Antimicrobial Profile of Potential Pyridine Derivative: 2,6-Diaminopyridine (DAP)-A Review

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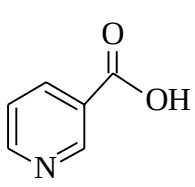
Abstract:

Pyridine is a useful nitrogen-based heterocyclic molecule that is found in a wide range of naturally occurring bioactive compounds. It is also frequently employed in drug design and development in pharmaceuticals. Pyridine derivatives with formyl or amino groups go through a Schiff base condensation process with the right substrate and under the right circumstances, producing Schiff base as the end product, which acts as a versatile and multidentate bioactive ligand. 2, 6-diaminopyridine, a pyridine derivative, is an N-donor ligand with both N heterocyclic and aromatic amine characteristics. Because of the existence of ring nitrogen atoms with a localised pair of electrons, they behave as excellent ligands. It is regarded as a flexible pharmacophore group and have a wide range of bioactivities, including antibacterial, antiviral, antitubercular, antifungal, antioxidant, anticonvulsants, antidepressant, anti-inflammatory, and anticancer action. In this review we only highlight the most significant examples of 2,6-diaminopyridine derivatives possess the antimicrobial activity.

Keywords: Pyridine, 2,6-diaminopyridine, Schiff bases, Antimicrobial activity.

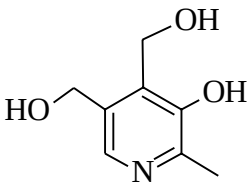
Introduction:

Nitrogen-based heterocyclic compounds are widely distributed in nature and are found in a wide range of alkaloids, vitamins, essential oils, amino acids, metabolites, and other molecules that are all required for various biochemical processes and cell survival. Pyridine is one of the most significant nitrogen-based heterocyclic compounds found in many medicinal substances. Many plant-based alkaloids have them as a partial structure. Nicotine and Anabasine, for example, are found in tobacco, whereas Ricinine is found in castor oil and Arecoline is found in betelnut [1]. Nicotinamide adenine dinucleotide phosphate is a cofactor that is used by all types of biological life in anabolic processes, vitamins such as Niacin (Vitamin B3) and Pyridoxine (Vitamin B6) and nucleic acid synthesis [2] (**1**). They can be utilised as prodrugs or as drug molecules, and have a wide range of therapeutic uses such as antitubercular, antibacterial, anticholinesterase, antihistamine, antiulcer, antianginal, and so on [3] (**2**).



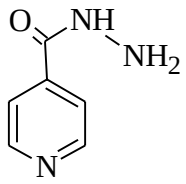
Niacin

(Vitamin B_3)



Pyridoxine

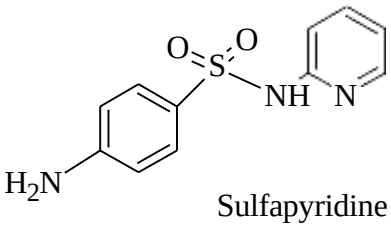
(Vitamin B_6)



Isoniazid

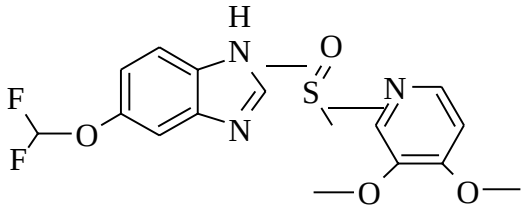
(Antitubercular)

(**1**)



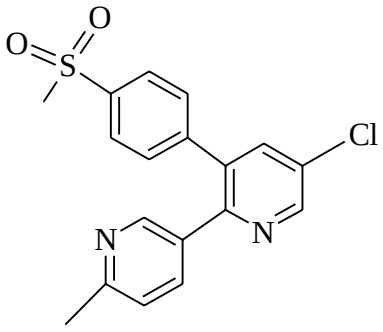
Sulfapyridine

(Antibacterial)



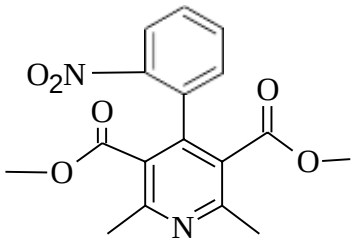
Pantaprazole

(Proton pump inhibitor)



Etrocoxib

(Analgesic/Anti-inflammatory)



Nifedipine

(Antianginal)

(**2**)

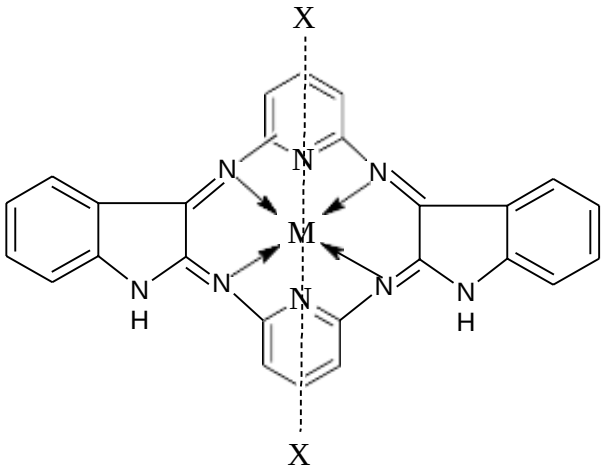
With the right substrate and adequate conditions, pyridine derivatives containing formyl or amino groups can easily undergo Schiff base condensation. Schiff bases are a subclass of imines that are formed via the condensation of primary amines and carbonyl compounds. Because of the presence of imine nitrogen, which is basic in nature and shows -acceptor characteristics, they operate as an efficient organic ligand. Schiff bases are among the most common organic substances. Schiff bases have been demonstrated to have antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic effects

along with its utilization as pigments and dyes, catalysts, organic synthesis intermediates, and polymer stabilizers [4].

2,6-diaminopyridine is an N-donor ligand that possesses both N-heterocyclic and aromatic amine characteristics [5]. Because of the existence of ring nitrogen atoms with a localised pair of electrons, they behave as excellent ligands. They have a wide range of biological functions, are a flexible pharmacophore, and have emerged as a powerful class of medicines. [6,8]. Its derivatives have attracted a lot of attention in the recent few decades as a biological active chemical [7], such as antiatherosclerotic, antidiabetic, antimalarial, antiinflammatory, antibacterial, hepatoprotactive, and tyrosine kinase inhibitory drugs [4].

Antimicrobial Properties:

D.P. Singha *et al* (2010) [9] When isatin and 2,6-diaminopyridine are coupled in the presence of divalent metal ions, macrocyclic complexes of the type $[M(C_{26}H_{16}N_8)X_2$ are produced, where M denotes either Co(II), Ni(II), Cu(II), Zn(II), or Cd(II), and X denotes either Cl, NO_3, or CH_3COO (**3**). The antibacterial activity of the complexes was tested in vitro. Several of the complexes displayed excellent antibacterial activities against a few selected bacterial species.

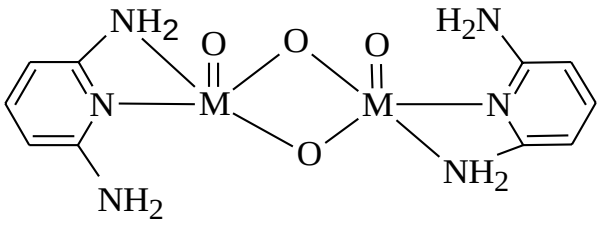


Where M= Co(II), Ni(II), Cu(II), Zn(II), Cd(II); X= Cl−, NO_3−, CH_3COO−

(**3**)

Ahmed A. Soliman *et al* (2012) [10] The reaction of Cr, Mo, and W in ethanol with 2,6-diaminopyridine (dap) resulted in the production of binuclear oxo complexes with the typical

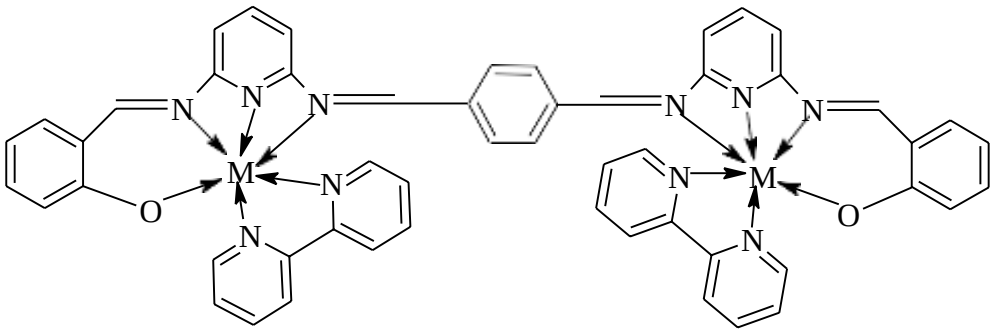
formulae $[M_2(O)_4(dap)_2]$ (**4**). DAP and its complexes have been tested for their biological action as antibacterial and antifungal reagents. The complexes (dap) and tested exhibited significant action against a variety of bacteria and fungi, but the complex $[W_2(O)_4(dap)_2]$ was shown to be inert against *S. aureus*. Against the fungus Candida albicans, all complexes are more active than the free ligand (dap). However, the complex $[Mo_2(O)_4(dap)_2]$ has the highest activity against *A. niger*, while the complexes $[Cr_2(O)_4(dap)_2]$ and $[Mo_2(O)_4(dap)_2]$ have greater activities against *E. coil* than the ligand (dap).



$[M_2(O)_4(dap)_2]$ complexes, M = Cr, Mo or W

(**4**)

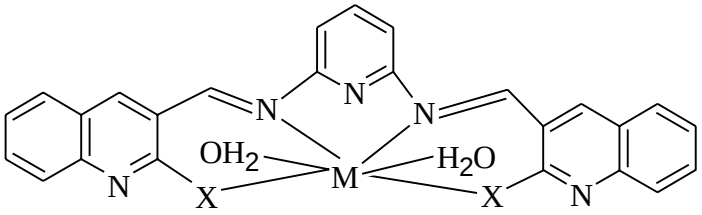
M. Usharani *et al* (2013**)** [8] The symmetrical Schiff base ligand was synthesised using benzene1,4-dicarbaldehyde, pyridine-2,6-diamine, and 2-hydroxybenzaldehyde, and it was then allowed to react with metal salts to form binuclear Schiff base metal complexes (**5**). In comparison to their metal complexes, the synthesized ligands were evaluated for antibacterial activity against the bacterial species *S. aureus*, *E. coli, B. subtilis*, and *K. pneumonia*. The antibacterial activity details show that the metal complexes are more efficient against one or more bacterial species than the parent chemical ligands.



M=Cu(II), Co(II), Ni(II) & Mn(II)

(**5**)

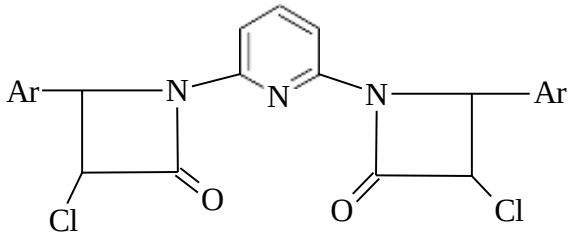
Narayanachar *et al* (2013) [11] Combining 2,6-diaminopyridine (DAP) with 2-mercapto-3-formyl quinoline/2-hydroxy-3-formyl quinoline yielded a number of Schiff bases and their associated transition metal complexes (**6**). The Schiff bases and their metal complexes were tested for analgesic, anti-inflammatory, and antipyretic effects. Copper complexes had the highest pharmacological action of any drug tested.



M= Co(II), Ni(II), Cu(II), Zn(II)
X= O, S

(**6**)

Kasem Murad *et al* (2014) [12] A number of Schiff bases of 2,6-diaminodipyridine have been synthesized by condensing with a variety of aromatic aldehydes in ethanol. After being treated with chloroacetylchloride in the presence of triethylamine, these Schiff's bases yielded substituted 2-azetidinone (**7**). The synthesised compounds shown strong antibacterial activity against pathogens such as *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebsiella pneumonia.*

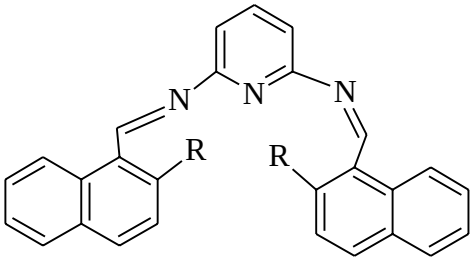


Where, Ar: phenyl, 4-chlorophenyl, 4-hydroxyphenyl, 3-nitrophenyl, 4-methoxyphenyl, 4-dimethylamino phenyl, 4-methylphenyl

(**7**)

Devika Bhai. R *et al* (2014) [13] The use of lemon juice as a catalyst allows for a green route to the synthesis of Schiff bases produced from 2, 6 diamino pyridine. This approach is easy to test, rapid, clean, and high yielding. The use of lemon juice increases the purity and yield of the reaction while avoiding the use of typical dehydration agents such as glacial acetic acid. This approach has been effectively expanded for the synthesis of several Schiff bases produced from 2,6 diamino pyridine, such as N,N'-bis(2-hydroxy-1-napthalene)-2,6-pyridiamine, N,N'-bis(2-methoxy-1-napthalene)-2,6-pyridiamine, and N,N'-bis(naphthalene)-2,6-pyridiamine(**8**).

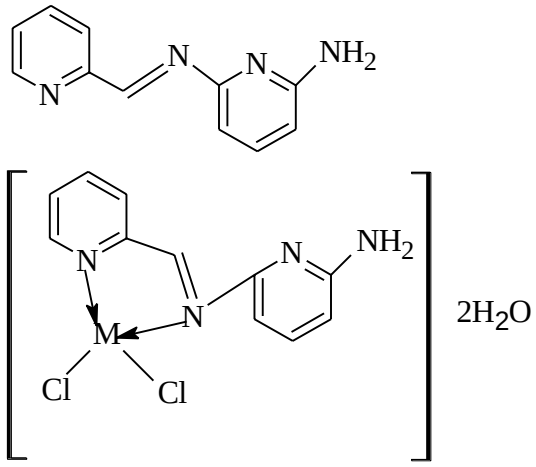
Compounds are evaluated for antifungal and antibacterial activities. The compound's hydroxyl derivative demonstrated considerable antibacterial efficacy against all tested microorganisms.



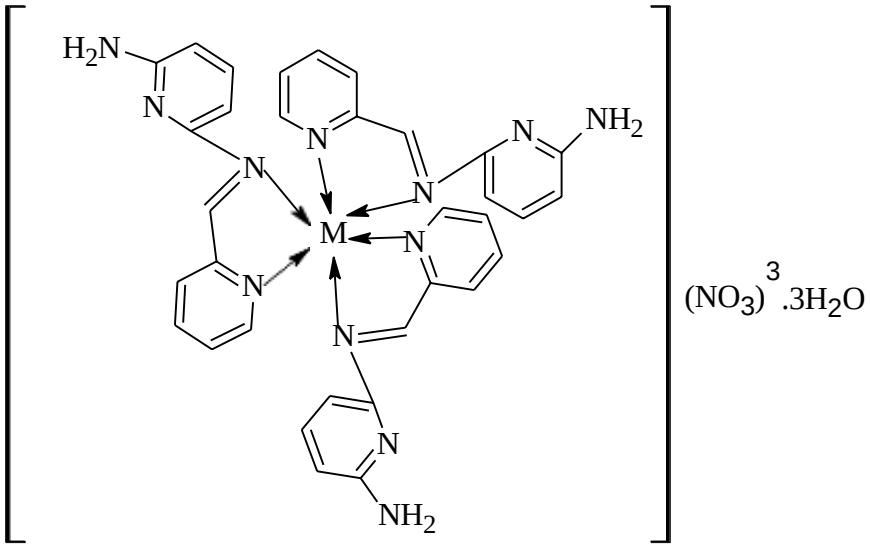
R= OH, OCH_3

(**8**)

Omyma A.M. Ali *et al* (2015) [14] When 2,6-diaminopyridine with 2-pyridinecarboxaldehyde react it yielded 2-[(pyridin-2-ylmethylidene)amino](L) -6-aminopyridine (**9**) Schiff base. This was then exposed to the synthesis of metal complexes with the following general formulas: :$[M(L)Cl_2]2H_2O$ (where M = Cu(II), Ni(II) and Co(II)) (**10**) and $[La(L)_3](NO_3)_3 3H_2O$ (**11**). The antibacterial activity of Schiff base ligand and its complexes has been evaluated using both one-gram positive bacteria, *S. aureus*, and one-gram negative bacteria, *E. coli*. All of the compounds tested positive for biological activity against bacteria. According to the findings, all complexes outperformed the ligand in terms of antibacterial activity. Chelation of the whole ring improves the capacity of complexes to permeate lipid membranes and inhibit metal binding sites in microbial enzymes. Furthermore, the complexes under investigation may interfere with cellular respiration, obstructing protein synthesis and preventing further development of the organisms.

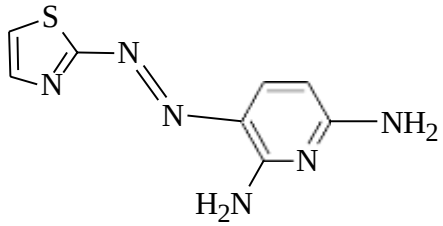


(**9,10**)



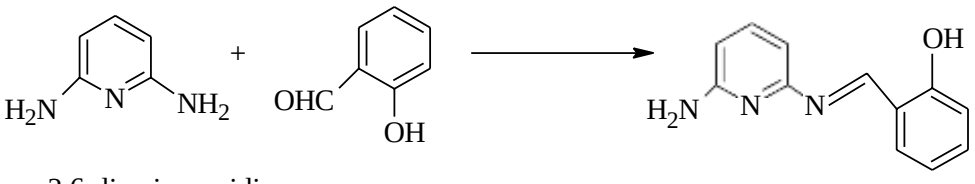
(**11**)

Akkharadet Piyasaengthong *et al* (2015) [15] synthesize the a metal complex of Au(III) with 3-(2′-thiazolylazo)-2,6-diaminopyridine (TADAP) (**12**) and evaluated the its pepsin inhibition properties, results showed that at the concentrations between 0–200 μM if inhibit pepsin activities.

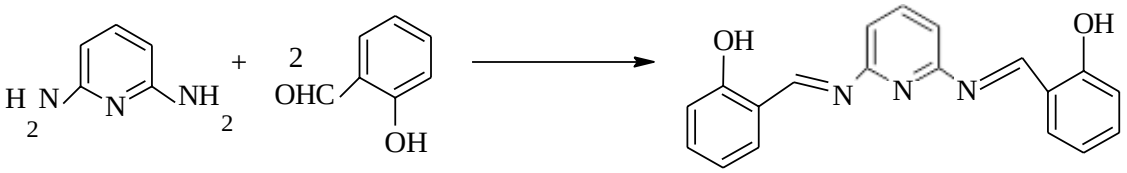


TADAP(**12**)

A.K. Surabhi, K. Pradeepkumar (2016) [16] The condensation process between 2,6-diaminopyridine and 2-hydroxybenzaldehyde produced two Schiff bases, L1 and L2. Their Cu(II) complexes were generated by reacting L1 and L2 (**13**) ligands with Cu(II) acetatete monohydrate (**14**). The agar well-diffusion technique was used to assess the antibacterial activity of the parent Schiff base ligands and their metal complexes against Gram +ve and Gram -ve bacteria. The activity of the ligands was greater than that of the complexes. Among the ligands, L2 is the most effective, with the greatest antibacterial action against the pathogen *S. Aureus*.

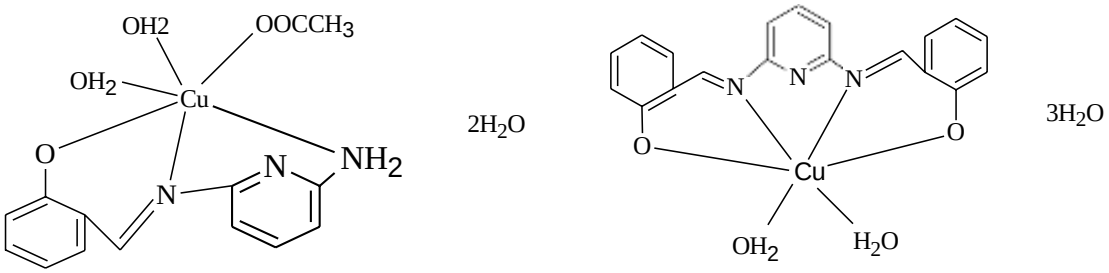


2,6-diaminopyridine 2-hydroxybenzaledehyde L1



2,6-diaminopyridine 2-hydroxybenzaledehyde L2

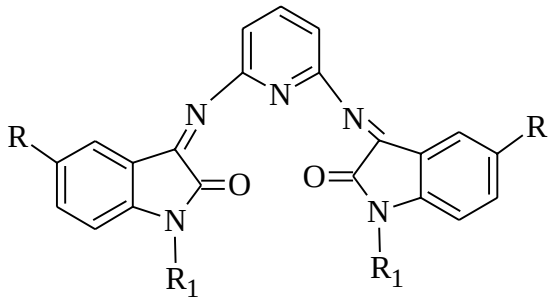
(**13**)



Cu complex with L1 Cu complex with L2

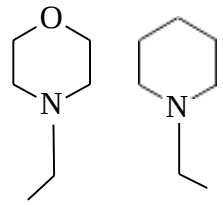
(**14**)

Nadia G. Kandile *et al* (2017) [17] Three distinct classes of bis-Schiff bases were synthesized by reacting 5-substituted isatins with benzidine, 3,3-dimethoxybenzidine, and 2,6-diaminopyridine. Mannich bases and metal complexes of various Schiff bases were also synthesized (**15**) employing a few secondary animes and Co, Cu, Ni metal (**16**). Using a broth dilution method, in vitro antimicrobial activity was evaluated in terms of minimum inhibitory concentrations (MIC) against four bacterial pathogens and two fungi, as well as anticancer effects against HELA cervix. According to the study, several chemicals had great antibacterial activity against Gram-positive and Gram-negative bacteria, while copper-containing metal compounds showed promising anticancer efficiency against the HELA cervix.

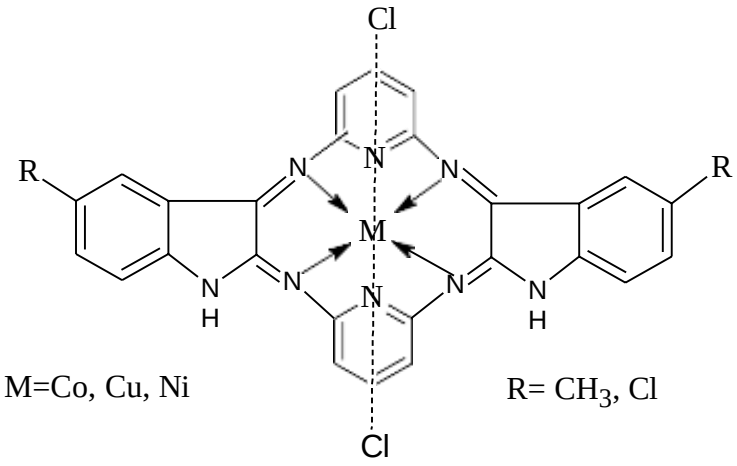


R= H, CH_3, Cl, NO_2, F

R_1=



(**15**)

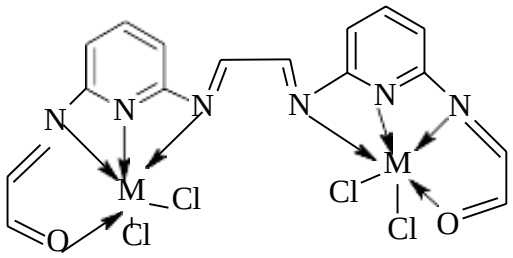


M=Co, Cu, Ni

R= CH_3, Cl

(**16**)

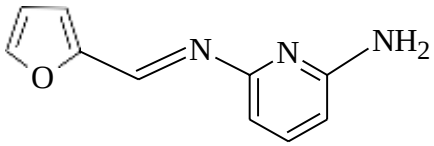
Jayalakshmi Rajendran *et al* (2017) [18] The metal complexes of Schiff base generated from 2,6-diaminopyridine and glyoxal were synthesised as homo-binuclear Cu(II), Co(II), Ni(II), and Mn(II) (**17**). *In vitro* antibacterial activity against bacterial and fungal species and cyto-toxicity against human breast cancer (MCF7) cell lines were investigated for both the Schiff base and its metal complexes. Results showed that metal complexes have greater antimicrobial activity than Schiff bases and Cu(II) and Co(II) complexes were more effective against MCF7 cell line without causing significant damage to normal cells than their Schiff base ligand and other metal complexes (Ni(II) and Co(II)).



M= Co(II), Ni(II), Cu(II), Mn(II)

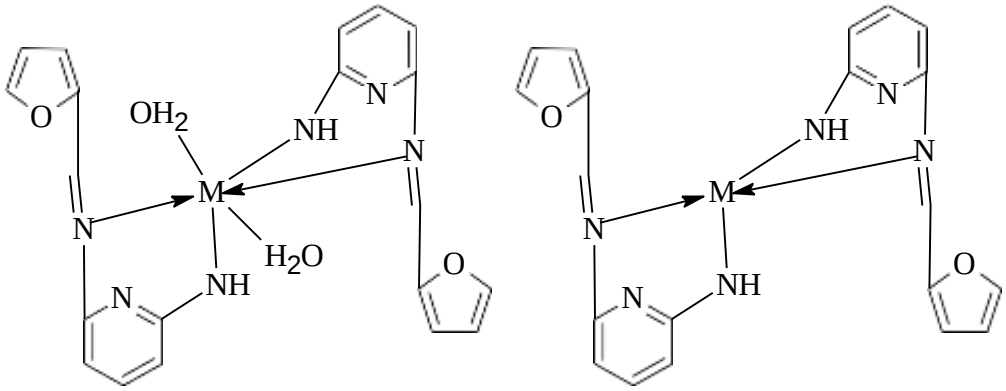
(**17**).

Sathya R. and Xavier A (2018) [19] Aldehyde (2-Furaldehyde) is combined with Aromatic Amine (2,6,-diaminopyridine) to generate Schiff base ligand (L), i.e. 2,6-diaminopyridine-2-furaldimine (Ligand) (**18**). Metal complexes of Schiff bases (Copper acetate (II), Nickel Sulphate (II), and Vanadium pentoxide (V)) (**19**) were synthesized in a 1:2 molar ratio and tested for antibacterial and antifungal activities. Copper complexes have greater antibacterial action than ligands, whereas nickel complexes have greater antifungal activity. The complexes outperform the free ligand in terms of anti-oxidant action.



Ligand

(**18**)

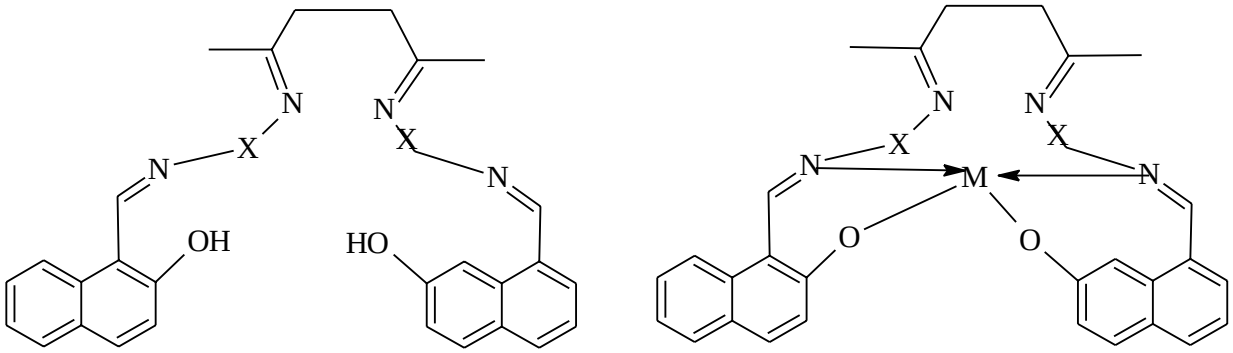


M=Ni(II),V(V) M=Cu(II

Metal Complexes

(**19**)

Hasan A. Hasan and Khaled Salman (2018) [20] Two tetradentate ligands (N_2O_2) were synthesized in a 2:1 mole ratio reaction of 2,6-diamine pyridine or 2,4-diamine tolylene with 2,5-hexanedione. Metal complexes including Co(II), Ni(II), and Zn(II) ions (**20**) were created by reacting the ligands with similar quantities of metal chloride. All complexes and ligands were screened for antibacterial activity.



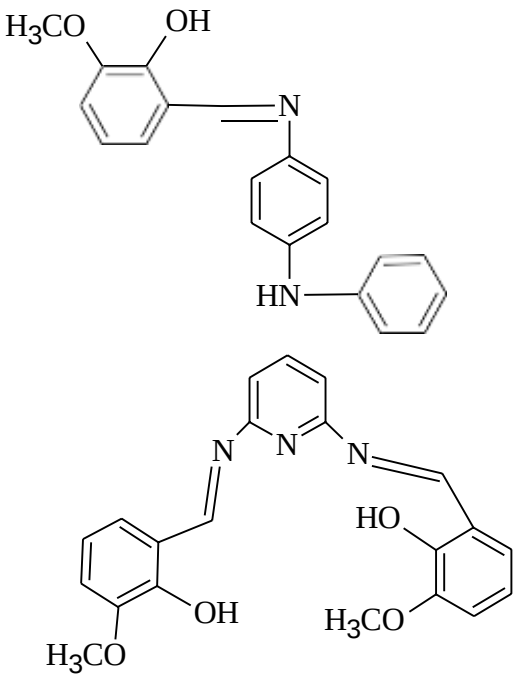
Ligand **Metal Complex**

M= Cu(II), Co(II), Ni(II), Zn(II), Cd(II)

X= 2,6-diamine pyridine or 2,4-diamine tolylene

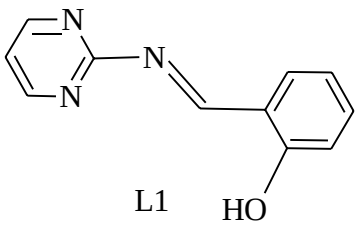
(**20**)

Sani S. *et al* (2018) [21] Schiff bases of aromatic primary amines like N-Phenyl-benzene-1,4-diamine and 2,6-diaminopyridine, were effectively synthesised using 2-hydroxy-3-methoxybenzaldehyde (2**1**). The antibacterial properties of synthetic Schiff base on various bacterial and fungus strains were investigated using the agar well diffusion method. The antibacterial activity of the (H2L1) Schiff base ligand against *E. coli* was shown to be considerably more effective.

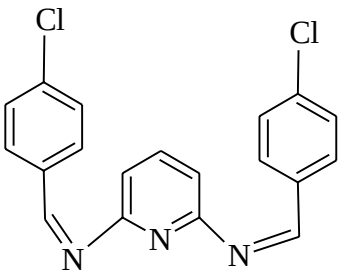


(2**1**)

Lubna Khalid Farhan *et al* (2019) [22] Some heterocyclic Schiff base ligands were synthesized through the use of 2-aminopyrimidine with 2-hydroxybenzaldehyde (L1) and 2,6-diaminopyridine with 4-chlorobenzaldehyde (L2) (**22**). These ligands were employed in the preparation of complexes of Fe(III), Ni(II), Co(II), and Cu(II).General formula of complexes are $[X(L1)_2(H_2O)_2]$ and $[X(L2)_2(H_2O)_2]$ (**23**). All complexes were tested for their anticancer activity against ($L_{20}B$) cell line by using the (MTT) assay. The results revealed all complexes showed the considerable inhibition.

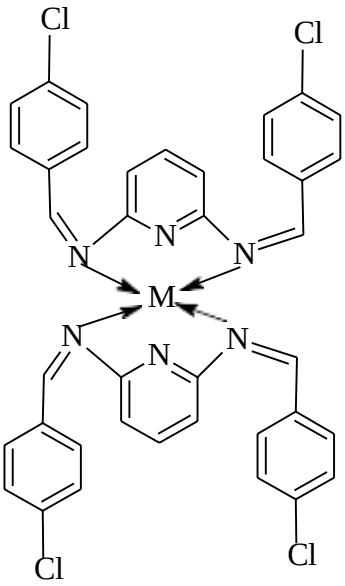


L1



L2

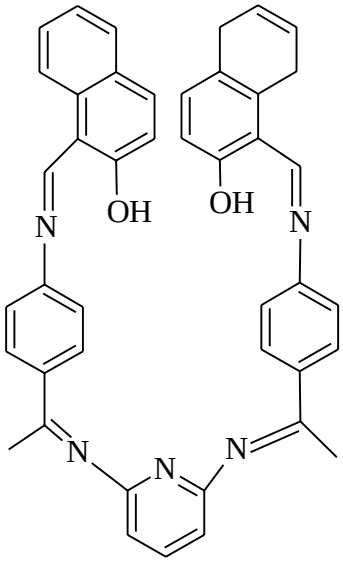
(**22**)



Metal Complexes of L2

(**23**)

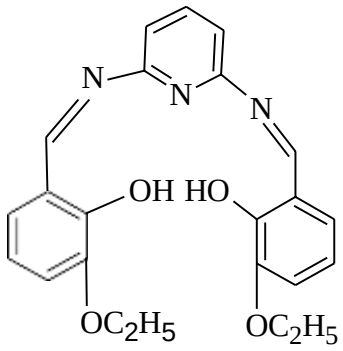
Barıs ¸ Kurt *et al* (2020) [23] Schiff base (Ligand) was synthesised using [1-(4-[(3-hydroxynaphthalen-2-yl)methylidene]amino phenyl)ethan-1-one and 2,6-diamino pyridine (**24**). This Schiff base ligand was used to synthesise complexes of Cu(II), Fe(II), and Pd(II). The DNA binding properties of the ligand and its metal complexes were investigated, and docking tests were carried out. As a consequence, H2O2 boosted ligand and copper complex DNA binding activity.



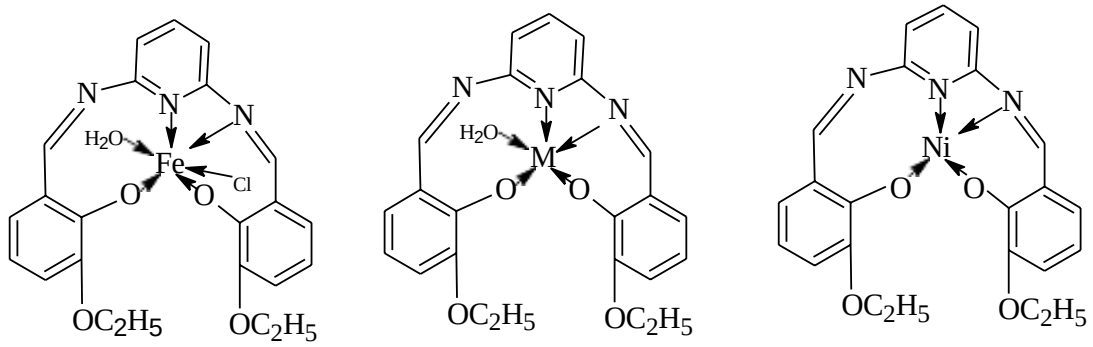
Structure of Ligand

(**24**)

Noura O AlZamil (2020) [24] A new H2L ligand was created by combining 2, 6-diamino pyridine and 3-ethoxy salicyaldehyde in a 1:2 molar ratio (**25**). CuL, CoL, NiL, FeL, and VOL complexes (**26**) were formed when a ligand combines with different metal salts. The antibacterial activities of the ligand and its complexes were evaluated against Gram-+ve bacteria, two Gram--ve bacteri and fungus. The data showed that the complexes outperformed the ligand in antibacterial activity, with the VOL complex having especially strong antimicrobial potency. H_2L, NiL, CuL, CoL, FeL, and VOL all have higher antibacterial and antifungal action.



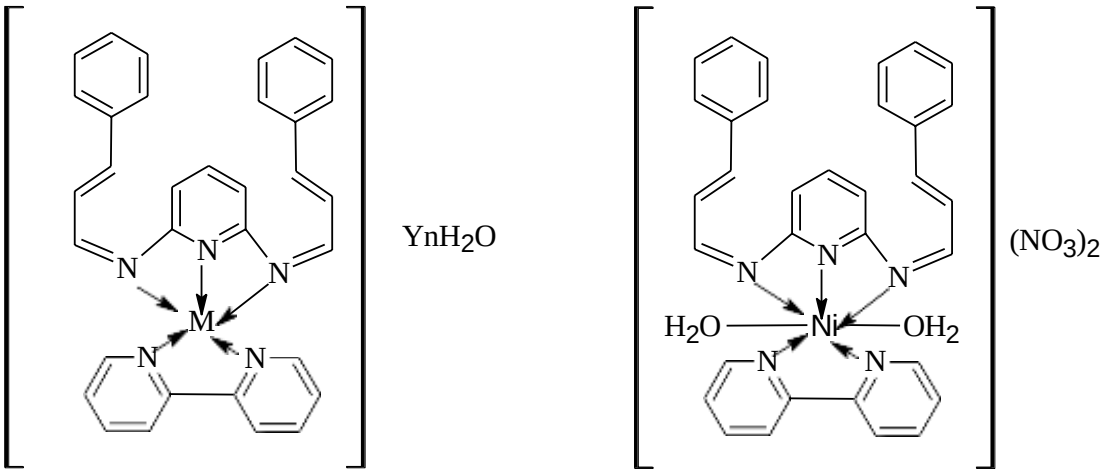
(**25**)



M= Co(II), Cu(II)

(**26**)

Diary I. Tofiq *et al* (2021) [25] It was feasible to synthesize a symmetrical Schiff base ligand from 2,6-diaminopyridine and cinnamaldehyde in formic acid as a catalyst and solvent-free conditions. Novel heteroleptic complexes of Cu(II), Co(II), Ni(II), Pt(II), Pd(II), and Zn(II) were synthesised utilising Schiff base and 2,2'-bipyridine (2,2'-bipy) (**27**). Biological activity testing revealed that numerous metal chelates outperformed Schiff base against Gram-positive and Gram-negative. Finally, it was revealed that Zn(II) and Pd(II) complexes outperformed imine and other metal complexes in killing both types of bacteria tested.



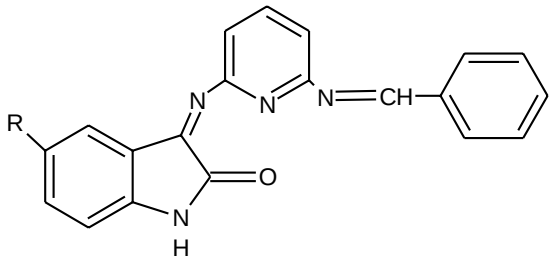
M=Cu, Co, Zn Y=2NO_3, n=1

M=Pt, Pd Y=2Cl, n=0

(**27**)

Shobhit Shrivastava and Dharmendra Ahuja (2023) [26] were prepared N^2-Benzylidenepyridine-2,6-Diamine (**28**) by the reacting 2,6-diaminopyridine with benzaldehyde.

This compound were subjected to reaction with 5-subbstituted isatin and resulatant Schiff bases were screened for antibacterial and antifungal activity. While all of the newly synthesized Schiff bases of isatin shown strong antibacterial activity against the tested strain of bacteria, only a few compounds were found to be antifungal.



R= H,F,Cl,NO_2,CH_3

(**28**)

Conclusion:

This review reveals that the pyridine compounds have a significant potential in the field of numerous biological activities that are still studied in light of their stated pharmacological characteristics. Modern coordination chemistry has greatly benefited by the synthesis of chemical moiety produced from heterocyclic molecules like 2,6-diaminopyridine. Due to the existence of one or more nitrogen atoms with a localised pair of electrons, 2,6-diaminopyridine and similar compounds make suitable ligands. Schiff bases have been continually developed from pyridine's amino derivatives like 2,6-diaminoderivatives and assessed for their biological potential. Its this property makes it a very useful and effective anti-carbicidal agent. They are regarded as a flexible pharmacophore with a wide range of biological activities along with antimicrobial that have made them an effective class of pharmaceuticals for the creation of novel drugs and remain a focus of ongoing study in medicinal chemistry.

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