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Research Article

Overview of Schiff Bases of Isatin Derivatives

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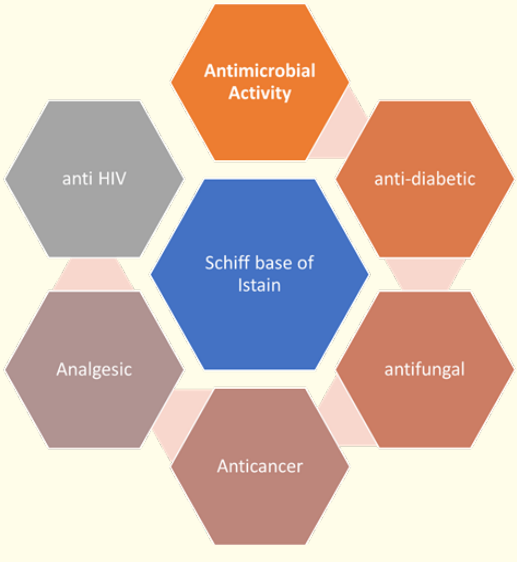
Abstract

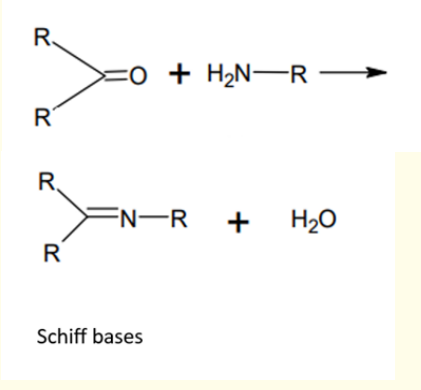
Schiff bases (SBs) are a class of chemical compounds where the stereochemistry of a nitrogen atom with a double bond is maintained. Schiff bases are incredibly versatile and find their way into a variety of fields, from pharmaceuticals and agriculture to analytical chemistry and industrial processes. They're celebrated for their impressive biological activities, which include antimicrobial, antifungal, anticancer, anti-inflammatory, antiviral, and antioxidant effects. Beyond their medicinal benefits, Schiff bases also play a crucial role as ligands in coordination chemistry, where they interact with metal ions to create complexes that are useful in catalysis, therapy, and material science.



Keywords: Schiff Bases; Chemistry

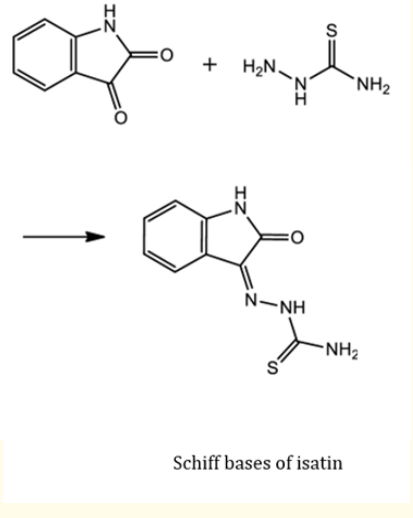
Introduction

Schiff bases are the condensation products of primary amine and carbonyl compounds developed by a German chemist, Hugo Schiff (Nobel Prize in Chemistry in 1864) [1]. He had condensed carbonyl compounds and primary amines to obtain azomethine group (>C=N) as follows [2] (Scheme 1).



Scheme 1

Schiff bases of isatin, characterized by their azomethine (-C=N-) functional group, are a prominent class of bioactive compounds synthesized via the condensation of isatin (1H-indole-2,3-dione) with primary amines (Scheme 2).



Scheme 2

Schiff bases stem from the German chemist Hugo Schiff's work as he first depicted these compounds in 1864. These bases are a class of compounds created from the reaction of a primary amine with a carbonyl compound (aldehyde or ketone) reaction which the primary amine carbonyl gives imine compound of general form R1R2C=NR' (where R' is not hydrogen).

To form a Schiff Base, we carry out a condensation reaction with a primary amine and a carbon compound which can be either an aldehyde or a ketone. We first carry out nucleophilic addition of the amine to the carbon, resulting in the formation of a compound called hemiaminal. The hemiaminal either loses a water molecule or undergoes dehydration to form the imine functional group which is characteristic of Schiff bases (R1R2C=NR3) where R3 is either an alkyl or aryle group and not a hydrogen atom.

Key applications of Schiff bases are quite fascinating:

- **Biological and Therapeutic Uses:** Biological and medicinal uses: The biological functions of schiff bases and their metal compounds have been explored as antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory as well as exhibiting antioxidant and antidiabetic effects. They have been studied for their possible therapeutic uses and as biological compounds for possible enzyme or DNA interaction and inhibition.
- **Agricultural Applications:** Schiff bases and their metal complexes have been found to possess insecticidal properties that effectively target pests. Additionally, they serve as plant growth regulators, playing a crucial role in influencing hormones such as auxins and cytokinins.
- **Analytical Chemistry:** Schiff bases play a crucial role in both quantitative and qualitative analysis as chelating agents, creating stable complexes with metal ions.
- **Industrial Uses:** These compounds play a vital role as catalysts in polymerization processes, as well as stabilizers, dyes, pigments, and corrosion inhibitors. Schiff base metal complexes are also utilized in petroleum refining and in the development of nonlinear optical materials.

- Schiff bases can be both potentially toxic and biologically active, depending on their chemical structure and how they're used. These organic compounds feature a carbon-nitrogen double bond, which is created when a primary amine reacts with a carbonyl compound.
- **Toxicity:** Schiff bases can be harmful if swallowed or inhaled, leading to symptoms like nausea, vomiting, diarrhea, headaches, and dizziness. It's important to take precautions to prevent exposure, particularly in industrial environments or areas where Schiff bases are utilized in textiles or chemicals.

Schiff bases are known for their diverse biological activities and therapeutic potential. They showcase a range of effects, such as antimicrobial, antimalarial, and gastroprotective properties. Many Schiff base derivatives are deemed safe for pharmaceutical applications, exhibiting very low cellular toxicity, which bolsters their promise as viable drug candidates.

When it comes to environmental and synthetic safety, there have been some exciting advancements in green synthesis methods for Schiff bases. These new techniques utilize safe catalysts, such as lemon juice, which highlights the importance of eco-friendly practices in their production.

Schiff bases are defined by the presence of the imine or azomethine functional group, and they generally have a specific structure It has been exciting for chemists to investigate the long history of Schiff base by creating the best analogues with its medicinal benefits for the benefit of humanity. When paired with metals, Schiff bases form a new stable molecule that can be used as an antifungal, antibacterial, anticancer, or antiproliferative drug. Combining Schiff base with heterocyclic substances such as imidazole or pyrazole moieties simultaneously produces several chemical entities with antifungal characteristics. Schiff base and benzene derivatives can also combine to form a new molecule that has strong antibacterial qualities. This review offers up-to-date information on the most active isatin bis-Schiff bases, which would include anticancer, antimicrobial, antiviral, anticonvulsant, anti-inflammatory, and analgesic activities. These observations can lead to new molecular modifications that result in compounds with more desirable pharmacological properties.

Isatin, an indole derivative initially developed by oxidizing indigo, possesses a wide range of biological properties [3]. Schiff bases made from isatin exhibit antimicrobial, antifungal, anticancer, anti-HIV, and antihelminthic capacities [4-15]. Some were even analysed for anticonvulsant potential [16]. This led researchers to strategize that synthesizing a series of novel isatin-derived Schiff bases using diverse aromatic aldehydes with imesatin could yield structures with intricate functions. Their chemical compositions were subsequently validated through IR, 1H NMR, 13C NMR, mass spectrometry, and elemental examination. Meanwhile, isatin Schiff bases displaying promising *in vitro* outcomes permit *in vivo* investigation to further explore applicable treatments. Though progress has provided insightful frameworks, refining innovative analogues while elucidating underlying interactions could impact promising avenues for therapeutic intervention.

Schiff bases are produced by the condensation reaction between carbonyl amines, and were named after Hugo Schiff, a Nobel prize winner German chemist. For the first time, in 1864, Schiff described the reaction of aniline with aldehydes, such as acetaldehyde, benzaldehyde and cinnamaldehyde [17]. Figure 1 E and Z geometric isomers for Schiff bases.

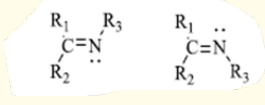


Figure 1: E and Z geometric isomers for Schiff bases.

Biological activities of Schiff base of Isatin-

Tamer El Malah El., *et al*. (2025) Synthesized Isatin-Schiff Base and 1,2,3-Triazole Hybrids as Anti-SARS-CoV-2 Agents and studied DFT, Molecular Docking, and ADMET Figure 2 [18].

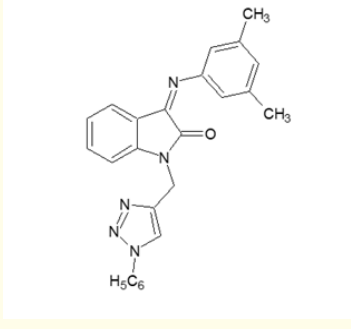


Figure 2: Isatin-Schiff Base and 1,2,3-Triazole Hybrids.

Muğlu halit., *et al*. (2025) Characterized through synthesis, spectroscopic analysis, DFT investigations, and evaluation of the antioxidant properties of novel 5-substituted isatin/thiosemicarbazones (Figure 3) [19].

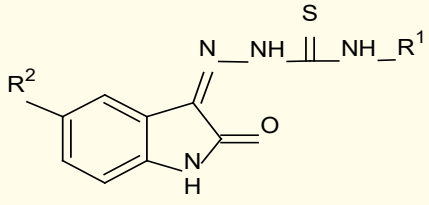
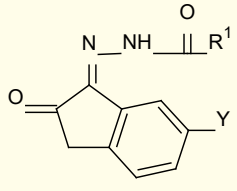


Figure 3: Novel 5-substituted isatin/thiosemicarbazones.

Sukhmeet Kaur., *et al*. (2024) Investigated the antibacterial potential of novel N-Boc isatin Schiff bases: (Figure 4) Combining synthesis with *in-vitro* and *in-silico* studies. *In vitro* antibacterial evaluations were performed using the agar diffusion technique, which demonstrated that compounds displayed significant activity against both gram-positive (*B. subtilis*, MRSA) and gram-negative (*E. coli*) bacterial strains [20].

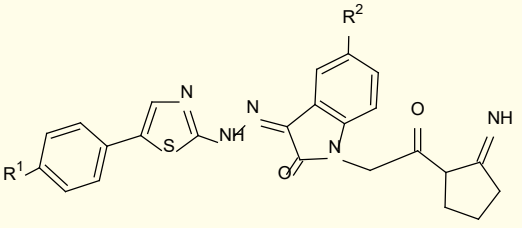


R_1=IBUPROFEN, OR MEFENAMIC ACID PORTION

Y = Cl, NO_2

Figure 4: Novel N-Boc isatin Schiff bases.

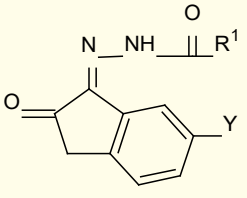
Patil Sunidhi., *et al*. (2024) synthesized and characterized a series of isatin-thiazole derivatives (Figure 5) utilizing various spectroscopic methods. The compounds exhibited *in vitro* inhibitory activity against α-glucosidase, with IC50 values ranging from 28.47 to 46.61 µg/ml, in comparison to the standard drug acarbose, which had an IC50 value of 27.22 ± 2.30 µg/ml. Notably, compound (Figure 5) demonstrated therapeutic effects superior to the standard pioglitazone by effectively reducing glycemia and triglyceride levels in diabetic animal models. Additionally, a molecular docking study was performed to clarify the binding interactions of these compounds within the α-glucosidase enzyme binding pocket (PDB ID 3A47), and the stability of these interactions was confirmed by dynamics simulation trajectories compounds [21].



R^1=CH_3, OCH_3 R^2 = H, F

Figure 5: Series of isatin-thiazole derivatives.

Daud Saima., *et al*. (2024) presented a novel series of Schiff base derivatives of ibuprofen and mefenamic acid that include isatin, functioning as dual inhibitors of the enzymes α-glucosidase and urease. The synthesized derivatives were structurally characterized using 1H NMR, 13C NMR, and high-resolution mass spectrometry. FIGURE 6 showed as dual inhibitors of urease (thiourea and enzymes. The bioactive derivatives were investigated for their effects on cell viability in mononuclear cells, demonstrating favourable cytocompatibility. Additionally, in silico molecular docking studies were performed to forecast the binding interactions of the new derivatives with target enzymes, which aligned well with the findings from *in vitro* research [22].



R_1=IBUPROFEN, OR MEFENAMIC ACID PORTION

Y = Cl, NO_2

Figure 6: Novel series of Schiff base derivatives of ibuprofen and mefenamic acid that include Isatin.

Neelufar., *et al*. (2024) A new series of novel isatin Schiff base metal complexes have been synthesized. A new series of novel isatin Schiff base metal complexes have been synthesized. Among the synthesized complexes, Co (II) metal complex Figure 7exhibited the highest antidiabetic and anticancer activity against HepG2 (Liver) and MDA-MB 231 (Breast) cancer cells [23].

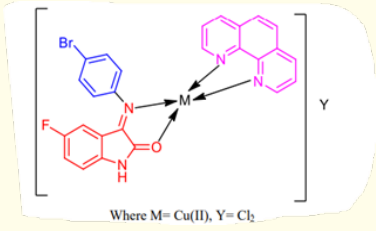


Figure 7: Series of novel isatin Schiff base metal complexes.

In the study conducted by Temel Kan Bakır., *et al*. (2023), a novel series of Schiff bases were synthesized from monothiolcarbohydrazones derived from isatins with various substituents, including 5-F, 5-Br, 5-I, and 5-MeO. The chemical structures of the resulting compounds were characterized through 1H NMR, 13C NMR, FTIR spectroscopy, and elemental analysis. The antioxidant activities of figure 9 compounds were evaluated using the DPPH radical scavenging method. Among these figure 8 which is a Schiff base of 5-bromoisatin featuring a 3-methoxy-4-hydroxy group, exhibited the highest percent inhibition at a concentration of 10 μM (see Figure 3) [24].

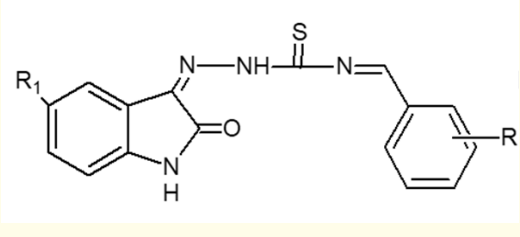


Figure 8: OCH3, R = OH.

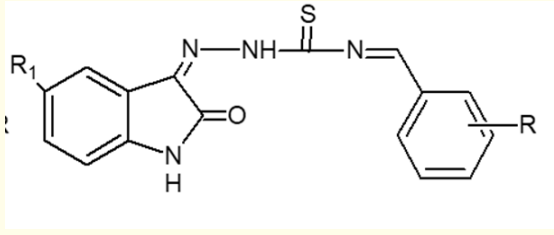
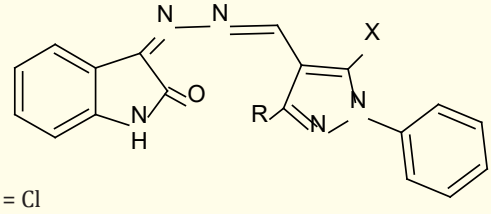


Figure 9: OR = 3,5 dimethoxy monothiolcarbohydrazones derived from isatins.

Ashraf S. Hassan., *et al*. (2023) Novel derivatives of isatin-based Schiff bases have been synthesized by the reaction of 3-hydrazinoisatin (1) with aryl aldehydes, hetero-aryl. Additionally, *in vitro* biological studies were performed, including antioxidant, antidiabetic, anti-Alzheimer, and anti-arthritic activities. The four derivatives possess the highest activities. Among the four potent derivatives, compound (Figure 10) exhibited the highest antioxidant and scavenging activities aldehydes, and dialdehydes [25].



R = CH_3, X = Cl

Figure 10: Of isatin-based Schiff bases.

Eman A. Fayed et.al (2023) A series of isatin-Schiff's base and chalcone compounds were synthesized and evaluated for their anticancer properties against three human cell lines: MCF-7, HepG-2, and HCT-116. The compounds demonstrated moderate to high antitumor activity, with IC50 values between 0.68 and 35.60 μM, in comparison to Imatinib, which served as a reference standard. Among the tested Figure 11 and Figure 12 showed the highest activity, with IC50 values ranging from 0.68 to 5.85 μM across the three cell lines. (Figure 3) [26].

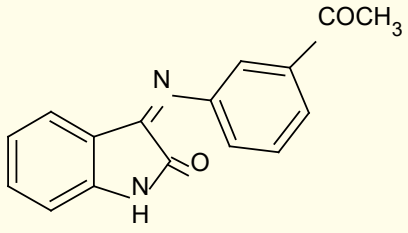


Figure 11

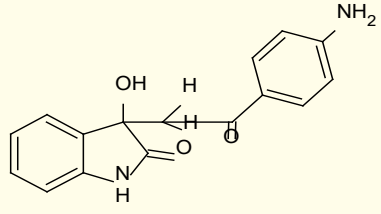
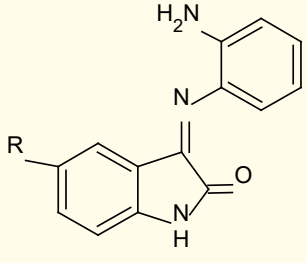


Figure 12

Isatin-Schiff's base and chalcone compounds

Nain Sumitra., *et al*. (2023) A number of Schiff base derivatives had been produced through two distinct methods (synthetic and microwave) by reacting isatin with o-phenylenediamine. The resulting compounds were characterized structurally, and their *in-vivo* antimicrobial efficacy was evaluated against both Gram-negative and Gram-positive bacteria using the inhibition zone method. Several of the newly synthesized isatin derivatives demonstrated significant antimicrobial properties, with notable potency observed in compounds. Specifically, compound (Figure 13) exhibited superior antimicrobial activity compared to the standard drug Amoxicillin, showing effectiveness against Staphylococcus aureus at a higher concentration of 16 µg/mL and against Escherichia coli at a lower concentration of 1 µg/mL [27].



R = 3c = Cl

Figure 13: Schiff base derivatives.

Azadeh Mesripour., *et al*. (2023) were synthesized some of the N-benzylated/N-alkylated isatin derivatives bearing Schiff bases and evaluated for antidepressant activity in FST and MBT models. Results showed that while all compounds had possible anxiolytic effects by reducing MB behavior; compounds Figure 14 only in 25 mg/kg dose had antidepressant-like activity [28].

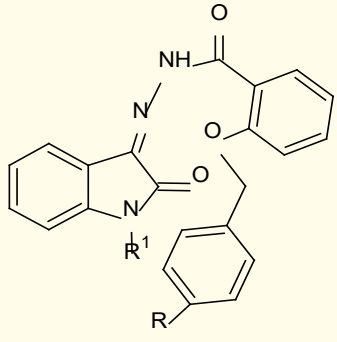


FIG $-CH_2C_6H_5$ R= H

Figure 14: N-benzylated/ N-alkylated isatin derivatives bearing Schiff bases.

Bhagwat Vhanale., *et al*. (2022) synthesized, spectral studies, antioxidant and antibacterial evaluation of aromatic nitro and halogenated tetradentate Schiff bases. The (-NO2, -Cl, -Br, -I) substituted compounds have shown good antibacterial activity against tested organisms. Also, Figure 15 was exhibited higher antioxidant activity by given methods [29].

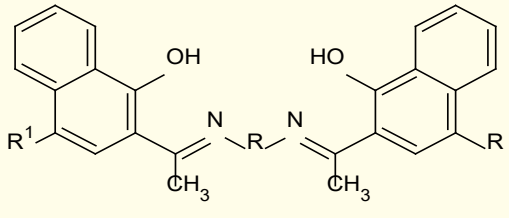
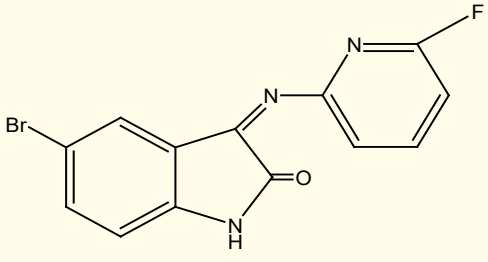


Figure 15: Aromatic nitro and halogenated tetradentate Schiff bases.

Mishra Richa., *et al*. (2021) described a new series of novel Schiff bases has been designed, synthesized and tested for *in vitro* antimicrobial activity. QSAR studies followed by antibacterial screening using broth dilution technique showed excellent MIC values against four human pathogens, namely *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus cerus* and *Staphylococcus aureus*. The Figure 16 showed good activity against *F. oxysporum* at 100 µg/mL with inhibitory index 70% and 82.5%, respectively [30].

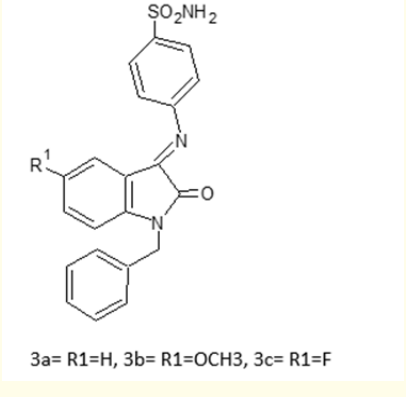


(*Z*)-3-(6-fluoropyridin-2-ylimino)-5-bromoindolin-2-one

Figure 16

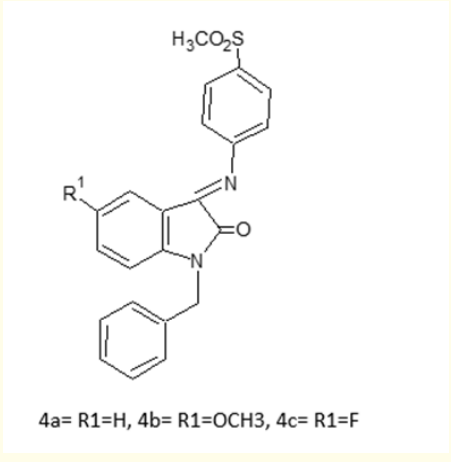
Tayseer Hamid Shakir., *et al*. (2020) Synthesized and preliminary Evaluated antimicrobial activity of Schiff Bases of N -Benzyl Isatin Derivatives. The synthesized Schiff bases Figure 17 and Figure 18 were examined for their *in vitro* antimicrobial activity using different Gram-positive bacteria, Gram-negative bacteria, and Candida albicans as fungi. The obtained results were compared with standard drugs: amoxicillin, ciprofloxacin, and fluconazole. All the compounds show no antifungal activity at any concentrations used, while most of them show moderate antibacterial activity at concentration 5 mg/mL toward most bacteria except Klebsiella pneumonia [31].

Schiff Bases of N-Benzyl Isatin Derivatives.



3a= R1=H, 3b= R1=OCH3, 3c= R1=F

Figure 17: Schiff bases.



4a= R1=H, 4b= R1=OCH3, 4c= R1=F

Figure 18: Schiff bases.

Fatih Sonmez., *et al*. (2019) prepared a series of novel spiro-isatin-based Schiff bases and evaluated antioxidant activity. A new series of 21 Schiff bases of spiro-isatin was synthesized, and their DPPH, CUPRAC and ABTS cation radical scavenging abilities were investigated for antioxidant activity. The results showed that all the synthesized compounds exhibited antioxidant activity for each assay. Figure 19 containing two hydroxyl groups, exhibited the highest antioxidant activities for all assays [32].

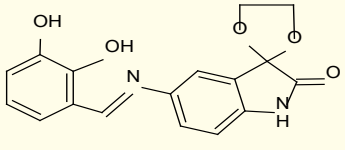


Figure 19: Novel spiro-isatin-based Schiff bases.

E. Riazimontazer., *et al*. (2019) were Designed, synthesized and evaluated biological activity of novel tacrine-isatin Schiff base hybrid derivatives. The compounds Figure 20 were found to be good inhibitors of AChE-induced amyloid-beta (Aβ) aggregation [33].

A.M. Omer., *et al*. (2019) developed and characterized a unique chitosan Schiff base by coupling chitosan with isatin under acidic conditions to form isatin /chitosan Schiff base Figure 21. Antibacterial activity was tested against four different bacterial strains one gram-positive: (*Staphylococcus aureus*) and three gram negative (*Pseudomonas aeruginosa, Salmonella and Proteus vulgaris*). The results showed increases in the antibacterial activity of substituted chitosan against both gram-negative and gram-positive bacteria by the rise in isatin content [34].

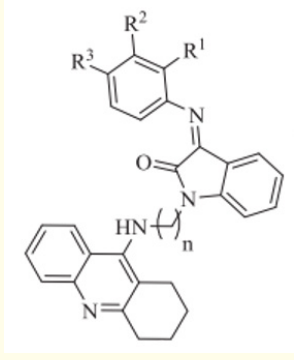


Figure 20: Novel tacrine-isatin Schiff base hybrid derivatives n = 6, R^1 = H,R^2 = Cl, R^3 = H, Novel tacrine-isatin Schiff base hybrid derivatives n = 6, R^1 = H,R^2 = NO_2, R^3 = H.

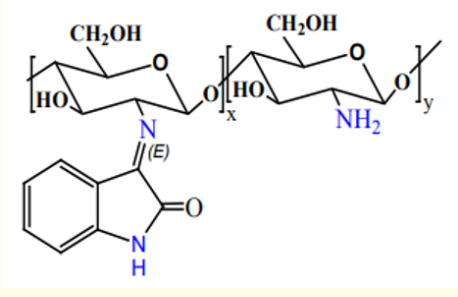


Figure 21: Isatin/chitosan Schiff base.

Ovas Ahmad Dar., *et al*. (2019) synthesized a series of isatin based mixed ligand complexes Figure 22 and Figure 23 of [Cu(dbm) LClH2O] (mlc1), [Co(dbm)LCl2] – (mlc2) and [Ni(dbm) LClH2O] (mlc3) and evaluated their antifungal activity alone and in combination with fluconazole (FLC) against seven different Candida albicans. The biological results revealed that these compounds, with special emphasis to mlc3, have a potential to be used as antifungal drugs and significant potentiators with known antifungal azole drug, Fluconazole [35].

Suzan A. Matar., *et al*. (2017) revealed Six Schiff bases were prepared by reacting 3,3' -diaminodipropylamine with different benzaldehyde derivatives. The prepared compounds Figure 24 was evaluated *in vitro* for their antimicrobial activity against a number of pathogenic Gram-positive and Gram-negative bacteria and Candida by the twofold serial dilution method. These compounds showed bacteriostatic rather than bactericidal activities against Gram positive and Gram-negative bacteria. In addition, compound Figure 24 c exhibited significant anticandidal activity with an MIC of 24 microgram/ml [36].

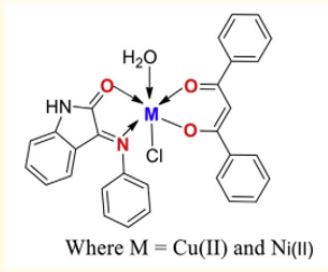


Figure 22: Synthesis of isatin based ligand (L) and mixed ligand complexes (mlc1-mlc3).

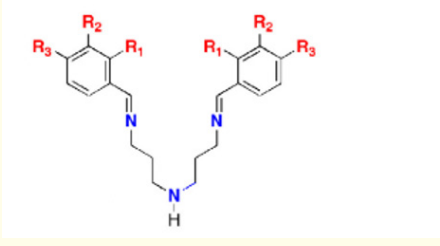


Figure 24: Synthesis of five Schiff bases compounds.

Compound	R1	R2	R3
25a	OH	H	H
25b	OCH_3	H	H
25c	OH	H	OH
25d	H	H	H
25e	H	H	NO_2

Table 1

Rajaram Prakash Chinnasamy., *et al*. (2010) a series of novel Schiff bases of isatin were synthesized by condensation of imesatin with different aromatic aldehydes. The imesatins were synthesized by the reaction of isatin with p-phenylenediamine. These compounds were screened for the analgesic activity by the tail-immersion method at a dose of 200 mg/kg body weight. Among the tested Figure 25 exhibited better analgesic activity when compared to standard pentazocine [37].

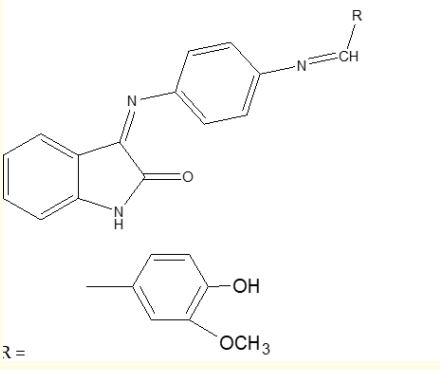


Figure 25: 3-(4-(4-hydroxy-3-methoxylbenzylideneamino) phenylimino) indoline-2-one.

Conclusion

Schiff bases are fascinating compounds known for their carbon-nitrogen double bond (C=N). They've caught a lot of attention because of their diverse applications, particularly in fields like coordination chemistry, catalysis, and medicine. That said, they do come with some limitations, but there are also exciting prospects for their future!

When it comes to Schiff bases, one of the main challenges is their low solubility in water and their tendency to break down easily in acidic environments. This makes it tough to use them effectively, particularly in biological systems and watery settings. Because of this instability, they're mostly limited to use in basic conditions.

Schiff bases, while known for their impressive chelating abilities, haven't really made a splash in analytical chemistry. This is mainly due to issues with solubility and stability that hold them back. When it comes to biological applications, Schiff base metal complexes encounter hurdles like bioavailability, selectivity, and stability in living organisms, which limits their potential as effective therapies. The effectiveness of Schiff base complexes is also influenced by their molecular structure, particularly the length of the bridging groups. This geometry and flexibility play a crucial role in how well they perform in various applications.

Future prospects of Schiff bases catalysis

- Schiff bases are still key players in catalytic processes, like biomimetic catalysis and olefin hydrogenation. Their knack for stabilizing different metal ions and steering catalytic reactions makes them invaluable.
- **Biomedical Applications:** There's a rising interest in Schiff base metal complexes for therapeutic purposes, especially as potential anticancer, antibacterial, antifungal, and antiviral agents. They work through mechanisms such as generating reactive oxygen species (ROS), binding to DNA, inhibiting enzymes, and showcasing antioxidant properties, which positions them as exciting candidates in drug development.
- **Nanotechnology and Drug Delivery**: The future looks bright with the integration of Schiff base complexes into nanocarriers, aimed at enhancing targeted drug delivery and effectiveness.
- **Improved Design and Hybrid Systems:** Upcoming research is set to delve into the structure-activity relationships to fine-tune biological effects and create hybrid compounds that merge Schiff bases with other drug molecules, boosting therapeutic results while minimizing side effects.
- **Corrosion Inhibition:** Schiff bases are being investigated as effective corrosion inhibitors because they can form stable protective monolayers on metal surfaces through chemisorption.
- **Advanced Characterization and Synthesis:** Innovations in crafting Schiff base ligands with customized structures and metal centers will improve their stability, activity, and specificity for a range of industrial and biomedical applications.

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