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Antimicrobial Activity of Hydrazone Metal Complexes: A Review

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A B S T R A C T

Now a day's the remarkable biological activity of hydrazone and the dependence of their mode of chelation with metal ions present in living system have been a significant interest. Inspite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades revealed a substantial medical need for new classes of antimicrobial agents. Due to the outbreak of infectious diseases caused by different pathogenic bacteria and fungi, researchers are looking towards hydrazone metal complexes as a new antimicrobial agent. This review aims at highlighting the antimicrobial activities of hydrazone metal complexes, within years from 2010 to 2016.

Keywords: Hydrazones, Hydrazone metal complexes, Antimicrobial agent, Antibacterial, Antifungal activity.

A R T I C L E I N F O

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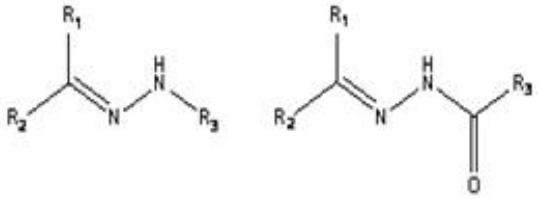
1. Introduction

The field of bioinorganic chemistry, which deals with the study of role of metal complexes in biological systems, has opened a new horizon for scientific research in coordination compounds. The pharmacological activity of metal complexes is highly dependent on the nature of metal ions and the donor sequence of the ligands because different ligands exhibit different biological properties. Research interest in the field of hydrazones stems from their biological activities. The chemistry of hydrazones has been intensively investigated in recent years, owing to their

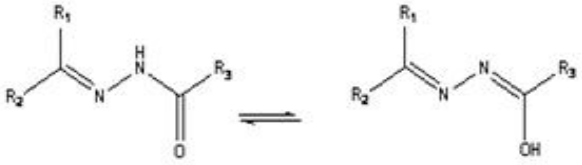
coordinating capability, pharmacological activity, antibacterial and antifungal properties [1]. Metal complexes of hydrazones have been found to have biological and therapeutic activity and this is one practical reason for the continuing interest in these materials. Hydrazones –NH–N=CRR′(R and R′ = H, alkyl, aryl) are versatile ligands due to their applications in the field of analytical [2] and medicinal chemistry [3]. Much interest has been focused on the hydrazone complexes due to their antimicrobial activities [4].

2. Hydrazones

Hydrazones are a class of azomethines having the group ⁻C=N⁻N⁻ [5] are interesting ligands in coordination chemistry. Hydrazones are versatile class of ligands which have been studied for a long time as potential multifunctional ligands with various coordination modes [6]. They contain characteristic ⁻N⁻N⁻ linkage and obtained by the condensation reaction between a hydrazide which is a derivative of hydrazine with carbonyl compounds like aldehyde and ketones [7]. Introduction of a ⁻C=O group in the hydrazide part increases the electron delocalization and denticity of the hydrazone (I) and the resulting compound known as an acylhydrazone (II), (Figure1). An attractive aspect of the acylhydrazones is that they are capable of exhibiting tautomerism. Due to their facile amido -iminol tautomerization (Figure 2) and the availability of several potential donor sites depending on the nature of the substituents attached to the hydrazone unit, represent good polydentate chelating agents for a variety of metal ions [8].



Hydrazone (I) Figure – 1: General formulae of a substituted hydrazone and acylhydrazone



Keto form **Enolic form**

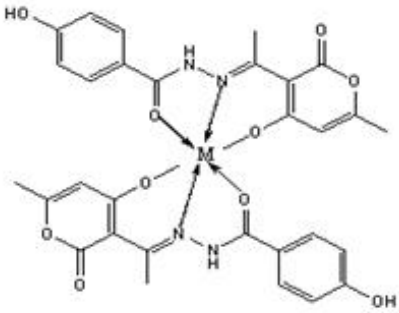
Figure –2: Keto-enol tautomerism of a substituted hydrazone

3. Bioactivity of hydrazone complexes

According to literature servey, some important factors, such as the nature of the metal ion, nature of the ligand, coordinating sites, geometry of the complex, concentration, hydrophilicity, lipophilicity and presence of co-ligands, have considerable influence on the antimicrobial activity [9]. Metal complexes of hydrazones found to have biological and therapeutic activity and this is one practical reason for the continuing interest in these materials. The bio-activity of hydrazones may be due to the presence of multidentate coordination centers and their ability to form stable chelates with essential metal ions which organisms need in their metabolism. It has also been shown that the azomethine N, which has a lone pair electrons in a sp2 hybridized orbital is biologically important [10]. Hydrazones and their ability to coordinate with transition metal ions, synthesis of their metal complexes and the study of such complexes may lead to a greater understanding of the role of these compounds in biological systems and may also contribute to the development of new metal based chemotherapeutic agents. From given literature reviews, [11-14] it was observed that most of review papers focused on various biological activities of hydrazones and there are very few review papers which study antimicrobial activity of hydrazone complexes. Therefore to overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency, which encourages us to review the papers published on antimicrobial study of hydrazone metal complexes from 2011 – 2016.

4. Antimicrobial activity

Antimicrobial resistance of the bacterial pathogens is of great anxiety on human health and well-being worldwide, to overcome such problems a new series of biologically active metal complexes of M = Co (II), Ni (II), Cu (II), Mn (II), Zn (II) (Figure 3) with tridentate hydrazone ligand (L)4-Hydroxy-N'-(1-(4-hydroxy-5-methyl-2-oxo-2H-pyran-3-yl)ethylidene) benzo- hydrazide (PDLH), were synthesized and screened for their *in vitro* antibacterial activity by the agar well diffusion method in DMSO using Penicillin G and Oxacillin as standard drugs. The bioactivity order of the ligand and its complexes found in present study was Cu (II) > Ni (II) > Zn (II) > Co (II) > L = Mn (II). Thus Cu (II) complex possess good level of antibacterial activity with MICs of 64, 64, 32, 64µg/mL for *B. subtilis, P.*syringae, *P.aeurginosa*,*S.aureus* respectively. [15] Cu -HBBH complex (Figure 4) derived from ligand (E)-N'-[2-hydroxy benzylidene] benzohydrazide (HBBH) shows inhibitory activity against gram negative bacteria



Figure–3

E. coli (15mm) and the fungal strain *C albicans* (11mm) but less active than Ciprofloxacin (30mm) and Ketoconazole (20mm) used as standard against bacteria and fungi respectively. As the concentration of Cu (II)-HBBH complex increases the activity also increased. [16]

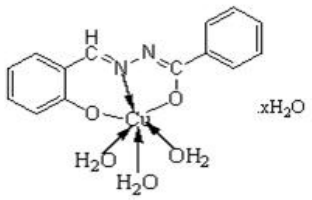


Figure –4

Antibacterial activities of ternary complexes of copper (II) (Figure 5) with ligand (2-((2- phthalazin-1- hydrazono) methyl) phenol) SAH-hydrazone in the presence of some biologically important co-ligands of amino acids (AA) viz., glycine (gly), L-alanine (ala), L- valine (val) and L-phenylalanine (phe) were studied against gram +ve organisms (*S.epidermidis and B.cereus*) and gram -ve organisms (*E. Coli* and *K.pneumonia*) by modified Kirby-Bauer disc diffusion method using standard drug Ciprofloxacin. [Cu(SAH)(Val)(H_2O)] has a lower dipole moment (μ = 6.81), thus it has a more lipophilic nature and a higher biological activity than the other complexes with MIC values, *S. epidermidis* complexes. [18]

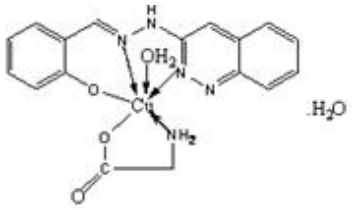


Figure – 5

Ligand dipyridylglyoxal bis (2- hydroxylbenzoyl hydrazone), copper (II) mononuclear [CuLM] .nH_2O, M= Zn(II), Cu(II), Ni(II), Co(II) and copper (II) – metal (II) binuclear complexes[(H_2L) Cu] .H_2O (Figure 6) were screened for their in vitro antibacterial activity against five Gram-positive (*S. aureus, S. hominis, Bacillus sp1, Bacillus sp2* and *Bacillus sp3*) and three Gram-negative (*E. coli, Salmonella sp1, and Salmonella sp2*) bacterial strains using gel diffusion and respirometric methods. Antimicrobial inhibition shows that copper (II) complexes and [(H_2L) Cu] .H_2O exhibit comparable activities to standrad ofloxacin antibiotics. According to authors, the higher antimicrobial activity of copper (II) complexes relative to zinc (II) complex may be attributed to copper (II) forming stronger ligand bond than Zn (II), increasing the lipophilic character of copper (II) complexes.[18]

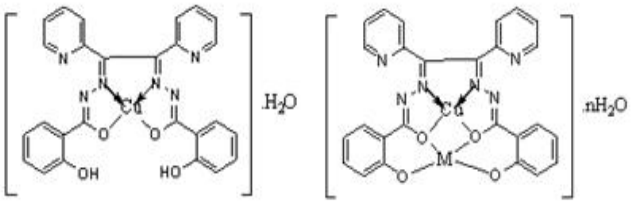


Figure – 6

MICs of the hydrazones2-acetylpyridine benzoyl hydrazone (H_2AcPh), 2-acetyl pyridine *para*-chloro- benzoyl hydrazone (H_2Ac*p*ClPh) and 2 - acetylpyridine *para*-nitro-benzoyl hydrazone (H_2Ac*p*NO_2Ph) and their organotin complexes screened against *S. aureus* and *C. albicans*. Antimicrobial activities of tin complexes of (H_2AcpClPh) ligand have highest activity than other complexes indicates enhancement of activity due to presence of –Cl group.

The MIC values of antifungal activity of complexes [Bu^nSn(2Ac*p*ClPh)Cl_2], [Bu^nSn(2Ac*p*NO_2Ph)Cl_2], [PhSn (2Ac*p*ClPh)Cl_2] and [PhSn(2Ac*p*NO_2Ph)Cl_2] are 0.045, 0.096, 0.046, 0.093 mmol mL^{-1} respectively, relative to the organotin salts. The MIC values for complexes [Bu^nSn(2Ac*p*ClPh) Cl_2] and [PhSn (2Ac*p*ClPh) Cl_2] (0.045 mmol mL^{-1}) were the same, suggesting that the *n*-butyl or the phenyl group in the metal coordination sphere have the same effect. [19]

2-acetylpyridine- and 2- benzoyl pyridine (H_2AcPh), (H_2AcpClPh), (H_2AcpNO_2Ph), ligand bond than Zn (II), increasing the lipophilic character of copper (II) (H_2BzPh), (H_2BzpClPh) and (H_2BzpNO_2Ph) derived hydrazones and their copper (II) complexes are tested against *S. aureus, E. Faecalis, P. aureginosa* and *C. albicans* and are reported by MIC using the macro-dilution test.

The antimicrobial activities of the compounds are found to be improved after coordination to copper (II). The best results were obtained for complexes [Cu (2AcPh)Cl].2H_2O (49μmolL^{-1}), [Cu(2AcpClPh)Cl].2H_2O (10 μmolL^{-1}) and [Cu(2BzPh)Cl] (20μmolL^{-1}) against *S. aureus*, and [Cu(2BzPh)Cl] (62 μmolL^{-1}) against *E. faecalis*. Complexes [Cu (2AcpClPh) Cl].2H_2O (52μmolL^{-1}) and [Cu (2BzpClPh) Cl] (47 μmolL^{-1}) were more active than their respective hydrazones (86 and 69 μmolL^{-1}) against *C. albicans*. Hence from antimicrobial study the complexes could be acts as an interesting new antifungal drug candidate. [20]

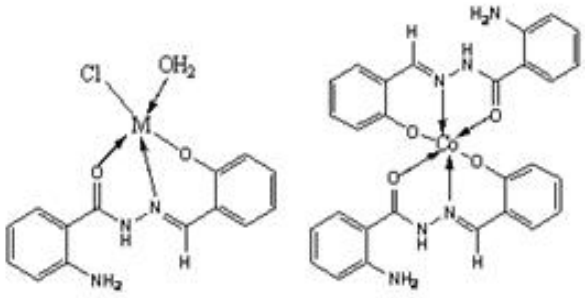


Figure – 8

Schiff base LH3, from 3-ketobutane hydrazide and salicylhydrazide and their metal complexes Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Zr(OH)2(IV), MoO2(VI) and UO2(VI) ions were synthesized and studied their antimicrobial activity . The compound [Cu (LH)] 2 (Figure 9) was found to be the best as they exhibit the lowest MIC of 32 μg/mL against S. aureus and 16 μg/mL against B. subtilis. Thus according to authours it can be further used as an antibacterial agent in pharmaceutical industry for mankind, after testing its toxicity to human beings. [22]

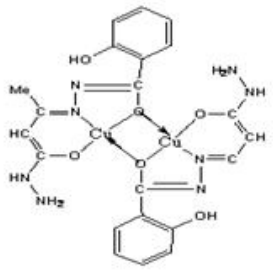


Figure – 9

From MIC values of oxovanadium (V) which is a aromatic ring present in their complex (Figure 10), it was observed that the complex showed more potent antimicrobial activity compared to the ligand 3-chloro-*N′*-(3,5-dichloro-2-hydroxybenzylidene) benzohydrazide (H_2L). In the case of *S. aureus* (0.78µM) and *B. subtilis* (0.88µM) the complex is more effective than the reference drugs ofloxacin and ciprofloxacin, while it is just opposite for *P. aeruginosa* (3.86µM) and *E. coli* (3.26µM). [23]

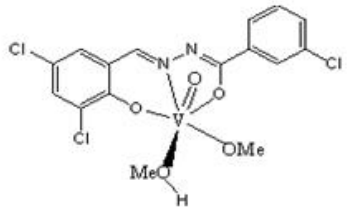


Figure –10

The antimicrobial activity of M = Cu (II) and Ni (II) (Fig.11) complexes of hydrazone o-methoxybenzaldehyde benzoylhydrazone (MBH) was screened against Gram-positive bacteria, (*S. aureus* and *B. subtilis*) Gram-negative bacteria (*P. aeruginosa* and *E. coli*) and fungi (*A. fumigates, P.italicum, Syncephala- strumracemosum* and *C. albicans*) by a disc-diffusion method. The activity order of the synthesized ligand and its metal complexes against microorganism can be represented as Cu-MBH > Ni-MBH >MBH ligand. The biological activity of ligand and its metal complexes are due to presence of the structures constituent of many biological systems. [24]

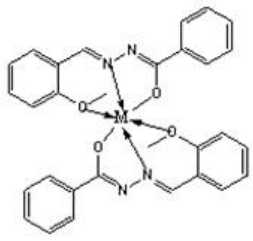
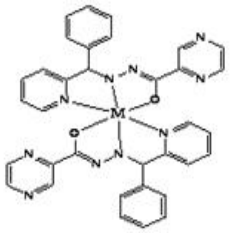


Figure – 11

In vitro antibacterial activity of ligands pyrazine-2-carboxylicacid(phenyl-pyridin-2-yl-methylene)-hydrazide HL_1, pyrazine-2-carboxylic acid (pyridin-2-ylmethylene)-hydrazide HL_2 and their complexes [M=Mn(II), Co (II), Ni (II), Cu (II), Zn (II)] (Figure 12) were assessed against a series of Grampositive *B. subtilis*, *Micrococcus luteus* and Gram negative *P.aeruginosa*, *P.mendocina* using agar plate disc method in DMSO using standard drug streptomycin. Complexes of HL_1 with divalent transition metal ion were found to be more active as compared to complexes of HL_2 are due to the presence of phenyl ring, which release electrons towards azomethine nitrogen, thereby increase interactions with active centers of cell. Among these complexes Cu(II) (22-24mm) complexes were found to be most active, compared to other complexes.The trend of growth inhibition in the complexes was found to be in the order: Cu(22-24mm)>Mn(18-23mm) > Ni (18-22mm) > Co (15-18mm) > Zn (14-18mm). [25]



Figure–12

Zone of inhibition of metal complexes of Cu(II), Ni(II), Co(II) and Zn(II) shows greater activity than ligand isonicotinoyl hydrazone-2-aldehyde fluorene (INHAF) against bacteria *S. aureus, E. coli and K. pneumonia*. Complex [Co (INHAF) Cl_2] **(**Figure 13) manifest maximum activity to all germs, *S. aureus* (29mm), *E. coli* (27mm), *K. pneumonia* (22mm) as compared to other complexes and ligand.[26]

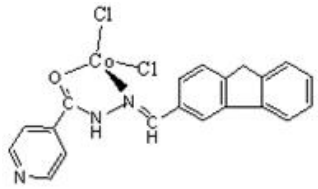


Figure – 13

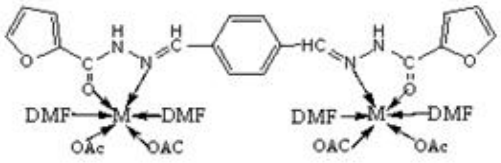
Metal complexes [M = Co (II), Ni (II), Cu (II), Cd (II), Zn(II), Hg(II)] of L = Schiff's base derived from the condensation of naphthofuran-2- carbo hydrazide with 8-formyl-7-hydroxy-4-methyl coumarin have been synthesized and were screened against *E. coli , S. aureus, B. subtilis, P. aeruginosa* bacteria and *A. flavus, A. niger, C. oxosporum* and *C. albicans* fungal strains. Antimicrobial activity of metal complexes (12.50-25 µg/mL) are more promising than ligand (50-75 µg/mL) against all the test bacterial /fungal strains and are comparable with standard drug Gentamycin and Amphotericin with MIC=12.50 µg/ml. [27]

Antimicrobial activities of Cu complexes(II), Co (II) and Ni (II) synthesized from ligand N-(2-pyridinecarbaldehyde)-N-[4-(4- chloro-phenylsulfonyl) benzoyl]-hydrazone (L) were studied on the basis of their geometries. It was found that tetra coordinated complexes have better action than the hexa coordinated compounds. The tetrahedral complexes of Cu (II) inhibit the growth of *P.aeruginosa* and *E.coli* (MIC= 32–64 mg/mL) and have no significant effect against *S. aureus* and *B. subtilis* comparative with the

control drug Streptomycin (MIC= 8 mg/ml) and are more active than the square-planar Ni (II) complex (MIC= 128 mg/mL) and octahedral complex Co (II) (MIC= 64 mg/ml). [28]

Schiff base derived from the condensation of benzofuran-2-carbohydrazide with thiophene-2-aldehyde and its metal complexes Co (II), Ni (II), Cu (II), Zn (II), Cd (II) and Hg (II) were tested for antibacterial activities against *E.coli*, *S. aureus*, and *S. typhi* and antifungal activities against *A. niger*, *A. flavus*, and *C. spp.* A comparative study of the ligand and complexes (MIC values) indicated that the complexes (12.50-25μg/mL) exhibited higher antimicrobial activity than the free ligand (50-75μg/mL). Most of the complexes show similar activity like standard drug gentamycine and fluconazole (12.50μg/mL). [29]

Synthesis of binuclear complexes [M= Co (II), Ni(II), Cu (II), Zn (II)] (Figure 14) of Schiff base ligand, Furo-(phenyldimethine) - carbohydrazone L were reported and Schiff base (L), its Zn (II) complex have been screened for their antibacterial and antifungal activities. Both compounds showed good inhibition against bacteria *S. pyogenes*, *S. aurues* with MIC value(25-50 μg/ml) and *E. coli* and *fungi C. albicans*, *A. fumigates* and *P. marneffei* (25-50 μg/ml). The MBC (minimum bacterial concentration) MFC (minimum fungicidal concentration) of these compounds were found to be two or four times higher than corresponding MIC results. [30]



Figure–14

Half-sandwich organometallic (rhodium and irridium) complexes (Figure 15) were synthesized from ligands (L1 = Pyridin-2-ylmethylene picolinichydrazine) and (L_2 = Pyridin-3-ylmethylenepicolinichydrazine). Antibacterial activity of the complexes was determined against two different bacterial species *viz.*, *Proteus vulgaris* and *Vibrio parahaemolyticus* according to the agar well diffusion method using standard antibiotic Amoxicillin. In the case of activity against *Proteus vulgaris*, Ir complexes are more effective than the postitive control Amocixillin. [31]

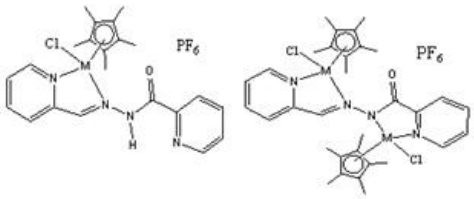


Figure – 15

Ligand ortho-vanillin- 2-hydrazino pyridine hydrazone (VHP) and its organotin (IV) complexes [RnSnCl4–n(VHP)] are screened for antibacterial study against Gram-positive bacteria, B. cereus and S. aureus and Gram-negative bacteria, E. coli and E. aerogenes in DMSO using reference anti-bacterial drug (Doxycycline). Results reveal that the ligand (9mm-15mm) shows moderate activity while among the four complexes, diphenyltin (IV) complex (9.7mm-18.0mm) and butyltin (IV) complex (11.7mm-12.3mm) were more active than the others. The presence of phenolic –OH group, phenyl ring and presence of Cl ion in the complex can enhances the antibacterial activity. [32]

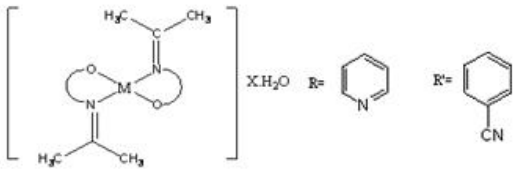


Figure – 16

Amongst the complexes of type [M $(BAAH)_2$ X_2 .H_2O] [M = Ni (II), Co (II), Cu (II), X = Cl^-, Br^-,SO_4^{-2}] synthesized from schiff base benzoyl acetic acid hydrazone, amongst all complexes copper complexes that is $Cu[BAAH]_2$ SO_4. H_2O (20mm-27mm) and $Cu[BAAH]_2Cl_2$ (15mm-20mm) were found to be most active against all the microbes tested against *E. Coli*, *P. aeroginosa* (bacteria), *A. nigger*, *C. albicans* (fungi), as compared to their ligand benzoyl acetic acid hydrazone BAAH (10 mm - 14 mm) but less as compared to standard drugs ciproflaxacin and flucanozole. This is due to the faster diffusion of the Cu (II) complexes through cell wall of microorganisms. [34]

Complexes of type [M $(HL)_2Cl_2$], where M = Co (II), Ni (II) and Cu (II), (Figure 17) were synthesized from 4-chloro-N'-(4-methoxy benzylidene)-benzohydrazide Schiff base (HL) show higher bacterial activity against Gram-positive bacteria S. aureus ATCC 29253, S. aureus ATCC 3160 as Gram-negative as compared to the fungus S. cereviscae MTCC 316, C. albicans. It is of interest to note that the mononuclear Co (II) complex exhibit approximately equal inhibition to the standard antibiotic which reveals the biological efficiency of these complexes and showed the possibility to be useful as new drug. [35]

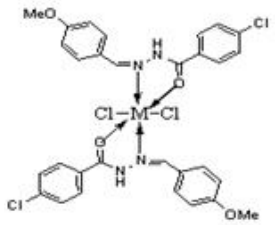


Figure – 17

Metal complexes [M = Co (II), Ni (II), Cu (II) and Zn (II)] of Schiff bases of N'-[(E)-(2-hydroxyquinolin -3 - yl) methylidene] - 2 - [(4-methyl – 2 – oxo - 2H – chromen – 7 - yl) oxy] acetohydrazide (OHQZ) and 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(E)-(2-sulfanyl quinolin-3-yl)methylidene] acetohydrazide (SHQZ) have been prepared and screened against two bacteria (*E. coli* and *S. aureus)* and two fungi (*A. niger* and *P. chrysogenum*)

strains by MIC method which reveals that Cu (II) complexes (13-20mm at 50 µg/L) exhibits higher activity against all strains as compared to other complexes and ligands at all concentration but less than Standard. Ligand SHQZ (11-16mm**)** shows more activity than ligand OHQZ (8-12mm) at 50µg/L due to presence of –SH group. [36]

Mononuclear transition metal complexes M = Mn (II), Co (II), Ni (II), Cu (II) (Figure 18) prepared from hydrazone ligand (L) derived from pyrazine-2- carbo hydrazide and 2-hydroxy acetophenone exhibit significant activity against all bacterial strain *S.aureus*, *S. pyogenes*, *B. subtilis*, *E. coli*, *P aeruginosa* & *E. faecalis* and fungal stains *A. Niger*, *A. clavatus*, *C. albicans*. According to authour this may be due to the presence of NH group on the ligand playing an important role in the activity. In addition, these complexes also contain chloride ion inside the structure which may also be responsible for higher activity. Cu (II) complex shows highest activity against *S. aureus* (18mm). [37]

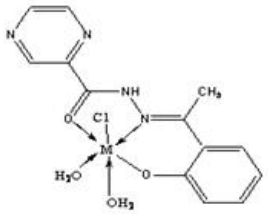


Figure – 18

Synthesized Cu (II) complexes (Figure 19) from ligands, (E)-N-(2- hydroxyl-1, 2-di(pyridin-2-yl) ethylidene) aroyl hydrazide (H_2L_1, H_2L_2) were screened against five bacteria methicillin resistant *S. aureu, Bacillus sp., E. coli, P. aeruginosa* and *Salmonella sp*. Antibacterial activity data shows that, all ligands are nearly inactive toward most of the studied species. Due to the high medical importance of MRSA, the effect of Cu (II) complexes on its growth and activity was investigated. Lower MIC values (0.25-0.5mgmL^{-}1) for [(H_2L_2) Cu (H_2O)] (ClO_4)$_2$ compared to MIC values (1.0-2.0 mgmL^{-1}) of [(H_2L_1) Cu (H_2O)] (ClO_4)$_2$ are observed. This increased antimicrobial activity can be attributed to the methyl group making the complex less planar, more polar and more lipophilic, leading to additional antimicrobial activity to the complex. [38]

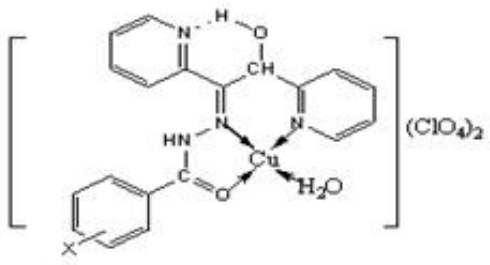


Figure – 19

The antibacterial activity of (E)-N-(2-hydroxybenzylidene) acetohydrazide [HL] and mixed-ligand Cu (II) complex [Cu L (phen)] **(**Figure 20) Complex shows highest activity than ligand against bacteria *Staphylococcus aureus* (40mm & MIC = 62.5 µg/ml) and fungi *Candida albicans* (45mm & MIC = 39.0 µg/ml). The values clearly indicated that Cu (II) complex is most effective antifungal agent. [39]

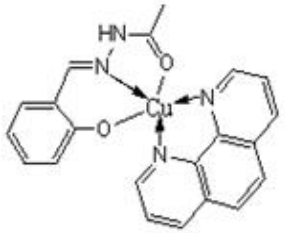


Figure – 20

A new mononuclear Schiff base complex, MoO2L (C2H5OH)] (Figure 21) some mixed-ligand mononuclear cis-dioxo molybdenum(VI) complexes, [MoO2 L(Imz)] and [MoO2L(1-MeImz)] and a diimine bridged dinuclear cis-dioxo molybdenum (VI) complex, [(MoO2L)2(l-4,4′-bipy)] obtained from benzoylhydra- zone ligand of 2-hydroxybenzaldehyde (H2L) have been synthesized. MIC values observed for complexes [MoO2L(Imz)] and [MoO2L(1-MeImz)] show the most promising results as compared to the other compounds MoO2L(C2H5OH)] and [(MoO2L)2(µ-4,4′-bipy)], this difference in activity is attributed to the presence of imidazole as co-ligand. Specially complex [MoO2L(Imz)] shows MIC value 15.6 µg/mL against Escherichia coli & Bacillus and [MoO2L(1-MeImz)] shows MIC value 15.66 µg/mL against Escherichia coli which is lower than standard drug Vancomycin (30 µg/mL) examined and value against E. coli, thus these compounds are potential lead molecules for drug design. [40]

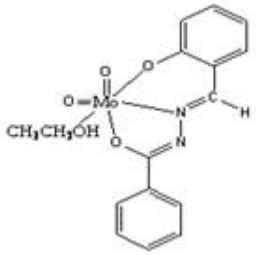
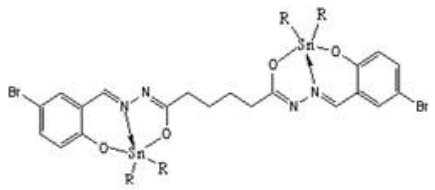


Figure – 21

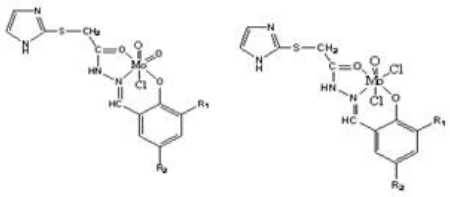
Four bis[diorganotin(IV)] complexes (Figure 22) are synthesized from ligand N′^{1},N′^{6}-bis(5-bromo-2-hydroxy benzyl idene)adipodihydrazide screened for antimicrobial activity. From graphical result obtained shows that Bis [dibutyltin (IV)] complex was found to be the most potent bactericide and showed the highest antibacterial activity against *B. subtilis* (20-22mm) and *S. typhi* (20mm). However, none of the synthesized complex is more active than the reference drug Imipenum. All the complexes were active against *F. solani* and the highest antifungal activity was shown by Bis[dibutyltin(IV)] complex (80%). The lipophilic nature of the central Sn atom and alkyl groups bonded to the tin atom play a significant role in the diffusion of metal complex through the bacterial cell wall. [41]



R= C_2H_5 (**a**), C_4H_9 (**b**)
Figure – 22

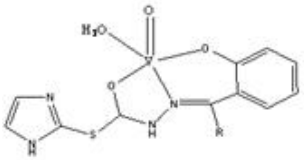
Ligands L_a is [(E)-N-(3-bromo-2-hydroxy benzylidene)-2-methoxy benzo hydrazide (HL_a) and L_b is (E)-N′-(2-hydroxy-3-methylbenzylidene)-2-methoxybenzo hydrazide (HL_b) shows moderate to good activity against tested bacteria and MIC values of complex 2[VOLaL] · CH_3OH has stronger activities against *B. subtilis* (4.7µg mL^{-1}), *S. aureus* (9.4 µg mL^{-1}), and *E. coli* (75 µg mL^{-1}) than complex [VOL_bL]. The ligands and complexes show no activity against P. *fluoresence* and two fungal strains (*C.albicans and A.niger).* [42]

Two new oxomolybdenum (V) [MoO (LH) Cl_2] and dioxomolybdenum (VI) [MoO_2 (LH)Cl] complexes (Figure 23) obtained from 2-imidazolyl mercapto acetohydra- zone (LH_2) were synthesized. The study of antibacterial activity against *S. paratyphi* and *B. cirroflagellosus* reveals that [$MoO(LH)Cl_2$] complex (20-24mm) show higher activity than the [MoO_2(LH)Cl] complex (15-18mm). Authour suggests that the low activity of Dioxo-complexes may be due to low lipid solubility, steric and pharmacokinetic factor. [43]



R_1= H, OCH_3, CH_3 and R_2= H, H, CH_3
Figure – 23

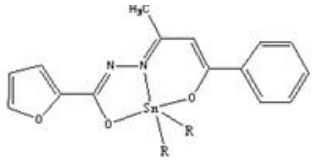
Antimicrobial activities of the ligand (LH_2) obtained from 2-hydroxy aryl ketones and 2- imidazolyl mercaptoaceto hydrazide and its Oxovanadium (IV) complexes (Figure 24) of general formula [VO (L) H_2O] was studied by cup plate method at differentconcentration. From zone of inhibition it is observed that ligand (13-18mm) show less activity than its Oxovanadium (IV) complexes [VO (L) H_2O] (18-26mm) against bacteria *E. coli* and *S. aureus* and against fungi *T. polysporum* and *C. albican.* It is observed that the activity of the complexes generally increases with increasing the concentration of the compounds. [44]



R = CH_3, C_2H_5, C_6H_5
Figure – 24

Diorganotin (IV) complexes synthesized from Iigands [5-bromo-2- hydroxy benzaldehyde furan-2-carbohydrazone (H_2L^a) and 2-hydroxynaphthaldehyde furan-2-carbohydrazone (H_2L^b)] have been evaluated against gram-positive (*B. cereus* and *S. aureus*) and gram-negative (*E. coli* and *P. aeruginosa*) bacteria. $SnPh_2L^b$ (13-20mm) is most active compound and this activity may be due to presence of the naphthalene ring which increases lipophilicity [45] and $SnMe_2L^c$,$SnPh_2L^c$,$SnBu_2L^c$ complexes synthesized from ligands [N-(5-bromo-2-hydroxybenzylidene) isonicotinohydrazide] (H_2L^a), N - ((2-hydroxynaphthalene-1-yl) methylene) isonicotinohydrazide (H_2L^b) and N-(2,4-dihydroxy benzylidene) isonicotino hydrazide (H_2L^c)] are most active than other complexes due to presence of –OH group inside the ligand. [46]

Similarly organotin (IV) complexes synthesized from ligand [H_2L = (Furan-2-yl) (5-hydroxy-3- methyl-5-phenyl-4, 5- dihydro-1*H*-pyrazol-1-yl)-methanone], $SnPh_2L$ complex (12-22mm at conc.3.2 mg/disc) have higher inhibition on microbial growth than $SnMe_2L$ complex **(**Figure 25). It is interesting that, in all synthesized above organotin (IV) complexes, bacteria *P. aeruginosa* was inhibited, towards which most of standard drugs do not show any activity and di phenyltin complexes show more inhibition on microbial growth than dimethyltin complexes. The presence of two phenyl groups increases the solubility in lipids. [47]



R = Me (**a**), Ph (**b**)
Figure – 25

The antibacterial activity of metal complexes [M = Co (II), Mn (II), La(III), Ce (III) and Cu(II)] (Figure26) synthesized from bidentate Schiff base, N-benzylidene-2-hydroxyl benzohydrazide was screened against bacteria such as *S. aureus* and *E. coli* results shows the order Cu (II) (24-26mm) > Co (II) (18-20mm) > Mn (II) (19-21mm) > La(III) (16-17mm) > Ce (III) (17-18mm) at 1000µg/mL and antifungal activity against *A. Niger* and *Trichoderma* follow the order Cu (II) (85-93%) > Co (II) (85-92%) > Mn (II) (84-89%)> La(III) (79-83%)> Ce (III) (76-79%). Comparison of the activities of ligand and its metal chelates shows that the copper complex is more active than ligand and other compounds. Tranition metal complexes Cu (II), Co (II) and Mn (II) show good antibacterial and antifungal activity as compared to inner trasition metal complexes La (III) and Ce (III). [48]

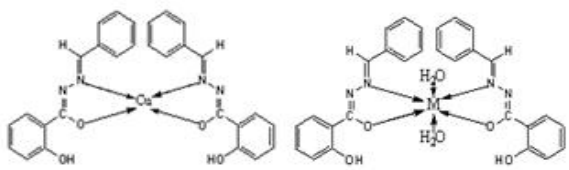


Figure 26

Monomeric oxomolybdenum (V) and cis-dioxomolybdenum (VI) complexes with 2-benzimidazolyl mercaptoaceto hydrazone ligand (LH_2) of the general formula $[MoO(LH)Cl_2]$ and $[MoO_2 (L). H_2O]$ respectively have been synthesized and studied their antibacterial activity against *S. Paratyphi* and *B. Cirro flagellosus* by cup-plate method. Results shows that oxo- complexes $[MoO(LH)Cl_2]$ (15-18mm) showed higher activity than the dioxo-complexes $[MoO_2(L).H_2O]$ (14-16mm). The low activity of dioxo-complexes may be due to low lipid solubility, steric and pharmacokinetic factors which play vital roles in deciding the potency of an antibacterial agent. [49]

A series of new coordination complexes of Cu (II), Co (II), Ni (II), Mn (II), Zn(II), Hg(II) and Fe(III) with the Schiff base 3- chloro-*N*-[(1*E*)-(2-hydroxyphenyl) methylene]-6-methoxy-1-benzothiophene-2- carbohydrazide (HL) have been synthesized and studied their antimicrobial activity. Complexes Hg (II) (20-21mm) and Mn (II) (18mm) showed good activity against bacterial species *E. coli* and *S. aureus* when compared with standard streptomycin (21-22mm). Ligand showed less antifungal activity while the complex of Hg (II) showed good activity against fungal species *A. Niger* (18mm) and *A. flavus* (17mm) as compared to other complexes but less than standard fluconazole (19-20mm). [50]

Manganese (II) complex $[Mn_2Cl_2L_2 (OH_2)_2] \cdot 2CH_3OH$ (II) (3.125-12.5 mg ml^{-1}) exhibits greater antimicrobial activity than those of its hydrazone ligand *N'*-(2-hydroxy-3-methoxybenzylidene) isonicotinohydrazide (HL) (12.5-25 mg ml^{-1}) and shows highest activity against *Bacillus anthracis* (3.125 mg ml^{-1}). It has stronger activities against *P. aeruginosa* (6.25 mg ml^{-1}) and especially *Streptococcus agalactiae* (6.25 mg ml^{-1}) as compared to the gentamicin (20 mg ml^{-1}). [51]

New tetradentate Schiff base, formed by the condensation of 5-fluoro-3-hydrazono indolin-2-one with isophthalaldehyde and its M = Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) complexes (Figure 27) are synthesized and studied there in vitro antibacterial and antifungal activities against two Gram-negative (*Shigella flexneri* and *Enterococcus aerogens*) and one Gram-positive (*Micrococcusluteus*) bacterial strains and against three fungal strains (*Candida krusiae*, *Candida parasilopsis* and *Malassesia pachydermatis*) by cup-plate method. Complexes have higher antimicrobial activity than the free ligand against both bacterial and fungal strains. The complexes Zn (II) (28-36mm) and Hg (II) (26-37mm) exhibited significant activity against all microbial strainsbutlessthan standard drug Ampicillin (32-40mm) and Nystatin (34-42mm). [52]

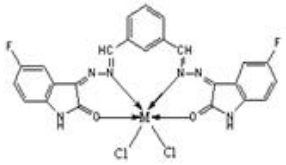


Figure – 27

The hydrazone ligand (LH) formed by the condensation of the isonicotinic acid hydrazide with 2,3-dione 1H-indole and all their metal complexes M = Cu (II), Co (II), Ni (II), Zn (II) (Figure 28) were screened for antibacterial activity by diffusion technique Kirby-Bayer. In case of the *S. Typhimurium*, all complexes have a greater inhibitory capacity than the ligand (LH). Zn (II) (14mm) have quite double value of inhibition zone than ligand and smaller than the same parameter for the Ciprofloxacin antibiotic. The test of the ligand (11mm) and obtained complexes (8mm-14mm) against *E. coli* bacteria indicates that the new compounds have a much intense activity than the Gentamycin (1mm) antibiotic. Towards *S. aureus*, only the Co (II)(16mm) complex exceeded the inhibition capacity of the ligand (LH) (13mm); while the ligand and its complexes are less active than the Ampicilin antibiotic. [53]

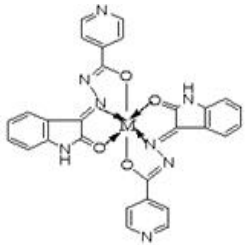
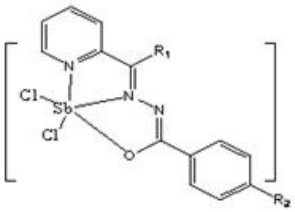


Figure – 28

Antimicrobial activity of antimony (III) complexes (Figure 29) were studied against Gram-positive bacteria *S. aureus* and *S. sanguini* and Gram-negative bacteria *Citrobacter freundii*, *E. coli*, *P. aeruginosa* and *S. typhimurium* and the antifungal effect on *C. albicans*, *C.dubliniensis*, *C. glabrata*, *C. lusitaniae*, *C. parapsilosis*, *C. tropicalis.* Result showed no significant activity against all bacterial strains at 250 µg mL^{-1}. IC_{50} values for the hydrazones and complexes against the studied *Candida* strains revels that upon complexation with antimony (III) the antifungal activity improved. In some complex, $[Sb(2Bzp ClPh)Cl_2]$ (IC_{50} = 4.91 ± 1.20 µmol L^{-1}) was as active as nystatin (IC_{50} = 4.44 ± 0.76 µmol L^{-1}) and twofold more active against *Candida dubliniensis.* Complex $[Sb (2Bzp NO_2Ph) Cl_2]$ (IC_{50} = 8.54 ± 2.21µmolL^{-1}) proved to be as active as nystatin (IC_{50} = 5.31 ± 0.84 µmol L^{-1}). [54]



R_1= -CH_3, - Ph, R_2= -H,-Cl, -NO_2, -OH

Figure – 29

Mn (II) complex (Figure 30) synthesized from ortho hydroxyl propiophenone isonicotinoyl hydrazone ligand were screened against gram-negative bacteria *K. pneumoniae* and *E. coli* and gram-positive bacteria *S. aureus* and *B. subtilis* by the agar disc diffusion method in DMF. Both ligand (14mm) and Mn (II) complex (22mm)

shows highest activity against *E. coli* but less than standard antibiotics ampicillin (40-43mm) and tetracycline (30-33mm). [55]

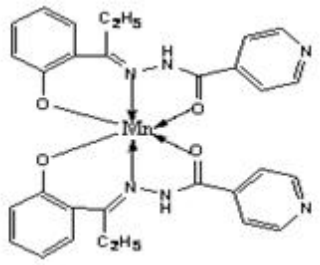


Figure – 30

Oxovanadium (V) complexes, [VO (SO_4) L_1] and [VO (SO_4) L_2] (Figure 31) from Pyrazine-2-carboxylic acid (phenyl- thiophene-2-yl-methylene) - hydrazide (HL_1) and Pyrazine-2-carboxylicacid (phenyl-pyridin-2-yl-methylene) -hydrazide (HL_2), respectively were screened for in vitro antibacterial activity against Gram positive *B. subtilis, Micrococcus Luteus* and Gram negative *P. aeruginosa, P. mendocina* and antifungal activity against fungi *Verticillum, Cladosporium, Tinospora.* On the basis of zone of the inhibition complex [VO (SO_4) L_1] shows maximum antibacterial (21-23mm) and antifungal (%inhibition 65.3 - 69.2) activity than complex [VO (SO_4) L_2] antibacterial activity (17-19mm) and antifungal (%inhibition60.2-69.9) activity at 200µg/ml concentration as compared to ligands but less than standard Streptomycin (25-30 mm) and Fluconazole (% inhibition 79.2-81.2) respectively. Complex [VO (SO_4) L_1] showed maximum zone of inhibition this is due to thiophene ring present in ligand. [56]

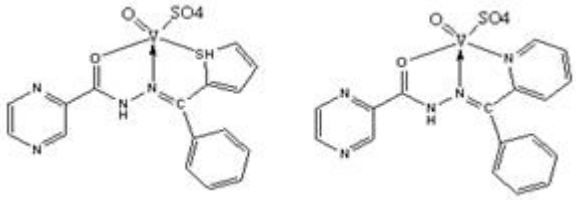


Figure – 31

Metal complexes M= Cu (II), Ni (II),Co (II), Zn (II), Cd (II), Hg (II) of biologically active Schiff's base derived from reaction between benzofuran-2- carbohydrazide with 2-acetylthiophene was reported and studied their antibacterial activity. Complex Hg (II) showed significantly enhanced antibacterial activity (E.coli and S. aureus) comparable with standard Gentamycin (MIC =25 mg/ml) and antifungal activity (A.niger and A. flavus) with MIC =25 mg/ml more than standard Amphotericin (MIC =100-400 mg/ml) than other complexes and ligand. [57]

The mixed ligand complexes M= Co (II), Ni (II), Cu (II), Zn (II), Cd (II) and Hg (II) (Figure 32) derived from L= primary ligand obtained by reaction between benzofuran-2-carbohydrazide and 3,4,5-trimethoxy benzaldehyde (TMeOBFC) and L′=secondary ligand, malonyldihydrazide (mdhz) have been studied for their antibacterial activity against *E. coli* and *S. aureus* and antifungal activity against *A. niger* and *A. flavus* by agar diffusion method respectively in DMF. A comparative study of the ligands and their complexes indicates that complexes exhibit higher antimicrobial activity than the free ligands. It is clear that Co (II) (18mm-21mm), Cu (II) (18mm-21mm) and Cd (II) (18mm-20mm) complexes are found to be more potent than other investigated complexes comparable with standard gentamycin (20-22mm) and fluconazole (22-23mm). [58]

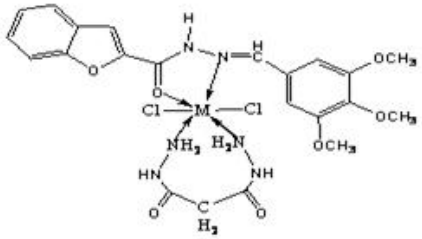


Figure – 32

Metal complexes M = Co (II), Ni (II), Cu (II), Cd (II), Zn (II), Hg (II) of L = Schiff's base derived from the condensation of naphthofuran-2-carbohydrazide with 8-formyl-7-hydroxy-4-methylcoumarin have been synthesized, were screened against E. coli , S. aureus, B.subtilis, P.aeruginosa bacteria and A. flavus, A. niger, Cladosporium oxosporum and C. albicans fungal strains. Antimicrobial activity of metal complexes (12.50-25 µg/mL) are more promising than ligand(50-75 µg/mL) against all the test bacterial/fungal strains and are comparable with standard drug Gentamycin and Amphotericin with MIC=12.50 µg/ml. [59]

A new chelating agent, N-(4-methoxy benzylidene)-2-oxo-2-(phenylamino) aceto hydrazide (H_2OMPH) and its complexes with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Hg(II) and U(IV)O_2^{2+} ions have been prepared,were screened against *S. epidermalies, S. pyagenies* as Gram + ve bacteria and *E. coli, Klebsiella spp*. as Gram ⁻ve bacteria by cup diffusion method. From inhibition zone diameter data, it is observed that ligand and Mn (II), Zn (II) complexes are inactive against all tested bacteria. While Hg (II) (51-55mm) and Cu (II) (13-40mm) complexes shows higher activity as compared to other complexes. [60]

Complexes of the type [LnL2 NO_3 H_2O] • $2NO_3$ where, Ln = La (III), Pr (III), Nd (III), Sm (III), Eu (III), Gd (III), Tb (III), Dy (III) and Y (III), were synthesized from the heterocyclic ligand 2-anilino-N'-[(1E)-1- pyridin-2-ylethylidene]acetohydrazide (Apeah) [61] and 2-amino N′-[(1E)-1-pyridine-2-ylethylidene]benzohydrazide (Apbz) [62] have reported and were screened for their in-vitro antimicrobial activity against two pathogenic bacteria [P. aeruginosa , B. cirroflagellosus] and fungi [P. notatum , A. niger] by cup plate method. Antimicrobial results reveals that, ligand (Apeah) and (Apbz) was less active as compared to complex compounds, which are moderately active against all microorganisms and less than standards, Griseofulvin and Norfloxacin used.

5. Conclusion

In this review, we have focused on the remarkable antimicrobial activity of hydrazones and their metal complexes. Above studies predicted that hydrazone metal chelates exhibits variable growth inhibition capacity against various types of microorganisms and have higher antimicrobial activity than the free ligand. This pronounced activity can be explained on the basis of chelation theory [63]. From above mentioned complexes, most of the complexes are potential lead molecules for drug design. Antimicrobial profile of hydrazone complexes represented in this review which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines.

6. References

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