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Synthesis and Antibacterial Activity of New Amide Derivatives of Pyrimidinediones

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ABSTRACT A series of ten new pyrimidinedione derivatives **(4a-j)** was synthesized from a common scaffold, 1-(((benzyloxy) carbonyl)methyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-5-carboxylic acid **(2)**. The compound **(2)** was subjected to acid–amine coupling with different amines **3(a-j)**. The coupling reaction was performed using HATU as a coupling reagent at room temperature for 3h using the base *N*-methylmorpholine and solvent DMF. The desired derivatives were obtained with good yields. The synthesized compound's purity was determined by HPLC analytical techniques. The structures of the pyrimidinediones were analyzed by Fourier-transform infrared spectroscopy, proton nuclear magnetic resonance (^{1}H NMR), ^{13}C NMR, liquid chromatography–mass spectrometry, and Human Resource Management System data. All ten amide derivatives were tested for antibacterial efficacy using *Staphylococcus aureus* (Gram-positive strain bacteria) and *Pseudomonas putida* (Gram-negative strain bacteria). Compounds **4g** as well as **4h** showed significant antibacterial effectiveness, with good minimum inhibition concentration values. A molecular docking study was also performed with the protein 3FQO selected from the Protein Data Bank. The amide compounds **4g** and **4h** displayed good docking scores. The results of the *in silico* study complemented the antibacterial effectiveness of the two analogs **4g** and **4h**. The presence of electron donating groups in these target molecules may be attributed to their high efficacy.

KEYWORDS Antibacterial activity, Dihydrofolate reductase, Disk diffusion method, Pyrimidinediones.

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INTRODUCTION

Bacterial infections have plagued humanity since time immemorial, and despite vast strides in modern medicine, they continue to pose a significant threat to public health.[1-3] The rise of antibiotic-resistant bacteria has only exacerbated this problem, making it increasingly difficult to treat bacterial illnesses with conventional antibiotics. Antibiotics have proven to be an impressive arsenal for a wide range of infections. However, resistance to antimicrobials has a monumental impact on health and the health care system.[4] According to recent reports, the rampant spread of antibiotic-resistant bacteria could result in a staggering 10 million deaths over the next three decades.[5] Among these bacteria, methicillin-resistant *Staphylococcus aureus* is one of the most pervasive and alarming.[6,7] To tackle this looming health crisis, we need to explore new and innovative ways to combat bacterial infections and develop broad-spectrum antibacterial agents that can effectively treat drug-resistant strains.[8]

Heterocyclic compounds have turned out to be potent scaffolds for many biological activities.[9] Pyrimidines, pyrimidinones, pyrimidinediones and indole are few examples of heterocyclic compounds with varied applications in health care. The six-membered heterocyclic ring system of pyrimidine-2,4-dione having two nitrogen atoms in positions

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have played an important role in the good docking scores for the compounds **4g** and **4h**. There is scope for further expanding the study of amides of pyrimidinediones by synthesizing and analyzing a wider variety of derivatives which could provide valuable insights into their biological activities.

Supplementary file: The spectral data of Pyrimidinediones are available with the authors.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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