WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Unveiling the Versatility of Schiff Bases: A Comprehensive Review of Synthesis Strategies and Biological Potentials

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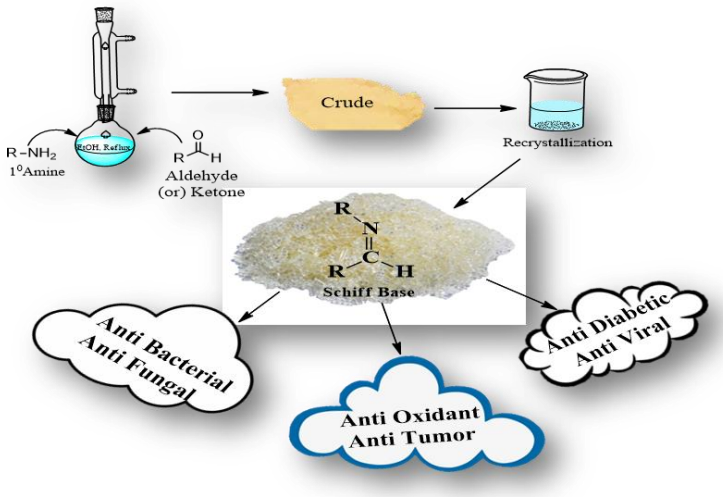
DOI : https://doi.org/10.55248/gengpi.5.1024.3010

A B S T R A C T

A dehydration process results in the condensation of amines with aromatic and aliphatic aldehydes, producing Schiff base, sometimes referred to as azomethine. An azomethine linkage (-C = N-) found in Schiff bases binds two or more physiologically active aromatic/heterocyclic scaffolds together to produce a range of molecular hybrids with fascinating biological properties. Any metal may be coordinated by Schiff bases, which are adaptable metal complexing agents, to create stable metal complexes with various therapeutic applications. We provide a new friendly condensation reaction technique that allows for synthesizing several Schiff's bases. This approach has shorter response times, is green, high-yielding, clean, and easy to experiment with. Simple filtering is used to purify the product, which is washed with water and dried. Schiff bases are the right substance with the widest range of applications in both inorganic and organic chemistry. Schiff base ligands and their complexes have been proven to effect on medicinal applications due to their wide spectrum of biological effects. Furthermore, their antioxidant activity, antibacterial, antifungal, and anti-tumor activity, anti-diabetic and antiviral property was determined.

Keywords: Schiff base, Azomethine, Synthesis, Biological properties, Anti-bacterial, Anti-viral, Anti-inflammatory.

Graphical Abstract



1. Introduction

Schiff bases are imine-containing compounds, sometimes referred to as azomethine. German scientist and Nobel laureate Hugo Schiff made this discovery. Azomethine (Manvatkar VD P. R., 2023)is produced via condensation of both aliphatic and aromatic aldehydes and amines by a dehydration process. The first imine synthesis using Schiff base in the 1864s (Berhanu AL, 2019) (Abu-Dief AM) (Juyal VK, 2023).

$$R - C = N - R^1$$

Water does not dissolve Schiff bases, and diluted mineral acids may easily hydrolyze the weak bases. Schiff bases, which form stable complexes with various transition metal ions and are still of considerable interest in inorganic chemistry, are an important family of ligands in coordination chemistry. Because of their easy synthesis, structural variety, and remarkable chemical characteristics, Schiff bases have shown to be interesting leads for both synthetic and structural studies.

Numerous new compounds with applications in diverse scientific fields are published annually, contingent on the kind of condensation moieties—ketonic or aldehydic—with the main amine. The functional group of a Schiff base can improve the bio-membrane traversal capabilities and is created based on specific desirable qualities. The biological significance of a molecule is predicted by an examination of its charge topology under theoretical expression. Schiff bases have been shown to exhibit significant biological activity, including antimicrobial and depressive properties (A.B. Thomas, 2016) . In addition to their non-ulcerogenic properties (S.V. Bhandari, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel S-substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives, 2008), antitumor (G. Hu, 2012) , antioxidant (C. Yuan, 2009) , antiviral, antihypertensive (K.S. Kumar, 2010) , antidiabetic, and anti-inflammatory properties, these compounds also have anti-dyslipidemic (K.V. Sashidhara, 2009), anthelmintic, antitubercular (M.J. Hearn, 2009),anti-convulsant, anti-inflammatory (S.V. Bhandari, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel S-substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives, 2008), and analgesic properties. It is essential to create new, more potent anti-inflammatory, analgesic, anti-bacterial, anti-viral, and antipyretic medications with no or fewer side effects because the side effects of the anti-inflammatory, analgesic, and antipyretic medications currently on the market have been seriously impairing their clinical applications.

Because of the azomethine group, Schiff bases have well-known biological uses as antibacterial, antifungal, antiviral, and anticancer drugs (L. Cheng, 2010) (M. Nath, 2010). Natural compounds with essential pharmacophores make up the Schiff base family. To create agrochemicals and medications, such as fungicides, bactericides, antivirals, antioxidants, antiproliferative drugs, and antimicrobial drugs, it may be utilized as the perfect lead structure.

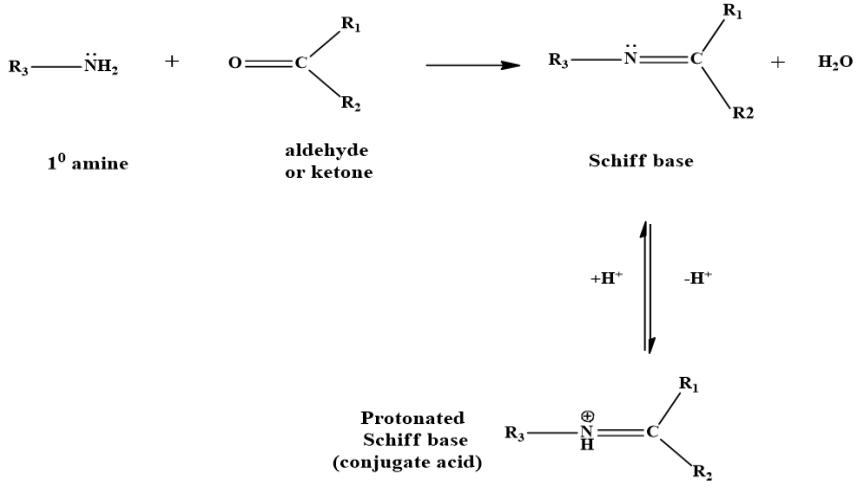
2. Metal-ligated Schiff base

When it comes to coordinating a range of metal ions in various coordination geometries and oxidation states, Schiff bases are useful ligands. Schiff bases have been demonstrated to form complexes with all of the d-block metals and lanthanides. In medicinal chemistry, sulfonamide Schiff bases and their metal complexes are unique due to their diverse biological properties (Abdul Hameed, 2017) . When metal ions interact with other molecules' electron-donating groups in a way that creates a stable, typically five- or six-membered chelate ring, stable coordination is achieved. The imine nitrogen atom can function as a Lewis base, or electron donor, towards metal ions. This need is often satisfied when there is an azomethine bond next to other groups or atoms that donate electrons, on the molecular scaffold, such as side chains or ring heteroatoms. Accordingly, Schiff base ligands with good, and in some cases even selective, metal ion coordination properties have a lot of design flexibility because of the azomethine linkage. Schiff bases are therefore often employed as analytical reagents in analytical chemistry for the identification of metal ions (E., 2008).

3. Synthesis

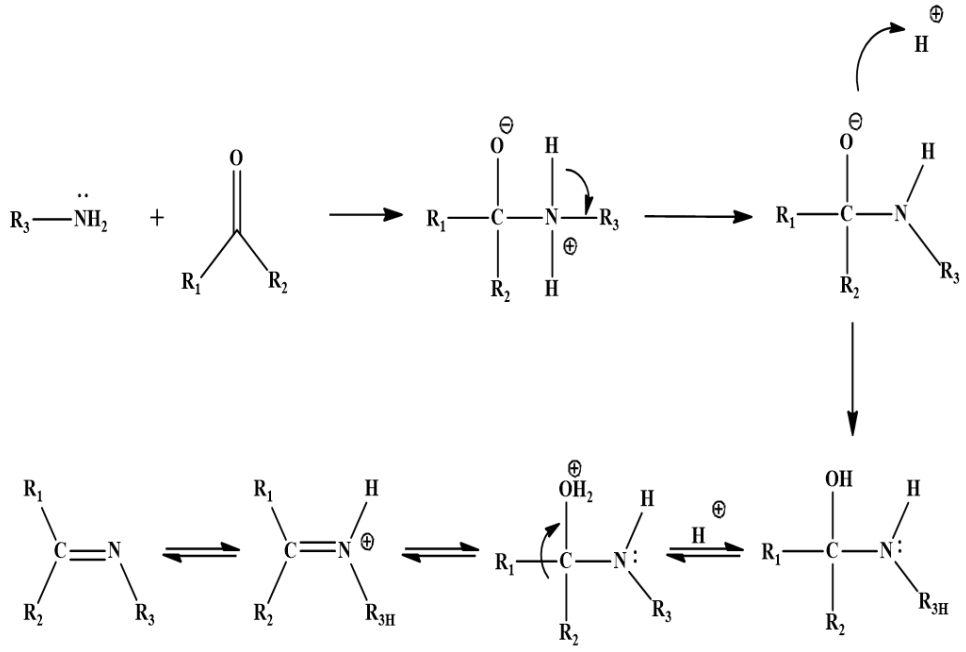
3.1 Typical process for generating Schiff bases

A combination of primary amine and the equimolar concentration of the appropriate active aldehyde or ketone in 15 mL of anhydrous methanol was refluxed for 5 hours at 80 ºC while stirring continuously and with a few drops of acetic acid present. TLC tracked the reaction's development. The reaction was finished, and the mixture was cooled. The resultant heavy precipitate was separated from the methanol and chloroform by filtering and then recrystallization (Asiri AM, 2010).



3.1.1 Reaction Mechanism

A different kind of nucleophilic addition to the carbonyl group—in this case, the amine—is the mechanism behind the creation of the Schiff base. When an amine and carbonyl combine, an unstable addition molecule called carbinolamine is created. There are two ways to remove water from the carbinolamine: base- or acid-catalysed. Since carbinolamine is an alcohol, it dehydrates in the presence of acid (Xavier A, 2014).



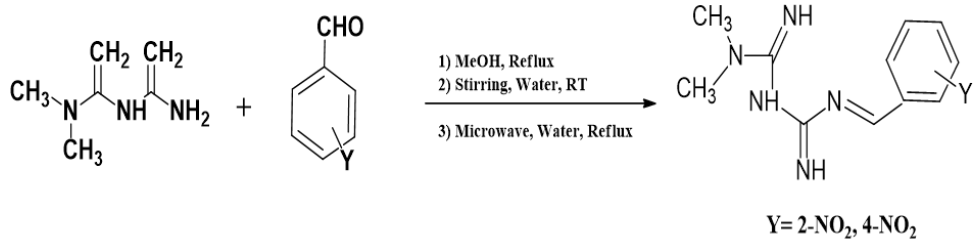
3.2 Synthesis of Metformin Schiff base

3.2.1 General Method

After being made in 20 milliliters of methanolic basic medium, a combination of equimolar quantities (10 mmol each) of metformin-HCl and the (ortho)para-substituted benzaldehyde refluxed for two to three hours. TLC was utilized to track the reaction's advancement. Upon the conclusion of the reaction, the solutions ranging in color from pale to strong yellow were placed on ice, purified, dried, and separated from ethanol by recrystallization (Al-Qadsy I S. W.-O.-F., 2020).

3.2.2 Green Synthesi

A comparison was conducted between the previously described traditional approach and two innovative ecologically friendly methods of synthesizing metformin-based Schiff bases using (ortho)para-nitrobenzaldehyde. A standard procedure involved creating a basic aqueous medium with equimolar (10 mmol) concentrations of metformin and nitro-substituted benzaldehydes. As shown by TLC, the mixture has been refluxed using microwave irradiation (Strategy II) or agitated with an electromagnetic stirrer at room temperature (Strategy I). Following the traditional technique approach, the products were gathered and purified.



Y= 2-NO_2, 4-NO_2

3.3 Synthesis of Schiff base Mannich (HL)

a) Preparation of 1-{[2-(1H-Indol-3-yl)-ethylimino] methyl}-naphthalene-2-ol (A)

2 hydroxy naphthalene 1 carbaldehyde (0.01 mmol) and 2 (1H – Indol – 3yl) – ethylamine (mmol) were condensed in an ethanol solution to create this chemical. TLC was used to monitor the mixture's development while it felt anxious and had reflux for three hours at 85°C. When the reaction was complete, the reaction mixture was cooled, and the resulting product was filtered out and washed with cold ethanol. After being dried under vacuum, the solid was re-crystallized from heated ethanol.

b) Preparation of 1-[(2-{1-[(dicyclohexylamino)-methyl]-1H-indol-3-yl}-ethylimino) -methyl]-naphthalen-2-ol (HL)

Formaldehyde (37% v/v) was mixed with a Schiff base combination (10 mmol) and Di-cyclohexyl amine (10 mmol). The solution combination was properly mixed and periodically cooled for about three hours. After 12 hours in the fridge, a small quantity of precipitate gradually separated from the mixture. A glass rod was used to scrape the beaker walls after an excessive amount of petroleum ether was introduced into the mixture. All of the precipitate suspension abruptly became solid and levelled out. This was dried, filtered, and thoroughly cleaned with 15 millilitres of petroleum ether. The ethanol allowed the crude substance to recrystallize (Al Zoubi W A.-H. A., 2018).

c) Synthesis of Schiff base Mannich complexes

The corresponding hydrated metal chlorides (VOSO4.H2O, CrCl3.6H2O, MnCl2.4H2O, FeCl3.2H2O, and PdCl2) (1 mmol) dissolved in 20 mL of distilled water (20 mL) were added to an ethanolic solution dropwise the ligand L1 (0.295 g, 1 mmol) while stirring. The stirring procedure was carried out at room temperature for one to one and a half hours. After filtering the solid to collect it, it was cleaned with pure ethanol and crystallized again from methanol chloroform (1:3 v/v). After obtaining the coloured complexes, they were vacuum-dried on CaCl2.

Table 1 - Information on the ligand and its complexes, both analytically and physically.

Compound	***Formula***	***Molecular weight***	***Color***	***Melting point (^{0}c)***	***Yield %***
HL	$C_{34}H_{41}N_3O$	*507.71*	*Orange*	*188-190*	*88*
[Mn (L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3ClMn$	*633.12*	*Light Yellow*	*232*	*69*
[Pd(L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3ClPd$	*684.60*	*Red-brown*	*210*	*60*
[Cd(L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3ClCd$	*690.60*	*Light brown*	*194*	*81*
[Hg(L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3ClHg$	*778.77*	*Light brown*	*182*	*77*
[Cr(L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3Cl_2Cr$	*665.63*	*Dark green*	*215*	*82*
[Fe(L) $(H_2O)_2$] Cl	$C_{34}H_{44}N_3O_3Cl_2Fe$	*669.48*	*Red-brown*	*217*	*73*

3.4 Synthesis of Isoniazid-derived Schiff bases

0.258 g (2.0 mmol) of 4-(dimethylamino)-benzaldehyde was added to a solution containing isoniazid (0.274 g, 2.0 mmol) that had been dissolved in 5.0 mL of warm methanol. A yellow solution was obtained by refluxing the mixture in a water bath at 70°C Over 4 hours, constantly stirring. Using a 40% isopropyl alcohol/60% hexane solvent solution, TLC was used to track the reaction's progress. Yellow crystals were created by letting the solution sit for two days to cool while the solvent evaporated (Mainsah EN, 2013) (Parekh J, 2005) (Kumar PP, 2011). The final product underwent filtration, a cold methanol wash, and desiccation on anhydrous CaCl2. The iso-nicotinic acid hydrazide salt was used to create the identical chemical, which subsequently had 24-hour reflux in an ethanol/water solvent system (Sahebalzamani H, 2011).

3.5 Microwave-accelerated synthesis of Schiff base

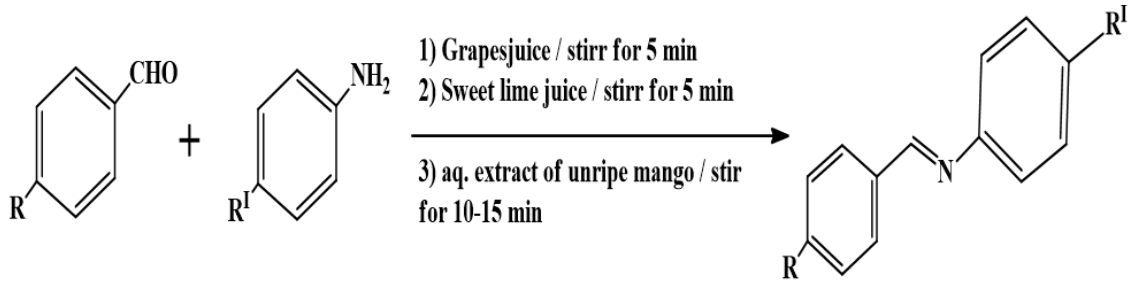
The following ingredients were combined in a beaker for microwave-aided synthesis: 0.175 g of 3,5-dichlorobenzaldehyde, one 0.316 g of ß-ethoxyethanol as a wetting reagent, and three amino-6-bromo-2-phenylquinazoline-4(3H). Through brief cooling intervals, the reaction mixture was exposed to radiation for approximately three minutes in a 200 W MC767W (Electrolux) modified system. TLC tracked the reaction. Ice water was used to chill the flask once the reaction was finished, or three minutes. Ice-cold water was then added to dilute it. After being extracted from ethyl acetate, the Schiff bases were dried, filtered, and recrystallized. All extra compounds were created using the same procedure in three to five minutes (180 to 300 seconds). Adjusting the microwave power between 180 and 600 watts has optimized every reaction (Bhusnure OG, Innovative Green synthesis of Schiff bases and their Antimicrobial Activity, 2015).

3.6 Green Synthesis of Schiff Base by using Natural Acid Catalyst

a) Preparation of Catalyst

Locally sourced sweet lime, unripe mango, and grapes were used to make liquid juice by pressing them through a fruit juice extractor and filtering them through cotton. The sweet lime fruits were sliced open with a knife, and the fruit pieces were then squeezed into a fruit juicer to create a semisolid mass that was filtered through cotton to produce liquid juice that could be utilized as a catalyst (S. Patil, 2012). The hard, green, fleshy content (5 g) from the

premature mango fruit was taken from its upper shell. It was then cooked with 100 ml of water, cooled, and filtered through muslin fabric to obtain a clear liquid component that would be utilized as a catalyst for the process (Pal, 2013).



b) Schiff base synthesis using grape juice, sweet lemon juice, and an aqueous extract of immature mango in a solvent-free environment by stirring method

In separate beakers, an equimolar mixture of 0.1 mol of benzaldehyde and 0.1 mol of aniline was added. A natural acid catalyst, or grape juice, was added in varying volumes (0.5, 1, 1.5, 2.0, and 2.5 ml) to those reaction solutions, and next, they were dropped off at five to ten minutes. After the reaction was finished, for a further two to four minutes at room temperature, each reaction mixture was vigorously stirred. The result was a pale-yellow solid crude product that could be cleaned with distilled water and refined by recrystallization using the least quantity of ethanol. Mango aqueous extract and sweet lemon juice are used in the same way (Yadav G, 2015).

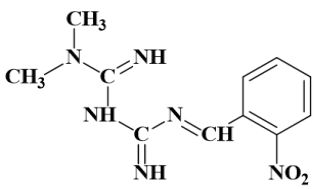
4. Biological Properties

4.1 Anti-Bacterial Activity

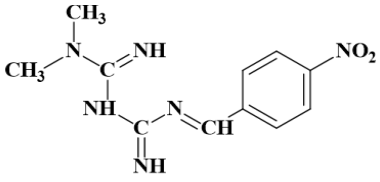
Using the agar well diffusion method, the antibacterial activity of Compound 1 and Compound 2 against two types of bacteria strains was examined: Gram-negative (E. coli, P. aeruginosa, and K. pneumoniae) and Gram-positive (S. aureus, M-R S. aureus, and E. faecalis). A range of quantities were investigated experimentally, and it was shown that the lowest concentration of Compound 1 and Compound 2 that showed an inhibitory effect was 10 mg/mL^{-1}. By quantifying the observed inhibitory zone diameter, the antibacterial activity was assessed. The average of the data from two separate tests is shown in Table.

Table 1 - Inhibition zone of Compound 1 and Compound 2 for antibacterial activity on the studied species of bacteria.

Bacterial Species		**Diameter of Inhibition Zone(mm)**		
		Compound 1 (10 mg/mL^{-1})	**Compound 2 (10 mg/mL^{-1})**	**Streptomycin (1 mg/mL^{-1})**
Gram-positive	S. aureus (ATCC 25923)	24.33 ± 0.33	20.67 ± 0.33	30.33 ± 0.33
	MRSA (ATCC 43300)	-	-	24.67 ± 0.33
	E. faecalis (ATCC 29212)	15.0 ± 0.58	17.67 ± 0.88	27.33 ± 0.33
Gram-negative	E. coli (ATCC 25922)	16.33 ± 0.33	14.67 ± 0.33	25.33 ± 0.33
	K. pneumoniae (ATCC 700603)	23.67 ± 0.88	20.67 ± 0.33	32.67 ± 1.20
	P. aeruginosa (ATCC 27853)	-	-	20.33 ± 0.33



Compound 1



Compound 2

Compound1 has greater activity against nearly all of the investigated bacterial strains in comparison to Compound 2, as per the acquired results. Even though the concentration of the control (streptomycin) is ten times lower, the measured zone of inhibition (ZOI) for both substances is smaller than that of the drug. This result indicates that the conventional antibiotic had greater antibacterial activity than the compounds that were investigated. Additionally, with ZOIs of 24.33 and 23.67 mm against S. aureus and K. pneumoniae, respectively, Comp1 has stronger activity than Comp2, which has ZOIs of 20.67 and 20.67 mm. Both compounds, however, have a moderate inhibitory effect on E. coli and E. faecalis. These compounds have no efficacy against P. aeruginosa or MR S. aureus, according to the data. There are pictures of a few chosen test plates displayed (Al-Qadsy I S. W.-O.-F., Novel metformin-based schiff bases: synthesis, characterization, and antibacterial evaluation, 2020).

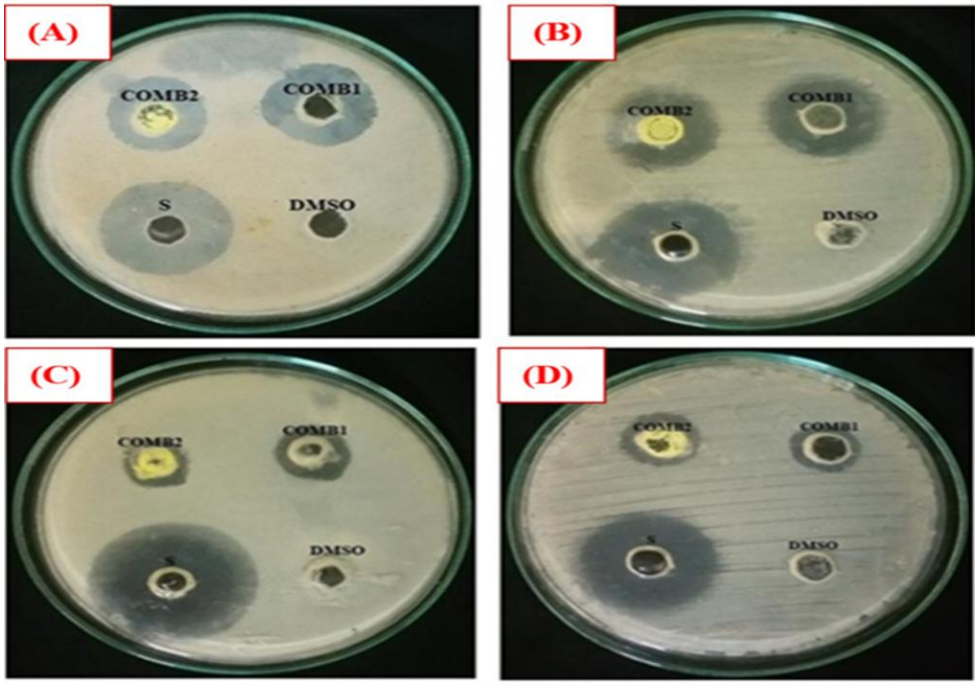


Fig. 1 - Plate pictures of specific antibacterial activity tests against K. pneumoniae (A), E. coli (B), S. aureus (C), and E. faecalis (D). Dimethyl sulfoxide (DMSO) is the negative control; S is the standard (positive control) (1 mg/mL); Comp1 and Comp2 are compounds 1 and 2, respectively, at 10 mg/mL (Al-Qadsy I S. W.-O.-F., Novel metformin-based schiff bases: synthesis, characterization, and antibacterial evaluation, 2020).

Antimicrobial Properties of Metformin Schiff Bases

Employing the diffusion method of agar wells, in vitro antibacterial activity was evaluated (Esimone, Adikwu, & Okonta, 1998) (Adeniyi, Odelola, & Oso, 1996). A final dosage of 1–10 mg/mL of dimethyl sulfoxide (DMSO) was used to dissolve metformin compounds Compound 1 and Compound 2. Noteworthy is the use of DMSO as well as a negative control which has demonstrated no inhibition against the organism under investigation (Asiri & Khan, 2010). Following a standard procedure, Plates of nutrient agar were prepared and let to settle. Initially, cotton swabs were used to distribute 100 L of bacterial suspension which had been adjusted to 0.5 MacFarland turbidity standard over the plate surfaces. Using a sterile cork borer, wells of 8 mm in diameter were created on the agar plates. Next, 100 L of Comp1, Comp2 were poured into the wells., the positive control (streptomycin), and the negative control (DMSO) and labeled. After 18 to 24 hours at 37 C, the plates were incubated. Millimeters were utilized to gauge the diameters of the inhibitory zones. Duplicate studies were conducted, and averages were taken. The statistical evaluation of the data was performed using SPSS version 20.0 software, yielding the mean and standard error of the mean (SEoM) after a one-way ANOVA.

4.1.1 Anti-Bacterial activity of Schiff base metal complexes

5 bromosalicylaldehyde (bs) and α-amino acids [(L-alanine (ala), -phenylalanine (phala), L-aspartic acid (aspa), L-histidine (his), L-arginine (arg)] are used to create Schiff base amino acid complexes. Using 5-bromosalicylaldehyde and 2-aminomethylthiophene, Cu(II), Ni(II), Mn(II), Co(II), and Zn(II) metal complexes were produced along with Schiff base. To determine if these Schiff base compounds and their complexes of metals have antibacterial qualities, a disc diffusion approach that is harmful to bacteria is performed. According to their findings, metal complexes exhibit antibacterial properties. Under the experimental conditions, metal complexes exhibit both increased inhibitory activity and antibacterial properties when compared to their parent ligands. To explain the antibacterial action, the chelation hypothesis was employed. As a consequence, Gram-positive and Gram-negative bacterial strains were successfully combated by the studied complexes, as evidenced. When it comes to Gram-positive bacteria, the complexes have more potency than Gram-negative strains (Yadav P, Synthesis and biological activities of schiff bases and their derivatives: a review of recent work. , 2019) (Venkatesh G, Synthesis and spectroscopic characterization of schiff base metal complexes, biological activity, and molecular docking studies., 2024).

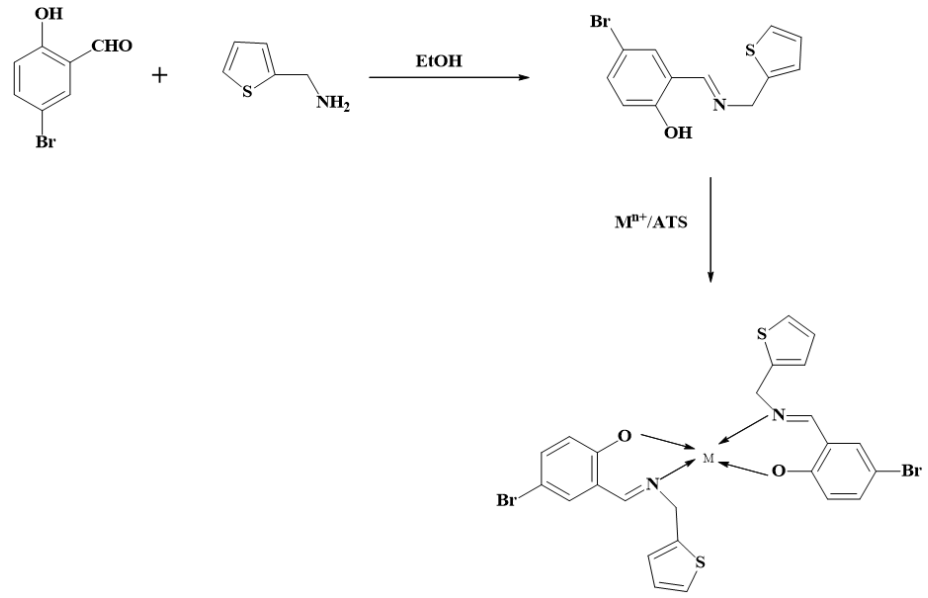


Fig. 2 – Preparation of Schiff base metal complex

4.1.2 Cup plate technique for measuring in-vitro antibacterial action

Screening was utilized to evaluate the antibacterial activity of the compounds synthesized in this investigation. Four common microorganisms, representing gram-positive and gram-negative representative types, were used in antibacterial tests. These comprised Aspergillus coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853, Bacillus substiles ATCC 29212, and Staphylococcus aureus ATCC 25923 are the four different species tested. With a test chemical concentration of 50 µg/ml and 100 µg/ml, the evaluation of the antibacterial activity of compounds was done using the cup-plate technique.

a) Materials used

The items that were sterilized included Petri dishes, a 6 mm cork borer, an inoculation loop, test tubes, graded pipettes, and watch glasses. A culture that grew for 18–27 hours in nutrient broth, sterile forceps with tiny tips, and sterile tubercular syringes.

b) Preparation of Nutrient broth

20g of peptone and 5g of beef extract are yeast extracts.5 grams of sodium chloride, 1000 millilitres of diluted water. After dissolving all of them, the reaction mixture's pH is adjusted to roughly 7.2, steam is allowed to build up to a pressure of 15 pounds per square inch for 20 minutes, and the nutrient broth is eventually generated. The day before the test, the organisms taken from the lab stock were sub cultured into sterile nutritional broth and left to incubate for 18 to 24 hours at 37 degrees Celsius. As inoculums for the antibacterial tests, the resulting culture growth was utilized.

c) Building the nutritional agar medium

20grams of bacteria-based peptone, 5 g of beef extract, 5 g of sodium chloride, 20 g of agar, and 1000 ml of distilled water will be used. Agar was dissolved by heating it over a hot water bath after measured amounts of peptone and beef extract were dissolved in de-tilled water by mild warming. Next, distilled water is added to bring the volume of the finished solution up to 1000 ml, and sodium chloride is added to balance the pH of the solution mentioned above. After that, the previously produced nutritional agar medium is autoclaved for 20 minutes at 1210C and 15 lbs/in2 of pressure to kill any bacteria.

d) Preparation of test solution

Separately, DMF was placed in 100 millilitres of 5 mg and 10 mg of the sample compound. Ten millilitres of each of them were collected and diluted with DMF to get one hundred millilitres. Currently, the test compound's concentrations are 50 µg/ml and 100 µg/ml. Sterilized test jars with appropriate labels were used to create these sample solutions.

e) Preparation of standard solution

Ampicillin is the standard medication utilized in this investigation. This medication is soluble in water and has a concentration of 25–50 µg/ml by adjustment.

f) Method of testing

To achieve consistent cooling, gently shake the nutritional agar media which that had been made above until it reaches 450 C. 18–24 hours old culture (0.5–0.6 ml) was aseptically injected into this and well mixed with light shaking. This was then transferred to the Petri dishes and left for an hour to set.

Using a sterile cork borer, the set agar was then punched into the cups, and the punched portion was removed. Each cup measured 6 mm in diameter. One hundred and fifty microliters of the DMF-prepared test compound were added to each of these cups. Once the medication solution was added, it was left to diffuse at room temperature for approximately 45 minutes. The plates were then placed in an incubator and left at 370 C for 24 hours. Following 24-hour period, the zone of inhibition was measured in millimetres to determine the extent of its diameter (Bhusnure OG, Innovative Green synthesis of Schiff bases and their Antimicrobial Activity, 2015).

4.2 In vitro anti-diabetes studies

4.2.1 Enzyme inhibitory action of ∝ amylase

Ibitoye et al.'s modified method was used (Ibitoye OB, 2018) . An evaluation was conducted on the α-amylase enzyme activity to ascertain the inhibitory impact of ligands L1 - L3. In a 20,000 µM buffer solution (mono/dibasic sodium phosphate salt, pH 6.8) containing 5 U/mL pancreatic α-amylase, acarbose or escalating dosages (63–500 µg/mL) of the ligands were placed in an incubator for 10 minutes at 37 °C. Once 200 µL of a 10 mg/mL starch solution was added, the solution was allowed to further equilibrate for an additional 20 minutes at 37 °C. Before boiling at 100°C in a boiling water bath for ten minutes, 0.6 mL of DNSA was added. Comparing the coloured mixture's optical density at 540 nm to a control solution free of inhibitors revealed the colour difference.

4.2.2 Inhibitory action of the ∝ glucosidase enzyme

A significantly modified approach from the literature was utilized to reveal the activity of ligands L1 - L3 on the α-glucosidase enzyme. The substrate used was p-nitrophenol glucopyranoside (pNPG) (Olofinsan KA, 2022). The combination was incubated at 37 ◦C for 15 minutes after adding 0.4 mL of yeast α-glucosidase (1 U/mL) to 0.5 mL of L1-L3 or acarbose solution and 500 µL of 100 millimolar buffer solution (mono/dibasic sodium phosphate salt, pH 6.8). Once 0.2 ml of pNPG (0.005 M) was added, the quantity of yellow p-nitrophenol released from the substrate was measured at 405 nm.

4.3 Anti-oxidant activity

There were comparisons made between the metal complexes and ligands at different dosages between 50 and 500 mM about ascorbic acid's antioxidant activity. Observations were made about the antioxidant activity. The complexes' percentage of inhibition is represented in the sequence that follows, with comparisons to the control. The reactivity of the complexes Cu(II), Co(II), Zn(II), and H_2L is arranged as follows: Cu(II) > Co(II) > Zn(II) > H_2L, indicating that Cu(II) has a greater degree of activity than the other complexes. The inverse correlation between the IC50 finding and antioxidant capability is consistent with this conclusion. The molecular activity of the diamine derivative to stabilize unpaired electrons and scavenge radicals is increased by the nitro group substituted in the aromatic ring, which also boosts the stability of the free radicals assembled within the metal complexes that were created. The study's conclusions therefore establish a connection between the usage of artificial chemicals and the management and avoidance of clinical conditions brought on by oxidative stress (Venkatesh G, Synthesis and spectroscopic characterization of schiff base metal complexes, biological activity, and molecular docking studies., 2024).

4.4 Antiviral activity

4.4.1 Infection of chicken embryonated eggs with poultry viruses

Antiviral studies that used embryonated chicken eggs from a local hatchery, which were seven to eleven days old, were conducted using the inoculation strategy. Before the eggs were inoculated, they were candied. From the chorioallantois fluid of the eggs, the susceptible viruses were injected. To inoculate the eggs, the broader ends of the candled eggs were drilled using a sterile needle. After injecting the eggs, the hole was sealed with melted wax, and they were incubated at 37 degrees Celsius. Utilizing the allantoic fluid, hemagglutination (HA) tests were done. For antiviral research, 48 hours after vaccination (Aslam, 2016).

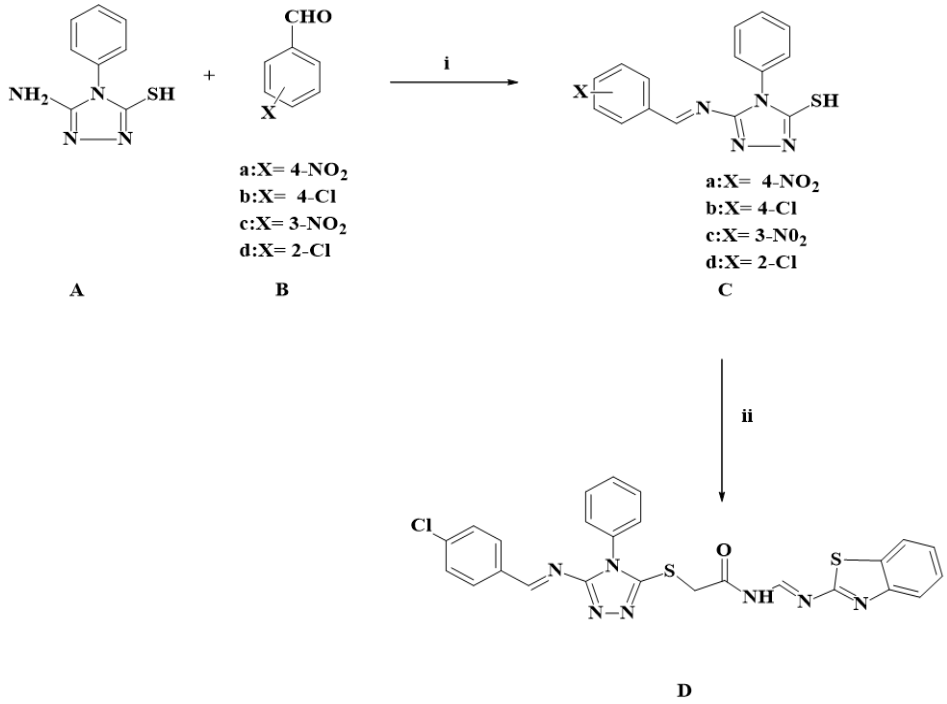
4.4.2 Hemagglutination test

After collecting chicken blood in newly made Alsevior Solution and centrifuging it for five minutes at 4000 rpm, the Hemagglutination test was conducted. Red blood cells (RBCs) were preserved at pH 7.2 by washing them in phosphate-buffered saline (PBS) solution after discarding the supernatant solution. There were three iterations of the next phase. A 1 ml solution of phosphate-buffered saline (PBS) with a pH of 7.2 was combined with 10 µl of packed cells to create a 1% suspension. Subsequently, the conventional HA test was conducted using the produced cells (Hirst, 1942) (Mahmood W, 2022).

4.4.3 Antiviral of Novel compounds

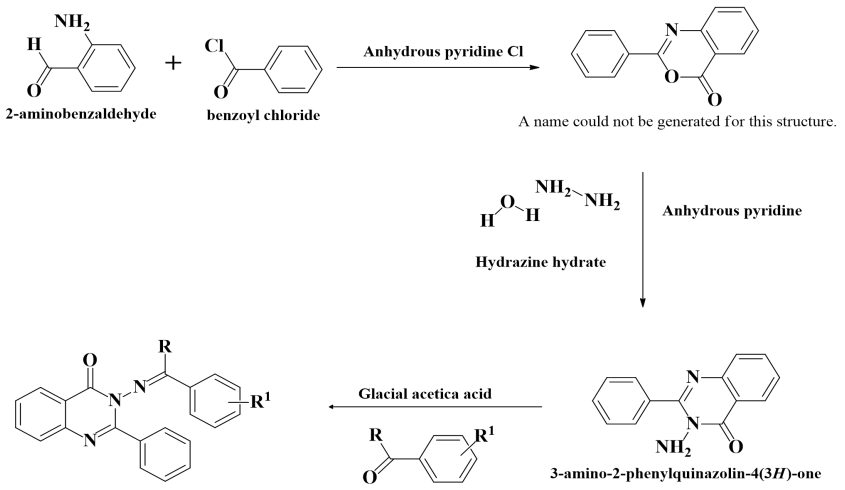
5-amino-4-phenyl-4H-1,2,4 triazole-3-thiol A was reacted with a variety of substituted benzaldehydes (Ba–Bd) to create several new Schiff base ligands in this work. Metal complexes containing Cu(II), Fe(II), Au(III), and Mn(II) utilized these ligands to create them as well. Coupling the reactant molecule with N-(benzothiazol 2-yl)-2-chloroacetamide allowed for the production of a new benzothiazole derivative (D). It looked at the subject's

spectral characteristics. The capacity to reduce "HIV-induced cytopathogenicity in MT-4 cells" evaluated the anti-HIV-1 and HIV-2 activity of the newly created and synthesized Schiff-based ligands and metal complexes that correlate with them. In cell culture, compound D demonstrated noteworthy inhibitory action against HIV1, with EC50 values of 12.2 µg/mL (selectivity index (SI) = 4) and > 2.11 µg/mL (SI = > 1), concurring. With an EC50 value of 10.2 µg/mL and a selectivity index of 9. Compound D appears to have potential for additional improvement and refinement based on this discovery (Al-Masoudi NA, 2009).



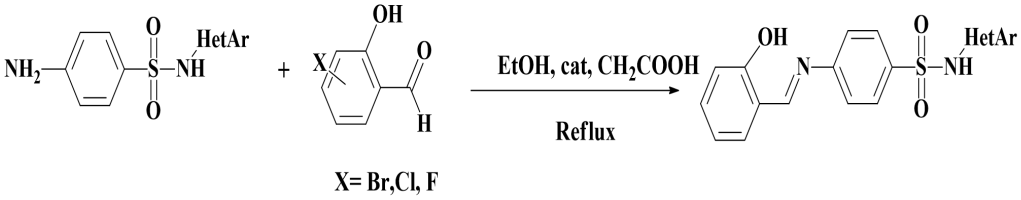
3-(benzylideneamino) compounds are the subject of a recently produced new series. Manufacturing Schiff bases from 3-amino compounds was a step in the synthesis of 2-phenylquinazoline-4(3H)-ones. The reaction between several substituted carbonyl compounds and -2-phenyl quinazoline-4(3)H-one. The compounds' chemical arrangements were identified with the use of spectrum analysis. Both the cytotoxicity and antiviral activity of the investigated compounds were assessed against a range of viruses, including the vaccinia virus, the herpes simplex virus-1 TK-KOS ACVr, the influenza B virus, the respiratory syncytial virus, the vesicular stomatitis virus, the para influenza-3 virus, the Punta Toro virus, the herpes simplex virus-2 (G), the para influenza-3 virus, the Sindbis virus, the Coxsackie virus B4, the vesicular stomatitis virus, the respiratory syncytial virus, and the feline coronavirus (FIPV). The substance produced showed stronger antiviral efficacy when tested against all virus strains (Kumar KS, 2010) .This work describes a novel approach to nitrogen substitution employing various ketone and substituted benzaldehyde derivatives to synthesize new prodrugs, such as abacavir.

With an EC50 value of 0.05 lM, compound 3-(2-(4-methylaminobenzylideneamino)-6 (cyclopropylamino)-9H-purin-9-yl)cyclopentyl)methanol (38c) revealed the greatest degree of efficiency against HIV in the in vitro studies. The chemical also exhibited a selectivity index higher than 2000 and an EC50 value above 100 lM. With a 32-fold increase in activity as indicated by its EC50 value of 1.6 lM, compound 38c demonstrated a substantially greater potency than the original medicine. The hydrolytic half-life (t1/2) showed a range of 120 to 240 min at a pH of 7.4 and three hundred and sixty degrees Celsius (Sriram D, 2006).



4.5 Antifungal Property

The most recent effort involved adding Schiff bases to the main chain of the reactant, which chemically altered the structure of diabetes insulin. With the use of carbon-13 NMR, proton NMR, and FT-IR spectroscopy, structures of around six distinct insulin derivatives were identified. These derivatives were made utilizing a straightforward procedure (Chen Y). By using phenoxide ions or phenolic groups, the structures showed differences in the amount and positional substitution of the benzene ring. Further research was conducted after then to find out more regarding their biological functions, particularly their antioxidant and antifungal properties. The assessment of antioxidant activity encompassed not only antioxidant activities but also the determination of scavenging capabilities against superoxide, hydroxyl, and DPPH radicals. Inulin has demonstrated a significant improvement when compared to certain inulin-related activities. Also, the antifungal activity against three distinct types of plant-pathogenic fungi was evaluated in vitro using the mycelium growth rate technique (Al Zoubi W A.-H. A., 2016) (Cheng LX, 2010). A significant reduction in the antifungal effect of the former was observed. The number of phenolic hydroxyl groups present and their location, together with the degree of substitution (DS), all affected the inulin derivatives' biological activity. Products explained in this publication have a great deal of potential as biomaterials with advantageous bioactivity and biocompatibility. In the future, further research projects should look at the structure-activity relationship (Devi P, 2023).



Sulfa medications that are commercially accessible, such as sulfamethoxazole, sulfamethazine, and sulfamethoxypyridazine, were combined with appropriate "substituted aromatic aldehydes" to create Schiff base derivatives of sulfa pharmaceuticals. By employing a variety of solvents with differing polarity levels, the reaction conditions were tuned. The combination of ethanol and a tiny amount of acetic acid was ultimately shown to be the most efficient solvent combination for condensation operations.

4.5.1 Antifungal properties of Schiff base metal complexes

The designed Schiff-based ligands and their complexes of metals were examined for antifungal activity using the excellent diffusion method, often referred to as the Kirby-Bauer method. The fungal strains of M.phaseolina and S.rolfsii. The produced ligands of Schiff bases and the activity of their complexes of metals were screened using different minimum inhibitory concentrations (MIC), according to the antifungal activity data. When the chemicals are concentrated to 1 mg/mL, they show antifungal action; at lower concentrations, no antifungal activity was found. As per the antifungal activity data, the Schiff base metal complexes demonstrated superior antifungal activity in comparison to the Schiff base ligand.

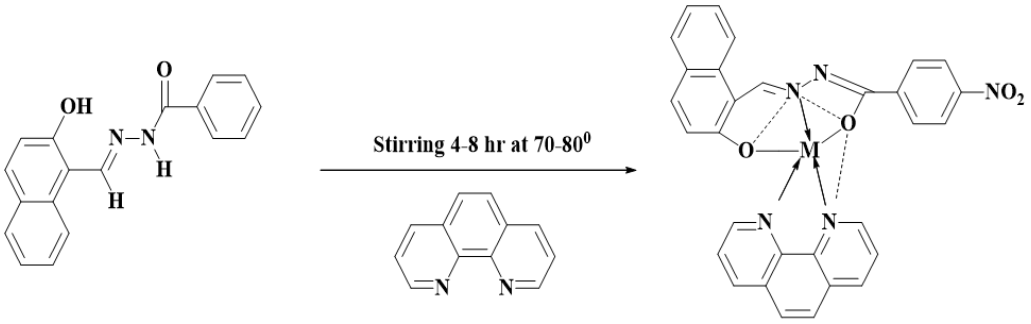


Fig. 3 – Synthesis route to Cu(II), Zn(II), Ni(II) and Co(II) ternary complexes.

From salicylalidene-4-imino-2,3 dimethyl-1-phenyl-3-pyrazoline-5-one and 2-aminothaiazole, Zn(II), VO(II), Cu(II), Co(II), and Ni(II) new cationic Schiff base metal complexes are identified. These Schiff base metal complexes' structural properties may be understood by elemental analysis employing FTIR, EPR, Fluorescence Emission, Powder XRD, FESEM, and FAB-Mass spectrum measurement. Using potato dextrose agar as the medium, the good diffusion technique is used to screen these Schiff base complexes and their various metal complexes in order to determine the antifungal effects of chelate against Candida albicans, Rhizoctonia bataicola, Aspergillus flavus, Aspergillus niger, and Rhizopus stolonifera. The findings of the screening against antifungal activities indicate that Schiff base metal complexes are more potent than Schiff base complexes, or, to put it another way, they function better than Schiff base ligands (Yadav P, Synthesis and biological activities of schiff bases and their derivatives: a review of recent work., 2019).

4.6 Anticancer metalloproteins

An important goal of modern therapeutic research and drug design is the synthesis of metallodrugs featuring pharmacological characteristics different from those of clinically proven platinum-derived medications (L. Ronconi, 2018). Metalloenzyme-copying synergist metal-based pharmaceuticals have advanced significantly toward clinical approval for a range of ailments. Another intriguing step towards the development of drugs with unique modes of action is the use of metal complexes to catalyse biorthogonal alterations in live cells (B.S. Murray and P.J. Dyson, 2020). One of the most promising possibilities now available is ruthenium (Ru) (Magistrato, 2017) . The Ru(II)-arene Investigated for p53-independence activity were Schiff base compounds. Poor chemotherapy outcomes and resistance to clinical medications are influenced by the tumour suppressor gene (p53) being inactivated in malignant cells. New anti-cancer possibilities may be suggested by the increased hydrophobicity, which implies greater cytotoxicity and cellular accumulation (M.J. Chow, 2016). In addition, copper is a viable substitute for improving new anticancer operators (A. Hussain, 2019)I.e. Nevertheless, there has been a strong push to concentrate on the aberrant glycolytic pathway in tumours due to the established role that glucose and glucose-containing carbohydrates play in the enrichment of cancer cells. Organometallic ruthenium (II)-arene, gold (I/III), titanium (IV), vanadium in different oxide states, and gallium (III) are among the metal centres whose exploitation has shown promise as a methodology (P. Zhang, 2017) (L. Xiang, 2019) (Ding Y, 2016).

5. Conclusion

The preparation of the Schiff base and its complexities were covered in this article. Both the industrial and medical domains have made substantial use of these ligands and their metallic complexes. For applications in industrial domains, the Schiff bases serve as the general investigators. It is therefore appropriate to investigate the biological actions of this family of Schiff base compounds. While research on Schiff base and its derivatives is ongoing, there has been a significant increase in the number of studies revealing the role of Schiff base in antibacterial, antidiabetic, antifungal, anti-tumor, anti-oxidant and antiviral agents of therapeutic interest.

Summary

- Schiff bases are an important family of substances that have become more well-known due to how simple and inexpensive it is to have them ready with conveniently available supplies (aldehydes/ketones and primary amines).
- Simple azomethine linkage may be used to quickly bind structurally varied, physiologically active scaffolds together, providing access to a large library of molecular hybrids with a variety of biological characteristics.
- The structure of Schiff bases may be readily modified to coordinate various metal ions in a range of oxidation states and coordination numbers, making them flexible ligands for metal coordination.
- This review discusses the synthesis of metal complexes from Schiff bases and their many medicinal biological features, including antibacterial, antifungal, antiviral, anti-diabetic, anti-tumor, and anti-oxidant effects.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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