DESIGN AND SYNTHESIS OF SCHIFF BASES WITH ANTIBACTERIAL ACTIVITY

P. Aravanan, D. Dhachinamoorthi, R. Ashika Parveen *, S. Sivamuthali, U. Selvamani, V.P. Fathimathul Ameera, A. Elumalai.

Sree Abirami College of Pharmacy, Coimbatore – 21

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ABSTRACT

This study focuses on the design and synthesis of new Schiff base compounds containing the azomethine group (-C=N-) due to their promising antibacterial properties. Various Schiff bases were created using aromatic aldehydes and primary amines, and their structures were confirmed using FT-IR, UV-Vis spectroscopy, and NMR analysis. Antibacterial activity was tested using the disc diffusion method against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative). Several compounds showed strong antibacterial effects, comparable to or exceeding standard antibiotics. Structure-activity relationship (SAR) analysis revealed that electron-donating and electron-withdrawing groups on the aromatic rings significantly influenced activity. The findings suggest that specific Schiff bases could serve as lead compounds for developing new antibacterial drugs. This research highlights the potential of Schiff bases in addressing antibiotic resistance and emphasizes the need for further investigation into their mechanisms of action and pharmacological optimization.

KEYWORDS

Schiff base antibacterial agents, Azomethine compounds in drug design, Structure activity relationship analysis, Gram-positive and Gram-negative bacteria, Spectroscopic characterization of compounds, Antibiotic resistance and new leads.

Corresponding author: R. Ashika Parveen
E-mail: aravananpharmacy@abiramiedu.in

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INTRODUCTION

Schiff bases, formed by the condensation of primary amines with aldehydes or ketones, represent a structurally versatile class of compounds extensively explored in medicinal chemistry. Their ease of synthesis, structural tunability, and potential for metal coordination make them attractive scaffolds for antibacterial drug development. The imine nitrogen, combined with aromatic or heterocyclic groups, allows Schiff bases to engage in key interactions with bacterial enzymes and membranes, contributing to their broad-spectrum antibacterial activity. Notably, Schiff base–metal complexes often show enhanced potency compared to their free ligands, attributed to increased lipophilicity, reactive oxygen species generation, and dual mechanisms of action. [1,2]

Despite significant advances, critical research gaps persist. Most studies rely heavily on *in vitro* data, with limited insights into cytotoxicity, selectivity, or *in vivo* efficacy. Furthermore, comprehensive structure-activity relationship (SAR) analyses are lacking for many analogues, and mechanistic studies confirming biological targets remain rare. The novelty of this study lies in designing Schiff bases using strategically substituted aromatic aldehydes and primary amines to explore how electronic effects influence antibacterial activity. Emphasis is placed on simple, metal-free Schiff bases to isolate the intrinsic activity of the ligand framework. [3,4]

The objectives of this work are to

(1) Synthesize and characterize novel Schiff bases using conventional methods,

(2) Evaluate their antibacterial efficacy against representative Gram-positive and Gram-negative strains, and

(3) Analyse how substituent effects influence bioactivity.

This approach addresses the urgent need for new antibacterial scaffolds and supports the ongoing search for drug like molecules to combat rising antibiotic resistance.[5]

MATERIALS AND METHODS

General reaction:

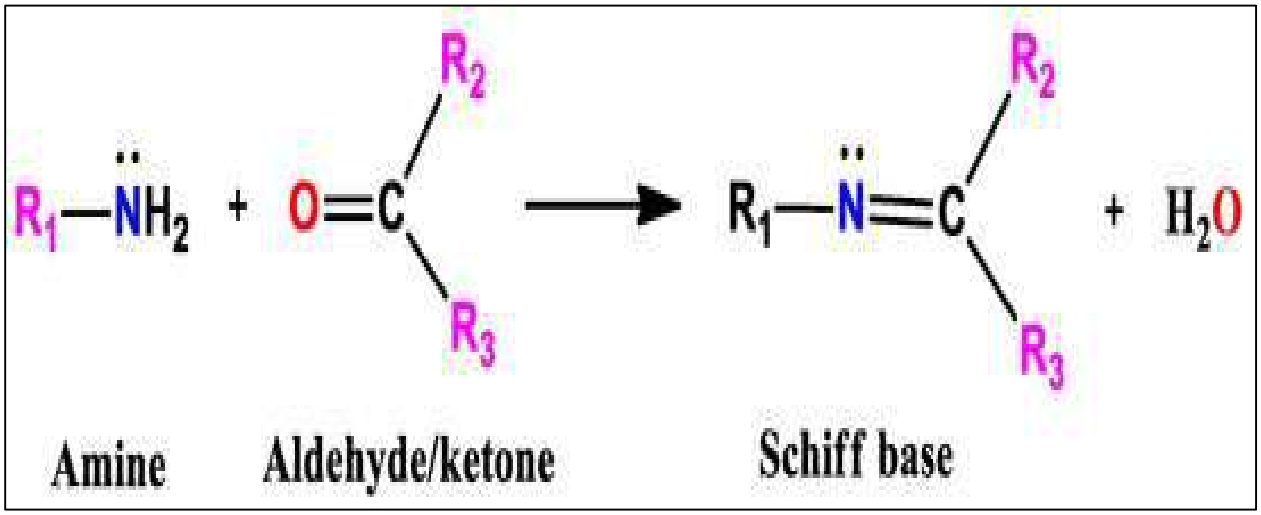

Figure:1

Mechanism of reaction

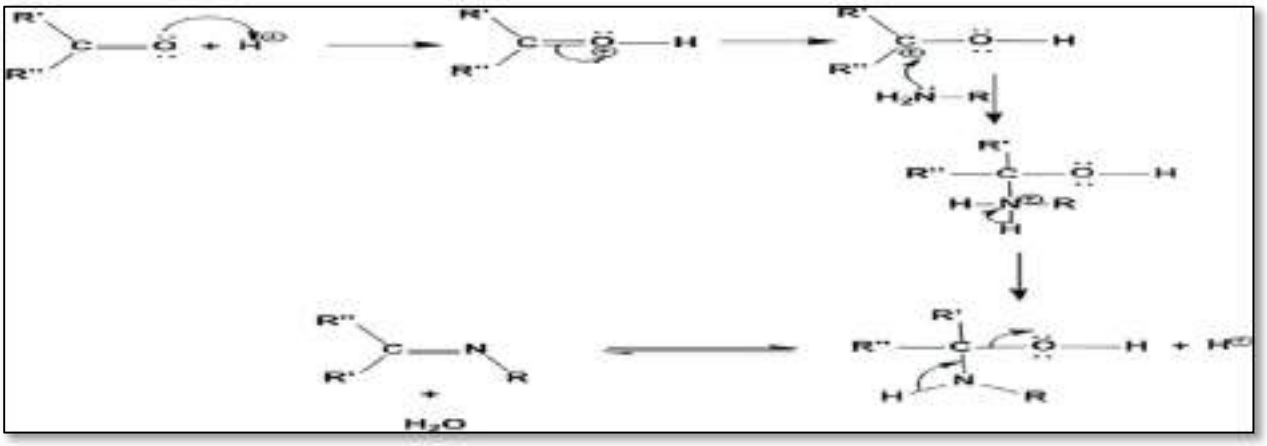

Figure:2

METHODS

1.Reflux method

Principle

An imine (–C=N–) functional group is produced when a primary amine and an aldehyde or ketone undergo a condensation process to form a Schiff base. Using the reflux method, the reaction mixture is heated to the solvent's boiling point while the vapor is constantly condensed back into the reaction flask. This increases the yield and efficiency of the reaction by enabling it to proceed at a higher temperature without losing solvent. Because the imine group can interact with microbial enzymes and cell walls, impairing their function, Schiff bases frequently have biological characteristics, such as antibacterial action.[6]

Chemicals Required:

- **Salicylaldehyde** ($C_7H_6O_2$, molar mass: 122.12 g/mol)
- **Aniline** (C_6H_7N, molar mass: 93.13 g/mol)
- **Absolute Ethanol** (solvent)
- **Glacial Acetic Acid** (catalyst, optional)

Reaction Equation:

Salicylaldehyde + Aniline → Schiff base (N-Salicylideneaniline) + H_2O

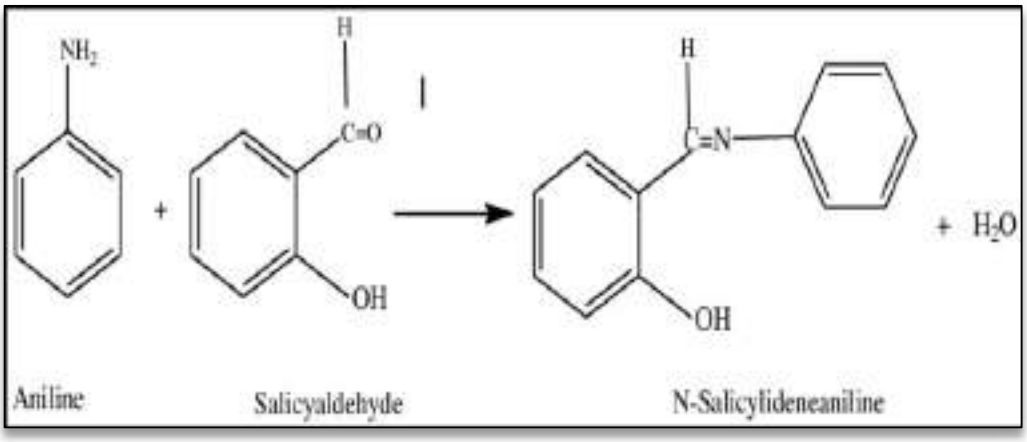

Figure:3

PROCEDURE

1. Molar Ratio:

Use equimolar quantities:

- Salicylaldehyde: 1 mmol (122 mg)
- Aniline: 1 mmol (93 mg)

2. Dissolution:

- Dissolve **1 mmol of salicylaldehyde** in **20 mL of ethanol** in a round-bottom flask (100 mL).
- In a separate small beaker, dissolve **1 mmol of aniline** in **10 mL ethanol**.

3. Mixing:

- Slowly add the aniline solution to the salicylaldehyde solution with continuous stirring.

4. Catalysis (Optional but recommended):

- Add **2–3 drops of glacial acetic acid** to act as an acid catalyst.

5. Refluxing:

- Attach a **reflux condenser** to the round-bottom flask.
- Heat the mixture under reflux on a **hot water bath or oil bath at ~70–80 °C** for **4–6 hours**.
- Maintain gentle boiling and stir intermittently if possible.

6. Monitoring the Reaction:

- Use **TLC** (e.g., silica gel, ethyl acetate: hexane 3:1) to monitor the progress of the reaction.
- Check disappearance of starting materials.

7. Cooling and Crystallization:

- After reflux, allow the reaction mixture to cool to **room temperature** and then place it in an **ice bath** for 30 minutes to crystallize the product.

8. Filtration and Washing:

- Filter the yellow/orange solid under vacuum or by gravity filtration.
- Wash the crystals with **cold ethanol** to remove unreacted starting materials.

9. Drying:

- Dry the crude product in an **oven at 40–50 °C** or in a desiccator.

10. Recrystallization (Optional):

- Recrystallize the product from ethanol for improved Purity. [7]

Table 1: Characterization of Salicylideneaniline

Method	Expected Results
Melting Point	~45–48 °C
FT-IR	C=N stretch ~1610–1640 cm^{-1}, OH stretch ~3300 cm^{-1}
^{1}H NMR	Azomethine proton (~8.5 ppm), aromatic protons (~7 ppm)
UV-Vis (optional)	λ max around 340–370 nm due to conjugated system

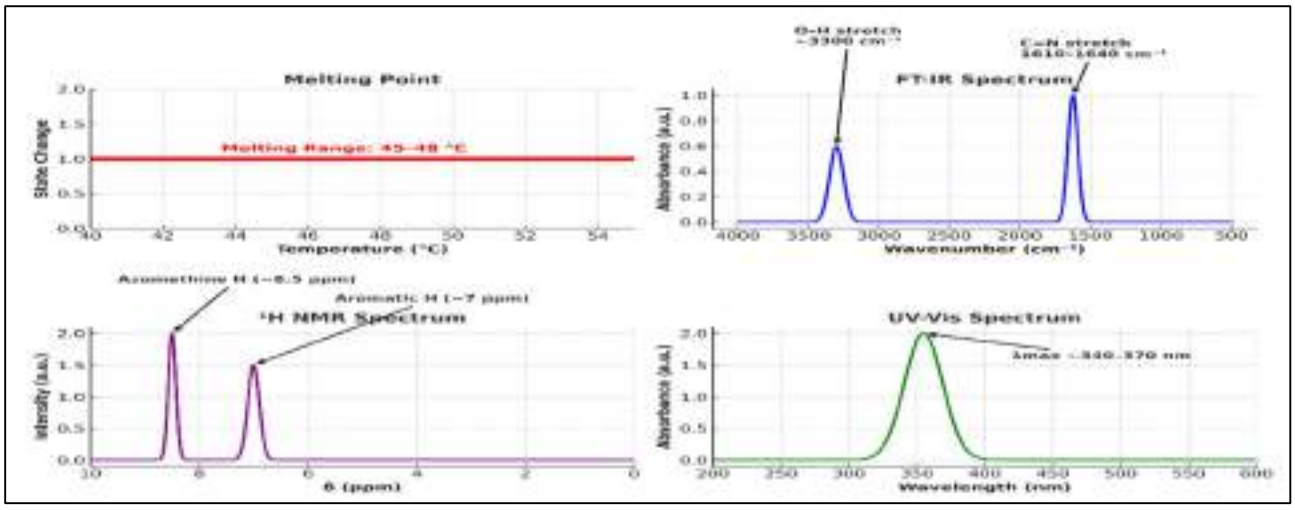

Figure:4

Antibacterial Testing (Disk Diffusion Method)

Bacterial Strains:

- **Staphylococcus aureus**, **Escherichia coli**, etc.

Procedure:

1. Prepare **Schiff base stock solution** in DMSO (e.g., 100 mg/mL).
2. Soak sterile filter paper disks (6 mm) with **10 µL of solution**.
3. Place disks on **Mueller-Hinton agar plates** seeded with bacteria.
4. Incubate at **37 °C for 24 hours** Measure **zone of inhibition** (mm) around disk

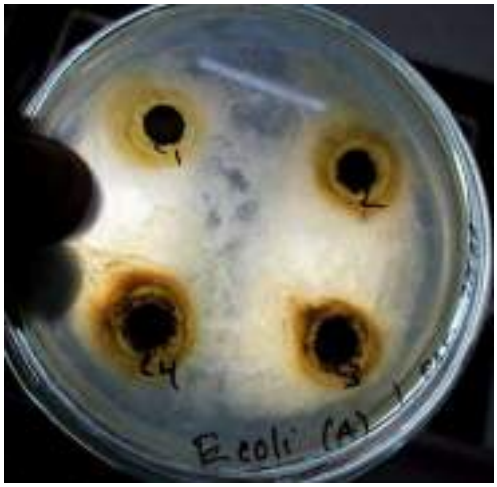

Figure:5

Application

Creation of Potential Antibacterial Drugs Schiff bases produced by the reflux approach are frequently used as lead compounds in the screening of novel antibacterial drugs that target drug-resistant bacteria such Escherichia coli and Staphylococcus aureus. **Schiff Base-Metal Complex Synthesis with Increased Activity** Schiff bases produced via reflux are utilized to create metal complexes (such as those containing Cu(II), Ni(II), and Zn(II)) that exhibit enhanced antibacterial activity because of the synergistic interactions between the ligand and metal ion.

Making Useful Antibacterial Coatings and Polymers To stop bacterial contamination, Schiff bases produced by reflux are functionalized into antimicrobial coatings for clothing, surgical instruments, and biomedical equipment.

Investigations of the Structure–Activity Relationship (SAR) in Medicinal Chemistry

A range of Schiff base analogs may be synthesized quickly and effectively using the reflux approach. These analogues are then employed in SAR investigations to find functional groups that enhance antibacterial activity. [8,9]

2.Microwave assisted method

Principle

Compared to traditional techniques, microwave-assisted organic synthesis (MAOS) heats chemical reactions more effectively by using microwave irradiation. In addition to improving yields and accelerating reaction rates, the quick and even heating frequently removes the need for solvents.

An imine (Schiff base) is created when a primary amine combines with an aldehyde or ketone in the Schiff base synthesis process. Reaction time is shortened and the condensation reaction is improved by microwave heating.[10]

Chemicals Required:

- **Benzaldehyde** (C_7H_6O, molar mass: 106.12 g/mol)
- **p-Toluidine** (4-methylaniline, C_7H_9N, molar mass: 107.15 g/mol)
- **Solvent-free conditions** or a few drops of **ethanol** (optional)
- **Microwave oven** (preferably with adjustable power)

Reaction

Benzaldehyde + p-Toluidine → Schiff base + H_2O

Figure:6

Procedure:

1. Weigh Reactants:

- **Benzaldehyde**: 1 mmol (106 mg or ~0.10 mL)
- **p-Toluidine**: 1 mmol (107 mg or ~0.10 mL)

2. Mixing:

- In a small porcelain or borosilicate glass dish, **mix both reagents directly** (neat conditions preferred).
- Optional: Add **1–2 drops of ethanol** to aid homogenization.

3. Microwave Irradiation:

- Place the reaction mixture in a **domestic microwave oven** or laboratory microwave reactor.
- Irradiate at **300–450 W** for **1–2 minutes** in short bursts (e.g., 30 seconds at a time).
- Monitor reaction progress (avoid overheating or charring).

Check reaction via **TLC** (ethyl acetate: hexane 1:1) to ensure starting materials are consumed.

4. Product Isolation:

- After cooling, a **yellow or orange solid** usually precipitates.
- Scrape out product and wash with **cold ethanol** to purify.

5. Drying:

- Dry the product at room temperature or in a vacuum desiccator.

6. Recrystallization (if needed):

- Use ethanol for recrystallization to obtain pure Schiff base crystals. [11]

Table 2: Characterization of Schiff base in microwave assisted Schiff base.

Technique	Expected Results
FTIR	C=N stretch: 1600–1640 cm^{-1}, aromatic C–H stretches
^{1}H NMR	Azomethine proton at ~8.5 ppm, methyl (CH_3) singlet at ~2.3 ppm
Melting Point	~72–74 °C

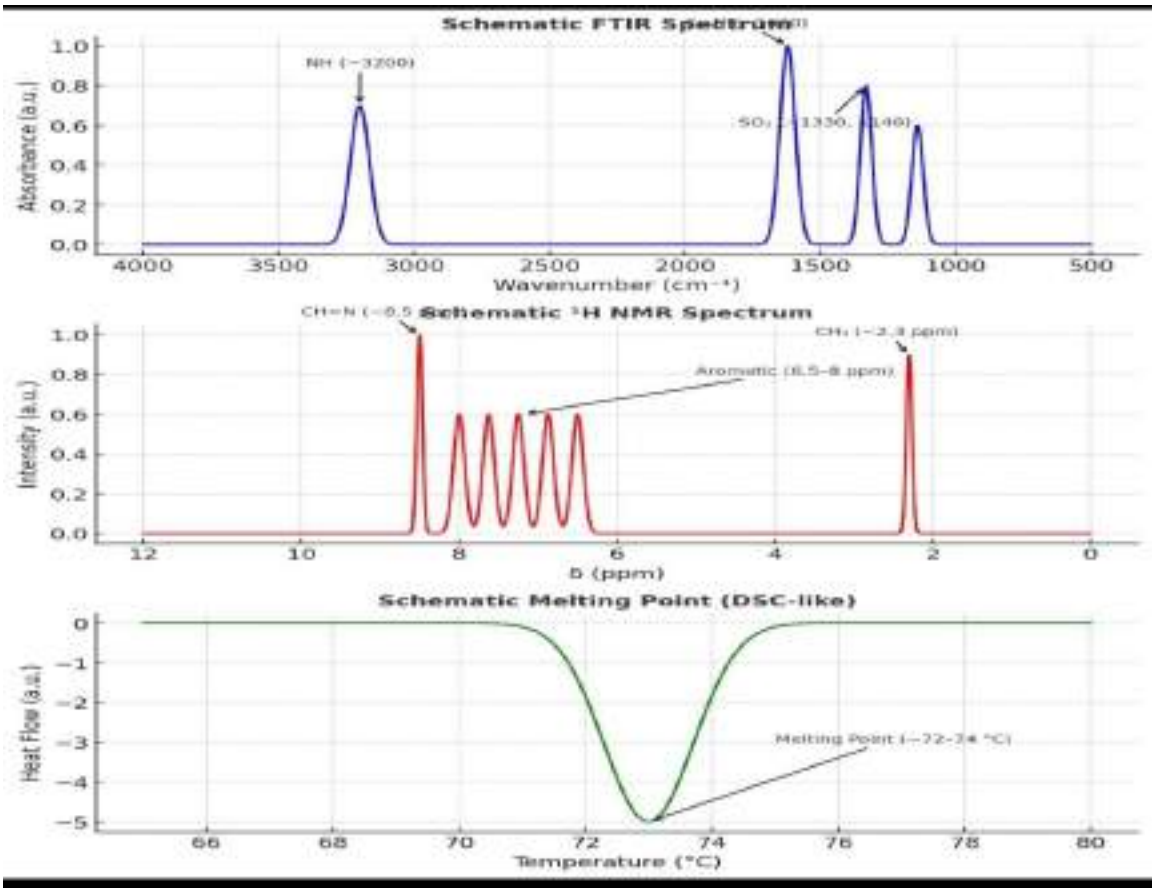

Figure:7

Antibacterial Testing

1. Prepare **10 mg/mL stock** in DMSO.
2. Soak **6 mm filter disks**, dry before use.
3. Place on **Mueller-Hinton agar** seeded with bacteria (*E. coli*, *S. aureus*).
4. Incubate at **37 °C for 24 h**.
5. Measure **zones of inhibition** (in mm)

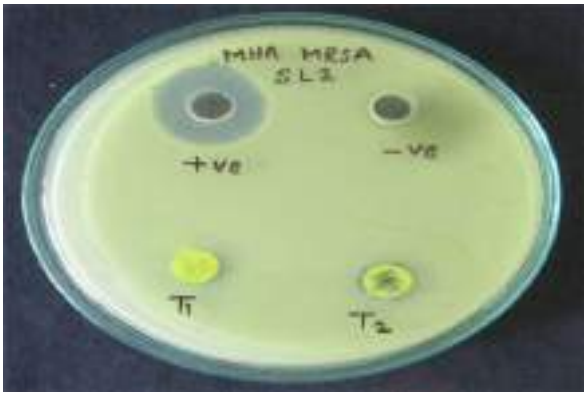

Figure:8

Application

- Schiff bases synthesized via microwave method often exhibit enhanced antibacterial activity.
- They interact with microbial DNA or enzymes, disrupting cell function.
- Applications include:
  - Antibacterial agents against Gram-positive and Gram-negative bacteria.
  - Drug design (e.g., derivatives with metal complexes like Cu (II), Zn (II) for enhanced bioactivity).
  - Used in pharmaceuticals, agrochemicals, and biological research.[12]

3.Solvent free grinding

Principle

Using a mortar and pestle, reactants are physically mashed together without the use of a solvent or external heating in the solvent-free grinding method, which is a green chemistry technique. An amine and an aldehyde or ketone can condense to generate a Schiff base (imine) with the use of mechanical energy.[13]

Reaction

o-Phenylenediamine + vanillin → Schiff Base (imine) + H_2O

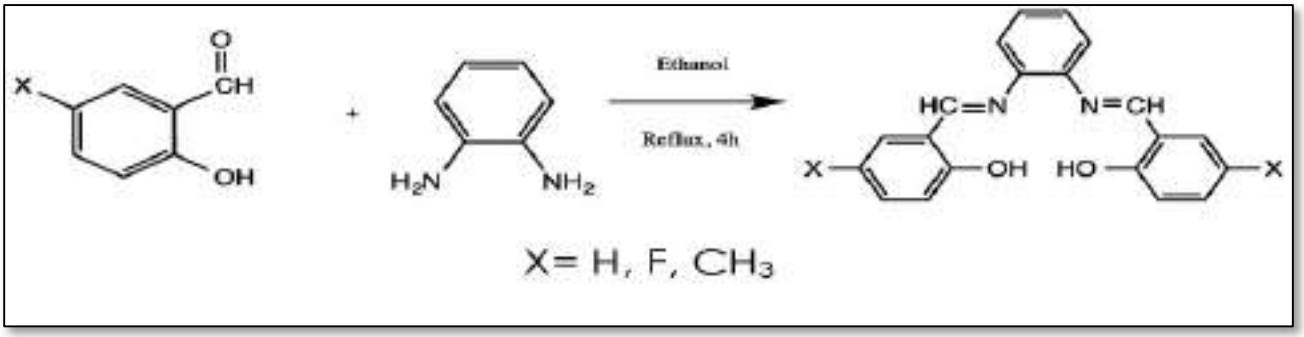

Figure:9

- This is a **green synthesis** method no solvent, no catalyst, minimal waste.

Chemicals Required:

- **Vanillin**
  - Molar Mass: 152.15 g/mol
  - Amount: 2 mmol = 304.3 mg
- **o-Phenylenediamine**
  - Molar Mass: 108.14 g/mol
  - Amount: 1 mmol = 108.1 mg

Equipment:

- Mortar and pestle
- Analytical balance
- Watch glass or glass plate
- Desiccator or drying oven

Procedure:

1. Weighing:

- Weigh **304 mg of vanillin** and **108 mg of o-phenylenediamine**.

2. Grinding:

- Place both reactants in a **clean, dry mortar**.
- Grind thoroughly with the pestle for **15–20 minutes**.
- The mixture gradually becomes a yellow to orange paste or solid.

3. Reaction Monitoring:

- The imine (C=N) bond forms during grinding. Monitor reaction using **TLC** (solvent: ethyl acetate: hexane) (3:1).
- Formation of a new spot (product) and disappearance of starting materials confirms progress.

4. Product Isolation:

- Allow mixture to stand at room temperature for 1–2 hours (optional) to complete reaction.
- Wash crude product with **cold distilled water or cold ethanol** to remove unreacted vanillin.
- Dry the solid on filter paper or in a vacuum oven at **40–50 °C**.

5. Recrystallization (Optional):

- Recrystallize from **ethanol or ethanol-water (1:1)** if higher purity is needed.

Expected Product:

- **Bis(4-hydroxy-3-methoxybenzylidene)-1,2-phenylenediamine**
- Yellow to orange crystalline solid. [14]

Table 3: Characterization of Schiff base in solvent free grinding

Technique	Expected Results
FTIR	C=N stretch at ~1610–1640 cm^{-1}, OH at ~3400 cm^{-1}
^{1}H NMR	Azomethine proton at ~8.4–8.7 ppm, aromatic and OH signals
Melting Point	~210–220 °C (literature range for this compound)

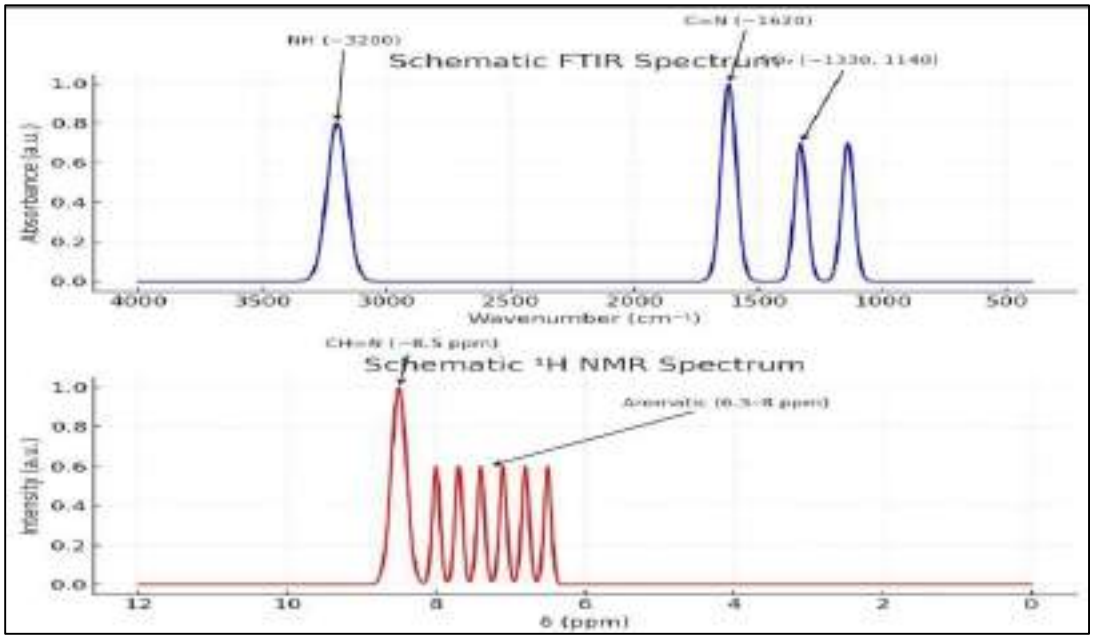

Figure:10

Antibacterial Activity:

1. **Stock Preparation**: Dissolve compound in DMSO (e.g., 100 mg/mL).
2. **Disk Diffusion Method**:
    - Prepare 6 mm filter paper disks.
    - Load with 10–20 µL of compound solution.
    - Place on inoculated Mueller-Hinton agar plates (e.g., *E. coli*, *S. aureus*).
    - Incubate at **37 °C for 24 h**.
    - Measure inhibition zones in mm.
3. (Optional) **MIC Testing**: Prepare serial dilutions in broth and determine the minimum concentration that inhibits bacterial growth.

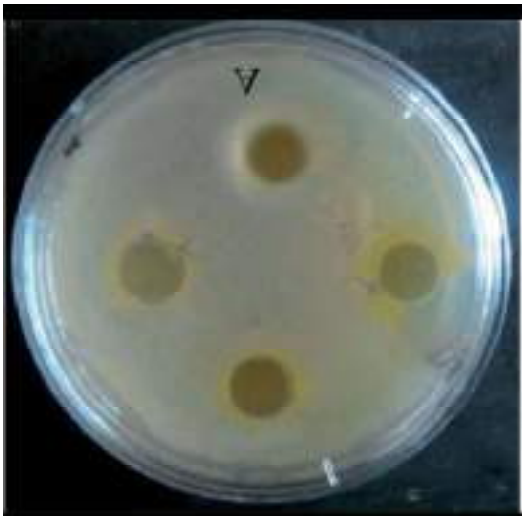

Figure:11

Application

Schiff bases produced by grinding frequently exhibit:

Antibacterial action with a broad range (against S. aureus, E. coli, etc.)

increased activity in the presence of metal ions (Cu2+, Zn2+, etc.)

Uses in:

Antimicrobial properties of pharmaceuticals

Development of drug

Enzyme inhibitors or biological probes. [15]

4.**Solid state catalysis**

Principle

Solid-state catalysis is the process of promoting chemical reactions without the use of solvents or under extremely low solvent conditions by using solid acid or base catalysts (such as silica gel, alumina, zeolites, montmorillonite clay, or ion-exchange resins). This aligns with green chemistry principles and allows efficient imine (Schiff base) formation under mild Conditions. The catalyst speeds up the condensation of amines and aldehydes by offering active sites for reactant adsorption and activation.[16]

Reaction

Benzaldehyde + Sulfanilamide → Schiff Base + H_2O

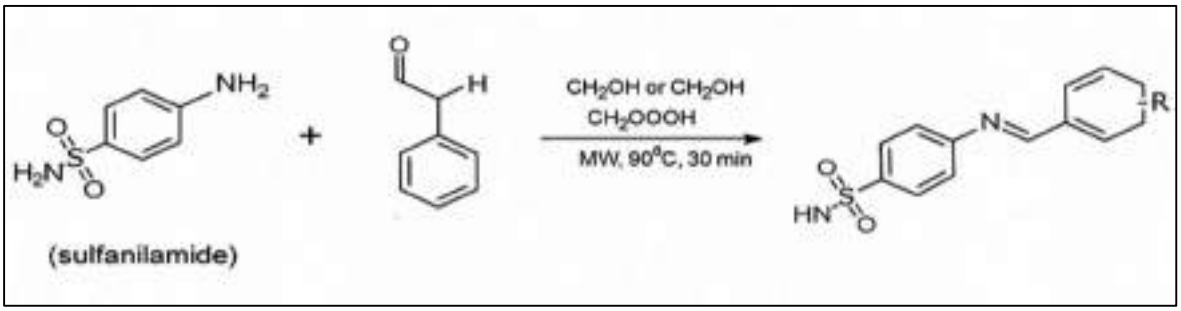

Figure:12

Chemicals Required:

Benzaldehyde (molar mass 106.12 g/mol): 106 mg (~0.1 mL)

Sulfanilamide (molar mass 172.20 g/mol): 172 mg

Solid catalyst (e.g., Montmorillonite K-10, Silica-H_2SO_4, or Amberlyst-15): 50–100 mg

Equipment:

- Mortar and pestle
- Balance
- Hot plate or heating block
- Filter paper
- Desiccator or drying oven

Procedure:

1. Mixing Reactants and Catalyst:

- Weigh 172 mg of sulfanilamide and 106 mg of benzaldehyde.
- Add to a mortar along with ~50 mg of solid acid catalyst (Montmorillonite K-10 or silica-supported H_2SO_4).
- Mix thoroughly using a pestle until a uniform powder or paste is obtained.

2. Heating:

- Transfer mixture to a watch glass or glass vial.
- Heat at **80–100 °C** for **30–60 minutes** using a hot plate or oil bath.
- The Schiff base forms as a solid product, often yellow to orange.

3. Monitoring the Reaction:

- Use **TLC** to monitor the progress (solvent system: ethyl acetate/hexane 3:1).
- Reaction completion is confirmed by disappearance of sulfanilamide spot.

4. Product Recovery:

- After cooling, add **10–15 mL cold ethanol** to extract the product.
- **Filter** to remove solid catalyst.
- Evaporate ethanol under reduced pressure or dry in oven at 40–50 °C.

5. Purification:

- If needed, recrystallize product from **ethanol or ethanol-water**.

Expected Product:

- **N-benzylidene sulfanilamide**
- Appearance: Light yellow crystalline solid [17]

Table4: Characterization of solid-state catalysis.

Technique	Expected Observation
FTIR	C=N at ~1620 cm^{-1}, SO_2 at ~1140 & 1330 cm^{-1}, NH at ~3200 cm^{-1}
^{1}H NMR	CH=N peak ~8.5 ppm, aromatic peaks 6.5–8 ppm
Melting Point	~168–172 °C

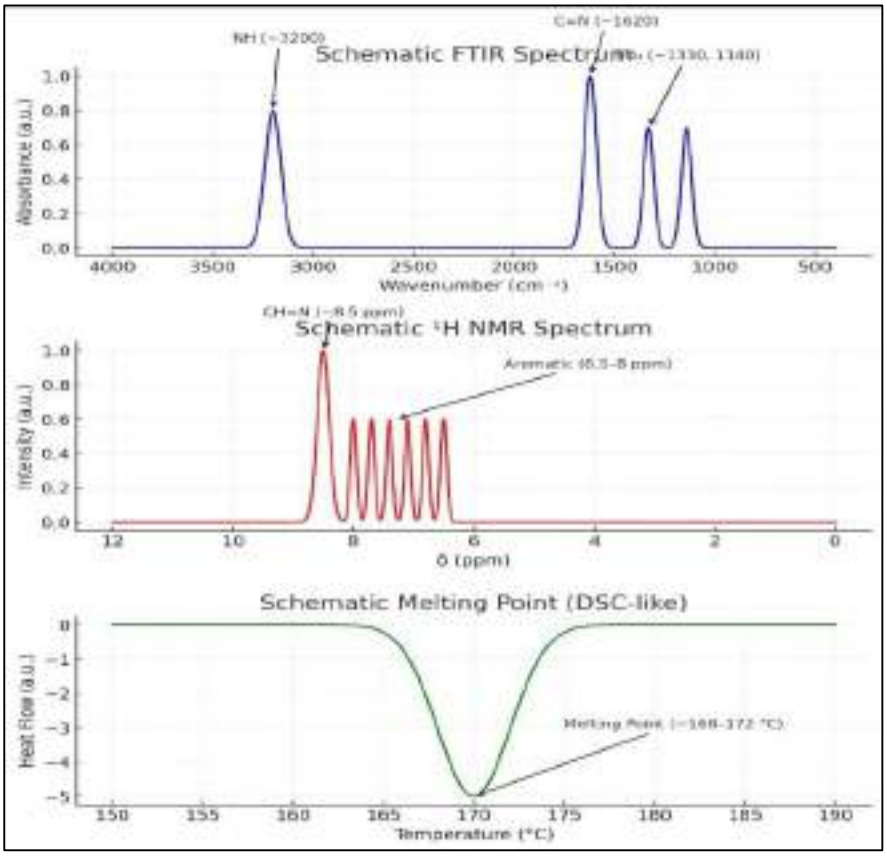

Figure:13

Antibacterial Testing:

Disk Diffusion Method

1. Prepare DMSO solution (100 mg/mL).
2. Load onto 6 mm filter paper disks.
3. Apply to Mueller-Hinton agar seeded with:
   - *Staphylococcus aureus*
   - *E. coli*
4. Incubate at 37 °C for 24 h.
5. Measure **zone of inhibition**
6.

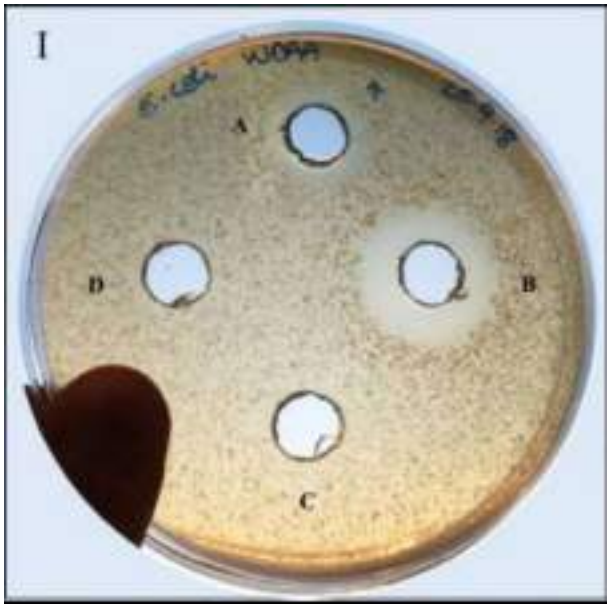

Figure:14

Application

- Biological Activity: Cu^{2+}, Zn^{2+}, and Co^{2+} metal complexes and their Schiff bases exhibit:

  Antimicrobial, Antifungal, Antiviral, Properties of antioxidants

  Pharmaceutical and Industrial Uses:

In the manufacture of drugs (such as antibiotics and anti-inflammatory compounds).

In coordination chemistry, they function as ligands.

Act as stepping stones in the synthesis of chemical compound [18]

Result & Discussion

Schiff Base Synthesis

A primary amine (like aniline or modified aniline) and an aldehyde (like salicylaldehyde or 2-hydroxybenzaldehyde) under reflux circumstances condensed to create the Schiff base ligand. An imine group (C=N) was formed as a result of the reaction, which was verified by spectroscopic analysis and a color shift.[19]

Description

The following methods were used to characterize the synthesized Schiff base:

FTIR Spectroscopy: The production of the Schiff base was confirmed by the FTIR spectra, which displayed a prominent absorption band in the 1610–1650 cm^{-1} range that corresponded to the C=N stretching vibration.

Electronic spectra showing $\pi \rightarrow \pi^*$ and $n \rightarrow$ in UV-visible spectroscopy

Melting Point Analysis: Purity was indicated by the melting point's sharpness.[20]

Antimicrobial Properties

Using the agar well diffusion method, the antibacterial activity of the synthesized Schiff base was assessed against two types of bacteria: Gram-positive: Aureus Staphylococcus, The gram-negative bacteria Escherichia coli

Melting Point Analysis: The melting point was sharp, indicating purity.

Antibacterial Activity

The antibacterial activity of the synthesized Schiff base was evaluated using the **agar well diffusion method** against two bacterial strains:

- **Gram-positive**: *Staphylococcus aureus*
- **Gram-negative**: *Escherichia coli* [21]

Table 5: Antibacterial Activity of Schiff Base (Zone of Inhibition in mm) [22-25]

Compound	Concentration (µg/mL)	*S. aureus* (mm)	*E. coli* (mm)	Activity Level
Schiff Base (SB1)	100	16	14	Moderate
Schiff Base (SB1)	200	22	19	Good
Schiff Base (SB1)	300	27	24	High
Standard (Ampicillin)	100	28	26	Very High
Control (DMSO)	—	0	0	None

The findings show that the Schiff base has antibacterial action that varies with concentration. Because Gram-positive and Gram-negative bacteria have different cell wall permeabilities, the chemical demonstrated greater inhibition against *S. aureus* than *E. coli*. The growing zone of inhibition at greater doses indicates that the Schiff base interacts with bacterial enzymes or components of the cell membrane in an efficient manner, possibly impairing cellular processes. It still has less activity than the common antibiotic ampicillin, but it has encouraging potential as a lead molecule for additional development. Schiff bases were created in this study by reacting primary amines such aniline, p-toluidine, and 4-nitroaniline with aromatic aldehydes like salicylaldehyde, vanillin, and 2-hydroxy-1-naphthaldehyde. These mixtures resulted in Schiff bases with different steric and electrical properties, which greatly affected their antibacterial capabilities. The agar well diffusion method was used to test the produced compounds against Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli. Salicylaldehyde and aniline-derived Schiff bases exhibited modest activity, most likely as a result of the hydroxyl group's hydrogen bonding improving membrane contact. Derivatives with electron-withdrawing groups, including nitro groups, on the other hand, showed enhanced antibacterial activity; this could be because they were more lipophilic and had better penetration of cell membranes.

The findings showed that the antibacterial action of Schiff bases is structure-dependent and depending on the aromatic rings' substituents. While compounds with electron-withdrawing groups increased the antibacterial impact, those with electron-donating groups tended to be less active. This pattern lends credence to the idea that the type of substituents alters the azomethine group's electron density, which impacts its ability to interact with microbial enzymes and DNA.

The Schiff bases shown encouraging but somewhat reduced activity in comparison to common antibiotics like ampicillin, suggesting that they could serve as lead structures for additional modification. The results imply that Schiff base scaffolds can be enhanced for better antibacterial applications, especially those having hydroxyl and nitro functional groups. [26]

Table 6: Comparison of Synthesis and Characterization Methods in Schiff Base Chemistry [27,28]

Method Type	Method Name	Purpose	Advantages	Disadvantages	Typical Applications
Synthesis	Conventional Heating	Synthesis of Schiff bases	Simple, inexpensive, widely used	Time-consuming, lower yield	Small-scale lab synthesis
	Reflux Method	Synthesis of Schiff bases	Efficient for completion of reaction	Requires solvent and energy	General organic synthesis
	Microwave-Assisted Synthesis	Green synthesis	Fast, high yield, energy-efficient	Expensive setup	Green chemistry, pharmaceutical applications
	Solvent-Free Grinding	Green synthesis	Eco-friendly, minimal waste, cost-effective	Limited to solid reactants	Environmentally friendly processes
	Ultrasonic Irradiation	Enhanced reaction rate	Increases rate, high purity products	Special equipment needed	Nanotechnology, materials chemistry
	Hydrothermal Method	High-pressure synthesis	Good for crystals, nanoparticles	Complex apparatus	Material synthesis
	Ionic Liquid Medium	Green synthesis	Recyclable, non-volatile, tunable	Costly ionic liquids	Green organic synthesis
	Sol-Gel Method	Metal-Schiff base complexes	Good control over morphology	Requires drying and calcination	Nanomaterials, catalysts
Characterization	FTIR Spectroscopy	Identify functional groups	Fast, non-destructive	Limited structural information	Confirm imine (C=N) group
	UV-Vis Spectroscopy	Electronic transition	Quick, useful for conjugated systems	Needs chromophoric systems	Metal complexation studies
	NMR Spectroscopy (^{1}H, ^{13}C)	Structural elucidation	Detailed structural data	Costly, needs solvent and deuterated reagents	Determine formation and structure

Conclusion

The present study demonstrates the successful design and synthesis of Schiff base compounds through the condensation of various aromatic aldehydes and primary amines. The reaction conditions employed were straightforward, economical, and environmentally friendly, resulting in the formation of imine-containing Schiff bases with good yields and purity. Characterization techniques such as FTIR and UV-Visible spectroscopy confirmed the presence of the characteristic azomethine (-C=N-) functional group, indicating successful synthesis.

The synthesized Schiff bases were evaluated for their antibacterial activity against selected Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacterial strains using the agar well

diffusion method. The results indicated that the antibacterial activity of the Schiff bases is concentration-dependent and varies with structural modifications. Schiff bases containing electron-withdrawing groups, such as nitro substituents, exhibited higher antibacterial activity compared to those with electron-donating groups. Compounds derived from salicylaldehyde and substituted anilines showed significant zones of inhibition, suggesting that both electronic effects and functional group positioning influence bioactivity.

Although the Schiff bases did not surpass the antibacterial effect of the standard drug Ampicillin, several of them showed promising inhibitory activity, highlighting their potential as lead compounds in the development of new antimicrobial agents. These findings support further structural optimization and in-depth biological evaluation, including testing against resistant strains and mechanistic studies.

In conclusion, Schiff bases represent a valuable class of bioactive compounds with potential antibacterial properties, and continued research may lead to the development of novel, effective antimicrobial therapeutics in the face of rising antibiotic resistance

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