Article

Reaction of Dihydroprimidine compounds containing a Styrene group with acetyl ketene intermediate

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Abstract

In this work we present the synthesis of new acetoacetylated pyrimidine derivatives in this work. These chemicals were produced via acetoacetylation of pyrimidine precursors in a two-step of chemical events. First step we presents the successful synthesis of pyrimidine derivatives through catalyst-free methods by utilizing specific reaction conditions, we were able to achieve efficient synthesis without the need for traditional catalytic agents. The absence of catalysts in the reaction not only simplifies the process but also reduces potential side reactions and environmental impact. The compositions of all newly created compounds are investigated utilizing spectroscopic methods like ^{1}H and ^{13}C NMR. The possible biological activities of the synthesized pyrimidine derivatives were assessed, and preliminary findings suggest promising uses in medicinal chemistry. To fully understand their therapeutic potential and mode of action, more research is being conducted.

Keywords: Acetoacetylation, Dihydropyrimidine, Pyrimidine, Synthesis

1. Introduction

It would be impossible to research all of the uses for heterocycles in organic chemistry due to their wide range of applications. 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.

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. 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.

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 N1 to C6 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. (1)

2. Materials and Methods.

The methods developed and refined in this work were used to produce novel acetoacetylation pyrimidine derivatives. 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 ^{1}H 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.

Tools and devices used in the experiments are listed below:

1. Agilent 400/54 / A5C Premium brand NMR instrument for 1H and 13C NMR.
2. Merck TLC Plate Silica Gel 60 F254.
3. Gallenkamp Melting Point Apparatus.
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. Glassware**.**

3. Synthesis of Compounds.

3.1 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 ,the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by absolute ethanol. MR-1 Melting point 232-236℃, 6.98g (Yield = 76.1%) (Figure 1) (Figure 2)(2).

3.2 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, the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by absolute ethanol. MR-2 Melting point 240-244℃, 7.54g (Yield = 88.1%) (Figure 3)(Figure 4). (3).

3.3 (*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 ,the product was precipitated, the solution filtrate and dried. Then, the participate were recrystallized by in absolute ethanol. MR-3 Melting point 219-223℃, 5.84g (Yield = 76.1%) (Figure 5) (Figure 6) (4).

3.4 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 ,the product was precipitated, the solution was filtrate and dried. Then, the participate were recrystallized by absolute ethanol. MR-4 Melting point 207-211℃, 4.84g (Yield = 64.1%) (Figure 7) (5).

3.5 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 the reaction was followed up by TLC ,the product was precipitated .The solution was filtrate and dried. Then, the participate were recrystallized by absolute ethanol. MR-5 Melting point 194-198℃, 6.04g (Yield = 71.1%) (Figure 8).(6)

3.6 (*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, the product was precipitated. The solution was filtrated and dried. Then , the participate were recrystallized by absolute ethanol. MR-6 Melting point 241-245℃, 5.84g (Yield = 73.1%) (Figure 9) (7).

3.7 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 product is separated by column chromatography hexane / ethyl acetate(1/1). The formed dry then take ^{1}H, ^{13}C-NMR. MR-7 Melting point 137-141 °C, 0.80g (Yield =62.5 %).(Figure 10)(Figure 11).

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

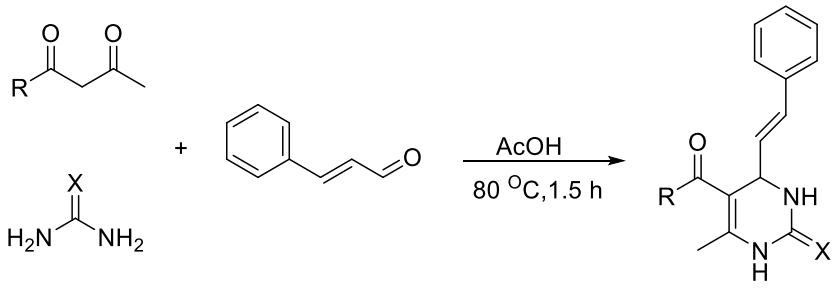
MR-2 (1.0 g) dissolved in 20 ml of 1,4-dioxane then added 2,2,6-Trimethyl-4H-1,3-dioxine-4-one (0.6 ml) was mixed. The reaction mixture was refluxed with N_2 for 3 hr. and was proceeded by TLC. The reaction mixture was cooled, and the liquid phase was evaporated. Then, crude product is separated by Column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

3.9 (*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 product is separated by Column chromatography hexane / ethyl acetate (1/1). The formed dry then take ^{1}H-NMR. MR-9 Melting point 137-141 °C, 0.80g (Yield =62.5 %).

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

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

If we examine the NMR of one of the dihydroprimidine derivatives synthesized, 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.

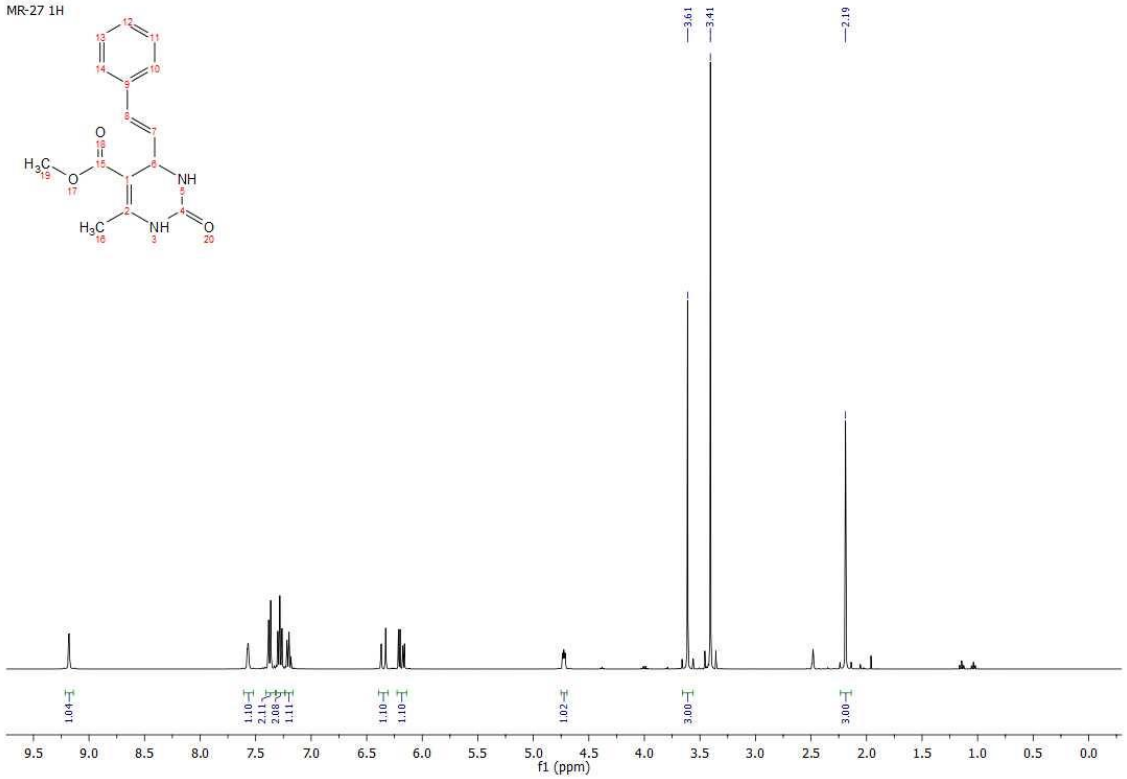


Figure 1: ^{1}H-NMR of MR-1

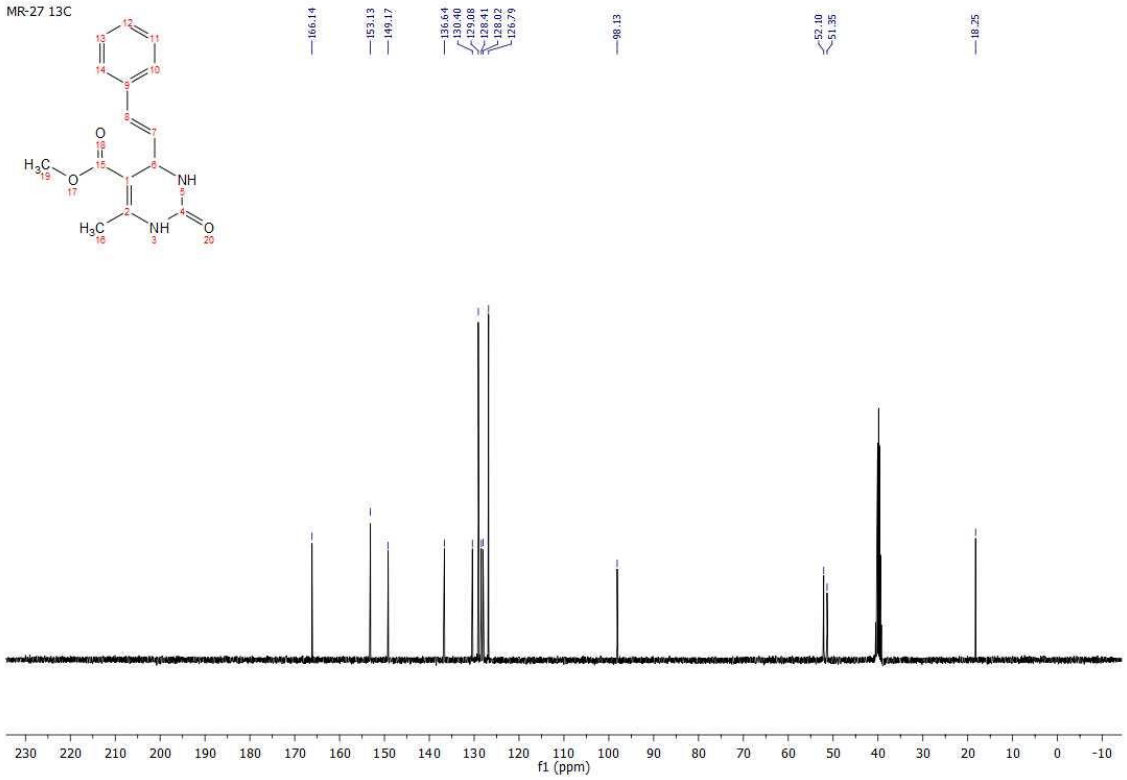


Figure 2: ^{13}C-NMR of MR-1

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

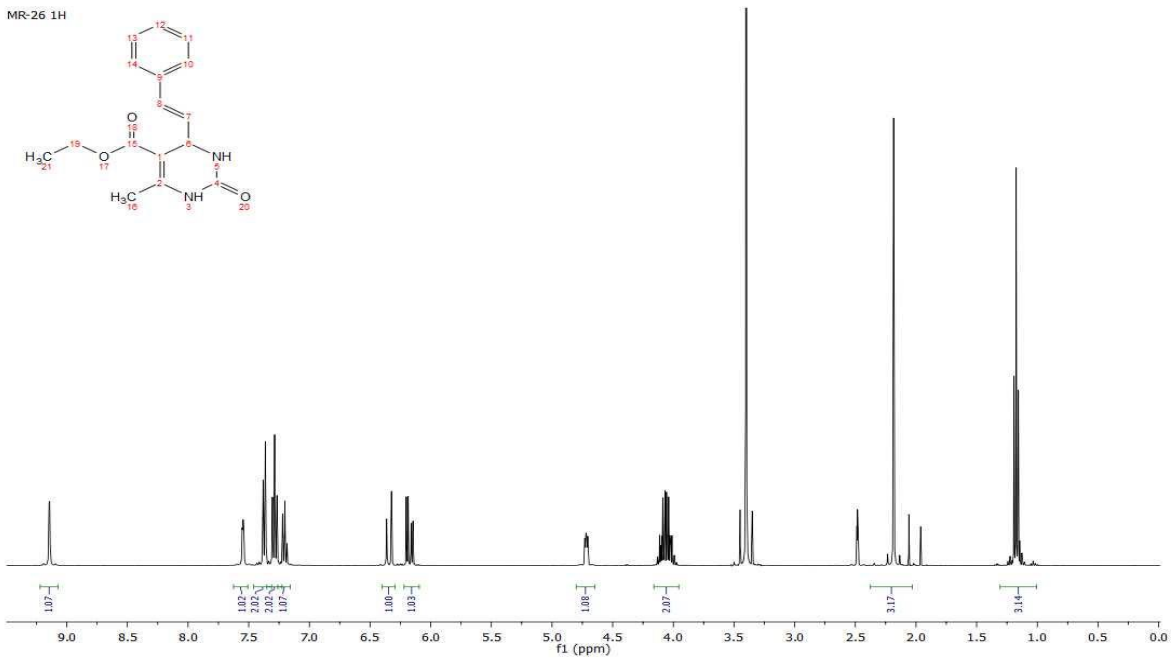


Figure 3: ^{1}H-NMR of MR-2

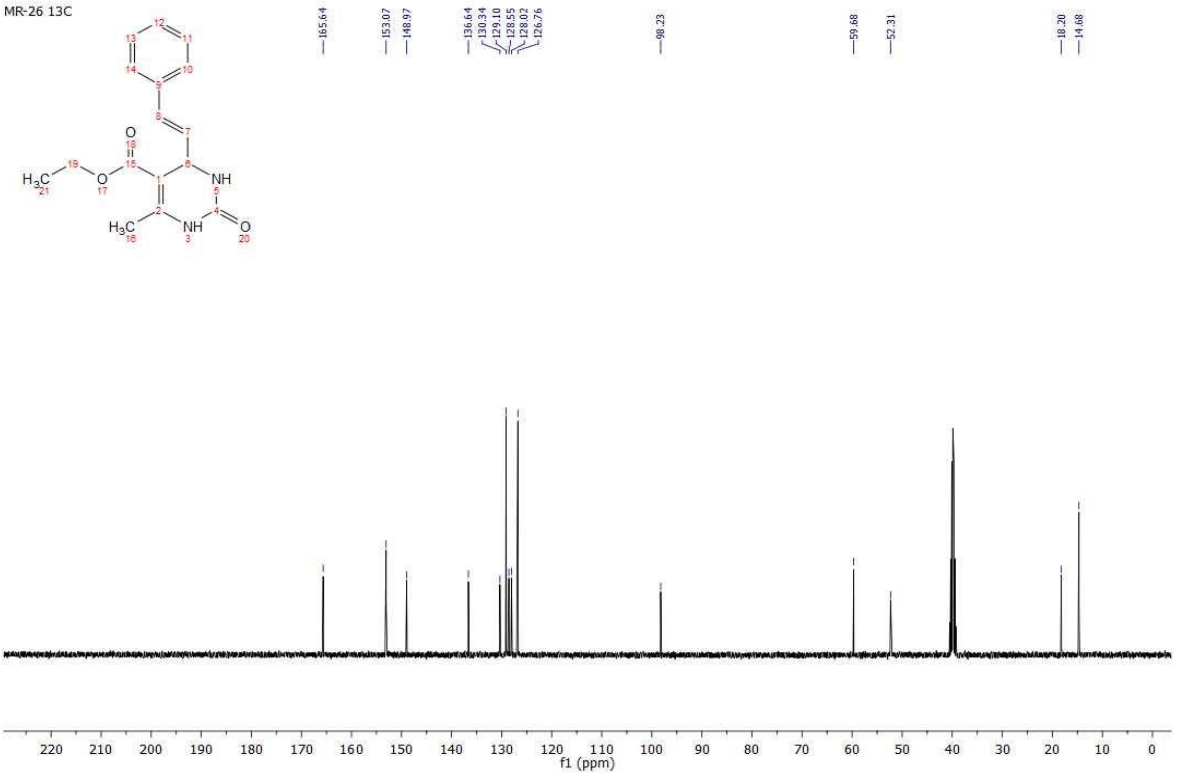


Figure 4: ^{13}C-NMR of MR-2

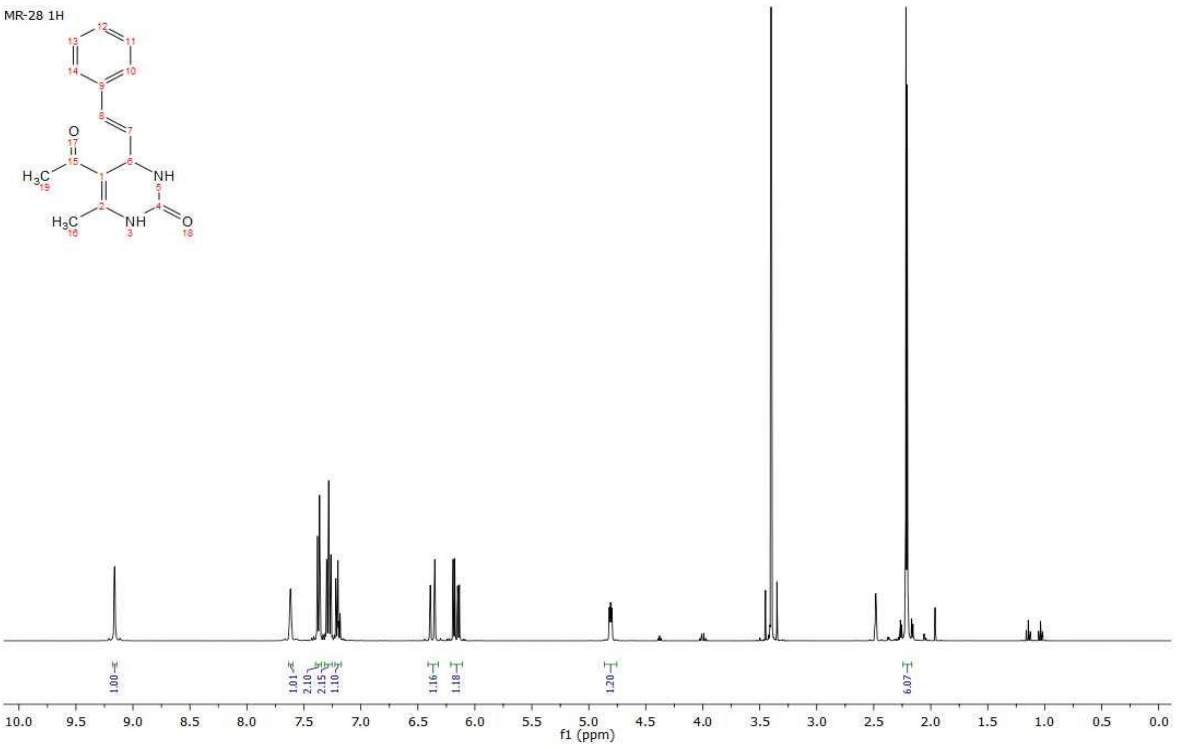


Figure :5 ^{1}H-NMR of MR-3

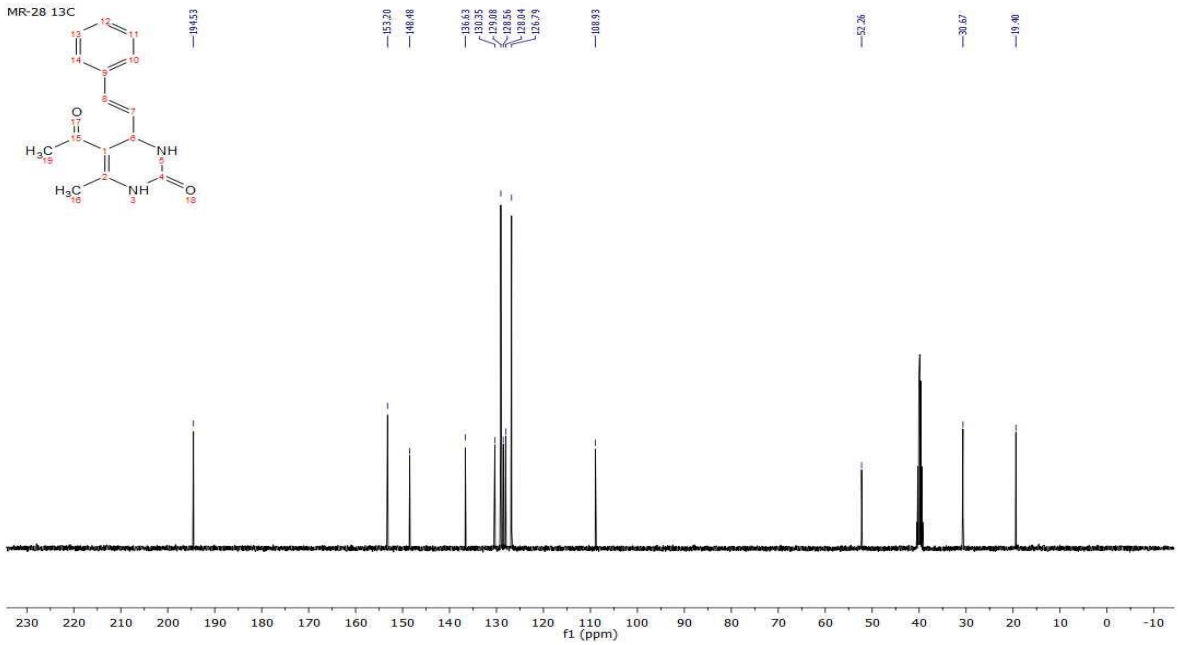


Figure 6: ^{13}C NMR of MR-3

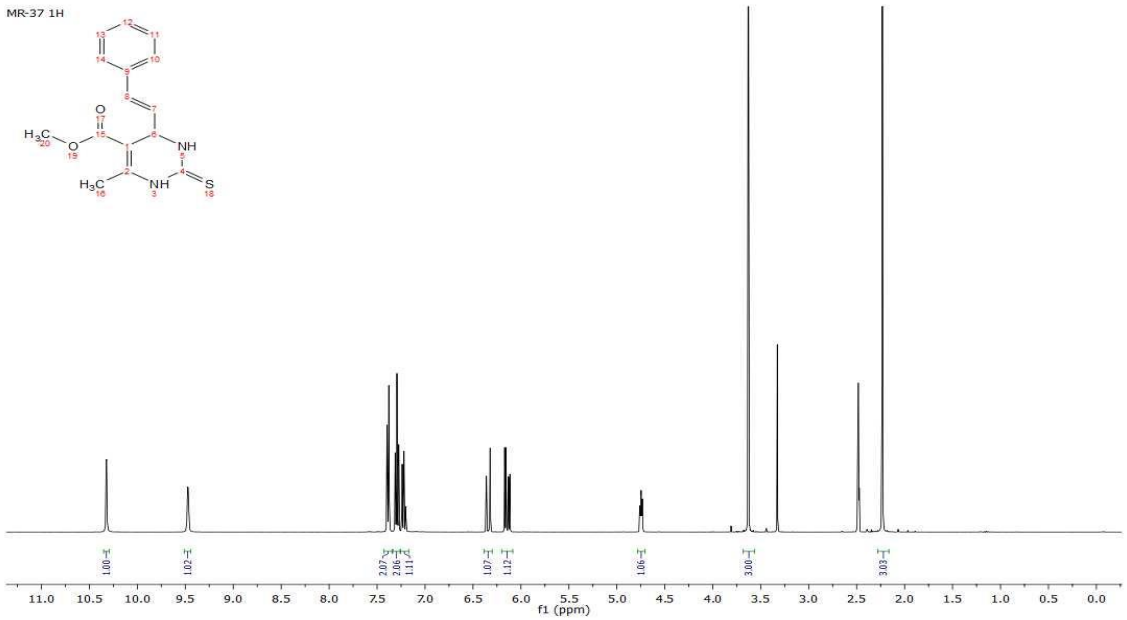


Figure 7: ^{1}H-NMR of MR-4

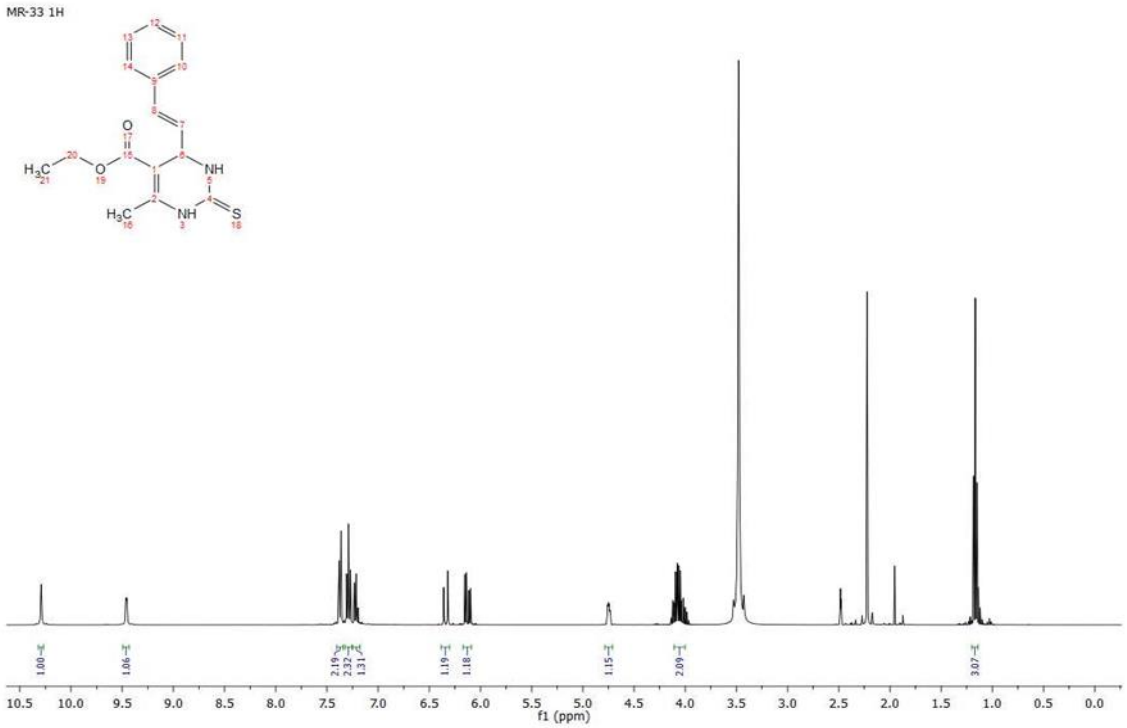


Figure 8: ^{1}H-NMR of MR-5

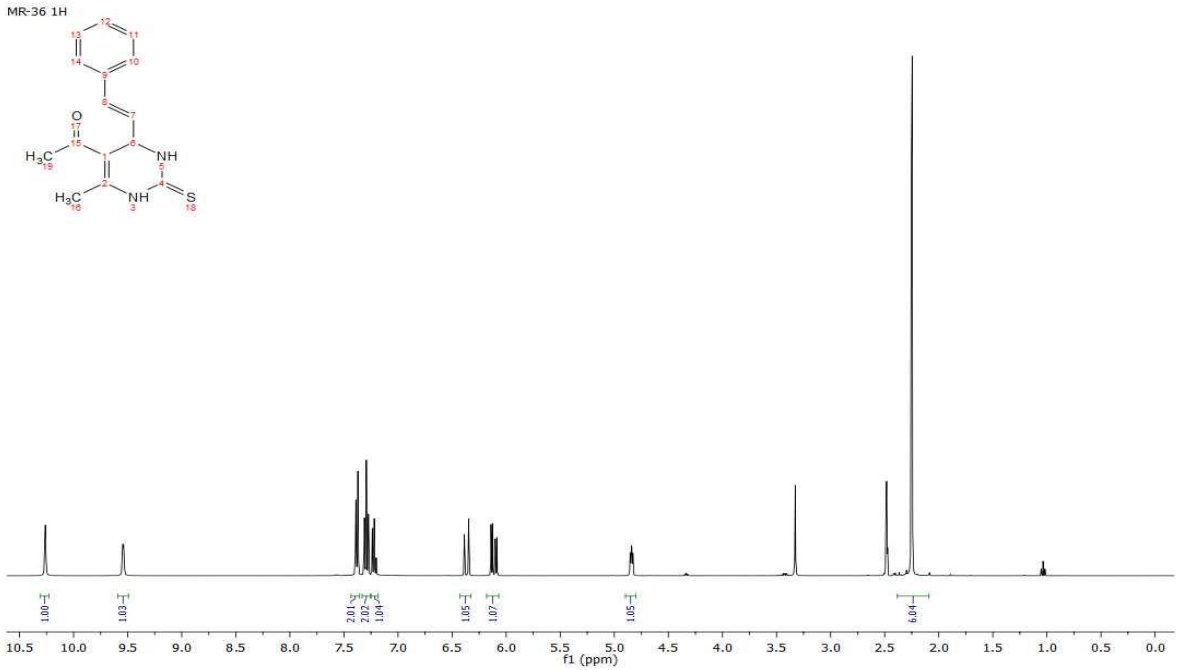
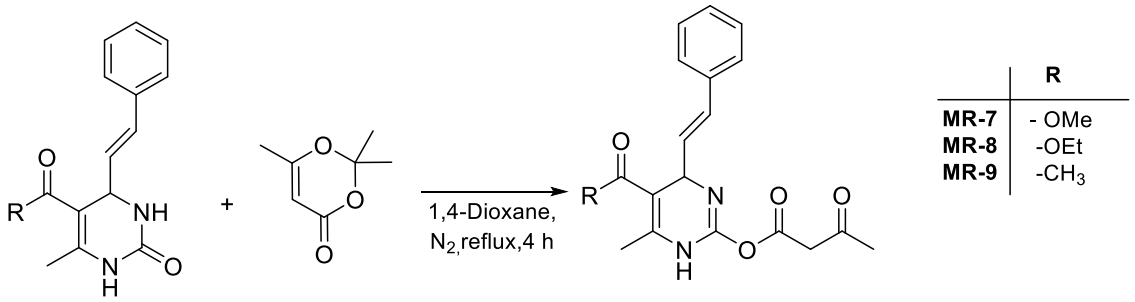


Figure 9: ^{1}H-NMR of MR-6

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.



	R
MR-7	- OMe
MR-8	-OEt
MR-9	$-CH_3$

Scheme 2: 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.

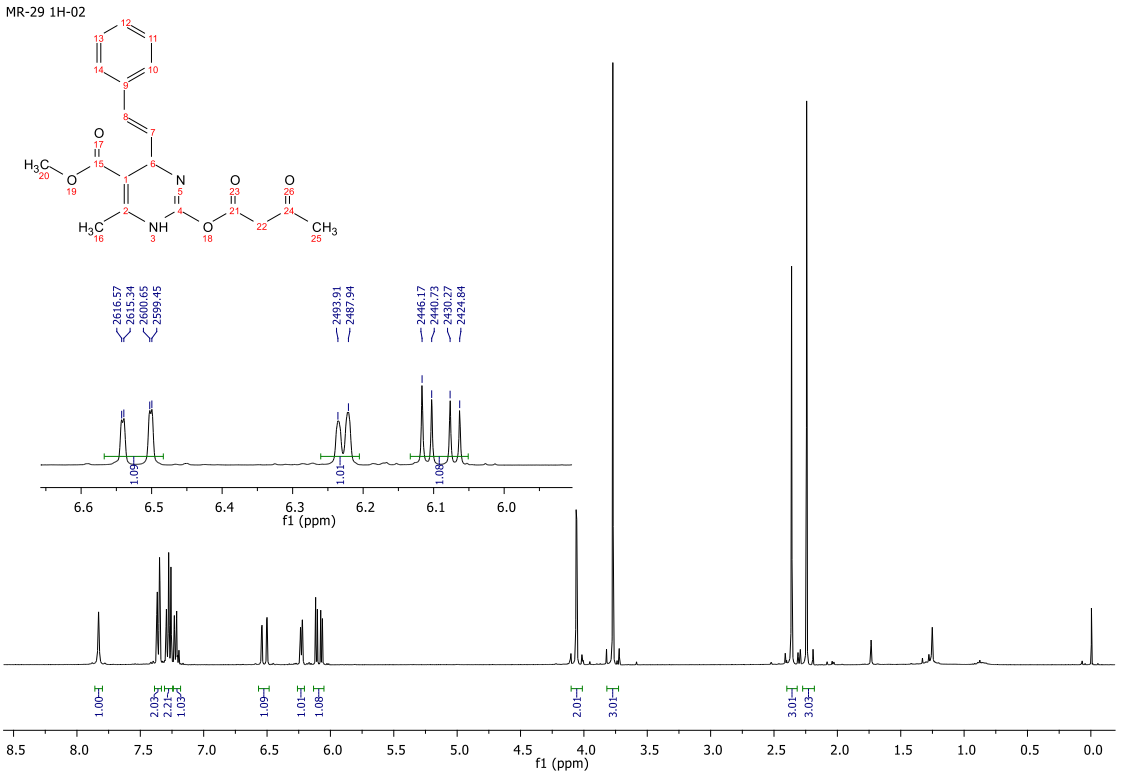


Figure 10: ^{1}H-NMR of MR-7

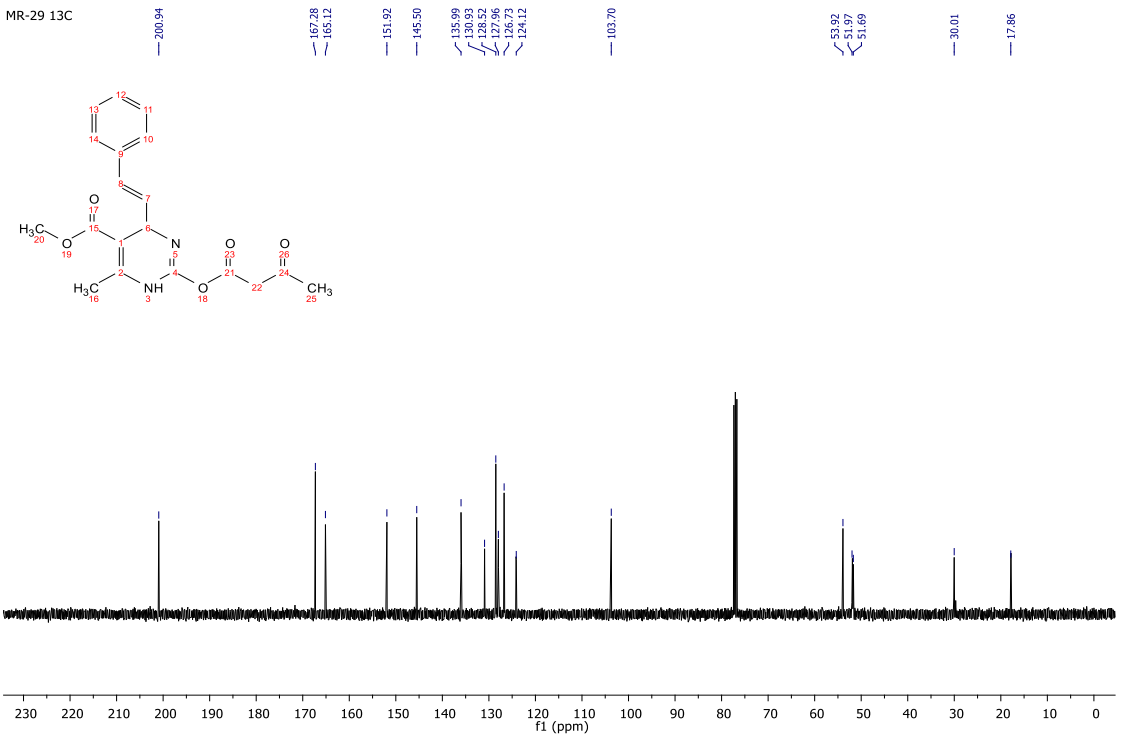
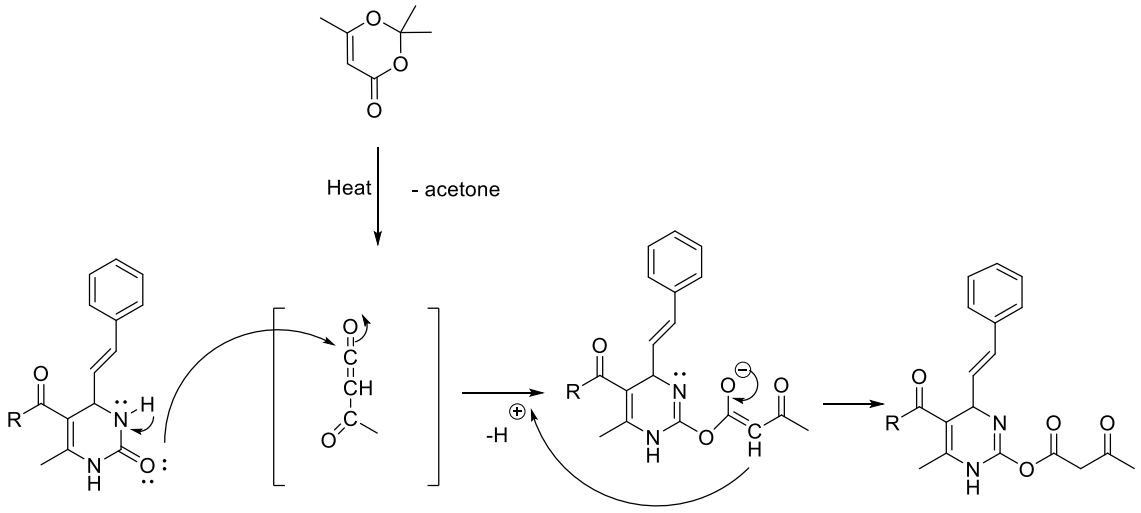


Figure 11: ^{13}C-NMR of MR-7

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 tautomerization of pyridine easily reacts with the reactive intermediate acetyl ketene to form acetoacetlation product.



Scheme 3 : Proposed mechanism of acetoacetylation reaction.

5. Conclusion

In this study, new acetoacetylated pyrimidine derivatives were synthesized 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 synthesized using Biginelli reaction and their second step acetyl acetylation reactions were investigated. In the second step, the pyrimidine derivatives synthesized 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.

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