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TETRAHYDROPYRIMIDINES VIA THE BIGINELLI REACTION: SYNTHETIC STRATEGIES AND BIOLOGICAL ACTIVITIES

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ABSTRACT

Tetrahydropyrimidine nucleus has shown a significant rise in interest in the past few years which has been commonly synthesized through the well-known Biginelli's one-pot synthesis. This review focuses on the timeline of Biginelli's reaction, starting from the discovery to the strategies used to modify the nucleus to produce various derivatives, showing significant therapeutic activities like anti-microbial, anti-diabetic, anti-inflammatory, anti-cancer, etc. The intrinsic mechanism followed, the expected intermediates in this one-pot synthesis, and the reaction conditions have also been discussed.

KEYWORDS: Tetrahydropyrimidine, Biginelli, DHPM, anti-microbial, anti-diabetic, anti-inflammatory, anti-cancer.

INTRODUCTION

Multicomponent Reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where all or most of the atoms contribute to the newly formed product. Because multicomponent reactions address both variety and complexity in organic synthesis, they have gained popularity in organic, medicinal, and combinatorial chemistry. These processes shorten turnaround times and conserve energy and raw resources.

The significant rise in interest in 1,2,3,4-tetrahydropyrimidines (THPM) throughout the past few decades may be attributed to two primary, interrelated factors. The first is that they are very simple to prepare and effective in a variety of derivatizations; the second is that 1,2,3,4-

THPM derivatives have been identified as excellent pharmacophores with a broad range of pharmacological actions.

The pyrimidine scaffold that makes up 1, 2, 3, 4-THPM is similar in structure to the nucleic acid bases present in DNA and RNA. Their function as nucleic acid bases has a major impact on medication design.[1]

The databases of PubMed, Science Direct, and scopus indexed journals were searched for suitable research articles based overview of tetrahydropyrimidines and their pharmacological activities.

HISTORY

The discovery and study of tetrahydropyrimidine, a six-membered heterocyclic compound containing both nitrogen and carbon atoms, is a significant topic in organic and medicinal chemistry. Tetrahydropyrimidines are derivatives of pyrimidines, which are well-known for their roles in nucleic acids such as DNA and RNA.[2]

Pyrimidines as a group were first isolated in the late nineteenth century, with uracil found in 1900. Uracil, cytosine, and thymine are pyrimidines and are essential building blocks of nucleic acids.

As scientists investigated hydrogenation processes and the biological functions of these molecules, the hydrogenated forms of pyrimidine, such as dihydropyrimidine and tetrahydropyrimidine, came to attention. Pyrimidines were reduced to create derivatives of tetrahydropyrimidine (THPM).[3]

The multi-component chemical process known as the Biginelli reaction was developed in 1891 by the Italian scientist Pietro Biginelli. It produces dihydropyrimidinones (DHPM), which include tetrahydropyrimidines, which are significant heterocyclic molecules. In this reaction, urea, a β-keto ester, and an aldehyde condense in an acidic environment.

Organic chemistry was developing quickly in the late 19th century as scientists looked for new methods to create complicated compounds. This larger endeavour to create effective synthesis pathways for novel chemicals with possible biological action included Biginelli's discovery. Biginelli's initial process produced ethyl 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-

tetrahydropyrimidine-5-carboxylate by reacting benzaldehyde, ethyl acetoacetate, and urea in the presence of acetic or hydrochloric acid as an acidic catalyst.

The Biginelli response did not immediately become well-known, despite its early effectiveness. The importance of the reaction was not completely understood until the middle of the 20th century, when new analytical methods and a rising interest in heterocyclic compounds were introduced. When scientists started looking into its possibilities and constraints, they found that different urea derivatives, β-keto esters, and aldehydes may take part in the process and produce a wide range of tetrahydropyrimidine derivatives.

The dihydropyrimidinone core is formed by a series of stages including the nucleophilic addition of the β-keto ester, cyclization, and dehydration after the aldehyde and urea combine to produce an iminium ion. In-depth research on this process was conducted in the second half of the 20th century.

The Biginelli reaction had a resurgence in the late 20th and early 21st centuries as chemists looked for more effective and environmentally friendly synthetic processes. Several environmentally friendly catalysts and microwave irradiation techniques were explored as modifications to the original process to increase yields and reaction speeds.[4]

Mechanism

There has been significant discussion and controversy regarding the Biginelli reaction mechanism, which has been covered in several experimental and theoretical publications. Three methods involving protonated intermediates have been postulated, as Figure 1.1 illustrates.

The first process, referred to as the "iminium route," is the result of condensation between urea and aldehyde, which produces an iminium intermediate. This intermediate then reacts nucleophilically with a benzo ester to produce DHPM. The second process using the "enamine route"a is based on the condensation of urea and benzo ester, which produces an intermediate protonated enamine that combines with aldehyde to produce the DHPM. A Knoevenagel-style reaction mechanism is a part of the third mechanism. A carbenium ion intermediate is created by the reaction of aldehyde with β-keto ester, and this intermediate interacts with urea to produce the DHPM.[5,6]

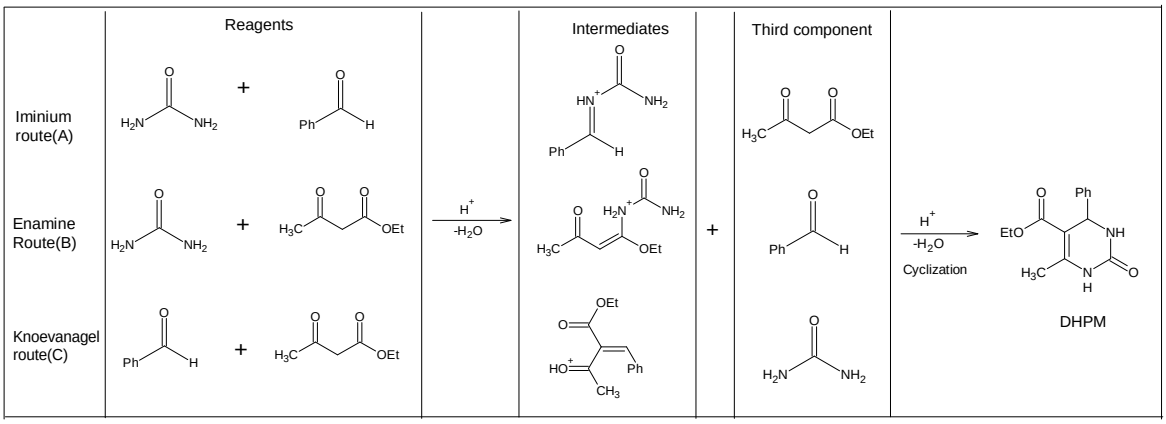


Fig. No. 1.1: Routes followed in Biginelli Reaction.

Catalysts and Conditions

Catalysts

The Biginelli reaction, the main method for the synthesis of dihydropyrimidinone (DHPM) compounds, has been studied with a variety of catalysts, including acidic catalysts to determine whether the reaction needs a catalyst at all or whether something can cause it to work. Various catalysts have been explored to optimize the Biginelli reaction, encompassing biocatalysts, Brønsted/Lewis acids, heterogeneous catalysts, and organocatalysts, among others. Nanocatalysts have emerged as a particularly promising avenue for enhancing both the environmental sustainability and reaction kinetics of the Biginelli reaction.[7] Some evidence indicates that the reaction can proceed successfully without catalysts, especially in solvents such as acetic acid/ethanol mixtures or pure dimethyl formamide (DMF). Also, other techniques such as microwave irradiation or reagent fusion have been successful without the need for catalysts. Sodium chloride has also been proposed as a catalyst, emphasizing the versatility of the catalysts required in this reaction.[8,9]

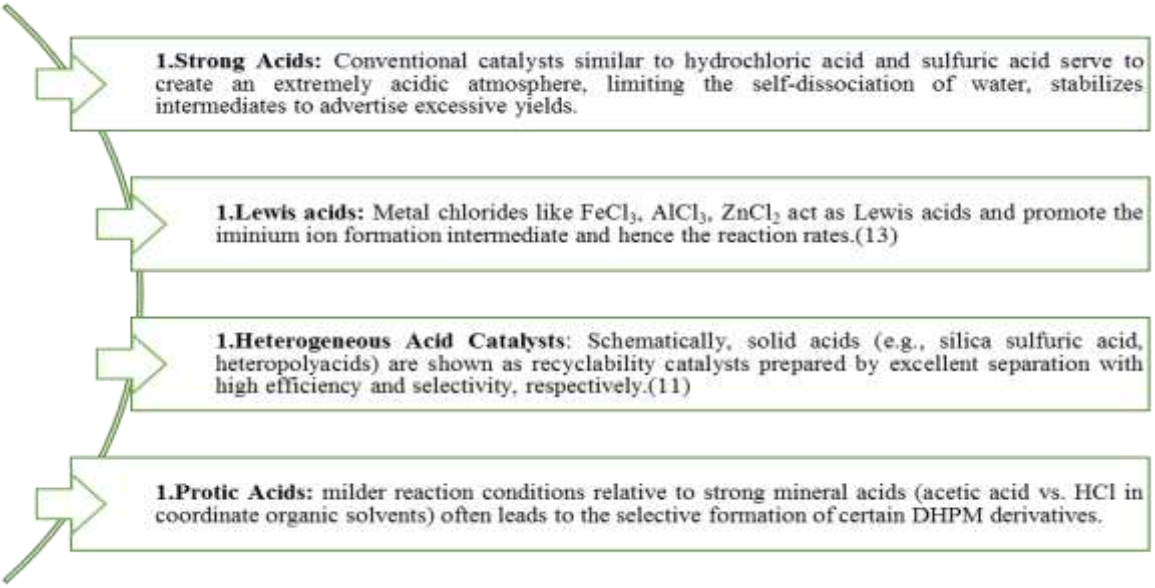
Nevertheless, asymmetric catalytic Biginelli reactions employing chiral acids have demonstrated promise in terms of enantioselectivities, highlighting the need for a catalyst in some circumstances. Important intermediates such as disubstituted urea are formed during the Biginelli condensation method and can combine with β-dicarbonyl compounds to produce DHPMs. Remarkably, in acidic circumstances, unsaturated carbonyl species may also take part in the reaction, however longer reaction periods are needed.[10,11]

The Biginelli reaction has been extensively studied since the mid-1930s, with early research relying on acid catalysis. Recent studies have further elucidated the mechanism, emphasizing the role of bis-ureides in DHPM formation. Polymer binding of acetoacetate has been shown

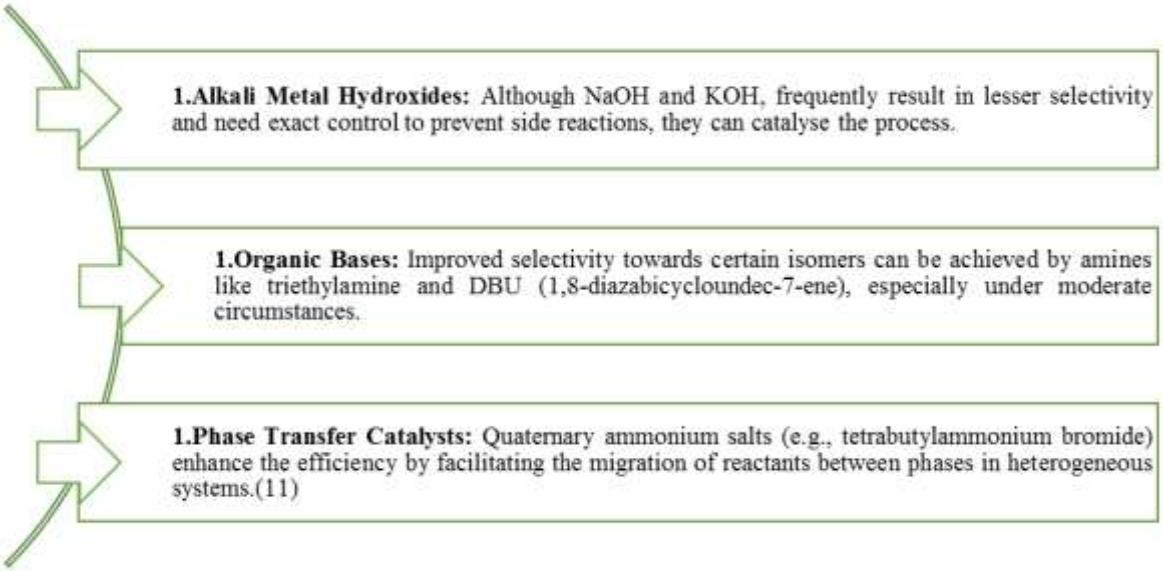
to initially precipitate the bis-ureides, which eventually convert to DHPM over a longer reaction time.[12]

Ultimately, although the Biginelli reaction may occur in a variety of settings, including the absence of catalysts, the search for novel catalysts is still ongoing. The efforts involved are motivated by non-scientific as well as scientific causes. Despite this, improving the Biginelli reaction's efficiency and usefulness in organic synthesis still depends on comprehending the reaction mechanism and investigating substitute catalytic techniques.[11]

Acidic Catalysts



Basic Catalysts



Reaction Conditions

While reactions carried out at room temperature tend to be more selective but slower, higher temperatures in the Biginelli reaction typically enhance reaction speeds but may compromise selectivity and cause undesirable side reactions. Another important consideration is the kind of solvent used; polar solvents, like as methanol and ethanol, frequently increase reaction speeds and yields, but non-polar solvents may promote the synthesis of certain products because of variations in solubility. Benefits like improved atom economy and decreased waste can be obtained in solvent-free conditions, although careful control over other reaction parameters would be necessary.

Another method that can drastically shorten reaction times and increase yields is microwave irradiation, which also frequently results in improved selectivity because of uniform heating. Comparably, reactions aided by ultrasound have the potential to generate greater yields through enhanced mass transfer and shortened reaction durations. Ionic liquids offer special environments that improve selectivity and efficiency, frequently enabling reactions to happen under gentle circumstances. They can operate as both solvents and catalysts.[13]

These various catalysts and reaction conditions offer versatile approaches to optimizing the Biginelli reaction, balancing efficiency, selectivity, and sustainability.

Synthetic Approaches

Classical Biginelli Reaction

In 1893, P. Biginelli described the acid-catalyzed cyclocondensation reaction involving ethyl acetoacetate, benzaldehyde, and urea. The reaction was performed by heating a mixture of these three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. Upon cooling, the product, 3,4-dihydropyrimidin-2(1H)-one, precipitated out. This novel one-pot, three-component synthesis is now known as the "Biginelli reaction," "Biginelli condensation," or "Biginelli dihydropyrimidine synthesis." Initially, urea, an aromatic aldehyde, and a β-ketoester were usually utilised in this cyclocondensation procedure. However, by changing any one of the three building ingredients, this synthesis's scope has been substantially enlarged and a vast range of multifunctionalized pyrimidine derivatives have been made possible. The Biginelli condensation is highly dependent on the amount of acidic catalyst present in the reaction medium. Traditionally, strong Brønsted acids like hydrochloric or sulfuric acid have been used. However, the current preference is for Lewis acids such as BF_3OEt_2, $CuCl_2$, $FeCl_3$, or $Yb(OTf)_3$.[14]

Another economic approach to the Biginelli reaction involves using potassium hydrogen sulphate as the promoter in ethylene glycol. This catalyst is effective for both open-chained and cyclic 1,3-dicarbonyl compounds. The synthesis completes within 2 hours at 100°C, yielding very high product yields. Results demonstrated that a wide range of aldehydes can participate in this reaction, producing excellent yields (85-95%).[15]

Another traditional method, known as Grindstone Chemistry, represents a highly evolved approach derived from Toda's original method of grinding solids together to facilitate solvent-free chemical reactions. This technique has been described and its utility demonstrated through successful applications, particularly in simplifying the process of conducting the multi-component Biginelli reaction. This reaction is pivotal for synthesizing physiologically active tetrahydropyrimidinones. Grindstone Chemistry involves grinding reactants together without the use of solvents, thereby promoting eco-friendly and efficient synthesis routes. By eliminating solvent use, this method not only enhances atom economy but also simplifies the reaction setup and work-up procedures. The approach leverages mechanical grinding to initiate and sustain reactions, which can lead to improved yields and selectivity in complex chemical syntheses. The application of Grindstone Chemistry to the Biginelli reaction underscores its versatility in modern organic synthesis, offering a promising alternative to traditional solvent-based methods. Its adaptability extends to various reaction conditions and substrate combinations, making it a valuable tool for green chemistry initiatives and sustainable chemical processes.[16]

Modified Biginelli Reactions

One major drawback of the classical Biginelli procedure, apart from the long reaction times involving reflux temperatures, is the moderate yields that are frequently obtained when using more complex building blocks. Over the past two decades, numerous improved procedures for preparing DHPMs (Biginelli compounds) have been reported. (8) One such method involves using $BF_3.OEt_2$ is a promoter, as reported by Hu and Sidler.[17] Kappe and coworkers further enhanced this reaction by employing microwave irradiation with PPE, resulting in higher yields of dihydropyrimidinone products. More recently, the use of lanthanide compounds, various Lewis acids, silica sulfuric acid, and $InBr_3$ has also led to improved yields.[11] These advancements in synthetic methods have successfully addressed some of the limitations of the classical Biginelli reaction, offering more efficient and higher-yielding alternatives.

Urea modification

The Atwal modification was the first significant alteration of the urea counterpart in a Biginelli-type reaction.

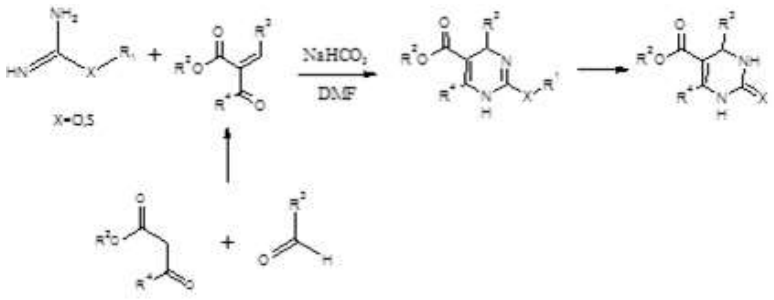


Fig. No. 1.5a: Atwal modification reaction.

This method included condensing O, S-substituted isoureas in a basic media together with a premade unsaturated carbonyl compound. By using this technology, the Biginelli synthesis was able to be carried out more efficiently, particularly when dealing with aliphatic and aromatic aldehydes that were somewhat inhibited by ortho-substituents. Via Knoevenagel condensation, the equivalent β-keto esters and aldehydes were synthesised separately to provide the unsaturated carbonyl compound.[18]

Using this method, Rovnyak et al. synthesised readily functionalized α-benzylidene β-keto esters as the starting point for specifically designed dihydropyrimidines. The purpose of synthesising these derivatives was to determine structural and conformational factors in calcium channel regulation. A basic medium could be used to perform the classical three-component reaction with O-methyl isourea, ethyl acetoacetate, and substituted benzaldehydes to form DHPMs. These compounds were then derivatized through a selective reaction with phenacyl bromides at N3, yielding derivatives that demonstrated good antihypertensive, anti-inflammatory, and analgesic activity, along with low ulcerogenic activity. Preformation of the α-benzylidene β-keto esters was not always required.[19]

One of the most effective ways to synthesise selenium-containing heterocycles is to start with selenourea. This starting material has been used to prepare selenoxopyrimidines through an acidic one-pot multicomponent reaction with ethyl acetoacetate and aromatic aldehydes.[20]

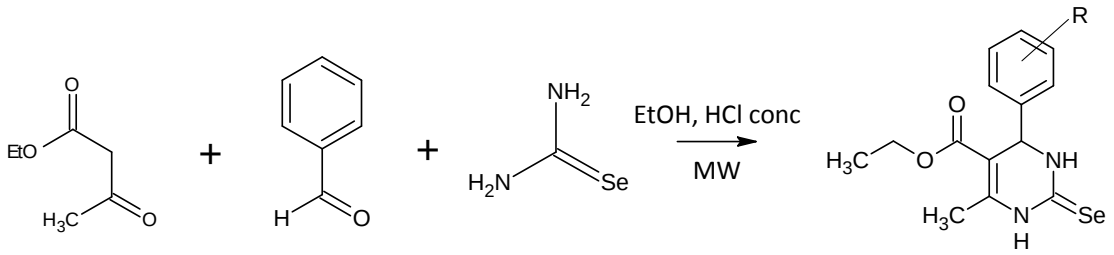


Fig. No. 1.5b: Chemical reaction of selenium-containing heterocycles.

Aldehyde modification

Dihydropyrimidones were synthesised recently by A. A. Malik and colleagues using the sequential Kornblum oxidation/Biginelli reaction. Benzaldehydes are produced in situ from benzyl halides in a catalyst-free process, and they are then transformed into dihydropyrimidones in a single pot using microwave (MW) radiation. The oxidation of benzyl halide to aldehyde under Kornblum oxidation conditions was a crucial step in this transition. When DMSO was used as the solvent and no catalyst was present, the reaction was carried out at 80 °C under microwave irradiation to get the best synthetic results for this oxidation.[21]

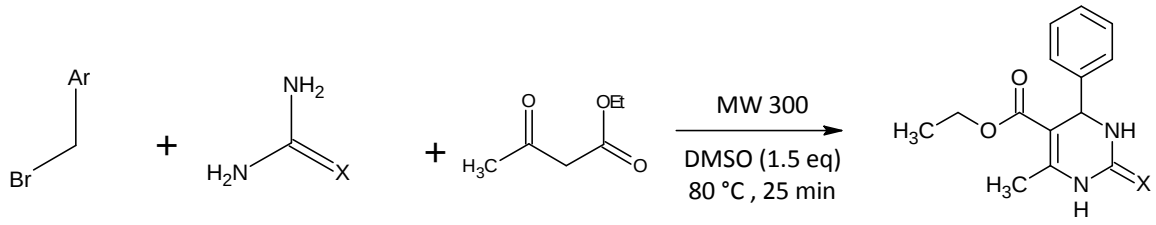


Fig. No. 1.5c: Chemical reaction of Kornblum oxidation based on microwave irradiation.

N-substituted isatins were reported to be used as carbonyl substrates in an asymmetric Biginelli-like reaction catalysed by Brønsted acid by Stucchi et al. The authors were able to achieve moderate-to-good yields of enantio-enriched spiro (indoline-pyrimidine)-dione derivatives with the use of phosphoric acid catalyst obtained from BINOL. The yield and energy efficiency were not significantly impacted by the halogen substitution at the aryl ring. Similarly, methyl and benzyl acetoacetates yielded good yields and moderate energy efficiency in the final products. On the other hand, N-Me isatin produced a higher yield (93% to up to 63%), despite having a lower energy efficiency (50% to up to 80%) than the corresponding N-benzyl, N-p-nitrobenzyl, and N-p-methoxybenzyl ones.[22]

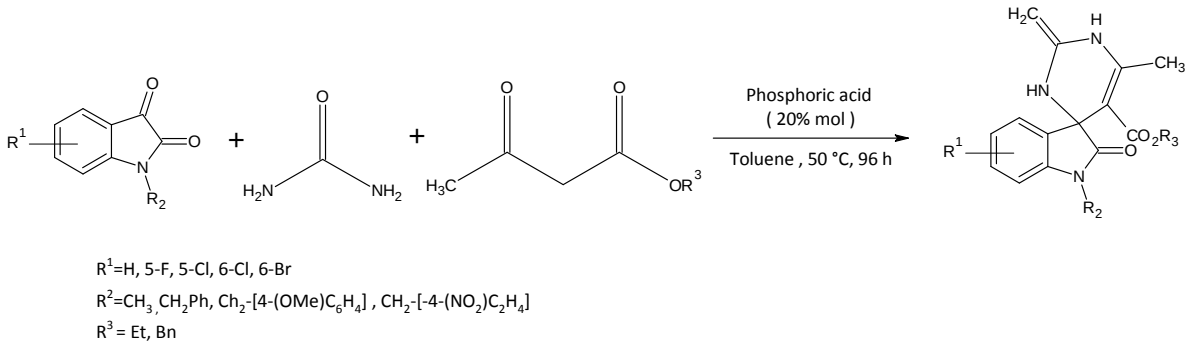


Fig No 1.5d: Chemical reaction of spiro(indoline-pyrimidine)-dione derivatives with the use of phosphoric acid as catalyst.

Keto ester modification

The synthesis of 5-acetyl-6-methyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-3,4-dihydropyrmidin-2(1H)-thione is a recent example of the use of acetylacetone as the 1,3-dicarbonyl compound in the Biginelli reaction. This compound was achieved in high yield by one-pot three-component synthesis using $CaCl_2$ in refluxing EtOH. The authors used this compound as the starting material to synthesise a new series of 5-pyrazolyl; isoxazolyl; pyrimidinyl derivatives as well as fused isoxazolo[5,4-d]pyrimidine and pyrazolo[3,4-d]pyrimidine. These compounds were assessed for their antibacterial, antifungal, and anti-inflammatory properties.[23]

Synthesis of novel Biginelli 1,4-dihydropyrimidines using p-toluene sulfonic acid as a catalyst, a multicomponent cyclization process including aliphatic, aryl, and heteroaryl aldehydes, o-methyl acetoacetanilide, and excess urea or thiourea in 100% ethanol produced the required compounds by parallel synthesis.[24]

Synthesis of pyrimidinethione derivatives by the condensation of substituted acetophenones, a pyrazol-4-carbaldehyde, thiourea and sulfamic acid as the catalyst in presence of TMSCl encouraged the intermediates DHPMs to aromatize.[25]

Starting with phenylacetylene, 1-azidopropan-2-one, urea, and aromatic aldehydes, the monotriazole-DHPM hybrids were created using a one-pot multicomponent process comprising a copper (I)-catalyzed alkyne-azide cycloaddition (CuAAC) and a Biginelli-like reaction. Conversely, the ditriazole-DHPM hybrids were produced by a multistep series of reactions that comprised bromination, azidation, and a CuAAC.[26]

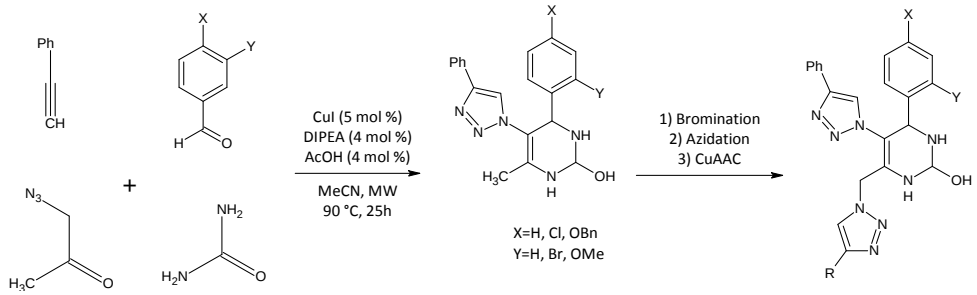


Fig No 1.5e: Chemical Reaction of Monotriazole and Ditriazole-DHPM hybrids.

Pharmacological Activities of Tetrahydropyrimidines

Antimicrobial activity

Marisa Castro Jara et. Al., showed that following 3 biginelli compounds exhibited strong antibacterial activity *in vitro* against hospital microbes that are resistant to many drugs. Additionally, the cytotoxicity analysis demonstrated the specificity of each compound's antimicrobial effect by showing no discernible harm against mouse fibroblast cell lines at the highest dose tested. Antibacterial activity was demonstrated by all three compounds against gram-negative bacilli and Gram-positive cocci.[27]

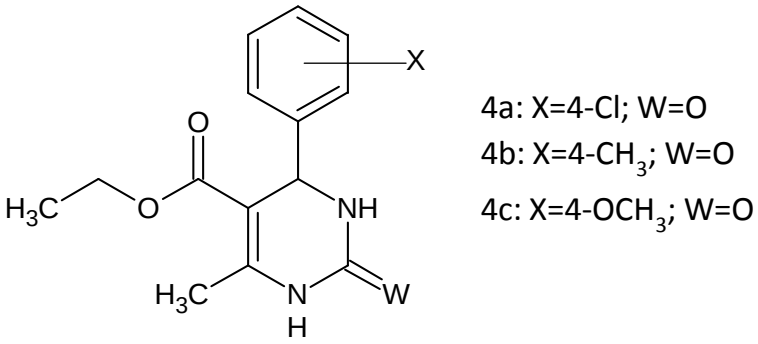


Fig. No. 1.6a: Derivatives showing antibacterial activity.

D. Priya Matharasia demonstrated that, in comparison to the common therapy-streptomycin, compound 6M3NP demonstrates good microbiological action. It displays a significant inhibition zone surrounding the site, in relation to the reference, which indicates how susceptible microbes are to the 6M3NP.[17]

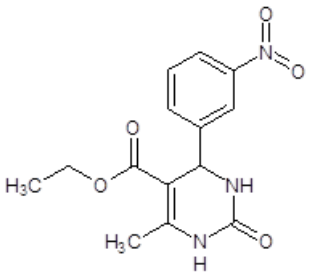


Fig. No. 1.6b: 6M3NP.

Saifudin A et. al., using ampicillin and erythromycin as positive controls, the well technique conducted an antibacterial test against *S. aureus, E. coli, and P. aeruginosa* in Mueller-Hinton medium (Sigma-Aldrich, USA). Every test was run independently at least three times.

Based on the E. coli test findings, compounds A and D suppressed the bacteria at minimum inhibitory concentrations (MIC) of 12.5 and 50 µg/mL, respectively. Additionally, A showed an apparent 50 µg/mL active inhibitory effect against *S. aureus* and *P. aeruginosa*. Additionally, compound C had the highest potency against *S. aureus*, with a MIC value of 25 µg/mL. It was shown that compounds A and C can serve as model compounds for the upcoming creation of compounds that are anti-*E.coli* and anti-*S.aureus*. With regards to the phenyl group, B demonstrated little efficacy against every type of bacterium. Therefore, compounds A, C, and D lost some of their antibacterial activity due to the presence of methoxy and hydroxyl groups.[28]

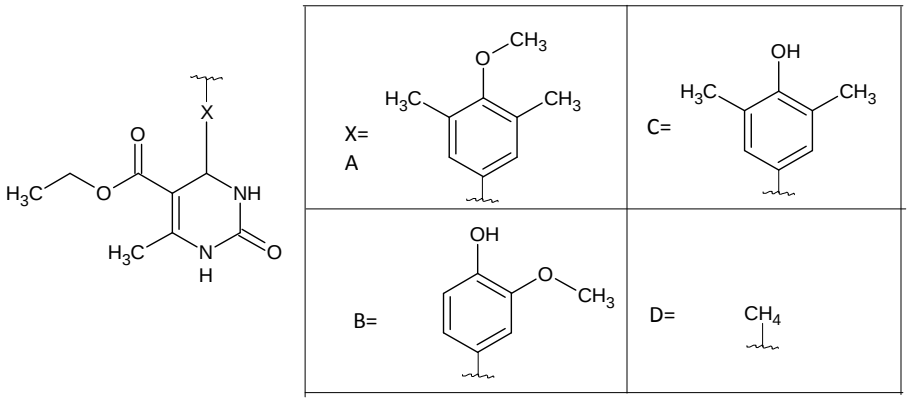
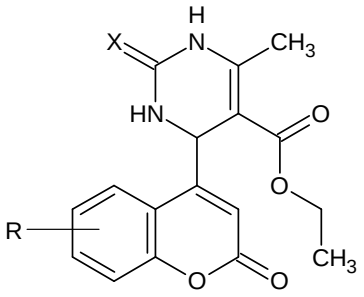


Fig. No. 1.6c: Compounds showing activity against *S. aureus* and *P. aeruginosa*.

The physiologic system contains gelatinases, which are important in inflammatory and autoimmune conditions. Dermal fibroblasts and activated inflammatory cells can release several proteinases known as matrix metalloproteinases (MMPs), which are capable of breaking down every macromolecule found in connective tissue. Among them are

gelatinases, such as MMP-2 and MMP-9, which have been shown to have a role in the remodelling of connective tissue following inflammation together with interstitial collagenase.



80a: R = 6 - OCH_3 ;X=O
80b: R = 6 - OCH_3; X=O
80c: R = OCH_3 ; X=O
80d: R = OCH_3 ; X=O
80e: R = 7-8-Benzo ; X=O
81a: R = 6 - OCH_3; X = S
81b: R = 6 -OCH_3 ; X = S
81c: R = 6 - Cl ; X = S
81d: R = 7 - Me ;X = S
81e: R = 7-8-Benzo; X = S

Fig. No. 1.6d: Scaffold for action against MMP-2 and MMP-9.

All of the compounds 80a–80e and 81a–81e were shown to be very active against MMP-2 (72 kDa gelatinase A), according to the obtained data. The compounds 80e, 81a, 81b, 81d, and 81e showed significant action against MMP-9 (92 kDa gelatinase B), whereas compounds 80b and 80d demonstrated little inhibitory effect, and the other compounds did not exhibit any activity against MMP-9.29

Anti-diabetic activity

Bairagi K *et. al.*, performed antidiabetic analysis of newly synthesised DHPM derivatives. These agents were administered in the same dose as gliclazide which is the standard drug (STD). The results of the one-way analysis of variance statistical analysis reveal hypoglycaemic activity, with a significant difference ($p < 0.01$) between the means of the treatment groups and the STZ group. Furthermore, all of the recently synthesised dihydropyrimidine compounds had an impact on blood glucose levels following diabetes induction, according to the data. In comparison to the newly synthesised compounds, standard treatment had a superior lowering impact at a dose of 50 mg/kg (dose by dose).

Table No. 1.1: Substitutions for THPM.

Compound	R^1	R^2	X
4a	3-Br, 6-OH	C_2H_5	S
4b	3-OH	C_2H_5	O
4c	3-CH_3, 2-OH	CH_3	O
4d	3-CH_3, 2-OH	C_2H_5	O

4e	3-OCH_3, 2-OH	CH_3	O
4f	3-OC_2H_5, 4-OH	C_2H_5	S
4g	4-OCH_3, 3-OH	CH_3	O
4f	4-OCH_3, 2-OH	CH_3	O

Comparing the compounds 4a, 4e, 4f, and 4g with the STZ-treated group and other newly synthesised compounds, however, showed a substantial ($p < 0.05$) reduction in blood glucose levels. The research has demonstrated that the recently synthesised dihydropyrimidine compounds have the potential to be hypoglycemic. Gliclazide showed a mean percentage reduction of 47.9%, while the corresponding values for 4a, 4e, 4f, and 4g were 18.06, 21.66, 21.76, and 20.64. Therefore, it is evident that these novel compounds have the ability to reduce high blood glucose levels since they were able to attenuate STZ-induced hyperglycemia.[29]

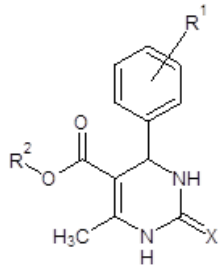


Fig. No. 1.6e: General chemical structure of THPM.

Sibtain Ahmed *et al*. synthesised 8 new compounds or derivatives of THPM in one pot strategy through a solvent free conditions and evaluated them for anti-diabetic activity. Following *in silico* and combinatorial *in vitro* studies, the compound 5g was discovered to have potential in the fight against diabetes. By creating their structural analogues or by undergoing further futural derivatization, its biological activity can be increased. Thus, all things considered, the target compounds that were synthesised turned out to be promising therapeutic agents, thereby piquing interest in pyrimidine derivatives and potentially leading to their evolution in the fields of synthesis medicine.[30]

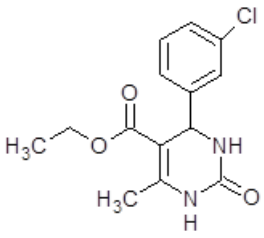


Fig. No 1.6f: The Compound 5g having anti-diabetic activity.

Anti-inflammatory

New DHPM analogues were described by Mahgoub S *et al*., and several of these scaffolds—namely, 5a, 7b, 8a, and 9a—exhibited potential anti-inflammatory effects by lowering the production of IL-6 and CRP in LPS-stimulated THP-1 cells.[31]

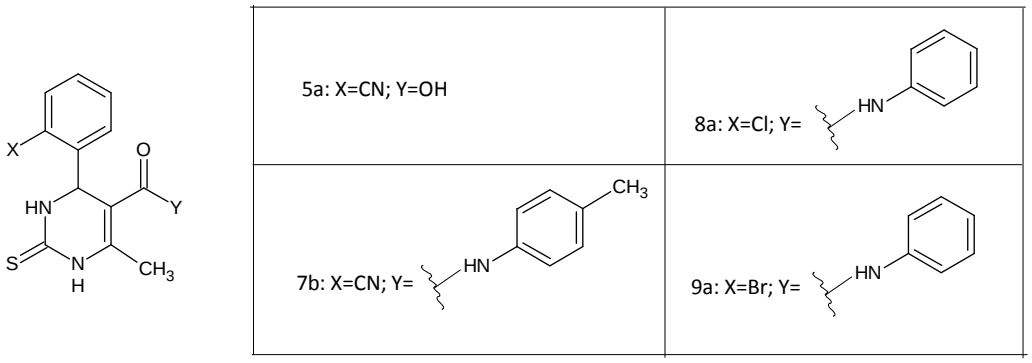


Fig. No. 1.6g: Scaffolds exhibiting potential anti-inflammatory activity.

Anticancer activity

A series of dihydropyrimidinone compounds containing different heteroaryl groups were designed, produced, and examined for their potential anticancer effects by Mostafa A *et. al.* Of all the compounds that were synthesised, compound 19 showed the strongest anticancer properties. Against the NCI-H460, SK-MEL-5, and HL-60(TB) cell lines, it had notable effects. This compound showed dual inhibition of the mTOR and VEGFR-2 pathways. Additional analysis with A549 cells demonstrated that compound 19 resulted in cell cycle arrest. The G2/M phase was the precise time of the cell cycle arrest. This indicates that it encouraged cancer cells to undergo programmed cell death. Compound 19 was notable for having strong inhibitory effects.[32]

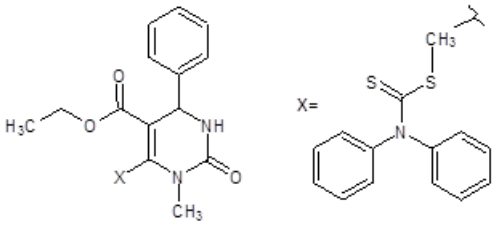


Fig. No. 1.6h: Compound 19 showing anti-cancer activity.

Jovana Ristovski *et al.*, conducted a study to evaluate 24 THPM derivatives for their anticancer study using the appropriate QSRR approach. It was shown that RP-TLC chromatography may be used to accurately estimate the retention characteristics of

structurally identical Biginelli hybrids by employing the MR1 and MR2 models. The most promising possibilities, compound 11 and 19, have good selectivity against cancer cells and acceptable pharmacokinetic qualities, according to the MTT assay.[33]

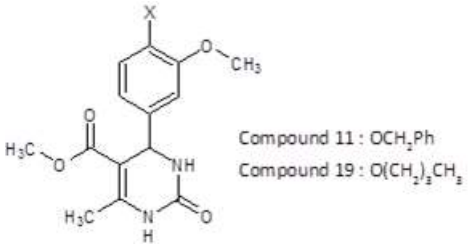


Fig. No. 1.6i: Compound 11 and 19 showing Anti-cancer activity.

CONCLUSION

Since its discovery in 1893, the Biginelli dihydropyrimidine MCR reaction has seen significant advancement. This reaction has been optimized with various catalysts, including biocatalysts, Brønsted/Lewis acids, and nanocatalysts. While some conditions allow the reaction to proceed without catalysts, chiral acids have shown promise in achieving enantioselectivity. Understanding the reaction mechanism and exploring new catalytic techniques remain crucial for enhancing the efficiency and application of the Biginelli reaction in organic synthesis.

Studies that concentrate on the mechanistic intricacies have demonstrated that iminium ion, enamine and carbenium ion species operate as an intermediary in the process. By creating vast libraries of molecules, the intriguing and diverse biological activity of dihydropyrimidines has been studied.

The tetrahydropyrimidine core's various functional groups and substitutions have a significant impact on these compounds' efficacy. For example, methoxy and hydroxyl groups tend to decrease the antibacterial activity of aromatic aldehydes, but methyl, chlorine, or nitro groups replaced in them have shown strong antibacterial activity. Remarkably, blood glucose levels have been effectively lowered by bromine, ethoxy, methoxy, and hydroxyl replacements on the aromatic ring (aldehydic part), suggesting possible antidiabetic effects.

The investigation of heteroaryl groups and modicfication of the keto-ester portion has also demonstrated a noteworthy influence on anticancer activity and anti-inflammatory activity respectively, highlighting the adaptability of DHPMs in medicinal uses. The synthesis of new DHPMs has increased significantly over the last 20 years, mostly due to the desire to improve

therapy for a variety of diseases, particularly those with high death rates like AIDS and cancer, as well as to create new treatments against resistant fungi and bacteria.

In an attempt to create new skeletons based on DHPM and bioactive chiral DHPMs, recent efforts have concentrated on creating straightforward and eco-friendly processes for the asymmetric Biginelli reaction. This move to more environmentally friendly synthesis techniques is in line with a larger chemical movement to reduce environmental effect. Significant medical issues may be addressed by further research and development in the synthesis and use of DHPMs, opening up new therapeutic and treatment options.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this review**.**

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