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A Review on Synthetic Mechanisms and Biological Properties of Dihydropyrimidines Derivatives

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ABSTRACT

A review mainly focuses on the synthesis of dihydropyrimidine derivatives by biginelli reaction. It includes synthetic mechanisms of the biginelli reaction and the biological properties of dihydropyrimidines derivatives. In which the reaction of 1, 2-dicarbonyl compound, thiourea, various series of aldehyde are condensed under ethanolic conditions by using different catalysts. Dihydropyrimidine derivatives having versatile biological activities such as antimicrobial, antifungal, anti-ulcer, anti-convulsant, anti-tubercular, anti-viral, etc. Although the original reaction conditions suffered from low yields with substrate limitation in the recent discovery of dihydropyrimidine biological activity has led to a renewed exploration of the reaction conditions, reveals a variety of compatible solvents, acid catalysts, and expanded substrate scope. It includes the latest schemes of dihydropyrimidines derivatives which are feasible and helpful for the synthesis.

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INTRODUCTION

Heterocyclic Chemistry

Heterocyclic chemistry is a core part of organic and synthetic methods. Heterocyclic compounds are cyclic compounds with at least one hetero (i.e., noncarbon) atom in the ring. The most common heteroatoms are oxygen, nitrogen, and sulfur, although other elements do participate[1]. They may be cyclic or non-cyclic. Heterocyclic compounds have a wide range of applications. They are predominantly used as pharmaceuticals, as agrochemicals and veterinary products. They also find applications as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, dyestuffs. They are used as vehicles in the synthesis of other organic compunds[2].

General features of Heterocyclic Compounds

Most of the common heterocycles are those having five-or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). Simple heterocyclic compounds containing pyridine, pyrrole, furan, thiophene, and pyrimidine. An important characteristic of the structure of many heterocyclic compounds is to incorporate functional groups either as substituents or as part of the ring itself for a reaction. For example, basic nitrogen atoms can be incorporated both as amino substituents and as part of a ring. This means that the structures are particularly useful by providing, or mimicking a functional group. For example, the uses of the tetrazole ring system as a mimic of a carboxylic and functional group because of its similarity in acidity and steric requirement. Tetrazole group is superior in terms of metabolic stability, bioavailability and four nitrogen atoms present in the tetrazole ring can create a greater charge distribution. Heterocyclic compounds are also finding increasing use as intermediates in organic synthesis[2].

Importance of Heterocycles

Heterocycles are biologically and industrially important for synthetic purposes. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic in nature. An industrial application ranging from cosmetics, reprography, plastics, and paints are contained heterocyclic compounds. It is also important for the drug industry, to obtained core scaffold in defined 3D representations. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-third are fully or partially

aromatic and approximately half are heterocyclic. Presence of heterocyclic in all types of organic compounds in electronics, biology, optics, pharmacology, material science. All-natural and synthetic heterocyclic compounds can participate in chemical reactions in the human body. Fundamental manifestations of life as the provision of energy, transmission of nerve impulses, reflex action sight, metabolism and transfer of hereditary all information are all based on chemical reactions involving the participation of many heterocyclic compounds such as vitamins, enzymes, coenzymes, amino acid, histamine nucleic acid, ATP and serotonin[3]. Heterocycles have been found a key structural in medical chemistry and biologically active compounds having antifungal, anti-inflammatory, antibacterial, antioxidant, anticonvulsant, antiallergic, enzyme inhibitors, herbicidal activity, anti-HIV, antidiabetic, anticancer activity, insecticidal agents[4].

Why does nature utilize heterocycles?

Because it depends upon the pH of medium that behave as acids or bases and forming anions and cations. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance due to presence of different heteroatoms that makes tautomeric forms of given heterocycles. Synthetic heterocycles possesses versatile biological activities such as antibacterial, antifungal, anti-HIV, antitubercular, antimalarial, analgesic, anti-inflammatory, anticancer etc. Synthetic heterocyclic compounds possesses applications such as fungicide, herbicides, anticorrosive, photo stabilizers, agrochemicals, dyestuff, antioxidant in rubber and flavouring agent[3].

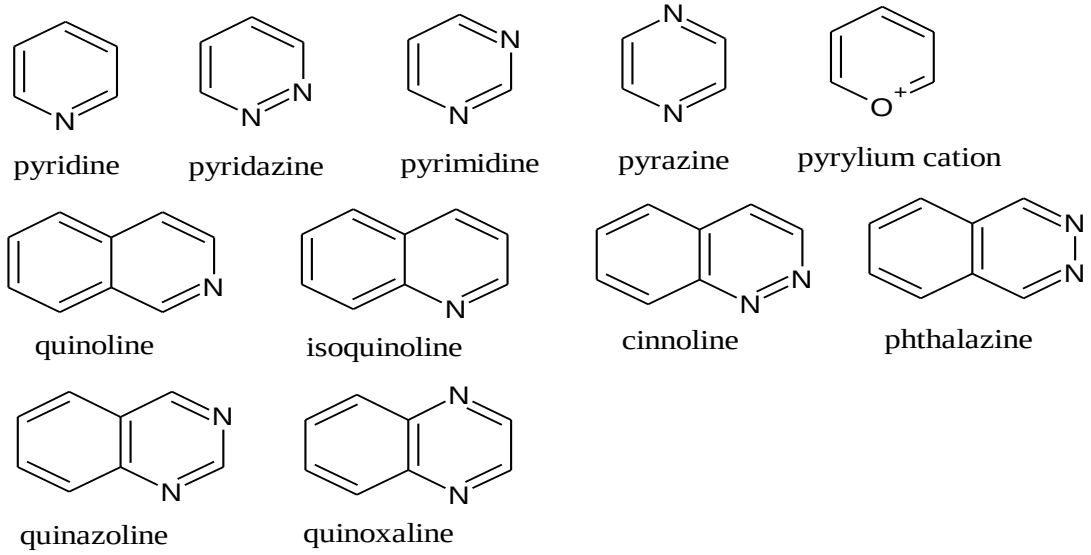


Fig. 1: Six-membered Aromatic Heterocycles

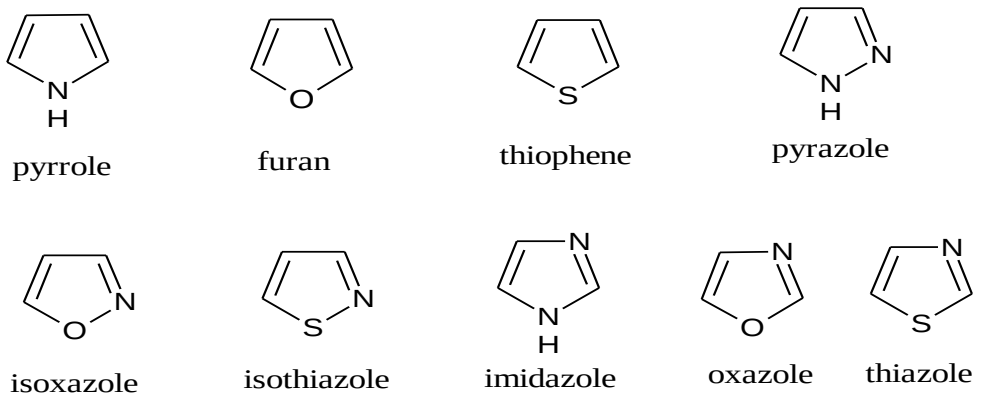


Fig. 2: Five-membered Aromatic Heterocycles

Pyrimidine

Pyrimidine (cytosine, thymine, and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and four nitrogen atoms respectively. Pyrimidine is heterocyclic aromatic compound similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six-membered ring. Pyrimidine is biologically very important heterocycle contain diazine family with uracil and thymine being part of RNA and DNA. Pyrimidine skeleton is also present in many natural products such as vitamins B1 and synthetic compounds presence of pyrimidine base in thymine, cytosine, and uracil are the building blocks of nucleic acids. Pyrimidine nucleus shows versatile activites[5].

Clinical and Pharmacological applications of pyrimidine in Microbial World:
1) Antibacterial against folic acid and sulpha drugs which are sulfur containing pyrimidine derivatives drugs

2) Antifolates-2-amino4-hydroxypyrimidine (Antagonist of Folic acid) Tri and Tetra substituted derivatives

3) Sulpha Drugs (Mono-substituted and Tri-substituted derivatives)

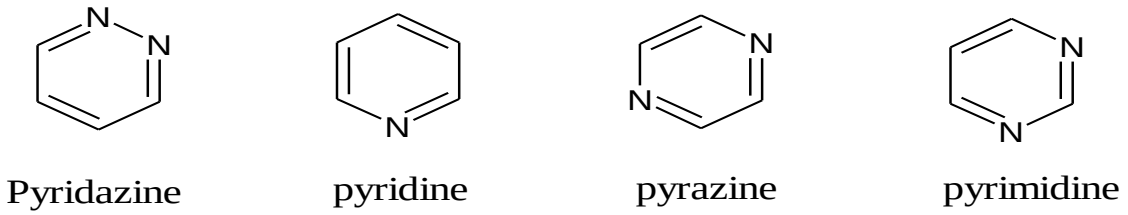


Fig. 3: Nitrogen Containing Heterocycles

Synthesis of 3,4-dihydropyrimidine by biginelli Reaction

In 1893 Pietro Biginelli reported the first synthesis of 3,4-dihydropyrimidin-2(1H)-ones by a simple one pot condensation reaction of aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution. This efficient approach to partly reduced pyrimidines known as a Biginelli reaction or Biginelli condensation. In recent years, an interest in these compounds has increased rapidly, and the scope of the original cyclo-condensation reaction has been widely extended by variation of all three components. The present popularity of these dihydropyrimidines derivatives is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers of the nifedipine-type and other antihypertensive agents[6].

Building Blocks of Biginelli Reaction

1) Aldehyde: Aromatic aldehyde is preferred than aliphatic aldehyde due yields optimization. Substitution in ortho, meta or para position with either electron withdrawing or donating groups shows potent activity. Good yields are usually obtained with meta or para-substituted aromatic aldehyde carrying electron withdrawing substituents. Heterocyclic aldehyde derived from furan, thiophene and pyridine also generally furnish acceptable yields of dihydropyrimidine derivatives[7,8].

2) CH-Acidic Carbonyl Components: Traditionally simple alkyl acetoacetate is used but others types of 3-oxoalkanoic esters or thioesters are more successfully used. It is important for cyclo-condensations of aldehyde and urea. Generally, ethyl acetoacetate,4-bromoacetoacetate, acetoacetamide, ß-diketones and other cyclic ß-dicarbonyl compounds are used in reaction. Nitro-acetone also serves as a good building block, leading to 5-nitro-substituted dihydropyrimidines derivatives in generally high yields[7,8].

3) Urea: It is the most restricted component of biginelli reaction in terms of structural diversity. Simple monosubstituted alkylureas react equally well, in a regiospecific manner, to provide good yields of N1-substituted dihydropyrimidines. Thiourea and substituted thioureas required longer reaction times to achieve good conversions[7,8].

General Scheme of synthesis

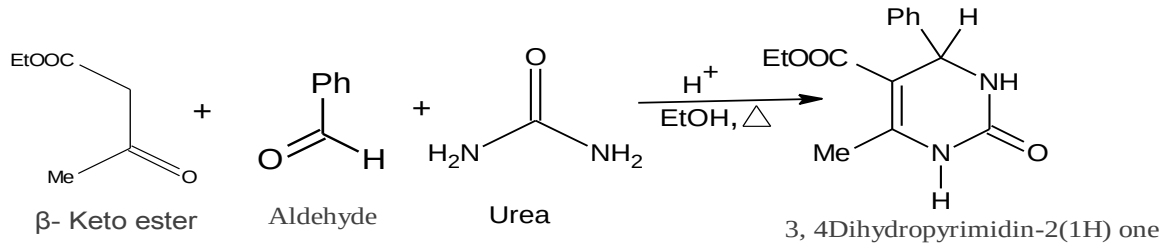
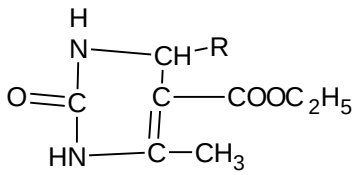


Fig. 4: Biginelli Dihydropyrimidines Synthesis

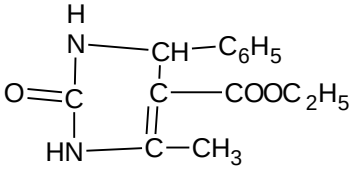
Mechanistic Aspects of Dihydropyrimidines

1) Folkers and Johnson (1933) [9,10]

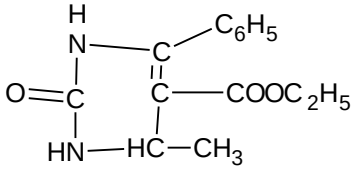
The first attempt made to understand the correct pathway of this reaction was by Folkers et al. in 1933. The reaction of numerous aldehydes with urea and a ß-keto ester to give a tetrahydropyrimidine was discovered by Biginelli. Structure I, as formulated by Biginelli, may be used to represent these tetrahydro pyrimidines, in which R is the grouping joined to -CHO of the particular aryl, alkyl or arylalkyl aldehyde employed in conjunction with urea and ethyl acetoacetate. When benzaldehyde was used, Biginelli obtained a pyrimidine which by condensations and to be represented as structure II, namely, 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydro- pyrimidine. Proof in favour with substitution of the double bond was the preparation of the isomeric pyrimidine or structure III.



I

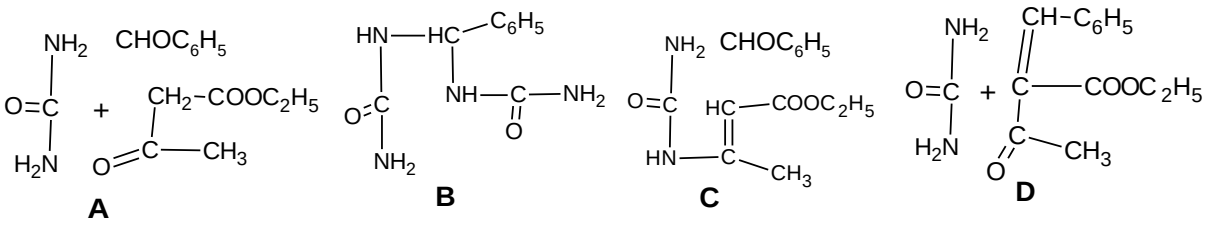


II

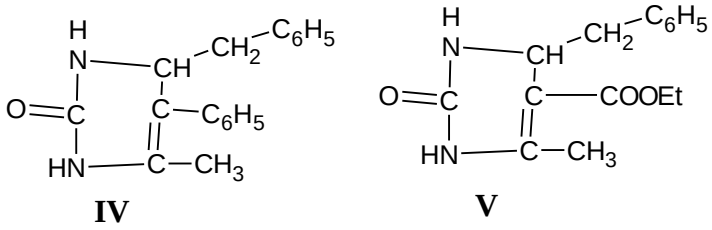


III

Pyrimidine II, could be obtained experimentally in four different ways. The systems of reactants representing these four methods are: (A) urea, benzaldehyde and ethyl acetoacetate; (B)benzal-bisurea and ethyl acetoacetate; (C) ethyl ß-carbamidocrotonate and benzaldehyde; and (D) urea and ethyl a-benzalacetoacetate. Systems B, C and D represented the three primary bimolecular reactions that were possible from system A.



Hydrolysis of ethyl 3-carbamido-crotonate(C) by two ways with phenylacetaldehyde and urea under the same experimental conditions used for the preparation of pyrimidine II to form a new type of pyrimidine derivative, namely, 2- keto-benzyl-5-phenyl-l,2,3,4-tetrahydropyrimidine IV and 4-benzylpyrimidine derivative V.



Mechanism

Pyrimidine II, could be formed by the direct interaction of benzal-bisurea and ethyl acetoacetate (system B), and ethyl p-carbamidocrotonate and benzaldehyde (system C), and that these two systems were possibly related according to the following scheme.

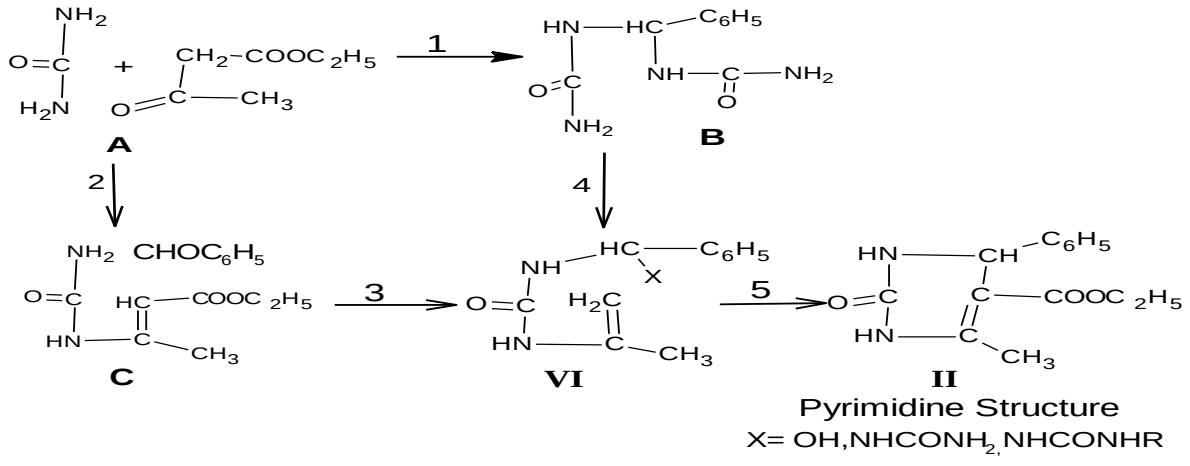
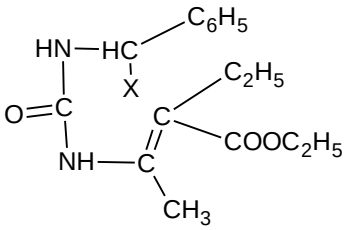
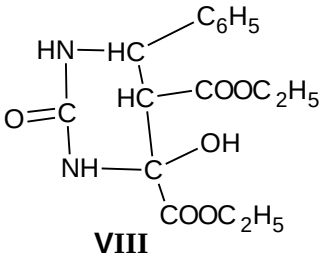


Fig. 5: Mechanism proposed by Folkers and Johnson

Biginelli and the present authors were unable to isolate a pyrimidine from the system ethyl a-ethyl acetoacetate, urea and benzaldehyde. This hypothesis would explain such a failure, for the structure VII would have no hydrogen atom available for cyclization. By the interaction of ethyl oxaloacetate, benzaldehyde and urea, biginelli obtained the 6-hydroxypyrimidine and further on dehydration gives tetrahydropyrimidine derivative.



VII



VIII

It include that mechanism of formation of 2-keto-4-phenyl-5-carbethoxy-G-methyl-1,2,3,4-tetrahydropyrimidine from urea, benzaldehyde and ethyl acetoacetate by the Biginelli reaction, it has been concluded that the urea reacted first with benzaldehyde to form benzal-bis urea, or with the ethyl acetoacetate to form ethyl 6-carbamidocrotonate. Then, one, or both, of these intermediates further reacted with the proper remaining component (ethyl acetoacetate and benzaldehyde, respectively), and by a final cyclization reaction the pyrimidine was formed.

2) Sweet and Fissekis (1973) [9,11]

After several decades the reaction was reinvestigated by Sweet and Fissekis who advocated contradictory mechanism to Folkers suggestion as indicated above in route 1, proceeding through aldol reaction (through carbenium ion intermediate)**.** In this reaction**,** 5-vinyluracil,3-(5-uracilyl) propanoic acid as a intermediate which is prepared from when urea treated with sodium formylacetic ester in presence of concentrated hydrochloric acid gives ureide. When methyl 3-methoxy acrylate with urea in comparable stoichiometric ratio of 2:1 the only isolated product under a variety of conditions were3,4-dihydro-2(1*H)*-pyrimidinones. Acid-catalyzed condensation of a urea with a 2-formyl ester or 2-formyl lactone gives a ureide that can readily cyclize to uracil in the presence of base. However, similar condensations with a 3-alkoxy 2-formyl ester lead directly to 3,4-dihydro-2(1*H*)-pyrimidiones. Similar compound also produced in biginelli reaction.

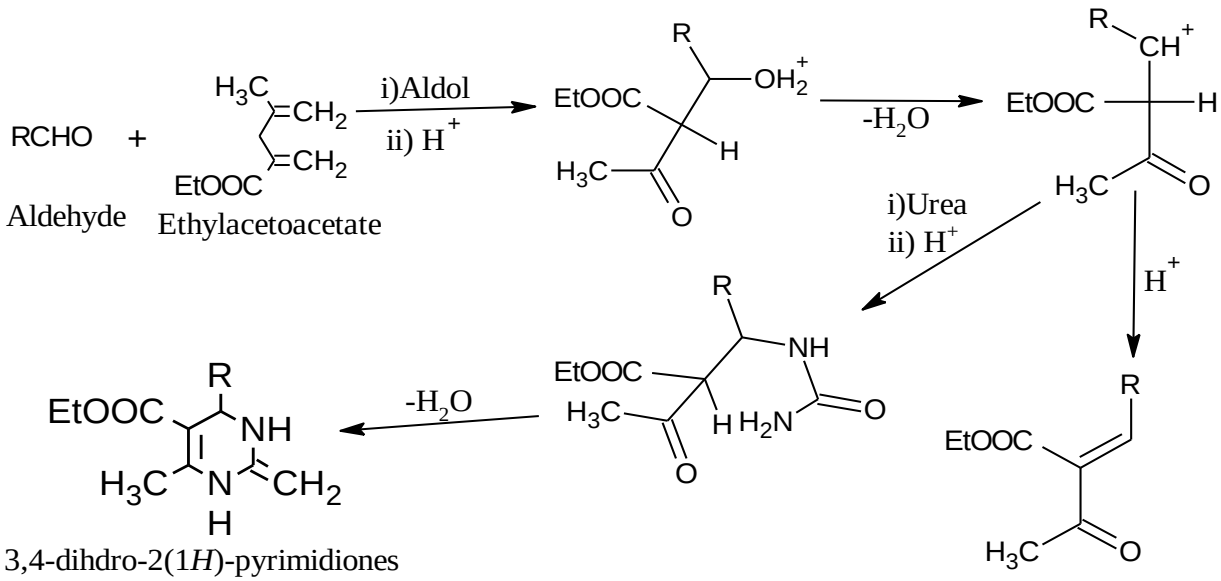


Fig. 6: Mechanism of 3,4-dihydropyrimidinone via aldol condensation

3) Atwal and Co-workers (1987) [9,12]

Atwal and his associates, gave a proposal to surmount troubles linked with poor yield of the typical Biginelli compounds mainly in the case of aliphatic aldehydes and aldehydes having a slightly hindered carbonyl function by ortho-substituents. In this reaction, substituted 1.2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidine carboxylic acid esters from 2-methylene-3-oxobutanoic acid esters and O-methylisourea hydrogen sulfate is reported. They proposed a synthesis of proceeding via methoxypyrimidine. Reaction of O-methylisourea hydrogen sulfate with unsaturated keto ester in presence of sodium bicarbonate gives methoxypyrimidine and hydrolyzed with HCL. This new approach involving two steps, first step concerned with separate synthesis of unsaturated carbonyl compound via Knoevenagel condensation and second step involved the base catalyzed addition of substituted ureas.

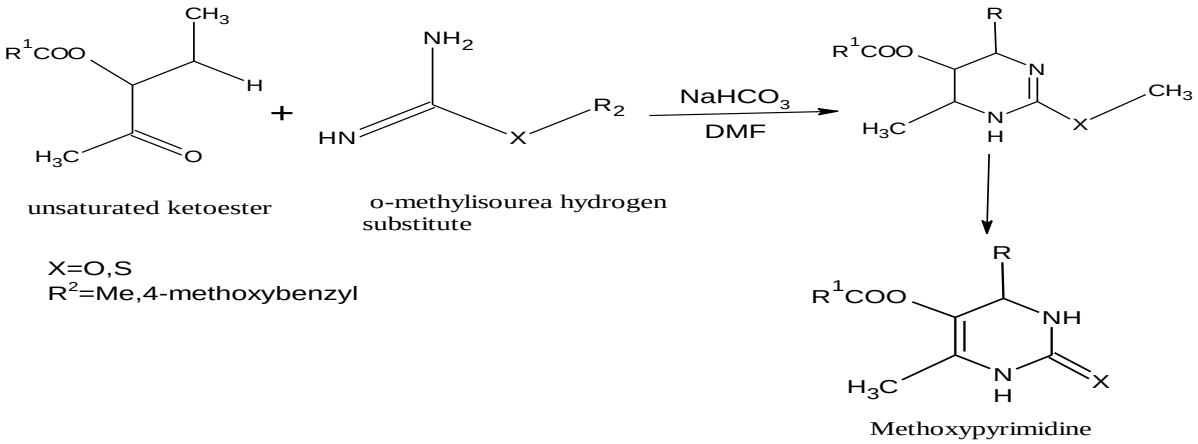


Fig. 7: Mechanism of 3,4-dihydropyrimidinone via Knoevenagel condensation

4) C. Oliver Kappe (1993) [6]

In which reaction the condensation of ethyl acetoacetate, an aromatic aldehyde and urea, using protic conditions, leading to the synthesis of reduced pyrimidines is known as 3,4-dihydropyrimidin-2(1H)-ones termed Biginelli compounds.

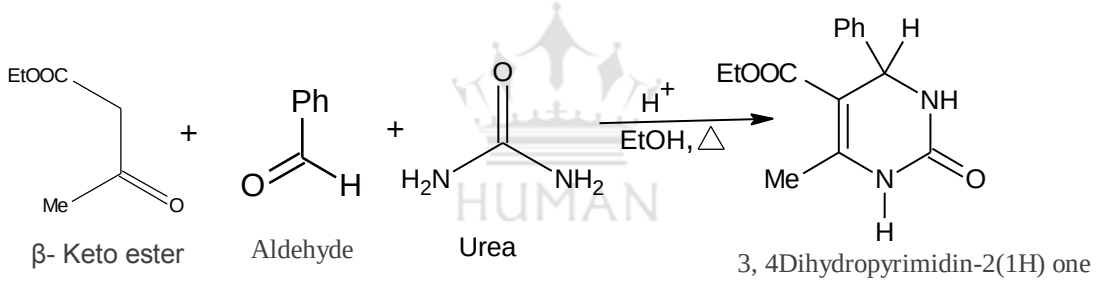


Fig. 8: Mechanism of 3,4-dihydropyrimidin-2(1*H*)-one

5) C.Oliver Kappe (1997) Revisited [9]

In this proposed mechanism, the first step involved nucleophilic attack of urea on the electron deficient carbon of the aldehyde function under acidic conditions results formation of N-acyliminium ion intermediate takes place at the expense of acid catalysed dehydration. In the next step, active methylene compound adds onto this intermediate in a Michael fashion. He found that in this reaction dihydropyridines were always formed in minor quantities, O. Kappe (1997) On the basis of spectral techniques like H1/C13 NMR spectroscopy and further re-examined the mechanism of this multicomponent reaction.

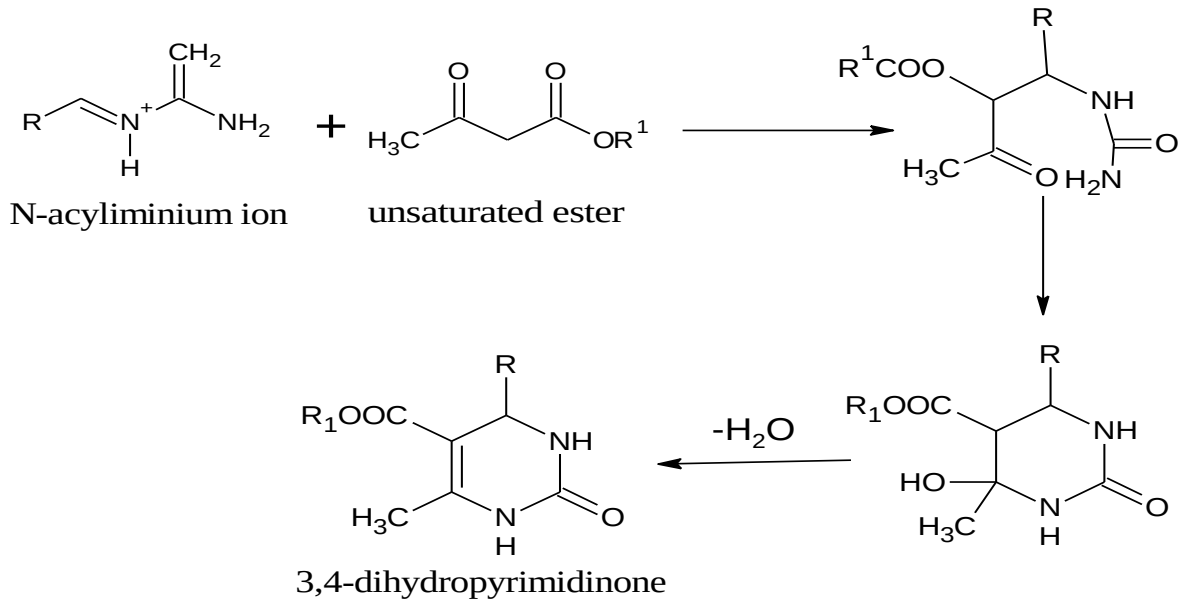


Fig. 9: Mechanism of 3,4-dihydropyrimidinone via N-acyliminium ion

6) Cepanec (experimental evidence) (2007) [9,13]

In this reaction antimony (III) chloride (SbCl3) catalyses the aromatic aldehydes and acetoacetate esters and urea yielding the dihydropyrimidine derivatives. Initially, the catalytic effect of SbCl3 was studied on the model reaction of urea, benzaldehyde and sterically demanding methyl iso-butyryl acetate to give 6-isopropyl-5-methoxycarbonyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one reactions were conducted in refluxing toluene, absolute ethanol and acetonitrile as solvent.

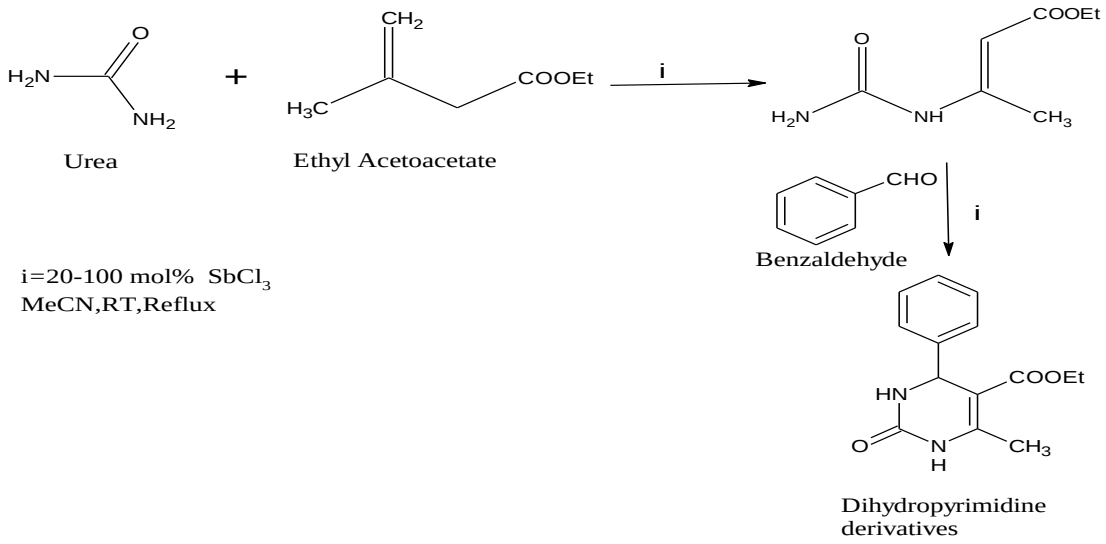
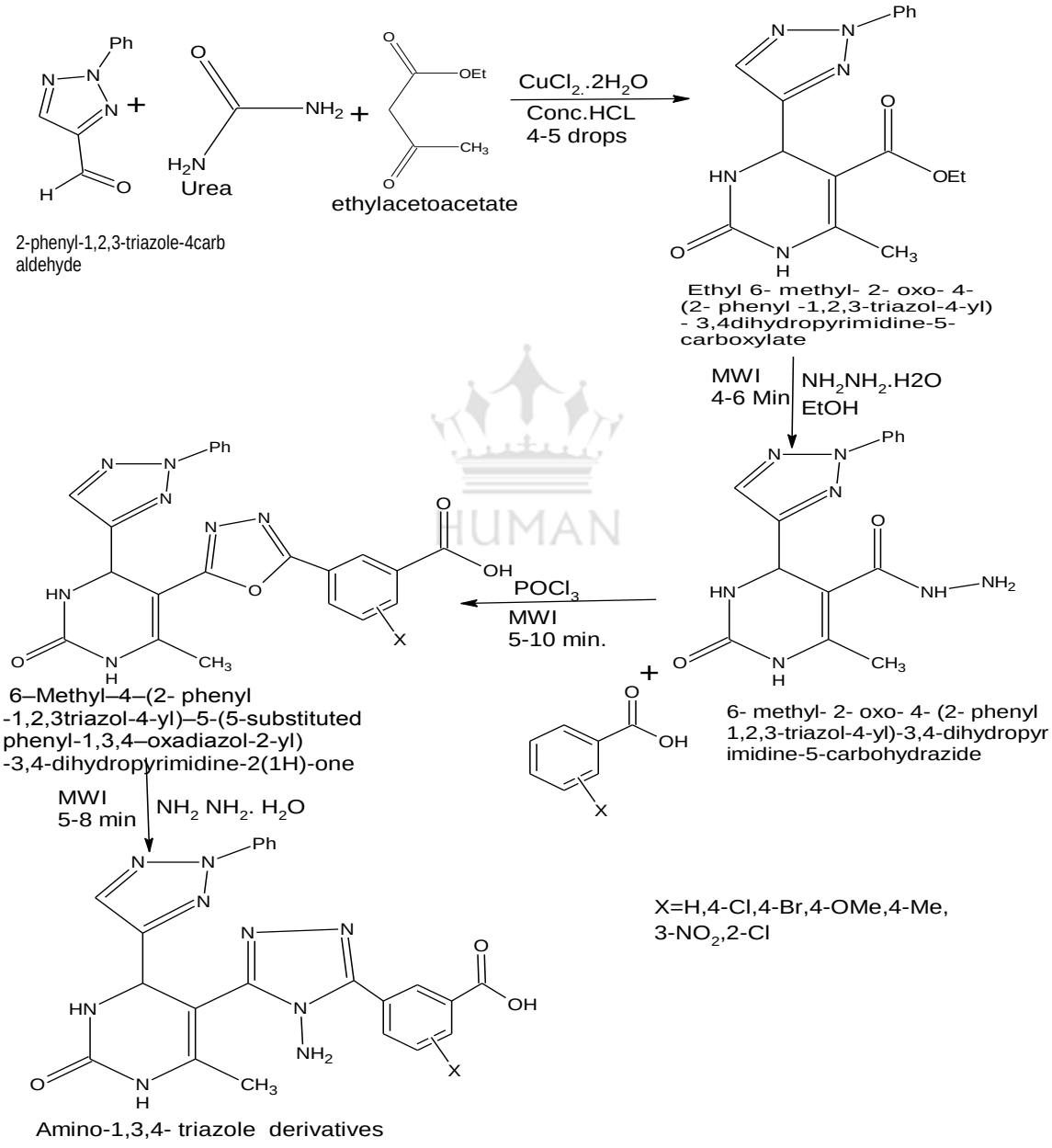


Fig. 10: **Mechanism of 3,4-dihydropyrimidinone via 3-ureido-crotonate**

Methods of Preparation of Dihydropyrimidines Derivatives

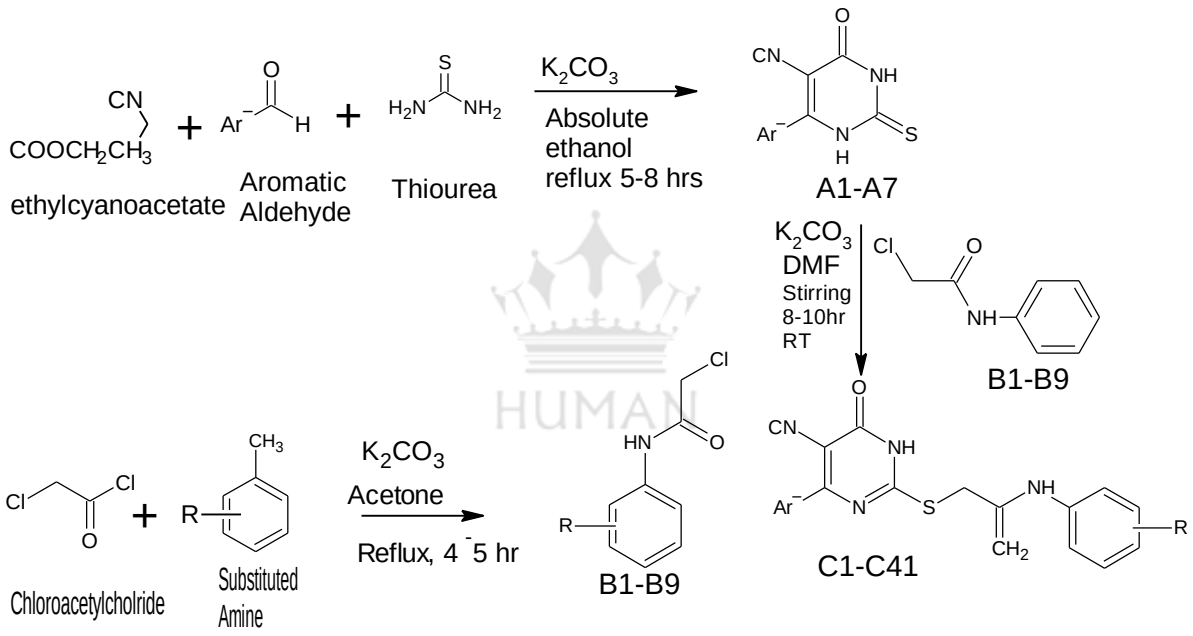
1. Dawle *et al.*, (2012) reported green synthesis of novel heterocycles carrying triazole derivatives of dihydropyrimidine. Novel heterocycles of Ethyl-6-methyl-2-oxo-4-(2-phenyl-1,2,3-triazol-4-yl)-3,4dihydropyrimidine-5-carboxylate have been synthesized from 1,3-dicarbonyl compounds, appropriate aldehyde and urea or thiourea under green method in presence of hydrazine hydrate, substituted benzoic acid, phosphorous oxychloride by microwave irradiation method[14].



Scheme 1

Reagents and conditions: a) Copper Chloride b) Conc. HCL c) Hydrazine Hydrate MWI for 4-6 Min d) Phosphorous Oxychloride MWI for 5-10 Min e) Hydrazine Hydrate MWI for 5-8 Min.

2. Rami *et al.*, (2013) reported synthesis, antifungal activity, and QSAR studies 1,6-dihydropryrimdine derivatives. New series of 5-cyano-6oxo-1,6-dihyropyrimdine derivative namely 2-(5-cyano-6-oxo-4-substituted(aryl)-1,6-dihydropyrimidin-2ylthio)-N-substituted (phenyl) acetamide (C1-C41) were synthesized and characterizes by FTIR, NMR Mass analysis. Quantitative structure activity relation ship (QSAR) studies of a series of 1,6-dihydropyrimdie were carried out to study various structural requirements for fungal inhibition[15].



Where Ar= C_6H_5; 4-ClC_6H_4; 4-$NO_2C_6H_5$; 3,4-$(OCH_3)_2C_6H_3$; 3,4,5-$(OCH_3)_3C_6H_2$; 2-furyl; 1-naphthyl

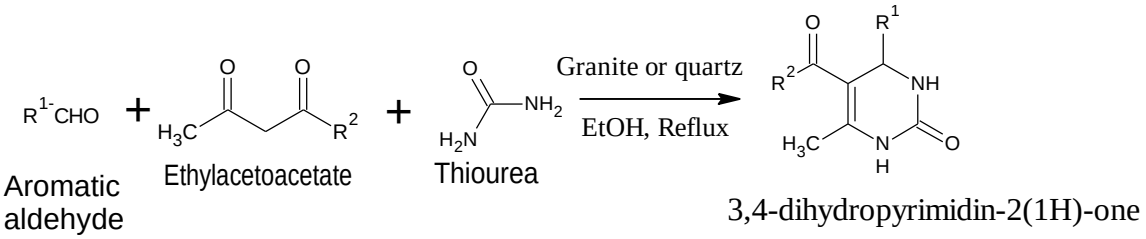
R= H; 4-CH_3; 4-Cl; 4-OCH_3; 4-F; 3-Cl,4-F; 4-Br; 2,4-$(Cl)_2$; 3,4-$(Cl)_2$

Scheme 2

Reagents and Conditions: a) Potassium Carbonate, Absolute Alcohol Reflux 5-8 hrs b) Potassium Carbonate, DMF, stirring 8-10hrs c) Potassium carbonate, Acetone, reflux 4-5hrs using Choloacetylchloride and substituted amine.

3. A. M. Elmaghraby et al., (2013) reported synthesis of 3,4-dihydropyrimidin-2(1H)-one and 3,4-dihydropyrimidin-2(1H)-thione derivatives from aldehydes, 1,3-dicarbonyl

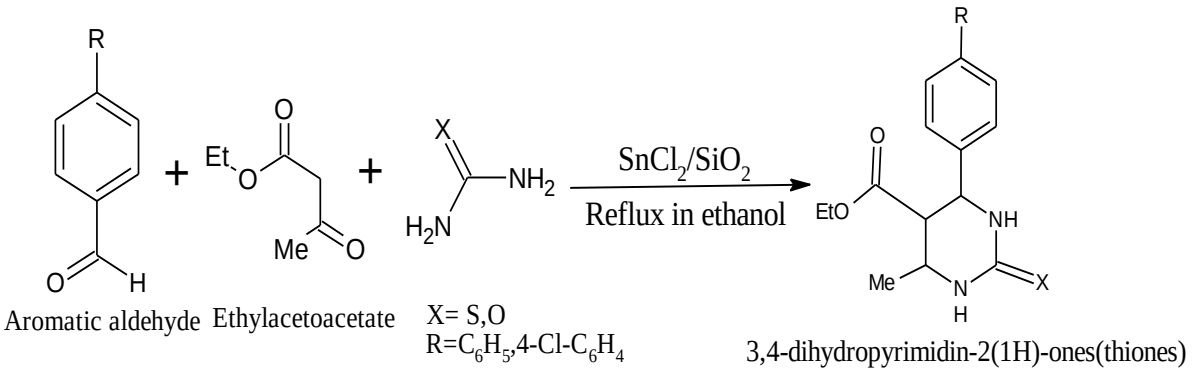
derivatives and urea or thiourea using granite and quartz as new, natural and reusable catalysts. Some of the 3,4-dihydropyrimidin- 2(1H)-thione derivatives were used to prepare new heterocyclic compounds. The antimicrobial activity of selected examples of the synthesized compounds was tested and showed moderate activity[16].



Scheme 3

Reagents and Conditions: a) Granite or quartz in ethanolic condition reflux b) Methyl Iodide in dry acetone, potassium carbonate, anhydrous c) Chloroacetylchloride, DMF.

4. Ghomi *et al.*, (2013) reported a green synthesis of 3,4-dihyropyrimidine-2(1*H*)-one/thione derivatives using Nanosilica-supported Tin (II) Chloride as a Heterogeneous Nanocatalyst which includes the reaction of urea/thiourea, aldehydes and ethyl acetoacetate. The catalyst is used in the synthesis which involves reaction of aldehydes, ethyl acetoacetate and urea/thiourea using SnCl2/nanoSiO2 (0.45mol %) as a green catalyst. And by using ethanol under reflux the 3, 4-dihydropyrimidines were obtained in very high yields. This method of synthesis is quite easy and simple, utilizes easy work-up, the thermal stability is high and activity of the catalyst is very good and other benefits of this method involves neutral reaction conditions and use of commercial solvents. And this method was effective with variety of substituted aromatic aldehydes[17].



Scheme 4

Reagents and Conditions: a) Tin(Π) chloride/nanosilica-oxide, Reflux in ethanol

Biological Activities of Dihydropyrimidines Derivatives

Mohammad Rahmat Ali *et al.,* (2015) synthesized 6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile and their derivatives which are newer and among all the synthesized compounds two was found to be most potent anticonvulsant agents. And these two compounds were emerged as the lead anticonvulsant agents. These two compounds (Fig.11, Fig.12) were reported to exhibit activity at a lower dose of $30mgkg^{-1}$ at 0.5 and 0.4 hrs. The anticonvulsant activity of synthesized compounds was compared with phenytoin and higher than that of carbamazepine and he reported that increase in lipophilicity will increase the anticonvulsant activity[18].

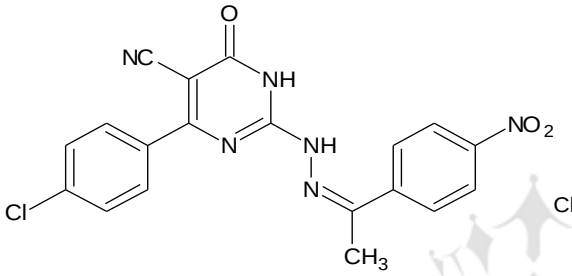


Fig. 11

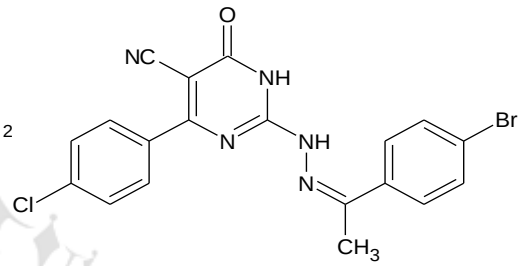


Fig. 12

B.K. Singh *et al.,* (2008) reported synthesised a series of 4-Aryl-6-methyl-2-sulfanyl-1,4-dihydropyrimidines in good yield by the reaction of 5-methyl-6-phenyl-2-thi-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid ethyl esters with different alkyl or aralkyl halides in the presence of a anhydrous K_2CO_3 and tetrabutylammonium bromide. All the synthesized compounds were evaluated for antifilarial activity against adult parasite of human lymphatic filarial parasite *Brugia malayi* in vitro and in vivo at various concentrations. From all the synthesized series of 4-Aryl-6-methyl-2-sulfanyl-1, 4-dihydropyrimidines one compound (Fig.13) showed most potent antifilarial activity[19].

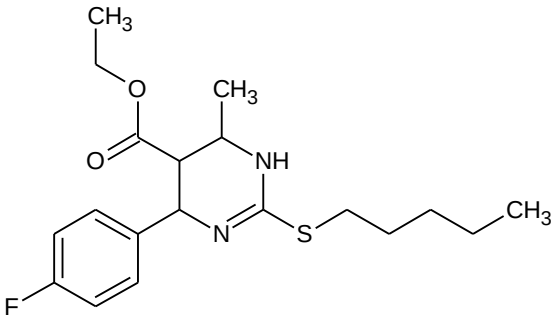


Fig. 13

V.N.Bhadani *et al.,* (2015) reported the synthesis 1,4-dihydropyrimidines from isopropyl acetoacetanilides were treated with 4-(difluoro-methoxy)-3-hydroxybenzaldehyde and thiourea/urea in presence of acid catalyst with good yield. Two synthesised compounds (Fig.14, Fig.15) having antibacterial activity against *S. aureus, M. luteus, E.coli, S. typhi,* and antifungal activity against *C. albicans* with MICs between 40 and 80 µg/mL[20].

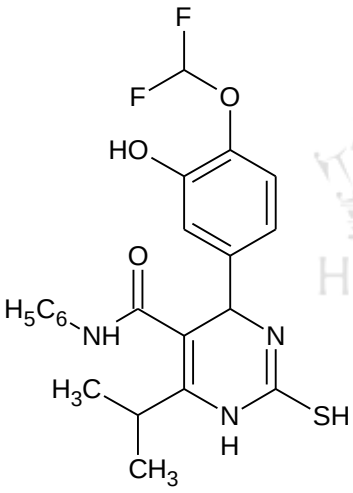


Fig. 14

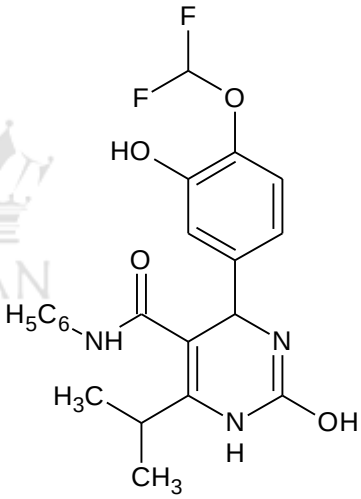


Fig. 15

Sufiyan Ahmed *et al.,* (2016) reported the dihydropyrimidines compounds having the Acetylcholinesterase inhibitory activity. The dihydropyrimidines (thiopyrimidines and amino pyrimidines) linked with acetamide linker to substituted aromatic anilines were synthesized and was evaluated for activity of acetylcholinesterase and butyrylcholinesterase inhibitors. Among all the synthesized compounds the two compounds (Fig.16, Fig.17) of them to be most potent with IC_{50} values of 0.17± 0.01µM and BChE 0.39 ± 0.04 µM. Following are the structure of these several compounds which possess the Acetylcholinesterase activity[21].

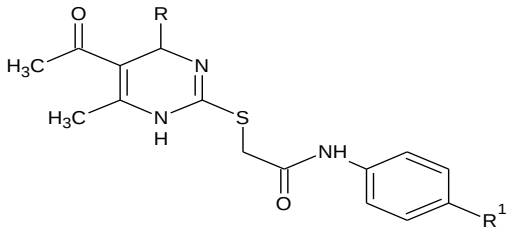


Fig. 16

R= H,4-Br,4-CH_3
R^1= H,H,4-CH_3

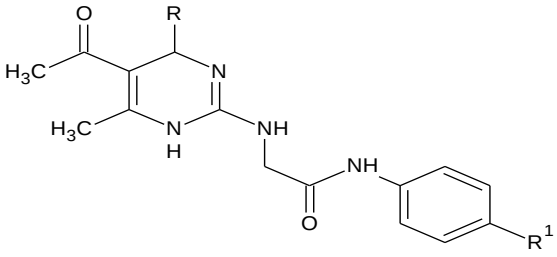


Fig. 17

R= H,4-Br,4-Cl
R^1= H,4-CH_3,4-CH_3,

Gopal Garg *et al.,* (2014) reported synthesis of 1,4-Dihydropyrimidine derivatives due to benzyl substitution and ester moiety shows significant anti-ulcer activity. In which tetrahydropyrimidine as an intermediate for synthesis. Anti-ulcer activity of synthesized compounds has been done by using ethanol induced ulcer model. Synthesized compound (Fig.18) showed 35.03 and 58.18% inhibition of ulcer[22].

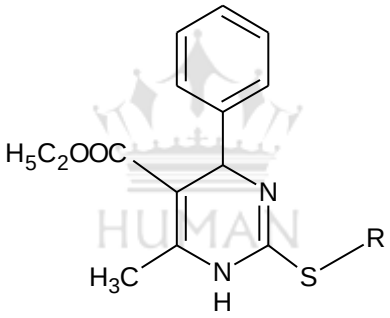


Fig. 18

R=-CH_2Cl,-C_4H_9,C_6H_5

Safari *et al.,* (2020) reported synthesis of dihydropyrimidine analogues which screened for in vitro anticancer activity. These analogues possess good cytotoxic activity against three human cancer cell lines including MCN-7, HepG-2, and A549. 2-thioxo-tetrahydropyrimidine-5-benzoate derivatives were introduced as new cytotoxic scaffolds It was concluded that incorporating electron withdrawing substituents such as ─NO_2 group on C4 position of phenyl ring of dihydropyrimidine derivatives provided good cytotoxic activity and it shows antiproliferative potency. In silico molecular docking, study shows probable relationship between experimental activity and calculated binding affinity for active site[23].

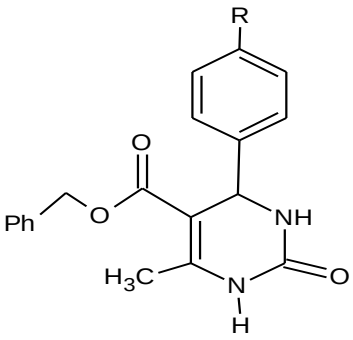


Fig.19

R= H,*m*-Cl.

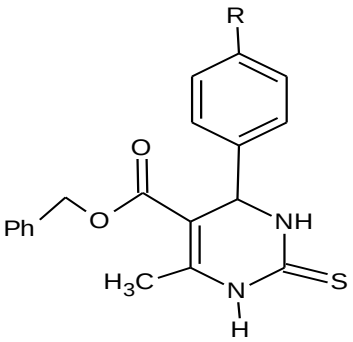


Fig. 20

R= *m*-Br,OCH_3,*p*-NO_2

SUMMARY

The development of the Biginelli reaction has advanced considerably since its discovery 120 years ago. Mechanistic Aspects have provided rational modifications to the experiment protocols, allowing dihydropyrimidines to be synthesized in high yield. In this review, we concluded that the synthesis of dihydropyrimidines derivatives in different ways using different catalysts. It is revealed that substitution of essential groups at different positions gives characterized biological activity of dihydropyrimidines.

REFERENCES

1. Buntrock RE. Review of Heterocyclic Chemistry. Journal of Chemical Education. 2012;11:1349-1350.
2. Arora P, Arora V, Lamba HS, Wadhwa D. Importance of heterocyclic chemistry: A review. International Journal of Pharmaceutical Sciences and Research. 2012 Sep 1;3(9):2947.
3. Dua R, Shrivastava S, Sonwane SK, Srivastava SK. Pharmacological significance of synthetic heterocycles scaffold: a review. Advances in Biological Research. 2011;5(3):120-44.
4. Al-Mulla A. A review: biological importance of heterocyclic compounds. Der Pharma Chemica. 2017;9(13):141-72.
5. Sharma V, Chitranshi N, Agarwal AK. Significance and biological importance of pyrimidine in the microbial world. International Journal of medicinal chemistry. 2014;2014.
6. Kappe CO. 100 years of the Biginelli dihydropyrimidine synthesis. Tetrahedron. 1993 Aug 6;49(32):6937-63.
7. Kappe CO, Stadler A. The Biginelli Dihydropyrimidine Synthesis. Organic reactions. 2004 Apr 15;63:1-16.
8. Kappe CO. The generation of dihydropyrimidine libraries utilizing Biginelli multicomponent chemistry. QSAR & combinatorial science. 2003 Aug;22(6):630-45.
9. Sandhu JS. Past, present and future of the Biginelli reaction: a critical perspective. ARKIVOC: Online Journal of Organic Chemistry. 2012 Jan 1.
10. Folkers K, Johnson TB. Researches on Pyrimidines. CXXXVI. The Mechanism of Formation of Tetrahydropyrimidines by the Biginelli Reaction1. Journal of the American Chemical Society. 1933 Sep;55(9):3784-91.
11. Sweet F, Fissekis JD. Synthesis of 3, 4-dihydro-2 (1H)-pyrimidinones and the mechanism of the Biginelli reaction. Journal of the American Chemical Society. 1973 Dec;95(26):8741-9.

12. O'REILLY BC, Atwal KS. Synthesis of substituted 1, 2, 3, 4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters: The Biginelli condensation revisited. Heterocycles (Sendai). 1987;26(5):1185-8.
13. Cepanec I, Litvic M, Filipan-Litvic M, Grungold I. Antimony (III) chloride-catalysed Biginelli reaction: a versatile method for the synthesis of dihydropyrimidinones through a different reaction mechanism. Tetrahedron. 2007 Nov 26;63(48):11822-7.
14. Dawle JK, Mathapati SR, Bondge AS, Momin KI. Green Synthesis of Novel Heterocycles Carrying Triazole Derivatives of Dihydropyrimidine. Asian Journal of Research in Chemistry. 2012;5(6):707-11.
15. Rami C, Patel L, Patel CN, Parmar JP. Synthesis, antifungal activity, and QSAR studies of 1, 6-dihydropyrimidine derivatives. Journal of Pharmacy & Bioallied Sciences. 2013 Oct;5(4):277.
16. Elmaghraby AM, Mousa IA, Harb AA, Mahgoub MY. Three component reaction: an efficient synthesis and reactions of 3, 4-dihydropyrimidin-2 (1H)-ones and thiones using new natural catalyst. ISRN organic chemistry. 2013 Aug 18;2013.
17. Ghomi JS, Teymuri R, Ziarati A. A green synthesis of 3, 4-dihydropyrimidine-2 (1H)-one/thione derivatives using nanosilica-supported tin (II) chloride as a heterogeneous nanocatalyst. Monatshefte fur Chemie-Chemical Monthly. 2013 Dec 1;144(12):1865-70.
18. Ali MR, Verma G, Shaquiquzzaman M, Akhter M, Alam MM. Synthesis and anticonvulsant activity of some newer dihydro-pyrimidine-5-carbonitrile derivatives: Part II. Journal of Taibah University Medical Sciences. 2015 Dec 1;10(4):437-43.
19. Singh BK, Mishra M, Saxena N, Yadav GP, Maulik PR, Sahoo MK, Gaur RL, Murthy PK, Tripathi RP. Synthesis of 2-sulfanyl-6-methyl-1, 4-dihydropyrimidines as a new class of antifilarial agents. European journal of medicinal chemistry. 2008 Dec 1;43(12):2717-23.
20. Bhadani VN, Patel PA, Purohit HD, Purohit DM. Synthesis, antibacterial and antifungal activity of 5-aryl amido-6-isopropyl-2-(mercapto/hydroxy)-4-[(4′-difluoro methoxy)(3′-hydroxy) phenyl]-1, 4-dihydro pyrimidine. International Letters of Chemistry, Physics and Astronomy. 2015 Jan 1;51:54.
21. Ahmad S, Iftikhar F, Ullah F, Sadiq A, Rashid U. Rational design and synthesis of dihydropyrimidine based dual binding site acetylcholinesterase inhibitors. Bioorganic chemistry. 2016 Dec 1;69:91-101.
22. Gupta SP, Tiwari A, Upmanyu N, Garg G. Synthesis and Evaluation of Dihydropyrimidine Derivatives as Antiulcer Agents. Journal of Current Pharma Research. 2014 Oct 1;5(1):1351.
23. Safari S, Ghavimi R, Razzaghi-Asl N, Sepehri S. Synthesis, biological evaluation and molecular docking study of dihydropyrimidine derivatives as potential anticancer agents. Journal of Heterocyclic Chemistry. 2020 Mar;57(3):1023-33.