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SYNTHESIS OF PHARMACEUTICAL IMPORTANT OF ZN(II)COMPLEX FROM ANTIDEPRESSANT RESIDUES OF 4-OXOPIPERIDINE HYDRAZONE: ANTIBACTERIAL, ANTIFUNGAL, AND UV-VISIBLE STUDIES

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Abstract:
The $[Zn(L)(H_2O)_2Cl]$ complex was synthesised from with salt of $Zn(II)Cl_2.6H_2O$ and 2-hydroxynaphthalen-1-yl) methylene-4-oxopiperidine-1-carbohydrazide Schiff base (H_2L). The newly synthesized Schiff base and its Zn(II) complex was screened against the various pathogenic species viz. Escherichia coli, Salmonella typhi, Staphylococcus aureus, Bacillus subtillis, Candida albicans, and Aspergillus niger with the popular antibiotics of ofloxacin, azithromycin, and fluconazole. On the basis of inhibition zone data of Zn(II) metal complex was enhancing the potential activities and may be a good antimicrobial candidate in the biological science.
Additionally, The Zn(II)complex was characterized by molar conductivity, magnetic moment. The Schiff base ligand shows a dibasic in nature, ONO tridentate moiety and bonding occurred by the phenolic-O, azomethine-N (H-C=N-) and enolic-O atoms with the Zn(II) complex.
Keywords: *Schiff base, Zn(II)complex, X-ray diffraction, antibacterial and antifungal activities.*

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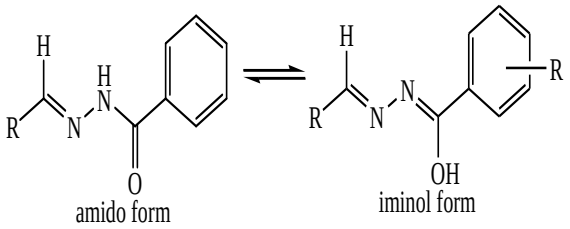
INTRODUCTION:

The heterocyclic aroyl hydrazide-based Schiff bases were found enormous applications in the field of pharmacology and exhibits the antibacterial, antifungal, antidepressant, antianalgesic, anticonvulsant, antimalarial, antitumaral activities, antiviral anti-HIV, antipsychotic, trypanocidal, anticoagulant activities, polymers initiators, antioxidants, plasticizers [1-3].



Hydrazone and its derivatives was very important class of ligands because of their physiological activity, coordinative capability and applications in analytical and medicinal chemistry [4].

Hydrazones containing an azomethine (-CH=N<) have been demonstrated significant role in the field of medicinal chemistry therapeutic applications such Alzheimer disease (AD) common neurodegenerative disorder of the central nervous system (AD) is associated with memory loss, difficulties in thinking, problem-solving, speaking or language and many other cognitive disorders. The therapies are only effective transiently in the early stage of disease. In search of new therapeutic agents 1,4-oxazepine analogues have been patented as anti-β-secretases inhibitors [5].The buildup of essential amines with carbonyl compounds was first revealed by Hugo Schiff a German chemist (1934-1915) and build up items are regularly alluded to as Schiff bases. Schiff's bases are the product of primary amine and active carbonyl groups compound synthesized by nucleophilic addition, subsequently undergoes acid catalysed dehydration to form a stable imine molecule. Imines, known to an azomethine or Schiff bases and are represented by the general formula [$R^3R^2C=NR^1$]. The substituents was incorporated as R^2 and R^3 position may be alkyl / aryl and heteroaryl, hydrogen. The substituent at the N-imino (C=N) may be alkyl, aryl, heteroaryl, hydrogen atom [6-9].In azomethine derivatives, (>C=N) linkage is very important for biological activity, reported remarkable activities as an antibacterial, antifungal, anticancer and diuretic properties. The Schiff bases that can be coordinates to metal ions through azomethine N-atom and have been studied extensively from the last several years. The development of a Schiff base is a significant stage in numerous biochemical responses. The nitrogen of >C=N group is mixed with other contributor bunches present in the atom make Schiff bases great ligands. The Schiff base class is extremely adaptable as mixtures can have a wide range of substituents and they can be unabridged or N,N'-cross over. Schiff bases that contain aryl substituents are considerably more steady and all the more promptly orchestrated, while those which contain alky substituents are generally unsteady. Schiff bases of aliphatic aldehydes are generally temperamental and promptly polymerizable, while those with fragrant aldehydes having compelling formation are steadier. The development of Schiff base from an aldehyde or ketones is a reversible response and by and large happens under acid or base catalysis, or after warming [10-14]. As a rule, aldehydes respond quicker than ketones in Schiff base buildup as the response focus of aldehyde is sterically less prevented than that of ketone. Moreover, the additional carbon of ketone means electron thickness, and hence makes the ketone less electrophilic contrasted with aldehyde. **fig.1-2**

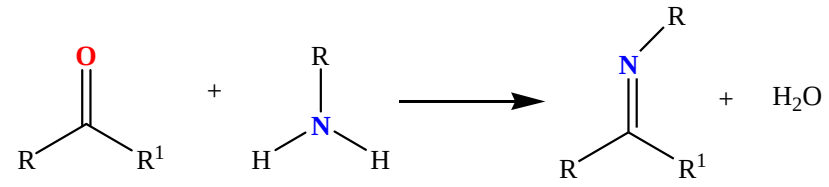


Fig.1 General synthesis of Schiff base

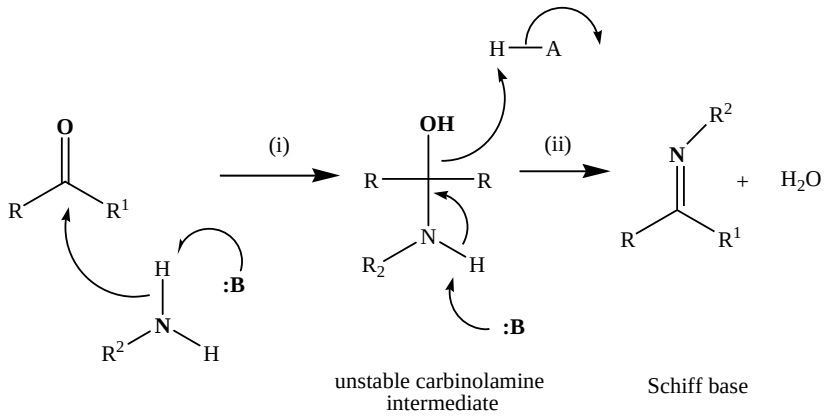


Fig.2.Mechanism of Schiff base (imine) formation

EXPERIMENTAL:

2.1 The synthesis of the hydrazones Schiff base ligand:

The hydrazone Schiff base ligand are synthesized from condensation reaction of carbonyl compound (acyl/aroyl aldehyde or ketone) and a hydrazine hydrate by the elimination of a water molecule contain the triatomic group (> C=N-N<). The initiation of a –C=O group in the hydrazine which may increases the electron delocalization and the ligation properties of hydrazone referred as an acyl/aryl hydrazone shown in **fig.3**.

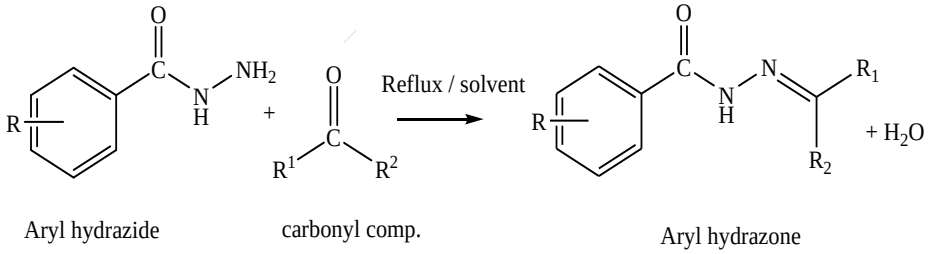


Fig.3. Synthesis of Aryl hydrazone

MATERIALS AND METHODS:

All chemical are of AR, and Zn(II)Cl_2.6H_2O of 97 % purity (S.D. fine chemicals, India), 2-hydroxynaphthalene-1-carbaldehyde (Alpha Aesar). All the solvents were utilized obtained from commercial sources and used after double distillation. The decomposition points were carried on standard melting point apparatus in open capillaries. The elemental analysis (i.e. C, H, and N) were performed on a Carlo Erba-1108 analyser. Molar conductivities of Zn(II)complex in DMSO was measured by using180-Elico conductivity meter. Electronic spectra were recorded on a Shimadzu UV-Vis spectrophotometer of model-1800.The X-Ray diffraction pattern study was carried on a Bench top Rigaku X-ray diffractometer Miniflex (600).

2.1.1. SYNTHESIS OF Zn(II) METAL COMPLEX:

The Zn(II) complex was synthesized an equimolar amount of ligand and metal salt (0.025 mol each) was dissolved separately in 20 mL of warm dimethyl sulfoxide and ethyl alcohol, respectively. The reaction mixture was heated at 77 ^{0}C in an oil bath. The reaction mixture was cooled at ambient temperature, solid product formed was filtered, washed by hot ethanol, and dried over $CaCl_2$. Molecular formula, elemental analysis and molar conductance data of these complexes are presented in Table 1.

Table 1. Analytical data of hydrazone Schiff base and Zn(II) complex

Compounds[a] and standard drugs*	Gram –ve bacteria		Gram +ve bacteria		Fungus	
	E.coli (NCBI-0157)	*S.typhi* (NICM-2257)	*S. aures* (NDCM-2257)	*B.substillis* (NICM-2477)	*C.albican* (MTCC-1637)	*A.niger* (NCIM-1005)
Hydrazone Schiff base ligand	08	09	10	10	11	09
Zn (II)complex	19	20	14	17	25	13
Ofloxacin*	30	30	-	-	-	-
Azithromycin*	-	-	15	20	-	-
Fluconazole*	-	-	-	-	28	30

RESULTS AND DISCUSSION:

Experimental Section of Anti-bacterial and antifungal evaluation:

Mono microbial sensitivity disc was used for semi qualitatively to evaluate the in *vitro* susceptibility of antimicrobial agents of rapidly growing bacteria and several difficult species by an agar diffusion method. The standard procedure was published by the World Health organization "WHO" expert committee on biological standardization, (1992) Technical report series 822,W.H.O.Geneva [15],Clinical and Laboratory standard Institute,2012,CLCI [16] and European Committee on Antimicrobial susceptibility Testing (EUCAST) [17].

Principle:

The disc diffusion method is completely based on the fact of a given antibiotic, the size of zone of inhibition is inversely related to the MIC of the strain being tested. The antimicrobial susceptibility testing with discs is very simple, fast and accurate method with reproducible means of testing bacterial sensitivity to maximum antibiotics as well as chemotherapeutic agents.

Material:

Trypticase Soya Broth(5ml), Potato Dextrose Agar, sterile Normal Saline, discs stability $+2^0$c to $+8^0$c. Disc size 10 mm.

Procedure:

1) **Preparation of Plates:** The Potato dextrose agar pH 7.3 was poured into plates kept on a levelled surface. The depth of medium should be approx. 4mm when the medium was solidified, dry the plate for 30 min. in incubator $+35^0$c to + 37^0c to remove moisture from surface area.

2) **Preparation of Inoculum**: The pure culture used for gram staining before preparing an inoculum. The selected 4-5 similar colonies were selected and transferred them into a test tube of 5 ml of Trypticase soya broth. The diluted the broth culture of actively growing organism with sterile broth to obtain a turbidity equivalent to McFarland Standard 0.5 which was prepared by adding 0.5ml of 1.175 % $BaCl_2.2H_2O$ solution to 99% ml of 0.36N H_2SO_4. Overnight cultures of aerobes, on-fastidious organisms generally have too much growth used undiluted. The colonies directly suspended into a small volume of saline. The diluted and standardized inoculum should not be allowed to stand longer than 20-25 minutes before the plates were inoculated.

3)**Inoculation**: After dipping a sterile cotton swab into diluted culture inoculum and rotated inside wall of tube. A sterile cotton swab was dipped in diluted culture inoculum and on the entire disc surface was spread the agar surface of the plate.

4) **Incubation:** The plates were incubated at temperature $+35^0$c to + 37^0c for 17 to18 hours.

5) **Reading of Zones:** The zone of inhibition was measured in the diameter of zone of last of incubation period.

6) **Interpretation of result**: The zone of inhibition and susceptibility organism was recorded to standard antibiotic i.e density of inoculum, depth, diffusion of antibiotic. The size of inhibition zone was considered on the basis of resistivity and intermediate or sensitivity and result were presented.

The ligand (2-hydroxynaphthalen-1-yl) methylene-4-oxopiperidine-1-carbohydrazide (H_2L) and its Zn(II) metal complexes was tested for their *in vitro* antibacterial activity against *Staphylococcus aureus*, *Bacillus substillus Escherichia coli, Salmonella typhi* and fungal species *Candida albicans and Aspergillus niger* at 1.10 mg/mL using disc diffusion method and evaluated the zone of inhibition after 20-24 h of incubation period. The standard drugs as a positive control viz. *Ofloxacin*, *Azithromycin* and *Fluconazole* and highly polar solvent DMSO as negative control.

The experimental data are good and greater enhancing activity causes due to the presence of extra aryl ring in hydrazone in Zn(II) the metal complexes [18]. The results are presented in Table 2 and in their graphical form in Fig.5. The results showed that the antimicrobial activity of the ligand became more with the Zn(II) ions. The inhibition data suggest Escherichia coli, and Salmonella. typhy is more active than staphylococcus aureus and Bacillus substillus. The increasing in lipophilic character in the complex formation increase activity upon on the basis of the chelation theory [19-20]. The chelation theory described the polarity of metal ion which is reduced due to the overlapping orbital of ligand due to the delocalization of pi electron in the ring and *affect in respiration process of cell*, and retarding the growth of the synthesis of proteins and well as restricts growth of organisms. Moreover, the aryl ring palys important role in the structure of ligand and its metal complexes reveals the increases potency against the bacterial species and fungal species. The group of azomethine (H-C=N) exchangeable proton towards the metal complexes affecting the destroying capacity of the pathogenic colonies [21-23].

Compounds	Mol.Formula	Formula wt.	Colour	Elemental analysis (%) found (calc.)				
				C	H	N	Cl	M
Hydrazone Schiff base	$C_{17}H_{24}N_4O_3$	332.40	Bright yellow	61.70 (61.42)	7.50 (7.27)	16.90 (16.85)	---	---
$[Zn(L)(H_2O)]$	$ZnC_{17}H_{24}N_4O_4$	413.78	Lemonade	49.50 (49.34)	5.90 (5.84)	13.70 (13.54)	---	15.95 (15.80)

Table 2. Inhibition zone growth of microorganism of H_2L ligand and its complexes (mm)

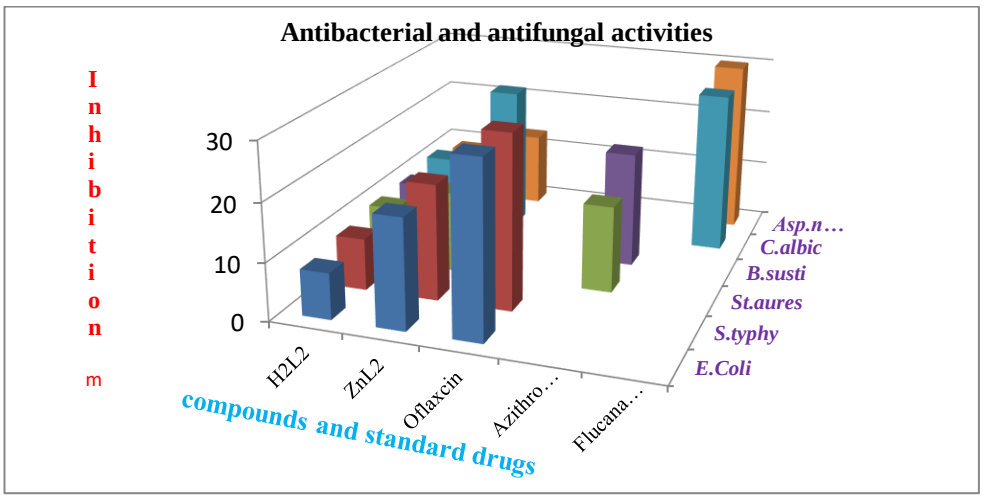
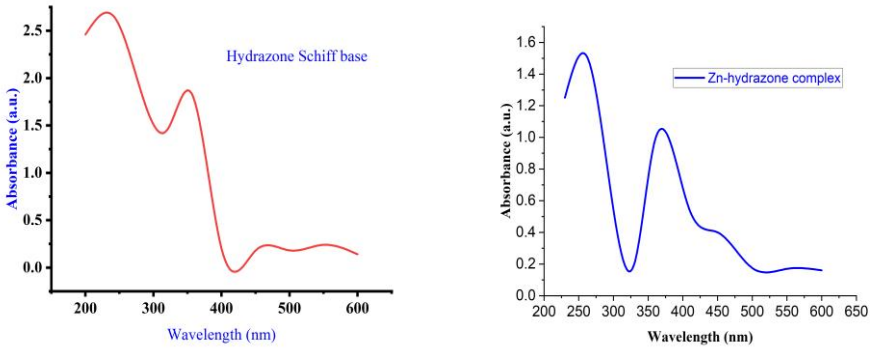


Fig.4 Inhibition zone growth of hydrazone Schiff base and Zn(II) metal complex

3.4. Uv-Visible absorption spectra of Zn(II) complex

The magnetic moments and Uv-Visible spectral data of metal complexes are summarised in Table 3 and its spectra recorded on a Shimadzu double beam UV-Vis spectrophotometer in the scan range 220-1100 nm with a conc. of ($2x10^{-4}$M) in DMSO and spectra are reproduced is given in Figs.3.(a-b). The significant absorption bands are observed at various wavelength due to the presence of substituent group on basic chromophores which changes the position and intensity of absorption bands. The substituents increases the intensities of absorption due to auxochromes >C=O, O=C, >C=C<, -OH, >N=CH, groups. The Zn(II) complex possessing prominent absorption maxima at 364,255 nm are due to intra ligand charge transfer (ILCT) and forbidden in d-d ($t_2g \longrightarrow eg$) transitions, respectively. The transition appears due to ligand chromophore group in ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$) respectively. Moreover, the complex was found to be diamagnetic as expected for d^{10} configuration and neutral nature. All complexes show only residual conductance values in the range 6.14-26.15 Sm^2mol^{-1} indicating that they are

nonelectrolytes [24-25].



(a) (b)

Fig.5 Uv-visible absorbance spectra of (a) hydrazone Schiff base and (b) Zn(II) complex

Table 3.- Solution conductivity, Magnetic moment, Electronic spectral data of hydrazone ligand and Zn(II) complex

Metal complex	Solution /molar conductivity (Sm^2mol^{-1})	Nature	μ_{eff} (B.M.)	Absorption maxima (λ=nm)	Spectral Assignments
Hydrazone	0.00	Neutral	Diamagnetic	432 331	π→π*, n→π*,
[Zn(L)(H_2O)]	6.14	Neutral	Diamagnetic	364 255	*ILCT (n→ π*)* *ILCT (n→ π*)*

CONCLUSION:

Antibacterial activity against *Staphylococcus aureus*, *Bacillus substillus Escherichia coli*, *Salmonella typhi* and fungal species *Candida albicans and Aspergillus niger* have been biologically screened and data results suggested that Zn(II) complex are more potentially active than the parent ligand.

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Disclosure statement:

The author have no conflict of interest.

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