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COMPREHENSIVE INVESTIGATION OF THERMAL AND BIOLOGICAL PROPERTIES OF NOVEL ZN(II) PYRAZOLONE LIGANDS

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ABSTRACT

This research presents a comprehensive exploration of the thermal and biological properties of newly synthesized Zn(II) complexes derived from pyrazolone ligands. The synthesis of these compounds involved the utilization of various 4-acyl pyrazolones, followed by rigorous characterization using multiple analytical techniques, including 1H NMR, IR, 13C NMR, elemental analysis, and UV spectroscopy for the ligands. Furthermore, the resulting complexes were extensively characterized through elemental analysis, UV spectroscopy, IR spectroscopy, and thermal analysis techniques, including TGA/DTG and DSC. In addition, biological potential of these compounds was evaluated through antibacterial testing. The findings unveiled promising antibacterial properties, underscoring their potential for further exploration in the realm of antimicrobial agents.

Keywords: Pyrazalone, Heterocycles, Schiff base ligand, Co-ordination chemistry, Metal Complexes, Antimicrobial Activity

INTRODUCTION

Heterocycles have emerged as the subject of perhaps the most in-depth aspects of organic chemistry study for almost a hundred years. It has greatly influenced society's biological, industrial development, as well as the study of biological functions and efforts that enhance

life quality **[1]**. Almost half of the 20 million organic chemicals reported mostly by conclusion of the 2nd Millennium are aromatic, and over two-thirds are entirely or mostly heterocyclic **[2]**. Heterocyclic compounds are abundant in nature and serve as the foundation for a vast range of components that are necessary for survival. Indeed, the fundamental constituents of Deoxyribonucleic acid, that holds the gene that regulates the growth and maintenance of each and every organism in existence, are heterocyclic nitrogenous bases located in Genetic molecule. Furthermore, the oxygen transporters in both mammals and plants, and photosynthetic pigment and prosthetic unit of haemoglobin, are both equivalents of porphyrin ring **[3, 4]**. Medications having the heterocyclic component are commonly utilized as antimicrobials, antiseptics, and anti-inflammatory compounds. Certain heterocycles have antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, and antidiabetic properties **[5-8]**. Schiff bases are generally produced through the condensation of a primary amine and an aldehyde/ketone. The resulting chemical, R1R2C=NR3, is known as a Schiff base, with R1 being an aryl group, R2 being a hydrogen atom, and R3 that are either an alkyl or an aryl group. Nevertheless, molecules in which R3 is an alkyl or aromatic group are also considered Schiff bases. Transition metal complexes containing Schiff bases have grown enormously in popularity, encompassing a wide range of themes such as metal organic compounds and many elements of bio-coordination chemistry **[9]**. These kinds of ligands are commonly used in industrial estimation, either via formation of complex by processes resulting through the reaction between NH2 and C=O compounds to form carbon nitrogen complex, or through variations in characteristic spectroscopic features as pH and solvent modifications **[10]**. 4-AAP is an excellent starting molecule for the condensation of various Schiff base ligands with aldehydes, ketones, thio semi carbazides, carbazides, amines, and hydrazides because it contains both a keto and an amino group. According to reports, most of these Schiff bases and their metal complexes have superior antibacterial properties than 4-AAP **[11-14]**. Schiff bases are one of the chemical groups that scientists have spent the most time studying because of their adaptability, alertness, sensitivity, stability, and ease of synthesis, to name just a few. This has resulted in a wide range of applications for Schiff bases **[15-18]**.

MATERIALS AND METHODS

This section discusses the reagents used, as well as the various

analytical and physicochemical techniques used in the characterization experiments. It also includes the production and analysis of ligands and transition metal complexes used in the latest research.

Step 1: Synthesis of pyrazalone derivative (1-phenyl 3-methyl-5-pyrazolone)

Initially, Pyrazalone derivative was been synthesized. A 100 ml of conical flask was taken in which 6.5 gm of ethyl acetoacetate was been added. With some amount of stirring, 2.5 gm of phenyl hydrazine was then dropwise added. The temperature of the process mixture was preserved at 60 degrees. A crystalline substance separated after one hour of continuous stirring. Thereafter, the mixture was chilled in an ice bucket to create the crystalline stability. It was purified with ordinary filter paper. Later, the colourless crystal was recovered and desiccated. It was then recrystalized by ethanol and used further.

Step 2: General procedure synthesis of ligands

Prepare a two-necked round bottom flask with 7.83 grams of 1-Phenyl 3-methyl 5-pyrazolone. After stirring for around 30 minutes, 28 ml of 1,4-Dioxane will entirely dissolve the pyrazalone derivative in the RBF. At room temperature, completely dissolve the resulting mixture by stirring with a magnetic stirrer. Now, 7 grams of calcium hydroxide powder should be added to the mixture. Using an additional funnel, add catalytic amount of the acylating agent gradually into the solution over the span of 15 minutes, observing that the thickness signified the complex's formation. Now the solution appears to be dark brown in colour. To prevent compound loss during reflux, immerse the reflux condenser in an oil bath as well as cover one of the flask's necks. Reflux the mixture for a period of four to five hours at 90 to 110 degrees Celsius. Then, take 25 millilitres of concentrated HCl and mix it with crushed ice. Add the product into the mixture with constantly stirring it. And after a little time, the solution must be filtered to achieve the desired result. The ligands **(L1-L6)** are generated according to the method as displayed in **Table 1**.

Step 3: Binding of 4-sulfonamido phenyl hydrazine with synthesized ligands

Using a magnetic stirrer, dissolve 1.15 grams of 4-sulfonamido phenyl hydrazine in a small amount of water in a round bottom flask. Take up 2 grams of synthesised acylated compound in the beaker. Dissolve the compound in 30 ml of methanol. Then, add the alcoholic solution dropwise over just a 20-minute interval to RBF. Then again add 20 ml methanol to in mixture. After a one-hour the product seem to

appear. Now provide the wash of methanol and water to eliminate impurities from the product to obtain pure product.

Step 4: Zn (ii) metal binding with synthesized sulphonated ligands

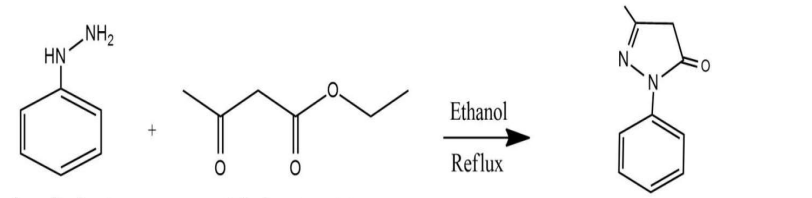
Take 2 grams of compound (ligand) and 15 ml methanol in a round bottom flask and stir by using a magnetic stirrer. Take 0.52 grams of Zinc Chloride in the beaker and dissolve it in 5 ml of methanol. Now add this solution dropwise in RBF for 15 minutes. Keep the temperature between 60-70 °C. After two hours add 2 ml methanol in a mixture in the Round Bottom Flask. Continue the stirring until the mixture gets transparent. After one hour the mixture becomes transparent and the product appears. Now take this transparent solution in a petri dish and evaporate the solvent with the help of fuming wood. After evaporation, the solution becomes crystal solid form and then dissolve it in a minimum amount of water for 15 minutes by using a magnetic stirrer. Now filter the solution with filter paper and dry the product in oven. The obtained dried product is the Metal Complex.

Table 1: Ligands used in the Synthesis

Ligands	-R
L1	$-C_6H_5NO_2$
L2	$-CH_2CH_2CH_3$
L3	$-CH_2CH_3$
L4	$-CH_3$
L5	$-C_4H_3O$
L6	$-C_6H_5$

Synthetic reaction of Zn metal complex (ML1)

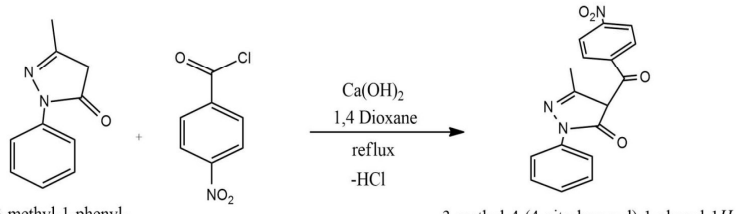
STEP 1: Synthesis of pyrazalone derivative (1-Phenyl 3-methyl-5-Pyrazolone)



phenylhydrazine Ethyl acetoacetate 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one

STEP 2: **Synthesis of 1-Phenyl 3-methyl 4-(4-nitro benzoyl chloride)**

5-Pyrazolone



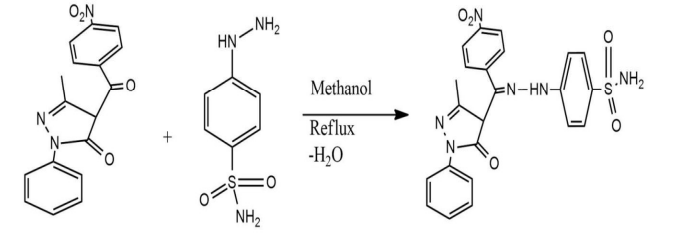
3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one

4-nitrobenzoyl chloride

3-methyl-4-(4-nitrobenzoyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one

STEP 3: **Binding of 4-sulfonamido phenyl hydrazine with 4-(-nitro benzoyl)**

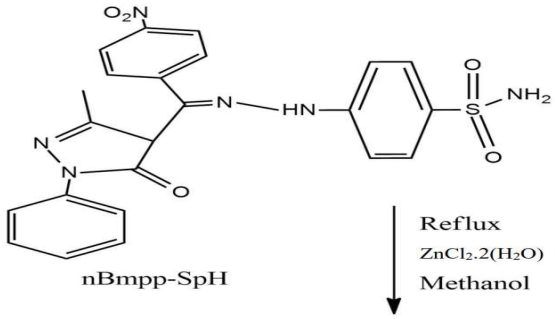
1-Phenyl 3-methyl 5-pyrazolone

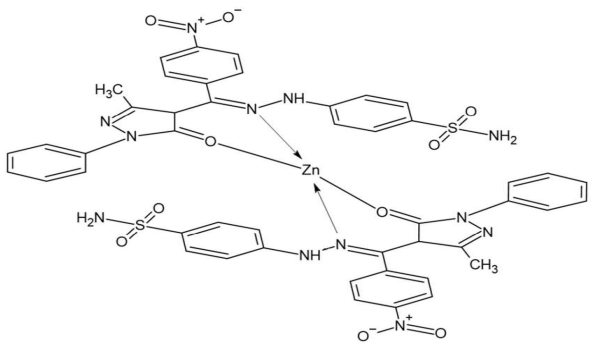


3-methyl-4-(4-nitrobenzoyl)-1-phenyl-1*H*-pyrazol-5(4*H*)-one

4-sulfonamido phenyl hydrazine

4-(2-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(4-nitrophenyl)methylene)hydrazinyl)benzenesulfonamide





RESULTS AND DISCUSSION

Pyrazalone chemistry is essential in the domain of heterocyclic chemistry. The pyrazole system, which consists of three carbon and two N atoms in a heterocycle having five atoms, is an important and adaptable example among the numerous natural and synthetic molecules. The significance of pyrazalone chemistry derives from its unique position in heterocyclic chemistry due to their vast use in numerous domains such as industrial, medical therapy, and agriculture.

FT.IR- analysis of data

With the purpose of identifying the binding behaviour of the Schiff base ligands to the Zn (II) ion in the Complexes, the IR spectra of the implicated Complexes and the Schiff base ligands have been analysed. FT-IR spectra was obtained using KBr pellets and a Nicolet-400D spectrophotometer. The positions of the absorption bands for several of the active groups of compounds are described in depth by these spectra. A sharp band at 1607 cm^{-1} was seen in the IR spectra of ligands and was linked to the ν(C=O) stretching mode. Also, the value of ν(C=N) is shown to be 1554 cm–1. The complexes show bands within the range 585–595 cm-1 and 470– 490 cm-1 due to the ν(M-N) and ν(M-O). The ligand is present in a form of solid substance as the enol form, according to the azomethine lone pair. The spectra of the Schiff base ligands (L1 to L6) show a prominent and intense band at 1531 to 1558 cm^{-1}, which corresponds to the C=N vibration of the acyclic azomethine group. However, this band shifts from 1618 to 1597 cm-1 at low energies in complexes, exhibiting coordination through the nitrogen of the azomethine **(Table 2) [19-20]**.

Table 2: FT-IR data of Ligands

Ligands	ν (O-H)	ν (N-H)	ν (C=O)	ν (C=N)
L1	**3342**	**3256**	**1612**	**1568**
L2	**3240**	**3289**	**1607**	**1554**
L3	**3352**	**3301**	**1610**	**1534**
L4	**3348**	**3198**	**1598**	**1525**
L5	**3349**	**3296**	**1629**	**1519**
L6	**3241**	**3245**	**1619**	**1529**

UV-visible spectroscopic analysis of data

As shown in Graph, the UV-visible spectra of the ligands (L1-L6) and their respective metal complexes were observed in DMSO solutions between 200 and 800 nm. The two bands of free ligand display the π- π* transition of heterocyclic entities while n- π * transition of azomethine group of the ligand. While the formation of metal complexes, results in shifting the transitions to longer wavelengths. Shifting of transitions to longer wavelengths denotes the formation of M-L coordination bond. The data reported by UV-Visible technique confirms the formation of synthesized product. By comparing the data with the standard values of the obtained result, it was confirmed to be a success in complex formation.

NMR data & spectra of ligand

1H NMR data of ligand for L1-L6:

L1: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=1.88 (3H, s, -CH3); 7.01 -8.65 (Ar-H).

L2: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=3.0 (3H, s, -CH3); 1.79-1.88 (2H, q, -CH2), 2.79-2.86 2H, m, -CH2);0.97-1.60(3H, t, -CH3);6.89-7.99 (Ar-H).

L3: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=2.08 (3H, s, -CH3); 1.34-1.40 (3H, t, -CH3);2.66- 2.68(2H, q, -CH2) 6.98-7.99 (Ar-H).

L4: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=2.06 (3H, s, -CH3); 2.67-2.69 (3H, s, -CH3); 6.98-7.56 (Ar-H).

L5: 1H NMR (400 MHz, DMSO-d6): δ (ppm)= 2.12 (3H, s, -CH3); 7.56-8.99 (Ar-H).

L6: 1H NMR (400 MHz, DMSO-d6): δ (ppm)= 1.98 (3H, s, -CH3); 6.87-7.98(Ar-H).

The tautomerism of pyrazolone has been extensively studied **[21-22]**. 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**.** 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. It was determined from the 1H NMR spectroscopic data that the Schiff base ligand occurs in solution as the keto-enol form.

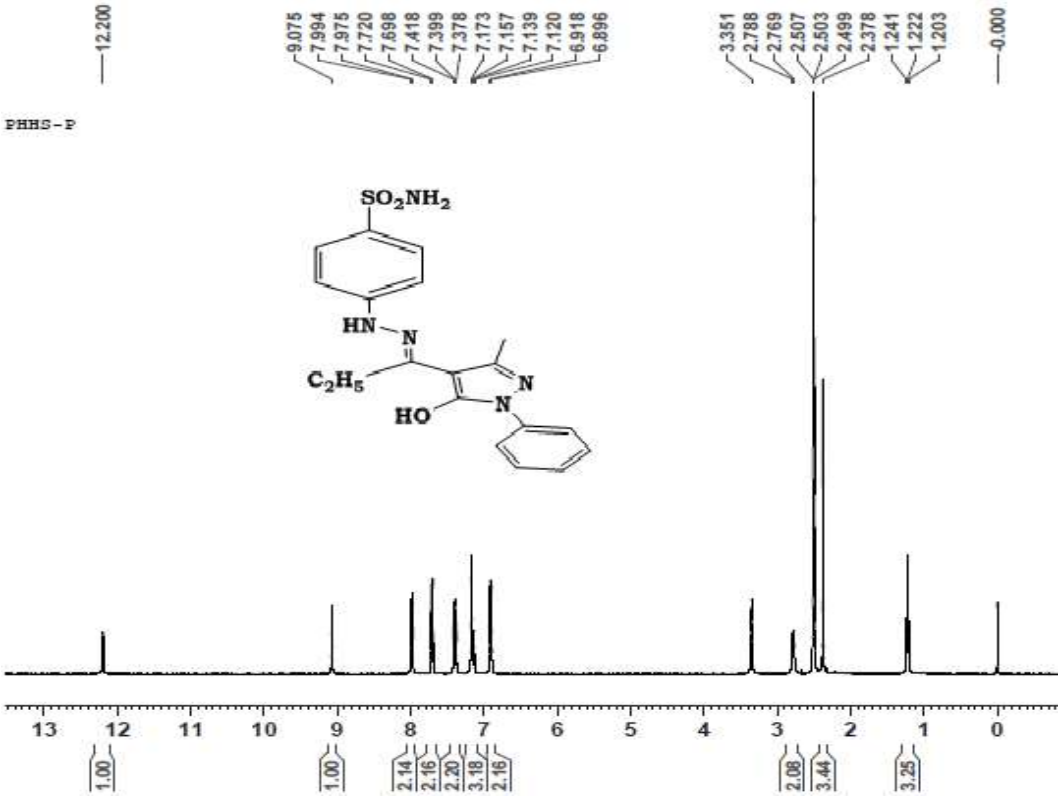


Figure 1: 1H NMR Spectra of ligand [L3]

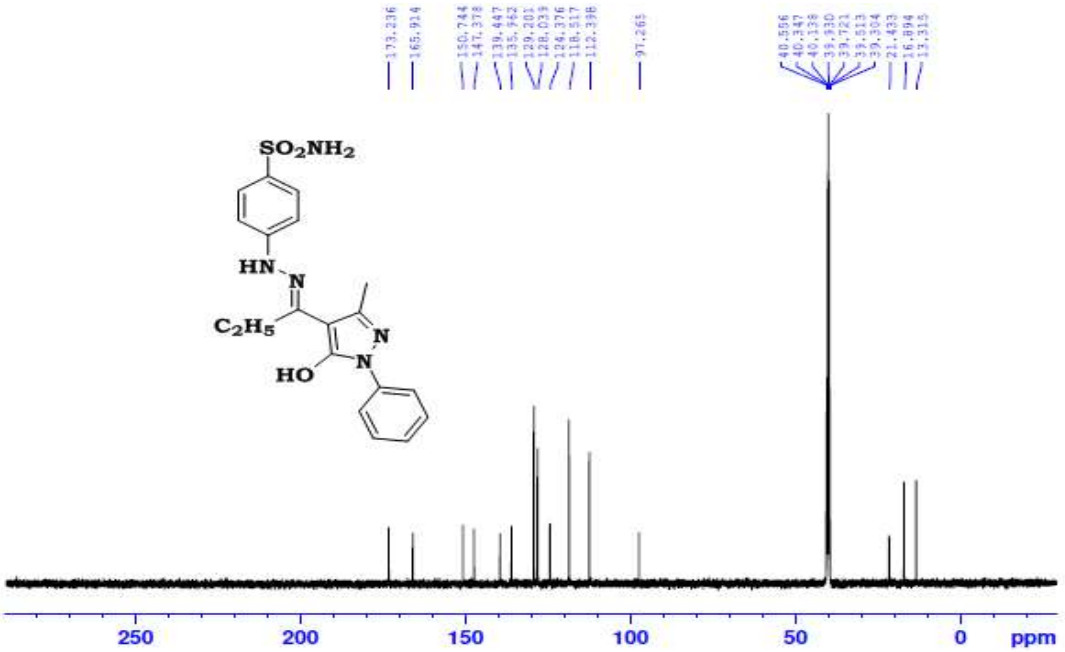


Figure 2: 13C NMR Spectra of ligand [L3]

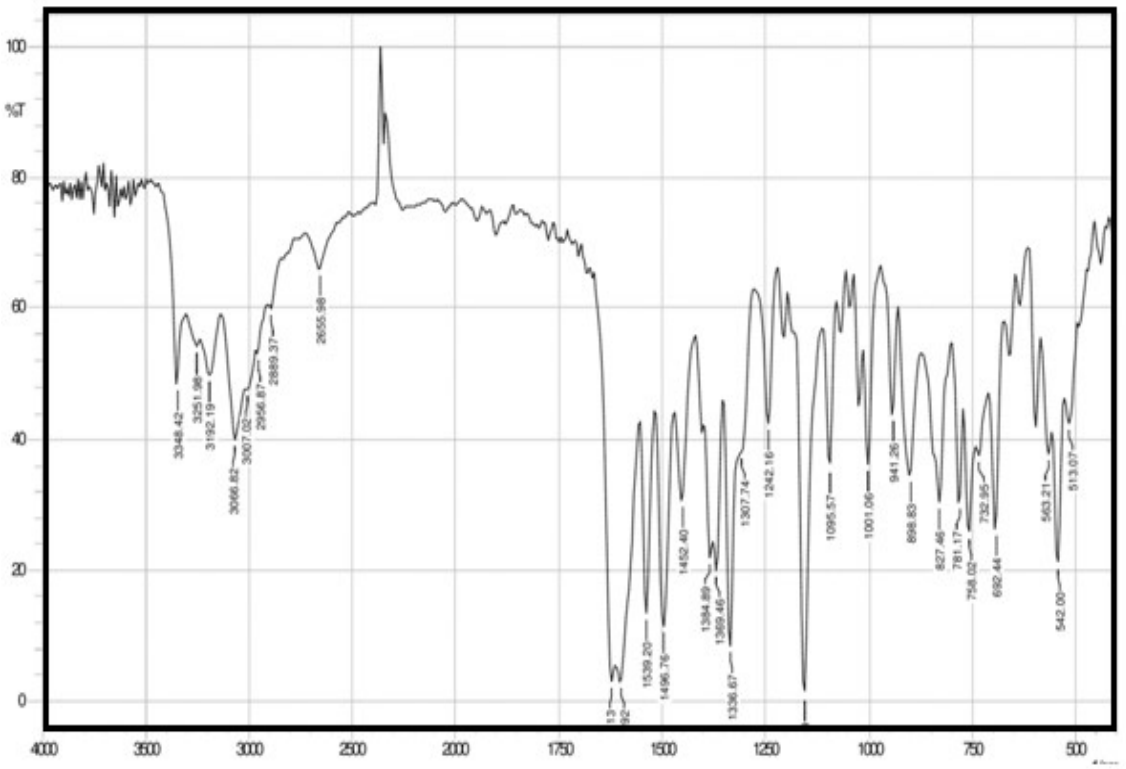


Figure 3: IR Spectra of ligand [L3]

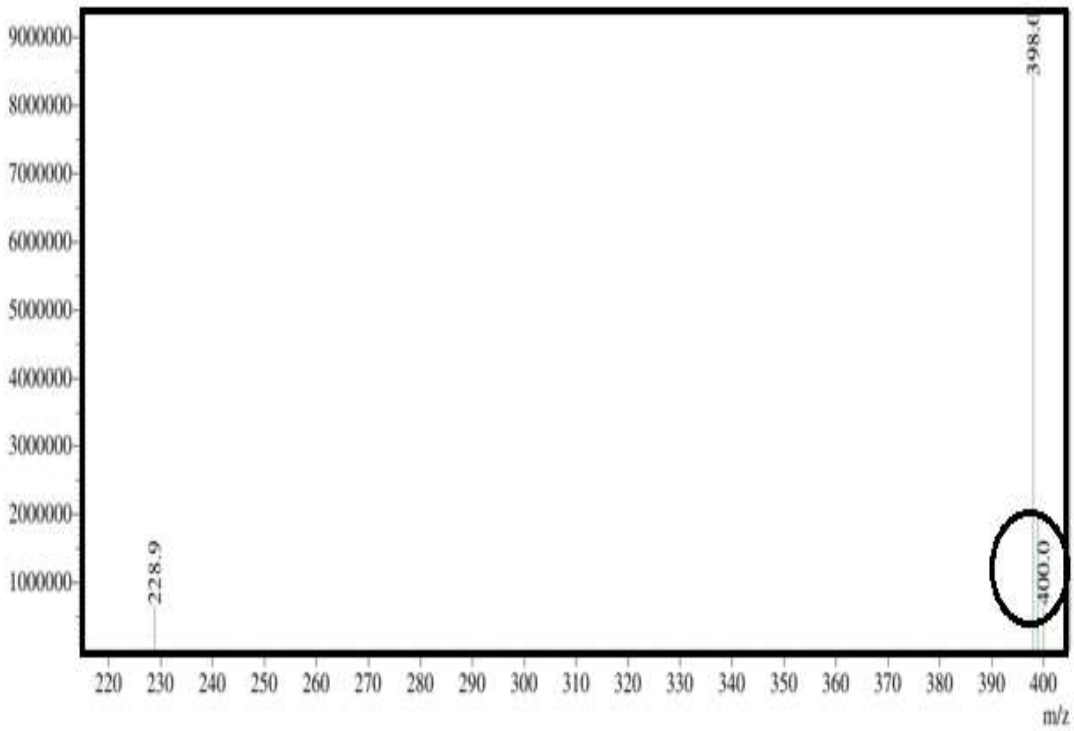


Figure 4: Mass Spectra of ligand [L3]

Table 3: Elemental Analysis data of Ligands										
	Ligands	Molecular Formula	Melting Point	Colour & % Yield	Data Found (%)			Data Calculated (%)		
					C	H	N	C	H	N
L1	4- Nitro benzoyl hydrazine pyrazolone	$C_{23}H_{20}N_6O_5S$	260˚C	Yellow (70%)	56.15	4.14	17.09	56.09	4.09	17.06
L2	4- butryl hydrazine pyrazolone	$C_{20}H_{23}N_5O_3S$	223˚C	White (71%)	57.10	5.23	17.46	57.13	5.30	17.53
L3	4- propionyl hydrazine pyrazolone	$C_{19}H_{21}N_5O_3S$	220˚C	Cream Colour (78%)	58.16	5.70	16.98	58.09	5.61	16.94
L4	4- acetyl hydrazine pyrazolone	$C_{18}H_{19}N_5O_3S$	214˚C	Pink (72%)	56.11	4.89	17.96	56.09	4.97	18.17
L5	4- Furoyl hydrazine pyrazolone	$C_{21}H_{19}N_5O_5S$	250˚C	Brown (79%)	57.74	4.33	15.89	57.66	4.38	16.01
L6	4- benzoyl hydrazine pyrazolone	$C_{23}H_{21}N_5O_3S$	256˚C	Light Pink (69%)	61.88	4.79	15.62	61.73	4.73	15.65

Table 4: Elemental Analysis of Metal Complexes									
Sr. No.	Metal Complexes	Molecular Weight	Colour & % Yield	Data Found (%)			Data Calculated (%)		
				C	H	N	C	H	N
1	ML1	1050.42	Yellow (65%)	53.06	3.68	16.56	52.60	3.84	16.00
2	ML2	892.39	Yellow (70%)	52.98	4.76	16.26	52.80	4.90	16.21
3	ML3	864.34	Pink (73%)	54.01	4.98	16.06	53.84	5.20	15.70
4	ML4	836.28	Light Yellow (66%)	52.06	4.34	15.97	51.70	4.58	16.75
5	ML5	940.35	Brown (59%)	53.78	3.89	15.49	53.64	4.07	14.98
6	ML6	960.42	Light Brown (74%)	52.67	4.09	15.67	52.92	4.03	15.98

Impost of the resistance of zinc metal complex of pyrazalone derived compounds against bacteria

With the objective to develop a stock solution with a concentration of 10 mg/mL, the chemical was combined with double-distilled water and the least quantity of DMF. One litre of distilled water was subsequently included along with Luria broth (20 g; SRL, India) and bacteriological agar (20 g), to form the artificial medium. The solution that emerged was subsequently introduced onto sterile Petri plates to solidify. Then, these plates were utilised for inoculation. Separate cultures of the target the microbes were activated in Luria broth medium. Using a sterilised micropipette, 100 L of the activated strain were evenly dispersed across the surface of an agar plate for inoculation. Two 10 mm-diameter wells were created into each plate using a sterile borer. Sterilised stock solutions (10 mg mL-1) were then applied to the previously inoculated agar plate's wells. Gram-positive bacteria were grown on the plates for 24 hours at 30°C, whereas Gram-negative bacteria were grown on the plates for 24 hours at 37°C. The inhibition region around the disc was then

measured in millimetres, as seen in the image below. Without employing any additional test compounds, control trials were conducted by applying solvent alone (equivalent volume). The zone of inhibition was measured in millimetres **[23]**. This synthesis of Pyrazalone derived ligand and its zinc metal complex was interpreted with (Bacillus Megaterium) and (E. Coli) bacterium. Onto the test, the synthesized compounds had a variety of inhibitory actions. Both synthesized ligands and metal complexes showed several activities but on comparison, the metal complex was observed to be more bactericidal than the ligand. This observation leads on to the conclusion that the Schiff base's biological activity enhanced as a result of the complex formation with zinc metal.

Table 5: Anti-Bacterial effects of ligands and metal complexes (mm)

Sr. No.	Compounds	Gram-Positive	Gram-Negative
		Bacillus Megaterium	*E. Coli*
Reference Drug	Penicillin	35	28
1	L1	16	10
2	L2	11	04
3	L3	08	10
4	L4	19	22
5	L5	18	25
6	L6	17	22
7	ML1	18	14
8	ML2	13	09
9	ML3	11	14
10	ML4	20	25
11	ML5	22	28
12	ML6	19	25

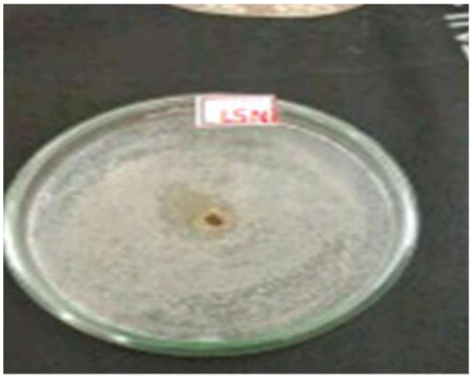


Figure 5: Anti-Bacterial Activity on Ligand

Figure 6: Anti-Bacterial Activity of Zinc Metal Complex

CONCLUSIONS

This study concludes the successful synthesis of a pyrazalone derivative compound. The novelty in the research was attained by addition of 4-Sulphanamido phenyl hydrazine compound to the molecule which resulted in a formation of a new ligand. The ligand was synthesized and was further binded to Zinc chloride and Zinc Metal complex was formed. The Zinc metal complex shows good amount of Anti-Microbial Property. The result obtained from IR Spectroscopy, UV-visible spectroscopy, NMR Spectroscopy and Elemental Analysis confirms the absolute synthesis and formation of the desired molecule. The desired compound obtained is Zinc Metal complex of synthesized Schiff base ligand. Because of their biological action against bacteria, Schiff base chemicals are more suited for use in cells and tissues.

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