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p-TSA-Promoted Efficient Synthesis of Some New Thiophene Hybridized Thiadiazolyl Schiff Bases as Antibacterial Agents

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ABSTRACT A new series of thiophene hybridized thiadiazolyl Schiff bases was designed and synthesized employing $FeCl_3$-mediated cyclization of thiosemicarbazoneinto thiadiazoles and their subsequent Schiff bases formation using *p*-TSA in benzene. To understand the interaction of the proposed compounds with β-lactamase (Protein Data Bank [PDB] ID: 3UDI), a molecular docking was performed. All the compounds demonstrated an optimal binding affinity with β-lactamase (−8.17 to −9.75 kcal/mol) and showed crucial hydrogen bonds and π–π interaction with the leading amino acids Arg298, Ala300, and Val391 located at the active site of β-lactamase. The *in vitro* antibacterial activity of the desired molecules was conducted against few gram-positive and Gram-negative bacterial strains using amoxicillinas reference drug. The compound having *p*-hydroxyphenyl substituent **(3c)** was found to be potentially effective to inhibit *P. aeruginosa* and *E. coli* with MIC value 7.5 µg/mL and 9.0 µg/mL, respectively, whereas other compounds exhibited moderate to good activity. Altogether, the primary *in-vitro* screening of newly synthesized thiophene hybridized thiadiazole Schiff bases opens a new venture towards the development of promising alternatives of β-lactamase inhibitors as anti-bacterial agents.

KEYWORDS Antibacterial activity, FeCl3-mediated cyclization, p-TSA-catalyzed synthesis, Thiophene-Thiadiazolyl Schiff base, β-Lactamase inhibitors.

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INTRODUCTION

Since the invention of penicillin, the development of bacterial resistance to antibiotics has been a significant issue. β-Lactam antibiotics incorporate 60% of all the antibiotics used worldwide and are considered one of the best treatment options.[1] Thus, the inhibition of β-lactamase(β-lactam-hydrolyzing enzyme) is thought to be the most significant and precise mechanism of bacterial resistance.[2] A significant contribution was made by β-lactam antibiotics towards the treatment and cure of bacterial infections[3], however, their overuse has led to the gradual occurrence of various types of bacterial resistance.[4,5] The need for the discovery of novel antibiotics that are effective in treating bacterial infections is due to their high frequency and quick transmission.[6] Another reason is to overcome resistance and decrease their own toxicity and side effects.[5] Clavulanic acid, sulbactam, and tazobactam are the three most often used β-lactamase inhibitors, which share a β-lactam backbone in common. As a result, these inhibitors prevent β-lactamases from

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