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Design, Synthesis and Biological Evaluation of Benzothiazole Derivatives for Antimicrobial Activity

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KEYWORDS
Molecular docking, Benzothiazole, anti-bacterial, anti-fungal, heterocyclic compounds.

ABSTRACT:

Benzothiazoles are a crucial class of heterocyclic compounds known for their broad spectrum of biological activities, particularly their antimicrobial properties. This study investigates the synthesis, molecular docking, and biological evaluation of various benzothiazole derivatives for their potential antimicrobial activity. A series of benzothiazole derivatives were synthesized and characterized using spectroscopic methods. Molecular docking studies were performed to predict the binding affinities of these derivatives to target microbial enzymes, providing insights into their mechanisms of action.

Biological evaluation involved testing the synthesized compounds for their antifungal and antibacterial activities against selected microbial strains. Compounds A1, A2, A4, A6, and A9 demonstrated significant antifungal activity against Aspergillus niger and Candida albicans (NCIM 3102), with Amphotericin-B used as the standard antifungal drug for comparison. Among these, compounds A1, A2, and A9 also exhibited promising antibacterial activity against Escherichia coli (ATCC 25922) and Staphylococcus aureus (ATCC 29737), with Ciprofloxacin serving as the standard antibacterial drug.

The results indicate that specific structural modifications in the benzothiazole core can enhance antimicrobial efficacy, suggesting that these compounds have potential as therapeutic agents. Further studies, including in vivo testing and optimization of lead compounds, are warranted to fully explore their clinical potential.

1.Introduction

Benzothiazoles are a prominent class of heterocyclic compounds that contain a benzene ring fused to a thiazole ring. [1-3] They are notable for their broad spectrum of biological activities, which make them important scaffolds in medicinal chemistry and pharmaceutical research. This overview discusses the structure, synthesis, and diverse biological activities of benzothiazole derivatives, highlighting their significance in drug discovery and development.

Benzothiazole is characterized by a fused ring system consisting of a benzene ring and a thiazole ring (a five-membered ring containing nitrogen and sulfur). The basic structure of benzothiazole allows for various

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substitutions on the benzene and thiazole rings, which can significantly alter their chemical and biological properties. These modifications enable the design of compounds with tailored activity for specific therapeutic targets.[4]

The synthesis of benzothiazole derivatives can be achieved through several methods. Some of the common synthetic routes include: Cyclization of 2-aminothiophenols with aldehydes or ketones is a widely used method for synthesizing benzothiazoles.

This reaction typically involves the formation of a Schiff base intermediate, which cyclizes to form the benzothiazole ring system. Substitution reactions on preformed benzothiazole rings can introduce various functional groups, allowing for fine-tuning of biological activity.[5-7]

Biological Activities

Benzothiazole derivatives exhibit a wide range of biological activities, making them valuable in various therapeutic areas:

Antimicrobial Activity

Benzothiazoles have been extensively studied for their antimicrobial properties. They are effective against a variety of bacterial and fungal pathogens. 2-Substituted benzothiazoles showing potent activity against Staphylococcus aureus and Escherichia coli.[8]

Anticancer Activity

Certain benzothiazole derivatives have shown significant anticancer activity by targeting specific cellular pathways involved in cancer progression. 2-(4-Aminophenyl)benzothiazole has been investigated for its ability to inhibit tumor growth.[9]

Anti-inflammatory Activity

Benzothiazoles can also exhibit anti-inflammatory properties by modulating inflammatory pathways and cytokine production. Benzothiazole derivatives inhibiting COX-2 enzyme, which plays a key role in inflammation.[10]

The versatility of benzothiazole derivatives in interacting with various biological targets makes them promising candidates for drug development. They serve as core structures in many drugs currently under clinical investigation or already in therapeutic use. The ability to modify the benzothiazole scaffold enables the development of compounds with optimized pharmacokinetic and pharmacodynamic properties. Benzothiazoles are an essential class of heterocyclic compounds with diverse biological activities.

Their structural flexibility and the ability to undergo various chemical modifications make them valuable in the design and development of new therapeutic agents. Continued research into benzothiazole derivatives holds promise for discovering new drugs to treat a range of diseases, including infections, cancer, and inflammatory conditions.

2. EXPERIMENTAL WORK

2.1 Molecular Docking:

Molecular docking is a computational technique used to predict the preferred orientation of a ligand when it binds to a protein receptor. This process provides crucial information about the protein-ligand interactions that govern biological functions.

In this work, we utilize several tools for different stages of molecular docking, including LigPlot+ for creating 2D interaction diagrams, Discovery Studio Visualizer for analyzing docking results, Chem3D and ChemDraw for ligand preparation, and AutoDock Vina for molecular docking calculations. The steps are as follows : [11]**Selection of Target Receptor**

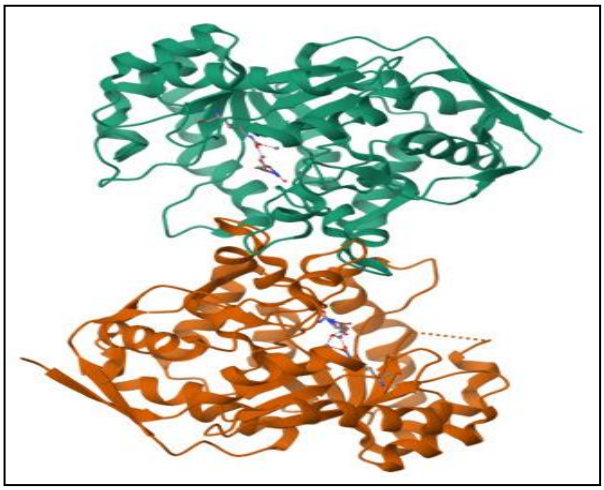

Fig.01 TARGET: Thr109Gly dihydroorotase (PDB ID- 2Z2A)

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Table no.01 Ligand used for Docking:

Parameters	Details	Standards
Protein Id and method of experiment	2Z2A X-RAY Diffraction	- X-RAY Diffraction
Mutation	No	No
Resolution	2.60 Å	Near about 2.00 A^0
wwPDB Validation	Blue side	Better
Ramchandran Plot (by PROCHECK server) Residues in favoured + Allowed regions	100%	>88.3 %

Ligand Preparation:

Benzothiazole derivatives with antimicrobial activity were created using ChemDraw and saved as .mol files. These ligand structures were then optimized using Chem3D, where energy minimization was carried out using the MM2 force field. Once optimized, the structures were converted into the PDBQT format required for AutoDock Vina.

Receptor Preparation: The crystal structure of Thr109Gly dihydroorotase (PDB ID- 2Z2A) was obtained from the Protein Data Bank. The protein structure was prepared by removing water molecules, adding polar hydrogens, and assigning Gasteiger- Marsili charges. The prepared protein was then saved in PDBQT format.

Grid Box Generation:

Within Auto Dock Tools, a grid box was generated around the active site of Thr109Gly dihydroorotase. The dimensions and center of the grid box were adjusted to encompass the entire active site, ensuring all possible binding poses were considered during the docking calculations.

Molecular Docking:

The Benzothiazole derivatives were docked into the active site of dihydroorotase using Auto Dock Vina. The output was produced in PDBQT format, and the docking computations were performed with default parameters. Auto Dock Vina's scoring function ranked the docking poses based on their estimated binding affinities.

Analysis of Docking Results:

Discovery Studio Visualizer was used to analyze and display the docking results. The protein-ligand complexes were examined to determine essential interactions, such as hydrophobic contacts, π-π stacking, and hydrogen bonding, which support the specificity and affinity of the designed compounds' binding. The binding positions of the Benzothiazole derivatives were compared to those of known inhibitors to assess their potential as antimicrobial agents.

2D Interaction Diagrams:

LigPlot+ was employed to generate 2D interaction diagrams of the protein- ligand complexes. These diagrams provided a clear representation of the key interactions between the Benzothiazole derivatives and Thr109Gly dihydroorotase , facilitating a deeper understanding of the structure-activity relationships (SAR) governing their antimicrobial activity. The molecular docking method described here employs a combination of computational tools, including Auto Dock Vina, Chem3D, Chem Draw, Discovery Studio Visualizer, and LigPlot+, to predict and analyze the binding interactions between Benzothiazole derivatives and Thr109Gly dihydroorotase, aiding in the rational design of novel antimicrobial agents[12].

2.2 SYNTHESIS OF COMPOUND

2.2.1 Scheme for Benzothiazole Derivatives

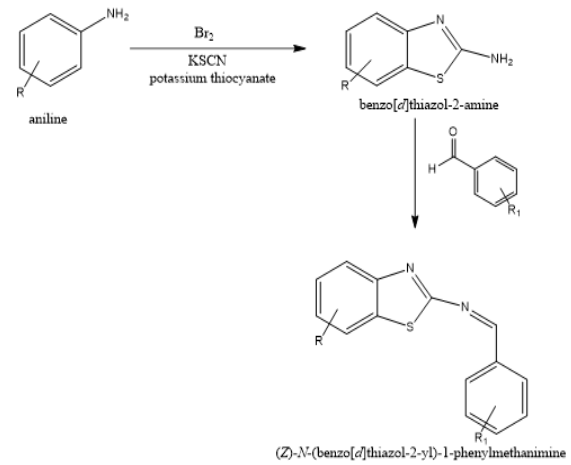

Fig.02Scheme for Benzothiazole Derivatives

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Table 02: Derivatives of Benzothiazole

Sr. No.	Label	R	R_1
1	A1	2-CL	2-OH
2	A2	2-CL	2-CH_3
3	A3	2-CL	2-CL
4	A4	4-CL	2-OH
5	A5	4-CL	2-CH3
6	A6	4-CL	2-CL
7	A7	3-CL	2-OH
8	A8	3-CL	2-CH_3
9	A9	3-CL	2-CL

2.2.2General procedure for synthesis of Scheme

To synthesize 2- substituted amino benzothiazole using potassium thiocyanate, begin by mixing aniline (1 mole) and potassium thiocyanate (1 mole) in a suitable reaction vessel. Then heat the mixture under reflux with the addition of a hydrochloric acid until the reaction is complete, as indicated by the appearance of a characteristic color change. Then dissolve the resulting 2-mercaptobenzothiazole in ethanol and add an excess of sodium hydroxide to the solution. Reflux the mixture until the conversion to 2-amino-benzothiazole is achieved. After completion, cool the reaction mixture, neutralize it with dilute hydrochloric acid, and extract The product using an ethanol. Purify the crude product through recrystallization method, and confirm the identity and purity of 2-amino-benzothiazole using spectroscopic techniques such as NMR, IR spectrometry. Safety precautions should be strictly followed throughout the procedure, conducted in a well-ventilated laboratory, and optimized based on specific reaction conditions and reagents used.

STEP 2

To synthesize the Schiff's base of 2-amino-benzothiazole and benzaldehyde, begin by adding 2-amino-benzothiazole (1 equivalent) and benzaldehyde (1 equivalent) to a suitable reaction vessel. Stir the mixture at room temperature in the presence of an ethanol until the Schiff's base is formed, typically evidenced by the appearance of a characteristic color change. To enhance the reaction efficiency, used acetic acid, can be employed. Once the reaction is complete, precipitate the Schiff's base by adding a diethyl ether to the reaction mixture. Collect the precipitate through filtration, wash it with the solvent, and allow it to air-dry. Purify the Schiff's base further, if necessary, using technique recrystallization. Confirm the identity of the synthesized compound through spectroscopic methods such as NMR, IR spectrometry. Adherence to safety protocols, such as proper ventilation and protective measures, is crucial during the synthesis, and the procedure may be optimized based on specific reaction conditions and desired product characteristics.

2.3 Physiochemical Characteracterization:

Physiochemical characteracterization of synthesized product includes;

- **Melting point determination:**

Melting point is a valuable criterion for the purity of the organic compound. The melting points were determined by open capillary method using digital melting point apparatus.

- **Solubility determination:**

The solubility of synthesized compounds was tested in different polar, semi polar, and non-polar solvent.

- **TLC analysis (R_f value):**

Thin Layer Chromatography is an important technique which provides information regarding progress of reaction and determines the purity of compounds. RF Value is the characteristic for each compound and calculated through TLC analysis by using the equation given below:

$$R_f = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

2.4 SPECTROSCOPIC CHARACTERIZATION:

2.4.1 STRUCTURAL INTERPRETATION OF SCHIFF'S BASES OF 2-AMINO-BENZOTHIAZOLE DERIVATIVES

Interpreting the structural features of Schiff's bases of 2-amino-benzthiazole derivatives using spectroscopic techniques such as Infrared Spectroscopy (IR), Nuclear Magnetic Resonance Spectroscopy (NMR)can provide valuable insights into their chemical composition and bonding patterns:

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Infrared Spectroscopy (IR):

IR spectroscopy provides information about the functional groups present in a molecule based on the absorption of infrared radiation by specific chemical bonds. In Schiff's bases of 2-amino-benzthiazole derivatives, characteristic IR absorption bands may include: The C=N stretching vibration: Typically appears in the range of 1600-1670 cm^-1, indicating the presence of the Schiff base functional group. Aromatic C-H stretching vibrations: Present as sharp peaks in the region of 3000-3100 cm^-1 for the aromatic rings of benzothiazole derivatives. C-S stretching vibration: Observed around 600-700 cm^-1, confirming the presence of the thiazole ring. The absence of absorption bands corresponding to carbonyl groups (around 1700 cm^-1) would indicate successful formation of the Schiff base, as the carbonyl group of the aldehyde or ketone is involved in the condensation reaction.

^{1}HNMR Spectra:

All the synthesized compounds were characterized by ^{1}HNMR spectral analysis. The results of NMR spectra resemble to molecular structure.

2.5 MICROBIOLOGICAL SCREENING [13-14]

2.5.1 ANTI-BACTERIAL ACTIVITY

Nutrient agar plates were prepared by pouring 15-20 mL of the medium into each sterilized Petri dish and were allowed to set at room temperature. The cell suspension was standardized to the density of 530 nm using spectrophotometer and was inoculated over the surface of agar medium using sterile cotton swab. The cups were scooped in each plate using a sterile cork borer of 6 mm diameter. Then the solutions of test compounds (0.10 mL) were added in cups by using micropipettes and these plates were incubated at 37°C for 48 hrs. The zone of inhibition was measured in mm for each organism.

2.5.2 ANTI-FUNGAL ACTIVITY

Sabouraud-Dextrose agar plates were prepared by pouring 15-20 mL of the medium into each sterilized Petri dish and were allowed to set at room temperature. The cell suspension was standardized to a density of 530 nm using a spectrophotometer and was inoculated over the surface of medium using a sterile cotton swab. Three cups were scooped in each plate using a sterile cork borer of 6mm diameter, standard and test solution. The solution of each test compound (0.10 mL/0.15 mL) was added in the cups by using micropipettes and these plates were subsequently incubated at 37°C for 48 hrs. The zone of inhibition was measured in mm for each organism.

3. RESULTS AND DISCUSSION

3.1 Results of Molecular Docking:

Table 03: Ligand energies (kcal/mol) and binding affinities (kcal/mol)of molecule of Scheme (fig.03)

Label	Docking score
A1	**-7.1**
A2	**-6.7**
A3	**-6.8**
A4	**-7.1**
A5	**-6.9**
A6	**-6.9**
A7	**-7.2**
A8	**-7.1**
A9	**-7.1**
Native Ligand	**-5.8**

Table 04: The active amino residues, bond length, bond category, bond type, ligand energies:

Active Amino acid	Bond length	Bond Type	Bond Category
Compound: A1			
PRO334	2.44189	Hydrogen Bond	Conventional Hydrogen Bond
HIS218	3.74837	Hydrogen Bond	Carbon Hydrogen Bond
SGLU323	4.04807	Electrostatic	Pi-Anion

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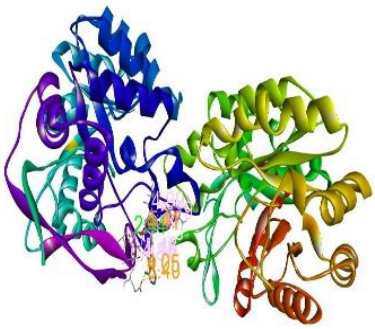
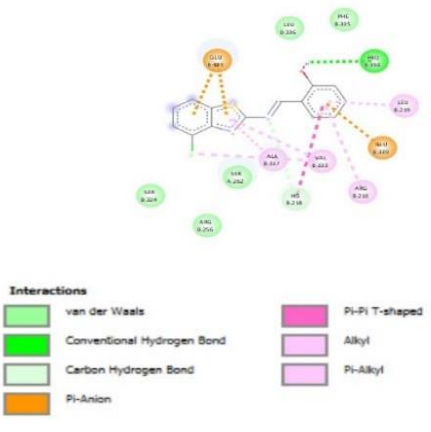
GLU323	3.40452	Electrostatic	Pi-Anion

GLU339	4.41414	Electrostatic	Pi-Anion
HIS218	5.47267	Hydrophobic	Pi-Pi T-shaped
VAL333	4.33986	Hydrophobic	Alkyl
VAL333	5.18254	Hydrophobic	Pi-Alkyl
ALA337	4.4342	Hydrophobic	Pi-Alkyl
ARG216	5.19267	Hydrophobic	Pi-Alkyl
LEU219	4.99047	Hydrophobic	Pi-Alkyl
Compound: Ethoxzolamide			
GLU323	2.47146	Hydrogen Bond	Conventional Hydrogen Bond
ALA337	2.29404	Hydrogen Bond	Conventional Hydrogen Bond
GLU339	4.136	Electrostatic	Pi-Anion
GLU339	3.37678	Electrostatic	Pi-Anion
LEU219	4.61797	Hydrophobic	Alkyl
PHE205	4.34292	Hydrophobic	Pi-Alkyl
ALA337	4.72352	Hydrophobic	Pi-Alkyl
LEU219	5.33141	Hydrophobic	Pi-Alkyl

3.2 3D and 2D poses of Ligand.

Table 05: 2D and 3D poses of Ligand and protein interactions.(A1)

3D-docking poses	2D-docking poses
	

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3.3 MELTINF POINT, MOLECULAR FORMULA, PERCENTAGE YIELDS AND RF VALUES SYNTHESIZED DERIVATIVES OF SCHME I: -

Table No.06: Analytical data of compounds A_1-A_9

Comp	Mol. Formula	Mol. Wt.	M.P ^{0}C	Rf Value	Yield %
A_1	$C_{14}H_9N_2ClOS$	288.75	224-226	0.46	67
A_2	C15H11ClN2S	286.77	250-252	0.65	78
A_3	$C_{14}H_9N_2Cl2OS$	307.19	218-221	0.53	67
A_4	$C_{14}H_9N_2ClOS$	288.75	191-193	0.52	66
A_5	C15H11ClN2S	286.77	228-229	0.48	75
A_6	$C_{14}H_9N_2Cl2OS$	307.19	212-214	0.48	61
A_7	$C_{14}H_9N_2ClOS$	288.75	132-134	0.51	63
A_8	C15H11ClN2S	286.77	135-138	0.51	44
A_9	$C_{14}H_9N_2Cl2OS$	307.19	131-133	0.56	64

Table 07: Percentage yield and spectral frequencies of synthesized compound

Label	Structure
A1	Yield: 67%, M.p: 224-226°C, Rf value: 0.46, Chemical formula: $C_{14}H_9N_2ClOS$.**FTIR (cm-1):** 3243.88 -OH stretching; 3013.46 Ar-CH stretching; 1496.17 -C=N stretching; 917.82 -C-Cl stretching; 687.48 -C-S-C stretching.**1H NMR (δppm):** 5.551 (1H of -OH); 6.2-7.63 (7H of -C6H5); 4.7 1H of (-CH=N).
A2	Yield: 78%, M.p: 250-252°C, Rf value: 0.65, Chemical formula: $C_{15}H_{11}ClN_2S$.**FTIR (cm-1):** 3029.77 Ar-CH stretching; 2817.88 -CH2 stretching; 1506.80 -C=N stretching; 869.37 -C-Cl stretching; 669.21 -C-S-C stretching.**1H NMR (δppm):** 6.5-7.63 (7H of -C6H5); 4.7 1H of (-CH=N); 1.66-2.11 (3H of -CH3).
A3	Yield: 67%, M.p: 218-221°C, Rf value: 0.53, Chemical formula: $C_{14}H_9N_2Cl_2OS$.**FTIR (cm-1):** 3027.52 Ar-CH stretching; 1521.94 -C=N stretching; 855.18 -C-Cl stretching; 640.35 -C-S-C stretching. **1H NMR (δppm):** 6.54-8.45 (7H of -C6H5); 4.76 1H of (-CH=N).
A4	Yield: 66%, M.p: 191-193°C, Rf value: 0.52, Chemical formula:$C_{14}H_9N_2ClOS$.**FTIR (cm-1):** 3470.71 -OH stretching; 3340.02 -NH stretching; 1620.60 C=N stretching; 1564.00 C=C stretching; 1498.51 C=C stretching; 1424.37 C-H stretching; 1339.65 C-N stretching; 1234.16 C-O stretching; 1162.57 C-H (In plane bend); 1091.54 C-H (Out of plane bend); 734.80 C-Cl stretching; 657.07 C-S stretching.**1H NMR (δppm):** 2.012-2.168 (3H of CH_3); 2.387 (1H of -CH); 3.051-3.714 2H of (-CH_2); 4.310 (1 H of OH); 6.450-6.700 (3H of Aromatic Protons); 7.410-7.540 (4H of Aromatic Protons); 7.639 (1H of CH=N)
A5	Yield: 75%, M.p: 228-229°C, Rf value: 0.48, Chemical formula: $C_{15}H_{11}ClN_2S$.**FTIR (cm-1):** 2903.03 -CH2 stretching; 1551.83 -C=N stretching; 868.90 -C-Cl stretching. 677.96 -C-S-C stretching. **1H NMR (δppm):** 6.55-8.14 (7H of -C6H5); 3.87 1H of (-CH=N); 1.63-2.94 (-3H of CH3).

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A6	Yield: 61%, M.p: 212-214°C, Rf value: 0.48, Chemical formula: $C_{14}H_9N_2ClOS$.**FTIR (cm-1):** 3055.19 Ar-CH stretching; 1599.34 -C=N stretching; 849.82 -C-Cl stretching. 647.67 -C-S-C stretching. **1H NMR (δppm):** 6.48-9.14 (7H of -C6H5); 4.76 1H of (-CH=N).
A7	Yield: 63%, M.p: 131-134°C, Rf value: 0.51, Chemical formula: $C_{14}H_9N_2ClOS$.**FTIR (cm-1):** 3265.32 -OH stretching; 3185.29 -NH stretching; 2356.68 -CH stretching; 1768.76 C=O stretching. 1717.55 C=O stretching; 1396.13 C-H bend; 1013.55 C-O stretching; 744.36 C-Cl stretching; 695.95 C-S stretching; 638.13 C-H stretching.**1H NMR (δppm):** 5.21 (1H of -OH); 6.34-7.42 (7H of -C6H5); 3.512 1H of (-CH=N).
A8	Yield: 44%, M.p: 135-138°C, Rf value: 0.56, Chemical formula: $C_{15}H_{11}ClN_2S$.**FTIR (cm-1):** 3422.89 -NH stretching 1614.18 C=N stretching; 1509.20 C=C stretching; 1879.73 C-H stretching. 1323.39 C-N stretching; 1253.15 C-H stretching; 1059.03 C-H (In plane bend); 984.89 C-H Out of plane bend; 864.31 C-Cl stretching; 787.24 C-H Out of plane bend; 726.92 C-S stretching.**1H NMR (δppm):** 1.909-2.009 (3H of CH3); 2.206 (1H of -CH); 3.421-4.021 (2H of CH2);4.901(1H OF NH);6.754-6.988(3H of Ar.Proton);7.001-7.900(5H of Ar.proton)
A9	Yield: 64%, M.p: 131-133°C, Rf value: 0.56, Chemical formula: $C_{14}H_9N_2Cl_2OS$.**FTIR (cm-1):** 2903.03 Ar-CH stretching; 1551.83 -C=N stretching; 868.909.37 -C-Cl stretching. 677.96 -C-S-C stretching.**1H NMR (δppm):** 6.48-8.27 (7H of -C6H5); 3.98 1H of (-CH=N).

3.4 Biological Activity:

3.4.1 Results of *In Vitro* Antibacterial and Antifungal activity of compounds

Table No. 08: Anti-bacterial and Anti-fungal activity of compounds A1-A9

Compd.	***Zone of inhibition at 200µcg/mL (in mm.)***			
	E. coli	***S. aureus***	***A. niger***	***C. albicans***
A_1	**19**	**21**	**20**	**19**
A_2	**21**	**21**	**23**	**21**
A_3	17	18	19	17
A_4	14	13	**24**	**20**
A_5	18	**20**	15	18
A_6	16	18	**21**	**21**
A_7	15	17	14	19
A_8	**19**	12	17	15
A_9	**21**	**23**	**20**	**23**
Ciprofloxacin	**25**	**26**		-
Amphotericin-B	-	-	**26**	**25**

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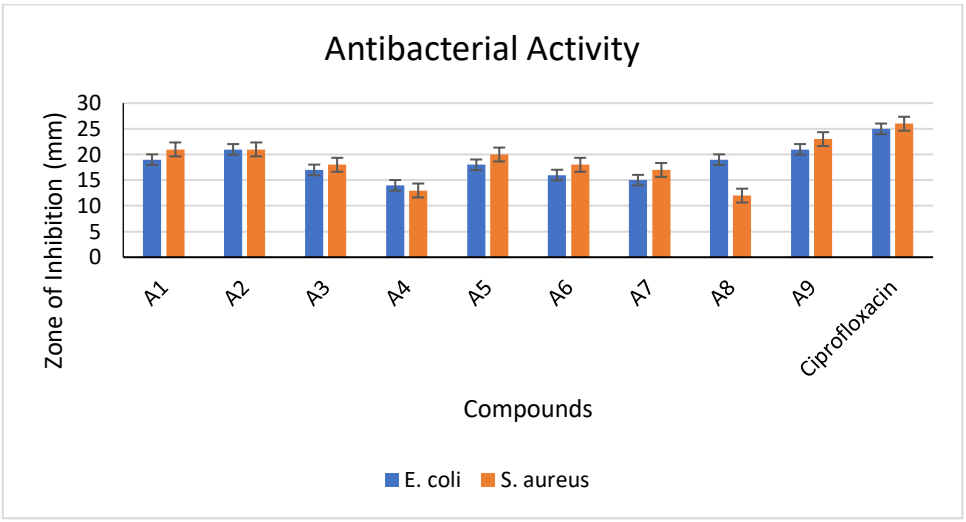

Figure no.03: Graphical representation of Antibacterial Activity of compounds

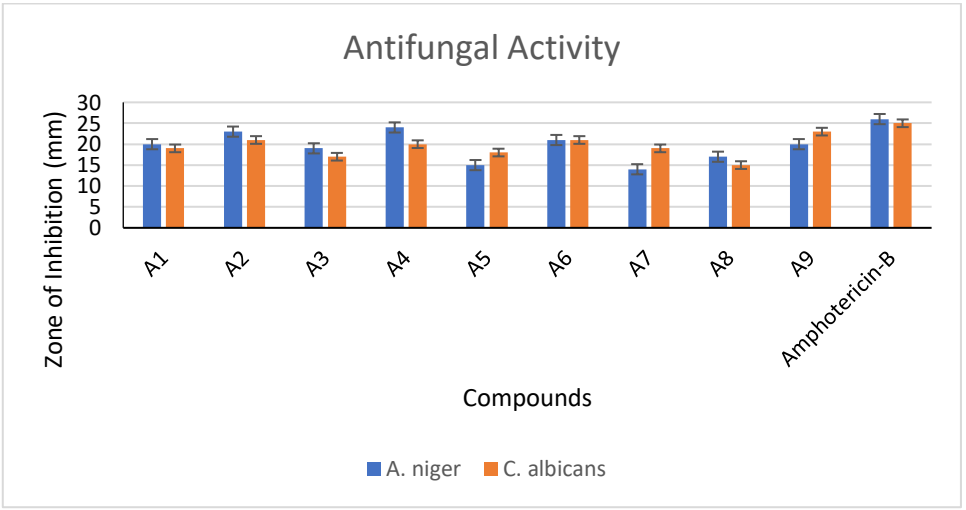

Figure:04 Graphical representation of Antifungal Activity of compounds

Discussion:

Compounds **A_1, A_2, A_4, A_6, A_9** have shown promising **antifungal** activity against *A.niger*, *C.albicans* (NCIM 3102). **Amphotericin-B** was used as standard drug. Compounds **A_1, A_2,A_9** have shown promising **antibacterial** activity against *E.coli* (ATCC25922**)) ,** *S. aureus* (ATCC 29737). Ciprofloxacin was used as std.drug The integration of molecular docking, synthesis, and biological evaluation has led to the identification of benzothiazole derivatives with significant antimicrobial activity. The molecular docking studies provided insights into the binding affinities and interaction mechanisms of the synthesized compounds with key microbial enzymes, such as DNA gyrase and dihydrofolate reductase. These computational predictions guided the design and synthesis of benzothiazole derivatives, ensuring that they possess the structural characteristics necessary for high antimicrobial efficacy.

Antifungal Activity

Compounds A1, A2, A4, A6, and A9 exhibited notable antifungal activity against Aspergillus niger and Candida albicans. The zones of inhibition produced by these compounds were comparable to those of Amphotericin-

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B, indicating their potential as effective antifungal agents. The presence of specific functional groups, such as electron-donating or withdrawing substituents, likely contributed to their enhanced activity.

Antibacterial Activity

Compounds A1, A2, and A9 demonstrated strong antibacterial properties against Escherichia coli and Staphylococcus aureus. The zones of inhibition for these compounds were comparable to those of Ciprofloxacin, a widely used antibacterial drug. The structure-activity relationship (SAR) analysis revealed that certain substitutions on the benzothiazole ring enhance the compounds' ability to interact with bacterial targets, thus improving their antibacterial potency.

The promising antimicrobial activity of these benzothiazole derivatives suggests their potential for development as therapeutic agents. The findings from this study highlight the importance of structural modifications in optimizing the biological activity of benzothiazole derivatives. Future research should focus on further optimization of these lead compounds to enhance their efficacy and minimize potential toxicity.

4. CONCLUSION

The integration of molecular docking, synthesis, and biological evaluation has successfully identified benzothiazole derivatives with significant antimicrobial activity. Compounds A1, A2, A4, A6, and A9 showed notable antifungal activity, while A1, A2, and A9 exhibited strong antibacterial properties. These findings underscore the potential of benzothiazole derivatives as effective antimicrobial agents. Further optimization and in vivo studies are essential to fully explore their clinical potential and to develop these compounds into viable therapeutic options.

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