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Biological Applications of Isoniazid Derived Schiff Base Complexes: An Overview

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Authors' contributions

This work was carried out in collaboration among all authors. Author KEZ designed the study. Author AF performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EU, NAB and RI managed the analyses of the study. Authors SH, NU, MH, MAA, AA, FH managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Antibiotic resistance has been growing at an alarming rate and consequently the activity of antibiotics against Gram-negative and Gram-positive bacteria has dropped dramatically day by day. In this sense there is a strong need to synthesis new substances that not only have good field of activity, but having new appliances of action. Inorganic compounds particularly metal complexes have played a significant role in the development of new metal based drugs. Like few compounds, isonicotinic acid hydrazide (Isoniazid INH) is well known as first-line anti-tuberculosis (TB) drug to treat TB infection worldwide for more than 60 years. Unfortunately, people are only dependent on this drug and consequently, the rate of use of this drug has been increasing day by day. As the bacterial strains resistant to isoniazid are getting same for the long-term extensive use and even

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abuse so there is an urgent need to synthesis new drugs not only for anti-tuberculosis properties but also for having significant activity in various biological areas with mechanisms of action. Isoniazid derivatives and their metal complexes, particularly medicinal inorganic metal complexes have been considered as new drugs for their antimicrobial activities like anti-bacterial, anti-fungal, anti-tuberculosis, DNA binding, antioxidant, cytotoxic, scavenging and antiviral activities. In this review, we have focused on the various synthesized metal complexes of isoniazid and its hydrazones and have compared their biological activities which are more or less strong against microorganisms. It is found that INH has moderate to strong antimicrobial activity.

Keywords: Isoniazid; metal complex; anti-bacterial; anti-fungal;anti-tuberculosis; cytotoxic; anti-virial, antioxidant; DNA-binding; anti-onchocercal; scavenging activity.

1. INTRODUCTION

Tuberculosis (TB) is a potentially serious chronic disease created by bacteria known as Mycobacterium tuberculosis [1]. It is infectious and easily transmits from one person to another through tiny droplets released into the air via coughs and sneeze that is called airborne [2]. TB is one of the most dangerous diseases that kill between two and three million people all over the world per year [3,4]. According to the report of World Health Organization (WHO), TB has dispersed across the world and over 5,000 people die daily for TB and it is considered as the major cause of mortality among the people those are affected by HIV [5]. Since the 1980's, the number of cases of Tuberculosis increased dramatically because of the spread of HIV, the virus that causes AIDS. Moreover, WHO announced a prediction report about deaths and new cases of TB and estimated 8.6 million new cases and 1.3 million deaths worldwide in 2012 as well as 8.7 million new cases in 2011 and also 480,000 new cases of multidrug-resistant in 2015 [6-8].Isoniazid [Fig. 1] is an organic compound that is one of the most potent drugs as well as the first-line medication drugs for treating and preventing tuberculosis. It is considered as standard treatment material by the World Health Organization (WHO) against Mycobacterium tuberculosis bacteria because of its high antibacterial activity [9-12]. Despite this, the alarming estimation by the world health organization is that TB may infect almost 0.22 billion people globally by the year 2030, about 79 million people could die unless new anti-TB drugs are generated [13]. Therefore, it is crucial time for the researchers to develop a more potent anti-TB drug against both drug-sensitive and resistant M. tuberculosis (MTB). As a result, scientists are being devoted for discovering novel drugs which are more effective against bacterial strains [14].It is proved by many researches that isoniazid (INH) based metal complexes have anti-bacterial activity in which INH acts as mono-, bi- or poly-dentate ligand as well as complexes of isoniazid also shows promising biological activities. Likewise, these types of compounds are more effective and to a lesser extent hepatotoxic than isoniazid [15-17]. In this review, we have explored the biological activities of isoniazid (INH) based metal complexes and its hydrazone with various strategies.

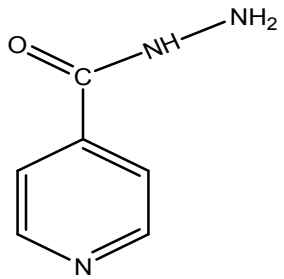


Fig. 1. Isoniazid (INH)

2. BIOLOGICAL ACTIVITY STUDIES OF ISONIAZID CONTAINING METAL COMPLEXES

2.1 Antibacterial Activity

2-acetyl-pyridyl-isonicotinoylhydrazon (ligand) [Fig. 2] with metal perchlorate or sulphate having Cu(II), Co(II), Ni(II), Mn(II) and Zn(II) were synthesized to obtain ten metal complexes by refluxing on a water bath in methanolic solution by Lucica Viorica Ababei and et al. Comparing antibacterial activity of the transition metal complexes against *Staphylococcus aureus, Escherichia coli and Salmonella Typhimurium,* it was shown that $[ZnL_2](ClO_4)_2$ where L = 2-acetyl-pyridyl-isonicotinoylhydrazon which did not display the highest activity with a diameter of inhibition of 4 mm against all selected strains than others . On the other hand, complex $[Co(2\text{-acetyl-pyridyl-isonicotinoylhydrazon})_2](ClO_4)_2$ exhibited the most positive screening between 7 and 12 mm on all strains. To sum up, overall the metal complexes showed moderate activity [18].

Cu(II), Zn(II) and Cd(II) complexes of mixed isoniazid- ascorbic acid (1:1:1 ratio) were synthesized using metal salts $CuSO_4$, $CuCl_2$ $ZnSO_4$, $CdSO_4$ by Lawal M. et al. The mixed ligand complexes were tested for antibacterial activities at the concentration (1 mg/mL) against *Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella pneumonia, and Escherichia coli*. Moreover, it was found that the ligands were less active compared to the three metal complexes. Besides, among the ligands and metal complexes, Cu(II)complexes [Fig. 3] showed the highest activities with the zone of inhibition ranging between 0.5 and 16.0 mm against *Staphylococcus aureus, Pseudomonas aureginosa and Klebsiella pneumonia* [19].

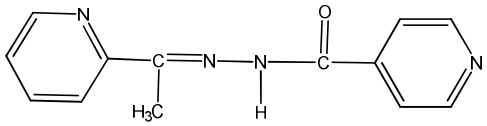


Fig. 2. The structural formula of 2-acetyl-pyridyl-izonicotinoylhydrazone (ligand)

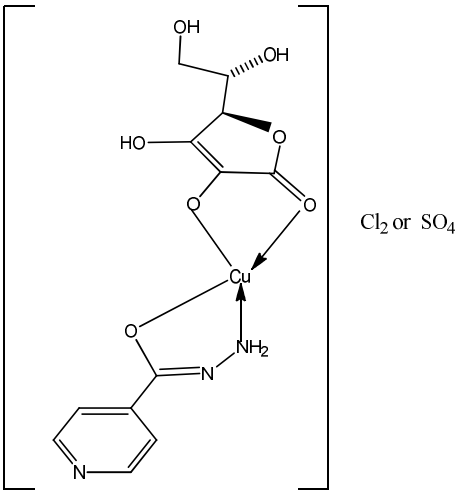


Fig. 3. Structure of Cu(II) complexes

*Khlood S. Abou-Melha*prepared a Schiff base isonicotinic acid (2-hydroxybenzylidene) hydrazide [Fig. 4] from the reaction of saclicylaldehyde with isonicotinic acid hydrazide and synthesized Cu(II), Ni(II), Co(II), Mn(II), Fe(III) and UO_2(II) complexes with the ligand. Antibacterial screening effects of all the synthesized complexes (in DMSO solvent) were studied by measuring the minimum inhibitory concentrations (MIC) for concentrations of 1, 25, 50 and 100% against *Staphylococcus aureus* and *Escherichia coli*. The Ni(II), Co(II), Mn(II) and Fe(II) complexes among all complexes exhibited higher activity against all bacterial strains in its 25, 50 and 100% concentrations. Also, all synthesized complexes were more active against all strains only in its 100% concentration but all compounds were inactive in its 1% concentration [20].

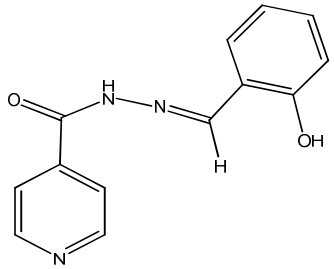
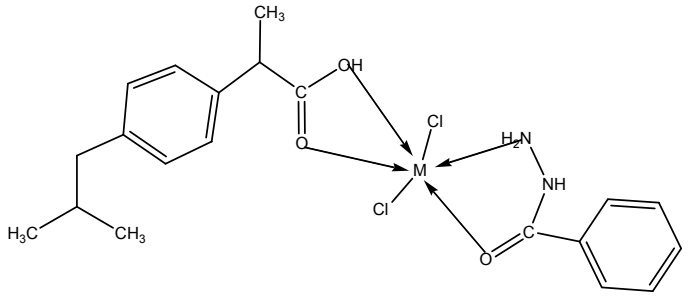


Fig. 4. Structure of schiff base isonicotinic acid (2-hydroxybenzylidene) hydrazide

Mercy O. Bamigboye, et al. synthesized metal complexes using Isoniazid (ISO)-Ibuprofen(IBR) mixed ligands using the chloride salts of the metals; Cu^{2+}, Zn^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}. In the case of complexes and ligands, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were carried out against some microorganisms like *Escherichia Coli, Staphylococcus aureus, and Pseudomonas aeruginosa.* InMIC, the obtained results showed that the antibacterial activity of Cu complex was less active than Ni, Cd and Co complexes against *Escherichia Coli, Staphylococcus aureus, and Pseudomonas aeruginosa*. On the contrary, $[Ni(ISO)(IBR)Cl_2]$, $[Co(ISO)(IBR)Cl_2]$, $[Cd(ISO)(IBR)Cl_2]$ complexes [Fig. 5] were more effective compared to $[Cu(ISO)(IBR)Cl_2]$ complex in MBC. But there was no positive activity of free ligands against the organisms in all cases of MIC and MBC [21].

Md. Sajjad Hossain, et al. made Cu^{2+} and Ni^{2+} metal mixed ligand complexes getting with N-(4-methoxybenzylidene) isonicotinohydrazone Schiff base ligand and 2.2′-bipyridine ligand by refluxing on a water bath. In complexes, the metals coordinated to the ligands through carbonyl oxygen, the nitrogen of azomethine and pyridine. As well, the $[Cu(L_1)(L_2)](NO_3)_2$, $[Ni(L_1)(L_2)](NO_3)_2$, and the primary ligand, were estimated for antibacterial activity against *Escherichia coli* and *Bacillus cereus*. The activity of Schiff base ligand was very low with zone of inhibition of 4 mm than two mixed ligand complexes ranging from15 to 20 mm against two strains. Therefore, in the case of all compounds [Fig. 6], the antibacterial screenings were positive [22].



M= Ni, Cu, Cd and Co

Fig. 5. Structure of[Ni(ISO)(IBR)Cl_2], [Co(ISO)(IBR)Cl_2], [Cd(ISO)(IBR)Cl_2] complexes

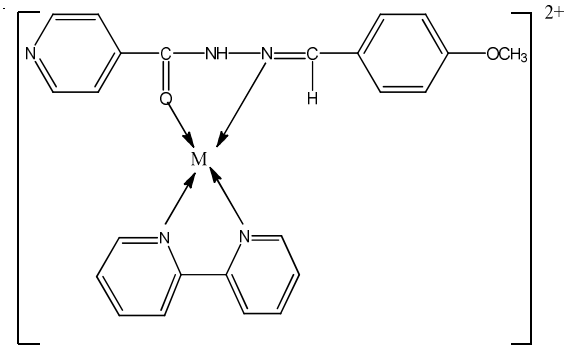


Fig. 6. Structure of mixed ligand complexes (where, M= Cu(II) and Ni(II))

Six Schiff bases compounds (L_1-L_6) of mixed isoniazid-fluorinated benzaldehydes were prepared and four copper(II) complexes ;Cu-L_1, Cu-L_2, Cu-L_3 and Cu-L_6 were synthesized by Ladislav Habala et al. However, antibacterial studies of those compounds were done against *Staphylococcus aureus* and *Escherichia coli* by evaluating minimum inhibitory concentration (MIC, mM). It was observed that only N-[(5-fluoro-2-hydroxyphenyl) methylidene] pyridine-4 carbohydrazide (**L4**) displayed noticeable activity against *E. coli* (MIC 1.55 mM) but no inhibition observed in case of N-[(4-fluorophenyl) methylidene]pyridine-4 carbohydrazide monohydrate (**L3**) and N-[(5-fluoro-2-hydroxyphenyl) methylidene] pyridine-4-carbohydrazide (**L4**) against *Staphylococcus aureus.* On the other hand, the synthesized Cu-L_6 complex displayed marked activity among the four Cu(II) complexes against *S. aureus* (MIC 0.76 mM) [23]. *Bamigboye M. O and et al.* synthesized some complexes of Mn^{2+}, Fe^{2+}, Cu^{2+} , Co^{2+} , Zn^{2+} and Cd^{2+} chloride or sulphate with mixed Trimethoprim-Isoniazid ligands in where the complexes are tetrahedral with the ligands. Besides, the antibacterial activity of the complexes was examined on the microorganism; *Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella pneumonia, Escherichia coli* at concentrations of 20,40, 50 and 100 ppm.Finally, it appeared that the free ligands were less active than the complexes [24]. The ligand N- (4-methoxybenzylidene) isonicotinohydrazide [Fig. 7] was prepared by Md. Sajjad Hossain, et al. condensing Isoniazid and 4-methoxybenzaldehyde and then metal Cu(II) and Ni(II) complexes were synthesized. Antibacterial screening results of the two complexes and the ligand were investigated against gram-negative *Escherichia coli* and gram-positive *Bacillus cereus.* Furthermore, it was found that the Ni^{2+}complex was better antibacterial activity with values of 12 and 10 mm among all compounds. Eventually, all compounds were moderately active against the tested species [25].

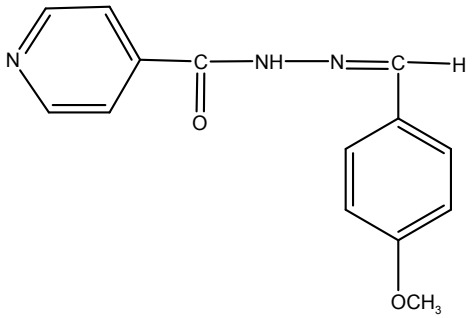


Fig. 7. Isonicotinehydrazone based schiff base ligand

Zahid H. Chodhan, et al. prepared six isonicotinoylhydrazide Schiff's bases ligands; L_1-L_6 [Fig. 8] by the reaction of furyl-2-carboxaldehyde and thiophene-2-carboxaldehyde with isoniazid. Then, Co (II), Cu (II), Ni (II) and Zn (II) containing twenty-four complexes were synthesized and all were determined for antibacterial activity against *M. tuberculosis, E. coli, K. pneumonia, P. mirabilis,*

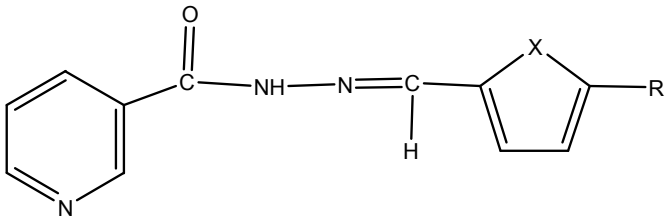
P. aeruginosa, S. typhi, S. dysenteriae, B. cereus, C. diphtheriae, S. aureus and S. pyogenes bacterial strains. Most of the metal complexes normally showed significant activity against eight or nine strains, some were moderate but there was no weak activity. From another point of view, some of the ligands (1-6) exhibited good activity, moderate and very lowest activity against one or two bacterial species [26].

Cu (II), Co (II) and Ni (II) complexes with a new Schiff base ligand derived by the condensation of Isoniazid and Furfuraldehyde have been synthesized by Md. Masuqul Haque, et al. The synthesized complexes were screened for their inhibition of bacterial growth activity in DMSO against *Escherichia coli (E. coli)* and *Bacillus Cereus (B. cereus)*. Additionally, the prepared ligand showed lower bacteriostatic activity with a diameter of inhibition of 5 mm compared to all metal complexes with values from 6 to 15 mm. Cobalt(II) complex presented significant activity than other compounds [27]. Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of 2-thiophenecarbonyl and isonicotinoylhydrazones of 3-(N-methyl)isatin (HL^1 and HL^2, respectively) were synthesized by Maria C. Rodriguez-Arguelles, et al. The HL^1 and their four metal complexes for antibacterial activity were carried out against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Haemophilus influenza* respectively expressed as MIC (µg/mL). The synthesized HL^1 and its complexes demonstrated significant antibacterial activity against *Haemophilus influenza* (MIC 0.15–1.50 (µg/mL) while these compounds showed moderate inhibition of bacterial growth against *Bacillus subtilis* and *Staphylococcus aureus* (3–25 µg/mL and 12–200 µg/mL). Only, the synthesized Co(II) and Ni(II) were active against Escherichia coli at concentrations of 50 µg/mL and 200 µg/mL) [28].

2.2 Antifungal Activity

K. P. Deepa, et al. synthesized Co(II), Ni(II), Mn(II), Cu(II) and Zn(II) complexes using omega-bromoacetoacetanilideisonicotinylhydrazone as a Schiff base ligand and looked into antifungal activities of these compounds against *Aspergillus niger*, *Candida albicans*, *Trichosporon sp*., and *Penicillium Sp*. by a cup-plate technique. Likewise, the ligand and the complexes revealed remarkable results against taken four microbes. Moreover, the prepared ligand [Fig. 9] was detected to be lower active with values of 15, 15, 20 and 22 mm against *Aspergillus niger, Penicillium Sp*., *Candida albicans* and *Trichosporon sp*., respectively compared to the chelates and also in where Co(II) and Ni(II)complexes showed more activity almost between 20 and 30 mm [29].

Nine complexes of Cu(II), Co(II) and Ni(II) with Isoniazid and benzilmonohydrazone as a ligand (L) having the chemical formula of the type $[M(L)(H_2O)_2]_2Cl_2$,$[M(L)(H_2O)_2]_2(CH_3COO)_2$ and $[M(L)(H_2O)_2]_2(NO_3)_2$ where M= Cu(II), Co(II) and Ni(II) were prepared by *N. Panda* and *et al.* and the synthesized binuclear complexes [Fig. 10] were tried out for the fungicidal action against three pathogenic fungus *Aspergillus niger, Helminthosporium oryzae and Fusarium oxysporium* at concentration 100 ppm. After testing, it was noticed that the antifungal activity of ligand have less expected result against *Aspergillus niger* and *Fusarium oxysporium* than the metal complexes. Overall, copper(II) complex exhibited significant activity compared to two Ni(II) and Co(II) complexes [30].



L_1 : X=O; R=H L_2 : X=O; R=CH_3
L_3 : X=O; R=NO_2 L_4 : X=S; R=H
L_5 : X=S; R=CH_3 L_6 : X=S; R=NO_2

Fig. 8. Structure of the isonicotinoylhydrazidederived schiffbase ligands

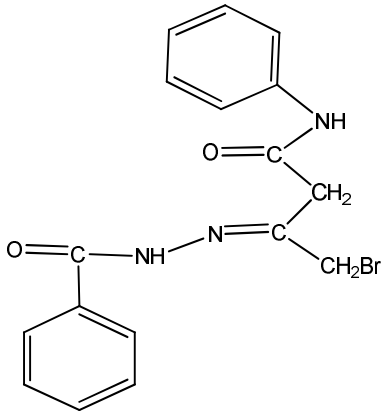


Fig. 9. Structure of omega-bromoacetoacetanilideisonicotinylhydrazoneligand

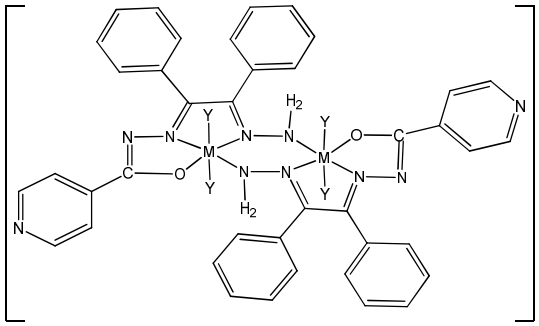


Fig. 10. Structure of the metal complexes.When M= Cu(II) and Co(II), and Y=H_2O or when M= Ni(II), Y= Nil

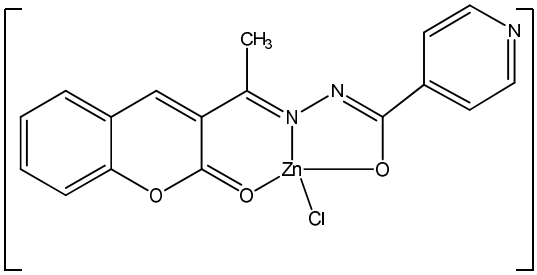


Fig. 11. Structure of Zn(II) complex

*Rekha S. Hunoor*and *et al.* condensed 3-acetylcoumarin and isonicotinoylhydrazide to form Schiff base containing 3-acetylcoumarin–isonicotinoylhydrazone ligand and its corresponding metal (II) chlorides viz. Co(II), Ni(II), Cu(II) and Zn(II) complexes were synthesized . Trigonalbipyramidal geometry was suggested for both Ni(II) and Cu(II) complexes whereas both Co(II) and Zn(II) complexes were tetrahedral .However, antifungal activity study of the ligand and the metal complexes were determined against *Candida albicans* (CA, ATCC 2091) and *Aspergillus fumigates* (AF, ATCC 25691) by using Minimum Inhibitory Concentration (MIC) with standard Flucinozole. The obtained results revealed that ligand (MIC = 50, 25 µg/mL), Co(II) complex(MIC= 25, 12.5 µg/mL), Ni(II) complex(50, 25 µg/mL), Cu(II) complex (25, 12.5 µg/mL) and Zn(II) complex (25, 6.25 µg/mL) exhibited less activity compared to standard antifungal drug . Zinc (II) complex [Fig. 11] exhibited the highest antifungal activity than others cause MIC value was very low; 6.25 µg/mL [31].

Nickel(II) complexes having formula of $[Ni(L)_2X_2]$ or $[Ni(L)_3](ClO_4)_2$, where L=N-isonicotinamido-furfuraldimine (INH-FFL) and X = Cl− or NCS− were synthesized by reacting isonicotinylhydrazide with furfuraldimine by Surendra Prasad, et al. and were investigated their antifungal activity against the pathogenic fungal species; *Aspergillus niger* and *Candida albicans*. The results of fungicidal studies demonstrated that all the synthesized compounds showed moderate active but salicylic acid was more active against all tested fungal species than the synthesized nickel(II) compounds [32]. Krishna K. Sharma, et al. prepared two Pd(II) and Pt(II) complexes with N-isonicotinamido-2-furanketimine (INH-F^1) and N-isonicotinamido-5-methyl-2-furanketimine (INH-F^2) [Fig. 12]. The ligands and their complexes were tested for antifungal studies against *Aspergillus niger* and *Fusarium oxysporum* at different concentrations; 0.5, 1.0, 1.5 mg/mL. It was found that the complexes were more powerful with values of inhibition between 50 and 80% than the ligands below 70% as the activity enhanced with increasing concentration. Therefore, all synthesized compounds exhibited good antifungal activity [33].

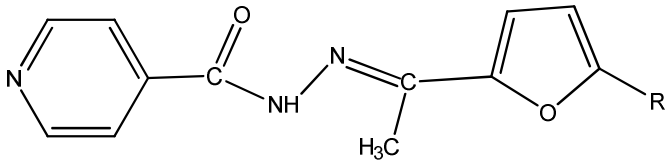


Fig. 12. N-isonicotinamido-2-furanketimine (INH-F[1]) when R= H and N-isonicotinamido-5-methyl-2-furanketimine (INH-F[2]) when R= CH_3

Isoniazid was reacted with Curcumin by Jeyaraman Porkodi, et al. to form curcumin derived hydrazone which was Schiff base ligand and this ligand was mixed metal (II) chlorides [Cu(II), Ni(II), Co(II), Zn(II)] to synthesize four transition metal complexes [Fig. 13]. The effect of these complexes as well as this ligand on their antifungal activity against five pathogenic strains like *Aspergillus niger, A. flavus, Curvularia lunata, Rhizoctonia bataticola and Candida albicans* were studied by using minimum inhibitory concentration (MIC, µM). It was proved that all the complexes showed more efficient activity compared to the ligand and overall, copper(II) complex presented excellent inhibitory property with MIC value of average 11.46×10^{-4} µM against all tested strains than other complexes [34].

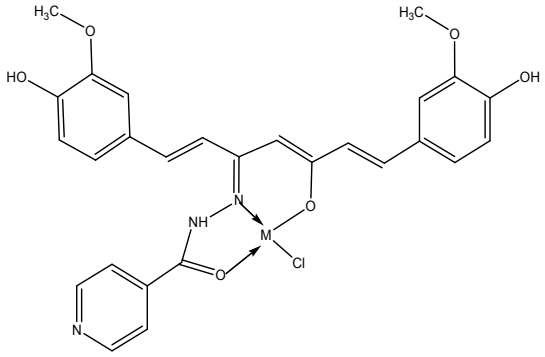


Fig. 13. Structure of metal complexes; M= Cu(II), Ni(II), Co(II), Zn(II)

Nine complexes of $Cr^{3+,}$ Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pd^{2+} with 2,5-hexanedionebis(isonicotinylhydrazone) [HINH] and four complexes of Co^{2+}, Cu^{2+}, Zn^{2+} and Hg^{2+} with N-(2,5-dimethyl-1H-pyrrol-1-yl) isonicotinamide [DINA] have been synthesized by Bakir Jeragh, et al. For antifungal effect; HINH, DINA and some of the synthesized complexes viz. $[Co_2(HINH)(H_2O)_4Cl_4]$, $[Ni_2(HINH)(H_2O)_4Cl_2]Cl_2.2H_2O$,$[Pd_2(HINH)(H_2O)_2Cl_4].5H_2O$, $[Cd_4(HINH)Cl_8].3H_2O$ have been studied here against *Candida albicans PA47*, *Candida albicans PA48* and *Saccharomyces cereviciae*. The $[Cd_4(HINH)Cl_8].3H_2O$ exhibited the highest antifungal activity against the selected fungal strains than other compounds. Besides, all compounds were the most active against *Saccharomyces cerevisiae* than *albicans PA47, Candida albicans PA48* [35].

2.3 Antimycobacterial Activity

Kehinde O. Ogunniran, et al. *synthesized a* (*E*)-N'-(4-cyanobenzylidene) nicotinohydrazidelig and (HL^5) by the condensation reaction of acid hydrazide and 4-cyanobenzaldehyde and its metal complexes; Mn(II), Mo(V), Fe(II), Cu(II) and Zn(II) were prepared. *In vitro* anti-tubercular activities of the synthesized compounds were carried out against *Mycobacterium tuberculosis* H37Rv by measuring MIC values. Also, the Zn(II) complex showed a more MIC value of 0.62 µg/mL among the compounds .On the other hand, Fe(II) complex displayed a very lower MIC value of 1.15 µg/mL than the others. Hence, it was found that HL^5 and its metal complexes except for Fe(II) complex exhibited powerful anti-tubercular activity againstsome of the standard drugs [36]. A series of Cr^{+3}, Co^{+2}, Cu^{+2}, Fe^{+3}, and Ni^{+2} complexes with alanine (ala), glycine (gly) which are amino acid ligands and isoniazid were synthesized by Juboori, et al. A distorted octahedral geometry was confirmed for the synthesized complexes. However, anti-tubercular activity for the prepared complexes and isoniazid ligand were tested against sensitive and resistant tuberculosis bacteria. The obtained results revealed that the five complexes and isoniazid exhibited significant activity against normal tuberculosis bacteria. In contrast, these compounds were found to be a non- significant activity against only the resistance tuberculosis bacteria [37]. Ogunniran Kehinde, et al. prepared an isonicotinehydrazone Schiff base ligand bycondensingnicotinic acid hydrazide and 2,5-dimethoxylbenzaldehyde and then some metal complexes were synthesized with the ligand .The prepared compounds were screened for in vitro antimycobacterial activity against *Mycobacterium tuberculosis*, H37Rvby using micro-diluted method. The ligand (HL) and isoniazid(INH)

demonstrated lower activity compared to some of the metal complexes. In general, it has been observed that the compounds found to be potential anti-tubercular agents [38]. Bottari, et al. prepared a series of Cu(II) and Ni(II) complexes with isonicotinoylhydrazones as ligands. These metal chelates and ligands were carried out for in vitro anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv by using MIC (µg/mL). Among the synthesized complexes, three complexes exhibited MICs ≤0.2 µg/mL that was the highest improved anti-tubercular potency whereas other complexes from 0.39 and 12.5 µg/mL. On the other hand, the MIC values of all hydrazones were from 0.025 to 0.2 µg/mL except for one where these ligands showed good activity, equal or higher than that of rifampin used as standard drug. Hence, overall the synthesized hydrazones exhibited more powerful than their copper(II) and nickel(II) complexes [39]. Kehinde Olurotimi Ogunnirana, et al. synthesized *(E)-N′*-(2,4-dihydroxybenzylidene)nicotinohydrazide ligand [Fig. 14] from the reaction of Nicotinic acid hydrazide and 2,4-dihydoxylbenzaldehyde by using ethanol solvent. Thereafter, five complexes of Mn(II), Fe(II), Pt(II) Zn(II) and Pd(II) with *E)-N′*-(2,4-dihydroxybenzylidene)nicotinohydrazide were prepared. However, comparing In vitro antimycobacterial study among the ligand and the complexes against *Mycobacterium tuberculosis*, H37Rv, it was found that (PtL_1) (MIC = 0.56 µg/mL), (ZnL_1) (MIC = 0.61 µg/mL), (MnL_1) (MIC = 0.71 µg/mL), (FeL_1) (MIC = 0.82 µg/mL), (MnL_1) (MIC = 0.71 µg/mL and (H_3L_1)(MIC=1.02 µg/mL). Moreover, the ligand showed lower antibacterial activity than the complexes which exhibited to be more potent than isoniazid [40].

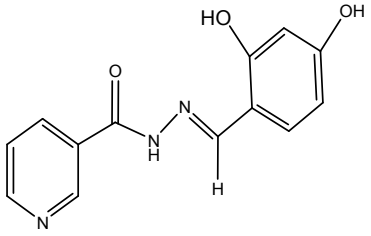


Fig. 14. Structure ofacylhydrazone based ligands (H_3L^1)

Complexes of ruthenium; trans-$[Ru(NH_3)_4(L)(INH)]^{2+}$ where L= SO_2 or NH_3 were separated and antimycobacterial screening effects of Ru^{2+} complex and Isoniazid (INH) were studied against the H37Rv and CF45 and CF74 resistant strains of Mycobacterium tuberculosis (MTb) by Inara de Aguiar, et al. The minimal inhibitory concentration (MIC) values exhibited that $[Ru(NH_3)_5(INH)]^2$+ [Fig. 15] was to be more remarkable activity (MIC= 1.06, 0.17 µg/mL) against both resistant and sensitive strains of MTb. On the other hand, non-coordinated isoniazid as well as trans-$[Ru(NH_3)_4(SO_2)(INH)]^{2+}$ revealed positive sign with value of 0.50 µg/mL against only the sensitive strain [41].

Four complexes of copper (II) with 2-pyridine carboxaldehydeisonicotinoylhydrazone (HPCIH), 2-acetylpyridine-(HAPIH), 2-pyridineformamide-(HPAmIH) and pyrazineformamide-(HPzAmIH), having the formula of complexes viz.$[Cu(HPCIH)Cl_2].4H_2O$(1), $[Cu(HAPIH)Cl_2].5H_2O$ (2), $[Cu(HPAmIH)Cl_2].H_2O$ (3) and $[Cu(HPzAmIH)Cl_2].5H_2O$ (4) were synthesized by Gisele, et al. The compounds were effected for their antimycobacterial study against *Mycobacterium tuberculosis H37Rv ATCC 27294 strain*. The obtained Complexes 1 and 2 showed significant activity against M. tuberculosis where values of MIC = 0.85 and 1.58 µM, respectively than isoniazid (MIC = 2.27 µM) [42].Ni(II) 2,6-diacetylpyridine bis (isonicotinoylhydrazonate) (3) and Ni(II) 2,6-diacetylpyridine bis (benzoylhydrazonate) (4) were synthesized mixing with two ligands 2,6-diacetylpyridine bis (isonicotinoylhydrazone) (1) and2,6-diacetylpyridine bis (benzoylhydrazone) (2) by Bottariand et al. The nickel(II) chelates and ligands in case of anti-tubercular in vitro activity were evaluated against *Mycobacterium tuberculosis*, H37Rv (ATCC 27294) comparing with standard drugs RMP and INH. The complex 4 (MIC=0.025 µg/mL) showed the highest activity among all compounds even than RMP but equal to isoniazid [43]. Julie Laborde, et al. synthesized Fe(II) complexes containing isoniazid as well as pyrazinamide derivatives as ligand and investigated their anti-tubercular activity against MTB growth *in vitro* and in vivo including on resistant strains by evaluating the MIC. The obtained results revealed that INH-Fe(II) complex [Fig. 16] exhibited significant restrictive activity toward InhA enzyme against *Mycobacterium tuberculosis* organism rising. Some complexes of pyrazinamide derivatives -Fe(II) complex did not display any remarkable anti-mycobacterium activity [44].

2.4 Cytotoxic Activity

Cu(II)complexes (C_5-C_8) have been synthesized with four isonicotinoylhydrazonesas ligands (L_1-L_4) by Pulipaka Ramadevi, et al. Moreover, the ligands and their Cu(II) complexes have been examined for their cytotoxicity studies on A549

human lung cancer cell by measuring IC_{50} values. The cytotoxic effect brought out that cis-platin drug ((IC_{50} = 26 μM) was higher toxic than all ligands and their metal complexes. Furthermore, it has been observed that the ligands (L1=500 μM, L2=340 μM, L=503 μM, L4=325 μM) showed lesser cytotoxicity as compared to the copper complexes (C5= 60 μM, C6= 475 μM, C7=92μM, C8 = < 50 μM) to A549 cells [45]. N-benzyl-2-isonicotinoylhydrazine-1-carbothioamide,H_3L [Fig. 17] was prepared by condensing benzyl isothiocyanate and isonicotinichydrazide and its metal Co^{2+},Ni^{2+}, Cu^{2+} and Zn^{2+} complexes were synthesized by Mohamed H. Abdel-Rhman, et al. *In vitro* Cytotoxicity IC_{50} (µg/mL) of ligand (H_3L) and its metal Zn(II) complex were investigated against human tumor cells; HePG2 and HCT116. Also, Zn(II) complex displayed lesser cytotoxicity with approximately 45-56 µg/mL as compared to the ligand (17.64 µg/mL) against HePG2 cell line and colon cancer cell lines (HCT116) [46].

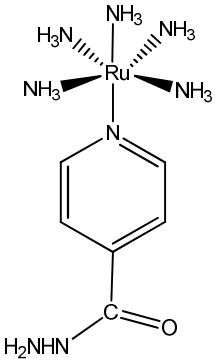


Fig. 15.Structure of $[Ru(NH_3)_5(INH)]^{2+}$ complex

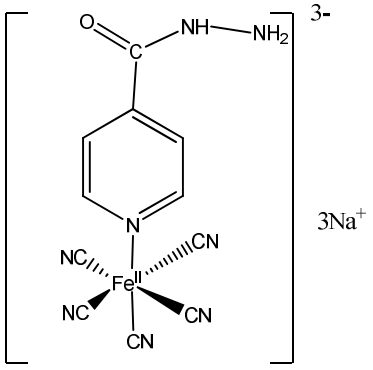


Fig. 16. Structure of $Na_3[Fe^{II}(CN)_5(INH)]$ complex

Muhib Ahmed, et al. condensed the reaction of isoniazid (INH) and 1,10-phenanthroline- 5,6-dione(phendione) to prepare (Z)-N'-(6-oxo-1,10-phenanthrolin-5(6H)-ylidene) isonicotino hydrazide as Schiff base ligand 1 [Fig. 18] and its metal Ag^+ and Mn^{2+} complexes; $[Ag(1)_2]BF_4$, $[Ag(1)_2]NO_3.2H_2O$, $[Mn(1)_2](NO_3)_2.2H_2O$ were synthesized. For cytotoxic activity, the ligand 1 and its complexes were checked out on A549 epithelial cells. Also, the Ag^+ and Mn^{2+} exhibited three more times toxic than ligand 1 against mammalian A549 cells whereas metal-free isoniazid and 1,10-Phenanthroline were the least harmful [47].

Two isonicotinoyl Schiff base ligands HAPIH, HPAmIH and its gallium(III) complexes, $[Ga(HAPIH)(APIH)](NO_3)_2.2H_2O$ (**1**) and $[Ga(HPAmIH)(PAmIH)](NO_3)_2{\cdot}2H_2O$ (**2**) were synthesized by Gisele dos S.S. Firmino, et al. By studying cytotoxicity of HPAmIH, HAPIH [Fig. 19] as well as its complex **1** and **2**; it has been observed that complex **2** and HPAmIH exhibited very low activity against HL- 60, MCF-7, HCT-116 and PC3 tumor cell lines at 10 µM whereas the complex **1** and HAPIH showed extremely toxicity against HL-60 and HCT-116 cells by IC_{50} values (µM) but exception results in case of MCF-7. Besides, HAPIH was less powerful than Complex **1** against HCT-116 cells [48].

$[Zn(C_6H_7ON_3)_2](ClO_4)_2.6H_2O$ was synthesized by the reaction of isoniazid (INH) and zinc(II) perchlorate hexahydrate by *Maria C.R. Freitas* and *et al*. Toxicity of complex and free ligand INH was executed against *A. salina* for some human tumors. The LD_{50} values of the synthesized Zn(II) complex and free ligand INH were 268µM and 2240 µM in where lapachol was 281 µM which is used as a standard compound. Furthermore, free INH was about 8.5-fold lower active than the Zn(II) complex against *A. salina* [49]. Four copper(II) complexes with ligands from 2-hydroxy-8-R-tricyclo[7,3,1,02,7]-13-one-tridecane (R: CH_3, C_2H_5, n-C_3H_7, i-C_3H_7) with isoniazid were synthesized by IrinaZarafu, et al. The ligands(1-4) and complexes(1-4) were treated on the capability of normal growth and development of HaCaT cells. Compounds $[CuL_1(CH_3COO)_2].H_2O$ (1) and $[CuL_3(CH_3COO)_2]$ (4) caused a monolithic death of the immortalized HaCaT cells. Also, the complexes 1 and 4 displayed the most toxic about 1.5 µg/mL than others [50].

2.5 DNA Binding and Other Important Activities

A Schiff base ligand, 7-methoxychromone- 3-carbaldehyde-isonicotinoyl hydrazone (L)

[Fig. 20] and its La(III) as well as Sm (III) complexes were synthesized by *Qian Wang* and *et al*. Also the Schiff base ligand and its two complexes were performed their DNA binding interactions in hypochromism and bathchromism apart from antioxidant activities by evaluating their scavenging effect on hydroxyl radical and superoxide radical. The obtained results exhibited that the DNA binding affinity of the Sm(III) complex and the ligand was weaker than that of the La(III) complex. Besides that, the anti-oxidative abilities of the tested compounds showed significant activity [51].

For analyzing the DNA binding, antitumor properties, and hydroxyl radical scavenging activities, oxovanadium (IV) complexes; VO(PAHN)(phen) (1), VO(PAHN)(bpy) (2), VO(PAH)(phen)(3), VO(PAH)(bpy) (4) have been synthesized by Xiangwen Liao, et al. Among the novel four prepared complexes on DNA binding, the complex 1 displayed the

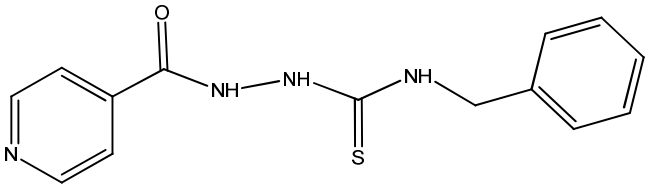


Fig. 17. Structure of N-benzyl-2-isonicotinoylhydrazine-1-carbothioamide (H_3L)

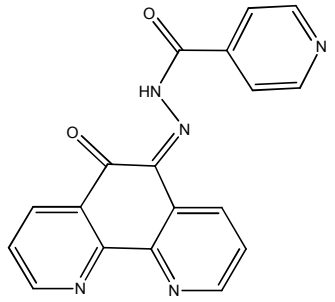


Fig. 18. Schiff base ligand,(Z)-N'-(6-oxo-1,10- phenanthrolin-5(6H)-ylidene)

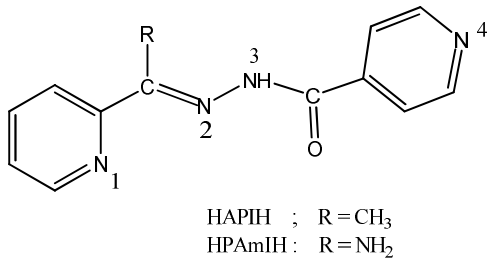


Fig. 19. Structure of 2-acetylpyridine-(HAPIH) and 2-pyridineformamide-(HPAmIH) isonicotinoylhydrazones

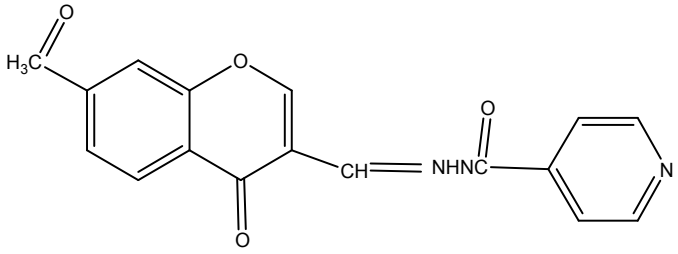


Fig. 20. Structure of 7-methoxychromone- 3-carbaldehyde-isonicotinoyl hydrazone (L)

strongest binding affinity and also the greatest powerful antitumor agent against human cancer cells. Additionally, their hydroxyl radical scavenging effects were investigated and the results were found that complex **1** had the highest inactivity [52]. *Arun Srivastava* synthesized Cu(I)and Cu(II) complexes with isoniazid (INH) for estimating their putative antiviral activity *in vitro*. The Cu+-INH and Cu++-INH complexes hindered RT activity by about 88% and 95% respectively at the alike concentration .The copper(II) complex exhibited to be more potent exhibitor than isoniazid against RNA tumor viruses which is known as retroviruses [53]. Six isoniazid-derived Schiff bases were prepared by Evans N. Mainsah, et al. by condensation of isoniazid and several aromatic aldehydes in methyl alcohol. Zn (II) and Cu (II) complexes were synthesized and for anti-onchocercal activity, it was found that the ligands and Zn (II) complexes were inactive against microfilaria. On the other hand, the Cu (II) complexes exhibited noteworthy activity against both micro-and microfilaria with IC_{50} values of 5 µg/mL and 10 µg/mL respectively [54].

3. CONCLUSION

Metal complexes with isoniazid and Schiff base derived from isoniazid have been reported to have several biological activities such as antibacterial, antifungal, anti-tuberculosis, cytotoxicity, DNA binding, antioxidant, scavenging and antiviral activities. After studying all sorts of activities, In this review, it has been concluded that isoniazid and isoniazid derived Schiff base containing metal complexsynthesis is an active line of research which has contributed to creating antimicrobial agentsand this review will provide ample references for researchers to further their research in this area and will be profitable to students as well.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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