T.R.
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY

# REACTION OF DIHYDROPYRIMIDINE COMPOUNDS CONTAINING A STYRENE GROUP WITH ACETYL KETENE INTERMEDIATE

M.Sc. THESIS

Mohammed Rafaat MOHAMMED
Supervisor: Asst. Prof. Dr. Furgan ASLANOĞLU

VAN-2024

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## ACCEPTANCE AND APPROVAL PAGE

This thesis entitled '**Reaction of Dihydropyrimidine Compounds Containing a Styrene Group with Acetyl Ketene Intermediate**' presented by Mohammed Rafaat MOHAMMED under supervision of Asst. Prof. Dr. Furgan ASLANOĞLU in the department of Chemistry has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education in 08/01/2024 with unanimity of votes members of jury.

Chair: Prof. Dr. Esvet Akbaş Signature:

Member: Assoc. Prof. Dr. Adem Korkmaz Signature:

Member: Asst. Prof. Dr. Furgan Aslanoğlu Signature:

This thesis has been approved by the committee of 'The Institute of Natural and Applied Science on...……../...../…...….... with decision number.....

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## ETHICAL DECLARATION

I declare that all information presented in the thesis was obtained and presented within the framework of ethical behavior and academic rules. And that in this thesis, which has been prepared in accordance with the thesis writing rules, all kinds of statements and information that do not belong to me have been fully cited.

Signature
Mohammed Rafaat MOHAMMED

## ABSTRACT

### REACTION OF DIHYDROPYRIMIDINE COMPOUNDS CONTAINING A STYRENE GROUP WITH ACETYL KETENE INTERMEDIATE

MOHAMMED, Rafaat Mohammed

M.Sc. Thesis, Department of Chemistry
Supervisor: Asst. Prof. Dr. Furgan ASLANOĞLU
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In organic chemistry, a class of molecules known as heterocyclic compounds includes pyrimidine derivatives. Many pyrimidines are synthesized for a variety of applications, including material chemistry and drug development. Pyrimidine compounds with high biological activity are used as antibacterial, anti-inflammatory, anti-cancer, and anti-parasitic medications. The first stage in this inquiry was to create pyrimidine derivatives using the Biginelli reaction, which is a part of the versatile cyclocondensation reaction (MCR) techniques. The effective synthesis of acetylacetylation was achieved in the second stage by reacting the primidine compounds with the acetoacetylation reagent. The compositions of all newly created compounds are investigated utilizing spectroscopic methods like 1H and 13C NMR.



**Keywords:** Acetoacetylation, Dihydropyrimidine, MCR, Pyrimidine, Synthesis

# ÖZET

## STİREN GRUBU BULUNDURAN DİHİDROPİRİMİDİN BİLEŞİKLERİNİN ASETİL KETEN ARA ÜRÜNÜYLE REAKSİYONU

MOHAMMED, Rafaat Mohammed
Yüksek Lisans Tezi, Kimya Anabilim Dalı
Danışman: Dr. Öğr.Üyesi Furgan ASLANOĞLU
Ocak 2024, 67 sayfa

Pirimidin türevleri heterosiklik bileşiklerin önemli bir kısmını oluşturmaktadır. Birçok pirimidin, malzeme kimyası ve ilaç geliştirme dahil olmak üzere çeşitli uygulamalar için sentezlenir. Yüksek biyolojik aktiviteye sahip pirimidin bileşikleri antibakteriyel, antiinflamatuar, anti-kanser ve anti-parazit ilaçlar olarak kullanılmaktadır. Bu araştırmanın ilk aşaması, çok yönlü siklokondensasyon reaksiyonu (MCR) tekniklerinin bir parçası olan Biginelli reaksiyonunu kullanarak pirimidin türevlerini oluşturmaktı. İkinci basamakta sentezlenen bu primidin bileşikleri reaksiyon ortamında oluşturulan asetil keten ara ürünü ile reaksiyona sokularak yeni asetl astilasyon ürünleri oluşturuldu. Yeni oluşturulan tüm bileşiklerin yapıları $^{1}H$ ve $^{13}C$-NMR gibi spektroskopik yöntemler kullanılarak aydınlatıldı.



**Anahtar kelimeler:** Asetoasetilleme, Dihidropirimidin, MCR, Pirimidin, Sentez

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2024

Mohammed Rafaat MOHAMMED

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## SYMBOLS AND ABBREVIATIONS

Some symbols and abbreviations used in this study are presented below, along with descriptions.

| Symbols | Description |
|---|---|
| **%** | Percentage Sign |
| **∆E** | Energy Difference |
| **∆N** | The Fractional Number of Electrons Transferred |
| **$^{13}C$** | Carbon-13 |
| **$^{1}H$** | Proton |
| **A** | Electron Affinity |
| **BA** | Benzaldehyde |
| **℃** | Degree Centigrade |
| **$CaCl_2$** | Calcium Chloride |
| **$CDCl_3$** | Deuterated Chloroform |
| **G** | Gram |
| **$H_2SO_4$** | Sulfuric Acid |
| **Hrs** | Hours |
| **HCN** | Hydrogen Cyanide |
| **Min** | Minute |
| **Ml** | Milliliter |
| **Mmol** | Millimole |
| **N** | Number of electrons |
| **N2** | Nitrogen |
| **NaOH** | Sodium Hydroxide |
| **P** | Momentum |
| **Kg** | Kilogram |
| **V** | Velocity |
| **ß** | Beta |
| **η** | Hardness |
| **λ** | Wavelength |

| Symbols | Description |
|---|---|
| **χ** | Electronegativity |
| **ψ** | Wave Functions |
| **ω** | Electrophilicity Index |

| Abbreviations | Descriptions |
|---|---|
| **AcOH** | Acetic Acid |
| **Ar** | Aryl Group |
| **B.C.** | Before Christ |
| **B-3CR** | Biginelli Three Component Reaction |
| **CR** | Component Reaction |
| | Chemical Shift (Delta) |
| **D** | Doublet |
| **DBM** | Dibenzoylmethane |
| **DHPM** | Dihydropyrimidine |
| **DMF** | Dimethylformamide |
| **DMSO-$d_6$** | Deuterated Dimethyl Sulfoxide |
| **DNA** | Deoxyribonucleic Acid |
| **EQ.** | Equivalent |
| **HIV** | Human Immunodeficiency Virus |
| **IUPAC** | International Union of Pure and Applied Chemistry |
| **M.P** | Melting Point |
| **MCR** | Multicomponent Reaction |
| **Me** | Methyl Group |
| **MeCN** | Acetonitrile |
| **$NH_4Cl$** | Ammonium Chloride |

| Abbreviations | Descriptions |
|---|---|
| **$NH_4CO_3$** | Ammonium Carbonate |
| **$NH_4OH$** | Ammonium Hydroxide |
| **Ph** | Phenyl Group |
| **PKa** | Acid Dissociation Constant |
| **PM** | Parametric Method |
| **Ppm** | Part Per Million |
| **p-TsOH** | Para-Toluenesulfonic Acid |
| **Q** | Quarter |
| **QCI SDm** | Quadratic CI (Single, Doubles and Triples) |
| **R** | Alkyl Group |
| **RNA** | Ribonucleic Acid |
| **RT** | Room Temperature |
| **S** | Softness |
| **SE** | Semiempirical |
| **Sext** | Sextet |
| **t** | triplet |
| **TLC** | Thin Layer Chromatography |
| **TMSCl** | Trimethylsilyl Chloride |
| **TS-MCRs** | Two Separate Multicomponent Reactions |
| **UV** | Ultraviolet |

## 1. INTRODUCTION

Due to the extensive range of roles that heterocycles play in organic chemistry it would be unfeasible to analyze each specific use of these structures. Hence, our primary aim will be to thoroughly investigate the process of generating biologically potent compounds via carbonyl-mediated heterocyclic synthesis. Even among these specific molecules, it is not feasible to offer a fully thorough explanation for every often observed heterocyclic structure. Furthermore, it was necessary to choose a particular subset of heterocycles.

The medications utilized in human medicine, (Kumar et al., 2018), encompass a wide array of chemical structures. However, the bulk of these drugs are either tiny molecules with heterocyclic properties or contain heterocyclic structural components. Prior to the advancement of modern chemistry, heterocyclic alkaloids served as the active components in numerous natural treatments. Some of these alkaloids, such as morphine derivatives, continue to be utilized in present times. Instead of employing intricate systematic nomenclature, medications are assigned 'trivial' generic names, and drugs that operate on the same pharmacological principles frequently possess interconnected names.

The subject matter focuses on heterocycles. Therefore, the subsequent coverage does not necessarily indicate the varying medical significance of different sections. While achieving comprehensive coverage of all significant areas is clearly unattainable, the objective is to provide an understanding of the extensive and diverse significance of heterocycles in medicine. Heterocycles are present in medications used in several fields, but they are especially significant in systems that use heterocyclic neurotransmitters, for reasons that are easily understandable.

Seven small molecule pharmaceuticals were among the top-selling prescription drugs in value from June 2006 to June 2007 (Joule and Mills, 2010). Heterocycles are a class of chemical compounds that include various drugs used for specific medical purposes. Some examples of these drugs are atorvastatin, which is a statin used to reduce cholesterol levels, esomeprazole, which is a proton-pump inhibitor used to reduce gastric acid production, clopidogrel, which is an anti-platelet agent used to prevent blood clots, olanzapine and risperidone, both of which are anti-schizophrenic medications, amlodipine, which is an anti-hypertensive agent used to treat high blood pressure, and quetiapine, which is used to treat both schizophrenia and bipolar disorder

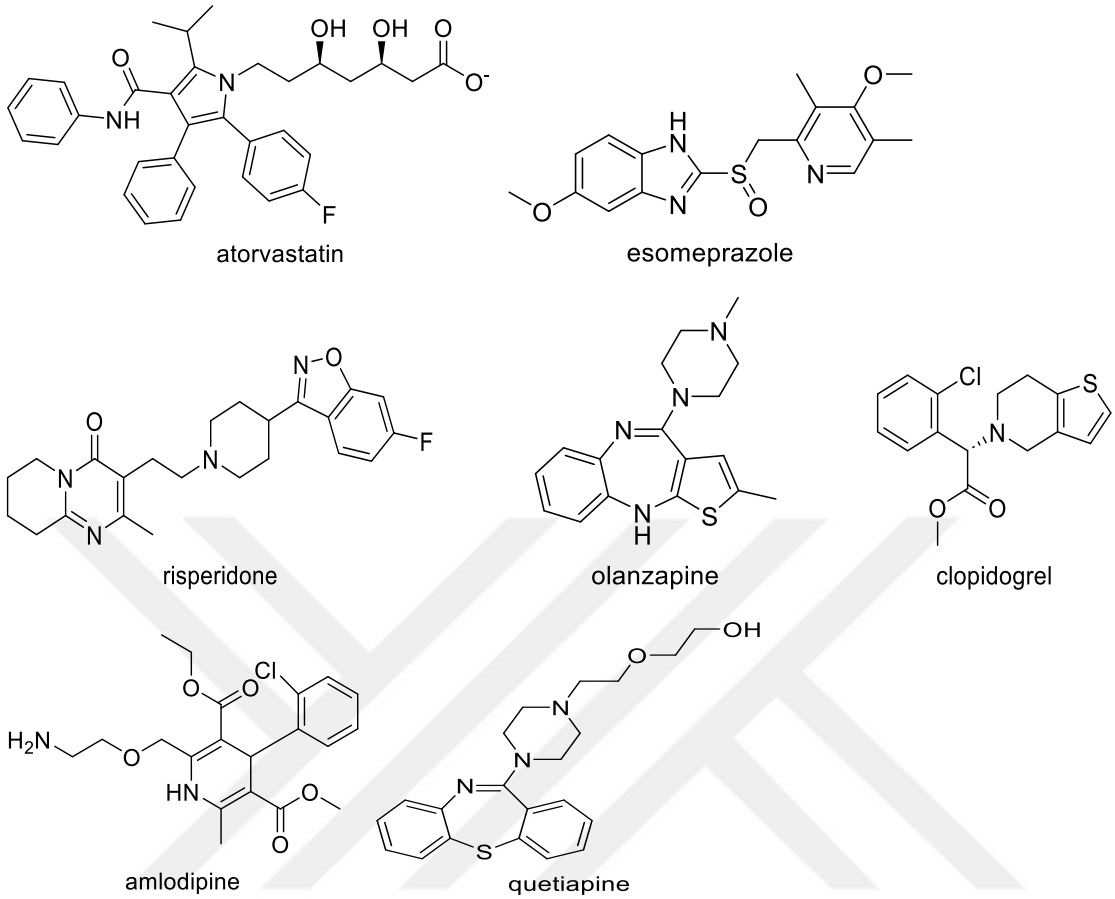



Figure 1.1 Based on sales from June 2006 to June 2007, these are the most valued prescription drugs with pyrimidine rings (Joule and Mills, 2010)

Pyrimidines are nitrogenous heterocyclic compounds consisting of a 6-membered ring made of carbon and nitrogen atoms. They exist ubiquitously in nature in several manifestations and serve as the fundamental constituents of countless organic molecules, ranging from antibiotics to vitamins and liposaccharides. The pyrimidines most widely acknowledged are the nucleobases found in RNA and DNA, with cytosine, thymine, and uracil being the most prevalent (Figure 1.2). The name pyrimidine was first used in 1884 by Pinner, who derived it from the combination of the term's pyridine and amidine due to the structural resemblance to these molecules. Subsequent to these first inquiries, a multitude of pyrimidine-containing substances have been discovered in the field of biochemistry. The multitude of alterations to this framework and its inherent significance in the natural world make it a captivating subject of investigation.

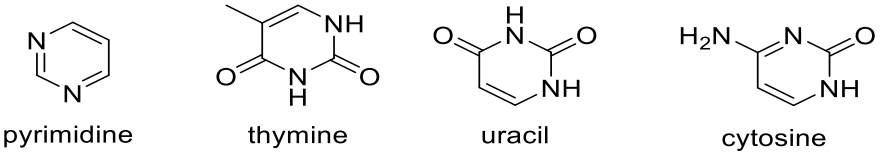



Figure 1.2 The most well-known pyrimidines are RNA and DNA nucleobase (Sathisha et al., 2016)

## 1.1 Pyrimidine

The synthesis of pyrimidine was first accomplished by Gabriel in 1899. The pyrimidine nitrogen's fundamental nature is emphasized by the extensive information gathered over a century. During a fairly ordinary acylation operation, a surprising 2,4,6-triaminopyrimidine dimer was accidently formed. The structure of this dimer, as determined by NMR, has revealed new possibilities for the protonation of pyrimidines. Through a series of interesting deviations in the course of determining the structure, we have reached a carbon-protonated structure, namely a stable σ-complex. In a historical analysis, we emphasize the emergence of perplexing inquiries during the interpretation of NMR spectra, as well as the subsequent resolution of these issues. This approach highlights the Pillars and Mental Traps that either hindered or accelerated the development of structure determination.

Based on their ability to create complementary pairings with adenine and guanine, cytosine, thymine, and uracil are essential components in the process of base-pairing interactions that occur inside DNA and RNA. The genetic code, the process of gene replication, and the expression of genes are all deeply rooted in these interactions. Furthermore, pyrimidine derivatives and analogs have a wide range of uses in the field of drug development. For example, the structure of pyrimidines has been used to generate treatments for a variety of disorders, including cancer, viral infections, and other conditions (Sathisha et al., 2016)

Pyrimidines have crucial roles in several metabolic pathways, coenzyme activities, and cellular energy transfer mechanisms, extending beyond genetics and pharmacology. Their diversity and relevance in both the molecular machinery of life and therapeutic applications highlight their importance in the biological and chemical sciences. The significance of pyrimidine in the investigation of life's molecular foundations and its practical uses in medicine and biochemistry is emphasized in this introduction.

### 1.1.1 Basic Fragments of Pyrimidine Skeleton

Therefore, the production of pyrimidines is an ongoing and very active field of study, with new techniques being regularly introduced. The Pinner synthesis has traditionally been the preferred method for synthesizing pyrimidines. The reaction between an amidine or a urea and a 1,3-dicarbonyl derivative enables the synthesis of pyrimidines with different substituents. Nevertheless, the use of severe reaction conditions and the occurrence of low yields in some instances have often impeded the effectiveness of this method. Consequently, many techniques, including cycloaddition reactions, multicomponent processes, and tandem processes, have been explored to broaden the range and enhance the chemical efficiency of pyrimidine synthesis (Figure 1.3).

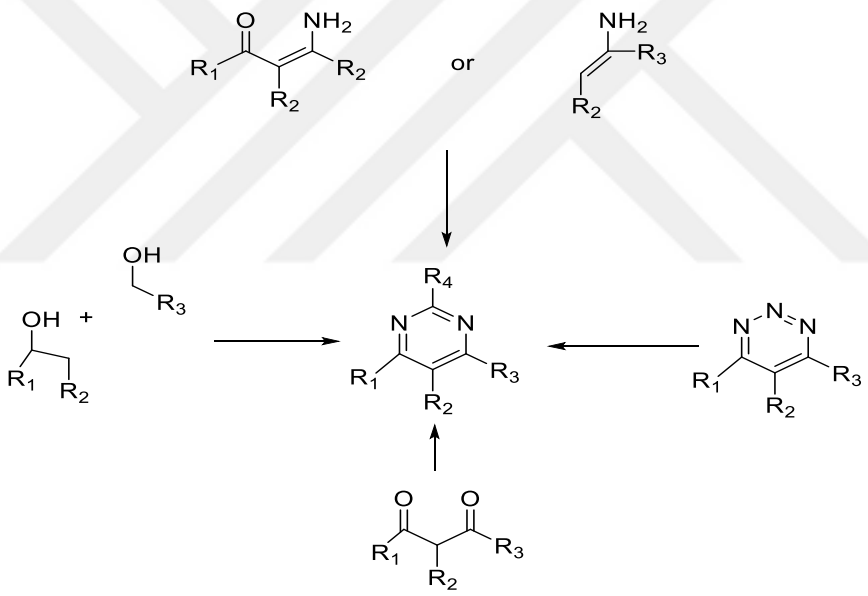



Figure 1.3 Basic fragments of pyrimidine skeleton (Tolba et al., 2022)

Recently, this basic feature of pieces has been used to show different pyrimidine scaffolds. Researchers have found that the N-C-N and C-C-C pieces are the most famous and widely used ways to make pyrimidine. In this cyclization process, double cyclization was used, and a neutral molecule could have been left out or not. There are a lot of different basic pieces that can be used to make the pyrimidine pattern, which makes the synthesis process versatile. For example, 4,6-dimethyl-2-phenylpyrimidine was made by mixing acetyl acetone with benzimidamide hydrochloride, which is a

building block, while potassium carbonate was present in a liquid medium that was being boiled.

This method can make a number of different substituted pyrimidine derivatives, depending on the starting material and how the N-C-N building blocks are changed. It might go through more derivatization, which could make the many medically important pyrimidine patterns. It was just recently found out that many efforts have been made to change the structure of the pyrimidine molecule by using different building blocks. Because small changes in the basic pyrimidine scaffold can make a lot of biologically or pharmaceutically active pyrimidine scaffolds, the catalytic system might need to be changed or new methods may need to be used.

To find out more about the usefulness and medical worth of pyrimidine, all six of its nucleus places have been moved from $N_1$ to $C_6$ in the basic pyrimidine scaffold. So far, nitrogen building block types like amidine, guanidine, urea, thiourea, and other easily accessible analogs have been used to study the new pyrimidine pattern. There are many types of ammonium compounds, such as amide, enamine, aliphatic or aromatic amine, alkyl thiocyanate, alkyl cyanate, alkyl nitrile, amide, and 1,3,5-triazine. The adaptability of different nitrogen building blocks that are used to make pyrimidine scaffolds is explained in (Mahfoudh et al., 2017). This work looks at the study on pyrimidine ring formation (Figure 1.4).

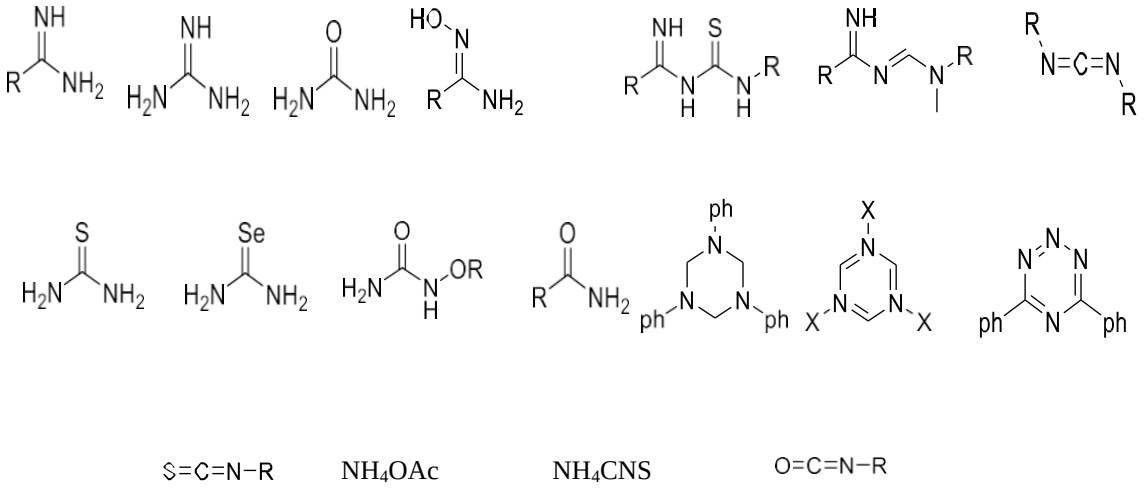



Figure 1.4 Different kinds of building blocks are used to create pyrimidine (Selvam et al., 2012)

### 1.1.2 Reactions of Pyrimidine

#### 1.1.2.1 Alkylation

Pyrimidine may undergo alkylation by alkyl halides or alkylating agents. This process enables the incorporation of alkyl groups onto the nitrogen atoms of the pyrimidine ring. Diazines undergo a reaction with alkyl halides to form mono-quaternary salts, however this reaction occurs somewhat less easily compared to pyridines. Simple alkyl halides are not capable of undergoing dialkylation. However, the highly reactive trialkyloxonium tetrafluoroborates can convert all three systems into di-quaternary salts.

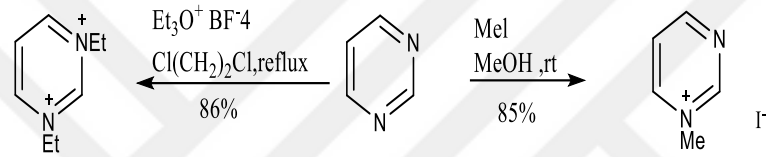



Figure 1.5 Alkylation of pyrimidine to mono- and di-quaternary salt

#### 1.1.2.2 Oxidation

Pyrimidines react with peracids (Koelsch and Gumprecht., 1958: *23*; Kubota et al., 1963: 36), when working with pyrimidines, caution should be exercised due to the very unstable nature of the products formed under acidic circumstances, which can result in the production of N-oxides. When dealing with pyrimidines, it is important to exercise caution due to the very unstable nature of the products in an acidic environment pyrimidines often provide low amounts of N,N'-dioxides, unless in cases where extra activation is present (Figure 1.6).

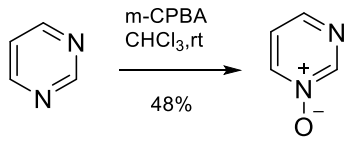



Figure 1.6 Pyrimidine oxidation

### 1.1.2.3 Halogenation

The halogenation of pyrimidines takes place under very gentle circumstances, indicating that it is most likely that an addition/elimination sequence occurs, rather than a traditional aromatic electrophilic substitution (Figure 1.7).

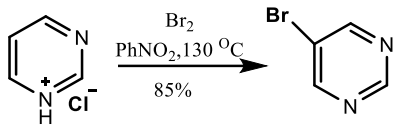



Figure 1.7 Chlorination of 2-methylpyrazine and pyrimidine

### 1.1.2.4 Nucleophilic Substitution with Displacement of Good Leaving Groups

'Soft nucleophiles,' including amines, thiolates, and malonate anions, react quickly with substitution of the halide in all halo-diazines except 5-halo-pyrimidines. Microwave heating can even bring 5-bromopyrimidine into reactivity with nucleophiles. The relative reactivities can be summarized as follows: all examples are more reactive than 2-halo-pyridines (Cherng, 2002) (Figure 1.8).

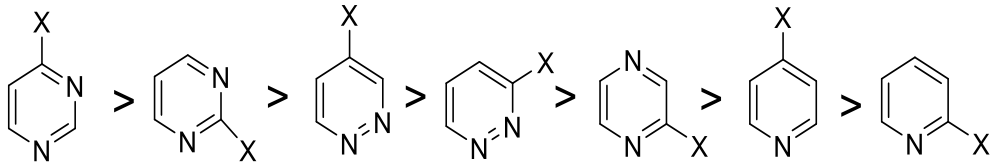


Figure 1.8 "Soft nucleophiles" react favorably with all halo-diazines, with the exception of five halo-pyrimidines

The disparity in reactivity between 2- and 4-halo-pyrimidines is minimal, making it worthwhile to examine the selectivity in nucleophilic displacement reactions of 2,4-dichloropyrimidine, which is a significant synthetic intermediate (Figure 1.8).

The reaction between sodium methoxide in methanol exhibits a strong preference for the 4-chloro substituent, as seen. On the other hand, lithium 2-(trimethylsilyl) ethoxide shows an equal preference, but for the 2-chloro substituent. The first scenario, where 4-chloro is replaced by 2-chloro, is the typical situation for nucleophilic displacements. However, the second case is an exception. In this case, the strong coordination of lithium in a non-polar solvent to the nitrogen atom (N-1), which is more basic, leads to activation.

Additionally, there may also be internal attack at carbon atom 2 (Figure 1.9). Under conditions of high acidity, a nearly equal mixture of the two methoxy compounds is produced in a ratio of around 1:1. In this case, the hydrogen bonding with the proton on N - 1 facilitates the process of promoting attack at C - 2. The selectivity towards other nucleophiles is contingent upon the characteristics of the nucleophile as well as the conditions of the reaction.

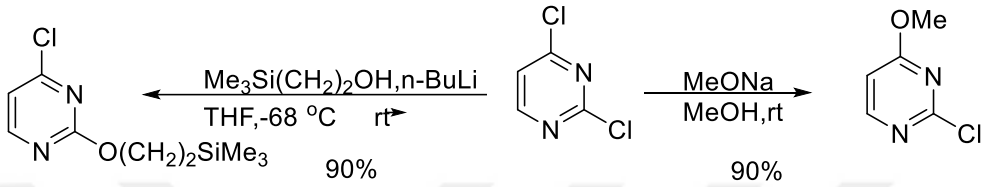



Figure 1.9 Sodium methoxide in methanol is very selective for the 4–chloro substituent, while lithium 2–ethoxide is equally sensitive for the 2–chloro substituent

### 1.1.3 Pyrimidine Applications

Pyrimidines are nitrogenous heterocycles renowned for their anticancer, anti-HIV, antifungal, and antibacterial properties. Pyrimidines, which include this heterocycle, are prevalent in numerous pharmaceuticals. In light of these discoveries, we have additionally documented the production and physiological effects of possible pyrimidine analogues. This review article offers a thorough examination of medically approved medications that include pyrimidine, as well as new studies that focus on the wide-ranging effects of pyrimidine analogs. This study examines the key characteristics of pyrimidine analogs, including their abilities to combat cancer, induce sedation, fight infections, combat viruses, reduce inflammation, provide pain relief, and inhibit microbial growth. These diverse activities make pyrimidine analogs an appealing foundation for the development of novel medications.

#### 1.1.3.1 Nucleic Acids (DNA and RNA)

Pyrimidines are important constituents of DNA and RNA. They function as the fundamental units for the storage and transmission of genetic information. Cytosine (C) and thymine (T) are pyrimidine nucleobases present in DNA, whereas cytosine (C) and uracil (U) are pyrimidine nucleobases found in RNA. Comprehending the chemistry of

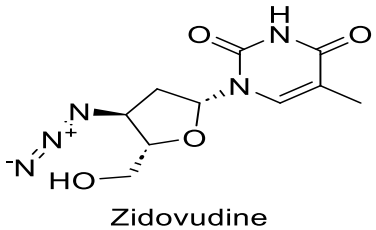
pyrimidine is essential for deciphering the enigmas of genetics and molecular biology.

### 1.1.3.2 Pharmaceuticals

Pharmaceuticals extensively utilize pyrimidine derivatives. Several pharmaceuticals incorporate pyrimidine-based compounds as their active constituents. As an illustration, the anticancer medication 5-fluorouracil is a compound similar to pyrimidine that disrupts the process of creating DNA and RNA in cancerous cells. Allopurinol is a pharmaceutical compound that incorporates a pyrimidine ring and is employed for the treatment of gout (Folkers and Johnson, 1933).

### 1.1.3.3 Antiviral Agents

Pyrimidine derivatives, specifically nucleoside analogs, have been extensively employed as antiviral medicines. They disrupt viral replication by impeding the synthesis of DNA or RNA. Notable examples encompass pharmaceuticals such as acyclovir (used to combat herpes viruses), lamivudine (utilized against HIV and hepatitis B), and remdesivir (prescribed for COVID-19). These chemicals aid in the management and treatment of diverse viral infections, mitigating their intensity and transmission. Zidovudine (AZT) (Figure 1.10) is an antiviral medicine used to treat HIV. It works by incorporating pyrimidine analogs to hinder the reproduction of the virus (Somkuwar and Chaubey, 2023).



Zidovudine

Figure 1.10 Zidovudine (AZT) is an antiviral drug used to treat HIV

### 1.1.3.4 Agrochemicals

This patent pertains to pyrimidine derivatives and their application in various compositions. The invention also encompasses methods for producing and utilizing these compositions. Additionally, the pyrimidine derivatives are specifically explored for their potential as adjuvants, notably in the field of agrochemicals. The present invention specifically pertains to compositions that include a pyrimidine derivative (Bell et al., 2013).

### 1.1.3.5 Luminescent Compounds

Certain pyrimidine derivatives possess luminous characteristics, rendering them valuable in the advancement of light-emitting substances and devices. Materials possessing both bright and antibacterial properties are advantageous for various applications in biology, including sensors, biomedical imaging, and bacterial imaging. Pyrimidine-containing solid-state fluorescent compounds with antibacterial properties have been developed recently. We were drawn to the pyrimidine ring due of its notable electron affinity. To our knowledge, while there have been reports on efficient host materials and electron transport materials containing pyrimidine, most of these materials were built with a pyrimidine core. However, there is no existing report on the electronic properties of luminescent materials that contain a 4-monosubstituted pyrimidine moiety. In this study, a set of bipolar molecules (PM1–PM5), (Figure 1.11) were developed, incorporating the electron acceptor pyrimidine and the electron donors carbazole or triphenylamine. The primary objective of our current research is to investigate the correlation between the molecular structure and photoelectric characteristics of the PM compounds, which include PM1 to PM5. The chemical medicine was used to deliberately alter the photophysical and electrical properties of the PM compounds in a systematic manner. Furthermore, the study also included the utilization to predict the photoelectric properties of the PM compounds, density functional theory (DFT) and time-dependent density functional theory (TD-DFT) calculations are used. Click or tap here to enter text.

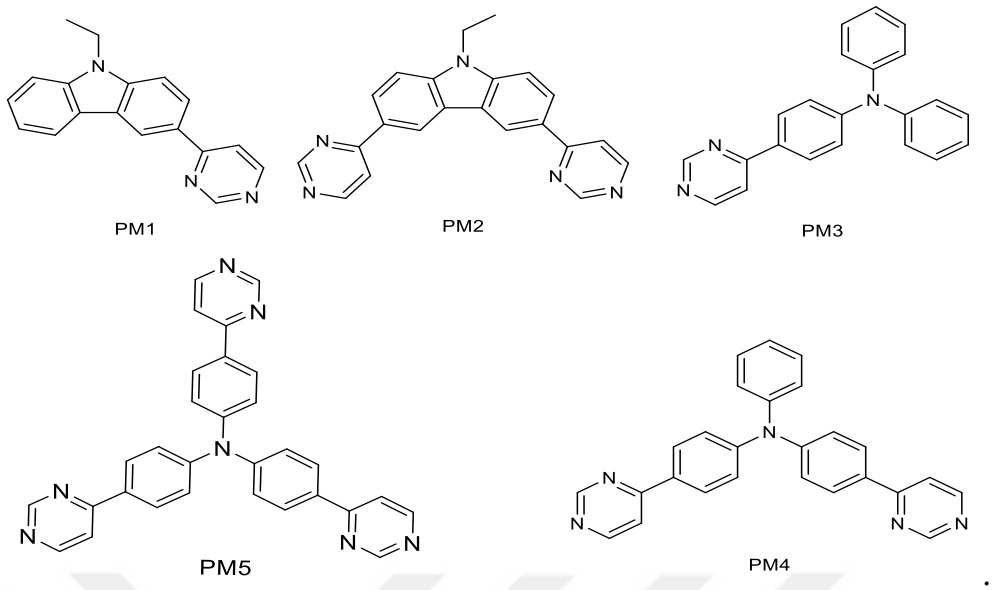



Figure1.11 Bipolar molecules with pyrimidine as the electron acceptor and carbazole or triphenylamine as the electron donor were developed (Folkers and Johnson, 1933)

### 1.1.3.6 Dyes and Pigments

Pyrimidine-based dyes and pigments are used in various applications, including textiles, paints, and colorants. The current invention pertains to new diamino pyrimidine dispersing azo dyes, a procedure for making such dyes and dyeing or printing semi-synthetic and synthetic hydrophobic fiber materials, especially textiles (Figure 1.12).

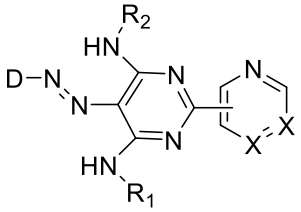


Figure 1.12 Structure of diamino pyrimidine

The versatility of pyrimidines and their derivatives in various applications highlights their importance in many aspects of science, technology, and medicine. Researchers continue to explore and develop new uses for pyrimidines in these and other fields.

## 1.2 Dihydropyrimidine

Dihydropyrimidine, or 1, 2-dihydropyrimidine, is a chemical molecule that is intimately associated with pyrimidine. It is generated from pyrimidine through the addition of two hydrogen atoms to the pyrimidine ring, which leads to the decrease of the double bonds in the ring structure. This reduction reaction transforms the pyrimidine ring, which consists of six members, into a saturated ring with six members. The dihydropyrimidine compound is represented by the chemical formula $C_4H_6N_2$. It shares the same carbon and nitrogen makeup as pyrimidine, but exhibits a distinct ring structure. Dihydropyrimidine exhibits isomerism, with its multiple forms determined by the location of the double bonds inside the ring structure. Dihydropyrimidines and their derivatives play a crucial role in various chemical and biological processes, encompassing.

### 1.2.1 Dihydropyrimidine Synthesis

Dihydropyrimidine derivatives are depicted in Figure 1.12 illustrates the dihydropyrimidine derivatives. Biginelli successfully identified this tricomponent condensation process in 1893. Therefore, this type of reaction is currently referred to as the "Biginelli reaction," "Biginelli condensation," or the "Biginelli dihydropyrimidine synthesis." The early applications of this cyclo-condensation method predominantly employed a 13-ketoester, aromatic aldehyde, and urea. Nevertheless, the scope of this synthesis of heterocycles has greatly broadened by the modification of all three constituents, facilitating the generation of a multitude of multifunctional zed pyrimidine derivatives of type I. In the field of literature, the word DHPM has been universally accepted to refer to this particular heterocyclic framework, and it is regularly employed throughout this chapter. The importance of multicomponent reactions in combinatorial chemistry has revived interest in the Biginelli reaction, leading to a continuous increase in articles and patents on novel DHPM equivalents. In 1993, a comprehensive study on the Biginelli reaction and the potential for synthesizing DHPMs was previously published. An evaluation of the biological characteristics of DHPM derivatives was conducted in the year 2000, with a particular focus on providing a thorough examination of the latest advancements in the Biginelli approach. This chapter specifically examines

three-component condensations that contain carbonyl compounds with CH-acidic properties, which are well-suited for the reaction.

The Biginelli idea encompasses the study of aldehydes and urea-type building blocks. Hence, this study encompasses reactions that utilize 1,3-diketones or nitoacetone as starting materials, resulting in the formation of DHPMs with the substitution pattern depicted in (Figure 1.13). This is in contrast to previous reviews on the subject.

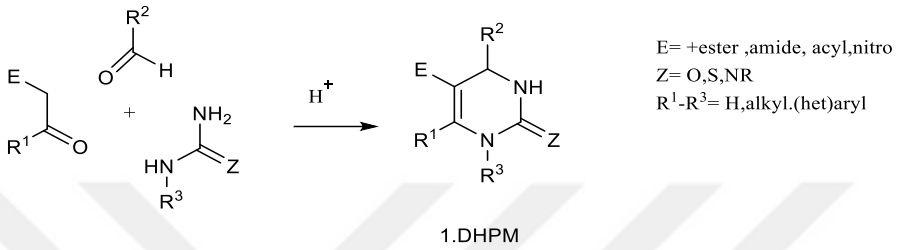



Figure 1.13 1,3-Diketone or nitoacetone processes that produce DHPMs

### 1.2.1.1 Mechanism

Various research groups have examined the mechanism of the Biginelli reaction. The reliance on acidic catalysis in the Biginelli system has been empirically confirmed, and extensive research has been conducted on all three potential major reaction pathways of this three-component system.

The key step in the Biginelli sequence, (Figure 1.13) shows the acid-catalyzed production of a type 2 N-acyliminium ion intermediate from aldehyde and urea precursors, the Biginelli sequence's essential step. The CH-acidic carbonyl component of Th4 interacts with the iminium ion 2, likely in its enol tautomer, to create an open-chain ureide 3. Subsequently, this molecule undergoes cyclization, resulting in the formation of hexahydropyrimidine 4. The dehydration of 4, facilitated by acid catalysis, ultimately leads to the synthesis of the ultimate DIIPM product I. The chemical process can be described as an alpha-amidoalkylation, or more accurately, as an alpha-urcidoalkylation. The number is unknown. Following this mechanistic formulation. Monosubstituted ureas and thioureas produce only *N-1* alkylated DHPMs. *NN'*-Disubstituted ureas are unreactive under the given reaction conditions (Kappe, 2000).

While it is not possible to isolate or directly witness the highly reactive *N*-acyliminium ion species **2**, evidence supporting the mechanism shown in (Figure 1.14) is

obtained via the isolation of a hexahydro pyrimidine analog **4** using electron-deficient 1,3-dicarbonyl compounds. When the compound is in the form of $R_1$= CF3, such as in the case of hexahydro pyrimidine, the cascade of reactions halts unless specific circumstances that promote dehydration are applied. Typically, all DHPMs produced using traditional Biginelli condensations are obtained in the form of racemates (Kappe, 1993a).

The elucidation of the mechanism underlying the Biginelli multicomponent reaction has ignited a newfound enthusiasm for improving the effectiveness of this approach. Currently, novel catalysts, particularly Lewis acids, are used to facilitate the Important N-acyliminium ion intermediates are formed and trapped. Lewis acids may stabilize N-acyliminium by establishing coordination connections with urea oxygen. Some methods suggest chelating the 1,3-dicarbonyl component with Lewis acids to stabilize the resulting tautomer. Experimental Conditions analyzes Lewis acid conditions as given by Lewis (Gohain et al., 2004).

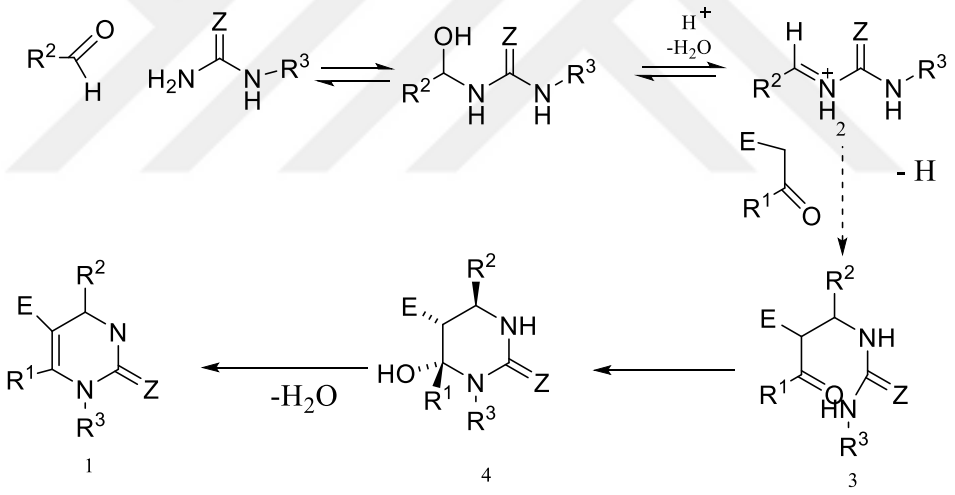



Figure 1.14 The acid-catalyzed synthesis of a type 2 N-acyliminium ion intermediate from aldehyde and urea precursors is the key step in the Biginelli sequence

### 1.2.1.2 Building Blocks

#### 1.2.1.2.1 Aldehydes

Out of the three components in the Biginclli reaction, the aldehyde component provides the highest level of unpredictability. Usually, the reaction shows its best performance when used with aromatic aldehydes. These can be substituted in the ortho,

Meta, or para position with either electron-withdrawing or electron-donating groups. Aromatic aldehydes that have substituents in the Meta or para positions, and these substituents have the ability to extract electrons, usually have favorable outcomes. Ortho-substituted benzaldehydes containing bulky substituents frequently demonstrate significantly diminished yields. Sufficient quantities of Dihydropyrimidine (DHPM) products can be made by utilizing heterocyclic aldehydes derived from furan, thiophene, and pyridine.

The Biginelli reaction typically yields low amounts (10-40%) when aliphatic aldehydes are used, unless certain reaction conditions such as Lewis's acid catalysts or solvent-free techniques are applied. Alternatively, the aldehydes might be utilized in a protected state. As an illustration, the 4-cyanomethyl-DHPM 5 is effectively synthesized by reacting oxazolidine-protected cyanoacetaldehyde with ethyl acctoacetate and urea (Figure 1.14) (Singh et al., 1999)."The C4 unsubstituted DHPM can be synthesized using appropriate formaldehyde precursors in a similar fashion."

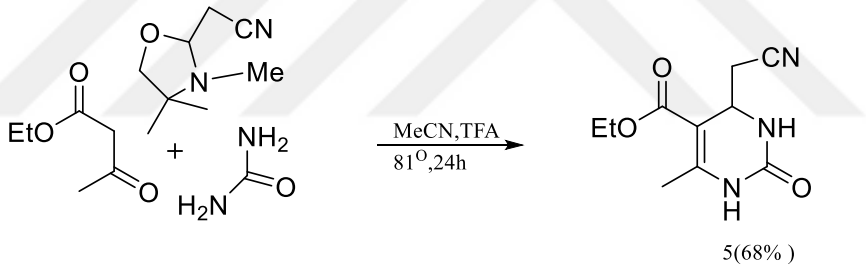



Figure 1.15 Synthesis of 4-cyanomethyl-DHPM 5 involves reacting oxazolidine protected cyanoacetaldehyde with ethyl acctoacetate and urea

Reactions that involve an aldehyde generated from a carbohydrate are particularly intriguing. During these transformations, DHPMs with a sugar-like component at position 4 (known as C-nucleoside analogs) are produced (refer to Figure 1.16) (Dondoni and Massi, 2001). "The utilization of these chiral aldehydes is also significant in the pursuit of creating an asymmetric version of the Biginelli reaction However, the current chemical yields and diastereoselective that may be attained are not practically useful.

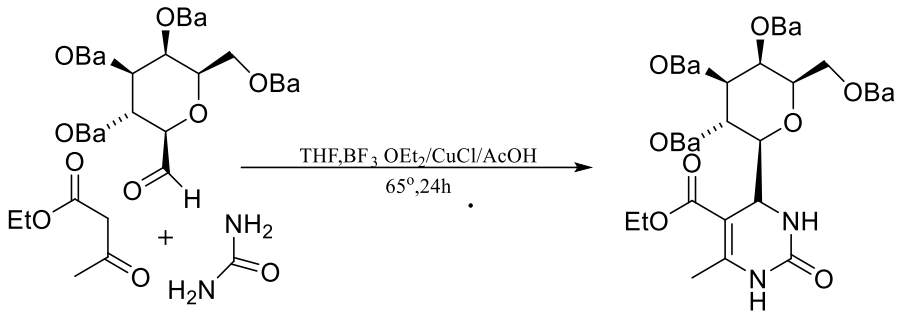



Figure 1.16 Aldehyde reactions from carbohydrates are fascinating

Bisaldehydes have been employed as building blocks in Biginelli reactions. For instance, when terephthalaldehyde is subjected to microwave irradiation, it gives the desired bis-DHPM product in high yields (Figure 1.17) (Stadler and Kappe, 2001).

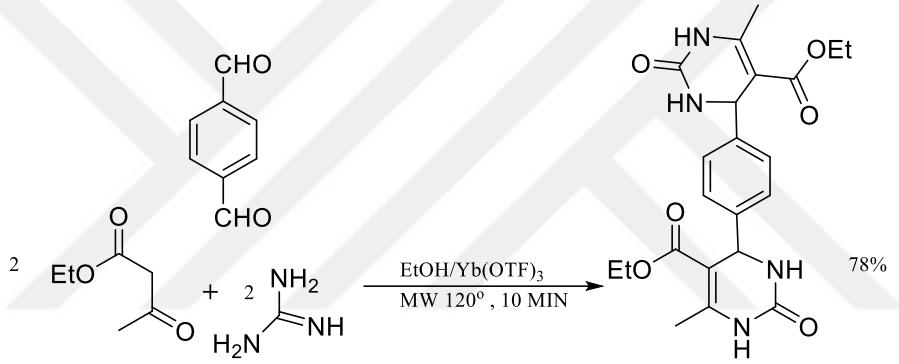



Figure 1.17 Aldehyde reactions from carbohydrates are fascinating

### 1.2.1.2.2 CH-Acidic Carbonyl Components

Typically, basic alkyl acetoacetates are used as CH-acidic carbonyl building blocks, however other forms of 3-oxoalkanoic esters or thioesters can also be effectively utilized. The use of ethyl 4-bromoacetoacetate yields 6-bromomethyl-substituted DHPMs, which can be utilized as excellent templates for subsequent synthetic transformations (Figure 1.18) (Kappe, 1993a).

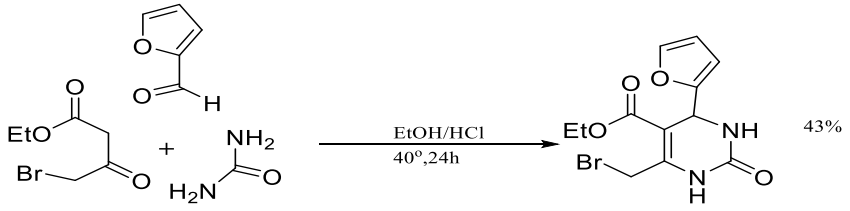



Figure 1.18 Primary alkyl acetoacetates are CH-acid carbonyl building components

Benzoylacetic esters exhibit similar reactivity, however the resulting yields are often lower and the whole condensation process is slower. Acetoacetamides of primary, secondary, and tertiary nature can serve as substitutes for esters in the synthesis of pyrimidine-5-carboxamides. Furthermore, B-diketones can be used as suitable substrates in Biginelli reactions. Condensation can also be accomplished by employing cyclic B-diketones, such as cyclohexane-1,3-dione, and other cyclic B-dicarbonyl compounds (Figure 1.19) (Kidwai and Rastogi, 2008).

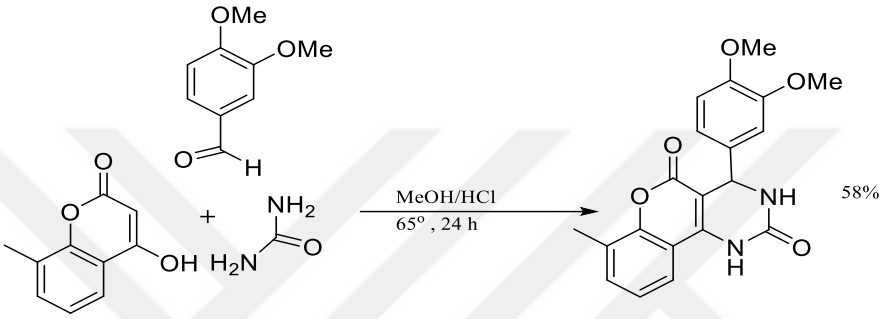



Figure 1.19 Biginelli reactions work with B-diketones

In order to synthesize a C6-unsubstituted DHPM derivative, one can use the equivalent 3-oxopropanoic ester derivative, where the aldehyde function is concealed as an acetal (Figure 1.20) (Borse et al., 2012). In addition to ester-derived carbonyl compounds that are CH-acidic, nitroacetone is also a useful precursor, resulting in 5-nitro-substituted DHPM derivatives with consistently high yields.

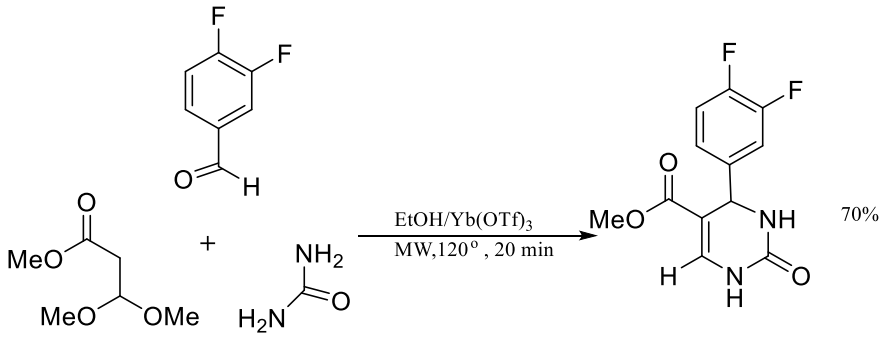



Figure 1.20 3-oxopropanoic ester derivative, hiding aldehyde as acetal

### 1.2.1.2.3 Urea Building Blocks

The user's text is empty. Urea exhibits the highest level of limitation in terms of permissible structural variations within the Biginelli reaction. Consequently, the majority of the recorded instances incorporate urea as the fundamental component. Nevertheless, straightforward monosubstituted alkyl ureas typically exhibit equivalent reactivity, following a regiospecific pattern, resulting in high yields of N1-substituted DHPMs. Classical Biginelli condensations do not yield N3-substituted analogs. In addition, it should be noted that N, N'-disubstituted ureas do not undergo any reaction when subjected to Biginelli conditions. There is a scarcity of published research that provides evidence for the successful involvement of N-aryl ureas in Biginelli condensations. Twenty-nine point three zero.

Thiourea and its substituted derivatives adhere to the same fundamental principles as ureas, albeit necessitating extended reaction durations to attain satisfactory conversions. The yields are generally lower when compared to the comparable urea derivatives. Occasionally. Unprotected guanidine has been utilized in a three-component Biginelli-type condensation, as shown in (Figure 1.21) (Kappe, 2000).

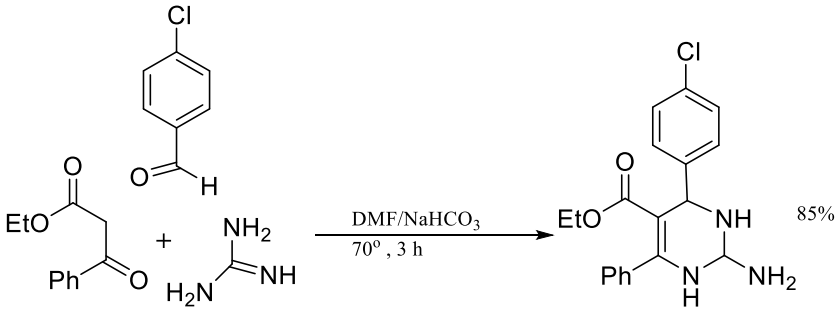



Figure 1.21 Unprotected guanidine was used in a three-component Biginelli condensation

## 1.3 Acytoacetalation

Acetoacetylation is a chemical reaction when a molecule undergoes the addition of an acetoacetyl group, which is a β-diketone moiety. This reaction is frequently employed in organic synthesis to incorporate acetoacetyl functionality into diverse molecules. The acetoacetyl group is composed of the atoms \(CH_3-CO-CH_2-CO-\) and is commonly denoted as AcAc (Clemens and Hyatt, 1985).

Acetoacetylation is a valuable method for creating molecules with the acetoacetyl group, which is a versatile intermediate for synthesizing different chemical compounds. Acetoacetyl compounds are utilized in the production of medicines, agrochemicals, dyes, and other specialized chemicals.

The overall process of acetoacetylation entails the interaction between a nucleophile and either acetoacetyl chloride or a similar acetoacetylating chemical. The nucleophile can encompass a diverse array of chemicals, including amines, alcohols, or other reactive species, contingent upon the intended final product. The reaction often occurs under precise conditions, frequently requiring the utilization of a base or acid catalyst.

The acetoacetyl group is highly esteemed in organic synthesis because of its capacity to undergo many chemical transformations. As an example, it can engage in condensation processes to produce β-diketones, or it can undergo additional modifications to incorporate other functional groups.

Aniline, an aromatic primary amine, readily interacted with diketene to produce acetoacetanilide with a high yield. Furthermore, there have been reports indicating that aminoheterocycles, such as 2-aminopyridine , undergo a reaction with diketene resulting in the formation of its acetoacetate, referred to as compound  (Figure 1.22).

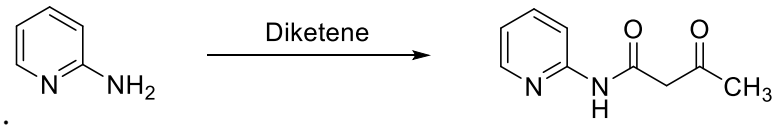



Figure 1.22 Synthesis of butanamide derivative

# 2. LITERATURE REVIEW

## 2.1 MCRs

MCRs are reactions where three or more starting elements react to generate a product, with most or all atoms contributing to the new product (Ugi et al., 1994). MCRs offer advantages over typical sequential assembly of target molecules, justifying their usage. MCRs construct molecules in one step by mixing starting components, unlike traditional methods that need numerous consecutive stages. MCRs may construct complex compounds simultaneously. Reducing effort and saving time are significant benefits of this approach.

### 2.1.1 Asymmetric Isocyanide-based MCRs

The utility of isonitrile-based multicomponent reactions in synthesizing intricate pharmacologically important compounds with few steps and diverse inputs is widely recognized gr (Dömling and Alqahtani, 2014). However, the issue of stereochemistry poses a significant challenge. In Passerini and Ugi reactions, the formation of a new stereogenic center is a common occurrence. Nevertheless, most of the described reactions so far demonstrate minimal or absent stereoselectivity. MCRs seem to be adhering to the evolutionary pattern observed in past conventional organic syntheses. During the 1960s and 1970s, the main emphasis was on discovering novel reactions. During the 1980s and 1990s, the focus switched to selectivity, namely stereoselectivity, leading to the creation of highly effective methods. The occurrence of comparable outcomes with MCRs is highly probable. Promising results are already seen in the literature.

### 2.1.2 The Biginelli Reaction

In 1893, Pietro Biginelli, an Italian scientist at the University of Florence, was the first to document the acid-catalyzed cyclocondensation reaction using ethyl acetoacetate 1, benzaldehyde 2, and urea 3. The reaction was carried out by heating a mixture of the three parts that were dissolved in ethanol along with a small amount of HCl to the point where it boils and then condenses. The compound that was made in a one-pot,three

component process and solidified when the reaction mixture cooled was identified as 3,4-dihydropyrimidin-2(1H)-one 4 (Figure 2.1) (Kappe, 2003). The reaction is currently known as the "Biginelli reaction," "Biginelli condensation," or "Biginelli dihydropyrimidine synthesis."

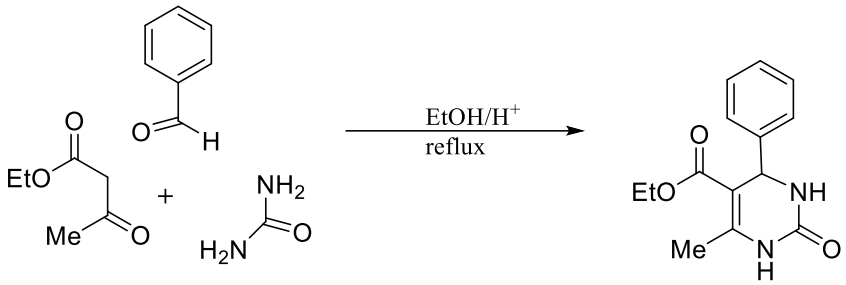



Figure 2.1 The orginal dihydropyrimidine condensation (Kappe, 1993a)

The initial instances of this cyclocondensation process primarily utilized a betaketoester, aromatic aldehyde, and urea. However, the range of this synthesis of heterocycles has significantly expanded by modifying all three components, enabling the production of numerous multifunctional zed pyrimidine derivatives. The literature and this chapter utilize the term DHPM to refer to this specific heterocyclic scaffold. Owing to the relevance of multicomponent reactions in combinatorial chemistry there has been increased interest in the Biginelli reaction, and the number of publications and patents reporting the synthesis of novel DHPM analogues is continually expanding. This chapter comprehensively discusses the Biginelli concept, specifically focusing on three-component condensations that involve CH-acidic carbonyl compounds, aldehydes, and urea-type building blocks. Given the publication of several review papers and monographs on different elements of the Biginelli response (Kappe, 1993a), this study will focus on recent advancements in the field during the past few years.

### 2.1.3 Free-Radical-Mediated Multicomponent Coupling Reactions

Additions of radicals to unsaturated bonds create additional radicals, which are then added to others. Iteratively performing this chemical sequence produces polymers. However, the normal radical polymerization sequence also exhibits radical-induced multicomponent assembly events, given the sequence and quantity of components are

regulated. How may radical addition reactions be controlled to be multicomponent reactions? Kinetics, radical polar effects, one-electron transfer quenching, and a radical chain system with a careful radical mediator are all conceivable. This chapter offers several answers. Each example suggests that multicomponent coupling processes are more efficient than uncontrolled radical polymerization reactions, which can reduce efficiency.

The nature of the different components is a crucial issue in the design of multicomponent coupling processes. In general, carbon radical species, including alkyl radicals, aryl radicals, vinyl radicals, and acyl radicals, are categorized as nucleophilic radicals. These radicals are highly reactive towards alkenes that lack electrons (Giese, 1983: 22). To illustrate, kinetic findings on tert-butyl and pivaloyl radical addition are shown in (Figure 2.2).

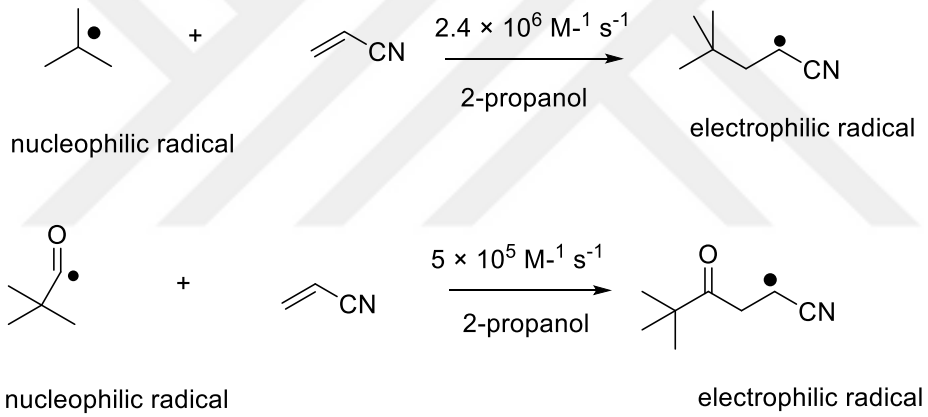



Figure 2.2 Kinetics of adding tert-butyl and pivaloyl radicals

### 2.1.4 Multicomponent Reactions with Organoboron Compounds

Multicomponent reactions (MCRs) involve consecutive reactions of three or more reactant components in the same reaction mixture. MCRs are efficient when components are compatible and do not react irreversibly to generate additional products or byproducts. In recent years, MCRs have gained popularity in the chemical and pharmaceutical industries due to their high convergence and atom economy, which lower production and environmental costs and provide access to many novel and diverse structures. Some of the fundamental principles and immense potential of MCRs have only become widely realized in the last decade with the rise of combinatorial chemistry (Negishi and De

Meijere, 2003). As a result, MCRs continue to draw attention, leading to new MCRs, modifications of old ones, and applications in organic synthesis, combinatorial chemistry, medicinal chemistry, and process chemistry.

### 2.1.5 Applications of Multicomponent Reactions in Drug Discovery

The superiority of an MCR synthesis compared to an equivalent linear synthesis is evident, as the size of a library created via a linear approach is determined by the number of stages and individual inputs. For instance, the library resulting from a three-step synthesis with 10 inputs at each step would consist of 103 compounds. On the other hand, the library obtained via a three-component multicomponent reaction (MCR) with 10 inputs/components would have the same size, but it could be done in a single chemical operation (Armstrong, 1997). The efficiency of MCRs is the primary factor driving the increase in research and assessment of recent literature. A clear analysis of recent publications indicates a significant rise in the number of articles each year on MCRs (Bienaymé and Bouzid, 1998). The facilitative potential of these interactions is evident at many phases of the drug discovery process.

***Diversity-Oriented Synthesis (DOS):*** MCRs allow for the rapid construction of complex molecular scaffolds, leading to the generation of diverse compound libraries. This diversity is crucial in drug discovery to explore a wide range of chemical space and identify potential lead compounds (Biggs-Houck et al., 2010).

***Efficient Synthesis of Complex Molecules:*** MCRs enable the simultaneous assembly of multiple functional groups, reducing the number of synthetic steps required to generate complex molecules. This efficiency is valuable in the synthesis of drug candidates, where a streamlined process can save time and resources (Heijden et al., 2013).

***Fragment-Based Drug Discovery (FBDD):*** MCRs can be used to synthesize libraries of fragments that can be screened for their binding affinity to a target protein. These fragments can then be further optimized and combined to develop more potent drug candidates (Law et al., 2009).

***Lead Optimization:*** MCRs facilitate the rapid modification of lead compounds, allowing for the introduction of various functional groups in a single step. This accelerates the lead optimization process by providing quick access to analogs for structure-activity relationship (SAR) studies (Younus et al., 2021).

***Parallel Synthesis:*** MCRs are amenable to parallel synthesis strategies, enabling the simultaneous generation of multiple compound analogs. This parallelization is beneficial in high-throughput screening campaigns, where a large number of compounds need to be evaluated for biological activity (Obrecht et al., 2009).

***Scaffold Hopping****:* MCRs enable the synthesis of molecules with novel scaffolds, offering a way to explore chemical space beyond traditional compound classes. Scaffold hopping can be crucial in overcoming limitations associated with existing drugs and developing innovative therapeutic agents (Dömling et al., 2012).

***Green Chemistry:*** Many MCRs are atom-economical and generate minimal waste, aligning with principles of green chemistry. The reduced environmental impact makes MCRs attractive in drug discovery programs with a focus on sustainability (Cioc et al., 2014).

***Bioorthogonal Chemistry:*** MCRs can be designed to be compatible with biological systems, allowing for bioorthogonal reactions. This is particularly useful in the development of prodrugs or imaging agents that can be selectively activated in the presence of specific biomolecules (Parker and Pratt, 2020).

***Natural Product Synthesis:*** MCRs have been employed in the synthesis of natural products and their analogs. Natural products often serve as inspiration for drug discovery, and MCRs offer efficient routes to access complex structures found in these bioactive molecules (Touré and Hall, 2009).

***Late-Stage Functionalization:*** MCRs can be employed for the late-stage functionalization of drug candidates, allowing for the introduction of additional

functionalities to improve pharmacokinetic or pharmacodynamic properties (Ricardo et al., 2019).

In summary, the applications of multicomponent reactions in drug discovery are diverse, ranging from the rapid synthesis of compound libraries to the optimization of lead compounds and the exploration of novel chemical space. Their efficiency, versatility, and compatibility with modern synthetic and screening methods make MCRs valuable tools in the pursuit of new therapeutic agents.

### 2.1.6 Metal-catalyzed Multicomponent Reactions

With the rise in multicomponent reaction research, wonderful metal-catalyzed coupling mechanisms have been discovered. Metal catalysts' bond-forming mechanisms help this field. Metal-mediated intermolecular reaction cascades via non-isolable intermediates like catalytic organometallic species are ideal for designing "ideal" multicomponent reactions that allow the simultaneous addition of all reactants, reagents, and catalysts at the start of the reaction and their unique ordered combination under the same reaction

Palladium, nickel, and ruthenium are popular transition metals because they may drive cascade reactions with strong chemo-, regio-, and stereoselectivities in mild conditions. Metal-mediated multicomponent reactions use cascade processes to assemble well-designed building blocks. Serendipity still turns up such methods (Han et al., 2019).

Beyond the "cascade strategy." other alternatives based on sequences of distinct transformations in a one-pot process to avoid intermediate isolation have gained acceptance. Reactant, reagent, and catalyst addition may be delayed in "formal" multicomponent processes to enhance efficiency and avoid side reactions. We can also change reaction parameters during multi-reaction chemical processes. This approach can be utilized for many metal-catalyzed procedures using the same or different catalyst. Other organic transformations can be combined with metal-catalyzed processes.

One benefit of transition metals is their ability to incorporate carbon monoxide into various places in the final molecule, broadening the variety of processes. Numerous three-component reactions resulting from carbonylative processes, such as alkoxy-, amino-, hydroxycarbonylations, and formylations, have been widely reviewed (Negishi

and Meijere, 2005). Thus, only those reactions will be reported here. Coupling procedures with carbon monoxide as a fourth partner. This article presents creative tactics that prioritize diversity and variance rather than a comprehensive literature review. We will also describe less typical multicomponent processes for target synthesis.

### 2.1.7 Catalytic asymmetric Multicomponent Reactions

The process entails the synthesis of chiral compounds through the simultaneous addition of three or more reagents. This type of addition and reaction offers several advantages compared to traditional divergent reaction procedures, including reduced costs, time, and energy requirements, as well as more environmentally sustainable elements. The numerous benefits, along with the notable level of stereoselectivity achieved in certain reactions, will compel chemists in both industry and academia to embrace this novel synthesis technique, or at the at least, regard it as a feasible alternative (Ramón and Yus, 2005). Catalytic asymmetric multicomponent processes are highly beneficial but require significant effort, and only a limited number of examples have been successfully achieved thus far. Here we present a concise summary of this dynamic and swiftly expanding field. Many catalytic asymmetric multicomponent reactions (MCR) rely regarding deoxo-bisubstitution reactions of carbonyl compounds, specifically the Mannich and Strecker reactions. During these processes, a single oxo-group is substituted with two new σ-bonds, one connecting to a nitrogen atom and the other to a carbon atom.

#### 2.1.7.1 Mannich Reaction

The Mannich reaction is a chemical reaction that involves three components: an enolizable CH-acidic carbonyl molecule, an amine, and an aldehyde. This reaction results in the formation of baminocarbonyl compounds. The direct Mannich reactions can present significant selectivity challenges since both the aldehyde and The CH-acidic substrate often has the ability to act as either a nucleophile or an electrophile. Aldol addition and condensation can compete. Useful electrophiles include imines, iminium salts, hydrazones, and nucleophiles such enolates, enamines, and enol ethers are regularly utilized. This technique simplifies the process of identifying specific functions for each carbon component that contains a carbonyl group (Figure 2.3). Therefore, the earliest

catalytic enantioselective Mannich reactions that were established, however sophisticated and beneficial, were all carried out indirectly.

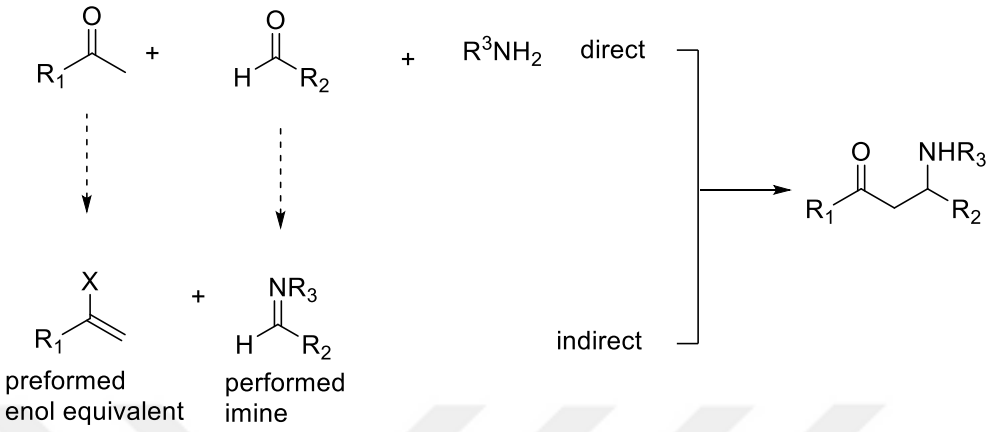



Figure 2.3 Direct and indirect Mannich reaction

The initial direct three-component catalytic enantioselective Mannich reaction (Armstrong, 1997). In this reaction, propiophenone 1, paraformaldehyde 2, and pyrrolidine 3 were combined and reacted using (R)-LaLi$_3$tris (binaphthoxide) [(R)-LLB, 4] as the catalyst. This resulted in the formation of Mannich product 5 with an enantiomeric excess of 64% and a yield of 16% (Figure 2.4).

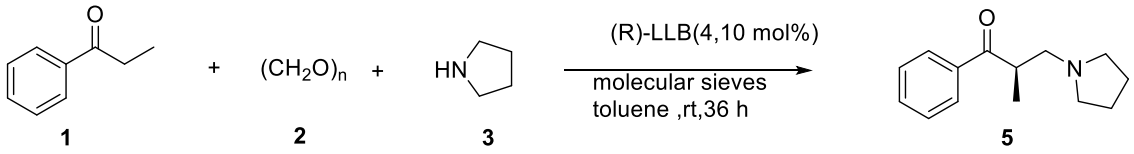



Figure 2.4 (R)-LaLi3tris (binaphthoxide)-catalyzed enantioselective three-component Mannich reaction

### 2.1.7.2 Strecker Reaction

The Strecker reaction is a chemical process that involves three components: an aldehyde (or ketone), ammonia (or another amine), and hydrogen cyanide (or equivalents). This reaction produces a-amino nitriles, which can be further hydrolyzed to form a-amino acids. The reaction is illustrated in (Figure 2.5).

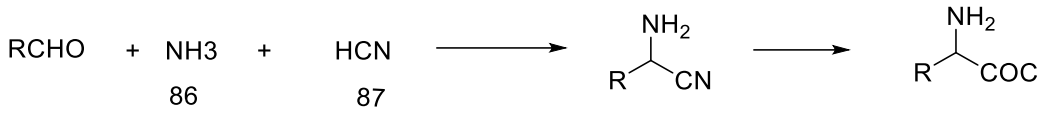



Figure 2.5 Synthesis of α-amino via a Strecker reaction

The Strecker reaction has been extensively employed in industrial settings for synthetic purposes. Racemic α-amino acids are a class of amino acids that exist in both enantiomeric forms, with one being left-handed and the other being right-handed. Furthermore, there exist asymmetric variants of these amino acids. Nevertheless, most of the recorded catalytic asymmetric Strecker-type reactions are of an indirect character and utilize preformed imines are commonly derived from aromatic aldehydes (Masamba, 2021).

### 2.1.8 Algorithmic Approaches for the Identification of New Multicomponent Reactions

Combinatorial chemistry is being used by organic chemists in the pharmaceutical sector to accelerate the process of discovering physiologically active compounds. It is also employed to identify novel agrochemicals, catalysts, polymers, and other materials with specific desirable qualities.

Combinatorial chemistry is an experimental approach used to identify the specific combination of substituents for a given chemical backbone that would demonstrate the required qualities. Consequently, the use of combinatorial synthesis has created a need for innovative synthetic techniques that produce unique chemical structures. Multicomponent reactions (MCRs) are considered particularly fascinating since they include more than two starting components that actively contribute to the formation of the bulk of the product's structure. These reactions are seen as a promising approach to address the aforementioned requirements. MCRs provide the potential for new and innovative processes and intellectual property connected to compounds.

Additionally, they facilitate the automation of synthesizing, analyzing, and evaluating the physicochemical or biological features of the reaction products that are produced as a consequence. Hence, the identification of novel MCRs enhances the efficacy of combinatorial chemistry and presents an intriguing research endeavor in the

field of organic chemistry. Considering these factors together, the identification of new multicomponent reactions may be regarded as a captivating subject for scholarly investigation that also fulfills a utilitarian aspect of applied sciences.

Although there is considerable interest in this area, the discovery of novel reaction types in organic chemistry has often been serendipitous rather than the result of deliberate design or logical analysis.

#### 2.1.8.1 What Exactly are Novel MCRs?

Firstly, it would be beneficial to provide a generic definition of what constitutes a "new" reaction.

Multiple techniques exist for categorizing chemical reactions. The oldest categorization system examines whether a specific compound class or chemical scaffold can be successfully produced under specific reaction conditions. This is frequently named after the chemist who first discovered or made significant contributions to these reactions. There are around 700 to 900 responses that have been given specific names. The classification primarily revolves upon the product, although in certain instances, it can be linked to certain initial substances, such as the nitrosamine rearrangement (Zarganes-Tzitzikas et al., 2015).

#### 2.1.8.2 Unexpected Products Yield Novel MCRs

The current utilization of parallel combinatorial chemistry methodologies involves a significantly greater number of independent reactions of a specific reaction type compared to previous practices. It is common for us to notice that certain expected reaction products in a compound library are not produced. This is because the starting materials may not result in the desired product due to several reasons, under the specific reaction circumstances specified. Alternatively, unforeseen reaction byproducts may arise in certain instances.

One such instance involved the observation of an unforeseen reaction result in three separate research laboratories. While attempting to create a collection of Ugi-type four-component compounds using different isonitriles, aldehydes, acids, and amines, the reaction did not provide the intended Ugi-type four-component output when amino

pyridine-like starting materials were employed as the amine component.

Regarding 2-amino pyridine-type amines, the production process is achieved without any impurities. imidazo[1,2-a]pyridines was found by a novel three-component reaction instead of the anticipated 4-CR product (Figure 2.6) (Bienayme and Bouzid, 1998; Groebke et al., 1998).

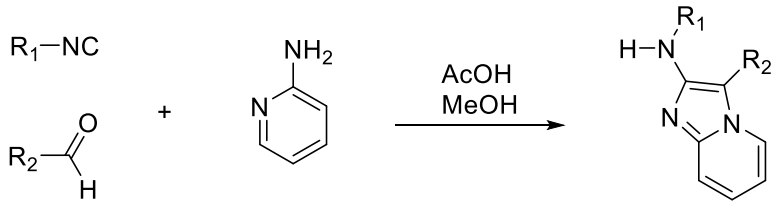



Figure 2.6 Novel imidazo [1,2-a]accidental pyridine synthesis

### 2.1.8.3 Experimental Designs to Search for New MCRs

Data significantly influences our ability to handle reaction data. Therefore, a different approach to discovering new MCRs was suggested using the concept of combinatorial reaction discover. Ten distinct initial substances were chosen for this experiment, as depicted in Scheme (Figure 2.7).

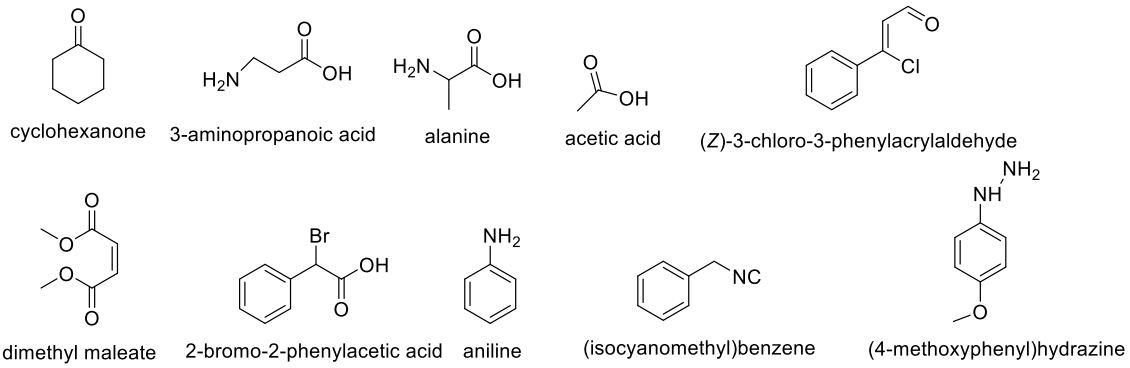



Figure 2.7 Ten Starting Components for Systematic Research into New Reactions

### 2.1.8.4 Combinatorial Optimization of Reaction Conditions

Optimizing the conditions for multiple-component reactions (MCRs) is more challenging compared to single-step reactions due to the diverse variety of reactions and their specific requirements. The task of identifying the most effective catalysts, solvents or solvent combinations, temperatures, concentrations of the initial substances, and

reaction duration is inherently a combinatorial challenge. Combinatorial methods, in conjunction with experimental design techniques like genetic algorithms, can be employed to discover the most favorable reaction conditions for these multi-component reactions (MCRs). Therefore, a collection of diverse one specific multicomponent reaction (MCR) can be conducted using parallel reaction conditions.

The output of the anticipated reaction product was employed as feedback in an illustrative case A genetic algorithm (GA)-guided technique provides new reaction conditions. Through several synthesis and analysis iterations, yield of this reaction was substantially enhanced by implementing superior reaction conditions. Subsequently, a series of diverse Multiple Criteria Runs (MCRs) were conducted simultaneously, each with its own unique set of conditions. These MCRs were then refined using a Genetic Algorithm (GA) to identify the most favorable conditions that were similar throughout all runs (Weber, 2002).

## 2.2 The Aim of Project

Our present objective is to alter acetoacetylation pyrimidines utilizing distinct and advantageous techniques that we have devised in two phases, aligning with our comprehensive analysis of existing literature. The investigation of these structures, initial synthesis methods, and novel molecular synthesis methods is lacking in depth. In the second phase, pyrimidine derivatives undergo acetoacetylation to generate novel compounds. There is a scarcity of research on the practical application of these substances. The existing pyrimidine synthesis methods exhibit low efficiency, intricate reaction conditions, restricted range of derivatives, costly catalysts, and a multi-step procedure. The Biginelli reaction was utilized to synthesize pyrimidine compounds that were functionalized with aldehyde groups. The final product was obtained through acetoacetylation of pyrimidine derivatives in the second stage.

# 3. MATERIALS AND METHODS

## 3.1 Materials

To create novel acetoacetylation pyrimidine derivatives, the techniques created and improved in this study were applied. Nuclear magnetic resonance spectroscopy using the $^{1}H$ and $^{13}C$-NMR spectra was used to characterize the compounds. Dichloromethane ($CH_2Cl_2$) was used as the solvent on an Agilent NMR (400 MHz) Spectrometer to acquire the $^{1}H$ and $^{13}C$-NMR spectra. They were additionally, utilizing Dimethyl sulfoxide (DMSO) serving as a benchmark internally and chemical shift values (δ) reported in (ppm). The symbols below represent the various spin multiplicities represented by the 1H NMR data. Carbons of the following categories are listed in the $^{13}C$-NMR data: C, CH, $CH_2$, and $CH_3$. to perform flash chromatography, silica gel was used, and thin layer chromatography (TLC) was used to monitor all reactions. TLC was used to confirm the separation and purification of the chemicals. Before usage, the appropriate drying agents were used to distill and then dry all of the organic solvents. Without exception, $MgSO_4$ was used to dry the organic extracts.

### 3.1.1 Chemical Substances

Chemicals from manufacturers including Merck, Fluka, and Sigma-Aldrich, which were of analytical quality, were utilized in this thesis. Additionally, a variety of organic solvents that are employed in preparative organic chemistry have been explored and used in the purification procedures and organic synthesis.

### 3.1.2 Equipment and Instruments

Tools and devices used in the experiments are listed below:

1. Agilent 400/54 / A5C Premium brand NMR instrument for $^{1}H$ and $^{13}C$ NMR.
2. Merck TLC Plate Silica Gel 60 F254.
3. Gallenkamp Melting Point Apparat--

4. Heidolph 4100 Brand Rotary Evaporator.
5. Memmert Universal Oven UN55.
6. Shimadzu ATX 224 Analytical Balance.
7. CAMAG UV Lamp 4, Double Wavelength 254/366 nm.
8. Heidolph and Wisd brands Hotplate Magnetic Stirrer.
9. Shimadzu IRMRfinity-1S FTIR Spectrophotometer.

## 3.2 Glassware. Synthesis of Compounds

### 3.2.1 Methyl (*E*)-6-methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (MR-1)

Methyl acetoacetate (3.6 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and urea (1.8 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to yellow mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produce bulk solid product. When the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by in ethanol. MR-1 Melting point 232-236 ℃, 6.98g (Yield = 76.1%) (Figure 3.1) (Xia and Wang, 2002).

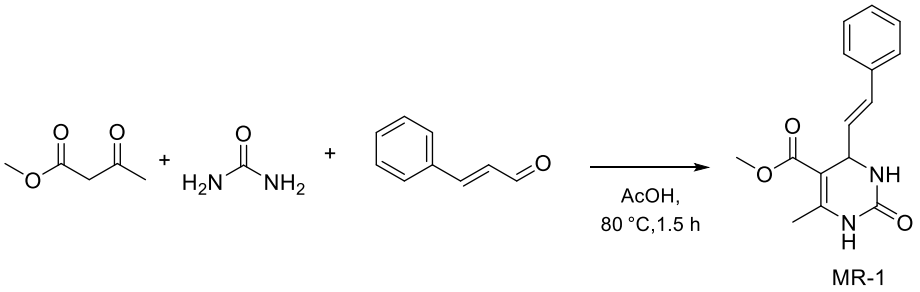



Figure 3.1 Formation of the MR-1 molecule

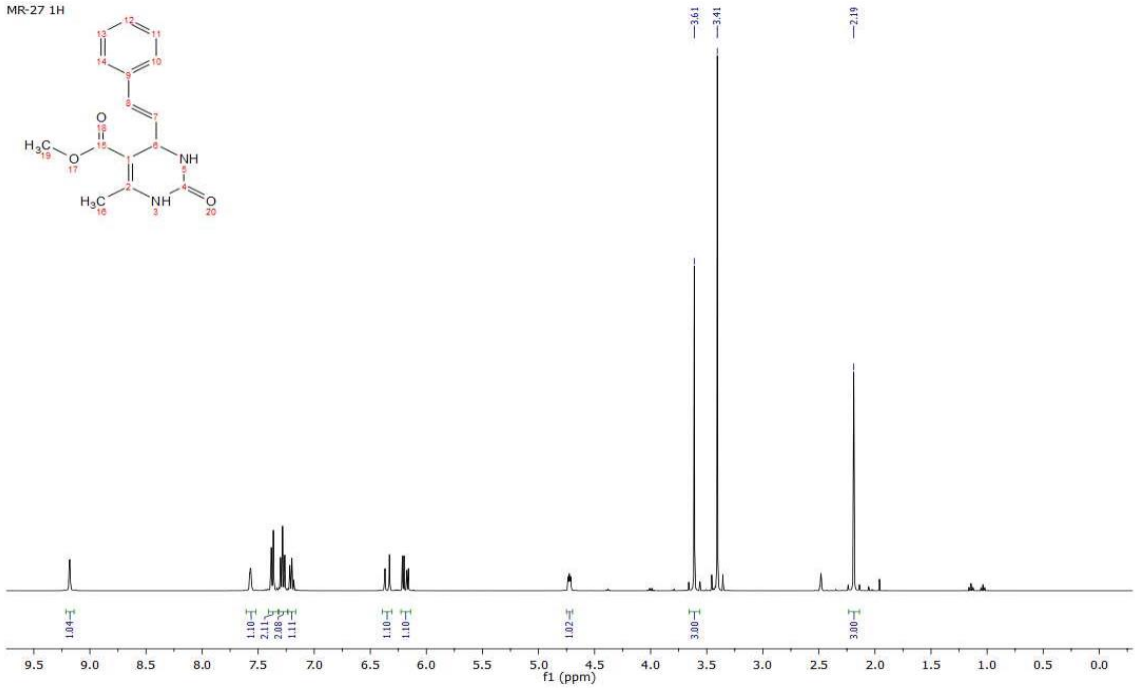



Figure 3.2 $^{1}$H-NMR of MR-1

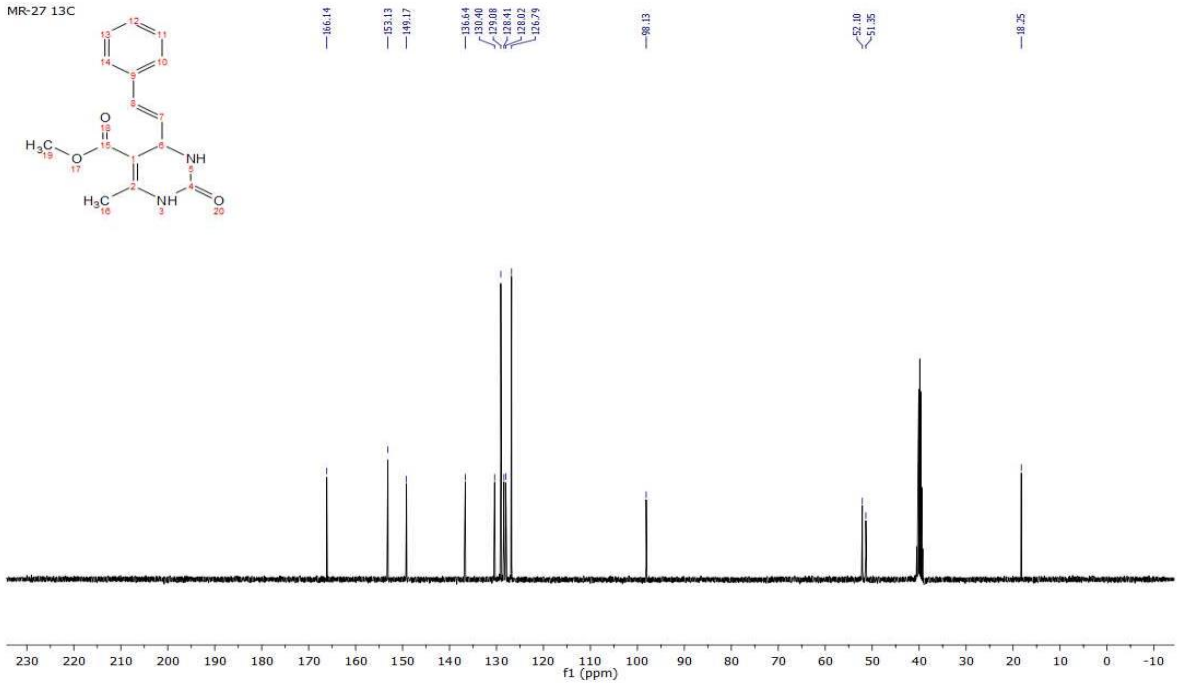



Figure 3.3 $^{13}$C-NMR of MR-2

### 3.2.2 Ethyl (*E*)-6-methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (MR-2)

Ethyl acetoacetate (3.8 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and urea (1.8 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to dark yellow mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produced bulk solid product. When the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by in ethanol. MR-2 Melting point 240-244℃, 7.54g (Yield = 88.1%) (Figure 3.4). (Gangadasua et al., 2004).

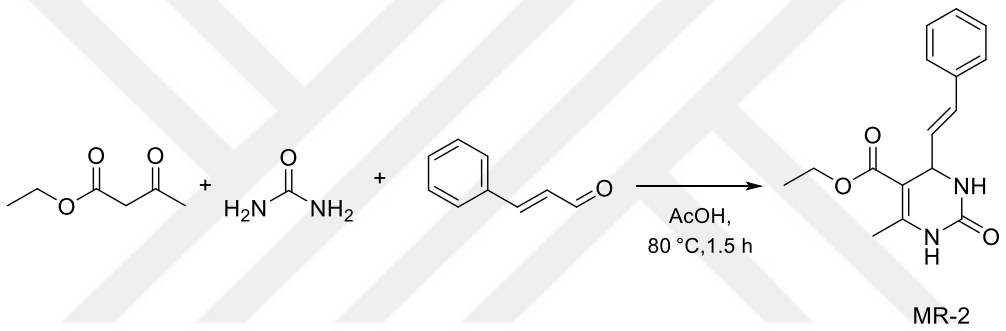



Figure 3.4 Formation of the MR-2 molecule

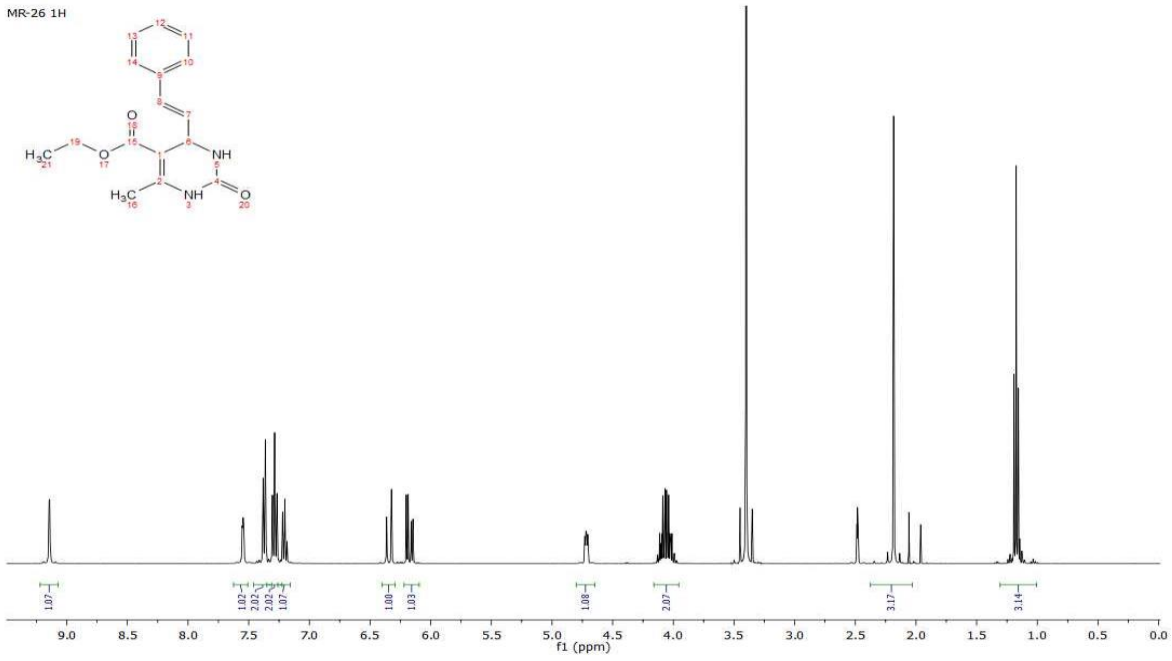



Figure 3.5 $^{1}$H-NMR of MR-2

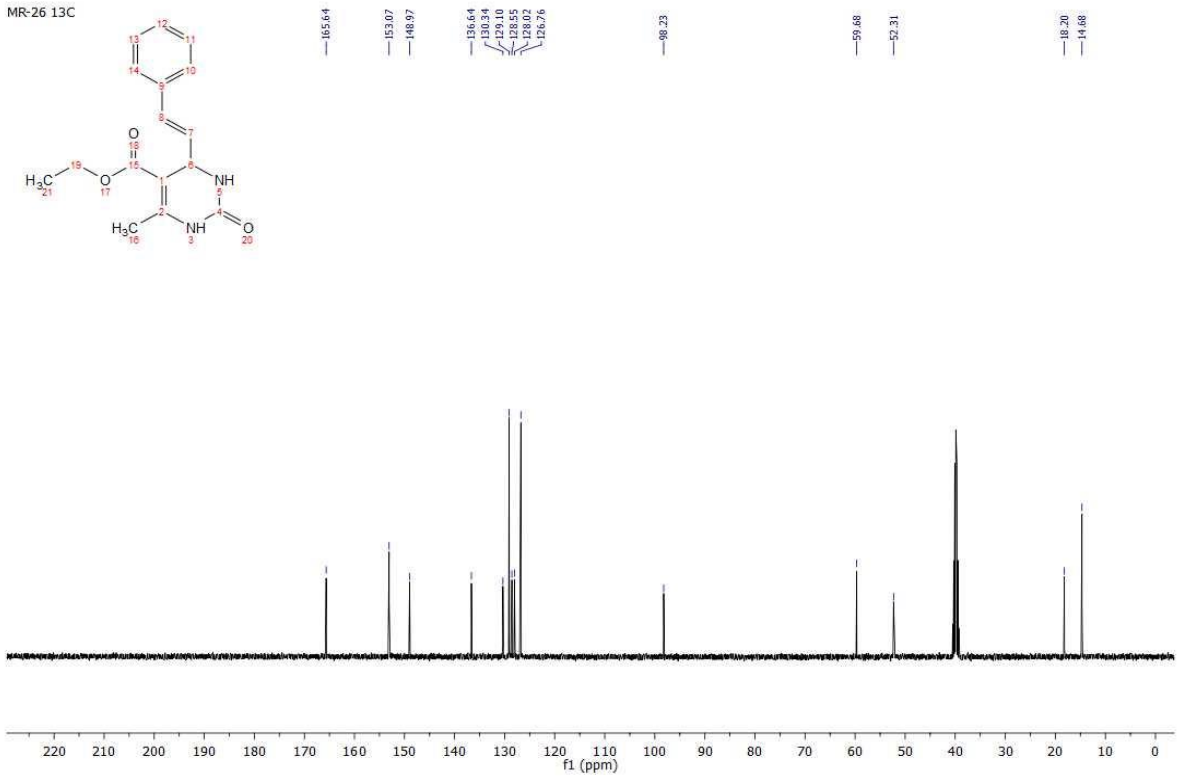



Figure 3.6 $^{13}$C-NMR of MR-2

### 3.2.3 (*E*)-5-acetyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one (MR-3)

Acetylacetone (3.1 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and urea (1.8 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to red mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produce bulk solid product. When the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by in ethanol. MR-3 Melting point 219-223℃, 5.84g (Yield = 76.1%) (Figure 3.7) (Sun et al., 2004).

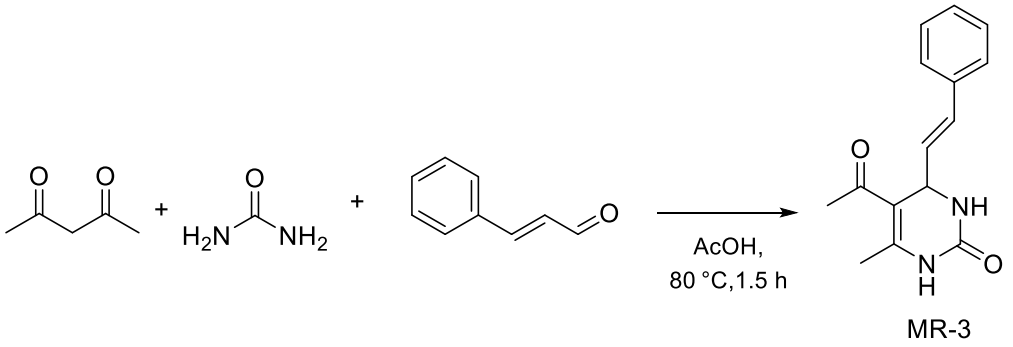



Figure 3.7 Formation of the MR-3 molecule

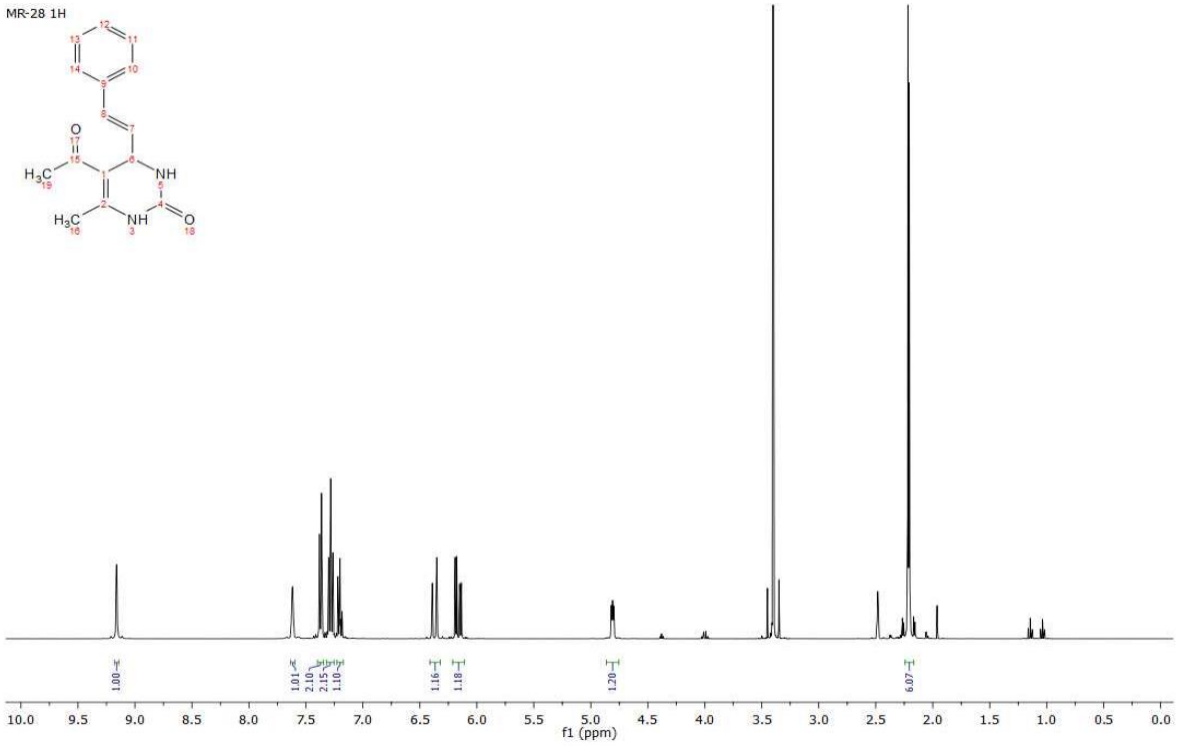



Figure 3.8 $^{1}$H-NMR of MR-3

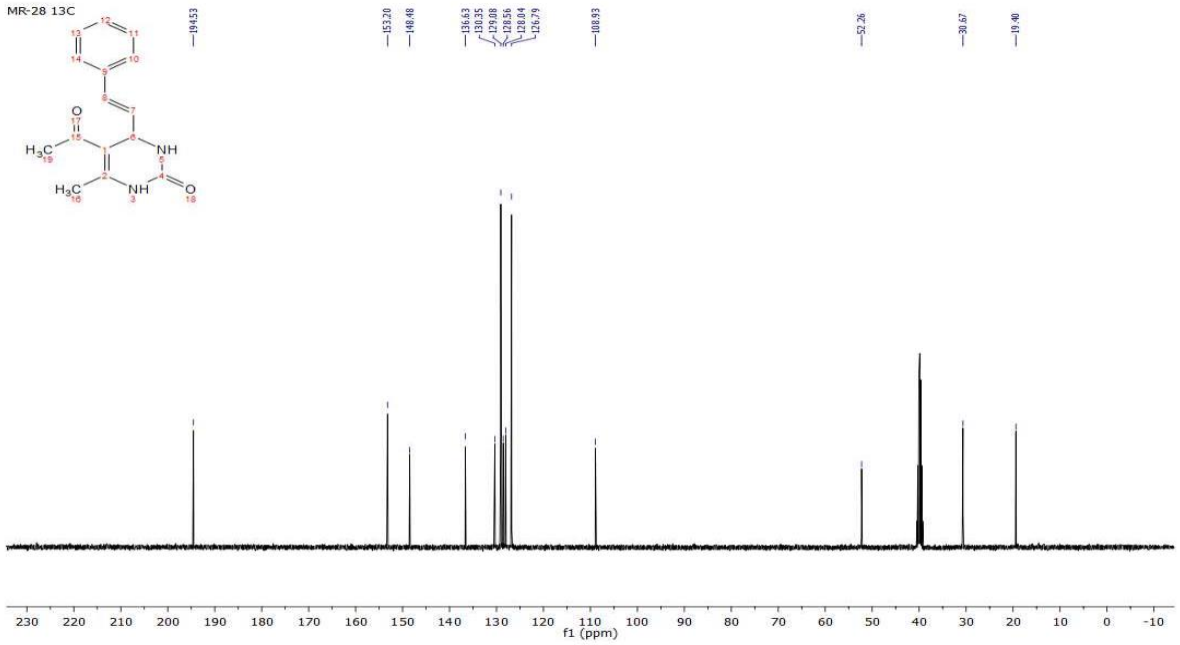



Figure 3.9 $^{13}$C NMR of MR-3

### 3.2.4 Methyl (*E*)-6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (MR-4)

Methyl acetoacetate (3.6 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and thiourea (2.28 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to red mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produce bulk solid product. When the product was precipitated, the solution was filtrate and dried. Then, the participate were recrystallized by ethanol. MR-4 Melting point 207-211℃, 4.84g (Yield = 64.1%) (Figure 3.10). (Kulkarni et al., 2009).

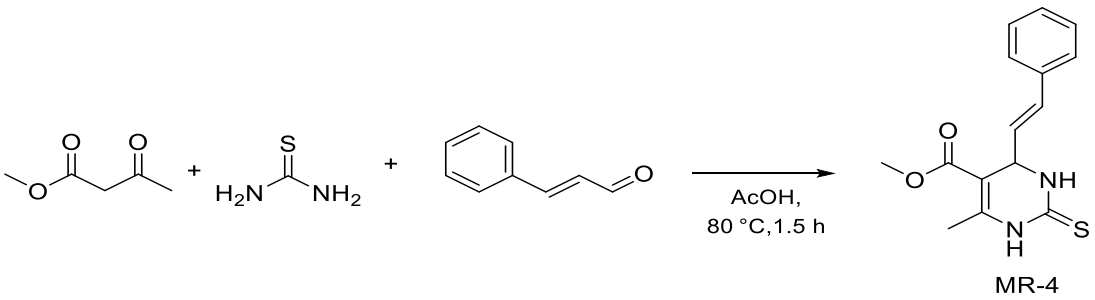



Figure 3.10 Formation of the MR-4 molecule

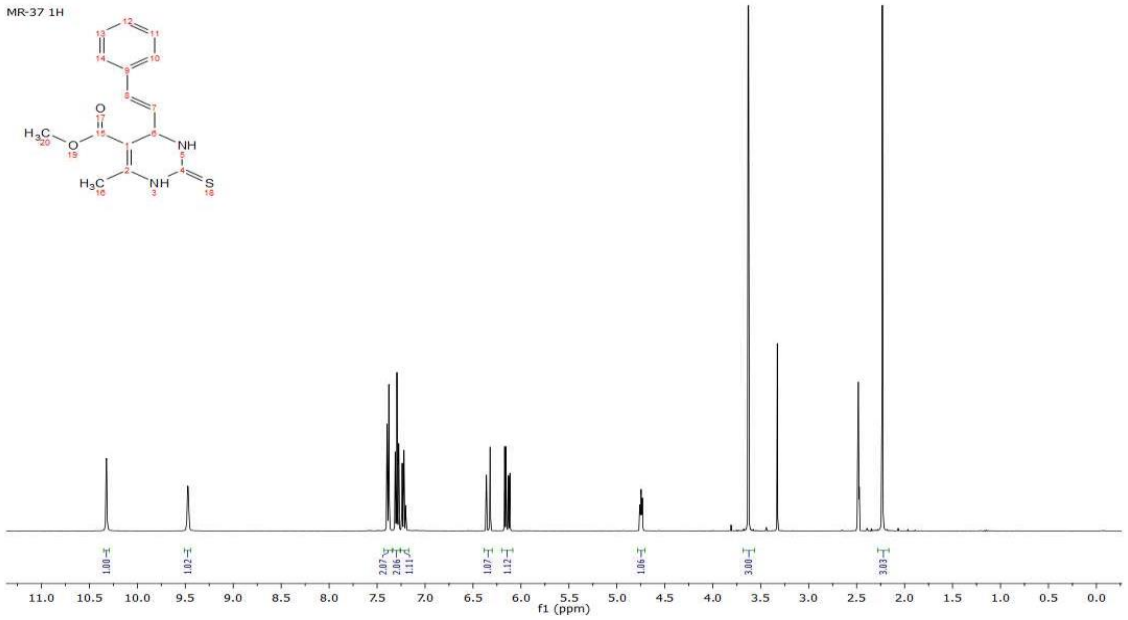



Figure 3.11 $^{1}$H-NMR of MR-4

### 3.2.5 Ethyl (E)-6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (MR-5)

Ethyl acetoacetate (3.6 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and thiourea (2.28 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to yellow ow mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produce bulk solid product. When the product was precipitated, the solution was filtrate and dried. Then, the participate were recrystallized by ethanol. MR-5 Melting point 194-198℃, 6.04g (Yield = 71.1%) (Figure 3.12) (Pore et al., 2010).

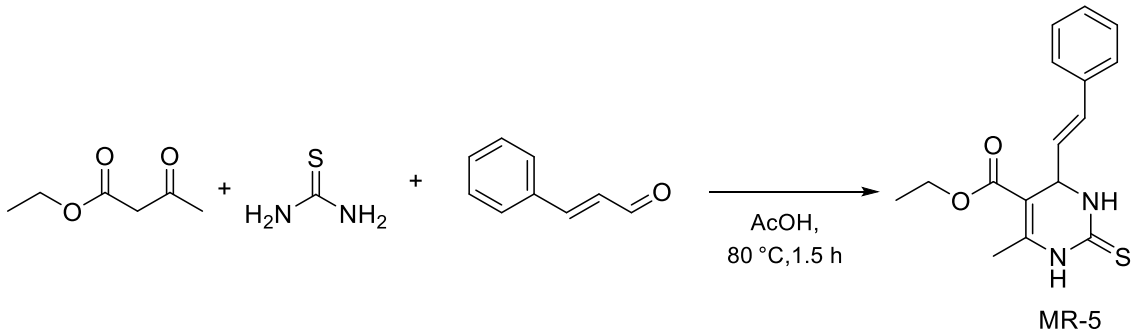



Figure 3.12 Formation of the molecule MR-5

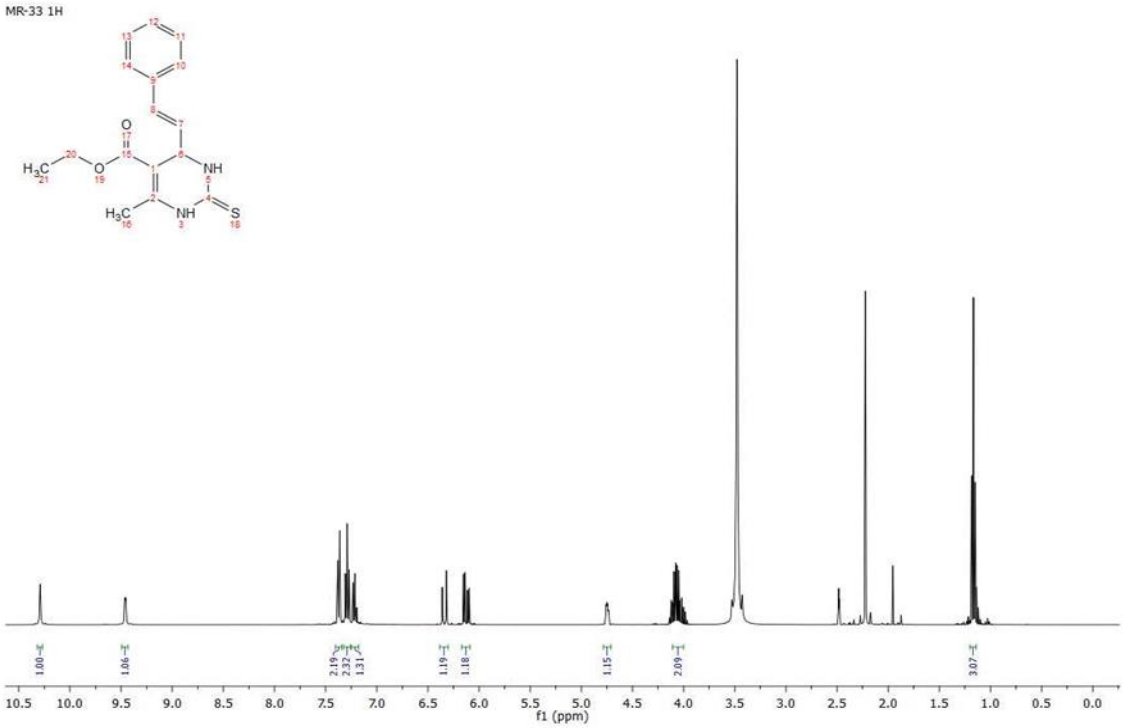



Figure 3.13 $^{1}$H-NMR of MR-5

### 3.2.6 (*E*)-1-(6-methyl-4-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one (MR-6)

Pentane-2,4-dione (3.1 ml, 30 mmol), cinnamaldehyde (3.7 ml, 30 mmol) and urea (2.28 g, 30 mmol) were solved in 10 ml of acetic acid. Then, the solution was heated until 80 °C for 1.5 hour and the reaction was followed up by TLC also color (color less mixture to red mixture reaction). When it was decided to finish the reaction, the heating of the reaction turned off but stirring go on until produce bulk solid product. When the product was precipitated, the solution was filtrated and dried. Then, the participate were recrystallized by ethanol. MR-6 Melting point 241-245℃, 5.84g (Yield = 73.1%) (Figure 3.14) (Hussein et al., 2012).

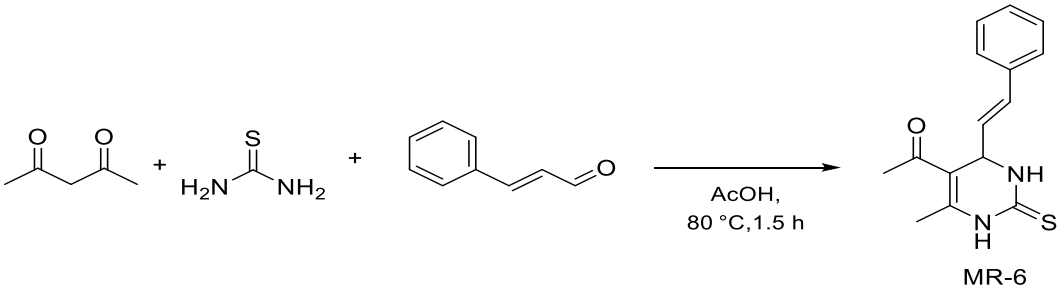



Figure 3.14 Formation of the molecule MR-6

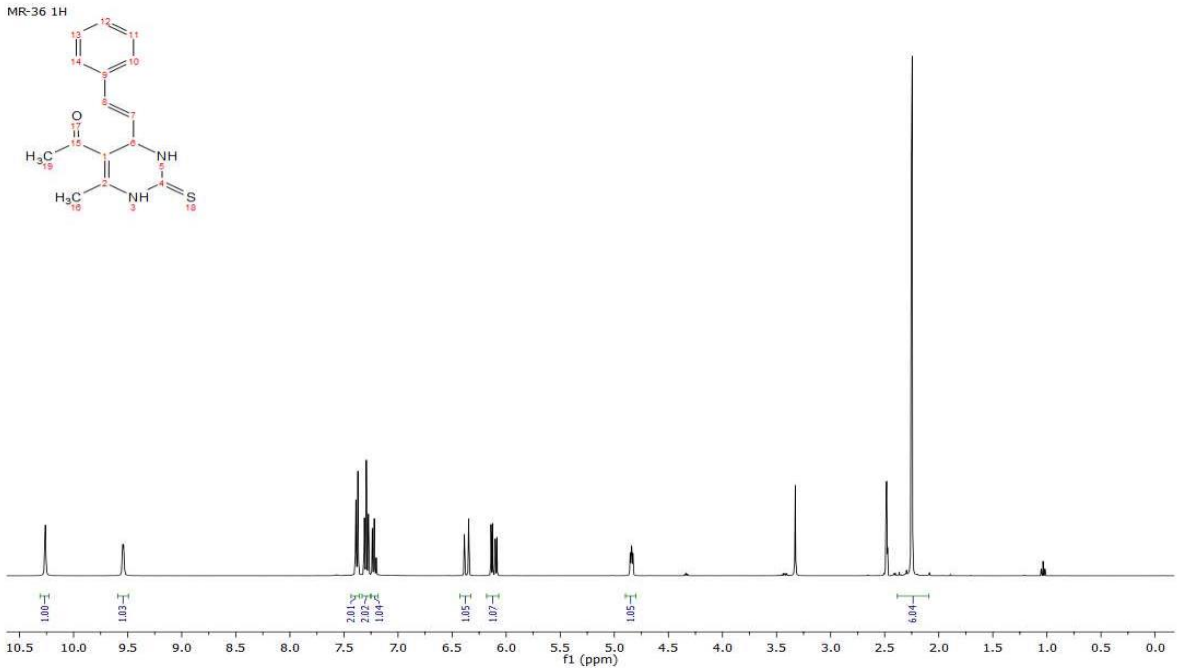
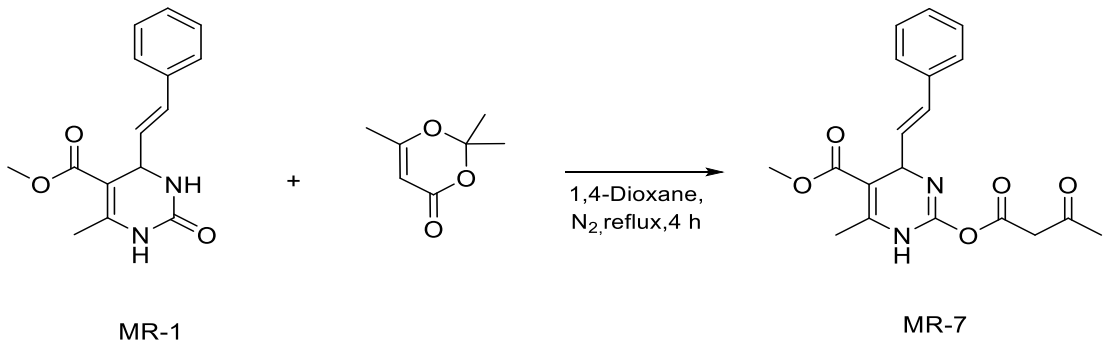



Figure 3.15 $^{1}$H-NMR of MR-6

### 3.2.7 Methyl (*E*)-6-methyl-2-((3-oxobutanoyl)oxy)-4-styryl-1,4-dihydropyrimidine-5-carboxylate (MR-7)

MR-1 (1.0 g) dissolved in 20 ml of 1,4-Dioxane then added 2,2,6-trimethyl-4*H*-1,3- dioxine-4-one (0.6 ml) was mixed. The reaction mixture was refluxed with $N_2$ for 4 hr and was proceeded by TLC. The reaction mixture was cooled, and the liquid phase was evaporated. Then, crude products are separated by column chromatography (1H/1E). The formed dry then take $^{1}$H, $^{13}$C-NMR. MR-7 Melting point 137-141 °C, 0.80g (Yield =62.5 %), (Figure 3 .16)




MR-1 MR-7

Figure 3.16 Formation of the molecule MR-7

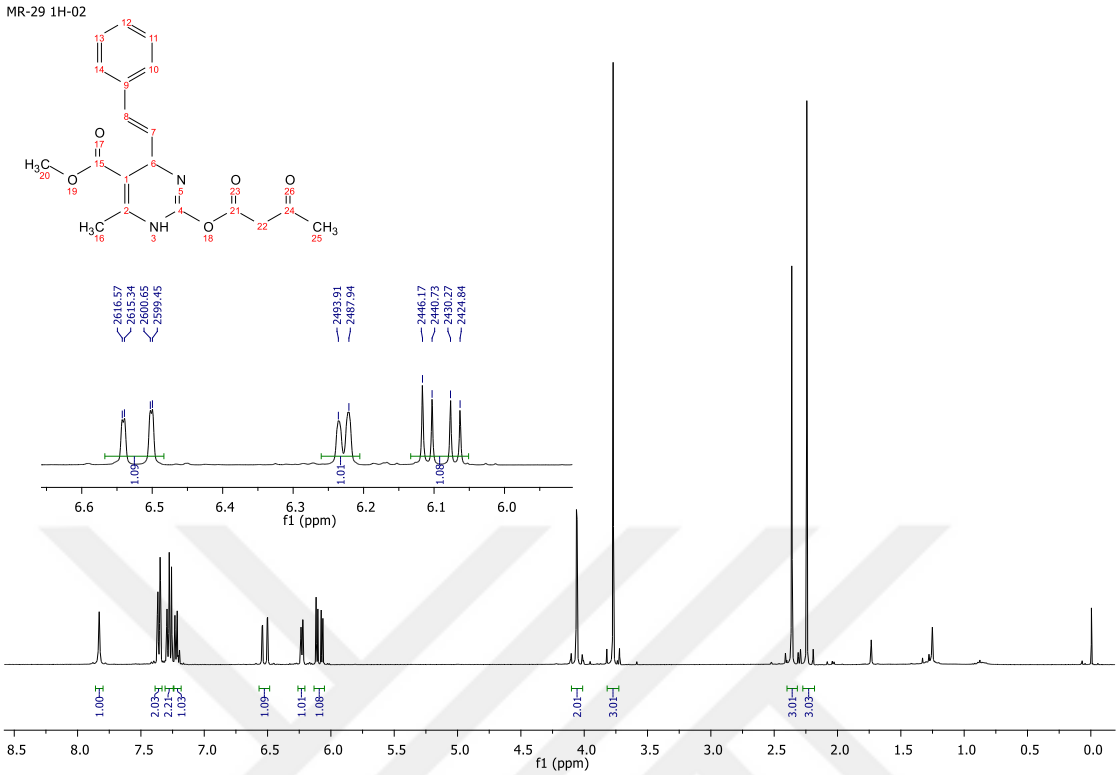



Figure 3.17 $^{1}$H-NMR of MR-7

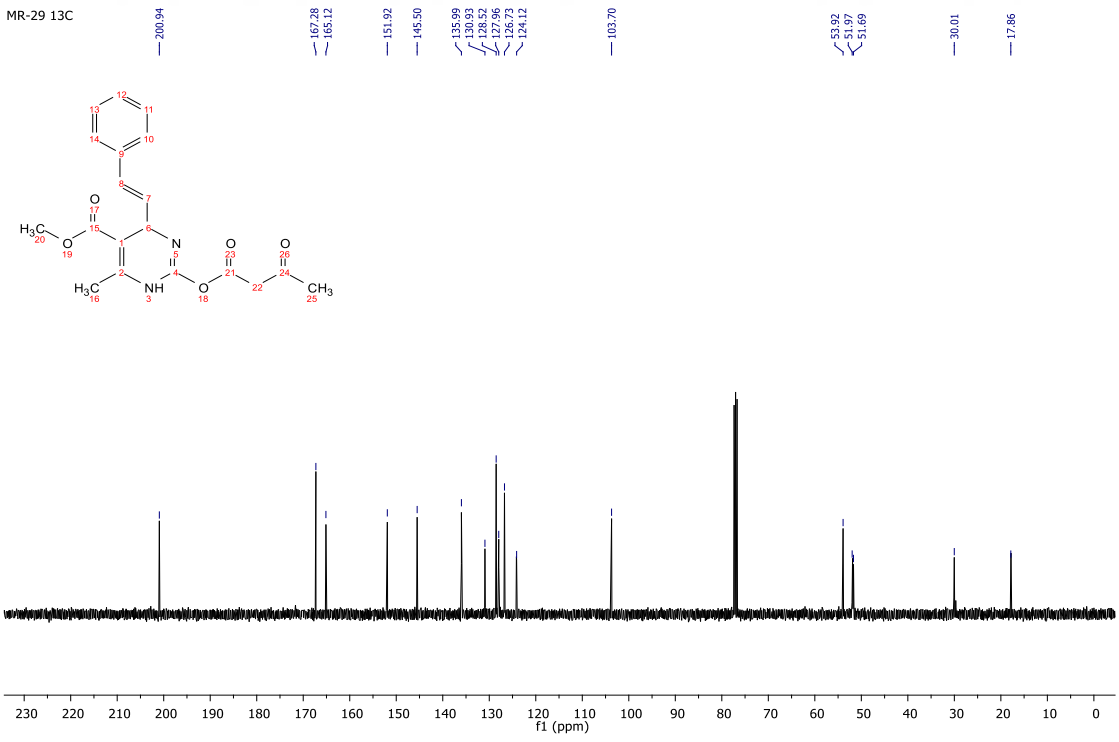



Figure 3.18 $^{13}$C-NMR of MR-7

### 3.2.8 Ethyl (*E*)-6-methyl-2-((3-oxobutanoyl)oxy)-4-styryl-1,4-dihydropyrimidine-5-carboxylate (MR-8)

MR-2 (1.0 g) dissolved in 20 ml of 1,4-dioxane then added 2,2,6-Trimethyl-4H-1,3- dioxine-4-one (0.6 ml) was mixed. The reaction mixture was refluxed with $N_2$ for 3 hr. and was proceeded by TLC. The reaction mixture was cooled, and the liquid phase was evaporated. Then, crude products are separated by Column chromatography (1H/1E). The formed dry then take $^{1}H$, $^{13}C$-NMR. MR-4 Melting point 145-149 °C, 0.49g (Yield =37.9 %), (Figure 3 .19).

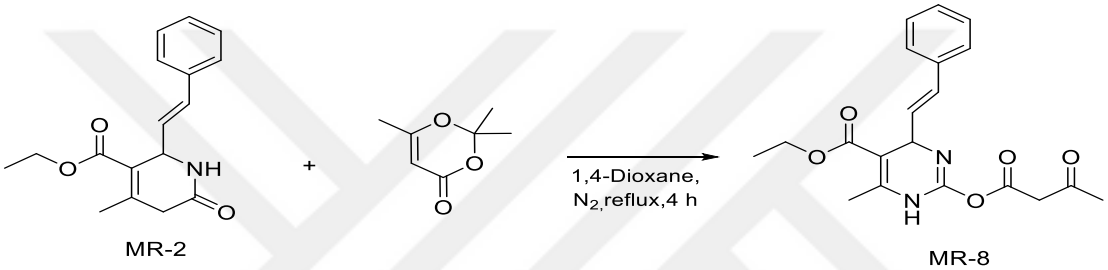



Figure 3.19 Formation of the molecule MR-8

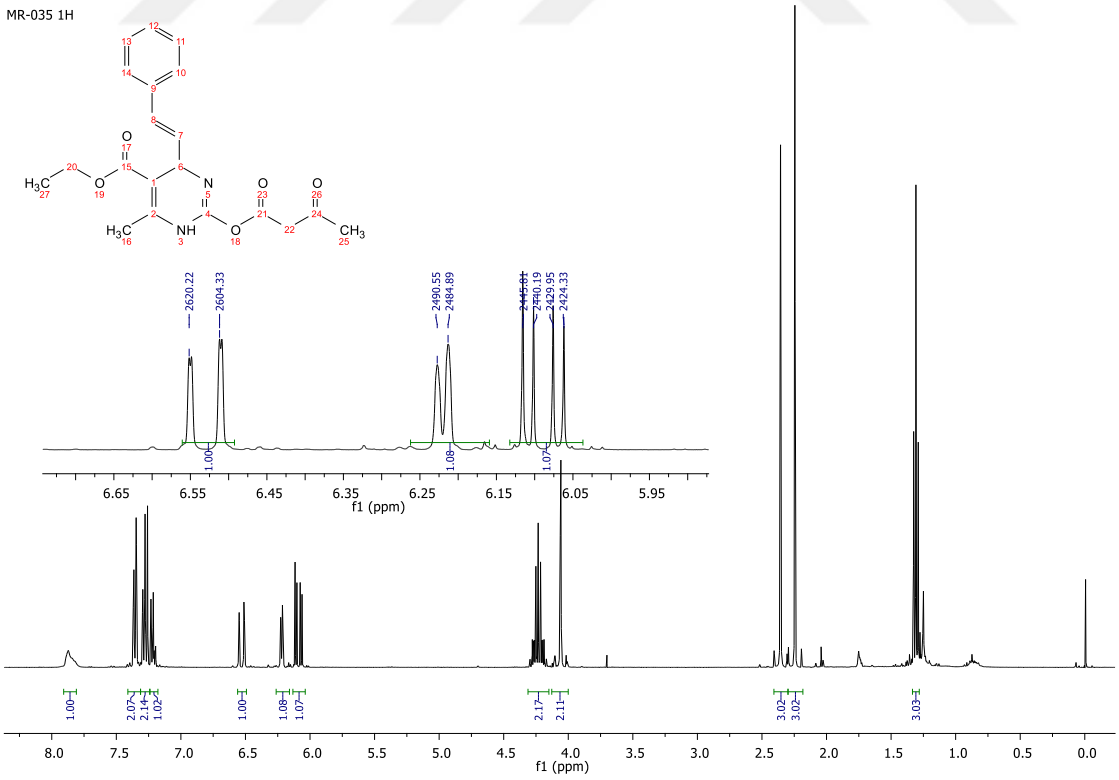



Figure 3.20 $^{1}H$ NMR of MR-8

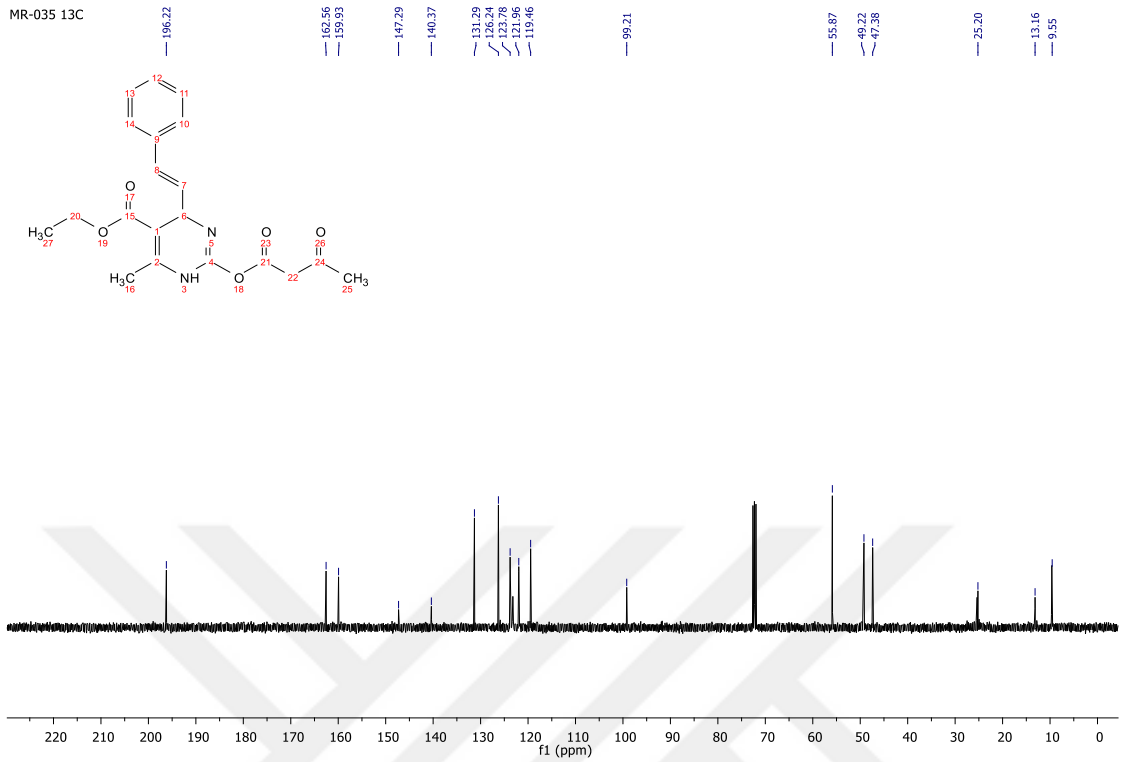



Figure 3.21 $^{13}$C NMR of MR-8

### 3.2.9 (*E*)-5-acetyl-6-methyl-4-styryl-1,4-dihydropyrimidin-2-yl-3-oxobutanoate (MR-9)

MR-3 (1.0 g) dissolved in 20 ml of 1,4-dioxane then added 2,2,6-trimethyl-4*H*-1,3- dioxine-4-one (0.6 ml) was mixed. The reaction mixture was refluxed with $N_2$ for 4 hr and was proceeded by TLC. The reaction mixture was cooled, and the liquid phase was evaporated. Then, crude products are separated by Column chromatography (1H/1E). The formed dry then take $^1$H-NMR. MR-9 Melting point 137-141 °C, 0.80g (Yield =62.5 %), (Figure 3 .22).

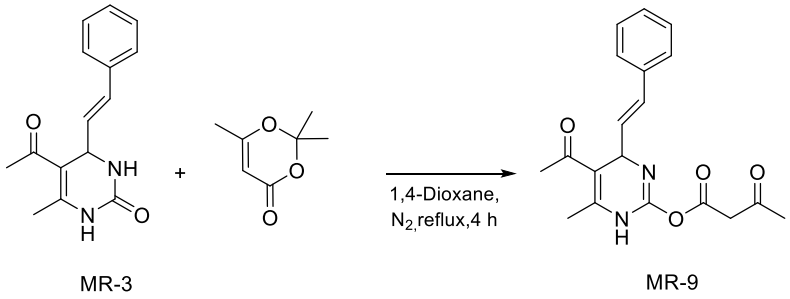



Figure 3.22 Formation of the molecule MR-9

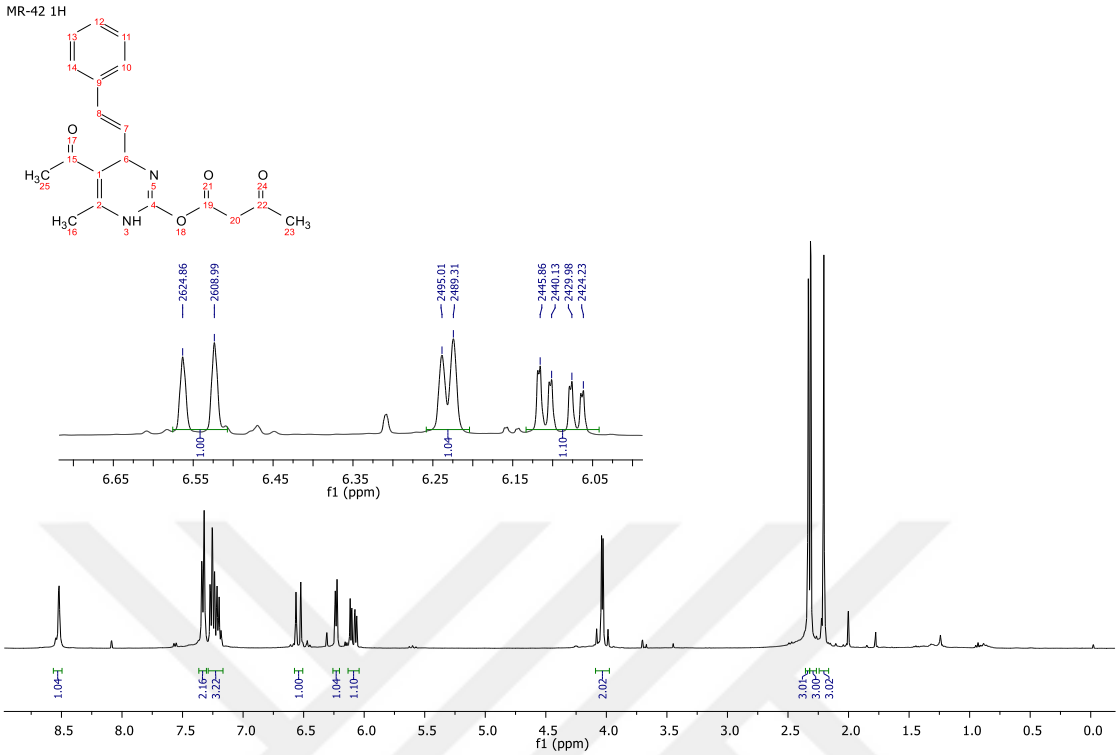
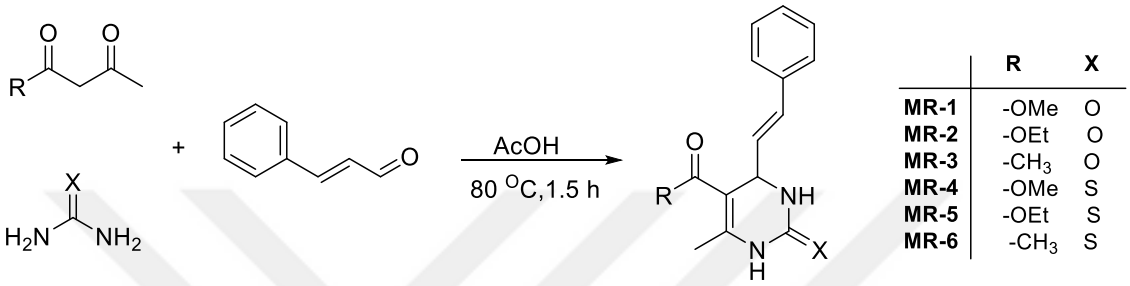



Figure 3.23 1H NMR of MR-9

## 4. RESULTS AND DISCUSSION

Commercially available dicarbonyl compounds was reacted with trans-cinnamaldehyde and urea in 10 ml of acetic acid to obtain 4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives. The reaction proceeded cleanly; no side products were formed during this addition reaction.




| | R | X |
|---|---|---|
| MR-1 | -OMe | O |
| MR-2 | -OEt | O |
| MR-3 | $-CH_3$ | O |
| MR-4 | -OMe | S |
| MR-5 | -OEt | S |
| MR-6 | $-CH_3$ | S |

Figure 4.1. Formation of 4-Styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylates

If we examine the NMR of one of the dihydroprimidine derivatives synthesised, which contains a styrene group. In the $^{1}$H-NMR spectrum of MR-1, the protons of N-$H^3$ and N-$H^5$ in pyrimidine ring resonate as broad singlet at 9.20 ppm and 7.58 ppm respectively. The aromatic ring protons resonate as a multiplet between 7.40- 7.14. C-$H^6$ resonate at 4.72 ppm as a broad triplet. C-$H^7$ resonate as a doublet of doublet at 6.16 ppm. C-$H^8$ resonates as a doublet at 6.35 ppm. The other aliphatic protons -$OCH_3$ and -$CH_3$ resonate at 3.63 and 2.10 ppm as a singlet respectively. In the $^{13}$C-NMR spectrum of MR-1, carbonyl carbon resonates 116.14 ppm. Quaternary carbons which are $C^4$, $C^2$ and $C^1$ resonate at 153.13, 149.17 and 128.41 ppm. Aromatic carbons resonate at 136.64, 130.40, 129.08, 126.79 ppm. C=C double bond carbons resonate at 128.02 and 93.13 ppm. Aliphatic carbons resonate at 52.12, 51.35 and 18.25 ppm. In the light of these data, it was observed that $^{1}$H-NMR and $^{13}$C-NMR were compatible with the proposed structure.

Also consistent with the proposed structure are the NMR spectra of compounds MR-2, MR-3, MR-4, MR-5, MR-6.

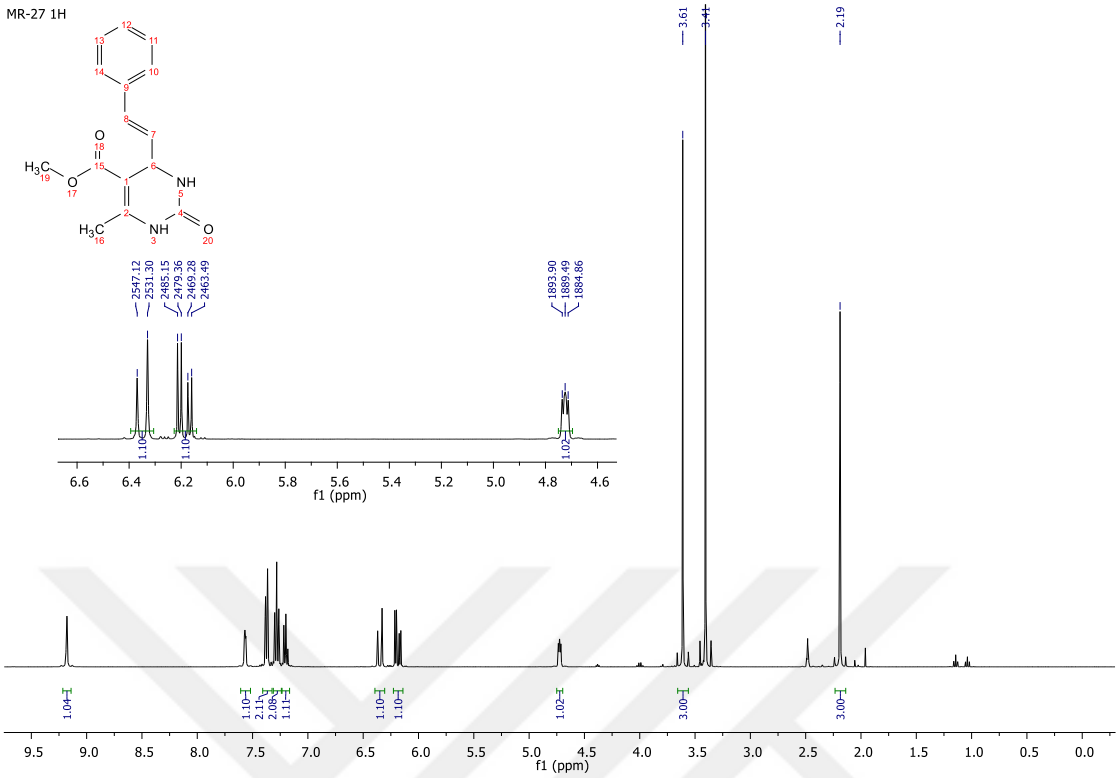



Figure 4.2 $^{1}$H-NMR of MR-1

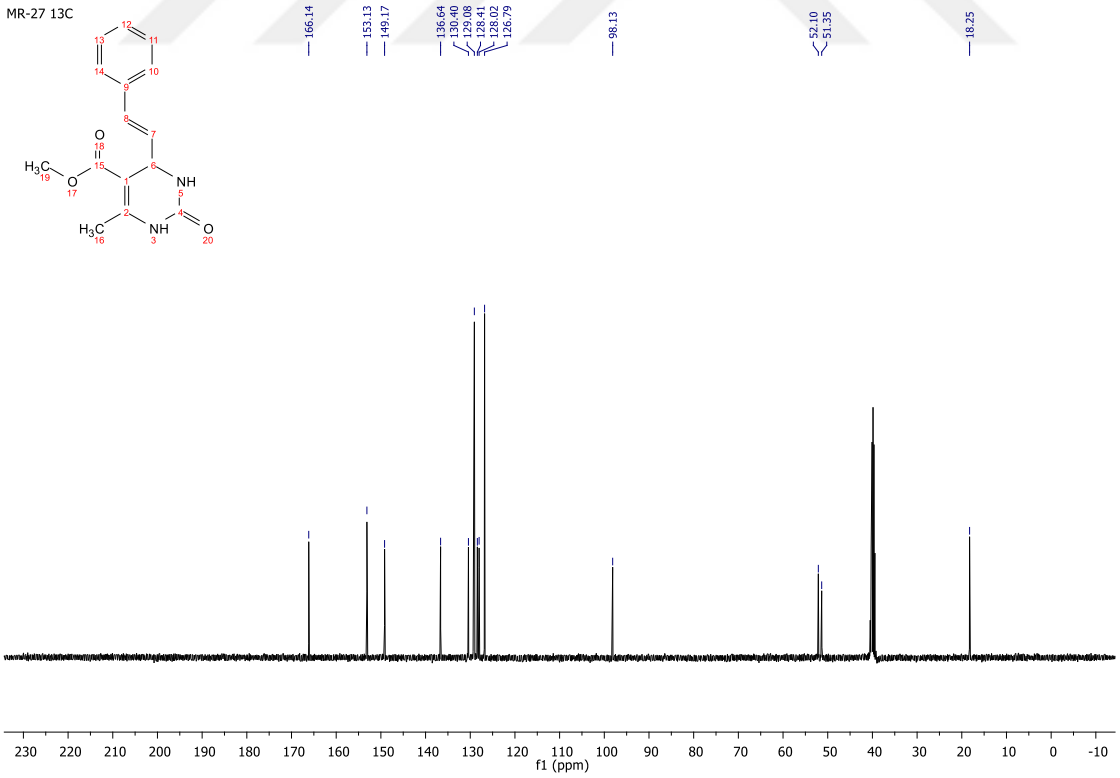



Figure 4.3 $^{13}$C-NMR of MR-1

After synthesized compound MR-1, MR-2 and MR-3 by the procedure through Biginelli, in the second step compound these compounds was reacted with 2,2,6-trimethyl- 4*H*-1,3-dioxin-4-one in the $N_2$ atmosphere as a result new compounds MR-7, MR-8 and MR-9 were obtained.

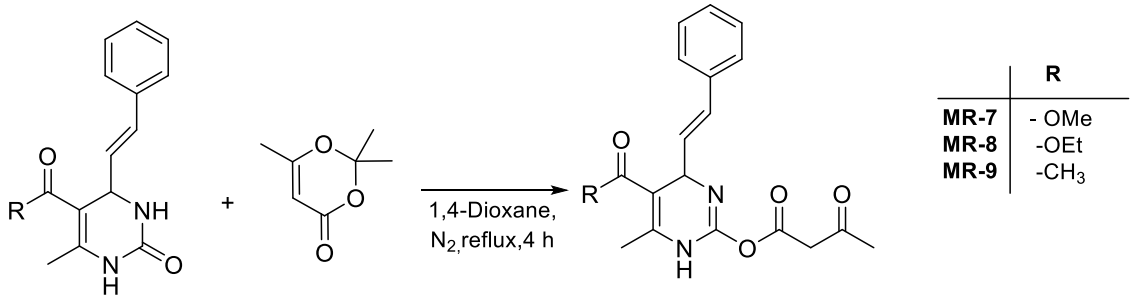



Figure 4.4 Formation of 6-methyl-4-styryl-1,4-dihydropyrimidin-2-yl-3-oxobutanoates

To prove that the target molecules have the proposed structure, we can compare the $^1$H-NMR of the starting molecule MR-1 with the target molecule MR-7. It was observed that the resonate N-H$^3$ peak at 9.20 ppm in the $^1$H-NMR of MR-1 disappeared in the $^1$H-NMR of MR-7. When the $^1$H-NMR of MR-7 is compared with MR-1 $^1$H-NMR, it is seen that a new methyl peak at 2.25 ppm and a new methylene peak at 4.08 ppm resonate in the $^1$H-NMR of MR-7. The observation of these new peaks in the $^1$H-NMR of MR-7 indicates that an aceto acetyl group was added to the structure. Comparing the $^1$H NMR of MR-7 and MR-1, a new methine proton is formed at 6.22 ppm in the $^1$H NMR of MR-7 and methine peak disappears at 4.72 ppm in the $^1$H NMR of MR-1. In order to explain the reason for this change, it is necessary to examine the region between 6.60 ppm and 6.05 ppm in the $^1$H-NMR of MR-7. In the $^1$H NMR of MR-7, three different methine groups resonate in this region at 6.52 ppm ($J$=15.95 Hz), 6.22 ppm ($J$=5.48 Hz) and 6.07 ppm ($J$=15.88 Hz and $J$=5.44 Hz). These three methine groups are found to be adjacent when the coupling constants are examined. In the light of these data, the methine peak resonate at 4.72 ppm in the $^1$H-NMR of MR-1 shifted to 6.22 ppm in the $^1$H-NMR of MR-7. For this shift to occur, a sp$^2$ hybridized group must be formed in the neighborhood of the methine carbon as a result of this reaction. In this case, it can be seen that the acetoacetylation reaction takes place via the carbonyl oxygen, which results in the double bond of the nitrogen. Also consistent with the proposed structure are the NMR spectra of compounds MR-8 and MR-9.

The proposed mechanism for the acetoacetylation reaction is as follows. If the compound 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, which is stable at room temperature, is heated to 100 °C, acetyl ketene and acetone are formed. Oxygen converted to enol form as a result of toutomerisation of pyridine easily reacts with the reactive intermediate acetyl ketene to form acetoacetlation product.

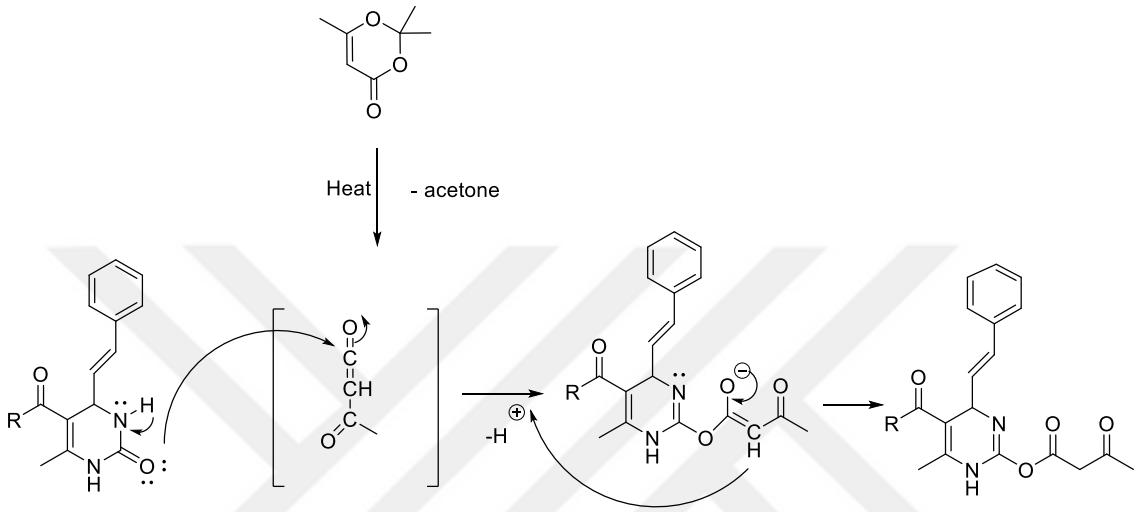



Figure 4.5 Proposed mechanism of acetoacetylation reaction

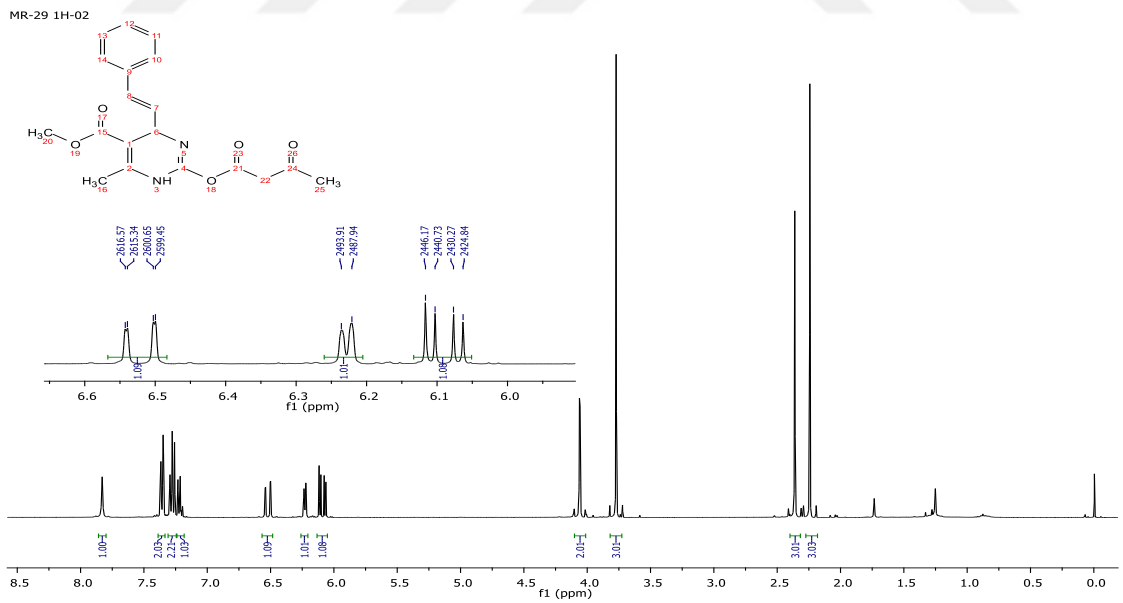



Figure 4.6 $^{1}$H NMR of MR-7

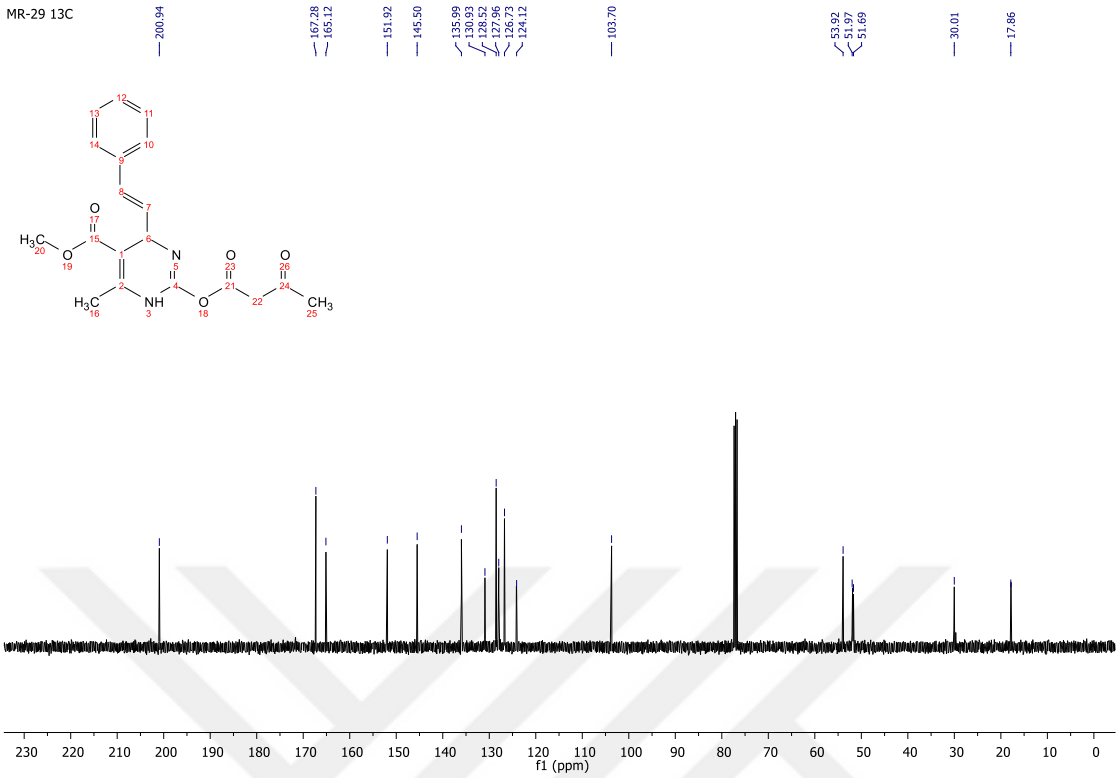



Figure 4.7 $^{13}C$ NMR of MR-7

## 5. CONCLUSION

In this study, new acetoacetylated pyrimidine derivatives were synthesised and their structures were characterised. In the first step of the study, MR-1, MR-2, MR-3, MR-4, MR-5 and MR-6 were synthesised using Biginelli reaction and their second step acetyl acetylation reactions were investigated (Figure 5.1).

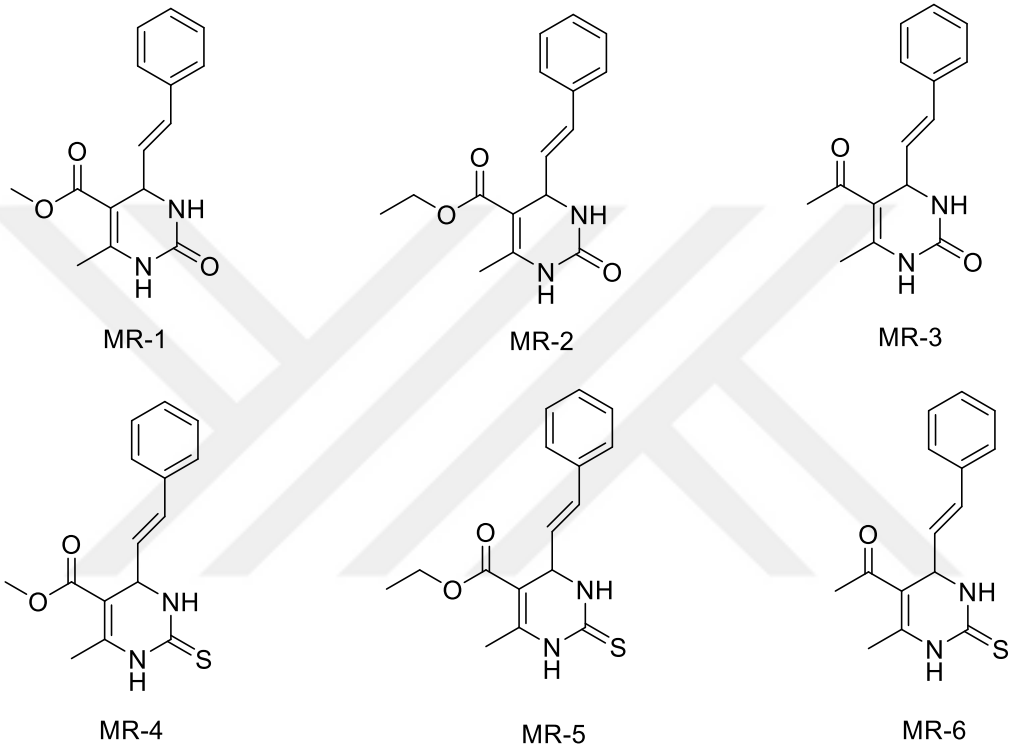



Figure 5.1 Compounds of 4-Styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

In the second step, the pyrimidine derivatives synthesised in the first step (MR-1, MR-2 and MR-3) were reacted with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to obtain acetoacetylation products (MR-7, MR-8 and MR-9). The $^{1}$H NMR/$^{13}$C NMR spectra of these compounds were in consistent with the proposed structures.

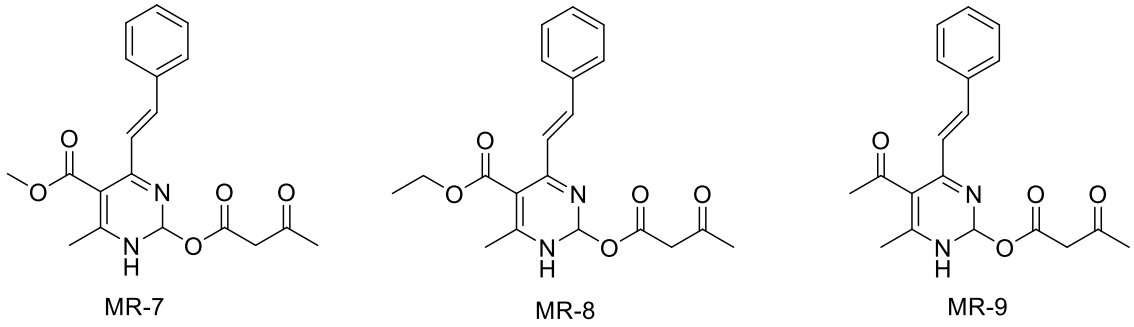



Figure 5.2 Compounds of 6-methyl-4-styryl-1,4-dihydropyrimidin-2-yl-3-oxobutanoate

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## EXTENDED TURKISH SUMMARY
## (GENİŞLETİLMİŞ TÜRKÇE ÖZET)

# STİREN GRUBU BULUNDURAN DİHİDROPİRİMİDİN BİLEŞİKLERİNİN ASETİL KETEN ARA ÜRÜNÜYLE REAKSİYONU

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Yüksek Lisans Tezi, Kimya Anabilim Dalı
Danışman: Dr. Öğr.Üyesi Furgan ASLANOĞLU
Ocak 2024, 67 sayfa

Pirimidin türevleri heterosiklik bileşiklerin önemli bir kısmını oluşturmaktadır. Birçok pirimidin, malzeme kimyası ve ilaç geliştirme dahil olmak üzere çeşitli uygulamalar için sentezlenir. Yüksek biyolojik aktiviteye sahip pirimidin bileşikleri antibakteriyel, antiinflamatuar, anti-kanser ve anti-parazit ilaçlar olarak kullanılmaktadır. Bu araştırmanın ilk aşaması, çok yönlü siklokondensasyon reaksiyonu (MCR) tekniklerinin bir parçası olan Biginelli reaksiyonunu kullanarak pirimidin türevlerini oluşturmaktı. Asetilasetilasyonun etkili sentezi, ikinci aşamada primidin bileşiklerinin asetoasetilasyon reaktifi ile reaksiyona sokulmasıyla sağlandı. Yeni oluşturulan tüm bileşiklerin bileşimleri, $^{1}H$ ve $^{13}C$ NMR gibi spektroskopik yöntemler kullanılarak araştırılmıştır.

**Anahtar kelimeler:** Asetoasetilleme, Dihidropirimidin, MCR, Pirimidin, Sentez

# 1. GİRİŞ

Heterosikllerin organik kimyadaki geniş bir yere sahip olması nedeniyle bu bileşiklerin reaksiyonları ön görülemez bileşiklerin oluşumu ile sonuçlanmaktadır. Ön görülemez bileşiklerin oluşumu hem kimyasal hem de mekanistik açıdan önemli sonuçların oluşumuna sebep olabilmektedir. Ayrıca bu bileşikler biyolojik anlamda da önemli bileşikler olabilmektedirler.

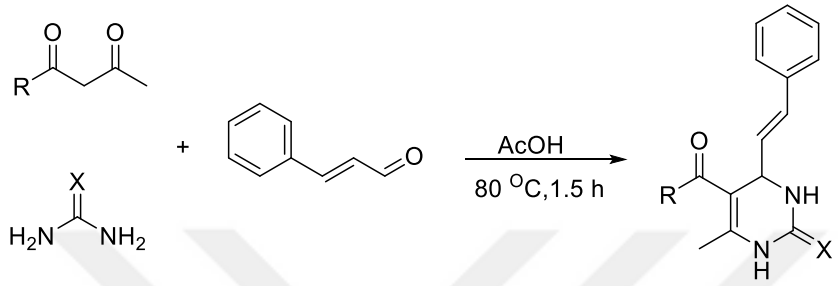
Kumar vd. (2018) tarafından tanımlandığı üzere, insan tıbbında kullanılan ilaçlar, çok çeşitli kimyasal yapılar içerir. Ancak bu ilaçların çoğunluğu ya heterosiklik özelliklere sahip küçük bileşiklerden oluşur ya da heterosiklik yapısal bileşenler içerir. Çağdaş kimyanın ilerlemesinden önce, heterosiklik alkaloitler çeşitli bitkisel ilaçlarda aktif bileşenler olarak işlev görüyordu. Morfin çeşitleri de dahil olmak üzere bazı alkaloitler günümüzde hala kullanılmaktadır. İlaçlara karmaşık sistematik terminolojisi kullanmak yerine basit jenerik isimler verilmektedir. Benzer şekilde çalışan ilaçların sıklıkla ilgili isimleri vardır.

Bu nedenle, beraberindeki kapsam, çeşitli bölümlerin tıbbi açıdan farklı olduğu anlamına gelmemektedir. Tüm önemli alanları tam olarak kapsamak mümkün olmasa da amaç, heterosikllerin tıptaki geniş ve çeşitli önemine ilişkin bir farkındalık sağlamaktır. Heterosikller çeşitli alanlarda kullanılan farmasötiklerde bulunur, ancak kolayca anlaşılır gerekçeler için heterosiklik nörotransmiterleri kullanan sistemlerde özel bir öneme sahiptirler.

Joule ve Mills'e (2010) göre, Haziran 2006'dan Haziran 2007'ye kadar en çok kazanç sağlayan reçeteli ilaçların yedisi küçük moleküllü ilaçlardı. Heterosikller, kolesterol seviyelerini düşürmek için kullanılan atorvastatin, mide asidi üretimini azaltmak için kullanılan esomeprazol, kan pıhtılarını önlemek için kullanılan klopidogrel, her ikisi de şizofreni tedavisinde kullanılan olanzapin ve risperidon içeren bir bileşik sınıfıdır. Yüksek tansiyon tedavisinde kullanılan amlodipin ve şizofreni ve bipolar bozukluğun tedavisinde kullanılan ketiapin önemli heterosiklik bileşiklerdendir.

## 2. MATERYAL, YÖNTEM VE BULGULAR

Bu çalışmada, yeni asetoasetil grubu bağlanmış pirimidin türevleri sentezlenmiş ve karekterizasyonları yapılmıştır. Biginelli reaksiyonu kullanılarak MR-1, MR-2, MR-3, MR-4, MR-5 ve MR-6 bileşikleri sentezlenmiştir (Şekil 1).

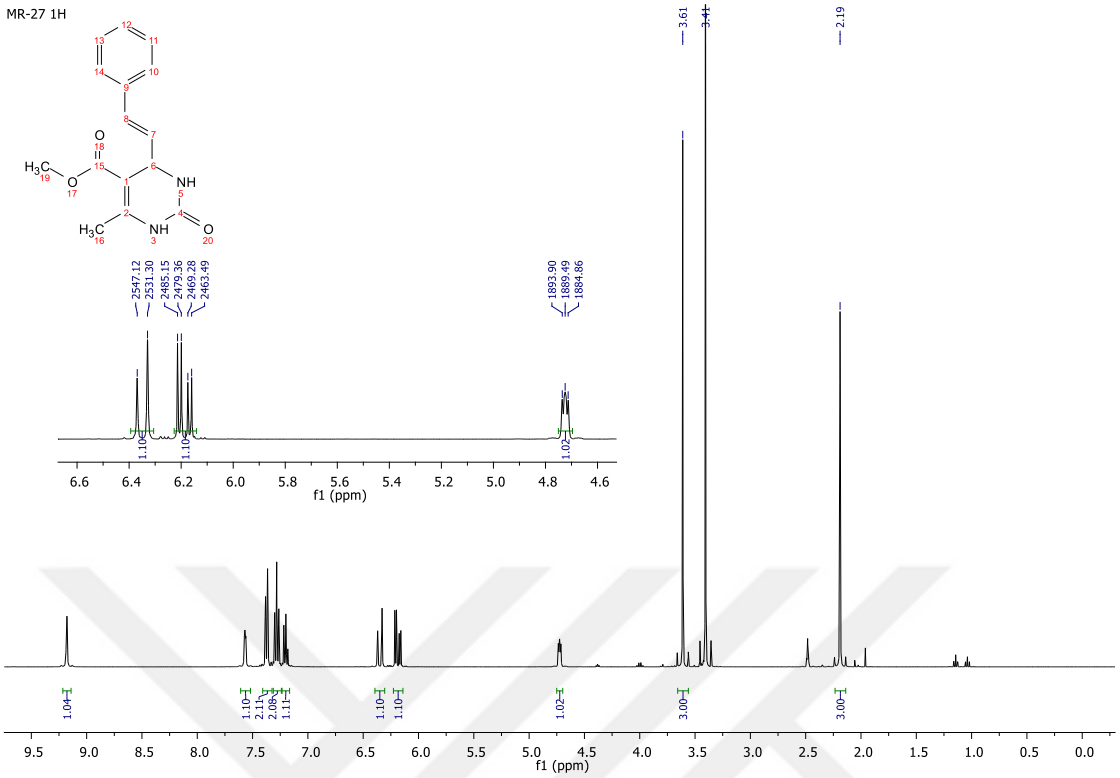



| | R | X |
|---|---|---|
| MR-1 | -OMe | O |
| MR-2 | -OEt | O |
| MR-3 | -$CH_3$ | O |
| MR-4 | -OMe | S |
| MR-5 | -OEt | S |
| MR-6 | -$CH_3$ | S |

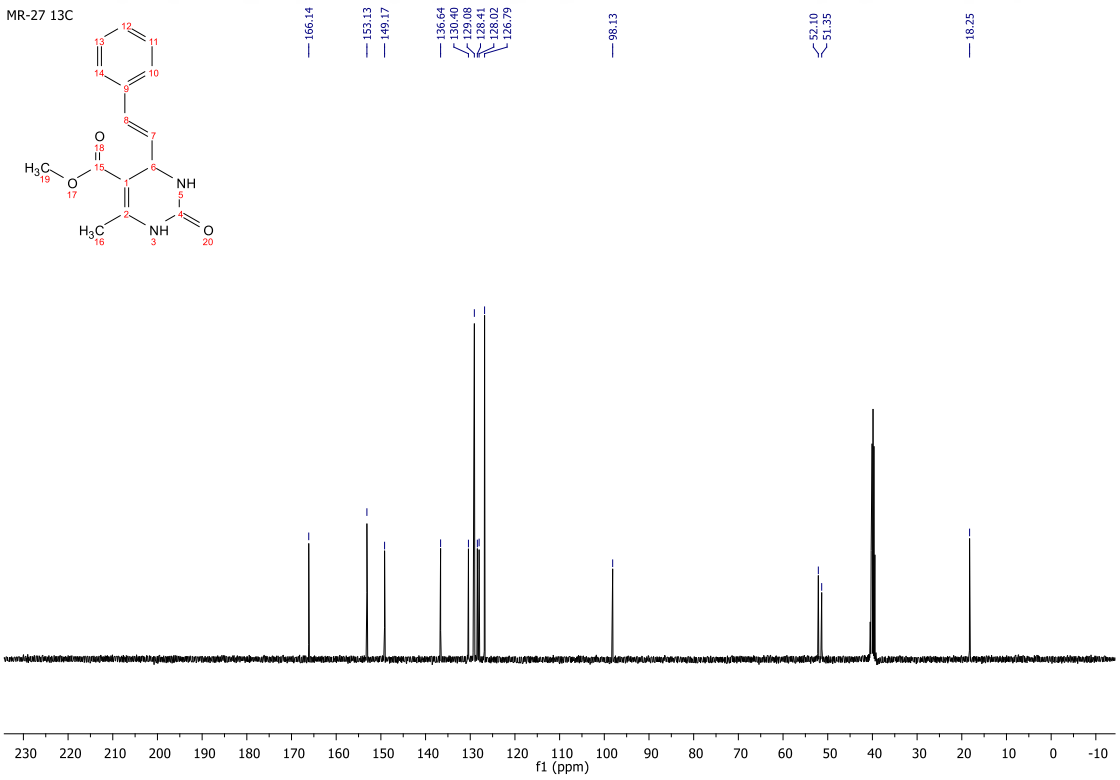
Şekil 1. 4- Stiren -1,2,3,4-tetrahidropirimidin-5-karboksilatların oluşumu

Sentezlenen dihidroprimidin türevlerinden MR-1'in NMR'ını inceleyecek olursak. MR-1'in 1H-NMR spektrumunda, pirimidin halkasındaki N-$H^3$ ve N-$H^5$ protonları sırasıyla 9.20 ppm ve 7.58 ppm'de singlet olarak rezonansa girmektedir. Aromatik halka protonları 7.40- 7.14 arasında bir multiplet olarak rezonansa girmektedir. C-$H^6$ 4.72 ppm'de triplet olarak rezonansa girmektedir. C-$H^7$ 6.16 ppm'de dubletin dubleti olarak rezonansa girer. C-$H^8$ 6.35 ppm'de dublet olarak rezonansa girer. Diğer alfatik protonlar -$OCH_3$ ve -$CH_3$ sırasıyla 3.63 ve 2.10 ppm'de singlet olarak rezonansa girer. MR-1'in 13C-NMR spektrumunda karbonil karbonu 116.14 ppm'de rezonansa girmektedir. $C^4$, $C^2$ ve $C^1$ olan kuaterner karbonlar 153.13, 149.17 ve 128.41 ppm'de rezonansa girmektedir. Aromatik karbonlar 136.64, 130.40, 129.08, 126.79 ppm'de rezonansa girmektedir. C=C çift bağ karbonları 128.02 ve 93.13 ppm'de rezonansa girer. Alifatik karbonlar 52.12, 51.35 ve 18.25 ppm'de rezonansa girmektedir. Bu veriler ışığında 1H-NMR ve 13-C-NMR'ın önerilen yapı ile uyumlu olduğu görülmüştür (Şekil-2, Şekil-3).

Ayrıca MR-2, MR-3, MR-4, MR-5, MR-6 bileşiklerinin NMR spektrumları da önerilen yapı ile uyumludur.

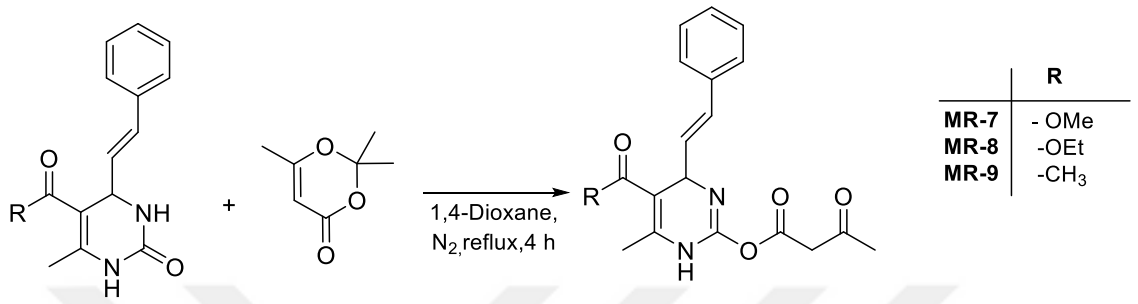



Sekil 2. MR-1'in$^{1}$H NMR spekturumu




Sekil 3. MR-1'in$^{13}$C-NMRspekturumu

Biginelli prosedürü ile MR-1, MR-2 ve MR-3 bileşikleri sentezlendikten sonra, ikinci adımda bu bileşikler $N_2$ atmosferinde 2,2,6-trimetil-4*H*-1,3-dioksin-4-on ile reaksiyona sokuldu ve sonuç olarak yeni bileşikler MR-7, MR-8 ve MR-9 elde edildi (Şekil-4).

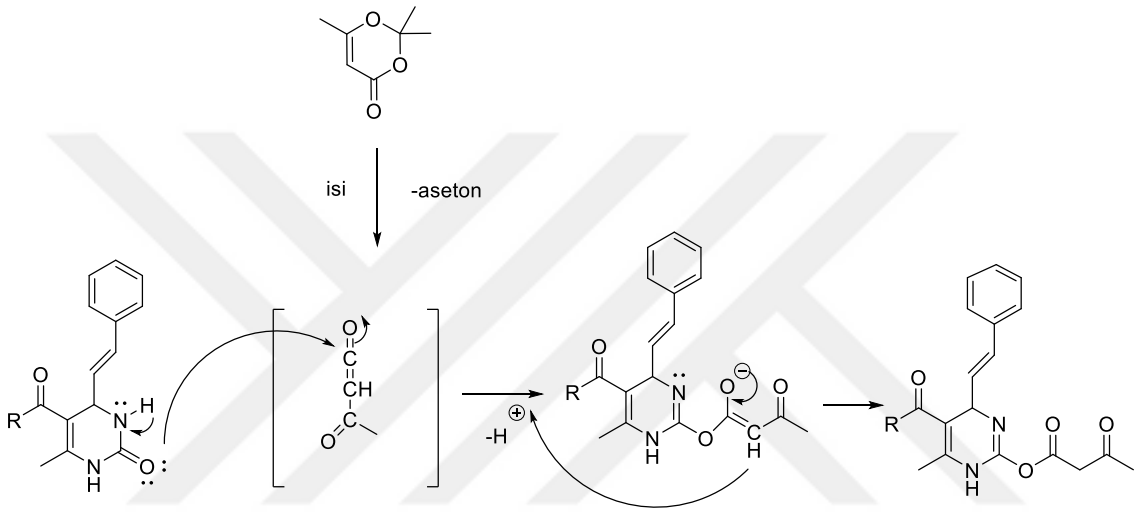



Şekil 4. 6-metil-4-stiril-1,4-dihidropirimidin-2-il-3- oksobütanoatların oluşumu

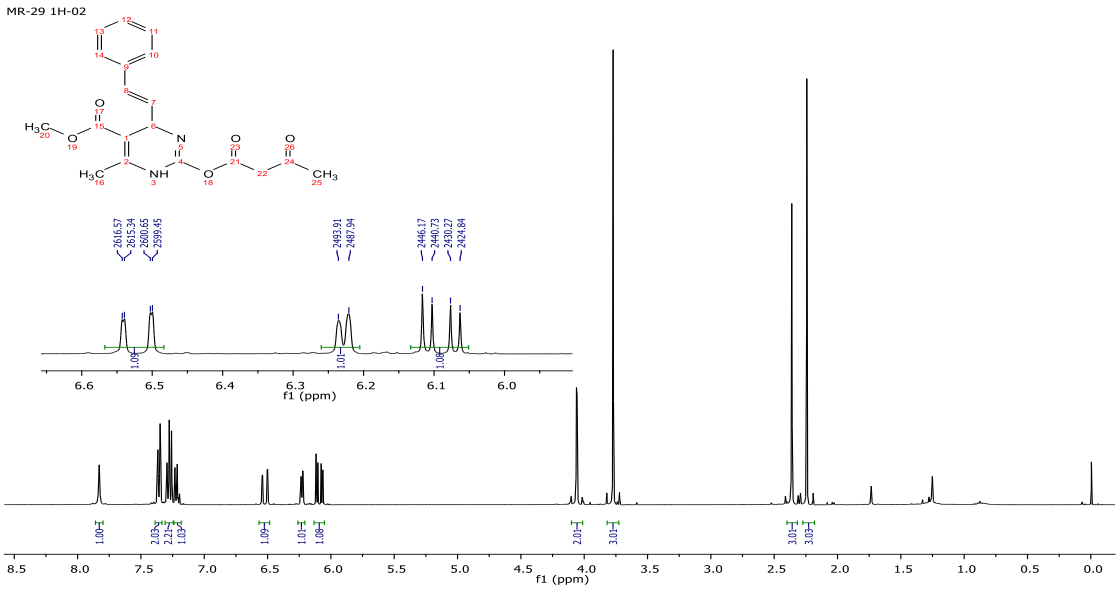
Hedef moleküllerin önerilen yapıya uyumlu olduğunu kanıtlamak için, başlangıç molekülü MR-1 ile hedef molekül MR-7'nin $^1$H-NMR'ını karşılaştırabiliriz. MR-1'in $^1$H-NMR'ında 9.20 ppm'de rezonansa giren N-H[3] pikinin MR-7'nin $^1$H-NMR'ında kaybolduğu gözlenmiştir. MR-7'nin $^1$H-NMR'ı ile MR-1 1H-NMR'ı karşılaştırıldığında, MR-7'nin $^1$H-NMR'ında 2.25 ppm'de yeni bir metil piki ve 4.08 ppm'de yeni bir metilen pikinin rezonansa girdiği görülmektedir. MR-7'nin $^1$H-NMR'ında bu yeni piklerin gözlenmesi yapıya bir aseto asetil grubunun eklendiğini göstermektedir. MR-7 ve MR-1'in $^1$H NMR'ları karşılaştırıldığında, MR-7'nin $^1$H NMR'ında 6.22 ppm'de yeni bir metin protonu oluşurken, MR-1'in 1H NMR'ında 4.72 ppm'de metin piki kaybolduğu gözlenmiştir. Bu değişimin nedenini açıklamak için MR-7'nin $^1$H-NMR'ında 6.60 ppm ile 6.05 ppm arasındaki bölgenin incelenmesi gerekmektedir. MR-7'nin $^1$H NMR'ında üç farklı metin grubu 6.52 ppm (*J*=15.95 Hz), 6.22 ppm (*J*=5.48 Hz) ve 6.07 ppm'de (*J*=15.88 Hz ve *J*=5.44 Hz) bu bölgede rezonansa girmektedir. Etkileşim sabitleri incelendiğinde bu üç metin grubunun bir birlerine komşu olduğu görülmektedir. Bu veriler ışığında MR-1'in $^1$H-NMR'ında 4,72 ppm'de rezonansa giren metin piki MR-7'nin $^1$H-NMR'ında 6,22 ppm'e kaymıştır. Bu kaymanın gerçekleşmesi için, bu reaksiyon sonucunda metin karbonunun komşuluğunda sp2 hibridize bir grubun oluşması gerekir. Bu durumda, asetoasetilasyon reaksiyonunun karbonil oksijeni üzerinden gerçekleştiği ve bunu sonucundada azotun çift bağ yapıp $sp^2$ hibdizasyonuna sahip bir azota dönüşmüştür.

Bunun sonucundada MR-1'in $^{1}$H-NMR'ında 4,72 ppm'de rezonansa giren metin piki MR-7'nin $^{1}$H-NMR'ında 6,22 ppm'e kaymıştır (Şekil-6, Şekil-7).

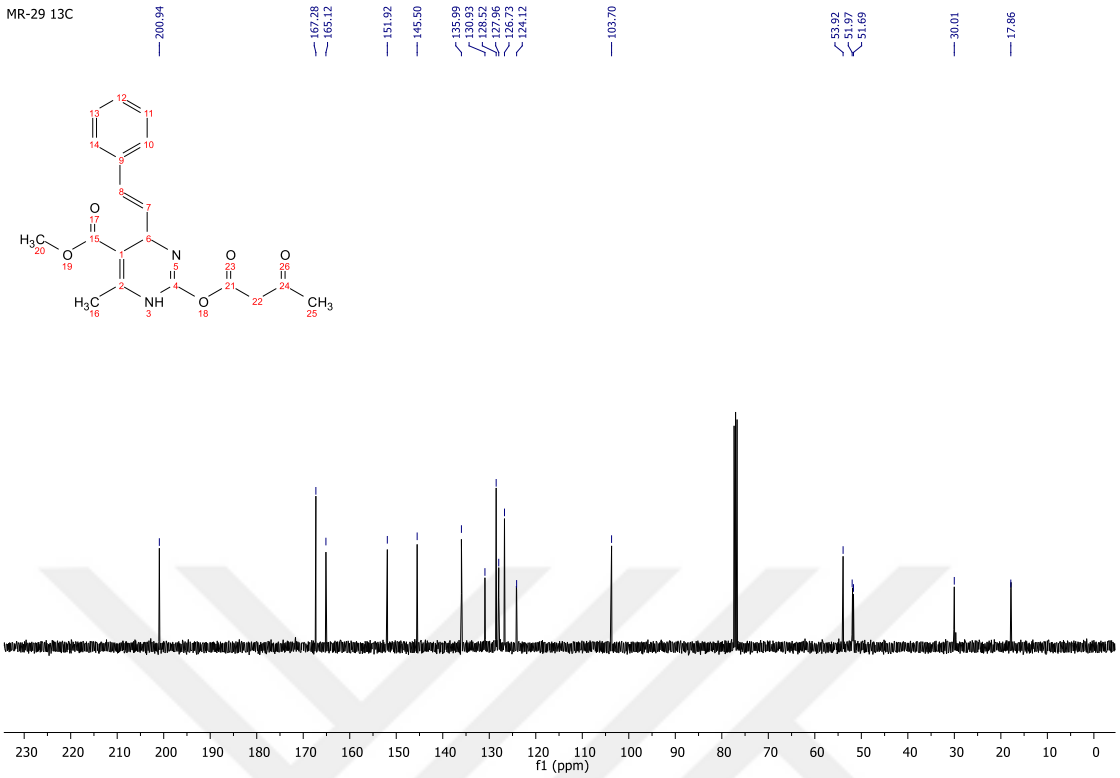
Aseto asetilasyon reaksiyonu için önerilen mekanizma aşağıdaki gibidir. Oda sıcaklığında kararlı olan 2,2,6-trimetil-4*H*-1,3-dioksin-4-on bileşiği 100 °C'ye kadar ısıtılırsa asetil keten ve aseton oluşur. Piridinin toutomerizasyonu sonucu enol formuna dönüşen oksijen, reaktif ara ürün olan asetil keten ile kolayca reaksiyona girerek asetoasetilasyon ürününü oluşturur (Şekil-5).




Şekil 5. Asetoasetilasyon reaksiyonunun önerilen mekanizması



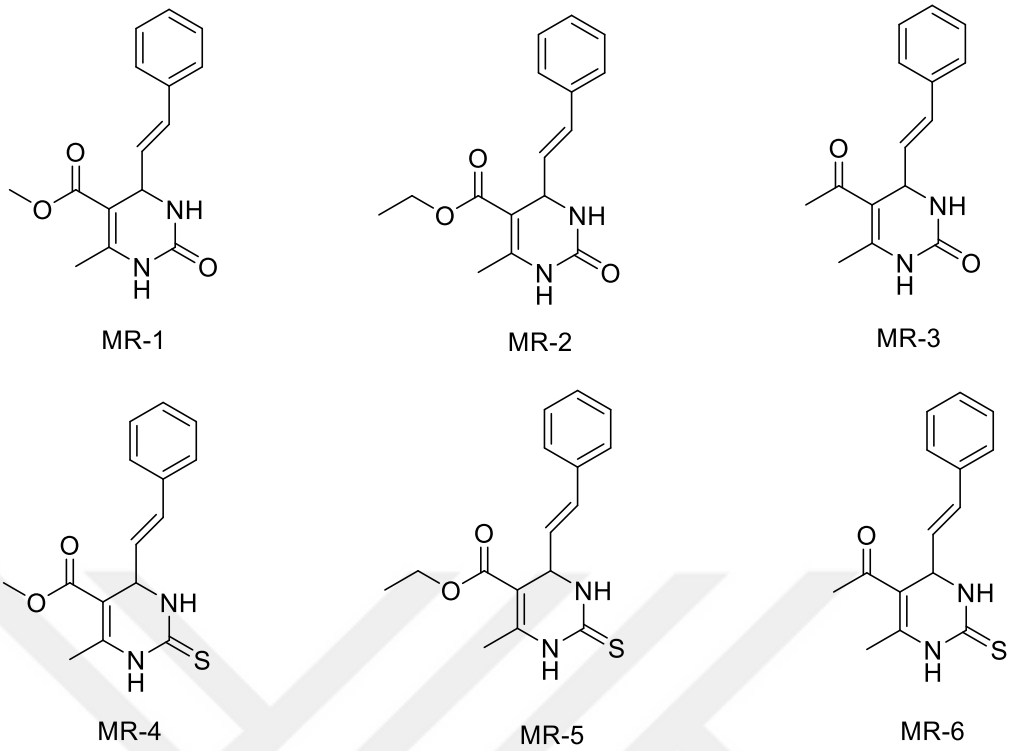

Şekil 6. MR-7'nin$^{1}$H NMRspekturumu




Sekil 7. MR-7 $^{13}C$ NMRspekturumu

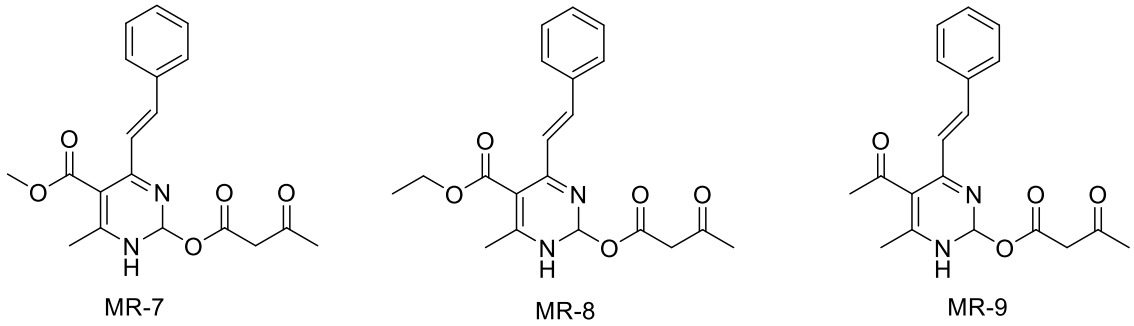
## 3. SONUÇ

Bu çalışmada, yeni asetoasetaliyon pirimidin türevleri sentezlenmiş ve bu bileşiklerin yapıları karakterize edilmiştir. Çalışmanın birinci basamağında Biginelli reaksiyonu kullanılarak MR-1, MR-2, MR-3, MR-4, MR-5 and MR-6 sentezlenmiş ve bunların ikinci basamak asetil asetilasyon reaksiyonları araştırılmıştır (Şekil 5.1).




Şekil 8. 4-Stiril-1,2,3,4-tetrahidropirimidin-5-karboksilat bileşikleri

İkinci basamakta, birinci basamak reaksiyonunda sentezlenen pirimidin türevleri (MR-1, MR-2 ve MR-3) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one ile reaksiyona sokularak asetoasetilasyon ürünleri olan (MR-7, MR-8 ve MR-9) elde edildi. Bu bileşiklerin $^{1}$H-NMR / $^{13}$C-NMR spektrumları önerilen yapılar ile uyumlu olduğu gözlemlendi.




Şekil 9. 6-metil-4-stiril-1,4-dihidropirimidin-2-il-3- oksobütanoat bileşikleri

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