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**Filière : Chimie**

**Spécialité: Chimie Analytique**

# Green Synthesis of Azomethine Compounds

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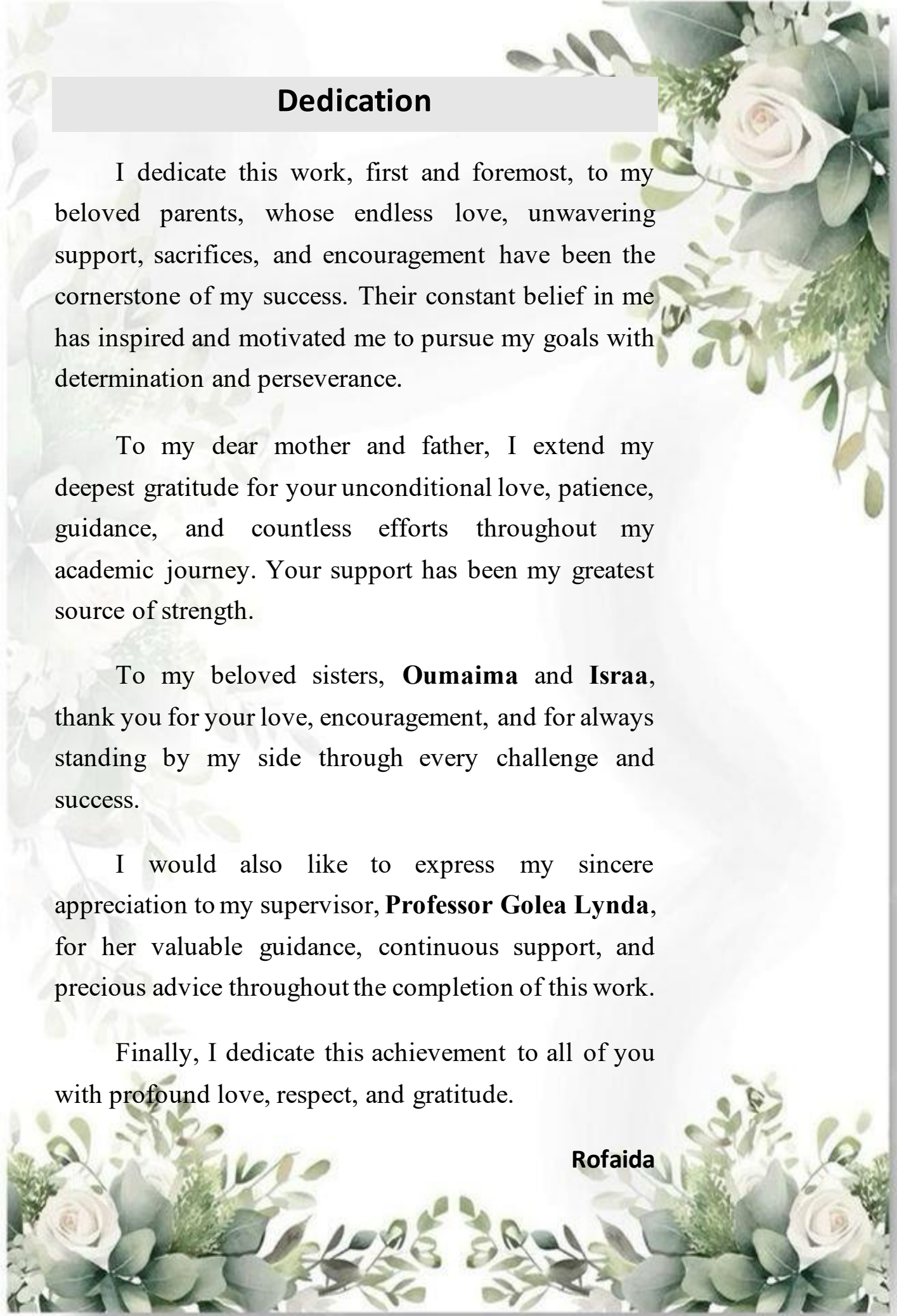
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## Dedication

I dedicate this work, first and foremost, to my beloved parents, whose endless love, unwavering support, sacrifices, and encouragement have been the cornerstone of my success. Their constant belief in me has inspired and motivated me to pursue my goals with determination and perseverance.

To my dear mother and father, I extend my deepest gratitude for your unconditional love, patience, guidance, and countless efforts throughout my academic journey. Your support has been my greatest source of strength.

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I would also like to express my sincere appreciation to my supervisor, **Professor Golea Lynda**, for her valuable guidance, continuous support, and precious advice throughout the completion of this work.

Finally, I dedicate this achievement to all of you with profound love, respect, and gratitude.

**Rofaida**



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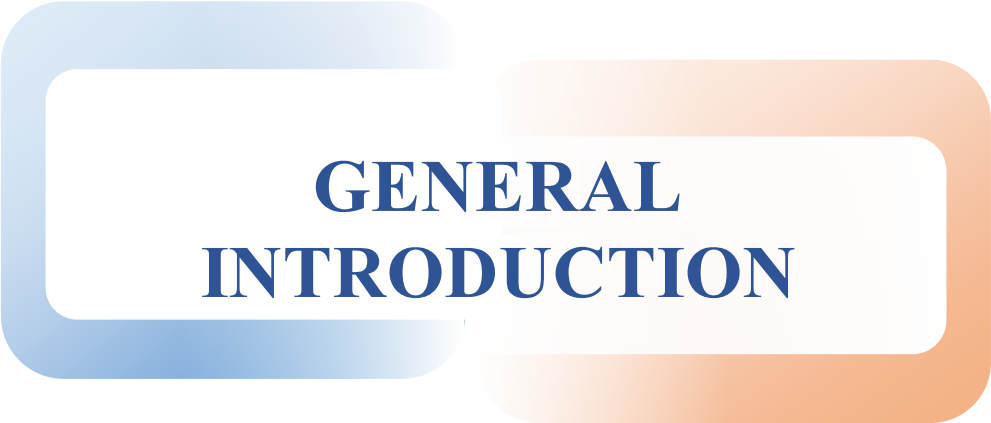
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## List of Abbreviations

| Abbreviation              | Definition                                                 |
|---------------------------|------------------------------------------------------------|
| <b>AChE</b>               | Acetylcholinesterase                                       |
| <b>ATRP</b>               | Atom Transfer Radical Polymerization                       |
| <b>C=N</b>                | Imine (azomethine) bond                                    |
| <b>COSY</b>               | Correlation Spectroscopy (NMR technique)                   |
| <b>DES</b>                | Deep Eutectic Solvent                                      |
| <b>DMSO</b>               | Dimethyl Sulfoxide                                         |
| <b>E-factor</b>           | Environmental factor (mass of waste per mass of product)   |
| <b>EE</b>                 | Enantiomeric Excess                                        |
| <b>FT-IR</b>              | Fourier-Transform Infrared Spectroscopy                    |
| <b>HMBC</b>               | Heteronuclear Multiple-Bond Correlation (NMR)              |
| <b>HOMO</b>               | Highest Occupied Molecular Orbital                         |
| <b>HSQC</b>               | Heteronuclear Single-Quantum Coherence (NMR)               |
| <b>IC<sub>50</sub></b>    | Half Maximal Inhibitory Concentration                      |
| <b>LUMO</b>               | Lowest Unoccupied Molecular Orbital                        |
| <b>MeOH</b>               | Methanol                                                   |
| <b>NMR</b>                | Nuclear Magnetic Resonance Spectroscopy                    |
| <b>pK<sub>a</sub></b>     | Acid Dissociation Constant (logarithmic scale)             |
| <b>ppm</b>                | Parts Per Million                                          |
| <b>R<sub>f</sub></b>      | Retention Factor (in TLC)                                  |
| <b>ROS</b>                | Reactive Oxygen Species                                    |
| <b>Salen</b>              | Salicylaldehyde-ethylenediamine Schiff base ligand         |
| <b>SB1</b>                | Schiff Base derived from 4-Aminophenol and Benzaldehyde    |
| <b>SB2</b>                | Schiff Base derived from 4-Aminophenol and Acetophenone    |
| <b>SB3</b>                | Schiff Base derived from Sulfanilamide and Benzaldehyde    |
| <b>TLC</b>                | Thin-Layer Chromatography                                  |
| <b>UV-Vis</b>             | Ultraviolet-Visible Spectroscopy                           |
| <b><sup>1</sup>H NMR</b>  | Proton Nuclear Magnetic Resonance Spectroscopy             |
| <b><sup>13</sup>C NMR</b> | Carbon-13 Nuclear Magnetic Resonance Spectroscopy          |
| <b>ε</b>                  | Molar Absorptivity (L mol <sup>-1</sup> cm <sup>-1</sup> ) |



# **GENERAL INTRODUCTION**

## GENERAL INTRODUCTION

Organic chemistry has always sought to develop new compounds with useful biological and chemical properties. Among the many families of compounds studied, azomethines also called Schiff bases hold an important place. These molecules are formed by a simple condensation reaction between a primary amine and a carbonyl compound (aldehyde or ketone), producing a characteristic imine bond (C=N) with elimination of water. They were first described by the German chemist Hugo Schiff in 1864, and since then they have been extensively studied due to their ease of synthesis and their wide range of properties.

Schiff bases are particularly interesting because their structure can be easily modified by changing the amine or carbonyl component, which allows researchers to tune their physical, chemical, and biological properties. They have been reported to show antibacterial, antifungal, anticancer, and anti-inflammatory activities, making them relevant candidates in the field of medicinal chemistry. They are also used in coordination chemistry, as they form stable complexes with metal ions, and in industrial applications such as dyes and corrosion inhibitors.

In the context of green chemistry, Schiff base synthesis is especially attractive because it produces only water as a by-product, uses simple and inexpensive reagents, and can be carried out in eco-friendly solvents such as ethanol under mild conditions. This makes it a suitable reaction for environmentally responsible laboratory work.

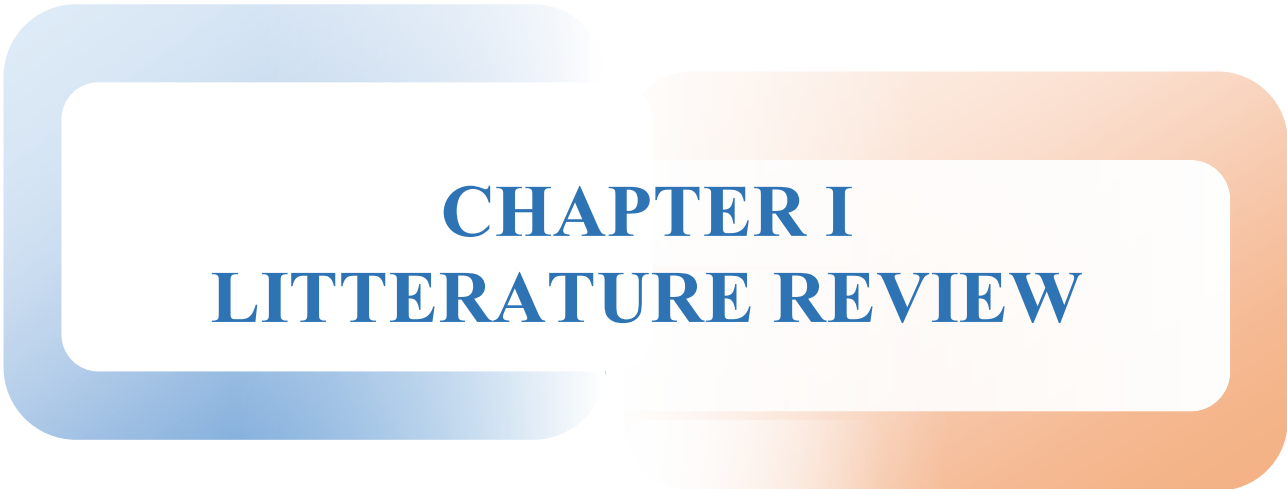
The focus of this dissertation is at the creation of azomethine products along with their chemical structure being identified. The organization of the paper is structured into three principal areas indicated by chapters.

**Chapter One:** This chapter contains an overview of what azomethines and their importance are within biological science literature.

**Chapter Two:** This chapter explains the experiments that were performed in order to do research associated with the previous chapter.

**Chapter Three:** This chapter contains a record of all the procedures performed, results obtained, and evidence of those results through NMR ( $^1\text{H}$ ,  $^{13}\text{C}$ ), infrared, and

ultraviolet analysis, as well as a theoretical study through Density Functional Theory (DFT).



# **CHAPTER I**

## **LITTERATURE REVIEW**

## I. General Overview of Azomethine Compounds

### 1.1. Definition and general structure

The general structure of azomethine compounds is represented by the formula  $R_1R_2C=NR_3$ , where  $R_1$  and  $R_2$  are hydrogen atoms, alkyl, or aryl groups derived from the carbonyl compound, and  $R_3$  is an alkyl or aryl substituent from the amine (Tidwell, 2008). The nature and electronic properties of these substituents profoundly influence reactivity, stability, spectroscopic properties, and biological activity (Qin et al., 2013). The C=N bond shows partial double-bond character due to resonance between the neutral form (C=N) and the zwitterionic form (C<sup>+</sup>-N<sup>-</sup>), with the relative contributions of each form depending on the electronic nature of the substituents (Przybylski et al., 2009).

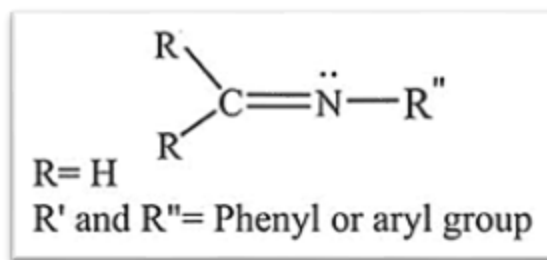


**Figure I.1** General structure of an azomethine compound (Schiff base).

The C=N double bond is planar, restricting rotation and leading to geometric (E/Z) isomerism when the substituents on the imine carbon are different. The E-isomer is generally thermodynamically favored due to reduced steric interactions, although the Z-isomer can be stabilized by intramolecular hydrogen bonding (Hadjoudis & Mavridis, 2004). The introduction of heteroatoms such as oxygen, sulfur, or nitrogen adjacent to the azomethine group generates multidentate ligands capable of forming stable chelate complexes with metal ions (Gupta & Sutar, 2008).

### 1.2. Historical development

The history of azomethine chemistry dates back to the pioneering work of Hugo Schiff (1864), who first reported the condensation of benzaldehyde with aniline to give a crystalline product accompanied by the elimination of water (Layer, 1963). subsequently provided a comprehensive review consolidating decades of research and establishing systematic nomenclature and reactivity patterns. The recognition of azomethines as effective chelating ligands emerged in the mid-twentieth century, Pfeiffer (Pfeiffer et al., 1933) described the first stable metal complexes, and Jacobsen (Jacobsen, 1994) later

demonstrated that chiral manganese-salen complexes could catalyze highly enantioselective epoxidation, establishing their central role in asymmetric catalysis.

Contemporary research has expanded beyond simple condensation products to include macrocyclic Schiff bases, polymeric azomethine materials, and hybrid structures that combine the imine motif with other functional groups (Brodowska & Łodyga-Chrścińska, 2019). The integration of computational methods has enabled the rational design of azomethine compounds with targeted properties, thereby accelerating the discovery of new derivatives for specific applications (Da Silva et al., 2011).

## I.2. Synthesis and Reaction Mechanisms

### I.2.1. Classical synthesis methods

The classical approach to Schiff base synthesis involves the direct condensation of primary amines with aldehydes or ketones in organic solvents such as ethanol, methanol, benzene, or toluene under reflux, often in the presence of an acid catalyst. The use of aromatic solvents facilitates azeotropic removal of the water formed, shifting the equilibrium toward product formation; a Dean–Stark apparatus or molecular sieves serve the same purpose (Tanaka & Toda, 2000). Solvent selection significantly influences reaction rate and yield: protic solvents stabilize intermediates through hydrogen bonding, while aprotic media generally afford cleaner reactions.

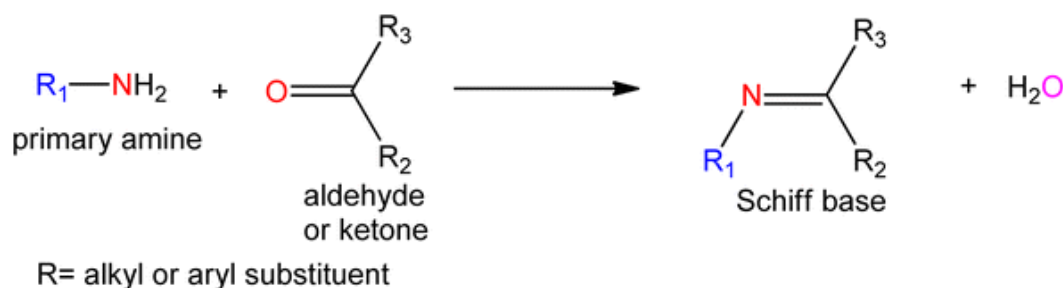


**Figure I.2** General equation for Schiff base synthesis.

Aromatic amines and aldehydes often condense without an added catalyst, whereas less reactive substrates particularly aliphatic ketones or sterically hindered amines require acid catalysis (Cordes & Jencks, 1962). Acid catalysts range from mineral acids (HCl, H<sub>2</sub>SO<sub>4</sub>) to mild organic acids (acetic acid, *p*-TsOH) and Lewis's acids (TiCl<sub>4</sub>, BF<sub>3</sub>·OEt<sub>2</sub>). Strong acids maximize catalytic activity but risk side reactions; mild organic acids provide greater selectivity for complex substrates (Vázquez et al., 1989). Macrocyclic azomethines

are accessible through template-directed condensations, where metal ions organize reactants for intramolecular ring closure (Vigato & Tamburini, 2004).

### I.2.2. Mechanistic pathways

The generally accepted mechanism for imine formation proceeds through a multistep sequence (Jencks, 1959). In the first step, the nucleophilic nitrogen atom of the primary amine attacks the electrophilic carbonyl carbon forming a tetrahedral carbinolamine intermediate, also known as hemiaminal. This step is reversible and depends on the nucleophilicity of the amine and the electrophilicity of the carbonyl compound, both of which are influenced by the electronic and steric nature of the substituents. The carbinolamine represents a critical species whose fate determines whether the reaction proceeds to imine formation or reverts to the starting materials. Under acidic conditions, protonation of the carbinolamine hydroxyl group facilitates its elimination as water, generating an iminium ion, which is subsequently deprotonated to yield the azomethine product. The dehydration step is generally rate-limiting for aromatic substrates under mildly acidic conditions, whereas carbinolamine formation may become rate-limiting at higher pH or with less reactive amines (Sayer et al., 1974) Figures I.3 and I.4.

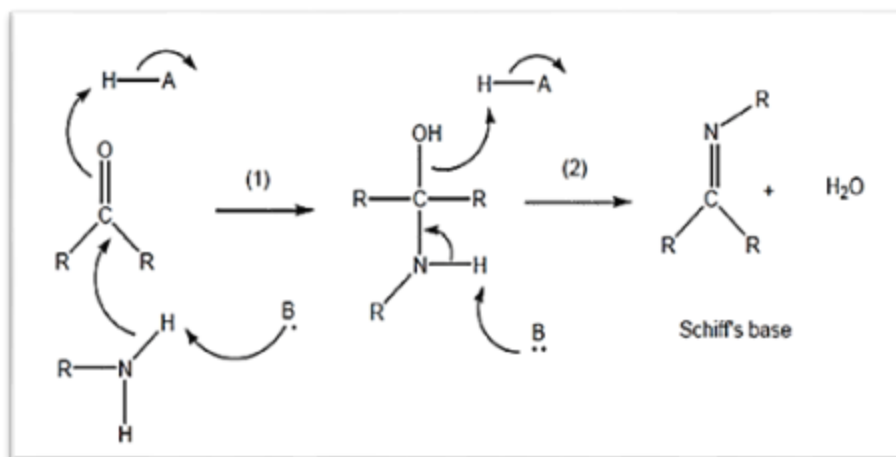


**Figure I.3** Mechanistic pathway for imine formation under acidic conditions.

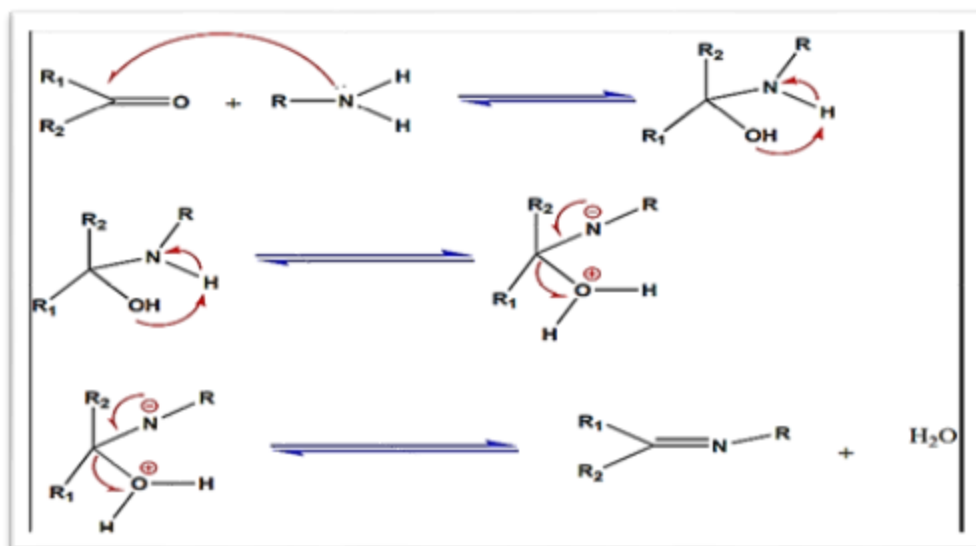


**Figure I.4** Mechanistic pathway for imine formation under basic conditions.

The pH dependence of Schiff base formation exhibits a bell-shaped profile, reflecting opposing mechanistic requirements. At very low pH, extensive protonation of the amine reduces its nucleophilicity; at very high pH, the lack of protons prevents efficient dehydration of the carbinolamine. Optimal pH typically falls within the range of 4-6 (Cordes & Jencks, 1962). The dehydration step is generally rate-limiting for aromatic substrates under mildly acidic conditions, whereas carbinolamine formation may become rate-limiting at higher pH or with less reactive amines (Sayer et al., 1974). The reversibility of imine formation particularly the susceptibility of the C=N bond to hydrolysis under acidic or basic conditions has important implications for stability and applications.

### I.3. Classification of Azomethines

#### I.3.1. Aldimines and ketimines

The most fundamental classification distinguishes aldimines ( $R-CH=N-R'$ ), which are derived from aldehydes, from ketimines ( $R_1R_2C=N-R'$ ), derived from ketones. Aldimines bear one hydrogen atom on the imine carbon, making them more reactive toward nucleophiles and susceptible to deprotonation ( $pK_a$  18–25) for C–C bond-forming transformations (Jones et al., 1985). Ketimines lack this acidic hydrogen and therefore exhibit greater resistance to hydrolysis due to steric protection of the electrophilic imine carbon. The synthesis of Ketimines is generally more demanding than aldimine synthesis, requiring elevated temperatures, stronger catalysts, or specialized dehydrating agents (Westheimer & Taguchi, 1971) Figures I.5 and Table I.1.

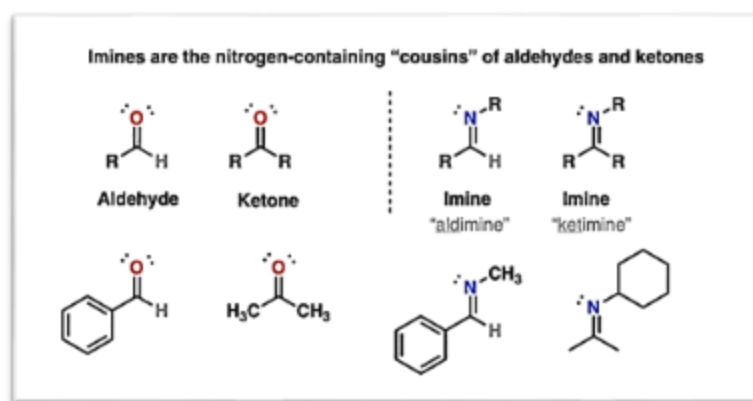


**Figure I.5** Structural comparison of aldimines and ketimines derived from aldehydes and ketones respectively.

**Table I.1** Comparison of aldimines and ketimines

| Feature                     | Aldimines                               | Ketimines                                          | Remarks                                                     |
|-----------------------------|-----------------------------------------|----------------------------------------------------|-------------------------------------------------------------|
| General structure           | $\text{R}-\text{CH}=\text{N}-\text{R}'$ | $\text{R}-\text{C}(\text{R}')=\text{N}-\text{R}''$ | Aldimines contain at least one hydrogen on the imine carbon |
| Origin (precursor carbonyl) | Derived from aldehydes                  | Derived from ketones                               | Formed by condensation with primary amines                  |
| Substituents on C=N carbon  | One alkyl/aryl group + one hydrogen     | Two alkyl/aryl groups                              | Structural difference                                       |
| Reactivity                  | More reactive                           | Less reactive                                      | Due to lower steric hindrance                               |
| Stability                   | Less stable                             | More stable                                        | Ketimines stabilized by two substituents                    |
| Steric hindrance            | Lower                                   | Higher                                             | Affects reaction rate                                       |

### I.3.2. Linear and cyclic azomethines

Linear azomethines of with the general formula  $\text{R}-\text{CH}=\text{N}-\text{R}'$  (Figure I.6) are subdivided into aliphatic ( $\text{R}$  and  $\text{R}' = \text{alkyl}$ ), aromatic ( $\text{R}$  and  $\text{R}' = \text{aryl}$ ), and mixed (one aryl and one alkyl) subclasses (Patai, 1970). Aliphatic aldimines exhibit higher basicity but lower stability than their aromatic analogues, which benefit from  $\pi$ -conjugation and resonance stabilization. Salicylaldimines, bearing an ortho-phenolic hydroxyl group, form intramolecular hydrogen bonds that confer additional stability and photochromic behavior (Hadjoudis & Mavridis, 2004). The degree of conjugation markedly affects electronic absorption, shifting UV-Vis maxima to longer wavelengths and intensifying color (Qin et al., 2013).

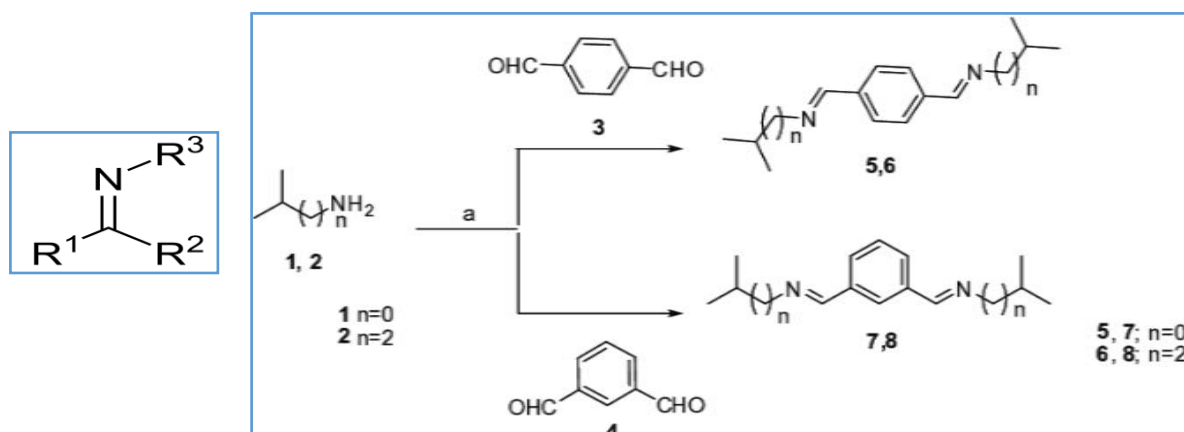


**Figure I.6** Representative linear azomethines: aliphatic, aromatic, and mixed subclasses.

Cyclic azomethines incorporate the imine nitrogen within a ring structure, introducing conformational constraints that strongly influence their chemical and biological properties (Stanovnik & Svete, 2004). Five-membered cyclic imines ( $\Delta^1$ -pyrrolines) and six-membered cyclic imines occur widely in natural products and pharmaceuticals. Macrocyclic azomethines, large rings of twelve or more atoms can bind metal ions cooperatively; their synthesis is greatly facilitated by template-directed condensation using metal ions as structural organizers (Vigato & Tamburini, 2004), (Busch, 1978). Salen-type ligands (Figure I.7), featuring two salicylaldehyde units bridged by a diamine linker, represent a critically important tetradentate subclass in asymmetric catalysis (Cozzi, 2004).

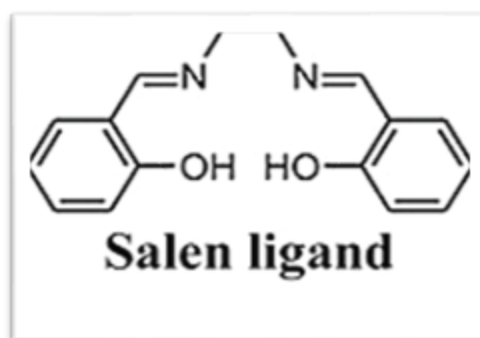


**Figure I.7** Representative cyclic azomethines including macrocyclic and Salen-type structures.

## I.4. Green Synthesis Approaches

### I.4.1. Principles of green chemistry

The conceptual framework of green chemistry, articulated through the twelve principles of Warner and Anastas (1998), provides a comprehensive foundation for designing environmentally responsible chemical processes. These principles emphasize waste prevention, atom economy, the use of safer reagents and solvents, energy efficiency, and exploitation of renewable feedstocks (Warner et al., 2004). Applied to azomethine synthesis, green chemistry motivates the development of reactions that minimize hazardous byproducts and energy consumption. The inherent simplicity of Schiff base condensation, producing only water as byproduct-means that theoretical atom economy can approach 100%, making azomethine synthesis particularly amenable to green approaches (Trost, 1991), (Sheldon, 2008).



**Figure I.8** The twelve principles of green chemistry

Practical implementation focuses on solvent replacement, catalyst optimization, and alternative energy sources. The E-factor (mass of waste per mass of product) and atom economy are the principal metrics used to evaluate environmental impact (Sheldon, 2008). Green synthesis approaches employ equimolar reactant ratios, catalytic rather than stoichiometric promoters, and activation methods that reduce both reaction time and energy demand (Clark & Macquarrie, 2007).

#### **I.4.2. Green solvents and solvent-free methods**

Solvent selection is critical in green chemistry, as solvents typically constitute the largest mass fraction in chemical processes and are major contributors to waste (Capello et al., 2007). Water represents the ultimate green solvent due to its non-toxicity, non-flammability, and abundance (Lidström et al., 2001). On water catalysis where reactions occur at the interface between insoluble organic reactants and the aqueous phase often provides rate enhancements relative to organic solvents (Narayan et al., 2005). Ethanol, producible from renewable biomass, provides a practical bio-based alternative for azomethine synthesis under mild conditions with excellent yields (Jessop, 2011), (Nagar et al., 2023). Deep eutectic solvents (DES), formed by mixing hydrogen bond donors and acceptors such as choline chloride/urea, offer a biodegradable alternative to ionic liquids at lower cost (Abbott et al., 2003).

Solvent-free synthesis eliminates all issues of solvent toxicity and disposal. Neat reactions between liquid reactants, mechanochemical grinding (ball-milling) of solid reactants, and microwave or ultrasound activation of solid mixtures all represent viable solvent-free approaches (Tanaka & Toda, 2000), (Rothenberg et al., 2001). Mechanochemistry, in particular, has demonstrated quantitative yields for azomethine synthesis in short reaction times and is readily scalable (James et al., 2012), (Rodríguez et al., 2007).

#### **I.4.3. Energy-efficient techniques**

Microwave-assisted synthesis achieves rapid, uniform heating through the direct interaction of electromagnetic radiation with polar molecules, eliminating thermal gradients characteristic of conventional conductive heating. For azomethine synthesis, microwave irradiation typically reduces reaction times from hours to minutes while maintaining or improving yields and product purity, particularly when combined with solvent-free conditions (Nagar et al., 2023).

Ultrasound-assisted synthesis exploits acoustic cavitation the formation, growth, and implosion of bubbles under ultrasonic irradiation which generates extreme local temperatures and pressures (Mason & Lorimer, 2003), (Suslick, 1990). Azomethine synthesis under ultrasound typically proceeds within 15–60 min with improved yields compared to reflux methods. Combining ultrasound with environmentally benign solvents

such as water or ethanol offers a particularly attractive green approach (Al Zoubi et al., 2016). Table I.2 summarizes the main green synthesis methods for azomethines.

**Table I.2** Comparison of green synthesis methods for azomethine compounds

| Green synthesis method                 | Reaction medium / catalyst                            | Conditions                               | Main advantages                                                         |
|----------------------------------------|-------------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------|
| Solvent-free grinding                  | No solvent, mechanical mixing of aldehyde and amine   | Room temperature, mortar–pestle grinding | Simple, low cost, no solvent waste, short reaction time                 |
| Microwave-assisted synthesis           | Often solvent-free or green solvents (ethanol, water) | Microwave irradiation, few minutes       | Very fast reaction, high yield, energy efficient                        |
| Ultrasound-assisted synthesis          | Ethanol or water as solvent                           | Ultrasonic irradiation, mild temperature | Accelerates reaction, improves yield, reduces reaction time             |
| Aqueous medium synthesis               | Water as green solvent, sometimes acid catalyst       | Mild temperature (25–80 °C)              | Non-toxic solvent, environmentally friendly, easy work-up               |
| Ionic liquids / Deep eutectic solvents | Ionic liquid or DES as solvent and catalyst           | Mild heating (50–100 °C)                 | Recyclable medium, high selectivity, reduced volatile organic compounds |

## I.5. Spectroscopic Characterization Techniques

Spectroscopic characterization plays a pivotal role in confirming the structure, purity, and properties of azomethine compounds. The distinctive C=N double bond and conjugated systems produce characteristic signals in UV-Vis, FT-IR, and NMR spectroscopy, with each technique providing complementary information (Silverstein et al., 2015), (Pavia et al., 2014).

### I.5.1. UV–Visible spectroscopy

UV-Vis spectroscopy characterizes the electronic transitions of the imine chromophore in the 200–800 nm range (Figure I.9). Two transitions are diagnostic for azomethines (Silverstein et al., 2015). The  $\pi \rightarrow \pi^*$  transition, arising from the promotion of a bonding  $\pi$  electron of the C=N bond to the  $\pi^*$  antibonding orbital, typically appears at 220–250 nm for simple aliphatic imines with high molar absorptivity ( $\epsilon > 10,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ ). The weaker  $n \rightarrow \pi^*$  transition ( $\epsilon < 1,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ ), involving promotion of a nitrogen lone pair to  $\pi^*$ , occurs at 250–350 nm.

Extended conjugation with aromatic substituents shifts absorption maxima bathochromically; aromatic aldimines typically show strong conjugated  $\pi \rightarrow \pi^*$  bands at 280–350 nm (Da Silva et al., 2011). Electron-donating substituents ( $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{NH}_2$ ) raise the HOMO energy and reduce the HOMO-LUMO gap, causing red shifts, while electron-withdrawing groups ( $-\text{NO}_2$ ,  $-\text{CN}$ ) lower the LUMO energy (Skoog et al., 2017). Salicylaldimines exhibit particularly complex UV-Vis behavior due to enol-imine/keto-amine tautomeric equilibria, manifesting in photochromic and thermochromic phenomena.

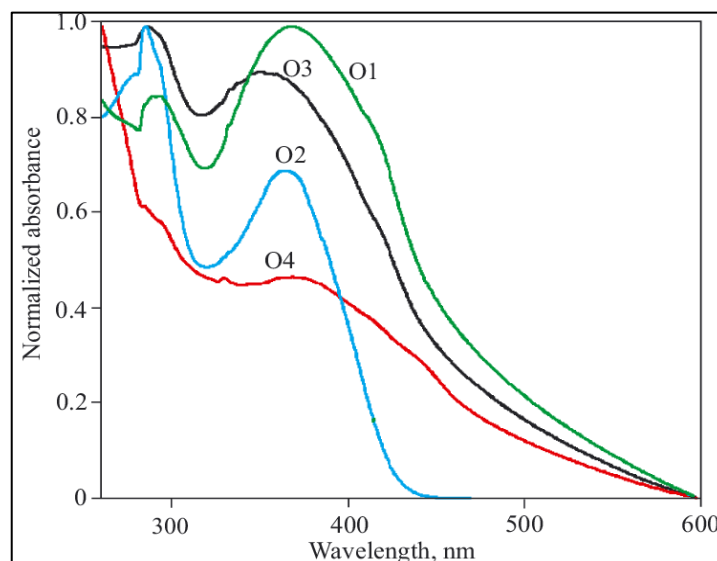


**Figure I.9** UV-Visible absorption spectra of azomethine compounds.

### I.5.2. FT-IR spectroscopy

FT-IR spectroscopy (Figure I.10) identifies functional groups through their characteristic vibrational frequencies. The most diagnostic feature in azomethine spectra is the imine  $\text{C}=\text{N}$  stretching vibration, appearing as a medium-to-strong band at 1630–1690  $\text{cm}^{-1}$  (Silverstein et al., 2015), (Socrates, 2001). Aromatic azomethines absorb at lower frequencies (1620–1650  $\text{cm}^{-1}$ ) due to resonance delocalization, while aliphatic derivatives absorb at higher frequencies (1660–1690  $\text{cm}^{-1}$ ) reflecting greater double bond character.

Confirmation of successful Schiff base formation relies on the disappearance of starting material bands: the  $\text{C}=\text{O}$  stretch of the aldehyde or ketone (1705–1740  $\text{cm}^{-1}$ ) and the twin  $\text{N}-\text{H}$  stretching bands of the primary amine (3300–3500  $\text{cm}^{-1}$ ). Aromatic  $\text{C}-\text{H}$  stretching appears above 3000  $\text{cm}^{-1}$  while aliphatic  $\text{C}-\text{H}$  stretching falls below 3000  $\text{cm}^{-1}$  (Stuart, 2004). Salicylaldimines exhibit a broad  $\text{O}-\text{H}$  stretch at 2500–3300  $\text{cm}^{-1}$  from strong

intramolecular hydrogen bonding. The fingerprint region ( $400\text{--}1500\text{ cm}^{-1}$ ) is unique to each compound and serves as confirmation of identity.

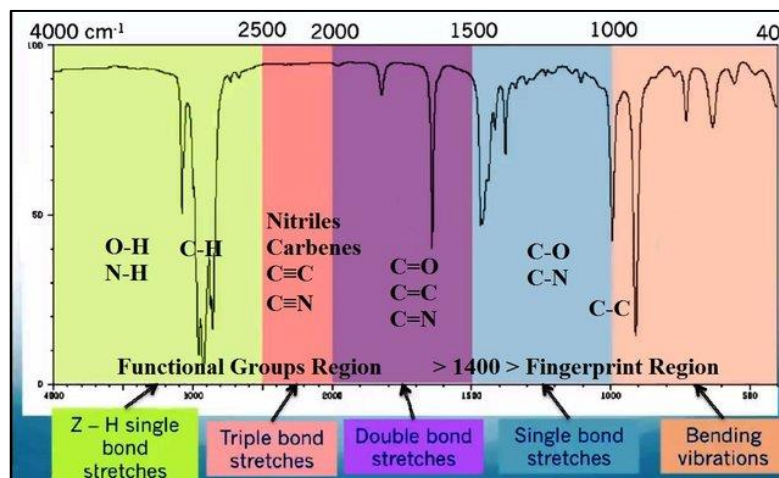


**Figure I.10** FT-IR Spectrum Regions and Characteristic Functional Group Vibrations.

### I.5.3. NMR spectroscopy

Nuclear magnetic resonance spectroscopy NMR is the most powerful technique for comprehensive structural characterization of azomethines. The most diagnostic  $^1\text{H}$  NMR signal is the imine proton ( $\text{HC}=\text{N}$ ), appearing as a singlet at  $\delta$  7.5–8.5 ppm for aromatic aldimines, reflecting deshielding by the electronegative nitrogen and  $\text{sp}^2$  hybridization of the carbon (Pavia et al., 2014), (Kemp, 1991). Integration of this signal to exactly one proton confirms an aldimine structure. Aromatic protons appear at  $\delta$  6.5–8.5 ppm, with coupling constants providing substitution information ( $^3J = 6\text{--}10\text{ Hz}$  ortho;  $^4J = 1\text{--}3\text{ Hz}$  meta). Salicylaldimines exhibit a broad downfield O–H signal at  $\delta$  12–16 ppm due to strong hydrogen bonding.

In  $^{13}\text{C}$  NMR, the imine carbon ( $\text{C}=\text{N}$ ) resonates at  $\delta$  150–170 ppm for aromatic azomethines and  $\delta$  140–160 ppm for aliphatic derivatives, while the disappearance of the carbonyl carbon from starting materials ( $\delta$  190–210 ppm) confirms complete conversion (Pavia et al., 2014; Silverstein et al., 2015). Two-dimensional NMR techniques COSY ( $^1\text{H}\text{--}^1\text{H}$  couplings), HSQC (direct  $^1\text{H}\text{--}^{13}\text{C}$  correlations), and HMBC (long-range  $^1\text{H}\text{--}^{13}\text{C}$  couplings) enable unambiguous assignment of all signals in complex azomethines (Hadjoudis & Mavridis, 2004), (Claridge, 2016).

## **I.6. Applications of Azomethine Compounds**

### **I.6.1. Coordination chemistry and catalysis**

The coordination chemistry of azomethines represents one of their most extensively studied application areas, with Schiff base ligands forming stable complexes with virtually all transition metals (Vigato & Tamburini, 2004). The imine nitrogen provides a strong donor site, while additional heteroatoms in the ligand framework enable chelate complexes with enhanced thermodynamic stability (Gupta & Sutar, 2008). The geometric and electronic properties of metal–azomethine complexes can be systematically tuned through substituent variation, enabling precise control over reactivity and selectivity (Cozzi, 2004).

Salen-type ligands, featuring two salicylaldehyde units bridged by a diamine linker, are privileged scaffolds in asymmetric catalysis (Alyar et al., 2022). Metal-salen complexes of manganese, chromium, cobalt, and titanium catalyze asymmetric epoxidation, kinetic resolution of epoxides, CO<sub>2</sub>–epoxide copolymerization, and conjugate additions. Jacobsen's manganese-salen catalyst achieves highly enantioselective epoxidation of cis-disubstituted and trisubstituted olefins with enantiomeric excess (EE) values exceeding 90% (Jacobsen, 1994). Beyond asymmetric catalysis, copper-azomethine complexes catalyze atom transfer radical polymerization (ATRP), and nickel and palladium complexes facilitate cross-coupling and olefin oligomerization (Gupta & Sutar, 2008).

### **I.6.2. Biological and medicinal applications**

Azomethine compounds exhibit a diverse spectrum of biological activities including antibacterial, antifungal, antiparasitic, anticancer, anti-inflammatory, antioxidant, and analgesic effects (Przybylski et al., 2009), (Kajal et al., 2013). The C=N group serves as a pharmacophore in numerous bioactive molecules, participating in reversible covalent interactions with biological targets and facilitating metal chelation within biological systems. Antibacterial activity arises from inhibition of cell wall synthesis, membrane disruption, interference with nucleic acid synthesis, and chelation of metal ions essential for microbial enzymes. Metal complexes of azomethines frequently exhibit enhanced biological activity compared to the free ligands (Vigato & Tamburini, 2004).

Anticancer activity is observed for numerous azomethine derivatives against various cancer cell lines through DNA intercalation, topoisomerase inhibition, apoptosis

induction, and reactive oxygen species generation (Emam et al., 2020). The reversibility of imine bond formation enables some azomethines to act as prodrugs, releasing active compounds under specific physiological conditions. Incorporation of heterocyclic rings such as quinoline, pyridine, or thiazole often enhances biological activity through improved membrane permeability and specific enzyme interactions.

Recent comprehensive reviews covering the period 2018–2023 have further documented the breadth of biological activity exhibited by Schiff base metal complexes (Emam et al., 2020). A key structural feature underlying these activities is the azomethine ( $-C=N-$ ) moiety, which bears an electron-deficient carbon and an electron-rich nitrogen, enabling diverse electrophilic and nucleophilic interactions at both centers and facilitating the mechanism of transamination and racemization in biological systems. This electronic duality, combined with the capacity to coordinate transition metals, makes Schiff bases among the most versatile pharmacophores available for drug design.

With respect to antibacterial activity, Schiff base metal complexes consistently outperform their free ligand counterparts. Copper(II) complexes have shown particularly strong antibacterial profiles; for instance, a cellulose-based Schiff base–Cu(II) complex demonstrated marked activity against both *Escherichia coli* and *Staphylococcus aureus*, with the complexation itself being responsible for the enhancement since the uncomplexed cellulose fiber was inactive (Emam et al., 2020). Among zinc complexes, a 5-((3,4-dimethoxybenzylidene)amino)-4H-1,2,4-triazole-3-thiol Zn(II) complex exhibited the broadest antibacterial spectrum against nine food pathogens compared to its Co(II), Cu(II), and Ni(II) analogues, while additionally displaying strong antioxidant capacity and superior  $\alpha$ -amylase inhibitory effects relative to the therapeutic standard acarbose. These observations illustrate how metal identity profoundly modulates the bioactivity profile of otherwise structurally similar complexes.

Antifungal studies have provided equally compelling evidence for structure–activity relationships in this compound class. Cobalt(III) Schiff base complexes have been reported to display broad-spectrum antifungal activity against *Candida* and *Cryptococcus* yeasts in the micro- to nanomolar range, with no cytotoxicity toward bacterial or human cells and acceptable tolerability in in vivo models (Chandra & Gupta, 2020). Zinc(II) complexes of thiosemicarbazone ligands similarly exhibited high antifungal activity against *Candida tropicalis* and *Candida glabrata*, with molecular docking studies on the sterol 14 $\alpha$ -demethylase (CYP51) enzyme providing a plausible mechanistic rationale for

the observed inhibition. A general trend noted across studies is that chelation to a metal center increases antifungal potency relative to the free ligand, attributed to the reduction in metal polarity upon complexation, which enhances lipophilicity and thus membrane penetration.

The anticancer potential of metal-coordinated Schiff bases has been reinforced by recent *in vitro* and *in silico* investigations. A copper(II)-coordinated Schiff base complex was found to suppress growth in SGC-7901 and BGC-823 gastric cancer cell lines with an  $IC_{50}$  of 1  $\mu$ M, substantially lower than the 2.5–50  $\mu$ M range typical of cisplatin, with the mechanism involving NF- $\kappa$ B inhibition, reactive oxygen species generation, and autophagy induction (Alyar et al., 2022). Palladium (II) and platinum(II) complexes derived from Schiff base ligands have also shown cytotoxicity against HeLa, MCF-7, and HCT116 cell lines, with  $IC_{50}$  values comparing favorably with carboplatin and doxorubicin in several cases. These results underscore the growing interest in Schiff base metal complexes as alternatives or adjuncts to conventional platinum-based chemotherapy.

### **1.6.3. Industrial and materials applications**

In materials science, azomethines serve as components of polymers, dyes, pigments, liquid crystals, sensors, and corrosion inhibitors (Hamada & Aboul-Enein, 2015). Polyazomethines, with imine linkages in the polymer backbone, display excellent thermal stability and semiconducting properties useful in organic electronics and photovoltaics (Sarwade et al., 1988), (Wang et al., 1996). Azomethine dyes and pigments exploit the extended conjugation of the imine chromophore for vivid colors with good fastness; photochromic and thermochromic azomethines find applications in smart materials and security printing (Hadjoudis & Mavridis, 2004).

Azomethines group as effective corrosion inhibitors for metals in acidic and neutral environments, adsorbing onto metal surfaces through the imine nitrogen to form protective films (Hamada & Aboul-Enein, 2015). In analytical chemistry, azomethines serve as chromogenic and fluorogenic reagents for metal ion detection, with formation of colored complexes enabling spectrophotometric determination, and fluorescence-based sensors applicable to environmental monitoring and biological imaging (Valeur, 2000).

## I. 7. Conclusion

This literature review has provided a systematic survey of azomethine compounds, from their foundational definition and historical development to state-of-the-art synthetic and characterization methods. Schiff bases are structurally versatile molecules whose properties can be tailored through judicious selection of amine and carbonyl precursors. Classical synthesis methods, while reliable, are increasingly complemented by green approaches aqueous media, bio-based solvents, microwave and ultrasound activation, and mechanochemistry that align with the principles of sustainability without compromising efficiency.

Spectroscopic characterization by UV-Vis, FT-IR, and NMR provides unambiguous structural elucidation through the complementary information each technique affords. The broad applications of azomethines in coordination chemistry, catalysis, medicinal chemistry, and advanced materials underscore their enduring importance across multiple scientific disciplines. The bibliographic framework established here provides the conceptual foundation for the green synthesis protocols and spectroscopic analyses that will be presented in [Chapters II](#) and [III](#).



**CHAPTER II**

**Materials and methods**

## II. Experimental Techniques

This chapter describes the experimental procedures employed in the synthesis and characterization of three Schiff base derivatives (**SB1–SB3**). The first section presents the analytical techniques used to identify and confirm the structures of the synthesized compounds, namely Thin-Layer Chromatography (TLC), UV–Visible spectroscopy, Infrared spectroscopy (FT-IR), and Nuclear Magnetic Resonance (NMR) spectroscopy. The second section details the reagents and general condensation protocol.

### II. 1. Thin-Layer Chromatography (TLC)

#### II.1.1. Definition and Principle

Thin-layer chromatography (TLC) was carried out on aluminum plates coated with silica gel 60 F<sub>254</sub>. The plates were developed in glass chambers saturated with the appropriate eluent, consisting of a binary solvent mixture.

Chromatography is a physical separation technique based on the different affinities of compounds toward two phases: a stationary phase (silica gel) and a mobile phase (solvent). The sample components are adsorbed onto the stationary phase and transported by the mobile phase, migrating at different rates depending on their polarity ([Layer, 1963](#)).

#### II.1.2. Instrumentation

- Glass development tank.
- Stationary phase: aluminum plates coated with silica gel 60 F<sub>254</sub>.
- Mobile phase: chloroform/methanol mixture (9:1).
- UV lamp (254 nm) for spot visualization.

Thin-layer chromatography (TLC) separates the constituents of a mixture through the migration of a mobile phase over a stationary phase by adsorption and partition phenomena. The spots are visualized under UV light at 254 nm [Figure II.1](#).

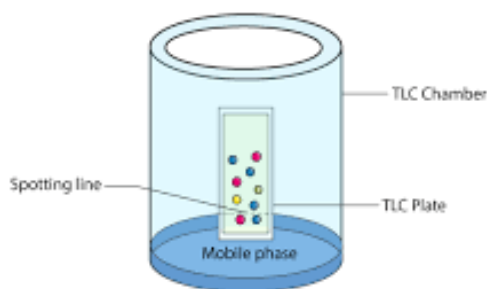


**Figure II.1** Thin-layer chromatography (TLC) setup.

**Retention factor (Rf):** Each compound is characterized for a given system by:

$$Rf = \frac{\text{distance travelled by the compound } (h)}{\text{distance travelled by the eluent } (H)}$$

The Rf value is a dimensionless number between 0 and 1. The reaction is considered complete when the spot corresponding to the starting amine disappears and a single new spot with a distinct Rf value is observed.

## II.2. UV-Visible Spectroscopy

UV–Visible spectroscopy is based on the ability of molecules to absorb electromagnetic radiation at specific wavelengths in the ultraviolet and visible regions. It is primarily used for quantitative analysis (Pretsch et al., 2009).

Domain and principle: The UV–visible region extends approximately from 800 to 10 nm (visible region: 800–400 nm; near-ultraviolet region: 400–200 nm). In organic molecules, UV–visible absorption involves energies ranging from 13,000 to 50,000 cm<sup>-1</sup>, inducing electronic transitions between different molecular energy levels rather than bond cleavage Figure II.2.

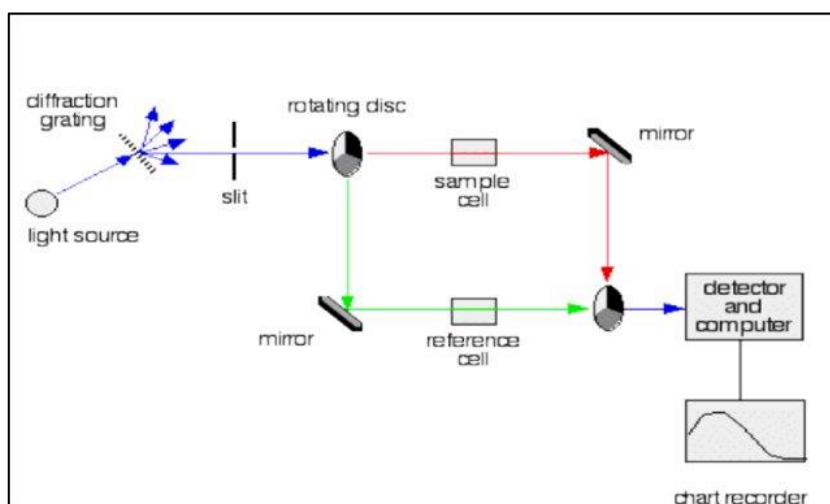


**Figure II.2** Schematic diagram of a double-beam UV-Visible spectrophotometer.

Quantitative absorption measurements are described by the Beer–Lambert law:

$$A = \log \left( \frac{I_0}{I} \right) = \epsilon \times C \times l$$

Where:

- **A**: absorbance.
- **I<sub>0</sub>** and **I**: intensities of the incident and transmitted light, respectively.
- **ε**: molar extinction coefficient ( $\text{L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ ).
- **C**: molar concentration of the solution ( $\text{mol} \cdot \text{L}^{-1}$ ).
- **l**: optical path length of the cell (usually 1 cm).

For the synthesized Schiff bases, UV–Visible spectra were recorded in absolute ethanol ( $c \approx 10^{-4} \text{ mol} \cdot \text{L}^{-1}$ ) over the range 200–500 nm. Two characteristic electronic transitions are expected :

- $\pi \rightarrow \pi^*$  transition at  $\lambda \approx 220\text{--}260 \text{ nm}$  (high intensity,  $\epsilon > 10,000 \text{ L} \cdot \text{mol}^{-1} \cdot \text{cm}^{-1}$ ), attributed to the conjugated aromatic system and the C=N bond.
- $n \rightarrow \pi^*$  transition at  $\lambda \approx 310\text{--}380 \text{ nm}$  (lower intensity), attributed to the lone pair of the imine nitrogen. This band constitutes a diagnostic marker of the azomethine function.

### II.3. Infrared Spectroscopy (FT-IR)

Infrared (IR) spectroscopy measures the amount of light absorbed by a compound as a function of wavelength. It is a non-destructive technique used to identify functional groups through their characteristic vibrational modes (Pretsch et al., 2009), (Silverstein et al., 2015) Figure II.3.

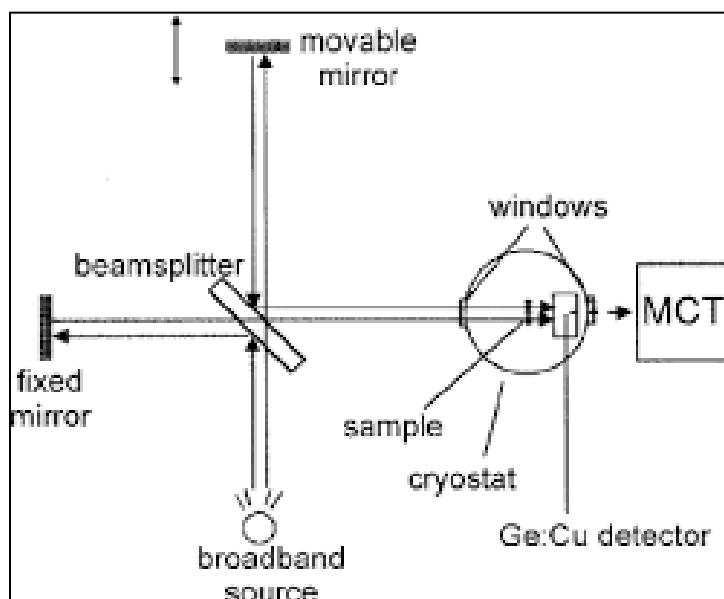


**Figure II.3** Schematic diagram of an FT-IR spectrophotometer (Michelson interferometer).

### II.3.1 Principle

When a molecule absorbs infrared radiation, its bonds vibrate through stretching (symmetric and asymmetric) and bending modes. Each functional group absorbs at characteristic wavenumbers, enabling the identification of the chemical functions present (Pretsch et al., 2009), (Golea et al., 2023), (Derardja, 2023).

For the synthesized Schiff bases, FT-IR analysis confirms the appearance of the C=N (azomethine) stretching band in the region  $1620\text{--}1690\text{ cm}^{-1}$ , which is the principal diagnostic signal indicating imine formation.

The disappearance of the C=O stretching band of the starting aldehyde or ketone ( $1700\text{--}1740\text{ cm}^{-1}$ ) confirms the complete conversion of the carbonyl compound.

- The reduction or disappearance of the primary amine N–H stretching bands ( $3300\text{--}3500\text{ cm}^{-1}$ , doublet) confirms the consumption of the amine group.

### II.4 Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) spectroscopy determines molecular structure by measuring the interaction between the natural magnetic moment of nuclei and an external magnetic field. The Larmor frequency, which governs this interaction, depends on the type of nucleus (e.g.,  $^1\text{H}$ ,  $^{13}\text{C}$ ) and its chemical environment, including neighboring atoms and the electron density involved in chemical bonding Figure II.4.

This dependence allows structural differentiation within a molecule: for example, a methyl proton resonates at a different frequency than an aldehydic or aromatic proton. The chemical shift ( $\delta$ , expressed in ppm), referenced to tetramethylsilane (TMS,  $\delta = 0.00\text{ ppm}$ ), provides detailed information about the molecular structure and electronic environment (Chebaki et al., 2025).

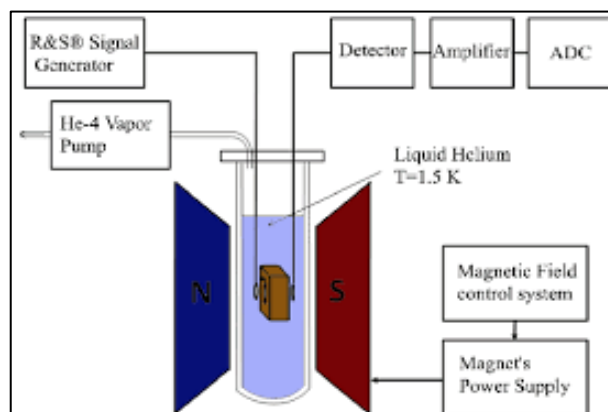


**Figure II.4** Schematic diagram of a continuous-wave NMR spectrometer

For solution-state NMR, the sample (8–30 mg) is dissolved in deuterated solvents such as DMSO- $d_6$  or  $CDCl_3$  and placed in a rotating glass tube at the center of the radiofrequency coil. A radiofrequency pulse is then applied, and the resulting oscillatory response is recorded (Gup & Külçü, 2007), (Clayden et al., 2012).

- The azomethine proton ( $=CH-N$ ) appears as a singlet at  $\delta$  8.0–8.5 ppm for aldimines, representing the most diagnostic signal confirming imine formation (integration = 1H).
- For ketimines, the absence of the azomethine proton is observed; instead, a methyl singlet ( $-CH_3$ ) appears at  $\delta$  ~2.2 ppm, characteristic of the ketimine  $C=N$  environment.
- Aromatic protons resonate in the  $\delta$  6.5–8.0 ppm region, with coupling constants  $^3J = 6$ –10 Hz (ortho) and  $^4J = 1$ –3 Hz (meta).
- The disappearance of primary amine N–H signals ( $\delta$  4.5–6.0 ppm) and the aldehydic proton signal ( $\delta$  ~10.0 ppm) confirms the completion of the condensation reaction.

## II.5 Synthesis

### II.5.1 Reagents Used

The reagents used for the synthesis are listed in Table II.1.

**Table II.1** List of reagents used for the synthesis of SB1–SB3

| Reagent             | Formula                                                       | State  | Density<br>(g/cm <sup>3</sup> ) | MW<br>(g/mol) | Purity | Quantity |
|---------------------|---------------------------------------------------------------|--------|---------------------------------|---------------|--------|----------|
| Benzaldehyde        | C <sub>7</sub> H <sub>6</sub> O                               | Liquid | 1.04                            | 106.12        | ≥99%   | 50 mL    |
| Acetophenone        | C <sub>8</sub> H <sub>8</sub> O                               | Liquid | 1.03                            | 120.15        | ≥99%   | 50 mL    |
| 4-Aminophenol       | C <sub>6</sub> H <sub>7</sub> NO                              | Solid  | 1.29                            | 109.13        | ≥98%   | 20 g     |
| Sulfanilamide       | C <sub>6</sub> H <sub>8</sub> N <sub>2</sub> O <sub>2</sub> S | Solid  | 1.08                            | 172.20        | ≥98%   | 25 g     |
| Glacial acetic acid | CH <sub>3</sub> COOH                                          | Liquid | 1.05                            | 60.05         | ≥99.7% | 10 mL    |
| Absolute ethanol    | C <sub>2</sub> H <sub>5</sub> OH                              | Liquid | 0.79                            | 46.07         | ≥99.8% | 200      |

## II.6 Experimental Setup

### II.6.1. Synthesis of Azomethine Derivatives (SB-1 to SB-3)

Schiff bases are obtained by the condensation of a primary amine with a carbonyl compound (aldehyde or ketone) in the presence of an acid catalyst, with elimination of water and formation of an imine bond ( $C=N$ ) (Gup & Külçü, 2007), (Clayden et al., 2012). Three compounds were synthesized in this work:

**SB1:** 4-Aminophenol + Benzaldehyde.

**SB2:** 4-Aminophenol + Acetophenone.

**SB3:** Sulfanilamide + Acetophenone.

### II.6.2. General Operating Procedure

The same general protocol (Figure II.5) was applied to all three syntheses (SB1-SB3); only the conditions specific to each compound differ (see below) :

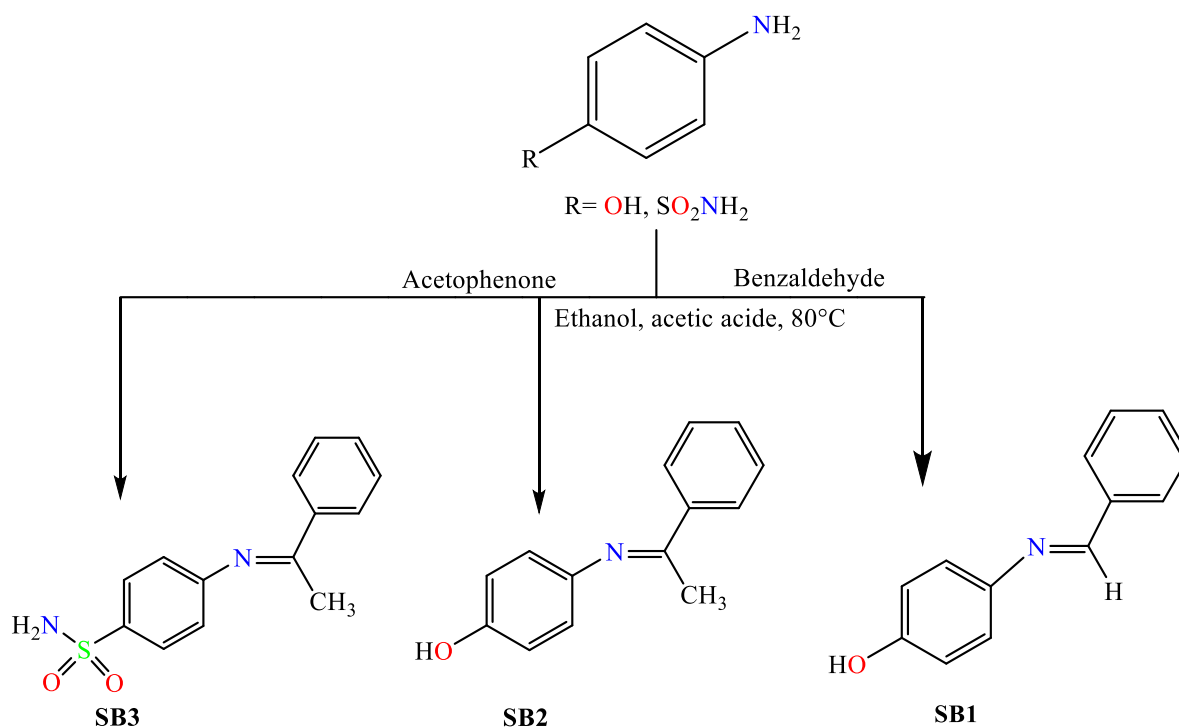
- The amine component was dissolved in 20 mL of absolute ethanol under magnetic stirring.
- The carbonyl compound (in equimolar proportion) was added, followed by a few drops of glacial acetic acid as catalyst.
- The mixture was heated under reflux ( $\sim 78^\circ\text{C}$ ) with continuous magnetic stirring.
- The reaction progress was monitored by TLC ( $5\times 8$  cm plates;  $\text{CHCl}_3/\text{MeOH}$  9:1) every 30 minutes until the disappearance of the starting amine spot.
- The reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with a water/methanol mixture, and dried to constant mass.



**Figure II.5** Different stages in the synthesis of Schiff bases (SB1-SB3)

The [Scheme II.1](#) illustrates the synthesis of Schiff bases through condensation reactions between primary aromatic amines and carbonyl compounds in ethanol under acidic reflux conditions (80 °C). In the first pathway, 4-aminophenol reacts with benzaldehyde or acetophenone in the presence of acetic acid to produce the Schiff bases **SB1** and **SB2**, respectively. The amino group ( $-\text{NH}_2$ ) of 4-aminophenol attacks the electrophilic carbonyl carbon of the aldehyde or ketone, followed by elimination of a water molecule, leading to the formation of the characteristic imine bond ( $\text{C}=\text{N}$ ), highlighted in the scheme.

In the second pathway, sulfanilamide reacts with acetophenone under the same experimental conditions to form **SB3**. The condensation occurs selectively at the aromatic amino group because the sulfonamide nitrogen is deactivated by the electron-withdrawing  $-\text{SO}_2-$  group, making it less nucleophilic. The acidic medium and heating under reflux accelerate the condensation process and improve the formation of the Schiff base products.



**Scheme II.1** General scheme for the synthesis of Schiff bases.

Condensation of sulfanilamide **SB3** takes place mainly on the free aromatic amine group when compared to sulfonamide group. The sulfonamide group ( $-\text{SO}_2\text{NH}_2$ ) is a very strong electron-withdrawing group which causes the electron density of the sulfonamide nitrogen's lone pair to be lower via both inductive and resonance effects. This reduced electron density makes the sulfonamide much less nucleophilic as compared to the aromatic

amine group which retains enough electron density to attack the electrophilic carbon of an aldehyde or ketone and form an imine bond (C=N) typical of Schiff bases. For this reason, condensation occurs selectively at the free aromatic amine group.

## **II.7. Conclusion**

This chapter summarises the experimental processes used to create and analyse the three Schiff base derivatives (**SB1** to **SB3**). A similar condensation technique was selected for all samples of Schiff bases ; but each individual Schiff base's molar ratios, reaction times and isolation processes were reported separately. Three analytical techniques were used to identify the structures of the Schiff bases: FT-IR, UV-visible spectroscopy and <sup>1</sup>H NMR spectroscopy. The actual reaction of condensation occurs primarily at the free aromatic amine group (-NH<sub>2</sub>) of sulfanilamide because it has greater nucleophilicity than that of the sulphonamide group (-SO<sub>2</sub>NH<sub>2</sub>); thus, it is the most efficient site of reaction. The -SO<sub>2</sub> moiety is an electron-withdrawing substituent, which reduces the reactivity of the sulphonamide nitrogen; however, the aromatic amine can still react with sulfanilamide to give rise to the characteristic imine (C=N) bond of Schiff bases. Therefore, the electronic effect discussed above allows for the regioselectivity of the reaction and ultimately facilitates the successful production of all three Schiff base derivatives.



**CHAPTER III**

**Results and discussion**

### III.1 Introduction

Schiff bases are very important structures in synthetic organic chemistry and are generally characterized by the presence of an imine group ( $-N=CH-$ ), which helps to clarify the mechanism, racemization, and transamination interactions in biological systems. These compounds play an important role in medicinal fields because of their broad spectrum of biological and pharmacological activities. Many of them exhibit antibacterial, antifungal, and antitumor effects as biologically active molecules.

In our work, we describe a highly efficient synthetic method for the preparation of Schiff bases (SBs). To ensure the efficiency of the synthetic methods, carbonyl compounds must be highly electrophilic, and amines must be strongly nucleophilic (Chebaki et al, 2025).

A Schiff base is formed when an aldehyde or ketone reacts with an amine under acidic or basic catalysis, or upon heating with the elimination of water. Due to the presence of effective conjugation, aromatic aldehydes form more stable Schiff bases compared to aliphatic aldehydes (Figure III.1).

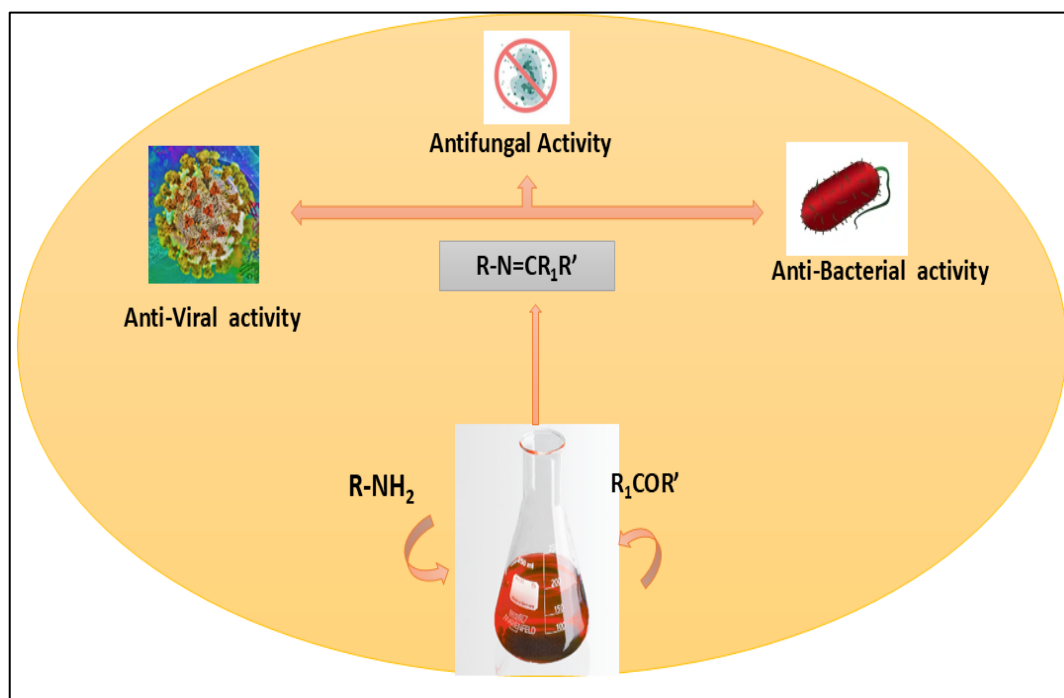
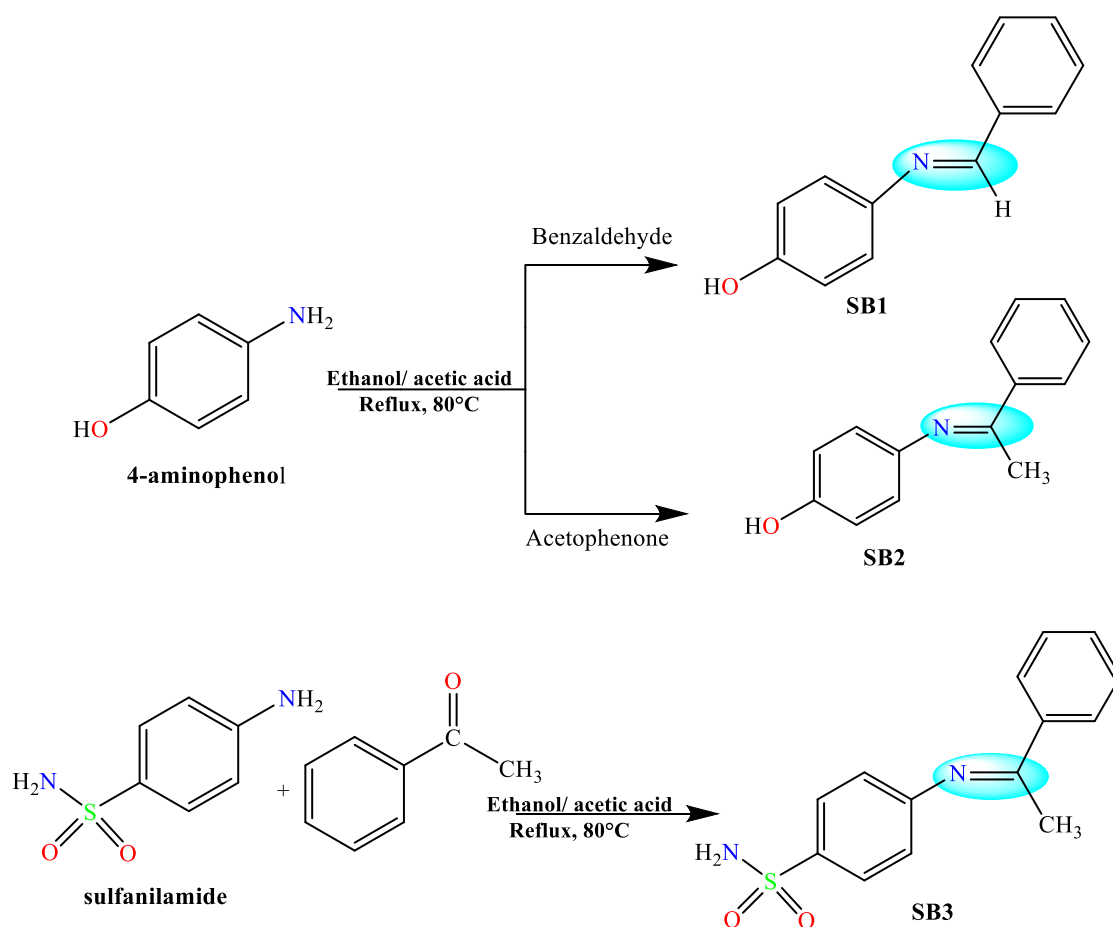


**Figure III.1.** Synthesis and Biological Activities of Schiff Bases

### III.2 Reactivity of Schiff Bases

Imines are considered important intermediates in organic synthesis and are also widely used in the development of new molecules. Numerous derivatives have demonstrated their effectiveness in both asymmetric synthesis and cyclization reactions. The aim of this section is the synthesis and characterization of Schiff base ligands of 4-aminophenol and sulfonamide.

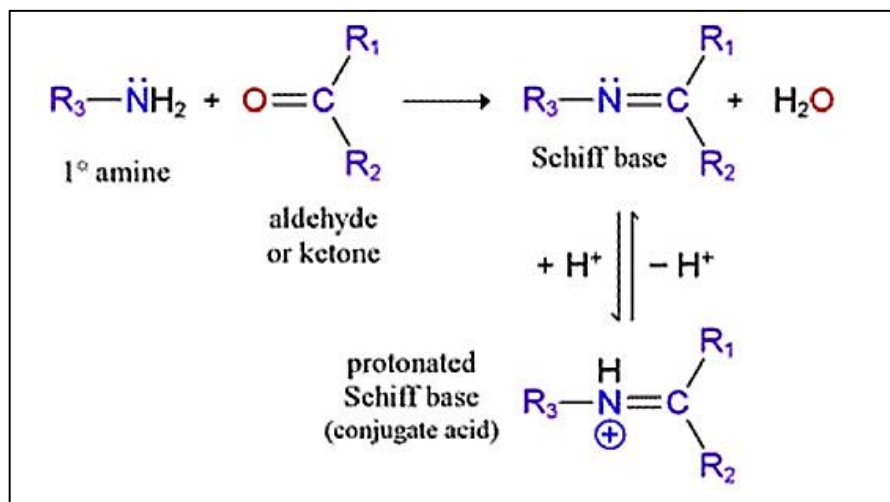
Our approach to these imines is represented in Synthetic Scheme III.1.



**Scheme III.1.** General reactions of imine compounds SB1–SB3

The methodology adopted for this study is based on: the synthesis of our product, namely substituted Schiff bases, and the spectroscopic characterization of the obtained products.

The formation of products **SB1–SB3** is illustrated by the proposed mechanism below. The reaction mechanism for the formation of compounds **SB1–SB3** can be summarized as follows: the nucleophilic attack of the amine group on the carbonyl function, followed by the elimination of a water molecule and the formation of an imine, according to [Scheme III.2](#) below.



**Scheme III.2.** Reaction mechanism for the synthesis of Schiff bases **SB1–SB3**

Following the experimental protocol described in the literature, in which ethanol is used as the reaction solvent, all products were obtained as solids and were purified by recrystallization from ethanol. They were subsequently identified as nucleophilic addition products. The reaction time ranged from 4 to 6 hours at minimum. The data for these products are summarized in [Table III.1](#).

**Table III.1.** Physical properties of compounds **SB1–SB3** using ethanol as the solvent.

| Products   | Color          | Molecular Formula                                               | Rendement (%) | Elemental Analysis (calc.) |      |       |       |       |
|------------|----------------|-----------------------------------------------------------------|---------------|----------------------------|------|-------|-------|-------|
|            |                |                                                                 |               | C                          | H    | N     | O     | S     |
| <b>SB1</b> | Yellow solid   | C <sub>13</sub> H <sub>11</sub> NO                              | 65            | 79.17                      | 5.62 | 7.10  | 8.11  | -     |
| <b>SB2</b> | White solid    | C <sub>1</sub> H <sub>13</sub> NO                               | 60            | 79.59                      | 6.20 | 6.63  | 7.57  | -     |
| <b>SB3</b> | Yellow crystal | C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S | 80            | 61.29                      | 5.14 | 10.21 | 11.66 | 11.69 |

The completion of the reaction was monitored by thin-layer chromatography (TLC). A  $\text{CHCl}_3/\text{MeOH}$  (9/1, 10%) solvent system was used for all compounds **SB1**–**SB3**. It is observed that the yields are very high. All the usual spectroscopic data are consistent with the structures of the obtained products and the proposed structures.

### III.3. Ultraviolet–Visible Analysis

**SB1**, **SB2**, and **SB3** UV-Visible spectroscopy were recorded in absolute ethanol at a concentration of approximately  $10^{-4} \text{ mol}\cdot\text{L}^{-1}$ , demonstrating features related to  $\pi\rightarrow\pi^*$  electronic transition (aromatic) and  $n\rightarrow\pi^*$  electronic transition (azomethine  $\text{C}=\text{N}$ ). **SB1** showed the most significant degree of absorption at two separate wavelengths (241, 390 nm), indicating strong conjugation and possibly intramolecular hydrogen bonding. **SB2** exhibited two absorption wavelengths (241, 295 nm); however, the blue shift in **SB2** is due to the methyl substitutions resulting in less conjugation than **SB1**. For **SB3**,  $\pi\rightarrow\pi^*$  and  $n\rightarrow\pi^*$  transitions will occur at maximum absorption wavelengths of both 230 and 302 nm respectively, due to the electron-withdrawing properties of the sulfonamide group ( $-\text{SO}_2\text{NH}_2$ ), which limits ring conjugation and produces absorption at shorter wavelengths relative to **SB1** and **SB2**. This is slightly bathochromically shifted, attributable to the interaction of the sulfonamide moiety with the imine nitrogen through the aromatic ring, modifying the electronic environment of the lone pair (Elangovan et al., 2021).

Overall, how substituent groups influence both electronic transition and ring conjugation of the synthesized compounds can be further verified through analysis of the spectral data from the three synthesized Schiff Bases (Figure III.2). The absorption maxima observed for each compound are summarized in Table III.2.

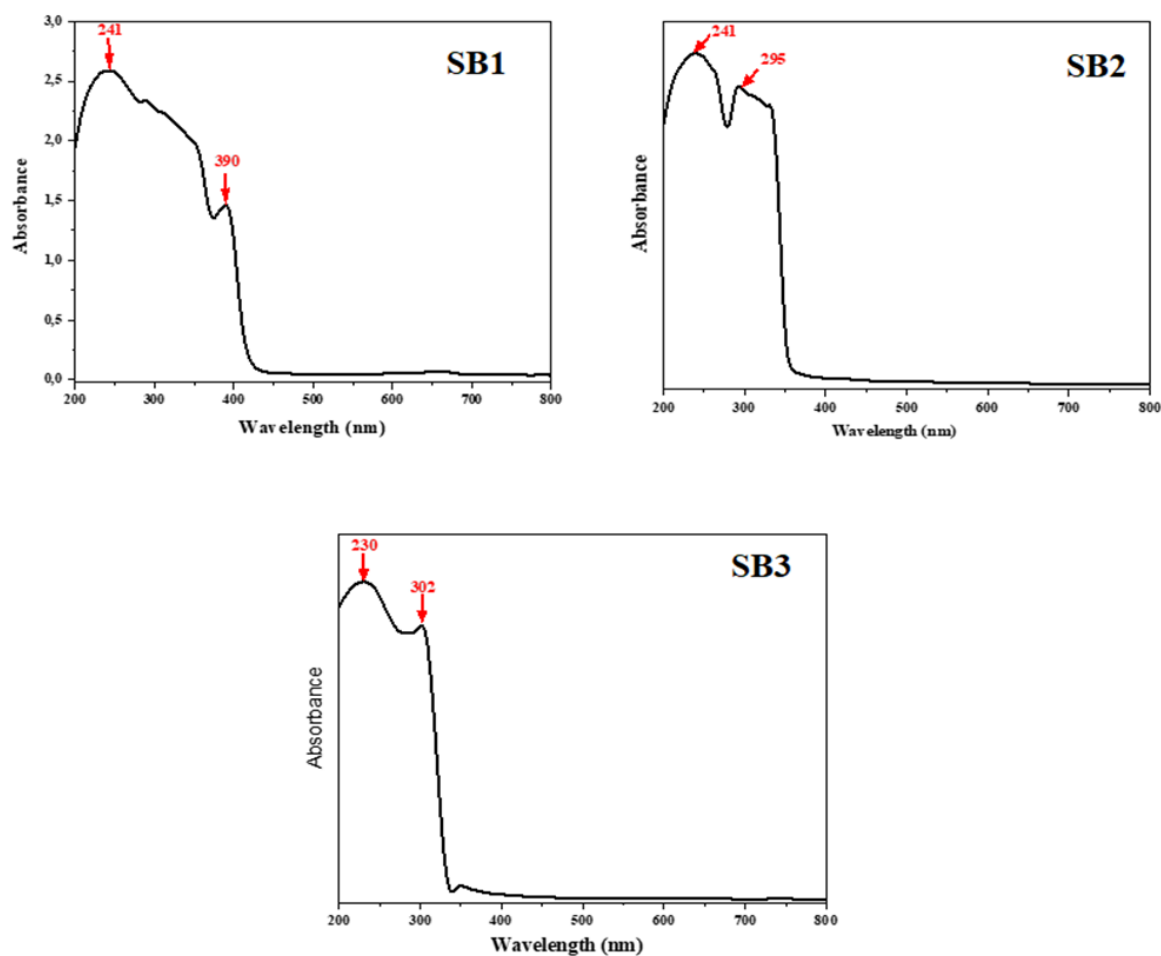


**Figure III.2.** UV–Vis spectra of compounds SB1–SB3

**Table III.2.** UV–Visible absorption maxima of SB1–SB3 in absolute ethanol.

| Compounds | $\lambda_{\text{max}} (\pi \rightarrow \pi^*)$ nm | $\lambda_{\text{max}} (n \rightarrow \pi^*)$ nm | Assignment     |
|-----------|---------------------------------------------------|-------------------------------------------------|----------------|
| SB1       | 241                                               | 390                                             | Aldimine (C=N) |
| SB2       | 241                                               | 395                                             | Ketimine (C=N) |
| SB3       | 230                                               | 303                                             | Ketimine (C=N) |

#### III.4. FT-IR Analysis

Fourier Transform Infrared (FT-IR) spectroscopy is used to determine the presence of functional groups in organic molecules and to identify structural features in certain simple molecules. IR spectroscopy is a commonly used analytical technique ; however, in recent years, it has been somewhat overshadowed by Nuclear Magnetic Resonance (NMR) spectroscopy, which allows molecular structures to be determined with greater precision.

The FT-IR spectra of **SB1**, **SB2**, and **SB3** (Figure III.3) corroborated that the synthesized Schiff bases were produced by their associated functional group vibrations. For example, in **SB1**, the broad O–H stretching band at  $3439\text{ cm}^{-1}$  related to the phenolic functional group and the bands between  $2949\text{--}2864\text{ cm}^{-1}$  quantified the aliphatic C–H stretching vibrations. The signal of azomethine (C=N) stretching at  $1625\text{ cm}^{-1}$  strongly confirmed the formation of Schiff bases whereas the aromatic C=C stretching bands were assigned at  $1574$  and  $1490\text{ cm}^{-1}$ . The band's placement observed in **SB2** indicating both O–H and azomethine (C=N) vibrations were noted at  $3445$  and  $1609\text{ cm}^{-1}$  (Sevvanthi et al., 2020), respectively and the additional C–N and C–O groups between  $1325\text{--}1040\text{ cm}^{-1}$  assisted with their construction. Similarly with **SB3**, the bands located at  $3472$  and  $3384\text{ cm}^{-1}$  were the asymmetric and symmetric stretching modes (Subashini & Periandy, 2017), respectively for  $\text{NH}_2$  groups. The strong azomethine (C=N) signal was noted at  $1623\text{ cm}^{-1}$  and the distinctive banding at  $1312$  and  $1149\text{ cm}^{-1}$  demonstrated the presence of the sulfonamide  $\text{SO}_2$  group. Overall, the results of FT-IR supported the intended presence of all of the functional groups to validate the synthesized Schiff base derivative successfull **SB1-SB3**. The key IR absorption bands for all three compounds are summarized in Table III.3.

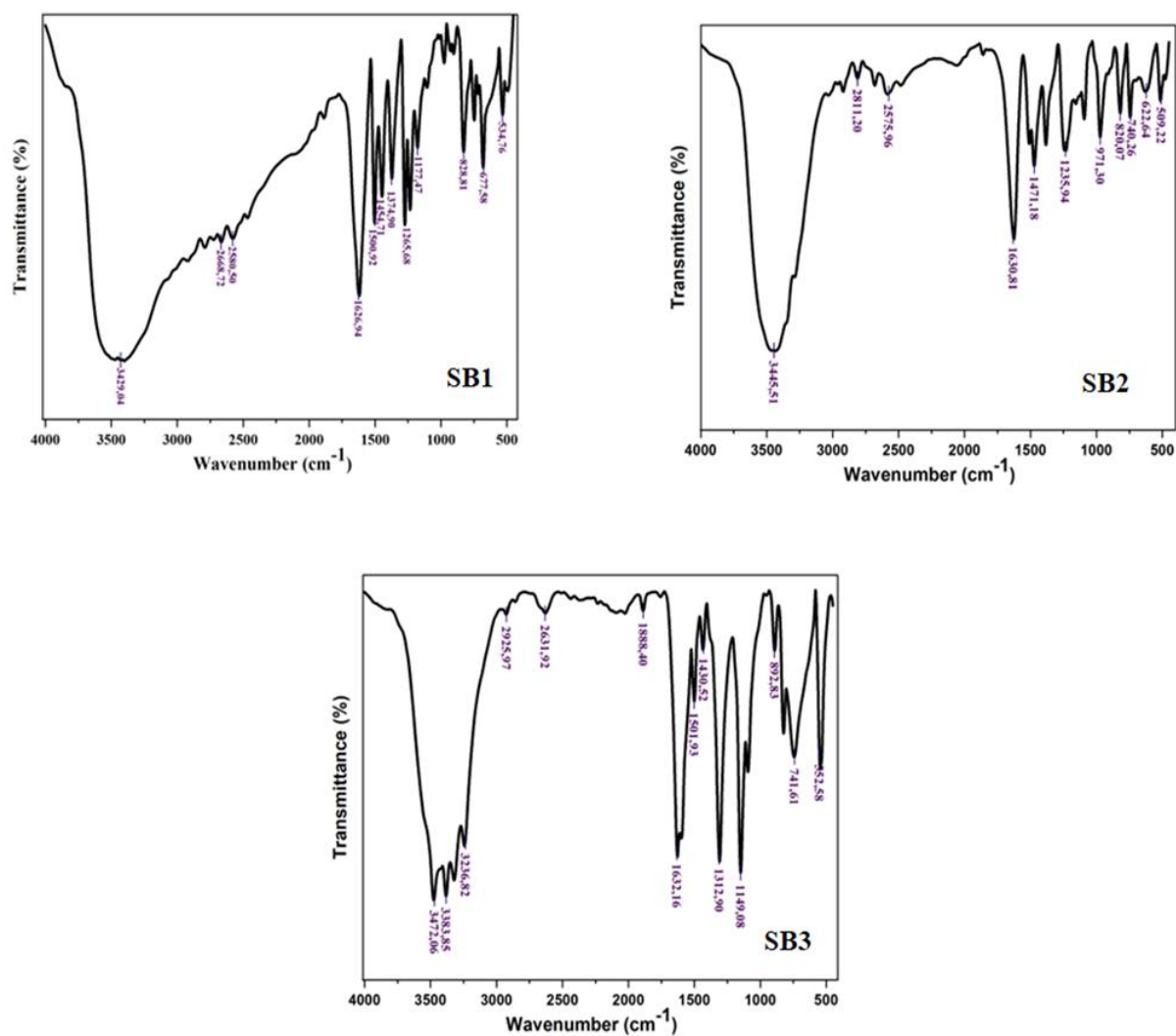


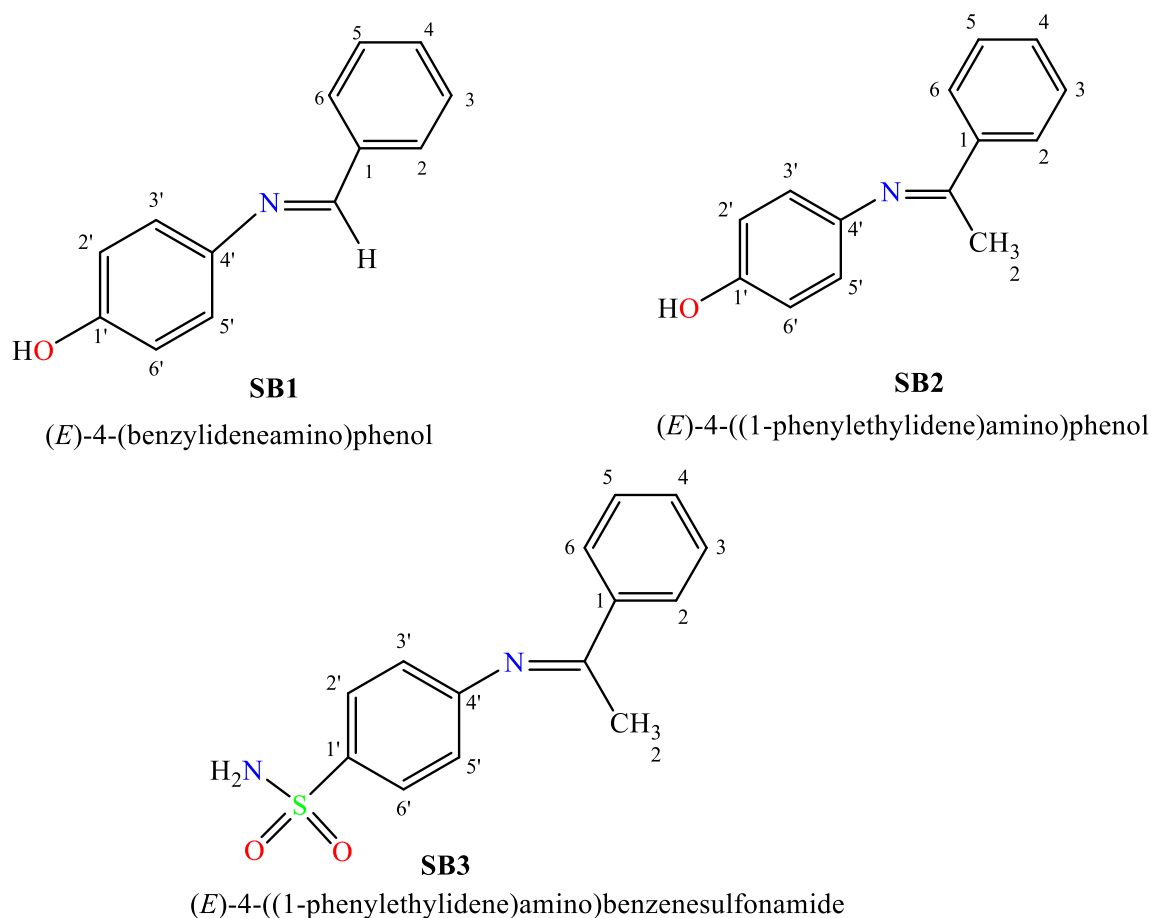
**Figure III.3.** FT-IR spectra of compounds SB1-SB3.

**Table III.3.** Selected FT-IR absorption bands ( $\text{cm}^{-1}$ ) for SB1-SB3.

| Compounds | $\nu(\text{O-H/N-H}) \text{ cm}^{-1}$ | $\nu(\text{C=N}) \text{ cm}^{-1}$ | $\nu(\text{C-O}) \text{ cm}^{-1}$ | $\nu(\text{SO}_2) \text{ cm}^{-1}$ |
|-----------|---------------------------------------|-----------------------------------|-----------------------------------|------------------------------------|
| SB1       | 3429 (broad)                          | 1626                              | 1265                              | -                                  |
| SB2       | 3445 (broad)                          | 1630                              | 1235                              | -                                  |
| SB3       | 3472,3383 ( $\text{NH}_2$ )           | 1632                              | —                                 | 1312, 1149                         |

### III.5. $^1\text{H}$ and $^{13}\text{C}$ NMR Analysis

Nuclear Magnetic Resonance (NMR) spectroscopy is an analytical technique used to determine the overall structure of a sample. It involves analyzing the interaction of spinning nuclei in strong and weak magnetic fields. In NMR spectroscopy, a constant external magnetic field causes specific nuclei in molecules to selectively absorb radiofrequency radiation. The numbering of molecules (**SB1–SB3**) is shown in [Scheme III.2](#) below.



**Scheme III.2.** Numbering of the title compounds **SB1–SB3**

#### III.5.1 $^1\text{H}$ and $^{13}\text{C}$ NMR Analysis of **SB1**

[Figure III.4](#) displays the  $^1\text{H}$ -NMR chemical shifts. The  $^1\text{H}$ -NMR spectrum shows how many different types of hydrogen protons are within a compound as well as where each type of hydrogen proton is located within its environment ([Elangovan et al., 2022](#)). In this compound **SB1**, the azomethine proton ( $-\text{CH}=\text{N}-$ ) is experimentally observed at  $\delta$  8.69 (s, 1H) ppm, confirming the formation of the Schiff base linkage. The H2 proton

appears at  $\delta$  8.05 (*d*, 1H) ppm, while H6 is observed at  $\delta$  8.0 (*d*, 1H), both signals strongly deshielded due to their ortho position relative to the electron-withdrawing azomethine group. The proton downfield shifts of imine protons result from C=N inductive (-I) and resonance effects that decrease the amount of electron density in the aromatic system. The overall spectrum confirms Schiff base formation and is consistent with the proposed molecular structure. At 7.50 ppm (*m*, 5H), the signal corresponds to the aromatic protons of the phenyl ring. The signal appearing at 7.50 ppm (*d*, 2H) is attributed to H2' and H6' of the phenol ring. Although the OH group exhibits an electron-donating (+M) effect, which shifts their signals downfield.

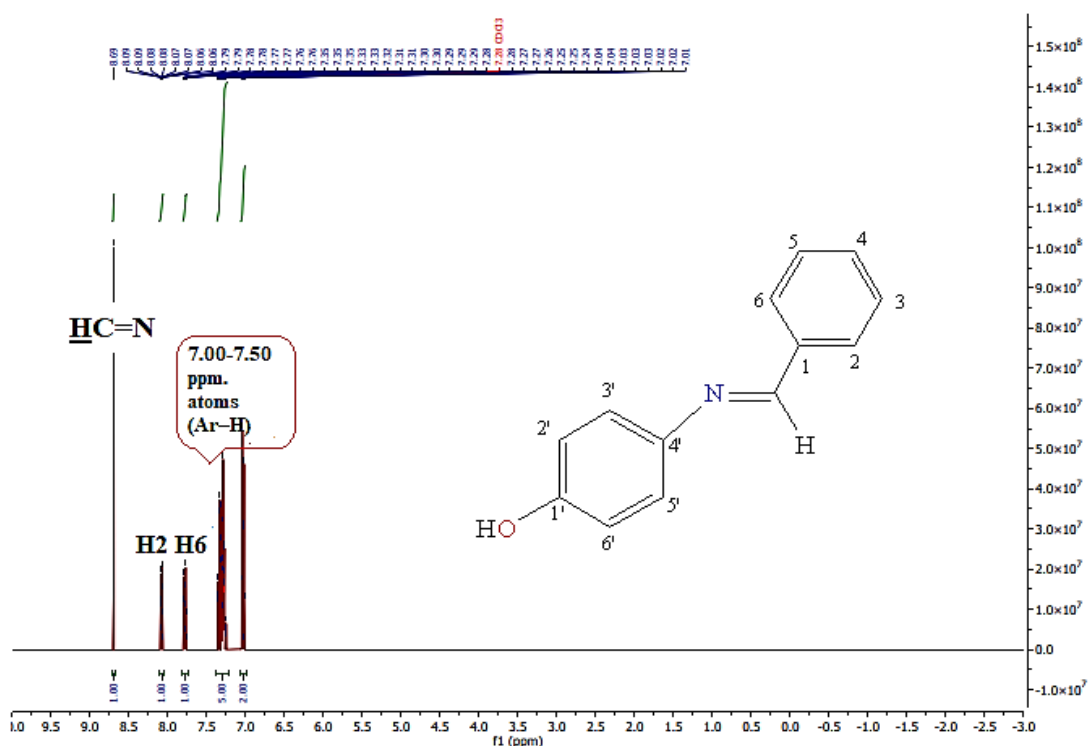


**Figure III.4.**  $^1\text{H}$  NMR spectrum of **SB1**

The spectrum (Figure III.5) shown corresponds to the  $^{13}\text{C}$  NMR spectrum of **SB1**, which is a Schiff base derived from 4-aminophenol and benzaldehyde. The observed signals can be assigned as follows:

- ✓ The signal at around 160.04 ppm is attributed to the imine carbon (CH=N), confirming the formation of the Schiff base.

- ✓ The resonance near 159.05 ppm corresponds to the is attributed to the phenolic carbon bonded to the OH group (C1'). This carbon is strongly deshielded due to the electronegative oxygen atom.
- ✓ The signals appearing between 110-134 ppm are assigned to the aromatic carbons of the two phenyl rings.

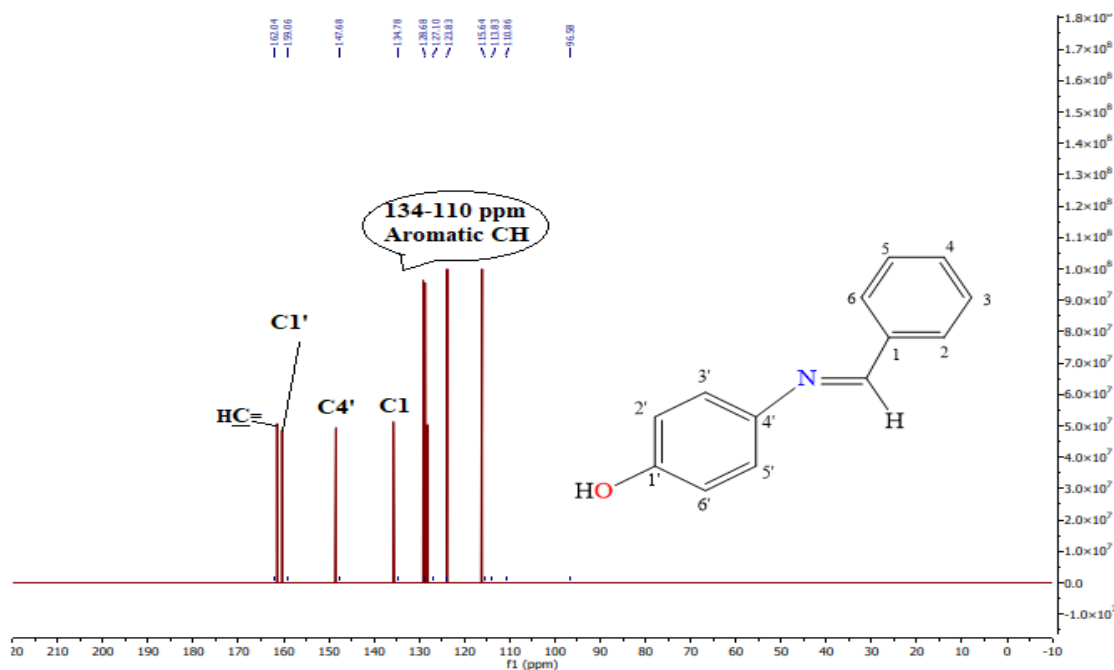


**Figure III.5.**  $^{13}\text{C}$  NMR spectrum of **SB1**

### III.5. 2. $^1\text{H}$ and $^{13}\text{C}$ NMR analysis of **SB2**

The  $^1\text{H}$  NMR spectrum of compound **SB2** (Figure III.6) is almost identical to that of compound **SB1**. However, the singlet at 8.96 ppm corresponding to the  $\text{HC=}$  proton disappears, while a new singlet integrating for 3H appears, which is characteristic of a  $\text{CH}_3$  group. The remaining proton signals appear in the same chemical shift regions that **SB1**.

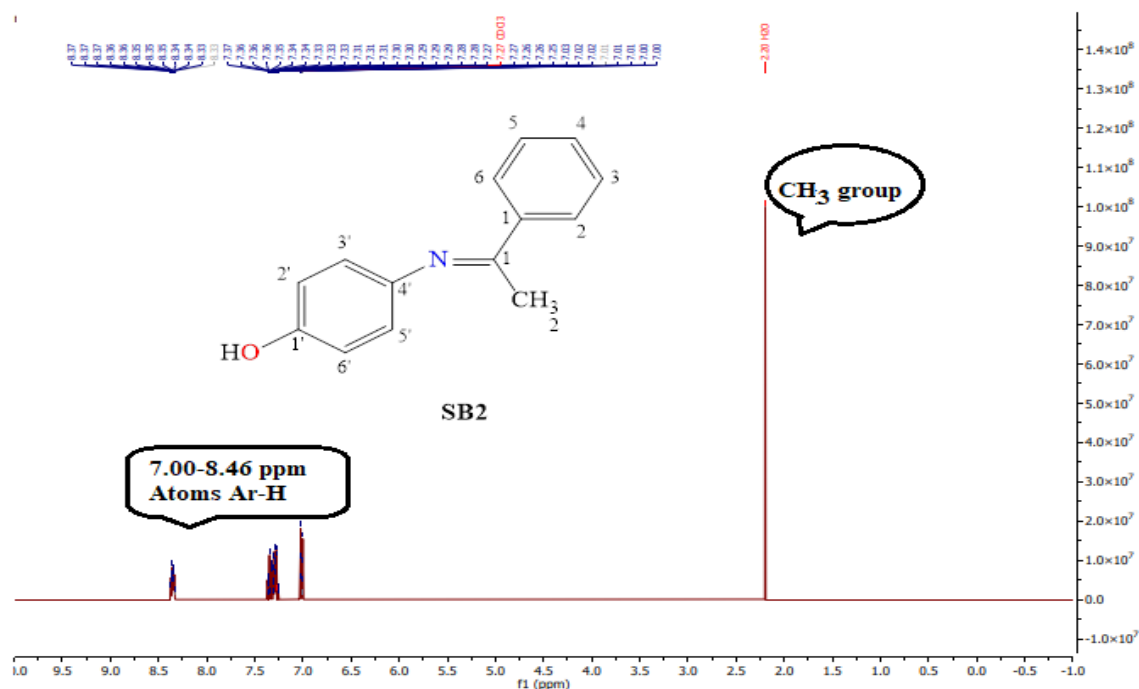


**Figure III.6.**  $^1\text{H}$  NMR spectrum of **SB2**

The  $^{13}\text{C}$  NMR spectrum of compound **SB2** (Figure III.7) exhibits characteristic signals confirming the proposed structure. The two signals observed at 162.73 ppm and 160.40 ppm are assigned respectively to the phenolic carbon bonded to the hydroxyl group ( $\text{C1}'$ ) and to the imine carbon ( $\text{C}=\text{N}$ ), both strongly deshielded due to the electron-withdrawing effect of oxygen and nitrogen atoms. The various peaks appearing between 115.28 and 131.25 ppm correspond to the aromatic carbons of the two benzene rings. Among these, the signals of the substituted quaternary carbons appear in the more deshielded region, whereas the protonated aromatic carbons resonate in the more shielded regions. Finally, the signal observed at 20.30 ppm is characteristic of the methyl group carbon ( $\text{CH}_3$ ) attached to the imine carbon. Altogether, these spectral data confirm the formation of the expected Schiff base.

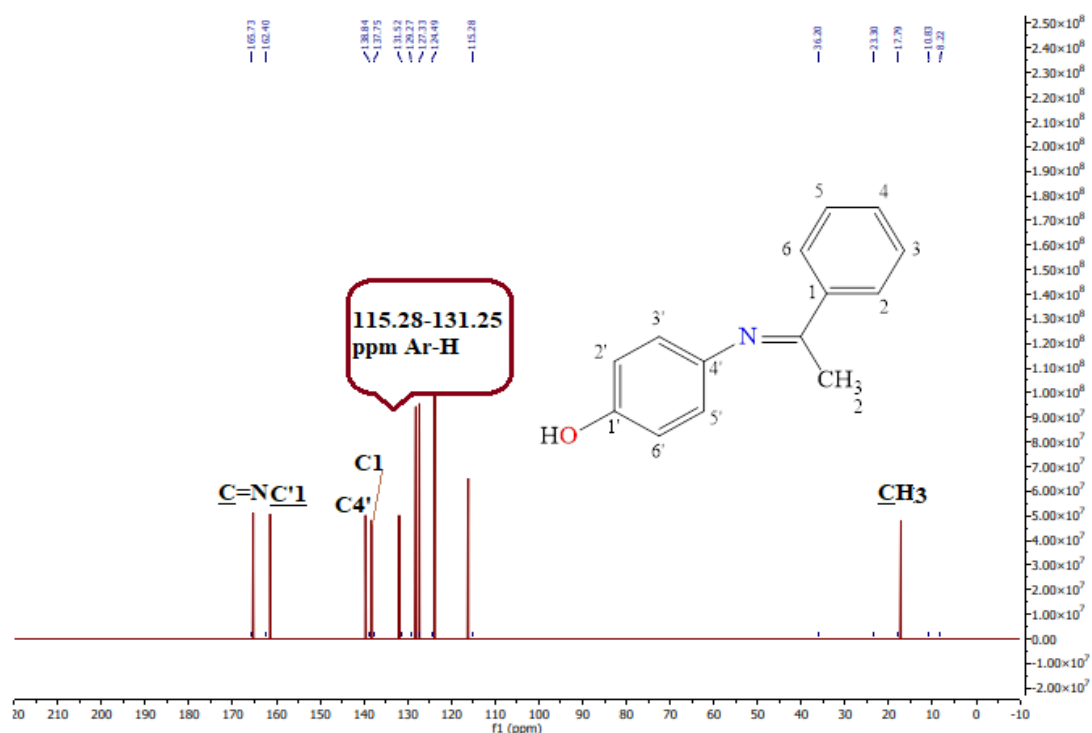


Figure III.7.  $^{13}\text{C}$  NMR spectrum of SB2

### III.5.3. $^1\text{H}$ and $^{13}\text{C}$ NMR Analysis of SB3

Schiff bases derived from sulfonamides include compounds such as (*E*)-4-((1-phenylethylidene) amino) benzene sulfonamide (**SB3**), a significant chemical entity due to combining sulfonamide's medicinal implications with an imine's reactive characteristics. Two aspects of **SB3** contribute to this enhanced activity and coordination behavior and stability; it contains two aryl rings and an azomethine linkage, providing further stabilization through electronic conjugative interactions (Kanagavalli et al., 2022). The obtained product was characterized using various spectroscopic techniques such as FT-IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectroscopy, which confirmed the formation of the imine bond and the proposed molecular structure **SB3**.

$^1\text{H}$  NMR Spectroscopy of (*E*)-4-(1-Phenylethylideneamino)benzenesulfonamide (**SB3**) (Figure III.8) reveals signals that are characteristic of the proposed molecular structure. The aromatic protons from the two benzene rings create a multiplet signal from 7.30–8.33 ppm because of the complex coupling and deshielding effects (due to the conjugation with the sulfonamide,  $-\text{SO}_2\text{NH}_2$ , and  $\text{C}=\text{N}$  groups). The methyl protons from

the imine at 2.1–2.3 ppm confirm that the 1-phenylethylidene fragment is present in this molecule. The overall pattern of the NMR signals is consistent with the successful synthesis of the Schiff base and is consistent with the expected molecular structure of **SB3**.

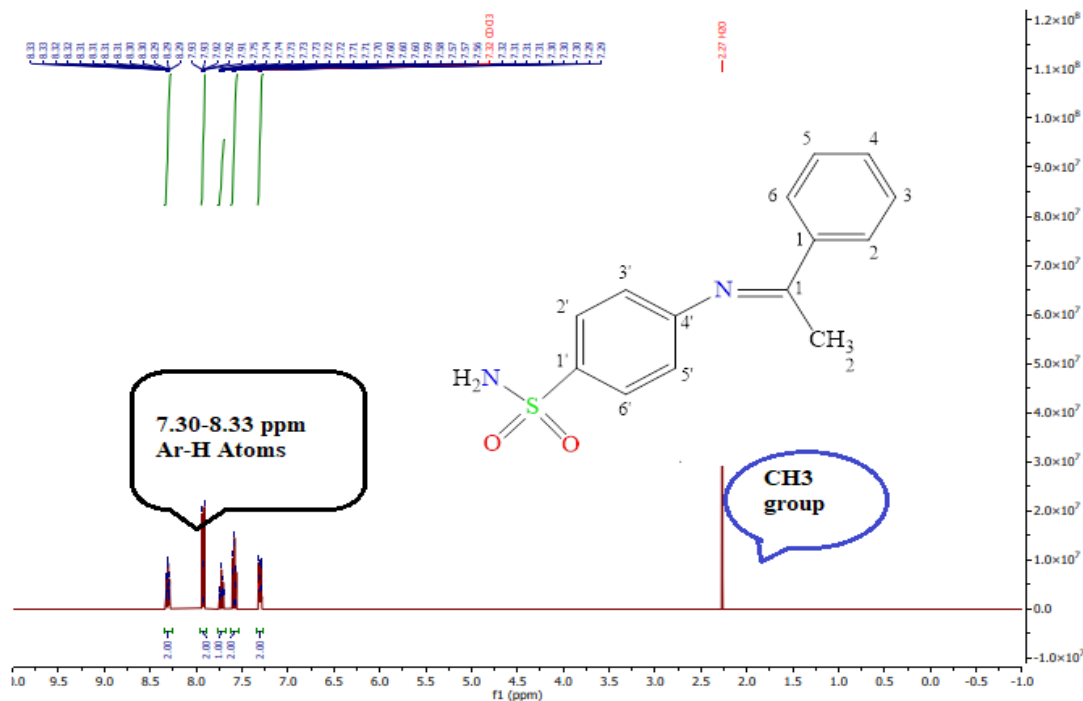


**Figure III.8.**  $^1\text{H}$  NMR spectrum of **SB3**

The structure of the synthesized Schiff base is confirmed through characteristic carbon signals in the  $^{13}\text{C}$  NMR spectrum (Figure III.9). A resonance at approximately 163.3 ppm is attributed to the azomethine carbon ( $\text{C}=\text{N}$ ) denoting the formation of the Schiff base linkage. Aromatic carbons from the two phenyl rings appear in the region of 123.79–136.0 ppm, corresponding to both protonated and quaternary aromatic carbons. Signals C1, C1', and C4' arise from substituted aromatic carbons directly coupled to electronegative substituents such as sulfonamide ( $-\text{SO}_2\text{NH}_2$ ) and imine functionalities. Further, signals at around 16.9 ppm are in fact methyl carbon ( $\text{CH}_3$ ) from acetophenone. The absence of a carbonyl carbon signal in the region of 190–200 ppm affirms that the ketone precursor is converted into the desired imine product.

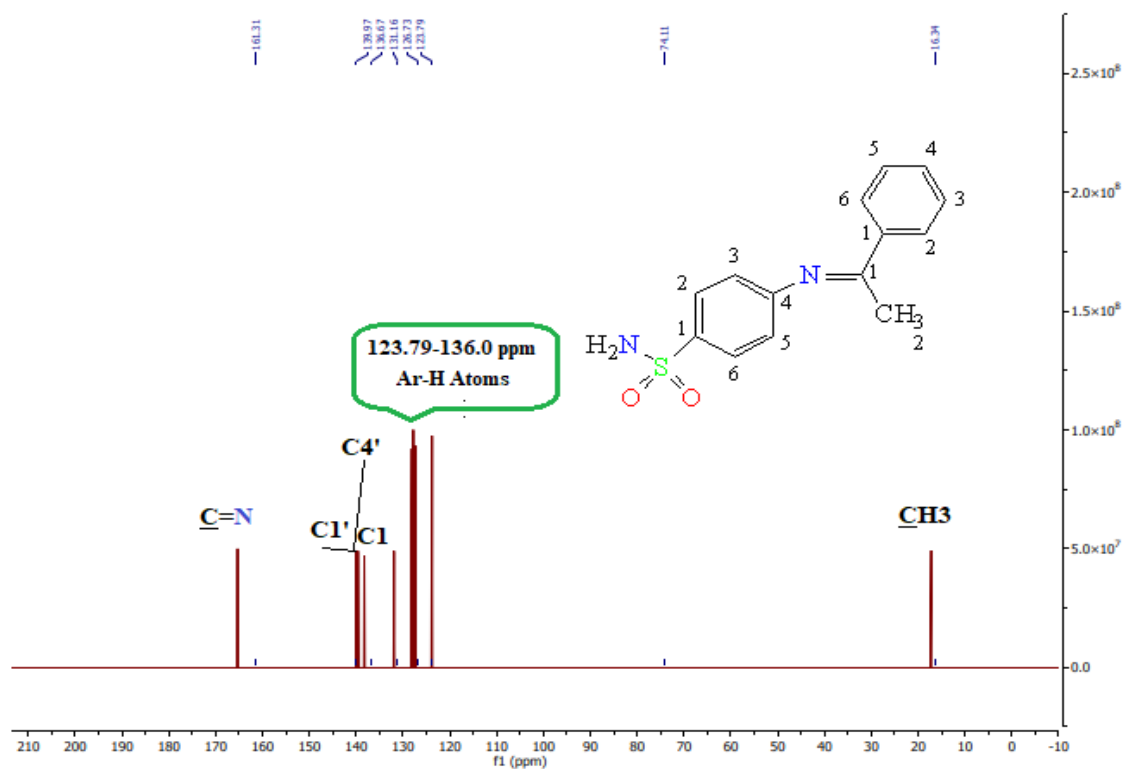


**Figure III.9.**  $^{13}\text{C}$  NMR spectrum of **SB3**

### III.6. Computational Details

Density Functional Theory (DFT) is a quantum mechanical technique used to calculate the electronic properties of atoms and molecules. Hohenberg, Kohn, and Sham originally developed DFT circa 1964–1965; it is now a powerful and trusted method for investigating many chemical, physical, and biological phenomena. B3LYP is one of the most common hybrid functionals in DFT and it provides much better accuracy than Hartree–Fock. The B3LYP/6-31G(d) level of theory is often used as a baseline computational model for many types of work in chemistry and materials science (Becke, 1986), (Lee et al., 1988).

#### III.6.1. Frontier Molecular Orbital Theory (FMO Theory)

In the 1970s, Fukui introduced the concept of frontier molecular orbitals, emphasizing the importance of the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital). These orbitals play a crucial role in molecular reactivity: the HOMO provides information about the nucleophilic character of a molecule, whereas the LUMO reflects its electrophilic character. The frontier orbital

energies ( $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$ ) and the energy gap ( $\Delta E$ ) between them are essential parameters in quantum chemistry, as they strongly influence the reactivity and stability of molecular structures. A smaller energy gap generally indicates a higher probability of chemical reaction and greater molecular reactivity (Derardja et al., 2025).

To study chemical reactivity and electronic properties of **SB1**, **SB2**, and **SB3**, a frontier molecular orbital (FMO) analysis yields that HOMOs are primarily distributed throughout the azomethine group ( $-\text{CH}=\text{N}-$ ) and the aromatic rings; as a consequence, these areas can be considered as rich in electrons and consequently can donate electrons. In contrast, the LUMOs are contained within the conjugated pi system and the electron-withdrawing substituents, indicating that the LUMOs are capable of receiving electrons. The calculated energy gaps ( $E_g$ ) between the two types of orbitals are 3.48 eV for **SB1**, and 3.60 eV each for both **SB2** and **SB3**; thus indicating that **SB1** has much higher kinetic instability and is more chemically reactive than either **SB2** or **SB3**, leading to much easier intramolecular charge transfer. In addition, the larger  $E_g$  values for **SB2** and **SB3** could imply that both of these Schiff bases are more stable than **SB1** and therefore much less electronically reactive. Overall, the analysis of the two types of orbitals dictates that the electronic transitions occurring in Schiff bases primarily result from a ( $\pi \rightarrow \pi^*$ ) transition along the conjugated molecular structure (Figure III.10).

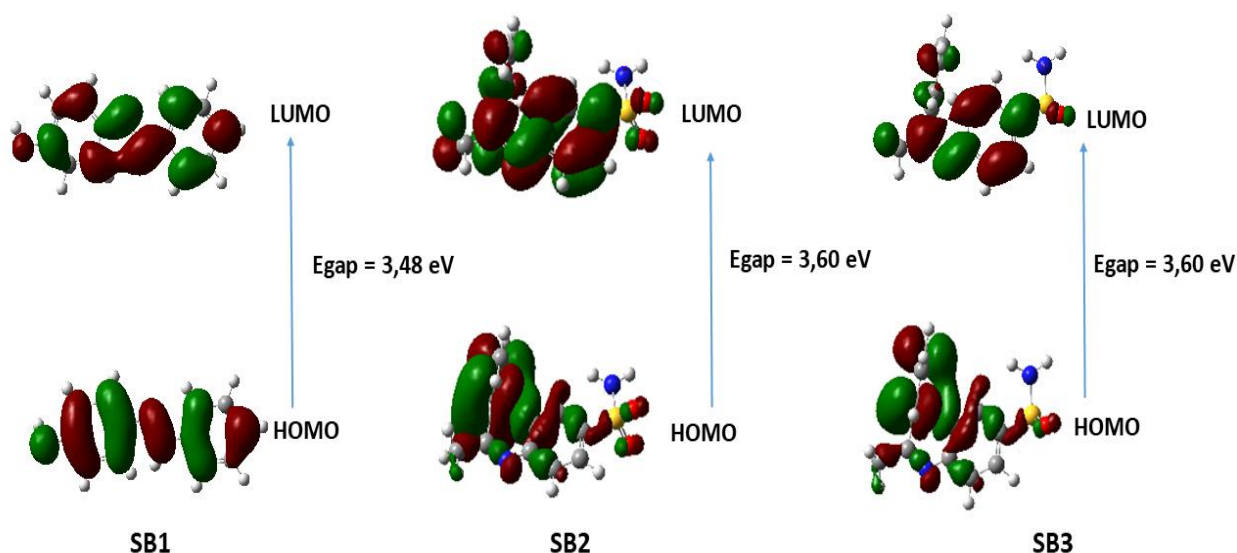
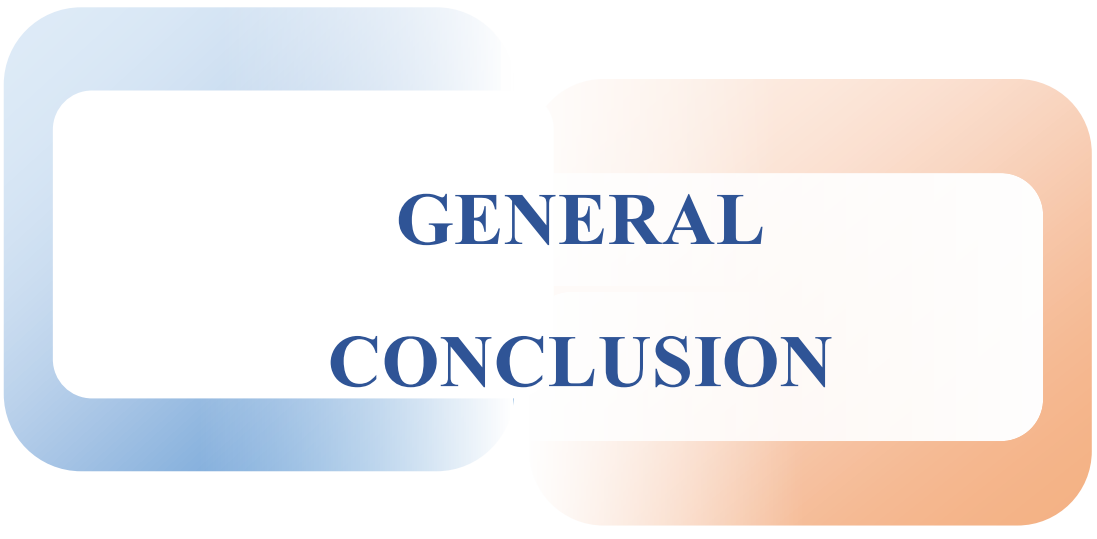


**Figure III.10.** HOMO and LUMO Energy Levels with the Energy Gap ( $\Delta E$ ) of **SB1–SB3**

### III.7. Conclusion

The three Schiff base derivatives were successfully synthesized based on the presence of the imine (C=N) bond demonstrated by the spectral data obtained from spectrophotometry (UV-Vis), FT-IR, and NMR, differences between the aldimines (**SB1**) and ketimines (**SB2** and **SB3**), based on the spectral signals and expected structures as a result of UV-Vis shifts and NMR data. The additional IR and NMR signals used to characterize **SB3** confirm the existence of the  $-\text{SO}_2\text{NH}_2$  group and the regioselective condensation. The combined evidence suggests that the compounds synthesized possess the characteristics of the expected molecular structures. The results of the Frontier Molecular Orbital analysis suggest that there are moderate HOMO–LUMO gaps among the studied compounds indicating that they possess a balance of stability/reactivity, thereby providing the potential chemical significance of the synthesized compounds.



# **GENERAL CONCLUSION**

## GENERAL CONCLUSION

The main objective of this work was the development of new Schiff-base compounds with potential biological and therapeutic applications, containing the azomethine motif as a key substructure. These derivatives, which constitute our starting material, were readily obtained via a Claisen–Schmidt condensation reaction with good yields (up to 70%) and were characterized using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, UV–Vis spectroscopy, and FT-IR spectroscopy.

In this work, three Schiff-base derivatives were prepared :

- (*E*)-4-(benzylideneamino)phenol
- (*E*)-4-((1-phenylethylidene)amino)phenol
- (*E*)-4-((1-phenylethylidene)amino)benzenesulfonamide

Using spectrophotometric (UV-Vis), FT-IR, and NMR analysis, it was demonstrated that the three Schiff base derivatives were formed using the imine ( $\text{C}=\text{N}$ ) bond and that they were produced as aldimines (**SB1**) and ketimines (**SB2** and **SB3**), as indicated by the difference in the spectral signals and anticipated molecular structure as indicated by the spectral shift of the UV-Vis and the number of NMR signals obtained for SB3 confirming the  $-\text{SO}_2\text{NH}_2$  group and indicating that the regioselective condensation of the compounds occurred as expected. Overall, the three Schiff bases have the expected structural characteristics as shown in the combined analytical data.

Similarly, the importance of this work lies in the synthesis of new classes of compounds **SB1-SB3** with potential therapeutic applications containing the azomethine (Schiff base) motif, and in the study of their effects on bacterial strains and other biological properties, as well as in the investigation of structure–activity relationships. These aspects may represent new challenges and a strong motivation for the development of organic chemistry based on azomethine motifs within our laboratory.

The synthesis of Schiff base derivatives **SB1**, **SB2**, and **SB3** occurred successfully as shown in both the experimental and theoretical results (syntheses were conducted under mild conditions). The spectroscopic and computational data corroborated the structure of the synthesized products as well as their electronic properties. Furthermore, this study

exemplifies the value of azomethine chemistry as an environmentally friendly and versatile synthetic methodology, as well as supports the need to utilize a combination of characterization techniques in order to accurately analyze the structures of synthesized compounds.

In conclusion, this master's dissertation provides evidence that green synthesis of azomethine derivatives is a valid scientific method as well as an environmentally friendly procedure for creating compounds with bioactivity. Integrating synthetic chemistry, spectroscopic characterization, and computer modelling represents the interdisciplinary nature of this work and supports the integrative nature of current analytical chemistry research, which serves as a strong basis on which to continue conducting research in this area in the future.



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# ABSTRACT

## Abstract

This work presents the synthesis and spectroscopic characterization of three azomethine derivatives also known as Schiff bases, obtained by condensation of two aromatic amines (4-aminophenol and sulfanilamide) with two carbonyl compounds (benzaldehyde and acetophenone) under eco-friendly conditions. The reactions were carried out under reflux in ethanol using acetic acid as a catalyst, in accordance with the principles of green chemistry.

The three synthesized compounds (**SB1-SB3**) were characterized by Thin-Layer Chromatography (TLC), UV–Visible spectroscopy, Fourier-Transform Infrared spectroscopy (FT-IR), and Proton Nuclear Magnetic Resonance ( $^1\text{H}$  NMR) spectroscopy. The formation of the imine bond ( $\text{C}=\text{N}$ ) was confirmed in each case by the disappearance of the carbonyl  $\text{C}=\text{O}$  stretch and primary amine  $\text{N}-\text{H}$  bands in the FT-IR spectra, and by the characteristic azomethine proton signal in the  $^1\text{H}$  NMR spectra.

For the sulfanilamide-derived compound (SB-3), the reaction proceeded selectively at the primary aromatic amine group rather than at the less nucleophilic sulfonamide nitrogen. The results confirm that TLC, UV–Vis, FT-IR, and  $^1\text{H}$  NMR together constitute a reliable and complementary toolkit for structural elucidation of azomethine compounds. The synthesized Schiff bases represent promising candidates for further investigation of their biological and coordination chemistry properties.

**Keywords:** Schiff base, azomethine, synthesis, spectroscopic characterization, sulfanilamide, 4-aminophenol.

## Résumé

Ce travail présente la synthèse et la caractérisation spectroscopique de trois dérivés azométhines également appelés bases de Schiff obtenus par condensation de deux amines aromatiques (4-aminophénol et la sulfanilamide) avec deux composés carbonylés (le benzaldéhyde et l'acétophénone) dans des conditions respectueuses de l'environnement. Les réactions ont été réalisées sous reflux dans l'éthanol en présence d'acide acétique comme catalyseur, principes de la chimie verte.

Les trois composés synthétisés (**SB1-SB3**) ont été caractérisés par chromatographie sur couche mince (CCM), spectroscopie UV–Visible, spectroscopie infrarouge à transformée de Fourier (FT-IR) et résonance magnétique nucléaire du proton ( $^1\text{H}$  RMN). La formation de la liaison imine ( $\text{C}=\text{N}$ ) a été confirmée dans chaque cas par la disparition des bandes d'élongation  $\text{C}=\text{O}$  du carbonyle et  $\text{N}-\text{H}$  de l'amine primaire dans les spectres FT-IR, ainsi que par le signal caractéristique du proton azométhine dans les spectres  $^1\text{H}$  RMN.

Pour le composé dérivé de la sulfanilamide (**SB3**), la réaction a eu lieu sélectivement au niveau du groupe amine aromatique primaire plutôt qu'au niveau de l'azote sulfonamide, moins nucléophile. Les résultats confirment que la CCM, la spectroscopie UV–Vis, la FT-IR et la  $^1\text{H}$  RMN constituent ensemble un ensemble d'outils fiables et complémentaires pour l'élucidation structurale des composés azométhines.

**Mots-clés :** base de Schiff, azométhine, liaison imine, caractérisation spectroscopique, sulfanilamide, 4-aminophénol.

## الملخص

يقدّم هذا العمل تركيب ثلاث مشتقات أزوميثينية - المعروفة أيضاً بقواعد شيف - وتوصيفها الطيفي، وقد حصلنا عليها عن طريق تفاعل تكثيف بين أمينين أروماتيين-4) أمينوفينول والسلفانيلاميد (ومركبين كربونيلين (البنزالديهيد والأسيتوفينون (في ظروف عادية. أجريت التفاعلات تحت الارتداد في الإيثانول بوجود حمض الأسيتيك كمحفّز، انسجماً مع مبادئ الكيمياء الخضراء.

وصّفت المركّبات الثلاثة المُصنّعة (SB1-SB3) بواسطة كروماتوغرافيا الطبقة الرقيقة (TLC)، وطيف الأشعة فوق البنفسجية والمرئية (UV-Vis)، وطيف الأشعة تحت الحمراء بتحويل فورييه (FT-IR)، والرنين المغناطيسي النووي للبروتون ( $^1\text{H NMR}$ ). وقد تأكّدت في كل حالة تكوين الرابطة الإيمينية ( $\text{C}=\text{N}$ ) من خلال اختفاء شريط امتداد  $\text{C}=\text{O}$  للكربونيل وأشرطة  $\text{N}-\text{H}$  للأمين الأولي في أطياف FT-IR، وكذلك من الإشارة المميزة لبروتون الأزوميثين في أطياف  $^1\text{H NMR}$ .

بالنسبة للمركّب المشتق من السلفانيلاميد (SB3)، جرى التفاعل بصورة انتقائية عند مجموعة الأمين الأروماتية الأولية دون مجموعة النيتروجين السلفوناميديّة ذات النكليوفيلية الأضعف. تؤكّد النتائج أن TLC و UV  $^1\text{H NMR}$ ، FT-IR تُشكّل معاً مجموعة أدوات موثوقة ومتكاملة لتحديد البنية الجزيئية لمركّبات الأزوميثين.

**الكلمات المفتاحية:** قاعدة شيف، أزوميثين، رابطة إيمينية، توصيف طيفي، سلفانيلاميد، 4-أمينوفينول.