

Past, present and future of the Biginelli reaction: a critical perspective

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Abstract

This review covers up to 2010 and some available references of 2011 of synthetic advances in the Biginelli reaction, including recent mechanistic advances, new building blocks, new pharmacological disclosures and asymmetric syntheses. Also present account is covering all aspects of the reaction whereas some of previous ones emphasized one aspect and others had passing reference.

Keywords: Biginelli reaction, multicomponent reactions, green process

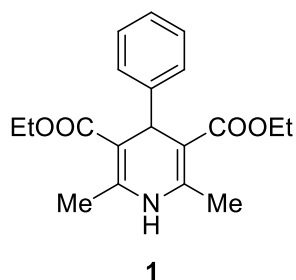
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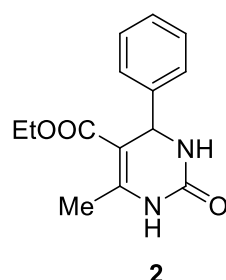
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1. Introduction

Hantzsch,¹ Knoevenagel,² and Biginelli reactions,³ have some similarity; as each one of these employs aldehyde, acetoacetic ester (active methylene compound). The earliest of these seems to be the discovery of the Hantzsch reaction which was reported in 1881,¹ wherein Hantzsch heated acetoacetic ester, an ammonia source, and an aldehyde, to obtain the now well-known dihydropyridines or Hantzsch pyridines **1**. A decade later the Italian chemist P. Biginelli,³ reacted same two components in equimolar ratio *viz.* acetoacetic ester, aldehyde and third component as urea in acidic alcoholic solution to obtain a new compound, the now well-known 3,4-dihydropyrimidin-2(1*H*)-ones or Biginelli compounds,⁴ **2** which are obvious aza-analogues of the Hantzsch dihydropyridines. Biginelli did not detect any Hantzsch dihydropyridines **1** as byproducts.⁵



Hantzsch pyridines
(Dihydropyridine)



Biginelli compound
(Dihydropyrimidine)

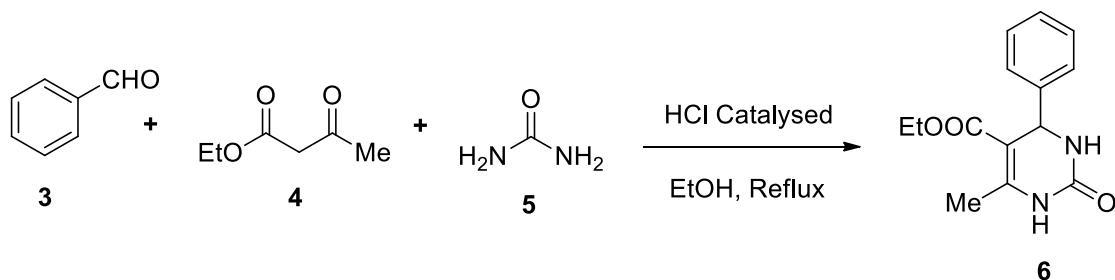
He apparently did this reaction in a multicomponent way, and currently the development of multicomponent reactions (MCRs) is an integral part of numerous research efforts around the world involved in the drug development programs to achieve synthetic targets in expeditious way. It seems old discoveries are new fashions of the present times. Subsequent investigators have tried to understand the course of reaction and they invoke the participation of the Knoevenagel reaction.

In the initial years there was not much synthetic activity in this reaction but during last 100 years or so this reaction received much attention and as a result there were nearly five hundred research publications, mostly involving catalyst changes. During these years from its discovery emphasis was on understanding the course of reaction, with some emphasis on structural variants. Subsequent to these academic developments the Biginelli scaffold was shown to be of great value from a pharmaceutical point of view; because of this importance, investigations were very fast, and virtually every major journal was flooded with papers on the Biginelli reaction.⁶ Major emphasis being on process streamlining mainly Lewis acid catalyst etc. In this account, update on catalyst variations, asymmetric synthesis, scaffold variations and Biginelli like reactions aspect of this reaction is presented. During the past decade or so publications have been so fast and numerous, some of these may get missed incidently so authors feel sorry for that if it happens.

2. Discovery

Historically, Italian chemist Pietro Biginelli (University of Florence) reported this reaction for the first time which is taken as the birth of this reaction; it is popularly named after him i.e. Biginelli Reaction.³ Classically, he did it as acid-catalyzed condensation of ethyl acetoacetate, benzaldehyde, and urea in ethanol by refluxing the mixture and on cooling he obtained a solid crystalline product 3,4-dihydropyrimidin-2(1*H*)-one which apparently was a three component reaction (Scheme 1), the acid used here was hydrochloric acid. 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 following pages these developments shall be discussed and catalysts used changes made are from mild Bronsted acids to strong Lewis acid what so ever was at hand rather it raise questions is catalyst really needed.⁶⁽¹⁾



Scheme 1. Classical synthesis of Biginelli product.

The most attractive part for this motif is biological activity and asymmetric synthesis of compounds which will be discussed in separate sections. When one goes through all this research activity other than asymmetric synthesis or the motif modification remaining seems to be of academic interest only. These two, namely asymmetric synthesis and motif modifications required a good amount of effort, good chemistry and also are of applied in nature since this may lead to some applications.

3. Mechanism

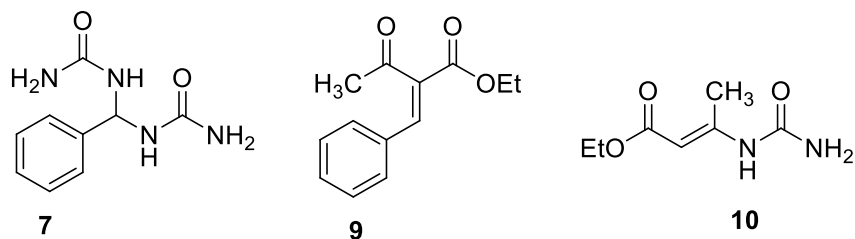
As a normal curiosity of chemists after the discovery/observation of a reaction there were studies to find the expected pathway followed by this reaction some possibilities are as under. As Biginelli reaction involves condensation of three component aldehydes **3**, 1,3-carbonyl compounds **4** and (thio)urea **5**, keeping these reactants reactivity in mind plausibly the reaction could proceed in following ways.

1. Condensation of aldehyde **3** with 1,3-carbonyl compounds **4** via aldol condensation followed by nucleophilic attack of urea **5** molecule.
2. Condensation of aldehyde **3** with 1,3-carbonyl compounds **4** via Knoevenagel subsequently nucleophilic addition of urea **5**.
3. Condensation of aldehyde **3** with urea molecule **5** (via N-benzylidene-urea) and then nucleophilic addition of 1,3-carbonyl compound **4**.
4. Condensation of aldehyde **3** with two urea molecules **5** (via N,N-benzylidenebisurea) & further nucleophilic addition of 1,3-carbonyl compound **4**.

5. Nucleophilic condensation of urea **5** on 1,3-carbonyl compound **4** (via 3-ureido-crotonates) and after that again nucleophilic attack of this condensate to aldehyde **3**.

Folkers and Johnson (1933)

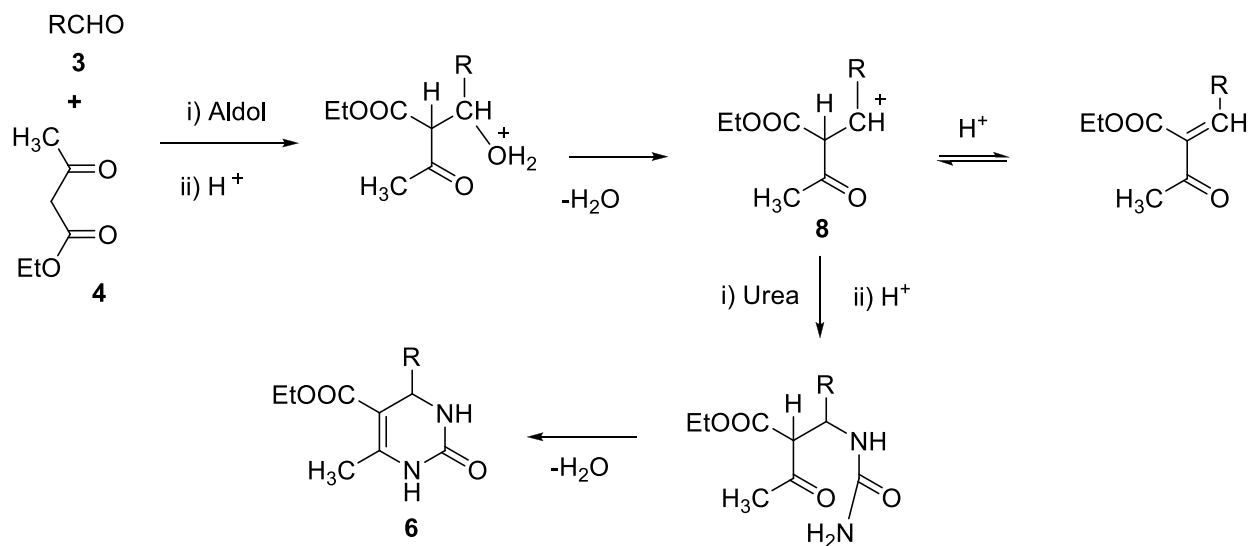
The first attempt made to understand the correct pathway of this reaction was by Folkers *et al.* in 1933.⁷ Under acidic conditions they could prove an intermediate 1,1'-(phenylmethanediyl)diurea **7** to transform to end product Biginelli compound (as shown in route 4); they proposed the intermediacy of **9** and **10** (see scheme 2).



Scheme 2. Intermediate proposed by Folkers and Johnson.

Sweet and Fissekis (1973)

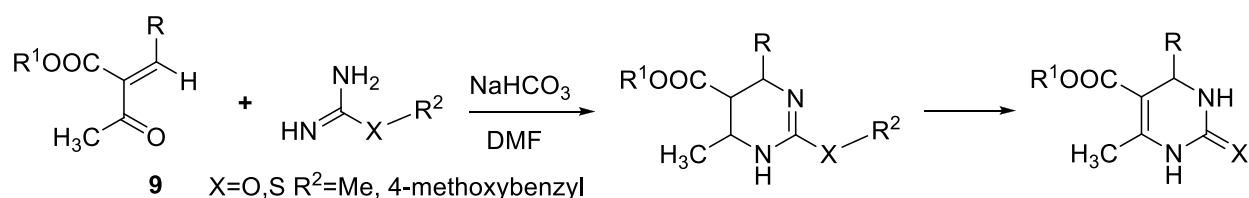
After several decades the reaction was reinvestigated by Sweet and Fissekis⁸ who advocated contradictory mechanism to Folkers suggestion as indicated above in route 1, proceeding through aldol reaction (through carbenium ion intermediate **8**) (Scheme 3).



Scheme 3. Formation of 3,4-dihydropyrimidinone via aldol condensation.

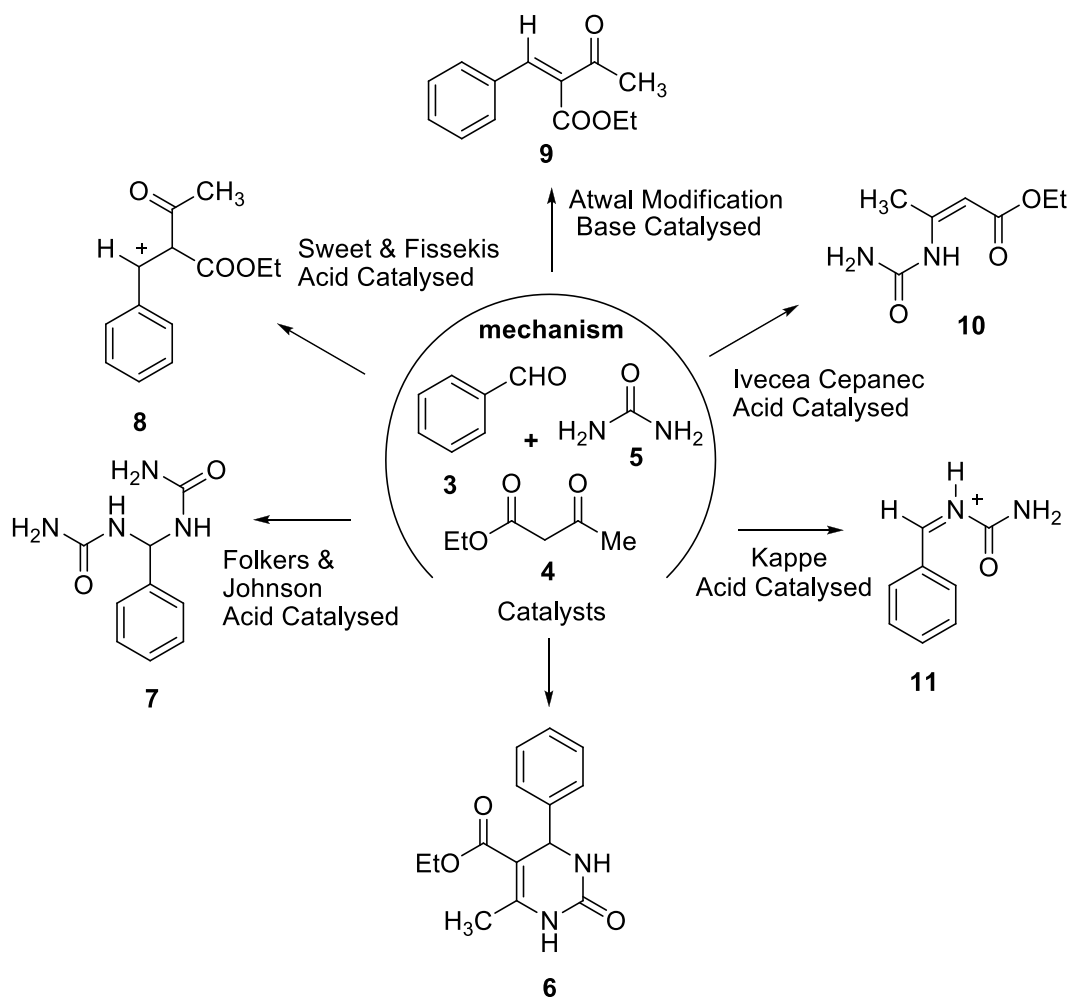
Atwal and O'Reilly (a two step process) (1987)

Atwal and his associates,⁹⁻¹¹ 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. This new approach involving two steps, first step concerned with separate synthesis of unsaturated carbonyl compound **9** via Knoevenagel condensation and second step involved the base catalyzed addition of substituted ureas as shown in Scheme 4, as in route 2.



Scheme 4. Formation of 3,4-dihydropyrimidinone via Knoevenagel condensation.

It is pertinent to mention here that this modification of the Biginelli reaction has rarely been used in recent years, since it involves two steps.



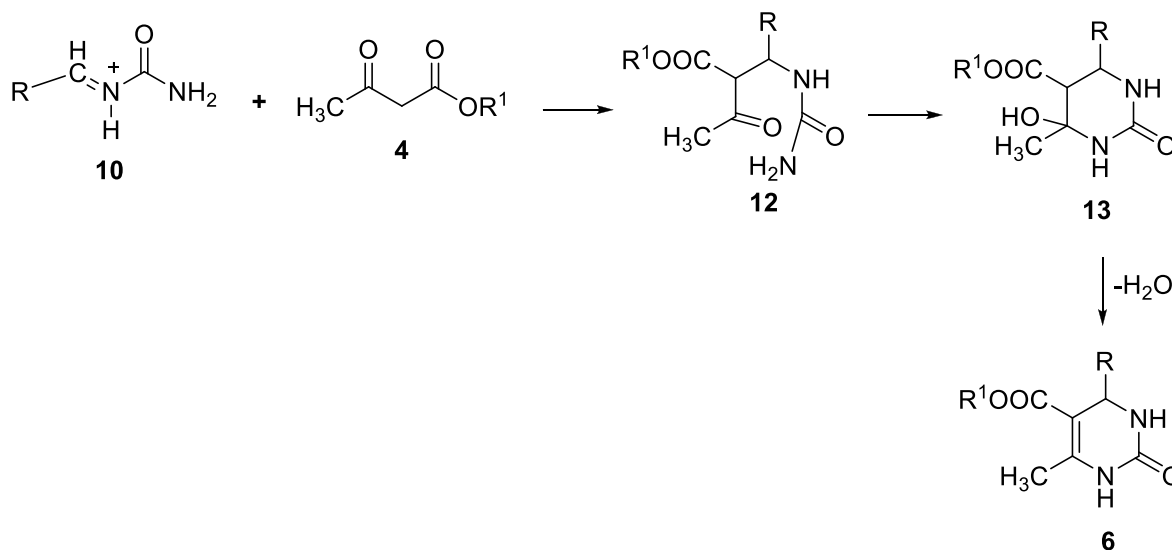
Scheme 5. Investigated intermediates by various workers.

Depicting of all these mechanistic proposals so far advanced were necessary to be presented here because there are very few synthetic studies on mechanism aspect of this reaction prior to or after Kappe's mechanistic proposal though this reaction has attracted the attention of large number of chemists around the world as far as number of publications are concerned clearly these were catalysts efficacy/ catalyst development investigations only. It is not out of point to mention here every research journal was flooded describing these changes i.e. catalysts and every paper made a mention of Kappe's mechanism which was based upon spectroscopic evidence only and is given below.

O. Kappe (1997)

On the basis of spectral techniques like H^1/C^{13} NMR spectroscopy, Kappe,¹² further re-examined the mechanism of this multicomponent reaction. 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 **11** takes place at the expense of acid catalysed dehydration. In the next step, active methylene compound

adds onto this intermediate in a Michael fashion as in route 3. He found that in this reaction dihydropyridines were always formed in minor quantities,⁶ which had not been observed by earlier research groups (Scheme 2).

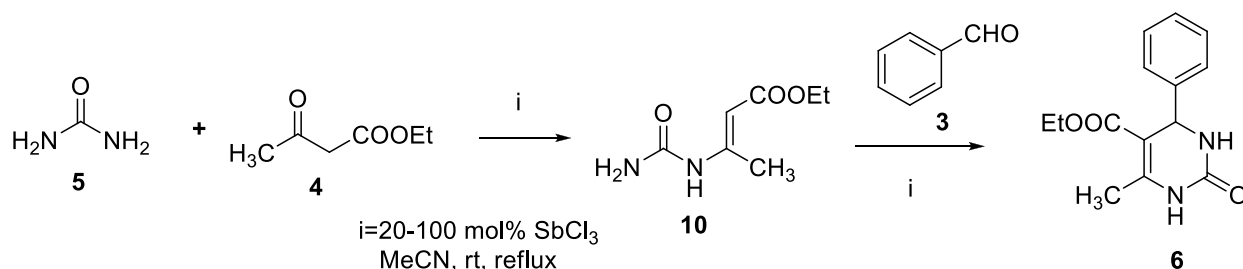


Scheme 6. Formation of 3,4-dihydropyrimidinone via *N*-acyliminium ion.

When Saloutina and co-workers¹³ used $\text{CF}_3\text{COCH}_2\text{CO}_2\text{Et}$ in place of acetoacetic ester they isolated the intermediate **13** and the dehydration is done in the next step using *p*-toluenesulfonic acid. Using GaCl_3 as Lewis acid the dehydration part in this mechanism was also investigated by us.¹⁴ We observed that anhydrous GaCl_3 yields final products in excellent yields in contrast to hydrated GaCl_3 ,¹⁵ which does not perform well in this reaction.

Cepanec (experimental evidence) 2007

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 **10** and not iminium formation as proposed by Kappe authors are reproducing actual scheme see below:



Scheme 7. Formation of 3,4-dihydropyrimidinone via 3-ureido-crotonates.

This Lewis acid behaviour places questions on several reports describing the Biginelli reaction and proposing Biginelli mechanism similar to Kappe without working out actual details.

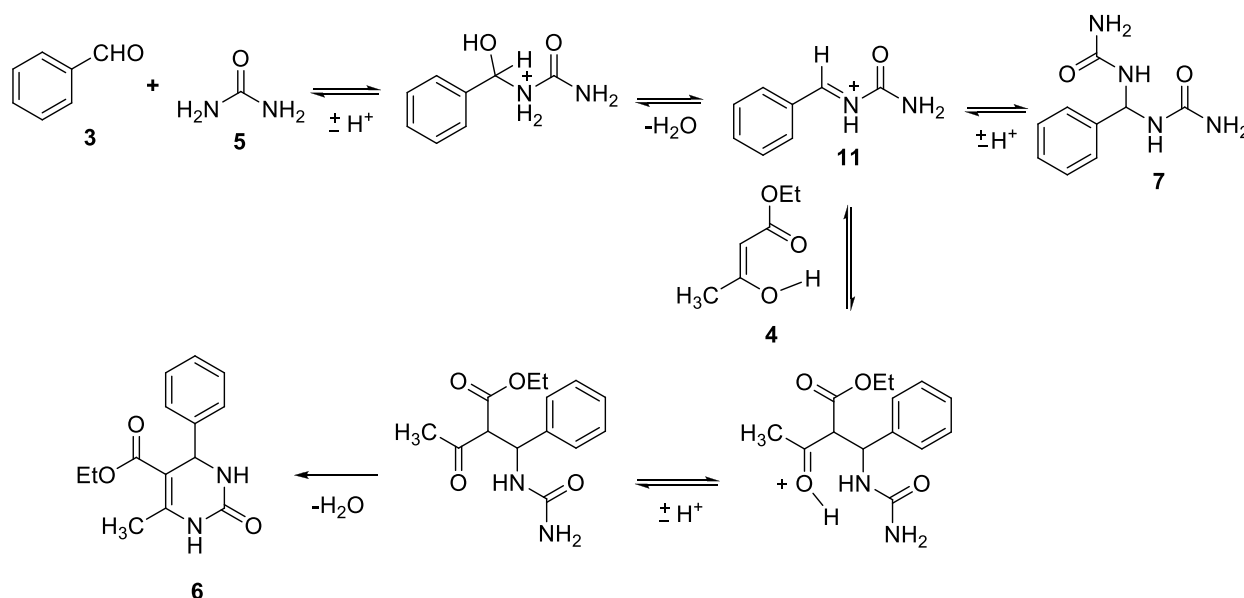
Jian-Hua Zhou (DFT Study) 2008

DFT study is reported via condensation of benzaldehyde, urea, and ethyl acetoacetate is investigated under classical reaction conditions and these authors¹⁷ also confirmed Kappe's proposal.

De Souza 2009

Lately of course there are mechanistic investigations De Souza *et al.*¹⁸ investigated Biginelli reaction and concluded in favour of Folkers and Johnson proposal, they based their conclusions on density functional theory calculations (DFT), they have used a mass spectrometer having accessories for various ionizations: for details see reference 18.

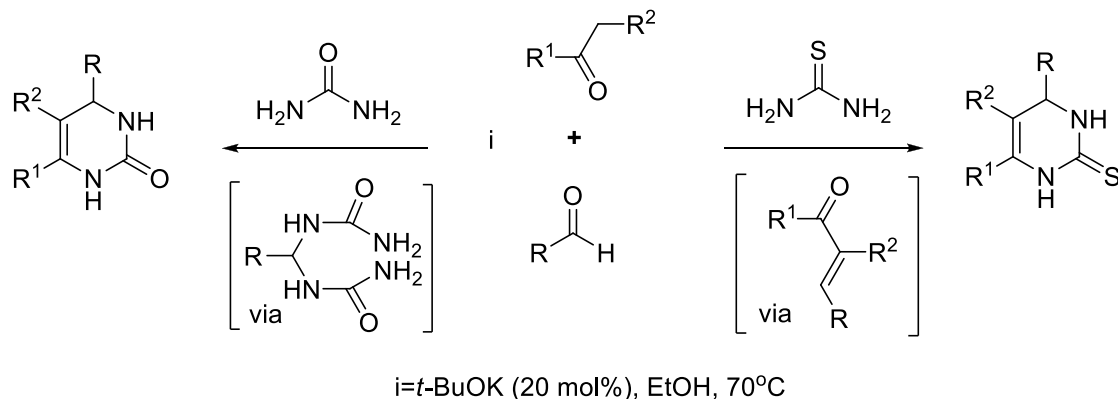
Under acidic condition (formic acid was used) found their experimental and theoretical investigations regarding reaction the mechanism in favor intermediate *N,N*-benzylidenebisurea **7** as proposed by Folkers and Johnson. They examined the reaction pathway using direct infusion electrospray ionization mass spectrometry (ESI-MS) and density functional theory (DFT). In this way, these workers support the formation of **7** with traces of intermediate **9** and **10**. As mentioned by us chase for easy publications is slowing down and trend is there for actual path determinations. So another research group Boumoud *et al.* also reported their investigation using catalyst nickel(II) nitrate hexahydrate and they concluded in favour of Folkers mechanism.



Scheme 8. Formation of 3,4-dihydropyrimidinone via iminium mechanism 11.

Shun-Jun Ji 2010 (base catalysed)

A large number of investigations have been on the use Lewis acid acid like catalysts, and only very few papers describe basic catalysts. Very recently, Chinese workers,¹⁹ have described the use of strong bases and proposed different pathways as shown below.

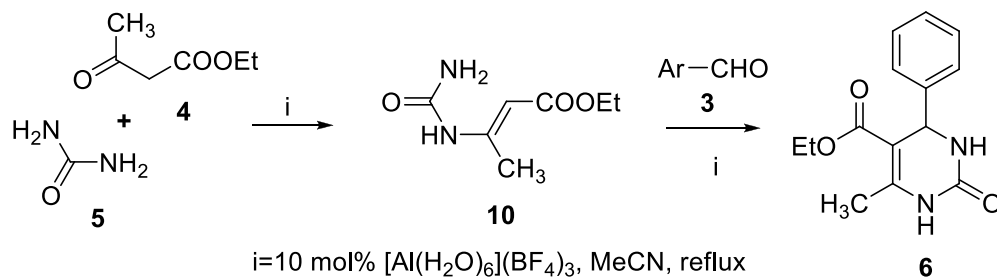


Scheme 9. Base catalysed synthesis of 3,4-dihydropyrimidinone.

All the above mentioned processes and mechanism reinvestigations with each catalysts used seems to be an healthy trend in this reaction in contrast to earlier reports casually mentioning that our reaction seems to follow Kappe mechanism. In mechanism advancements yet another mechanism report is there using hexaaquo-Al(III) BF₄.²⁰

Litvic 2010 (Brønsted acid)

The mechanism of this reaction reported to via ‘ureido-crotonate’ formation **10** as reported by Capanec in contrast to acylimino intermediate **11** (Kappe suggestion).²⁰



Scheme 10. Acid catalysed synthesis of 3,4-dihydropyrimidinone.

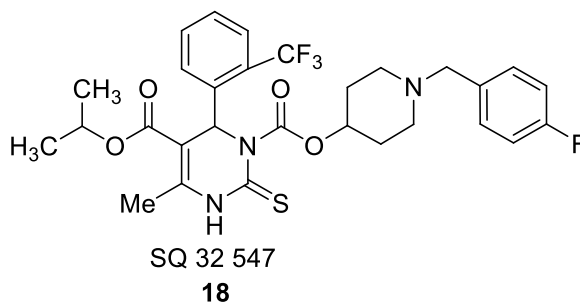
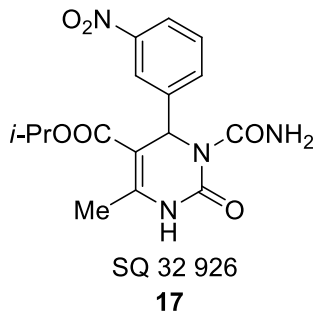
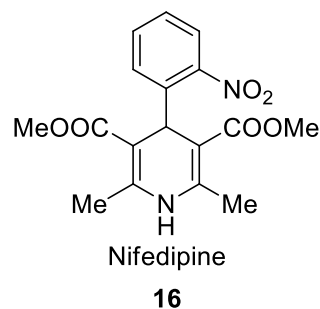
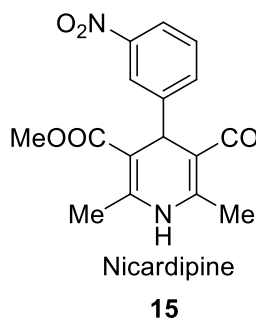
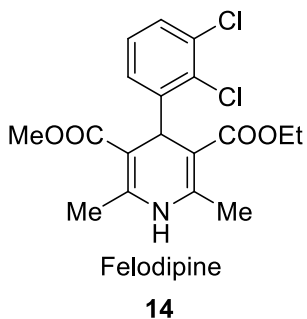
4. Pharmacology

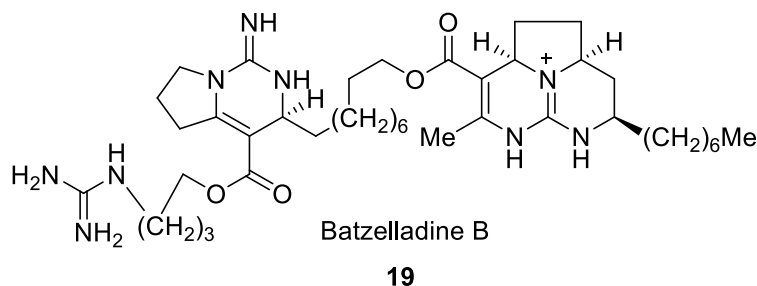
In this part of this account biological aspects of this motif are discussed. A biologist needs readily available, stable molecules for evaluation/study which this scaffold fulfills. In 1930, wool

protection activity of these molecules was patented.²¹ There followed further intensive investigation because of their resemblance to clinically used nifedipine **14-16** Biginelli being their aza-analogue **17-18** further they had resemblance to marine natural alkaloids batzelladine B **19** (for this complete comparison see below).^{22,23}

Variation of all three building blocks, viz. active methylene, ureas, aldehyde component lead to extension of the scope original multi-component resulting in large molecular diversity of dihydropyrimidines. The biological investigation of these various molecules via molecular manipulation showed activities like antiproliferative, antiviral, antitumor, anti-inflammatory, antibacterial, antifungal, and antitubercular activity. Similarly, the structural core of quinoline is frequently associated with medicinal applications such as anticancer, antimicrobial, HIV-1 integrase inhibition, HIV protease inhibitors, antileishmanial activity, NK-3 receptor antagonists, PLT antagonists, and antimalarial activity.

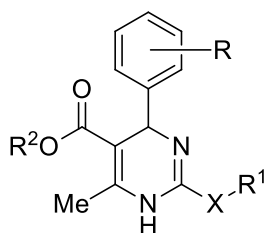
In search of more potent and effective medicinal important molecules numerous Biginelli dihydropyrimidine related annulated or multifunctionalized pyrimidines heterocyclic have been investigated or tested against different dangerous diseases which is arise due to stress or pollution. It is worth mentioning here that these new dihydropyrimidines are synthesized in classical fashion or employing different reaction condition which are discussed in the catalyzt section. In the following paragraphs only selective molecules are presented which are have significant activity and they are examined with clinically used drugs in vivo/in vitro and establishing QSAR.





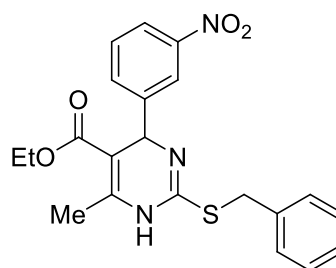
4.1 Antihypertensive agents

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 viz SQ 32926 **17**, SQ 32547 **18** (effective orally active antihypertensive agents) are promising targets for bringing them to actual use. Hetero-substituted DHPMs **20** 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 **21** is potent mimic of dihydropyridine calcium channel blockers.²⁴



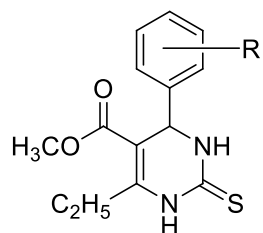
R=2-NO₂, 3-NO₂, 2-CF₃, 2,3-Cl.
 R¹=Me, CH₂CH=CH₂, CH₂(CH₂)₃CH₃,
 CH₂C₆H₅, CH₂CH₂N(Me)Bn, CH₂CH₂NMe₂.
 R²=Et, *i*-Pr, Me, SBu, CH₂CH₂N(Me)Bn.
 X=O, S.

20 (20)



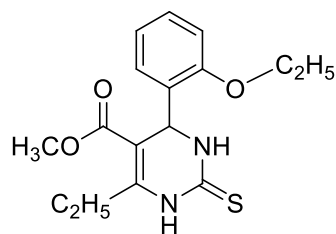
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Other significant molecules like **22-27** are under serious investigation.

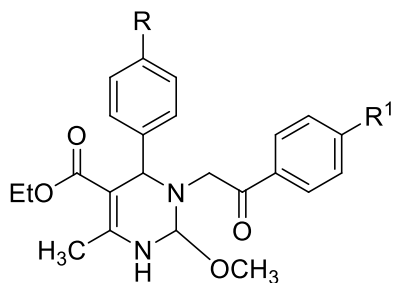


R=2-Cl, 3-Cl, 4-Cl, 3-Br, 4-Br,
2-CH₃, 3-CH₃, 4-CH₃, 2-OCH₃,
2-NO₂, 3-NO₂, 2-F, 3-F, 2-OC₂H₅,
2-OH-5-Br.

22 (16)

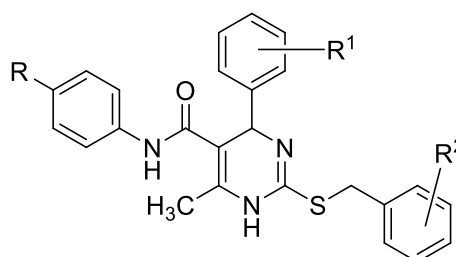


23



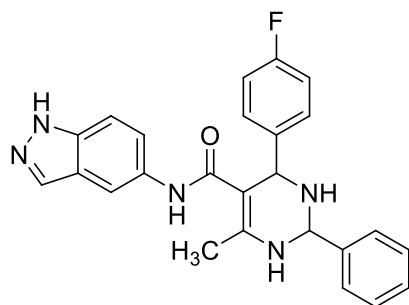
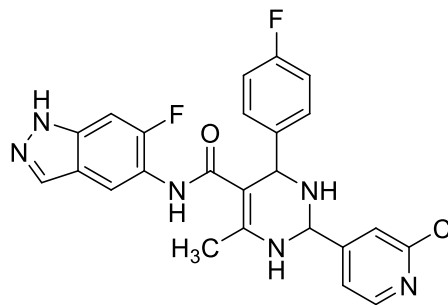
R=CH₃, OCH₃.
R¹=H, OCH₃.

24 (11)



R=F, Br, NO₂.
R¹=2,4-Cl, 4-Br, 3-NO₂, 4-NO₂,
3,4-OCH₃, 4-OCH₃.
R²=H, 2-Cl, 3-Cl, 4-Cl, 4-F.

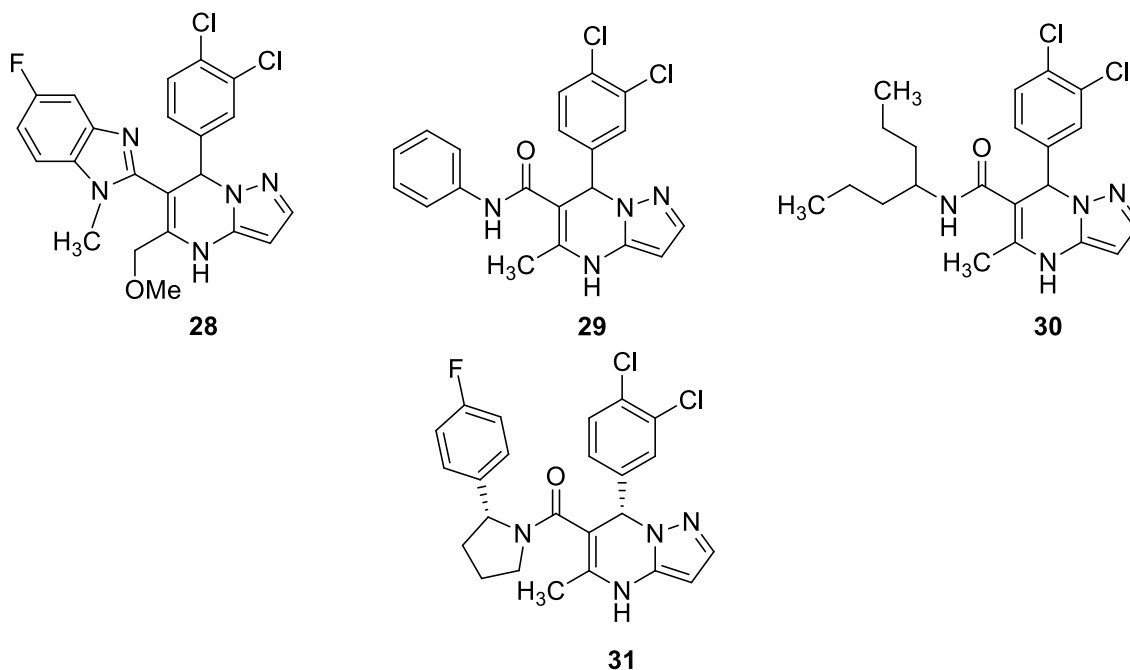
25

26^{24(e)}27^{24(e)}

Numericals in brackets show the number of molecules derived from respective structure investigated.

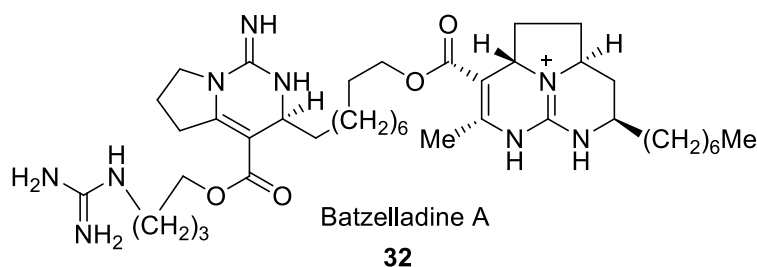
4.2 Potassium channel antagonists

Annulation of benzimidazole ring **28** with this Biginelli showed potassium channel antagonists activity and these are at preclinical developments **28-31**.²⁵



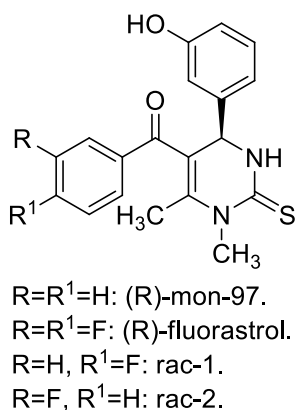
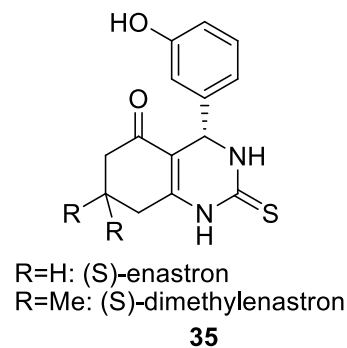
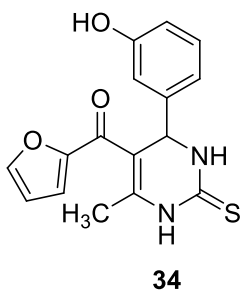
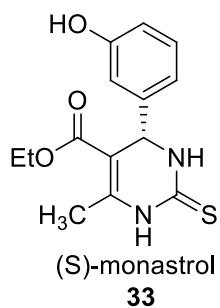
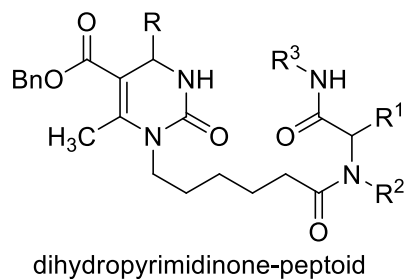
4.3 Anti-HIV agents

Batzelladine A **32** and B **19** 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.²²

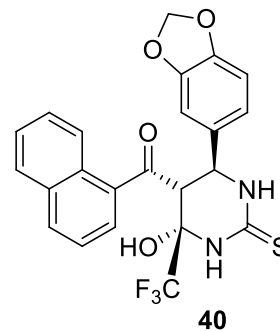
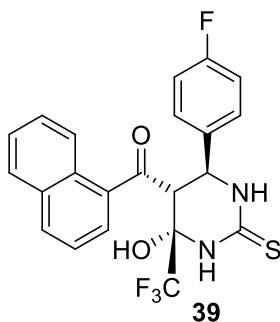
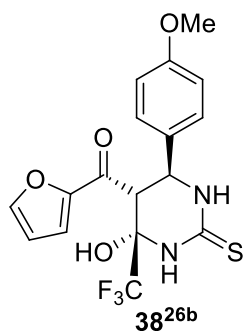


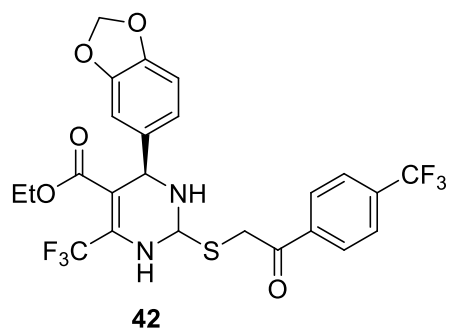
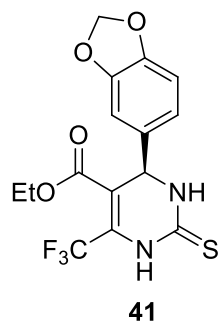
4.4 Antitumor activity

Human kinesin Eg5, an interesting drug target for the development of cancer chemotherapeutics. Monastrol **33** 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 **34** appeared more potent than monastrol by a fivefold factor. Reported compounds enastron **35**, mon-97 **36**, dimethylenastron **35**, and fluorastrol,^{26b} **36** potency of these new inhibitors, have been compared with the monastrol which are better fit of the ligand to the allosteric binding site and the addition of fluorine atoms.²⁶

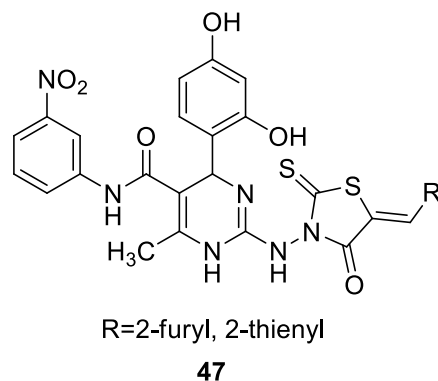
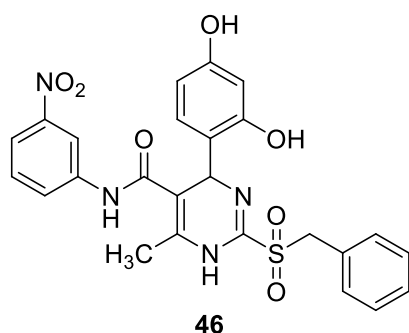
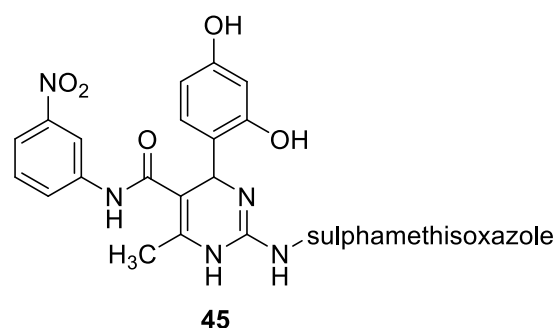
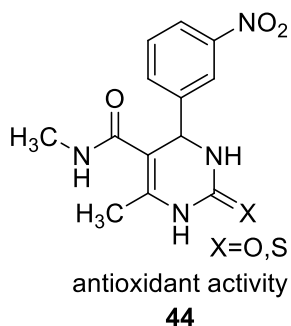
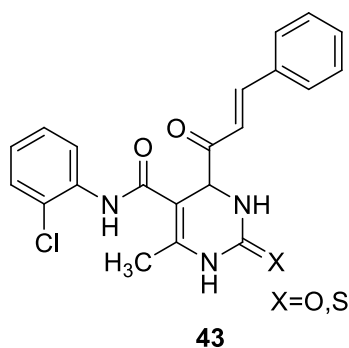
**36****37**

Pyrimidinone-peptoid hybrid molecules **37** are also identified as Hsp70 modulators that inhibit cell proliferation. Trifluoromethylated hexahydropyrimidine and tetrahydropyrimidine derivatives **38-42** represent promising new leads for the development of highly potent and selective anticancer compounds and also their in vitro cytotoxic activities were determined in colon cancer cell line.



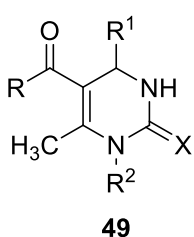
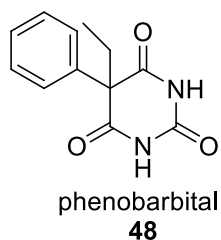


Other structures **43-47** also have significant activity.



4.5 Anti-epileptics

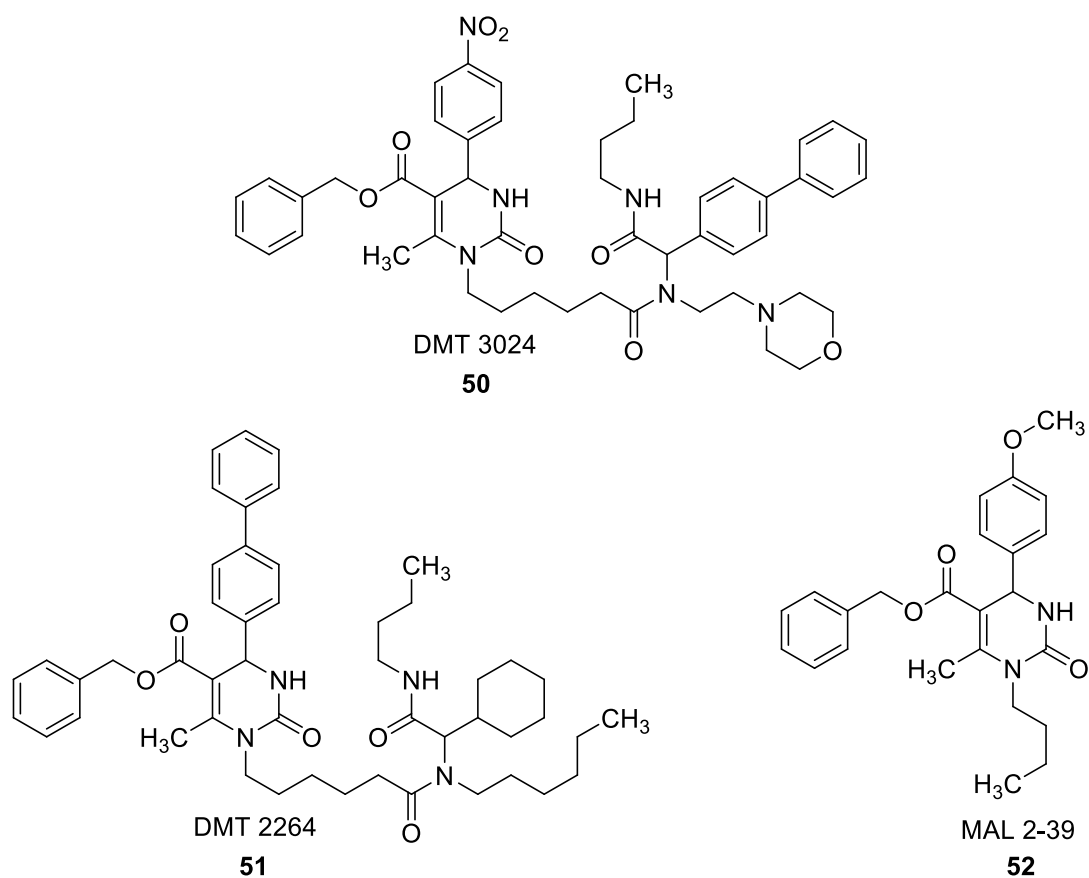
Phenobarbital **48** is well known drug for epilepsy when one sees Biginelli compounds it has similar structural framework and as a natural tendency when compounds of the type **49** were examined for epilepsy they have shown promising anti-epilepsy activity.²⁷

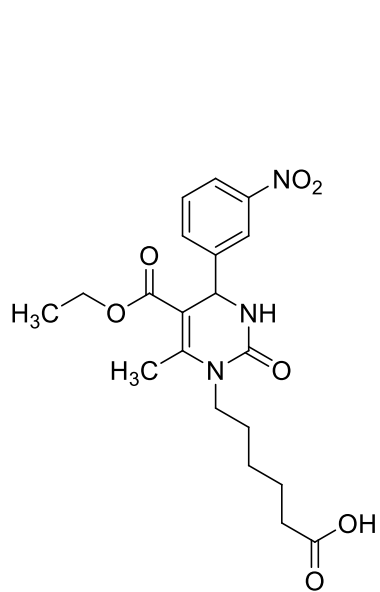


R=OMe, Me, OH, NH₂, OMePh.
R¹=Ph, 4-Br-C₆H₄, 3-OMe-C₆H₄,
4-NO₂-C₆H₄, 3-OMe-4-OH-C₆H₃,
C₃H₇, 3-OH-C₆H₄.
R²=H, Me.
X=O,S.

4.6 Anti-malarials

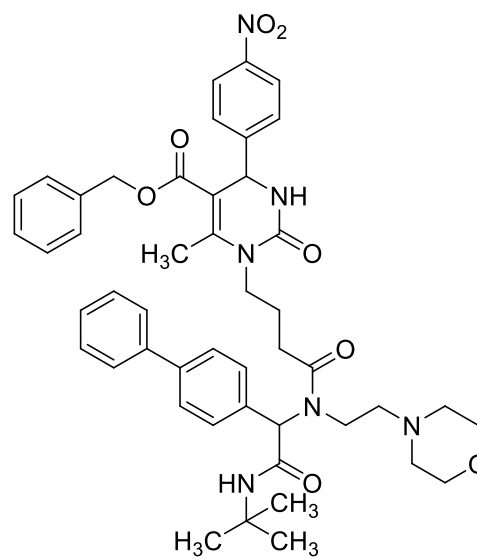
Pyrimidinone-amides derivatives of DHPMs **50-58**, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic *P. falciparum* stages in human red blood cells. Nine compounds are selected as anti-malarial agents and are being investigated further.²⁸





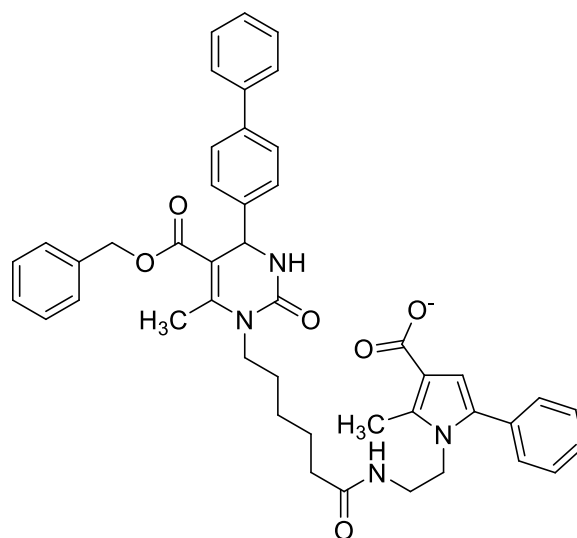
MAL 2-29

53



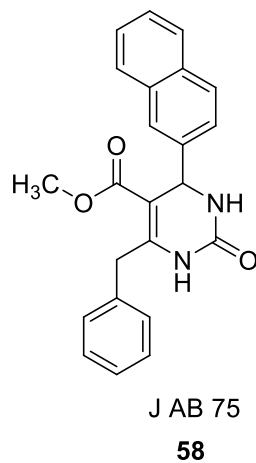
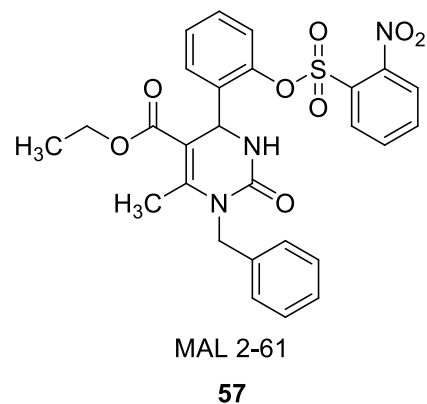
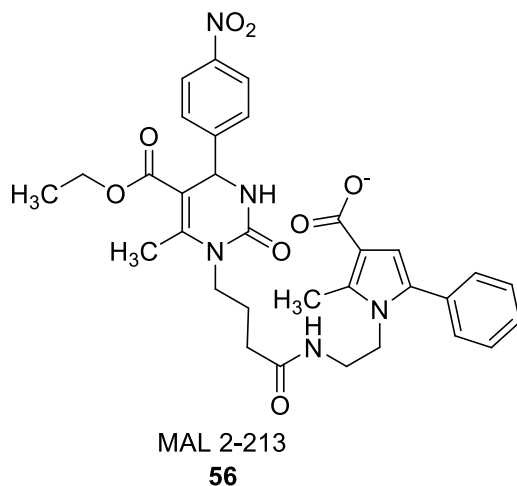
MAL 3-39

54



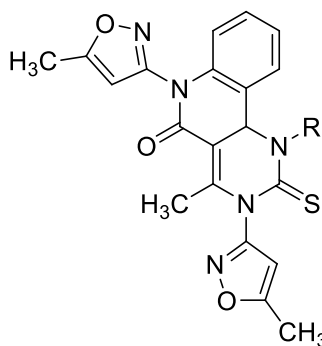
MAL 2-215

55



4.7 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-1H-pyrimido[5,4-c]quinolin-5-ones **59** showed anti microbial also apart from antibacterial, antifungal, and antimalarial activities.²⁹

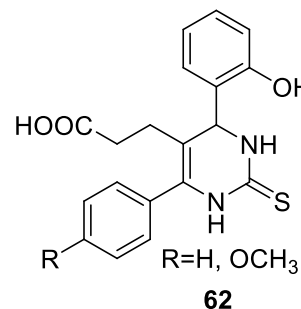
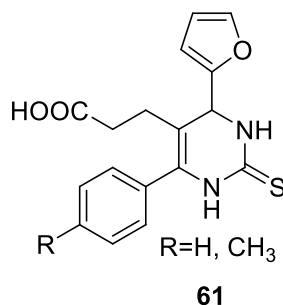
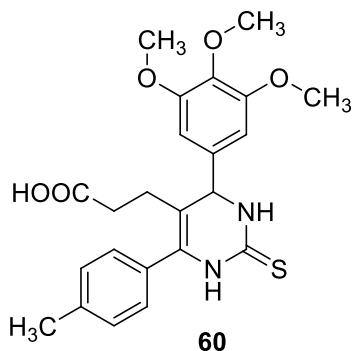


R=C₆H₅, 4-CH₃C₆H₄, 4-CH₃OC₆H₄,
4-BrC₆H₄, C₆H₅CH₂, 4-ClC₆H₄,
3-CH₃OC₆H₅, 2-ClC₆H₄.

59

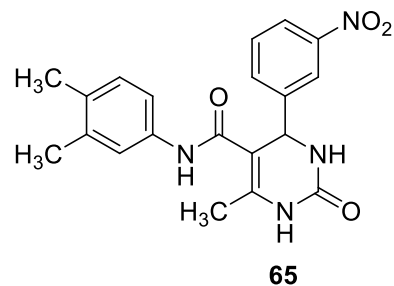
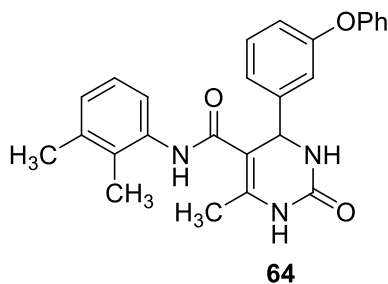
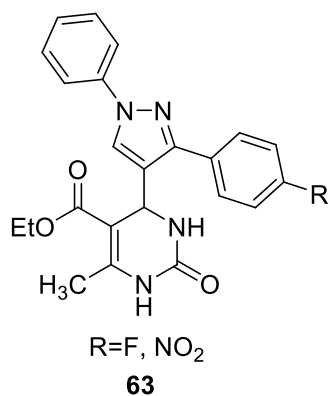
4.8 Anti-inflammatories

A series of compounds 3-(4,6-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives **60-62** were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant anti-inflammatory activity.³⁰



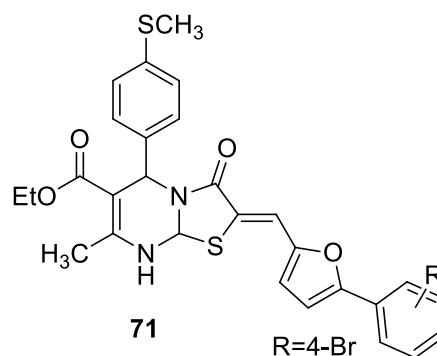
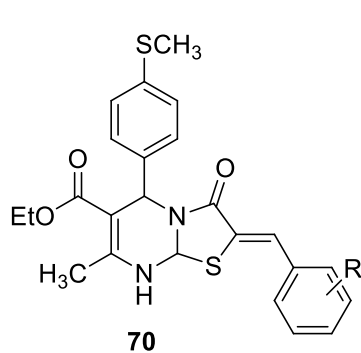
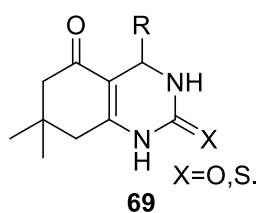
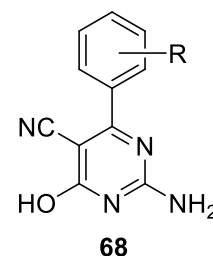
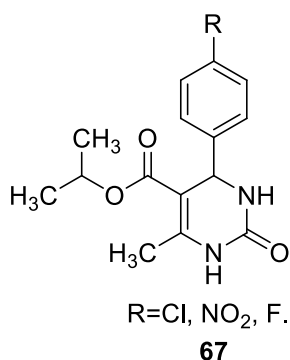
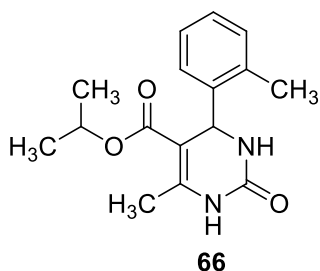
4.9 Anti-tubercular activity

Dihydropyrimidines (30 examples) also were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv. This study was in vitro only. Only 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 **63** were shown to be the most active compounds and found to be more potent than isoniazid. Compounds **64** and **65** with 2,3-dimethylphenyl and 3,4-dimethyl carbamoyl side chain, respectively, showed 65% and 63% inhibition against *Mycobacterium tuberculosis* H37Rv.³¹



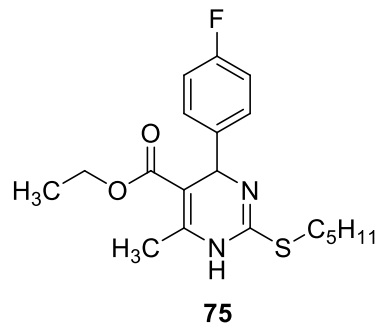
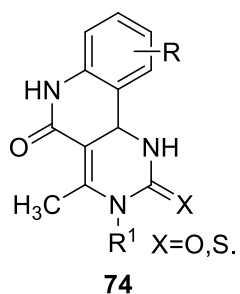
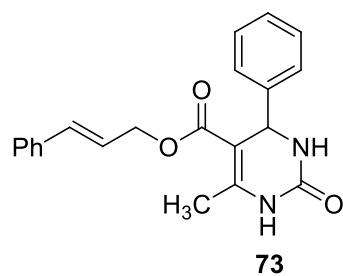
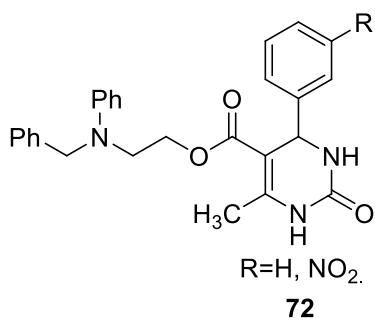
4.10 Anti-bacterial activity

Ester, cyanide and some other substituted Biginelli **66-71** are reported to be promising anti-bacterial agents.³²

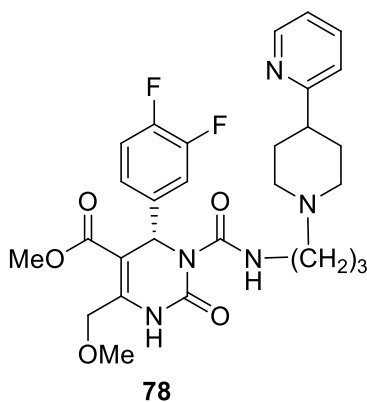
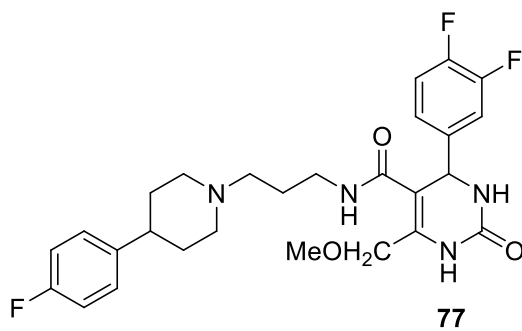
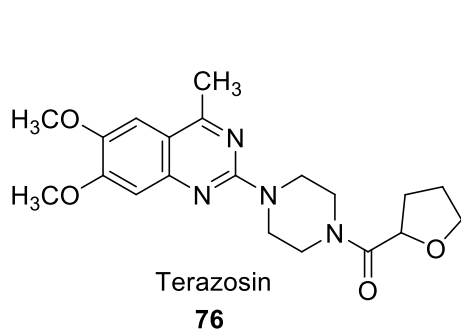


4.11 Miscellaneous activities

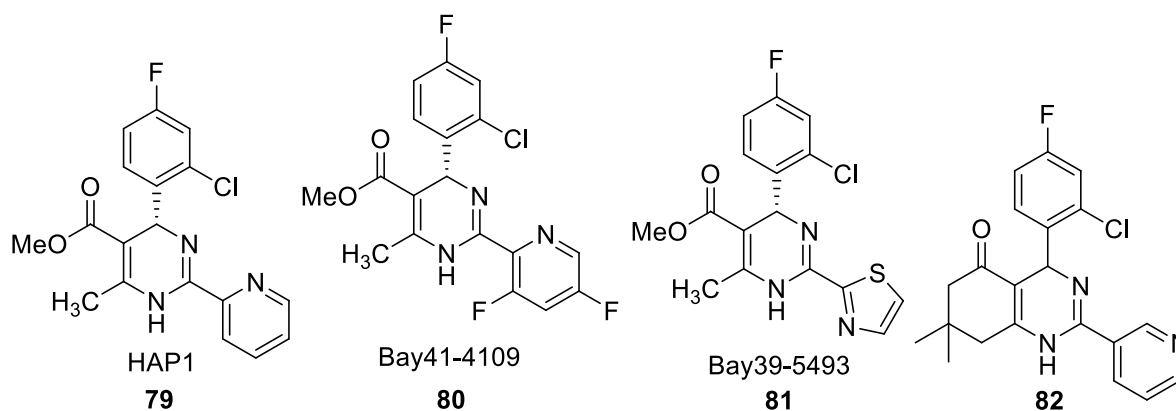
Since our major objective in this account is to keep present description brief following structure are presented and given below them is given their activities.



Anti-oxidants³³ **72-74** and Anti-filarial agents **75**.³⁴



α -_{1A} Adrenergic receptor antagonists³⁵ **76-78**.



Anti-HBV (hepatitis B virus) agents³⁶ **79-82**.

5. Scope of reaction/developments in structural variants

To develop/explore Biginelli chemistry all commonly available as well as other variants of typical reactants aldehydes, ureas and active hydrogen components have been used so far.

5.1 Aldehyde

In case of aldehydes all the available aliphatic, aromatic, heterocyclic and rare aldehydes have been used including sugars aldoses. Biginelli reactions of formyl- and 1,10-diformylferrocene is also reported (see Table 1).

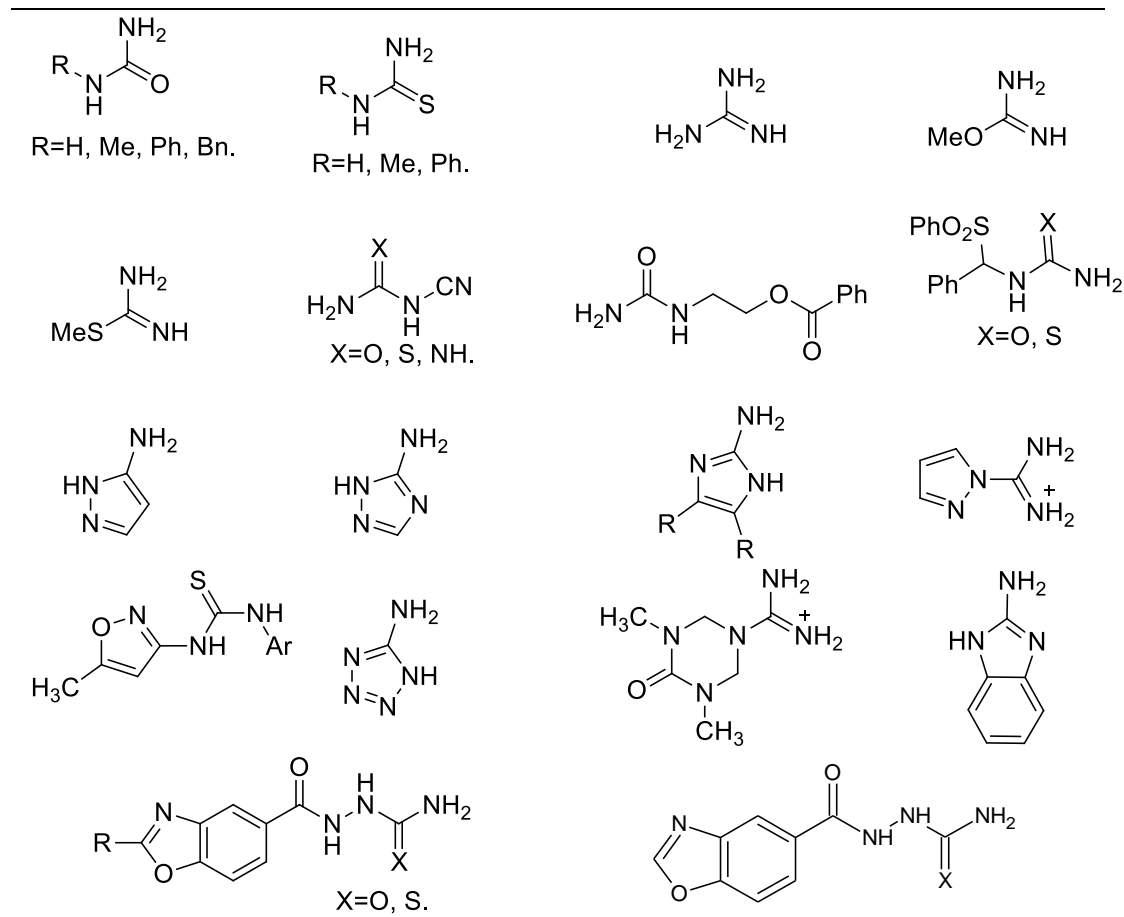
Table 1. Aldehydes Building Blocks Used in Biginelli Reaction

X=H, Cl, Br, CH ₃ , CF ₃ , NO ₂ etc.			

5.2 Urea

Regarding urea component, thiourea, and resin bonded urea and other related systems like guanidine are very successfully used. Various N-mono/di substituted ureas have been employed in this reaction to obtain pharmacologically potent molecules see Table 2.

Table 2. Urea and thiourea building blocks used in Biginelli reactions



5.3 Active hydrogen component

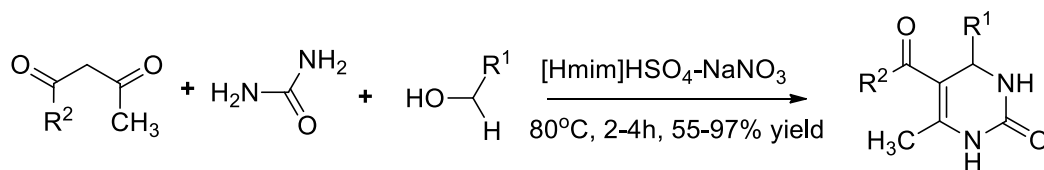
In active hydrogen family varies conventional and unconventional (which can be activated) active methylene compounds have been utilized in this reaction: see Table 3. Even then there are major gaps regarding this structural partner which will be discussed in an appropriate section. Now some cases are presented below for clarity and understanding of the readership.

Table 3. Active hydrogen building blocks used in Biginelli reactions

R=Me, Ph, CH ₂ Br, CF ₃ . R ¹ =Me, OMe, <i>i</i> -PrO, Et ₂ N, EtS.	R=substituted phenyl, 2-thienyl, 2-furyl.	R=alkyl, aryl.	
			R=Ph, Me.
R=H, Me.			X=O, S, SO ₂ .
	X X=H, Me.		

5.4 Use of alcohols in place of aldehydes

Recently, alternative to the classical synthesis of Biginelli compounds has been reported directly from aromatic alcohols under mild conditions are also reported using ionic liquid 1-methylimidazolium hydrogen sulfate [Hmim]HSO₄. In this method aromatic aldehydes formed in situ via oxidation of aromatic alcohols with NaNO₃ (Scheme 11).³⁷



Scheme 11. Using alcohols instead of aldehydes; synthesis of 3,4-dihydropyrimidinones.

Classically the above mentioned three components are involved in this reaction and fourth is catalyst. Medium employed in this reaction in the original report is alcohol at reflux temperature. As a natural curiosity variations have been investigated to have access to these structurally diverse Biginelli compounds. All these variables are presented in the following pages.

6. Catalyst Variations

Because the "privileged" nature of this scaffold is of prime importance, academic institutions were busy keeping this property as a driving force in the generation of a large number of reports in pursuit of efficient processes and procedures for these molecules. Essentially, these reports reported catalyst variations only on the following types of catalysts so far. Since several workers reported catalyst variations for the effective production of this motif authors are presenting this aspect from the latest to the earlier ones over the past decade or so: see Table 4.

Table 4. Variety of catalysts used

2011

I₂/MWI,³⁸ sulfonated β-cyclodextrine,³⁹ Cu(OTf)₂/MWI,⁴⁰ Sulfated tungstate,⁴¹ Melamine trisulfonic acid,⁴² Yb(PFO)₃,⁴³ HCl/EtOH,⁴⁴ N,N'-Dichlorobis(2,4,6-trichlorophenyl)urea (CC-2),⁴⁵ H₃PO₃/Pd-Cat.,⁴⁶ hv/DMSO,⁴⁷ TFA/THF/MWI,⁴⁸ TMSCl/CAN,⁴⁹ HCl or H₂SO₄ or TEBA,⁵⁰ FeCl₃/Al-MCM,⁵¹ silica immobilized Ni(II),⁵² Ca(OCl)₂,⁵³ BPAT-TfOH,⁵⁴ L-(+)-tartaric acid-urea mixtures,⁵⁵ AcOH,⁵⁶ Mg(NO₃)₂,⁵⁷ chloroacetic acid,⁵⁸ PPA-SiO₂,⁵⁹ gypsum,⁶⁰ Nano-BF₃.SiO₂,⁶¹ Organocatalytic,⁶²

2010

HCl/MWI,⁶³ Me₃SiCl,⁶⁴ [Hmim]HSO₄-NaNO₃,⁶⁵ NH₄VO₃/MWI,⁶⁶ CeCl₃.7H₂O,⁶⁷ Me₃SiCl/DMF,⁶⁸ p-TSA.H₂O,⁶⁹ TMSCl/DMF,⁷⁰ Sm(ClO₄)₃,⁷¹ AcOH,⁷² TSIL,⁷³ vitamin B1/EtOH,⁷⁴ HCl/EtOH,⁷⁵⁻⁷⁶ BAIL,⁷⁷ Cl₃CCO₂H,⁷⁸ 1-Carboxymethyl-3-methylimidazolium hydrogen sulfate,⁷⁹ sulfamic acid, ultrasonic radiation,⁸⁰ I₂/MWI,⁸¹ neat condition,⁸² PEG-400,⁸³ Copper methanesulfonate (CMS),⁸⁴ TEA,⁸⁵ Diphenylammonium Triflate,⁸⁶ Al-mesoporous silica,⁸⁷ aluminium-planted mesoporous silica,⁸⁸ Cerium (IV) ammonium nitrate,⁸⁹ NbCl₅/Primary Amine,⁹⁰ amine derived from quinine QNH₂,⁹¹ tartaric acid,⁹² NiCl₂/KI,⁹³ Gallium(III) Iodide,⁹⁴ Brønsted acidic ionic liquid-promoted,⁹⁵ dioxane/acetic acid,⁹⁶

NaHSO₄,⁹⁷ (diacetoxyiodo)-benzene,⁹⁸ TMSCl,⁹⁹ TiO₂,¹⁰⁰ HBF₄-SiO₂,¹⁰¹ HCl/EtOH,¹⁰² MgSO₄·7H₂O,¹⁰³ [Bmim]HSO₄,¹⁰⁴ 1,3-Dichloro-5,5-dimethylhydantoin,¹⁰⁵ Y(OAc)₃,¹⁰⁶ Nickel Nanoparticles,¹⁰⁷ Tributyl Borate,¹⁰⁸ V(HSO₄)₃,¹⁰⁹ Nafion-H,¹¹⁰ CuCl₂,¹¹¹ Dodecylphosphonic Acid,¹¹² *p*-aminobenzene sulfonic acid,¹¹³ Phosphoric Acids,¹¹⁴ ammonium carbonate,¹¹⁵ PEG-embedded thiourea dioxide,¹¹⁶ thiamine hydrochloride,¹¹⁷ hexaaquaaluminium(III) tetrafluoroborate,²⁰ piperidinium triflate,¹¹⁸ aluminium-planted mesoporous silica,¹¹⁹ Borax,¹²⁰ FeCl₃·6H₂O,¹²¹ Cu(NO₃)₂·3H₂O,¹²² Ce(SO₄)₂-SiO₂,¹²³ Fe(NO₃)₃·9H₂O,¹²⁴ aluminium-planted mesoporous silica,¹²⁵ H₃PMo₁₂O₄₀,¹²⁶ Silica-supported tin chloride and titanium tetrachloride,¹²⁷ Lewis acid,¹²⁸

2009

PS-PEG-SO₃H,¹²⁹ trifluoro acetic acid,¹³⁰ trifluoromethane sulfonic acid,¹³¹ PS-AFDPAT,¹³² Ytria-Zirconia-Based Lewis Acid,¹³³ TMSCl,¹³⁴ TMSCl and Co(OAc)₂·4H₂O,¹³⁵ ytterbium chloride,¹³⁶ Calcium fluoride,¹³⁷ mesoporous aluminosilicate,¹³⁸ Al₂O₃/MeSO₃H,¹³⁹ Acidic Ionic Liquids,¹⁴⁰ Al(H₂PO₄)₃,¹⁴¹ Alumina Sulfuric Acid,¹⁴² Zinc Oxide,¹⁴³ Copper Nitrate,¹⁴⁴ Cellulose Sulfuric Acid,¹⁴⁵ Lactic acid,¹⁴⁶ ionic liquid,¹⁴⁷ NaHSO₄·H₂O,¹⁴⁸ H₂SO₄ Supported on Silica Gel or Alumina,¹⁴⁹ Al(HSO₄)₃ and Al₂O₃-SO₃H,¹⁵⁰ NaH,¹⁵¹ SnCl₂,¹⁵² TBAB,¹⁵³ Mg/MeOH,¹⁵⁴ PTSA,
Sc(OTf)₃ or La(OTf)₃,¹⁵⁵ L-proline/TFA,¹⁵⁶ NaCl,⁶⁽¹⁾ Copper(II) Sulfamate,¹⁵⁷ I₂/MWI,¹⁵⁸ UV irradiation,¹⁵⁹ I₂,¹⁶⁰ Amberlyst-70,¹⁶¹ Etidronic Acid,¹⁶² Fe³⁺, Co²⁺, Zn²⁺, Li⁺ salts,¹⁶³ NBS/silica sulfuric acid/MWI,¹⁶⁴ 1,3-Dibromo-5,5-dimethylhydantoin (DBH),¹⁶⁵ Uncatalysed,¹⁶⁶ oxone on wet alumina or hydrogen peroxide-vanadyl sulfate,¹⁶⁷ PdO,¹⁶⁸ Indion 130,¹⁶⁹ TMSCl/DMF,¹⁷⁰ Proline Ester Salts,¹⁷¹ HCO₂H,¹⁸ CBPA-Thiourea,¹⁷² Yb-bis(perfluorooctanesulfonyl)imide,¹⁷³ I₂,¹⁷⁴ phosphinite ionic liquid,¹⁷⁵ Organocatalyst,¹⁷⁶ alumina-supported trifluoromethane sulfonic acid,¹⁷⁷ etidronic acid,¹⁷⁸ zinc tetrafluoroborate,¹⁷⁹ ammonium dihydrogen orthophosphate,¹⁸⁰ lipase,¹⁸¹ Na₂SeO₄,¹⁸² Bifunctional Organocatalyst,¹⁸³ NiSO₄·7H₂O,¹⁸⁴ NaIO₄,¹⁸⁵ Phosphoric Acids.¹⁸⁶

2008

MgCl₂/AcOH,¹⁸⁷ MCM-41-R-SO₃H,¹⁸⁸ MWI,¹⁸⁹ ZrCl₄/Ultrasound,¹⁹⁰ Titanium(IV) Chloride,¹⁹¹ HCl/AcOH/MWI,¹⁹² KF-alumina,¹⁹³ HCl, *p*-TsOH or H₂NSO₃H,¹⁹⁴ PhI(OAc)₂/t-BuOOH,¹⁹⁵ PPE,¹⁹⁶ L-prolinium sulfate,¹⁹⁷ [HOC₂mim][PF₆]/MWI,¹⁹⁸ HCl/AcONa,¹⁹⁹ LaCl₃/ethanol,²⁰⁰ Ultrasonification,²⁰¹ H₂NSO₃H, TMSCl,²⁰² Me₃SiCl,²⁰³ Zeolite,²⁰⁴ Cu(TFA)₂·4H₂O,²⁰⁵ LaCl₃·Hydrates,²⁰⁶ Pr(CH₃SO₃)₃·2H₂O,²⁰⁷ 2-chloro-4-nitrobenzoic acid/*trans*-4-hydroxyproline derivative,²⁰⁸ Ferric Perchlorate,²⁰⁹ Polystyrene-supported AlCl₃,²¹⁰ DDQ,²¹¹ Oxalic acid,²¹² AcOH,²¹³ tungstate sulfuric acid,²¹⁴ KHSO₄ and HCl,²¹⁵ MWI,²¹⁶ SnCl₄,²¹⁷ CuCl₂·2H₂O-HCl,²¹⁸ citric acid,²¹⁹ Pb(NO₃)₂,²²⁰ HCl,²²¹ LiBr,²²² [Bmim][FeCl₄],²²³ TMSCl/DMF,²²⁴ Lanthanide halides derived from mischmetal (LnCl₃·7H₂O)/HCl/EtOH,²²⁵ LaCl₃/graphite/HCl/MWI,²²⁶ Alumina-sulfuric acid,²²⁷ Fe(HSO₄)₃,²²⁸ CuCl₂·2H₂O/C₁₂H₂₅SO₃Na/H₂O,²²⁹ Pyrazolidine dihydrochloride,²³⁰ TiCl₄,²³¹ SiCl₄/DMF,²³² Sulfonic salicylic acid,²³³ Pr(MeSO₃)₃,²³⁴ CuCl₂·2H₂O/HCl/grinding,²³⁵ Ph₃P,²³⁶ H₃PW₁₂O₄₀,²³⁷ Scolecite,²³⁸ HClO₄-SiO₂,²³⁹ ZrO₂-nanopowder/MWI,²⁴⁰ Pb(NO₃)₂.²⁴¹

2007

Zn(ClO₄)₂×6H₂O,²⁴² TsOH,²⁴³ VCl₃,²⁴⁴ TEBA,²⁴⁵ HClO₄/MWI,²⁴⁶ Polystyrenesulfonic acid (PSSA)/MWI,²⁴⁷ Bi(NO₃)₃,²⁴⁸ Bakers yeast,²⁴⁹ HCO₂H/MWI,²⁵⁰ SiO₂-Si(CH₂)₃SO₃H,²⁵¹ Metallophthalocyanines,²⁵² Nafion-H resin,²⁵³ Amino Acetic Acid,²⁵⁴ AlCl₃,²⁵⁵ PhCO₂H,²⁵⁶ MgSO₄,²⁵⁷ SiO₂/ZnCl₂,²⁵⁸ Silica sulfuric acid,²⁵⁹ H₄SiW₁₂O₄₀nH₂O,²⁶⁰ [C₄mim][HSO₄]/MWI,²⁶¹ R₃N⁺ (CH₂)₃SO₃⁻,²⁶² [Hmim]HSO₄,²⁶³ H₆P₂W₁₈O₆₂×24H₂O,²⁶⁴ ZnBr₂,²⁶⁵ TiCl₃,²⁶⁶ ZrOCl₂×8H₂O or ZrCl₄/neat,²⁶⁷ Y(NO₃)₃×6H₂O,²⁶⁸ AlCl₃ or AlBr₃,²⁶⁹ GaCl₃/MWI or GaBr₃/MWI,¹⁴ Ziegler-Natta catalyst system (TiCl₄-MgCl₂-4CH₃OH),²⁷⁰ HClO₄,²⁷¹ SmI₂,²⁷² NaBF₄,²⁷³ DSA,²⁷⁴ PEG 400,²⁷⁵ TMSCl/MWI,²⁷⁶ Silica triflate,²⁷⁷ Silica-chloride,²⁷⁸ TMSCl/DMF,²⁷⁹ TMSCl/DMF/sonication,²⁸⁰ ClCH₂CO₂H,²⁸¹ CuI/H₂O,²⁸² HBF₄,²⁸³ Trichloroisocyanuric acid,²⁸⁴ H₄PMo₁₁VO₄₀,²⁸⁵ KH₂PO₄/glycol,²⁸⁶ FeCl₃×6H₂O/MWI,²⁸⁷ Nafion-H resin,²⁸⁸ CuCl₂×2H₂O/MWI,²⁸⁹ SbCl₃,¹⁶ TaBr₅,²⁹⁰ Propane phosphonic acid anhydride (n-C₃H₇PO₂)₃/AcOEt,²⁹¹ ZnI₂/MWI,²⁹² KHSO₄,²⁹³ P₂O₅,²⁹⁴ HCl/AcOH,²⁹⁵ Cu(BF₄)₂×xH₂O/neat,²⁹⁶ Fe(CF₃CO₂)₃ or Fe(OTf)₃,²⁹⁷ MoO₃/Al₂O₃,²⁹⁸ Ca(HSO₄)₂, Zn(HSO₄)₂ or Oxone,²⁹⁹ Bi(NO₃)₃,³⁰⁰ [BMIm]Sac,³⁰¹ Cu/silica xerogel composite,³⁰² Silica sulfuric acid/[Bmim]Br,³⁰³ BF₃.Et₂O/PhMe/Mol. Sieves,³⁰⁴ K-10 clay/MWI,³⁰⁵ [HOC₂mim][PF₆],³⁰⁶ Co(NO₃)₂·6H₂O/K₂S₂O₈,³⁰⁷ [bmim]BF₄ immobilized Cu(acac)₂.³⁰⁸

2006

NaHCO₃/DMF,³⁰⁹ *p*-TSA/MWI,³¹⁰ *n*-BuLi/THF,³¹¹ CAN/NaHCO₃,³¹² PEG-SO₃H,³¹³ SbCl₃ on alumina,³¹⁴ Sulfated zirconia,³¹⁵ Sulfated zirconia,³¹⁶ EtOH/AcOH,³¹⁷ EtOH/AcOH,³¹⁸ NH₂SO₃H/grinding,³¹⁹ [BMim][BF₄],³²⁰ [CMIm][HSO₄],³²¹ 1-*n*-Butyl-3-methylimidazolium saccharinate [BMIm]Sac,³²² Dowex-50W,³²³ K₅CoW₁₂O₄₀3H₂O,³²⁴ H₃PW₁₂O₄₀/sulfated zirconia/MWI,³²⁵ TMSCl/DMF,³²⁶ (NH₄)₂HPO₄,³²⁷ Ce(NO₃)₃6H₂O,³²⁸ Binol- and H₈-binol-based phosphoric acids,³²⁹ Polyaniline salts & complexes,³³⁰ ZrOCl₂×8H₂O,³³¹ Zeolite,³³² (L)-Pro-OMe×HCl,³³³ Cu(NTf₂)₂, or Ni(NTf₂)₂, or Yb(NTf₂)₃,³³⁴ PhB(OH)₂,³³⁵ Zn(NH₂SO₃)₂,³³⁶ Zn(NH₂SO₃)₂,³³⁷ Dowex-50W,³³⁸ RuCl₃×*n*H₂O,³³⁹ H₂SO₄,³⁴⁰ CuBr₂,³⁴¹ PEG-SO₃H/MWI,³⁴² NH₄Cl/ultrasound irradiation,^{33(a)} Sr(NO₃)₂,³⁴³ H₃PMo₁₂O₄₀,³⁴⁴ Supported H₃PW₁₂O₄₀ or H₃PMo₁₂O₄₀,³⁴⁵ Keggin-type heteropolyacids-H₃PW₁₂O₄₀, H₃PMo₁₂O₄₀ or H₄SiW₁₂O₄₀,³⁴⁶ H₃PW₁₂O₄₀ or H₃PW₁₂O₄₀-SiO₂,³⁴⁷ Ion exchange resin Nafion NR-50,³⁴⁸ H₃PW₁₂O₄₀/SiO₂,³⁴⁹ KAl(SO₄)₂×12H₂O/SiO₂,³⁵⁰ Zn(NO₃)₂,³⁵¹ ClSO₃H,³⁵² [BPy]BF₄,³⁵³ I₂/ultrasound,³⁵⁴ H₂SO₄/MWI,³⁵⁵ β-Cyclodextrin/HCl,³⁵⁶ two-phase system,³⁵⁷ H₃PW₁₂O₄₀/MWI,³⁵⁸ Mg(ClO₄)₂/ultrasound.³⁵⁹

2005

Bi(NO₃)₃.5H₂O,³⁶⁰ Formylphenylboronic acid,³⁶¹ IL phase-linked aldehyde,³⁶² HCl,³⁶³ SrCl₂.6H₂O-HCl,³⁶⁴ H₃BO₃,³⁶⁵ TMSCl,³⁶⁶ SmI₂,³⁶⁷ FeCl₃.6H₂O,³⁶⁸ Ionic liquids (IL),³⁶⁹ Polymer-supported IL,³⁷⁰ Me₃SiI,³⁷¹ Yb(OTf)₃/chiral hexadentate amino phenol ligand,³⁷² Sulphated SnO₂,³⁷³ ZnCl₂/MWI,³⁷⁴ BiOClO₄.*n*H₂O,³⁷⁵ CoCl₂.6H₂O/MWI, MnCl₂.4H₂O/MWI, SnCl₂.2H₂O/MWI,³⁷⁶ Bi(NO₃)₃,³⁷⁷ TEBA,³⁷⁸ Polyaniline-fluoroboric acid-dodecylhydrogensulfate salt (PANIHBF₄-DHS),³⁷⁹ In(OTf)₃,³⁸⁰ RuCl₃,³⁸¹ MeSO₃H,³⁸² Sc(OTf)₃,³⁸³ MgCl₂×6H₂O,³⁸⁴ Natural phosphate doped with metal halides MCl₂

(M=Cu,Zn,Co,Ni)/PhMe,³⁸⁵ CuCl₂/LiCl,³⁸⁶ Uronium hydrogen sulfates,³⁸⁷ TiCl₄,³⁸⁸ CaAl₂Si₇O₁₈×6H₂O,³⁸⁹ Si(OEt)₄/FeCl₃,³⁹⁰ Sr(OTf)₂,³⁹¹ H₃PW₁₂O₄₀,³⁹² I₂/Al₂O₃/MWI,³⁹³ CeO₂ supported on poly(4-vinylpyridine-co-divinylbenzene)(PVP-DVB)/H₂O,³⁹⁴ Fluoroapatite Ca₁₀(PO₄)₆F₂/MCl₂/toluene (M=Zn, Cu, Ni),³⁹⁵ *n*-Bu₂SnO,³⁹⁶ [BMIm]Sac,³⁹⁷ Expansive graphite,³⁹⁸ Hydroxyapatite doped with ZnCl₂, CuCl₂, NiCl₂ and CoCl₂,³⁹⁹ NH₂SO₃H,⁴⁰⁰ *hν*/MeOH,⁴⁰¹ 1-[2-(4-formylbenzoyloxy) ethyl]pyridiniumhexafluorophosphate.⁴⁰²

2004

Bi(NO₃)₃×5H₂O,⁴⁰³ *p*-TSA/grinding,⁴⁰⁴ NaHSO₄/acetic acid,⁴⁰⁵ InBr₃/THF,⁴⁰⁶ Envirocat EPZ₁₀ (clay-supported ZnCl₂)/PhMe,⁴⁰⁷ NbCl₅,⁴⁰⁸ (L)-proline,⁴⁰⁹ H₃BO₃/glycol,⁴¹⁰ TMSCl,⁴¹¹ Ag₃PW₁₂O₄₀,⁴¹² ZnCl₂,⁴¹³ [Bmim]Cl×2AlCl₃,⁴¹⁴ IL/ultrasound,⁴¹⁵ FeCl₃·6H₂O/Me₃SiCl,⁴¹⁶ SnCl₂·2H₂O,⁴¹⁷⁻⁴¹⁸ HCl/MWI,⁴¹⁹ CaCl₂/MWI,⁴²⁰ Bu₄NHSO₄,⁴²¹ MgBr₂,⁴²² KHSO₄/glycol,⁴²³⁻⁴²⁴ Al₂O₃(acidic)/montmorillonite K10 clay,⁴²⁵ Polyaniline- Bismoclite complex,⁴²⁶ NBS/MWI,⁴²⁷ CdCl₂,⁴²⁸ I₂,⁴²⁹ I₂/PhMe,⁴³⁰ Bi(NO₃)₃×5H₂O,⁴³¹ SnCl₂×2H₂O/LiCl,⁴³² Al(HSO₄)₃,⁴³³ BiONO₃,⁴³⁴ H₃PW₁₂O₄₀,⁴³⁵ CuCl₂×2H₂O/CuSO₄×5H₂O/MWI,⁴³⁶ SiO₂/NaHSO₄,⁴³⁷ ZnI₂/high pressure,⁴³⁸ TMSOTf,⁴³⁹ In(OTf)₃,⁴⁴⁰ PVP-DVB/CuSO₄,⁴⁴¹ Mg(ClO₄)₂,⁴⁴² [Bmim]BF₄/MWI,⁴⁴³ (CH₃SO₃)₃Nd,⁴⁴⁴ MWI or EtOH/MWI, with heat sinks,⁴⁴⁵ LiOTf/MeCN,⁴⁴⁶

2003

Multistep polymer assisted synthesis,⁴⁴⁷ VCl₃,⁴⁴⁸ TAFF/neat/IR light,⁴⁴⁹ AcOH/MWI,⁴⁵⁰ LiBr,⁴⁵¹ NH₂SO₃H/ultrasound,⁴⁵² Silica sulfuric acid,⁴⁵³ Silica sulfuric acid,⁴⁵⁴ Bi(OTf)₃,⁴⁵⁵ Montmorillonite KSF clay/MWI,⁴⁵⁶ TMSI (TMSCl/NaI),⁴⁵⁷ PPA/PEG400 support/MWI,⁴⁵⁸ Yb(OTf)₃,⁴⁵⁹ Yb(OTf)₃ or Sc(OTf)₃ or La(OTf)₃,⁴⁶⁰ Yb(OTf)₃/4Å mol. sieves,⁴⁶¹ CeCl₃, InCl₃,⁴⁶² In(OTf)₃/MWI/Na₂SO₄ solid support,⁴⁶³ Al₂O₃(acidic)/MWI,⁴⁶⁴ TsOH/MWI,⁴⁶⁵ Zn(OTf)₂,⁴⁶⁶ SmCl₃×6H₂O/Montmorillonite clay/MWI,⁴⁶⁷ PPE/MWI,⁴⁶⁸ PPE/MWI,⁴⁶⁹ *hν*,⁴⁷⁰ CeCl₃×7H₂O,⁴⁷¹ InBr₃ or InCl₃×4H₂O,⁴⁷² Cu(OTf)₂,⁴⁷³ PhCH(Me)N⁺Me₂BuBr⁻,⁴⁷⁴ NH₄Cl,⁴⁷⁵ Silica/Fe (Ferrihydrite silica aerogels),⁴⁷⁶ Si-MCM-41 supported metal halides/MWI,⁴⁷⁷ H₃PW₁₂O₄₀,⁴⁷⁸ InBr₃,⁴⁷⁹ Ph₃PH⁺ClO₄⁻,⁴⁸⁰ *N*-butyl-*N,N*-dimethyl-*p*-phenylethylammonium bromide,⁴⁸¹ H₃BO₃/glacial acetic acid.⁴⁸²

2002

TsOH,⁴⁸³ LiBr,⁴⁸⁴ FeCl₃·6H₂O or NiCl₂·6H₂O,⁴⁸⁵ Yb(OTf)₃/THF,⁴⁸⁶ FeCl₃×6H₂O/MWI,⁴⁸⁷ InBr₃,⁴⁸⁸ ZrCl₄,⁴⁸⁹ [BMIm]BF₄ or [BMIm]PF₆,⁴⁹⁰ CoCl₂×6H₂O or LaCl₃×7H₂O/HCl,⁴⁹¹ SnCl₂ or CuCl₂×2H₂O or FeCl₃×6H₂O or ZnCl₂/HCl/MWI,⁴⁹² La(OTf)₃/100°C/sf,⁴⁹³ NiCl₂×6H₂O,⁴⁹⁴ InBr₃,⁴⁹⁵ Neat/MWI,⁴⁹⁶ PEG-supported/MWI.⁴⁹⁷

Over the past two decades or so a large number of publications dealt with catalyst changes rather than any major structural variations (basic skeleton and variations shall be discussed in later section). To discuss all the catalysts individually used so far, does not seem to be

possible/relevant in this account, so it is decided to present important/salient catalyst developments only.

6.1 Brønsted acids

Apart from HCl, many protonic acids like H₂SO₄, *p*-toluenesulfonic acid, methanesulfonic acid, HBF₄, molybdophosphoric acid, phenylboronic acid, PEG-SO₃H, boric acid, silica sulfuric acid, acetic acid, formylphenylboronic acid, trifluoro acetic acid, trifluoromethane sulfonic acid etc have been used in this reaction see table 4.

6.2 Lewis acids

These catalysts leave scope for further mechanistic investigations. Authors are leaving to readers to think how fast these catalysts are reported details of each and every paper are omitted in this write-up. It may not be the worth while to discuss each and every reagent here in this section it may not be possible to list all because while doing so such papers would exceed four hundred. In Biginelli chemistry Lewis acids halides, triflates and other salts of Li, Bi, Fe, Cu, Zn, Ru, Rh, W, Mo, Mg, Co, Ni, Sb, Yb, La, Zr, Ce, Sm, Sc, V, Cd, Al, Ag, Nd, Ca, I, B, Sr, Si, Nd, Nb, K, Na, Ga, Pb, Sn etc (sometimes even repeatedly in different journals) have been employed to achieve excellent yields and reduce reaction time as well (Table 4).

6.3 Ionic liquids

ILs are considered as the green solvent of present century which obey the twelve principles of the green chemistry and are extensively used as catalysts or solvent or both in the organic synthesis.⁴⁹⁸ In this decade the use of ILs in Biginelli reaction have attracted much attention either to enhance rate of reaction or to make synthetic protocol greener. In the synthesis of DHPMs a variety of ILs viz task-specific,^{263,415} Polymer-supported,³⁷¹ chiral ionic liquid¹⁹⁷ have been used like [Bmim][FeCl₄],²²³ [Hmim]HSO₄,²⁶⁴ [C₄mim][HSO₄],²⁶² [Bmim]BF₄ immobilized Cu(acac)₂,³⁰⁹ [Bmim]Sac,^{302,323,392} [Bmim][PF₆],^{490,499} [Bmim][BF₄],^{321,443} [Bmim]Cl×2AlCl₃,⁴¹⁴ n-butyl pyridinium tetrafluoroborate,³⁵⁴ tri-(2-hydroxyethyl) ammonium acetate¹⁴⁷ etc see Table 4.

6.4 Biocatalysts

Reports on an elegant use of fermenting yeast,²⁵⁰ and enzyme,^{181,500} for Biginelli reaction is described see table 4. Evidently more work is needed in the use of biocatalysts in this reaction.

6.5 Organocatalysts

For efficient production of Biginelli compound various organo catalysts like tartaric acid, oxalic acid, citric acid, lactic acid etc are also employed by authors and others.^{55,62,74,92,114,162,176,212,219}

7. Rate enhancements

In the past sonication and presently microwave irradiations are at the forefront of tools employed for time economy and rate enhancement of organic reactions.

7.1 Sonication

Though sonication of reaction mixture proved quite fruitful and there is a large amount of literature available on this topic, a detailed discussion on this topic is beyond the scope of this account as it is on general organic chemistry. As far as Biginelli reaction is concerned there are several reports,^{80,190,201,452,527,530} using this technique and along with suitable catalysts systems.

7.2 Microwave irradiations

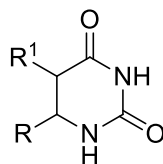
Gedye,⁵⁰¹ introduced the use of a domestic microwave oven in organic reaction in 1986. There after, there has been very fast investigation of organic reactions employing this technique and the use of microwave in Biginelli reaction is reported by Gupta and co-workers.⁵⁰² As far as our survey is concerned this seems to be first ever application in this reaction. Later on microwave is frequently used in this reaction and more than two dozen protocols are reported employing various solvents/solvent-free and catalysts/catalysts-free for detail see Table 4.

7.3 Miscellaneous processes

Other improved techniques used in this reaction are fluorous phase,⁵⁰³ solid phase,^{59,88,101,119,125,149,177,193,504} resins,^{39,110,161,169,253} nanoparticles,^{52,61,87,107,138,240} etc.

8. Biginelli scaffold variations and Biginelli-like reactions

Variations in the basic scaffold of classical Biginelli structure have attract much attention recently because these structural variations enhance the pharmacological activities of this motif. In this century, the desire for very effective drug molecules which have great pharmacological value, so in this search and to explore synthetic utility in case of Biginelli compound variation have been made at every position of the pyrimidine nucleus from N₁ to C₆.

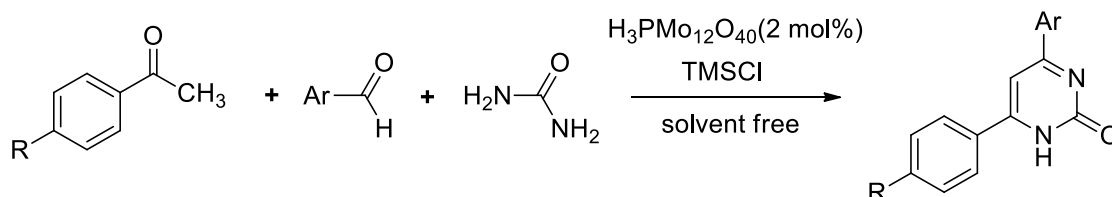
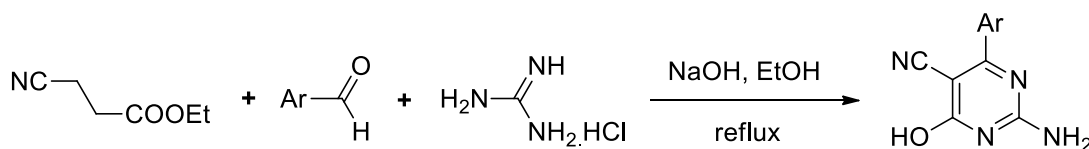
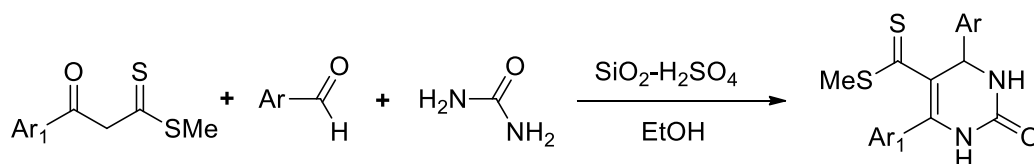


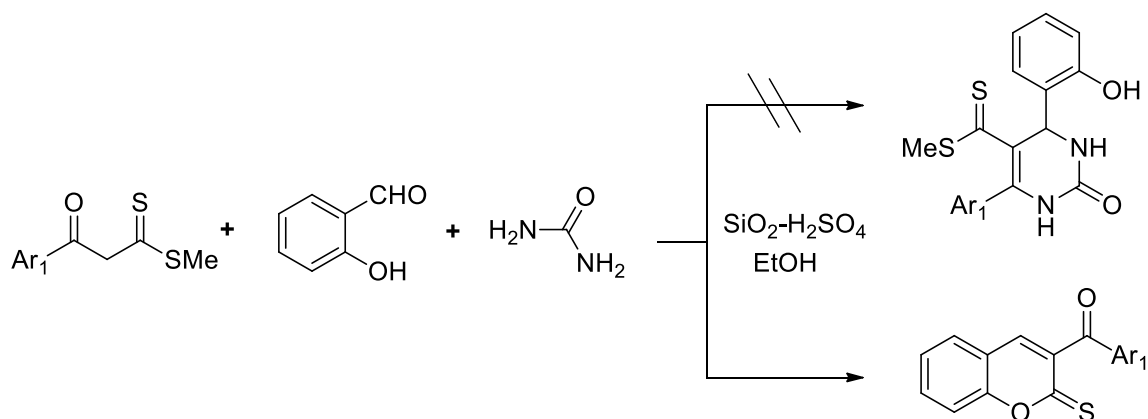
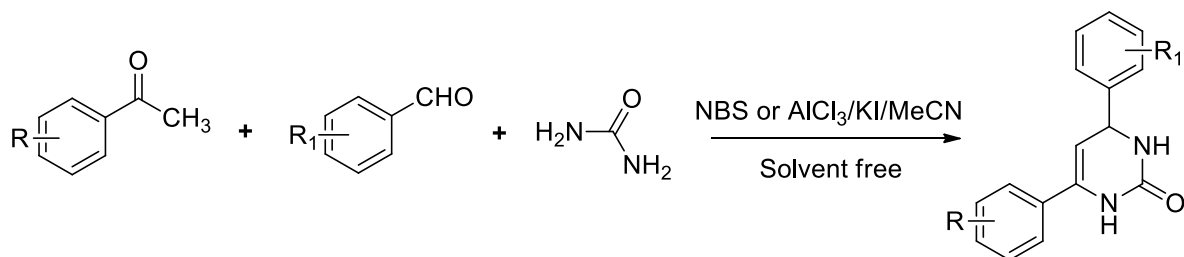
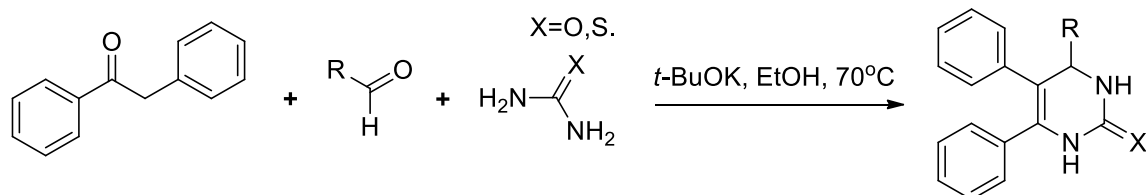
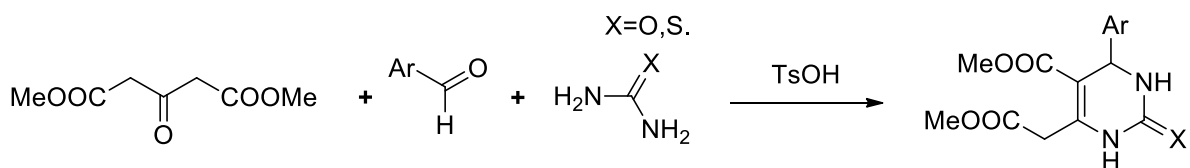
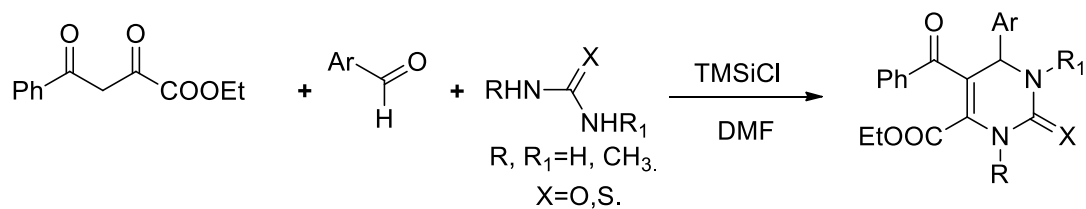
R or R¹=H, alkyl, aryl.

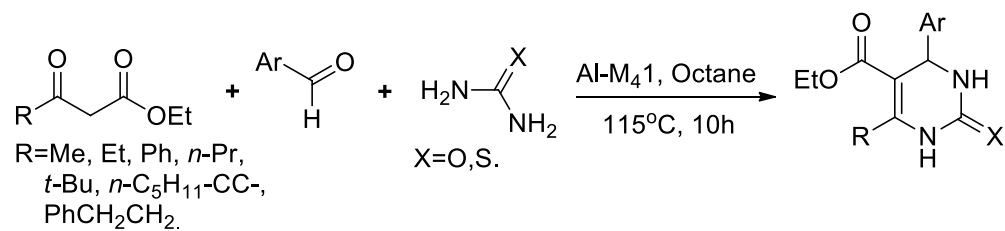
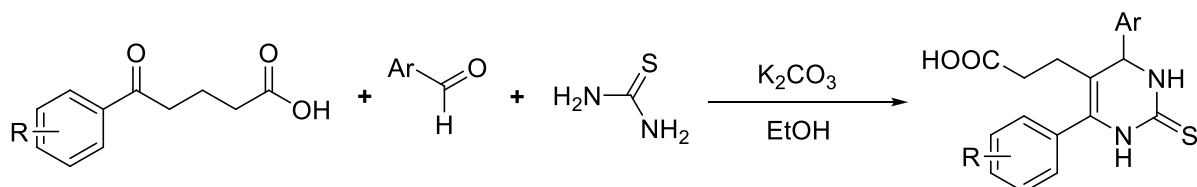
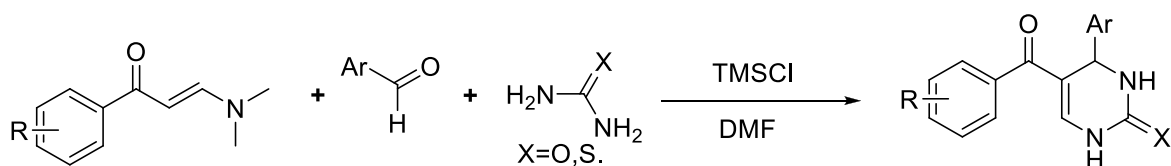
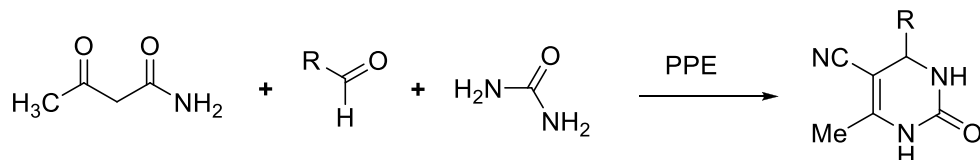
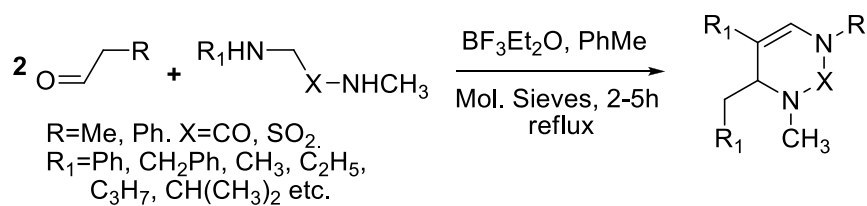
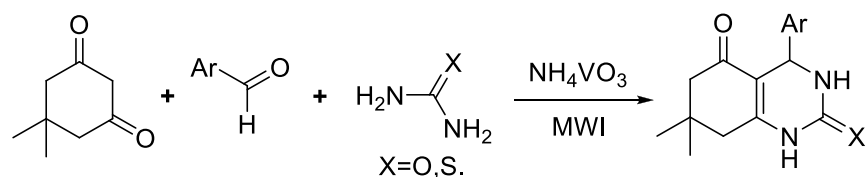
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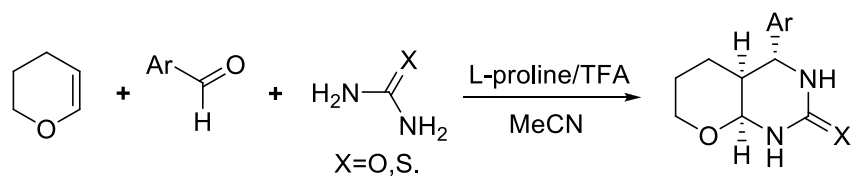
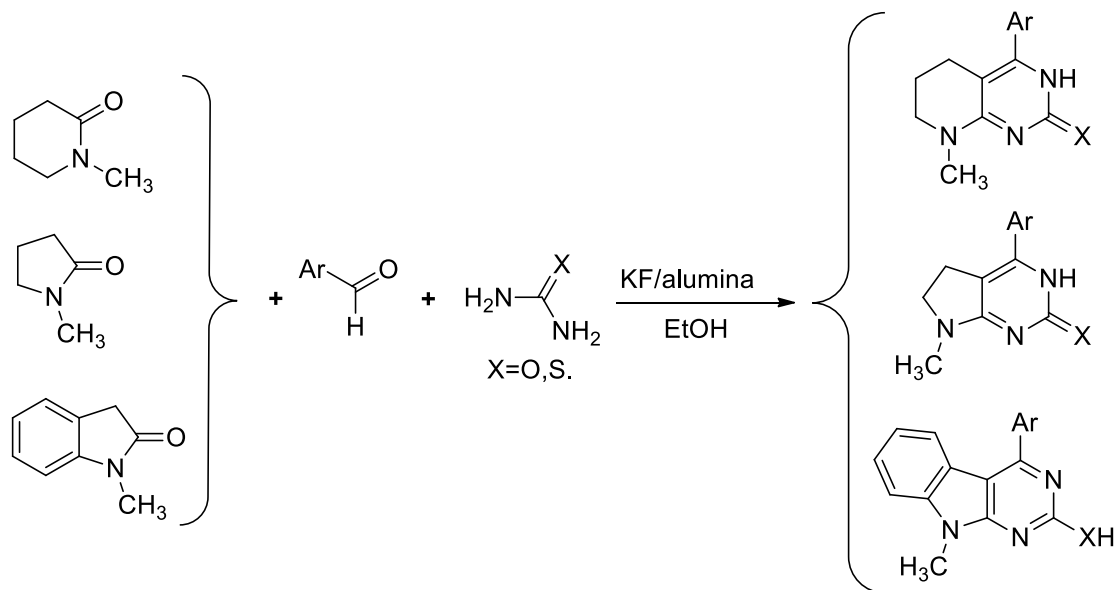
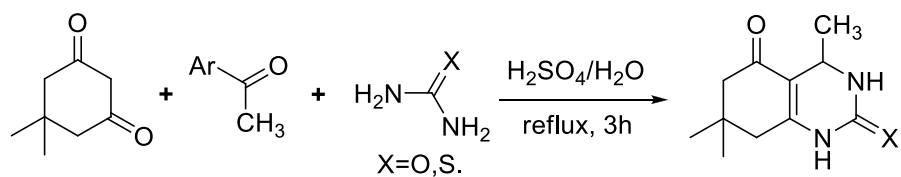
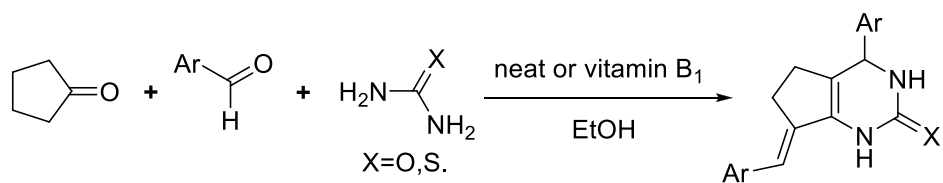
If looked at carefully in this scaffold C₆ methyl and C₅ substituents are somewhat obstacles in developing the chemistry of this molecule.^{6(b)} Both the substituents are so rigid that these can

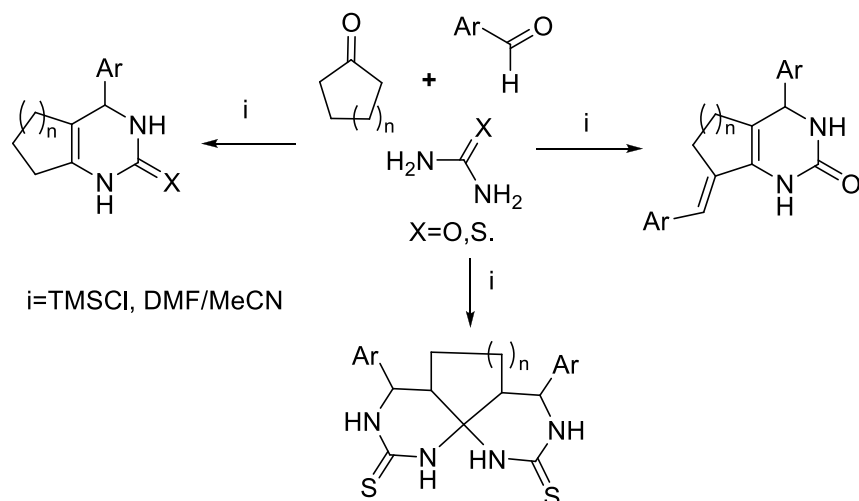
not be readily functionalized or transformed to other function. When these substituents are not there in the well known oxo-analogue **83** of this molecule C₅-C₆ bond shows the typical character of enamines and excellent chemistry is developed/being developed on this face.⁵⁰⁵ In this direction authors and others have made considerable efforts to produce C₅ unsubstituted compounds. C₅-C₆ face of Biginelli compounds has been decorated or altered by employing a variety of acyclic (see Schemes 12-24) and cyclic (see Schemes 25-31) CH-acid components viz ethyl cyanoacetate, 2-phenylacetophenone, β-oxodithioesters, dialkyl acetone-1,3-dicarboxylates, ethyl diazoacetate, 5-(4-substituted phenyl)-5-oxopentanoic acid, enaminone, oxalacetic acid, 2,4-dioxo-4-phenylbutanoate, acetophenone derivatives, 5,5-dimethyl-1,3-cyclohexanedione, 3,4-dihydro-(2H)-pyran, 1-methyl-1H-pyrrol-2(3H)-one 1, 1-methylpiperidin-2-one 2, 1-methylindolin-2-one 3, or 1,3-dimethyl-dihydropyrimidine-2,4-dione, cycloalkanones etc., see Schemes 12-30.

Scheme 12^{124,126}Scheme 13^{32b}Scheme 14⁵⁰⁶

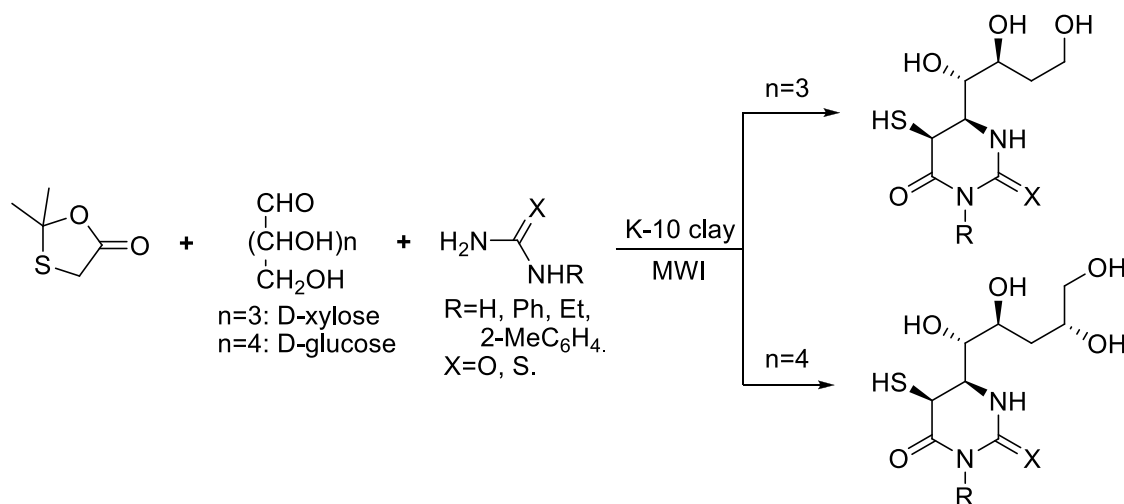
Scheme 15⁵⁰⁶Scheme 16^{160,293,507}Scheme 17^{19,134}Scheme 18¹⁹⁴Scheme 19⁶⁴

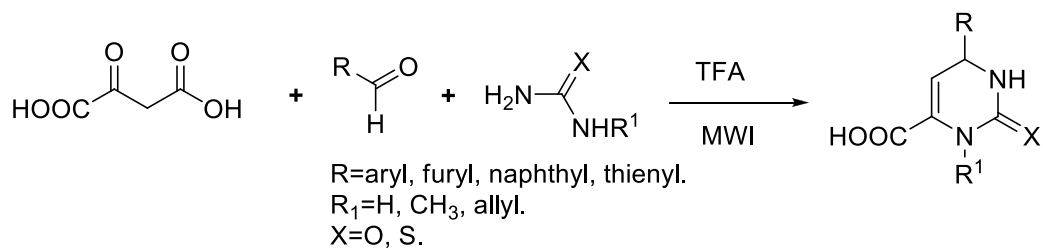
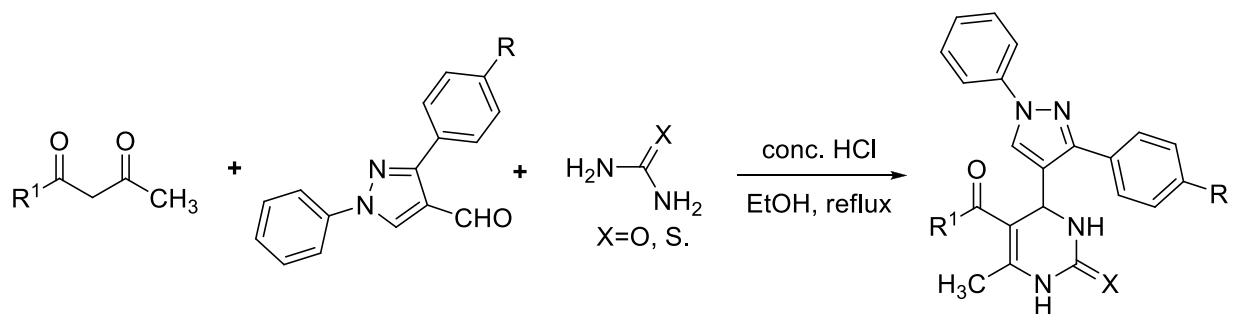
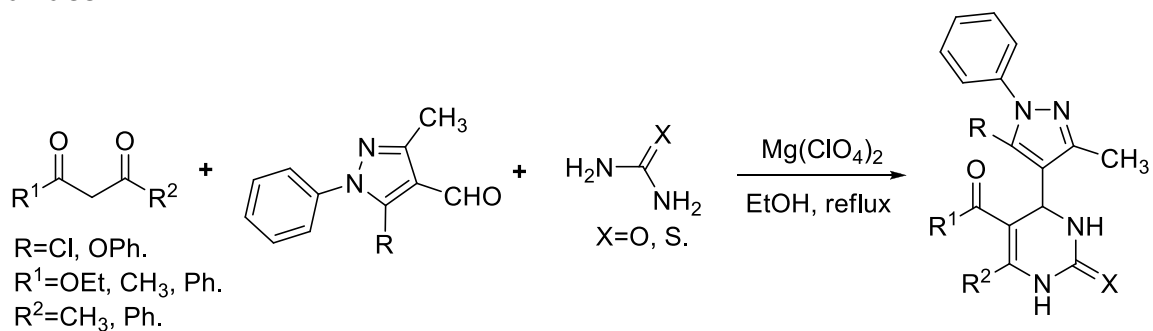
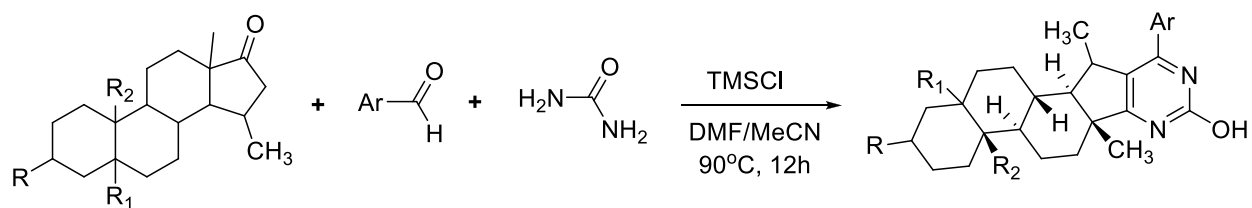
Scheme 20⁸⁷Scheme 21^{30(a)}Scheme 22¹⁷⁰Scheme 23¹⁹⁶Scheme 24³⁰⁵Scheme 25⁶⁶

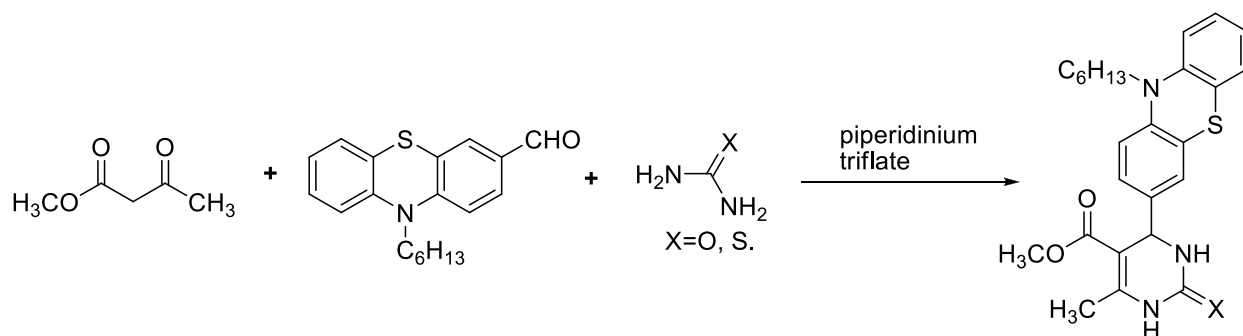
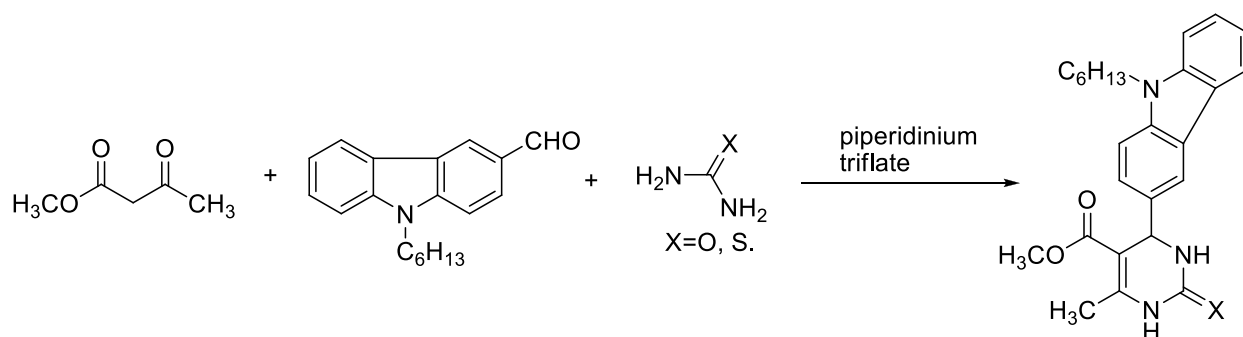
**Scheme 26**^{156,508}**Scheme 27**¹⁹³**Scheme 28**^{341,509}**Scheme 29**^{74,135}

Scheme 30³⁶⁷

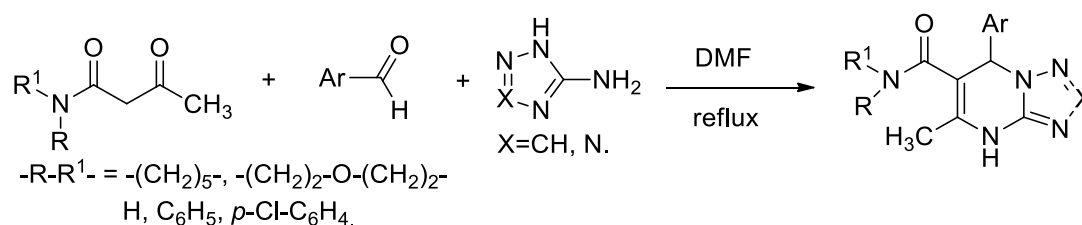
The C-4 position viz. the aldehydic part, has been modified also by different research groups to synthesize Biginelli using an unprotected aldose and 2-methyl-2-phenyl-1,3-oxathiolan-5-one as a mercaptoacetylating active methylene building block with urea/thiourea is reported and which yields diastereoselectively, thiosugar-annulated multifunctionalized dihydropyrimidines via intramolecular domino cyclocondensation reactions of an isolable intermediate Scheme 32. In another case 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones having carboxylic group at C₄ position achieved by one-pot reaction between oxalacetic acid, thiourea/urea, and aldehyde under microwave irradiation Scheme 33. Similarly 5-chloro/phenoxy-3-methyl-1-phenyl-4-formylpyrazole, steroid-17-ones etc when exchanged with aldehydes used in classical Biginelli corresponding Biginelli like products have been obtained see Scheme 31-37.

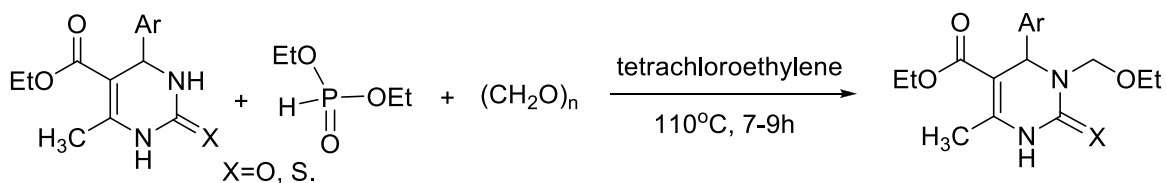
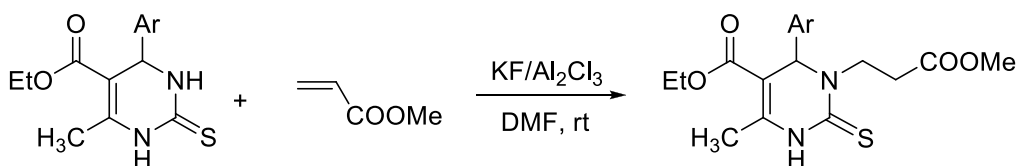
Scheme 31^{306,510}

Scheme 32⁴⁸Scheme 33⁵¹¹Scheme 34³⁶⁰Scheme 35⁵¹²

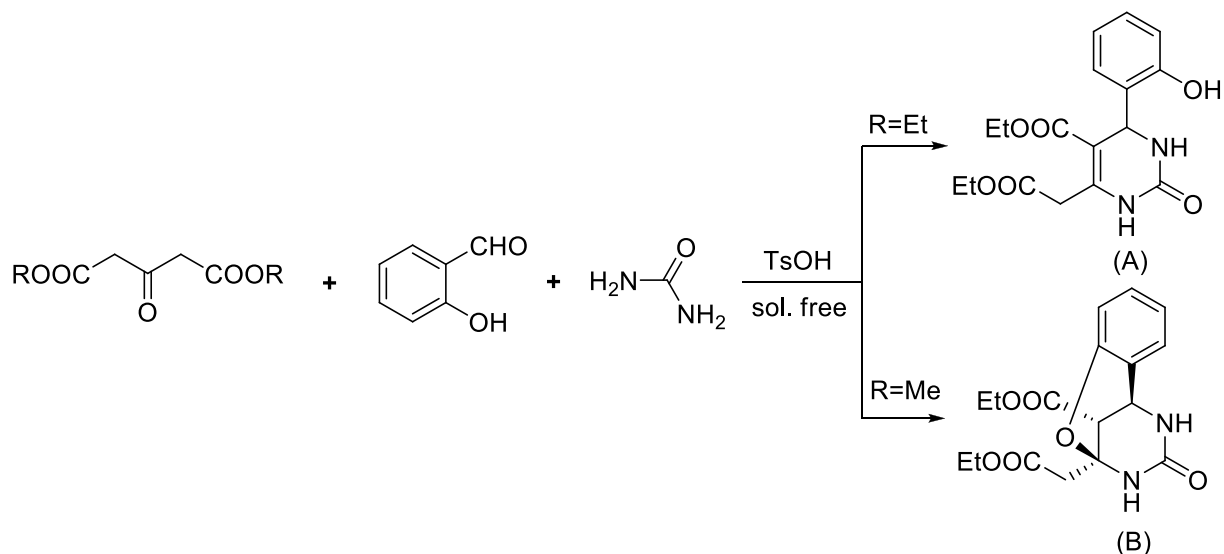
Scheme 36¹¹⁸Scheme 37¹¹⁸

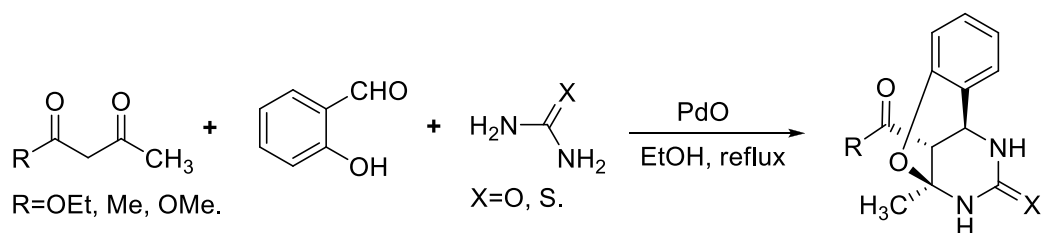
Biginelli-like cyclocondensations based on three-component treatment of 3-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and 1,3-dicarbonyl compounds (see Scheme 38) has been investigated to produce a number of novel derivatives of dihydrotriazolo- and -tetrazolopyrimidines. N-Alkoxy methylation of heterocyclic compounds with diethyl phosphite via cleavage of P-O bond was investigated and a series of N₃-ethoxymethylated heterocyclic compounds have been synthesized Scheme 39. Synthesis of N-3-substituted 3,4-dihydropyrimidinones by aza-Michael addition reactions of 3,4-dihydropyrimidinones to αβ-ethylenic compounds catalyzed by KF/Al₂O₃ has been described see Scheme 40.

Scheme 38⁵¹³

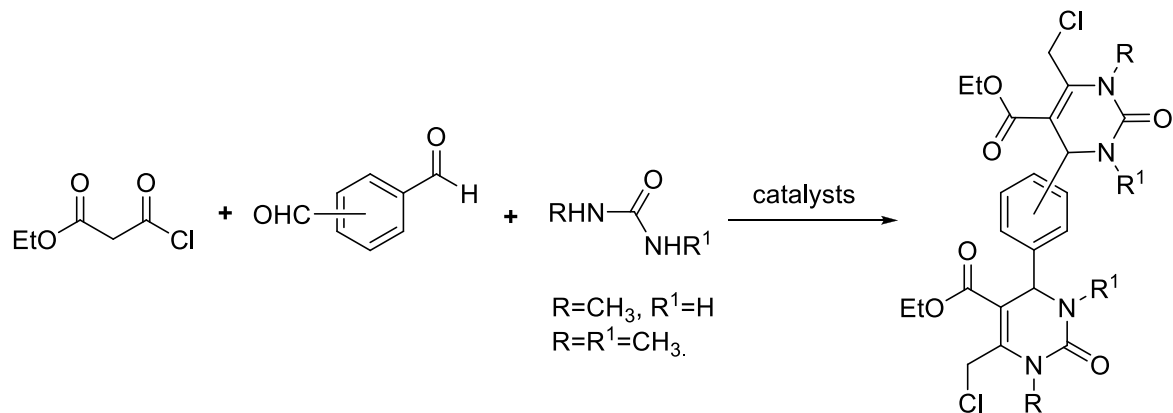
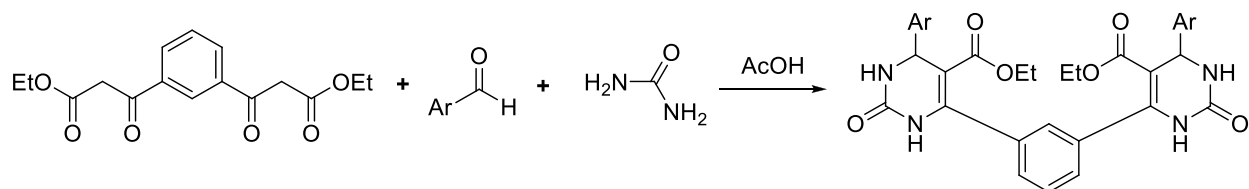
Scheme 39⁵¹⁴Scheme 40⁵¹⁵

Svetlik reported that under traditional Biginelli salicylaldehyde, diethyl acetone-1,3-dicarboxylate, and urea can be easily cyclocondensed into compound A, and if diethyl acetone-1,3-dicarboxylate is changed to dimethyl acetone-1,3-dicarboxylate, the result compound will be compound B (Scheme 41). PdO catalyzed condensation of salicylaldehyde, ethyl acetoacetate, and urea affords oxygen-bridged pyrimidine tricyclic derivatives in very good yield Scheme 42 which is investigated by Jing.

Scheme 41¹⁹⁴

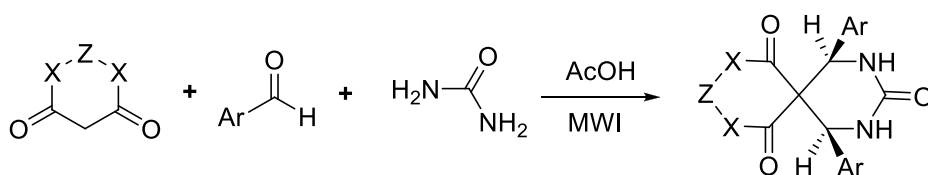
**Scheme 42**¹⁶⁸

A one-pot synthesis of bis-1,2,3,4-tetrahydropyrimidine-5-carboxylates is reported via three-component condensation of terephthalic aldehyde, 4-chloroacetoacetic ester, and ureas under Biginelli reaction conditions. Interaction of the obtained precursors that contain two highly reactive binucleophilic groups with primary amines leads to bis-heterocyclization with formation of (1,4-phenylene)-bis(pyrolo[3,4-d]pyrimidine-2,5-diones) Scheme 43. Condensation of diethyl isophthaloyldiacetate, aromatic aldehyde, and urea in the presence of TMSiCl to form 1,3-bis(2-oxo-1,2,3,4-tetrahydropyrimidin-6-yl)benzene derivatives capable to give inclusion complexes with DMF see Scheme 44.

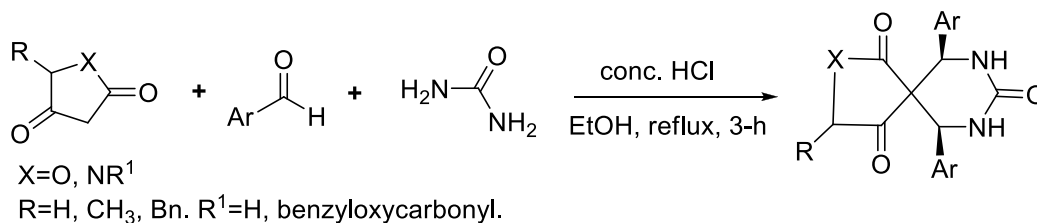
**Scheme 43**^{75,127,516}**Scheme 44**⁵¹⁷

Spiro-fused Biginelli heterocycles are synthesized by a pseudo four-component reaction of an aldehyde, urea and a cyclic β -diester or $\alpha\beta$ -diamide such as Meldrum acid or barbituric acid derivatives using microwave irradiation under solvent-free conditions in good to high yields

Scheme 45. Other cyclic β -keto ester reacts with one molecule of urea and two molecules of aldehyde to give a new family of spiro heterobicyclic aliphatic rings in good yields Scheme 46.



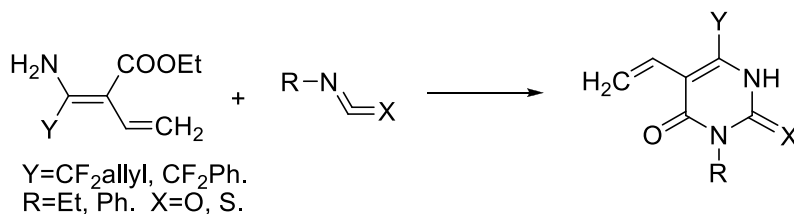
Scheme 45^{38,405,518}



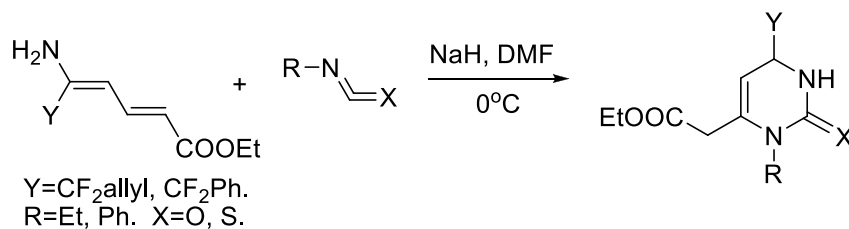
Scheme 46⁵¹⁹

A new family of 3,4-dihydropyrimidinones (DHPMs) bearing fluorinated substituents at C-6 have been prepared from gem-difluorinated nitriles, alkyl 3-butenates and iso(thio)cyanates via tandem nucleophilic addition aza-Michael reaction Schemes 47 and 48. Hetero Diel-Alder reaction on Biginelli substrate is also reported Scheme 49.

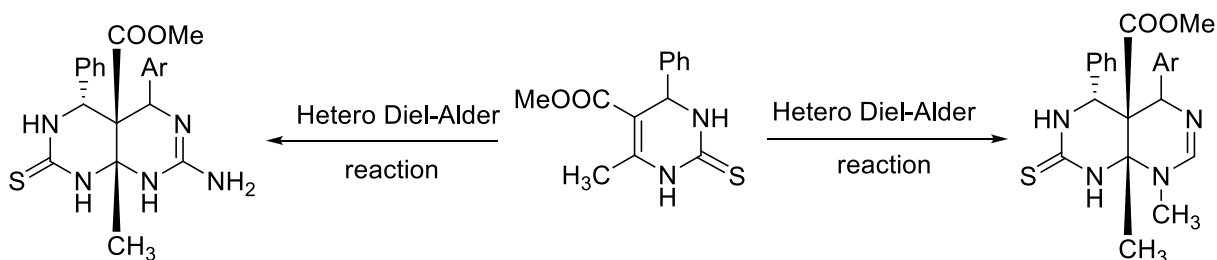
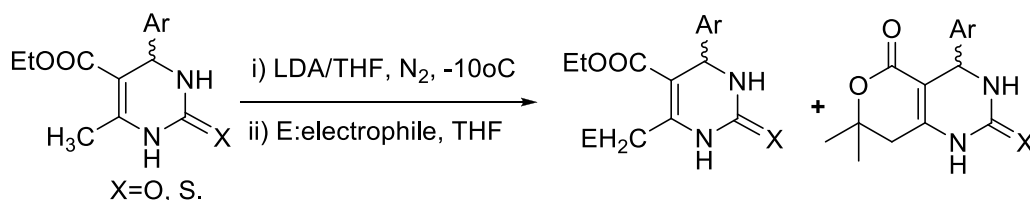
Another important report worth mentioning is variation in the C₆methyl group, a development by Kamaljit Singh and co-workers: Scheme 50.



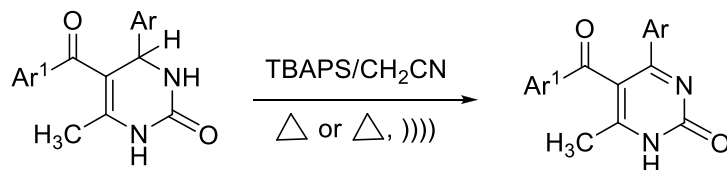
Scheme 47⁵²⁰

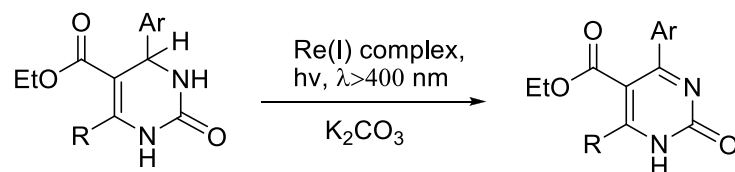


Scheme 48¹⁵¹

Scheme 49⁵²¹Scheme 50⁵²²

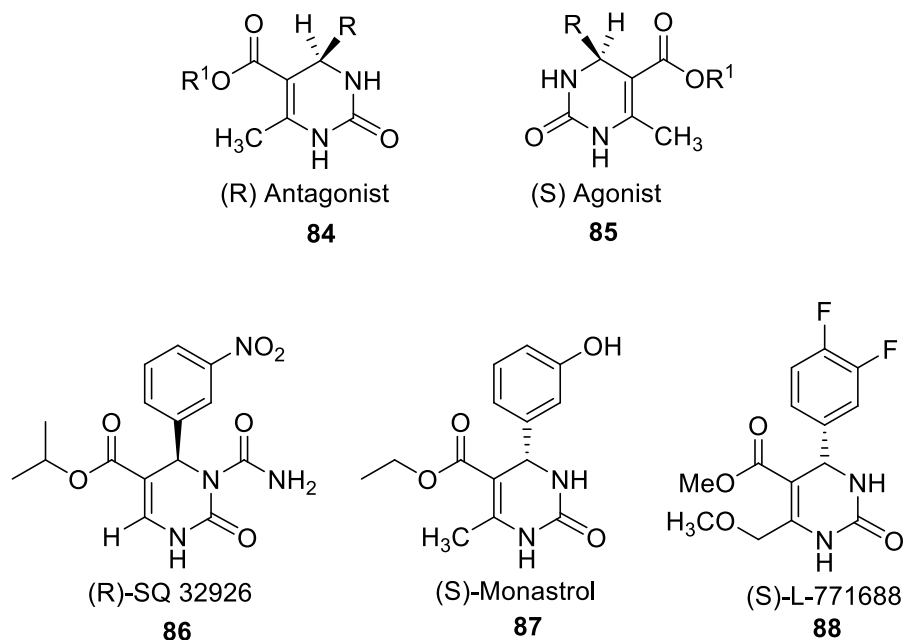
Unlike the large number of reports that are available for achieving nearly quantitative aromatization of Hantzsch dihydropyridines to pyridines *in vitro* and *in vivo*, the structurally similar DHPMs are extremely difficult to oxidize because of their higher oxidation potential compared with that of the dihydropyridines and the sensitivity of the methyl group at C-6 to oxidizing agents.^{9(a),523} Dehydrogenation of DHPMs has been attempted employing strong oxidants, like DDQ,⁵²⁴ HNO₃,⁵²⁵ TBHP/CuCl₂,⁵²⁶ CAN/NaHCO₃,³¹³ Co(NO₃)₂/K₂S₂O₈,³⁰⁸ K₂S₂O₈/ultrasound,⁵²⁷ TBHP/PhI(OAc)₂,¹⁹⁵ PCC,⁵²⁸ NaNO₂,⁵²⁹ Ca(OCl)₂,⁵³ etc. Very recently dehydrogenation of various 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides (THPMs) to 2-oxo-1,2-dihydropyrimidine-5-carboxamides (DHPMs) using tetrabutylammonium peroxydisulfate (TBAPS) as an efficient oxidizing agent under thermal and sono-thermal conditions has been investigated,⁵³⁰ (Scheme 51) and another report is of a photochemical conversion from 3,4-dihydropyrimidin-2(1*H*)-ones to pyrimidin-2(1*H*)-ones at room temperature with visible light irradiation ($\lambda > 400$ nm) of rhenium(I) complexes (P1-P4),⁵³¹ see Scheme 52.

Scheme 51^{53,308,530}

Scheme 52⁵³¹

9. Asymmetric Biginelli reactions

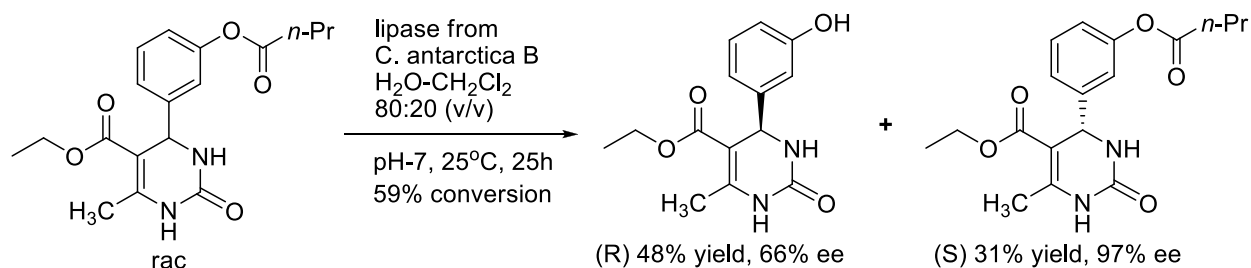
During the past few decades there has been intensive researches started to develop methods for producing/ synthesizing one or other of the enantiomers because it is a common observation that individual enantiomers exhibit unlike or even opposite **84-85** biological activities.^{6(d),6(i)} Biginelli compounds contain a stereogenic center,⁵³² and the influence of the absolute configuration on the biological activity,^{373,462,486,523,533} has been investigated e.g. in SQ 32926 the (*R*)-enantiomer **86** exhibits >400-fold more powerful antihypertensive activity than the (*S*)-isomer,⁵³⁴ and the (*S*)-enantiomer of Monastrol **87** has 15-fold more potent anti-cancer activity than (*R*)-Monastrol.⁵³⁵ In a similar way, (*S*)-L-771688 (**88**) is more potent for the treatment of prostatic hyperplasia (BPH) than the (*R*)-enantiomer.³⁵ It is also documented that the marine alkaloids i.e. batzelladine A and B in enantiomerically pure state have potential anti-HIV activity.^{22,536}



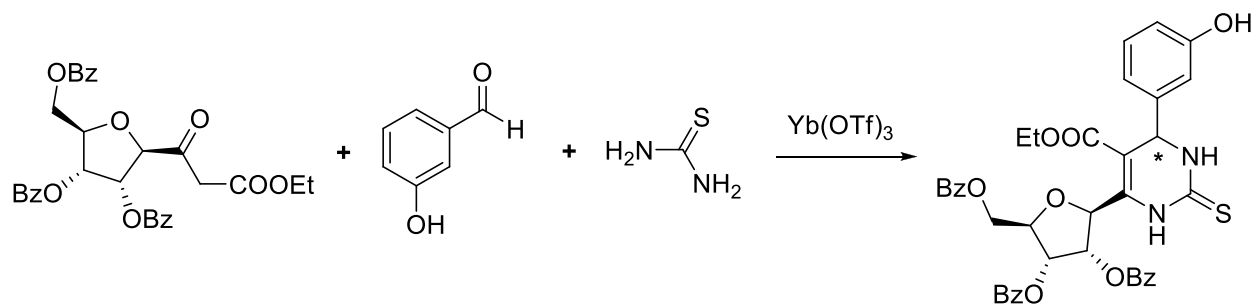
Therefore, enantio-control in the synthesis of DHPMs has been an objective of primary importance where significant pharmacological activity is concerned. Major achievements of synthetic chemists in the case of DHPMs are discussed here. In this investigation enantiomeric

pure isomers has been reported employing chiral catalysts, chiral metal complexes, chiral substrate (one of three component viz. aldehydes, urea and active hydrogen component) and enzymatic resolution of a racemic mixture.

Recently, M. A. Blasco *et al.* reported biocatalytic highly enantioselective synthesis of (*S*)-monastrol of course they used enzymatic resolution employing enzymes lipase from *Candida antarctica* B and lipase from *Candida rugosa* yielding the (*R*) enantiomer in 48% yield (66% ee) and (*S*) in 31% yield (97% ee) Scheme 53.⁵³⁷ Optically active DHPMs have also been synthesized through auxiliary assisted asymmetric Biginelli synthesis by Dondoni *et al.* using chiral starting materials such as *C*-glycosyl substrates **90**, **91** and in this investigation the synthesis of two diastereomers of Monastrol analogs bearing the ribofuranosyl moiety has been successfully achieved via formation of diastereomeric *N*-3-ribofuranosyl amides from racemic Monastrol and separation of both diastereomers and subsequent amide hydrolysis of the desired diastereomer: Scheme 54.⁵³⁸



Scheme 53

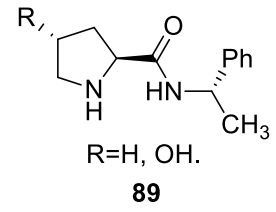
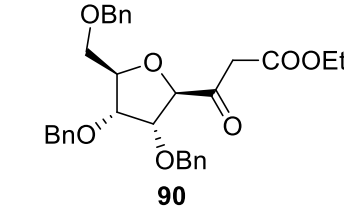
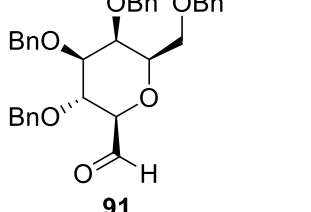
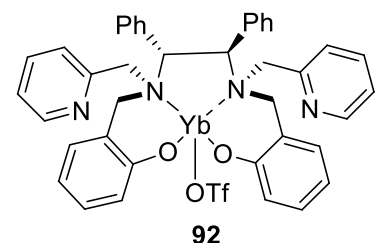
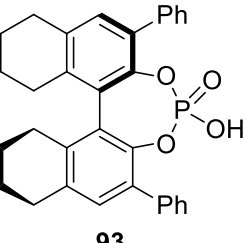
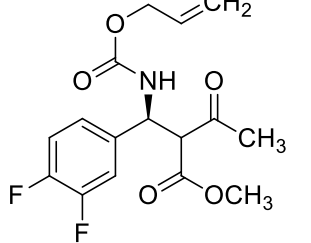
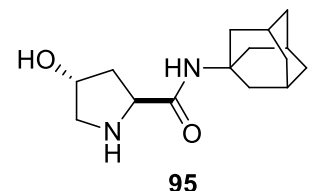
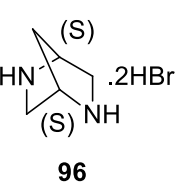
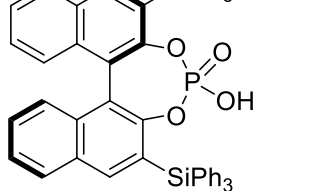
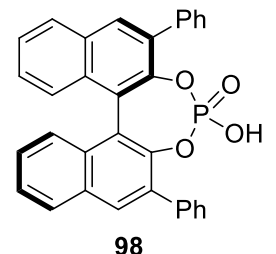
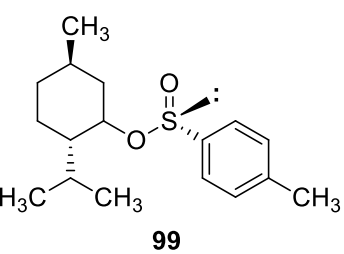
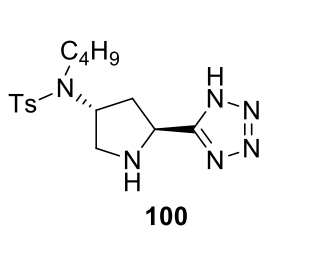
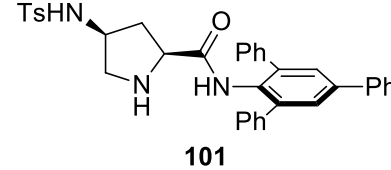
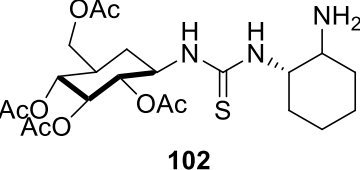


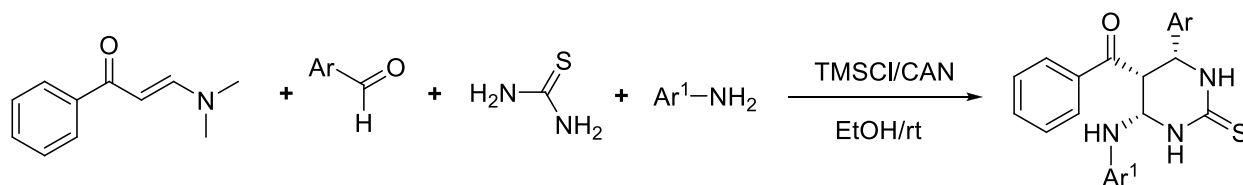
Scheme 54

Zhu and co-workers reported an enantioselective Biginelli reaction employing a chiral metal catalyst synthesized from ytterbium triflate and a hexadentate ligand **92** which afforded (*R*)-enantiomer of monastrol with 80% yield and excellent 99% ee.⁵³⁹ Catalytic amount of chiral organocatalyst based on chiral Binaphthol-derived phosphoric acid **93**, **97**, **98** leading to dihydropyrimidines with enantiomeric excess.⁵⁴⁰ Versatile organocatalytic asymmetric reactions using chiral 5-(pyrrolidin-2-yl)-tetrazole derivatives, *trans*-4-hydroxyproline derived secondary amine, (2*S*,4*R*)-4-tosylamido-*N*-(2,4,6-triphenylbenzene)pyrrolidine-2-carboxamide etc. **89**, **94**-

96, 99-102 (Table 5) in combination with achiral Bronsted acid have furnished DHPMs in good yields with excellent (up to 98%) enantioselectivity.⁵⁴¹

Table 5. Use of chiral catalysts and substrate in Biginelli reactions

 <p>89 R=H, OH.</p>	 <p>90</p>	 <p>91</p>
 <p>92</p>	 <p>93</p>	 <p>94</p>
 <p>95</p>	 <p>96</p>	 <p>97</p>
 <p>98</p>	 <p>99</p>	 <p>100</p>
 <p>101</p>	 <p>102</p>	

Scheme 55⁵⁴²

Multicomponent synthesis of tetrahydropyrimidinethiones via condensation four-component aromatic aldehyde, enaminone, aromatic amine, and thiourea also affords products with excellent diastereoselectivity at room temperature: see Scheme 55.⁵⁴²

10. Conclusions; Future Outlook

As may be seen in this account, initially there was slow activity in this reaction; later it picked up to understand the mechanism etc. In the past two decades or so after the disclosure that this structure is biologically significant, a spate of publications appeared virtually in all less known/regional and reputed international journals of organic chemistry using all types of catalysts variants, basic, acidic Lewis acids simple salts ionic liquids, nano-particles etc, and there are reports describing no catalysts is needed in this reaction. Also for optimizing the production of these compounds techniques like microwave, sonication, etc. are also reported. In these research publications quite often reference is made to C. O. Kappe's mechanism which is based on spectral data without going into actual details. Now some more mechanistic pathways/proposals are advanced which leaves a question mark on the mechanism followed in this reaction at least in the case of Lewis acids used. Certainly in each and every case there can not be single route adopted in this reaction. The real problem in this area was preparation of an optically pure Biginelli scaffold which was achieved recently and further refinements are being actively pursued by several groups. Now biological aspects of these molecules are being examined more intensively and several new activities are being observed, hopefully in near future some molecules in this class may be in clinical use which can lead to real commercial significance to these molecules.

Regarding, further synthetic advancements modification of this scaffold is being attempted and is suitably being tailored to suit the biological needs also there is a large scope of exploring cycloaddition chemistry on this molecule using the different substituents on this or using the double bond available it here is much wider scope of developments. No doubt some scattered efforts in this direction is already there. We sincerely hope that our suggestions and this account as a whole will stimulate further serious research in this still fertile area.

11. Acknowledgements

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Heterocycles and also contribute to green chemistry namely functional group transformations based on catalysts developments, including enzymes, ionic liquids etc. using green techniques like ultrasound, microwave irradiation, grinding etc. as a result of these researches 27 Ph.D students received their degrees and are established in academic and industry institutions and abroad also. His broad area of research is heterocyclic chemistry, cycloadditions 1-3 (1,3 dipolar), 1-4, inter & intera molecular ones. He has published 255 research papers in reputed journals, apart from some, patents as well as reviews and Books. He is life member of several learnt bodies of this country like, chemical society, chemical research society of India and is Fellow of National Academy of science Allahabad (FNASc) and is also fellow of Indian Science Academy (FNA), New Delhi.



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