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Original Article

Synthesis of Dihydropyrimidinone (DHPM) Derivatives through a Multicomponent Reaction (MCR) and Their Biological Activity

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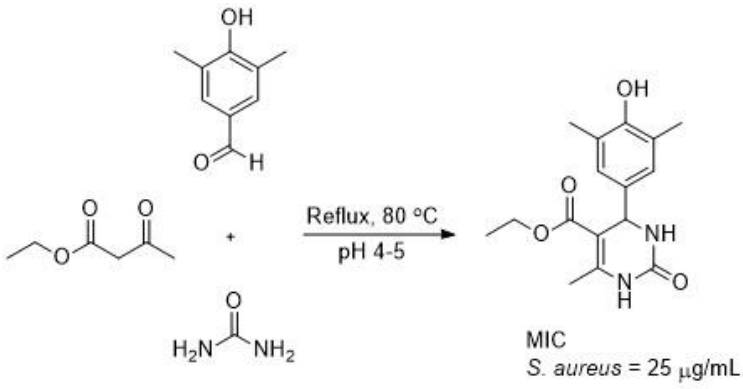
ABSTRACT

The spread of incurable diseases, especially infectious diseases caused by antibiotic-resistant bacteria and certain cancers, has become a serious public health concern. Consequently, the search for potent drug scaffolds has played an essential role in drug lead discovery. The multicomponent reaction (MCR) offers a novel method for efficient synthesis. It is rapidly evolving and is important for the discovery of novel molecules. We synthesized four dihydropyrimidinone (DHPM) derivatives with the one-pot MCR method, obtaining compounds **1-4**. According to the NMR spectra analyses, compound **3** is a new derivative. In this experiment, we optimized the pH of the process. Based on the results, **1-4** had yields of 66.6, 72.9, 35.9, and 69.0%, respectively, at a pH of 4. In contrast, all yields significantly rose by 79.4, 91.9, 81.7, and 84.0% at pH 5. A pH of 5 was therefore advantageous for getting a high yield from these reactions. Compound **1** showed a significant inhibition against *E. coli* with an MIC value of 12.5 µg/mL with moderate activity against the breast cancer cell lines T47D and 4T1. Compound **3** was the most potent against *S. aureus,* with an MIC value of 25 µg/mL.

GRAPHICAL ABSTRACT



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Introduction

The spread of antibiotic-resistant bacteria has given rise to a major risk of morbidity and mortality worldwide because of its profound implications for patient life and the insufficient priority of drug development in annual state budgets. In 2016, the World Health Organization (WHO) announced a global priority for the development of new drugs, particularly for antibiotic-resistant infections [1, 2]. Moreover, it is clear that cancer has also become a disease with a wide scope due to its wide range of affected organs and is as a significant mortality factor. In 2020, it was predicted that there will be approximately 19 million new cancer cases (18.1 million excluding nonmelanoma skin cancer), and nearly 10 million cancer deaths would occur in 2020 [3]. However, the adequate pharmacotherapy programs for cancers have not provided satisfactory outcomes. Thus, it is necessary to produce scaffolds to develop new leads for further therapeutic purposes. In fact, the new drug development approach has been carried out with various procedures, such as combining existing drugs [4], use of natural ingredients [5], synthesis of new compounds [6, 7], and the development of environmentally friendly synthesis (green chemistry) [8].

The multicomponent reaction (MCR) is an approach to achieve the efficient synthesis. This approach is continually evolving and is important for the discovery of novel chemicals. Combining MCR with modern *in silico* and *in vitro* testing has the potential to boost the possibilities for new drug development [9]. The fundamental advantage of MCR is that it reduces overall waste by eliminating multiple steps in the synthesis as a result of the efficient synthesis. MCR has a strong chemistry and region selectivity, limiting byproduct production. Furthermore, the produced byproducts are often tiny molecules such as water, alcohol, amines, or salts, which are safer and easier to remove [10]. Multicomponent reactions, such as the Biginelli reaction, the Ugi reaction, the Kabachnik-Fields reaction, the Knoevenagel reaction, the Reissert reaction, and the Passerini reaction have been developed to offer a novel method of synthesis [11]. The Biginelli reaction involves the one-pot synthesis of 3,4-dihydropyrimidine-2 (1*H*)–ones (DHPMs) with an acid catalyst using readily available starting ingredients, particularly aldehydes, active methylene compounds, and (thio)urea. To create a novel DHPM derivative, a green chemical approach to the Biginelli reaction is currently being investigated. DHPM is increasingly used in the creation of materials such as pharmaceutical compounds, polymers, adhesives, and textile dyes [12]. DHPM derivatives have been investigated in pharmaceutical research for antibacterial development [13, 14], anti-inflammatory [15], anticancer [16], anti-Parkinson [17], antidiabetic [18, 19], antihypertensive [18], and antitumor activities [20]. In this study, we reported a number of dihydropyrimidinone derivatives through schemes **1-4**, with pH changes between **4** and **5**. Taking pH into account, the Biginelli reaction tends to occur at acidic pH circumstances [21, 22]. To induce greater iminium ion production, we analyzed the pH effect on the reaction yield. In addition, antibacterial and cytotoxic characteristics of the resultant compounds were tested.

Materials and Method

All the chemicals and solvents used were analytical grade. They were used without further purification treatment. In this experiment, anisaldehyde, vanillin, 3,5-dimethyl-4-hydroxybenzaldehyde, acetaldehyde, ethyl acetoacetate, and urea were obtained from Merck (Darmstadt, Germany). The proton nuclear magnetic resonance spectra were recorded on a 500-JEOL (Tokyo Japan). Molecule ion were measured on LC-MS/MS Waters Xevo-TQD (Massachusetts, USA) and FTIR Perkin-Elmer Spectrum Two (Massachusetts, the USA). For the purity test using thin layer chromatography plate (Merck, Germany) and Waters 2998 HPLC-PDA (Massachusetts, USA) with RP-18 column (Merck LiChrosorb RP-18 250 x 4.6 mm, 5 µm).

General procedure for DHPMs derivatives

In a round-bottom flask, 20 mmol of aldehydes, 40 mmol of urea, and 40 mmol of ethyl acetoacetate were added, and then 1-2 drops of

concentrated H_2SO_4 were added (kept pH between 4-5). The mixture was refluxed for one hour at 80 °C. The mixture is filtered after being rinsed with aquadest. The resultant substance is subsequently recrystallized using ethanol.

*Procedure for synthesis of ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**)*

4-Methoxybenzaldehyde (2.7 g, 20 mmol), urea (2.4 g, 40 mmol), and ethyl acetoacetate (5.2 g, 40 mmol) were stirred in a round-bottom flask, and the pH was adjusted to 4 or 5 by adding H_2SO_4. The mixture was refluxed for 1 hour at 80 °C, and the resulting product was then recrystallized with ethanol (Scheme 1).

*Procedure for synthesis of ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**)*

The mixture of 4-hydroxy-3-methoxybenzaldehyde (3.0 g, 20 mmol), urea (2.4 g, 40 mmol), and ethyl acetoacetate (5.2 g, 40 mmol) was refluxed for 1 hour at 80 °C. The product was deliberately washed using aquadest through filter paper. The resulting product was then recrystallized with ethanol (Scheme 2).

*Procedure for synthesis of ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3**)*

The mixture of 4-hydroxy-3,5-dimethylbenzaldehyde (3.0 g, 20 mmol), urea (2.4 g, 40 mmol), and ethyl acetoacetate (5.2 g, 40 mmol) in a round-bottom flask was refluxed for 1 hour at 80 °C. The precipitate was washed using aquadest and filtered. Similarly, the resulting product was then recrystallized with ethanol (Scheme 3).

*Procedure for the Synthesis of ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4**)*

The mixture solution of acetaldehyde (0.88 g, 20 mmol), urea (2.4 g, 40 mmol), and ethyl acetoacetate (5.2 g, 40 mmol) in a round-bottom flask was refluxed for 1 hour at 80 °C. The solid product was then washed using aquadest and filtered through a paper filter. The resulting product was then recrystallized with ethanol prior to being dried (Scheme 4). The pH reaction condition of **2**-**4** was maintained at that of **1**.

*Characterization of compound (**3**)*

*Ethyl 4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxo-3,4-dihydro-1H-pyrimidine-5-carboxylate ($C_{16}H_{20}N_2O_4$) (**3**)*

Yield: (pH 4: 81.7%; pH 5: 35.9%), mp 230-236 °C, IR (ATR): 3242 (NH), 3107 (CH), 1640 (CC), 1473 (C=N), 1214 (CH), 802 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.0 (t, 3H), 2.0 (s, 6H), 2.1 (s, 3H), 3,9 (t, 2H), 5.0 (d, 1H), 6,7 (s, 2H), 7.5 (d, NH), 8.0 (s, OH), 9.0 (s, NH). HRMS (m/z): calcd for $C_{16}H_{20}N_2O_4$ $[M + H]^+$, 304.9686; found 304.3410.

Antibacterial test

Antibacterial test was carried out by using the well method with positive control of ampicillin (AMP10) and erythromycin (E15). The bacteria used for this experiment are *E. coli, P.aeruginosa* and *S. aureus*. All synthesis compound dissolved with DMSO with 1 mg/mL was then diluted to 200 µg/mL, 100 µg/mL, 50 µg/mL, 25 µg/mL, and 12.5 µg/mL.

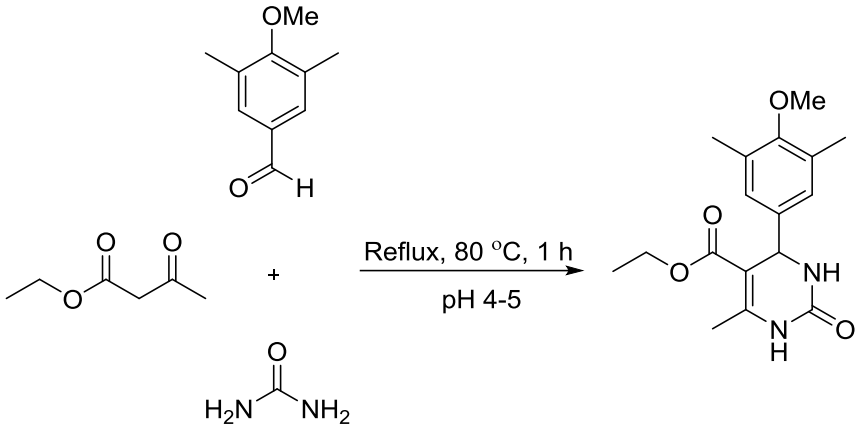
Cytotoxic test

The cytotoxic test was performed using the MTT assay method, using t47D and 4T1 cells [23, 24]. Tests were carried out by diluting of each compound at the concentrations of 500, 250, 125, 62.5, and 31.25 µg/mL, respectively in DMSO. Doxorubicin used as positive control with concentrations of 100, 50, 25, 12.5, and 6.25 µg/mL, respectively. The cells were grown on 96 wells. The sample compound and doxorubicin were put in the well and incubated for 24 hours. The results were read using a Biotex microplate reader.

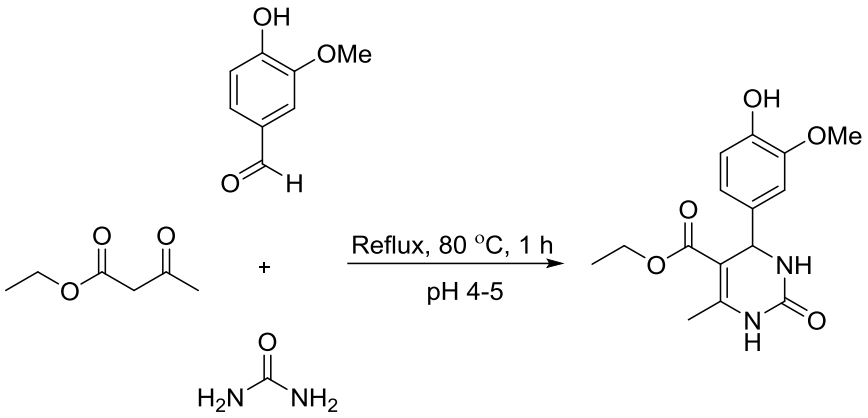
Results and Discussion

The synthesis of DHPM derivatives was carried out using the one-pot multicomponent reaction method with a variety of aldehydes, ethyl acetoacetate, and urea. The process employed is a combination of heating and condensation with

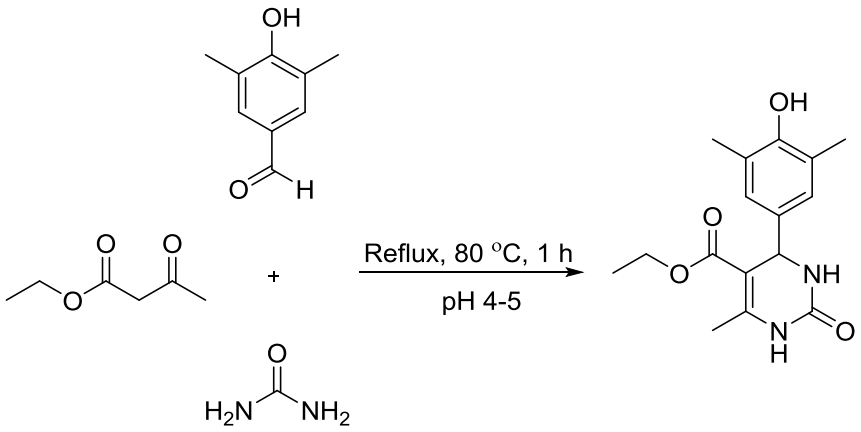
reflux. We examined how pH levels of **4** and **5** affected the results of a chemical reaction. This was based on the premise that iminium reacts well at pH 4-5. A round-bottomed flask was filled with aldehyde (20 mmol), urea (40 mmol), and ethyl acetoacetate (40 mmol), after which H_2SO_4 was added and the pH was kept at 4 or 5. At 80 °C, the mixture was refluxed for an hour. The mixture was then filtered after being rinsed with aquadest. The resulting product was then recrystallized using ethanol. This technique is an improvement on one that had been previously reported [23–25].



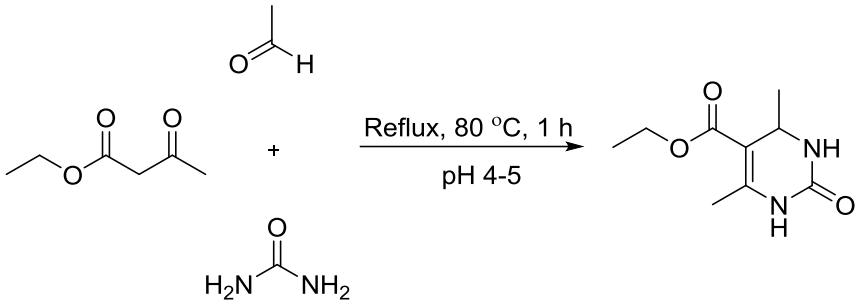
Scheme 1: synthesis of **1**



Scheme 2: synthesis of **2**



Scheme 3: synthesis of **3**



Scheme 4: synthesis of **4**

Given that the iminium ion formed under acidic conditions most likely produced higher yields, optimization reactions were conducted at pH of 4 and 5. A pH of 4 resulted in **1**-**4** with concentrations of 66.6, 72.9, 35.9, and 69.0%, respectively. On the other hand, at pH 5, all yields dramatically increased by 79.4, 91.9, 81.7, and 84.0%, respectively. Thus, a pH of 5 was favorable for obtaining a high yield of these reactions.

The optimization was based on an iminum-initiated reaction for the DHPM formation according to previous studied [26]. The reaction started when amines on urea on the aldehyde carbon attacked nucleophilic bonds. The positive iminium ion that was created in the presence of acid works as an electrophile and is therefore easily attacked by ethyl acetoacetate. The final phase of the reaction comprised the nucleophilic addition of an amide to the carbonyl carbon group of ethylacetoacetate, which resulted in the creation of a ring. Iminium production was affected by pH. The main target for nucleophiles, iminium, will be sparingly protonated at low pH due to the insufficient proton concentrations at higher pH conditions.

The reaction procedures for **1**-**4** were quite convenient without any complicated steps. The procedure was carried out at 80 °C. Based on our previous preliminary work, temperatures above 80 °C immediately led to the reaction and generated a solid product. Moreover, at temperatures below 80 °C, the reaction proceeded slowly. We concluded that the optimum temperature for this reaction was 80 °C with a reaction time of 1 hour. To achieve the final product, simple washing procedures with distilled water and 90% ethanol provided a satisfactory yield. Purity examinations based on TLC and HPLC profiling showed that the pH 5 provided good purity (supplemental data). Thus, the experimental results at a particular pH and temperature can contribute to Biginelli's reaction conditions. The advantage of our method over other research is that it is simpler, with only a few processes and few reagents. Furthermore, after pH optimization, a high yield was obtained, reducing the amount of disposed chemical waste.

On the basis of structural examination through 1D spectra analysis, **1**, **2**, and **4** showed good agreement with previously reported NMR data. However, compound **3** has not yet been reported. Its HMBC spectra data showed distinct data correlations with the current reports. The spectral signals showed a correlation between two proton methyls at δ 2.08 ppm (6H) and two aryl carbons at δ 126.6 and 152.8 ppm inherited from its 4-hydroxy-3,5-dimethylbenzaldehyde starting material. Hence, this starting material may be of interest in future studies to obtain various derivatives. The 1D and 2D NMR spectral data of compound **3** can be found in the supplementary data.

The antibacterial test was performed by the well method against *S. aureus*, *E. coli*, and *P. aeruginosa in Mueller-Hinton media* with positive controls of ampicillin (AMP10) and erythromycin (E15) (Sigma-Aldrich, USA). All of the tests were conducted at least three times independently. The results obtained from the test against *E. coli* showed that compounds **1** and **4** inhibited E. coli with MIC values of 12.5 and 50 µg/mL, respectively. **1** also demonstrated an apparent active inhibitor against *P. aeruginosa* and *S. aureus* with a value of 50 µg/mL. Moreover, **3** showed the most potent compound against *S.*

aureus with an MIC value of 25 µg/mL. Most likely, **1** and **3** can be model compounds for the future development of anti-*E. coli* and anti-*S. aureus* compounds, respectively. Concerning the phenyl group, **2** posed weak activity against all of the bacteria. Thus, the presence of methoxy and hydroxyl groups decreased the antibacterial activities of compounds 1, **3**, and **4**. In contrast to **2**, the groups in **3** became the important contributors against *S. aureus*. In this experiment, the DMSO negative control and the erythromycin positive control demonstrated good functions. The cytotoxicity test was performed with the MTT assay method using t47D and 4T1 cells. The cytotoxicity test against t47D showed that compounds **1**, **2**, and **4** had apparent IC_{50} values of 57.2, 69.8, and 90.4 µg/mL, respectively. In the test against 4T1 cells, **1** and **2** had IC_{50} values of 99.1 and 165.9 µg/mL, respectively, but no activity was found for **4**. On the other hand, **3** had no activity for either cell line and gave good results in t47D cells with an IC_{50} of 90.4 µg/mL. The positive control doxorubicin showed inhibitory activity with IC_{50} values of 7.8 µg/mL (t47D) and 9.7 µg/mL (4T1).

Conclusion

To sum up, compared with previous research, the strategy we investigated is rather straightforward and yields the excellent outcomes. At a temperature of 80 °C and pH 5 is favorable for the synthesis of compounds 1-4 with yields ranging from 79-92%. At pH 5, iminium might be generated more quickly and nucleophilic addition reactions can proceed instantly with urea, resulting in a more rapid reaction. Compound **1** showed significant inhibition against E. coli with an MIC value of 12.5 µg/mL with moderate activity against the breast cancer cell lines T47D and 4T1. Investigations revealed that the compound **1** could be explored for anti-*E. coli* scaffold studies. Compound **3** was the most potent against *S. aureus*, with an MIC value of 25 µg/mL. Whereas **3** could be the fundamental model for anti-*S. aureus*. Compound **3** is a novel compound that has never before been reported. This substance has the potential to function as an antibacterial agent.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

Supplementary data

Supporting Information of 1D -2D NMR, MS, and IR spectra of compound **3** can be found in the online package.

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