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A Review On The Synthetic Methodologies And Therapeutic Significance Of 3,4-Dihydropyrimidinones

Saritha Boora[1], S.Geja Lakshmi[*2]

[*1]Department of pharmaceutical chemistry, Dr.M.G.R. Educational And Research Institute, Velappanchavadi, Chennai-77, India

[2]Department of pharmaceutical chemistry, Faculty of pharmaceutical sciences, Dr.M.G.R Educational And Research Institute, Velappanchavadi, Chennai-77, India

***Corresponding author:**

S. Gejalakshmi

Email ID: gejampharm@gmail.com

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ABSTRACT

3,4-Dihydropyrimidinones are the most important heterocyclic compounds that are significant in the synthesis of nucleic acids. Dihydropyrimidinones have been produced by multi-component processes like the Biginelli reaction and the Hantzschdihydropyridine reaction.Due to extreme pharmacological action of dihydropyrimidinones, Biginelli reaction has been focused and derivatives are synthesized from past decades utilizing various catalysts and solvents to enhance more yield and decrease reaction time and to better pharmacological properties. In this review, we emphasize current advancements in this area, highlighting the recently developed DHPMs having better anti-inflammatory, antibacterial, antioxidant, antifungal, anticancer activities than the present standards.

Keywords: *3,4-Dihydropyrimidinones, DHPMs, anti-inflammatory, antioxidant, anticancer, catalysts, green synthesis.*

1. INTRODUCTION

Significance of Multicomponent reactions-The synthesis and therapeutic applications of 3,4-dihydropyrimidinones (DHPMs) have garnered substantial interest in recent years due to their diverse pharmacological activities and versatile synthetic methodologies. DHPMs constitute a class of heterocyclic compounds that exhibit a variety of biological characteristics, such as antiviral, antibacterial, anti-inflammatory, and anticancer effects. As such, they present a promising avenue for drug discovery and development (Trivedi et al., 2017). Due to the fact that multicomponent reactions have advantages in both the economy and the environment, they are thought to be becoming increasingly crucial over time. To create 3,4-dihydropyrimidin-2(1H)-ones, or DHPMs, an aldehyde, a β-ketoester, and urea are blended together in the three-component Biginelli reaction (Saha et al., 2014).The prominence of DHPMs emerges from their structural diversity and synthetic accessibility, which have facilitated the exploration of their medicinal potential (Song et al., 2017). Novel approaches to the synthesis of DHPMs have been made possible by the advancement of traditional synthetic techniques like the Biginelli reaction, enabling the generation of libraries of structurally diverse analogs for biological evaluation(Kumar et al., 2017).

Advances in synthetic methodologies-Notable advances has been achieved presently in the synthesis of 3,4-dihydropyrimidinones, driven by innovative synthetic methodologies and catalytic processes(Kaur et al., 2016). Palladium- and copper-catalyzed cross-coupling reactions and the cascade reaction are a pair of transition metal-catalyzed reactions that have become effective tools to develop DHPM scaffolds with excellent regio- and stereoselectivity (Bhosle et al., 2015).

Therapeutic potential of DHPMs-Moreover, the therapeutic potential of 3,4-dihydropyrimidinones s has been extensively explored across various disease areas, including cancer, viral infections, cardiovascular diseases, and neurological disorders (Lauro et al., 2014). Studies have demonstrated the cytotoxic effects of DHPM derivatives against cancer cell lines through various mechanisms, including inhibition of key enzymes and induction of apoptosis (Naidu et al., 2015). Additionally, DHPMs have shown promising antiviral activity against a range of viruses, include hepatitis C virus (HCV), herpes simplex virus (HSV), and HIV highlighting their potential as antiviral agents.Furthermore, the development of DHPM-based inhibitors targeting specific enzymes and receptors involved in disease pathogenesis has shown encouraging results in

preclinical and clinical studies. These include inhibitors of dihydrofolatereductase (DHFR) for the treatment of cancer and antibacterial agents targeting dihydrofolate synthase (DHFS) in bacterial infections(Soni et al., 2014).

Overview of recent advancements-The objective of this review is to provide an overview of the existing synthetic techniques for the preparation of 3,4-dihydropyrimidinones, focusing on recent advancements in catalytic methodologies and strategies for the synthesis of structurally diverse analogs (Dragovich et al., 2013). Additionally, we will discuss the therapeutic applications of DHPMs across various disease areas, highlighting their potential as promising candidates for the development of novel medications (George et al., 2019).

Pyrimidine-Based Compounds in Medicinal Chemistry-In medicinal chemistry, pyrimidine derivatives are employed in numerous distinct therapeutic applications. The existence of a pyrimidine base in thymine, cytosine, and uracil—essential building components of nucleic acids, DNA, and RNA—is a particular hypothesis as to reason these molecules are active. Many chemical compounds with pyrimidine as the core nucleus have been developed and examined for their ability to treat hypertension, fight cancer, fight microbes, control blood sugar levels, arrest arrhythmia, reduce inflammation, treat HIV, and fight tuberculosis(Matos et al., 2018). Owing to the numerous medicinal properties, scientists have been drawn to creating novel dihydropyrimidine compounds.Some therapeutically active dihydropyrimidinones are mentioned in **Figure 1**.

Therapeutically Active DHPM Derivatives-Some of the anticancer drugs that contain DHPM nucleus are 5-Fluorouracil, Capecitabine, Tegafur. Monastrol is investigated as a mitotic kinesin Eg5 inhibitor, primarily in cancer research(Mathapati et al., 2017). It inhibits the kinesin Eg5 motor protein, which is essential for mitotic spindle formation, thus blocking cell division. SQ 109 is an antitubercular agent that inhibits the MmpL3 transporter, it functions in the movement of mycolic acids, essential components of the cell wall of mycobacteria(Liu et al., 2019).

Batzelladine alkaloidsare isolated from marine sponges used for their potential antiviral and anticancer properties. It exhibit various biological activities, including inhibition of HIV-1 gp120-CD4 binding and other enzyme inhibitory effects. DABCO derivatives are explored for their antimicrobial and anticancer properties. These compounds often act through inhibition of essential enzymes or disruption of cellular processes in pathogens or cancer cells(Kumar et al., 2019).

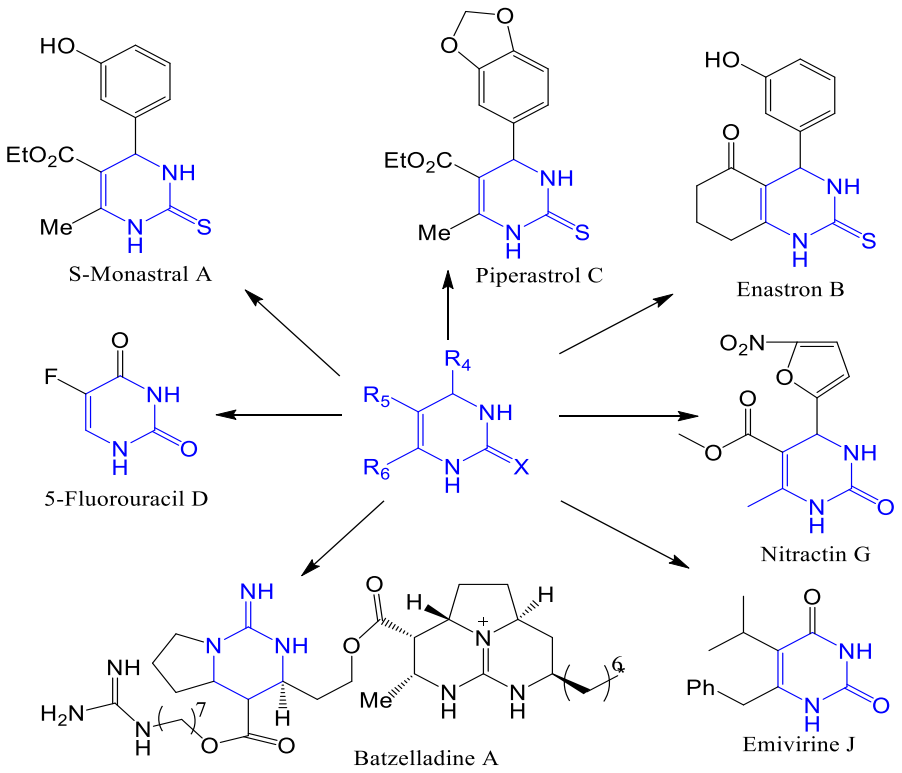


Figure 1.Dihydropyrimidinonenucleus containing drugs

CHEMISTRY OF DIHYDROPYRIMIDONE

Dihydropyrimidinones are small, chemicals that are incredibly advantageous and have several medicinal applications. Their chemical formula is $C_4H_6N_2O$, and they possess a broad spectrum of biological activities. Two N-atoms are included in the heterocyclic moiety at positions 1 and 3. They are pyrimidine derivatives which contain an additional ketone group(Naughton et al., 2006).

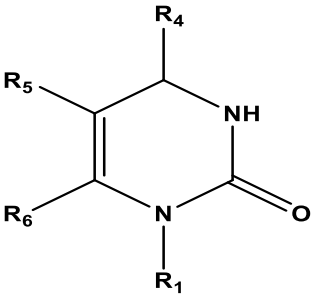


Figure 2. 3,4-Dihydropyrimidinones

Reactivity:*Carbonyl Group (C=O) at 2nd position*- a) Nucleophilic attack: Tetrahedral intermediates can be formed as a result of nucleophiles attacking the electrophilic carbonyl carbon. b) Reduction: Reducing agents such as NaBH4 or LiAlH4 can be used to reduce the carbonyl group to an alcohol.

Nitrogen at positions 1 and 3: a) Protonation/Deprotonation: In an acidic environment, nitrogen atoms can undergo protonation, while in a basic one, they can undergo deprotonation. These nitrogens have the ability to function as nucleophiles, particularly the one at position 3, which is capable of taking part in substitution processes. ***Carbon 4 and Carbon 5 Have a Double Bond:***Electrophilic Addition: Just like alkenes, the double bond is capable of electrophilic addition processes. Hydrogenation: The fully saturated 1,3,4,5-tetrahydropyrimidinone can be formed by hydrogenating (reducing) the double bond.

2. SYNTHETIC STRATEGIES

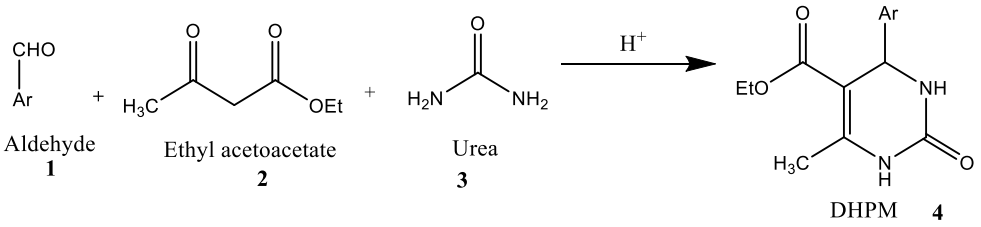
Biginelli Reaction-TheBiginelli reaction, a multicomponent synthesis comprising the condensation of an aldehyde, urea or thiourea, and a β-keto ester, is one of the most frequently employed methods for synthesizing DHPMs. The typical steps are:

1. Condensation: An intermediate is produced when the urea/thiourea and aldehyde react.

2. Cyclization: The intermediate undergoes cyclization.

3. Dehydration: Loss of water forms the dihydropyrimidinone ring.

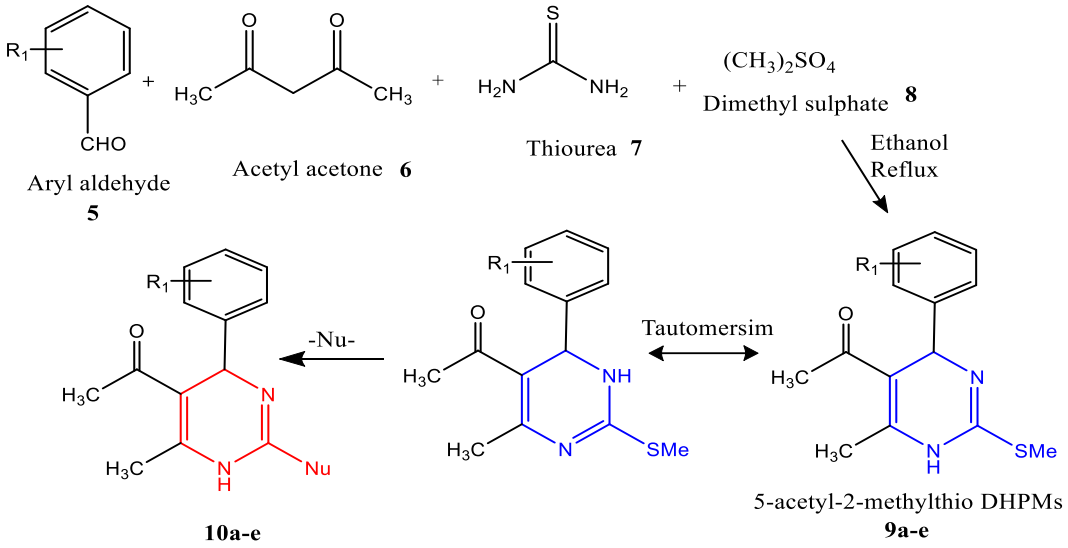
The method to yield 3,4-dihydropyrimidines by applying a one-pot, three-component condensation process was discovered by Italian chemist PietroBiginelli in 1893, and it later became known as the Biginelli reaction.Dihydropyrimidones**4**are intriguing chemicals with potential applications in therapeutics that can be rapidly and easily synthesized using this three-component reaction comprising an aldehyde**1**, ß-ketoester**2**, and urea**3**, which is catalyzed by an acid in **Scheme 1**(Kappe et al., 2000).



Scheme 1. The first Biginelli multicomponent synthesis

Tautomers

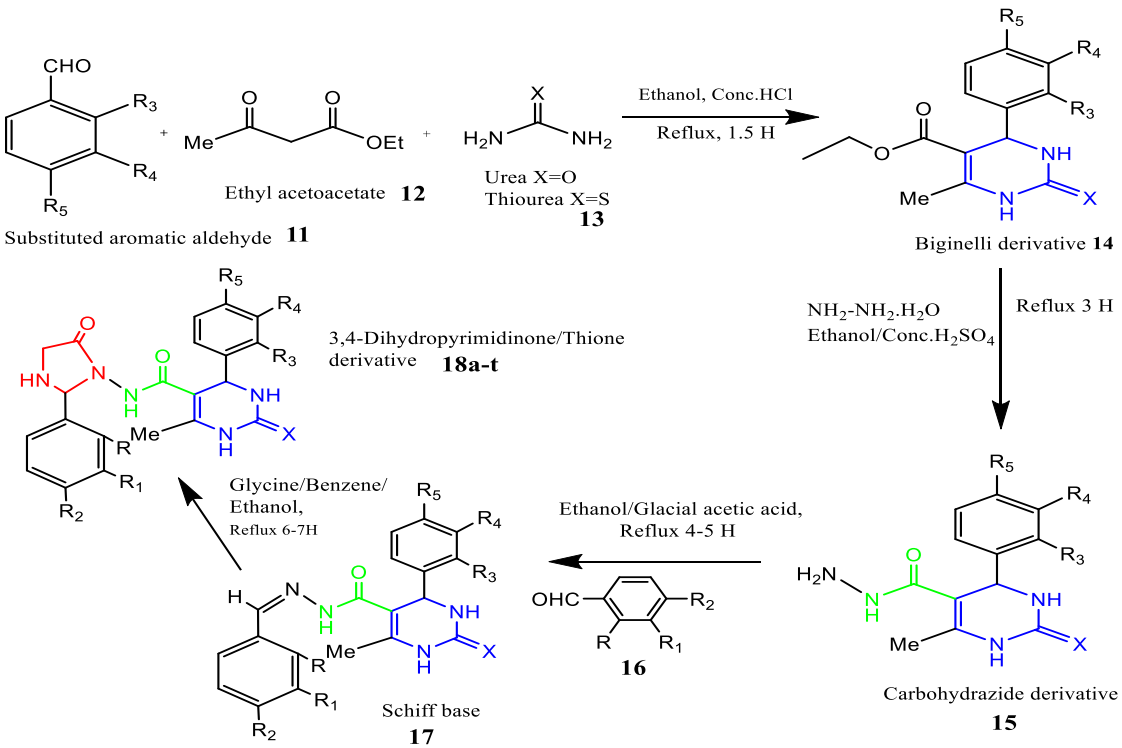
HarshaNarkhede et al., 2021 described the creation of C-2 functionalized dihydropyrimidines has been accomplished via a newly developed four-component modified Biginellireaction (Nagarajaiah et al., 2016). This approach combines the less-explored acetyl acetone (compound 6) with thiourea (compound 7), dimethyl sulfate (compound 8), and an aromatic aldehyde (compound 5) to form a novel 5-acetyl 2-methylthio dihydropyrimidine system (compounds 9a-e). This system serves as an efficient intermediate for generating C-2 modified Biginellilibraries that incorporate nitrogen nucleophiles. Phenyl hydrazine, semicarbazide, and aryl semicarbazide, when used as N-nucleophiles, successfully produce C-2 functionalized dihydropyrimidine derivatives (compounds 10a-e) that meet active pharmacophorerequirements(Kaur et al., 2017). The reaction conditions for synthesizing these DHPMs are detailed in Scheme 2. The primary advantages of this innovative method include time and step efficiency, along with a one-pot reaction yielding moderate to excellent results(deFátima et al., 2015).



Scheme 2.C2 functionalized DHPMs produced via N-nucleophiles

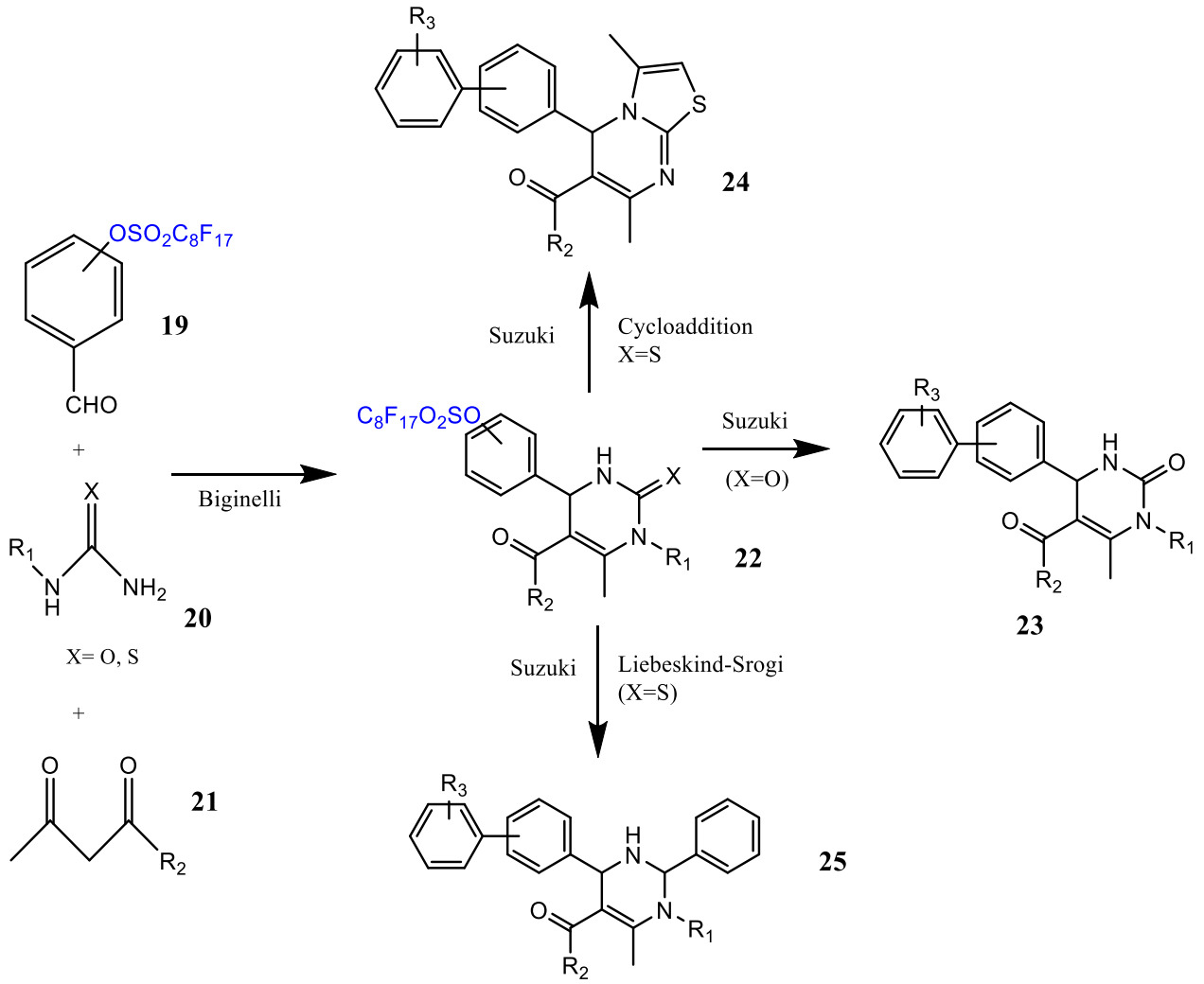
High-Throughput Screening

M.K.M. Abdul Lathiff et al., 2024 reported a library of 200 ligands, featuring 3,4-dihydropyrimidinones or their thiones, was designed and synthesized from Schiff bases connected to imidazolidinones via amide linkages. Molecular docking studies were performed, and 20 ligands demonstrated the best docking scores and binding interactions (Matos et al., 2018). The desired compounds are produced in four steps from compounds **11, 12, 13** it produces substituted biginelli derivatives **14**, further carbahydrazide derivatives**15**, Schiff bases**17**and DHPMs **18a-t** are synthesizedas mentioned in **Scheme 3**and The in vitro anticancer activity against human topoisomerase II alpha (TOP2α or TOP2A) was evaluated using DU-145 and PC-3 prostate cancer cell lines through the SRB assay method. This investigation involved the molecular docking and synthesis of the target compounds via a series of organic nucleophilic addition reactions, including the Biginelli one-pot condensation reaction(Malik et al., 2019).



Scheme 3.Synthetic strategy for 3,4-dihydropyrimidinone/thione derivatives

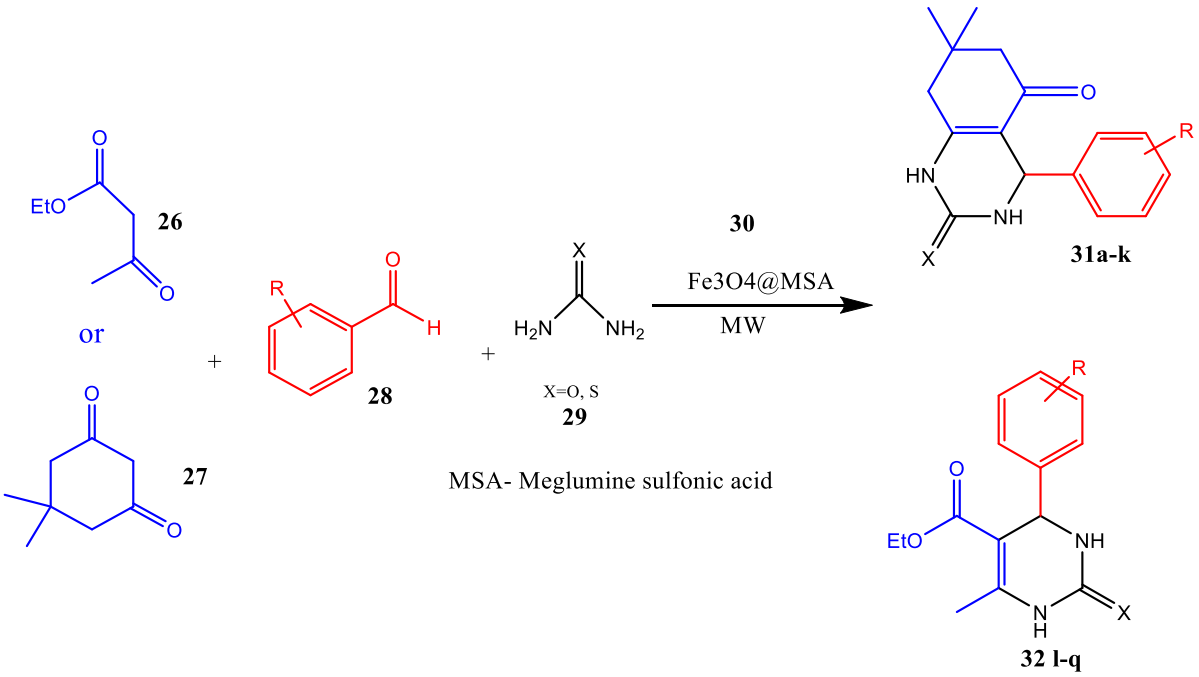
Bruno Piqani et al., 2011 reported that compounds identified as Biaryl-substituted dihydropyrimidinone**23**, dihydropyrimidine**25**, and thiazolopyrimidine**24** are synthesized through Biginelli reactions involving benzaldehydes attached toperfluorooctanesulfonylgroups(Gasperi et al., 2015). These compounds **22**are then used as common intermediates for post-condensation modifications such as cycloaddition, Suzuki coupling and Liebeskind-Srogl reaction as depicted in **Scheme 4**. The utilization of Fluorous solid-phase extractions (F-SPE) were employed for simplified purification, and a multi-component reaction was used to enhance atom economy, and microwave heating for quick reaction times all contribute to the diversity-oriented synthesis demonstrated high efficiency(Zhu et al., 2015).



Scheme 4.Synthesis of various compounds associated with dihydropyrimidines

Catalysts

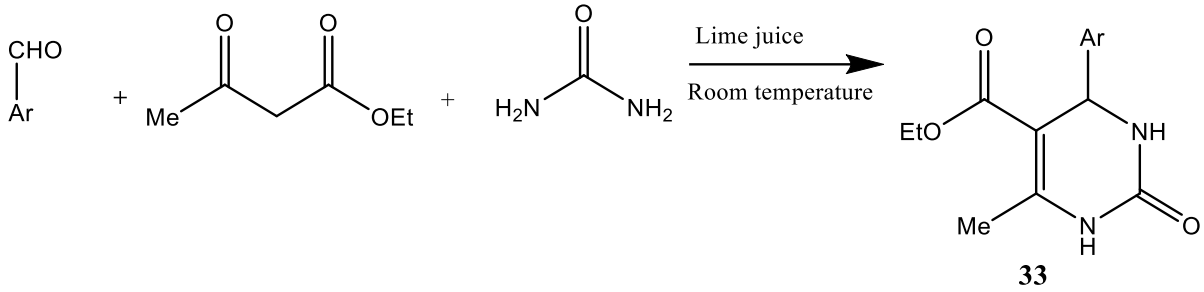
Leila Moradi et al., 2018 described a straightforward and uncomplicated procedure was used to create the new solid acid catalyst, a helpful strategy for increasing catalyst efficiency is heterogenization of homogeneous catalyst(Graebin et al., 2019). The work that was presented described a novel technique for creating a heterogeneous and potent catalyst by adhering meglumine sulfate, a homogenous highly soluble catalyst, to the surfaces of magnetite nanoparticles. The produced heterogeneous, reusable solid acid catalyst**30** performs exceptionally well in the Biginelli compound synthesis.3,4-Dihydropyrimidinone derivatives**31a-k, 32l-q**are synthesized as shown in **Scheme 5**.The Microwave radiation was used to complete the reaction quickly and environmentally. The method's primary benefits are its simplified setup, high product yield (90–98%) in brief reaction durations (40–200s), and reusable catalyst(Singh et al., 2012).



Scheme 5.Synthesis of 3,4-DHPMs using Fe_3O_4@MSA

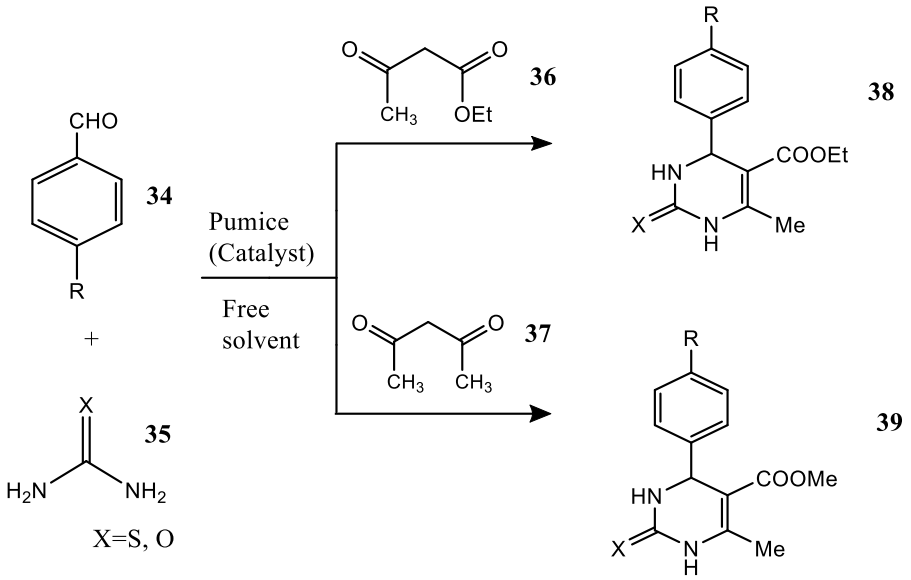
Green Chemistry Approaches-

TanayPramanik et al., 2015 synthesized A series of dihydropyrimidinone (DHPM) derivatives **33** were synthesized using urea, ethyl acetoacetate, and both electron-rich and electron-deficient aromatic aldehydes through the Biginelli reaction under eco-friendly and green conditions, as shown in **Scheme 6**. Their antimicrobial activities were tested against several common pathogenic microorganisms. It was found that the electronic nature of the phenyl ring in DHPM significantly affected their antimicrobial properties (Nielsen et al., 2020).



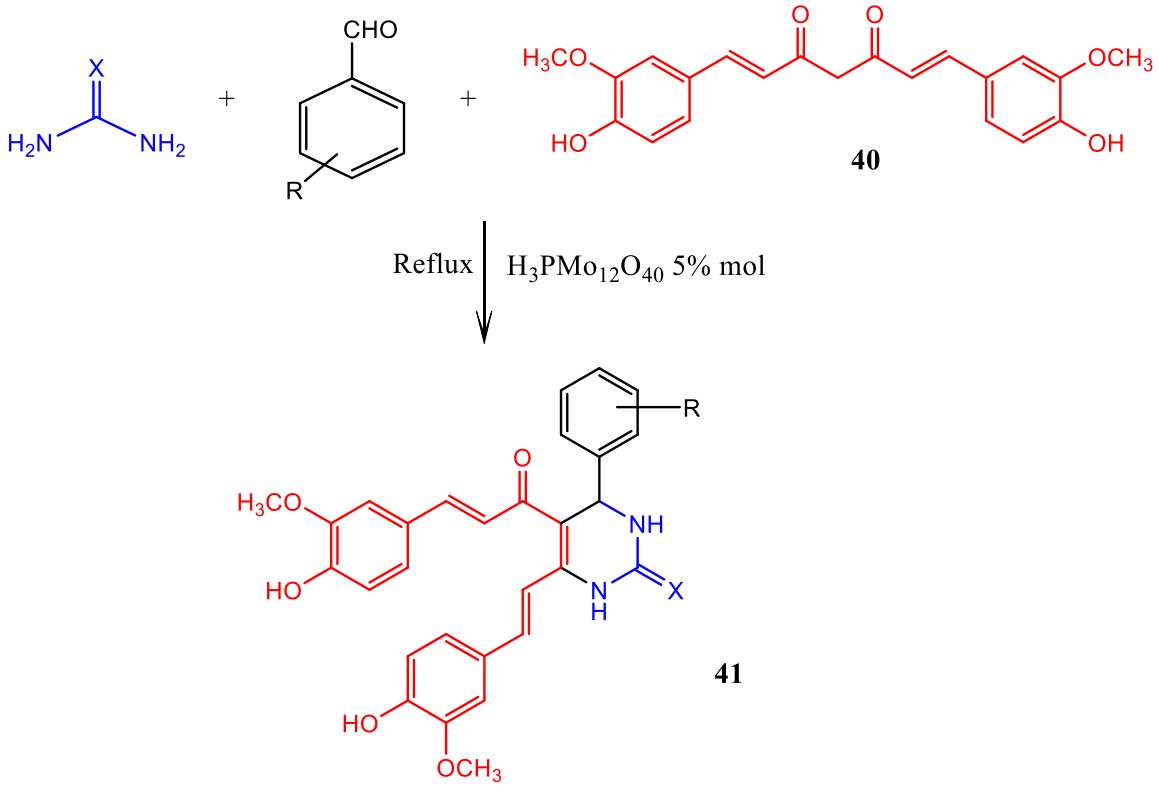
Scheme 6. Synthesis of 3,4-Dihydropyrimidinones with Lime juice

Hany M. Abd El-Lateef et al, 2022utilized pumice as a unique natural heterogeneous catalyst for the one-pot multi-component condensation of aromatic aldehydes **34**, urea or thiourea**35**, and ethyl acetoacetate **36** or acetylacetone**37** produces various 3,4-dihydropyrimidine-2-(1H)-one/thione derivatives **38** and **39** with high yields (up to 98%).. The catalyst's chemical and physical characteristics were investigated (Abdul Lathiff et al., 2024). Their composition was shown to be basaltic by geochemical research. Its composition of amorphous elements containing the zeolite minerals clinoptilolite and heulandites within their pores was further revealed by X-ray diffraction. In addition, Pumice features a mesoporous structure with pore sizes between 21.1 and 64.5 nm and a porosity of 78.2–83.9% by volume. Its surface area varies from 0.053 to 1.47 m^2/g, while the pore volume ranges from 0.00531 to 0.00781 m^2/g.The latter made it possible for the reaction to continue quickly and with good yields. This method allows for the use of inexpensive, easily accessible, non-toxic, and thermally stable pumice catalyst. In the solvent-free environment, the reactions proceeded efficiently and the products were extracted in excellent yields and great purity without the need for laborious workup methods (Yazdan et al,, 2015). Pumice can, in fact, be reused for a minimum of five times without losing its effectiveness. The reaction with pumice was described below in **Scheme 7**.



Scheme 7. Synthesis of 3,4-Dihydropyrimidinones in presence of Pumice

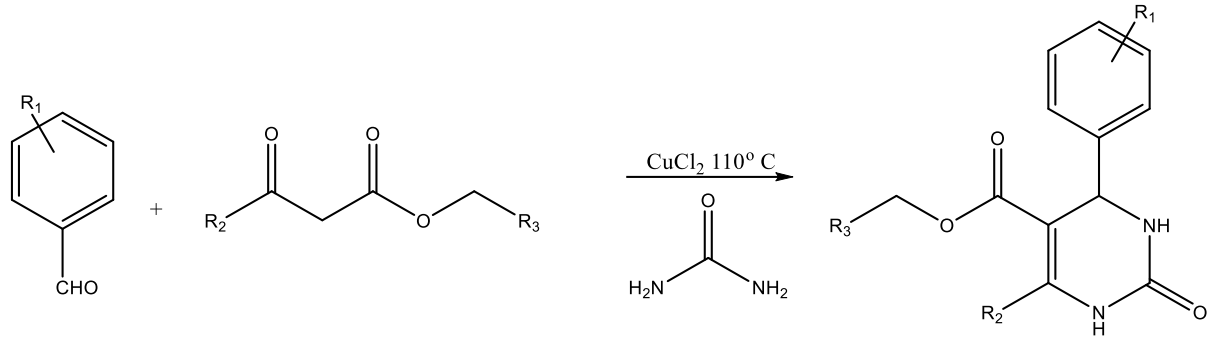
NassimaKhaldi-Khellafi et al., 2019 reported that in a reduced volume of ethanol, curcumin**40**, substituted aromatic aldehydes, and urea/thiourea were reacted to obtain 3,4-Dihydropyrimidin-2(1H)-one/thione analogs **41** in a relatively high yield (NassimaKhaldi-Khellafi et al., 2019). This reaction was catalyzed making use of the non-toxic, recyclable commercial heteropolyacidKeggin type $H_3PMo_{12}O_40$ at 5% mol under traditional heating and microwave irradiation illustrated in **Scheme 8**. We tested each of the produced derivatives of curcumin, 4a–n, for antibacterial and antioxidant properties. Biological activity data indicated that most of the synthesized compounds exhibited greater antioxidant and antibacterial effects compared to curcumin. The B3LYP method with the 6-31G* basis set was used for the analysis to optimize the geometric properties of the synthesized molecules.



Scheme 8. Synthesis of 3,4-dihydropyrimidinones/thiones of curcumin

Transition Metal-Catalyzed Reactions

Maryam Maardasi et al., 2016 carried out a highly efficient one-pot synthesis of dihydropyrimidinone derivatives **42** is achieved under solvent-free conditions using CuCl2, an inexpensive and readily accessible reagent, via the Biginelli condensation reaction of aldehyde derivatives, 1,3-dicarbonyl compounds, and urea, as detailed in **Scheme 9**. This green protocol offers excellent yields, rapid reaction times, and straightforward work-up procedures (Trivedi et al., 2022).



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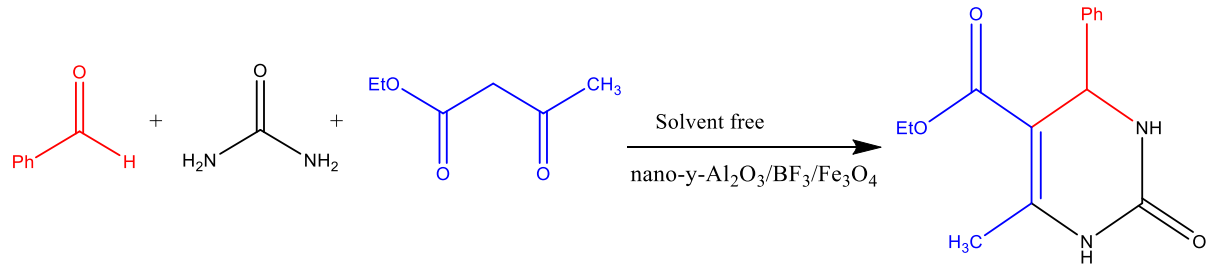
Scheme 9. Synthesis of 3,4-dihydropyrimidinones in presence of $CuCl_2$

Abdolhamid Bamoniri et al., 2020 reported that Fourier Transform Infrared (FT-IR), Powder X-ray diffraction (XRD), Transmission Electron Microscopy (TEM), Vibrating Sample Magnetometer (VSM), Field Emission Scanning Electron Microscopy (FESEM),Thermal Gravimetric Analysis (TGA) and Brunauer–Emmett–Teller (BET) analysis were utilized to synthesize and characterize nano-γ-Al_2O_3 /BF_3/Fe_3O_4 nanoparticles**43,** reaction was mentioned in **Scheme 10**. Solvent-free, mild and environmentally friendly one-pot multicomponent synthetic process of 3,4-dihydropyrimidine-2(1H)-ones/thiones was successfully carried out using nano-γ-Al_2O_3/BF_3/Fe_3O_4 nanoparticles as a promising catalyst (Babaei et al., 2019). The Biginelli reaction produces dihydropyrimidinone by passing through components mentioned in reaction below. In brief reaction period, excellent yields of dihydropyrmidinones were aquired. The proposed method offers several advantages, such as rapid reaction times, high efficiency, quick purification, clean reactions, and simple catalyst recovery.



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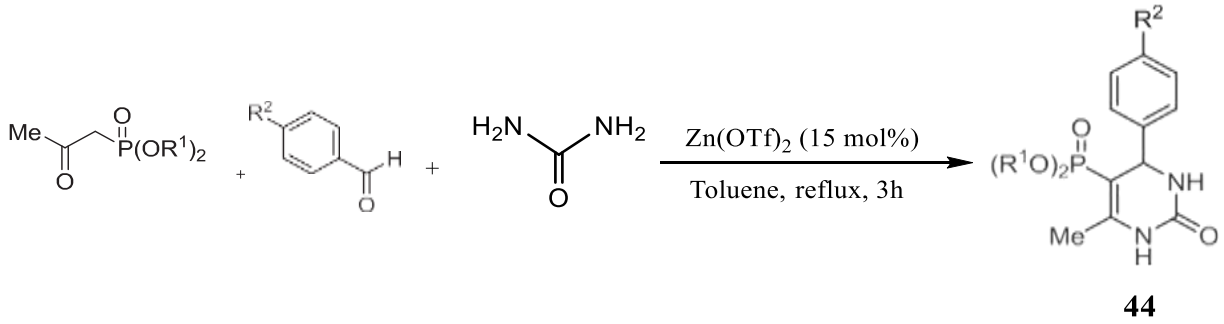
Scheme 10. Synthesis of 3,4-dihydropyrimidine-2(1H)-one in the presence of nano-γ-Al_2O_3 /BF_3/Fe_3O_4

3. PHYSIOLOGICAL ACTIVITIES

3.1. Anti-inflammatory activity

IdrisEssid et al., 2017 presenteda reliable and extremely simple one-pot three-component synthesis of 5-phosphonato-3,4-dihydropyrimidin-2(1H)-ones 44 is achieved through a Biginelli-type reaction involving β-ketophosphonates, urea and aldehyde,which is catalyzed by zinc triflate (Nevagi et al., 2014) described in **Scheme 11**. Many spectroscopic techniques, including as infrared, mass spectrometry, XRD and NMR spectroscopy, were done to characterize the compounds that were produced are mentioned in **Figure 2**. Using female Wister rats and carrageenan-induced hind paw edema method, all the synthesized compounds were evaluated for anti-inflammatory activity for the first time. Compounds **46**, **47**, and **50** showed notable anti-inflammatory effects, surpassing the standard drug indomethacin. Among them, compound **50** exhibited the highest anti-inflammatory activity at 58.42%.



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Scheme 11.Synthesis of3,4-dihydropyrimidinones withzinc triflate

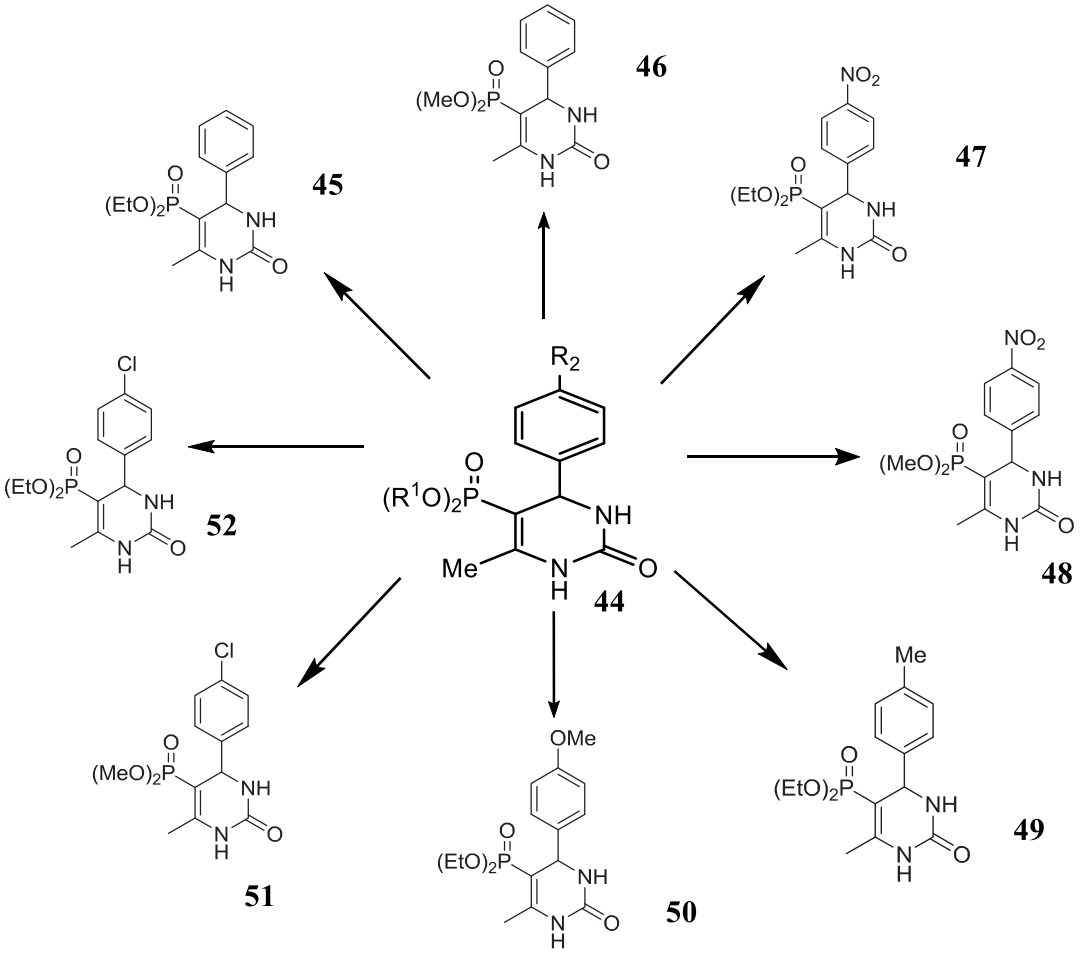
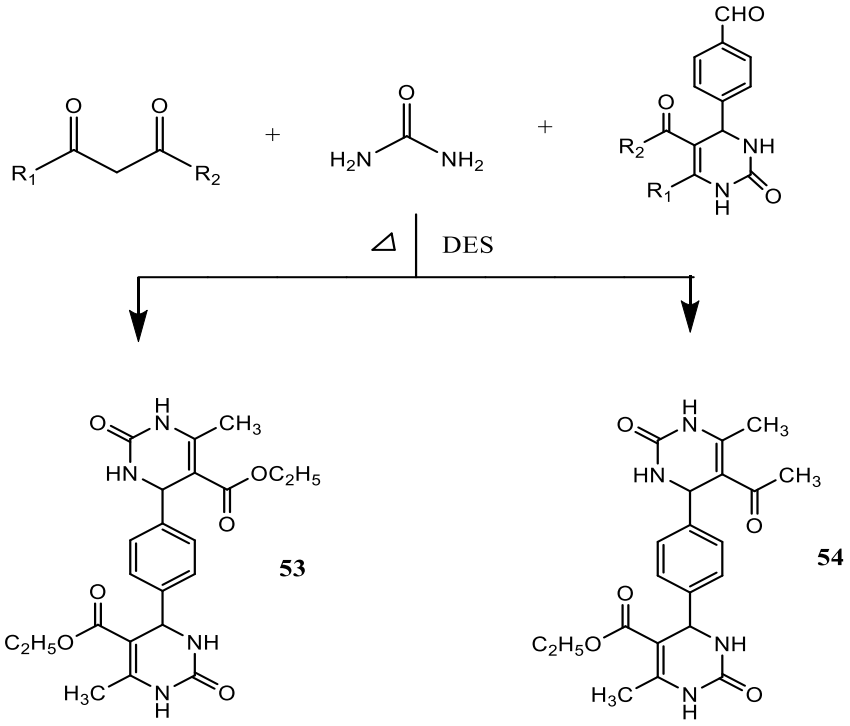


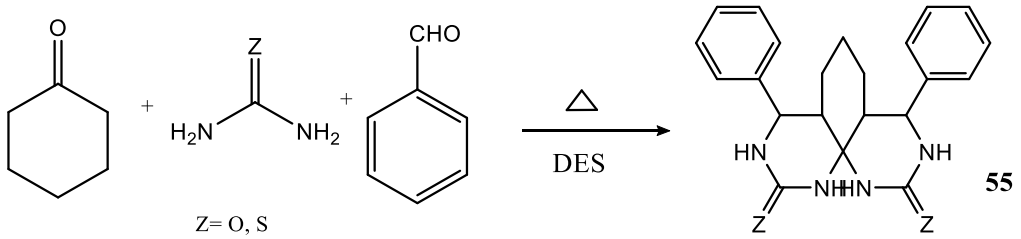
Figure 2.Structures of active DHPMs with anti-inflammatory activity

3.2. Antibacterial activity

Nilesh S. pawar e al., 2021 synthesized "libraries from libraries" Bis compounds 53 and 54, along with spiro cyclic products of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs), were effectively synthesized by refluxing a reaction mixture of the three components in a deep eutectic solvent (DES) (Mats Larhed et al.,1996) **55**mentioned in **Scheme 12** and **Scheme 13** respectively. The urea moiety of synthesized spiro fused heterotricyclic compounds gives them strong antibacterial properties. Overall, it was discovered in investigation that several of the synthesized 3,4-DHPM compounds have antibacterial activity.



Scheme 12. Synthesis of bis-3,4-dihydropyrimidin-2(*1H*)-ones from DES



Scheme 13. Heterocyclic molecules spirofused

3.3. Antioxidant activity

N. Khaldi-Khellafi et al., 2018 carried out Dihydropyrimidinone derivatives' curcumin analogues production, and their antibacterial and antioxidant properties were evaluated (Beller et al., 2002). As Figure 3 illustrates, several compounds had beneficial antioxidant properties but somewhat modest antibacterial activity. The compound **56**, which was produced by reacting urea with 3,4-dihydroxybenzaldehyde, had the strongest antioxidant and moderate antibacterial properties than Curcumin.

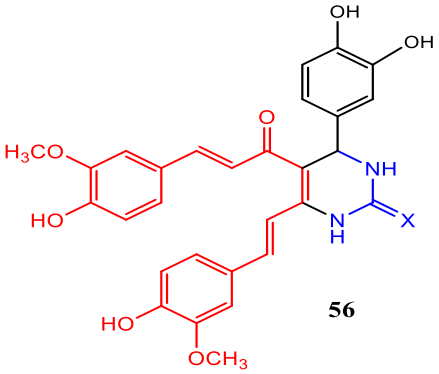


Figure 3. Curcumin derivative showing anti-oxidant and Anti-bacterial activity

M.K.M. Abdul Lathiff et al., 2024 synthesized twenty novel 3,4-dihydropyrimidinones with imidazolidin-4-one derivatives. Their radical scavenging potential was assessed using the DPPH assay to evaluate the antioxidant properties of these newly synthesized Biginelli derivatives. Compared to reference drug ascorbic acid, the test compounds all exhibited good to excellent antioxidant potency (Zheng et al., 2015) 10 produced compounds exhibited a good level of scavenging potency. Interestingly, 3 compounds **57, 58, 59**showed considerable action mentioned in **Figure 4**. The study says that compounds containing additional groups, such as -OCH3, -CH3, and -Cl may show excellent scavenging potency, along with compounds containing an OH group. In addition, the conjugated system- that is, the amide linkage connected to the 3,4-dihydropyrimidinone ring or the presence of multiple labile hydrogen atoms attached to nitrogen atoms may be responsible for the studied compounds' potential for radical scavenging. This stabilization of the compounds, when they become radicals by donating an electron to ROS, would have been further supported.

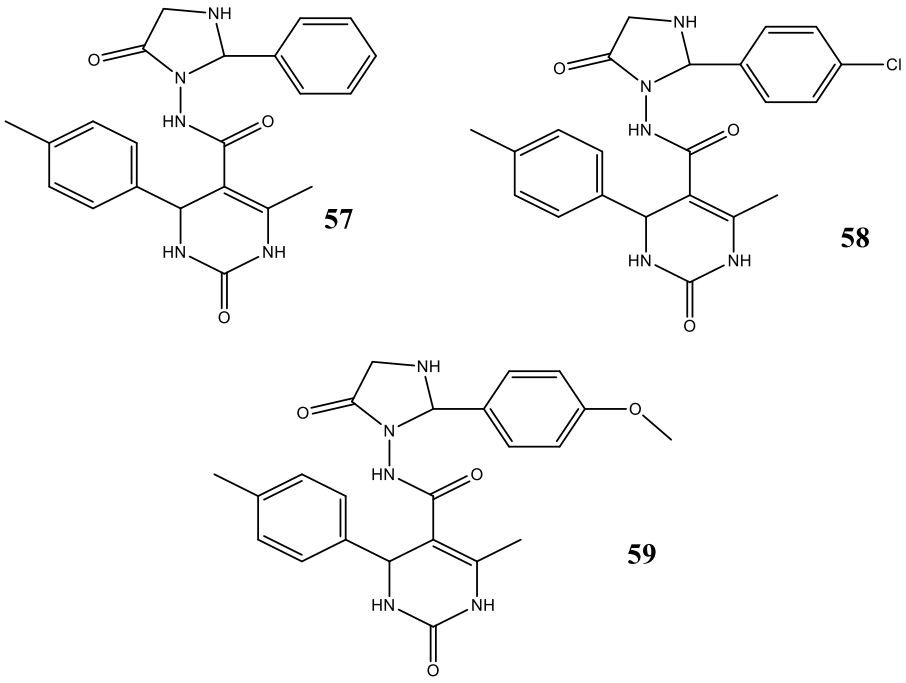


Figure 4. Compounds exhibiting good spectrum scavenging potency of DPPH Assay

3.4. Antifungal activity

Shahid Shaikh et al., 2015developed a unique chalcone series to synthesis new 3, 4-dihydropyrimidine compounds**60** illustrated in **Figure 5**. By testing the synthetic chemical 5a-r's antibacterial activity against four bacterial and fungal microorganisms, we were able to determine the biological significance of the substance (Zhang et al., 2018). All of the produced compounds shown strong antibacterial activity against every test microorganism, while 6 compounds mentionedwith substituents in**Table 1** exhibited the strongest antifungal activity, displaying the largest inhibition zone against both Candida parapsilosis and Aspergillusfumigatu.

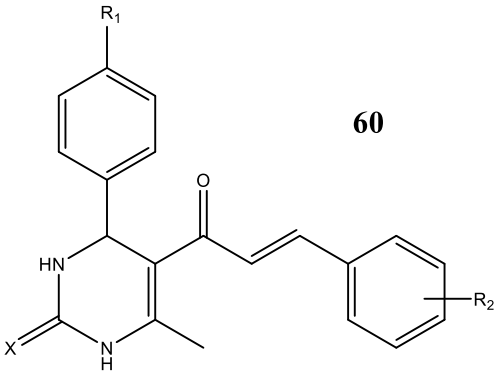


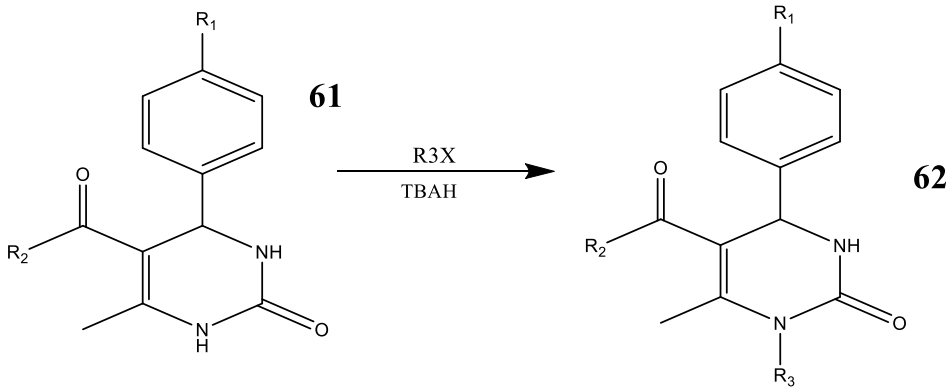
Figure 5.3, 4-dihydropyrimidinone/thione derivative

Table 1. Substituents of 3, 4-dihydropyrimidinone/thione derivative in Figure 5

Compound	R1	R2	X
1	4-OMe	4-Cl	O
2	3-NO_2	4-Cl	S
3	4-H	3,4,5-$(OCH_3)_3$	O
4	4-Cl	3,4,5-$(OCH_3)_3$	O
5	4-H	3,4-$(OCH_3)_2$	O
6	4-Cl	3,4-$(OCH_3)_2$	O

3.5. Anticancer activity

Ye Liu et al., 2022 reported that tetrabutylammonium hydroxide was utilized to investigate the selective alkylation of N1(Joshi et al., 2015). According to an in vitro cytotoxicity assay conducted on all developed compounds, the anti-proliferative activity of DHPMs was enhanced by the introduction of an aryl chain at R3 and a low electron-donating group at R1. **Table 2** provides the inhibitory concentration (IC50) values. Higher partition coefficient (Log P) values and adequate polar surface area (PSA) values were linked to the maintenance of anticancer activity. molecule**62**, shown in **Scheme 14**, offers a great deal of promise as a lead molecule for creating novel anti-tumor medications for the treatment of gliomas, according to the outcomes of an in vivo investigation. The structure-activity interactions of DHPMs were also investigated using pharmacophore analysis, which provided information for designing potential bioactive 3,4-dihydropyrimidin-2(1H)-one molecules.



Scheme 14. Generation of N1-alkylated DHPMs using various halohydrocarbons

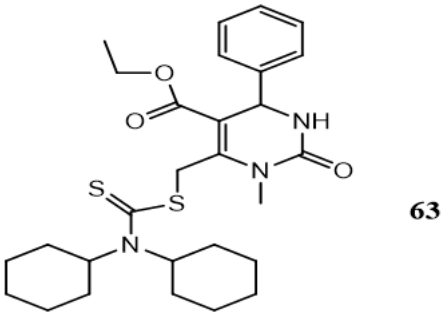
Table 2. Molecules analyzed in U87 and U251 cell lines for half maximum inhibitory concentration (IC50)

Compound	IC_{50} (µM)	
	U87	U251
1	9.72 ± 0.29	13.91 ± 0.86
2	9.30 ± 0.81	14.01 ± 0.76
3	12.02 ± 0.5	6.36 ± 0.73
4	9.52 ± 0.81	7.32 ± 0.86
BIIB021[a]	2.07 ± 0.13	0.3 ± 0.043

BIIB021 as a positive control.

Amany S. Mostafa et al., 2018 designed and produced several of N-heterocyclic moieties-containing dihydropyrimidinone derivatives. Using 60 cancer cell lines, twelve novel compounds were tested for their cytotoxic potential in accordance with NCI (USA) protocol (Yadlapalli et al., 2012). Among all, compound**63** in **Figure 6,**In contrast to doxorubicin, it was

discovered to be less harmful to normal cells. It also had notable efficacy against the NCI-H460, SK-MEL-5, and HL-60 (TB) cell lines, with growth suppression rates of 88%, 86%, and 85%, accordingly. The compound**63**showed remarkable potency in an enzyme inhibition experiment in comparison with the standard substances sorafenib (IC50 = 0.3 μM) and rapamycin (IC50 = 0.43 μM), against mTOR (IC50 = 0.64 μM) and VEGFR-2 (IC50 = 1.97 μM).



63

Figure 6. dihydropyrimidinone derivatives

4. CONCLUSION

Dihydropyrimidinones were created by multi-component procedures such as the Hantzschdihydropyridine reaction and the Biginelli reaction. Because dihydropyrimidinones have such strong pharmacological effects, researchers have concentrated on the Biginelli reaction and have produced variants throughout the past few decades using a variety of solvents and catalysts to improve yield, shorten reaction times, and improve pharmacological characteristics. We highlight recent developments in this field in this review, emphasizing how newly discovered DHPMs exhibit superior anti-inflammatory, antibacterial, antioxidant, antifungal, and anticancer effects than the current standards.

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