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A REVIEW OF BIOLOGICAL APPLICATIONS OF TRANSITION METALS SCHIFF BASE COMPLEXES SYNTHESIZED FROM ISONIAZID

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ABSTRACT

Schiff bases are compounds containing the azomethine (-C=N-) functional group in their structures. They are versatile ligands which are synthesized from the condensation of primary amines with carbonyl compounds. Works on Schiff bases are rapidly developing from the simple fact that Schiff base ligands are easily prepared and have potentials to form very stable metal complexes. Schiff bases and their transition metal complexes have been extensively studied and known to show a wide spectrum of biological activities, catalytic, analytical and industrial applications. Isoniazid contains free NH_2 group which reacts with carbonyl compounds to form various Schiff base ligands. Therefore this review focused only on the biological applications of Schiff bases derived from isoniazid in the area of preclinical pharmacological screenings like anti-bacterial, anti-fungal, anti-tuberculosis, anti-inflammatory, anti-cancer, DNA- interaction and anti-tumor action.

Key words: Isoniazid, Schiff bases, complexes, biological, applications.

INTRODUCTION

Isoniazid goes by various trade names such as isonicotinylhrazide (INH), isonicotinic acid hydrazide or pyridine-4-carbohydrazide [1-4]. It is a nicotinamide analogue made up of a pyridine ring and a hydrazide group [5-7]. The structure of isoniazid (Fig. 1a) also consist of a carbonyl (C=O) group and an amino group (NH_2) through which it undergoes several chemical reactions [8-10]. The presence of the free NH_2 group in the hydrazine moiety makes it possible for isoniazid to react with various carbonyl compounds to form various Schiff bases [11-14]. It has been a front line drug for the treatment of tuberculosis since 1952 because of its great effect on *M. tuberculosis* [15-18]. It was first prepared in 1912 but its importance was not known until in 1952 when it was found to have antibacterial properties [9][19-20].

Studies have shown that INH forms complexes with the transition metal ions easily because it possesses donor atom such as carbonyl oxygen, hydrazide nitrogen and amino nitrogen atoms [21-23]. The process of formation of the complexes by INH begins with the formation of its anion chelating specie as shown in Fig. 1b [24]. Research has shown that acetylation tends to reduce the therapeutic properties of isoniazid [25-26]. Therefore to achieve better biological activities, the hydrazine unit of the INH is modified by addition of a substituent that prevents acetylation [1][27-28]. Conversely, substitution at the C2 position of the pyridine ring could lead to modification of the INH structure. The substituent here could be *O*-derivatives, phenyl analogues, halogenated derivatives and alkyl derivatives [29-31]. When such modifications occur, they lead to increased anti-tubercular activities of the INH [32-33]. The metal complexes formed by INH and hydrazones have been found to show better biological properties than only INH [][34-38]. For example, incorporation of Zn and Cu ions into isoniazid formed square planar complexes with improved anti-tubercular properties [21]. Also, Co(II) and Zn(II) trimethoprim-isoniazid complexes have been reported to give better anti-tubercular properties than INH [39-40]. Cu(II) N-isonicotinoyl-N-(3-methoxy-2-hydrobenzaldehyde)-hydrazone was also found to show better anti-tubercular properties than isoniazid [38]. Apart from biological activities, complexes of INH have been used as excellent analytical reagents. This is because of their ability to produce absorption spectra with metal ions. [41]. However, this review will focus on the biological applications of Schiff base and complexes synthesized from isoniazid.

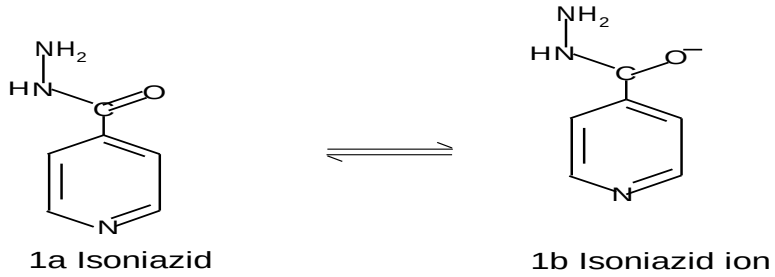
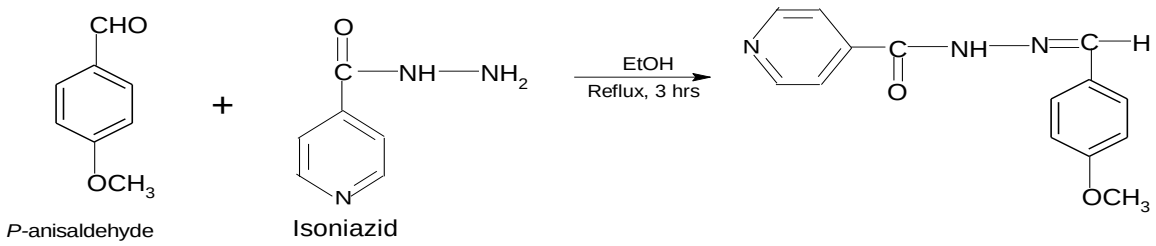


Fig. 1a and 1b: Isoniazid and its anion.

The synthesis of Schiff base ligands from isoniazid and *p*-anisaldehyde (L1) and 2,2-bipyridine (L2) (Scheme 1) and its Cu(II) and Ni(II) mixed ligand complexes (Fig. 2) have been published [43]. The complexes were found to be square planar with the formula $[M(L1)(L2)]^{2+}$ where M= Cu(II) or NI(II). The ligand (L1) was mixed with the Cu(II) and Ni(II) ions and ligand L2 to obtain the mixed ligand complexes- $[Cu(L1)(L2)](NO_3)_2$ and $[Ni(L1)(L2)](NO_3)_2$. These

complexes were screened against *E. coli* and *B. cereus* strains by Kirby Bauer's disc diffusion technique. The zones of inhibition produced by L1 was 4 mm for each of the strains while that of the complexes were between 12-22 mm compare to 32 and 35 mm obtained for kanamycin on *E. coli* and *B. cereus* respectively.



Scheme 1: Synthesis of Schiff base from isoniazid and p-anisaldehyde (L1)

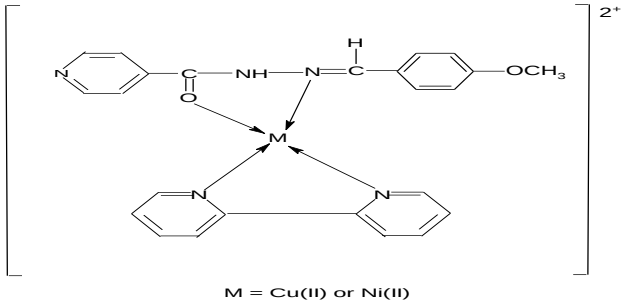
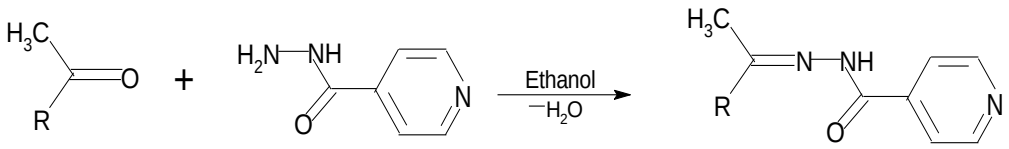


Fig. 2: Mixed ligand complexes obtained from isoniazid, p-anisaldehyde and 2,2-bipyridine

The synthesis of four imines of ethanone isonicotinoylhydrazone was reported by Gurjar *et al*. [43] in Scheme 2. The manganese(II) complex of each of the imines was prepared. The synthesized compounds were seen to have different colours depending on their wavelength of maximum absorptions. The melting points of the compounds were found to be high (134-248 ^{o}C) with magnetic moments between 5.73-6.05 BM. The compounds had a molar ratio of 1:1 and were of the formula $MnCl(L)(H_2O)$. From the infrared spectra data of the ligands and complexes coupled with the observed uv transitions, tetrahedral geometry were assigned to the complexes. The zones of inhibition recorded on *Candida albicans*, *Aspergillus niger*, *Bacillus subtilis* and *Eschirichia coli* were high (19.0-38.0 mm). These high zones of inhibition show that the compounds have excellent antimicrobial strength.



Where R= 2-furanyl, 2-thienyl, 2-pyridyl and 2-naphthyl

Scheme 2: Synthesis of ethanone isonicotinoylhydrazones

The synthesis of (Z)-N'- benzylideneisonicotinohydrazide, (SBBZINH); L1 and (E)-N'-(4-chlorobenzylidene)isonicotinohydrazide, (SBCBZINH); L2 and their four oxovanadium (IV) complexes (Fig. 3) have been reported by Shukla *et al.* [44]. The ligands L1 and L2 were synthesized by condensing isonicotinylhydrazide with benzaldehyde (L1) and isonicotinylhydrazide with p-chlorobenzaldehyde (L2) in ethanol. The anti-diabetic activities of the compounds were examined through the inhibition of α-amylase, an enzyme active in the digestion of starch, which thus reduces the absorption of glucose. The complexes showed good amylase percentage inhibition in the range of 60-72.34%. All the ligands and their metal complexes were screened for antibacterial activity on *Escherichia coli* by the agar well diffusion method while the MIC evaluation was carried out by successive dilution method. The order of *Escherichia coli* growth inhibition by the synthesized compounds was 2> 4> 3> 1> L1>L2 while the MIC was between 30-35 µg/mL.

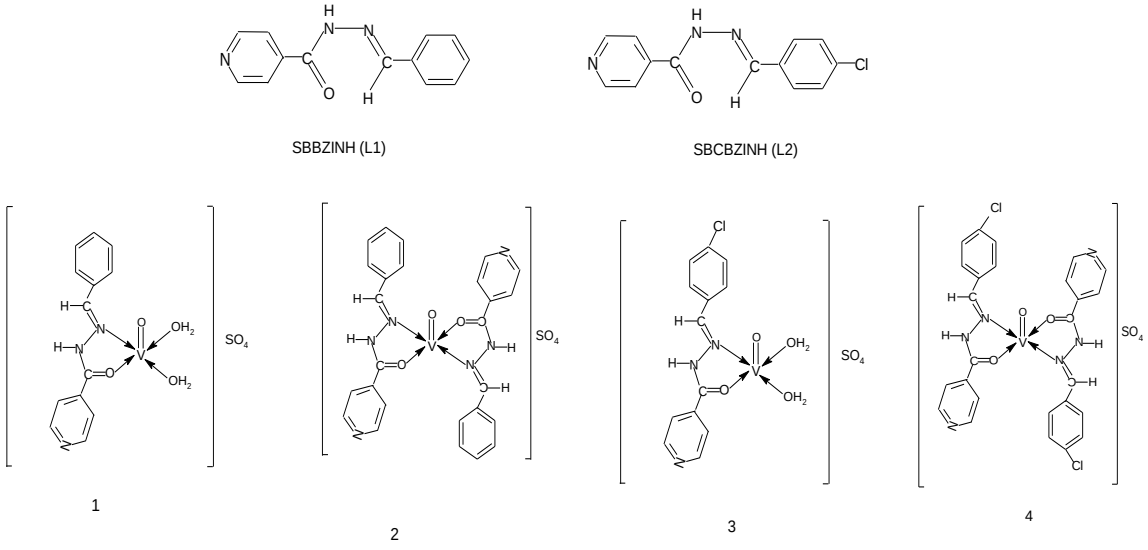
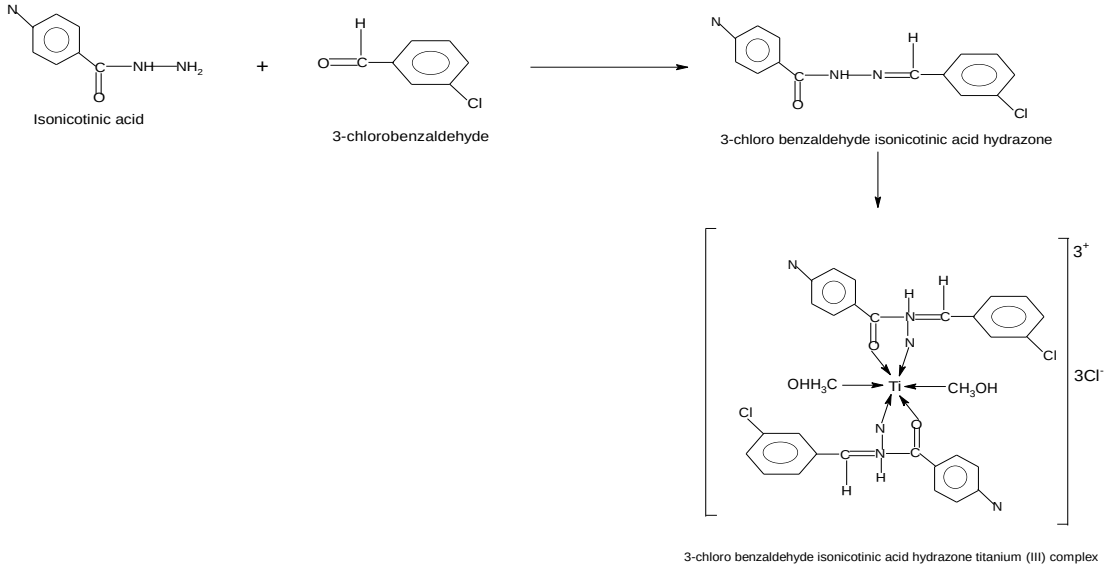


Fig. 3: SBBZINH, SBCBZINH and four oxovanadium (IV) complexes

The Schiff base, 3-chlorobenzaldehyde-isonicotinic acid hydrazone have been prepared from isonicotinic acid and 3-chlorobenzaldehyde [45]. The Schiff base ligand had a high melting point (171 ^{o}C) and was soluble in DMSO. The ligand was used to prepare the titanium (Ti^{3+}) complex as proposed in Scheme 3. The elemental analysis proved that the complexes had a formula of $[C_{13}H_{10}N_3OCl].2CH_3OH.TiCl_3$ with a M:L ratio of 1:2 while the magnetic moment was 1.70 BM. The spectroscopic analysis revealed that the ligand was tridentate while the complex had an octahedral geometry. The ligand displayed higher inhibition (20 mm) against *A. niger* than the Ti^{3+} complex (14 mm).



Scheme 3: Synthesis of 3-chlorobenzaldehyde-isonicotinic acid hydrazone

Novel Cu^{2+}, Zn^{2+} and Cd^{2+} complexes of a Schiff base obtained from isoniazid and ascorbic acid have been synthesized by Lawal *et al* [46]. The ligand and complexes were characterized using infrared, electronic absorption data, elemental analysis, molar conductivity, melting point and solubility. The compounds were found to have high melting points (170- 316 ^{o}C) while the conductivities were in the range of 7.67- 9.04 μs. The spectroscopic analysis suggested that the ligand was bidentate with nitrogen and oxygen donor atoms. The antimicrobial studies of the synthesized compounds were tested on strains of *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aureginosa* and *Salmonella typhi* at a concentration of 1 mg/ml. The results proved that complexes (Fig. 4) have better antimicrobial activities compared to the isoniazid and ascorbic acid alone.

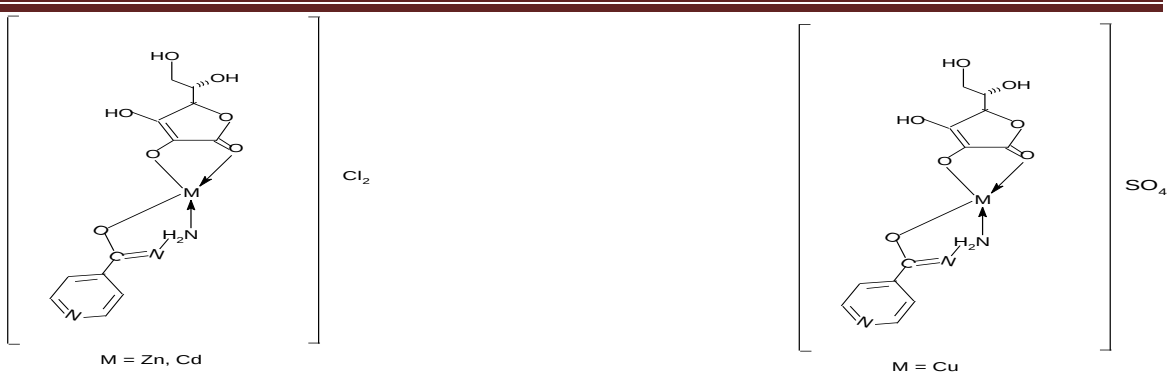


Fig. 4: Cu^{2+}, Zn^{2+} and Cd^{2+} complexes of a Schiff base obtained from isoniazid and ascorbic acid

The Schiff base ligand 2-formylpyridine isonicotinylhydrazone with an excellent yield of 76 % was prepared by Moksharagni & Reddy [41]. From the synthesized ligand, the La(III), Ce(III), Pr(III), Nd(III) and Sm(III) complexes were prepared and found to be of the form $[Ln(FPNH)_2(NO_3)](NO_3)_2.nH_2O$ (Fig. 5). From the spectroscopic analysis it was found that the ligand behaved as a neutral tridentate ligand and coordinated to the metal ions through its NNO donor atoms. From the absorption titrimetric analysis, it was confirmed that the metal complexes have very good binding properties and binds well to DNA. The antimicrobial activities of the ligand and its lanthanide (III) complexes were tested on strains of *Bacillus subtilis*, *Staphylococcus aureus*, *Salmonella typhi*, and *Escherichia coli*. From the results, it was very clear that the lanthanide complexes were better antimicrobial agents when compared to the free ligand.

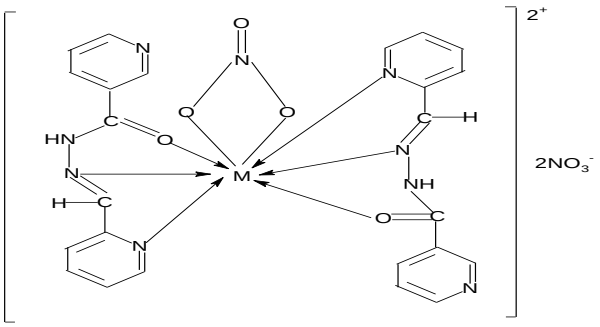


Fig. 5: La(III), Ce(III), Pr(III), Nd(III) and Sm(III) complexes of 2-formylpyridine Isonicotinylhydrazone

The synthesis and characterization of Cu (II), Zn (II) and Cd (II) mixed ligand complexes of isonicotinylhydrazide–pyridoxine (Fig 6) have been reported [46]. The ligands and its metal complexes were characterized by physical and spectroscopic studies such as melting point, conductivity measurement, TLC, FT-IR and UV-visible spectroscopy. The antimicrobial

activities of the metal complexes were performed using the agar well diffusion method on isolates of *Eschericha coli*, *Klebsiella pneumonia*, *Pseudomonas aureginosa* and *Stapylococcus species*. The zones of inhibition measured for each microbial strain were compared to that of isonicotinylhydrazide and piyridoxine. The results showed that the complexes inhibited the growth of the microbes better than isonicotinylhydrazide and pyridoxine alone.

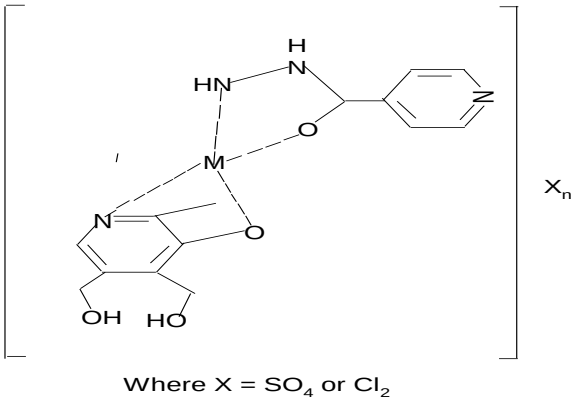
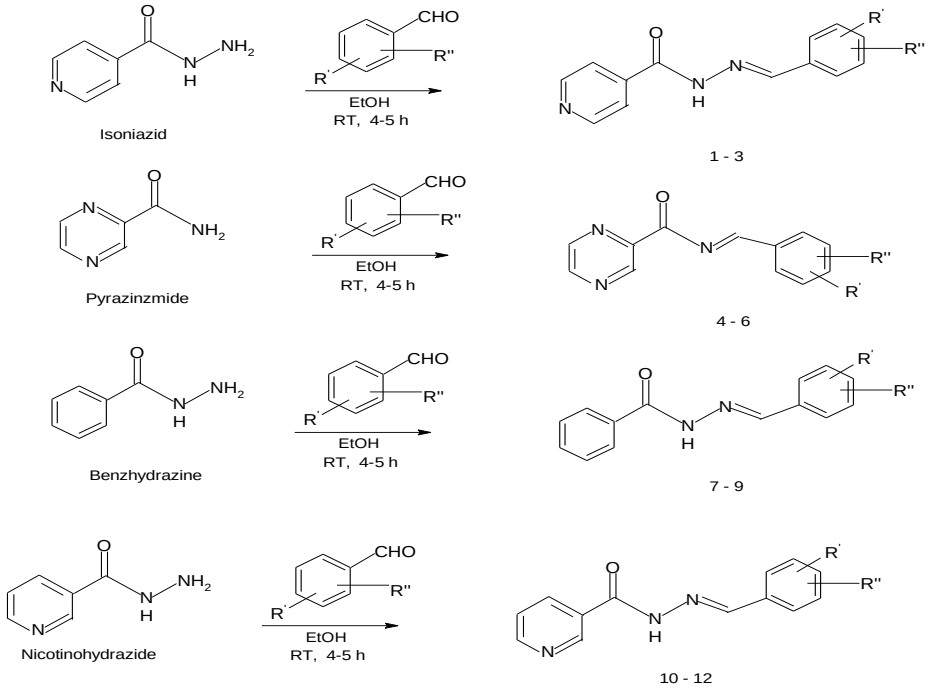


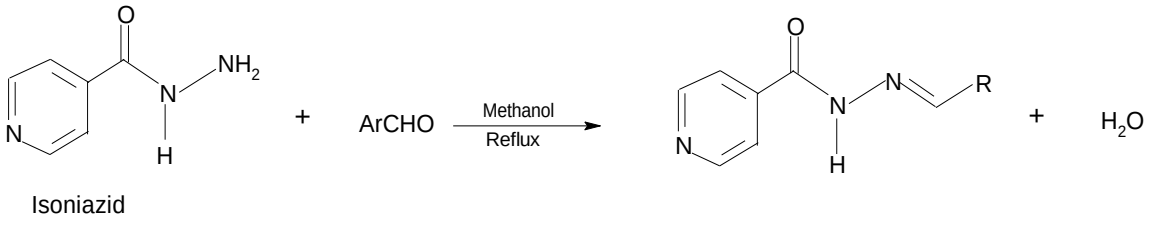
Fig. 6: Cu(II), Zn(II) and Cd(II) complexes of isonicotinylhydrazide–pyridoxine

Three imine ligands were synthesized by the condensation of isoniazid with pyrazinamide, benzhydrazide, and nicotinylhydrazide [23] as shown in Scheme 4. The ligands were further used to prepare their respective Cu(II) complexes and characterized. The molar conductance of the complexes in DMF were between 66-93 Ω^{-1} cm^2 mol^{-1} and were found to exist in the metal-ligand ratio of 1:1. From the IR data, electronic transitions and magnetic moments of 1.86-2.07 BM, a square pyramidal geometry was suggested for the Cu(II) complexes. The antimicrobial studies were carried out by the paper disc diffusion method on strains of *S. aureus, Bacillus, S. pyogenes, E. coli, and Enterobacter faecalis*. The results obtained showed that the Cu(II) complexes have better antimicrobial and anti-tubercular properties compared to streptomycin.



Scheme 4: Synthesis of Schiff bases from isoniazid

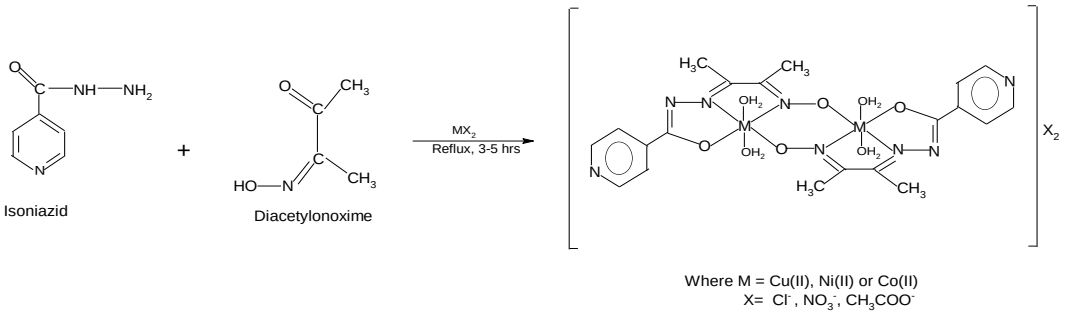
The synthesis of nineteen Schiff base ligands from isoniazid with some aldehydes (Scheme 5) have been published [29]. The melting points of the ligands were between 138-238 ^{o}C. The anti-microbial activities of the synthesized ligands were determined by the paper disc diffusion method on *E coli*, *S. enterica*, *S. typhi*, and *S. aureus* strains. The results showed that the ligands had smaller inhibition zones (7-11 mm) compared to 22 and 25 mm obtained for gentamicin and chloramphenicol respectively. The Schiff base ligand N'-(pyridine-2-carboxaldehyde) isonicotinoylhydrazone, was the most active and showed activity against all the bacterial strains used while compound 4 was inactive against all strains.



Scheme 5: Synthesis of various Schiff bases from isoniazid and some aldehydes

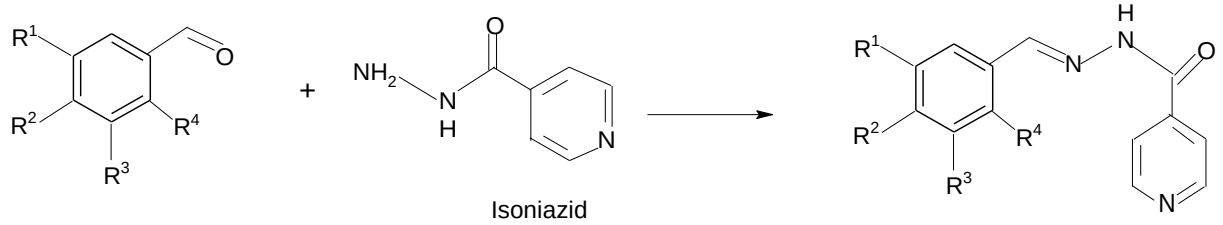
The preparation of an imine from the reaction between isoniazid and disacetylomonoxime has been reported [47]. The prepared imine was used to synthesize Cu(II), Ni(II) and Co(II)

complexes (Scheme 6). The coloured and paramagnetic complexes were found to possess high melting points (279 – 296 ^{o}C) and high conductivities (140 –160 $Ohm^{-1}cm^{2}$ mol^{-1}). Spectroscopic analysis proved that the ligand is tridentate with ONO donor atoms and formed six coordinate geometry complexes with the metal ions. The XRD proved that the Cu^{2+} and Ni^{2+} complexes were tetragonal and Co^{2+} complex was monoclinic. The complexes produced moderate antifungal activities on strains of *A. niger, H. oryzae and F. oxysporium* and in the order of Ni(II) < Co(II) < Cu(II) complexes.



Scheme 6: Synthesis of Schiff base from isoniazid and disacetylomonoxime and its Cu(II), Ni(II) and Co(II) complexes

The synthesis of six Schiff base ligands by the condensation reactions between isoniazid and appropriately substituted benzaldehydes in methanol-chloroform mixture (Scheme 7) has been reported [48]. The copper(II) complexes of each of the ligand were prepared by combining ethanolic solutions of the Schiff base with copper (II) acetate. The antimicrobial activities of the ligands and the copper complexes were determined on strains of *E. coli*, *S. aureus* and *C. albicans*. The results showed that the L1 and L4 gave good activity against *C. albicans* with MIC of 0.037 mM and 0.048 mM respectively. All Cu (II) complexes showed excellent inhibitory properties, whereas the ligands exerted only weak activity. The best activity (0.49±0.01 µM) was observed in the Cu (II) complex of N-[[(4-(trifluoromethyl)phenyl]methylidene]pyridine-4-carbohydrazide (Cu-L1).

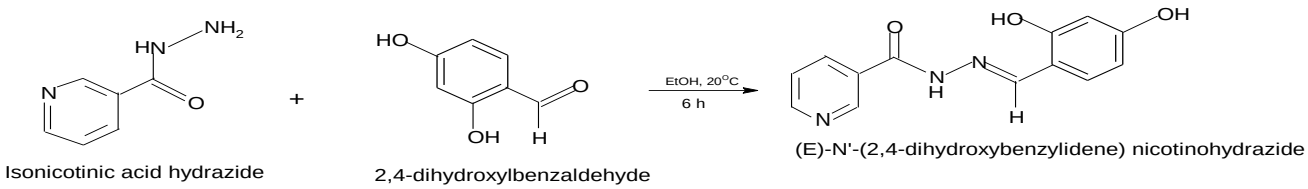


Scheme 7: Synthesis of Schiff base ligands L1-L6 from isoniazid and appropriately substituted benzaldehydes in methanol-chloroform mixture

L1: R^2 =CF_3, R^1 = R^3 = R^4 =H., L2: R^4 = CF_3, R^1 = R^2 = R^3 = H. L3: R^2 = F, R^1 = R^2 = R^4 = H;

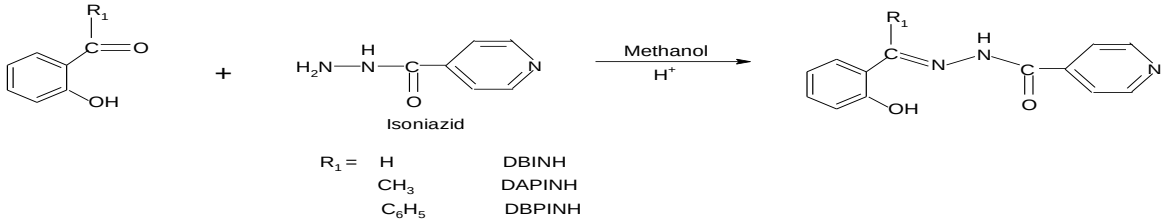
L4: R^1 = F, R^4 = OH, R^2 = R^3 = H; L5: R^3 =F, R^4 = OH, R^1 = R^2 = H; L6: R^1 = R^2 = R^3 = R^4 = H

The anti-tubercular activity of (E)-N'-(2, 4-dihydroxybenzylidene)nicotinohydrazide (Scheme 8) and its Mn(II), Fe(II), Pt(II) Zn(II) and Pd(II) have been evaluated by Ogunniran *et al* [49]. The ligand was synthesized from nicotinic acid hydrazide and 2,4-dihydoxylbenzaldehyde at 20 ^oC. The anti-tubercular activity of the tridentate ONO donor ligand and its metal(II) complexes were evaluated against *Mycobacterium tuberculosis* by the micro-diluted method. The MIC results obtained for the complexes were: (PtL = 0.56 mg/mL), (ZnL = 0.61 mg/mL), (MnL = 0.71 mg/mL) and (FeL = 0.82 mg/mL) which were better than that obtained from the first line drug, isoniazid (INH = 0.9 mg/mL) and the ligand (H_3L=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.



Scheme 8: Synthesis of (E)-N'-(2, 4-dihydroxybenzylidene)nicotinohydrazide

The synthesis of three Schiff bases by reacting isoniazid with 2-hydroxybenzaldehyde (DBINH), 2-hydroxyacetopheneone (DAPINH) and 2-hydroxybenzopheneone (DBPINH) (Scheme 9) has been published [50]. The novel iron(III) complexes of formula $Fe(L)_2Cl$ (Fig. 7) were prepared from each of the Schiff base and their interaction with DNA investigated. The complex was characterized by elemental analysis, molar conductivity, magnetic susceptibility, IR, and electronic spectroscopy. The complexes were found to have strong π-stacking interaction with DNA.



Scheme 9: Synthesis of DBINH, DAPINH and DBPINH

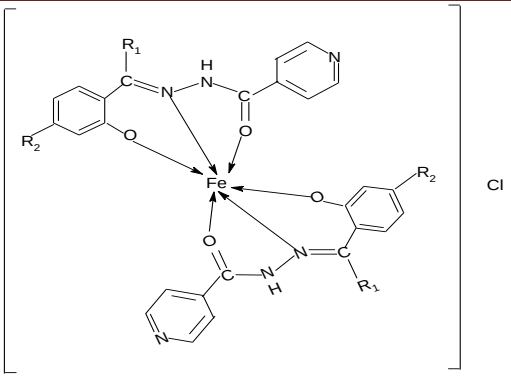
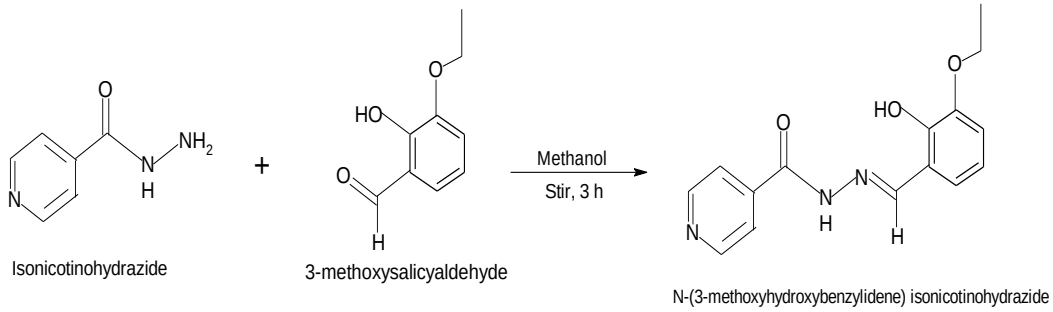


Fig.7: Fe(III) complexes of DBINH, DAPINH and DBPINH

A new Schiff base ligand has been synthesised from isonicotinoylhydrazide and 3-ethoxy-2-hydroxybenzilidine as presented in Scheme 10 [38]. The antimicrobial properties of the synthesized compounds were tested on *S. aureus* (SA, ATCC 9144), *E. coli* (EC, ATCC 87261) and compared with ciprofloxacin and ceftriaxone. The ligand was found to show higher antibacterial strength against *S. aureus* (MIC 8 µg/mL) than the standard ciprofloxacin and ceftriaxone (0.100 and 0.015 µg/mL respectively). The ligand was also found to inhibit the growth of *M. Tuberculosis* H37RV at a concentration of 4µg/mL

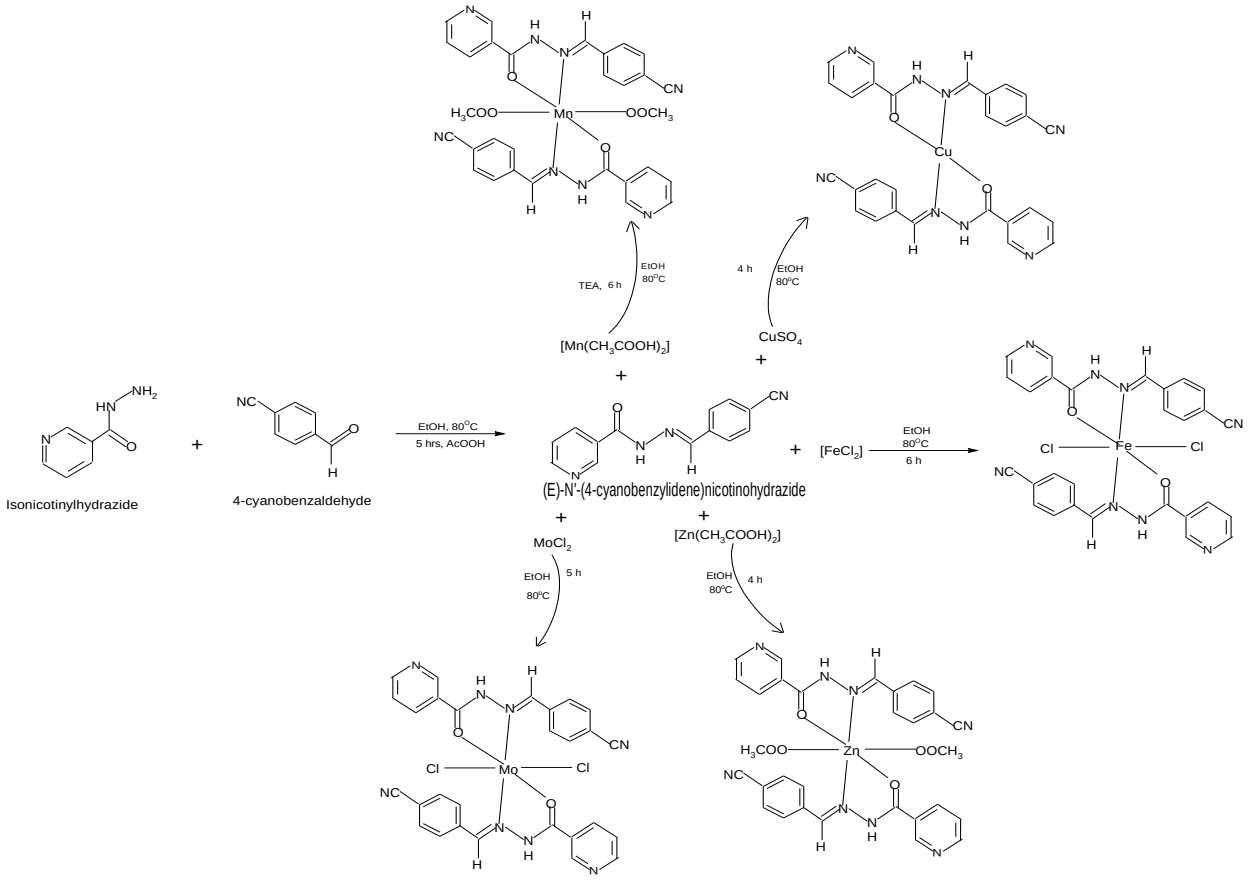


Scheme 10: Synthesis of N-(3-methoxyhydroxybenzylidene) isonicotinohydrazide

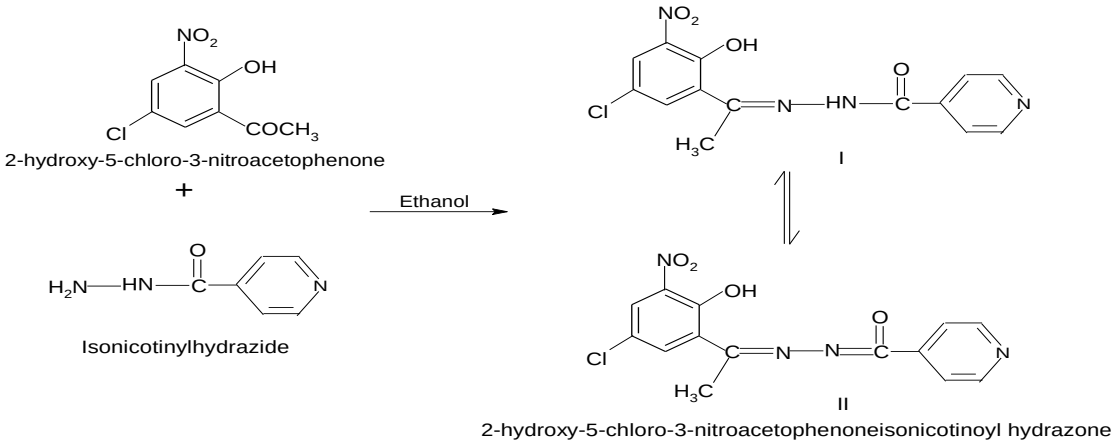
Mn(II), Mo(V), Fe(II), Cu(II) and Zn(II) complexes of the Schiff base ligand (E)-N'-(4-cyanobenzylidene)nicotinohydrazide) as presented in Scheme 11 has been prepared [51]. The ligand was prepared from the condensation of nicotinic acid hydrazide and 4-cyanobenzaldehyde in ethanol. The in vitro anti-mycobacterial properties of the compounds were evaluated against *Mycobacterium tuberculosis* H37Rv by using micro-diluted method. The results obtained showed that the ligand and its metal (II) complexes exhibited promising anti-tubercular activity. The MIC of Zn (II) complex (0.62 µg ML^{-1}) showed that it has a higher anti-tubercular activity than Fe (II) with MIC value of 1.15 µg ML^{-1}. The result of cytotoxicity studies revealed that

ligand and Zn (II) complex with IC_{50} of 2.17 and 1.72 µM, respectively were not toxic compared to isoniazid while the Mn (II) complex was however found to be the most toxic.

Scheme 13 shows the synthesis of the Schiff base ligand 2-hydroxy-1-naphthaldehyde-3-isonicotinylhydrazone [52]. The ligand which was prepared from isonicotinylhydrazide with 2-hydroxy-1-naphthaldehyde was complexed with Co(II), Zn(II), and Cu(II) to obtain the respective complexes (Fig. 8). The results of the elemental analysis proved the complexes formed were of the formula $[M(L)_2]$. nH_2O with a metal-ligand stoichiometry of 1:2.

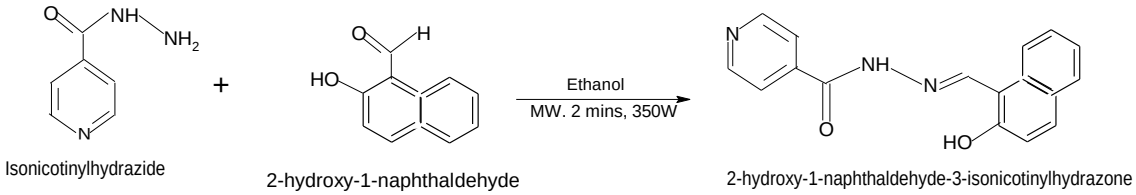


Scheme 11: Synthesis of (E)-N'-(4-cyanobenzylidene)nicotinohydrazide) and its metal (II) complexes



Scheme 12: Syntheses of 2-hydroxy-5-chloro-3-nitroacetophenoneisonicotinoyl hydrazone

Octahedral geometry was assigned to the complexes based on spectroscopic analysis. The antimicrobial study was carried out on *Escherichia coli*, *Staphylococcus aureus*, *Aspergillus flavus and Candida albicans* by the paper disc diffusion method. The result showed that the metal complexes gave enhanced antimicrobial inhibition.



Scheme 13: Synthesis of 2-hydroxy-1-naphthaldehyde-3-isonicotinylhydrazone

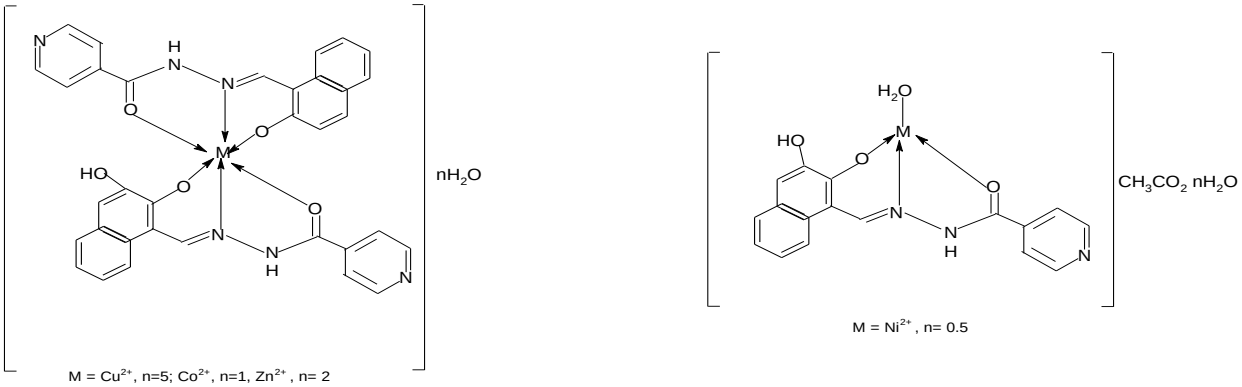
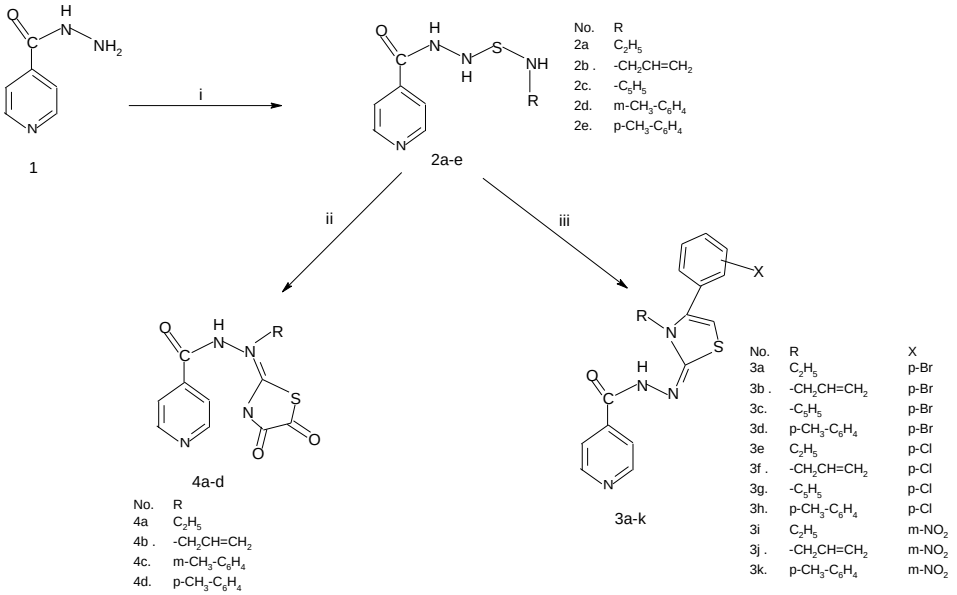


Fig. 8: Co(II), Zn(II), and Cu(II) complexes of 2-hydroxy-1-naphthaldehyde-3-Isonicotinylhydrazone

A series of isonicotinylhydrazide Schiff bases; 3,4-disubstituted

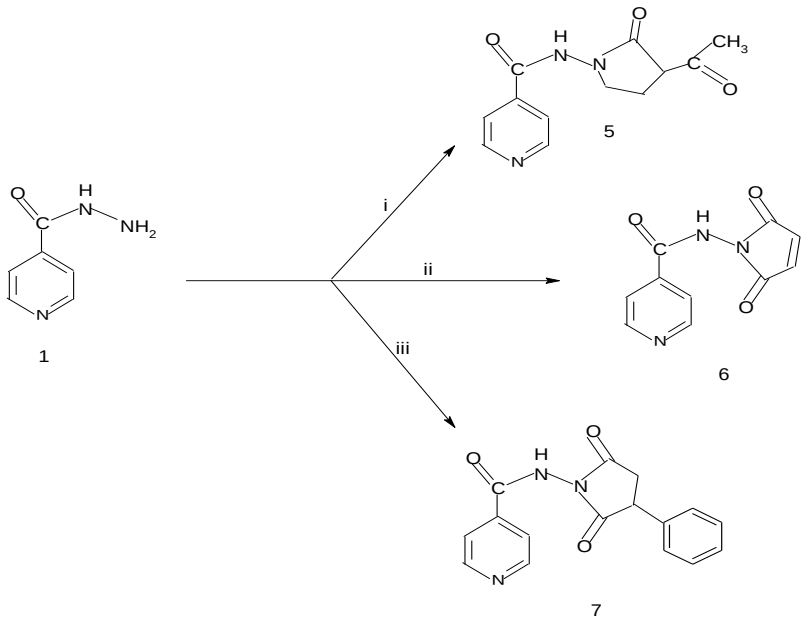
Thiazolylideneisonicotino hydrazide derivatives 3a–k, 2-substituted thiazolidinylisonicotin amide derivatives 4a– d and pyrrolylisonicotin amide derivatives 5, 6 and 7 have been synthesised and shown in Scheme 14a-b [53]. The Anti-tuberculous activity of all the synthesized Schiff base ligands were carried out on *M. tuberculosis* H37Ra 7131 strain by the broth dilution method. Results showed that compound 3g, a thiazolidine derivative, has comparable activity to that of isoniazid while compounds 3b, 3h, 4a, 4b, 4c, 3a and 3f exhibited moderate anti-TB activity. In addition, compounds 3c, 3i, 3j and 4d demonstrated poor anti-TB activity. On the other hand, the pyrrolyl derivative 6 was found to be more active than compounds 5 and 7 yet it is less active than the thiazolidine derivatives.

The Mn^{2+}, Fe^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+} and Cd^{2+} complexes of mixed of trimethoprim-isoniazid (Fig. 9) were synthesized and characterized by Bamigboye *et al* [39]. The ligand was found to coordinate to the metal ions through the nitrogen of the pyrimidine group and the nitrogen of the amine group. The antimicrobial activities of the complexes were tested on strains of *Staphylococcus aureus*, *Pseudomonas aureginosa*, *Klebsiella pneumonia* and *Escherichia coli*. The results show that the complexes were more active than the free ligand.



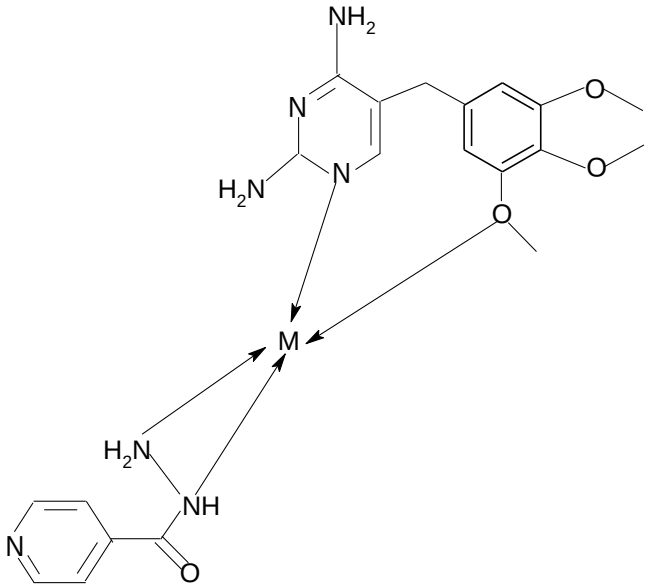
Reagents and conditions: i. = RCNS, ethanol, reflux 4 hrs
ii. = $(COCl)_2$, dry benzene, reflux 3hrs
iii. = substituted phenacylbromide, ethanol/ methanol, reflux 7hrs

Scheme 14a: Synthesis of compounds 3a– k and 4a –d from isoniazid (1)



Reagents and conditions
i. 2-acetyl-3-butyrolacetone, gl. acetic acid / acetic anhydride, reflux, 13 hrs
ii. maleic anhydride, gl. acetic acid / acetic anhydride, reflux, 13 hrs
iii. phenyl succinic anhydride gl. acetic acid / acetic anhydride, reflux, 13 hr

Scheme 14b: Synthesis of target compounds 5, 6 and 7



Where M= Cd, Fe, Zn, Cu, Mn or Co

Fig. 9: Mn^{2+}, Fe^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+} and Cd^{2+} complexes of mixed isoniazid–trimethoprim

CONCLUSION

From this review, it was observed that transition metal Schiff base complexes obtained from isoniazid have numerous biological functions. With isoniazid and its derivatives, more potent antimicrobial, anti-tubercular anti-bacterial, anti-fungal, anti-inflammatory, anti-cancer, DNA-interaction and anti-tumor agents can be synthesised. This is an active area of research since isoniazid and its derivatives have been proved to be promising leads for the design of more competent antimicrobial agents.

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