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A Recent Review On Synthesis and Pharmacological Applications of Schiff Bases and Their Transition Metal Complexes

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ABSTRACT
The Schiff base is a versatile compound containing azomethine group and prepared by condensation of primary amine with aldehyde or ketone. Schiff base transition metal complex is a unique class of compound that has a wide range of applications in coordination chemistry, analytical chemistry, catalysis, pharmaceutical chemistry, etc. The medicinal study of Schiff base transition metal complexes shows that they are effective against various strains of microorganisms. Schiff base and their transition metal complexes show pharmaceutical applications due to their biological activity like anticancer, antifungal, antibacterial, anti-inflammatory, antiviral, and antidiabetic activity. This review summarizes the synthesis and pharmacological applications of Schiff bases transition metal complexes.
Keywords: Schiff bases, Metal complexes, Pharmacological applications.

I. INTRODUCTION

The Schiff base is a compound with the general formula ($R_2C=NR_1$), where R_1 represents an alkyl/aryl group but not hydrogen, and it contains the azomethine functional group[1]. Hugo Schiff noted that it is normally produced by condensing primary amine with aldehyde or ketone while eliminating one water molecule.

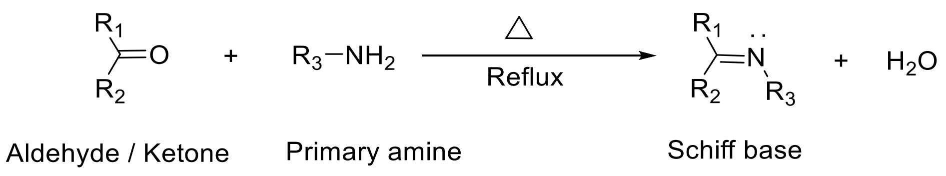

Fig. 1: Synthesis of Schiff base by condensation reaction.

The presence of a single pair of electrons on nitrogen atoms of the azomethine group (-C=N-) illustrates Schiff bases' higher chelating activity, particularly if paired with one or more donor atoms such as -OH, -COOH, C=S, and -SH nearby to the azomethine group[2]. Schiff bases are an important type of ligands in coordination chemistry, and they interact with metal ions through azomethine nitrogen[3]. Schiff base ligands have been extensively studied in coordination chemistry, owing primarily to their ease of synthesis and electrical characteristics. Schiff-base coordination chemistry has grown more attractive as a result of its potential applications in metallurgy, organic synthesis, metal refining, analytical chemistry, electroplating, and photography[4–6]. Schiff-base transition metal complexes have been used in medicine to treat infections caused by viruses. The (-C=N-) moiety is crucial for biological activity in Schiff base compounds. Schiff base transition metal complexes have medical and pharmaceutical applications comprising antifungal, anticancer, antibacterial, antioxidant, anti-inflammatory, disorders of the nervous system, and diuretic abilities[7–20]. Schiff bases are additionally applied as catalysts, organic synthesis intermediates, dyes, pigments, polymer stabilizers, and corrosion inhibitors[21,22]. This article presents an overview of the synthetic techniques used to synthesize Schiff bases and also addresses antibacterial, antifungal, and anticancer Schiff bases.

I. Biological importance of Schiff base transition metal complexes

Transition metals have varying oxidation states, which allows them to interact with ligands to form complexes, making them valuable for the manufacturing of metal-based medicines with promising pharmacological uses. Schiff base metal complexes have an essential role in medical biochemistry due to their anti-cancer, antibacterial, antifungal, antiviral, anti-inflammatory, and anti-diabetic properties.

II. Pharmacological activity of Schiff base transition metal complexes

Lotfi M. Aroua et al., 2023 synthesized Schiff base ligand by condensation of (1H-benzimidazole-2-yl)methanamine, with 2-hydroxynaphthaldehyde. Furthermore, synthesized metal complexes of Zn(II), Cr(III), and Mn(II). Synthesized metal complexes show promising activity against *E. coli* and *Bacillus subtilis*, as well as modest activity against *Aspergillus niger*. The diffusion method was used in the microbiology area to carry out these tests. *E. coli* and *Bacillus subtilis* were utilized to assess antibacterial activity. The antifungal activity of the DMSO solution was tested using *Aspergillus niger*. As a control, an empty poured disc was used. The extent to which the chemical solutions inhibited the growth of microbes was determined for the 10^{-3} M drugs studied. To compare inhibition, tetracycline, and nystatin were used as positive controls for antibacterial and antifungal activity. Bacterial and fungal growth inhibitions were found in millimeter-sized regions near the holes[23].

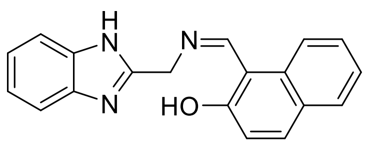

Fig.2: (Z)-1-((((1H-benzo[d]imidazol-2-yl)methyl)imino)methyl)naphthalen-2-ol

Priyanka Devi et al,.2023 synthesized 5-methyl-3-((5-bromosalicylidene) amino)-pyrazole Schiff base by condensation of of methanolic solutions of 3-amino-5-methylpyrazole and 5-bromo- salicylaldehyde for five hours in the presence of 3-4 drops glacial acetic acid. The synthesized Schiff base and its metal complexes have been examined for antibacterial properties with three Gram- positive and two Gram-negative bacteria using the well diffusion method.

The compounds were tested against foodborne pathogens such as *Staphylococcus aureus*, *sub.aureus*, *Clostridium perfringens*, *Listeria monocytogenes*, *E. coli, Pseudomonas aeruginosa* , and fungi *Aspergillus fumig atus, Aspergillus niger, and Candida albicans*. The complexes were discovered to have greater biological impacts on distinct organisms than the newly developed Schiff base[24]

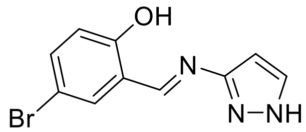

Fig. 3: (E)-2-(((1H-pyrazol-3-yl)imino)methyl)-4-bromophenol

In 2023, K. Jagadesh Babu et al. synthesized a Schiff base ligand by refluxing a methanolic solutions of 5-cyclohexyl-2-methoxyaniline and salicylaldehyde in a 1:1 mole ratio, and thereafter, synthesized its metal complexes. The agar well diffusion method was used to test the antibacterial activity of synthesized compounds and the standard drug Gentamycin sulfate against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative *E. coli* and *Klebsiella pneumonia* bacterial stains. Inhibition zones were measured in mm and compared to standard drug zones. The Agarwell diffusion method was used to evaluate the antifungal activity of produced compounds against *Aspergillus niger* and *Candida albicans*. A one-week-old fungal culture was employed as an inoculum. Nystatin was utilized as the reference antifungal medication. Compounds' antifungal activity was measured based on their inhibition zone. In-vitro investigations reveal that the complexes exceed the parent ligand in terms of antibacterial and antioxidant activity. Complexes exhibited higher cytotoxicity against A549 and MCF7 cell lines compared to their parent ligand [25].

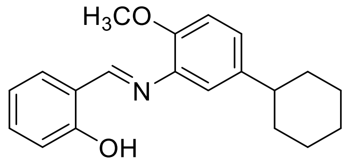

Fig. 4: (E)-2-(((5-cyclohexyl-2-methoxyphenyl)imino)methyl)phenol

In 2023, Bushra Mohan and Naser Shaalan prepared a tetradentate Schiff base by condensation of 2-Hydroxy naphthaldehyde with 2-amine benzhydrazide and subsequently synthesized its novel Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes. Schiff base and its metal complexes were examined and assessed for antibacterial and antifungal activities using the etch-diffusion technique. Two species of pathogenic bacteria, Gram-negative Klebsiella pneumonia, Gram-positive Staphylococcus aureus, and Candida albicans, were chosen to test at 24 hours under aerobic conditions at 37°C. Bacteria and fungi were preserved in nutrients, and the Schiff's base and its metal complex tests were positive. Zinc complex was more effective against gram-positive bacteria, whereas cobalt and copper complexes were most effective against gram-negative bacteria. Copper was particularly effective against Candida albicans [26].

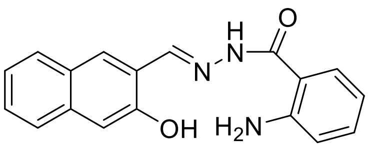

Fig. 5: (E)-2-amino-N'-((3-hydroxynaphthalen-2-yl)methylene)benzohydrazide

Dipti D. Gharat et al., 2023 synthesized the Schiff base ligand by condensation of 2-amino-6-chloro benzothiazoles and 2, 4-dihydroxybenzaldehyde in a 1:1 molar ratio, followed by the formation of bivalent complexes with metals of Fe, Cu, Co, Ni, Pd, and Zn. Using the disc diffusion method, two Gram-positive bacterial strains *B. subtilis* and *S. aureus,* two Gram-negative bacterial strains *E. coli* and *P. aeruginosa*, and two fungal strains *C. albicans* and *A. cerevisiae* were used to test all of the synthesized compounds for antibacterial and antifungal activity in vitro. The in vitro cytotoxicity effects of the ligand and its metal complexes against Artemia salina were also examined using the brine shrimp bioassay. The results confirmed that the ligand's biological functioning expanded during complexation [27].

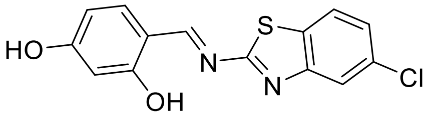

Fig. 6: (E)-4-(((5-chlorobenzo[d]thiazol-2-yl)imino)methyl)benzene-1,3-diol

In 2023, Onder Idil et al. synthesized Schiff bases of 5-bromo-3-nitro salicylaldehyde utilizing varying sulfonamide group compounds and their Cu(II) complexes. The antimicrobial activity of ligands and developed complexes has been studied in vitro against Gram-negative and Gram-positive bacteria, as well as yeast Candida albicans. The microdilution method has been applied to investigate the influence of antimicrobial compounds on bacterial colony formation and time-killing kinetics. Copper complexes exhibit stronger antibacterial activity than their equivalent ligands. It had stronger effects on *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared to *E. coli, L. monocytogenes,* and *C. albicans*[28].

Nuha Ayad Abd AL Qadir et al., 2023 synthesized the Schiff ligand by refluxing (Z)-3-hydrazineylideneindolin-2-one and hexane-2,5-dione in the presence of glacial acetic acid for four hours. It subsequently generated metal complexes of Ni(II), Mn(II), Zn(II), and Cu(II). The synthesized Schiff base and its complexes have been studied on positive bacteria *Staphylococcus aureus* and negative bacteria *Escherichia coli*, with 0.001M DMSO as a control. The results demonstrate that the Schiff base ligand and the Nickel complex have a negative inhibitory effect on *Staphylococcus aureus* bacteria [29].

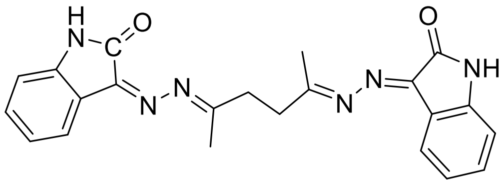

Fig. 7: (3Z,3'E)-3,3'-(((2E,5E)-hexane-2,5-diylidene)bis(hydrazine-2,1-diylidene))bis(indolin-2-one)

In 2023, Khalidah Hamil Manati Al Furaiji et al. synthesized Schiff base (4-((3-mercapto-5-(naphthalene-1-ylmethyl)-4H-1,2,4-triazole-4-yl)imino)methyl)methoxy) by stirring a methanolic solution of (4-amino-5(naphthalene-1-ylmethyl)-4H-1,2,4-triazole-3-thiol(thione)) with a methanolic solution of 4-methoxy benzaldehyde in the presence of 2-3 drops of glacial acetic acid for 24 hours. Then synthesized its metal complex of Cr(III), Mn(II), and VO(IV). In vitro study of *P. aeruginosa* and *B. subtilis* strains revealed that Schiff base has antibacterial action against both Gram-positive and Gram-negative pathogens. Metal complexes outperform the Schiff base against both types of bacteria [30].

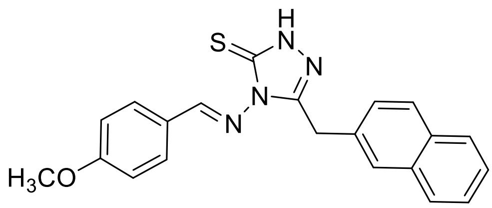

Fig. 8: (E)-4-((4-methoxybenzylidene)amino)-5-(naphthalen-2-ylmethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione

Riaz Hussain et al. (2023) synthesized two hydrazone ligands: 4-chloro-2-((4-isopropylphenyl)-hydrazono)methylphenol and 4-(2-(5-chloro-2 hydroxybenzylidene) hydrazinyl)benzonitrile, as well as their Cu(II), Ni(II), and Co(II) complexes. utilizing a disk diffusion approach, synthesized Schiff base ligands and metal complexes were tested on Gram-positive strains *Bacillus halodurans* and *Micrococcus luteus*, Gram-negative strains *E. coli* and *Salmonella*, and fungal strains *Aspergillus flavus* and *Aspergillus niger*. The results proved that the ligands were more efficient than the metal complexes against pathogenic bacteria.The Schiff base ligand 4-chloro-2-((4-isopropylphenyl)-hydrazono)methylphenol has a maximum inhibition against *E. coli* and *B. halodurans* bacterial strains, with lower activity. The second Schiff base 4-(2-(5-chloro-2 hydroxybenzylidene) hydrazinyl)benzonitrile has a 15 mm zone of inhibition against *the E. coli* bacterium strain. Ni(II) Complex of the second ligand has the strongest activity against *E. coli*, *B. halodurans*, and *M. luteus*, with inhibition zones measuring 13, 18, and 14 mm, respectively [31].

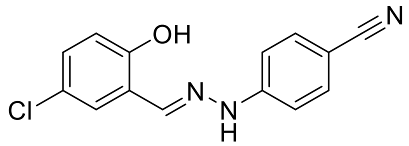

Fig. 9((E)-4-(2-(5-chloro-2-hydroxybenzylidene)hydrazinyl)benzonitrile

Haruna A. et al., 2023 synthesized the Schiff base ligand 4[(4,6-Dimethylamino-2-hydroxybenzylidene)amino]-N-thiazole-2-ylbenzenesulphonamide was produced by refluxing an ethanolic solution of sulphathiazole and 4-diethylaminosalycyaldehyde for 4 hours, followed by the synthesis of its Mn(II) complex. The antibacterial activity of the ligand and its complexes has been investigated against two Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, as well as two Gram-negative bacteria *E. coli* and *Klebsiella pneumoniae*, using the paper disk diffusion technique. The antifungal susceptibility of Schiff base ligand and its Mn(II)complex was determined using the disk diffusion method with the fungi pathogens *Aspergillus niger* and *Candida albicans*. The antimicrobial assessment results demonstrated that metal (II) complexes had more antibacterial effects than the free Schiff base ligand [32].

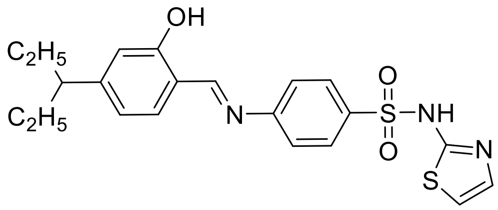

Fig. 10: (E)-4-((2-hydroxy-4-(pentan-3-yl)benzylidene)amino)-N-(thiazol-2-yl)benzenesulfonamide

Laila H. Abdel Rahman et al. (2023) synthesized two Schiff bases. 4-bromo-2-[(E)-{[4-(2-hydroxyethyl)phenyl]imino{methyl]phenol and 2-[(E)-{[4-(2-hydroxyethyl)phenyl]imino}methyl]-4-methoxyphenol by refluxing 1 mmol ethanolic solution of 2-(4-aminophenyl)ethan-1-ol with an ethanolic solution of 1mmol 5-methoxy salicylaldehyde and 1 mmol of 5-bromo salicylaldehyde, respectively. Then their metal complexes with Cr(III), Mn(II) and Fe(III). The newly synthesized compounds were tested against various bacterial species, including *Staphylococci aureus*, *Escherichia coli* , *Bacillus subtilis* , *Pseudomonas vulgaris, A. Albicans, and A. fumigatus*. The cytotoxicity for both ligands and their Mn(II), Fe(III), and Cr(III) complexes was tested on the Hep-G2 liver carcinoma and MCF7 breast cancer cell lines. All compounds did better activity relative to free ligands. The Mn(II) complex demonstrated the highest activity [33].

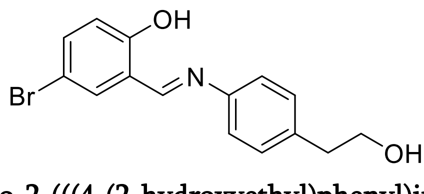

Fig. 11: (E)-4-bromo-2-(((4-(2-hydroxyethyl)phenyl)imino)methyl)pheno

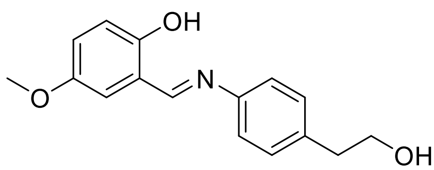

Fig. 12: (E)-2-(((4-(2-hydroxyethyl)phenyl)imino)methyl)-4-methoxyphenol

Isyaky A. et al. (2023) synthesized a Schiff base by condensing an ethanolic solution of isatin and thiosemicarbazide in a 1:1 molar ratio in the presence of acetic acid for two hours. Then synthesized its Ni(II) and Co(II) complexes. The ligand and its Co(II) and Ni(II) complexes was examined in vitro against *E. coli, Salmonella Typhimurium, and Staphylococcus aureus*. The Schiff base and its metal complexes were additionally examined against the *Mucor, Aspergillus flavus,* and *Aspergillus niger* fungal organisms species. The complexes outperformed the ligand against bacteria species, except *E. coli*, where the ligand outperformed the Co(II) complex at 300 and 400 µg/disc, respectively. At all doses, Co(II) and Ni(II) complexes outperformed the Schiff base against *Mucus* and *Aspergillus flavus* fungal isolates. However, against *Aspergillus niger,* the Schiff base outperformed the metal complexes. The Schiff base and Co(II) combination have no efficacy against *Aspergillus flavus* [34].

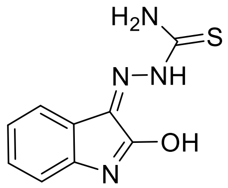

Fig. 13. (Z)-2-(2-hydroxy-3H-indol-3-ylidene)hydrazine-1-carbothioamide

In 2023, Doaa A. Nassar et al. synthesized Schiff base ligands by stirring Pyridine-2,6-diamine with 5-methyl-2-carboxaldehyde-thiophene for 6-7 hours, followed by metal complexes. The biological effects of Schiff base and its metal complexes were studied on two fungi and four bacteria. The Schiff base ligand has little effectiveness against *E. coli, A. flavus, and C. albicans*, but moderate activity against *S. aureus, B. subtilis,* and *P. vulgaris*. The Co, Ni, and Cu complexes exhibited higher activity than the ligand. The agar dilution method was used to determine the minimum inhibitory concentration (MIC) of the highly active Cd(II) complex against *S. aureus, B. subtilis,* and *E. coli* [35].

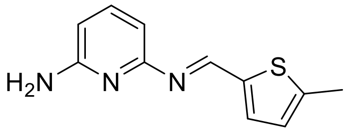

Fig. 14 (E)-6-(((5-methylthiophen-2-yl)methylene)amino)pyridin-2-amine

In 2023 Jyoti C. Ajbani et. Al., Synthesized Schiff base ligand Gabapentin - 2-hydroxy naphthaldehyde by Microwave method. Microwave irradiation of a methanolic solution containing 0.03M Gabapentin and 0.03M 2-hydroxy naphthaldehyde at 110 watts for one minute with a 30-second pulse and the reaction progress monitored by TLC. The antibacterial activity of Schiff bases and complexes was investigated in vitro against *E. coli* and *Salmonella enteric*. The well diffusion method was applied to isolate *Klebsiella pneumoniae*, *Staphylococcus aureus, Streptococcus agalactiae, Aspergillus niger,* and *Aspergillus flavus*. The culture media were Muller Hinton agar and Potato dextrose agar. Some metal complexes had considerable antibacterial and antifungal action [36].

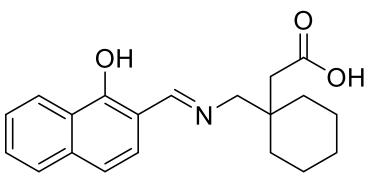

Fig. 15: Gabapentin-2-hydroxynaphthaldehyde

Binesh Kumar et. Al., 2023 synthesized the hydrazone ligands by refluxing a methanolic solution of 3,5-bis(trifluoromethyl)benzohydrazide for 5-6 hours with 2-methoxy-1-napthaldehyde or 3-bromo-5-ethoxy-4-

hydroxybenzaldehyde in the presence of 2 drops of glacial acetic acid. The metal complexes were then produced using Co(II), Ni(II), Cu(II), and Zn(II) acetate salt. In vitro, the synthesized compounds were tested for anti-TB activity against Mycobacterium tuberculosis H37Rv strain utilizing a microplate alamar blue procedure in triplicate, using streptomycin as the standard. Cu(II) and Zn(II) metal complexes have the most potential to prevent tuberculosis deformity. In comparison to streptomycin, the Zn(II) combination has roughly four times the potency to suppress tuberculosis. The Zn(II)complex had higher antibacterial and anti-inflammatory activity, with lower MIC and IC50 values [37].

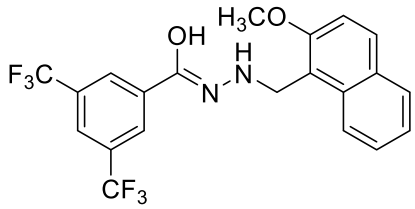

Fig. 16: (Z)-N-((2-methoxynaphthalen-1-yl)methyl)-3,5-bis(trifluoromethyl)benzohydrazonic acid

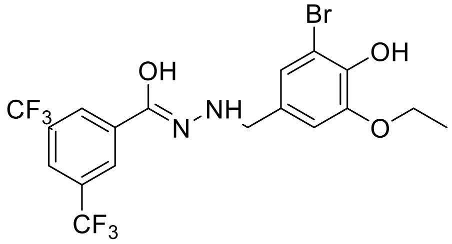

Fig. 17: (Z)-N-(3-bromo-5-ethoxy-4-hydroxybenzyl)-3,5-bis(trifluoromethyl)benzohydrazonic acid

In 2023 Emam M. Komyha et. Al., Schiff base ligand was synthesized by condensing an ethanolic solution of benzohydrazide and (E)-1-(2-(p-tolyl)hydrazono)propan-2-one in a 1:1 molar ratio for 4 hours. The metal complexes were then synthesized of Cr(III), Mn(II), Co(II), Ni(II), and Cu(II). The disc diffusion technique was utilized to evaluate the antibacterial and antifungal characteristics of gentamycin, ampicillin, and amphotericin B, which were used as positive controls for Gram-positive, Gram-negative, and fungi, respectively. Bacteria employed included Gram-positive *Bacillus subtilis, Bacillus cereus, and Staphylococcus aureus*, Gram-negative *E. coli, Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae*, and fungal *Candida albicans and Aspergillus flavus*. The complexes demonstrated better efficacy against the tested strains than the synthetic Schiff base ligand. The Skehan and Storeng approach was used to assess the cytotoxicity of synthetic substances. The Mn(II) compound showed promising effectiveness against HepG2 cells, with a low IC50 of 1.537 μg/ml [38] .

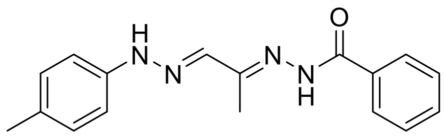

Fig. 18: N'-((1E,2E)-1-(2-(p-tolyl)hydrazono)propan-2-ylidene)benzohydrazide

Abhay Bagul et al. (2023) synthesized the Schiff base ligand 4-[2-(2-chlorobenzylidene)Hydrazinyl]-7H-pyrrolo[2,3-d]pyrimidine refluxing a hot solution of 2-chlorobenzaldehyde with a solution of pyrolopyrimidinehydrazide for 7 hours and then synthesized its metal complexes Cr(III), Fe(II), Co(II), Ni(II), and Cu(II). The synthesized Schiff base ligand 4-[2-(2-chlorobenzylidene)hydrazinyl]-7H-pyrrolo[2,3-d]Pyrimidine and its metal complexes have been studied for antibacterial properties against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative bacteria *E. coli* and *Pseudomonas aeruginosa,* and fungi *Aspergillus niger, Aspergillus flavous, and Fusarium* species, as well as cytotoxic studies against Artemia salina. Metal complexes were found to be more potent against bacteria and fungus in antibacterial and cytotoxic tests compared to the Schiff base ligand [39].

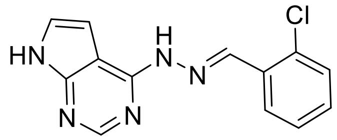

Fig. 19: (E)-4-(2-(2-chlorobenzylidene)hydrazinyl)-7H-pyrrolo[2,3-d]pyrimidine

Hawraa M Alabidia et al., 2023 synthesized Schif base ((E)-4-((4-hydroxy-3-methoxybenzylidene) amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one) by refluxing a solution of vanillin (4-hydroxy-3-methoxy benzaldehyde) and 1 ml glacial acetic acid with an ethanolic solution of 4-Amino antipyrine for 5 hours. Then Azo-Schiff derivative (4-((E)-3-((E)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)diazenyl)-4-hydroxy-5-methoxybenzylidene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one) was synthesized utilizing an azo compound 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-diazonium chloride . Azo-Schiff at a concentration of 200 mg/ml, exhibits significant antibacterial effects against Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa), with inhibition zones of 16.11 ± 0.1035 mm and 13.21 ± 0.4044, respectively. Thereafter, new Schiff base complex with Cu(II) and Ni(II) metal was prepared [40].

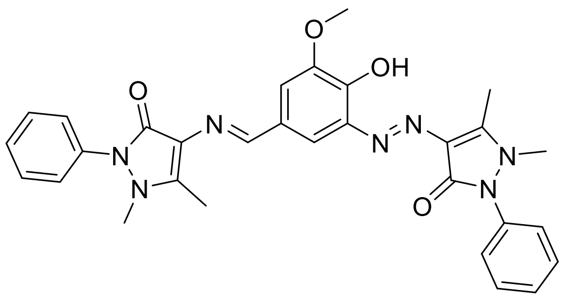

Fig. 20: 4-(((E)-3-((E)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)diazenyl)-4-hydroxy-5-methoxybenzylidene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

Ilonwa Ifeanyichukwu et al. (2023), synthesized Schiff base 4-[(3-hydroxybenzalidene)amino]antipyrine by condensing an ethanolic solution of 4-aminoantipyrine and 4-hydroxybenzaldehyde in a 1:1 molar ratio for two hours. Cu(II) metal complex was then synthesized. The disc diffusion method was applied to evaluate the antibacterial effects of both the ligand and the complex. Additionally, the minimum inhibitory concentrations (MIC) were determined using the broth dilution method. The MIC data showed that the copper complex had greater antibacterial action than the Schiff base against the examined microorganisms [41].

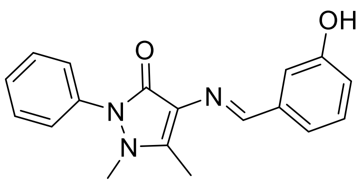

Fig. 21: (E)-4-((3-hydroxybenzylidene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

In 2023, Nagesh Gunavanthrao Yernale et al. synthesized a novel Schiff base ligand, 3-chloro-N'-(4-(diethylamino)-2-hydroxybenzylidene)-benzo[b]thiophene-2-carbohydrazide is by the condensation of 3-chlorobenzo[b]thiophene-2-carbohydrazide and 4-(diethylamino) salicylaldehyde. After that, Cu(II), Co(II), Ni(II), and Zn(II) complexes were produced. The antimicrobial activity investigation demonstrated that complex formation increased the activity of the free ligand, and the Cu(II) complex may be considered a prospective antibacterial agent, while the Ni(II) and Zn(II) complexes are promising antifungal agents. Cu(II) and Zn(II) metal complexes have displayed promising anti-tuberculosis behavior against M. tuberculosis. Furthermore, the benzo[b]thiophene-based ligand and its metal complexes were examined for in vitro antioxidant activity [42].

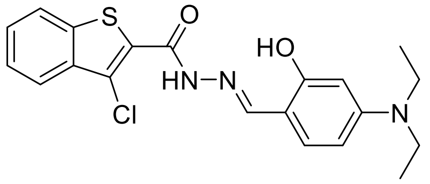

Fig. 22: (E)-3-chloro-N'-(4-(diethylamino)-2-hydroxybenzylidene)benzo[b]thiophene-2-carbohydrazide

In 2023, Noor S. Hassan and Waleed K. Mahdi synthesized a novel Schiff base ligand, N-(4-Bromo-2-methylphenyl)-1-(furan-2-yl) methenamine, by condensation of ethanolic solution of furfural and 4-Bromo-2-methylaniline in a 1:1 molar ratio in the presence of 2-3 drops of glacial acetic acid for five hours. They additionally synthesized metal complexes with VO(II), Cr(III), Mn(II), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II). The antibacterial effects of the synthesized Schiff base ligand and its complexes were investigated against Gram-positive bacteria Staphylococcus aureus, Gram-negative bacteria E. coli, and fungal strains Candida albicans were shown to be the most effective biologically active. The Cd(II) and Co(II) complexes are more efficient against the bacteria Staphylococcus aureus, but the Cd(II) and Ni(II) complexes inhibit the bacteria E. coli with greater efficacy. Cu(II) and Cd(II) complexes were more effective at inhibiting fungi [43].

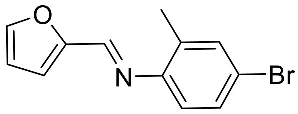

Fig. 23: (E)-N-(4-bromo-2-methylphenyl)-1-(furan-2-yl)methanimine

In 2023, Rehab Ghalib Hammoda and Naser Shaalan synthesized a novel Schiff base ligand by refluxing a 1:2 molar mixture of pyridine carboxaldehyde and Malonic acid dihydrazide in the presence of two drops of anhydrous acetic acid for four hours in an inert atmosphere. Furthermore, new complexes have been established of nickel (II), copper (II), and zinc (II). The ligand's antibacterial activity in vitro was investigated using both Gram-negative *Staph* and *E. coli* and Gram-positive *Bacillus* and *Pseudomonas* bacteria. The synthesized Schiff base ligand experienced the highest activity among its complexes against all tested bacterial species, with the Cu(II) complex showing the most activity against *Bacillus* and the Zn(II) complex showing the highest activity against *Staph* germs. Antifungal activity against several fungus strains was also assessed for the synthesized Schiff base ligand and its complexes. The synthesized Schiff base ligand has the highest action against *Candida* than its complexes [44].

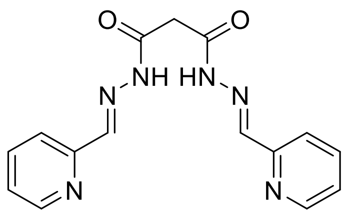

Fig. 24: N'1,N'3-bis((E)-pyridin-2-ylmethylene)malonohydrazide

I. Wazirie et. al., 2023 produced the Zn(II) complex of (Z)-4-((4-nitrophenyl)amino)pent-3-en-2-one. The Schiff base ligand (Z)-4-((4-nitrophenyl)amino)pent-3-en-2-one was produced by stirring a hot methanolic solution of 4-nitroaniline and hot acetylacetone in a 1:1 molar ratio, with five drops of formic acid, at room temperature for 6 hours. The Schiff base ligand itself and its complex were examined for antimicrobial efficacy against *Staphylococcus aureus, Streptococcus pyrogens, E. coli,* and *Klebsiella pneumoniae*, among others by using a modified disc agar diffusion technique. The broth microdilution method was used to determine the MIC of each drug. The antimicrobial investigation revealed that the Zn(II) complex has stronger antibacterial activity than the Schiff base ligand and the control Streptomycin [45].

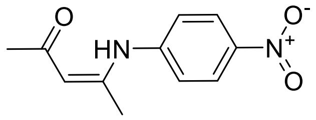

Fig. 25: (Z)-4-((4-nitrophenyl)amino)pent-3-en-2-one

In 2023, Elham S. Aazam and Maryam A. Majrashi synthesized a novel Schiff base ((E)-2-ethoxy-6((pyren-1-ylimino)methyl)phenol) and its metal complexes (Zn(II), Cu(II), Co(II), Cr(III), and Fe(III). The cytotoxic effects of the Schiff base ligand and its synthesized metal complexes were investigated on human breast cancer (MCF-7) cells. Cu(II) and Zn(II) complexes were found to be more effective than fluorouracil cancer drug against the tested cell line, particularly MCF-7 cells[46].

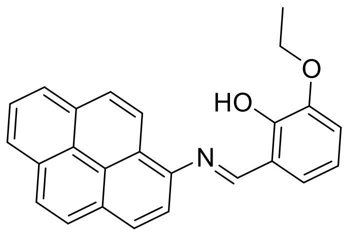

Fig. 26: (E)-2-ethoxy-6-((pyren-1-ylimino)methyl)phenol

In 2024, Kavita Poonia et. Al., synthesized a Schiff base ligand (Z)-2-(2-methyl-1-phenylpropylidene)hydrazine-1-carbothioamide by adding a hot absolute methanolic solution of isobutyrophenone to a hot methanolic solution of thiosemicarbazide in an equimolar ratio (1:1:1) along with three drops of HCl with constant stirring on a magnetic stirrer and then in micro oven for 7 minutes. The Co(II) and Mn(II) complexes were then prepared. The Schiff ligand and its metal derivatives have been tested for antibacterial, antitubercular, and anticancer properties.The antibacterial activity of the named compounds against E. coli (3 ATCC25922) and S. aureus (ATCC25923) was assessed using Muller Hinton Agar medium and the Disc diffusion procedure.The antifungal activity of the named compounds was evaluated using Sabouraud dextrose agar medium and the disc diffusion method, which is analogous to antibacterial action testing. The fungus strains employed in this investigation were Aspergillus fumigatus and Candida albicans. The fast culture - MGITTM DST method was used to perform automated antibacterial susceptibility testing of several drugs against M. tuberculosis bacteria. The metal complexes were found to be more effective antibacterial agents than the ligands, notably Mn(II) complexes against Staphylococcus aureus[47].

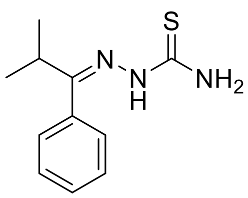

Fig. 27: (Z)-2-(2-methyl-1-phenylpropylidene)hydrazine-1-carbothioamide

In 2024, S. Sindhu et. Al., synthesized the Schiff base Ni(II) complex by condensing bis(2-hydroxy-3-methoxybenzaldehyde) nickel (II) and n-propylamine in methanol. The synthesized Ni(II) complex has been investigated for antibacterial activity by the Agar well diffusion method. Three DMSO doses (100 µg/ml, 200 µg/ml, and 300 µg/ml) were tested for their effect on the growth of Staphylococcus aureus and Escher using the well diffusion method. The results reveal significant antibacterial action against Escherichia coli and

Staphylococcus aureus when the concentration approaches 200 μg/mL. The antifungal study demonstrates substantial suppression using imidazole as a positive control (PC). Small values of MIC and MBC/MIC show that less complex is required to inhibit the growth of microorganisms[48].

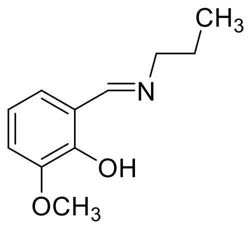

Fig. 28: Schiff base (E)-2-methoxy-6-((propylimino)methyl)phenol

II. CONCLUSION

This review article discusses current advances in Schiff bases and transition metal complexes, including synthesis, structure, and biological applications. Schiff base ligands and metal complexes play a vital role in medical domains. In the medical field, they are commonly employed as antibacterial, antifungal, and antiviral medications. Schiff bases and their complexes are extremely powerful chemotherapeutic medicines for treating a variety of malignancies. These Schiff base transiton complex actions are extremely diverse. There is a pressing need for more effective antibacterial and antifungal medicines due to high death rates from bacterial and fungal infections, as well as an increase in multidrug-resistant strains.

III. REFERENCES

[1]. Ainscough, E. W.; Brodie, A. M.; Dobbs, A. J.; Ranford, J. D.; Waters, J. M. Antitumour Copper (II) Salicylaldehyde Benzoylhydrazone (H2sb) Complexes: Physicochemical Properties and the Single-Crystal X-Ray Structures of [{Cu (H2sb)(CCl3CO2) 2} 2] and [{Cu (Hsb)(ClO4)(C2H5OH)} 2] and the Related Salicylaldehyde Acetylhydrazone (H2sa) Complex,[Cu (Hsa) Cl (H2O)]· H2O. Inorganica Chim Acta 1998, 267 (1), 27–38.

[2]. Osowole, A. A.; Ott, I.; Ogunlana, O. M. Synthesis, Spectroscopic, Anticancer, and Antimicrobial Properties of Some Metal (II) Complexes of (Substituted) Nitrophenol Schiff Base. Int J Inorg Chem 2012, 2012.

[3]. Vigato, P. A.; Tamburini, S. The Challenge of Cyclic and Acyclic Schiff Bases and Related Derivatives. Coord Chem Rev 2004, 248 (17–20), 1717–2128.

[4]. Pfeiffer, P.; Buchholz, E.; Bauer, O. Innere Komplexsalze von Oxyaldiminen Und Oxyketiminen. Journal für Praktische Chemie 1931, 129 (1), 163–177.

[5]. Pfeiffer, P.; Breith, E.; Lübbe, E.; Tsumaki, T. Tricyclische Orthokondensierte Nebenvalenzringe. Justus Liebigs Ann Chem 1933, 503 (1), 84–130.

[6]. Pfeiffer, P.; Pfitzner, H. Hochatomare Nebenvalenzringe Mit Meta-und Para-Kondensation. Journal für Praktische Chemie 1936, 145 (3-9), 243–256.

[7]. Bassanetti, I.; Atzeri, C.; Tinonin, D. A.; Marchio, L. Silver (I) and Thioether-Bis (Pyrazolyl) Methane Ligands: The Correlation between Ligand Functionalization and Coordination Polymer Architecture. Cryst Growth Des 2016, 16 (6), 3543–3552.

[8]. Ibrahim, F. M. Polyether Hexadentate Schiff Base Ligand with Trivalent Chromium, Iron, Cobalt Ions. J Al-Nahrain Univ Sci 2017, 20 (4), 1–6.

[9]. Abu-Hussen, A. A. A. Synthesis and Spectroscopic Studies on Ternary Bis-Schiff-Base Complexes Having Oxygen and/or Nitrogen Donors. J Coord Chem 2006, 59 (2), 157–176.

[10]. Jaros, S. W.; Guedes da Silva, M. F. C.; Florek, M.; Smoleński, P.; Pombeiro, A. J. L.; Kirillov, A. M. Silver (I) 1, 3, 5-Triaza-7-Phosphaadamantane Coordination Polymers Driven by Substituted Glutarate and Malonate Building Blocks: Self-Assembly Synthesis, Structural Features, and Antimicrobial Properties. Inorg Chem 2016, 55 (12), 5886–5894.

[11]. Mladenova, R.; Ignatova, M.; Manolova, N.; Petrova, T.; Rashkov, I. Preparation, Characterization and Biological Activity of Schiff Base Compounds Derived from 8-Hydroxyquinoline-2-Carboxaldehyde and Jeffamines ED®. Eur Polym J 2002, 38 (5), 989–999.

[12]. Karthikeyan, M. S.; Prasad, D. J.; Poojary, B.; Bhat, K. S.; Holla, B. S.; Kumari, N. S. Synthesis and Biological Activity of Schiff and Mannich Bases Bearing 2, 4-Dichloro-5-Fluorophenyl Moiety. Bioorg Med Chem 2006, 14 (22), 7482–7489.

[13]. Singh, K.; Barwa, M. S.; Tyagi, P. Synthesis, Characterization and Biological Studies of Co (II), Ni (II), Cu (II) and Zn (II) Complexes with Bidentate Schiff Bases Derived by Heterocyclic Ketone. Eur J Med Chem 2006, 41 (1), 147–153.

[14]. Pandeya, S. N.; Sriram, D.; Nath, G.; DeClercq, E. Synthesis, Antibacterial, Antifungal and Anti-HIV Activities of Schiff and Mannich Bases Derived from Isatin Derivatives and N-[4-(4′-Chlorophenyl) Thiazol-2-Yl] Thiosemicarbazide. European Journal of Pharmaceutical Sciences 1999, 9 (1), 25–31.

[15]. Panneerselvam, P.; Nair, R. R.; Vijayalakshmi, G.; Subramanian, E. H.; Sridhar, S. K. Synthesis of Schiff Bases of 4-(4-Aminophenyl)-Morpholine as Potential Antimicrobial Agents. Eur J Med Chem 2005, 40 (2), 225–229.

[16]. Sridhar, S. K.; Saravanan, M.; Ramesh, A. Synthesis and Antibacterial Screening of Hydrazones, Schiff and Mannich Bases of Isatin Derivatives. Eur J Med Chem 2001, 36 (7–8), 615–625.

[17]. Mladenova, R.; Ignatova, M.; Manolova, N.; Petrova, T.; Rashkov, I. Preparation, Characterization and Biological Activity of Schiff Base Compounds Derived from 8-Hydroxyquinoline-2-Carboxaldehyde and Jeffamines ED®. Eur Polym J 2002, 38 (5), 989–999.

[18]. Walsh, O. M.; Meegan, M. J.; Prendergast, R. M.; Al Nakib, T. Synthesis of 3-Acetoxyazetidin-2-Ones and 3-Hydroxyazetidin-2-Ones with Antifungal and Antibacterial Activity. Eur J Med Chem 1996, 31 (12), 989–1000.

[19]. Nagajothi, A.; Kiruthika, A.; Chitra, S.; Parameswari, Kjrj. Fe (III) Complexes with Schiff Base Ligands: Synthesis, Characterization, Antimicrobial Studies. Research Journal of Chemical Sciences ISSN 2013, 2231, 606X.

[20]. Dave, S.; Bansal, N. Application of Schiff Bases as Therapeutic Agent-a Review. Int J Curr Pharm Res 2013, 5 (1), 6–7.

[21]. Dhar, D. N.; Taploo, C. L. Schiff Bases and Their Applications. J Sci Ind Res 1982, 41 (8), 501–506.

[22]. Li, S.; Chen, S.; Lei, S.; Ma, H.; Yu, R.; Liu, D. Investigation on Some Schiff Bases as HCl Corrosioninhibitors for Copper. Corros Sci 1999, 41 (7), 1273–1287.

[23]. Aroua, L. M.; Alhag, S. K.; Al-Shuraym, L. A.; Messaoudi, S.; Mahyoub, J. A.; Alfaifi, M. Y.; Al-Otaibi, W. M. Synthesis and Characterization of Different Complexes Derived from Schiff Base and Evaluation as a Potential Anticancer, Antimicrobial, and Insecticide Agent. Saudi J Biol Sci 2023, 30 (3), 103598.

[24]. Devi, P.; Singh, K.; Kubavat, B. Synthesis, Spectroscopic, Quantum, Thermal and Kinetics, Antibacterial and Antifungal Studies: Novel Schiff Base 5-Methyl-3-((5-Bromosalicylidene) Amino)- Pyrazole and Its Transition Metal Complexes. Results Chem 2023, 5, 100813. https://doi.org/https://doi.org/10.1016/j.rechem.2023.100813.

[25]. Babu, K. J.; Ayodhya, D. Comprehensive Investigation of Co (II), Ni (II) and Cu (II) Complexes Derived from a Novel Schiff Base: Synthesis, Characterization, DNA Interactions, ADME Profiling, Molecular Docking, and in-Vitro Biological Evaluation. Results Chem 2023, 6, 101110.

[26]. Mohan, B.; Shaalan, N. Synthesis, Spectroscopic, and Biological Activity Study for New Complexes of Some Metal Ions with Schiff Bases Derived From 2-Hydroxy Naphthaldehyde with 2-Amine Benzhydrazide. Ibn AL-Haitham Journal For Pure and Applied Sciences 2023, 36 (1), 208–224.

[27]. Gharat, D. D.; Mhatre, K. P.; Yamgar, R. S.; Ajagekar, S. D. Synthesis, Spectral Studies and Antimicrobial Screening of Metal Complexes of Schiff Base Derived from Substituted Salicylaldehyde and 2-Amino-6-Chloro Benzothiazole. J Surv Fish Sci 2023, 4298–4304.

[28]. İdil, Ö.; Şahal, H.; Canpolat, E.; Özkan, M. Synthesis, Characterization, Antimicrobial and Time Killing Activities of New Sulfa-Derived Schiff Bases Coordinated with Cu (II). Indonesian Journal of Chemistry 2023.

[29]. Alabidi, H. M.; Farhan, A. M.; Salh, N. S.; Aljanaby, A. A. J. New Azo-Schiff Compounds and Metal Complexes Derived from 2-Naphthol Synthesis, Characterization, Spectrophotometric, and Study of Biological Activity. Curr Appl Sci Technol 2023, 10–55003.

[30]. Al Furaiji, K. H. M.; Al Hassani, R. A. M.; Hussein, H. H. Synthesis and Antibacterial Activity of Azomethine Ligand and Their Metal Complexes: A Combined Experimental and Theoretical Study. Indonesian Journal of Chemistry.

[31]. Hussain, R.; Rubab, S. L.; Maryam, A.; Ashraf, T.; Arshad, M.; Lal, K.; Sumrra, S. H.; Ashraf, S.; Ali, B. Synthesis, Spectroscopic and Nonlinear Optical Properties, and Antimicrobial Activity of Cu (II), Co (II), and Ni (II) Complexes: Experimental and Theoretical Studies. ACS Omega 2023, 8 (45), 42598–42609.

[32]. Haruna, A.; Sirajo, I. T.; Rumah, M. M.; Albashir, Y. Synthesis, Characterization, Biological Properties, ADMET and Drug-Likeness Analysis of Mn (II) Complexes with Schiff Bases Derived from Sulphathiazole and 4-Diethylaminosalicyaldehyde/Salicyaldehyde. Journal for Research in Applied Sciences and Biotechnology 2023, 2 (6), 58–68.

[33]. Abdel-Rahman, L. H.; Abdelghani, A. A.; AlObaid, A. A.; El-ezz, D. A.; Warad, I.; Shehata, M. R.; Abdalla, E. M. Novel Bromo and Methoxy Substituted Schiff Base Complexes of Mn (II), Fe (III), and Cr (III) for Anticancer, Antimicrobial, Docking, and ADMET Studies. Sci Rep 2023, 13 (1), 3199.

[34]. Isyaku, S.; Bello, J.; Aliyu, H. N.; Abubakar, T.; Imam, M. Synthesis, Spectroscopic Determination and in Vitro Antimicrobial Studies of Cobalt (Ii) and Nickel (Ii) Complexes of a Schiff Base Derived from 1h-Indole-2, 3-Dione with Hydrazinecarbothioamide. Science World Journal 2023, 18 (3), 341–347.

[35]. Nassar, D. A.; Ali, O. A. M.; Shehata, M. R.; Sayed, A. S. S. Spectroscopic Investigation, Thermal Behavior, Catalytic Reduction, Biological and Computational Studies of Novel Four Transition Metal Complexes Based on 5-Methylthiophene Schiff Base Type. Heliyon 2023.

[36]. Ajbani, J. C.; Revankar, D. S.; Revanasiddappa, M.; Krishna, S. B. N.; Shankara, S. Synthesis, Characterization and Antimicrobial Studies of Gabapentin Schiff Base Metal Complexes Containing Heterocyclic Ligand via Microwave-Assisted Method. Curr Trends Biotechnol Pharm 2023, 17 (Supplement 3A), 1116–1128.

[37]. Kumar, B.; Devi, J.; Dubey, A.; Tufail, A.; Taxak, B. Investigation of Antituberculosis, Antimicrobial, Anti-Inflammatory Efficacies of Newly Synthesized Transition Metal (II) Complexes of Hydrazone Ligands: Structural Elucidation and Theoretical Studies. Sci Rep 2023, 13 (1), 15906.

[38]. Komyha, E. M.; Mahmoud, W. H.; Hosny, W. M.; El-Sherif, A. A. Design, Structural Characterization, Molecular Docking and Biomedical Applications Of Hydrazone-Based Schiff Base Metal Complexes. Egypt J Chem 2023, 66 (13), 1219–1230.

[39]. Bagul, A.; Gaikwad, D.; Patil, Y. Synthesis and Characterization of Some Transition Complexes with 4-[2-(2-Chlorobenzylidene) Hydrazinyl]-7H-Pyrrolo [2, 3-d] Pyrimidine: Antimicrobial and Cytotoxic Activity. 2023.

[40]. Alabidi, H. M.; Farhan, A. M.; Al-labban, H. M. Y.; Aljanaby, A. A. J. New Derivatives from 4-Amino Anti-Pyrine and Vanillin, Synthesis Characterization and Antibacterial Activity. Egypt J Chem 2023, 66 (1), 175–181.

[41]. Ifeanyichukwu, I.; Eunice, E. U.; Ajoko, I. T.; Jim-Halliday, T. T. Molecular Docking, Synthesis and Antimicrobial Evaluation of 4-[(3-Hydroxybenzalidene) Amino] Antipyrine and Its Copper Complex. Sch Int J Chem Mater Sci 2023, 6 (9), 149–162.

[42]. Yernale, N. G.; Mathada, B. S.; Shivprasad, S.; Hiremath, S.; Karunakar, P.; Venkatesulu, A. Spectroscopic, Theoretical and Computational Investigations of Novel Benzo [b] Thiophene Based Ligand and Its M (II) Complexes: As High Portentous Antimicrobial and Antioxidant Agents. Spectrochim Acta A Mol Biomol Spectrosc 2023, 302, 123114.

[43]. Hassan, N. S.; Mahdi, W. K. Spectroscopic and Antimicrobial Studies of Some Metal Complexes of Furfural Schiff Base Derivative Ligand. 2023.

[44]. Hammoda, R. G.; Shaalan, N. Synthesis, Spectroscopy and Biological Activity Study of Some New Complexes with Schiff Base Derived From Malonic Acid Dihydrazide with 2-Pyridine Crboxaldehyde. Baghdad Science Journal 2023.

[45]. Waziri, I.; Wahab, O. O.; Mala, G. A.; Oselusi, S. O.; Egieyeh, S. A.; Nasir, H. Zinc (II) Complex of (Z)-4-((4-Nitrophenyl) Amino) Pent-3-En-2-One, a Potential Antimicrobial Agent: Synthesis, Characterization, Antimicrobial Screening, DFT Calculation and Docking Study. Bull Chem Soc Ethiop 2023, 37 (3), 633–651.

[46]. Aazam, E. S.; Majrashi, M. A. Novel Schiff Base Derived from Amino Pyrene: Synthesis, Characterization, Crystal Structure Determination, and Anticancer Applications of the Ligand and Its Metal Complexes. Molecules 2023, 28 (21), 7352.

[47]. Ghanghas, P.; Poonia, K. Synthesis, Characterization and Biological Activities of Novel Schiff Base Ligand and Its Co (II) and Mn (II) Complexes. Results Chem 2024, 7, 101221.

[48]. Sindhu, S.; Arockiasamy, S. Synthesis, Crystal Structure, Thermal Stability and Biological Study of Bis {(2-Methoxy-6-[(E)-(Propylimino) Methyl] Phenolato} Nickel (II) Complex. Heliyon 2024.