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Docking related survey on heterocyclic compounds based on Mur-F enzyme inhibitors and their antimicrobial potential

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Abstract
Heterocyclic compounds represent one of the most significant and diverse classes of organic molecules. In recent years, interest in these compounds has grown substantially due to their broad range of applications in both synthetic chemistry and biomedical research. Notably, many heterocyclic structures exhibit potent antibacterial properties, showing effectiveness against a wide spectrum of Gram-positive and Gram-negative bacterial species. Their structural versatility and ability to interact with various biological targets make them valuable candidates in the development of new antimicrobial agents. Some of the derivatives of these compounds show excellent antimicrobial and antibacterial activity. Heterocyclic compounds have been reported anti-atherosclerotic, antidibetic, antiviral, antihypertensive, antibacterial, antihistaminic, anticancer, antispasmodic, anti-inflammatory, antiallergic, neurotropic and analgesic activities. The new antimicrobial compounds deactivate the enzyme serve as a novel approach for researchers. The molecular docking technique helps to find out the new drugs molecule by acting on new targets. This review highlights heterocyclic compounds that have been investigated for their antimicrobial properties by using Mur -F enzyme as target. The results of in-vitro and in-silico have been compared and critically discussed.

Keywords: Heterocyclic compounds, MUR- F, molecular docking, peptidoglycan, antimicrobial etc.

Introduction
According to IUPAC (2017), heterocyclic compounds are defined as cyclic structures that contain atoms of at least two different elements within the ring system. Typically, these heteroatoms include nitrogen, oxygen, or sulfur. Heterocyclic compounds can be classified based on the type of heteroatom and the size of the ring, which is determined by the total number of atoms forming the cycle[1]. Heterocyclic atoms act as antibacterial, Anticonvulsant, Anti-inflammatory, Anti-viral Anti-fungal, Antitumor [2].

Researchers have tried to find out new targets for search better antimicrobial via novel mechanism. Mur- F enzyme present in peptidoglycans (PG) biosynthesis occurs in the cytoplasm [3]. Peptidoglycan (PG) is a vital structural component of the bacterial cell wall, playing a crucial role in maintaining cell shape, supporting elongation, and facilitating cell division [4, 5]. The enzyme MurF is also involved in the biosynthesis of peptidoglycan and contributes to processes such as secretion, virulence, and the formation of cell wall-associated molecules like teichoic acids and lipopolysaccharides. The peptidoglycan structure is mesh-like and primarily composed of polymerized N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) units [6, 7]. Inhibiting the biosynthetic pathway that converts UDP-N-acetylglucosamine (UDP-GlcNAc) to UDP-N-acetylmuramyl-pentapeptide (UDP-MurNAc-pentapeptide) presents a promising strategy for the development of novel antimicrobial agents [8, 9].

The increasing demand of newer and better antimicrobials searches the newer techniques they enhance efficacy and affinity of new drugs [10]. Therefore, molecular docking techniques can be employed to identify new biological targets and aid in the discovery of novel antimicrobial compounds. This review specifically highlights heterocyclic compounds that have been previously investigated for their antimicrobial potential and antibacterial activity by using Mur-F enzyme as target [11, 12]. The outcomes of both in silico and *in vitro* approaches have been compared and critically analyzed.

Molecular Docking Studies of Mur -F Enzyme with Heterocyclic Compounds

Natural Anthraquinolones: Molecular docking and computational pharmacokinetic studies identified four compounds like Termstrin B, Fridamycin A, Maduralactomycin A, and Natalenamide C as potential candidates due to their strong binding affinities and favorable protein-ligand interactions. Among these, Maduralactomycin A exhibited the greatest stability against the MurF enzyme, demonstrated by the lowest average RMSD value and minimal standard deviation[13]. It also showed the strongest binding energy and highly favorable dynamic behavior. Termstrin B also displayed a robust interaction with the target protein, evidenced by the highest average number of hydrogen bonds formed. These results suggest that both Maduralactomycin A and Termstrin B are promising lead compounds for further drug development against *Acinetobacter baumannii* [14, 15].

Table 1: Molecular docking studies were conducted to evaluate the binding potential of Termstrin B, Fridamycin A, Maduralactomycin A, and Natalenamide C against the MurF enzyme.

Compounds	Binding Energy	Bonding Pattern
Maduralactomycin A	−348.48 kcal/mol.	Thr120,Gly141, Glu166, Lys119, Thr121,Arg318Tyr334
Termstrin B	−321.19 kcal/mol.	Thr120,Glu166,Lys119,Thr121,Asn287,Lys119
Natalenamide C	−299.65 kcal/mol.	Glu166,Thr120, Gly141, Lys119,Asn335, Ser340,His283
Fridamycin A	−297.20 kcal/mol.	Glu166,Thr120,Asp332

Among the four, Maduralactomycin A displayed the strongest binding affinity, supported by the lowest docking score and the most stable conformation during simulation, as indicated by a low root mean square deviation (RMSD) and minimal fluctuation. Termstrin B also exhibited significant binding interaction, forming the highest average number of hydrogen bonds, which contributes to its stability within the active site of the target protein. Fridamycin A showed moderate interaction with MurF, indicating potential for further structural refinement to improve its binding efficacy. Natalenamide C, while showing interaction with the active site, had the lowest binding affinity among the compounds tested, suggesting a comparatively weaker interaction with the target. These results indicate that Maduralactomycin A and Termstrin B are promising lead molecules for further investigation as potential antibacterial agents. At the end the result indicates that Madura lactomycin A have strongest and Natalenamide C have weakest binding energy against Mur-F protein of A. baumanni [16].

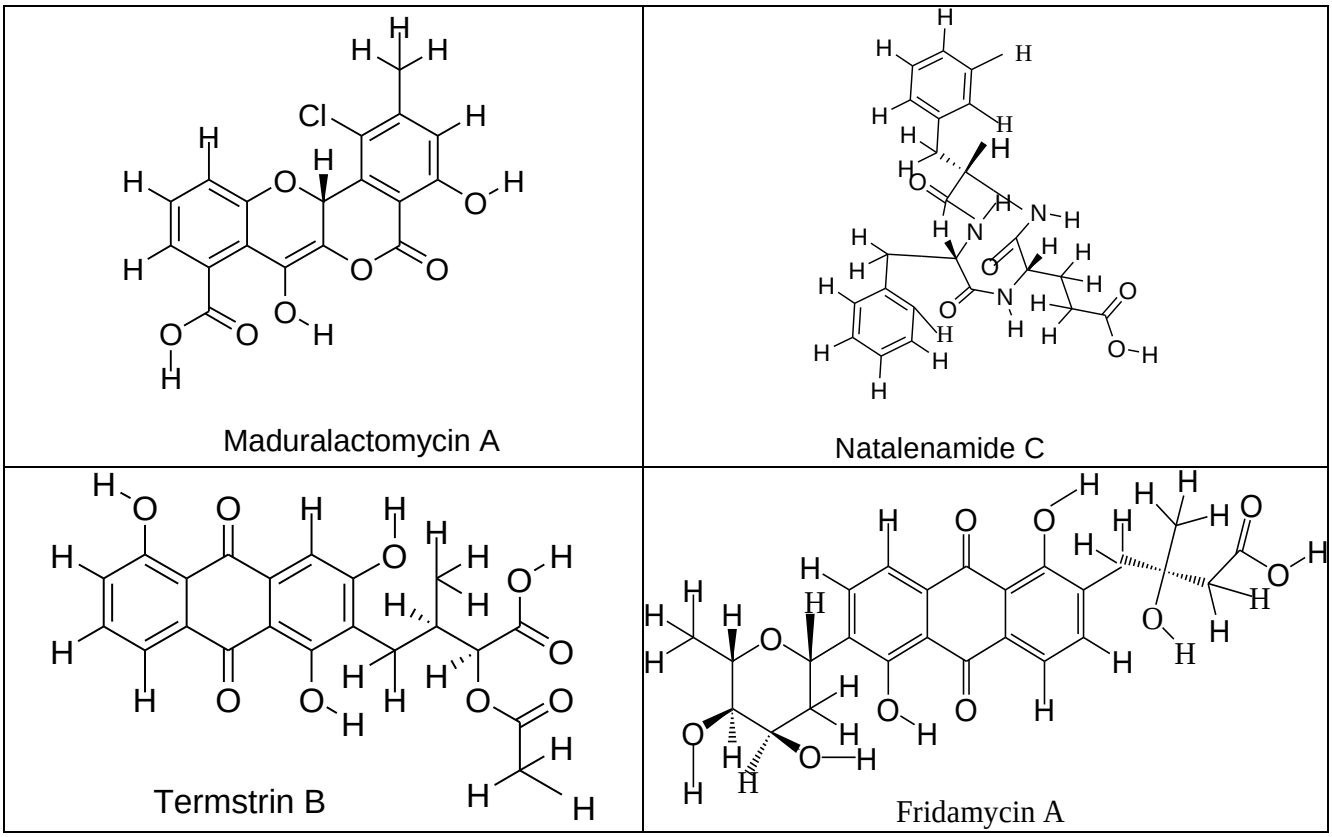


Fig 1: Chemical structure of active Termstrin B, Fridamycin A, Maduralactomycin A, and Natalenamide C.

Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives: In this study 21 compounds were synthesized but some compounds involve in the intracellular step of peptidoglycan biosynthesis and analyze the synthesis of peptide moiety. Through virtual screening investigate a chemical class of Benzene-1, 3-dicarboxylic acid and 2, 5-dimethylpyrrole derivatives show inhibitory activity against Mur- C to Mur - F. This study shows antibacterial activity against three pathogenic bacteria *S.aureus* (ATCC29213), Enterococcus faecalis (ATCC29212), Haemophilus I

influenza (ACTT49766) shows MIC higher than 128 microgram per milliliter. The compounds 1-7 shows inhibitory concentration against E. coli at 250 micro molar describe in table 2 [17, 18].

Table 2: IC50 Value of Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives against E. coli.

Compounds	IC50 (Mur-F)
1.	84%
2.	68%
3.	75%
4.	344 Micromolar
5.	78%
6.	86%
7.	60%

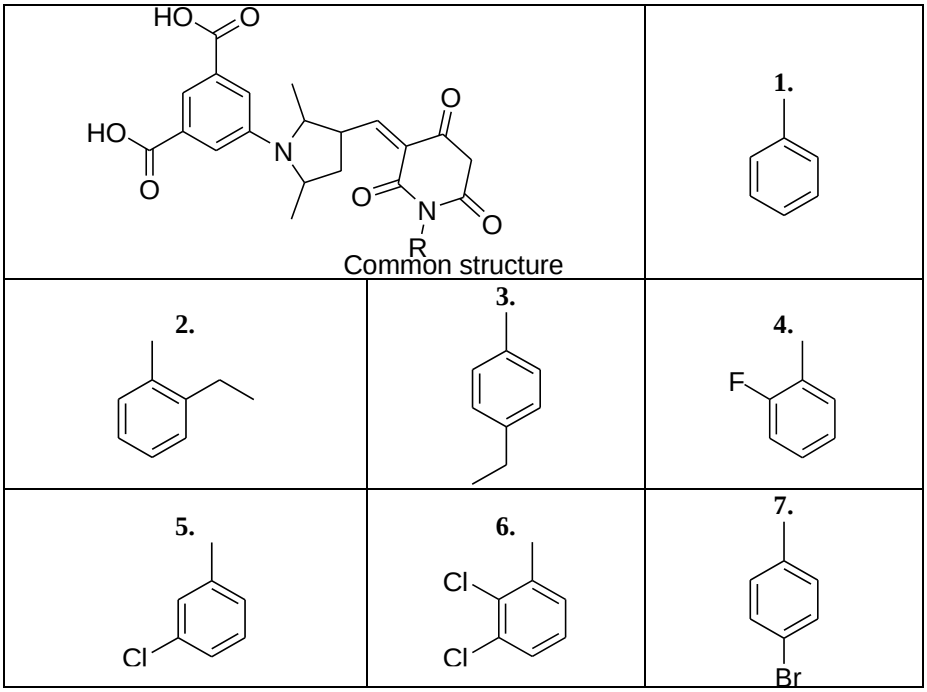
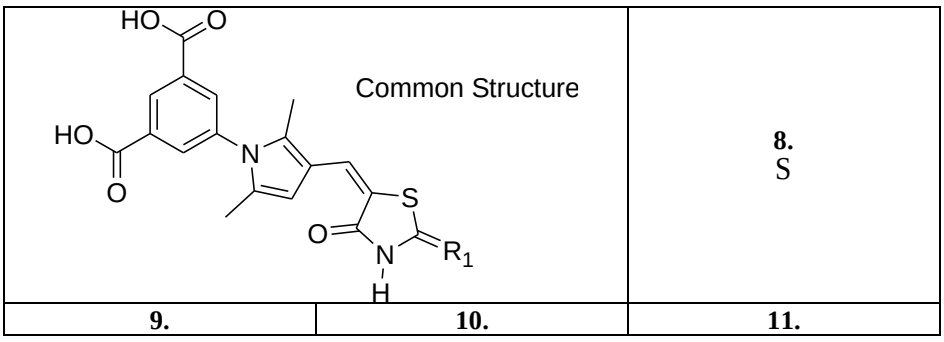


Fig 2: Chemical structure of active Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives.

The compounds 8-14 were assayed by malachite green assays against Mur- C to Mur- F. The compounds 10-14 shows inhibition against all four Mur enzymes but the best compound 13 was show low micromolar range inhibition [19, 20]. The in-vitro result of novel compounds included substituted rhodanine moiety against Mur-F shown in figure. 3.

Table 3: IC50 Value of Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives against E. coli.

Compounds	IC50(Mur-F)
8	89%
9	95%
10	298 Micromolar
11	201 Micromolar
12	281 Micromolar
13	89 Micromolar
14	102 Micromolar



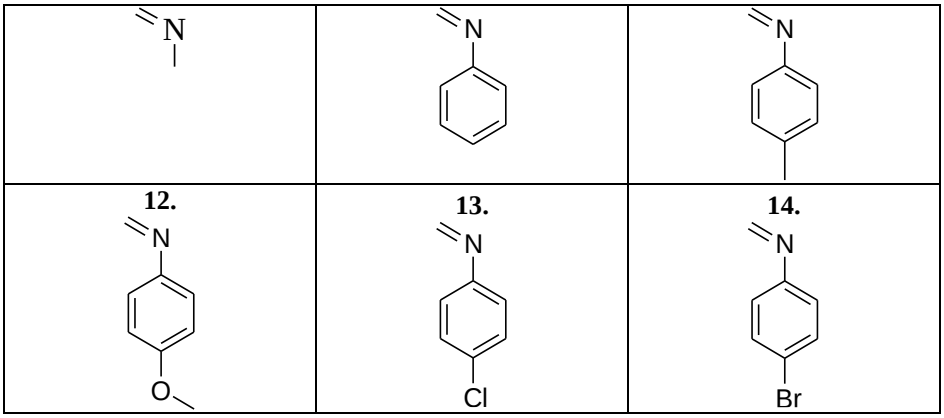


Fig 3: Chemical structure of active Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives.

The compounds 15-21 were also showed inhibition against E. coli except compound 16. The result of in-vitro study was described in table 4.

Table 4: IC50 Value of Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives against E. coli.

Compounds	IC50(Mur-F)
15	75%
16	20%
17	95%
18	81%
19	93%
20	67%
21	75%

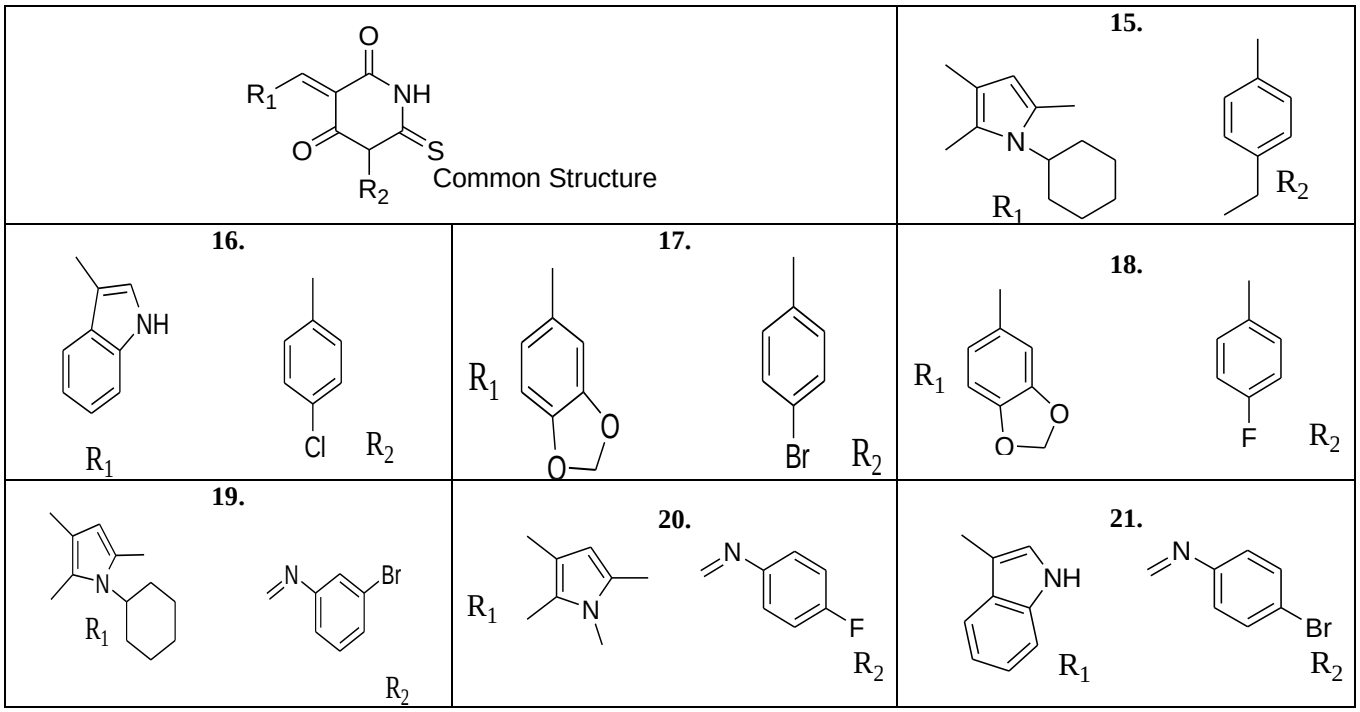


Fig 4: Chemical structure of active Benzene-1, 3-dicarboxylic acid and 2, 5- dimethylpyrrole derivatives.

Pyridothienopyrimidine derivatives

In this study 12 new compounds were synthesizing by five membered heterocyclic ring incorporated with pyridothienopyrimidines. The compounds 2,5,6,7,8 and 12 was pyrazole derivatives, compounds 3 and was pyrazolopyrimidine derivatives and compounds 10 and 11 was thiazole derivatives can shows antibacterial activity against three micro-organisms i.e B. subtilis (ATCC-6633), P. aeruginosa(ATCC-27853) and Streptomyces species(Actinomycetes). The result was found to be compounds 6, 7, 8 and 11 show highest activity against B. subtilis (MIC-75Micro gram per milliliter). The compound 5 shown inhibitory activity against P. aeruginosa but the compounds 4,5,7 and 8 shown highest activity against Streptomyces species (MIC-75Micro gram per milliliter)[21,22]. This results encourages the researcher for further studies of new target based antibacterial activity shown in table 5.

Table 5: Inhibitory concentration of compounds against different species

Species	Active Compounds	MIC
B. subtilis(ATCC-6633)	Compounds 6,7,8 and 11	75Micro gram per milliliter
P. aeruginosa(ATCC-27853)	Compound 5	75Micro gram per milliliter
Streptomyces species(Actinomycetes)	Compounds 4,5,7 and 8	75Micro gram per milliliter

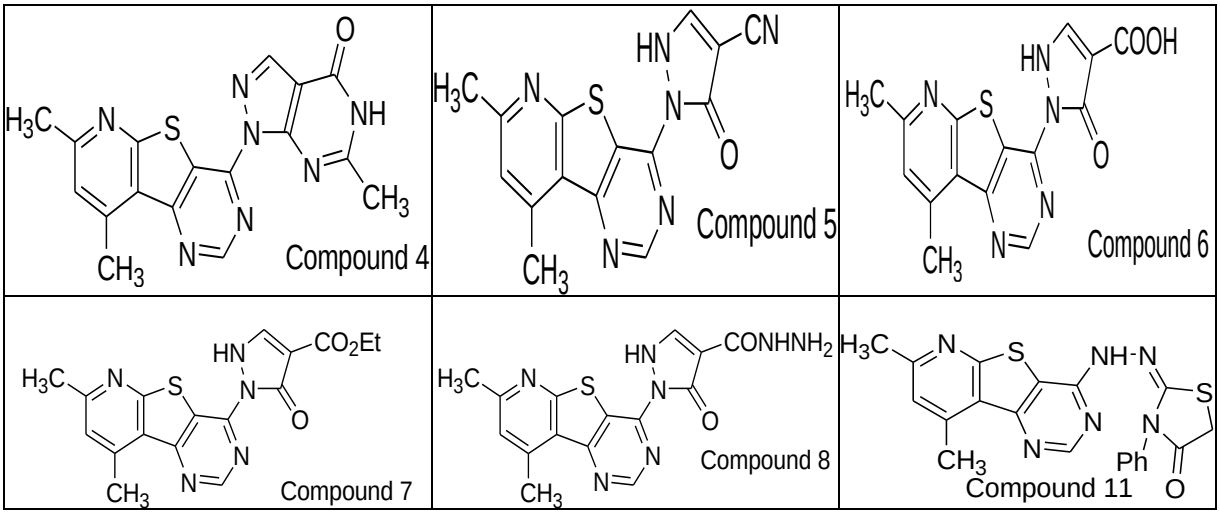


Fig 5: Chemical structures of most active compounds against different species.

Cyanothiophene derivatives

In this study 40 compounds were studied but the compound 2 was found to be more active against Mur - Fsp and Mur-FEc. The IC50 value of sp was found to be 126 micro moles and Ec was found to be 56 micro moles. Compound 1 and 2 occupy the same active site and overlapping with three ring system. In both compounds nitrile moiety formed two h bonds with the backbone nitrogens of Ala48 and Arg 49. In the amide nitrogen formed H-bond with Thr 330 which is common in both structure [23, 24]. In compound 1 phenyl moiety formed π-stacking interactions with Phe31 but in compound 2 no other interaction was predicted except weak vanderwalls bonds. In compound 1 sulphonamide oxygen formed two H-bonds with Asn326, Asn 328 and morpholine oxygen formed weak H-bond with the backbone nitrogen of Gly140.10. So, the due to loss of three H- bond IC50 of compound 2 higher as compared to compound 1 as Shown in figure-6

Table 6: Molecular docking results of compound 1 and 2.

Compound 2	IC 50
Mur - Fsp	126 micro mole
Mur-FEc	56 micro mole

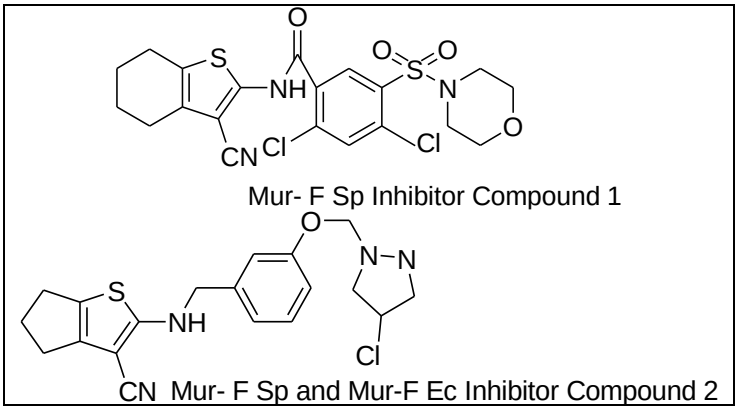


Fig 6: Chemical structure of most active nitrile moiety compound 2 and compound 1.

Conclusion

This study supports the potential of heterocyclic compounds in antimicrobial drug discovery, particularly those targeting the MurF enzyme. Several heterocyclic scaffolds have been reported with promising MurF inhibitory activity. In the present investigation, twelve novel pyridothienopyrimidine derivatives were synthesized by incorporating a five-membered heterocyclic ring into the pyridothienopyrimidine core. These compounds were evaluated for antibacterial activity against *Bacillus subtilis* (ATCC 6633), *Pseudomonas aeruginosa* (ATCC 27853), and *Streptomyces* species (Actinomycetes). Among them, compounds 6, 7, 8, and 11 exhibited the most potent activity against *B. subtilis*, with a minimum inhibitory concentration (MIC) of 75 µg/mL. The compound 5 shown inhibitory activity against P. aeruginosa but the compounds 4,5,7 and 8 shown highest activity against Streptomyces species (MIC-75Micro gram per milliliter). This results encourages the researcher for further studies of new target based antibacterial activity

The S. pneumonia was used against Mur- F the result was

found for kinetic parameters the Km value of UMtri- LLYS, D-Ala- D-Ala and ATP were 40, 86 and 69 micro molars. According to this data Mur - F inhibitors was designed for potential antibacterial activity [25]. 40 compounds were assayed by ligand based virtual screening (*In vitro* methods) the 2 compounds was identified as a hit compound. The result shows micromolar inhibitory activity against Mur- F Ec and Mur- F Sp at IC 50 value of 56 and 126 micro molars. According to this study compound 2 was found to be cynothiophene type Mur- F inhibitor. Compound 2 appears to be a promising lead for the development of new broad-spectrum antibacterial agents, as supported by docking studies using the crystal structure of the MurF enzyme (PDB ID: 2AM1). Molecular docking of various heterocyclic compounds has provided insight into the inhibition mechanism of MurF, reinforcing their potential as effective antimicrobial agents. This study may serve as a valuable reference for researchers focused on antimicrobial drug discovery targeting MurF inhibition [26].

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- **Competing Interests:** - The authors declare that they have no competing interests.
- **Ethics approval and consent to participate:** - Not applicable
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Abbreviations: -MIC-Minimum inhibitory concentration, Mur - Fsp- S. pneumoniae, Mur-FEc- E. coli, RMSD- Root mean square distance, UDP- Uridine- 5 diphosphate, GlcNAc- N- Acetyl Glucosamine and MurNAc- N- Acetyl Muramic acid.

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