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Review Article

One-Pot Three-Component Biginelli Synthesis of Dihydropyrimidinones Under Green Catalysis and ITS Evaluation

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ABSTRACT

“The Biginelli reaction is an important multicomponent reaction in heterocyclic chemistry that enables the synthesis of dihydropyrimidinone (DHPM) derivatives through the one-pot condensation of an aldehyde, a β -keto ester, and urea or thiourea. Dihydropyrimidinones have attracted considerable attention in medicinal chemistry because of their diverse pharmacological potential, including antimicrobial, antioxidant, anti-inflammatory, anticancer, and cardiovascular activities. However, conventional synthetic methods often involve prolonged reaction times, harsh reaction conditions, hazardous catalysts, and excessive solvent consumption, highlighting the need for environmentally sustainable synthetic approaches”. The present research aims to develop an efficient and environmentally friendly one-pot three-component Biginelli synthesis of dihydropyrimidinone derivatives using green catalysis. Citric acid is proposed as a green catalyst to facilitate the condensation reaction under optimized experimental conditions. The study will involve the optimization of catalyst concentration, reaction temperature, and solvent conditions to improve reaction efficiency and product yield. A series of substituted aromatic aldehydes, β -dicarbonyl compounds, and urea or thiourea will be employed to synthesize structurally diverse dihydropyrimidinone derivatives. The synthesized compounds will be isolated, purified, and characterized using Fourier-transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance spectroscopy ($^1\text{H-NMR}$), and mass spectrometry to establish their structural identity. Furthermore, the compounds will be evaluated for their in-vitro antioxidant potential using DPPH, ABTS, and nitric oxide radical scavenging assays. Structure–activity relationship (SAR) analysis will be performed to investigate the influence of different substituents on the biological properties of the synthesized derivatives. The proposed study is expected to contribute to the development of a simple, cost-effective, and environmentally sustainable synthetic methodology for dihydropyrimidinone derivatives.

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The findings may provide a useful foundation for further investigation of these heterocyclic compounds as potential pharmacologically active molecules.

INTRODUCTION

2.1 Introduction

The Biginelli reaction is an established multicomponent reaction used for the synthesis of 3,4-dihydropyrimidin-2 (1H)-ones (DHPMs) and related dihydropyrimidinethiones. In its conventional form, an aldehyde, a β -keto ester or another suitable 1,3-dicarbonyl compound, and urea or thiourea react in the presence of an acid catalyst. The reaction is attractive because three components are combined in one vessel, reducing the need for repeated isolation of intermediates. Since the first report by Pietro Biginelli in 1893, the reaction has been widely investigated in synthetic and medicinal chemistry [1,2].

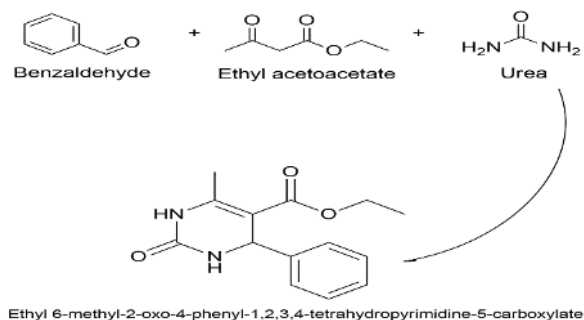
The current research proposes to study a one-pot, three-component Biginelli synthesis using green catalytic conditions, with particular attention to citric acid as a potential catalyst. The synthesized products are proposed to be characterized using FT-IR, ^1H -NMR and mass spectrometry and evaluated in selected in-vitro antioxidant assays. The literature relevant to the project therefore includes the reaction mechanism, catalytic improvements, green synthesis, biological significance of DHPMs and antioxidant evaluation.

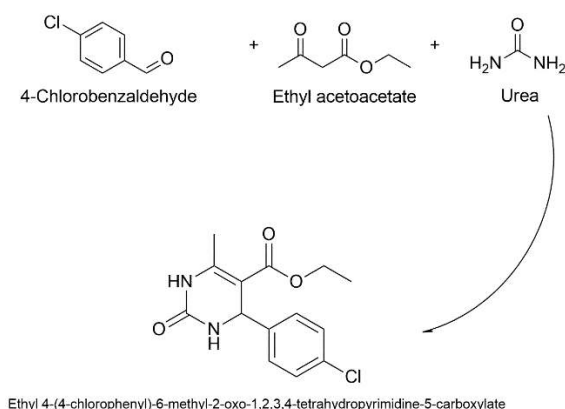
2.2 Development and Mechanism of the Biginelli Reaction

Biginelli originally described the acid-catalysed condensation of an aromatic aldehyde, urea and ethyl acetoacetate to form a substituted dihydropyrimidinone. Subsequent work explored the reaction's scope and the effect of reaction conditions on product formation. Kappe's review of the first century of Biginelli chemistry describes the historical development of this transformation and its importance as a route to functionalized dihydropyrimidines [1].

Mechanistic studies have helped explain how the three reactants combine. Kappe's mechanistic reinvestigation supported a pathway involving formation of an N-acyliminium intermediate from the aldehyde and urea, followed by addition of the enol form of the β -keto ester and subsequent cyclization/dehydration to produce the DHPM ring [3]. The precise pathway and rate of reaction can depend on the catalyst, solvent, substrate and temperature; therefore, the mechanism should be treated as a literature-supported model rather than assumed to be identical under every reaction condition.

For the proposed study, the mechanistic literature is relevant because acid catalysis may facilitate activation of the carbonyl-containing reactants and formation of intermediates needed for cyclocondensation. The effect of catalyst amount and reaction conditions should be determined experimentally rather than inferred from acidity alone.





2.3 Medicinal-Chemistry Significance of DHPMs

DHPMs have attracted medicinal-chemistry interest because biological activity has been reported for selected members of this structural family. Kappe reviewed Biginelli-type DHPMs investigated as calcium-channel modulators, α 1a-adrenoceptor-selective antagonists and compounds affecting the mitotic machinery [2]. These reports show that substitution around the DHPM scaffold can influence biological properties; they do not establish that every new DHPM derivative will have the same activity.

Monastrol is a well-known example of a biologically active DHPM derivative. Mayer and co-workers reported a small molecule that inhibits mitotic spindle bipolarity, helping demonstrate the potential of this scaffold for biological investigation [4]. Batzelladine-related marine alkaloids containing a related dihydropyrimidine framework have also been investigated for inhibition of HIV gp120–CD4 binding [5]. Such examples provide background for studying substituted DHPMs, but any pharmacological claim about newly prepared compounds requires direct testing and appropriate controls.

The present project focuses on chemical synthesis and in-vitro antioxidant screening. Accordingly, the review should emphasize literature directly related to the synthesis of DHPMs and antioxidant evaluation, while keeping other pharmacological activities as brief context.

2.4 Conventional and Improved Catalytic Methods

The classical Biginelli reaction is commonly described as an acid-catalysed process. However, the efficiency of a particular protocol can vary with the aldehyde, 1,3-

dicarbonyl component, urea or thiourea, catalyst, solvent and temperature. The limitations of older procedures encouraged researchers to investigate alternative catalysts and activation methods. Kappe's review of advances in Biginelli synthesis describes the expansion of this reaction into modern synthetic chemistry, including approaches intended to improve reaction efficiency and substrate scope [6].

Ranu, Hajra and Jana reported an indium (III)-chloride-catalysed one-pot synthesis of DHPMs [7]. Other studies have examined ammonium chloride catalysis under solvent-free conditions and ultrasound-assisted protocols [8,9]. These studies illustrate that catalyst selection and reaction activation can alter reaction performance. Their results should be compared using the conditions and values reported in the original papers, including reaction time, isolated yield, purification requirements and catalyst recovery.

A green-synthesis claim should be based on the overall process rather than the catalyst name alone. Solvent volume, energy requirements, corrosivity, toxicity, work-up, waste generation and reusability are all relevant when comparing methods. A method that produces a high yield may still require substantial solvent or energy, while a mild catalyst may not necessarily provide high conversion for every substrate.

2.5 Green Catalysis and Sustainable Biginelli Synthesis

Green chemistry seeks to reduce hazardous substances and waste, improve atom and energy efficiency, and favour safer reaction conditions. In Biginelli synthesis, these aims have motivated the use of organic acids, supported catalysts, ionic liquids, plant-derived materials, nanoparticles, solvent-free methods and

alternative heating or irradiation techniques. A 2026 review of sustainable Biginelli chemistry summarizes a range of green approaches, including catalysts and reaction media intended to improve environmental performance [10].

The different approaches have distinct strengths and limitations. Heterogeneous catalysts may be easier to separate and reuse, but their preparation and metal content should be considered. Solvent-free methods reduce solvent use but may require careful control of mixing and temperature. Microwave or ultrasound methods may shorten reaction time in some systems, but require suitable equipment and reproducible operating conditions. These approaches are useful comparators; the proposed work should remain focused on the selected experimental method and should not imply that every green technique will be used.

For a meaningful comparison, the study should record catalyst loading, reactant ratio, solvent or solvent-free condition, temperature, reaction time, isolated yield, purification method and, where practical, evidence of catalyst recovery or waste reduction.

2.6 Organic Acids and Citric Acid as Catalysts

Organic acids are relevant candidates for acid-catalysed Biginelli condensation. Particularly important to the present project, de Vasconcelos and co-workers reported the use of citric acid or tartaric acid to promote Biginelli synthesis in ethanol. Their study also evaluated the antioxidant capacity of the resulting compounds using the DPPH radical-scavenging assay and a thiobarbituric acid-reactive substances test. The authors reported antioxidant effects for two compounds and reduction of lipid peroxidation at the concentrations examined [11]. This publication is directly relevant because it connects naturally occurring organic-acid-promoted synthesis with antioxidant evaluation.

The existence of this earlier study means the present synopsis should not claim that citric-acid-catalysed Biginelli synthesis or antioxidant evaluation is entirely unexplored. Instead, the research rationale should identify the specific contribution intended—for example, a defined substrate set, optimization of catalyst loading and reaction conditions, a comparative assessment of products, use of additional antioxidant assays,

or a locally feasible and reproducible procedure. The novelty claim must be finalized only after checking the exact scope and methods of prior studies.

Citric acid should be evaluated as a candidate catalyst through systematic experiments. Relevant variables may include catalyst loading, reaction temperature, reaction time, reactant ratio and solvent conditions. The optimal condition should be selected from observed results such as isolated yield, purity, reproducibility and ease of work-up, rather than assuming in advance that citric acid is superior to all other catalysts.

2.7 Structural Characterization of Synthesized DHPMs

Characterization is required to establish whether the isolated product is consistent with the intended DHPM structure. FT-IR spectroscopy can provide evidence for functional groups such as N–H, carbonyl and aromatic groups. ¹H-NMR can help assess the proton environments expected for the DHPM ring, substituents and ester group. Mass spectrometry can support the proposed molecular mass. These methods provide complementary evidence; no single spectrum should be interpreted in isolation.

In the proposed work, the spectra should be interpreted against the expected structure and relevant published data. Observed peaks, chemical shifts, molecular-ion signals and any inconsistencies should be reported transparently. Purity should not be claimed solely from the presence of expected functional-group bands.

2.8 Antioxidant Evaluation of DHPM Derivatives

Antioxidant screening can provide an initial comparison of the radical-scavenging or related chemical activity of synthesized compounds. Published work by de Vasconcelos and co-workers provides a directly relevant example of DHPM synthesis using naturally occurring organic-acid promoters followed by DPPH and lipid-peroxidation-related evaluation [11]. A review of Biginelli adducts with pharmacological properties also discusses studies in which DHPM-related compounds were investigated for antioxidant activity [12].

The present project proposes to use DPPH, ABTS and nitric oxide radical-scavenging assays, with ascorbic acid as a reference antioxidant. The literature review



should describe the principle of each assay and the controls used, and the final methodology should specify the reagent concentrations, incubation conditions, measurement wavelength and calculation formula based on validated protocols. Results should be expressed consistently, for example as percentage inhibition at defined concentrations and, where the data support it, an IC₅₀ value.

Results from chemical antioxidant assays are preliminary in-vitro findings. They do not by themselves demonstrate clinical efficacy, safety or therapeutic benefit. Appropriate blanks and controls are important because a compound's own colour, solubility or turbidity may affect spectrophotometric measurements.

2.9 Summary of Relevant Published Studies

Study	Approach	Main contribution reported	Relevance to present work
Biginelli (1893) [1]	Three-component condensation	Original report of the reaction	Historical foundation
Kappe (1993) [1]	Review of Biginelli chemistry	Summarized reaction development and synthetic scope	Background and mechanism
Kappe (1997) [3]	Mechanistic reinvestigation	Supported an N-acyliminium-ion pathway	Explains acid-catalysed reaction
Ranu et al. (2000) [7]	Indium(III) chloride catalysis	Reported an improved one-pot protocol	Catalyst-method comparison
Shaabani et al. (2003) [8]	Ammonium chloride, solvent-free conditions	Demonstrated an alternative catalytic approach	Green-method comparison
de Vasconcelos et al. (2012) [11]	Citric/tartaric acid in ethanol; antioxidant testing	Reported DHPM synthesis and evaluated DPPH and lipid-peroxidation-related activity	Directly related to citric acid and antioxidant work
Matos et al. (2018) [12]	Systematic review of DHPM biological activity	Reviewed biological evidence for DHPM derivatives	Context for biological evaluation
Rajni et al. (2026) [10]	Review of sustainable Biginelli methods	Summarized green catalysts and approaches	Current context for green synthesis

2.10 Research Gap and Justification

Published literature establishes the Biginelli reaction as a versatile route to DHPM derivatives and describes several ways to modify its catalyst and reaction conditions. Importantly, citric acid and tartaric acid have already been reported as promoters for Biginelli synthesis, and antioxidant evaluation of selected products has also been published [11]. Therefore, the research gap should be defined specifically rather than as a complete absence of prior work. 25 Oct 2026

The proposed study will investigate a selected one-pot, three-component Biginelli protocol under green catalytic conditions, optimize the reaction parameters, isolate and characterize the products using FT-IR, ¹H-NMR and mass spectrometry, and evaluate the products using DPPH, ABTS and nitric oxide radical-scavenging assays. The contribution of the work should be judged from the exact substrate scope, optimization data, characterization evidence, reproducibility and

comparative antioxidant results. The final claim of novelty must be supported by a focused search of recent original research articles.

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