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Exploring the antibacterial potential of novel fenamate-based derivatives: insights from molecular docking studies

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ABSTRACT

The rapid emergence of antibiotic-resistant bacteria poses a critical global health threat, highlighting the urgent need for novel antimicrobial agents. In this context, fenamate-based drugs (non-steroidal anti-inflammatory compounds containing a fenamic acid scaffold) have recently gained attention as promising antibacterial candidates. These agents have demonstrated potent activity against a spectrum of pathogenic bacteria, including multidrug-resistant (MDR) strains. In the present study, several newly synthesized derivatives incorporating a fenamate moiety were evaluated for their antibacterial properties against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* by using the agar diffusion technique. Most of the fenamate derivatives exhibited notable antibacterial activity, particularly against *E. coli*. Compounds 1, 3, and 5 showed the highest inhibitory effects, with compound 3 demonstrating the most potent activity, effectively suppressing all tested bacterial strains at concentrations as low as 250 μg/mL. These findings underscore the therapeutic potential of fenamate-based compounds in combating antibiotic resistance. Their capacity to overcome MDR mechanisms, possible synergistic interactions with existing antibiotics, and additional immunomodulatory properties render them compelling candidates for further investigation as next-generation antimicrobial therapies.

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1. Introduction

The rise of antibiotic-resistant bacteria has become a major global health concern in recent decades. Infections caused by multidrug-resistant (MDR) pathogens are increasingly common and pose a significant threat to public health[1]. Certain bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and *Clostridioides difficile*, have developed resistance to many (or in some cases all) available antibiotic treatments, making them extremely difficult to eradicate[2].

The World Health Organization has warned that without the development of new antibacterial agents, we risk entering a "*post-antibiotic era*" in which common infections and minor injuries could become life-threatening. This underscores the urgent need for innovative strategies to combat the growing threat of antibiotic resistance.

The rapid evolution of antibiotic resistance is driven by several factors, including the overuse and misuse of antibiotics, inadequate infection control practices, and a stagnation in antibiotic development within the pharmaceutical industry[3]. To address this critical issue, substantial investment and collaborative research efforts are required to stimulate the discovery of new antibacterial agents. Promising approaches include targeting bacterial virulence factors, exploiting metabolic pathways, and leveraging the human microbiome.

At the forefront of this search is β-ketoacyl-acyl carrier protein synthase III (FabH); a pivotal enzyme in *Escherichia coli* that catalyses the initial condensation reaction in fatty acid biosynthesis[4]. FabH is essential for the production of fatty acids that maintain bacterial membrane integrity and overall cellular function, making it a compelling target for antibiotic development. The inhibition of FabH could disrupt fatty acid synthesis and thereby offer a strategic route to novel antibacterial agents[5].

In this context, tolfenamic acid and other fenamate-based drugs have emerged as promising candidates for antibacterial development. Tolfenamic acid is a nonsteroidal anti-inflammatory drug (NSAID) belonging to the fenamate class. Recent studies have shown that tolfenamic acid and its structural analogues exhibit potent antibacterial activity against a range of pathogenic bacteria, including MDR strains[6]. Proposed mechanisms of action include disruption of bacterial membranes, inhibition of key enzymes, and interference with quorum sensing; a signalling system critical for bacterial communication and virulence[6].

Fenamate-based drugs have demonstrated activity against resistant strains such as MRSA and CRE[7], suggesting their potential utility in treating infections caused by drug-resistant pathogens. Furthermore, tolfenamic acid and its derivatives have shown synergistic effects when combined with conventional antibiotics, enhancing the efficacy of these agents[7]. Such combination therapies may help revitalize existing antibiotics and delay the emergence of further resistance. In addition to their direct antibacterial properties, fenamate-based drugs possess anti-inflammatory and immunomodulatory effects, which may enhance the management of bacterial infections. By reducing inflammation and modulating host immune responses, these compounds could contribute to the overall effectiveness of antimicrobial treatment.

Although the development of tolfenamic acid and related fenamate-based antibacterial agents remains in its early stages, current evidence indicates significant promise. Continued research (including mechanistic studies, optimization of drug candidates, and clinical evaluation) is essential in order to fully assess their potential as novel antibacterial therapies.

2. Methodology

The titled compounds (Figure 1) were synthesized previously according to established procedures[8]. Newly synthesized derivatives were screened for antibacterial activity against selected bacterial strains: Gram-negative *E. coli* and *Pseudomonas aeruginosa*, and Gram-positive *S. aureus*, using the agar diffusion technique. Various concentrations of the derivatives, dissolved in dimethyl sulfoxide (DMSO), were placed individually into wells in the

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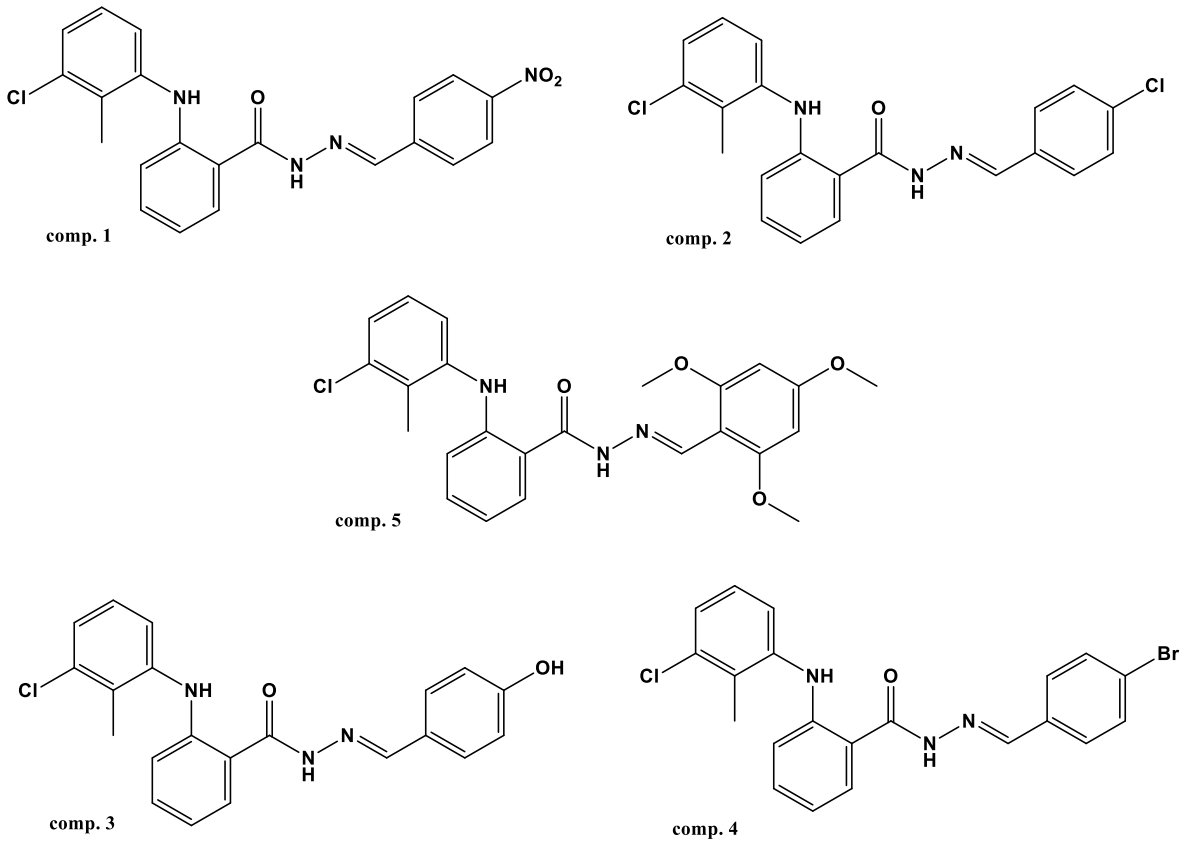

Figure 1. *The synthesized compounds 1–5.*

agar medium. All plates were incubated overnight at 37°C, and inhibition zones were measured after 24 h.

Chemical structures of the compounds were drawn using ChemDraw Office Suite 20.01 and converted to MOL format for dataset inclusion. Ligands were imported into Molecular Operating Environment (MOE) docking software and subjected to energy minimization using the AMBER force field in order to optimize atomic interactions within the compounds and between the compounds and the receptor.

The protein structure of FabH from *E. coli* (Protein Data Bank / PDB ID: 5BNS, complexed with a small-molecule inhibitor) was retrieved from the Research Collaboratory for Structural Bioinformatics PDB and prepared using MOE's default QuikPrep function. Selection criteria included a resolution of 2 Å or better and an R-value below 0.5 to ensure structural quality. Geometric parameters such as bond lengths and angles were verified, confirming that protein 5BNS met the necessary standards for docking studies[9].

The active site was identified using MOE's Site Finder tool, which delineated the region of ligand-receptor interaction. This defined the docking area and isolated relevant atoms and backbone structures to facilitate rigid receptor docking. Docking simulations were performed by using default parameters, evaluating both visual interactions and ligand fit. A lower docking score indicates a more favourable interaction, reflecting

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reduced energy requirements for ligand binding to the receptor's active site[9].

3. Results and Discussion

Antibacterial activity assays revealed that most synthesized compounds exhibited substantial inhibitory effects against all tested microorganisms. At a concentration of 250 μg/mL, compounds 1 and 5 demonstrated the highest activity against *P. aeruginosa*, with inhibition zones of 2.4 cm and 1.4 cm, respectively, comparable to the reference antibiotic azithromycin (2.4 cm). Compound 3 strongly inhibited all tested bacteria at the same concentration, with inhibition zones of 2.0 cm (*E. coli*), 1.0 cm (*S. aureus*), and 1.9 cm (*P. aeruginosa*).

Docking analyses of compounds 1–5 against the active site of FabH (PDB ID: 5BNS) revealed favourable binding interactions. Visual inspection of two-dimensional receptor-ligand interactions and docking scores (representing binding free energy) indicated that compounds 4 and 3 exhibited strong receptor affinity, with scores of -7.094 kcal/mol and -6.874 kcal/mol, respectively. Compound 4 formed two hydrogen bonds, one hydrophobic interaction, and one water bridge with the receptor, while compound 3 formed two hydrogen bonds and two hydrophobic interactions. These docking results highlight the influence of aromatic side-chain substitutions on receptor binding affinity.

4. Conclusion

This study underscores the potential of novel antibacterial agents targeting FabH in *E. coli* as effective alternatives against resistant bacterial strains. Molecular docking analyses elucidate their binding modes, offering a foundation for further optimization. These promising findings suggest that continued development and synthesis of fenamate-containing compounds may represent a valuable direction for future antimicrobial research.

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Conflicts of interest

None exist.

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