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A Review: Schiff Bases as Promising Agents and Their Pharmaceutical Applications

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ABSTRACT

Schiff bases have been a very important category of chemical molecules in medicine and pharmacology over the last several decades. Their structure contains an azomethine functional group (-C=N-).This group is typically formed by the condensation of primary amines with aldehydes or ketones. Schiff bases are relatively easy to synthesize, and their structural versatility allows modification for diverse biological applications. From a medicinal standpoint, Schiff bases have demonstrated a wide range of biological activities, including antimicrobial, anticancer, anti-inflammatory, antioxidant, and antiviral effects.Multiple studies suggest that even small alterations in chemical structure, such changes in substituent characteristics or the introduction of heterocyclic groups, may substantially affect biological efficacy. Schiff bases are also recognized for their ability to coordinate with metal ions, which has led to the development of numerous metal complexes with new or improved pharmacological characteristics.The medicinal significance of Schiff bases is further supported by their proposed mechanisms of action, including enzyme inhibition, interaction with microbial cell membranes, DNA binding, and modulation of oxidative stress pathways.These characteristics make Schiff bases attractive frameworks for the development of novel therapeutic agents.This review aims to highlight the pharmaceutical importance of Schiff bases by focusing on their chemical characteristics and key antibacterial, antifungal, antiviral, and anticancer activities, while also discussing their potential applications in drug discovery and development

Keywords: Schiff moiety, azomethines, medical activity, chemical reactions, synthesis, review

INTRODUCTION

According to Juyal et al., in 1864, Hugo Schiff first elucidated by a chemical process the production of Schiff bases involving amine and several carbonyl substances [1–6]. As shown in"Figure1, the azomethine group also named for Schiff bases ,denoted in chemistry as R1-N=CHR [7, 8] . A relevant alkyl groups may serve as R or R1 in Schiff bases. These bases are predominantly called as imines groups in chemical chemistry [9, 10] . Hassan, A et al., Schiff bases are extensively used in several industrial applications, including pigments manufacture, chemical semiconductors, polymers, and corrosion inhibitors [65,66] .Ortho-vanillin is also the most important taste and smell ingredient in a vanilla plant. It is used to flavor food, beverages, and medicines [67] .It is widely researched in therapeutic domains due to its many biological actions [68] . Schiff bases group was collect because their substances have the ability to act as , anti-fungal, anti-microbial, anti-tumor and have many other activity such as being catalysts and dyes [71] .

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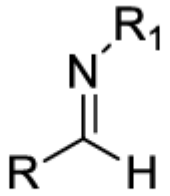
The existence of two pairs is ascribed to its sp2 hybrid, since the molecule exhibits significant reactivity owing to the carbon and nitrogen atoms. These compounds are very significant due to their robust features, including flexibility, simplicity, and usefulness [11, 12] . According to El-Sonbati AZ et al the relevance of Schiff bases in biological tests lies in their ability to create various functional groups.An improved methodology regarding the inherent characteristics of Schiff bases may be beneficial in addressing biological deficiencies and enhancing the efficiency of Schiff base pharmaceuticals [13–17] as shown in"Figure1".



Schiff Base

Figure 1: Schiff bases chemical structure

Acoording to Ghanghas P et al Identification of Schiff originated in the eighteenth century when chemist Hugo first recorded a process demonstrating the chemical process the production of Schiff bases involving amine and several carbonyl substances. In recent times, the field of scientific investigation concerning Schiff organizing chemistry has seen considerable development and extension [22, 23] .Importance of Schiff interactions in the domains of materials research, medical applications, inorganic chemistry, coated techniques, and molecular chemistry.Molecular chemistry ,catalysis, separation and the synthesis of substancess having extraordinary properties. The significance structures has been broadly recognized and thoroughly analyzed in the current research [24–27] .The study has recorded the use of Schiff produced from aldehydes as regulators of plant growth, in addition to demonstrating antimicrobial activities [28–30] . Acoording to El-Gammal OA et al, Schiff have shown analysis use as well. Importance of these bases elucidates a complex dynamics inside biological systems and provides a clear understanding of the azomethine group's action. Howver exhibit wide efficacy against more species, including bacterial species and fungal species [31–34] .Acoording to Ma L et al, Schiff bases are important in metal complexes because they may build a framework that binds shift metals bases with the reaction products of the condensation process. Studies of metals such as (mercury (II), Gold (III), Copper(II), cobalt(II), Nickel(II), zinc (II), Y(III), aluminum (III), lead(II), and silver (II) have proven this [35–44] . Acoording to Almashal FA et al, Schiff bases have been the subject of a lot of investigation because they make great catalysts. These substances may help hydrogenate alkene.. Mimetic catalytic processes are relevant in several circumstances. Schiff bases serve as very effective corrosion inhibitors due to their intrinsic capacity to automaticity form protective single layer on the surface of target. Many industrial suppresor generally include Schiff bases in their structure, because of the C=N bond and give it more effects [45–48] . Acoording to Anush SM et al, the principal way of interaction is the adsorotion chemically between inhibitors with metals. Via electron transfer the inhibitor molecule shiould include active moeity that can form complex with the metal. In such circumstances , the inhibitor act as a nucleophile and the other is electrophil. Protective chemical contains oxygen and nitrogen atoms that act as a nucleophilic, which have unshared electron pairs readily available for electron sharing. Alongside the benzene ring atoms, the portions provide a lot of active sites for the nucleophile, promoting a formation of a stable single layer [49–51] . Acoording to Kajal A et al, the medical characteristics have been recorded in this study involve of activity against bacteria and fungal infection for schiff bases , due to anticancer and herbicidal fields of metal complexes have attracted considerable interest in the scientific reserches. These organisms serve as exemplars for species of considerable biological significance [52–58].

Pharmaceutical Relevance

Antimicrobials

Acoording to Chemchem M et al, Very successful treatment strategy in medicine is the antibacterial activity.Nonetheless, effectiveness of antibacterials are considerably compromised by increase of activity against-resistant bacteria. By using the chemical reaction between isatin and more amino acids, like leucine phenylalanine, cysteine, alanine, valine, and glycine will produced schiff bases of amino acids. These amino acids shown significant antimicrobials effectiveness [60, 61] .A novel azomethine groups were synthesized using a reflux reaction involving 5-amino pyrazoles and aldehydes [63] .A production synthesized substantial amounts for required chemicals.

The evaluated of schiff bases of antimicrobials effect using in laboratory studies versus resistance organism of the drug.Under typical conditions, most Schiff base compounds demonstrated enhanced biological effectiveness.

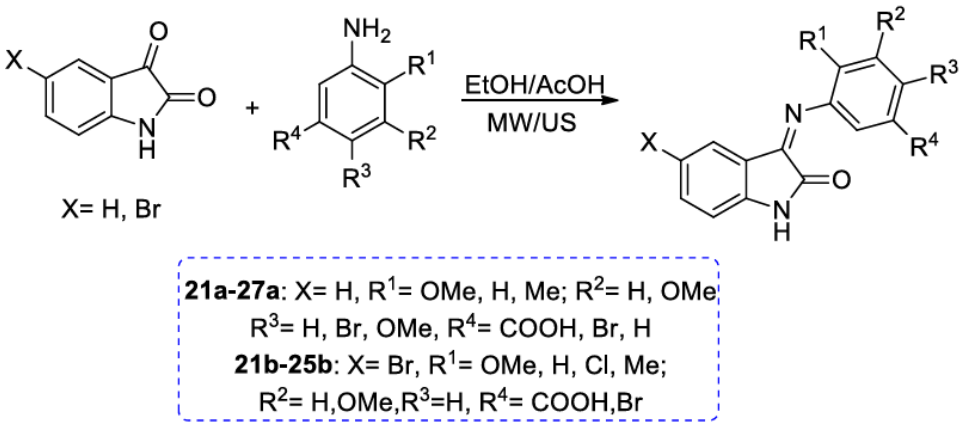


Figure 2: Schematic diagram of Isatin use for produced of schiff bases [69].

According to HASSAN, A et al, as shown in (Figure 2). Reacted of of isatin and 5-bromoisatin with diverse amine group the production of Schiff bases (21a–27a, 21b–25b) (12) group .The production technique microwave (MW) and ultrasonic (US) used for good environment principles, notably using microwave (MW) and ultrasonic (US) aid. Antibacterial activity for each species was evaluated against (9) microbes strains, consist of the Agar-well diffusion method. 78 µg/mL the(MIC)for 21b and 21a against Pseudomonas aeruginosa were evaluated , being the lowering value recorded. The identification of all synthesized substances was achieved through various characterization techniques, including (UV) spectroscopy, proton (NMR), IR spectroscopy,13CNMR , Molecular Electrostatic Potential Surface (MEPS) study as well as ("QSAR") examination.A results of the ("QSAR") examination, utilizing the density functional theory (DFT)-based, steric, and hydrophobic descriptors, it is shown that species exhibiting heightened hydrophobicity and decreased the forces of dipole had antimicrobial activity against "Klebsiella pneumoniae ATCC700603"[69].

According to Chandra N et al, in accordance with this procedures depicted in (Figure 3), reaction of amino derivatives like L-cysteine with chlorobenzene through condensation in alcohol to yield (28) Schiff bases. In alcohol methanol similar reaction will occure between methoxybenzene with amino mercapto acids via condensation to yield (29) Schiff base. 77% and 85% for compounds 2 and 1 were yield [70] .Thin layer chromatography were using to assess of advancement produced substances for clean. Silica gel was the immobile phase, whereas the other phase consisted of alcohol primary, which rose on the detector curve. We employed FT-IR, 13C, and 1H NMR spectroscopy to look at the substances twenty-eight and twenty-nine that were recently manufactured. Compound 28 was more effective towards bacteria than compound 29, whereas the newly made Schiff bases were effective against the designated pathogens.The evaluated global chemical reactivity metrics indicate that Schiff base 1 exhibits moderate reactivity and more stable behavior in natural circumstances. Still, more research will be needed in the future to fully understand how these molecules work to kill germs. [71] .

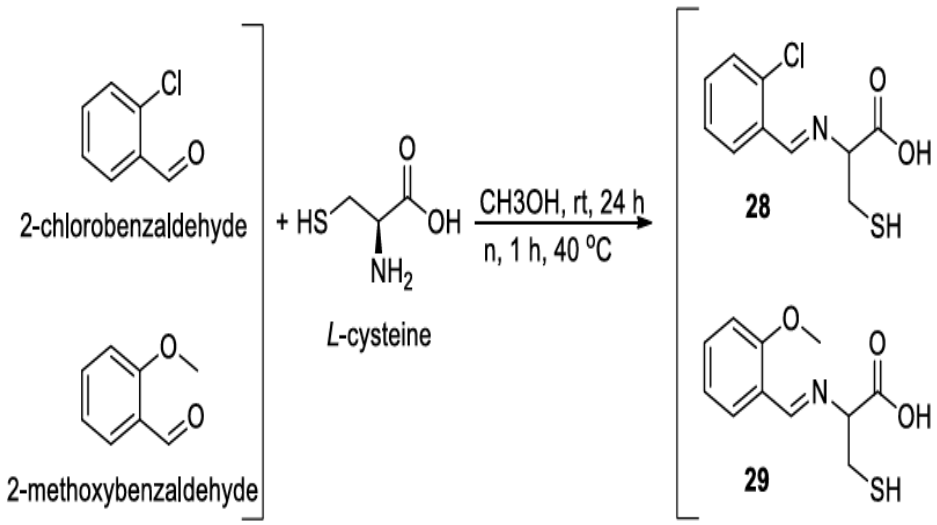


Figure 3: Schematic diagram for Synthesis of Schiff compounds [71] .

Antifungal

Mushtaq et al. according to this study,to make Schiff base derivatives of sulfa drugs, widely available drugs including the sulfamethoxazole compound, sulfamethazine, and sulfamethoxypyridazine were mixed with the right substituted cyclic aldehydes. To improve the conditions for reactions, a number of solvents with different levels of polarity were utilized. Finally, the best solvent combination for the condensation activities was found to be one that included alcoholic beverages and a little amount of acetic acid, as shown in (Figure 4). In each instance, an amount for «sulfonamides» and substituting aromatic aldehydes" was utilized, and the results of the reaction ranged from 35% to 92%. Before being characterized, the chemicals were cleaned up by recycling or liquid column chromatography. Before being deemed suitable for bacterial examination, all compounds were verified to have a minimal purity of 95% [63] .

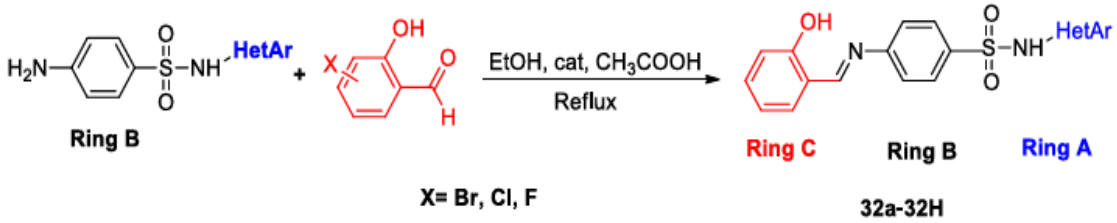


Figure 4: Schematic diagram of the conditions required for the process that makes Schiff chemical derivatives (32a-32h)

Ali U et. el.This study as shown in (Figure5) investigates the antifungal potential of chitosan extracted from the desert grasshopper *Schistocerca gregaria* and its chemically modified derivatives. Chitosan was produced by deacetylation of chitin isolated from the insect exoskeleton. To enhance its biological performance, chitosan was converted into Schiff bases using aromatic aldehydes and subsequently coordinated with ferrous and copper ions for make ion coordinator. FTIR analysis confirmed for formation of azomethine (C=N) groups and successful metal coordination through nitrogen and oxygen donor atoms.The antifungal activity of native chitosan, its Schiff bases, and metal complexes was evaluated against *Aspergillus flavus*, *Aspergillus niger*, and *Trichoderma* species using minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) assays. Unmodified chitosan showed moderate antifungal activity, with MIC values generally ranging from 125 to 250 µg/mL. The Schiff bases demonstrated improved effectiveness, particularly against *A. flavus* and *Trichoderma* spp., where complete inhibition was observed at lower concentrations.The ion coordination showing rise antifungal performance in comparism with chitosan and its Schiff bases. The ferrous complex showed strong fungicidal action, with minimum inhibitory concentration (MIC) values indicating total growth inhibition. The Cu(II) complex also displayed notable antifungal effects, although its activity varied depending on the fungal strain. The increased activity of metal complexes is attributed to chelation, which increases lipophilicity and facilitates penetration into fungal cell membranes. Additionally, metal ions may interfere with fungal enzyme systems and disrupt cellular metabolism.Overall, the results demonstrate that chemical modification of chitosan into Schiff bases and metal complexes significantly enhances its antifungal properties, making these derivatives promising candidates for antifungal applications [74] .

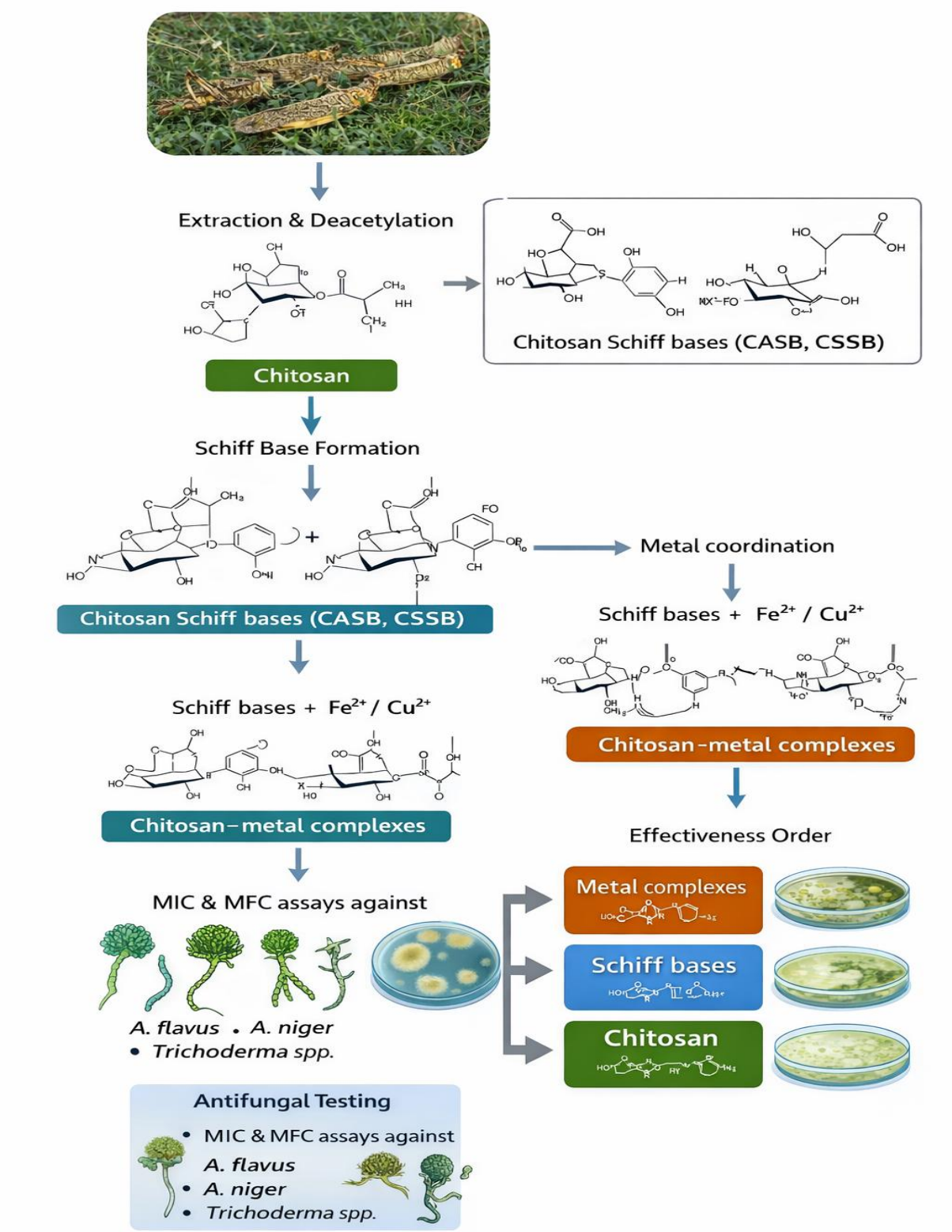


Figure 5: Schematic diagram for Synthesis pathway for Schiff bases of Chitosan as antifungal

Antiviral

Vaccination has successfully eradicated or controlled certain viral diseases, including smallpox, polio, and rubella; nevertheless, it is relatively insufficient toward infectious viruses such as the liver disease hepatitis C and human immunodeficiency virus (HIV). These viral infections are a serious concern to those with weak immune systems, thus antiviral treatment has to be quick and effective.

Sriram D et al. As shown in (Figure 6) but many of the antiviral therapies that are available currently don't work very well because viruses mutate fast, and they could also induce side effects that aren't good. This has

caused a search for new antiviral medications that function better and are safer.Schiff bases have emerged as appealing frameworks for the development of antiviral pharmaceuticals. Salicylaldehyde Schiff bases derived from 1-amino-3-hydroxyguanidine tosylate have shown considerable antiviral effectiveness. Among them, **compound 54** exhibited significant activity for rat virus of the liver, achieving 50% viral increase inhibition at a low concentration of **3.2 µM**.Additionally, abacavir-derived Schiff bases (compounds 55–65) were synthesized as prodrugs to enhance the antiviral activity of abacavir, a nucleoside analogue used in HIV therapy. These medicines worked extremely well against HIV-1 in human leukemic (CEM) cells, Howver derivative **57** is the best powerful , displaying antiviral activity at **50 nM** while remaining non-harmful to healthy tissues much more concentrations greater than one hundered micro molary.The high potency and low cytotoxicity of these Schiff bases highlight their potential as lead compounds for the development of new antiviral agents [(73)] .

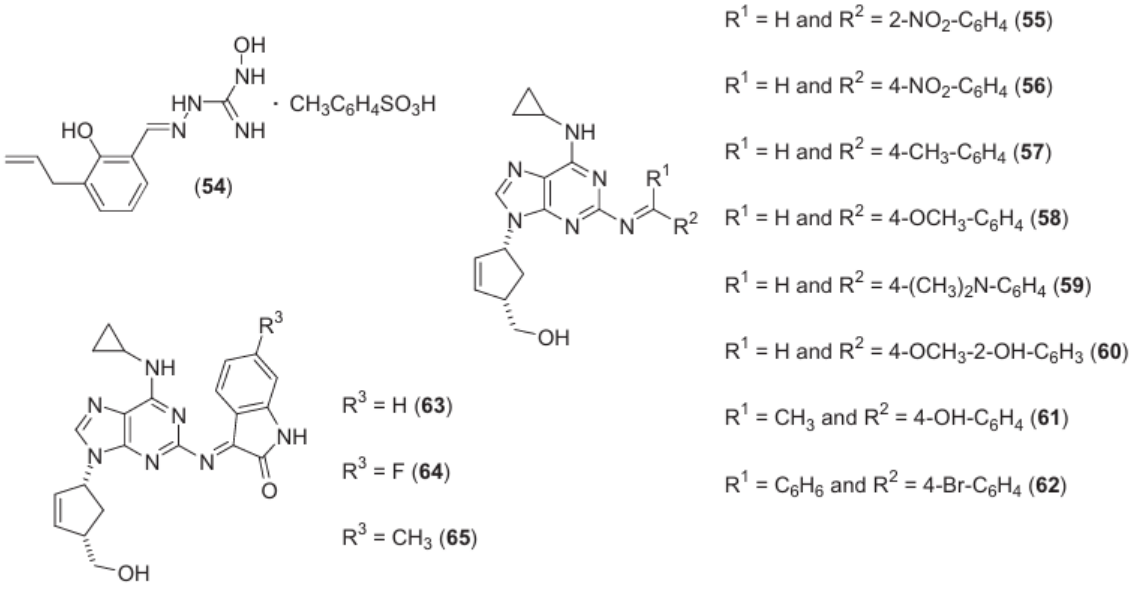


Figure 6: Schematic diagram for derivatives of Schiff bases that act as antiviral.

As shown in (Figure7) that this work introduces an innovative method for synthesizing new prodrugs, includes abacavir, by N replacement act diverse chemical compounds and alternative aldehydes substitution. Laboratory testing results demonstrated that the compound piperazine deravitives (38) molecule had the highest activity against HIV, as shown by EC_{50} value of 0.05 µM. The chemical also had an EC_{50} value of 100 µM, which gave it a targeting of more than 2000. An EC_{50} value of 1.6 µM for molecule for (38) showed that it was 32 times more effect than the original medication. The their hydrolytic half-life (t1/2) was between 120-240 minutes when the acidity was 7.4 and the temperature was 37 °C [(63)] .

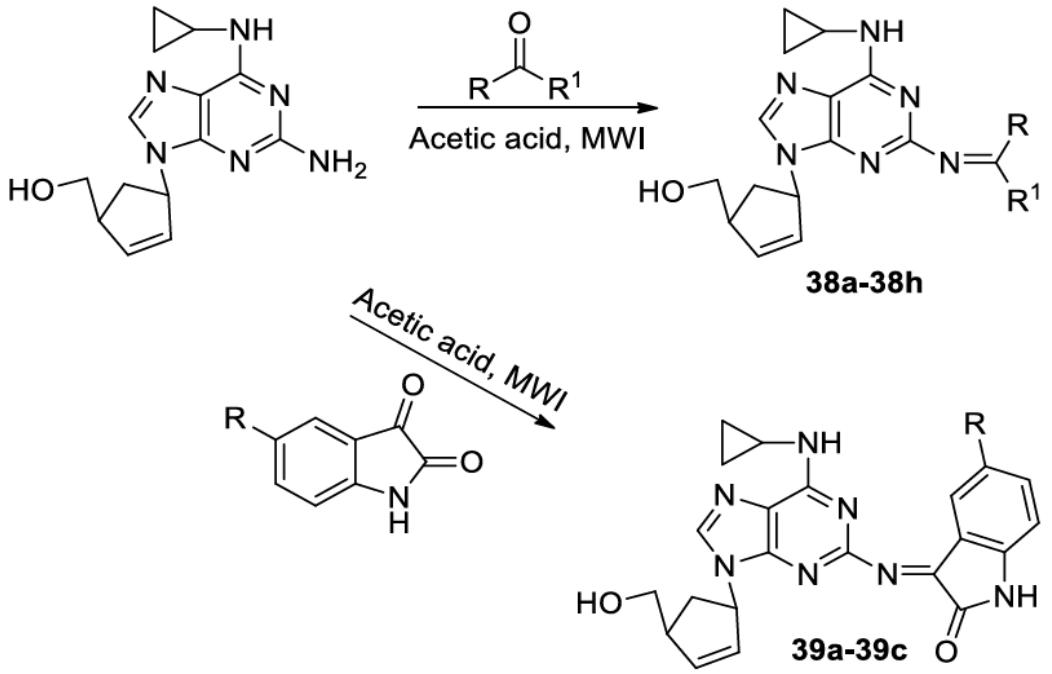


Figure 7: Schematic diagram for derivatives of Abacavir for production of Schiff bases [63].

Anticancer

K. Meenakshi et al .This study describes the synthesis and anticancer evaluation of a series of sulphamoyl isatin Schiff base derivatives. Isatin is a biologically active heterocyclic compound, and chemical modification of its structure can improve its therapeutic potential. The researchers prepared several new derivatives as shown in (Figure 8)by converting 5-sulphamoyl isatin into a hydrazino intermediate followed by condensation with aromatic aldehydes to produce the final Schiff base derivatives .It employed IR, proton nuclear magnetic resonance (NMR), and mass spectroscopy to make sure that the compounds we synthesized had the right chemical structures.It tested these medications' ability to fight cancer by utilizing an Ehrlich Ascites Cancer (EAC) model consisting of Swiss albino mice. This type of cancer is characterized by rapid tumor growth and the accumulation of ascitic fluid. It assessed the size of the lesions, the number of both live and dead cells inside, and how long the animals that had the chemicals lived.5-fluorouracil served as an ordinary baseline drug. The compounds that were made showed a lot of antitumor activity. These drugs made the tumors much smaller, killed more cancer cells, and raised the number of cells that were not alive. Them also helped pets with tumors survive longer. The heightened activity is thought to be linked to their ability to limit the nutritional environment necessary for tumor cell development [71].

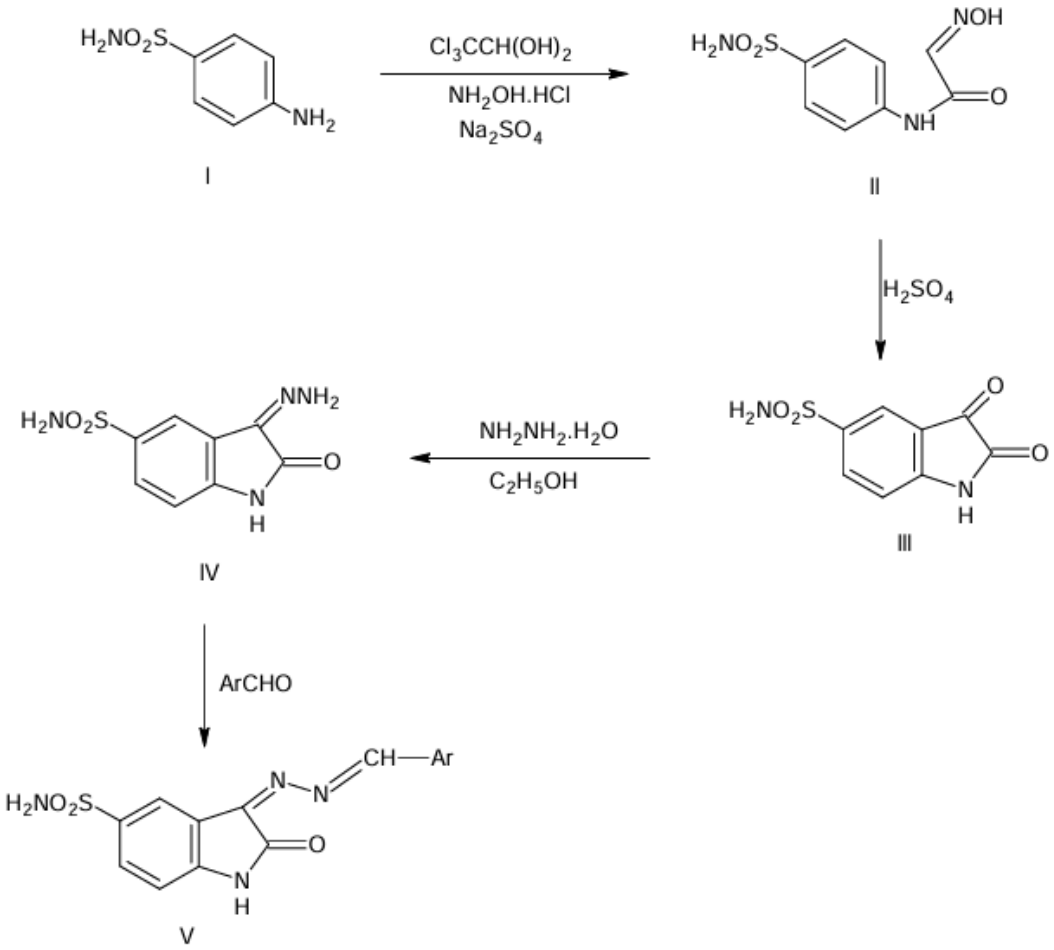


Figure 8: Schematic diagram for Production of Schiff bases that have an anticancer activity

Hassan et al .This study investigated the anticancer potential of newly synthesized metal complexes incorporating aromatic compounds and azo benzene for synthesis of Schiff bases.The substance that binds and its transformation into compounding metals about Cu(II), Mn(II), Co(II), Ni(II), and Zn(II) are synthesized utilizing a heated green synthesis method.Which provided high yields in short reaction times. The structures of the compounds were confirmed using spectroscopic and analytical techniques, ensuring successful coordination between the ligand and metal ions through nitrogen and oxygen donor atoms.The anticancer activity of the Schiff bases drug and its ion coordinator was evaluated versus HepG-2 hepatocellular carcinoma cells and human colon cancer cell lines using an MTT assay. This drug exhibted medium cytotoxicity; however, metal complex significantly increase the anticancer effect. Among all tested compounds as shown in (Figure 9), the Cu(II) complex exhibited the strongest cytotoxic activity, with IC_{50} values of approximately 18 µg/mL for HepG-2 and 22 µg/mL for human colon cancer cells. Mn(II) complex also showed notable anticancer activity, while Co(II), Ni(II), and Zn(II) complexes were less effective.

The enhanced anticancer activity of the metal complexes is attributed of activity against nucleic acid , induce oxidative stress, also disrupt cancer cell metabolism, leading to cell death. These findings demonstrate that metal complex, particularly with Cu(II), plays a crucial role in improving the anticancer properties of Schiff base compounds and highlights their potential as promising candidates for future anticancer drug development [(72)] .

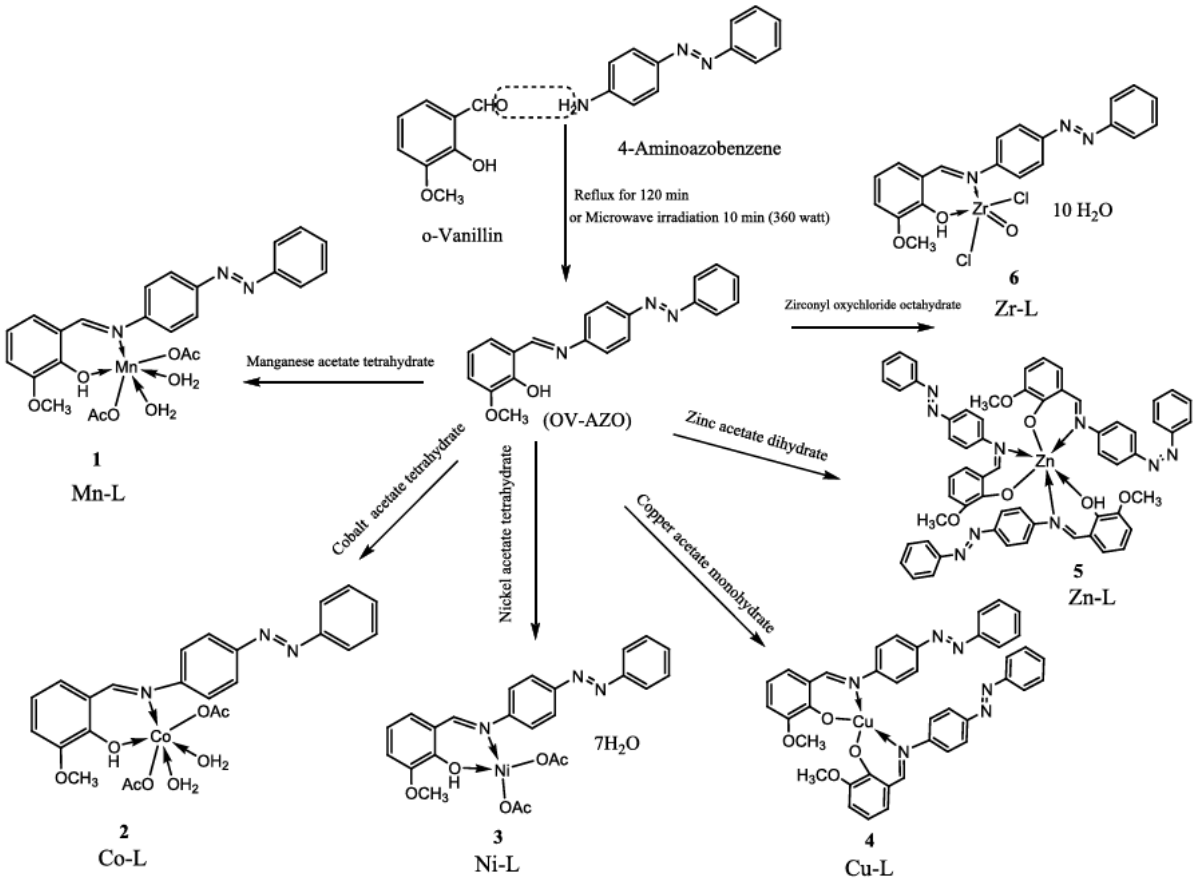


Figure 9: Schematic diagram of the Proposed Molecular Structures of (OV-AZO) and Its Metal Complexes

Conclusion

There is a lot of interest in Schiff bases because of their pharmacological value. This research intends to provide light on their antibacterial, antifungal, antiviral , anticancer activities properties.The antibacterial drugs generated from Schiff bases shown significant activity toward microbes via changing in chemical shape, whereas antifungal agents derived from Schiff bases have shown efficacy against dermatophytes and other pathogenic fungi, particularly in dermatological infections, and also in cases against systemic pathogens. Drugs that has activity against viral made from Schiff base drugs are utilized for fighting viral infections such as shingles, influenza, herpes simplex outbreaks, and HIV. The anticancer efficacy of the schiff base-derived drugs and its metal complex were assessed versus HepG-2 hepatocellular carcinoma cells and carcinoma of the colon cell lines through an MTT assay. The literature elucidates the methods by which diverse chemicals are produced and their possible activation groups. Also, there are comprehensive activities for various microbes that can help scientists test new chemicals. Structural versatility and ease of synthesis make Schiff bases attractive candidates for further pharmaceutical development. Future research should focus on systematic evaluation of the most active scaffolds, exploration of their clinical translation challenges, and optimization of formulations to maximize therapeutic potential.

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CONFLICTS OF INTEREST

The authors did not disclose any conflicts of interest.

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None

ETHICS STATEMENTS

This article is a review and does not involve studies with human participants or animals; therefore, ethical approval is not required.

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مراجعة: قواعد شيف كعوامل واعدة وتطبيقاتها الدوائية

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الخلاصة

تُعد قواعد شيف (Schiff bases) من الفئات الكيميائية المهمة في مجالي الطب وعلم الأدوية خلال العقود الأخيرة، نظرًا لما تتميز به من خصائص بنيوية ووظيفية فريدة. تحتوي هذه المركبات على مجموعة الأزوميثين (-C=N-) التي تتكون عادةً نتيجة تفاعل تكاثف بين الأمينات الأولية مع الألدهيدات أو الكيتونات. وتمتاز قواعد شيف بسهولة تحضيرها وإمكانية تعديل تركيبها الكيميائي، مما يتيح توظيفها في نطاق واسع من التطبيقات الحيوية.

من الناحية الدوائية، أظهرت قواعد شيف طيفًا واسعًا من الأنشطة البيولوجية، بما في ذلك النشاطات المضادة للميكروبات، والمضادة للسرطان، والمضادة للالتهابات، والمضادة للأكسدة، إضافةً إلى فعاليتها المضادة للفيروسات. وتشير العديد من الدراسات إلى أن التعديلات الطفيفة في التركيب الكيميائي، مثل تغيير طبيعة المستبدلات أو إدخال حلقات غير متجانسة، قد تؤثر بشكل ملحوظ في الفعالية الحيوية لهذه المركبات.

علاوةً على ذلك، تُعرف قواعد شيف بقدرتها على الارتباط مع الأيونات الفلزية، مما أدى إلى تطوير العديد من المعقدات الفلزية ذات الخصائص الدوائية المحسّنة أو الجديدة. كما تُعزى أهميتها العلاجية إلى آليات عمل متعددة، تشمل تثبيط الإنزيمات، والتفاعل مع أغشية الخلايا الميكروبية، والارتباط بالحمض النووي (DNA)، وتنظيم مسارات الإجهاد التأكسدي.

وبناءً على هذه الخصائص، تُعد قواعد شيف هياكل واعدة في تصميم وتطوير عوامل علاجية جديدة. يهدف هذا المقال الاستعراضي إلى تسليط الضوء على الأهمية الصيدلانية لقواعد شيف، من خلال التركيز على خصائصها الكيميائية وأبرز أنشطتها المضادة للبكتيريا والفطريات والفيروسات والسرطان، إضافةً إلى مناقشة إمكاناتها في اكتشاف وتطوير الأدوية.

الكلمات المفتاحية:قواعد شيف، الأزوميثينات، النشاط الدوائي، التفاعلات الكيميائية، التخليق، مراجعة علمية.