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Review Article

Synthetic methodologies and pharmacological applications of sulphonamide containing Schiff bases and their metal complexes: A comprehensive review

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ABSTRACT

Schiff bases are useful chemical compounds with a wide range of applications. The Schiff bases are synthesized via the condensation reaction between carbonyl compounds (aldehydes or ketones) and compounds having an amine group and the Schiff base is characterised by an imine or azomethine (-C=N-) group. These compounds are extensively used as ligands to form coordination complexes with metal ions and are widely utilized in the treatment of various ailments. Sulphonamides are biologically significant class of drug-like chemical derivatives due to their good oral absorption and urine excretion. Sulphonamides are widely used as antimicrobial, anti-inflammatory, anticancer and antiviral drugs in addition to acting as powerful Carbonic anhydrase hCA inhibitors, HIV protease inhibitors, anti-obesity and anti-thyroid agents because of their less poisonous, more reactive and cost-effective nature. Sulphonamide-based Schiff bases and their metal chelates have attracted the focus of researchers due to their broad range of pharmacological characteristics. In this review, various pharmacological uses of Schiff base metal complexes generated from sulphonamide derivatives are discussed.

1. Introduction

Hugo Schiff, a German scientist, first used the term "Schiff's base" in 1864 to describe the compounds generated when primary amines were combined with carbonyl compounds. To create the diversity of these compounds, various alkyl or aryl substituents are combined to form the fundamental group of compounds known as Schiff bases (-C=N-), which are identified by the presence of a double bond between carbon and nitrogen atoms (Figure 1). Even a decade after the invention of Schiff bases in coordination chemistry, they continue to play a significant role as ligands. To determine the potential of Schiff bases to form complexes with transition metal ions, azo-methine is a crucial component.[1,2]

Schiff bases are essential in the biological field due to the presence of the nitrogen atom in azomethine responsible for exhibiting pharmacological actions.[3,4] According to the literature, the hydrogen bonding between the active centres of cell components and the imino group of Schiff bases is related to therapeutic efficacy. In coordination chemistry, Schiff bases are frequently utilized as chelating ligands because they are known to form durable complexes with metal ions. Schiff bases have a major impact on inorganic chemistry by producing incredibly stable complexes with a variety of transition and inner-transition metals. Schiff

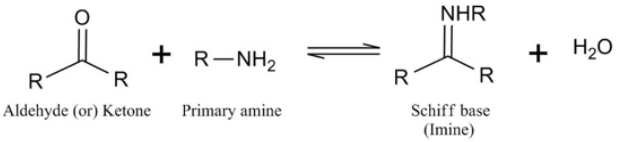

Fig. 1: General synthesis of schiff base

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base metal complexes have a crucial role to play in the treatment of many diseases as well as in the development of antibacterial, antifungal, anticancer and anti-inflammatory properties. Additionally, these organometallic materials are used as a catalyst in numerous reactions, including Aldol reaction, polymerization reaction, oxidation reaction and others. These metal complexes act by interacting with intracellular biomolecules, enhancing lipophilicity, altering cell membrane functions, inhibiting enzymes and arresting cell cycle. These metal complexes have attracted a lot of attention. It is generally known that the coordination of metals in the active sites of various metallo-biomolecules depends profoundly on the N, O and S atoms. [5–9]

Sulphonamides are biologically significant class of drug-like chemical derivatives. Due to their good oral absorption and urine excretion, sulphonamides are biologically relevant class of compounds. As a result, these molecules are less toxic, more reactive and cost-effective. Sulphonamides are now widely employed as antimicrobial, anti-inflammatory, anticancer and antiviral drugs in addition to acting as powerful Carbonic anhydrase hCA inhibitors, HIV protease inhibitors, anti-obesity and anti-thyroid agents. Sulphonamide-based Schiff base ligands and their metal complexes have attracted more attention from scientists due to their pharmacological characters. These Schiff bases were synthesised by the condensation of sulphonamide compounds with atleast a -NH_2 group and aldehyde which could lead to physiologically active compounds. [10,11]

In this review, only the literature indexed in ScienceDirect, PubMed, Springer, Google Scholar, ResearchGate and Wiley Online databases were surveyed. The keywords for this survey include Schiff bases, sulphanilamide, metal complexes, biological activity and coordination chemistry, both individually and in combination were applied and shortlisted according to the purpose of this study. This review focuses on the synthetic and pharmacological applications of Schiff base metal complexes derived from sulphanilamide derivatives.

2. Synthesis and Biological Applications of Sulphonamide-Based Schiff Base Metal Complexes

Adetoye et al. synthesized sulphanilamide-based Schiff base by adding an equimolar amount of isatin dissolved in methanol to sulphanilamide gradually at room temperature with continuous stirring. To the reaction mixture, a few drops of concentrated H_2SO_4 was added as an acid catalyst and stirring was continued for 60 min resulting in a yellow-coloured product. The prepared ligand was then again stirred with an equimolar amount of metal salts including $CoCl_2.6H_2O$, $MnCl_2.4H_2O$, $Cu(CH_3COO)_2.H_2O$ and $NiCl_2.6H_2O$ dissolved in methanol with the addition of 5mL of concentrated ammonia solution. The colour of the complexes observed in a short period of time and the coloured products were produced after the reaction mixture was refluxed for 2 h (Figure 2). [12]

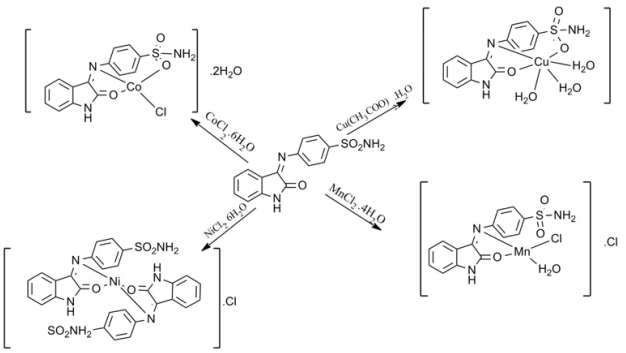

Fig. 2: Synthesis of Sulphanilamide based Schiff base metal complexes

Athar et al. synthesized the Schiff base ligands namely 3-{[(1E)-(2-hydroxy-7-methylquinolin-3-yl)methylene]amino}benzenesulphonamide and 3-{[(1E)-(2-hydroxy-7-methoxyquinolin-3-yl)methylene]amino}benzenesulphonamide by refluxing 3-aminobenzenesulphonamide with 2-hydroxy-7-methylquinoline-3-carbaldehyde and 2-hydroxy-7-methoxyquinoline-3-carbaldehyde in ethanol using con. H_2SO_4 as a catalyst for 5 h at 75 °C. The resulted Schiff bases were refluxed with Cu, Co, Ni and Zn salts in 2:1 ratio for 5-7 h at 70-75 °C. Using the disc diffusion technique, the antibacterial potential of the synthesized ligand and complexes were determined against gram-positive bacteria such as *Bacillus cereus* and *Streptococcus pneumoniae* and gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*. The results showed that the metal chelates had higher antibacterial activity than the Schiff base ligands (Figure 3). [13]

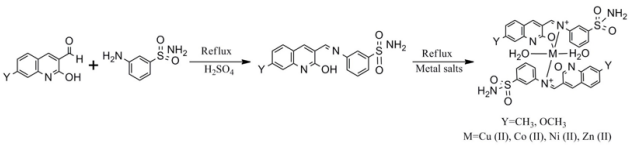

Fig. 3: 3-{[(1E)-(2-hydroxy-7-methyl/methoxy quinolin-3-yl)methylene]amino}benzenesulphonamide Schiff base metal complexes

Anacona et al. synthesized sulphathiazole-based Schiff base by refluxing 1 mmol of cephalexin with 1 mmol of sulphathiazole in hot methanol and the reaction mixture was refluxed under a nitrogen atmosphere at 70 °C for 3 h. To the ethanolic solution of Schiff base ligand, the metal acetate salts of manganese, cobalt, nickel and zinc dissolved in water were slowly added with continuous stirring and potassium hydroxide solution was added to adjust the pH to 7-8 and the reaction mixture was refluxed for 4 h. The antibacterial efficacy of the Schiff base ligand and its metal

chelates were evaluated against *Staphylococcus aureus* and *E. coli* and the results revealed that the ligand exhibited 12.0 ± 1.0 and 15.0 ± 1.0 mm of zone of inhibition and metal complexes exhibited between 6.0 ± 1.0 and 18.0 ± 1.0 mm of zone of inhibition against the respective organisms (Figure 4).[14]

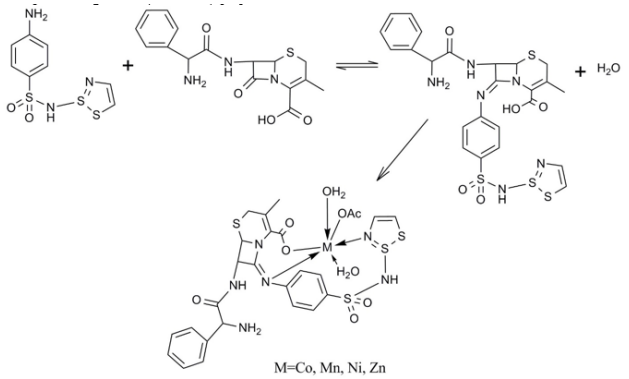

Fig. 4: Synthesis of sulphathiazole based Schiff base metal complexes

Sulphadiazine Schiff base ligand was synthesized by refluxing 1mmol of cephalothin and 1mmol of sulphadiazine in hot methanol at 70°C for 3 h under a nitrogen atmosphere. The acetate salts of cobalt, manganese, nickel and zinc dissolved in water were added slowly to the ethanolic solution of Schiff base with continuous stirring and potassium hydroxide solution was added to adjust the pH to 7-8 and the reaction mixture was refluxed for 4 h. The antibacterial action of the Schiff base ligand and its metal complexes were determined against *E. coli* and *S. aureus* using the disc diffusion method and the results showed that the ligand exhibited 13.0 ± 1.0 and 16.0 ± 1.0 mm of zone of inhibition and metal complexes exhibited between 5.0 ± 1.0 and 19.0 ± 1.0 mm of zone of inhibition against the respective organisms (Figure 5).[15]

Reiss et al. synthesized a tridentate sulphathiazole based (ONN) Schiff base by refluxing sulphathiazole with salicylaldehyde in ethanol for 3 h. The resulted orange-coloured product was refluxed with the ethanolic solution of metal salts (cobalt, nickel and copper) for 4 h. The antimicrobial efficacy of the Schiff base and its metal chelates were determined against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *E. coli* and *S. aureus* using amoxicillin as standard. The results revealed that all the complexes were found to be more active against all these organisms in the order of Cu complex<Co complex< Ni complex. The Cu complex showed 40, 45, 42 and 43 mm of zone of inhibition, Ni complex showed 33, 37, 36 and 37 mm of zone of inhibition and Co complex showed 35, 40, 37 and 38 mm of zone of inhibition against *E. coli*, *S. aureus*, *B. subtilis* and *P. aeruginosa*.[16]

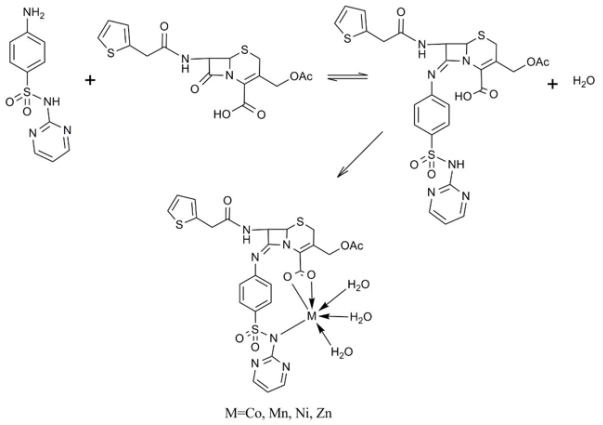

Fig. 5: Synthesis of Sulphadiazine based Schiff base metal complexes

Ejelonu and co-workers synthesized the sodium salt of sulphadiazine Schiff base by stirring sodium hydroxide with sulphadiazine Schiff base for 1 h. To 1mmol of ligand, 1mmol of metal salts such as $CoCl_2.6H_2O$, $CuCl_2.21/2H_2O$, $Ni(NO_3)_2.21/2H_2O$ and $ZnCl_2$ were added slowly and continued stirring for 2 h. After adding 1mmol of aniline dithiocarbamate and stirring for 3 h, the coloured mixed ligand complexes were formed. The antimicrobial activity of the ligand and metal complexes were determined against the bacterial strains including *E. coli, Proteus vulgaris, Salmonella pneumonia, P. aeruginosa, Vibro chlolerae, Klebseilla pneumonia, Salmonella typhi, Shigella flexneri, S. aureus, B. subtilis* and Streptococcus pneumonia and fungal strains including *Aspergillus flavus, Mucor mucedo, Aspergillus niger, Fusarium solani, Candida albicans, Aspergillus fumigatus, Rhizopus stolon, Saccharo mycodis ludwigii, Mucor mucedo and Monilia amaricana*. The results showed that the metal complexes were more efficient than the parent ligand (Figure 6).[17]

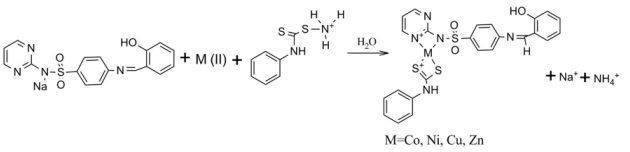

Fig. 6: Synthesis of tridentate sulphathiazole based Schiff base metal complexes

Sharaby prepared 2-thiophene carboxaldehyde-sulphametrole Schiff base by refluxing N1-(4-methoxy-1,2,5-thiadiazol-3-yl)sulphanilamide with 2-thiophene carboxaldehyde at 60 °C for 2 h. The metal complexes were synthesized by refluxing Cu, Mn, Ni and Zn chloride salts with the prepared ligand at 60 °C for 1 h with continuous stirring. The antimicrobial activity was evaluated against *E. coli, S. aureus, Bacillus subtilis, S. typhi, A. flavus* and

Aspergillus terreus. The results revealed that metallation increases the activity of the Schiff base ligands (Figure 7).[18]

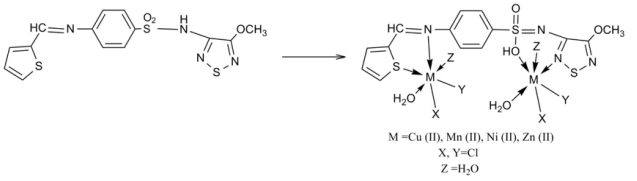

Fig. 7: Synthesis of 2-thiophene carboxaldehyde-sulphametrole based Schiff base metal complexes

Sulphametrole [N'-(4-methoxy-1,2,5-thiadiazol-3-yl]sulphanilamide and acetyl-acetone was refluxed with continuous stirring for 3 h to synthesize a novel sulphonamide based Schiff base. For the preparation of metal complexes, the chloride salts of copper and zinc in dry ethanol were added slowly dropwise to the ligand and refluxed for 2 h. For the preparation of mixed ligand complexes, synthesized Schiff base ligand as a primary ligand and glycine as a secondary ligand dissolved in dry ethanol were added. The ethanolic metal salts were added to the reaction mixture dropwise and heated under reflux for 2 h. The antimicrobial potential of the Schiff base, metal complexes and mixed ligand complexes were evaluated against *S. typhimurium, B. subtilis, S. aureus, E. coli, Aspergillus fumigatus and C. albicans*. The mixed ligand complexes and metal complexes were found to be efficient against the microorganisms than the ligands. The anticancer activity of the ligands, mixed ligand complexes and metal complexes were evaluated against the human breast (MCF-7) cancer cell line. The results indicated that the Schiff base ligand showed 21.7 μg of IC_{50} value, Cu and Zn metal complexes showed 4.31 and 8.88 μg of IC_{50} value and Cu and Zn mixed ligand complexes showed 9.32 and 11.1 μg of IC_{50} value against the breast cancer cell line (Figure 8).[19]

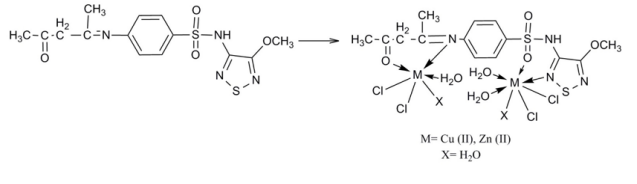

Fig. 8: Synthesis of Sulphametrole-acetylacetone based Schiff base metal complexes

Chohan and co-workers prepared 4-{[(Z)–(5-Bromo-2-hydroxyphenyl)methylidene]amino}-N-(5-methylisoxazol-3-yl)benzenesulphonamide and 4-(2-{[(E)–(5-Bromo-2-hydroxyphenyl)methylidene]amino}ethyl)-benzenesulphonamide Schiff bases by refluxing the ethanolic solution of sulphamethoxazole and 5-bromosalicylaldehyde for 3 h with continuous stirring. To a hot magnetically stirred dioxane Schiff bases, Cu, Co, Ni and Zn salts were added and refluxed for 2 h. For Schiff base ligands and metal complexes, in vitro antibacterial activity was determined against bacterial strains namely E. coli, Shigella flexneri, P. aeruginosa and *S. typhi* and the antifungal activity was determined against fungal strains namely *C. albicans, Candida glabrata, A. flavus, Fusarium solani* and *Microsporum canis*,. The results revealed that the antibacterial and antifungal activity of ligands increased upon coordination. The chelation/coordination process increases the metal's lipophilicity by reducing the polarity of the transition metal ion through coordination with ligands. This lipophilic nature of metal enhanced its penetration through the lipoid layer of the cell membrane of the microorganism. The cytotoxicity of the Schiff base ligands and metal complexes was determined using Brine shrimp bioassay and the results showed that all the complexes were more active especially, Zn complexes of 4-(2-{[(E)–(5-Bromo-2-hydroxyphenyl)methylidene]amino}ethyl)-benzenesulphonamide exhibited excellent cytotoxic activity against Artemia salina (Figure 9).[20]

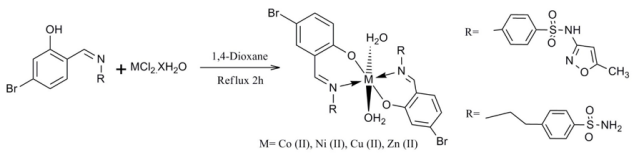

Fig. 9: Synthesis of Sulphamethoxazole-5-bromosalicylaldehyde Schiff base metal complexes

A novel sulphonamide, 1-tosyl-1-H-benzo(d)imidazol-2-amine (TBZA) was synthesized in one step by dissolving 4-dimethylaminopyridine (4-DMAP), p-toluenesulphonyl chloride and Et3N (triethylamine) in dry CH_2Cl_2 at room temperature under argon environment. The Cu, Co and Zn complexes were prepared by dissolving metal salts namely $CuCl_2.2H_2O$, $CoCl_2.6H_2O$ and $ZnCl_2.H_2O$ with TBZA ligand. The antifungal efficiency of the ligand TBZA and its complexes were determined against *C. albicans, C. glabrata, Candida tropicalis, Candida krusei, Candida guilliermondii, Candida dubliniensis, Cryptococcus gattii and Cryptococcus neoformans*. The results indicated that the ligand and complexes showed maximum zones of inhibition against C. neoformans in the range of 18±3, 20±3, 15±1, and 22±3 mm. The TBZA ligand and its complexes were proved to be significant antifungal agent (Figure 10).[21]

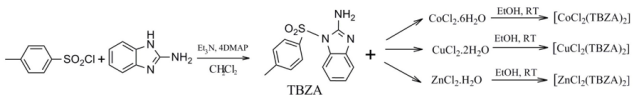

Fig. 10: Synthesis of TBZA Schiff base metal complexes

Sekhar et al. prepared a novel Schiff base ligand namely 4-((thiophen-2-ylmethylene)amino)benzenesulphonamide (TMABS) by refluxing 4-aminobenzene sulphonamide with thiophene-2-carbaldehyde in methanol with a small amount of glacial acetic acid for 3 h. The prepared TMABS ligand was refluxed with chloride and acetate salts of Cu, Co, Ni and Zn for 3 h. The antioxidant efficiency of the ligand and its metal chelates were determined using DPPH assay. Among the different complexes, Co and Cu complexes showed 13±00.2 and 9.5±0.1 μM of IC_{50} values. The antimicrobial actions of the Schiff base and its complexes were determined against *E. coli, B. subtilis, S. aureus, S. typhi, Penicillium rubrum* and *A. niger* using the agar well diffusion method. The results indicated that none of the synthesized molecules showed greater efficiency than the standards fluconazole (38–52 mm Zone of Inhibition) and streptomycin sulphate (22–28 mm Zone of Inhibition) (Figure 11).[22]

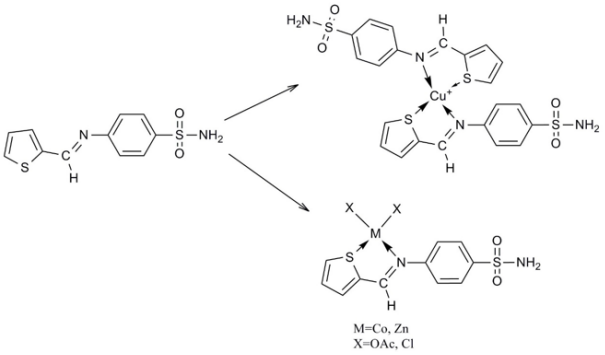

Fig. 11: Synthesis of TMABS Schiff base metal complexes

Ebrahimi et al. synthesized two Schiff bases namely 4-(2-hydroxy-3-methoxybenzylidenamine)-N-(5-methylisoxozaol-3-yl) benzenesulphonamide and 4-(2-hydroxy-3-methoxybenzylidenamine)-N-(thiazole-2-yl) benzene sulphonamide by refluxing sulphamethoxazole / sulphathiazole with o-vanillin dissolved in ethanol with a small amount of glacial acetic acid for 2 h. For the synthesis of metal complexes, metal acetate salts and ligands in hot methanol were refluxed for 3 h with a few drops of sodium hydroxide to adjust the pH to 7.8-8.0. The antibacterial potential of the prepared molecules were determined against *S. aureus, E. coli and P. aeruginosa* using the disc diffusion method. The results showed that the prepared compounds exhibited significant antibacterial potential especially, Zn complexes exhibited greater antibacterial potential against all the organisms due to the chelation process which reduces the polarity of the metal ions by coordinating with ligands (Figure 12).[23]

Mohamed and Sharaby synthesized a novel Schiff base by refluxing sulphametrole and o-vanillin in ethanol at 60 °C for 2 h. The metal complexes were synthesized by refluxing the hot ethanolic solution of metal salts with Schiff base for

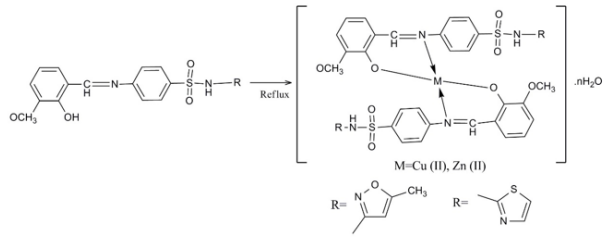

Fig. 12: Synthesis of Sulphamethoxazole / Sulphathiazole Schiff base metal complexes

1 h. The antimicrobial action of the prepared compounds was determined against *E. coli, Bacillus subtilis, S. aureus, S. typhi, A. terreus* and *A. flavus*. The result indicated that the metal ions improved the antimicrobial efficiency of the ligand and in some cases a higher or similar activity than the standard drug Griseofulvin (Figure 13).[24]

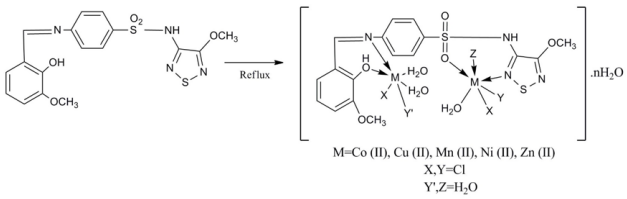

Fig. 13: Synthesis of sulphametrole schiff base metal complexes

Idemudia et al. prepared 4-benzoyl-3-methyl-1-phenyl-2-pyrazolin-5-one sulphanilamide Schiff base by the condensation of sulphanilamide with acylpyrazolone carbonyl precursor namely 4-acyl-3-methyl-1-phenyl-2-pyrazolin-5-one in hot methanol and refluxed for 4 h. The metal complexes were synthesized by refluxing hot ethanolic solution of Cu, Co, Ni and Mn metal salts to the Schiff base ligand for 4 h with continuous stirring and the complexes were precipitated by the addition of sodium hydroxide. The antibacterial activity of the Schiff bases and their metal complexes was evaluated against *S. aureus, Bacillus pumilus, Proteus vulgaris* and *Aeromonas hydrophila* using the disc diffusion method. The results showed that the prepared compounds showed greater activity against *A. hydrophila*. The antioxidant potential was determined using DPPH assay. The results revealed that the complexes exhibited excellent antioxidant potential than the Schiff base as compared to the standard Ascorbic acid (Figure 14).[25]

El-Nawawy and co-workers synthesized a novel sulphamethoxazole Schiff base, (E)-4-(4-methoxybenzylideneamino)-N-(5-methylis-oxazol-3-yl) benzenesulphonamide by refluxing p-methoxy benzaldehyde, sulphamethoxazole and a few drops of triethylamine with continuous stirring for 4 h. For the preparation of the metal complex, $(CH_3COO)_2$. Cu. H_2O

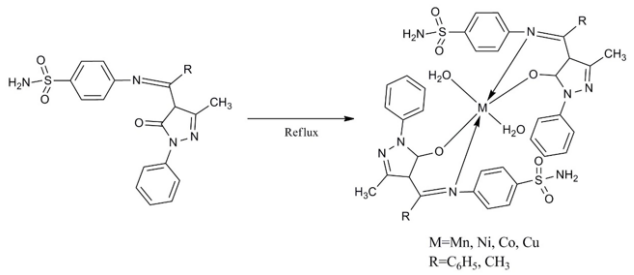

Fig. 14: Synthesis of 4-Benzoyl-3-methyl-1-phenyl-2-pyrazolin-5-one sulphanilamide Schiff base metal complexes

in absolute ethyl alcohol was refluxed with the synthesized ligand for 6 h. The antibacterial and antifungal efficacy of the compounds was determined against bacterial strains namely *S. aureus, Bacillus, P. aeruginosa* and *E. coli* and fungal strains namely *A. fumigates, Geotrichum candidum, C. albicans* and *Syncephalastrum racemosum* using *Penicillin G, Streptomycin, Clotrimazole* and Itraconazole as standards. The results revealed that the copper complex exhibited better antimicrobial action than the standard drugs (Figure 15).[26]

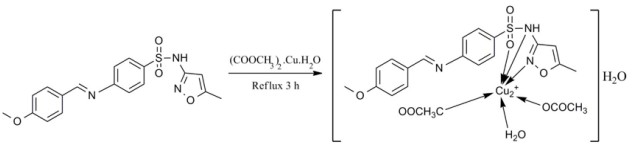

Fig. 15: Synthesis of Sulphamethoxazole Schiff base (E)-4-(4-methoxybenzylideneamino)-N-(5-methylis-oxazol-3-yl) benzenesulphonamide Schiff base-Copper complexes

Ul-Hassan et al. synthesized sulphanilamide-based Schiff base by refluxing sulphanilamide and salicylaldehyde. The metal complexes were prepared by refluxing the hot ethanolic solution of Schiff base with an aqueous solution of copper, cobalt and nickel for 3 h. The carbonic anhydrase inhibitory action of Schiff base was determined as mild-moderate action against the isoenzymes hCA I, II and IV which play an essential role in the physiological processes and the Schiff base metal complexes showed greater affinity in binding to the isoenzymes hCA I, II and IV than the parent form (Figure 16).[27]

Maurya and co-workers prepared a novel sulphanilamide Schiff base [N-(salicylidene)-sulphamerazine] by treating the hot ethanolic solution of salicylaldehyde with hot methanolic solution of sulphamerazine for 4-5 h using water bath. 5mmol of Schiff base and 5,5'-bipyridine in ethanol were refluxed for 2 h with continuous stirring using a magnetic stirrer resulting in the formation of mixed ligand complexes. Subsequently, the ethanolic solution of $Ni(OOCCH_3)_2.4H_2O$, $Co(OOCCH_3)_2.4H_2O$, $Cu(OOCCH_3)_2.H_2O$ and $Zn(OOCCH_3)_2.2H_2O$ were added

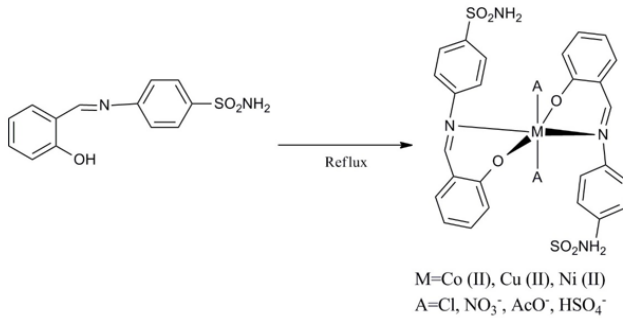

Fig. 16: Synthesis of sulphanilamide-salicylaldehyde schiff base metal complexes

slowly dropwise to the reaction mixture with continuous stirring and refluxed for 4 h using heating mantle (Figure 17).[28]

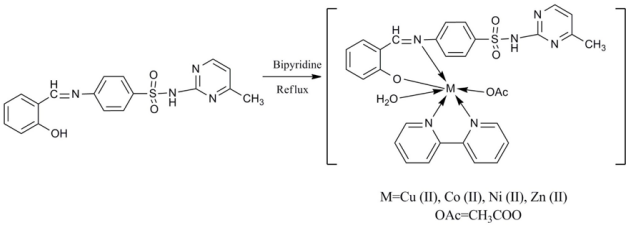

Fig. 17: Synthesis of [N-(salicylidene)-sulphamerazine] Schiff base metal complexes

By condensing an ethanolic solution of sulphanilamide, 2-hydroxy-6-methoxybenzaldehyde and a little amount of glacial acetic acid as an acid catalyst for two hours, Lokesh et al. created 4-[(2-hydroxy-6-methoxybenzylidene) amino] cyclohexa-1, 5-diene-1-sulphonamide Schiff base. The Schiff base ligand was refluxed with the hot ethanolic solution of metal salts, such as copper chloride, cobaltous chloride, and zinc chloride, for 30 minutes in a water bath. As a secondary ligand, 1,10-phenanthroline was then added to an ethanolic solution, and reflux was maintained for 3–4 hours to create mixed ligand complexes. The produced complexes' DNA binding affinities were assessed, and the findings showed that all of the metal complexes were superior to traditional DNA intercalators in terms of intrinsic binding constant (Kb). The compounds' antibacterial efficacy against *B. subtilis, S. typhi, E. coli, S. aureus, C. albicans* and *A. niger* was demonstrated. The outcomes showed that, in comparison to the standard, all of the complexes had moderate to good efficiency against the corresponding bacteria. The DPPH Scavenging assay was used to measure the antioxidant activity, and the results showed that metal chelates were more effective than uncoordinated ligands. The binding affinity of complexes with the human estrogen receptor and tyrosine kinase (RTK) was evaluated using a molecular docking study

that exhibited a lowest binding energy than the ligand and the standard indicating that the complexes have a high inhibiting property for cancer-causing receptors (Figure 18).[29]

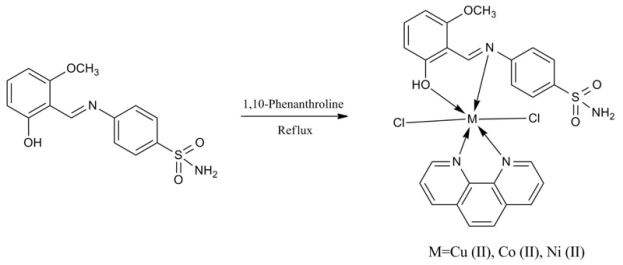

Fig. 18: Synthesis of 4-[(2-hydroxy-6-methoxybenzylidene) amino] cyclohexa-1, 5-diene-1-sulphonamide Schiff base metal complexes

Danish et al. synthesized a Schiff base ligand 4-((4-Bromophenylsulphonamido)methyl)benzoic acid by stirring tranexamic acid with an equivalent amount of p-bromo benzenesulphonyl chloride and 1M sodium carbonate was added slowly to maintain the pH to 9 and to the reaction mixture dilute hydrochloric acid was added to adjust the pH to 3 after the appearance of a clear solution. An equivalent amount of sodium carbonate was added to the synthesized Schiff base and it was stirred until the pH was neutral. Then the reaction mixture was refluxed with the metal salts (Cu, Co, Mn and Ni) for 30 min with continuous stirring. The cytotoxic potential of the compounds was performed on human breast cancer (MCF-7) and human corneal epithelial (HCECs) cell lines using MTT colorimetric assay. The results revealed that the Cu complexes exhibited 52.92 and 41.27 % of cell viability after treatment. The antioxidant efficacy of the Cu complex of sulphonamide showed the greatest antioxidant potential with IC_{50} value of 137 ± 1.0 μg. The enzyme inhibitory action of the enzymes *acetylcholinesterase* and *butylcholinesterase* of the Cu complex was found to be 191±1.8 and 199±1.8 μg of IC_{50} value. The antimicrobial potential of the complexes was determined against Halomonas halofphla, Halomonas salina, Chromohalobacter israelensis, Chromohalobacter salexigens, Shigella sonnei, Sachromyces aroses and Neisseria gonorrhoeae using Ampicillin as a standard. The results revealed that the Mn complex exhibited greater antimicrobial potential against all the microorganisms (Figure 19).[30]

Pervaiz and co-workers prepared a novel Schiff base ligand namely 4-amino-N-(5-methyl-3-isoxazolyl)benzene sulphonamide by refluxing 3-amino-5-methylisoxazol and p-acetamidobenzen sulphonyl chloride at room temperature. The metal complexes were synthesized by refluxing the synthesized ligand with the metal salts (Co, Cu, Ni, Mn and Zn). Due to the coordination, the complexes have significantly more antibacterial and cytotoxic activity than

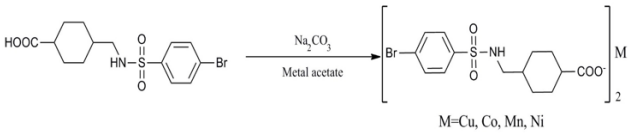

Fig. 19: Synthesis of Tranexamic acid-p-bromo benzenesulphonyl chloride Schiff base metal complexes

the Schiff base ligand (Figure 20).[31]

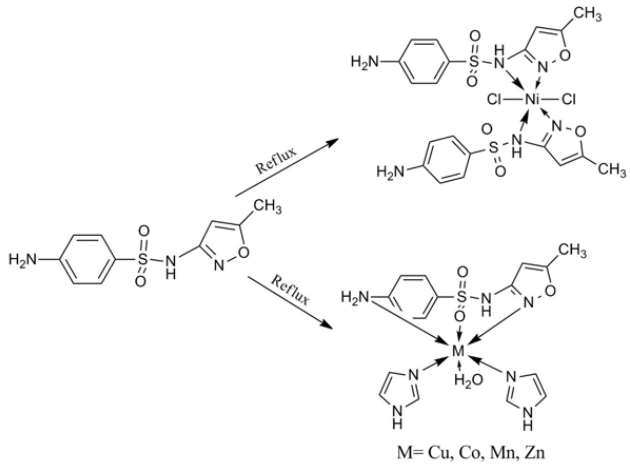

Fig. 20: Synthesis of 4-amino-N-(5-methyl-3-isoxazolyl)benzene sulphonamide Schiff base metal complexes

Surve and Sankpal synthesized (E)-4-(1H-imidazol-2-yl)methyleneamino)benzene sulphonamide and (E)-4-(1-(4-methyl-2,6-dioxocyclohex-3-enyl)ethylideneamino)benzenesulphonamide Schiff base ligands by the condensation of sulphanilamide with imidazole-2-carboxaldehyde/dihydroxy acetone dissolved in ethanol for 3 h. Nickel chloride was gently added to the ethanolic solution of Schiff bases and refluxed for two hours in a 2:1 ratio. To maintain the pH of the reaction mixture between 7.5 and 8.0, a small amount of diluted ammonia was added. The antibacterial property of the synthesized compounds was evaluated against E. coli, Streptococcus pyogenes, *S. aureus* and *P. aeruginosa*. The nickel complexes were found to be more active against *E. coli* and *P. aeruginosa* in the range of 14-16 mm of a zone of inhibition (Figure 21).[32]

Elsamra and co-workers synthesized a novel Schiff base ligand refluxing sulphanilamide with substituted aromatic aldehyde with a small amount of acetic acid as a catalyst for 5-8 h at 150 °C. An aqueous solution of $Ni(NO_3)_2.6H_2O$ was refluxed with the hot ethanolic solution of ligand with continuous stirring for 2 h at 70 °C and to the reaction mixture, a small amount of ammonia solution was added to maintain the pH to 8. The antimicrobial efficiency was determined against *E. coli, B. subtilis* and *A. fumigatus* using

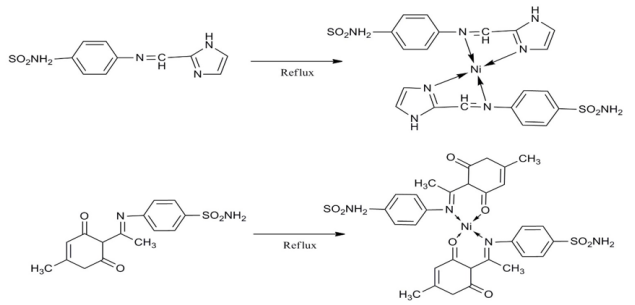

Fig. 21: Synthesis of Sulphanilamide with imidazole-2-carboxaldehyde/dihydroxy acetone Schiff base-Nickel complexes

a Microdilution broth assay. The ligand was found to be potent antimicrobial agent against the tested strains. The cytotoxicity of the synthesized compounds was determined against the human breast (MCF-7) cancer cell line. Both the ligand and complex showed appreciable cytotoxicity against the breast cancer cell line (Figure 22).[33]

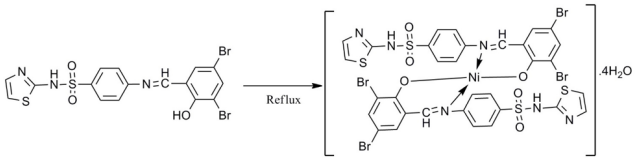

Fig. 22: Synthesis of Sulphanilamide-substituted aromatic aldehyde Schiff base-Nickel complex

Rani et al. prepared sulphanilamide-based Schiff base ligands by refluxing an equimolar amount of 4-aminobenzenesuphanilamide with 1-(furan-2-yl)ethanone/1-(thiophene-2-yl)ethanone/1-acetylindoline-2,3-dione. The bidentate ligands were reacted with Cu, Co, Ni and Zn chlorides in ethanol to synthesize metal complexes. The antibacterial and antifungal potential was screened against *B. subtilis, Shigella flexneri, S. typhi, E. coli, S. aureus, P. aeruginosa, C. albicans, Trichophyton longifusus, A. flavus, Microsporum canis, Fusarium solani*, and *C. glabrata*. The Ni complex was found to exhibit excellent antimicrobial potential than all the complexes and the parent ligand (Figure 23).[34]

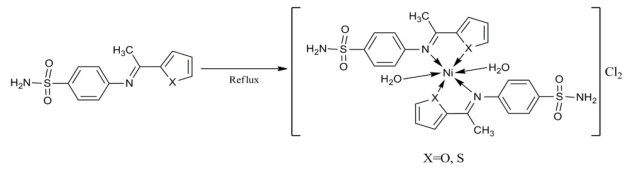

Fig. 23: Synthesis of 4-aminobenzenesulphanilamide with 1-(furan-2-yl)ethanone/1-(thiophene-2-yl)ethanone/1-acetylindoline-2,3-dione Schiff base-Nickel complex

Sumrra et al. synthesized a Schiff base ligand by the reaction between 2-hydroxy-3-methoxybenzaldehyde dissolved in ethanol and 4-aminobenzene-1-sulphonamide/ 4-amino-N-(3-methyl-2,3-dihydro-1,2-oxazol-5-yl)benzene-1-sulphonamide for 8 h. The metal complexes were synthesized by refluxing the ethanolic solution of a Schiff base with the metal salts (Co, Cu, Ni and Zn) for 4-6 h. The antimicrobial activity was determined against *S. aureus, K. pneumonia*, *E. coli, B. subtili, A. niger* and *A. flavus*. The results revealed that the synthesized complexes exhibited 9-32 mm of zone of inhibition against the respective microorganisms. The antioxidant potential was determined using the DPPH assay and the compounds showed 46-94.4 % of activity because of the presence of phenolic compounds. Enzyme inhibition studies of the prepared compounds were determined against *protease, α-amylase, acetylcholinesterase* and *butylcholinesterase* enzyme and the results exhibited a significant inhibitory effect against these four enzymes (Figure 24).[35]

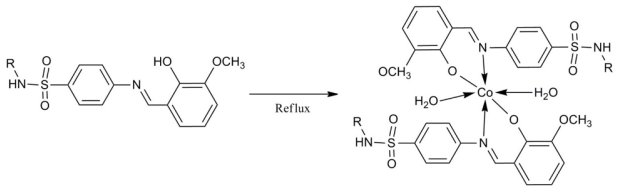

Fig. 24: Synthesis of 2-hydroxy-3-methoxybenzaldehyde with 4-aminobenzene-1-sulphonamide/ 4-amino-N-(3-methyl-2,3-dihydro-1,2-oxazol-5-yl)benzene-1-sulphonamide Schiff base-Cobalt complex

Hosny et al. synthesized a novel Schiff base ligand namely N-(4, 6-dimethylpyrimidin-2-yl)-4-(((2-hydroxyl naphthalene-1-y l) methylene) amino) benzene-sulphonamidesulphonyl)amide by refluxing a mixture of sulphadimidine sodium with 2-hydroxy-1-naphthaldehyde in ethanol for 4 h using 5 % HCl to maintain the neutral pH. The Cu metal complex was prepared by refluxing the ethanolic solution of a ligand with $CuCl_2.2H_2O$ in 1:1 ratio for 4-6 h at 70 °C. The anti-proliferative efficacy of the synthesized compounds was screened against the human liver (HepG2) cancer cell line using Cisplatin as a standard. The results revealed that the nano-complexes exhibit a greater ability to bind DNA due to their small particle size, which can also be used extensively in economic anticancer studies by the scientists (Figure 25).[36]

Topala and co-workers prepared a Schiff base ligand namely N-(2-(pyridine-2-yl)ethyl)quinolone-8-sulphonamide by the condensation of solid quinolone-8-sulphonyl chloride with 2-(pyridine-2-yl)ethanamine at 0 °C for 1 h, followed by 2.5 h at room temperature and 2 h in an ice bath. Then the metal complexes were synthesized by refluxing the methanolic solution of metal salts (Co, Cu, Ni and Zn) with the Schiff base ligand at room temperature

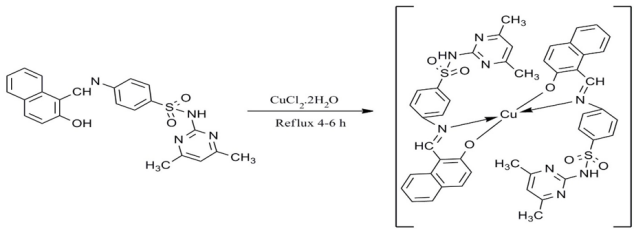

Fig. 25: Synthesis of N-(4, 6-dimethylpyrimidin-2-yl)-4-(((2-hydroxyl naphthalene-1-y l) methylene) amino) benzene-sulphonamidesulphonyl)amide Schiff base-Copper complex

for 1 h with continuous stirring. The results indicated that complexes exhibited potent DNA cleavage activity and the Co complex has no ability for DNA cleavage (Figure 26).[37]

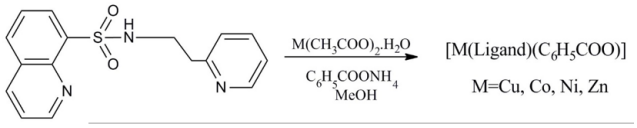

Fig. 26: Synthesis of N-(2-(pyridine-2-yl)ethyl)quinolone-8-sulphonamide Schiff base metal complexes

Yaqoob et al. synthesized a novel sulphanilamide Schiff base 4-[(2-hydroxynaphthalene-1-ylmethylene)-amino]-benzenesulphonamide by refluxing an equivalent amount of sulphanilamide and 2-hydroxynaphthaldehyde in methanol with a small amount of acetic acid for 8 h. The metal complexes were prepared by refluxing $CuCl_2.2H_2O$, $Ni(CH_3COO)_2.4H_2O$, $Co(CH_3COO)_2.4H_2O$ and $Zn(CH_3COO)_2.2H_2O$ with the ethanolic solution of Schiff base and ammonium acetate for 6 h. The anti-glycation activity of the synthesized compounds were screened using rutin as a standard drug. The results revealed that these compounds exhibited excellent anti-glycation activity and Schiff base ligand showed 265.11 ± 1.86 μM, Co complex showed 184.11 ± 2.11 μM, Cu complex showed 276.43 ± 1.16 μM, Ni complex showed 254.56 ± 1.73 μM and Zn complex showed 211.26 ± 2.14 μM of IC_{50} value. The antioxidant potential was determined using DPPH radical scavenging activity. The ligand, Co complex, Cu complex, Ni complex and Zn complex exhibited 65.58 ± 1.29 μM, 112.14 ± 1.11 μM, = 86.11 ± 1.12 μM, 126.27 ± 1.54 μM and 37.05 ± 1.53 μM of IC_{50} value (Figure 27).[38]

A series of Schiff bases N-({4-[(E)-(2Zhydroxybenzylidene) amino]phenyl}sulphonyl) acetamide, N-({4-[(E)-(2- hydroxybenxiliden) amino]phenyl}sulphonyle) benzamide and 4-((4-oxopentan2ylidene)amino)benzenesulphonamide were synthesized by the condensation of sulphacetamide/ sulphanilamide/ sulphabenzamide with salicylaldehyde or acetylacetone in ethanol for 3 h in presence of acetic acid as a catalyst. The Cu complexes were synthesized by the condensation of Schiff base ligand with $Cu(OAC)_2.H_2O$ in

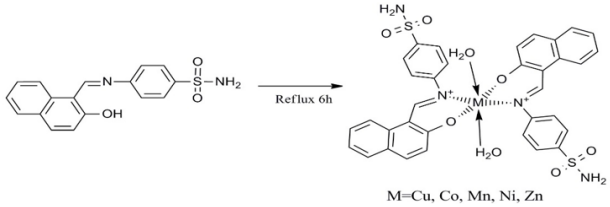

Fig. 27: Synthesis of 4-[(2-hydroxynaphthalene-1-ylmethylene)-amino]-benzenesulphonamide Schiff base metal complexes

methanol for 3 h resulting in light green, dark brown and dark green coloured complexes. The antibacterial activity was screened against *S. aureus, K. pneumonia, E. coli* and *Enterococcus faecalis* using the broth dilution method. The complexes showed 11.4-22.8 μg/ml of minimum inhibitory concentration (Figure 28).[39]

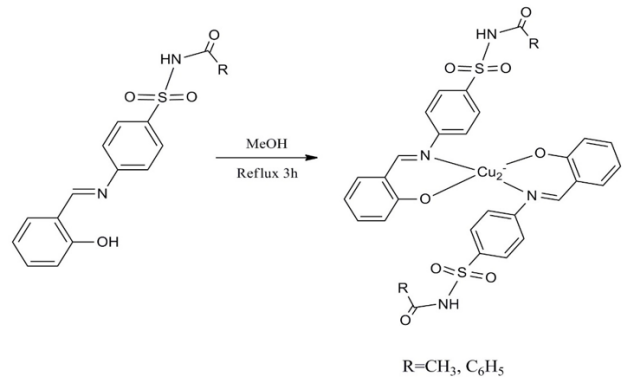

Fig. 28: Synthesis of sulphacetamide/sulphabenzamide/sulphanilamide Schiff base-Copper complexes

Sumathi et al. prepared a new sulphanilamide based Schiff base by stirring 3-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one (HPOC) and sulphanilamide in ethanol at room temperature for 6 h in presence of piperidine. The metal complexes were synthesized by stirring the ethanolic solution of Schiff base ligand and the metal salts (Co, Cu, Ni, Mn and Zn) using a magnetic stirrer. The in vitro antimicrobial potential was screened against P. aeruginosa, E. coli, S. aureus and C. albicans using well diffusion method and the results revealed that the Cu(II) and Ni(II) complexes exhibited greater antimicrobial potential against the respective microorganisms (Figure 29).[40]

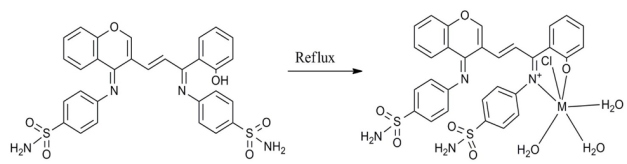

Fig. 29: Synthesis of 3-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one -sulphanilamide Schiff base metal complexes

Mohamed et al. synthesized a Schiff base ligand namely 3-(4'-ethylazomethinobenzene sulphonamide)-4-methoxy1,2,5-thiadiazole by the condensation of hot ethanolic solution of sulphametrole and varelaldehyde for 3 h. To the hot solution of the prepared ligand, a hot ethanolic solution of metal chloride was added and refluxed for 1 h at 60 °C. The antimicrobial potency was determined against *S. aureus, E. coli, C. albicans* and *A. flavus* using the standards namely Tetracycline and Amphotericin B. The ability of the synthesised compounds to combine with the lipophilic layer to increase the membrane permeability of the Gram-negative bacteria is demonstrated by the fact that the synthesised ligand and its complexes displayed greater activity against *S. aureus* and *E. coli* (Figure 30).[41]

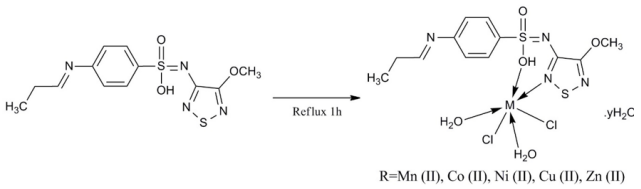

Fig. 30: Synthesis of 3-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4H-chromen-4-one -sulphanilamide Schiff base metal complexes

Gomathi and co-workers synthesized 4-(3-ethoxy2-hydroxybenzylideneamino)-N-(pyridin-2-yl)benzene sulphonamide (ESSP) Schiff base by refluxing sulphapyridine and 3-ethoxysalicylaldehyde with ethanol for 3 h. By gradually adding the metal acetate salt solution to a magnetically stirred hot ethanolic solution of Schiff base with dimethyl formamide for 5–6 hours on a water bath, the metal complexes including Co(II), Ni(II), and Cu(II) complexes were synthesized. Using the disc diffusion method, the antibacterial and antifungal efficiency was tested against *E. Coli, P. aeruginosa, S. aureus, Klebsiella sp, A. niger* and *Mucor sp*. According to the results, the metal complexes have superior antibacterial capability over the Schiff base ligand. (Figure 31).[42]

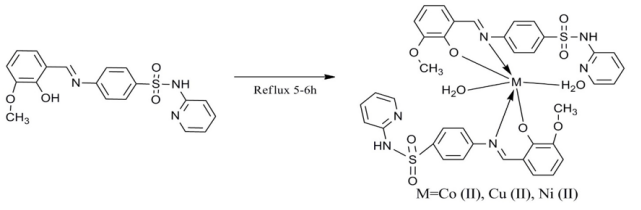

Fig. 31: Synthesis of 4-(3-ethoxy2-hydroxybenzylideneamino)-N-(pyridin-2-yl)benzene sulphonamide Schiff base metal complexes

3. Conclusion

Due to the presence of azomethine nitrogen, Schiff bases constitute a significant family of ligands in coordination chemistry and are simple to synthesise using affordable catalysts. Because of their widespread availability, simple synthesis, and favourable electronic characteristics, Schiff base ligands have attracted a great deal of attention in the field of coordination chemistry. Sulphonamides are a significant class of drug-like chemical derivatives with broad biological significance because of their effective oral absorption and urine excretion. In this review, Schiff base metal complexes synthesized from sulphanilamide are described along with their synthesis and pharmacological applications. With decreased toxicity, greater reactivity and lower cost, the sulphonamide Schiff base metal complexes have a wide range of pharmaceutical applications. The study revealed that the Schiff bases and the metal complexes synthesized from the sulphonamide derivatives exhibited excellent pharmacological actions with lesser side effects. Especially, the coordinated metal complexes had superior pharmacological effects over the uncoordinated Schiff bases. Therefore, it would be beneficial in considering sulphonamides for designing novel organic and inorganic compounds.

4. Conflict of Interest

None.

5. Funding Sources

None.

6. Author Contribution

Shridharshini Kumar prepared the manuscript, Praveen Sekar revised and contributed in drafting the manuscript and Senthil Kumar Raju read and approved the final manuscript.

7. Acknowledgement

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