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Synthesis, Application and Biological Activities of Ligand, Schiff base and Metal Complexes: Review

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***Abstract* - Schiff bases are created by stirring, catalyst-free, reflux, and conventional methods using a range of aldehydes, ketones, and amines. Since complexation usually increases activity, understanding the properties of both ligands and metals may result in the synthesis of highly active compounds. The Schiff base was characterized by an imine or azomethine (-CH=N-) group and is generally formed through the condensation reaction of carbonyl compounds (like ketones or aldehydes) with molecules containing an amine group. Also, Schiff bases have wide-ranging uses in magnetic and electronic materials, catalysts in organic reactions, corrosion prevention, cosmetics, show many biological activities and the pharmaceutical industry. Furthermore, Schiff bases represent a new class of drugs capable of enhancing immunity and addressing various diseases, including liver cancer (HepG2) and colon cancer in human cancer cell lines. Consequently, medicinal chemists are presently focused on creating new chemotherapeutic Schiff bases along with their metal complexes. This overview compiles the various synthesis techniques and uses of Schiff bases and related metal complexes.**

Keywords: Schiff bases, Metal complexes, condensation, chemotherapeutic, cancer.

I. INTRODUCTON

The effectiveness of biological therapeutic procedures relies on inorganic minerals. The Schiff base compounds are recognizable because of the azomethine group (-CH=N), formed when amine-containing compounds react with aldehydes or ketones[1]. Schiff bases were originally documented in 1864 by Hugo Schiff [2]. Moreover, Schiff bases are highly adaptable and can exist in various forms. Numerous Schiff base compounds and their properties have been investigated due to the various structures of these compounds [3]. The typical methods for producing Schiff bases involve heat or the use of acidic or basic catalysts. Also, Schiff bases generally exhibit mild basicity and occur as crystalline solids; however, certain ones can form strong, insoluble, acidic salts. Schiff bases are utilized to create a range of unique metal complexes in the process of synthesizing amino acids as ligands or intermediates [4]. The action mechanisms of all organic compounds utilized in medicine are not purely organic; some are activated by metal ion metabolism or experience biotransformation. Currently, numerous studies and interesting areas utilize Schiff bases as ligands. In addition, Schiff bases can be formed through an easy condensation reaction and are often used in coordination chemistry because of their ability to donate electrons as ligands. Even though there is a synthetic interaction between aldehyde groups and amino acids, the pH plays a crucial role in forming Schiff bases, and most Schiff bases are produced in the presence of bases [5]. Schiff bases, often tri-dentate or bi-dentate ligands, can create highly stable transition metal complexes. They are utilized as liquid crystals under certain conditions. In chemical synthesis, Schiff base reactions can aid in the formation of carbon-nitrogen bonds [6]. Not only that, but also Schiff bases are extensively utilized as ligands in coordination chemistry for several reasons, such as the occurrence of photochromism and thermochromism in Schiff base compounds' solid state, which is attributed to proton transfer from the hydroxyl (O) to the imine (N) atoms, alongside the hydrogen bonds between the (O) and (N) atoms within molecules, which are crucial for the formation of metal compounds. In numerous biochemical reactions involving an enzyme, Schiff bases seem to play a crucial role [5].

II. RESULT AND DISCUSSION

In this study, lemon juice was utilized as a catalyst to create Schiff bases. XRD tests indicate that SB-1 possesses a triclinic crystal structure, whereas SB-2 exhibits a tetragonal structure. Studies on the antidiabetic properties of these compounds might lower postprandial glucose levels, serving as a crucial approach for managing blood sugar. Both Schiff bases 1 and 2 exhibited a significant cytotoxic impact on the human lung cancer cell line 549.The α-amylase inhibitory activity of the Schiff

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bases was assessed both in vitro and in silico. Schiff base-2 showed the greatest inhibition when compared to the reference medication acarbose. To synthesize Schiff Base-1 (SB-1) and Schiff Base-2 (SB-2), ten millimoles of 2-nitro and 4-hydroxy benzaldehyde were mixed with a minimal quantity of 100% ethanol in two different beakers. Through continuous swirling, these solutions were slowly incorporated into two separate beakers holding a solution of 5 mmol of 3,3′-dimethyl-[1,1′-biphenyl]-4,4′-diamine in ethanol. After the blending of the mixtures at room temperature, every participant was given two milliliters of freshly squeezed lemon juice. TLC was utilized to observe and record the progress of the reaction as the mixture was stirred continuously. The findings indicated that Schiff base-1 (SB-1) produced a solid tea-green substance, while Schiff base-2 (SB-2) resulted in a yellow-colored product. These products underwent recrystallization with DMSO after the water had been purified and filtered. The schematic for the synthesis pathway of Schiff bases 1 and 2 is shown in (Figure 1)[7].

Figure 1: Synthesis of Schiff base-1 (SB-1) and Schiff base-2 (SB-2)

The researchers have created two derivatives, TZ1 and TZ2, illustrated in Fig. 2. Weight loss and electrochemical investigations how that these derivatives lower the corrosion rate of carbon steel. Surface examination tests are conducted to analyze the morphology and composition of the carbon steel surface immersed in HCl solution and subsequent to the addition of inhibitors. Creation of inhibitors A combination of 4-amino-5-hydrazineyl-4H-1,2,4-triazole-3-thiol (1) (0.146 g, 1 mmol) and 3-acetyl-coumarine (2) (0.188 g, 1 mmol) or 9H-fluoren-9-one (3) in methanol (20 ml) with 3–4 drops of concentrated. H2SO4 was heated under reflux for 10 minutes. The precipitate obtained was hot, then filtered and rinsed with hot methanol (20 ml) to eliminate any unreacted starting materials. Ultimately, the resulting precipitates of compounds TZ1 and TZ2 were dried in the oven at 80 °C[8].

Figure 2: Synthetic pathways for the compounds TZ1 and TZ2

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The authors of the paper detail the synthesis, crystallographic and spectral characterization, along with DFT studies of the enolimine (EI) ⇌ keto-amine (KA) tautomeric properties of a new Schiff base. Observations from electronic absorption spectra indicate that the major tautomer in solution varies with the solvent type; KA is formed in protic solvents and EI in aprotic solvents. Computational simulations indicate that the energy difference between the two forms is minimal, with the EI form being slightly preferred in the gas phase and in nonpolar solvents, while the KA form is preferred in methanol.The dynamically computed NLO responses indicate that KA exhibits a superior NLO response compared to EI. The method for forming the Schiff base, known as LMAP, is illustrated in Fig. 3. A methanolic solution of 2-amino-4-methyl phenol (0.6158 g, 5.0 mmol) in 20 mL is mixed with a methanolic solution of 4-(N,N-diethylamino) salicylaldehyde (0.9662 g, 5.0 mmol in 20 mL). The blend was mixed thoroughly and left to sit at ambient temperature. After approximately 4 hours, dark brown crystals appropriate for single crystal X-ray examinations were isolated. (yield: 73% M.P. 183±2℃) [9].

Figure 3: synthesis of LMAP

In this study, the efficacy of a Schiff base, 3-((5-mercapto-1,3,4-thiadiazol-2-yl) imino) indolin-2-one (MTIO), to avertmild steel corrosion in HCl was examined through weight loss metrics, potentiodynamic polarization analysis, electrochemical impedance spectroscopy methods, and surface analysis. The experimental results indicated that 0.5 mM MTIO demonstrated a satisfactory inhibition efficiency of 96.9% at 303 K. The mild steel surface hosted MTIO molecules that were adsorbed physically and chemically, adhering to the Langmuir model and creating a dense protective film due to the thiazole ring present in the MTIO structure. The inhibitory performance rises with higher MTIO concentration and falls with higher temperature.

Figure 4: The chemical structure of MTIO

MTIO particles chemically adhere and form weak bonds with metal substrates, while the inhibition effectiveness decreases with rising temperatures. The performance inhibition grows with higher MTIO concentration and diminishes with rising temperature. MTIO mitigates corrosion of metallic substrates by forming a protective layer of MTIO particles at the interface of steel and electrolyte [10].

The ligand (ATHSB, HL) was utilized to form a new array of Mn(II), Cu(II), and Zn(II) complexes of innovative aminothiohydantoin Schiff base ligands through the reaction of metal (II) chlorides in a 1:1 M ratio, as stated by the colleagues. We studied the coordination properties, stereochemistry, and stoichiometry of HL with Mn(II) ions (Fig. 5).

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Figure 5: Schematic diagram to producethe transition metal complexes of aminothiohydantoin Schiff base ligand (ATHSB, 3) and its derivatives (M(II)ATHSB, 4a-c)

All the complexes exhibit greater cytotoxicity compared to their parent ligands. Human cancer cell lines exist for colon cancer (HCT116) and liver cancer (HepG2).Zinc (II) ATHSB appears to be a strong contender and could serve as a viable alternative to standard chemotherapy treatments, as it is the most effective at killing HepG2 while inflicting minimal harm on normal human liver cells (HL7702). 32 mL of glacial acetic acid and 0.24 mol of anhydrous zinc chloride powder were warmed to 140°C in a sand bath to produce dihydroxyacetophenone. Subsequently, 0.2 mol of dry resorcinol was incorporated while the mixture continued to be stirred at the same temperature. The reaction mixture was subsequently heated to 150 °C for 20 minutes, or until it began to boil. The liquid was chilled to 5 °C prior to the addition of 50 mL of 18% HCl. Following extraction from the contaminated, separated filtration, the white product underwent cleaning with diluted HCl. For the desired outcome, the material was recrystallized using hot water.Semicarbazide hydrochloride (1,4-Dihydroxyacetophenone thiosemicarbazone synthesis) and anhydrous sodium acetate (0.9 g) were recrystallized from hot water to achieve the desired outcome. Synthesis of 2,4-Dihydroxyacetophenone Thiosemicarbazone (2) A transparent solution was formed by gradually heating distilled water (5 mL), semicarbazide hydrochloride (1 g), and anhydrous sodium acetate (0.9 g). After the addition of 5 mL of ethanol, a 1 g solution of 2,4-dihydroxyacetophenone was stirred. Subsequently, the reaction mixture was gradually heated for 15 minutes at 55 °C in a water bath to promote the crystallization of the desired semicarbazone. The product was separated, thoroughly rinsed with distilled water, and drained after cooling.3-((1-(2,4-dihydroxyphenyl) ethylidene) amino) ATHSB synthesis Hot dry ethanol (20 mL) along with a catalytic quantity of anhydrous sodium acetate (0.75 g, 9.14 mmol) was employed to dissolve -2-thiohydantoin-4-one) (3)2,4-Dihydroxyacetophenone thiosemicarbazone (2) (1.13 g, 5.12 mmol) and ethyl chloroacetate (0.62 mL, 5.11 mmol). The mixture was subsequently heated for five hours while being stirred and refluxed. TLC monitored the progression of the reaction to investigate the absence of (2) and, in the end, the conclusion of the reaction. The reaction mixture was permitted to cool to room temperature before being added to an ice-water mixture once (2) had disappeared. The yellow crystals of the necessary ligand (3)were produced by filtering, drying, and crystallizing the solid outcome from heated ethanol Fig. 6.

Figure 6: Structural and geometrical features of the new M(II)ATHSB complexes

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ATHSB complicated (4a-c) preparation:

ATHSB complexes (4a-c) were synthesized following the general procedure outlined below. A heated ethanolic solution (25 mL) of ATHSB (0.265 g, 1 mmol) combined with several drops of NH_3/NH4Cl-buffer (pH 9.2) was blended with a heated aqueous ethanolic solution (1:1, 25 mL) of the divalent metal salt (MCl_2xH_2O; $CuCl_2{\cdot}2H_2O$, $MnCl_2{\cdot}4H_2O$, $ZnCl_2$) (1 mmol). The reaction mixture was heated under reflux for two hours. To facilitate the precipitation of the desired products, the reaction mixture was brought to room temperature after most of the solvent was evaporated under reduced pressure. Post-filtration, the products were washed with O (5 mL × 3), treated with EtOH (5 mL × 2) under heat, and then dried in a vacuum (Fig. 6)[11].

This study details the synthesis and characterization of new Schiff bases derived from different amines and aldehydes employing the magnetic stirrer technique. Schiff bases seem to serve as a crucial intermediary in various enzymatic reactions that involve the interaction between an enzyme and either an amino or a carbonyl group of the substrate. A crucial category of catalytic mechanism is the biochemical process that encompasses the condensation of a primary amine, typically a lysine residue within an enzyme, with the substrate's carbonyl group to produce an imine or Schiff base. Thiadizole derivative of salicylaldehyde was discovered to be highly effective as an antibacterial agent against Bacillus cereus and as an antifungal agent against Aspergillus niger and amines by an aqueous acid or base.

Ligand Synthesis:

The Aromatic aldehyde/substituted aldehyde in ethanol (20 mmol) is combined with 20 mmol of Amine/substituted amine, and the blend is stirred for 1-2 hours using a magnetic stirrer (Fig. 7,8,9,10)[4].

Figure 7: Synthesis of carbinolamine at acidic PH

Figure 8: Synthesis of ligand 2

Figure 9: Synthesis of ligand 3

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Figure 10: Synthesis of ligand 4

In this work, Azomethine amino ligands were synthesized from the reaction of 3-methoxysalicylaldehyde (MS) or 4-diethylaminosalicylaldehyde (DS) with a-amino acids (L-phenylalanine (P) and DL-tryptophan (T)). The ligands and their complexes were tested for antimicrobial effects against various types of bacteria. The findings from these studies show that the metal complexes demonstrate greater antibacterial and antifungal effectiveness than their corresponding ligands. The complexes' interaction with CT-DNA was observed through spectral analyses, viscosity assessments, and gel electrophoresis. Moreover, it was discovered that the synthesized complexes could interact with DNA in an intercalating manner.

Three Schiff bases were derived from L-Phenylalanine (P) or DL-Tryptophan (T) and either 3-methoxysalicylaldehyde or 4-diethylaminosalicylaldehyde. Imines derived from L-Phenylalanine (P) or DL-Tryptophan (T) were obtained by adding a 30 ml ethanolic solution of 5 mmol of 3-methoxysalicylaldehyde or 4-diethylaminosalicylaldehyde (0.76 g, 0.995 g, respectively) to 5 mmol of L-Phenylalanine or DL-Tryptophan dissolved in heated ethanol. The mixture was stirred and refluxed for 2 hours, after which it was cooled to room temperature. After 24 hours, the resulting precipitate was filtered and rinsed with hot ethanol.

Three new complexes were created by combining 40 ml aqueous solutions of amino acids derived from dissolving 5 mmole of either 0.825g phenylalanine or 1.045 g tryptophan with 50 ml hot ethanolic solutions of 3-methoxysalicylaldehyde (5 mmole, 0.76g) or 4-diethylaminosalicylaldehyde (5 mmole, 0.995 g). Subsequently, the blend was mixed at 70 ^{o}C for one hour. Subsequently, a 40 ml aqueous-ethanol solution containing 2.5 mmole of ($Cu(CH_3COO)2$. H_2O (0.5 g) or 30 mlaqueous-ethanol of 2.5mmole $(NH_4)2Fe(SO_4)2•6H_2O$ (0.98 g). To inhibit the oxidation of Fe(II), a few drops of glacial acetic acid were added. The blend was agitated at ambient temperature for 3 hours. The hue shifted from yellow to green for MSPCu, blue for DSTCu, and dark brown for MSTFe. The final product was left to evaporate overnight. The solid obtained was filtered, rinsed with water, and dried under vacuum over anhydrous are shown in (Fig. 11)[12].

<table>
<tr><td colspan="2"></td><td colspan="2"></td><td>Side chain</td></tr>
<tr><td>Aldehyde</td><td>Ligand abbrviation</td><td>Aldehyde</td><td>Ligand abbrviation</td><td>R</td></tr>
<tr><td rowspan="3">3-methoxysalicyladehyde</td><td>MSP</td><td rowspan="3">4 diethylamino-salicylaldehyde</td><td>DSP</td><td></td></tr>
<tr><td rowspan="2">MST</td><td>DST</td><td></td></tr>
<tr><td>DSH</td><td></td></tr>
</table>

Figure 11: The synthesized ligands of Schiff base amino acids

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The researchers synthesized free ligands and their metal complexes were evaluated for in vitro biological activities against bacteria, fungi, and yeast. The metal complexes exhibit stronger activities than Schiff base ligands. This set of novel Schiff bases, exhibiting potential biological activity, originated from the acid-catalyzed condensation of aryl aldehydes with both aromatic and heteroaromatic amines. The structures of the Schiff bases obtained from 2-amino-Benzthiazole, 4-amino-Salicylic acid, and 4-aminophenol are displayed in Fig.12.

Figure 12: The Schiff bases created from 4-aminophenol, 4-amino-salicylic acid, and 2-amino-benzthiazole

Synthesis of Schiff Bases of 2-Amino-benzthiazole

2g of 2-Amino-benzthiazolewas combined with an equivalent quantity of the corresponding aldehyde in 25 ml ofethanol. The obtained mixture was subjected to reflux for 2 hours, and the solidproduct that formed was isolated through filtration, purified byrecrystallization using ethanol, washed with ethanol, and subsequently dried (Fig. 13).

Figure 13: Synthesis of Schiff bases of 2-amino-benzthiazole

Synthesis of 4-Amino-salicylic acid Schiff Bases

2 grams of 4-Amino-salicylic acid were combined with an equal amount of the respective aldehyde in 25 milliliters of ethanol. The obtained mixture was maintained under reflux for 2 hours, after which the solid product was isolated through filtration, purified via recrystallization from ethanol, rinsed with ethanol, and subsequently dried (Fig. 14).

Figure 14: Formation of Schiff bases of 4-amino-salicylic acids

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Synthesis of 4-Aminophenol Schiff Bases:

2g of 4-Aminophenol was combined with an equal amount of the respective aldehydes in 25 ml of ethanol. The mixture obtained was maintained under reflux for 2 hours, and the resulting solid product was isolated through filtration, purified by recrystallization using ethanol, rinsed with ethanol, and subsequently dried Fig.15 [13].

Figure 15: Synthesis of 4-aminophenol Schiff bases

The team members collaborated to create a new class of Fe(II) tridentate Schiff base amino acid complexes. The Schiff bases generated from o-hydroxynaphthaldehyde are the monoanionic tridentate ligands L-alanine (nal), L-phenylalanine (nphal), L-aspartic acid (nas), and L-arginine (nar).The synthesized complexes were evaluated for toxicity on chick embryos and determined to be safe up to a concentration of 100 µg/egg with complete embryo development. The interaction between the studied complexes and CT-DNA was monitored through spectrophotometry and viscosity measurements. The prepared complexes were found to bind to DNA through the classical intercalative mode and exhibited varying DNA cleavage activities in the order: nhi > nari > nali > nasi > nphali. The thermodynamic profile of the nphali complex binding with CT-DNA was developed by examining experimental results from absorption titration and UV melting analyses using the McGhee equation, van't Hoff's equation, and the Gibbs–Helmholtz equation. The Kf values obtained, which rise in the sequence of Nhi < Nasi, nphali < Nail, and Nail < Naari, indicate the significant stability of the produced compounds.

Acronym		R
Ligand	Complex	
Nal	nali	CH_3
Naphal	nphali	$CH_2C_6H_5$
Nas	nasi	CH_2COOH
Nh	nhi	
Nar	nari	

Figure 16: The Schiff base ligands' and their associated complexes' structures and acronyms

Schiff bases were prepared for examination

The mixture of aqueous ethanol was combined with 3 mmol of an amino acid solution (ala, phala, aspa, his, or arg) following the dissolution of 3 mmol of 2-hydroxy-1-naphthaldehyde in 40 ml of ethanol. A rotary evaporator was employed to remove the solvent after the mixture refluxed for five hours, and the residue crystallized at ambient temperature. Subsequently,

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yellow crystals of L-aspartic acid, L-phenylalanine, and L-alanine were allowed to rest at room temperature for a day. In contrast, L-histidine formed green crystals, while L-arginine yielded brown ones. The precipitate of ethanol/diethyl ether was recrystallized, as seen in Figure 16.

Production of the complexes

The ethanolic ligand solution was mixed with an ethanolic solution containing 5 mmol of $FeSO_4$_$(NH_4)2SO_4$_$6H_2O$. To prevent the oxidation of Fe(II), several drops of glacial acetic acid were included. The obtained solution was magnetically stirred for 12 hours at 25 °C and then left to evaporate overnight. Subsequently, the obtained solid product was filtered, rinsed with water and dry ether in sequence, and ultimately dried in a desiccator. (Fig. 16)[14].

The synthesized ligands and their metal complexes underwent screening for in-vitro antibacterial activity. The findings from these studies indicate that the metal complexes exhibit greater antibacterial/antifungal activity against one or more species in comparison to the uncomplexed Schiff base ligands. The brine shrimp bioassay was performed as well to examine their in-vitro cytotoxic characteristics. Just three compounds (2, 11, and 17) exhibited strong cytotoxic effects with LD50 values of 8.196 × 10−4, 7.315 × 10−4, and 5.599 × 10−4 M/ml, respectively, against Artemia salina.

Synthesized of Schiff bases (L1 –L5)

A solution of glycine (20 mmol) in water (20 ml) was stirred, to which salicylaldehyde (20 mmol) in ethanol (10 ml) was added. The solution was refluxed for 3 hours. At this moment, the solution changed its color to orange. The reaction's completion was observed using TLC.

Each additional ligand was synthesized in an identical manner, utilizing the same salicylaldehyde, under consistent conditions, and with the same molar ratio (Fig. 17).

Figure 17: Reaction that produces the first acids (L1–L5)

Preparation of metal(II) complexes

To a magnetically stirred suspension of the corresponding amino acid-derived Schiff base (0.02 mol) in water (20 ml), equimolar KOH (0.02 mol) was added. The blend was mixed for thirty minutes. An ethanol (30 ml) solution of the respective metal (II) salt (0.01 M) as chloride was subsequently added to this mixture and refluxed for 1 hour. The resulting solution was filtered and its volume was halved by evaporating the solvent under vacuum. The resultant solid was rinsed with ethanol (2 × 15 ml) followed by ether and dehydrated. The desired products were obtained through recrystallization using aqueous–ethanol (20: 80). Regrettably, only microcrystalline powders were produced, making them unsuitable for X-ray structural analysis Fig.18 [15].

Figure 18: Proposed structure of the metal (II) complex

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In this study, Schiff bases of 2-amino-5-aryl-1,3,4-thiadiazole derivatives have been produced using various aromatic aldehydes. Derivatives of 1,3,4-thiadiazole were synthesized through the reaction of thiosemicarbazide, sodium acetate, and an aromatic aldehyde. Every synthesized compound displayed pain-relieving, antimicrobial, and anti-inflammatory properties. Compounds 4a, 4b, 4c, and 4e exhibited notable analgesic effects on Swiss albino mice. Derivatives of 1, 3, and 4-thiadiazoles effectively target lung, breast, and central nervous system cancer cell lines. They also demonstrated effective cytotoxicity against SI leukemia and SF-268 CNS tumors. The impacts of 2-Dimercapto-1,3-thiadiazoles, including photographic development darkening, increased vulcanization speeds, corrosion prevention, and protection against sunburn, are recorded in the existing literature.

R=OCH_3	R‘=OH	R=OCH_3	R‘=NO_2
R=OH	R‘=OH	R=OH	R‘=NO_2
R=Cl	R‘=OH	R=Cl	R‘=NO_2
R=NO_2	R‘=OH	R=NO_2	R‘=NO_2
R=$N(CH_3)_2$	R‘=OH	R=$N(CH_3)_2$	R‘=NO_2

Figure 19: The compounds' IR and 1H NMR spectrum data were used to determine their structures

Synthesis of Thiosemicarbazone 2(a):

Thiosemicarbazide (0.01 m) and crystalline sodium acetate (0.02 m) were placed in a round-bottom flask, and 8-10 ml of water along with 0.5 g of aldehyde was gradually added while stirring continuously. The solution was cloudy, so methanol was added until it became clear; the mixture was shaken for a few minutes and then left to settle. Thiosemicarbazone was obtained as a precipitate from the cold solution. Remove the precipitate and recrystallize using ethanol (Fig. 19).

Synthesis of 2-Amino-5-aryl-1, 3, 4-thiadiazole 3(a):

Thiosmicarbazone 2a (0.01 m) and sodium acetate (0.02 m) were solubilized in 30-40 ml of glacial acetic acid placed in a round-bottom flask fitted with a separating funnel for the inclusion of bromine. Bromine (0.7 ml in 5 ml of glacial acetic acid) was gradually incorporated into it, while mixing with magnetic force. After thirty minutes of stirring, the mixture was poured onto crushed frozen water. The obtained solid was isolated, dried, and recrystallized using ethanol (Fig. 19).

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Synthesis of Schiff Bases of 2-Amino-5-aryl-1, 3, 4-thiadiazole 4(a):

A 3a solution (0.01 m) was made in 20 ml of alcohol using a round bottom flask. Necessary Aldehyde (0.01 m) dissolved in 15 ml of alcohol was subsequently added to it. The blend was refluxed for 5 to 6 hours. The amount of alcohol was cut by half through distillation at reduced pressure. The resulting mixture was poured over crushed ice. The precipitate that was isolated was dried and recrystallized using ethanol Fig. 19.[16]

This article details the synthesis and characterization of an isatin Schiff base, specifically 2-(2-oxoindolin-3-ylidene) hydrazinecarbothioamide (OHB). OHB's ability to inhibit corrosion was assessed on mild steel samples in 1 M HCl through gravimetric methodsand electrochemical techniques, including electrochemical impedance spectroscopy (EIS) and potentiodynamic methods, along with microscopic examination. The findings revealed that OHB acts as a mixed-type inhibitor and demonstrated effective corrosion inhibition, achieving a peak corrosion inhibition efficiency of 96.7% at a concentration of 0.5 mM and 303 K. The performance of inhibition rose with higher OHB concentration and fell with elevated temperature. The electrochemical impedance analyses also showed that the charge transfer resistance rose with a rise in OHB concentration. The morphological analysis verified the inhibition efficacy of OHB, and the protective barrier film adhered to Langmuir monolayer adsorption principles.

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Figure 20: The chemical structure of OHB

Synthesis of inhibitors: Equal amounts (0.03 mol) of isatin and thiosemicarbazide were dissolved in heated ethanol with 1 ml of glacial acetic acid. The reaction mixture was refluxed for 8 hours, then concentrated and recrystallized in ethanol, producing 88% OHB, with purity assessed by TLC (Fig. 20)[17].

Amino acid derivative Schiff base was synthesized by reaction of leucine with salicyldehyde in basic medium. All compounds engaged with different bacterial andfungal strains in order to check the inhibitory action of compounds. The results showed that the metal complexes have greater antimicrobial activities than ligand.

Figure 21: Synthesis of Schiff base ligand

The ligand was produced by combining equal molar amounts of leucin and salicyldehyde.

In this reaction, 0.7 grams of Leucine was dissolved in ethanol, and 1.2 grams of salicyldehyde was incorporated. to this resolution. The sodium hydroxide solution (50% solution in water) was made and incorporated. to the aforementioned solution to facilitate the reaction in a basic medium. The mixture of reactants was refluxed efficiently for 7 hours at 500 degrees Celsius. The reaction was observed through thin layer chromatography (TLC) assays. The substance was cooled and the solvent was eliminated using a rotary evaporator. The substance was filtered, the resulting product was rinsed with ethanol and dried (Fig. 21).

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Figure 22: Schiff base metal complexes (M = Co, Mn, Cu, and Cd) are synthesized

The ligand and metal acetates (Co, Mn, Cu, and Cd) were combined in a (1:2) molar ratio in to create the sequence of metal complexes. The acetates of metal were dissolved in toluene individually and ligand was mixed in ethanol. Both solutions were combined in a 250ml reaction flask. The contents of the flask were refluxed at 50 ℃ for 6-7 hours individually for each metal Fig. 22. [1]

This document outlines and details the following: A range of imidazole derivatives conjugated with amino acids were synthesized and analyzed using standard spectroscopic methods. These substances were assessed for their antibacterial and antifungal properties. The activity profile indicated that compounds with aromatic amino acids have demonstrated significant outcomes alongside the advantageous electron attracting hydroxyl groups. The occurrence of thio (Met) and imino (Pro) amino acids has demonstrated moderate activity in contrast to Lys, which is a basic amino acid. These target molecules have demonstrated selective efficacy against A. niger fungal species. Compounds with a phenyl ring, indole ring, and –OH (phenolic) group demonstrated significant antioxidant activity, likely attributable to the electron-donating capacity and resonance characteristics of the phenyl ring.

Figure 23: Schematic for target compounds

General procedure for N-alkylation

Compound 1 (2.0 g, 0.008 mol) was dissolved in acetone, after which base K_2CO_3 (2.3 g, 2 mol) was added, and then 4-chlorobenzyl chloride (1.33 g, 0.008 mol) was gradually incorporated. The reaction was sustained for 10 hours at reflux (observed by TLC), filtered using K_2CO_3, the solvent was evaporated, then cooled and recrystallized the N-alkylated product 2 from ethanol.

The general process for hydrolysis

Compound 2 (2.0 g, 0.0054 mol) was mixed with methanol, and 0.1 N NaOH solution (0.43 g, 0.011 mol) was added, then the reaction was sustained for 5 hours at 50 °C. The reaction's progress was tracked by TLC, then cooled, and the pH was adjusted to 1-2 with diluted acid. HCl solvent. The compound was extracted using DCM and rinsed with water Fig. 23. [18]

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In this study, the subsequent Schiff bases were synthesized by reacting benzaldehyde or acetone with the amino acid phenylalanine in basic conditions, along with its complexes of Co (II), Ni (II), and Cu (II), employing sodium hydroxide as a catalyst. Certain prepared metal complexes were assessed for in-vitro antibacterial effectiveness against both Negative and Positive Bacteria. The complexes exhibited considerable antibacterial properties.

Preparation of Schiff Bases

The Schiff base was synthesized by slowly adding 10 ml of benzaldehyde or acetone ethanolic solution (0.01 mol) while stirring to an equal volume of ethanolic solution of phenylalanine (0.01 mol) through gradual addition, then adding sodium hydroxide ethanolic solution (0.01 mol) to the mixture over 30 minutes. The solution was subjected to reflux heating for (5-6) hours. Following cooling, the mixture was filtered, rinsed multiple times with ethanol, and then dried. The synthesized Schiff bases dissolve in water and in various organic solvents.

Preparation of Complexes

The Schiff base solution (post-reflux) was gradually combined with an ethanolic solution (0.005 mol) of Co(II), Ni(II), Cu(II) chloride salts, and the mixture was refluxed for 2 hours. Colored complexes were precipitated in each instance, filtered, and washed repeatedly with ethanol before being dried at approximately 50°C. The synthesized complexes are insoluble in many organic solvents and soluble in DMSO. [5]

In this study, Schiff base analogues of 4-aminoantipyrine were synthesized through a condensation reaction with substituted benzaldehydes, and their properties for reducing inflammation and acting as antioxidants were subsequently evaluated. The analysis of structure and activity suggests that the antioxidant properties of the Schiff base analogues of 4-aminoantipyrine are greatly affected by the type and position of the substituent on the benzylidene phenyl ring.The anti-inflammatory effects of 3f, which also showed remarkable antioxidant properties, were assessed by measuring its inhibition of NO production, an inflammatory modulator, in LPS-pretreated RAW 264.7 cells through the Griess method. Compound 3f was found to notably decrease NO production and suppress LPS-induced iNOS and COX-2 mRNA expressions in a dose-dependent way.

Figure 24: Synthesis of 4-aminoantipyrine analogues 3a–m

Anhydrous ethanol solution (10 mL) containing 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one (203 mg, 1 mmol) was combined with an anhydrous ethanol solution (10 mL) of substituted benzaldehyde (1 mmol) and heated under reflux at 80 °C for 4–6 hours under atmospheric conditions, adhering to the standard method for synthesizing Schiff base derivatives of 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one (3a–m) (Fig. 24). The reaction's progress was monitored using TLC.

Figure 25: The production of 4-aminoantipyrines 4 and 5

Analogues of Schiff base for 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one are synthesized using phthalaldehyde2. Phthalaldehyde (268 mg, 2 mmol) and 4-amino-1,5-dimethyl-2-phenylpyrazol-3-one (203 mg, 1 mmol) were combined in 20 mL of dry ethanol at ambient temperature. The reaction mixture was permitted to cool to room temperature after six hours of refluxing under the same conditions (Fig. 25). TLC tracked the advancement of the reaction. Compounds 4 and 5 were synthesized through column chromatography on silica gel utilizing n-hexane-dichloromethane (2:1) following the removal of the solvent. [19]

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III. CONCLUSION

The Schiff base was effectively formed through a condensation reaction involving an aldehyde/ketone and a primary amine under suitable conditions. The formation of the imine (–C=N–) bond verified that the Schiff base was synthesized successfully. Schiff bases have wide-ranging uses in electronics, polymers, corrosion inhibitors, cosmetics, and pharmaceuticals. Schiff bases represent a new class of drugs that can enhance immune response and address various diseases, including liver cancer (HepG2) and colon cancer in human cancer cell lines. This review gathered synthesis methods for specific Schiff bases and their complexes and highlighted their applications.

DECLARATION OF COMPETING INTEREST

We are the authors declare that we worked together in this work in collecting the data and writing it. We worked together in all the parts of paper.

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DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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