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Synthesis of Coumarin–Triazene–Alkoxyphenyl Derivatives and In Silico Simulation for Potential Antimicrobial Activity

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Abstract—The use of antibiotics is causing rapid growth of antibiotic-resistant bacteria. This can result in significant challenges for controlling pathogenic diseases in the future. The search for new potential antimicrobial compounds is critical, and natural-based scaffolds such as coumarin offer promising lead compounds for the development of new antibacterial compounds through structural hybridization. This study aims to synthesize coumarin–triazene–alkoxyphenyl hybrids **4a**–**4c** bearing a long alkoxy chain and evaluate their antimicrobial potential via docking simulation. The synthesis started with the preparation of alkoxyanilines **2a**–**2c** and cyanocoumarin **3** as precursors under microwave irradiation, resulting in a better yield (68–82 and 61%, respectively) in a few minutes. Diazo coupling reaction of **2a–2c** and **3** produced coumarin–triazene hybrids **4a**–**4c** with 47–63% yield. In silico simulation showed that compound **4a** had a binding affinity (–6.7 kcal/mol) toward bacterial DNA gyrase similar to clorobiocin as reference compound, which indicates its potential to influence and inhibit the activity of the bacterial enzyme. These preliminary findings could establish a useful basis for discovering new antimicrobial compounds through derivatization or modification of the coumarin scaffold.

Keywords: microwave-assisted synthesis, diazo coupling, molecular docking, DNA gyrase, Knoevenagel condensation, Williamson etherification

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INTRODUCTION

The rapid growth of antimicrobial resistance in bacteria has serious implications for pathogenic disease control. This is due to the uncontrolled use of antibiotics in various sectors such as agriculture, waste management, and healthcare, worsened by the excessive uses during COVID-19 [1, 2]. Infectious diseases caused by pathogenic bacteria are the leading cause of death globally, and there will be 10 million fatalities worldwide by 2050 [3, 4]. Hence, research on new potential antimicrobial compounds is important as an insurance to overcome this issue. Natural products remain the primary source of novel drug scaffolds. In the past, natural ingredients were used to develop most medicines to treat a variety of human illnesses [5]. With known molecular structure and biological properties, natural compound is an excellent scaffold for the preparation of new potential synthetic drugs with excellent pharmaceutical properties through structural hybridization [6, 7].

Coumarin derivatives are among many bioactive compounds found in nature. They possess a wide range of biological activities with high medicinal values [8, 9]. There are many coumarin-based pharmaceutical drugs that are commercially available such as acenocoumarol (anticoagulant agent), novobiocin (antibiotic drug), auraptene (chemopreventive agent), and batoprazine (antiaggressive agent) [10]. The antimicrobial properties of coumarin derivatives are well studied, and their excellent antimicrobial effect is due to their ability to bind to the DNA gyrase subunit B enzyme in bacterial cells, thus inhibiting bacterial