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A Review on 3,4 Dihydropyrimidinone Derivatives

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ABSTRACT

3, 4-Dihydropyrimidinones are six-membered heterocyclic compounds with a pyrimidine ring that has two nitrogens as heteroatoms and two keto groups—one on the ring and one at the α position relative to the ring. The chemical has different biological activities due to the presence of keto groups and pyrimidine rings in its structure. Biginelli three-component reactions are mostly used in the synthesis of dihydropyrimidinone. The yield of the traditional Biginelli reaction is frequently low and needs a long reaction time. In contrast to the traditional Biginelli reaction, we focus on a number of modified synthetic protocols of this three-component reaction in order to synthesize 3, 4-Dihydropyrimidinones with a shorter reaction time and a higher product yield. Due to these moieties' wide spectrum of biological actions, the molecule has the potential to develop into a variety of medications with cytotoxic, antiviral, antibacterial, antioxidant, and anti-cancer properties. According to a number of published research, 3, 4-Dihydropyrimidinones can be improved to produce pharmacological moieties that function better than current benchmarks.

Keywords: Biginelli reaction, Dihydropyrimidinone, Anti-oxidant, Anti-viral, Cytotoxic, Anti-bacterial.

INTRODUCTION

The bulk of drugs have basic structures that are heterocyclic molecules. Therefore, research on them is essential in the field of medicinal chemistry. Among these heterocyclic substances with a variety of biological activities is pyrimidine. Since pyrimidines are the building blocks of nucleic acids, they are better ligands for a wide range of biological targets.[1] The basic structure of the 3, 4-Dihydropyrimidinone derivatives is pyrimidinone, and two keto groups are present, one on the ring, and the other connected to the ring at the α point.[2] This particular core is responsible for the various biological actions of the compound. Researchers have been drawn to their diverse variety of activities, prompting them to investigate and create compounds for the production of different drugs. 3, 4-Dihydropyrimidinone-containing moieties as the fundamental centre. [3]

The simplest and most common method for the synthesis of 3, 4-Dihydropyrimidinone was reported first by Biginelli in 1983. It is a one pot three component reaction involving the condensation reaction with Benzaldehyde, Ethyl acetoacetate and Urea/thiourea. This reaction is called as the Biginelli reaction. A longer reaction period of about 20 hours is needed for the traditional Biginelli reaction, and certain aldehydes don't yield well. Being the simplest method, researchers were studying the reaction and have been developed various modified protocols of the conventional Biginelli reaction which are having less reaction time and improved yield of the product. [1, 3]. The basic reagents remain the same, only the conditions of the reaction, derivatives of the reagents and certain catalysts are the new modifications introduced. The reported studies shows these modified protocols shows better yield of the product in lower reaction time compared to the conventional Biginelli reaction.

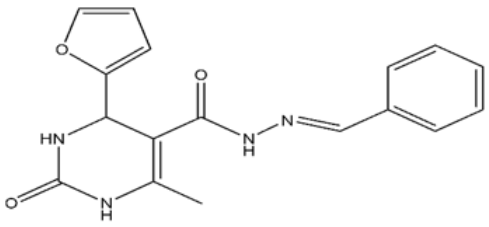

FIG 1: Basic Structure of 3,4 Dihydropyrimidinone derivative

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DIFFERENT REACTION CONDITIONS USING THREE COMPONENT BIGINELLI CONDENSATION FOR THE SYNTHESIS OF 3, 4-DIHYDROPYRIMIDINONE

1.Green synthesis in presence of Fruit juice

The synthesis of 3, 4-Dihydropyrimidinone was investigated by Anandarao A. Kale in 2019 using a green synthesis methodology in the presence of fruit juices such as amla, orange, and lime juice. This process involves the condensation of an aromatic aldehyde, a β keto ester, and urea in lemon juice using a single pot and three components. Urea, aromatic aldehydes, and ethyl acetoacetate were used to create several 3, 4-Dihydropyrimidinone derivatives. The aldehydes utilized in this investigation are 4-methoxybenzaldehyde, chlorobenzaldehyde, such as salicylaldehyde, anisaldehyde, and cinnamondehyde. IR and NMR spectroscopy were used to characterize the produced chemicals. In comparison to the traditional procedures (80–95%), the yield was higher. The primary benefits of this approach's operation simplicity and improved yield of the product, a quicker reaction time, and no organic given that this is a green synthesis, solvents. The general reaction is illustrated below.[4]

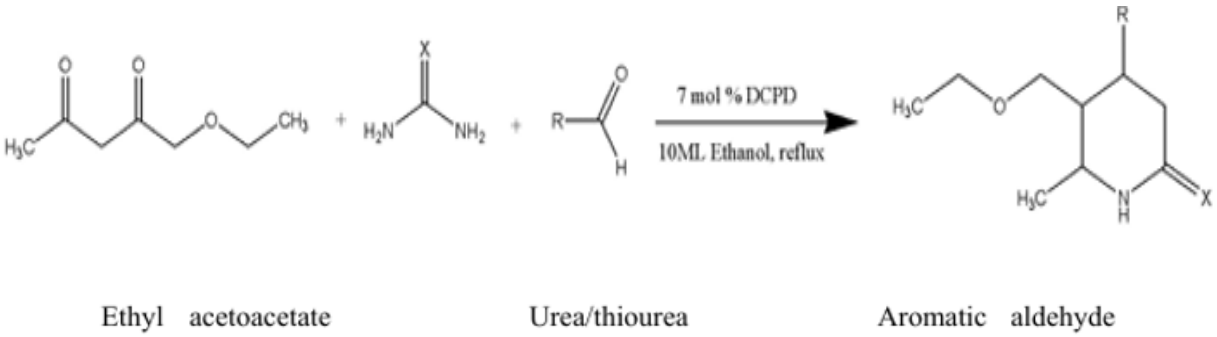

FIG 2: Synthesis of 3,4-Dihydropyrimidinones in presence of Lime juice

2.Green synthesis of Dihydropyrimidinones/ thiones derivatives of Curcumin.

2018, N. Khaldi-Khellafi et al. produced 3, 4-Dihydropyrimidinone analogues of curcumin. Curcumin is used as the β keto ester in this experiment. Curcumin exhibits a range of biological activities, including anti-inflammatory, anti-microbial, anti-cancer, and antioxidant properties. The idea of mixing curcumin with dihydropyrimidinones was motivated by this. This is the reason for the thought of combining Curcumin with Dihydropyrimidinones. Curcumin, substituted aromatic aldehyde, urea/thiourea, and a commercial hetero poly acid Keggin type H3PMo12O40 are used in the study's reaction, which is conducted in less ethanol volume and with the use of both conventional heating and microwave irradiation as reusable catalysts. . By using this catalyst a yield of 80-98% was obtained. .By using this catalyst a yield of 80- 98% was obtained. Furthermore, the microwave approach only needs a two to three minute reaction time. Promising findings were found when the Curcumin analogues were evaluated for antibacterial and antioxidant properties. Below is the general response.[5]

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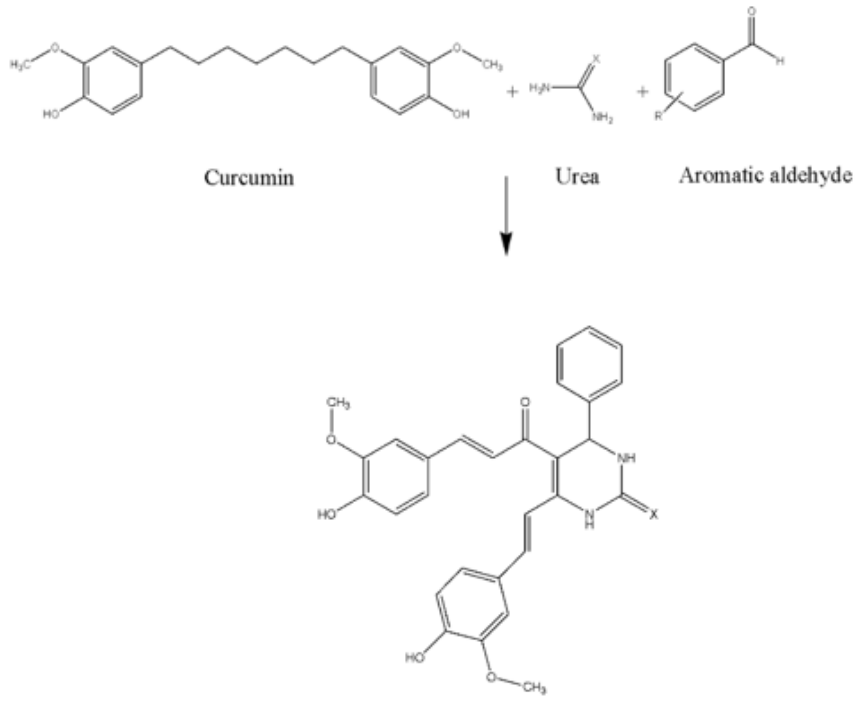

3,4-dihydropyrimidinones/thiones of curcumin

FIG 3: Synthesis of Curcumin analogues of Dihydropyrimidinones

3.Solvent free Biginelli synthesis of Dihydropyrimidinones using CuCl2

Dihydropyrimidinone was synthesized in 2018 by Ramin Rezaei and Mohammed Hosein Farjam using a green methodology. With CuCl2 acting as a catalyst, aromatic aldehyde, 1, 4-Diketone, and urea can be synthesized efficiently in a single pot. The analysis demonstrates that compared to traditional processes, the product was manufactured in a shorter amount of time. [6]

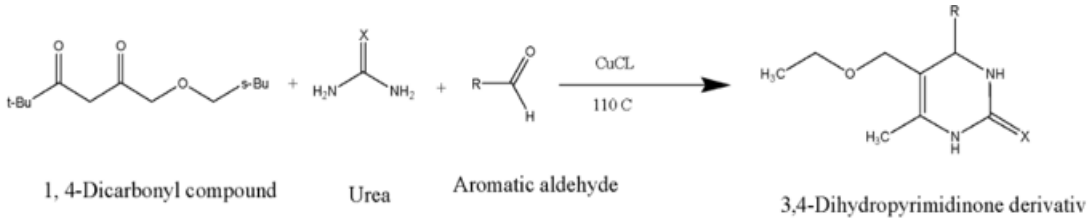

FIG 4: Synthesis of Dihydropyrimidinone using CuCl2 as catalyst

Additionally, this approach yielded a somewhat higher yield. This reaction is environmentally benign because it produces dihydropyrimidinones without the need for organic solvents and the catalyst can be reused.

A Green one pot Biginelli condensation using Dicalcium Phosphate as reusable Catalyst

In 2017, Zakaria Benzekri and colleagues conducted a green protocol to synthesize derivatives of 3, 4-Dihydropyrimidinone/thiones, employing dicalcium phosphate dihydrate as a reusable catalyst. According to the study, compared to the usual method, there is a great yield of product in shorter reaction times. A yield range of 51% (lowest yield) to 98% (best yield) is shown in the study. The response time was between 25 and 35 minutes.[7]

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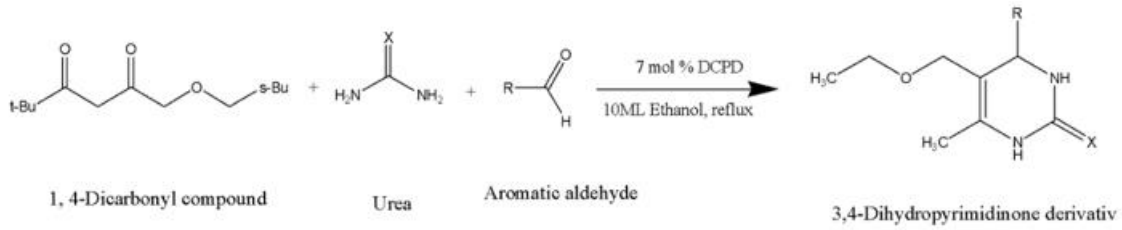


Figure 5: Synthesis of Dihydropyrimidinone using DCPD as catalyst

4.Synthesis of 3, 4-Dihydropyrimidinone/thiones/imines via a Lewis base catalyzed Biginelli reaction under solvent free conditions.

In 2016, S. Sheik Mansoor et al. used a modified Biginelli cyclo condensation process, mediated by triphenylphosphine (PPh3), to synthesize 3, 4-Dihydropyrimidinone/thiones/imines. According to the research, there was an 8-hour reflux period and a yield of 80–90%. Because the reaction is conducted without the use of a solvent, it is regarded as an environmentally friendly technique.[8]

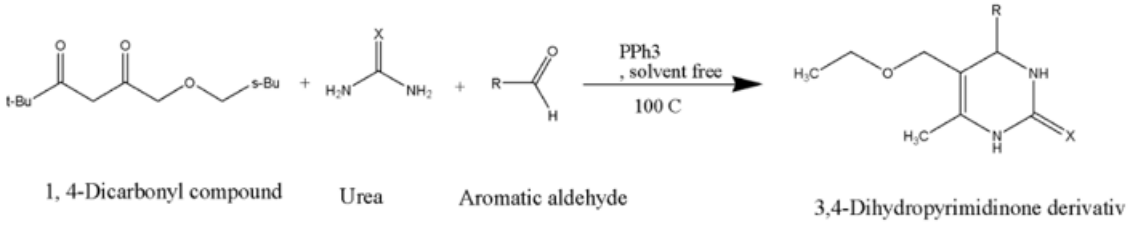


FIG 6: Synthesis of Dihydropyrimidinone

5.Green Chemistry approach for the Synthesis of 3, 4- Dihydropyrimidinone derivatives under solvent free conditions.

2015 saw a small modification of the Biginelli protocol in order to study the synthesis of 3, 4-Dihydropyrimidinone/thiones by Hajelsiddig and Saeed. It entails the reflux-monitored TLC-monitored three-component condensation of different aldehydes, ethyl acetoacetate, and urea/thiourea, without the use of any solvent. According to the study, there was a superior yield of 76–96% and a quicker response time (2–4.5 hours). Benzaldehyde, acetaldehyde, furfural, cinnamon aldehyde, and salicylaldehyde are the aldehydes that were employed in the investigation.[2]

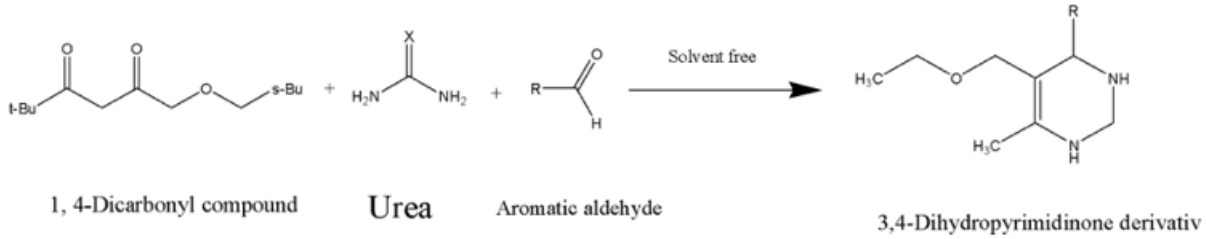


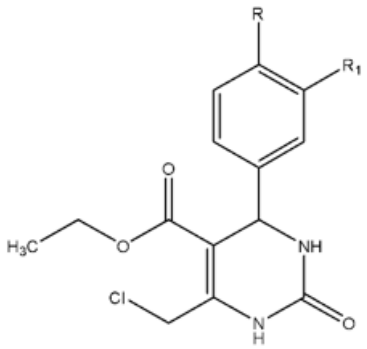
FIG 7 : Synthesis of Dihydropyrimidinone

BIOLOGICAL ACTIVITIES OF 3, 4-DIHYDROPYRIMIDINONE DERIVATIVES

1.Dihydropyrimidinone derivatives as Cytotoxic and Anti- Cancer agents

Designed and screened cytotoxic and tubulin inhibitory actions of aryl α-halo acrylamide linked Dihydropyrimidinone derivatives.(2) The study shows promising cytotoxic and tubulin inhibitory activities. The screening was done in human cancer cell lines like MCF-7 (Human breast cancer), MDA-MB-231(human breast cancer), HCT-116 (human colon cancer), HCT 15 (human

colorectal adenocarcinoma), HT-29(human adenocarcinoma), DU145 (human prostate cancer) and HFC-1(normal lung fibroblast). Cytotoxic activity of synthesized compounds was found out and expressed as IC50 value of 0.54 ± 0.12 to 8.35 ± 0.82 for the screened cell lines. Certain compounds found to inhibit tubulin polymerization (IC50 6.91± 0.43μM) with microtubule destabilizing activity. [9]



In accordance with NCI (USA) methodology, S Mostafa and K.B. Selim investigated the synthesis of a series of Dihydropyrimidinone derivatives containing N-heterocycles in 2018 and tested for their anti-cancer efficacy utilizing 60 cancer cell lines. A few substances shown noteworthy efficacy against many cancer cell lines, exhibiting growth inhibition rates ranging from 85-88%.

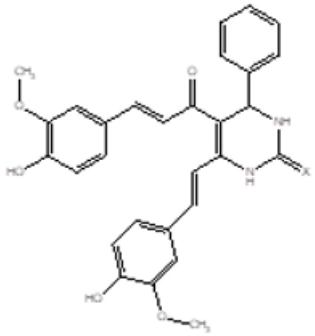


Figure 8: Synthesized compound with anticancer activity

2.Curcumin analogues of Dihydropyrimidinones with Anti-oxidant and Anti-bacterial activities

N. Khaldi-Khellafi *.et. al.* (2018) synthesized Curcumin analogues of 3, 4-Dihydropyrimidinone. In this study in place of ethylacetoacetate Curcumin is used as the βketoester.(3) In the study the reaction is carried out with Curcumin, substituted aromatic aldehyde and urea/thiourea in less volume of ethanol in the presence of a commercial heteropolyacide Keggin type H3PMo12O40 as recyclable catalyst by means of conventional heating and also microwave irradiation. By using this catalyst a yield of 80- 98% was obtained. And the microwave method requires only short reaction time of 2-3 mins. The Curcumin analogues were screened for anti-oxidant and antibacterial activities and promising results were obtained

FIG 9: Curcumin analogue of Dihydropyrimidinones having anti-oxidant and Anti-bacterial activity

J. Lal et al. synthesized many curcumin dihydropyrimidinones in 2016 and assessed their anti-inflammatory and antioxidant properties. The study's findings indicate that most synthetic substances have more activity than curcumin.

3. Anti-SARS activity of 3, 4-Dihydropyrimidinone derivatives

A number of pyrimidine derivatives, including dihydroprimidinone derivatives, were synthesized by Ramajayam et al. in 2010 and tested for their ability to prevent severe acute respiratory syndrome (SARS). The drugs were evaluated using previously established

testing techniques against SARS-CoV 3CLpro. Two compounds with nitro and chloro modifications in this investigation shown strong anti-SARS activity, with IC50 values of 10.6 and 6.1, respectively.[1]

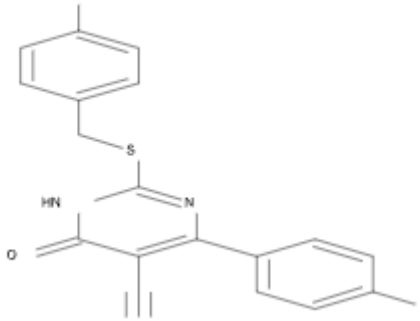
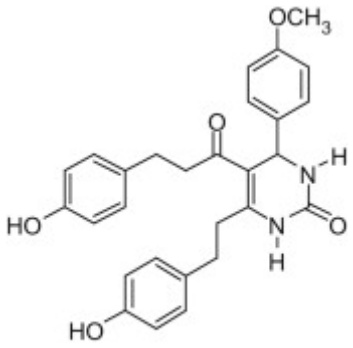


Figure 9: Compound having Anti-SARS activity

4. Novel racemic tetrahydrocurcuminoid dihydropyrimidinone analogues as potent AChE Inhibitors

Using the multi-component Biginelli reaction with copper sulphate as a catalyst, racemic tetrahydrocurcumin-(THC-),tetrahydrodemethoxycurcumin-(THDC-),& tetrahydrobisdemethoxycurcumin-(THBDC-) dihydropyrimidinone (DHPM) analogues were synthesized. These substances had greater inhibitory activity than their parent equivalents when evaluated as acetylcholinesterase inhibitors for Alzheimer's disease. With an IC50 value of 1.34 ± 0.03 μM, THBDC–DHPM exhibited the most inhibitory effect, surpassing the efficacious drug galanthamine (IC50 = 1.45 ± 0.04 μM).[10



IC_{50} = 1.34 ± 0.03 μM

FIG 10

5.Antonio L. Braga *et. al.* (2020)

This paper describes the synthesis and evaluation of new dihydropyrimidinone(DHPM)-derived selenoesters as potential multi-targeted agents for the treatment of Alzheimer´s disease.(6) A series of DHPM-derived selenoesters was obtained with high structural diversity through a short and modular synthetic route. The antioxidant activity was evaluated by TBARS and iron chelation assays. These compounds were also evaluated as acetylcholinesterase inhibitors (AchEi). The compounds demonstrated good antioxidant activity; since they presented excellent lipid peroxidation inhibition and good iron chelation activity. In addition, they showed acetylcholinesterase inhibition activity and some of them presented activity superior to that of the standard drug galantamine. Therefore, the series of DHPM-derived selenoesters described herein displayed good potential for the development of antioxidant and anticholinesterase agents in the search for new multi-targeted therapeutics for the treatment of Alzheimer's disease.

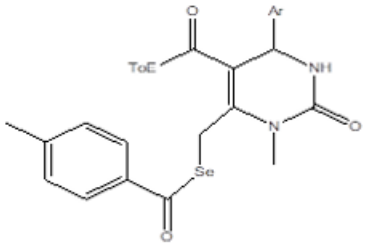


FIG 11

6.Karthikeyan Elumalai *et. al.* (2021)

Prepared A new series of some novel pyrazinamide condensed 1,2,3,4-tetrahydro pyrimidines by reacting N-(3-oxobutanoyl)pyrazine-2- carboxamide with urea/thiourea and appropriate aldehyde in the presence of the catalyticamount of laboratory made p-toluene sulfonic acid as an efficient catalyst. (8) Confirmation of the chemical structure of the synthesized compounds was substantiated by TLC, different spectral data IR, ^{1}H NMR, mass spectra and elemental analysis. The synthesized compounds was evaluated for acetyl and butyl cholinesterase (AChE and BuChE) inhibitor activity. The titled compounds exhibited weak, moderate or high AChE and BuChE inhibitor activity.

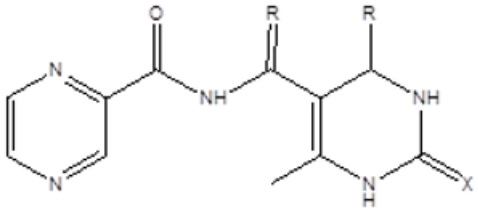


FIG 12

CONCLUISION

3, 4-Dihydropyrimidinones possess a range of biological properties, including antiviral, antibacterial, anti-oxidant, and anti-cancer properties. As a result, they serve as a foundation for the creation of numerous innovative medications. The research and development of new medications derived from dihydropyrimidinone derivatives has been drastically disrupted by the more recent improved synthesis techniques. According to published research, dihydropyrimidinone compounds exhibit encouraging activity. Dihydropyrimidinone research and optimization are thus opening up new avenues in medicinal chemistry.

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Conflict of Interest Statement: All authors have nothing else to disclose.