THE AMALGAMATION OF STRUCTURALLY DIVERSE 3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES DERIVATIVES

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Abstract

Because of their enormous biological importance, 3,4-dihydropyrimidine-2(1H)-(thio)ones are gaining more and more attention every day. The traditional method of obtaining these scaffolds is through the Biginelli reaction, albeit there are some restrictions on the product diversity. Two key strategies have been developed to get around these limitations. The first one deals with altering the traditional Biginelli reaction components, while the second one discusses altering the Biginelli products after the fact. In this paper, both tactics have undergone substantial revision. Regarding the first, it was initially discussed how to modify one of the components. The modification of the keto ester counterpart was by far the most widely used strategy, and a wide range of different enolizablecarbonylic compounds were used. Additionally, changes in two or the three components were also described, extending the range of substitutes for the final dihydropyrimidines. In addition to these adjustments, decorating the final heterocyclic structure also benefited greatly by the usage of Biginelli adducts as a starting point for additional modifications.

keywords: *Amalgamation*, dihydropyrimidine, Biginelli
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INTRODUCTION

Functionalized nitrogen heterocycles are important components of medicinal chemistry and have been employed extensively as scaffolds for the synthesis of new drugs. Because of the unique pharmacological profile that pyrimidine compounds possess, they are of special significance in this context. It is possible that the existence of a pyrimidine ring in molecules like nucleic acid, uric acid, several vitamins, and certain purines might explain the biological significance of such compounds in therapies that include them. These rings are involved in a number of biological activities, each of which is important in its own right. The pyrimidine heterocyclic ring system is the one that has received the most attention from researchers since it is found in a wide variety of bioactive natural products and pharmaceutical compounds with pharmacological action. 1-2 Because the pyrimidine ring system is present in such a wide variety of compounds, including vitamins (such as vitamin B1), medications (such as hypnotics, antibiotic, and antimalarials, etc.), and nucleic acid building blocks (such as cytosine and uracil), it has emerged as an important research topic in the discipline of science.

THREE-COMPONENT SYNTHESIS OF STRUCTURALLY DIVERSE 3, 4-DIHYDROPYRIMIDIN-2(1H)-THIONE DERIVATIVES

In the year 1893, Pietro Biginelli3 was credited with carrying out an acid-catalyzed cyclocondensation procedure consisting of ethyl acetoacetate, benzaldehyde, and urea. This method was said to have been successful. The reaction was carried out by heating a combination of the three components

dissolved in ethanol with a catalytic amount of HCl at a temperature where reflux was occurring. The reaction was brought about as a result of this. Biginelli was able to correctly identify the precipitated result of this novel three-component synthesis as dihydropyrimidin-2-one. This synthesis only required one pot and three components. After the reaction mixture had been cooled, it was discovered that this product had crystallized out of solution. The synthetic potential of this core heterocyclic approach was not examined for a substantial length of time as a result of this reason. Researchers were able to obtain access to a significant number of multifunctional zeds dihydropyridine derivatives (DHPMs) as a result of the steady development in interest in the Biginelli condensation that occurred throughout the 1970s and 1980s. This interest gradually grew over the course of these decades. As the 1980s came to a close, there was another big uptick in Biginelli synthesis, as seen by the ever-increasing volume of scholarly publications and patents devoted to the topic. One possible explanation for this rise is that more people are becoming interested in the region. There is a considerable degree of structural similarity between DHPMs and well-known 1,4-dihydropyridine calcium channel modulators of the nifedipine type. These two classes of calcium channel modulators also have comparable pharmacological properties. In point of fact, it has been shown that the aza-analogs of standard Hantzsch 1,4-dihydropyridine calcium channel modulators, such as SQ 32926 and SQ 32547, are powerful orally active antihypertensive medicines (Fig.-1).

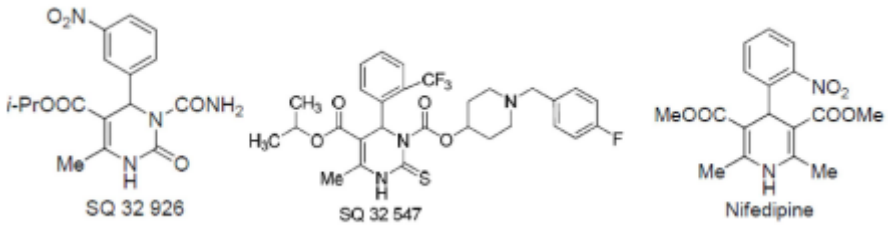


Figure 1: Antihypertensive medications that can be taken by mouth

There is some evidence to suggest that DHPMs can slow or stop the progression of cancer. 6-12 An attractive pharmacological target for the investigation and development of novel cancer chemotherapies is the human kinesin Eg5 protein. It has been proven that the compound known as substantial dihydropyrimidinemonastrol 1, which has the capacity to disrupt the action of Eg5, shows extraordinary anticancer efficacy. A different dihydropyrimidine called furyl derivative 2 had activity that was five times higher than that of the conventional medication monastrol. Researchers have discovered that a class of compounds called Hsp70 modulators, which stands for heat shock protein 70 and is also known as pyrimidinonepeptoid hybrid molecules 3, can inhibit cell growth. Trifluoromethylatedhexahydropyrimidine and tetrahydropyrimidine derivatives 4-5 also provide potential fresh leads for the creation of exceptionally effective and selective anticancer medicines, and their in vitro cytotoxic activities were also evaluated in colon cancer cell line. Both of these types of pyrimidines are derivatives of hexahydropyrimidine.

Additionally, specific DHPMs with a general formula of 6 have been found to be effective as adrenoceptor-selective antagonists for the treatment of benign prostatic hyperplasia. This discovery was made possible by recent research.

In conclusion, in addition to nonnatural DHPMs, the dihydropyrimidine-5-carboxylate core unit has been detected in some marine alkaloids that have been recovered from several species of sponges. These marine alkaloids were found to be present in these marine alkaloids. It was discovered that several of these naturally occurring compounds, specifically batzelladines A and B (Fig.2), were the first natural products with a

low molecular weight that were able to prevent the binding of HIV gp120 to CDsx4 cells. As a consequence of this, they are of significant interest as potential novel leads for the development of drugs for the treatment of AIDS. 18 Additionally, batzelladines C–E have been demonstrated to be cytotoxic, and batzelladines F and G have the potential to be useful drugs for the treatment of autoimmune illnesses as well as allograph rejection. 19 (-)-ptilomycalin A is an additional marine natural product that possesses a tricyclic guanidinium core. It was isolated from the sponge Ptilocaulisspiculifer and displayed extremely high levels of cytotoxicity in addition to antifungal and very excellent levels of antiviral activity.

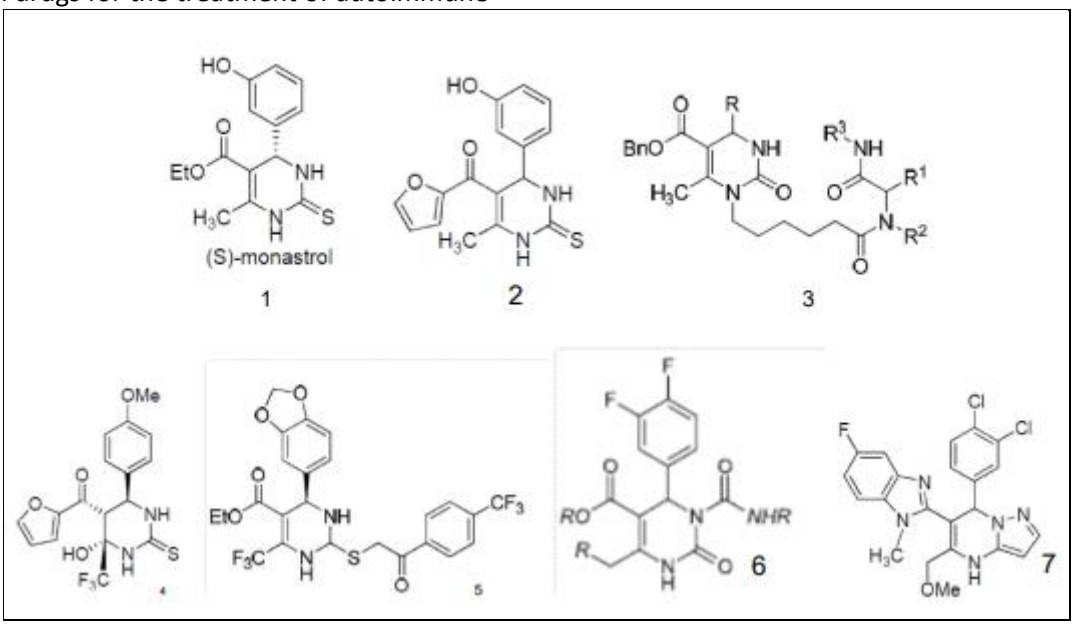


Figure 2: Molecules of Dihydropyridine That Have Biological Activity

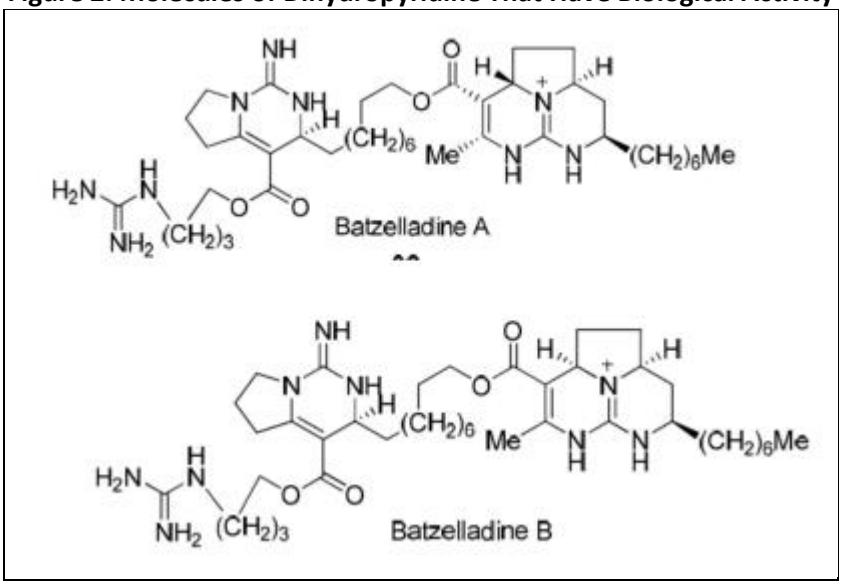


Figure 3: Natural marine alkaloids that include the DHPM core unit

The annulation of benzimidazole ring 7 with dihydropyridine revealed activity as potassium channel antagonists, and preclinical testing is currently underway for these compounds. The biological investigation of various dihydropyridine molecules through the use of molecular manipulation revealed activities such as anti-oxidants, anti-filarial, anti-inflammatory, antifungal, antitubercular,26anti-HBV (hepatitis B virus), antimalarial, and vasorelaxant, among other activities. (Fig3)

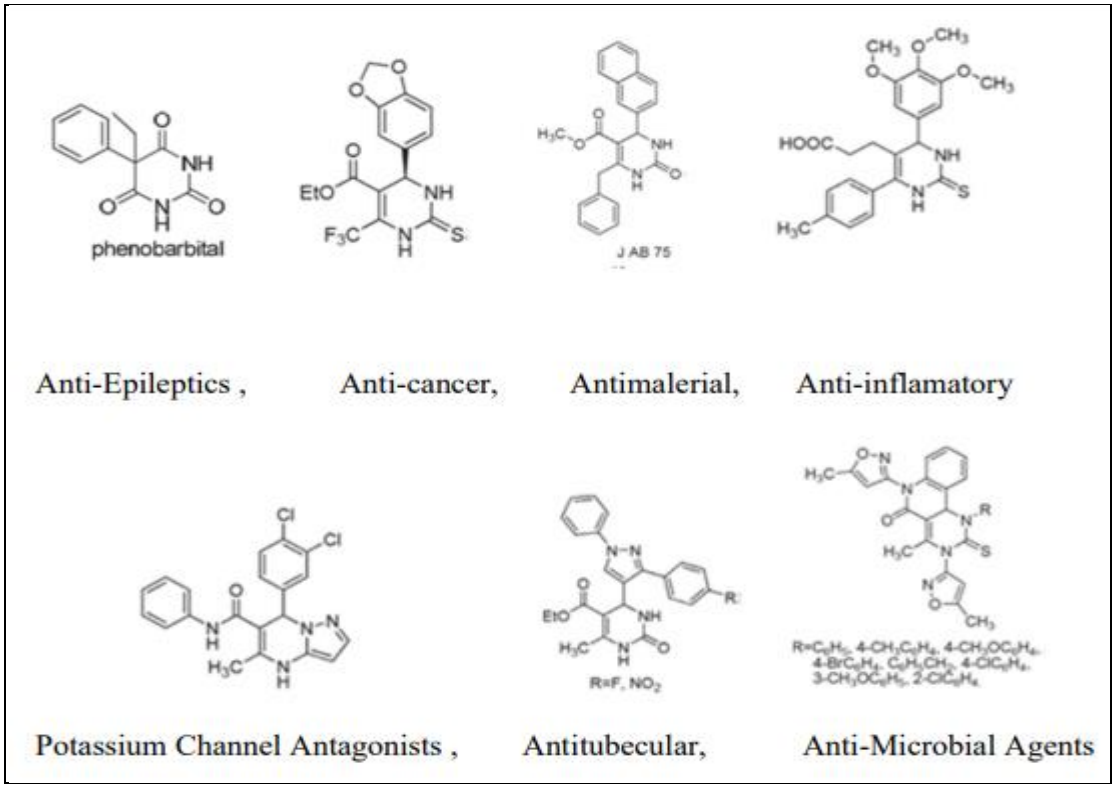


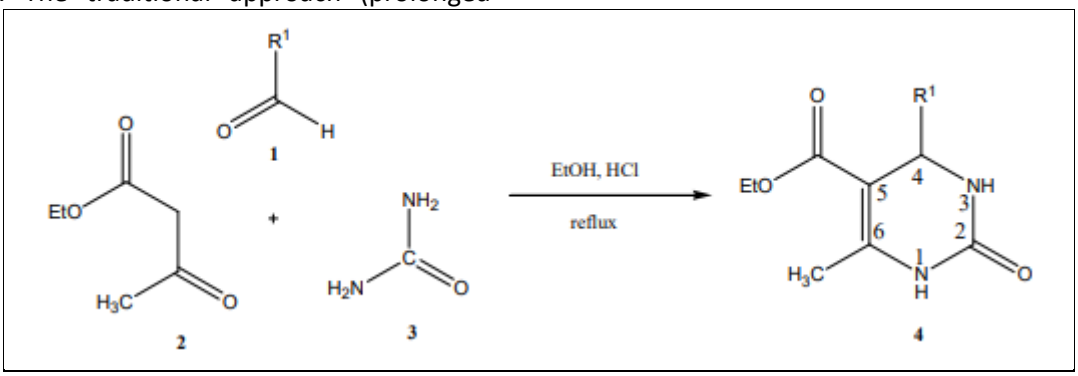
Figure 4 :Biological active dihydropyrimidines.

The biological processes carried out by related groups or structures are frequently identical. On the other hand, their levels of potency are typically distinct. Investigations into the structure-activity relationship (SAR) are a tried-and-true technique that can be helpful in the hunt for new medications. On the other hand, SAR is typically calculated by making a few tweaks to the structure of an already existing chemical and analysing how those modifications affect the compound's biological activity. Numerous dihydropyrimidine-related annulated or multifunctionalized pyrimidine heterocyclics have been explored or tested against various harmful diseases that emerge as a result of stress or pollution in the search for more potent and effective medicinally important molecules. Because of this, the biological profile of DHPMs and related pyrimidine species appears to be alluring enough to concentrate the attention of chemists on the synthesis of dihydropyrimidinones via the Biginelli reaction. As a result, the development of strategies for efficient lead structure identification as well as for pharmacophore variation of dihydropyrimidine motif combinatorial synthesis and high-throughput screening techniques has now become the golden objective for many different research groups.

The formation and breaking of bonds inside organic molecules is the primary focus of organic synthesis as a scientific discipline. Multicomponent reactions, also known as MCRs, are powerful tools for the expedient building up of compound libraries with molecular complexity and diversity30. This is accomplished through the simple formation of several new covalent bonds in a one-pot transformation. Among the various synthetic methodologies that are available for the synthesis of compound libraries, MCRs are one of the most effective tools. Therefore, they get pretty near to the concept of an ideal synthesis, and they are especially well matched for combinatorial synthesis.

Because high structural diversity in the desired scaffolds can be introduced in a single synthetic step simply by varying the precursors in the appropriate manner, multicomponent synthesis of heterocycles is particularly well-suited. This method also eliminates the need for workup and purification of the intermediates that are produced between the various stages of the reaction. Pietro Biginelli intuitively foresaw the synthetic potential of multicomponent

reactions by putting in a single flask the reactants of two separate reactions leading to the same result. This allowed him to realize the potential of multicomponent reactions. Heating a mixture of three components (aldehyde 1, -keto ester 2, and urea 3) in ethanol that contained a catalytic quantity of strong acid was part of the original Biginelli methodology for the production of 3,4-dihydropyridine- 2(1H)-ones (4). (Structure 3.01). The traditional approach (prolonged reflux, HCl as a catalyst) can only be used with a select few 1, 3-dicarbonyl compounds because of its stringent reaction conditions and lengthy reaction times, as well as its low yields, particularly for substituted aromatic and aliphatic aldehydes 34-38. Additionally, the scope of the classical Biginelli synthesis is restricted to the use of these aldehydes because of its reliance on the traditional approach.



Structure 3.01

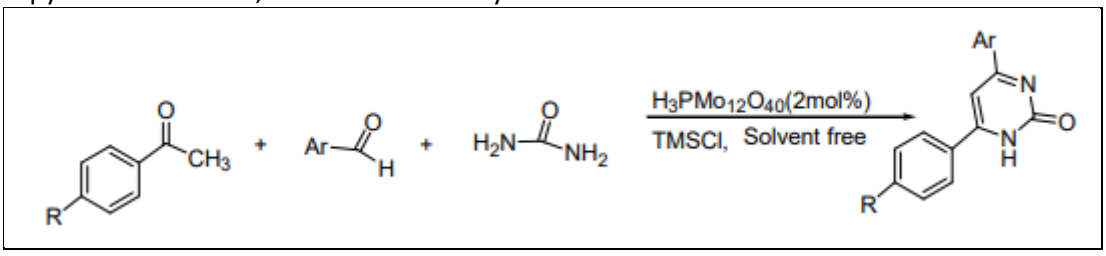
In addition, certain side processes that are generated by extended reflux in a medium that is extremely acidic have a tendency to diminish the selectivity of the reaction, in addition to the yields of the product that is sought. However, there have been adaptations created to improve yields; however, because these techniques are often multi-step processes, they lack the simplicity of the one-pot approach. The scope of this reaction was steadily expanded by the modification of all three building blocks, which made it possible to gain access to a vast number of multifunctionalized dihydropyrimidines that have applications in the medical field. In the case of aldehydes, all of the available aliphatic, aromatic, heterocyclic, and uncommon aldehydes have been utilised; this is regardless of whether or not they contain electron-donating or electron-withdrawing groups.

This includes sugars and aldoses. In terms of the urea component, thiourea and resin-bonded urea, in addition to other related systems like guanidine, have proven to be quite effective. In order to create compounds with significant pharmacological activity, this process has been carried out using a variety of N-mono and N-di substituted ureas. In the family of active hydrogen compounds, a variety of active methylene compounds, both conventional and unconventional (those that can be activated) have been used in this reaction. The "privileged" nature of this scaffold is of the utmost significance, and as a result, the catalytic variation property functions as a driving force in the development of effective processes and procedures for this molecule. Several different synthetic methods are currently known for the preparation of dihydropyrimidinones (DHPMs).

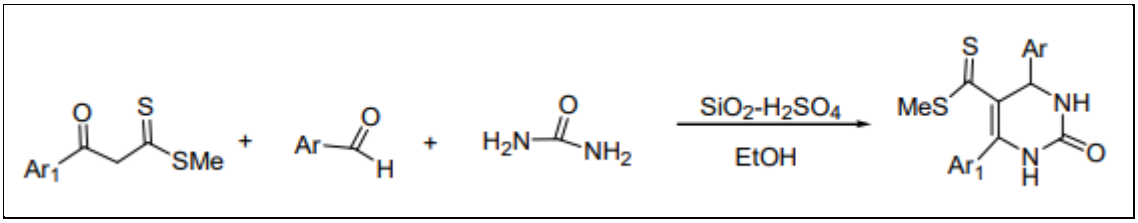
These methods are carried out in the presence of various protic or Lewis acids, including [Cu(OTf)2], metal acetate, GaI3, FeCl3 immobilised in Al-MCM4, melaminetrisulfonicacid, 4-aminobenzenesulfonic acid,45 nano-BF3SiO2, silica-gel-supported poly In order to ensure the successful manufacture of the Biginelli compound, a number of different organocatalysts, such as tartaric acid, oxalic acid, citric acid, lactic acid, and others, are utilised. In this decade, the use of ionic liquids in the Biginelli reaction has gained a lot of attention either because it can speed up the reaction or because it can make the synthetic procedure more environmentally friendly.

It has also been shown that the Biginelli reaction can be facilitated by biocatalysts such as fermenting yeast and enzyme61. In the past, sonication was at the forefront of techniques used for time economy and rate enhancement of organic reactions. These days, microwave irradiations are at the forefront of these same instruments. The Biginelli reaction makes excellent use of both of these methods. For this reaction, it is important to note that other enhanced approaches such as fluorous phase, solid phase, resins, and nanoparticles are also worth noting. For the synthesis of dihydropyrimidinones, a number of different synthetic techniques including modifications in the Biginelli reaction have been reported. These can all be summed up as follows:

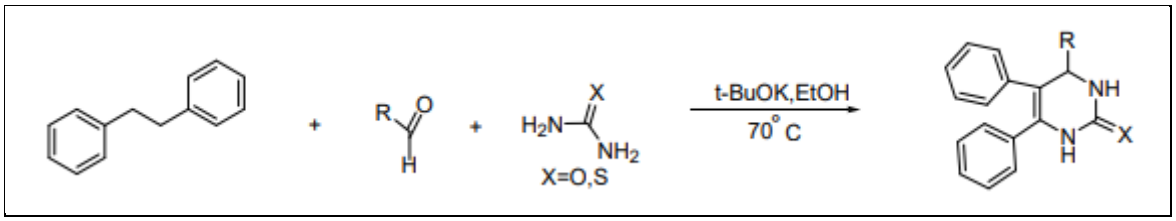
Because these structural modifications boost the pharmacological activities of this motif, alterations have been made at every location of the pyrimidine nucleus, from N1 all the way to C6, in order to look for and investigate the synthetic value of the dihydropyrimidine scaffold. Both the C6 methyl and the C5 substituent in this scaffold are quite stiff, which prevents either of them from being easily functionalized or changed into another function. When these substituents are absent from the oxa analogue of pyrimidine, the C5-C6 bond reveals the characteristic behaviour of enamines, and excellent chemistry is produced or is in the process of being developed on this face. In this direction, scientists have put in a significant amount of work to synthesise C5 molecules that are unsubstituted. C5-C6 face of Biginelli compounds has been decorated or altered by employing a variety of acyclic (Structures 3.02-4.04) and cyclic CH-acid components. This has been accomplished through the use of a range of CH-acid components (Structures 3.05- 3.07).



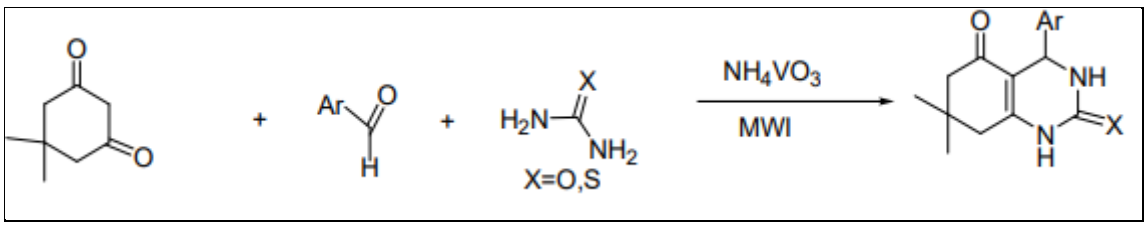
Structure 3.02



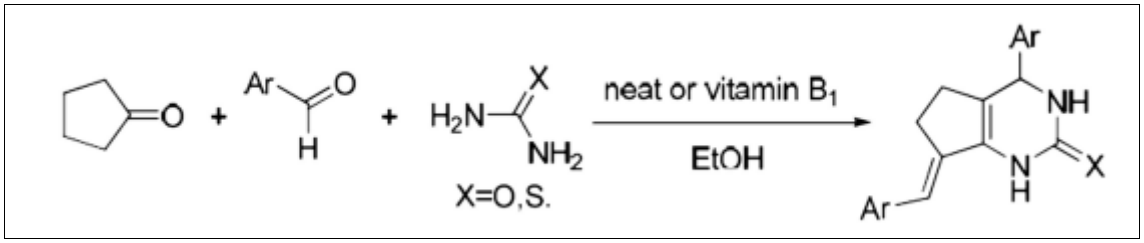
Structure 3.03



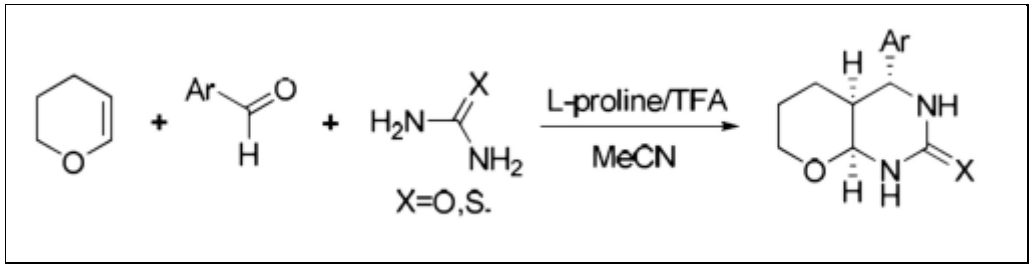
Structure 3.04



Structure 3.05

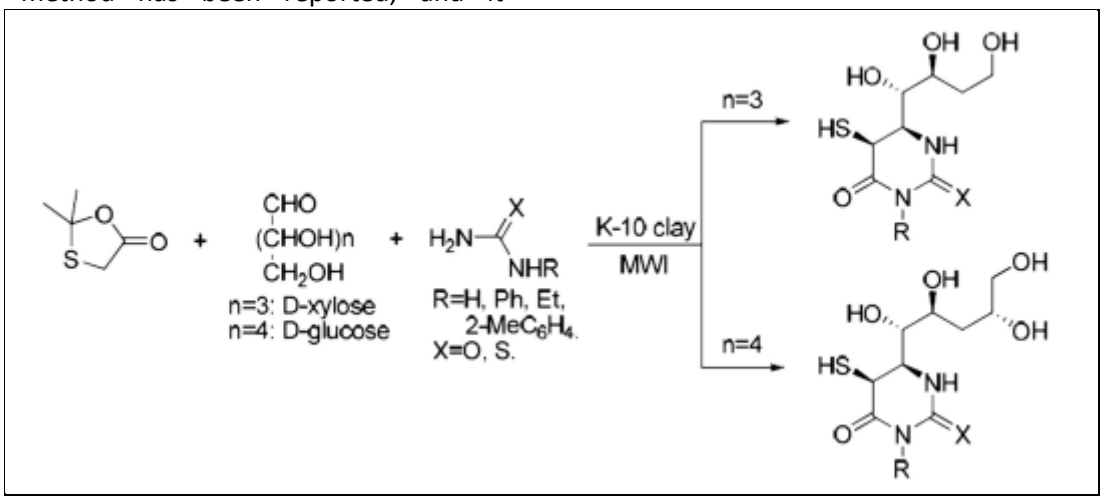


Structure 3.06

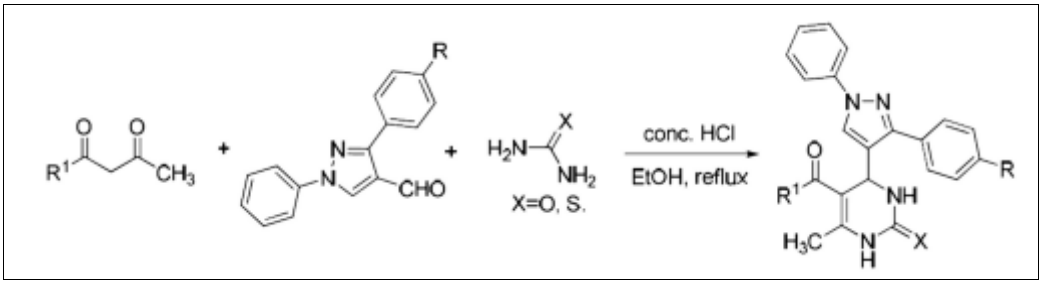


Structure 3.07

The C-4 position, also known as the aldehydic part, has been altered by a number of different research groups in order to synthesise 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. This method has been reported, and it produces diastereo selective, thi (Structure 3.08). In a similar manner, equivalent Biginelli-like compounds can be produced from 5-chloro/phenoxyl-3-methyl-1-phenyl-4-formylpyrazole by exchanging it with aldehydes that are utilised in standard Biginelli synthesis (Structure 3.09).



Structure 3.08



Structure 3.09

By treating 3-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and 1,3-dicarbonyl compounds based on three component Biginelli-like cyclocondensations, researchers have investigated the production of a number of novel derivatives of dihydroimidazole- and – tetrazolopyrimidines. These novel derivatives include

dihydrotriazolopyrimidines and te (Structure 3.10).

CONCLUSIONS

For the purpose of synthesizing structurally diverse 3,4- dihydropyrimidin-2(1H)-thiones derivatives of pharmacological interest, we have presented an efficient and simple one-pot three-component reaction of ethyl acetoacetate with substitute thiourea and aromatic aldehydes in the presence of a catalytic amount of p-TSA in ethanol. This reaction can be carried out in the presence of ethanol. The simplicity of the reaction, the great yields of products that may be obtained without any kind of purification, and the easy availability of the starting components are the primary benefits of using this approach.

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