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Synthesis, Spectral and Molecular Docking Study of Antiviral Agent

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Abstract

The emergence of drug resistance in Human Immunodeficiency Virus (HIV) therapy necessitates the continuous development of novel antiviral agents targeting key viral enzymes. Reverse transcriptase (RT) plays a pivotal role in HIV replication and remains an attractive target for non-nucleoside reverse transcriptase inhibitors (NNRTIs). In the present study, a novel indole-based Schiff base, (E)-4-hydroxy-3-[(5-methoxy-1H-indol-3-yl)methyleneamino]benzoic acid (MIMH), was synthesized and evaluated for its antiviral potential through molecular docking studies. The compound was synthesized via acid-catalyzed condensation and structurally confirmed using FT-IR and ^{1}H NMR spectroscopy. Molecular docking was performed against HIV-1 reverse transcriptase (PDB ID: 1REV) using AutoDock Vina following protein and ligand preparation protocols. The docking results revealed a strong binding affinity, with a minimum binding energy of –11.2 kcal/mol, indicating stable interaction within the NNRTI binding pocket. Key interactions, including π–sigma, π–sulfur, carbon–hydrogen bonds, and hydrogen bonding, were identified using PyMOL and Biovia Discovery Studio. These findings highlight the potential of MIMH as a promising NNRTI candidate and support further experimental validation for antiviral drug development.

Keywords: *Preparation, Antiviral, Indole Derivative.*

I. INTRODUCTION

Human Immunodeficiency Virus (HIV) infection remains a major global health concern despite significant advances in antiretroviral therapy. One of the major challenges in HIV treatment is the rapid emergence of drug-resistant viral strains, which reduces the long-term efficacy of existing therapies. HIV-1 reverse transcriptase (RT), an essential enzyme responsible for the conversion of viral RNA into DNA, continues to be a critical molecular target in antiviral drug discovery (Singh et al., 2024). Non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit RT by binding to an allosteric hydrophobic pocket adjacent to the enzyme's active site, leading to conformational changes that suppress enzymatic activity. Indole derivatives have gained considerable attention as NNRTIs due to their structural versatility, strong π–π interactions, and favorable binding within hydrophobic enzyme cavities [Vanangamudi et al., 2023). Several indole-based molecules have demonstrated potent antiviral activity and improved resistance profiles (Ali et al., 2025, Chen et al., 2022).

Schiff bases containing an azomethine (–C=N–) linkage are well known for their diverse biological activities, including antiviral, antimicrobial, and anticancer properties (Azzouzi et al., 2024). The incorporation of functional groups such as phenolic –OH, carboxylic acid –COOH, and methoxy substituents further enhances molecular interactions through hydrogen bonding and electrostatic stabilization. Combining the indole scaffold with a Schiff base framework may therefore yield compounds with improved antiviral potential (Maiti et al., 2024).

II. MATERIALS AND METHODS

Indole derivatives have demonstrated potential as non-nucleoside reverse transcriptase inhibitors (NNRTIs) for HIV-1 treatment, targeting the essential reverse transcriptase (RT) enzyme in viral replication. This study focuses on evaluating the antiviral activity of an indole derivative through molecular docking with RT (PDB ID: 1REV).

- Protein Preparation: The RT structure (PDB ID: 1REV) was obtained from the Protein Data Bank. Water molecules were removed using PyMOL, and chain A was selected based on its superior binding cavity as identified in the literature. The protein and ligand files

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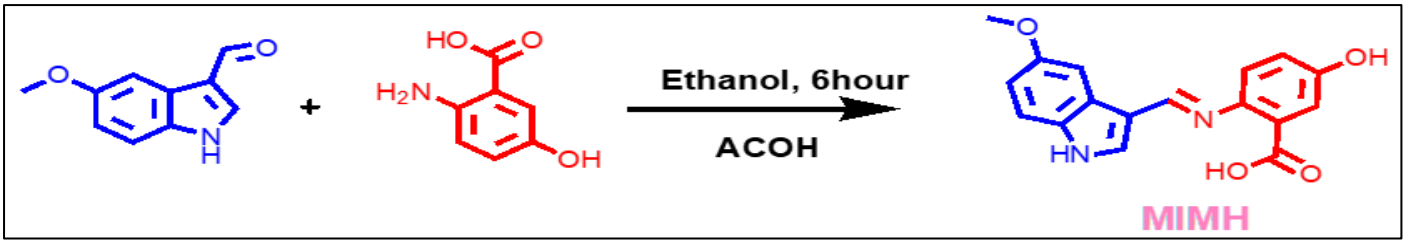
were prepared in PDBQT format using AutoDock tools, with nonpolar hydrogens added and Kollman charges assigned.

Ligand Preparation: IUPAC-Style Name of MIMH

(E)-4-hydroxy-3-[(5-methoxy-1H-indol-3-yl)methyleneamino]benzoic acid



- Preparation of MIMH: An equimolar mixture of the indole-based aldehyde (1.0 mmol) and the corresponding aminobenzoic acid derivative (1.0 mmol) was dissolved in ethanol (20 mL). To this solution, 2–3 drops of glacial acetic acid were added as a catalyst. The reaction mixture was refluxed with continuous stirring for approximately 6 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) using a suitable solvent system.

After completion, the reaction mixture was allowed to cool to room temperature, resulting in the formation of a solid precipitate. The product was filtered, washed with cold ethanol to remove unreacted starting materials, and dried under vacuum. The crude product was purified by recrystallization from ethanol to afford the Schiff base MIMH in good yield.

III. RESULTS

➢ *FTIR [Fourier Transform Infrared] Spectra of MIMH is Shown in Figure 1*

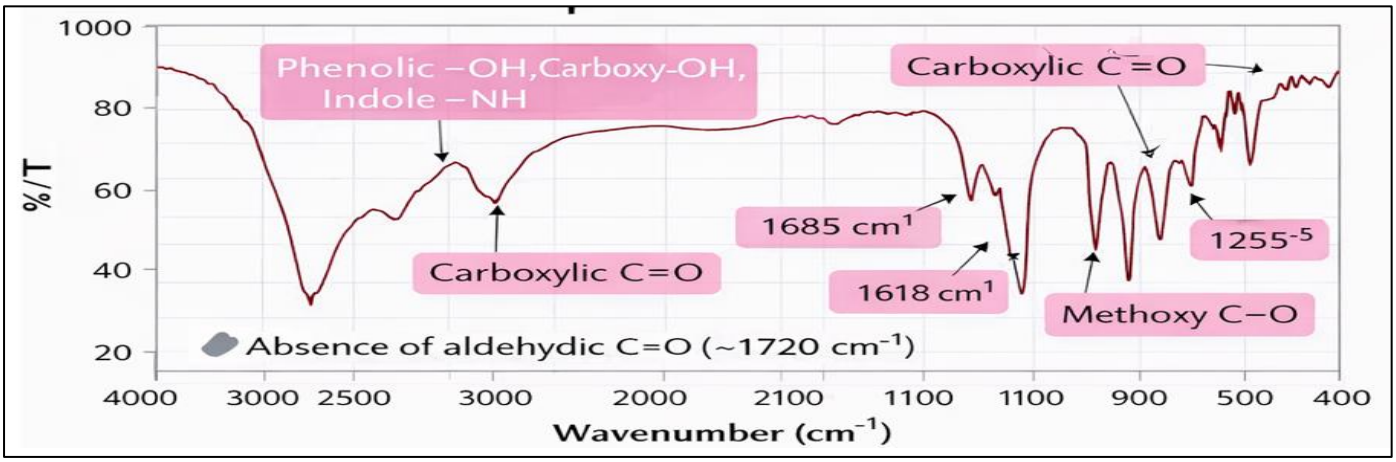


Fig 1 FTIR of MIMH

➢ *Proton NMR Spectra of MIMH is Shown in Figure 2*

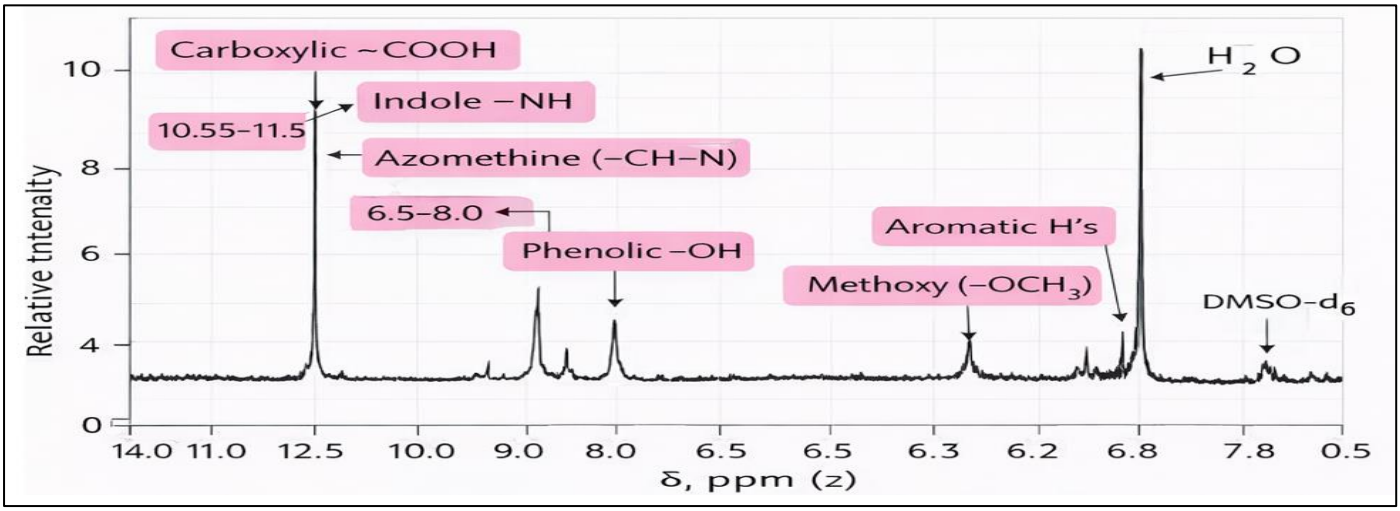


Fig 2 ^{1}H NMR of MIMH

➢ *Molecular Docking Results are Shown in Table 1 and Figure 3*

Table 1 Represents the Affinity, RMSD Lower Bound (l.b.), and RMSD Upper Bound (u.b.) for Each Mode.

Mode	Affinity (kcal/mol)	RMSD (l.b.)	RMSD (u.b.)
1	-10.0	0.000	0.000
2	-9.0	2.961	6.274
3	-8.9	2.252	5.286
4	-8.8	2.221	3.987
5	-8.5	3.126	6.119
6	-8.5	1.717	6.100
7	-8.2	1.603	2.312
8	-8.2	2.692	4.125
9	-7.9	4.044	6.113

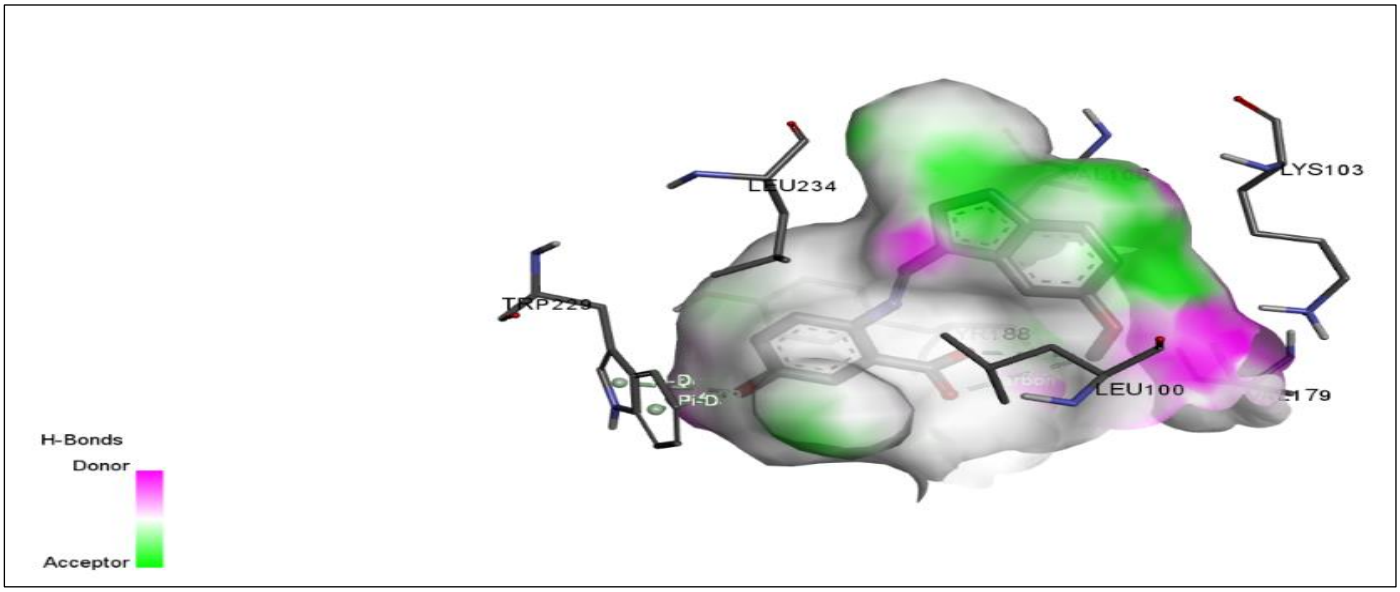


Fig 3 3D Molecular Docking Visualization of Protein-Ligand Interactions

IV. DISCUSSION

➢ *FT-IR Spectral Analysis of MIMH:*

The FT-IR spectrum of MIMH confirms the formation of the Schiff base and the presence of key functional groups. A broad absorption band at 3400–3200 cm^{-1} is attributed to overlapping stretching vibrations of the phenolic –OH, carboxylic –OH, and indole –NH groups. A strong band observed at 1680–1705 cm^{-1} corresponds to the C=O stretching vibration of the carboxylic acid group. The appearance of a sharp band at 1610–1630 cm^{-1} is assigned to the azomethine (–C=N–) stretching vibration, confirming successful Schiff base formation. Aromatic C=C stretching vibrations appear in the region 1500–1450 cm^{-1}. The band at 1250–1270 cm^{-1} is due to C–O stretching of the methoxy group. Peaks in the region 750–850 cm^{-1} are assigned to aromatic C–H out-of-plane bending vibrations.

➢ *^{1}H NMR Spectral Analysis of MIMH:*

The ^{1}H NMR spectrum further supports the proposed structure of MIMH. A downfield broad singlet at δ 12.0–13.0 ppm corresponds to the carboxylic acid (–COOH) proton. The indole –NH proton appears as a singlet in the region δ 10.5–11.5 ppm. A characteristic singlet at δ 9.0–9.5 ppm is assigned to the azomethine proton (–CH=N–), confirming Schiff base formation. Aromatic protons of the indole and benzene rings resonate as multiplets in the range δ 6.5–8.0 ppm. The phenolic –OH proton appears as a singlet around δ 5.0–6.0 ppm, often broad due to hydrogen bonding. A singlet at δ 3.7–3.9 ppm is attributed to the methoxy (–OCH_3) protons.

➢ *Molecular Docking:*

Molecular docking visualization of protein-ligand interactions was performed using PyMOL and Biovia Discovery Studio, highlighting interactions such as Pi-sigma, Pi-sulfur, and carbon-hydrogen bonds, etc. The optimal binding affinity score achieved was -10.0 kcal/mol, indicating strong interaction between the ligand and Reverse transcriptase enzyme (Danladi et al., 2025).

➢ *Binding Site Prediction and Docking:*

Binding site prediction was carried out using CASTp and literature references. A grid was generated in AutoDock, and the molecular docking was performed using AutoDock Vina. Output and log files were generated for analysis (Chandra et al., 2025).

V. CONCLUSION

In the present study, a novel indole-based Schiff base, MIMH, was successfully synthesized using a simple and efficient acid-catalysed condensation method. Structural

confirmation by FT-IR and ^{1}H NMR spectroscopy verified the formation of the azomethine linkage and the presence of key functional groups essential for biological activity. Molecular docking studies against HIV-1 reverse transcriptase (PDB ID: 1REV) revealed strong binding affinity, with a minimum docking score of –10.0 kcal/mol, indicating favourable interaction within the NNRTI binding pocket. Visualization of protein–ligand interactions highlighted multiple stabilizing interactions, including π–sigma, π–sulfur, carbon–hydrogen bonds, and hydrogen bonding with active-site residues. These results underscore the potential of indole-based Schiff bases as effective NNRTIs and suggest that MIMH may serve as a promising lead compound for further in vitro and in vivo antiviral studies. The findings contribute valuable insight toward the rational design of next-generation antiretroviral agents.

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➢ *Disclosure and Conflicts of Interest:*

- I declare that no conflict of interest in my research.

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