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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF PYRAZOLE DERIVATIVES AND METAL CHELATES WITH Ni (II), Cu (II), Cr (III), Co (III) and Zn (II) ions

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ABSTRACT

Pyrazole, a five-membered heterocycle containing two nitrogen atoms, is extensively found as a core framework in a huge library of heterocyclic compounds that envelops promising agro-chemical, fluorescent and biological potencies. Attributed to its several potential applications, there is a rise in the significance of designing novel pyrazoles, disclosing innovative routes for synthesizing pyrazoles, examining diffexrent potencies of pyrazoles, and seeking for potential applications of pyrazoles. This review consists of two parts. The first part provides an overview on the synthetic approaches to prepare pyrazoles derivatives and the synthesis of metal chelates using synthesized ligand and metal ions such as Ni (II), Cu (II), Cr (III), Co (III) and Zn (II).

The second part provides the overview of physical, analytical, spectral parameters and biological study of synthesized metal chelates from pyrazole derivative. Numerous pyrazoline derivatives have been found to possess considerable biological activities, which stimulated the research activity in this field. They have several prominent effects, such as antimicrobial, antimycobacterial, antifungal, antiamoebic, anti-inflammatory, analgesic, antidepressant and anticancer activities. The present review provides an insight view to pyrazolines synthesis and its biological activities along with the compilation of recent patents on pyrazolines.

KEYWORDS: *TPDHP (1,3,5-triphenyl-4,5-dihydro-1H-pyrazole), TGA, Antimicrobial, antifungal*

1. INTRODUCTION

One of five membered aromatic heterocyclic compounds with two adjacent nitrogen atoms and three carbon atoms is the pyrazole [1]. Pyrazole ring is not present in natural products but it is the part of many pharmaceuticals, agrochemicals and dyes. The pyrazole and its derivatives have known for their antipyretic properties [2], analgesics and herbicides [3].

Pyrazole containing drugs are known for their broad “range of biological activities, including anti-inflammatory [4], analgesics and anticancer properties” [5]. In agriculture pyrazole and derivatives have been used as fungicides, insecticides, pesticides and herbicides [6]. Pyrazole derivatives have been recently the area of great interest due to their interesting pharmaceutical activities such as anticancer, antioxidant, antirheumatic and anti-HIV [7]. Cyclic pyrazole derivatives exhibit cytotoxicity property to human cancer cell through apoptosis Coumarin and coumarin derivatives are widely distributed natural products with low induction [8].

From the above observations, it was through worthwhile to synthesize the transition metal chelates of “1,3,5-triphenyl-4,5-dihydro-1H-pyrazole with Ni (II), Cu (II), Cr (III), Co (III) and Zn (II) metal ion. The solid metal complexes have prepared and studied by elemental and thermal analysis (TGA and DTA) as well as UV, IR, 1H NMR, magnetic susceptibility and molar conductance to throw more light on the bonds formed and elucidate the coordination properties of these ligands with these transition metal ions”.

1.1 Experimentation: Synthesis of 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole ligand

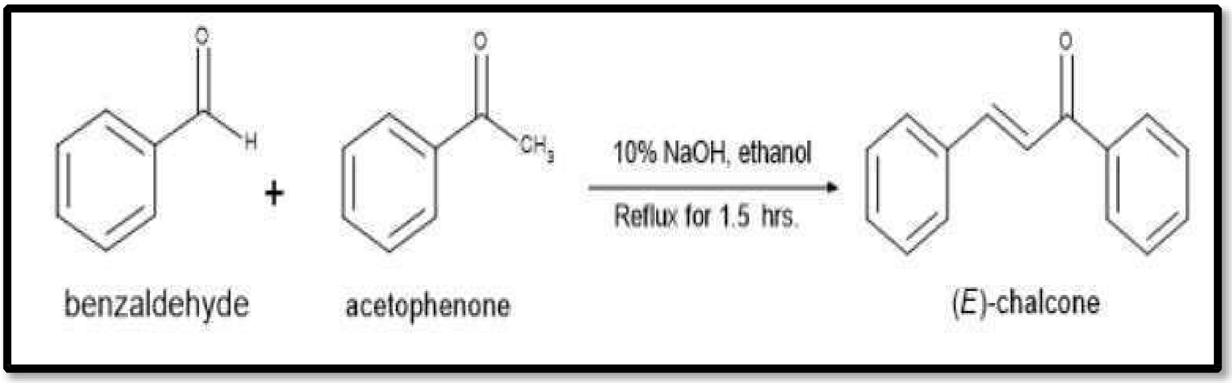
Synthesis of “1,3,5-triphenyl-4,5-dihydro-1H-pyrazole” ligand can be achieved in two steps. first step is formation of chalcone from the corresponding aldehyde and ketone. Second step is to form ligand by refluxing chalcone in first step with phenyl hydrazine. The detailed procedure given as follows.

- **Synthesis of (E) Chalcone from Benzaldehyde and acetophenone:**

A 5 cm3 (0.05 mol) round-bottom flask contained benzaldehyde. Adding 5.21 cm3 (0.05 mol) acetophenone, 15 cm3 10% sodium hydroxide, and 10 cm3 ethyl alcohol, the mixture was heated under reflux condenser on water bath for 1.5 hours at 80°C with regular shaking. In icy water, the reaction mixture cooled.

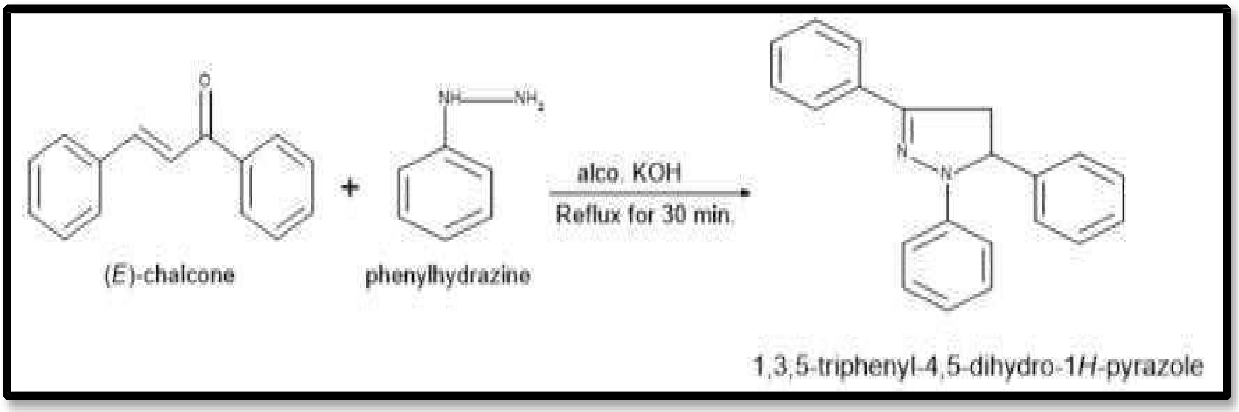
Filter the obtained solid using Whatman filter paper and was recrystallized with hot ethanol. Yield of compound was 11.3 gm and melting point was 45 °C. the progress of reaction and formation of product is checked by TLC using Toluene and ethyl acetate solvents (9:1) [9].

Reaction



- **Synthesis of "1,3,5-triphenyl-4,5-dihydro-1H-pyrazole from Chalcone" and Phenyl hydrazine:**

A 10.40 gm (0.05 mol) of (E) chalcone formed in first step was taken in round bottom flask. To it add 5.4 cm3 (0.05 mol) of phenyl hydrazine and 10 cm3 of 10 % potassium hydroxide and was heated under reflux condenser on water bath for 30 min at 80°C with frequent shaking. After cooling the reaction mixture was poured into ice cold water. Filter the obtained yellow solid using Whatman filter paper and was recrystallized with hot ethanol. Yield of compound was 10.5 gm and melting point was 1300C [10].



- **Synthesis of metal chelates with TPDHP ligand:**

To an ethanolic solution of "1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (0.01M) was added to the hot ethanolic solution of Ni (II)Cl2, Cu (II)Cl2, Co (III)Cl2, Cr (III)Cl2 and Zn (II)Cl2 (0.01M) in the ratio of 1:2 drop wise with constant stirring using magnetic stirrer". Mixture was refluxed in water bath for 3 hours. After cooling, the reaction mixture was adjusted to PH 7–8 with alcoholic ammonia [11]. The solids were separated by refluxing the reaction mixture for 1.5–2 hours in water bath. Finally, shaking, the reaction mixture was put into distilled water. The yellowish (Pista) sediments at the end were digested, filtered, and washed with alcohol and water. Product dried in desiccator [12].

2. RESULTS AND DISCUSSION

2.1 Physical and Analytical Parameters

Table No. 1 lists the produced metal complexes' molar conductance, decomposition point, chloride ion percentage, and metal-to-ligand ratio. Metal complexes produced from "Ni (II), Cu (II), Cr (III), Co (III), and Zn (II)" ions with TPDHP ligand are intensely colored. DMSO and DMF dissolve them, whereas water and organic solvents do not. Decomposition points above 2200C indicate strong thermal stability at room temperature and are given in [13-14]. The synthesized complexes' molar conductance and chloride ion fraction indicate that "Cu (II), Cr (III), and Co (III)" complexes are electrolytes, while Ni and Zn complexes are not. [15-16]. Magnetic moments of "Ni (II), Cu (II), Cr (III), Co (III)" complexes indicate paramagnetic character, while Zn (II) complex is diamagnetic.

The analytical data and Physical parameters of "Ni (II), Cu (II), Cr (III), Co (III), and Zn (II)" complexes formed from TPDHP ligand are summarized in Table No.1. The empirical Formula and metal to ligand ratio were assigned by using TGA-DTA measurement and Elemental analysis and summarized in Table No.2.

Table No.1: Analytical data and physical properties of "1,3,5-triphenyl-4,5 dihydro- 1H-pyrazole" (TPDHP and their metal chelates).

Ligand/Metal Chelates	D.P 0C	M: L ratio	Yield %	Color	% Cl, Cal. (Obs.)	Molar Cond. S cm2mol-1	Magnetic Moment. µ
TPDHP(C21H18N2)	130	-	80.5	Yellowish	-	-	
[Ni (TPDHP)2Cl2] H2O	>300	1:2	69.6	Pista	9.54 (9.53)	20.4	Paramagnetic
[Cu (TPDHP)2Cl.H2O] H2O. Cl	240	1:2	72.5	Greenish	9.26 (9.20)	13.5	Paramagnetic
[Cr (TPDHP)2Cl.H2O] Cl2	>300	1:2	75.2	Grey	13.66 (13.60)	25.2	Paramagnetic
[Co (TPDHP)2Cl2] Cl.H2O	232	1:2	69.6	Yellw	13.66 (13.55)	14.2	Paramagnetic
[Zn (TPDHP)2Cl2]	298	1:2	70.4	Pale yellow	9.69 (9.60)	8.86	Diamagnetic

Table No.2: "Percent C, H, N, O and Cl atoms in ligand and metal" ion in TPDHP metal complexes

Ligand/Metal Chelates	Mol. Wt.	Empirical Formula	Elemental Analysis (Obs/Cal)				
			C	H	O	N	M
TPDHP (C21H18N2)	298	(C21H18N2)	84.56 (84.40)	6.04 (5.90)	-	9.39 (9.20)	-
[Ni (TPDHP)2Cl2] H2O	743.5	[Ni(C21H18N2)2Cl2] H2O	67.77 (66.65)	5.1 (4.95)	2.15 (2.1)	7.53 (7.4)	7.89 (7.89)
[Cu (TPDHP)2Cl.H2O] H2O.Cl	766.5	[Cu(C21H18N2)2Cl. H2O] H2O.Cl	65.75 (65.7)	5.22 5.15	4.17 (4.1)	7.31 (7.1)	8.28 (8.28)
[Cr (TPDHP)2Cl.H2O] Cl2	779.4	[Cr(C21H18N2)2Cl. H2O] Cl2	64.66 (64.6)	4.87 (4.8)	2.05 (2)	7.18 (7.1)	6.67 (6.66)
[Co (TPDHP)2Cl2] Cl.H2O	779.4	[Co(C21H18N2)2Cl2] Cl.H2O	64.66 (64.35)	4.87 (4.8)	2.05 (2)	7.18 (7.05)	7.56 (7.51)
[Zn (TPDHP)2Cl2]	732.3	[Zn(C21H18N2)2Cl2]	68.81 (68.75)	4.91 (4.85)	-	7.65 (7.62)	8.92 (8.92)

2.2 "Electronic Spectral Data of TPDHP and its metal complex

The shift of absorption band of ligand to lower and higher frequencies indicates the metal ligand interaction. The absorption band, molar absorptivity and transition are given in Table No. 3. "The ligand exhibits strong absorption band around 21810.25 cm^{-1} and 30312 cm^{-1} due to n-π^* and π -π^* transition respectively".

Table No. 3: Electronic Transition of TPDHP and its metal complexes

Compounds	**Absorption Band cm-1**	**Molar Abs.× 104**	**Transition**
TPDHP (C21H18N2)	30312	10.8	π -π*, n-π*
	21810		
[Ni (TPDHP)2Cl2] H2O	28571	12.43	π -π*, n-π*, C→T
	24703		
[Cu (TPDHP)2Cl.H2O] H2O.Cl	27624	2.348	π -π*, n-π*, C→T
	22202		
[Cr (TPDHP)2Cl.H2O] Cl2	27777	13.104	π -π*, n-π*, C→T
	25000		
[Co (TPDHP)2Cl2] Cl.H2O	28985	2.35	π -π*, n-π*, C→T
	22084		
[Zn (TPDHP)2Cl2]	28248	10.82	π -π*, n-π*, C→T”
	24844		

The electronic spectra of “Ni (II), Cu (II), Cr (III), Co (III) and Zn (II)” complexes shows that transition is shifted towards longer frequency, which confirms the ligand is involved in the coordination. Also, UV-Visible “spectra of complexes show absorption band between 22084 to 25000 cm^{-1} assigned metal to ligand charge transfer band” [17].

2.3 : Infrared Spectral Analysis:

The complex bonding pattern can be determined by comparing ligand and metal complex IR absorption bands. Infrared spectrum of ligand TPDHP exhibits bands at “3034 cm-1 due to presence of ʋ (C-H) aromatic stretching frequency. A band was observed at 1672 cm-1 can be assigned due to ʋ (C=N) stretching frequency due to azomethine functional group [18-19]. Along with this ligand also shows peak at 1387 cm-1 can be assigned to ʋ (C=N) stretching frequency due to nitrogen atom. A band was observed at 1387 cm-1 is due to presence of ʋ (N-N)” frequency due to single bonded nitrogen atom. There was a significant change in the IR stretching frequencies of ligand on complexation [20] which is given in following table.

Table No.4: Absorption frequencies data of Ligand TPDHP and their Metal Complexes

Compound	**ʋ (H2O)**	**ʋ (-C=N-)**	**ʋ (C-N)**	**ʋ (N-N)**	**ʋ (M-Cl)**	**ʋ (M-N)**
TPDHP (C21H18N2)	-	1671	1387	914		
[Ni (TPDHP)2Cl2] H2O	-	1672	1391	915	870	688
[Cu (TPDHP)2Cl.H2O] H2O.Cl	3329	1672	1358	967	842	691
[Cr (TPDHP)2Cl.H2O] Cl2	3360	1670	1393	963	870	564
[Co (TPDHP)2Cl2] Cl.H2O	-	1674	1364	963	814	686
[Zn (TPDHP)2Cl2]	-	1675	1390	1025	870	690

2.4 : ^{1}H-NMR Spectra:

^{1}H NMR Spectrum of synthesized ligand TPDHP (1,3,5-triphenyl-4,5-dihydro-1H- pyrazole)” (fig. 4.12) exhibits triplet at 3.20 ppm due to one hydrogen and 3.90 ppm (t) due to one hydrogen atom of methylene group. The signal at 5.4 ppm (d) due to one proton for the methine group. The value is more deshielded due to resonance effect of phenyl ring and more electronegative nitrogen at the adjacent position [21].

The signal between “6.5 to 7.20 ppm is due to monosubstituted benzene ring attached to the 5-position of pyrazole ring. The signal between 7.50 to 7.80 ppm is due to phenyl group attached to the azomethine carbon” while 6.20 to 7.20 ppm is due phenyl ring attached to the 1-nitogen atom.

2.5 : Thermal Analysis:

Thermal stability, lattice and coordinated water molecules, and decomposition pattern of metal complexes are suggested by thermogravimetric analysis. Complexes heated to R.T- 1100C lose lattice water molecules, while the coordinated water molecules can be lost at the temperature range of 120-2000C. the decomposition of ligand along with substituents occurs at the temperature range of 350-9000C and observed the corresponding metal oxide residue. All the synthesized metal complexes were scanned in the range of temperature to room temperature to 9000C in presence of nitrogen atmosphere [22]. Gravimetric analysis and TGA curves yield the same mass loss percentages.

3. ANTIBACTERIAL ACTIVITY TESTING

Heterocyclic ligands and metal complexes were evaluated against Gram-positive bacteria, specifically Staphylococcus aureus and Streptococcus pyogenes, as well as Gram- negative bacteria, including Escherichia coli and Pseudomonas aeruginosa. Broth Dilution Method were used for the testing of samples [23-25]. To make stock solutions for testing, ligands and metal complexes were mixed with DMSO. Serial dilutions were utilized for both primary and secondary screening. To subculture the control tube without antibiotics, spread a loopful equally over a quarter of a plate of medium that is good for the test organism and put it in an incubator at 370C overnight. Keeps the tubes warm overnight. Check the concentrations of the medicines by reading the MIC of the control organism. MIC is the lowest concentration that stops the growth of organisms. The growth of the control tube (original inoculum) prior to incubation is compared [26-28].

Table No. 5: Results of Antibacterial activity testing

Sr. No	Compounds	E. coli	Aeruginosa	Aureus	S. Pyogenus
1	TPDHP (C21H18N2)	15 mm	18 mm	14 mm	12 mm
2	[Ni (TPDHP)2Cl2] H2O	-ve	-ve	-ve	-ve
3	[Cu (TPDHP)2Cl.H2O] H2O.Cl	-ve	-ve	-ve	-ve
4	[Cr (TPDHP)2Cl.H2O] Cl2	-ve	-ve	-ve	-ve
5	[Co (TPDHP)2Cl2] Cl.H2O	12 mm	10 mm	14 mm	16 mm
6	[Zn (TPDHP)2Cl2]	4 mm	3 mm	4 mm	6 mm

On observing the growth of E. coli, Aeruginosa, Aureus and S. Pyogenus on agar plate under the well sterilized and controlled conditions in presence of various metal ion complexes. The results were revealed that $[Ni (TPDHP)_2Cl_2] H_2O$., $[Cu (TPDHP)_2Cl.H_2O] H_2O.Cl$ and $[Cr (TPDHP)_2Cl.H_2O] Cl_2$ show negative zone of inhibition towards E. coli, Aeruginosa, Aureus and S. Pyogenus. Large zone was observed for $[Co (TPDHP)_2Cl_2] Cl.H_2O$ and $[Zn (TPDHP)_2Cl_2]$ towards Aures and S. Pyogenus this was 14 mm and 16 mm respectively and shows strong antibacterial activity. The TPDHP ligand show maximum zone of inhibition towards E. coli, Aeruginosa, Aureus and S. Pyogenus, show a strong antibacterial activity.

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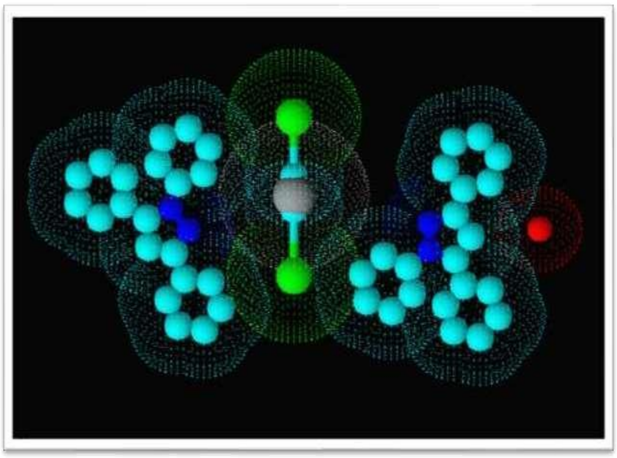
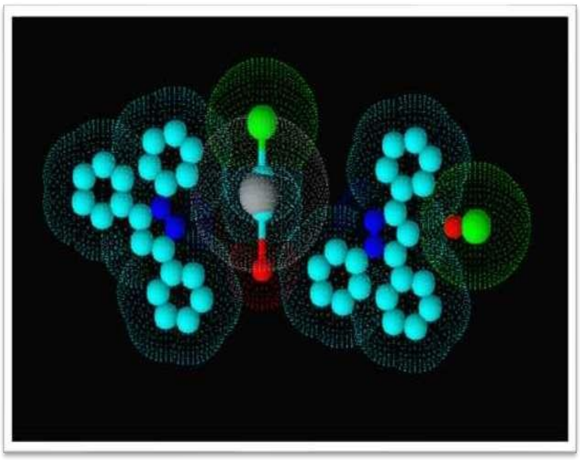
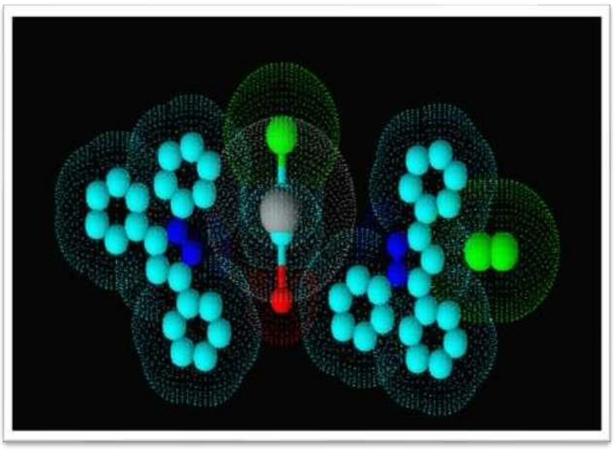
Proposed Structures In 3D Form



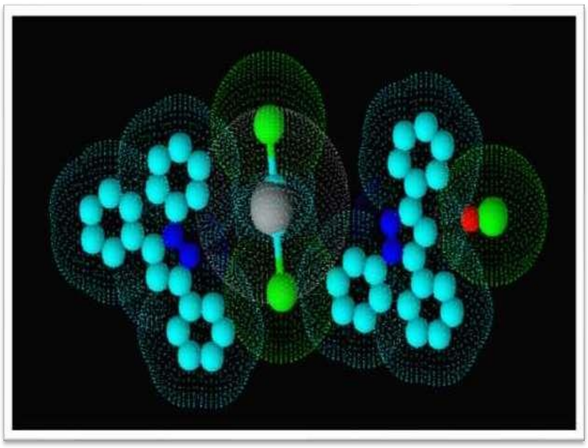
[Ni (TPDHP)$_2$ Cl$_2$.H$_2$O] Cl complex



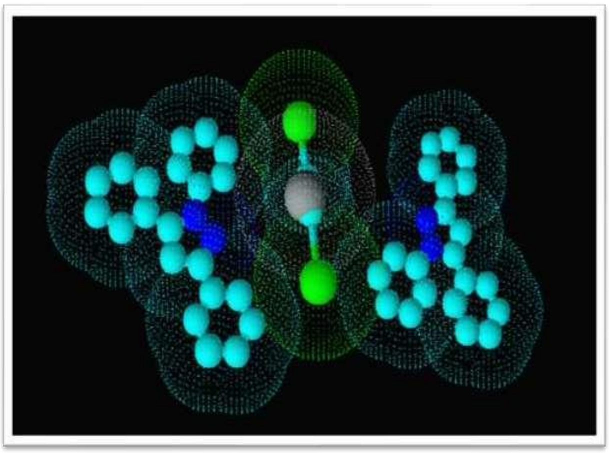
[Cu (TPDHP)$_2$ Cl.H$_2$O] H$_2$O.Cl complex



[Cr (TPDHP)$_2$ Cl.H$_2$O] Cl$_2$ complex



[Co (TPDHP)$_2$ Cl$_2$] Cl.H$_2$O complex



[Zn (TPDHP)$_2$ Cl$_2$] complex

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