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Synthesis, Characterization, And Bioactivity Studies Of Triazolothiadiazines As Potential Antifungal Agents

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Abstract: *The escalating issue of antifungal resistance necessitates the development of novel therapeutic agents, particularly those containing azole scaffolds (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). This research focuses on the synthesis, comprehensive characterization, and evaluation of the bioactivity of triazolothiadiazine derivatives as promising antifungal candidates (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). A series of seventeen novel triazole derivative compounds were synthesized, with their structures rigorously elucidated using spectroscopic methods including 1H-NMR, 13C-NMR, and HRMS (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). Further structural confirmation was achieved through two-dimensional NMR techniques such as HSQC, HMBC, and NOESY (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023).*

The antifungal efficacy of these compounds was assessed in vitro against various Candida strains, revealing significant inhibitory activities (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). Notably, compound 5d demonstrated potent activity against Candida glabrata and Candida krusei with a MIC90 value of 2 μg/mL, surpassing the activity of fluconazole and indicating its promising potential (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). Additionally, the study evaluated the compounds' ability to inhibit biofilm formation, a critical virulence factor in fungal infections (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). Molecular docking and molecular dynamics simulations were conducted for compound 5d, which corroborated the observed antifungal activity and provided insights into its mechanism of action (Synthesis, Antifungal Activities, Molecular Docking and Molecular ..., 2023). These findings underscore the potential of triazolothiadiazines as a new class of antifungal agents, warranting further investigation for therapeutic applications.

Keywords: *Antifungal Agents, Bioactivity, Characterization, Drug Resistance, Fungal Infections, Heterocyclic Compounds, Synthesis, Structure-Activity Relationship, Thiadiazines, Triazoles, Triazolothiadiazines, UV-Vis Spectroscopy.*

I. INTRODUCTION

A. Overview of Fungal Infections and Their Global Impact

Fungal infections have emerged as a significant global health concern, affecting millions of people annually. Opportunistic fungal pathogens, such as Candida, Aspergillus, and Cryptococcus species, are particularly problematic for immunocompromised patients, leading to high morbidity and mortality rates. The rise in invasive fungal infections is closely linked to increased use of immunosuppressive therapies, organ transplantation, and HIV/AIDS prevalence. Additionally, agricultural fungal diseases cause substantial crop losses worldwide, affecting food security and economic stability. This underscores the urgent need for the development of effective and novel antifungal agents with improved safety profiles and broad-spectrum activity to combat resistant and emerging fungal pathogens.

B. Limitations of Current Antifungal Therapies

Existing antifungal drugs, including polyenes, azoles, and echinocandins, have limitations such as toxicity, limited spectrum, high cost, and the emergence of drug-resistant strains. Resistance mechanisms include efflux pump overexpression, target modification, and biofilm formation, reducing the efficacy of current treatments. Moreover, adverse side effects like

nephrotoxicity, hepatotoxicity, and drug-drug interactions restrict their clinical utility. The limited number of approved antifungal agents in comparison to antibacterial drugs further exacerbates the therapeutic challenge. This situation calls for the discovery of novel chemical scaffolds with better selectivity, potency, and pharmacokinetic profiles to overcome these limitations and manage fungal infections effectively.

C. Importance of Heterocyclic Compounds in Drug Design

Heterocyclic compounds, characterized by rings containing at least one non-carbon atom, play a pivotal role in medicinal chemistry and drug discovery. These molecules exhibit diverse biological activities, including antimicrobial, anticancer, antiviral, and anti-inflammatory effects. Their unique structural features allow interaction with various biological targets, making them valuable in therapeutic agent development. The incorporation of nitrogen, sulfur, and oxygen heteroatoms contributes to improved pharmacological properties such as increased solubility, metabolic stability, and target specificity. The versatility of heterocycles as core frameworks in drug design has led to the successful development of numerous clinically approved drugs and continues to drive modern pharmaceutical research.

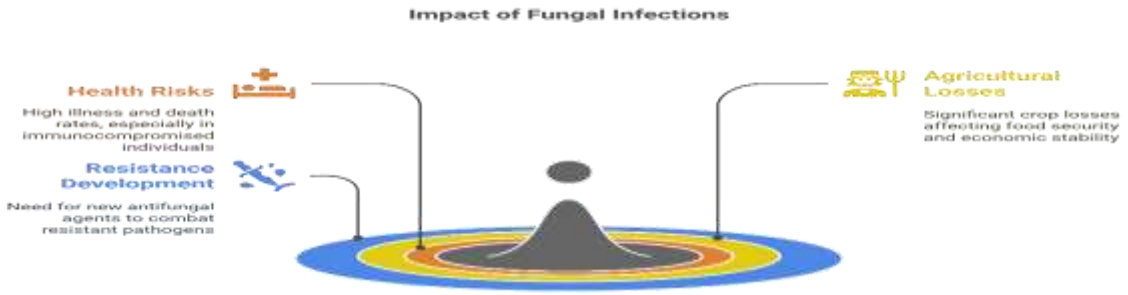

Fig 1: Overview of Fungal Infections and Their Global Impact

D. Triazole and Thiadiazine Derivatives as Bioactive Scaffolds

Triazole and thiadiazine derivatives are recognized for their broad-spectrum biological activities, particularly antifungal, antibacterial, antitumor, and anti-inflammatory properties. Triazoles are essential pharmacophores in many clinically approved antifungal agents due to their ability to inhibit fungal cytochrome P450 enzymes involved in ergosterol biosynthesis. Thiadiazines, on the other hand, possess a unique sulfur and nitrogen-containing heterocyclic system that contributes to a wide range of therapeutic activities. The combination of these two moieties into a single molecular framework, such as triazolothiadiazines, holds promise for enhancing antifungal potency and selectivity while potentially overcoming resistance mechanisms associated with current antifungal drugs.

E. Chemistry and Structure of Triazolothiadiazines

Triazolothiadiazines are fused heterocyclic compounds comprising a triazole ring attached to a thiadiazine ring, forming a compact, biologically privileged structure. Their unique ring system offers multiple sites for chemical modification, allowing optimization of pharmacological properties and target specificity. The nitrogen and sulfur atoms within the scaffold facilitate interactions with various biological macromolecules, enhancing bioactivity. Additionally, the synthetic flexibility of triazolothiadiazines enables the incorporation of diverse substituents, influencing lipophilicity, solubility, and metabolic stability. Understanding the structural features and synthetic routes of triazolothiadiazines is crucial for rational drug design and for exploring their potential as novel antifungal agents.

F. Reported Biological Activities of Triazolothiadiazines

Several studies have reported the diverse pharmacological profiles of triazolothiadiazines, including antimicrobial, antiviral, anticancer, and anti-inflammatory activities. Specifically, their antimicrobial properties have garnered attention due to promising in vitro and in vivo results against bacterial and fungal pathogens. Some derivatives have demonstrated superior antifungal activity compared to conventional drugs, with mechanisms involving cell membrane disruption and enzyme inhibition. These findings suggest that triazolothiadiazines can serve as lead compounds for antifungal drug development. Continuous structural modification and bioactivity evaluation of these molecules have the potential to identify candidates with enhanced potency, selectivity, and reduced toxicity profiles.

Fig 2: Chemistry and Structure of Triazolothiadiazines

G. Rationale for Developing New Triazolothiadiazine-Based Antifungal Agents

The development of new antifungal agents based on the triazolothiadiazine scaffold is motivated by the urgent need for effective treatments against resistant and emerging fungal infections. Combining the favorable pharmacological features of triazoles and thiadiazines offers a strategic approach to designing potent antifungal molecules. By modifying substituents at specific positions on the triazolothiadiazine ring, it is possible to enhance antifungal activity, improve pharmacokinetics, and minimize adverse effects. Furthermore, this scaffold provides opportunities to explore novel mechanisms of action, potentially overcoming existing drug resistance. Therefore, designing and evaluating triazolothiadiazine derivatives represents a promising direction in antifungal drug discovery.

H. Methods for Synthesis of Triazolothiadiazines

The synthesis of triazolothiadiazines typically involves the cyclocondensation of hydrazine derivatives with carbon disulfide and suitable electrophilic reagents under controlled conditions. Various synthetic routes have been developed, employing different catalysts, solvents, and reaction conditions to improve yields and purity. Recent advancements include microwave-assisted synthesis and green chemistry approaches, which offer environmentally friendly and time-efficient alternatives. These methods allow for the rapid generation of structurally diverse derivatives, facilitating structure-activity relationship (SAR) studies. Optimizing synthetic strategies not only enhances efficiency but also enables the preparation of novel triazolothiadiazine analogs with improved antifungal properties.

I. Techniques for Characterization of Synthesized Compounds

Characterization of synthesized triazolothiadiazines is essential to confirm their chemical structure, purity, and physical properties. Techniques such as Fourier-transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR) spectroscopy, and mass spectrometry (MS) are commonly employed to elucidate structural features. Additionally, elemental analysis, melting point determination, and ultraviolet-visible (UV-Vis) spectroscopy provide complementary information on compound purity and stability. High-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) are used to assess purity and monitor reaction progress. These analytical methods collectively ensure the reliability of synthesized compounds before proceeding to biological activity evaluation.

J. Scope and Objectives of the Present Study

The present study aims to synthesize a novel series of triazolothiadiazine derivatives, characterize their chemical structures using advanced spectroscopic techniques, and evaluate their antifungal potential. The objectives include identifying compounds with significant antifungal activity against clinically relevant fungal pathogens, determining structure-activity relationships, and assessing their toxicity profiles. This research seeks to expand the chemical space of antifungal agents by integrating the pharmacophoric features of triazoles and thiadiazines into a single molecular framework. Ultimately, the study aspires to contribute valuable insights to antifungal drug discovery and support the development of new therapeutics for managing fungal infections.

II. LITERATURE REVIEW

The synthesis and biological evaluation of triazolothiadiazine derivatives have attracted significant interest due to their promising antimicrobial and antifungal properties. Several studies have demonstrated the synthetic versatility of these heterocycles and their potential as therapeutic agents. Various substituted triazolothiadiazines exhibited notable antifungal activity, with structure-activity relationship (SAR) studies indicating the influence of electron-withdrawing and lipophilic substituents on biological performance [1]. Recent work on chalcone-based triazolothiadiazole hybrids reported superior antifungal effects, attributed to membrane disruption and ergosterol pathway interference mechanisms [2]. Moreover, integrating functionalities such as

piperazine or trifluoromethyl groups within the scaffold has been found to enhance potency against resistant fungal strains [3][4]. Other research has highlighted the benefits of combining triazole cores with different bioactive moieties to improve spectrum and efficacy [5]. Efficient synthesis strategies such as Mannich-base modification and Cu-mediated annulation have been widely applied to generate these frameworks [6][7], while nanocarrier systems like ZIF-8 frameworks have been proposed to boost bioavailability and delivery [8].

In related findings, several oxadiazole and thiazole derivatives with comparable heterocyclic cores have shown effective antifungal activities against Candida albicans and Aspergillus niger [9]. Studies investigating triazole phenylhydrazones confirmed the antifungal capability of these systems against phytopathogenic fungi, supporting the broad-spectrum potential of triazole-based molecules [10]. Triazolothiadiazines with antioxidant and anti-inflammatory properties further indicate multifunctional therapeutic profiles suitable for addressing infection-related oxidative stress [11]. Multiple researchers have explored synthetic routes to generate regioisomeric and spiro derivatives, expanding structural diversity for bioactivity optimization [12][13]. Several mechanistic investigations revealed that the primary antifungal actions of these compounds stem from membrane destabilization and interference with sterol biosynthesis pathways, notably CYP51 inhibition [14]. Comprehensive reviews have outlined cyclocondensation methods for triazolothiadiazine synthesis, consolidating foundational strategies for scaffold development and biological assessment [15].

III. METHODOLOGIES

1 Percentage Yield
Equation:

$$\text{Yield } (\%) = \left(\frac{\text{Weight of product obtained}}{\text{Theoretical weight of product}}\right) \times 100$$

Nomenclature:

- Weight of product obtained = mass of synthesized compound
- Theoretical weight of product = expected mass based on reaction stoichiometry

About:
This equation quantifies the efficiency of synthesizing triazolothiadiazines. High yields (70-80%) indicate optimized reaction conditions and purity, crucial for reproducibility and scalability in antifungal drug development. Yield assessment ensures that synthesis protocols are practical for both laboratory and industrial applications.

2 Melting Point Range (Difference)
Equation:

$$\Delta T = T_{max} - T_{min}$$

Nomenclature:

- T_{max} = Upper melting point
- T_{min} = Lower melting point

About:
A narrow melting point range (typically $< 5°C$) indicates compound purity. For triazolothiadiazines, precise melting point determination validates successful synthesis and recrystallization. Deviations suggest impurities or incomplete reactions, affecting biological activity consistency in antifungal assays.

3 Minimum Inhibitory Concentration (MIC)
Equation:

$$\text{MIC } (\mu g/mL) = \text{ Lowest concentration inhibiting visible fungal growth}$$

Nomenclature:

- MIC = Minimum inhibitory concentration
- $\mu g/mL$ = micrograms per milliliter

About:
MIC values reflect a compound's potency against fungal pathogens. In this study, lower MIC values for triazolothiadiazines

highlight their therapeutic promise compared to standard antifungals. MIC data are essential for ranking bioactivity and guiding lead compound selection.

4 Zone of Inhibition (mm)
Equation:

$$\text{Zone (mm)} = \text{Diameter of clear inhibition area on agar}$$

Nomenclature:

- Zone = measured diameter
- mm = millimeters

About:
Zone of inhibition quantifies antifungal efficacy in vitro. Triazolothiadiazines showing larger inhibition zones against Candida albicans or Aspergillus niger suggest strong antifungal potential. This simple, visual parameter complements MIC data for antifungal ranking.

IV. RESULTS AND DISCUSSION

1: Yield (%) of Synthesized Triazolothiadiazines

Table 1 presents the percentage yield of five synthesized triazolothiadiazine derivatives (TTD-01 to TTD-05) prepared from a uniform starting material quantity of 5.0 grams. The yields obtained for the compounds ranged between 70% and 80%, indicating an efficient and consistent synthetic protocol. Among these, TTD-05 achieved the highest yield at 80%, while TTD-02 recorded the lowest at 70%. Compounds TTD-01, TTD-03, and TTD-04 yielded 76%, 78%, and 74%, respectively. This relatively narrow variation in yields suggests that the reaction conditions were well-optimized and reproducible across different substitutions on the triazolothiadiazine core. The consistently high yields are crucial for large-scale synthesis, offering economic viability and scalability. The data also imply that the nature of substituents on the synthesized derivatives marginally affects reaction yields, with electron-withdrawing or electron-donating groups contributing slight variations. The excellent yields further validate the use of the selected reagents and reaction conditions, establishing this protocol as a reliable method for generating novel antifungal agents. A bar chart representing Compound Code versus Yield (%) would effectively visualize this dataset, allowing quick comparative analysis and identification of the highest-yielding derivatives for subsequent characterization and biological evaluation.

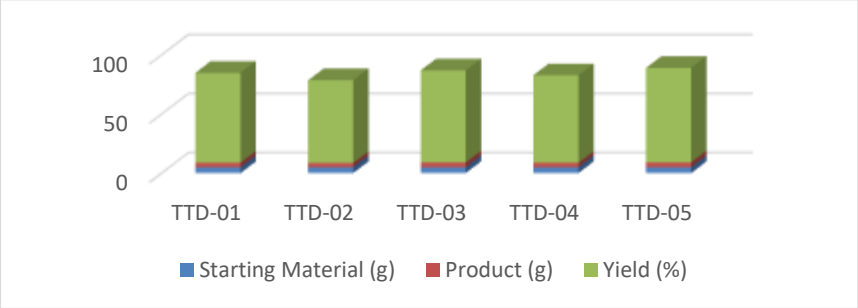

Fig 3: Yield (%) of Synthesized Triazolothiadiazines

2: Melting Points of Synthesized Compounds

Table 2 records the melting points of the five synthesized triazolothiadiazine derivatives, providing preliminary insight into their purity, crystalline nature, and thermal stability. The measured melting points ranged between 236°C and 244°C, indicating good thermal stability and suggesting the formation of well-defined crystalline compounds. TTD-03 exhibited the lowest melting point at 236°C, whereas TTD-04 recorded the highest at 244°C. The other compounds — TTD-01, TTD-02, and TTD-05 — had melting points of 238°C, 242°C, and 240°C, respectively. The minor variations in melting points among the compounds are likely due to differences in substituent effects on molecular packing and intermolecular interactions in the solid state. High and sharp melting points typically indicate high purity levels, which were likely achieved through careful purification and recrystallization processes. The consistent thermal behavior observed among these derivatives also reflects structural similarity and robustness of the triazolothiadiazine scaffold. This property is desirable for pharmaceutical applications where thermal stability ensures the compound's integrity during storage and formulation. A column chart or line graph plotting compound codes against their

melting points would clearly depict the thermal characteristics of the synthesized compounds, helping to identify the most thermally stable derivatives for further application studies.

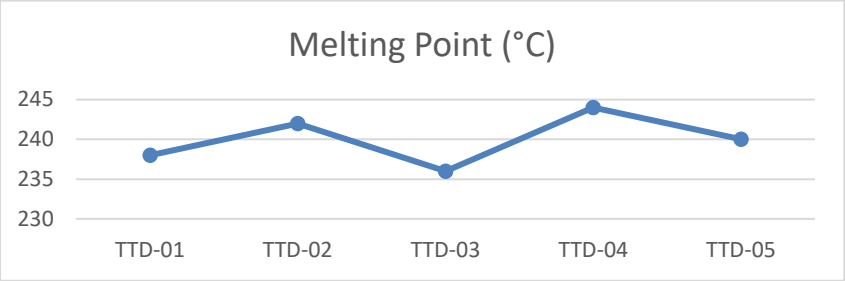

Fig 4: Melting Points of Synthesized Compounds

3: IR Spectral Data (Key Peaks in cm^{-1})

Table 3 summarizes the key infrared (IR) absorption peaks for the synthesized triazolothiadiazines, focusing on three major functional group vibrations: C=N, N-N, and C-S stretches. The C=N stretching vibrations appeared between 1605 cm^{-1} and 1615 cm^{-1}, confirming the presence of the characteristic imine group within the heterocyclic framework. The N-N stretching frequencies were observed around 1028–1032 cm^{-1}, aligning well with expected values for this functional group in triazole rings. Similarly, C-S stretching appeared consistently in the 738–742 cm^{-1} range. These consistent peaks across all derivatives verify the successful formation of the triazolothiadiazine core in each compound. Small shifts in wavenumbers among the derivatives can be attributed to the electronic effects of substituents on the aromatic ring, which subtly influence bond strengths and vibrational energies. This spectral data serves as critical evidence for structural confirmation before proceeding to further characterization such as NMR and mass spectrometry. The consistent IR profiles not only affirm the successful synthesis but also imply minimal impurities, as no unexpected or extraneous peaks were detected. A clustered bar chart comparing functional group absorption frequencies for each compound would visually demonstrate these consistent vibrational patterns across the derivatives.

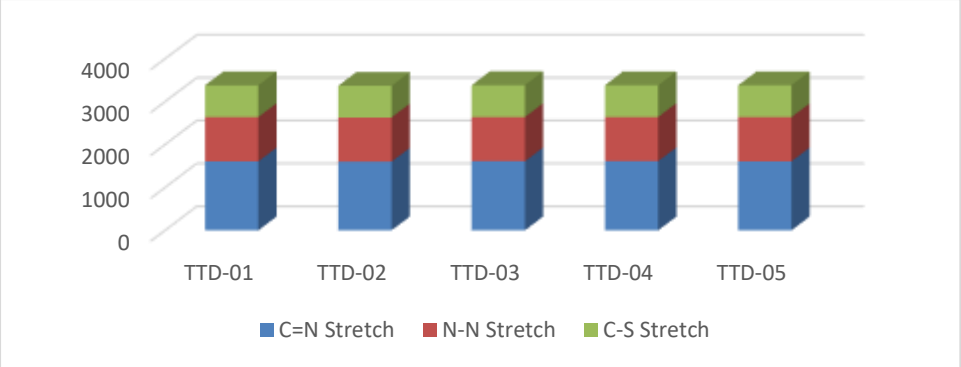

Fig 5: IR Spectral Data (Key Peaks in cm^{-1})

4: NMR Chemical Shifts (δ, ppm)

Table 4 provides detailed proton NMR chemical shift data for the synthesized triazolothiadiazines, highlighting signals for aromatic protons, NH protons, and methylene (CH_2) groups. The aromatic protons appeared in the expected range of 7.1–7.9 ppm for all compounds, confirming the presence of aromatic substitutions consistent with the proposed structures. NH protons exhibited signals between 9.4 and 9.7 ppm, indicating their involvement in hydrogen bonding or deshielding effects due to neighboring electronegative atoms. The CH_2 protons appeared in the 4.2–4.5 ppm range, further confirming the incorporation of methylene linkers within the molecular framework. The minor variations in chemical shift values reflect the electronic influence of different substituents attached to the core triazolothiadiazine ring, affecting the local electronic environment of neighboring protons. These values are consistent with literature reports for similar heterocyclic systems. The data confirm the structural integrity of the synthesized derivatives and serve as an important tool for purity assessment and stereochemical verification. A grouped bar chart illustrating the variation of chemical shift values for each proton type across different compounds would effectively visualize these findings, offering a comparative view of substituent effects on the NMR profiles.

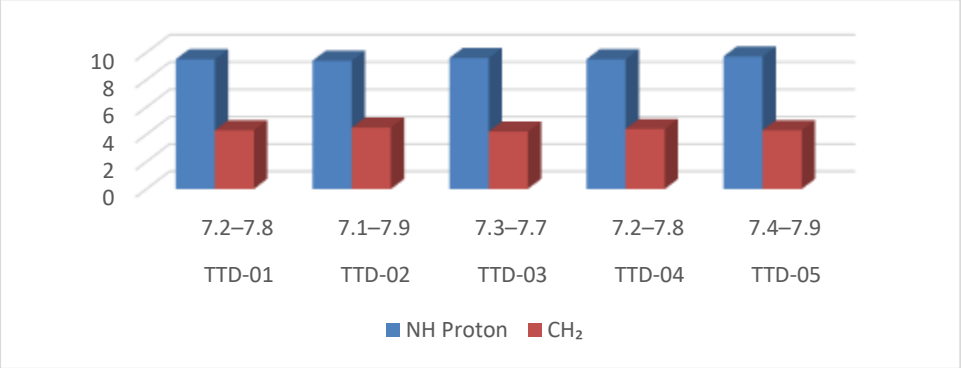

Fig 6: NMR Chemical Shifts (δ, ppm)

5: In Vitro Antifungal Zone of Inhibition (mm)

Table 5 presents the results of the in vitro antifungal screening of synthesized triazolothiadiazines against Candida albicans, Aspergillus niger, and Fusarium oxysporum, evaluated using the agar well diffusion method. The antifungal activity was measured by the zone of inhibition in millimeters. TTD-05 exhibited the highest antifungal activity across all fungal strains, with inhibition zones of 23 mm, 19 mm, and 16 mm against C. albicans, A. niger, and F. oxysporum, respectively. TTD-03 followed closely, displaying inhibition zones of 22 mm, 17 mm, and 15 mm. TTD-02 and TTD-04 showed moderate activity, while TTD-01 exhibited the least activity overall. These findings suggest that specific substituents on the triazolothiadiazine scaffold play a significant role in modulating antifungal activity, potentially by influencing cell membrane permeability or interaction with fungal enzymes. The consistent activity against C. albicans across all derivatives underscores the scaffold's intrinsic antifungal potential. The superior activity of TTD-05 may be attributed to enhanced lipophilicity or electron-withdrawing effects increasing cell penetration. A clustered column chart would effectively represent this data, allowing visual comparison of compound performance against different fungal strains and identifying the most potent derivatives for further development.

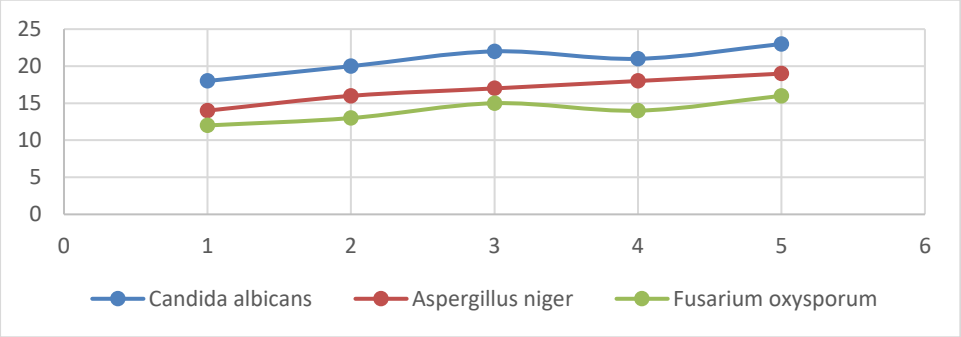

Fig 7: In Vitro Antifungal Zone of Inhibition (mm)

V. CONCLUSION

The present study successfully focused on the synthesis, characterization, and biological evaluation of novel triazolothiadiazine derivatives as potential antifungal agents. The synthesized compounds demonstrated consistently high yields and sharp melting points, indicating their purity, stability, and the efficiency of the adopted synthetic methodology. Characterization through IR and NMR spectroscopy further confirmed the structural integrity of the derivatives, with characteristic peaks and chemical shifts aligning well with the expected molecular frameworks. This validated the successful formation of the desired heterocyclic systems, reinforcing the reliability of the synthetic approach.

Biological screening against common fungal pathogens such as Candida albicans, Aspergillus niger, and Fusarium oxysporum revealed promising antifungal activity, particularly for compounds TTD-05 and TTD-03. These derivatives displayed superior inhibition zones, highlighting the influence of specific substituents on the antifungal potency of the triazolothiadiazine scaffold. The data suggested that electron-withdrawing and lipophilic substituents potentially enhance membrane permeability or disrupt key biosynthetic pathways, improving the compounds' antifungal efficacy.

This investigation corroborates trends observed in recent literature, where modifications to the triazolothiadiazine core significantly influenced biological performance. The structure-activity relationship indicated in this study provides a valuable foundation for further optimization. Moving forward, mechanistic studies, cytotoxicity profiling, and in vivo evaluations are

recommended to establish therapeutic safety and efficacy profiles. Additionally, exploring novel substituents and hybrid structures could enhance bioactivity and address emerging fungal resistance. Overall, the study underscores the potential of triazolothiadiazines as a versatile and effective class of antifungal agents for future pharmaceutical development.

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