Review Article

A Review on 3, 4-dihydropyrimidinone Derivatives

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ABSTRACT

3, 4-Dihydropyrimidinones are considered as six membered heterocyclic compounds containing pyrimidine ring having two nitrogens as heteroatoms and two keto groups, one on the ring and one on α position to the ring. The pyrimidine ring and keto groups in the structure impart various biological actions to the compound. The synthesis of Dihydropyrimidinone is mostly done by Biginelli three component reactions. The classical Biginelli reaction requires high reaction time and often the yield is low. Here we emphasize on various modified synthetic protocols of this three-component reaction for the synthesis of 3, 4-Dihydropyrimidinones with low reaction time and better yield of product compared to the conventional Biginelli reaction. The broad range of biological activities of these moieties makes it a cascade for the development of the compound into various drugs having Anti-viral, Anti-bacterial, Anti-oxidant, Anti-cancer and Cytotoxic activities. The various reported studies show that 3, 4-Dihydropyrimidinones when optimized gives drug moieties having better action than the existing standards.

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

INTRODUCTION

Heterocyclic compounds are the basic structures in majority of the drugs. Hence their study is inevitable in the field of medicinal chemistry. Pyrimidine is one of these heterocyclic compounds having a wide range of biological activity. Pyrimidines are the fundamental structures of nucleic acids, which makes them a better ligand for various biological targets.[1] The 3, 4-Dihydropyrimidinone derivatives contains Pyrimidine as the core structure along with two keto groups one on the ring and the other attached to the α position to the ring.[2] This particular core is responsible for the various biological actions of the compound. Their wide range of activities have called the attention of researchers for studying and developing the compound for producing various drug moieties having 3, 4-Dihydropyrimidinone as the basic nucleus.[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, Ethylacetoacetate and Urea/thiourea. This reaction is called as the Biginelli reaction. The conventional Biginelli reaction requires longer reaction time around 20 hrs and also some aldehydes don't give good yields. 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.

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

1. Green synthesis in presence of Fruit juice

Anandarao A. Kale in 2019 studied the synthesis of 3, 4-Dihydropyrimidinone via a green synthesis protocol in presence of Fruit juices like Amla, Orange and Lime juice. This reaction is a one pot three component condensation of an aromatic aldehyde, a β keto ester and urea in lemon juice. Different types of 3, 4- Dihydropyrimidinone derivatives were synthesized using urea, aromatic aldehydes and ethyl acetoacetate. The various aromatic aldehyde used in this study are Benzaldehyde, 4-chlorobenzaldehyde, 4-methoxy Benzaldehyde, anisaldehyde, cinnamaldehyde and salicylaldehyde etc. The synthesized compounds were characterized by IR and NMR spectroscopy. The yield was better compared to the conventional methods (80-95%). The main advantages of this method is the operation simplicity, better yield of the product, lower reaction time and it doesn't use any organic solvents since it is a Green synthesis. The general reaction is illustrated below.[4]

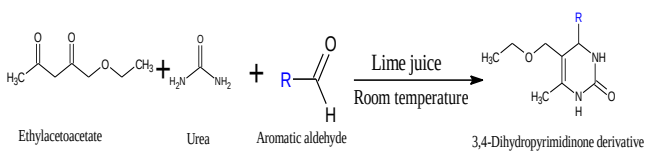

Figure 1: Synthesis of 3,4-Dihydropyrimidinones in presence of Lime juice

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

N. Khaldi-Khellafi et al in 2018 synthesized Curcumin analogues of 3, 4-Dihydropyrimidinone. In this study in place of ethylacetoacetate Curcumin is used as the βketoester. Curcumin is known for its various biological actions like anticancer, anti-microbial, anti-inflammatory and antioxidant actions. This is the reason for the thought of combining Curcumin with Dihydropyrimidinones. 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 $H_3PMo_{12}O_{40}$ 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 anti-bacterial activities and promising results were obtained. The general reaction is given below.[5]

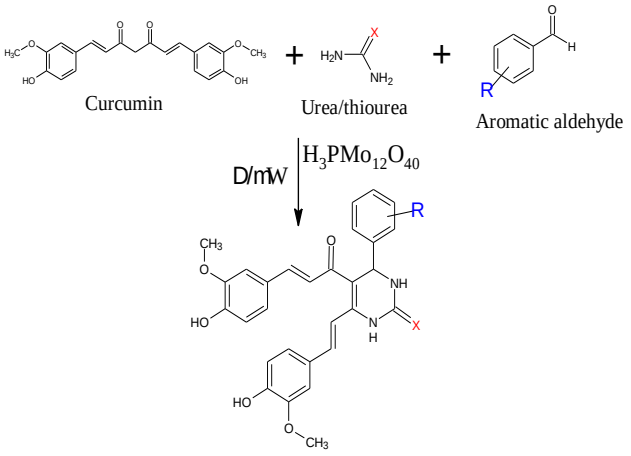

Figure 2: Synthesis of Curcumin analogues of Dihydropyrimidinones

3. Solvent free Biginelli synthesis of Dihydropyrimidinones using $CuCl_2$

Mohammed Hosein Farjam and Ramin Rezaei in 2018 carried out the synthesis of Dihydropyrimidinone through a green protocol. It is an effective one pot synthesis using aromatic aldehyde, 1, 4-Diketone and urea in the presence of $CuCl_2$ as catalyst. The study shows that the product was formed in short reaction time than conventional methods.

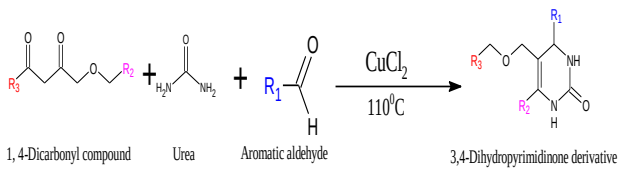

Figure 3: Synthesis of Dihydropyrimidinone using $CuCl_2$ as catalyst

Also the yield was comparatively higher in this method. In this reaction the catalyst is reusable and there is no use of organic solvents, so it is an environment friendly method for the synthesis of Dihydropyrimidinones.[6]

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

Zakaria Benzekri et al in 2017 carried out the synthesis of 3, 4-Dihydropyrimidinone/thiones derivatives through a green protocol using Dicalcium Phosphate dihydrate as a reusable catalyst. The study reports there is excellent yield of product in shorter reaction times compared to the conventional method. The study shows a yield of 51% (lowest yield) to 98% (highest yield). The reaction time taken was 25-35 mins.[7]

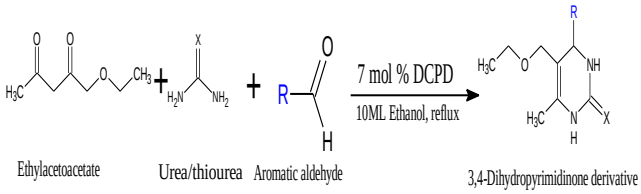

Figure 4: Synthesis of Dihydropyrimidinone using DCPD as catalyst

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

S. Sheik Mansoor et al in 2016 carried out the synthesis of 3, 4-Dihydropyrimidinone/thiones/imines by a modified Biginelli cyclocondensation reaction catalyzed by Triphenylphosphine (PPh_3). The study reports there was a yield of 80-90% and the reflux period was 8hrs. The reaction is carried out in a solvent free condition hence it is considered as an environment friendly protocol.[8]

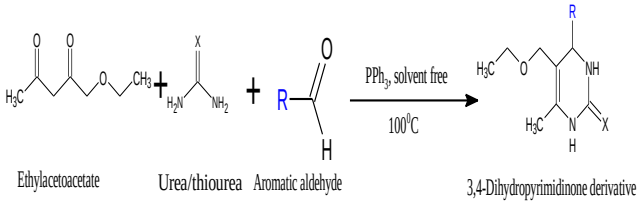

Figure 5: Lewis base catalyzed synthesis of 3,4-Dihydropyrimidinones

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

Hajelsiddig and Saeed in 2015 studied the synthesis of 3, 4-Dihydropyrimidinone/thiones by slight modification of Biginelli protocol. It involves the three-component condensation of various aldehydes, ethylacetoacetate and urea/thiourea without any solvent under reflux monitored by TLC. The study shows the reaction time was shorter (2-4.5hr) and there was excellent yield of 76-96%. The aldehydes used in the study are Benzaldehyde, acetaldehyde, furfural, cinnamaldehyde and salicylaldehyde.[2]

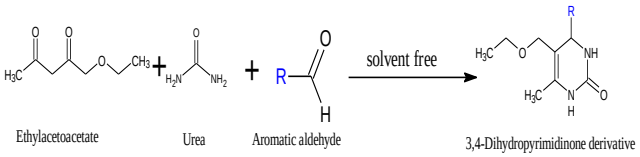

Figure 6: Solvent free synthesis of 3, 4-Dihydropyrimidinones

BIOLOGICAL ACTIVITIES OF 3, 4-DIHYDROPYRIMIDINONE DERIVATIVES

1. Dihydropyrimidinone derivatives as Cytotoxic and Anti-Cancer agents

S. Sana et al in 2019 studied the designing and cytotoxic and tubulin inhibitory actions of aryl α-halo acrylamide linked Dihydropyrimidinone derivatives. 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 IC_{50} value of 0.54 ± 0.12 to 8.35 ± 0.82 for the screened cell lines. Certain compounds found to inhibit tubulin polymerization (IC_{50} 6.91± 0.43µM) with microtubule destabilizing activity.[9]

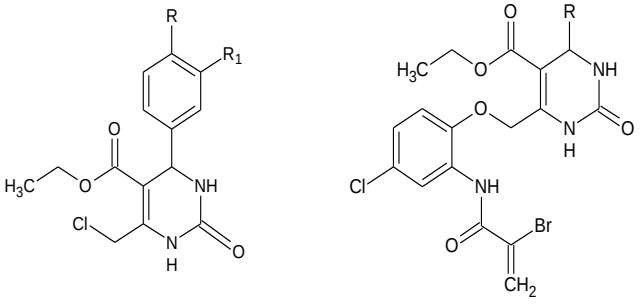

Figure 7: Compounds showing cytotoxic and tubulin inhibitory action

A.S Mostafa and K.B. Selim in 2018 studied the synthesis of a series of Dihydropyrimidinone derivatives bearing N-heterocycles and screened for their anti-cancer activity using 60 cancer cell lines according to NCI (USA) protocol. Certain compounds showed significant activity against various cancer cell lines with growth inhibition of 85-88%.[10]

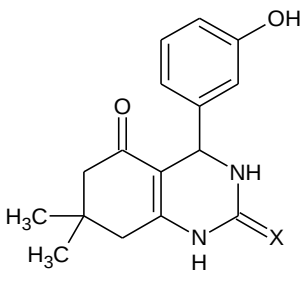

Figure 8: Synthesized compound with anticancer activity

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

N. Khaldi-Khellafi et al in 2018 studied the synthesis of Curcumin analogues of Dihydropyrimidinone derivatives and screened them for anti-oxidant and anti-bacterial activity. The study reports that most of the synthesized compounds show better anti-oxidant and anti-bacterial activity than Curcumin.[5]

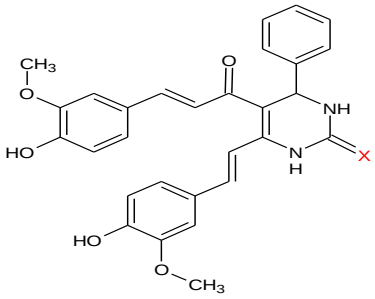

Figure 9: Curcumin analogue of Dihydropyrimidinones having anti-oxidant and Anti-bacterial activity

In 2016 J. Lal et al synthesized various Curcumin Dihydropyrimidinones and evaluated their anti-oxidant and anti-inflammatory activity. The results of the study reveals most synthesized compounds show higher activity compared to Curcumin.[12]

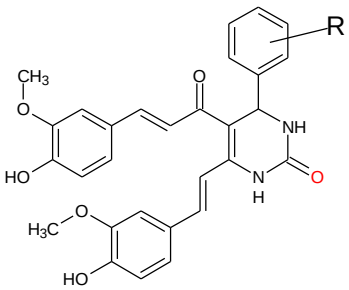

Figure 10: Curcumin Dihydropyrimidinone having anti-oxidant and anti-inflammatory activity

4. 3, 4-Dihydropyrimidinone derivatives having Antiviral activity

D. Kumaraswamy et al in 2017 synthesized and evaluated invitro for various DNA and RNA viruses. The compounds show good activity against various viruses especially Punta Toro virus, a member of Bunyaviridae.[11]

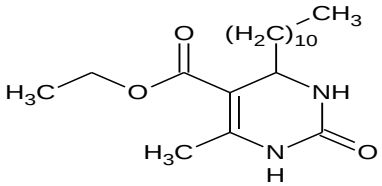

Figure 11: Compound having potent Anti-viral activity

Sari et al. in 2015 synthesized dihydropyrimidine α, γ-diketobutanoic acid derivatives and screened their activity against HIV Integrase. They synthesized 20 new molecules out of which 7 molecules were found to have potent activity against HIV Integrase.[1]

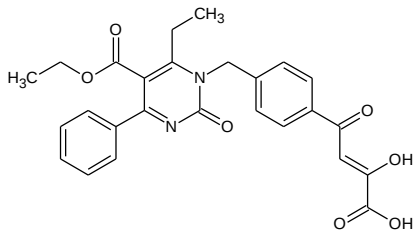

Figure 12: Compound having Anti-HIV activity

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

In 2010, Ramajayam et al synthesized various pyrimidine derivatives including dihydroprimidinone derivatives and screened for their activity against Severe Acute Respiratory Syndrome (SARS). The compounds were tested against SARS-CoV $3CL^{pro}$ using previously developed assay methods. In this study two compounds having nitro and chloro substitutions showed potent activity against SARS with IC_{50} values 10.6 and 6.1 respectively.[1]

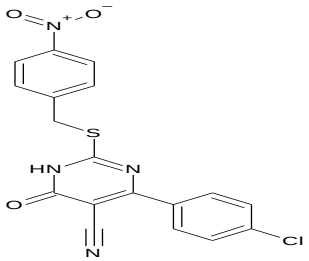

Figure 13: Compound having Anti-SARS activity

CONCLUSION

3, 4-Dihydropyrimidinones are having various biological activities like anti-cancer, anti-bacterial, anti-oxidant and anti-viral activities. Hence they are a scaffold for the development of variety of novel drugs. The newer modified methods for the synthesis have significantly uprooted the study and designing of novel drugs from Dihydropyrimidinone derivatives. The reported studies are showing promising activity for Dihydropyrimidinone derivatives. Hence the study and optimization of Dihydropyrimidinones are paving a new path in the field of medicinal chemistry.

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