A Mini Review: Biginelli Reaction for the Synthesis of Dihydropyrimidinones

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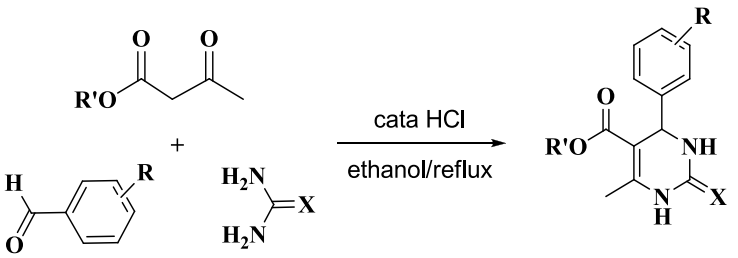
ABSTRACT

Dihydropyrimidinones and their corresponding derivatives were synthesized by the union of 1,3-diketones (or) β-ketoester, arylaldehyde and urea/thiourea under Bronsted acid catalysis condition was pioneered by Pietro Biginelli in 1893. This review wraps recent mechanistic advances, new pharmacological revelations and new building block of dihydropyrimidinones up to 2014. On the other hand it also swathe the most recently developed asymmetric synthetic methodologies to offer the enantio enrich dihydropyrimidinone derivatives.

Keywords: *Arylaldehydes, Dihydropyrimidinones, B-Ketoester, Biginelli Reaction.*

1. INTRODUCTION

A multi component reaction (MCR) is a process in which three or more reactants combined together in one pot to form a product that introduces structural features of each reagent [1]. MCRs have played a central role in the development of modern synthetic methodology due to its selectivity, synthetic convergency and atom-economy for pharmaceutical and drug discovery research [2]. MCRs are cornerstones of both combinatorial chemistry and diversity-oriented synthesis [3]. Combinatorial chemistry is helpful to introduce structural variations in targeted compounds of interest where as Diversity oriented synthesis is helpful to explore chemical structure space in search of new bioactive small molecules. Both approaches are benefit from the complexity-generating characteristics of MCRs. Another important feature of these reactions implies that the diminution of waste production because of reducing synthetic or isolation steps along with saving time [4]. Significant advantages were offered by the multi component strategies over conventional linear-type syntheses[5] .One-pot multicomponent synthesis offers simple and valuable synthetic tool to prepare drugs within a minimum number of synthetic steps [6].Therefore, MCRs have gained tremendous importance in the synthesis of drug moieties. One of the widely used classical multicomponent strategies for the synthesis of N-heterocyclic compounds is the Biginelli reaction which was pioneered by Pietro Biginelli in 1893 [7]. Biginelli synthesized dihydropyrimidin-2(1H)-(thi) one (4) (DHPM) derivatives by the three-component condensation of an aldehyde , a β-keto ester and urea or thiourea under Bronsted acid catalysis condition **(Scheme 1)** [8].



Scheme 1: Classical Biginelli Reaction in Synthesis of Pyrimidines

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The backbone of the human life is DNA and RNA which are consisting of the pyrimidine derivatives. Out of the five major bases in Nucleic acids three are pyrimidine derivatives which comprises of Cytosine which is found in DNA and RNA, Uracil in RNA and Thymine in DNA. Because of their involvement as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry. These structures have stimulated the invention of a wide range of synthetic methods for the synthesis and chemical transformations. In addition to this, some important vitamins are also consisting of pyrimidine derivatives (Fig.1) 3.Thus the importance of pyrimidones compounds to the human life creates the synthetic interest to organic chemist.

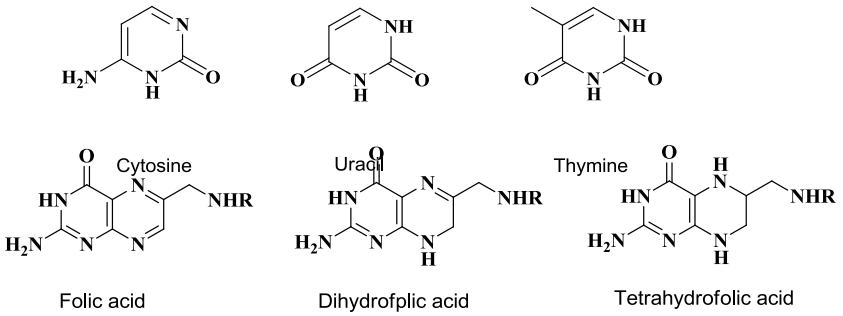

Figure 1: Pyrimidine Containing Derivatives

Though it is more than 100 years acidic catalysts continue to be used though the number of variation done in this catalysts system run into hundreds so is the case of solvent systems and several heating mode changes have been carried in a flood of research publications in the development of Biginelli's dihydropyrimidinone.

1.1) Mechanistic Aspects

As a normal curiosity of chemists after the discovery/observation of a reaction there were studies to find the expected pathway which involves Biginelli's condensation of three component aldehydes **1a,** 1,3-carbonyl compounds 3a and urea/thiourea **2a**. The mechanism of the Biginelli reaction has been investigated by several research groups. Its dependence upon acid catalysis has been experimentally established and a mechanism proposed by Folkers and co-workers in 1933 was accepted for four decades and the reaction mechanism was reinvestigated by Sweet and Fissekis in 1973. Atwal proposed a mechanism in 1987 which losses the beauty of Biginelli reaction and in 1997, C. O. Kappe proposed a mechanism with high supported spectroscopic data. Still date there is a number of mechanic aspects are introduced by different groups which are mimic to Kappe mechanism. However, It seems that further work on the probably rather complex mechanism of the three-component Biginelli reaction is required. Also it should be noted that dihydropyridines of the Hantzsch type are sometimes isolated as side products in the standard Biginelli reaction.

1.1.1) Folkers and Johnson Proposed Mechanism (1933)

Since its first report in 1893, a number of mechanisms have been forwarded for the Biginelli reaction. During the 1930s, Folkers and Johnson proposed that **4a, 5a,** and **6a (Scheme 2)** could be involved [9]. The N,N-benzylidenebis-urea **(4a)** would result from intermolecular condensation of benzaldehyde **(1a)** and two equivalents of urea **(2a)**. Inter-mediate **5a** is an enamine formed by condensation of **3a** and **2a**, whereas intermediate **6a** is known as the Knoevenagel adduct formed by condensation of **3a** and **1a**. Four possible combinations of the three reaction components were examined for the generation of dihydropyrimidine (DHPMs) (i) the teramolecular reaction between benzaldehyde, ethyl acetoacetate, and two equivalent of urea, (ii) the combination of ethyl

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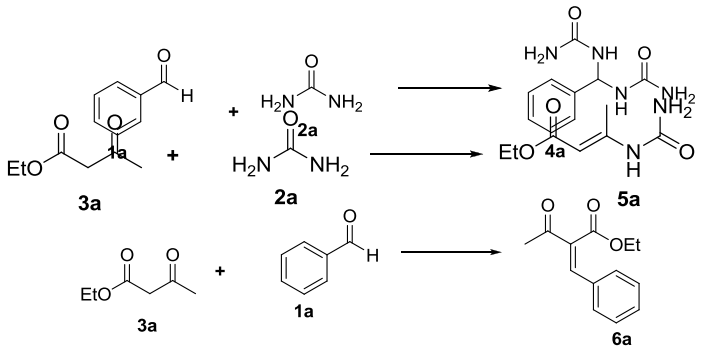
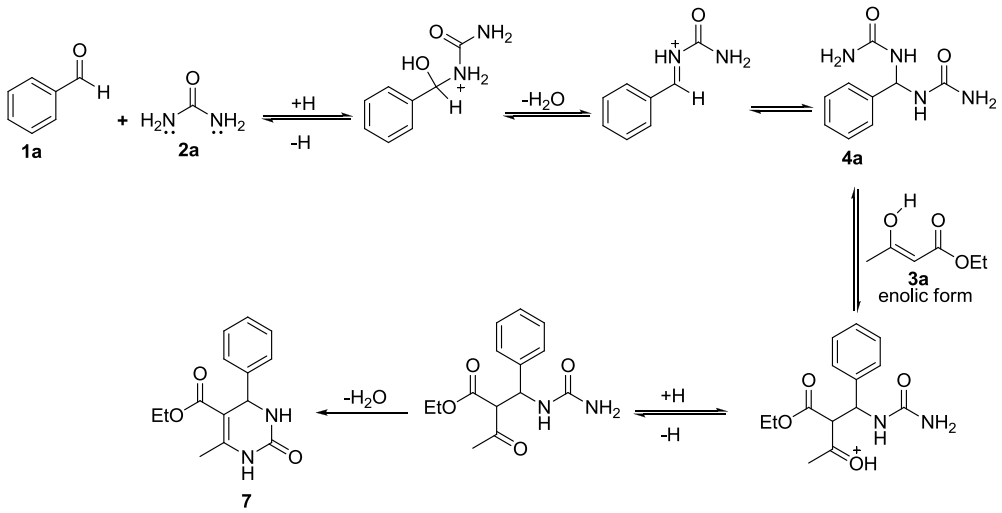
acetoacetate **(3a)** and benzal-bisurea **(4a)** **(Scheme 3)**, (iii) the reaction of benzaldehyde **(1a)** and ethyl β-carbamidocrotonate **(5a)** **(Scheme 4)**, and (iv) the reaction of ethyl α-benzalacetoacetate **(6a)** and urea **(2a)** **(Scheme 5).**



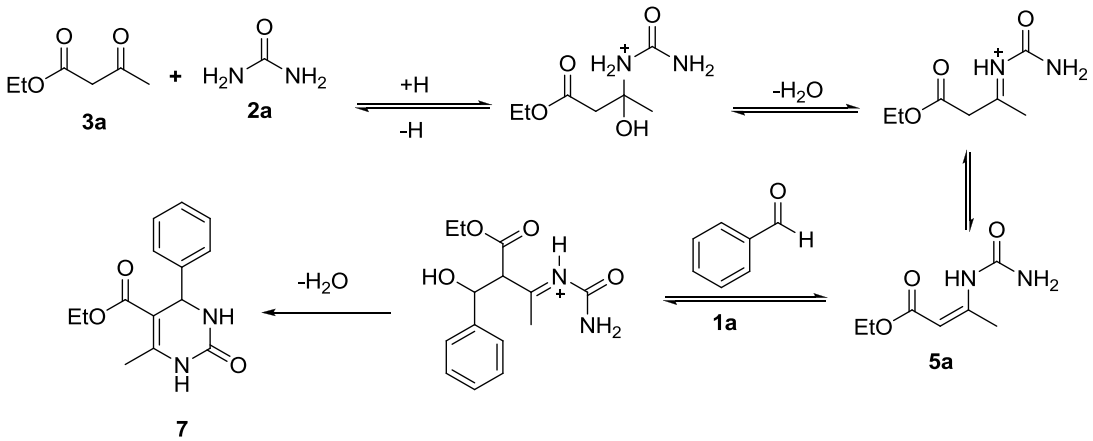
Scheme 2: Intermediates Proposed by Folkers and Johnson for the Biginelli Reaction

1.1.1a) Iminium Mechanism (Combination of Ethyl Acetoacetate and Benzal-Bisurea)



Scheme 3: Iminium Mechanism For The Biginelli Reaction

1.1.1b) Enamine mechanism (reaction of benzaldehyde and ethyl β-carbamidocrotonate)



Scheme 4: Enamine Mechanism for the Biginelli Reaction

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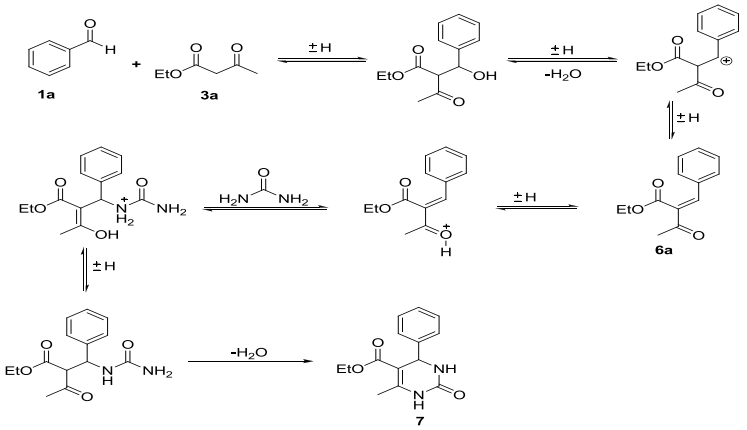
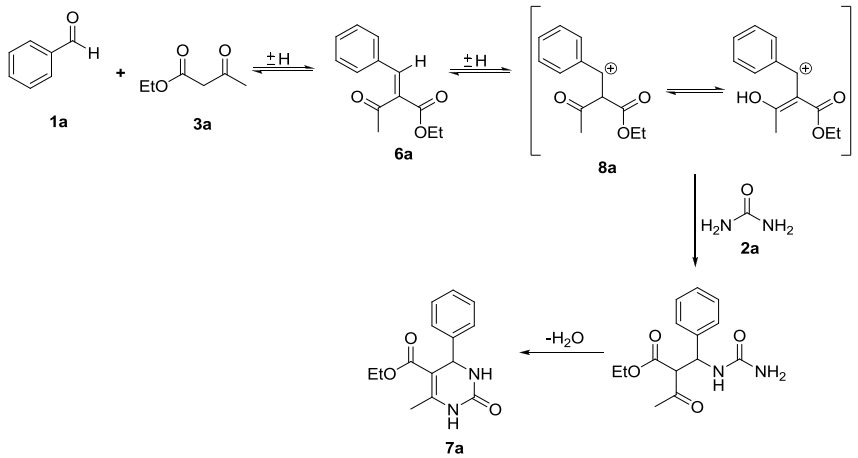
1.1.1c) Knovenagel Mechanism (Reaction of Ethyl A-Benzalacetoacetate and Urea)



Scheme 5: Knovenagel Mechanism for the Biginelli's Reaction

1.1.2) Sweet and Fissekis Proposed Mechanism (1973)

In 1973, forty years after Folkers'pioneering work, Sweet and Fissekis[10] proposed a more detailed mechanistic interpretation for the Biginelli reaction. This proposal involves a Knoevenagel condensation between benzaldehyde **(1a)** and ethyl acetoacetate **(3a)** which has became known as the Knoevenagel mechanism (Scheme 5).



Scheme 6: Sweet and Fissekis Proposal for the Biginelli Reaction

Their mechanism is based on the formation of a carbenium ion **(8a)** in the rate-limiting step of an acid-catalyzed Knoevenagel reaction. Intermediate 8a was proposed to react with urea **(2a)** forming adduct product, which would undergo an intramolecular condensation reaction to give the Biginelli dihydropyrimidine **(7a).** The observation that independently prepared 6a reacts with urea **(2a)** under acidic conditions to generate **(7a)** provides evidence in support of this mechanism **(Scheme 6).**

1.1.3) The Atwal Modification (1987)

Although the classical Biginelli reaction has been used widely in the past decades it is not always reliable and often gives only moderate yields, in particular when aliphatic or ortho-substituted aromatic aldehydes are employed. A more reliable approach to Biginelli compounds was reported in 1987 by K. Atwal and co-workers [11]. In the first step an unsaturated ketoester **(6a)** is condensed with a suitable protected urea **(9a)** or thiourea derivative **(9b)** in the presence of sodium bicarbonate. The reaction presumably proceeds through a Michael addition product of type 10 undergoes cyclization and affords dlhydropyrimidlnes **11a, 11b**. Deprotection with HCl (for **11a**) or

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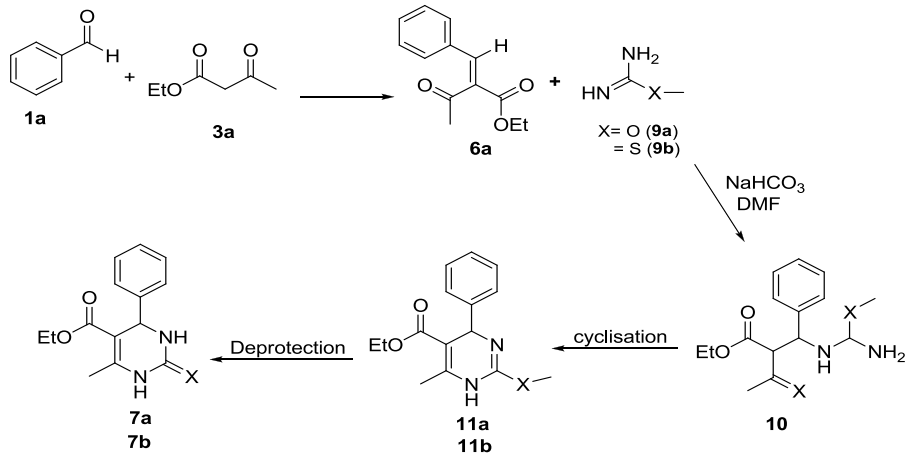
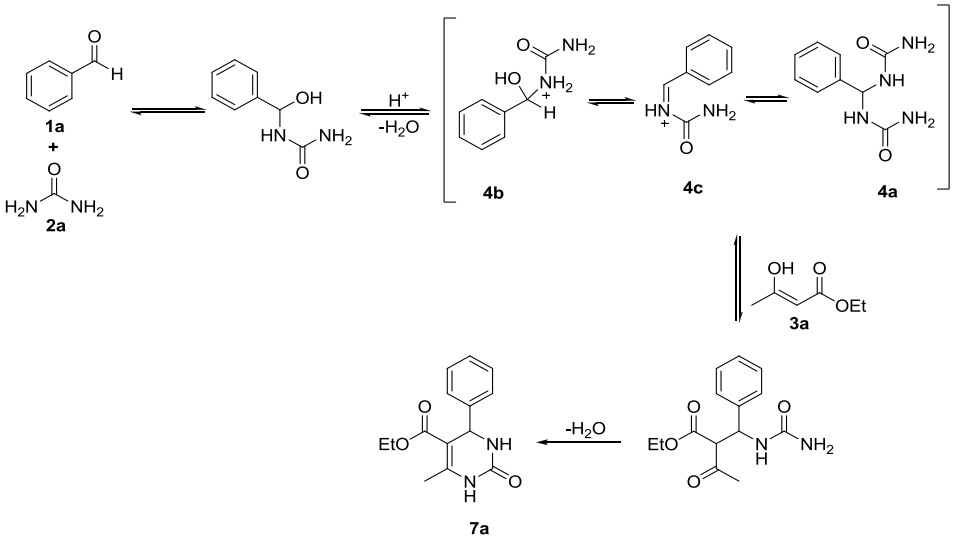
trifluoroacetlc acid/ethanethrol (for **11b**) leads to the desired Bigaelll compounds **7a** (urea), and **7b** (thiourea) in high overall yield **(Scheme 7).** Although this method requires prior synthesis of the unsaturated ketoesters **(6a),** its reliability and broad applicability makes it an attractive alternative to the standard Biginelli condensation. Similar results are obtained when 6a is condensed with guanidine or N,N-dimethyl guanidine to give 2-amino-substituted pyrimidines **7** (X=NH).[12]



Scheme 7: Atwal Modification for Biginelli Reaction

1.1.4) C. O. Kappe Proposed Mechanism (1997)

More recently, Kappe [13] used NMR to investigate Biginelli intermediates. Monitoring the reaction of benzaldehyde **(1a)** and ethyl acetoacetate **(3a)** in CD3OH/HCl by 1H and 13C NMR spectroscopy, he found no evidence for a Knoevenagel reaction or any other reaction between the two components at room temperature. Further, Kappe also observed the formation of bisureide **(4a) (Scheme 8)** by 1H NMR spectroscopy (CD_3OH, HCl), but no other intermediate **(4b or 4c)** was detected **(Scheme 8).** Kappe assumed that the first addition step of benzaldehyde with urea give adduct **(1a + 2a to give 4b)** is the rate-determining step and that both the subsequent acid-catalyzed dehydration **(4b to 4c)** and the addition of a second equivalent of urea to the iminium ion **(4c + 2a to give 4a)** are fast steps. Final desired product **(7a)** was observed by the addition of enolic form of acetoacetate **(3a)** followed by dehydration.



Scheme 8: Kappe Proposal for the Biginelli Reaction

However, evidence to support this mechanism was provided by two trapped species, **12** and **13**[14-15] **(Scheme 9).** Use of a sterically bulky β-keto ester allows isolation of ureide **12**, which has been independently converted to the dihydropyrimidine product. In a similar fashion, the electron-deficient

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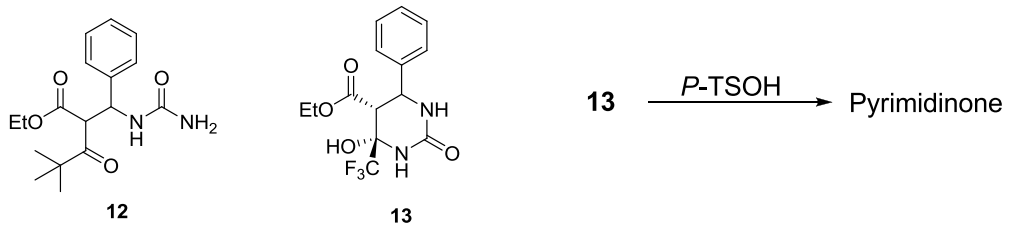
nature of the trifluoromethyl group destabilizes the carbocation intermediate necessary for dihydropyrimidine formation, allowing the isolation of **13**, whose relative configuration has been confirmed by single crystal X-ray analysis. This intermediate is converted to the corresponding dihydropyrimidine (**7a**) via *p*-toluenesulfonic acid mediated dehydration. Kappe's proposal is currently the accepted mechanism for the Biginelli reaction.



Scheme 9: Intermediates 12 and 13 Obtained from Electron-Deficient or Sterically Bulky Acetoacetates

Cepanec (2007) proposed a mechanism using antimony trichloride[16], a typical Lewis acid catalyst reaction mechanism was in real terms studied rather it was found under these conditions that reaction proceeds via intermediate β-cabamidocrotonate and not iminium formation as proposed by Kappe. **De Souza *et al[17].*** (2009) investigated Biginelli reaction and concluded in favour of Folkers and Johnson proposal via iminium intermediate, they based their conclusions on density functional theory calculations (DFT), they have used a mass spectrometer having accessories for various ionizations.Very recently, **Shun-Jun Ji** (base catalysed, 2010) Chinese workers[18], have described the use of strong bases in synthesis of Biginelli's dihydropyrimidinones and it follows the Knovenagel intermediate (α-benzalacetoacetate) mechanism and **Litvic** (Brønsted acid) was also reported in 2010 of this reaction reported to via 'ureido-crotonate' formation as reported by Cepanec in contrast to acylimino intermediate (C. O. Kappe).

1.2) Biological Significance

In 1893, the synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate was reported for the first time by P. Biginelli. In the past decades, such Biginelli-type dihydropyrimidones have received a considerable amount of attention due to the interesting pharmacological properties associated with this heterocyclic scaffold.

1.2.1) Antihypertensive Agents

As a usual temptation biologists saw Biginelli products resemblance to Hantzsch 1,4-dihydropyridine (indeed these were side products in original experiment) as being aza-analogues of nifedipine and other related molecules which are well-known calcium channel modulators and Biginelli compounds **14**, **15** (effective orally active antihypertensive agents) are promising targets for bringing them to actual use.

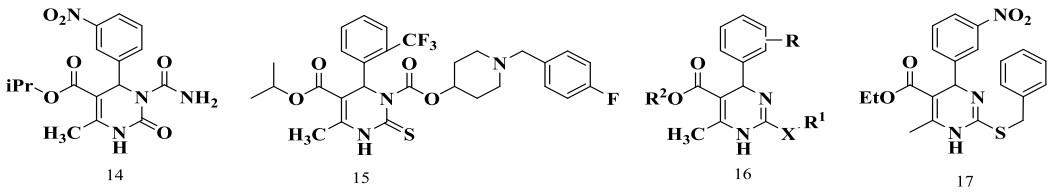


Figure 2:

R= 2-NO_2, 3-NO_2, 2-CF_3, 2,3-Cl
R^1= CH_3, $CH_2CH{=}CH_2$, $CH_2(CH_2)_3CH_3$, $CH_2CH_2N(CH_3)_2$
R^2= C_2H_5, i-Pr, CH_3, SBu
X= O, S

DHPMS against Anti-Hypertensive Activity

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Hetero-substituted DHPMs **16** with a branched ester (e.g. isopropyl, sec-butyl) and an alkylthio group (e.g. SMe) was found to be optimal for biological activity. In these compound **17** is potent mimic of dihydropyridine calcium channel blockers [19].

1.2.2) Potassium Channel Antagonists

Annulation of benzimidazole ring **18** with this Biginelli showed potassium channel antagonists activity and these are at preclinical developments **18-21**[20].

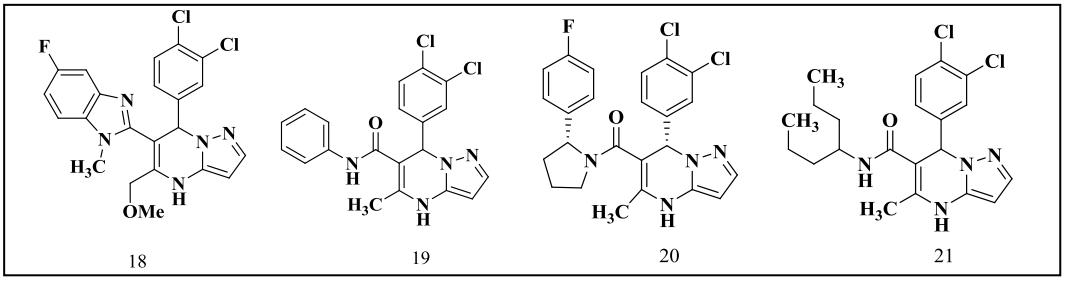

Figure 3: DHPMs against Potassium Channel Blockers

1.2.3) Anti-HIV Agents

Batzelladine A **22** and B **23** derivatives of DHPMs obtained from marine natural source have promising anti HIV activity. These low molecular weight derivatives inhibit the binding of HIV gp-120 to CD4 cells [21].

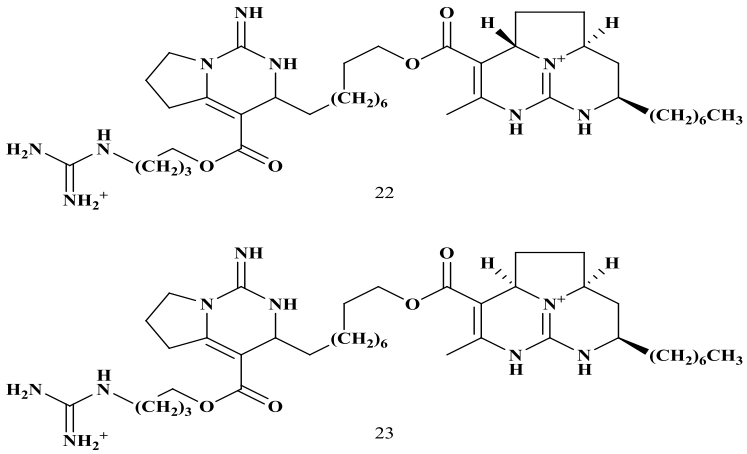

Figure 4: DHPMs against HIV Activity

1.2.4) Antitumor Activity

Human kinesin Eg5, an interesting drug target for the development of cancer chemotherapeutics. Monastrol **24** is the first Biginelli compound which has excellent anticancer activity, further a series of compounds for their ability to inhibit Eg5 activity has been investigated using two in vitro steady-state ATPase assays (basal and microtubule-stimulated) as well as a cell-based assay. In an attempt, another dihydropyrimidine i.e. furyl derivative **25** appeared more potent than monastrol by a fivefold factor[22]. These are the some compounds found against anti-tumor activity.

Figure 5: DHPMs against Antitumor Activity

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1.2.5) Anti-Malarials

Pyrimidinone-amides derivatives of DHPMs **26-30**, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic *P. falciparum* stages in human red blood cells[23].

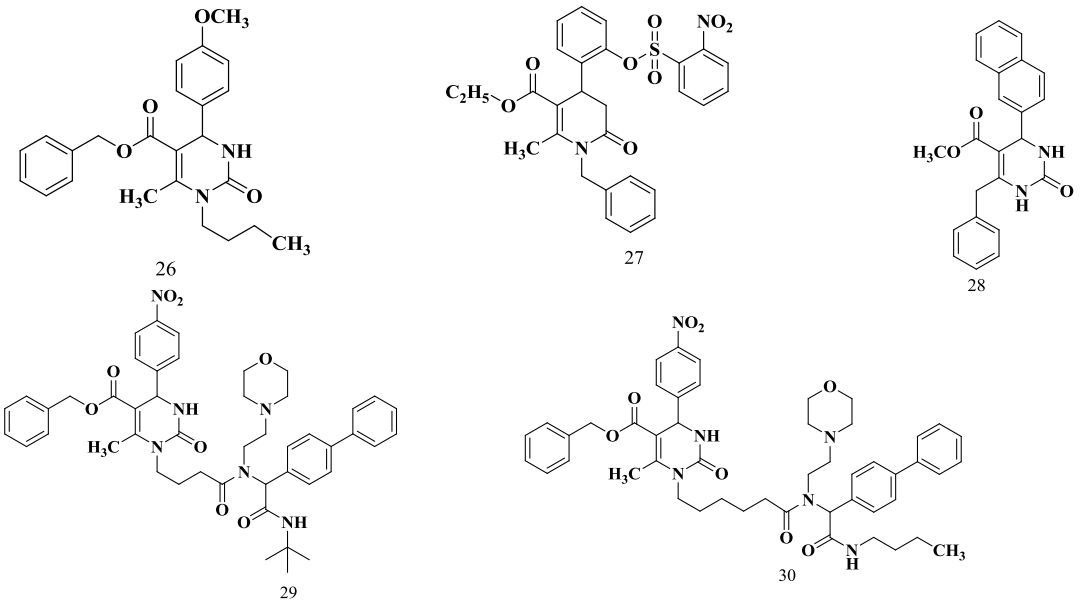
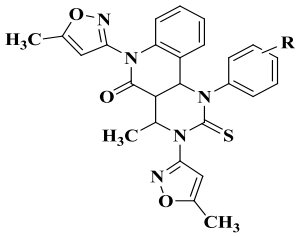


Figure 6: DHPMs against Anti-Malaria Activity

1.2.6) Anti-microbials

Biginelli compounds multi-functionalized with isoxazole amines i.e. 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10b-tetrahydro-1*H*-pyrimido[5,4-*c*]quinolin-5-ones **31** showed anti microbial also apart from antibacterial, antifungal, and antimalarial activities[24].



R = H, 4-CH_3, 4-OCH_3, 4-Cl, 2-Cl

31

Figure 7: DHPMs against Anti-Microbial Activity

1.2.7) Anti-inflammatories

A series of compounds 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives **32-34** were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant anti-inflammatory activity [25].

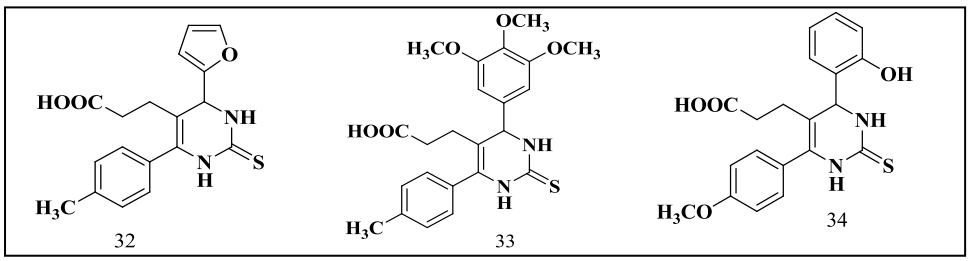


Figure 8: DHPMs against Anti-Inflammatories

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1.2.8) Anti-tubercular Activity

Dihydropyrimidines also were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv.

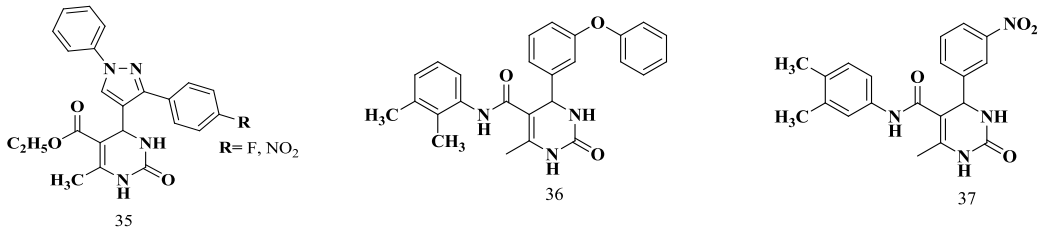

Figure 9: DHPMs found against Anti-Tubercular Activity

Two compounds, ethyl 4-[3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5 carboxylate and ethyl 4-[3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4- tetrahydropyrimidine-5-carboxylate **35** were shown to be the most active compounds and found to be more potent than isoniazid [26]. The compounds **36, 37** are the compounds found against anti-tubercular activity.

1.2.9) Anti-bacterial Activity

Ester, cyanide and some other substituted Biginelli 38-40 are reported to be promising antibacterial agents [27].

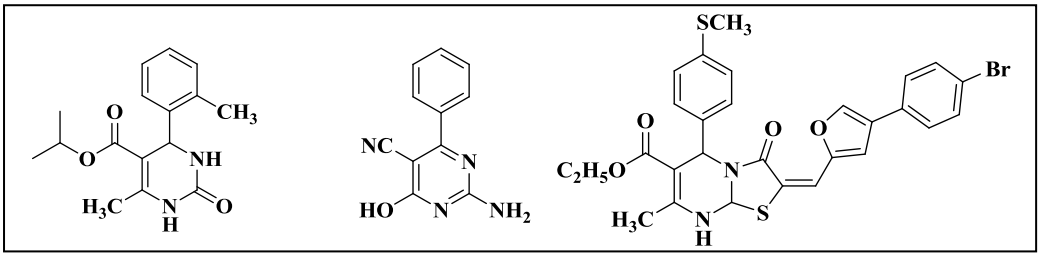

Figure 10: DHPMs found against Anti-Bacterial Activity

1.2.10) Miscellaneous Activities [28-30]

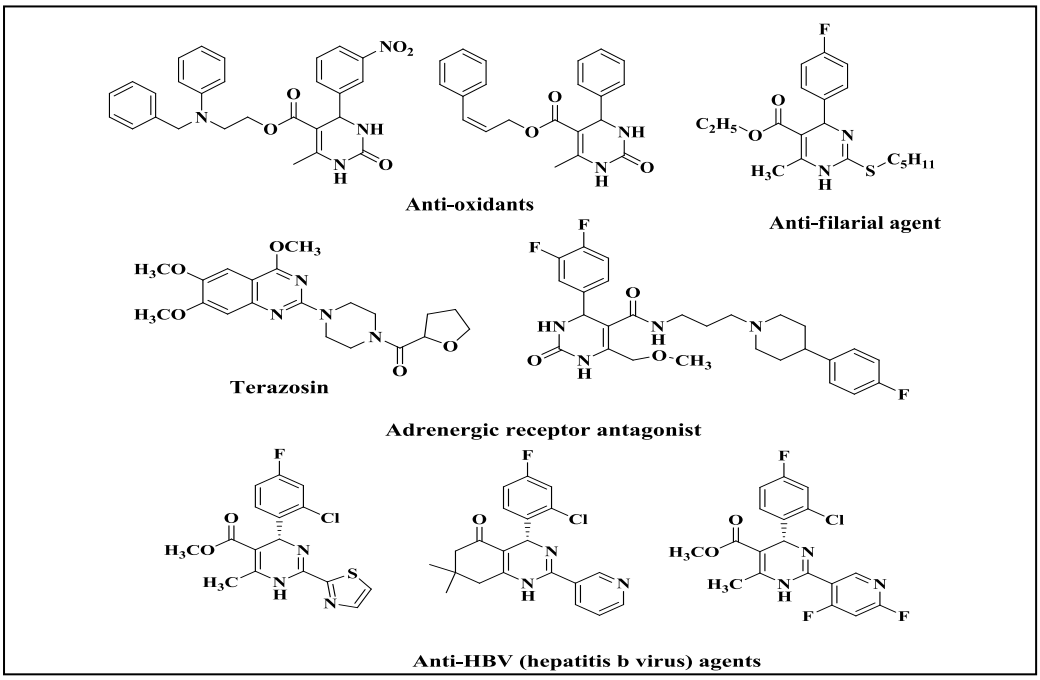

Figure 11: DHPMs found against Various Types Bio-Activities

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2. CONCLUSIONS

The development of the Biginelli dihydropyrimidine MCR reaction has advanced considerably since its discovery in 1893. Mechanistic insights have provided rational modifications to the experiment protocols, allowing dihydropyrimidines to be synthesized in enantioselective total synthesis of complex natural products. The interesting and miscellaneous biological activity of dihydropyrimidines has been investigated through the generation of huge libraries of compounds. The frontier of the Biginelli reaction will continue to be developed as new asymmetric methods are reported and as the biological importance of this class of compounds is explored in greater detail.

3. ACKNOWLEDGEMENTS

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