T.R.
VAN YUZUNCU YIL UNIVERSITY
INSTITUTED OF NATURAL AND APPLIED SCIENCE
DEPARTMENT OF CHEMISTRY

DESIGN, SYNTHESIS, INVESTIGATION OF CYCLIZATION REACTIONS AND DETERMINATION OF ELECTRONIC PROPERTIES OF 3,4-DIHYDROPYRIMIDINE-2 (1*H*) DERIVATIVES

M.Sc. THESIS

PREPARED BY: Khdir Ahmed OTHMAN
SUPERVISOR: Prof. Dr. Esvet AKBAŞ

VAN-2021

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ACCEPTANCE and APPROVAL PAGE

This study entitled " **Design, Synthesis, Investigation of Cyclization Reactions and Determination of Electronic Properties of 3,4-Dihydropyrimidine-2 (1*H*) derivatives** " presented by Khdir Ahmed OTHMAN under supervision of Prof. Dr. Esvet AKBAŞ in the Department of Chemistry (Organic Chemistry) has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education on 29/12/ 2020 with unanimity / majority of votes members of jury.

Chair: Prof. Dr. Esvet AKBAŞ Signature:

Member: Associate Prof. Dr. Fatih Çağlar ÇELİKEZEN Signature:

Member: Assistant Prof. Dr. Erdem ERGAN 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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THESIS STATEMENT

All information presented in the thesis obtained in the frame of ethical behavior and academic rules. In addition, all kinds of information that does not belong to me have been cited appropriately in the thesis prepared by the thesis writing rules.

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Khdir Ahmed OTHMAN

ABSTRACT

DESIGN, SYNTHESIS, INVESTIGATION OF CYCLIZATION REACTIONS AND DETERMINATION OF ELECTRONIC PROPERTIES OF 3,4-DIHYDROPYRIMIDINE-2 (1*H*) DERIVATIVES

OTHMAN, Khdir Ahmed
M.Sc. Thesis, Department of Chemistry
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In this study, pyrimidine derivative compounds were obtained by using Biginelli reaction which is one of the multicomponent cyclocondensation reaction (MCR) methods. by reacting pyrimidine derivative compounds with bromoacetic acid and various aryl-aldehydes in the same vessel by one step, arylidene-bicyclic thiazolo-pyrimidine compounds were synthesized in good yield.

The structures of all new compounds were analyzed using spectroscopic methods such as IR, ^{1}H, and ^{13}C NMR. At the same time, quantum chemical calculations (QCC) of all compounds, density functional theory (DFT) method, 6-31G (d, p) base set and B3LYP functions were performed with Gaussian09W software package.

Keywords: Biginelli, DFT, MCR, Pyrimidine, Theoretical chemistry.

ÖZET

3,4-DİHİDROPİRİMİDİN-2(1*H*) TÜREVI BİLEŞİKLERİN TASARIMI, SENTEZİ, HALKALANMA REAKSIYONLARININ ARAŞTIRILMASI VE ELEKTRONİK ÖZELLİKLERININ BELİRLENMESİ

OTHMAN, Khdir Ahmed
Yüksek Lisans Tezi, Kimya Anabilim Dalı
Danışman: Prof. Dr. Esvet AKBAŞ
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Bu çalışmada, multikomponent siklokondenzasyon reaksiyon (MCR) yöntemlerinden biri olan Biginelli reaksiyonu kullanılarak pirimidin türevi bileşikler elde edildi. Pirimidin türevi bileşiklerin aynı kap içerisinde tek basamakta bromoasetik asit ve çeşitli aril-aldehitler ile reaksiyona sokulmasıyla, iyi bir verimle, ariliden-bisiklik tiyazolo-pirimidin bileşikleri sentezlendi.

Tüm yeni bileşiklerin yapıları IR, ^{1}H, ve ^{13}C NMR gibi spektroskopik yöntemler kullanılarak analiz edildi. Aynı zamanda tüm bileşiklerin kuantum kimyasal hesaplamaları (QCC), yoğunluk fonksiyonel teorisi (DFT) metodu, 6-31G (d, p) baz seti ve B3LYP fonksiyonları kullanılarak Gaussian09W yazılım paketi ile gerçekleştirildi.

Anahtar kelimeler: Biginelli, DFT, MCR, Pirimidin, Teorik kimya.

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First, I give thanks to God for providing me knowledge, protection, and ability to do the work. I would like to express the deepest appreciation to my master thesis advisor Professor Esvet AKBAŞ who suggested such an important topic and he enlarged my vision about scientific outlook, without his kind direction, proper guidance, and persistent help this dissertation would not have been possible.

I would like to express my special gratitude and thanks to Assistant Prof. Dr. Erdem ERGAN for giving me attention and time in every stages of my thesis work. He taught me how to do a literature search, how to collect data and a lot of practical lessons.

I convey my sincere gratitude to my Family and to my darling wife, for their kind cooperation, continuous support and encouragement which helped me in the completion of my thesis.

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2021

Khdir Ahmed OTHMAN

TABLE OF CONTENTS

Pages

Pages

Pages

LIST OF TABLES

Table **Pages**

Table **Pages**

LIST OF FIGURES

Figure **Pages**

Figure **Pages**

Figure **Pages**

Figure **Pages**

SYMBOLS AND ABBREVIATIONS

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

Symbols	Description
%	Percentage sign
ΔE	Energy difference
ΔN	The fractional number of electrons transferred
∇	Nabla operator, in a cartesian coordinate system
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
A	Electron affinity
A1	(*E, Z*)-6-benzoyl-2-benzylidene-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one
A10	(*E, Z*)-6-benzoyl-5,7-diphenyl-2-(thiophen-2-ylmethylene)-5*H*-thiazolo [3,2-*a*]pyrimidin-3(2*H*)-one
A2	(*E, Z*)-6-benzoyl-2-(4-chlorobenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one
A3	(*E, Z*)-6-benzoyl-2-(3-nitrobenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one
A4	(*E, Z*)-6-benzoyl-2-(4-methoxybenzylidene)-5,7-diphenyl-5*H*-thiazolo [3,2-*a*]pyrimidin- 3(2*H*)-one
A5	(*E, Z*)-6-benzoyl-2-(4-methylbenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one
A6	(*E, Z*)-6-benzoyl-5,7-diphenyl-2-(4-(trifluoromethyl) benzylidene) -5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one
A7	(*E, Z*)-6-benzoyl-5,7-diphenyl-2-(4-(trifluoromethyl) benzylidene)-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one

Symbols	Description
A8	(*E, Z*)-6-benzoyl-2-(2-methoxy-3-methylbenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one
A9	(*E, Z*)-6-benzoyl-2-(2,4-dimethoxybenzylidene)-5,7-diphenyl-5*H*-thiazolo [3,2-*a*]pyrimidin-3(2*H*)-one
$Ag_3PW_{12}O_{40}$	Neutral silver salt of tungstophosphoric acid
AM1	Austin Model One
Ar	Aryl group
B.C.	Before Christ
B-3CR	Biginelli three component reaction
B3LYP	Beck's three parameter exchange functional and Lee–Yang–Parr nonlocal correlation functional
BA	Benzaldehyde
c	Speed of light
$CaCl_2$	Calcium Chloride
$CDCl_3$	Deuterated chloroform
CR	Component Reaction
D	Dipole moment
d	doublet
DBM	Dibenzoylmethane
DFT	Density Functional Theory
DHPM	Dihydropyrimidine
DMF	Dimethylformamide
DMSO-d_6	Deuterated dimethyl sulfoxide
DNA	Deoxyribonucleic acid
E	Energy
EDG	Electron-Donating Group
E_{HOMO}	Energy of the Highest Occupied Molecular Orbital.
E_{LUMO}	Energy of the Lowest Unoccupied Molecular Orbital

Symbols	Description
eV	Electronvolt
EWG	Electron Withdrawing Group
g	Gram
GBB-3CR	Groebke-Blackburn-Bienaymé Three Componen tReaction
h	Planck's constant
H_2SO_4	Sulfuric acid
HCN	Hydrogen cyanide
HF	Hartree–Fock
HIV	Human Immunodeficiency Virus
HOAc	Acetic Acid
HOMO	Highest Occupied Molecular Orbital
hrs	Hours
I	Ionization energy
IMCR	Isocyanide-Based Multicomponent Reactions
IR	Infrared Spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
K1	(4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl) methanone
KBr	Potassium Bromide
LUMO	Lowest Unoccupied Molecular Orbital
m	Mass
m	multiplet
M.P	Melting Point
MCR	Multicomponent Reaction
MeCN	Acetonitrile
MHz	Megahertz
ml	Milliliter
MM	Molecular Mechanic

Symbols	Description
mmol	Millimole
MP2	2nd Order Møller-Plesset- Perturbation Theory
MP4	4th Order Møller-Plesset -Perturbation Theory
N	Number of electrons
NaOH	Sodium Hydroxide
NH_4Cl	Ammonium Chloride
NH_4CO_3	Ammonium Carbonate
NH_4OH	Ammonium Hydroxide
NIMCR	Nonisocyanide-Based Multicomponent Reactions
ºC	Degree Centigrade
p	Momentum
Ph	Phenyl group
PK-3CR	The Pauson–Khand Three Component Reaction
PKa	Acid dissociation constant
PM	Parametric Method
ppm	Part Per Million
***p*-TsOH**	*Para*-Toluenesulfonic acid
PTU	Phenylthiourea
QCC	Quantum Chemical Calculations
QCISDm	Quadratic CI (Single, Doubles and Triples)
QM	Quantum Mechanics
RM1	Recife Model One
RNA	Ribonucleic Acid
RT	Room Temperature
S	Softness
s	singlet
SE	Semiempirical
ß	*Beta*

Symbols	Description
t	triplet
t-buOK	Potassium tert-butoxide
TLC	Thin Layer Chromatography
TMSCl	Trimethylsilyl Chloride
TS-MCRs	Two Separate Multicomponent Reactions
TU	Thiourea
U.S. FDA	United States Food and Drug Administration agency
UV	Ultraviolet
v	Velocity
V	Potential energy
$ZnBr_2$	Zinc Bromide
δ	Chemical shift (delta)
η	Hardness
λ	Wavelength
μ	Chemical potential
χ	Electronegativity
ψ	Wave functions
ω	Electrophilicity index

1. INTRODUCTION

Heterocyclic rings including those carbocyclic compounds in which one or more carbon atoms have been replaced by different heteroatoms. The most found heterocyclic compounds are those having five/six-membered rings and containing nitrogen heteroatom, then oxygen and sulfur come after. However, several other atoms in the periodic table include metallic and nonmetallic heteroatoms that can form stable heterocyclic compounds. According to IUPAC report in 1983, fifteen elements from Group II to IV of the Periodic table have the ability of forming heterocyclic ring system with the carbon element (Powell, 1983). Heterocyclic compounds have been used in various purpose especially in the field of pharmacy, the recent databases of U.S. FDA in 2020s, reveal that more than 75% of approved drugs and they are currently available in the markets based on nitrogen containing heterocyclic compounds (Kerru, et al., 2020).

To broaden the field, the parent heterocyclic ring may be fused with different type of rings that causes new variable ring systems such as spirocyclic compounds in these compounds the rings are connecting by sharing one atom, fused bicyclic compounds in these compounds the rings joining by sharing two atoms and bridged bicyclic compounds include these compounds that forming by sharing more than two atoms between the rings). Furthermore, hydrogen atoms around these ring systems can be replaced by a several substituents, consequently; so many of heterocyclic compounds were recognized (Tyrell and Quin, 2010).

The important features of any heterocyclic system are knowing the ring size, the type and number of heteroatoms that form up the heterocyclic compound, these features become helpful in the naming of heterocyclic compounds, the common method is known as the Hantzsch–Widman system and is the basis of the nomenclature applied nowdays by the IUPAC with some minor modifications, among the great number of nitrogen covering heterocyclic structures, diazines (six-member with two nitrogen heteroatoms) and thiazoles (five-member with two different nitrogen and sulfur heteroatoms) can be considered as two classes gaining the highest interest (Schnürch and Mihovilovic, 2013).

1.1. Diazines

The diazines skeleton composed of (six-atom ring structures with two nitrogen heteroatoms) (Gupta, 2009), there are three types of diazines based on the location of two nitrogen's in the heterocyclic system; pyridazine, pyrimidine, and pyrazine (Figure 1.1), (Joule and Mills, 2013).

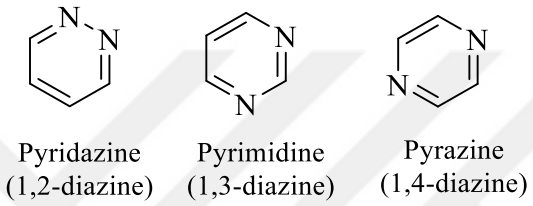


Figure 1.1. Structure of diazines.

In the last decades, treasure of reports discussed the preparation, modification, and uses of diazine compounds arose, because diazines are omnipresence in nature, and they have biological and electrochemical characteristics, these properties make diazines used as a basic part for drugs, semiconducting material, polymers, dyes, flavors, scents, and chemical agents (Gribble and Joule, 2017). The most important naturally occurring among diazines is pyrimidine (Joule and Mills, 2010).

1.2. Pyrimidines

Pyrimidine is the common name for 1,3-diazine; in benzene ring two carbon atoms on *meta*-location exchanged by nitrogen heteroatoms. The pyrimidine class is essential in the branch of heterocyclic chemistry. Pyrimidines are found among the nucleic acids (DNA and RNA) such as cytosine, thymine, uracil, adenine, and guanine. Adenine and guanine contain the purine skeleton, purine is a bicyclic compound formed from joining of imidazole and pyrimidine rings (Figure 1.2). In addition, pyrimidine structure is present in numerous natural molecules such as vitamin B1, vitamin B2 (riboflavin), the plant kingdom-alkaloids (such as caffeine), and so on (Tyrell and Quin, 2010). The bicyclic pyrazino-pyrimidine part at any

complex molecule is known as a pteridine such as in folic acid (Figure 1.2, Figure 1.3). Because of several nucleic acid bases contain pyrimidine ring in their composition, perhaps it isn't surprising that pyrimidines are famous as a highly active as medical therapies such as; neuroleptics, cholesterol reduction, cancer, impotence, and antivirals (Tyrell and Quin, 2010).

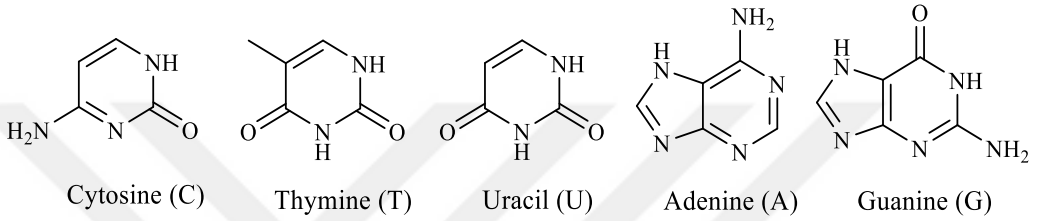


Figure 1.2. Structures of cytosine, thymine, uracil, adenine, and guanine.

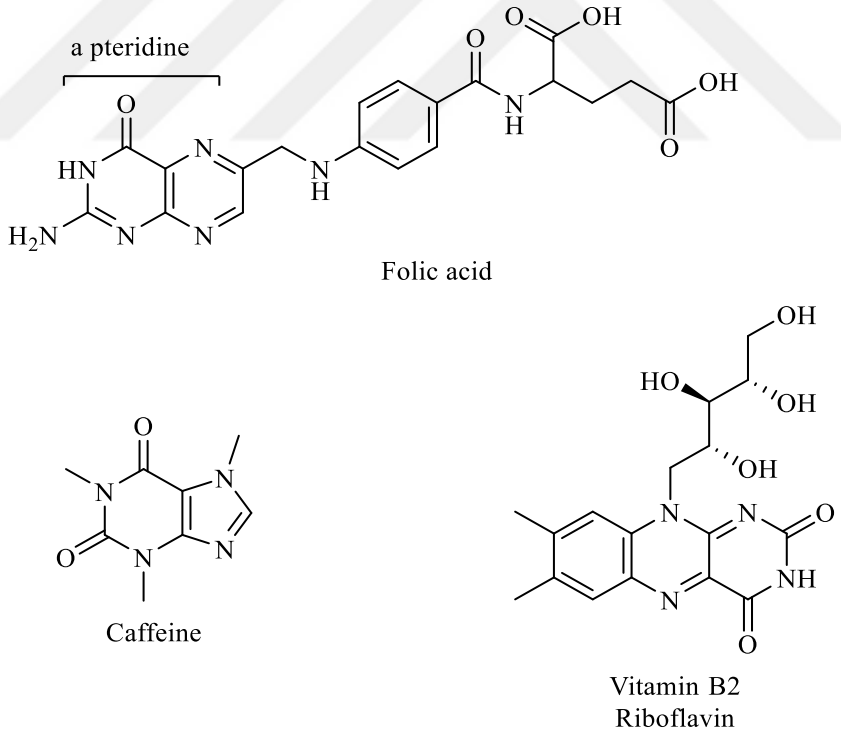


Figure 1.3. Structures of folic acid, caffeine and vitamin B2.

Heterocyclic pyrimidine compounds have been used medicinally for a long time, in natural resources as seen in 2735 (B.C.) the plant *Ch'ang Shan* had been used for treating

fevers, this plant identified that it contains pyrimidine compounds (Chou, et al., 1948) for example, ß-dichroine (Figure 1.4), (Tyrell and Quin, 2010).

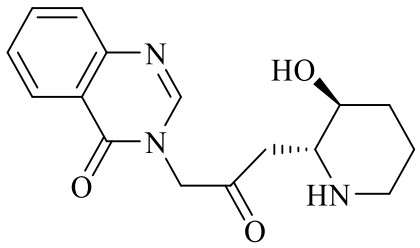


Figure 1.4. Structure of *beta*-dichroine.

On the other hand, one of the early class of synthetic heterocyclic drugs that contains pyrimidine skeleton such as malonylurea (barbituric acid) (Figure 1.5), which was obtained by Von Baeyer in 1864 (Kauffman, 1980), later in 1912 the phenobarbital was announced by Bayer pharmaceuticals, and it has been used for epilepsy treatment (Sneader, 2005).

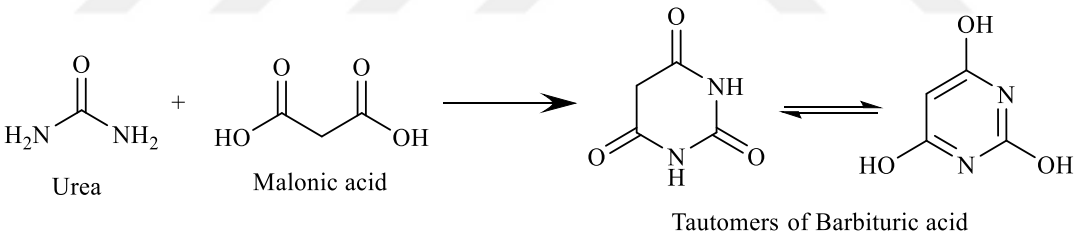
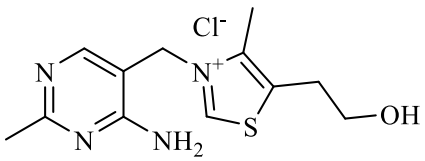


Figure 1.5. Synthesis of barbituric acid.

Another important class of heterocyclics that related to this thesis is a five-member heterocyclic that contains both nitrogen and sulfur heteroatoms which referred as a thiazole ring, there are many important compounds that associated with thiazole skeleton, such as vitamin-B1 (thiamin) which is the first vitamin chemically identified in 1910 and it contains both thiazole and pyrimidine rings **(**Figure 1.6), (Scriven and Ramsden, 2017). Similarly, the application of thiazoles and their derivatives have been found in different fields, thiazole in the form of fully reduce structure incorporated in the famous antibiotic penicillin (Figure 1.7), (Lobanovska and Pilla, 2017).



Vitamin B1
Thiamine

Figure 1.6. Structure of vitamin B1.

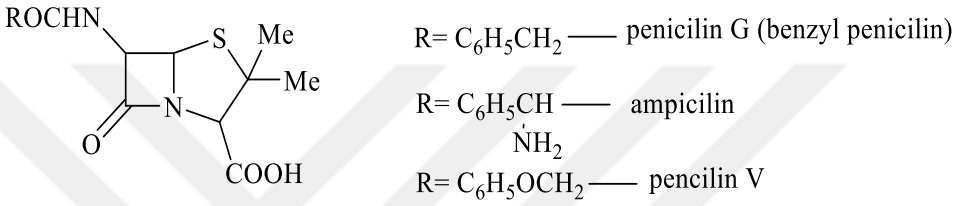


Figure 1.7. Structures of penicillin compounds.

1.2.1. Thermodynamic aspects of pyrimidine

The 2,4-substituent tautomerism of pyrimidines is extremely important, such as hydroxy-oxo, amino-imino, and thiol-thioxo tautomerism. 2-hydroxypyrimidine shows two tautomeric forms and 4-hydroxypyrimidine show three tautomeric forms (Figure 1.8), (Undheim and Benneche, 1996; Stanovnik, et al., 2006; Katritzky, et al., 2008).

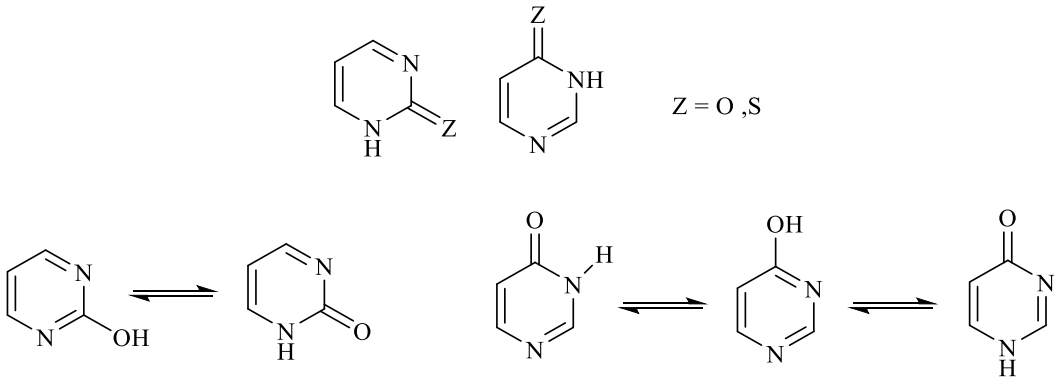


Figure 1.8. Prototropic tautomerism of pyrimidines and hydroxy-oxo tautomerism at two or four positions.

1.2.2. Pyrimidine synthesis

Various aspects of synthesis pyrimidine ring have been reviewed in a lot of reports, here; synthesis methods classified by number of components that participate in the reaction (Katritzky and Rees, 1984; Brown, et al., 1994).

From two reactants of five and one ring atoms (A + B-C-D-E-F), example of this synthetic approach is the cyclization of five-atom unit enamide esters (C2-N1-C6-C5-C4) with primary amines (N3) in the presence trimethylaluminium causing to formation of 3-substituted 3*H*-pyrimidin-4-ones (Figure 1.9), (Jeong, et al., 2004).

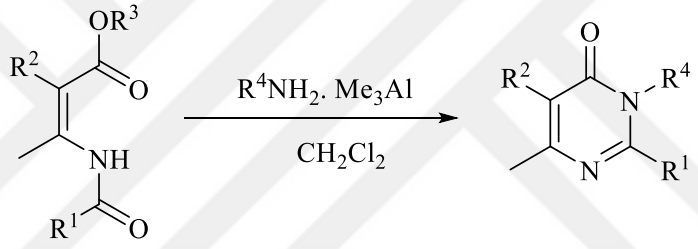


Figure 1.9. Synthesis of pyrimidine by combination of (C2-N1-C6-C5-C4 + N3).

From two reactants (A-B + C-D-E-F); example of this strategy when the two-atoms N1–C2 (such as nitriles) and the four-atom parts can be unsaturated ß-amino nitrile, ß-amino amide, thermally react to form of 2-trichloromethyl and 2-trifluoromethyl pyrimidines (Figure 1.10), (Sosnovskikha, et al., 2002).

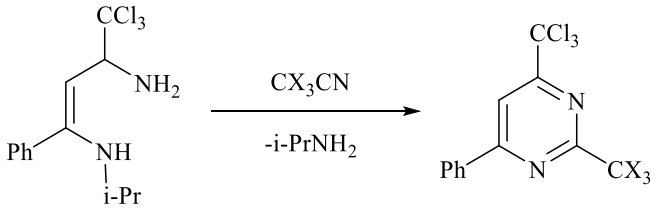


Figure 1.10. Synthesis of pyrimidine by combination of (N3-C4-C5- C6 + N1–C2).

From two reactants (A-B-C + D-E-F), example of this route the one of three units C4–C5–C6 such as (ß-keto esters) with other three units N1–C2–N3 such as (amidine) component which is attached to a solid support, where oxidation and hydrolytic cleavage of

the thio linker from the solid support produce 2,4-pyrimidinediones (Figure 1.11), (Parlato, et al., 2004).

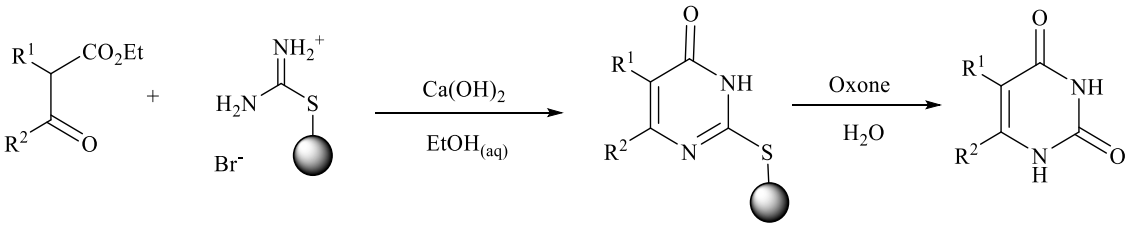


Figure 1.11. Synthesis of pyrimidine by combination of (C4–C5–C6 + N1–C2–N3).

From three reactants (A + B-C-D + E-F), the extremely important example of this strategy is Biginelli three component reaction, in this route methylene ketone (C5-C6), an aldehyde (C4), and urea/thiourea type compounds (N1-C2-N3), react to give partially reduced pyrimidine DHPM (Figure 1.12), (Kappe, 1993). The Biginelli multicomponent reaction is described in details in the next section (1.3.3, Biginelli).

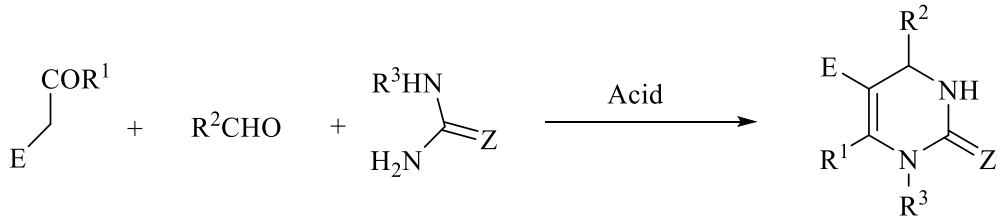


Figure 1.12. Synthesis of pyrimidine by combination of (C4 + C5-C6 + N1-C2-N3).

Pyrimidines can be synthesis through several bond breaking and bond formation reactions (Figure 1.13), for example by combination four components-unsaturated ester (C4-C5-C6), N,O-bis(trimethylsilyl)hydroxylamine (N1), phenylchloroformate (C2), and ammonia(N3) to obtain 6-substituted uracil compounds, this method was effectively used as part of the general synthesis of the freshwater cyanobacterial hepatotoxins cylindrospermopsin and 7-epicylindrospermopsin (Keen and Weinreb, 2000).

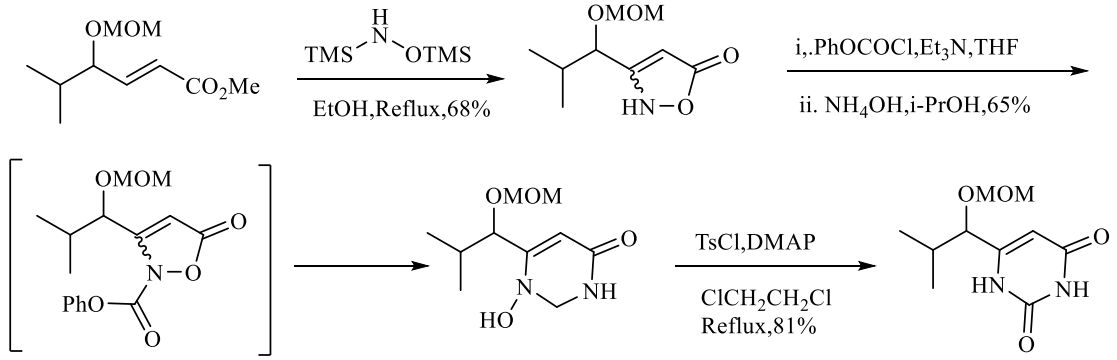


Figure 1.13. Synthesis of pyrimidine by combination of (N1 + C2 + N3 + C4-C5-C6).

1.2.3. Pyrimidine reactivity

The pyrimidine contain two imine nitrogen atoms results in an irregular distribution of electron density (Tyrell and Quin, 2010), the availability of nitrogen lone pair(s) withdraws electron density from the ring carbons and this strongly influences on the reactivity and the physical properties, so the carbons of unsubstituted pyrimidine are resistant to electrophilic substitution, but high tendency toward nucleophile reactions (Joule and Mills, 2010). The electron density around N1 and N3 atoms causing to electrophilic reactions happening on nitrogen atoms (Joule and Mills, 2013).

1.3. Multicomponent Reactions (MCRs)

As stated from the pyrimidine synthesis discussion one of the most important way for synthesis pyrimidine derivatives is multicomponent reaction rout such as Biginelli above.

MCRs can be defined as chemical reactions in which more than two substrates react in one synthetic process (one-pot) to form highly selective products with high atom efficiency (Orru and Greef, 2003), these actions often show high levels of regio-, chemo-, and stereoselectivity (Ramon and Yus, 2005). MCR have appeared as powerful strategy compare to the other classical methods (linear, iterative, or divergent synthesis), (Guillena, et al., 2007; Padwa and Bur, 2007). Moreover, MCRs collect the classical preoccupations such as

convergence, productivity, selectivity, molecular complexity and variety (Vugts, et al., 2006; Nielsen and Schreiber, 2008), with current concerns such as atom and time economy (fewer steps and overall yield) (Trost, 2002; Wender, et al., 2003), also environment friendly method, generally MCRs relatively near to the idea of an ideal synthesis (Wender, 2014).

One ineffable example is adenine probably obtained through the addition of five molecules of isocyanic acid, this include heating the solution of HCN (1 to 15 Molar) in NH_4OH for a proper time at moderate temperatures (27 to 100 ^oC) (Figure 1.14), (Oro and Kimball, 1961; Zhu and Bienayme, 2005).

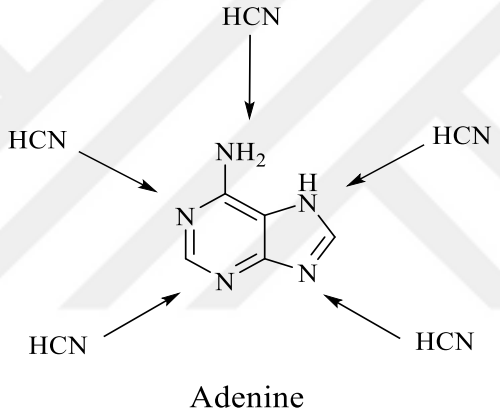


Figure 1.14. A prototype MCR of the formation adenine.

The initial MCR published by Strecker in 1850**,** after that MCR idea has been widely discovered (Orru and Eelco, 2010). There have been several reports on MCRs so far, multicomponent reactions can be subcategorized into two general classes, isocyanide-based multicomponent reactions (IMCRs) includes (GBB-3CR, Orru-3CR, van Leusen-3CR, Passerini-3CR Ugi-3CR/4CR/5CR) and nonisocyanide-based multicomponent reactions (NIMCRs) includes (Hantzsch-3CR, Biginelli reaction, PK-3CR, Gewald-3CR, Dobener-3CR, Povarov-3CR, Betti-3CR, Petasis-3CR (Herrera and Lopez, 2015; Ameta and Dandia, 2017).

Most of these MCRs have been more improved and numerous alternatives are being published over the years. There are first MCRs with only two other MCRs were mentioned here that associated to this work.

1.3.1. Strecker

The world first MCR was discovered by Strecker in 1850, in this MCR three substates aldehydes, hydrogen cyanide, and ammonia react together to afford α-amino acids (Figure 1.15), (Strecker, 1850).

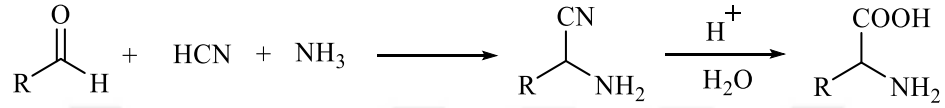


Figure 1.15. The world's first MCR, synthesis of *a*-amino acids by Strecker in 1850.

1.3.2. Hantzsch

After Strecker discoveries in 1850, in 1881 Hantzsch discovered new NIMCR to afford 1,4-dihydropyridine molecules, through reaction of ß-keto esters, aldehydes, and ammonia (Figure 1.16), (Hantzsch, 1881). After that in 1890 Hantzsch find another nonisocyanide-multicomponent reaction for synthesis of pyrroles through replacing two reactants by two different molecules which have closely some compositions **(**Figure 1.17), (Hantzsch, 1890).

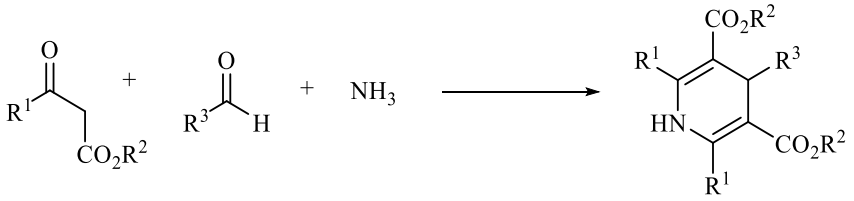


Figure 1.16. Synthesis of pyridine derivatives by Hantzsch in 1881.

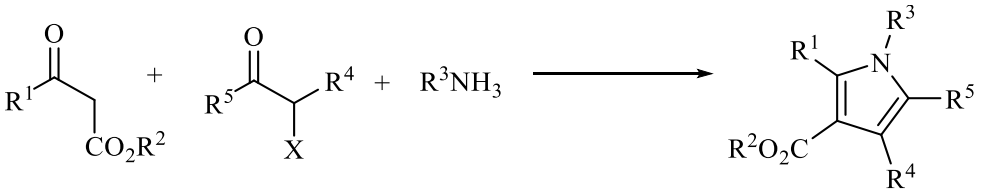


Figure 1.17. Synthesis of pyrroles by Hantzsch in 1890.

1.3.3. Biginelli

The Biginelli reaction (Figure 1.18), discovered by Pietro Biginelli in 1891 (Biginelli, 1891), this multicomponent reaction (one-pot, three-component) leads to partially reduced pyrimidine derivatives, the original Biginelli involving cyclocondensation reaction of aldehydes, urea, and ß-ketoesters in the presence strong acidic catalyst to afford 3,4-dihydropyrimidin-2-ones.

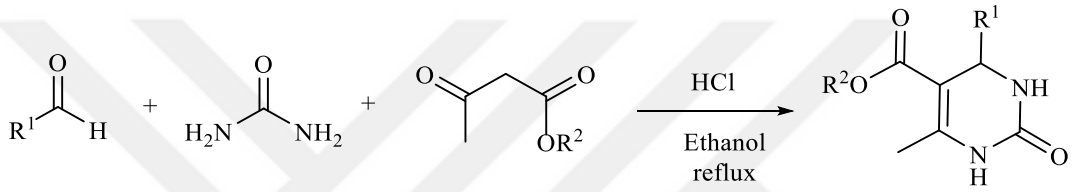


Figure 1.18. Synthesis of DHPM by original Biginelli in 1891.

Importance of Biginelli has been proofed in the large number reports described in the past years (Herrera and Lopez, 2015). DHPMs can act as antihypertensive, antiviral, antibacterial, anti-inflammatory, or anticancer agents and potent calcium channel blockers (Zhu and Bienayme, 2005). Additionally, it is interesting that DHPMs might be gained as asymmetric molecules (chiral compounds) through Biginelli, and the configuration of the stereocenter at carbon four (C4) is critical to determine their biological properties (Gong, et al., 2007).

1.3.3.1. Mechanistic studies of Biginelli

The steps of the Biginelli reaction for synthesis DHPM has been the topic of some discussion over the past periods. There are three possible mechanisms proposed for Biginelli (Figure 1.19):

1- In 1933 Folkers and Johnson recommended that bisureide is the primary intermediate in the reaction between benzaldehyde and urea (Folkers and Johnson, 1933), later in 1997, Kappe reanalyze the pathway by using $^{1}H/^{13}C$ NMR instrumentation and trap ping experiments (Kappe, 1997), and in 2009 this route was confirmed by combined

experimental and theoretical data, these investigations proposed that aldehyde and urea react to form N-acyliminium ion intermediate, the iminium ion connected with enol form of ethyl acetoacetate, open-chain ureide was formed, which finally cyclizes and water eliminate to form DHPM (Souza, et al., 2009).

2- In 1973 Sweet and Fissekis explained different mechanism and recommended that in the first step aldehyde and ethyl acetoacetate react in the presence acid catalysis to form carbenium ion intermediate, later urea is participating to produce DHPM (Sweet and Fissekis, 1973).

3- Another approach mechanism of the Biginelli reaction in the presence base catalysis proceeds via a hemiaminal pathway by reaction ß-ketoesters with urea type compounds, according to electrospray ionization/mass spectrometry measurements.

However, it is important to note that bis-ureide was obtained in acidic medium. So far there aren't any evidence on the synthesis of bis-ureide in basic medium (Raj, et al., 2011), also separated bis-ureide readily reacted with verity of ß-dicarbonyl substrates to form the Biginelli product "ureidocrotonate mechanism", while arylmethylene ß-keto esters like cannot react with third component (urea) or gave extremely low yields (1.5–3.8%) under the same conditions (Kolosov, et al., 2008).

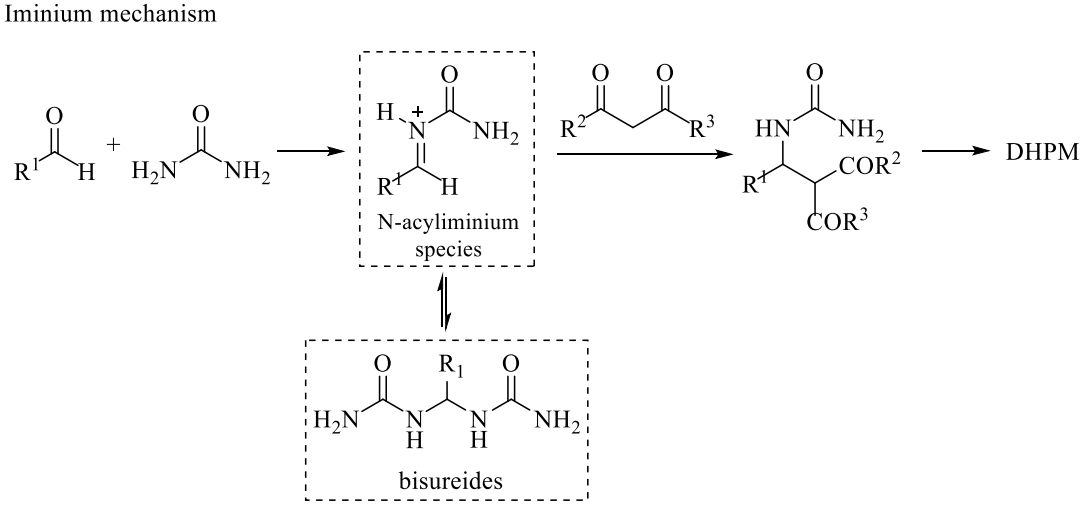


Figure 1.19. Three possible mechanism of Biginelli.

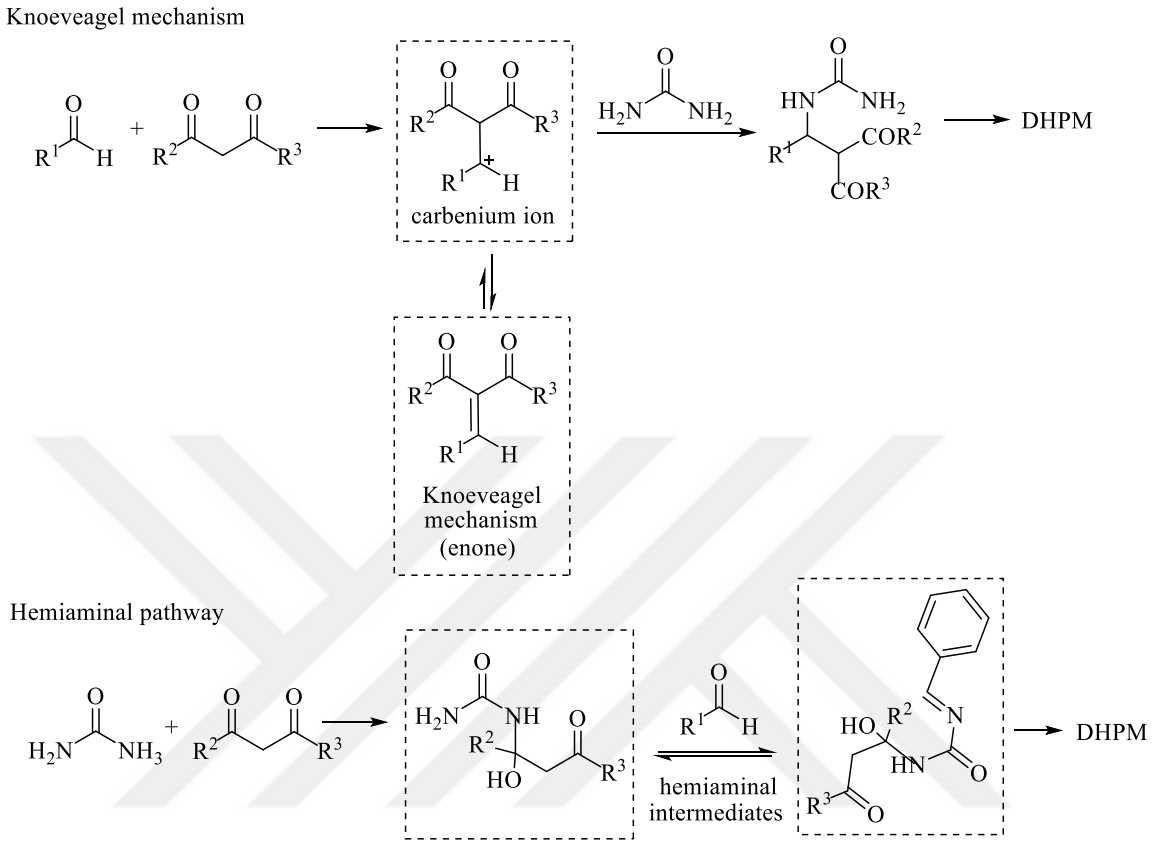


Figure 1.19. Three possible mechanism of Biginelli (continue).

1.3.3.2. Reaction conditions for Biginelli

The original Biginelli procedure (reflux in ethanol and hydrochloric acid as a catalyst) often suffers from low yield and impure of product, the impurities were mainly Knoevenagel condensation products due to the reaction between methylene-carbonyl and aldehyde components.

Several modifications and variety of suitable reaction conditions for performing Biginelli have led to in the finding of milder and more effective practical routes, also using active catalysts and choosing different building blocks caused to allowing access to many multifunctionalized pyrimidine derivatives with high amount pure product, moreover the use of mild conditions probably also prevents undesired transformations and provides the complete transformation of the reagents with simplified isolation of the products as pure compounds (Dallinger and Kappe, 2005). DHPMs have low solubility in alcohols at room

temperature, this helpful in separation by simple filtration or just by addition of water caused to precipitation of the DHPMs.

An abundant literature covers more than 200 different experimental procedure including a recent catalyst or a source of radiations (Kolosov, et al., 2008).

1.3.3.3. Solvents in Biginelli

Traditionally, the solvents choice for Biginelli condensation are alcohols (ethanol or methanol) (Stefania, et al., 2006), acetic acid is essential to use as a solvent especially when the intermediate doesn't dissolve in alcohols such as bisureide type compounds (Hassani, et al., 2006), using aprotic solvents such as DMF, dioxane or acetonitrile, generally all starting components soluble in acetonitrile at the same time DHPMs dissolve only in small amount (Stadler, et al., 2003). The non-polar solvents such as toluene couldn't give satisfying yield, in some case not all reactants dissolve in non-polar solvents (Tajbakhsh, et al., 2005), also the reaction could be carrying out under solvent-free conditions in presence *p*-TsOH (Azizian, et al., 2007).

1.3.3.4. Catalysts for Biginelli

Catalysis capable to have diverse roles, such as obtaining the desired stereo control or choosing certain product over the other. The amount of catalysts has effective role in the Biginelli reaction (Jose, et al., 2012). Usually, strong acids are employing such as hydrochloric or H_2SO_4/water (Hassani, et al., 2006), nowadays several various catalysts are employing such as $CaCl_2$/Ethanol (Akhaja and Raval, 2011), there are also reports on the use of acidic clay (Choudhary, et al., 2003), a zeolite (Rani, et al., 2001), Ionic liquids (Shaabani and Rahmati, 2005). A heteropoly acid such as $Ag_3PW_{12}O_{40}$/water (Yadav, et al., 2004), several organic acids (both mono and dicarboxylic acids) reported by (Noreen, et al., 2013), base catalysts such as *t*-buOK, NaOH (Shen, et al., 2010), more catalysts mentioned in (Kolosov, et al., 2008). Presence some type of catalysts caused to the competition between Hantzsh-3CR and Biginelli reactions such as urease biocatalysts/water that caused

dissociation of urea into ammonia (Tamaddon and Ghazi, 2015), also presence NH_4CO_3/water (Raj, et al., 2011).

1.3.3.5. Energy source for Biginelli

Biginelli reaction are typically not fast at RT, so applying of heat is requiring to activate the reaction, the ideal temperature was determined to be 120°C, this achieving of short reaction times with high yield.

Apart from classical heating methods, other source of energy such as micro wave can be used (*p*-TsOH/acetic acid/microwave, 20 mins) (Tu, et al., 2003), it is also possible using ultrasound activation for B-3CR for example, NH_4Cl/methanol/ ultrasound (Stefania, et al., 2006), IR irradiation (Osnaya, et al., 2003), or photochemical methods (Foroughifar, et al., 2003).

1.3.3.6. Building blocks for Biginelli

Still the molar ratio of starting materials concerned, generally the pure and highest product amount were achieving by employing an excess amount of the urea type components (Stadler, et al., 2003).

1.3.3.7. Aldehyde substrates for Biginelli

Aldehyde component is one of three building blocks in the B-3CRs that can be exchanged with wide range similar components, overall, aromatic aldehydes provide the good results with various branches in the *ortho*-, *meta*- or *para*- location with either electron-withdrawing (EWG) or electron-donating groups (EDG), high yields are typically gained with *meta*- or *para*-substituted aromatic aldehydes bearing EWGs (such as NO_2, CN, $COCH_3$, COOH, $COOCH_3$, CHO, I, Br, Cl, F). The amount of product usually lower when aromatic aldehydes have big branches in *ortho*-position (Shaabani, et al., 2004). However, the yield decreases significantly in the presence of EDGs on the aromatic aldehyde (such as

NH_2, OH, OCH_3, $NHCOCH_3$, NMe_2, CH_3 and Ph), it is probable due to the aldehyde carbonyl group becomes less actives (Gong, et al., 2002). with decreasing in the electrophilicity of the methylene carbonyl and aldehyde components used, the time required to obtain Biginelli compounds increases to 2-14 days while the yields are somewhat decreased to 72-97% (Dzvinchuk, et al., 2003).

Aliphatic aldehydes in B-3CR usually gave low product amount until the proper strategy was employed, steric effect has great influence when aliphatic aldehydes were used, for instance, the reaction of urea and ethyl acetoacetate with ether *n*-butyl aldehyde or *iso*-butyl aldehyde gave the product in 85%, 54% yield respectively (Han, et al., 2005).

1.3.3.8. ß-ketoester alternative compounds for Biginelli

Traditionally, open chain ß-dicarbonyl compounds such as alkyl acetoacetates are used as CH-acidic starting component (Shaabani, et al., 2004), despite of that other forms such as 3-oxoalkanoic esters or thioesters, ß-tricarbonyl compounds have been employed successfully were in enol form in solution whereas keto forms were formed in solid phase (Saçmaci, et al., 2008), also cyclic ß-diesters or ß-diamides can be employed as a (CH) acid instead of open chain cyclic ß-dicarbonyl compounds (Mokrosz, et al., 1989; Byk, et al., 2000).

1.3.3.9. Dinucleophile component, urea (thiourea) in Biginelli

Among components of B-3CR, the dinucleophilic component faces the greatest limitations toward permission of structural variety. Hence, most of the reported experiments include urea or thiourea as a starting material. So far, the straight affording of N, N-disubstituted DHPMs remains as a hard task for researcher (Singh, et al., 2006). An excess amount of the dinucleophilic component is essential to make up the loss of this component due to undesired transformations such as hydrolytic decomposition (Dzvinchuk, et al., 2002).

1.3.3.10. Alternative synthetic methods of DHPM.

Except the classical Biginelli, only a few synthetic approaches providing DHPMs. none of these routs have interested in research area or can compete with the Biginelli because most of these methods involve complexity in experimental or theoretical part.

Atwal modification (Figure 1.20), involve multi-step procedure, the first step an enone type compound is react with a protected urea or thiourea derivatives. In the final step the deprotection lead to 1,4-DHPM (Atwal, et al., 1987; 1989).

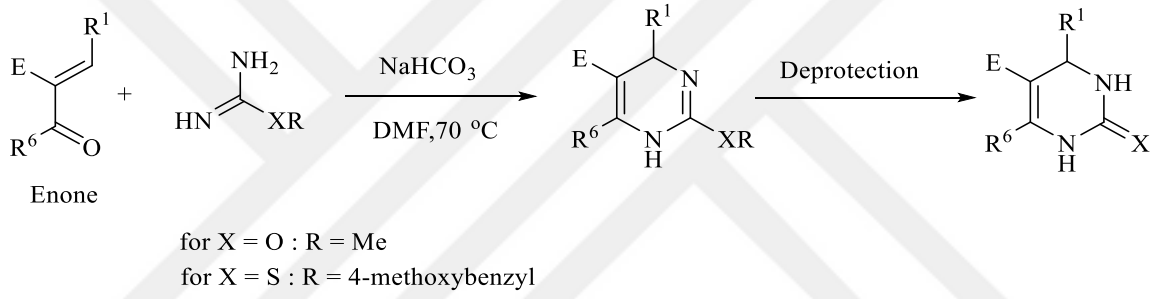


Figure 1.20. Synthesis of DHPMs by multi-step Atwal approach in 1987.

A unique approach that affords bicyclic dihydropyrimidine derivative was established by Taguchi and coworkers (Figure 1.21), the condensation of trimolecular of an enamine, acetaldehyde, and isocyanic at room temperature (Taguchi, et al., 1977).

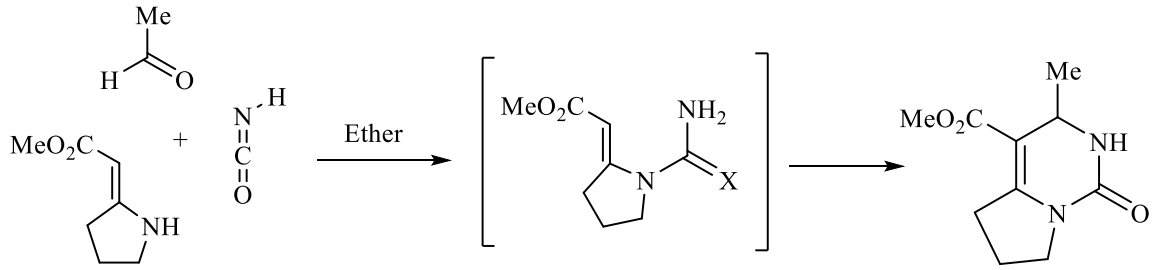


Figure 1.21. Synthesis of DHPMs by Taguchi approach in 1977.

Another way of synthesis DHPMs has been designated by Kishko and coworkers (Figure 1.22), this method involving condensation of *a*-tosyl-substituted urea/thiourea with the 1,3-dicarbonyl derivatives to form hexahydropyrimidines which finally leaded to

DHPMs. In this approach aliphatic aldehydes can be employing to obtained high amount yield of the favorite compound (Kishko, et al., 1998).

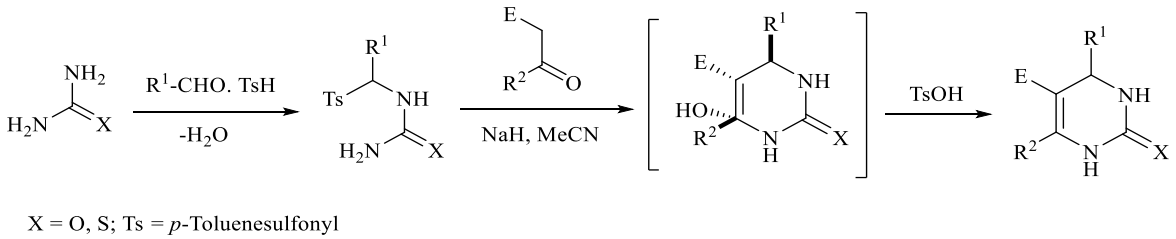


Figure 1.22. Synthesis of DHPMs by Kishko approach in 1998.

Novel approach (Figure 1.23), in which initially aldehyde and urea compounds are react in the presence of benzotriazole to obtain aminal, treatment of aminal with the active methylene CH acidic compound in the attendance Lewis acid $ZnBr_2$ and 1,2-dichloroethane gives the DHPMs with a proper yield (Abdel-Fattah, 2003).

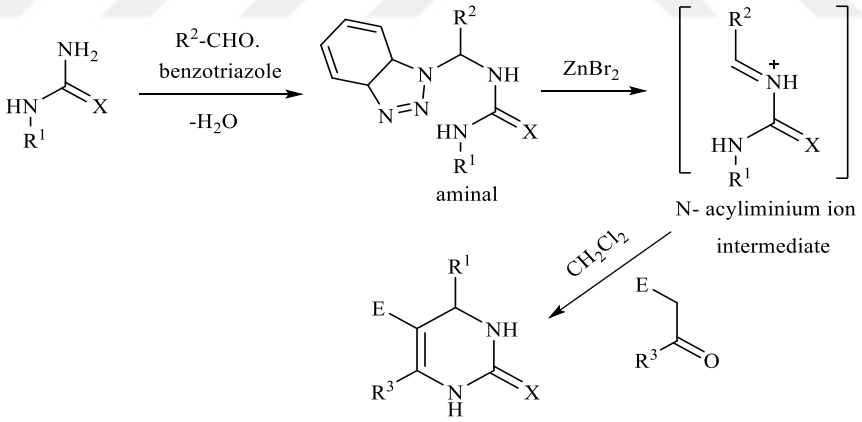


Figure 1.23. Synthesis of DHPMs by using benzotriazole meditation in 2003.

1.3.3.11. Further reaction of DHPMs

The six variety positions around the DHPMs central of the Biginelli product (N1, C2=Z, N3, C4, C5 and C6) and the presence at least two nitrogen atoms in its structure with capability of tautomerism, these features make DHPMs valuable chemical precursors of multifunctionalized pyrimidines, there are several examples as following;

N1-functionalization, DHPMs can be alkylated regioselectivity at N1-position when react with alkyl halides with appropriate base, under special drastic conditions DHPM undergo further alkylation at N3-location to form dialkyl derivatives (cho, et al., 1988). C2-functionalization is almost hard when cyclic urea present in (Figure 1.24, DHPM Z = O), compare to cyclic thiourea (Figure 1.24, DHPM, Z = S), however there is a literature shows the S-alkylation and desulfurization of dihydropyrimidine-2-thiones (Dallinger and Kappe, 2005). Also, another reported on synthesis C2-multifunctionalized pyrimidines from DHPM (both Z = O, S), by dehydrogenation-Mitsunobu reaction through using various nucleophiles (Xi, et al., 2011). N3-functionalization, synthesis N3-acetylated or formylated DHPMs (Singh and Singh, 2006), also synthesis of DHPMs possessing N3-nitro substituent have been reported by (Kaur and Knaus, 2007). In the most cases the mixture of N1 and N3 were formed which is relay on the type of substitutes around the DHPM core (Dallinger and Kappe, 2005).

Modification of C4-position of DHPMs, through changing aldehyde building blocks as a starting material for preparation of DHPMs. C5-functionalization**,** at (Figure 1.24, E = benzyl esters or allyl esters), these substitutes can be converted to free carboxylic acids which serve as important reactants for further decoration at the C5-postion of the DHPMs (Schnell, et al., 2000). C6-functionalization, when methyl group attached to DHPMs at C6 position, bromination of the methyl group caused to formation 6-dibromomethyl derivatives, the bromomethyl compounds can undergo substitution reaction with diversity of nitrogen, sulfur, and oxygen atom nucleophiles substitution reactions to form six-substituted DHPMs (Dallinger and Kappe, 2005).

Apart from the above methods of derivatization there are some strategies allow the formation bicyclic analogs for examples C2-N3 cyclization reaction of DHPMs with sodium azide for synthesis of tetrazolo[1,5-*a*]pyrimidines (Wang, et al., 2011), C2-N3 cyclization for synthesized different heterocyclization-pyrimidines (Akbas, et al., 2017a), and C5-C6 cyclization for several different bicyclic compounds (Dallinger and Kappe, 2005), (Figure 1.24).

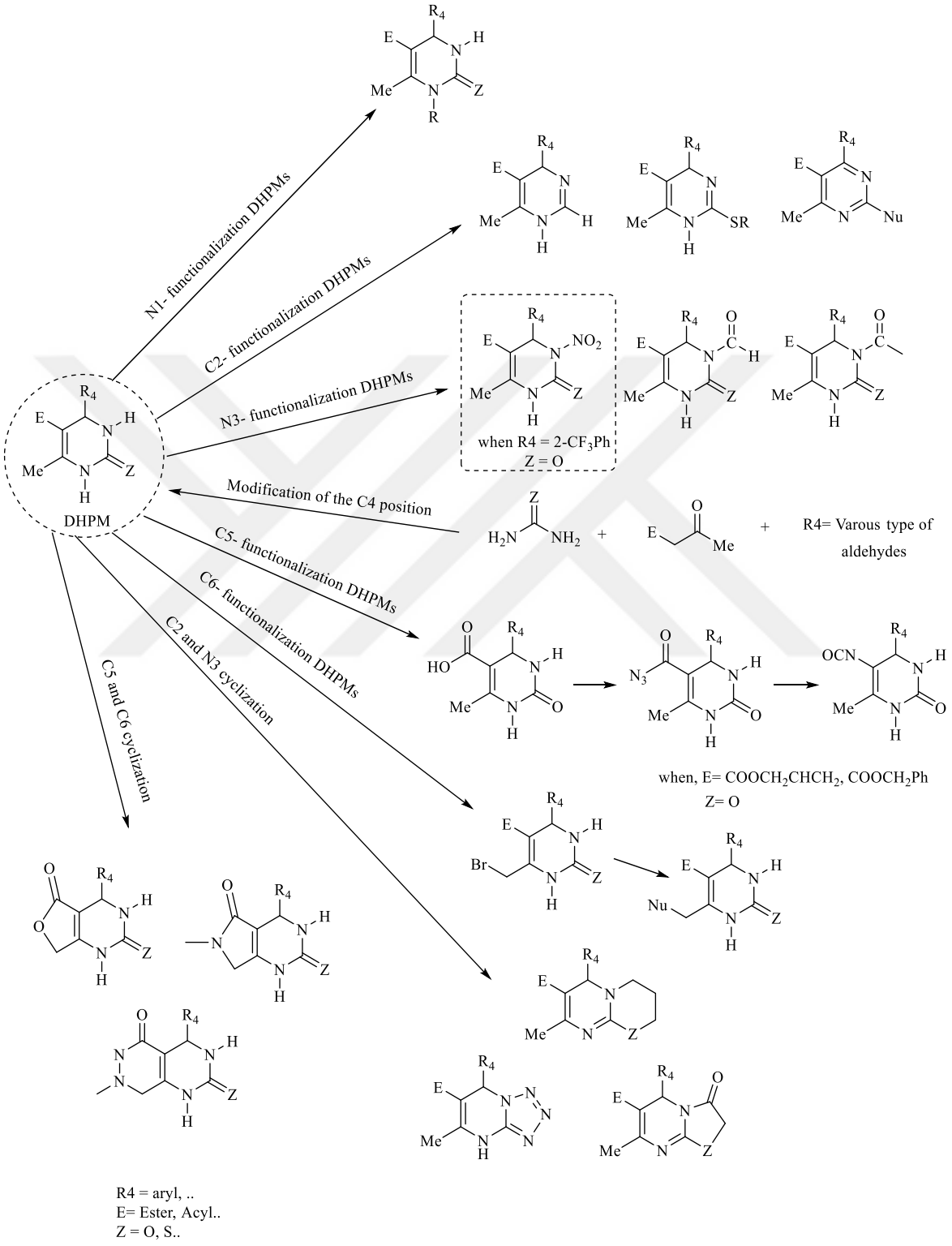


Figure 1.24. Scaffold decoration at all six points around DHPMs.

1.4. Computational Chemistry

Theoretical chemistry collects general ideas from classical physics laws to quantum physics fundamental laws and combine them with mathematical methods to study processes of chemical relevance. Computational chemistry is commonly applicable in the pharmaceutical area to choose the proper drug ability to connect with biomolecules, for instance, by docking a suitable drug into the active site of an enzyme (Bove, 2014), moreover, it is applying to examine the characteristics of solid substances (e.g., plastics), (Goldman and Leszczynski, 2019). As far as, theoretical chemistry cannot replace experimental chemistry which reveal the ultimate reality about universe (Lewars, 2011). Computational chemistry calculates:

- Geometry: molecular shape (bond lengths, angles between atoms, and dihedral between three atoms).
- Energy: this gives information about activation energy of reactants also help to determine the desire isomer products.
- Reactivity: it shows the electron density around the molecules (nucleophilic sites) and (electrophilic sites) this gives prediction at which site chemical reaction occurs.
- Spectrum such as (IR, UV, and NMR): by prediction the spectra of drawing molecular structure.
- The contact of a molecules with an enzyme: shows which substrate have better interaction with enzyme surface to select the best candidate drags.
- The physical characteristics of materials: how molecules behave physically (Chattaraj and Ghosh, 2013; Dixon, 2015; Jensen, 2017).

1.4.1. Historical background

To understand the computational chemistry, it should understand the physics parameters such as (energy, force, speed, length, wavelength, frequency, attraction, and repulsion and so on…) from the big giant heavy, slow moving macroscopic systems such as galaxies based on classical physics to a very tiny microscopic system that are assumed it

is consist a group of charged particles, positive nuclei and negative cloudy electrons based on quantum mechanics (QM). Electrons binds at relatively fixed position around the nuclei because the attraction in the internuclear region of electrons and nuclei, nuclei much heavier (about 2000 more massive) than electrons and electrons are in rapid motion in contrast of the nuclei therefore the geometry parameters of molecule are nuclear coordinates, and the energy related parameters are electron coordinates, but depend on the nuclear coordinate parametrization (Jensen, 2017).

Chemistry dealing with microscopic system therefore quantum chemistry begins after these discoveries that caused to the evolution from classical to modern physic. In 1901 the journey starts with Planck's explanation of the black-body radiation inspired by that energy is exchanged in substances, in 1905 Einstein explained the facts of the photoelectric effect, Einstein went further after Planck and guessed that not only absorption-emission phenomena of light quantized, but also light by its own was quantized, light consist of particles of energy, those particles recognized as photons. In 1913, Bohr's showed the model of the hydrogen spectrum, incorporating quantization of angular momentum, (Lewars, 2011), later in 1915, general relativity published by Einstein ($E = mc^2$), these discovers leading to Prince Louis De Broglie principle in 1923 (Eq. 1.1) that said every substances with momentum, it also have wavelength its mean that every big to small objects with a momentum has duality of wave and particle properties (Trindle and Shillady, 2008).

$$\lambda = \frac{h}{mv} = \frac{h}{p} \tag{1.1}$$

Wavelength (λ), Planck's constant (h), multiplying mass (m) and velocity(v) become a momentum (p).

Light behave as a wave and particle and these phenomena should be explain by QM, at the same time electrons have very light mass this also must be define by QM (Jensen, 2017). Now, it is possible to think of that quantum mechanics help to calculate the features of molecules, atoms, and subatomic particles in the microscopic level.

In 1926 the QM guided to the Schrödinger formula and this paved the way to quantum chemistry, QM based on the particle motion in the form of waves, for the wave moving of the electron around the nucleus in the three-dimensional space proposed by the following equation which is known by Schrödinger wave equation (Eq. 1.2).

$$\nabla^2\psi + \frac{8\pi^2 m}{h^2}(E - V)\psi = 0 \qquad (1.2)$$

This is a how typically Schrödinger equation has been writing. It associates the amplitude (ψ) of the particle/wave to the mass of the particle, its total energy (E) and potential energy (V). The denotation of ψ itself is, debatably, but the commonly interpretation of ψ^2, due to Born and Pauli is that it is relational to the possibility of discovering the particle near a point P (x, y, z).

In 1998, for the first time the chemistry and physics society celebrated for achieving Nobel prize in development the efficient computational methods for quantum chemistry by Walter Kohn and John A. Pople (Leszczynski, 2017).

1.4.2. Computational chemistry tools

Upon the classical physics and QM foundations computational chemistry involve two broad parts that managing the structure and its energy of molecules which molecular mechanics (MM) and electronic structure theory which including (ab initio, semiempirical and density functional theory, and molecular dynamics) (Frisch and Foresman, 1996).

1.4.2.1. Molecular mechanics (MM)

Since the beginning of theoretical chemistry, the Molecular mechanic (or forcefield) methods have been used to calculate chemistry problems which are based on the rules of classical physics to guess the structure and properties of substances. In MM model of a molecules are considered to composed a group of balls (atoms) connected together by springs

(bonds),to geometry optimization of the molecule several multidimensional function may be carried out to change the shape of molecule till the minimum energy, and to evaluate the energy of the structure if we know the length of spring and the angel between balls (i.e. bond length and bond angel between atoms), and the amount of energy required to stretch and bend the model then it can analyze the overall energy given by the model spring and balls (bond and atoms), in MM method the geometry optimization of molecule determined at lowest energy (Figure 1.25).

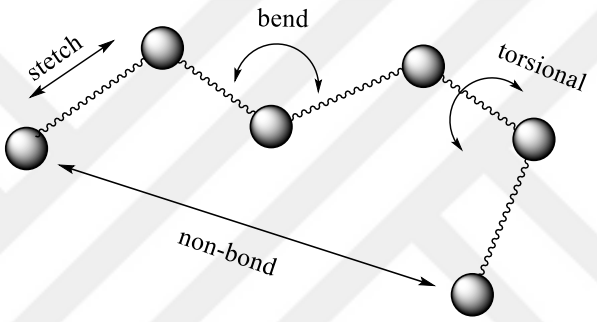


Figure 1.25. Illustrations of the fundamental force field energy terms.

The energy of all systems formed from the summation of energy required for either bond stretching, angle bending, dihedral angles and nonbonded interactions (Eq. 1.3).

$$E = \sum_{bonds} E_{\text{stretch}} + \sum_{angels} E_{\text{bend}} + \sum_{dihedrals} E_{\text{torsion}} + \sum_{pairs} E_{\text{nonbond}} \qquad (1.3)$$

MM is fast can be applicable for computing the geometries and energies of small to large biological systems or material involve many thousands to millions of atoms, since 1960s, the Allinger group is behind the progress of the “MM-series” of programs, beginning with MM1 remaining with the currently commonly used MM2, MM3, and MM4 (Frisch and Foresman, 1996).

The basic elements of MM system are atoms and electrons are clearly ignored (Lewars, 2011), it means that MM calculation of molecule cannot solve chemical problems where electrons dominate, for instance chemical properties; reactivity with other chemicals,

toxicity, coordination number, flammability, enthalpy of formation, heat of combustion, oxidation states, chemical stability, and types of chemical bonds (Cramer, 2004; Jensen, 2017).

1.4.2.2. Electronic structure methods

Electronic structure approaches depend on QM rules for their calculation. In this approach the energy and other related properties of substances gained by approximate calculating of the Schrödinger formula. subclasses of electronic structure methods are:

1.4.2.2.1. Ab initio methods

Relay on approximate calculating of the Schrödinger formula, this is one of the fundamental of quantum mechanics (QM) equations that describe how the electrons act in a molecule. This method can calculate energy and wavefunction by calculating of the Schrödinger formula for a molecule, from wavefunction the electron distribution of molecule can be solve and from the electron distribution the polarity, nucleophiles and electrophiles part of the molecules can be determining (Lewars, 2011).

Ab initio approaches, does not use any experimental parameters in their calculation rather it relies only on QM rules- physical constants. The commonly known method of ab initio approach is a Hartree-Fock (HF) calculation.

1.4.2.2.2. Semiempirical (SE)

Its derived from the ab intio method (HF mode) based on solve of more approximations form of the Schrödinger equation, in this approach the value of experimental parameter add to mathematical equation to obtaining more accurate results this is called parameterization, the combining theory and experiment called "semiempirical". Today the most popular semiempirical methods are AM1 which is improved to (RM1), PM3 (PM6) (Lewars, 2011).

1.4.2.2.3. Density functional theory (DFT)

DFT is relatively new compare with ab initio and SE computation, DFT computations are similar to SE and ab intio methods also depend on approximation of solving Schrödinger equation, DFT does not solve wavefunction that is a basic concept of ab initio and SE calculations, in DFT the electron distribution obtained directly (electron density function). DFT relies on Hohenberg–Kohn theorems, which mentioned the electron density function of an atom/molecule are responsible for its ground-state properties. The speed of four essential methods of computational calculations;
MM (roughly 100 times) > SE > DFT > ab initio (Lewars, 2011).

1.4.2.2.4. Molecular dynamics calculations

Apply the laws of motion to molecules. Thus, one can simulate the motion of an enzyme as it changes shape on binding to a substrate, or the motion of a swarm of water molecules around a molecule of solute, quantum mechanical molecular dynamics also allows actual chemical reactions to be simulated (Lewars, 2011).

Finally, usually MM is use to gain proper starting structures, this is typically done by drawing the molecular structure with a graphical user interface builder, the MM-optimized structure become a sample to DFT, ab intio and SE computations (Frisch and Foresman, 1996). Nowadays the molecules with several hundreds of atoms can be computation in fair accuracy, over the 50 years period the speed and capability of computer's rise about 100 billion times. This means an hour of computations now equal about 10,000 years of computing in 1960, and less expensive with more informative (Leszczynski, 2017).

1.4.3. Gaussian

Gaussian computer program package is a software application that convert the foundations of classical and quantum mechanics in the term of text to computational coding program (Frisch and Foresman, 1996).

The menu part of a Gaussian input file determines the category of calculation to be made. The category of calculation involves three key steps:

- The job types include (optimization, energy, frequencies, so on...)
- The method
- The basis set

The Gaussian program involve several proper steps that equivalent to various evaluation approaches (referred to as different levels of theory). The methods usually used in Gaussian are listed in the following table (Table 1.1), (Frisch, et al., 1995).

Table 1.1. Methods mostly used in Gaussian program

Keywords	Method	Availability
HF	Hartree-Fock Self-Consistent Field	Through 2nd derivatives
B3LYP	Becke-style 3-Parameter Density Functional Theory, (using the Lee-Yang-Parr correlation functional)	Through 2nd derivatives
MP2	2nd Order Møller-Plesset- Perturbation Theory	Through 2nd derivatives
MP4	4th Order Møller-Plesset -Perturbation Theory, {including Singles, Doubles, Triples and Quadruples by default)	Energies only
QCISDm	Quadratic CI (Single, Doubles and Triples)	Energies only

Among all methods the DFT is selected as effective method in providing theoretical visions to calculating global and local indices which indicate the chemical properties of the system like; chemical potential (μ), electronegativity (χ), hardness (η), softness(*S*), electrophilicity index(ω) and local reactivity descriptors such as Fukui function and local softness (Udhayakalaa, et al., 2013a).

Basis Set; is a mathematical depiction of the molecular orbitals within a molecule. The basis set can be interpreted as restricting each electron to a particular region of space. More accurate results require more input data, time, large bases set with correspondingly more expensive computationally.

2. LITERATURE REVIEW

Based on the previous findings, as mentioned before about importance of pyrimidine compounds as a result many DHPM derivatives have been synthesized by Biginelli reaction (Figure 2.1) through structural modifications of building block compounds (Akbaş, et al., 2007).

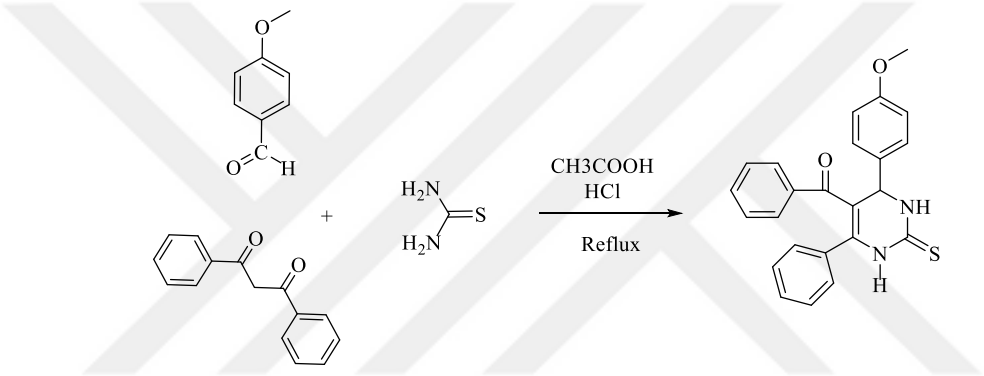


Figure 2.1. Biginelli reaction example.

Moreover; thiazole was initially synthesized by Hantzsch, based on this method the modified Hantzsch synthesis of thiazoles is presented here, in which thiourea is reacted with *alpha*-chloroaldehyde, in the (Figure 2.2) thiourea is presented in its tautomeric configuration, as a result 2-aminothiazole was prepared which is a remarkable precursor in the pharmaceutical area, it is a building block of sulfathiazole, this has been clinically significant sulfa medicines (Tyrell and Quin, 2010).

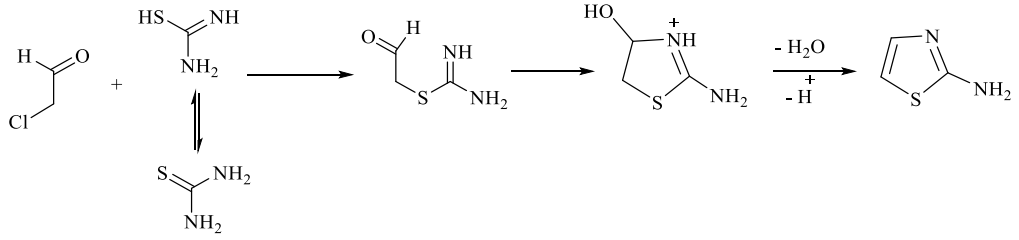


Figure 2.2. Synthesis of thiazole derivatives though Hantzsch modification.

In addition for two above reactions, another important reaction that contributed in this thesis is Knoevenagel condensation that can be described by condensation of the active methylene (CH-acids) molecules with aldehydes, apart from 1,3-dicarbonyl molecules any structures including cyclic CH-acids or noncyclic CH-Acids with PKa < 16, that can be deprotonate by a proper base are suitable to participate in this reaction (Mola and Massa, 2012), it can be referring by the general formula (EWG-CH_2-EWG') of (Figure 2.3), the EWGs attract electron density around methylene C-H acids and make these type compounds easily lose protons, this reaction is widely applying for building carbon-carbon bond connection as a result variable mixture of regioisomers have been observed through Knoevenagel reaction (Orru and Eelco, 2010).

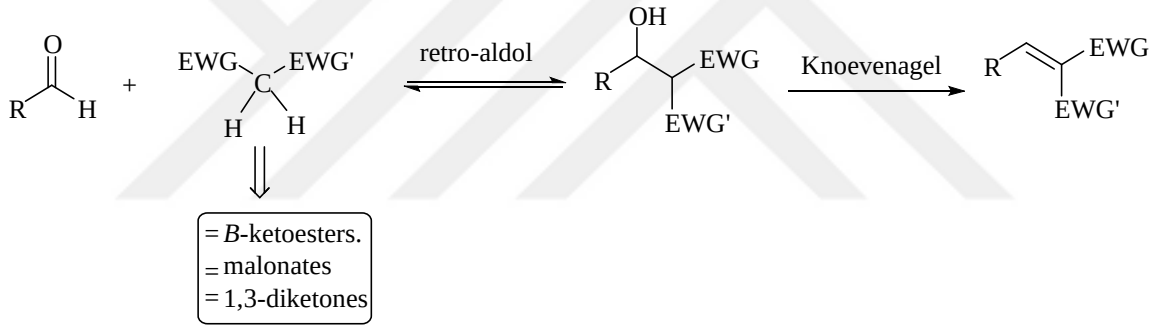


Figure 2.3. General Knoevenagel condensation.

Form above reactions there are some reports which they carried out multistep procedure to obtained a great number of very interesting functionalized DHPMs derivatives, as mentioned in the series articles (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018), for instance; DHPM product of (Figure 2.1) has C=S group with two nitrogen atoms, in the first step react with bromoacetic acid under the proper reaction conditions to give bicyclic-thiazolo-pyrimidine through Hantzsch modification method after purification process this compound is stable under normal conditions, but due to the presence of C-H acids in the second step the bicyclic thiazolo-pyrimidine can be future treated with benzaldehyde in ethanoic acid to give arylidene-bicyclic thiazolo-pyrimidine through Knoevenagel condensation (Figure 2.4).

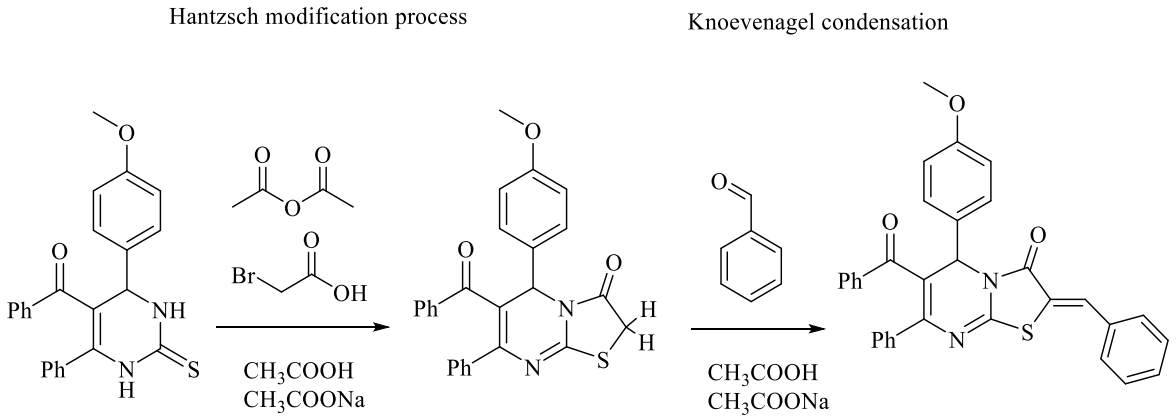


Figure 2.4. Multistep procedure for decoration of DHPM.

The above mention multistep procedure for synthesis arylidene-bicyclic thiazolo-pyrimidine derivatives can be done in one step by mixing Biginelli product with all other reactants in a single reactor (one pot) by one step procedure, thus; this single step procedure with participation three substrates could be classified as a multicomponent reaction.

This work inspired by above reactions, which involves obtaining pyrimidine derivative compounds by using Biginelli multicomponent cyclocondensation reaction (Biginelli-MCR). In the next step the pyrimidine derivatives of the Biginelli product can undergo further reaction with bromoacetic acid and various aryl-aldehydes molecules in a single vessel (one pot) through Hantzsch heterocyclization/ Knoevenagel condensation to achieving several novel bicyclic arylidene-thiazolo-pyrimidine compounds in a good yield, in both steps more than two substrates react in a single reactor therefore it can be referred that this process is involving two separate multicomponent reaction consecutively, this can be considered as a helpful method to obtained the desire compounds in a short reaction time with a good yield (Figure 2.5).

The structures of all new compounds were analyzed via spectroscopic devices such as IR, ^{1}H, and ^{13}C NMR. At the same time QCC of all compounds were performed with Gaussian09W software package with input file [DFT/ 6-31G(d,p)/ B3LYP], the QCC data can be helpful for future investigation of the structural, physical and chemical behavior of each new compound.

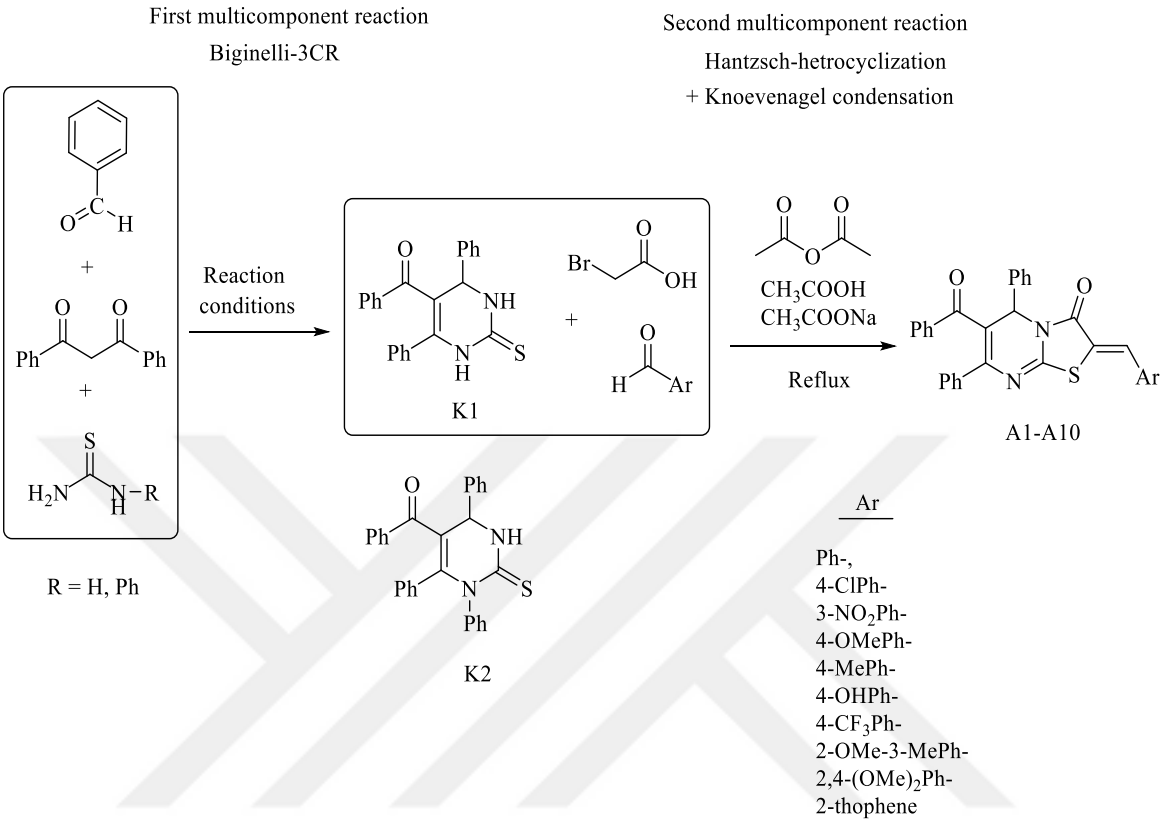


Figure 2.5. Two separate multicomponent reactions (TS-MCRs), [K1; (Akbaş, et al., 2007)].

3. MATERIALS AND METHODS

3.1. Materials

3.1.1. Chemical substances

The chemicals used in this thesis were of analytical purity and the products of companies such as Merck, Fluka and Sigma-Aldrich. In addition, various organic solvents which used as a solvent in preparative organic chemistry have been tried and used in the purification processes and organic synthesis.

3.1.2. Equipment and instruments

Tools and devices used in the experiments are listed below.

- Gallenkamp Melting Point Apparatus.
- Heidolph 4100 Brand Rotary Evaporator.
- Memmert Universal Oven UN55.
- Shimadzu ATX 224 Analytical Balance.
- Merck TLC Plate Silica Gel 60 F_{254}.
- CAMAG UV Lamp 4, Double Wavelength 254/366 nm.
- Heidolph and Wisd brands Hotplate Magnetic Stirrer.
- Shimadzu IRAffinity-1S FTIR Spectrophotometer
- Agilent 400/54 / A5C Premium brand NMR instrument for ^{1}H and ^{13}C NMR

3.2. Methods

3.2.1. Synthesis methods

In this thesis, the compound K2 was synthesized by following Biginelli reaction and

the compound K1 was obtained via procedure (Akbaş, et al., 2007), (Figure 3.1).

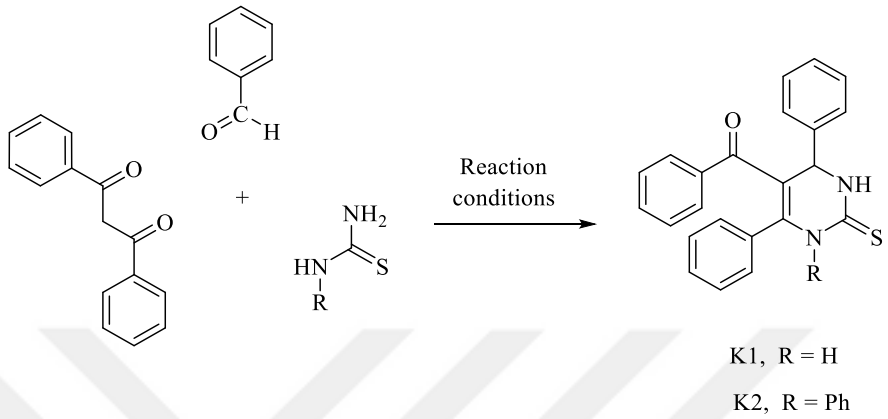


Figure 3.1. Synthesis of the compounds K1 and K2 via Biginelli reaction.

In the next step compound K1 further participated in another MCR with bromoacetic acid and aryl-aldehydes in the presence of acetic anhydride, ethanoic acid, and anhydrous sodium acetate to give ten new arylidene-bicyclic thiazolo-pyrimidine derivatives (A1-A10) in one pot reaction (Figure 3.2). The structure of all new products (K2 and A1-A10) was deduced by melting point determination, IR, ^{1}H-NMR, and ^{13}C NMR instrumentation, some supplementary books and related articles were used to interpretation and evaluation the data obtained from spectroscopic analysis.

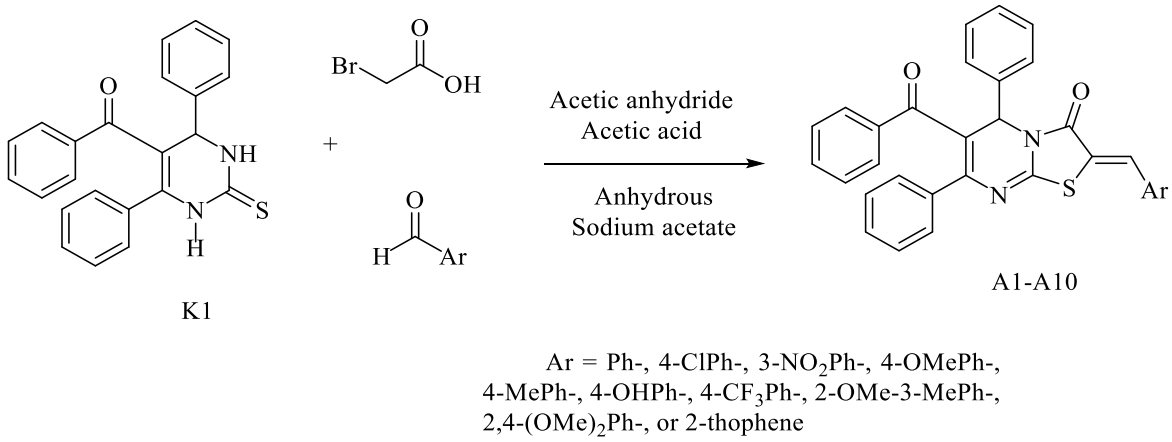


Figure 3.2. Second multicomponent reaction for synthesis compounds A1- A10.

The compound K1 can be easily achieved with highly purity under suitable Biginelli reaction procedure (acetic acid, hydrochloric acid) with a little modification. But under the same conditions only small amount product (K2) formation were observed after prolonged reflux with a lot of side products according to TLC, the impurities were mainly due to the condensation DBM and aldehyde components via the Knoevenagel reaction as identified by NMR spectra, these type compounds are oily and poorly soluble compounds, it makes the procedure difficult to obtain pure the desire products, in some case excepts the three spots of reactants on TLC plate four new spots appeared, total seven very close spots were observed it was difficult to separate the product. Therefore, variety of reaction conditions have been tried to find appropriate procedure that suitable for DBM, PTU with BA as a reactant to obtain pure and high yield of K2 as mentioned in the relevant literatures (Table 3.1).

Table 3.1. Synthetic procedures tried to obtain K2

	Solvent	Catalyst	Time hrs.	Temp.	BA	DBM	PTU	Yield %	References
1	HOAc 15 ml	HCl 2 drops	8-24	Reflux	1 1.1	1 1.6	1 1.1	low	(Akbas, et al., 2017a)
2	Ethanol 10 ml	*p*-TsOH 25 mg	24	Reflux	1	1.2	1.5	low	(Jin, et al., 2011)
3	DMF 5 ml	*p*-TsOH 25 mg	48-72	150 °C	1	1	1	low	Roughly
4	DMF 1 ml	TMSCl 6 mmole	+72	RT	1	1	1	low	(Itamar, et al., 2018)
5	DMF 1 ml	H_2SO_4 2 drops	8-24	Reflux	1	1.2	1	low	(Adhikari, et al., 2012)
6	Acetonitrile 1.5 ml	TMSCl 1 mmole	8-24	120 °C	1	1	1.5	low	(Lauro, et al., 2014)
7	DMF/MeCN 1:2	TMSCl 1 mmole	3-24	RT	1	1	2	low	(Zhu, et al., 2004)
8	Ethanol 5 ml	NaOH 1 equiv.	+12	70 °C	1	1.1	2	low	(Shen, et al., 2010)

It's important to know that during using TMSCl, be aware of that the boiling point of TMSCl is 57 °C, volatile liquid, therefor carrying out the reaction at room temperature would be important point, also TMSCl is react with H_2O, alcohols.

3.2.2. Computational chemistry methods

To obtain information about the three-dimensional geometries of electronic structures and their energy at the ground state of all new synthesized pyrimidine derivatives, the Gaussian09W software package was employed within the framework of the DFT base on Beck's three parameter exchange functional and Lee-Yang-Parr nonlocal correlation functional (B3LYP) (Becke, 1992; 1993; Parr, et al., 1998) / 6-31G (d, p) level and the 6-31G (d, p) orbital basis sets (Frisch, 2009). The progressions in systematical and application of DFT calculations has widely extended where guessing the geometry and characteristics with acceptable accuracy can be acquired.

The energy values of molecular orbital boundary orbitals (E_{HOMO}, E_{LUMO} and ΔE_{gap}) of molecules were obtained and interpreted, these gives information on how the reaction will take place (Deng, et al., 2009). The frontier HOMO and LUMO orbitals of any substances are essentials in determining its activity, high energy value E_{HOMO} shows the high capability of substances to give electrons to a proper acceptor substance with low value of E_{LUMO} (i.e., metal-Iron) (Hasanov and Bilgi, 2007). The E_{LUMO} associated with the capability of the substances to receiving electrons (electrophilicity), the low value E_{LUMO} of a molecule interpreted as having high electrophilicity character (Amin, et al., 2010). Moreover, as orbitals of HOMO and LUMO close to each other the value of the energy gap decreases (ΔEgap), (Figure 3.3) this provides high reactivity toward chemical reaction, usually related to high polarization with low kinetic stability, vice versa (Wang, et al., 2007). E_{HOMO} of the molecule is related to ionization energy ($I = - E_{HOMO}$), E_{LUMO} of the molecule is related electron affinity ($A = - E_{LUMO}$).

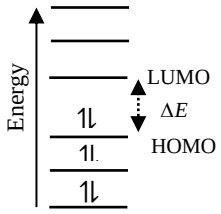


Figure 3.3. The energy diagram of HOMO, LUMO and the energy gap (ΔE).

Analysis of absolute electronegativity (x) as the negative of chemical potential (μ) in density functional theory follow (Parr, et al., 1978; Wang, et al., 2007; Bendjeddoua, et al., 2016), (Eq. 3.1).

$$x = -\mu = -\left(\frac{\partial E}{\partial N}\right) \qquad \text{Also, according Mulliken's definition of electronegativity} \qquad x = \frac{I + A}{2} \tag{3.1}$$

The expression of global hardness (η) is connected to the polarizability, meanwhile decreasing value of ΔE typically allow milder polarization of the substance (Pearson, 1989) (Eq. 3.2), where E is the overall electronic energy, N is the number of electrons.

$$\eta = \frac{\Delta E}{2} = \frac{I - A}{2} = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right) \tag{3.2}$$

Both hardness (η) and softness (S) are essential parameters in evaluating the structural stability and reactivity, a hard molecule associate with high ΔE value and a soft molecule associates with low ΔE value, the global softness is the contrary of the global hardness (Eq. 3.3), (Fleming, 2010).

$$S = \frac{1}{\eta} \tag{3.3}$$

The electrophilicity index (ω) was presented by (Parr, et al., 1999), this descriptor can determine the tendency of molecules to receiving electrons (Eq. 3.4).

$$\omega = \frac{\mu^2}{2\eta} \tag{3.4}$$

If two chemical species A and B connected, electrons should move from lower electronegativity substance (i.e., inhibitor) to the higher electronegativity substance (i.e., metal surface unless the two chemicals potentially reach equilibrium (Fleming, 2010),

ΔN fraction is measure the electron transferred from low (x) to high (x) on formation of *AB* (Pearson, 1989), (Eq. 3.5, 3.6).

$$A + B = AB \tag{3.5}$$

$$\Delta N = \frac{x_m - x_{inh}}{2(\eta_m + \eta_{inh})} \tag{3.6}$$

Where x_m is the electronegativity of electron accepting system (i.e., x_{Fe} = absolute electronegativity of Iron), and x_{inh} denote to absolute electronegativity of chemical inhibitor, η_m and η_{inh} represent the global hardness of electron accepting chemical species and the inhibitor molecule, respectively (Tomic, et al., 2010).

In this thesis the capability of compounds (K2, A1-A10) evaluated as an inhibitor to electron acceptor Iron metal, therefor; to calculate the value of ΔN some observable values have been used such as x_{Fe} = 7.0 eV (Sastri and Perumareddi, 1997) and η_{Fe} = 0 by considering that for a metallic bulk $I = A$ (Dewar and Thiel, 1977).

An electronic back donation action probably happening during the interaction of inhibitor with the metal surface (Go´mez, et al., 2006), specifically charge transfer from the inhibitor and back-donation to the inhibitor, changing in energy is indirectly proportional to the hardness (η) of the molecule (Eq. 3.7), (Karzazi, et al., 2014).

$$\Delta E_{\text{backdonation}} = -\frac{\eta}{4} \tag{3.7}$$

The electric properties of molecules such as Dipole moment (*D*) are essential in determining the properties of substances (Leif and Christopher, 2014). Another local parameter is atomic Fukui indices, which is useful in predicting local properties such as which atoms in a molecule are has probability of undergoing nucleophilic, electrophilic, or radial attacks, this also can be analysis by molecular electrostatic potentials (Mineva, et al., 2001).

3.2.3. Experimental procedures

3.2.3.1. Procedure for synthesis K1

The compound K1 obtained via procedure (Akbaş, et al., 2007), (Figure 3.4).

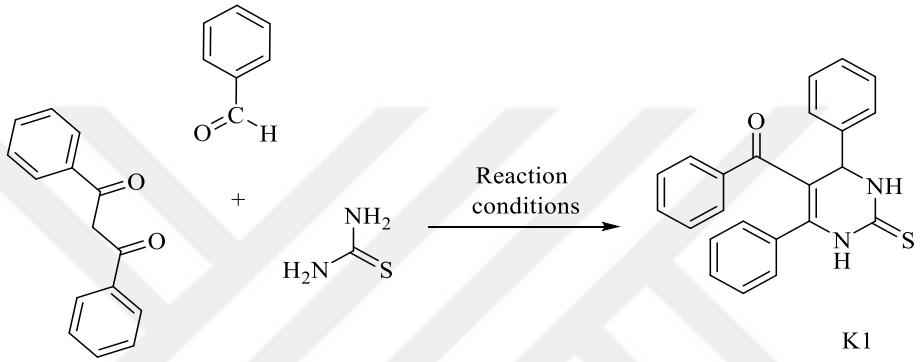
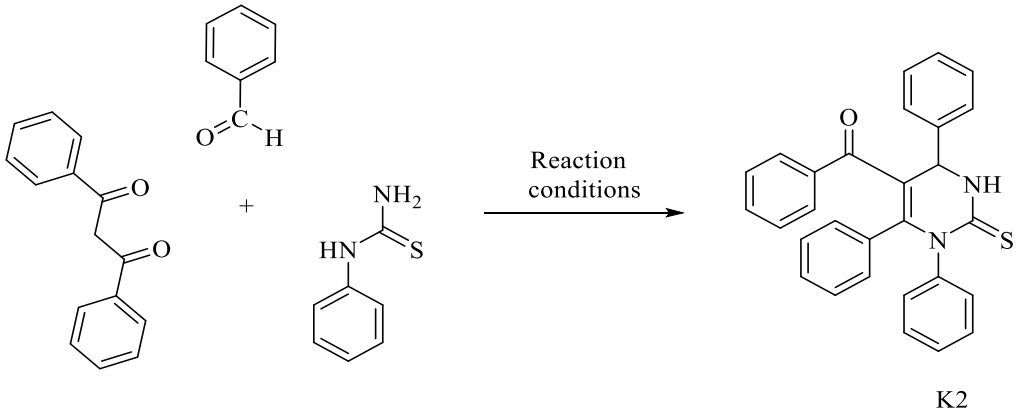


Figure 3.4. Synthesis reaction of the molecule K1.

3.2.3.2. Procedure for synthesis K2

In 50 ml round bottom flask, dibenzoylmethane (0.224 g, 1 mmol), benzaldehyde (0.111 ml, 1 mmol) and phenylthiourea (0.228 g, 1.5 mmol) were mixed, 15 ml of glacial acetic acid was added to the mixture, then less than 2 drops of concentrated of hydrochloric acid was poured to the solution, the solution was refluxed and kept at around 200 ^{o}C > temperature for 72 hrs., the development of reaction was checked by TLC. Cool the solution to room temperature, filtrated the solution, a little white precipitate formed, it doesn't give any spot-on TLC plate, it seems that this precipitate doesn't the desired product, the liquid phase evaporated in vacuum evaporator, the unevaporated crude mixture dissolve in 10 ml ethanol then leaved for 24 hours at RT, the product was precipitated in the form of crystal, filtrated the solution and wash the crystals with a little ethanol and ether. K2 Melting point: 228-230 °C, 0.052 g (11.65% Yield), (Figure 3.5).



K2

Figure 3.5. Synthesis reaction of the molecule K2.

3.2.3.3. General procedure for synthesis A1-A10

1 mmole, 0.370 g K1, 1.1 mmole bromoaceticacid, 1.5 ml aceticanhydride, 1.3 mmole aryl-aldehyde derivatives and 1 mmole anhydrous sodiumacetate were mixed in 10 ml acetic acid, then reflux the reaction mixture for 6 to 10 hrs., until the spot of K1 completely disappeared on the TLC plate and only one spot product will be appeared with the spot of excess aldehydes. Then, the reaction solution was cooled to RT directly the crystal settled under round bottom flask, filtered the solution and the precipitate recrystallized in a suitable solvent.

But in the case of A7, the precipitate was not formed at room temperature despite it was leaved for 24 hrs., therefore very carefully add the reaction mixture of A7 to crashed ice water (it should be ice, do not heat the reaction mixture in the presence of water, the reversible reaction was observed in the case of hot water), then filtrate the precipitate and recrystallized in ethanol. For the remaining product in the main solution for A1-A10 could be separated by the same procedure used to obtained A7, the total yield product obtained for each compound higher than 90% with exactly high purity (Figure 3.6, Table 3.2).

Note that, bromoacetic acid, sodium acetate, acetic anhydride, acetic acid does not give a spot-on TLC plate, longer reaction time doesn’t have effect on the reaction pathway usually solid aryl-aldehydes took more time than liquid aryl-aldehydes, the reaction finished in less than 10 hours after completely reacting of K1.

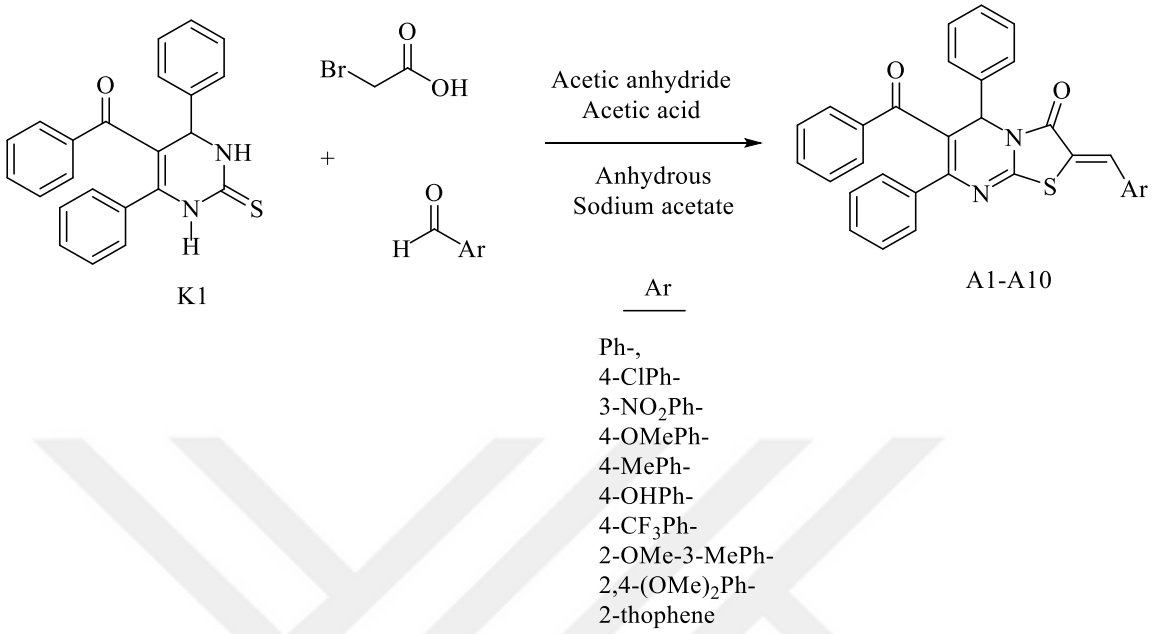


Figure 3.6. General synthesis of the compounds A1-A10.

Table 3.2. Experimental data of the compounds (K2, A1-A10)

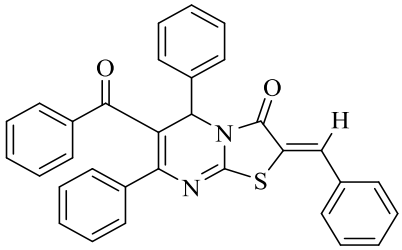
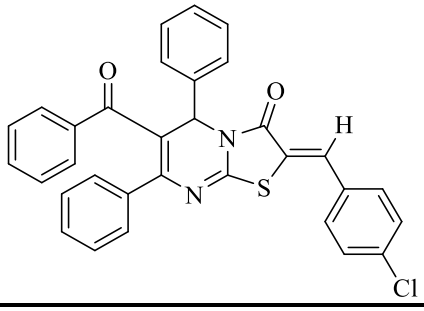
Compounds	Structure	Time (hrs.)	M.P (°C)	Practical weight, Yield%
A1		6	225-226	0.4621g (93%)
A2		6	212-213	0.5012g (94%)

Table 3.2. Experimental data of the compounds (K2, A1-A10)

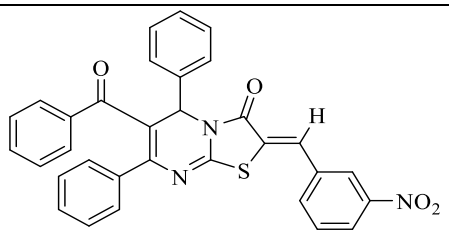
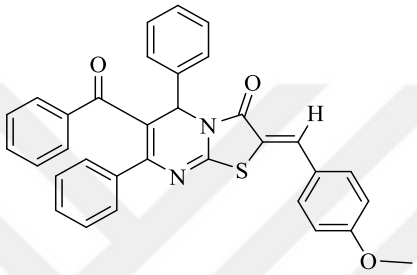
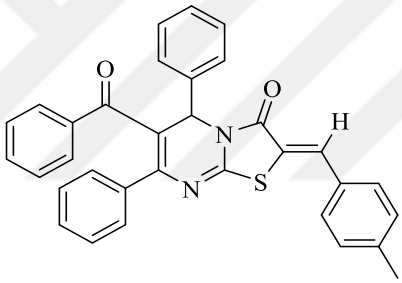
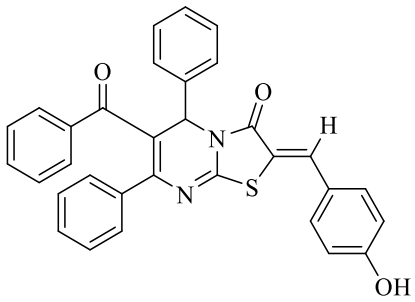
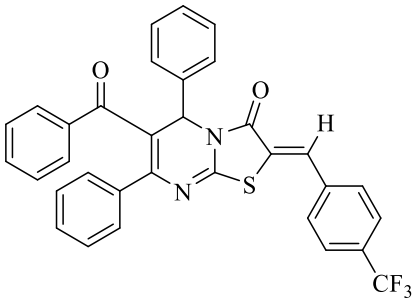
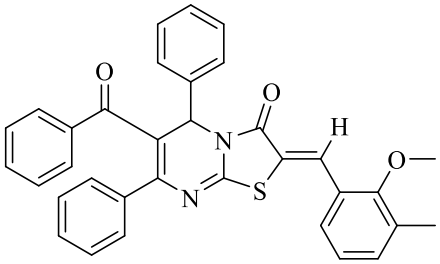
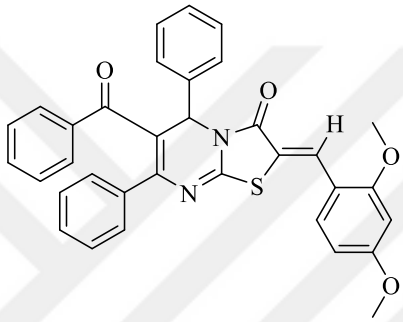
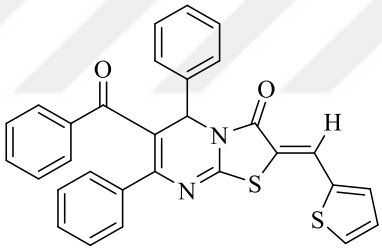
Compounds	Structure	Time (hrs.)	M.P (°C)	Practical weight, Yield%
A3		9	195-197	0.5211g (96%)
A4		8	236-237	0.4923g (93%)
A5		8	215-216	0.482g (94%)
A6		10	230-231	0.48g (93%)
A7		7	130-132	0.5087g (90%)

Table 3.2. Experimental data of the compounds (K2, A1-A10) (continue)

Compounds	Structure	Time (hrs.)	M.P (°C)	Practical weight, Yield%
A8		8	199-200	0.5145g (95%)
A9		8	220-221	0.507g (91%)
A10		10	218-219	0.4722g (94%)

3.2.4. Computational chemistry procedure

The calculations have been done for (K2 and A1-A10). After installing Gaussian09W and GaussView 5.0.8 software packages on a computer, the electronic structure of molecules were drawn, in the calculation set up section the keywords [#opt freq b3lyp/6-3g(d,p) guess=(mix.always.save) maxdisk=7GB geom=connectivity, charge/mult: 01] have been selected to run the calculation.

4. RESULT AND DISCUSSION

4.1. Structure Analysis of Synthesized Compounds

4.1.1. Phenyl(1,4,6-triphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methanone (K2)

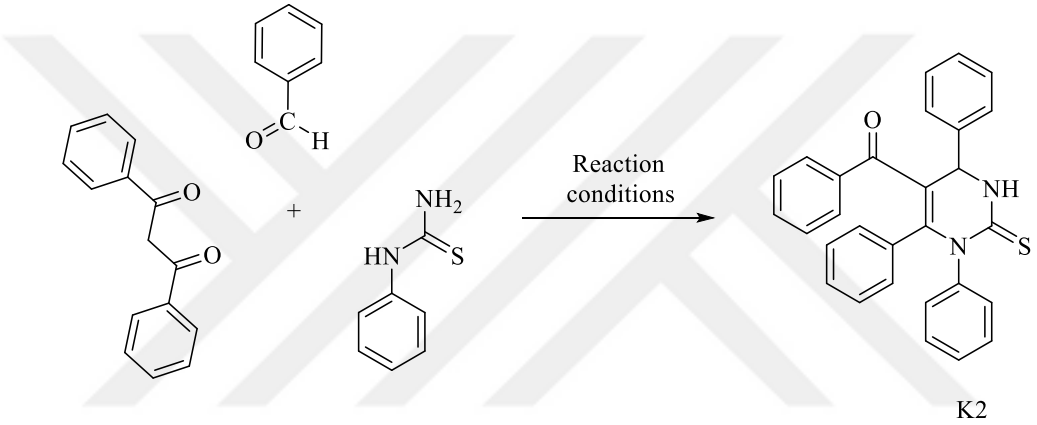


Figure 4.1. Synthesis reaction of the molecule K2.

Melting point of (K2) molecule: 228-230 °C; 0.052 g (11.65% Yield): Chemical formula: $C_{29}H_{22}N_2OS$; Molecular weight: 446.57 g/mol.

Despite several approaches for synthesis pure and high yield of the compound K2, only low yield was achieved compared to the other sources (see Table 3.1) which they employed similar substrates as mention in the literates (Zhu, et al., 2004; Shen, et al., 2010; Jin, et al., 2011; Adhikari, et al., 2012; Lauro, et al., 2014; Akbas, et al., 2017a; Itamar, et al., 2018), this is may be because the starting materials used for synthesis K2 surrounded by large functional groups also phenylthiourea has less reactivity compare to thiourea.

IR (KBr, cm^{-1}) for K2; 3252 cm^{-1} (pyrimidine N-H), 2974, 3061 cm^{-1} (aromatic C-H), 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1638, 1591, 1530, 1491, 1447, 1437, or 1408 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, N-H_{bend}, or C=S) (Figure 4.2).

In the ^{1}H-NMR (400, MHz / DMSO-d_6) spectrum of K2, the proton of (5N-H) gives singlet peak at downfield shifts around δ = 9.30 ppm, the other signals B(m), C(m), D(m), E(m), H(m), and G(d) are belonging to the aromatic ring protons which observes in the range (6.73-5.97 ppm), the F(d) doublet signal of (6C-H) proton of pyrimidine ring was observed at δ = 4.55 ppm. thus, the total integral shows that the compound K2 consists of 22 hydrogens (Figure 4.3, Table 4.1).

In the ^{13}C-NMR (400 MHz / DMSO-d_6) spectrum of K2 the benzoyl carbonyl carbon (8C=O) gives the signal at δ = 195.6 ppm and the signal of thiocarbonyl carbon (4C=S) appears at δ = 178.4 ppm, the signals of other carbons in compound K2 between the range (144.6-116.4 ppm) are; (1C-2C carbons and aromatic region carbons), the signal of (6CH) appears at δ = 55.4 ppm, the ^{13}C NMR spectrum shows 21 peaks with 8 symmetric carbons in the structure, thus; the total carbon number of the compound K2 equal to 29 carbons (Figure 4.4, Table 4.2).

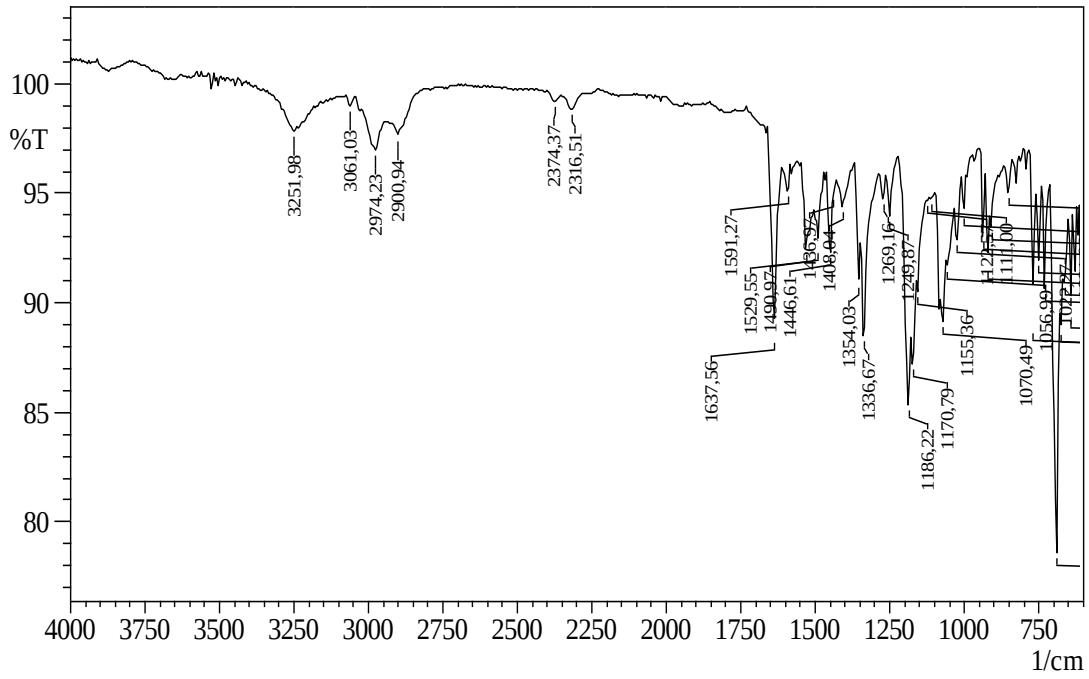


Figure 4.2. IR spectrum of compound K2.

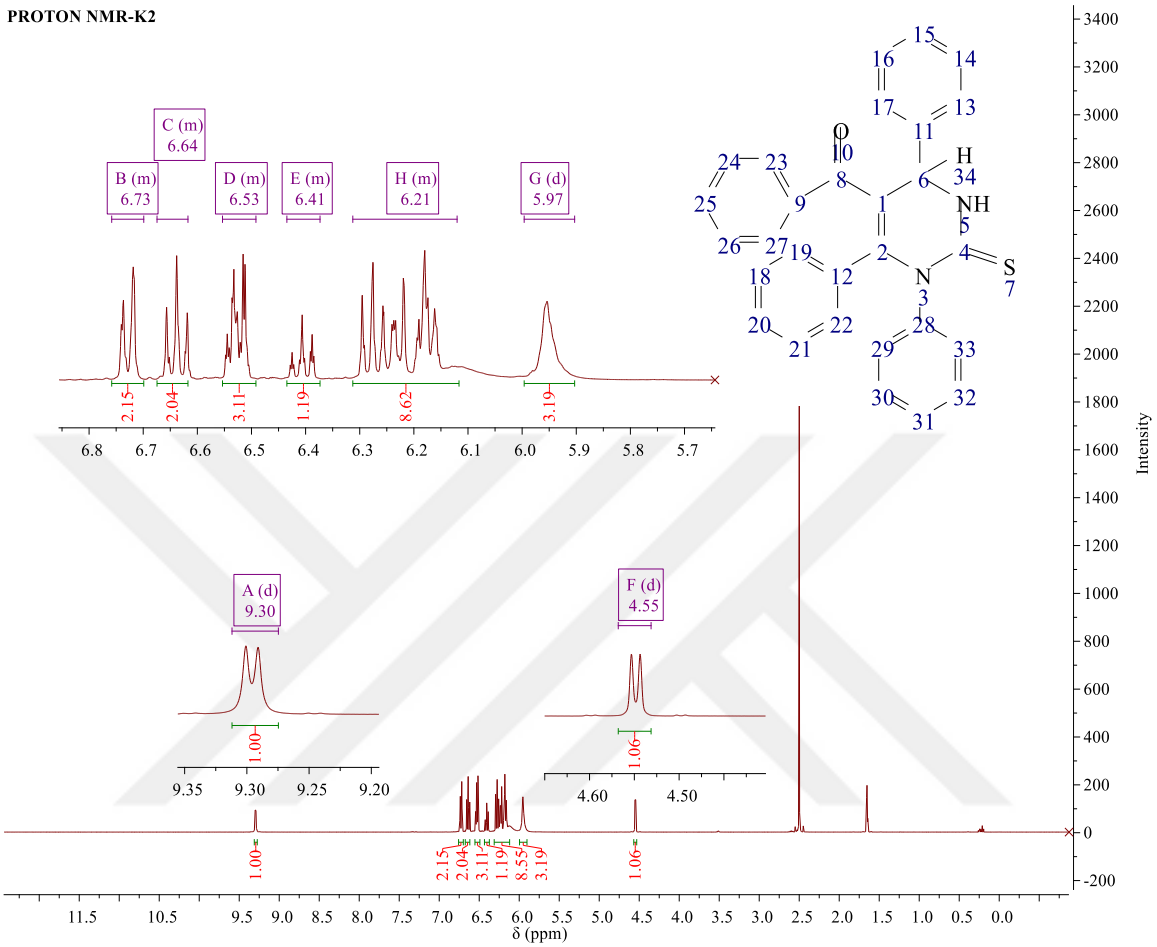


Figure 4.3. ^{1}H NMR spectrum of compound K2.

Table 4.1. ^{1}H NMR spectrum data of compound K2

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(d)	9.30	9.31- 9.27	1	1.00	d	3.91	5N-H
2	B(m)	6.73	6.76 - 6.70	2	2.15	m		aromatic
3	C(m)	6.64	6.67 - 6.62	2	2.04	m		aromatic
4	D(m)	6.53	6.55 - 6.49	3	3.11	m		aromatic
5	E(m)	6.41	6.43 - 6.37	1	1.19	m		aromatic
6	H(m)	6.21	6.31 - 6.12	9	8.55	m		aromatic
7	G(d)	5.97	6.00 - 5.90	3	3.19	d	10.79	aromatic
8	F(d)	4.55	4.57 - 4.53	1	1.06	d	3.88	6C-H

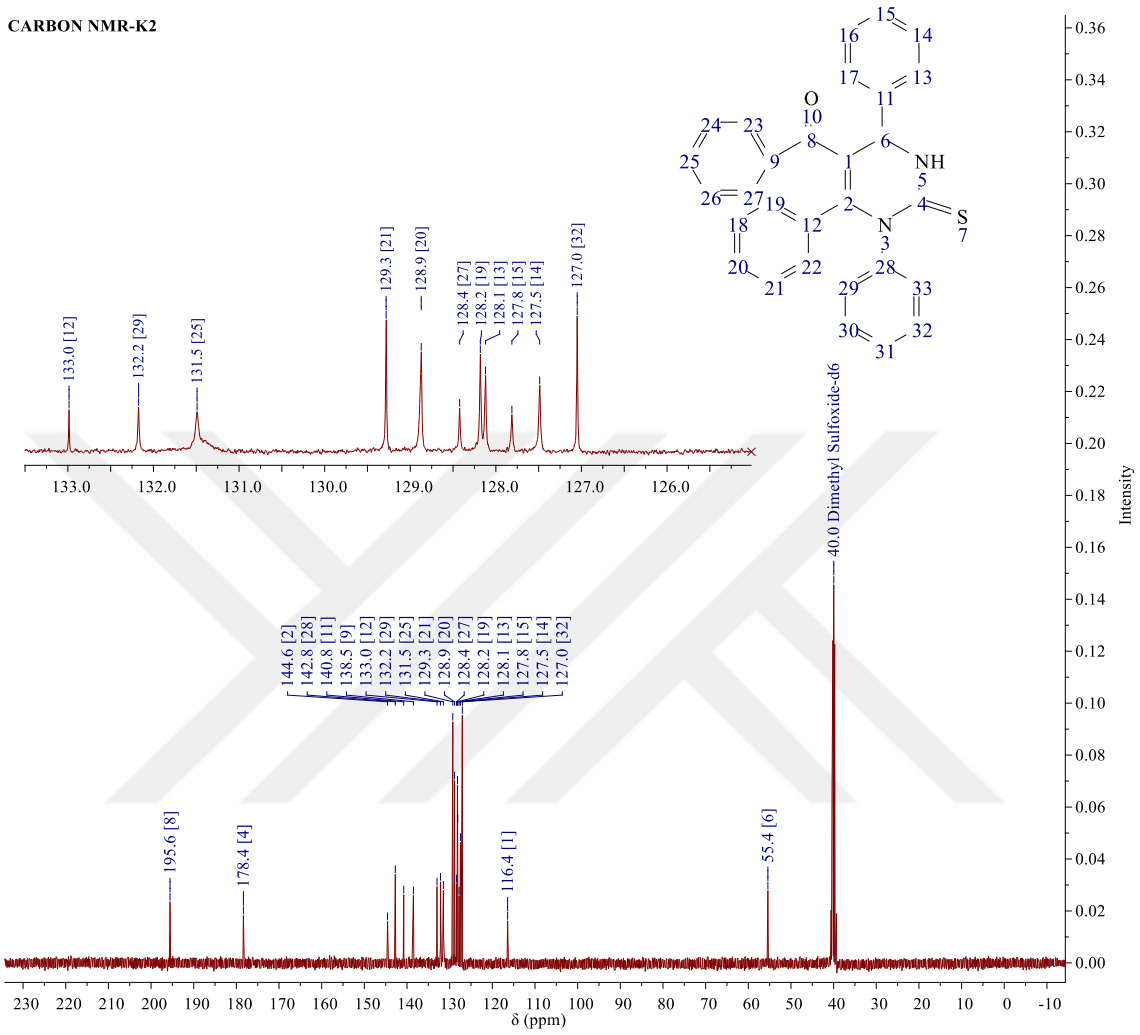


Figure 4.4. ^{13}C NMR spectrum of compound K2.

Table 4.2. ^{13}C NMR chemical shift assignments of compound K2

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
8C	195.6	12C	133.0	20CH	128.9	17CH	128.1	26CH	127.0
4C	178.4	29CH	132.2	23CH	128.4	15CH	127.8	30CH	127.0
2C	144.6	33CH	132.2	27CH	128.4	31CH	127.8	32CH	127.0
28C	142.8	25CH	131.5	19CH	128.2	14CH	127.5	1C	116.4
11C	140.8	18CH	129.3	22CH	128.2	16CH	127.5	6CH	55.4
9C	138.5	21CH	129.3	13CH	128.1	24CH	127.0		

4.1.2. (*E, Z*)-6-benzoyl-2-benzylidene-5,7-diphenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*) one (A1)

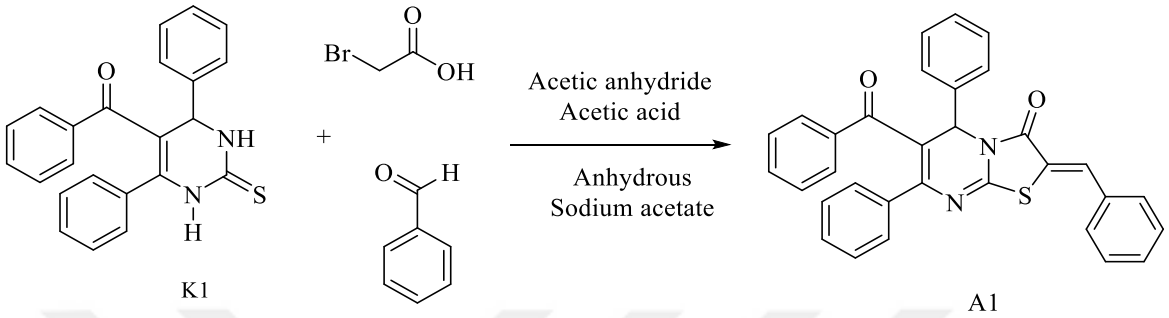


Figure 4.5. Synthesis reaction of the molecule A1.

Melting point of (A1) molecule: 225-226 ℃; Chemical formula: $C_{32}H_{22}N_2O_2S$; Molecular weight: 498.60 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and benzaldehyde as a result compound A1 was obtained with 93% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b, 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A1; 2976 cm^{-1} (C-H alkene and aromatic), 2901 cm^{-1} (C-H aliphatic). One of these strong sharp peaks in the range (1709, 1690, 1630, 1599, 1551,1491, 1447, or 1437 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, N-H_{bend}, or C=S) (Figure 4.6).

In the ^{1}H-NMR (400 MHz / DMSO-d_6) spectrum of compound A1, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons around δ = 9.00 ppm and the appearance of singlet peak A(s) at δ = 7.80 ppm which can be interpreting to the 8C=14C-H proton attached to the thiazole ring, signals for peaks B(d), C(m), D(tdd), E(m) and F(m) originate from aromatic ring protons, the G(s) singlet signal seen at δ = 6.30 ppm

can be interpreting to (6C-H) proton, the total integral shows that 22 hydrogens formed up the structure of molecule A1 (Figure 4.7, Table 4.3).

In the ^{13}C-NMR (400 MHz / DMSO-d_6) spectrum of molecule A1, the signal at δ = 196.3 ppm represent the benzoyl carbon (10C=O) and the signal at δ = 164.7 ppm represents the carbonyl carbon (9C=O) in the thiazole ring. The signals of other carbons in compound A2 between the range (155.0-127.7 ppm) are; (2C-35C and 37C, carbon and aromatic region carbons) were exited at 120.3 ppm (1C carbon), 117.7 ppm (8C) and 57.7 ppm (6CH carbon), the ^{13}C NMR spectrum shows 24 peaks with 8 symmetric carbons in the structure of A1, thus; the total number of carbons equal to 32 carbons (Figure 4.8, Table 4.4).

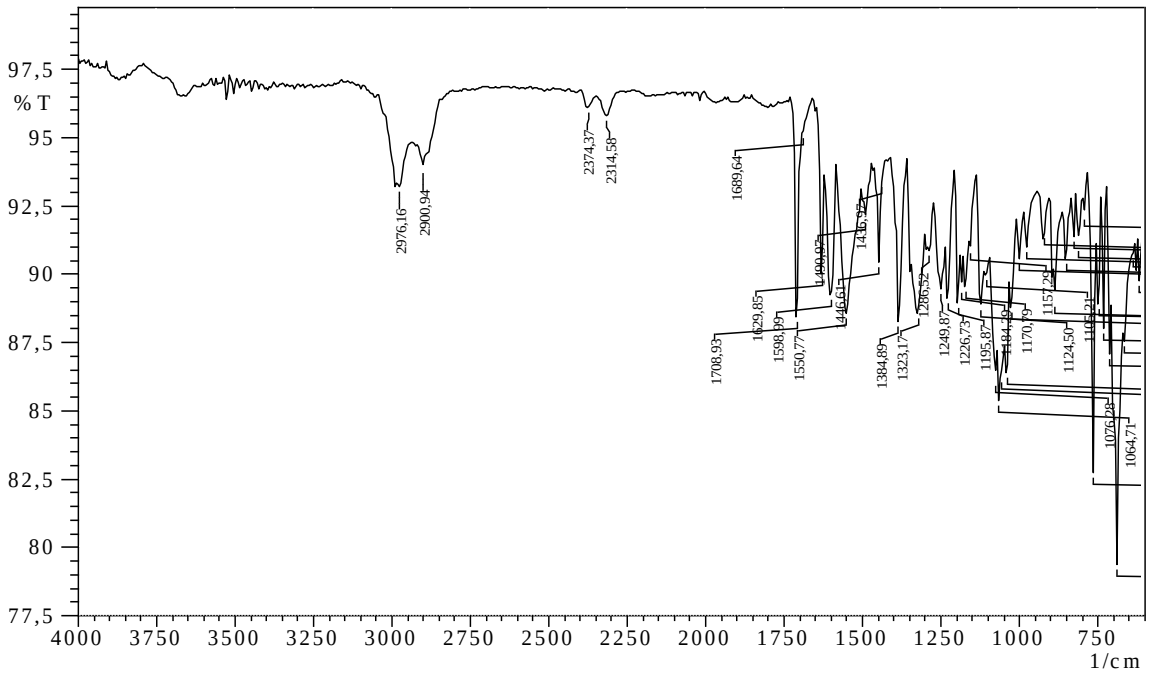


Figure 4.6. IR spectrum of compound A1.

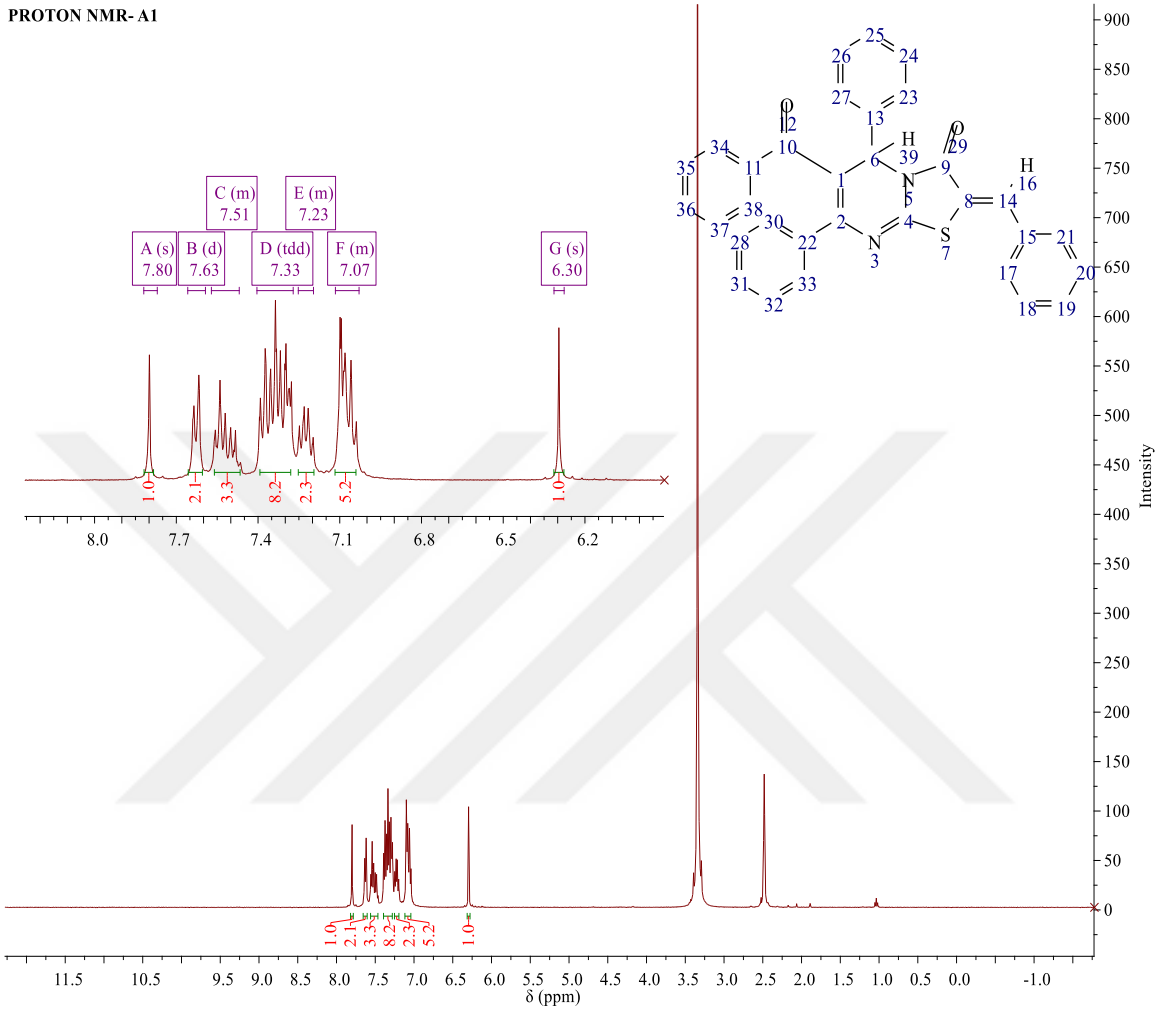


Figure 4.7. ^{1}H NMR spectrum of compound A1.

Table 4.3. ^{1}H NMR spectrum data of compound A1

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.80	7.82 - 7.77	1	1.00	s		14C-H
2	B(d)	7.63	7.66 - 7.59	2	2.03	d	7.17	Aromatic
3	C(m)	7.51	7.57 - 7.47	3	3.14	m		Aromatic
4	D(tdd)	7.33	7.40 - 7.27	8	8.24	tdd	2.21, 6.51, 7.93, 7.93	Aromatic
5	E(m)	7.23	7.25 - 7.20	2	2.06	m		Aromatic
6	F(m)	7.07	7.12 - 7.03	5	5.05	m		Aromatic
7	G(s)	6.30	6.31 - 6.28	1	0.94	s		6C-H

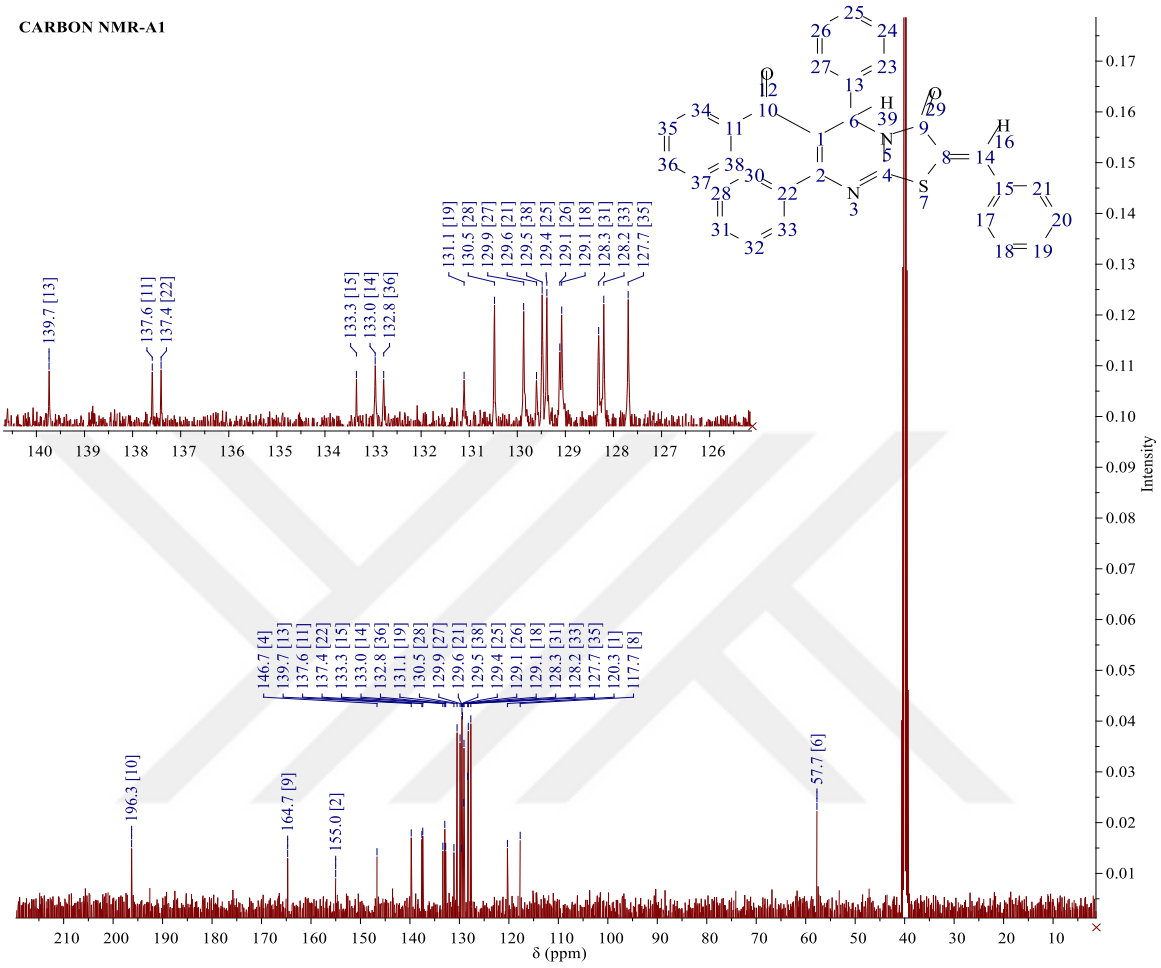


Figure 4.8. ^{13}C NMR spectrum of compound A1.

Table 4.4. ^{13}C NMR chemical shift assignments of compound A1

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.3	22C	137.4	32CH	130.5	38CH	129.5	31CH	128.3
9C	164.7	15C	133.3	23CH	129.9	25CH	129.4	30CH	128.2
2C	155.0	14C	133.0	27CH	129.9	26CH	129.11	33CH	128.2
4C	146.7	36CH	132.8	17CH	129.6	24CH	129.11	35CH	127.7
13C	139.7	19C	131.1	21CH	129.6	18CH	129.07	37CH	127.7
11C	137.6	28CH	130.5	34CH	129.5	20CH	129.07	1C	120.3
								8C	117.7
								6CH	57.7

4.1.3. (*E, Z*)-6-benzoyl-2-(4-chlorobenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A2)

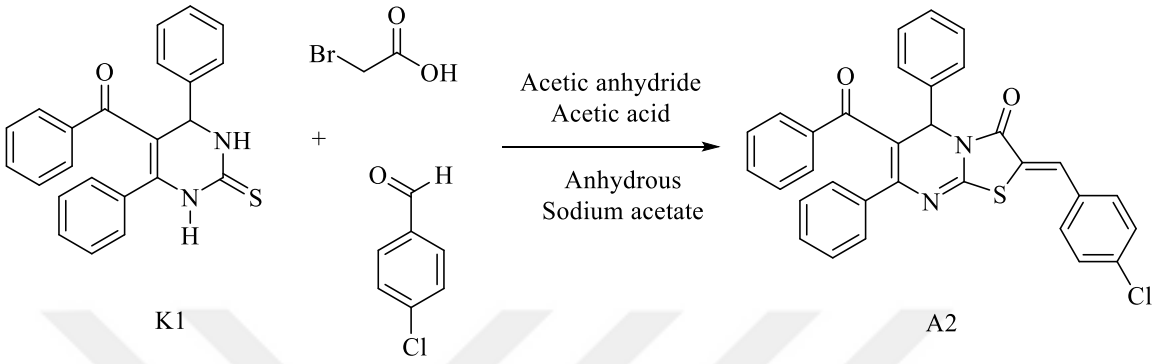


Figure 4.9. Synthesis reaction of the molecule A2.

Melting point of (A2) molecule: 212-213 ℃; Chemical formula: $C_{32}H_{21}ClN_2O_2S$; Molecular weight: 533.04 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 4-chlorobenzaldehyde as a result compound A2 was obtained with 94% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b, 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A2; 2976 cm^{-1} (C-H alkene and aromatic), 2901 cm^{-1} (C-H aliphatic). One of these strong sharp peaks in the range (1705, 1688, 1611, 1599, 1557, 1528, 1491, or 1445 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, N-$H_{bend,}$ or C=S) (Figure 4.10).

In the ^{1}H-NMR (400 MHz / DMSO-d_6) spectrum of compound A2, due to presence of weak EWG chlorine on carbon (19C-Cl) gives 13 unsymmetric hydrogens, therefore; the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons around δ = 9 ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appearing at δ = 7.79 ppm, other signals B(td), C(dddd), D(m), E(m) originate from aromatic ring protons. The

F(s) singlet signal seen at δ = 6.30 ppm can be interpreting to (6C-H) proton. The total integral shows that 21 hydrogen formed up the structure of compound A2 (Figure 4.11, Table 4.5).

In the ^{13}C-NMR (400 MHz / DMSO-d_6) spectrum of A2, the presence of weak EWG chlorine on carbon nineteen (19C-Cl) gives 24 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appears at δ = 196.2 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appears at δ = 164.7 ppm. The signals of other carbons in the compound A2 between the range (154.73-127.72 ppm) are (2C, 4C, 14C, carbons and aromatic region carbons) were exited at δ = 121.1 ppm (1C carbon), δ = 117.8 ppm (8C) and δ = 57.8 ppm (6CH carbon) (Figure 4.12, Table 4.6).

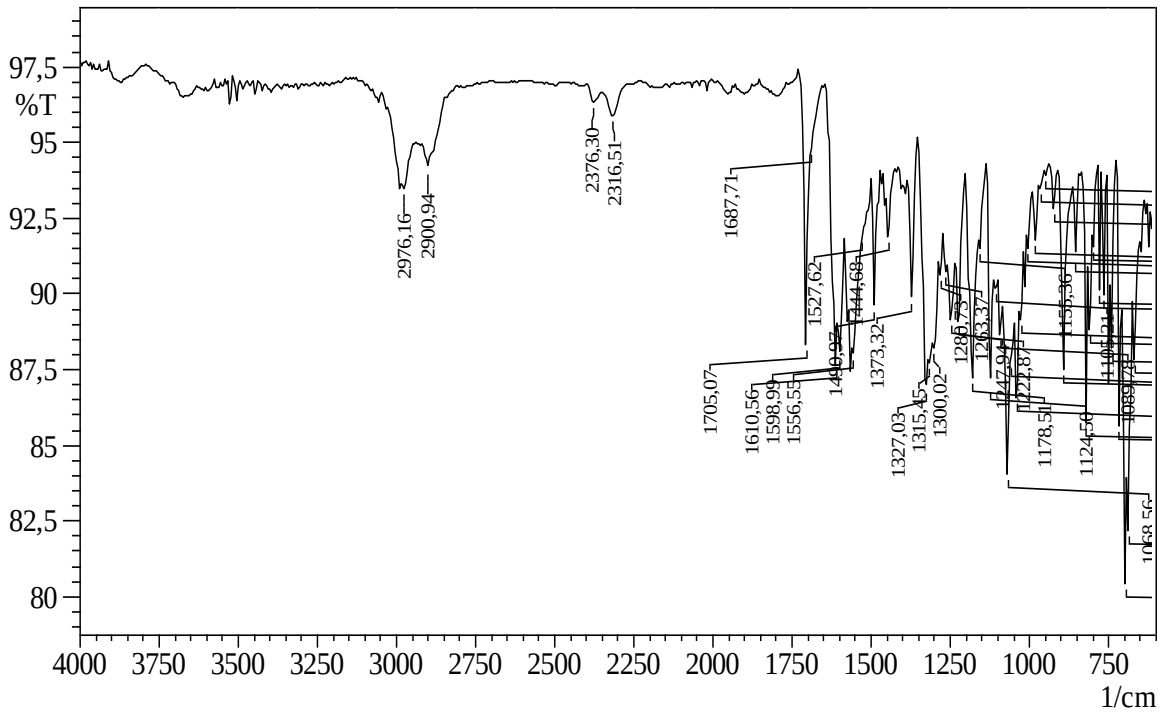


Figure 4.10. IR spectrum of compound A2.

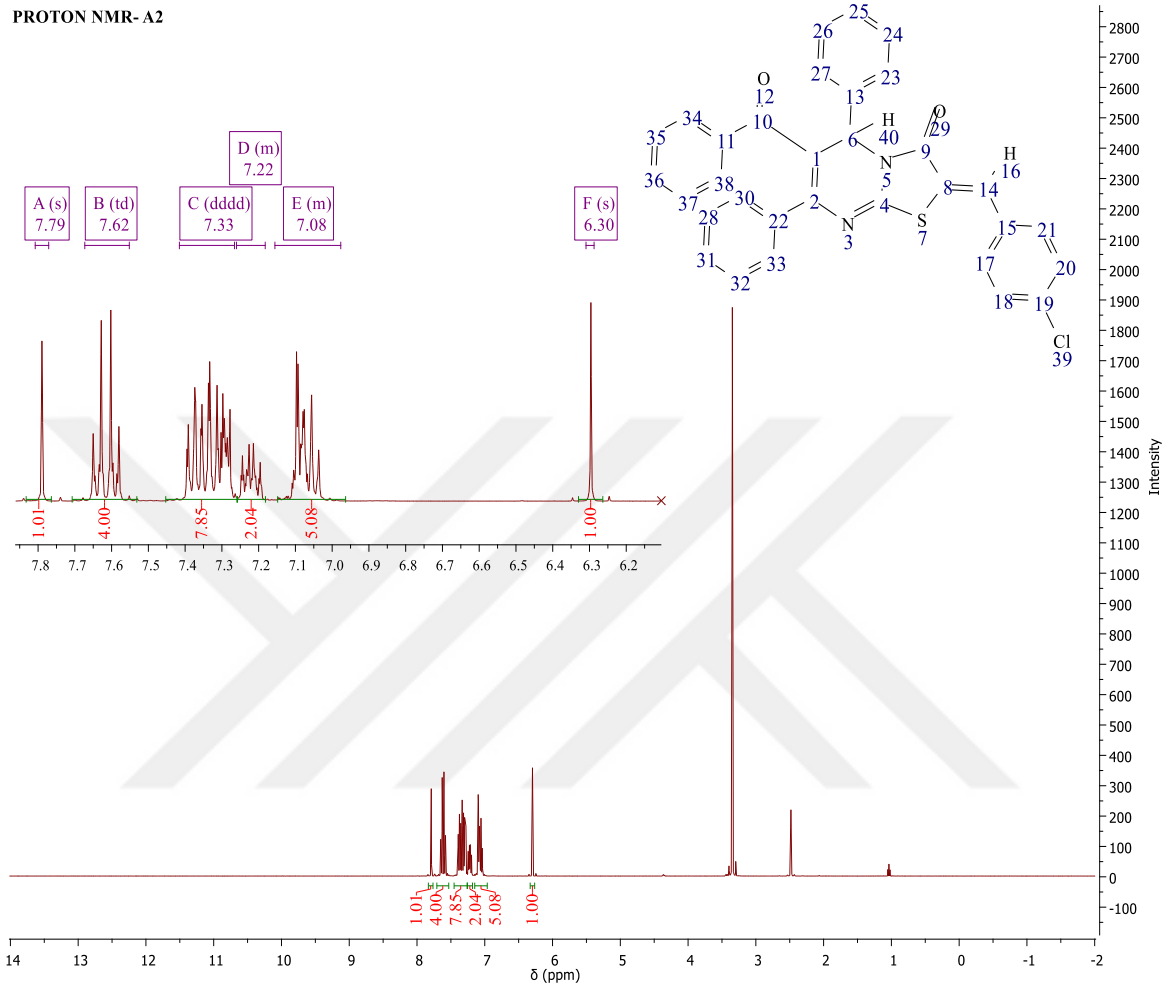


Figure 4.11. ^{1}H NMR spectrum of compound A2.

Table 4.5. ^{1}H NMR spectrum data of compound A2

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.79	7.81 - 7.77	1	1.01	s		14C-H
2	B(td)	7.62	7.67 - 7.55	4	4.00	td	6.56, 8.78, 8.77	Aromatic
3	C (dddd)	7.33	7.42 - 7.27	8	7.85	dddd	2.19, 6.58, 6.15, 7.78	Aromatic
4	D(m)	7.22	7.26 - 7.18	2	2.04	m		Aromatic
5	E(m)	7.08	7.16 - 6.98	5	5.08	m		Aromatic
6	F(s)	6.30	6.31 - 6.29	1	1.00	s		6C-H

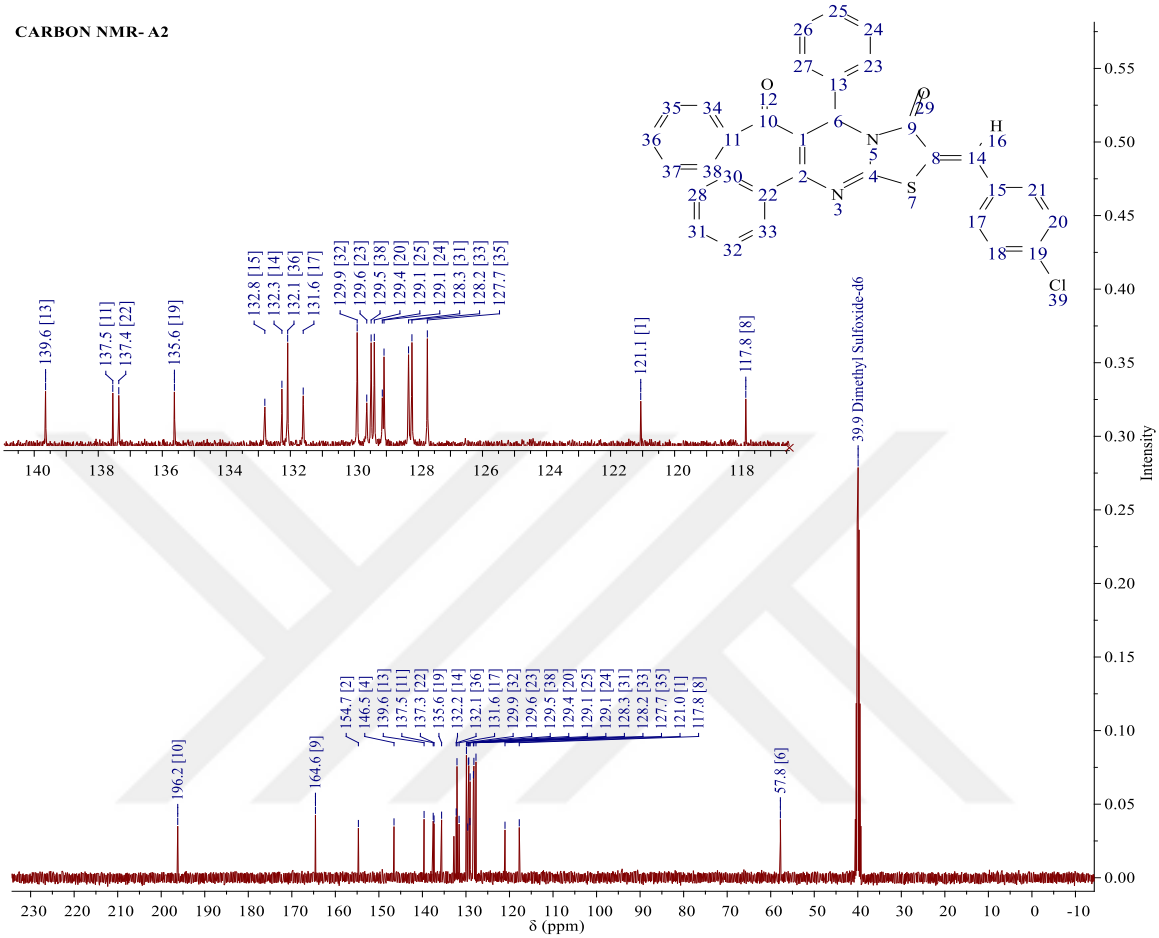


Figure 4.12. ^{13}C NMR spectrum of compound A2.

Table 4.6. ^{13}C NMR chemical shift assignments of compound A2

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.2	22C	137.4	21CH	131.6	38CH	129.5	31CH	128.3
9C	164.6	19C	135.6	28CH	129.9	18CH	129.4	30CH	128.2
2C	154.7	15C	132.8	32CH	129.9	20CH	129.4	33CH	128.2
4C	146.6	14C	132.3	23CH	129.6	25CH	129.1	35CH	127.7
13C	139.6	36CH	132.1	27CH	129.6	24CH	129.1	37CH	127.7
11C	137.5	17CH	131.6	34CH	129.5	26CH	129.1	1C	121.1
								8C	117.8
								6CH	57.8

4.1.4. (*E, Z*)-6-benzoyl-2-(3-nitrobenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A3)

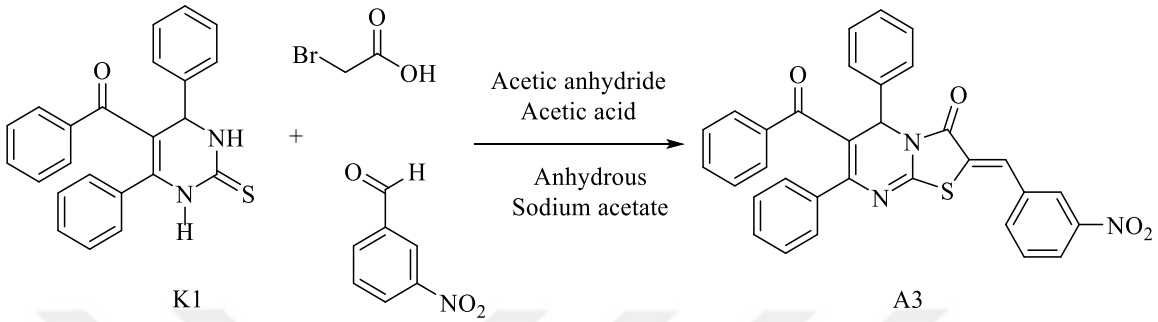


Figure 4.13. Synthesis reaction of the molecule A3.

Melting point of molecule (A3): 195-197 ℃; Chemical formula: $C_{32}H_{21}N_3O_4S$; Molecular weight: 543.60 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 3-nitrobenzaldehyde as a result compound A3 was obtained with 96% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A3; 2988 cm^{-1} (C-H alkene and aromatic), 2901 cm^{-1} (C-H aliphatic). One of these strong sharp peaks in the range (1705, 1638, 1531, 1331, 1310, 1279, 1250, or 1229 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, N-H_{bend}, C=S, or N=O) (Figure 4.14).

In the ^1H NMR (400 MHz, $CDCl_3$) spectrum of compound A3, the presence of high electron withdrawing nitro-group on carbon twenty (20C-NO_2) gives 15 unsymmetric hydrogens, the ^1H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons at δ = 9.00 ppm of K1, at the same time A(m) peak interpreted to the (14C-H) proton moved downfield compare all other compounds at δ = 8.37 ppm, due to presence strong EWG (NO_2).

The signals B(m), C(m), D(m), E(m), F(m), G (m), H(m), I(m) and J(m) originate from aromatic ring protons. The K(s) singlet signal seen at δ = 6.53 ppm can be interpreted to (6C-H) proton. The total integral shows that 21 hydrogen formed up the structure of compound A3 (Figure 4.15, Table 4.7).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A3 the presence of high electron withdrawing nitro-group on carbon twenty (20C-NO_2) gives 26 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.4 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 164.5 ppm. The signals of other carbons in compound A3 between the range (153.9-124.1 ppm) are; (2C, 4C, 14C, carbon and aromatic region carbons) were exited at 123.9 ppm (1C carbon), 118.2 ppm (8C) and 57.9 ppm (6CH carbon). The total peak numbers of ^{13}C NMR for compound A3 is 26 peaks with 6 symmetric carbons, thus; total of carbons equals to 32 carbons (Figure 4.16, Table 4.8).

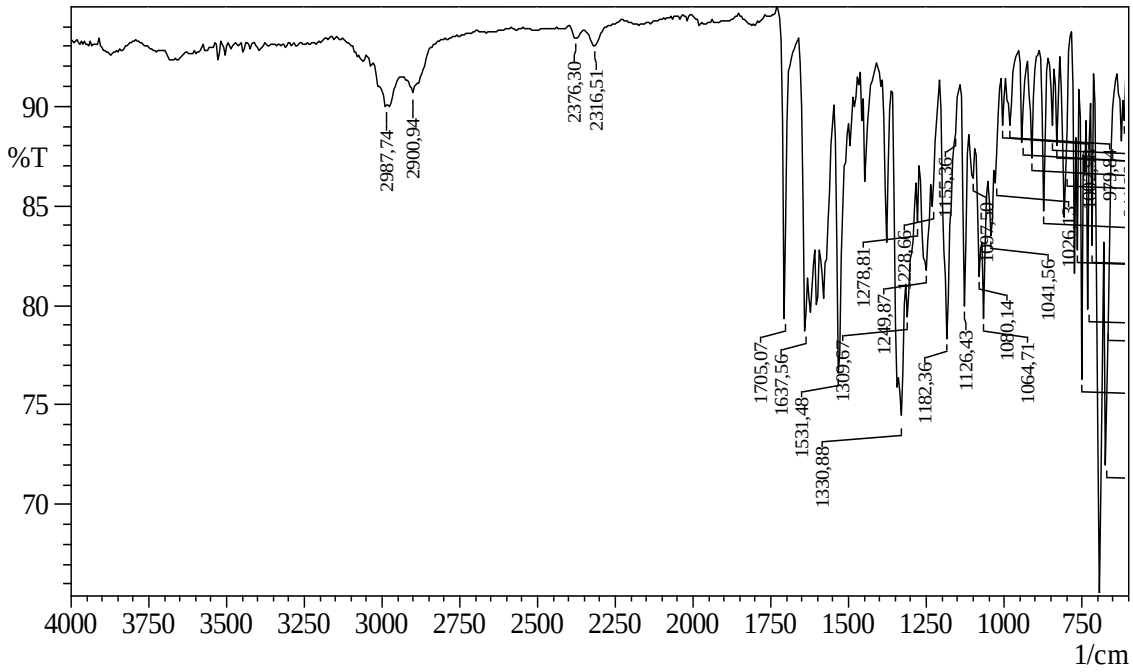


Figure 4.14. IR spectrum of compound A3.

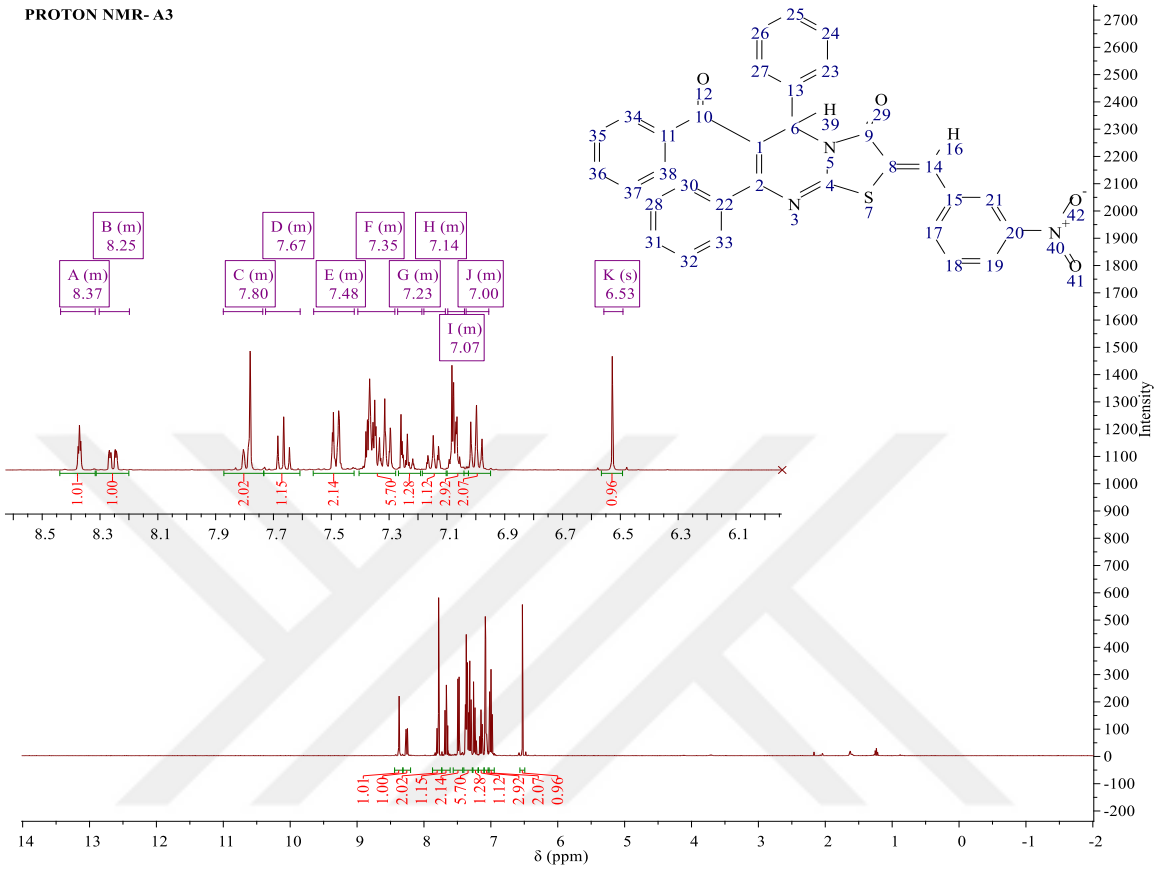


Figure 4.15. ^{1}H NMR spectrum of compound A3.

Table 4.7. ^{1}H NMR spectrum data of compound A3

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(m)	8.37	8.44 - 8.32	1	1.01	m		14C-H
2	B(m)	8.25	8.30 - 8.20	1	1.00	m		Aromatic
3	C(m)	7.80	7.87 - 7.74	2	2.02	m		Aromatic
4	D(m)	7.67	7.73 - 7.61	1	1.15	m		Aromatic
5	E(m)	7.48	7.56 - 7.42	2	2.14	m		Aromatic
6	F(m)	7.35	7.41 - 7.28	6	5.70	m		Aromatic
7	G(m)	7.23	7.27 - 7.19	1	1.28	m		Aromatic
8	H(m)	7.14	7.18 - 7.11	1	1.12	m		Aromatic
9	I(m)	7.07	7.10 - 7.04	3	2.92	m		Aromatic
10	J(m)	7.00	7.03 - 6.96	2	2.07	m		Aromatic
11	K(s)	6.53	6.56 - 6.49	1	0.96	s		6C-H

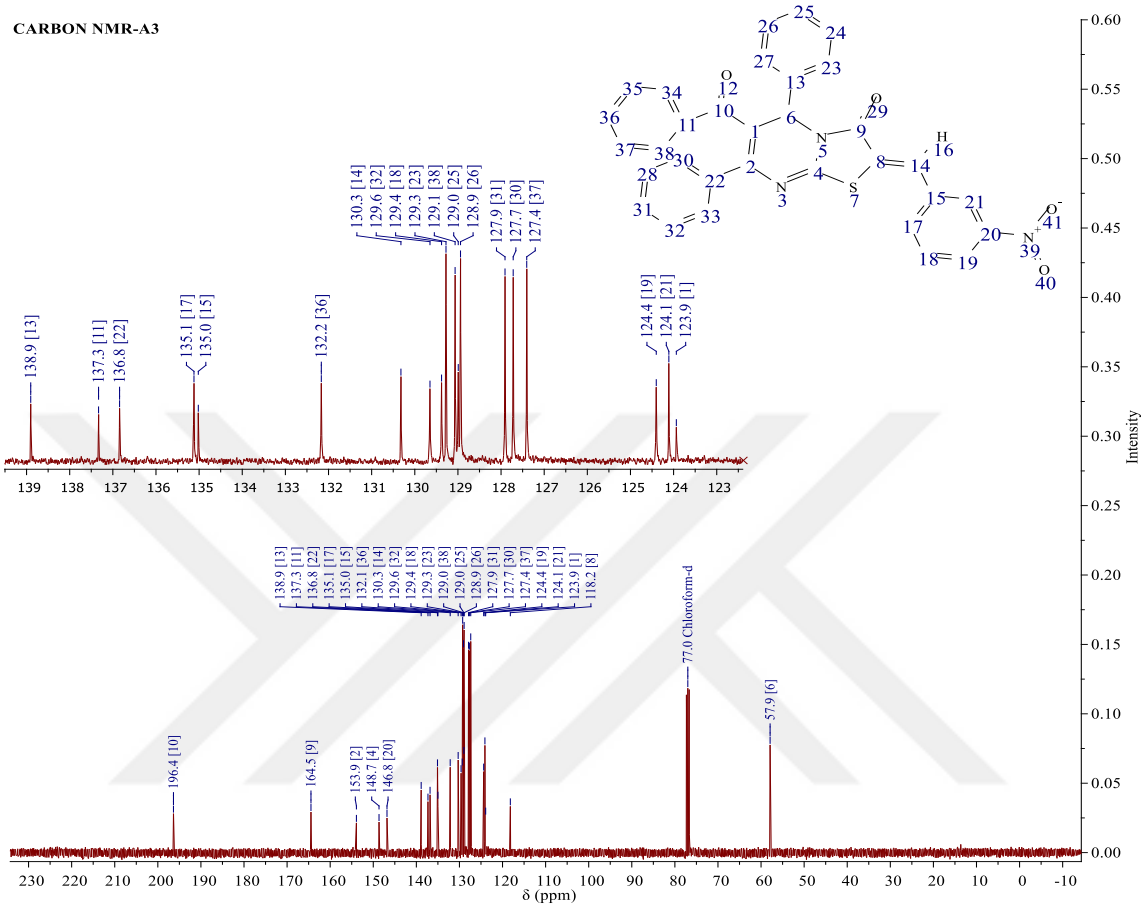


Figure 4.16. ^{13}C NMR spectrum of compound A3.

Table 4.8. ^{13}C NMR chemical shift assignments of compound A3

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.4	11C	137.3	32CH	129.6	34CH	129.1	30CH	127.7
9C	164.5	22C	136.8	28CH	129.6	25CH	129.0	37CH	127.4
2C	153.9	17CH	135.1	18CH	129.4	26CH	128.9	35CH	127.4
4C	148.7	15C	135.0	27CH	129.3	24CH	128.9	19CH	124.4
20C	146.8	36CH	132.2	23CH	129.3	31CH	127.9	21CH	124.1
13C	138.9	14C	130.3	38CH	129.1	33CH	127.7	1C	123.9
								8C	118.2
								6CH	57.9

4.1.5. (*E, Z*)-6-benzoyl-2-(4-methoxybenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A4)

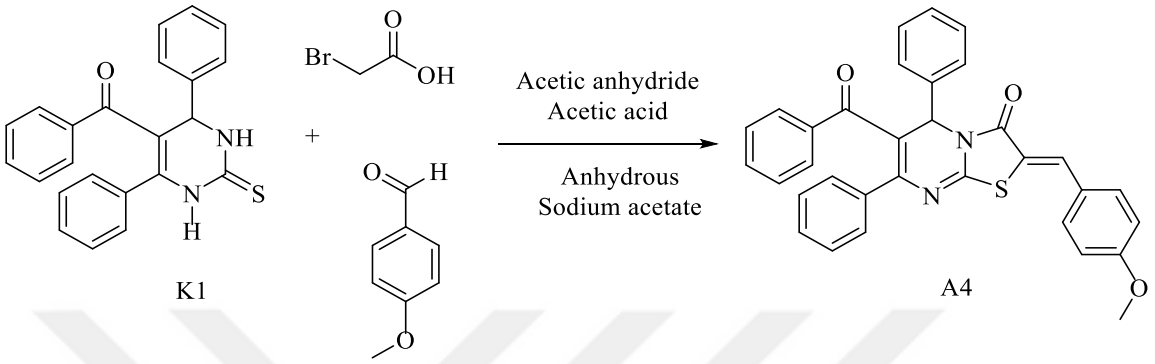


Figure 4.17. Synthesis reaction of the molecule A4.

Melting point of molecule (A4): 236-237 ℃; Chemical formula: $C_{33}H_{24}N_2O_3S$; Molecular weight: 528.63 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 4-methoxybenzaldehyde as a result compound A4 was obtained with 93% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A4: 3059, 2986 cm^{-1} (aromatic and alkene C-H). 2928, 2901 cm^{-1} (aliphatic C-H, -CH_3). One of these strong sharp peaks in the range (1709, 1651, 1613, 1587, 1551, 1512, 1491, 1447, or 1422 cm^{-1}), can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-H_{bend}) (Figure 4.18).

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound A4, the presence of strong EDG methoxy group on carbon nineteen (19C-OCH_3) gives 14 unsymmetric hydrogens, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons at δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appeared at δ = 7.74 ppm. The signals B(m), C(m), D(m), E(m), F(m) and G(m) originate from aromatic ring

protons. The H(s) singlet signal seen at δ = 6.51 ppm can be interpreted to (6C-H) proton and the I(s) high intensity singlet signal seen at δ = 3.86 ppm can be interpreted to the three hydrogens on 40CH_3 proton. The total integral shows that 24 hydrogen formed up the structure of the compound A4 **(**Figure 4.19, Table 4.11).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A4, the presence of strong EDG methoxy group on carbon nineteen (19C-OCH_3) gives 25 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.4 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 165.4 ppm. The signals of other carbons in compound A4 between the range (161.4-114.8 ppm) are; (2C, 4C, 14C, 1C, 8C carbon and aromatic region carbons), the peak of methoxy carbon (6CH) appeared at δ = 57.5 ppm and the signal for (40CH_3 carbon) appeared at δ = 55.5 ppm. The total peak numbers of ^{13}C NMR for compound A4 is 25 peaks with 8 symmetric carbons, thus; the total number of carbons equaled to 33 carbons (Figure 4.20, Table 4.12).

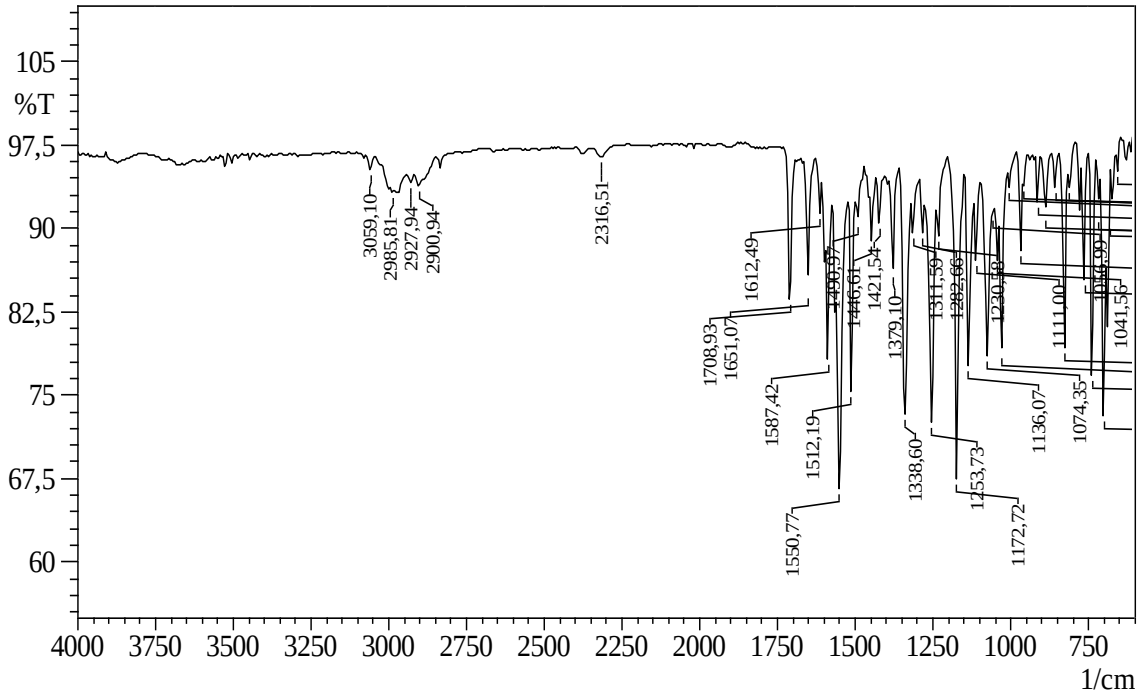


Figure 4.18. IR spectrum of compound A4.

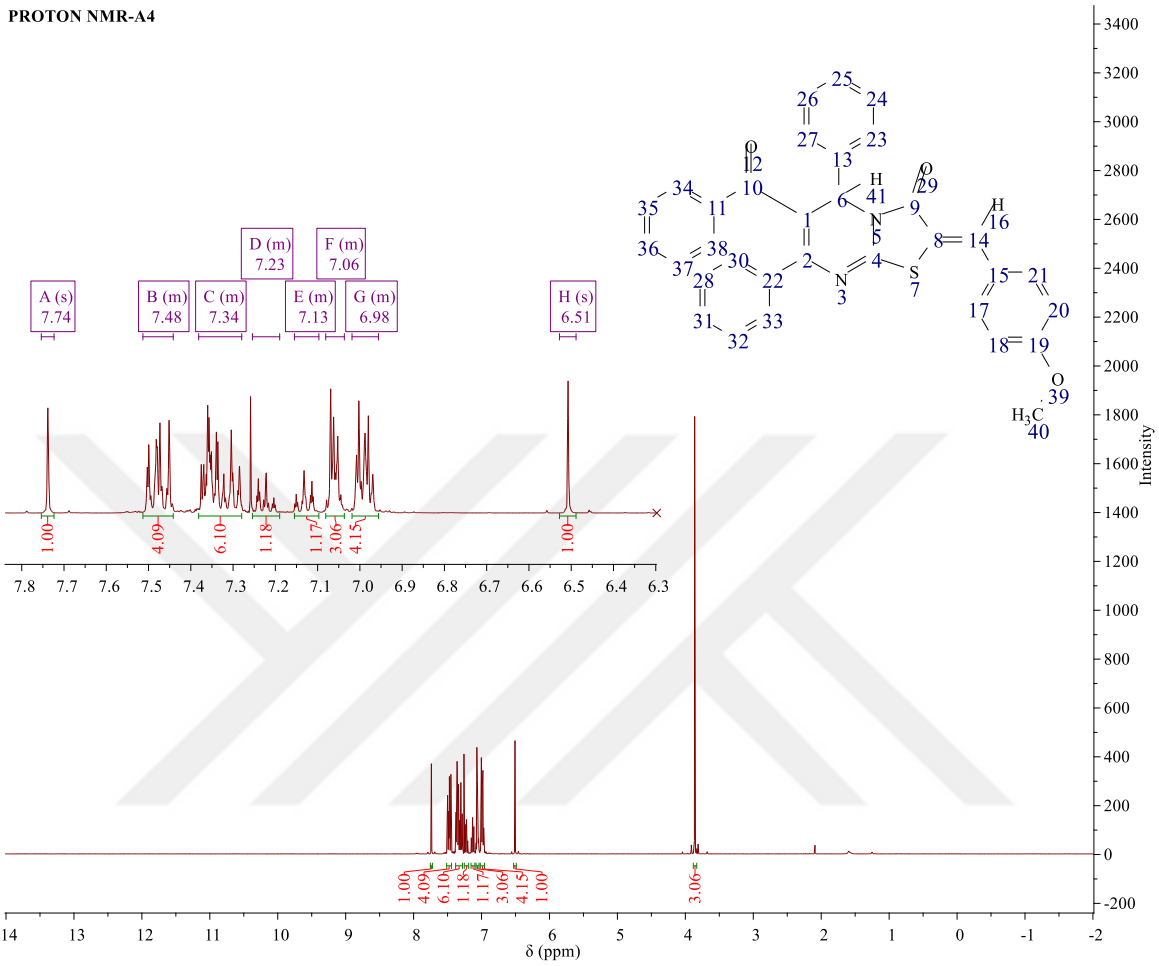


Figure 4.19. ^{1}H NMR spectrum of compound A4.

Table 4.9. ^{1}H NMR spectrum data of compound A4

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.74	7.75 - 7.72	1	1.00	s		14C-H
2	B(m)	7.48	7.51 - 7.44	4	4.09	m		Aromatic
3	C(m)	7.34	7.38 - 7.28	6	6.10	m		Aromatic
4	D(m)	7.23	7.25 - 7.19	1	1.18	m		Aromatic
5	E(m)	7.13	7.15 - 7.10	1	1.17	m		Aromatic
6	F(m)	7.06	7.08 - 7.04	3	3.06	m		Aromatic
7	G(m)	6.98	7.02 - 6.96	4	4.15	m		Aromatic
8	H(s)	6.51	6.53 - 6.49	1	1.00	s		6C-H
9	I(s)	3.86	3.88 - 3.83	3	3.06	s		40CH_3

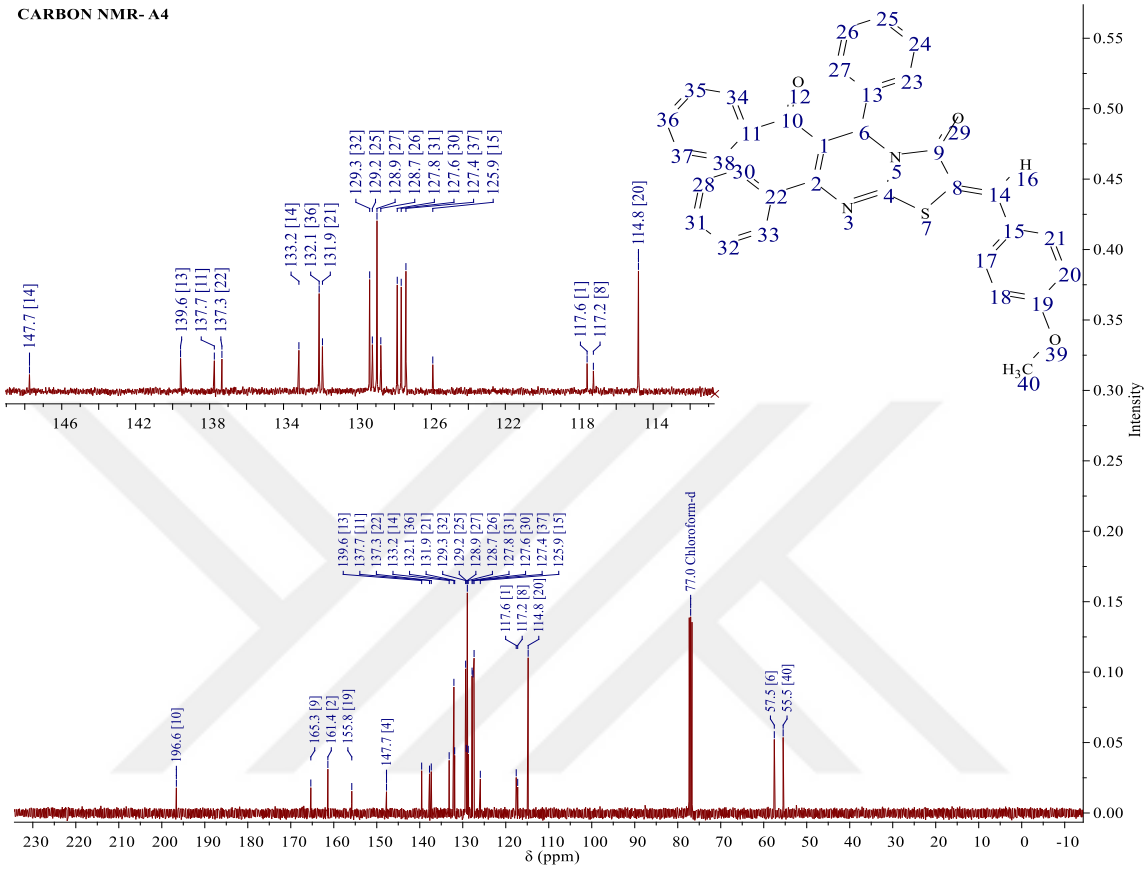


Figure 4.20. ^{13}C NMR spectrum of compound A4.

Table 4.10. ^{13}C NMR chemical shift assignments of compound A4

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.6	13C	139.6	28CH	129.3	38CH	128.9	35CH	127.4
9C	165.4	11C	137.7	32CH	129.3	24CH	128.7	37CH	127.4
2C	161.4	22C	137.3	25CH	129.2	26CH	128.7	15C	125.9
19C	155.8	36CH	132.1	23CH	128.9	31CH	127.8	1C	117.6
4C	147.7	17CH	131.9	27CH	128.9	30CH	127.6	8C	117.2
14C	147.7	21CH	131.9	34CH	128.9	33CH	127.6	18CH	114.8
								20CH	114.8
								6CH	57.5
								40CH3	55.5

4.1.6. (*E, Z*)-6-benzoyl-2-(4-methylbenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A5)

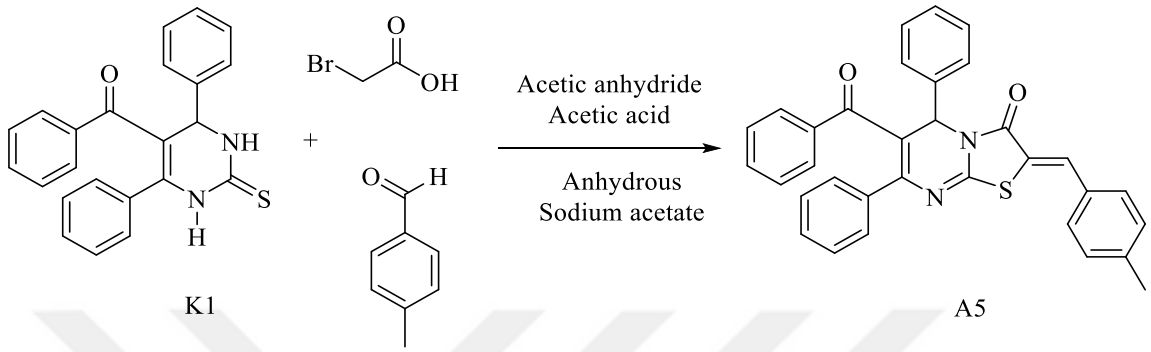


Figure 4.21. Synthesis reaction of the molecule A5.

Melting point of molecule (A5): 215-216 ℃; Chemical formula: $C_{33}H_{24}N_2O_2S$; Molecular weight: 512.63 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 4-methylbenzaldehyde as a result compound A5 was obtained with 94% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A5: 2988 cm^{-1} (C-H alkene and aromatic) 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1707, 1630, 1595, 1553, 1510, 1489, 1449, 1381,1348, or 1323 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic or N-$H_{bend.}$) (Figure 4.22).

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound A5, the presence of weak EDG methyl group on carbon nineteen (19C-CH_3) gives 14 unsymmetric hydrogens, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons around $\delta = 9.00$ ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appeared at $\delta = 7.76$ ppm. The signals B(dd), C(m), D(m), E(m), F(m) and G(m) originate from

aromatic ring protons. The H(s) singlet signal seen at δ = 6.51 ppm can be interpreted to 6C-H proton and the I(s) high intensity singlet signal seen at δ = 2.40 ppm can be interpreted to the three hydrogens on methyl group 39CH_3 proton. The total integral shows that 24 hydrogen formed up the structure of A5 compound (Figure 4.23, Table 4.11).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A5 the presence of weak EDG methyl group on carbon nineteen (19C-CH_3) gives 25 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.6 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 165.3 ppm. The signals of other carbons in compound A5 between the range (155.6-117.7 ppm) are; (2C, 4C, 14C, 1C, 8C carbon and aromatic region carbons), the signal for (6CH carbon) appeared at δ = 57.6 ppm and the peak of methyl group carbon (39CH_3) appeared at δ = 21.6 ppm. The peak numbers of ^{13}C NMR for compound A5 is 25 peaks with 8 symmetric carbons, thus; the total number of carbons equal to 33 carbons (Figure 4.24, Table 4.12).

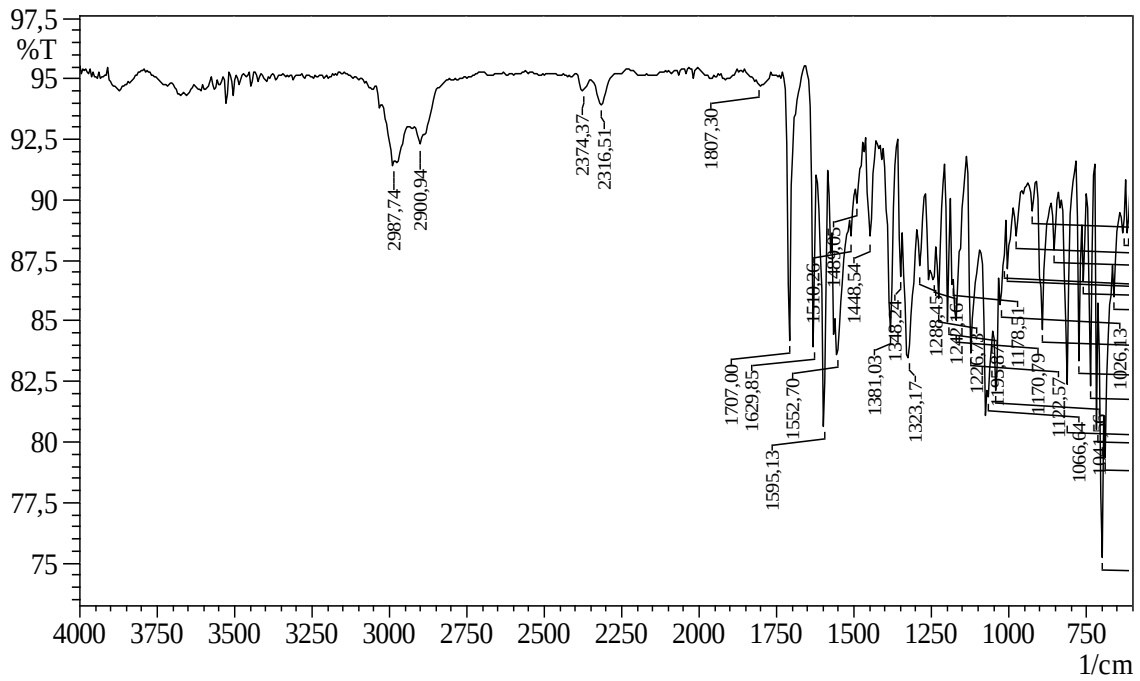


Figure 4.22. IR spectrum of compound A5.

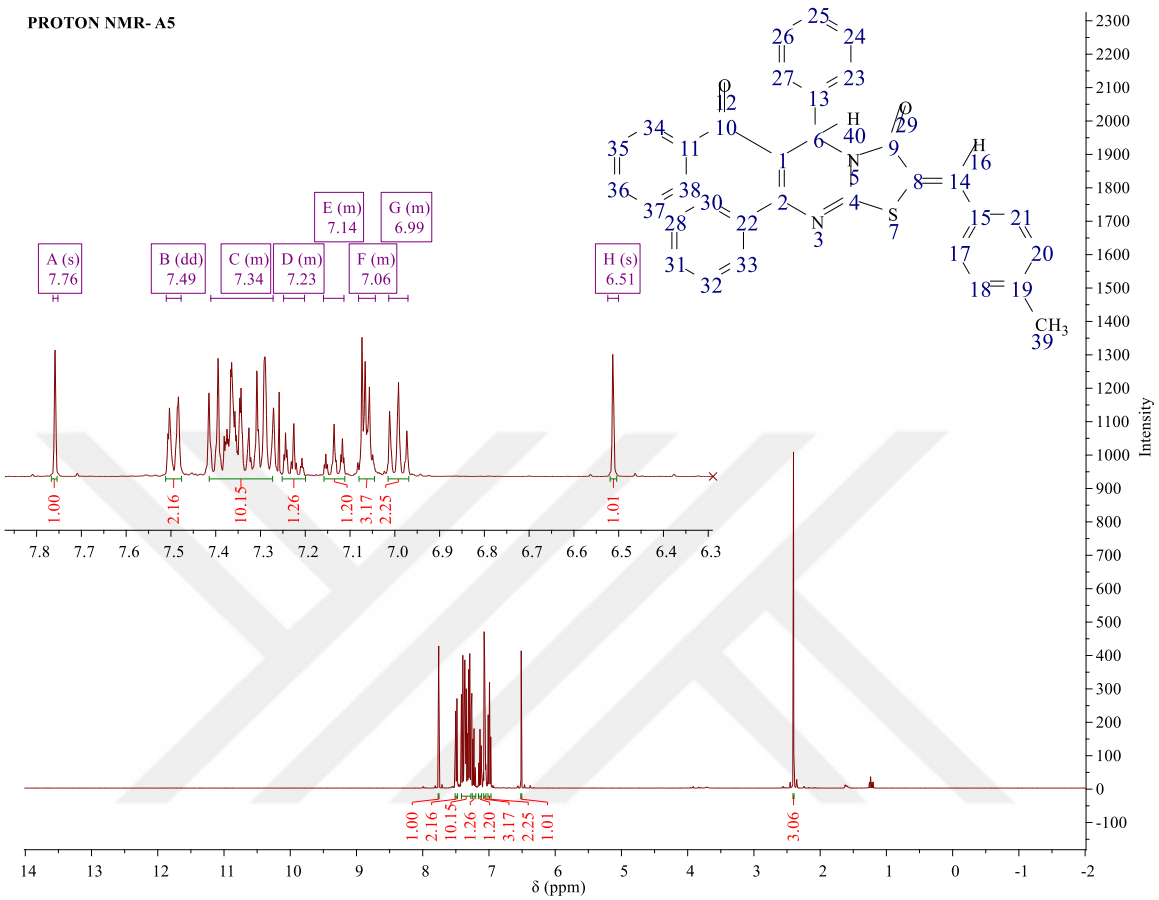


Figure 4.23. ^{1}H NMR spectrum of compound A5.

Table 4.11. ^{1}H NMR spectrum data of compound A5

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.76	7.76 - 7.75	1	1.00	s		14C-H
2	B(dd)	7.49	7.51 - 7.48	2	2.16	dd	1.14, 8.25	Aromatic
3	C(m)	7.34	7.41 - 7.27	10	10.15	m		Aromatic
4	D(m)	7.23	7.25 - 7.20	1	1.26	m		Aromatic
5	E(m)	7.14	7.16 - 7.11	1	1.20	m		Aromatic
6	F(m)	7.06	7.08 - 7.04	3	3.17	m		Aromatic
7	G(m)	6.99	7.01 - 6.97	2	2.25	m		Aromatic
8	H(s)	6.51	6.52 - 6.50	1	1.01	s		6C-H
9	I(s)	2.40	2.41 - 2.39	3	3.06	s		39CH_3

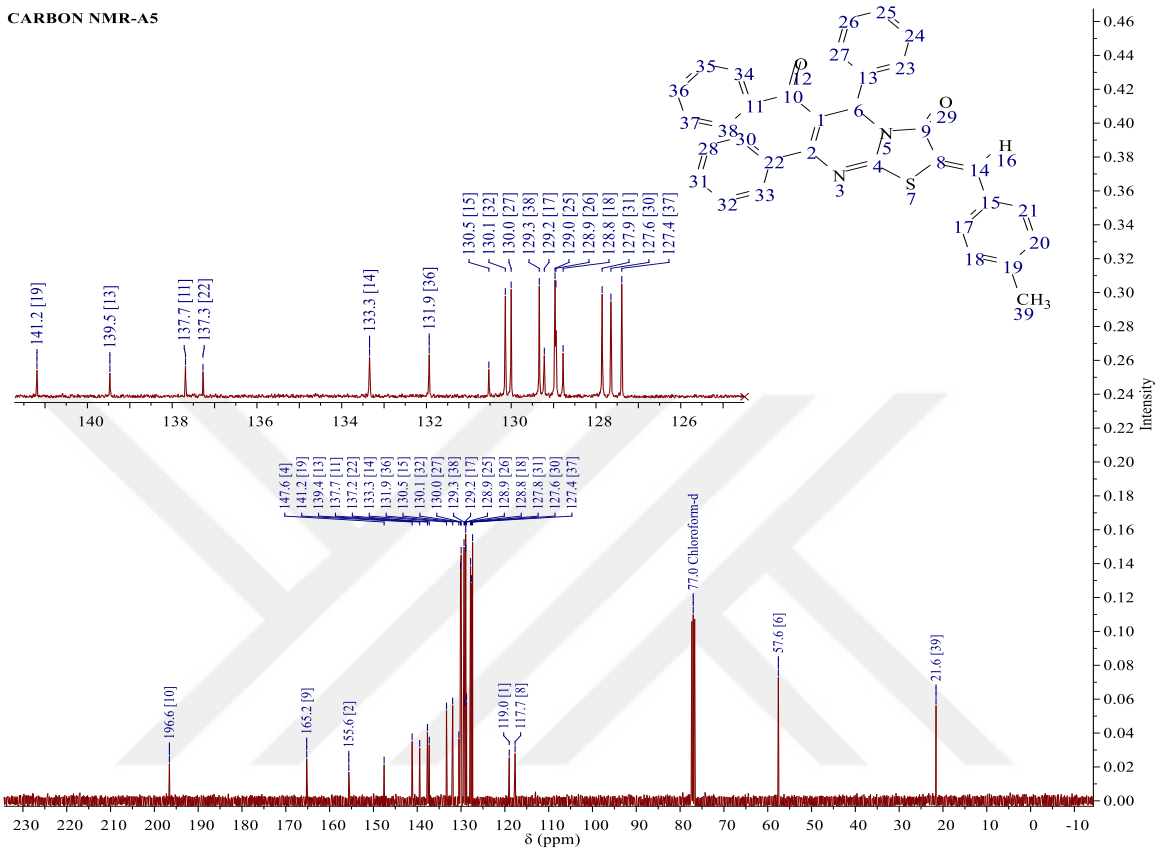


Figure 4.24. ^{13}C NMR spectrum of compound A5.

Table 4.12. ^{13}C NMR chemical shift assignments of compound A5

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.6	11C	137.7	32CH	130.1	21CH	129.2	31CH	127.9
9C	165.3	22C	137.3	23CH	130.0	25CH	129.0	30CH	127.6
2C	155.6	14C	133.3	27CH	130.0	24CH	128.9	33CH	127.6
4C	147.6	36CH	131.9	34CH	129.3	26CH	128.9	35CH	127.4
19C	141.2	15C	130.5	38CH	129.3	18CH	128.8	37CH	127.4
13C	139.5	28CH	130.1	17CH	129.2	20CH	128.8	1C	119.0
								8C	117.7
								6CH	57.6
								39CH3	21.6

4.1.7. (*E, Z*)-6-benzoyl-2-(4-hydroxybenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A6)

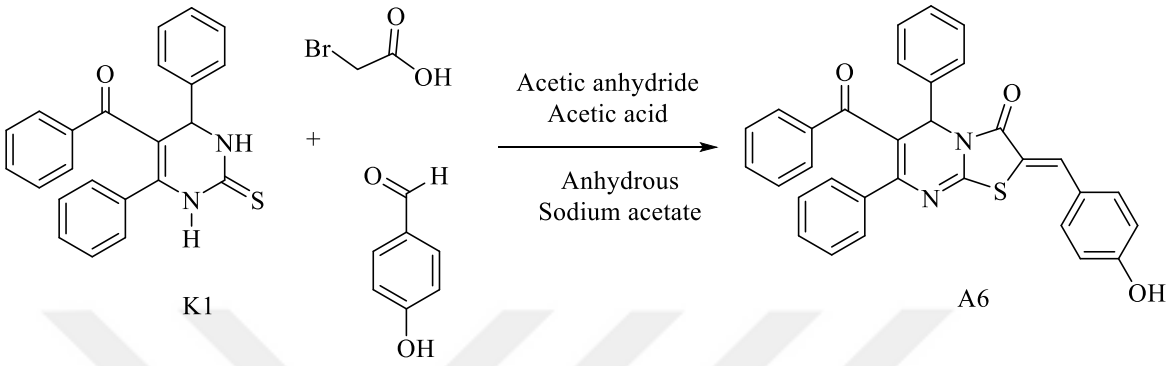


Figure 4.25. Synthesis reaction of the molecule A6.

Melting point of molecule (A6): 230-231 ℃; Chemical formula: $C_{32}H_{22}N_2O_3S$; Molecular weight: 514.60 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 4-hydroxybenzaldehyde as a result compound A6 was obtained with 93% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A6: 2974 cm^{-1} (C-H alkene and aromatic) 2884 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1767, 1713, 1643, 1595, 1555, 1508, 1379, or 1337 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-$H_{bend.}$) (Figure 4.26).

In the ^1H NMR (400 MHz, $CDCl_3$) spectrum of compound A6 the presence of high EDG hydroxyl group on carbon nineteen (19C-OH) gives 14 unsymmetric hydrogens, the ^1H NMR shows the absence of the two peaks for 3N-H, 5N-H protons around δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appeared at δ = 7.75 ppm. The signals B(m), C(m), D(m), E(m), F(m) and G(m) originate from aromatic

ring protons. The H(s) singlet signal seen at δ= 6.51 ppm can be interpreted to (6C-H) proton and the signal of hydroxyl hydrogen does not appear on ^{1}H NMR because may be the hydrogen on O-H group was exchanging its proton with the solvent $CDCl_3$ high. The total integral shows that 21 hydrogen formed up the structure of A6 compound (Figure 4.27, Table 4.13).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A6, the presence of high EDG hydroxyl group on carbon nineteen (19C-OH) gives 24 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.5 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 169.0 ppm. can be said. The signals of other carbons in compound A6 between the range (165.0-117.8 ppm) are; (2C, 4C, 14C, 1C, 8C carbon and aromatic region carbons), the signal for (6CH carbon) appeared at δ = 57.7 ppm. The total peak numbers of ^{13}C NMR for compound A6 is 24 peaks with 8 symmetric carbons, thus; the total number of carbons equal to 32 carbons (Figure 4.28, Table 4.14).

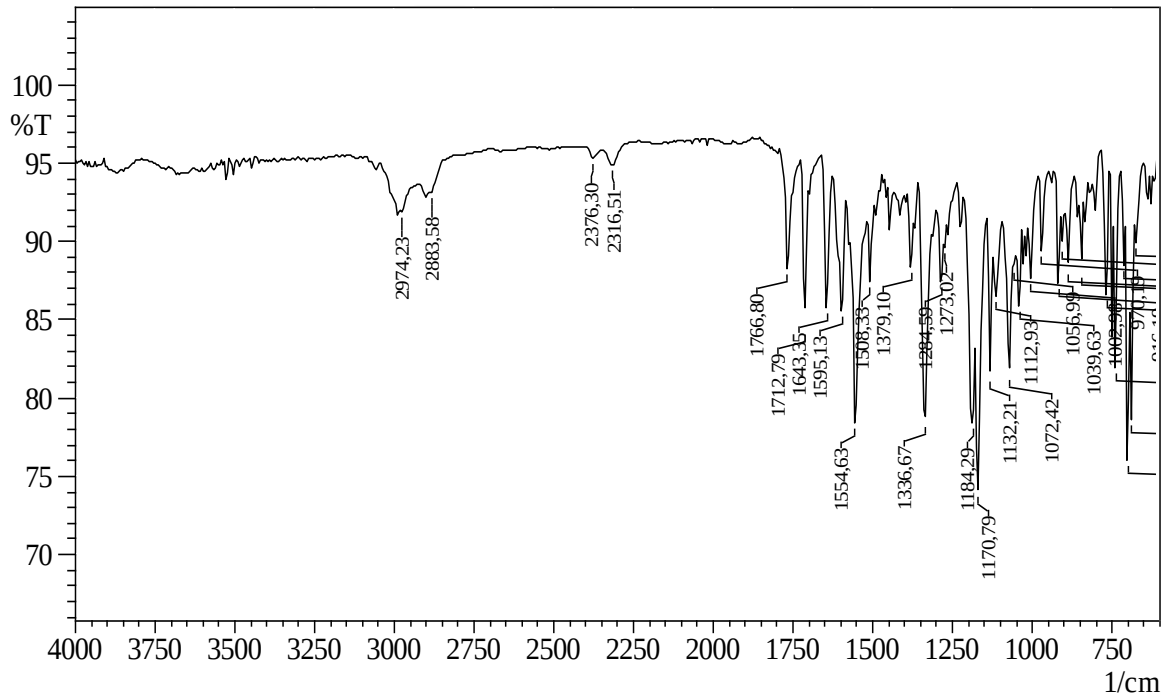


Figure 4.26. IR spectrum of compound A6.

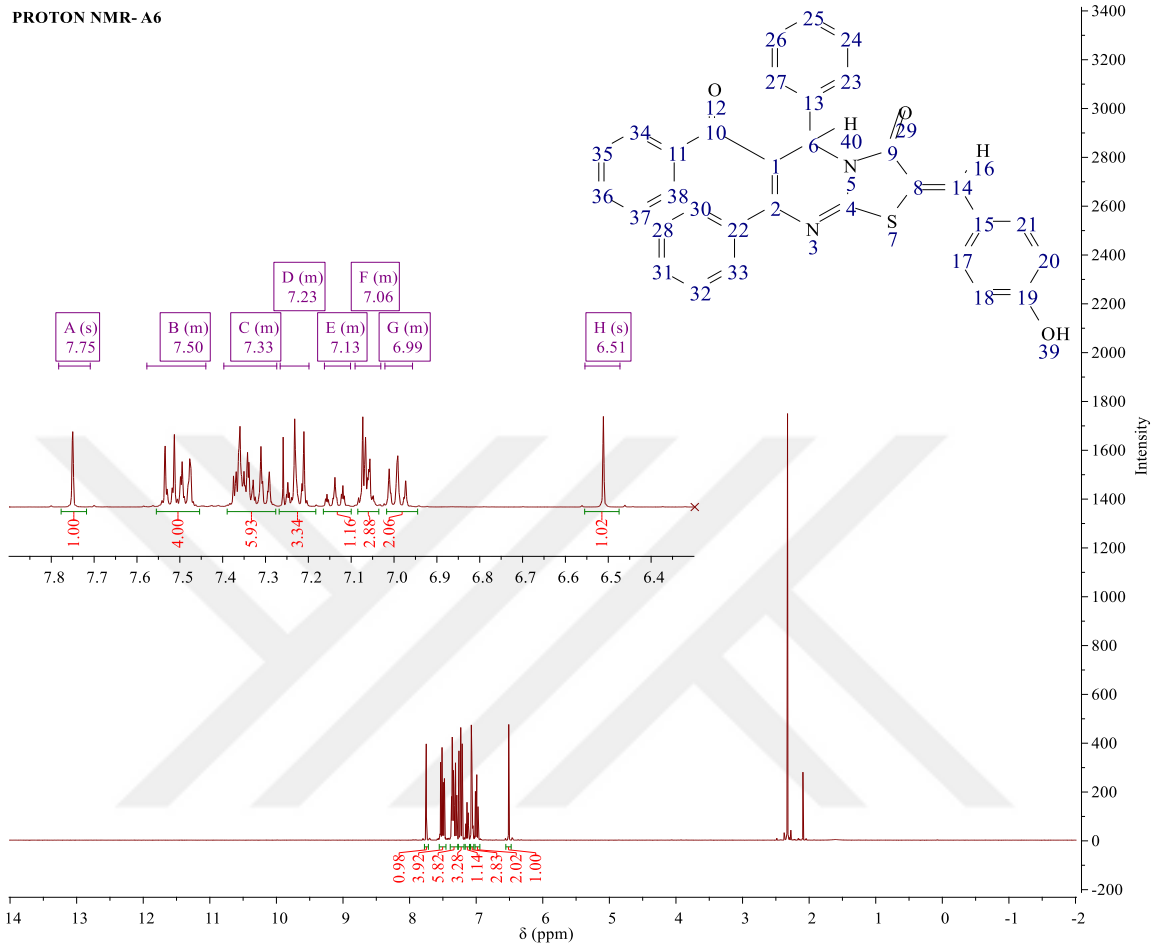


Figure 4.27. ^{1}H NMR spectrum of compound A6.

Table 4.13 ^{1}H NMR spectrum data of compound A6

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.75	7.78 - 7.71	1	0.98	s		14C-H
2	B(m)	7.50	7.58 - 7.44	4	3.92	m		Aromatic
3	C(m)	7.33	7.40 - 7.27	6	5.82	m		Aromatic
4	D(m)	7.23	7.27 - 7.20	3	3.28	m		Aromatic
5	E(m)	7.13	7.16 - 7.10	1	1.14	m		Aromatic
6	F (m)	7.06	7.09 - 7.03	3	2.83	m		Aromatic
7	G(m)	6.99	7.02 - 6.96	2	2.02	m		Aromatic
8	H(s)	6.51	6.55 - 6.47	1	1.00	s		6C-H

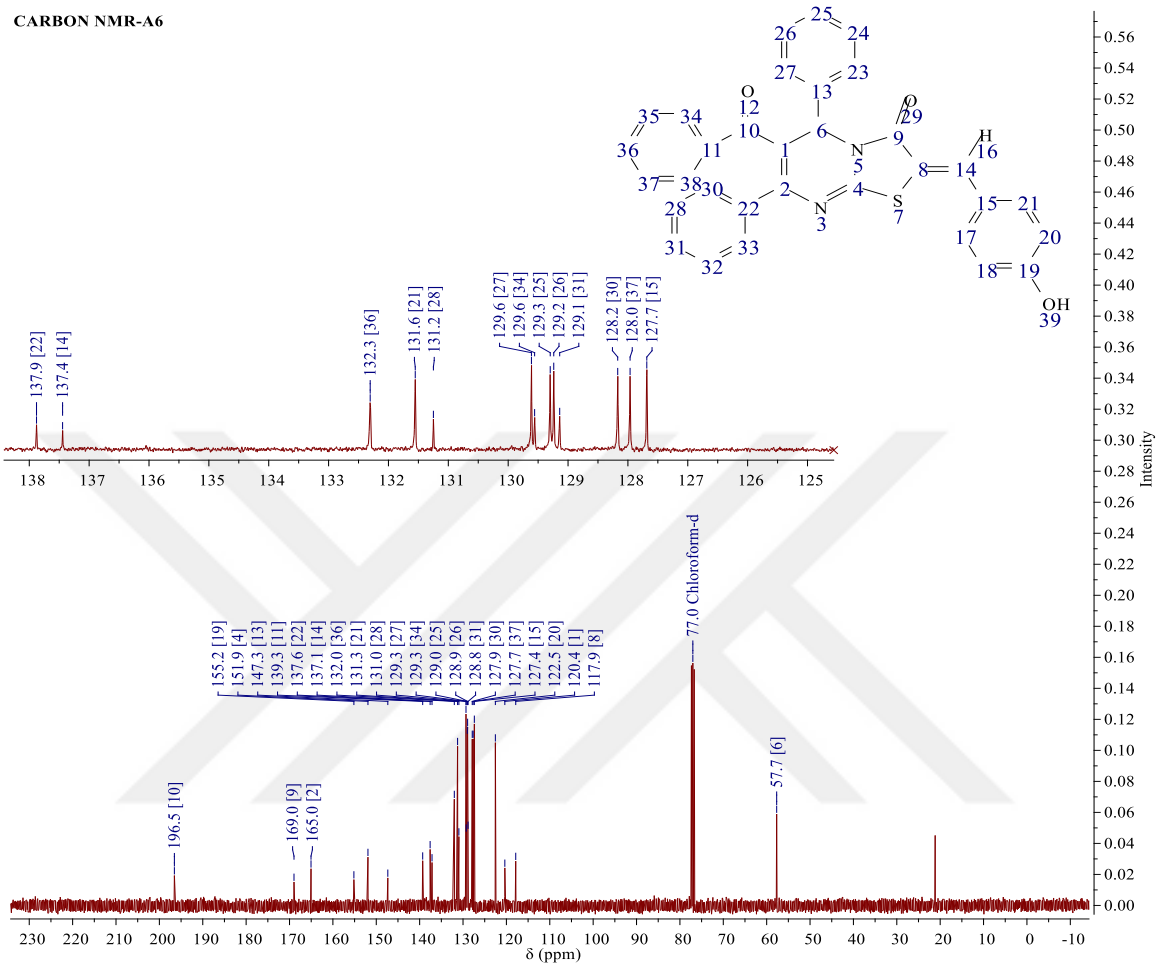


Figure 4.28. ^{13}C NMR spectrum of compound A6.

Table 4.14. ^{13}C NMR chemical shift assignments of compound A6

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.5	11C	139.3	28CH	131.0	25CH	129.0	35CH	127.7
9C	169.0	22C	137.6	32CH	131.0	24CH	128.9	37CH	127.7
2C	165.0	14C	137.1	23CH	129.3	26CH	128.9	15C	127.4
19C	155.2	36CH	132.0	27CH	129.3	31CH	128.8	18CH	122.5
4C	151.9	17CH	131.3	34CH	129.3	30CH	127.9	20CH	122.5
13C	147.3	21CH	131.3	38CH	129.3	33CH	127.9	1C	120.4
								8C	117.8
								6CH	57.7

4.1.8. (*E, Z*)-6-benzoyl-5,7-diphenyl-2-(4-(trifluoromethyl)benzylidene)-5*H*-thiazolo [3,2-*a*]pyrimidin-3(2*H*)-one (A7)

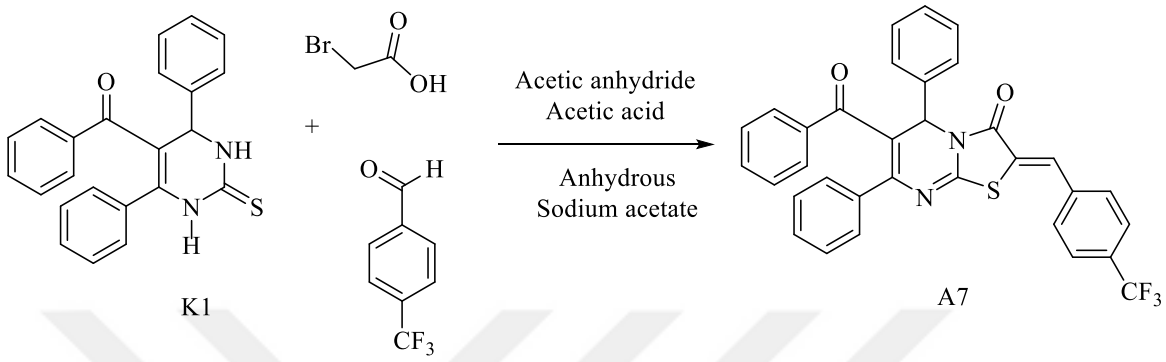


Figure 4.29. Synthesis reaction of the molecule A7.

Melting point of molecule (A7): 130-132 ℃; Chemical formula: $C_{33}H_{21}F_3N_2O_2S$; Molecular weight: 566.60 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 4-(trifluoromethyl)benzaldehyde as a result compound A7 was obtained with 90% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A7: 2988 cm^{-1} (C-H alkene and aromatic) 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1713, 1599, 1564, 1447, 1375, 1319, or 1250 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-$H_{bend.}$) (Figure 4.30).

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound A7, the presence of strong EWG trifluoromethyl group on carbon nineteen (19C-CF_3) gives 13 unsymmetric hydrogens, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons around δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appeared at δ = 7.77 ppm, the signals B(d), C(d), D(dd), E(m), F(ddd), G(ddd), H(m) and I(dd)

originate from aromatic ring protons. The J(s) singlet signal seen at δ = 6.53 ppm can be interpreted to (6C-H) proton. The total integral shows that 21 hydrogen formed up the structure of compound A7 (Figure 4.31, Table 4.15).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A7, the presence of strong EWG trifluoromethyl group on carbon nineteen (19C-CF_3) gives 25 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.4 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 164.7 ppm. can be said. The signals of other carbons in compound A7 between the range (154.4-118.1 ppm) are; (2C, 4C, 14C, 1C, 8C carbon and aromatic region carbons), the signal for (6CH carbon) appeared at δ = 57.8 ppm. The peak numbers of ^{13}C NMR for compound A7 is 25 peaks with 8 symmetric carbons, thus; the total number carbons equaled to 33 carbons (Figure 4.32, Table 4.16).

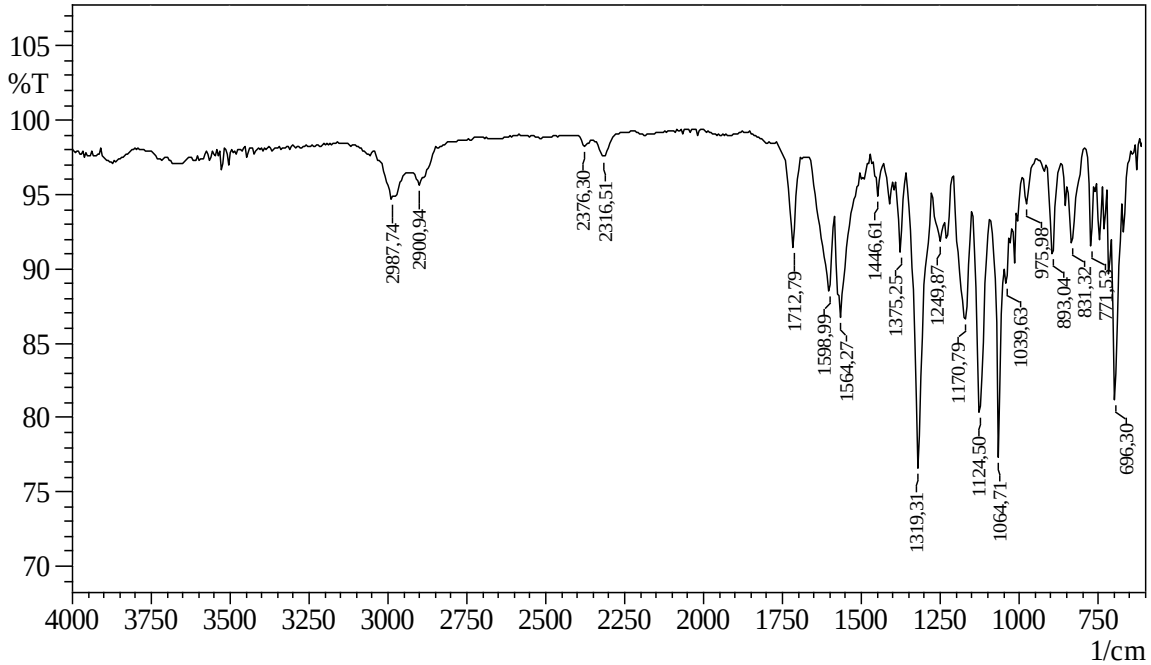


Figure 4.30. IR spectrum of compound A7.

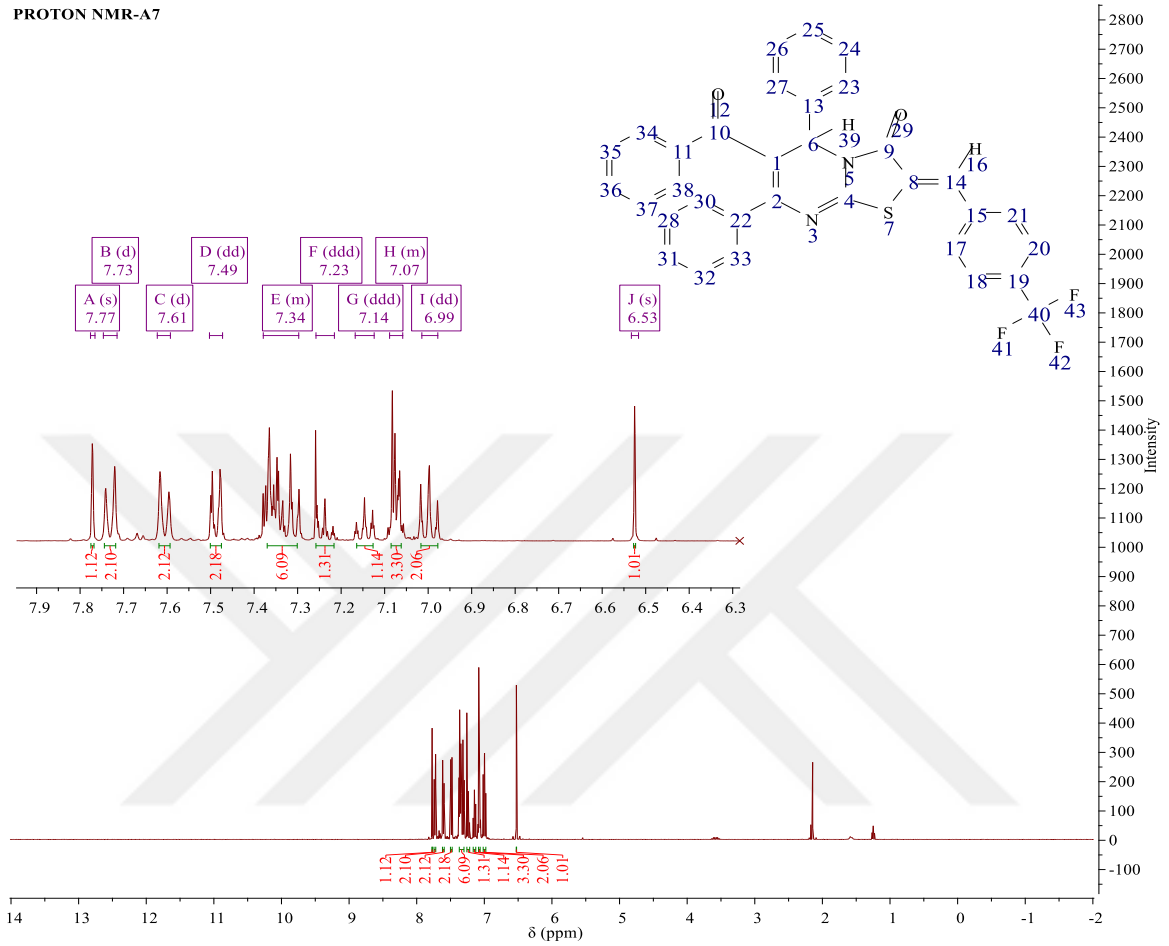


Figure 4.31. ^{1}H NMR spectrum of compound A7.

Table 4.15. ^{1}H NMR spectrum data of compound A7

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.77	7.78 - 7.77	1	1.12	s		14C-H
2	B(d)	7.73	7.75 - 7.72	2	2.10	d	8.31	Aromatic
3	C(d)	7.61	7.62 - 7.59	2	2.12	d	8.24	Aromatic
4	D(dd)	7.49	7.50 - 7.47	2	2.18	dd	3.28, 5.24	Aromatic
5	E(m)	7.34	7.38 - 7.30	6	6.09	m		Aromatic
6	F(ddd)	7.23	7.26 - 7.22	1	1.31	ddd	1.25, 3.84, 6.27	Aromatic
7	G(ddd)	7.14	7.17 - 7.12	1	1.14	ddd	1.25, 4.11, 6.94	Aromatic
8	H(m)	7.07	7.09 - 7.06	3	3.30	m		Aromatic
9	I(dd)	6.99	7.01 - 6.98	2	2.06	dd	4.09, 9.83	Aromatic
10	J(s)	6.53	6.53 - 6.52	1	1.01	s		6C-H

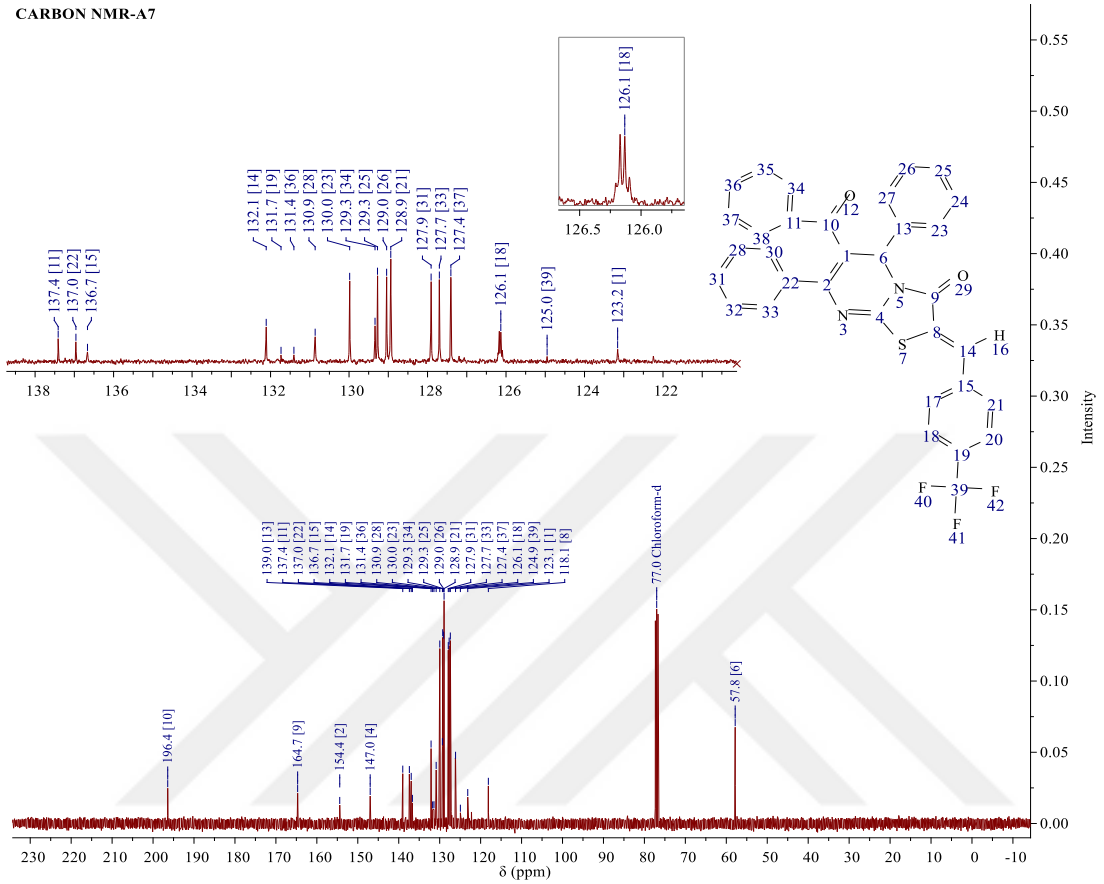


Figure 4.32. ^{13}C NMR spectrum of compound A7.

Table 4.16. ^{13}C NMR chemical shift assignments of compound A7

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.4	22C	137.0	32CH	130.9	24CH	129.0	33CH	127.7
9C	164.7	15C	136.7	23CH	130.0	26CH	129.0	35CH	127.4
2C	154.4	14C	132.1	27CH	130.0	17CH	128.9	37CH	127.4
4C	147.0	19C	131.7	34CH	129.3	21CH	128.9	18CH	126.1
13C	139.0	36CH	131.4	38CH	129.3	31CH	127.9	20CH	126.1
11C	137.4	28CH	130.9	25CH	129.3	30CH	127.7	39C	125.0
								1C	123.2
								8C	118.1
								6CH	57.8

4.1.9. (*E, Z*)-6-benzoyl-2-(2-methoxy-3-methylbenzylidene)-5,7-diphenyl-5*H*-thiazolo [3,2-*a*]pyrimidin-3(2*H*)-one (A8)

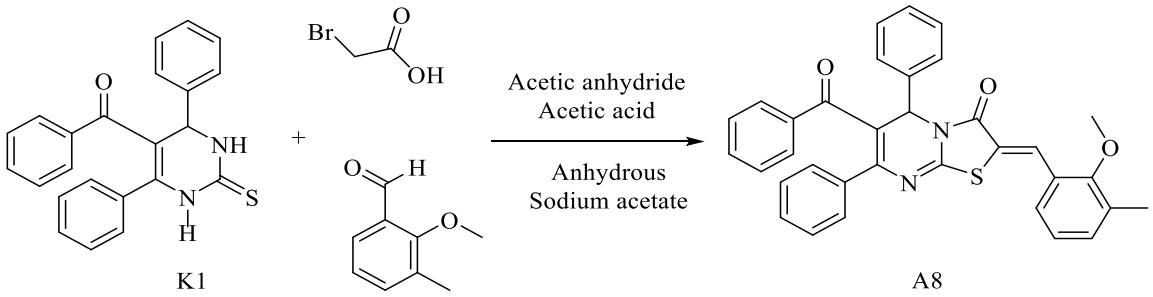


Figure 4.33. Synthesis reaction of the molecule A8.

Melting point of molecule (A8): 199-200 ℃; Chemical formula: $C_{34}H_{26}N_2O_3S$; Molecular weight: 542.65 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 2-methoxy-3-methylbenzaldehyde as a result compound A8 was obtained with 95% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A8: 2974 cm^{-1} (C-H alkene and aromatic) 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1715, 1599, 1564, 1445, 1375, 1319, 1261, or 1250 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-$H_{bend.}$) (Figure 4.34).

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound A8 the presence of two strong EDGs methoxy group on carbon (21C-O-40CH_3) and moderate methyl groups on carbon (20C-41CH_3) gives 16 unsymmetric hydrogens, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons around δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the (14C-H) proton appeared at δ = 7.71 ppm. The signals B(dt), C(m), D(m), E(m), F(m), G(m) and H(d) originate from aromatic ring protons. The I(s)

singlet signal seen at δ = 6.51 ppm can be interpreted to 6C-H proton, the J(s) singlet signal seen at δ = 3.88 ppm can be interpreted to the protons of the methoxy group on carbon ($40CH_3$) and the K(s) singlet signal seen at δ = 2.24 ppm can be interpreted to the methyl group carbon protons ($41CH_3$). The total integral shows that 26 hydrogen formed up the structure of A8 compound (Figure 4.35, Table 4.17).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A8, the presence of two strong EDGs methoxy group on carbon ($21C-O-40CH_3$) and moderate methyl groups on carbon ($20C-41CH_3$) gives 28 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.6 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 165.4 ppm. The signals of other carbons in compound A8 between the range (159.8-110.4 ppm) are; (2C, 4C, 14C, 1C, 8C carbon and aromatic region carbons), the signal for (6CH) carbon appeared at δ = 57.5 ppm, the signal for ($40CH_3$ carbon) seemed at δ = 55.5 ppm and the signal for ($41CH_3$ carbon) seemed at δ = 16.4 ppm. The peak numbers of ^{13}C NMR spectrum for compound A8 is 27 signals, it should be 28 peaks but may be several carbons in aromatic region have approximately the same chemical shift, while only 6 symmetric carbons are present in the molecule A8, thus; the total number of carbons equaled to 34 carbons (Figure 4.36, Table 4.18).

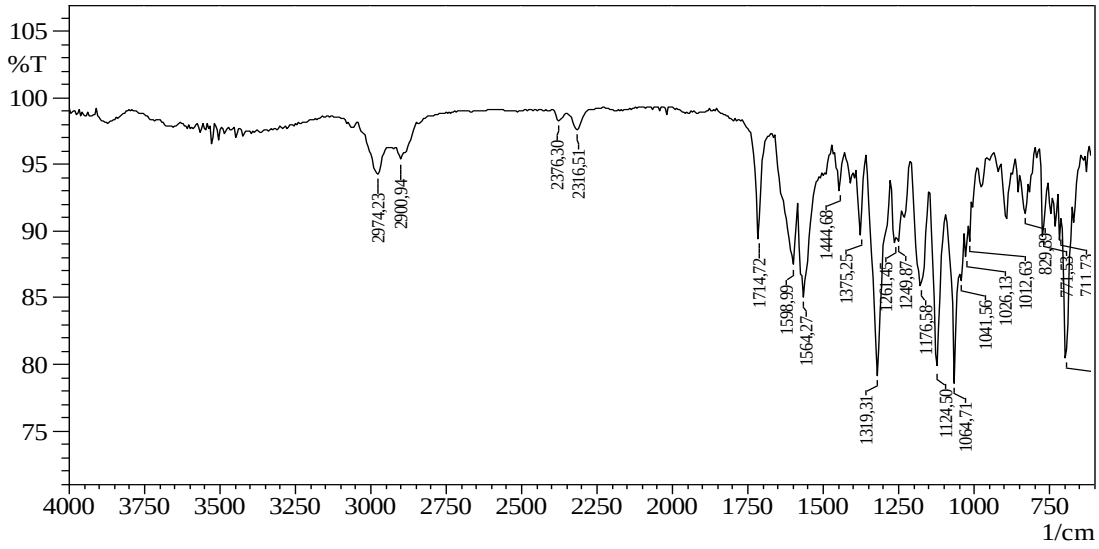


Figure 4.34. IR spectrum of compound A8.

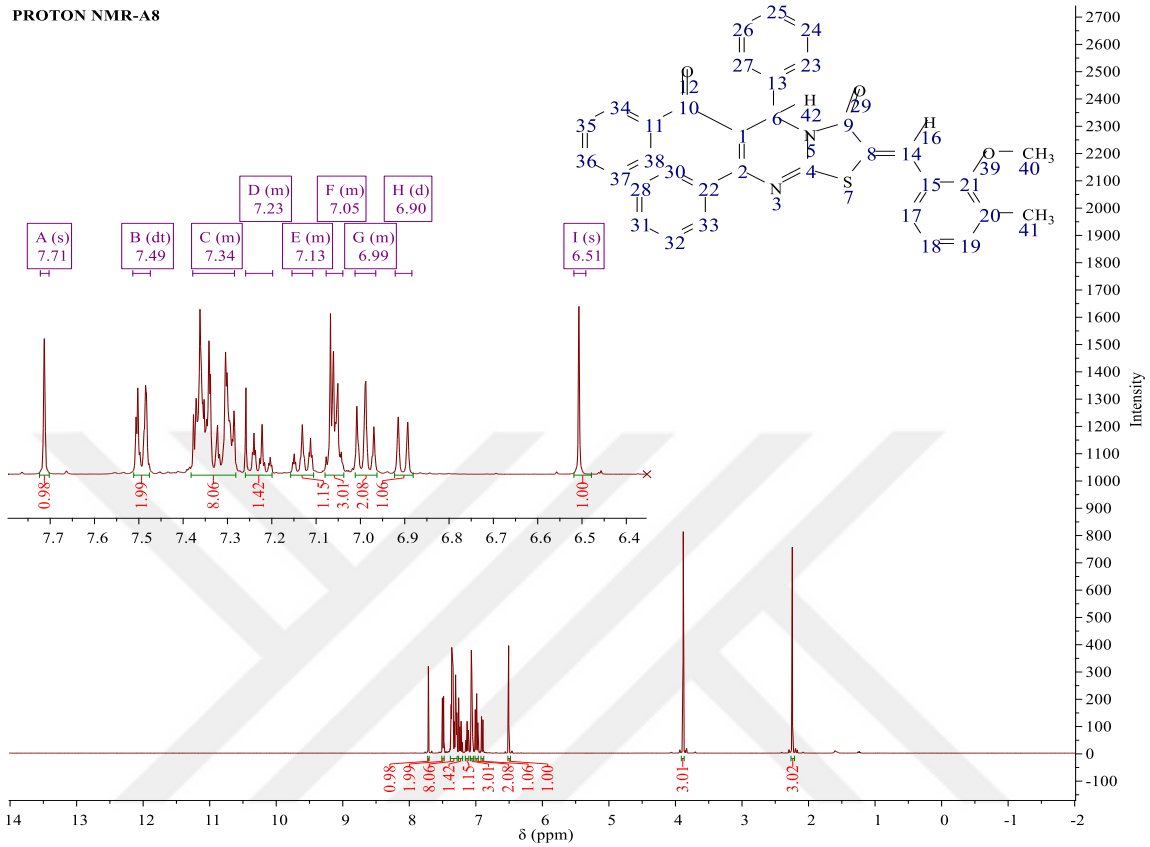


Figure 4.35. ^{1}H NMR spectrum of compound A8.

Table 4.17. ^{1}H NMR spectrum data of compound A8

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.71	7.72 - 7.70	1	0.98	s		14C-H
2	B(dt)	7.49	7.51 - 7.47	2	1.99	dt	1.90, 1.90, 3.12	Aromatic
3	C(m)	7.34	7.38 - 7.28	8	8.06	m		Aromatic
4	D(m)	7.23	7.26 - 7.20	1	1.42	m		Aromatic
5	E(m)	7.13	7.15 - 7.11	1	1.15	m		Aromatic
6	F(m)	7.05	7.08 - 7.04	3	3.01	m		Aromatic
7	G(m)	6.99	7.01 - 6.97	2	2.08	m		Aromatic
8	H(d)	6.90	6.92 - 6.88	1	1.06	d	8.54	Aromatic
9	I(s)	6.51	6.52 - 6.49	1	1.00	s		6C-H
10	J(s)	3.88	3.90 - 3.87	3	3.01	s		40CH_3
11	K(s)	2.24	2.26 - 2.23	3	3.02	s		41CH_3

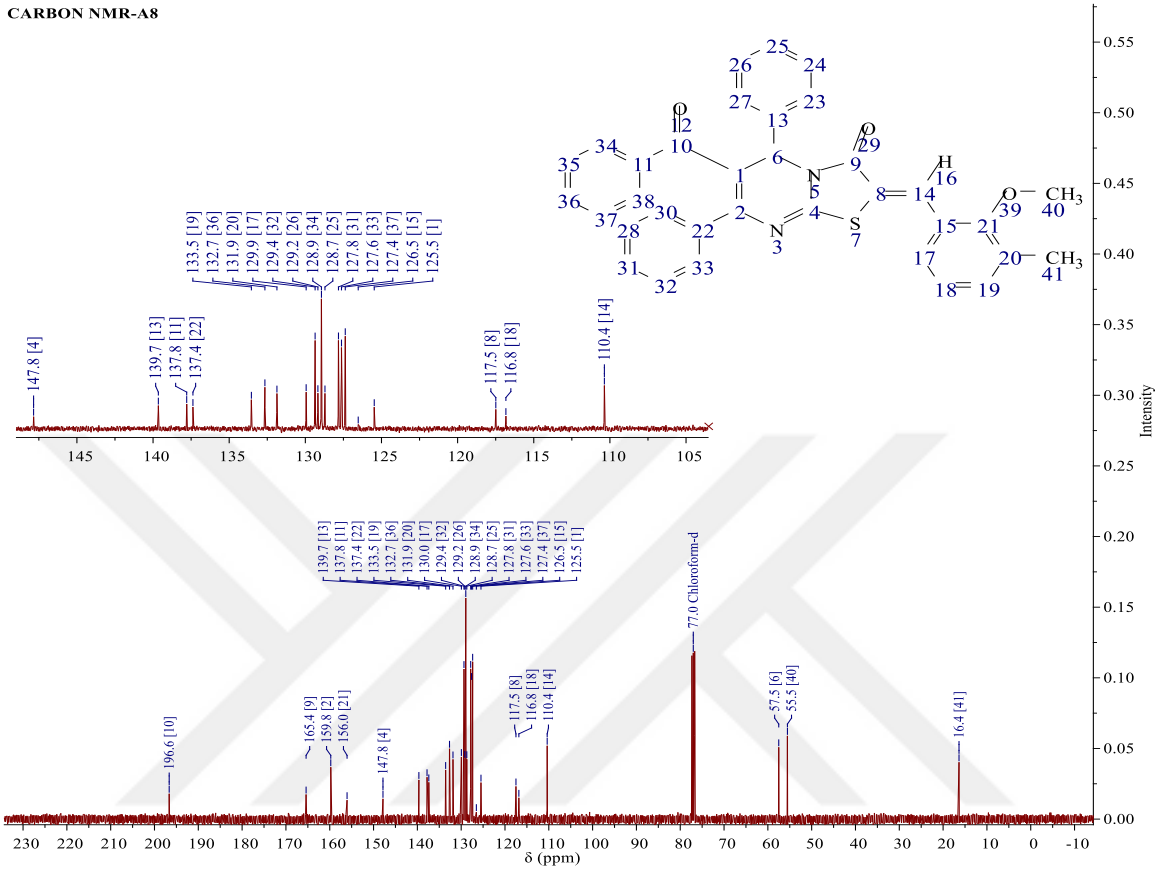


Figure 4.36. ^{13}C NMR spectrum of compound A8.

Table 4.18. ^{13}C NMR chemical shift assignments of compound A8

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.6	11C	137.8	28CH	129.4	34CH	128.9	35CH	127.4
9C	165.4	22C	137.4	32CH	129.4	38CH	128.9	37CH	127.4
2C	159.8	19CH	133.5	24CH	129.2	25CH	128.7	15C	126.5
21C	156.0	36CH	132.7	26CH	129.2	31CH	127.8	1C	125.5
4C	147.8	20C	131.9	23CH	128.9	30CH	127.6	8C	117.5
13C	139.7	17CH	129.9	27CH	128.9	33CH	127.6	18CH	116.8
								14C	110.4
								6CH	57.5
								40CH3	55.5
								41CH3	16.4

4.1.10. (*E, Z*)-6-benzoyl-2-(2,4-dimethoxybenzylidene)-5,7-diphenyl-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A9)

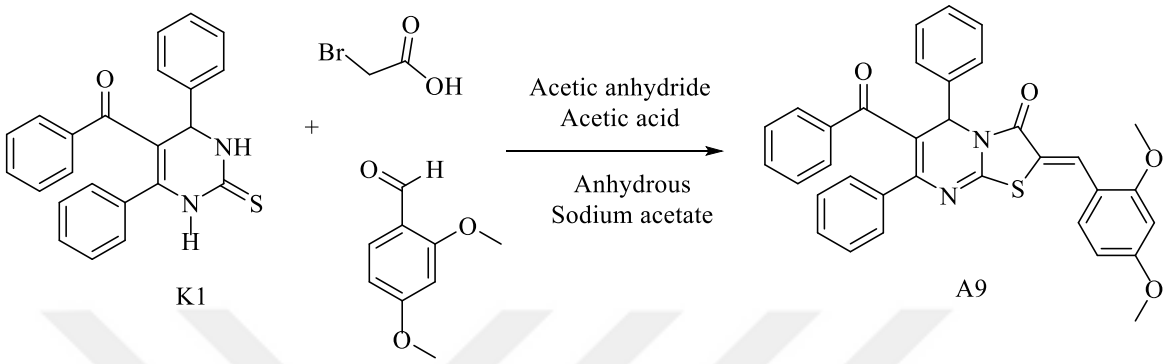


Figure 4.37. Synthesis reaction of the molecule A9.

Melting point of molecule (A9): 220-221 ℃; Chemical formula: $C_{34}H_{26}N_2O_4S$; Molecular weight: 558.65 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 2,4-dimethoxybenzaldehyde as a result compound A9 was obtained with 91% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed.

IR (KBr, cm^{-1}) for A9: 2988 cm^{-1} (C-H alkene and aromatic) 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1711, 1607, 1589, 1566, 1377, 1327, or 1294 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-$H_{bend.}$) (Figure 4.38).

In the ^1H NMR (400 MHz, $CDCl_3$) spectrum of compound A9, the presence of two strong EDGs methoxy groups on carbon (19C-OCH_3) and (21C-OCH_3) gives 16 unsymmetric hydrogens, the ^1H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons at δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the (14C-H) proton appeared at δ = 8.09 ppm, the Signals B(dd), C(m), D(m), E(m), F(dd), G(dd)

and I(d) originate from aromatic ring protons. The H(s) singlet signal seen at δ = 6.51 ppm can be interpreted to 6C-H proton, the integral of J(m) multiplet signal at δ = 3.88 ppm showed that two broad peaks can be interpreted to the protons of the two methoxy groups on carbon (40CH_3 and 42CH_3). The total integral shows that 26 hydrogen formed up the structure of compound A9 (Figure 4.39, Table 4.19).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A9, the presence of two strong EDGs methoxy groups on carbon (19C-OCH_3) and (21C-OCH_3) gives 28 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.7 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 165.5 ppm. The signals of other carbons in compound A9 between the range (160.0-98.5 ppm) are; (2C, 4C, 14C, 1C, 8C carbons and aromatic region carbons), the signal for (6CH) carbon appeared at δ = 57.4 ppm, the signal for (40CH_3) carbon appeared at δ = 55.6 ppm and the signal for (42CH_3) carbon appeared at δ = 55.5 ppm (Figure 4.40, Table 4.20).

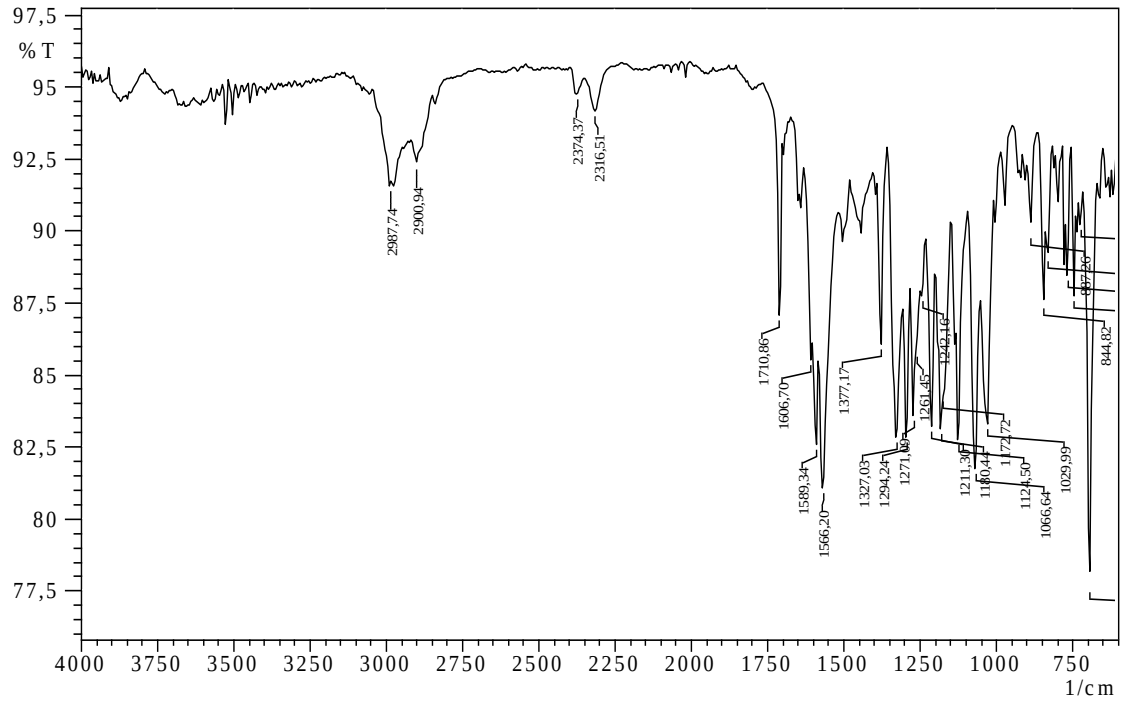


Figure 4.38. IR spectrum of compound A9.

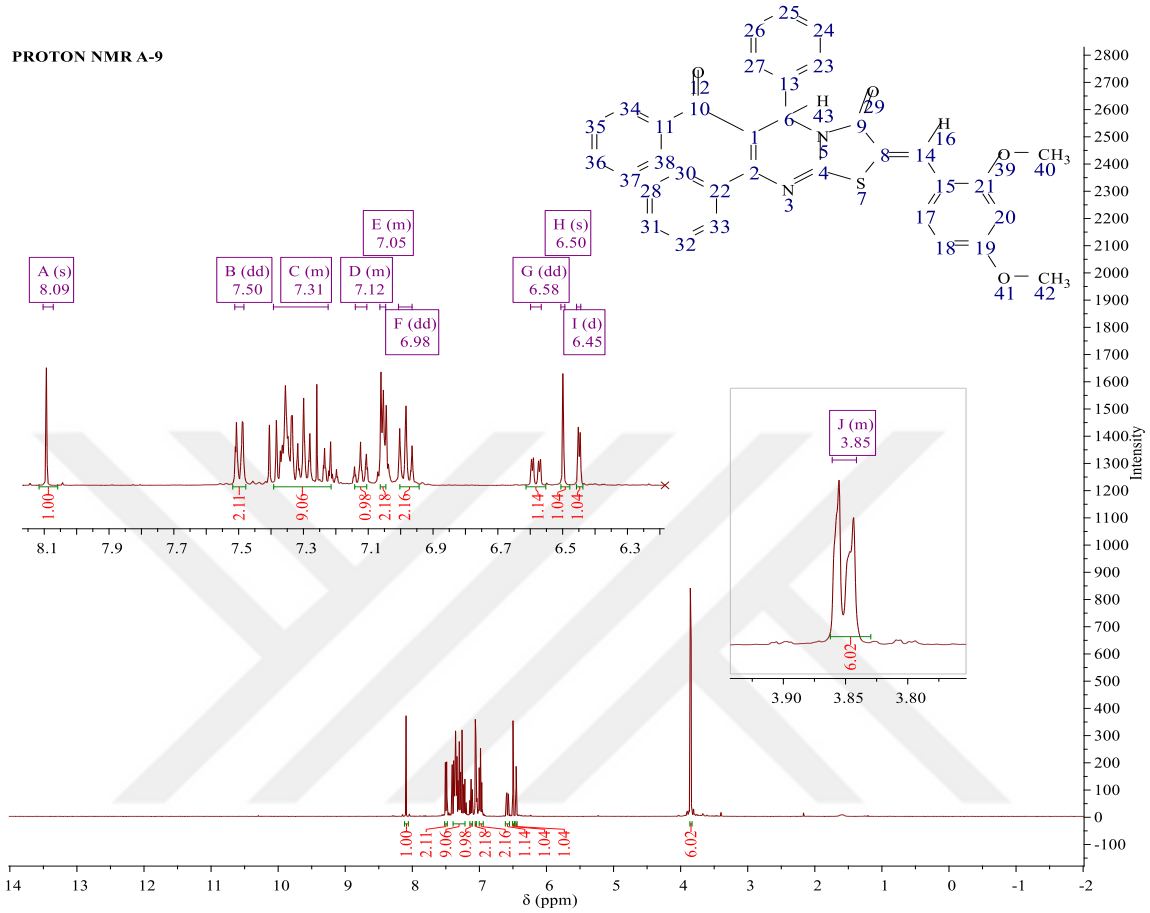


Figure 4.39. ^{1}H NMR spectrum of compound A9.

Table 4.19. ^{1}H NMR spectrum data of compound A9

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	8.09	8.10 - 8.07	1	1.00	s		14C-H
2	B(dd)	7.50	7.51 - 7.48	2	2.11	dd	1.10, 8.23	Aromatic
3	C(m)	7.31	7.39 - 7.22	9	9.06	m		Aromatic
4	D(m)	7.12	7.14 - 7.10	1	0.98	m		Aromatic
5	E(m)	7.05	7.06 - 7.05	2	2.18	m		Aromatic
6	F(dd)	6.98	7.01 - 6.96	2	2.16	dd	4.69, 10.47	Aromatic
7	G(dd)	6.58	6.60 - 6.57	1	1.14	dd	2.34, 8.67	Aromatic
8	H(s)	6.50	6.51 - 6.49	1	1.04	s		6C-H
9	I(d)	6.45	6.46 - 6.44	1	1.04	d	2.32	Aromatic
10	J(m)	3.85	3.86 - 3.84	6	6.02	m		40CH_3 and 42CH_3

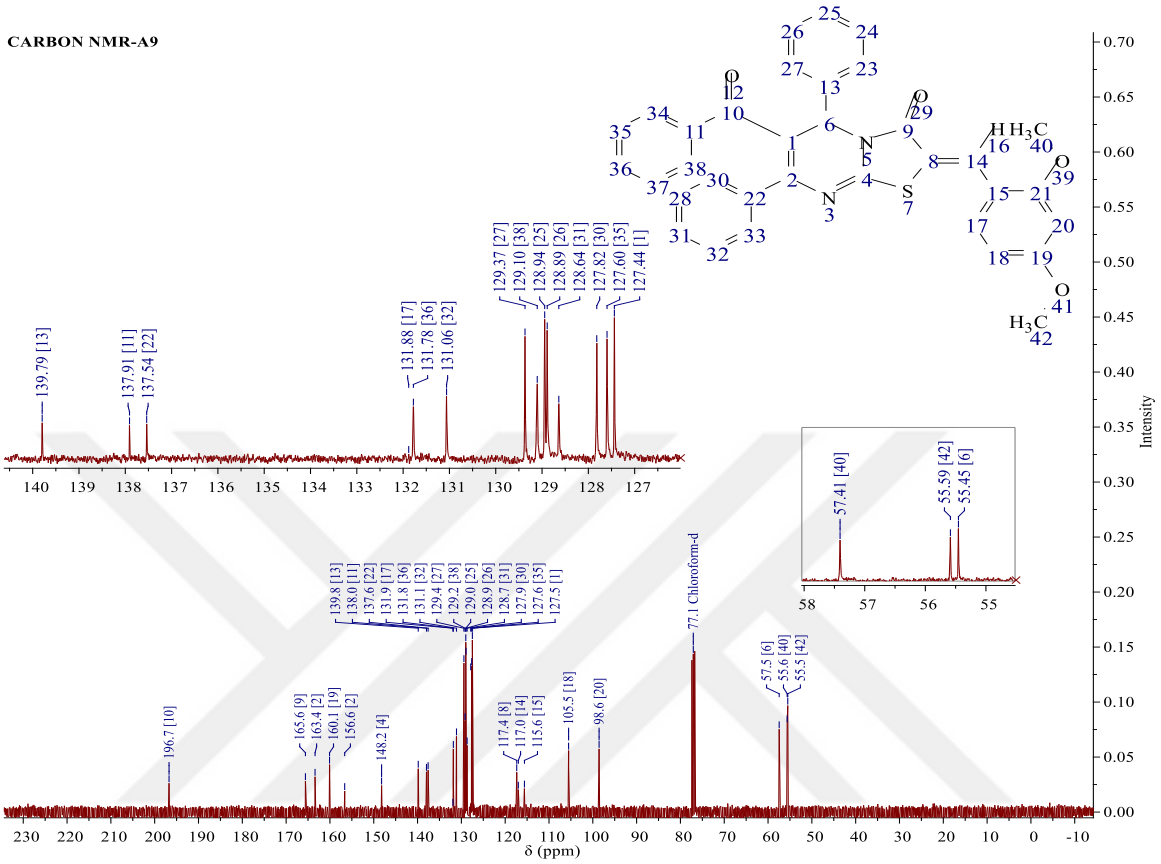


Figure 4.40. ^{13}C NMR spectrum of compound A9.

Table 4.20. ^{13}C NMR chemical shift assignments of compound A9

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.7	13C	139.8	32CH	131.1	24CH	128.9	37CH	127.6
9C	165.6	11C	138.0	23CH	129.4	26CH	128.9	1C	127.5
2C	163.4	22C	137.6	27CH	129.4	31CH	128.7	8C	117.4
19C	160.1	17CH	131.9	34CH	129.2	30CH	127.9	14C	117.0
21C	156.6	36CH	131.8	38CH	129.2	33CH	127.9	15C	115.6
4C	148.2	28CH	131.1	25CH	129.0	35CH	127.6	18CH	105.5
								20CH	98.6
								6CH	57.5
								40CH3	55.6
								42CH3	55.5

4.1.11. (*E, Z*)-6-benzoyl-5,7-diphenyl-2-(thiophen-2-ylmethylene)-5*H*-thiazolo[3,2-*a*] pyrimidin-3(2*H*)-one (A10)

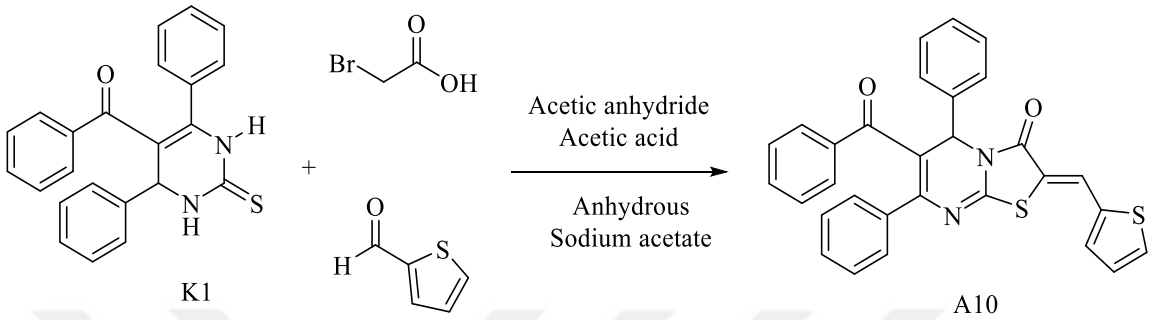


Figure 4.41. Synthesis reaction of the molecule A10.

Melting point of molecule (A10): 218-219 ℃; Chemical formula: $C_{30}H_{20}N_2O_2S_2$; Molecular weight: 504.62 g/mol.

After synthesized compound K1 by the procedure (Akbaş, et al., 2007) through biginelli-3CR, with a little higher yield due to some modification in the synthetic pathway. In the second MCR compound K1 participated in a one pot reaction with bromoacetic acid and 2-Thiophenecarboxaldehyde as a result compound A10 was obtained with 94% yield which is much higher compared to other sources (Abdel-Latif, 2005; Akbaş, et al., 2017b; 2018) to obtained this similar compound, on the other hand most literatures carried out this type reaction in a several complex procedure steps but in this thesis the short and effective pathway was employed

IR (KBr, cm^{-1}) for A10: 2978 cm^{-1} (C-H alkene and aromatic) 2901 cm^{-1} (aliphatic C-H). One of these strong sharp peaks in the range (1703, 1628, 1678, 1595, 1554, 1489, 1416, or 1383 cm^{-1}) can be represented as one of these functional groups (C=O, C=N, C=C alkene, C=C aromatic, or N-$H_{bend.}$) (Figure 4.42).

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound A10 presence of thiophene group five member ring attached to carbon fourteen instead of benzaldehyde derivative six member ring precursors, in this case compound A10 gives 14 unsymmetric hydrogens, the ^{1}H NMR shows the absence of the two peaks for (3N-H, 5N-H) protons at δ = 9.00 ppm of K1, at the same time A(s) singlet peak interpreted to the 14C-H proton appeared at δ = 7.94 ppm, the signals B(dd), C(m), D(m), E(m), F(m), G(m) and H(m) originate from aromatic

ring protons. The I(s) singlet signal seen at δ = 6.51 ppm can be interpreted to (6C-H) proton, the total integral shows that 20 hydrogen formed up the structure of compound A10 (Figure 4.43, Table 4.21).

In the ^{13}C-NMR (400 MHz, $CDCl_3$) spectrum of A10, the presence of thiophene group five-member ring attached to carbon fourteen instead of benzaldehyde derivative six-member ring precursors, in this case compound A10 gives 24 unsymmetric carbons, the signal of benzoyl carbonyl carbon (10C=O) appeared at δ = 196.6 ppm and the signal of carbonyl carbon in the thiazole ring (9C=O) appeared at δ = 164.9 ppm. The signals of other carbons in compound A10 between the range (155.2-117.8 ppm) are; (2C, 4C, 14C, 1C, 8C carbons and aromatic region carbons), the signal for (6CH) carbon appeared at δ = 57.7 ppm. The total number of peaks equal to 24 signals with 6 symmetric carbons, thus; the total 30 carbons consist of the compound A10 (Figure 4.44, Table 4.22).

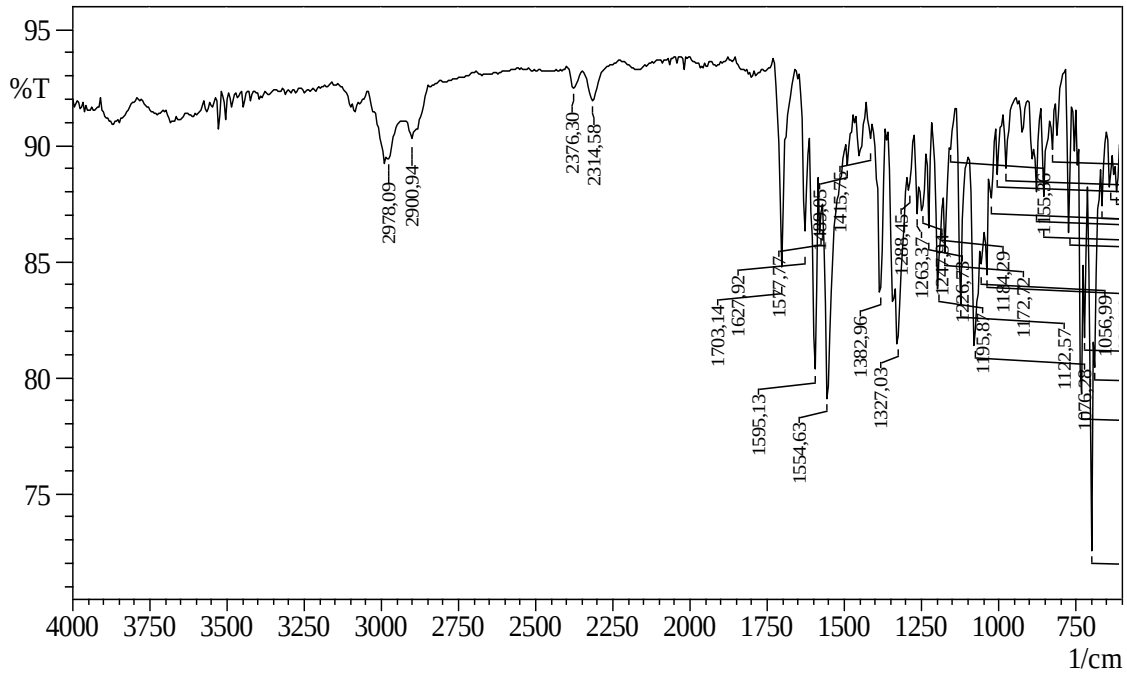


Figure 4.42. IR spectrum of compound A10.

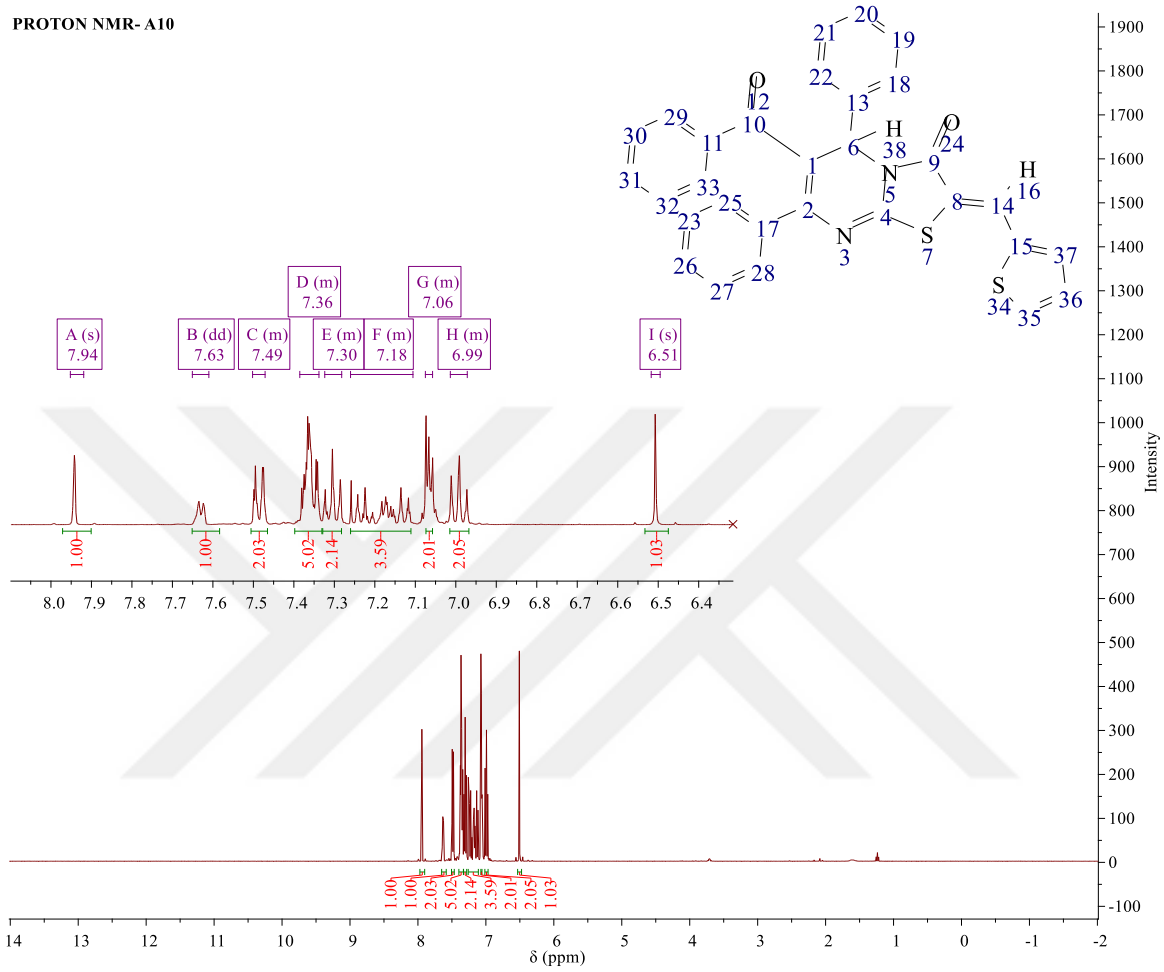


Figure 4.43. ^{1}H NMR spectrum of compound A10.

Table 4.21. ^{1}H NMR spectrum data of compound A10

	Name	Shift	Range	H's	Integral	Class	J's	Position
1	A(s)	7.94	7.95 - 7.92	1	1.00	s		14C-H
2	B(dd)	7.63	7.65 - 7.61	1	1.00	dd	0.60, 4.96	Aromatic
3	C(m)	7.49	7.50 - 7.47	2	2.03	m		Aromatic
4	D(m)	7.36	7.39 - 7.34	5	5.02	m		Aromatic
5	E(m)	7.30	7.32 - 7.28	2	2.14	m		Aromatic
6	F(m)	7.18	7.26 - 7.11	4	3.59	m		Aromatic
7	G(m)	7.06	7.08 - 7.06	2	2.01	m		Aromatic
8	H(m)	6.99	7.01 - 6.97	2	2.05	m		Aromatic
9	I(s)	6.51	6.52 - 6.50	1	1.03	s		6C-H

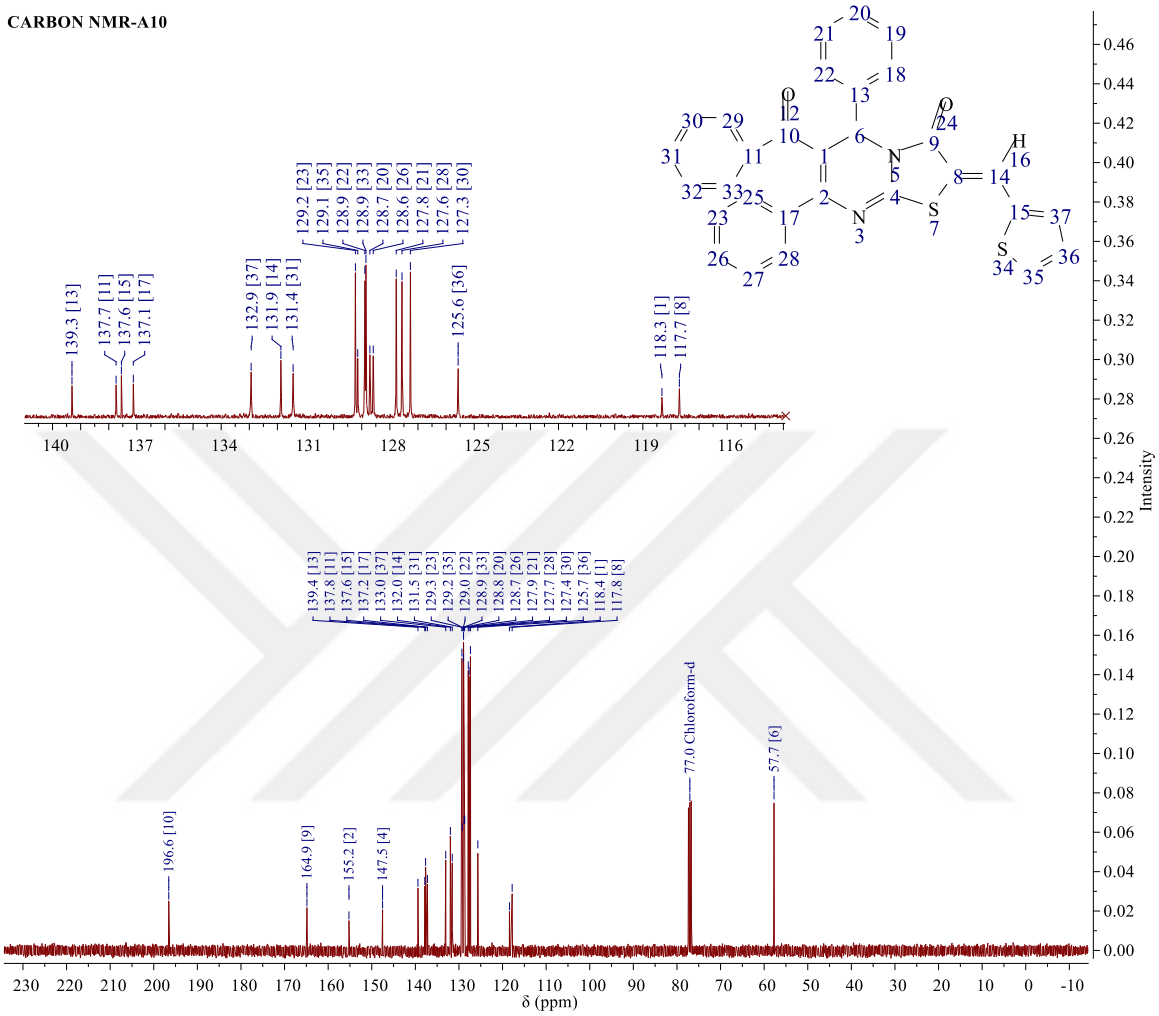


Figure 4.44. ^{13}C NMR spectrum of compound A10.

Table 4.22. ^{13}C NMR chemical shift assignments of compound A10

Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
10C	196.6	15C	137.6	27CH	129.3	20CH	128.8	30CH	127.4
9C	164.9	17C	137.2	35CH	129.2	26CH	128.7	32CH	127.4
2C	155.2	37CH	133.0	18CH	129.0	19CH	127.9	36CH	125.7
4C	147.5	14C	132.0	22CH	129.0	21CH	127.9	1C	118.4
13C	139.4	31CH	131.5	29CH	128.9	25CH	127.7	8C	117.8
11C	137.8	23CH	129.3	33CH	128.9	28CH	127.7	6CH	57.7

4.2. Quantum Chemical Calculation Results

Full structural optimizations of all compounds were accomplished in the ground state by DFT method at the level of B3LYP / 6-31G (d, p). The frontier molecular orbitals (HOMO and LUMO) shapes were visualized by GaussView 5.0.8 visualization software (Figure 4.45, Figure 4.46). Through QCCs the values of various quantum parameters were calculated to investigate the reactivity and properties of synthesized compounds, the relevant values are given in (Table 4.23.a,b).

The binding capability of the inhibitor to the metal surface rises with increasing of the E_{HOMO} value and decreasing of the E_{LUMO} value. A3 with the presence nitro-group act as electron-withdrawing group has the lowest E_{HOMO} (- 5.3789 eV) with lowest E_{LUMO} (- 4.5098 eV), A10 has the highest E_{HOMO} (- 5.0056 eV) with highest E_{LUMO} (- 3.2673 eV), A3 has highest ionization energy (5.3789 eV) and highest electron affinity (4.5098 eV) it mean A3 more likely tend to act as electrophile to accept electrons, it will be hard to lose electrons, but A10 has lowest ionization energy (5.0056 eV) and lowest electron affinity (3.2673 eV) it mean that A10 more likely tend to act as nucleophile to donate electrons because it requires small amount of energy to eliminate electron (Table 4.23.a), these results agree with the lectures (Hasanov and Bilgi, 2007; Wang, et al., 2007).

Electronegativity (x), indicating the capability of molecules to attract electrons, it can be associated with the chemical potential μ (eV) which measures the escaping tendency of an electron (x = - μ). Values displayed in (Table 4.23.b) shows that compound A3 has higher electronegativity value (x = 4.9444) and lower chemical potential value (μ = - 4.9444), thus; A3 is more difficult to lose an electron but easier to accept electron. But molecule A10 has lowest electronegativity value (x = 4.1365) and highest chemical potential value (μ = - 4.1365) compared to all the molecules, these trends make molecules A3 and A10 are the least stable and the most reactive among all the compounds, it agrees with the comparation of (Parr, et al., 1978; Wang, et al., 2007; Bendjeddoua, et al., 2016). The results as indicated in (Table 4.23.a) show that compound A3 and A10 have the lowest energy gap (ΔE = 0.8691, 1.7383 eV) respectively. This means that these two compounds A3 and A10 are more polarizable and it is associated with the high chemical activity and low kinetic

stability in comparison to the other compounds as described by (Amin, et al., 2010). The hardness and softness are another two QCC parameters to measure the stability and reactivity of the chemical species, a hard molecule has a large ΔE and a soft molecule has a small ΔE gap, in this thesis the molecule A3 has low energy gap with lowest hardness value ($\eta = 0.4346$ eV), and it has the highest global softness value ($S = 2.3012$ eV), soft compounds considered to be more polarizable than hard compounds (Table 4.23.b), these values concentrated the methods used in (Fleming, 2010). The dipole moment D (Debye) is another significant descriptor that results from unequal spreading of charges on the different atoms in the molecule, in this study A3 has the highest dipole moment value (6.2908 Debye) which it has strong EWG and agree with (Leif and Christopher, 2014), (Table 4.23.b).

The fraction of electrons transferred (ΔN) from the inhibitor molecule to the metallic atom was calculated according to Pearson electronegativity scale, the highest fraction of electrons transferred is associated with the best inhibitor, A3 has the lowest ΔN (0.4466), lowest energy gap ($\Delta E = 0.8691$eV), highest electrophilicity index ($\omega = 28.1286$) and highest $\Delta E_{\text{Backdonation}}$ (- 0.1086), on the other hand A8 has the highest ΔN (1.3045), highest ΔE (1.8918 eV), lowest electrophilicity index ($\omega = 9.5110$) and lowest $\Delta E_{\text{Backdonation}}$ (- 0.2365). Electrophilicity (ω), indicates the capability of the inhibitor species to gain electrons, higher values represent the presence of a good electrophile (Table 4.23.b). Charge transfer to the molecule and back-donation from the molecule, the calculated $\Delta E_{\text{Backdonation}}$ values for the inhibitors indirectly proportional with the hardness the results confirming the work by (Karzazi, et al., 2014).

The overall data as listed in (Table 4.23) reveals that despite A3 has the lowest ΔE at the same time it has the lowest ΔN but A8 has highest ΔE and highest ΔN, this is mean for every molecule with low ΔE doesn't mean it has good inhibitor efficiency this is in contrast with lecture (Udhayakalaa, et al., 2013a), it is most likely depend on the value of fraction of charge transfer which indicated that A8 has the highest ΔN, maybe it has the best inhibitor efficiency. From compared the data of A9 and A5 it reveals that ΔE (A9<A5) and at the same time ΔN (A9>A5) in this case it's possible to say A9 has smaller ΔE and higher ΔN than A5, thus; A9 associated with both higher chemical reactivity and higher inhibitor efficiency than A5 and this agree with results in (Udhayakalaa, et al., 2013b).

The fraction of electrons transferred demonstrated that the order of ΔE and Δ*N* for all molecules follows the sequence:

ΔE A3<A10<A7<A2<A4<A6<A1<A9<A5<A8<K2

Δ*N* A3<A7<A2<A4<A6<A1<A10<A5<A9<A8<K2

It's noteworthy to note that A3 hold (-NO_2) substitute which is act as strong EWG, the effect of nitro group can be clearly seen on both NMR spectrum and QCC data.

Table 4.23a. Theoretical data through QCC for all compounds (K2, A1-A10)

	Total Energy (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	Ionization Potential "I(eV)"	Electron-Affinity "A(eV)"
K2	-46289.1862	-5.3616	-2.1598	3.2018	5.3616	2.1598
A1	-51441.0732	-5.2492	-3.4153	1.8339	5.2492	3.4153
A2	-63947.5442	-5.3049	-3.5315	1.7734	5.3049	3.5315
A3	-57003.2828	-5.3789	-4.5098	0.8691	5.3789	4.5098
A4	-54557.2868	-5.2486	-3.4292	1.8194	5.2486	3.4292
A5	-52503.6639	-5.2137	-3.3337	1.8800	5.2137	3.3337
A6	-53487.7527	-5.2470	-3.4268	1.8202	5.2470	3.4268
A7	-60612.4250	-5.3156	-3.5533	1.7623	5.3156	3.5533
A8	-55626.6528	-5.1877	-3.2959	1.8918	5.1877	3.2959
A9	-57673.4545	-5.1947	-3.3236	1.8711	5.1947	3.3236
A10	-60169.7123	-5.0056	-3.2673	1.7383	5.0056	3.2673

Table 4.23b. Theoretical data through QCC for all compounds (K2, A1-A10)

	Electro Negativity "χ (eV)"	Chemical Hardness "η(eV)"	Chemical Softness "S"	$\Delta E_{backdonation}$	Transfer Electron Fraction ΔN	Dipole-Moment (Debye) D	Electro-Phylicity Index (ω)
K2	3.7607	1.6009	0.6246	0.4002	2.5929	6.2387	4.4172
A1	4.3323	0.9170	1.0906	0.2292	1.2231	4.5177	10.2341
A2	4.4182	0.8867	1.1278	0.2217	1.1446	3.7126	11.0074
A3	4.9444	0.4346	2.3012	0.1086	0.4466	6.2908	28.1286
A4	4.3389	0.9097	1.0993	0.2274	1.2104	3.3841	10.3474
A5	4.2737	0.9400	1.0638	0.2350	1.2813	5.2267	9.7153
A6	4.3369	0.9101	1.0988	0.2275	1.2118	3.3135	10.3333
A7	4.4345	0.8812	1.1349	0.2203	1.1303	3.7348	11.1583
A8	4.2418	0.9459	1.0572	0.2365	1.3045	4.6084	9.5110
A9	4.2592	0.9356	1.0689	0.2339	1.2821	3.8805	9.6950
A10	4.1365	0.8692	1.1505	0.2173	1.2444	5.7738	9.8431

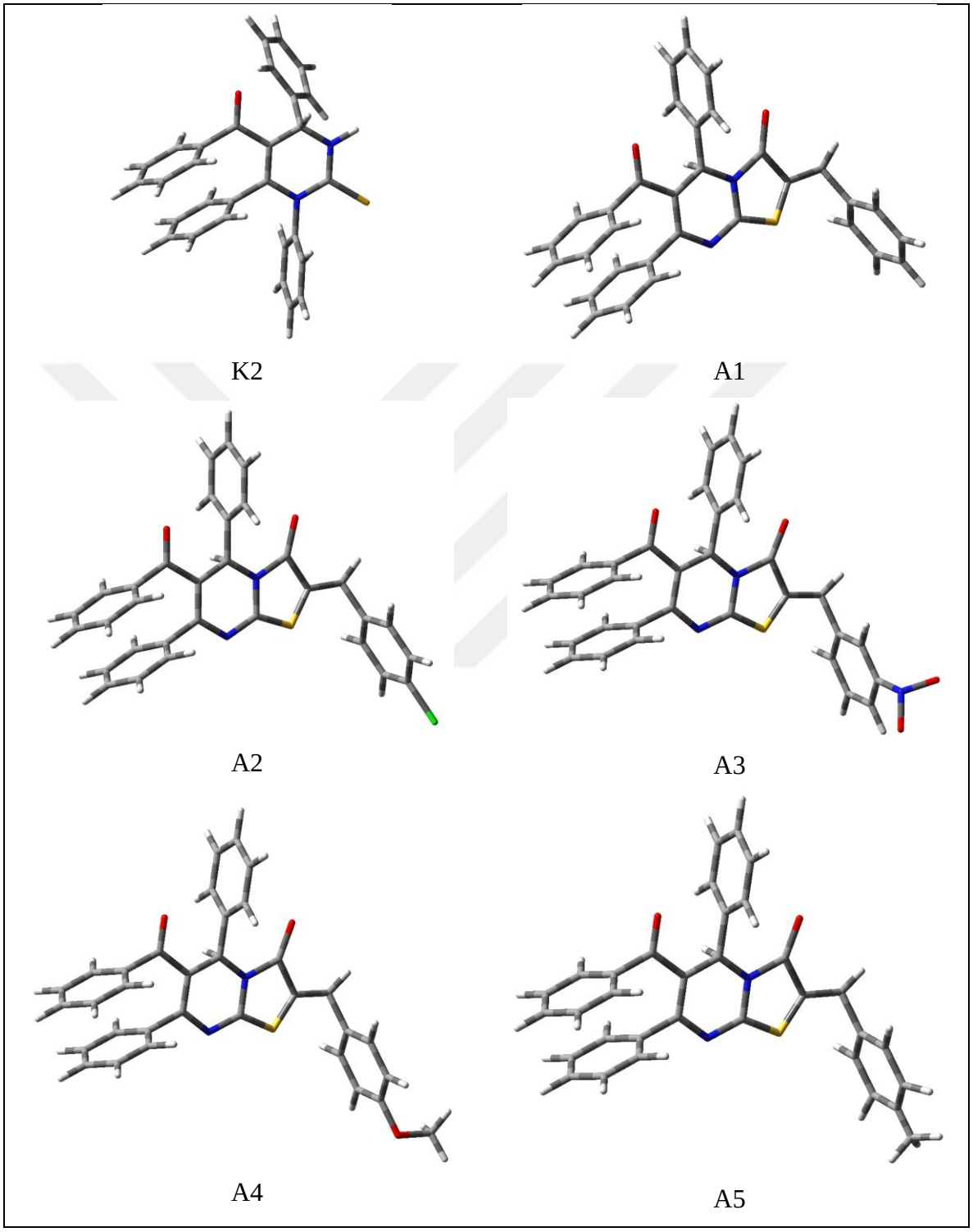


Figure 4.45. The optimized structure of molecules (K2, A1-A10) by QCC.

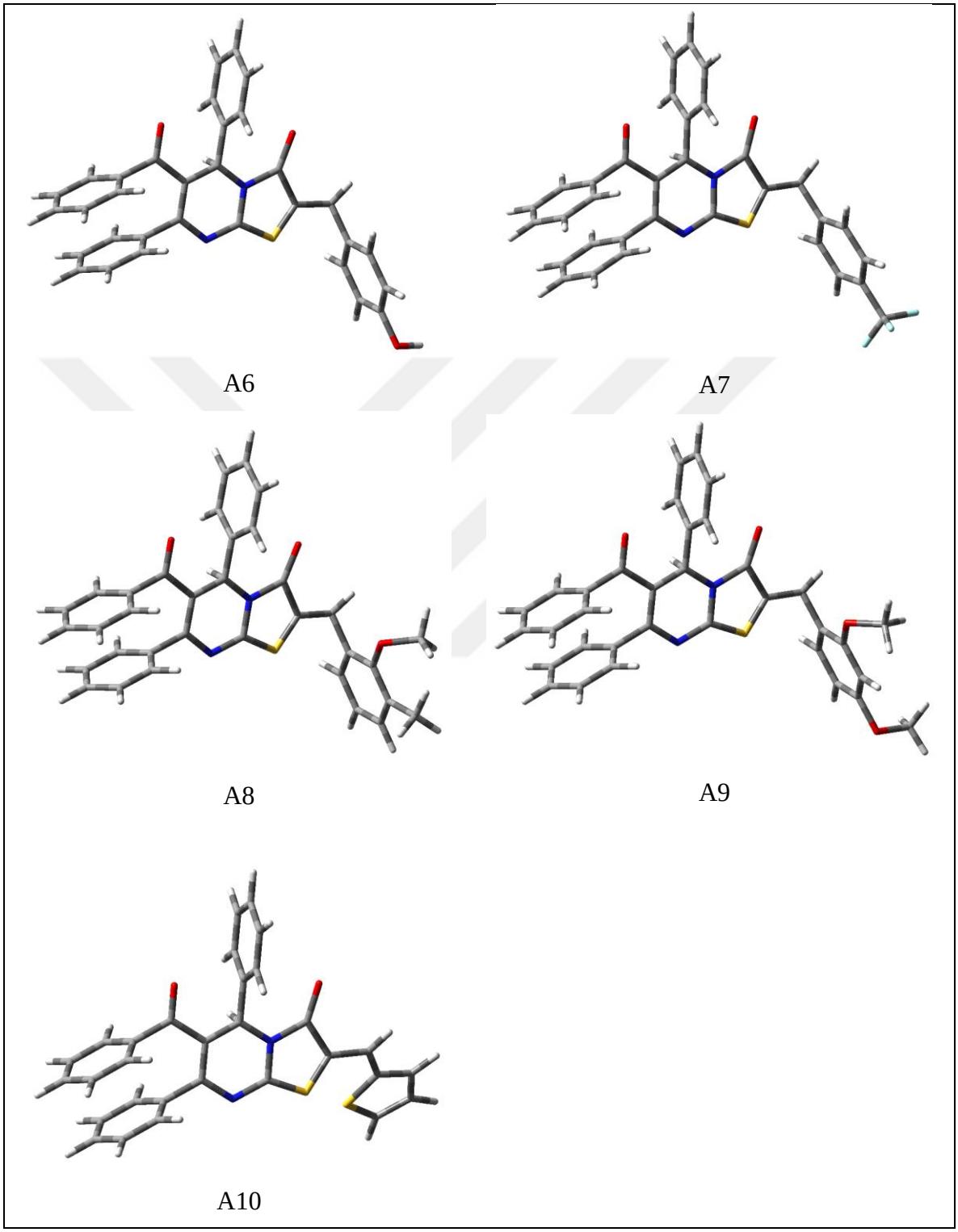


Figure 4.45. The optimized structure of molecules (K2, A1-A10) by QCC (continued).

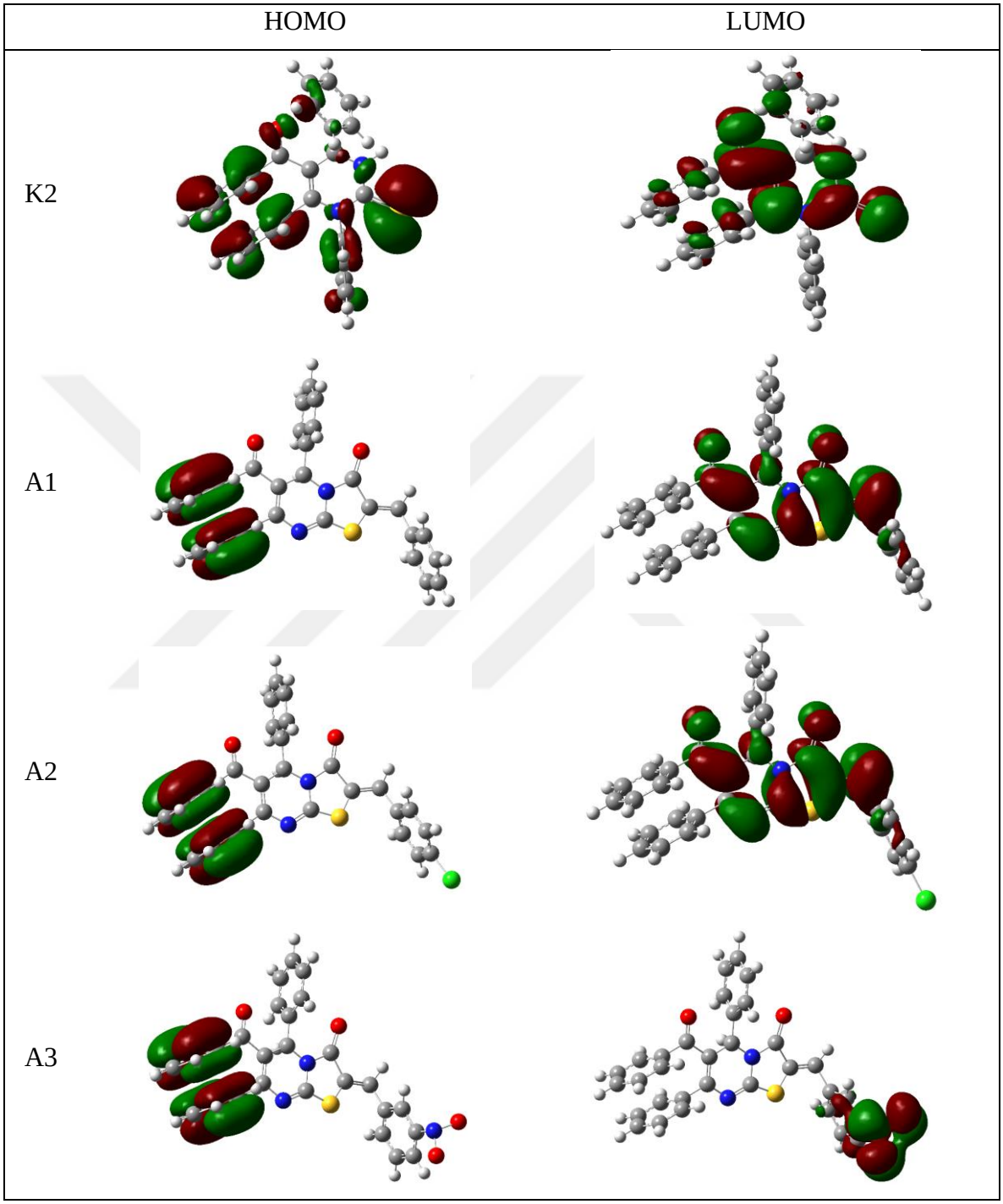


Figure 4.46. The frontier HOMO and LUMO orbital shapes of molecules (K2, A1-A10).

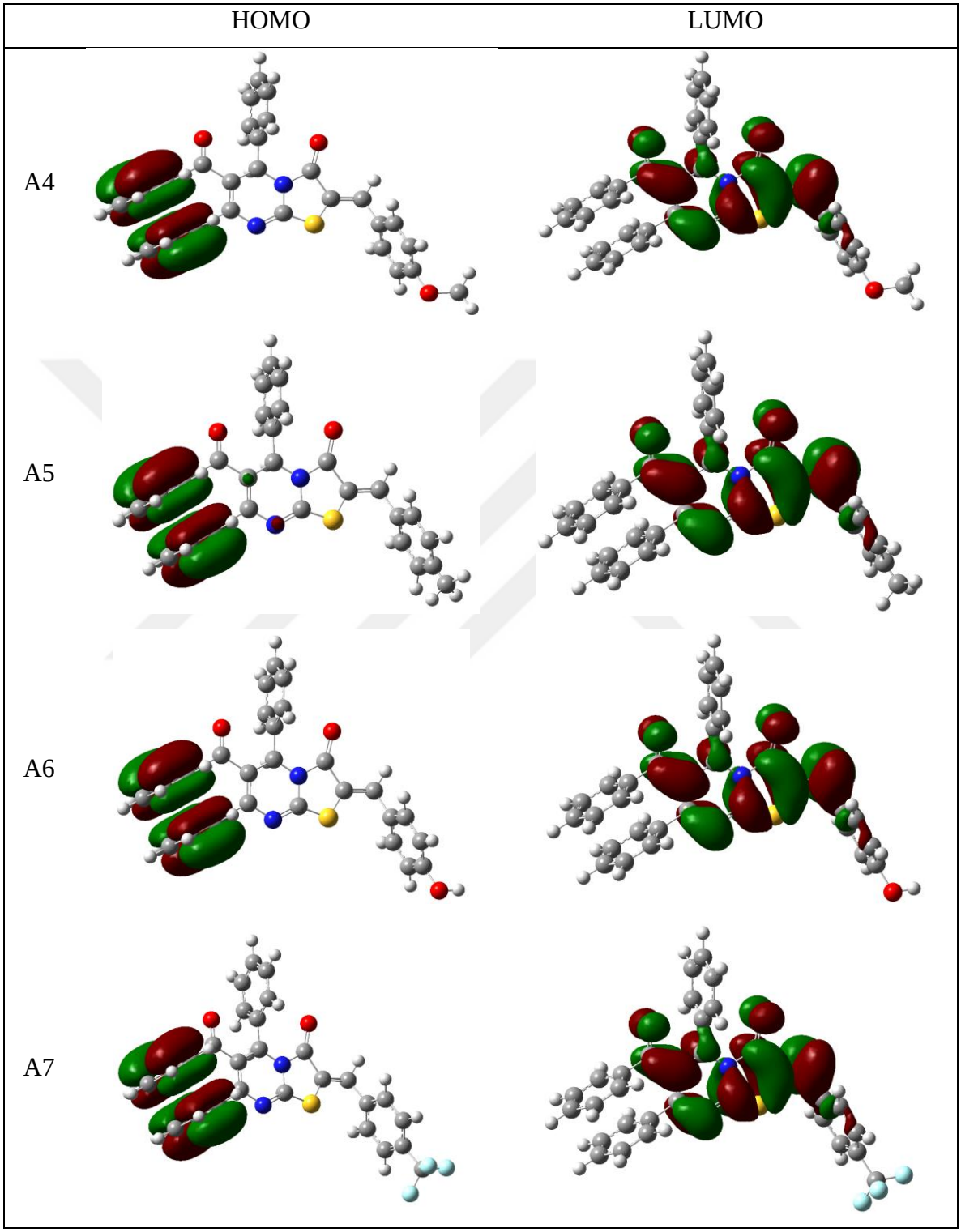


Figure 4.46. The frontier HOMO and LUMO orbital shapes of molecules (K2, A1-A10).

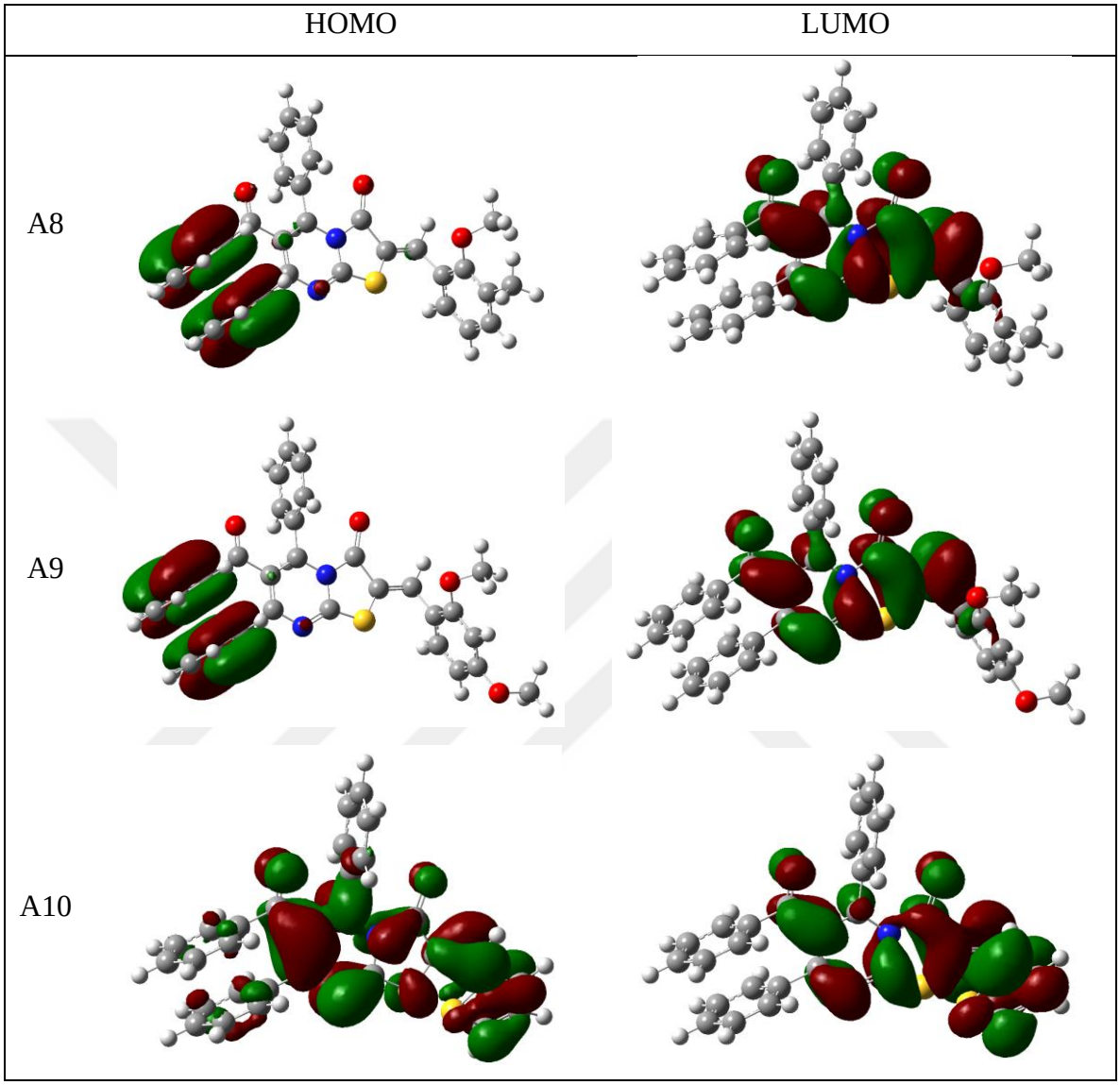


Figure 4.46. The frontier HOMO and LUMO orbital shapes of molecules (K2, A1-A10) (continued).

5. CONCLUSION

In conclusion, practically eleven novel compounds have been synthesized, K1 and K2 were obtained via Biginelli reaction. The compound K1 followed heterocyclization Hantzsch/Knoevenagel condensation with various substituted aromatic aldehydes for synthesis several arylidene-bicyclic thiazolo-pyrimidine (A1-A10). The ^{1}H NMR/^{13}C NMR spectrum were completely consistent with the predictable structures. At the same time the synthesized compounds further investigated through QCC/ Gaussian programing package, theoretical results showed that A3 has the smallest energy gap (ΔE) which makes this compound kinetically unstable and most reactive among other compounds this is may be due to presence strong electron withdrawing group (-NO_2), simultaneously, the results reveal that A3 has the lowest ΔN, which means it has the lowest inhibitor efficiency, these are proving that every compound with low ΔE doesn't mean it has the high inhibitor efficiency, at the same time A8 has the largest energy gap and the largest ΔN, A8 holds methyl and methoxy groups both groups act as an electron donating group, these are also confirming that A8 with low ΔE still has high inhibitor efficiency compared to other compounds.

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EXTENDED TURKISH SUMMARY
(GENİŞLETİLMİŞ TÜRKÇE ÖZET)

3,4-DİHİDROPİRİMİDİN-2(1*H*) TÜREVI BİLEŞİKLERİN TASARIMI, SENTEZİ, HALKALANMA REAKSIYONLARININ ARAŞTIRILMASI VE ELEKTRONİK ÖZELLİKLERİNİN BELİRLENMESİ

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ÖZ

Bu çalışmada, multikomponent siklokondenzasyon reaksiyon (MCR) yöntemlerinden biri olan Biginelli reaksiyonu kullanılarak pirimidin türevi bileşikler elde edildi. Pirimidin türevi bileşiklerin aynı kap içerisinde tek basamakta bromoasetik asit ve çeşitli aril-aldehitler ile reaksiyona sokulmasıyla, iyi bir verimle, ariliden-bisiklik tiyazolo-pirimidin bileşikleri sentezlendi.

Tüm yeni bileşiklerin yapıları IR, ^{1}H, ve ^{13}C NMR gibi spektroskopik yöntemler kullanılarak analiz edildi. Aynı zamanda tüm bileşiklerin kuantum kimyasal hesaplamaları (QCC), yoğunluk fonksiyonel teorisi (DFT) metodu, 6-31G (d, p) baz seti ve B3LYP fonksiyonları kullanılarak Gaussian09W yazılım paketi ile gerçekleştirildi.

Anahtar kelimeler: Biginelli, DFT, MCR, Pirimidin, Teorik kimya.

1. GİRİŞ

Heterosiklik halkalar, bir veya daha fazla karbon atomunun farklı heteroatomlarla değiştirildiği karbosiklik bileşiklerdir. En çok bulunan heterosiklik bileşikler, beş / altı üyeli halkalara sahip olan ve azot heteroatomu içeren yapılardır, ardından oksijen ve kükürt atomlarının bulunduğu heterosiklik bileşikler gelir. Bununla birlikte, periyodik tablodaki diğer birkaç atom, kararlı heterosiklik bileşikler oluşturabilen metalik ve metalik olmayan

heteroatomları içerir. 1983 IUPAC raporuna göre, Periyodik tablodaki Grup II'den IV'e kadar on beş element, karbon elementi ile heterosiklik halka sistemi oluşturma yeteneğine sahiptir. Heterosiklik bileşikler, özellikle eczacılık alanında, 2020'li yıllarda ABD FDA'nın son veri tabanlarında, onaylı ilaçların% 75'inden fazlasının, azot içeren heterosiklik bileşiklere dayalı olarak piyasalarda mevcut olduğunu ortaya koymaktadır.

Alanı genişletmek için, ana heterosiklik halka, halkaların bir atomu paylaşarak bağladıkları bu bileşiklerde spirosiklik bileşikler gibi yeni değişken halka sistemlerine neden olan farklı halkalar ile kaynaşabilir, bu bileşiklerde kaynaşmış bisiklik bileşikler, halkaların paylaşarak katılması iki atom ve köprülü bisiklik bileşikler, halkalar arasında ikiden fazla atomu paylaşarak oluşan bu bileşikleri içerir. Ayrıca, bu halka sistemlerinin etrafındaki hidrojen atomları, farklı sübstitüentlerle yer değiştirebilir, sonuç olarak heterosiklik bileşiklerin birçoğu tanınır.

Herhangi bir heterosiklik sistemin önemli özellikleri; halka büyüklüğünü, heterosiklik bileşiği oluşturan heteroatomların türünü ve sayısını bilmektir. Bu özellikler heterosiklik bileşiklerin isimlendirilmesinde yardımcı olur, Hantzsch–Widman sistemi ve günümüzde bazı küçük değişikliklerle uygulanan IUPAC sistemi isimlendirmenin temelini oluşturan en yaygın yöntemlerdir. Çok sayıda azot içeren heterosiklik yapılar arasında, diazinler (iki azot heteroatomuna sahip altı üyeli) ve tiyazoller (birer azot ve kükürt atomlarına sahip beş üyeli) en çok dikkat çeken iki sınıf olarak kabul edilebilir.

2. BULGULAR VE TARTIŞMA

Bu çalışmada, deneysel olarak iki ayrı çok bileşenli reaksiyon gerçekleştirilmiş ve teorik olarak sentezlenen tüm bileşikler için bazı kuantum kimyasal parametreler hesaplanmıştır. Sentez pirimidin halkasının çeşitli yönleri, birçok raporda gözden geçirilmiştir, ancak MCR'nin diğer reaksiyon türlerine (doğrusal, yinelemeli veya ıraksak sentez) göre avantajı nedeniyle, bu nedenle bu tezin ilk adımında Biginelli üç bileşenli reaksiyon DHPM'lerin sentezi için seçilmiştir. Biginelli ürününün DHPM çekirdeği etrafındaki altı çeşitlilik noktası, bu tip bileşikleri çok işlevli pirimidinler için değerli bir kimyasal öncü haline getirmektedir. Bu çalışmanın bir sonraki adımında Biginelli ürününün

pirimidin türevlerine maruz kalabilir. Hantzsch heterosiklizasyon / Knoevenagel yoğunlaştırma yoluyla tek bir kapta (bir kap) bromoasetik asit ve çeşitli aril-aldehit molekülleri ile her iki adımda da iyi bir verimle birkaç yeni bisiklik ariliden-tiyazolo-pirimidin bileşiği elde etmek için ilave reaksiyon İkiden fazla substrat tek bir reaktörde reaksiyona girer, bu nedenle bu çalışmanın art arda iki ayrı çok bileşenli reaksiyonu içerdiği belirtilebilir, bu, arzu edilen bileşikleri kısa bir reaksiyon süresi içinde elde etmek için yararlı bir yöntem olarak kabul edilebilir yüksek verim**.**

2.1. K1 ve K2 Bileşiklerinin Hazırlanma Yöntemleri

İlk çok bileşenli reaksiyonda, iki heterosiklik dihidropirimidin (K1 ve K2), uygun reaksiyon koşulları altında Tiyoüre / Feniltiyoüre, Dibenzoilmetan ve Benzaldehit arasında Biginelli'nin üç bileşenli siklokondensasyon reaksiyonu ile sentezlendi.

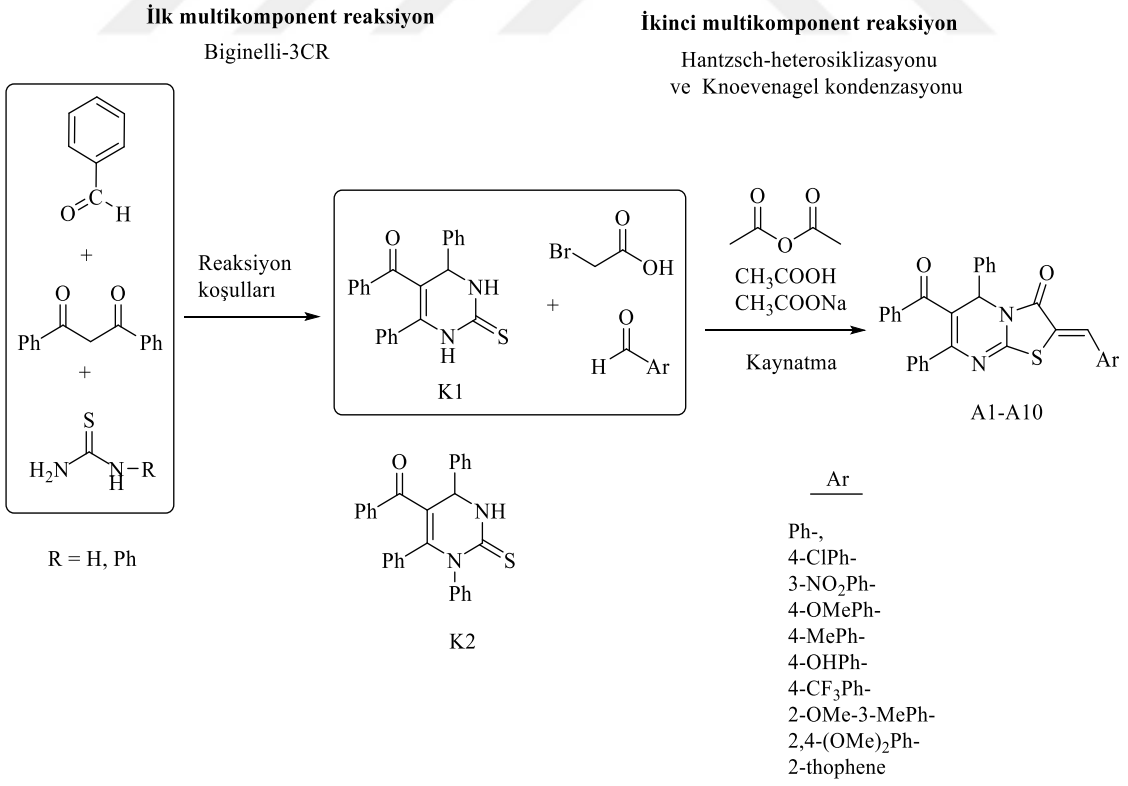
K1 bileşiği, uygun Biginelli reaksiyon prosedürü (asetik asit, hidroklorik asit) altında, küçük bir modifikasyon ile yüksek derecede saflıkla elde edilebilir. Ancak aynı zamanda altında, TLC'ye göre çok sayıda yan ürünle uzun uzun yayın akıştan sonra sadece küçük ürün (K2) oluşum gözlendi, safsızlıklar esas olarak, tanımlandığı gibi Knoevenagel reaksiyonu yoluyla DBM ve aldehit bileşenlerinden kaynaklanıyordu. NMR spektrumlarına göre, bu tip bileşikler yağlı ve zayıf çözünür bileşiklerdir, prosedürü saf ürünleri elde etmeyi zorlaştırır, bazılarında TLC plakasındaki üç reaktan noktası hariç dört yeni nokta çıktı, toplam yedi çok yakın nokta ürünü ayırmanın zor olduğu gözlendi. Bu, güvenli ve yüksek K2 verimi elde etmek için DBM, BA ile reaktan olarak PTU için uygun olan uygun olan prosedürü bulmak için sekiz farklı reaksiyon koşulu denenmiştir.

2.2. A1-A10 Bileşiklerinin Hazırlanma Yöntemleri

İkinci çok bileşenli reaksiyonda, Biginelli ürünü K1 ile Bromoasetik asit ile elektron veren veya elektronun çeşitli ikamelerini taşıyan katı / sıvı Aril-aldehitler arasındaki reaksiyon yoluyla birkaç ariliden-bisiklik tiyazolo-pirimidin bileşiği (A1-A10) hazırlanmıştır. Bir kap sentetik işlemde asetik anhidrit, asetik asit ve susuz sodyum asetat

varlığında farklı pozitiyolarda grupları geri çekerek, reaksiyon karışımı 6 ila 10 saat boyunca geri akışta, K1 noktası tamamen kaybolana kadar. TLC plakası ve fazlalık aldehitlerin bulunduğu noktada yalnızca bir spot ürün görünecektir. Daha sonra, reaksiyon çözeltisi, doğrudan oda sıcaklığına kadar soğutuldu, kristal, yuvarlak tabanlı şişenin altına yerleştirildi, çözelti süzüldü ve çökelti, uygun bir çözücü içerisinde yeniden kristalleştirildi.

Fakat A7 durumunda, 24 saat bekletilmesine rağmen oda sıcaklığında çökelti oluşmadı, bu nedenle A7 reaksiyon karışımını çökmüş buzlu suya çok dikkatli bir şekilde ekleyin (buz olmalı, reaksiyonu ısıtmayın su varlığında karışım, sıcak su durumunda tersine çevrilebilir reaksiyon gözlemlendi, daha sonra çökelti süzüldü ve etanol içinde yeniden kristalleştirildi. A1-A10 için ana çözeltide kalan ürün, A7'yi elde etmek için kullanılan prosedürün aynısı ile ayrılabilir, tam olarak yüksek saflıkta yüzde doksandan daha yüksek (% 90) her bileşik için elde edilen toplam ürün ürünü, Tüm yeni bileşiklerin yapıları IR, ^{1}H ve ^{13}C NMR gibi spektroskopik yöntemler kullanılarak analiz edilmiştir.



Şekil E1. Sentezlenen bileşikler için iki ayrı çok bileşenli reaksiyonların genel şeması (K1, K2 ve A1-A10), [K1; (Akbaş, et al., 2007)].

2.3. Kuantum Kimyasal Hesaplamalar

Teorik kimya, klasik fizik kanunlarından kuantum fiziğinin temel kanunlarına kadar genel fikirleri toplar ve bunları, kimyasal alaka düzeyindeki süreçleri incelemek için matematiksel yöntemlerle birleştirir. Hesaplamalı kimya, farmasötik alanda biyomoleküllerle bağlanmak için uygun ilaç kabiliyetini seçmek için yaygın olarak uygulanabilir, örneğin, uygun bir ilacı bir enzimin aktif bölgesine yerleştirerek, dahası, katının özelliklerini incelemek için uygulanır. maddeler (örneğin plastikler). Teorik kimya, evren hakkındaki nihai gerçekliği ortaya çıkaran deneysel kimyanın yerini alamaz. Hesaplamalı kimya şunları hesaplar:

- Geometri: moleküler şekil (bağ uzunlukları, atomlar arasındaki açılar ve üç atom arasındaki dihedral).
- Enerji: reaktanların aktivasyon enerjisi hakkında bilgi verir, aynı zamanda arzu edilen izomer ürünlerinin belirlenmesine yardımcı olur.
- Reaktivite: Moleküller (nükleofilik bölgeler) ve (elektrofilik bölgeler) etrafındaki elektron yoğunluğunu gösterir, bu, kimyasal reaksiyonun hangi bölgede meydana geleceğini tahmin eder.
- (IR, UV ve NMR) gibi spektrum: moleküler yapının çizilmesinin spektrumlarını tahmin ederek.
- Moleküllerin bir enzimle teması: En iyi aday sürüklemeleri seçmek için hangi substratın enzim yüzeyi ile daha iyi etkileşime sahip olduğunu gösterir.
- Malzemelerin fiziksel özellikleri: moleküllerin fiziksel olarak nasıl davrandığı.

Tüm yeni sentezlenmiş pirimidin türevlerinin (K2 ve A1-A10) temel durumundaki enerjileri ve elektronik yapıların üç boyutlu geometrileri hakkında bilgi edinmek için bu hesaplamalar gerçekleştirilmiştir. Gaussian09W ve GaussView 5.0.8 yazılım paketleri bilgisayara yüklendikten sonra hesaplama DFT yöntemi ile B3LYP / 6-31G (d, p) seviyesinde yapıldı. Kuantum kimyasal hesaplama verileri ile her yeni bileşiğin yapısal, fiziksel ve kimyasal davranışının araştırılması gelecek araştırmalara yardımcı olabilir. Sentezlenen bileşiklerde hem elektron yoğunluklu azot hem de oksijen atomları ve π-

elektronlarının varlığı, bileşiklerin korozyon önleyici etkilere sahip olabileceği izlenimini verdiğinden, ilgili bileşiklerin korozyon önleyici etkileri teorik olarak incelendi.

3. SONUÇ

Sonuç olarak, pratikte on bir yeni bileşik sentezlendi, Biginelli reaksiyonu yoluyla K1 ve K2 elde edildi. İkinci aşamada K1 bileşiğinin, birkaç ariliden-bisiklik tiyazolo-pirimidin (Al-A10) sentezi için çeşitli sübstitüe aromatik aldehitlerle heterosiklizasyon Hantzsch / Knoevenagel kondenzasyonu takip etti. ^{1}H NMR ve ^{13}C NMR spektrumları tahmin edilebilir yapılarla tamamen tutarlıydı. Bu çalışmaların yanı sıra, sentezlenen bileşiklerin teorik olarak Kuantum kimyasal hesaplamaları Gaussian programlama paketi ile de araştırıldı. Teorik sonuçlar A3'ün yapısında güçlü elektron çekici grup (NO_2) olmasından dolayı bu bileşiği kinetik olarak kararsız hale getiren ve diğer bileşikler arasında en reaktif yapan en küçük enerji boşluğuna (ΔE) sahip olduğunu gösterdi. Aynı zamanda A3 bileşiğinin en düşük ΔN'ye sahip olduğunu ortaya koymaktadır. Bu en düşük inhibitör verimliliğine sahip olduğu anlamına gelir; bunlar, düşük ΔE'ye sahip her bileşiğin, yüksek inhibitör verimliliğine sahip olmadığı anlamına geldiğini göstermiştir. A8 bileşiği incelendiğinde ise en büyük enerji boşluğuna ve en büyük ΔN' ye sahiptir. A8 bileşiğinde metil ve metoksi grupları elektron sağlayıcı gruplar olarak işlev görür. En yüksek ΔN'ye sahip olan A8 bileşiğinin diğer bileşiklerle kıyaslandığında en iyi inhibitör etkinliğine sahip olduğu söylenebilir.

CURRICULUM VITAE

He was born in Sulaymaniyah-Iraq in 1992. After completing his primary, secondary, and high school education in Qalat Dizah, he went Koya University, Faculty of Science and Health, Department of Chemistry in 2010. He graduated from the mentioned Department in 2014. He has been working at Koya University as an assistance chemist since 2015. Later in 2019 he has been accepted to study M.Sc. in Van-Turkey. In 2021, he started his graduate education at Van Yuzuncu Yil University-Instituted of Natural and Applied Science-Department of Chemistry.

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