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Synthesis and Applications of Schiff Bases from Some Sulfa Drugs and Their Metal Complexes: Review

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ABSTRACT

The review summarizes the synthesis, characterization, and antimicrobial activities of sulfa drugs metal complexes, keeping in mind the importance of sulfa drug-based transition metal complexes. Several fertile restraints contain aldehydes or amines, but the bond (C=N) is supposedly attributed to the Schiff bases' more stable role in many situations. Compounds containing an azomethine group (–CH=N–) are known as Schiff bases, and the development of a new chemotherapeutic Schiff base is now attracting attention. Sulfadiazine is a sulfonamide antibiotic that is on the Essential Medicines List of the World Health Organization. It works by preventing the bacterial cell from producing folate, which kills bacteria that cause infections. It's commonly used to treat infections of the urinary tract.

Keywords: Chemometric assisted spectrophotometric method; Synthetic binary mixtures; Perindopril; Losartan

INTRODUCTION

Sulfa drugs

Sulfonamide is a moiety of functional (a molecule part) that is the rule of many moieties of drugs, that are designated sulphonamides, sulpha drugs or sulfa drugs. They were discovered in the 1930s by Domagk, and then over 4500 derivatives of sulfanilamide (1935-1948) were prepared and estimated for efficacy of antimicrobial e.g., the anticonvulsant sultiame [1]. Development of sulfanilamide is a datum area due to apply in medicine design. However, the pharmacokinetic importance of a sulfanilamide nucleus has been well confirmed in the pharmaceutical chemistry. The sulfanilamide of antibacterial consists of a broad range of ingredients that are structural analogues of PABA; they interfere with microbial development by competitively inhibiting the enzyme synthase dihydrogenase, by blocking the PABA incorporation into folic acid necessary for the biosynthesis of bacterial purines, some amino acids, and thymidine [2].

Therefore, it is a drug of an antibacterial that is active with the G (-)ve and G (+)ve bacteria. After that, they were used extensively to treat a wide range of bacterial diseases *also used in the treatment of inflammatory bowel disease*.

Sulfanilamide derivatives, principally derivatives of sulfonamide N1, were applied as the primary effective drugs of antibacterial for treating human contagions of bacterial, *as allergies and cough, as well as antimalarial functions and antifungal.* Followed by the widespread utilize and the introduction of penicillin during the 1940s which occupied the major infection [3].

Preparation

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. Certain sulfonamides (sulfadiazine or sulfamethoxazole) are sometimes mixed with the drug trimethoprim, which acts against dihydrofolate reductase. As of 2013, the Republic of

Ireland is the largest exporter worldwide of sulfonamides, accounting for approximately 32% of total exports [4].

Sulfanilamide Structure and Mechanism of Action Sulfanilamide structure is considered to contain the minimum or "parent" pharmacophore. A "pharmacophore" is the structural component(s) in a drug molecule necessary for that drug to have biological activity. Sulfanilamide contains a benzene ring, para substituted with an amino group and a sulfonamide group. Second generation sulfa drugs (those developed after sulfanilamide was established as an effective antimicrobial agent) contain the essential pharmacophore. However, the structures of these second generation sulfa drugs have been manipulated to enhance activity, solubility and excretion [5].

Structural activity relationship of sulfonamides

Great numbers of sulfonamides of synthetic antibacterial with diverse the amendments allowed investigating the effect of structural change on antibacterial efficacy. According to sulfonamides are rather small molecules (as appeared in the main structure) and there are not many variations that can be made without altering the core nucleus, these results have led to the next inferences

1- The moieties of sulfonamide and (N4) amine for antibacterial efficacy should be on the ring of the benzene in the 1,4 p-sites. [6] Nevertheless, the N4 should be substituted or un-substituted to form pro-drugs of amide or azo or new analogs.

2- Replacing the ring of benzene with other systems of a ring or replacing it with a non-position 1.4 will eliminate or reduce antibacterial efficacy.
3- The exchange of the SO_2NHR moiety of sulfonamide with $SO_2Ph\text{-}p\text{-}NH_2$ sulfone will maintain the efficacy [7].

4- The moiety of Sulfonamide is fundamental for the efficacy of biological and the amide should be secondary (N1). The existence of the p-amino-benzene sulfonyl group is important in preserving the efficacy of antibacterial. Thus, all attention is focused on the N1 alternatives.

These alternatives seem to affect the physicochemical and pharmacokinetic properties of the drug. The already established replacement sites are:
All of the attentiveness is concentrated on substituents of N_1 [8]. These substituents found to impact the characteristics of the pharmacokinetic and physicochemical of the drug. The formerly determined sites of substitution are:

A- substitution of N_1 with diverse impacts of un-heteroaromatic and heteroaromatic (R"), the stretch for a protein of plasma linking which in turn affects the drugs' plasma concentration in addition to their onset and duration of action. Furthermore, the nature of the (R") group influence the drug's pka, its lipophilic-lipophobic solubility behavior, its excretion, and its toxicity profile [9].

B- azo of N4 and derivatives of acyl as pro-drugs

(1.4.2) Sulfadiazine

Niacinamide, as well known as nicotinamide and amide of nicotinic acid. Niacin is a vitamin B3 kind that vitamin has the ability to soluble in water, that is converted in vivo into nicotinamide, and even though the two are conformable in vitamins' functions, nicotinamide does not have the similar influences of toxic and niacin pharmacokinetic. Nnevertheless, nicotinamide can be the liver toxic when possessed for adults in dosages overriding (3 g / day) [10]. In cells, niacin is incorporated into nicotinamide adenine nucleotide phosphate (NADP) and nicotinamide adenine dinucleotide (NAD), although the pathways of nicotinamide and nicotinic acid are very similar. $NADP^+$ and NAD^+ are co-enzymes in an extensive assortment from reactions of enzymatic oxidation-reduction.

Sulfadiazine is considered as a Sulfa-drug derived from the parent compound, Sulfanilamide, which consider important class of drugs with several types of pharmacological agents possessing antibacterial, antithyroid, diuretic, hypoglycaemic, and anti-carbonic anhydrase

General introduction of Schiff bases and Schiff bases metal complexes:

Schiff bases ligands

It named after the German chemist Hugo Schiff who prepared these compounds from simple condensation between aldehydes and ketones with primary amines:
Schiff bases have been known by different names such as imines, azomethines, and anils which common for Schiff bases derived from ketones, aldehydes and aromatic amines. In general, the Schiff bases which have been derived from aldehydes are called aldimine and from ketones as ketamine and the stability of the final product depend on the nature of aldehyde, ketone, and amine.

Numerous studies have shown which the presence of one pair of electrons in the sp^2 hybrid orbit of a nitrogen atom from the group of imines has important biological and chemical significance (that may be shifted consisting of the type of alternatives present on rings of the aromatic). Because of the relative ease of synthesis, artificial flexibility, and distinctive objects of the C = N moiety, the Schiff bases are usually excellent chelating agents, particularly when a functional moiety such as –SH or –OH is present near the azomethine group to conduct six or five members with Metal ion.

The scalability of the Schiff base links and the industrial uses and biological analytical of its complexes create additional research in this region that is highly needed.

The mechanism of Schiff base consisted of the addition of a proton to the carbonyl group to yields conjugated acid in which carbon of carbonyl group is more electrophilic, thus facilitating the attack of amine on carbonyl group. The added acid will enhance the elimination of water molecules to obtain the final output of ligands, thus the proper pH and suitable solvent are required.

The Schiff bases are vastly utilized in the chemistry of chelation as ligands. They are easily obtainable, versatile and relying on the starting materials kind. They exhibit various denti-cities and functionalities. Furthermore, the number, the nature, and the proportional site of the granter

atoms of a Schiff base let good domination over the stereo-chemistry of the metallic stations, in addition to over the metal ions number within hetero and homo-poly nuclear complexes. All these advantages make ligands good nominees in the potential to synthesize complexes of attention in chemistry of bioinorganic, mechanisms of catalysis includes in enzyme primary amine intensification. Schiff bases find a multilateral employ; some of them are the basic unity confirmed dyes, whilst, some are utilized as liquid crystals in chemistry. Reactions of Schiff base are helpful in making bonds of nitrogen-carbon in organic preparation. Schiff bases display to be significant intermediates in many reactions of enzymatic sharing the enzyme interaction with substrate moiety an amino or a carbonyl and processes of encapsulation, transport, and separation. Noteworthy utilize of these components is their enforcement as an efficient abrasion restraint, which is decided on their capacity to unexpectedly form a monolayer on the exterior to be safe.

They are usually formed by condensation of a primary amine with a carbonyl compound where R= aliphatic group of Schiff base aldehydes is easily polymerizable and comparatively unsettled while those are more steady having an active system of conjugation in aromatic.
Schiff bases derived from the sulfonamide drug interest were obtained due to their system of biological. Components including sulfonamide drugs were used as a disease drug. They are the primary compound due to a wide range of biological activities, their industrial application and have been found to have procedures of pharmacological such as antipruritic, campaigns, antibacterial, antifungal, antimalarial, anti-inflammatory and antiviral. They also act as the backbone to produce different heterogeneous compounds.

Schiff bases are the compounds containing azomethine group (-HC=N-) – first reported by Hugo
Schiff – formed by the reaction of primary amines with a ketone or carbonyl compounds placed under base catalysis, acid, or heat . These compounds are used in the development of coordination chemistry and numerous potential applications in various biological and pharmacological fields. In this regard, the sulfonamide and its derivatives containing group

$–SO_2NH–$ is known as the simplest molecule that belongs to sulfa drugs.

These simple compounds have a high potential in toxicological and pharmacological activities when administered in the form of Schiff base ligands. This potential is attributed to the exchanges of different functional groups without modification of the structural –SO2NH– feature. In the past, sulfur-containing compounds have long been used as drugs for diseases and burn treatment. Today, sulfonamides are used as antibiotics to treat infectious diseases, as inhibitory agents against tumor cells, anti-thyroid, hypoglycaemic, diuretic, and several other activities. Thus, it seems worthwhile to continue investigations in this area. Therefore, we were prompted to synthesize a series of Schiff base ligands (**1**) and (**2**) derived from sulfonamide derivatives.

Sulfamethoxazole (SMZ or SMX), is an antibiotic. It was used for bacterial infections such as urinary tract infections, bronchitis and prostatitis and is effective against both gram negative and positive bacteria such as Listeria monocytogenes and E. coli. It is a sulfonamide and bacteriostatic. It resembles a component of folic acid. It prevents folic acid synthesis in the bacteria that must synthesize their own folic acid. Mammalian cells and some bacteria do not synthesize but require preformed folic acid (vitamin B9), they [23] are therefore insensitive to sulfamethoxazole, the trade name for SMZ is Gantanol. Other names include: sulfamethalazole, sulfisomezole and sulfamethazole. Schiff bases are characterized by azomethine group (-N=CH-), Several studies showed that the presence of a lone pair of electrons in SP2 hybridized orbital of N atom of the azomethine group is of biological importance moreover Schiff bases are excellent chelating agents, especially when a functional group like -OH or -SH is present close to azomethine group so as to form a five or six membered ring with the metal ion. Sulphur is one of elements that strongly coordinates silver in geometries from linear to octahedral. Fungal infection usually are not only limited to the contamination of surface tissues. Recently there was a considerable increase in the incidence of systemic fungal infection, which are potentially life- threatening .To overcome this problem attempt has been made to prepare complex of silver with Schiff base obtained from SMZ and selected substituted benzaldehyde.

Schiff base metal complexes

Many effect elements, containing elements of transitional, have been renowned for its importance as curative factors and are utilized as in collection with productions of multivitamin or a portion for supplements of nutritional which have been applied to remedy diseases like mania cancer, ulcers, and rheumatoid arthritis. drugs of metal-beared which have taken a significant status in the science of medicine are the CIS (which contains platinum), components of gold, salts of lithium bismuth, and aluminum. The complexity of metallic elements with bioactive and then efficient components has been shown to make past and last activity more efficient. There is still a need to explore the mechanism involved in this enhancement of biological activity at complexity using the metal ion. Studies (in-vitro) have specified that some components of biologically efficient may become more carcinogenic and bacteria stable when complicated with ions of metal. This complexity of transition metallic ions with nucleic acids amino, acids, and peptides are of the enormous significance of biological, and many reviews appear which the metal composition of these compounds extremely affects their biological behavior with an emphasis on the metals catalytic assignment in several operations of biological. Schiff bases often have a luminescence characteristic, especially when their complexes have a structure of solid level and rich electronic coupling. Schiff base vehicles occupy an important place in optical and fluorescent analysis e.g., base aromatic components as salicylidene o-aminophenol have been studied and have been applied as helpful reagents for fluorine measures for, magnesium, aluminum and other ions of metal. Schiff base assemblies are among the most well-known interactive mineral complexes.

There was a lot of interest in copper, e.g., because it is a fundamental component of life. It is linked to several copper-based enzymes that are fundamental in the operation of biological. Then, zinc in the biological system has a multifaceted role as a component of proteins and enzymes that belong to the cellular signaling pathways. Transitional minerals have an important place in the biochemistry of medical. On the other hand, cefradine is known to be a moderate product of UVA rays and O^{2-} under sunlight, and subsequently, the aim of this study is to design new mineral element complexes that may play an important role in reducing the activity of the drug molecule or/and enhancing from poisoning. Several drugs have modified pharmaceutical and toxic characteristics when they are in the complexes form. The farthest vastly studied metal in this attach is copper (II) that has been displayed to be useful in diseases like stomach ulcers; cancers stomach ulcers, tuberculosis, and rheumatoid arthritis. These results prompted us to inspect with the metal ions of transition and d^{10} in the chelation chemistry of antibiotics in an attempt to check the state of solid binding methods and study biological activity. They are usually bactericidal against sensitive bacteria and act by inhibiting the synthesis of mucopeptide in the cell wall resulting in defective barrier and osmosis.

The reaction of sulfanilamide with substituted benzene- and heterocyclic aldehydes yielded a series of Schiff bases in 1996, according to CT Supuranl. Standard procedures were used to characterize the compounds, which were then tested for inhibitors of the zinc enzyme carbonic

anhydrase (CA). In contrast to traditional inhibitors, which are 17-33 times less effective against CA IV, the new compounds act as inhibitors against isozymes CA I and II (cytosolic) and CA IV (membrane-bound). This is the first evidence of high-affinity CA IV inhibitors, which could lead to the development of low molecular weight CA IV isozyme-specific derivatives.

Ishwar Bhat K prepared a series of novel Azetidinone derivatives from intermediate Schiff bases in 2011. They are made from the sulfamethoxazole group by reacting various aromatic aldehydes with the hydrazide. They have demonstrated moderate to good antifungal and antibacterial activity against a variety of fungi and bacteria.

In 2011 M. A. El-Nawawy A new Sulfamethoxazole Schiff base, and its copper complex .Also the biological activity of the Schiff base and its Cu complex were studied.

R. C. Maurya was born in the year 2013. A new class of mixed-ligand complexes of Cu(II), Ni(II), Co(II), Zn(II), Sm(III), and U(VI)O2 with the Schiff base derived from salicylaldehyde and the sulfa drug sulfamerazine, [N-(salicylidene)-sulfamerazine] (LH), and the heterocyclic base 2,2'-bi (bpy)

Zahid H. Chohan created a new series of Schiff base ligands derived from sulfonamide and their metal(II) complexes in 2012. Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani, and Candida glabrata ligands and metal(II) complexes were tested for antifungal activity against fungal strains, Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani, and Candida glabrata, These assays allowed the metal complexes to be identified as an effective antimicrobial agent with low cytotoxicity.

H. Ebrahimi was born in 2013. The condensation of indole-3-carboxaldehyde with various sulfa drugs such as sulfanilamide, sulfapyridine, sulfadiazine, sulfamerazine, sulfamethoxazole, sulfamethoxypyridazine, and sulfacetamide sodium resulted in the first synthesis of a new series of Schiff bases. Starting from optimized geometry, the highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), and Mulliken atomic charges of the studied molecules were calculated using the B3LYP method and standard 6-31 + G(d,p) basis set. The gauge independent atomic orbital (GIAO) approach was used to calculate the theoretical 13C chemical shift results, and linear correlations were found. The results show that B3LYP/6-31 + G(d,p) produces chemical shifts that are in good agreement with the observed chemical shifts.

In 2013, Sofian S. Mohamed synthesized sulfanilamide Schiff base derivatives and used molecular modeling programs to design them as docked in the colchicine binding site of -tubulin. The antitumor activities were then tested on human breast and lung cancer cells using a cell counting assay. With IC50 values ranging from 90 to 166 M, some of the compounds tested showed potent and selective activity against breast cancer (MCF-7). Compounds 4, 8, and 13 with IC50 values ranging from 96 to 140 M have shown potent antitumor activity against human breast and human lung cells.

Bharti Jain et al. synthesized Cu(II) and Hg(II) metal complexes with a Schiff base of sulfamethoxazole [4-amino-N-(5-methyl-3-isoxazolyl) benzene sulfonamide] and salicylaldehyde in 2013. Urinary tract infections are treated with sulfa drugs that concentrate in the urine before being excreted. Metal-ligand ratios of 1:2 for both Cu(II) and Hg(II) complexes have been suggested by conductometric titrations.

The novel aromatic sulfonamide ligand (PMBS) and its Cu(II), Co(II), and Zn(II) complexes were synthesized by Saeed-Ur-Rehman in 2013. Both gram negative bacteria like Pseudomonas aeruginosa, Salmonella typhi, and Eschericia coli and gram positive bacteria like Bacillus subtilus, Staphylococcus aureus, Staphylococcus epidermis, and Streptococcus pneumonia are tested for antimicrobial activity.

Zanab Hussain et al. synthesized Schiff's bases in an ethanolic solution in 2014, and used glacial acetic acid as a catalyst to make substituted sulfamethoxazole compounds. Some Schiff's bases with a sulfamethoxazole nucleus have been synthesized and studied. It is hoped that the current compounds will be used to improve the photostability of PVC.

Some complexes of the Schiff base derived from sulfadiazine with Co(II), Ni(II), and Cu(II) ions were discovered in Badr Awad in 2014. Antimicrobial screening of the synthesized ligand and its complexes was carried out. HL, a Schiff base ligand, demonstrated weaker to significant activity against one or more bacterial and fungal strains. Coordination with metal ions resulted in higher activities in the majority of cases (II). Furthermore, in silico calculations of the Pharmacokinetic parameters show promising features for using the ligand as a drug.

Apoorva Gupta synthesized a series of azomethines in 2014 by condensation of aromatic substituted aldehydes, including groups of allyloxy and allyl, with various sulphonamide derivatives. The compounds were tested for antibacterial activity against a variety of human pathogens, including E. coli, P. aeruginosa, S. aureus, and Bacillus subtilis. The disc diffusion assay revealed antibacterial activity for the synthesized azomethine compounds. Streptomycin and Penicillin-G were used as reference antibacterial drugs for E. coli, P. aeruginosa, S. aureus, and B. subtilis. Synthesized imines exhibit high biological activity and yield.

Complexes Schiff bases derived from 2, 5- hydroxybenzaldehyde with cephalexin, amoxycillin, trimethoprim, and sulphamethoxazole were synthesized by Abdulbaset A. Elgellal. Antibacterial activity is present in all of the compounds under investigation. The antibacterial activity followed this pattern: Schiff base ligands are more effective than parent drugs. When compared to the parent drug, the Schiff bases derived from cephalexin showed significantly increased activity against P. aeruginosa. In addition, all Schiff Base were found to be effective against kaolin paw oedema, whereas the parent drugs were ineffective.

Metal(II) coordination compounds of a cephalothin Schiff base (H_2L) derived from the condensation of cephalothin antibiotic with sulfadiazine were synthesized by J.R. Anacona in 2014. Mononuclear $[ML(H_2O)_3]$ is a Schiff base ligand. Magnetically diluted dinuclear copper(II) complexes $[CuL(H_2O)_3]$ and (M(II) = Mn, Co, Ni, Zn) complexes 2 The biological applications of complexes were investigated using the agar diffusion disc method on two bacteria strains (Escherichia coli and Staphylococcus aureus).

Abdalla M. Khedr was born in 2015. For potential chemotherapeutic use, two sulfadiazine azo-azomethine dyes with two active coordination centers and their bi-homonuclear UO_2 (II)-complexes were synthesized. Using a modified literature procedure, the ligands were made by coupling sulfadiazine dizonium salt with acetylacetone, then condensation with ethylenediamine and 1,6-hexanediamine (HLI and HLII). To evaluate their antimicrobial potential, the ligands and their complexes were tested for antibacterial and antifungal activities against Aspergillus niger and Candida

albicans, as well as antibacterial and antifungal activities against Staphylococcus aureus and Escherichia coli. The findings revealed that metallization boosts antimicrobial activity when compared to free ligands.

In 2015, I. Rama created a ligand by reacting 5-nitrosalicylaldehyde with sulfamethoxazole. The Schiff base and its copper complex have been studied as antibacterial and antifungal agents against a variety of microorganisms. The ligand and its copper complex were tested for cytotoxicity in vitro in two different human tumor cell lines, HCT-116 and MDA – MB – 231. According to the cytotoxicity studies, the complex was more active against MDA – MB – 231 than cisplatin and carboplatin.

Al-Khodir F. A. I. synthesized new Ca(II), Zn(II), and Au(III) sulfamethoxazole complexes in 2015, and the gold(III) complex demonstrated good anticancer activity against human colon carcinoma (HCT-116) cells and human hepatocellular carcinoma (HepG-2) cells.

The silver complex of Schiff base synthesized from Sulfamethoxazole and m-nitro benzaldehyde by microwave irradiation followed by complexation with silver metal was synthesized, characterized, and biologically evaluated in 2017. They were also tested in vitro for antibacterial and antifungal activity against two bacteria, E. coli and Staphylococcus aureus, as well as two fungi, Candida albicans and Aspergillus niger. Both bacterial and fungal pathogens were significantly inhibited by the newly synthesized silver complex. Incorporation of silver metal into the Schiff base also reduced the MIC value without reducing the diameter of the inhibition zone.

Martin Krátk, in 2017, Resistance among microbes has necessitated the development of new drugs. As a result, we created a series of Schiff bases using the sulfa drug sulfadiazine and a variety of salicylaldehydes. They were identified and tested for cytotoxicity against Gram-positive and Gram-negative bacteria, yeasts, molds, Mycobacterium tuberculosis, and nontuberculous mycobacteria (M. kansasii, M. avium). The genus Staphylococcus, which includes methicillin-resistant S. aureus, had the highest susceptibility among bacteria, with minimum inhibitory concentrations starting at 7.81 M. Candida sp. and Trichophyton interdigitale growth were inhibited at concentrations as low as 1.95 M. 4-[(2,5-Dihydroxybenzylidene)amino] With no apparent cytotoxicity and a selectivity index greater than 16, -N-(pyrimidin-2-yl)-benzene sulfonamide was found to be the most selective Schiff base for these strains. Unsubstituted 4-[(2-hydroxy-benzylidene)amino]-N-(pyrimidin-2-yl)benzene sulfonamide meets the selectivity requirement for M. tuberculosis and M. kansasii, which were inhibited at concentrations ranging from 8 to 250 M Dihalogenation of the salicylic moiety improved antibacterial and antifungal activity while also increasing cytotoxicity, particularly as the atomic mass increased. Some derivatives have better properties than the parent sulfadiazine, making them promising candidates for antimicrobial drug development.

Sonu and Arvind Kumar conducted research in 2017 with the goal of synthesizing better antimicrobial compounds using various substituted aromatic aldehydes / acetophenone as the starting material for the synthesis of Schiff bases. Sulphonamide aids in the formation of Schiff bases in the presence of alcohol and acidic reagent. To determine the potency of synthesized derivatives, antibacterial activity of the synthesized derivatives was compared to ampicillin as a standard. All of the two bacteria strains, Gram positive (Staphylococcus aureus) and Gram negative (Escherichia coli), showed sensitivity to all derivatives at higher concentrations (50g/ml and 100g/ml) but no sensitivity at lower concentrations.

In 2018 Schiff base from the condensation of sulfamethoxazole andisatin and its complexes with Co(II) Cu(II) and Zn(II) have been synthesized.The Schiff base and its metal chelates have been screened for their antimicrobial activity against six pathogenic microbes(Staphyloccus aureus, Escherichiacoli, Salmonella typhi, Aspergillus flavus, Aspergillus niger and Mucorindicus). The Schiff base showed mild activity, whereas the complexes show higher antimicrobial activity against the tested isolates.

A novel and simple method for the synthesis of some a new series of complexes of 4-((3-Formyl-4-hydroxyphenyl) diazenyl) -N-(4-methyloxazol-2-yl) benzenesulfonamide with the metal salts of Cu(II), Ni(II), Zn(II), and Ag(I) using microwave irradiation was developed in 208 Hany M. Z. El These compounds were tested in vitro for antibacterial activity against Staphylococcus aureus and Streptococcus mutans (Gram positive bacteria), Escherichia coli, Pseudomonas aeruginosa, and Klebsiella (Gram negative bacteria), and antifungal activity against Candida albicans (Gram negative bacteria). The antimicrobial activity studies revealed that metal complexes have higher activities than the parent ligand. Furthermore, the ligand demonstrated strong antioxidant activity.

Maysoon M. Abdul Hassan and Adnan HA created a new series of metal complexes in 2018 by combining 4-amino-N-(5-methylisoxazole-3-yl)-benzene -sulfonamide (L1) as a chelating ligand in the presence of the co-ligand trimethoprim (L2) with Vanadium (V), Cadmium (Cd), and Silver (Ag). V(IV), Cd(II), Ag(I), TMP, and SMX biological activity was investigated at different concentrations (50, 100, 250, 500, and 1000)ppm, and complexes with chelating ligand and co-ligand were tested against Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli after incubation for 24 hours at 37°C. After incubation for 24 hours at 37 degrees Celsius, the results showed that L1 and L2 enhance the effect of (V) against the growth of (Staph. aureus and E. coli) at concentrations of (50, 100, 250, 500, and 1000)ppm, while Ps. aeruginosa was sensitized to (Cd) and (Ag) at concentrations greater than (250)ppm. The SMX, on the other hand, has a problem with Staph. aureus, Pseudomonas aeruginosa, and E. coli.

This research included three steps in the preparation of new Sulfamethoxazole drug derivatives in 2018. The first step involved converting Sulfamethoxazole to Schiff's bases (1), which was accomplished by reacting Sulfamethoxazole with various specific aldehydes in ethanol, followed by presence in glacial acetic acid. In the second step, Schiff's bases (1) were combined with sodium azide in the presence of Benzene (dry) to produce new tetrazole derivatives (2). Finally, the third reaction necessitates the synthesis of thiazolidine (3) through the reaction of Schiff's bases (1) with 2-mercaptoacetic acid. The prepared compounds were characterized by physical properties, as well as some of them by IR and 1H-NMR spectroscopy, and their biologic efficacy against two types of bacteria was investigated.

Muhammad Pervaiz was born in 2018. Sulfa drug ligands and their derivatives have long been recognized as pre-eminent compounds in the fields of synthetic and pharmaceutical chemistry. Transition metal complexes of 4-amino-N-(5-methyl-3-isoxazolyl)benzene sulfonamide are made by reacting it with metals such as Mn(II), Co(II), Fe(II), Fe(III), Cr(III), Ni(II), Cu(II), and Zn (II). Sulfa drug metal complexes have been used for biological (as antibacterial and antifungal agents) as well as catalytic (as in Olefin Polymerization) purposes. The sulfa drug derived complexes are found to be very important in pharmaceutical and medical chemistry due to their broad spectrum range. With the importance of sulfa drug-based transition metal complexes in mind, the review summarized the synthesis, characterization, and antimicrobial activities of 4-amino-N-(5-methyl-3-isoxazolyl) benzene sulfonamide metal complexes.

In 2019 Cristian Cezar Login has been Schiff bases (SBs) are chemical compounds displaying a significant pharmacological potential. They are able to modulate the activity of many enzymes involved in metabolism and are found among antibacterial, antifungal, anti-inflammatory, antioxidant, and antiproliferative drugs. A new thiazolyl-triazole SB was obtained and characterized by elemental and spectral analysis. The antibacterial and antifungal ability of the SB was evaluated against Gram-positive and Gram-negative bacteria and against three Candida strains. SB showed good antibacterial activity against L. monocytogenes and P. aeruginosa; it was two times more active than ciprofloxacin. Anti-Candida activity was twofold higher compared with that of fluconazole. The effect of the SB on cell viability was evaluated by colorimetric measurement on cell cultures exposed to various SB concentrations. The ability of the SB to modulate oxidative stress was assessed by measuring MDA, TNF-α, SOD1, COX2, and NOS2 levels in vitro, using human endothelial cell cultures exposed to a glucose-enriched medium. SB did not change the morphology of the cells. Experimental findings indicate that the newly synthetized Schiff base has antibacterial activity, especially on the Gram-negative P. aeruginosa, and antifungal activity. SB also showed antioxidant and anti-inflammatory activities.

In 2019, U. A. Abubakar, the emergence of new infectious diseases, the resurgence of previously controlled infections, and the rise in bacterial resistance have necessitated research aimed at developing new antimicrobials. Co and Ni mixed drug metal (II) complexes with Sulfamethoxazole and ampicillin trihydrate as ligands were synthesized. The standard drugs and their mixed complexes were also tested for antibacterial activity against Salmonella typhi (gram negative bacteria) and Staphylococcus aureus using the agar diffusion method (gram positive bacteria). The zones of inhibition revealed that Co and Ni complexes at 20 g/disc have antibacterial activity against Staphylococcus aureus (24.3 and 22.3 mm) and Staphylococcus typhi (15.3 and 14.0), respectively.

Sangar A. Hassan was born in the year 2019. This research shows the synthesis and spectroscopic analysis of new -lactam and novel Pyrrolone derivatives, as well as the antioxidant and antibacterial activities of these compounds. The synthesis of imine derivatives (3a-j) from sulfadiazine was the first of two major steps in this study. The synthesis of 2-Azetidinone and Pyrrolone (5a-j) heterocyclic compounds was carried out in the second step, which involved reacting synthesized imine derivatives with chloroacetyl chloride and fumaryl chloride, respectively, in the presence of triethylamine. Finally, all products were tested for antioxidant activity as well as resistance to two bacteria strains: Staphylococcus aureus G (+ve) and Escherichia coli G (-ve). When compared to standard ascorbic acid, the products had lower to higher antioxidant activity. Some products were found to be inactive, while others had moderate to high activity against both types of bacteria.

The present study, according to 2020Kamoon RA, involves the synthesis of four different azo-azomethine derivatives in two steps: the first is the diazotization of sulfonamides (sulfanilamide, sulfacetamide, sulfamethoxazole, and sulfadiazine) separately, followed by the second step, the coupling reaction of diazotized compounds with the isatin bis-Schiff base. The reaction of 3-hydrazono-indolin-2-one with p-nitrobenzaldehyde yielded the latter (bis-Schiff base). The antimicrobial potential of the synthesized azo compounds was tested in vitro using the well diffusion method. Only compounds 2b and 2c have antibacterial activity against Pseudomonas aeruginosa, while all of the target compounds clearly inhibited Escherichia coli and Candida albicans. Compound 2b is the most effective azo compound against E. coli, Pseudomonas aeruginosa, and Candida albicans among the prepared azo compounds.

Haider Husine Abd-Ali synthesized a series of Schiff-bases in 2020 through the condensation reaction of Salicylaldehyde with Sulfadiazine, Sulfanilamide, Sulfathiazole, and Sulamerazine. Then, azo compounds with aldehyde groups were created by converting Sulfanilamide, Sulfadiazine, and Sulfathiazol to dizonium salts and then coupling them with 2-hydroxy benzaldehyde in alkaline media. Furthermore, azo Schiff bases were created through the condensation of ethylene diamine and various sulfa drugs. The antioxidant activity of some of the above-mentioned compounds has also been determined in vitro for their fungicidal activity against Candida albicans and Aspergillus niges, as well as antimicrobial activity against Escherichia coli and Staphylococcus aureus.

Cu(II), Co(II), Ni(II), Fe(III), and Cr(III) complexes with sulfadiazine Schiff base derivative were synthesized by Marwa Hassan in 2020. The biological activity of the ligand and metal complexes was also investigated, including the cytotoxic effect on normal cells and liver malignant cells, as well as antimicrobial activity.The ligand and its novel metal-containing complexes had moderate antimicrobial activity, but the metal complexes, particularly those containing Cr(III), Fe(III), and Cu(II), had a superior chemotherapeutic effect on the HepG2 cell line when compared to the ligand with very few or rare cytotoxic effects on normal human cells. New sulfadiazine Schiff base derivative-containing metal complexes with improved therapeutic potential were efficiently manufactured and tested on experimental models for the treatment of a variety of infections and cancers.

Mujahid Abas developed a series of azaheterocyclic Schiff base derivatives bearing sulfonamides as carbonic anhydrase inhibitors in 2020. The aromatic sulfonyl hydrazides were obtained by reacting the substituted benzene sulfonyl chlorides 1(a-d) with N_2H_4. To make azaheterocyclic sulfonamide Schiff bases, the intermediate hydrazides were treated with substituted aldehydes. The formation of the final products was confirmed by the spectral data of synthesized compounds. The inhibitory effects of 3(a-j) on carbonic anhydrase activity were investigated, and it was discovered that derivative 3c has the highest potency of all the derivatives, with an IC500 of 84 0:12 M, and is also more active than standard acetazolamide (IC500:91 0:12). The results of the Line weaver-Burk plots for enzyme inhibitory kinetics revealed that compound 3c inhibits the enzyme in a noncompetitive mode with a Ki value of 8.6 M. The molecular docking studies of the synthesized analogues 3(a-j) were evaluated, ensuring that the synthesized compounds bind well inside the target enzyme's active binding site. The toxic effects of the synthesized analogues on human keratinocyte (HaCaT) and MCF-7 cell lines were studied, and it was discovered that the majority of the synthesized analogues were nontoxic on these cell lines and that the toxic effects were dose-dependent. According to our findings, analogue 3c could be used as a core structure for developing more potent carbonic anhydrase inhibitors.

In 2021 Saliha Alyar ,Herein we present the synthesis, and biological evaluation of new Schiff bases incorporating (2–hydroxy5-methylbenzaldehyde sulfisoxazole and 2–hydroxy-5-methylbenzaldehyde sulfamethoxazole derived from sulfisoxazole /sulfamethoxazole and substituted salicylaldehyde and their Pd (II), Cu(II) complexes. The single crystal X-ray diffraction technique was also used to determine the molecular structure of S2M-S1, which was discovered to crystallize in the monoclinic space group P1 21/n 1. The effects of molecules on human carbonic anhydrase isoenzyme II were investigated. Cu (S2M-S1)2, Pb(S2M-S1)2, Pb(S1M-S1)2, and Cu(S1M-S1)2 were found to have inhibitory effects with IC50 values of 10, 20, 42, and 67 M, respectively. In addition, molecular Docking studies were conducted, and the anticancer activities of newly synthesized compounds were assessed using the sulfonamide B test against three human cancer cell lines. Against all cell lines, S2M-S1, S1M-S1 compounds, and their Cu (II) complexes showed promising cytotoxic activity. For S2M-S1, S1M-S1 compounds, and their Cu (II) complexes, the IC50 values for breast (MCF7) cells are 40 M.

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