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Review Article

Review on Green Synthesis of 3-4dihydropyrimidinone Using NaDES

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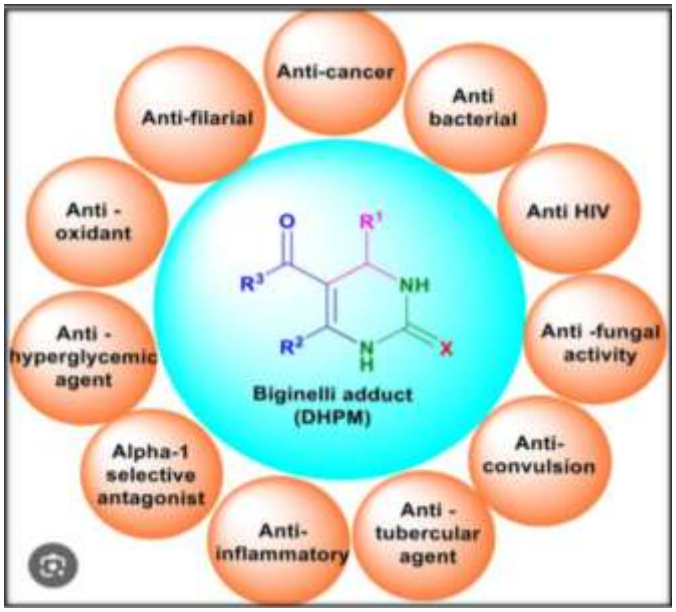
The present project focuses on the green synthesis of 3,4-dihydropyrimidinones (DHPMs) using Natural Deep Eutectic Solvents (NaDES) as an eco-friendly reaction medium. DHPMs are important heterocyclic compounds possessing various pharmacological activities such as antibacterial, anti-inflammatory, and antihypertensive properties. The synthesis was carried out through the Biginelli reaction involving an aldehyde, β-ketoester, and urea in the presence of NaDES. The use of NaDES not only replaces toxic organic solvents but also improves reaction efficiency, giving high yields in a shorter time. This method follows the principles of green chemistry and provides a sustainable and efficient approach for the synthesis of biologically active heterocyclic compounds.

Keywords: Cancer treatment , Dihydropyrimidines (DHPMs) , Deep eutectic solvents (DESs) , Biginelli Reaction , Antitumor , multicomponent reactions.

INTRODUCTION

Despite numerous advancements in cancer treatment, cancer remains the second most common cause of death globally. In 2020 alone, there were about 10.0 million cancer-related fatalities. [2] One the WHO predicts that by the end of 2030, this number will increase to 13.1 million if current trends continue. Cancer is still a subject of great interest because of drug resistance and treatment-related harm. [3,4] This calls for more recent drug research and discovery initiatives to address these issues in cancer treatment. Because heterocyclic compounds frequently display essential biological characteristics, they remain appealing candidates for synthesis. Dihydropyrimidinones (DHPMs) in particular are widely recognised for their diverse bioactivities. [1] Potential anticancer, anti-inflammatory, antioxidant, and antibacterial properties, as well as antimalarial and antitubercular actions, are among the many pharmacological characteristics linked to DHPM compounds. Furthermore, a variety of alkaloids from various marine sources contain DHPMs. These alkaloids are essential in the realm of medicine because they aid in the production of physiologically active natural compounds. Certain alkaloids have demonstrated antiviral action against the herpes simplex virus, antifungal activity against Candida albicans, and cytotoxicity against several tumour cell lines [6]. Additionally, a DHPM unit was discovered to be present in the structure of two naturally occurring marine alkaloids, Batzelladine A and B. Given that these alkaloids are thought to prevent HIV gp-120 from attaching to CD4 cells, [5,7]



Pyrimidine serves as the basic structure of the 3, 4-Dihydropyrimidinone derivatives, which also contain two keto groups, one on the ring and the other linked to the α position. [9] The different biological activities of the chemical are caused by its specific core. Their diverse range of activities has drawn the interest of scientists who are researching and developing the molecule to produce different pharmacological moieties with 3, 4-Dihydropyrimidinone as the fundamental nucleus. [10]**] In** 1983, Biginelli described the most straightforward and widely used method for synthesising 3, 4-Dihydropyrimidinone. The condensation reaction with benzaldehyde, ethyl acetoacetate, and urea/thiourea is a one-pot, three-component synthesis. The Biginelli reaction is the name given to this reaction. [8] One-pot reactions involving three or more starting ingredients that result in a product are known as multi-component reactions (MCRs). MCRs have excellent selectivity and atom economy [12–14]. These reactions have several benefits, including increased synthetic productivity, ease of use, fewer isolation and purification stages, energy, time, and cost savings, and waste reduction [15–18]. One of the best MCRs is the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones (DHPMs), which was first described by Pietro Biginelli and involves a three-component one-pot reaction involving urea, ethyl acetoacetate, and an aldehyde in the presence of strong acid [19]. Hard reaction conditions, lengthy reaction periods, and low yields are some of the drawbacks of the traditional Biginelli reaction [20–22,11].

Deep Eutatic solvent:

A new class of eco-friendly solvents called deep eutectic solvents is made mostly of non-toxic ingredients [24]. As a result, the benefits of low toxicity and biodegradability emerge, which are consistent with the worldwide trend of "green chemistry" and significantly lower application costs [25], [26]. Additionally, DES synthesis is a simple and practical choice for preparation and application because it doesn't require complicated methods. Because of these characteristics, DES is frequently employed in chemical synthesis, separation, and other domains [27], [28]. Since DES was developed, it has been used consistently as an extractant in the extraction and separation of heavy metals [29], [30], as well as in the enrichment, extraction, and removal of heavy metals in environmental samples, water samples, and food analysis [23]. A DES is a eutectic mixture of two or three constituent components that, when mixed at the correct molar ratio, have a lower melting point than each component. These components often interact through hydrogen bonding. These transparent liquid mixtures consist of hydrogen bond donors (HBDs) and acceptors (HBAs). The most popular HBA for making DES is choline chloride. Furthermore, betaine—an analogue of choline chloride—was employed. However, compared to utilising choline chloride, creating a DES with betaine is thought to be more difficult [32]. A novel DES derivative is called natural deep eutectic solvents (NADES). [33], [31]. Table 1 summarises the seven

different methods that have been identified to yet for the preparation of NaDES. The unique characteristics of the eutectic components, especially their heat sensitivity, have a major role in choosing the best approach. This is a crucial factor to take into account because exposure to high temperatures might cause some substances to degrade or cause interactions with water that could produce unwanted byproducts. Therefore, when selecting the proper preparation method, a thorough assessment of the components' thermal stability is crucial. [34]

Table 1 NaDES preparation methods [35]

Method	Description	Benefits	Limitations
Starting from the pure compounds			
Heating and stirring	Stirring and moderate heating	Simplicity	Possible thermal degradation
Grinding	Mixing using a mortar and pestle	Suitable for heat-sensitive materials	No temperature control during the process
Twin screw extrusion	Continuous mixing using a twin-screw extruder	Scalability	Specialised equipment needed
Microwave irradiation	As above, using microwave heating	Speed, simplicity	Possible thermal degradation
Ultrasound-assisted preparation	As above, using ultrasounds	Speed, simplicity	
Starting from solutions of the compounds			
Lyophilisation	Lyophilisation of frozen aqueous solutions of the NaDES components	Suitable for heat-sensitive materials	Not suitable for NaDES containing volatile compounds
Vacuum evaporation	Distillation of water from aqueous solutions of the NaDES components under reduced pressure		

Reaction conditions:

The traditional Biginelli reaction method implies that urea, benzaldehyde, and ethyl acetoacetate condense in a single pot under extremely acidic conditions. The reaction takes a lengthy time (15–20 h) and proceeds with low yields. The optimisation of reaction conditions to raise the yields of target DHPMs has been the focus of a large number of studies. Recent research has examined the effects of catalysts and solvents on the yields of the target products produced in the Biginelli reaction. (37) Optimising the solvents (acetic acid, acetonitrile, THF, DMFA, etc.) and choosing suitable catalyst systems (organic and inorganic acids [38], Lewis acids [39], ionic liquids [40], etc.) are two methods. Experiments using ultrasonication, infrared irradiation, and microwave irradiation have been conducted to speed up the reaction, cutting the reaction time to a few minutes and raising yields to 98%. [36] [41]

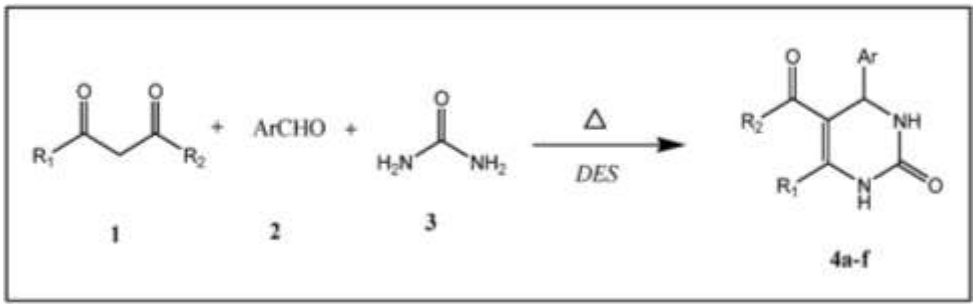
MATERIAL AND METHOD:

Every chemical and solvent utilised was of analytical quality. They were put to use without any additional purification. Merck (Darmstadt, Germany) provided the anisaldehyde, vanillin, 3,5-dimethyl-4-hydroxybenzaldehyde, acetaldehyde, ethyl acetoacetate, and urea used in this experiment. A 500-JEOL (Tokyo, Japan) was used to record the proton nuclear magnetic resonance spectra. Molecule ions were measured using FTIR Perkin-Elmer Spectrum Two (Massachusetts, USA) and LC-MS/MS Waters Xevo-TQD (Massachusetts, USA). The Waters 2998 HPLC-PDA (Massachusetts, USA) and thin layer chromatography plate (Merck, Germany) with RP-18 column (Merck LiChrosorb RP-18 250 x 4.6 mm, 5 µm) were used for the purity test. General protocol for derivatives of DHPMs After adding 20 mmol of aldehydes, 40 mmol of urea, and 40 mmol of ethyl acetoacetate to a round-bottom flask, 1-2 drops of Concentrated H2SO4 was added, maintaining a pH of

4-5. The mixture was refluxed at 80 °C for an hour. The mixture is rinsed with aquadest and then filtered. Ethanol is then used to recrystallise the resulting material. [42]

RESULT & DISCUSSION:

Using a range of aldehydes, urea, and ethyl acetoacetate, the one-pot multicomponent reaction technique was used to synthesise DHPM derivatives. The method used combines reflux with condensation and heating. We looked at how a chemical reaction was impacted by pH values of 4 and 5. The idea that iminium reacts favourably at pH 4-5 served as the foundation for this. Aldehyde (20 mmol), urea (40 mmol), and ethyl acetoacetate (40 mmol) were added to a round-bottom flask, and the pH was then maintained at 4 or 5. For an hour, the mixture was refluxed at 80 °C. After rinsing with aquadest, the mixture was filtered. After that, ethanol was used to recrystallise the final product. (43–45)



CONCLUSION:

In conclusion, 3,4-dihydropyrimidinones were successfully synthesized using Natural Deep Eutectic Solvents (NaDES) through a green and sustainable approach. The synthesized DHPMs exhibited promising anticancer activity, indicating their potential as biologically active compounds. This study provides an environmentally friendly and cost-effective method for the synthesis of valuable heterocyclic compounds using renewable natural resources.

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