



# MOLAR REFRACTIVITY STUDIES OF SUBSTITUTED FURAN-BASED SCHIFF BASES STRUCTURAL CORRELATION AND DRUG-LIKENESS EVALUATION

**Gajanan Dnyandeo Rawate**

Assistant Professor

Department of Chemistry

Shri R. R. Lahoti Science College, Morshi Dist:-Amravati (Maharashtra) 444905, India.

[gajananrawate7@gmail.com](mailto:gajananrawate7@gmail.com)

**Abstract :** The present study reports the temperature- and concentration-dependent molar refractivity behavior of a series of newly synthesized furan-based Schiff bases derived from 5-nitrobenzene-1,2-diamine. Molar refractivity measurements were carried out for five Schiff bases (3a–3e) at temperatures ranging from 298.15 to 318.15 K and concentrations between 0.000625 and 0.01 mol kg<sup>-1</sup> in 100% DMSO-water. The results reveal a systematic increase in molar refractivity with increasing temperature and concentration for all compounds. Substituent effects play a significant role, with molar refractivity increasing in the order 3a < 3b < 3c ≈ 3d < 3e, which correlates well with increasing atomic size and polarizability of the substituents. The positional variation of bromine substitution shows negligible influence on molar refractivity. Furthermore, preliminary drug-likeness evaluation based on Lipinski's Rule of Five indicates that the synthesized Schiff bases possess acceptable physicochemical properties, suggesting potential pharmaceutical relevance. The study highlights strong structure–property relationships and provides insight into the molecular polarizability and solution behaviour of these Schiff bases.

**Index Terms** - Schiff bases; Molar refractivity; Polarizability; Substituent effect; Temperature dependence; Lipinski's rule of five.

## I. INTRODUCTION:

Schiff bases are an important class of organic compounds characterized by the presence of an azomethine functional group (–C=N–), first reported by Hugo Schiff in 1864<sup>1</sup>. These compounds are generally synthesized through the condensation of primary amines with aldehydes or ketones, resulting in the formation of imine linkages<sup>2</sup>. In contrast, reactions involving secondary amines commonly lead to the formation of enamines under suitable conditions<sup>3</sup>. Schiff bases containing aromatic substituents often exhibit enhanced structural stability and have attracted considerable attention because of their versatile coordination properties. The nitrogen atom of the azomethine group can act as a donor site, enabling these compounds to coordinate with various transition-metal ions and form stable metal complexes<sup>4</sup>. Such coordination compounds have been investigated for applications in catalysis, materials science, and industrial processes.

In addition to their chemical versatility, Schiff bases and their metal complexes have demonstrated promising biological activities. Several metal complexes exhibit improved antimicrobial and antifungal effects compared with their corresponding uncoordinated ligands<sup>5–6</sup>, although their activities depend on the metal ion, ligand structure, and experimental conditions. Schiff base complexes have also been studied for their antioxidant properties and potential applications in medicinal chemistry, including cancer diagnosis and anticancer research<sup>7–8</sup>. Furthermore, selected Schiff base compounds and their metal complexes have been explored as functional materials in dye-sensitized solar cells<sup>2–4</sup>. These diverse properties make Schiff bases valuable candidates for further investigation in coordination chemistry, biological sciences, and advanced materials research.

Molar refractivity (RM) is an important physicochemical parameter directly related to molecular polarizability and volume. It provides valuable insight into intermolecular interactions, electronic distribution, and structural effects in solution. The study of molar refractivity as a function of temperature and concentration is particularly useful for understanding solute–solute and solute–solvent interactions.

Furan-based Schiff bases are of special interest due to the heteroaromatic ring's ability to enhance  $\pi$ -electron delocalization and biological activity. Substituent variation on the furan ring, especially with electron-donating and electron-withdrawing groups, significantly alters molecular polarizability and refractive behavior.

In recent years, early-stage drug discovery has increasingly relied on physicochemical screening tools such as Lipinski's Rule of Five, which provides guidelines for assessing oral bioavailability. Parameters such as molecular weight, hydrogen bond donors and acceptors, and lipophilicity are closely linked to refractivity and polarizability.

In this context, the present work aims to investigate the molar refractivity behaviour of five substituted furan-based Schiff bases over a wide range of temperatures and concentrations and to correlate the experimental findings with molecular structure and drug-likeness considerations.

## II. MATERIALS AND METHODS

### II.1 Materials

All chemicals used for the synthesis of Schiff bases were of analytical reagent grade and used without further purification. The Schiff bases (3a–3e) were synthesized by condensation of 5-nitrobenzene-1,2-diamine with appropriately substituted furan-2-carboxaldehydes.

### II.2 Structural Description of Schiff Bases

**3a:** N1-((5-methylfuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine

**3b:** 5-nitro-N1-((5-nitrofuran-2-yl) methylene) benzene-1,2-diamine

**3c:** N1-((5-bromofuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine

**3d:** N1-((4-bromofuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine

**3e:** N1-((5-iodofuran-2-yl) methylene)-5-nitrobenzene-1,2-diamine

### II.3 Preparation of Solutions

Solutions of Schiff bases were prepared in 100% DMSO-water binary solvent at concentrations of 0.01, 0.005, 0.0025, 0.00125, and 0.000625 mol kg<sup>-1</sup>

### II.4 Measurement of Molar Refractivity

The molar refraction of solvent, dimethyl sulphoxide water mixtures are determined from,

$$R_{\text{mixture}} = X_1R_1 + X_2R_2$$

Where,  $R_1$  and  $R_2$  are molar refraction of Dimethylsulphoxide and water respectively. The molar refraction represents actual or true volume of substance molecules in 1 mole. The molar refraction of solutions of ligand in DMSO - water mixtures are determined from following relation.<sup>9-10</sup>

$$R_{\text{mixture}} = [(n^2-1)/(n^2+2)] \{ [X_1M_1 + X_2M_2 + X_3M_3]/d \} \quad \text{----- (1)}$$

Where  $n$  – Refractive index of Schiff base solution in 100% DMSO-water.

$X_1$  - Mole fraction of dimethyl sulphoxide

$X_2$  - Mole fraction of water

$X_3$  - Mole fraction of Schiff base (3a, 3b, 3c, 3d and 3e)

$M_1$  - Molecular weight of dimethyl sulphoxide

$M_2$  = Molecular weight of water.

$M_3$  = Molecular weight of solute (Schiff base 3a, 3b, 3c, 3d and 3e).

The molar refraction of ligand is calculated as

$$RM_{\text{ligand}} = R_{\text{mixture}} - R_{\text{DMSO-Water}} \quad \text{----- (2)}$$

The electronic polarizability,  $\alpha$  which is a result of displacement of individual electrons, is proportional to  $RM$ . Polarizability of a substance can be determined by measuring the refractive index of the Schiff base solution

$$RM_{\text{ligand}} = (4/3) \pi N_o \alpha \quad \text{----- (3)}$$

$$\text{Polarizability constant } (\alpha) = 3RM / 4 \pi N_o$$

Where  $\alpha$  – Polarizability constant of Schiff base in 100 % DMSO-water.

$N_o$  = Avogadro Constant ( $6.023 \times 10^{23} \text{ mol}^{-1}$ ).

### III.RESULTS AND DISCUSSION

#### III.1 Effect of Concentration

For all Schiff bases, molar refractivity decreases systematically with decreasing concentration at a fixed temperature. This behaviour can be attributed to the reduction of solute–solute interactions upon dilution. At higher concentrations, enhanced dipole–dipole and  $\pi$ – $\pi$  interactions increase effective molecular polarizability.

#### III.2 Effect of Temperature

At constant concentration, molar refractivity increases with temperature for all compounds. This is due to increased thermal motion and expansion of molecular volume, leading to greater distortion of the electron cloud and higher polarizability

#### III.3 Substituent Effect

The molar refractivity values follow the order  $3a < 3b < 3c \approx 3d < 3e$ . This trend reflects the increasing atomic size and polarizability of the substituents ( $-\text{CH}_3 < -\text{NO}_2 < -\text{Br} < -\text{I}$ ). The near-identical values of 3c and 3d indicate that the position of bromine substitution has minimal influence compared to its atomic contribution.

#### III.4 Structure–Property Relationship

The observed trends confirm that molar refractivity is strongly dependent on molecular polarizability and substituent nature. Heavier halogen substitution enhances refractivity due to diffuse electron clouds

#### III.5 Lipinski's Rule of Five Consideration

All synthesized Schiff bases (3a–3e) satisfy Lipinski's Rule of Five<sup>11-12</sup> without any violations (Table-1). The molecular weights of all compounds are significantly below the recommended threshold of  $500 \text{ g}\cdot\text{mol}^{-1}$ . The presence of two hydrogen bond donors and five to six hydrogen bond acceptors supports favourable solubility and permeability characteristics. The estimated logP values increase with halogen substitution, reflecting enhanced lipophilicity, yet remain within the acceptable range. These results indicate that the studied Schiff bases possess suitable physicochemical properties for oral bioavailability and may serve as promising lead compounds for further pharmacological investigation.

**Table: Lipinski Rule of Five Evaluation for Schiff bases (3a -3e)**

| Schiff Base Compound            | Molecular Weight ( $\text{g}\cdot\text{mol}^{-1}$ ) | Hydrogen Bond Donor (DBD) | Hydrogen Bond Acceptor (HBA) | Log P Estimated | Ro 5 Compliance |
|---------------------------------|-----------------------------------------------------|---------------------------|------------------------------|-----------------|-----------------|
| Lipinski's Rule of Five (Limit) | $\leq 500 \text{ g}\cdot\text{mol}^{-1}$            | $\leq 5$                  | $\leq 10$                    | $\leq 5$        |                 |
| 3a                              | 245.234                                             | 2                         | 5                            | ~2.1            | No violation    |
| 3b                              | 276.205                                             | 2                         | 6                            | ~2.4            | No violation    |
| 3c                              | 310.1035                                            | 2                         | 5                            | ~3.1            | No violation    |
| 3d                              | 310.1035                                            | 2                         | 5                            | ~3.1            | No violation    |
| 3e                              | 357.104                                             | 2                         | 5                            | ~3.8            | No violation    |

### IV. CONCLUSION

The molar refractivity behavior of substituted furan-based Schiff bases has been systematically investigated over a wide range of temperatures and concentrations. Molar refractivity increases with temperature and concentration and shows a clear dependence on substituent polarizability. Halogen-substituted Schiff bases exhibit higher refractivity, with iodinated derivatives showing the maximum values. Positional isomerism has negligible influence on refractivity. The compounds also demonstrate acceptable physicochemical characteristics under Lipinski's Rule of Five, suggesting their potential relevance in pharmaceutical research. The present study establishes a strong correlation between molecular structure and refractive behavior.

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