Review Article

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

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To cite this article:
Md. Saddam Hossain, Md. Abdul Mannan, F. K. Camellia, A. K. B. Zaman, C. M. Zakaria, Md. Kudrat-E-Zahan. Isoniazid Containing Metal Based Drugs as Potential Antimicrobial Agent: A Short Review. Science Journal of Chemistry. Vol. 5, No. 5, 2017, pp. 62-70.
doi: 10.11648/j.sjc.20170505.11

Received: July 17, 2017; Accepted: July 31, 2017; Published: September 18, 2017

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 eradication 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-dimethoxybenzylidene)nicotinohydrazide) (HL) (Figure 1) was synthesized by Ogunniran Kehinde and et al. [10] condensing nicotinic acid hydrazide and 2,5-dimethoxybenzaldehyde 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. 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.

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)$_2$], [Cu(INNMH)(ac)$_2$], were synthesized and characterized. All complexes were characterized based on elemental analyses, 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].

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.

Kehinde Olurotimi Ogunnirana and et al. [13] were condensed Nicotinic acid hydrazide and 2,4-dihydroxybenzaldehyde 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, 13C 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 synthesized 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, 1H-NMR, 13C-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), Fe(II), 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,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 metallo drugs against TB with the aim to overcome resistance. Reactivity studies were conducted with hydrogen peroxide, hexacyanoferrate(III), and aquopentacyanofer rrate(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 cyanoferate 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(NH3)5(izd)]4+ and [Ru(NH3)3(izd)]5+ (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 metallo-drugs. D lesudurai & S Vancheesam [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(NH3)5(INH)]7+ (L = SO2 or NH3) were isolated and their chemical and antituberculosis properties studied. The minimal inhibitory concentration (MIC) data show that [Ru(NH3)5(INH)]7+ 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(NH3)5(INH)]7+ and trans-[Ru(NH3)4(SO2)(INH)]10+ 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(NH3)5(INH)]7+ 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 macroyclic complexes are found to have good antimicrobial activities against the pathogenic fungus Aspergillus niger, Helminthosporium oryzae and Fusarium oxysporum. The bimetallic metal complexes were found to possess potent antimicrobial, antifungal activity better than the ligand. Isoniazid (INH) is a widely used front-line antitubercular agent with bactericidal activity at concentrations as low as 150 nM against Mycobacterium tuberculosis. INH is a prodrg 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 prodrg due to point mutations in the katG gene. In addition to mutations in katG, mutations in several other loci, such as the alkylhydroperoxidase AphC 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 dinucleotide 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 acetylohydroxamic acid [21].

The N, N, O metal chelator 2-pyridinecarboxaldehyde isonicotinoyl hydrazide (HPCIH, 1) and its derivatives 2-acetylpyridine-(HAPII 2), 2-pyridineformamid-(HPAmI, 3) and pyrazineformamide-(HPzAmI, 4) were employed in the synthesis of four copper(II) complexes, [Cu(HPCIH)Cl2.4H2O (5), [Cu(HAPII)Cl2.5H2O (6), [Cu(HPAmI)Cl2.5H2O (7) and [Cu(HPzAmI)Cl2.5H2O (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 hydrazines at 5 μg/mL, whereas only complex 7 was more cytotoxic toward OVCAR-8 lines than its ligand HPAmI. 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-hydrazine derived from isoniazid namely 2-hydroxy-5- methoxybenzaldehyde isonicotinoylhydrazine (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. Antimour 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 lirvidum, 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-benzoquinolium formation [25]. Some isonicotinoyldithiocarbazate complexes of nickel(II) and copper(II), of general formulae M(IN-DtczH), [M(IN-DtczH-Sal)]Cl₂, [NH₂(IN-DtczH-Sal)]Cl₂ and [M(IN-DtczH-Sal)Ni]Cl₂ (M = Ni(II); Cu(II); NĐtcz = 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-DtczH-Sal)Cl₂] exhibit NS linkage of the ligands, while Cu(IN-DtczH)₂Cl₂ and [Cu(IN-DtczH)₂]Cl₂ have CNS binding of the ligands. The nickel(II) dithiocarbazates have [NiN₂S₂] chromophores. Magnetic and solution electronic absorption spectral data reveal square-planar geometry for Ni(IN-DtczH)₂ and the existence of square-planar–tetrahedral equilibrium for [Ni(IN-DtczH-Sal)]Cl₂ and [Ni(IN-DtczH-Sal)Ni]Cl₂. Copper(II) dithiocarbazates, namely Cu(IN-DtczH)₂, [Cu(IN-DtczH-Sal)]Cl₂, with ONS ligands having dimeric or polymeric octahedral structures, and [Cu(IN-DtczH-Sal)Ni]Cl₂, 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-DtczH)]Cl₂ and [Cu(IN-DtczH-Sal)]Cl₂, respectively, while it could not be evaluated for Cu(IN-DtczH) 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-DtczH-Sal)]Cl₂ 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 (H₂L), diethylentetramine-N,N',N''-triacetylsisoniazide N,N''-bisacetic acid, and its four non-iron transition metal complexes, ML₂.nH₂O (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 (R₁) 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 4.34 mmol−1 s−1, respectively. The relaxivity of MnL is larger than that of Gd(DTPA)²⁻.
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.

3. Conclusion

Acknowledgements

The authors are greatly thankful to the Chairman Department of Chemistry, University of Rajshahi, Bangladesh.

References

[1] Zhang, Y.; Young, D. B. (1993) Molecular mechanisms of isoniazid: A drug at the front line of tuberculosis control. Trends Microbial., 1, 109–113.
[2] Vikranjeet, J.; Balasubramanian, N.; Munish, A. (2012) Isoniazid: The magic molecule. Med. Chem. Res., 21, 3940–3957.

[3] WHO, 2009, Treatment of tuberculosis: guidelines. WHO, 2012, Global Tuberculosis Control: WHO report 2011.

[4] M. C. D. S. Lourenco, M. D. L. Ferreira, M. V. N. De Souza, M. A. Peralta, T. R. A. Vasconcelos, M. D. O. Henriques, Eur. J. Med. Chem. 43, 1344 (2008).

[5] T. Aboul-Fadl, F. A. S. Bin-Jubair, O. Aboul-Wafa, (2010) Eur. J. of Med. Chem. 45, 4578.

[6] M. Shahar Yar, M. A. Ali, M. M. Abdullah, (2007) Med. Chem. Res., 16, 292.

[7] M. V. N. De Souza, Drug Discovery 1, 33 (2006).

[8] T. Aboul-Fadl, H. A. Abdel-Aziz, M. K. Abdel-Hamid, T. Elsaman, J. Thanassi, M. J. Pucci, Molecules 16, 7864 (2011).

[9] Bagmigboyo M. O, Obayele J. A Lawal M. and Aluko O. M. (2012) Synthesis, Characterization and Antimicrobial Study Of Mixed Isoniazid-Trimethoprim Metal Drug Complexes. Chemistry and Materials Research. 2(3): 1-8.

[10] Elsamane, J. Thanassi, M. J. Pucci, Molecules 16, 7864 (2011).

[11] M. V. N. De Souza, Drug Discovery 1, 33 (2006).

[12] Elsaman, J. Thanassi, M. J. Pucci, Molecules 16, 7864 (2011).

[13] M. V. N. De Souza, Drug Discovery 1, 33 (2006).

[14] T. Aboul-Fadl, H. A. Abdel-Aziz, M. K. Abdel-Hamid, T. Elsaman, J. Thanassi, M. J. Pucci, Molecules 16, 7864 (2011).

[15] Bagmigboyo M. O, Obayele J. A Lawal M. and Aluko O. M. (2012) Synthesis, Characterization and Antimicrobial Study Of Mixed Isoniazid-Trimethoprim Metal Drug Complexes. Chemistry and Materials Research. 2(3): 1-8.

[16] Eduardo Henrique Silva Sousa, Luiz Augusto Basso, Dio’ genes S. Santos, Izaura Cirino Nogueira Dio’ genes. (2012) Elisane Longhinotti, Luiz Gonzaga de Fran‡e, Lopes, I’ caro de Souza Moreira. Isoniazid metal complex reactivity and insights for a novel anti-tuberculosis drug design. J Biol Inorg Chem 17: 275–283.

[17] D lesudurai & S Vanchesasan, (2003) Coordination of isoniazid, an anti-tuberculosis (TB) drug with chromium, molybdenum, and tungsten metal carbonyls. Indian Journal of Chemistry, 42(A): 1609-1616.

[18] Inara de Aguier, Aline Tavares, Antonio. Roveda Jr. Augusto C. H. da Silva, Leonardo B. Marino, Érica O. Lopes, Fernando R. Pavan, Luiz G. F. Lopes. (2015) Antitubercular activity of Ru (II) isoniazid complexes. European Journal of Pharmaceutical Sciences 70: 45–54.

[19] N. Panda, S. K. Tripathy, N. K. Behera, A. K. Panda, P. K. Das, (2015) Synthesis, Spectroscopic and Anti-microbial studies of Binuclear Schiff Base Complexes derived from the Ligand prepared from Isoniazid and Benzilmonohydrazone. International Journal of Innovative Science, Engineering & Technology, 2(4): 783-795.

[20] A Bekier kunst, (1966) Nicotinamide-Adenine Dinucleotide in Tubercle Bacilli Exposed to Isoniazid, Science, 152(3721): 525.

[21] Ladi slav Habala, Samuel Varényi, Andrea Bil kova, (2016) Antimicrobial Activity and Urease Inhibition of Schiff Bases Derived from Isoniazid and Fluorinated Benzaldehydes and of Their Copper(II) Complexes, Molecules, 21(12): 1742.

[22] Gisele S. S. Firmin o, Marcus Vinicius Nora de Souza, Claudia Pessa o, Josane A. Lessa, (2016) Synthesis and evaluation of copper(II) complexes with isoniazid-derived hydrazones as anticancer and antitubercular agents. Bio Metals 29(6): 47-51.

[23] M. K. Prasanna, K. K. Pradeep, (2013) Synthesis, characterisation and antimicrobial studies of transition metal complexes of 2-hydroxy-5-methoxybenzaldehydeisonicotinoylhydrazone. Research Journal of Chemistry and Environment, 17(6): 61-67.

[24] Krishna K. Sharma, Ritu Singh, Nighat Fahmi, R V Singh. (2010) Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid-derived hydrazones as anticancer and antitubercular agents. Bio Metals 29(6): 47-51.

[25] N. V. Log inova, T. V. Koval’chuk, V. M. Shkumatov, (2010) Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid Schiff bases. Journal of Coordination Chemistry 63(17): 3071-3082.

[26] N. V. Log inova, T. V. Koval’chuk, V. M. Shkumatov, (2010) Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid Schiff bases. Journal of Coordination Chemistry 63(17): 3071-3082.

[27] N. V. Log inova, T. V. Koval’chuk, V. M. Shkumatov, (2010) Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid Schiff bases. Journal of Coordination Chemistry 63(17): 3071-3082.

[28] N. V. Log inova, T. V. Koval’chuk, V. M. Shkumatov, (2010) Synthesis, coordination behavior, and investigations of pharmacological effects of some transition metal complexes with isoniazid Schiff bases. Journal of Coordination Chemistry 63(17): 3071-3082.
[28] Zheng-Yin Yang, Ru-Dong Yang, Kai-Bei Yu, (2000) Crystal structure and antitumor activity of some rare earth metal complexes with Schiff base. Polyhedron, 19(26-27): 2599-2604.

[29] Zahid H Chohan, M. Arif, Zahid Shafiq, Muhammad Yaqub, (2006) In vitro antibacterial, antifungal & cytotoxic activity of some isonicotinoylhydrazide Schiff’s bases and their cobalt (II), copper (II), nickel (II) and zinc (II) complexes, Journal of Enzyme Inhibition and Medicinal Chemistry, February; 21(1): 95–103.

[30] Arun Srivastava, (2014) Antiviral Activity of Copper Complexes of Isoniazid against RNA Tumor Viruses, Resonance, 754-760.

[31] Zheng-Yin Yang, (2000) Synthesis, Characterization and Scavenger Effects on $O_2^-$ of 3d Transition Metal Complexes of Isonicotinoyl Hydrazone Derived from Isoniazid with PMBP, Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry, 30(7): 1265-1271.

[32] K P Deepa, K. K. Aravindakshan, (2004) Synthesis, Characterization, and Antifungal Studies of Transition Metal Complexes of α-Bromoacetacetanilide Isonicotinylhydrazine, Applied Biochemistry and Biotechnology 118(1-5): 283-92.

[33] Jesudural D, S. Vancheesan, (2003) Coordination of isoniazid, an anti- tuberculosis (TB) drug with chromium, molybdenum, and tungsten metal carbonyls, Indian Journal of Chemistry Section a 42A(7): 1 609-1616.

[34] Shamsher Singh Kanwar, Kamakshi Lumba, S. B. Kalia, (2008) Synthesis and mycobactericidal properties of metal complexes of isonicotinoyldi thiocarbazic acid. Biotechnology Letters 30(4): 677-80.

[35] A Cole, P M May, D R Williams, (1983) Metal binding by pharmaceuticals. Part 3. Copper (II) and zinc (II) interactions with isoniazid, Agents and Actions 13(1): 91-97.