76%]	58.12	5.64	16.96	58.09	5.61	15.82
4	4-Benzoyal hydrazine-pyrazolone	$C_{23}H_{21}N_5O_3S$	250°C	Light pink powder [75%]	61.75	4.71	15.67	61.73	4.73	15.65
5	4-Nitrobenzoyalhydrazine-pyrazolone	$C_{23}H_{20}N_6O_5S$	261°C	Yellow powder [68%]	56.11	4.12	17.09	56.09	4.09	16.96
6	4-Furoylhydrazine-pyrazolone	$C_{21}H_{19}N_5O_5S$	253°C	Brown powder [70%]	55.62	4.22	15.44	55.43	4.13	15.09

Table 2: FT-IR data of ligands (KBr, cm^{-1})

Sr. No.	Ligand	ν(O–H)	ν(N-H)	ν(C=O)	ν(C=N)
1	L1	3340	3240	1625	1543
2	L2	3348	3251	1600	1539
3	L3	3358	3226	1618	1531
4	L4	3342	3182	1595	1516
5	L5	3200	3076	1597	1558
6	L6	3351	3230	1612	1535

1H NMR data of ligand for L1-L6

L1:1H NMR (400 MHz,DMSO_d6): δ (ppm)=2.3 (3H, s, -CH_3); 2.48-2.49 (3H, s, -CH_3); 6.86-7.98 (Ar-H).

L2:1H NMR (400 MHz,DMSO-d6): δ (ppm)=2.5 (3H,s,-CH_3); 1.20-1.24 (3H,t,-CH_3);2.76-2.78(2H,q,-CH_2) 6.89-7.99 (Ar-H).

L3 : 1H NMR (400 MHz,DMSO_d6): δ (ppm)=2.5 (3H,s,-CH_3); 1.60-1.64 (2H,q,-CH_2),2.71-2.75(2H,m,-CH_2);0.97-1.60(3H,t,-CH_3);6.89-7.99 (Ar-H).

L4:1H NMR (400 MHz,DMSO-d6): δ (ppm)=1.88 (3H,s,-CH3); 6.86-7.98(Ar-H) .

L5:1H NMR (400 MHz,DMSO-d6): δ (ppm)=1.92 (3H,s,-CH_3); 7.14 -8.26(Ar-H).

L6:1H NMR (400 MHz,DMSO-d6): δ (ppm)= 2.02 (3H,s,-CH3); 6.35 -7.49(Ar-H).

General Procedure for complexes

The complexes were created and isolated using a standardised process. Hot methanol was used to dissolve the $NiCl_2.6H_2O$, and a 1:1 molar solution of the matching Schiff bases was then added. The resulting combination was then heated for four hours at 70°C before being let to sit at RT overnight. The resultant crystals were extensively cleaned with water and methanol.Then finally add diethyl ether before being air dried. The crystals displayed unique colours.

RESULTS AND DISCUSSION

Using elemental analysis, IR spectroscopy, TGA/DTG, and DSC studies, the structural properties of the synthesized Schiff base ligands and complexes were examined. The experimental component of the paper also contains comprehensive 1H NMR data for the Schiff base ligands. The complexes analytical and physical data were displayed in table 3. When compared to DMF and DMSO, the complexes showed weak solubility in methanol, it was found. Furthermore,

over an extended length of time, the complexes demonstrated excellent stability in ambient air.

Table 3: Analytical and Physical data of Complexes

Compound	Molecular Weight	Color % Yield	Analysis (%) Found (Cal)		
			C	H	N
ML1	898.46	Light Yellow(79%)	55.87(56.09)	4.50(4.97)	18.09(18.17)
ML2	926.52	Yellow(68%)	56.95(57.13)	5.01(5.30)	17.43(17.53)
ML3	954.57	Light pink(72%)	56.29(56.86)	5.55(5.73)	16.63(16.58)
ML4	1036.63	Light brown(70%)	61.40(61.73)	4.55(4.73)	14.63(15.65)
ML5	1112.60	Yellow(68%)	49.66(49.70)	3.44(3.48)	15.11(15.05)
ML6	971.68	Brown(65%)	51.92(50.87)	4.56(4.41)	14.41(13.97)

1H NMR Spectra studies of ligand:

The tautomerism of pyrazolone has been extensively studied [17][18]**.** In DMSO-d6 at room temperature, 1H NMR measurements were conducted to analyse the Schiff base ligand. Details of the ligand's 1H NMR spectrum are provided in the experimental section. This spectrum showed two sharp singlets in the range of 12 to 13 ppm, which correspond to one and two protons and are indicative of the -OH group [19][20]**.** When a D_2O exchange experiment was performed, this signal disappeared. While singlets for the methyl group in the Schiff base ligands emerged in the range of 1.5 to 3.0 ppm, aromatic protons were seen in the range of 6.8 to 9.0 ppm. It was difficult to clearly identify each signal as belonging to a particular aromatic or -NH proton because it was revealed by the NMR spectrum of L1 that the signals of -NH protons occasionally overlapped with those of aromatic protons [21]. It was determined from the 1H NMR spectroscopic data that the Schiff base ligand occurs in solution as the keto-enol form.

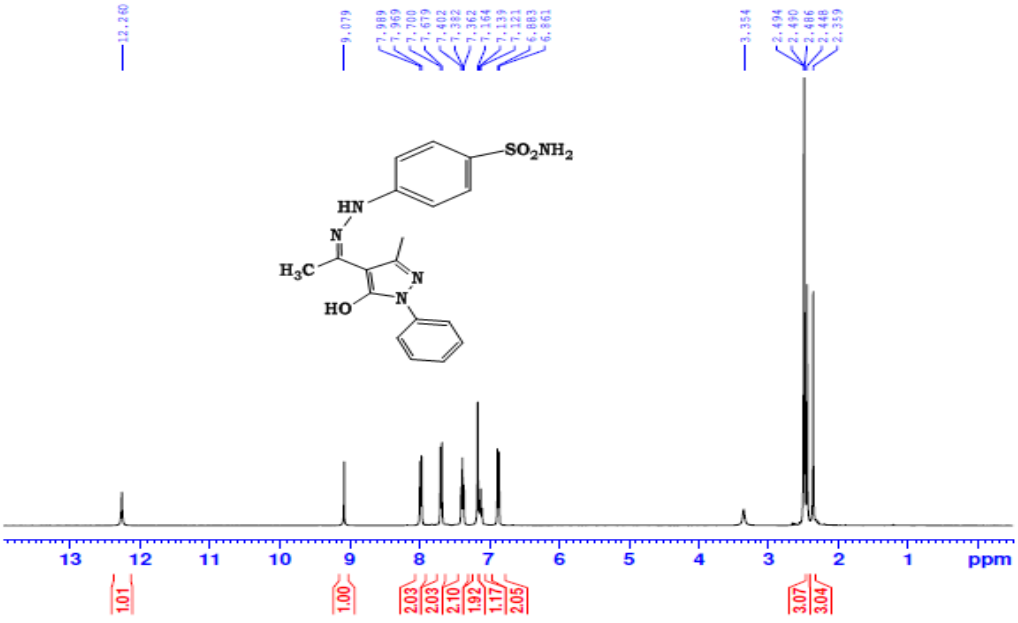


Figure 1 : 1H NMR Spectra of ligand[L1]

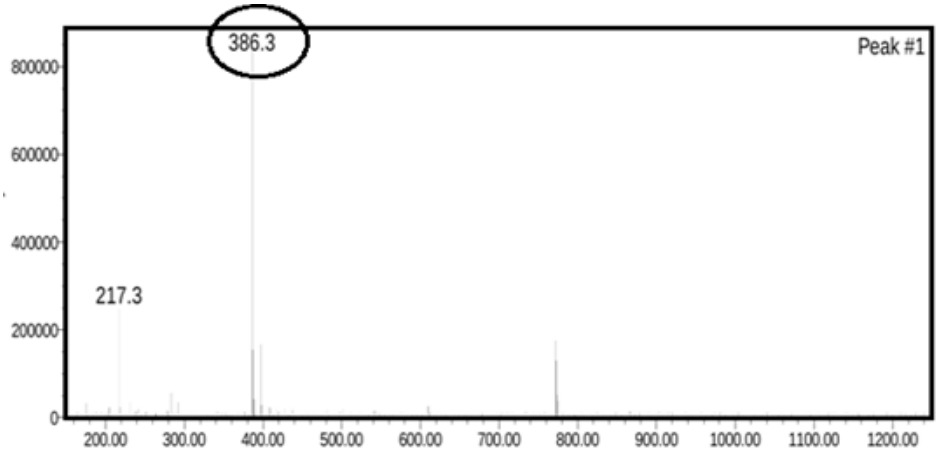


Figure 2 : Mass spectra of ligand (L1)

IR spectra studies :

The IR spectra of the Schiff base ligands and the associated Complexes were compared in order to determine the binding mode of the Schiff base ligands (L1 to L6) to the Ni(II) ion in the Complexes. According to this study's Schiff base ligand's broad band, centred around 3199 to 3345 cm-1, the 5-OH group participates in intramolecular hydrogen bonding [22–25].

The azomethine lone pair indicates that the ligand is present in the solid state as the enol form. The acyclic azomethine group's (C=N) vibration is represented as a distinct and strong band in the spectrum of the Schiff base ligands (L1 to L6) at 1531 to 1558 cm-1. However, this band exists at a low-energy shift in complexes, shifting from 1618 to 1597 cm-1, indicating coordination through the nitrogen of the azomethine[26][27].

The stretching force constant of the pyrazolone group exhibits a large negative shift of 25–30 cm-1 in the IR spectra of the Complexes, which is consistent with coordination through the oxygen atom of the ligand. This information confirms that the ligands (L1 to L6) form a conjugate chelate ring and function as dinegative bidentate ligands. The ligand also exists in the Complexes in the form of enolic ligands.

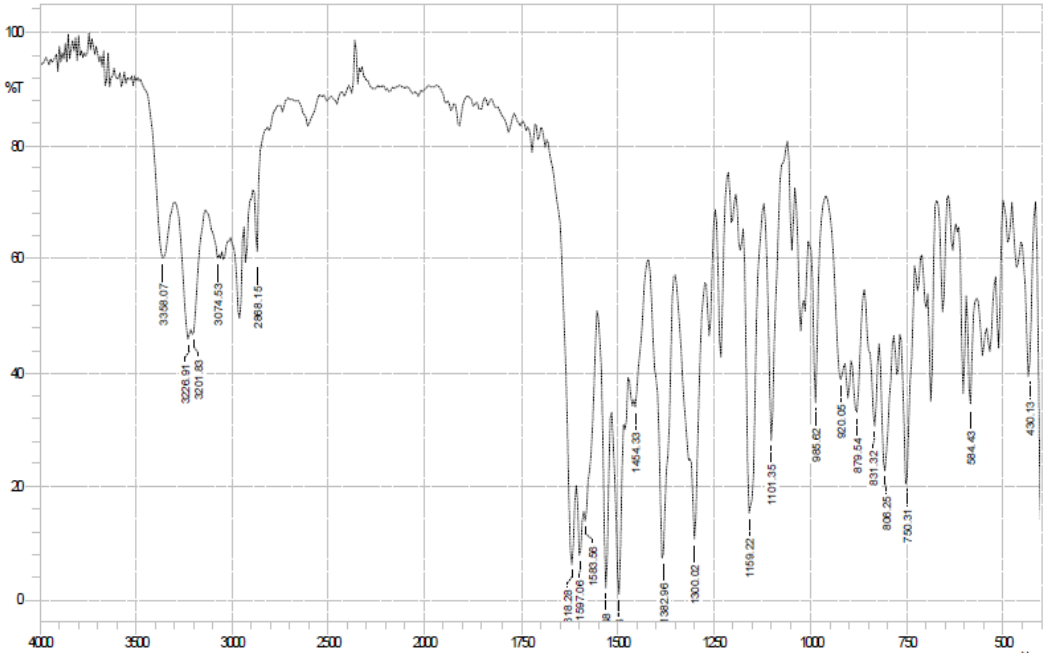


Figure 3 : IR Spectra of ligand[L3]

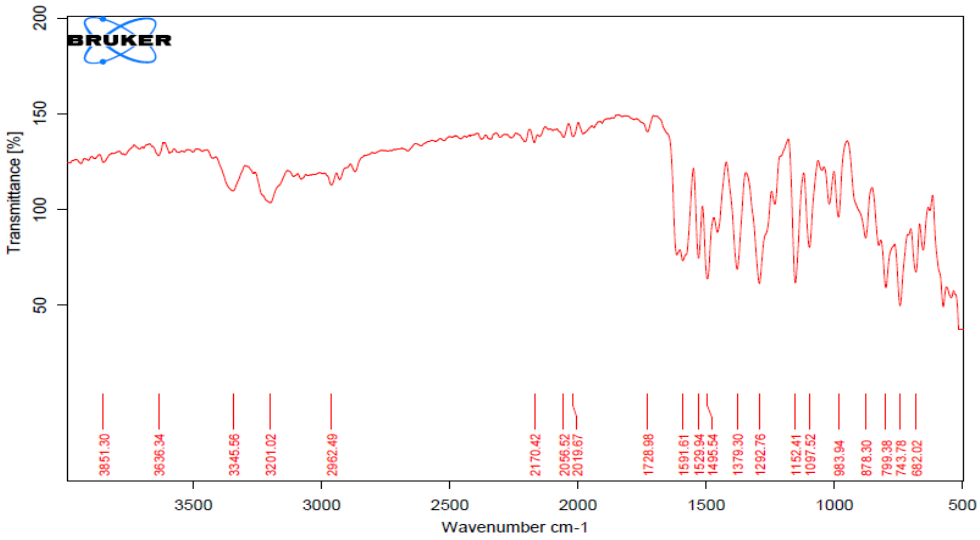


Figure 4 : IR Spectrc of metal complex[ML3]

Thermal studies: Every process of decomposition follows a trend**.**

The process for thermally fragmenting Complexes [Ni(L3).Cl].n.H2O.m.Cl is as shown below

$$\text{Solid-1} \xrightarrow{\text{heat}} \text{Solid-2} + \text{Gas}$$

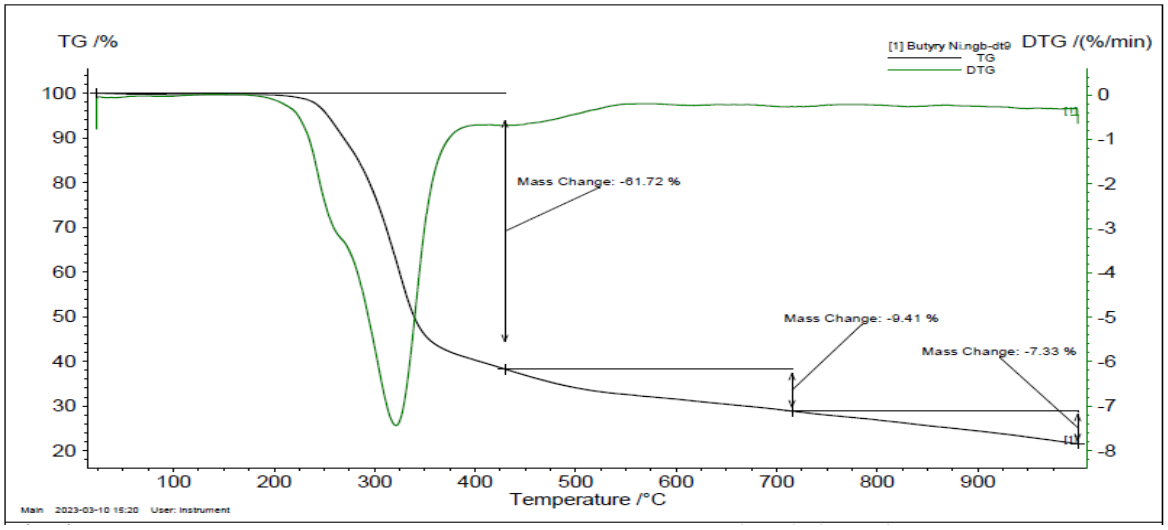
There are various steps in this entire procedure.

$$[Ni(L_3).Cl].n.H_2O.m.Cl \xrightarrow[\text{crystaline Cl} + H_2O]{\text{Removel of}} [Ni(L_3).Cl] + n.H_2O.m.Cl$$

$$[Ni(L_3).Cl] \xrightarrow[\text{coordinate Cl} + H_2O]{\text{Removel of}} [Ni(L_3)]$$

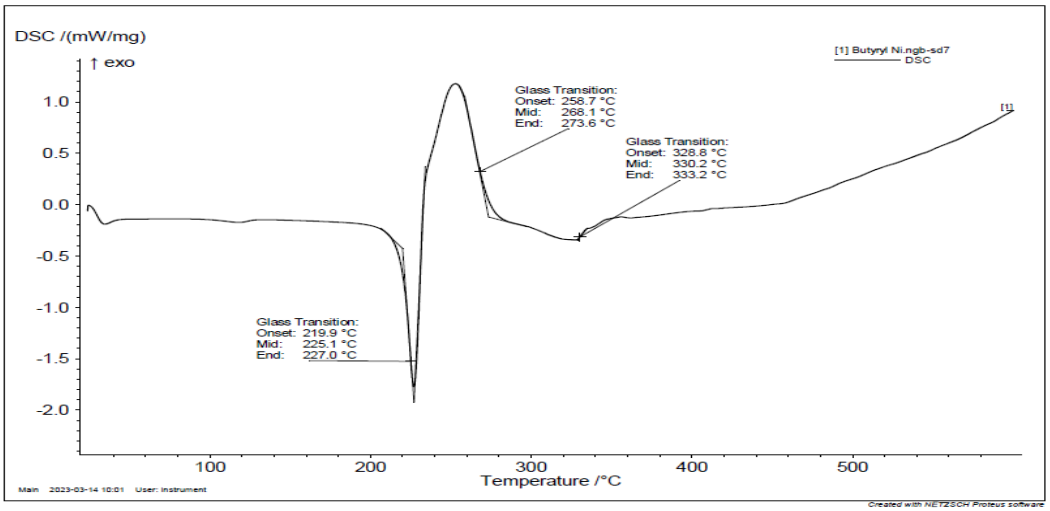
$$[Ni(L_3)] \xrightarrow[\text{ligand}]{\text{Removel of}} Ni_3O_4$$

Graph 1 shows the TG/DTG curves for the Complexes $[Ni(L_3).Cl]_2H_2O$. Three phases make up the breakdown of the Complexes $[Ni(L_3).Cl]_2H_2O$. Two molecules of crystalline H_2O are eliminated in the first stage. A portion of the L3 ligand decomposes in the another stage, the temperature range is 251 to 400°C, leading to an observed mass loss of 61.72%. In the third stage, the remaining L3 ligand is broken down, resulting in the synthesis of Ni_3O_4 at temperatures between 400 and 900 °C and a 16.74% mass loss.



Graph 1 : TGA/DTG Analysis of heterochelate[ML3]

DSC curves of Ni(II) Complexes shown in graph 2



Graph 2 : DSC curve of ML3

Zone of inhibition:

The chemical was mixed with double-distilled water and the least amount of DMF to make a stock solution with a concentration of 10 mg mL-1. Luria broth (20 g; SRL, India) and bacteriological agar (20 g) were combined with one litre of distilled water to create a fictional medium. In order to solidify, the resultant liquid was transferred onto clean Petri dishes. Then, inoculation was performed using these plates. The target bacteria were activated in separate cultures in Luria broth medium. 100 L of the activated strain was distributed uniformly across the surface of an agar plate for inoculation using a micropipette with sterilisedtips.Each plate had two 10 mm-diameter wells that were drilled with a sterile borer. The wells of the previously inoculated agar plate were treated with sterilised stock solutions (10 mg mL-1). The plates were incubated for 24 hours at 30°C for Gram-positive bacteria and 37°C for Gram-negative bacteria with discs in the wells. The millimetres of the inhibitory zone surrounding the disc were then measured, as seen in below picture. Control studies were carried out without any additional test chemicals using solvent alone (equivalent volume). The millimetre length of the zone of inhibition was noted.[28]

Figure 5 : Zone of inhibition of ligand and its metal complexes

APPLICATION

The antimicrobial screening of all the synthesised ligands L1–L6 and their metal complexes[ML1–ML6] (M = Ni), were conducted against diverse bacterial species. According to the results of the antimicrobial screening as shown in table 4, the Complexes exhibit stronger inhibitory effects on both Gram-positive and Gram-negative bacteria than the ligands. Strong bactericidal effects are particularly present in the ligands and Complexes against E. coli. The overtone notion [29] and the chelation theory can be used to explain the higher activity seen in the Complexes compared to the ligands.

Table 4 :Antimicrobial effect of ligands and metal complexes (mm)

S.No.	Compounds	Gram-Positive	Gram-Negative
		[Bacillus megaterium]	***[E.coli]***
[Ref. drug]	[Penicillin]	*35*	*28*
1	L1	17	10
2	L2	10	06
3	L3	06	07
4	L4	20	24
5	L5	15	20
6	L6	13	17
7	ML1	19	15
8	ML2	11	09
9	ML3	10	08
10	ML4	23	26
11	ML5	19	20
12	ML6	17	19

***IN-VITRO*ANTIMALARIALSCREENING:** At the Microcare laboratory and TRC in Surat, Gujarat, the synthesised chemicals were examined for their ability to treat malaria. 96-well microtitre plates and the micro assay method developed by Rieckmann and colleagues were used to conduct the in vitro antimalarial assay with a few minor modifications. In addition to 10% heat-inactivated human serum, 1% D-glucose& 0.23% sodium bicarbonate than add 25 mM HEPES, the RPMI 1640 medium in which the P. falciparum 3D7 strain cultures were raised also included these other ingredients.The P. falciparum asynchronous parasites were brought into sync and only in a ring stage parasitized cells were separated after a 5% D-sorbitol treatment. For the experiment, an initial ring stage parasitemia ranging from 0.8% to 1.5% was determined using Jaswant Singh Bhattacharya (JSB) staining. The parasitemia level was continuously maintained in a total volume of 200 l of RPMI-1640 medium with a 3% hematocrite. Red blood cells (RBCs) made up half of the medium and were all O+. Test samples were made in DMSO at a conc of 5 mg/ml, and they were then diluted with culture media After being diluted by 20 l, the test samples were added to the test wells. This resulted in final concentrations that ranged from 0.4 g/ml to 100 g/ml after five times dilutions. With each dilution, the parasitized cell preparation was poured into three separate wells. The culture plates were then placed in a candle jar and heated to 37°C for incubation. After aapproximately 40 hour incubation period. On the slides microscopic observations were made to demonstrate how ring stage parasites evolved into trophozoites and schizonts when exposedto various concentrations of the test chemicals.The concentration of the test substance at which complete growth into schizonts was inhibited was known as the minimal inhibitory concentration (MIC). Chloroquine served as the comparable drug as a reference. Observations were made during the in vitro antimalarial screening after a 38-hour incubation period to establish the typical trophozoites&schizonts per 100 parasites in triplicate wells. It was also calculated how much maturation inhibition there was compared to the control group[30 to 35].Anti malarial activity [*Plasmodium falciparum*]

Table 5: Minimum Inhibitory Concentration (MIC)

Sr. No.	Compounds	Mean IC50 Values
1	L1	1.6 µg/ml
2	L2	1.98µg/ml
3	L3	1.74µg/ml
4	L4	1.79µg/ml
5	L5	1.68µg/ml
6	L6	2.89µg/ml
7	ML1	0.86 µg/ml
8	ML2	0.92 µg/ml
9	ML3	0.64 µg/ml
10	ML4	0.68 µg/ml
11	ML5	0.60 µg/ml
12	ML6	0.74 µg/ml

CONCLUTION

A novel sulphonamide phenyl hydrazone ligand's ability to be developed and synthesized has been effectively demonstrated. The ligand can exist in solid and solution states as a keto-enol tautomerism with intra molecule H-bonding, according to FT-IR, 1H NMR, and mass spectrum investigations. We have prepared many novel Ni(II) Complexes and characterised their properties using a sulphonamide phenyl hydrazone derivative. All of the synthesised substances were examined for their biological activity. The Complexes have high action against Gram positive *(Bacillus magaterium)* and Gram negative *(E. coli)* organisms when compared to the penicillin drug & ligand and they both were more efficient against more than one bacterial strains, leading to the introduction of a new class of metal-based bactericidal medicines. The highest level of *In-vitro* antimalarial screening is shown by Complexes.

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