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Review Article

Isoniazid Containing Metal Based Drugs as Potential Antimicrobial Agent: A Short Review

Md. Saddam Hossain[1], Md. Abdul Mannan[1], F. K. Camellia[1], A. K. B. Zaman[2], C. M. Zakaria[1], Md. Kudrat-E-Zahan[1, *]

[1]Inorganic Research Laboratory, Department of Chemistry, University of Rajshahi, Rajshahi, Bangladesh

[2]Department of Dermatology, Barind Medical College and Hospital, Rajshahi, Bangladesh

Email address:

kudrat.chem@ru.ac.bd (Md. Kudrat-E-Zahan)

[*]Corresponding author

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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 spectrum of activity, but having new mechanisms of action. Inorganic compounds particularly metal complexes have played an important role in the development of new metal based drugs. A significantly rising interest in the design of metal complexes as drugs and diagnostic agents is currently observed in the area of scientific inquiry, specifically termed medicinal inorganic chemistry. In this review we have focused on research undertaken over the past few decades which has sought to possess preclinical pharmacological screenings like anti-bacterial, anti-fungal, anti-tuberculosis, anti-inflammatory, anti-cancer, DNA- interaction and anti-tumor action of isoniazid containing synthetic metal complexes.

Keywords: Metal Based Drugs, Antibacterial, Antifungal, Anti-Tuberculosis, Anti-Cancer, DNA-Interaction and Anti-Tumor Activity

1. Introduction

Metal complexes appear to provide a rich platform for the design of novel chemotherapeutic drugs. We can choose the metal itself and its oxidation state, the numbers and types of coordinated ligands and the coordination geometry of the complexes. The ligands can not only control the reactivity of the metal, but also play critical role in determining the nature of secondary coordination sphere interactions involves in the recognition of biological target sites such as DNA, enzymes and protein receptors. Also the ligands themselves can sometimes undergo biologically-important redox reactions or other modifications (e.g hydrolysis) *in vivo* mediated by the metal. These variables provide enormous potential diversity for the design of metallo-drugs. Since its discovery in 1921, isoniazid has enjoyed a lot of attention due to its antituberculostatic, antidepressant and antibacterial properties [1]. The discovery of these properties has enabled further research on isoniazid and its derivatives [2]. Tuberculosis, caused by Mycobacterium tuberculosis (MTb), is the second leading cause of death from an infectious disease and it is surpassed by the human immunodeficiency virus (HIV) [3]. Tuberculosis (*tubercle bacillus*) that kills between 2 and 3 million people every year [4, 5] in the world. It is the only disease which does not require any vector for transportation from one person to another or to cross the physical boundary of the countries [6]. It is one of the single largest diseases encountered by both developing and developed countries [7] over the years. Despite the alarming outbreak of TB and the severe rise of MDR strains, it is prime essential to search a new vaccine or development of the BCG vaccine has been very slow. Since the discovery of rifampicin in the 1960s no new drug has been introduced in the market to treat tuberculosis [8]. WHO declared TB as a global emergency

but since that time, no new drug have successfully been developed for the treatment of the disease. With the global emergence of multidrug-resistant tuberculosis (MDRTB) and extensively drug resistant tuberculosis (XDRTB), there is an urgent need to develop more potent and fast acting anti-TB drugs with new modes of action to overcome the cross-resistance with current drugs and low toxicity profiles that can be tolerated for long period of treatment. Thus it is high time to discover highly effective metal based drugs for the complete eradiation of TB. The researchers now a day are trying to discover isoniazid containing new metal based drugs that would be most effective against TB. In this review we explored the overview application of isoniazid based metal complexes.

2. Antimicrobial Activity Studies of Isoniazid Containing Metal Complexes

Bamigboye M. O and *et al.* were synthesized $Mn^{2+,}$ Fe^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+} complexes of mixed of Trimethoprim-Isoniazid. In Trimethoprim complexes, the metal coordinated to the ligands through the nitrogen of the pyrimidine group and the nitrogen of the amine group. The antimicrobial activity of the complexes was carried out against *Staphylococcus aureus, Pseudomonas aureginosa, Klebsiella pneumonia, Escherichia coli.* The results showed that the complexes were more active than their ligands [9]. The (*E*)-*N'*-(2,5-dimethoxylbenzylidene)nicotinohydrazide) (HL) (Figure 1) was synthesized by Ogunniran Kehinde and *et al.* [10] condensing nicotinic acid hydrazide and 2,5-dimethoxylbenzaldehyde with ONO coordination pattern. *In vitro antimycobacterial* activity study of the compounds was evaluated against *Mycobacterium tuberculosis*, H37Rv, by using micro-diluted method. Some of the metal complexes displayed higher activity than the ligand (HL) and isoniazid (INH). Also some of the complexes showed moderate activity when compared to isoniazid. Generally, the results obtained revealed that the compounds exhibited promising antitubercular activity. However, the metal complexes were found to be more toxic than isoniazid drug.

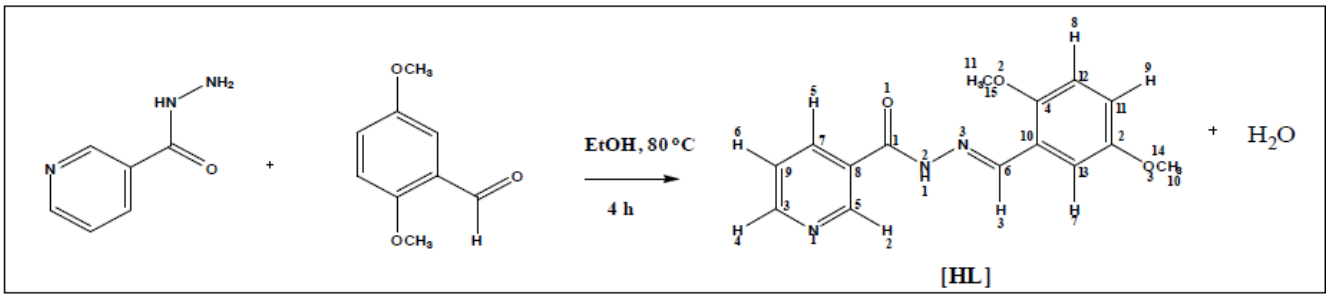

Figure 1. *Synthesis route of isonicotine hydrazone Schiff base.*

Eight complexes of Cu(II), Co(II), Ni(II) and Zn(II) with isonicotinic acid hydrazide (isoniazid, (INH)) and isonicotinic acid (1-naphthylmethylene) hydrazide (INNMH), having the formula of the type $[M(INH)(ac)_2]$ or $[M(INNMH)(ac)_2]$ (M = Co(II), Ni(II) and Zn(II)) and $[Cu(INH)(ac)_2]_2$, $[Cu(INNMH)(ac)_2]_2$, were synthesized and characterized. All complexes were characterized based on elemental analyses, and IR, UV–VIS–NIR and EPR spectroscopy, as well as by thermal analysis and determination of their molar conductivity and magnetic moments. The structure of INNMH was established by single crystal X-ray analysis (Figure 2). In all complexes, both ligands were coordinated to the metal *via* N and O. The complexes of Cu (II) were dimeric, with four bridges between acetate ions and Cu(II) [11].

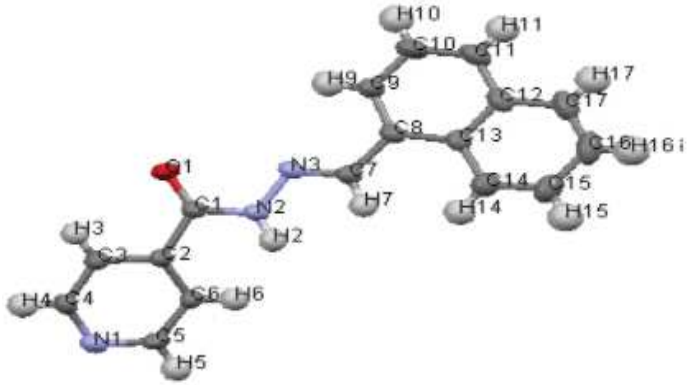

Figure 2. *The crystal structure of isonicotinic acid (1-naphthylmethylene) hydrazide, INNMH.*

Evans N. Mainsah and *et al.* [12] were prepared six isoniazid-derived Schiff bases (Figure 3) by condensation of isoniazid and various aromatic aldehydes in methanol. The complexes were synthesized in the metal to ligand molar ratio of 1:2. The ligands and the Zn(II) and Cu(II) complexes were characterized by 1H- and 13C-NMR, as well as infrared

spectroscopy. From the spectroscopic data, the ligands were found to coordinate to the central metal ions through the carbonyl oxygen atom as well as the azomethine nitrogen atom. The Zn(II) complexes were octahedral while the Cu(II) complexes were tetrahedral. The ligands and their Zn(II) complexes were inactive against microfilaria while the Cu(II) complexes showed significant activity against both micro- and microfilariae with IC50 values of 5 µg/mL and 10 µg/mL respectively.

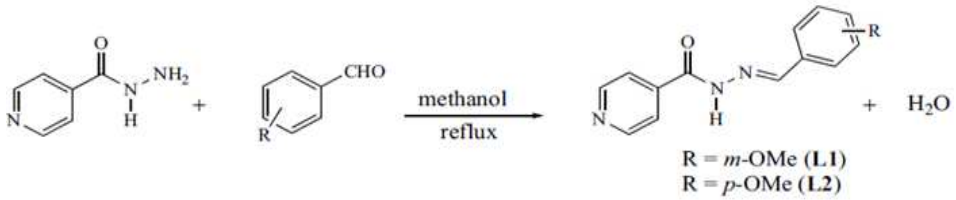

Figure 3. *Synthesis route of Schiff bases derived from isoniazid.*

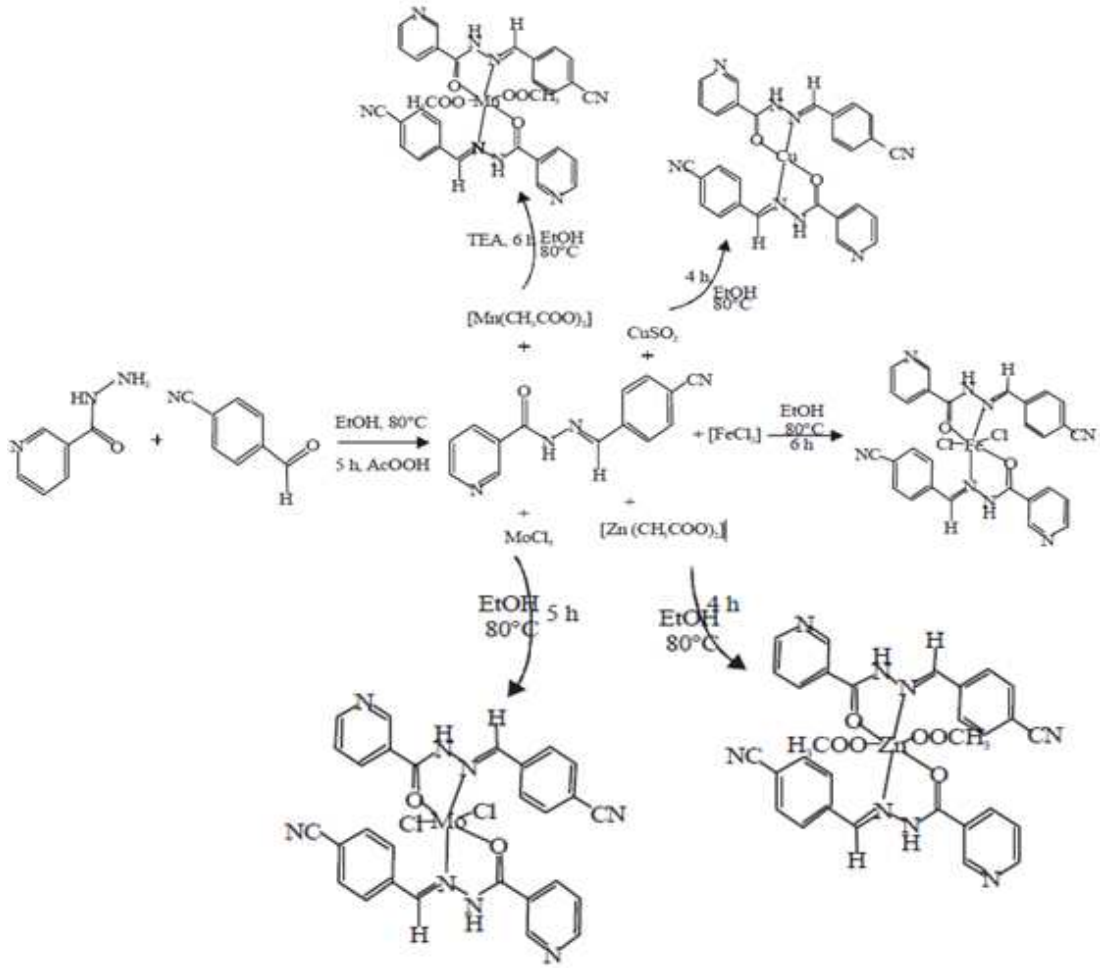

Figure 4. *Reaction path for HL[5] and its metal complexes.*

Kehinde Olurotimi Ogunnirana and *et al*. [13] were condensed Nicotinic acid hydrazide and 2,4-dihydoxylbenzaldehyde at 20°C to form an acylhydrazone (H3L1) with ONO coordination pattern. The structure of the acylhydrazone was elucidated by using CHN analyzer, ESI mass spectrometry, IR, 1H NMR, ^{13}C NMR and 2D NMR such as COSY and HSQC. Thereafter, five novel metal complexes [Mn(II), Fe(II), Pt(II) Zn(II) and Pd(II)] of the hydrazone ligand were synthesized and their structural characterization were achieved by several physicochemical methods namely: elemental analysis, electronic spectra, infrared, EPR, molar conductivity and powder X-ray diffraction studies. An octahedral geometry was suggested for both Pd(II) and Zn(II) complexes while both Mn(II) and Fe(II) complexes conformed with tetrahedral pyramidal. However, Pt(II) complex agreed with tetrahedral geometry. *In vitro* antitubercular activity study of the ligand and the metal complexes were evaluated against *Mycobacterium tuberculosis*, H37Rv, by using micro-diluted method. The results obtained revealed that (PtL1) (MIC = 0.56 mg/mL), (ZnL1) (MIC = 0.61 mg/mL), (MnL1) (MIC = 0.71 mg/mL) and (FeL1) (MIC = 0.82 mg/mL), exhibited a significant

activity when compared with first line drugs such as isoniazid (INH) (MIC = 0.9 mg/mL). H3L1 exhibited lesser antitubercular activity with MIC value of 1.02 mg/mL. However, the metal complexes displayed higher cytotoxicity but were found to be non- significant different ($P > 0.05$) to isoniazid drug. Kehinde O. Ogunniran and *et al.* [14] were syntheiszed one step condensation of nicotinic acid hydrazide and 4-cyanobenzaldehyde formed a bidentate acylhydrazone ligand (HL5). The acylhydrazone was characterized by ESI mass spectrometer, CHN analyzer, IR spectrometer, ^{1}H-NMR, ^{13}C-NMR and 2D NMR (COSY and HSQC). Thereafter, Mn(II), Mo(V), Fe(II), Cu(II) and Zn(II) complexes of the acylhydrazone ligand (Figure 4) were synthesized and characterized based on conductivity measurements, melting point determination, CHN analysis, AAS, magnetic measurement, UV/Visible study, IR spectroscopy, ESR and TGA/DTA studies. The information obtained corroborated results from powder X-ray analysis to arrive at the model structures for the complexes. *In vitro* antimycobacterial properties of the compounds were evaluated against *Mycobacterium tuberculosis* H37Rv by using micro-diluted method. The result obtained revealed that HL5, Mn(II), Mo(V), Cu(II) and Zn(II) complexes exhibited promising antitubercular activity. Zn(II) complex had the highest MIC value of 0.62 µg MLG1, while Fe(II) complex exhibited the lowest MIC value of 1.15 µg MLG1. However, the result of cytotoxicity study indicated that acylhydrazone and Zn(II) complex with IC50 of 2.17 and 1.72 µM, respectively were not toxic compared to isoniazid. Mn(II) complex was however found to be the most toxic.

Elena Pahont and et al [15] Hydrazone complexes of Cu(II), Co(II), Zn(II), Ni(II) and Pt(II) with N-isonicotinoyl-N_0-(3-metoxy-2hydroxybenzaldehyde)-hydr azone (HL) were synthesized and characterized by different physico-chemical techniques. The crystal structure of ligand was determined by single crystal X-ray diffraction studies. Spectral data showed that hydrazone behaves as an ONO tridentate ligand through the azomethine nitrogen, phenolate and keto oxygen atoms. For the copper (II) complexes, metal–ligand bonding parameters were evaluated from the EPR spectra. The effect of these complexes on proliferation of human breast cancer (MCF-7 and SKBR-3), human melanoma (A375), lung adenocarcinoma cells (NCI-H1573) and their antibacterial activity against Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Candida albicans strains were studied and compared with those of free ligand. The ligand and complexes(Figure 5) 1–3 showed significant antimicrobial activity against the Gram-positive bacteria Staphylococcus aureus and Candida albicans in comparison to the control drugs. The complexes 2–4 could be potential antitumor agents, leading to a significant improvement of the cytotoxic activity when compared with HL.

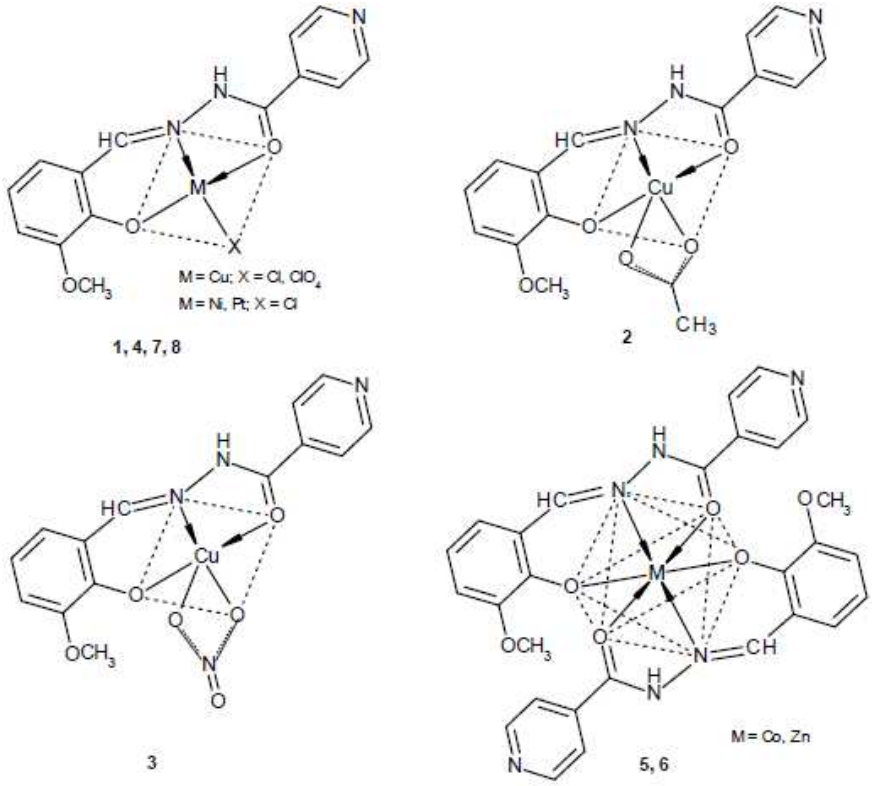

Figure 5. *Proposed structure of the metal complexes.*

Eduardo Henrique Silva Sousa and et al. [16] investigated the reactivity of isoniazid metal complexes as prototypes for novel selfactivating metallodrugs against TB with the aim to overcome resistance. Reactivity studies were conducted with hydrogen peroxide, hexacyanoferrate(III), and aquopentacyanoferrate(III). The latter species showed a

preference for the innersphere electron transfer reaction pathway. Additionally, electron transfer reaction performed with either free isoniazid or (isoniazid) pentacyanoferrate(II) complex resulted in similar oxidized isoniazid derivatives as observed when the KatG enzyme was used. However, upon metal coordination, a significant enhancement in the formation of isonicotinic acid was observed compared with that of isonicotinamide. These results suggest that the pathway of a carbonyl-centered radical might be favored upon coordination to the Fe(II) owing to the p-back-bonding effect promoted by this metal center; therefore, the isoniazid metal complex could serve as a potential metallodrug. Enzymatic inhibition assays conducted with InhA showed that the cyanoferrate moiety is not the major player involved in this inhibition but the presence of isoniazid is required in this process. Other isoniazid metal complexes, $[Ru(CN)_5(izd)]^{3-}$ and $[Ru(NH3)_5(izd)]^{2-}$ (where izd is isoniazid), were also unable to inhibit InhA, supporting our proposed self-activating mechanism of action. The authors proposed that isoniazid reactivity can be rationally modulated by metal coordination chemistry, leading to the development of novel anti-TB metallodrugs. D lesudurai & S Vancheesan [17] synthesized isoniazid containing metal carbonyl complexes and investigated their antituberculosis activity. The coordination of INH to ruthenium metal centers was investigated as a strategy to enhance the activity of this drug against the sensitive and resistant strains of MTb by Inara de Aguiar [18]. The complexes trans-$[Ru(NH_3)_4(L)(INH)]^{2+}$ (L = SO_2 or NH_3) were isolated and their chemical and antituberculosis properties studied. The minimal inhibitory concentration (MIC) data show that $[Ru(NH_3)_5(INH)]^{2+}$ was active in both resistant and sensitive strains, whereas free INH (non-coordinated) showed to be active only against the sensitive strain. The coordination of INH to the metal center in both $[Ru(NH_3)_5(INH)]^{2+}$ and trans-$[Ru(NH_3)_4(SO_2)(INH)]^{2+}$ complexes led to a shift in the INH oxidation potential to less positive values compared to free INH. Despite, the ease of oxidation of INH did not lead to an increase in the in vitro INH activity against MTb, it might have provided sensitivity toward resistant strains. Furthermore, ruthenium complexes with chemical structures analogous to those described above were synthesized using the oxidation products of INH as ligands (namely, isonicotinic acid and isonicotinamide). These last compounds were not active against any strains of MTb. Moreover, according to DFT calculations the formation of the acyl radical, a proposed intermediate in the INH oxidation, is favored in the $[Ru(NH_3)_5(INH)]^{2+}$ complex with respect to the free INH. This result suggests that the stabilization of the acyl radical promoted by the metal center would be a more important feature than the oxidation potential of the INH for the antituberculosis activity against resistant strains. Binuclear Schiff base complexes have been prepared newly using different transition metals at their stable oxidation states as Cu(II), Ni(II), and Co(II) with the ligand (L) obtained by the condensation of isoniazid and benzilmonohydrazone. The metallo- ligands as well as the macrocyclic complexes are found to have good antimicrobial activities against the pathogenic fungus *Aspergillus niger, Helminthosporium oryzae and Fusarium oxysporium*. The binuclear metal complexes were found to possess potent antimicrobial, antifungal activity better than the ligand. Isoniazid (INH) is a widely used front-line antituberculous agent with bactericidal activity at concentrations as low as 150 nM against Mycobacterium tuberculosis. INH is a prodrug and requires activation by an endogenous mycobacterial enzyme, the catalase-peroxidase KatG, before exerting toxic effects on cellular targets. Resistance to INH develops primarily through failure to activate the prodrug due to point mutations in the katG gene. In addition to mutations in katG, mutations in several other loci, such as the alkylhydroperoxidase AhpC and the enoylreductase InhA, may contribute to INH resistance. Although these markers can be used to accurately predict clinical INH resistance in a large number of cases, the molecular mechanisms involved remain largely speculative and incomplete [19]. There is a decrease in the content of nicotinamide-adenine dinucleotide of tubercle bacilli grown in the presence of isoniazid. In extracts of tubercle bacilli, the activity of nicotinamide-adenine dinucleotidase is nil or very small; after incubation with the drug the enzyme becomes active. Isoniazid also increases the activity of the enzyme after it is partially activated by heating. There may be a correlation between the capacity of isoniazid to activate the enzyme and the decrease in the dinucleotide content of the tubercle bacilli by A Bekierkunst [20]. In order to evaluate the influence of substitution on biological properties of Schiff bases, a series of differently substituted fluorine-containing Schiff bases starting from the drug isoniazid (isonicotinylhydrazide) and their Cu(II) complexes were prepared and their structures were established by single-crystal X-ray diffraction. The prepared compounds were evaluated for their antimicrobial activity and urease inhibition. Two of the Schiff bases exerted activity against *C. albicans*. All copper(II) complexes showed excellent inhibitory properties against jack bean urease, considerably better than that of the standard inhibitor acetohydroxamic acid [21].

The N, N, O metal chelator 2-pyridinecarboxaldehyde isonicotinoyl hydrazone (HPCIH, 1) and its derivatives 2-acetylpyridine-(HAPIH 2), 2-pyridineformamide-(HPAmIH, 3) and pyrazineformamide-(HPzAmIH, 4) were employed in the synthesis of four copper(II) complexes, $[Cu(HPCIH)Cl_2].4H_2O$ (5), $[Cu(HAPIH)Cl_2].5H_2O$ (6), $[Cu(HPAmIH)Cl_2]\cdot H_2O$ (7) and $[Cu(HPzAmIH)Cl_2]\cdot 5H_2O$ (8). The compounds were assayed for their action toward Mycobacterium tuberculosis H37Rv ATCC 27294 strain and the human tumor cell lines OVCAR-8 (ovarian cancer), SF-295 (glioblastoma multiforme) and HCT-116 (colon adenocarcinoma). All copper(II) complexes were more effective in reducing growth of HCT-116 and SF-295 cells than the respective free hydrazones at 5 μg/mL, whereas only complex 7 was more cytotoxic toward OVCAR-8 lines than its ligand HPAmIH. 6 proved to be cytotoxic at submicromolar doses, whose IC50 values (0.39–0.86 μM) are similar to those ones found for doxorubicin (0.23–0.43 μM). Complexes 5 and 6 displayed high activity against M.

tuberculosis (MIC = 0.85 and 1.58 μM, respectively), as compared with isoniazid (MIC = 2.27 μM), which suggests the compounds are attractive candidates as antitubercular drugs [22]. A heterocyclic hydrazide-hydrazone derived from isoniazid namely 2-hydroxy-5- methoxybenzaldehyde isonicotinoylhydrazone (MSINH) and its Zinc (II), Nickel (II), Manganese (II) and Copper (II) complexes were synthesized by M. K. Prasanna and et al. [23]. The authors have proposed a tetrahedral geometry to the Zinc, square planar to the Nickel and Copper and octahedral geometries to the Manganese complexes. Ligand and complexes were subjected to antibacterial and antifungal studies and it was found that Copper(II), Nickel(II) and Manganese (II) complexes have moderate activity against gram positive *Staphylococcus aureus* and gram negative *E. Coli*, whereas the ligand and other complexes have no notable activity against the tested bacterial species. Among the compounds reported in this work Zinc complex showed the highest antifungal activity against the fungal species *Aspergillus flavus*. Antitumour studies revealed that the ligand (MSINH) and its copper complex have promising antitumour activities. Pd(II) and Pt(II) complexes of two isoniazid Schiff bases, N-isonicotinamido-2-furanketimine (INH-F1) and N-isonicotinamido-5-methyl-2-furanketimine (INH-F2), possessing potential N and O coordination sites have been prepared by the reaction of isoniazid with 2-acetylfuran and 2-acetyl-5-methylfuran, respectively. In all the complexes, the monobasic bidentate nature of the ligand is evident. Antibacterial and antifungal studies of these compounds against various pathogenic bacterial and fungal strains have been carried out. Both the ligands and their metal chelates were active against all the microbial strains investigated. However, the chelates were found to be more active than the ligands. The antimycobacterial activity of the ligands and their metal complexes has been evaluated against Mycobacterium smegmatis, which showed clear enhancement in this activity upon metal complexation with Schiff bases [24].

Novel redox-active metallotherapeutic agents were used to develop effective antimicrobial remedies differing from standard antibiotics in their mechanism of action with participation of free-radical intermediates. For this purpose redox-active compounds carrying sterically hindered 1,2-dihydroxybenzene moieties along with metal ions in a single scaffold have been synthesized and characterized by means of chemical and physicochemical methods as well as screened for their antimicrobial activity against Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens), Gram-positive bacteria (*Bacillus subtilis, Sarcina lutea, Staphylococcus aureus, Mycobacterium smegmatis*), yeasts (*Cryptococcus laurentii, Lipomyces lipofer, Candida albicans, Candida boidinii, Candida utilis, Saccharomyces cerevisiae*) and fungi (*Aspergillus niger, Alternaria alternata, Mucor spp., Botrytis cinerea, Monilia spp, Fusarium spp., Penicillium lividum, Sclerotinia sclerotiorum*). This screening revealed silver(I) complexes that may be considered as potential chemotherapeutic agents with activity higher than or comparable to that of some standard drugs such as tetracycline, streptomycin, chloramphenicol, isoniazid, amphotericin B, fluconazole, terbinafine. Using the method of cyclic voltammetry, we have shown some phenolic ligands as well as their silver(I) complexes to be also of a pronounced reducing ability. Bacterial cytochrome c-like enzymes being among the first targets for redox-active antimicrobials on their way into the cell, spectrophotometric investigation was carried out in order to estimate the rate of bovine heart cytochrome c reduction with the compounds synthesized. Oxidation of 1, 2-dihydroxybenzene derivatives and their silver(I) complexes in vitro under anaerobic conditions can include two successive one-electron steps of oxidation of their ionic forms to yield o-benzoquinones on interaction with cytochrome c via intermediate o-benzosemiquinone formation [25]. Some isonicotinoyldithiocarbazate complexes of nickel(II) and copper(II), of general formulae $M(IN\text{-}Dtcz)_2$, $[M(IN\text{-}DtczH)_2]Cl_2$, and $[M(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$ (M = Ni(II), Cu(II); INDtcz = isonicotinoyldithiocarbazate; IN-DtczH = isonicotinoyldithiocarbazic acid; IN-DtczH-Sal = salicylaldehyde Schiff base of isonicotinoyldithiocarbazic acid), have been synthesized. The three nickel(II) dithiocarbazates and $[Cu(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$ exhibit NS linkage of the ligands, while $Cu(IN\text{-}Dtcz)_2$ and $[Cu(IN\text{-}DtczH)_2]Cl_2$ have ONS binding of the ligands. The nickel(II) dithiocarbazates have $[NiN_2S_2]$ chromophore. Magnetic and solution electronic absorption spectral data reveal square-planar geometry for $Ni(IN\text{-}Dtcz)_2$ and the existence of square-planar–tetrahedral equilibrium for $[Ni(IN\text{-}DtczH)_2]Cl_2$ and $[Ni(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$. Copper(II) dithiocarbazates, namely $Cu(IN\text{-}Dtcz)_2$, $[Cu(IN\text{-}DtczH)_2]Cl_2$, with ONS ligands having dimeric or polymeric octahedral structures, and $[Cu(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$, with NS binding having dimeric square-planar structure, exhibit antiferromagnetism. Super exchange pathway involving the bridging nitrogen and sulfur of the isonicotinoyl dithiocarbazate ligands rather than direct metal–metal exchange is suggested for antiferromagnetic interactions. The spin exchange parameter, $-2J$ = 202.14 and 29.26 cm, has been evaluated for $[Cu(IN\text{-}DtczH)_2]Cl_2$ and $[Cu(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$, respectively, while it could not be evaluated for $Cu(IN\text{-}Dtcz)_2$ because the slope was negative due to the non-variation of its magnetic moment with temperature. The difference in antiferromagnetic behavior and inconsistency of 2J for $[Cu(IN\text{-}DtczH\text{-}Sal)_2]Cl_2$ has been attributed to different electronic and steric factors of the three ligands, that is, isonicotinoyl dithiocarbazate, its acid, and salicylaldehyde Schiff-base derivative [26]. A novel ligand (H_2L), diethylenetriamine-N,N′,N″-triacetylisoniazide N,N″-bisacetic acid, and its four non-ion transition metal complexes, $ML \cdot nH_2O$ (M = Mn, n = 4; M = Co, Ni, n = 2; M = Cu, n = 1), have been synthesized and characterized by Ding-Wa Zhang and et al. [27]. In addition, relaxivity (R^1) of the complexes was determined, the relaxivity of MnL, CoL, NiL, CuL as well as $Gd(DTPA)^{2-}$ used as a control are 6.94, 2.79, 2.52, 1.59 and 4.34lmmol−1s−1, respectively. The relaxivity of MnL is larger than that of $Gd(DTPA)^{2-}$. The

results show that the complex of MnL may be a potential MRI contrast agent. The ligand 1-phenyl-3-methyl-5-hydroxy-4-pyrazolyl phenyl ketone (PMBP) isonicotinoyl hydrazone (H_2L) was prepared by condensation of PMBP with isoniazid. Seven complexes of rare earth metals with H_2L were synthesized and characterized by Zheng-Yin Yang and *et al*. [28]. The general formula of the complexes is $Ln(HL)_3 \cdot 3.5H_2O$ (where Ln(III)=La, Eu, Gd, Tb, Dy, Ho and Er). X-ray diffraction analysis showed that the coordination polyhedron of the Eu complex is a tricapped trigonal prism. The La and Eu complexes possess antitumor activity, and the inhibitory rates for leukemia cells (L1210) are 87.1% and 78.5%, respectively. Isonicotinoylhydrazide Schiff's bases formed by the reaction of substituted and unsubstituted furyl-2-carboxaldehyde and thiophene-2-carboxaldehyde with isoniazid and, their Co (II), Cu (II), Ni (II) and Zn (II) complexes have been synthesized, characterized and screened for their in vitro antibacterial activity against Mycobacterium tuberculosis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Shigella dysenteriae, Bacillus cereus, Corynebacterium diphtheriae, Staphylococcus aureus and Streptococcus pyogenes bacterial strains and for in vitro antifungal activity against Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani and Candida glabrata. The results of these studies show the metal complexes to be more antibacterial and antifungal against one or more bacterial/fungal strains as compared to the uncomplexed compounds [29]. Arun Srivastava was synthesized Cu(II) complexes containing isoniazid derivatives as ligand and investigate their antiviral activity [30]. The 3d transition metal complexes of isonicotinoyl hydrazone derived from isoniazid with l-phenyl-3-methyl-4-benzoyl-5-pyrazolone (PMBP) have been synthesized and characterized by Zheng-Yin Yang [31]. The general formula of the complexes is $ML\ nH_2O$ (where M(II) = Cr, Mn, Fe, Co, Ni and Cu, n = 0, 1). It has been discovered that the complexes possess certain scavenger effects on O^{2-} radicals. K P Deepa and et al. [32] synthesized five new metal chelates of omega-bromoacetoacetanilide isonicotinylhydrazone. The ligand behaved as a tridentate monoanion or as a tridentate dianion in the complexes. They also carried out antifungal studies of these compounds against four selected pathogenic fungal strains using a cup-plate technique. Both the ligand and its metal chelates were active against all fungal strains investigated. However, the chelates were found to be more active than the ligand. Isoniazid, an anti-tuberculosis (TB) drug has been coordinated with chromium, molybdenum, and tungsten metal carbonyls and three new zero-valent complexes fac-$[M(CO)_3(isoniazid)_3]$ (M = Cr, Mo, and W; 4, 5, and 6) (isoniazid = 4-$H_2NHNOCC_5H_4N$) have been synthesized by Jesudural D and et al. [33]. Reaction of the complex precursors fac-$[M(CO)_3(CH_3CN)_3]$ (M = Cr, Mo, and W; 1, 2, and 3) prepared 'in situ' with three equivalents of isoniazid in methanol at room temperature afforded high yields of isoniazid substituted metal carbonyl complexes 4, 5, and 6. The bulky -$CONHNH_2$ group of isoniazid molecules made more impact on the M-C bond strength of metal carbonyls and affects their fundamental modes of vibrations leading to the appearance of more number of v(C≡O) bands. These steric effects are also reflected in the 1H NMR spectral features of the complexes when considering the complexes as a whole, wherein the four protons on the pyridine ring of the coordinated isoniazid molecules resonate at different chemical shifts. All the three complexes exhibit similar XRD pattern suggesting similar geometry. An isonicotinoyl dithiocarbazic acid (IN-DtczH) ligand, synthesized from isoniazid, was complexed with transition metals and evaluated for anti-mycobacterial activity as well as toxicity towards human-transformed rhabdomyosarcoma (RD) cells in vitro by Shamsher Singh Kanwar [34]. Complexes with Ni, Co and Zn showed MIC of 2, 2 and 50 μg/ml against Mycobacterium tuberculosis H37Rv, and 10, 100 and 50 μg/ml against a multidrug-resistant strain of M. tuberculosis. They had little cytotoxic effect on the RD cells. In contrast, the Cu complex was highly cytotoxic with a low anti-mycobacterial activity. Formation constants for copper (II) and zinc(II) complexes of isonicotinoylhydrazine (isoniazid) and guanosine-5'-monophosphate have been measured potentiometrically at 37 degrees C, I = 150 mmol dm^{-3} [NaCl]. These constants have been used in computer models to assess the extent of complex formation by the drug in vivo. The simulations indicate that the predominant complexes existing in blood plasma are ternary species formed with histidinate. However, at clinical levels of isoniazid, it seems unlikely that these complexes are physiologically significant. On the other hand, ternary complex formation with nucleosides may be involved in the binding of isoniazid to viral RNA [35].

3. Conclusion

Isoniazid is considered as anti-tuberculosis drugs over the years decay. Schiff base derived from isoniazid and their transition and inner transition metal complexes have been shown moderate to strong antimicrobial activity. In this review we have explored the various synthesis routes of Schiff bases, their metal complexes and their antibacterial antiviral antifungal anti-tuberculosis activities.

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